6.01
Pyridazines and their Benzo Derivatives

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6.01.1 INTRODUCTION

6.01.1.1 Background

Until the 1970s pyridazine and its benzo derivatives were believed to be entirely synthetic compounds, and this was one reason offered to explain the modest interest shown in these systems in comparison to the pyrimidines. While there are still only a limited number of examples of naturally occurring pyridazine derivatives, there is no such limit on the interest taken in them. The expansion of work in this area following the commercial introduction of derivatives such as the antihypertensive hydralazine, the herbicide maleic hydrazide, and the antibacterial sulfamethoxypyridazine in the middle of the twentieth century has continued, and new selective herbicides and pharmaceuticals have been developed. The chemistry and pharmacology of pyridazines have been the subject of a series of biannual international conferences held in Strasburg, Vienna, Como, and Bled.

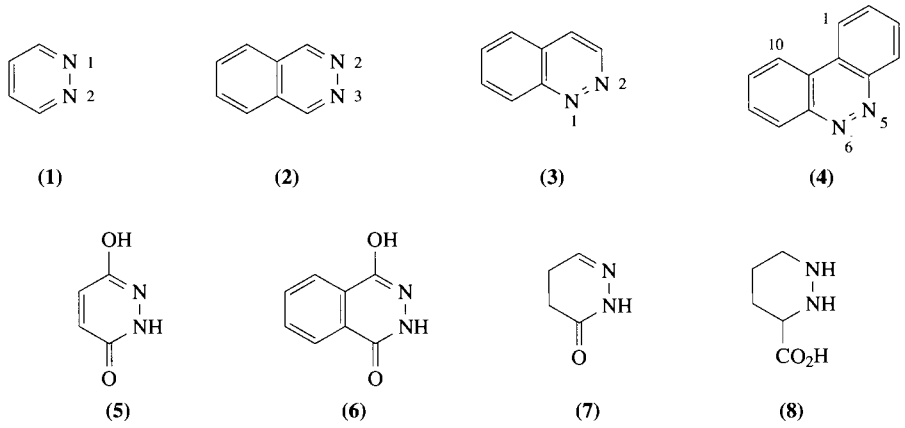
Pyridazines and their benzo derivatives were reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(3B)1⟩ and major reviews listed therein include those on pyridazines ⟨73HC(28)1⟩, cinnolines ⟨73HC(27)1⟩, phthalazines ⟨73HC(27)323⟩, and benzo[*c*]cinnolines ⟨79AHC(24)151⟩. Reviews that have appeared since include those on the pharmacological activity of pyridazines ⟨B-90MI 601-01, B-92MI 601-01⟩.

6.01.1.2 Scope of the Present Chapter

The three parent systems covered by this chapter are pyridazine, phthalazine, and cinnoline, which are normally drawn in their dominant canonical forms (**1**)–(**3**). It is worth noting that cinnoline differs from the others in that it has a double bond between the nitrogens. This difference is accentuated in benzo[*c*]cinnoline (**4**), in which the two benzene rings are fused together by an azo link, and results in the different reactivity of that heterocyclic system.

While nomenclature for the parent systems is standard, the use of a diaza type of nomenclature is sometimes found in the modern literature. The trivial names maleic hydrazide and phthalhydrazide are often used for 6-hydroxy-3(2*H*)-pyridazinone (**5**) and 4-hydroxy-1(2*H*)-phthalazinone (**6**), respectively. Maleic hydrazide, like many other potential diketo heterocyclic tautomers, exists in the hydroxy-keto form used throughout this review for this and related compounds. Similarly, the keto tautomer will generally be used for monoketo/hydroxy heterocyclic derivatives for which a keto tautomer can be drawn. There is sometimes confusion in the literature regarding the use of "-one" and "-thione" or "oxo" and "thioxo" nomenclature as regards the oxidation state of the heterocyclic ring. The former terms imply unsaturation, while some degree of saturation must be specified in the latter; compare 4,5-dihydro-3(2*H*)-pyridazinone and 3-oxo-2,3,4,5-tetrahydropyridazine for structure (**7**). Nomenclature of the saturated and partially saturated derivatives is

usually based on the parent names, although, for example, the amino acid (**8**) has the trivial name piperazic acid and the amino acid abbreviation Piz.



This update covers material that appeared in *Chemical Abstracts* in the 10-year period to the end of 1993, with limited reference to subsequent papers. Over 7600 references to pyridazines or to phthalazines, cinnolines, and their benzo derivatives were identified for this period. While many are not concerned primarily with pyridazine and its benzo derivatives, it is interesting to consider their composition. The majority, about two thirds, refer to pyridazine derivatives, while the remainder are concerned mainly with phthalazines, cinnolines, and their benzo derivatives, with a few containing material common to both pyridazine and its benzo derivatives. Approximately a quarter of all of the references are to patent applications, and while these include some in which a pyridazine function is a nonessential part of the invention, a significant number include pyridazine and benzo derivatives as an important part of the invention. The patent activity is an indication of the expansion of industrial interest in these heterocyclic derivatives. Analysis of a representative sample of patent applications in the early 1990s revealed that in approximately 30% the diazine was an important part of the invention, while the distribution of end uses was pharmaceuticals (43%), agrochemicals (31%), other materials such as photographic reagents and liquid crystals (18%), and analytical applications (8%).

6.01.2 THEORETICAL METHODS

In CHEC-I ⟨84CHEC-I(3B)1⟩, theoretical methods, particularly the calculation of bond lengths, bond angles, and electron densities were discussed alongside consideration of structure, and physical and spectroscopic properties. Theoretical aspects since 1984 are summarized below.

A linear relationship has been demonstrated between experimental pK_a values and the average local ionization energy, a property rigorously defined within the SCF-MO theory, calculated for a series of azoles and azines (including pyridazine) via *ab initio* generation of optimized structures at the STO-3G level and computation of wave functions at the 3-12G level. In addition to the prediction of pK_a values, these calculations may be used to indicate which ring positions are most likely to interact with an electrophile ⟨91JOC2934⟩. Protonation of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone has been investigated through density function (using the DZVP/2 basis set at the LSD and NLSD levels) and *ab initio* calculations (at the 4-21G* and 6-31G** levels) for the pyridazinone and its three monoprotonated ions ⟨94H(38)1957⟩.

Theoretical approaches to aromaticity which have been used include an estimation of the aromatic energy from heats of union and of hydrogenation using the AM1 semiempirical method ⟨89H(28)1135⟩; consideration of bond order using the semiempirical MO method SINDO1 ⟨83JOC1344⟩ and a statistical method based on observed bond lengths, which has also been used to indicate a greater stability for hydroxy-keto rather than diketo pyridazine tautomers ⟨86T89⟩; unification of bond order based aromatic indices using a Huckel MO method into a single aromaticity index I_A, which displays a good relationship with resonance energies for examples including pyridazine and cinnoline ⟨92T335⟩; calculation of resonance energy from the eigen values of the lowest localized and delocalized orbitals using the NLMO and Boys methods applied to electronic structures calculated at the 3-21G level ⟨90IJQ843⟩; and the calculation of ΔH_f° values using MNDO

and 4-31G/MNDO based on calculated and observed bond lengths ⟨85JOC4894⟩. The last methods fail to give reasonable ΔH_f° values relative to pyrimidine and pyrazine, and a correction factor is required to compensate for the underestimation in MNDO of the lone pair electron repulsion between vicinal nitrogens. Underestimation of the interactions due to vicinal nitrogens is also invoked to explain the poor relative resonance energy of pyridazine, calculated by the LNMO method, while the Boys method gives the correct order of pyrazine ≈ pyrimidine > pyridazine > pyridine.

Principal component analysis has been used to investigate aromaticity as a quantitative concept and revealed a dichotomy between "classical" and "magnetic" aromaticity ⟨90JPR853, 90JPR870⟩. Principal component analysis has also been used to demonstrate a correlation between aromaticity and IR parameters obtained by *ab initio* 4-31G MO calculations ⟨93JST(101)97⟩.

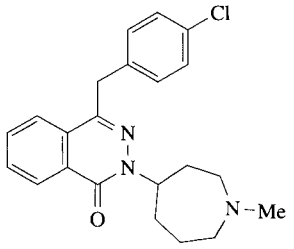
Ab initio calculations have been performed on the 1,4-dihydropyridazine nucleus which indicate considerable enamine character for this system ⟨83JHC855⟩, and MO calculations have been carried out for different geometries of 1,2-dihydropyridazine at the 6-31G* level using structures optimised at the 4-31G level ⟨89JST(60)17⟩.

6.01.3 EXPERIMENTAL STRUCTURAL METHODS

6.01.3.1 X-ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

Data summarized in CHEC-I ⟨84CHEC-I(3B)1⟩ includes electron diffraction, microwave spectroscopy, and x-ray analysis of pyridazine and simple derivatives consistent with a planar structure and significant N—N single bond character. The ring bond lengths are unaffected by alkylation or quaternization, and the x-ray dimensions of pyridazine and 3,6-dichloropyridazine are given.

Further work includes the x-ray analysis of 3,6-pyridazinedicarboxylic acid, which indicates that the bond lengths are similar to those in other nonprotonated pyridazines; the carboxylic acid groups are twisted out of plane (more so than, e.g., in picolinic acid) and the bonds to the pyridazine ring are relatively long (1.512 Å) ⟨87JHC1285⟩. The x-ray crystal structure determination of a phthalazine derivative, the hydrate of the antiallergic antihistamine drug azelastine (**9**), has revealed two distinct conformations of the molecule. The major difference between the conformers lies in the disposition of the chlorobenzyl group, which has a broadly *syn* or *anti* orientation with respect to the phthalazinone 2-substituent ⟨88AP(321)205⟩. X-ray analysis of the nitration product (**10**) of EG-626 (**11**) confirmed the presence of the phthalazinone-2-nitro substituent, and revealed a larger out of plane deformation of the carbonyl group than was predicted by calculation (AM1); the potent inductive effect of the 2-nitro group was confirmed by the comparatively short carbonyl and long N—N bond lengths ⟨92CPB3327⟩.



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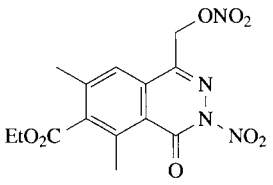

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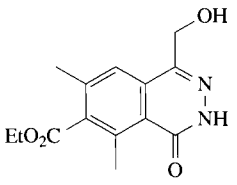

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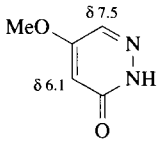
6.01.3.2 NMR Spectroscopy

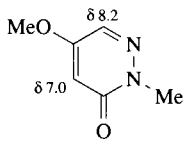
6.01.3.2.1 Proton NMR

The ^{1}H NMR spectral properties of pyridazines were surveyed in CHEC-I ⟨84CHEC-I(3B)1⟩, and chemical shifts and coupling constants tabulated for series of simple (methyl, chloro, and methoxy substituted) pyridazine and pyridazinone derivatives, and for N-oxides. The parent pyridazine in $CDCl_3$ resonates at δ 9.24 (3,6-H) and 7.54 (4,5-H) while the 3-H to 6-H resonances for the

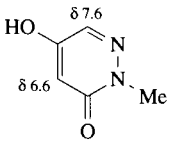
corresponding *N*-oxide are δ 8.54, δ 7.22, δ 7.83, and δ 8.26, respectively. As expected, significant upfield shifts are observed with electron donor groups such as methoxy, so that, for example, the 4,5-protons of 3,6-dimethoxypyridazine resonate at δ 6.72, while for the corresponding dichloro compound there is little change (δ 7.57) compared to the parent heterocycle. The pyridazinone function is also associated with a strong upfield shift of adjacent protons, particularly when it has the potential to exist in the hydroxy form. The effects of hydroxy and pyridazinone functions are illustrated by the shifts observed for 5-hydroxy-3(2*H*)-pyridazinone and its methylated derivatives (**12**)–(**15**) in DMSO solution ⟨89M329⟩. This series of compounds also illustrates the variation seen in coupling constants, and that the 3- or 6-H resonances are always downfield of those of the 4- and 5-H.



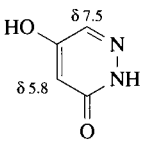
(**12**) J = 1 Hz



(**13**) J = 1.5 Hz



(**14**) J = 2.5 Hz

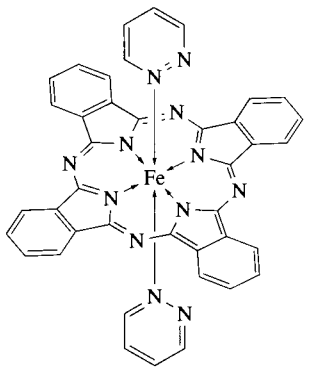


(**15**) J = 1.5 Hz

Simple unionized derivatives of pyridazine can show a range of about 4 ppm for the resonance of protons on ring carbons, ranging from over $\delta = 9$ for the 3- or 6-H of 4- or 5-nitropyridazines to $\delta = 5.47$ for the 4-H of 5-amino-3(2*H*)-pyridazinone ⟨89H(29)1077⟩. Pyridazinone NH protons are acidic and usually resonate well downfield in DMSO solution, typically δ 12–14.

Coupling constants decrease in the order 4,5 > 3,4/5,6 > 3,6 ≈ 3,5/4,6 and have useful diagnostic value, with J values for 4,5 (8–10 Hz) and 3,4/5,6 (4.5–6.5 Hz) coupling clearly differentiated from the smaller *meta* and *para* coupling constants. For the use of coupling constants and chemical shifts in the assignment of isomeric substitution patterns in pyridazine and pyridazinone derivatives see for example ⟨82JHC1285, 83JHC369, 84JHC1389, 91JHC583⟩. Coupling between pyridazine *C*-methyl substituents and adjacent protons is commonly seen and is usually of the order of about 1 Hz. This type of four-bond coupling has been used to demonstrate bond localization in heterocycles, but with 4-methylpyridazine the magnitude of the coupling to H-3 (0.96 Hz) is similar to that to H-5 (0.78 Hz), which indicates that the pyridazine ring is substantially delocalized ⟨92JHC935⟩.

The differential shielding of the *ortho*, *meta*, and *para* protons of the phenyl group in 3(6)-phenylpyridazines is lost when an isopropyl group is introduced into the adjacent 4- or 5-position, due to the effect of the bulky group on ring coplanarity ⟨91JHC583⟩. An interesting example of ring current shielding is provided by the phthalocyaninato(pyridazine)iron complex (**16**), which is soluble in chloroform and whose structure has been confirmed by ^{1}H NMR. Coordination of a single nitrogen from each ligand is evident from the nonequivalence of the pyridazine protons, which all show an upfield shift with respect to the free ligand due to the ring current in the phthalocyanine group. Shielding is most marked for the proton adjacent to the donor atom, which resonates at δ 2.8 instead of δ 9.24 for the free ligand ⟨83AG(E)784⟩.



(**16**)

The complex ^{1}H NMR spectra of cinnolines were summarized in CHEC-I ⟨84CHEC-I(3B)1⟩ and spectral data for a series of simple derivatives were tabulated. In general, the 3- and 5-H resonances are easily identified with the former occurring downfield, usually below δ 8.7, and found at δ 8.7 for the parent. In phthalazine the 1-H/4-H resonances are found at δ 9.44. The ^{1}H NMR spectra of

simple 1(2*H*)-phthalazinones in DMSO solution have been described: in the absence of marked substituent effects they are characterized by a complex of signals around δ 7.7–8.0 for H-5, 6 and 7, with those for H-4 (singlet) and H-8 found further downfield; the acidic NH usually resonates around δ 12.5 ⟨85MRC795⟩.

6.01.3.2.2 ^{13}C NMR

There has been a considerable expansion in the use of ^{13}C NMR in theoretical and structural studies since the publication of CHEC-I in 1985, but in many instances ^{13}C NMR data is recorded for the purposes of characterization without detailed assignment of the chemical shifts. Selected assigned data from the review period for pyridazines and pyridazinones is shown in Table 1. Compared with these aromatic systems, dihydropyridazinones show normal ^{13}C shifts as shown by the methylene (δ 25.9 and 23.8) and carbonyl (δ 166.6) carbons of 6-benzyl-4,5-dihydro-3(2*H*)-pyridazinone in DMSO ⟨89JHC1787⟩. Care should be taken in making comparisons involving potentially tautomeric systems like the pyridazinones; note, for instance, the equivalence of 3,6- and 4,5- ^{13}C resonances of maleic hydrazide. A good range of data has been tabulated for 3,6-disubstituted pyridazine derivatives ⟨91CJC972⟩.

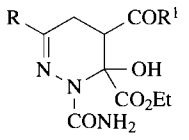
Table 1 Selected ^{13}C spectral data for pyridazines and pyridazinones.

Substituents					*δ*				*Solvent*	*Ref.*
2	*3*	*4*	*5*	*6*	*C-3*	*C-4*	*C-5*	*C-6*		
	H	H	H	H	151.7	126.7			a	10
	Cl	CH	H	Cl	155.7	131.6			a	10
	Br	H	H	Br	147.8	134.3			a	10
	I	H	H	I	126.6	138.1			a	10
	OMe	H	H	OMe	161.6	121.2			a	10
	C≡CPh	H	H	C≡CPh	145.3	129.6			a	10
	COPh	H	H	COPh	158.1	128.6			a	10
	Cl	H	H	I	156.4	129.8	139.8	125.4	a	10
	Cl	H	H	OMe	150.5	131.3	120.5	164.4	a	10
	Cl	H	H	Me	154.2	128.1	130.2	159.7	a	10
	Cl	H	H	CO_2H	158.2	129.5	130.5	151.6	a	10
	Me	H	H	CN	162.5	127.5	130.9	137.3	a	10
	CO_2H	H	H	CO_2H	153.5	129.5			a	1
	Me	CO_2Et	H	H	150.8	128.1	126.1	150.3	a	2
	Ph	NH_2	NO_2	H	154.8	138.0	127.7	143.2	b	3
	Ph	NH_2	CN	H	150.7	144.8	91.5	149.7	b	3
	CH=NR	H	H	H	155.9	123.2	127.4	151.9	a	4
	H	CH=NR	H	H	147.8	134.9	122.9	151.7	a	4
Me	=O	H	H	H	160.7	129.3	131.6	136.1	c	5
Me	=O	H	H	Me	159.9	129.4	133.3	144.1	c	5
Me	=O	H	H	OMe	159.3	132.5	126.4	152.9	c	5
Me	=O	H	H	Cl	159.2	131.6	133.7	137.1	c	5
H	=O	H	H	OH	156.5	130.5	130.5	156.5	a	10
H	=O	Cl	Cl	H	157.0	133.4	136.8	136.7	a	6
H	=O	H	H	Cl	159.7	132.6	134.7	137.4	a	10
H	=O	H	H	Me	160.4	129.5	134.8	144.3	a	10
H	=O	H_2NNH	H	OH	NG	NG	88.5	NG	a	7
Ph	=O	H	H	OH	157.9	134.1	127.5	152.9	a	8
Ph	=O	Cl	Cl	OH	153.9	136.1	130.7	148.5	a	8
H	=O	H	OH	H	162.2	102.5	158.8	132.3	a	9

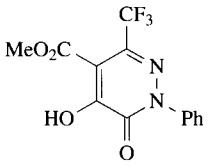
NG, value not given. Solvents: a, d_6-DMSO; b, D_3COD; c, $CDCl_3$. References: 1 ⟨87JHC1285⟩; 2 ⟨91JHC1043⟩; 3 ⟨88JHC831⟩; 4 ⟨89H(29)1399⟩; 5 ⟨91JHC417⟩; 6 ⟨82JHC1447⟩; 7 ⟨84H(22)1801⟩; 8 ⟨89JHC1649⟩; 9 ⟨89M329⟩; 10 ⟨91CJC972⟩.

Among examples of the use of ^{13}C (and ^{1}H) NMR for structural elucidation are the application of one bond C—H coupling constants to differentiate between 4- and 5-substituted derivatives of 3,6-disubstituted pyridazines ⟨91JHC583⟩, determination of the site of *N*-oxidation in 3-substituted pyridazines ⟨83JOC2998⟩, and confirmation of the structure (**17**) as a tetrahydropyridazine and not an open chain semicarbazone ⟨83H(20)551⟩. A detailed ^{13}C NMR study was used to study the conformations of di-, tetra-, and hexahydropyridazines ⟨87T2443⟩, while the site of protonation of

4,5-dichloro-2-methyl-3(2*H*)-pyridazinone was assigned to oxygen on the basis of the large increases in ^{13}C NMR relaxation times for C-3 and C-4 ⟨94H(38)1957⟩.



(17)



(18)

All of the ^{13}C signals from 1(2*H*)-phthalazinone and some 1- and 4-substituted derivatives have been assigned. The parent system C-1 and C-4 resonate (DMSO solution) at 159.7 ppm and 138.3 ppm respectively and C-4 is characterized by a large (186 Hz) one-bond CH coupling ⟨85MRC795⟩.

6.01.3.2.3 ^{15}N and ^{17}O NMR

The ^{15}N chemical shifts of ring nitrogens in heteroaromatic compounds usually fall in the low field half of the spectrum. For benzo(pyridazines) in DMSO the following shifts, which are typical for azo-type groups, have been observed (values relative to a nitromethane external standard): pyridazine (+20), 3-methylpyridazine (N-1, +19; N-2, +15), phthalazine (+10), cinnoline (N-1, +44; N-2, +41), and benzo[*c*]cinnoline (+60). The resonances of the unsymmetrical compounds were assigned on the basis of the two-bond $^{15}N^{1}H$ coupling of about 10–11 Hz observed for N-1 of 3-methylpyridazine and N-2 of cinnoline ⟨84OMR(22)201⟩.

Long range heteronuclear coupling in the ^{15}N NMR spectra of the *N*-phenyl pyridazinone (**18**) in formamide-DMSO was used to determine to which nitrogen the phenyl substituent was attached. The nitrogen closer to the trifluoromethyl group (δ −68 ppm) was observed as a quartet due to coupling to the fluorines, and was unaffected by proton decoupling, while that bearing the phenyl substituent (δ −161 ppm) was observed as a sharp signal in the decoupled spectrum but was broadened in the uncoupled spectrum due to the proximity of the phenyl protons ⟨93JHC1501⟩.

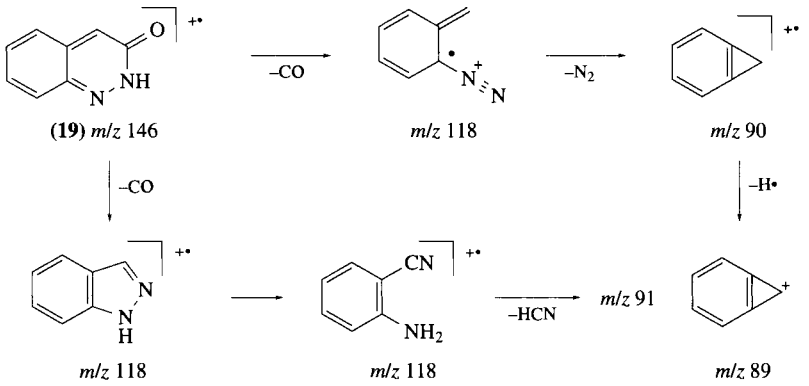
Natural abundance ^{17}O NMR chemical shifts of the diazine *N*-oxides have been measured. Pyridazine *N*-oxide has the greatest downfield shift (412 ppm) indicative of the greater degree of back bonding of the *N*-oxide oxygen to the ring, but the compression effect of the adjacent lone pair may also contribute to the deshielding ⟨85JHC981⟩.

6.01.3.3 Mass Spectrometry

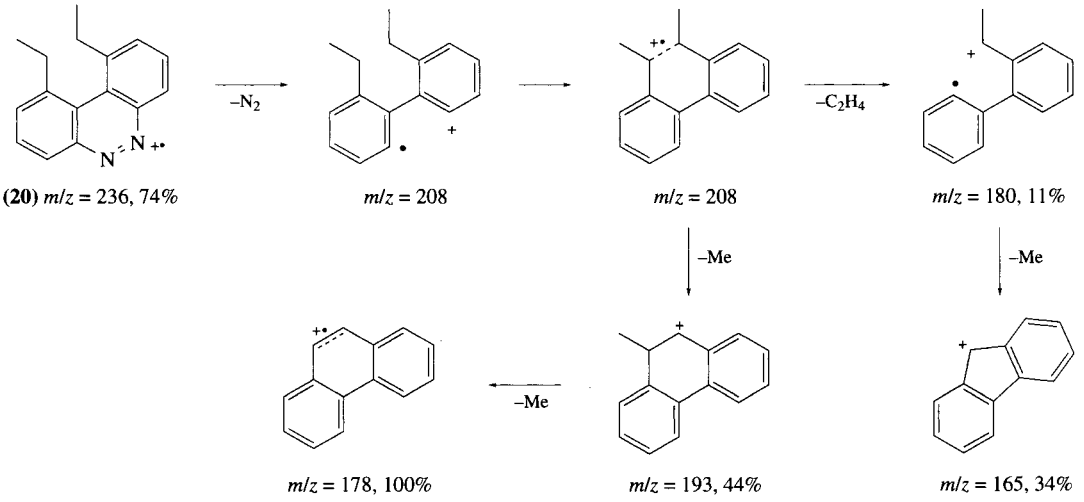
The mass spectral characteristics of simple pyridazines and of phthalazine are summarized in CHEC-I ⟨84CHEC-I(3B)1⟩. Pyridazine undergoes fragmentation to give $C_4H_4^+$ and $C_3H_2N^+$, while loss of HCN is more marked with phthalazine, which can give benzyne by a second loss of HCN. Pyridazinone undergoes loss of CO and then nitrogen. An earlier mass spectral study of styrylpyridazine derivatives has been extended ⟨84JHC435⟩.

High resolution EI mass spectra of 3(2*H*)-pyridazinone, 1(2*H*)-phthalazinone, and 3(2*H*)-cinnolinones have been compared and the mass spectra of 2-substituted 3(2*H*)-cinnolinones discussed. For 3(2*H*)-cinnolinone (**19**) the parent peak is the base peak; studies of metastable peaks with and without deuterium labelling at N-2 indicated the likelihood of two isomeric ions *m/z* 118 formed by loss of CO (Scheme 1). Considering 2-substituted derivatives of 3(2*H*)-cinnolinones, the methyl compound shows some similarity with the parent but shows a significant loss of CHO; for the isopropyl and benzyl analogues there is significant fragmentation of the substituent, which in the case of the 2-(4-methoxybenzyl) compound dominates the spectrum ⟨90JHC209⟩.

The mass spectral fragmentation pattern of 1,10-diethylbenzo[*c*]cinnoline (**20**), (Scheme 2) has been used in an explanation for the difference in flash vacuum pyrolysis of this compound, which gives a complex mixture containing phenanthrene, and its dimethyl analogue which gives 1,8-dimethylbiphenylene as a major product. The base peak of (**20**) is that due to phenanthrene, *m/z* 178 ⟨88JOC4333⟩.



Scheme 1



Scheme 2

6.01.3.4 UV, IR, and Photoelectron Spectroscopy

The apparent loss of the phthalazinone carbonyl band in the IR spectrum of a phthalazinone nitration product (**10**), initially thought to be consistent with the formation of the 1-nitroxy derivative, was shown by model studies to be due to a high frequency shift of the band on nitration at N-2 (from 1644 to 1719 cm^{-1}) causing the band to overlap with that of an ethoxycarbonyl group also present in the molecule ⟨92CPB3327⟩.

The differences between the average ionization potential, calculated using substituent parameters, and the value determined experimentally by photoelectron spectroscopy for the ionization of 1,2-dialkylhexahydropyridazines, have been explained in conformational terms. Large deviations are associated with di-*equatorial* conformations of the alkyl substituents in which the nitrogen lone pairs are orientated at an angle of about 180° to each other ⟨84JOC1891⟩. The UV spectra of methylated hexahydropyridazine radical cations have been described ⟨85JOC4749⟩.

6.01.3.5 ESR Spectroscopy

The results of variable temperature ESR studies on methylated hexahydropyridazine radical cations are consistent with the half chair conformation, with an approximately planar CNNC structural component as the most stable conformation. For *trans*-1,2,3,6-tetramethylhexahydropyridazine, the 3-*axial*, 5-*equatorial* conformation was more stable than the *equatorial*, *equatorial* by about 1 kcal mol^{-1} ⟨85JOC4749⟩.

6.01.4 THERMODYNAMIC ASPECTS

6.01.4.1 General Physical Properties

The physical properties of pyridazine including experimental and calculated dipole moments are summarized in CHEC-I ⟨84CHEC-I(3B)1⟩. Comparison of pyridazine and its benzo derivatives with the corresponding deaza aromatic hydrocarbons (Table 2) reveals the effects of the introduction of the electronegative nitrogen atoms with their ability to form H-bonds to hydroxylic solvents. This is seen most clearly with pyridazine, which is completely miscible with water and alcohols as well as with benzene and ether, and shows a marked increase in boiling point relative to benzene because of the permanent dipole of pyridazine of around 4 D. Hydroxypyridazines show a marked increase in melting point relative to the parent compound, consistent with increased intermolecular association due to H-bonding between the polar amidic keto tautomers. Thus 3(2*H*)-pyridazinone melts at 104–105 °C compared with 42–43 °C for the *N*-methyl derivative (the *O*-methyl derivative is an oil) and 40–42 °C for phenol. Examples of melting points of other keto derivatives are: 4(1*H*)-pyridazinone 245–246 °C, 1(2*H*)-phthalazinone 183–184 °C, and 3(2*H*)-cinnolinone 201–203 °C. Many pyridazinone derivatives are stable solids which melt at very high temperatures (>300 °C) without decomposition, though sublimation near the melting points is often observed, if not commonly reported in the literature.

Table 2 Melting and boiling points of pyridazine, phthalazine, and cinnoline, and of their diaza analogues.

	Pyridazine	*Benzene*	*Phthalazine*	*Naphthalene*	*Cinnoline*
mp (°C)	−8	5	89–92	80–82	40–41
bp (°C)	208	80	315–317	218	114/0.35 mm

Pyridazine and many simple derivatives are amenable to gas chromatography, unless they contain polar functionality (as in pyridazinones with a free NH group). GLC has been used for the analysis of reaction mixtures and product distribution (e.g., ⟨91JHC583⟩). All three systems are amenable to LC with easy detection by UV, and reverse phase HPLC can be very useful for the more polar derivatives for which GC is unsuitable. As expected, simple *O*- or *N*-alkyl derivatives of otherwise polar compounds such as pyridazinones show greatly reduced polarity. Solubility, particularly of large molecules and polar compounds such as some pyridazinone derivatives, can be a limiting factor in column chromatography. The linear correlation between log *P* and the more convenient HPLC-derived capacity factors log k' or log k_w breaks down with H-bond acceptors such as pyridazine, but deviations are minimized by the use of 50% aqueous methanol as the reverse phase HPLC eluent ⟨92CPB925⟩.

6.01.4.2 Ionization

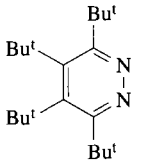
The acidity and basicity, particularly of pyridazine derivatives, has been reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. Pyridazine (pK_a 2.3) is less basic than pyridine (pK_a 5.2) but more basic than the other diazines (pyrimidine 1.3, pyrazine 0.6) perhaps because of repulsion between the adjacent nitrogen lone pairs. For comparison, the pK_as for proton gain by phthalazine and cinnoline are 3.5 and 2.3, respectively. Pyridazin-3(2*H*)-one is about as acidic as phenol with a pK_a of 10.5, while the 4-isomer is more acidic (pK_a 8.7), as are both thione analogues (pK_a 8.3 and 6.5, respectively). The introduction of a second hydroxy or thiol substituent into pyridazinones and thiones causes a further increase in acidity as shown by maleic hydrazide (pK_a 5.7) and its dithio analogue (pK_a 2.1), and for 5-hydroxy-3(2*H*)-pyridazinone, which has a pK_a of 4.81 for proton loss ⟨89M329⟩.

6.01.4.3 Aromaticity

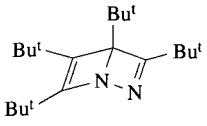
Theoretical treatments of the aromaticity of pyridazine and its derivatives have been considered in Section 6.01.2. Pyridazine is clearly aromatic with the same order of aromatic stabilization as the other diazines and pyridine, despite evidence for bond localization. Pyridazine and its benzo analogues are thus quite stable ring systems, and their electron-deficient character gives increased

stability of amino and hydroxy derivatives towards oxidation. The lack of aromaticity of the heterocyclic ring only really becomes marked with benz[c]cinnoline, and the N=N unit is much more susceptible to reactions of an isolated diazo group such as extrusion and reduction.

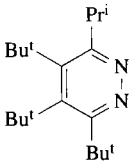
Some interesting observations have been reported concerning sterically hindered pyridazines. Thus, 3,4,5,6-tetra-*t*-butylpyridazine (**21**) is converted into its Dewar isomer (**22**) when irradiated in pentane with UV of wavelength >300 nm. Irradiation of this product at shorter wavelengths, or thermolysis, gives rise to further reaction ⟨91TL57⟩. Steric crowding in 3,4,5-tri-*t*-butyl-6-isopropylpyridazine (**23**) causes deformation of the normally planar pyridazine ring and inhibits ring inversion. The isopropyl methyl groups resonate as two doublets in the ^{1}H NMR, with coalescence only occurring at high temperatures and with an activation barrier to the interconversion of the two forms of 22 kcal mol^{-1}. The addition of a chiral shift reagent confirmed that (**23**) is chiral. X-ray analysis of this hindered compound revealed that it has a twisted-ring conformation with an angle of 24.6° between the planes containing atoms N-1 to C-4 and C-4 to N-1 ⟨91AG(E)1484⟩.



(**21**)



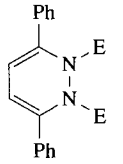
(**22**)



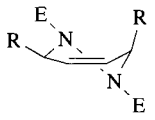
(**23**)

6.01.4.4 Conformation of Nonconjugated Compounds

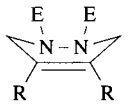
Conformational studies using ^{13}C NMR show that the 1,2-dihydropyridazine (**24**) is planar, while the 1,2,3,6-tetrahydropyridazines (**25**) and (**26**) have a half chair or boat conformation, respectively, as a consequence of the position of ring substituents. The hexahydropyridazine (**27**) probably exists as a mixture of three conformers due either to restricted rotation or inversion of the *N*-substituents with the bromines di-*axial*. In the absence of the 4,5-methyl groups the situation is made more complex by the additional presence of di-*equatorial* bromines ⟨87T2443⟩.



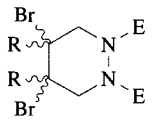
(**24**)
E = CO_2Et



(**25**)
R = Me, Ph; E = CO_2Et



(**26**)
R = H, Me; E = CO_2Et



(**27**)
R = Me; E = CO_2Et

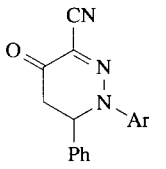
Cyclic voltammetry has been used to study the reversible oxidation of 5,6-diphenyl- and 5,6-dimethyl-5,6-dihydrobenzo[*c*]cinnoline in liquid sulfur dioxide. Both substrates start with an *axial, axial* conformation, but the conformation is changed on formation of the radical cation to *equatorial, equatorial* because of the sp^2 hydridization. This conformational change has a dramatic effect on the redox potential for the formation of the dication, most marked in the case of the diphenyl compound where the second redox potential is lower than that of the first ⟨86AG(E)1021⟩.

6.01.4.5 Tautomerism

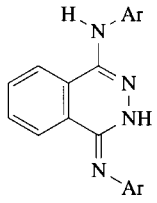
Tautomerism, particularly keto-enol, thione-thiol and amino-imino, was discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. In general, hydroxy substituents at all positions of the heterocyclic ring of pyridazines, phthalazines, and cinnolines exist in the keto form, with the exception (noted in CHEC-I) of the 3- and 5-hydroxy derivatives of pyridazine 1-oxide. In cases where two hydroxy or thiol substituents are present, the normal situation is for only one to be in the keto or thione form. In contrast, amino derivatives usually exist as such.

6.01.4.5.1 Keto–enol tautomerism

1-Aryl-3-cyano-6-phenyl-5,6-dihydro-4(1*H*)-pyridazinones (**28**) exist in the keto form in both the solid and solution phases as shown by IR, ^{1}H, and ^{13}C NMR studies but react via the enol in aldol condensations ⟨86JHC93⟩. X-ray analysis indicates that 5-hydroxy-3(2*H*)-pyridazinone (**15**) exists in the 5-hydroxy-3-oxo form ⟨89M329⟩. An NMR study failed to reveal any evidence of the lactim tautomer in a series of 1(2*H*)-phthalazinones ⟨85MRC795⟩.



(**28**)



(**29**)

6.01.4.5.2 Amino–imino tautomerism

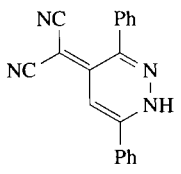
Despite some early claims to the contrary, it was concluded in CHEC-I ⟨84CHEC-I(3B)1⟩ that most aminopyridazines and cinnolines exist in the amino form. This generalization also extends to aminophthalazines, but 1,4-di(pyridylamino)phthalazines (**29**) are an exception and the presence of the imino tautomers is clearly shown by the unsymmetrical proton NMR spectrum with two distinct NH resonances, and a marked difference in the shifts of the *peri* benzo protons ⟨83JHC345⟩.

6.01.4.5.3 Double-bond tautomers in nonconjugated systems

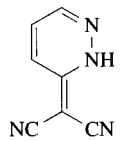
NMR studies have shown that the 1,4-dihydropyridazine is the dominant tautomer in 3,6-di- and 3,4,6-triphenyl-, and 4,4-dimethyl-3,6-diphenyldihydropyridazines; the 4,5-dihydro form is a minor tautomer ⟨83JHC855⟩. 3,6-Diaryl-4,5-dimethyldihydropyridazines exist in the 4,5-dihydro tautomeric form as indicated by the symmetrical ^{1}H NMR spectrum, while 1-substituted analogues have the 1,4-dihydro conformation. In contrast, it is claimed that 3,6-dimethyl-1-(4-sulfamoylphenyl)-dihydropyridazines exist in the 1,2-dihydro form ⟨87JHC1745⟩.

6.01.4.5.4 Methyl–methylene tautomerism

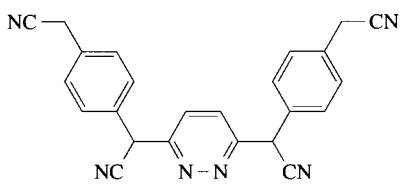
While there are reports of arylidene methylene tautomers of 3-substituted derivatives of 5-arylmethyl-6-methylpyridazines ⟨85JHC1615, 88CPB1558, 88CPB5000⟩, which include a proof of structure based on nOe studies ⟨90CPB3009⟩, these compounds are most likely to exist as their aromatic 5-arylmethylpyridazine tautomers. 6-Aryl-5-methyl-3(2*H*)-pyridazinones, obtained as minor products from the cyclization of 3-aroyl-3-butenoic acids with hydrazine, exist in the methyl, not methylene, form ⟨90JHC205⟩. However, there are clear examples of methylene tautomers. Spectroscopic studies (IR, ^{1}H and ^{13}C NMR) have shown that 4-(dicyanomethylene)-3,6-diphenyl-1*H*-pyridazine (**30**) exists as the 1*H*-4-ylidene tautomer ⟨86JHC557⟩. The 3-(dicyanomethylene)pyridazine (**31**) also exists in the ylidene form, but in contrast 4,4′-[(3,6-pyridazinediyl)bis(cyanomethyl)]bis(benzeneacetonitrile) (**32**) is a *meso dl* mixture of the fully aromatic tautomer, rather than a bis- or mono-ylidene derivative ⟨91JOC5318⟩.



(**30**)



(**31**)



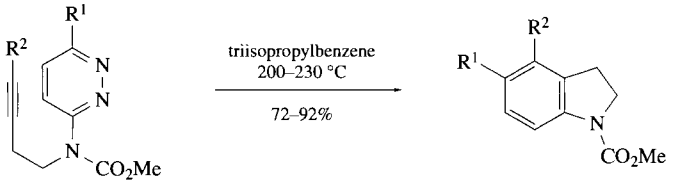
(**32**)

6.01.5 REACTIVITY OF FULLY CONJUGATED RINGS

6.01.5.1 Intramolecular Thermal and Photochemical Reactions

6.01.5.1.1 Intramolecular thermal reactions

Since the publication of CHEC-I in 1984, in which the thermal rearrangements of perfluoropyridazines, azidopyridazine *N*-oxides, and a 4-diazo-5,6-dioxotetrahydropyridazine were reviewed ⟨84CHEC-I(3B)1⟩, significant developments of intramolecular thermal reactions have occurred, particularly from the view of the design and application of intramolecular Diels–Alder reactions. Thus, intramolecular cyclization of 3-(*N*-(alkynylethyl)-*N*-methoxycarbonylamino)pyridazines (**33**) gives indolines (**34**, Equation (1)) which, when $R^1 = Cl$ and $R^2 = CH_2OTBDMS$, have been used for the synthesis of CC-1065 skeletal fragments ⟨84JOC2240⟩; this chemistry has been developed for the total synthesis of the related PDE II methyl ester ⟨86JOC3250⟩. Triisopropylbenzene is the solvent of choice for these cyclization reactions, the success of which is due to entropic factors as similar intermolecular reactions are unsuccessful in the absence of activation of the diene and dienophile. Terminal substitution of the alkyne reduces the rate of reaction, which is generally unsuccessful for the preparation of larger rings and oxygen analogues, including fused furans.

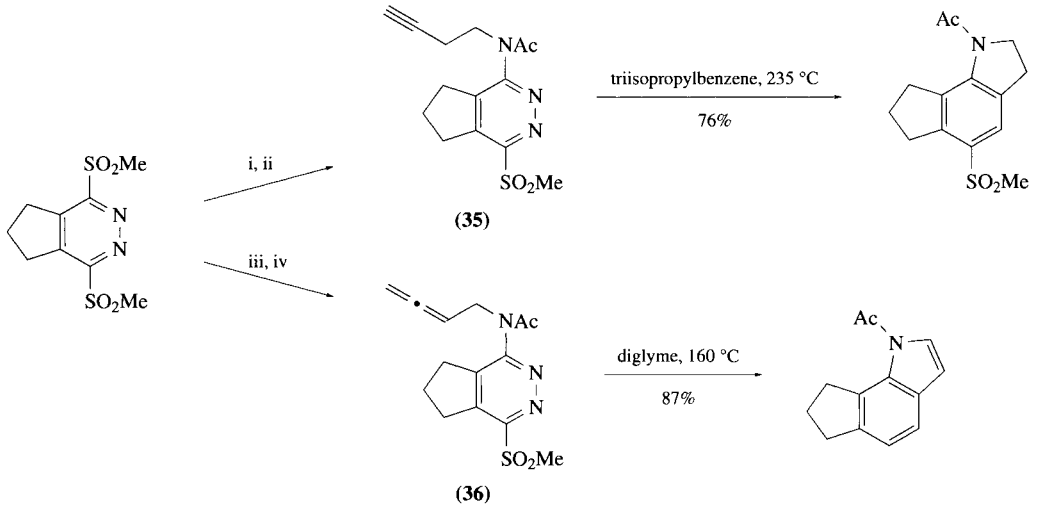


(1)

(**33**) R^1 = H, Cl; R^2 = H, Me, CH_2O-TBDMS (**34**)

In a development of this approach, the *N*-acetyl derivatives of 3-(3-butynylamino or 2,3-butadienylamino)-4-and/or 5-substituted-6-methylsulfonylpyridazines, the preparation of which involves a key cycloaddition step, undergo intramolecular Diels–Alder reactions (e.g., Scheme 3). The acetylenic substrates (**35**) give *N*-acetyl-5-methylsulfonylindolines, while *N*-acetylindoles are obtained from allenes (**36**) because the methylsulfonyl group is eliminated in an aromatization step. The reactivity of allenes was noticeably higher than that of acetylenes, probably due to the greater inherent dienophilicity of the former assisted by entropic factors. This potentially useful synthesis is particularly attractive because the key functionality, which controls whether indolines or indoles are produced, is introduced near the end of the synthesis ⟨88JOC1415⟩.

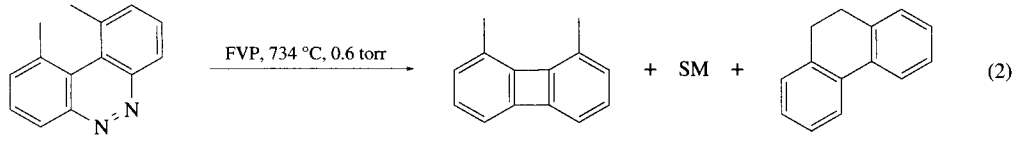
Flash vacuum pyrolysis of (benzo)pyridazine derivatives has been investigated. Thus, 1,10-



i, 3-butynylamine; ii, Ac_2O, NaOAc; iii, 2,3-butadienylamine; iv, Ac_2O, NaOAc

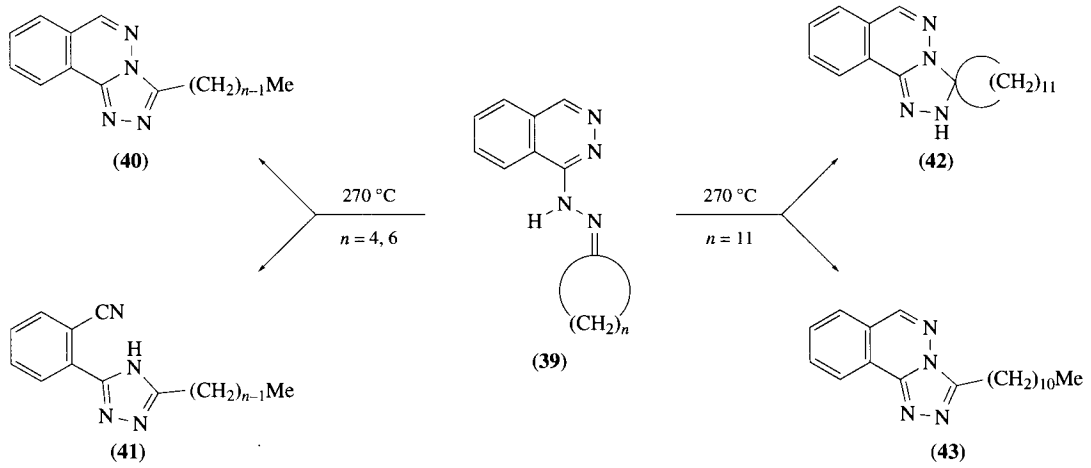
Scheme 3

dimethylbenzo[*c*]cinnoline (**37**) gave 1,8-dimethylbiphenylene (**38**) as the major product (Equation (2)). This is a practical route to the dimethylbiphenylene (**38**), which can be obtained pure in yields of 56% provided the scale does not exceed about 5 grams. Application of similar conditions to the 1,10-diethyl analogue resulted in reasonable mass balance, but a complex mixture was produced and the mass spectral breakdown pattern (Section 6.01.3.3) was used to explain this result ⟨88JOC4333⟩. The FVP of pyridazine *N*-oxide and of methyl and phenyl derivatives required temperatures of 650–750 °C for significant reaction, and some products were observed that resulted from N—N bond cleavage ⟨87H(26)2677⟩.



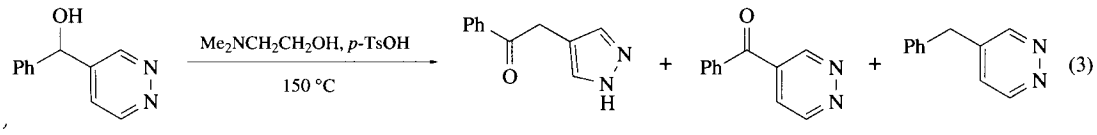
(37) (38) major minor (2)

Pyrolysis of cyclic hydrazones from 1-hydrazinophthalazine has been investigated and the work of Druey and Ringier from the early 1950s has been corrected and extended (Scheme 4). The 5- and 7-membered cyclic hydrazones (**39**) undergo intramolecular ring closure followed by ring opening reactions to give the alkyltriazolo[3,4-*a*]phthalazines (**40**) and 1,2,4-triazolylbenzonitriles (**41**) as the major isolated products, while the 12-membered analogue gave the spirotriazolo[3,4-*a*]phthalazine (**42**) and undecyltriazolo[3,4-*a*]phthalazine (**43**) but the product of phthalazine ring opening, the benzonitrile, was not isolated. Ionic mechanisms were proposed proceeding via the phthalazone hydrazone tautomer, but radical processes may be involved under the vigorous reaction conditions ⟨95JOC1908⟩.



Scheme 4

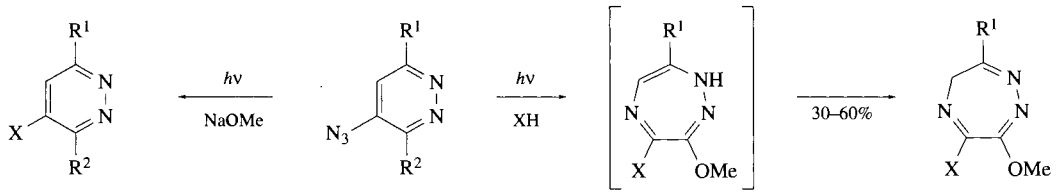
In an attempt at etherification of aryl(4-pyridazinyl)methanols with dimethylaminoethanol and *p*-toluenesulfonic acid at 150 °C the substrate (**44**) underwent an unusual pyridazine to pyrazole ring contraction, in addition to disproportionation reactions (Equation (3)). The driving force for the ring contraction reaction is likely to be extended conjugation of the products, as their enols, under the strongly acid conditions of the reaction. The reaction does not occur with 1-(4-pyridazinyl)ethanol ⟨84JHC1727⟩. This rearrangement has been investigated by the use of the 4,5-^{13}C-pyridazine substrate, which showed that the pyridazine-4,5-C atoms become the pyrazole-3-C and the methylene group. The product was also shown not to be the isomeric benzyl pyrazolyl ketone; a mechanism has been proposed ⟨89JHC1009⟩.



(44) (3)

6.01.5.1.2 Intramolecular photochemical reactions

Photochemical reactions of pyridazines, phthalazines and cinnolines were extensively reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩, with many reactions proceeding via ring contraction. Since 1985, the photolysis of 4-azidopyridazines to give significant yields of ring expansion products, unsaturated 1,2,5-triazepines, has been demonstrated. Thus, 3-methoxy derivatives (**45**) react, via formation of a nitrene and ring opening of an intermediate fused azirine with methoxide or diethylamine, to give 4-methoxy (or dimethylamino)-1,2,5-triazepines (**46**), (Scheme 5); the intermediate N1—H tautomers are unstable and undergo base-catalysed tautomerization. In the absence of the 3-methoxy substituent, 4-azidopyridazines do not undergo ring expansion, but some reduction of the azido group or displacement by methoxide occurs ⟨88CPB4240, 90CPB2992⟩.



R^2 = H, Me
X = OMe or NH_2

(**45**)
R^1 = H, Me, OMe

R^2 = OMe
X = OMe or NEt_2

(**46**)

Scheme 5

6.01.5.2 Electrophilic Attack at Nitrogen

6.01.5.2.1 Introduction

The (benzo)pyridazines are inherently electron deficient ring systems, more so than pyridine, and while there are many examples of electrophilic reaction of (benzo)pyridazines on nitrogen, reactions such as protonation and *N*-oxidation occur less readily than with pyridine.

6.01.5.2.2 Proton acids

Protonation of (benzo)pyridazines has been mentioned in Section 6.01.4.2 and was reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. Pyridazine (pK_a 2.3) is more basic than the other diazines due to reduced lone pair : lone pair repulsion on formation of the cation. There is no equivalent to the benzene-like 3-position of pyridine, and in the absence of marked steric effects all mesomeric electron donors will show a strong interaction with an *ortho*, or more especially a *para* nitrogen, and for example, 3- and 4-aminopyridazines have pK_as of 5.19 and 6.69, respectively. The site of protonation of substituted pyridazines is usually only adjacent to a 3-substituent when that is a powerful +M group, as inductive and steric factors normally favour protonation at the more remote nitrogen. For 4-substituents protonation is *para* to +M and *meta* to −M substituents. With 3,6-disubstituted pyridazines, protonation is directed α to the most activating, least bulky group. However, with pyridazinones protonation is more likely to be on the amide oxygen than on the ring nitrogen as shown by theoretical and experimental studies for 4,5-dichloro-3(2*H*)-pyridazinone ⟨94H(38)1957⟩. In contrast to other (benzo)pyridazines, 1*H*-benzo[*de*]cinnoline contains a pyrrole-like nitrogen and, as a consequence of electron donation from N-1, undergoes protonation at C-7 as shown by ^1H NMR ⟨75JCS(P1)419⟩.

6.01.5.2.3 Metals

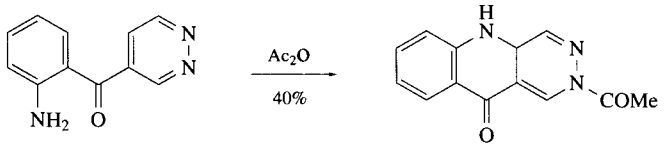
The (benzo)pyridazines are able to form complexes with a variety of metal ions, and examples of complexes with iron (Section 6.01.3.2.1) and with silver and ruthenium (Section 6.01.12.6) are given.

6.01.5.2.4 Alkyl and aryl halides

The quaternization of (benzo)pyridazines by alkyl halides (these systems are not readily susceptible to arylation) was reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. Monoquaternization of pyridazines occurs more readily than other diazines but less readily than pyridine, reflecting the intermediate basicity/nucleophilicity of pyridazine. Diquaternization of pyridazine can only be achieved with oxonium salts, particularly $Me_3O^+BF_4^-$. As with protonation and *N*-oxidation, mixtures of products are often obtained on quaternization of unsymmetrical pyridazines and have been the subject of theoretical studies. A number of 2-(ribofuranosyl)-3(2*H*)-pyridazinones have been prepared by stannic chloride catalyzed alkylation of 3-(trimethylsilyloxy)pyridazines with protected 1-*O*-acetylribofuranose ⟨83JHC369⟩. The quaternization behavior of phthalazines is similar to that of pyridazines, but with cinnolines alkylation usually occurs at N-2, unless there is a particularly bulky substituent at C-3.

6.01.5.2.5 Acyl halides and related compounds

This topic was not specifically addressed in CHEC-I. As with pyridine, (benzo)pyridazines will react with acyl halides and the like, but to give reactive species generally only used as intermediates. Thus, acylation of pyridazine and 3-methylpyridazine with trichloroethyl chloroformate gives 1-trichloroethoxycarbonyl derivatives which are susceptible to the addition of carbon nucleophiles at C-4 ⟨87CPB2243, 90CPB45⟩, while *N*-acylated phthalazines are susceptible to nucleophilic attack at the adjacent carbon ⟨93JHC1663⟩ and intramolecular trapping of these intermediates has been utilized. Thus, acetylation of 4-(2-aminobenzoyl)pyridazine (**47**) occurs on N-2 with intramolecular addition of the amino group to the acylpyridazinium salt at C-5 (Equation (4)) to give a pyridazino[4,5-*b*]quinolinone derivative (**48**) ⟨92AP(325)119⟩. Further examples are considered with Reissert reactions (Section 6.01.5.4.5.iii).



(47) (48) (4)

6.01.5.2.6 Peracids

The *N*-oxidation of (benzo)pyridazine derivatives was extensively reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. The ease and position of *N*-oxidation is affected by substituents in a similar way to that of protonation, and mixtures of *N*-oxides are often obtained. However, reasonable selectivity is observed where substituents have marked steric (when adjacent to nitrogen) or electronic differences. The formation of the di-*N*-oxides can be achieved but it requires forcing conditions and yields are not high.

6.01.5.2.7 Aminating agents

The *N*-amination of pyridazines with hydroxylamine-*O*-sulfonic acid and its aryl derivatives was summarized in CHEC-I ⟨84CHEC-I(3B)1⟩. For 3-substituted pyridazines *N*-amination occurs at N-2 in the case of methyl and amino, but at N-1 in 3-methoxy derivatives.

6.01.5.3 Electrophilic Attack at Carbon

Electrophilic attack at carbon was well covered in CHEC-I ⟨84CHEC-I(3B)1⟩. The electron deficient (benzo)pyridazine systems are not normally susceptible to electrophilic attack at ring carbons of the heterocyclic ring unless one or preferably two activating substituents (e.g., amino, hydroxy/keto) or an *N*-oxide function are present, and are quite stable under oxidizing conditions. The benzo rings

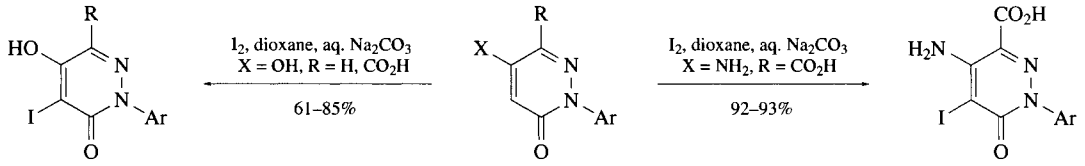
of fused pyridazine derivatives are of course susceptible to electrophilic attack, and nitration, for example, occurs readily but often to give mixtures. Examples have been given of nitration, halogenation, and Mannich reactions, while electrophilic hydrogen exchange of aminopyridazines and pyridazinones have also been discussed. Some additional examples of electrophilic reactions are given below.

In contrast to other (benzo)pyridazines, 1*H*-benzo[*de*]cinnolines show a marked susceptibility to electrophilic attack due to the pyrrole-like N-1 and, for example, 6-methoxy derivatives undergo formylation at C-7 and C-9 with Vilsmeier's reagent ⟨81ZOR2444⟩ and condenses with aldehydes at C-9 ⟨82ZOR415⟩.

While chlorination of pyridazines is not very common, the 4-dicyanomethylidene-1*H*-pyridazine system (**30**) with sulfuryl chloride gives the 5-chloro derivative (**49**) in quantitative yield (Equation (5)); the reactivity of this system is presumably due to the enamine nature of the substrate ⟨86JHC557⟩.

(30) (49) (5)

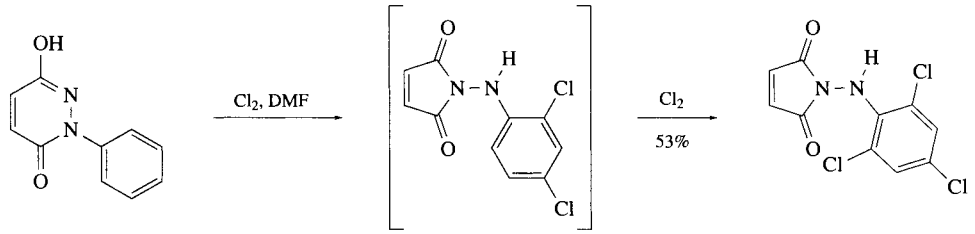
2-Substituted-5-hydroxy-3(2*H*)-pyridazinones, their 6-carboxy analogues, and 2-substituted-5-amino-6-carboxy-3(2*H*)-pyridazinones that are soluble in sodium carbonate solution are readily mono-iodinated (Scheme 6) in the 4-position in high yields ⟨90JHC471⟩.



Ar = 4-ClC_6H_4, 3-$CF_3C_6H_4$

Scheme 6

Direct chlorination of 2-phenyl-6-hydroxy-3(2*H*)-pyridazinone (**50**) in polar solvents (DMF, acetic acid) resulted in chlorination of the phenyl ring and rearrangement of the pyridazinone to give the trichlorophenylaminopyrrole-2,5-dione (**51**) as the major product; the dichlorophenyl-aminopyrrole-2,5-dione (**52**, Scheme 7) was isolated as an intermediate. It is proposed that the pyridazinone is less stable after dichlorination of the phenyl ring and rearranges to the *N*-amino-maleimide (**52**), but the reasons for this are unclear ⟨89JHC1649⟩.

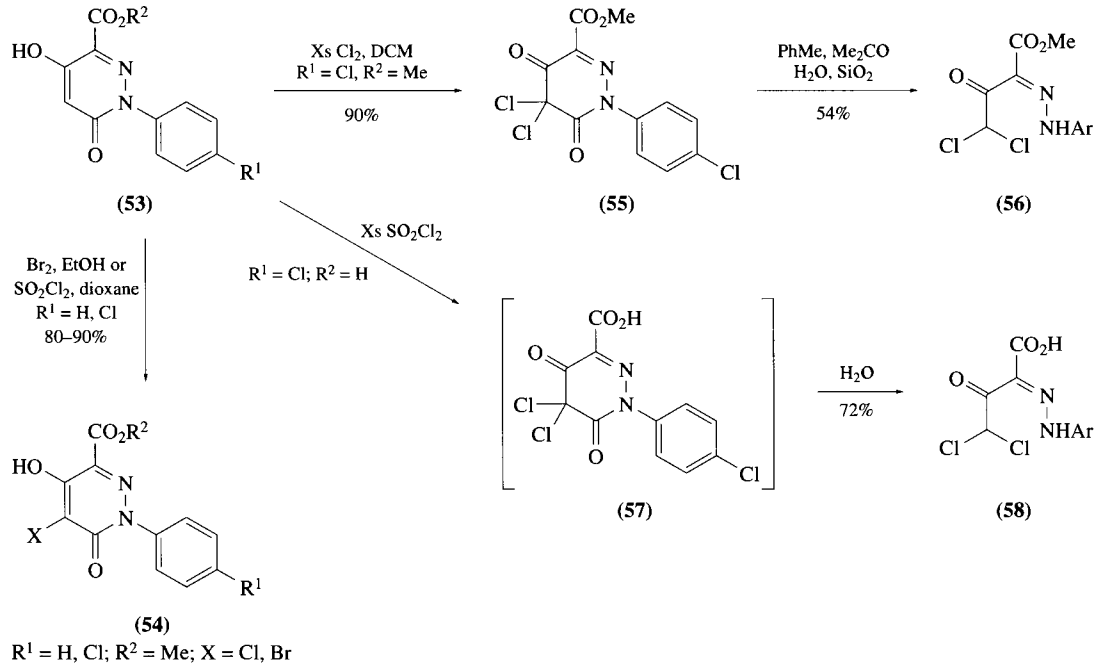


(50) (52) (51)

Scheme 7

Halogenation of 5-hydroxy-3(2*H*)-pyridazinones can give stable 4,4-dihalo derivatives but the 6-methoxycarbonyl analogues (**53**) are less reactive and the dihalo products less stable due to the electron withdrawing nature of the ester group (Scheme 8). Thus, the mono halo compounds (**54**) can be made in 80–90% yields, but only with an excess of chlorine in dichloromethane could a dihalo compound (**55**) be made cleanly; 4,4-dibromination was not observed under any conditions, and reaction with an excess of sulfuryl chloride gave mixtures due to incomplete reaction. In the absence of a 4-chloro substituent in the 2-phenyl ring, attempts at dihalogenation gave more complex

mixtures caused by competing halogenation of the pyridazine and phenyl rings. Attempted column purification of the 4,4-dichloro compound (**55**) resulted in hydrolytic ring opening and *N*-decarboxylation to give the hydrazone (**56**), a reaction which could not be achieved by solution chemistry in the absence of silica gel. Interestingly, the corresponding 4,4-dichloro 6-carboxylic acid (**57**) could not be isolated, but gave the hydrazone (**58**) on aqueous work up ⟨90M565⟩.



Scheme 8

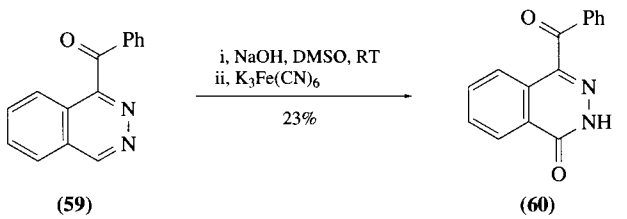
6.01.5.4 Nucleophilic Attack at Carbon

6.01.5.4.1 Introduction

The heterocyclic rings of (benzo)pyridazine systems are electron deficient and thus susceptible to attack by nucleophiles. However, in the absence of a suitable leaving group this is usually unfavoured due to loss of aromaticity. For example, covalent hydration is not observed, though pseudobase formation can occur with subsequent disproportionation to give, for example, phthalazinones and dihydrophthalazines.

6.01.5.4.2 Hydroxide

Brief treatment of 1-benzoylphthalazine (**59**) with sodium hydroxide in dimethylsulfoxide (Equation (6)) resulted in hydroxylation of the phthalazine ring to give, after oxidation, 4-benzoyl-1(2*H*)-phthalazinone (**60**) ⟨85CPB4193⟩.

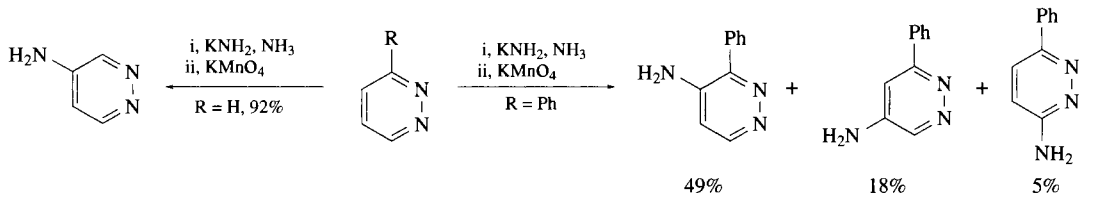


(6)

6.01.5.4.3 Amines and amide ions

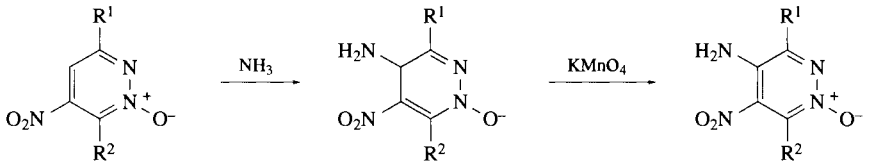
The only reaction of this type mentioned in CHEC-I is the formation of 3-*N*-benzoylanilinopyridazine from pyridazine *N*-oxide and *N*-phenylbenzonitrilium ion ⟨84CHEC-I(3B)1⟩.

However, significant chemistry, particularly the application of ammonia/amide reactions has been reported since 1984. Thus, while pyridazine is resistant to the Chichibabin reaction, a variety of pyridazines form σ-adducts in ammonia/potassium amide which can be oxidized by the addition of potassium permanganate to yield 4(5)-aminopyridazines, often in excellent yields. For example, dissolution of pyridazine in ammonia/potassium amide leads to the almost complete formation of the anionic adduct, which can be oxidized to give 4-aminopyridazine in excellent yield, while reaction of 3-phenylpyridazine (Scheme (9)) gives a mixture of the three isomeric amination products in which the 4- and 5-amino isomers predominate ⟨82JHC1285⟩.



Scheme 9

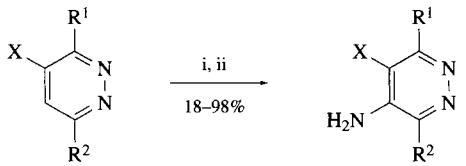
This amination reaction has been applied to methoxypyridazines, and 3-methoxypyridazine gave the 4-isomer selectively, along with a bipyridazine byproduct. The more electron deficient nitropyridazines and pyridazine *N*-oxides are sufficiently reactive to form the initial adducts in the absence of added amide ion and 5-nitropyridazine 1-oxides give 4-amino derivatives (Scheme 10). The formation of the intermediate σ-adducts was demonstrated by ^{1}H NMR ⟨86JHC621⟩.



R^1 = H, Cl, OMe; R^2 = H, OMe

Scheme 10

4-Nitro-, 3-aryl-5-nitro- and 3,6-diaryl-4-nitropyridazines react almost instantly in liquid ammonia to give the 4(or 5)-σ-adducts while 5-cyano-3-aryl- and 4-cyano-3,6-diarylpyridazines require the addition of amide ion for the initial amination reaction (Equation (7)). Both types of adduct can be oxidized to give the 4(or 5)-aminopyridazine derivatives and NMR studies with the nitro and cyano derivatives show conclusively that amination occurs at the 4- or 5-positions ⟨88JHC831⟩.



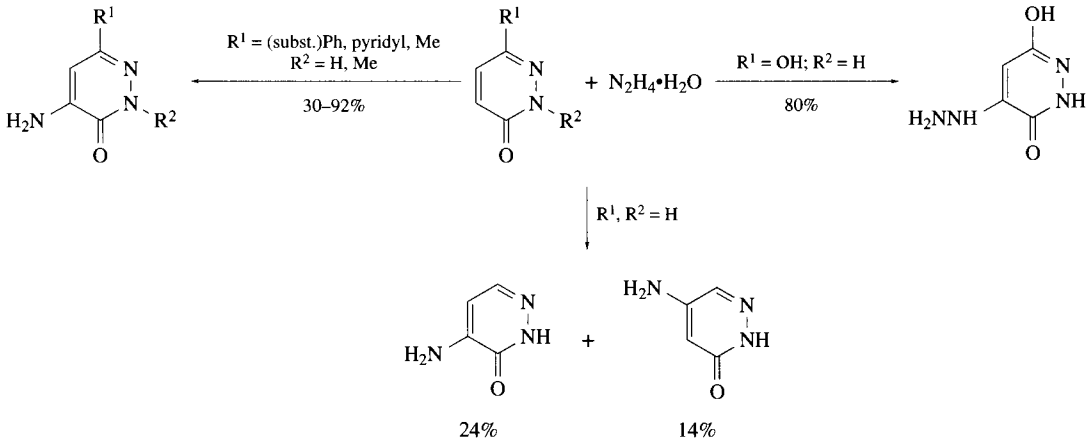
(7)

i, NH_3; ii, $KMnO_4$ (X = NO_2); i, NH_3/KNH_2; ii, $KMnO_4$ (X = CN)

$R^1 = R^2$ = H, 2-Py; R^1 = H, R^2 = Ph; X = CN, NO_2

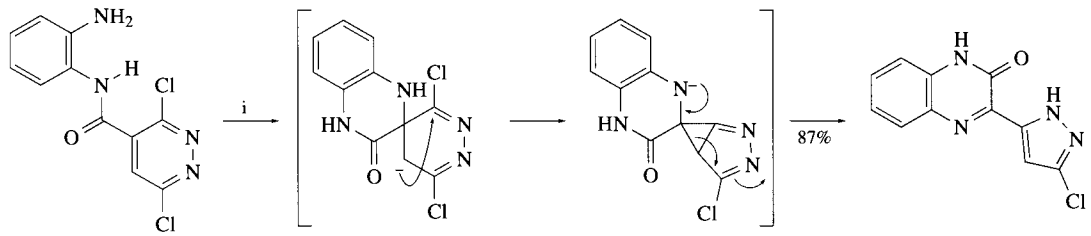
Direct amination of 3(2*H*)-pyridazinones occurs when they are heated with hydrazine hydrate and this is a convenient route to many 4-amino-6-substituted-3(2*H*)-pyridazinones (Scheme 11). The reaction generally gives high yields and amination is regiospecific when the 6-position is occupied by an aromatic or heteroaromatic ring, but the parent 3(2*H*)-pyridazinone gives a mixture of the 4- and 5-amino-3(2*H*)-pyridazinones. The reaction tolerates *N*-methyl substitution of the pyridazinone, but is sensitive to steric factors: the presence of a 5-substituent causes a marked reduction in reaction rate, and amination does not occur with 4-phenyl-3(2*H*)-pyridazinone. With maleic hydrazide 4-hydrazination occurs, possibly by displacement of an intermediate amino compound or by oxidation of an intermediate 4,5-dihydro-4-hydrazino adduct; both 4-hydrazino- and

4,5-dihydro-4-hydrazino-3(2*H*)-pyridazinones have been identified as byproducts in the reactions of 6-substituted-3(2*H*)-pyridazinones ⟨84H(22)1801, 89H(29)1077⟩. The direct amination has been observed before ⟨72JCS(P1)1483⟩ but occurred with 6-hydrazino- and 6-methoxy-3(2*H*)-pyridazinones formed *in situ* from 3,6-dimethoxypyridazine, and the site of amination was incorrectly assigned ⟨74JCS(P1)696⟩. This work has been corrected ⟨93H(35)1313⟩.



Scheme 11

Reaction of *N*-(2-aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide (**61**) with base did not give the expected pyridazino[3,4-*b*][1,5]benzodiazepine derivative but instead gave 3-(5-chloro-3-pyrazolyl)-2(1*H*)-quinazolinone (**62**) (Scheme 12) via reaction at C-4 rather than C-3 ⟨94H(38)2081⟩.



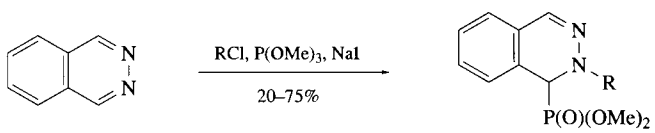
(61) **(62)**

i, NaH, DMF, 100 °C

Scheme 12

6.01.5.4.4 Phosphorus

Dimethylphosphoryl Reissert type adducts are prepared by the reaction of phthalazine with acid and sulfonyl chlorides in the presence of trimethyl phosphite and sodium iodide (Equation (8)). Phthalazine is not very reactive under these conditions, especially with the acid chlorides; the structure of the methylsulfonyl derivative was confirmed by x-ray analysis ⟨90CPB1504⟩.



(8)

R = SO_2Me, SO_2Ph, COMe, COPh, $CONPh_2$

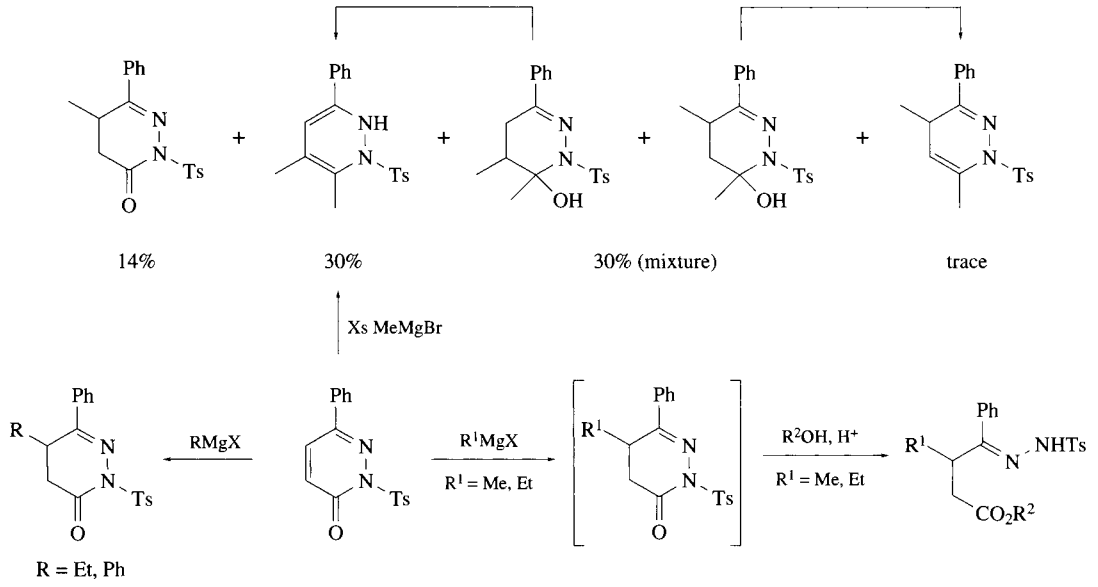
6.01.5.4.5 Carbon nucleophiles

(i) Organometallic compounds

The reactions of Grignard and organolithium reagents, especially with pyridazine derivatives, was discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. Pyridazine derivatives tend to undergo addition to C-

4(5) to give dihydro products while some lithium reagents may add to C-3 (this may depend on the solvent). Some of these reactions are complicated by the hydrolytic and/or oxidative stability of the initial adducts. With 3(2*H*)-pyridazinones, addition of PhLi or PhMgBr appears to occur at the 6-, 3-, and 5-positions to give di- or tetrahydro adducts, while 1(2*H*)-phthalazinones give addition at the 4-position followed by addition at the carbonyl group and loss of water. 1-Substituted phthalazine *N*-oxides undergo addition at C-4. The reaction of cinnoline *N*-oxides with phenylmagnesium bromide gave complex mixtures. Some of the examples published since 1984 are discussed below, but the addition of organometallic reagents to other pyridazines, particularly pyridazinones substituted by an appropriate leaving group (CN, Cl) is discussed in Sections 6.01.7.5 and 6.01.7.15.5.

Reactions of Grignard reagents with 6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone, in which the toluenesulfonyl group was introduced to increase reactivity of the carbonyl group, is complex (Scheme 13). With an excess of methylmagnesium bromide, addition appears to be to the 4,5-bond with secondary addition to the carbonyl group; the carbinol products were isolated in about 30% yield and were readily dehydrated to the dihydropyridazines. With ethyl or phenyl Grignard reagents the only isolable products were the 5-substituted-6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones. With less of an excess of alkyl Grignard reagent, and an acidic alcoholic quench, the intermediate dihydropyridazinones were ring opened by attack of the alcohol at the carbonyl group ⟨85JHC927⟩. Addition of phenyllithium to benzo[*c*]cinnoline occurs to the 5,6-azo bond to give 5-phenyl-5,6-dihydrobenzo[*c*]cinnoline ⟨85AG(E)596⟩.



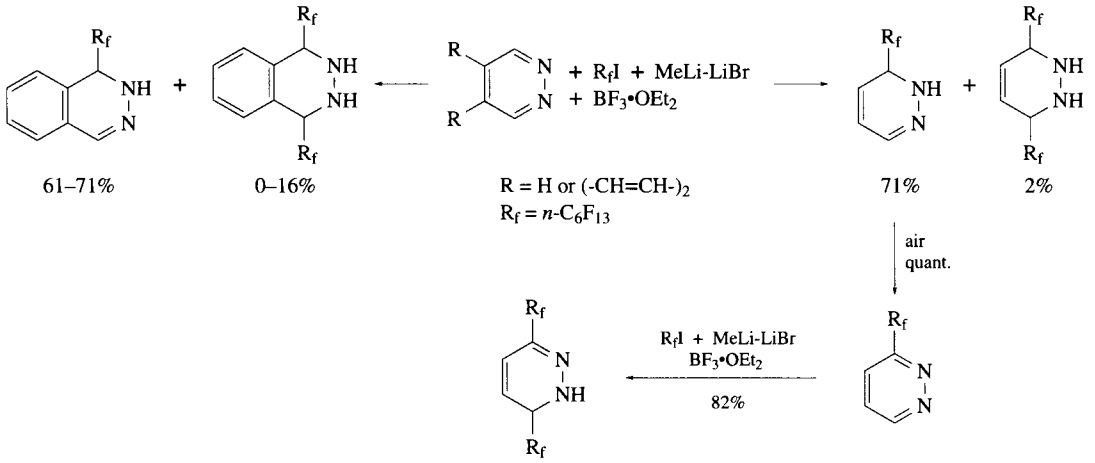
Scheme 13

Nucleophilic addition of perfluoroalkyllithium reagents, generated *in situ* from the perfluoroalkyl iodides and methyllithium–lithium bromide, is promoted by boron trifluoride complexation at nitrogen. Addition is exclusively *ortho* to nitrogen and disubstitution is only a minor side reaction amounting to 16% in the presence of excess of reagent with phthalazine (Scheme 14). The dihydropyridazine adducts are quantitatively oxidized in air and the resultant 3-perfluoroalkylpyridazine can then react with further perfluoroalkyllithium ⟨91T6231⟩.

(ii) Activated methyl and methylene carbanions

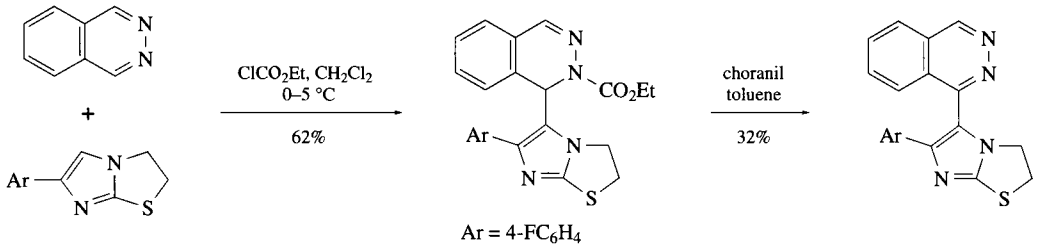
Among examples of reactions of (benzo)pyridazines with activated CH reagents reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩ are the methylation and ethylation of 3(2*H*)-pyridazinones, substituted with, for example, 4-carboxy, by the corresponding nitroalkanes in DMSO, and the application of the Reissert reaction to phthalazines. More recent examples, including those utilising an acylated intermediate similar to the Reissert reaction, are discussed in Section 6.01.5.4.5.iii.

Nucleophilic addition of 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazole to phthalazine can be achieved via an *N*-acyl salt of phthalazine (Scheme 15). This reaction is not restricted to the 4-fluorophenyl



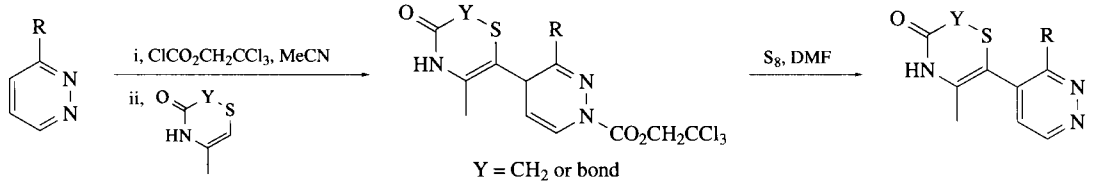
Scheme 14

analogue shown, but is claimed to be successful for a range of 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles and the 1,2-dihydro adducts can be oxidized to 1-substituted phthalazines by treatment with chloranil ⟨93JHC1663⟩.



Scheme 15

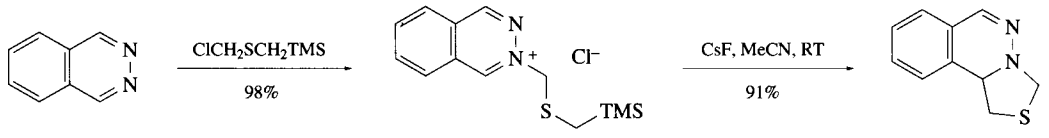
A similar approach with pyridazine and 3-methylpyridazine, but using 1-trichloroethoxycarbonyl derivatives, allows the nucleophilic addition of thiazolones and 1,4-thiazinones (Scheme 16). The initial 1,4-dihydro adducts are oxidised and deacylated by treatment with sulfur in boiling DMF ⟨87CPB2243, 90CPB45⟩.



Scheme 16

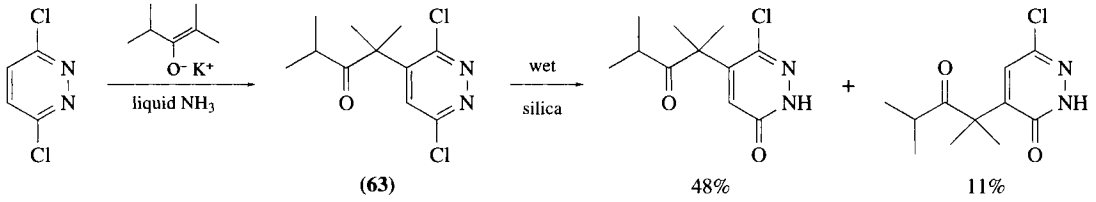
Following the almost quantitative quaternization of phthalazine with chloromethyl trimethylsilylmethyl sulfide, fluoride mediated desilylation liberates a carbanion which is trapped by intramolecular reaction (Scheme 17) to give a thiazolophthalazine derivative ⟨87JOC4423⟩.

3,6-Dichloropyridazine reacts with the potassium enolate of diisopropyl ketone by nucleophilic



Scheme 17

non-radical addition at C-4 to give the labile dihydro adduct (**63**), which was hydrolyzed in the presence of wet silica gel to two isomeric dihydropyridazinones (Scheme 18). The reactivity of 3,6-dichloropyridazine contrasts with that of other dihalo π-deficient nitrogen heterocycles which, under similar conditions, tend to undergo reaction by an $S_{RN}1$ mechanism leading to replacement of the halogens ⟨83JOC1180⟩.

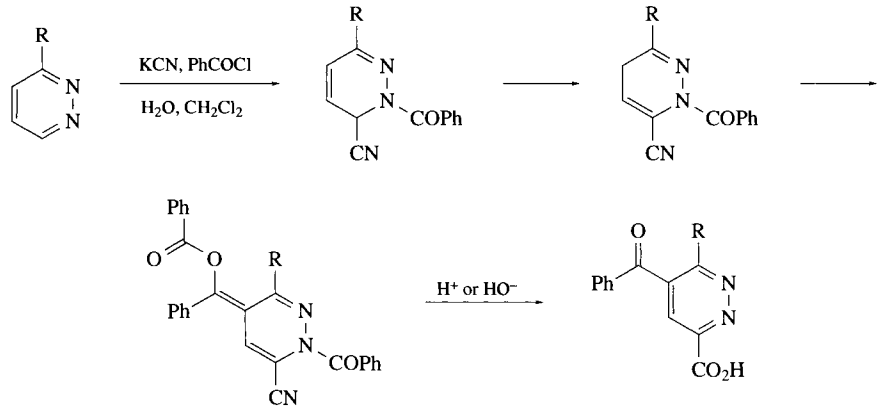


Scheme 18

(iii) Cyanide ions, including Reissert reactions

Reissert type reactions of pyridazine 1-*N*-oxides to give 6-cyanopyridazines in poor yield, and the alkylation of a phthalazine Reissert compound to give 1-methylphthalazine after hydrolysis, were discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. Examples of the use of Reissert type chemistry and an unusual reaction with cyanide ion are described below.

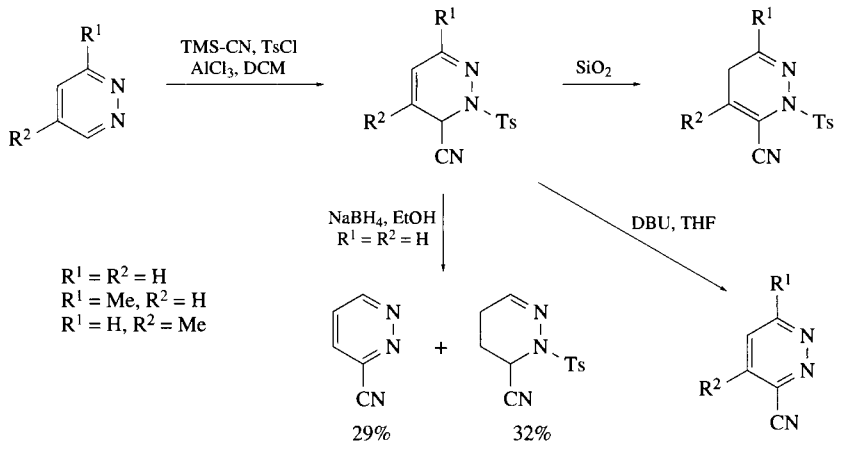
Reaction of 3-methylpyridazine with TMSCN/benzoyl chloride gives the normal Reissert adduct. However, reaction of pyridazine and 3-methylpyridazine with potassium cyanide/benzoyl chloride in water/dichloromethane is complicated by tautomerizm of the initial product under the reaction conditions; the initial 2,3-dihydro adduct is completely tautomerized to the 2,5-dihydro adduct on silica gel. The 2,5-dihydro tautomer formed *in situ* undergoes further benzoylation (Scheme 19) and finally hydrolysis gives 5-benzoylpyridazine-3-carboxylic acid via the corresponding 5-(hydroxybenzyl) derivative, which is oxidized under the reaction conditions ⟨85JHC1543⟩.



Scheme 19

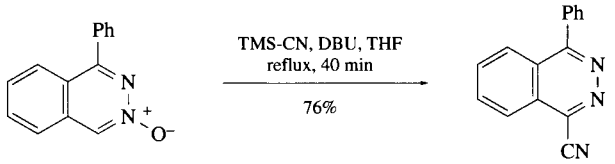
TMSCN/*p*-toluenesulfonyl chloride is much more effective than TMSCN/benzoyl chloride for the preparation of Reissert compounds from pyridazine and methylpyridazines; 4-methylpyridazine reacts exclusively at N-2/C-3. Some of the Reissert compounds undergo facile tautomerism on silica gel, but treatment of the crude compounds with DBU provides an efficient synthesis of 3-cyanopyridazines in about 75% overall yield (Scheme 20). With sodium borohydride instead of DBU, competing reductions give a mixture of the pyridazine and tetrahydropyridazine nitriles ⟨86H(24)793⟩.

Modified conditions have been developed for the preparation of cyanoheteroarenes from heteroarene *N*-oxides by the Reissert–Henze reaction, using TMSCN and DBU (Equation (9)). DBU as base is much more productive than triethylamine, which gave only 37% yield in 180 minutes compared to 76% in 40 minutes for the example shown ⟨92H(33)211⟩. The use of tri-*n*-butyltin cyanide with benzoyl chloride for the preparation of Reissert compounds when applied to phthalazine gave



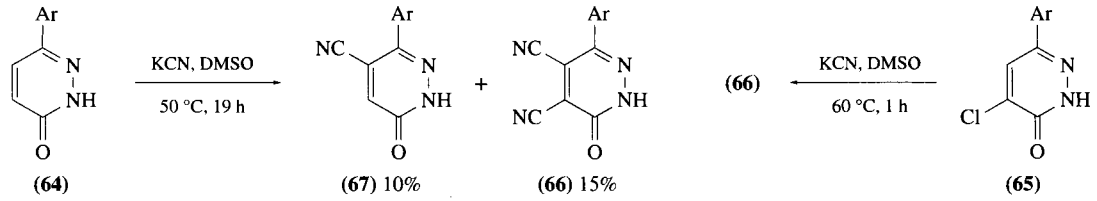
Scheme 20

79–91% yields in dichloromethane at room temperature ⟨85H(23)2193⟩. The application of ultrasonics in the preparation and reaction of phthalazine Reissert compounds under phase transfer catalytic conditions has been described ⟨88JHC917⟩.



(9)

Both 6-(4-(1-imidazolyl)phenyl)-3(2*H*)-pyridazinone (**64**) and its 4-chloro analogue (**65**) reacted with potassium cyanide in DMSO to give the 4,5-dicyano derivative (**66**) (Scheme 21). The 5-cyano-3(2*H*)-pyridazinone (**67**) was isolated from reaction of the des-chloropyridazine, but the 4-cyano analogue was not observed from either substrate. This unusual reaction proceeds faster in an oxygen atmosphere and more slowly under an inert atmosphere; the nitriles were not produced in other solvents or when copper cyanide was used ⟨86JHC1515⟩.



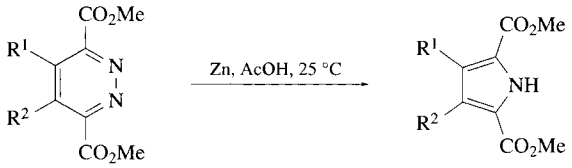
Scheme 21

6.01.5.4.6 Chemical reduction

Reduction of the (benzo)pyridazine derivatives was not discussed in CHEC-I, but reduction of these systems is known to occur readily. Cleavage of the N—N bonds can occur, in addition to hydrogenation of the ring, to give open chain products (e.g., tetramethylenediamine from pyridazine) which may re-cyclize (e.g., to give indoles from cinnolines). Examples of work from the current review period are given below.

Dimethyl pyridazine-3,6-dicarboxylates are particularly susceptible to reduction, and with zinc in acetic acid at room temperature the corresponding pyrroles are formed in high yield, presumably by a reduction, ring opening, 5-ring closure and reductive cleavage sequence (Equation (10)). This reduction can be applied successfully in the presence of a range of substituents including alkyl

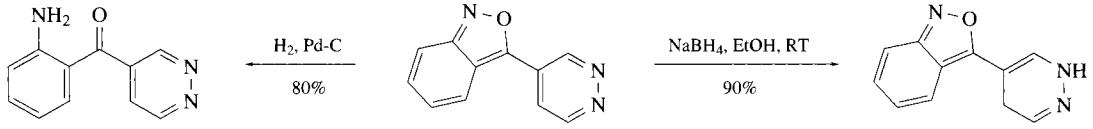
ketones and benzyl ethers, but it does seem to require both carboxylates to be present, as pyridazine and methyl pyridazine-3-carboxylate failed to give good yields of pyrroles ⟨84JOC4405⟩.



(10)

R^1 = Me, Et, Ph, OMe, OBn; R^2 = Me, H, COMe
R^1R^2 = $(CH_2)_4$, 3,4-(*N*-carbomethoxynortropino)

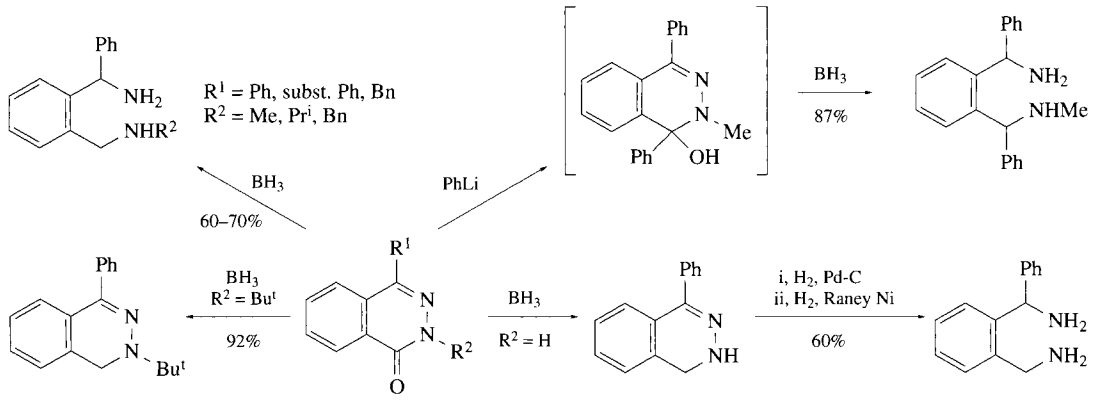
While catalytic reduction of the benzisoxazole (**68**) (Scheme 22) gave the expected 4-(2-aminobenzoyl)pyridazine (**69**), reduction with sodium borohydride resulted in selective reduction of the pyridazine to give the 1,4-dihydropyridazinyl derivative (**70**) in high yield ⟨92AP(325)119⟩.



(**69**) (**68**) (**70**)

Scheme 22

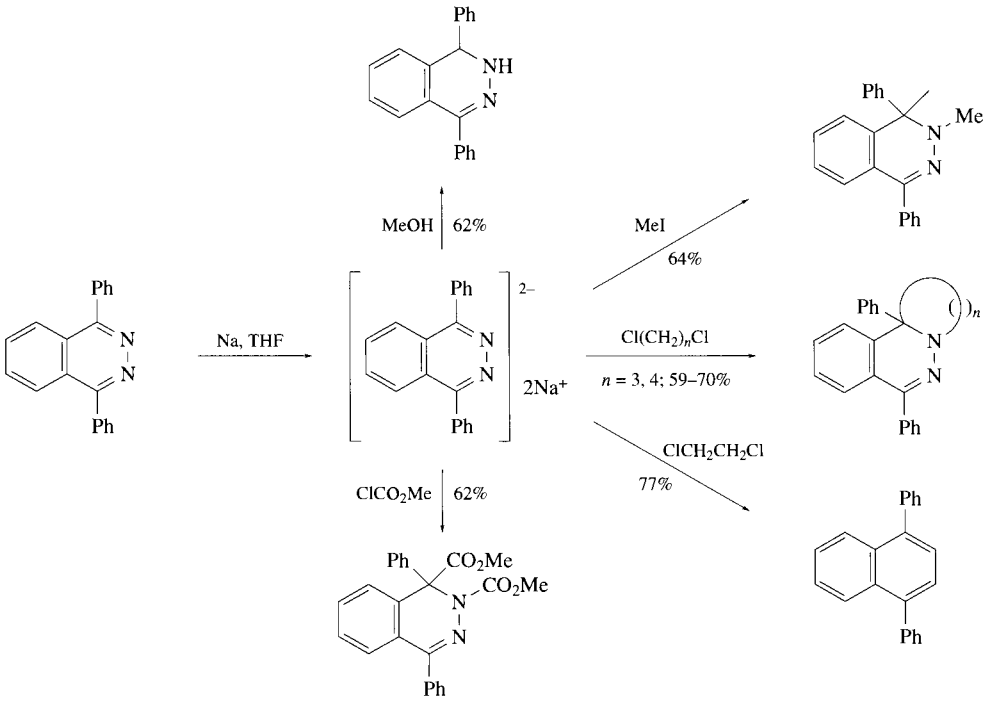
Complete reduction of pyridazine and 3-methylpyridazine occurs in alkaline solution with aluminum–nickel alloy to give 1,4-diaminobutane and 1,4-diaminopentane, respectively, in good yields. Many other aromatic heterocycles are also fully reduced under these conditions, but benzene is unaffected so that phthalazine gives *ortho*-xylenediamine ⟨87JOC1043⟩. Phthalazinium salts are also completely reduced with borane in THF to give substituted *ortho*-xylenediamines: 1-phenyl-2-benzylphthalazinium chloride gives 2-(1-phenylaminomethyl)benzenemethanamine ⟨91JOC5218⟩. Borane reduction of 4-substituted-1(2*H*)-phthalazinones is offered as a useful synthetic route to α-substituted-1,2-benzenedimethanamines and preliminary reaction with aryllithium reagents extends this approach to include α,α′-disubstituted derivatives (Scheme 23). It is known that the phthalazinone-N-2 must be substituted, but not by *t*-butyl otherwise only reduction of the carbonyl group occurs at a significant rate. In the case of the free NH compound further reduction to the benzendimethanamine is possible using hydrogen with palladium on carbon followed by Raney nickel ⟨91JOC5218⟩.



Scheme 23

1,4-Diphenylphthalazine with sodium in THF is reduced to the dianion as a deep purple-blue solution. The dianion can be quenched with methanol to give the 1,2-dihydro derivative, which is unstable and readily undergoes oxidation to regenerate the phthalazine. However, reaction with some other electrophiles, including dichloroalkanes, gives stable 1,2-dihydro products (Scheme 24).

The exception is 1,2-dichloroethane which gives 1,4-diphenylnaphthalene, presumably via 1,4-addition, elimination of nitrogen and aromatization ⟨86JHC13⟩.



Scheme 24

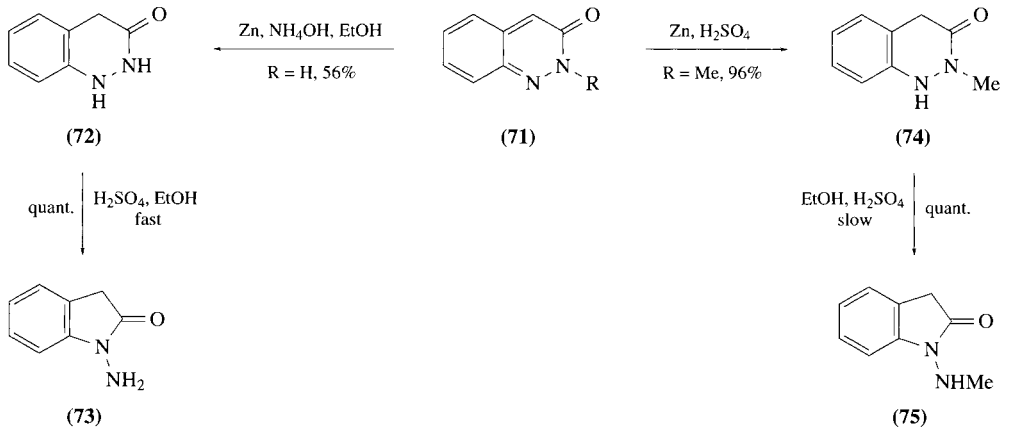
Reduction of the cinnoline nucleus was a side reaction in the stannous chloride reduction of the nitro group in 4-carboxamido-3-nitrocinnoline, but was minimized by the careful use of just three equivalents of the reductant ⟨84JOC289⟩. A mechanistic study of the electroreduction of benzo[*c*]-cinnoline has shown that the ArNHNAr radical is an intermediate which breaks down by disproportionation to give benzo[*c*]cinnoline and 5,6-dihydrobenzo[*c*]cinnoline. The latter is the product obtained after two-electron reduction by electrolysis at −1.1 V in aqueous medium ⟨88JOC5781⟩.

The outcome of reduction of 3(2*H*)-cinnolinones under acidic conditions has been clarified. Reduction of 3(2*H*)-cinnolinone (**71**, R = H) with zinc and ammonium hydroxide gives the 1,4-dihydro-3(2*H*)-cinnolinone (**72**) which rapidly rearranges to 1-amino-2-indolinone (**73**) in sulfuric acid (Scheme 25). Zinc and sulfuric acid reduction of 2-methyl-3(2*H*)-cinnolinone (**71**, R = Me) gives 1,4-dihydro-2-methyl-3(2*H*)-cinnolinone (**74**), which only very slowly rearranges in sulfuric acid to the methylaminoindolinone (**75**). Taken together these results are consistent with zinc and sulfuric acid reduction of the parent 3(2*H*)-cinnolinone to 1-amino-2-indolinone proceeding via 1,4-dihydro-3(2*H*)-cinnolinone ⟨87JHC1261⟩.

6.01.5.5 Nucleophilic Attack at Hydrogen Attached to Ring Carbon or Nitrogen

6.01.5.5.1 Metalation at carbon

Successful metalations of pyridazines have been reported, using lithium 2,2,6,6-tetramethylpiperidide in THF in the cold, with 3,6-dichloropyridazine ⟨90JHC1377⟩ and 3,6-dimethoxypyridazine, ⟨90JOC3410⟩. Reactions of the resultant 4-lithio derivatives with electrophiles are discussed in Section 6.01.7.16; yields of products are generally low to moderate but can be high from the dimethoxypyridazine. Similar conditions are also successful in the absence of the directing groups and pyridazine generally gives 3- or 3,6-substituted derivatives ⟨95JOC3781⟩.



Scheme 25

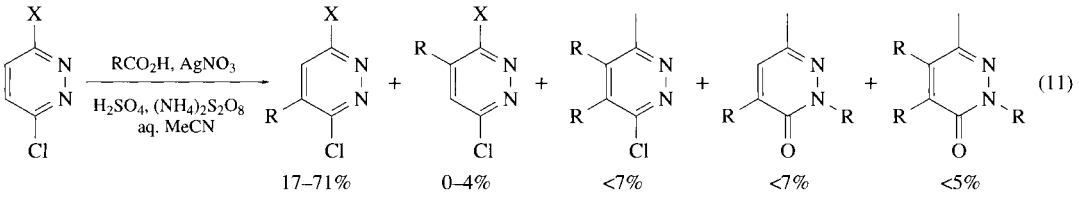
6.01.5.5.2 Alkylation of anions formed by deprotonation of azinones

Alkylation of 3-ethoxycarbonyl-4(1*H*)-cinnolinones by alkyl iodides or dialkyl sulfates with potassium carbonate in DMF gives a mixture of the 3-ethoxycarbonyl-1-alkyl-4(1*H*)-cinnolinones along with the anhydro bases formed by alkylation of N-2. The latter compounds undergo hydrolysis and decarboxylation in acid ⟨89CPB93⟩.

6.01.5.6 Reactions with Radicals

Some radical reactions of pyridazines, including acylation at the 4(5)-position, are described in CHEC-I ⟨84CHEC-I(3B)1⟩ but there has been considerable expansion in the investigation and application of radical reactions in this area.

Homolytic alkylation of 3-chloro-6-phenylpyridazine with radicals generated by silver catalysed decarboxylation showed marked regioselectivity for 4-substitution and gave high yields with Bu^t and Pr^i radicals; yields were lower with Et radicals (Equation (11)). Only with Pr^i was any of the isomeric 5-alkyl product obtained. The regioselectivity of radical alkylation was investigated further with 3-chloro-6-methylpyridazine, in which the 3- and 6-substituents are about the same size. Using Et, *i*-Pr, *t*-Bu and cyclohexyl radicals the high regioselectivity for the 4-position was maintained to give yields of 54–71%. Traces of the isomeric 5-alkyl derivatives were detected, but more significant byproducts, accounting for up to 4–7% each, were 4,5-dialkylated products and 6-methyl-2,4-dialkyl- and 2,4,5-trialkyl-3(2*H*)-pyridazinones. The substitution pattern in the major products was confirmed by reduction and measurement of the pyridazine 3,5*H* coupling (about 2–2.5 Hz) ⟨91JHC583⟩.

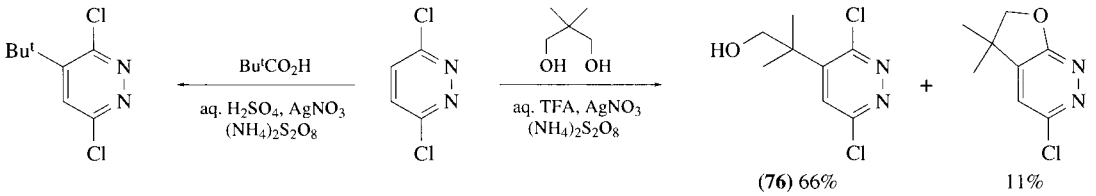


(11)

X = Me, Ph; R = Et, Pr^i, Bu^t, cyclohexyl

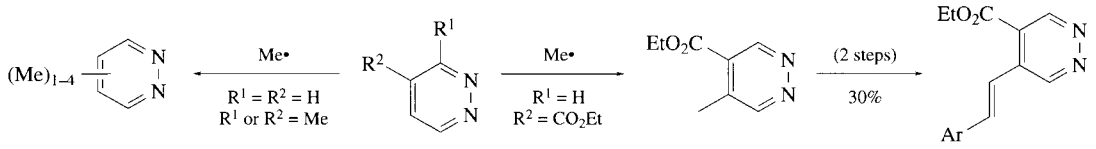
3,6-Dichloropyridazine can be successfully alkylated and hydroxyalkylated by free radicals (Scheme 26). 4-*t*-Butyl-3,6-dichloropyridazine is prepared in high yield ⟨88OPP117⟩, and in a novel radical hydroxyalkylation, hydroxy-*t*-butyl radicals generated *in situ* from 2,2-dimethyl-1,3-propanediol react to give the 4-hydroxy-*t*-butyl derivative (**76**), along with some of the fused dihydrofuropyridazine byproduct; the product (**76**) can be obtained pure in 55–60% yield by recrystallization. In the latter 3,6-dichloropyridazine reaction, trifluoroacetic acid and silver nitrate both catalyse hydrolysis of the dichloropyridazine substrate, but if the acid is omitted, or the quantity

of silver nitrate is reduced below 0.5 equivalents, then the reaction does not go to completion ⟨88JOC5704⟩.



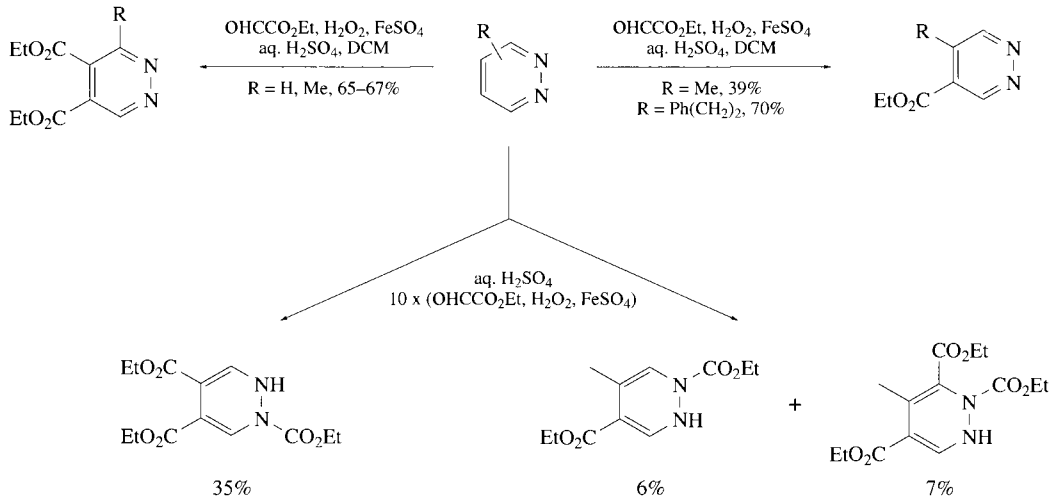
Scheme 26

Radical methylation of pyridazine and 3- or 4-methylpyridazine occurs preferentially at the 4,5-positions, but selectivity is less marked than for radical acylation. Thus all of the possible methylation products were observed and preparative isolation of the individual products, which were identified by GC-MS, was not possible (Scheme 27). Similarly, the major product from ethyl pyridazine-4-carboxylate, the 5-methyl derivative, could not be purified, but was characterized as readily isolable benzylidene derivatives ⟨84H(22)1395⟩.



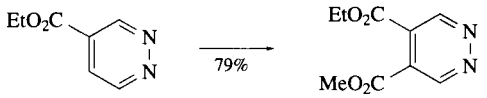
Scheme 27

Minisci-type radical ethoxycarbonylation of pyridazines occurs at all unsubstituted positions, including nitrogen, but predominately at C-4,5. The tendency to give multiply substituted products is exacerbated by the need for an excess of reagents to give reasonable conversion rates, but the use of a three-fold excess of reagents under heterogeneous conditions (Scheme 28) favours the formation and simplifies the isolation of single major products which, being less basic than the starting materials, are concentrated in the organic phase ⟨85T1199⟩. Ethoxycarbonylation of pyridazines at nitrogen can be a significant reaction, but only under homogeneous conditions when a large excess of reagents are used. This side reaction is thought to occur by radical attack at the unprotonated nitrogen followed by reduction of the radical cation with ferrous ion to give 1,2-dihydropyridazine products in yields of up to about 35% ⟨88T2449⟩.



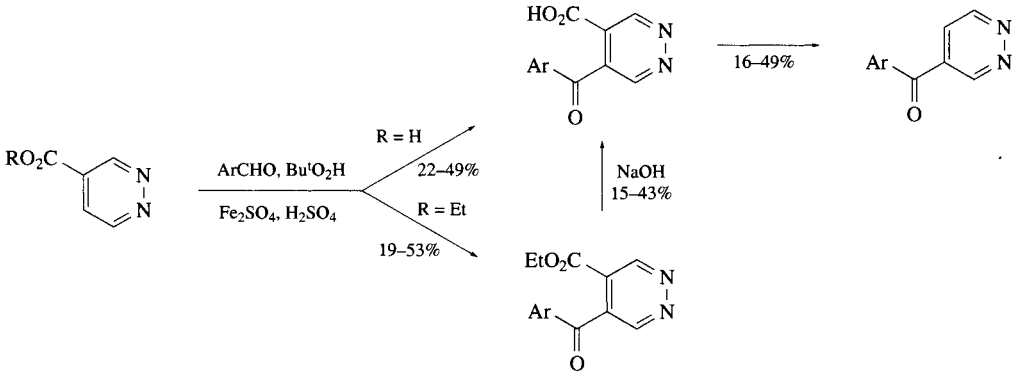
Scheme 28

The Minisci alkoxycarbonylation reaction can be used successfully (Equation (12)) for the preparation of mixed pyridazine-4,5-dicarboxylic acid esters in high yield using a two phase reaction mixture ⟨87H(26)731⟩.



(12)

Minisci-type radical aroylation of ethyl pyridazine-4-carboxylate gives 5-aroyl derivatives in low to moderate yields, and while these can be saponified yields are low and the free acids are better prepared by direct radical aroylation (Scheme 29). The acids can be decarboxylated to give overall a process for the preparation of 4-aroylpyridazines, though yields are not good ⟨83AP(316)508⟩.



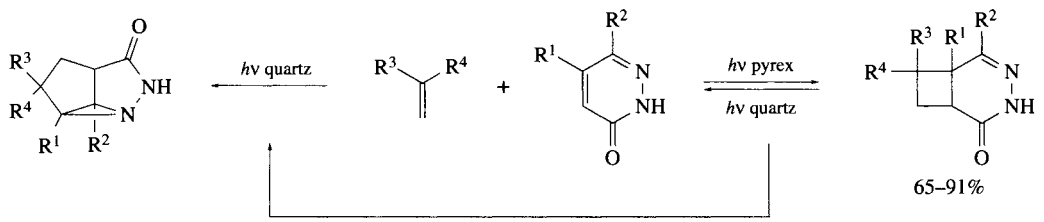
Scheme 29

6.01.5.7 Cycloaddition Reactions

Cycloaddition reactions were illustrated in CHEC-I by, for example, reactions of benzyne with pyridazine *N*-oxides and *N*-acetylimides (to give 2-hydroxy- and 2-acetylaminophenylpyridazines), inverse electron demand cycloaddition reactions of pyridazinecarboxylates with electron rich acetylenes (to give pyridines and benzenes) and dipolar cycloaddition reactions of a pyridazinone with 2-diazopropane and of triphenylcyclopropene with pyridazinium and phthalazinium dicyanmethylides ⟨84CHEC-I(3B)1⟩. There has been a significant extension of the cycloaddition chemistry of (benzo)pyridazine derivatives.

6.01.5.7.1 [2 + 2]-Cycloaddition reactions

Methyl-3(2*H*)-pyridazinones undergo [2 + 2]photoaddition with alkenes to give 3,4-diazabicyclo-[4.2.0]oct-4-en-2-ones in high yields when a pyrex filter is used (Scheme 30). Irradiation of some of these reactants with a quartz filter gave 2,3-diazatricyclo[3.3.0.$0^{2,8}$]octan-4-ones, which may also be formed along with some retro products on irradiation of the bicyclo products under the same conditions ⟨88H(27)1665⟩.

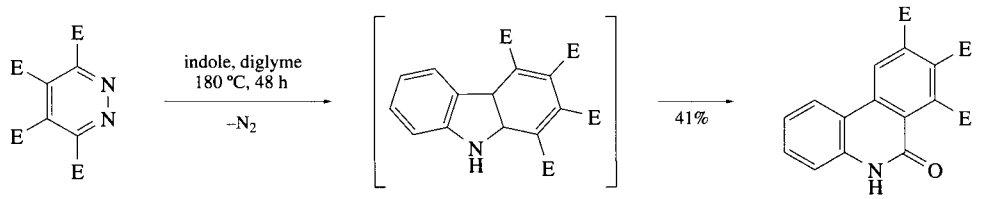


R^1 or R^2 = Me, other = H; R^3 = H, Me; R^4 = CH_2OH, Me, OEt, CO_2Me

Scheme 30

6.01.5.7.2 [2 + 4]-Cycloaddition reactions

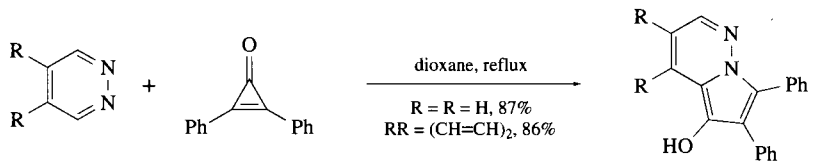
Tetramethyl pyridazine-3,4,5,6-tetracarboxylate, but not 3,6-dichloropyridazine or dimethyl phthalazine-1,4-dicarboxylate, takes part in a Diels–Alder reaction with indole under very concentrated conditions (Scheme 31). The adduct produced after elimination of nitrogen aromatizes by ring opening and the resultant aniline attacks the adjacent ester group to give the phenanthridone (**77**) ⟨90JOC3257⟩. While dimethyl pyridazine-3,6-dicarboxylates are sufficiently reactive to take part in Diels–Alder reactions with electron rich dienes, the corresponding 3,6-bis(methanesulfonyl)-pyridazines are unreactive ⟨88JOC1415⟩.



Scheme 31

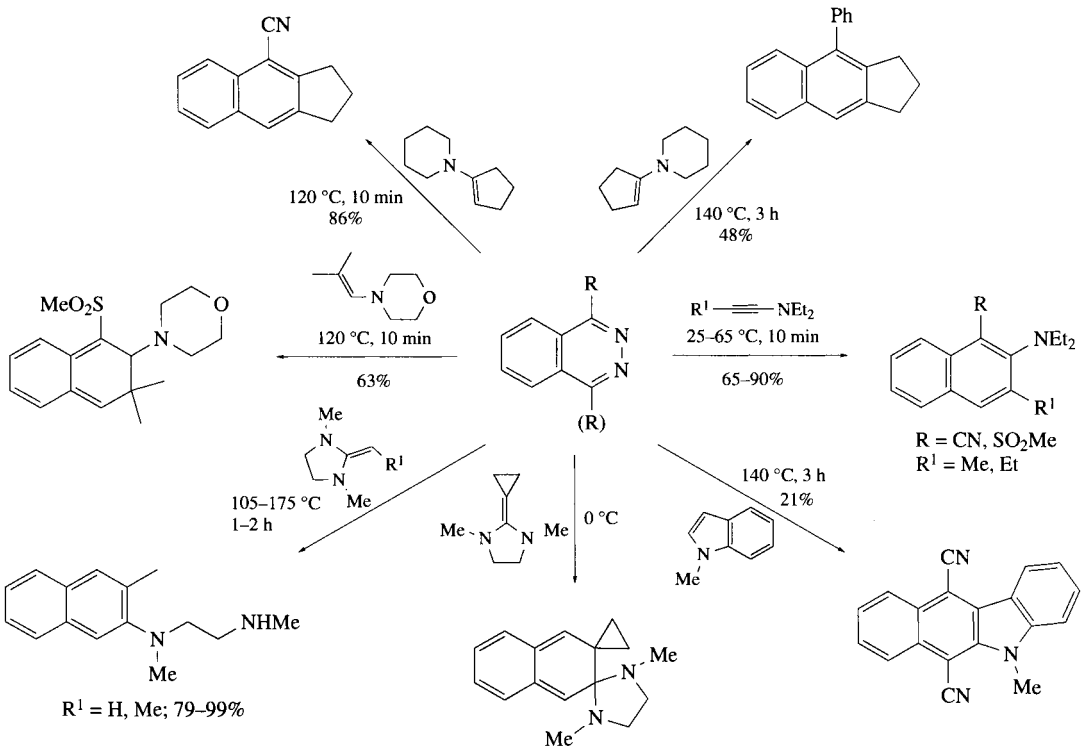
Phthalazines undergo inverse electron demand Diels–Alder reactions with enamines to give naphthalene derivatives. Reactivity of the phtahlazine and yields of the products are highest with a strong electron-withdrawing group (cyano, methylsulfonyl) in the 1-position. Higher temperatures and longer reaction times are required for the unsubstituted and 1-chloro analogues, but particularly for the methyl, phenyl, and methylthio analogues; reaction did not occur with 1-methoxyphthalazine. The initial cycloaddition is regioselective and the adducts lose nitrogen followed by the enamine amine where there is an *ortho* proton. Ynamines react rapidly under moderate conditions to give high yields of dialkylaminonaphthalenes. While *N*-methylindole failed to react with 1-cyanophthalazine, it did react with 1,4-dicyanophthalazine under vigorous conditions to give a moderate yield of 5-methyl-5*H*-benzo[*b*]carbazole (by oxidation of the initially formed adduct) ⟨90CPB3268⟩. 2-Alkylidene-1,3-dimethylimidazolidines are very reactive enamine dienophiles that react with pyridazines and particularly with phthalazines, even in the absence of electron withdrawing groups in the heterocycle, to give, after loss of nitrogen and aromatisation by ring opening of the imidazolidine, high yields of (*N*-(methylamino)ethyl-*N*-methylamino) derivatives of benzene and naphthalene. 3-Methylpyridazine with 2-methylidene-1,3-dimethylimidazolidine gives a mixture of regioisomers of which the major can be obtained as sole product by the use of the 2-ethylidene analogue. The strained 2-cyclopropylidene-1,3-dimethylimidazolidine is even more reactive, and reacts rapidly with both pyridazine and phthalazine at 0 °C with the elimination of nitrogen to give spiro products ⟨87TL6027⟩. Examples of the reactions with phthalazines are shown in Scheme 32.

Diphenylcyclopropenone reacts smoothly with a variety of aromatic *N*-heterocycles and the reaction can be followed by disappearance of the 1850 cm^{-1} band in the IR. The structures of the products have now been established and the method improved: pyridazine and phthalazine give high yields of 2,3-diphenyl-1-hydroxypyrrolo[1,2-*b*]pyridazine and 2,3-diphenyl-1-hydroxypyrrolo[1,2-*a*]phthalazine, respectively (Equation (13)), and not the 1,2-diphenyl-3-hydroxy isomers as previously thought. These products can be derivatized as their acetates and methyl ethers without isolation ⟨91JOC5594⟩.



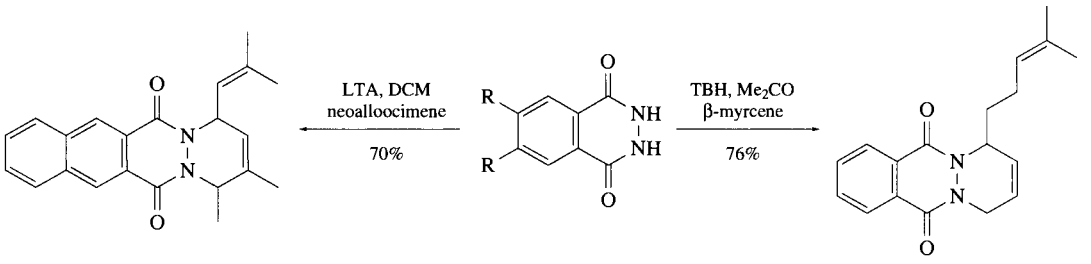
(13)

Diels–Alder reactions of phthalazine-1,4-dione and benzo[*g*]phthalazine-1,4-dione, generated *in situ* by LTA or *t*-butyl hypochlorite oxidation of the cyclic hydrazides, with isoprenoid dienes gave the expected cycloadducts (Scheme 33), sometimes in high yields ⟨87H(25)193⟩. *N*-Bromosuccinimide has been claimed to be a superior oxidant for the *in situ* preparation of phthalazine-1,4-dione for



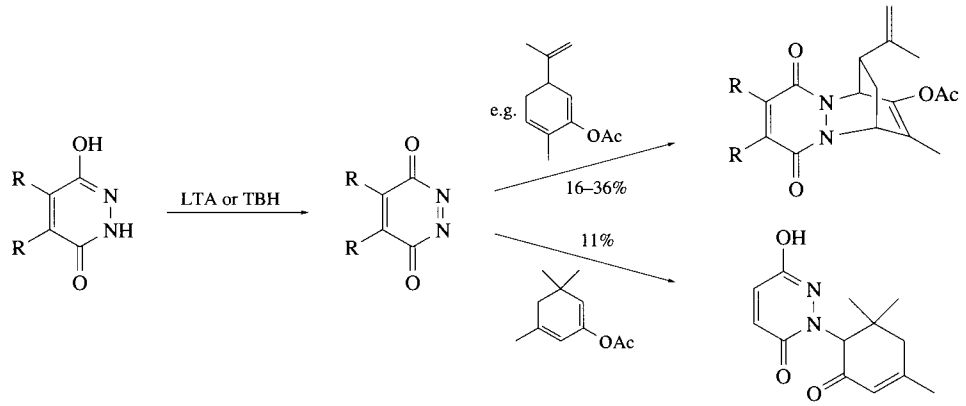
Scheme 32

Diels–Alder cycloaddition with, for example, butadiene ⟨85JOC5604⟩. *N*-Bromosuccinimide can be used to oxidise the initial adduct formed between phthalazine-1,4-dione and 1,4-diphenylbutadiene via benzylic bromination and thermal elimination of hydrogen bromide; the intermediate bromide is, however, very labile towards nucleophiles, and base causes cleavage of the phthaloyl residue, leaving 3,6-diphenylpyridazine ⟨86JOC3123⟩.



Scheme 33

Phthalazine-1,4-dione has been used in the protection of dienes because it is an extremely reactive and readily prepared dienophile whose adducts can be cleaved to regenerate the diene. Thus, cycloaddition to the diene system of vitamin D_2 acetate gave good yields of cycloadducts that could be cleaved subsequently by a high yield two stage process: treatment with anhydrous hydrazine to remove phthalhydrazide and leave a hexahydropyridazine adduct, followed by oxidation of the latter and elimination of nitrogen to release the diene ⟨86JOC4819⟩. This approach has been extended to cycloaddition reactions of diazaquinones, prepared from 6-hydroxy-3(2*H*)-pyridazinone and its benzo analogues, with acyloxydienes derived from terpenoids to give fused derivatives having the enol acetate functionality for further elaboration. However, yields are only poor to moderate (Scheme 34). A nonfused product (**78**) was obtained from 3,6-pyridazinedione and isophorone enol acetate ⟨89H(28)791⟩.

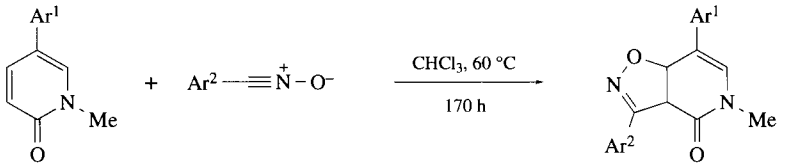


R,R = H,H; benzo, naphthaleno (78)

Scheme 34

6.01.5.7.3 1,3-Dipolar cycloaddition reactions

Arylcarbonitrile oxides undergo site and regioselective 1,3-dipolar cycloaddition to the 4,5-double bond of 6-aryl-2-methyl-3(2*H*)-pyridazinones to give 3a,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4-ones (Equation (14)). The site of cycloaddition is consistent with frontier molecular orbital calculations (MNDO); the HOMO of the nitrile oxide interacts with the pyridazinone LUMO. The orientation of the addition to the 4,5-double bond is probably charge controlled, with the negative oxygen of the nitrile oxide adding to C-5, which has more positive character as estimated by consideration of resonance structures and a Mulliken overlap population analysis ⟨89JHC553⟩.



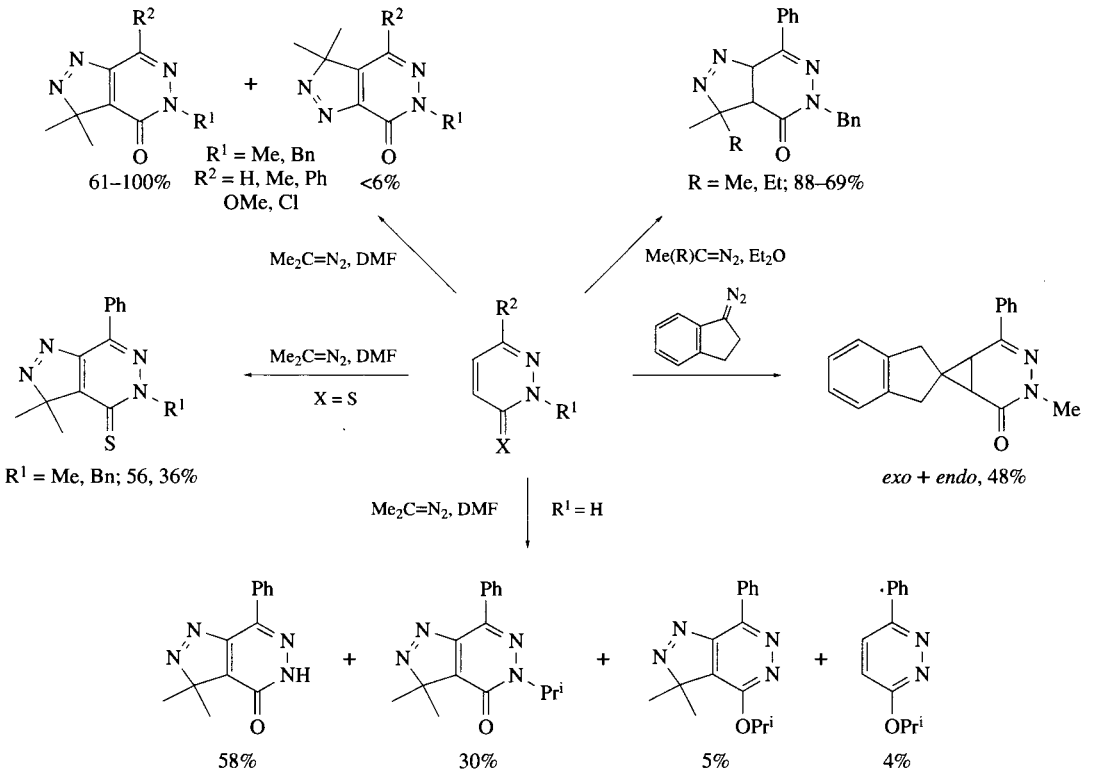
(14)

Ar^1 = Ph, 4-Me- or 4-$MeOC_6H_4$
Ar^2 = 2,4,6-$Me_3C_6H_2$, 2,6-$Cl_2C_6H_3$

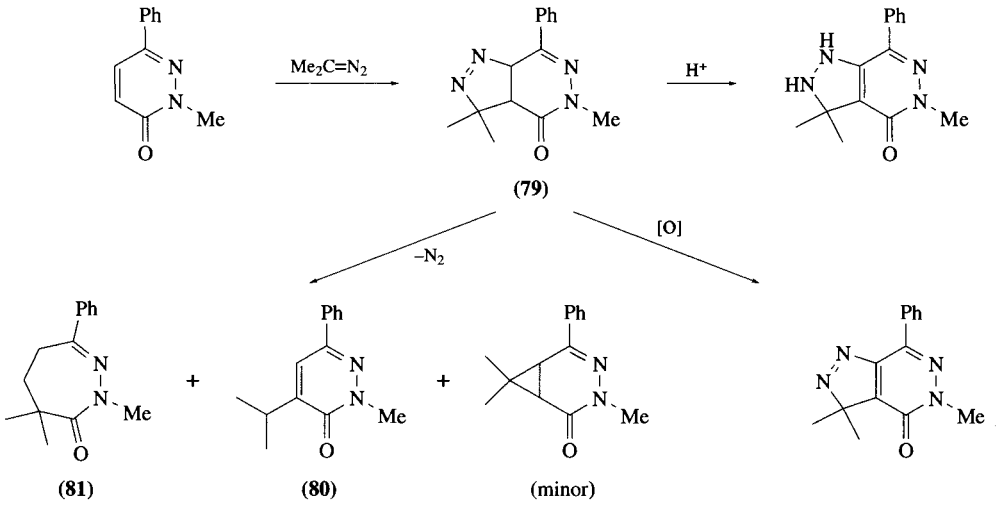
1,3-Dipolar cycloaddition of diazoalkanes to a series of 2,6-disubstituted-3(2*H*)-pyridazinones and thiones proceeds in high yield with almost complete regioselectivity to give 3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones and thiones (Scheme 35) in which the diazoalkane carbon reacts at C-4 of the 3(2*H*)-pyridazinone system. Intermediate dihydro adducts were isolated when ether was used as a reaction solvent in which they had poor solubility. The rate of the cycloaddition reactions was much faster for the thiones, and was also dependent upon the 6-substituent, being fast for 6-chloro and slow for 6-methyl; 1-diazo-1-phenylethane was less reactive than diazopropane. In the absence of a blocking group at N-3, pyridazinones with diazopropane gave mixtures of products due to *N*- or *O*-alkylation of the pyridazinone. The initial cycloadduct between 1-diazoindane and 2-methyl-6-phenyl-3(2*H*)-pyridazinone could only be detected by TLC and decomposed to give a 1 : 1 mixture of the *exo* and *endo* spiro products ⟨91JHC417⟩.

A detailed reinvestigation of the 1,3-dipolar cycloaddition of 2-diazopropane to 2-methyl-6-phenyl-3(2*H*)-pyridazinone has shown that the initial adduct (isolated in 68% yield) is the thermally labile pyrazolopyridazine (**79**), which undergoes subsequent tautomerization, oxidation, or rearrangement with loss of nitrogen, depending on the conditions (Scheme 36). The isopropylpyridazine (**80**) is the major product formed in polar solvents (DMSO) while the diazepine (**81**) predominates when less polar solvents such as dichloromethane are used ⟨90T6915⟩.

The regioselectivity of the cylcoaddition reaction between 6-methoxy-2-methyl-3(2*H*)-pyridazinone and diazopropane can be completely controlled by the presence of an appropriate leaving group at C-4 or C-5. Thus, while the 5-chloro or phenylsulfinyl analogues give the same regioisomer as the 4,5-unsubstituted compound (but as the sole products), the 4-chloro or phenylsulfinyl analogues give as sole products the opposite regioisomer (Scheme 37). Yields for these reactions are high, but the corresponding phenylthio analogues gave poor yields though the regiocontrol was



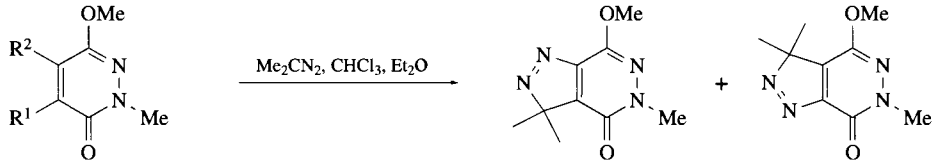
Scheme 35



Scheme 36

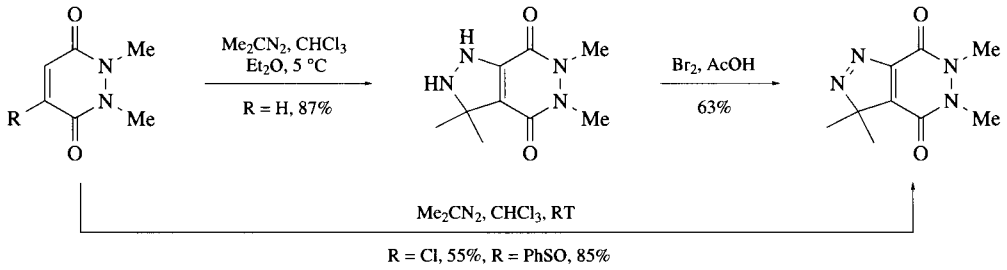
maintained. When this approach was extended to the 5-phenylsulfonyl analogue, nitrogen rather than phenylsulfinic acid was eliminated and rearrangement occurred to give a diazepine which underwent further cycloaddition ⟨91JHC369⟩.

1,2-Dimethylpyridazine-3,6-(1*H*,2*H*)-dione and its 4-chloro and 4-phenylsulfonyl derivatives are much more reactive in cycloaddition reactions with diazopropane than their 3(2*H*)-pyridazinone analogues. The 4,5-unsubstituted compound gave the dihydro adduct which could be oxidized to give the same material as is obtained directly from the 4-substituted starting materials in high yield (Scheme 38). The greater reactivity of the pyridazinedione was also demonstrated by its reaction with 1-diazoindane to give a spiropyrazolo adduct in 78% yield ⟨91JHC369⟩.



$R^1 = R^2 = H$	82%	5%
R^1 = Cl, PhSO; R^2 = H	0%	65–70%
R^1 = H; R^2 = Cl, PhSO	70–83%	0%

Scheme 37

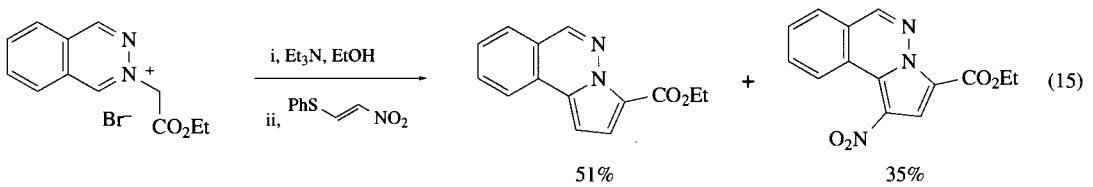


Scheme 38

Reaction of 2-methyl-4 or 5-substituted-3(2*H*)-pyridazinones with an excess of diazomethane proceeds via dipolar 1,3-cycloaddition, in which the carbon of the dipole is attached to the unsubstituted 4- or 5-position, to give methylated pyridazinones or pyrazolopyridazinones (Scheme 39). The observed regioselectivity is consistent with frontier molecular orbital theory with interaction between the HOMO of diazomethane and the LUMO of the pyridazinone. Reactivity is highest at C-4 and with electron withdrawing 4- or 5-substituents, and the better electron withdrawing substituents favour the formation of the methylated rather than the fused products. One example of an initial cycloadduct (**82**) was isolated and characterized; in solution it either undergoes cycloreversion to give the starting material (**83**), or loss of nitrogen to give the methylated pyridazinone (**84**) ⟨88H(27)1431⟩.

The *N*-dicyanomethylids of pyridazine, and especially of phthalazine, undergo 1,3-dipolar cycloaddition with bis(trimethylsilyl)acetylene to give fused pyrrolo derivatives (Scheme 40) which can be quantitatively desilylated with TBAF ⟨83H(20)1009⟩.

1-Nitro-2-(phenylthio)ethylene reacts with the *N*-ethoxycarbonylmethylid of phthalazine, produced *in situ*, to give a mixture of pyrrolo[2,1-*a*]phthalazines (Equation (15)) in which the minor product is presumably formed by oxidation competing with elimination ⟨88H(27)2345⟩.

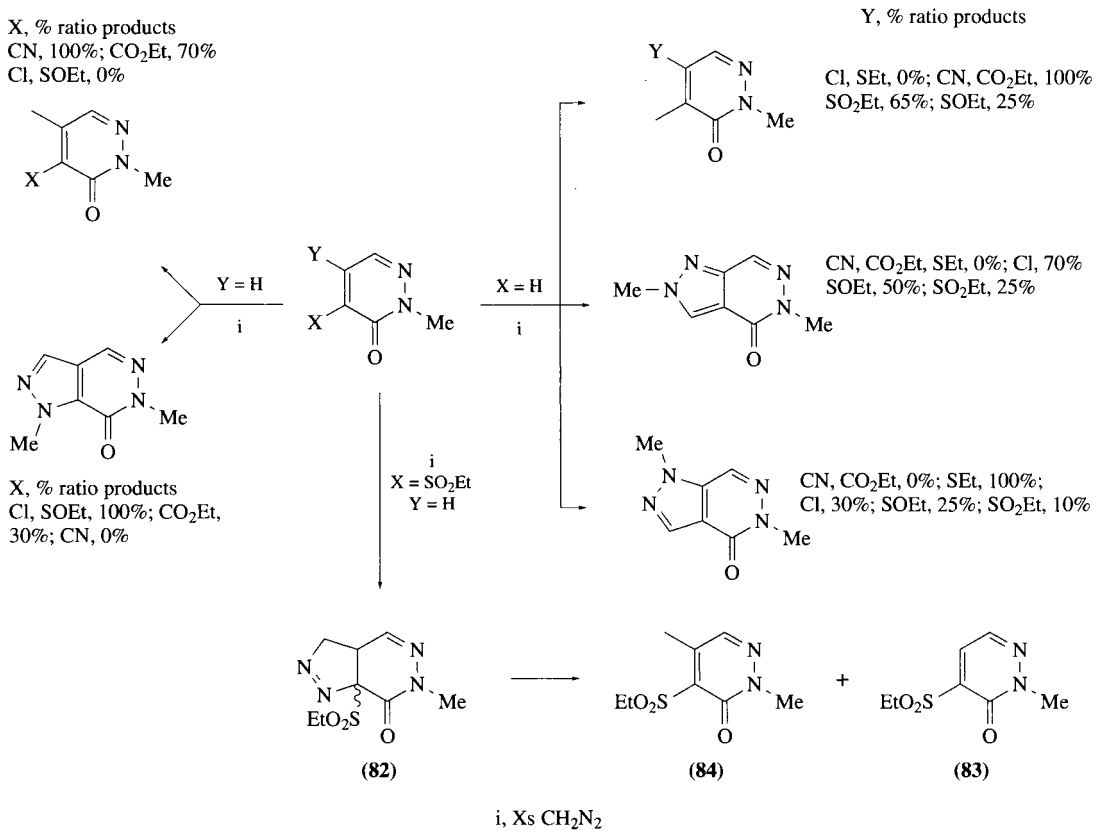


51% + 35% (15)

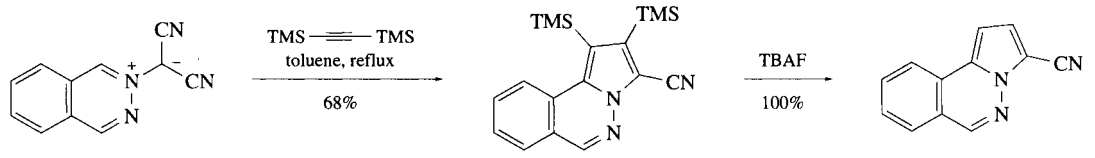
6.01.6 REACTIVITY OF NONCONJUGATED RINGS

6.01.6.1 Introduction

In CHEC-I the reactivity of nonconjugated rings was discussed under the heading of Saturated and Partially Saturated Rings ⟨84CHEC-I(3B)1⟩. In the current work the more rigorous definition of nonconjugated rings, which only covers those compounds which contain at least one sp^3 hybridized carbon or nitrogen atom, is used. Compounds such as 3(2*H*)-pyridazinones are now discussed in the section on conjugated rings. In CHEC-I the discussion of the reactivity of dihydro compounds



Scheme 39



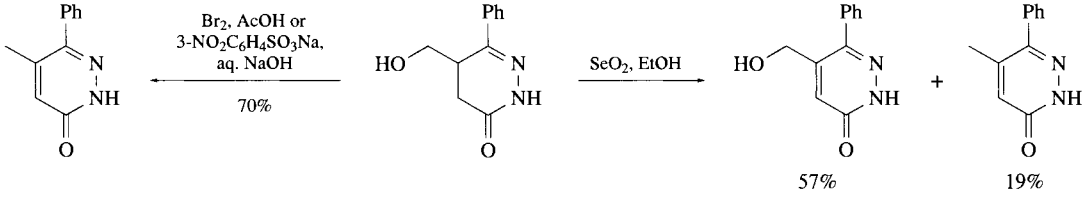
Scheme 40

included reference to ring inversion and ring opening reactions of diazanorcaradienes, but was particularly focused on 4,5-dihydro-3(2*H*)-pyridazinone derivatives ⟨84CHEC-I(3B)1⟩. Topics covered were the lability of these derivatives under aqueous acidic and basic conditions (hydrolysis to butyric acid derivatives), reduction to tetrahydro derivatives with lithium aluminum hydride (hydrolysis occurs under Wolff–Kishner conditions), dehydrogenation with bromine in acetic acid (but with concomitant bromination of reactive 6-aryl substituents), and reaction with Grignard and lithium reagents which, depending on the reagent and substrate, gave products from reaction at the carbonyl or azomethine function. Other topics discussed in CHEC-I were the thermal decomposition of tetrahydropyridazines and conformational studies of hexahydropyridazines ⟨84CHEC-I(3B)1⟩.

6.01.6.2 Dihydro Derivatives Containing a Carbonyl Group in the Ring

The role of carbonyl compounds is dominant in the chemistry of dihydro derivatives of pyridazines. Dihydro-3(2*H*)-pyridazinone derivatives are more stable than the corresponding simple dihydropyridazine derivatives and constitute the majority of dihydro compounds reported. The analogous derivatives are of course not possible in the phthalazine and cinnoline series, though 1,4-dihydro-3(2*H*)-cinnolinones are known.

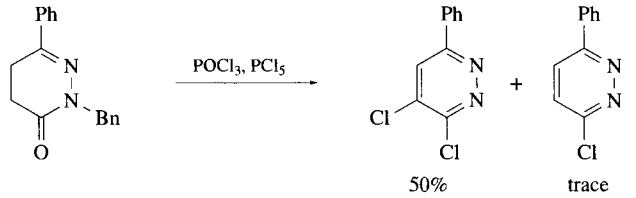
In addition to the bromination of reactive aryl groups during oxidation of 4,5-dihydro-3(2*H*)-pyridazinones to 3(2*H*)-pyridazinones with bromine in acetic acid, loss of labile groups can also occur due to the liberated hydrogen bromide. Both problems are avoided by oxidation with sodium *m*-nitrobenzenesulfonate in aqueous sodium hydroxide solution (originally introduced by Bachmann, ⟨69BRP1168291⟩ and this process is now quite widely used (e.g., ⟨90JMC1735⟩). Bromination is not always a side reaction and in a series of 5-dialkylaminomethyl-6-(2-thienyl)-4,5-dihydro-3(2*H*)-pyridazinones, bromine in acetic acid gave oxidation without bromination to yield the required pyridazinone, which was also prepared by sodium *m*-nitrobenzenesulfonate oxidation ⟨91AP(324)455⟩. However, in the preparation of 5-hydroxymethyl-6-phenyl-3(2*H*)-pyridazinone from the corresponding dihydro compound (Scheme 41), both of these reagents were found to give 5-methyl-6-phenyl-3(2*H*)-pyridazinone by a dehydration reaction and only selenium dioxide gave the required compound ⟨90H(31)1967⟩. Hydrolysis of labile groups may also occur under the alkaline conditions of the nitrobenzenesulfonate oxidation method, and a hydroxylation side reaction has been reported ⟨95JHC79⟩. Selenium dioxide, while not normally the reagent of choice for oxidation of 4,5-dihydro-3(2*H*)-pyridazinones, has also been used in the case of a thienyl substituted derivative to give a 91% yield of the 3(2*H*)-pyridazinone ⟨85AP(318)243⟩, and the use of manganese dioxide has been reported for imidazolyl derivatives (e.g., ⟨87JMC623⟩).



Scheme 41

While bromine in acetic acid effectively oxidises 4-, 5-, and 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones to the corresponding 3(2*H*)-pyridazinones in high yields, the use of NBS in wet DMSO was only effective in the case of the 4- and 5-phenyl-3(2*H*)-pyridazinones, consistent with the greater propensity for these derivatives to undergo oxidation. In this connection it was noted that 5-(3-allyoxyphenyl)-4,5-dihydro-3(2*H*)-pyridazinone underwent aerial oxidation to give 67% of 5-(3-allyloxyphenyl)-3(2*H*)-pyridazinone. In addition to their easy oxidation, 4- and 5-phenyl-4,5-dihydro-3(2*H*)-pyridazinones are readily reduced to the tetrahydropyridazinones in high yields using platinum oxide and hydrogen at atmospheric pressure ⟨85JCS(P1)1627⟩. 1,4-Dihydro-3(2*H*)-cinnolinone and its 2-methyl analogue are readily oxidized by LTA or *t*-butyl hypochlorite to the corresponding 3(2*H*)-cinnolinones in good yields ⟨88JHC847⟩.

In an unusual reaction, treatment of 2-benzyl-6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone with a mixture of phosphorus oxychloride and pentachloride resulted in debenzylation, aromatization, and chlorination (Equation (16)). The presence of the benzyl group in the substrate is important, as the dichloropyridazine product is only formed in very low yield from the corresponding reaction of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone ⟨83JHC1473⟩.

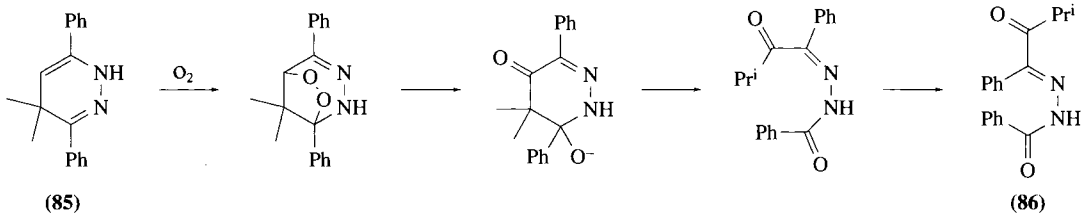


(16)

6.01.6.3 Dihydro Derivatives Without a Carbonyl Group in the Ring

While dihydropyridazines which can be oxidized to the aromatic system usually react rapidly with oxygen in solution to give pyridazines, presumably by addition of oxygen, hydroperoxide

formation and elimination of hydrogen peroxide, 4,4-dimethyl-3,6-diphenyl-1,4-dihydropyridazine (**85**) undergoes ring opening and geometrical isomerization (Scheme 42) to give (**86**) ⟨83JHC855⟩.



(85) **(86)**

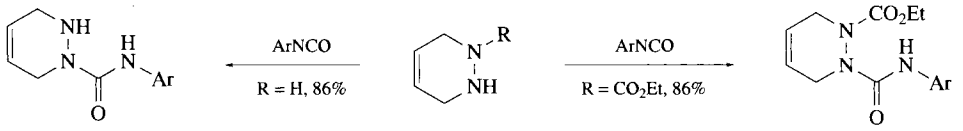
Scheme 42

Reissert analogues of phthalazine are known and the anions have been shown to undergo alkylation and addition to aldehydes, leading after an *in situ* or subsequent hydrolysis step to, for example, 1-methylphthalazine and α-phenyl-1-phthalazinemethanol, though yields are poor. Hydrolysis of the Reissert analogue 1-cyano-2-diethylcarbamoyl-1,2-dihydrophthalazine with acid or base regenerates the parent phthalazine, in contrast to the behavior of isoquinoline Reissert compounds ⟨85JHC1065⟩. Reissert compounds are discussed in more detail in Section 6.01.5.4.5.iii.

5-Phenyl-5,6-dihydrobenzo[*c*]cinnoline can be arylated by nucleophilic displacement of activated aryl halides to give what is essentially a tetrasubstituted hydrazine ⟨85AG(E)596⟩.

6.01.6.4 Tetrahydro Derivatives

The amino nitrogen of 2,3,4,5-tetrahydropyridazines behaves normally and reacts with methyl isothiocyanate to give the 2-(*N*-methylthiocarbamoyl) derivative ⟨84JHC889⟩. Similarly, both 1,2,3,6-tetrahydropyridazine and its 1-ethoxycarbonyl derivative react with arylisocyanates (Scheme 43) to give high yields of aryl carbamoyl derivatives ⟨93JHC45⟩.



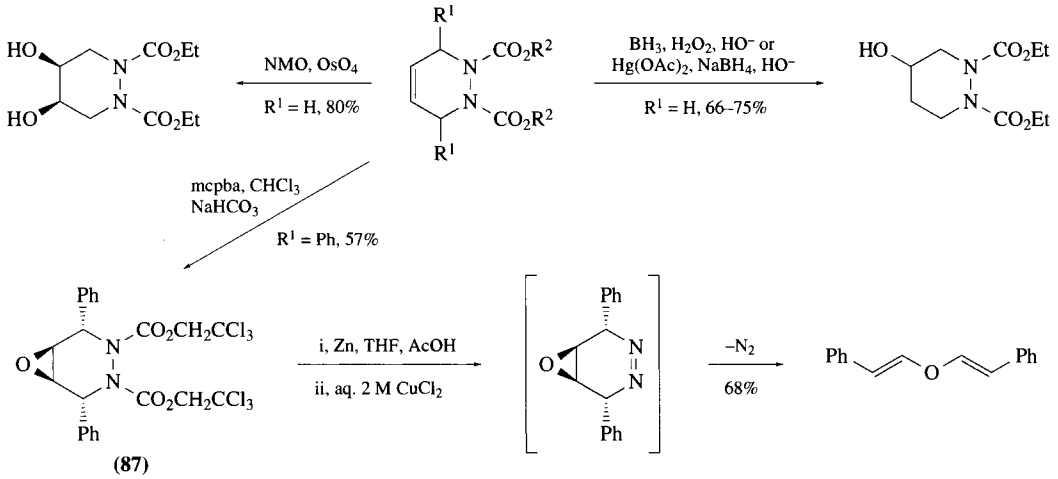
Scheme 43

The 4,5-double bond in tetrahydropyridazines behaves as a normal alkene and hydration, *cis*-hydroxylation, and epoxidation can be achieved in good yields (Scheme 44) by either hydroboration–oxidation or oxymercuration–demercuration ⟨90JHC2125⟩, by osmium tetroxide catalyzed hydroxylation ⟨93JHC45⟩, and by MCPBA oxidation ⟨85JOC4899⟩ respectively, of 1,2-dialkoxycarbonyl derivatives. The structure of the epoxide (**87**) was shown to be *exo*, *exo*-diphenyl by x-ray analysis. Removal of the trichloroethoxycarbonyl protecting groups from the latter and oxidation of the hexahydro intermediate gave a 3,4,5,6-tetrahydro derivative which was not isolated but underwent spontaneous ring opening to give bis(2-phenylvinyl)ether in 68% yield.

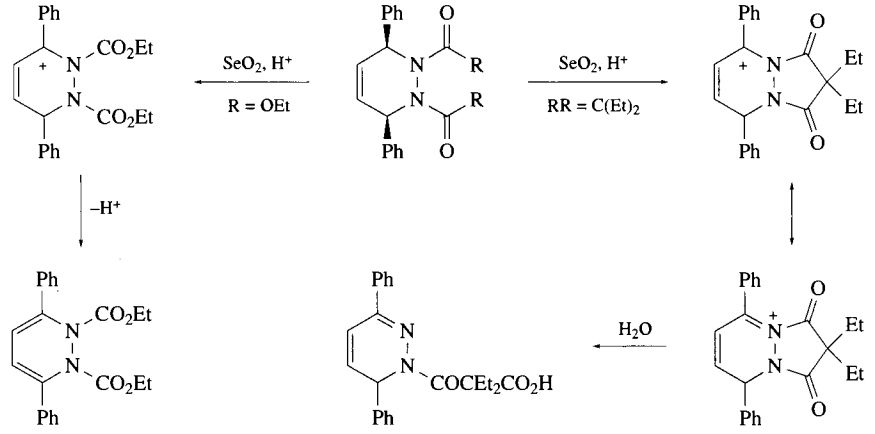
Oxidation of diethyl 3,6-diphenyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate with selenium dioxide gives the corresponding 1,2-dihydro analogue, but the related bicyclic system (RR = CEt_2) reacts by a different mechanism to give a 2,3-dihydro product (Scheme 45). Conformational differences between the starting materials are consistent with the two different reaction pathways. Thus the fused system is approximately planar and in the intermediate carbocation the charge is delocalised onto nitrogen, leading to ring opening, while the monocyclic compound exists in a fairly rigid half chair conformation and delocalization of the nitrogen lone pair is not favoured ⟨87JOC101⟩.

Oxidation of adjacent enantiomeric piperazic acids in the cyclic peptide (**88**) with air or hypochlorite ⟨89MI 601-01⟩ gave the corresponding peptide containing two 2,3,4,5-tetrahydropyridazine-3-carboxylic residues (**89**), but interestingly further oxidation with DDQ resulted in regioselective oxidation of the 4,5-bond in the (*S*)-residue to give a 2,3-dihydropyridazine (**90**), while alkaline hydrogen peroxide caused hydration of the 5,6-bond in the (*S*)-residue to give a hexahydro-6-oxopyridazine (**91**) (Scheme 46). The peptide (**89**) was also shown to undergo regio- and stereoselective alkylation, at C-5 of the (*S*)-residue, with Eschenmoser's salt in the presence of camphorsulfonic acid ⟨90JMC2321⟩.

The 1,4,5,6-tetrahydropyridazine derivatives (**92**), prepared by reaction of α-halogeno semi-



Scheme 44



Scheme 45

carbazones and carbanions from ethyl ketopyruvates, gave two entirely different products on acid treatment depending on the substituents. Thus, those derived from phenacyl halides (R = Ph) gave imidazopyridazinediones, while those from haloacetone (R = Me) gave *N*-ureidopyrroles (Scheme 47). Under acid conditions the tetrahydropyridazine undergoes ring opening and either reclosure or, when R = Me, isomerization of the hydrazone and rapid ring closure to give the pyrrole ⟨83H(20)551⟩.

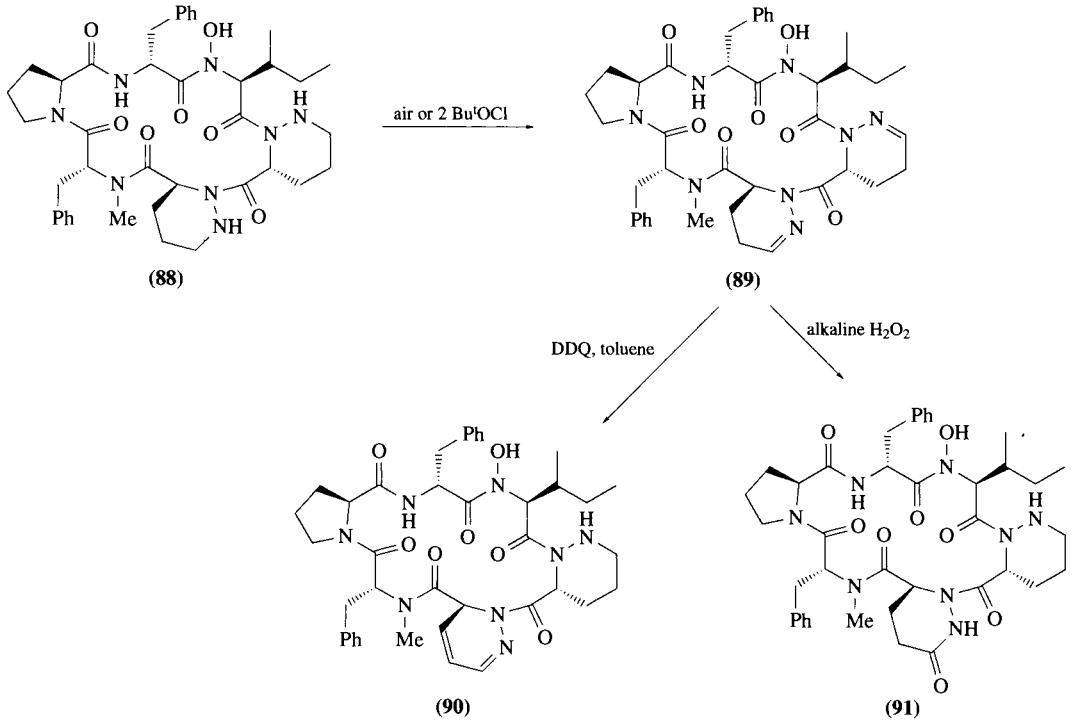
6.01.6.5 Hexahydro Derivatives

Piperidazine takes part in conjugate addition to esters of *trans*-cinnamic acid to give a saturated pyrazolo[1,2-*a*]pyridazine, but with chiral esters there was only marginal asymmetric induction; reduction of the adducts with sodium in ammonia (Scheme 48) cleaves the N—N bond to form a 1,5-diazacyclononanone ⟨87H(26)85⟩.

6.01.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBONS

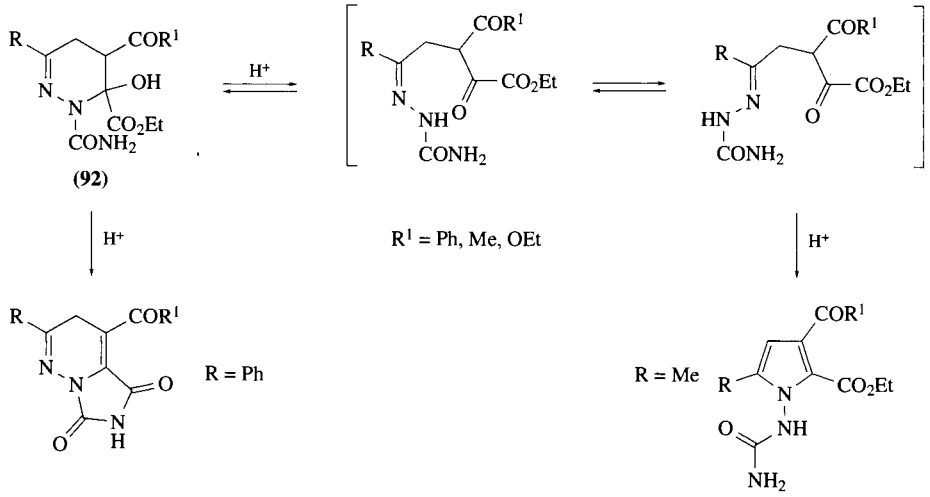
6.01.7.1 Benzenoid Substituents

The reactivity of substituents on the fused benzene rings of (benzo)pyridazine derivatives was not discussed in CHEC-I because it is little different from that of the corresponding fused carbocycles,



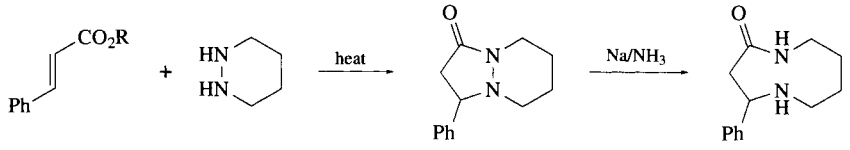
(88) (89) (90) (91)

Scheme 46



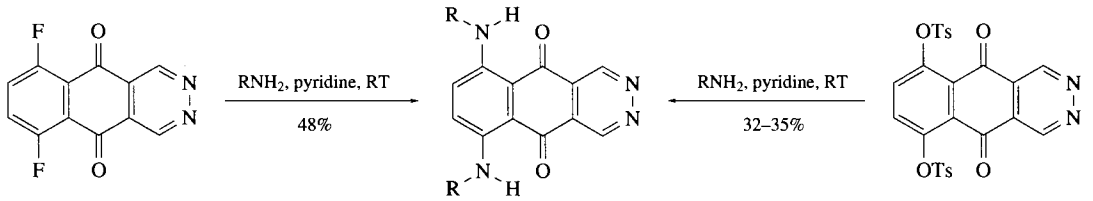
(92)

Scheme 47



Scheme 48

for example nucleophilic substitution reactions are not normally favoured, but in the case of 6,9-difluoro or di-*O*-tosyl derivatives of benzo[*g*]phthalazine-5,10-dione (Scheme 49) activation by the carbonyl groups allows displacement of both substituents with amines ⟨93JHC1597⟩. The pyridazine ring is more resistant to oxidation than benzo-fused rings, so that oxidation of alkyl and aryl substituted benzopyridazines may give pyridazinedicarboxylic acids.



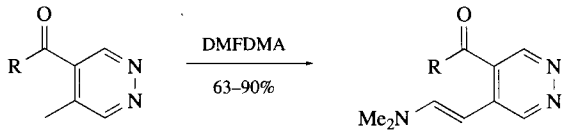
R = $(CH_2)_2NMe_2$, $(CH_2)_2NHBOC$

Scheme 49

6.01.7.2 Alkyl Groups

The reactivity of pyridazine and pyridazine *N*-oxide methyl substituents is reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. In particular, susceptibility to oxidation to the aldehydes or acids, condensation with aldehydes, and reactions of lithiated intermediates are discussed; for instance, treatment of 3-methylpyridazine-1-oxide with acetic anhydride gives, after hydrolysis, 3-hydroxymethylpyridazine.

Among more recent work, from the early 1990s, is the reinvestigation of the oxidation of 3-chloro-6-methylpyridazine with acid dichromate. 3-Chloro-6-pyridazine carboxylic acid can be obtained in 35% yield, but 31% of the corresponding pyridazinone is also formed by hydrolysis of the chloro substituent, and is the sole product if the reaction is allowed to proceed for a longer period ⟨92JHC1583⟩. When adjacent to an ester or ketone substituent a pyridazine 4-methyl substituent is sufficiently activated to undergo reaction with dimethylformamide dimethyl acetal (Equation (17)); the dimethylaminovinyl products cyclize on treatment with ammonia to give pyrido[3,4-*d*]pyridazines ⟨89JHC933⟩. Similarly, the 3-methyl group in ethyl 3-methyl-4-pyridazinecarboxylate can be enaminated with Bredereck's reagent and the crude dimethylaminoenamine, obtained in about 70% yield, was suitable for reaction with amines to give pyrido[4,3-*c*]pyridazin-5(6*H*)-ones ⟨91JHC1043⟩.



(17)

R = OEt, Ph, 4-ClC_6H_4

Free radical chlorination of 4-*t*-butyl-3,6-dichloropyridazine with sulfuryl chloride gives 4-(2-chloro-1,1-dimethylethyl)-3,6-dichloropyridazine as the major product, but only when the reaction is stopped after about 20% conversion. Further reaction results in random chlorination of the *t*-butyl group and the 4-(2-chloro-1,1-dimethylethyl) product is better made from the corresponding alcohol ⟨88JOC5704⟩.

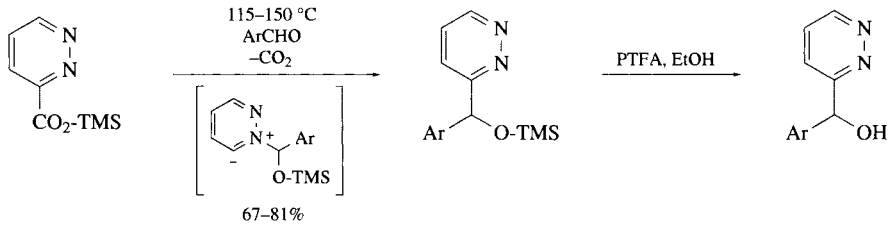
6.01.7.3 Carboxylic Acids and Esters

The preparation and reactivity of carboxylic acids and esters was outlined in CHEC-I, with particular emphasis on the ease and practical use of decarboxylation of acids (especially pyridazine-3-carboxylic acids), and the choice of esterification methods ⟨84CHEC-I(3B)1⟩. The high acidity of the acids (e.g., pyridazine-4-carboxylic acid, pK_a 2.8) was also discussed. Some more illustrations of the chemistry of carboxylates are given here.

Pyridazine-3,6-dicarboxylic acid undergoes facile decarboxylation in acid but esterification is successfully accomplished by adding thionyl chloride to alcoholic solutions of the diacid at −30 °C

⟨87JHC1285⟩. The decarboxylation of 4-alkoxypyridazine-3-carboxylic acids also appears to be particularly facile, and proceeds in high yield in aqueous acid at room temperature ⟨86JOC3250⟩. Another example of selective decarboxylation of pyridazine-3-carboxylic acids is the quantitative preparation of pyridazine-4-carboxylic acid from the 3,4-dicarboxylic acid at 170°C ⟨90JHC579⟩. 2-Aryl-5-hydroxy-3-oxo-2,3-dihydropyridazine-6-carboxylic acids are readily decarboxylated at 280°C in good yields and the corresponding methyl esters react readily with ammonia and hydrazine ⟨89JHC169⟩. The reactivity of pyridazine-3-carboxylates towards nucleophiles may be greater than that of pyridazine-6-substituents such as chloro, and the only practical synthesis of methyl 6-alkylaminopyridazine-3-carboxylate from the corresponding 6-chloro compound was to convert the ester into the primary amide, introduce the required alkylamino substituent, and then convert the primary amide back into the methyl ester with boron trifluoride/methanol ⟨92H(34)225⟩.

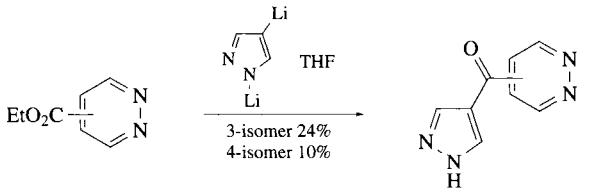
The Hammick reaction (*ipso* substitution by an electrophile of a carboxylic group under decarboxylation conditions) with pyridazine-3-carboxylic acid is not very successful, but it is considerably improved by the use of the TMS ester. Thus, trimethylsilyl pyridazine-3-carboxylate reacts with aldehydes to give, probably via an ylide, good yields of TMS protected alcohols (Scheme 50). The trimethylsilyloxy product is readily desilylated, so this process is equivalent to the reaction of a 3-pyridazinyl organometallic reagent with an aldehyde ⟨88T3281⟩.



Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

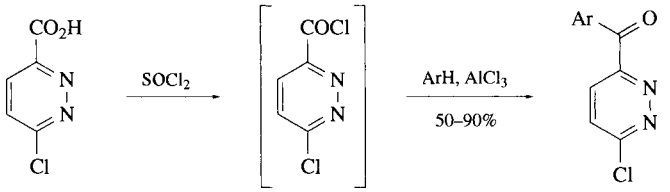
Scheme 50

Ortho-lithiated aniline derivatives can add to methyl 3-pyridazinecarboxylate to give ketones, though the yields are at best only moderate and reactions of the 4-analogue were still less successful ⟨90JHC1645⟩. Similarly, addition of dilithiopyrazole to ethyl pyridazinecarboxylates gives 4-pyrazolyl-3- and 4-pyridazinyl ketones (Equation (18)); tertiary alcohol formation is suppressed by inverse addition ⟨91JHC1189⟩.



(18)

3-Chloro-6-pyridazinecarboxylic acid chloride was prepared from the acid in thionyl chloride. The acid chloride is unstable, but direct reaction of the unpurified material in Friedel–Crafts acylation reactions (Scheme 51) gave moderate to excellent yields of aroylpyridazines ⟨92JHC1583⟩.

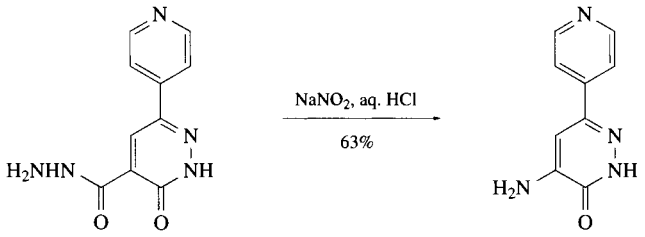


Ar = Ph, 4-FC_6H_4, 2-thienyl

Scheme 51

6.01.7.4 Carboxylic Amides

The ease of dehydration of pyridazine carboxamides, their hydrolysis, and Hofmann degradation to amines was outlined in CHEC-I ⟨84CHEC-I(3B)1⟩. More recently, in the early 1990s, the Curtius rearrangement (Equation (19)) of the 4-carboxylic hydrazide of 6-(4-pyridyl)-3(2*H*)-pyridazinone to give an aza analogue of amrinone has been reported ⟨90H(31)2163⟩.

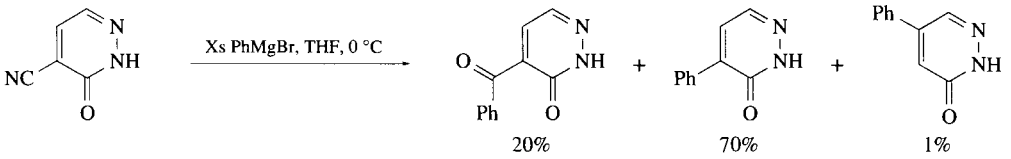


(19)

6.01.7.5 Nitriles

The reactions of nitriles to give amidines, amides and ketone derivatives were only briefly mentioned in CHEC-I ⟨84CHEC-I(3B)1⟩. The nitriles are reactive and, for example, 3-amino-4-pyridazinecarbonitriles are readily hydrolyzed in good yields to primary carboxamides with aqueous ammonia ⟨88JHC119⟩. The enzymatic hydrolysis of pyridazine nitriles using *Rhodococcus* species has been investigated ⟨92JHC93⟩.

While phenyllithium tends to attack the pyridazine ring of 3-cyanopyridazine to give a low yield of the ketone, phenylmagnesium bromide reacts normally to give 3-benzoylpyridazine in 59% yield ⟨89JHC1787⟩. In contrast, phenylmagnesium bromide reacts with 4-cyano-3(2*H*)-pyridazinone predominantly by addition to C-4 and elimination of cyanide, with addition to the nitrile a secondary reaction (Equation (20)). The addition is regioselective, with only 1% of the isomeric 5-phenyl-3(2*H*)-pyridazinone isolated, but this regioselectivity is not explained by electron densities or LUMO coefficients obtained by MNDO calculations on the anion of 4-cyano-3(2*H*)-pyridazinone, which must be the substrate for the reaction ⟨91T8573⟩. A similar reaction also occurs with 4,5-dichloro-3(2*H*)-pyridazinone (see Section 6.01.7.15.5).



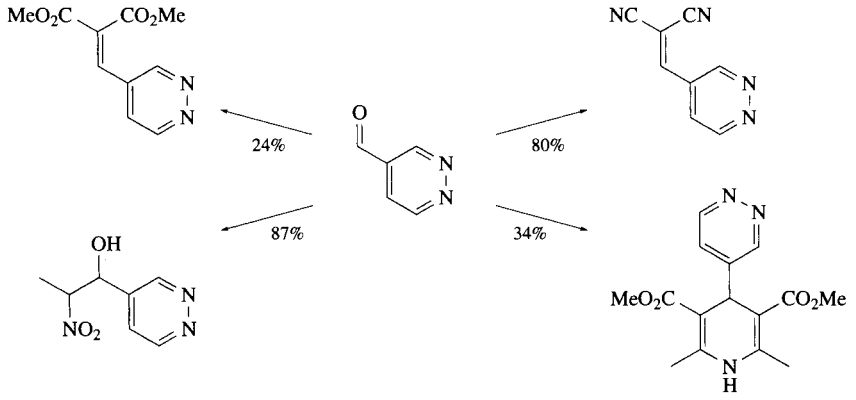
(20)

6.01.7.6 Aldehydes and Ketones

The normal reactivity of carbonyl derivatives (e.g., hydrazone formation of aldehydes, Wolff–Kishner reduction of ketones to alkylpyridazines, sodium in ethanol reduction of ketones to alcohols) was very briefly discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. Some examples of reactions are given here.

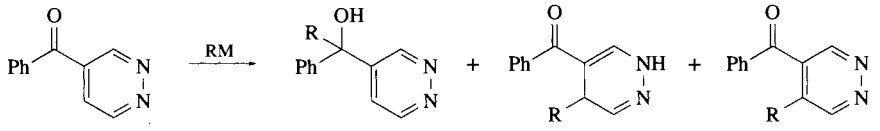
The reactivity of pyridazine-3- and 4-carbaldehydes towards active methylene reagents under the conditions of Knoevenagel, Wittig, and Hantzsch-type reactions has been examined. The 4-aldehyde reacts readily with malononitrile and methyl cyanoacetate, and less readily with triethyl phosphonoacetate, indane-1,3-dione and alkyl acetoacetates/ammonia (e.g., Scheme 52). Condensation with nitroethane is successful, but nitromethane gives an unstable intermediate which decomposes. The 3-aldehyde has similar reactivity to the 4-aldehyde, but some reactions are unsuccessful due to reduced reactivity, or instability of the products ⟨90JHC1313⟩.

3-Benzoylpyridazine is reduced with sodium borohydride in ethanol to α-(3-pyridazinyl)phenylmethanol in 95% yield and this alcohol is a useful intermediate for the preparation of other substituted alkyl derivatives ⟨89JHC1787⟩. 4-Aroylpyridazine ketones are similarly reduced to alcohols in high yield, but reaction with Grignard reagents is complicated by competing reaction of the pyridazine ring. Thus, 4-benzoylpyridazine with methylmagnesium iodide gave a 3 : 1 mixture of



Scheme 52

the alcohol and the 4-methyl-1,4-dihydropyridazine ketone (Equation (21)) and phenylmagnesium bromide gave the dihydropyridazine adduct as the only isolable product. Methyllithium gave a good yield of the alcohol, in keeping with the tendency of lithium reagents to add 1,2 rather than 1,4, and only traces of the 4-methyldihydropyridazine and its oxidation product were detected ⟨84JHC1727⟩.



RM	%	%	%
MeMgI	59	20	
MeLi	75	4	3
PhMgBr		33	

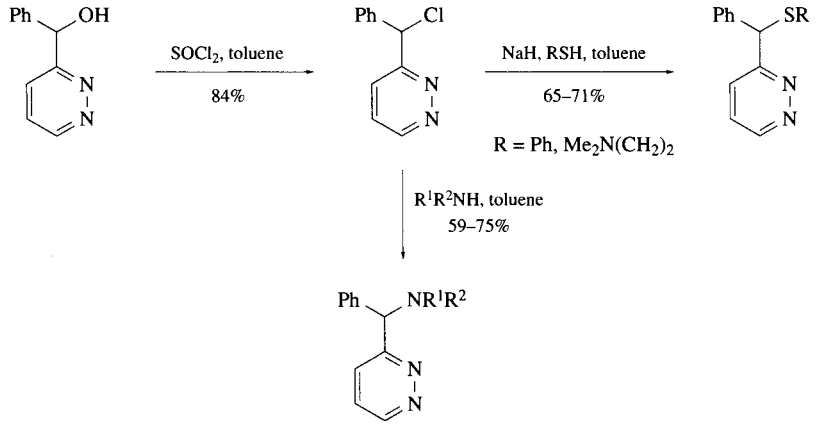
(21)

6.01.7.7 Other Substituted Alkyl Groups

The reactions of other substituted alkyl groups were not specifically addressed in CHEC-I except for oxidation and chlorination reactions of hydroxyalkyl groups ⟨84CHEC-I(3B)1⟩. α-(3-Pyridazinyl)phenylmethanol is easily converted with thionyl chloride into the chloride (Scheme 53) which undergoes successful displacement reactions with a range of amines and sulfur nucleophiles ⟨89JHC1787⟩. The only products isolated are those from direct displacement of chloride, in contrast to reactions with the 4-pyridazinyl isomer in which some *tele* substitution also occurs ⟨84M1171⟩. Chlorination of 3,6-dichloro-4-(2-hydroxy-1,1-dimethylethyl)pyridazine with thionyl chloride gives the corresponding fungicidal chloro compound in 76% yield as the final step in a potential industrial preparation ⟨88JOC5704⟩.

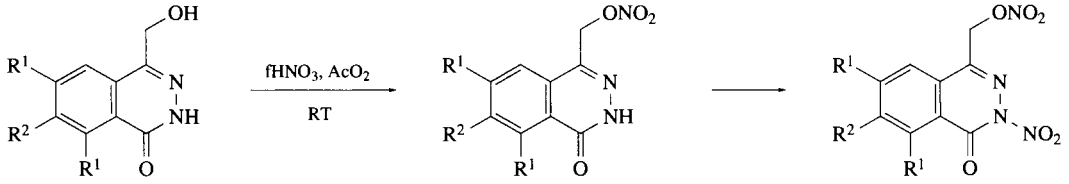
Nitration of 4-hydroxymethyl-1(2*H*)-phthalazinone and its derivative EG-626 with acetyl nitrate has been shown to give, after formation of the methyl nitrate esters, the N-2-nitro derivatives (Scheme 54). An earlier suggestion that the second nitration of EG-626 occurred on the phthalazinone oxygen was disproved by a combination of spectroscopic methods and an x-ray structure determination ⟨92CPB3327⟩.

Oxidative decyanation of phenyl-3-pyridazinylacetonitriles, by passing a brisk stream of oxygen into an aqueous sodium hydroxide/DMSO solution of the substrate containing triethylbenzylammonium chloride, is a convenient method for the synthesis of phenyl 3-pyridazinyl ketones (Scheme 55). Modified reaction conditions allow the one pot conversion of α-(6-chloropyridazin-3-yl)phenylacetonitrile into ketones with concomitant hydrolysis or methoxylation of the chloro substituent; the direct one pot preparation of 3,6-dibenzoylpyridazine from 3,6-dichloropyridazine is achieved in 48% yield ⟨93JHC1685⟩.



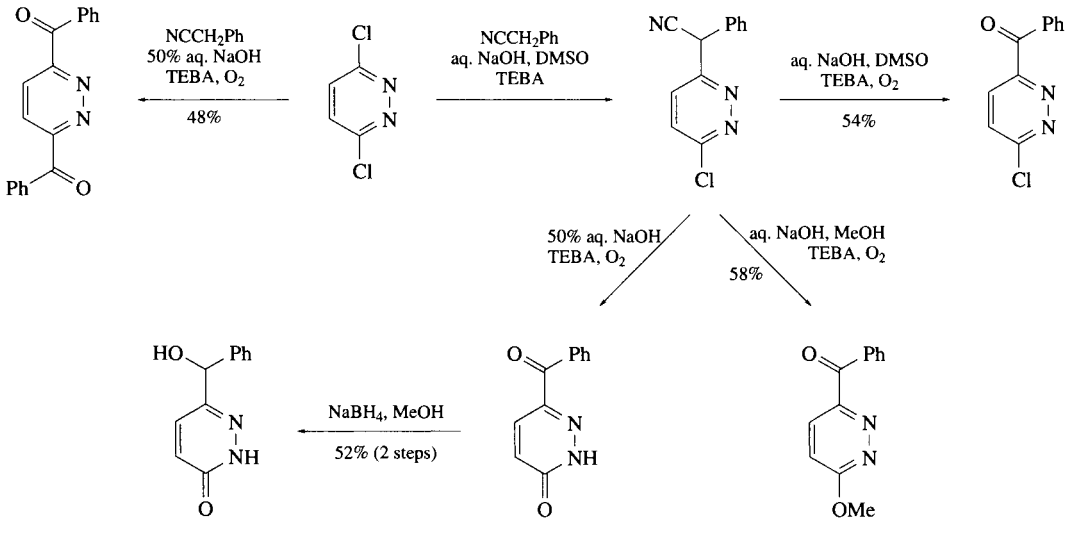
R^1 = H, Me; R^2 = Ph; R^1R^2 = $(CH_2)_4$, $(CH_2)_5$; R^1R^2 = $(CH_2)_2X(CH_2)_2$, X = O, NMe

Scheme 53



R^1, R^2 = H; R^1 = Me, R^2 = CO_2Et (EG-626)

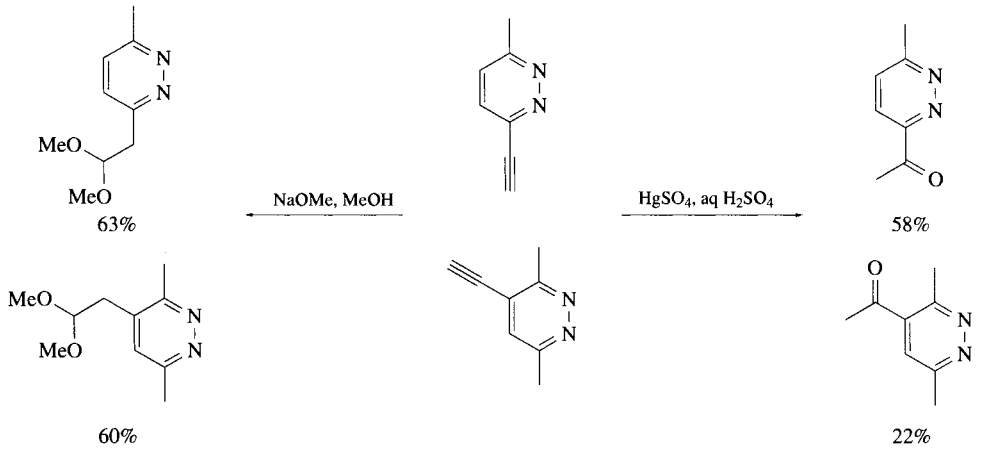
Scheme 54



Scheme 55

6.01.7.8 Alkynyl Groups

The reactivity of alkynyl substituents was not directly addressed in CHEC-I. Methoxylation of 3- and 4-ethynylpyridazines gives good yields of the 2,2-dimethoxyethyl derivatives via a double Michael addition (Scheme 56) while mercuric sulfate catalysed Markovnikov hydration gives methyl ketones ⟨84S245⟩.



Scheme 56

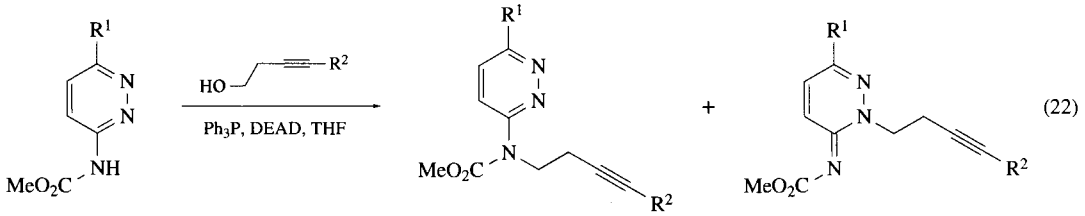
6.01.7.9 Amino and Imino Groups

6.01.7.9.1 Reaction of electrophiles at the amino group

In CHEC-I the acylation and sulfonylation of aminopyridazines was summarized ⟨84CHEC-I(3B)1⟩. These reactions usually occur at the amino group. However, with, for example, 4-amino-3,6-dimethoxypyridazine, tosylation also occurs on the ring nitrogens; with aminopyridazinones there is competition between oxygen and nitrogen. The formation of aminomethyleneamino derivatives by condensation with Vilsmeier and Brederick-type reagents was also described. Examples of these reactions are given in ⟨84S263, 84H(22)1545⟩.

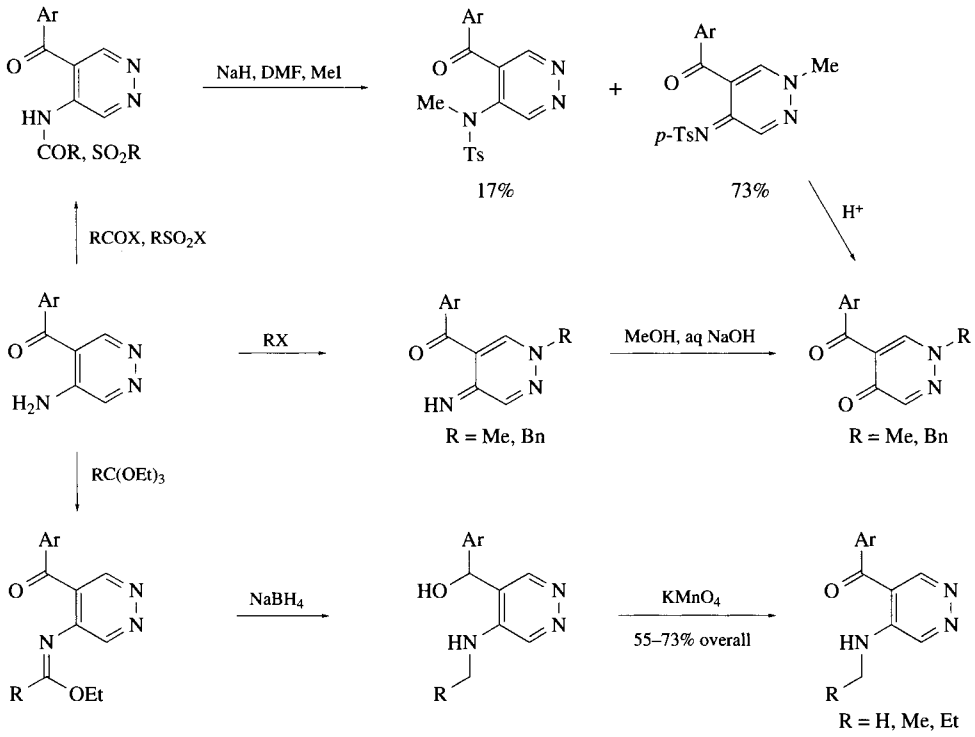
The orientation of reaction of aminopyridazines with electrophiles, and further reaction of the intermediates is illustrated by a study with 4-amino-5-aroylpyridazines. Acylation and sulfonylation occurs on the amino nitrogen, while alkylation occurs, as expected, at N-1; the acylamino derivatives are relatively unstable, but the toluenesulfonamide is quite stable to acid and to base. Methylation of the toluenesulfonamide gives a mixture of ring and amino alkylated products with the latter predominating. Hydrolysis of the ring *N*-alkylated compounds gives 4(1*H*)-pyridazinones (Scheme 57). Selective amino-alkylation of the 4-amino-5-aroylpyridazines is achieved via the imidate by reduction and subsequent oxidation of the alcohol ⟨85H(23)2651⟩.

Alkylation of 3-methoxycarbonylaminopyridazines with butynols under Mitsunobu conditions gave mixtures of side chain and ring alkylated products, which are difficult to separate, in a ratio of from 0.5–2 : 1 (Equation (22)). Other methods of direct alkylation using sodium hydride with alkyl halides and tosylates failed to afford any products ⟨84JOC2240⟩.

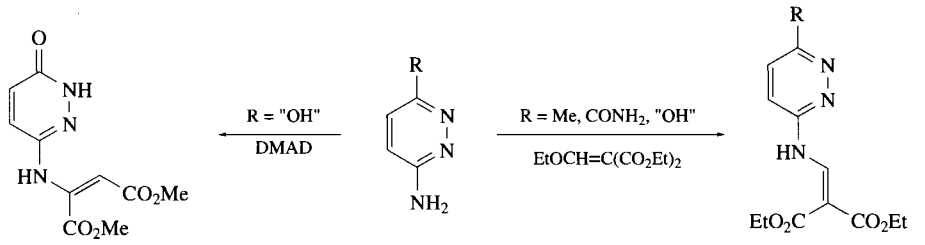


R^1 = H, Cl; R^2 = H, Me, CH_2O-THP

In contrast to the reaction of many 3-aminopyridazines with DMAD and acetylenemonocarboxylates, to give pyrimido[1,2-*b*]pyridazin-2(2*H*)-ones (see e.g., ⟨83H(20)2225⟩), 6-amino-3(2*H*)-pyridazinone reacts by a Michael-type addition to give the aminobutenedioate (Scheme 58), which can be cyclized in acetic acid to the isomeric pyrimido[2,1-*b*]pyridazin-4(4*H*)-one system. Condensation of 3-aminopyridazines and 6-amino-3(2*H*)-pyridazinones with diethyl ethoxymethylenemalonate proceeds in the expected Michael fashion to give aminomethylenemalonates which can be cyclized thermally ⟨88JHC1535⟩.



Scheme 57



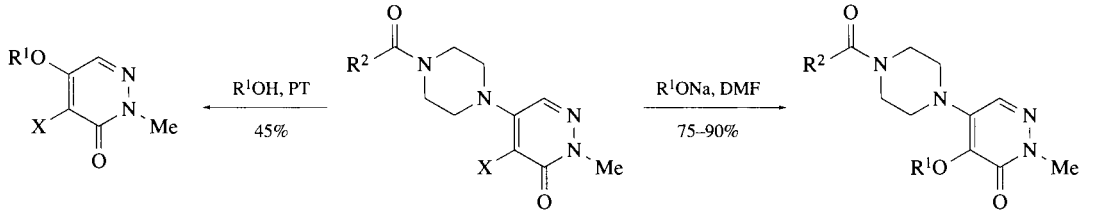
Scheme 58

6.01.7.9.2 Diazotization

Diazotisation was reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. In general the reaction has limited use because the diazonium salts are very susceptible to hydrolysis to give pyridazinones, with the exception of amino derivatives of *N*-oxides which may react normally to give, for example, chloropyridazine *N*-oxides.

6.01.7.9.3 Reaction of amino groups with nucleophiles

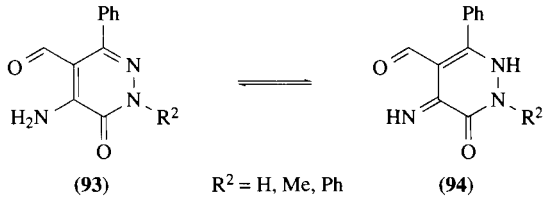
The displacement of amino groups with nucleophiles is not normally very favourable and was not directly addressed in CHEC-I. However, substituted amino groups can compete with halogen in nucleophilic displacement reactions depending upon conditions. Thus, in the preparation of 5-(substituted amino)-4-alkoxy-3(2*H*)-pyridazinones from 5-(substituted amino)-4-chloro or bromo-3(2*H*)-pyridazinones (Scheme 59), reaction with alcohols under phase transfer conditions resulted in displacement of the amino substituent, while alkoxides in dipolar aprotic solvent gave the required displacement of halide ⟨86AP(319)60⟩.



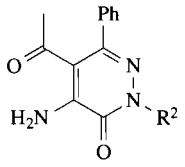
Scheme 59

6.01.7.9.4 Amino–imino tautomerism

The amino derivatives of (benzo)pyridazines usually exist as such. It is claimed that the 4-amino-5-formyl-3(2*H*)-pyridazinones (**93**) exist in solution in their imino forms (**94**), in contrast to the amino tautomers of the corresponding ketones (**95**), on the basis that the NH protons of (**94**) are observed as two well separated peaks in the proton NMR spectra (Equation (23)). However, an alternative explanation for this nonequivalence is that of restricted rotation in (**93**), due to intramolecular H-bonding between the formyl and amino groups. This is not seen with the ketones, for steric reasons ⟨91H(32)1173⟩.



(23)



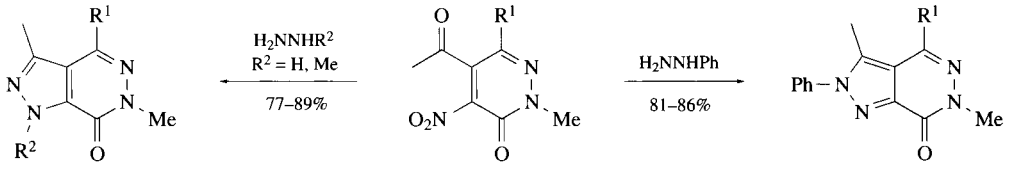
(**95**)

6.01.7.10 Other *N*-linked Substituents

6.01.7.10.1 Nitro groups

The reactivity of nitro groups was considered in CHEC-I ⟨84CHEC-I(3B)1⟩, largely from the aspect of reduction, which is readily accomplished by a range of methods. Reduction can be selective in the presence of *N*-oxides, though condensation products are sometimes produced.

The nitro group is an excellent leaving group and is displaced by methoxide along with one of the chlorines from 4,5-dichloro-6-nitro-3(2*H*)-pyridazinones ⟨83JHC369⟩. It is also readily displaced by amines and other nucleophiles from the 5-acetyl-4-nitro-3(2*H*)-pyridazinone (**96**). In reactions of (**96**) with hydrazines (Scheme 60) the more nucleophilic nitrogen first displaces the nitro group and then condensation of the second hydrazino amino function occurs to give pyrazolopyridazinones ⟨89H(29)1595⟩. 4-Nitropyridazine is reportedly too unstable to be isolated and decomposes to give, *inter alia*, 4(1*H*)-pyridazinone and nitrous fumes, but can be prepared and used in solution ⟨88JHC831⟩.



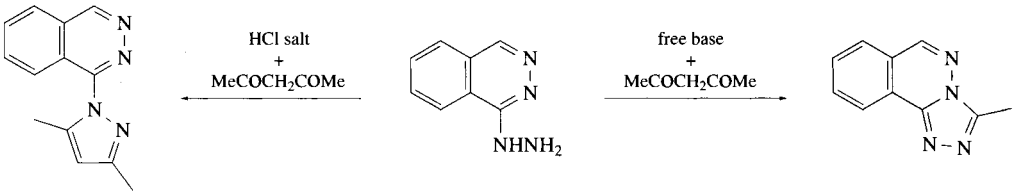
(96)
R^1 = Me, Ph

Scheme 60

6.01.7.10.2 Hydrazino groups

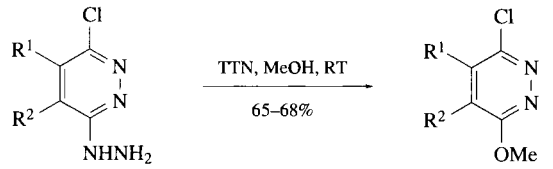
Hydrazinopyridazines were reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. Hydrazino groups react readily to give hydrazones, acyl derivatives, and azides, but when adjacent to a ring nitrogen some of these derivatives react further to give cyclic products, for example, tetrazolo[1,5-*b*]pyridazines. Reductive cleavage of hydrazino groups is a practical route to aminopyridazines from less reactive halo precursors. A lot of work has been carried out on hydrazino derivatives of (benzo)pyridazines as many show marked antihypertensive activity.

The condensation of 1-hydrazinophthalazine with polycarbonyl compounds can give a variety of products (open chain, fused cyclic, and nonfused cyclic) depending in particular on the presence of acid ⟨83JHC1231⟩ and this has led to some inconsistencies in the literature. This type of reaction has now been studied in detail and, for example, the hydrochloride salt of hydralazine with acetylacetone has been shown to give 1-(3,5-dimethylpyrazolyl)phthalazine, while the free base reacts (Scheme 61) to give a triazolo[3,4-*a*]phthalazine ⟨87H(26)1177, 87H(26)1277, 87H(26)1853⟩.



Scheme 61

Oxidative cleavage of hydrazino substituents in pyridazines and phthalazines proceeds with thallium trinitrate in methanol, under mild conditions (Equation (24)) to give the corresponding methoxy derivatives in moderate yields ⟨95JOC1466⟩.



(24)

R^1, R^2 = H, H; H, Me; R^1R^2 = $(CH{=}CH)_2$

6.01.7.11 Hydroxy and Oxo Groups

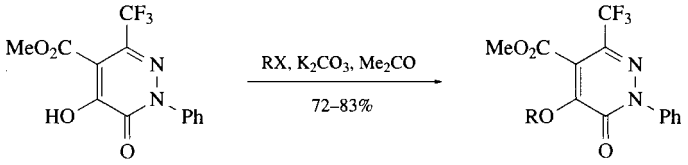
Information on the reactivity of hydroxy and oxo groups is presented in CHEC-I ⟨84CHEC-I(3B)1⟩. Alkylation generally favours *N*-substitution though the use of different reagents and conditions, for example silver salts, may increase the degree of *O*-substitution. Cinnolin-4(1*H*)-ones can give pseudo bases by alkylation at N-2. Other subjects covered include alkylation when more than one HO/C=O group is present, the potential complication of thermal $O \rightarrow N$ methyl group migration, acylation (generally on nitrogen), and other types of reaction on nitrogen such as Michael addition and Mannich reaction, and the addition of Grignard reagents to phthalazin-1(2*H*)-ones to give 1-aryl derivatives.

6.01.7.11.1 Hydroxy groups and hydroxy-oxo tautomeric equilibria

All of the monohydroxy derivatives of the diazine ring of pyridazine and its benzo derivatives exist predominantly in the oxo form, while the dihydroxy derivatives of pyridazine and phthalazine exist in the monohydroxy, monoketo forms (see Section 6.01.4.5). All of these derivatives are weak acids, with acidity ranging from that of a simple phenol for 3(2*H*)-pyridazinones to that of alkanoic acids for those with second hydroxy groups and/or strong electron withdrawing substituents (see Section 6.01.4.2). The acidity and reactivity of the hydroxy-oxo groups often hinders successful reaction of other substituents, particularly where strong bases are used. In the event that the free NH is required in the final product so that simple blocking with alkyl or aryl residues is not acceptable, then a suitable protecting group must be chosen. However, many nitrogen protecting groups are insufficiently stable on the amide pyridazinone function, while *N*-benzyl is often difficult to remove; benzyloxymethyl has been used ⟨93H(36)519⟩. An alternative approach is to use *O*-methyl derivatives as protected azinones, but these are not readily available directly from the azinones.

6.01.7.11.2 Reactions with electrophiles

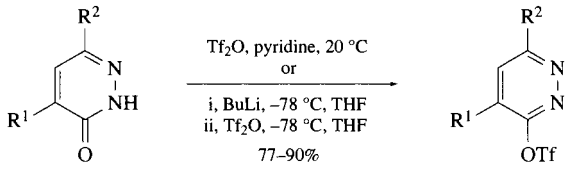
While alkylation of pyridazinones/hydroxypyridazines with alkyl halides and base usually gives predominantly *N*-alkylated products, reaction of the hydroxypyridazinone (**97**) with a variety of alkyl halides in acetone/potassium carbonate (Equation (25)) gave high yields of the *O*-alkyl derivatives as the only products. In this example steric factors and the electron density of the trifluoromethyl group may hinder the approach of the electrophile to the pyridazine nitrogen ⟨93JHC1501⟩. Diazomethane alkylation of 5,6-dichloro-3(2*H*)-pyridazinone preferentially gave N : O methylation in a ratio of about 3 : 1, contrary to earlier reports of selective *O*-methylation ⟨87CPB350⟩.



(25)

(**97**) R = Me, Et, Pr^i, CH_2CO_2Me

3-Pyridazine triflates are readily prepared in high yield by reaction of triflic anhydride either with 3(2*H*)-pyridazinones in pyridine at room temperature or with the lithium salts in THF at −78 °C (Equation (26)). These triflates, which are white crystalline solids stable at 0 °C, are useful in palladium catalysed coupling reactions ⟨94H(38)1273⟩.



(26)

R^1 = H, Me; R^2 = Me, Ph

6.01.7.11.3 Reactions with nucleophiles

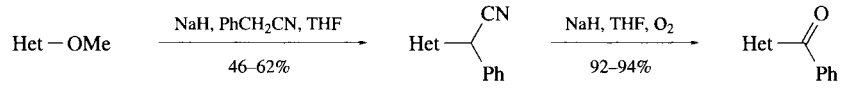
The most common type of nucleophilic reaction of the hydroxy-oxo derivatives is the formation of chloro compounds or thiones by reaction with phosphorus reagents, but these are dependent upon an initial electrophilic attack of the oxygen at the phosphorus, followed by nucleophilic displacement of the oxygen substituent favoured by the formation of the P=O bond. For the formation of chloropyridazines, phosphorus oxychloride is most commonly used, while the pentachloride may be required for some phthalazine derivatives. Phosphorus pentasulfide is used for conversion into thiones, though the use of Lawesson's reagent is claimed to be advantageous with 3(2*H*)-pyridazinones ⟨82H(19)2283⟩. Hydroxy groups are not usually susceptible to direct nucleophilic

displacement. However, while that in 2-aryl-6-methoxycarbonyl-5-hydroxy-3(2*H*)-pyridazinones cannot be displaced by amine nucleophiles such as aniline or benzylamine ⟨90JHC471⟩, that in a 4-hydroxy-5-nitro-3(2*H*)-pyridazinone has been displaced by ammonia ⟨84JHC481⟩.

6.01.7.12 Other *O*-Linked Substituents

6.01.7.12.1 Alkoxy and aryloxy groups

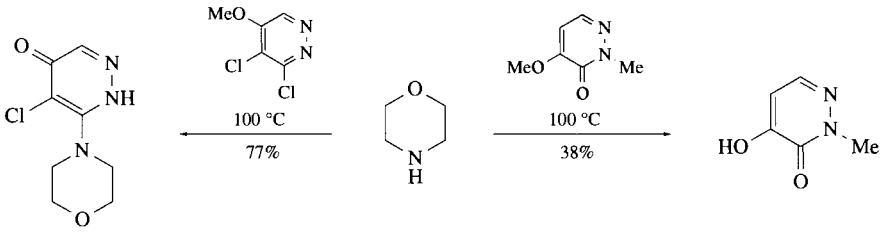
The reactivity of alkoxypyridazines (hydrolysis to pyridazinones and rearrangement of *N*-oxides to *N*-methoxypyridazinones) was summarized in CHEC-I ⟨84CHEC-I(3B)1⟩. While methoxy is not normally regarded as a good leaving group, phenylacetonitrile anion has been shown to displace methoxy from pyridazines, phthalazines, and cinnolines (Scheme 62) in moderate yields. Phenylacetonitrile is much more effective than, for example, malononitrile, and the α-phenyl(heteroaromatic)acetonitriles can be converted into benzoylheteroaromatics in high yield by passing oxygen through THF solutions of their sodium salts, making this a useful two-step preparation of benzoyl derivatives ⟨90H(31)895⟩.



Het = 3- and 4-pyridazinyl, 4-cinnolinyl, 1-phthalazinyl

Scheme 62

O-Demethylation has been observed as well as, or instead of, nucleophilic displacement on reaction of 3,4,5-chloro/methoxy pyridazines and 4,5-chloro/methoxy-2-methyl-3(2*H*)-pyridazinones with morpholine (e.g., Scheme 63). Demethylation was observed at all ring positions, but usually adjacent to chlorine or a carbonyl group, and *N*-methylmorpholine was isolated, consistent with demethylation rather than hydrolysis. The demethylation can also occur with other primary and secondary amines such as diethylamine, butylamine, and piperidine, but not with pyrrolidine and aniline ⟨87H(26)1⟩. 3-Phenolic ethers of pyridazines are resistant to reductive cleavage of the aryl ether bond under the conditions of phase transfer catalytic hydrogenolysis ⟨82T3775⟩.

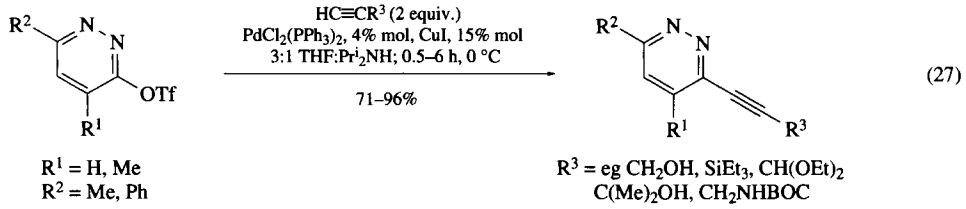


Scheme 63

6.01.7.12.2 O-Triflates

Because 3-chloropyridazines were not found to be very reactive in palladium coupling reactions and the bromo and iodo analogues are not readily available, the preparation and use of triflate esters of pyridazines have been developed. The readily prepared triflates undergo coupling with terminal acetylenes in the presence of palladium and copper iodide (Equation (27)). Reactions are rapid, normally complete in 0.5 to 6 hours at room temperature, and yields are high. In a comparative experiment 3-chloro-4-methyl-6-phenylpyridazine with 3,3-dimethyl-3-hydroxy-1-propyne gave only a 33% yield of 3-(3,3-dimethyl-3-hydroxy-1-propynyl)-4-methyl-6-phenylpyridazine after 12

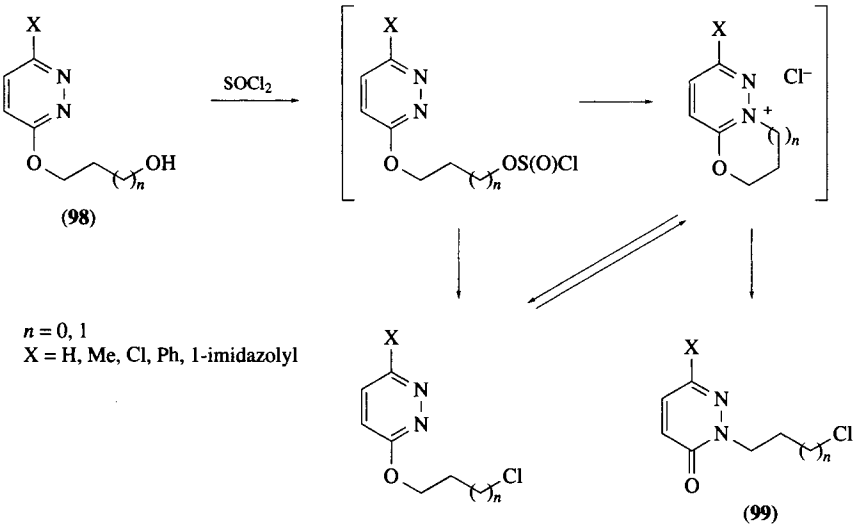
hours reaction in THF under reflux, while the corresponding triflate gave an 80% yield in 3 hours at room temperature ⟨94H(38)1273⟩.



(27)

6.01.7.13 Hydroxyalkyl Substituents Attached via Nitrogen or Oxygen

Chlorination of 3-(3-hydroxypropoxy- or 2-hydroxyethoxy)-6-substituted pyridazines (**98**) with thionyl chloride generally results in concomitant rearrangement to give 2-(chloroalky)-3(2*H*)-pyridazinones (**99**). ^{1}H NMR studies showed that the rearrangement is intramolecular and proceeds via fused ring intermediates (Scheme 64). While simple chlorination without rearrangement was observed with the 6-unsubstituted-3-hydroxyalkoxypyridazines, this was at best only a side reaction with a range of 6-substituted derivatives ⟨89H(29)67⟩.

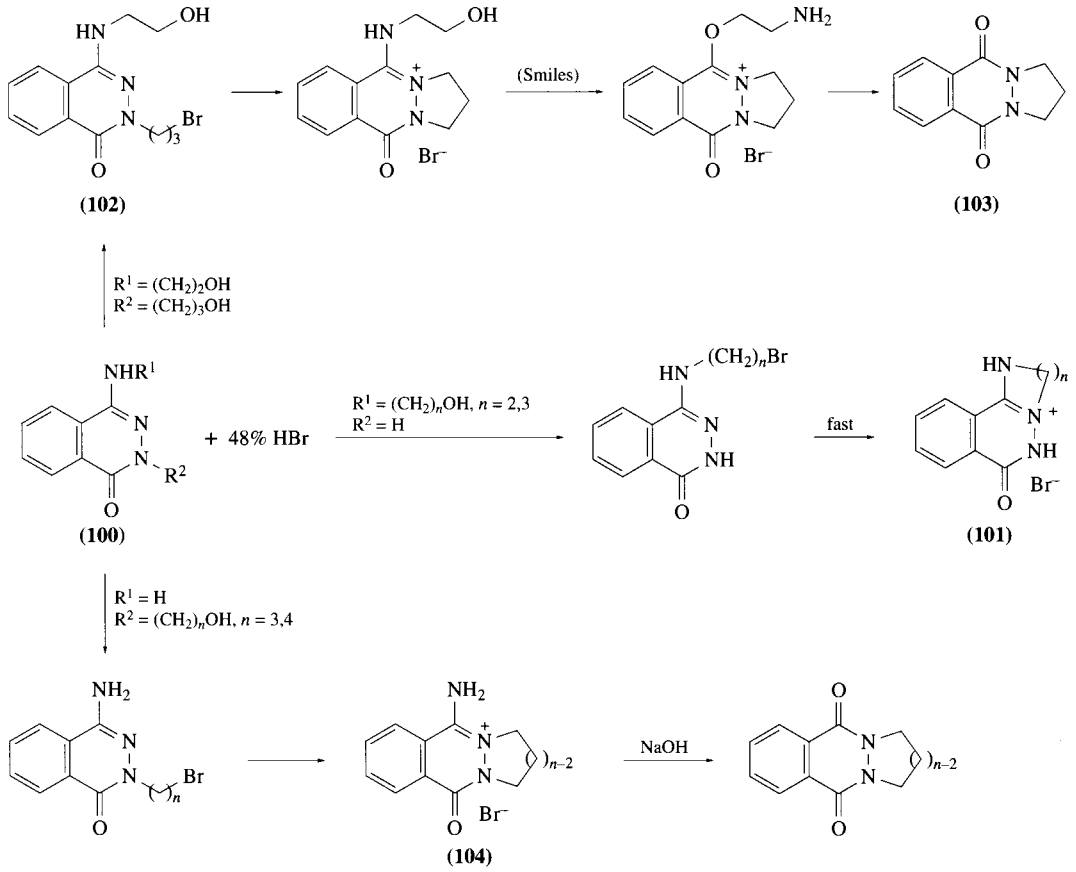


Scheme 64

Side chain bromination of 4-(hydroxyalkylamino)-1(2*H*)-phthalazinones (**100**, R^2 = H) with HBr (which is followed by rapid intramolecular quaternization to give (**101**)) is much slower for the ethyl than for the propyl analogue due to the reduced basicity of the hydroxy group closer to the amidinium centre (Scheme 65); no such rate differences were observed for the 2-(hydroxyalkyl) derivatives (**100**, R^1 = H). With 2-(3-hydroxypropyl)-4-(2-hydroxyethylamino)-1(2H)-phthalazinone, intramolecular alkylation of the initially formed 2-(3-bromopropyl) derivative (**102**) leads, probably via a Smiles rearrangement, to the phthalazinedione (**103**). Some support for the Smiles rearrangement is provided by reaction of the primary amino analogues (**100**, R^1 = H) which give quaternary products (**104**) that are stable under the reaction conditions and require alkaline hydrolysis to form diones ⟨91T4457⟩. For detailed studies of related reactions, see, for example, ⟨89T5539, 92T1507⟩.

6.01.7.14 *S*-Linked Substituents

The reactivity of sulfur derivatives was discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. The major reactions of these substituents all take place at sulfur including alkylation and arylation (by a wide range of



Scheme 65

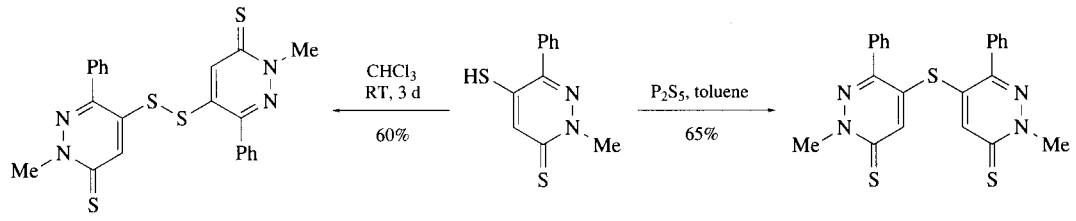
activated halides), acylation, and Michael addition. Oxidation of thioethers readily gives sulfoxides and sulfones, while thiols can give disulfides. Displacement of thiones and thioethers occurs much more readily than with oxygen linked substituents.

6.01.7.14.1 Thiol-thione tautomerism

Monothiol derivatives of the (benzo)pyridazines all exist predominantly in the thione form and dithiones as the monothione, monothiol. They are more acidic than the corresponding (benzo)-pyridazinones.

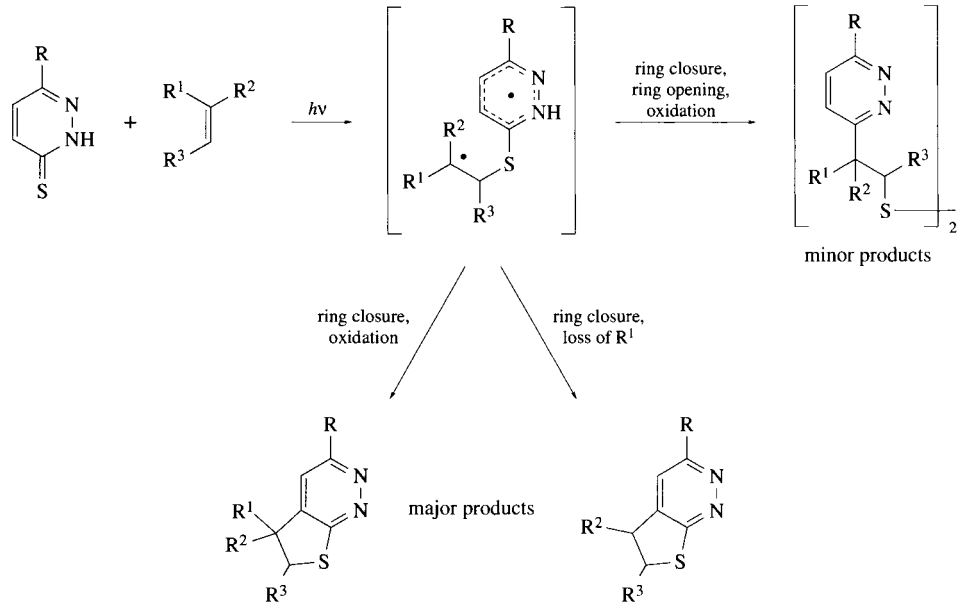
6.01.7.14.2 Thiones

Some of the potential problems in utilising thiol derivatives, aerial oxidation to disulfides and also displacement of one thiol group by another, are illustrated (Scheme 66) for 5-thiol-3(2*H*)-pyridazinethiones ⟨88JHC1719⟩.



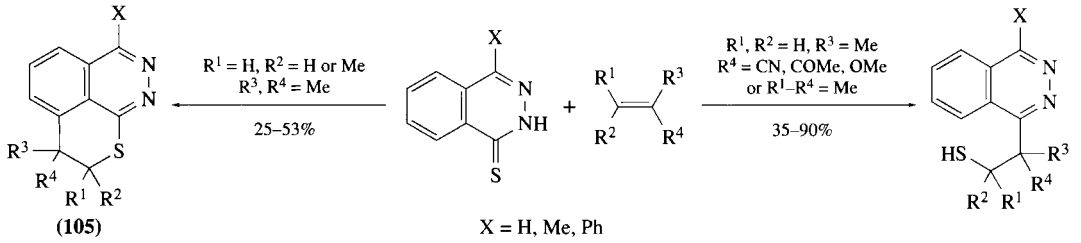
Scheme 66

Photoaddition of alkenes to pyridazin-3(2*H*)-thiones gives two types of product via initial [2 + 2] addition of the thione to the alkene to give a diradical (Scheme 67). Subsequent bond formation between the terminal alkyl radical and the pyridazine radical occurs either at C-3, to give a spiro intermediate which undergoes ring opening and oxidation to minor disulfide products, or at C-4 to give thienopyridazine derivatives which undergo aromatization of the pyridazine by oxidation or loss of an appropriate leaving group to give the major products ⟨86CPB3061⟩.



Scheme 67

Phthalazine-1(2*H*)-thione reacts in a similar manner with alkenes by [2 + 2] addition, but the intermediate diradical either cyclizes on to the *peri*-position to give, after oxidation, the fused tricyclic system (**105**), or undergoes hydrogen transfer to give open chain sulfides (Scheme 68). The formation of the fused products is favoured by stabilization of the terminal alkyl radical by geminal methyl substitution ⟨90CPB1205⟩.

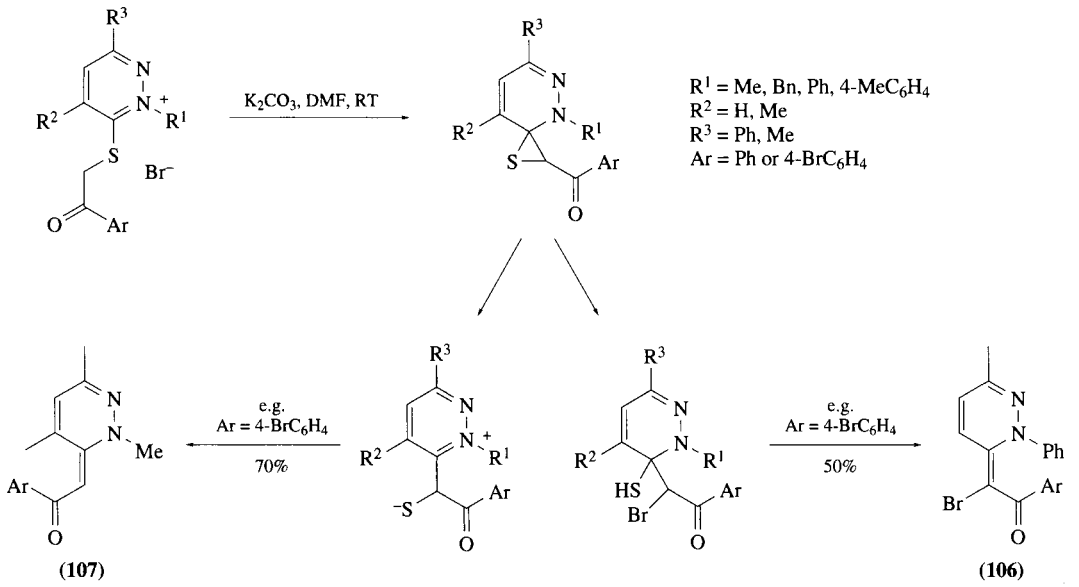


Scheme 68

6.01.7.14.3 Alkylthio, alkylsulfinyl and alkylsulfonyl groups

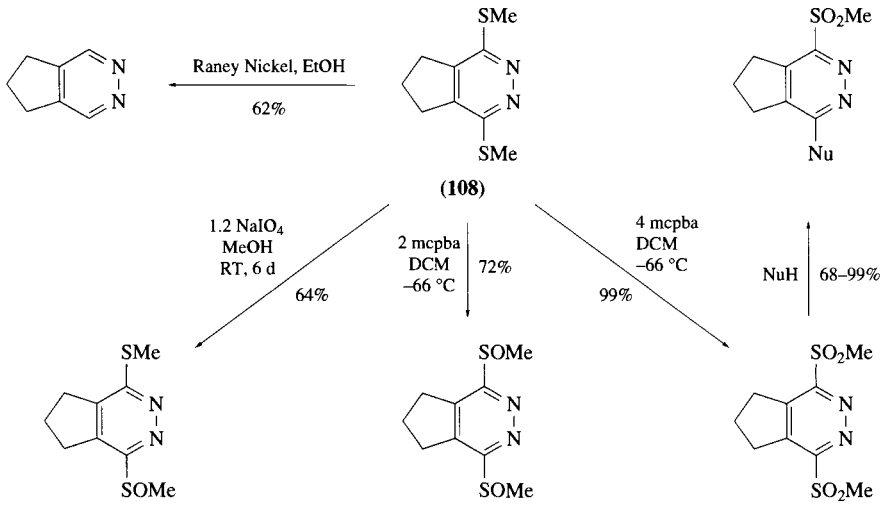
Sulfur can be lost from 2-substituted-3-(phenacylthio)pyridazinium bromides by treatment with a nonnucleophilic base to give two types of phenacylidene product, probably formed via a common thiirane intermediate (Scheme 69). The outcome of the reaction is affected by substitution in the pyridazine ring: 2-phenyl-3-(phenacylthio)pyridazinium bromides tend to give the brominated phenacylidene products (**106**) via ring opening of the thiirane by bromide and loss of sulfur effectively as hydrogen sulfide. Bromide is not involved in the reaction of the 2-methyl analogues and the nonbrominated products (**107**) are formed by the extrusion of sulfur. It is suggested that electron

donor 2-substituents give the nonbrominated product via intramolecular ring opening of the thiirane by the nitrogen lone pair, while electron attracting substituents are more likely to undergo intermolecular ring opening by bromide, but mixtures are obtained from the 2,6-diphenyl and 2-(4-methylphenyl)-6-methyl substrates ⟨83T2295⟩.



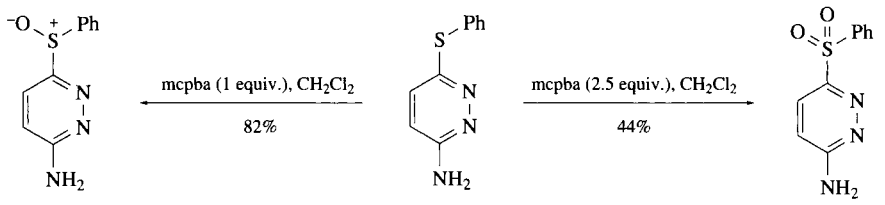
Scheme 69

Conditions for the reductive desulfurization of 3,6-bis(methylthio)pyridazine (**108**), (Scheme 70) with Raney nickel have been developed as part of a synthetic approach to 4- or 4,5-disubstituted pyridazines based on Diels–Alder reactions of 3,6-bismethylthio-1,2,4,5-tetrazine. Selective oxidation of (**108**) can give the monosulfoxide, bis(sulfoxide), and bis(sulfone) depending on the conditions used, and the bis(sulfone) was susceptible to nucleophilic displacement of one sulfonyl group. These studies were limited to the symmetrical substrate (**108**) ⟨88JOC1415⟩.



Scheme 70

Other examples of selectivity in reactions of thio derivatives include the dealkylation of 3-*t*-butylthiopyridazines in the presence of a 5-*t*-butylthio group with hydrochloric acid ⟨88JHC1719⟩ and oxidation of 3-amino-6-phenylthiopyridazine with one equivalent of MCPBA to give the sulfoxide in excellent yield (Scheme 71) with the sulfone as a byproduct; the use of an excess of MCPBA gave only a moderate yield of the sulfone ⟨93JHC1365⟩.



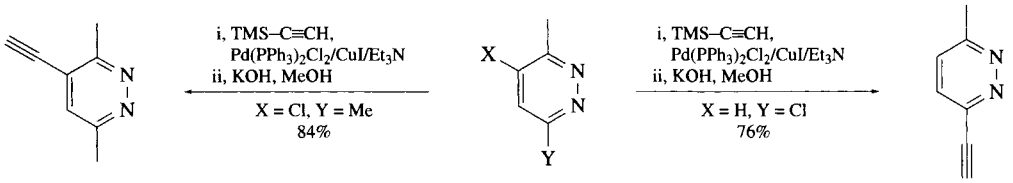
Scheme 71

6.01.7.15 Halogen Atoms

This is an important topic, because of the reactivity of halo substituents and the availability of a wide range of substrates. It was reviewed with particular reference to pyridazines in CHEC-I ⟨84CHEC-I(3B)1⟩. An early summary ⟨68M15⟩ of the preparation and derivatization of chloropyridazines and pyridazinones is still useful. Halogens, usually chlorine, are readily displaced from all pyridazine positions by a wide range of nucleophiles, though reactivity is reduced as halogens in polyhalo substrates are replaced and selective monosubstitution and sequential substitutions are often possible. The order of reactivity in pyridazines is 4,5 > 3,6; with pyridazine *N*-oxides it is 5 > 3 > 6 > 4; and in 3(2*H*)-pyridazinones the order is 5 > 4 > 6, though in many examples mixtures may be obtained. In addition to nitrogen, oxygen, and sulfur nucleophiles, carbon nucleophiles may also displace halogens, and early examples of nickel- and palladium-catalyzed coupling reactions are given in CHEC-I in addition to displacement by Grignard and active methylene compounds such as sodiomalononitrile ⟨84CHEC-I(3B)1⟩.

6.01.7.15.1 Replacement of halogen by a metal, or by coupling

2-Thienylmagnesium bromide is reported to undergo an exothermic coupling reaction with 3,6-dichloropyridazine in the presence of catalytic bis(1,3-diphenylphosphino)propane nickel(II) to give 3,6-bis(1-thienyl)pyridazine in 90% yield ⟨85JHC719⟩. An ethynyl substituent can be introduced in place of chlorine at C-4 or C-3 of pyridazines via palladium-catalysed coupling of trimethylsilylacetylene (Scheme 72); yields are high and the trimethylsilyl group is readily removed ⟨83S312⟩. Palladium-catalysed coupling with alkynes is also successful with ethyl 6-chloropyridazine-3-carboxylate, to give intermediates to alkyl and arylethyl derivatives ⟨92H(34)225⟩, and with 1-chlorophthalazine ⟨91CPB2009⟩.

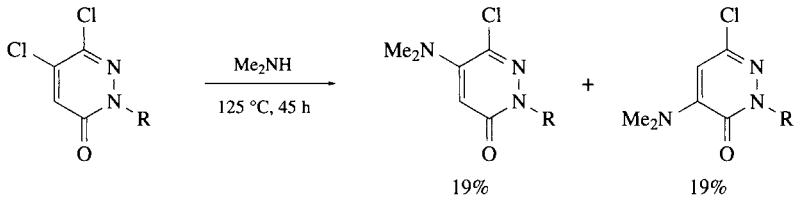


Scheme 72

6.01.7.15.2 Reactions via heteroarynes

Reaction of 2-(tribenzoylribofuranosyl)-5,6-dichloro-3(2*H*)-pyridazinone with neat dimethylamine gave a mixture of the 4- and 5-dimethylamino debenzoylated derivatives (Equation (28)).

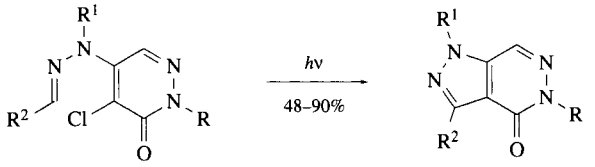
Reaction may be by an aryne mechanism, or the unexpected product may arise via dimethylamine addition to C-4 and loss of HCl from the dihydro adduct ⟨83JHC369⟩.



(28)

6.01.7.15.3 Radical reactions

Hydrazones of 4-chloro-5-hydrazino-3(2*H*)-pyridazinones undergo photolytic cyclization (Equation (29)) to give pyrazolo[3,4-*d*]pyridazinones ⟨84JHC1249⟩.



(29)

R = Me, Ph, Bn, H ; R^1 = Me, Bn; R^2 = H, Ph, Me, subst. Ph

6.01.7.15.4 ANRORC reactions

The possible involvement of an ANRORC mechanism in the nucleophilic displacement of halogen by hydrazine from a series of 3-halopyridazines and 4-halophthalazines was studied using ^{15}N labelling and mass spectral analysis. With pyridazine substrates the ANRORC mechanism operated to the extent of 17–30%, but it was not observed at all with the phthalazines ⟨83JHC1259⟩.

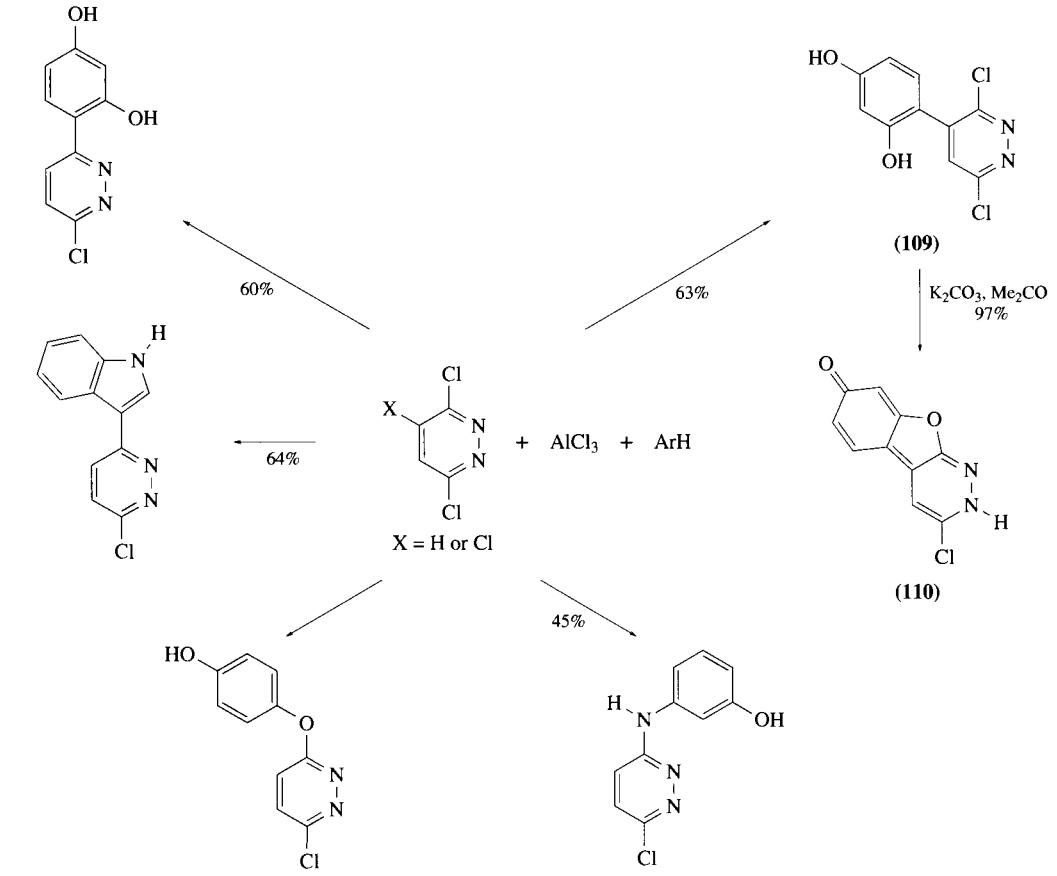
6.01.7.15.5 Nucleophilic displacement by classical S_{AE} mechanism

The reactivity of 3,6-dichloropyridazine toward nucleophiles is enhanced by initial complexation with aluminum trichloride and it is then susceptible to arylation with the relatively powerful aromatic nucleophiles resorcinol and indole, but not, as previously reported, with hydroquinone, which leads to ether formation (Scheme 73); 3-aminophenol gave 6-chloro-3-(3-hydroxyanilino)pyridazine. The reaction is thus rather limited, but it has been extended to 3,4,5-trichloropyridazine, which with resorcinol gave 3,6-dichloro-4-(2,4-dihydroxyphenyl)pyridazine (**109**) along with small amounts of the 3- and 6-aryl isomers, in line with the normal regioselectivity seen with 3,4,6-trichloropyridazine. Intramolecular nucleophilic displacement of the 3-chloro substituent of (**109**) occurs readily to give the benzofuro[2,3-*c*]pyridazine (**110**) ⟨90JOC5418⟩.

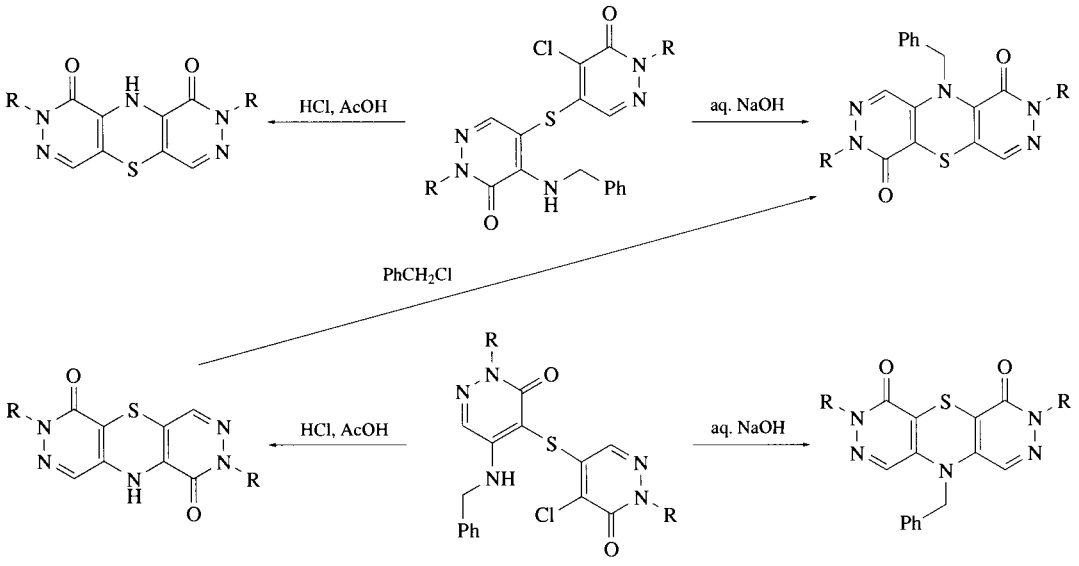
1,4-Addition of Grignard reagents to pyridazines has been exploited in what amounts to nucleophilic displacement of chlorine by aromatic rings: 4,5-dichloro-3(2*H*)-pyridazinone reacts with ArMgBr regioselectively to give 4-aryl-5-chloro-3(2*H*)-pyridazinones in good yield. Phenyllithium can also be used, but reaction with alkyl Grignard reagents was unsuccessful; the course of the reaction is unaffected by methylation of the pyridazinone ⟨85EUP138344, 94MI 601-01⟩.

Reactions of dihalopyridazines with bidentate nucleophiles to give cyclic products directly or via a Smiles type rearrangement was mentioned in CHEC-I ⟨84CHEC-I(3B)1⟩ and it has been studied further. In one example, cyclization reactions of the *N*-benzylated intermediates from reaction of 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone with 4-amino-5-thio- and 5-amino-4-thio-2-methyl-3(2*H*)-pyridazinones showed that each intermediate can give either of two products depending upon conditions (Scheme 74, illustrated for 4-chloro intermediates). In acid an Ullmann-type coupling reaction occurs, while in base a Smiles-type rearrangement gives the isomeric product via *ipso* attack, ring opening and ring closure ⟨84H(22)675⟩.

Nucleophilic fluorination of chloropyridazines has been demonstrated. Thus, with KF/crown



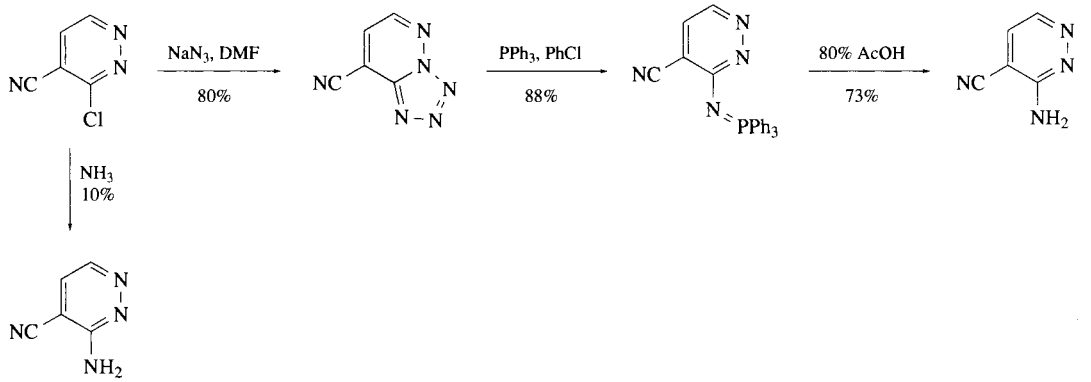
Scheme 73



Scheme 74

ether the more reactive chlorine in a 2-substituted 5,6-dichloro-3(2*H*)-pyridazinone is displaced to give a 27% yield of the corresponding 5-fluoro-6-chloro derivative ⟨83JHC369⟩, while 3-chloro-6-phenylpyridazine with an excess of neat tetrabutylphosphonium hydrogen fluoride at 100 °C gave 89% of the corresponding 3-fluoro derivative ⟨92H(34)1507⟩.

A range of strategic approaches to the displacement of halogens has been illustrated in the review period, in addition to, for example, using amines in increasing order of nucleophilicity and boiling point for sequential displacements, and using a more powerful nucleophile such as hydrazine to introduce a primary amino function in a two-step process. The chlorine in 3-chloro-4-cyanopyridazine is readily displaced by aniline, but not by ammonia; the primary amine can be made in 51% overall yield (Scheme 75) by reaction with sodium azide to give the tetrazolo[1,5-*b*]pyridazine, treatment with triphenylphosphine, and hydrolysis of the intermediate triphenylphosphoranylamino compound ⟨88JHC119⟩. The reactivity of 5-chloro-6-phenyl-3(2*H*)-pyridazinone was too low for the effective preparation of 5-(aroylpiperazine) derivatives by direct displacement, but reaction with the more reactive piperazine followed by aroylation was successful ⟨90H(31)1967⟩. The 5-chloro substituent in a 4,5-dichloro-3(2*H*)-pyridazinone can be displaced by nitro using sodium nitrite in DMF, and the remaining chloro group is then very readily replaced by hydroxy under acidic conditions ⟨84JHC481⟩.



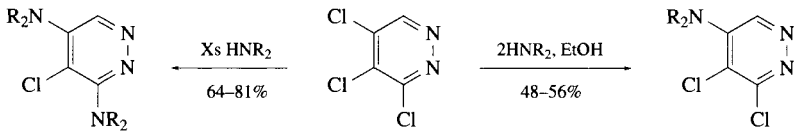
Scheme 75

(i) Aspects of selectivity in reactions of polyhalo compounds

Regioselective displacement of chlorine from 4,5-dichloro-3(2*H*)-pyridazinones has been shown to be exceptionally dependent on the solvent and has been the subject of several studies. With 2-methyl and 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinones as substrates, reaction with alkoxides occurs selectively at C-4 in less polar solvents (carbon tetrachloride, dioxane, THF, *t*-BuOH, pyridine), is nonselective in solvents of intermediate polarity (acetone, 2-propanol), and is selective for C-5 in polar solvents (EtOH, MeOH, DMF, DMSO) with the exception of acetonitrile, in which mixtures are obtained. Similar selectivity was seen with phenol and ethanethiol, but with thiophenol and ethyl 2-thioacetate selectivity was less pronounced and 4,5-disubstitution was significant ⟨88JHC1757⟩. Similarly, 4,5-dichloro-2-substituted-3(2*H*)pyridazinones with sodium alkoxides in toluene gave 66–92% of 4-alkoxy derivatives (with up to 10% of the 5-alkoxy isomers) while use of sodium carbonate in the appropriate alcohol gave 59–96% of the 5-alkoxy products ⟨85MI 601-01⟩. Solvent-dependent regioselectivity of nucleophilic attack was also seen in reactions of *N*-benzylaminoethanol with 2-(benzyloxymethyl)-4,5-dichloro-3(2*H*)-pyridazinone, which gave preferentially 4- or 5-[*N*-benzyl-*N*-(2-hydroxyethyl)amino] derivatives in nonpolar (toluene) or polar (water) solvents, respectively ⟨93H(36)519⟩. The kinetic and theoretical aspects of the regioselectivity in these nucleophilic displacements was studied using a range of benzylamines and 4,5-dichloro-2-methyl- or -phenyl-3(2*H*)-pyridazinone. Orbital coefficients, energies, and net atomic charges were calculated for the pyridazinones and benzylamines by the AM1 method, and kinetic parameters determined by ^{1}H-NMR using deuterated ethanol and toluene as solvents. Preferential attack at C-5 is consistent with the charge difference between C-5 and C-4, with the latter the more negative. The reversed regioselectivity seen in toluene is explained by the greater dipole moment of the C-5 transition state, which therefore requires a greater degree of solvation than that of C-4. Increased solvation results in an unfavourable entropic contribution to the activation energy, which in ethanol is more than compensated for by lowering of the enthalpy component due to the solvation. However, in toluene, increased solvation of the C-5 transition state does not lead to sufficient stabilization to overcome the entropy term, and the less solvated C-4 transition state is energetically preferred. Reaction rates

for benzylamination were slower in toluene than in ethanol, but the reduction in rate was more marked for reaction at C-5, consistent with the greater polarity of the C-5 transition state ⟨93H(36)785⟩.

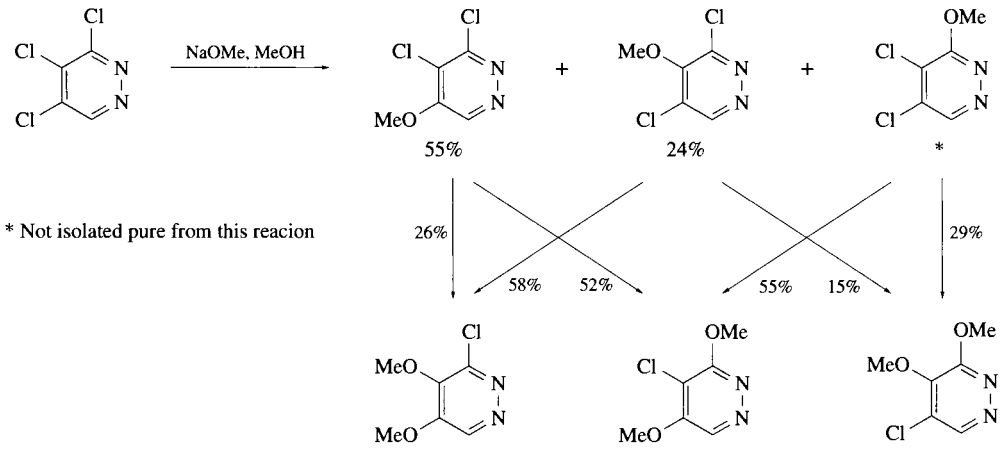
While reaction of 3,4,5-trichloropyridazine with ethanolic ammonia is reported to be nonselective, giving 35–38% of both the 4- and 5-amino derivatives, and benzylthiolate gave 4,5-bis(benzylthio)-3-chloropyridazine, reactions with secondary amines (Scheme 76) show a greater selectivity; crude products containing at least 80% of a single pyridazine were obtained and moderate to high yields of pure products (shown) were obtained. The use of two equivalents of the amine in ethanol favoured 5-substitution, while an excess of the reagent in the absence of solvent gave 3,5-disubstitution ⟨84JHC1389⟩.



HNR_2 = pyrrolidine, piperidine, morpholine

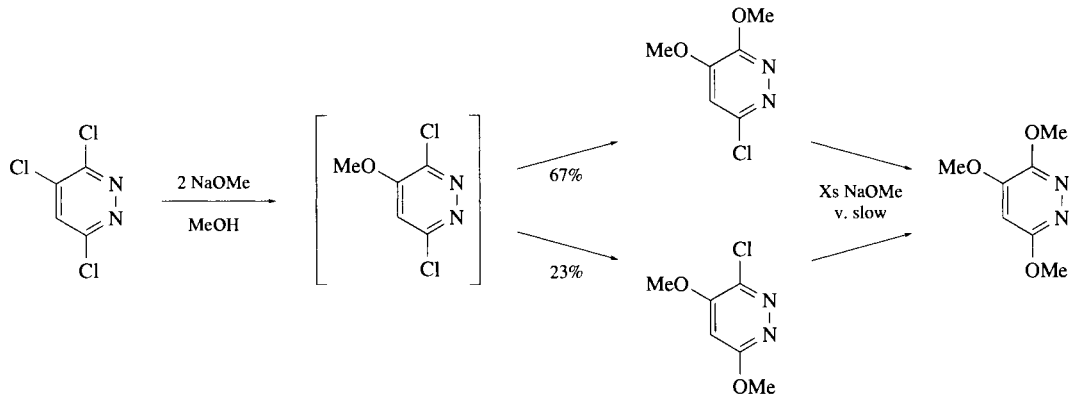
Scheme 76

The reaction of 3,4,5-trichloropyridazine towards methoxide has been reinvestigated. The relative reactivity of the chlorines towards displacement is 5 > 4 ≫ 3, and monomethoxylation gave a mixture of the 3-, 4-, and 5-methoxy derivatives in a ratio of 1 : 3 : 6 (Scheme 77). Further methoxylation of the 3,5- and 4,5-dichloro-4- or -3-methoxypyridazines occurs largely at the 5-position, while with 3,4-dichloro-5-methoxypyridazine a greater preference is shown for reaction at the 3- rather than the 4-position, possibly because of steric factors. The ease of displacement of the final chlorine from the dimethoxy derivatives is in the order 3 > 5 ≫ 4 ⟨87CPB421⟩. The acidity or basicity of reaction conditions can affect the selectivity of reaction of polyhalopyridazines, and, for example 3,4,5-trichloropyridazine with catechol under basic conditions gives 1-chloro[1,4]benzodioxino[2,3-*d*]-pyridazine by reaction at C-4,5, while fusion of the reactants in the absence of base leads to the formation of the isomeric [2,3-*c*] derivative via reaction at C-3,4 ⟨93JHC789⟩. Interestingly, both of these products rearrange on reaction with sodium methoxide to give methoxy derivatives of the other isomer by ANRORC processes.



Scheme 77

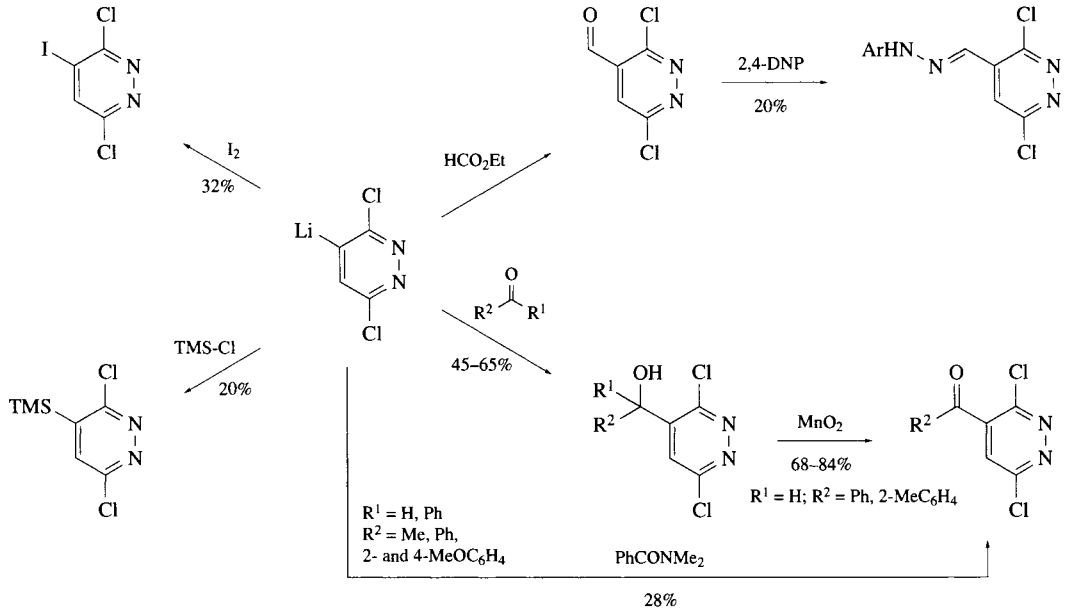
Methoxylation of 3,4,6-trichloropyridazine with sodium methoxide in methanol has also been re-investigated in detail (Scheme 78). Reaction with two equivalents of methoxide leads, via 3,6-dichloro-4-methoxypyridazine, to a 3 : 1 mixture of 6-chloro-3,4-dimethoxypyridazine and 3-chloro-4,6-dimethoxypyridazine. The latter product was obtained as a 1 : 1 addition compound with its isomer, and could only be isolated by preferential basic hydrolysis of the isomer. Both compounds only reacted very slowly to give 3,4,6-trimethoxypyridazine ⟨87CPB350⟩.



Scheme 78

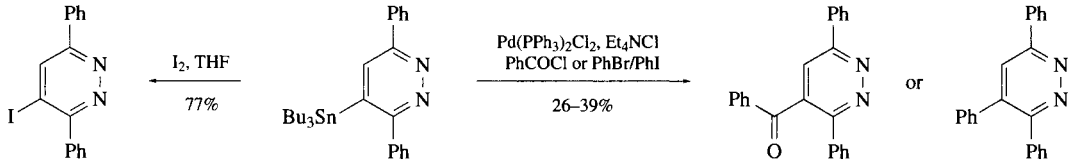
6.01.7.16 Metals and Metalloid Derivatives

The reactions of 3,6-dichloro-4-lithiopyridazine, prepared from the readily available synthetic building block 3,6-dichloropyridazine by lithiation at −70°C with lithium tetramethylpiperidide, with a range of electrophiles has been reported (Scheme 79). Quite good yields were obtained on reaction with aldehydes and ketones, but with other less reactive electrophiles the yields were only moderate, perhaps a reflection of the stability of the reagent and competing reactions. Reaction with *N,N*-dimethylbenzamide gave the 4-benzoyl derivative in 28% yield, but a better result was obtained by reaction with benzaldehyde followed by oxidation of the secondary alcohol. 3,6-Dichloro-4-formylpyridazine, prepared from ethyl formate, was too sensitive to air and light to be isolated and it had to be characterized as its 2,4-dinitrophenylhydrazone ⟨90JHC1377⟩. In contrast to the reactions of 3,6-dichloro-4-lithiopyridazine, yields from the dimethoxy analogue appear to be higher, though a smaller range of electrophiles was used, and benzoyl chloride gave a complex mixture ⟨90JOC3410⟩.



Scheme 79

Electrophilic substitution of 4-(tributystannyl)pyridazines, prepared from tributylstannyl acetylenes and tetrazines, has been demonstrated (Scheme 80) with iodination, and palladium-catalyzed benzoylation and phenylation ⟨91H(32)1387⟩.



Scheme 80

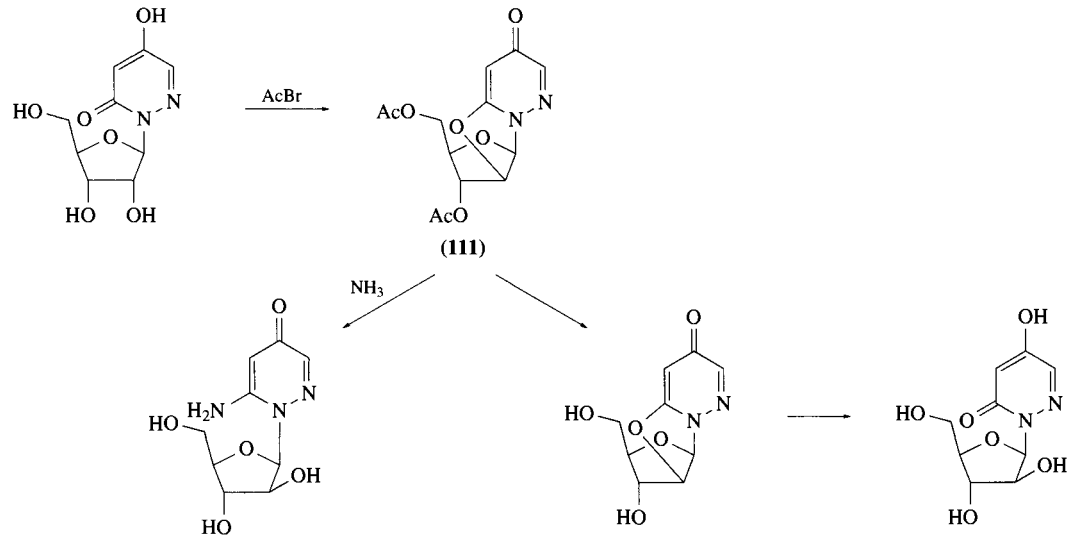
6.01.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGENS

The reactivity of substituents attached to ring nitrogens was only briefly discussed in CHEC-I because it was considered in most cases to be similar to that of carbon linked substituents ⟨84CHEC-I(3B)1⟩. The most important reaction, deoxygenation of *N*-oxides, was summarized: many methods are successful but the reagent must be selected to minimize side reactions, such as reductive dehalogenation.

6.01.8.1 Alkyl Groups

The benzyloxymethyl group has been used for the protection of the pyridazinone NH group. It is unaffected by a variety of acidic, basic, and reductive conditions and while removal by hydrogenolysis was erratic, the use of boron trichloride in DCM at −78 °C is effective ⟨84JHC481⟩. Ethyl (3-oxo-2,3-dihydropyridazin-2-yl)acetates react normally with ammonia and hydrazine to give the amides and hydrazides respectively ⟨90CPB3009⟩.

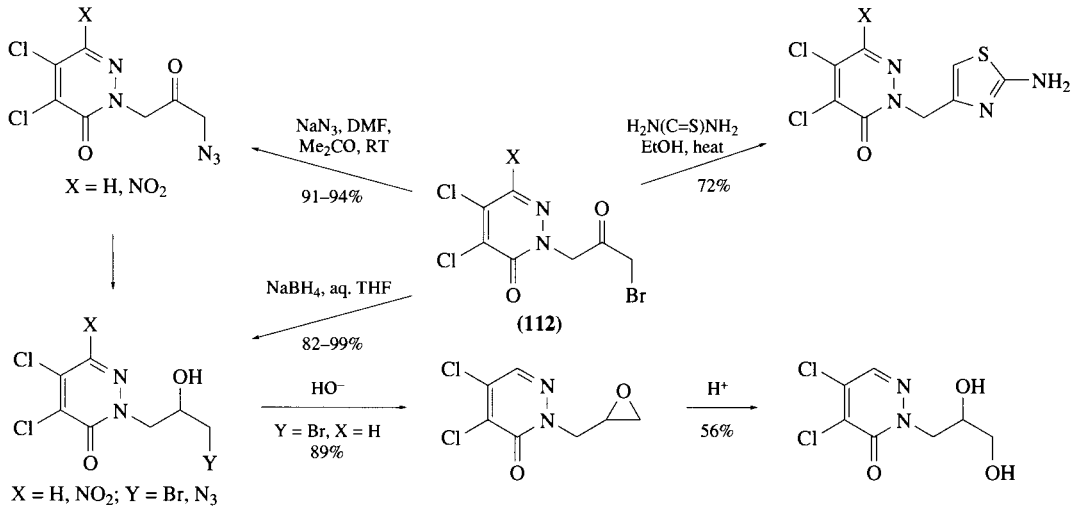
Cyclonucleosides can be formed by intramolecular reaction of some *N*-ribofuranosyl pyridazinone derivatives. Thus, reaction of 4-hydroxy-1-β-D-ribofuranosylpyridazine-6(1*H*)-one with acetyl bromide affords the cyclic derivative (**111**) which can be deprotected and hydrolysed to give the anomer of the starting material, or treated with ammonia to accomplish ring opening and deprotection to give the amino analogue (Scheme 81). Cyclonucleoside formation from other nucleosides, including derivatives of 4-amino-6(1*H*)-pyridazinone and ring formation to the ribose 5′-position, have also been investigated ⟨83JOC3765⟩.



Scheme 81

The reactivity of a 2-(2-oxopropyl) substituent in 4,5-dichloro- and 4,5-dichloro-6-nitro-3(2*H*)-pyridazinones, especially towards bromination, has been investigated. In the presence of sodium acetate/acetic acid in chloroform, bromination can be controlled to give mainly mono- or dibromination of the methylene group, while in the absence of the buffer monobromination of the methyl group is favoured. The dibromomethylene derivative is readily hydrolyzed under mild basic conditions to regenerate the *N*-unsubstituted pyridazinone ⟨91JHC385⟩. Reactions of the monobromomethyl derivative (**112**) include displacement of bromine with azide, reduction to

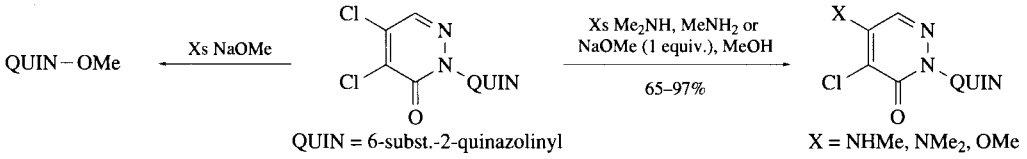
synthetically useful bromohydrins, and formation of 2-aminothiazoles by reaction with thiourea (Scheme 82). In contrast, while the isomeric monobromomethylene derivatives formed 2-amino-4-methylthiazoles with thiourea, they suffer replacement of one or more chlorines and cleavage of the nitrogen substituent on reaction with sodium azide ⟨91JHC1235⟩.



Scheme 82

6.01.8.2 Aryl Groups

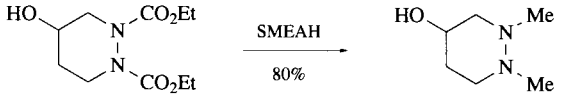
Because many aryl groups will have a reactivity profile complementary to that of the pyridazine function (greater susceptibility to electrophilic rather than nucleophilic reactions) selective reaction can often be performed on either the aryl substituent or the pyridazine function. However, though C—N bond cleavage is not easy it must be remembered that the diazinones can function as leaving groups. For example, while nucleophilic displacement of chlorine from a 4,5-dichloro-2-quinazolinyl-3(2*H*)-pyridazinone (Scheme 83) was successful with methylamine, dimethylamine, and one equivalent of methoxide, reaction with an excess of methoxide caused cleavage of the 2-quinazolinyl group ⟨85H(23)2603⟩.



Scheme 83

6.01.8.3 Acyl Groups

N-Acyl derivatives of the fully conjugated systems tend to be sensitive to hydrolysis and are not usually isolated. It has been reported that the reduction of a 1,2-diethoxycarbonyl hexahydropyridazine to the *N*-methyl derivative (Equation (30)) proceeds much better with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) than with lithium aluminum hydride ⟨90JHC2125⟩.



(30)

6.01.8.4 *O*-Linked Substituents (*N*-Oxides)

Further examples of inter- and intramolecular cycloaddition reactions of pyridazine *N*-oxides have been reported. Flash vacuum pyrolysis of 6-benzylpyridazine 1-*N*-oxide gave a low yield (14%)

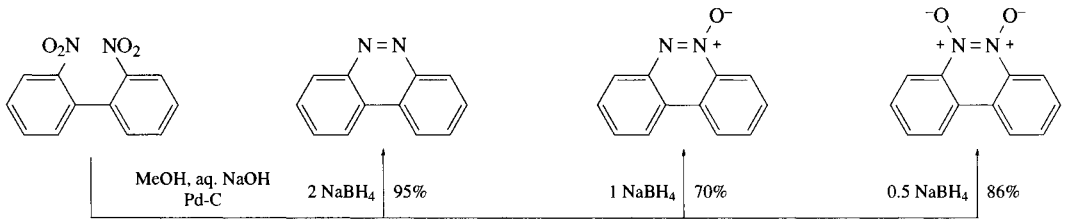
of pyridazino[2,3-*a*]indole as unstable orange coloured needles ⟨83S1037⟩. Cycloaddition reactions of pyridazine, 3-phenylpyridazine, and 3,6-dimethoxypyridazine 1-*N*-oxides with pyridynes give low to moderate yields of pyridooxepins. With 3,6-dimethylpyridazine *N*-oxide and 2,3-pyridyne a benzofuranopyridazine was isolated in low yield ⟨90H(31)1937⟩.

6.01.9 RING SYNTHESES

6.01.9.1 Formation of One Bond

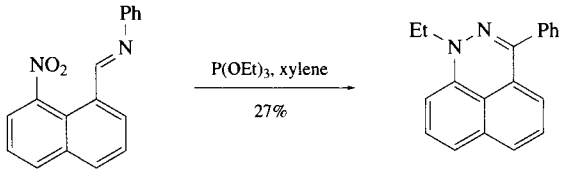
6.01.9.1.1 Between two heteroatoms

The synthesis of (benzo)pyridazine derivatives by formation of the N—N bond was a development in the mid-1980s, and oxidative formation of pyridazine 1,2-dioxides and 3,4,5,6-tetrahydropyridazines from unsaturated 1,4-dioximes and 1,4-diaminohexanes was described in CHEC-I ⟨84CHEC-I(3B)1⟩. Since then, reductive procedures have been developed for the synthesis of cinnolines. Controlled reduction of 2,2′-dinitrobiphenyl is achieved with 2,1 and 0.5 molar equivalents of sodium borohydride, in the presence of palladium on carbon and sodium hydroxide, to give benzo[*c*]cinnoline, its *N*-oxide, and *N*,*N*′-dioxide, respectively, in high yield (Scheme 84). 2,2′-Diaminobiphenyl is a byproduct in the formation of benzo[*c*]cinnoline and the sole product (formed directly and not via benzo[*c*]cinnoline) when an excess of sodium borohydride is used ⟨87JHC745⟩. Formation of benzo[*c*]cinnoline *N*,*N*′-dioxide from 2,2′-dinitrobiphenyl with sodium borohydride is reported to be quantitative when carried out in the presence of catalytic diphenyltelluride ⟨89JOC4169⟩. Activated samarium metal has been used for the reduction of nitroarenes to azoxy compounds, and 2,2′-dinitrobiphenyl, with samarium metal (eight equivalents) in THF/HMPA, is reported to give benzo[*c*]cinnoline *N*-oxide and benzo[*c*]cinnoline in 12% and 65% yields, respectively, along with 22% yield of an unidentified product ⟨88JOC3118⟩. An improved synthesis of hundred gram quantities of 1,10-dimethylbenzo[*c*]cinnoline utilizes the lithium aluminum hydride reduction in 96% yield of 6,6′-dimethyl-2,2′-dinitrobiphenyl; the solvent composition (3 : 4 ether : benzene) is critical to avoid overreduction ⟨88JOC4333⟩.



Scheme 84

Alkylation and rearrangement occured on reductive cyclization of the phenylhydrazone of 8-nitro-1-naphthaldehyde with triethyl phosphite to give 1-ethyl-3-phenyl-1*H*-benzo[*de*]cinnoline (Equation (31)); a mechanism is suggested ⟨86G405⟩.



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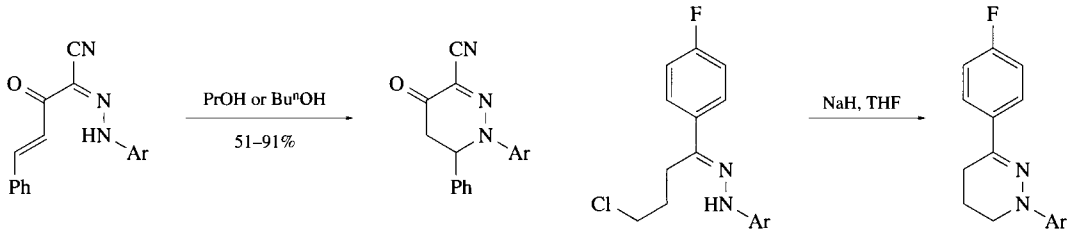
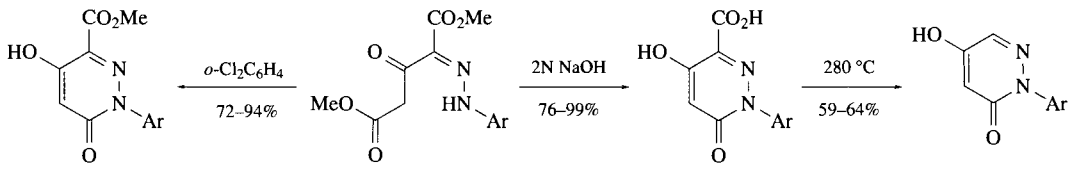
6.01.9.1.2 Adjacent to a heteroatom

This type of cyclization was reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩, particularly with reference to the formation of pyridazines by formation of a bond between the terminal nitrogen of hydrazones and an appropriately positioned cyano group or Michael acceptor. Developments of this approach have been published, including application to the synthesis of phthalazines and cinnolines.

The synthesis of pyridazine derivatives from hydrazones includes the thermal cyclization of 2-arylhydrazono-3-oxo-5-phenyl-4-pentenenitriles (readily obtained from ethyl cinnamate by condensation with acetonitrile followed by Japp–Klingemann type reactions) to 1-aryl-3-cyano-6-phenyl-5,6-dihydro-4(1*H*)-pyridazinones (Scheme 85) ⟨86JHC93⟩, and base-induced cyclization of a hydrazone of a 4-chloro-1-arylbutan-1-one to prepare a 2,3,4,5-tetrahydropyridazine (Scheme 85) ⟨88JHC1543⟩. An earlier route to 6-carboxy-5-hydroxy-2-phenyl-3(2*H*)-pyridazinone via condensation of benzenediazonium chloride and dimethyl acetonedicarboxylate has been adapted to give a series of aryl derivatives either as esters (by thermal cyclization) or as acids (by cyclization with hydroxide). Both cyclizations proceed in high overall yield (Scheme 86) and decarboxylation of the acids also proceeds in high yield ⟨89JHC169⟩.



Scheme 85

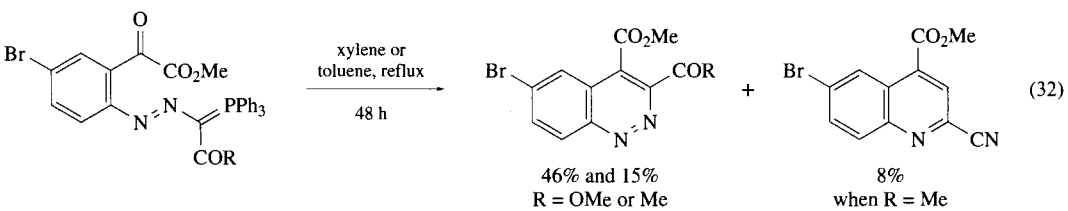


Scheme 86

The half amide hydrazide of 5-nitronaphthalic acid, obtained as an intermediate in the attempted cyclization of the naphthalamide with hydrazine, required heating in diethylene glycol to give good yields of the 1-hydroxy-6-nitrobenzo[*g*]phthalazine-4(3*H*)-one. It should be noted that the yield from cyclization of the corresponding naphthalic anhydride with hydrazine to give the same benzo-[*g*]phthalazine increased with the boiling point of the solvent (EtOH, 20%, BuOH, 33%, diethylene glycol 90%) ⟨85S197⟩.

Cinnolines may be formed by the cyclization of 2-hydrazone or 2-hydrazonophosphorane derivatives of 3-(2-fluoro- or chlorophenyl)-3-oxopropionates (Scheme 87), which are prepared from the oxopropionates via reaction with *p*-toluenesulfonyl azide and treatment of the diazo derivatives with phosphines. Simple hydrazones undergo cyclization by displacement of fluoride under thermal or basic conditions, and reaction of chloro compounds is successful under basic conditions, though Wolff–Kishner reduction may compete in the absence of a methyl group on the terminal nitrogen. The diazo compounds cyclize, via tri-*n*-butylphosphazines, more readily than do the hydrazones and base catalysis is not required; it may be that cyclization proceeds via a phosphonium salt, with subsequent hydration and elimination of tri-*n*-butylphosphine oxide. The triphenylphosphazines do not cyclize, but are labile intermediates to the hydrazones ⟨88CPB1321⟩.

When heated in toluene certain arylazomethylenetriphenylphosphoranes (prepared from isatoic acids) undergo an intramolecular Wittig reaction to give 3,4,6-trisubstituted cinnolines (Equation (32)). For successful reaction the *ortho* keto acid function must be present as its ester to increase the reactivity of the adjacent carbonyl group towards the Wittig reagent, and if the Wittig reagent is prepared from a ketone, then the yield of cinnoline is reduced by the formation of a quinoline rearrangement product ⟨90JHC1103⟩.



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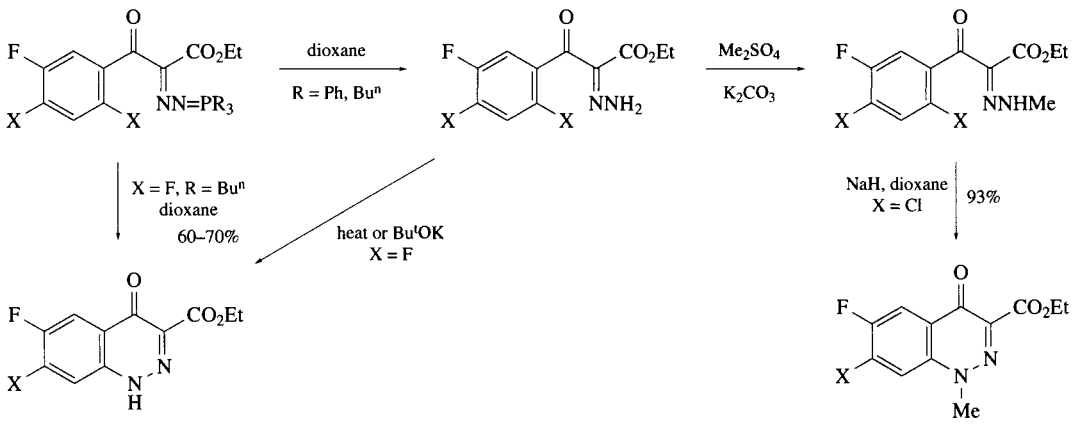
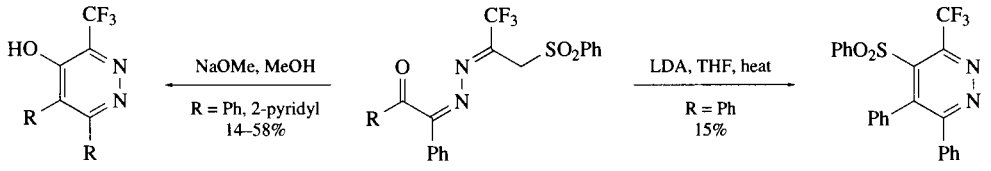


Scheme 87

6.01.9.1.3 γ to the Heteroatom

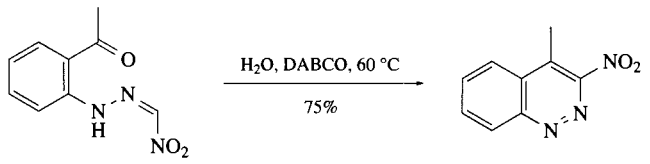
When reviewed in CHEC-I some examples of cyclization γ to the heteroatom had been described for the synthesis of pyridazines, but the method was of most importance in the synthesis of cinnolines. Examples of pyridazine syntheses included cyclization of ketazines with LDA, and intramolecular Wittig reactions of phosphoranes derived from phosphacumuleneneylides and the hydrazones produced from 1,3-dicarbonyl compounds and aryldiazonium salts. Synthetically useful approaches to cinnolines given include the intramolecular Friedel–Crafts acylation of the diacid chlorides derived from the condensation products of aryldiazonium salts and diethyl malonate to give 4(1*H*)-cinnolinones, and thermal cyclization of iminium hydrazones obtained from enamine esters and aryldiazonium salts.

Some 3-trifluoromethylpyridazines have been prepared from unsymmetrical azines by an intramolecular condensation of a phenylsulfonyl-activated methylene with a ketone (Scheme 88). The azines, which are made in two steps from readily available 2-amino-1,1,1-trifluoro-3-phenylsulfonyl-2-propanol, are cyclized under basic conditions. Yields are only poor to moderate, with the best resulting from the use of sodium methoxide with concomitant hydrolysis of the phenylsulfonyl residue ⟨93H(35)909⟩.



Scheme 88

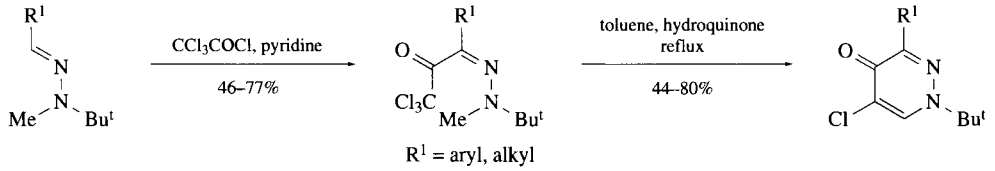
DABCO is a good catalyst for the smooth cyclization of the 2-acetylphenylhydrazone of nitroformaldehyde in a two phase aqueous system to 4-methyl-3-nitrocinnoline (Equation (33)) ⟨84JOC289⟩.



(33)

5-Chloro-4(1*H*)-pyridazinones are made in moderate to good yields in an unusual synthesis from

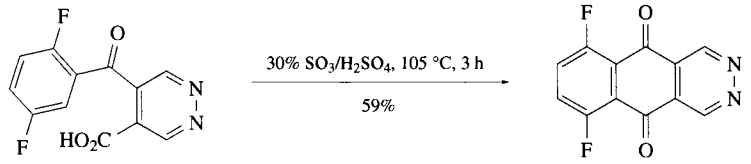
the trichloroacetyl derivatives of N^1-methyl-N^1-*t*-butylhydrazones of aldehydes (Scheme 89). The trichloroacetylated hydrazones are heated in toluene in the presence of hydroquinone, which is necessary in order to obtain reasonable yields ⟨90S467⟩.



Scheme 89

6.01.9.1.4 Formation of benzo rings

Methodology used for the synthesis of polycyclic aromatic compounds can be applied to the annelation of benzene rings on to (benzo)pyridazines. For example 6,9-difluorobenzo[*g*]phthalazine-5,10-dione has been prepared by an intramolecular acylation reaction under vigorous conditions in oleum (Equation (34)). The intermediate aroylpyridazinecarboxylic acid is made from 4,5-pyridazinecarboxylic anhydride and an aryllithium reagent ⟨93JHC1597⟩.

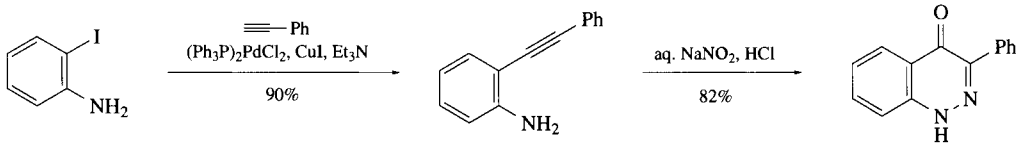


(34)

6.01.9.2 Formation of Two Bonds

6.01.9.2.1 From [5 + 1] fragments

This approach was described in CHEC-I as of importance only for the synthesis of cinnolines ⟨84CHEC-I(3B)1⟩. Most of the examples given involve the insertion of nitrogen as the sixth atom by diazotization of *o*-aminophenyl derivatives, in which the *ortho* substituent is generally an alkene, alkyne, or enolisable ketone. Another example is the synthesis of 3-substituted-4(1*H*)-cinnolinones via diazotisation of *o*-aminophenylalkynes (Scheme 90); the precursor is readily made by palladium and copper iodide catalysis ⟨89H(29)1255⟩.

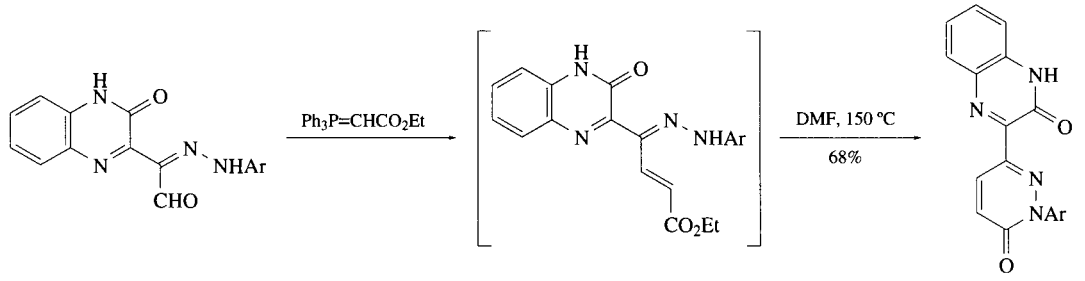


Scheme 90

In a novel synthesis of pyridazinones, a Wittig–Horner reaction is used to prepare an intermediate hydrazone of an α,β-unsaturated γ-keto ester, which undergoes geometrical isomerization and cyclization when heated under reflux in DMF (Scheme 91). The starting α-formylhydrazone is prepared from ascorbic acid ⟨87H(26)2101⟩.

6.01.9.2.2 From [4 + 2] fragments

This category covers the major approaches to pyridazines and phthalazines, particularly reaction of hydrazines with 1,4-dicarbonyl compounds or their equivalents, but also the synthesis of (benzo)-pyridazines by [2 + 4] cycloaddition reactions using azo or diazo dienophiles, and was thoroughly



Scheme 91

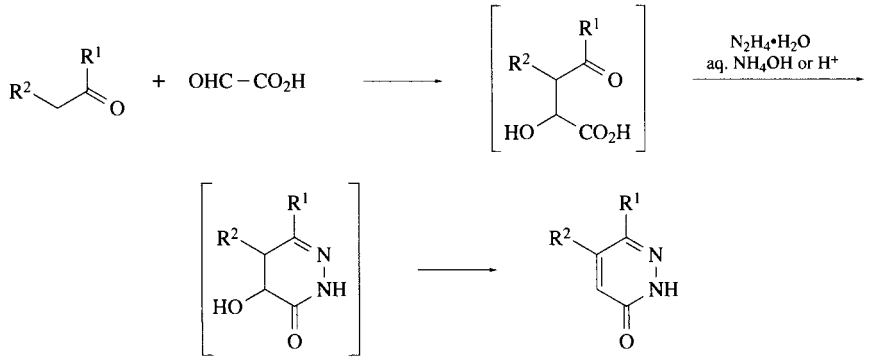
reviewed in CHEC-I ⟨84CHEC-I(3B)1⟩. A wide range of 1,4-dicarbonyl compounds can be used, though with some examples specific conditions may be necessary to avoid alternative modes of cyclization. Unsaturated 1,4-dicarbonyl compounds react best when *cis*, and unsaturated 4-keto acids are often subjected to an initial Michael addition to the double bond to improve the cyclization reaction. Cycloaddition reactions described were concerned with the use of azodicarboxylates, diimide, cyclic azadienes, and aryldiazonium and diazo compounds. Minor synthetic approaches also mentioned include the reaction of 1,4-dihalo compounds with hydrazines and nitrothioacetic acid hydrazide with gyloxal. New or improved processes and other interesting examples are included below.

(i) Cyclization with hydrazines

1-Tetralone-8-carboxylic acid, an example of a *cis* unsaturated 1,4-dicarbonyl compound, cyclizes with phenylhydrazine to give 2,7,8,9-tetrahydro-2-phenyl-3*H*-benzo[*de*]cinnolin-3-one in over 90% yield ⟨81S59⟩.

The use of precursors which allow aromatization by elimination after cyclization avoids the need for a separate oxidation step and has been exploited in several approaches to pyridazine derivatives. Thus, cyclization of hydroxy 4-keto acids with hydrazine and subsequent elimination of water allows direct access to pyridazinones and this approach, developed for the industrial preparation of 6-phenyl-3(2*H*)-pyridazinone, has been exploited to give one-pot processes for the synthesis of a range of pyridazinones from ketones (Scheme 92). The conditions required for the preparation of the intermediate hydroxy keto acids depend upon the substrate, but the subsequent cyclization with hydrazine under ammoniacal or acidic conditions generally gives good yields of pyridazinones. The intermediate hydroxydihydropyridazinones can sometimes be isolated, particularly when substituents are present at the 5-position, and are of course the final products in the case of 5,5-disubstituted-4-hydroxy-4,5-dihydro-3(2*H*)-pyridazinones ⟨93S334⟩. Elimination of water also allows the direct synthesis of pyridazine itself from the monodiethyl acetal of hydroxysuccindialdehyde in 80% yield ⟨84T1085⟩.

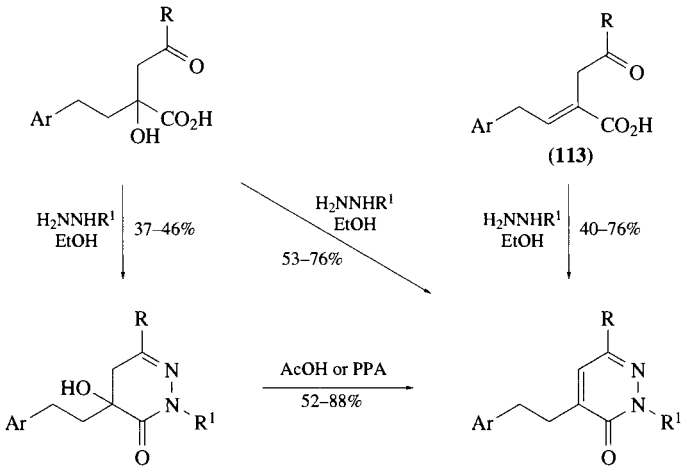
Similarly, condensation of hydrazines with 4-aryl-2-hydroxy-2-(substituted-phenacyl)butanoic



R^1 = Bu^t, aryl, heteroaryl; R^2 = H, Me

Scheme 92

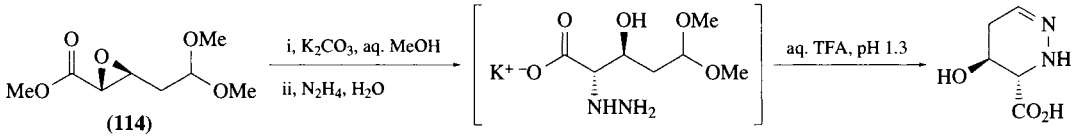
acids gives 4-(2-arylethyl)-6-substituted-3(2*H*)-pyridazinones in good yield, either directly or via the isolated 4-hydroxy-4,5-dihydro-3(2*H*)-pyridazinones (Scheme 93). The same products are produced from the dehydrated starting materials, the butenoic acids (**113**), but note that while this reaction may proceed via 4-arylethylidene-4,5-dihydropyridazinones, the final products all exist in the stable 4-arylethyl-3(2*H*)-pyridazinone form ⟨87JHC63⟩.



Ar = 4-ClC$_6$H$_4$; R = Me, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$; R^1 = H, 4-BrC$_6$H$_4$

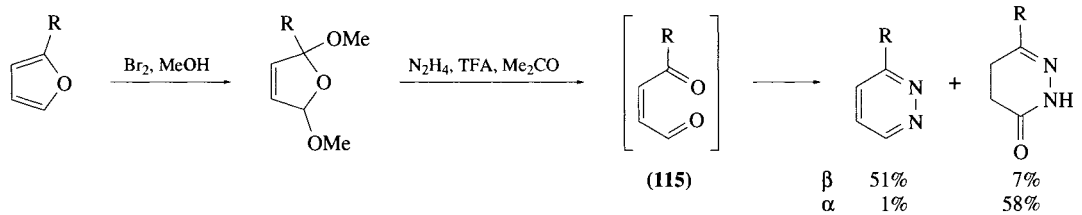
Scheme 93

The total synthesis of 3(*S*)-carboxy-4(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine, the unusual amino acid constituent of luzopeptin A, in 32% overall yield from malonaldehyde dimethyl acetal utilizes regioselective ring opening of a chiral epoxide (**114**), (Scheme 94). Immediate acidification of the relatively unstable intermediate hydrazono acid with trifluoroacetic acid gives the product in 65% yield from (**114**); the *cis*-isomer was made as a racemate ⟨89JOC3260⟩.



Scheme 94

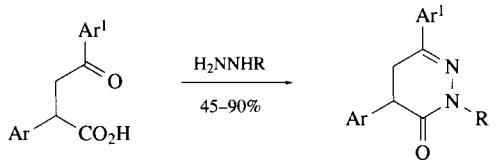
Some 2-(ribofuranosyl)furans have been converted into pyridazines using the Clauson–Kaas method via the enediones (**115**) which are cyclized with hydrazine (Scheme 95), but unexpectedly dihydropyridazinones were formed in addition to the pyridazine products, and in the case of the α-ribofuranosyl derivative, the dihydropyridazinone was the major product ⟨83JOC2998⟩. The origin of the latter product type is unknown, but it ought to involve the generation of a 4-oxobutanoic acid precursor, perhaps by a redox reaction of (**115**).



R = 2-(2,3,5-tribenzoyl- β or α-furanosyl)

Scheme 95

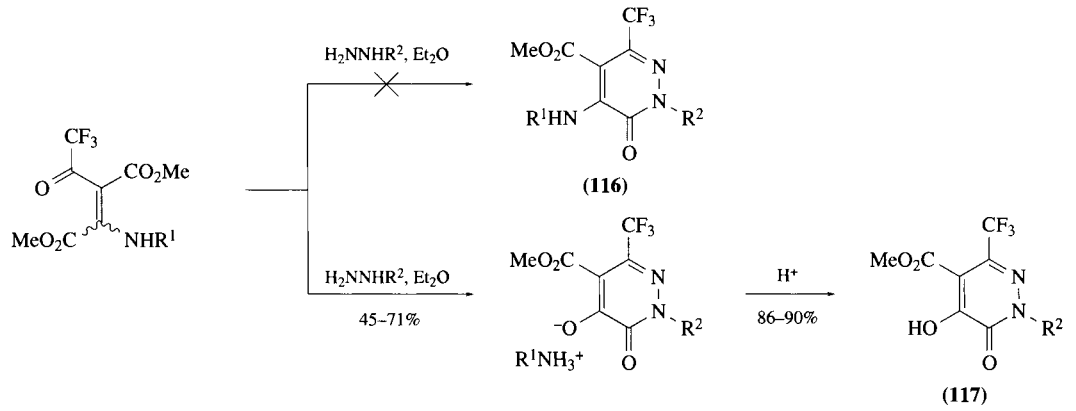
4,6-Diaryl-4,5-dihydro-3(2*H*)-pyridazinones with differently substituted aryl rings are available by condensation of hydrazines with 2,4-diaryl-4-oxobutanoic acids (Equation (35)) made from chalcones by addition of hydrogen cyanide followed by hydrolysis ⟨88JHC799⟩.



(35)

Ar = Ph; Ar^1 = aryl; R = H, Me

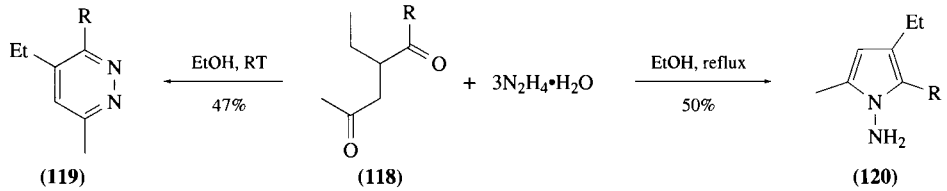
While the condensation conditions required for pyridazine formation are often relatively mild, hydrolytic side reactions may be observed. For example, reaction of 2-(alkylamino)-3-(trifluoroacetyl)butenedioates with hydrazines failed to give the expected 1,6-dihydro-5-alkylamino-6-oxo-3-trifluoromethyl-4-pyridazinecarboxylates (**116**), but gave the alkylamino salts of the corresponding 5-hydroxy derivatives in good yields; the free hydroxy compounds (**117**) were obtained by acidification in water (Scheme 96). It is not known whether the hydrolysis of the alkylamino substituent occurs before or after pyridazine formation ⟨93JHC1501⟩.



R^1 = alkyl; R^2 = H, aryl, alkyl

Scheme 96

In some instances there may be competition between 5- and 6-membered ring formation, for example in the condensation of hydrazine in acetic acid with 3-(substituted-benzoyl)-3-butenoic acids, pyrazole formation dominates and the pyridazinone products are formed in very low yields ⟨90JHC205⟩. Cyclization of the 1,4-diketone (**118**) was shown to be temperature dependent (Scheme 97, R = 4-carbomethoxy-2,3-dichlorophenyl). Thus in ethanol at room temperature with hydrazine hydrate the pyridazine (**119**) was produced, but when the reactants are heated under reflux in ethanol then the aminopyrrole (**120**) is formed instead ⟨92AP(325)13⟩. However, even when alternative modes of cyclization might be expected they may not be observed, as in the case of the reaction of 4-aryl-4-keto-3-(bis(methylthio)methylidene)butyronitriles with hydrazine hydrate in ethanol to give good yields of 6-aryl-5-bis(methylthio)methyl-3(2*H*)-pyridazinones without competing pyrrole or pyrazole formation ⟨88S89⟩.

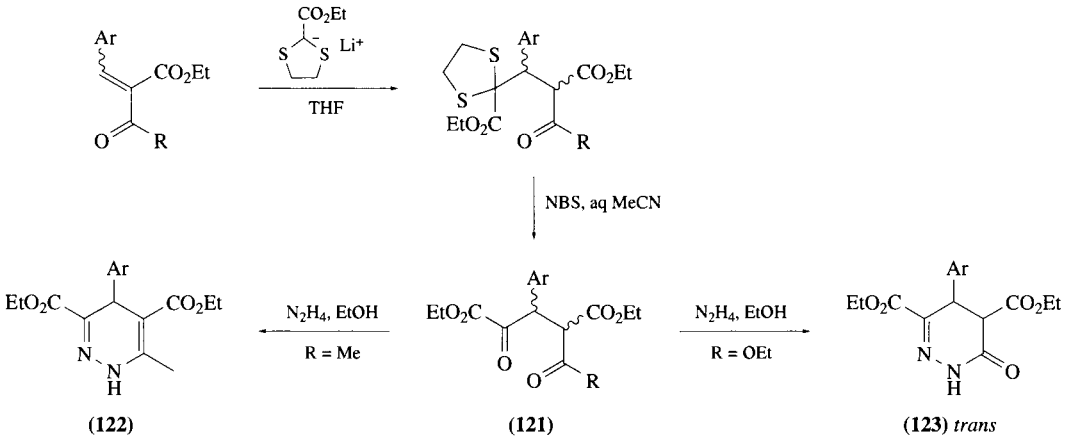


(**119**) (**118**) (**120**)

Scheme 97

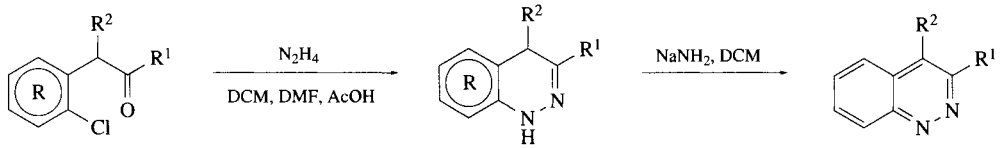
A new route to pyridazine analogues of dihydropyridine calcium antagonists has been devised. Ethyl 1,3-dithiolane-2-carboxylate was found to add efficiently, as its lithium salt, to benzylidene derivatives prepared from aryl aldehydes and diethylmalonate or ethyl acetoacetate; the dithiolane adducts were readily deprotected using NBS (Scheme 98). The resultant diketo derivatives (**121**) were cyclized with hydrazine to give either 1,4-dihydropyridazines (**122**) or 1,4,5,6-tetrahydro-6-

oxopyridazines (**123**); the latter was shown to be the *trans* isomer by proton NMR in which the 4- and 5-protons appeared as singlets ⟨89JHC1353⟩. 3,5-Diaryl-2,5-diketopentanoates cyclize with hydrazine to give 4,6-diaryl-3-ethoxycarbonyl-1,4-dihydropyridazines which are oxidized to pyridazines with manganese dioxide ⟨93CPB156⟩.



Scheme 98

In a novel approach to the synthesis of cinnolines, iron cyclopentadienyl complexes of 3-(2-chlorophenyl)propanones are cyclized with hydrazine and the 1,4-dihydrocinnoline complexes demetalated with sodium amide to give 3- or 3,4-disusbstituted cinnolines (Scheme 99). Yields of both steps are 70–80% and the cinnoline 4-substituent can be varied by alkylation of the intermediate 3-(2-chlorophenyl)propanone complex ⟨88JHC1107⟩.



R = Fe(Cp*)PF_6; R^1 = Me, Ph; R^2 = H, Me

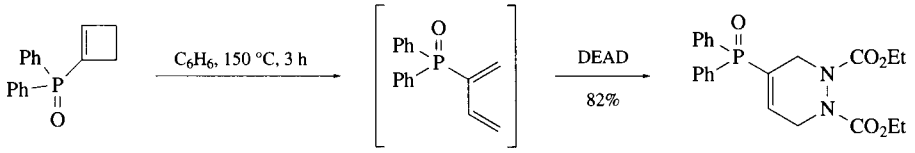
Scheme 99

(ii) [4 + 2] Cycloaddition reactions of C-4, N-2

Both 1,4-dimethoxy- and 1,4-di-*t*-butyloxy-1,3-butadiene give moderate yields of diethyl 3,6-dialkoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylates by [4 + 2] cycloaddition with diethyl azodicarboxylate. The butadienes are formed as mixtures of geometrical isomers, and at least for the *t*-butyloxy case, it was shown that the (*Z*,*Z*) isomer did not react under the conditions used ⟨82JOC5083, 83JOC3096⟩. 2-Cyanobutadiene, produced *in situ* from 3-cyano-2,5-dihydrothiophene dioxide, reacts with diethyl azodicarboxylate to give diethyl 4-cyano-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate in 95% yield ⟨88T6451⟩. Bis(trichloroethyl) azodicarboxylate undergoes cycloaddition with 1,4-diphenylbutadiene (toluene, 85°C) to give bis(trichloroethyl) 3,6-diphenyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate in 91% yield ⟨85JOC4899⟩. Thermal cycloreversion of 1-cyclobutenyl(diphenyl)phosphine oxide liberates 2-(diphenylphosphonyl)-1,3-butadiene which can be trapped (Scheme 100) with diethyl azodicarboxylate to give a phosphonyl substituted 1,2,3,6-tetrahydropyridazine ⟨86JOC2210⟩.

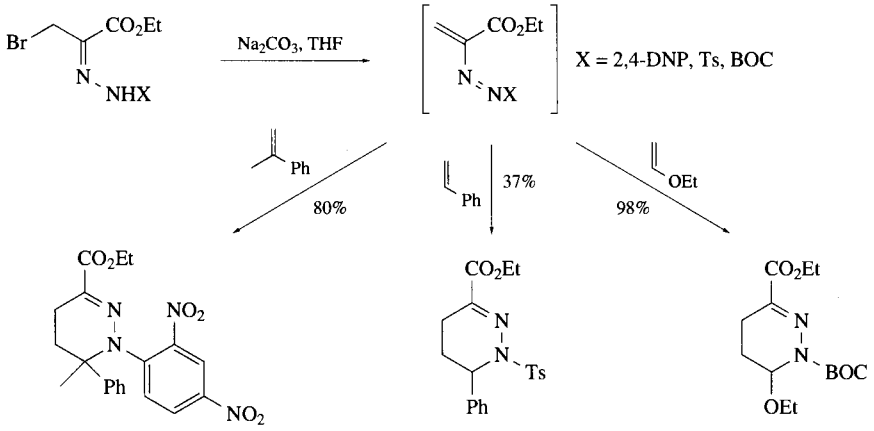
(iii) [4 + 2] Cycloaddition reactions of C-2N-2, C-2

2,3,4,5-Tetrahydropyridazines are produced by cycloaddition of azoalkenes, derived from hydrazones of ethyl bromopyruvate, with electron rich alkenes (Scheme 101). Good yields are obtained



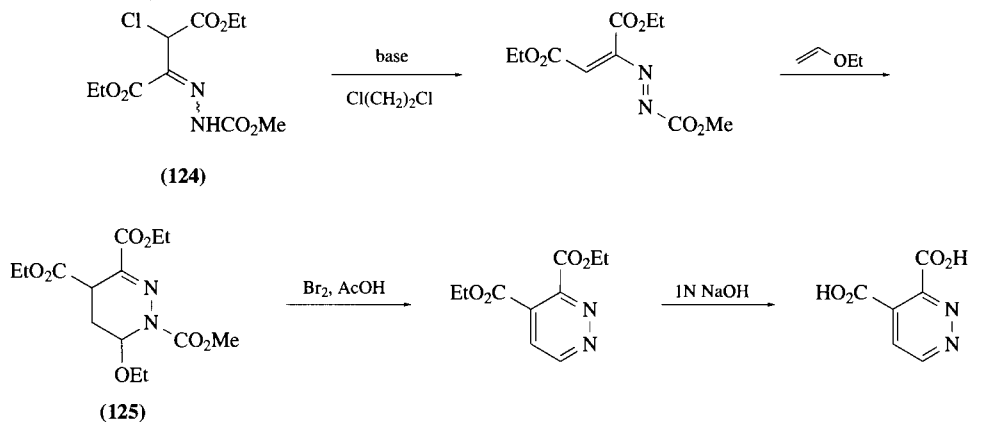
Scheme 100

when the azo substituent is 2,4-dinitrophenyl or *t*-butyloxycarbonyl, but the tosyl analogue is less reactive. The BOC reagent is the least stable, but is a good heterodiene and offers the possibility of easy removal of the protecting group from the pyridazine products ⟨91T5615⟩.



Scheme 101

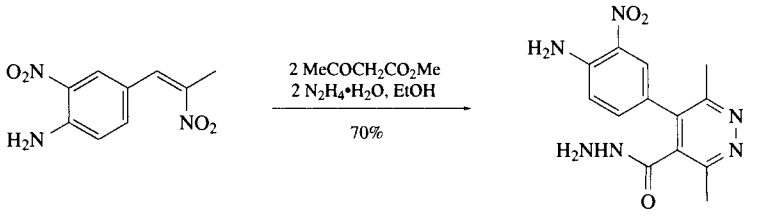
A convenient synthesis of pyridazine-3,4-dicarboxylic acid based on [4 + 2] cycloaddition of an electron deficient diazadiene has been developed (Scheme 102) and carried out on a molar scale. The azadiene is generated *in situ* from the precursor (**124**) (prepared from diethyl oxaloacetate and methyl carbazate followed by chlorination with sulfuryl chloride) and trapped with ethyl vinyl ether. The regiospecific cycloaddition gives the tetrahydropyridazine (**125**) as a mixture of *cis* and *trans* isomers which, with bromine in acetic acid, are transformed into diethyl pyridazine-3,4-dicarboxylate. Saponification gives the diacid in an overall yield of 52% ⟨90JHC579⟩. In a similar approach from the readily available ethyl 2-chloro-3-oxobutanoate, an efficient route to ethyl 3-methylpyridazine-4-carboxylate has been developed which gives the product in 56% overall yield. This route is claimed to be a practical alternative to the radical ethoxycarbonylation of pyridazines ⟨91JHC1043⟩.



Scheme 102

6.01.9.3 Formation of Three Bonds

The formation of pyridazines from three components was reviewed in CHEC-I and the most common examples are of reaction of an α-diketo compound, a hydrazine, and an ester or nitrile containing an adjacent activated methylene group, to give compounds like 4-cyano-3(2*H*)-pyridazinone or 3-amino-4-cyanopyridazines. A different type of example is illustrated by the condensation of a nitrostyrene with two equivalents each of methyl acetoacetate and hydrazine hydrate (Equation (36)) to give the pyridazine (**126**) in good yield ⟨87JHC23⟩.



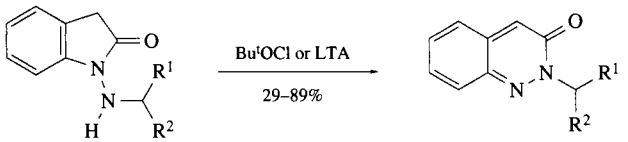
(36)

(126)

6.01.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

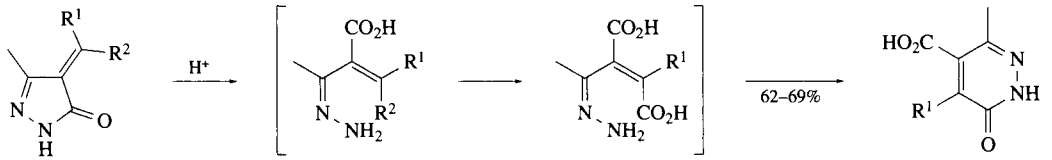
6.01.10.1 By Ring Expansion

Syntheses of this type considered in CHEC-I are largely concerned with base catalyzed rearrangements of 2-aminoisoindolones to 4(1*H*)-pyridazinones and of *N*-aminophthalimide to 4-hydroxy-1(2*H*)-phthalazinone, and oxidative ring expansion of *N*-aminopyrrolidines and *N*-amino-2-indolinone to tetrahydropyridazines and 3(2*H*)-cinnolinones, respectively. The last reaction is also successful with 1-methylamino-2-indolinone, which undergoes oxidative rearrangement to 2-methyl-3(2*H*)-cinnolinone with LTA or *t*-butyl hypochlorite. The mechanism of this reaction, which is essentially the reverse of the acid catalyzed reductive ring contraction reaction shown in Section 6.01.5.4.6 (Scheme 25), has been discussed ⟨88JHC847⟩ and the approach extended ⟨89JHC1437⟩ to 2-(substituted-alkyl)-3(2*H*)-cinnolinones (Equation (37)). The required 1-(substituted-alkylamino)-2-indolinones are prepared from 1-amino-2-indolinone by condensation with carbonyl compounds followed by catalytic reduction.



(37)

The rearrangement of 2,3-diazabicyclo[3.1.0]hex-2-enes, prepared from cyclopropenes and diazoalkanes, to pyridazines has been further exemplified. Thus the 6,6-dimethyl-1-trimethylsilyl derivative on treatment with base gives the rather unstable 3-trimethylsilyl-4,4-dimethyl-1,4-dihydropyridazine in high yield ⟨87T215⟩. 3-Benzoyl 1- or 2-pyrazolines when heated in solution undergo rearrangement followed by oxidation to give phenylpyridazinones, but in very low yields ⟨83H(20)2385⟩. Acid catalyzed ring opening, hydrolysis, and ring closure of 4-alkylidene-2-pyrazolin-5-ones derived from malononitrile or ethyl acetoacetate gives good yields of 4-cyano- or 4-acetyl-5-carboxy-3(2*H*)-pyridazinones (Scheme 103) ⟨84S972⟩.

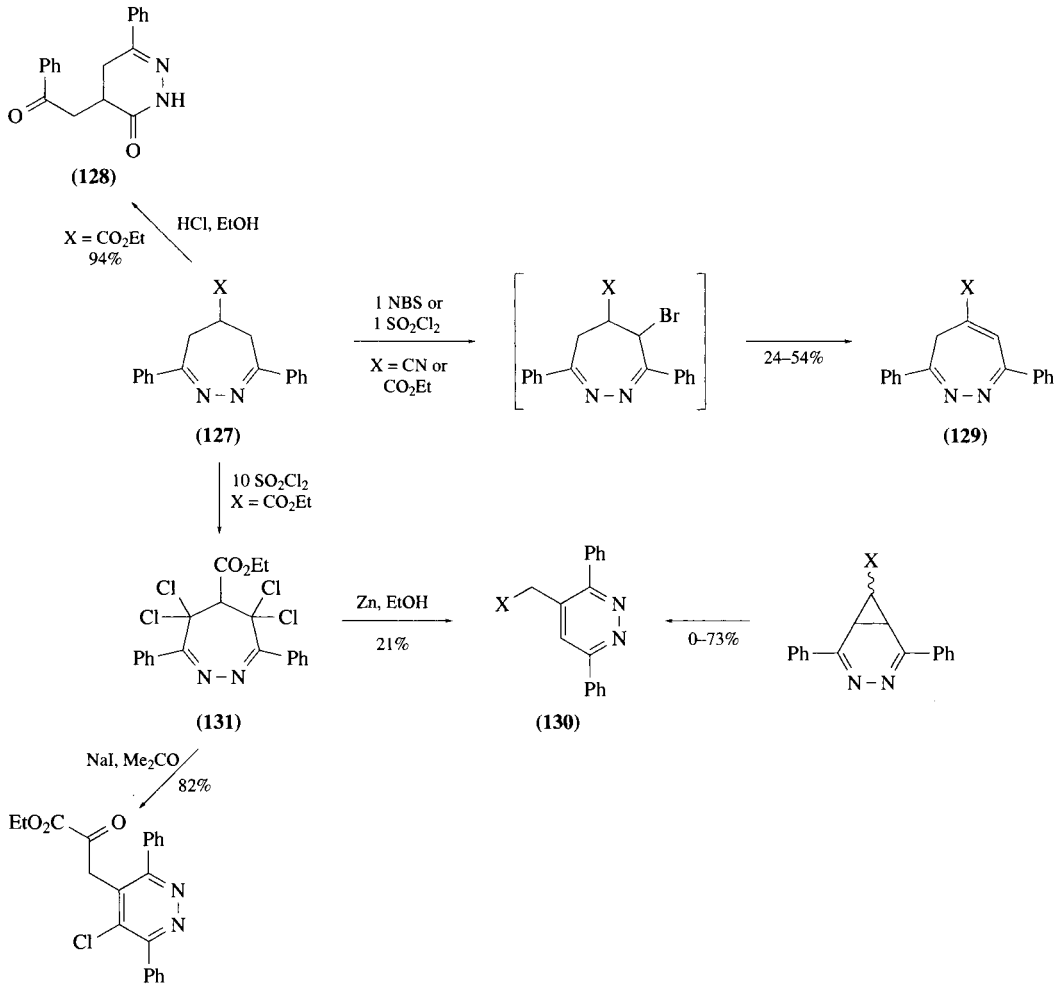


R^1 = CN, COMe; R^2 = CO_2Et

Scheme 103

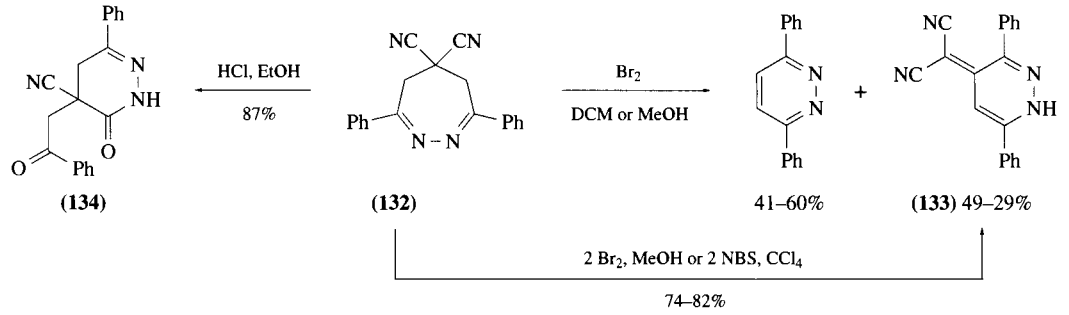
6.01.10.2 By Ring Contraction

Further studies of the transformation of 1,2-diazepines into pyridazines ⟨84CHEC-I(3B)1⟩ have been published. Ring contraction of 5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepines substituted with a single electron withdrawing group has been shown to yield a variety of pyridazines ⟨86H(24)3059⟩. Treatment of the ethoxycarbonyl derivative (**127**) with hydrochloric acid in ethanol leads to 4,5-dihydro-4-phenacyl-6-phenyl-3(2*H*)-pyridazinone (**128**) in 94% yield, while halogenation reactions give more complex results (Scheme 104). Bromination with a single equivalent of NBS in carbon tetrachloride or sulfuryl chloride in dichloromethane gave mixtures of the 4*H*-1,2-diazepines (**129**) and 4-substituted-3,6-diphenylpyridazines (**130**) produced by competing α-elimination of HBr or internal nucleophilic displacement and ring opening, respectively. Rapid treatment of the ethoxycarbonyl diazepine with a 10-fold excess of sulfuryl chloride gave the 4,4,6,6-tetrachloro derivative (**131**), which underwent ring contraction to pyridazines with sodium iodide in acetone or zinc dust in ethanol.



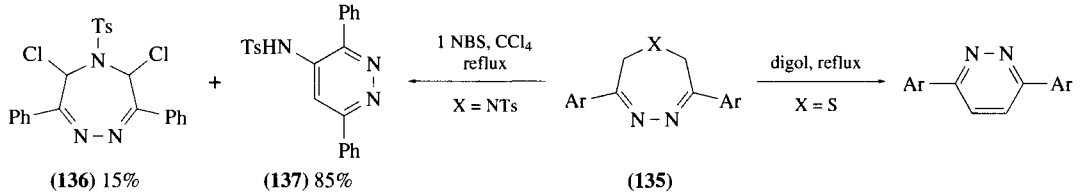
Scheme 104

Bromination of the corresponding dicyano derivative (**132**) (readily prepared from 2-bromoacetophenone azine) gives mixtures of 3,6-diphenylpyridazine and 4-dicyanomethylene-1,4-dihydro-3,6-diphenylpyridazine (**133**), but with two molar equivalents of bromine in methanol or of NBS in carbon tetrachloride a high yield of (**133**) can be obtained; the diazanorcaradiene intermediate was not detected (Scheme 105). Similar reactions occurred with the corresponding 4-cyano-4-ethoxycarbonyldiazepine but the diazonorcaradiene intermediate could be isolated in this case in up to 85% yield. Chlorination reactions of both substrates were much more complex. Acid hydrolysis of (**132**) resulted in ring opening and ring closure to give the dihydropyridazinone (**134**) ⟨86JHC557⟩.



Scheme 105

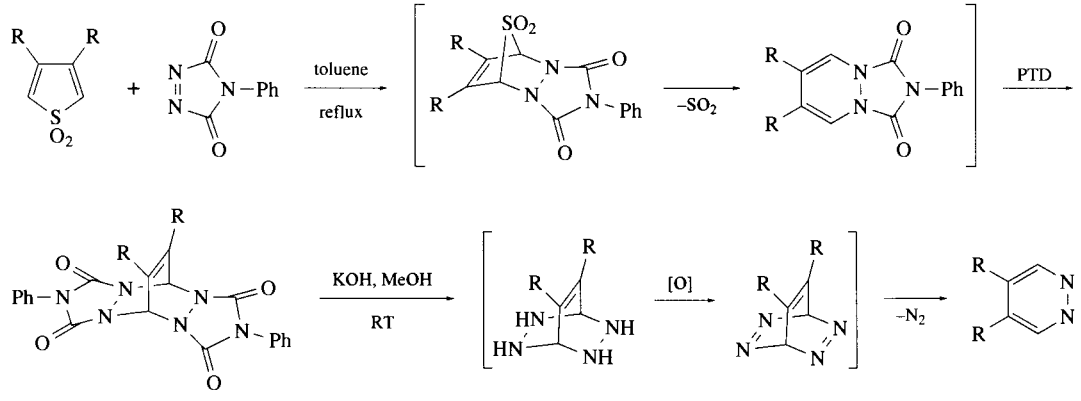
A novel ring contraction of 4,6-dihydro-3,7-diphenyl-5-(4-methylphenylsulfonyl)-1,2,5-triazepine (**135**, X = NTs) occurs under specific, monochlorination conditions ⟨85H(23)1675⟩. An excess of chlorine or sulfuryl chloride in dichloromethane leads to the dichlorotriazepine derivative (**136**), but with one equivalent of sulfuryl chloride in dichloromethane, or one equivalent of NBS in carbon tetrachloride, formation of the dichlorotriazepine is minimized and up to 86% of 4-tosylamino-3,6-diphenylpyridazine (**137**) is produced (Scheme 106). In polar solvents other, 5-membered ring, products are produced. Thermal decomposition of a series of 3,6-diaryl-2,7-dihydro-1,4,5-thiadiazepines (**135**, X = S) gave 3,6-disubstituted pyridazines in high yield ⟨89BCJ2608⟩.



Scheme 106

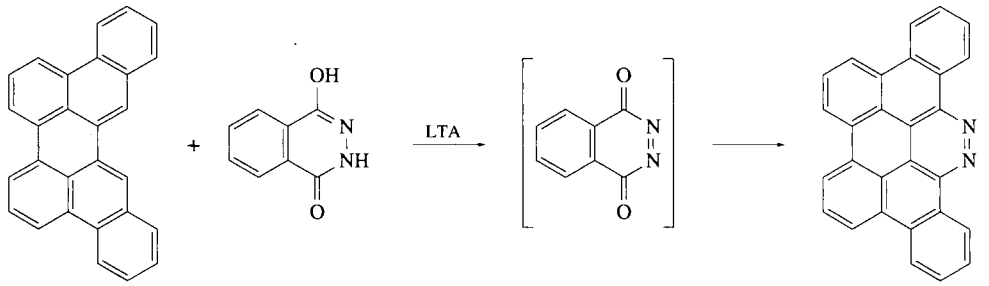
6.01.10.3 By Cycloaddition

Cycloaddition of diazo compounds such as diimide and diazonium salts, but especially cyclic derivatives like 4-phenyl-1,2,4-triazole-3,5-dione (PTD) and 1,4-phthalazinedione, to dienes to produce pyridazine derivatives was discussed in CHEC-I ⟨84CHEC-I(3B)1⟩. With the cyclic reagents reduced pyridazines are released by hydrolytic cleavage of the triazole or phthalazine function of the cycloadducts. In contrast, more recent work includes a neat synthesis of aromatic 4,5-disubstituted pyridazines. Thus, the previously unknown 4,5-di-*t*-butyl- and 4,5-(di-1-adamantyl)pyridazines have been prepared from the corresponding 3,4-di-substituted thiophene 1,1-dioxide and PTD in a high yield two-step process which starts with cycloaddition. Extrusion of sulfur dioxide and addition of a second molecule of PTD, followed by hydrolysis, aerial oxidation, and expulsion of nitrogen completes the synthesis (Scheme 107) ⟨90JA5654, 90JA7648⟩.



Scheme 107

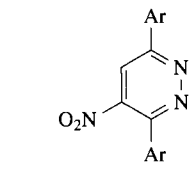
Diels–Alder addition of phthalazine-1,4-dione (prepared *in situ* by oxidation) to bay region polycyclic aromatic hydrocarbons, produces polycyclic pyridazines which contain the cinnoline core (e.g., Scheme 108). The reaction, which proceeds without isolation of intermediates, is also successful starting from 6-hydroxy-3(2*H*)-pyridazinone and its 4,5-dichloro analogue, though yields are less good ⟨82S854⟩. Other cycloaddition reactions of interest include those between aldazines and mesoionic oxazolones to give 5-benzamido-substituted 4-oxo-3,4,5,6-tetrahydropyridazines ⟨84H(22)2483⟩, the selective preparation of 3,4- or 4,5-(dialkylamino)pyridazine derivatives from substituted diaminopropenylium salts and diazomethane derivatives ⟨86JHC385⟩, the preparation of highly hindered tetrasubstituted pyridazines such as 3,4,5-tri-*t*-butyl-6-isopropylpyridazine in high yield by rearrangement of cyclopropenyldiazomethane derivatives ⟨91AG(E)1484⟩, and the preparation of pyridazine-4,5-dicarboxylic acid by cleavage of the polymer supported cycloadduct from 3,4-diaza-2,4-cyclopentadienone and acetylenedicarboxylate ⟨91JOC5417⟩.



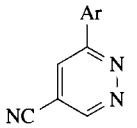
Scheme 108

The inverse electron demand Diels–Alder cycloaddition reactions of 1,2,4,5-tetrazines were identified in CHEC-I as a useful approach to the synthesis of (benzo)pyridazines ⟨84CHEC-I(3B)1⟩. Tetrazines with electron-withdrawing groups at C-3, C-6 react with a wide range of alkenes and alkynes, including enol ethers and enamines, to give pyridazine derivatives. Several general examples are given, including a comparison between the reaction of alkynes, which are less reactive but give pyridazines directly, and those of alkenes, which are more reactive but proceed via dihydropyridazines and require an additional oxidation step. This chemistry has been developed during the review period and the utility extended, in particular by the use of dienophiles incorporating electron donor groups which facilitate the cycloaddition and serve as leaving groups in the aromatization step. With the more reactive tetrazines the initial cycloaddition reactions can be very rapid, but the loss of the deep colour of the tetrazines only confirms that the tetrazine has been consumed, and the second oxidation or elimination step may be much slower. Examples of the range of pyridazine derivatives obtained by these cycloaddition reactions are shown: (**138**), (**139**) ⟨85H(23)683⟩, (**140**) ⟨88AP(321)889⟩, (**141**)–(**143**) ⟨84JOC4405⟩, (**144**), (**145**) ⟨87AG(E)332⟩ and some of the chemistry is described below. 1,2,3-Triazines also react as dienes with electron rich dienophiles, but by competing non-concerted ionic and orbital controlled reactions, to give mixtures of pyridines and pyridazines, respectively, though pyridine formation generally predominates. Reaction of diethylaminopropyne with 5-phenyl-1,2,3-triazine gives a slight excess of the 3-diethylamino-4-methyl-6-phenylpyridazine product, but the yield is low and reaction incomplete after 92 hours ⟨90CPB2108⟩.

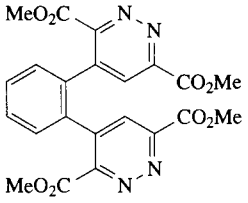
Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate undergoes exothermic inverse electron demand Diels–Alder reactions with electron-rich alkenes accompanied by the immediate evolution of nitrogen. Subsequent aromatization by loss of the electron donor group (alkoxy, silyloxy, pyrrolidino, morpholino) is the rate-limiting step in the formation of pyridazines, which in some instances may be catalyzed by the addition of acid; cycloaddition of electron-rich alkynes leads directly to pyridazines and, for example, benzyloxyacetylene gives (**141**) in high yield. This general synthetic approach has been used to prepare, in good yield, a variety of 4- and 4,5-disubstituted-3,6-pyridazinedicarboxylates such as (**141**)–(**143**) some of which are readily hydrolyzed and decarboxylated to provide access to 4- and 4,5-disubstituted pyridazines ⟨84JOC4405⟩. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate undergoes cycloaddition with naphthalenes but yields of benzo[*f*]phthalazines are generally poor. With 1-methoxy and 1-dimethylaminonaphthalenes loss of methanol (or dimethylamine) to give the unsubstituted benzo[*f*]phthalazine competes with oxidation of the intermediate, and in toluene 1-dimethylaminonaphthalene reacts with two moles of the tetrazine to give the bis(4-pyridazinyl)benzene derivative (**140**) in 47% yield. With 2-dimethylaminonaphthalene there is still



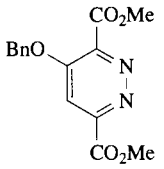
(138)
e.g. Ar = 4-pyridyl



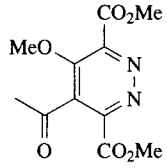
(139)
e.g. Ar = Ph



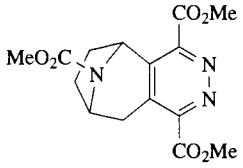
(140)



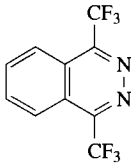
(141)



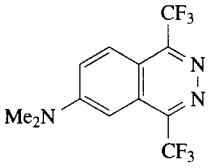
(142)



(143)



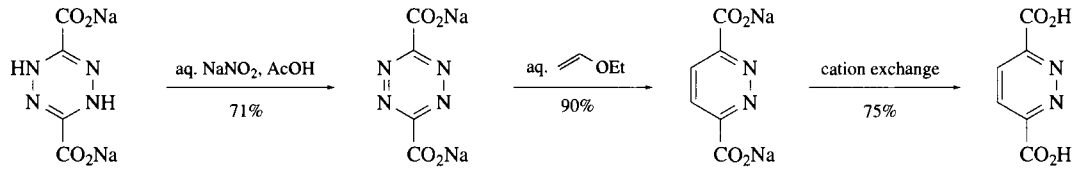
(144)



(145)

competition between oxidation and elimination, but the initial addition is to the unsubstituted ring ⟨88AP(321)889⟩.

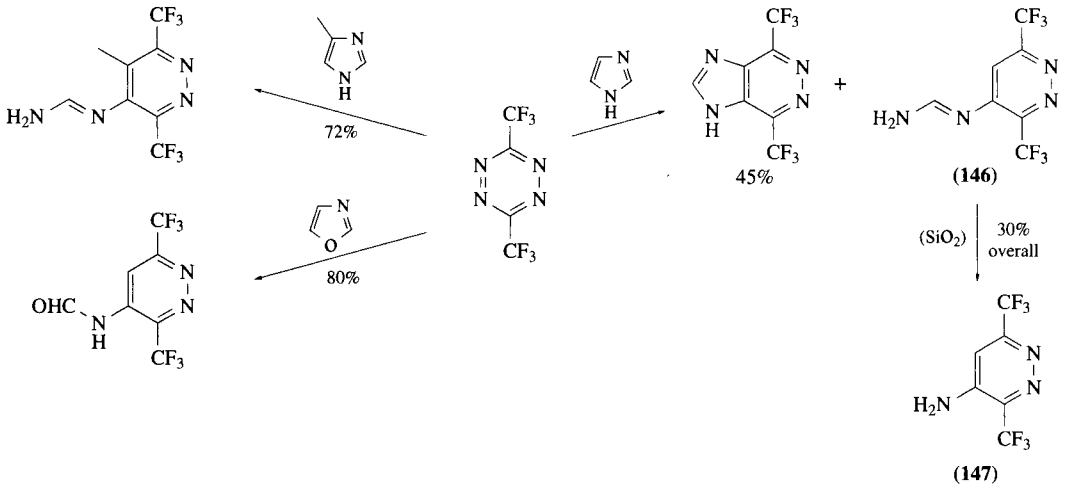
Cycloaddition of ethyl vinyl ether to the 3,6-tetrazinedicarboxylic acid disodium salt has been developed as an efficient multigram synthesis of 3,6-pyridazinedicarboxylic acid (Scheme 109). A key feature of this process is that the otherwise facile decarboxylation reactions of acids are minimized by use of their sodium salts, and if required the free acid is obtained by ion exchange ⟨87JHC1285⟩.



Scheme 109

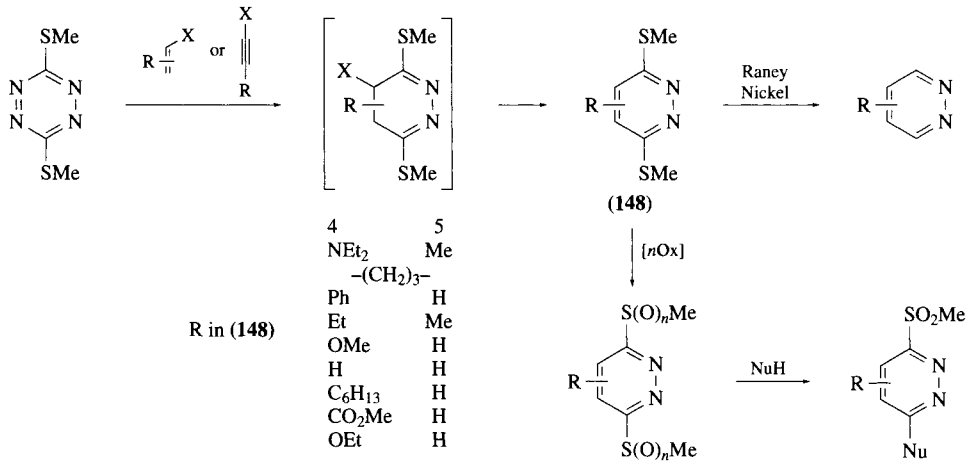
3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine is particularly reactive and cycloaddition with benzyne gives a quantitative yield of 1,4-bis(trifluoromethyl)phthalazine (**144**). This product is also obtained in good yield using benzene since the adduct formed, after cycloaddition and elimination of nitrogen by cycloreversion, is very susceptible to oxidation. Similarly bis(trifluoromethyl)-substituted benzo[*f*]- and naphtho[2,3-*f*]phthalazine are obtained from naphthalene and anthracene, respectively, in moderate yields. Reasonable yields of 1,4-bis(trifluoromethyl)-6-substituted phthalazines, for example (**145**), are obtained when electron donor-substituted benzenes are used in this reaction, and the regioselectivity is in agreement with frontier molecular orbital theory and MNDO calculations ⟨87AG(E)332⟩. Azulene also reacts with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine, to give 1,4-bis(trifluoromethyl)benzo[*f*]phthalazine as the major product (40% yield) along with minor products including the corresponding azuleno[*d*]pyridazine ⟨93AP(326)29⟩. Inverse electron demand Diels–Alder reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine with electron-rich five-membered heterocycles has also been investigated. Cycloaddition and elimination of nitrogen gives adducts which aromatize by oxidation to give fused pyridazines or undergo ring opening to give non-pyridazines. Oxidation predominates in the case of imidazole, 2-methyl-imidazole, and 1-methylpyrazole, while nonfused pyridazines are the major products from 1-methyl- and 1-benzylimidazole, 4-methylimidazole, and oxazole (Scheme 110). *N*-(4-(3,6-Bis(trifluoromethyl)pyridazinyl))-formamidine (**146**) underwent hydrolysis on silica during chromatography to give 4-amino-3,6-bis(trifluoromethyl)pyridazine (**147**) ⟨89AP(322)415⟩.

Inverse electron demand Diels–Alder reactions of 3,6-bismethylthio-1,2,4,5-tetrazine with a wide range of dienophiles have been shown to give substituted 3,6-bismethylthiopyridazines (**148**), generally in yields of 60% to 90% (Scheme 111). The reactivity of electron-rich alkynes and alkenes shows the expected order of ynamines > enamines > ketene acetals > enamides > trimethylsilyl or alkyl enol ethers > enol acetates; reaction with ynamines is complete at room temperature in one



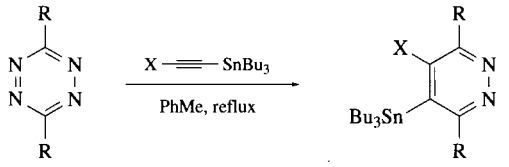
Scheme 110

hour. With enamines the initial cycloaddition and loss of nitrogen is rapid, and the slow step is elimination of the secondary amine. Reactions with unactivated alkynes such as phenylalkyne and cyclohexyalkyne are slow but productive, while ethoxyalkyne, diphenylalkyne, electron-deficient alkynes including methyl propiolates and dimethyl alkynedicarboxylate, and strained unactivated alkenes such as cyclopentene, fail to react or give low yields. 3,6-Bismethylthio-1,2,4,5-tetrazine is less reactive than the corresponding dialkyl carboxylates, even in cycloaddition reactions of electron deficient dienophiles, but is much more reactive than the 3,6-bis(alkylamino- or acylalkylamino)-1,2,4,5-tetrazines. The use of 3,6-bismethylthio-1,2,4,5-tetrazine in cycloaddition reactions for the preparation of pyridazines offers greater scope for substituent modification in the products than is the case with the dicarboxylates: the methylthio substituents can be removed or oxidised and used for nucleophilic displacement reactions. This approach forms the basis of a synthesis of substituted indoles and indolines (see Section 6.01.5.1.1) ⟨88JOC1415⟩.



Scheme 111

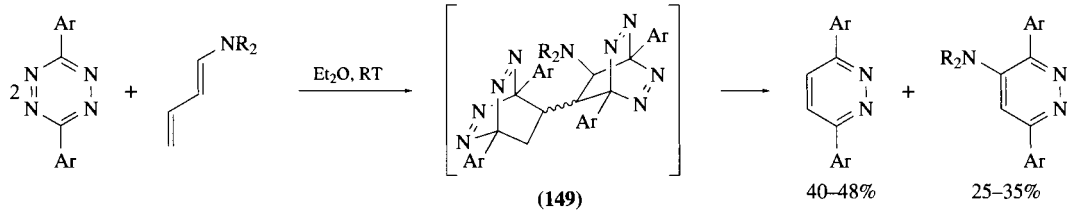
Inverse electron demand Diels–Alder reactions of 1,2,4,5-tetrazines with alkynes has the advantage that pyridazines are produced directly with the elimination of nitrogen only, and the substituents on the acetylene are retained. Thus tributylstannylacetylenes give pyridazines with a 4-tributystannyl substituent (Equation (38)) which can be further elaborated by electrophilic substitution. In general, yields in this cycloaddition–elimination sequence are good, except for bis(tributylstannyl)alkyne with which good yields are only obtained with the more reactive dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. The latter substrate gives high yields in a short reaction time ⟨91H(32)1387⟩.



(38)

R = Ph, Me, CO_2Me; X = H, Bu, OEt, Ph, Bu_3Sn

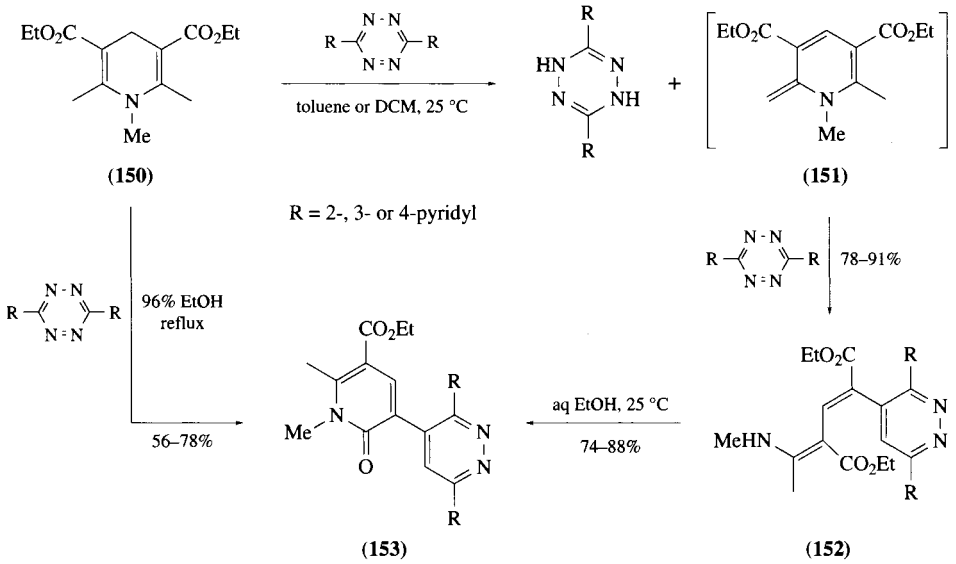
Two atypical reactions of tetrazines involve a dienamine and a dihydropyridine. Acyclic dienamines react with two molecules of 3,6-diaryl-1,2,4,5-tetrazines to give a mixture of 3,6-diarylpyridazines and the corresponding 4-dialkylamino derivatives (Scheme 112): reaction proceeds by cycloaddition to the terminal double bond and then to the enamine double bond by a second tetrazine to give the postulated intermediate (**149**), followed by loss of nitrogen and, finally, aromatization is achieved by an unusual carbon–carbon cleavage to give the two products ⟨87H(26)337⟩. The expected inverse electron demand Diels–Alder reaction between the *N*-methyl-1,4-dihyropyridine (**150**) and 3,6-dipyridyl-1,2,4,5-tetrazines catalysed by Fe^{3+}-doped K-10 clay was not observed, but instead an initial redox reaction occurred to give 1,4-dihydrotetrazines and the 2-methylidene-1,2-dihydropyridine (**151**), (Scheme 113). Cycloaddition of the latter with a second molecule of the tetrazine gave, via the open chain intermediate (**152**), the pyridinone substituted pyridazine (**153**) which can also be prepared in 56–78% yields in a one-pot process from (**150**) in ethanol ⟨87JOC2026⟩.



(**149**)

Ar = Ph, 4-MeOPh; R = NEt_2, NMe_2

Scheme 112

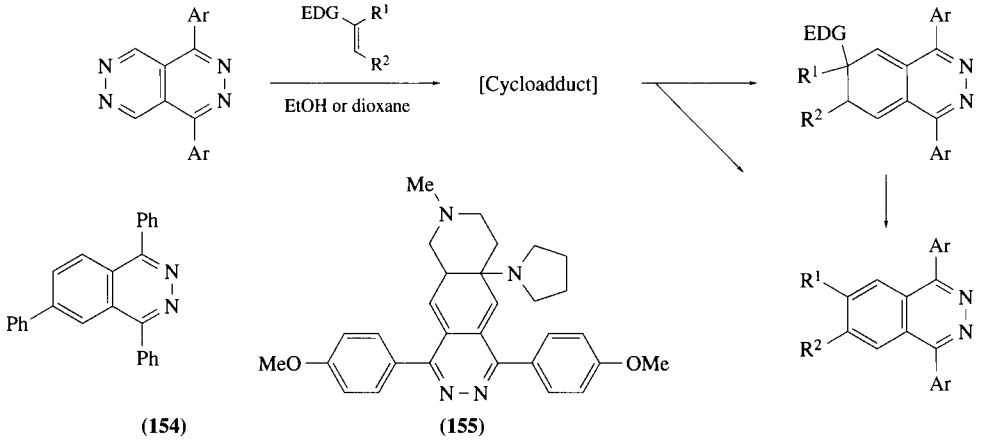


(**150**) (**151**) (**153**) (**152**)

Scheme 113

Annelation of an electron deficient 6-membered ring to pyridazine lowers the LUMO energy levels and facilitates cycloaddition of electron rich dienophiles. With the diarylpyridazino[4,5-*d*]pyridazines (readily available via radical aroylation of pyridazine and cyclization with hydrazine) the rate of reaction of the phenyl derivatives is greater than that for the 4-methoxyphenyl analogues, as expected, and addition is always to the less hindered pyridazine ring (Scheme 114). Following

cycloaddition and loss of hydrazine some of the intermediate dihydro adducts undergo spontaneous loss of amine to give the phthalazines (e.g., (**154**)), while other more stable dihydro intermediates (e.g., (**155**)) may be isolated and aromatized thermally or by acid catalysis in a subsequent step; yields are good ⟨91T3959⟩.



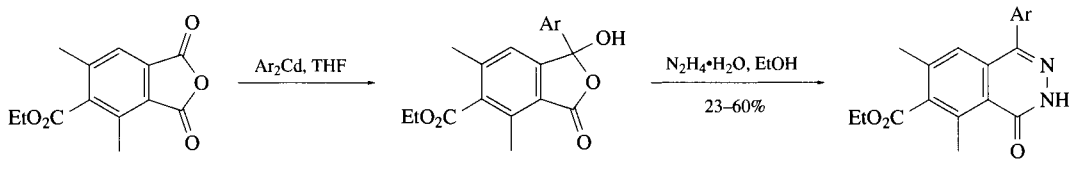
(**154**) (**155**)

Scheme 114

6.01.10.4 By Reaction of Hydrazines with Cyclic Equivalents of 1,4-Diketo and Related Compounds

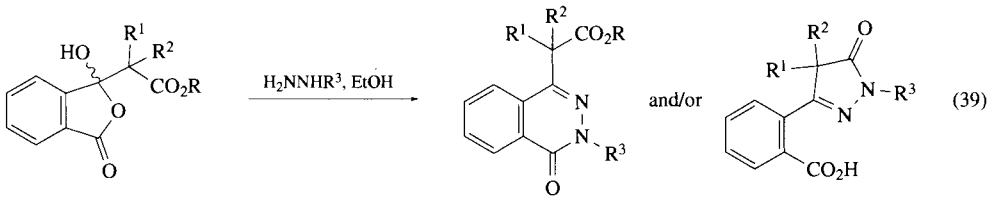
Cyclic equivalents of 1,4-diketo and related compounds include cyclic anhydrides and lactones, which may be in equilibrium with their open-chain tautomers, as well as nontautomeric cyclic compounds such as furan derivatives; analogous preparations from open chain diketo compounds are major routes to pyridazines and phthalazines considered in Section 6.01.9.2.2. The use of cyclic equivalents is discussed in two sections in CHEC-I ⟨84CHEC-I(3B)1⟩. Major synthetic approaches discussed include the preparation of 1(2*H*)-phthalazinones and 4-hydroxy analogues from 3-hydroxyphthalides and phthalic anhydrides, reaction of maleic anhydrides with hydrazines to give a wide range of 6-hydroxy-3(2*H*)-pyridazinones, and the reaction of unsaturated γ-lactones (e.g., mucohalic acids) with hydrazines to give 3(2*H*)-pyridazinones; the use of certain furan derivatives is also considered. More examples of synthesis from 1,4-dicarbonyl equivalents are given below.

Reaction of bis-iminoisoindolines, triaza analogues of phthalic anhydrides, with hydrazine gave 4-amino-1(2*H*)-phthalazineimine derivatives ⟨83JHC345⟩. The synthesis of a series of 4-aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinones (Scheme 115) has been achieved by reaction of 3-aryl-3-hydroxyphthalides, obtained by reaction of the corresponding phthalic anhydrides with arylcadmium reagents, with hydrazine hydrate ⟨91CPB2009⟩.



Scheme 115

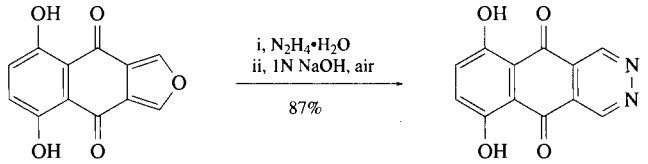
Competition between the two carboxy residues in the cyclization of alkyl 1,3-dihydro-1-hydroxy-α,α-disubstituted-3-oxo-1-benzoisofuranacetates with hydrazines can lead to phthalazinones and/or pyrazolones (Equation (39)). With ethyl esters a mixture of both products may be obtained, and while increased bulk at the α-position leads to the pyrazolone as the sole product, phthalazinones are the exclusive products from *t*-butyl esters ⟨91JOC2587⟩.



R	R^1	R^2	R^3	*Yield*	*Note*	*Yield*
Et	H	H	H		1:1 mixture	
Et	H	Me	H		1.5:1 mixture	
Et	H	Ph	H		sole product	84%
Et	Me	Me	H		sole product	85%
Bu^t	H	H	H	52%	sole product	
Bu^t	Me	Me	Bn	96%	sole product	

(39)

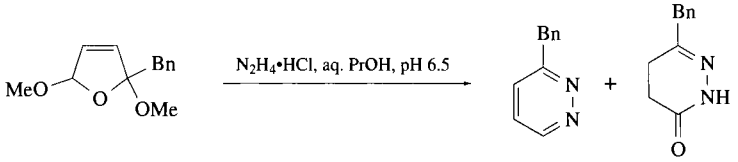
In an unusual reaction, a furan derivative has been cyclized with hydrazine to give, after aerial oxidation in alkali, 6,9-dihydroxybenzo[*g*]phthalazine-5,10-dione in excellent yield (Equation (40)). Normally furans need to be converted into unsaturated 1,4-dicarbonyl derivatives (bromine/methanol, followed by hydrolysis) prior to reaction with hydrazine to give pyridazines, but in this case the carbonyl groups activate the furan to attack by hydrazine ⟨93JHC1597⟩.



(40)

Methyl 2-trimethylsilyloxycyclopropanecarboxylates behave as 4-oxoalkanoate equivalents and react with hydrazine to give 4,5-dihydro-3(2*H*)-pyridazinones in excellent yield, though pyridazines are not formed with phenylhydrazine ⟨84S786⟩. A mixture of regioisomers is obtained when *cis*-aconitic anhydride is allowed to react with methylhydrazine free base in dimethoxyethane, but reaction with the sulfate in water gives the 4-carboxymethyl compound as the sole product ⟨83H(20)2347⟩.

Condensation of 2-benzyl-2,5-dimethoxy-2,5-dihydrofuran with hydrazine gave less than 40% of the expected 3-benzylpyridazine, as a significant proportion of the dihydrofuran underwent dismutation under the reaction conditions and up to 40% of 6-benzyl-4,5-dihydro-3(2*H*)-pyridazinone was obtained as a byproduct (Equation (41)) ⟨89JHC1787⟩.

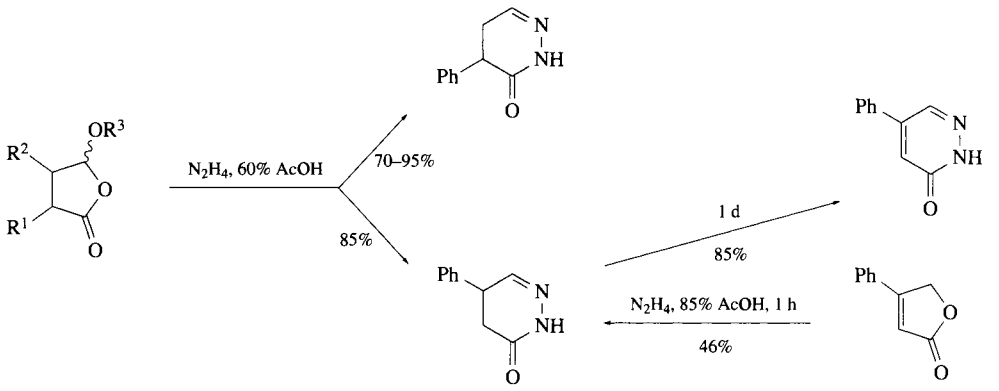


(41)

Reaction of 5-hydroxy- or 5-ethoxy-γ-lactones with hydrazine has been developed as a route to 4- and 5-aryl-3(2*H*)-pyridazinones (Scheme 116). With 3- or 4-phenyl derivatives of these lactones, 4- or 5-phenyl-4,5-dihydro-3(2*H*)-pyridazinones were formed in good yield by cyclization with hydrazine in aqueous acetic acid, with the best yields obtained from the ethoxylactones. In contrast to the saturated lactones, the related 4-phenylfuran-2(5*H*)-one reacted only very slowly under the same reaction conditions, and the concentration of acetic acid had to be increased from 60% to 85% to achieve a reasonable reaction rate. Under these conditions the furanone gave a moderate yield of 5-phenyl-4,5-dihydro-3(2*H*)-pyridazinone in one hour, but prolonged reaction gave only the oxidised product 5-phenyl-3(2*H*)-pyridazinone ⟨85JCS(P1)1627⟩.

6.01.10.5 By Cleavage of a Second Fused Ring

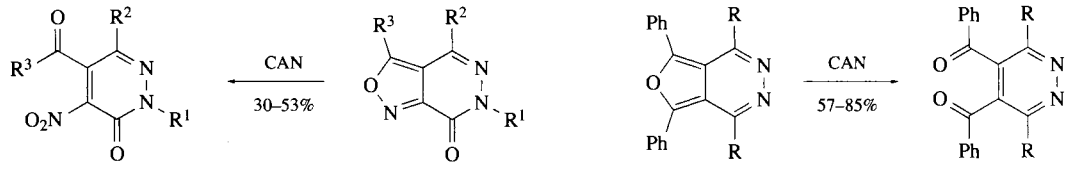
The synthesis of pyridazines by cleavage of a second fused ring was not discussed in CHEC-I, but general examples of this approach include oxidative degradation of benzene rings of benzohet-



Scheme 116

erocycles to leave carboxylic acid derivatives of more stable heterocycles. More interesting examples are given below which may have utility in the synthesis of particular types of substituted pyridazine.

Oxidative cleavage of 7-oxo-6,7-dihydroisoxazolo[3,4-*d*]- and diphenylfuro[3,4-*d*]pyridazines with ceric ammonium nitrate gives 5-acyl-4-nitro-3(2*H*)-pyridazinones and 4,5-dibenzoylpyridazines (Scheme 117), some of which can be difficult to synthesize in other ways ⟨83S1018, 89S213⟩.

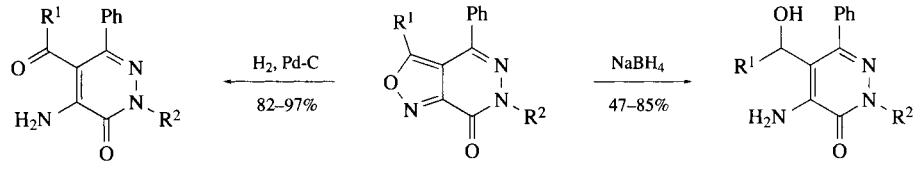


R^1 = alkyl, aryl; R^2 = Me, Ph; R^3 = alkyl

R = H, Ph

Scheme 117

Reductive cleavage of 7(6*H*)-isoxazolo[3,4-*d*]pyridazinones by catalytic hydrogenolysis or sodium borohydride (Scheme 118) gives 4-amino-3(2*H*)-pyridazinones substituted at the 5-position with keto or hydroxyalkyl groups, respectively ⟨91H(32)1173⟩. Conversion of isoxazolo[3,4-*d*]pyridazinones into pyridazinones has also been achieved in high yield by ring opening of 3-aryl derivatives with hydrazine to give 4-amino-5-(5-aryl-3-pyrazolyl)-3(2*H*)-pyridazinones ⟨86H(24)3143⟩, and by reduction of 3-methyl derivatives to give 4-amino-5-acetyl-3(2*H*)-pyridazinones ⟨89H(29)1595⟩.

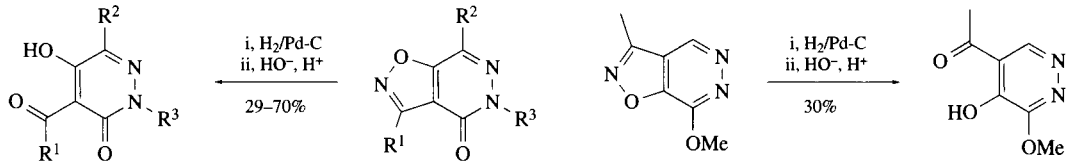


R^1 = H, Me; R^2 = H, Me, Ph

Scheme 118

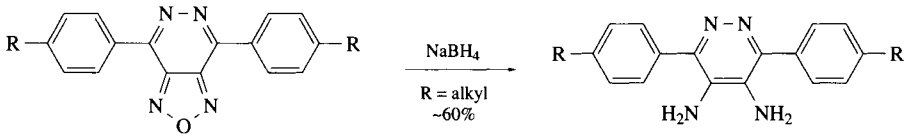
A hydrogenolysis–hydrolysis sequence applied to isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones and to 7-methoxy-3-methylisoxazolo[4,5-*d*]pyridazine gives moderate to good yields of novel 4-acyl-5-hydroxy-6-substituted-3(2*H*)-pyridazinones ⟨90JHC927⟩ and 5-acetyl-4-hydroxy-3-methoxypyridazine ⟨85JHC1561⟩ that can be difficult to prepare by other means (Scheme 119). The utility of the method depends upon the availablity of the substrates, which in the case of the isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones are made from ethyl 3-methylaminobutenoate by reaction with acetoxyacetyl chlorides, cyclization with hydroxylamine, oxidation of alcohol to carbonyl, and cycli-

zation with hydrazines, which allows variation of the 3-, 5-, and 7-substituents of the substrates ⟨90JHC927⟩.



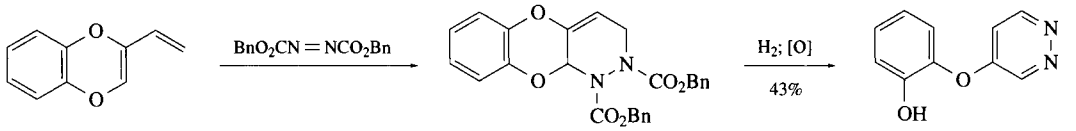
Scheme 119

Reduction of diaryloxadiazolo[3,4-*d*]pyridazines with borohydride has been used as a route to symmetrically substituted 3,6-diaryl-4,5-diaminopyridazines (Equation (42)) ⟨92JHC87⟩.



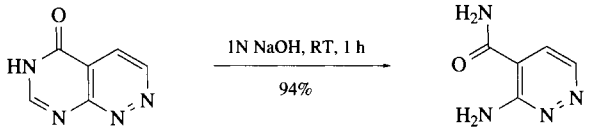
(42)

A Diels–Alder reaction between dibenzyl diazodicarboxylate and 2-vinyl-1,4-benzodioxin gave a fused pyridazine which on hydrogenolysis underwent debenzylation, decarboxylation, ring opening, and aromatization to give 4-(2-hydroxyphenoxy)pyridazine (Scheme 120) ⟨90T921⟩.



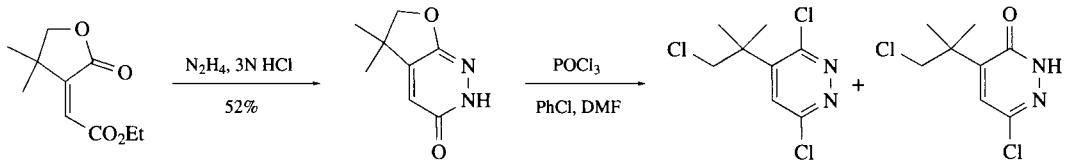
Scheme 120

3-Amino-4-carboxamidopyridazine can be obtained in high yield by aqueous base hydrolysis of 4(3*H*)-pyrimido[4,5-*c*]pyridazinone (Equation (43)). The pyrimido[4,5-*c*]pyridazinone, which is readily prepared from 6-hydrazino-4(3*H*)-pyrimidinone by condensation with glyoxal sodium bisulfite followed by treatment with trifluoroacetic acid, is even hydrolyzed in boiling water. This lability is shared by some derivatives ⟨85JOC346⟩.



(43)

Cyclization of the unsaturated ester lactone (**156**) with hydrazine gives the fused furopyridazine derivative (**157**) which undergoes ring opening on chlorination with phosphorus oxychloride to give the dichloropyridazine (**158**), (Scheme 121), but the yields are only moderate ⟨88JOC5704⟩.

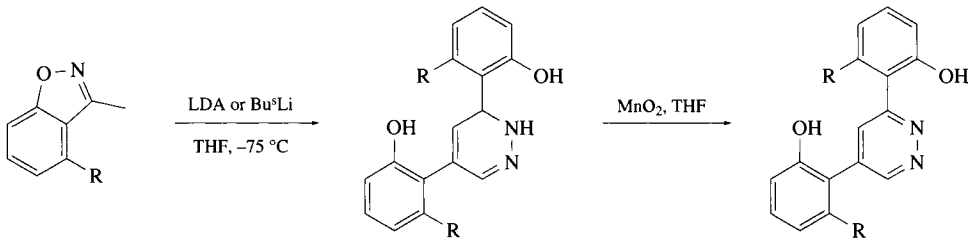


(**156**) (**157**) (**158**) 50% 15%

Scheme 121

6.01.10.6 By Other Methods

An unexpected example of the less common N—N bond formation in the preparation of pyridazines is provided by the reaction of 3-methyl-1,2-benzisoxazoles with strong base in the absence of an electrophile (Scheme 122). The reaction, which is postulated to proceed via an *o*-hydroxyphenylazirine, gives about 40% yields of the dihydropyridazines (**159**) which are very labile with respect to oxidation and tautomerization, but manganese dioxide oxidation without purification of the crude intermediate (**159**, R = OH) gives a 61% yield of 3,5-bis(2,6-dihydroxyphenyl)pyridazine (**160**, R = OH) ⟨89JOC4970⟩.

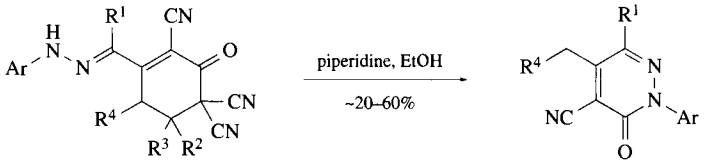


(159) (160)

R = OH or O-TBDMS

Scheme 122

2-Aryl-4-cyano-3(2*H*)-pyridazinones (**161**) with 5- or 5,6-alkyl substitution (including 5,6,7,8-tetrahydrocinnolin-3(2*H*)-ones, $R^1R^4 = (CH_2)_3$) are produced from 3-arylhydrazonomethyl-2,6,6-tricyanocyclohexen-2-ones (**162**) (obtained from aromatic diazonium salts and alkylidenemalononitrile dimers) by treatment with catalytic piperidine in ethanol (Equation (44)). The reaction involves a formal loss of an alkylidenemalononitrile unit and bond formation between the hydrazone and the carbonyl group; in toluene the substrate only undergoes tautomerization to an enol. Yields of pyridazinones are in the lower range with the bulkier R^2, R^3 substituents ⟨93AP(326)29⟩.

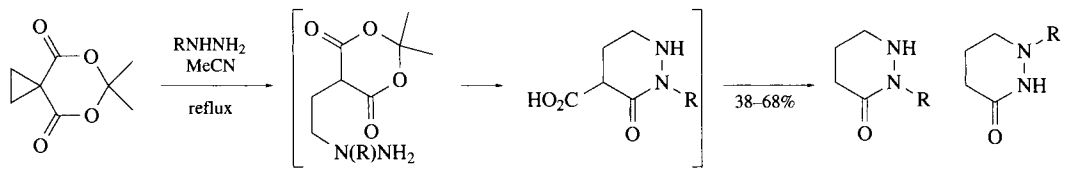


(44)

(162) (161)

R^1, R^4 = H, alkyl; R^2, R^3 = alkyl; Ar = Ph, 4-subst. C_6H_4

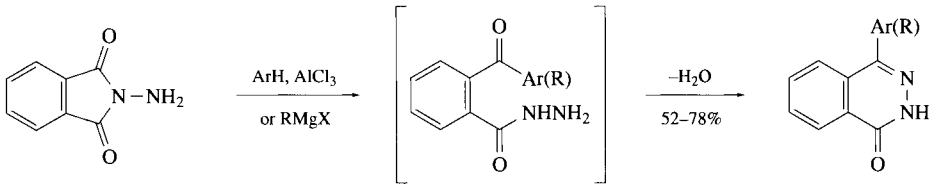
Reaction of monosubstituted hydrazines with the readily available spirocyclic cyclopropanedicarboxylates (**163**) gives 1-substituted 1,4,5,6-tetrahydropyridazin-3(2*H*)-ones (**164**) in a one-pot reaction (Scheme 123). Initial attack is thought to be a homo-Michael type of addition by the substituted hydrazine nitrogen; decarboxylation occurs under the reaction conditions. The formation of the alternative pyridazinone (**165**) by attack of the unsubstituted hydrazino nitrogen was only observed (< 5%) with (4-chloro-2-methylphenyl)hydrazine ⟨93H(36)219⟩.



(163) R = aryl, Bu^t (164) (165)

Scheme 123

4-Aroyl-1(2*H*)-phthalazinones can be made by a new Friedel–Crafts type reaction of *N*-aminophthalide ⟨84T2983⟩. Suitable aromatic substrates such as toluene are acylated in the presence of aluminum chloride and the intermediate hydrazides recyclize under the reaction conditions to give phthalazinones (Scheme 124). The range of products available by this approach is limited by the reactivity and regioselectivity of aromatics in Friedel–Crafts acylation reactions, but may be extended by the use of Grignard reagents to give additional products including benzyl derivatives.



Scheme 124

6.01.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

6.01.11.1 Introduction

The best methods for the synthesis of the parent compounds and some important derivatives were covered in CHEC-I ⟨84CHEC-I(3B)1⟩. Factors to take into account in the selection and comparison of suitable routes for the synthesis of target (benzo)pyridazines include consideration of the chemistry of these ring systems, the synthetic utility of commercially available (benzo)pyridazines, the availability of precursors, and safety. In many instances the flexibility of the synthetic approach, and factors such as scale and cost, will also be important.

In general the (benzo)pyridazines are electron deficient and thus the introduction of substituents into the heterocyclic ring will often be by nucleophilic substitution of a suitable leaving group, most commonly chlorine, while electrophilic substitution of hydrogen is only of use in the presence of powerful electron donors such as hydroxy (or keto tautomers) and amino groups. Derivatization via diazotization of amino groups in the heterocyclic ring is of limited use because of the marked susceptibility of the diazonium group to displacement by water. Regioselectivity is an important issue in the displacement of halogens from polyhalo compounds because of their ready availability and the ease of hydrogenolysis of residual halogens that are not required. Heterocyclic ring hydroxy/keto groups are useful in synthesis as, in addition to their electron donor properties, they may be converted into other functional groups such as chloro and thio, and allow alkylation of a ring nitrogen. The utility of *N*-oxides in modifying the reactivity of pyridine-like ring systems may also be exploited.

Many (benzo)pyridazines are made from 1,4-diketo compounds, and the industrial supply of, for example, maleic and phthalic anhydrides and mucohalic acids make them attractive and widely used starting materials, which can be used in conjunction with substituted hydrazines to give a range of *N*-substituted derivatives. Some other 1,4-diketo compounds are commercially available on a smaller scale, including, for example, certain 3-benzoylpropionic acids from which 6-aryl-4,5-dihydro-3(2*H*)-pyridazinones can be prepared. When such precursors are not commercially available then ease and scope of synthetic approaches to the starting materials must be considered, but for established routes, such as 6-aryl-4,5-dihydro-3(2*H*)-pyridazinones from 3-aroylpropionic acids, a variety of synthetic methods have been developed so that a wide range of (substituted)aroyl derivatives can be prepared. Synthetically useful preformed (benzo)pyridazine derivatives that are commercially available include 4,5-dichloro-3(2*H*)-pyridazinone, 3,6-dichloropyridazine, and 1,4-dichlorophthalazine.

Many syntheses of (benzo)pyridazines involve the use of hydrazine and its derivatives, and the safe handling and disposal of these materials should be given careful consideration. Hydrazine and its salts are potential carcinogens and many hydrazine derivatives have, or are likely to have, toxic properties and all should be handled with care. In addition, hydrazine can react violently with oxidizing agents and the explosive decomposition of hydrazine vapor in air can be catalyzed by, for instance, rust.

6.01.11.2 Parent Compounds

The parent compounds pyridazine, phthalazine, and cinnoline are commercially available. However, if synthesis is necessary then pyridazine is easily prepared by catalytic hydrogenation of 3,6-dichloropyridazine, the most readily available halo precursor. Phthalazine can be prepared in a similar manner from 1,4-dichlorophthalazine, though cyclization of α,α,α′,α′-tetrachloro-*o*-xylene with hydrazine sulfate may be more economic. Phthalazine has also been prepared in 68% yield from 1,4-dihydrazinophthalazine by treatment with oxygen in the presence of sodium hydroxide; the dihydrazino precursor is readily made in 83% yield from the cheap starting material 1,2-dicyanobenzene ⟨86JMC1329⟩. Reductive approaches are not very successful for the synthesis of cinnoline, which is still best prepared by thermal decarboxylation of the 4-carboxylic acid ⟨51JCS1971⟩, while benzo[*c*]cinnoline is conveniently prepared by sodium borohydride reduction of 2,2′-dinitrobiphenyl ⟨87JHC745⟩. Benzo[*de*]cinnoline can be prepared in about 50% yield by reaction of hydrazine with 8-hydroxy-1-naphthaldehyde ⟨75JCS(P1)419⟩.

6.01.11.3 Derivatives

Pyridazinones constitute a major class of pyridazine derivatives. In the case of 6-(hetero)aryl-4,5-dihydro-3(2*H*)-pyridazinones these compounds are generally prepared from 4-(hetero)aryl-4-oxobutanoic acid derivatives. However, if the dihydro-3(2*H*)-pyridazinone is only an intermediate to the corresponding, oxidized, 3(2*H*)-pyridazinone, then the direct one-pot preparation of the latter from methyl heteroarylketones will almost invariably be advantageous even if the appropriate ketone is not commercially available ⟨93S334⟩. The isomeric 5- and 4-(hetero)aryl-3(2*H*)-pyridazinones are less well known, but 5-aryl derivatives can be prepared from arylacetaldehydes ⟨81JOC4889⟩, though these starting materials are not very convenient. 4-(Hetero)aryl-3(2*H*)-pyridazinones are readily prepared from 4,5-dichloro-3(2*H*)-pyridazinones by reaction with (hetero)aryl Grignards and hydrogenolysis of the residual 5-chlorine ⟨94MI 601-01⟩.

4(1*H*)-Cinnolinones are usually prepared by the Borsche synthesis, that is, by cyclization of the diazonium salts prepared from *o*-aminophenyl alkyl ketones under strongly acidic conditions, while 3(2*H*)-cinnolinones can be obtained from sodium *o*-aminomandelates via *o*-hydrazinomandelic acids by cyclization then dehydration in acid (Neber–Bossel synthesis). 1(2*H*)-Phthalazinones are prepared from phthalides by condensation with hydrazines.

Halo derivatives of pyridazines are particularly important both as intermediates and in their own right. 4,5-Dichloro-3(2*H*)-pyridazinone is an especially useful intermediate, readily prepared from mucochloric acid and semicarbazide in a two-step process ⟨83JHC199⟩. Other valuable chloropyridazines, such as 3,4,5- and 3,4,6-trichloropyridazines are made from the corresponding 4,5-dichloro- or 4-chloro-6-hydroxy-3(2*H*)-pyridazinones by treatment with phosphoryl chloride. The high reactivity of polyhalopyridazines, and other halopyridazines substituted with electron withdrawing groups, results in a high potential for the compounds to be irritant, even vesicant, a problem exacerbated by the significant vapour pressures of some of the simple polyhalo derivatives. In addition, hydrolysis, particularly acid-catalysed hydrolysis, can occur during reaction work up (methods to minimize this and subsequent side reactions have been detailed ⟨63JOC218⟩) and the reactive halo derivatives may have limited shelf life. Normally pyridazinones are very reactive towards phosphoryl chloride and only short reaction times under relatively mild conditions are required; apparently incomplete reaction may be due to hydrolysis of the product. In the presence of phosphoryl and phosphorus pentachlorides additional chlorination of the ring can occur, for example 6-phenyl-3(2*H*)-pyridazinone gives 3,5-dichloro-6-phenylpyridazine ⟨94MI 601-02⟩.

Synthetic approaches that have been developed or extended in the review period and have the potential for general use include: radical alkoxycarbonylation to give 4-alkoxycarbonylpyridazines (Section 6.01.5.6); preparation of 4(5)-aminopyridazines by direct amination with ammonia or amide ions followed by oxidation (Section 6.01.5.4.3); C—C bond formation by palladium catalyzed coupling reactions of pyridazine *O*-triflates (Section 6.01.7.12.2) and halopyridazines (Section 6.01.7.15.1); inverse electron demand Diels–Alder reactions for the synthesis of 3,6-disubstituted pyridazines and 1,4-disubstituted phthalazines (Section 6.01.10.3). The utility of the Staudinger reaction for the preparation of primary aminopyridazines from azides by hydrolysis of the resultant phosphazenes should also be mentioned. Thus, azides are easily prepared by displacement of chlorine and the reaction sequence is applicable to a wide range of substrates for which catalytic hydrogenation is either inappropriate or, in the case of azides α to the ring nitrogens, unsuccessful due to the unfavourable equilibrium between the azido and tetrazolo forms ⟨89S666⟩.

6.01.12 IMPORTANT COMPOUNDS AND APPLICATIONS

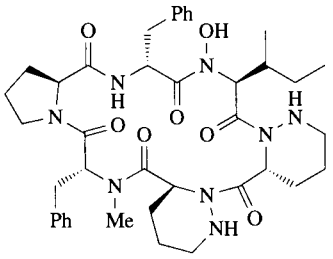
6.01.12.1 Introduction

In CHEC-I the applications of pyridazines, cinnolines and phthalazines were briefly summarized ⟨84CHEC-I(3B)1⟩. The antibacterial monamycins were cited as a rare example of naturally occurring pyridazines, while the growth retardant, herbicidal, and fungicidal activities of synthetic pyridazine derivatives are mentioned. Note was made of the hypotensive and antihypertensive activities of hydralazine and dihydralazine, and that in the cinnoline series only 3-and 4-amino derivatives exhibit biological activity.

6.01.12.2 Compounds That Occur in Nature

Pyridazine derivatives are not commonly found in nature but those that do occur include the monamycin and cirratiomycin antibiotics, and luzopeptin A, a dimeric cyclic depsipeptide which intercalates with DNA and has antibiotic and antitumor activity. These compounds contain hexahydro- or tetrahydropyridazine residues which, in the case of luzopeptin A and the cirratiomycins, is present as the novel amino acid unit 3(*S*)-carboxy-4(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine ⟨89JOC3260⟩.

Additional examples that have been reported include the antibiotic verucopeptin, a 19-membered cyclodepsipeptide containing a single piperazic acid residue, which has *in vivo* antimelanoma activity ⟨93JAN928⟩. This compound is structurally related to other cyclodepsipeptides that contain two piperazic acid residues: azinothricin ⟨86JAN17⟩, A83586C ⟨88JAN726⟩, variapeptin and citropeptin ⟨90JAN477⟩ and L-156,602 ⟨91JAN249⟩. Another related natural product (**166**) has been identified as a lead to oxytocin antagonists and chemical modification of the two enantiomeric piperazic residues has been undertaken to give more potent compounds, for example, (**91**) ⟨90JMC2321, 92JOC4394⟩. The piperazic structure is also found in the matlystatins, a series of acyclic derivatives of which matlystatin A (**167**) is a reversible inhibitor of type IV collagenase ⟨92JAN1723, 92JAN1733⟩. Pyridazomycin (**168**) is an antifungal antibiotic in which the terminal nitrogen of an ornithine residue is incorporated into a pyridazine ring; pyridazine-4-carboxamide is produced by mild basic hydrolysis ⟨88JAN595⟩.



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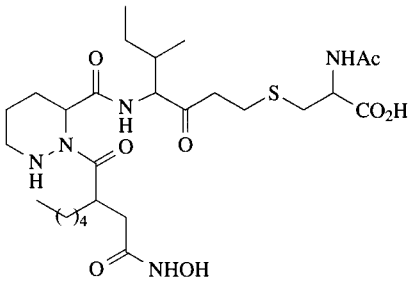

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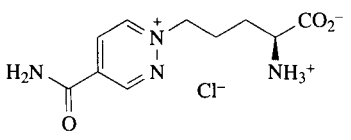
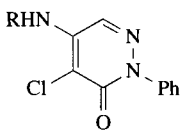


(168)

6.01.12.3 Agrochemicals

One of the simplest pyridazine derivatives, maleic hydrazide, is a long established herbicide which is still widely used, among other purposes, to retard the growth of established plants such as hedges

and grass verges to reduce the need for cutting. Many other pyridazines have herbicidal activity, particularly derivatives of 4,5-dichloro-3(2*H*)-pyridazinone such as the pre-emergent herbicides Chloridazone (**169**, R = H), Norflurazone (**169**, R = Me), and BAS 44521 (**170**), which may act by the inhibition of chlorophyll synthesis. Pyridate (**171**) is a structurally different type of herbicide which is manufactured on a considerable scale.



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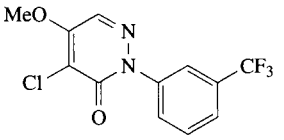

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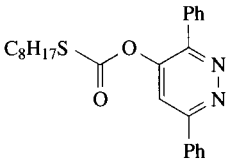

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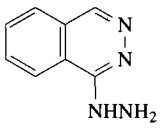
6.01.12.4 Pharmaceuticals

The first major product from the (benzo)pyridazine class was Hydralazine (**172**), a direct acting pre-capillary vasodilator, introduced in the early 1950s as an antihypertensive agent. This compound is still in use, though a large part of the market has been taken by other types of antihypertensive agents. Papers continue to be published on the chemistry of this compound, and it is frequently used as a standard vasodilator in experimental work. Sulfamethoxypyridazine (**173**) was one of the early long-acting sulfonamide antibacterial agents, introduced in the mid 1950s. The phthalazine Azelastine (**9**) is an antihistamine used in the treatment of allergic rhinitis, while the pyridazine Amezinium metilsulfate (**174**) is a sympathomimetic agent with cardiostimulant properties that is available in some markets.



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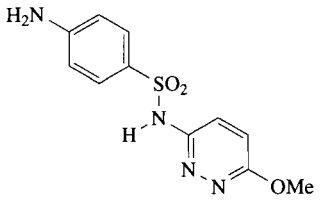

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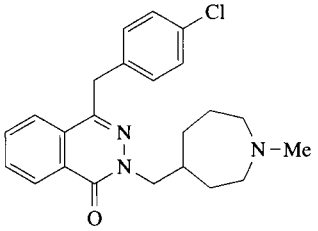

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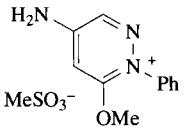

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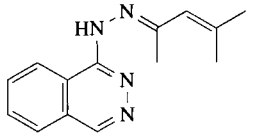
Compounds which have reached the stage of being launched as pharmaceutical products include Budralazine (**175**), an antihypertensive, Cinoxacin (**176**), a cinnoline analogue of quinoline antibacterials used for urinary tract infections, Minaprine (**177**), an atypical antidepressant which may act through a dual serotoninergic/dopaminergic mechanism, and Emorfazone (**178**), an analgesic antiinflammatory agent.



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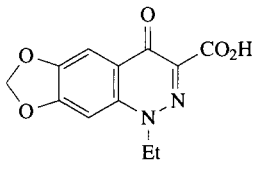

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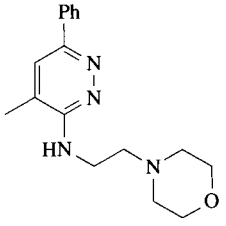

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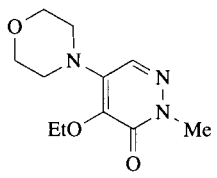

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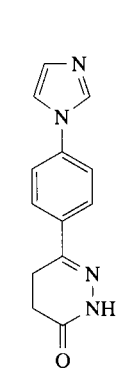
Significant commercial interest in the development of (benzo)pyridazine derivatives, particularly pharmaceutical uses of pyridazines, over the review period is shown by the large number of patents filed in this area, and a review of the pharmacological activity of pyridazine derivatives (for the period 1975–1988) had to be divided into two parts because of the number of references which warranted mention ⟨B-90MI 601-01, B-92MI 601-01⟩. It is usual for very few drug candidates to reach the market and this is true for the many 4,5-dihydro-3(2*H*)-pyridazinones designed, as positive inotropic agents for the treatment of congestive heart failure, to replace older less satisfactory drugs

such as the cardiac glycosides and catecholamines. The newer agents are mostly selective inhibitors of the cGMP-inhibited phosphodiesterase (PDE III), and while many are effective in increasing the force of contraction of the heart in animals and man, some early examples of this pharmacological class were thought to show increased mortality in clinical trials. The development of newer agents of this group has thus been hampered by the possibility that this effect is class dependent, with the attendant ethical implications of testing the compounds in man, and the need for large scale clinical trials to prove that mortality is not adversely affected. PDE III inhibitors also have other pharmacological effects, including vasodilatation, bronchodilatation, and the inhibition of blood platelet aggregation, and a drug may yet emerge from this class. Pyridazinones which have PDE III inhibition as a major component of their mechanism of action include Imazodan (**179**), Bemoradan (**180**), KF-15232, Levosimendan, ORG 20494 (**181**), Pimobendan (**182**), Siguazodan (**183**), SK&F 95654, Indolidan (**184**) and MCI-154; the increased activity seen with the 5-methyl-4,5-dihydro-3(2*H*)-pyridazinone PDE III inhibitors is associated with the *S*-methyl configuration. Some pyridazinones, such as Zardaverine (**185**), show combined PDE III and PDE IV inhibitory activity and have been investigated for the treatment of asthma as they may show combined bronchodilatory and antiinflammatory activities. Yet further PDE inhibition, this time of PDE V, is shown by phthalazines like MY 5445 (**186**).



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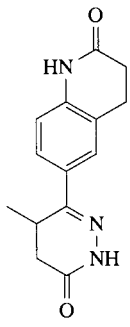

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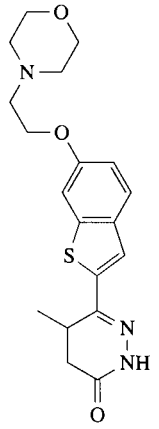

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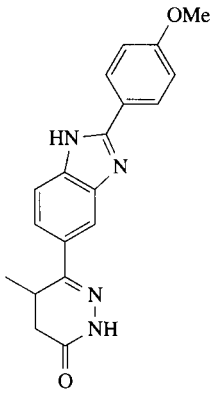

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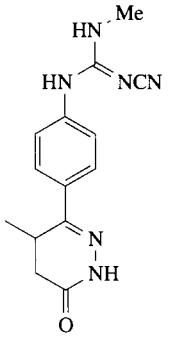

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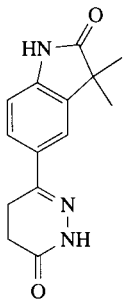

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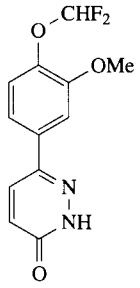

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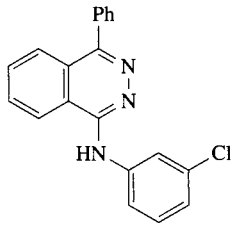
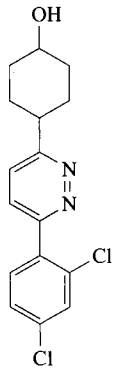


(**186**)

In addition to Minaprine, which has been marketed as an antidepressant, a number of other (benzo)pyridazine derivatives have been under investigation for their central nervous system activity. These include Endixaprine (**187**), a sedative hypnotic with a benzodiazepine-like profile, F-2692 (**188**), an anxiolytic, ICI-D-7569 (**189**), an anxiolytic with D2 partial agonist activity, and SR-46559 (**190**), a selective muscarinic M1 receptor partial agonist with memory-enhancing effects of potential use in Alzheimer's disease. Gabazine (**191**) is a potent and selective GABA-A antagonist used as a tool compound in GABA-A binding assays, while the thiomuscimol analogue (**192**) is an order of magnitude more potent; these type of compounds cause convulsions in mice ⟨92JMC4092⟩.

Other compounds which have been in development include several cardiovascular agents such as the antihypertensives Cadralazine (**193**), a hydrazinopyridazine derivative, GYKI-12743 (**194**), a peripheral post synaptic α1/α2 antagonist, and the potassium channel activator EDM-57283 (**195**),



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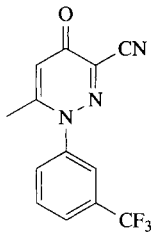

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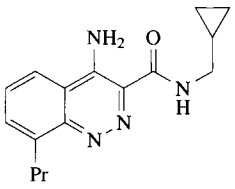

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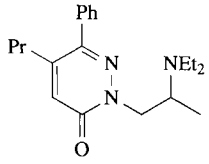

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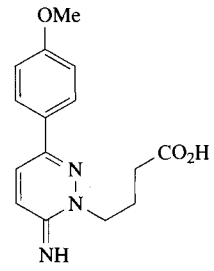

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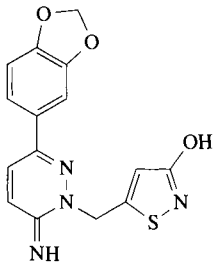

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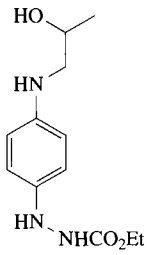

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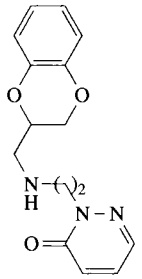

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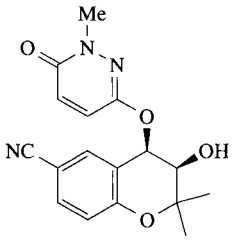
which as a vasodilator and bronchodilator may have use in the treatment of hypertension, coronary artery disease, and asthma. NZ-107 (**196**) was in development as an antiasthmatic agent. Zopolrestat (**197**) is a phthalazinone that has been in clinical trials; it inhibits aldose reductase and has potential use in the prevention of retinopathy, neuropathy, and cataract formation in diabetes.



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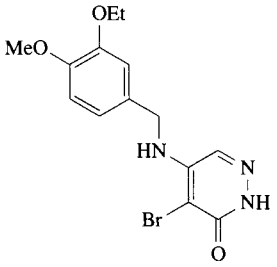

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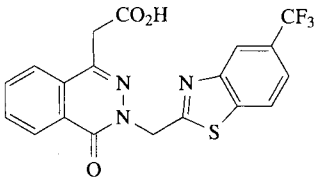

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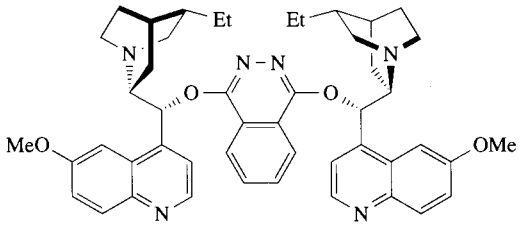
6.01.12.5 Asymmetric Dihydroxylation Catalysts

Asymmetric synthesis has grown in importance since the early 1980s, especially in the context of pharmaceuticals where regulatory pressure is toward the development of single stereoisomers which may have advantages of selectivity, and older racemic products may be redeveloped as single enantiomers. A major development in the catalytic asymmetric dihydroxylation of alkenes using osmium tetroxide has been the discovery of the 1,4-phthalazine class of cinchona alkaloid ligands, for example the dihydroquinidine $(DHQD)_2$-PHAL (**198**) and dihydroquinine $(DHQ)_2$-PHAL (**199**) derivatives, from over 300 examples investigated by Sharpless and coworkers. These catalysts, which are effective at concentrations of 1 mole% or less, promote the asymmetric dihydroxylation of four out of the six classes of alkene, that is 1,1-, 1,2-*trans*, 1,2,3-, and monosubstituted alkenes.

Best results are obtained with 1,2- and 1,2,3-substituted (especially aromatic) alkenes, for which reaction rates can be further promoted by organic sulfonamides. Reactions are normally carried out in 50% aqueous *t*-butanol at 0 °C and give high enantioselectivity (70–99.5% *ee*) and yields (80–



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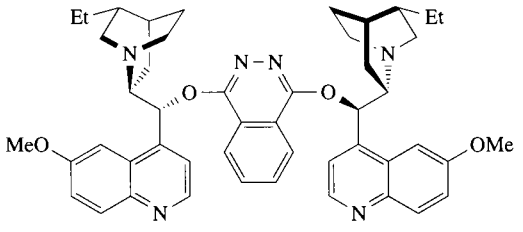
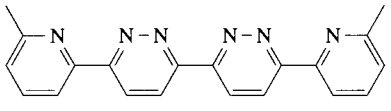


(199)

98%); reciprocity between the pseudo-enantiomeric ligands is good. The ligands are readily prepared, reportedly on a 250 gram scale, by reaction of the free base akaloids with 1,4-dichlorophthalazine and solid potassium carbonate and potassium hydroxide in toluene under azeotropic distillation conditions. For small scale reactions the catalytic ligands and osmium tetroxide can be blended with the bulk inorganic reagents (potassium ferricyanide and potassium carbonate) to give convenient reagent mixtures which are also commercially available. The cheaper quinidine and quinine ligands are virtually as effective as catalysts, despite rapid dihydroxylation of the double bonds in these ligands under the reaction conditions. An x-ray structure of $(DHQ)_2$-PHAL has been published and it has been demonstrated that each quinuclidine ligand acts independently as activity is unaffected by quaternisation of one alkaloid residue ⟨92JOC2768, 93JOC844⟩. Detailed kinetic studies have been carried out in an attempt to understand the factors controlling the high enantioselectivity. With the phthalazine ligands both the rate of reaction and the enantioselectivity are increased, probably due to stabilisation of the transition state by off-set parallel and edge-to-face interaction of the aromatic substituent of the substrate in the cleft formed between the phthalazine and two methoxyquinoline rings ⟨94JA1278⟩. This technology is already available for commercial scale manufacture, and its use in, for example, the synthesis of carbohydrates in tandem with enzymatic aldol reactions has been described ⟨94JA558⟩. Asymmetric dihydroxylation using $(DHQ)_2$-PHAL catalyst has been utilized in an efficient synthesis of the *N*-benzoyl-3-phenylisoserine C-13 side chain of taxol. Methyl cinnamate is dihydroxylated to give methyl 2,3-dihydroxy-3-phenylpropionate in high yield and as the single (2*R*,3*S*) enantiomer. In this procedure, carried out on up to the 2 molar scale with only 0.5 mole% catalyst, *N*-methylmorpholine *N*-oxide was used as the oxidant because this allowed the reaction to be run under more concentrated conditions than is possible with potassium ferricyanide ⟨94JOC5104⟩. Similar asymmetric dihydroxylation catalysts based on a 3,6-pyridazine linker have also been described ⟨93JA3828, 93JA12579⟩.

6.01.12.6 Other Uses

The ability of pyridazines to form metal complexes has found applications. For example, a series of diazacrown ethers, modified by the introduction of heterocyclic substituents on to the aza links (by high pressure reaction with, for example, 3-chloro-6-methylpyridazine) show significantly modified properties and are particularly selective for the extraction and transport of silver ⟨92JOC542⟩. In the development of artificial photosynthetic systems the synthesis and properties of ruthenium complexes of 3,3′-bispyridazine-6,6′-oligo(ethylene glycol) derivatives as potential photosensitizers has been described. The bispyridazinyl derivatives are much more stable than the corresponding pyridine derivatives with respect to photolytic degradation, clearly an important requirement for this type of compound ⟨93JA12362⟩. Pyridazine complexes have also found application in the growing area of molecular self-assembly. Thus, 6,6′-bis[2-(6-methylpyridyl)]-3,3′-bipyridazine (**200**) and silver ions have been shown to assemble into a supermolecule consisting of six ligands and nine ions arranged as a 3×3 grid with a silver ion located at each junction ⟨94AG(E)2284⟩.



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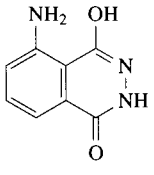

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The chemiluminescence reactions of luminol (**201**) and related phthalazines have found analytical application, particularly in biological systems where the inherent signal strength and low signal to noise ratio contribute to sensitivity. The hydrogen peroxide/luminol system has been used for the on-line determination by chemiluminescence of nitric oxide (the active principle of the biological messenger "endothelium derived relaxant factor") in isolated organ perfusates. The method, which has a lower detection limit of 100 fM and linear response to 1 nM, was used to correlate prefusion pressures in isolated kidneys with nitric oxide levels ⟨93ANC1794⟩. A chemiluminescent detection system for the analysis of naturally occurring α-keto acids has been developed based on their condensation with 6,7-diamino-2,3-dihydrophthalazine-1,4-dione to produce chemiluminescent pyridazino[4,5-*g*]quinoxaline derivatives ⟨90CPB3491⟩. A sensitive assay for *N*-acetyl-β-D-glucosamidinase activity has been devised by the incorporation of an enzyme cleavable *N*-acetyl-D-glucosaminoside group into phthalazinedione containing a fluorogenic 7-(6-diethylaminobenzofuranyl) substituent. Following enzymatic cleavage the liberated 7-(6-diethylaminobenzofuranyl)-2,3-dihydrophthalazine-1,4-dione is detected by chemiluminescence produced by hydrogen peroxide/ferric ion catalysed oxidation ⟨91CPB411⟩. Luminol itself has been derivatized in a similar way to give a nonchemiluminescent product, from which luminol is liberated by the action of glucosamidinase and detected by its chemiluminescence ⟨90CPB1323⟩.

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6.02
Pyrimidines and their Benzo Derivatives

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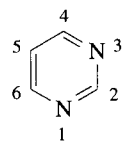
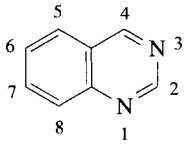
6.02.1 INTRODUCTION

Pyrimidine (**1**) is the trivial name for 1,3-diazine; two *meta*-oriented CH units in benzene have been replaced by nitrogen atoms. Quinazoline (**2**) is benzo-fused pyrimidine and is defined by the fusion nomenclature as benzo[*d*]pyrimidine, alternatively as 1,3-diazanaphthalene by the replacement nomenclature. Perimidine (**3**) is the trivial name for the *peri*-naphtho-fused pyrimidine system. It may be called (fusion names) 1*H*-benzo[*de*]quinazoline or 1*H*-naphtho[1,8-*de*]pyrimidine, or alternatively 1*H*-1,3-diazaphenalene by the replacement nomenclature. However, the three "trivial names" are all system names accepted by IUPAC and approved as parents for further fusion name formation; the benzo- and naphtho-pyrimidine names are therefore not used. In principle, additional rings can be fused onto the benzo or naphtho moiety in either quinazoline or perimidine without any profound alteration in heterocyclic reactivity. Aceperimidylene (**4**) and aceperimidine (**5**) are the trivial names for two cyclopenteno and cyclopentano fused perimidines.



(1)



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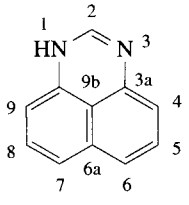

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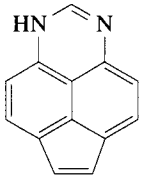
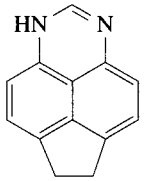


(4)

Aceperimidylene



(5)

Aceperimidine

Pyrimidine, and in part quinazoline, chemistry, was reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). The most comprehensive review of pyrimidine chemistry to date is found in the book "The Pyrimidines" with Brown as the main editor, and in previous books with the same title and author ⟨B-94MI 602-01⟩. A comprehensive volume on quinazoline chemistry dates back to 1967; the title is "Quinazoline" with Armarego as main editor ⟨B-67MI 602-01⟩. Collected literature on the perimidines can be found in a review article published in 1981 ⟨81RCR816⟩.

An extensive compilation and tabulation of melting points, with reference to spectroscopic data when available, and pK_a values, is published in ⟨B-94MI 602-01⟩.

Pyrimidine has one axis of symmetry, about the 2,5 -axis, it has three different pairs of bond lengths and four different bond angles. Accordingly, in ^{1}H and ^{13}C NMR spectra the ^{1}H- and ^{13}C-nuclei are found at three different chemical shifts. Symmetry is lost on unequal substitution at the 4- and/or 6-position. Quinazoline has no symmetry except for the molecular plane. Perimidine, however, is effectively symmetrical about the 2-position and the central (9b,6a)-bond because of prototropy between N1 and N3.

Pyrimidine is π-deficient because of electronegative *N*-atoms. Consequently, the electron densities at the 2- and 4-/6-positions are depleted, and these positions become strongly electrophilic, and are herein referred to as the electrophilic positions. The electron density at the 5-position is only slightly depleted; the ring therefore retains benzenoid properties at this position, which is herein referred to as the benzenoid position. The electron density at the *N*-atoms is greatly enhanced; the *N*-atoms constitute the basic and nucleophilic centers in pyrimidine. In quinazoline, the pyrimidine ring retains the properties of the parent heterocycle while the carbocyclic ring has benzene-like properties.

Perimidine is one of the few azines in which the lone pair of a pyrrole-like nitrogen participates in the π-system of the molecule. Perimidine is therefore a 14-π electron system, isoelectronic with the phenalenyl anion. An important consequence of this interaction is a transfer of electron density from the heterocyclic ring into the naphthalene moiety. Therefore perimidine exhibits simultaneously the characteristics of both π-deficient and π-excessive systems ⟨87H(26)1029⟩.

Hydroxy, thiol, and amino groups in pyrimidine exist in tautomeric equilibria with oxo, thioxo, and imino forms. This complicates the nomenclature. These derivatives are normally named according to the dominant tautomeric form. An amino group in an electrophilic position exists predominantly as such; the compound is named as an amine. Pyrimidines with a hydroxy or thiol group in an electrophilic position are dominated by the oxo or thioxo forms and are named as such, or with -one or -thione suffixes, if these are the principal groups, together with an indication of the main location of the *H*-atom. In the benzenoid 5-position, these derivatives are mainly present in the hydroxy, thiol, or amino forms and are named as such. Similar considerations apply to the nomenclature of quinazolines and perimidines.

6.02.2 THEORETICAL METHODS

The electron distribution diagrams for pyrimidine (**6**), quinazoline (**7**) and perimidine (**8**), and aceperimidylene (**9**) show gain or loss of π-electrons at each atom (Figure 1). The values for pyrimidine are calculated by the VESCF method. It is evident that there is a considerable depletion of electron density at the 2- and 4-/6-positions, and a slight depletion at the 5-position. There is a greatly enhanced density at the *N*-atoms.

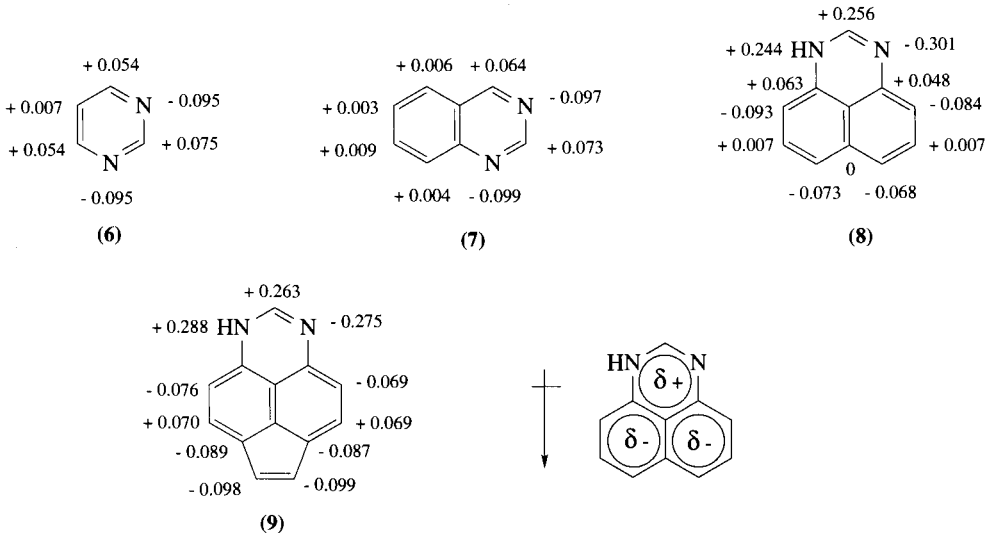


Figure 1 Electron distribution diagrams for pyrimidine (**6**), quinazoline (**7**), perimidine (**8**), and aceperimidylene (**9**).

The figures from electron density calculations for quinazoline vary with the method used. The values given were calculated as for pyrimidine. The electron density values for the 2- and 4-positions are comparable to those for the corresponding positions in pyrimidine. The benzo-carbons in quinazoline are roughly comparable to C5 in pyrimidine ⟨67MI 602-02⟩.

For perimidine, quantum-mechanical calculations with the simple Hückel method, the Pariser–Parr–Pople method, or the CNDO/2 method show transfer of electron density from the heterocyclic to the carbocyclic system with gain or losses of π-electrons at each atom. C2 in the hetero-ring has relatively high positive charge, whereas the naphthalene ring is negatively charged with maximum negative charge in the 4- and 9-positions, less in the 6- and 7-positions, and virtually zero in the 5- and 8-positions which corresponds to the *o*-, *p*-, and *m*-positions, respectively, in the naphthalenediamine system. Hence electrophilic substitution chemistry similar to that of 1,8-naphthalenediamine is to be expected in the naphthalene moiety, while substitution chemistry in the heterocyclic moiety in the 2-position will be nucleophilic in nature. Perimidine has a 14π-electron system but a pair of its electrons is not delocalized, which results in lower aromaticity than expected for a 14π-system. There is a formal excess of electrons in its hetero-ring which contains seven π-electrons. The expulsion of the "superfluous" super-Hückel electron from the hetero-ring to the naphthalene moiety leads to polarization of the π-cloud (Figure 1) ⟨81RCR816⟩.

Aceperimidylene (**9**) shows a corresponding uneven charge distribution; the highest negative charge is located in the CH=CH bridge. Quantum mechanical calculations are also available for 2-phenyl and 2-*o*-hydroxyphenylperimidine, for the perimidinium ion, for 2-perimidinone, and for 2,3-dihydroperimidine ⟨81RCR816⟩.

Calculations of resonance values for pyrimidine have given figures in the range 8–40 kcal mol^{-1} (33–167 kJ mol^{-1}) compared with the value 41 kcal mol^{-1} (172 kJ mol^{-1}) for benzene. In a theoretical study of π-electron delocalization via an analysis of the first $\pi \rightarrow \pi^*$ transitions, via calculations of hydrogenation energies, and via an analysis of the wave functions, it was suggested that the delocalization energies are essentially the same for benzene, pyridine, and the diazines. The calculated energies for the addition of one equivalent of hydrogen suggested that the "resonance energies" of benzene (36 kcal mol^{-1} [151 kJ mol^{-1}]), pyridine (34 [142]), pyrazine (32 [134]) and pyrimidine (33 [138]) are essentially the same; pyridazine (26 [109]) somewhat less. The distribution of π-electron density around the ring was not strongly perturbed by replacement of CH by N ⟨89JA4178⟩.

The resonance energy for quinazoline has been calculated to be 30.4 kcal mol^{-1} (127.3 kJ mol^{-1}), which is close to the value 30.5 kcal mol^{-1} (127.7 kJ mol^{-1}) for naphthalene ⟨69JA6321⟩.

Ab initio calculations at the UHF and CASSCF levels on vibronic coupling in the lower triplet states of pyrimidine demonstrate influence on the molecular and electronic structure of the molecule in the $^3B(n\pi^*)$, $^3A_2(n\pi^*)$, and $^3A_1(\pi\pi^*)$ states. For the $n\pi^*$ states, conformations corresponding to minimum energy have been found that deviate significantly from planar. For the $^3A_1(\pi\pi^*)$ state, vibronic coupling similar to that between the $^3B_{1u}$ and $^3E_{1u}$ states of benzene has been found. The calculations show a dynamic out-of-plane distortion of the molecule in the $^3B_1(n\pi^*)$ state, which provides for a coherent description of the results of optical and magnetic resonance data available for the lowest triplet state of pyrimidine. The out-of-plane distortions occurring in the $^3B_1(n\pi^*)$ and $^3A_2(n\pi^*)$ states conform to the increased antibonding character of the π-electron system upon $n\pi^*$ excitation ⟨92JA9544⟩.

The electronic effect of pyrimidine and other heterocycles can be determined and calculated quantitatively by sets of σ-constants, the inductive constant σ_I and the resonance constant σ_R. The σ_I constant characterizes the overall polar effect of the aromatic group. The values quoted for pyrimidine were derived from ^{19}F chemical shifts in the spectra of substituted benzenes, *viz.* *m*- and *p*-fluorophenylpyrimidines: 2-isomer σ_I 0.12, σ_R 0.09; 4-isomer σ_I 0.17, σ_R 0.09; 5-isomer σ_I 0.3, σ_R −0.04. These values are about twice those of pyridine so the effect of the two nitrogen atoms in the ring seems additive. A fused benzene ring has little influence on the electronic effects of azinyl groups; the inductive and mesomeric constants for the 2-quinazolinyl (0.06 and 0.10) and 2-pyrimidinyl (0.05 and 0.10) substituent in benzene are the same when obtained via ^{13}C NMR in acetone. From the ^{19}F chemical shifts of *m* and *p*-fluorophenyl derivatives of perimidine, the σ_I and σ_R constants have been calculated: for uncharged 2-perimidinyl group σ_I 0.24 and σ_R 0.10, and cationic perimidinyl group σ_I 0.31 and σ_R 0.25. The *para* fluorine atom has been assumed to be polar conjugated with the perimidine system, which leads to the summation in the σ_R constant of two effects: mesomeric and polar conjugation. The electron-withdrawing effect of the neutral 2-perimidinyl group is comparable to that of substituents such as halogens. The charged 2-perimidinyl group exceeds in this respect even a nitro group ⟨87AHC(42)1⟩.

Studies on transmission of the electronic effects of substituents in the pyrimidine systems show that the transmission of inductive effects through the pyrimidine ring is somewhat higher than that

through the benzene ring. But a more significant increase is observed in the transmission of resonance effects. The ability of the pyrimidine ring to transfer the resonance effect from one even-numbered position to another such (formally to a *meta*-position) is 1.5 to 2 times as high as that of the benzene ring. The 4- and 6-positions of the pyrimidine ring prove to be the most conjugated, and in this respect are only slightly inferior to the *para*-position of the benzene ring. The transmission from the 5-position of the pyrimidine ring to the 2-position is close to the same effect in the benzene ring, but it increases somewhat when transferred from the 2-position of the ring ⟨87AHC(42)1⟩.

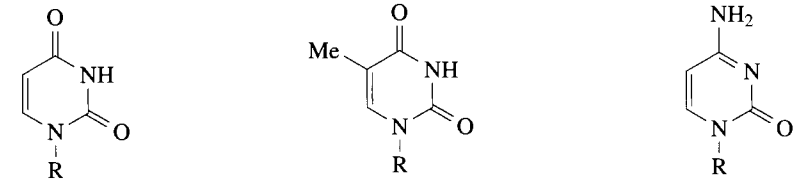
The gas and aqueous-phase basicities of pyrimidine are distinctly smaller by 3.4 and 1.1 pK_a units, respectively, than those of pyridazine. A theoretical explanation has been proposed by considering important NH^+ and lone pair electrostatic interactions that act from the 2-position. The proton-transfer equilibrium for the basicity comparison shows that the position of equilibrium is in the direction expected for the dominant effect to be the relief of the destabilization imparted by electrostatic repulsion between lone pair electrons, i.e., to the left in the equation (Equation (1)). Another significant contribution to ΔG° values is the field inductive effect of the electronegative aza substituent, which is less at the 3- than at the 2-position. This aza substituent effect destabilizes cations. Second-order attractive interactions between the lone pair electrons and the adjacent NH^+ in the conjugate acid of pyridazine are also invoked. The attractive electrostatic interaction in the conjugate acid of pyridazine, and the predominant lone pair repulsion in pyridazine, are opposed by a favorable aza substituent effect. This accounts for the positive ΔG°(g) value. Solvation by water is expected to preferentially stabilize the neutral species or ion which is internally destabilized. The result is a smaller equilibrium shift in solution compared with the gas phase ⟨86JA3237⟩.

(1)

ΔG° (g) = + 4.6 ± 0.2 kcal mol^{-1} (19.3 ± 0.8 kJ mol^{-1})

ΔG° (aq) = + 1.46 ± 0.2 kcal mol^{-1} (6.1 ± 0.8 kJ mol^{-1})

The dioxo form in uracil has been found, both experimentally and theoretically, to be the most stable. Current interest is in the less stable oxo-hydroxy tautomers. Improved data over the data available from the standard semiempirical molecular orbital methods is becoming available by *ab initio* methods. Calculation at the 6-31G** SCF level of the geometric structures of the three lowest-energy tautomers of uracil, with the inclusion of correlation and zero-point energy effects, provides agreement that the dioxo form is the most stable, and finds the 2-hydroxy-4-oxo and 4-hydroxy-2-oxo forms higher in energy by 46 and 52 kJ mol^{-1}, respectively ⟨90JCS(P2)329⟩. The same relative stabilities of the 2-hydroxy and 4-hydroxy-2-oxo forms is reported from AM1 SCF and SCRF calculated relative heats of formation $\delta\Delta H_f^\circ$. These calculations include all the tautomeric forms of uracil, thymine, and cytosine and their *N*1-methyl derivatives (Figure 2) and were carried out for the isolated molecules, and for the same molecules in a polarizable dielectric medium with the relative permittivity of water using the self-consistent reaction field method. In almost all cases, the same tautomer is predicted as most stable regardless of the method used and environment applied. However, the calculations imply significant quantitative differences in the relative stabilities of the tautomers in different media. The relative values refer to the oxo tautomers shown (Figure 2), which have been established conclusively as the predominant structures whether it be in the crystalline state, in aqueous solution, in solutions of nonpolar solvents, or in the gas phase ⟨91JA1561⟩.



R = H, Me

Figure 2 Uracil, thymine, and cytosine.

6.02.3 EXPERIMENTAL STRUCTURAL METHODS

6.02.3.1 Molecular Dimensions by X-ray Structure Analysis

X-ray structure analysis (Figure 3) shows the pyrimidine ring to be flat with bond lengths 1.33–1.41 Å (**10a**) as compared with 1.40 Å in benzene. Bond angles, 115(*N*)–129.7°, are shown in (**10b**) ⟨B-94MI 602-01⟩. Bond lengths and bond angles for quinazoline are shown in (**11a**) and (**11b**) (Figure 3) ⟨76AX(B)998⟩.

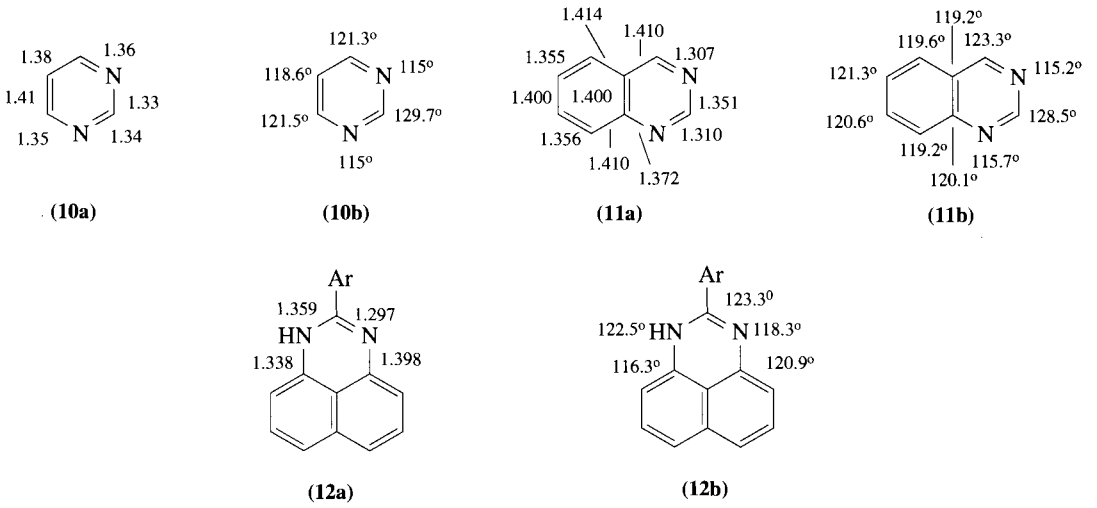


Figure 3 X-ray structure analysis (bond lengths in Å).

X-ray structure data for 2-(2-methoxyphenyl)perimidine shows the compound to be roughly planar ((**12a**) and (**12b**) in Figure 3). The naphthalene moiety presents a similar pattern of bond distances and angles as in naphthalene ⟨93MI 602-01⟩. X-ray structure data for 1-methyl-1*H*-perimidin-2(3*H*)-one and its 1,3-dimethyl derivative show lack of planarity with the methyl groups eclipsed with the C=O group ⟨94HCA121⟩.

6.02.3.2 NMR Spectroscopy

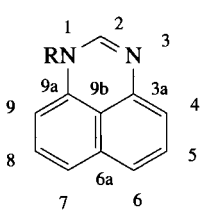
Proton NMR data for pyrimidines was reviewed in CHEC-I together with ^{13}C and $^{15}N/^{14}N$ NMR data. A 1994 review includes tabulation of ^{1}H, ^{13}C, ^{14}N, and ^{15}N NMR data of simple pyrimidines ⟨B-94MI 602-01⟩. Carbon-13 NMR data (ppm) for quinazoline in $CDCl_3$: 156.1 (C2), 161.1 (C4), 128.1 (C5), 128.8 (C6), 135.1 (C7), 129.3 (C8), 151.3 (C8a), and 126.0 (C4a). There is a dramatic change in the chemical shifts upon hydration, for example, in 4-hydroxy-3,4-dihydroquinazoline as shown for C2 at 148.1 and C4 at 72.4 ppm ⟨75AG356⟩.

In ^{1}H NMR spectra, the aromatic protons in perimidines show a characteristic upfield shift on the average 0.8–1.2 ppm relative to naphthalene and naphthoimidazoles. The H4 and H9 protons resonate at considerably higher field than the remaining protons. In 1-alkylperimidines the time average degeneracy of these protons no longer exists, and the protons give rise to well-resolved quarters, the signal for H9 being at the higher field locations. The remaining protons, as well as H2, give rise to a complex multiplet. In perimidinium ions the H2 signal is displaced downfield relative to the other protons. An electron-withdrawing group (acyl, nitro, sulfonyl) simplifies the perimidine spectra particularly in the 6- and 7-positions because of deshielding of the second *peri*-proton ⟨81RCR816⟩.

The ^{13}C spectrum (15.04 MHz) of perimidine (**13**; R = H) (Table 1) is consistent with a symmetrical structure, reflecting rapid prototropic tautomerism between the annular nitrogen atoms as found for ^{1}H NMR. Tautomerism is excluded in 1-alkyl derivatives as shown for (**13**; R = Me) in Table 1. The relative ^{13}C chemical shifts parallel those of the corresponding protons in the ^{1}H NMR spectrum. The relative order of the chemical shifts in ^{13}C NMR of 1,8-naphthalenediamine is the same as in perimidine. All carbocyclic peaks other than C9b exhibit a pronounced upfield shift, in accord with the π-excessive character of the carbocyclic rings in the perimidine system. On the other hand, C2

is electron deficient and has the highest chemical shift in perimidine, at 146.3 ppm. Tautomerism is rapid on the NMR time scale in 2-substituted perimidines, and three peaks appear for the tertiary (CH) carbons, that at the highest field due to C4/C9 by analogy to ^{1}H NMR data, and with the ^{13}C NMR spectrum of 1,8-naphthalenediamine. Since the quaternary carbon C9b has a relatively long relaxation time, it gives rise to a characteristic broad peak of low intensity. Its position is little changed by substituents in the carbocyclic ring system. This position, however, is affected by protonation in the heterocyclic ring and is moved upfield. Likewise, C3a and C9a undergo upfield shifts. In perimidine itself, protonation causes a downfield shift of C9b.

Table 1 Carbon-13 chemical shifts (ppm) of perimidines.



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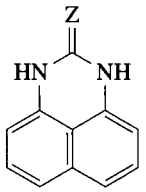


(14)

Comp.	*R/Z*	*C2*	*C3a/C9a*	*C4/C9*	*C5/C8*	*C6/C7*	*C6a*	*C9b*
(13)	H	146.3	141.0	107.6	128.3	118.4	135.3	122.9
(13)	Me	146.3	143.7	114.0	128.5	119.3	134.8	122.1
			138.4	100.5	127.7	118.6		
(14)	O	151.0	137.9	104.6	128.2	118.2	134.6	114.3
(14)	S	172.8	135.4	104.5	128.1	119.0	133.9	116.1

The chemical shifts for 2-perimidinone (**14**; Z = O) and the 2-thione (**14**; Z = S), the last two rows in Table 1, are not time average degenerated, but arise from the more symmetrical structure implied in (**14**). C9b resonates at 114.3 and 116.1, respectively, since the predominant tautomers do not contain an imine-type unsaturation. These derivatives are not π-deficient and resemble *N*-acylated 1,8-naphthalenediamine (C8a, δ 117.7).

C3a and C9a (formally *ipso* carbons) are strongly shielded on protonation of perimidine, owing to drift of the electron density from the carbocyclic ring towards the protonated carbon. This results in deshielding of C4/C9 and C6/C7 ⟨88MRC191⟩. The ^{1}H and ^{13}C NMR spectra of 2-aminoperimidine in DMSO-d_6 solution show that the base is protonated on the ring nitrogens rather than on the exocyclic amino group ⟨77JMR(28)321⟩.

Spectroscopic properties of reduced pyrimidines are discussed in Section 6.02.6.1.1.

6.02.3.3 Mass Spectrometry

Pyrimidine and simple derivatives have loss of HCN as a primary fragmentation route on electron impact in mass spectrometry. The loss of HCN originates from C4 + N3. Subsequent loss of HCN (C2 + N1) gives ionized alkyne as the base peak in the spectrum. Related is the primary fragmentation of uracil and thymine with loss of HNCO, which can be rationalized as due to a retro Diels–Alder reaction; barbituric acid suffers loss of two HNCO units as a major fragmentation route. The substitution pattern in pyrimidines may direct the preferential fragmentation routes. Reference literature is available in ⟨B-94MI 602-01⟩ and in fuller detail in ⟨B-85MI 602-01⟩.

Quinazoline breaks down in a similar manner on electron impact, with formation of what can be rationalized as an ionized benzyne as a major route. The primary fragmentation may be expulsion of HCN involving C4 + N3. Again, substitution will affect the preferential breakdown pattern, especially in reduced species.

The EI mass spectra of a series of 2,2,4-trisubstituted 1,2-dihydroquinazolines were characterized by fragment losses due to the substituents, and the relative abundances of the ions change with the nature of the substituents. The dihydroquinazolines do not lose RCN or HCN as is typical for quinazolines. Positive- and negative-ion fast atom bombardment (FAB) coupled with collision-

induced decomposition (CID)—FAB–CID spectra—provided data regarding the masses of each substituent ⟨92OMS(27)916⟩.

The mass spectra of perimidine, 2-perimidinone, and 2-thioperimidinone by electron impact are characterized by a strong molecular ion, by a very intense peak due to a doubly charged molecular ion, and relatively weak fragmentation ⟨81RCR816⟩.

6.02.3.4 UV and Fluorescence Spectra

The UV absorption of fully conjugated pyrimidine in cyclohexane has maxima at 243 ($\log \varepsilon = 3.31$) and 298 (2.51) nm. In buffered neutral solution the maxima are at 271 (2.63) and 243 (3.51) nm. The absorption at 298 nm is attributed to $n \rightarrow \pi^*$, and at 243 nm to $\pi \rightarrow \pi^*$ transition. In aqueous solution, the lone pair on nitrogen becomes involved in H-bonding which leads to hypsochromic shifts (energy increase) for the $n \rightarrow \pi^*$ transition. Under acidic conditions, maximum absorption is at 242 (3.74) nm. The absorption is sensitive to the substitution pattern, the polarity and H-bonding of the environment and the pH of the solution. Thus 2(1*H*)-pyrimidinone has absorption maxima at 298 (3.68) and 212 (4.03) nm at neutral pH, and at 292 (3.66) and 220 (4.07) nm at basic pH. A very useful tabulation of UV data for simple, selected pyrimidines is to be found in (⟨B-94MI 602-01⟩, p. 854).

The UV spectrum of quinazoline in cyclohexane shows three $\pi \rightarrow \pi^*$ transitions with maxima at 311 (3.32), 267 (3.49) and 220 (4.61) nm with an inflection point at 330 nm of low intensity (2.30) assigned to $n \rightarrow \pi^*$. The 4-position in quinazoline is highly electrophilic; the electrophilicity is accentuated in the protonated species. Covalent adduct formation between quinazoline or 4-unsubstituted quinazolines and water occurs in aqueous acidic solutions. The hydroxyl group enters the 4-position and the 3,4-dihydro derivative is formed. The hydrated species of quinazoline has absorption maxima at 260 and 208 nm ⟨63PMH(1)1⟩.

4(3*H*)-Quinazolinone in dioxane has absorption maxima at 222 (4.34), 267 (3.51) and 305 (3.38) nm; in 2-propanol at 225 (4.43), 264 (3.68) and 301 (3.68).

A number of substituted 4-quinazolinones in solvents of different polarities show three main absorption bands in the 220–240, 270–290, and 300–320 nm regions. The shortest wavelength bands have high molecular absorption coefficients (>4.0) due to $\pi \rightarrow \pi^*$ transition. The long-wavelength bands also have high absorption coefficients (3.4–3.8) caused by $\pi \rightarrow \pi^*$ transition, as shown by their small shifts in protic solvents. The long-wavelength tail into the 315–325 nm region has been attributed to $n \rightarrow \pi^*$ transition due to the nitrogen lone pair. The wavelengths of the bands of the fluorescent excitation and emission spectra of the above molecules are located close to those of the absorption spectra. For quinazoline in cyclohexane the fluorescent emission maxima were at 348 nm with a shoulder at 360 nm for excitation at 288 nm; in 2-propanol at 328 nm with excitation at 285 nm; for 4(3*H*)-quinazolinone in dioxane the fluorescent emission maxima were at 322 nm and 352 nm for excitation at 290 nm; in 2-propanol at 330 nm and 342 nm for excitation at 285 nm. In a series of substituted 4-quinazalinones the emission spectra have a main band in the 340–380 nm region ⟨91SA(A)419⟩. Additional studies of fluorescence of simple quinazolines and their alkaloid derivatives are available ⟨81RTC161, B-85MI 602-02⟩.

Perimidine has absorption maxima in ethanol at 229.5 nm (4.54) and 331 nm (4.13). Perimidine is bright yellow, with absorption bands in the region 235, 330, and 400 nm in solvent. 2,3-Dihydroperimidines are colorless. The lower wavelength bands in perimidines are also present in the spectra of 2,3-dihydro derivatives and 1,8-naphthalenediamines. The band at 330 nm is ascribed to $n \rightarrow \pi^*$ transition into the naphthalene ring, and the band at 235 nm to electronic transitions within the naphthalene ring. The high-wavelength band is responsible for the color of perimidines. In less resolved spectra it will appear as a shoulder on the major bands. The 400 nm band persists in the spectra of perimidinium salts, which excludes $n \rightarrow \pi^*$ transition. According to calculations, the band is due to π-electron transfer from the naphthalene to the hetero ring, which means that the band is due to charge transfer between the π-donor and the π-acceptor components of the perimidine system. Consistent with this interpretation is the finding that strongly electron-donating substituents in the 2-position (e.g., NHR, OR) give non-colored compounds whereas a strong π-acceptor results in deeply colored perimidines; for example, 2-benzoylperimidine is dark wine-red, while 2-nitrophenyl- and 2-nitrofurylperimidines are violet. Electron-donating substituents in the naphthalene ring also deepen the color; the UV spectra of several substituted perimidines have been recorded ⟨81RCR816⟩.

Simple perimidines hardly fluoresce on irradiation with UV light, but 2,3-dihydro derivatives are

frequently fluorescent. 4(9)- and 6(7)-Acylperimidines fluoresce strongly, and aceperimidylenes show intense fluorescence ⟨81RCR816⟩.

The UV spectra of reduced pyrimidines are discussed in Section 6.02.6.1.1.

6.02.3.4.1 π-Electron donating properties

Perimidine forms deeply colored charge transfer complexes with π-acids, including weak acids such as 4-nitrobenzaldehyde. The complexes usually have 1 : 1 composition in the crystalline state. In terms of the π-donor capacity, perimidines are superior to well-known π-donors such as phenothiazine. 2,3-Dihydroperimidine exhibits the same π-donor capacity as perimidines. Aceperimidylene, perimidinones, thioperimidinones, and 2-imino-2,3-dihydroperimidines are inferior to perimidines as π-donors ⟨81RCR816⟩.

6.02.3.5 IR and Raman Spectra

The IR spectra of pyrimidin-2- and 4-ones show strong bands for C=O and N—H stretching absorption. The N—H stretching band falls in the region 3360–3420 cm^{-1} which is associated with an azine *ortho*-quinoid structure and means that the major tautomeric form of the 4-isomer is as a 4(3*H*)-pyrimidinone; the N—H stretching band for a 4(1*H*)-pyrimidinone would be expected in the 3415–3445 cm^{-1} region.

The 2- and 4-pyrimidinamines show two N—H stretching bands at 3400 and 3500 cm^{-1} due to symmetric and unsymmetric vibrations; imines absorb at 3300 cm^{-1} ⟨B-94MI 602-01⟩. Interpretation of quinazoline spectra is also available ⟨70JSP(36)310⟩.

In the IR spectra of perimidine and of its 2-methyl and 2-aryl derivatives in the solid state there are no stretching vibration bands due to free *NH* groups, but a broad band at 3200–2500 cm^{-1} is found due to intermolecular *H*-bonding. A sharp peak at 3440 cm^{-1} in dilute solution is assigned to free *v*(*NH*) vibration. The *v*(*NH*) band may also appear when the *NH*-proton is involved in intramolecular *H*-bonding. 2,3-Dihydroperimidines are considerably less acidic than perimidine and therefore less *H*-bonded. Perimidines with a free *NH* group generally have three intense bands in the range 1500–1700 cm^{-1}. The absorption at the higher wavelength has been ascribed to stretching vibration of the amidine system, and is displaced by 20–35 cm^{-1} towards higher frequencies in spectra of perimidinium salts, which is typical for cyclic amidines. In 2-substituted perimidines a very intense doublet is frequently present in the range 1580–1650 cm^{-1}. 2,3-Dihydroperimidines usually have a single intense band near 1600 cm^{-1} ⟨81RCR816⟩.

The vibrational spectra of reduced pyrimidines are discussed in Section 6.02.6.1.1.

6.02.3.6 ESR Spectroscopy

The ESR spectrum of quinazoline in the triplet state at 77 K has been recorded ⟨87JMR(71)303⟩.

6.02.3.7 Dipole Moments

Experimentally determined dipole moments for pyrimidine lie in the range 2.1–2.4 D; calculated values fall in the range 2.13–2.25 D.

The ground-state dipole moments for quinazoline, 4(3*H*)-quinazolinone and several derivatives thereof in morpholine-dioxane (100 : 60) at 22°C were: quinazoline 3.40 D (±0.30); 4(3*H*)-quinazolinone 3.12 D (±0.53); 2,4(1*H*,3*H*)-quinazolinedione 3.85 D (±0.17); 2(1*H*)-thioxo-4(3*H*)-quinazolinone 3.21 D (±0.17). Calculations of ground state dipole moments gave good correlations with experimental values for a series of substituted quinazolines, but not for the parent molecule and 4(3*H*)-quinazolinone. The same structure exceptions apply to excited singlet state dipole moments. The excited singlet-state dipole moments are considerably higher than in the ground state, differences lying in the range 1–2.5 D ⟨91SA(A)419⟩.

The fairly high dipole moments of perimidines are consistent with an unsymmetrical electronic

structure and polarization. Dipole moments are given for: perimidine 3.18 D; 2-methylperimidine 3.48 and 3.66 D; 1-methylperimidine 3.25 D; 2-phenylperimidine 3.03. In calculations the CNDO/2 method has given good correlations between calculated and experimental data ⟨81RCR816⟩.

6.02.3.8 Magnetic Properties

The magnetic susceptibility data for perimidines is consistent with the presence of a single EPR signal with a width of about 7 G for crystalline specimens; the signal intensity obeys the Curie law and corresponds to a single spin per 5000 to 10000 molecules ⟨81RCR816⟩.

6.02.3.9 Ionization

Pyrimidine has basic pK_a 1.3 (mono-) and −6.9 (di-protonation), which compares with 5.2 for pyridine. The very marked lowering of basicity in pyrimidine is attributed to the electronegativity of the second ring nitrogen. Electron-releasing substituents will counteract the electron deficiency of the ring and thereby increase the basicity; 2-methylpyrimidine has pK_a 2.3. Electron-withdrawing groups have the opposite effect.

The basic pK_a values for 2(1*H*)-pyrimidinone, 4(3*H*)-pyrimidinone and 5-hydroxypyrimidine are 2.2, 1.7, and 1.8, respectively. The basic pK_a for 2-methoxypyrimidine is 0.5, which is significantly different from the value of 2.5 for its isomeric 1-methyl-2(1*H*)-pyrimidinone. The pK_a values for the isomer pair 4-methoxypyrimidine and 1-methyl-4(1*H*)-pyrimidinone are close, however (2.5 and 2.0, respectively).

The acid pK_a values for 2(1*H*)-pyrimidinone, 4(3*H*)-pyrimidinone and 5-hydroxypyrimidine are given as 9.2, 8.6, and 6.8, respectively, which compares with the less acidic pK_a of 11.7 for 2(1*H*)-pyridinone. The dioxo derivative 2,4(1*H*,3*H*)-pyrimidinedione (uracil) has acidic pK_a 9.4, and the trioxo derivative 2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione (barbituric acid) has pK_a 2.8.

Thiones are stronger acids than their oxygen analogs: 2(1*H*)-pyrimidinethione has acid pK_a 7.0 and basic pK_a 1.4. The π-deficiency of the pyrimidine ring is expressed in relatively low pK_a values for the 2-, 4-, and 5-pyrimidinecarboxylic acids: 2.9, 3.0, and 3.2, respectively.

The strongly electron-donating properties of an amino group raises the pK_a value from that of pyrimidine (1.3) to pK_a 2.6 for 5-pyrimidinamine and to 3.7 and 5.7 for 2- and 4-pyrimidinamine, respectively. Protonation is at a ring nitrogen. Hence the relatively high basic strengths for the 2- and 4-pyrimidineamines can be explained by stabilization of the protonated ring nitrogen by resonance from the exocyclic amino group. This sort of resonance stabilization is excluded in the protonated 5-amino isomer. Alkylation of an exocyclic amino group affects the basicity only slightly; 2-methylaminopyrimidine has pK_a 3.8. Alkylation on the nitrogen atom of the ring in 2-and 4-pyrimidinamines, however, gives imines which are strongly basic; 1-methyl-2(1*H*)-pyrimidinimine has pK_a 10.8, 1-methyl-4(1*H*)-pyrimidinimine pK_a 12.2. An extensive compilation and tabulation of acidic and basic pK_a values for simple pyrimidines in water at 20–25 °C has been published (⟨B-94MI 602-01⟩, p. 824).

Quinazoline and its 2-methyl derivative have basic pK_a values 3.51 and 4.52, respectively. In contrast, 4-methylquinazoline has pK_a 2.52, which compares with pK_a 2.0 for 4-methylpyrimidine ⟨63PMH(1)1⟩. The relatively high basicities of quinazoline and its 2-methyl derivative are rationalized by formation of a covalent 3,4-hydrate from the protonated species; this is less likely when the electrophilic 4-position is occupied by a methyl group. The acidic pK_a values for the quinazolinones fall in the range 7.3–8.6. When covalent hydration is allowed, quinazolinones, methoxyquinazolines and quinazolinamines are significantly stronger bases than corresponding pyrimidines. When the hydration is excluded, the pK_a values are comparable with those for pyrimidine analogs ⟨67HC(24)1⟩.

pK_a values for the perimidinium ion and its alkyl derivatives are approximately 6. Thus perimidines are stronger bases than pyrimidines. The basicity of 2,3-dihydro derivatives is two orders of magnitude lower than that of perimidine itself in water, and by five orders lower in acetonitrile. The basicity of aceperimidine and aceperimidylene is lower than that of perimidines by two orders of magnitude. Additional data is available for basicities of various 1-alkyl- and 2-allylperimidines, 2-arylperimidines, nitroperimidines and 2,3-dihydroperimidines ⟨81RCR816⟩.

6.02.4 THERMODYNAMIC ASPECTS

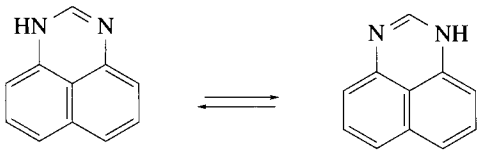
6.02.4.1 Prototropic Tautomerism

6.02.4.1.1 Introduction

Information about tautomeric systems relies on physical measurements which do not affect the tautomeric equilibria; reactions of tautomeric systems give no reliable information about equilibria. In tautomeric studies of hydroxy-, thiol-, and aminopyrimidines, or heterocycles in general, methylation has been used to "isolate" the various tautomeric forms which were to serve as models for comparison of spectroscopic data (UV, IR, NMR) or pK_a values. However, recent NMR techniques allow direct tautomeric determinations in solution. X-ray structure data gives full information in the solid, crystalline state.

6.02.4.1.2 Perimidine

Physicochemical data shows that the *NH*-proton in perimidines, as in imidazoles, migrates rapidly between the nitrogens (**15**) (degenerate tautomerism of the amidine type). Tautomerism with migration of the *NH*-proton to the 4(9)- or 6(7)-position has not been seen, but derivatives of these tautomeric forms are known. Uneven substitution in the carbocyclic moiety of perimidine leads to two energetically different *NH*-tautomers which can be seen by physical measurements. An estimate based on pK_a indicates the ratio of 6- and 7-nitro isomers in an equilibrium mixture to be approximately 35 : 65. A nitro or acyl group in an *ortho* position, however, displaces the equilibrium almost entirely towards the 9-nitro tautomer (**16**), which can be rationalized by strong intramolecular H-bonding ⟨81RCR816⟩.



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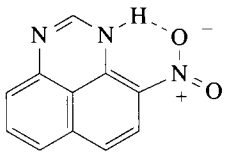

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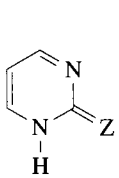
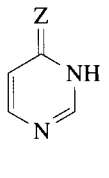
6.02.4.1.3 Hydroxy–oxo tautomerism

Physiocochemical techniques show that 2- and 4-hydroxypyrimidines are predominantly in the oxo forms; the former as (**17a**) and the latter in the *ortho*-quinonoid structure (**18**; Z = O) in preference to its *para*-quinonoid isomer ⟨B-94MI 602-01⟩. 2- and 4-Hydroxyquinazolines exist predominantly in the analogous oxo forms (**19**) and (**20**), respectively, for Z = O ⟨B-67MI 602-01⟩. 2-Hydroxyperimidine is dominated by the oxo form (**14**) ⟨81CR816⟩.



(17a) Z = O
(17b) Z = S



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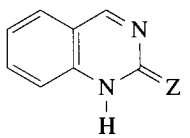

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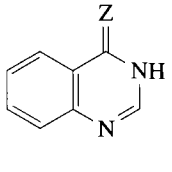

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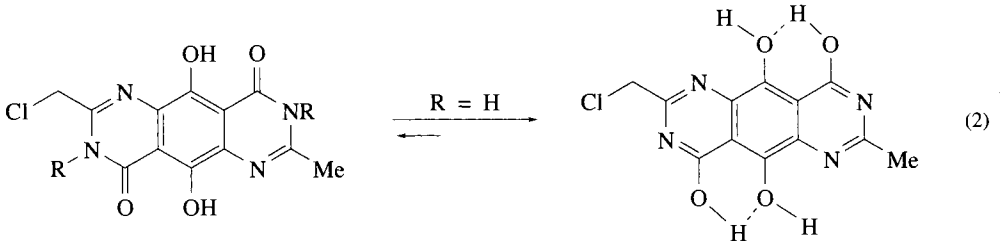
A pyrimidine with a hydroxy group in the benzenoid 5-position exists as the pyrimidinol corresponding to a phenolic hydroxyl group in the carbocyclic ring of quinazoline or perimidine. In dihydroxy derivatives, such as uracil, the dioxo form 2,4(1*H*,3*H*)-pyrimidinedione is the predominant form, and in the trihydroxypyrimidine, barbituric acid, the 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione form is predominant ⟨B-94MI 602-01⟩.

The normal tautomeric preference may be completely changed with the possibility for stabilization

by intramolecular hydrogen bonding. One example is provided by the fused pyrimidinone rings of *N*-unsubstituted pyrimido[4,5-*g*]quinazoline hydroquinone (**21**; R = H), which exists in aqueous solution as the enol tautomer (**22**) (Equation (2)). The driving force for the enolization is the formation of internal hydrogen bonds to the hydroquinone hydroxyl groups (UV, electrochemical studies, and p*K* measurements) ⟨88JOC4209⟩.



(2)

(**21**) R = H, Me (**22**)

The stabilization of the pyrimido[4,5-*g*]quinazoline hydroquinone (**22**) by internal hydrogen bonds raises the quinone reduction potential by 65 mV (NHE; normal hydrogen electrode). In contrast, the *N*-methylated analogue (**21**; R = Me), which cannot form internal hydrogen bonds, possesses relatively low quinone reduction potentials. The pK_a value for acid dissociation from the hydroquinone hydroxyl group is also greatly affected by internal hydrogen bonding, which stabilizes the hydroxyl anion ⟨92JOC5649⟩.

6.02.4.1.4 Thiol–thioxo tautomerism

Pyrimidines with a thiol group in an electrophilic position exist predominantly in the thione form as shown in the structures (**17b**) and (**18**) (Z = S), and in the benzenoid 5-position as a thiol ⟨B-94MI 602-01⟩. In the perimidine series, 2-thiol perimidines exist almost exclusively in the thione form (**20**; Z = S) ⟨81RCR816⟩.

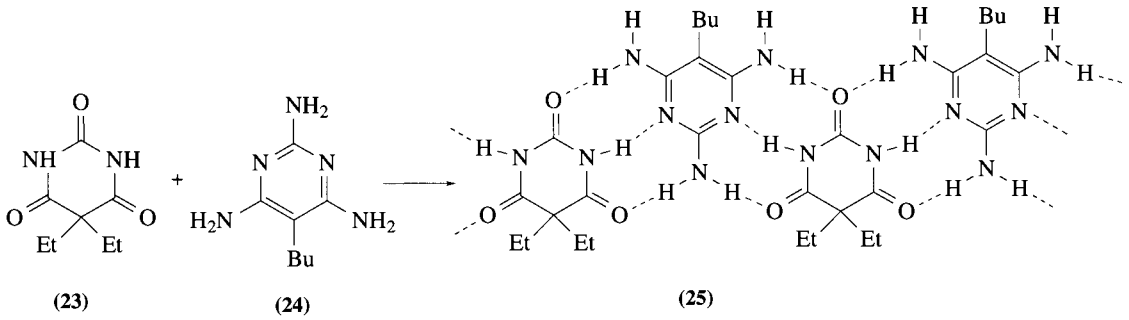
6.02.4.1.5 Amino–imino tautomerism

All spectroscopic and pK_a studies of aminopyrimidines and aminoquinazolines show the amino form to an overwhelming extent ⟨B-94MI 602-01⟩. Spectroscopic studies of 2-aminoperimidines indicate about 2% of the imine tautomer in equilibrium with the amine. In 1-substituted 2-acylaminoperimidines and aceperimidines, the equilibrium is almost entirely in favor of the imino form, but in the absence of a substituent in the 1-position, the amino form persists. In both cases the preferred tautomer is stabilized by intramolecular H-bonding ⟨81RCR816⟩.

6.02.4.1.6 Hydrogen bonding systems in self-assembly

Self-assembly in hydrogen bonding systems has been extended to pyrimidine structures. The complementary 5,5-diethylbarbituric acid (**23**) and 5-butylpyrimidine-2,4,6-triamine (**24**) each presents two identical binding faces. Full use of the hydrogen-bonding potential leads to formation of three hydrogen bonds between the binding sites of the complementary partners. When solutions of the two are mixed, rapid precipitation of a hydrogen-bonded complex results. The information possessed by these symmetrical components could generate two independent geometric expressions, either a ribbon-like polymeric motif (**25**) (Equation (3)) or a cyclic hexamer. X-ray crystallography showed the ribbon-like structure. The 4,6-diamino-5-octyl-2(1*H*)-pyrimidinone and 2-amino-5,5-dibutyl-4,6(1*H*,3*H*)-pyrimidinedione pair are complementary to each other as well as being self-complementary. One single spatial relationship with neighboring subunits is available for this pair, and this will lead to the expression of a hetero-macrocyclic hexamer. On mixing the substrates, the

self-associated ribbon polymer (**26**) with a zig-zag polymeric motif (x-ray analysis) was precipitated selectively because of low solubility. The other homopolymer remained in solution ⟨92JCS(P2)461⟩.



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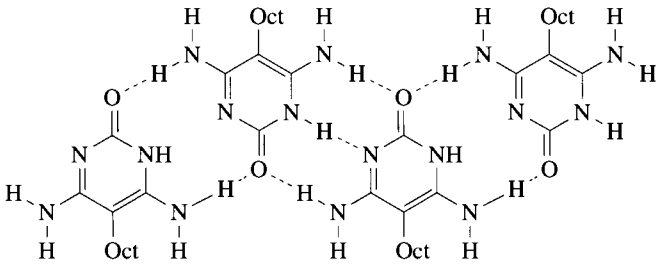
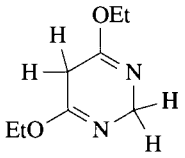


(26) (3)

6.02.4.1.7 Tautomerism in dihydropyrimidines

Tautomeric studies on dihydropyrimidines have usually been carried out on pyrimidines substituted by strongly conjugative groups or on geminally disubstituted derivatives to reduce the number of tautomeric forms. X-ray structure analysis is often used for information in the solid phase. NMR is most frequently used for tautomeric equilibrium studies in solution. A short summary is available (⟨B-94MI 602-01⟩, p. 817).

4,6-Diethoxy-2,5-dihydropyrimidine (**27**) has a flat ring in the crystalline solid phase, and the molecule is not involved in enamine–imine tautomerism in solution ⟨86JOC4623⟩. The 4,6-diphenyl analogue (**28**), however, is in equilibrium with its 1,2-dihydro tautomer (**29**) in solution (Equation (4)), and in the solid state the ring has C2 and C5 out of the ring plane ⟨85AHC(38)1⟩. Quantitative studies using ^{1}H NMR on the tautomeric 1,4-dihydro ⇆ 1,6-dihydro process of the 6-methyl derivative, 6-methyl-2,4-diphenyl-1,4-dihydropyrimidine (**30**) (Equation (5)), showed that two mechanisms contribute to the reaction: a monomolecular process and a bimolecular reaction ⟨84JA8021⟩. Tautomerism in the 1,4-dihydropyrimidines (**31**) in solution is dependent on the substitution pattern and polarizing effects of the substituents ⟨88JA4832⟩. 5-Acyl-1,4-dihydropyrimidines exist as such in the solid state, but were found to be involved in tautomerism with the 1,6-dihydro tautomers in solution ⟨86JCS(P1)83⟩. In 4,4,6-trimethyl-3,4-dihydro-2-pyrimidinamine and related structures, deuteriation in the ring 5-position and in the 4-methyl group was used to demonstrate enamine tautomeric shifts ⟨91TL2057⟩.



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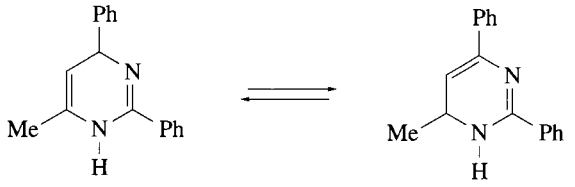
(28) (29) (4)



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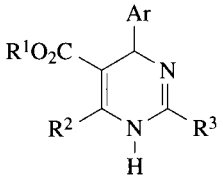

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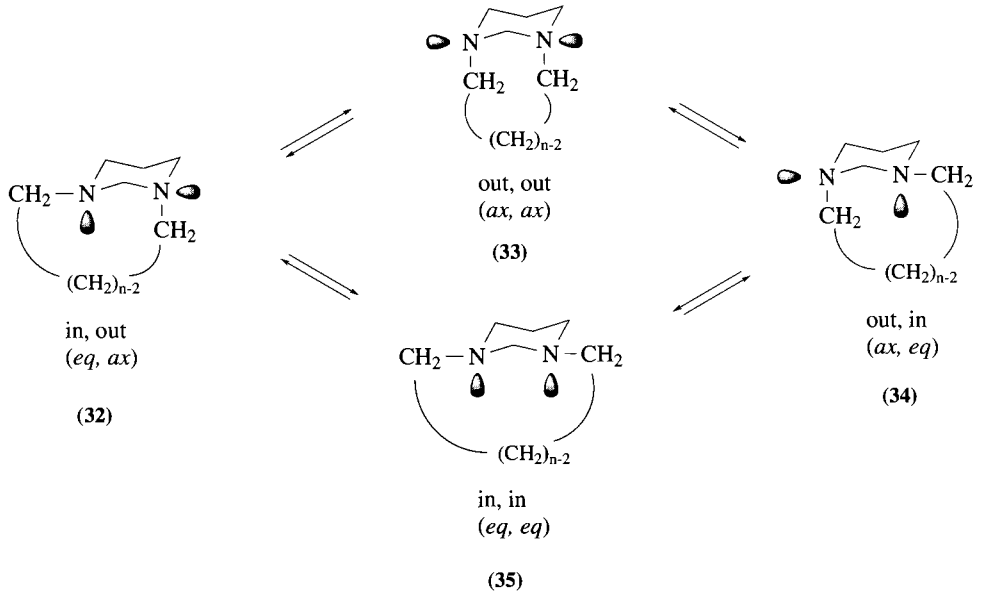
6.02.4.2 Conformational Equilibria

In solution at a particular temperature the conformation of hexahydropyrimidine is governed by two factors: the rate of ring inversions and the rates for inversion of the ring nitrogen atoms ⟨75CC255⟩. Molecular mechanics calculations suggest that a flattened chair is the most stable conformer of hexahydropyrimidine and its *N*-methyl derivatives ⟨88JST(176)89⟩. The conformer distributions with the N–Hs *axial–equatorial*, *equatorial–equatorial*, and *axial–axial* were calculated as 49.5 : 43 : 7.5, respectively. In 1,3-dimethylhexahydropyrimidine 66% of the *equatorial–equatorial* conformer was suggested by calculations; dipole moment measurements suggest 55%, ^{13}C NMR data 89% ⟨79JCS(P2)143⟩. In 1,2,3-trimethylhexahydropyrimidine, calculations suggest 15% of the *axial* 2-methyl conformer, and the amount of this conformer increases with the steric bulk of the *N*-substituents. Carbon-13 NMR data suggests 9–11% of the axial 2-methyl conformer for the former ⟨79JCS(P2)143⟩. In the simple *N,N'*-dialkylhexahydropyrimidines, the population of the *equatorial–axial* conformer is higher than would be expected on the basis of a comparison with 1,3-dialkylcyclohexanes. This difference has been attributed to generalized anomeric effects with net stabilization arising from lp–σ^* overlap when a lone pair (lp) is antiperiplanar to a C—X bond, where X is an electronegative element. In hexahydropyrimidines, this is realized in *equatorial–axial* and *axial–axial* conformations, but the latter is not significantly populated in simple monocyclic compounds, because of severe 1,3-diaxial interactions between the *N*-alkyl groups.

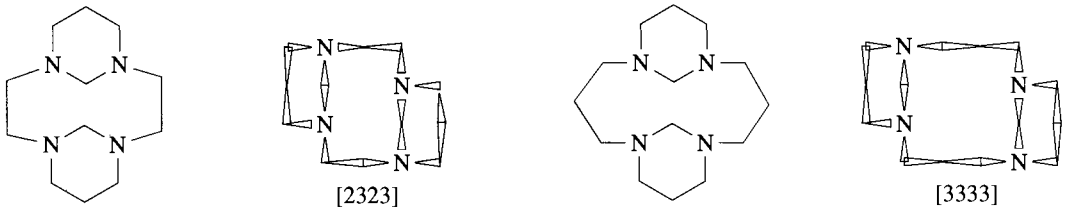
Hexahydropyrimidines *N,N'*-bridged by a chain of *n* methylene groups (**32**) adopt *out–out* (*axial–axial*) structures for $n = 2$, 3, and 4 (**33**) (Scheme 1). For $n = 6$, the photoelectron spectrum shows evidence for the presence of some of the *out–in* (*axial–equatorial*) isomers (**34**) in the gas phase, although none is found in solution. For $n = 6$ the compound is *out–in* (**34**) in the gas phase, but exists as a mixture of *out–out* (**33**) and *out–in* (**34**) conformers in solution. For $n = 7$ only the *out–in* isomer (**34**) can be detected in solution.

Tricyclic bis-aminals, the bispyrimidine derivatives (**36**) and (**38**), having 10- and 12-membered rings adopt [2323] (**37**) and [3333] (**39**) conformations, respectively, each having *out–in* bridged hexahydropyrimidine rings ⟨93JA6580⟩.

A 5-hydroxy group in hexahydropyrimidine is located in the *equatorial* position in D_2O where intermolecular H-bonding prevails, whereas internal hydrogen bonding in $CDCl_3$ solution favors



Scheme 1



the *axial* conformer (>95%). The conformer distribution is affected by 2-substituents ⟨91MI 602-01⟩.

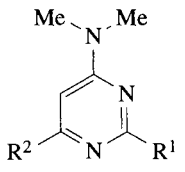
In general the rings in tetrahydropyrimidines are nonplanar ⟨84H(22)657, 85JOC4227, 88CC410⟩. In a series of 1-benzoyl-2-*t*-butyltetrahydro-4(1*H*)-pyrimidinones, conformational preferences from half chair to twist-boat were observed with the *t*-butyl group forced into *axial* or *flagpole* positions, respectively ⟨92HCA913⟩.

6.02.4.3 π-Barriers to Rotation

6.02.4.3.1 Hindered rotation around C—N bonds

Heteroaromatic amines exhibit partial double bond character for the exocyclic C—N bond because of conjugation of the nitrogen lone pair with the aromatic ring. Conjugation is suppressed in the transition state for rotation and gives rise to typical π-barriers. π-Deficient heterocycles exhibit higher barriers than π-rich carbocycles and heterocycles. The barrier to rotation around the exocyclic C—N bond in 4-*N*,*N*-dimethylaminopyrimidine (**40**; $R^1 = R^2 = H$), $\Delta G‡ = 51.1$ kJ mol^{-1}, up from $\Delta G‡ = 31.8$ kJ mol^{-1} for the 2-*N*,*N*-dimethylaminopyridine analogue because of the higher π-deficiency which promotes conjugation from the amino group. The rotational barrier on 2-amino-4-hydroxy substitution (**40**; $R^1 = NH_2$, $R^2 = OH$) is little affected, $\Delta G‡ = 52.7$ kJ mol^{-1}, but is increased to $\Delta G‡ = 62.3$ kJ mol^{-1} in the 2-pyrimidinone derivative (**41**) which is more strongly polarized. An example of steric intervention is provided by DNMR data on the 4-dimethylaminopyrimidine (**42**; R = H), $\Delta G‡ = 57.3$ kJ mol^{-1}, which is reduced to $\Delta G‡ = 32$ kJ mol^{-1} in the 5-methyl derivative (**42**; R = Me) because the methyl group destabilizes the ground state by steric

interactions ⟨79JCS(P2)1248⟩. The rotational barrier $\Delta G‡ = 34.7$ kJ mol^{-1} for the 4-*N*,*N*-dimethylaminoquinazoline (**43**) shows that benzo-annelation has a similar effect to that of the methyl group on the barrier ⟨72JCS(P2)451⟩. A correlation has been found between the observed barriers and the π-bond order of the C—N bond calculated by CNDO/2 ⟨79JCS(P2)330⟩.



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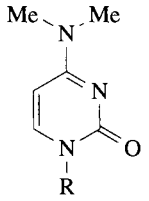

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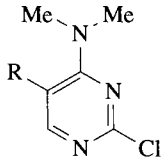

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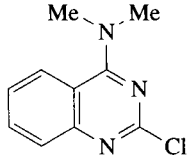

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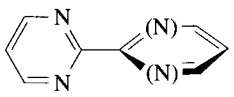
6.02.4.3.2 Hindered rotation around C—C bonds

In biphenyls the through-space interactions between *ortho* substituents are at a maximum when the two rings are coplanar and at a minimum in an orthogonal conformation.

NMR studies of azabiphenyls (**44**) have shown that coplanarity increases in the series biphenyl, 2-phenylpyridine, 2-phenylpyrimidine, and 2,2′-bipyridyl. It was deduced that the through-space C—H···N interactions are weaker than the C—H···H—C ones ⟨65RTC1399⟩. Calculations of the twist angle in polyazabiphenyls have given dihedral angles of 0° for 2,2′-bipyridyl and 2-phenylpyrimidine, 18.2° for 2-(2-pyridinyl)pyrimidine and 28.2° for 2,2′-bipyrimidyl. The calculations show that the barriers are quite low in the unsubstituted molecules and are little affected by remote substituents ⟨86IJQ541⟩. Thus repulsive interactions decrease in the order C—H···H—C > N:···N ≫ N:···H—C ⟨88AHC(43)173⟩.



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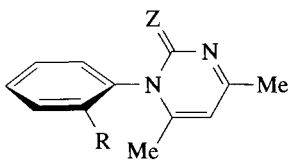
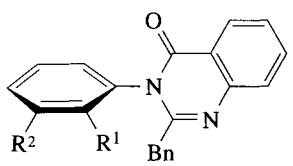
6.02.4.3.3 Rotational barriers in N-aryl-2-pyrimidinones

4,6-Dimethyl-1-aryl-2(1*H*)-pyrimidinones and their thione analogues (**45**) have been resolved into enantiomers with (+)-camphor-10-sulfonic acid. Their racemization barriers were determined by polarimetry ⟨80JCS(P1)1599⟩. The pyrimidinone series has the higher racemization barriers. The barriers to rotation about the aryl C—N bonds in 3-aryl-2-benzyl-4(3*H*)-quinazolinones (**46**) have been determined by DNMR. An *ortho* substituent on the phenyl ring raises the barrier to the extent that it was not overcome by DNMR ⟨75CJC3431⟩. Compounds without an *ortho* substituent in the phenyl ring have rotational barriers in the range 82.7–99 kJ mol^{-1} which are affected by substitution in the *meta* position in (**46**).



(45) R = Me, Et, Cl; Z = O, S



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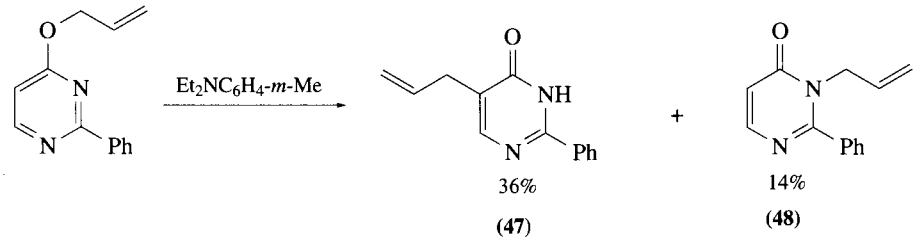
6.02.5 REACTIVITY OF FULLY CONJUGATED RINGS

6.02.5.1 Unimolecular Rearrangement Reactions

6.02.5.1.1 Thermally induced rearrangements

Thermally promoted Claisen rearrangement of simple allyloxypyrimidines is difficult to effect. 2-Allyloxypyrimidine largely resists rearrangement even at 200 °C. 4-Allyloxypyrimidines can be rearranged at elevated temperatures ⟨67AHC(8)143⟩; a mixture of the C5- (**47**) and the N3-allyl derivative (**48**) was formed from 4-allyloxy-2-phenylpyrimidine on heating in aniline (Equation (6)). 4-Allyloxyquinazoline is rearranged at 190–200 °C to form 3-allylquinazolin-4(3*H*)-one in 75% yield ⟨86T4873⟩. Rearrangement of 5-allyloxy-1,3-dimethyluracil proceeds with quantitative conversion to the 6-allyl derivative (**49**) (Equation (7)). Rearrangement of the 5-allylamino analogue is more difficult to effect ⟨71JOC1251⟩. 5-Propargyloxy-1,3-dimethyluracil gave a mixture of the fused furan and pyran derivatives on heating. The ratio of products, which are formed by competing cyclization of the initial Claisen rearrangement product, is solvent dependent; the five-membered ring is the major product in DMF, the pyran in xylene ⟨72JOC2858⟩. 6-Allyloxy-1,3-dimethyluracil behaves similarly to the 5-isomer; heating in dioxane gives the Claisen product (**50**) in 64% yield (Equation (8)) ⟨84H(22)2217⟩. 4-Allylthio-3-methyl-2(3*H*)-pyrimidinone is rearranged to the 5-allyl-4-thiouracil (**51**) in quantitative yield (Equation (9)) whereas the 1-methyl isomer resists rearrangement on heating in benzene. Allylation is on C5 in the 4-allylthiopyrimidinium derivative (**52**) in methanolic solution in the presence of carbonate; the product (**53**) is obtained as an adduct with methanol which is expelled on heating (Scheme 2) ⟨75CC993⟩.



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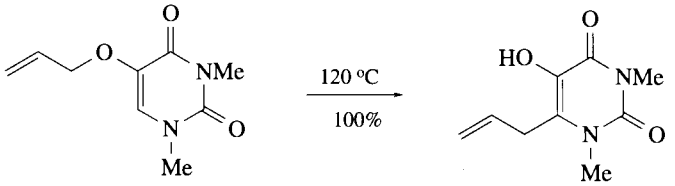

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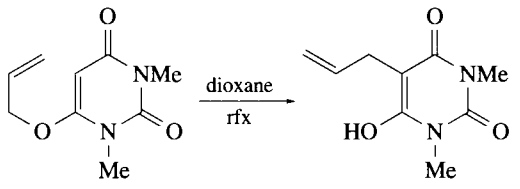

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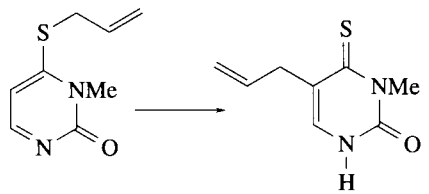

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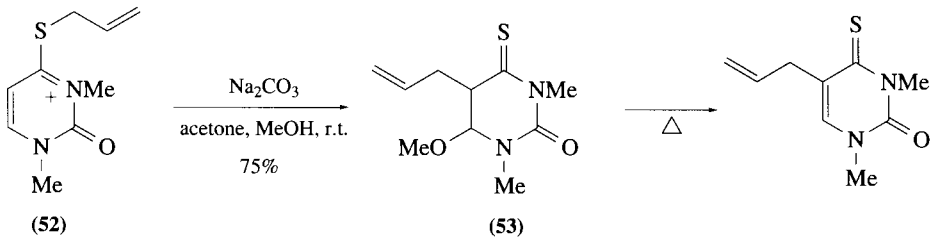
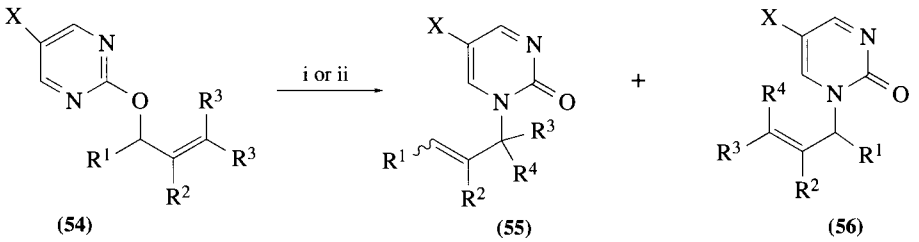


Scheme 2

6.02.5.1.2 Metal-catalyzed rearrangements

In allylic palladium complexes, the nucleophile will preferentially attack the more substituted allylic carbon. With the azines the allylation reaction is reversible, which means that the *N*-allylated product dissociates, and gradually the less substituted carbon becomes attached to the annular nitrogen ⟨89ACS251, 93ACS72⟩. Allylic rearrangements have been studied in some details for allylated pyrimidinones under the influence of either Pd(0)- or Pd(II)-catalysis. The reactions were run in dichloromethane at ambient temperature (Scheme 3). No rearrangement was observed in the absence of a catalyst. The product compositions from substituted allylic derivatives (**54**) depend on the catalyst used. Claisen (3,3) regioselectivity (**55**) is observed with a Pd(II)-catalyst, whereas Pd(0)-catalysis generally gives both (1,3) (**56**) and (3,3) (**55**) rearrangement products. The substitution pattern in the allylic system is important for the nature of the rearrangement product from the Pd(0)-catalyzed reaction, which is assumed to proceed via a π-allylpalladium complex. In the rearrangement of γ-alkyl- or γ-arylallyl derivatives, an equilibrium was set up between the allyloxy substrate and the two isomeric *N*-allyl rearrangement products (**57**) and (**58**). The major isomer, which may become the only detectable isomer in some cases, has the less substituted allylic carbon attached to the annular nitrogen ⟨89ACS251⟩.

A γ-stannyl or γ-silyl substituent is not affected in the Pd(0)-catalyzed allylic 1,3-rearrangement

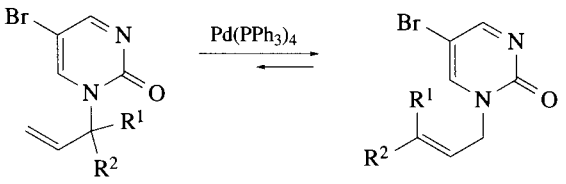


R^1, R^2, R^3, R^4 = H, Me, Pent, Ph, $SiMe_3$

X = Cl, Br

i, $Pd[(OiPr)_3P]_4$, CH_2Cl_2, THF

ii, $Pd(PhCN)_2Cl_2$, THF

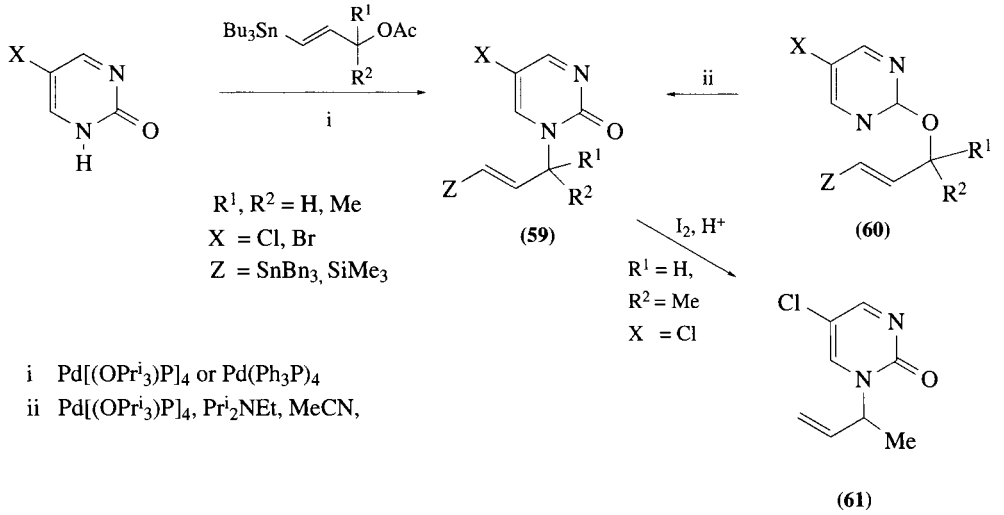


R^1 = H; R^2 = Ph, Me

R^1 = Me; R^2 = Me

Scheme 3

of (**60**), nor is the stannyl group affected in the P(0)-catalyzed alkylation when the ring is attached to the original allylic carbon (**59**) (Scheme 4) ⟨92ACS1215⟩.

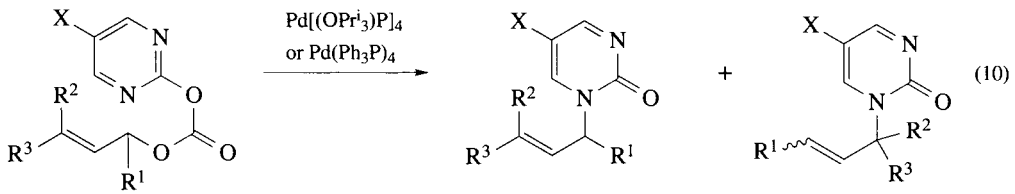


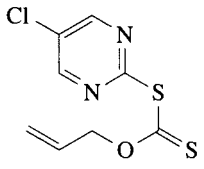
Scheme 4

Protonolysis with cleavage of the carbon–tin bond is achieved with iodine under acidic conditions to furnish the demetallated product (**61**) ⟨92ACS1215⟩.

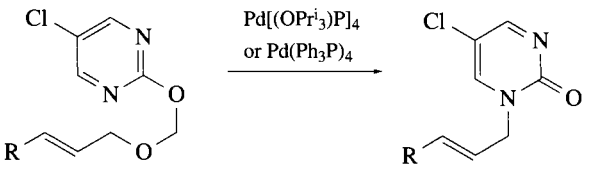
The rate of the Pd(0)-catalyzed rearrangement is dependent on the substitution pattern and is sometimes slow, which may be ascribed to slow formation of the intermediate π-allylpalladium complex.

Allyl carbonates have high reactivity in allylation reactions with carbon nucleophiles. In most cases the *N*-allylpyrimidinones are obtained in high yields from reactions of the carbonates (**62**) run at ambient temperature (Equation (10)) (for allyloxypyrimidines, reflux in THF was used; see above). Without the catalyst, no reaction occurred, and Pd(II) complexes did not cause any rearrangement. The product distribution, the ratio between (**63**) and (**64**), was similar to that from the corresponding allyloxypyrimidines since the reaction proceeds via the same π-allylpalladium complex. The 2-pyrimidinylthio analogue of the allylic carbonate (**65**) did not rearrange in the presence of Pd catalysts. From the acetal (**66**) a moderate yield of the rearranged product (**67**) was obtained (Equation (11)). The reaction is slow, and heating in DMF was used ⟨93ACS63⟩. The thio derivative (**65**) failed to rearrange, but the 2-thiouracil derivative (**68**) undergoes *S*→*N* allylic rearrangement to 1-allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**69**) and its 3-allyl isomer in a ratio >9 : 1 (Equation (12)) ⟨85JOC764⟩.

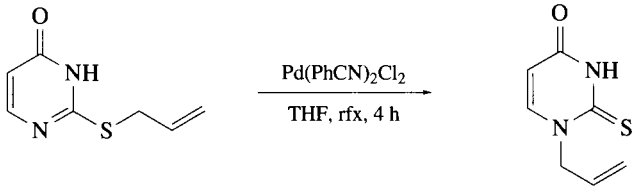




(**65**)

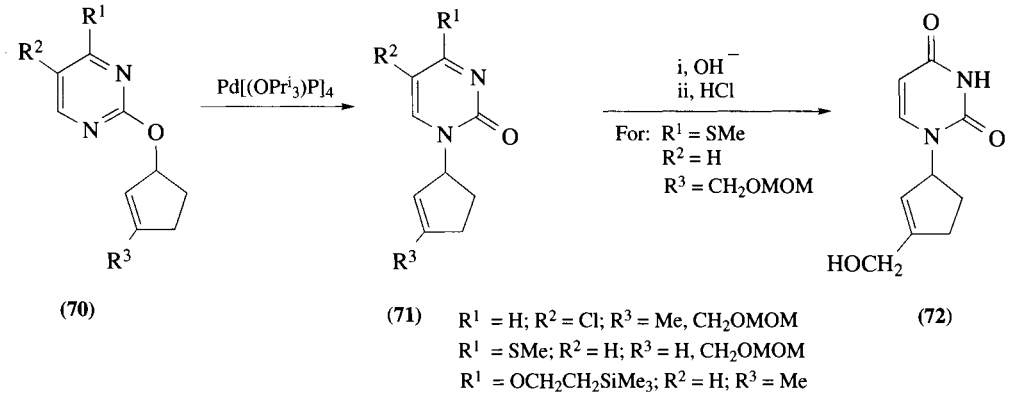


(66) R = H, Me (67) (11)



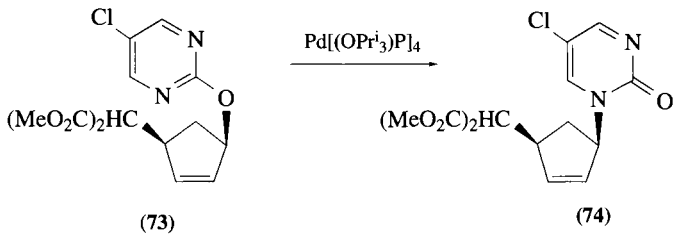
(68) (69) (12)

Palladium-catalyzed rearrangements of 2-allyloxypyrimidines can be used in the construction of carbonucleosides. Thus, allylic cyclopentenyl 2-pyrimidinyl ethers (**70**) can be rearranged on catalysis by tetrakis(tri-isopropyl phosphite)palladium, a Pd(0)-complex, in THF (Scheme 5). The allylic carbon in the substrate becomes attached to the heterocycle in the γ-substituted derivatives (**71**). The allylic derivatives are acid sensitive, and the presence in the reaction medium of a base such as caesium carbonate or triethylamine is frequently required. The stereochemical course was elucidated by reactions with the *cis*-4-malonylcyclopentenyl 2-pyrimidinyl ether (**73**). The carbonucleoside obtained (**74**) has *cis* stereochemistry and the regiochemistry shown. Removal of protecting groups in (**71**) furnished the carbonucleoside analogue (**72**) ⟨93ACS72⟩.



(70) (71) (72)

R^1 = H; R^2 = Cl; R^3 = Me, CH$_2$OMOM
R^1 = SMe; R^2 = H; R^3 = H, CH$_2$OMOM
R^1 = OCH$_2$CH$_2$SiMe$_3$; R^2 = H; R^3 = Me



(73) (74)

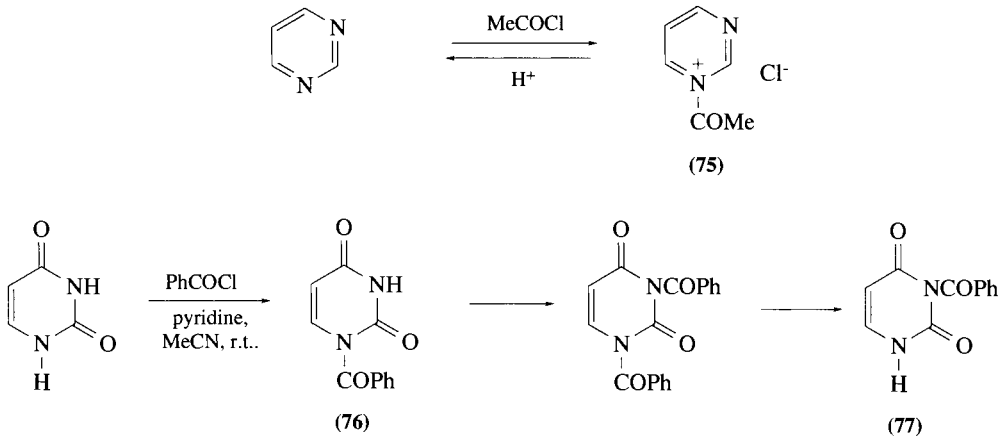
Scheme 5

6.02.5.2 Electrophilic Attack at Nitrogen

6.02.5.2.1 Acylation [1]

Acylation of a ring nitrogen in the fully conjugated pyrimidine derivative leads to a pyrimidinium salt. The *N*-acyl salts (**75**) are powerful acylating agents (Scheme 6). In the acylation of tautomeric

pyrimidinones either an acyloxypyrimidine, an *N*-acylpyrimidinone or a mixture of both are formed. Conditions for selectivity are not easily predictable. 1-Acetyl-4(1*H*)-pyrimidinone is formed in 50–60% yield from the 4-pyrimidinone on heating in Ac_2O ⟨86JHC1239⟩, and the 1-acetyl derivative is formed from uracil and thymine under similar conditions; the products are powerful acylating agents ⟨58JBC(232)185⟩. On the other hand, acylation is on the lactam oxygen in 2-methoxy-6-methyl-4(3*H*)-pyrimidinone using acetyl chloride in pyridine : MeCN at 20 °C; yield 78% ⟨88TL2741⟩. Prior silylation of the hydroxy groups may be used to promote *N*-acylation; the silyl ether reacts with an acyl chloride under mild conditions to afford an *N*-acylated pyrimidine ⟨84IZV1823⟩. Benzoylation of uracil gives 1-benzoyluracil (**76**); excess of benzoyl chloride takes the reaction to the 1,3-dibenzoyl derivative. Selective removal of the 1-benzoyl group can be effected under mild basic conditions to furnish the 3-benzoyl derivative (**77**). The selective hydrolysis may also take place during chromatography ⟨84TL681⟩.



Scheme 6

Reactions involving the *N*-acylation of perimidinone have been described ⟨81RCR816⟩.

Pyrimidinethiones are *S*-acylated under mild or moderate conditions, but may be isomerized to the *N*-acyl isomers at higher temperature.

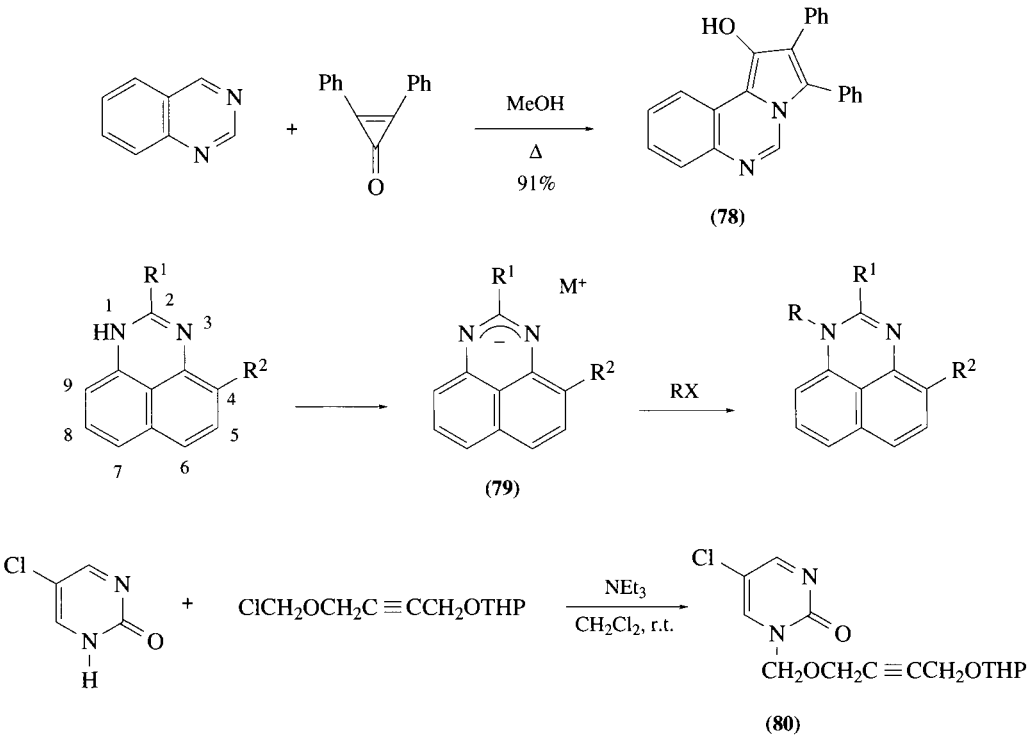
Primary and secondary pyrimidinamines undergo acylation at the amino group. Aminoquinazolines and -perimidines react similarly.

6.02.5.2.2 Alkylation

Reactions of electrophiles with annular nitrogens have been reviewed ⟨88AHC(43)127⟩. Simple alkylations of pyrimidines with non-tautomerizable substituents are largely controlled by steric factors; 4-*t*-butyl-6-methylpyrimidine with benzyl bromide in toluene forms exclusively the 1-benzylated product ⟨82JHC373⟩. Diquats are accessible through the use of oxonium alkylating reagents ⟨72JOC2259⟩. Quinazoline is preferentially *N*3-alkylated. The initial reaction of quinazoline with diphenylcyclopropenone is on *N*3 with subsequent cyclization to form 2,3-diphenyl-1-hydroxypyrrolo[1,2-*c*]quinazoline (**78**) (Scheme 7) ⟨91JOC5594⟩.

Perimidine has an acidic *NH* proton and therefore behaves differently from pyrimidine and quinazoline. The product is a neutral molecule. Like imidazoles, perimidines are best *N*-alkylated in alkaline media (**79**) in an inert atmosphere. Alkylation with primary alkyl bromides or iodides can be performed in an alcoholic solution. Dimethyl sulfate is recommended for methylation. Yields drop with secondary halides. *N*-Substitution reactions are sensitive to steric interference from 2- and 4(9)-substituents; 2-alkyl or aryl derivatives can be methylated but not alkylated by benzyl chloride or isopropyl, allyl or phenacyl bromides. 4(9)-Substituted perimidines are preferentially alkylated at the remote nitrogen.

1,4-Disubstituted perimidines could not be quaternized by methyl iodide even on prolonged heating. Alkylation of 6(7)-monosubstituted perimidines gives a mixture of the 1,6- and 1,7-isomers ⟨81RCR816⟩. 4(9)- or 6(7)-Nitroperimidine is difficult to *N*-alkylate. The anion of 2-trifluoromethylperimidine has resisted methylation. *C*-Alkylation in the nucleophilic 4(9)-position may be a



Scheme 7

competitive reaction to *N*-alkylation with allyl and benzyl halides. Perimidine could not be *N*-arylated by the Ullmann reaction, unlike imidazole. The *NH* group of perimidine will add to strongly electrophilic alkenes, and presumably to similarly activated alkynes. Michael addition with acrylonitrile illustrates one such reaction ⟨81RCR816⟩.

Alkylation of 2-hydroxy- ⟨66JOC3969⟩ and 4-hydroxy-⟨85JHC1077, 86ACS(B)381⟩ pyrimidines is largely governed by the nature of the alkylating agent, and by steric and electronic effects from adjacent substituents; for example, 4-methoxycarbonyl-5-chloropyrimidin-2(1*H*)-one as sodium salt is methylated principally at the 1-position by methyl iodide. The anionic form of 5-chloro-2(1*H*)-pyrimidinone, under phase-tranfer conditions, is selectively methylated and benzylated at the nitrogen ⟨79ACS(B)150, 81ACS(B)69⟩. Particularly useful for *N*-alkylation is dissolution of the 5-halo-2-pyrimidinone in dichloromethane as a triethylamine salt prior to reaction with the alkylating agent. With α-haloalkyl aryl sulfides, 5-halo-2(1*H*)-pyrimidinones are mainly *N*-alkylated, especially in the presence of tertiary amine bases, and in solvents of low dielectric constant ⟨85JHC1077⟩. Other soft electrophiles such as methyl iodide, benzyl bromide, and phenacyl halides give the *N*-alkylated product under these conditions ⟨81ACS(B)69, 91ACS177⟩, whereas alkylation with the relatively hard α-chloroalkyl ether electrophiles may give substantial amounts of *O*-alkylation by attack at the harder part of the ambident anion of the 5-halo-2-pyrimidinone ⟨83ACS(B)345⟩. Separation of the *N*-/*O*-alkyl isomers, however, is readily effected because of the higher lipophilicity of the *O*-alkylated isomer. The mild conditions allow the use of sensitive alkylating agents such as in reactions with chloromethyl propargyl ethers and substituted propargyl halides, as exemplified by the preparation of (**80**) (Scheme 7) ⟨91ACS731⟩. Second-order kinetics have been firmly established in the reaction of isopropyl bromide with 4-methylthio-2(1*H*)-pyrimidinone ⟨66JOC3969⟩ and for alkylation of 2-substituted-4(3*H*)-pyrimidinones ⟨70JOC2512⟩. *N*-Alkylation is sterically more demanding than *O*-alkylation. The rate of reaction at nitrogen will decrease relative to that of oxygen as the bulk of the alkylating reagent increases. Adjacent phenyl groups induce *O*-alkylation of 2-pyrimidinones ⟨84CHE1185⟩. There can be considerable solvent dependence on rates and regiochemistry in alkylation of 4(3*H*)-pyrimidinones. As the dielectric constant of the solvent decreases the *N*3 : *N*1 ratio may decrease sharply ⟨80BSF(2)559⟩.

Uracil and its *N*-unsubstituted derivatives generally form 1,3-dialkyl products under a variety of conditions ⟨81ACS(B)69, 81AJC1729, 81JHC339⟩. Large alkyl groups display a preference for the less hindered *N*1-nitrogen ⟨78TL3203⟩. In *N*1-substituted uracils, competition in the further alkylation is

between *N*3 and the 4-oxo oxygen. *N*-Alkylation is favored, but hindered alkyl halides and diazomethane give a high proportion of *O*-alkyl products ⟨71JOC848, 72BAU352⟩. Cytosine is alkylated largely on *N*1 or *N*3 depending on the reagent ⟨78JOC1593⟩. DMF dimethylacetal is a specific methylating agent for *N*1 of cytosine ⟨81S118⟩. Most 4-amino-6-hydroxypyrimidines are methylated preferentially at *N*1 ⟨62LA(657)149⟩.

Barbituric acid derivatives resemble uracils in their preference for *N*-alkylation with most reagents ⟨76AJC1769, 78AJC2517⟩. Large alkyl groups may favor *O*-alkylation. Diazomethane converts barbituric acid into 6-methoxy-1-methyluracil ⟨72CJC880⟩. Information is also available on the alkylation of perimidinones ⟨81RCR816⟩.

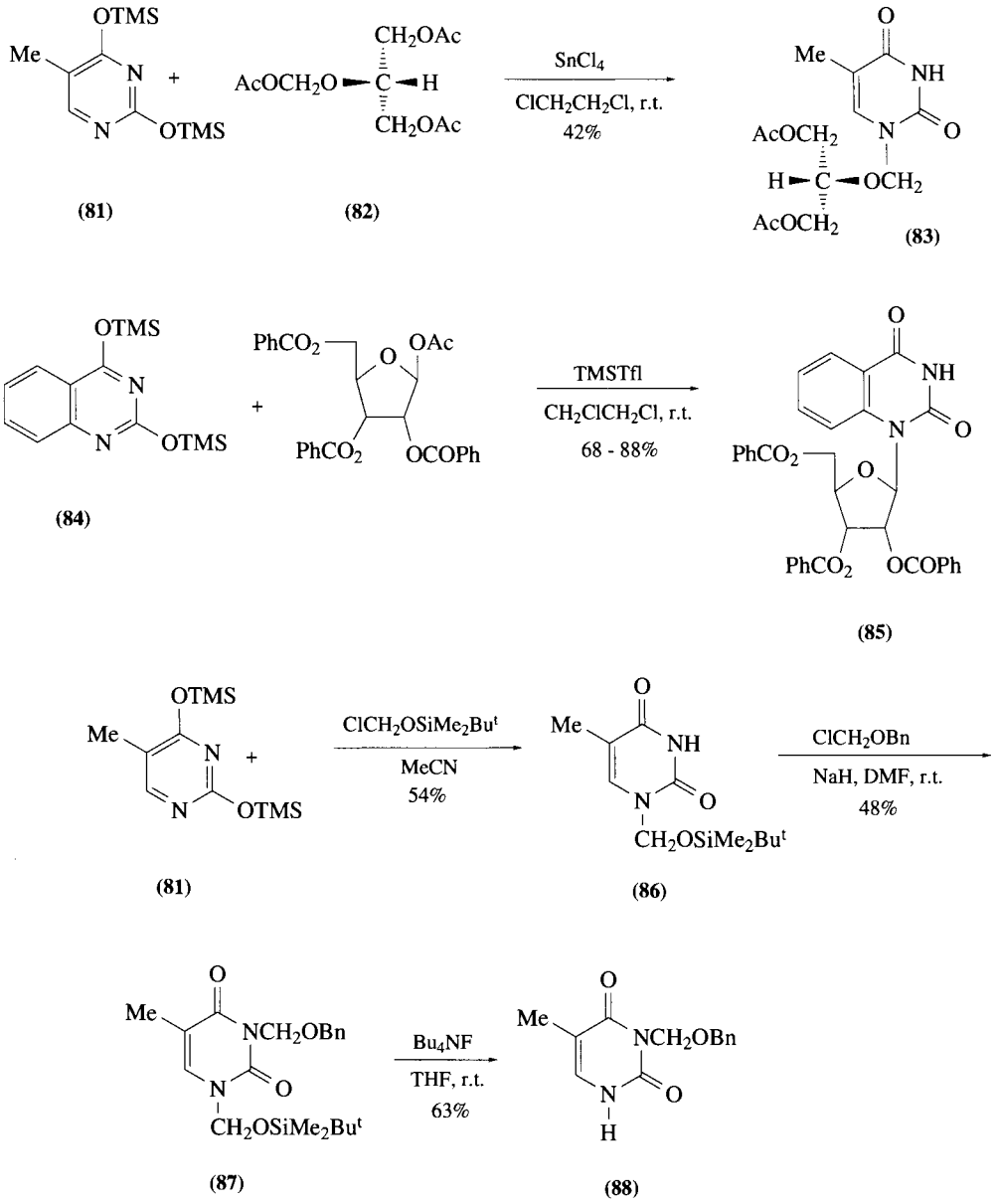
N-Alkylation is promoted by prior conversion of the pyrimidinones into their respective silyl ethers by heating the pyrimidinone in hexamethyldisilazane, usually until the pyrimidinone has dissolved, or by treatment of the pyrimidinone in solution with TMS-Cl and a tertiary amine. Besides selectivity in the alkylation reactions, silylation confers solubility on molecules which otherwise may be difficult to dissolve in nonhydroxylic organic solvents. One example (Scheme 8) is provided by an *N*-alkylation of persilylated thymine (**81**) with an acetal functionalized glycerol derivative (**82**) under conditions similar to those used for glycosylation of nucleoside bases; the Lewis catalyst was tin tetrachloride. The product (**83**) can be regarded as an open-chain thymidine analogue ⟨90CPB836⟩. Similarly, several 6- and 7-substituted-2,4-(1*H*,3*H*)-quinazolinediones have been persilylated, e.g., (**84**), and ribosylated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranoside using TMS triflate as the acid catalyst to form the riboside (**85**) in a highly stereoselective manner with the β-configuration ⟨91MI 602-02⟩. Selective *N*3-alkylation of uracils requires initial protection of *N*1. In the silylated thymine (**81**) *N*1 is initially protected (**86**) by alkylation with chloromethyl *t*-butyldimethylsilyl ether. The bulky silyl ether group is fairly stable to acidic and basic conditions, but it is removed under very mild conditions using fluoride ions in the form of TBAF. It is an excellent group for *N*- or *O*-protection. A benzylic type protecting group is sometimes used when its removal by hydrogenolysis at the end of the reaction sequence is compatible with the nature of the substituents present. Further alkylation of (**86**) with benzyl chloromethyl ether is on *N*3 to give the *N*1,*N*3-dialkylated product (**87**). The silyl ether protection is subsequently removed by fluoride ions thereby yielding the *N*3-alkylated product (**88**) ⟨88ACS(B)384⟩.

Tautomeric pyrimidinones also react with bis(tributyltin) oxide, $(Bu_3Sn)_2O$, to form corresponding tributylstannyloxypyrimidines on heating in a solvent such as benzene. The stannyloxypyrimidines undergo facile *N*-alkylation with loss of the stannyl grouping as in the formation of 1-allyl-5-chloro-2(1*H*)-pyrimidinone in the reaction from 5-chloro-2-tributylstannyloxypyrimidine using Pd(0) ⟨87ACS(B)577⟩. Thymine, activated as its bis-TMS ether (**81**) gave a mixture of the *N*-mono- and *N*,*N*′-diallylated product ⟨92ACS761⟩.

Palladium-catalyzed allylation has been used in the construction of carbonucleosides, as demonstrated in the preparation of a carbonucleoside of thymine (**90**) (Scheme 9). The coupling proceeds under mild conditions. Persilylated thymine (**81**) is coupled at room temperature with the allylic cyclopentenol acetate (**89**), with the primary alcohol protected as a thexyldimethylsilyl ether, to yield the carbonucleoside (**90**). The large silyl group is resistant to the conditions of the coupling, but it is readily removed from (**90**) by fluoride ions. The allylic alkylations can also be run on anionic pyrimidinones as shown for the reaction between the triethylamine salt of 5-chloro-2(1*H*)-pyrimidinone and the same allylic cyclopentenyl acetate (**89**) to give the *N*1-alkylated product (**91**). The stereochemical course is controlled by the stereochemistry of the Pd-template. The Pd(0)-catalyst adds on the opposite side of the outgoing acetate group. Subsequently a soft nucleophile will add to the same side of the template as the group which was displaced. With the *cis*-cyclopentenyl acetate (**89**), a *cis*-carbonucleoside (**90**) is formed. In the generation of the Pd-template, the original allylic position is lost once the leaving group has departed, and the regiochemistry in the subsequent bond-forming reaction will be controlled by the substituents in the allylic moiety of the template. Thus the change in the allylic regiochemistry in the carbocycle in the transformation of (**89**) to (**90**) results from nonbonded interactions between the approaching nucleophile and the other substituent in the cyclopentene ring ⟨92ACS761⟩.

The alkylation of tautomeric thiones invariably proceeds to give an *S*-alkyl derivative; any *N*-, *O*-, or *C*-alkylation is less rapid and can be avoided. *N*-Alkylation of a dihydropyrimidinethione has been reported ⟨87IJC(B)556⟩.

The Dimroth rearrangement is an isomerization initiated by ring fission and subsequent recyclization. In this process a ring-nitrogen and its attached substituent is exchanged with an imino group in the α-position (Scheme 10). Rearrangement of the 1-methyl-2-pyridinimine (**92**) to 2-methylaminopyrimidine proceeds by the addition of a hydroxide ion at C6 (**93**), ring opening (**94**)



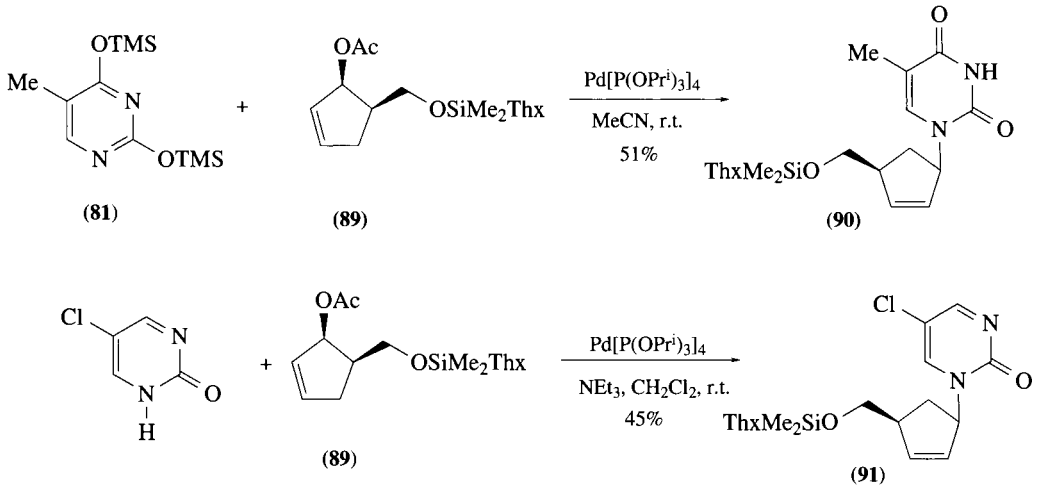
Scheme 8

and recyclization to the observed product. The reaction is reversible in that conditions for an equilibrium can be set up for 1-alkyl-2-alkylimino-1,2-dihydropyrimidines (**95**) and (**96**).

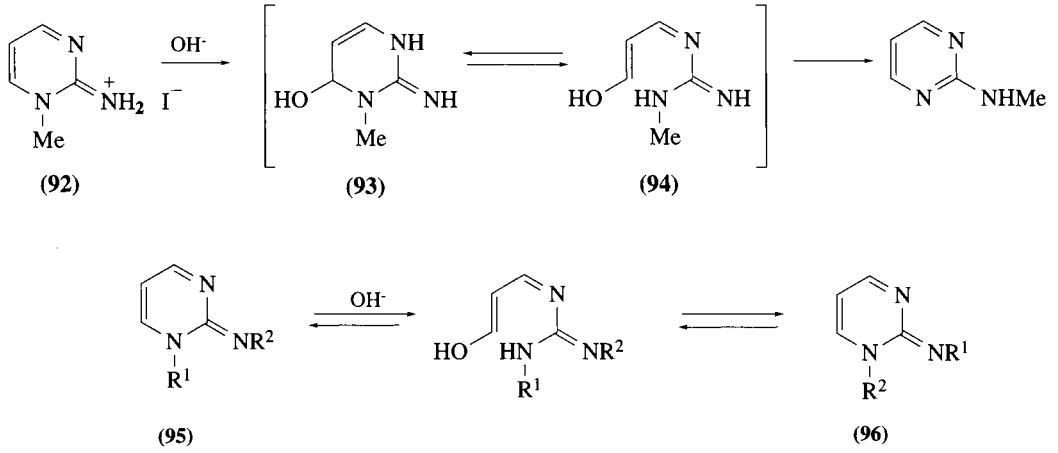
Unlike acylation, alkylation of a primary or secondary 2- or 4-/6-aminopyrimidine usually takes place on a ring nitrogen to afford a 1-alkyl (**92**) or 3-alkyl iminopyrimidine, which subsequently may undergo a Dimroth rearrangement to its alkylamino isomer ⟨B-94MI 602-01⟩.

6.02.5.2.3 N-*oxidation*

Pyrimidines and methylpyrimidines are susceptible to decomposition, ring-carbon oxidation and ring-opening reactions on direct *N*-oxidation, resulting in low yields of *N*-oxides. Activating substituents are required ⟨84CJC1176⟩. In strong acid low yields of pyrimidinones may result ⟨85JOC3073⟩. With *m*-chloroperbenzoic acid in chloroform, pyrimidine *N*-oxides result: 48% from



Scheme 9



Scheme 10

pyrimidine and 55% from 2-methylpyrimidine ⟨81H(16)573⟩. Pyrimidine 1,3-dioxides require high activation for direct formation ⟨80AJC131, 83CHE1003⟩. Unsymmetrical pyrimidines are oxidized preferentially at sites *para* to strong electron donors. Bulky groups and electron-withdrawing substituents decrease oxidation, and direct the attack to the more remote nitrogen ⟨84CJC1176⟩. Careful choice of reagent is necessary to reduce oxidative degradation ⟨81H(16)573⟩. Steric hindrance by a phenyl substituent is marked ⟨83CHE1003, 84CJC1176⟩. The steric effects of simple alkyl groups are smaller. 4-Methylpyrimidine gives a mixture of the 1- and 3-oxides in the ratio 1 : 1 ⟨84CJC1176⟩, 1 : 2.5 ⟨81H(16)573⟩, or 1 : 3 ⟨64TL19⟩ depending on the reagent. With 2,4-dimethylpyrimidine the regioisomeric ratio was 1 : 1 ⟨83CPB4533⟩, and 75% *N*-oxide from 4,6-dimethylpyrimidine ⟨84CJC1176⟩. Larger alkyl groups change the ratios ⟨81H(16)573⟩. Nitro groups deactivate and may prevent *N*-oxidation ⟨79AJC2049⟩. A chloro substituent also deactivates ⟨74RTC58, 84CJC1176⟩. 5-Bromopyrimidine gives the *N*-oxide in 29% yield with MCPBA ⟨85JOC3073⟩. Methoxy groups activate, but steric effects may dominate. 4-Methoxypyrimidine and derivatives form *N*1-oxides ⟨84CPB728⟩, but 2-methoxypyrimidine gave only 18% *N*-oxide with peracetic acid. An additional methyl or methoxy group in the 4-position led to increased yield of *N*-oxide ⟨84CJC1176⟩. Peracetic acid oxidation of 4-amino- and 4-alkylamino-pyrimidines gives low yields of *N*1-oxides. In 2-amino- and 2-alkylaminoalkylpyrimidines, oxidation is on an adjacent ring-nitrogen ⟨84CJC1176⟩. 2,4-Diaminopyrimidines are oxidized at *N*3 ⟨81AJC1539⟩. Uracil and thymine failed to form *N*-oxides

with MCPBA ⟨86CPB2354⟩. 5-Hydroxypyrimidines are highly active in the formation of *N*1-oxides ⟨83CHE1003, 83CHE1008⟩.

Direct oxidation of quinazolines is less explored than for pyrimidines. 4-Alkoxyquinazolines form *N*-oxides in moderate yields with peroxyphthalic acid ⟨B-67MI 602-01⟩.

6.02.5.3 Electrophilic Attack at Carbon

6.02.5.3.1 Nitration

Pyrimidine and its cation are highly π-deficient and resist nitration. The π-system in the 5-nitro derivative is further electron-depleted. Presumably adducts are formed which either are oxidized or ring-opened. At least one strongly electron-donating substituent is required. 2(1*H*)-Pyrimidinone, but not the 4-isomer, is nitrated in the benzenoid 5-position ⟨71JCS(B)1⟩. Introduction of a nitro group in the electrophilic positions would require either a nucleophilic substitution or an oxidation of an amino or nitroso function. Nitration proceeds readily in pyrimidines with more than one electron-releasing group ⟨77JOC3821⟩.

The similarities in rates of nitration of uracils and 1,3-dimethyluracil suggest that they are all nitrated in the dioxo forms; the rate for 2,4-dimethoxypyrimidine is slower by a factor of about 10^4. 2(1*H*)-Pyrimidinone and its 1-methyl derivative also react as the free base; the rates are much lower than those of the corresponding uracil and 100 times slower than for 3-methyl-2(1*H*)-pyridinone. These results reflect the deactivating effect of a second annular nitrogen and the presence of only one oxo function ⟨71JCS(B)1⟩.

Interpretation of the nitration results for aminopyrimidines is complicated by the formation of nitramines, which can rearrange. With aminopyrimidines, only nitramines appear to form. The nitramines formed at lower temperature rearrange to the 5-nitro products when heated in concentrated sulfuric acid ⟨01CB1234⟩.

Thio functions are normally oxidized under nitrating conditions.

Pyrimidine *N*-oxides, unlike pyridine *N*-oxide, cannot be nitrated unless they possess electron-donating substituents, e.g., 5-nitration in 2,6-diamino-4-ethylaminopyrimidine *N*-oxide ⟨79AJC2049⟩.

Aryl-substituted pyrimidines are most often nitrated preferentially in the aryl ring, with the protonated azine acting mainly as a *meta* director ⟨81JCR(S)104, 82CJC2668⟩. The nature of the nitrating agent, however, can affect product distribution. Thus 4-phenylpyrimidine with mixed nitric and sulfuric acids yields 4-*o*- and 4-*m*-nitrophenylpyrimidine in the ratio 2:3, nitric acid–acetic anhydride yields 2,4-diacetoxy-1,3,5-trinitro-6-phenyl-1,2,3,4-tetrahydropyrimidine ⟨67CJC1431⟩. In thienyl- or furfurylpyrimidines, nitration can occur in both α- and β-positions of the five-membered ring, with β-attack predominating ⟨81JCR(S)104, 82CJC2668⟩.

Nitration of quinazoline is in the 6-position in the benzene ring. 2- and 4-Substituted quinazolines are likewise nitrated in the 6-position ⟨49JCS1354⟩, but 4-chloro-2-phenylquinazoline reacts with mixed nitrating acid at 0 °C to yield the *m*-nitrophenyl derivative with concomitant loss of the chloro substituent, the product isolated being 2-*m*-nitrophenyl-4(3*H*)-quinazolinone ⟨91UP 602-01⟩.

The carbocyclic system of perimidine is π-rich; mild conditions are used to effect electrophilic substitutions in the carbocyclic ring. Perimidine with one molar equivalent of HNO_3 gives the 4(9)- and 6(7)-nitroperimidines in the ratio 2.5:1. Aceperimidine gives a mixture of the 4(9)-nitro derivative and the 4,9-dinitro derivative. Nitration can be effected with $NaNO_2$ in AcOH at room temperature. Up to three nitro groups can be introduced. 1-Methylperimidine is nitrated mainly in the 7(6)-positions. Perimidines with nitrogen dioxide give tetranitro derivatives ⟨81RCR816⟩.

6.02.5.3.2 Nitrosation

Nitrosation takes place in the benzenoid 5-position in pyrimidines with three strongly electron-donating groups, e.g., oxo, thioxo, or amino groups. In disubstituted pyrimidines, the relative positions of the substituents are decisive for any reaction; 4,6-diamino- and 4,6-dihydroxypyrimidines are 5-nitrosated whereas their 2,4-isomers fail to react. Nitrosation is brought about by nitrous acid or by nitrite esters. When the reaction is slow, an alkyl substituent may be nitrosated on the α-carbon; the product is an oxime. An extensive review on nitrosopyrimidines is available ⟨B-94MI 602-01⟩.

6.02.5.3.3 Diazo coupling

The diazonium electrophile is weak, and requires highly nucleophilic counterparts for reaction. At least two strongly electron-releasing substituents at C2 and C4 (or C6) are needed for pyrimidines to couple at C5 ⟨83AJC1659⟩. The reaction takes place under mild conditions that may not affect even quite labile substituents. Electrophilic substitution may be accompanied by exocyclic coupling at 2-, 4-, or 6-amino, -thiol, or -methyl groups ⟨80H(14)1753⟩. When the 5-position is occupied by an amino, hydroxy, or acetate group, but not by a methoxy, methylthio, or acetamido group, coupling at the 6-position can take place, or at the 2-position if C6 is blocked ⟨81JHC1639, 82CHE297⟩. Arylazopyrimidines have recently been reviewed ⟨B-94MI 602-01⟩.

Diazo coupling in quinazolines occurs in the benzene ring, with the normal benzene or naphthalene requirement for the presence of strongly electron-donating substituents. Perimidines couple readily in the 6(7)-position with diazonium salts to form blue azo derivatives. The reaction has been described for perimidine, 2-substituted derivatives, 6(7)-chloroperimidine, and 2-aminoperimidine ⟨81RCR816⟩.

6.02.5.3.4 Halogenation

Pyrimidines are halogenated directly by electrophilic reagents in the benzenoid 5-position. Halogenations in the electrophilic positions are by nucleophilic exchange reactions.

(i) Chlorination

Pyrimidine needs to be activated, for example by a hydroxy or amino group, for chlorination to occur in the 5-position. Reagents are chlorine in a suitable solvent ⟨81S701⟩, chlorine in the presence of a base ⟨90H(31)109⟩, phenyl iododichloride ⟨82CJC554⟩, NCS ⟨83JOC2719, 84TL3325, 92AJC877⟩, sulfuryl chloride with ferric chloride as catalyst ⟨83JHC219⟩, a chloride with an oxidizing agent ⟨81JOC2819⟩, and enzymic methods ⟨87CL2311⟩. A 2-*t*-butyl group gives sufficient activation for chlorination in the 5-position ⟨90H(31)109⟩.

Metallic derivatives frequently provide substrates for electrophilic chlorination. Chloro-demercuration using sulfur monochloride gave a 65% yield of 5-chlorouracil ⟨85CHE322, 88BAP499⟩. Similarly, *ipso* chlorination of 6-trimethylsilyl derivatives occurs on treatment with NCS ⟨84TL3325, 93AHC(58)271⟩.

(ii) Bromination

5-Bromopyrimidine is formed in 71–88% yield using bromine in solvents like benzene or nitrobenzene. Substitution on carbon is preceded by a vigorous reaction at lower temperatures involving *N*-bromination and perbromide formation ⟨90AHC(47)325⟩. Bromination in the vapor phase at 230 °C gives the 5-bromopyrimidine in 62% yield ⟨73JHC153⟩.

Amino, hydroxy, or oxo groups in the pyrimidine ring greatly assist electrophilic bromination. An amino or hydroxy group facilitates 5-bromination even in aqueous solution ⟨83JOC1064, 91JHC1981⟩. In uracils, cytosines, and barbituric acids, products of both addition and substitution can be identified in aqueous solution, and 5,5-dibromo products are common. Uracil bromination parallels that of 2(1*H*)-pyrimidinone in that addition products, including covalent hydrates, form rapidly. Acid-catalyzed dehydration to 5-bromouracils is a much slower step. Cytosine and related compounds behave similarly ⟨90AHC(47)325⟩. 2-, 4-, and 5-Methoxypyrimidine 1-oxide resist bromination in the absence of an additional activating group ⟨83CHE91, 83JOC1064⟩. *N*-Oxides may suffer deoxygenation during bromination ⟨84H(22)1195⟩.

(iii) Iodination

Iodination of pyrimidine requires the presence of an activating substituent. Reagents used in pyrimidine reactions are NIS in acetic acid ⟨83JOC2719, 86S555⟩, or in ethanol or ethanol–chloroform mixtures ⟨81RTC267⟩, and in a mixture of trifluoroacetic acid and its anhydride ⟨88SC855⟩. NIS can be generated *in situ* from sodium iodide and NCS ⟨84TL233⟩. Other reagents include I_2/pyridine/DMT

⟨83JOC2719⟩, I_2/Ag_2SO_4 ⟨90SC3391⟩. Electrophilic iodine can be generated from sodium iodide by an oxidizing agent ⟨90JOC4928⟩. Iodine monochloride is a convenient and useful reagent ⟨84S252, 85ACS(B)691⟩. Cross-linked polystyrene-4-vinylpyrimidinium dichloroiodate was an effective (>90% yield) iodination agent for uracils ⟨89JCS(P1)2279⟩.

Metallated pyrimidines are useful substrates for iodination, for example in halo-demercuration ⟨85CHE322, 88BAP499⟩. Use of lithiated species is more common ⟨83CPB2164, 91JHC283⟩. The 5-lithio derivative of 4-chloro-2,6-dimethylpyrimidine reacts with iodine in THF with 5-iodination (86%) ⟨91JHC283⟩.

(iv) Fluorination

Direct 5-fluorination can be effected on activated pyrimidines; for example, F_2 in HOAc or anhydrous HF have been used for the preparation of 5-fluoro-2(1*H*)-pyrimidinones ⟨77CCC2694⟩, and for 5,5-difluorination of 6-*O*-cyclouridines ⟨83TL1055⟩. Uracil and cytosine are 5-fluorinated by the same procedure ⟨80TL4605, 82CPB887⟩. Other methods for the preparation of 5-fluorouracils involve F_2 passed through an aqueous suspension of the substrate ⟨82CPB887, 84TL4885⟩, perfluoromethanol with the graphite intercalate $C_{19}XeF_6$ ⟨80TL277⟩, acetyl hypofluorite ⟨85JOC4152, 88JCS(P1)2547⟩, trifluoroacetyl hypofluorite ⟨81CPB3181⟩, cesium fluoroxysulfate ⟨83CC563, 90T3093⟩, fluorine monoxide ⟨81CB1176⟩ and *N*-fluoropyridinium salts ⟨90JA8563⟩.

The fluorination of uracil and cytosine using fluorine and acetyl hypofluorite involves a radical-cation mechanism ⟨86JOC1466⟩.

1,3-Dimethyluracil with caesium fluoroxyacetate in methanol gave the *cis* and *trans* adducts in ratio 11.5 : 1; base induced elimination of methanol gave the 5-fluoro uracil ⟨83CC563⟩. Fluorination of the exocylic nitrogen in 2- and 4-aminopyrimidines may occur ⟨84JFC(24)355⟩.

(v) Quinazolines

Electrophilic substitution in quinazoline takes place in the benzene ring; theoretical prediction of positional reactivity is $8 > 6 > 5 > 7 \gg 4$. 4(3*H*)-Quinazolinone was converted into a mixture of 6- and 8-chloro, and 6,8-dichloro products ⟨57JCS2521⟩. Initial bromination of 4(3*H*)-quinazolinone and its 3-methyl derivative is in the 6-position with slow formation of the 6,8-dibromoquinazolinone. Below pH 2, when the former substrate and its *N*3-methyl derivative exist mainly as cations, the latter was brominated slightly faster. The pathway is believed to involve bromine attack on covalent hydrates ⟨76JOC838, 93AHC(58)271⟩.

(vi) Perimidines

Halogenation of perimidines, perimidinones, and dihydroperimidines occurs at an *ortho* or *para* position in the naphthalene system, i.e., the 4-, 6-, 7-, 9-, positions in the perimidine system, where the donor effects from the nitrogens operate ⟨81RCR816⟩. With one equivalent of sulfuryl chloride in acetic acid, monochlorination of perimidine gives a mixture of the 6(7)- and the 4(9)-isomers in the ratio 8 : 1. With two equivalents a mixture results, but the 4,6,7-trichloroperimidine is the main product ⟨81RCR816⟩.

The perimidines should be *N*-substituted to avoid oxidation. With *N*-chlorobenzotriazole, chlorination leads to a mixture of 4- and 9-chloro derivatives. With 2 equivalents the 4,9-dichloro derivative results. Subsequent chlorinations yield the 4,7,9-trichloro and the tetrachloro derivative. 1,2-Dimethylperimidine reacts in the same way. In 1-isopropylperimidine steric interaction prevents chlorination at the 9-position; perchlorination produces the 4,6,7-trichloro derivative. The 1,3-dimethylperimidinium ion is chlorinated by either reagent in the 6-position. 1,3-Dimethylperimidin-2-one is dichlorinated in the same manner as 1-methylperimidine by *N*-chlorobenzotriazole in both 4- and 9-positions; clean monochlorination could not be effected ⟨81RCR816⟩.

6.02.5.3.5 Sulfonation

Sulfonic acids are conveniently made by oxidation of corresponding thiones or disulfides. Direct sulfonation is best effected with chlorosulfonic acid. 2-Aminopyrimidine and other strongly activated derivatives react to form 5-sulfonic acids ⟨61JOC3863, 63JOC1994⟩.

(i) Quinazolines

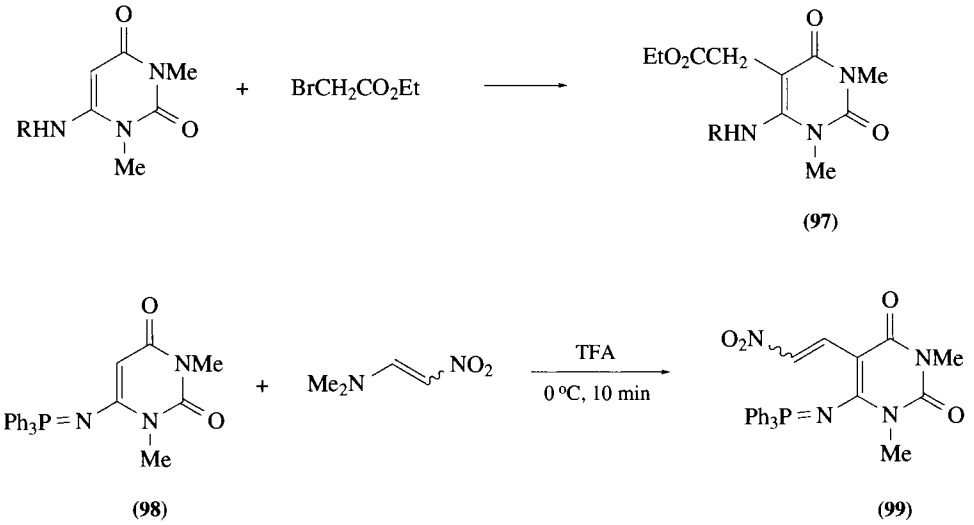
Introduction of the sulfonyl group as an electrophile is in the carbocyclic ring. 4(3*H*)-Quinazolinone is sulfonated in the 6-position by chlorosulfonic acid ⟨60JA2731⟩.

(ii) Perimidines

Concentrated sulfuric acid at 20 °C or below has been used for sulfonation of perimidine and its 2-substituted derivatives. Substitution is in the 6-position in excellent yield (time 10–15 min). Increase in temperature leads to polysulfonation. The 1,3-dimethylperimidinium ion and 2-oxoperimidine are sulfonated in the 6-position under the same conditions. 1,3-Dimethyl-2,3-dihydroperimidine, as a dication, is sulfonated at 60–70 °C ⟨81RCR816⟩.

6.02.5.3.6 Alkylation

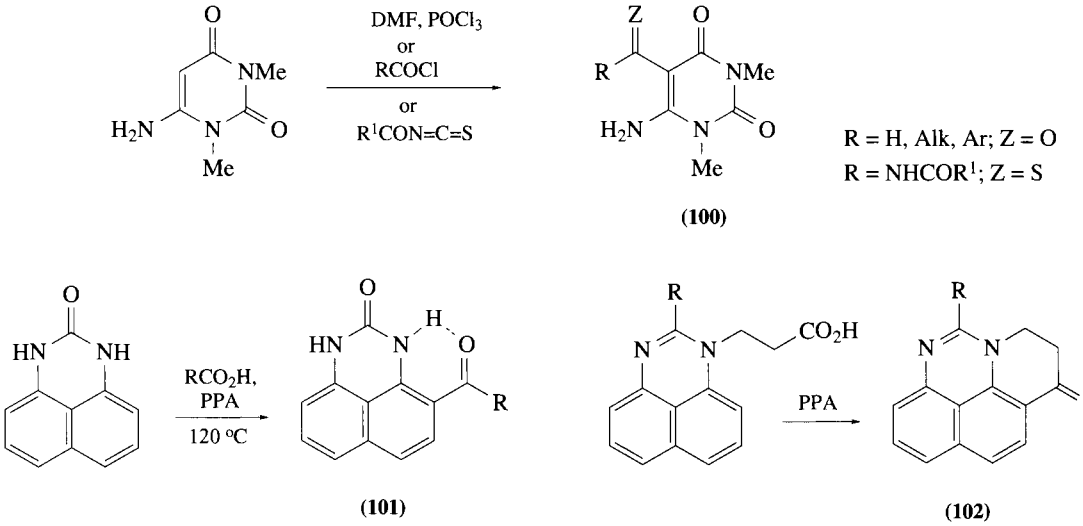
Direct electrophilic alkylation in the pyrimidine 5-position can be carried out on pyrimidines with at least two strongly donating groups, more readily with three such groups. The Mannich reaction on 6-amino-2-methyl-4(3*H*)-pyrimidinone with formaldehyde and piperidine gives the piperidinomethyl derivative. Isobarbituric acid and related compounds with an occupied 5-position may undergo Mannich attack at the otherwise electrophilic 6-position ⟨67JHC49⟩. Even uracil can be 5-hydroxymethylated by formaldehyde under alkaline conditions ⟨59JA2521⟩. Uracil also adds to aromatic aldehydes with subsequent dehydration ⟨78CC764⟩. α-Haloketones and α-bromocarboxylic esters can be used for direct alkylation of the 5-position in 6-aminouracil, for example in formation of (**97**) (Scheme 11). The 5-position is also activated for Michael additions ⟨92AHC(55)129⟩; an example is provided by 6-aminouracil or its 6-iminophosphorane (**98**) in a Michael type reaction with 1-dimethylamino-2-nitroethene and subsequent amine elimination to yield the 5-(2-nitroethene) (**99**) ⟨90S474⟩. Several similar reactions are to be found in a review on barbituric acid chemistry ⟨85AHC(38)229⟩. Pyrido[2,3-*d*]pyrimidines are easily constructed from 6-aminouracils when the Michael acceptor is functionalized for a subsequent reaction with the amino group, e.g., acrolein. The dihydro product is subsequently dehydrogenated. If the acceptor carries an alkoxy, amino, or a halo substituent on the β-carbon, elimination in the adduct gives the fully conjugated heterocycle ⟨92AHC(55)129⟩.



Scheme 11

6.02.5.3.7 Acylation

Both the Reimer–Tiemann and the Vilsmeier reactions lead to formylation in the 5-position in pyrimidines with at least two strongly releasing substituents. Thus 6-amino-1,3-dimethyluracils are readily formylated by DMF/$POCl_3$ ⟨84S589, 92AHC(55)129⟩, acylated by acid chlorides or converted into thiocarbamoyl derivatives by isothiocyanates (**100**) (Scheme 12) ⟨79H(12)503⟩.



Scheme 12

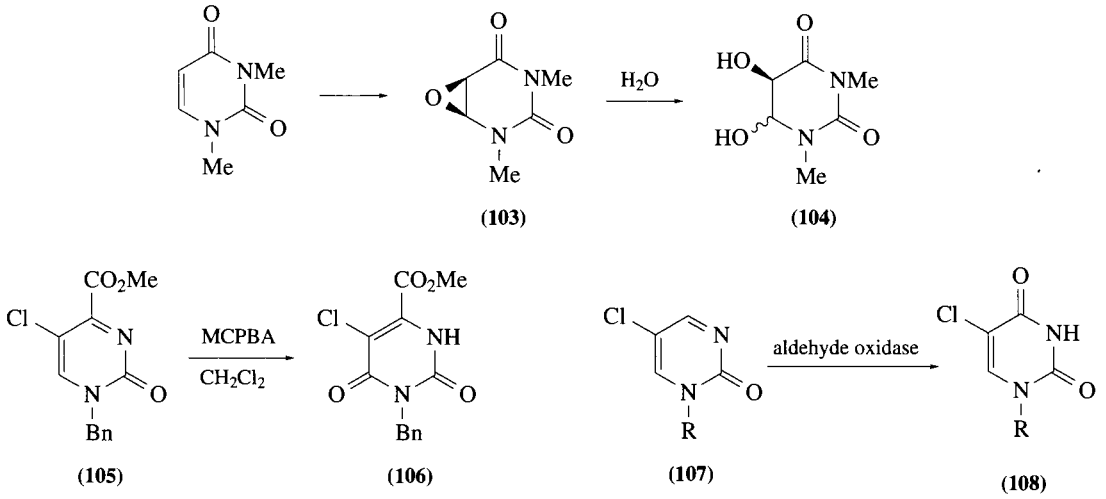
(i) Perimidines

Perimidine is readily acylated under Friedel–Crafts conditions in the carbocyclic ring system by analogy to acetamidonaphthalenes. The usual deactivating complex formation between the Lewis catalyst and an azine nitrogen, as in pyrimidines and quinazolines, is not operative. With polyphosphoric acid (PPA) at 70–85 °C perimidines with free NH are acylated mainly in the 6(7)-position, and to a lesser extent in the 4-position. At 120–150 °C 4(9)-acylpyrimidines (**101**) are obtained. Acylation of 1-methylperimidine gives a mixture of the 6- and 7-isomers as main product. Trifluoroacetylation of 1-methyl-, 1-phenyl-2-trifluoromethylperimidine proceeds with high yield in the 7-position. The 1,3-dimethylperimidinium ion is acylated in the 6(7)-position with AcOH:PPA under the same conditions as perimidine. Acylation of 2-perimidinones by carboxylic acids promoted by PPA gives a mixture of 4(9)- and 6(7)-acyl derivatives. Acylation of 1,3-dialkylperimidinones is in the 6(7)-positions. 1,3-Dimethylperimidinone is acylated by TFA-anhydride in the 6-position. Intramolecular acylation in perimidinones can be effected with appropriately spaced carboxylic acid derivatives (**102**) ⟨81RCR816⟩.

6.02.5.3.8 Oxidation

Oxygenated derivatives of dihydropyrimidines arise from addition of hydrogen peroxide to the 5,6-double bond to give 5,6-dihydroxy adducts ⟨B-94MI 602-01⟩. Potassium permanganate has been used for the oxidation of the 5,6-bond in uracils and osmium tetroxide has been found useful for the oxidation of cytosines (Scheme 13). The products are the expected *cis*-glycols from the cyclic ester intermediate in these oxidations. The *cis*-glycol, however, may partially isomerize, and the *trans*-isomer has been isolated. The reaction with peroxymonosulfate is thought to have a 5,6-epoxide (**103**) as an intermediate which is protonated and ring-opened to a stabilized carbocation. Bond formation at C6 with water would be expected to proceed with energetically favorable *cisoid* (*gauche*) stereochemistry to yield the *cis*-glycol. 5,6-Epoxide formation has been confirmed by product isolation. When 1,3-dimethyluracil was oxidized by dimethyldioxirane, which allows mild reaction conditions, a mixture of 1,3-dimethyl-5,6-epoxy-5,6-dihydrouracil (10%) (**103**) and 5,6-

dihydroxy-5,6-dihydrouracils (**104**) as the *cis* (50%) and the *trans* (25%) isomers was formed. Under conditions where most of the water was removed from the reagent, the oxirane (**103**) was obtained in 50% yield, and in water only the diols were obtained. 5- and 6-Methyl *N*-alkylated uracils gave higher yields of the epoxide ⟨93TL6313⟩. Oxidation of the highly π-deficient 2(1*H*)-pyrimidinone (**105**) with MCPBA gave oxidation in the vacant 6-position with formation of the corresponding uracil (**106**). The reaction is probably initiated by adduct formation with the peracid oxygen. Enzymatically, *N*1-substituted 2(1*H*)-pyrimidinones (**107**) are hydroxylated at C4 to form the corresponding *N*1-substituted uracils (**108**) by the enzyme system aldehyde oxidase ⟨B-89MI 602-01⟩.



Scheme 13

6.02.5.4 Nucleophilic Attack at Carbon

6.02.5.4.1 Halogenation

(i) Chlorination

Synthesis of 2-, 4-, or 6-chloro derivatives is usually by a nucleophilic process from hydroxy compounds using a phosphorus chloride reagent ⟨85ACS(B)691, 86ACS(B)764, 86JHC1079, 86TL6377, B-94MI 602-01⟩. The reactions are frequently carried out in the presence of a tertiary amine base such as *N*,*N*-diethylaniline, especially when more than one hydroxy group is to be replaced in the electrophilic positions. Amino, alkoxy, and alkylthio substituents are not affected. Oximes and primary carbamoyl functions are frequently converted into nitriles under the conditions for chlorination. [Warning: 2,4,5-trichloro- and 2,4,5,6-tetrachloropyrimidine are lachrymators and vesicants ⟨B-74MI 602-01⟩.]

Dichlorination of 6-trifluoromethyluracil has been effected using phosphoryl chloride, phosphorus pentachloride, and gaseous HCl; a 2-dichlorophosphate ester is the intermediate which is substituted by HCl ⟨83JHC219⟩. Thiones are chlorinated by milder chlorinating agents. 2-Chloropyrimidine is formed from pyrimidine-2(1*H*)-thione on treatment with elemental chlorine, or more conveniently with sulfuryl chloride below room temperature in an acetic acid–dichloromethane medium. Thionyl chloride is normally not able to convert hydroxy- into chloro-pyrimidines. The Vilsmeier reagent, chloromethylene-dimethylammonium chloride ($ClCH{=}^{+}NMe_2\ Cl^{-}$), may be used. It can be generated from DMF and phosgene, thionyl chloride, phosphoryl chloride, or oxalyl chloride either separately ⟨59HCA1653⟩ or *in situ* ⟨65CCC2052⟩. Side reactions such as formylation in the 5-position in electron-rich systems, or attack on an appended alkyl group, are to be expected on use of a Vilsmeier reagent.

Diazotization of a primary amine in the presence of a large excess of chloride ions yields the chloride in moderate yield, up to 50% in the case of 2-chloropyrimidine from 2-pyrimidinamine with 6 M LiCl in 4 M HCl ⟨75CCC1390⟩.

(ii) Bromination

Phosphoryl bromide is a solid which is normally diluted with phosphorus tribromide, an inert solvent, or a tertiary amine for the exchange of a hydroxy group by a bromine substituent. Diazotization of pyrimidinamines in the presence of a large excess of bromide ions provides the corresponding bromides in low to moderate yields ⟨B-94MI 602-01⟩.

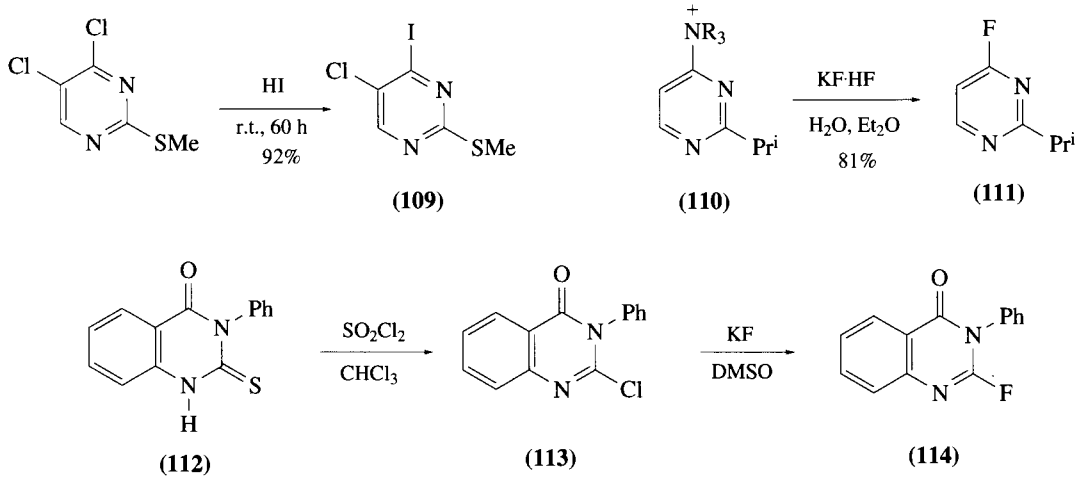
In the electrophilic positions, the chlorides are the most readily available halo derivatives. Transhalogenation is therefore of importance for the preparation of bromides and iodides. 2-Chloropyrimidine, on heating in phosphorus tribromide, is converted into 2-bromopyrimidine, 6-chloro-2,4(1*H*,3*H*)-pyrimidinedione into the 6-bromo analogue (70%) by heating in DMF containing ammonium bromide ⟨B-94MI 602-01⟩.

(iii) Iodination

Iodopyrimidines are normally made by transhalogenation of the corresponding chloro- or bromopyrimidines. Cold hydriodic acid is often used, for example in the selective replacement of the chlorine in the electrophilic 4-position in 4,5-dichloro-2-methylthiopyrimidine with formation of the 4-iodo derivative (**109**) (Scheme 14) ⟨86ACS(B)381⟩. On warming with HI, hydrolysis or reductive dehalogenation may be competive processes ⟨B-94MI 602-01⟩. Polyfluorinated pyrimidines on reaction with NaI in DMF are iodinated in the electrophilic 4- and 6-positions ⟨69JCS(C)1866⟩.

(iv) Fluorination

Fluorination in the electrophilic 2-, 4-, and 6-positions is effected by substitutions of other halides. Reagents to effect these transformations involve the use of hydrogen, sodium, potassium, cerium, antimony, and silver fluorides, and sulfur tetrafluoride. Products from nucleophilic fluorination processes are illustrated by 2,4,6-trifluoro (70%) ⟨62JOC2580⟩ or 93% ⟨85EGP221736⟩, 2-fluoro ⟨72CHE1281⟩, 2,4-⟨83GEP3131735⟩, 4,6-difluoro- (70%) ⟨60JA5107⟩, 2,4-difluoro-6-trifluoromethyl (73%) ⟨90EUP445644⟩, and 2,4-difluoro-5-trifluoromethylthio-pyrimidines ⟨86JHC1079⟩.



Scheme 14

Fluorination of uracil with F_2 or AcF using ^{18}F as a tracer gave the 5-F and 5,5-difluoro products besides fluorinated adducts. The product composition depends on the solvent, which was attributed to the fate of the radical cation obtained by a single electron transfer with the fluorinating reagent ⟨86JOC1466, 88JCS(P1)1203⟩. 2,4,5-Trifluoro-6-methylpyrimidine has been reported ⟨87JFC(35)373⟩.

The nucleophilicity of F^- is enhanced by the use of a crown ether. This methodology allows for

the preparation of 2,4-difluoropyrimidines without the need for silver(II) fluoride in an autoclave ⟨85JHC145⟩.

Chlorine in the 2-position is especially reactive with HF, whereas sodium fluoride initially replaces a 4-chloro substituent. In polar, aprotic solvents, fluorine–chlorine exchange is pseudo first-order ⟨87JFC(35)373⟩. High temperatures, about 150 °C, are normally applied to effect the substitution. An ammonio substituent in an electrophilic position can be replaced at low temperature, for example in the preparation of 4-fluoro-2-isopropylpyrimidine (**111**). Usual solvents in these reactions are water–ether or DMSO. The ammonio intermediate (**110**) is generated from the corresponding chloride and a tertiary amine ⟨74RTC111, 78AJC1391⟩.

2-Fluoro and 2,4-difluoropyrimidines have also been prepared in good yields directly from pyrimidinones by the use of anhydrous potassium fluoride in tetraglyme-18-crown-6 at elevated temperature ⟨85JHC145⟩. Synthesis of fluorinated pyrimidines via diazonium salts appears to be inferior to other methods ⟨85JHC145⟩.

The general kinetics of nucleophilic aromatic substitution in polyfluorinated compounds have been reviewed ⟨90JFC(47)361⟩. Polyfluorinated azaaromatics are highly activated toward nucleophilic aromatic substitution. The activating influence of ring N has been found to be: $o:m:p = 6.2 \times 10^4 : 8.5 \times 10^2 : 2.3 \times 10^5$, respectively ⟨82JFC(20)507⟩. From a study of the kinetics of substitution with NH_3 in dioxane and MeONa in methanol, it was concluded that the *ortho* activation arises out of a combination of ion–dipole interactions and the stabilization of the ionic σ-complex ⟨88JCS(P1)255⟩. Further studies include kinetics of acid-promoted hydrolysis of 2-fluoropyrimidines ⟨81JOC4363⟩, and fluorination of tetrachloropyrimidine, 2,4,6-trichloropyrimidine and trichloro-1,3-5-triazine with KF ⟨81JFC(17)385⟩.

(v) Quinazolines

Hydroxy groups in the electrophilic 2- and/or 4-position are substituted by a chlorine on heating with phosphoryl chloride, most often with an added molar equivalent of phosphorus pentachloride ⟨B-67MI 602-01⟩. References since the late 1960s include the conversion of 4(3*H*)-quinazolinone into 4-chloroquinazoline by phosphoryl chloride and phosphorus pentachloride ⟨80IJC(B)775⟩, and 2,4(1*H*,3*H*)-quinazolinedione into the dichloride using $POCl_3/NEt_3$ ⟨82CPB1947⟩. As in pyrimidines, either chlorine or sulfuryl chloride can be used to convert thiono derivatives (**112**) into chlorides (**113**) ⟨65MI 602-01⟩. Bromine gives the corresponding bromide. A halogen exchange reaction will provide a general access to bromo, iodo, and fluoro derivatives as for pyrimidines. This can be exemplified by the preparation of the 2-fluoro derivative (**114**) ⟨65IJ101⟩.

(vi) Perimidines

The oxygen atom in perimidin-2-one is replaced using phosphoryl chloride, with formation of 2-chloroperimidine ⟨81RCR816⟩. The other halides are expected to be available by halogen exchange reactions.

6.02.5.4.2 Amination

Aminolysis of active halogenopyrimidines is the normal way into pyrimidinamines. Regioselective substitutions in di- and tri-halo derivatives can in many cases be achieved. Chloro-, bromo-, and iodo substituents undergo aminolysis at approximately the same rates whereas a fluoro substituent reacts 60–200 times faster. 4(6)-Halo substituents react up to 10 times faster than 2-halo substituents. Electron-donating substituents (e.g., Me, Ph, OMe, NMe_2) decrease the rate of aminolysis whereas electron-withdrawing substituents (Cl, CF_3, NO_2) have the opposite effect ⟨B-94MI 602-01⟩. Elevated temperatures are usually used in the reactions with ammonia or amine. Attempted monoamination in 2- and 4-/6-dihalopyrimidines usually gives mixtures of monoaminated products. A strong electron-withdrawing substituent in the 5-position, however, activates the 4-position more strongly, which allows for full regioselective substitution in the 4-position.

Tautomeric 4/6-pyrimidinethiones undergo aminolysis more readily than the corresponding 2-pyrimidinethiones, allowing for selective substitution in the 4-position. Thus 2,4(1*H*,3*H*)-

pyrimidinedithione in neat aniline under reflux furnished 4-anilino-2(1*H*)-pyrimidinedithione (90%). It is more common to use alkylthiopyrimidines for aminolysis. Kinetic data shows that simple 4-alkylthiopyrimidines undergo aminolysis more rapidly than the respective 2-isomers ⟨B-94MI 602-01⟩. Frequently, it is advisable to oxidize the sulfide to a sulfone before substitution is attempted.

Amines can be formed directly from tautomeric pyrimidinones by heating with an amide of phosphoric or phosphorous acid, but the vigorous reaction conditions limit the application of this method ⟨B-94MI 602-01⟩.

Pyrimidinones are efficiently aminated in a one-pot procedure via silylation. The silylating agent converts the hydroxy groups into silyl ethers which are activated for nucleophilic substitution, and react *in situ* with ammonia, primary, or secondary amines to form the corresponding amines. With Lewis acid catalysis, the reactions usually proceed in high yield if the trimethylsilanol leaving group is converted *in situ* into hexamethyldisiloxane by excess of the silylating agent; for example, 2(1*H*)-pyrimidinone is aminated and uracil diaminated in amination reactions with HMDS ⟨84CB1523⟩. This reaction has proven to be a sufficiently mild amination method for nucleosides.

Alkoxy groups are less readily displaced than halo or sulfonyl substituents, but better than their alkylthio counterparts. Rate constants for aminolysis indicate that 4-methoxypyrimidine reacts more rapidly than does 2-methoxypyrimidine by a factor of 10, and that 2-chloropyrimidine is aminolyzed 4×10^4 times faster than is 2-methoxypyrimidine ⟨B-94MI 602-01⟩.

Aminolysis with hydrazines, hydroxylamine, and hydrazoic acid (sodium azide) proceeds in a similar manner with halogenopyrimidines ⟨B-94MI 602-01⟩.

Reaction of 1-aryl-2-methylthiopyrimidinium salts with hydrazine leads to rearrangement into 1,2-diaminopyrimidinium salts. The rearrangement is probably initiated by addition of the hydrazine to the electrophilic 4-position, ring-opening, and recyclization.

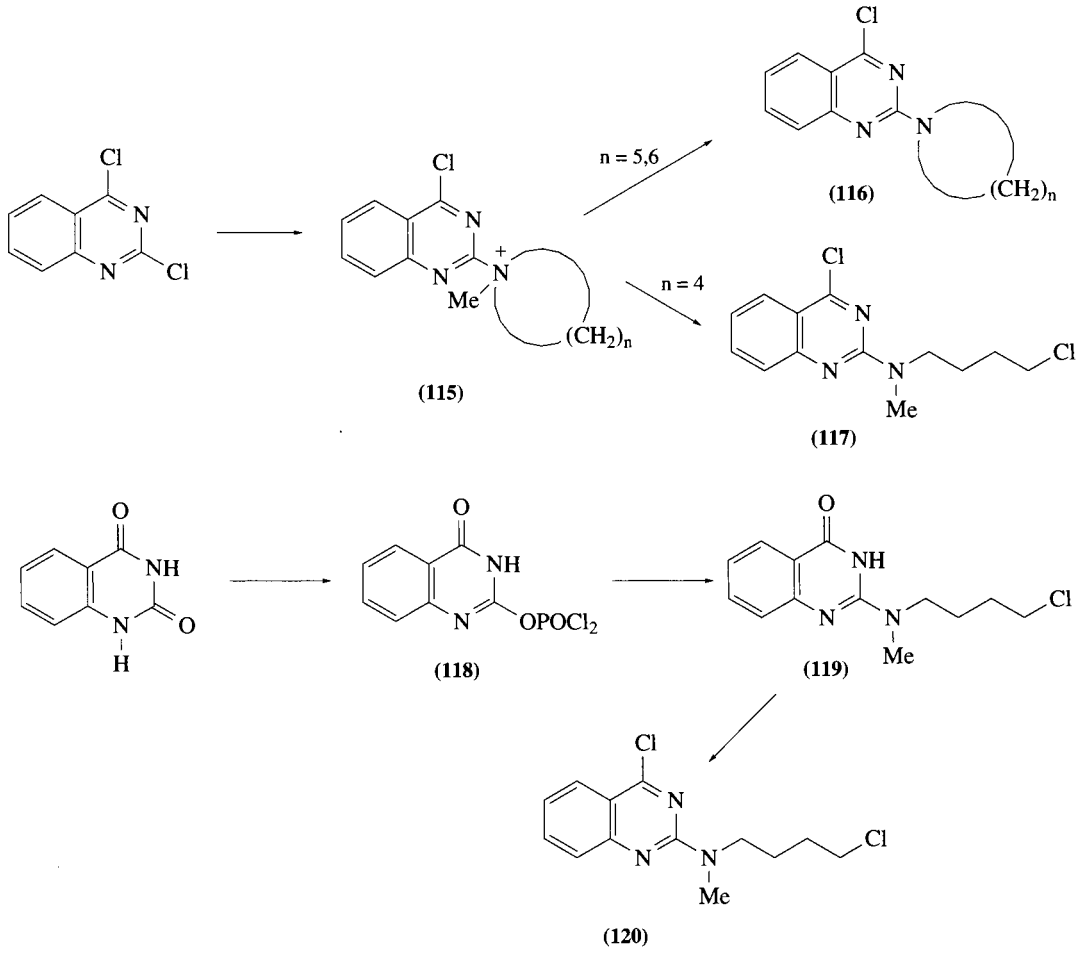
(a) Quinazolines. Chlorines in the electrophilic 2- and 4-positions of quinazoline are readily aminolyzed. Kinetic studies of the reaction between piperidine and 2-chloro- and 4-chloroquinazoline show that the latter reacts 6.4×10^3 times faster than the 2-isomer; compared with 4-chloropyrimidine the increase in reactivity is about 100-fold. The large difference in reactivity allows easy and stepwise amination in 2,4-dichloroquinazolines, starting in the 4-position ⟨B-67MI 602-01⟩.

Tertiary amines can be used to reverse the preferential 4-substitution in the reaction of secondary amines with quinazolines, and in 5-substituted 2,4-dichloropyrimidines. *N*-Methylpiperidine and 2,4-dichloroquinazoline in dioxane at 100°C react with substitution in the 2-position to yield 4-chloro-2-piperidinoquinazoline (**116**) (92%) (Scheme 15); the methyl group is lost from the intermediate ammonium salt (**115**). The same regiochemistry is seen in reactions with seven- and five-membered cyclic amines. The five-membered ring in the intermediate ammonium salt (**115**), however, is subsequently opened by the chloride ion, the product being the *N*-4′-chlorobutyl-*N*-methyl derivative (**117**) in preference to *N*-demethylation. In 2,4-dichloro-5-methylpyrimidine the same selective substitution reaction sequence is seen in the 2-position, whereas reactions with 2,4-dichloropyrimidine lead to mixtures of regioisomers. The results are rationalized in terms of steric factors. *peri*-Interaction in the 4-position in quinazolines directs the bulky amine to the 2-position. A similar interaction is found with the 5-methyl group in 2,4-dichloro-5-methylpyrimidine, which is therefore preferentially aminated in the 2-position ⟨92JCS(P1)919⟩.

When 2,4(1*H*,3*H*)-quinazolinedione reacts with phosphoryl chloride in the presence of excess of *N*-alkyl cyclic amines, mixtures of 2,4-dichloroquinazolines, and 4-chloro-2-(*N*-alkyl-ω-chloroalkylamino)quinazolines (**120**) result. Bulky amines favor dichloride formation. Almost exclusive formation of 2-aminated product results from *N*-methyl pyrrolidine, indicating that either 4-oxo-3,4-dihydro-2-quinazolinyl dichlorophosphate (**118**) or the 2-chloro analogue is a likely intermediate when the reaction proceeds via (**119**) ⟨82CPB3471⟩. Similarly, chlorination of 2,4(1*H*,3*H*)-quinazolinedione with phosphoryl chloride in the presence of triethylamine gives 4-chloro-2-diethylaminoquinazoline after loss of one ethyl group from the intermediate ammonium salt ⟨82H(19)7⟩.

Silylation of quinazolinones is equally effective as for pyrimidinones in converting hydroxy groups into silyl ether derivatives which react *in situ* with ammonia, primary or secondary amines to form corresponding amines (Scheme 16). 2,4(1*H*,3*H*)-Quinazolinedione is aminated in the 2-position (**121**) using HMDS for silylation at 130°C. Silylation with the higher-boiling (180°C) octamethylcyclotetrasilazane (OMCTS) (**122**) in the presence of the amine leads to diamination (**123**) ⟨84CB1523⟩.

(b) Perimidines. The chlorine substituent in the electrophilic 2-position in perimidines is readily displaced in reactions with ammonia or amines to form the corresponding perimidin-2-amine ⟨81RCR816⟩.



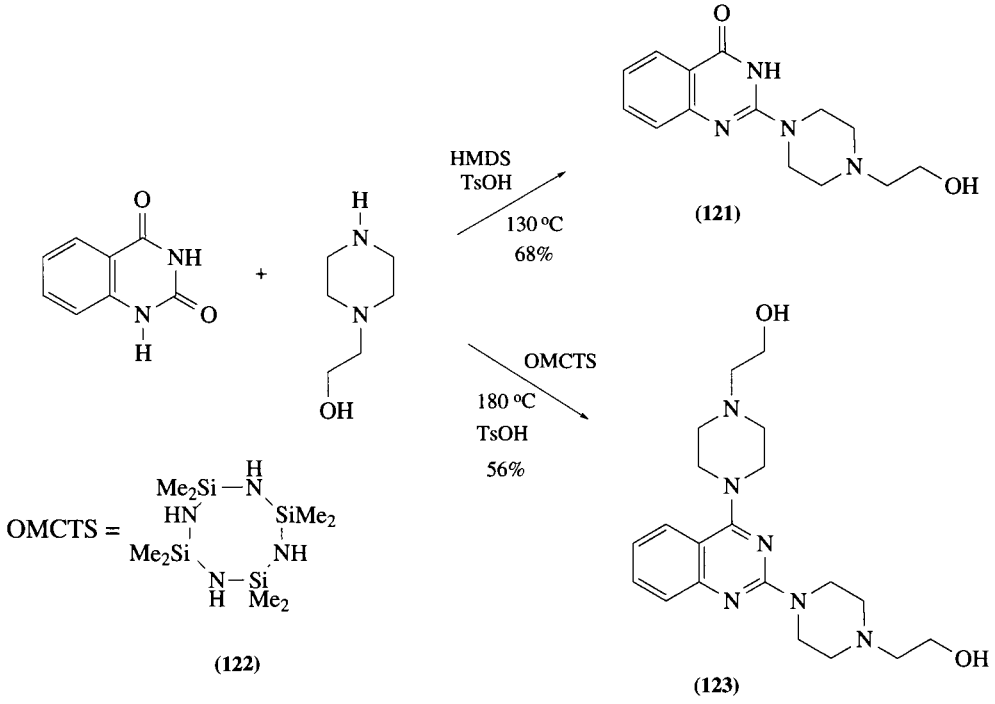
Scheme 15

(i) Amination by addition reactions

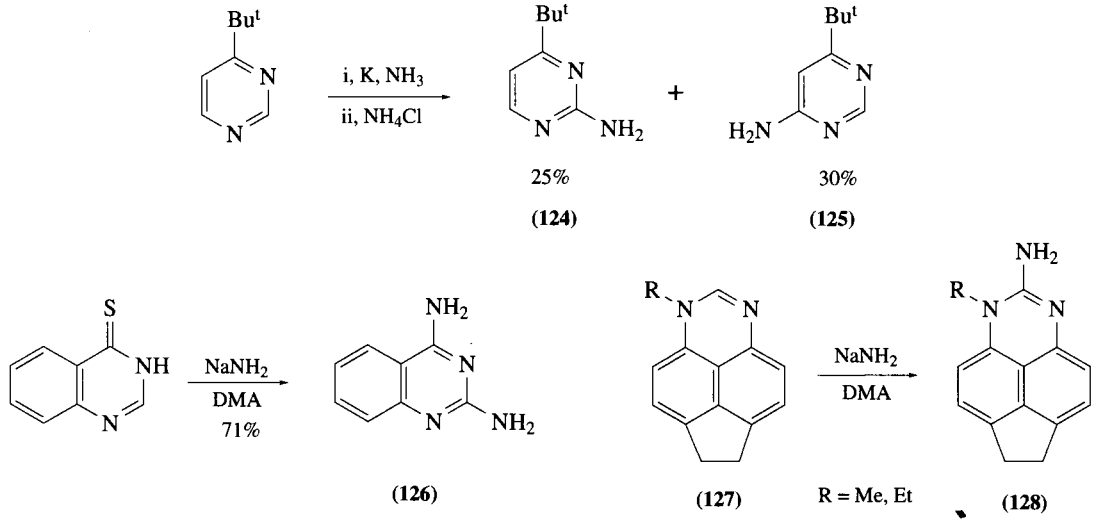
The Chichibabin reaction amounts to a nucleophilic displacement of a hydrogen atom by an amino group in an electrophilic azine position. The reaction proceeds through an addition–elimination mechanism $S_N(AE)$ with formation of a Meisenheimer σ-adduct intermediate ⟨88AHC(44)1⟩. 5-Phenylpyrimidine is aminated in the 4-position (70% yield) ⟨86MI 602-01⟩. 2-Alkylpyrimidines are also aminated in the 4-position although the first step is deprotonation of the alkyl group with anion formation, which deactivates the pyrimidine strongly for further nucleophilic attack and gives low to moderate yields of aminated products; no deprotonation occurs in 4-*t*-butylpyrimidine resulting in amination in either the 2- (**124**) or 6-position (**125**) (Scheme 17) ⟨87JHC1377⟩.

4-Phenylpyrimidine in liquid ammonia was shown by ^{15}N-labeling to be aminated by the S_N(ANRORC) mechanism; the product composition of the 2-amino- and the 6-aminopyrimidine varied with the conditions chosen for the reaction. Under heterogeneous conditions, labeling showed the ordinary $S_N(AE)$ mechanism to be operative, the main product being the 6-amino isomer. The same mechanism was operative in the amination of the 4-*t*-butyl derivative ⟨83RTC367⟩. For halogenated pyrimidines, dehydrohalogenation competes with elimination of the hydride ion; 5-bromopyrimidine gave 4-amino-5-bromopyrimidine (28%) and 4-aminopyrimidine (37%). The ring-opening pathway is not involved ⟨82JHC1285⟩. Amination of 4-*t*-butyl-5-chloropyrimidine and 2,4-di-*t*-butyl-5-chloropyrimidine with potassium amide in liquid ammonia is in the vacant 6-position but the products were admixed with the corresponding dechlorinated derivative ⟨78RTC288⟩.

(a) Quinazolines. An amine adduct is formed in the highly electrophilic 4-position with potassium amide in liquid ammonia; subsequent potassium permanganate oxidation gave the 4-aminoquinazoline (62%) ⟨82JHC1285⟩. The sulfur atom in thiones is displaced under Chichibabin



Scheme 16



Scheme 17

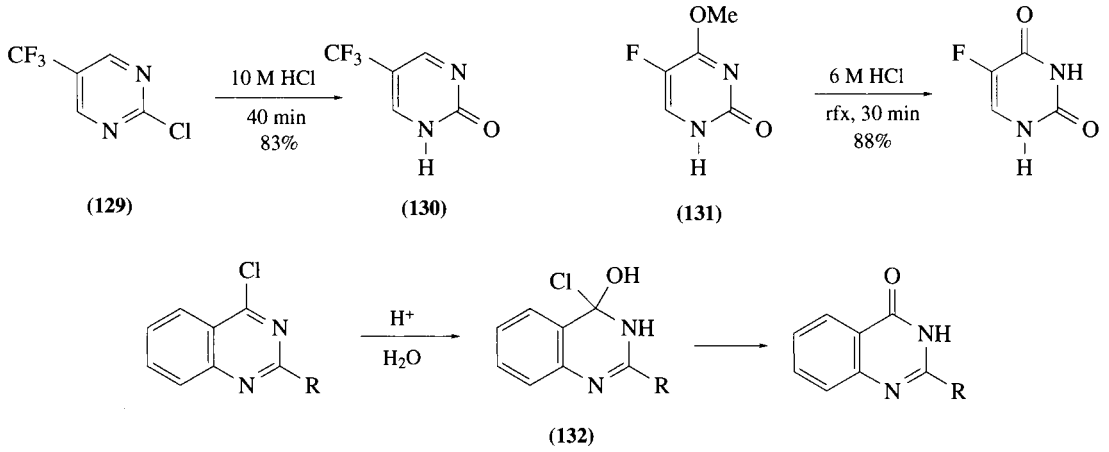
conditions, as shown for 4(3*H*)-quinazolinethione which gave the diamine (**126**). Benzo-fused homologues react similarly (Scheme 17) ⟨72JHC1449⟩.

(b) Perimidines. The N—H bond in perimidines must be protected by alkylation or arylation prior to treatment with sodium amide. 1-Alkyl-, 1-benzyl-, 1-phenyl-, 1-methoxymethyl-, and 1-dialkylaminoalkyl-perimidines undergo amination by sodium amide ⟨81RCR816⟩.

Generally good yields are obtained in DMA, with lower yields in xylene. Aceperimidines (**127**), substituted in the 1-position, were readily aminated to (**128**) in xylene ⟨70CHE1055⟩. Aceperimidylenes, however, were difficult to aminate ⟨85CHE310⟩.

6.02.5.4.3 Hydroxylation

Hydroxyl groups can be introduced by hydrolytic reactions in the electrophilic 2- and 4/6-positions. Direct hydrolysis of halopyrimidines can be effected under both acidic and alkaline conditions ⟨B-94MI 602-01⟩. Conditions for selective hydrolysis are known for a number of di- and trihalopyrimidines. Selectivity may be easier to achieve under alkaline conditions since the initial hydrolysis product forms an anion that tends to stabilize the remaining halo substituent(s). However, there are several examples of selectivity under acidic conditions. In 2,4-dichloropyrimidines it is normally the 4-position which is the more reactive, especially with added activation from an electronegative 5-substituent. Thus, selective hydrolysis of the 4-chlorine substituent in 2,4-dichloro-5-fluoropyrimidine gave 2-chloro-5-fluoro-4(3*H*)-pyrimidinone under alkaline conditions ⟨65JMC253⟩. The chlorine in 2-chloro-5-trifluoromethylpyrimidine (**129**) can be replaced under acidic conditions to form the 2-pyrimidinone (**130**) without hydrolysis of the fluorines in the trifluoromethyl group (Scheme 18). Under alkaline conditions, it is difficult to avoid the ready hydrolysis in the activated trifluomethyl group, leading to the 5-carboxylic acid ⟨84ACS(B)505⟩.



Scheme 18

Hydrolysis of pyrimidinamines under acid or alkaline conditions generally requires vigorous conditions. Alternative reactions are by diazotization ⟨B-94MI 602-01⟩.

In the hydrolysis of alkoxides, generally more vigorous conditions are required than for halo analogues. In highly activated systems, however, hydrolysis may be rapid; acidic conditions were used for the hydrolysis of the 4-methoxy group in (**131**) ⟨68JA709⟩.

Pyrimidinethiones can sometimes be hydrolyzed directly to pyrimidinones, but it is often better to convert the thiones into alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl derivatives before hydrolysis ⟨B-94MI 602-01⟩. Oxidation of thiones to sulfinic or sulfonic acids may be an alternative, but this reaction sequence may in part lead to desulfurization.

(i) Quinazolines

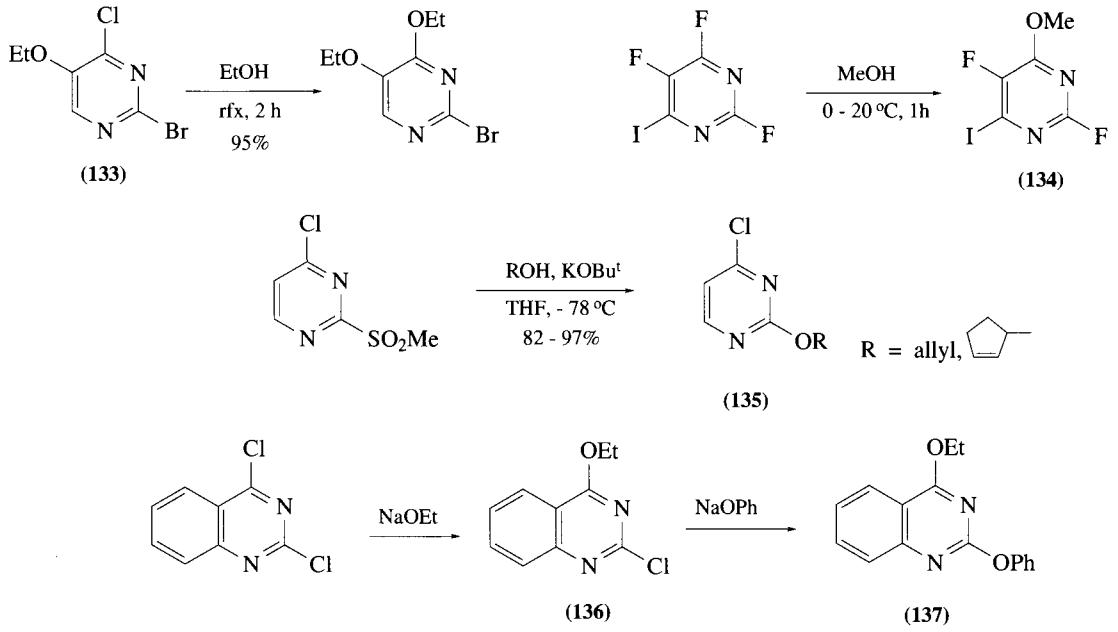
The high electrophilic character of the 2- and 4-positions in quinazoline makes hydrolysis to oxo derivatives easy. The significantly higher reactivity in the 4-position simplifies stepwise substitutions. Both 2- and 4-chloro substituents can be hydrolyzed in alkaline or acid solution. Hydrolysis of 4-chloro derivatives by boiling water is complete in minutes. The reaction is acid catalyzed, and is faster than in dilute alkali. A water adduct is postulated as an intermediate (**132**). Both 2- and 4-alkoxy- or aryloxyquinazolines are readily hydrolyzed by HCl to the corresponding quinazolinones ⟨B-67MI 602-01⟩.

(ii) Perimidines

The 2-position in perimidines is highly electrophilic. The reactive 2-chloroperimidines are easily hydrolyzed to perimidinones. *N*1-Substituted aceperimidines are also readily hydrolyzed. Any good leaving group in the electrophilic 2-position is prone to hydrolysis ⟨81RCR816⟩.

6.02.5.4.4 Alkoxylation and aryloxylation

Nucleophilic displacement of 2- and 4/6-halo substituents by alkoxy or aryloxy ions occurs readily except in the presence of strongly electron-releasing substituents in the ring ⟨B-94MI 602-01⟩. Several reports describe stepwise alcoholysis or phenolysis of di- and trihalides. In 2-bromo-4-chloro-5-ethoxypyrimidine (**133**) the chlorine in the more reactive 4-position is selectively substituted during ethanolysis (Scheme 19) ⟨63JOC2155⟩. A fluorine substituent in an electrophilic position usually displays higher reactivity than any other halogen towards nucleophilic substitution. Thus in 2,4,5-trifluoro-6-iodopyrimidine, it is the fluorine in the 4-position which suffers preferential methanolysis to form the 4-methoxy derivative (**134**) ⟨69JCS(C)1866⟩.



Scheme 19

Sulfenyl substituents are replaceable on prolonged heating with alkoxides or alcohols and a base present ⟨B-94MI 602-01⟩. The reactivity in the nucleophilic substitutions is much increased when the sulfide is oxidized to a sulfoxide or a sulfone prior to substitution; an added advantage is that the smell of sulfide is absent. The regioselectivity for nucleophilic substitution can be changed by having a sulfonyl substituent in the 2-position. Thus reactions between 4-chloro-2-methanesulfonylpyrimidine and potassium alkoxides give selectively the 2-allyl or 2-cyclopentenyl ethers (**135**) when the reactions are carried out at −78 °C. The diallyl ether is the main product at 0 °C ⟨93ACS72⟩.

(i) Quinazolines

Alkoxy derivatives in the electrophilic positions are readily available by nucleophilic substitution reactions as discussed for the oxo derivatives above. 2,4-Dialkoxyquinazolines can be prepared by boiling 2,4-dichloroquinazolines with two equivalents of alkali alkoxide in the appropriate alcohol. Mixed ethers (**137**) are possible because of the great difference in positional reactivity; the first substitution is in the 4-position (**136**). 4-Chloro- and 2,4-dichloro-quinazoline very readily suffer alcoholysis in the 4-position with acid catalysis, presumably via 4-adduct formation as in the facile hydrolysis discussed above.

(ii) Perimidines

The highly reactive 2-chloroperimidines react with alkoxides to form alkoxy derivatives ⟨81RCR816⟩. Other displaceable groups on the electrophilic 2-carbon will react similarly.

6.02.5.4.5 Thiation

Two main methods are used for the preparation of thiopyrimidines by substitution reactions: thiolysis of halopyrimidines and thiation of pyrimidinones ⟨B-94MI 602-01⟩. In the thiolysis of 2- and 4/6-halopyrimidines it is customary to use sodium hydrogen sulfide, or indirectly to use thioureas with alkaline degradation of the intermediate pyrimidinyl isothiourea.

Direct thiation of pyrimidinones can be effected by heating with phosphorus pentasulfide in an inert solvent, in pyridine or another tertiary amine. The Lawesson reagent (2,4-bis-*p*-methoxyphenyl-1,3,2,4-dithiadiphosphetane-2,4-disulfide) offers a convenient alternative, and it has been found useful in the conversion of oxo to thioxo groups in nucleosides. 4/6-Oxo substituents undergo thiation more readily than 2-oxo substituents, which allows for 4-monothiation in 2,4-pyrimidinediones. An example is provided by the 4-monothiation of 5-fluoro-2,4(1*H*,3*H*)-pyrimidinone by phosphorus pentasulfide in dioxane ⟨69ACS294⟩ or by Lawesson's reagent ⟨88S152⟩.

(i) Quinazolines

Thiation of 2- or/and 4- haloquinazolines can be carried out on heating with alkali metal hydrogen sulfide or thiourea as for the pyrimidines; the 4-position is the more reactive. Thiation of quinazolinones is effected by heating with phosphorus pentasulfide in an inert solvent or a tertiary amine ⟨B-67MI 602-01⟩. Application of the Lawesson reagent is an alternative. Thiones are also available from cyclization reactions in primary syntheses.

(ii) Perimidines

2(1*H*)-Perimidinethiones are readily available by cyclization reactions of 1,8-naphthalenediamines. Since the 2-position is strongly electrophilic, a chloro or any easily displaceable group in nucleophilic reactions can be substituted by alkali metal hydrogen sulfide or thioureas. Reagents for thiation of 2(1*H*)-perimidinones would be phosphorus pentasulfide or Lawesson's reagent as discussed for pyrimidines.

6.02.5.4.6 Alkylthioxylation and arylthioxylation

Alkylthio derivatives are normally prepared by alkylation of thiones, but they can also be prepared by alkanethiolysis reactions. Aromatic sulfides are commonly prepared by arenethiolysis in reactions with halopyrimidines ⟨B-94MI 602-01⟩. Selective thiolysis can be effected, as exemplified by the preparation of 2-chloro-4-ethylthio-5-fluoropyrimidine from 2,4-dichloro-5-fluoropyrimidine by sodium ethanethiolate (72%) ⟨69ACS294⟩.

(i) Quinazolines

Alkylthio derivatives are frequently made by *S*-alkylation of the corresponding quinazolinethiones. Arylthio, as well as alkylthio derivatives, can be prepared by nucleophilic substitution of halogenoquinazolines by the corresponding thiolates ⟨B-67MI 602-01⟩.

(ii) Perimidines

2-Alkylthioperimidines are simply prepared by alkylation of the 2(1*H*)-perimidinethione. Arylthio derivatives are prepared by nucleophilic substitution of a 2-halogenoperimidine by an arylthiolate, a method also applicable to the alkylthio derivatives.

6.02.5.5 Alkylation, Arylation, and Acylation at Carbon

6.02.5.5.1 Alkylation by electrophilic substitution

Alkylation by electrophilic substitution applies to pyrimidines carrying at least two strongly electron-donating substituents and has been discussed in Section 6.02.5.3.6.

6.02.5.5.2 Palladium-catalyzed alkenylation by hydrogen substitution

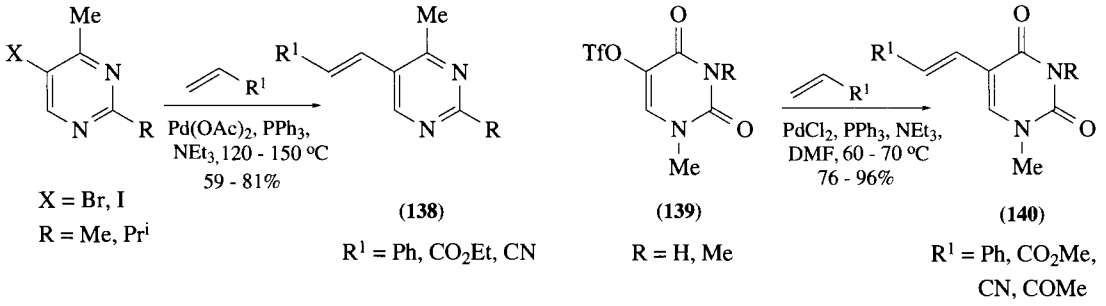
Until the early 1980s, substitution in π-deficient heterocyclic systems was largely limited to reactions with heteroatom nucleophiles. This situation was dramatically changed when organometallic and metal-catalyzed reactions became available for carbosubstitution reactions. In alkenylation reactions mediated by Pd-catalysis, the active species is a palladized heterocycle formed by oxidative insertion of the metal either into a halogen–carbon or oxygen–carbon bond, or by electrophilic substitution using a Pd(II)-species, or by a metal–metal exchange reaction. The subsequent addition of the metal complex to the alkene in the formation of the carbon–carbon bond is followed by metal elimination.

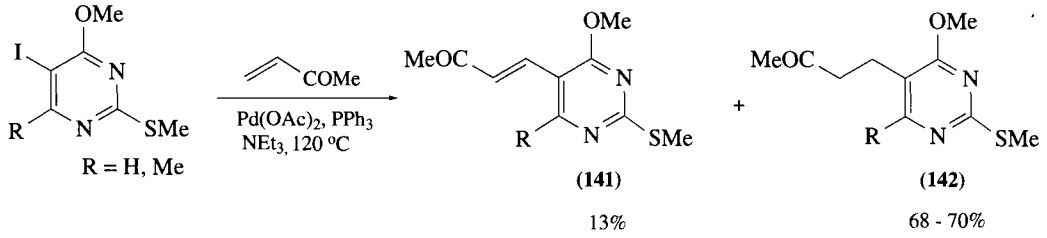
The alkenylation protocol between styrene, ethyl acrylate or acrylonitrile, and a 5-bromo- and 5-iodopyrimidine gives the coupling product (**138**) (Scheme 20) ⟨79CPB193, 81H(16)965⟩. Methoxy-, methylthio-, and amino groups are tolerated ⟨82CPB2410, 86S555⟩. A triflyloxy substituent may replace the iodo substituent. *N*-Methyl- and *N*,*N*′-dimethyluracil-5-yl triflate (**139**) are alkenylated (**140**) by styrene, acrylonitrile, methyl acrylate, or methyl vinyl ketone ⟨87H(26)55⟩. With methyl vinyl ketone the product was a mixture of (**141**) and the saturated analogue (**142**) as the major component ⟨88S771⟩. Formation of 4,4′-bipyrimidines (**144**) is a major pathway from 4-iodopyrimidines (**143**) under the relatively vigorous conditions required to form the cross-coupled product (**145**). In the absence of alkenes the homo-coupling (160 °C) is almost quantitative ⟨79CPB193⟩. The 2-iodo isomers (**146**) were less reactive. No alkenylation was observed with phosphine ligated-Pd ⟨79CPB193, 82CPB3647⟩, but moderate yields of 2-alkenylated pyrimidines (**147**) result in the absence of triphenylphosphine ⟨81H(16)965⟩. In 4,5-diiodopyrimidines (**148**; X = I) it is the 4-iodo substituent which is displaced (**149**) with triphenylphosphine ligated Pd catalyst ⟨79H(12)383⟩.

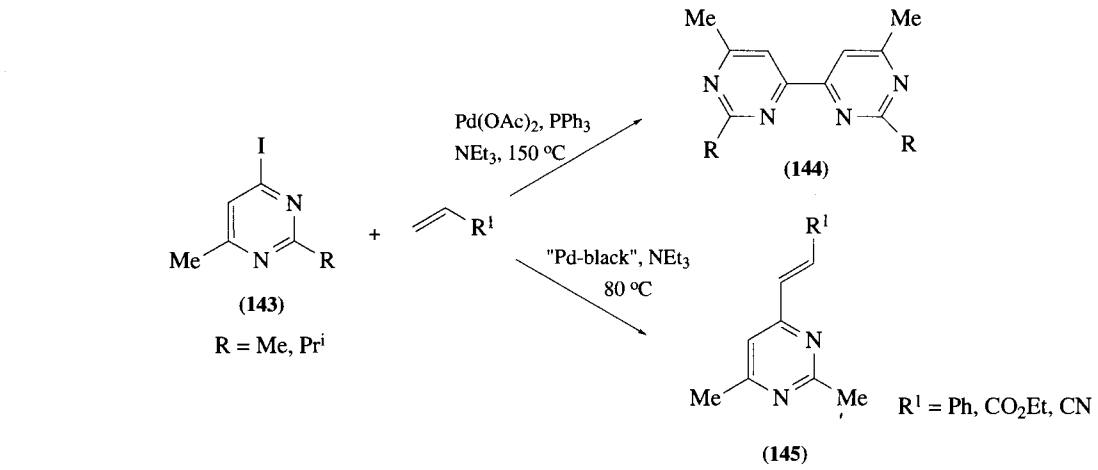
6.02.5.5.3 Palladium-catalyzed alkynylation by hydrogen substitution

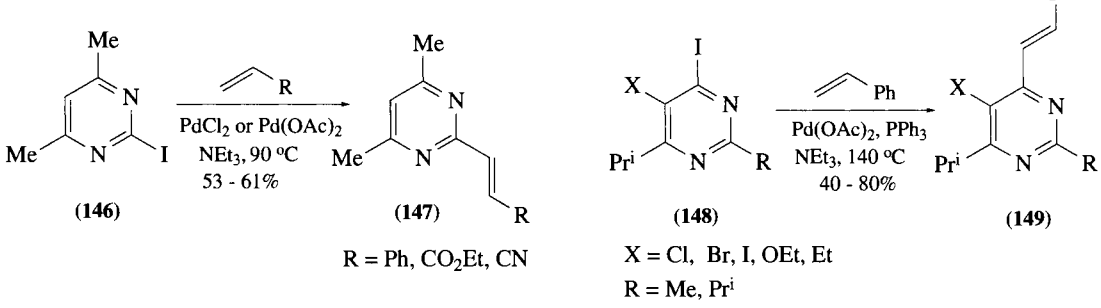
Reports on the alkynylation of pyrimidines go back to 1978. 2-Iodo- and 4-iodopyrimidines were readily alkynylated to (**150**) (Scheme 21). Unprotected propargyl alcohol gave modest yields of alkynylated products. 4,6-Diiodo-2-methylpyrimidine was dialkynylated to (**151**) ⟨78H(9)271⟩. Methoxy-, methio-, and piperidino-substituted iodopyrimidines react in the same manner, and 2- and 4-chloropyrimidines can be used as substrates though their reactivity was claimed to be inferior to that of 2- and 4-iodopyrimidines; reflux conditions in triethylamine are used for the chloro derivatives, room temperature for the iodo derivatives. In the benzenoid 5-position the halogen has to be a bromine or iodine for the alkynylation reaction. Disubstituted alkynes (**152**) were formed in the coupling of alkyne with 4-iodopyrimidines ⟨78CPB3843⟩. In the 4-chloro-5-iodopyrimidine (**153**) the iodine in the 5-position is selectively displaced in the alkynylation (**154**), and in the 5-chloro-4-iodo isomer coupling is in the 4-position ⟨82CPB2410⟩. In the silyl-protected 2-pyrimidinone (**155**) hydrolysis of the silyl ether function during the reaction was prevented (**156**) by the use of hexamethyldisilazane (HMDS) as a trapping agent for adventitious water ⟨86ACS(B)381⟩.

5-Iodo-1-methyluracil is alkynylated (**157**) by 1-hexyne (Scheme 22). A minor product (9%) from the reaction is furo[2,3-*d*]pyrimidin-6-one (**158**). The latter arises from (**157**) by a cyclization reaction. The cyclization was demonstrated by heating the alkynylated product (**157**) with NEt_3/MeOH, which gave a 92% yield of the furopyrimidine (**158**) ⟨81TL421, 83JOC1854⟩. This reaction constitutes a simple and general method for the preparation of furo[2,3-*d*]pyrimidines. The same reaction has been found useful for carbosubstitution in nucleosides. Coupling of 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**159**) with trimethylsilylacetylene gives the 5-alkynylated product (**160**) in high yield which is cyclized to the furo[2,3-*d*]pyrimidin-6-one nucleoside (**161**) as the major product ⟨83JOC1854⟩. Propargylic amines undergo rapid coupling with 5-iodouracil derivatives ⟨90TL3731⟩.

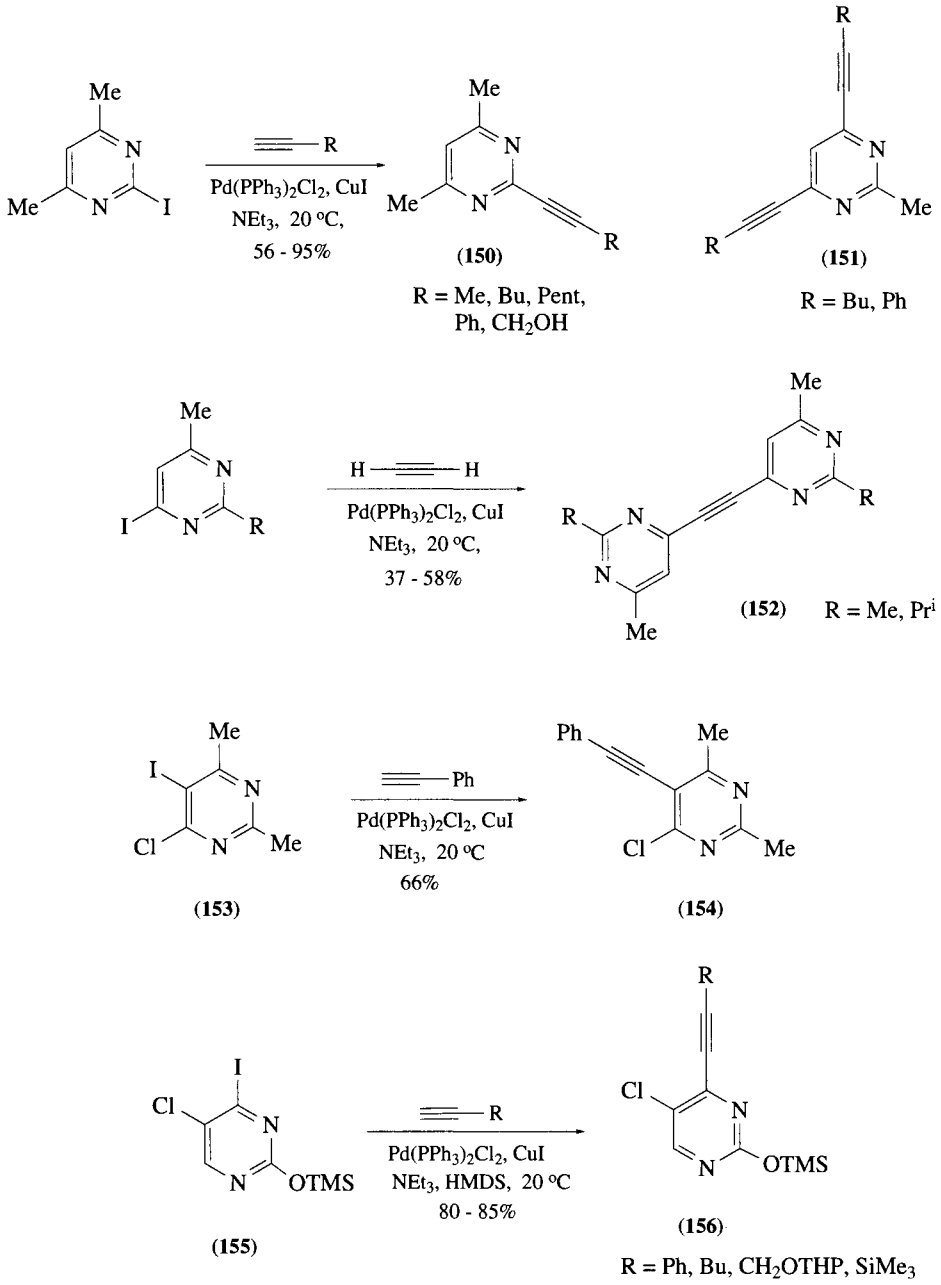

Me
X
N
N
R
R1
Pd(OAc)2, PPh3,
NEt3, 120 - 150 °C
59 - 81%
X = Br, I
R = Me, Pri
(138)
R1 = Ph, CO2Et, CN
TfO
O
NR
N
O
Me
(139)
R = H, Me
PdCl2, PPh3, NEt3,
DMF, 60 - 70 °C
76 - 96%
(140)
R1 = Ph, CO2Me,
CN, COMe


OMe
I
N
R
N
SMe
R = H, Me
COMe
Pd(OAc)2, PPh3
NEt3, 120 °C
MeOC
(141)
13%
(142)
68 - 70%


Pd(OAc)2, PPh3
NEt3, 150 °C
Me
N
R
(144)
I
Me
(143)
R = Me, Pri
"Pd-black", NEt3
80 °C
(145)
R1 = Ph, CO2Et, CN


Me
N
Me
I
(146)
R
PdCl2 or Pd(OAc)2
NEt3, 90 °C
53 - 61%
(147)
R = Ph, CO2Et, CN
X
Pri
(148)
X = Cl, Br, I, OEt, Et
R = Me, Pri
Ph
Pd(OAc)2, PPh3
NEt3, 140 °C
40 - 80%
(149)

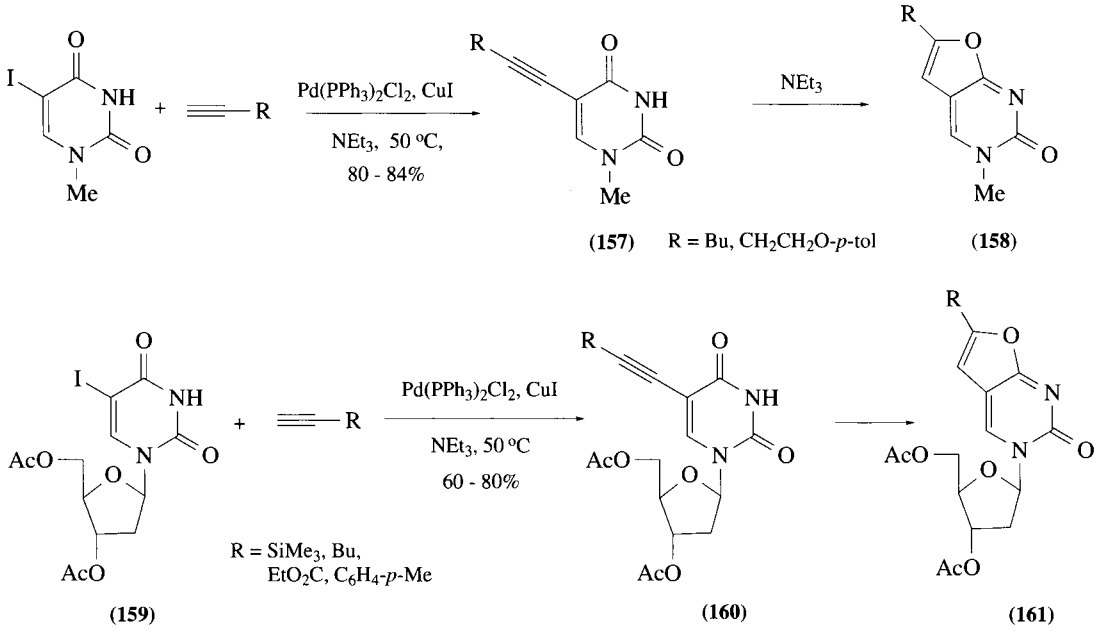
Scheme 20



Scheme 21

6.02.5.5.4 Alkylation and arylation by palladium-catalyzed reactions with stannanes

Organotin compounds have become important reagents in metal-catalyzed cross-coupling reactions because of their ease of preparation and handling and their high reactivity in the presence of Pd catalysts ⟨86AG504, B-87MI 602-01, 92S803⟩. The activation to the reactive species by the transition metals is caused by transmetallation; the organotin compound is converted into a new organometallic species of the catalyst metal which is the reacting species in the carbon–carbon bond formation. Coupling reactions between the 5-chloro-4-iodopyrimidine (**162**) and substituted alkenyltributylstannanes are regiospecific and stereospecific in the alkene reagent, with retention of the stereochemistry (**163**) (Scheme 23). In the reaction between styryltributylstannane and an equimolar mixture of the 4-iodopyrimidine (**162**) and iodobenzene the coupling product was derived exclusively from the 4-iodopyrimidine because of the higher electrophilic character in the pyrimidine ⟨87ACS(B)712⟩.



Scheme 22

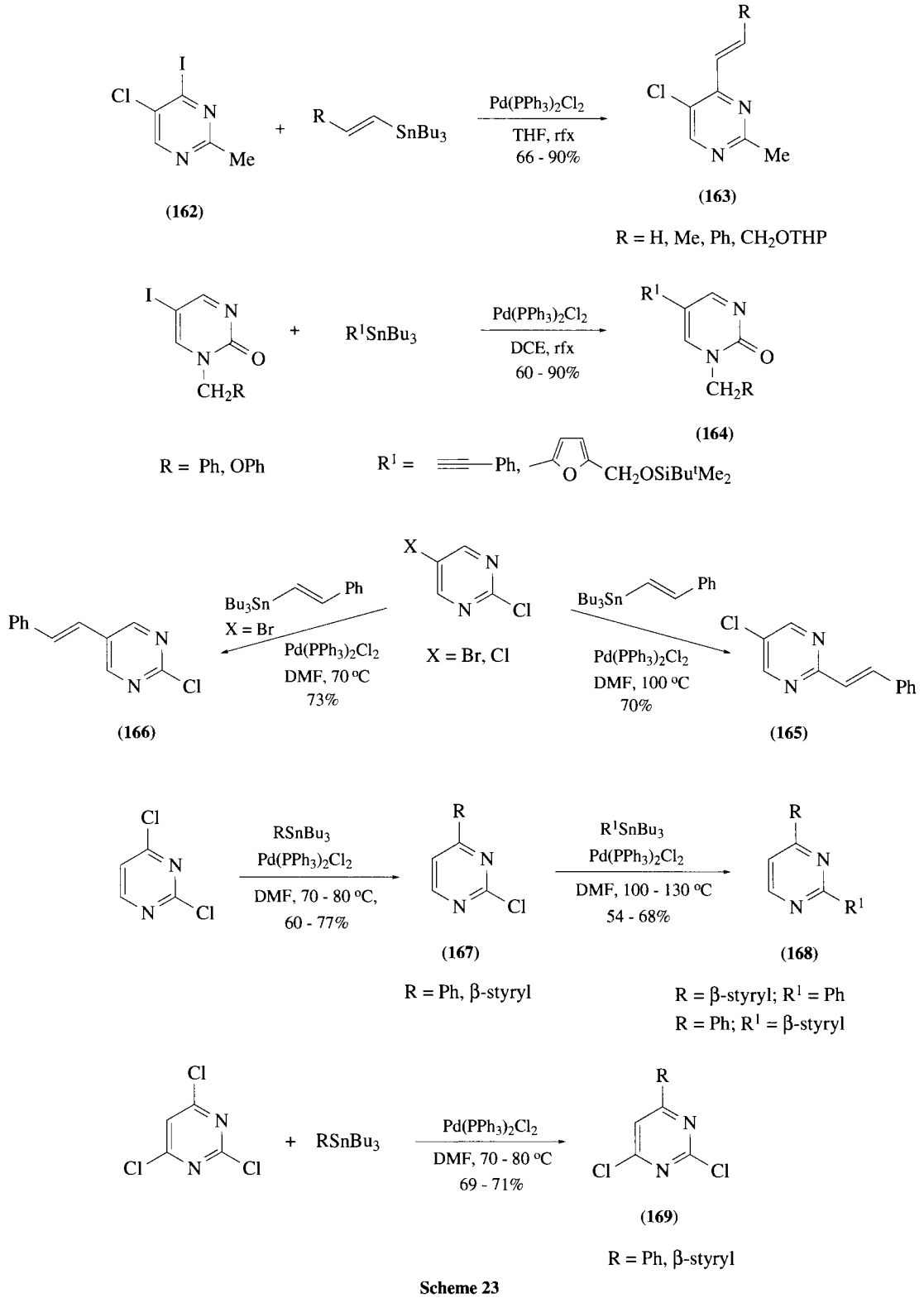
sp^3-Hybridized carbon attached directly to the metal is less reactive than sp^2- or sp-hybridized carbon in Pd-catalyzed reactions. Tetramethyl- or tetrabutyl-stannane can be used for the preparation of methyl and butyl derivatives, but these reactions require heating in DMF for a long time. The reactivity is enhanced when the sp^3-hybridized carbon carries an electronegative group. Therefore, in the reaction between benzyltributylstannane and an iodopyrimidine, it is the benzyl group which is transferred to the pyrimidine. With allyltributylstannane the product is the 4-*trans*-propenylpyrimidine ⟨87ACS(B)712⟩. Alkylzinc reagents or alkylaluminum reagents (see Sections 6.02.5.5.6 and 6.02.5.5.7) may be a better choice for simple alkylation reactions.

5-Bromopyrimidines give 5-alkenyl derivatives when coupled with alkenylstannanes ⟨88ACS(B)455⟩. 1-Substituted 5-iodo-2-pyrimidinones have been alkynylated (**164**) with phenylethynylstannane, and heteroarylated with 2-stannyl derivatives of 5-hydroxymethylfuran ⟨93ACS102, 94ACS279⟩. A chlorine in an electrophilic azine position, but not in a benzenoid position, can be replaced by a carbosubstituent in Pd-mediated catalytic reactions. The reaction between 2,5-dichloropyrimidine and styryltributylstannane occurs at the activated 2-position (**165**). 5-Bromo-2-chloropyrimidine, however, is coupled selectively at the 5-position (**166**). The 2-chlorine can be substituted subsequently. In reactions of 2,4-dichloropyrimidine with β-styryl- or phenyltributylstannane, the carbosubstituent goes selectively into the 4-position (**167**) ⟨89ACS62⟩. The same regioselectivity is observed for Ni-catalyzed coupling with organomagnesium reagents (see Section 6.02.5.5.9), and the regioselectivity corresponds to the relative reactivity of pyrimidine towards nucleophiles. A second carbosubstituent can subsequently be introduced into the 2-position (**168**). In 2,4,6-trichloropyrimidine one chlorine in the 4/6-position is replaced selectively under conditions for mono-coupling (**169**).

A good demonstration of the regio and chemoselectivity in these reactions is provided by the stepwise introduction of three different carbosubstituents into 5-bromo-2,4-dichloropyrimidine (Scheme 24). Initial styrylation is in position 4 (**170**), subsequent phenylation is in the 5-position (**171**), and finally thienylation is in the 2-position (**172**) ⟨89ACS62⟩.

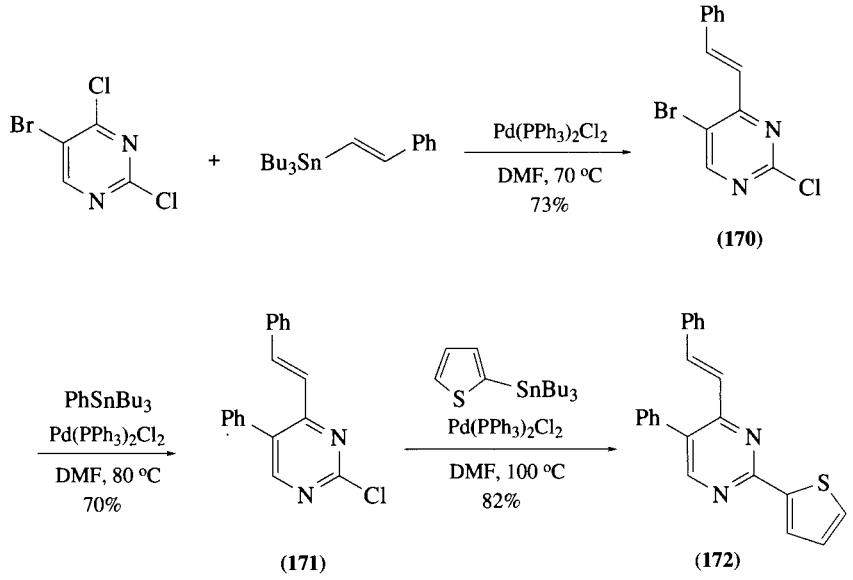
A chlorine in the electrophilic 4-position can be replaced by hydroxymethyl (**173**) (Scheme 25) ⟨89T993⟩. Coupling of the *t*-butyl ether of 5-bromouracil (**174**) with *N*-methylpyrrol-2-yl(trimethyl)-stannane gave the 5-coupled product (**175**) in low yield. Modest yields of coupling products were also obtained in reactions with 2-thienyl- and 2-selenylstannanes and unprotected iodouracil. Silylation of 5-bromouracil is recommended before the coupling reaction. Silyl-protected 5-bromouracil (**176**) reacts with formation of a number of biheteroaryl derivatives (**177**) ⟨90JHC2165⟩.

Pyrimidines have been triflated on O in the 2-position (**178**), in the 4-position (**180**), and in both 4- and 6-positions (**182**) (Scheme 26). Both 2- and 4-pyrimidinyl triflates readily couple with

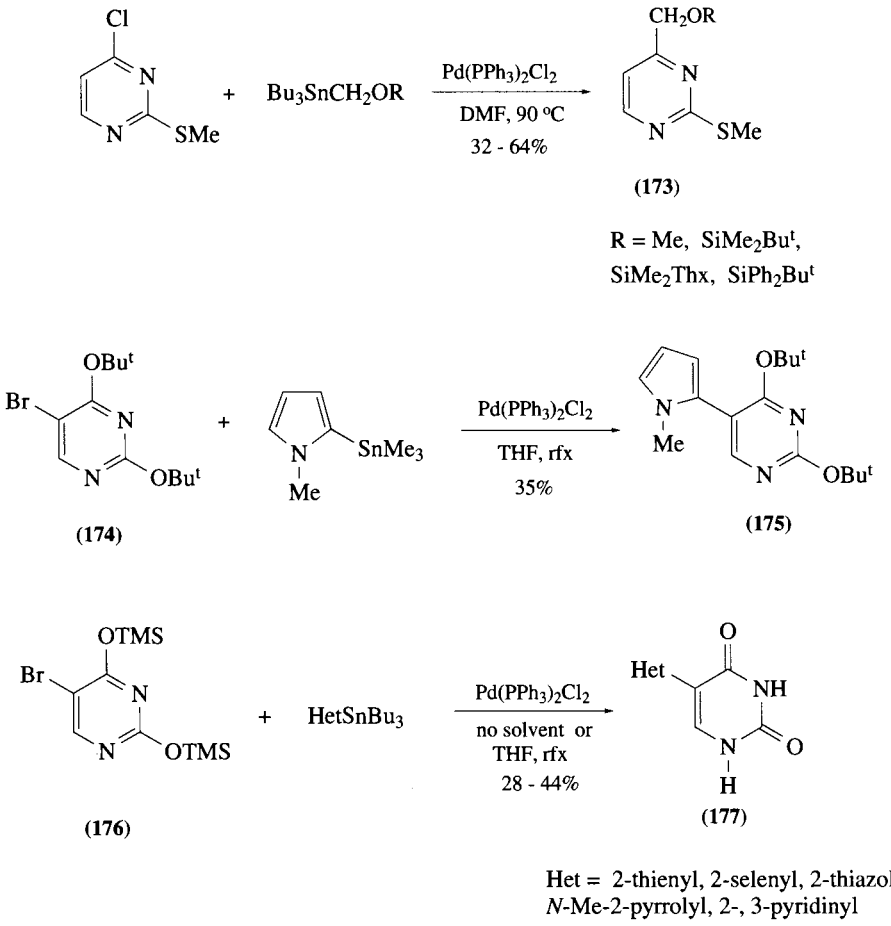


Scheme 23

stannanes in the presence of lithium chloride to give (**179**) and (**181**) ⟨94H(37)501⟩. The pyrimidinyl triflates show reactivity comparable to chlorides in electrophilic positions with stepwise coupling, for example, from the ditriflate (**182**) to the 4-thienyl derivative (**183**) and further to the dithienyl derivative (**184**). It is recommended that the triflation of pyrimidinones is carried out at low

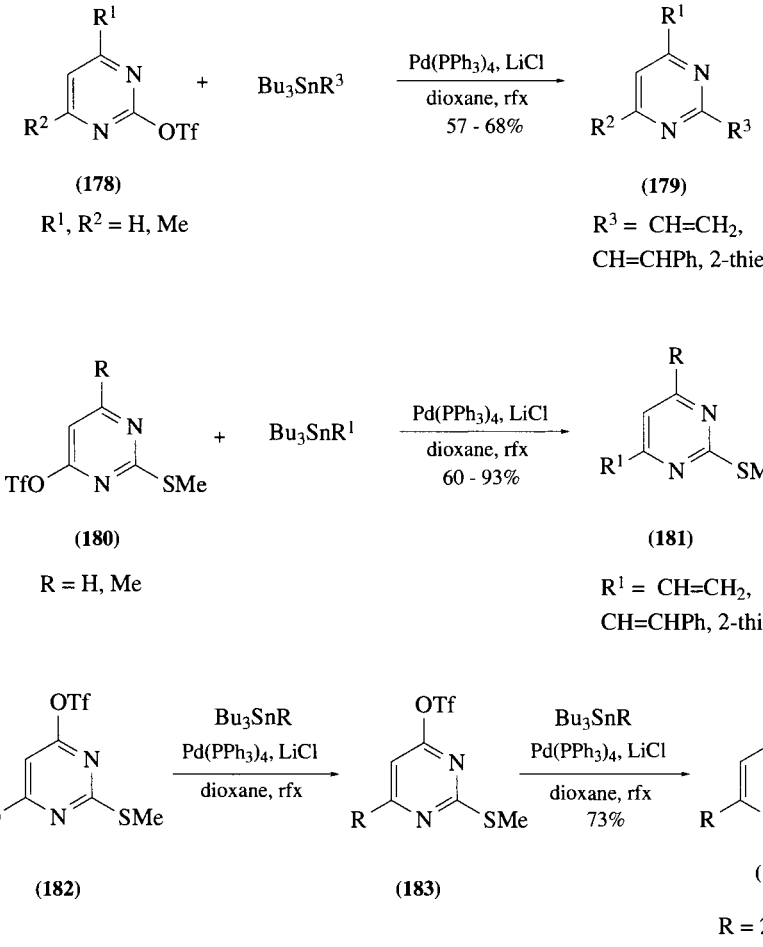


Scheme 24



Scheme 25

temperature (−78 °C). Thereafter the temperature is raised slowly to room temperature. Triflation carried out in this manner gives products stable for purification by preparative chromatography.

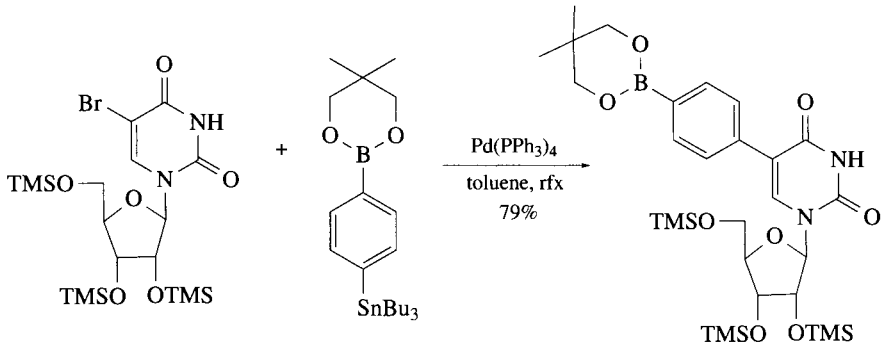


Scheme 26

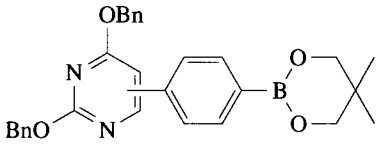
Palladium catalyzed coupling between halogenated nucleosides and arylstannanes containing a boronic acid substituent in the aryl group proceeds chemoselectively at the C—Sn bond rather than at the C—B bond to give boron-containing nucleosides (**185**) (Scheme 27). The method was developed to provide ^{10}B-containing nucleosides for neutron-capture therapy ⟨89JOC4734⟩. The same conditions can be used to introduce the benzeneboronic acid moiety into the 5-position (**186**) of *O*-benzyl-protected 5-iodouracil, and into the 6-position (**187**) in *O*-benzyl-protected 6-bromouracil ⟨89JOC4734⟩.

6.02.5.5.5 Alkylation and arylation by palladium-catalyzed reactions with organoboranes

Cross-coupling reactions between organoboranes and organic halides are effectively catalyzed by Pd(0) in the presence of a base. Couplings in simple pyrimidines are illustrated by the reaction between 2-chloropyrimidine and 2- or 3-thiophene- and selenophene-boronic acids which give the corresponding 2-substituted pyrimidines (**188**) (Scheme 28). In 2,4-dichloro- or 2,4-dibromopyrimidine it is the 4-halo substituent which is the more reactive, 2-chloro- or 2-bromo-4-(2-thienyl)pyrimidine (**189**) being the product from thiophene-2-boronic acid. It was necessary to protect 5-bromo- or 5-iodouracil before coupling; *t*-butyl and benzyl derivatives of the uracils were used in the preparation of the biheteroaryls ⟨86CS305, 90JHC2165⟩. In the nucleoside area, silyl protected 5-iodo uridine or 5-iodo-2′-deoxyuridine react in the same manner with arylboronic acids in the presence of a Pd catalyst to give moderate yields of the corresponding 5-aryluridines and 5-



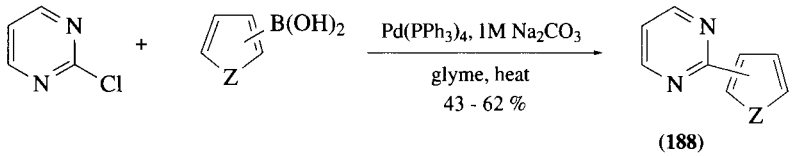
(185)



(186): 5-
(187): 6-

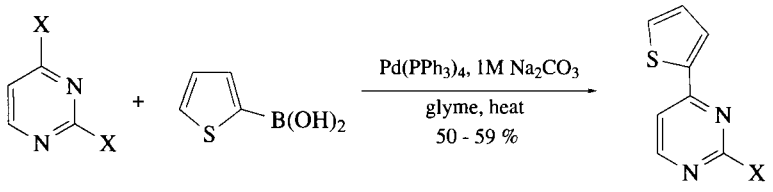
Scheme 27

aryl-2′-deoxyuridines. The coupling of arylboronic acids bearing electronegative groups was not successful (e.g., 4-CF_3). This limitation is overcome by using stannanes instead of boronic acids in the coupling reactions (see Section 6.02.5.5.4) ⟨91MI 602-03⟩.



(188)

Z = S, Se; 2-, 3-



X = Cl, Br

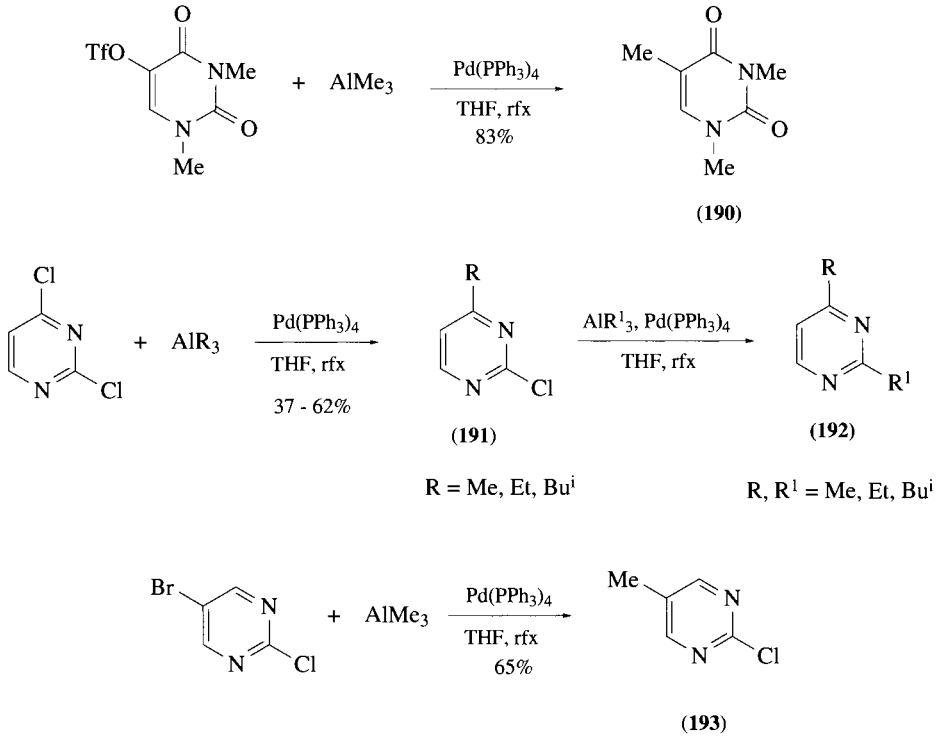
(189)

Scheme 28

6.02.5.5.6 Alkylation and arylation by palladium-catalyzed reactions with organoalanes

Palladium-catalyzed cross-coupling with organoaluminum derivatives in heterocycles has hitherto received but modest attention. However, alanes are promising reagents for the transfer of alkyl groups to heteroarenes (Scheme 29). Alanes are effective donors of an alkyl group to palladium after palladium insertion into a carbon–halogen or carbon–oxygen bond. 5-Hydroxy-1,3-dimethyluracil as triflate can be 5-methylated (**190**) in Pd-mediated reactions by trimethylaluminum in high yield ⟨89JCS(P1)2513⟩. Alkylation of 2,4-dichloropyrimidine can be effected in a stepwise manner;

initial alkylation is in the 4-position (**191**) with dialkylation as the final product (**192**). In 5-bromo-2-chloropyrimidine the bromine substituent in the benzenoid position is replaced by the methyl group to give the product (**193**) ⟨96MI 602-01⟩. Quinazolines are similarly alkylated ⟨96TL1309⟩.

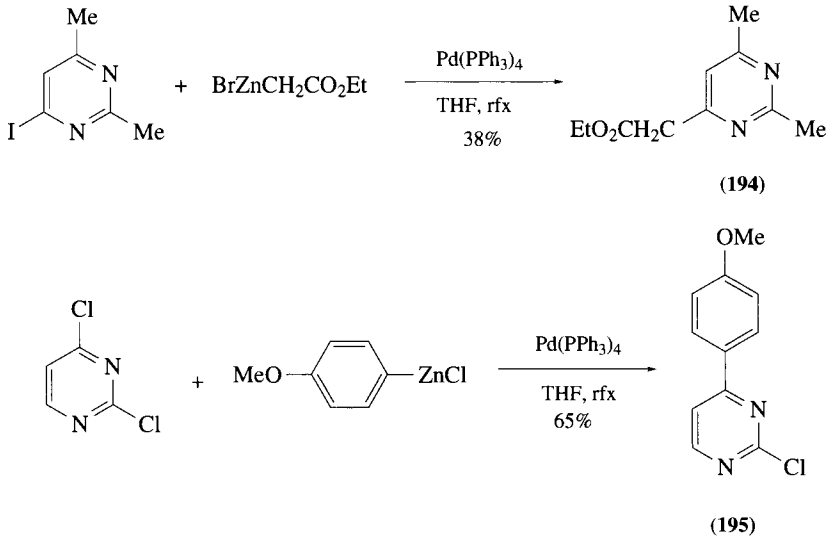


Scheme 29

6.02.5.5.7 Alkylation and arylation by palladium-catalyzed reactions with organozinc compounds

Cross-coupling with organozinc reagents using transition metal catalysis proceeds with high chemo-, regio-, and stereoselectivity ⟨92T9577⟩. Organozinc reagents are useful for the transfer of alkyl groups, better so than organotin analogues. The Reformatsky reaction is feasible in pyrimidines, and is exemplified by the introduction of an acetic acid unit (**194**) through substitution of a 4-iodopyrimidine (Scheme 30). In the reaction between 4-anisylzinc bromide and 2,4-dichloropyrimidine, it is the 4-position which is the more reactive, and the monoarylated 4-anisyl derivative (**195**) is formed using one equivalent of the zinc reagent ⟨93H(35)235⟩. The regioselectivity is the same as observed for the corresponding triflates, and for Pd-catalyzed reactions of the dichloride with stannanes ⟨93ACS102⟩. The chlorine in the 2-position can also be replaced by an excess of reagent. Another zinc or tin reagent would give a pyrimidine product with two different carbosubstituents.

The pyrimidinyl triflates show comparable reactivity to the chloropyrimidines in the Pd-catalyzed reactions. High yields result from coupling reactions with 2-triflyloxy- and 4-triflyloxypyrimidines (**196**) and (**197**) (Scheme 31). Even the Reformatsky reaction can be effected in moderate yields. Variable yields in reactions with *n*-butylzinc bromide result because of competitive alkene formation. 2-Methylthiopyrimidinyl 4,6-ditriflate reacts with arylzinc reagents to give dicoupled products (**198**) ⟨94H(37)501⟩. In the 2,4-ditriflate, the initial reaction is at the more electrophilic 4-position, as for the corresponding, 2,4-dichloride. With excess *p*-anisylzinc bromide the disubstituted product is formed. The intermediate monoarylated product (**199**) has been reacted further; the second coupling with 2-tributylstannylthiophene under Pd catalysis gives the 2-thienyl derivative (**200**) ⟨93H(35)235⟩. The coupling reaction with organozinc chlorides has been applied to substitution in 5-iodouridine ⟨81TL945, 84TL201⟩. A number of monosubstituted alkynes have been lithiated and treated with zinc

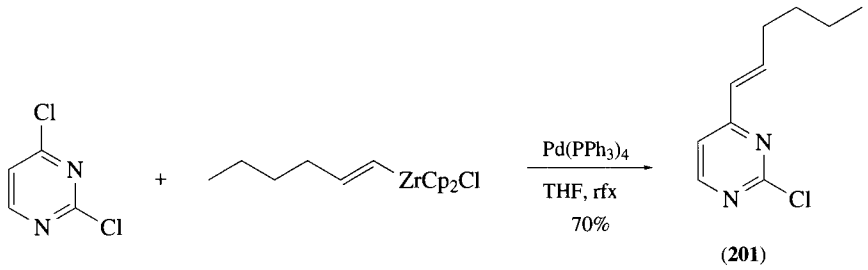


Scheme 30

chloride to form alkynylzinc chlorides which have subsequently been coupled under Pd catalysis to form 5-ethynylated nucleosides ⟨81TL945⟩. With heteroarylzinc chlorides, 5-heteroaryluridines are formed in low to moderate yields. 2,4-Dichloroquinazoline reacted similarly ⟨96MI 602-02⟩.

6.02.5.5.8 Alkenylation by palladium-catalyzed reactions with organozirconium compounds

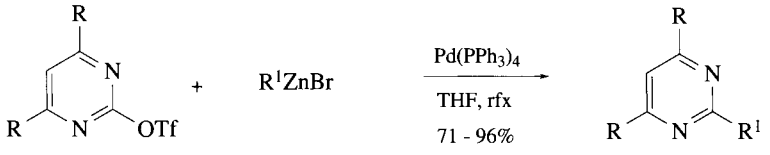
Coupling reactions with organozirconium reagents have hardly been explored in azines. In 1995 it was reported, however, that alkenylation can be effected by alkenylzirconocenes. The latter, in the *trans* configuration, are available by hydrozirconation of terminal alkynes; 1-hexyne was hydrozirconated and coupled *in situ* with 2,4-dichloropyrimidine. Selective reaction in the 4-position gave the 4-alkenylpyrimidine (**201**) (Equation (13)).



(13)

6.02.5.5.9 Alkylation and arylation by nickel-catalyzed reactions with organomagnesium reagents

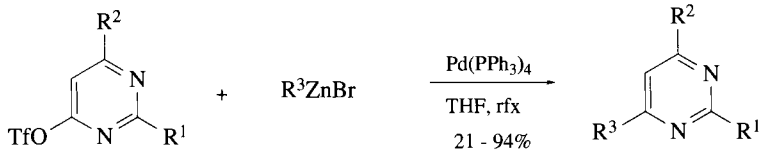
The sulfur functionality can be useful for carbosubstitution using nickel catalysis together with Grignard nucleophiles. Grignard reagents readily form 1 : 1-adducts with π-deficient azines. This can be avoided when the electrophilic positions are occupied as in 2-methylthio-4,6-dimethylpyrimidine; substitution is in the 2-position (**202**) (Scheme 32). With a free thione group two equivalents of the Grignard reagent are required, as exemplified by the preparation of (**203**) ⟨78CPB2160, 79CL1447⟩. Halo substituents can be replaced. The chlorine in the electrophilic 2- or 4-position is readily exchanged by carbosubstitution (**204**, **205**). The 2,4- and 4,6-dichloro pyrimidines are disubstituted. With chlorines in all the electrophilic positions, trisubstitution (**206**) results with excess of reagent, and the regiochemistry was difficult to control using one mole equivalent of Grignard reagent. The product from 2,4,6-trichloropyrimidine was a mixture of the trisubstituted and the disubstituted



R = H, Me

(196)

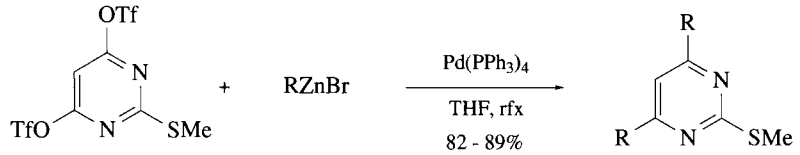
R^1 = *p*-anisyl, Bu, CH_2=CH, $CH_2CO_2Bu^t$



R^1 = Me, SMe
R^2 = H, Me

(197)

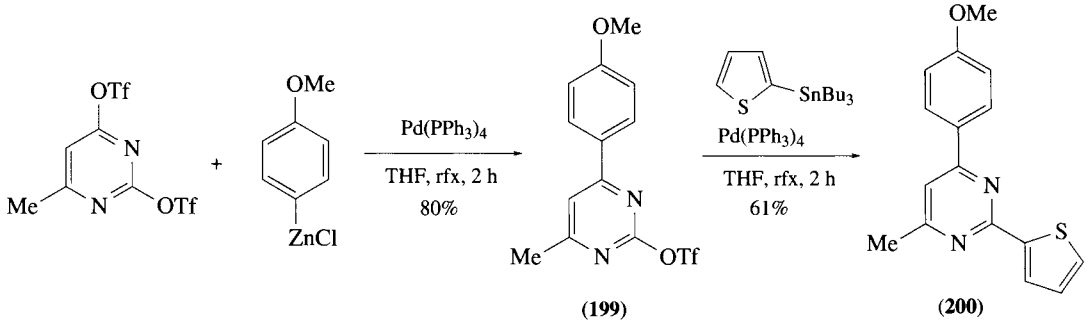
R^3 = Ph, *p*-anisyl, Bu, CH_2=CH, 2-thienyl, $CH_2CO_2Bu^t$



(197)

(198)

R = Ph, *p*-anisyl



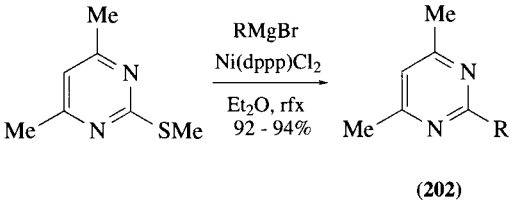
(199)

(200)

Scheme 31

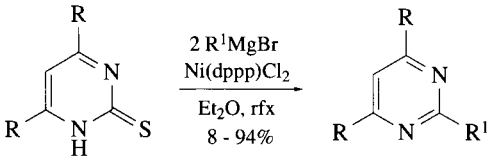
isomers, besides the trichloro substrate. This is in contrast to the behavior in the Pd-catalyzed reactions of stannanes, where the reaction can be controlled in a stepwise manner from the 4(6)-position to the 2-position (Section 6.02.5.5.4). The pyrimidines discussed carried substituents in all the electrophilic positions. When one of the electrophilic positions is vacant, as in 2,4,5-trichloro- and 2,4-dichloro-5-fluoropyrimidine, competition arises between a coupling reaction in a halogen-substituted position (**208**) and 1 : 1-adduct formation between the Grignard reagent and the heterocycle in the vacant electrophilic 6-position (**207**). The adduct formation is faster with phenyl- and benzylmagnesium reagents ⟨83ACS(B)109, 83ACS(B)160⟩.

Sequential substitution with the 6-phenyl derivative (**209**) can be effected; the chlorine in the 4-position is more reactive than that in the 2-position, giving the products (**210**). This allows for differential substitution using Grignard reagents in sequential addition (**211**).



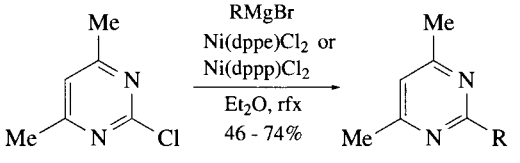
(202)

R = Ph, $Ph(CH_2)_3$

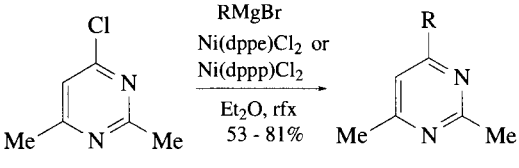


(203)

R^1 = Ph, $Ph(CH_2)_3$

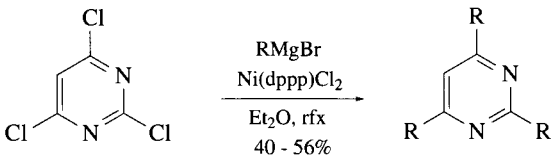


R = Et, Bu, Pent, Hex
Ph, Bn



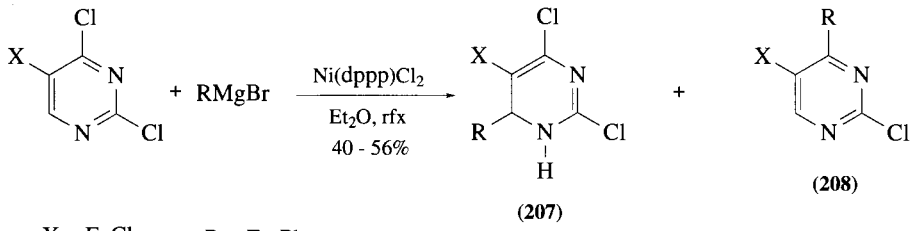
(205)

R = Et, Bu, Pent,
Hex, Ph, Bn



(206)

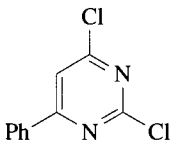
R = Et, Ph



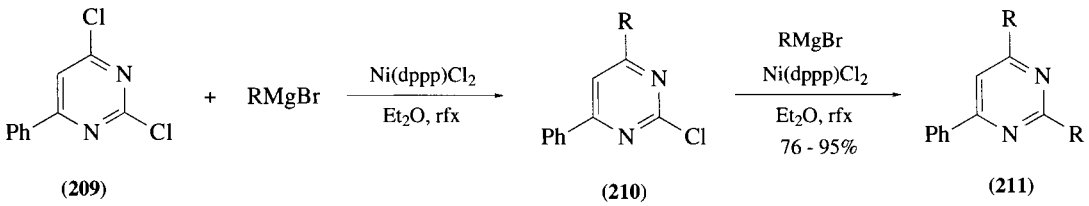
(207) **(208)**

X = F, Cl R = Et, Ph

X = Cl



(209)



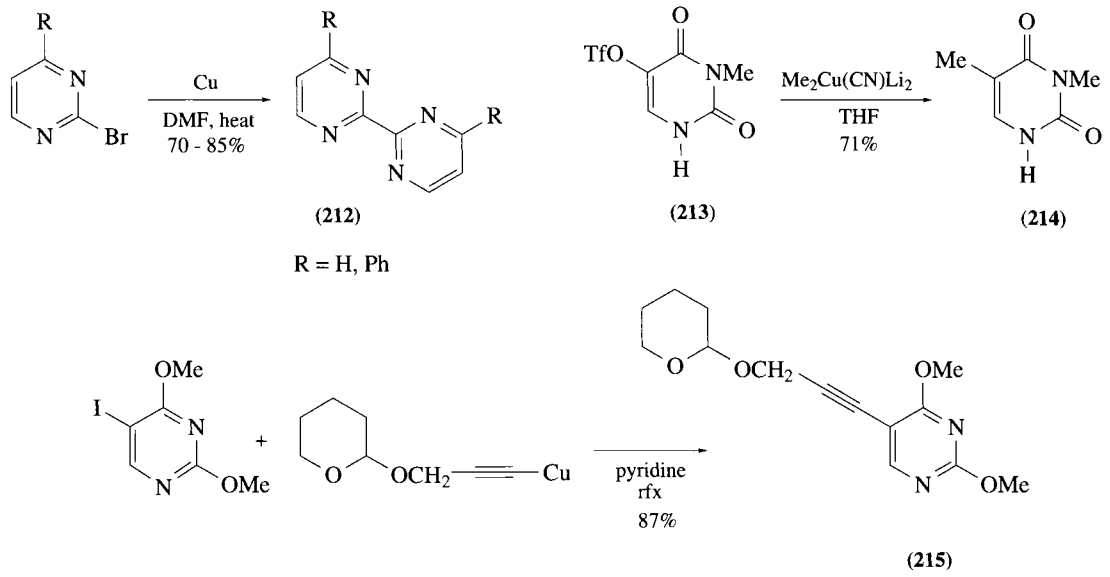
(209) **(210)** **(211)**

R = Et, Ph

Scheme 32

6.02.5.5.10 Alkylation and arylation by copper-catalyzed reactions

The Ullmann reaction is a copper-promoted homo- or hetero-coupling between two aryl halides ⟨74S9⟩. 2,2′-Bipyrimidine (**212**) ⟨62JOC2945⟩ and 4,4′-diphenyl-2,2′-bipyrimidine ⟨67JOC1591⟩ can be prepared from the corresponding 2-bromopyrimidine by Cu-mediated reactions on heating in DMF (Scheme 33). 4,4′-Bipyrimidine is formed by pyrolysis of the copper(II) salt of pyrimidine-4-carboxylic acids ⟨67JOC1591⟩. Coupling can be effected in all positions. Reactions between different positions correspond to cross-coupling. In 5-bromo-2-phenylpyrimidine, the coupling is between two benzenoid positions ⟨67JCS(C)1204⟩.



Scheme 33

In Cu-mediated alkylation, the 5-triflyloxy group in the uracil derivative (**213**) can be substituted by a methyl group to form the thymine (**214**) using the higher-order cuprate $Li_2Cu(CN)Me_2$. Coupling with the butyl reagent, $Li_2Cu(CN)Bu_2$, however, gave a mixture of the expected 5-butyl derivative (20%), the 6-butyl isomer (10%), and the uracil formed by a reductive process ⟨87H(26)355⟩. In the Stephens–Castro reaction, *O*-methylated 5-iodouracil has been reacted with THP-protected propargyl alcohol as a Cu-derivative to give the 5-alkynyl product (**215**).

Nucleophilic substitution in electrophilic azine positions with nonstabilized carbanionic reagents is difficult to effect. It has been found, however, that sulfoxides derived from an electrophilic azine position can react with a Grignard reagent with replacement of the sulfinyl group and carbosubstitution ⟨90AHC(48)1⟩.

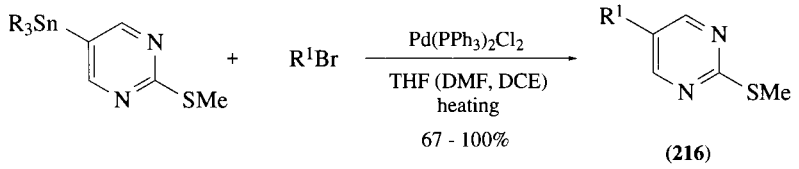
6.02.5.5.11 Tin, zinc, boron, and mercury metallopyrimidines in alkylation and arylation reactions

Metallations of pyrimidines and congeners are discussed in Section 6.02.5.6.

(i) Pyrimidinyltin compounds in alkylation and arylation reactions

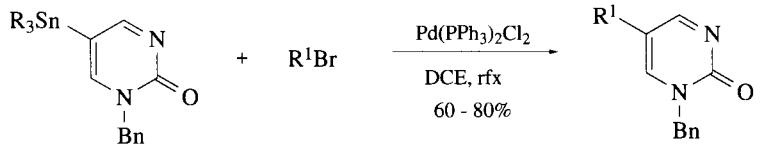
Stannylpyrimidines react readily with organohalides and -triflates under the influence of Pd catalysis (Scheme 34). 2-Methylthio-5-trimethyl- or tributyl-stannylpyrimidine reacts with bromostyrene or propenyl bromide to yield (**216**) ⟨88ACS(B)455, 89JCS(P1)255⟩. 5-Pyrimidinyl biheteroarenes are accessible from bromofurans, bromothiophenes or bromopyridines and stannylated pyrimidines ⟨89ACS684⟩. 5-Stannylated 2-pyrimidinones (**217**) are good substrates for coupling reactions (**218**). 4-Stannylpyrimidines react similarly. This reaction has been applied to pyrimidine nucleosides for substitution at C6. Initially LDA in THF at −78 °C was used for the regioselective metallation at C6 in uridine. The lithiated species was quenched with a stannyl chloride to form the stannane to be used in the coupling with an aryl iodide. The optimal conditions in most cases involve 10 mole%

$Pd(PPh_3)_4$ and 20 mole% CuI in a weakly coordinating solvent (DMF at 80 °C). Variously substituted alkenyl derivatives can also be introduced into the 6-position starting from the corresponding bromides ⟨93T2533⟩.



(216)

R^1 = propenyl, β-styryl, 2-(3-)furyl, 2-(3-)thienyl, 2-(3-,4-)pyridinyl, 2-thiazolyl, 2-(5-formyl) furyl, 2-(5-acetoxymethyl)furyl



(217) **(218)**

R^1 = Ph, β-styryl

Scheme 34

(ii) Pyrimidinylzinc compounds in alkylation and arylation reactions

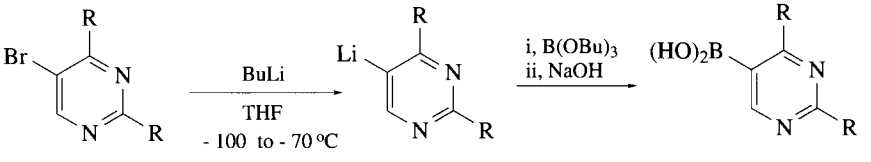
Zinc derivatives are available by transmetallation reactions as discussed in Section 6.02.5.6.4. Most work has been done with pyridines, but coupling reactions seem equally feasible with pyrimidines. An example is provided by 2-iodo-4,6-dimethylpyrimidine which is zincated in the 2-position and Pd-coupled with iodobenzene to furnish the 2-phenyl derivative in 26% yield ⟨93T9713⟩.

(iii) Pyrimidinylboron compounds in alkylation and arylation reactions

Boronation is generally effected by metal-exchange reactions as discussed in Section 6.02.5.6.5. Thus 5-bromopyrimidines have been lithiated, boronated (**219**), and the boronated species coupled with bromothiophenes and 3-bromoselenophene to form 5-heteroarylpyrimidines (**220**) (Scheme 35) ⟨86CS305⟩. Using 2,4-di-*t*-butoxypyrimidine-5-boronic acid a number of heterocycles have been coupled at the 5-position via bromides ⟨90JHC2165⟩.

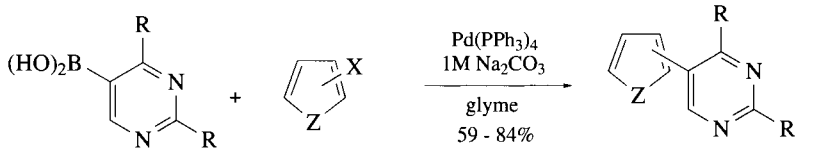
(iv) Pyrimidinylmercury compounds in alkylation and arylation reactions

Organomercurials are available by electrophilic substitution reactions in appropriate substrates or by metal–metal exchange reactions. Pyrimidine nucleosides react readily with Hg(II) acetate in the pyrimidine 5-position. Thus 2′-deoxyuridine has been mercurated and coupled with iodobenzene or substituted derivatives, by heating with diglyme in a Pd-mediated reaction, with formation of 5-aryl derivatives (**221**) (Equation (14)) ⟨84TL2431⟩. Heck couplings also run well ⟨78JA8106, 79TL1653⟩. 5-Chloromercury derivatives of 2′-deoxycytidine, cytidine nucleosides, and the uridine analogues



(219)

R = H, Bu^{t}O

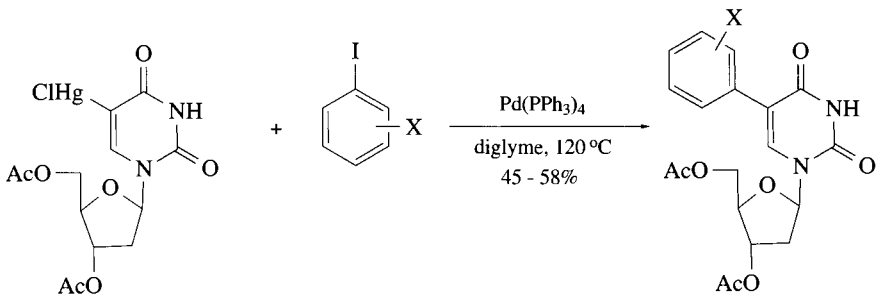


(220)

Z = Se 3-, S 2-, 3-

Scheme 35

can be allylated in the 5-position using substituted allyl chlorides or allyl triflates in Pd-mediated coupling reactions ⟨81JOC1423, 91CJC198⟩.



(14)

(221)

X = H, 2-OAc, 3-MeO, 4-Me, 4-CN

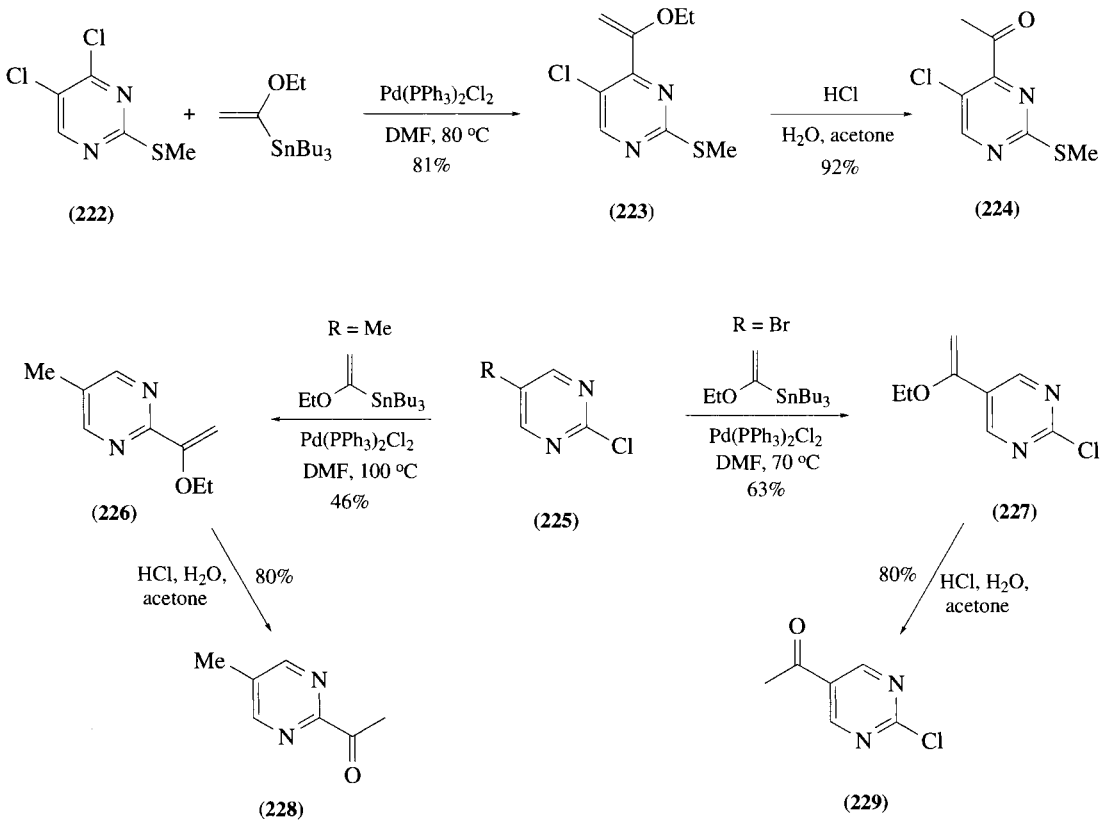
6.02.5.5.12 Acylation by electrophilic substitution

Acylation by electrophilic substitution applies to pyrimidines carrying at least two strongly electron-donating substituents and has been discussed in Section 6.02.5.3.7.

6.02.5.5.13 Acylation by palladium-catalyzed reactions with stannanes

α-Stannylated enol ethers provide a general and convenient substrate for introduction of acyl groups into azines. The stannanes are available from enol ethers by α-lithiation and quenching with trialkylstannyl chloride. Mild acid hydrolysis of the α-pyrimidinylethenyl ethers yields the acyl-substituted pyrimidines. In the 4,5-dichloro derivative (**222**) the masked acyl group is introduced into the electrophilic 4-position (**223**) (Scheme 36). In the 2,5-disubstituted pyrimidine (**225**) with a methyl group in the 5-position the product is a masked acyl group in the electrophilic 2-position (**226**). When the 5-substituent in the latter example is bromine, the chemoselectivity leads to masked

acylation in the 5-position (**227**). The vinyl ethers are cleaved to the respective ketones (**224**), (**228**) and (**229**) by mild acid hydrolysis ⟨89ACS62⟩.



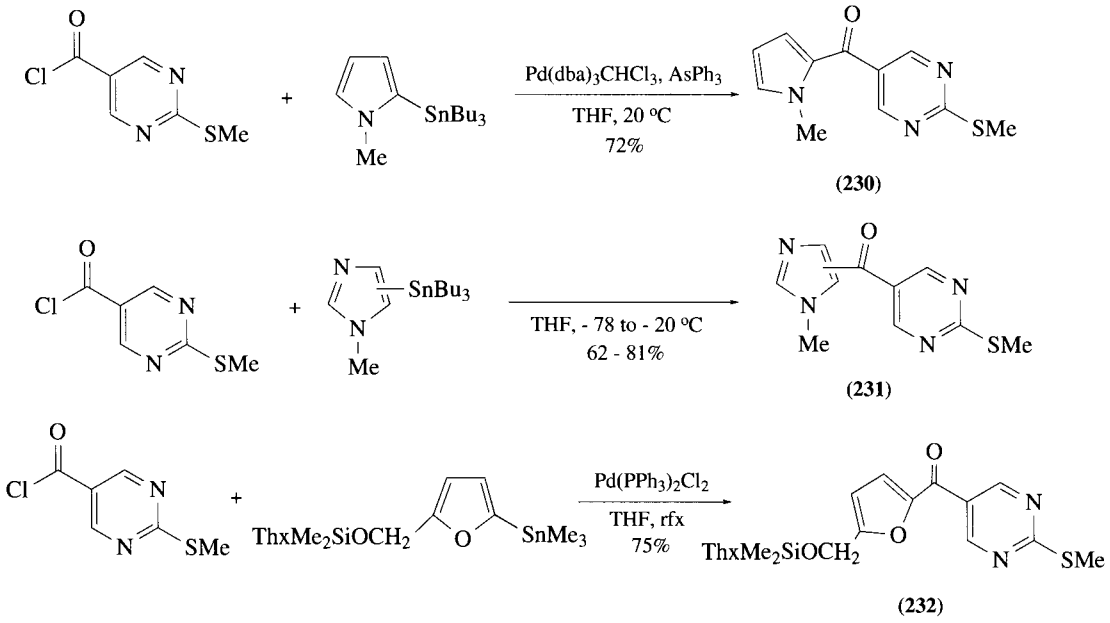
Scheme 36

In the benzenoid 5-position, ketones can be prepared from carbonyl chlorides using the Sn–Pd method (Scheme 37). The 5-(2-pyrrolylcarbonyl)pyrimidine (**230**) is available from pyrimidine-5-carbonyl chloride in a Pd-catalyzed reaction with the corresponding 2-pyrrolylstannane. The catalyst was ligated to triphenylarsine since the complex with triphenylphosphine was not active enough for a satisfactory conversion in this reaction. In the preparation of the imidazolyl ketones (**231**), the reactions were best effected without catalyst ⟨93ACS57⟩. Lithiation and metal exchange can also be used to prepare 5-stannylated furfuryl silyl ethers for synthesis of the 5-pyrimidinyl 2-furyl ketones (**232**) using $PdCl_2$ with triphenylphosphine as ligand ⟨91ACS914⟩.

6.02.5.5.14 Tin metallopyrimidines in acylation reactions

Pyrimidines stannylated in the 4-position are highly active in coupling reactions at low temperature and will couple with an acid chloride to form ketones such as (**233**) in the absence of catalyst (Scheme 38). 2-Stannylpyrimidines also react rapidly with acid chlorides to form the ketones (**234**) in the absence of catalyst ⟨94T275⟩.

Alkyl, aryl, and heteroaryl ketones (**236**) are available from 5-stannylpyrimidines (**235**) and carbonyl chlorides. The reaction with pyrroles was run on *N*-alkylated or *N*-acylated pyrrolecarbonyl chlorides to furnish the ketones (**237**) ⟨93ACS57⟩. 2-Pyrimidinones are protected and solubilized as *t*-butyldimethylsilyl ethers (**238**) for coupling. During the reaction the silyl group is cleaved off. The silyl function in the 5-acylated pyrimidine (**239**) is sensitive to cleavage because of the electron-withdrawing properties of the acyl group ⟨89JCS(P1)255⟩.



Scheme 37

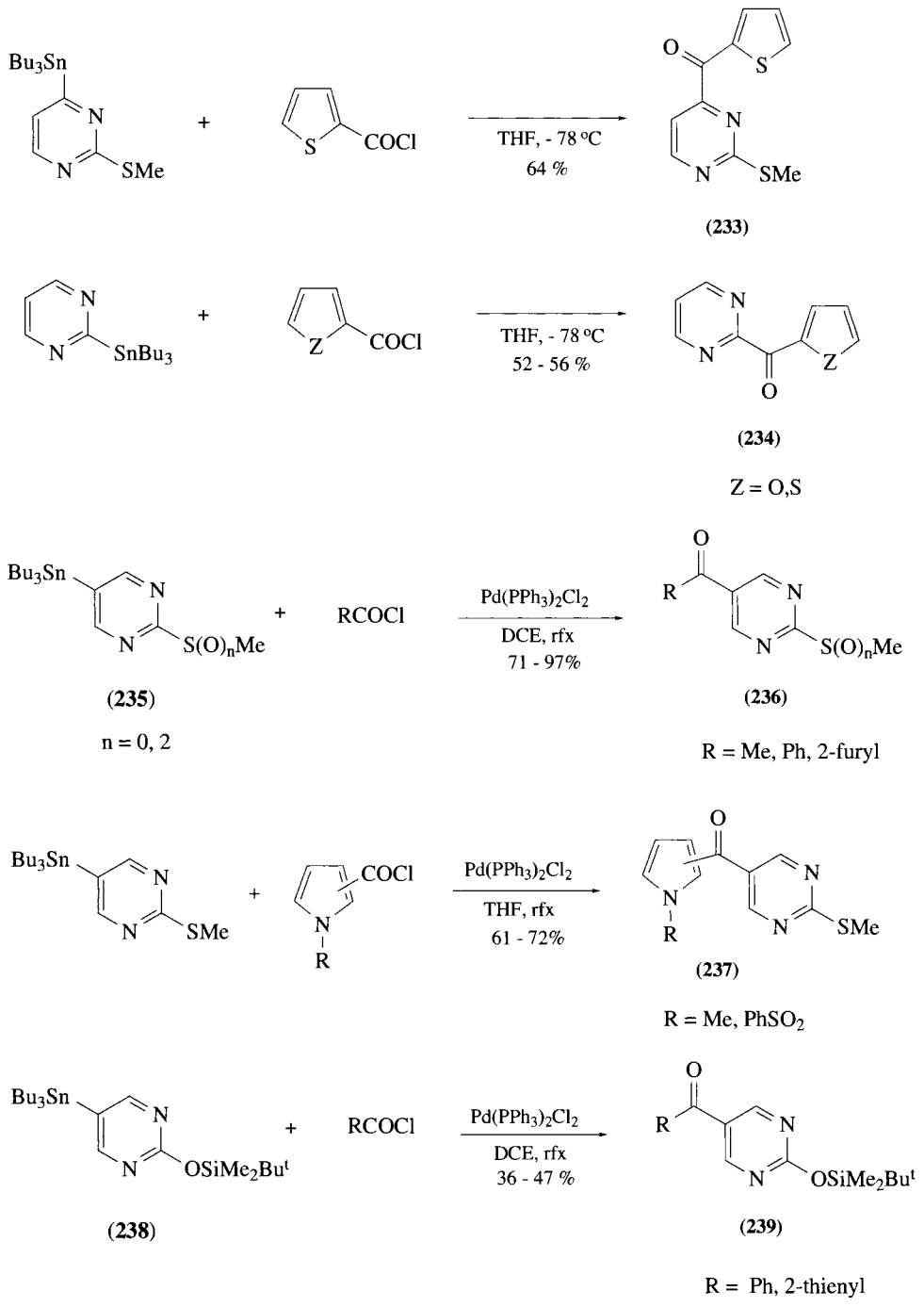
6.02.5.5.15 Coupling reactions in quinazolines and perimidines

(i) Quinazolines

Low to moderate yields have been reported for carbosubstitution in 4-chloroquinazolines using Grignard reagents. The carbosubstitution is improved when 4-cyanoquinazoline is the substrate for the Grignard reaction, which proceeds with loss of the cyano group; the yields of 4-substituted products (**240**) are moderate to good (Scheme 39). Moderate yields have also been obtained in reactions between 4-chloroquinazoline and compounds with an active methylene group in the presence of a strong base; 4-cyanoquinazoline is recommended as the more versatile substrate ⟨B-67MI 602-01⟩.

A rich chemistry on metal-catalyzed carbosubstitutions in quinazolines, however, is expected to develop allowing for regioselective alkylations, arylations, and acylations along the lines described above for carbosubstitutions in pyrimidines. The most readily available substituents for displacement in the electrophilic positions are found in chlorides, or alternatively triflates; and in the benzene moiety iodides, bromides, or triflates. Thus organometallic reagents based on Sn, Zn, B, Al, Zr, etc., are expected to couple under experimental conditions very similar to those used for pyrimidines. This is demonstrated by regio- and chemoselective mono, di-, and trialkynylations ⟨96MI 602-02⟩, and by 2,4-dichloroquinazolines ⟨96MI 602-01⟩. With alanes, stepwise alkylations are effected under mild conditions. It is the more electrophilic 4-position which is alkylated in the first step with formation of (**241**). The second chlorine substituent in the 2-position is subsequently replaced giving (**242**). In 6-bromo-2,4-dichloroquinazoline there is competition between reaction of the bromine in the benzene ring and the chlorines in the pyrimidine. Alkylation in the electrophilic 4-position (**244**) dominated over the benzenoid 6-position (**243**). In both cases the remaining two halogen substituents could be substituted by further alkylation (**245**), (**246**) ⟨96TL1301, 96MI 602-01⟩.

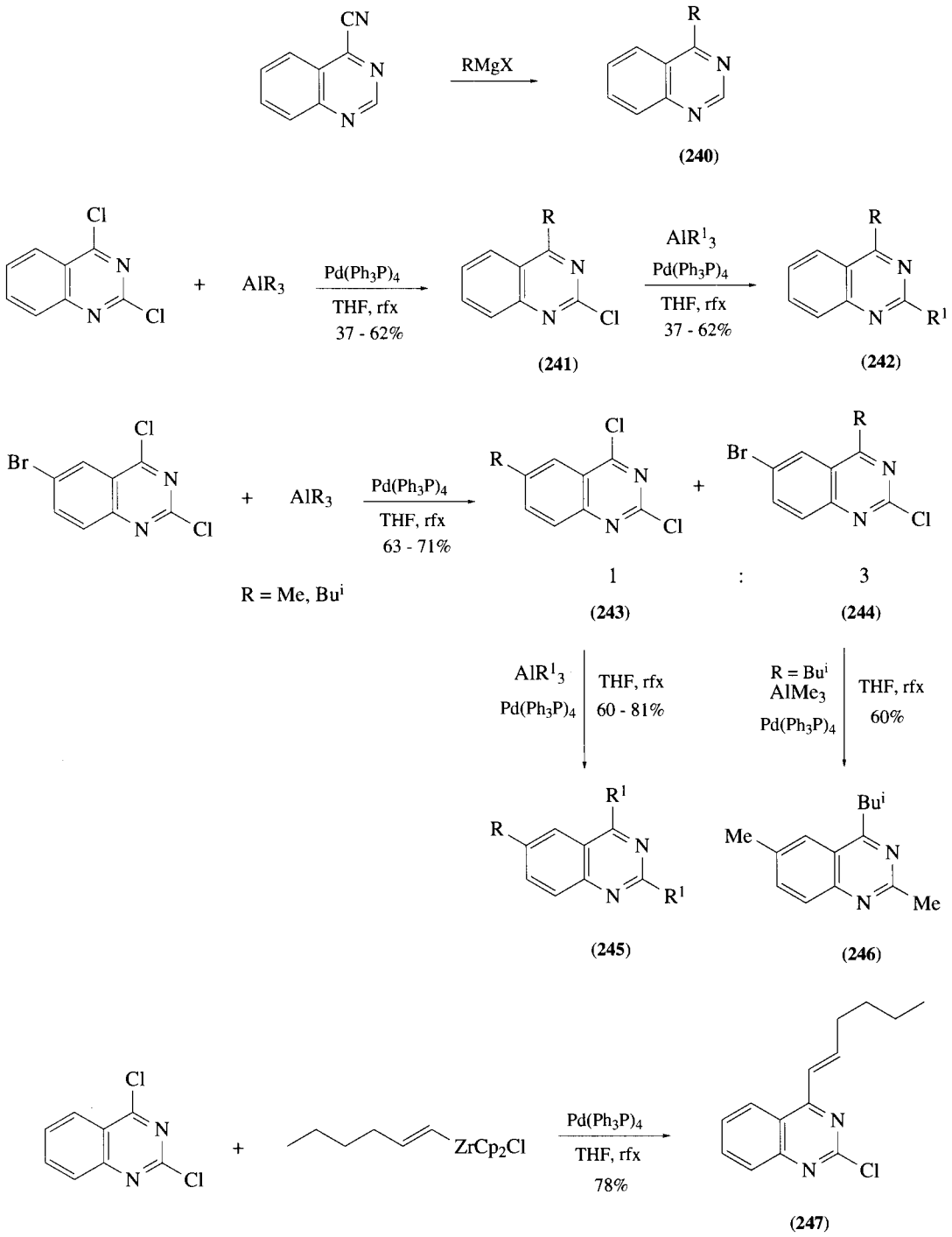
Organozirconium reagents have now been found to be useful ⟨96MI 602-02⟩. Selective alkenylation in the 4-position in 2,4-dichloroquinazoline with the formation of (**247**) results from the coupling reaction with chloro-*trans*-1-hexenylzirconocene which is generated *in situ* by hydrozirconation of 1-hexyne. Alkenyltin or -zinc reagents would also be expected to effect this reaction under the influence of Pd-catalysis.



Scheme 38

(ii) Perimidines

A chlorine substituent in the highly electrophilic 2-position is very reactive towards nucleophiles. With lithium or sodium organics the reported reactions seem to indicate adduct formation and hydrogenolysis in addition to substitution ⟨81RCR816⟩. Metal-catalyzed coupling reactions, as discussed for pyrimidines, are expected to provide for versatile carbosubstitutions.

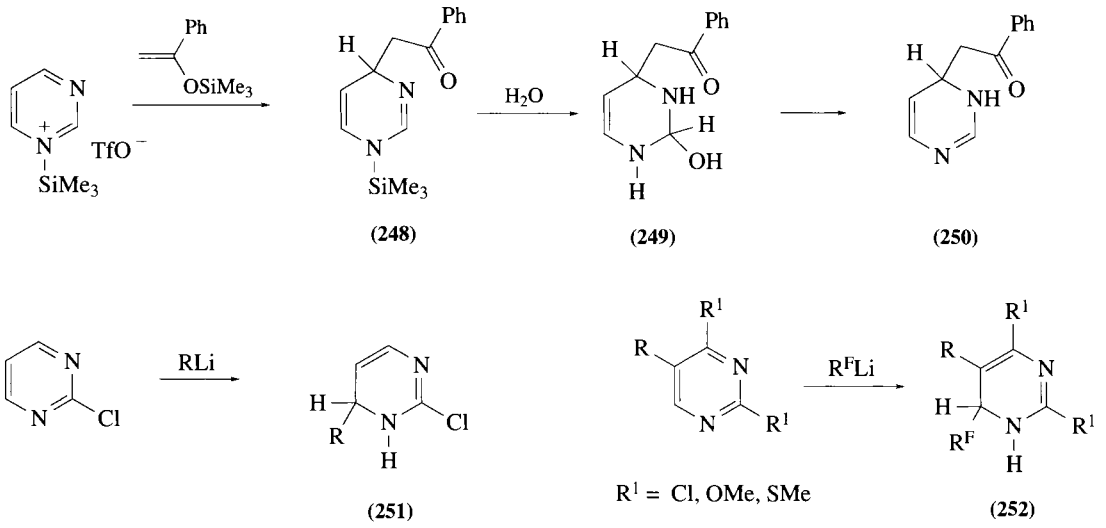


Scheme 39

6.02.5.5.16 Alkylation and arylation by organometallic adduct formation

Organometallics form 1 : 1-adducts with pyrimidines by adding across the 3,4-double bond. The products are dihydropyrimidines with a new carbon–carbon bond formed in the electrophilic 4/6-position. Adduct-forming reactions with organometallics are useful for the introduction of carbosubstituents into a vacant 4/6-position; the adduct formed is subsequently oxidized to the fully conjugated heterocycle. Pyrimidine forms adducts in the 4-position with aryl- and heteroaryllithium reagents at low temperature ⟨79AG1, 80RTC234⟩. Trimethylsilylpyrimidinium triflate, derived from

pyrimidine and trimethylsilyl triflate, adds silylated enol ethers to form 1,4-dihydropyrimidines (**248**) (Scheme 40). Aqueous workup afforded the covalent hydrate (**249**). *N*-Acylpyrimidinium tetrafluoroborates undergo analogous reactions, and in some cases dihydropyrimidines (**250**) were isolated in almost pure form ⟨85H(23)207⟩.



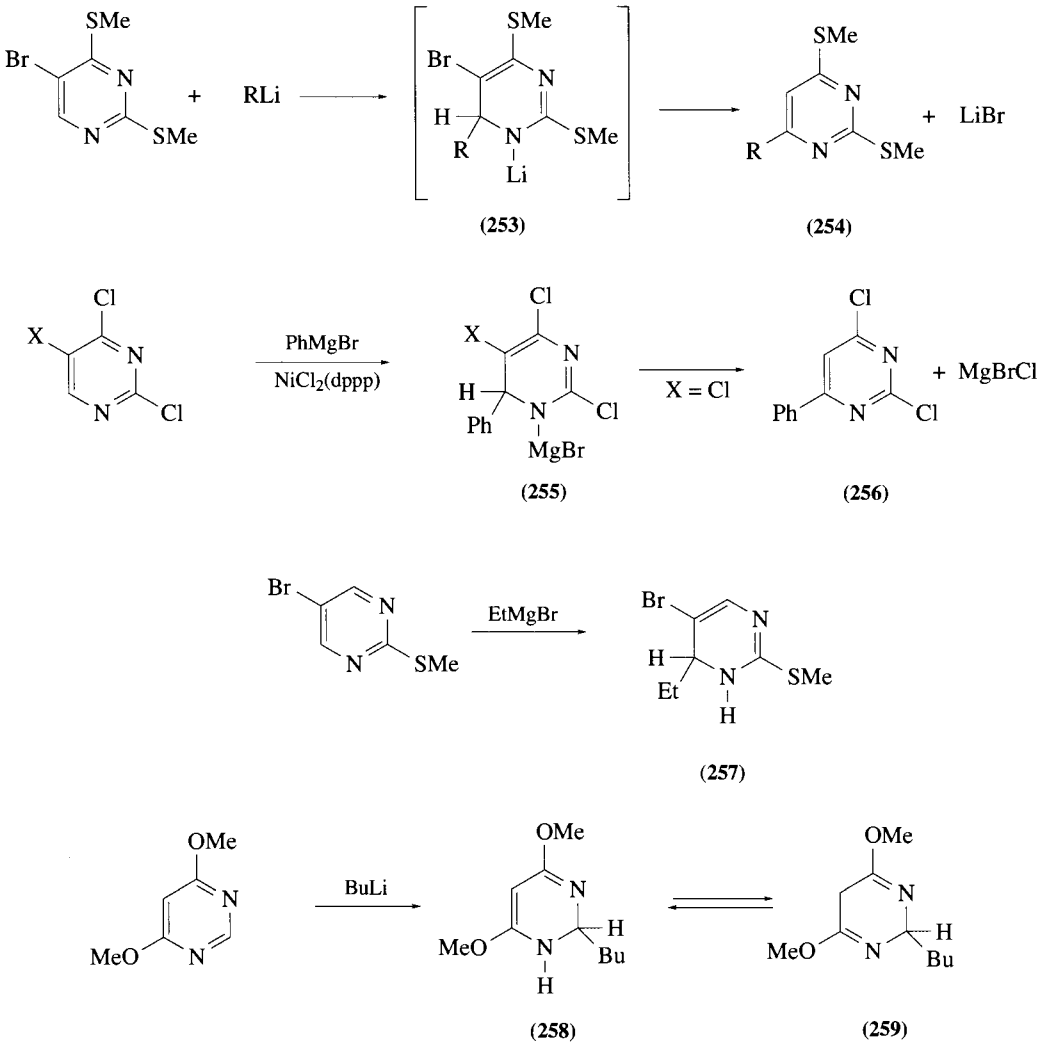
Scheme 40

In 2-chloropyrimidines, an organolithium or -magnesium reagent will enter a vacant electrophilic position to form 1,6-dihydro derivatives (**251**) ⟨80JHC1479⟩. With trihalopyrimidines as substrates, alkyl-, aryl-, and heteroarylpyrimidines have been prepared by 1,6-dihydro product formation. Addition of the nucleophile occurred preferentially at a vacant 4/6-position. Even when all the electrophilic positions were occupied, addition to the 4/6-position might occur with subsequent chloride elimination giving a fully conjugated product ⟨88JOC4137⟩. Both 2,4-bismethylthio- and 2,4-dimethoxypyrimidines form 1,6-dihydro adducts with organolithiums (**252**) ⟨87S579⟩. 2,4-Dichloropyrimidines react similarly ⟨85S686⟩.

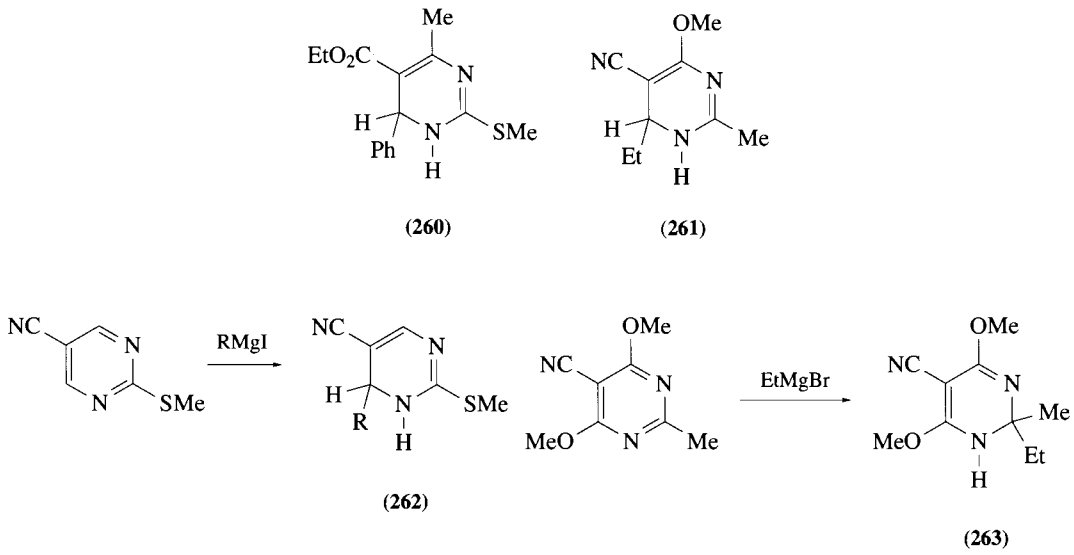
5-Bromo-2,4-bismethylthiopyrimidine forms adducts (**253**) in the vacant 6-position rather than being lithiated by halogen–metal exchange. The adducts undergo H migration and loss of LiBr to yield fully conjugated 6-substituted derivatives (**254**) (Scheme 41) ⟨88S70⟩. 2,4,5-Trichloro- and 2,4-dichloro-5-fluoropyrimidine add phenylmagnesium bromide in a nickel-promoted reaction in the vacant 6-position (**255**) and subsequently suffer elimination of the 5-chlorine as MgBrCl and H migration (**256**). No elimination from the initial adduct was seen when the 5-halogen was a fluorine ⟨83ACS(B)109, 83ACS(B)160⟩. In contrast to the above eliminations, 5-bromo-2-methylthiopyrimidine was reported to add ethylmagnesium bromide to form the 6-ethyl-1,6-dihydro derivative (**257**) without elimination ⟨79H(12)383⟩. 4,6-Dimethoxypyrimidine adds alkyllithiums at C2. The initial product (**258**) rapidly tautomerizes to the more stable 2,5-dihydro isomer (**259**) ⟨84JHC53⟩.

In ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate, addition is in the 6-position (**260**) rather than in the ester group. Grignard reagents add to the cyano group in 2- and 4-cyanopyrimidines, but preferential addition occurs in a vacant 6-position in 2,4-disubstituted 5-cyanopyrimidines (**261**) ⟨80CCC539⟩. In 5-cyano-2-methylthiopyrimidine methyl- and phenylmagnesium iodide add exclusively to the pyrimidine ring with the carbosubstituent in the 4-position (**262**) (Scheme 42) ⟨83ACS(B)613⟩. When all positions are occupied addition may still occur, this time in the 2-position (**263**) ⟨80CCC539⟩.

2(1*H*)-Pyrimidinones are highly polarized and form adducts with organometallics (Scheme 43). The new carbon–carbon bond may be formed in either the 4- or the 6-position. Regioselectivity has been claimed for reactions with organolithium and -magnesium ⟨79JHC545, 81JCS(P1)489⟩. However, the reactions between 1-benzyl-5-halogeno-2(1*H*)-pyrimidinones and organocopper, -lithium or -magnesium reagents lead to coformation of the 3,4- and 3,6-dihydro isomers ⟨85ACS(B)459⟩. In most cases the major product from the Grignard reactions was the 3,6-adduct (**266**), whereas organolithium and -copper reagents gave larger amounts of the 3,4-dihydro isomer (**264**). The effect of the halogen in the 5-position in the 2(1*H*)-pyrimidinones is two-fold. The electronegativity serves to activate the pyrimidine electronically, but the bulkiness of the halogen gives rise to steric



Scheme 41



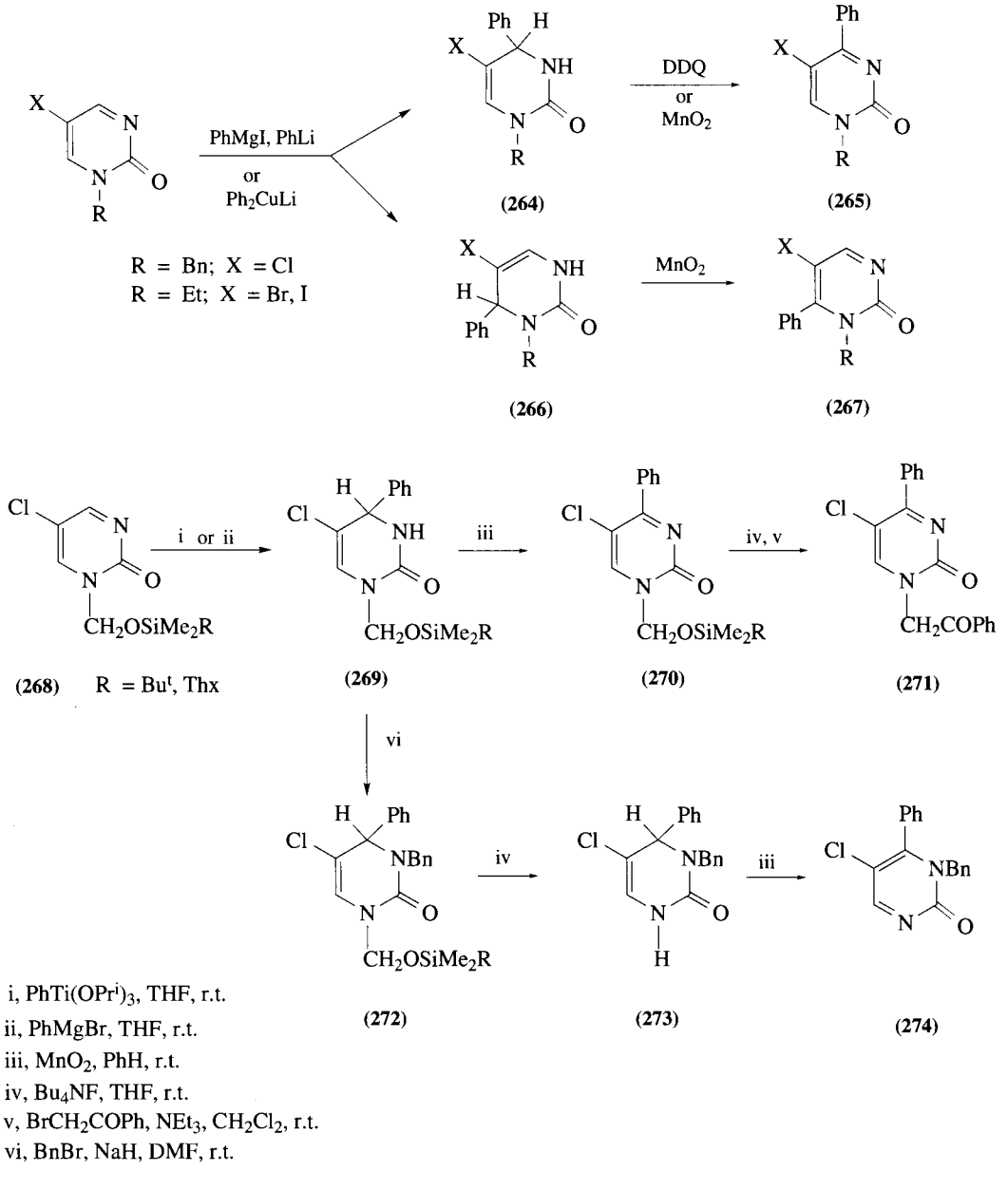
Scheme 42

interference. The steric effect is expected to be most severe in the 6-position with bulky reagents because of the additional interaction with the 1-substituent. The highest activation was seen in the 5-fluoro and 5-chloro derivatives. The 5-iodo derivative in most cases failed to form adducts. Full regioselective formation of 3,4-adducts (**264**) has been achieved with organotitanium reagents ⟨85JCS(P1)1997⟩. The nature of the 1- and 5-substituents did not affect the regiochemistry in reactions with phenyltriisopropoxytitanium. The regioselectivity observed may, in part, be rationalized as resulting from steric repulsion between the 1-substituent and the bulky aryltriisopropoxytitanium reagent, which therefore would be expected to favor bond formation at C4 in preference to C6. The formation of the 3,4-adduct can be regarded as a 1,2-conjugate addition in accordance with the behavior of titanates in their reactions with $\alpha\beta$-unsaturated carbonyl compounds ⟨83PAC1807, B-86MI 602-02⟩. In this comparison the N3–C6 part of the pyrimidinone is regarded as possessing electronic properties similar to those of an $\alpha\beta$-unsaturated imine system. Carbon–carbon bond formation at C6 corresponds to 1,4-conjugate addition. The aromatic substitution sequence at C4 (**265**), (**267**) is completed by oxidation of the dihydro compounds with DDQ or activated manganese dioxide. The latter is the more potent reagent and is used when the yields from the DDQ oxidations are unsatisfactory, or in the more difficult oxidation of the 3,6-adducts ⟨85ACS(B)459⟩.

An unsubstituted lactam nitrogen must be protected before the organometallic reaction. The organometallic reaction must also precede introduction of the *N*1 substituent when the *N*1 substituent is incompatible with the organometallic reagent. Silyloxymethyl protecting groups, which can be removed under mild conditions without hydrogenolysis, have been used. The (*t*-butyldimethylsilyloxy)methyl and the (dimethylthexylsilyloxy)methyl groups used are resistant to the organometallic reagents employed. The protected pyrimidinones (**268**) are prepared by alkylation with the chloromethyl silyl ether, and with triethylamine as base. With the phenyltitanium reagent, clean 3,4-adduct (**269**) formation was seen ⟨92T5647⟩. With phenylmagnesium bromide a 1 : 1 mixture of the 3,4-dihydro derivative and its 3,6-dihydro isomer resulted ⟨88ACS(B)384⟩. The 3,4-adduct can be a substrate for the preparation of either a 1,4-disubstituted pyrimidinone, for example (**271**), or a 1,6-disubstituted pyrimidinone, for example (**274**). The latter is prepared by *N*-alkylation of the adduct (**269**), removal of the protecting group in (**272**) by fluoride ions and aromatization of (**273**) with manganese dioxide. 1,4-Disubstituted isomers (**271**) are prepared by manganese dioxide dehydrogenation of the adduct to form (**270**) with subsequent cleavage of the protecting group by fluoride ions and *N*1-alkylation.

Phenylethynylmagnesium iodide in reactions with the pyrimidinones gives a mixture of the isomeric 3,4- (**275**) and 3,6- (**277**) dihydro isomers in almost equimolar amounts (Scheme 44). The isomers can be separated by chromatography on alumina; dehydrogenation by MnO_2 gives the conjugated structures (**276**) and (**278**). Complete regiocontrol and formation of the 4-isomer can be achieved by the use of phenylethynyltriisopropoxytitanium ⟨85JOM(291)139⟩. The latter is prepared *in situ* by quenching the corresponding lithium derivative with triisopropoxytitanium chloride. The adduct formation is slow, and an excess of the titanium reagent has to be used to compensate for its partial decomposition. Manganese dioxide is used for dehydrogenation of the adducts to form the 4-alkynylpyrimidinones. Alkyne is substituted into the pyrimidine nucleus with regiochemical control using the corresponding titanium reagent ⟨88JOM(338)341⟩. The latter is generated from lithium acetylide by titanating with triisopropoxytitanium chloride at −80 °C. The 3,6-dihydro isomer (**277**) is formed. The reason for the reversal of the regiochemistry remains unclear; the reactions with both ethynyltitanium reagents were run at low temperature. With lithium acetylide, a mixture of the 3,6-dihydro isomer and its 3,4-dihydro isomer was formed in the ratio 4 : 1 ⟨85JOM(291)139⟩. With ethynylmagnesium bromide almost equimolar amounts of the isomers were formed ⟨88JOM(338)341⟩. The ethynyl derivatives are unstable on storage when there is no substitution on the terminal alkynic carbon. Aromatization of the dihydro derivatives is difficult to achieve because the dehydrogenated products are also unstable ⟨86ACS(B)381⟩. The nature of the 5-halogen substituent in the pyrimidinone may affect the reactivity, because of steric and inductive effects; the 5-chloro- and the 5-fluoro- derivatives, but not the 5-bromo-1-benzyl-2(1*H*)-pyrimidinone homologue, form adducts.

The aldol reaction in carbonyl compounds has its equivalents in π-electron deficient heterocycles. In the carbanion approach, lithiated acetophenone added rapidly and regioselectively to 1-substituted 2-pyrimidinones to form the 3,4-dihydro isomer (**279**) (Scheme 45) ⟨85ACS(B)195⟩. The adducts are readily oxidized to their aromatic equivalents (**280**) by DDQ. With the lithium enolate of mesityl oxide, however, equal amounts of the two dihydro isomers were formed ⟨88JOM(338)341⟩. In highly π-electron deficient heterocyclic systems, aldol reactions will also take place under the influence of acid catalysis such as in the addition of acetone to the pyrimidinone (**281**); the product is fully conjugated (**282**) after DDQ dehydrogenation ⟨79ACS(B)150⟩.

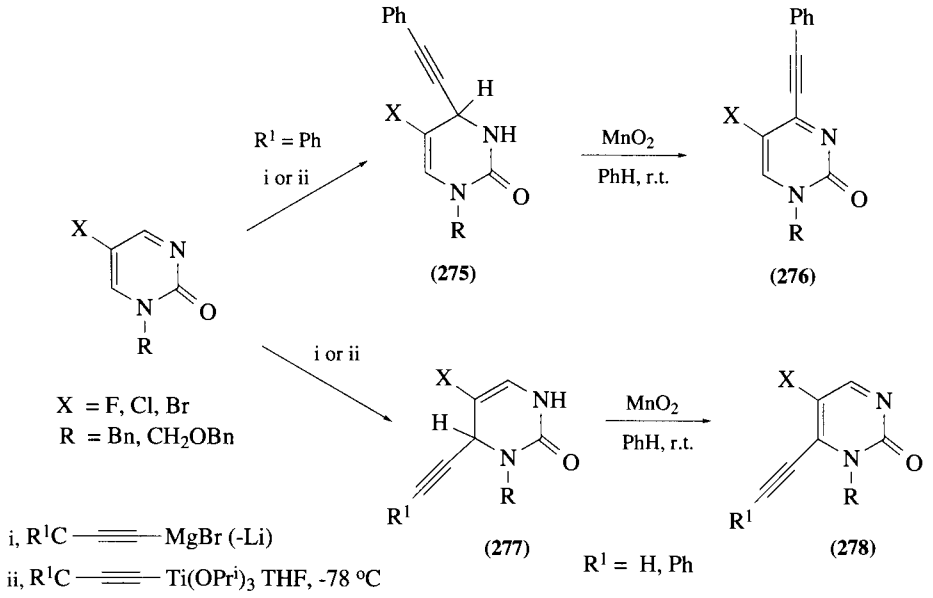


Scheme 43

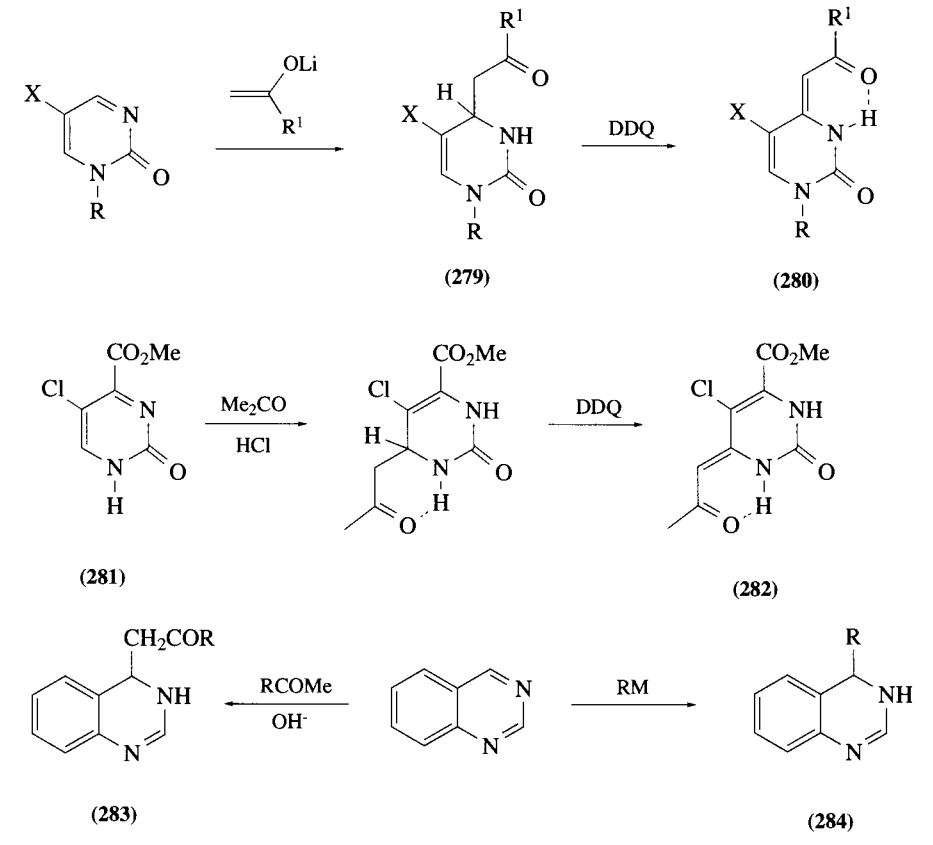
(i) Quinazolines

The high electrophilicity of the 4-position in quinazoline makes this position very reactive towards nucleophilic additions such as in alkylation by acetophenone, acetone, 2-butanone, or cyclohexanone, which all have been reported to add across the 3,4-double bond (**283**) (Scheme 45). Alkyl- and arylmagnesium halides and phenyllithium add similarly to give the corresponding 4-substituted 3,4-dihydroquinazolines (**284**) ⟨B-67MI 602-01⟩.

The favored course for the reaction between 1-methylperimidine and an alkyl- or aryllithium reagent involves addition across the imine-like double bond to give 2,3-dihydroperimidines. Metallation in the 2-position, as in imidazole, is only a minor pathway ⟨81RCR816⟩. Treatment of 1-methylperimidine with *n*-BuLi in THF at 0°C followed by propyl nitrate (a source of nitronium electrophile) gave the adduct while *t*-BuLi gave the cyclically conjugated perimidine after dehydrogenation of the adduct. With LDA in THF at −42°C, the products formed were consistent with radical anion intermediates ⟨88AJC139⟩.



Scheme 44



Scheme 45

6.02.5.6 Nucleophilic Attack at Hydrogen Attached to Carbon

6.02.5.6.1 Metallation in neutral rings by hydrogen substitution

Base-catalyzed hydrogen exchange involves proton abstraction by base to give a carbanion which is hydrogen bonded to the solvent. The generation of a carbanionic center adjacent to a neutral azine nitrogen is unfavored by charge repulsion by the nitrogen lone pair. Relative rates for base-catalyzed H–D exchange in pyrimidine have been quoted as $k_2 : k_4 : k_5 = 1.0 : 3.2 : 48.0$ ⟨69JA5501⟩. The relative high reactivity of the 5-position presumably arises from unfavorable juxtaposition of lone pairs for 2-, 4-, and 6-exchange; C5 is the only position not subject to the adjacent lone-pair effect. In pyrimidine *N*-oxide, the position α to the oxide function exchanges most readily, and at least 100 times as rapidly as in pyridine *N*-oxide, and C6 is 26 times as reactive as C2 which suffers the adjacent lone-pair effect, and both positions are less reactive than C2 of pyrazine *N*-oxide in 0.1 M NaOD. This confirms that the nonoxygenated nitrogen atom is much more effective in facilitating hydrogen exchange when it is *meta* to the exchanging position than when it is *para*.

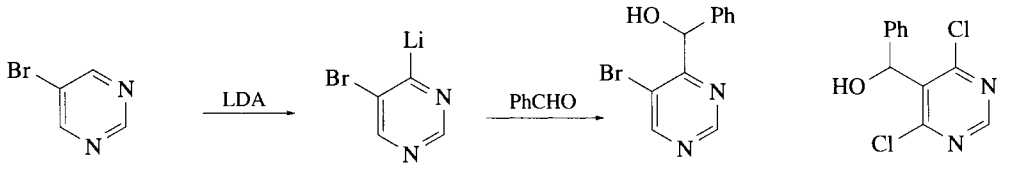
A linear relationship exists between log k_{H6} and σ_I for the 5-substituted pyrimidine *N*-oxides in 0.1 M NaOD (5H, Me, Br, OMe, NH_2), implying that the inductive effect of a substituent *ortho* to the exchanging proton is the controlling factor in the process. No such correlations hold for H2 exchange rates. In 1-methyl-4(1*H*)-pyrimidinone, exchange at C2 proceeds readily at a rate independent of the concentration of the base. The mechanism is rationalized as rate-limiting attack by OD^- on a cationic species to form an ylide intermediate. In uridine and cytidine, deuterium exchange occurs at C5 after initial attack at C6 by a nucleophile (D_2O or OD^-). When that nucleophile is able to abstract H6 to form a delocalized anion, some exchange at the 6-position is also observed ⟨90AHC(47)7⟩.

A problem to be avoided in the lithiation of pyrimidines is addition of the base to the azomethine (C=N) bond. The use of sterically hindered bases such as lithium tetramethylpiperidide (LiTMP) can often prevent this type of addition ⟨93AHC(56)155⟩. The azomethine addition is temperature dependent, enabling metallation reactions to be performed at low temperature. A substituent containing a heteroatom at C6 results in more efficient metallation at C5, whereas the presence of a 2-substituent also tends to increase the reaction efficiency, presumably by cutting down on alternative modes of reaction. Besides the nonnucleophilic LiTMP, LDA has frequently been used as base although BuLi can be used when the 2-position carries a substituent. Both 4- and 5-derivatives of pyrimidine can be prepared by this route ⟨93AHC(56)155⟩. This approach can be regarded as directed metallation, which is a powerful method for regioselective functionalization of aromatic and heteroaromatic compounds ⟨91AHC(52)187⟩. The following groups direct *ortho* metallation: halo, NHCOR, $NHCO_2R$, OR, $OCONR_2$, 2-oxazolino, CONHR, $CONR_2$, and masked RCHO, RCOR, and SO_2NR_2 groups. The directing groups have lone-pair electrons on heteroatoms which enable formation of coordination complexes with metal ions such as lithium, resulting in metallation at sites adjacent to the substituent. The carbanion can usually be masked or trapped as a more metalloid derivative, and be released in the presence of an electrophile. Trialkylsilane and trialkylstannane derivatives are most often used ⟨81T4069, 88G211⟩, for example in *ipso* substitution with acyl halides.

By fluoride-induced carbon–silicon bond cleavage from nonbasic silanes, low basic carbanionic species are generated which *in situ* add to a variety of electrophilic substrates including relatively acidic species such as enolizable aldehydes and ketones ⟨81T4069, 88G211⟩. Because the reaction appears to occur via a pentacoordinated organosilicon intermediate ⟨86JOC1745⟩, the free carbanion is never formed, and undesirable side-reactions are therefore minimized. Increased covalency of the carbon–metal bond, and hence decreased basicity of the carbanion, can also be achieved by transmetallation to more polarizable (softer) counterions, for example, copper ⟨75OR(22)253⟩.

Examples from halogen directed metallation include the lithiation of 5-bromopyrimidine by LDA (**285**), and the trapping of the lithiated species by benzaldehyde (the equilibrium shift procedure) with formation of the 4-substituted product (**286**) (Scheme 46) ⟨79JOC2081⟩. Similarly, the reaction between 4,6-dichloropyrimidine and benzaldehyde leads to product (**287**) in good yield ⟨86S886⟩. LiTMP Metallation of 2,4-dichloropyrimidine in THF/Et_2O at −100°C followed by acetaldehyde quench gave the 5-substituted (kinetic) product, whereas in THF/HMPA mixture at −70°C the corresponding 6-substituted (thermodynamic) derivative was formed in low yields: 11% and 16%, respectively. Minimum neglect of differential overlap (MNDO) calculations are in agreement with the observed results ⟨91JHC283⟩. From the use of alkoxy groups for directed metallation, reference is made to LiTMP metallation of 2,4-dimethoxypyrimidine followed by quenching with a variety of electrophiles which leads to variable yields of the 5-substituted products ⟨87H(26)585⟩. *Ortho*-directed

lithiation into the 5-position by a 4-methoxy group using LiTMP in THF at −75°C for 15 minutes, has been used for 5-substitution by trapping the lithiated species by TMS-Cl, MeI, PhCHO, or PhCOCl. Metallation can even be directed into the electrophilic 4-position by a 5-methoxy group; about 50% yield of trapped products were formed ⟨90JOC3410⟩.



(285) (286) (287)

Scheme 46

Related metallations of 6-chloro-2,4-dimethoxypyrimidine with *n*-BuLi have been used to prepare 5-TMS and 5-$SnMe_3$ derivatives ⟨88JOM(342)1⟩. The lithiation of 2-chloro-4-methoxypyrimidine by LiTMP at −70°C is directed into the 5-position ⟨92JHC467⟩. 5-Methoxy as well as 2,4-, 4,6-di-, and 2,4,6-tri-methoxypyrimidines have been lithiated under similar conditions (LiTMP/THF/−78°C) and reacted with electrophiles to form 4- and 5-substituted derivatives, respectively, in medium to high yields ⟨90JOC3410⟩. 5-Methylpyrimidine, which has no strongly directing group, gives the 6-lithiated species with LDA/Et_2O/−78°C, as evidenced by its reaction with benzophenone ⟨74TL2373⟩.

Pyrimidinones can also be C-metallated. Lithiation at the 6-position of uracils and related uridines and thymidines can be achieved with *n*-BuLi or LDA; the hydroxyl groups of the sugar are protected ⟨73BSF2715, 81CPB3565, 82T2635, 83CPB2164, 84TL3325, 85T861, 89MI 602-02⟩. Nonnucleoside derivatives of uracil and thymine have been metallated in a similar fashion ⟨89JMC2507, 91JMC1394, 91MI 602-02, 91YGK1142, 92JMC337⟩. When the 6-position in uridine nucleosides is blocked, lithiation can occur at the 5-position ⟨89MI 602-02⟩. With LDA, lithiation in the 6-position prevails. With *sec*-BuLi and TMEDA, however, lithiation is in the 5-position provided that the ribose or deoxyribose hydroxyl groups are protected by bulky groups such as the *t*-butyldimethylsilyl group ⟨87TL87, 89MI 602-02, 89TL2057, 90TL1295⟩. In contrast, the 4-ethoxy-β-*D*-arabinofuranosyl derivative has been 5-metallated using LDA at low temperature, and 6-lithiated at higher temperatures ⟨90TL1295⟩.

Little is known about metallation of reduced pyrimidines. 1,2- and 1,4-Dihydropyridines are metallated on the sp^2-carbon adjacent to the nitrogen to give α-lithio derivatives ⟨79OR(26)1, 82CRV223⟩. By analogy, *N*-tosyl-1,4,5,6-tetrahydropyrimidine gives the 2-lithio derivative with *n*-BuLi or LDA ⟨81LA103⟩. The lithiation is followed by ring opening and further reaction with the base, to give the dianionic species that is then able to add an electrophile at the metallated carbon ⟨91KGS798⟩.

(i) Perimidines

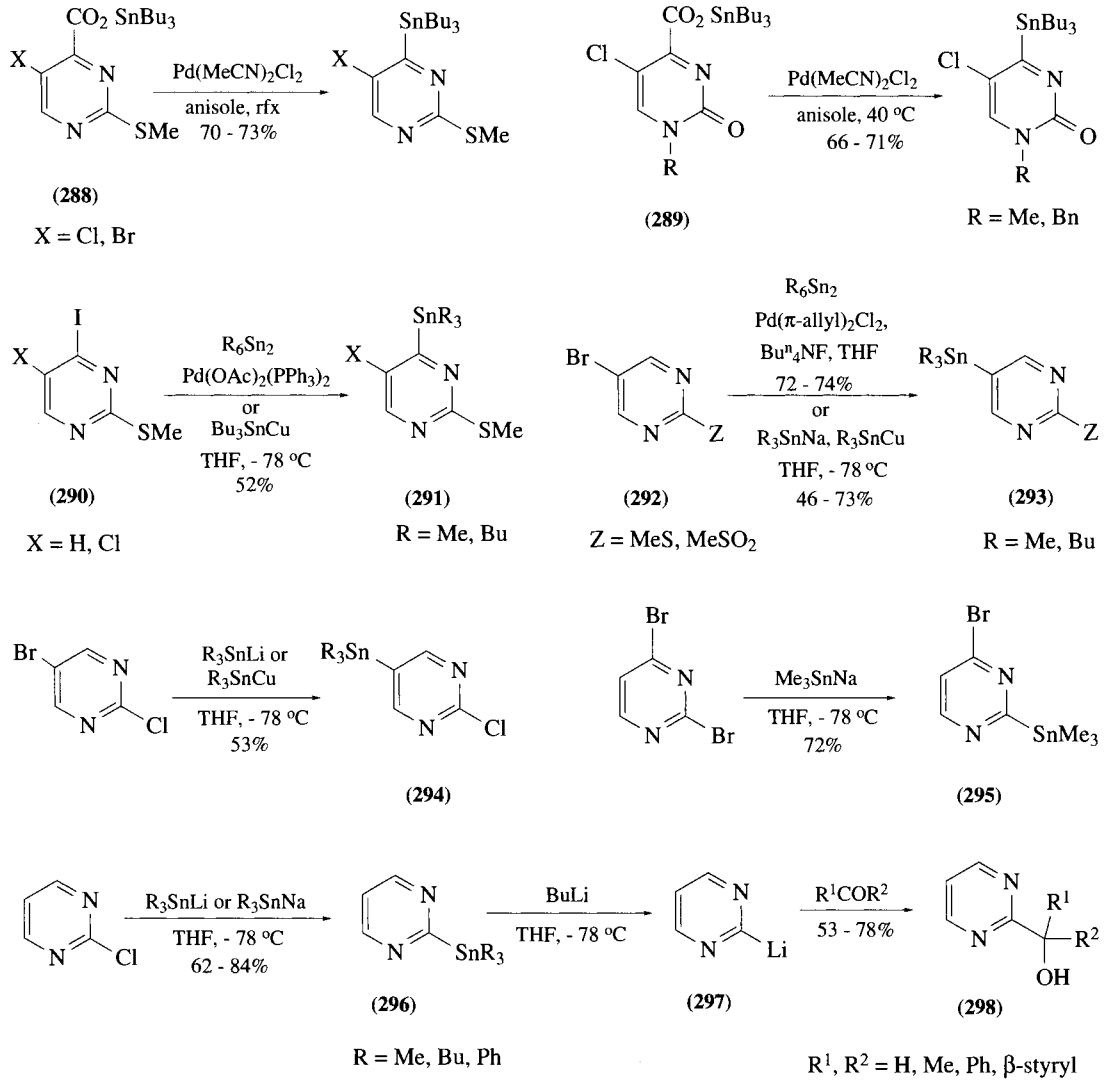
Lithiations of *N*-substituted perimidines so far have been restricted to the *N*-methyl derivative, which was found to undergo preferential addition across the imine double bond with alkyllithiums, and radical anion formation with LDA ⟨88AJC139⟩. Some C2 lithiation does occur, however, as indicated by the formation of an 8% yield of the 2-carboxylic acid after reaction with *n*-BuLi and carbon dioxide ⟨81RCR816⟩, and a 19% yield of bis(2-perimidinyl)carbinol after treatment with LDA and DMF ⟨88AJC139⟩.

6.02.5.6.2 Lithiation by halogen substitution

Halogen–metal exchange reactions ⟨51OR(6)339, B-87MI 602-02, B-88MI 602-01⟩ can be performed at temperatures as low as −100°C ⟨82ACR300⟩. Reaction occurs specifically at the halogenated carbon. Several 5-lithiated pyrimidines have been synthesized via halogen–metal exchange reactions with the analogous bromides ⟨85JOC841, 88ACS(B)455, 88ACS(B)530, 88JOM(342)1, 89ACS684⟩, and although this type of transformation has also been used to give 4-lithio derivatives ⟨56JA2136, 78JOC511, 85JOC841⟩, attempts at extending this reaction to the 2-isomeric system were unsuccessful ⟨65ACS1741⟩.

6.02.5.6.3 Stannylation by transmetallation and halogen–metal exchange reactions

Most stannanes are stable compounds which can be isolated and purified in the normal manner for organic compounds. Generally, stannylation is effected by a transmetallation reaction between an organostannyl chloride and a lithiated species. This method works well in the benzenoid position in pyrimidines. The metal–metal exchange is effected by quenching the lithiated species with a trialkylstannyl chloride ⟨88ACS(B)455, 89JCS(P1)255⟩. Stannylation in the electrophilic 4-position can be effected by thermal decarboxylation of a stannyl carboxylate such as (**288**) and (**289**) (Scheme 47). The reaction is promoted by Pd catalysis ⟨89T993⟩. Stannylation in the 4-position (**291**) can also be effected on the 4-iodopyrimidine (**290**) using hexaalkyldistannanes in the presence of fluoride ions and $Pd(OAc)_2(PPh_3)_2$ ⟨89T993⟩. Bis-(π-allyl)palladium chloride is the catalyst recommended for the coupling of 5-bromopyrimidines (**292**) with hexaalkyldistannanes to 5-stannanes. The presence of halide ions promotes the reaction, especially fluoride ions ⟨89ACS684⟩. The promoting effect is ascribed to the high affinity of fluoride ions for tin.



Scheme 47

Stannylation of (**290**) in the 4-position (**291**) and of (**292**) in the 5-position (**293**) can also be effected by stannyllithium, -sodium or -copper reagents in reactions run at −78 °C.

5-Bromo-2-chloropyrimidine is selectively stannylated in the 5-position (**294**) using stannyllithium or -copper reagents. The reaction of 2,4-dibromopyrimidine with trimethylstannylsodium results in

regioselective substitution in the 2-position to furnish 4-bromo-2-trimethylstannylpyrimidine (**295**), whereas reactions with the corresponding stannyllithium reagent failed ⟨94T275⟩.

The regiochemistry is not in accord with the relative reactivity of pyrimidines towards nucleophiles ⟨94T275⟩. In the 2-position, 2-chloropyrimidine is stannylated (**296**) by tributyl-, by trimethyl- or by triphenylstannyllithium ⟨94T275⟩. Direct stannylation in the 4-position has not been successful. 4-Iodo-2-methylthiopyrimidine has been stannylated by way of lithiation followed by quenching with a stannyl chloride. However, attempts to lithiate 2-chloro-, 2-bromo-, or 2-iodopyrimidine met with little success; adduct formation by addition of lithiated species to electrophilic pyrimidine positions is a major side-reaction. 2-Lithiopyrimidine (**297**), however, is formed selectively by reversing the order of metal exchange, i.e., a 2-stannylpyrimidine reacts with butyllithium giving metal–metal exchange to form 2-lithiopyrimidine; the transfer is confirmed by aldol reactions (**298**) with carbonyl compounds ⟨94T275⟩.

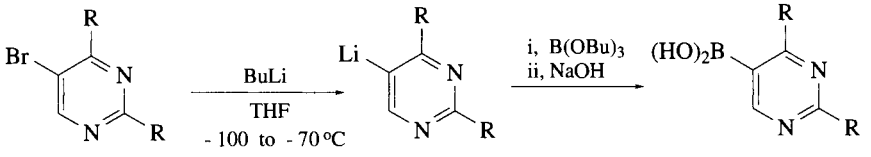
6.02.5.6.4 Zincation by transmetallation and halogen–metal exchange reactions

In general, zinc reagents are prepared by a transmetallation reaction of aryllithium or arylmagnesium halides with zinc halides at low temperature (−78 °C). The same approach can be used for heteroarenes in the absence of incompatible substituents, but has been little applied to pyrimidines.

The direct synthesis of arylzinc halides from the halide and activated zinc ⟨90TL4413, 91JOC1445⟩ can also be applied to heteroaromatic systems, (e.g. bromo- and iodopyridines). In the electrophilic pyrimidine 2-position zincation and coupling of the iodo derivative took place to the extent of 26% ⟨93T9713⟩.

6.02.5.6.5 Boronation by transmetallation

Pyrimidines lithiated in the 5-position can be boronated (**299**) (Scheme 48). The halogen–metal exchange between 5-bromopyrimidine and butyllithium has to be carried out at low temperature (−100 °C) to avoid 1 : 1-adduct formation with the lithiated species. The 2,4-di-*t*-butoxy analogue, however, can be lithiated in the normal manner at −78 °C. Boronation results from addition of tributyl borate with subsequent hydrolysis ⟨90JHC2165⟩.



(**299**)

R = H, Bu^{t}O

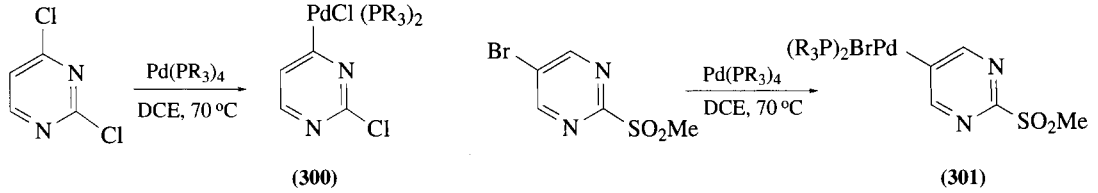
Scheme 48

6.02.5.6.6 Mercuration by hydrogen substitution

Organomercurials are available by electrophilic substitution reactions in appropriate substrates or by metal–metal exchange reactions. Most of the studies of azine mercurials have been in the field of nucleosides, especially on carbosubstitution of mercurials in the 5-position in pyrimidine nucleosides derived from uracil and cytidine. Pyrimidine nucleosides are readily attacked by electrophiles such as Hg(II) acetate in the pyrimidine 5-position. The acetate is used for solubility reasons, but is often changed to a halide before coupling reactions ⟨84TL2431⟩.

6.02.5.6.7 Palladation by oxidative insertion

The oxidative palladium 1 : 1-insertion complex intermediates (**300**) and (**301**) in the coupling reaction between 2,4-dichloropyrimidine, or 5-bromo-2-methanesulfonylpyrimidine, and tetrakis(triphenylphosphine)- or tetrakis(triisopropyl phosphite)-palladium can be isolated and purified by conventional methods (Scheme 49). The regioselectivity of the insertion reaction in 2,4-dichloropyrimidine is in accord with the 4-regiochemistry in coupling reactions (Section 6.02.5.5.4). The palladized pyrimidines react readily with organnostannnanes, and may serve as catalysts in coupling reactions between the respective pyrimidine precursor and stannanes ⟨90ACS927⟩.



(300) (301)

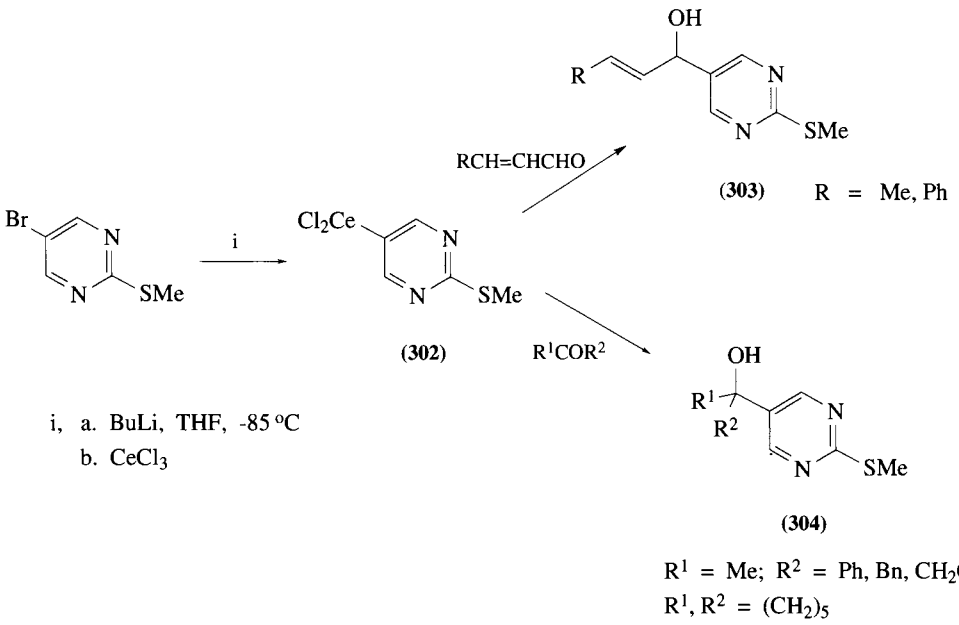
Scheme 49

6.02.5.6.8 Cupration

Cupration is well established in pyridines ⟨86T3981, 87CS519⟩, and can be expected to be applicable to reactions in pyrimidines.

6.02.5.6.9 Cerium derivatives by transmetallation reactions

Organocerium derivatives posses low basicity. 5-Pyrimidinylcerium dichlorides (**302**) are available by low-temperature metal–metal exchange using cerium trichloride and 5-lithiated pyrimidines (Scheme 50). The 5-pyrimidinylcerium dichloride was superior to its 5-lithio analogue in reactions with aldehydes and ketones, especially in reactions with enolizable aldehydes and ketones (**304**), and in the 1,2-addition to $\alpha\beta$-unsaturated carbonyl derivatives (**303**) ⟨89ACS816⟩.



Scheme 50

6.02.5.7 Reduced Pyrimidines by Reductive Procedures

Besides reductive reactions on pyrimidines, ring cyclization methods provide access to reduced forms of pyrimidines and congeners.

6.02.5.7.1 Dihydropyrimidines by catalytic hydrogenation

There are five dihydropyrimidines. The 1,4- and the 1,6-dihydropyrimidines can readily interconvert by tautomerism because of the mobile NH proton. The common metals to effect hydrogenation can be used ⟨B-94MI 602-01⟩. Platinum has been the catalyst of choice for the reduction of the 5,6-double bond of uracils, for example, in the addition of deuterium to uracil to produce [5,6-$^2H_2$]5,6-dihydrouracil. But in the reduction of 2(1*H*)-pyrimidinone and its *N*-methyl derivative it is the 1,6-dihydro derivatives which are formed. The addition of hydrogen to the 5,6-bond of thymidine and other 5-substituted uridines is stereospecific with rhodium-on-alumina as catalyst. Rhodium-on-charcoal has been useful for hydrogenation of the 5,6-double bond in uracils, uridine, and isocytosine. Raney nickel readily promotes saturation of the 5,6-double bond. Thio derivatives may either be dethiated or taken further to reduced forms by Raney nickel catalysts ⟨B-94MI 602-01⟩.

6.02.5.7.2 Dihydro- and tetrahydropyrimidines by metal hydride reductions

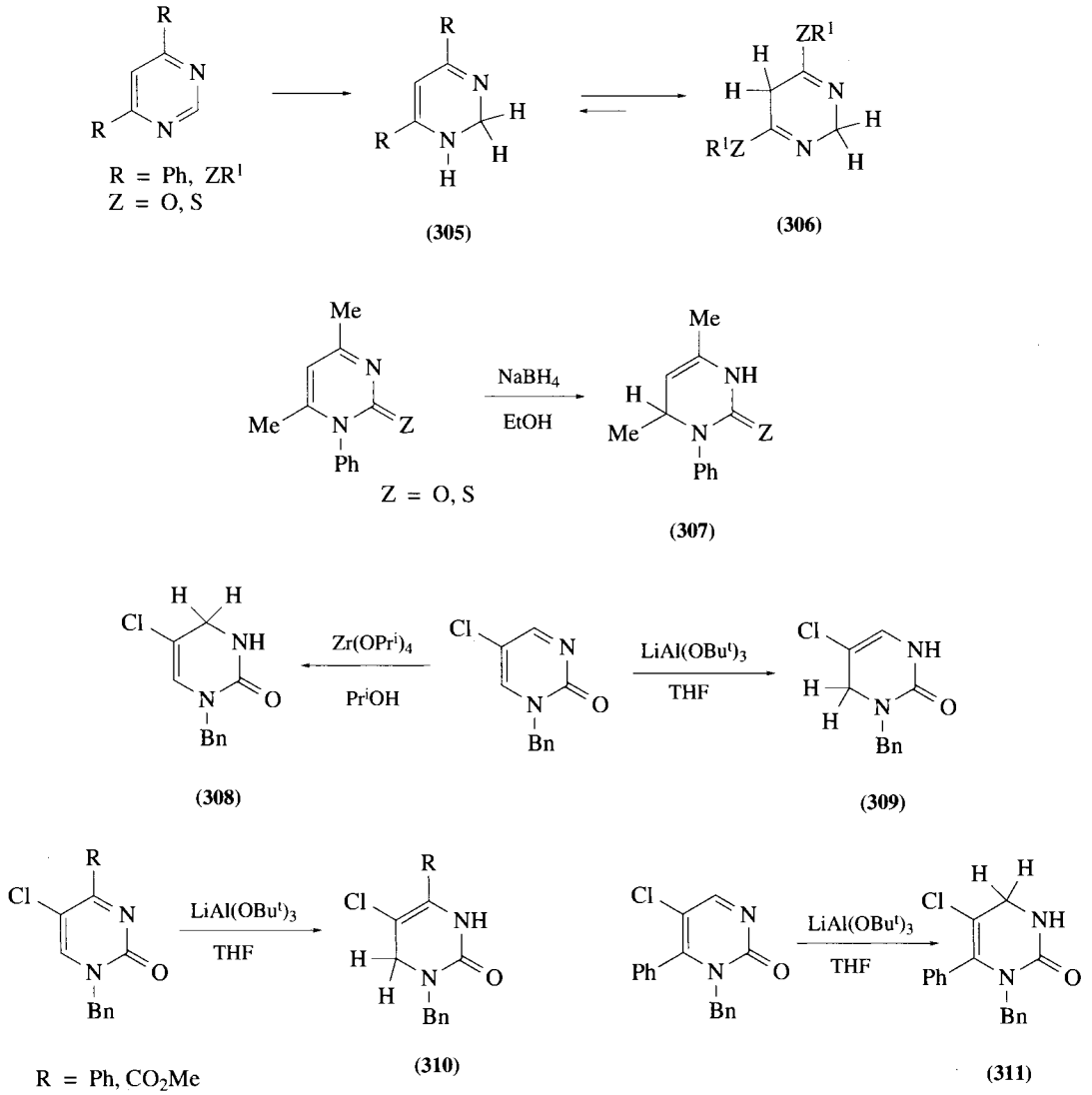
(i) Dihydro derivatives

Metal hydrides transfer the hydride ion to electrophilic centers, and hence the π-deficiency or polarization of the pyrimidine ring determines its reactivity towards metal hydrides. Thus $NaBH_4$ does not reduce pyrimidine and simple alkyl derivatives, but readily reduces their methiodides. The stronger reducing agent LAH, however, will reduce pyrimidine. In general, electron-withdrawing substituents promote reduction of the ring, while electron-releasing substituents have the opposite effect. The metal hydride may act as a base and abstract a proton from the α-position in a substituent, in which case the anionic substrate may resist reduction in the ring ⟨B-94MI 602-01⟩. 4,6-Diphenylpyrimidine is attacked by LAH in the vacant 2-position with formation of the 1,2-dihydro derivative (**305**), which in solution exhibits enamine–imine tautomerism (Scheme 51). 2-Phenylpyrimidine is reduced in the electrophilic 4-position. With alkoxy or alkylthio groups in the 4- and 6-positions, reduction with LAH gives the 1,2-dihydro derivatives (**305**) which tautomerize to the more stable 2,5-isomers (**306**) ⟨85H(23)1077, 86JOC4623⟩.

The polarized pyrimidinones are readily reduced. 4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone and its sulfur analogue react with $NaBH_4$ in ethanol to form the 3,6-dihydro derivatives (**307**). In methanol, coformation of the 3,4-dihydro isomer and the 3,4,5,6-tetrahydro derivative of the oxopyrimidine was seen ⟨81JCS(P1)1622⟩. In acetic acid, where the borohydride reagent is converted into the more powerful sodium acetoxyborohydride reducing agent, the reaction tended towards tetrahydro derivatives. LAH gave a mixture of dihydro and tetrahydro products.

With lithium tris(*t*-butoxy)aluminum hydride, reduction of 1-benzyl-5-chloro-2(1*H*)-pyrimidinone gave a mixture of the 3,4- (**308**) and 3,6-dihydro (**309**) isomers in the ratio 1 : 9, respectively ⟨85ACS(B)195⟩. The 3,4-isomer (**308**) is obtained exclusively by a zirconate-catalyzed Meerwein–Ponndorf–Verley reduction ⟨86JCS(P1)849⟩. Tetra-isopropoxyzirconium shows high functional group selectivity resulting from both steric and electronic effects. The reaction is relatively slow, but is promoted by an electron-withdrawing substituent in the 5-position. Triisopropoxyaluminum reacts less readily. Both the zirconium and the aluminum reagents add 1,2 to α,β-unsaturated carbonyl derivatives, which in an α,β-unsaturated imine model would correspond to the observed preference for the formation of the 3,4-dihydropyrimidine.

With a conjugative phenyl or methoxycarbonyl substituent in the 4-position, the 3,6-dihydro isomer (**310**) results. The 3,4-dihydro isomer (**311**), which is formed from the cyclically conjugated 6-phenyl derivative, has the double bond of the ring conjugated with the phenyl substituent ⟨85ACS(B)195⟩.

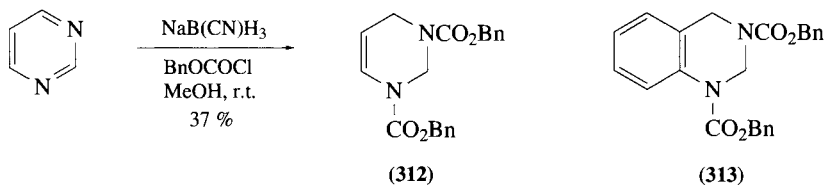


Scheme 51

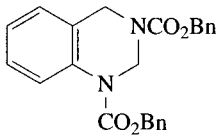
The 5,6-double bond in *N*1,*N*3-dialkylated uracils is specifically reduced by L-selectride. Both a 5-fluoro and a 5-ethynyl substituent were retained in the reduced product ⟨57JA4559⟩.

(ii) Tetrahydro derivatives

Reduction of pyrimidine or quinazoline by $NaB(CN)H_3$ in methanol, with concurrent trapping of the reduced forms by benzyl chloroformate, gives the diacylated tetrahydro derivatives, the pyrimidine enamine (**312**) and the quinazoline (**313**) from pyrimidine and quinazoline, respectively (Equation (15)) ⟨92JCS(P1)409⟩.



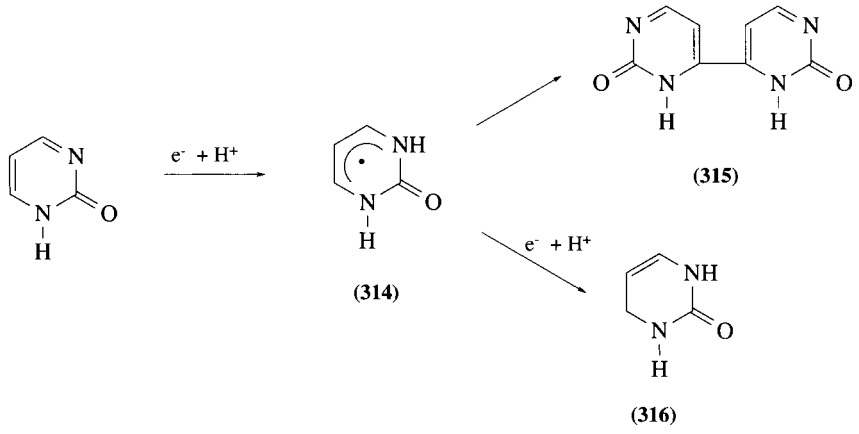
(15)



(313)

6.02.5.7.3 Dihydropyrimidines by electrochemical reduction

The behavior of pyrimidine during polarographic reduction depends on the pH of the aqueous solution. In acidic solution two one-electron waves are observed, while in neutral solution two two-electron waves result. In alkaline solution a four-electron reduction is effected via 1,6-dihydropyrimidine to give tetrahydropyrimidine ⟨84AHC(36)235⟩. The pathway for electrochemical reduction of 2(1*H*)-pyrimidinone involves initial addition of one electron and one proton to form a resonance stabilized radical (**314**) which can dimerize (**315**) or accept a second electron and proton to form a dihydro derivative (**316**) (Scheme 52). *N*- or *C*-Substitution in the pyrimidinone may favor one or the other pathway ⟨86TCC133⟩. Cytosine in solution undergoes a 3-electron reduction with elimination of ammonia to form 2(1*H*)-pyrimidinone which is reduced further as discussed above. 2(1*H*)-Pyrimidinethione, together with its 4,6-dimethyl and 1,4,6-trimethyl derivatives, are reduced to dimers as above ⟨B-94MI 602-01⟩.



(315)

(314)

(316)

Scheme 52

6.02.5.7.4 Dihydropyrimidines by adduct formation with organometallics

Addition of organometallics across the polarized 3,4-double bond leading to dihydro formation has been discussed in the section on alkylation reactions (Section 6.02.5.5.15).

6.02.5.7.5 Dihydropyrimidines by photochemical adduct formation

Formation of cyclobutane photodimeric products in which the pyrimidine ring has attained the dihydro level of reduction is treated in Section 6.02.5.8.1.

6.02.5.7.6 Dihydropyrimidines by adduct formation with N*-nucleophiles*

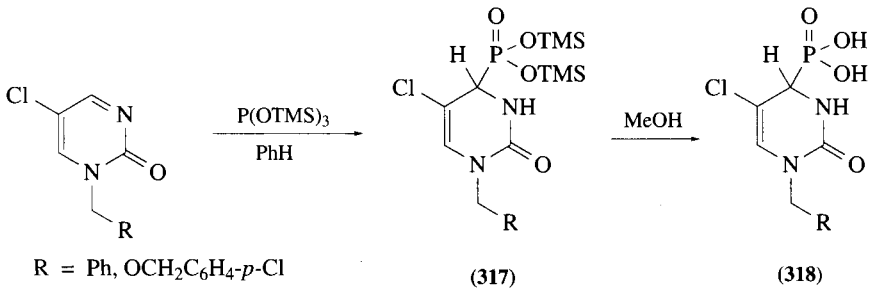
Amination by the Chichibabin reaction, which involves a dihydro intermediate, is discussed in the section on amination (Section 6.02.5.4.2).

Ammonia itself adds across the *N*1—*C*6 azomethine bond in highly electrophilic pyrimidines, for example, in 5-nitropyrimidine or quaternized pyrimidines. Other nucleophiles for additions are the

azide ion, amidines, guanidines, and thioureas. Isolation of products may be difficult because the adducts readily undergo ring-opening reactions ⟨82JOC1077, 90JCS(P1)123⟩. Another addend is hydroxylamine, which will add to cytosines with replacement of the amino or imino group besides addition of a second molecule across the 5,6-enamine bond ⟨80JHC29⟩. The additions are reversible. Adducts to the 5,6-bond in uracils are relatively stable when the uracil carries an electron-withdrawing substituent at C5 ⟨87JCS(P1)261⟩.

6.02.5.7.7 Dihydropyrimidines by adduct formation with P*-nucleophiles*

With tris(trimethylsilyl)phosphite, regiospecific and irreversible adduct formation with 2(1*H*)-pyrimidinones gives 3,4-dihydro-4-phosphonic acid silyl esters (**317**) which furnish the phosphonic acid (**318**) on treatment with methanol (Scheme 53). The regiochemistry is attributed to the bulkiness of the phosphite reagent. The carbon–phosphorus bond resisted cleavage by TFA ⟨87ACS(B)448⟩.



R = Ph, $OCH_2C_6H_4$-*p*-Cl (**317**) (**318**)

Scheme 53

6.02.5.7.8 Dihydropyrimidines by adduct formation with O*-nucleophiles*

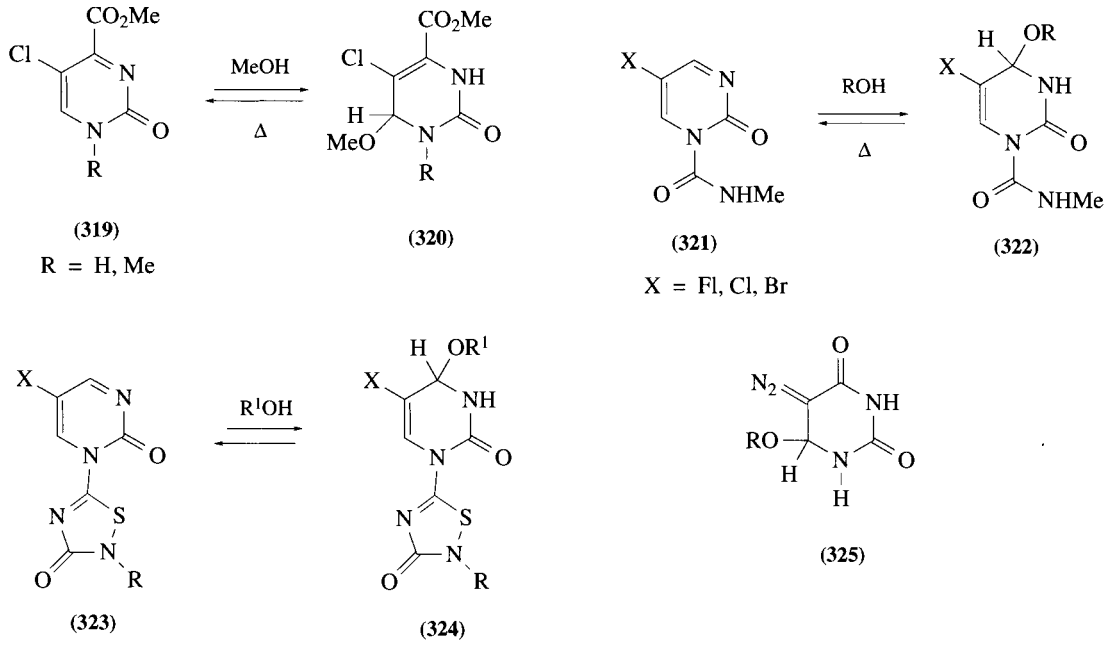
Adduct formation with oxygen nucleophiles is reversible, and the products can normally be isolated only if there is a strongly electron-withdrawing substituent in the ring. 5-Nitro-, 5-methylsulfonyl-, and 5-sulfinylpyrimidines in aqueous acid exist as hydrated cations ⟨B-94MI 602-01⟩. The polarized pyrimidinones form adducts reversibly with water or alcohols. 5-Chloro-2(1*H*)-pyrimidinone with a further activating carboxylic ester group in the 4-position (**319**) adds methanol in the vacant 6-position (Scheme 54). The adduct (**320**) is isolable but loses methanol on heating ⟨79ACS(B)150⟩. *N*1-Carbamoyl derivatives of 5-halo-2(1*H*)-pyrimidinones (**321**) also form adducts with water and lower alcohols. The oxygen is bonded exclusively at C4 (**322**), and the alcoholates can be isolated; the alcohol is lost on heating ⟨B-89MI 602-01⟩.

The electron-withdrawing power of *N*1 can be further increased by simple *N*-acylation, but the product is unstable. A similar effect is observed by using a strongly π-deficient heterocycle which itself is not involved in adduct formation. The *N*1-attached 1,2,4-thiadiazole derivatives (**323**) fulfil the criterion: the pyrimidine is completely hydrated as the 3,4-dihydro derivative (**324**). Dehydration proved difficult, but on heating in water or a simple alcohol, exchange of the solvent molecule in the adduct took place ⟨88ACS(B)362⟩.

5-Diazouracil forms a 1,6-dihydro hydrate in water, and a methanolate (**325**) in methanol ⟨81LA1429⟩.

6.02.5.7.9 Dihydropyrimidines by adduct formation with S*-nucleophiles*

The thiol nucleophile, as an anion, adds reversibly to π-deficient pyrimidines (Scheme 55). The percentage of adduct in solution, or the stability of the adducts, increases with the presence of electron-withdrawing substituents in the heterocycle. A ^{1}H NMR study on the equilibrium between 2(1*H*)-pyrimidinones and sodium 2-thiolethanesulfonate and their adducts in aqueous dioxane, showed no adduct for the parent compound (**326**; $R^1 = R^2 = X = H$), 93% adduct for the 5-chloro derivative (**326**; $R^1 = R^2 = H$, $X = Cl$), whereas the 4-carboxylic acid ester (**326**; $R^1 = H$, $R^2 = CO_2Me$, $X = Cl$), was all present as adduct. 35% of *N*-Benzyl-2(1*H*)-pyrimidinone (**326**; $R^1 = Bn$, $R^2 = X = H$) was in the adduct form, whereas the *N*-substituted 5-halo derivatives (**319**)



Scheme 54

were all present as adducts. Both the 3,4-(**327**) and 3,6-dihydro (**328**) isomers were formed from vacant 4/6-positions in slightly variable ratios within the range 40–60% of each isomer. The adduct formation with sodium 2-thiolethanesulfonate represents a way of solubilizing these lactams, which otherwise show low water solubility. The parent pyrimidinone is precipitated from an aqueous solution of the adduct by bubbling air through the solution, which oxidizes the liberated thiol to the disulfide ⟨89ACS489⟩.

Reversible addition of β-thiolethanol to the 5,6-bond in 1,3-dimethyl-5-nitrouracil shows 76% of the 6-adduct in the equilibrium in solution. In 5-halo-uracils and -uridines, adduct formation with thiols, including cysteine, may be accompanied by subsequent dehalogenation, as was also the case for bisulfite adducts ⟨B-94MI 602-01⟩.

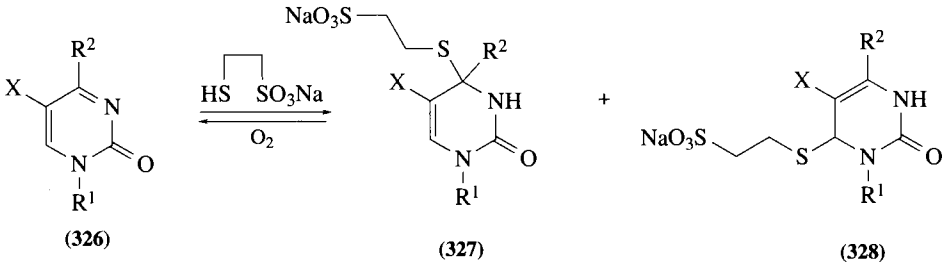
The bisulfite adducts of electrophilic pyrimidines are relatively stable, and several have been isolated. Thus, *N*-substituted 5-chloro-2(1*H*)-pyrimidinones readily form bisulfite adducts in aqueous solution. Both the 3,4- (**329**) and the 3,6-bisulfite (**330**) adducts are formed, with the former as the predominant isomer. In water, the 3,4-isomer was significantly less soluble and was precipitated selectively from concentrated solutions. Solubilization in more dilute aqueous solution, and addition of TFA, precipitates the parent heterocycle ⟨87ACS(B)448, 91ACS177⟩.

The 5,6-double bond in uracil, 5-fluorouracil, *N*-alkyluracils, thiouracils, and uridines is involved in adduct formation with sodium sulfite or bisulfite to give the corresponding 5,6-dihydro- 6-sulfonic acid salts. Bisulfite addition to cytosines and cytidine may be succeeded by a second reaction involving nucleophilic replacement of the amino group, for example, by water ⟨B-94MI 602-01⟩.

6.02.5.8 Cycloaddition Reactions

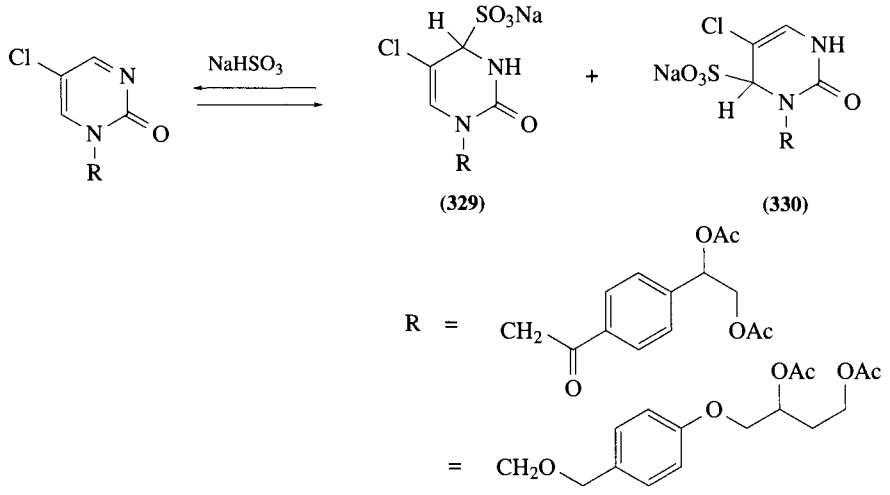
6.02.5.8.1 Photodimerization

Uracil and thymine, their 5- and/or 6-substituted derivatives, *N*-alkyl derivatives and their nucleosides and nucleotides, are dimerized in solution when irradiated by UV in the range 200–300 nm to yield cyclobutane dimers ⟨B-94MI 602-01⟩. This reaction also occurs in living tissue between adjacent thymine residues in each polynucleotide to form cyclobutane-type dimers, which are mutagenic, carcinogenic, and lethal in a variety of organisms. Photolyases repair damaged DNA by utilizing the energy of near-UV or visible light (300–500 nm) to cleave the cyclobutane ring of the dimer ⟨94JA3115⟩.



(326) (327) (328)

R^1 = H, Bn, CH_2ZPh, Z = O, S
R^2 = H, CO_2Me
X = H, F, Cl, Br



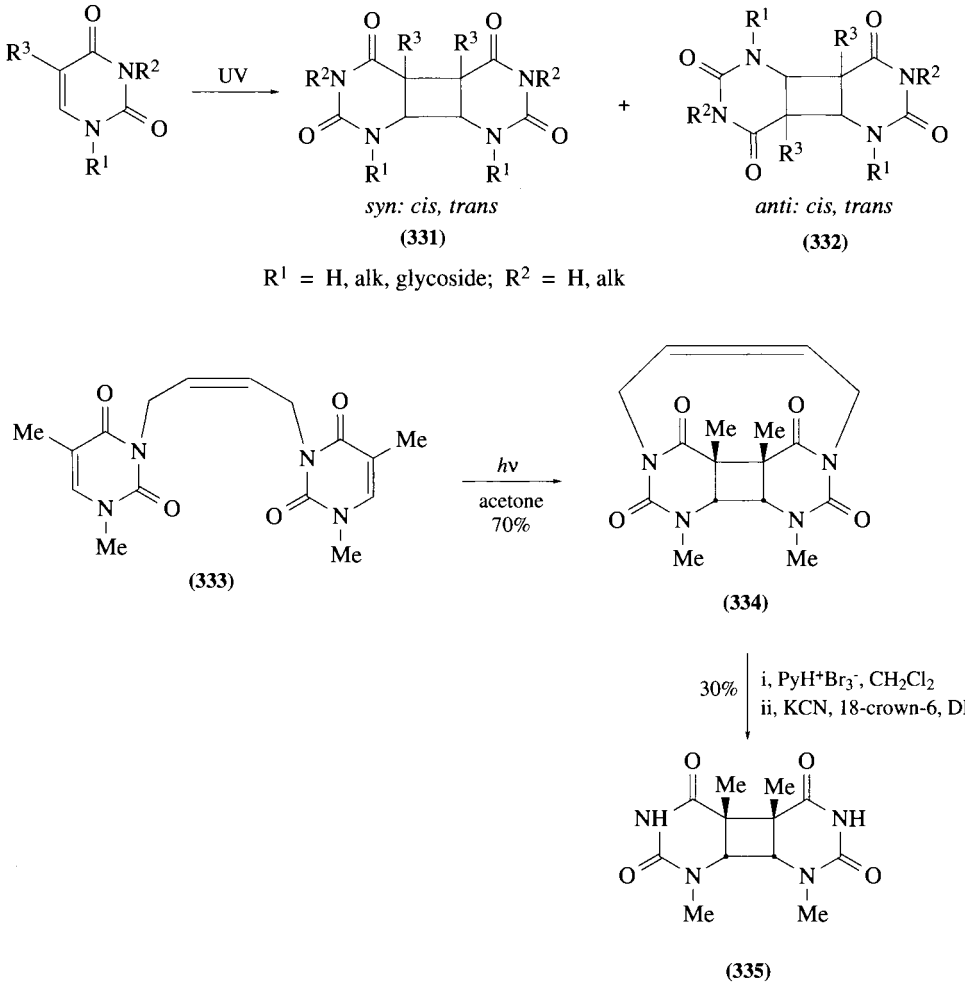
(329) (330)

Scheme 55

In the dimerization of uracils two regioisomers are formed in which the pyrimidine rings can be regarded as parallel or antiparallel, and which are referred to as *syn* (**331**) or *anti* (**332**), respectively (Scheme 56). Each regioisomer can have a *cis* or *trans* form in which the pyrimidine rings are on the same or on the opposite side of the cyclobutane plane. Preparation and isolation of a desired isomer may be complicated since several isomeric photodimers are generally formed, as in the irradiation of 1,3-dimethyluracil in acetonitrile, when the *cis–syn* (25%), *cis–anti* (61%), *trans–syn* (6%), and *trans–anti* (9%) stereoisomers were formed. All routes for the preparation of *cis–syn* dinucleotide photodimer rely on a photochemical reaction to form the cyclobutane. An efficient route for the preparation of a *cis–syn* isomer (**335**) has led to the use of a cleavable linker between *N*3 and *N*′3 to control the stereochemistry of the pyrimidine during photodimerization. UV irradiation of the bridged thymine (**333**) under acetone-sensitized photodimerization conditions gives exclusively the *cis–syn* photodimer (**334**). The double bond in the linker is brominated, and the photodimer deblocked, by heating the dibromide with KCN/18-crown-6 in DMF, which corresponds to a double retro-Michael addition after cyanide substitution ⟨92TL2133⟩.

6.02.5.8.2 Photocycloadditions across the 5,6-positions

The 5,6-double bond in uracils is involved in several [2 + 2] photochemical reactions. The cyclooctapyrimidine-2,4-dione (**338**) is formed by photocycloaddition of the *N*-substituted 6-chlorouracil (**336**) to benzenes in the presence of an acid, preferably TFA (Scheme 57). The reaction is assumed to proceed by *ortho*-addition, with a cyclobutane (**337**) as intermediate. Without acid, 6-phenyluracil is formed in low yield. In toluene as solvent and participating reagent, a regioisomeric mixture with the methyl group in the 6-, 7-, 8-, or 10-position was formed. In fluorobenzene, all of the regioisomers



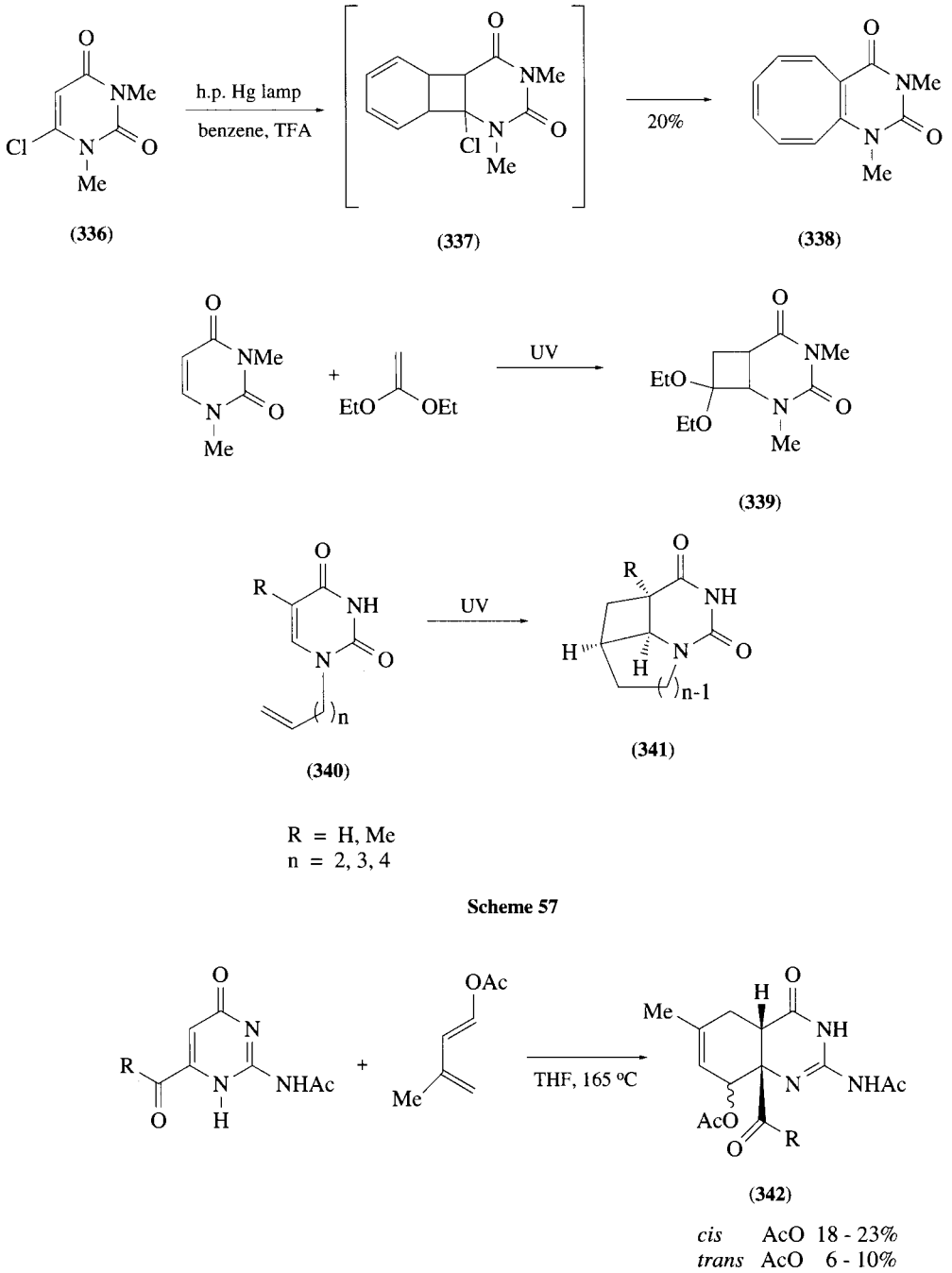
Scheme 56

except the 10-fluoro isomer were seen. In anisole the 5-methoxy isomer was obtained in low yield ⟨93CPB239⟩. Alkenes and alkynes form adducts on irradiation ⟨83JOC2337⟩. Ketene diethyl acetal has been added to 1,3-dimethyluracil to form the *cis*- and *trans*-cyclobutane adducts (**339**), in 6 : 1 ratio ⟨74JA4885⟩. Photolysis of 5-styryl-1,3-dimethyluracil with substituted alkenes led to selective additions to the 5,6-double bond with cyclobutane formation ⟨87CL45⟩. Intramolecular [2 + 2] photocycloadditions of uracil or thymine *N*1-tethered to an ω-alkene (**340**) give diazatricyclodiones (**341**). The structural assignment of the product from the butenyl derivative of uracil has been verified by x-ray as (**341**; R = H, $n = 2$) ⟨90H(31)1737⟩.

6.02.5.9 Thermal Cyclizations

6.02.5.9.1 Cycloadditions across the 5,6-positions

The 5,6-double bond in activated pyrimidines can participate in [4 + 2] cyclization reactions (Equation (16)). Diels–Alder reactions between 1-acetoxy-3-methylbutadiene and 2-acylamino-6-acetyl-4(1*H*)-pyrimidinones yield hydroquinazolines (**342**). The yields are modest, but the regiochemistry is clean. The major stereoisomer has the acetoxy and the acyl groups *cis*, the minor has the *trans* relationship. With 1,3-butadiene and with isoprene the cycloadducts were formed in low yields, and isoprene gave a mixture of the methyl regioisomers ⟨83JOC3627⟩.



(336) (337) (338) (339) (340) (341)

R = H, Me
n = 2, 3, 4

Scheme 57

(342)

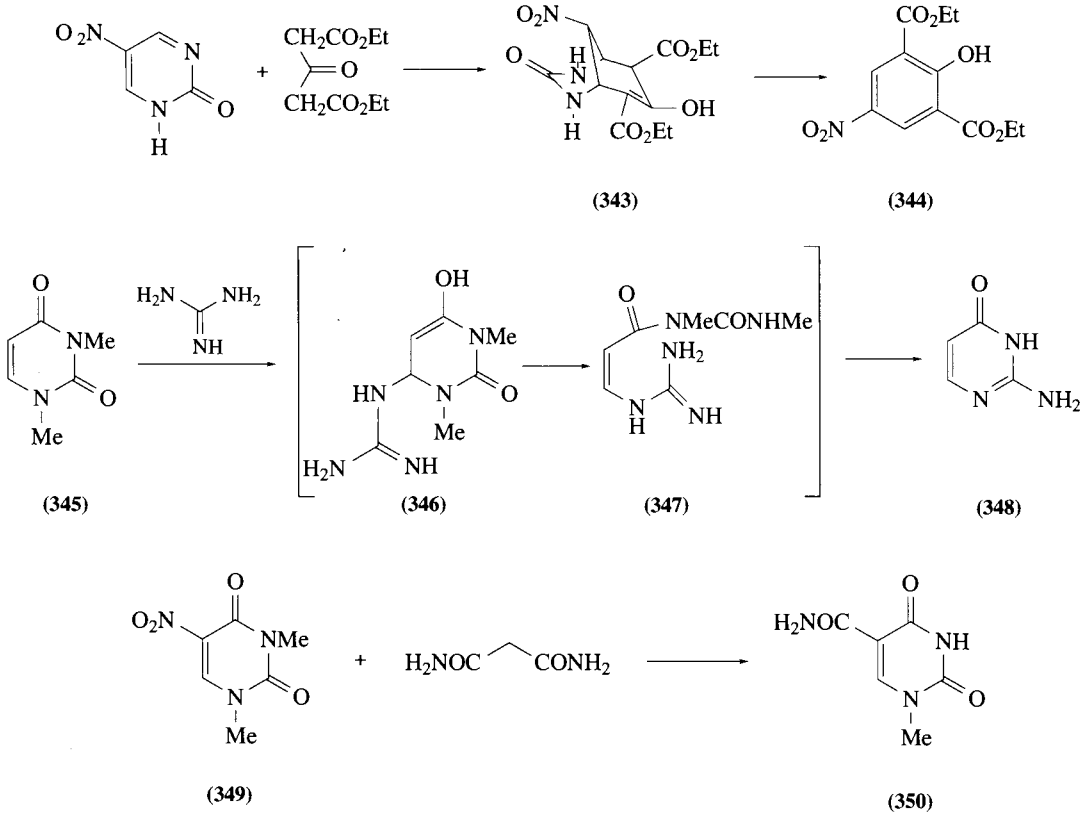
cis AcO 18 - 23%
trans AcO 6 - 10%

(16)

6.02.5.9.2 Cycloadditions across the 4,6-positions

meta-Bridging cyclization of azines with bifunctional nucleophiles usually occurs in two steps ⟨88AHC(43)301⟩. Transformation of 5-nitropyrimidin-2-ones into nitrophenols (**344**) by β-dicarbonyl compounds proceeds via the bicyclic *meta*-bridged intermediate (**343**) (Scheme 58) ⟨82JOC1018⟩, and so do corresponding reactions with phenylacetamidine with formation of 2-amino-3-phenyl-5-nitropyridine ⟨83JOC2667⟩. This reaction path, or a path involving an open structure as in ANRORC-type reactions, may be involved in the reaction between the uracil (**345**) and guanidine. The N1—C—N3 part of the uracil is replaced by the N—C—N part of the 1,3-dinucleophilic reagent to form the new pyrimidine (**348**). The transformation involves initial adduct formation (**346**) and an open-chain intermediate (**347**) ⟨83JCS(P1)1293, 84H(21)289, 84JCS(P1)1859, 84JHC1543, 85JOC1512⟩. The

use of bifunctional nucleophiles may be useful, as in the reaction between the 5-nitrouracil (**349**) with malonamide which forms the 5-carboxamide (**350**) with formal loss of the N3 substituent ⟨84JCS(P1)1859⟩, and in transformations of the pyrimidine ring in nucleosides ⟨84H(21)289⟩.



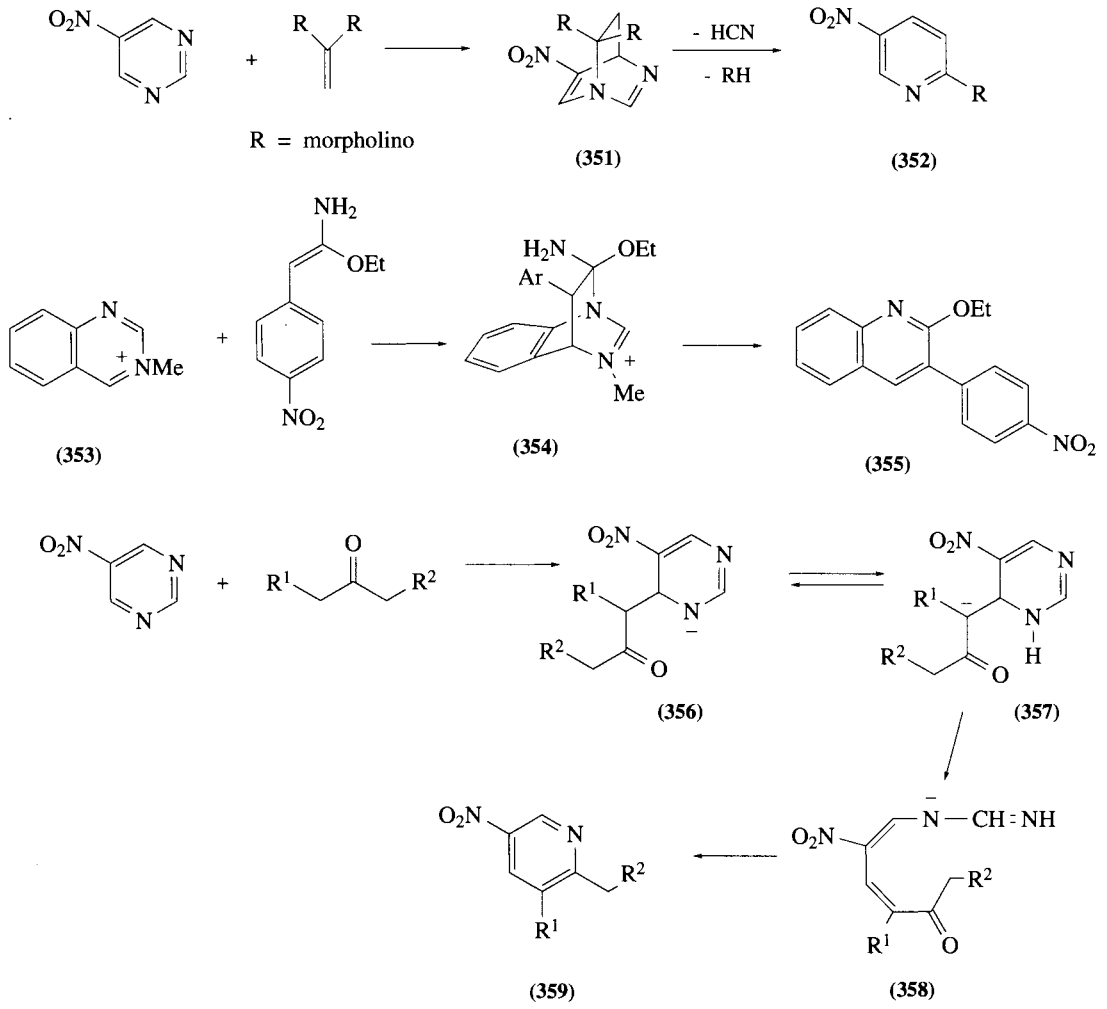
Scheme 58

6.02.5.9.3 Cycloadditions across the 1,4-positions

In *para*-additions the pyrimidine reacts as an azadiene in Diels–Alder type reactions with enamines (Scheme 59) ⟨83JOC2667⟩. The pyrimidine is activated by a 5-nitro group and participates in a Diels–Alder reaction with 1,1-dimorpholinoethene to yield 2-morpholino-5-nitropyridine (**352**) via the corresponding *para*-bridged cycloadduct (**351**). FMO perturbation theory correctly predicts an exclusive regiospecific addition of the enamine to *N*1 and *C*4 of the pyrimidine ring ⟨86JOC4070⟩. The transformation of quinazolinium salts (**353**) into quinoline derivatives (**355**) by action of *p*-nitrophenylacetimidate can be rationalized as proceeding via the Diels–Alder cycloadduct (**354**). Pyrimidine-to-pyridine (**359**) transformations can be presented as an initial adduct formation (**356**), a prototropic shift (**357**) before ring-opening and recyclization via an open-chain intermediate (**358**) ⟨84CPB2942⟩. The alternative route is by a [4 + 2] cycloadduct across the *N*3 and *C*6 positions of the pyrimidine ring provided that the active methylene compound is able to form a tautomer with a carbon–carbon double bond.

6.02.5.9.4 Cycloadditions across the 2,5-positions

Intramolecular Diels–Alder reactions with the inverse electron demand of cyclic azadienes can be set up in pyrimidines which have a dienophilic side-chain such as a terminal alkyne group (**360**) (Scheme 60). Upon heating, an intramolecular Diels–Alder reaction (**361**) and a subsequent retro Diels–Alder reaction with loss of HCN take place to yield annelated pyridines (**362**). This reaction is exemplified by the preparation of furo[3,4-*b*]pyridin-7(5*H*)-one (**363**). The reactivity of intramolecular Diels–Alder reactions is strongly related to the conformational properties of the side-



Scheme 59

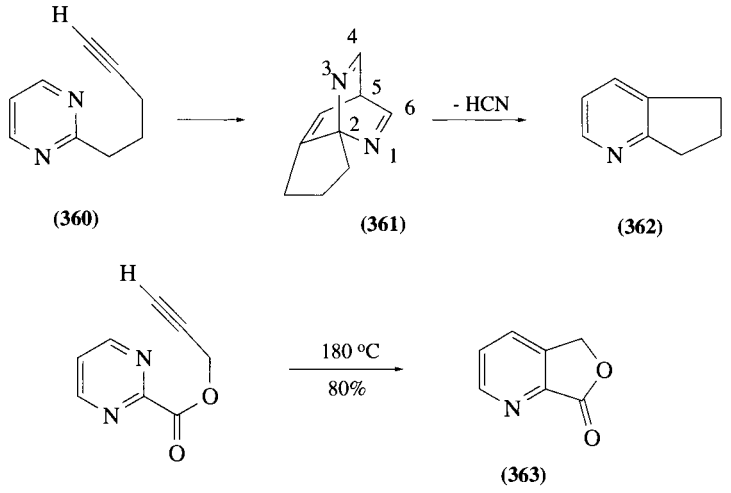
chain. Rate reduction has been found for molecules that are able to form stable conformations in which the azadiene and dienophile side-chain are positioned in such a way that their interactive approach becomes more difficult ⟨92JOC3000⟩.

6.02.5.10 Tetrahydropyrimidines

6.02.5.10.1 Reduction of pyrimidines

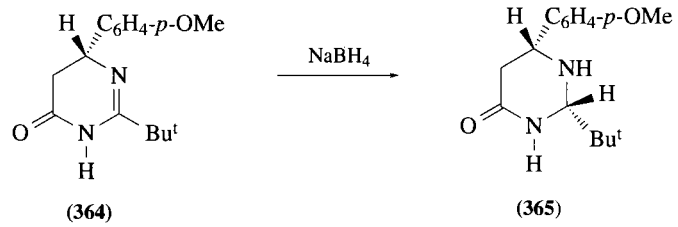
Palladium on charcoal (Pd/C) is commonly used in the catalytic hydrogenation of pyrimidines to tetrahydro derivatives. Two moles of hydrogen are absorbed by the pyrimidine in acidic media to form the 1,2,4,5 tetrahydro derivative which is stabilized as an amidinium salt; alkaline hydrolysis gives the 1,3-propanediamine ⟨62JOC2170, 65JCS1406⟩. *N*-Alkylated pyrimidinones ⟨80JPS1194⟩, and *N*-alkylated pyrimidinimines ⟨73JOC1591⟩ are reduced to tetrahydropyrimidines over Pd/C. With platinum 1,4,5,6-tetrahydro derivatives are formed from 2-pyrimidinamines ⟨65JOC115⟩, and from 4(3*H*)-pyrimidinones the 1,2,5,6-tetrahydro derivatives result ⟨65BSF2301⟩. Occasionally rhodium may be the preferred catalyst ⟨60JA486⟩. Reductive dethiation has been effected on 4-thiouracil and analogues with Raney nickel, whereby the tetrahydropyrimidine was formed ⟨60JA486⟩.

Metal hydrides can be used for reduction of the polarized bonds in pyrimidines. Sodium borohydride has been used to reduce the C=N bonds of various dihydropyrimidines, including the highly hindered imine bond in (**364**) with formation of (**365**) (Equation (17)) ⟨92JA1800⟩. Similarly,



Scheme 60

the 3,4-double bond in various chiral 1,2-dihydropyrimidines has been reduced to form chiral 1,2,3,4-tetrahydropyrimidines by sodium borohydride ⟨88CC410⟩.



(17)

LAH will reduce a C4/C6 carbonyl group to CH_2 before reducing a C2 carbonyl group ⟨83OMR(21)334⟩.

6.02.5.10.2 By addition reactions

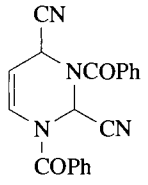
Pyrimidine reacts with trimethylsilyl cyanide and benzoyl chloride with aluminum chloride as catalyst, to give the Reissert-type compound (**366**) ⟨81JHC443⟩. The intermediate acylpyrimidinium cation (**367**) adds a soft nucleophile such as the silyl ether of acetophenone, and the adduct rapidly undergoes a second *N*-quaternization to (**368**) with a subsequent nucleophilic attack to form (**369**) (Scheme 61). The reactive intermediate can also be trapped by reactions with heteronucleophiles ⟨88JCS(P1)725⟩. Intramolecular nucleophilic addition is shown in the formation of the spiran derivative (**370**) ⟨92JOC2526⟩.

6.02.5.10.3 Hexahydropyrimidines

The hexahydropyrimidines are prepared almost exclusively by the condensation of substituted propane-1,3-diamines with aldehydes and ketones ⟨B-94MI 602-01⟩.

Starting from a pyrimidine, sodium borohydride reduces the C=N bond in various 1,2,5,6-tetrahydropyrimidines to the hexahydro derivative ⟨79RTC282⟩. Overreduction can be seen because C2 in the product, the hexahydropyrimidine, is an aminal carbon with the possibility for a dynamic equilibrium with imine and immonium forms which may be reduced to propane-1,3-diamines either by catalytic hydrogenation or by metal hydrides in the formation of an open-chain 1,3-diamine ⟨67AJC1643, 68JA771⟩.

Diisobutylaluminum hydride also attacks the C=N bond with cleavage to form 1,3-propanediamines ⟨81JA4186⟩.



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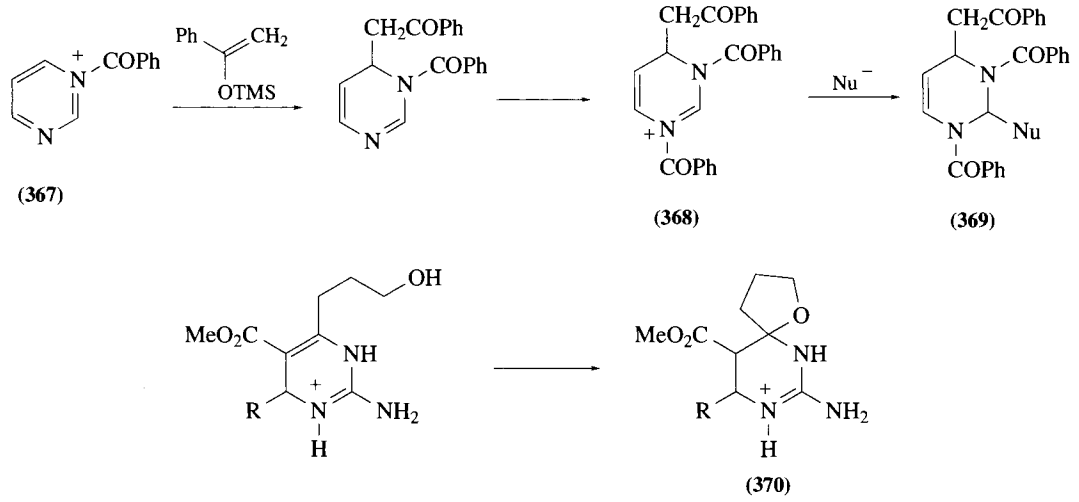


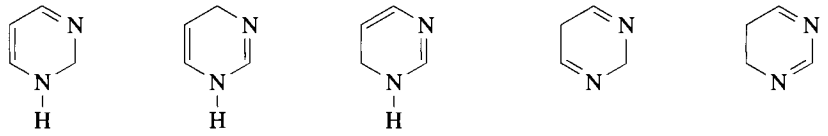
Scheme 61

6.02.6 REACTIVITY OF NONCONJUGATED RINGS

6.02.6.1 Dihydropyrimidines

6.02.6.1.1 Physical properties

There are five dihydropyrimidines (**371**). Most of the known dihydropyrimidines have either the 1,2- or the tautomeric 1,4- or 1,6-dihydro structures. Gaussian 70 *ab initio* calculations of the energy of unsubstituted dihydropyrimidines yielded the following order of stability: (**371**) (**c**) > (**b**) > (**a**) > (**d**) > (**e**). The results agree with the experimentally observed behavior of these compounds ⟨85AHC(38)1⟩.



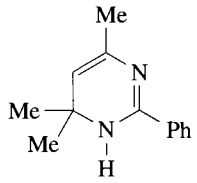
(a) (b) (c) (d) (e)

(371)

(i) Molecular geometry and conformation

X-ray diffraction study of 4,6,6-trimethyl-2-phenyldihydropyrimidine (**372**) ⟨82H(19)493⟩ showed that this 1,6-dihydropyrimidine deviates slightly from strict planarity (N1 and C6 atoms out of plane), while the lone pair on N1 undoubtedly takes part in conjugation with the double bonds. The structure of 2,4-diphenyl-6-methyl-1,4-dihydropyrimidine (**373**) shows atoms N1 and C4 out of the plane of the two double bonds C2=N3 and C5=C6 by about 10 pm and 25 pm, respectively,

thus forming a ring with a flat boat conformation ⟨82CC89⟩. The x-ray structure of 4,6-diphenyl-1,2-dihydropyrimidine (**374**) showed C2 and C5 to be out of plane and N1 nearly coplanar. N1 showed a high degree of conjugation with the double bonds.



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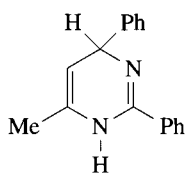

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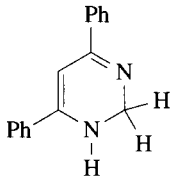


(374)

(ii) IR spectra

Dihydropyrimidines, substituted on one of the nitrogens, absorb in the 3100–3500 cm^{-1} region and show the characteristic stretching modes for bonded and nonbonded N—H groups. The absorptions of the N—H stretching frequencies are of medium intensity, at 3360–3490 cm^{-1} in solution. The N—H stretching frequencies of N-unsubstituted 1,2-dihydropyrimidines generally appear in the 3380–3450 cm^{-1} region ⟨84CL1773⟩. All dihydropyrimidines show absorptions in the region 1500–1700 cm^{-1}, which are assigned to the C=C or C=N stretching modes. These bands can be used to differentiate between tautomeric 1,4- and 1,6-dihydropyrimidines, since the C=N stretching band of the 1,4-tautomers has been consistently observed 30–60 cm^{-1} higher than for the 1,6-tautomer; the relative intensity correlates with the ratio of isomers in solution. The C=N absorption of 1,2-dihydropyrimidines usually appears in the 1595–1630 cm^{-1} region ⟨84CL1773, 85AHC(38)1⟩.

(iii) UV spectra

1,4-Dihydropyrimidines display $n \rightarrow \pi^*$ transitions for the C=C—N—C=N chromophore, which appears as a medium intensity band ($\varepsilon \approx 6500$) in the 250–260 nm region, while this absorption band for the 1,6-dihydro tautomer appears at a longer wavelength, 300–320 nm of medium intensity ($\varepsilon \approx 5000$). The highest-wavelength absorption appears in 1,2-dihydropyrimidines at 340–350 nm of medium intensity ($\varepsilon \approx 6000$) ⟨85AHC(38)1⟩.

(iv) NMR spectra

The alkenic proton at position 5 of 1,4- and 1,6-dihydropyrimidines resonates in the region δ 4.2–5.0; the signal for the 1,4-dihydro compound appears 0.4–0.6 ppm upfield from that of the 1,6-isomer. The signals at C4 are usually not affected by hybridization of the adjacent N atom. C5 protons in 1,2-dihydropyrimidines usually appear at δ 5.2–5.4, which is lower than for the corresponding 1,4- and 1,6-dihydro isomers. NH proton shifts vary with the solvent used.

The sp^3-carbons in dihydropyrimidines usually appear in the 50–70 ppm region, and the 5-carbon at δ 100–108, the relative shifts being in each case 1,6- < 1,4- < 1,2- ⟨85AHC(38)1⟩.

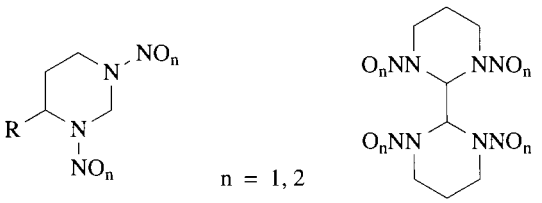
6.02.6.1.2 N-Alkylation and acylation

N-Alkylation and acylation reactions show the normal behavior for cyclic amines.

6.02.6.1.3 N-Nitrosation and nitration

Directed nitrosation of hexahydropyrimidine gives the 1,3-dinitroso compound (**375**; $n = 1$) which has been found to be carcinogenic ⟨83MI 602-01⟩. The dinitroso compound can be formally oxidized

to the dinitro compound (**375**; $n = 2$) by nitrolysis using nitric acid or a solution of N_2O_5 in nitric acid. 1,3-Dinitramines are explosive ⟨84JOC5147⟩. The tetranitroso compound (**376**; $n = 1$) results from direct nitrous acid treatment of the corresponding tetramine, and the tetranitro compound (**376**; $n = 2$) by nitration of the amine in a solution of fuming nitric acid in trifluoroacetic anhydride ⟨89JOC4771⟩.



(375) (376)

6.02.6.1.4 C-Alkylation

The C5 protons in reduced 4-pyrimidinones are acidic. LDA or other strong bases will remove an α-proton. The resultant enolate can be used for carbosubstitution in the 5-position. Of special interest is the use of reduced pyrimidinones as chiral auxiliaries (Scheme 62). Thus 1-benzoyl-2-*t*-butyl-3-methylperhydro-4(3*H*)-pyrimidinone (**377**) has been designed to serve as an effective reagent for asymmetric synthesis of α-substituted-β-amino acids (**380**). C2 is chiral and needs to be resolved. One of the enantiomers is used as the chiral auxiliary. The substrate (**377**) is prepared in a cyclization reaction between β-alanyl methylamine and pivalaldehyde and subsequent *N*-benzoylation. X-ray structure analysis shows one of the few occasions where the *t*-butyl group has the *axial* orientation. High stereoselectivity was observed for the reaction of the lithiated species (**378**) with electrophiles due to the steric hindrance generated by the axial disposition of the *tert*-butyl group at C2, which directs addition from the enolate face opposite to this group. A new stereogenic center is generated at C5 in the tetrahydropyrimidine (**379**). Acid hydrolysis cleaves the ring and gives the desired α-substituted β-amino acid (**380**) ⟨92JOC2396⟩.

An analogous strategy for asymmetric synthesis of β-amino-β-aryl acids from enantiomerically pure dihydro-4-pyrimidinones via tetrahydropyrimidinones is also available ⟨92JA1800, 92TL2725⟩.

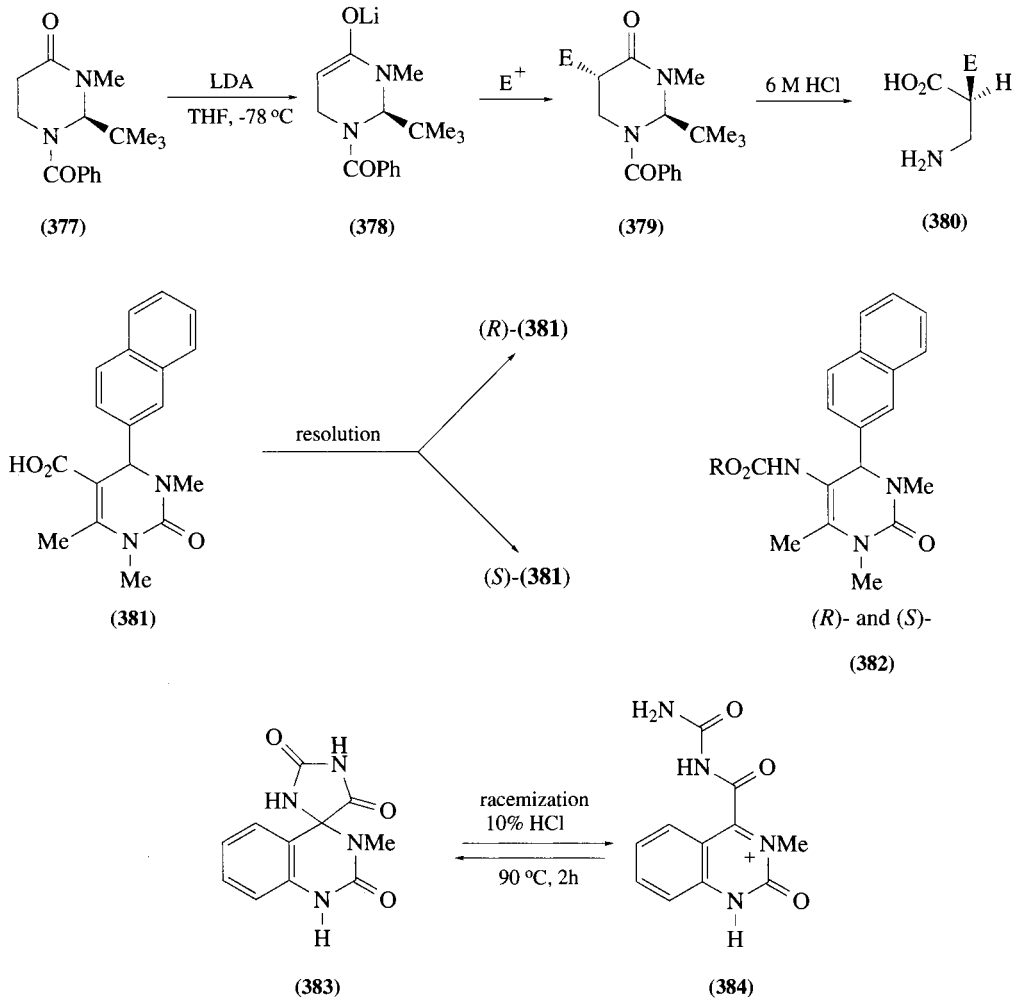
4-Substituted 3,4-dihydropyrimidines are inherently asymmetric. They are usually obtained as racemic mixtures. Enantiomerically pure and optically stable dihydropyrimidine-5-carboxylic acids (**381**) have been obtained by optical resolution effected by fractional crystallization of their diastereomeric α-methylbenzylammonium salts. The absolute stereochemistry was established by x-ray analysis of diastereomeric α-methylbenzylammonium carboxylate. The enantiomeric acids (*R*)-(**381**) and (*S*)-(**381**) were transformed to carboxylic acid azides, subjected to the Curtius rearrangement and reacted with an alcohol to yield optically active urethanes (**382**) ⟨92T5473⟩.

An example from the quinazoline series is provided by optically pure 3-methylspiro[imidazolidine-4,4′(1*H*)-quinazoline]-2,2′,5(3*H*)-trione (**383**), which was prepared by optical resolution using brucine. The resolved spirohydantoin is slowly racemized on heating in 1,2-dichloroethane, more rapidly in 10% HCl. The racemization proceeds via the *N*-acyliminium ion (**384**) generated by cleavage of the N—C hydantoin bond in the quinazoline 4-position ⟨92JOC1568⟩.

6.02.6.1.5 Oxidations (dehydrogenation)

The dihydropyrimidines are readily oxidized to the corresponding pyrimidines by dehydrogenation, hydrogen transfer, or disproportionation reactions. Oxidation agents include $KMnO_4$, DMSO, $K_3Fe(CN)_6$, DDQ, or MnO_2 ⟨B-94MI 602-01⟩. DDQ is widely used ⟨88S70, 89S381⟩. Manganese dioxide may effect dehydrogenation when DDQ fails ⟨84JHC53, 85ACS(B)459, 85JCS(P1)1997⟩. $KMnO_4$ in liquid ammonia facilitates *in situ* dehydrogenation of aminodihydro intermediates in the Chichibabin amination reaction ⟨83JOC1354⟩.

When the dihydropyrimidine carries a substituent with a conjugative β-group (**385**), a tautomer with preferential exocyclic conjugation may result after dehydrogenation (Scheme 63). Thus ^1H NMR in TFA showed the preponderance of the acetonylidene tautomer (**386**) ⟨79ACS(B)150⟩. The



Scheme 62

DDQ dehydrogenated product of 5-chloro-3,4-dihydro-1-methyl-4-phenacyl-2(1*H*)-pyrimidinone (**387**) is also the conjugated exocyclic enone (**388**). X-ray analysis shows that the pyrimidine ring and the phenacylidene side-chain are approximately coplanar, the torsional angle being within 5° except for the phenyl ring which is twisted 29° with respect to this plane. The (*Z*)-configuration is attributed to strong intramolecular hydrogen bonding between the *N*3-proton and the carbonyl oxygen in a six-membered pseudo ring. All bonding distances and angles are within the range normally reported ⟨85ACS(B)195, 88AX(C)1298⟩.

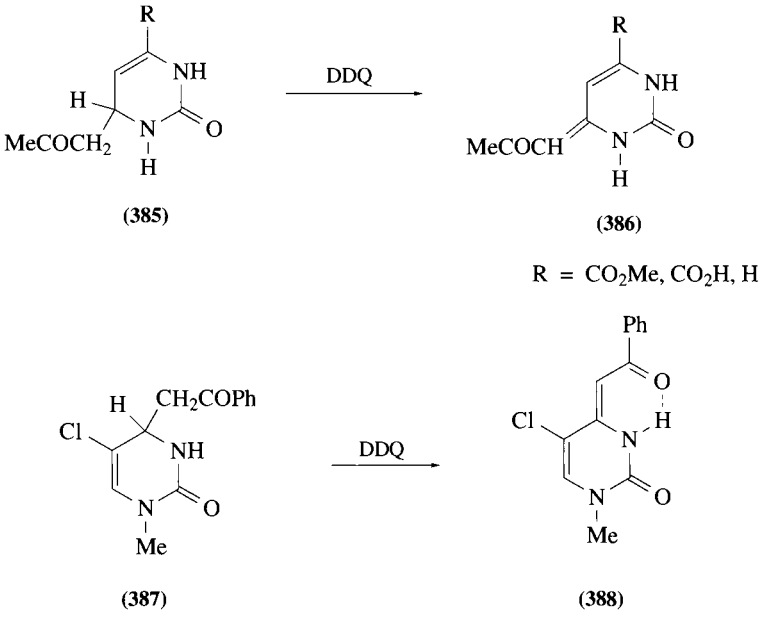
6.02.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

6.02.7.1 Reactivity of Alkyl Groups

6.02.7.1.1 Alkylation, elimination, addition, and condensation reactions

Until 1994 most alkylpyrimidines were prepared by primary syntheses, but are now in most cases more readily available by transition metal-catalyzed coupling reactions using alkyl-, alkenyl-, or alkynyl-metals (Section 6.02.5.5). Introduction of an unsaturated alkyl side-chain is followed by reduction ⟨94AHC362⟩. When desirable, substituents can be introduced into the alkyl group or its unsaturated precursors before the coupling operation and attachment to the heterocycle.

The α-carbon in an alkyl group in an electrophilic 2- or 4-/6-position is activated, and an α-proton



Scheme 63

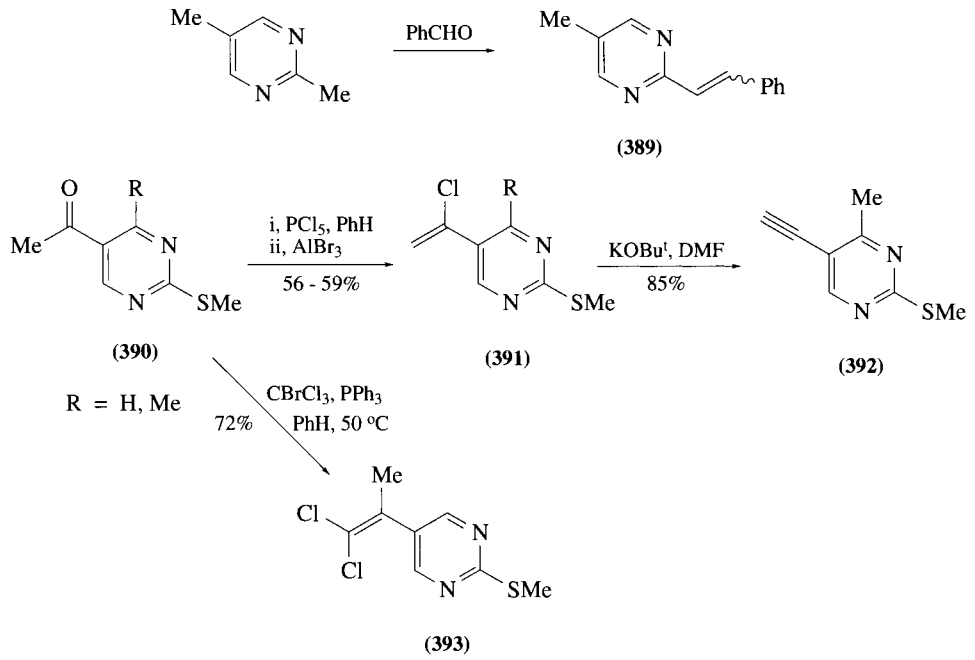
is removable by a strong base such as LDA. The charge on the carbanion is stabilized over the ring nitrogen atoms. In the benzenoid 5-position, an alkyl group is less activated but more strongly so than in an alkylbenzene. Selective deuteriation of methyl groups in the electrophilic positions under alkaline and acidic conditions can be effected under conditions which do not affect a 5-methyl group ⟨67JCS(B)171, 81JCS(P1)2943⟩. Deuteriation of higher alkyl groups is on the α-carbon ⟨75JCPB505⟩.

Once deprotonated by a strong base, the carbanion will react with electrophilic carbon in an alkyl halide or sulfonate ester to elongate the side-chain alkyl group, or with carbonyl carbon in an aldol or Claisen type reaction. The aldol readily loses water to form an alkenyl derivative, where the double bond is conjugated with the pyrimidine ring. Selective reactivity is demonstrated by the reaction of 2,5-dimethylpyrimidine with benzaldehyde, where only the electrophilic 2-methyl group reacts, to yield the 2-styryl derivative (**389**) (Scheme 64). Several examples are known ⟨B-94MI 602-01⟩.

Alkenyl and alkynyl derivatives have been prepared by elimination reactions. Phosphorus pentachloride treatment of the 5-acetyl derivative (**390**) and heating with catalytic amount of aluminum tribromide gave the α-chloro vinyl derivative (**391**). The initial product is an α,α-dichloro derivative which subsequently loses HCl under the influence of $AlBr_3$. Treatment with strong base leads to further HCl elimination and formation of the 5-alkyne (**392**). This reaction proceeds well when the 4-position in the pyrimidine ring is blocked by a methyl substituent, and in low yield (8%) when the 4-position is free. The Wittig reaction of the ketone (**390**) with the phosphorane from bromotrichloromethane gave the β,β-dichloroalkenyl derivative (**393**) ⟨83ACS(B)235⟩. Current developments in the applications of organometallics to synthesis, however, in general give more ready access to alkynes, and to most alkenes (Section 6.02.5.5).

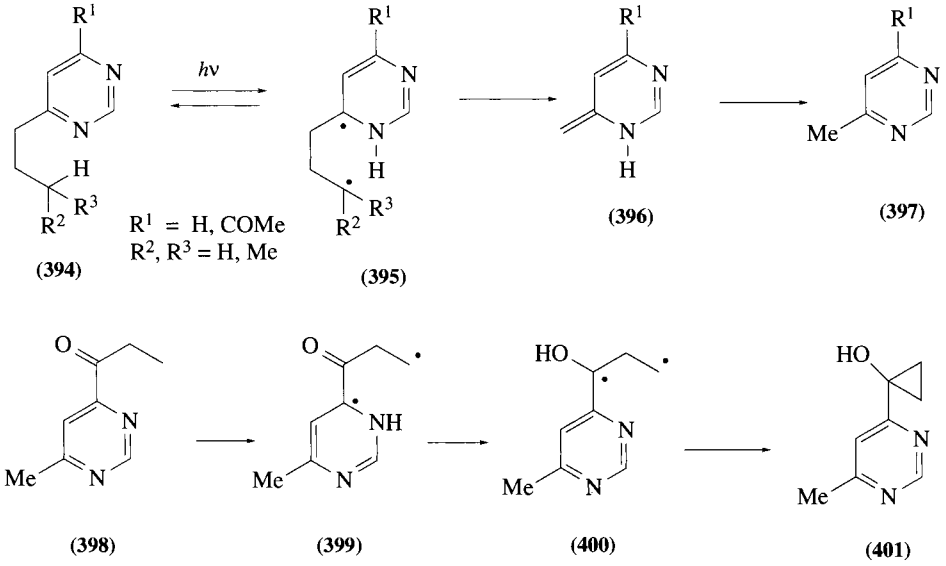
Selectivity in Claisen type reactions is seen in the reaction of 2,4,6-trimethylpyrimidine with either ethyl benzoate or ethyl acetate. The reaction is at the 4-methyl group to furnish the 4-phenacyl or acetonyl product ⟨55JA1559⟩. In the Mannich reaction the methylpyrimidine is warmed with formaldehyde and a secondary amine under acidic conditions in aqueous or alcoholic solution. In pyrimidines with strongly electron-releasing substituents, ring substitution may result. 4-Ethoxy-6-methylpyrimidine 1-oxide reacts with disubstitution in the methyl group to form 6-di(piperidinomethyl)methyl-4-ethoxypyrimidine 1-oxide ⟨80CPB1526⟩.

Photochemical hydrogen abstraction by singlet and triplet $n\pi^*$ states of aromatic nitrogen is to be expected in view of the related abstraction by carbonyl oxygen. In 4-alkylpyrimidines (**394**) with isopentyl, butyl, and propyl side chains, which provide tertiary, secondary, and primary hydrogen, hydrogen abstraction by *N*3 through a six-membered ring is realized on either direct irradiation in water or triplet-sensitized irradiation in acetone (Scheme 65). The hydrogen abstraction is from an $n\pi^*$ triplet state corresponding to a 1,5-hydrogen transfer (**395**), fragmentation (**396**), and



Scheme 64

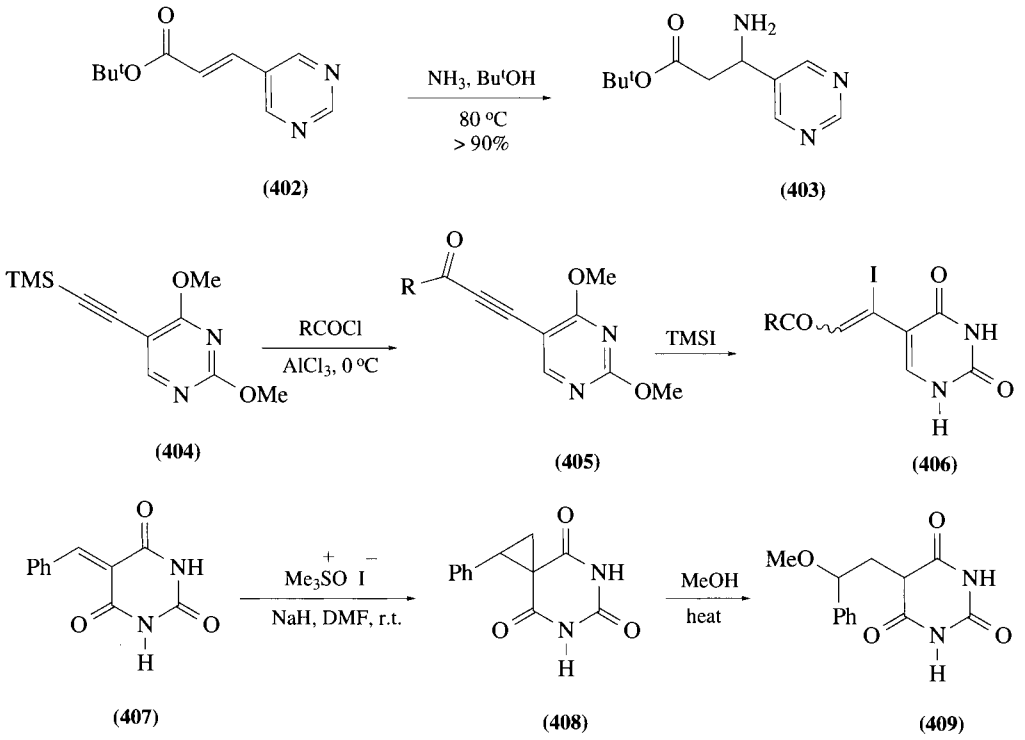
tautomerization to effect rearomatization (**397**) ⟨90JA3940⟩. This reaction sequence is analogous to the abstraction of γ-hydrogen by carbonyl oxygen. In the 4-acyl-6-alkylpyrimidine (**398**) direct irradiation ($\lambda > 340$ nm), or triplet sensitization by aromatic ketones, leads to hydrogen abstraction (**399**) by *N*3 from the *C*4-side-chain and a hydrogen shift (**400**) leading to the cyclopropanol (**401**) ⟨92JA1838⟩.



Scheme 65

In C-vinyl pyrimidines, the pyrimidine ring is an electron acceptor and nucleophiles add to the β-carbon of the vinyl group. In the pyrimidine-5-propenoate (**402**) there is an electron acceptor at both ends of the double bond: the ester carbonyl is the stronger acceptor in this molecule (Scheme 66). Addition of ammonia to the ester β-carbon to furnish the corresponding 3-amino-4-(5-pyr-

imidinyl)propanoate (**403**); the propenoic acid *t*-butyl ester substrate is available by a Heck coupling between 5-bromopyrimidine and the acrylate ⟨93TL8015⟩. In the 5-(2-trimethylsilylethynyl)-pyrimidine (**404**), the silyl group can be substituted under Friedel–Crafts conditions by an acyl group (**405**). The deblocking of protection by cleavage of the methoxy groups by iodotrimethylsilane leads to concurrent addition of HI across the triple bond with regiochemistry controlled by the oxo group (**406**); the triple bond was regenerated by base treatment ⟨90JMC1975⟩.



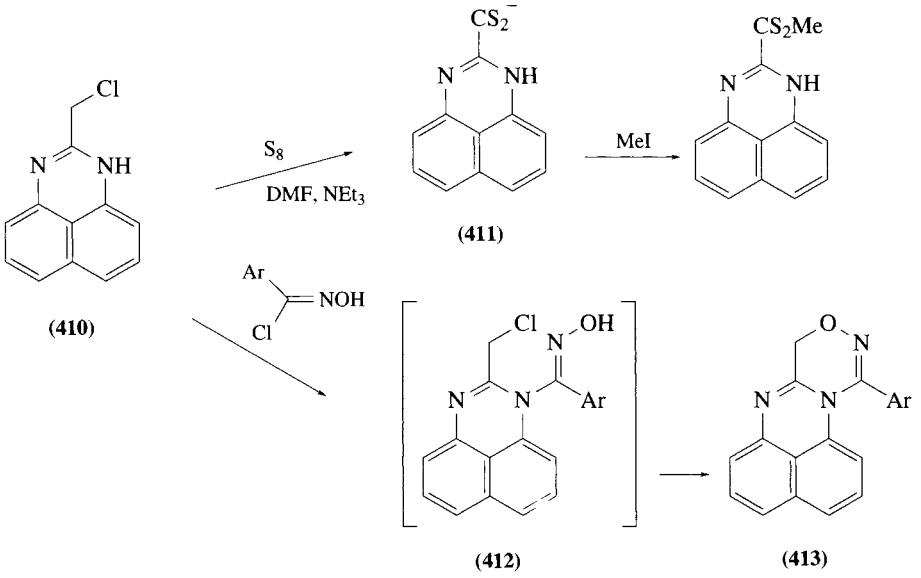
Scheme 66

Cyclopropanation of 5-arylidenebarbituric acids, from the condensation of barbituric acid with aryl aldehydes, with trimethylsulfoxonium ylid affords 5-spirocyclopropanebarbituric acids (**408**) in low or moderate yields. Higher yields of 5-spirocyclopropane derivatives were obtained in ring cyclization reactions between alkyl substituted 1,1-cyclopropanedicarboxylate diesters and urea with potassium *t*-butoxide as base. The cyclopropane ring is activated by the two adjacent carbonyl groups and undergoes nucleophilic ring opening (**409**) upon refluxing in alcohols; the nucleophile attacks the tertiary cyclopropane carbon ⟨90JCS(P1)3137⟩.

(i) Perimidines

Alkyl groups attached to the highly electrophilic 2-position have acidic α-hydrogens. A strong base therefore abstracts a proton. Metallation of the 2-methyl group in 1,2-dimethylperimidine is effected by Bu^{n}Li. The carbanion adds to carbonyl compounds. The 2-methyl group is activated to the extent that it can be made to condense with aldehydes in the absence of a base catalyst; with benzaldehydes 2-styrylperimidines are formed. The methyl group in 2-methylperimidinium salts is further activated and reacts in the same way. Spiropyrans have been prepared in this way from salicylaldehyde or from 2-hydroxy-1-naphthaldehyde. A halogen on α-carbon is readily substituted (Scheme 67). 1*H*-Perimidine-2-dithiocarbonic acid (**411**) is made from the corresponding 2-chloro-methyl derivative (**410**) which was oxidatively dithiated by sulfur. Subsequent alkylation gives the dithio ester which reacts with amine to form thioamides ⟨86JPR812⟩. With benzhydroximic acid

chloride, 2-chloromethylperimidine in the presence of triethylamine reacts initially on a ring nitrogen with subsequent cyclization to give 11-phenyl-8*H*-[1,2,4]oxadiazino[4,5-*a*]perimidine (**413**) in moderate yield ⟨80S155⟩.



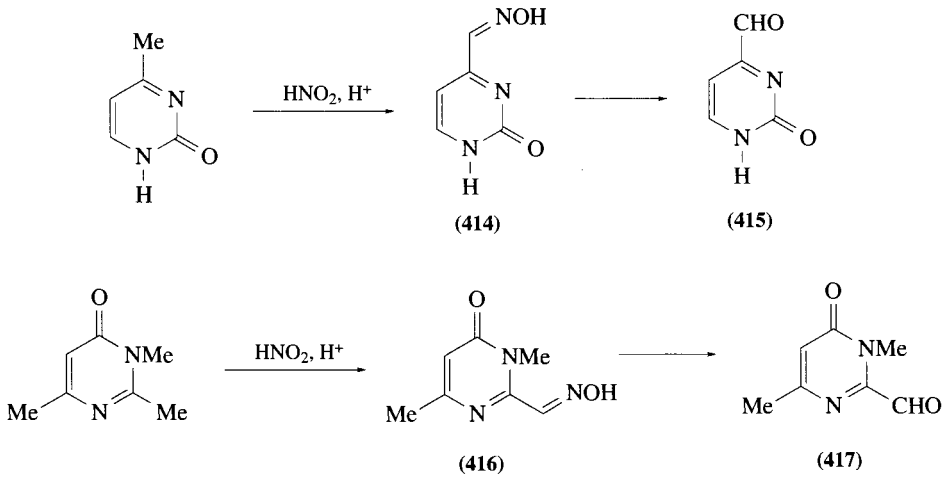
Scheme 67

6.02.7.1.2 Oxidation

The 2- or 4/6-methyl groups are oxidized to carboxy groups by oxidizing agents such as potassium permanganate. A 5-methyl group is more difficult to oxidize and an *N*-methyl group is resistant. Under milder oxidizing conditions, pyrimidinecarbaldehydes are formed. Ozonolysis of *C*-alkenylpyrimidines can also give pyrimidinecarbaldehydes ⟨B-94MI 602-01⟩. Often, a good method is to prepare carbonyl derivatives by way of pyrimidine aldoximes and ketoximes ⟨B-94MI 602-01⟩. Activated methylpyrimidines undergo α-nitrosation under acidic conditions (Scheme 68). The nitrosated species rapidly undergo prototropy to the corresponding aldoxime. A Claisen reaction with a nitrite ester in the presence of a strong base also yields aldoximes. Ketoximes are formed from higher alkylpyrimidines. Hydrolysis of the oximes gives the carbonyl compounds. Under acidic conditions 4-methyl-2(1*H*)-pyrimidinone in aqueous acetic acid yields the 4-carbaldehyde oxime (**414**) ⟨64JHC130⟩. By the Claisen procedure, 2,3,6-trimethyl-4(3*H*)-pyrimidinone gave selectively the 2-carbaldehyde oxime (**416**) ⟨78CPB842⟩. Hydrolysis gave the aldehyde (**417**).

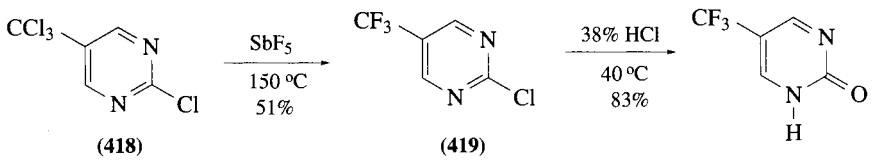
6.02.7.1.3 Halogenation

Simple alkylpyrimidines can be α-halogenated. Strongly electron-releasing groups may direct the halogenation into the pyrimidine 5-position ⟨B-94MI 602-01⟩. Monohalogenation in alkyl groups may be difficult to effect. 2,4-Dimethylpyrimidine has been reported to be trichlorinated in the 4-methyl group using $POCl_3$–PCl_5 ⟨79JHC1575⟩. 4- and 5-Ethylpyrimidine have been α-brominated under free radical conditions ⟨77CCC3464⟩. The conversion of a hydroxyalkyl into a haloalkyl substituent in pyrimidines can be carried out with standard reagents for the alcohol-to-halide conversion. α-Chlorination can also be effected by treatment of an *N*-oxide with phosphoryl chloride. Difluoro- or trifluoromethylpyrimidines are formed from carbaldehydes or carboxylic acids with sulfur tetrafluoride ⟨64JMC1, 66JMC876⟩. Fluorination can also be effected by an exchange reaction of other halo derivatives. In the formation of the trifluoromethyl derivative (**419**), the trichloride (**418**) was reacted with antimony pentafluoride (Scheme 69). The substrate for the fluorination was available by



Scheme 68

chlorination of the corresponding methyl derivative using sulfuryl chloride and UV irradiation. The trifluoromethyl group is sensitive to alkaline hydrolysis. Selective hydrolysis of the 2-chloro substituent to form the 2-pyrimidinone can be effected under acidic conditions ⟨84ACS(B)505⟩.



Scheme 69

6.02.7.2 Reactivity of Aryl Groups

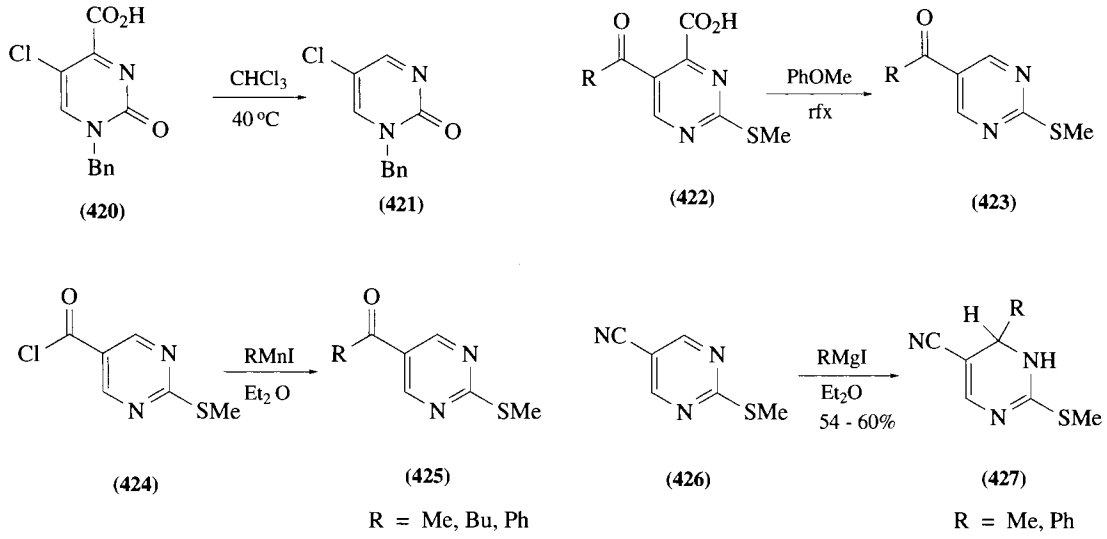
The behavior of an arylpyrimidine or a heteroarylpyrimidine towards substitution reactions and reactivity of substituents in the aryl ring is expected to reflect the behavior of biphenyls when one of the rings carries strongly electron-withdrawing substituents. With the organometallic techniques now available (Section 6.02.5.5), it is strongly recommended that arylpyrimidines substituted in the aryl group be constructed from simple halo- or hydroxypyrimidines and appropriately substituted arenes (or heteroarenes).

6.02.7.3 Carbonyl Derivatives

In general carboxylic acids, esters, and carboxamides show the normal reactivities for such groups. Esters are reduced by metal hydrides to the respective alcohols. Regioselectivity in reductions of two ester groups has been reported. Thus the 2-ethoxycarbonyl group in diethyl 6-amino-2,4-pyrimidinedicarboxylate on reduction with sodium borohydride in 2-propanol at $-30\,^{\circ}C$ to $-20\,^{\circ}C$ gave high selectivity for the formation of the 2-CH_2OH over the 4-CH_2OH isomer ⟨92JOC1631⟩.

Decarboxylation reactions in pyrimidines with a carboxylic acid group in electrophilic positions have received considerable attention since the carboxylic acid group may be an important group in a primary synthesis. Alkyl groups in electrophilic positions can also be removed by oxidation to a carboxylic acid followed by decarboxylation. Conditions for thermal decarboxylation vary considerably according to the compound. In the highly electrophilic positions, decarboxylation occurs very readily (Scheme 70). Thus the 4-carboxy-2-pyrimidinone (**420**) is decarboxylated at 40 °C ⟨B-89MI 602-01⟩. In the 4-carboxy-5-acylpyrimidine (**422**) decarboxylation to furnish (**423**) is effected by

heating in anisole at reflux temperature ⟨86ACS(B)588⟩. Diphenyl ether is another solvent suitable for high-temperature decarboxylations.



Scheme 70

Acid chlorides are prepared by standard methods and undergo the usual acid chloride reactions. They have found important applications as substrates in the syntheses of ketones by transition metal-catalyzed coupling reactions with organometallics (Section 6.02.5.5.14). Acid chlorides (**424**) are also good substrates for the preparation of ketones (**425**) using organomanganese(II) iodide, especially for the preparation of alkyl pyrimidinyl ketones ⟨86ACS(B)764⟩.

Most pyrimidine carbonitriles show normal nitrile chemistry: reductive reactions to methylamines by metal hydrides, hydrolytic reactions, reduction to aldehydes and formation of ketones with Grignard reagents. However, in highly electron-deficient pyrimidines, competition may arise between addition to an electrophilic substituent and the electrophilic pyrimidine ring. In the 5-cyano derivative (**426**), specific attack of organometallics is in the 4-position, with formation of the dihydro derivatives (**427**) instead of a ketone ⟨83ACS(B)613⟩.

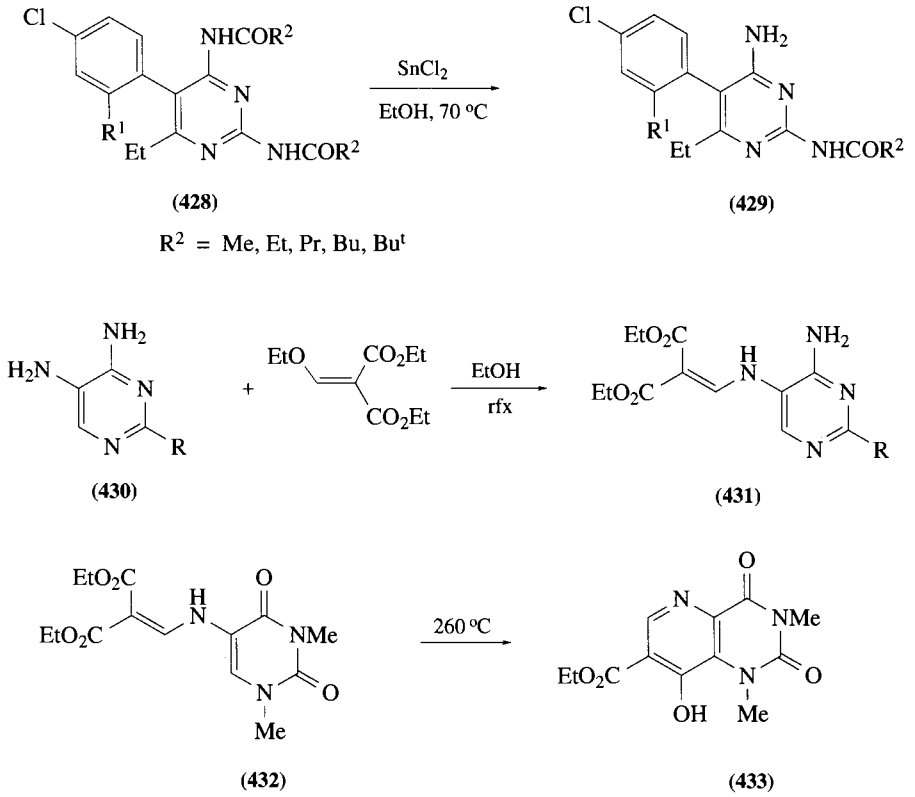
Aldehydes and ketones show expected behavior. Metal hydride reductions yield the corresponding alcohols and aldehyde oxidations furnish the corresponding acids.

6.02.7.4 Reactivity of Amino, Nitro, and Hydrazino Groups

Primary and secondary pyrimidinamines and hydrazines are acylated or sulfonylated on the exocyclic amino group under standard acylation conditions. The ease of reaction varies with the position and the type of amino group. A hydrazino group is more reactive than an amino group in any position, and the 5-amino group is the most reactive in the amino series. The two amino groups in 2,4-diaminopyrimidines differ in activation. Monoacylation is probably best effected by selective deacylation after initial diacylation (Scheme 71). Thus, deacylation of 2,4-diacylamino derivatives of the antimalarial pyrimethamine (**428**) and analogues, with tin(II) chloride in ethanol, affords exclusively 2-acylamino-4-aminopyrimidines (**429**). Ethanol or a similar alcohol is essential for the deacylation. With zinc chloride both acyl groups were lost ⟨92JCS(P1)1811⟩.

Treatment of a simple 2- or 4-/6-pyrimidinamine with an alkylating agent takes place initially on a ring nitrogen atom. This reaction may be accompanied by a subsequent Dimroth rearrangement whereby the alkylated annular nitrogen in the rearranged pyrimidine has become a ring substituent (Section 6.02.5.2.2).

Ethoxymethylenemalonate is an excellent reagent for the preparation of aminomethylenemalonates ⟨92AHC(54)1⟩. Vinylation of pyrimidinamines is on exocyclic nitrogen as in the preparation of 2-pyrimidinylaminomethylenemalonate ⟨72JMC1203⟩. In 4,5-pyrimidinediamines (**430**) and in 4,5,6-pyrimidinetriamines, the 5-amino group can be selectively vinylated (**431**); in 4,6-pyrimidinediamines monovinylation was observed ⟨68AF1214⟩.



Scheme 71

The aminomethylenemalonates can be cyclized at high temperature as in the formation of pyrido[3,2-*d*]pyrimidine-7-carboxylate (**433**) from (**432**) ⟨67JCS(C)1745⟩. With the aminomethylenemalonate group in the 4-/6-position in a free 2-pyrimidinone, cyclization is to the adjacent ring nitrogen ⟨82JHC1581⟩.

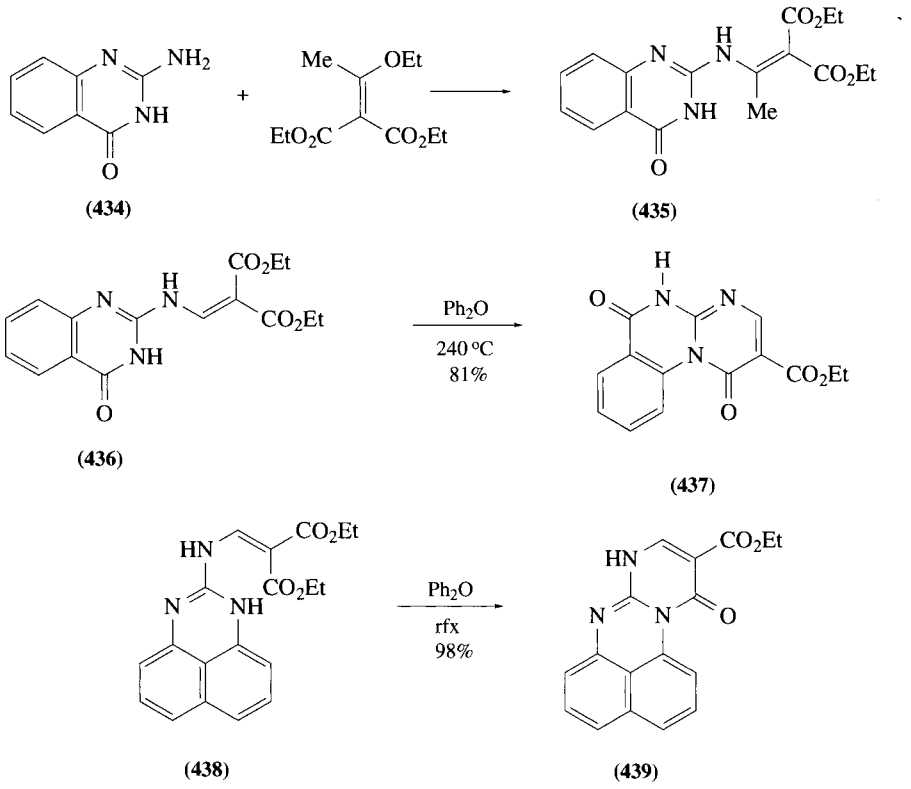
A number of catalytic conditions have been used for the reduction of 5-nitropyrimidines to amines using Pd or Raney-Ni. In the reduction of 4- and 5-nitrosopyrimidines, sodium dithionite is most commonly used. Hydrogenolysis of 5-arylazopyrimidines to form the 5-amino derivative is commonly done by catalytic hydrogenation. The 5-arylazopyrimidines are often prepared as intermediates in amination reactions. They are prepared from aryldiazonium salts, which couple with pyrimidines containing strongly electron-donating substituents ⟨B-94MI 602-01⟩.

6.02.7.4.1 Quinazolines

Quinazolinamines (e.g., **434**) are vinylated on exocyclic amino nitrogen (**435**) by ethoxymethylenemalonate (Scheme 72). The cyclization of *N*-(4-oxoquinazolin-2-yl)aminomethylenemalonate (**436**) by heating in diphenyl ether was to *N*1 (**437**) ⟨89JHC161⟩.

6.02.7.4.2 Perimidines

A 2-amino group in perimidine reacts with ethoxymethylenemalonate with formation of (**438**). Thermal cyclization of the resultant 2-perimidinylaminomethylenemalonate by heating in diphenyl ether yielded 11-oxopyrimido[1,2-*a*]perimidine-10-carboxylate (**439**) ⟨89AP(322)303⟩.



(434) (435) (436) (437) (438) (439)

Scheme 72

6.02.7.5 Reactivity of Hydroxy, Alkoxy, and Related Groups

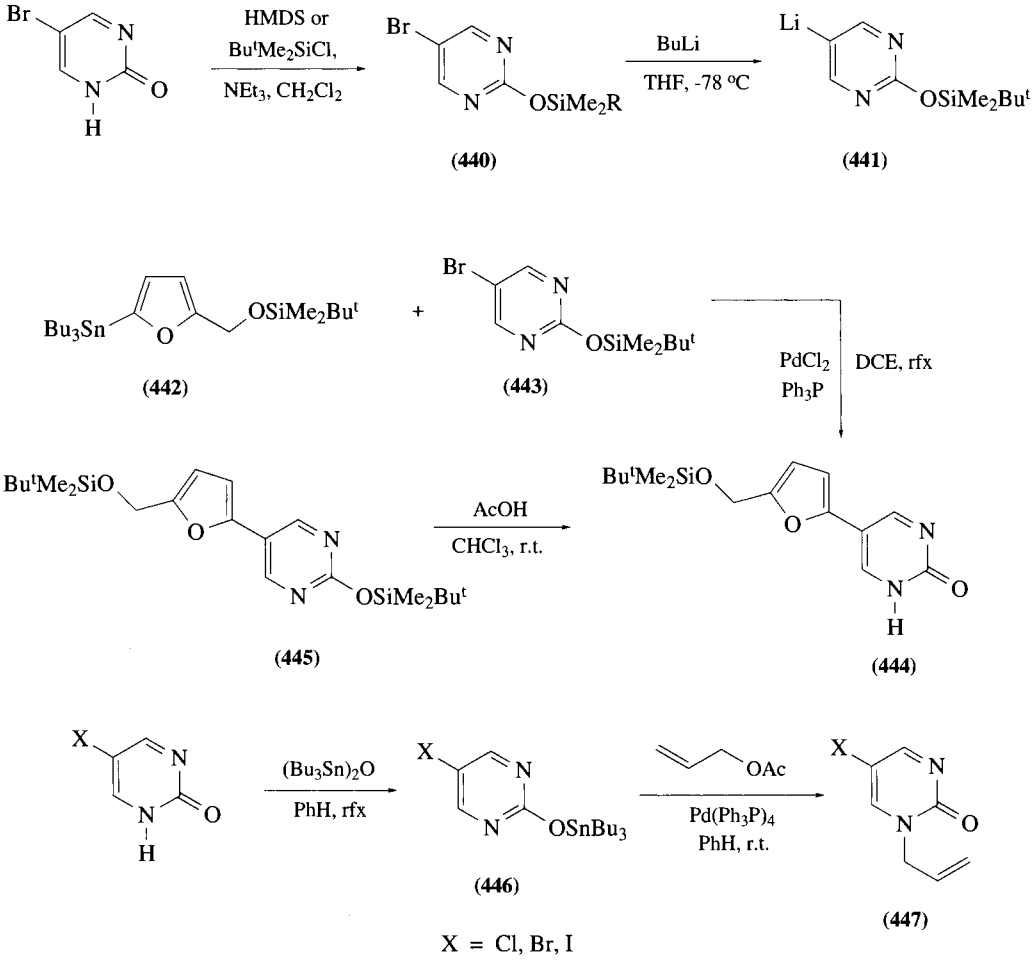
6.02.7.5.1 O-*Alkylation*

The ambident nature of a hydroxyl group in an electrophilic position, and its strong preference for the oxo form, often leads to a mixture of *N*- and *O*-alkylated products. The choice of reaction conditions will affect the outcome, but generally soft electrophiles favor *N*-alkylation and the harder electrophiles *O*-alkylation. This has been discussed in the section on *N*-alkylation (6.02.5.2.2).

6.02.7.5.2 Silylation and stannylation

Silylation is an important reaction for hydroxyl and sometimes amino protection during synthetic transformations. The trimethylsilyl group is most frequently used. Treatment of a pyrimidinone with chlorotrimethylsilane in the presence of a tertiary base, or often more conveniently by heating the pyrimidinone with hexamethyldisilazane, gives the corresponding *O*-trimethylsilane (Scheme 73). In the conversion of 5-bromo-2,4(1*H*,3*H*)-pyrimidinedione, TMS–Cl was used with triethylamine as the base in boiling benzene solution ⟨71BSF2110⟩, whereas $(TMS)_2NH$ was the reagent with ammonium sulfate as catalyst in the bis-silylation of the 5-chloro analogue ⟨83ACS(B)160⟩. Both methods gave high yields of bis-*O*,*O*′-TMS derivatives. Sometimes the silylation in $(TMS)_2NH$ is promoted by the addition of TMS–Cl ⟨73CB3039⟩. The silyl ethers of hydroxypyrimidines are very sensitive to hydrolysis, more so than alkyl silyl ethers. The stability increases with the size of the silyl substituents. The dimethylthexylsilyl group is very useful when a relatively resistant silyl group is desirable. On the phenolic hydroxyl groups of a pyrimidine, the silyl ether is formed from the silyl chloride in the presence of a tertiary base; conditions differ from those used for silylation of alcohols with this group. In the silylated pyrimidine (**440**), the TMS group is cleaved in the lithiation reaction of the 5-bromide whereas the TBDMS ether derivative is resistant and gives the lithiated species (**441**) ⟨88ACS(B)530⟩. In the coupling reaction between the furfuryl TBDMS ether (**442**) and the 2-silyloxy protected 5-bromopyrimidine (**443**), the silyl group attached to the phenolic oxygen of the

pyrimidine is selectively cleaved during the conditions of the coupling to give the alcohol protected product (**444**). In the bis-silyl ether (**445**) the pyrimidine *t*-butyldimethylsilyl group is cleaved rapidly by acetic acid at room temperature, whereas the more stable silyl ether of the furfuryl alcohol is resistant to cleavage under these conditions; the product is again (**444**). Cleavage of the silyl ether in (**444**) is effected by fluoride ions using tetrabutylammonium fluoride in dry THF. This reagent will also cleave silyl pyrimidinyl ethers ⟨94ACS279⟩.



Scheme 73

Tautomeric pyrimidinones are stannylated on oxygen (**446**) by analogy with the silylation reactions. Stannylation can be effected by heating the hydroxypyrimidine with bis-tributyltin oxide. The stannyloxypyrimidines, again by analogy with silyloxypyrimidines, are preferentially *N*-alkylated with loss of the stannyl group as in the palladium π-allyl coupling to give (**447**) ⟨87ACS(B)577⟩.

Quinazoline-2,4(1*H*,3*H*)-dione and HMDS give the corresponding 2,4-bis-(trimethylsilyloxy)-quinazoline ⟨71CCC246⟩.

6.02.7.5.3 Alkoxy and aryloxy derivatives

The chemistry of these compounds is largely confined to nucleophilic substitution reactions which proceed especially well under acidic conditions. The reactions of this type have been adequately covered ⟨B-94MI 602-01⟩.

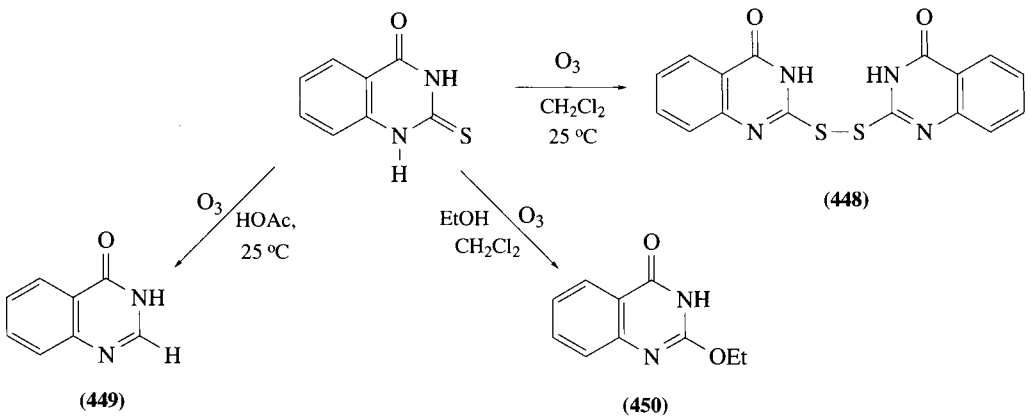
6.02.7.6 Reactivity of Thiols and Sulfides

6.02.7.6.1 Oxidation of the thiol group

Sulfur-containing pyrimidines are frequent intermediates in substitution reactions. Several methods exist for exchange of the thiol group with hydrogen, either by hydrogenolysis, especially by the use of Raney Nickel, or by oxidative desulfurization which involves a sulfinic acid intermediate. Oxidation may also lead to a sulfonic acid. The 2- and 4-/6-thiones are considerably more stable to air oxidation than 5-thiol derivatives. Disulfides are conveniently formed by oxidation with bromine. Oxidation with chlorine at low temperature can be used to prepare sulfonyl chlorides. These reactions have been summarized ⟨B-94MI 602-01⟩.

(i) Quinazoline

Oxidative desulfurization can be effected by ozonolysis (Scheme 74). 2-Thiol-4(3*H*)-quinazolinone on ozonolysis in dry dichloromethane yields the disulfide (**448**) which is resistant to further oxidation under the reaction conditions. In acetic acid, desulfurization results with hydrogen substitution (**449**). Rationalization of the reaction in acetic acid involves formation of an unstable sulfinic acid which loses SO_2 with replacement by hydrogen. In dichloromethane containing ethanol, the 2-ethoxy product (**450**) formed, corresponding to nucleophilic substitution of the reactive sulfinic acid from the oxidation. Similarly, ozonolysis of pyrimidine-2-thione acid gave bis-2-pyrimidinyl disulfide in dry dichloromethane and 2-ethoxypyrimidine in the presence of ethanol ⟨93TL1631⟩.

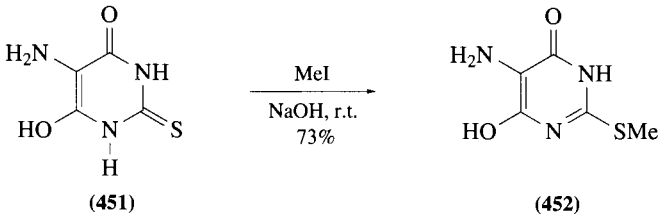


Scheme 74

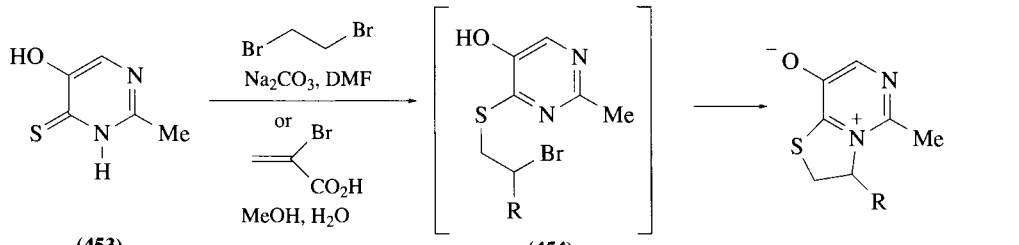
6.02.7.6.2 S-alkylations and S-aminations

Alkylation of pyrimidinethiones is on the sulfur atom (Scheme 75). Alkyl halides, sulfonates, or sulfates effect the reaction in the presence of a base under mild conditions ⟨B-94MI 602-01⟩. The high chemoselectivity is illustrated by the selective *S*-methylation of 5-amino-2-thioxo-4,6-pyrimidinedione (**451**) to furnish (**452**), and by *S*-alkylation of 5-hydroxy-2-methyl-4(3*H*)-pyrimidinethione (**453**); with 1,2-dibromoethane, initial *S*-alkylation (**454**) is succeeded *in situ* by *N*-alkylation and formation of the bicyclic dihydrothiazolo[3,2-*c*]pyrimidinium-8-oxide (**455**; R = H). *S*-Alkylation by a Michael addition of the thiono sulfur to α-bromoacrylic acid gives an intermediate 2-bromo-3-thiopropionic acid (**454**; R = CO_2H) which is rapidly cyclized to the 3-carboxylic acid derivative of the dihydrothiazolo[3,2-*c*]pyrimidine system (**455**; R = CO_2H) ⟨69ACS2437⟩. *S*-Vinylation can be effected by a Michael type addition of the thiol group to an electrophilic alkyne, exemplified by the reaction between 5-chloro-2(1*H*)-pyrimidinethione and 3-butyn-2-one. The

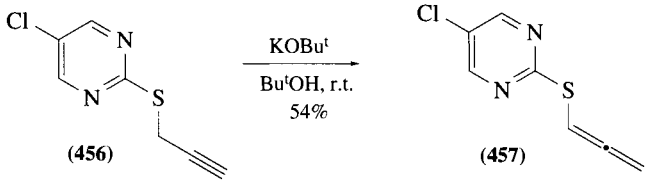
allenyl sulfide (**457**) has been prepared from the corresponding propargyl sulfide (**456**) by alkali-promoted rearrangement or by a primary synthesis ⟨83ACS(B)115⟩.



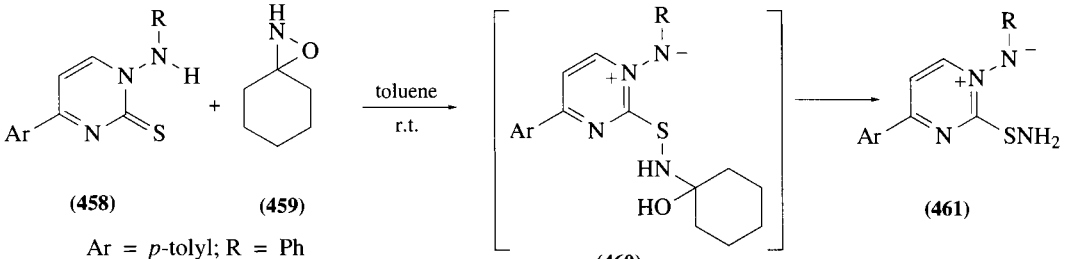
(**451**) (**452**)



(**453**) (**454**) (**455**) R = H, CO_2H



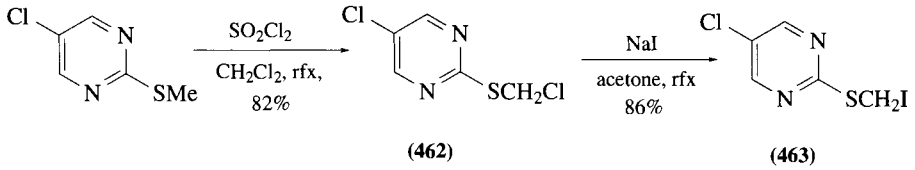
(**456**) (**457**)



(**458**) (**459**)

Ar = *p*-tolyl; R = Ph
R = COalk, COAr, CONHPh, C_6H_4-*p*-Me, C_6H_4-*p*-NO_2

(**460**) (**461**)



(**462**) (**463**)

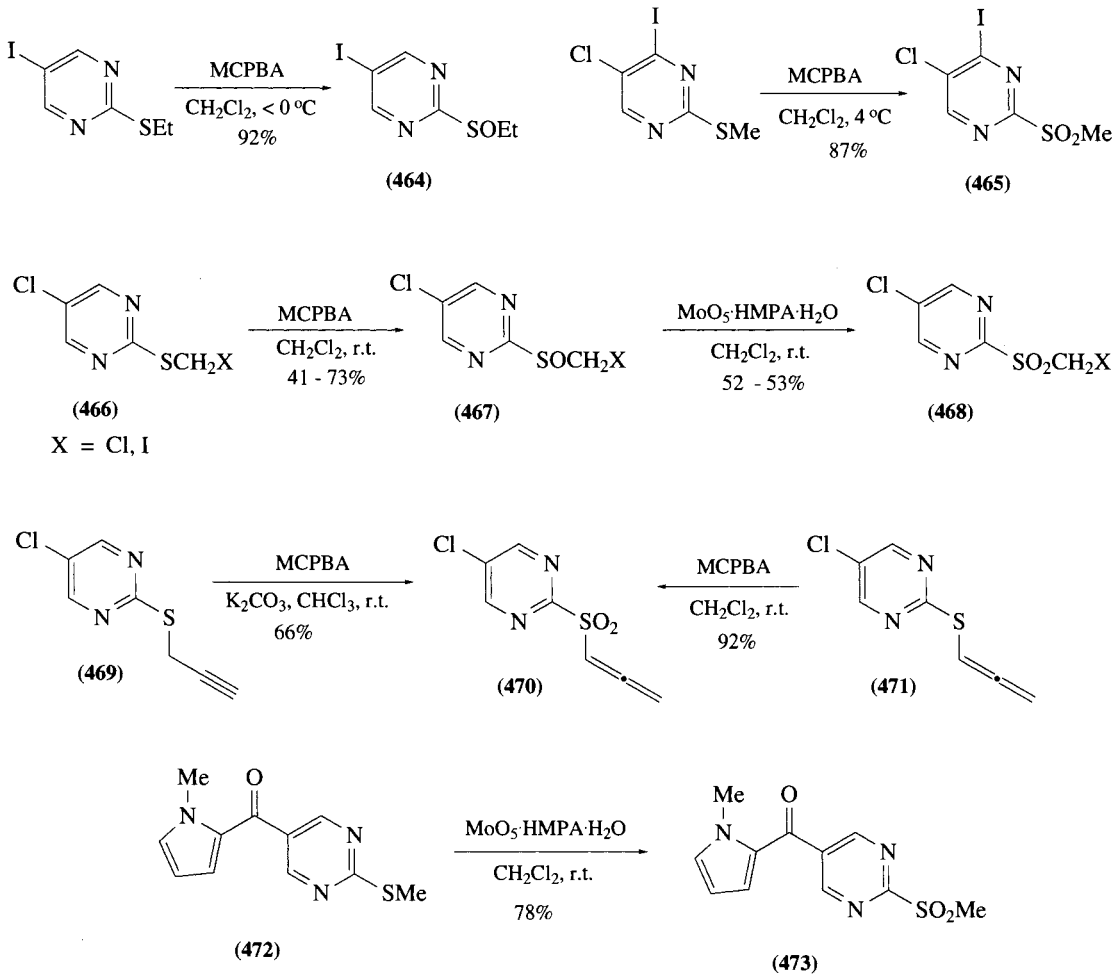
Scheme 75

3,3-Pentamethyleneoxaziridine (**459**) has been used to *S*-aminate thiouracils ⟨91S327⟩. Similarly, either 3,3-pentamethylenoxaziridine or hydroxylamine-*O*-sulfonic acid reacts with 1-acylamino, with 1-phenylureido-, or with 1-arylaminopyrimidine-2-thiones (**458**) to form *S*-aminated derivatives (**461**). A postulated intermediate (**460**) is arrived at by nucleophilic attack by the sulfur at the nitrogen of the oxaziridine ring. The structure of the *N*-ylide (**461**; Ar = *p*-tolyl, R = Ph) in the solid was verified by x-ray analysis ⟨93T3767⟩.

Sulfides can be α-halogenated. 5-Chloro-2-methylthiopyrimidine was monochlorinated in the methyl group (**462**) using sulfuryl chloride, and the chlorine in the side-chain exchanged with iodine (**463**) by heating with sodium iodide in acetone ⟨82CS11⟩.

6.02.7.6.3 Oxidations of sulfides

Sulfides in the electrophilic positions are often oxidized to sulfones to promote the ease of nucleophilic substitution. Peroxyacids are commonly used. The sulfoxide is initially formed, but the oxidation readily proceeds further to the sulfone depending on reagent and conditions (Scheme 76) ⟨B-94MI 602-01⟩. An iodo substituent survives the oxidation under mild conditions as in the formation of the sulfoxide (**464**) ⟨85ACS(B)691⟩. With two equivalents of peracid under mild conditions, oxidation to the sulfone level can also be effected without interference with an easily oxidizable iodine substituent (**465**) ⟨86ACS(B)381⟩. The halogen can be located in the side-chain. The 2-chloromethyl and iodomethylthiopyrimidines (**466**) are oxidized to their respective sulfoxides (**467**) by MCPBA. The molybdenum peroxide complex, $MoO_5 \cdot HMPA \cdot H_2O$, is a useful reagent for the oxidation of sulfides to sulfones, and far superior to MCPBA in the oxidation of the iodomethyl sulfide (**466**) to its sulfone (**468**) ⟨82CS11⟩.



Scheme 76

The oxidation of the propargyl sulfide (**469**) with MCPBA and sodium carbonate as base was accompanied by a prototropic rearrangement to the corresponding allene sulfone (**470**); the same product was formed by oxidation of the parent allene sulfide (**471**).

An acyl group in the 5-position makes a 2-sulfonyl derivative very prone to hydrolytic reactions. Application of $MoO_5 \cdot HMPA \cdot H_2O$ to the oxidation of the 5-acyl-2-sulfide (**472**) allows isolation of the sulfone (**473**) by chromatographic removal of the metal complex, thereby avoiding aqueous work-up of the reaction which would lead to hydrolysis ⟨92ACS867⟩.

6.02.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

6.02.8.1 Alkyl, Alkenyl, and Acyl Groups

Alkylation of a primary or secondary 2- or 4-/6- aminopyrimidine gives a 1- or 3-alkylated iminodihydropyrimidine as its acid salt ⟨B-94MI 602-01⟩. *N*-Vinylpyrimidines from hydroxy- and amino-substituted pyrimidines can be prepared by a vinyl interchange reaction with vinyl acetate involving mercuric acetate catalysis in acid solution ⟨70T1369⟩. 5-Fluoro-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**476**) has been made from the 1-*β*-hydroxyethyl derivative (**474**) by chemoselective chlorination of the alcohol (**475**) using thionyl chloride and a subsequent HCl elimination from (**475**) using potassium *t*-butoxide in DMSO (Scheme 77) ⟨79ACS(B)515⟩.

Selective *N*-alkylation or -alkenylation of pyrimidinethiones is difficult to achieve because of preferential reactivity of the sulfur with the electrophile. *S,N*-Disubstitution proceeds readily, however, as in the formation of the 2,3-dihydrothiazolo[3,2-*c*]pyrimidinium-8-olates (**477**). The protons of the dihydrothiazolo ring are acidic, especially in the 3-position. Strong base abstraction of an *H*3-proton leads to ring-opening to the *N*-vinylpyrimidinone (**479**). The latter is also formed from the 3-carboxy derivative (**478**) by ready pyrolytic decarboxylation promoted by the adjacent pyrimidinium nitrogen atom ⟨84JHC1149⟩.

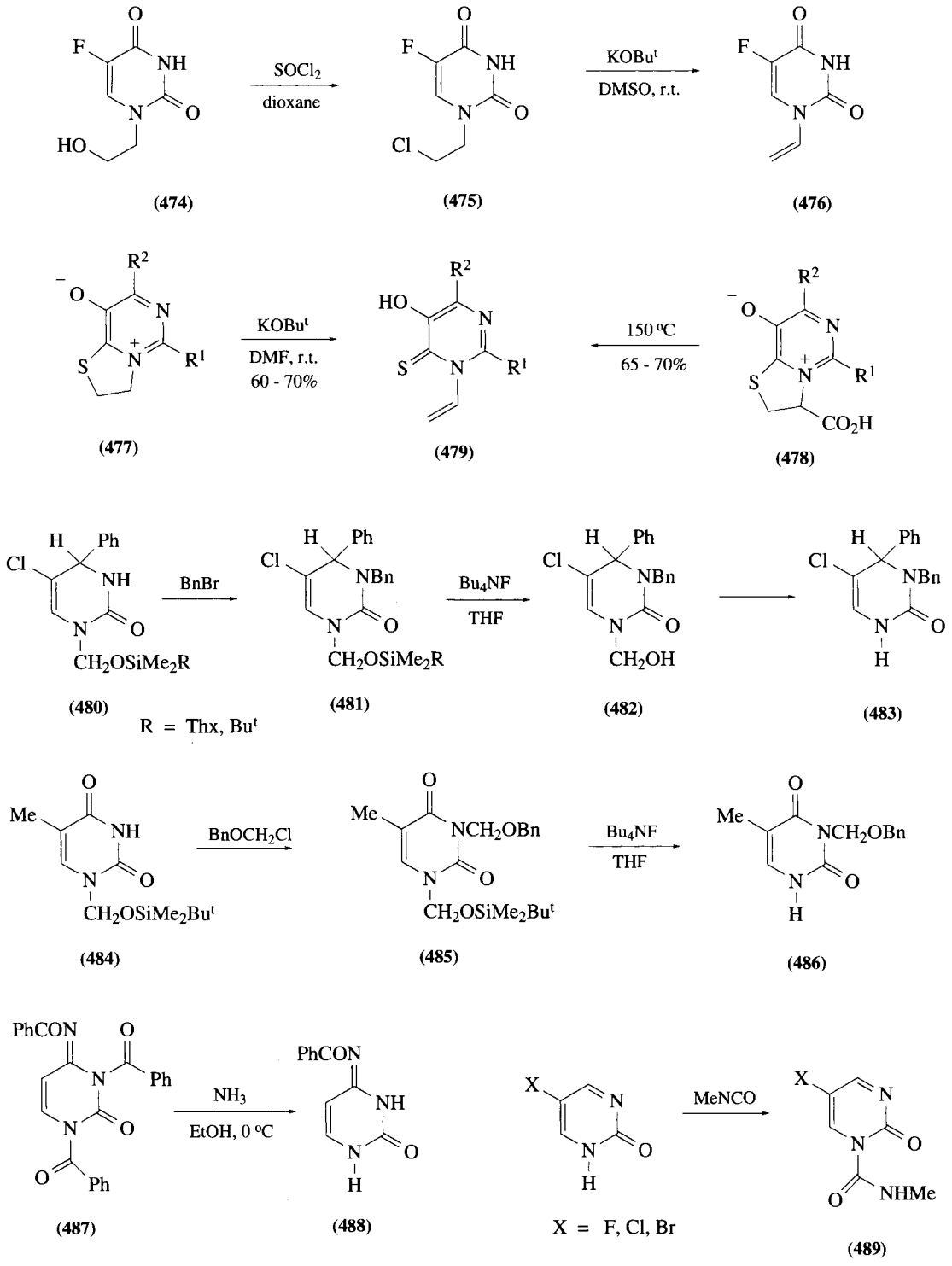
Benzylic protection of *NH* functionality in pyrimidinones is removable by hydrogenolysis. A few protecting groups and their removal have been summarized ⟨84H(22)527⟩. When hydrogenolysis is undesirable, but mild conditions otherwise are required for deprotection, a higher silyloxymethyl group is an excellent choice. *N*-Protection is effected by using a chloromethyl silyl ether for *N*-alkylation via the TMS ether of the pyrimidinone. In the example (**480**) the 3,4-dihydro-4-aryl derivative is alkylated at *N*3 (**481**) before removal of the protecting group by fluoride ions using TBAF in THF at room temperature. The initial product from the desilylation is a hydroxymethyl derivative (**482**), which can be isolated or allowed to dissociate to the pyrimidinone (**483**) and formaldehyde ⟨92T5647⟩. In the uracil derivative (**484**) the *t*-butyldimethylsilyloxymethyl group has been used to prevent the otherwise preferred *N*1-alkylation; the alkylating group is forced onto *N*3 (**485**). The *N*1-deprotection (**486**) is again effected by tetrabutylammonium fluoride ions in dry THF ⟨88ACS(B)384⟩.

Acylation is normally on exocyclic amino groups. Vigorous reaction conditions may lead to acylation of ring nitrogen as well. The difference in reactivity is seen in 1,3-dibenzoyl-4-benzoylimino-3,4-dihydro-2(1*H*)-pyrimidinone (**487**), where the benzoyl groups attached to the ring nitrogens are removed by ammonia (**488**) ⟨56JCS2384⟩.

2-Pyrimidinones are *N*-acylated by methyl isocyanate (**489**). The products can be isolated. In alcoholic or aqueous solutions they are extensively covalently solvated as 3,4- or 3,6-adducts ⟨B-89MI 602-01⟩.

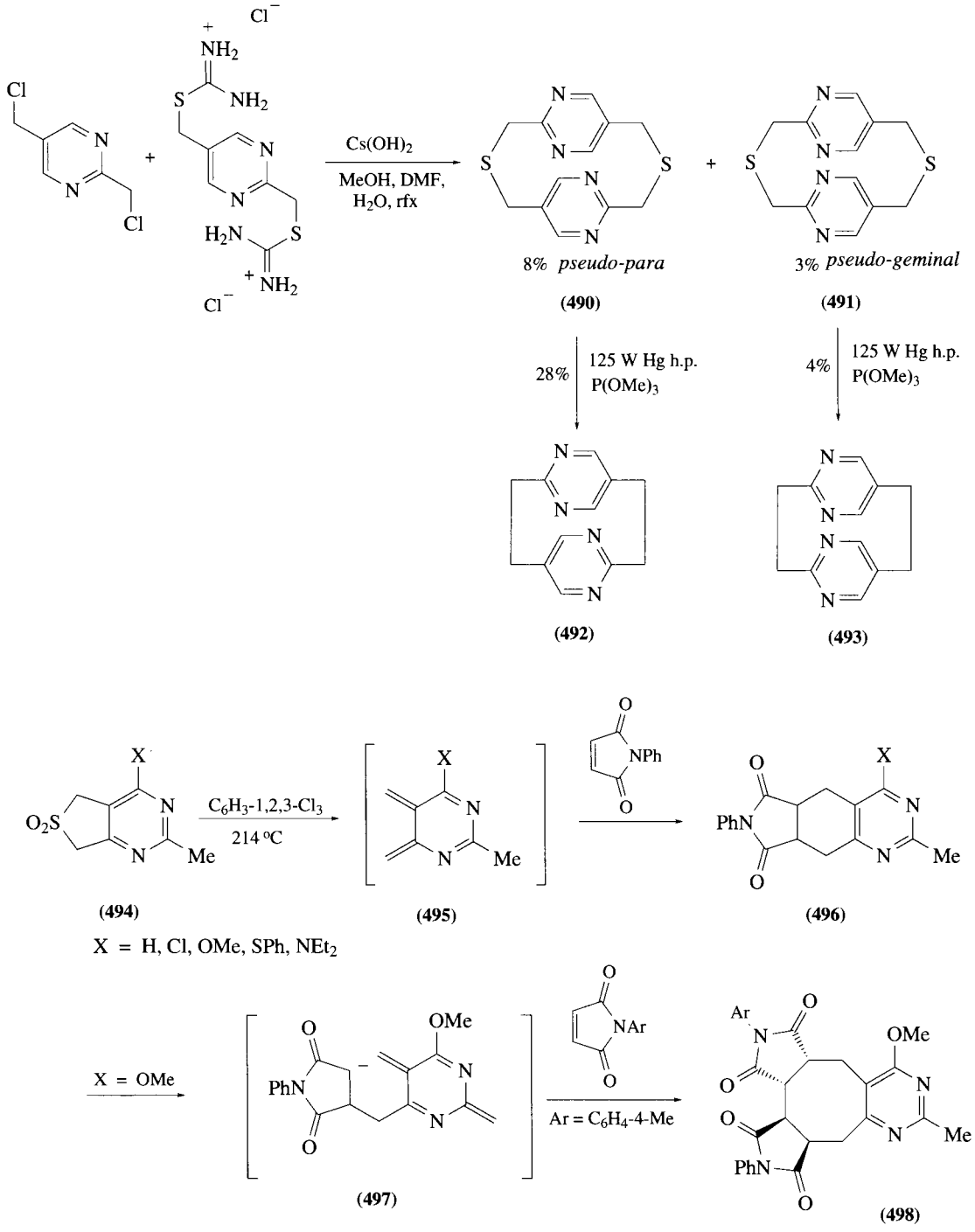
6.02.8.1.1 Special carbon-attached cyclic structures

Pseudo-para (**492**) and *pseudo-geminal* (**493**) [2,2](2,5)-pyrimidinophanes have been synthesized from the corresponding 2,11-dithia[3,3](2,5)pyrimidinophanes (**490**) and (**491**) by photolytic sulfur extrusion using a high-pressure Hg lamp (Scheme 78). The dithia derivatives (**490**) and (**491**) were prepared in low yields from 2,5-bis(chloromethyl)pyrimidine and 2,5-bis(isothiouroniomethyl)-pyrimidine dichloride. The molecular structures of both isomers were determined by x-ray structure analysis. Both [2,2](2,5)pyrimidinophanes avoid eclipsing of the pyrimidine atoms or groups by a slight shift parallel to the mean ring planes. The pyrimidine rings show twist boat-type deformation which is more pronounced than in the aromatic rings of [2,2]paracyclophane. Related phanes, [2,2](2,5)pyridinophanes and [2,2](2,5)-pyrazinophanes, also display increased flexibility in their ring components relative to the all-carbon system. Apparently, the aza ring components in [2,2]paracyclophanes contribute to a greater "softness" or flexibility with regard to deviation from planarity ⟨90CB1885⟩.



Scheme 77

Pyrimidine-fused dihydrothiophene *S,S*-dioxides (**494**) undergo thermal elimination of sulfur dioxide to give the pyrimidine *o*-quinodimethanes (**495**) which can be intercepted in Diels–Alder reactions to give substituted 5,6,7,8-tetrahydroquinazolines (**496**). The latter form cyclooctapyrimidines (**498**) on heating with more dienophile. The second addition was studied more closely for the 4-methoxypyrimidine derivative using *N*-*p*-tolylmaleimide which gave a single *cis* and *trans* pair of 1 : 1 : 1 mixed adducts believed to have the indicated regiochemistry. The second



Scheme 78

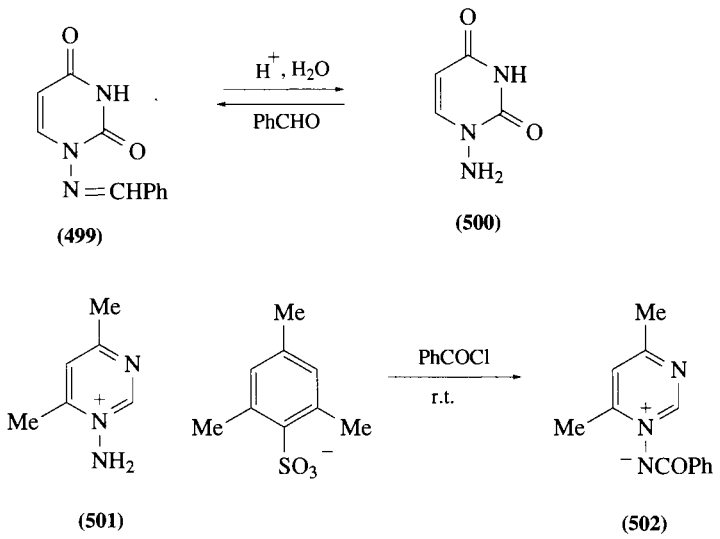
addition failed when the substituent in the pyrimidine 2-position was a phenyl group. Acidic protons abstractable from the methyl group, as shown in the proposed pathways, seem to be a requirement for the reaction to proceed ⟨93TL6639⟩.

6.02.8.2 Amino Derivatives

Most *N*1- and *N*3-aminopyrimidines have been made by primary synthesis. In this way 1-benzylideneamino-2,4(1*H*,3*H*)-pyrimidinedione (**499**) and its 3-benzylidenamino isomer have been

prepared from reagents where the amino group originates from benzaldehyde semicarbazone and benzaldehyde hydrazone, respectively. Acid hydrolysis gave the *N*-amines (**500**) (Scheme 79). In principle, amination can also be effected on a pyrimidine nitrogen atom. Treatment of 2,4(1*H*,3*H*)-pyrimidinedione with hydroxylamine-*O*-sulfonic acid gave a mixture of 1- and 3-amino-2,4(1*H*,3*H*)-pyrimidinedione besides some of the 1,3-diamine. The products were separated as benzylidene derivatives ⟨66M1117⟩. Dimroth rearrangement in reactions with 1-aryl-2-methylthiopyrimidinium salts and hydrazines gave 1,2-diaminopyrimidinium salts ⟨90JHC1441⟩. Additional *N*-amino derivatives are available ⟨84JHC1537⟩.

1-Amino-4,6-dimethylpyrimidinium mesitylenesulfonate (**501**) is benzoylated to yield the *N*-benzoylimino derivative (**502**) as an internal salt ⟨77RTC156⟩.



Scheme 79

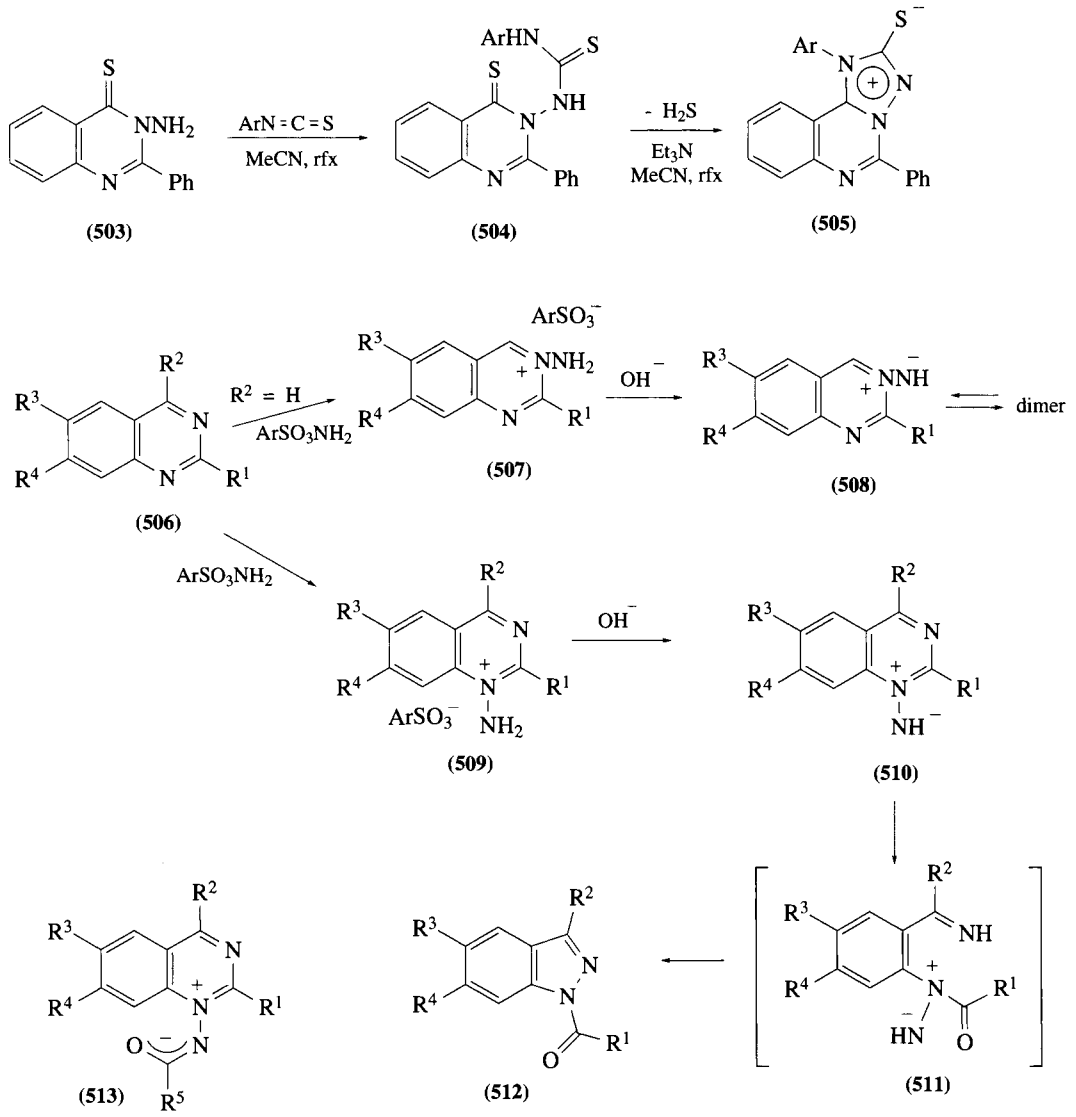
(i) Quinazoline

When 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**503**) is treated with aryl isothiocyanates in dry acetonitrile at reflux temperature in DMF, *N*,*N*′-disubstituted thioureas (**504**) are formed (Scheme 80). In acetonitrile containing triethylamine at reflux temperature, the reaction proceeds further by cyclization to the mesoionic compounds (**505**) ⟨84S881⟩.

*N*3-Amination of quinazolines bearing no substituent at C4 (**506**; $R^2 = H$) is effected with *O*-mesitylenesulfonylhydroxylamine to furnish mesitylenesulfonates of the 3-aminoquinazolinium cations (**507**). 4-Substituted quinazolines are aminated at *N*1 to form the *N*-amino salts (**509**). Upon alkaline treatment the 3-aminoquinazolinium mesitylenesulfonates yield the (quinazolin-3-io)amides (**508**) which exist predominantly in the form of dimers. (Quinazolin-1-io)amides (**510**), on the other hand, may suffer ring contraction via the ring-opened structure (**511**) to indazole derivatives (**512**) upon alkaline treatment. The corresponding *N*-(quinazolin-1-io)amidates (**513**) were stable towards the ring contraction reaction ⟨86JCS(P1)269⟩.

6.02.8.3 *N*-Oxides

Pyrimidine *N*-oxides are less readily prepared than the corresponding pyridine oxides, but the lower nucleophilicity of the pyrimidine nitrogens compared to the pyridine nitrogen can in part be overcome by using stronger peroxy acids for the oxidation. *N*-Oxides have been prepared more usually in primary syntheses by ring closure and in rearrangement reactions ⟨B-71MI 602-01, 90H(31)923, B-94MI 602-01⟩. The N—O bond in pyrimidine *N*-oxides is cleaved by reductive methods such as catalytic reduction, low-valent phosphorus (PCl_3 ⟨82H(19)2283⟩, $P(OEt)_3$ ⟨75TL2721⟩) and low-valent titanium ($TiCl_3$ ⟨75S335⟩) as well as by the more common metals used for hydrogenolysis.



Scheme 80

Reaction of methylpyrimidine *N*-oxides with acid chlorides give chloromethylpyrimidines. Given a choice, the regiochemistry may be substituent dependent; 2-ethyl-4-methylpyrimidine 3-oxide with a 6-phenyl substituent is chlorinated in the methyl group, whereas the 6-methoxy analogue is chlorinated on the α-carbon of the ethyl group in reactions with phosphorus oxychloride ⟨83CPB4533⟩. With anhydrides, oxy derivatives are formed. Pyrimidine 1-oxide reacts with acetic anhydride to form pyrimidin-4-yl acetate whereas 4,6-dimethylpyrimidine 1-oxide is attacked in a methyl group to form 6-methylpyrimidin-4-ylmethyl acetate ⟨59JCS525⟩.

6.02.8.4 Perimidine Oxides and Imides

Perimidine and its 1- and 2-substituted derivatives undergo *N*-amination with formation of 2-aminoperimidinium salts ⟨81RCR816⟩.

Perimidine is highly sensitive to oxidation reactions, which complicates the usual methodology for *N*-oxidation. The *N*-oxide of 2-methylperimidine has been claimed to be available by electrochemical reduction of 1-acetamido-8-nitronaphthalene ⟨72BSF1561⟩.

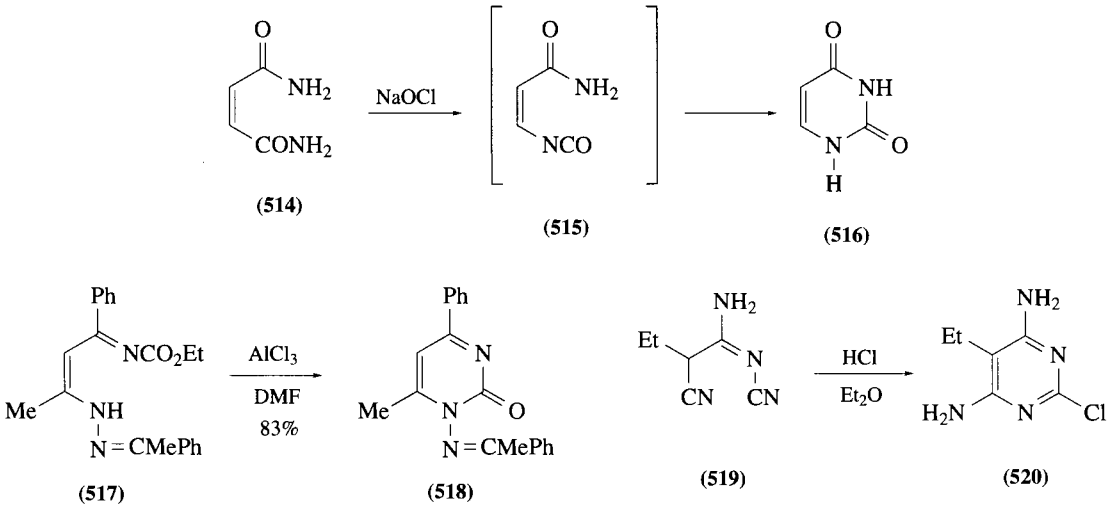
6.02.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

6.02.9.1 Six Ring Atoms

The main connections for ring formation are between N1—C2 and N3—C4.

6.02.9.1.1 N1—C2 Cyclizations

Examples are provided by Hofmann type degradation of appropriate diamides (e.g., **514**) (Scheme 81). These reactions proceed through an intermediate isocyanate (**515**) which is trapped by the neighboring amide nitrogen with cyclization (**516**). In another example, it is a urethane (**517**) which is cyclized by reaction with an appropriately positioned amino group as in the formation of the *N*1-benzylidenimine (**518**); the amine is liberated by acid hydrolysis ⟨84JCS(P1)611⟩. In the third example the carbonyl attached to the amino group is replaced by a cyano group (**519**); the cyano nitrogen eventually becomes a ring nitrogen. This comes about by addition of HCl to the *N*-cyano group, whereby the nitrogen becomes nucleophilic and adds to the appropriately positioned *C*-cyano group with formation of the 2,6-diamino-2-chloropyrimidine (**520**). Acylamino, carbamoyl, or isocyanato nitriles are other derivatives which can function as intermediates for the cyclization to the pyrimidine ring.

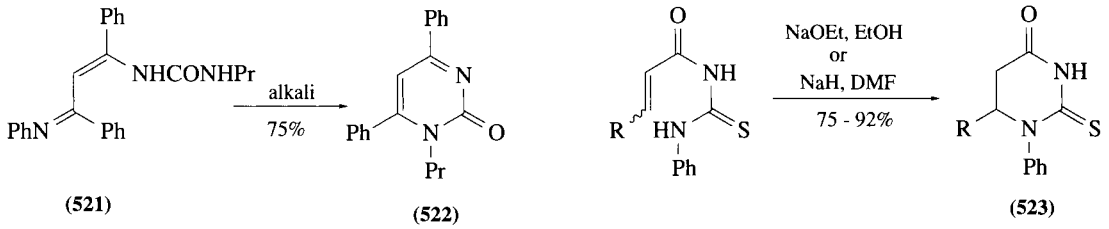


(514) (515) (516) (517) (518) (519) (520)

Scheme 81

6.02.9.1.2 N3—C4 Cyclizations

In most of these reactions it is a nitrogen of a urea, thiourea, isothiourea, or an amidine which is the nucleophile for the substitution, or more commonly addition to an appropriately situated electrophilic carbon. Conditions which enhance the electrophilic character of the carbon, or the nucleophilicity of the nitrogen, promote cyclization. In the formation of 4,6-diphenyl-1-propyl-2(1*H*)-pyrimidinone (**522**), the ureido nitrogen in the propylureido substrate (**521**) is made nucleophilic by running the cyclization under alkaline conditions (Scheme 82) ⟨84JCS(P1)239⟩. Cyclization can also be effected by addition of nucleophilic nitrogen to the electrophilic β-carbon of a Michael acceptor; an alkynyl acceptor will yield the fully conjugated ring, an alkenyl acceptor a dihydro derivative as in the formation of (**523**) ⟨88LA983⟩.



(521) (522) (523)

Scheme 82

6.02.9.2 From Two Components of One and Five Ring Atoms

In most reactions the one atom component is either N1, N3, or C2.

6.02.9.2.1 N1 or N3 in ring formation

In the synthetic strategy for cyclization from N1, C2, and C6 of the pyrimidine ring have strong electrophilic character in the acyclic precursor. Ring formation is effected by reaction of this precursor with ammonia or a primary amine. The electrophilic C2 carbon of the ring is frequently part of a urethane, an isocyanate or isothiocyanate, a carbamate, or a cyano group. The second electrophilic ring carbon, C6, in most of the examples is a β-carbon in a Michael acceptor, but it could equally well be a carbonyl carbon. When the Michael acceptor is an alkyne grouping, the fully conjugated ring is formed. Equivalent oxidation level is reached in a β-hetero-substituted (halogen atom, OR, SR, or NR^1R^2) alkene grouping, where the hetero substituent is a leaving group subsequent to the amine addition; the fully conjugated pyrimidine is again obtained. The latter approach allows for a 5-substituent in the pyrimidine.

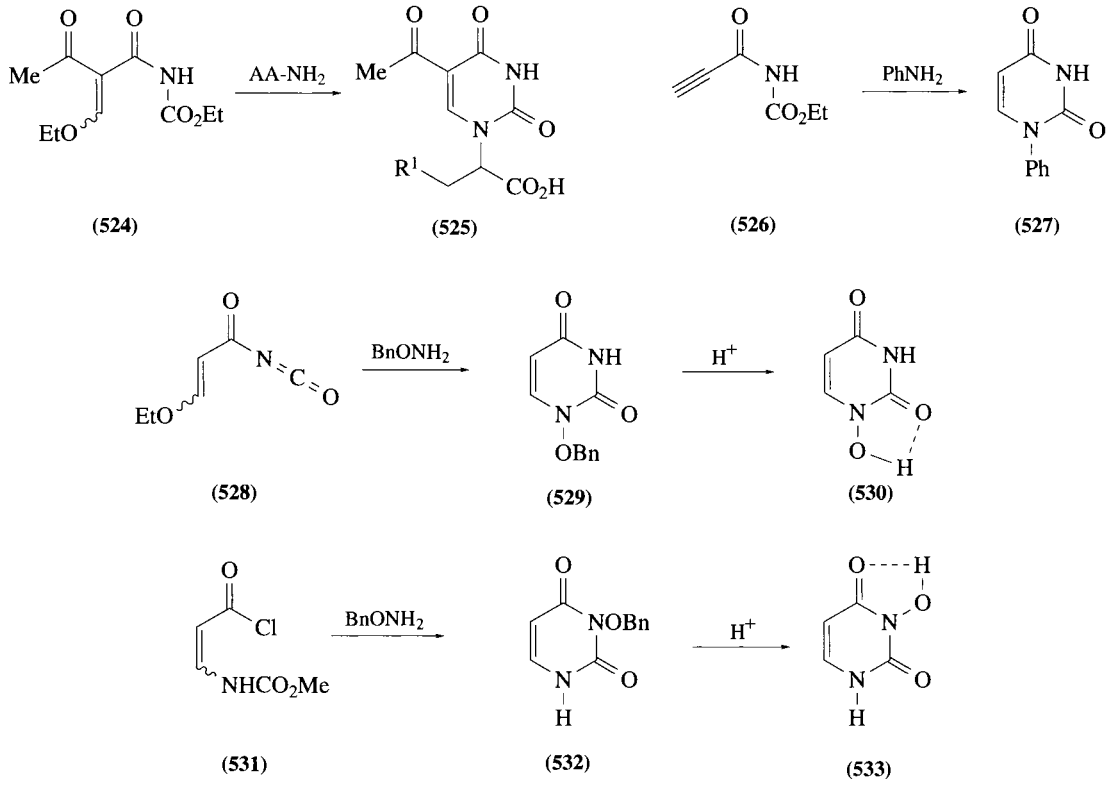
Activated methylene groups react with orthoesters such as triethyl orthoformate to form the corresponding ethoxymethylene derivatives such as (**524**) (Scheme 83). The latter readily add amines and cyclize to pyrimidines. When the amino group is that of an amino acid, a unique pyrimidine-derived amino acid is produced with retention of the amino acid configuration (**525**) ⟨64M1729⟩. In another example, a propynoylurethane (**526**) is the Michael acceptor for aniline with formation of the *N*-phenyluracil (**527**). These cyclizations constitute a good method for preparing *N*-aryl derivatives, and are of special importance because there is no good and general method available for *N*-arylation of pyrimidine rings. The final example of the N1-type shows the synthesis of a 1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**529**) from 3-ethoxyacryloyl isocyanate (**528**) and *O*-benzylhydroxylamine. An example of cyclization of *N*3 of the ring is provided by the β-ureidoacrylic acid derivative (**531**). *O*-Benzylhydroxylamine was reacted with the acid chloride (**531**) with subsequent cyclization under the alkaline conditions of the reaction to furnish 3-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**532**); acid hydrolysis gives the *N*1- and *N*3-oxides (**530**) and (**533**) from the respective benzyloxy precursors ⟨64M1729⟩.

6.02.9.2.2 C2 in ring formation

C2 is electrophilic in the examples available, most frequently as an activated carbonyl carbon of a carboxylic acid; aldehydes or ketones would yield dihydro derivatives (Scheme 84). The five-atom component constitutes a 1,3-diamine, a β-amino amide, a malondiamide, a malondiamidine, or a β-diimine, besides combinations and equivalent functions.

With aldehydes and ketones, a 1,3-diamine reacts to form a hexahydropyrimidine. With a carbon at the oxidation level of a carboxylic acid, as in the case of ethyl orthoformate, a tetrahydropyrimidine (**534**) is formed.

In the malondiamide condensation, one or both carbonyl oxygens can be replaced by sulfur. Thus *N*-methyl-2-thiocarbamoylacetamide reacts with ethyl formate to form the 6-thioxo-4(3*H*)-pyrimidinone (**535**) ⟨76LA768⟩. A carbonyl group at C2 requires the reagent carbon to be at the carbonic acid oxidation level as in the preparation of 3-ethyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione (**536**) ⟨76LA768⟩.



(524) (525) (526) (527) (528) (529) (530) (531) (532) (533)

Scheme 83

In reactions of β-amino amides, dimethylformamide dimethyl acetal was reacted with 3-aminothiocrotonamide to form the 4(3*H*)-pyrimidinethione (**537**) ⟨84MI 602-01⟩.

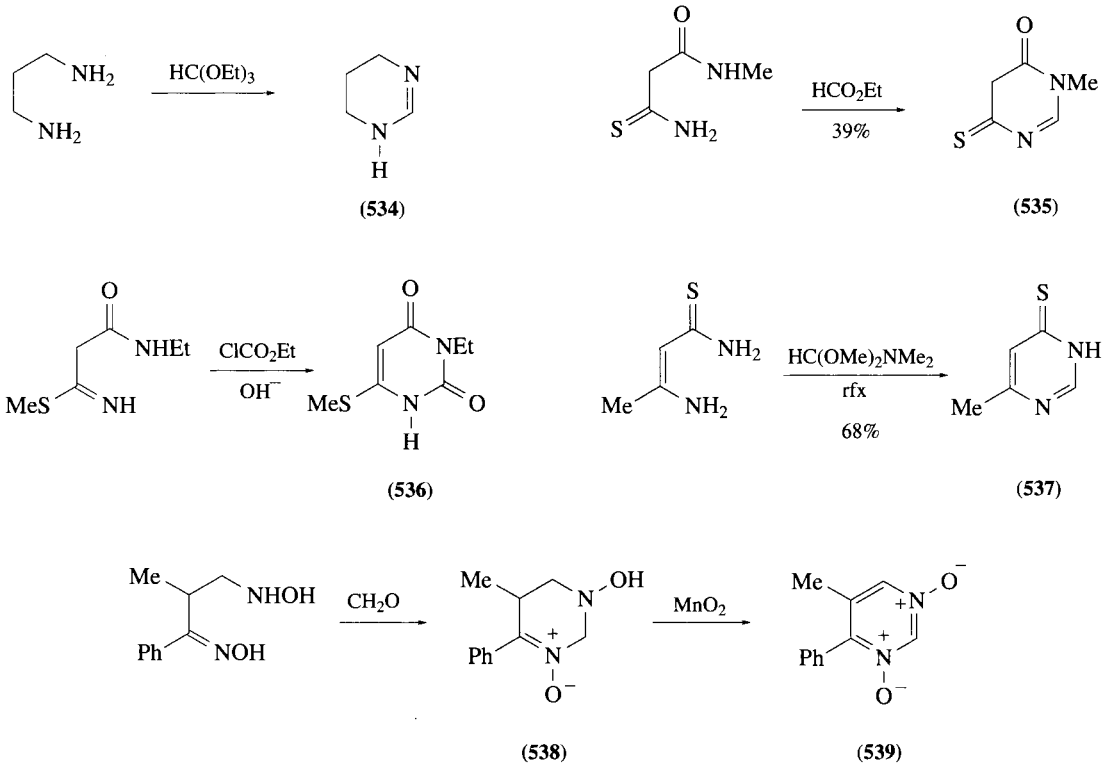
Cyclization of a β-amino imine with an aldehyde yields a tetrahydropyrimidine. At the hydroxylamino level the 1,2,5,6-tetrahydro-1-pyrimidinol 3-oxide (**538**) was formed. MnO_2 oxidation gave the 1,3-dioxide (**539**) in 56% yield. Without substituents, the yield of pyrimidine 1,3-dioxide was 8% ⟨75TL2721⟩.

6.02.9.3 From Two Components of Two and Four Ring Atoms

6.02.9.3.1 The two-atom component consists of N—C2

The four-atom unit is an unsaturated β-amino ester, β-amino nitrile, β-amino amide, or an equivalent structure (Scheme 85). The two-atom unit is an isocyanate or an isothiocyanate, a carboximidic ester or carboximidoyl chloride, a thioamide, an amide or amidine, a cyanamide, a carbodiimide, and a nitrile ⟨B-94MI 602-01⟩.

Several syntheses have been carried out using an unsaturated β-amino ester and an isocyanate to form *N*3-substituted uracils. Thus, phenylisocyanate reacts with the ethyl 3-anilinoacrylate (**540**) with triethylamine as base to form 6-methylthio-2,4-dioxo-1,3-diphenyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**541**). An imidate reagent is provided by ethyl 2-thiophenecarboximidate, which reacts with ethyl 3-aminocrotonate to furnish the 2-(2-thienyl)-4(3*H*)-pyrimidinone (**542**) ⟨66LA(700)87⟩. Phosphorus oxychloride attacks a carbonyl oxygen whereupon the carbonyl carbon becomes strongly electrophilic and is attacked by a cyano or possibly an iminochloride nucleophile, as shown in the formation of 6-chloro-2,4-diphenylpyrimidine (**543**) ⟨79AJC669⟩. Cyanamide reacts with 4-aminopent-3-en-2-one and 3-substituted derivatives in aqueous solution to form the 2-aminopyrimidines (**544**) in high yield ⟨87SC1309⟩. A carbodiimide reacts in an analogous manner. Heating 2-substituted 3-aminoacrylaldehydes and diphenylcarbodiimide gave 2-phenylimino-



Scheme 84

pyrimidines (**545**) ⟨78CB2003⟩. Ethyl 3-amino-2,4-dicyanocrotonate as its sodium salt, is treated with 2,2,2-trichloroacetonitrile, when the amino nitrogen initiates the reaction by addition to the cyano group of the acetonitrile, eventually forming (**546**) ⟨87H(26)497⟩.

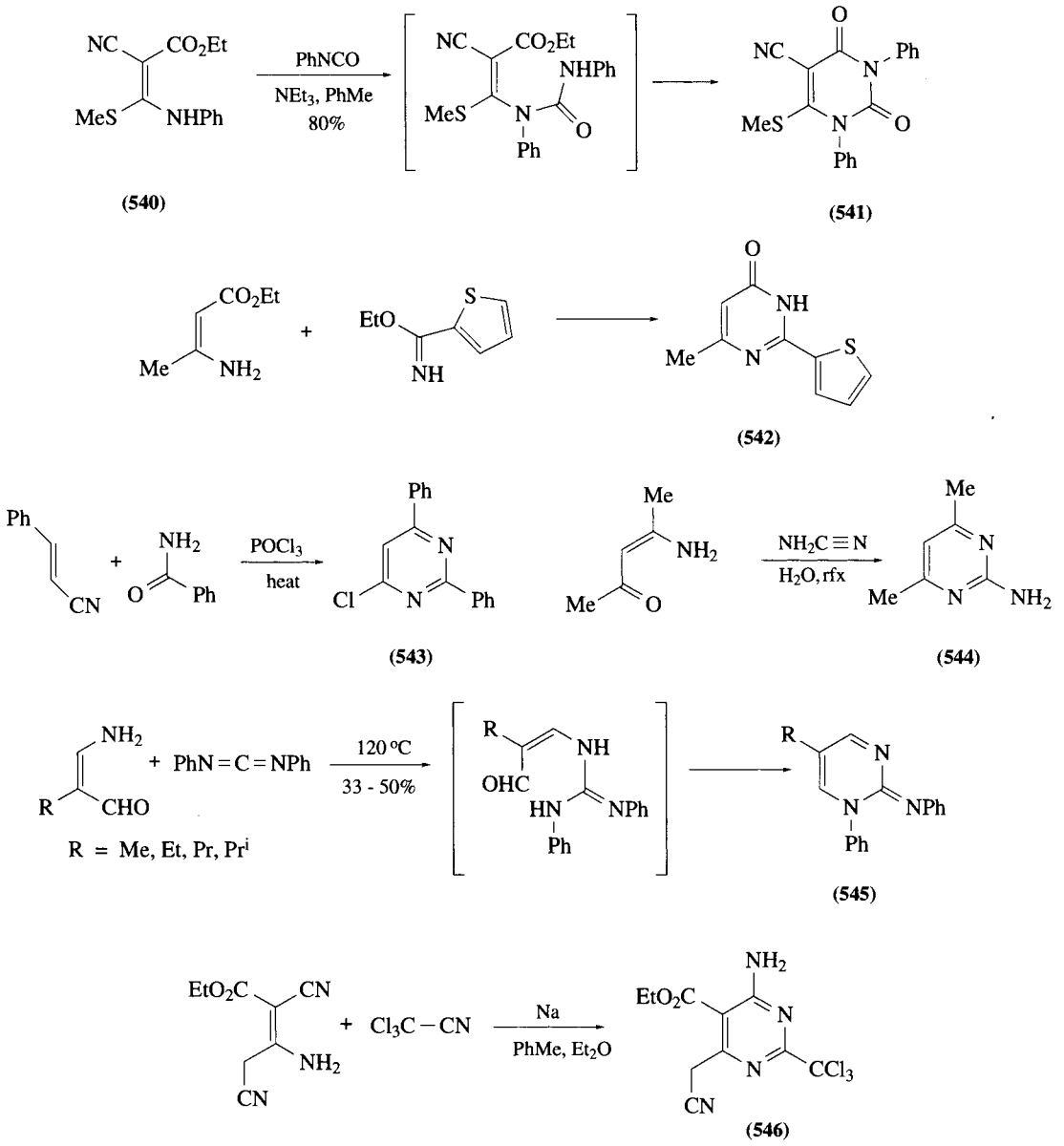
6.02.9.3.2 The two-atom component consists of C4—C5

The four-atom component is an *N*-formyl, *N*-cyano, or *N*-methylene amidine, an *N*-carbamoyl or *N*-cyano carboximidate, or an *N*-cyano or *N*-methylene urea or thiourea. The two-atom component is an oxo derivative or a nitrile with an α-hydrogen, or a Michael acceptor.

N-Formylamidines are generated *in situ* from trisacylaminomethanes in formamide at 150–200 °C with acid catalysis. Exemplification is provided by the reaction with dimethyl malonate, which yields the 4-oxo-3,4-dihydro-5-pyrimidinecarboxylate (**547**) (Scheme 86).

The *N*-cyano example is from the reaction between *N*-cyano-*S*-methylisothiourea and cyclohexanone, which forms 2-methylthio-5,6,7,8-tetrahydro-4-quinazolinamine (**548**). Acyclic ketones yield the corresponding 5,6-disubstituted pyrimidines but in inferior yields, for example, the 5-methyl-6-ethyl derivative from diethyl ketone ⟨81CPB948, 93AHC(57)1⟩.

Heterodienes, in particular azadienes, are useful tools for construction of heterocyclic compounds through pericyclic processes ⟨93AHC(57)1⟩. Thus the Diels–Alder reaction employing heterodienes represents a very efficient approach to nitrogen-containing six-membered heterocycles by [4 + 2] cycloaddition ⟨83T2869, 87H(26)777, B-87MI 602-02,B-90MI 602-01, 91MI 602-04⟩. Cyclization can be effected with electron deficient alkynes as in the preparation of (**549**) ⟨92TL3449⟩. Related reactions exist between substituted 1,3-diazadienes with DMAD ⟨76JCS(P1)1523, 76JCS(P1)1528, 90TL7357⟩. With ketenes, [4 + 2]-cycloaddition yields 4-pyrimidinones (**550**) ⟨86TL5875, 88TL921, 91S1026, 91T1473⟩. Cycloaddition reactions between the diazadiene (**551**) and 4-methyl-2-oxazolin-5-ones (**552**), as masked methyl amidoketenes, give 6-pyrimidinones (**553**) stereoselectively ⟨91TL5151⟩. Reversed polarization, as in the 2-trimethylsilyloxy- and 2-trimethylsilylthio-1,3-dienes (**554**), allow pericyclic

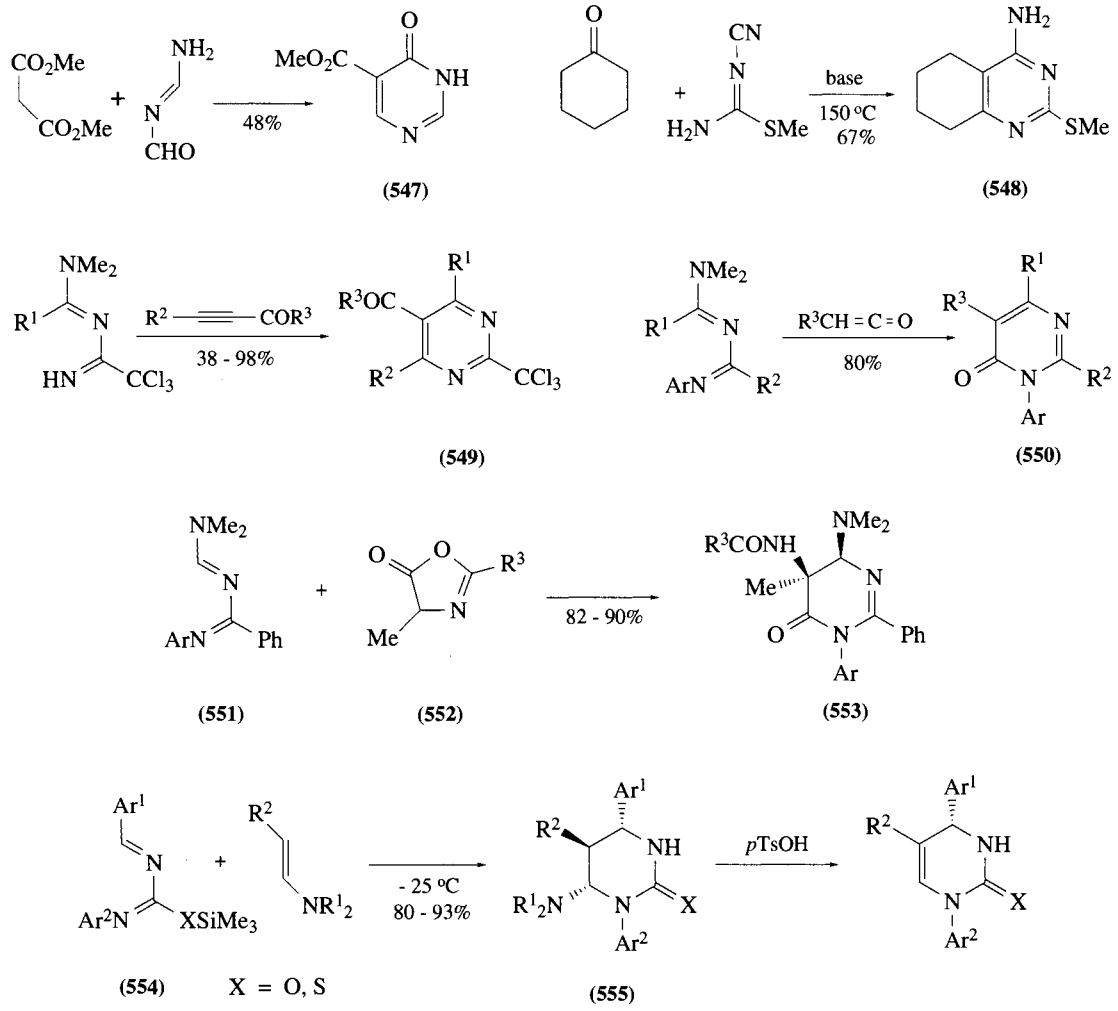


Scheme 85

reactions with acyclic or cylic enamines from pyrrolidines or morpholine. Pyrimidinones and pyrimidinethiones (**555**) are formed in high yields in dichloromethane in a regio- and stereoselective manner ⟨89TL4573, 90TH 602-01⟩.

(i) Quinazolines

Quinazolines can be prepared by pericyclic reactions. A wider scope for the preparation of quinazolines from benzene is discussed in Section 6.02.10.2.1. Pericyclic reactions such as the thermal six-electron electrocylic ring closure of 1-aryl-1,3-diazadienes (**557**) (Scheme 87) is illustrated by the reaction of *N*-imidoyliminotriphenylphosphorane (**556**; X = PPh_3) and aliphatic and aromatic aldehydes in boiling xylene to give 3,4-dihydroquinazolines (**558**) ⟨90TL903, 91T5819⟩. Similarly, *S,S*-dimethyl-*N*-(*N*-arylbenzimidoyl)sulfimides (**556**; X = SMe_2) furnished quinazolines (**559**) in 30–80% yield ⟨89S214⟩, or dihydroquinazolines (**558**) in 45–57% yield upon heating in refluxing tetralin with enamines derived from aldehydes and ketones, respectively ⟨90T3581⟩. Electrocyclic ring closure



Scheme 86

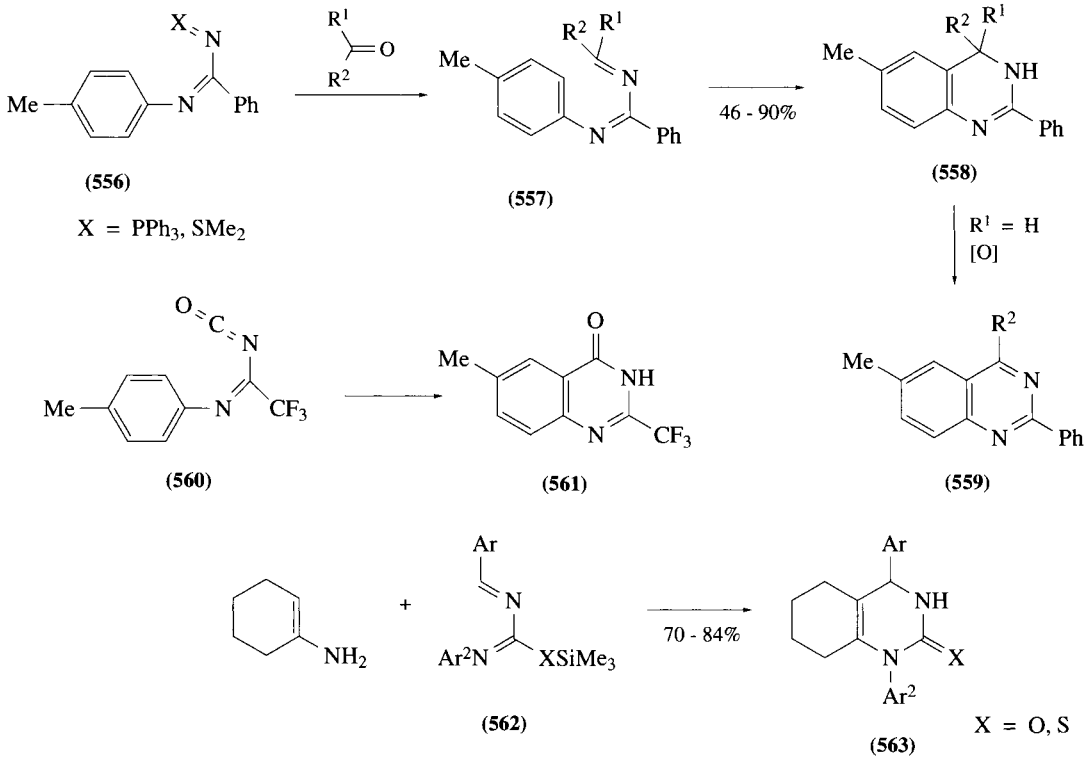
of the trifluoromethyl isocyanate (**560**) allows the construction of the 2-trifluoromethyl-4(3*H*)-quinazolinone derivative (**561**) ⟨90TL2717⟩. With reversed polarization, as in the 2-trimethylsilyloxy- and 2-trimethylsilylthio-1,3-dienes (**562**), pericyclic reactions with enamines derived from cyclohexanone gave quinazolinones and quinazolinethiones (**563**) ⟨89TL4573, 90TH 602-01⟩.

6.02.9.4 From Two Components with Three Ring Atoms

This constitutes by far the most important route for the preparation of pyrimidines. The routes can be divided into two classes: the combination of an N1—C2—N3 with a C4—C5—C6 component, and the combination of a C2—N3—C4 with a C5—C6—N1 component.

6.02.9.4.1 Synthesis by combination of an N1—C2—N3 and a C4—C5—C6 component

The ring atoms in the C3-component are from a 1,3-dicarbonyl derivative; the oxo group may be that of an aldehyde, ketone, ester, or equivalents such as an amide or a nitrile in any combination. The survey is subdivided according to these functionalities.



(556) (557) (558) (559) (560) (561) (562) (563)

Scheme 87

The N1—C2—N3 component is most frequently an amidine, a guanidine, a urea or a thiourea or their equivalents.

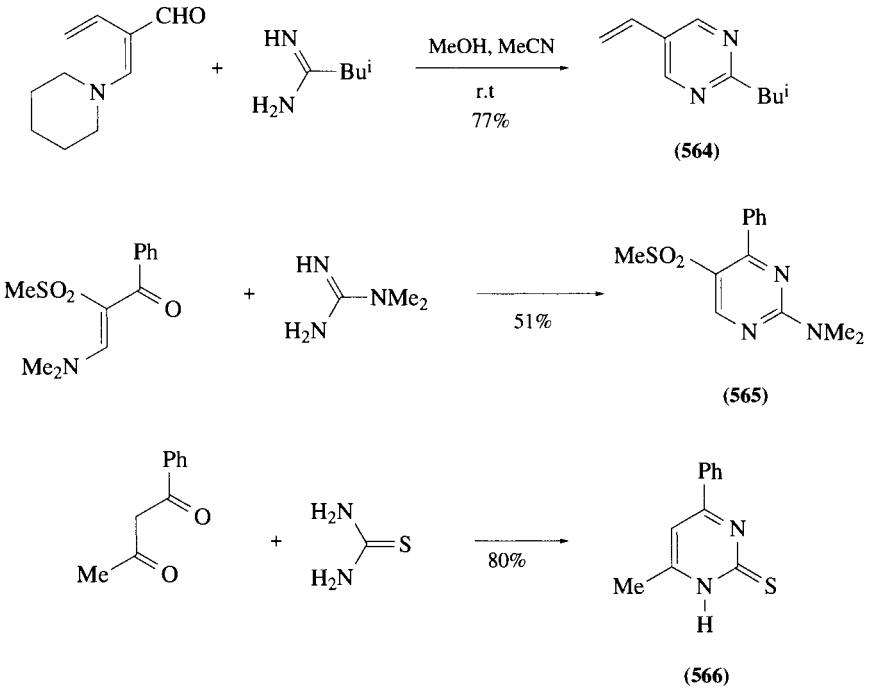
(i) β-Dialdehydes, aldehydo ketones, and β-diketones

Malonaldehyde itself is unstable and is employed as its diacetal, 1,1,3,3-tetraalkoxypropane. Substituted malondialdehydes form pyrimidines substituted in the 5-position with an alkyl, aryl, halo, or hetero substituent. The pyrimidine is unsubstituted in the 4- and 6-positions. β-Dialdehyde equivalents are frequently used in these reactions, for example, 3-alkoxy- or 3-aminoacroleins (Scheme 88). In the synthesis of 2-isobutyl-5-vinylpyrimidine (**564**), the β-aminoacrolein was 3-piperidino-2-vinylacrolein, which was reacted with isovaleramidine in methanolic acetonitrile ⟨86S786⟩. With aldehydo ketones, the pyrimidine carries a substituent in the 4-/6-position. Free aldehydo ketones are for stability reasons seldom employed. The formyl group in the ketone is normally masked as an alkoxymethylene ketone or as an aminomethylene ketone. An example of the latter type is provided by the reaction between 1-benzoyl-2-dimethylamino-1-methylsulfonylethene and *N*,*N*-dimethylguanidine, with formation of the 5-methanesulfonyl pyrimidine (**565**) ⟨86JHC77⟩.

Thioureas react readily with β-diketones, and reactions with thioureas in many cases give higher yields than ureas in pyrimidine cyclizations. *S*-Alkylisothioureas are frequently used instead of thioureas. The 2-alkylthio group in the pyrimidine is readily exchangeable, especially after oxidation. As a typical example, thiourea with benzoylacetone in acidic ethanol gives 6-methyl-4-phenyl-2(1*H*)-pyrimidinethione (**566**) ⟨84AJC155⟩.

(ii) β-Aldehydo esters, β-keto esters, and β-diesters

There are few cases in which free β-aldehydo esters have been condensed successfully with ureas. Commonly, alkoxymethylene esters are used (Scheme 89). The initial reaction leads to an acyclic



Scheme 88

intermediate that may require a separate treatment to induce ring closure. The reaction between *N*-benzyloxyurea and ethyl 3-ethoxyacrylate yields a precursor to uracil *N*1-oxide: 1-benzyloxyuracil (**567**) ⟨64M1729⟩. The reaction of a β-keto ester with urea may be a two-step process in which case acid catalysis can be used in the formation of an acyclic intermediate, with ring closure effected by strong alkali. In the synthesis of 2-methoxy-6-methyl-4(3*H*)-pyrimidinone (**568**), ethyl acetoacetate was reacted with *O*-methylisourea in an aqueous mixture ⟨84T3313⟩.

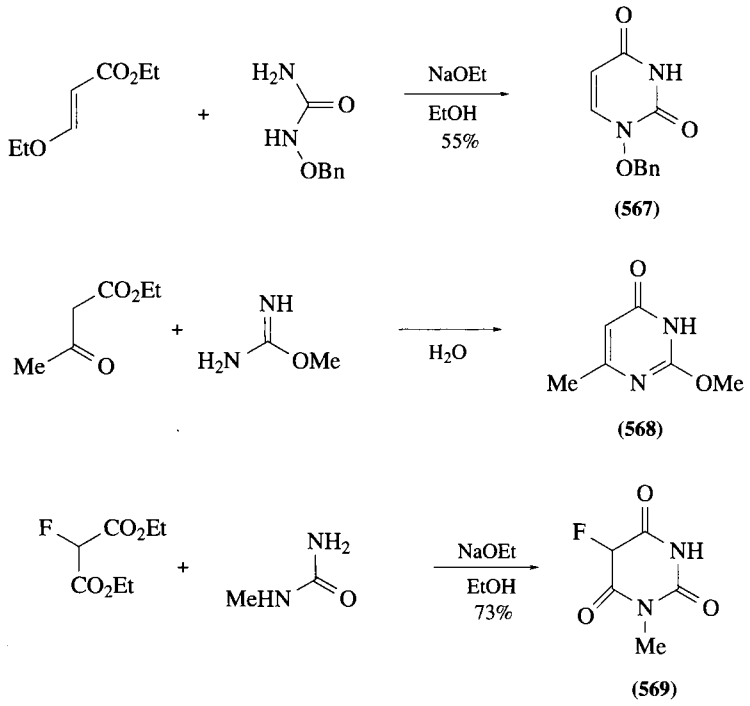
β-Diesters are malonates. Barbiturates are often made from substituted malonates by this route. Thus the reaction between diethyl fluoromalonate and *N*-methylurea gave 5-fluoro-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**569**) ⟨84CL1573⟩.

(iii) β-Aldehydo nitriles, β-keto nitriles, β-ester nitriles and β-dinitriles

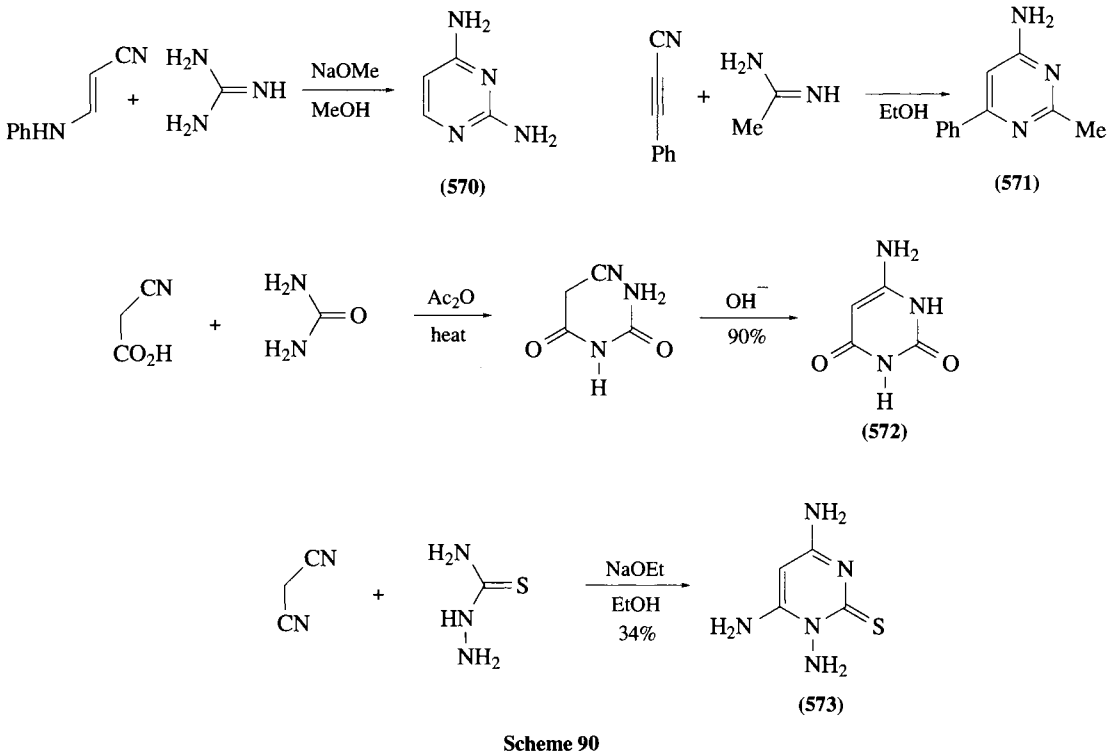
β-Aldehydo nitriles are readily available. 4-Amino-6-unsubstituted pyrimidines are formed which carry one or more substituents in any of the other positions. Equivalents of the formyl group are also often used, for example a 3-ethoxy-, 3-amino-, or 3-haloacrylonitrile (Scheme 90). The amino modification is exemplified in the reaction with guanidine yielding 2,4-pyrimidinediamine (**570**) ⟨86JCS(P1)747⟩. Most syntheses with β-keto nitriles are carried out with equivalents thereof. Such equivalents are β-substituted β-alkoxy-, β-amino-, or β-haloacrylonitriles. 3-Phenylpropynenitrile, an equivalent of 2-benzoylacetonitrile, reacts with ethanolic acetamidine to give 2-methyl-6-phenyl-4-pyrimidinamine (**571**) ⟨84JCS(P2)2677⟩.

β-Ester nitrile reactions are well established. New work is largely limited to improvements on old procedures. This type of reaction is exemplified by the synthesis of 4-amino-2,6(1*H*,3*H*)-pyrimidinedione (**572**) from cyanoacetic acid and urea; acetic anhydride is used to form the acyclic intermediate *N*-(cyanoacetyl)urea which is subsequently ring closed under strongly alkaline conditions ⟨70MI 602-01⟩.

Malononitriles and substituted malononitriles react readily with thiourea and *N*-substituted thioureas in refluxing ethanolic sodium ethoxide to form pyrimidine-4,6-diamines. With thiosemicarbazide as the thiourea reactant, the *N*-aminopyrimidine, 1,4,6-triamino-2(1*H*)-pyrimidinethione (**573**), is formed ⟨67JOC2379⟩.



Scheme 89

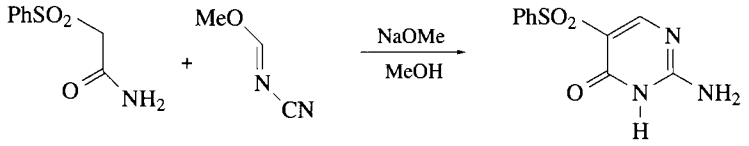


Scheme 90

6.02.9.4.2 Syntheses by combination of a C2—N3—C4 and a C5—C6—N1 component

Several examples of this approach are described in which the C5—C6—N1 component is an enamine in reactions with an acyl isothiocyanate, whereby 4(3*H*)-pyrimidinethiones are formed (Equation (18)). A 2-substituted acetamide is equivalent to an enamine in this reaction. Thus 2-

(benzenesulfonyl)acetamide reacts with methyl *N*-cyanoformimidate to yield 2-amino-5-benzenesulfonyl-4(3*H*)-pyrimidinone (**574**) ⟨85JCS(P1)87⟩.



(18)

(574)

6.02.9.5 From Three Components of Ring Atoms

6.02.9.5.1 Syntheses by combination of C2—N3, C4—C5, and C6—N1 components

The C2—N3 and C6—N1 components are usually the same. Formamide or a nitrile are common C—N components. A classical example is the trimerization reaction of acetonitrile at 150°C in the presence of sodium or potassium methoxide. The product is 2,6-dimethyl-4-pyrimidinamine ⟨B-94MI 602-01⟩.

6.02.9.5.2 Syntheses by combination of N1—C2—N3, C4—C5, and C6 components

Most reactions in this subgroup have been between a methylene ketone, an aromatic aldehyde and urea or thiourea. The product is a dihydropyrimidin-2-one or -2-thione ⟨B-94MI 602-01⟩.

6.02.9.5.3 Syntheses by combination of N1, C2—N3, and C4—C5—C6 components

The three-carbon component in this subgroup is either a β-dicarbonyl compound or a β-ketonitrile. The N and C—N components in the reactions with β-dicarbonyl compounds come from formamide, a nitrile, a thiocyanate, or a cyanamide ⟨B-94MI 602-01⟩. Treatment of a β-dicarbonyl compound with excess of formamide at elevated temperatures is a good route for the preparation of *C*-alkyl- and *C*-arylpyrimidines ⟨56AG151⟩.

6.02.9.5.4 Synthesis by combination of C2, N3—C4, and C5—C6—N1 components or by combination of N1—C2, N3—C4—C5, and C6 components

These subgroups are poorly represented in the literature.

6.02.9.5.5 Syntheses by combination of four components

Pyrimidines have been formed in reactions involving multiple bond formations. The reactions of this subgroup have a long history. No new significant developments appear to have been reported ⟨B-94MI 602-01⟩.

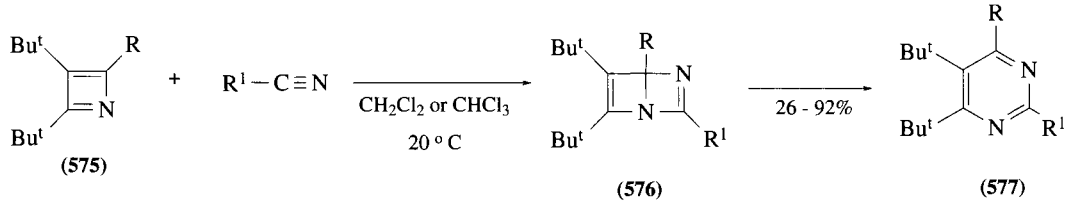
6.02.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Pyrimidines have been obtained after transformation of other monoheterocycles, or from fused pyrimidine heterocycles in reactions in which the pyrimidine ring is set free in ring opening or elimination reactions. The syntheses have been grouped according to the size and the nature of the ring system acting as substrate for the ring transformations.

6.02.10.1 Pyrimidines

6.02.10.1.1 Ring synthesis by transformation of a four-membered ring

Kinetically stabilized azetes (**575**) react with acceptor-substituted nitriles in a [4 + 2] cycloaddition step (Scheme 91). The initially formed Dewar pyrimidine (**576**) is subsequently isomerized to the pyrimidine (**577**). The sterically demanding substituents necessary for the stabilization of the azetes are thus introduced into the pyrimidine ring ⟨90SL401⟩.



R = Bu^t,C_6H_2-2,4,6-Me_3

R^1 = CO_2Et, CF_3, CN, *p*-Ts, C_6H_4-4-CF_3

Scheme 91

6.02.10.1.2 Ring synthesis by transformation of a five-membered ring

(i) Furans

Furans have occasionally been used as substrates for pyrimidine syntheses which involve acyclic intermediates as in most of the other ring structures used in the construction of the pyrimidine ring ⟨B-94MI 602-01⟩. In the furan example shown (Scheme 92), *N*-butylisomaleimide was reacted with trimethylsilyl azide, when the *N*3-butyluracil (**579**) was formed after simple removal of the *N*1-silyl group ⟨72JOC1738⟩.

(ii) Pyrroles

Reference is made to ⟨B-94MI 602-01⟩.

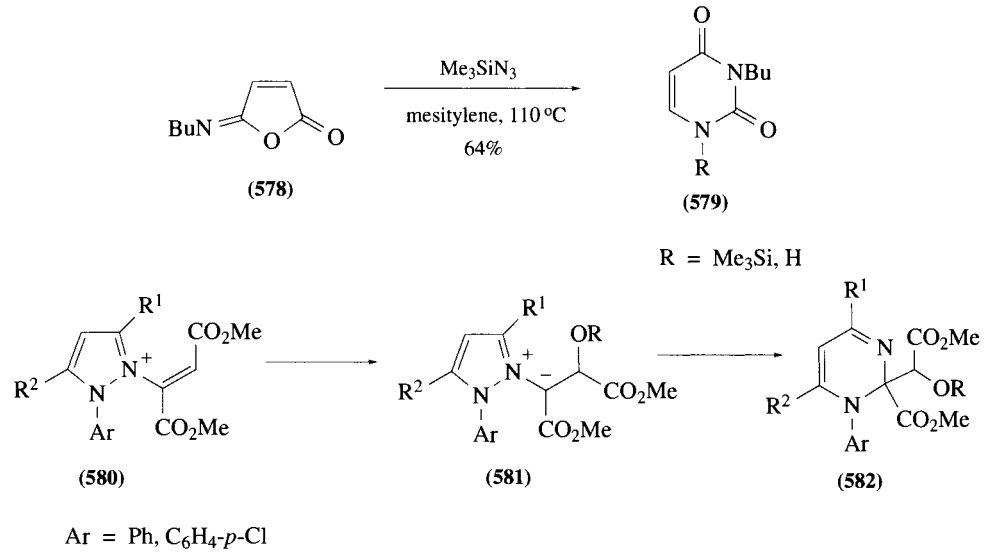
(iii) Diazoles, oxa-, and thiazoles

Reference is in general made to ⟨B-94MI 602-01⟩. One example from the early 1990s is provided by the rearrangement of pyrazoles to pyrimidines, which can be effected under mild conditions, pH about 9, and room temperature, by the addition of an oxygen nucleophile to an exocyclic double bond (**580**) (Scheme 92). The intermediate betaine (**581**) subsequently suffers ring expansion with formation of 1,2-dihydropyrimidines (**582**) ⟨92JOC4151⟩.

6.02.10.1.3 Ring synthesis by transformation of a six-membered ring

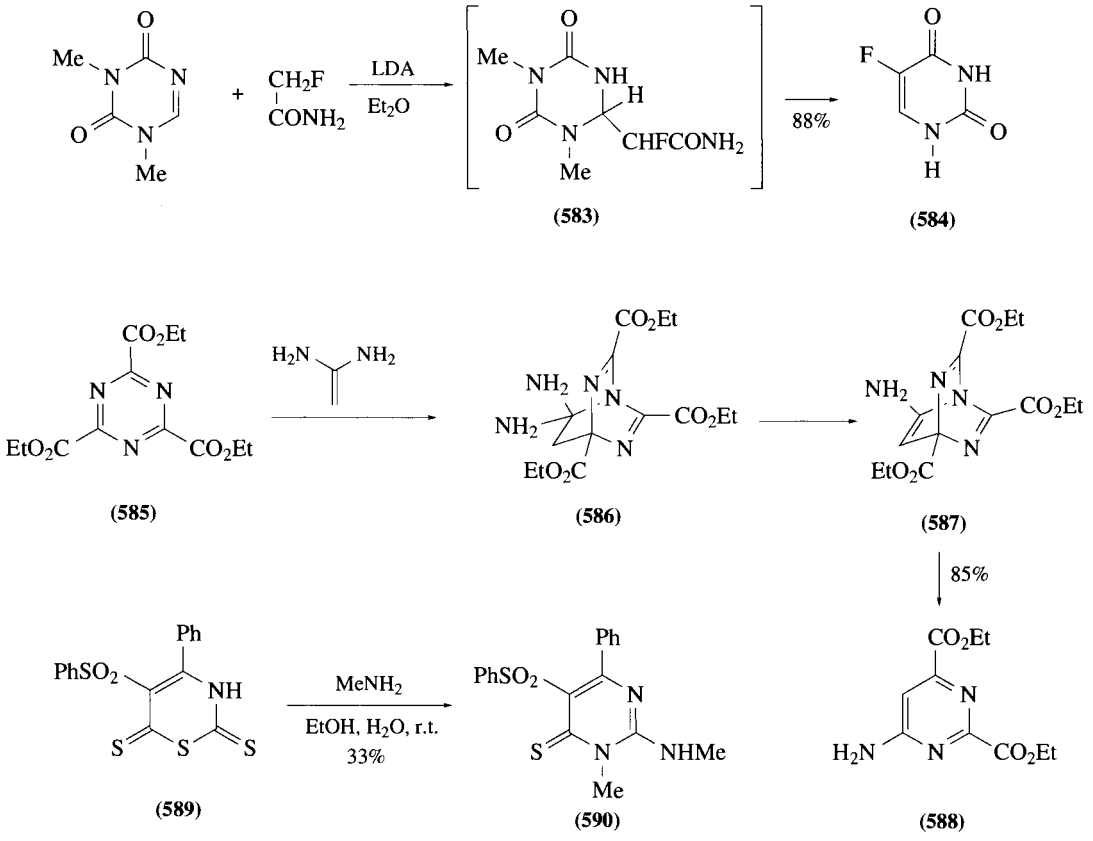
(i) Triazines

1,3,5-Triazines are versatile substrates for ring transformations. The ring system is highly electrophilic and will add nucleophiles to a ring carbon atom, especially in a vacant position. Adduct formation is succeeded by a ring opening or a second bond formation before an elimination reaction. Thus the methylene group of fluoroacetamide, after deprotonation by LDA, adds to 1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (Scheme 93). The intermediate adduct (**583**) loses *N*,*N*′-dimethylurea and 5-fluorouracil (**584**) is formed ⟨83JHC457⟩.



(578) (579) (580) (581) (582)

Scheme 92



(583) (584) (585) (586) (587) (588) (589) (590)

Scheme 93

[4 + 2] Cycloaddition reaction of triethyl 1,3-5-triazinetricarboxylate (**585**) with 1,1-diaminoethene, which is generated *in situ* from acetamidine hydrochloride, provides an adduct (**586**) which subsequently eliminates ammonia (**587**) and undergoes a retro Diels–Alder reaction with loss of ethyl cyanoformate, thereby forming the pyrimidine (**588**). The reaction sequence is highly dependent

on the reaction conditions. Temperatures >80°C facilitate amidine tautomerization to the reactive species for the Diels–Alder reaction, and the elimination of ammonia and the retro Diels–Alder reaction are both facilitated by the acid of amidine hydrochloride ⟨92JOC1631⟩.

(ii) Oxazines and thiazines

1,3-Oxazines and 1,3-thiazines have been used quite extensively as substrates in pyrimidine syntheses ⟨B-94MI 602-01⟩. 1,3-Thiazines are intermediate structures in several cyclization reactions involving thioxo substrates. Pyrimidine formation from thiazines may involve a Dimroth-like rearrangement of a thiazinamine, an aminolytic displacement of the ring sulfur atom, or a combination of both. Aqueous ethanol in methylamine converts 4-phenyl-5-phenylsulfonyl-2*H*-1,3-thiazine-2,6(3*H*)-dithione (**589**) into the pyrimidine (**590**) by displacement of the ring sulfur and a nucleophilic substitution of the thioxo sulfur in the 2-position (Scheme 93) ⟨88JHC835⟩.

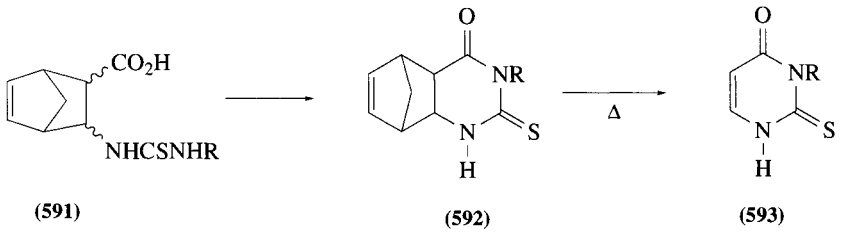
6.02.10.1.4 Ring synthesis from a fused pyrimidine with a five-membered ring

A great number of pyrimidines fused to five-membered rings have been degraded to substituted pyrimidines: furo[2,3-*d*]-, thieno[2,3-*d*]-, pyrrolo[1,2-*c*]-, pyrazolo[3,4-*d*]-, imidazo[1,2-*a*]-, imidazo[1,2-*c*]-, imidazo[4,5-*d*]-, *v*-triazolo[1,5-*a*]-, *s*-triazolo[1,5-*a*]-, isoxazolo[3,4-*d*]-, isoxazolo[5,4-*d*]-, oxazolo[3,2-*a*]-, isothiazolo[3,4-*d*]-, thiazolo[3,2-*a*]-, thiazolo[3,2-*c*]-, thiazolo[4,5-*d*]-, thiazolo[5,4-*d*]-, isoselenazolo[4,3-*d*]-, [1,3,2]-diazaphospholo[4,5-*d*]-, [1,2,3]oxadiazolo[5,4-*d*]-, [1,2,4]oxadiazolo[2,3-*a*]-, [1,2,4]oxadiazolo[4,3-*a*]-, [1,2,5]oxadiazolo[3,4-*d*]-, [1,3,4]oxadiazolo[3,2-*a*]-, [1,2,3]-thiadiazolo[4,5-*d*]-, [1,2,4]thiadiazolo[2,3-*a*]-, [1,2,4]thiadiazolo[2,3-*c*]-, [1,2,5]thiadiazolo[3,4-*d*]-, [1,3,4]thiadiazolo[3,2-*a*]pyrimidines. These reactions have been summarized in ⟨B-94MI 602-01⟩.

6.02.10.1.5 Ring synthesis from a fused pyrimidine with a six-membered ring

Pyrimidines fused to other six-membered rings, most frequently in the form of bicyclic structures, can be degraded to corresponding substituted monocyclic pyrimidines. Fused pyrimidine structures described are: benzo- (quinazolines), pyrano[2,3-*d*]-, pyrazino[2,3-*d*]- (pteridines), pyrimido[1,2-*a*]-, pyrimido[4,5-*d*]pyrimidines, and pyrimido[5,4-*e*]-*as*-triazines, pyrimido[5,4-*d*]-*v*-triazine, pyrimido[4,5-*d*][1,3]oxazines, pyrimido[5,4-*d*][1,3]oxazine, pyrimido[4,5-*b*][1,4]thiazines, pyrimido[5,4-*b*][1,4]thiazines, and pyrimido[4,5-*e*][1,2,4]thiadiazines. References to these reactions can be found in ⟨B-94MI 602-01⟩.

An example is provided by a retro Diels-Alder reaction in the preparation of *N*3-substituted 2-thiouracils (**593**) by pyrolysis of 3-substituted 2-thioxo-hexahydro-5,8-methanoquinzolin-4(1*H*)-ones (**592**) (Scheme 94). The latter are available by cyclization of *endo*- and *exo*-norbornene amino acids after prior conversion into thiourea derivatives (**591**) ⟨85JCS(P1)2483⟩.



(591) (592) (593)

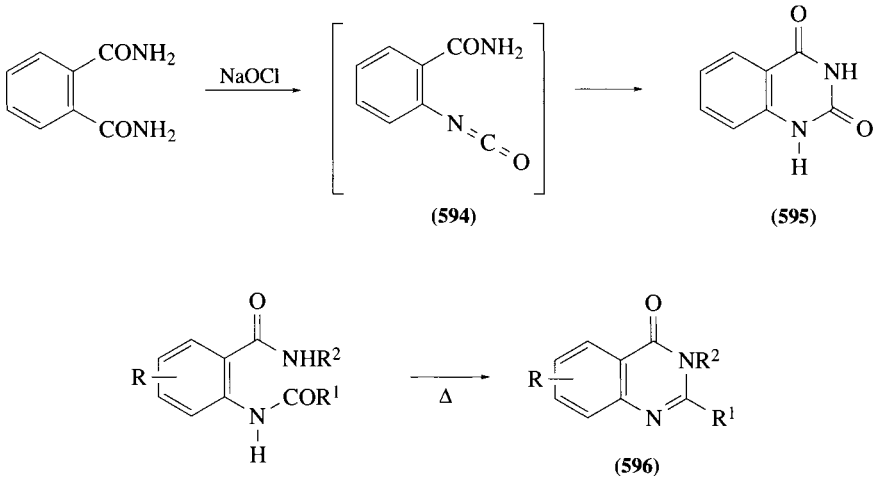
Scheme 94

6.02.10.2 Quinazolines

6.02.10.2.1 Benzenes as substrates classified by atom number in the pyrimidine ring

(i) Cyclization across C2—N3 with preformed intermediate

Hofmann type degradation of phthalic acid diamides proceeds through an intermediate isocyanate (**594**) which is trapped by the neighboring amide nitrogen with cyclization to a quinazoline (**595**) (Scheme 95). Thermal cyclization of *o*-acylaminobenzamides leads to 2-substituted 4(3*H*)-quinazolinones (**596**) ⟨B-67MI 602-01⟩. The benzamide may be generated *in situ* from an ester and an amine. High yields of 4-quinazolinones result from the corresponding benzonitriles by addition of alkaline hydrogen peroxide to the cyano group ⟨60JA3152, B-67MI 602-01⟩.

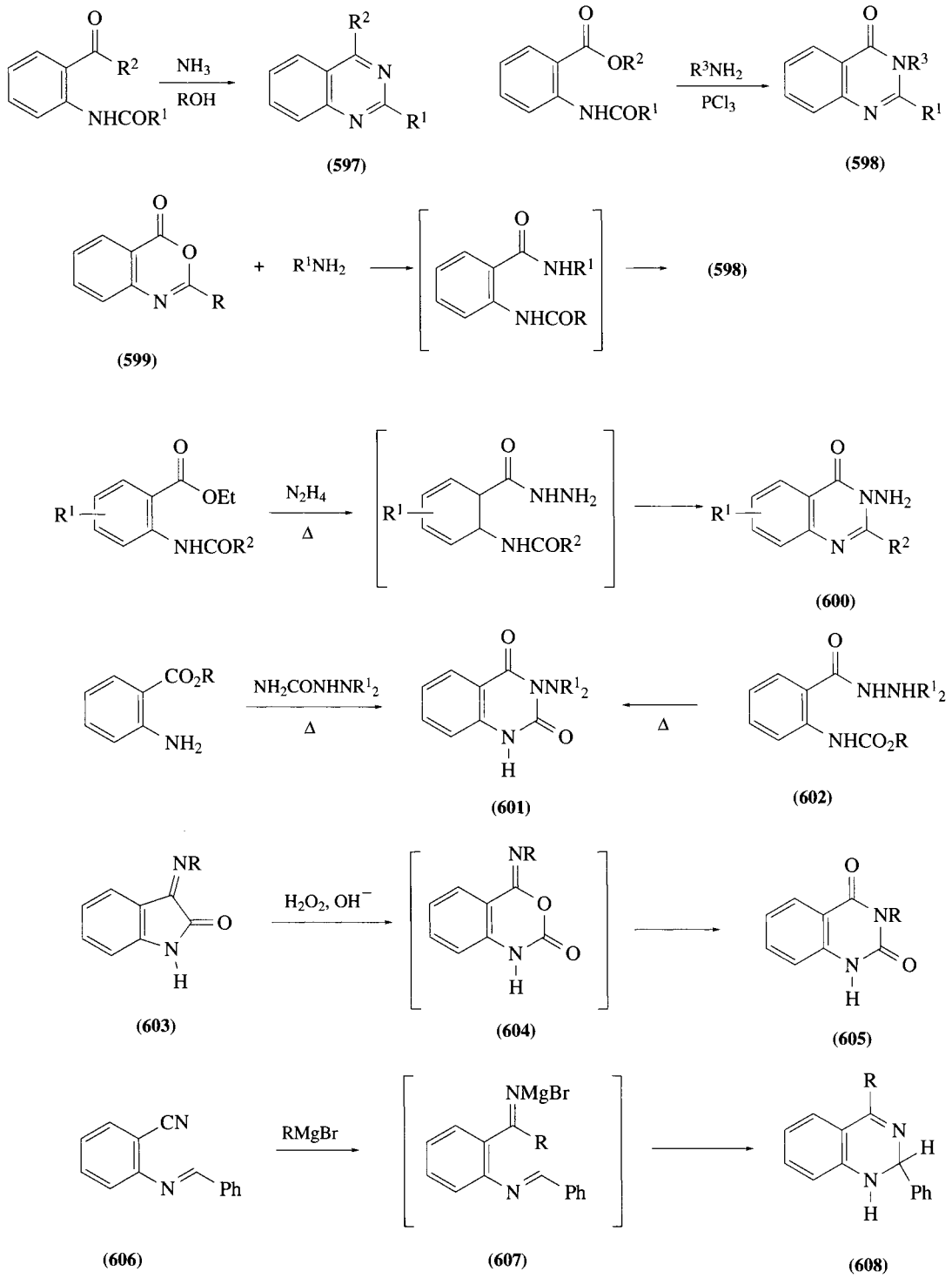


Scheme 95

(ii) C2-Insertion before cyclization

A general method for the preparation of quinazolines substituted in the heterocyclic ring by aryl or alkyl groups (**597**) is available by heating an *o*-acylaminobenzaldehyde or -ketone with ammonia or its salts (Scheme 96). The benzene ring, as in most of the cyclization reactions, can carry compatible substituents ⟨B-67MI 602-01⟩. A widely used method for the preparation of 2,3-disubstituted 4(3*H*)-quinazolinones (**598**) has been the reaction between an acylaminobenzoic acid and a primary amine with phosphorus trichloride as the condensing agent. The reaction proceeds via a phosphazo compound which is formed from the phosphorus halide and the amine ⟨46JA542, B-67MI 602-01⟩. The same sort of intermediate for cyclization to quinazolinones (**598**) is generated from 3,1-benzoxazin-4-ones (**599**). With primary amines, *N*3-substituted 4(3*H*)-quinazolinones (**598**) are formed ⟨B-67MI 602-01⟩.

Similarly, 3-amino-4(3*H*)-quinazolinones (**600**) are formed in high yields when methyl or ethyl *o*-acylaminobenzoates are heated with hydrazine in an alcohol. Alternatively, acylation and cyclization of an *o*-aminobenzoylhydrazine is effected by heating with anhydrous formic acid, ethyl orthoformate, or acetic anhydride. Related is the action of heat on a mixture of anthranilic esters and semicarbazides to yield *N*3-aminated 2,4(1*H*,3*H*)-quinazolinediones (**601**). Reactions which involve *o*-(alkoxycarbonylamino)-benzoylhydrazides (**602**) as intermediates, can be effected by thermal cyclization to 3-aminated quinazolinediones (**601**) ⟨B-67MI 602-01⟩. α-Isatin oximes are rearranged to 2,4(1*H*,3*H*)-quinazolinediones on heating with dilute sodium hydroxide. β-Imino derivatives of isatin (**603**) can be transformed into *N*3-substituted derivatives of 2,4(1*H*,3*H*)-quinazolinedione (**605**) via the intermediate (**604**) with hydrogen peroxide in alkaline solution ⟨B-67MI 602-01⟩. Addition of organometallic reagents to *o*-methyleneaminobenzonitriles (**606**) may be chemoselective for either the cyano or the methyleneamino function. Phenyl- and methylmagnesium bromide add to the cyano group, and the adducts (**607**) cyclize to the methyleneamino group with formation of 1,2-dihydroquinazolines (**608**); the latter are dehydrogenated by DDQ or otherwise to the fully conjugated heterocycle ⟨88TL4265⟩.

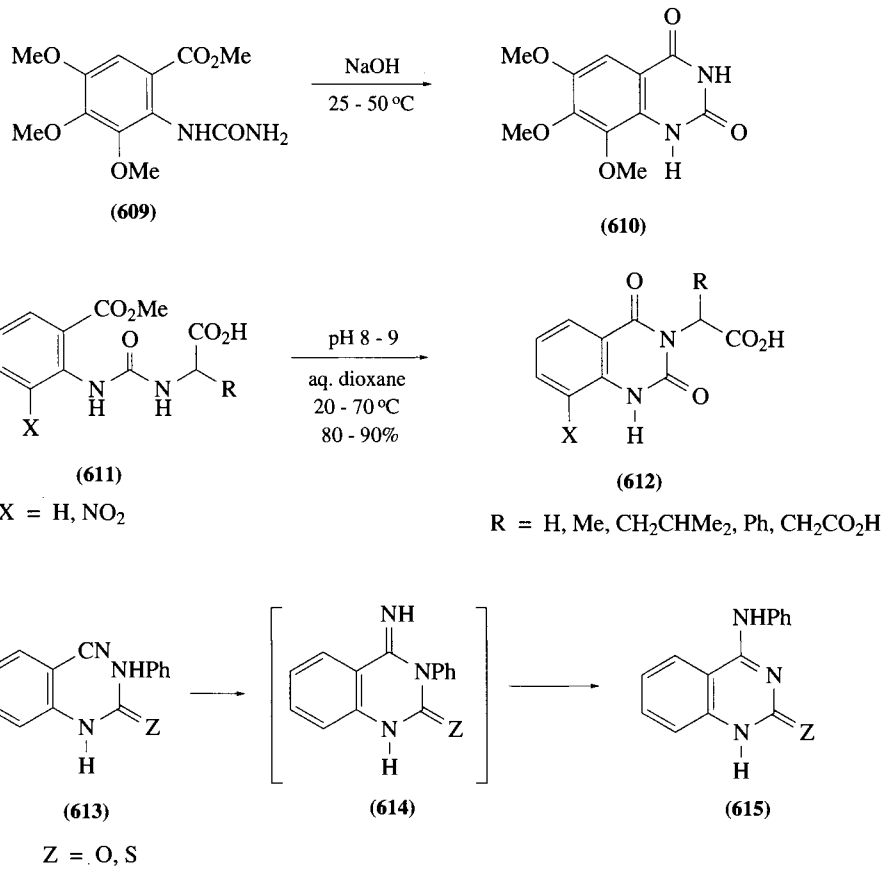


Scheme 96

(iii) Cyclization to N3—C4 with preformed intermediate

o-Ureidobenzoic acids, esters, or amides, for example (**609**), are available from the corresponding anthranilic acid derivative and potassium cyanate and are readily cyclized to 2,4(1*H*,3*H*)-quinazolinediones (**610**) by acids or alkali (Scheme 97). A practical route for the preparation of substituted 2,4-quinazolinediones on a kilogram scale has been described from the corresponding

anthranilic acids. The procedure was developed to supply material for quinazoline antihypertensive agents such as Prazosin and Trimazosin. The ureido intermediate for the cyclization is prepared from the amine with potassium cyanate; the pH should be within the range 6.8–7.3, and cyclization of the ureido acid ester was effected with aqueous sodium hydroxide ⟨87JHC1701⟩. 2,4(1*H*,3*H*)-Quinazolinediones (**612**), in which the nitrogen of an amino acid is incorporated into the fused pyrimidine ring at position 3, are prepared from 2-methoxycarbonylphenyl isocyanate and the amino acid via intermediate (**611**) in aqueous dioxan at pH 8–9. The mild conditions of the cyclization do not affect the chiral center of the amino acid; enantiomerically pure products are obtained ⟨93H(36)1305⟩. *o*-Ureidobenzonitriles (**613**; Z = O) cyclize to 4-imino-2(1*H*)-quinazolinones (**614**), which rearrange to the amine form (**615**), on heating or by reaction with sodium alkoxides. Thiourea gives the corresponding 4-amino-2(*H*)-quinazolinethiones (**615**; Z = S) ⟨B-67MI 602-01⟩.



Scheme 97

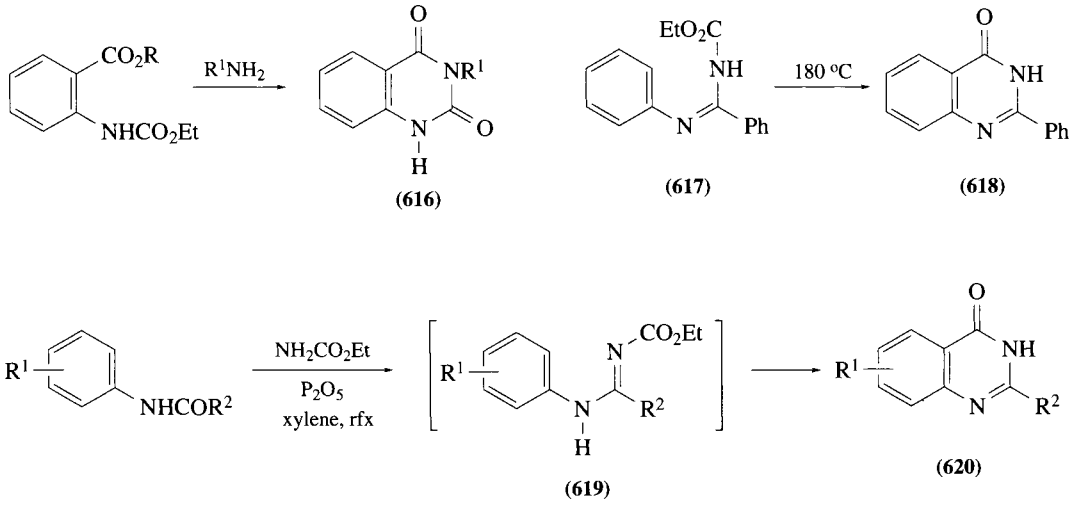
(iv) N3-Insertion before N3—C4 cyclization

*N*3-Substituted 2,4(1*H*,3*H*)-quinazolinediones (**616**) are formed when *o*-(ethoxycarbonylamino)-benzoic esters are heated together with primary amines (Scheme 98) ⟨B-67MI 602-01⟩.

(v) Cyclization of C4—C4a with preformed intermediate

N-Phenyl benzimidoyl chloride and the sodium derivative of urethane react to give *N*-ethoxycarbonyl-*N'*-phenyl phenylformamidine (**617**), which is a substrate for thermal cyclization to the corresponding quinazolinone (**618**) (Scheme 98) ⟨B-67MI 602-01⟩.

Formation of quinazolines from benzenes has also been discussed in the section on pericyclic reactions (Section 6.02.9.3.2; Scheme 87).



Scheme 98

(vi) C4-Insertion before C4—C4a cyclization

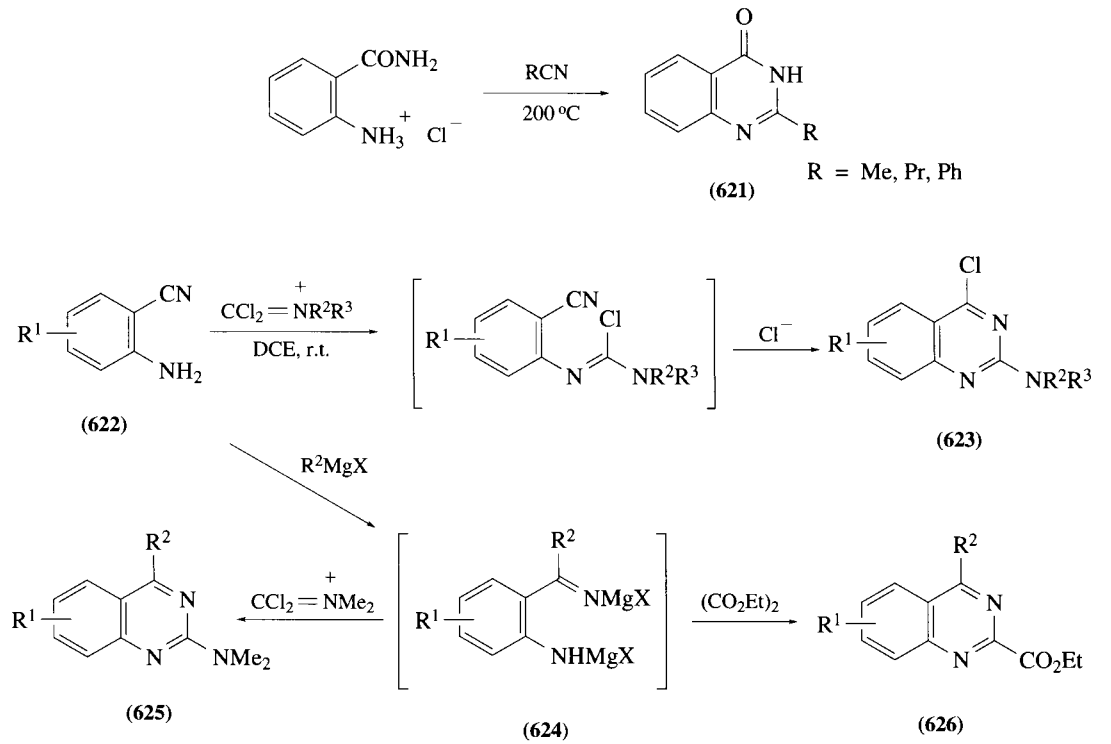
An anilide and urethane react together under the influence of phosphorus pentoxide on heating in xylene to form a 4-quinazolinone (**620**) (Scheme 98). The reactive intermediate for the cyclization reaction is the ethoxycarbonyl amidine (**619**) ⟨B-67MI 602-01⟩.

(vii) C2 Insertion before C4—C4a cyclization

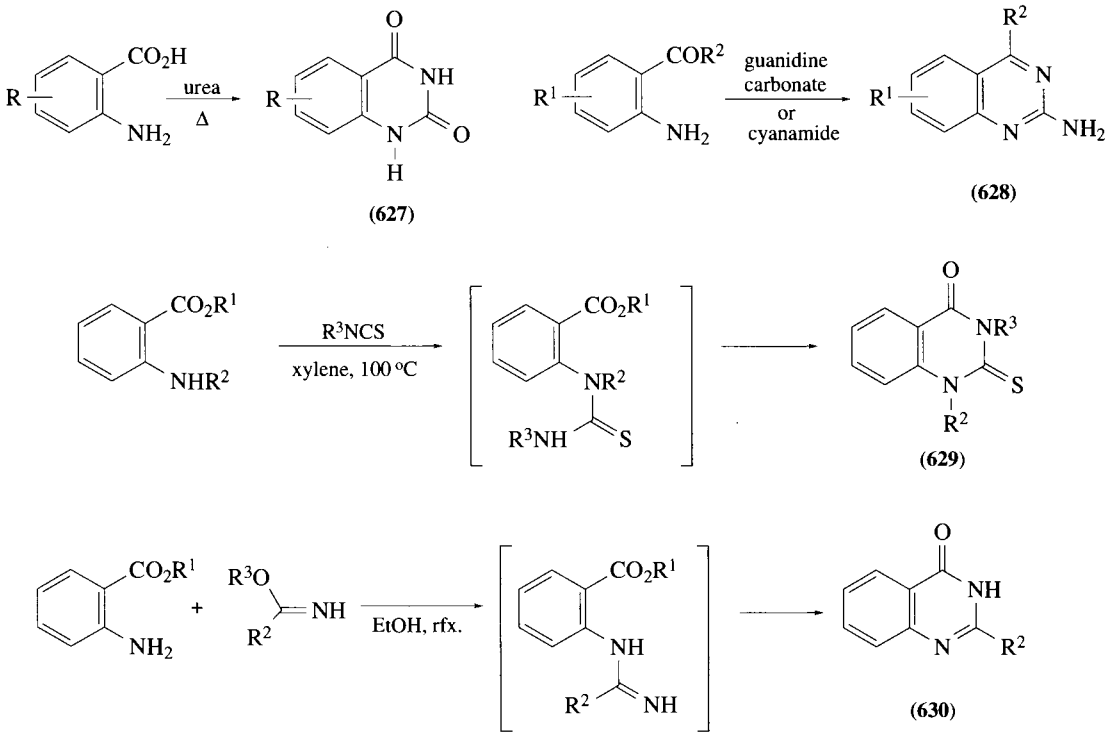
Isatoic anhydrides react readily with an equimolar quantity of amines to form *o*-aminobenzamides. The products are substrates for the reaction with acid anhydrides or methyl orthoformate to yield the corresponding *N*3-substituted 4-quinazolinones (Scheme 99) ⟨B-67MI 602-01⟩. The C2 component can be a cyanide, in which case 2-substituted 4(3*H*)-quinazolinones (**621**) are formed in low to moderate yields on heating ⟨B-67MI 602-01⟩. Heating *o*-aminothiobenzamides with an acid anhydride yields 4(3*H*)-quinolinethiones ⟨B-67MI 602-01⟩. Triphosgene is recommended instead of phosgene in large-scale synthesis of 2,4(1*H*,3*H*)-quinazolinediones by ring closure of *o*-aminobenzamides ⟨91SC285⟩. Phosgeniminium chlorides react with *o*-aminobenzonitriles (**622**) to furnish 2-alkylamino-4-chloroquinazolines (**623**). This procedure is important because the product carries an amino group in the less electrophilic quinazoline 2-position and a chlorine in the more electrophilic 4-position ⟨84TL1557⟩. When Grignard reagents are added to *o*-aminobenzonitriles, the adduct from the addition of the organometallic reagent to the cyano group (**624**) reacts with (dichloromethylene)-dimethylimmonium chloride to furnish 4-substituted 2-aminoquinazolines (**625**). When ethyl oxalate is the electrophile, the product is a quinazoline-2-carboxylate (**626**). When the electrophile is an acid chloride, a 2,4-disubstituted quinazoline is formed. With a chloroformate as the electrophile, the product is a 4-substituted 2(1*H*)-quinazolinone ⟨86T3697⟩.

(viii) C2—N3 Insertion before cyclization

A common method for the preparation of 2,4(1*H*,3*H*)-quinazolinediones (**627**) consists of fusion of anthranilic acid derivatives with urea (Scheme 100). The benzene ring is frequently substituted ⟨B-67MI 602-01⟩. The most satisfactory synthesis of 2-aminoquinazoline (**628**) is by the reaction of guanidine carbonate with *o*-aminobenzaldehyde in boiling decalin. Cyanamide or dicyanamide can be used instead of guanidine carbonate ⟨B-67MI 602-01⟩.



Scheme 99



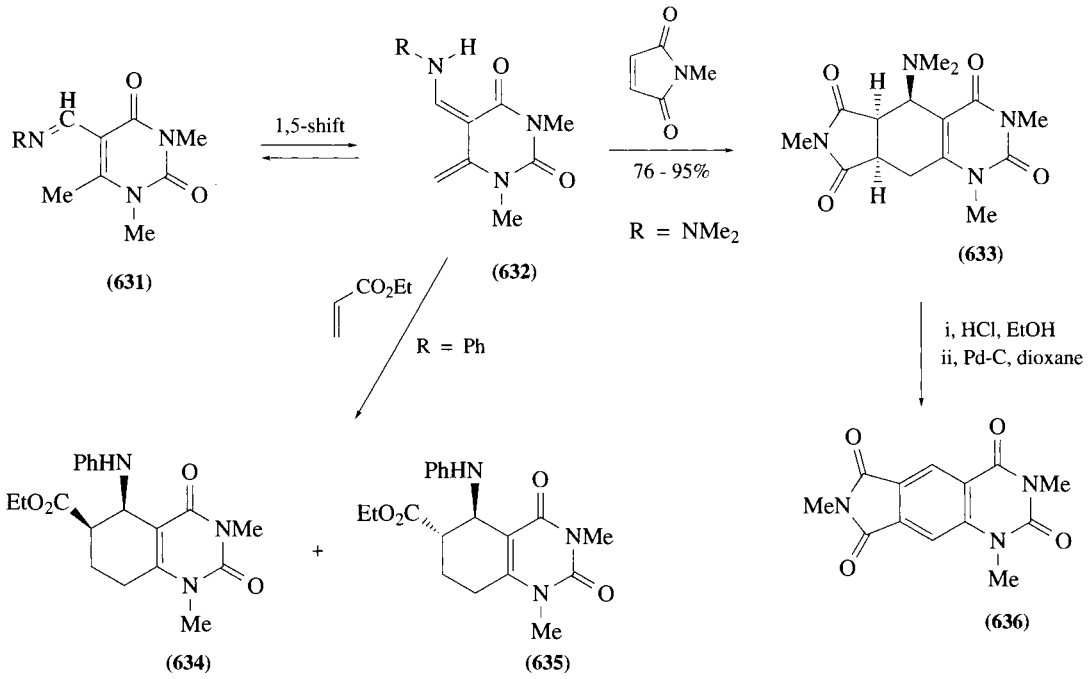
Scheme 100

When an anthranilic acid ester is heated with ammonium thiocyanate, 2-thioxo-4(3*H*)-quinazolinones (**629**) are formed. When alkyl- or aryl-isothiocyanates are used, the corresponding *N*3-substituted 2-thioxo-4-quinazolinones (**629**) are formed ⟨B-67MI 602-01⟩.

Imidates react with anthranilic acid or its methyl ester at elevated temperatures in much the same way as imidoyl chlorides to form 4-quinazolinones (**630**) ⟨B-67MI 602-01⟩.

6.02.10.2.2 Pyrimidines as substrates

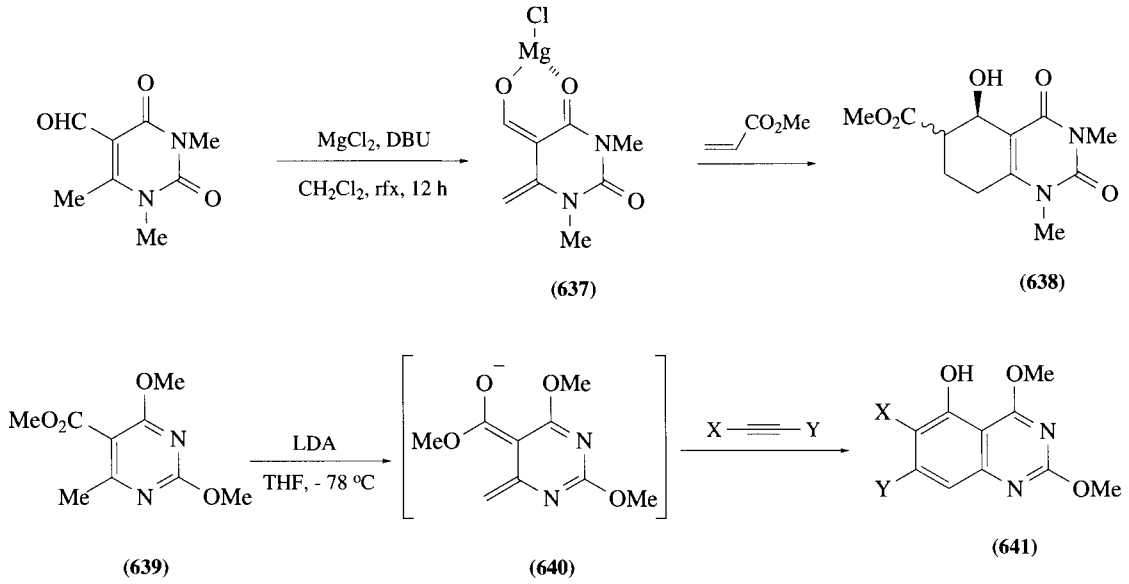
Perhydro-5,6-di(methylene)-2,4-dioxopyrimidine derivatives (**632**) are useful intermediates for the synthesis of fused pyrimidines such as pyrido[3,4-*d*]pyrimidine and pyrrolo[3,4-*d*]pyrimidine, and in particular for cycloaddition reactions leading to quinazoline derivatives (Scheme 101). Thus the reaction between 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine-5-carbaldehyde *N*,*N*-dimethylhydrazone (**631**; R = NMe_2) and *N*-methylmaleimide yields the Diels–Alder adduct (**633**). Substitution in the 6-methyl group in (**631**) leads to 8-substituted quinazoline adducts. Acid-catalyzed eliminations and dehydrogenation give fully conjugated quinazolines (**636**) ⟨89CL2115⟩. Similarly, the 6-methyl group in the aldimine (**631**; R = Ph) is activated and suffers a [1,5] hydrogen shift to give the 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediate (**632**). The intramolecular hydrogen bond between the NH and carbonyl oxygen at C4 plays an important role in stabilization of the system. The reaction with ethyl acrylate gave the 6-ethoxycarbonyl derivatives (**634**) and (**635**) with regiochemistry as indicated. Acrylonitrile and further substituted acrylates react similarly ⟨90BCJ2938⟩.



Scheme 101

In another modification, the 6-methyl group in 5-formyl-1,3,6-trimethyl-2,4-pyrimidinedione is deprotonated with LDA, whereby a lithiated enolate is formed which undergoes intermolecular cyclization reactions leading to fused pyrimidines. A more reactive and more selective metal dienolate can be generated by DBU deprotonation in the presence of magnesium dibromide or dichloride, which gives the magnesium dienolate (**637**) which is stable in methanol. The reaction is regioselective in the formation of the quinazoline adduct (**638**); the steroselectivity varied from 9 : 1 to 6 : 1 for the *cis* structure (Scheme 102). With magnesium dibromide etherate and DBU in dichloromethane, only the *cis* product was formed in the [4 + 2] cycloaddition. Other dienophiles include substituted acrylates and 2-cyclohexen-1-one ⟨92BCJ2845⟩. The lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**639**) undergoes anionic cycloaddition with electron-deficient alkynes to

furnish quinazolines (**641**). The adduct formation proceeds with moderate yields for a variety of electrophilic alkynes or ethylenes with high regioselectivity. Michael addition and subsequent cyclization is favored as reaction path, rather than [4 + 2] cycloaddition of the dienol isomer, since dimethyl fumarate and maleate gave the same stereochemistry in the product. Methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**639**), lithiated in the 6-methyl group (**640**), reacts with electrophilic alkenes or alkynes to form 5-hydroxy-6-substituted quinazolines (**641**) in moderate yields ⟨92JHC911⟩.



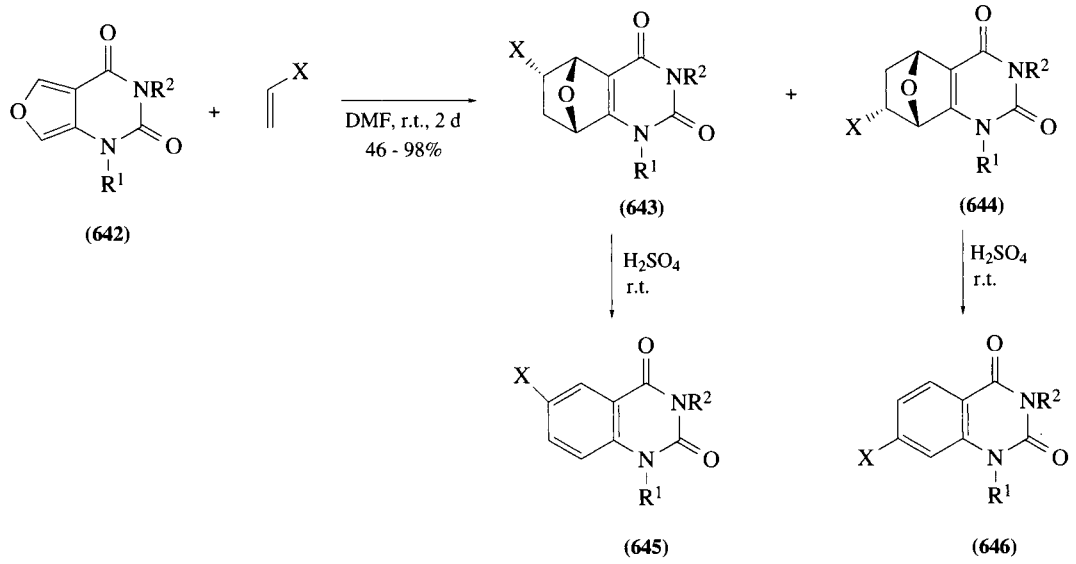
Scheme 102

*N*3-Substituted furo[3,4-*d*]pyrimidine-2,4-diones (**642**) with a number of dienophiles give Diels–Alder adducts under unusually mild reaction conditions (Scheme 103). The regioisomeric 5,8-epoxy-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione adducts (**643**) and (**644**) from methyl acrylate have the *endo* configuration. Other dienophiles give mixtures of mainly *endo* and some *exo* products as well as of regioisomers. In the case of the acrylate adduct, the ratio of 6-isomer to the 7-isomer is 4 : 1 for R = H, and 2 : 1 for R = Me. Alkenes with a single electron-withdrawing group are the best dienophiles. Dimethyl maleate requires heating at 80–100 °C. The sulfur analogue, thieno[3,4-*d*]pyrimidine-2,4-dione, failed to react even on heating. Dehydration of the Diels–Alder adducts to yield the quinazolines (**645**) and (**646**) is by sulfuric acid at room temperature or polyphosphoric acid at 120 °C ⟨91JOC245⟩.

6.02.10.3 Perimidines

6.02.10.3.1 Syntheses from 1,8-naphthalenediamines

Perimidine is a derivative of 1,8-naphthalenediamine. It is formed by ring closure by inserting a one-carbon unit between the nitrogens. Accordingly, 1,8-naphthalenediamines (**647**) are the natural substrates for the preparation of perimidines (Scheme 104). The 1,8-naphthalenediamines can be regarded as vicinal diamines and as such they react with a carboxylic acid or its equivalent via intermediates (**648**) or (**649**) to form cyclic amidines (**650**), which are the perimidines. Thus 1,8-naphthalenediamine and its *N*-substituted derivatives react with formic acid at reflux temperature to form the corresponding perimidine. Other substituted naphthalenediamines (**647**; R^2, R^3 = OH, Cl, Br, SO_3H) react similarly. Higher acids yield 2-substituted perimidines. Heating with an anhydride is a recommended procedure, for example for the preparation of 2-methyl or 2-trifluoromethyl derivatives from the parent or *N*-substituted diamine. It may be advantageous to carry out the reaction in two steps: after initial acylation, cyclization is effected in acid solution. The method has been used for the preparation of long-chain alkyl and alkenyl derivatives. Reflux in 4 M HCl

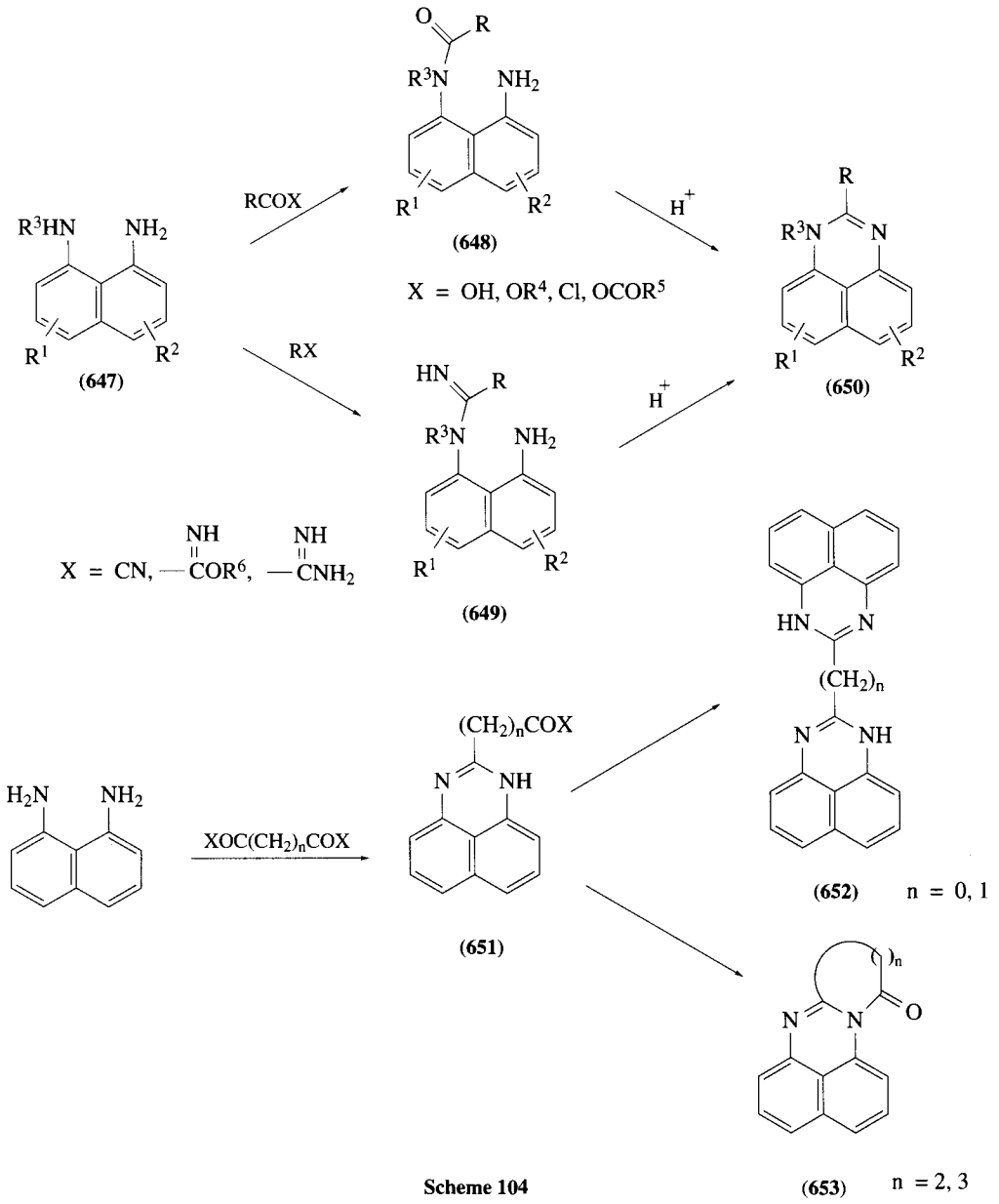


Scheme 103

has been recommended and used in the preparation of functionalized 2-substituents such as 2-hydroxymethyl, 2-α-hydroxybenzyl, 2-thiolbenzyl, 2-thiolmethyl, and 2-α-hydroxyethyl perimidines from glycolic, mandelic, thioglycolic, and lactic acids. Esters are widely used. Amides and nitriles generally require vigorous conditions. Prior conversion of nitriles into imino-ethers leads to milder reaction conditions; imino-ethers have been used for the preparation of perimidines containing complex or labile groups in the 2-position, e.g., R = CH_2CO_2Et, $CH(OEt)_2$, CH=NOH, CH_2CH_2NHR', *N*-oxido-2/4-pyridyl. With diacids, the first formed perimidine (**651**) may react further to furnish dimeric perimidines (**652**), for example from oxalyl chloride. When the spacing is appropriate for a five- or six-membered ring, cyclization by acylation of a nitrogen atom (**653**) occurs as in reactions with the anhydrides of succinic, maleic, and phthalic acids. The 2,3-dihydro derivatives are readily formed in reactions between 1,8-naphthalenediamines and aldehydes. Instead of the direct use of aldehydes, an α-chloroalkylpyridinium chloride, which is formed in a prior reaction between the aldehyde, pyridine, and thionyl chloride, is claimed to offer advantages in the preparation of certain aromatic derivatives ⟨92SC3141⟩.

Several methods are known for dehydrogenation of 2,3-dihydroperimidines (**654**) to the fully conjugated heterocycle (**655**), and therefore a two-step process constitutes a mild and efficient method for the preparation of perimidines (Scheme 105). Dehydrogenation by sodium pyrosulfite ($Na_2S_2O_5$) has been claimed to be a selective and high-yielding process. Aldehydes are not oxidized by pyrosulfite, but dihydroperimidines are dehydrogenated. This has been utilized for one-pot dehydrogenation. A refluxing mixture of sodium pyrosulfite, the aldehyde and 1,8-naphthalenediamine in aqueous EtOH or DMF, yields the perimidine directly. Yields are high (85–95%) from aliphatic, aromatic, and heteroaromatic aldehydes ⟨91SC2171⟩. *p*-Chloranil is another reagent for dehydrogenation of 1,2-disubstituted derivatives, and others are Pd–charcoal, MnO_2, and sulfur.

1,3-Disubstituted 2,3-dihydroperimidines have been converted into perimidinium salts by treatment with iodine, trityl perchlorate, or 1,3,5-trinitrobenzene. With dicarbonyl compounds, bridged 2,2′,3,3′-tetrahydro-2,2′-biperimidines are formed, for example, with glyoxal. Aromatic or heteroaromatic aldehydes react similarly. β,β-Dichlorovinyl ketones and β,β-dichloroacroleins form ketenaminals with primary or secondary amines. These reagents also react on the β,β-dichlorocarbon with 1,8-naphthalenediamine to provide in low to moderate yields the aminals (**656**) which are 2-alkylidene dihydroperimidines. The latter are in tautomeric equilibria with 2-β-oxoalkylperimidines (**657**) ⟨87JPR332⟩. Acylketene-*S*,*S*-acetals also react with 1,8-naphthalenediamine to form 2-acylmethylene-1,2-dihydroperimidines ⟨77JPC(319)545⟩. The first formed product (**658**) in the Michael addition reaction between diethyl or dimethyl acetylenedicarboxylate and 1,8-naphthalenediamine goes on to add the other amino group to the same electrophilic carbon, thereby yielding the corresponding 1,2-dihydroperimidine (**659**) ⟨83BCJ2338⟩.

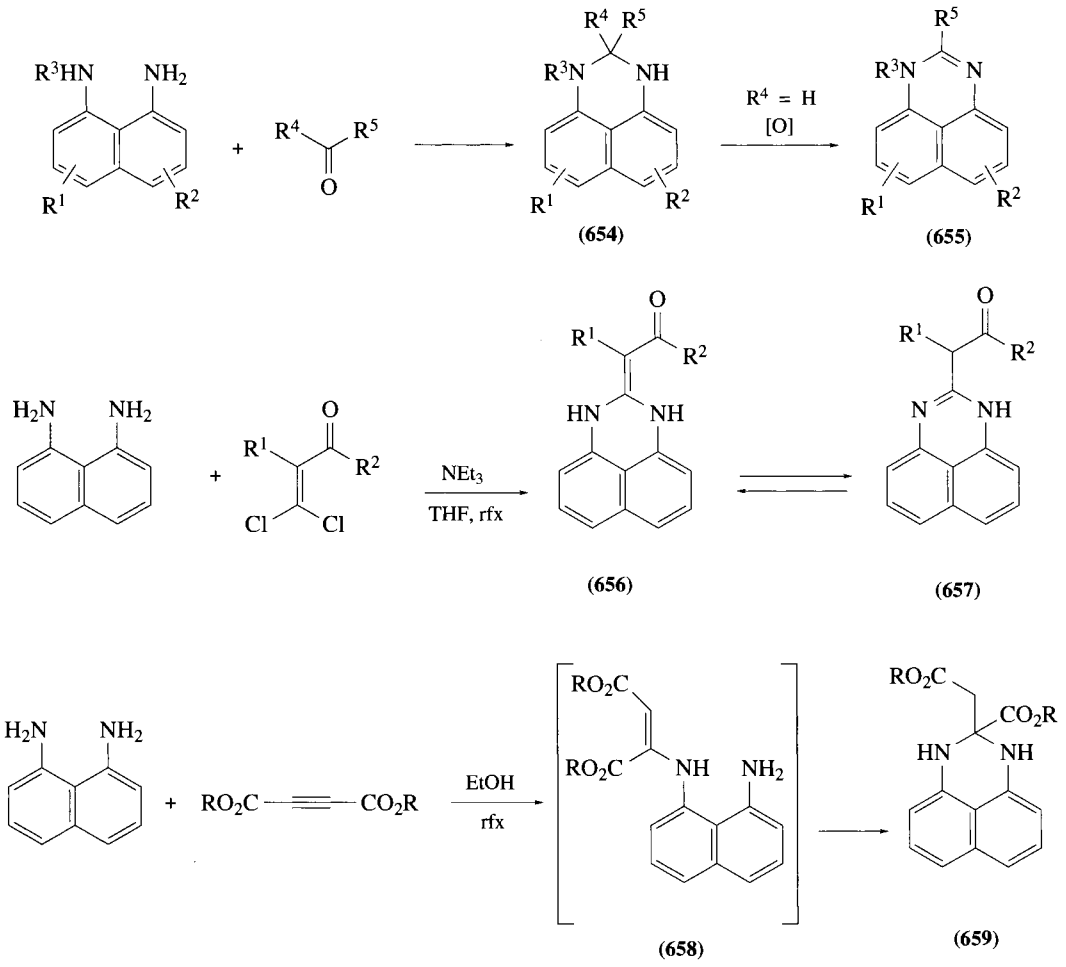


Scheme 104

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

6.02.11.1 Synthesis of Pyrimidine

Pyrimidine can be made in quantity from an acetal of malonaldehyde, such as 1,1,3,3-tetraethoxypropane, and formamide ⟨58CB2832⟩. Hydrogenolysis of 2,4-dichloropyrimidine over Pd–C is an alternative in small-scale operations in the presence of a base such as magnesium oxide ⟨53JCS1646⟩. The reduced form, 1,4,5,6-tetrahydropyrimidine, is available from propane-1,3-diamine by formylation and thermally induced ring closure ⟨62JCS527⟩, by hydrogenation of pyrimidine in HCl over Pd, or by hydrogenolysis and hydrogenation of pyrimidines with one or two chlorines in electrophilic positions ⟨55JOC829⟩. Hexahydropyrimidine is readily available from 1,3-propanediamine and aqueous formaldehyde at pH 4 ⟨67AJC1643, B-94MI 602-01⟩.



Scheme 105

6.02.11.2 Synthesis of Arylpyrimidines

Many combinations of arylpyrimidines can be constructed by primary syntheses. The great advances in organometallic coupling reactions and their applications to heterocyclic systems, however, have made derivatives with almost any aryl, heteroaryl, and combinations with alkyl groups available from readily accessible halo or hydroxypyrimidines. The coupling reactions are characterized by simple experimental procedures and relatively mild reaction conditions. The yields are normally high and the reactions regio- and chemoselective so that stepwise substitution with different arenes can be effected. A very recent review covers coupling reactions and gives reaction conditions for couplings in π-deficient heteroaromatic systems ⟨95AHC(62)305⟩. In the electrophilic 2- and 4/6-positions, chloro substituents are sufficiently activated for the coupling with a metalloarene, most commonly and preferably with Pd-catalysis. In the benzenoid 5-position, a bromine or iodine substituent is normally required. Hydroxypyrimidines, as triflates, are also good substrates, especially in the 5-position. Triflates in the electrophilic positions are very reactive, and therefore more difficult to handle and purify than the chlorides. Tin and zinc complexes of arenes are readily available, for example by metal–metal exchange with lithiated species and are used for the coupling in Pd-promoted reactions. The polarization of the reaction may be reversed by stannylation or zincation of the pyrimidine, which is then coupled in a Pd-mediated reaction with an aryl or heteroaryl iodide, bromide, or triflate.

6.02.11.3 Synthesis of Alkyl-, Alkenyl-, and Alkynylpyrimidines

Simple alkylpyrimidines can be prepared by the primary synthetic reactions, but the products frequently contain other substituents which have to be removed by subsequent operations. Alkyl derivatives are now regio- and chemoselectively available from halopyrimidines, as discussed for arylpyrimidines in the above section. Alkylstannanes, however, are not very reactive, and vigorous reaction conditions may be required to effect the coupling unless the metal-attached sp^3-carbon carries an activating substituent. Alkylzinc reagents are a better choice for alkylations. Alkylaluminums are expected to become important reagents using Pd catalysis in coupling reactions. Other choices are Grignard reagents in Ni-promoted coupling reactions.

The metal-promoted coupling reactions have made alkenyl and alkynyl derivatives readily available in any pyrimidine position. Unsaturated alkyl derivatives can be metallated and coupled with the appropriate halo or triflyloxypyrimidines since sp^2- and sp-hybridized carbon readily participates in coupling reactions. The scope for alkenylation and alkynylation reactions is further extended by Heck-type coupling reactions between alkenes or alkynes with halopyrimidines. These reactions are generally good, but proceed best for polarizable double and triple bonds ⟨95AHC(62)305⟩. In conclusion, the organometallic coupling reactions outlined will have a profound influence on the availability of pyrimidines unsaturated in the alkyl side-chain.

6.02.11.4 Synthesis of Acyl Derivatives

A number of C-acylpyrimidines can be made by primary synthesis, by oxidative processes of alkyl or substituted alkyl derivatives, and aldehydes also by reductive processes ⟨B-94MI 602-01⟩. In most cases, acyl derivatives are now more readily available by transition metal-mediated coupling reactions. Simple and high-yielding processes involve coupling a tin or zinc reactant with an acid chloride; a metallated pyrimidine is coupled by Pd catalysis with an acid chloride to furnish the ketone. Alternatively, a pyrimidine-carbonyl chloride is coupled with an organotin or organozinc reactant and Pd catalysis. For the preparation of alkyl and substituted alkyl ketones, a 2- or 4-/6-chloropyrimidine, or a 5-bromo- or iodopyrimidine, or a triflyloxypyrimidine, is coupled by Pd-catalysis with an α-metallated vinyl ether; tin and zinc vinyl ethers are readily accessible, but other metal derivatives would be expected to react similarly (see Sections 6.02.5.5.13 and 6.02.5.5.14).

6.02.11.5 Synthesis of Carboxy Derivatives

Many carboxy derivatives are available by primary syntheses. Otherwise the best route to simple pyrimidinecarboxylic acid derivatives is oxidative. This statement is even more applicable to our present situation with readily available acyl-, alkenyl-, or alkynylpyrimidine substrates from the coupling procedures, which serve as excellent substrates for oxidative reactions. The normal carboxylic acid reactions are observed: ester formation, ester hydrolysis, aminolysis, acid chloride formation and reactions. A carboxy group in an electrophilic position may readily be lost when the pyrimidine ring is further depleted of π-electrons by its substitution pattern; selective decarboxylation can be effected in pyrimidinedicarboxylic acids.

Pyrimidine-5-carbonitriles are best available by primary syntheses. Cyano groups in electrophilic positions have been introduced by nucleophilic substitution reactions with a metal cyanide.

6.02.11.6 Synthesis of Amino, Nitro, and Related Derivatives

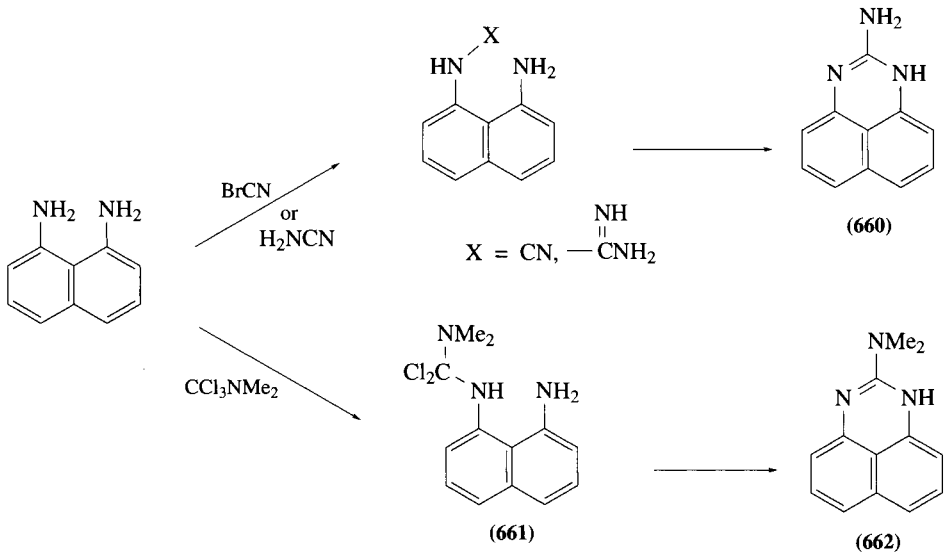
Methods for making pyrimidinamines fall into three chief categories: (i) by primary synthesis, (ii) by nucleophilic substitution reactions, and (iii) by reductive, degradative, or rearrangement type reactions ⟨B-94MI 602-01⟩. Nucleophilic substitution reactions with ammonia, amines, or heterosubstituted amines, which may be used as a metal derivative, are commonly used in the electrophilic positions. The halogen atom as halide is the common leaving substituent in an electrophilic position, commonly a chlorine atom, but a sulfenyl, sulfinyl, and in particular a sulfonyl group are also used. Hydroxy groups, as activated sulfonyl esters, provide alternatives. In the benzenoid 5-position nitro, nitroso, and phenylazo groups are available by electrophilic substitution reactions or by primary syntheses, and are convenient substrates for reductive reactions with amine formation.

6.02.11.6.1 Quinazolinamines

Quinazolinamines with the amino groups in the heterocyclic ring are prepared by the same sort of reactions as reviewed for pyrimidines. Amination, by way of electrophilic substitution, for example, by nitration or nitrosation in the carbocyclic ring, is substituent dependent and may have to be carried out in a precursor before formation of the quinazoline ring system.

6.02.11.6.2 Perimidinamines

In primary synthesis 2-perimidinamines (**660**) can be prepared from the naphthalene diamine with bromocyanogen or cyanamide (Scheme 106). 2-Anilino derivatives have been obtained in reactions with aryl isothiocyanates. 2-*N*,*N*-Dimethylamino derivatives (**662**) have been obtained via the alkylated amine (**661**) using dimethylamino(trichloro)methane. Nucleophilic substitution by amine readily occurs in the 2-position when carrying a halo, sulfenyl, or sulfonyl substituent ⟨81RCR816⟩.



Scheme 106

6.02.11.7 Synthesis of Hydroxy, Alkoxy, Aryloxy, and Related Derivatives

2- and 4-/6-Pyrimidinones are normally prepared by primary syntheses. A pyrimidine hydroxy group corresponds to an oxidation level of a carboxy group in the substrate used in the ring-forming reaction. Sometimes the cyclization reaction proceeds better with a sulfur analogue, for example a thiourea, isothiourea, or an isothiocyanate, in which case one or more successive oxidative and/or hydrolytic reactions convert the thioxo function to the oxo group. A hydroxy group in the 5-position is normally present in the substrate as an appropriately protected hydroxyl group before the cyclization reaction.

There is no satisfactory method for heteroatom arylation of oxygenated pyrimidines. *O*-Alkylation of hydroxypyrimidines competes with the favored *N*-alkylation; hard electrophiles may move the selectivity in favor of *O*-alkylation. Therefore, both *O*-arylation and *O*-alkylation are best effected in the electrophilic positions by substitution reactions on the chlorides, sulfides, and oxidized sulfides using a metal salt of the phenol or alcohol. In the 5-position, the options are vigorous reaction conditions for substitution of a bromine substituent, and *O*-alkylation in competition with *N*-alkylation.

N-Alkylation is the favored reaction path in competition with *O*-alkylation. *N*-Alkylation is further favored by using *O*-silyl or *O*-stannylpyrimidines as substrates. Simple alkoxypyrimidines

are commonly used in connecting the sugar and the base in nucleoside syntheses. A good and general method for *N*-arylation remains to be worked out.

Alkylation of 2- and 4-/6-pyrimidinamines is on the ring nitrogen, but the ensuing hydrolysis to afford the corresponding *N*-alkylated pyrimidinone frequently fails because of the Dimroth rearrangement. The product from the Dimroth rearrangement is the corresponding exocyclic *N*-alkylated pyrimidinamine.

6.02.11.7.1 Oxy and oxo quinazolines

Quinazolinones and 2/4-alkoxy- and aryloxyquinazolines are prepared by the same sort of reactions as described for pyrimidines. Oxy functions in the carbocyclic ring are best introduced via the substrate used for ring formation. Among alternatives are a diazotization reaction from the corresponding amine.

6.02.11.7.2 Oxy and oxo perimidines

2-Perimidinones are available from 1,8-naphthalenediamines in cyclization reactions with potassium cyanate, carbonate, and chlorocarbonate esters, phosgene, and urea; all methods give satisfactory results. 2-Alkoxy- and aryloxyperimidines are readily available by nucleophilic substitution reactions in the 2-position ⟨81RCR816⟩.

6.02.11.8 Synthesis of Mercapto, Alkylthio, Arylthio, and Related Derivatives

The best preparative method for mercaptopyrimidines varies from position to position ⟨B-94MI 602-01⟩. Pyrimidine-2-thiones are available by primary syntheses from thioureas and their equivalents. Thiones in any of the electrophilic positions are prepared by thiolysis of halopyrimidines, or commonly by thiation of pyrimidinones using phosphorus pentasulfide or, more recently, the superior Lawesson reagent: 2,4-bis-*p*-methoxyphenyl-1,3,2,4-dithiadiphosphetane 2,4-disulfide. Thiolysis in the 5-position requires a metal sulfide and a 5-bromide under vigorous conditions. Alternatively, pyrimidines substituted with strongly electron-donating substituents may be sulfonated, for example, by chlorosulfonic acid, in the 5-position with subsequent reduction to thiol.

Alkyl sulfides are most conveniently prepared by simple *S*-alkylation of the corresponding pyrimidinethiols/thiones. Both alkyl and aryl sulfides are made by thiolysis of halo- or sulfonylpyrimidines using alkyl or aryl sulfides activated as metal salts.

Pyrimidinethiols are sensitive to oxidations; the corresponding disulfides are formed. Preparatively, disulfide formation is simply and conveniently effected by adding bromine or iodine to a solution of the thiol. Other oxidizing agents can also be used.

Various oxidative reagents have been used for oxidation to pyrimidinesulfinic and pyrimidinesulfonic acids. Halogen oxidation gives the corresponding sulfonyl halide. Sulfoxides and sulfones are prepared almost exclusively by peracid or metal oxide oxidations of the corresponding sulfides.

Alkylation of pyrimidinethiols/thiones is almost exclusively on sulfur. *N*-Alkyl as well as *N*-arylpyrimidinethiones are therefore prepared by primary syntheses from the corresponding *N*-substituted thiourea in the 2-position, or in any of the electrophilic positions by thiation of the corresponding *N*-substituted pyrimidinone.

6.02.11.8.1 Thiated quinazolines

Thiol-, alkylthio-, and arylthio-quinazolines with the sulfur-containing substituent in the heterocyclic ring are prepared by the same sort of reactions as reviewed for pyrimidines. Sulfur functions in the carbocyclic ring are best introduced via the substrate used for ring formation. Thiation, by way of electrophilic substitution, for example by sulfonation reactions in the carbocyclic ring, is substituent dependent and may have to be carried out in a precursor before quinazoline ring formation.

6.02.11.8.2 Thiated perimidines

2-Thioxo derivatives are available from 1,8-naphthalenediamines in reactions with carbon disulfide or potassium xanthate (xanthogenate). In fusion reactions with ammonium thiocyanate or thiourea, mixtures of the 2-amino derivative and the thione can be formed. Thiation reactions in the carbocyclic system correspond to those in naphthalene chemistry.

6.02.11.9 Synthesis of Halo Derivatives

Halogens in the electrophilic positions of pyrimidine are normally introduced from the corresponding hydroxypyrimidines by a phosphoryl halide, commonly a chloride. In the 5-position halogen introduction is normally by an electrophilic substitution. A 5-halogen may also be part of one of the reagents in a primary synthesis. Halogen substitution as a diazotization reaction of an amino group is an alternative. Iodo and fluoro derivatives are normally made by transhalogenation of the corresponding chlorides. Hydriodic acid or sodium iodide in acetone are useful reagents for iodine introduction. Bromides can be prepared with the use of phosphoryl bromide or by halogen exchange using HBr or metal bromide salts.

The chemistry for introduction of a halogen substituent into the heterocyclic ring in quinazoline, or into the 2-position in perimidine, is the same as described for pyrimidine. In the carbocyclic rings of quinazoline and perimidine the chemistry is to be compared with that of benzene and naphthalene, respectively.

6.02.11.10 Synthesis of *N*-Oxides and Derivatives

N-Oxidation of pyrimidines is more difficult to effect than *N*-oxidation of corresponding pyridines using peroxyacids and metal oxide complexes. The oxidation may also be complicated by the question of regiochemistry when the pyrimidine is unsymmetrically substituted. Often the *N*-oxide function is built into the pyrimidine ring by a primary synthesis where at least one amino function is derived from hydroxylamine. The oxygen is normally protected, and the protecting group is removed by a hydrolytic reaction once the ring has been formed. In this manner selective *N*1- or *N*3-oxides or *N*1,*N*3-dioxides have been prepared ⟨B-94MI 602-01⟩.

Similarly, oxygenated amino groups in primary syntheses of quinazolines and perimidines yield the corresponding *N*-oxides.

6.02.12 IMPORTANT COMPOUNDS AND APPLICATIONS

6.02.12.1 Pyrimidines

6.02.12.1.1 Uracil [pyrimidine-2,4(1H,3H)-dione] and thymine (5-methyluracil)

Uracil was first isolated from herring sperm in 1900 and it originates from ribonucleic acids; hydrolytic breakdown gives initially the nucleotide which is further cleaved to uridine (1-β-D-ribofuranosidouracil) and finally to uracil. Thymine was originally isolated in 1893 from hydrolyzates of bovine thymus or spleen. It is one of the four bases in deoxyribonucleic acids which on hydrolysis give thymine via thymidine [3-(2′-deoxy-D-ribofuranosido)-thymine].

6.02.12.1.2 Cytosine [4-aminopyrimidin-2(1H)-one], 5-methyl-, and 5-hydroxymethylcytosine

Cytosine was first isolated in 1894 from the hydrolyzates of calf thymus. It is one of the four bases in both ribonucleic acid and deoxyribonucleic acids. Hydrolysis via the corresponding nucleotides gives cytosine deoxyriboside (2′-deoxycytidine) and cytosine riboside (cytidine), respectively. 5-Methylcytosine has been isolated by hydrolysis of deoxynucleotide fractions from thymus and wheat germ ⟨50MI 602-01⟩. 5-Hydroxymethylcytosine has been isolated from T-even bacteriophages of *Escherichia coli*, where it occurs instead of cytosine in the 2-deoxyribonucleic acid.

6.02.12.1.3 Orotic acid

Orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid) was first isolated in 1905 from the whey of cows' milk. It is the key substance in the biosynthesis of probably all naturally occurring pyrimidines starting with L-aspartic acid ⟨57MI 602-01⟩.

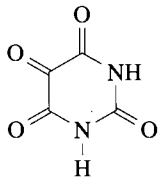
6.02.12.1.4 Alloxan and toxopyrimidine (pyramin)

Alloxan (**663**) has been observed in the mucus associated with dysentery. Its diabetogenic action appears to be associated with removal of essential zinc from insulin by chelation. Permanent diabetes can be induced in this manner, in fish, dogs, cats, and sheep, for instance, but not in man. Alloxan is formed by oxidation of barbituric acid ⟨52OS(32)6⟩.

Toxopyrimidine (**664**) results on acid hydrolysis of thiamine (vitamin B_1) or by bacterial thiaminase. Toxopyrimidine and close analogues produce convulsions and death in rodents; the effect is counteracted by administration of compounds from the vitamin B_6 group ⟨65JMC750⟩.

6.02.12.1.5 α-Amino acids; willardine and lathyrine (tingitanin)

Willardine is the (*S*)-α-amino acid 1-β-amino-β-carboxyethyluracil (**665**). It was first isolated from the seeds of *Acacia willardiana*, and later from other species of *Acacia* ⟨62JCS583⟩. Lathyrine (**666**) is another nonprotein α-amino acid, which was isolated from the seeds of *Lathyrus tingitanus* ⟨65JOC115⟩.



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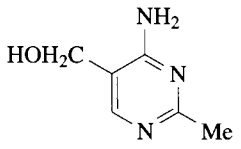

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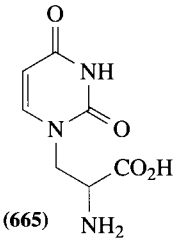

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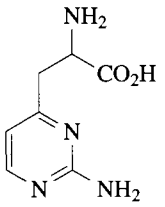

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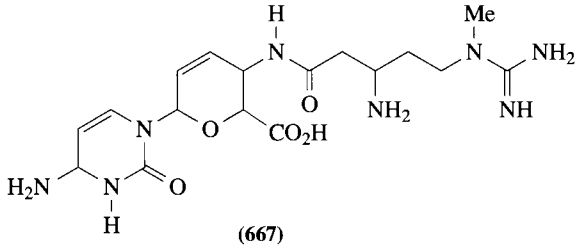
6.02.12.1.6 Pyrimidine antibiotics

Bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) was isolated from *Bacillus megatherium*. Its antibacterial activity spectrum covers several forms of yeasts and bacteria *in vitro*, and *in vivo* bacimethrin is active in staphylococcal infections. Anticarcinoma activity in mice has been demonstrated ⟨69MI 602-01⟩.

Blasticidin S (**667**), isolated from *Streptomyces griseochromogenes*, is active against certain fungal plant pathogens and may be used to protect growing rice from rice blast disease; it is toxic to animals. Gougerotin is structurally related to blasticidin and was isolated from *Streptomyces gougerotii*. Its activity spectrum covers mycobacteria, several Gram-positive and Gram-negative bacteria ⟨64MI 602-01⟩.

The phleomycin, bleomycin, and related families are wide-spectrum antibiotics which also possess antineoplastic activity. Bleomycin is used in clinical chemotherapy of cancer ⟨78MI 602-01⟩.



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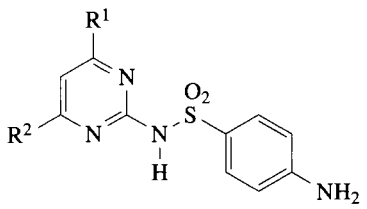
6.02.12.1.7 The barbiturates

The parent compound in this class is barbituric acid (2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione). In contrast to its 5-substituted derivatives, it has no hypnotic activity. The first hypnotic barbiturate was 5,5-diethylbarbituric acid (barbital). 5-Ethyl-5-phenylbarbituric acid (phenobarbital) is a long-acting CNS depressant. A large number of 5-substituted barbituric acid derivatives has been prepared. Several of the active compounds have been or are used in medicine ⟨B-75MI 602-01⟩.

5-Spirobarbiturates are of interest as inhibitors of dihydro-orotate dehydrogenase enzyme system (DHODase) ⟨90JCS(P1)3137⟩.

6.02.12.1.8 Pyrimidine sulfonamides

Sulfadiazine (**668**; $R^1 = R^2 = H$), sulfamerazine (**668**; $R^1 = Me$, $R^2 = H$), and sulfadimidine (**668**; $R^1 = R^2 = Me$) have all been used in bacterial therapy. Other pyrimidine sulfonamides include sulfazomidine (**669**; $R^1 = R^2 = Me$), sulfadimethoxine (**669**; $R^1 = R^2 = OMe$) and sulfametomidine (**669**; $R^1 = Me$, $R^2 = OMe$) ⟨69MI 602-01⟩.



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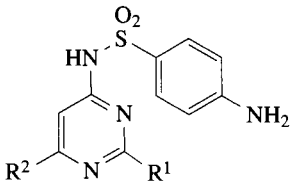

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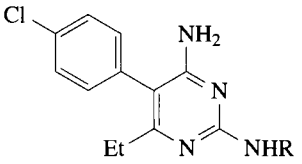

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6.02.12.1.9 Antimicrobial pyrimidine-2,4-diamines

Pyrimethamine (**670**; R = H) inhibits the enzyme system dihydrofolate reductase (DHFR), which is an essential coenzyme in nucleic acid synthesis. Pyrimethamine has a far higher affinity for protozoal than for mammalian DHFR, so that it may be used for malarial prophylaxis without adversely affecting human DHFR. For diaminoantifolates, a 2,4-diamino-*meta*-diazine pharmacophore is a prerequisite for inhibition of DHFR ⟨86MI 602-01⟩. Diacylamino analogues of pyrimethamine show superior antimalarial activity over the parent drug, presumably by serving as a pyrimethamine prodrug active after enzymatic deacylation. The aqueous solubility of the diacylated pyremethamine is substantially reduced, however, but is improved again in the monoacylated drug, the 2-acylamino-4-aminopyrimethamine (**670**; R = Ac) ⟨92JCS(P1)1811⟩.

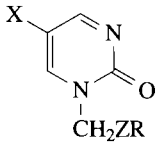
6.02.12.1.10 Antitumor agents

5-Fluorouracil has antineoplastic activity and is a valuable drug especially for the treatment of tumors of the colon or rectum, but it has a wider application in cancer chemotherapy.

Cytarabine, 4-amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one (cytosine arabinoside) is a valuable drug in cancer chemotherapy, as in the treatment of acute leukemias of childhood and adult granulocytic leukemia.

Certain 5-halo-2(1*H*)-pyrimidinones (**671**) will arrest the cell cycle of mouse and human cells grown in cultures. The arrest is in the relatively narrow metaphase region. Compounds have been found where the metaphase arrest is reversed when the active compound is removed, and the cells suffer no damage provided that the time of arrest is no longer than the cell cycling time. Cycling cells of all origin will be arrested in metaphase. With a rapid release of the block, parasynchronous resumption of the cell cycle leads to separation of the cells into groups because of kinetic differences between the different types of cells. The principle is thought to be applicable to achieve differential synchronization of cycling cells from normal and abnormal tissue in diseases caused by rapidly proliferating cells. Thus, sequential timed treatment with a phase-specific cytotoxic drug may be

used to increase the kill of abnormal cells after pretreatment with a synchronizing agent ⟨B-89MI 602-01, 91ACS177, 93EJM463⟩.



X = F, Cl, Br, I
Z = O, S, NR, CO, CH=CH, C≡C
R = Ar, Alk, H

(671)

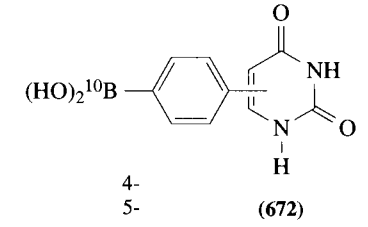
The 5-bromo and 5-chloro derivatives of 1-propargyl-2(1*H*)-pyrimidinones are inhibitors of the micotubule system in malignant cells. In rat glioma cells, arrest of mitosis was accompanied by repeated cycles of DNA synthesis, leading to different levels of polyploidization with formation of up to 16 and 32 ploid cells ⟨86MI 602-04⟩.

Synergistic cell inactivation effects were displayed when human NHIK 3025 cells cultivated *in vitro* were treated with 5-halo-2(1*H*)-pyrimidinones in combination with *cis*-diaminedichloroplatinum(II) (cisplatin) ⟨88MI 602-02⟩. *cis*-Diamineplatinum 1-methyluracil blue $[Pt_4(NH_3)_8(1\text{-MeU})_4]^{5+}$, where 1-MeU denotes 1-methyluracil, referred to as "platinum pyrimidine blues," belongs to a class of blue platinum complexes which are claimed to have a higher index of antitumor activity and lower nephrotoxicity than the anticancer drug *cis*-diaminedichloroplatinum(II). X-ray crystal structure data and magnetic and spectroscopic data are available ⟨84JA6428⟩.

The tetranuclear metal complex, [(1,2-diaminoethane)Pt(uracilate-*N*1,*N*3)]$^{4+}$, can be considered a special heterocalixarene, a metal analogue of calix[4]arene which functions as hosts for small molecules or ions and possesses metal binding properties, either in the cavity or at the periphery. The bridging unit of the classical calix[4]arene, usually a CH_2 group, is replaced by the (en)Pt(II) unit in the Pt-complex. This change, the replacement of the *p*-phenol by the 2,4-dioxopyrimidine and the positive charge introduced by the metal cations, leads to a number of differences as compared with the classical calix[4]arenes. Their preparation, x-ray crystal structure, and solution behavior have been described ⟨94JA616⟩.

Boron-containing pyrimidines have been prepared for specific testing as agents for boron neutron capture therapy (BNCT). The diverse pathways by which pyrimidines and their nucleosides are utilized in the cell make these bioactive molecules a particularly attractive target for boronation in order to concentrate ^{10}B in actively replicating tissue. 5-(Dihydroxyboryl)uridine (DBDU) and -uracils (**672**) are available ⟨85JOC841, 89JOC4734⟩.

2,4-Dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (**674**) is said to be a potential synthon for the preparation of 5-(1-*o*-carboranylmethyl)-6-methylpyrimidines; chemoselective nucleophilic substitution of the chlorine atoms can be effected, and the cage can be selectively degraded for the preparation of more water-soluble *nido*-undecarborate derivatives. Preparation of the target molecule (**674**) is effected by the addition of decaborane to an appropriate alkyne (**673**) as shown in Equation (19) ⟨91JOC2391⟩.



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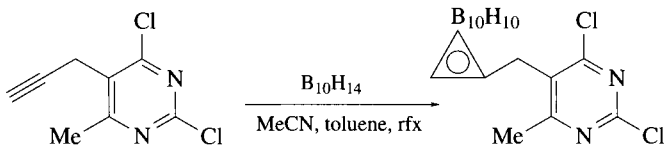

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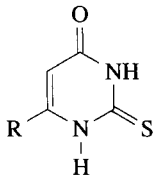
(673) **(674)**

6.02.12.1.11 Other activities

Cyclic thioureas such as 2-thiouracil (**675**; R = H), its 6-alkyl derivatives (**675**; R = Me or Pr) and thiobarbital (**676**) are effective thyroid drugs in hyperthyroidism by interference with the synthesis of the thyroid hormones ⟨71MI 602-02⟩.

The anticonvulsant Primidone (**677**) is used to control grand mal and psychomotor epilepsy. 5-Hydroxymethyl-6-methyluracil has been found to stimulate wound healing and the immune response in typhus infection ⟨73MI 602-01⟩.



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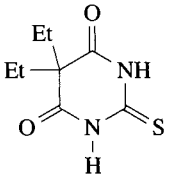

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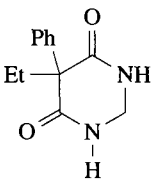

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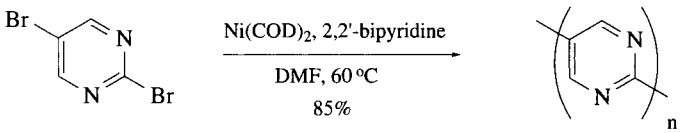
6.02.12.1.12 Technical applications

Both pyridine and quinoline polymers exhibit n-type electrical conducting properties originating from the π-deficient nature of the aromatic units. Pyrimidines are higher electron-accepting aromatic units. Thus, reaction of 2,5-dibromopyrimidine with zero-valent nickel complexes affords poly-(pyrimidine-2,5-diyl) (**678**) (Equation (20)). The polymer is converted into electrical conducting material by chemical and electrochemical reductions, the latter reduction occurring at the highest potential (-1.75 V *vs.* Ag/Ag^+) among reported π-conjugated polymers. Nondoped PPym is essentially an insulator with electrical conductivity (σ) of 7.1×10^{-11} S cm^{-1}. Doping with sodium or iodine gives electrically conducting material with electrical conductivity of 1.2×10^{-4} and 1.5×10^{-5} S cm^{-1}, respectively ⟨92CL583⟩.



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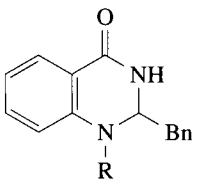
6.02.12.2 Quinazolines

6.02.12.2.1 Quinazoline alkaloids

Quinazoline alkaloids are found in at least six botanical families. Arborine (**679**; R = Me), glycosmicine (**680**), glycorine (**681**), and glycosminine (**679**; R = H) have been isolated from *Glycosmis arborea*. The alkaloid vasicine (**682**) has been isolated from *Adhatoda vasica* and two related alkaloids (**683**) from *Mackinlaya subulata* and *M. macrosciadia*. The alkaloid febrifugine (**684**), isolated from *Dichroa febrifuga*, has antimalarial properties. The quinazoline ring is embedded in several other complex alkaloid structures not cited here. A review is available ⟨B-78MI 602-01⟩.

6.02.12.2.2 Quinazoline toxins

Tetrodotoxin, a fully saturated 2-aminopolyhydroxyquinazoline, is a powerful nonprotein neurotoxin which occurs in the liver and ovaries of the Japanese puffer fish *Sphoerides rubripes* and *S. phyreus*, and in the Californian newt or salamander *Taricha torosa* ⟨79AJC1805⟩.



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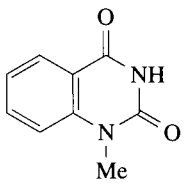

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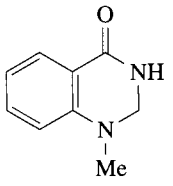

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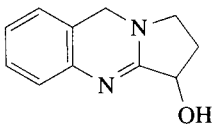

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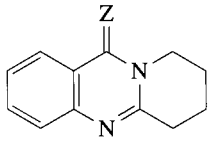
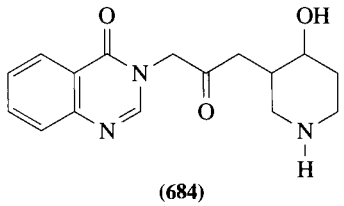


(683)

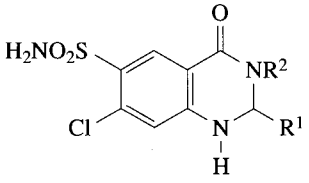
Z = 2H, O



(684)

6.02.12.2.3 Quinazoline drugs

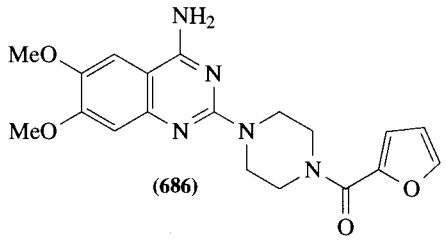
Quinethazone and Metolazone (**685**) are used in medicine as diuretics ⟨63AF660⟩. Another quinazoline, Prazosin (**686**) is a vasodilator which is used as an antihypertensive drug ⟨77MI 602-01⟩.



(685)

Quinethazone: R^1 = Et; R^2 = H

Metolazone: R^1 = Me; R^2 = C_6H_4-*o*-Me

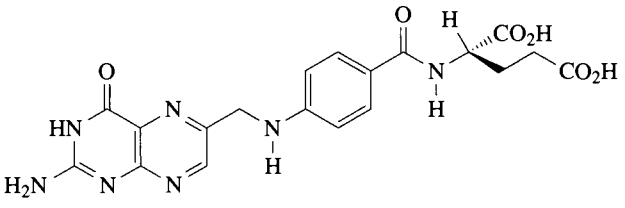


(686)

6.02.12.2.4 Antifolates

Pteridine is the heterocyclic ring system of folic acid (**687**). Diverse structural modifications to the folic acid molecule can produce potent antitumor agents that act through inhibition of thymidylate synthetase (TS) alone with no effect on other folate-dependent enzymes. Methotrexate is the classical drug; the 4-hydroxy group in the pteridine ring of folic acid has been replaced with an amino group and *N*10 in the side-chain has been *N*-methylated. By the 1950s deaza analogues of 2,4-diaminopteridines had been prepared for studies as TS inhibitors as exemplified by *p*-(2,4-diaminoquinazolin-6-ylamino)benzoic acid (**688**) as an *in vitro* active compound ⟨62JCS4678, B-62MI 602-01⟩. Work since the early 1960s has focused on quinazolines with a hydroxy group in the 4-position, as in folic acid. One such derivative is N^{10}-propargyl-5,8-dideazafolic acid (**689**; R = NH_2) which is a potent inhibitor of mouse and human TS with antitumor activity *in vitro*, but which failed in the clinic because of toxicity. Modifications of this structure involve exchange of the 2-amino group with a hydrogen, methyl, trifluoromethyl, hydroxymethyl, or by a methoxy group with improved water solubility; the C2-methyl analogue was the most potent antitumor agent ⟨91JMC2209⟩. In analogues where the *p*-aminobenzoate moiety contains fluorine substituents, antitumor activity varies with the substitution pattern ⟨92JMC2321⟩. Another modification leading to active compounds has been to replace the benzene ring with heterocyclic rings; a promising compound is said to be the thiophene analogue (**690**) ⟨91MI 602-03⟩. As another variation, a series of poly-γ-glutamates derived from quinazoline antifolates, as discussed above, were synthesized by a convergent route. The polyglutamates were more potent as inhibitors of TS in every case than the corresponding nonpolyglutamylated drug ⟨92MC859⟩. New inhibitors of TS structurally related to folic acid have

been described in which the pterin portion of the folate molecule is replaced by a benzo[*f*]quinazoline moiety, but which retain the natural methyleneamino link to the benzoylglutamate side-chain (**691**) ⟨94JMC838⟩. Replacement of the benzamide portion of the (*p*-aminobenzoyl)glutamate side-chain with substituted benzamido or heterocyclic substitutes gave the 2-isoindolinyl derivatives (**692**) as potent inhibitors of TS; the 5-aminoisoindole structure can be regarded as the *p*-aminobenzamide structure rigidified by an extra methylene grouping ⟨91JMC2209⟩.



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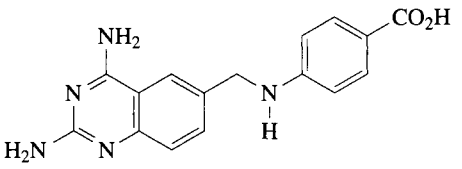

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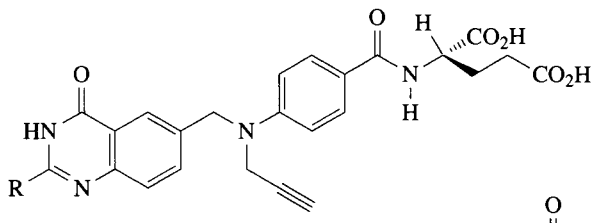
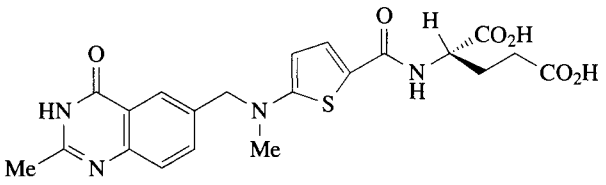


R = NH_2, Me

(689)



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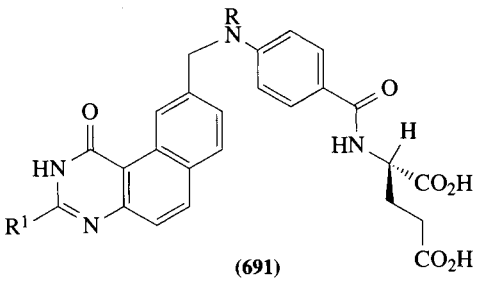
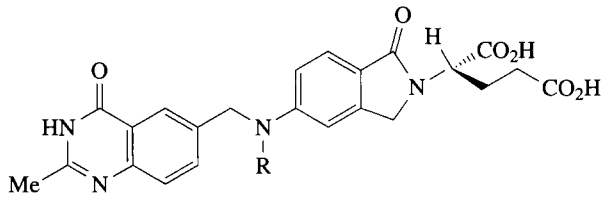


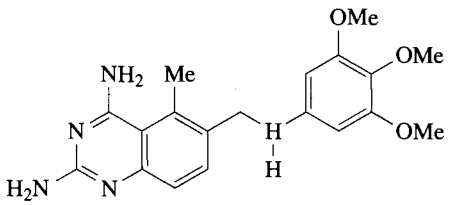
(691)

R^1 = NH_2, Me; R^2 = H, Me



(692)

R = Me, CH_2—≡



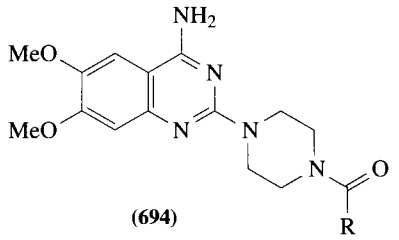
(693)

Nonclassical 2,4-diaminoquinazoline analogues of folic acid have been of interest as potential chemotherapeutic agents since the early 1970s. Some possess interesting levels of antibacterial activity and remarkable antimalarial effects. The drug trimetrexate (**693**) displays potent antimalarial, antibacterial, and antitumor activities, and has been through clinical trials as an anticancer

agent. It has a similar level of inhibitory potency as methotrexate toward L1210 dihydrofolate reductase (DHFR). Additional evaluations involve clinical trials for the treatment of *Pneumocystis carinii* infections in AIDS patients. Studies also show that relatively simple 5-substituted or 5,6-disubstituted 2,4-diaminoquinazolines can be potent human and rat liver DHFR inhibitors ⟨91JHC1981⟩.

6.02.12.2.5 Receptor blockage

A series of 2,4-diamino-6,7-dimethoxyquinazolines display high affinity and selectivity for α_1-adrenoreceptors. Agents of this class include prazosin and doxazosin (**694**) and are now widely available for the treatment of hypertension. In addition, these drugs produce potentially beneficial effects in plasma lipids, which may be important in reducing the risks of heart disease ⟨91MI 602-05⟩.



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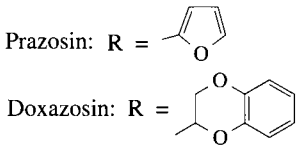
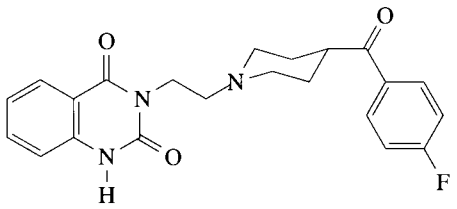


Prazosin: R =

Doxazosin: R =

5-HT_2 Serotonin receptors are of significant clinical interest because of their potential involvement in cardiovascular function and in certain mental disorders. Ketanserin (**695**) is a widely used 5-HT_2 antagonist in preclinical pharmacological investigations ⟨92JMC4903⟩.



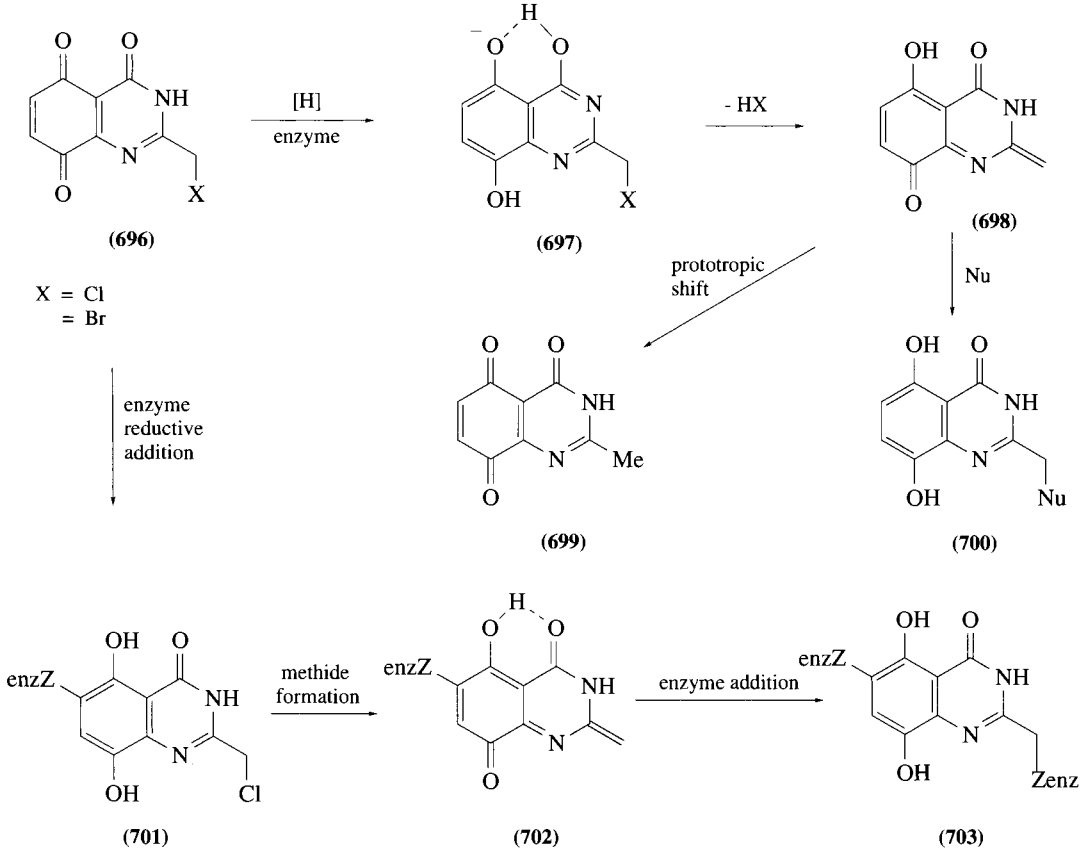
(695)

6.02.12.2.6 Reductive alkylating agents

The low reduction potentials exhibited by some tumor cells suggest reductive alkylating agents as selective antitumor agents. Naturally occurring quinone antitumor agents, for example, mitomycin and the anthracyclines, have a leaving group which permits quinone methide formation upon reduction. These have been used as models for the design of reductive alkylating agents based on the quinazoline ring system.

The 5,8-dihydroxy-4(3*H*)-quinazolinones possess three protons capable of dissociation in aqueous buffer, *viz.* N3—H and the protons of the 5- and 8-hydroxyl groups (Scheme 107). Initial acid dissociation of the N3 proton does not take place at low pH because electron-rich substituted quinazolin-4(3*H*)-ones possess pK_a values greater than 10. The first dissociation is from the 5-hydroxyl which affords an anion (**697**) which is stabilized by internal hydrogen bonding expressed by pK_a 7.3 (7.8). Cleavage of the halogen–carbon bond in the 2-substituent in (**697**) involves a rate-determining reaction of the hydroquinone monoanion and dianion species, since there is an approximate 100-fold difference in rate constants between the precursor 2-chloro (**696**; X = Cl) and

the 2-bromo (**696**; X = Br) derivatives. When a high potential quinone is the ketonization product (**699**), nucleophilic trapping (**700**) is favored.



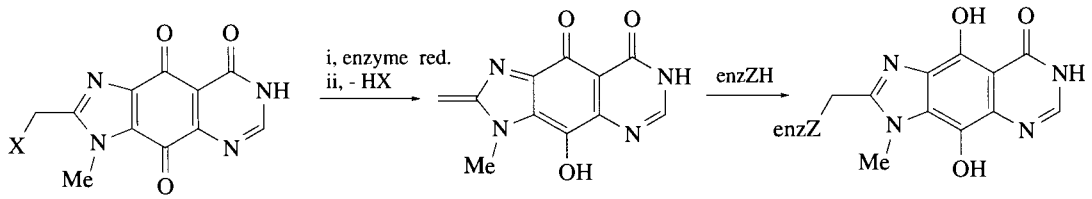
Scheme 107

The ability of quinazoline to enter the xanthine oxidase active site, and the presence of an active site nucleophile near the alkylating center, very likely accounts for enzyme inactivation by these hydroquinones. The quinone (**696**) acts as an oxidizing suicide substrate. It is able to enter the xanthine oxidase active-site, and by the enzyme reductive action and HCl elimination it becomes a reductive alkylating agent (**698**) targeted towards cellular structures important to the cancer cell ⟨88JOC6099⟩.

This concept has been extended. Thus the trione (**696**) rapidly and irreversibly inactivates human erythrocyte nucleoside phosphorylase (PNPase), which catalyzes the reversible phosphorylation of inosine and guanosine to the respective bases and ribose 1-phosphate. Inhibitors of this enzyme have several potential medical applications, for example, in the prevention of foreign tissue rejection, in the treatment of gout and malaria, and for the potentiation of antineoplastic nucleosides. Mechanistically the 5,8-dione (quinone) (**696**) enters the enzyme active site. An active-site nucleophilic residue subsequently converts the quinone moiety to a hydroquinone by reductive addition (**701**). The resulting hydroquinone affords an alkylating quinone methide species by elimination of HCl (**702**) and then traps a second nucleophilic enzyme residue by a Michael type reaction (**703**). Cross-linking of the active site rationalizes the observed potency ⟨91B8480⟩.

Purine-like reductive alkylating agents can also be designed by functionalizing the imidazo[4,5-*g*]quinazoline ring system as a quinone (4,9-dione) (**704**) related to hypoxanthine with a leaving group placed at the 2α-position. Enzyme reduction and HX elimination lead to the alkylating agent (**705**) which inactivates the enzyme (**706**) (Scheme 108). The possible utility of purine-like alkylating agents lies in their selective invasion of purine-utilizing enzymes in a low reduction potential environment ⟨86JOC4784⟩.

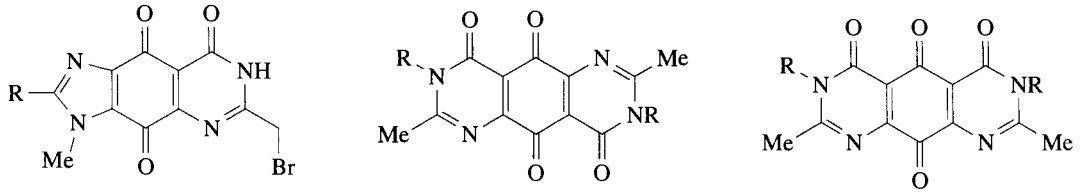
In a further extension, imidazo[4,5-*g*]quinazoline alkylating agents possessing a leaving group at the 6α-position (**707**) as well as an analogue possessing a leaving group at both the 2α- and 6α-



(704) (705) (706)

Scheme 108

position (**708**); the latter allows for cross-linking ⟨89JOC3611⟩. Reductive alkylation relies on stable quinone derivatives; only the hydroquinone derivatives should be active alkylators. In the design of hydrolytically stable high-potential quinones the search has also included pyrimido[4,5-*g*]quinazoline-5,10-diones (**709**) and pyrimido[5,4-*g*]quinazoline-5,10-diones (**710**). These systems consist of a benzoquinone ring bearing two fused pyrimidin-4(3*H*)-one rings ⟨88JOC4209⟩.

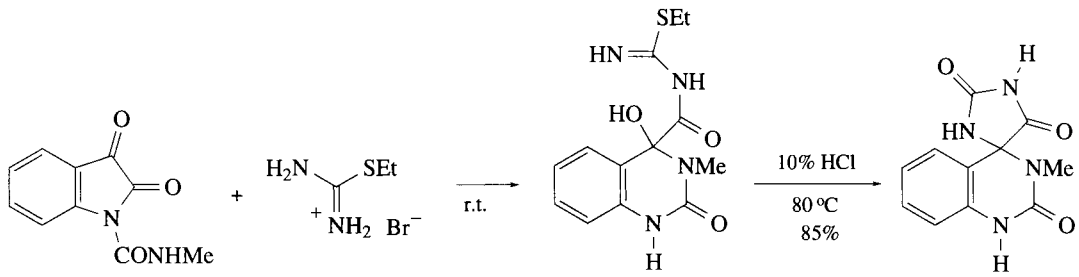


(**707**) R = Me
(**708**) R = CH_2Br

(**709**) (**710**)

6.02.12.2.7 Activities on enzyme systems

3′-Substituted spiro[imidazolidine-4,4′(1′*H*)quinazoline]-2,2′,5(3′*H*)-triones (**713**) (Scheme 109) have been prepared and tested as aldose reductase inhibitors, which are of therapeutic interest in counteracting chronic complications of diabetes (retinopathy, neuropathy, nephropathy, cataracts). The spiro derivatives (**713**) were prepared from 1-carbamoylisatins (**711**) and *S*-ethylisothiouronium bromide with subsequent treatment of the 4-(2-ethyl-2-isothioureido)carbonyl-3,4-dihydro-4-hydroxy-2(1*H*)quinazolinone (**712**) with acid ⟨91CPB1694⟩.

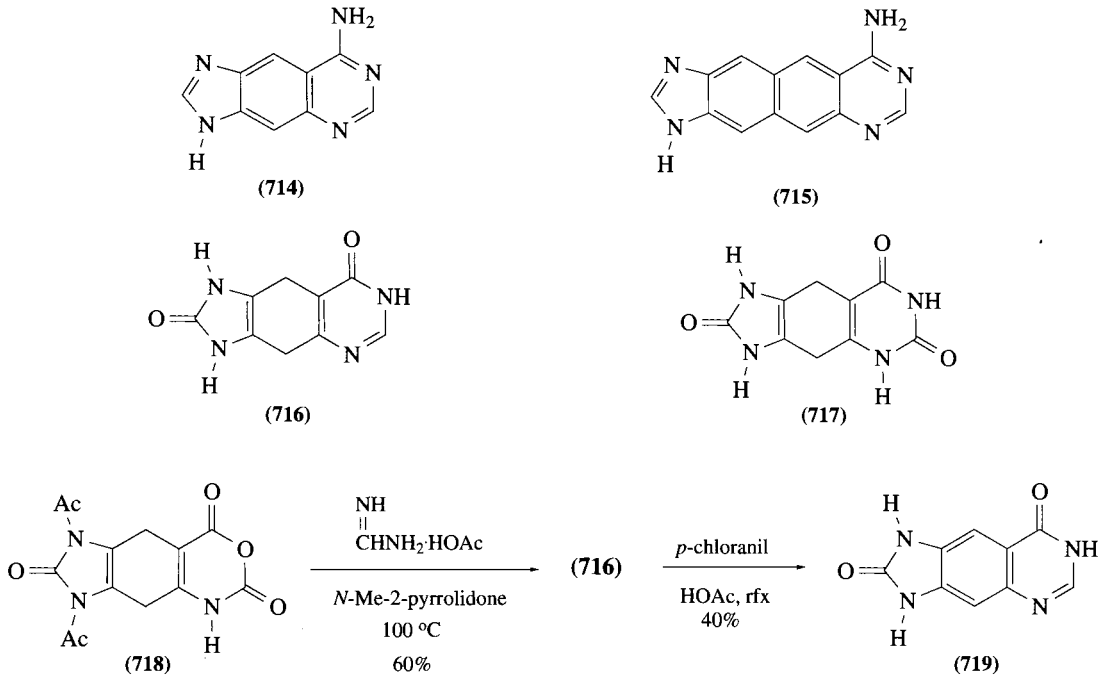


(**711**) (**712**) (**713**)

Scheme 109

Studies of the active sites of enzymes that require purines as substrates or cofactors have led to the synthesis of compounds that retain both the pyrimidine and imidazole rings present in purines, but they are separated by intervening chemical frameworks. The formal insertion of a benzene ring, with four additional carbons, into the middle of the adenine ring system leads to a molecule referred to as *lin*-benzoadenine (**714**) and of a naphthalene ring, an eight-carbon insertion, to an analogue referred to as *lin*-naphthoadenine (**715**). The benzene ring may be partially reduced as in the 4,9-dihydro derivative of (**714**) ⟨76JA3987, 84JOC2158⟩. Oxygenated purine analogs 4,9-dihydro-

imidazo[4,5-*g*]quinazoline-2,8(1*H*,7*H*)-dione (**716**) and 4,9-dihydro-*lin*-benzouric acid (**717**) have been investigated as probes for active sites on enzymes. The oxygenated purines were synthesized from the isatoic anhydride (**718**). Reaction with formamidine acetate gave the dihydro-*lin*-benzopurinedione (**716**), whereas reaction with urea gave 4,9-dihydro-*lin*-benzouric acid (**717**). Dehydrogenation of (**716**) by *p*-chloranil gave dihydroimidazo[4,5-*g*]quinazoline-2,8(1*H*,7*H*)-dione (**719**) (Scheme 110) ⟨86JOC616⟩.



Scheme 110

6.02.12.3 Perimidines

Perimidines substituted in the 1- and 2-position have been found to possess antiulcer properties, to be CNS active, and to be active as carcinostatic and antimicrobial agents.

For practical applications, the emphasis has been mainly on their use as dyes, frequently as components of azo dyes. Salts of 2-styrylperimidines, 4(9)- and *N*-aroylperimidinones, phthaloylperimidinones, 6(7)-azoperimidines, amides of perimidine-6,7-dicarboxylic acid, and 2-oxo derivatives have been proposed as dyes of synthetic fibers ⟨81RCR816⟩.

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6.03
Pyrazines and their Benzo Derivatives

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Yokohama City University, Japan

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6.03.1 INTRODUCTION

The first synthesis of a pyrazine was published by Laurent in 1844, who called tetraphenylpyrazine "amarone," the product of the reaction of benzoin with ammonia. Extensive reviews on pyrazines by Krems and Spoerri ⟨47CRV279⟩, Cheeseman and Werstiuk ⟨72AHC(14)99⟩, Barlin ⟨B-82MI 603-01⟩ and Porter ⟨84CHEC-I(3)157⟩, and on quinoxalines by Cheeseman *et al.* ⟨63AHC(2)203, 78AHC(22)367, B-79MI 603-01⟩ and Kurasawa *et al.* ⟨88H(27)2481⟩, have been published. Although there is an overlap of a few years with the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), the present survey covers 1980 through 1993 together with some selected references for 1994.

Owing to the amount of material available, it is not possible to include all relevant references. As in CHEC-I, references to patents generally have been omitted on account of the frequent difficulty of abstracting meaningful information from them. References to communications have been also omitted unless experimental details are included. Furthermore, where several references contain similar methodology and/or results, only those which are more commonly available have been selected.

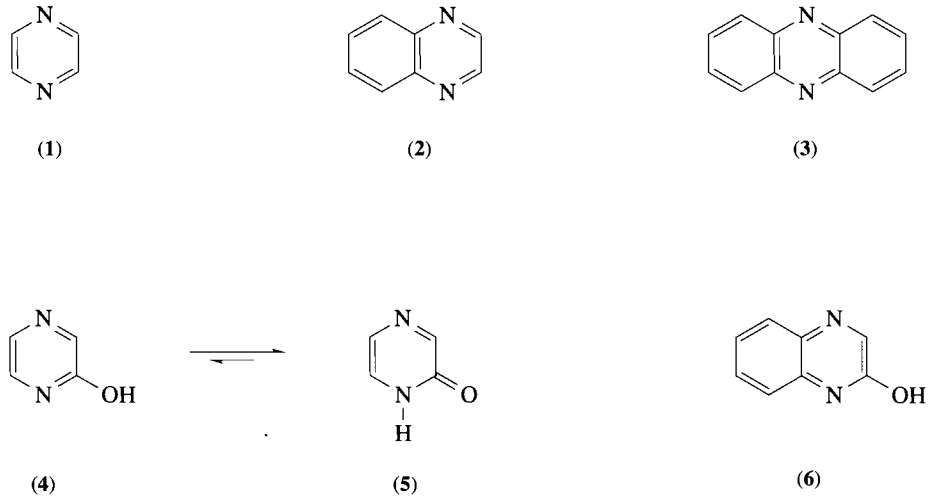
It should be noted that, as all carbon positions in pyrazine are identical, the locant "2-" in a monosubstituted derivative is superfluous.

All possible reduced derivatives of pyrazine (**1**), and several of those of its benzo analogues quinoxaline (**2**) and phenazine (**3**), are known ⟨84CHEC-I(3)157⟩. There are four dihydropyrazines, the 1,2-, 2,3-, 1,4- and 2,5-isomers, two tetrahydropyrazines, the 1,2,3,4- and 1,2,3,6-, and hexahydropyrazine or piperazine, the last of which is omitted in this review. The reduced quinoxalines are the 1,2- and 1,4-dihydro compounds and 1,2,3,4-tetrahydroquinoxaline. The only known reduced phenazine is 1,4-dihydrophenazine.

Hydroxypyrazine (**4**) and hydroxyquinoxaline (**6**) have been shown to exist in the tautomeric amide form by IR and other spectral studies, and therefore they are formulated as 2(1*H*)-pyrazinone (**5**) and 2(1*H*)-quinoxalinone, respectively. In contrast, aminopyrazine and aminoquinoxaline exist as described in the amino rather than the imino forms.

6.03.2 THEORETICAL METHODS

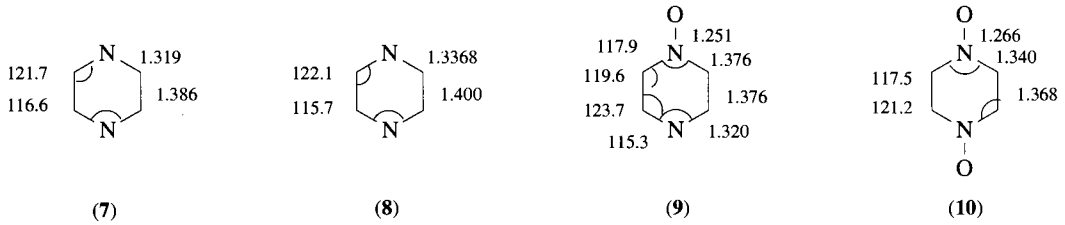
Developments in theoretical calculations have provided much information on the structure and thermochemistry of relatively complicated heterocyclic compounds. An *ab initio* self-consistent-field molecular orbital analysis of structural features of pyrazine has been carried out by 4-31G ⟨85JOC4894⟩, 3-21G/STO-5G ⟨89JST(187)95⟩ and 6-31G*/STO-5G levels ⟨91JST(236)283⟩. The optimized structure of pyrazine, computed at the 6-31G* level, is represented by formula (**7**) which is



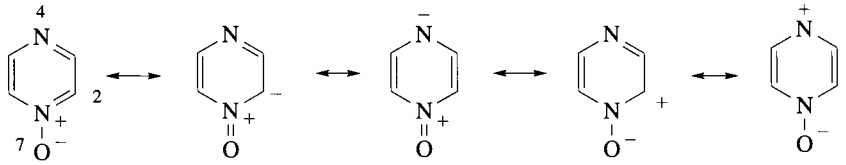
(1) (2) (3)

(4) (5) (6)

in agreement with experimental data of pyrazine (**8**) by electron diffraction ⟨88JA2758⟩. The geometries of pyrazine 1-oxide (**9**) and pyrazine 1,4-dioxide (**10**) were calculated in the same manner. Their N—O bond lengths which range from 1.25–1.27 Å, are shorter than that (1.404 Å) in trimethylamine oxide, indicating considerable double-bond character of the *N*-oxide N—O bond, i.e., an electron-donating effect of the *N*-oxide oxygen to the pyrazine ring as shown in the resonance contributors (**12**) and (**13**).



(7) (8) (9) (10)



(11) (12) (13) (14) (15)

These structural data for pyrazine and the *N*-oxides have been used to compute STO-5G electrostatic potentials and average local ionization energies on the respective molecular surfaces. The most negative electrostatic potentials (V_{min}) associated with the ring nitrogens and the *N*-oxide oxygens of molecules are given in Table 1. Nonoxidized nitrogen is more negative in pyrazine 1-oxide than in pyrazine, while *N*-oxide oxygen is considerably less negative in pyrazine 1-oxide than in pyridine *N*-oxide ($V_{min} = -73.4$ kcal mol^{-1}). These results strongly suggest the importance of the *p*-quinoid resonance form (**13**) of pyrazine *N*-oxide, with an electron-attracting nonoxidized nitrogen *para* to the *N*-oxide group.

The locations and magnitudes of the lowest surface ionization energies $\bar{I}_{S,min}$, are also given in Table 1. These are the points where the least amount of energy is required to remove an electron from the surface, and are believed to be the most reactive sites toward electrophilic attack. In fact, $\bar{I}_{S,min}$ of pyridine *N*-oxide (C_4, 14.52 eV) is slightly higher than that of benzene (14.3 eV at the STO-5G level), in agreement with experimental observation that the 4 position is only slightly deactivated relative to benzene. All values for the carbon atoms in pyrazine and its oxides are greater by 0.9 to 1.6 eV than those of benzene, reflecting the deactivation introduced by the ring nitrogens. The ring nitrogen atom $\bar{I}_{S,min}$ has been shown to be directly proportional to pK_a ⟨91JOC2934⟩. The calculated surface ionization energies permit the prediction of the pK_a value of pyrazine 1-oxide to be approxi-

Table 1 The most negative electrostatic potentials (V_{min}) and the locations and magnitudes of the lowest surface values ($\bar{I}_{S,min}$).

	V_{min} *(kcal mol^{-1})*	$\bar{I}_{S,min}$ *(eV) ring carbon*	$I_{S,min}$ *(eV) heteroatom*
pyrazine	N: −81.6	C: 15.78	N: 13.05
pyrazine 1-oxide	N^4: −84.7 O: −59.0	C^2: 15.15	N^4: 12.74 O: 15.07
pyrazine 1,4-dioxide	O: −64.0	C: 15.87	O: 14.48

mately 3.1, but this is inconsistent with the measured value of 0.05 ⟨70JOC3467⟩. Another approach to calculating the basicity of pyrazine has been made by the semiempirical molecular orbital methods INDO and AM1 ⟨92JST(254)481⟩.

The ^{13}C NMR chemical shifts of alkyl and aryl pyrazines have been found to be well correlated with charge densities ($\sigma + \pi$) calculated by the CNDO/2 method ⟨80OMR(13)172⟩. Those of pyrazine and other six-membered nitrogen heteroaromatic compounds have been calculated by the extended Hückel theory using gauge-invariant atomic orbitals (GIAO) ⟨82JST(88)61⟩. The carbon–hydrogen IR frequencies and intensities of pyrazines and related heterocycles have been obtained from *ab initio* molecular orbital calculations using the 4-31G basis set ⟨93JST(282)97⟩.

6.03.3 EXPERIMENTAL STRUCTURAL METHODS

6.03.3.1 X-ray and Electron Diffraction Analysis

Structural parameters and interatomic distances derived from electron diffraction ⟨77JST(42)121⟩ and x-ray diffraction studies ⟨76AX(B)3178⟩ were given in CHEC-I. The molecular structure of pyrazine has been determined by combined analyses of data obtained by gas-phase electron diffraction (ED) and liquid-crystal NMR (LCNMR) ⟨88JA2758⟩. The NMR spectrum gives structural information because the solute is partially oriented in the liquid–crystal solvent. The r_α structural parameters determined from the ED, LCNMR data and in a joint analysis of both are listed in Table 2. There the C—C bonded distance is fixed since LCNMR data give no information on the absolute size of the molecule. Since pyrazine itself has no dipole moment, it should not show a microwave (pure rotation) spectrum.

Table 2 r_α Structure of pyrazine.

Parameters	*ED alone*	*LCNMR alone*	*ED + LCNMR*
*r*CH (Å)	1.096	1.079	1.0831
*r*CN	1.3368	1.316	1.3376
*r*CC	1.400	1.3984 (fixed)	1.3968
CNC (deg)	115.72	118.7	115.65
CCH	117	119.94	119.96

6.03.3.2 NMR Spectroscopy

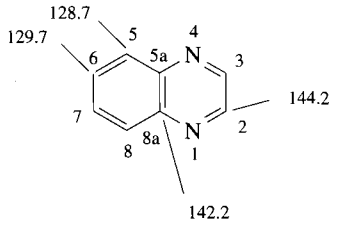
The ^1H NMR spectrum of pyrazine consists of a single peak at δ 8.59 in $CDCl_3$. The proton spectra of monosubstituted pyrazines were described by Cox and Bothner-By ⟨68JPC1646⟩, in which the $^nJ_{(H,H)}$ coupling constants are $^3J_{(H\text{-}5,\ H\text{-}6)} = 2.426$ to 2.857 Hz, $^4J_{(H\text{-}3,\ H\text{-}5)} = -0.112$ to -0.462 Hz, and $^5J_{(H\text{-}3,\ H\text{-}6)} = 1.331$ to 1.451 Hz. The same range of values has been found for the three isomers of disubstituted pyrazines in numerous studies, but exceptions are $^3J_{(H\text{-}5,\ H\text{-}6)}$ of 2(1*H*)-pyrazinones at 3.9–4.2 Hz ⟨68JPC1642⟩, pyrazinethiol at 4.0–4.1 Hz ⟨93JCS(P1)15⟩, and azidopyrazine at 4.6 Hz ⟨94S931⟩. This discrepancy arises because of the predominance of their tautomeric (prototropic or ring-chain) forms with an exocyclic double bond. In either case, the coupling constants are useful for structural determination of disubstituted pyrazines. The elucidation of *N*-oxide position in monosubstituted pyrazine *N*-oxides is also carried out from their coupling constants ⟨78JOC3367⟩: thus, 2-substituted pyrazine 1-oxides exhibit $^3J_{(H\text{-}5,\ H\text{-}6)} = 4.0$ to 4.3 Hz, $^4J_{(H\text{-}3,H\text{-}5)} = 0$ Hz

and $^5J_{(H\text{-}3,H\text{-}6)} = 0.5$ to 0.8 Hz, whereas the 3-substituted 1-oxides show $^3J_{(H\text{-}5,H\text{-}6)} = 4.0$ to 4.2 Hz, $^4J_{(H\text{-}3,H\text{-}5)} = 1.2$ to 1.6 Hz and $^5J_{(H\text{-}3,H\text{-}6)} = 0$ to 0.8 Hz.

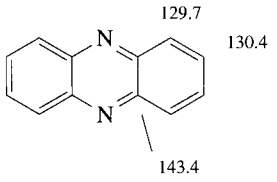
The ^{1}H NMR spectra of quinoxaline and its monosubstituted derivatives have been reported ⟨67JCS(B)1241⟩, and those of di- and trisubstituted quinoxalines have also been measured ⟨68JCS(C)1274⟩. The spectra of a number of phenazine derivatives have been reported ⟨66CPB419⟩. The ^{1}H NMR solvent shifts in acetone, carbon tetrachloride and cyclohexane have been measured for the parent pyrazine, quinoxaline and phenazine ⟨86BCJ1650⟩. For the last two compounds the NMR spectra of both for the neutral and the acidic species are reported ⟨91BCJ2668⟩.

The broadband-decoupled ^{13}C NMR spectrum of pyrazine in $CDCl_3$ shows a single resonance at 145.0 ppm from TMS ⟨80OMR(13)172⟩. Fully coupled and off-resonance-decoupled spectra provide the coupling constants of $^1J_{(C,H)} = 177$ to 187 Hz, $^2J_{(C,H)} = 8$ to 12 Hz, $^3J_{(C,H)} = 7$ to 11 Hz and $^4J_{(C,H)} = 1.2$ to 1.5 Hz. The signals can be assigned by additional consideration of the $J_{(C,H)}$ values from the gated decoupling. Hence, the ^{1}H and ^{13}C chemical shifts of 2-substituted pyrazines have been assigned using $J_{(H,H)}$ values and with application of selective decoupling ⟨90CCC2493⟩. The signal assignment has been found to be more conveniently performed by two-dimensional carbon-proton spectrum or CH COSY without the CH decoupling measurements.

The chemical shift values in the ^{13}C NMR spectrum of quinoxaline in $CDCl_3$ are shown in (**16**) ⟨82JCS(P1)357⟩. Typical values of the coupling constants are $^1J_{(C\text{-}2,H\text{-}2)} = 181.9$ Hz, $^2J_{(C\text{-}2,H\text{-}3)} = 11.4$ Hz, $^3J_{(C\text{-}4a,H\text{-}3)} = {}^3J_{(C\text{-}4a,H\text{-}6)} = 10.0$ Hz, $^3J_{(C\text{-}4a,H\text{-}8)} = 5.4$ Hz, $^1J_{(C\text{-}5,H\text{-}5)} = 162.6$ Hz, $^3J_{(C\text{-}5,H\text{-}7)} = 6.5$ Hz, $^1J_{(C\text{-}6,H\text{-}6)} = 159.4$ Hz and $^3J_{(C\text{-}6,H\text{-}8)} = 9.1$ Hz. Chemical shifts of phenazine from TMS in $CDCl_3$ are as shown in (**17**) ⟨83OMR(21)130⟩. The coupling constants between carbon-13 and nitrogen-15 have been obtained in ^{15}N-enriched phenazines as $^1J_{(NC)} = 1.5$ to 2.5 Hz, $^2J_{(N\text{-}10,C\text{-}1)} = 7.0$ to 10.4 Hz and $^2J_{(N\text{-}10,C\text{-}4a)} = 1.0$ to 1.9 Hz, $^3J_{(N\text{-}10,C\text{-}2)}$ and $^3J_{(N\text{-}10,C\text{-}4)} = 2.5$ to 4.9 Hz and $^4J_{(NC)} = 0.7$ to 1.0 Hz, whose values are used for the assignment of the signals of the aromatic carbons. Additivity of the substituent effects on the chemical shifts of the ring carbons is found in the limited examples of quinoxalines and phenazines.



(**16**)



(**17**)

The ^{15}N NMR spectrum of pyrazine in DMSO containing the relaxation reagent $Cr(acac)_3$ appears at −46.1 ppm (relative to external, neat nitromethane) quinoxaline at −50.1 and phenazine at −53.9 ppm ⟨84OMR(22)201⟩. For methyl-substituted pyrazines and quinoxalines, the ^{15}N signal assignments are based on INDO/S-SOS shielding calculations. Solvent effects on ^{14}N NMR shieldings in pyrazine have been examined ⟨91JMR(91)289⟩. Pyrazine 1-oxide shows two ^{15}N peaks at −75.7 ppm, assigned to the oxidized N-1 nitrogen, and at −70.4 ppm for the N-4 nitrogen, and quinoxaline 1-oxide at −80.7 ppm, assigned arbitrarily to N-1 and at −76.8 ppm to N-4 ⟨80HCA504⟩. Compared with the chemical shift values of the parent compounds, the upfield displacement of the oxidized nitrogen atom is ascribed to a positive charge on the quaternary nitrogen, whereas that of non-oxidized nitrogen is due to decrease in the double-bond character of the ring carbon–nitrogen bond resulting from localization of electrons on the atom as shown in the resonance contributor (**13**).

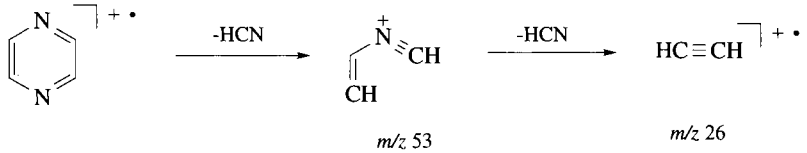
The ^{17}O chemical shifts of pyrazine and quinoxaline *N*-oxides at natural abundance are respectively 399 ppm and 394 ppm from external water in acetonitrile ⟨85JHC981⟩. Since ^{17}O NMR spectroscopy directly measures properties of the oxygen, it allows one to examine the relative back donation of various diazine *N*-oxides. The order of ^{17}O chemical shifts is the *N*-oxides of pyridazine (412 ppm) > pyrazine > pyridine (349 ppm) > pyrimidine (338 ppm), with the larger value corresponding to the greater double-bond character for the nitrogen–oxygen bond in the *N*-oxide group. This is in agreement with measurements on the ^{15}N chemical shifts of the parent compounds as well as with the difference in chemical shifts between the parent and the oxidized nitrogens. Additionally, ^{15}N chemical shifts of nonoxidized nitrogen and the difference from the parent nitrogen are also in same sequence. These facts strongly suggest that the ring nitrogen *para* and particularly *ortho* to the *N*-oxide function affects the back donation by attracting the ring electrons on the *N*-oxide oxygen atom. In the case of pyrazine *N*-oxides, the resonance structure (**13**) is predicted to be

preferred by far over others (**12**) having a nitrogen–oxygen double bond. The ^{17}O NMR spectra of pyrazine and quinoxaline *N,N'*-dioxides have been taken in ^{16}O normalized water solution. Phenazine *N,N'*-dioxide was insufficiently soluble to obtain a natural abundance ^{17}O spectrum in all solvents tried.

Paudler and Jovanovic attempted the classification between π-excessive and π-deficient heteroaromatics by a quantitative measure defined from the ^{13}C NMR chemical shifts ⟨82OMR(19)192⟩. They also examined back donation in pyrazine *N*-oxides based on the interrelationships between ^{15}N, ^{13}C chemical shifts and IR absorption frequencies ⟨82H(19)93⟩.

6.03.3.3 Mass Spectrometry

Mass spectrometry is of increasing importance in the detection and characterization of the naturally occurring pyrazines food flavors or pheromones. The electron impact (EI) mass spectrometric behavior of those compounds has been reviewed by Brophy and Cavill ⟨80H(14)477⟩ and Porter ⟨B-85MI 603-01⟩, the latter deals also with quinoxalines and phenazines. A common feature of fragmentation in pyrazine and quinoxaline is the loss of HCN from the molecular and the fragment ions (Scheme 1). Fragmentation reactions of both metastable and collisionally activated dications which are formed by EI ionization of pyrazine, quinoxaline, and phenazine have been investigated ⟨92OMS(27)89⟩. In contrast to the parent pyrazine, long-chain alkyl-substituted pyrazines show no molecular ions by EI ionization, but these are successfully detected using pulsed positive ion/negative ion chemical ionization (ppinici) with methane ⟨88H(27)2875⟩. Here, the mass spectra depend on analytical concentration and the results are affected strongly by the experimental conditions.



Scheme 1

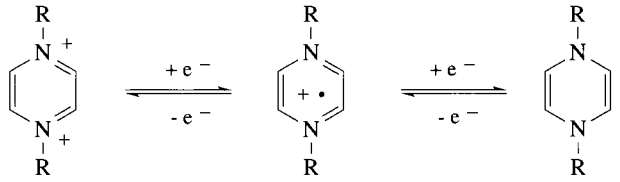
6.03.3.4 IR, UV, and Related Spectroscopies

Since modern structural determination depends heavily upon ^{1}H and ^{13}C NMR analysis, information from IR and UV spectroscopies is less abundant than formerly. However, these spectroscopies are still useful to study photophysical properties, chemical behavior, and electronic orientation of the substituents in heteroaromatics. The pH dependence of both electronic and IR spectra of pyrazine has been examined to obtained pK_a values and information about the solute–solvent interactions, respectively ⟨84JST(114)367⟩. Electronic absorption taken in conjunction with fluorescence spectra indicate that 1,4-dihydro-2,3-quinoxalinedione exists in its diketo form irrespective of the nature of the solvent, by comparison with the spectra of the parent quinoxaline and 1,4-dimethyl-2,3-quinoxalinedione ⟨87MI 603-01⟩. New measurements of the singlet-triplet absorption spectra of pyrazine and pyrazine-d_4 at longer pathlengths and higher vapor pressures have been recorded ⟨93CJC1537⟩.

Laser-induced multiphoton ionization spectroscopy has been applied to the parent, methyl-, and chloro-substituted pyrazines ⟨85ANC2911⟩. The ions produced by laser photoionization in the supersonic jet are mass-analyzed using a time of flight mass spectrometer, in which the spectra obtained reflect the absorption of the n-π^* transition. Mass-resolved excitation spectroscopy by laser ionization in the infrared region has also been applied to the conformational analysis of α-alkyl substituted pyrazines ⟨92JA5269⟩. Dynamic and structural properties of electronically excited states of pyrazine have been elucidated from high resolution laser spectroscopy with MHz resolution ⟨88JST(173)201⟩.

6.03.3.5 ESR and Related Spectroscopies

Kaim has shown that the single electron transfer (SET) reactions of AlH_3 and AlD_3 in THF with pyrazine (**1**), quinoxaline (**2**), and phenazine (**3**) can be studied by ESR spectroscopy, which fully characterizes persistent radical complexes formed as escape products besides the conventional diamagnetic reduction products ⟨84JA1712⟩. The same author was able to isolate unusually stable 1,4-diethylpyrazinium (**18**; R = Et) and 1,4-diethylquinoxalinium cation radicals, which are prepared by treatment of the parent heterocycles with trialkyloxonium tetrafluoroborate in 1,2-dichloroethane in the presence of sodium iodide. It was demonstrated by ESR and crystal structure analysis ⟨88CB2059⟩ that these radical ions are more stable than the phenazinium radical cation and do not associate in concentrated solution or in the solid. This kind of radical cation is also formed by oxidation of *N,N'*-disubstituted 1,4-dihydropyrazines (**19**) with $AlCl_3$ in dichloromethane, or, better, by their anodic oxidation ⟨89CB933⟩. Additional investigation of these radical cations was made by ^1H NMR spectroscopy, cyclic voltammetry, and UV/VIS spectroscopy ⟨91CB129⟩. The absorption spectra of the radical cations and the dication of *N,N'*-diethylpyrazine, -quinoxaline, and -phenazine have been analyzed by INDO/S calculations ⟨94JCS(P2)135⟩.



(**18**) (**19**)

Photoreduction of some quinoxaline and phenazine *N,N'*-dioxides leads to the major formation of the monooxides as deoxygenation products, in which the reaction has been proved to proceed via radical intermediates by ESR spectroscopy ⟨86H(24)659⟩. Proton hyperfine structure of quinoxalines has been observed in glassy matrices and in stretched polyvinyl alcohol films by ESR spectroscopy ⟨87JMR(71)303⟩.

When a series of pyrazines in dilute $CFCl_3$ solution at 77 K are exposed to ^{60}Co γ-rays, the corresponding radical cations are generated, which are identified by their electron paramagnetic resonance (EPR) spectra. Two distinct types of spectra have been observed depending on the substituent. Those obtained from the parent, mono- and dimethylpyrazines are assigned to n(σ)-radical cations: the other spectra, observed for the tetramethyl, methoxy, methylthio, and dialkylamino derivatives, are assigned to π-radical cations. On the other hand, radical anions are generated in the solid state by exposing dilute solutions in CD_3OD at 77 K to ^{60}Co γ-rays, and these also have been characterized by EPR spectroscopy ⟨92JCS(P2)85⟩.

A chemically induced dynamic nuclear polarization (CIDNP) is observed in the irradiation of quinoxalines in various solvents ⟨84JCS(P2)43⟩.

6.03.3.6 Dipole Moments

Comparison of dipole moments proved useful to elucidate the structures of pairs of isomeric *N*-oxides of chlorinated phenylpyrazines ⟨78JOC3367⟩. The observed dipole moments of pyrazine 4-oxides are in good agreement with the vectorial sum calculated from empirical group moments. Dipole moment data of several pyrazines are available from studies by Lumbroso and Palamidessi ⟨65BSF3150⟩ and by Katritzky *et al.* ⟨72JCS(P2)668⟩.

6.03.4 THERMODYNAMIC ASPECTS

6.03.4.1 Boiling Points, Melting Points, Solubility, and Stability

An extensive table by Barlin ⟨B-82MI 603-01⟩ of boiling points and melting points of simple pyrazines known up to 1978 with the addition of some compounds as far as 1980 is available. The relatively low boiling points of alkylpyrazines are linearly correlated with the retention indices of gas chromatographic analysis (see below). Halogenopyrazines also conform with such a relationship

in that series. Owing mainly to strong crystal-lattice forces operating through intermolecular hydrogen bonds from carbamoyl or carboxy groups to the ring nitrogen atoms, pyrazinecarboxamides and pyrazinecarboxylic acids have higher melting points than the corresponding benzenoid compounds, and in particular hydroxypyrazines or 2(1*H*)-pyrazinones show very different melting points from those of phenols. A *p*-disubstituted benzene has a higher melting point than an *o*- or *m*- because the *p*-isomer is more symmetrical and can form a more orderly and stronger crystal lattice in the solid. Although 2,5-disubstituted pyrazine isomers are not as symmetrical as the 2,3- and 2,6-isomers, ten cases in 15 sets are found to have the highest melting point of the three isomers.

N-Oxidation raises the melting point and reduces the solubility in organic solvents because of the more hydrophilic *N*-oxide portion. Because of the strong lattice force between molecules, carboxy acids, and carboxamides of pyrazines and 2(1*H*)-pyrazinones have poor solubility in nonpolar solvents.

The pyrazine ring is stable to permanganate oxidation, and this accounts for a variety of pyrazinecarboxylic acids that have been prepared from quinoxalines, benzo-fused quinoxalines including phenazines, and pyrido-fused pyrazines ⟨B-82-MI 603-01⟩. In other fused systems, particularly pteridines, the pyrimidine ring is easily hydrolyzed under either acidic or basic conditions to give numerous 3-aminopyrazinecarboxylic acid derivatives.

Pyrazinecarboxylic acids undergo decarboxylation at high temperatures above 200°C. By this procedure, alkyl- or arylpyrazines ⟨78JOC3367⟩, pyrazinones ⟨78JHC665⟩, and aminopyrazines ⟨80JHC143⟩ are effectively prepared from the corresponding carboxylic acids.

Thermal and photochemical reactions of pyrazines, quinoxalines and phenazines to other systems and the rearrangement into pyrazines are summarized in Sections 6.03.5.1 and 6.03.12, respectively. The stability of dihydropyrazines is discussed in Section 6.03.5.6.2.

6.03.4.2 Chromatographic Behavior

Like mass spectrometry, gas chromatography (GC) is a useful analytical method for pyrazine flavors. The retention indices of numerous pyrazine derivatives on OV-101 and Carbowax 20M columns have been predicted as the sum of the increments for substituent groups and the retention index of pyrazine ⟨85JC428, 87JC309⟩. The substituent increments have been determined from the observed retention index values of monosubstituted alkyl-, vinyl-, methoxy-, ethoxy-, phenoxy-, ethylthio-, phenylthio-, acetyl-, and chloropyrazines. The empirical values, further corrected by the positional increments of the substituents, are in good agreement with the experimental values. With regard to amine compounds, including nitrogen heteroaromatics, an attempt to correlate the observed retention indices with nonempirical factors such as the total energy or topological electronic index has still not been achieved but the energy of the HOMO level has been found to have an approximate relation to them ⟨85JC53, 86JC63⟩.

The liquid chromatographic behavior of pyrazine and its methyl derivatives is similar to that of aliphatic amines, anilines, and other nitrogen heteroaromatic compounds because these materials are retained strongly on a normal-phase silica gel with hexane as eluent due to strong acid-base interactions of the basic nitrogen atom with the acidic silanol groups in the silica gel. On this account the solutes sometimes have not been eluted from the column. Accordingly the separation of pyrazines has been carried out on reverse-phase methacrylate gel or octadecyl bonded silica gel columns utilizing acetonitrile—H_2O at various pH as the mobile phase ⟨85JLC2463⟩. A reverse-phase polystyrene gel column eluting with a MeOH—H_2O mobile phase offers the best separation for pyrazines, their *N*-oxides and particularly *N*,*N*′-dioxides, where a satisfactory linear correlation between the logarithm of the retention volume and solvent composition can be observed ⟨83YZ245⟩.

6.03.4.3 Aromaticity

Katritzky *et al.* have proposed that there are at least two types of aromaticity, namely classical and magnetic aromaticity ⟨89JA7, 90JPR853, 90JPR870⟩. The most usual criterion of classical aromaticity is provided by resonance energy, the order of which is benzene > pyridine > pyrazine > pyrimidine ≫ pyridazine ⟨92T335⟩. Instead of the resonance energy, Dewar *et al.* introduced a new index of aromaticity, aromatic energy, which is defined by the heats of formation derived from the AM1 semiempirical method ⟨89H(28)1135⟩. This value is equal to the stabilization energy in six-membered heteroaromatics and the order is benzene > pyridine > pyrimidine > pyrazine >

pyridazine. In both indices, the energies for pyrimidine and pyrazine are very close, so that the stability of the two diazines seems virtually identical.

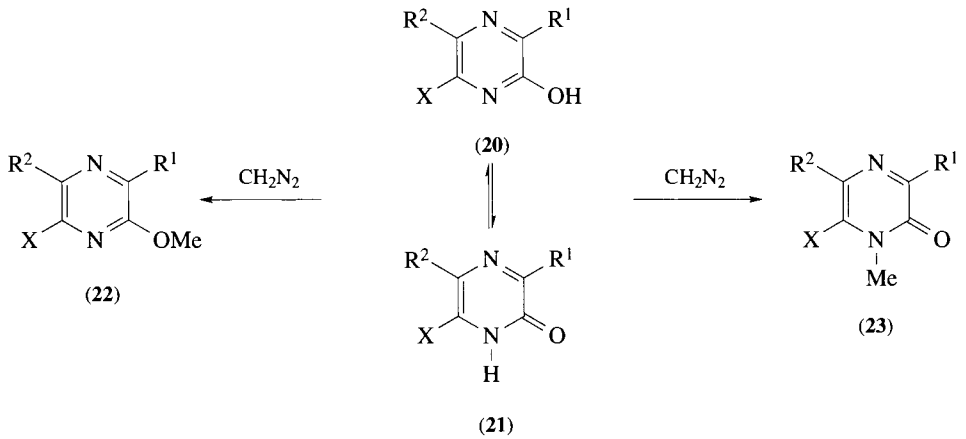
As the best available measure of classical aromaticity, Katritzky *et al.* commended the Bird I_6 parameter, which is a new index of aromatic character based on a statistical evaluation of the deviations in peripheral bond orders ⟨85T1409, 86T89⟩, and is later improved to I_A ⟨92T335⟩. Unlike the resonance and aromatic energetical order, the Bird I_6 or I_A estimates that pyrazine has a higher stability than pyridine and other diazines.

The second type of aromaticity is magnetic aromaticity with the ability to sustain an induced ring current. However, it is difficult to separate this diatropic from other effects, and consequently diamagnetic susceptibility exaltation (Λ) is used for the magnetic parameters as criteria for aromaticity. The order of Λ is pyridine > pyrimidine > benzene ≫ pyrazine ≫ pyridazine ⟨90JPR853⟩, which is identical with the above aromatic energy for the nitrogen heteroaromatics, but the difference between pyrimidine and pyrazine is greater than that in the classical aromaticity.

6.03.4.4 Tautomerism

A typical tautomerism is represented by the equilibrium between hydroxypyrazine (**4**) or (**20**) and 2(1*H*)-pyrazinone (**6**) or (**21**), in which the latter amide form predominates over the former. A similar situation exists in hydroxyquinoxaline (**5**). An IR study has been conducted on the tautomerism between hydroxy and keto forms in 2,5- and 2,6-dihydropyrazines which were found to exist in 5- and 6-hydroxy-2(1*H*)-pyrazinone forms by comparison with the carbonyl absorption of the corresponding methoxypyrazinones ⟨65JCS6681⟩. In addition to IR evidence predicated on the carbonyl absorption, the predominance of the amide form is proved by the ^{1}H NMR spectra of 2(1*H*)-pyrazinones, in which the ring protons appear to higher field by 0.4–0.9 ppm than those of 2-methoxypyrazine, indicating an increase in double-bond character or electron-localized structure of the unsaturated lactam form. 1-Hydroxy-2(1*H*)-pyrazinones, the tautomers of 2-hydroxypyrazine 1-oxides, show similar deviations in chemical shifts ⟨86JHC149⟩.

Another useful method for the elucidation of the hydroxypyrazine–pyrazinone tautomerism is UV spectral analysis. The objective structure in solution is easily estimated by comparison with the UV spectra of the proton-fixed compounds of two tautomers, *O*-methylated (**22**) and *N*-methylated derivatives (**23**), which are prepared by methylation of the hydroxypyrazines or pyrazinones with diazomethane (Scheme 2). For example, 6-amino-5-benzyl-3-methyl-2(1*H*)-pyrazinone (**21**; R^1 = Me, R^2 = CH_2Ph, X = NH_2) has been shown to predominate over the hydroxy form (**20**) because of its nearly identical UV spectrum with the corresponding *N*-methylated derivative (**23**) ⟨93JOC7542⟩. In contrast, 6-chloro-2-hydroxypyrazines (**20**; R^1, R^2 = Me or Ph, X = Cl) exist in the hydroxy form rather than as the tautomeric amide, which is an exceptional example of predominance of the hydroxy form with parallels in the chloro-pyridinone field ⟨71JCS(C)2977⟩.



Scheme 2

Tautomerism in hydroxy-, thiol- and amino-substituted pyrazines has been verified by ^{13}C,^{1}H spin–spin coupling constants, and the results are supported by ^{15}N NMR data ⟨82TL4785⟩.

Tetrazolo–azido tautomerism is exemplified by the 2-azidopyrazine-tetrazolo[1,5-*a*]pyrazine equi-

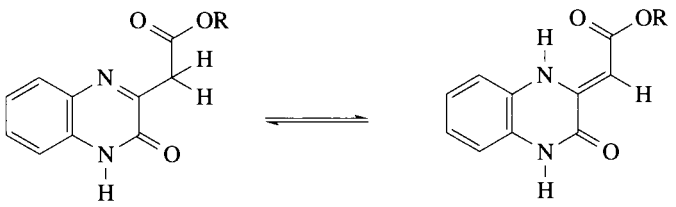
librium (Scheme 3), which in 2-azido-5,6-diphenylpyrazine is much influenced by the solvent. In $CDCl_3$ the tetrazolo–azido ratio is 10 : 3 by ^1H NMR spectroscopy whereas in DMSO-d_6 the tetrazole isomer exists exclusively ⟨71JOC446⟩. In TFA, it is claimed to shift completely into the azido tautomer. The equilibrium is also affected by the steric environment of the azido group, in particular the presence of a 6-substituent ⟨94S931⟩.

Scheme 3

Pyrazinyl β-dicarbonyl compounds (**24**) isomerize to the favored exocyclic double-bond form (**25**) in addition to the keto–enol tautomerism of the β-dicarbonyl moiety ⟨67JHC109⟩. A similar equilibrium of the β-unsaturated side chain is observed in 2(1*H*)-quinoxalinone (**26**) or analogues carrying oxadiazolyl, triazolyl or benzimidazolyl groups instead of the alkoxycarbonyl (Scheme 5). In most cases, both tautomers of methylene imine (**26**) and enamine forms (**27**) exist in DMSO-d_6 while the latter tautomer is sometimes favored in $CDCl_3$. In TFA, protonated methylene iminium forms predominate, especially in the quinoxalinones with five-membered nitrogen heteroaromatics in the side chain ⟨86H(24)2321⟩.

(**24**) (**25**)

Scheme 4



(**26**) (**27**)

Scheme 5

6.03.4.5 Miscellaneous

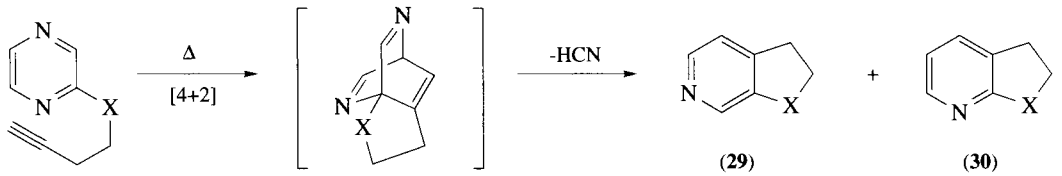
Ionization constants of pyrazine compounds are summarized by Barlin ⟨B-82MI 603-01⟩. The basicity constants of pyrazine and its methyl derivatives in water have also been measured, and show a linear inverse relationship with polarographic half-wave potentials ⟨85JHC1143⟩.

6.03.5 REACTIVITY OF FULLY CONJUGATED RINGS

Reactivity dealt with in the following sections is limited only to that of the heteroaromatic ring of pyrazines, quinoxalines, and phenazines. In general, any type of substitution reaction on quinoxaline and phenazine should be more facile than with pyrazine because of the resonance-stabilization effect of the additional benzenoid ring on the transition states leading to the products.

6.03.5.1 Thermal and Photochemical Reactions

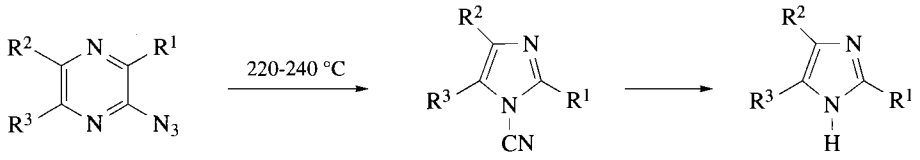
Heating of 2-(*N*-acetyl-3-butynylamino)pyrazine (**28**; X = NAc) at 165 °C brings about an intramolecular Diels–Alder reaction followed by loss of hydrogen cyanide leading to the formation of 1-acetyl-1,2-dihydropyrrolo[2,3-*c*]pyridine (**29**; X = NAc) along with the [2,3-*b*] isomer (**30**; X = NAc) as a minor product (Scheme 6) ⟨88T2977⟩. Similarly 2-(3-butynyloxy)pyrazine and 2-(3-butynylthio)pyrazine give mainly the [*c*]-fused products (**29**), whereas 2-(3-butynylsulfinyl)pyrazine and 2-(3-butynylsulfonyl)pyrazine are exclusively converted into [*b*]-fused pyridines (**30**). N-4-Quaternary pyrazinium salts and N-4-protonated pyrazines undergo the intramolecular Diels–Alder reaction under far milder conditions than the neutral pyrazines ⟨89T6519⟩. Irrespective of the substituent the products are the [*c*]-annulated pyridinium salts.



(**28**) X = NAc, O, S, SO SO_2 (**29**) (**30**)

Scheme 6

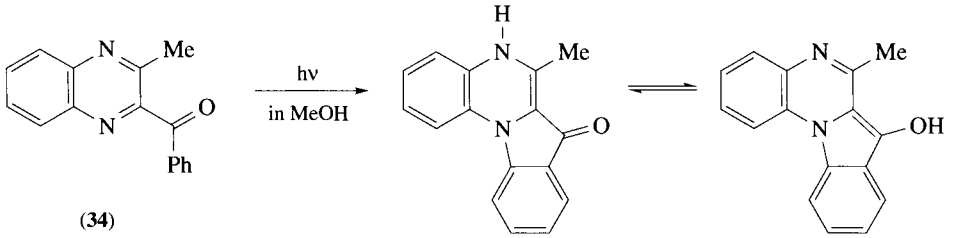
Pyrolysis of 2-azidopyrazines (**31**) at 200–240 °C leads to a vigorous evolution of nitrogen and gives 1-cyanoimidazoles (**32**) in excellent yields (Scheme 7) ⟨83JHC1277⟩. This ring transformation is also accomplished by irradiation in ethanol but the decyanated compounds (**33**) are additionally formed, which are alternatively prepared by hydrolysis of the cyanoimidazole (**32**). Cleavage of the pyrazine ring takes place on pyrolysis of 2,3-diazido-5,6-diarylpyrazines, which form *N*,*N*′-dicyano-1,2-diaryl-1,2-ethanediimines ⟨90JHC711⟩.



(**31**) (**32**) (**33**)

Scheme 7

2-Benzoyl-3-methylquinoxaline (**34**) on irradiation in methanol gives the purple 6-methylindolo[1,2-*a*]quinoxalin-7(5*H*)-one (**35**), the yield of which is markedly improved by reaction in the presence of TFA or TsOH (Scheme 8) ⟨90T6483⟩.



(**34**) (**35**)

Scheme 8

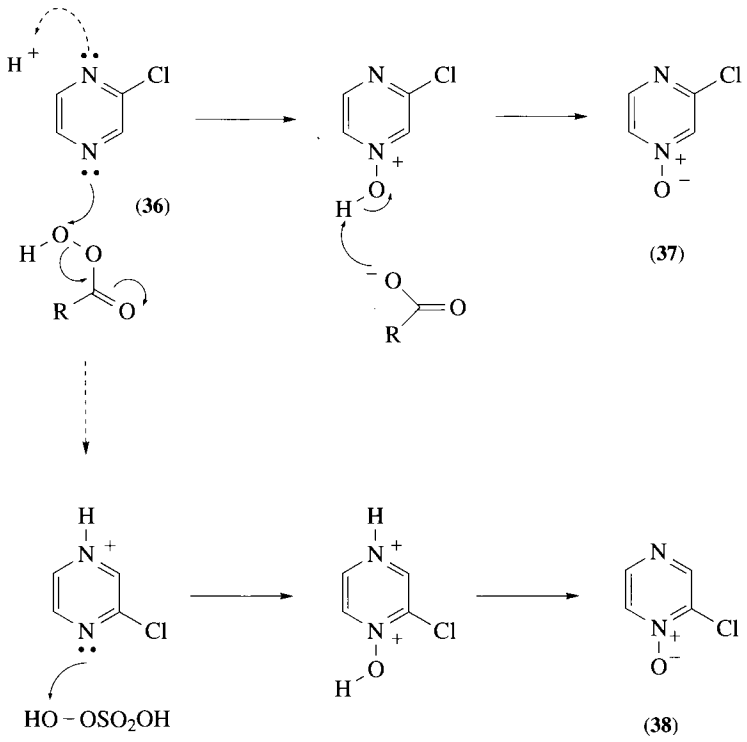
Photochemical decomposition of 2-azido-1-methoxyphenazine forms singlet and triplet nitrenes, which are trapped with the azide leading in acetonitrile at −20 °C to the dimeric product 3-[3-[[(1-methoxy-2-phenazinyl)imino]methoxymethyl]-2-quinoxalinyl]-2-propenenitrile ⟨91JOC6993⟩. Higher reaction temperatures result in the additional formation of aminophenazines and other 2,3-disubstituted quinoxalines ⟨87JOC1245⟩.

Photochemistry with other molecules including oxygen is dealt with in a later Section (6.03.5.7).

6.03.5.2 Electrophilic Attack at Nitrogen

Ring nitrogens in pyrazines and the benzo derivatives react with electrophiles to form quaternary ammonium species such as *N*-alkylpyrazinium salts and pyrazine *N*-oxides. *N*-Alkylation has generally been performed by treatment with a reactive alkyl iodide ⟨85H(23)2299⟩. The Meerwein reagent triethyloxonium tetrafluoroborate also effects the *N*-ethylation of pyrazines ⟨89T6519⟩. *N*-Oxidation of the parent heterocycles is readily accomplished by treatment with peracetic acid, MCPBA, peroxymaleic, or peroxytrifluoroacetic acid. The most convenient procedure for this transformation is treatment with hydrogen peroxide in acetic acid. Use of formic acid instead of acetic acid results in a considerable increase in the yield of *N*-oxide from pyrazinecarboxamide in a shorter reaction time ⟨90S659⟩. A new oxidizing reagent is sodium perborate, which has been used in acetic acid at 80 °C for oxidation of alkyl or aryl substituted pyrazines and their chloro derivatives to the mono *N*-oxides ⟨85S216⟩. This method avoids the use of the potentially hazardous concentrated peroxide. Molybdenum(IV) oxide is effective for catalysis of the hydrogen peroxide oxidation in aqueous medium; this procedure has industrial advantage because acetic acid is not used ⟨87JAP(K)181268⟩.

Mixan and Pew have shown that *N*-oxidation with peroxysulfuric acid, which is generated *in situ* from potassium persulfate in concentrated sulfuric acid, may be the method of choice for the *N*-oxide synthesis of highly deactivated pyrazines such as polychlorinated pyrazines in terms of availability of reagent and safety of handling ⟨77JOC1869⟩. A marked advantage of the peroxysulfuric acid oxidation is its effect on the direction of *N*-oxidation, for example 2-chloropyrazine (**36**) yields directly the corresponding 1-oxide (**38**), unlike oxidation with peroxycarboxylic acid which provides the 4-oxide (**37**) (Scheme 9). Similarly, 2-cyanopyrazine and 2-methoxycarbonylpyrazine can be converted into the corresponding 1-oxides, although in low yields ⟨83JHC169⟩. On the other hand, 2-aminopyrazine (**39**) and its methyl or phenyl derivatives are oxidized by MCPBA in acetone to the corresponding 1-oxides ⟨77SC509, 85JHC1145⟩.



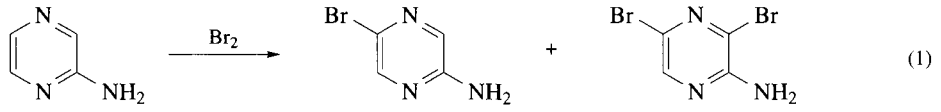
Scheme 9

All reactions dealt with in this section involve nucleophilic attack of the lone pair of electrons on nitrogen on the electrophiles. The progress of the reaction depends both on the basicity of the nitrogen atom and on the electrophilicity of the reagent. Therefore, the orientation of these reactions with substituted pyrazines is governed by the relative basicities of the ring nitrogens. The oxidation with peroxycarboxylic acid takes place on the nitrogen furthest removed from a methoxy, phenyl,

chloro, carbamoyl, or alkoxycarbonyl substituent, suggesting that these groups reduce the nucleophilicity of the adjacent nitrogen. It should be noted that the methoxy group behaves as an electron-withdrawing substituent, and the phenyl group has a similar effect when the mesomeric interaction with pyrazine ring is not interrupted ⟨78JOC3367⟩. In contrast, the electron-donating amino group increases the basicity on the nitrogen at N-1, resulting in the exclusive formation of the 1-oxide. The ease of *N*-oxidation relies on the electrophilicity of the peroxy acid, which depends upon the basicity of the leaving ion as can be seen from Scheme 9; consequently the approximate order of strength as oxidative reagent is peroxysulfuric acid > trifluoroperoxyacetic acid > peroxymaleic acid > performic acid ~ MCPBA > peracetic acid. In a strong acid such as concentrated sulfuric acid, however, both the ring nitrogens of 2-aminopyrazine, 2-methylpyrazine and pyrazine are protonated and as a result no *N*-oxide is formed. Conversely, the equilibrium favors the protonation of the more basic nitrogen, which is that oxidized by the usual peroxycarboxylic acid. Although the nucleophilicity of the remaining nitrogen is reduced by both the electron-withdrawing chlorine and protonated nitrogen, the electrophilicity of persulfuric acid is sufficient to effect oxidation. Therefore, the regiochemistry is opposite to that formed with a peroxycarboxylic acid.

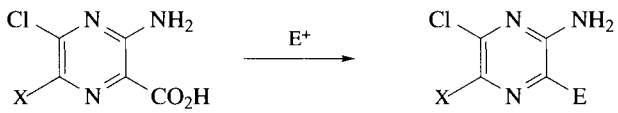
6.03.5.3 Electrophilic Attack at Carbon

Because of their electron-deficient ring system containing two nitrogen atoms, pyrazines do not undergo electrophilic substitution. When the ring is substituted by electron-donating groups, electrophilic reactions can take place, but these are limited in number. Bromination of 2-aminopyrazine (**39**) with bromine in chloroform in the presence of pyridine gives 2-amino-3,5-dibromopyrazine (**40**) in 54% yield ⟨82JHC673⟩. Under controlled conditions, 2-amino-5-bromopyrazine (**41**) is obtained in 36% yield (Equation (1)). The earlier procedure using bromine, acetic acid, and sodium acetate gives only 14% of dibromopyrazine (**40**). An improvement in the yield of (**40**) is achieved by changing the solvent and base ⟨83JOC1064⟩ or the reagent to NBS in aqueous DMSO ⟨90S659⟩. Iodination of 2-aminopyrazines and their 4-oxides also proceeds by treatment with iodine in the presence of triethylamine or other bases ⟨84H(22)1195⟩. The use of DMSO as solvent remarkably improves the yields for shorter reaction times without requiring added base. This reaction has been successfully applied to the *N*-alkyl derivatives but not to 3-acetamido, 3-methyl-, and 3-chloropyrazine 1-oxides.



(39) (41) (40) (1)

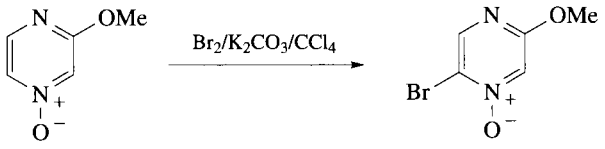
Electrophilic substitutions accompanied decarboxylation are induced by an electron-donating *ortho*-amino group (Equation (2)). Replacement of the carboxylic acid in 3-amino-5,6-dichloropyrazinecarboxylic acid (**42**; X = Cl) by a nitro group is accomplished by treatment with nitric acid in sulfuric acid, producing compound (**43**; X = NO_2) ⟨83JHC1089⟩. Decarboxylative iodination of 3,6-diamino-5-chloropyrazinecarboxylic acid (**42**; X = NH_2) occurs on heating in DMF with iodine ⟨89JOC1218⟩. Most likely, the products are formed via an addition–elimination sequence rather than decarboxylation being the initial step.



(42) (43) (2)

Unlike pyridine *N*-oxides where electrophilic substitution is facilitated by the electron-donating effect of the *N*-oxide oxygen, pyrazine *N*-oxides are inert to this substitution. For example, 2,5-dimethylpyrazine 1,4-dioxide could not be nitrated with sodium nitrate in sulfuric acid at 70 °C and 75% of the dioxide was recovered after 16 hours ⟨58JOC1603⟩. However, 3-methoxypyrazine 1-oxide (**44**) is converted into the 6-bromo derivative (**45**) (45% yield) by treatment with bromine in carbon

tetrachloride in the presence of potassium carbonate (Equation (3)) ⟨83JOC1064⟩. Since neither 2-methoxypyrazine nor its 1-oxide are brominated under these conditions, the substitution must be ascribed to the combined electron-donating effects of the methoxy and *N*-oxide functionalities.



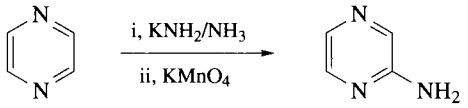
(44) (45) (3)

6.03.5.4 Nucleophilic Attack at Carbon

6.03.5.4.1 Displacement of ring protons

In contrast to benzene compounds, which undergo ready electrophilic substitution, the highly π-deficient pyrazine and quinoxaline nuclei are susceptible towards nucleophilic attack by a variety of reagents. The direct nucleophilic substitution with organolithium or Grignard reagents to form alkyl or aryl heteroaromatics, however, is rather ineffective, and the dihydro and/or tetrahydro compounds are formed preferentially. For example, reaction of pyrazine with phenyllithium affords 2-phenylpyrazine (5%) and the diphenyl tetrahydro derivatives (30%) ⟨86JHC1051⟩. Quinoxalines react with the β,γ-unsaturated Grignard reagents, allyl- or allenylmagnesium bromide, to give high yields of 2-allyl- or 2-propargyl-1,2-dihydro- and the 2,3-disubstituted-1,2,3,4-tetrahydroquinoxalines, the formation of which is affected both by the substituents of the starting substrate and by the reaction conditions ⟨87T2769⟩.

Carbanions generated from sulfones, sulfoxides, and sulfides with butyllithium undergo nucleophilic addition to quinoxalines across the 1,2- and 3,4-bonds to form hexahydrothieno[3,4-*b*]quinoxaline derivatives ⟨89H(29)141⟩. Other carbanions from α-haloalkyl sulfones, sulfonates, and sulfonamides react with quinoxalines to give bisannulated products of tetrahydro-bisazirinoquinoxalines in very good yields ⟨91CB577⟩. A typical reaction involving replacement of ring hydrogen is the Tschitschibabin reaction, in which pyrazine (**1**) is treated with KNH_2/NH_3 followed by potassium manganate oxidation to provide 2-aminopyrazine (**39**) in 65% yield (Equation (4)) ⟨82JHC1285⟩. The earlier procedure with $NaNH_2$ or KNH_2 in an inert solvent produced no satisfactory results. Quinoxaline (**2**) is also converted into 2-aminoquinoxaline (53%) and 2,3-diaminoquinoxaline (23%). Amination of 5- and 6-nitroquinoxalines in a liquid ammonia solution of potassium manganate was shown to take place on either the pyrazine or the benzene ring in moderate yields ⟨92LA899⟩.

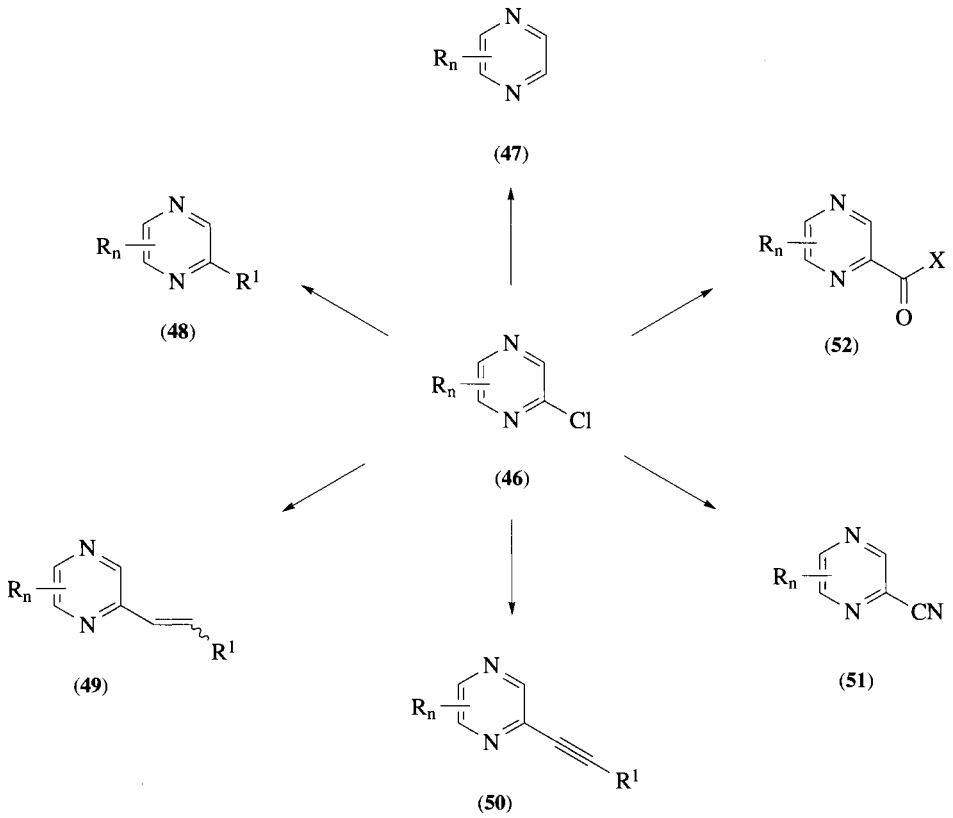


(1) (39) (4)

6.03.5.4.2 Nucleophilic displacement of substituents

Nucleophilic displacement of halogen in pyrazines and quinoxalines is the most common method for the synthesis of otherwise inaccessible heterocycles, in which, over the past 12 years, the most innovative methodology has been the organometallic catalyzed cross-coupling reaction (Scheme 10). The first example in the pyrazine series was the reductive dechlorination of chloropyrazines (**46**) to the parent compounds (**47**) ⟨81H(16)1325⟩, which is accomplished by treatment of (**46**) with sodium formate in DMF in the presence of tetrakis(triphenylphosphine)palladium(0) at 100 °C for several hours. This method is advantageous in avoiding deoxygenation of the *N*-oxide moiety, which

frequently takes place under reductive conditions. Hydrogenation instead of using sodium formate also effects the dechlorination ⟨86H(24)2093⟩.

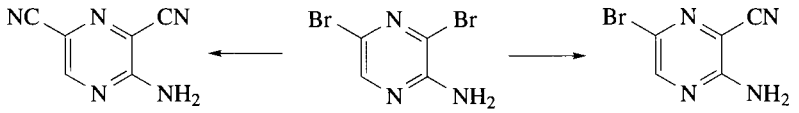


Scheme 10

Ohta *et al.* extensively investigated alkylation or arylation by the cross-coupling reaction of chloropyrazine or its *N*-oxides with organoaluminum ⟨85H(23)133, 87H(26)2449⟩, organoboron ⟨87H(26)2449, 89H(29)939⟩, and organotin compounds ⟨86H(24)785, 89H(29)123⟩. The best yields are obtained by using trimethylaluminum, triethylboron, and tetraaryltins for the corresponding alkyl or aryl substituted pyrazines (**48**). The latter two organometallic reagents are conveniently prepared *in situ* from Grignard reagents with boron trifluoride diethyl etherate and tin(IV) chloride, respectively. Areneboronic acids are also effective for arylation, most reactions of which are notably improved by use of the binuclear catalyst Pd(DPPF)$(OAc)_2$ ⟨88JOC2052⟩. A classical method for alkylation involves the cross-coupling reaction between a halogenopyrazine and a Grignard reagent, but the yields are very low ⟨78JOC3367⟩. This type of reaction has been found to be promoted by a nickel catalyst ⟨92JA5269⟩, for example, 2,6-diethylpyrazine is formed spontaneously at room temperature in the reaction of diethylzinc with 2,6-dichloropyrazine in toluene employing catalytic 1,3-bis(diphenylphosphino)propanenickel(II) dichloride. This method significantly improved the yield over that in which the palladium catalyst was used as described above. The palladium-catalyzed cross-coupling of chloropyrazines with ethylenes gave generally poor yields of alkenyl products (**49**) ⟨86JHC1481⟩ except with styrene ⟨82H(19)329⟩, although with ethynes the reaction proceeded readily to form the coupled products (**50**) in high yields ⟨82H(19)329, 83S312, 86CPB1447, 87JOC3997, 89JOC1218⟩. Alkynylpyrazine *N*-oxides are prepared in the same fashion from the chloropyrazine *N*-oxides ⟨86CPB1447, 90JHC503⟩.

Chloropyrazines are successfully cyanated with potassium cyanide under palladium-catalytic conditions to give cyanopyrazines (**51**) ⟨81S974⟩. Without the palladium complex, displacement of chlorine by the cyanide group cannot be satisfactorily accomplished ⟨56JA2141⟩. Cyanation of 2-amino-5-bromopyrazine needs the auxiliary reagents copper(I) iodide and 18-crown-6 ⟨87JHC1371⟩. Under identical conditions, 2-amino-3,5-dibromopyrazine (**40**) is convertible into the 3,5-dicyanopyrazine (**53**), but this method does not allow selective replacement of the bromine atoms. Mono-

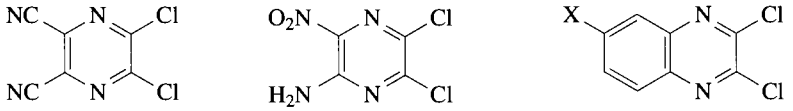
cyanation is realized by treatment with sodium dicyanocuprate, forming 2-amino-5-bromo-3-cyanopyrazine (**54**) in a best yield of 69% (Scheme 11) ⟨90S659⟩, which is a versatile intermediate for the synthesis of pteridines. Palladium-catalyzed carbonylation of chloropyrazines in methanol leads to pyrazinecarboxylic esters (**52**; X = OMe) in good yields ⟨90S923⟩. Similarly, pyrazinecarboxamides (**52**; X = NHR^1 or NR^1_2) are obtained by using dialkylamines or alkylamines as the solvent.



(**53**) (**40**) (**54**)

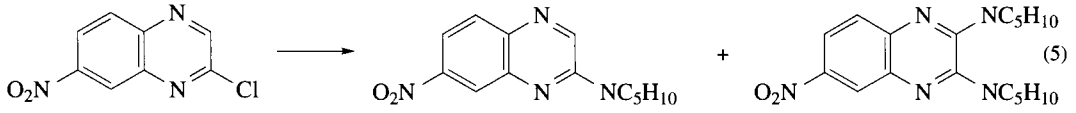
Scheme 11

A variety of nucleophiles displace halogeno or other substituents, and the ease of substitution depends upon the leaving group as well as the neighboring substituents. As a π-deficient ring system substituted fully by electron-withdrawing groups, 2,3-dichloro-5,6-dicyanopyrazine (**55**) is susceptible to attack by relatively less reactive enamines resulting in displacement of a chloro substituent to form 3-chloro-5,6-dicyanopyrazinyl vinylamines ⟨93JHC1571⟩. Bubbling ammonia through a solution of (**55**) in DMF at −10 °C for 15 min gives 2-amino-3-chloro-5,6-dicyanopyrazine in 61% yield ⟨86JHC1741⟩. Similarly, facile substitution occurs in 2-amino-5,6-dichloro-3-nitropyrazine (**56**), in which the chloro substituent *para* to the nitro group is easily displaced by amines in the presence of triethylamine at room temperature ⟨83JHC1089⟩. Nucleophilic displacement in 2-chloro-3-nitro- and 2-chloro-5-nitropyrazine with amines proceeds slower than in the tetrasubstituted pyrazine (**55**). The chloro substituent *para* to a carboxy or alkoxycarbonyl group is liable to hydrolysis or alcoholysis ⟨82JHC407⟩, for example, treatment of 5-chloro-2-pyrazinecarboxylic acid with refluxing 0.5 N sodium hydroxide for 1 hour gives quantitatively 5,6-dihydro-5-oxo-2-pyrazinecarboxylic acid. A benzoyl or nitro group at C-6 of 2,3-dichloroquinoxaline (**57**; X = NO_2 or COPh) facilitates displacement of the C-2 chloro substituent ⟨92JHC771⟩.

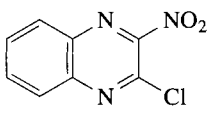


(**55**) (**56**) (**57**)

The nitro group in 2-chloro-7-nitroquinoxaline (**58**) is aminated by piperidine at C-3 carbon and then displacement of the chloro substituent ensues to afford 2,3-dipiperidino-6-nitroquinoxaline as well as the normal 2-piperidino-7-nitro product (Equation (5)) ⟨91TL1311⟩. In contrast, 2-chloro-3-nitroquinoxaline (**59**) undergoes displacement of the nitro group with amines to form 2-amino-3-chloroquinoxaline derivatives ⟨83JHC947⟩. Tetrachloropyrazine is also attacked by carbanions generated from malononitrile or malonic esters with NaH in THF, producing the corresponding trichloropyrazinylmalono compounds ⟨83JHC365⟩.

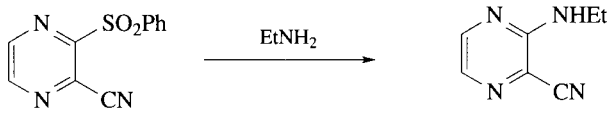


(**58**) (5)



(**59**)

Amination of 2-fluoropyrazine 1-oxide with a variety of amines proceeds smoothly at 40–50 °C to form excellent yields of the aminopyrazine *N*-oxides within 2 h ⟨84H(22)1105⟩. This reactivity is in contrast to that in the amination of 2-chloropyrazine 1-oxide, where higher temperatures (100–110 °C) are needed. An electron-withdrawing cyano substituent adjacent to a phenylsulfonyl group prompts its nucleophilic replacement by amines ⟨92JHC1689⟩, for example, reaction of 3-phenylsulfonylpyrazinecarbonitrile (**60**) with ethylamine in the presence of triethylamine at room temperature for 2 hours produces 3-(*N*-ethylamino)pyrazinecarbonitrile (**61**) in 78% yield (Equation (6)). In contrast, conversion of 2-methylsulfonylpyrazine into 2-(*N*-propylamino)pyrazine requires heating with propylamine at 150 °C for 18 hours ⟨67JCS(C)2473⟩. The fluoro and sulfonyl compounds are also liable to alkoxylation at room temperature, and the former are convertible into hydroxy or ethylthio compounds by treatment with aqueous sodium hydroxide or sodium ethyl sulfide. 2,3-Dicyanopyrazine undergoes nucleophilic alkoxylation and amination ⟨85JHC1365, 86JHC1299⟩, in which the leaving ability of cyano group is significantly inferior to that of the fluoro or sulfonyl.



(6)

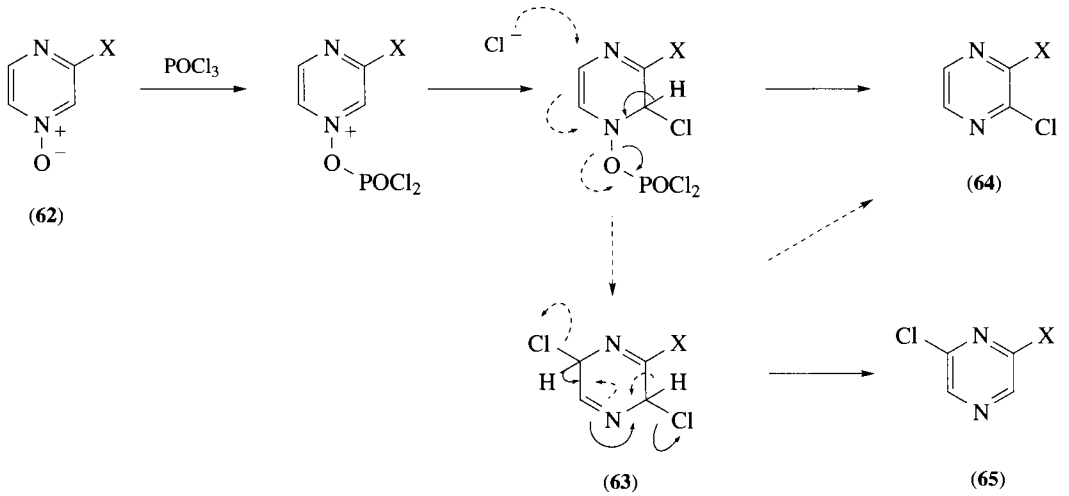
(**60**) (**61**)

Reaction of chloropyrazines with sodium azide in DMF leads to the formation of azidopyrazines or tetrazolo[1,5-*a*]pyrazines ⟨83JHC1277⟩. Thiation of halogenopyrazines ⟨83JHC1047, 91JHC1131⟩ and halogenoquinoxalines ⟨83JHC199, 83JHC623⟩ is effected by treatment with a thiol in the presence of sodium alkoxide. Diazotization of aminopyrazine *N*-oxides in concentrated hydrochloric or hydrobromic acid provides the corresponding halogenopyrazine *N*-oxides in moderate yields ⟨83H(20)2011⟩ but the fluoro derivative does not form in hydrofluoric acid ⟨84H(22)1115⟩.

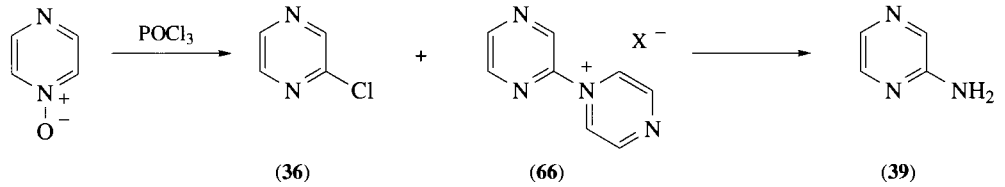
6.03.5.4.3 Deoxidative nucleophilic substitution of N*-oxides*

Deoxidative substitution of pyrazine or quinoxaline *N*-oxides with nucleophiles is a very important method for introducing a substituent into the heteroaromatic rings. In particular, reaction with phosphoryl chloride or other acid chlorides produces chloroheterocycles. However, regioselectivity in the chlorination of pyrazine *N*-oxides with phosphoryl chloride depends upon the substituent on the C-3 carbon. Thus, 3-aminopyrazine 1-oxide (**62**; X = NH_2) is chlorinated with loss of the *N*-oxide oxygen to give 2-amino-3-chloropyrazine as the sole product whereas 3-methoxy and 3-chloropyrazine 1-oxides (**62**; X = OMe and Cl) form approximately equal amounts of 3-chloro- (**64**) and 6-chloro-2-substituted pyrazines (**65**) along with a trace of the 5-chloro derivatives. Electron-withdrawing carbamoyl and cyano substituents increase the proportion of the 5-chlorinated pyrazines to give a nonregioselective mixture of all possible isomers. It is noteworthy in these reactions that substitution at the β-carbon to the *N*-oxide function is preferred to that at α. On the other hand, 2-substituted pyrazine 1-oxides produce more than an 85% relative ratio of the 2,6-isomer (**65**), and the 2,5-isomer cannot be detected in most cases ⟨84JCR(S)318⟩. A mechanism for formation of the 2,3- and 2,6- isomers from 3-substituted pyrazine 1-oxides has been proposed, as shown in Scheme 12. Formation of the α- and β-chlorinated products from both *N*-oxide isomers can be accounted for by competitive dehydrochlorination in the intermediate (**63**). Addition of amine to the reaction of 3-substituted pyrazine 1-oxides with phosphoryl chloride increases the formation of 3-chloro-2-substituted isomers, while use of chloroacetyl chloride improves remarkably the regioselectivity to the 6-chloro-2-substituted products ⟨94JHC1177⟩. Deoxidative chlorination with phosphoryl chloride has also been investigated with the *N*-oxides of 2-propyl- and 2-phenylpyrazine as well as of the phenyl-substituted 2-chloropyrazines ⟨82JHC1061, 84JCR(S)318⟩. An interesting finding in the reaction of pyrazine 1-oxide (**62**; X = H) with phosphoryl chloride (Scheme 13) is the formation (11%) of 2-aminopyrazine (**39**) together with a 49% yield of 2-chloropyrazine (**36**) ⟨84BCJ3015⟩. The intermediate in this unusual reaction is deduced to be 1-(2-pyrazinyl)pyrazinium salt (**66**) from the ^{1}H NMR spectrum of the reaction mixture prior to hydrolysis.

Irrespective of the position of the *N*-oxide group, most methyl groups on the pyrazine ring undergo chlorination, the proportion of which is approximately equal to or greater than that of ring substitution ⟨82JHC465, 85JHC1291⟩. The substitution in the side chain is more pronounced in acetoxylations, for example, 2,3-dimethylpyrazine 1-oxide in refluxing acetic anhydride gave only

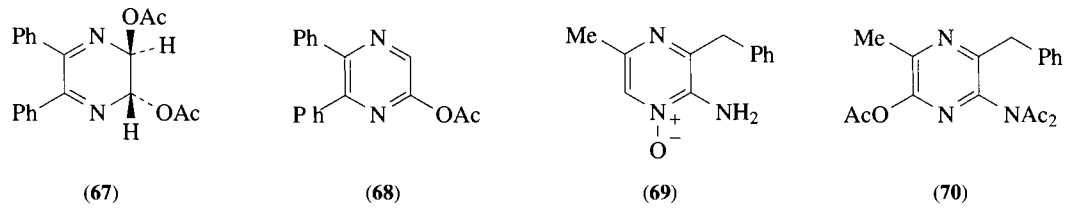


Scheme 12

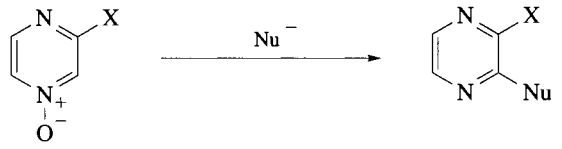


Scheme 13

2-acetoxymethyl-3-methylpyrazine in 77% yield. Interestingly, under identical conditions with refluxing acetic anhydride 2,3-diphenylpyrazine 1-oxide forms *trans*-2,3-diacetoxy-5,6-diphenyl-2,3-dihydropyrazine (**67**) in 82% yield, the structure of which was confirmed by x-ray diffraction analysis ⟨84JHC103⟩. Isolation of the dihydropyrazine convincingly indicates this type of intermediate on the pathway to the fully conjugated products. In fact, the dihydro compound (**67**) is successfully converted by heat into 2-acetoxy-5,6-diphenylpyrazine (**68**) in 86% yield. On the other hand, the parent and 3-methylpyrazine 1-oxides are inert to refluxing acetic anhydride, but the latter (**62**: X = Me) is successfully acetoxylated in the presence of triethylamine to produce an 18% yield each of 3-acetoxy- and 6-acetoxy-2-methylpyrazines ⟨94JHC1229⟩. Addition of potassium acetate to the acetoxylation also facilitates the conversion of 2-amino-3-benzyl-5-methylpyrazine 1-oxide (**69**) into the 6-acetoxy derivative (**70**), in which the reaction proceeds smoothly and is completed in 15 min at room temperature ⟨93JOC7542⟩. An earlier procedure for the acetoxylation of 2-aminopyrazine 1-oxides involves heating with acetic anhydride in acetic acid at reflux ⟨75JOC2341⟩.

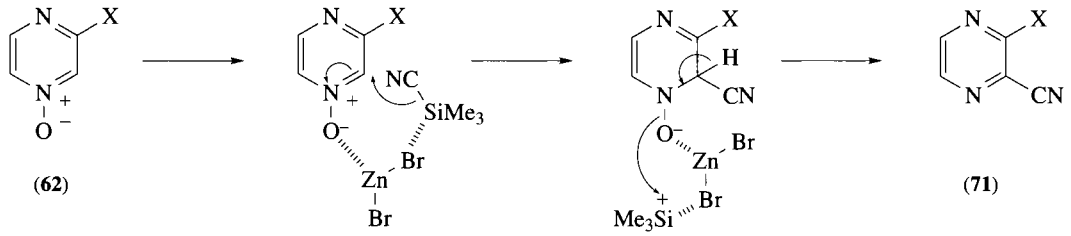


Some new substitution reactions have been reported, one of which is the deoxidative cyanation of pyrazine and quinoxaline *N*-oxides with TMS—CN ⟨89JHC817, 90CPB661, 91JCS(P1)2877⟩. Another is deoxidative azidation of pyrazine *N*-oxides with TMS—N_3 in the presence of *N,N'*-diethylcarbamoyl chloride (Equation (7)) ⟨94JCS(P1)885⟩. The auxiliary reagent also effects the thiation with 4-methoxytoluene-α-thiol ⟨93JCS(P1)15⟩. A further example is the carbamoylation of pyrazine and quinoxaline dioxides, which involves heating in formamide at temperatures up to 200 °C to afford pyrazine and quinoxaline carboxamides in about 30% yields ⟨87JHC949⟩.



(62) (71) (7)

For the deoxidative cyanation of 3-substituted pyrazine 1-oxides, the present author has proposed two different pathways to cyanopyrazines depending on the type of electronic effect of the substituents. One accounts for the reaction of *N*-oxides with an *ortho–para* directing group in aromatic electrophilic substitution, which mostly leads to the formation of 3-substituted 2-cyanopyrazine together with a minor 2,6-isomer. The reaction commences with the trimethylsilylation of *N*-oxide oxygen as the manner shown (for chlorination) in Scheme 12. Because of electron-withdrawing chloro substituent, the deoxidative cyanation of 3-chloropyrazine 1-oxide (**62**; X = Cl) does not proceed, but added zinc bromide induces the substitution to give 2-chloro-3-cyanopyrazine (**71**; X = Cl) in 68% yield. In other words, the process of cyanation is controlled by the nucleophilicity of the *N*-oxide oxygen. The use of the Lewis acid improves the yield and regioselectivity of other 3-substituted 2-cyanopyrazines. A plausible mechanism of the zinc bromide-promoted reaction is shown in Scheme 14.

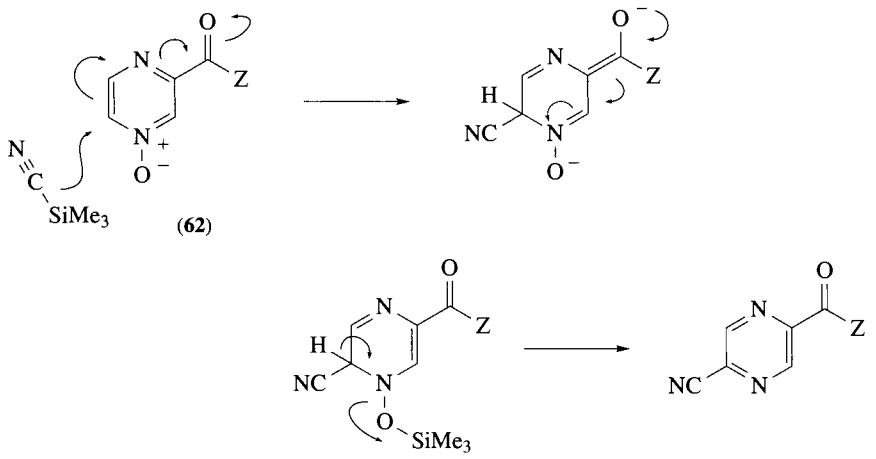


(62) (71)

Scheme 14

Despite their electron-withdrawing property, *meta*-directors bring about cyanation to give 3- and 5-substituted 2-cyanopyrazines in moderate yields. The reactions are not influenced by addition of the Lewis acid and consequently the attack of cyanide ion on the ring carbon occurs prior to trimethylsilylation of the *N*-oxide oxygen as illustrated in Scheme 15. The *ortho* substitution to form the 2,3-isomer is rather suppressed due to steric effect of the C-3 substituent against approaching TMS—CN. In this case, the driving force for the substitution is electron-deficiency in the pyrazine ring induced by the substituent.

The deoxidative acetoxylation reactions can be explained in the same mechanism ⟨94JHC1229⟩



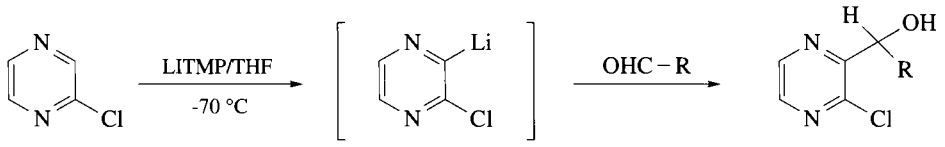
(62)

Scheme 15

but the thiation and the azidation are found to proceed only via the pathway relying on the nucleophilicity of the *N*-oxide oxygen whatever the electronic effect of the substituent on the pyrazine *N*-oxides. The orientation of cyanation depending on the substituent on the *N*-oxide is supported by semiempirical AM1 molecular orbital calculations ⟨93BCJ1149⟩.

6.03.5.5 Nucleophilic Attack at Hydrogen Attached to Carbon

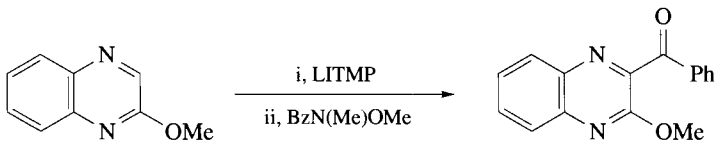
An electrophilic approach to pyrazine substitution involves an initial metalation followed by exposure to electrophiles. Thus, Quéguiner *et al.* have demonstrated that chloropyrazine (**36**) is metalated by LDA or LITMP in THF to form 2-chloro-3-lithiopyrazine (**72**), which reacts *in situ* with aldehydes to produce various derivatives of 3-chloropyrazinemethanol (**73**) in 55–90% yields (Scheme 16) ⟨88S881⟩. 2-Chloro-3-deuterio-, -3-formyl-, and -3-carboxypyrazines are prepared similarly by treatment of (**72**) with methanol-*d*, ethyl formate and carbon dioxide, respectively. This methodology has been applied to pyrazines carrying an electron-withdrawing substituent such as a methoxy, methylthio or *N*-*t*-butylcarbamoyl group ⟨90JOC3410, 91JHC765, 91JOM(412)301, 92JHC699⟩. In the cases of 2-chloro- and 2-methoxyquinoxaline, competitive dimerization occurs to form 2,2′-biquinoxalinyl compounds in low yields ⟨93JHC1491⟩.



(**36**) (**72**) (**73**)

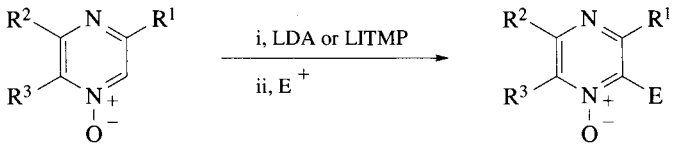
Scheme 16

The lithiation of 2-pivaloylaminoquinoxaline followed by treatment with iodine and carbon dioxide provides more than 50% yields of the 3-iodo and 3-carboxy derivatives, respectively. Under kinetic conditions, the predominant product from the *N*-*t*-butyl pyrazinecarboxamide is often the 5-substituted material. An electron-donating acylamino group results in a poor formation of electrophilic product ⟨92JHC699⟩. The alcohol (**73**) is easily oxidized with manganese(IV) oxide to the corresponding ketone in high yield. Benzoylpyrazines and -quinoxalines are obtained by reaction of the lithio intermediates with *N*-methoxy-*N*-methylbenzamide (Equation (8)) ⟨91JHC765⟩.



(8)

Disubstituted pyrazine *N*-oxides (**74**; R^{1-3} = alkyl, aryl and/or H) also undergo the electrophilic substitution with oxygen ⟨82H(17)151⟩, esters, aldehydes, and DMF under similar conditions ⟨91H(32)735⟩, yielding the corresponding functionalized pyrazine *N*-oxides (Equation (9)).



(9)

(**74**)

6.03.5.6 Reactions with Radicals and Reductions

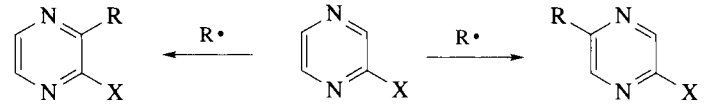
6.03.5.6.1 Radical reactions

The reaction of 2-chloropyrazine with ketone enolates in liquid ammonia exhibits characteristics consistent with a radical chain mechanism for substitution ⟨81JOC294⟩. 2-Chloroquinoxaline forms

two products via a thermal $S_{RN}1$ mechanism and a competing ionic, addition–substitution process, respectively ⟨82JOC1036⟩.

Minisci-type substitution is one of the most useful reactions for the synthesis of alkyl- and acyl-substituted heteroaromatics. Early in the 1970s the homolytic acylation of pyrazines ⟨72JCS(P2)2035⟩ and quinoxalines ⟨70JCS(C)929⟩ was developed by Minisci *et al.* Subsequent development has been reviewed extensively ⟨90JHC79⟩. These reactions can be promoted both by polar effects arising from the nucleophilic character of carbon-centered radicals and by the electron deficiency of the protonated heteroaromatic bases. The alkyl radicals are conveniently generated by redox decomposition with iron(II) from alkyl iodide, hydrogen peroxide and DMSO ⟨89JOC5224⟩, from alkyl iodide and *t*-butyl hydroperoxide, or by silver-catalyzed decarboxylation ⟨90T2525⟩. The acyl radicals are also formed by the redox decomposition from aldehyde and *t*-butyl hydroperoxide or by silver-catalyzed decarboxylation of an α-keto acid with persulfate. These homolytic substitutions reflect many aspects of Friedel–Crafts aromatic substitution, but with opposite reactivity and selectivity. Thus, electron-withdrawing groups enhance the reaction, whereas alkyl groups diminish it. Consequently, the introduction of an acyl group activates the heteroaromatic ring towards further substitution, to result in the formation of diacyl compounds. Arrest of the reaction at the monosubstitution stage can be achieved in a two-phase system because of the difference in basicity and lyphophilicity between the starting base and the monoacylated products ⟨91JOC2866⟩.

From the results of homolytic acylation of various monosubstituted pyrazines with a wide spectrum of substituents, it is found that methoxy and chloro substituents direct *ortho* substitution, giving the corresponding 2,3-disubstituted pyrazines (Scheme 17). Acetyl, alkoxycarbonyl, and carbamoyl groups direct *para* substitution, leading to the corresponding 2,5-disubstituted pyrazines. These selectivities result from a combination of the inductive and resonance effects of the substituents. Carboxy and cyano groups also effect *para* substitution ⟨88S119, 89JOC640, 91S581, 92JHC1685⟩. The Minisci-type alkoxycarbonylation reaction produces an 89% best yield of ethyl 2-pyrazinecarboxylate by redox treatment of pyrazine with ethyl pyruvate in a water–dichloromethane two-phase system ⟨86T5973⟩.

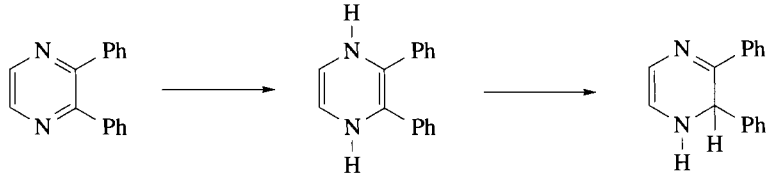


Scheme 17

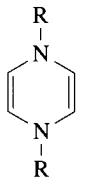
6.03.5.6.2 Reductions

Electrochemical reduction of 2,3-diphenylpyrazine and -quinoxaline in alkaline medium containing methanol or acetone leads to the corresponding 1,4-dihydro derivatives. The reduction product of quinoxaline can be isolated ⟨71CCC585⟩ but that of pyrazine is unstable and isomerizes to 1,2-dihydro-2,3-diphenylpyrazine (Scheme 18) ⟨74CJC3971⟩. 2,5-Diphenylpyrazine is reduced to 1,6-dihydro-2,5-diphenylpyrazine. Pyrazine and quinoxaline undergo reductive *N*-silylation on treatment with a combination of lithium and TMS—Cl, giving the 1,4-dihydro-1,4-bistrimethylsilyl derivatives (**75** and **76**; R = TMS) ⟨72JOM(37)57⟩, and the 1,4-dihydropyrazine, by further reaction with carbon dioxide, is converted into the bisurethane (**75**; R = CO_2TMS) ⟨89CB933⟩.

Chemical reduction results in the formation of piperazines and tetrahydroquinoxalines. For



Scheme 18



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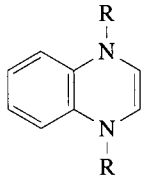
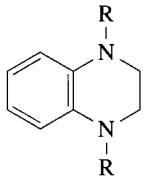


(76)

example, pyrazine and its methyl derivatives are reduced by nickel–aluminum alloy in potassium hydroxide to provide good yields of piperazines ⟨87JOC1043⟩. Hydrogenation of quinoxaline and its methyl derivatives with the homogenous (DIOP)RhH catalyst produces tetrahydroquinoxalines (**77**; R = H). In the presence of the catalyst, hydrosilylation by diphenylsilane is effected to afford *N,N'*-disilylated tetrahydroquinoxalines (**77**; R = $SiHPh_2$) ⟨87H(26)763⟩. Treatment of quinoxalines with sodium borohydride and benzyl chloroformate in methanol at −78 °C forms tetrahydro derivatives (**77**; R = CO_2Bn) ⟨92JCS(P1)1245⟩.

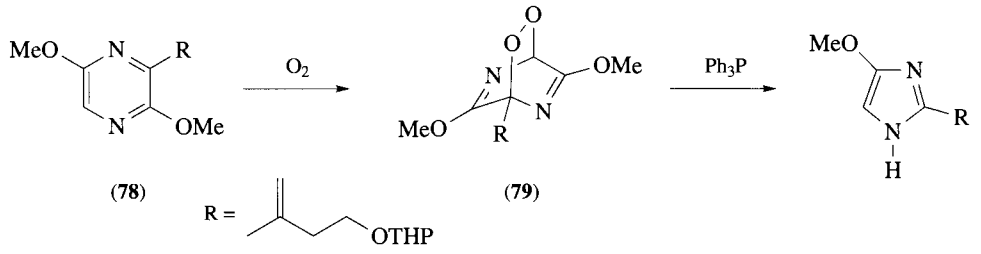


(77)

Fused benzenoid heterocyclic systems including quinoxaline derivatives in an ether solvent are reduced by sodium to the corresponding antiaromatic doubly charged species ⟨85JA1501⟩. These dianions represent a new class of charged species, *viz.*, nitrogen-containing polycyclic anions.

6.03.5.7 Cyclic Transition State Reactions with a Second Molecule

While many examples of cyclic transition state reactions appear in 1-substituted 2(1*H*)-pyrazinones and 2(1*H*)-quinoxalinones, dealt with in the next section, there are few examples of reactions in the fully aromatic systems. 2,5-Dimethoxy-3-alkenyl substituted pyrazines (**78**) undergo facile addition of singlet oxygen to form endoperoxides (**79**) ⟨89JCS(P1)453⟩. These products are relatively stable, remaining intact after several months when stored at 0–5 °C, but decompose when heated or on melting. The peroxides having a benzyl or isobutyl substituent at C-3 decompose mainly by loss of oxygen, regenerating the pyrazines in high yields. Deoxygenation with triphenylphosphine induces skeletal rearrangement, the pyrazine undergoing ring contraction to a substituted imidazole (Scheme 19). Reductive cleavage of the peroxide bond leads to unstable dihydroxy dihydropyrazines. 2-Alkoxy-5,6-diphenylpyrazine also reacts with singlet oxygen to yield the endoperoxide, which is too unstable to be isolated in pure form ⟨85JCS(P1)2497⟩.



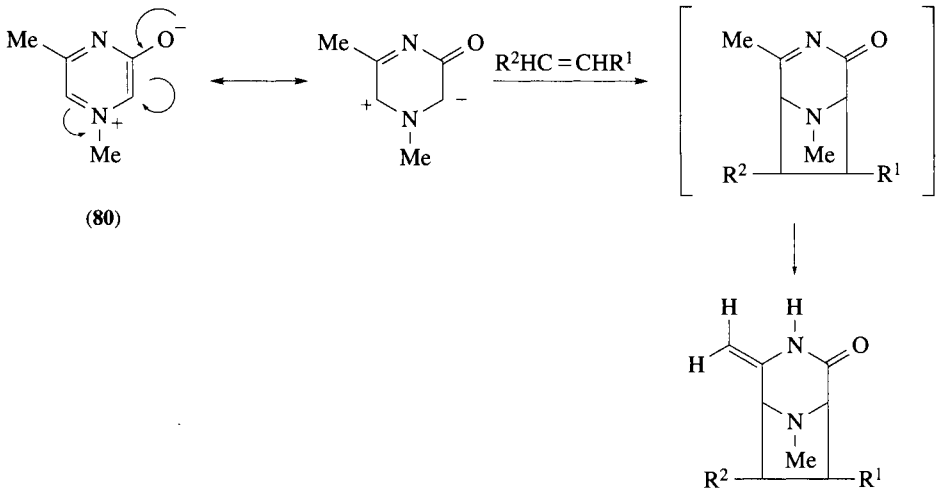
(78) (79)

R =

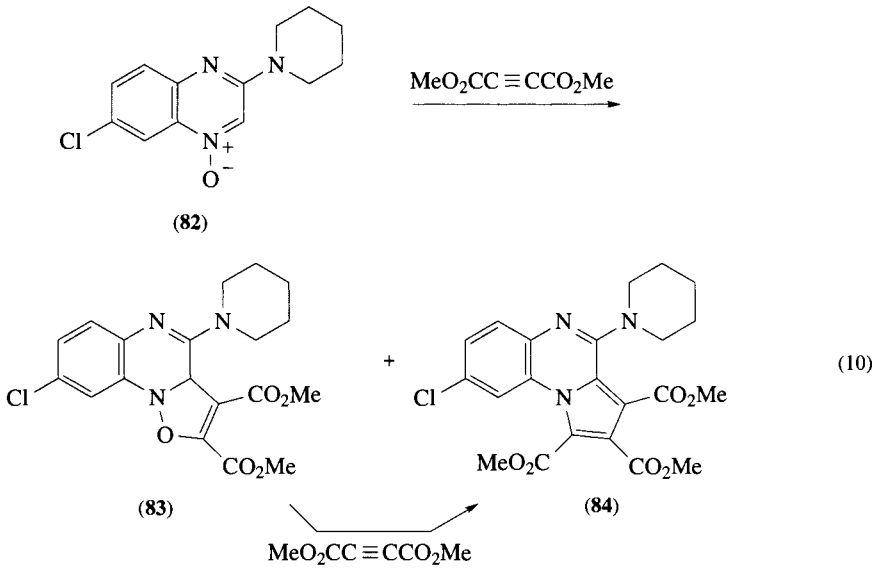
Scheme 19

1-Methyl-3-oxidopyrazinium salt (**80**) undergoes 1,3-dipolar cycloaddition with a variety of dipolarophiles to give the bicyclic compounds (**81**) (Scheme 20) ⟨87TL2186⟩. Quinoxaline 1,4-dioxides cycloadd to dibenzoylethyne leading with rearrangement to the formation of 3-(dibenzoylmethyl)-

quinoxaline 1-oxides ⟨82JOC1772⟩. Kurasawa *et al.* investigated the 1,3-dipolar cycloaddition of quinoxaline monooxides with a variety of dipolarophiles. For instance, 7-chloro-3-piperidinoquinoxaline 1-oxide (**82**) reacts with 2 mol equiv. of DMAD to give the pyrrolo[1,2-*a*]quinoxaline (**84**) via the isoxazolo[2,3-*a*]quinoxaline primary adduct (**83**), where the latter can be isolated using 1 mol equiv. of the ethyne (Equation (10)) ⟨89JHC871, 90JHC1119⟩. The reaction of 7-chloro-3-(1-methylhydrazino)quinoxaline 1-oxide with DMAD or 2-chloroacrylonitrile gives quinoxalines [2,3]-condensed with imidazole or seven-membered nitrogen heteroaromatics arising from intramolecular ring rearrangement of initially formed adducts ⟨89JHC1511, 90JHC1111, 90JHC2197⟩.



Scheme 20



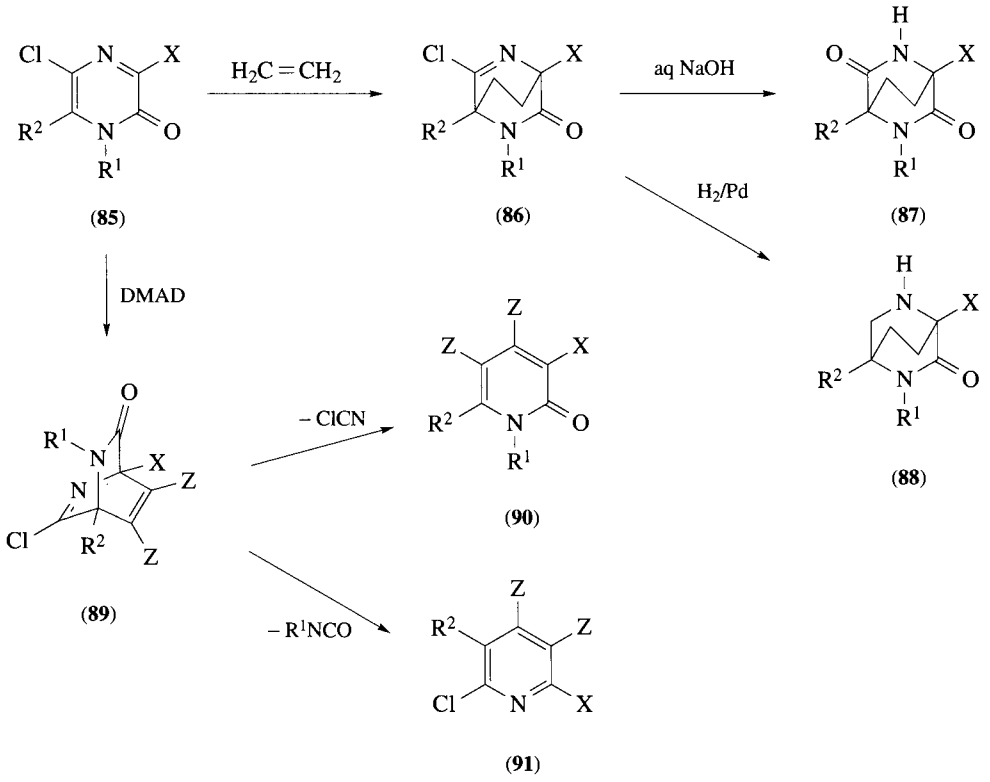
(10)

6.03.6 REACTIVITY OF PYRAZINONES AND QUINOXALINONES

6.03.6.1 1-Substituted 2(1*H*)-Pyrazinones and 2(1*H*)-Quinoxalinones

Several 1-substituted 2(1*H*)-pyrazinones (**85**) undergo [4 + 2] cycloaddition with ethene in toluene at 110°C to form bicyclic intermediates (**86**), the formation of which is more easy when the substituent X is a chloro, cyano, or thiocyanato group (Scheme 21). The adducts having an alkyl or aryl group as the substituent X are sensitive to moist air. Hydrolysis of the iminochloride

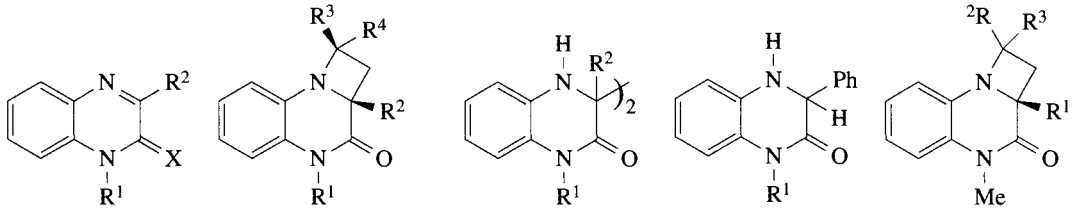
group of the crude adducts (**86**) with aqueous sodium hydroxide affords crystalline bislactams (**87**) ⟨91T9259⟩. Hydrogenation using Pd/C and dabco gives compounds (**88**) when the substituent X is chloro ⟨91T9269⟩. Heating of 2(1*H*)-pyrazinones (**85**) in an ethyne such as DMAD at 140 °C or at reflux gives 2-pyridones (**90**) and/or pyridines (**91**), the product distribution of which is highly dependent on the substitution pattern of the reactants. In these reactions the intermediate addition compounds (**89**) are not observed but some bicyclic adducts can be isolated from the reaction in acetonitrile at 60 °C, and these are converted by reflux in xylene into the pyridine mixtures in the same ratio as above. Therefore, the formation of pyridone (**90**) and pyridine (**91**) is ascribed to a retro Diels–Alder reaction with loss of cyanogen chloride or isocyanate from the bicyclo adducts formed initially ⟨90T5715⟩. The cycloaddition reaction of 2(1*H*)-pyrazinones (**85**) carrying a diethylamino substituent is followed by a novel rearrangement to yield 5-diethylamino-1,6-dihydro-6-oxo-2-pyridinecarbonitriles ⟨92JOC2935⟩.



Scheme 21

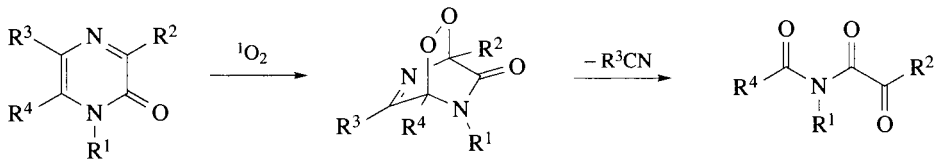
Irradiation of the parent or 1-substituted 2(1*H*)-quinoxalinones (**92**; X = O) in benzene or methanol-dichloromethane in the presence of an electron-deficient alkene leads to regiospecific [2 + 2] cycloadducts across the C—N double bond. So, 2(1*H*)-quinoxalinones (**92**; X = O, R^1 = H, Me, Et, or Ph) react with methacrylonitrile to produce selectively a more than 90% yield of 1 : 1 cycloadducts (**93**; R^3 = Me, R^4 = CN). However, reactions with methyl methacrylate give two stereoisomeric 1 : 1 adducts ⟨84JOC827⟩. Their competitive formation strongly suggests that this photoreaction occurs from the excited triplet state of quinoxalinone. Similar results have been obtained in photocycloadditions of quinoxalinone (**92**; X = O) with arylalkenes ⟨87JCS(P1)2611⟩. On the other hand, 2(1*H*)-quinoxalinethiones (**92**; X = S) undergo [2 + 2] cycloaddition on the C—S double bond with alkene forming the intermediate amino thietane, the (N—)C—S bond of which cleaves to aromatize forming 2-(2′-thiolalkyl)quinoxalines ⟨92HCA487⟩. Irradiation of the 2(1*H*)-quinoxalines (**92**; X = O) in the presence of amines leads to reductive dimerization giving tetrahydro biquinoxaline compounds (**94**). However, quinoxalinones where the R^2 substituent is a phenyl group are simply reduced to 3,4-dihydroquinoxalinones (**95**) ⟨90JCS(P1)565⟩. Photocyclization of 2(1*H*)-pyrazinones with electron-deficient alkenes proceeds to afford the azetidine compounds (**96**) in low to moderate yields ⟨91HCA225⟩.

Dye-sensitized photooxygenation of 1-alkyl-2(1*H*)-pyrazinones (**97**) gives endoperoxides (**98**), the



(92) (93) (94) (95) (96)

formation of which arises via [4 + 2] cycloaddition with singlet oxygen (Scheme 22). On heating the adducts (**98**) decompose by loss of R^3CN to afford *N*-alkylacetamide derivatives (**99**) ⟨85JCS(P1)2497, 88JCS(P1)2921⟩. Irradiation of 2(1*H*)-pyrazinones (**97**; $R^1 = H$) in alcohol under oxygen directly produces the acetamides (**99**), probably because the reactants (**97**) act as oxygen sensitizers themselves ⟨84JCS(P1)391⟩.



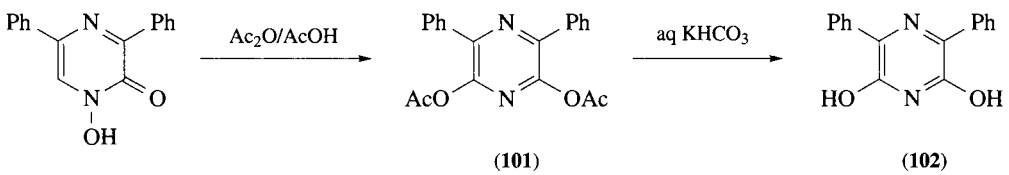
(97) (98) (99)

Scheme 22

The behavior of halogeno substituents on 1-substituted 2(1*H*)-pyrazinones is similar to that in the fully aromatic systems. Thus, 1-methyl- and 1-phenyl-3,5-dichloro-2(1*H*)-pyrazinones undergo nucleophilic substitution at C-3 with hydrazine and thiourea, whereas in a 5-chloro compound displacement is suppressed ⟨86JHC113⟩.

6.03.6.2 1-Hydroxy-2(1*H*)-pyrazinones

The title compounds are stable tautomers of the corresponding 2-hydroxypyrazine 1-oxides, and in fact 1-acetoxy-2(1*H*)-pyrazinones, not 2-acetoxypyrazine *N*-oxides, are obtained on treatment with acetyl chloride in the presence of pyridine at room temperature ⟨87JHC187⟩. Nevertheless, these compounds resemble the *N*-oxides in most of their reactions. Representative examples are deoxidative acetoxylation and chlorination. Treatment of 1-hydroxy-3,5-diphenyl-2(1*H*)-pyrazinone (**100**) with a refluxing mixture of acetic anhydride and acetic acid affords 2,6-diacetoxy-3,5-diphenylpyrazine (**101**), which is deacetylated with potassium hydrogen carbonate to give 2,6-dihydroxy-3,5-diphenylpyrazine (**102**) (or tautomer) (Scheme 23) ⟨71JCS(C)2977⟩. Acetoxylation of a methyl substituent occurs exclusively and then that of the pyrazine ring is suppressed completely. 1-Hydroxy-2(1*H*)-pyrazinones substituted with phenyl and/or methyl groups at C-3 and C-5 are chlorinated with phosphoryl chloride to the 6-chloro-2(1*H*)-pyrazinones. In contrast, the same reaction with 1-hydroxy-3-phenyl-2(1*H*)-pyrazinone furnishes the 5-chloro-2(1*H*)-pyrazinone under mild conditions and the 2,5-dichloropyrazine by heating at 180°C ⟨86JHC149⟩. At elevated temperatures, chlorination of a methyl group is favored over that on the pyrazine nucleus.



(100) (101) (102)

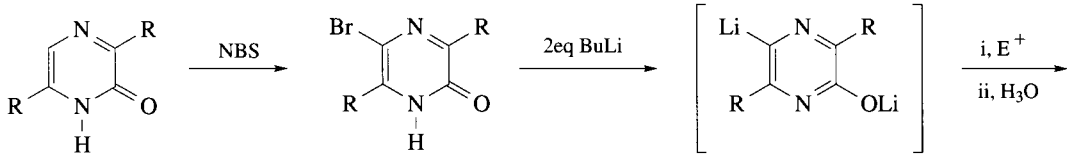
Scheme 23

6.03.6.3 2(1*H*)-Pyrazinones

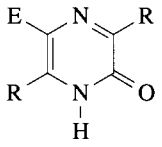
Hydroxypyrazines, or rather tautomeric 2(1*H*)-pyrazinones, undergo electrophilic substitution such as nitration and bromination *ortho* or *para* to the hydroxy or oxo substituent under mild conditions ⟨53JA5517, 56JA4071, 78JHC665⟩. When phenyldiazonium chloride is added to 2(1*H*)-pyrazinones in alkaline solution, phenylation of the nucleus takes place with evolution of nitrogen in the same substitution pattern as above.

The 2(1*H*)-pyrazinones can be converted into chloro- and acetoxypyrazines by treatment with phosphoryl chloride ⟨52JA1580⟩ and acetic anhydride ⟨83JHC951⟩, respectively.

It is observed that a halogen *para* to the carbonyl moiety of 2(1*H*)-pyrazinones is extremely inert towards nucleophilic displacement, whereas an *ortho* halogen is displaced relatively readily. However, use of butyllithium brings about lithio-dehalogenation in 5-bromo- or 5-iodo-2(1*H*)-pyrazinones (**104**), which are prepared from the corresponding 2(1*H*)-pyrazinones (**103**) with NBS or NIS, respectively ⟨91H(32)2407⟩. Electrophilic reagents with these lithio intermediates (**105**) then afford the 5-substituted 2(1*H*)-pyrazinones (**106**; Scheme 24).



(**103**) (**104**) (**105**)



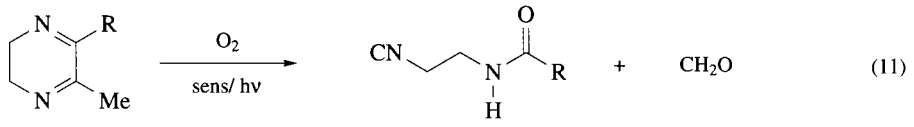
(**106**)

Scheme 24

2(1*H*)-Quinoxalinones undergo a Michael-type of reaction with methyl ketones to yield acetonyl quinoxalinone derivatives, in which the reaction is brought about by a catalytic amount of dimethyl sulfate ⟨83S145⟩.

6.03.7 REACTIVITY OF DIHYDRO AND TETRAHYDRO PYRAZINES AND QUINOXALINES

Dihydro and tetrahydro pyrazines and quinoxalines undergo dehydrogenation to produce the fully conjugated systems. DDQ is the most convenient reagent for this purpose ⟨87T2769⟩. Dye-sensitized photooxygenation of 5,6-dimethyl- and 5-methyl-6-phenyl-2,3-dihydropyrazine (**107**) (Equation (11)) does not yield the corresponding aromatized pyrazines but isocyanides (**108**) ⟨92JOC229⟩. 5,6-Diphenyl-2,3-dihydropyrazine is inert towards singlet oxygen.



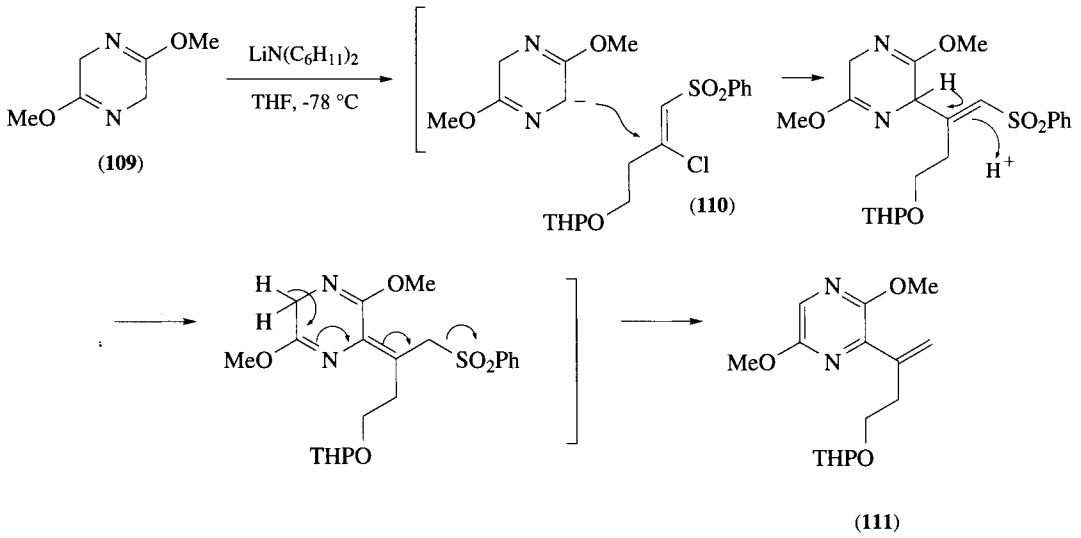
(11)

(**107**) (**108**)

2,5-Piperazinediones are the keto forms of 2,5-dihydroxy-3,6-dihydropyrazines, and many 2,5-piperazinedione derivatives have been found in nature. Numerous synthetic investigations for these compounds ⟨83H(20)1407, 93AHC(57)186⟩ have been carried out, particularly in an approach to the total synthesis of the antibiotic bicyclomycin ⟨85JA3253⟩ and the synthesis of chiral α-amino acids known as the Schöllkopf–Hartwig bislactim ether method. Direct introduction of a substituent on

the ring carbon is achieved by treatment of *N,N'*-dialkyl-2,5-piperazinedione with LDA followed by alkylation with alkyl halides, ketones, or ethylene oxide ⟨82JA6092⟩. This method can be applied to introduce a second substituent. Treatment of *N,N'*-diacetyl-2,5-piperazinediones with carbonyl compounds in the presence of potassium *t*-butoxide or triethylamine in DMF leads to the alkylidene substituted piperazinediones ⟨83H(20)405, 89JCS(P1)453, 89JHC821⟩. The alkylidene products are also obtained through reaction of the same starting piperazinedione with halogeno compounds instead of the ketones ⟨88JHC591, 89JHC821⟩.

2,5-Dimethoxy-3,6-dihydropyrazine (**109**), prepared by methylation of 2,5-piperazinedione with trimethyloxonium tetrafluoroborate, is susceptible to lithiation because the protons at C-3 and C-6 are activated by adjacent imine moieties. The lithium salt of this bislactim ether reacts with the 2-chloro-1-phenylsulfonyl alkene (**110**) to give the 3-substituted pyrazine (**111**) (Scheme 25) ⟨89JCS(P1)453⟩. The bislactim ether from piperazinedione cyclo(L-Val—Gly) is lithiated with butyllithium and then treated with ketones, alkyl halides, or others to form, nearly stereospecifically, *trans*-3-isopropyl-6-substituted piperazinediones due to the steric influence of the isopropyl group ⟨82S866, 83S673⟩. Similar stereoselective syntheses have been achieved in reactions starting from cyclo(L-Val—D,L-Ala) ⟨82S864, 91S939⟩. Acid hydrolysis of these products affords chiral α-amino acids.



Scheme 25

6.03.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

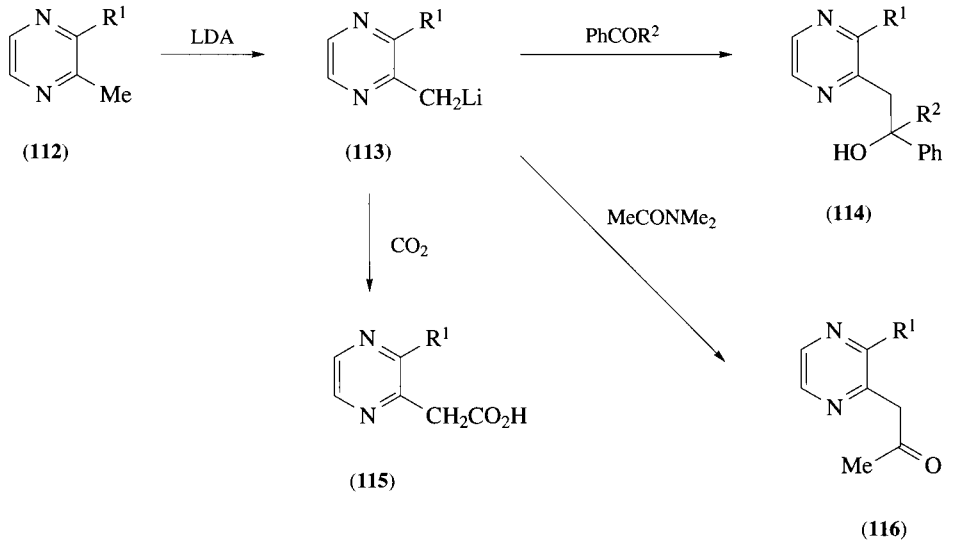
The reactivity of substituents dealt with in this section is limited to those on the heteroaromatic ring in pyrazines and quinoxalines. In Section 6.03.9 the reactions of the benzo-fused rings (regarded as a special type of ring-carbon substituent for the purposes of this review) are covered.

6.03.8.1 Carbon Substituents

Propyl and higher alkyl pyrazines undergo intramolecular photochemical hydrogen abstraction resulting in cleavage of the side chain to yield methylpyrazines ⟨94JOC178⟩.

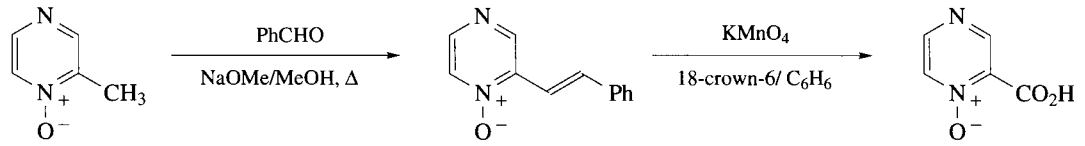
An alkyl group on the pyrazine ring is readily lithiated at the α-carbon. In the LDA-promoted lithiation of 2,3,5-trimethylpyrazine, the order of reactivity of the three methyl groups is formed to be 3 > 2 > 5 ⟨83JOC2130⟩. The methyl groups in 2,3-dimethylpyrazine are more easily metalated than either of the methyl groups in the other isomeric dimethylpyrazines. In 2-methylpyrazines (**112**) having a higher alkyl group at C-3, the methyl group is selectively lithiated, due probably to steric effects ⟨87JOC3971⟩. These pyrazinylmethyllithium (**113**) react with ketones ⟨87JOC3971⟩, carbon

dioxide ⟨86JHC581⟩, and *N*,*N*-dimethylacetamide ⟨91JHC1463⟩ to produce alcohols (**114**), carboxylic acids (**115**), and ketones (**116**), respectively (Scheme 26).



Scheme 26

A ring methyl group condenses with benzaldehydes to yield styryl compounds, but the condensation needs an auxiliary reagent such as acetic anhydride ⟨87S638⟩ or zinc halide, and forcing reaction conditions at reflux or temperatures above 200 °C. In contrast, the condensation of methylpyrazine *N*-oxides with benzaldehyde proceeds smoothly by treatment with sodium methoxide in refluxing methanol (Scheme 27) ⟨83JHC169⟩.



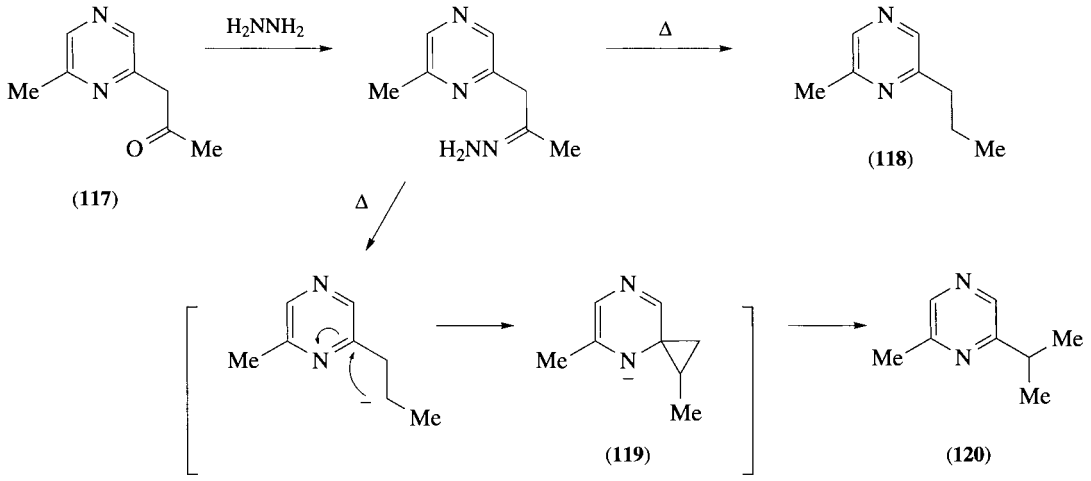
Scheme 27

Oxidation of the methyl group on heteroaromatics with selenium dioxide affords the formyl compounds ⟨84JHC1271⟩. Halogenation to a halogenomethyl group is effected by NCS or NBS in the presence of a free radical initiator such as $(BzO)_2$ or AIBN by irradiation ⟨85CB4907, 90JHC1633⟩. This transformation is also brought about by trichloroisocyanuric acid (TCC), where the reaction proceeds without the addition of an initiator ⟨87CB649⟩. Methyl groups on quinoxaline *N*-oxides are halogenated by chlorine in acetic acid at 70–85 °C ⟨84JHC1271⟩ and by bromine in methanol at room temperature ⟨83JMC1122⟩. These halogenomethyl quinoxalines as well as the pyrazine analogues provide the alkenyl derivatives via Wittig reactions ⟨87S638, 89JCR(S)59⟩. Electrochemical oxidation of 2-chloromethyl-5-methylpyrazine leads to the formation of 5-methylpyrazine-2-carboxylic acid ⟨90S207⟩. Reaction of 2-methylpyrazine with hot thionyl chloride followed by morpholine gives a 10% yield of 2-morpholinothiocarbamoylpyrazine ⟨89JHC1819⟩. A halogen on a side-chain methyl group is easily displaced by sulfur nucleophiles to produce thiomethyl derivatives ⟨83JMC1122, 85CB4907⟩.

Oxidation of an alkenylpyrazine with potassium permanganate in the presence of magnesium sulfate provides the vicinal diol ⟨89JCR(S)59⟩; when 18-crown-6 is used instead of magnesium sulfate cleavage of the C—C double bond results, forming pyrazinecarboxylic acid (Scheme 27) ⟨83JHC169⟩. Hydration of pyrazinylalkynes to acylpyrazines is achieved by treatment with aqueous sodium sulfide and hydrochloric acid ⟨89JOC1218⟩.

Cyanopyrazine reacts with cyclopropyllithium to give pyrazinyl cyclopropyl ketone ⟨91JHC1147⟩. Benzoyl pyrazine is formed by oxidative decyanation of α-pyrazinyl-α-phenylacetonitrile under phase-transfer catalytic conditions ⟨87JHC1061⟩. (2-Hydroxy-2-phenylethyl)pyrazines undergo retro-ene reaction on pyrolysis to yield methylpyrazines and benzaldehyde quantitatively ⟨87JOC3971⟩.

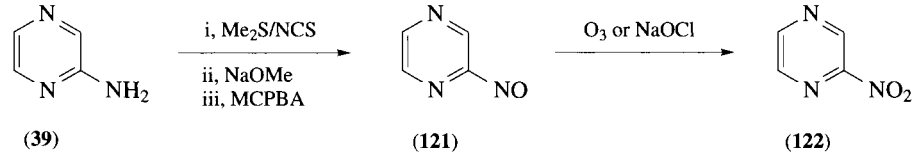
Wolff–Kishner reduction of 1-(6-methylpyrazin-2-yl)-2-propanone (**117**) leads to the formation of 2-isopropyl-6-methylpyrazine (**120**) in addition to the expected 6-methyl-2-propylpyrazine (**118**) ⟨91JHC1463⟩. A spirocyclopropane intermediate (**119**) is suggested for this rearrangement (Scheme 28). Irradiation of acylpyrazines induces intramolecular hydrogen abstraction to yield 1-pyrazinylcyclopropanol ⟨94JOC2125⟩.



Scheme 28

6.03.8.2 Nitrogen Substituents

Like 2-aminopyridines and 2-aminopyrimidine, 2-aminopyrazine (**39**) (Scheme 29) has been converted into the nitroso compound (**121**) by reaction with dimethyl sulfide and NCS followed by deprotonation of the resulting sulfonium salt with sodium methoxide to the *S,S*-dimethylsulfilimine and then oxidation with MCPBA ⟨82JOC552⟩. The extremely reactive nitrosopyrazine (**121**) condenses with 1,3-dienes to give 3,6-dihydro-1,2-oxazines and with aromatic amines in the presence of acid to gives azo compounds, and is smoothly oxidized with ozone or sodium hypochlorite to 2-nitropyrazine (**122**). Methyl 3-aminopyrazinecarboxylate reacts with thiophosgene to produce the 3-isothiocyanatopyrazinecarboxylic ester ⟨90JHC433⟩.

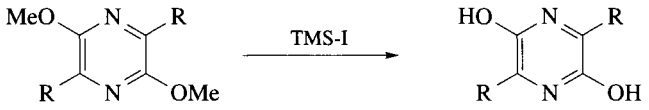


Scheme 29

6.03.8.3 Oxygen Substituents

As described in an earlier section (6.03.6.3), hydroxypyrazines can be acylated by an acid anhydride ⟨83JHC951, 84H(22)2369⟩ or acid chloride ⟨85JHC1173, 85JHC1643⟩ producing acyloxypyrazines, which have been shown to be useful acylating reagents for the protection of amines. Ether cleavage in methoxypyrazines is effected by TMS-I, whereby 3,6-disubstituted 2,5-dimethoxypyrazines are converted into the corresponding 2,5-dihydroxypyrazines (Equation (12)) ⟨86JHC1677⟩. Under ident-

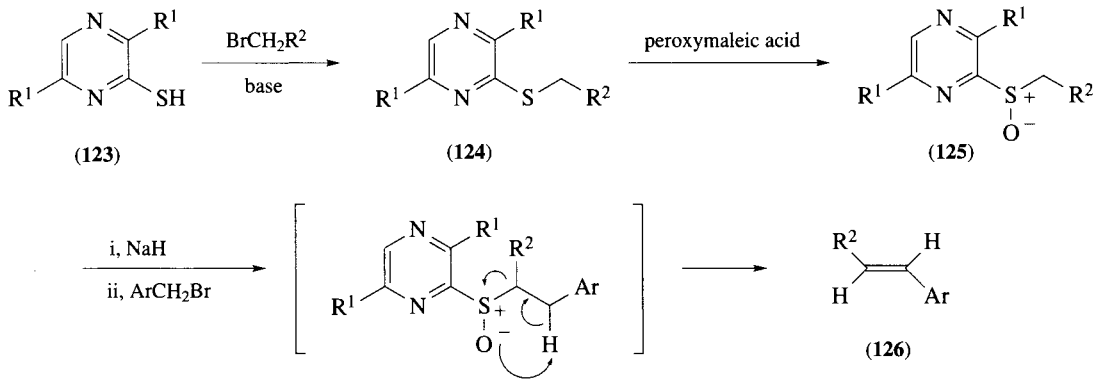
ical conditions, the 3-phenyl analogue gives not the dihydroxypyrazine but 3-phenyl-2,5-piperazinedione, with concomitant reduction by the iodide.



(12)

6.03.8.4 Sulfur Substituents

Pyrazinethiones (**123**) with alkyl halides in the presence of base produce pyrazinylthio compounds (**124**), which are easily oxidized with peroxymaleic acid to the sulfoxides (**125**). Cyanomethyl sulfoxide (**125**; $R^2 = CN$) is alkylated on the methylene carbon between the sulfoxide and cyano groups by benzyl bromide, and the product undergoes β-elimination to afford *trans*-cinnamonitriles (**126**; $R^2 = CN$) ⟨88H(27)261⟩. The sulfoxides (**125**; R^2 = alkyl or aryl) undergo the Pummerer rearrangement by treatment with TFAA and then aqueous potassium carbonate or NBS to give the aldehyde (**126**; $R^2 = CHO$) in excellent yields ⟨88H(27)1643⟩ (Scheme 30).



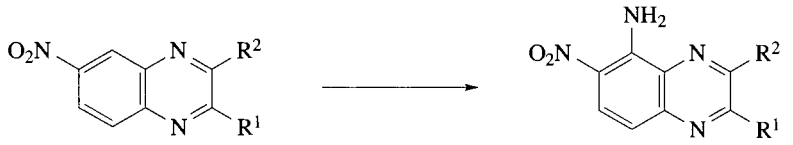
Scheme 30

2-Thiocyanatoquinoxaline is transformed into various compounds depending on the nucleophile used ⟨89CPB618⟩, for example, quinoxalinyl amines and sulfides have been obtained by treatment with aliphatic amines and Grignard reagents, respectively. Hydrolysis leads to the formation of quinoxalinethione.

6.03.9 REACTIONS AT BENZO-FUSED RINGS

The benzenoid rings in quinoxaline and phenazine are very resistant towards the usual electrophilic reagents employed in aromatic substitution because of the electron-deficient pyrazine moiety. Nitration of quinoxaline takes place only under forcing conditions, resulting in extremely low yields of 5-nitro- and 5,6-dinitroquinoxalines. Electron-donating groups on either the benzenoid or heteroaromatic ring usually facilitate the substitution but the regioselectivity depends very much upon the reaction conditions. Consequently, many substituted quinoxalines and phenazines have been prepared by construction from mono- and bicyclic precursors, respectively (see Section 6.03.11.1). A brief review of electrophilic substitutions of quinoxaline and phenazine has been presented by Porter ⟨84CHEC-I(3)157⟩. No further studies have been noted since the mid-1960s.

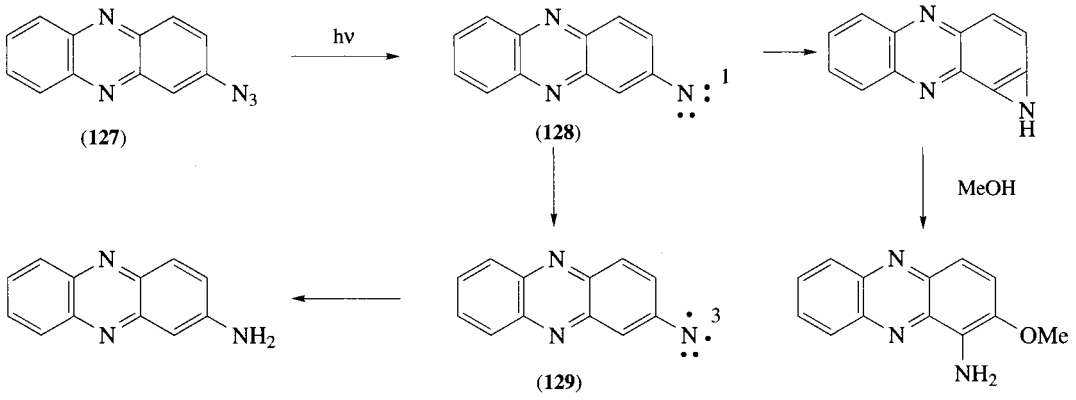
A nitro group at the 6-position in quinoxaline induces nucleophilic amination at C-5 (Equation (13)) and hydroxylamine ⟨89SC511⟩ or potassium permanganate in liquid ammonia ⟨92LA899⟩ can be used. Yields are <30% when the substituents R^1 and R^2 are hydrogen or alkyl, but the 2,3-dihalogeno-5-amino-6-nitro derivatives are obtained in 70–75% yields by treatment with hydroxylamine.



(13)

An additional example of nucleophilic substitution on the benzenoid ring is observed in the Reissert reaction of quinoxaline 1-oxide, which, on treatment with potassium cyanide and benzoyl chloride in aqueous solution, gives 6-chloroquinoxaline as the major product and the expected 2-cyanoquinoxaline as minor product ⟨89T7795⟩. Reaction of 2,3-diphenylquinoxaline 1-oxide with thionyl chloride results in chlorination of the benzene ring without accompanying deoxidation and gives the 5-chloro- and 6-chloroquinoxaline 1-oxides. Phenazine 1-oxide under the same conditions gives mainly 2-chlorophenazine together with minor amount of the 1-chloro isomer ⟨90BSB783⟩.

Photolysis and thermolysis of 2-azidophenazine (**127**) have been extensively investigated by Pietra *et al.* The photochemical decomposition of the azido compound leads to singlet (**128**) and triplet nitrenes (**129**), and the former species (**128**) can be trapped with nucleophiles such as amines or methanol, presumably through an azirine intermediate (Scheme 31) ⟨80G135, 82G13⟩. In contrast, the triplet nitrene abstracts hydrogen from solvents such as tetralin to form 2-aminophenazine in good yield. The other products generated via the triplet aryl nitrene are the dimers or products of trapping by radical scavengers ⟨93H(35)885⟩, the formation of which depends markedly on the reaction conditions. Photochemical decomposition of 1-methoxy and 1-pyrazolyl-substituted 2-azidophenazines has been examined to clarify the mechanism and to investigate substituent and solvent effects ⟨87JOC1245, 91JOC6993⟩.



Scheme 31

6.03.10 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN ATOMS

The major reactions in this section are those involving an *N*-oxide oxygen. Deoxygenation of 2,3-disubstituted quinoxaline 1,4-dioxides is achieved under mild conditions by treating with hexachlorodisilane, TMS-1, TFAA-sodium iodide, or titanium tetrachloride–zinc dust ⟨81H(16)411⟩. Quinoxaline and phenazine *N,N'*-dioxides are also deoxygenated under mild conditions by sodium hypophosphite catalyzed by Pd/C or by treatment with sodium iodide in the presence of pyridine/sulfur trioxide complex ⟨83JHC1735⟩. Deoxygenation of 6-chloro-2(1*H*)-quinoxalinone 4-oxide is effected particularly by sodium borohydride or sodium hydrosulfite ⟨85H(23)143⟩.

For loss of N—O oxygen concomitant with attack by nucleophiles at ring carbon see Sections 6.03.5.4.3 and 6.03.6.2.

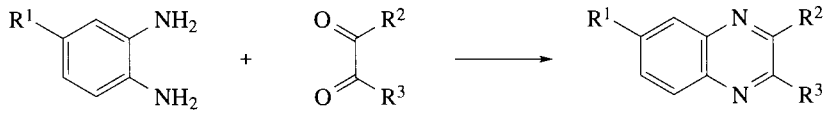
6.03.11 RING SYNTHESES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

The primary syntheses of pyrazines from aliphatic fragments were classified by Cheeseman and Werstiuk into six categories ⟨72AHC(14)99⟩, and this system was followed in CHEC-I. Although this

classification is a little oversimplified, it was useful to comprehend the origin of the various structural fragments and it was successfully applied to the synthesis of the benzo analogues in CHEC-I. In practice, however, this arrangement can be replaced by that according to the type of starting materials containing nitrogen atoms. In this section the existing syntheses (from the literature since 1982) are divided broadly into four categories: 1,2-diamines, α-aminonitriles, α-amino carbonyl compounds, and then miscellaneous starting materials.

6.03.11.1 From 1,2-Diamino Compounds and their Synthetic Equivalents ("[4 + 2] Components")

This type of synthesis is a very useful method for preparation of pyrazines and, in particular, quinoxalines, and it usually involves the condensation of a 1,2-diamino compound (enediamines and 2-amino carboxamides) with an α-diketo compound. The reaction sequence for quinoxaline formation is represented in Equation (14). The parent quinoxaline (**132**; $R^1 - R^3 = H$) is prepared in 95% by reaction of 1,2-diaminobenzene (**130**; $R^1 = H$) with 2,3-dihydroxy-1,4-dioxane in ethanol at room temperature for 30 min ⟨82S61⟩. The dioxane is a stable synthetic equivalent of anhydrous glyoxal, and is obtained by condensation of glyoxal with ethylene glycol. Similarly, 2,3-alkyl and/or aryl derivatives (**132**) are readily synthesized by condensation of (**130**) with the corresponding α-diketones (**131**) in refluxing ethanol ⟨86JCR(S)16, 92JOC6749⟩. Instead of phenylglyoxal, use of α,α-dianilinoacetophenone gives better yields for the preparation of 2-phenylquinoxalines ⟨83JHC1739⟩. The mechanistic progress of 2,3-diphenylquinoxaline formation in the condensation of benzil with 1,2-diaminobenzene has been followed by ^{13}C NMR spectroscopy ⟨94JCS(P2)323⟩.

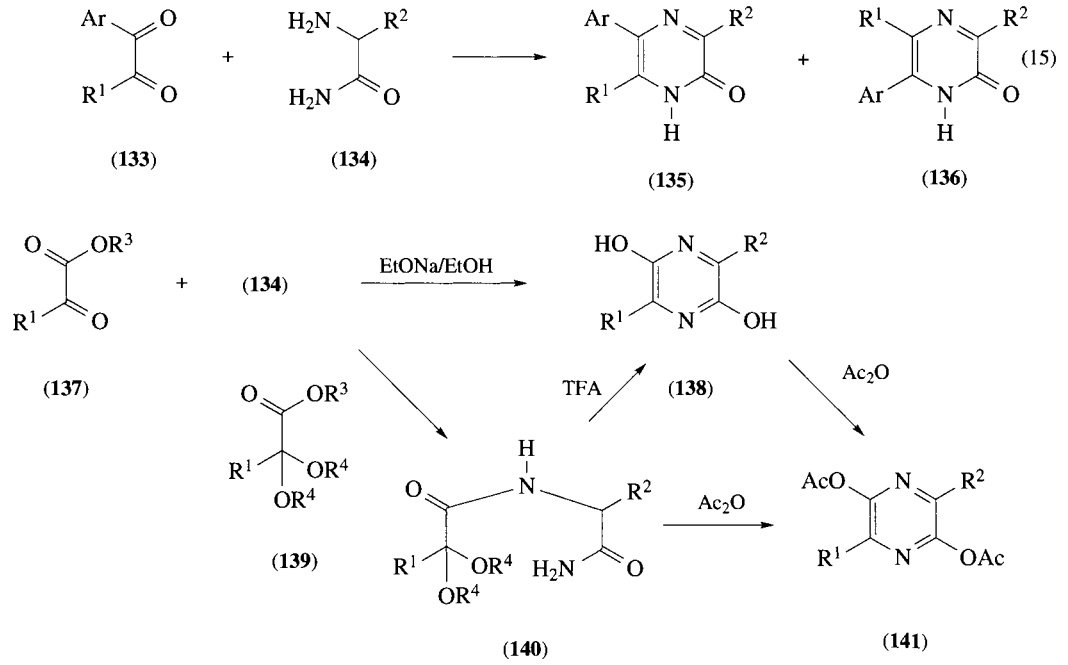


(130) (131) (132) (14)

Use of 1,4-dibromo-2,3-butanedione as the 1,2-dicarbonyl compound gives 2,3-bis(bromomethyl)quinoxalines (**132**; $R^1 = H$, $R^2 = R^3 = CH_2Br$) ⟨93JMC331⟩. Trifluoromethylquinoxalines (**132**; $R^1 = R^3 = H$, $R^2 = CF_3$) are obtained using trifluoropyruvaldehyde ⟨88JOC5088⟩. The condensation with tricarbonyl compounds such as 2,3,4-pentanetrione (**131**; $R^2 = Me$, $R^3 = Ac$) and α,β-diketo esters (**131**; $R^2 = Me$, Pr^n or Ph, $R^3 = CO_2R^4$) affords directly the corresponding 2-acetylquinoxaline and 2-alkoxycarbonylquinoxaline derivatives ⟨84JCS(P1)367, 90JOC2820⟩. Reaction of 1,2-diaminobenzenes with an α-keto acid (**131**; $R^2 = H$, Me or Ph, $R^3 = OH$) in ethanol at room temperature leads to 2(1*H*)-quinoxalinones in 85–92% yields ⟨92JHC129⟩, and this condensation has been studied kinetically ⟨87JHC1771⟩. The same type of product is also prepared by using an α-bromo carboxylic ester in the presence of a carbonate salt in DMF ⟨93JMC2335⟩. The oxime of 2(1*H*)-quinoxalinone is obtained by condensation with chloroethanedial dioxime ⟨84HCA1503⟩. 2,3-Bis(phenylazo)quinoxaline is produced by reaction with 1,2-dichloroglyoxal bisarylhydrazone followed by oxidation with [bis(trifluoroacetoxy)iodo]benzene ⟨89S751⟩. Since the benzene ring in quinoxalines is difficult to nitrate, 5-nitro- or 6-nitroquinoxalines (**132**; $R^1 = NO_2$) are synthesized from the corresponding nitro substituted 1,2-diaminobenzenes ⟨87H(26)2433, 92JHC1305⟩. Syntheses of quinoxalines by the reaction of 1,2-diaminobenzenes with nucleoside ⟨90JCS(P1)67, 93H(36)2591⟩ and ascorbic acid analogues ⟨90JCS(P1)2513, 93H(36)961⟩ have been also reported.

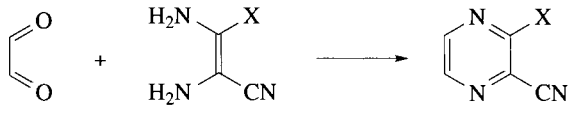
Condensation of an α-amino carboxamide with a 1,2-dicarbonyl compound is the most practical approach to 2(1*H*)-pyrazinones (Equation (15)), and this cyclization usually needs alkaline conditions, unlike that for quinoxaline. A possible drawback is in the regioselectivity of products when unsymmetrical diketones are used. Nevertheless, arylglyoxals (**133**; Ar = Ph or 2-furyl, $R^1 = H$) undergo exclusive condensation with aminoacetamide (**134**; $R^2 = H$) to form 5-aryl-2(1*H*)-pyrazinones (**135**; $R^1 = R^2 = H$) ⟨78JHC665, 82JHC407⟩. Another regioselective synthesis is accomplished by condensation of phenylglyoxylic acid (**133**; Ar = Ph, $R^1 = OH$) with aminoacetamide (**134**; $R^2 = H$) to give the hydroxypyrazinone (**135**; $R^1 = OH$, $R^2 = H$) in 30–40% isolated yields ⟨90H(31)1647⟩. The NMR of the crude product showed the formation of less than 10% of the regioisomer (**136**), which could easily be removed by recrystallization. Conversely, use of an α-keto ester (**137**) instead of the glyoxylic acid afforded 3,6-disubstituted 2,5-dihydroxypyrazines (**138**) (Scheme 32). The parent, monoalkyl, and monoaryl analogues could not be synthesized, probably

because of their extreme instability. Their diacetate derivatives (**141**), however, were obtained by treatment of aminoacetamides (**134**; R^2 = H, Me or Ph) with an α,α-dialkoxy acid or ester (**139**; R^3 = H, Me or Ph) followed by cyclization of the resulting amide (**140**) with acetic anhydride. The dihydroxypyrazines (**138**) are also prepared by treatment of the intermediate (**140**) with TFA ⟨86JHC871⟩.



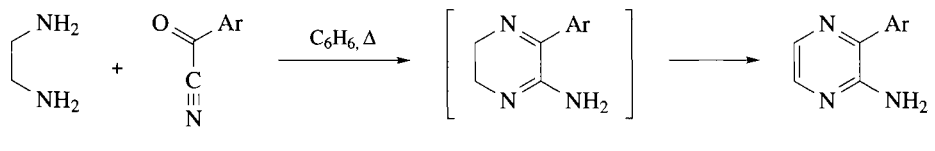
Scheme 32

Diaminomaleonitrile (**142**; X = CN) is an important precursor for the synthesis of 2,3-dicyanopyrazines (Equation (16)). Besides use of an α-diketone as the other fragment, oxalyl chloride reacts to produce 5,6-dioxo-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile, which is converted by thionyl chloride into 2,3-dichloro-5,6-dicyanopyrazine ⟨86JHC1419⟩. 2,3-Diamino-3-phenylthioacrylonitrile (**142**; X = SPh), an adduct of thiophenol to the trimer of hydrogen cyanide, also condenses with α-diketones, yielding 3-phenylthiopyrazinecarbonitrile (**143**; X = SPh) and a variety of its alkyl and aryl analogues ⟨88JAP(K)9049755, 92JHC1689⟩.



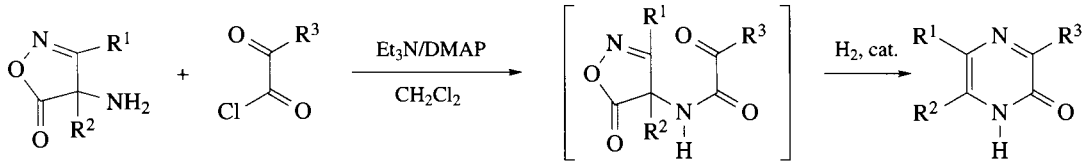
(16)

Reaction of 1,2-diaminoethane with a propargylic alcohol ⟨85S313⟩, *O*-methyl-α-ketophenylacetohydroximoyl chloride ⟨86JHC1861⟩, or diethyl maleate ⟨93JHC275⟩ gives dihydro- or tetrahydropyrazine derivatives. The cyclization with aroyl cyanides in refluxing benzene leads to 2-amino-3-arylpyrazines (**144**) in good yields (Scheme 33). Their formation results from spontaneous air-oxidation of the 5,6-dihydropyrazine formed initially ⟨87S914⟩.



Scheme 33

A protected form of a 1,2-diamine is a 4-amino-5(4*H*)-isoxazolone, which generates another amino functionality by hydrogenolysis of the isoxazole ring with loss of carbon dioxide. The regiospecific synthesis of 2(1*H*)-pyrazinones (Scheme 34) has been achieved in a two-step reaction sequence starting from 3,4-disubstituted isoxazolones (**145**) ⟨91S861⟩.

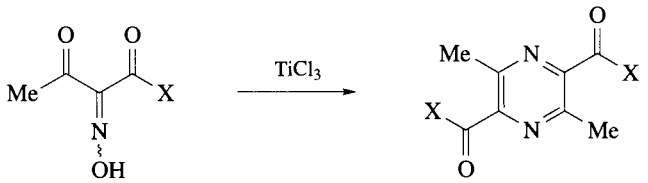


(**145**)

Scheme 34

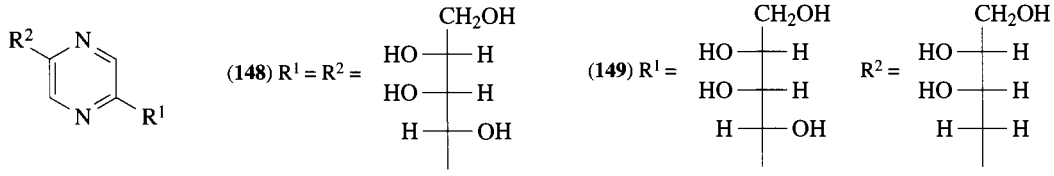
6.03.11.2 From α-Amino Ketones and α-Oximino Ketones ("[3 + 3] Components")

One of the classical methods for the synthesis of pyrazines involves dimerization of an α-amino carbonyl compound and subsequent aromatization. Oximes have often been used as the latent functionality to generate the amine by a variety of reductive processes. 3-Oxo-2-oximinobutanoic esters or the amides (**146**), which are formed by nitrosation of acetoacetic acid derivatives, are reduced by catalytic hydrogenation ⟨82CPB3424, 91JHC1731⟩ or titanium(III)-induced reduction ⟨88H(27)1123⟩ to give the tetrasubstituted pyrazines (**147**) (Equation (17)).

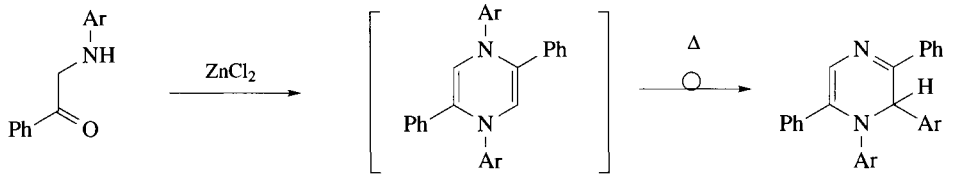


(**146**) (**147**) (17)

Cyclic dimerization of an α-amino ketone also leads to the formation of a pyrazine derivative ⟨92T7879⟩. Treatment of D-glucosamine hydrochloride under various conditions results in simultaneous formation of fructosazine (**148**) and deoxyfructosazine (**149**) in ratios of 1 : 28 to 100 : 1 ⟨91CPB792⟩. Zinc chloride-promoted dimerization of *N*-arylaminoacetophenone (Scheme 35) gives 1,2-diaryl-3,6-diphenyl-1,2-dihydropyrazine (**151**) through the thermally unstable intermediate 1,4-diaryl-2,5-diphenyl-1,4-dihydro isomer (**150**) ⟨87JCS(P1)1841⟩. The 2,6-diphenyl isomer, which is thermally stable, is prepared by treating the same starting material with bromoacetophenone under phase-transfer conditions and then condensing the resulting dicarbonyl compound with an arylamine. Aminoacetophenone hydrochloride condenses with sodium benzoylformate in the presence of dcc and hobt in dichloromethane to form the intermediate (**152**) (Scheme 36) which then is treated with ammonium acetate in ethanol to give the 3,5-diaryl-2(1*H*)-pyrazinone in 53–70% overall yield ⟨90H(31)1647⟩.

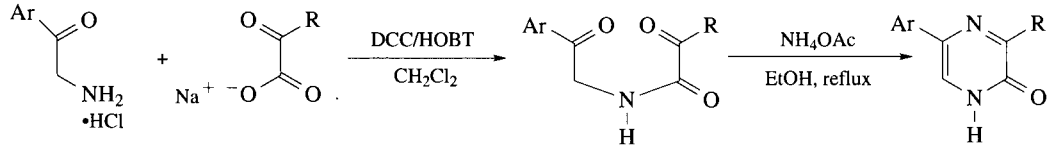


α-Oximino-ketones play an important role in Taylor's pteridine synthesis via 2-amino-3-cyanopyrazine 1-oxides (**154**) (Scheme 37). The oximino-ketone condenses with aminomalononitrile (**153**), used as the tosylate, in alcohol (usually using 2-propanol at room temperature) to give 5-substituted or 5,6-disubstituted 2-amino-3-cyanopyrazine 1-oxides (**154**) ⟨73JA6407, 73JA6413⟩. Several 5-substituted 2-amino-3-cyanopyrazine 1-oxides have been prepared in this way for pteridine synthesis ⟨85JHC5, 87JHC441, 87JHC1109, 88JHC1737⟩.



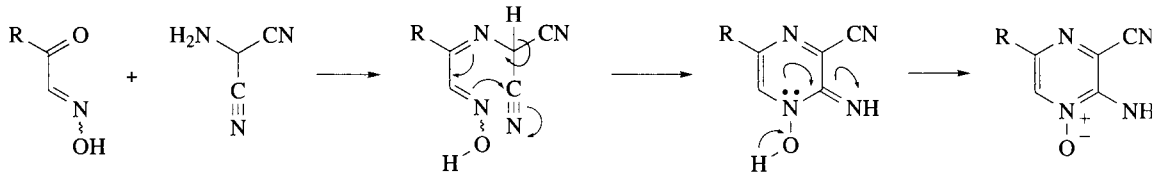
(150) (151)

Scheme 35



(152) (135)

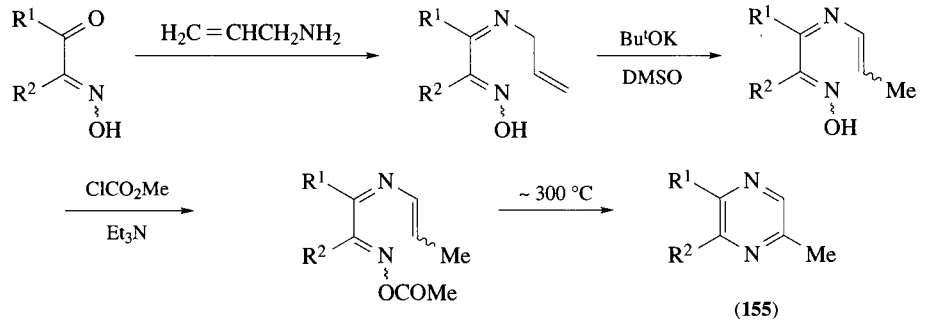
Scheme 36



(153) (154)

Scheme 37

A regioselective synthesis of alkylpyrazines (**155**) starts with condensation of α-oximino carbonyl compounds with allylamines (Scheme 38). The imine intermediates are isomerized in the presence of potassium *t*-butoxide to the corresponding 1-hydroxy-1,4-diazahexatrienes. Thermal cyclization–aromatization to pyrazines is best performed after *O*-acylation of the oximes with methyl chloroformate ⟨91JOC2605⟩.



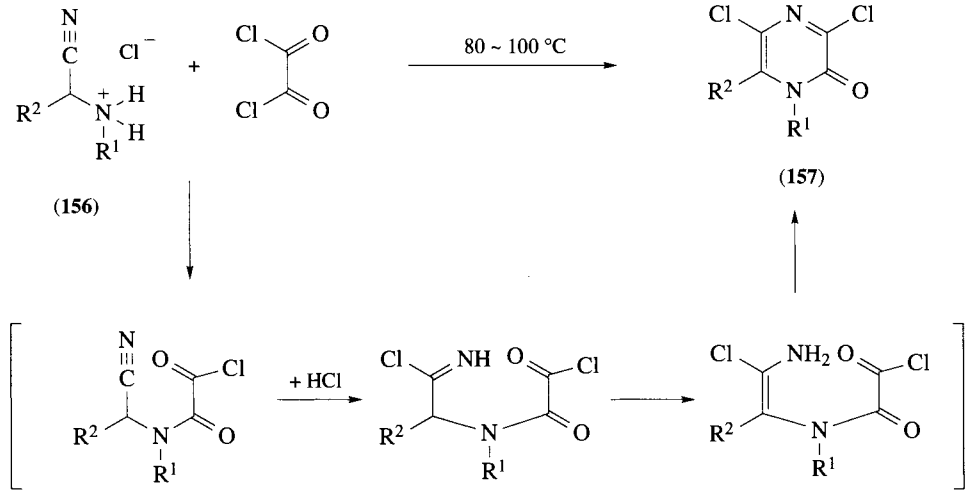
(155)

Scheme 38

6.03.11.3 From α-Amino Nitriles and Other Nitriles ("[4 + 2], [3 + 3] and [5 + 1] Components")

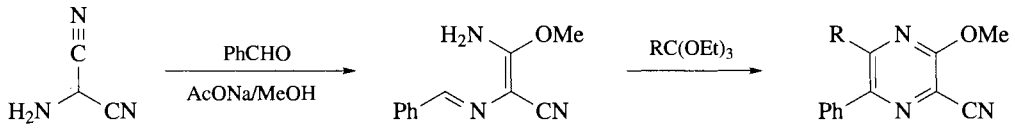
N-Substituted aminoacetonitrile hydrochlorides (**156**), which are easily prepared by the Strecker reaction from the corresponding aldehyde, condense with oxalyl chloride in 1,2-dichlorobenzene to give 3,5-dichloro-1-substituted-2(1*H*)-pyrazinones (**157**) ⟨83JHC919, 86JHC113⟩. A plausible pathway is illustrated in Scheme 39. Aminomalononitrile tosylate (**153**) reacts with benzaldehyde in methanol

containing sodium acetate to yield (1*E*,3*E*)-4-amino-3-cyano-4-methoxy-1-phenyl-2-azabutadiene (**158**), which undergoes cyclization with ortho esters to form 2-cyano-3-methoxy-6-phenylpyrazine derivatives (**159**) (Scheme 40). Reaction of the intermediate (**158**) with an arylaldehyde instead of the ortho ester affords 2-methoxy-5-phenyl-6-arylpyrazines in good yields ⟨92JOC550⟩.



(156) (157)

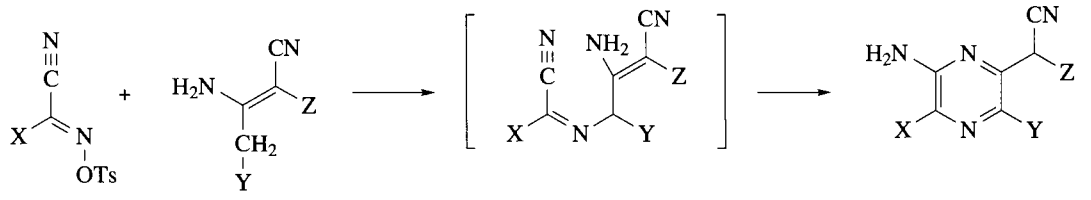
Scheme 39



(153) (158) (159)

Scheme 40

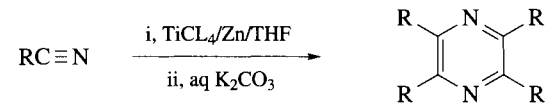
The tosylate of oximinomalononitrile or oximinocyanoacetic ester (**160**; X = CN or CO_2Et) reacts with enaminonitrile derivatives (**161**; Y, Z = CN and/or CO_2Et) in acetonitrile in the presence of triethylamine to produce polyfunctionally substituted pyrazines (**162**) (Scheme 41) ⟨83JHC1571, 88H(27)1301⟩.



(160) (161) (162)

Scheme 41

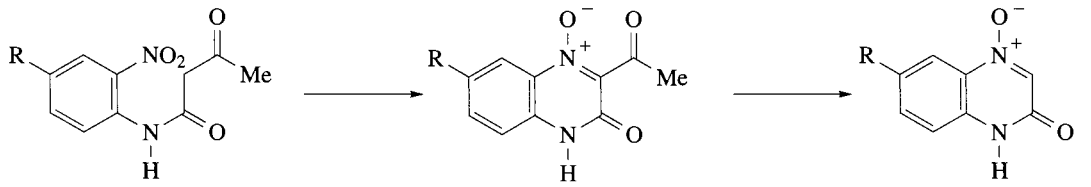
Intermolecular cyclization of 4-dialkylamino-2-aza-1,3-diene-1,1-dicarbonitriles proceeds on treatment with hydrogen bromide in acetic acid to yield 2-bromo-3-cyanopyrazine ⟨90HCA1210⟩. Tetraalkyl or -arylpyrazines are synthesized by reductive cyclization of the corresponding nitriles with titanium tetrachloride and zinc in modest to good yields (Equation (18)) ⟨90S701⟩.



(18)

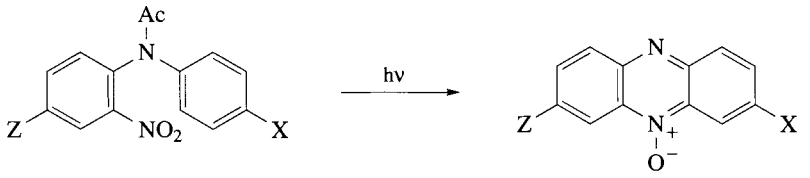
6.03.11.4 Other Syntheses

Meerwein–Ponndorf–Verley reduction of 3-(*o*-nitroanilino)-2-cyclohexenones leads to the formation of 3,4-dihydro-2(1*H*)-phenazinones ⟨82S852⟩. Similarly, 4′-substituted-2′-nitroacetoacetanilides (**163**) undergo intramolecular cyclization together with deacylation under basic conditions to produce 6-substituted 2(1*H*)-quinoxalinone 1-oxides (**164**) (Scheme 42), the formation of which is best effected by sodium or potassium hydroxide in yields >90% ⟨85H(23)143, 85H(23)2069⟩. When dbu is used instead of the alkali a 52% yield of the acetyl intermediate is isolated. Irradiation of 2,4-dinitrodiphenylacetamide brings about intramolecular cyclization via the triplet to form a phenazine *N*-oxide (Equation (19)). The cyclization goes much less readily in the absence of a second nitro group at C-4 ⟨92H(33)573, 92JCS(P1)2689⟩. This photocyclization is unsuitable for large-scale preparation because the irradiation must be carried out in very dilute solution.



(**163**) (**164**)

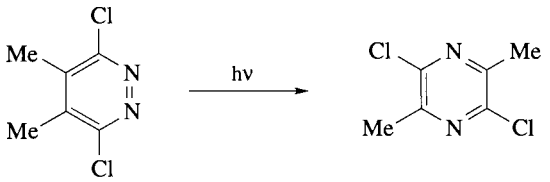
Scheme 42



(19)

6.03.12 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

2*H*-Azirines are dimerized under various conditions to form dihydropyrazines or their oxidized products pyrazines ⟨83JCR(S)122, 85S186⟩. Photoexcitation of tetrachloropyridazine in Freon leads to smooth rearrangement to tetrachloropyrazine, the yield of which was optimized to 80% by irradiating at 3000 Å and 35 °C ⟨82JOC398⟩. Irradiation at 2537 Å of 3,4,5- and 3,4,6-trichloropyridazines isomerizes both to trichloropyrazine. Although 4,5-dichloropyridazine rearranges smoothly to 2,5-dichloropyrazine, the isomeric 3,6-dichloropyridazine fails to rearrange. However, 3,6-dichloro-4,5-dimethylpyridazine (**165**) is successfully converted into 2,5-dichloro-3,6-dimethylpyrazine (**166**) (Equation (20)).

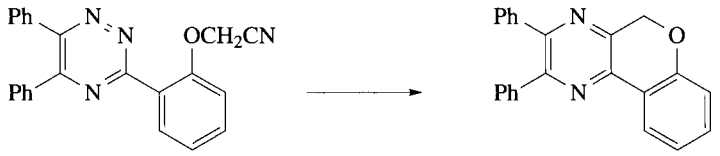


(**165**) (**166**)

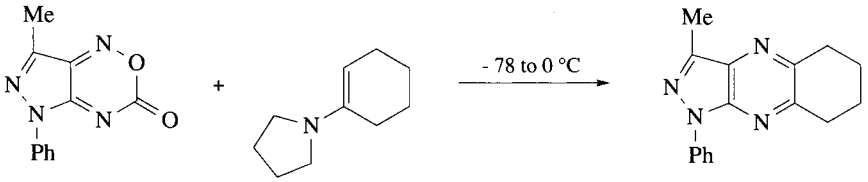
(20)

Thermolysis of 1,2,4-triazines with a side-chain terminal nitrile group leads to the formation of condensed pyrazines ⟨89JOC1245⟩. This reaction involves cycloaddition of the nitrile dienophile across C-3 and C-6 of the 1,2,4-triazine followed by aromatization of the intermediate cycloadduct by extrusion of the N—N bridge. As a typical example, the 5,6-diphenyl-1,2,4-triazine (**167**) is fused under nitrogen at 225–235 °C to form the condensed pyrazine (**168**) in 71% yield (Equation (21)). Intermolecular cyclization of oxadiazinones with enamines also yields condensed pyrazines. The bicyclic intermediates lose carbon dioxide to generate 1,4-diazadienes, which aromatize to the

pyrazines ⟨93JOC6155⟩. The pyrazolo-fused oxadiazinone (**169**) is treated with cyclohexenyl pyrrolidine at −78 °C then to 0 °C to give the fused tetrahydroquinoxaline derivative (**170**) in 81% yield (Equation (22)). At room temperature, the reaction occurs instantaneously with visible gas evolution. This method allows the synthesis of thieno[2,3-*b*]pyrazines; these compounds could not be prepared by the intramolecular Diels–Alder reaction of 1,2,4-triazines.



(**167**) (**168**) (21)



(**169**) (**170**) (22)

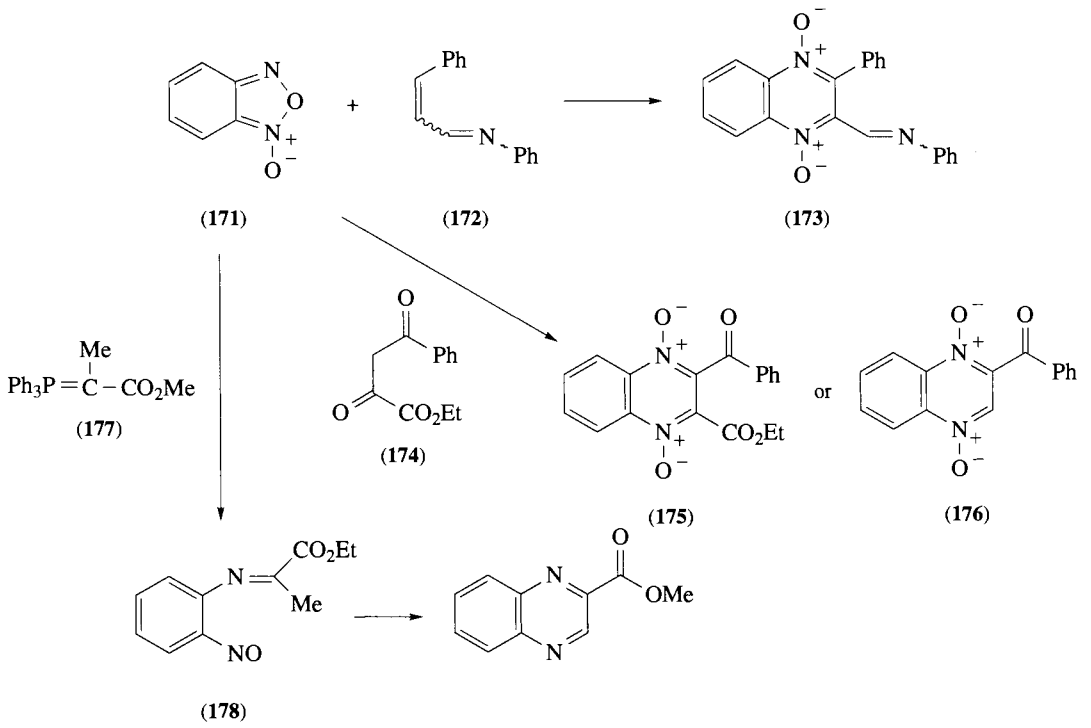
A simple, efficient, one-step synthesis of quinoxaline 1,4-dioxides from the reaction of benzofurazan oxide (**171**) with activated alkenes such as enamines was named the Beirut reaction in honor of the city of its discovery. Earlier developments to 1981 were surveyed by Porter ⟨84CHEC-I(3)157⟩, and later progress has been reviewed by Haddadin and Issidorides ⟨93H(35)1503⟩ who first demonstrated this reaction. Dienamines and azadienes (**172**) also react with benzofurazan oxide to yield 2-substituted or 2,3-disubstituted quinoxaline *N*,*N*′-dioxides, for example (**173**) ⟨84T1617, 84JHC1247, 89JHC427⟩. The benzofurazan oxide condenses with 1,3-diketones or β-keto esters in basic medium to give acyl derivatives. The cyclocondensations are readily performed in the presence of silica gel or molecular sieves, which is particularly effective in completing the reaction within 2 h at 90 °C in yields >80% ⟨93JHC1477⟩. The Beirut reaction of benzofurazan oxide with ethyl 2,4-dioxo-4-phenylbutyrate (**174**), catalyzed by triethylamine, gives first ethyl 3-benzoylquinoxaline-2-carboxylate 1,4-dioxide (**175**) and then, in a slower reaction, 2-benzoylquinoxaline 1,4-dioxides (**176**) in 66% best yield. Synthesis of the latter compound fails using 3-phenyl-3-oxopropanal or its morpholine enamine ⟨89JCS(P1)221⟩. Benzofurazan oxide reacts with the phosphonium ylide (**177**) to produce, via the imino intermediate (**178**), 2-quinoxalinecarboxylic ester in 45% yield (Scheme 43). The quinoxaline formation depends upon the ylide used; for example, the reaction of ethyl (triphenylphosphoranylidene)acetate provide benzimidazole derivatives ⟨86T3631⟩. Phenazine *N*,*N*′-dioxides are also prepared by the Beirut reaction of benzofurazan oxide with cyclohexane-1,2-dione, hydroquinones or 4-aminophenol ⟨93H(35)1503⟩.

A few examples have appeared of the formation of 3-amino-substituted pyrazine- and quinoxalinecarboxylic derivatives by nucleophilic decomposition of their pyrimidine-fused ring systems (pteridines and analogues) (see also Section 6.03.4.1) ⟨86JHC843, 87JHC1013, 91JHC1485⟩.

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

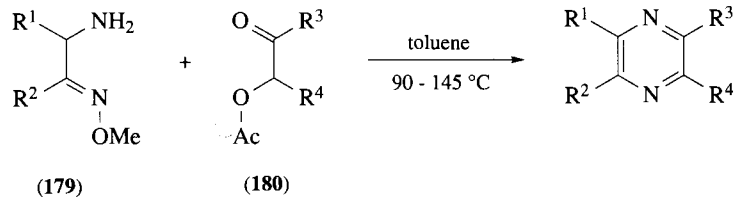
6.03.13.1 Alkyl- and Arylpyrazines, and Quinoxalines

A classical synthesis of alkyl- and arylpyrazines involves dimerization of α-amino carbonyl compounds, which may be produced by many methods such as reduction of α-oximino ketones, aminolysis of α-halogeno ketones (Section 6.03.11.2), oxidation of α-amino alcohols and reduction of α-amino acids ⟨B-82MI 603-01⟩. The condensation of 1,2-diamines with α-dicarbonyl compounds is available for the synthesis of particularly quinoxaline derivatives (Section 6.03.11.1). The synthetic methods which rely on self-condensation, however, provide only symmetrically substituted pyra-



Scheme 43

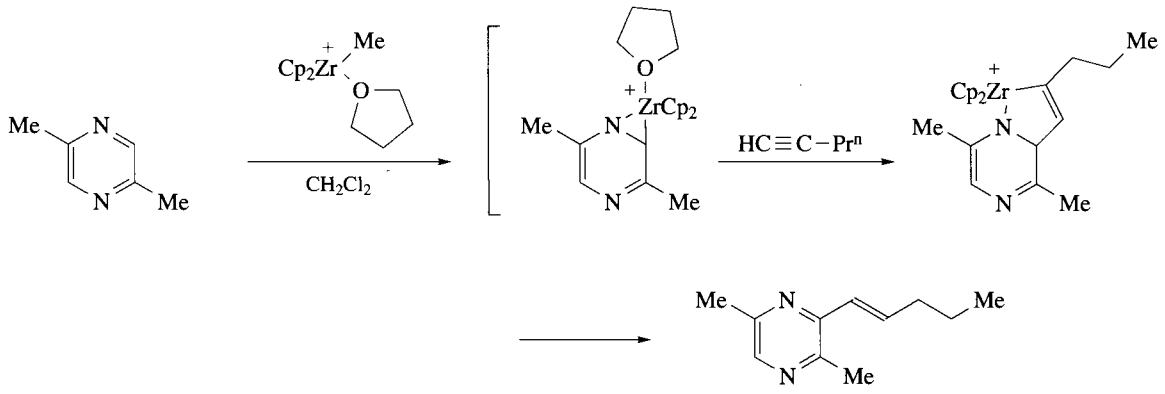
zines. A regiospecific preparation of trialkylpyrazines is achieved by a sequence of reactions starting from α-oximino ketones as shown in Scheme 38. Condensation of α-amino methoxyimino compounds (**179**) with α-acetoxy ketones (**180**) is another method effective for the site-selective synthesis of alkylpyrazines (Equation (23)), which was originally developed for the synthesis of cephalostatins (see Section 6.03.14.2) ⟨92JOC6379⟩.



(23)

An early procedure for introducing an alkyl group into alkyl- or arylpyrazines consisted of treatment with alkyllithium or Grignard reagents (Section 6.03.5.4.1). This method, however, suffers from poor regioselectivity. A new method for regio- and stereoselective synthesis of alkenylpyrazines has been developed by zirconium-mediated reactions of 2,5- and 2,3-dimethylpyrazines with alkynes ⟨92JOC5994⟩. The alkenylation proceeds smoothly at room temperature to afford (*E*)-alkenyl-substituted alkylpyrazines in excellent yields (Scheme 44). Minisci-type radical alkylation is effective (Section 6.03.5.6.1), but suffers from the drawback of low regioselectivity.

Transition metal-catalyzed cross-coupling reactions of halogenopyrazines is an efficient synthetic method for alkyl-, alkenyl-, and alkynylpyrazines (Section 6.03.5.4.2). Palladium and nickel complexes are particularly effective as catalysts in this reaction. The Wittig reaction of halogenomethylpyrazines likewise leads to the formation of alkenylpyrazines (Section 6.03.8.1). Dehalogenation of halogeno pyrazines is a very practical synthetic method for alkyl- or aryl-substituted pyrazines. For example, phenylpyrazine has been prepared by catalytic hydrogenolysis of the 2-chloro-3-phenyl compound in the presence of triethylamine. This product is also obtained by decarboxylation of 5-phenylpyrazine-2,3-dicarboxylic acid with copper(II) oxide at temperatures above 200°C ⟨78JOC3367⟩.



Scheme 44

6.03.13.2 Cyano, Carboxy, and Related Pyrazines and Quinoxalines

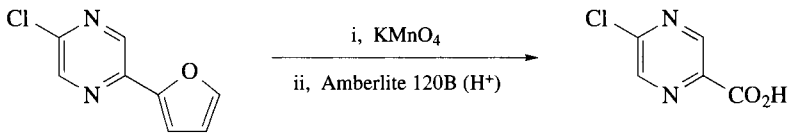
Cyanopyrazines were previously prepared by treatment of bromopyrazines with copper(I) cyanide in refluxing 4-picoline ⟨56JA2141⟩. These compounds can also be synthesized by palladium-catalyzed cyanation of the less reactive chloropyrazines with potassium cyanide (Section 6.03.5.4.2). Sodium dicyanocuprate is similarly effective for the cyanation of 2-amino-3-bromopyrazine, the halogen of which is almost inert to copper(I) cyanide. Dehydration of pyrazinecarboxamides with phosphoryl chloride, acetic anhydride or phosphorus pentoxide gives the carbonitriles.

Numerous 3-substituted 2-cyanopyrazines and quinoxalines are synthesized by reaction of the corresponding 3-substituted *N*-oxides with TMS-CN in the presence of triethylamine (Section 6.03.5.4.3). The primary synthesis of 2-cyano-3-methoxypyrazines was completed by a sequence of reactions starting from aminomalononitrile (Scheme 40).

Condensation of diaminomaleonitrile or 2,3-diamino-3-phenylthioacrylonitrile with 1,2-dicarbonyl compounds is a convenient synthetic method for 2,3-dicyano- and 2-cyano-3-phenylthiopyrazines (Section 6.03.11.1).

Pyrazinyl ketones have been prepared by treatment of pyrazinecarboxylic esters with an organometallic (alkyllithium or Grignard) reagent ⟨84MI 603-01⟩. Homolytic acylation of pyrazines and quinoxalines with α-keto acids is an important method for preparation of the acyl compounds (Section 6.03.5.6.1), but the procedure for monosubstitution needs care because the electron-withdrawing effect of the first-formed monoacyl compounds facilitates further substitution. An additional synthesis of pyrazinyl ketones is the lithiation of halogenopyrazines followed by treatment with carboxylic esters or carboxamides (Equation (8) and Scheme 24). Reaction of 2-chloropyrazine (**36**) with the enolate anion of cyclopentane forms a modest yield of 2-(2-pyrazyl)cyclopentane ⟨85JOC786⟩

Pyrazine and quinoxaline carboxylic acids are obtained by hydrolysis of the carboxylic esters, carboxamides, and carbonitriles ⟨B-82MI 603-01⟩. A general synthetic method for pyrazinecarboxylic acids is oxidation of an alkyl substituent, usually with potassium permanganate. The cleavage of an alkenyl-substituted pyrazine by permanganate oxidation is promoted by 18-crown-6 ⟨83JHC169⟩. A latent form of carboxylic functionality is the 2-furyl group, which can easily and quantitatively be cleaved by potassium permanganate to yield the corresponding pyrazinecarboxylic acid (Equation (24)) ⟨82JHC407⟩.



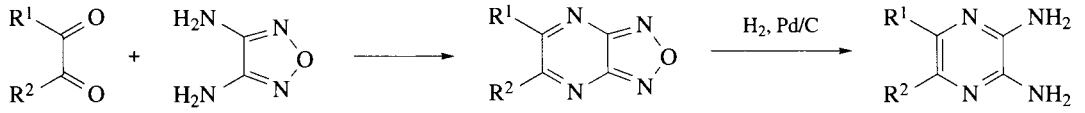
(24)

Palladium-catalyzed carbonylation of chloropyrazines in methanol and in amines yields the pyrazine carboxylic methyl esters and carboxamides, respectively. This procedure has been successfully applied to the synthesis of 2,5-pyrazinedicarboxylic acid derivatives and 3-methoxycarbonylpyrazine 1-oxide from the corresponding dichloropyrazines and *N*-oxides ⟨90S923⟩.

6.03.13.3 Amino Derivatives

The parent pyrazine and quinoxaline are directly aminated by the Tschitschibabin reaction to afford the corresponding amino derivatives (Section 6.03.5.4.1).

General syntheses of aminopyrazines are achieved by amination of halogenopyrazines, Hofmann degradation of pyrazinecarboxamides, or construction from aliphatic fragments such as α-aminoacetamidine ⟨B-82MI 603-01⟩. A disadvantage of the amination procedure is the necessity to use an autoclave, and the latter two syntheses suffer from the relative inaccessibility of the precursors. Although azidopyrazines usually exist predominantly as the tautomeric tetrazolopyrazines (Section 6.03.4.4) which are resistant to reduction, these compounds are convertible into aminopyrazines by proper choice of reduction method depending on the substituent pattern of the reactants. Catalytic hydrogenation provides 2,6-diaminopyrazine ⟨80JHC11⟩ and 2-amino-6-phenylpyrazine ⟨94S931⟩ from the corresponding azido compounds. Reduction of 2-azido-3-substituted pyrazines is successfully effected by tin(II) chloride in hydrochloric acid ⟨94S931⟩. 2,3-Diamino-5,6-diphenylpyrazine is also synthesized by catalytic hydrogenation of [1,2,5]oxadiazolo[3,4-*b*]pyrazines (Scheme 45) ⟨78JOC341⟩. This method can be applied to the preparation of 2,3-diaminopyrazines with at least one phenyl group; the parent and alkyl-substituted oxadiazolo-pyrazines were not obtained by condensation of 3,4-diaminofurazan with the corresponding 1,2-dicarbonyl compounds.



Scheme 45

Amine substitution of activated halogeno or other groups on pyrazines and quinoxalines has been described (Section 6.03.5.4.2). It is noteworthy that a variety of 2-amino-3-cyanopyrazines are produced by reaction of 2-cyano-3-phenylsulfonylpyrazine with the corresponding amines (Equation (6)).

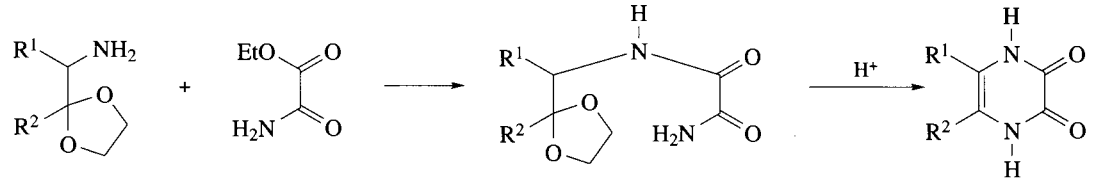
A new primary synthesis of 2-amino-3-arylpyrazines is accomplished by reaction of aroyl cyanides with 1,2-diaminoethane (Scheme 33). An important synthesis is that of 2-amino-3-cyano-5-substituted pyrazines, which are conveniently synthesized by condensation of aminomalononitrile with α-oximino ketones and then deoxygenation of the resulting pyrazine *N*-oxides (Scheme 37).

6.03.13.4 Pyrazinones and Quinoxalinones

Hydroxypyrazines, i.e., 2(1*H*)-pyrazinones, are readily prepared by condensation of α-aminoacetamide with 1,2-dicarbonyl compounds ⟨49JA78, 52JA1580⟩ (see Section 6.03.11.1). Similarly, 3-carbamoyl-2(1*H*)-pyrazinones are obtained by use of aminomalononitrile instead of α-aminoacetamide ⟨49JA78⟩. This type of reaction occasionally suffers from the disadvantage of low regioselectivity when unsymmetrical dicarbonyl compounds are employed. Diazotization of aminopyrazines in concentrated sulfuric acid followed by hydrolysis was an early synthetic method for pyrazinones. Chloropyrazines are usually inert to hydrolysis but their 1-oxides are easily hydrolyzed by refluxing aqueous potassium hydroxide to give 1-hydroxy-2(1*H*)-pyrazinones ⟨81JHC555⟩. Similar products are prepared by lithiation of 2,5-dialkyl- or 2,3,5-trialkylpyrazine 1-oxides and then oxygenation of the reaction mixture (Equation (9)).

The parent, 5- and 5,6-methyl and/or phenyl 2,3-dihydroxypyrazines, which exist as 1,4-dihydro-2,3-pyrazinediones, have been prepared by a two-step reaction sequence starting from α-aminoacetaldehyde ketals (Scheme 46). This class of compound was first synthesized by nitration of 2(1*H*)-pyrazinones and then hydrolysis ⟨53JA5517⟩. A number of 2,5-dihydroxypyrazines have been obtained from the corresponding 2,5-dimethoxypyrazines with methanolic sodium methoxide in a sealed tube at 175–182 °C ⟨57JA680⟩. The conversion is more easily achieved by treatment with TMS-I at room temperature (Equation (12)). The primary synthesis of these pyrazinones has been accomplished by condensation of α-aminoacetamide with α-ketoesters (Scheme 32). Regarding 2,6-dihydroxypyrazine, the one example reported is the 3,5-diphenyl derivative, which was synthesized by reaction of the 1-hydroxy-2(1*H*)-pyrazinone with acetic anhydride and subsequent hydrolysis (Scheme 23). An attempt to prepare the unsubstituted compound by debenzylation of 2,6-dibenzyloxypyrazine failed ⟨71JCS(C)2973⟩.

Generally, alkoxy derivatives have been obtained by treatment of halogeno compounds with sodium alkoxide in alcohol at room temperature up to about 120 °C in a sealed tube. Sometimes alkoxylation can be achieved by refluxing in alcohol with sodium or potassium hydroxide.



Scheme 46

6.03.13.5 Halogeno Compounds

Direct chlorination of pyrazine in 52% yield is easily effected by treatment of pyrazine with 1.2 equivalents of chlorine in DMF at 65–68 °C ⟨94JAP(K)73026⟩. 2,3-Dichloropyrazine is synthesized in a similar manner using 2.5 equiv. of chlorine in 74% best yield. Deoxidative chlorination of the *N*-oxides is a good preparative method for chloropyrazines and chloroquinoxalines ⟨B-82MI 603-01⟩. This reaction with monosubstituted pyrazine *N*-oxides occasionally leads to the less regioselective formation of chloropyrazines (see Section 6.03.5.4.3) but the regioselectivities are considerably improved, and furthermore each isomer can be effectively separated by HPLC. Electrophilic bromination of aminopyrazines (see Section 6.03.5.3) and 2(1*H*)-pyrazinones (see Section 6.03.6.3) provides the *ortho*- or *para*-bromo derivatives.

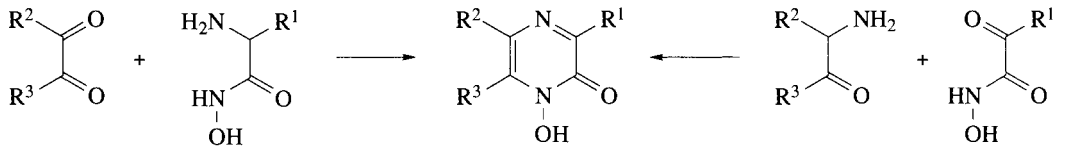
The most convenient synthesis of halogenopyrazines and -quinoxalines is by halogenation of pyrazinones and quinoxalinones with phosphoryl or other acid halides. A methoxy group is also displaced with phosphoryl chloride to yield chloropyrazine when the period of reaction is prolonged or the reaction is carried out at higher temperatures ⟨78JHC665⟩. Chloro- and bromopyrazine *N*-oxides are obtained by diazotization of aminopyrazine *N*-oxides in concentrated hydrochloric acid and hydrobromic acid, respectively (see Section 6.03.5.4.2).

6.03.13.6 Pyrazine and Quinoxaline Thiones

Pyrazine- and quinoxalinethiones have been synthesized by treatment of halogeno compounds with sodium or potassium hydrogen sulfide, sodium polysulfide, phosphorus pentasulfide, or thiourea ⟨B-82MI 603-01⟩. Pyrazinethiones are directly prepared by treating 2(1*H*)-pyrazinones with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) ⟨83H(20)797⟩. They are also obtained by treatment of (4-methoxybenzylthio)pyrazines with mercury(II) acetate and successive reduction ⟨93JCS(P1)15⟩.

6.03.13.7 Pyrazine and Quinoxaline *N*-Oxides

In general, pyrazine and quinoxaline *N*-oxides are easily synthesized by *N*-oxidation of the nitrogen heterocycles with a peroxy acid; the details of this reaction have been discussed (see Section 6.03.5.2). *N*-Oxides are also prepared by primary construction from oximes, as exemplified by the synthesis of 2-aminopyrazine 1-oxides from aminomalononitrile tosylate and α-oximinoketones (Scheme 37). Some other syntheses of *N*-oxides from α-functionalized oxime derivatives are available ⟨B-91MI 603-01⟩. Analogues of aspergillic acid, 1-hydroxy-2(1*H*)-pyrazinones, are prepared by condensation of α-aminohydroxamic acids with 1,2-dicarbonyl compounds ⟨49JCS2707⟩ or alternatively of α-oxohydroxamic acids with α-aminoketones ⟨50JCS3409⟩ (Scheme 47).



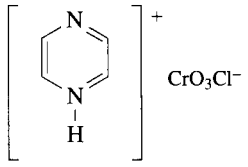
Scheme 47

The Beirut reactions, which involve condensation of benzofuroxan with various reagents, provide the most convenient synthetic methods for quinoxaline and phenazine *N,N'*-dioxides (see Section 6.03.12).

6.03.14 IMPORTANT COMPOUNDS AND APPLICATIONS

6.03.14.1 Reagents for Synthetic Use

Acyloxy- and acylthiopyrazines are convenient acylation reagents for benzylamine, aniline, pyrrolidine, and related compounds (see Section 6.03.8.3). The acylthio compounds are also useful for acylation of alcohols and phenols. Pyrazinyl alkyl sulfoxides (see Section 6.03.8.4) give aldehydes and ketones by treatment with TFAA ⟨91H(32)937⟩. The pyrazinium chlorochromate salt (**181**) is formed by addition of chromium(VI) oxide to a solution of pyrazine in hydrochloric acid, and it has proved to be more effective for the oxidation of aliphatic and allyl alcohols to the aldehydes than pcc ⟨83H(20)2029⟩.



(**181**)

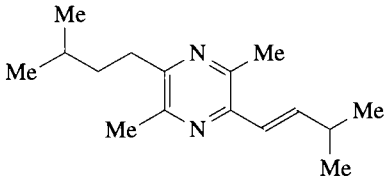
6.03.14.2 Naturally Occurring Products

Pyrazines in general seem to serve in ants both as trail-laying and alarm pheromones. Twelve new pyrazines have been found in worker ants of *Mesoponera* species in New Zealand and their structures were elucidated using mass spectrometry and confirmed by synthesis ⟨88T5045⟩. These compounds are derivatives of 2,5-dimethylpyrazines having alkenyl (**182**), α-hydroxyalkyl (**183**) and acyl side chains.

The cephalostatins are a group of complex steroidal pyrazine alkaloids that were isolated from the marine worm *Cephalodiscus gilchristi* ⟨89CJC1509⟩. They are among the most cytotoxic compounds ever screened against the PS cell line and therefore have potential application as antitumor agents. A few approaches to synthesize models for cephalostatin 1 (**184**) have been made ⟨92JOC6379, 93JCS(P1)2865⟩.

Rare phenazine L-quinovose esters have been isolated from a marine actinomycete ⟨92JOC740⟩. These compounds exhibit modest broad spectrum activity against numerous Gram-positive and Gram-negative bacteria. The esmeraldines A and B, green pigments of phenazine derivatives, were obtained from a strain of *Streptomyces antibioticus*, Tü 2706 ⟨88HCA2058⟩. Benthocyanins A (**185**; $R^1 = CO_2H$, $R^2 = H$), B (**185**; $R^1 = H$, $R^2 = CO_2H$) and C (**186**) from *Streptomyces prunicolor* are new free radical scavengers ⟨91TL943, 93JOC4170⟩, and the effect of the latter two substances is more potent than that of vitamin E, to ameliorate or overcome a variety of diseases such as atherosclerosis, inflammation, Parkinson's disease, and ischemia–reperfusion injury including cerebral trauma and stroke, which have been proven to be caused by oxygen-derived free radicals.

The total synthesis of several naturally occurring pyrazines has been accomplished by Ohta *et al.*; the target compounds were argecin (**187**) ⟨87H(26)3181, 88H(27)437⟩, (+)-septorine (**188**) ⟨91H(32)923⟩,



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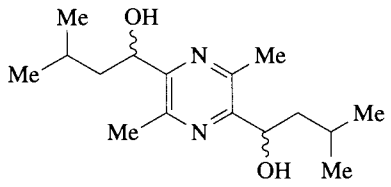

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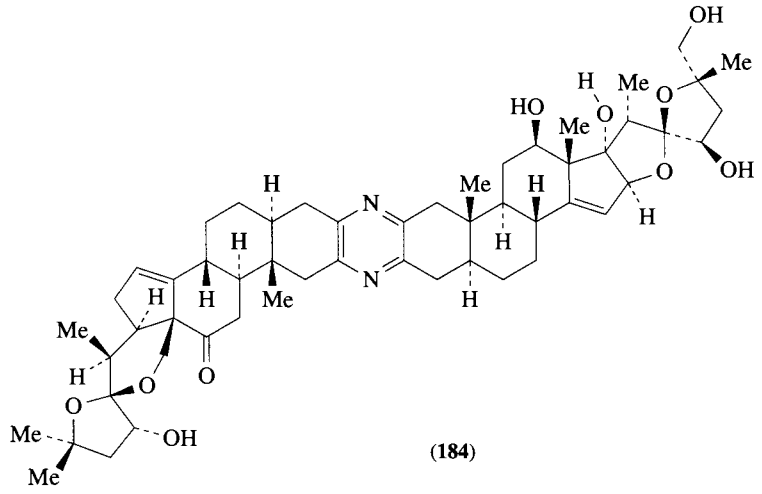

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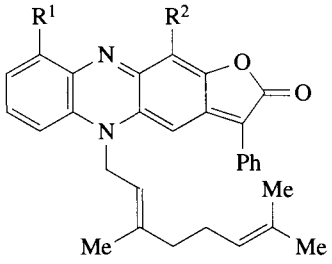

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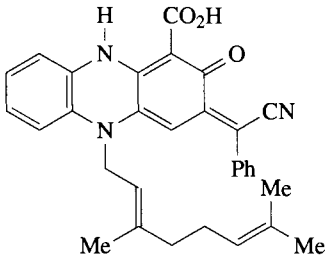


(186)

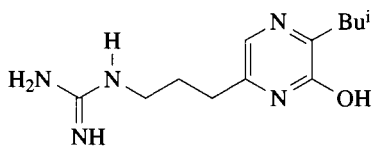
emeheterone (**189**) ⟨90H(31)1655⟩, OPC-15161 (**190**) ⟨92H(34)111⟩, and astechrome (**191**) ⟨93H(35)1279⟩, and their efforts have been summarized ⟨93MI 603-01⟩. In a study of the chemical constituents of caramels, (1,2-dihydroxyethyl)pyrazines have been prepared ⟨89JCR(S)59⟩.

6.03.14.3 Synthetic Chemotherapeutic Agents

Pyrazinamide (**192**) is a well-known synthetic antimycobacterial agent and is still used for the treatment of tuberculosis. Several pyrazinecarboxylic esters (**193**) have a substantially better effect than the first-line pyrazinamide against susceptible isolates of *Mycobacterium tuberculosis* as well as activity against pyrazinamide-resistant isolates ⟨92JMC1212⟩. Derivatives of pyrazinamide are also useful as antiallergic agents ⟨90CPB201⟩, and in particular 6-substituted *N*-(5-tetrazolyl)-pyrazinecarboxamides (**194**; R = H, Me or Cl) have been found to possess potent inhibitory activity on allergic histamine release ⟨90CPB1250⟩.

Quinuclidinyl- (**195**) and 1-azanorbornylpyrazine derivatives ⟨92JMC295⟩ as well as a series of (1,2,5,6-tetrahydro-1-methyl-3-pyridyl)pyrazines (**196**) ⟨92JMC4011⟩ have been found to have high affinity for central muscarinic receptors. Such muscarinic agonists may provide an appropriate therapy for alleviating the memory deficiency associated with Alzheimer's disease.

2-Acetyl-3-(methylsulfonylmethyl)quinoxaline 1-oxide (**197**) has been found to possess good antibacterial *in vitro* activity against some pathogens important to veterinary medicine as well as *in*



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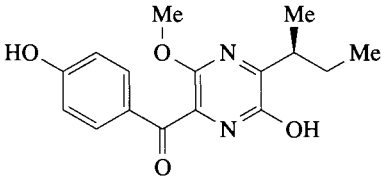

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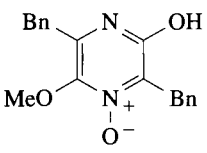

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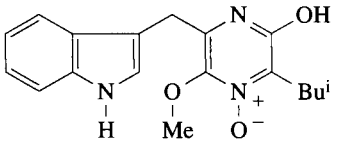

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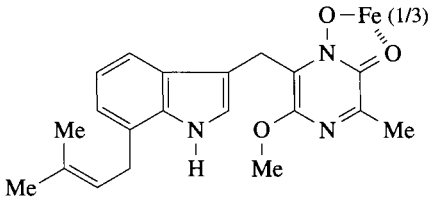

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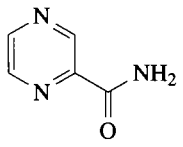

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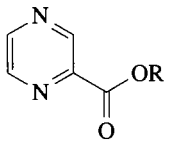

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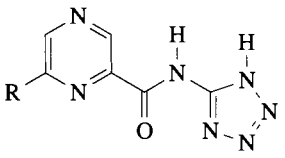

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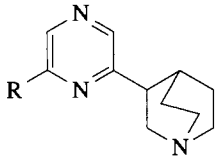

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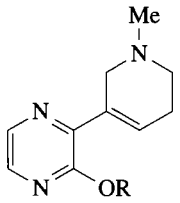

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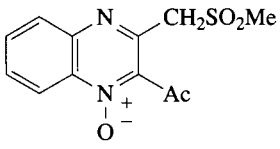
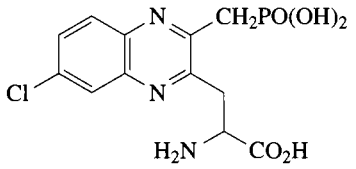
vivo activity against swine dysentery ⟨83JMC1122⟩. A review of the biological activity of quinoxaline derivatives up to 1987 has been published ⟨88H(27)2481⟩.



(197)

Considerable pharmacological research is being carried out on quinoxaline derivatives. For example, α-amino-7-chloro-3-(phosphonomethyl)-2-quinoxalinepropanoic acid (**198**) has been shown to be an antagonist of NMDA (*N*-methyl-D-aspartic acid) receptor ⟨93JMC331⟩. NMDA antagonists offer protection against permanent ischaemic damage even when administered several hours after the ischaemic event. Quinoxaline *N*-oxides (**199**) are potent angiotensin II receptor antagonists ⟨93JMC2335⟩, which are expected to be effective for the treatment of hypertension. Piperazinylcyanoquinoxalines (**200**) represent a new class of 5-HT_3 antagonists with a selective effect

on guinea pig peripheral receptors ⟨93JMC2745⟩. Some antagonists of this 5-HT receptor subtype are of high therapeutic interest for the prevention and treatment of vomiting associated with anticancer chemotherapy.



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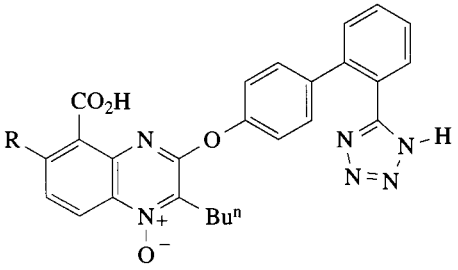

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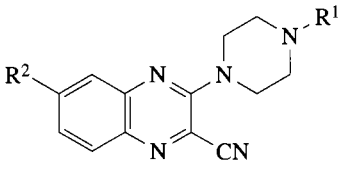

(200)

6.03.14.4 Miscellaneous

A highly efficient DNA strand scission is realized by oxygen radicals produced through the reductive activation of 2-[(3′-aminopropyl)amino]phenazine 5,10-dioxide ⟨91JA5099⟩. Phenazine compounds having both electron-donating and electron-withdrawing groups stabilize a radical due to its conjugation with the substituents ⟨89JHC435⟩. These compounds form electron–donor–acceptor (EDA) complexes with electron-acceptors such as TCNE (tetracyanoethene), which are expected to show conductive properties. Highly fluorescent cationic indicators have been obtained by reaction of heterocyclic bases including phenazine with 1,3-propanesultone ⟨82JHC841⟩. The fluorescence intensity of the cationic salts is practically pH-independent in the neutral pH range, which makes them useful reference substances for measuring fluorescence intensities in physiological studies.

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6.04
1,2-Oxazines and their Benzo Derivatives

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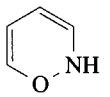
6.04.1 INTRODUCTION

1,2-Oxazines and their benzo derivatives were described, along with other oxazines and thiazines, by Sainsbury ⟨84CHEC-I(3)995⟩. Since 1984 the main developments have been in the preparation of 3,6- and 5,6-dihydro-1,2-oxazines and in their subsequent use as synthetic intermediates, particularly by reductive ring cleavage. Several research groups have investigated the asymmetric synthesis of 3,6-dihydro-2*H*-1,2-oxazines by cycloaddition of chiral nitrosocarbonyl compounds to dienes. There have also been significant advances in the characterization of salts of the fully conjugated 1,2-oxazinium cation bearing a variety of ring substituents and in the chemistry of transient 1,2-oxazinium cations.

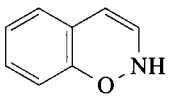
The nomenclature of some of the ring systems containing the 1,2-oxazine skeleton is shown in Figure 1. Examples of all the monocyclic systems, and of partially or fully hydrogenated analogues, are known. The fused-ring systems shown in Figure 1 are also all represented in the literature, although 2*H*-1,2-benzoxazines and 2*H*-naphth[1,2-*d*]oxazines occur only as partially reduced derivatives. The naphth[1,8-*de*]-1,2-oxazine ring system is unique because it is the only fully conjugated, neutral 1,2-oxazine derivative apart from those containing carbonyl functions, such as (**1**) and (**2**). There are a few examples of the naphth[1,8-*de*]-1,2-oxazine ring system in the literature and these have been briefly reviewed ⟨90AHC(51)1⟩.

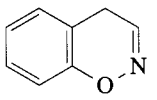
1,2-Oxazinium

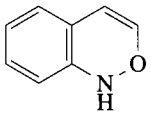

2*H*-1,2-Oxazine

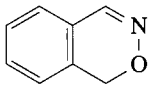
4*H*-1,2-Oxazine

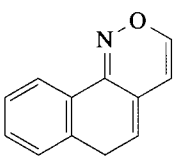
6*H*-1,2-Oxazine

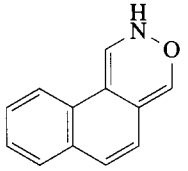

2*H*-1,2-Benzoxazine


4*H*-1,2-Benzoxazine


1*H*-2,1-Benzoxazine


1*H*-2,3-Benzoxazine


6*H*-Naphth[1,2-c][1,2]oxazine


2*H*-Naphth[1,2-d][1,2]oxazine

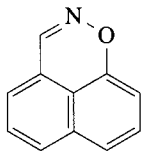
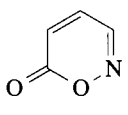
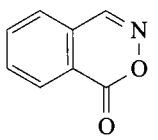

Naphth[1,8-*de*]-1,2-oxazine

Figure 1 Examples of well-known 1,2-oxazine ring systems.


(**1**)


(**2**)

The properties of the 1,2-oxazine ring system are described following the general pattern adopted in other chapters of this volume. Most of the information refers to the monocyclic systems but benzo fused-ring systems and carbonyl derivatives of the monocyclic systems are discussed where there are significant differences (for example, in methods of preparation). The balance of the coverage differs from that in some other chapters because the overwhelming majority of the literature citations concern partially or fully reduced 1,2-oxazines rather than the conjugated systems. The aim has been to include all significant developments up to mid-1994.

6.04.2 THEORETICAL METHODS

The geometry, heat of formation, ionization potential, and charges on the atoms of the 1,2-oxazinium cation have been calculated by the MINDO/3 method ⟨87ZOR717⟩. The calculated geometry and atomic charges are shown in Figure 2(a); the bond distances can be compared with those from the x-ray crystal structure of the tetramethyl-1,2-oxazinium cation shown in Figure 2(b) ⟨85JA5722⟩. The heat of formation of the 1,2-oxazinium cation was calculated as 162.9 kcal mol^{-1} and the ionization potential as 15.32 eV.

Calculations by SCF-MO LCAO methods have also been carried out on the oxazinones (**1**) and (**2**) ⟨85ZOR2445⟩. The effective charges at the ring atoms have been calculated in order to correlate these with the experimentally observed position of alkylation (the ring nitrogen or the oxygen of the carbonyl group).

A molecular mechanical (MM2 force field) parameter set has been obtained for compounds containing N—O bonds and this has been applied to calculations of the geometries and energies of tetrahydro-2*H*-1,2-oxazine and of its 2-methyl derivative ⟨93MI 604-01⟩. The geometrical parameters compare well with previously obtained experimental values.

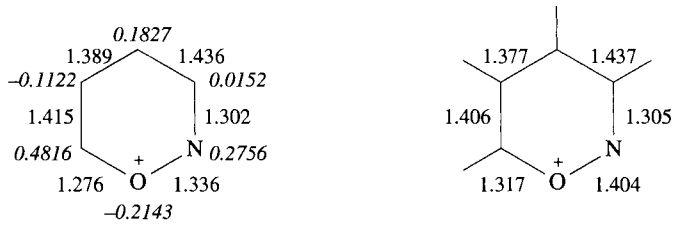


Figure 2 (a) Bond distances (Å) and charges at the atoms (q) in the 1,2-oxazinium cation, calculated by the MINDO/3 method; (b) bond distances in the 3,4,5,6-tetramethyl-1,2-oxazinium cation determined by x-ray crystallography.

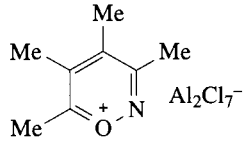
6.04.3 EXPERIMENTAL STRUCTURAL METHODS

6.04.3.1 X-Ray Crystal Structures

Crystal structure data have been obtained not only for the 1,2-oxazinium cation shown in Figure 2(b) and for perhydro-1,2-oxazines referred to above, but also for several partly saturated 1,2-oxazines. The C=N and N—O bond distances in 6*H*-1,2-oxazines ⟨80CSC523, 93JCS(P1)2507⟩ and in 5,6-dihydro-4*H*-1,2-oxazines ⟨88HCA822, 89AX(C)976, 92CPB1921⟩ are within the range expected for oxime ethers.

6.04.3.2 NMR Spectra

The ^{13}C chemical shift values for the tetramethyl-1,2-oxazinium salt (**3**) and for some 6*H*-1,2-oxazines and dihydro-1,2-oxazines (**4**)–(**8**) are given in Table 1.



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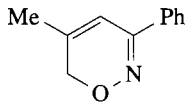

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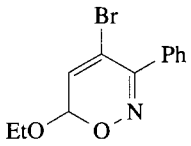

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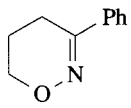

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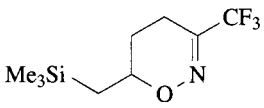

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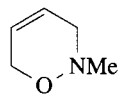


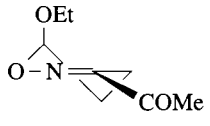
(8)

Table 1 ^{13}C NMR shifts of 1,2-oxazines (**3**)–(**8**)[a].

Compound	*C-3*	*C-4*	*C-5*	*C-6*	*Ref.*
(**3**)	165.1	157.3	139.7	197.5	85JA5772
(**4**)	156.8	110.9	141.4	66.5	89S908
(**5**)	156.2	112.9	127.8	94.7	94CB685
(**6**)	155.8	19.6	23.7	64.9	91LA851
(**7**)	146.8	19.1	22.4	75.5	92JOC339
(**8**)	56.6	123.5	125.8	68.5	77JCS(P2)619

[a]Spectra in $CDCl_3$ except for compound (**3**) (CD_2Cl_2).

The ^1H NMR spectra of a variety of 1,2-oxazines have proved useful in determining the lowest energy conformations of the rings. The ring systems adopt chair or half-chair conformations; substituents normally occupy equatorial or pseudoequatorial positions. The exception is that alkoxy and other electronegative substituents attached to C-6 occupy axial or pseudoaxial positions; this can be accounted for by the influence of a pronounced anomeric effect of the ring oxygen atom. For example, the spectrum of 3-acetyl-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (**9**) shows H-6 as a triplet (*J* 2.8 Hz) at δ 5.20, consistent with the conformation shown ⟨83JCS(P1)1283⟩. This is a general feature which has been observed with many other such dihydrooxazines including compounds (**10**) ⟨88BCJ461⟩ and (**11**) ⟨90LA217⟩. In the case of 3,6-dihydro-2*H*-1,2-oxazines ^{13}C NMR spectra were used for conformational analysis ⟨77JCS(P2)619⟩.



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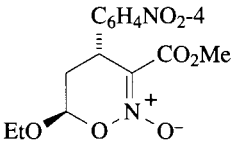

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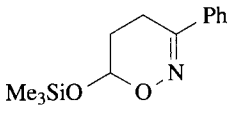
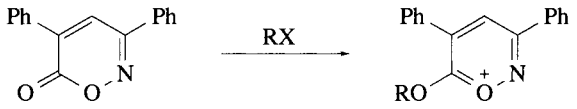


(11)

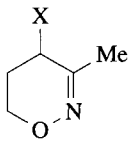
6.04.3.3 UV Spectra

The UV spectrum of the tetramethyloxazinium salt (**3**) (counterion $AlCl_4^-$) in 0.1 M acetic anhydride–$AlCl_3$ complex in dichloromethane shows a maximum absorption at 270 nm (log ε 3.92) ⟨85JA5722⟩. This has been ascribed to the π–π^* band and was taken as evidence that the cation is an aromatic ring system. UV spectra were earlier taken as evidence for the formation of aromatic oxazinium cations when 3,5-diphenyl-1,2-oxazinone (**12**) and related oxazinones are alkylated or protonated (Equation (1)) ⟨73ZOR1987, 74ZOR1513⟩. For example, the UV spectrum of compound (**12**) in methanol (λ_{max} 239 and 303 nm; log ε 4.20 and 4.10) is substantially different to that in concentrated sulfuric acid (λ_{max} 340 and 392 nm; log ε 4.02 and 4.26) ⟨73ZOR1987⟩.



(12) (RX = $Et_3O^+ BF_4^-$, Me_2SO_4, H_2SO_4) (1)

An unusual effect of halogen substitution has been observed in the UV spectra of 4-halooxazines (**13**) ⟨86IJ33⟩. The absorption maximum of compound (**6**) in hexane is at 212 nm (log ε 2.95); both the intensity and wavelength of the absorption maximum increases in compounds (**13**) in the sequence 234 (3.13) (X = F), 239 (3.43) (X = Cl), 247 (3.38) (X = Br) and 255 (3.55) (X = I). It has been suggested that the changes are due to the polarization of the substituent.



(**13**)

6.04.3.4 IR Spectra

The IR absorption which is of most diagnostic value is the C=N stretching frequency, which occurs at about 1590 cm^{-1} in a wide range of 5,6-dihydro-4*H*-1,2-oxazines ⟨83JCS(P1)1275, 83JCS(P1)1283, 88BCJ461, 90LA217⟩ and at a slightly lower frequency in 6*H*-1,2-oxazines ⟨91LA553, 92CB2243⟩. The C=C stretching frequency of 6*H*-1,2-oxazines appears at about 1660 cm^{-1}. The stretching frequency of the carbonyl group in a conjugated oxazinone, 5-methyl-3-phenyl-6*H*-1,2-oxazin-6-one, is 1730 cm^{-1} ⟨92CB2243⟩. Values between 1730 and 1760 cm^{-1} have been recorded for the C=O stretching frequency of 5,6-dihydro-4*H*-1,2-oxazin-6-ones ⟨91JCS(P1)3153⟩.

6.04.4 THERMODYNAMIC ASPECTS

6.04.4.1 Aromaticity of Conjugated Rings

The conclusion reached by the authors of the theoretical and experimental studies discussed in Section 6.04.2 is that the 1,2-oxazinium cation is a planar, aromatic cation, although the x-ray structure shown in Figure 2(b) reveals that the bond distances tend to alternate (for example, the C=N bond distance is not significantly greater than that in oximes and imines). The ring system is very susceptible to nucleophilic attack because of the high positive charge and for this reason only heavily substituted cations are so far available for experimental study.

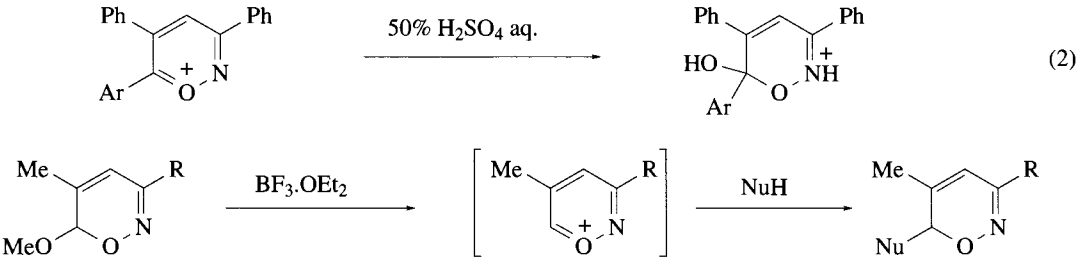
6.04.4.2 Conformations of Nonconjugated Rings

Experimental work carried out in the 1970s established that tetrahydro-1,2-oxazines adopt a chair conformation ⟨B-80MI 604-01⟩; in the 1990s, molecular mechanics calculations have been carried out which are in accord with the experimental results ⟨93MI 604-01⟩.

The evidence from ^1H NMR spectra of many 5,6-dihydro-4*H*-1,2-oxazines is that they adopt half-chair conformations (see Section 6.04.3.2) and this is supported by molecular mechanics calculations ⟨90LA217⟩. 3,6-Dihydro-2*H*-1,2-oxazines also adopt a half-chair conformation ⟨77JCS(P2)619⟩.

6.04.5 REACTIVITY OF FULLY CONJUGATED RINGS

Because of the highly electrophilic nature of the 1,2-oxazinium cation, virtually no studies have been carried out on isolated salts; no general chemistry has been developed comparable to that of the pyrylium salts. There are, however, some reports of reactions in which 1,2-oxazinium salts are likely to be transient intermediates. Early work on 3,5,6-triaryl-1,2-oxazinium cations indicated that on hydration they are converted into the corresponding 6-hydroxy-6*H*-oxazinium cations (Equation (2)) ⟨74ZOR1513⟩. A more general pattern of reactivity towards nucleophiles has been established by Reissig and his co-workers. They have shown that the 6-methoxy group of the 6*H*-oxazines (**14**) is readily replaced by nucleophiles in the presence of boron trifluoride etherate, and have suggested a mechanism (Scheme 1) involving the 1,2-oxazinium cations as intermediates ⟨89S908⟩. This is quite a general reaction in that a wide range of nucleophiles, including silyl enol ethers, allylsilanes and even activated aromatic compounds such as furan, can be used to give the corresponding 6-substituted oxazines in good yield. There are, however, some exceptions: when Lewis acid-catalyzed reactions of the oxazine (**14a**) were attempted with trimethylsilyl cyanide or with triethyl phosphite as nucleophiles, products of ring contraction were isolated ⟨92LA621⟩. It is suggested that these result from ring contraction of the oxazine (**14a**) instead of elimination to the oxazinium cation.



(2)

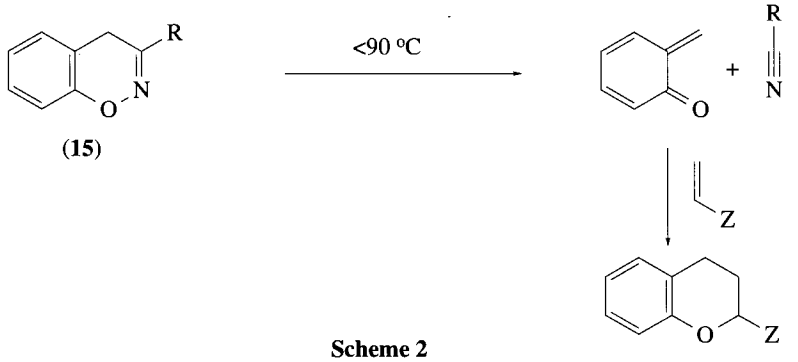
(**14**) **a**, R = Ph
b, R = CO_2Et
c, R = CF_3

Scheme 1

6.04.6 REACTIVITY OF NONCONJUGATED RINGS

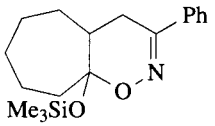
6.04.6.1 4*H*-1,2-Benzoxazines and 4*H*-1,2-Oxazines

It is known that several types of 1,2-oxazine undergo thermal pericyclic reactions in which the N—O bond is cleaved ⟨84CHEC-I(3)995⟩. A more recent reaction of this type is the thermal retro-Diels–Alder reaction of 3-substituted 4*H*-1,2-benzoxazines (**15**; R = Me, Ph). These compounds decompose on heating at, or below, 90 °C to give the corresponding nitrile and *o*-benzoquinone methide, which can be intercepted by alkenes (Scheme 2) ⟨90JA5341, 94TL7273⟩. A similar reaction of the bicyclic 5,6-dihydro-4*H*-1,2-oxazine (**16**) in the presence of traces of acid has been ascribed to the formation and decomposition of a transient 4*H*-1,2-oxazine (**17**) ⟨90LA469⟩. A monocyclic 4*H*-1,2-oxazine has been postulated as an intermediate in a related fragmentation ⟨95H(40)531⟩.

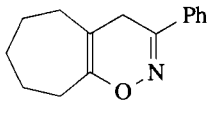


(**15**)

Scheme 2



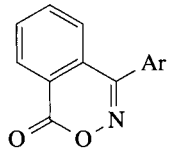
(16)



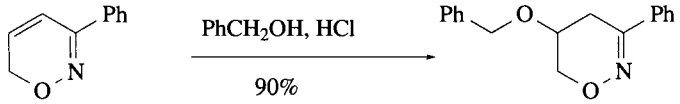
(17)

6.04.6.2 6*H*-1,2-Oxazines and 6*H*-1,2-Oxazin-6-ones

3-Phenyl-6*H*-1,2-oxazine undergoes HCl-catalyzed conjugate addition of benzyl alcohol (Equation (3)) ⟨91LA189⟩. This reaction is presumably initiatiated by protonation on nitrogen. Alkylation of the benzoxazinones (**18**) by triethyloxonium tetrafluoroborate also takes place on nitrogen ⟨82ZOR662, 85ZOR2445⟩. In the case of 6-methoxy-6*H*-1,2-oxazines (**14**) replacement of the 6-substituent by nucleophiles (Scheme 1) is initiated by attack of a Lewis acid on the methoxy group ⟨92LA621, 95H(40)531⟩; however, in other cases the Lewis acid can coordinate to the ring oxygen and this leads to cleavage of the ring ⟨92LA621⟩.



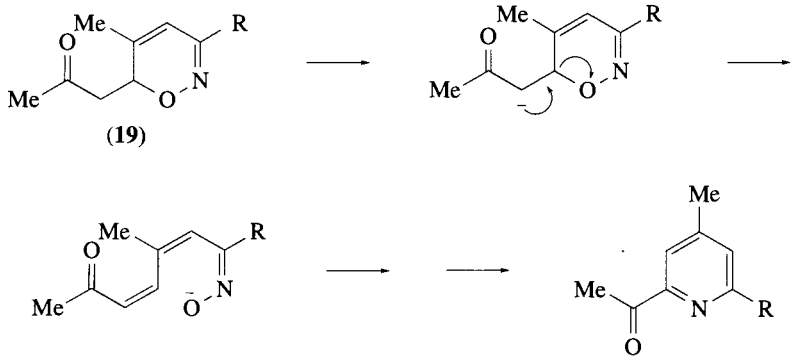
(18)



(3)

Other reactions of 6*H*-1,2-oxazines also result in ring cleavage. The oxazines (**19**) are converted by reaction with DBU into 2-acetylpyridines, the key step being eliminative cleavage of the ring (Scheme 3) ⟨87JCS(P1)2505⟩. A wide range of reductive cleavage reactions has also been observed (Scheme 4) ⟨92CB2243, 93LA1155⟩.

Benzoxazinones of type (**12**) have been subjected to electrochemical reduction in the presence of strychnine and other optically active bases to give optically active 2-(aminoalkyl)benzoic acids, but the optical yields are generally low ⟨82MI 604-01⟩.

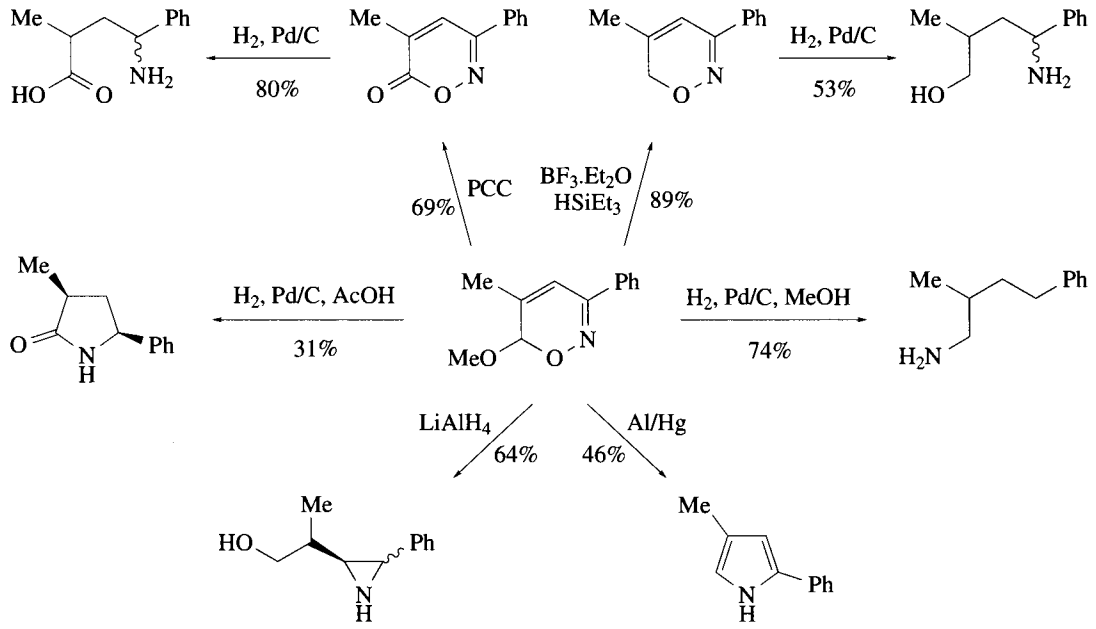


(19)

Scheme 3

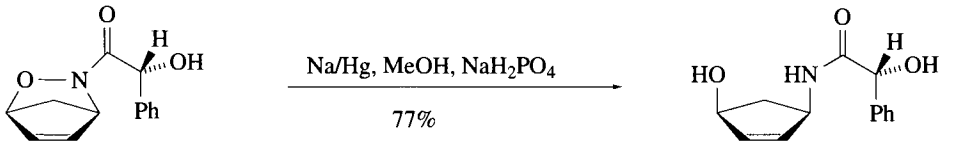
6.04.6.3 3,6-Dihydro-2*H*-1,2-oxazines

The most common reaction of 3,6-dihydro-2*H*-1,2-oxazines is reductive cleavage of the N—O bond, this being an important step in several synthetic schemes which are based on Diels–Alder



Scheme 4

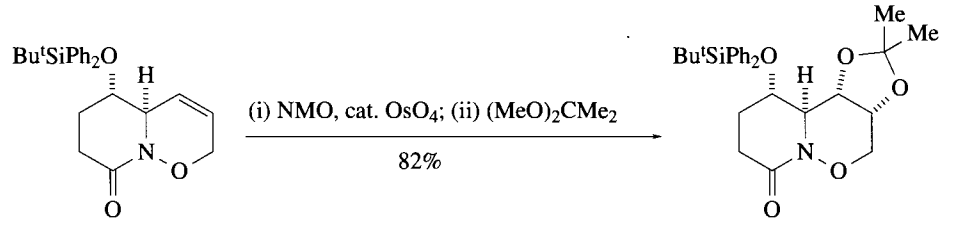
reactions of nitroso compounds ⟨94S1107⟩. The chemoselective cleavage of the N—O bond in the presence of the carbon–carbon double bond can be achieved by means of sodium amalgam if the N—O bond is activated. For example, the N—O bond of the oxazine (**20**) was selectively cleaved in good yield using sodium amalgam (Equation (4)) ⟨90TL1043⟩ and the method has been used with other chiral oxazines ⟨90TA363, 91JA5089⟩. A milder reagent, which is suitable only for activated N—O bonds, is aluminum amalgam ⟨79SC281⟩. For dihydrooxazines in which the N—O bond is not activated the bond can be cleaved using zinc and acetic acid ⟨90LA267, 91TL4325⟩. Reductive cleavage of the N—O bond by bacteria in the presence of mediators (methylviologen and hydrogen gas) has been recommended as a very mild chemoselective alternative ⟨87TL2677⟩.



(4)

(**20**)

Another synthetically useful reaction of 3,6-dihydro-1,2-oxazines is *cis* dihydroxylation of the carbon–carbon double bond ⟨88HCA822, 88HCA1642, 93JA6094, 93JOC6083, 93T2123⟩. It is often possible to achieve good diastereoselectivity, especially in bicyclic oxazines with an asymmetric ring junction, such as compound (**21**) (Equation (5)) ⟨93JOC6083⟩.

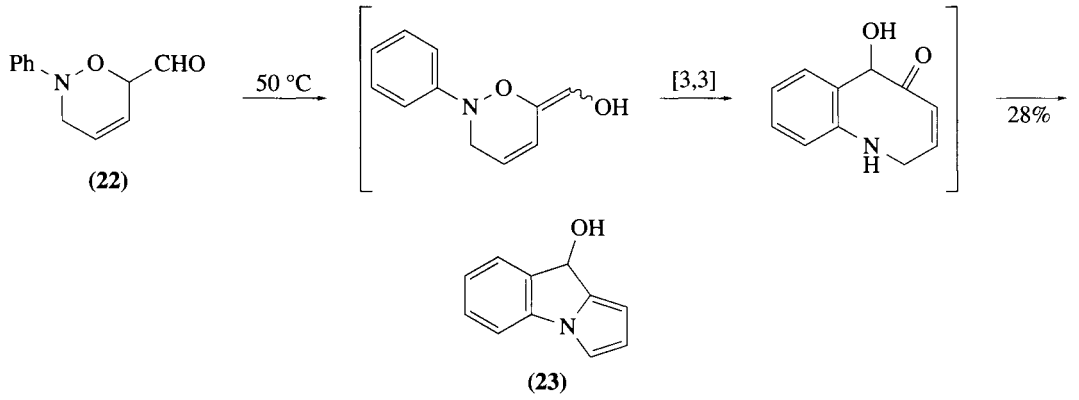


(5)

(**21**)

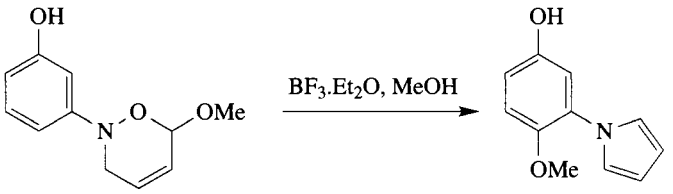
Some reactions of specific types of 3,6-dihydro-1,2-oxazines are worthy of note. The oxazine (**22**) and related compounds are converted into pyrroloindoles such as (**23**) when warmed in ethanol at 40–50 °C ⟨89HCA1199⟩. The mechanism shown in Scheme 5 was suggested by the authors, a key step

being a [3,3] sigmatropic rearrangement in which the N—O bond is cleaved. The pyrrole (**25**) was produced in moderate yield when the 6-methoxyoxazine (**24**) was treated with boron trifluoride etherate and methanol (Equation (6)) ⟨91JOC850⟩. In this reaction, which was investigated as a model for a step in a projected route to mitomycins, acid-catalyzed ring opening is accompanied by nucleophilic attack on the benzene ring at the position *ortho* to nitrogen by methanol. This unusual process is apparently initiated by the Lewis acid-catalyzed cleavage of the N—O bond, the developing positive charge on nitrogen being sufficient to activate an *ortho* carbon atom to nucleophilic attack. A different type of ring contraction occurs when *N*-Boc-3,6-dihydro-1,2-oxazines are treated with LDA: 2,5-dihydrofuranylamines are formed after cleavage of the N—O bond ⟨93TL961⟩.



(22) (23)

Scheme 5

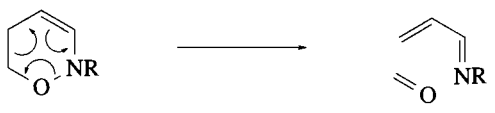


(6)

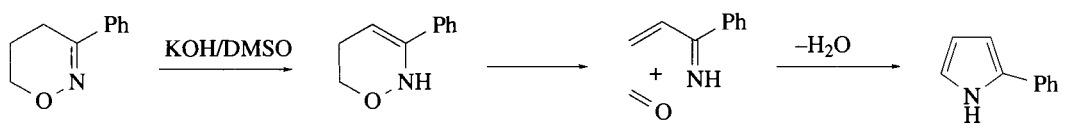
(24) (25)

6.04.6.4 5,6-Dihydro-2*H*-1,2-oxazines

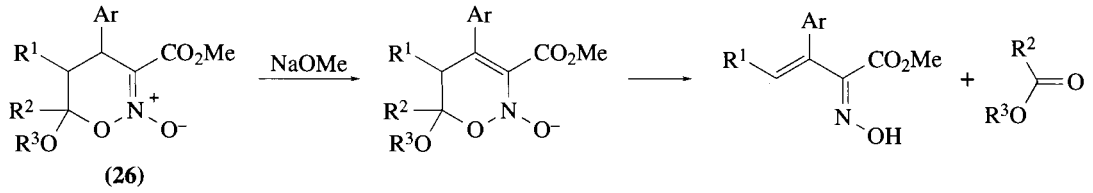
This ring system is known to be unstable: the N—O bond is cleaved by a retro-Diels–Alder process under very mild conditions (Equation (7)) ⟨84CHEC-I(3)995⟩. Further examples of this reaction have been reported ⟨83LA897⟩ and there are several other fragmentation reactions of 1,2-oxazines in which ring cleavage probably occurs in this way ⟨85HCA1998, 88BCJ461, 89TL3471⟩. The formation of 2-phenylpyrrole (44%) from 5,6-dihydro-3-phenyl-4*H*-1,2-oxazine and base can be explained by the sequence shown in Scheme 6 ⟨89TL3471⟩ and the cleavage of the oxazine *N*-oxides (**26**) is similar (Scheme 7) ⟨88BCJ461⟩.



(7)



Scheme 6



Scheme 7

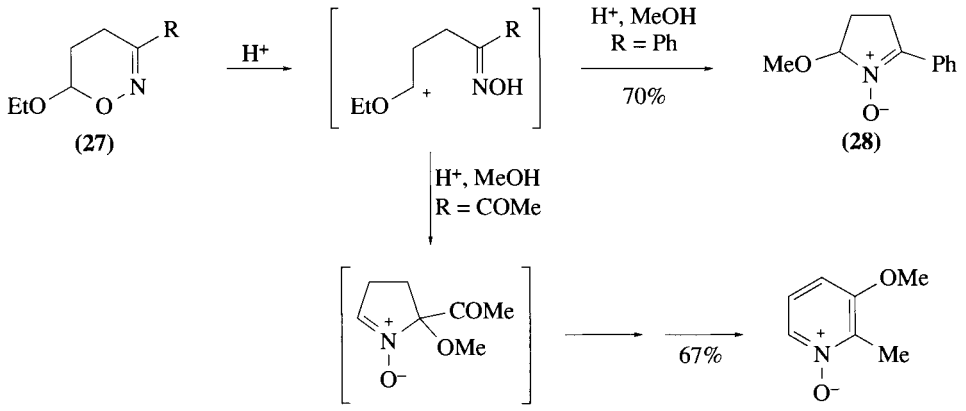
6.04.6.5 5,6-Dihydro-4*H*-1,2-oxazines

6.04.6.5.1 Unimolecular reactions

There are several thermal ring cleavage reactions of 4*H*-1,2-oxazines ⟨79CC1090, 81TL2557, 83JCS(P1)1479, 84CHEC-I(3)995⟩ but the type of ring opening varies according to the substituents. The 3-carboxylic acids decompose, with loss of carbon dioxide and opening of the ring, below 100°C ⟨79CC1090⟩. 4*H*-Oxazines which are formed by cycloaddition of nitrosoalkenes to 1-methyltetrahydrocarbazole undergo the reverse reaction when heated in xylene ⟨83JCS(P1)1479⟩ and 5,6-dihydro-6,6-dimethyloxazin-4-ones undergo ring contraction to pyrrolinone *N*-oxides under the same conditions ⟨81TL2557⟩. 5,6-Dihydro-3-phenyl-4*H*-1,2-oxazines also undergo photoinduced cleavage of the N—O bond ⟨81CL1561⟩.

6.04.6.5.2 Reactions with electrophiles

5,6-Dihydro-4*H*-1,2-oxazines which bear substituents at C-6 capable of stabilizing a positive charge are readily cleaved in acidic media. An example is the conversion of the dihydrooxazine (**27**; R = Ph) to the pyrroline *N*-oxide (**28**) by reaction with HCl in methanol (Scheme 8) ⟨85JCS(P1)2769⟩. The corresponding 3-acetyloxazine (**27**; R = COMe) is converted into 3-methoxy-2-methylpyridine *N*-oxide (**29**) under the same conditions. Ring contractions analogous to those of (**27**; R = Ph) to (**28**) also occur with 6-trimethylsilyloxy substituted oxazines ⟨90LA469⟩.

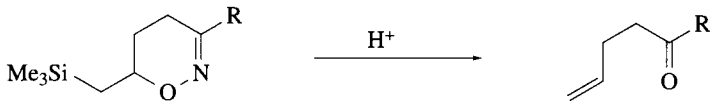


Scheme 8

Oxazines of the general structure (**29**) are also easily cleaved by acid catalysts (Equation (8)). The ability of the trimethylsilyl group to stabilize an adjacent cation undoubtedly promotes the ring opening reaction, which leads to the unsaturated ketones shown in Equation (8) for R = Ph ⟨87S77⟩ and R = CO_2Et ⟨86CC30⟩, or to the corresponding oxime for R = CF_3 ⟨92JOC339⟩. Oxazines (**30**) bearing both alkoxy and trimethylsilyloxy groups at C-6 are hydrolyzed by HCl to oxazinones (**31**) and to open chain oximes ⟨91JCS(P1)3153⟩. Dihydrooxazine *N*-oxides are easily cleaved to give carbonyl compounds by acids under Nef type conditions ⟨86HCA1971, 91TL5607⟩.

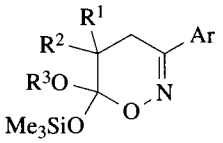
Simple 5,6-dihydro-4*H*-1,2-oxazines can be alkylated on nitrogen by reaction with triethyloxonium tetrafluoroborate to give the corresponding *N*-ethyloxazinium tetrafluoroborates (**32**) ⟨83LA897⟩; benzyl iodide has also been used as an alkylating agent ⟨91LA161⟩.

Several useful *C*-substitution reactions of 5,6-dihydro-4*H*-1,2-oxazines have been achieved after removal of a proton from C-4 with a strong base: these reactions are described in Section 6.04.7.1.



(8)

(29)



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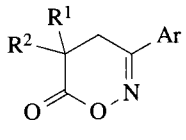

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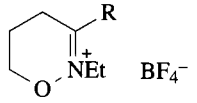
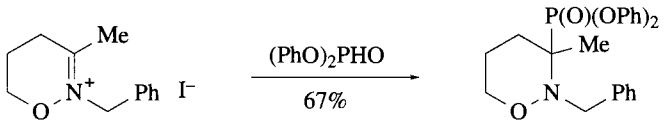


(32)

6.04.6.5.3 Reaction with nucleophiles

The 3-position of 5,6-dihydro-4*H*-1,2-oxazines is electrophilic and, when additional activation is present, a variety of nucleophiles can attack at this position. A 3-nitro substituent can be displaced by nucleophiles ⟨84CHEC-I(3)995⟩ and *N*-alkyloxazinium salts are attacked by nucleophiles including cyanide ⟨87JOC877⟩ and diphenyl hydrogen phosphite (Equation (9)) ⟨91LA161⟩. A halogen substituent at the 4-position of 5,6-dihydrooxazines can undergo S_N2 displacement by nucleophiles such as amines and azide, fluoride, and malonate anions ⟨86IJ33, 94CB685⟩.

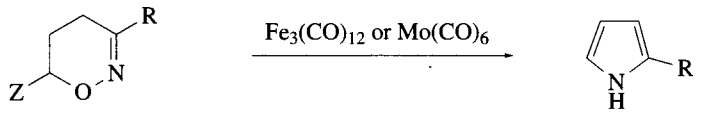


(9)

6.04.6.5.4 Reduction and reductive cleavage

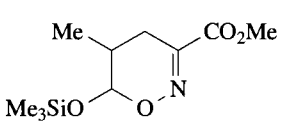
One of the most useful features of the chemistry of 5,6-dihydro-4*H*-1,2-oxazines is that, by careful control of the reagent and the conditions, they can be cleanly reduced to a variety of heterocyclic and open-chain compounds. A systematic survey of these reactions has been published ⟨90LA475⟩ and there are several other examples of synthetic applications.

Reductive deoxygenation of oxazines bearing alkoxy, trimethylsilyloxy, or dialkylamino substituents at the 6-position can be carried out using either $Fe_3(CO)_{12}$ ⟨90BCJ3595⟩ or $Mo(CO)_6$ ⟨90LA469⟩ and the reaction leads to the formation of pyrroles in good yield (Equation (10)). It is possible to prepare pyrroles in a "one-pot" procedure starting from α-halooximes and enamines, the dihydrooxazine being generated and then reduced by $Fe_3(CO)_{12}$ ⟨90BCJ3595⟩. The methodology has also been applied to the synthesis of the pheromone methyl 4-methylpyrrole-2-carboxylate (**34**) from the oxazine (**33**) ⟨92LA709⟩.



(10)

Z = OAlk, $OSiMe_3$, $N(Alk)_2$



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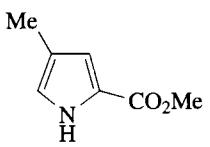
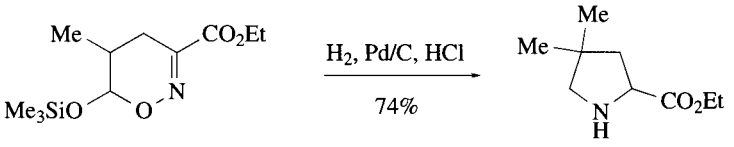


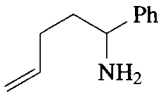
(34)

Dihydrooxazines of type (**33**) can be reduced to pyrrolidines by catalytic hydrogenation ⟨87JCR(S)180, 89S265, 90LA475, 95LA667⟩ or by reaction with aluminum amalgam. For example, the proline derivative (**35**) was prepared in good yield by catalytic hydrogenation (Equation (11)). Both aluminum amalgam and catalytic hydrogenation methods are effective for the reduction of 3-ethoxycarbonyl oxazines of this type, but the mechanisms may differ because the stereoselectivity of the reduction depends on the choice of reagent ⟨87JCR(S)180⟩. Sodium borohydride, LAH, and DIBAL-H have also been used for the reductive cleavage of several dihydrooxazines ⟨90LA475⟩; an example of a useful reductive cleavage is the formation of the benzylamine (**36**) (87%) by LAH reduction of the oxazine (**29**; R = Ph) ⟨87S77⟩. The C=N bond can be reduced without cleavage of the ring by reaction with sodium cyanoborohydride in acetic acid ⟨94S1050⟩.



(11)

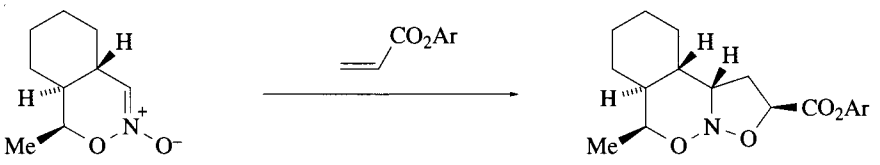
(35)



(36)

6.04.6.5.5 1,3-Dipolar cycloaddition reactions of 5,6-dihydro-4H-oxazine 2-oxides

5,6-Dihydro-4*H*-oxazine 2-oxides can be regarded as cyclic nitronic esters, and as such they can act as 1,3-dipoles in cycloaddition reactions with electron-deficient alkenes. The intermolecular reaction has been known since the 1960s and the reactions can show good regioselectivity and diastereoselectivity. For example, the structure of the adduct formed from 4-bromophenyl acrylate and an oxazine *N*-oxide (Equation (12)) was established as (**37**) by x-ray crystallography ⟨86JA1306, 86HCA1971⟩. Intramolecular 1,3-dipolar cycloadditions of this type have also been studied ⟨93JOC1853⟩.



(12)

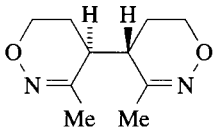
(37) (Ar = 4-BrC$_6$H$_4$)

6.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

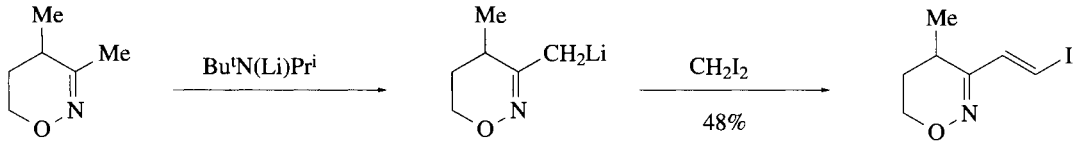
6.04.7.1 Ring Hydrogen Atoms

Some useful reactions of 5,6-dihydro-4*H*-1,2-oxazines are based on their selective deprotonation followed by reaction of the carbanions with electrophiles. The deprotonation reactions of 3-methyl-5,6-dihydro-4*H*-1,2-oxazine (**6**) have been investigated by Shatzmiller and co-workers. They showed that it was possible to selectively deprotonate the oxazine either at the 3-methyl group (by using lithium *t*-butylisopropylamide) or at the 4-position (by using butyllithium in a nonpolar solvent) ⟨81JA5916⟩. Deprotonation at the 4-position is achieved cleanly and rapidly at −65 °C with butyllithium in hexane and THF ⟨91LA381⟩. The 4-lithio species can be methylated with iodomethane

⟨81JA5916, 91LA381⟩ and halogenated by reaction with chlorine, bromine, or iodine ⟨86IJ33⟩. When the halogens are rapidly added to a solution of the lithium salt, the dimer (**38**) is formed as the major product ⟨91LA851⟩. The 3-lithiomethyl compound (**39**) reacts with diiodomethane to give the 3-(2-iodoethylidene) derivative (**40**) (Scheme 9); a radical mechanism has been suggested for this process ⟨91LA381⟩.



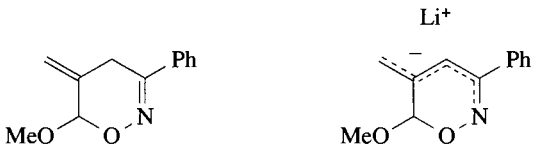
(**38**)



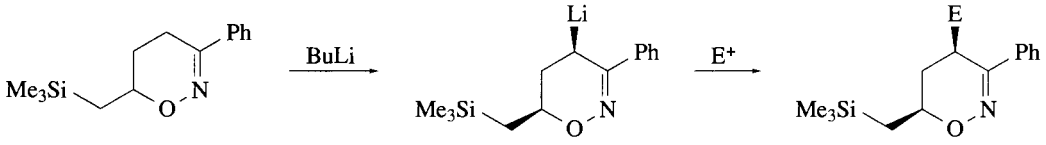
(**39**) (**40**)

Scheme 9

The scope of the chemistry of lithiated 1,2-oxazines has been greatly extended by Reissig and his co-workers ⟨91CB115, 91CB2279, 95LA667⟩. They have explored reactions with a wide range of electrophiles and with several 5,6-dihydrooxazines. The lithiation of the oxazine (**29**; R = Ph) is, unexpectedly, highly diastereoselective, the proton at C-4 which is *cis* to the 6-substituent being removed exclusively ⟨91CB115⟩. The selectivity is ascribed to coordination of butyllithium to the ring oxygen atom. Reaction of the intermediate with electrophiles then takes place mainly with retention of configuration (Scheme 10). The delocalized carbanion (**42**) formed by deprotonation of the oxazine (**41**) reacts with electrophiles either at C-4 (iodoalkanes) or at the terminus of the methylene group (deuterium oxide, carbonyl compounds, and dimethyl disulfide) ⟨91CB2279⟩.



(**41**) (**42**)



Scheme 10

An example of a deprotonation at C-4 by a much weaker base (DBU) is the eliminative rearrangement of the oxazines (**43**) (Equation (13)) ⟨87JCS(P1)2505⟩. It is also possible to substitute the 4-

position of dihydrooxazines directly (and diastereoselctively) by radical bromination (NBS and dibenzoyl peroxide) ⟨94CB685⟩.

(43) (13)

6.04.7.2 Other Substituents

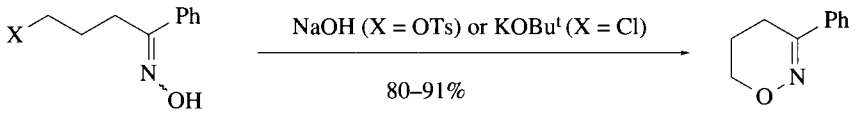
Nucleophilic displacement reactions of halogen substituents at C-4, and various reactions of substituents attached to C-6, have been described in Section 6.04.6. The 3-ethoxycarbonyl substituent, rather than the C=N bond, of ethyl 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate is reduced by sodium borohydride ⟨79JOC2487⟩.

6.04.8 RING SYNTHESES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

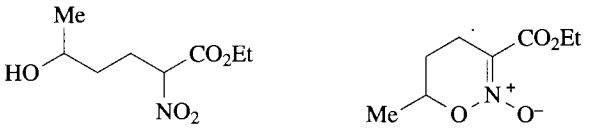
6.04.8.1 Intramolecular Cyclization

A standard synthetic approach to 1,2-oxazines of various types is the cyclization of an oxime bearing a side chain with an appropriate electrophilic centre. In most cases the oxime is isolated and cyclized in a separate step, but in some the oxime is made *in situ*, usually from the corresponding carbonyl compound. All such methods are described together in this section.

An example of this type of synthesis is the preparation of 3-phenyl-5,6-dihydro-1,2-oxazine shown in (Equation (14)) ⟨81CL1561, 89TL3471⟩. A disadvantage of the route, which applies to all types of oxime cyclizations, is that cyclic nitrones can also be produced if the nitrogen atom of the oxime acts as the nucleophile. The ratio of products seems in some cases to be determined more by the cyclization conditions than by the stereochemistry of the starting oxime ⟨92CC1537⟩. The same approach has been applied to the synthesis of oxazine *N*-oxides: for example, compound (**45**) was prepared in high yield by cyclization of the nitroalcohol (**44**) under Mitsunobu conditions (dead and triphenylphosphine) ⟨92TL6723⟩.



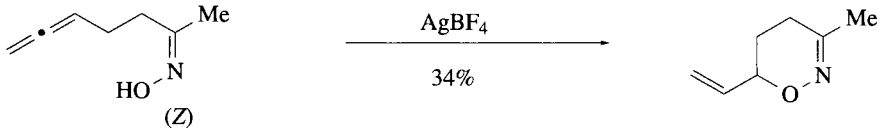
(X = OTs, Cl) (14)



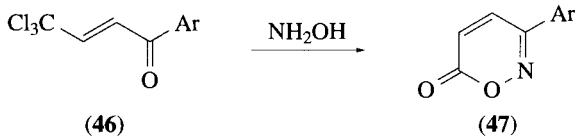
(44) (45)

1,2-Oxazines can also be synthesized by intramolecular addition of oximes to carbon–carbon double bonds. These reactions are not general: nitrones and other products can be formed in competition with oxazines. There are examples of conjugate addition to activated alkenes ⟨81TL2557, 91CPB2830⟩ and of acid or Lewis acid-catalyzed addition to simple alkenes ⟨88TL6805⟩ or allenes ⟨89JCS(P1)2415⟩. 3-Methyl-6-vinyl-5,6-dihydro-4*H*-1,2-oxazine was isolated in moderate yield from

a cyclization of this type (Equation (15)) ⟨89JCS(P1)2415⟩. Cyclization of 1,4-diketone monooximes was described previously as a route to 1,2-oxazines ⟨84CHEC-I(3)995⟩ and there are several more examples ⟨85JFC(28)139, 91ZN(B)809, 92JHC255⟩. A variant is the preparation of 1,2-oxazin-6-ones (**47**) by reaction of the unsaturated ketones (**46**) with hydroxylamine (Equation (16)) ⟨80ZC19⟩.



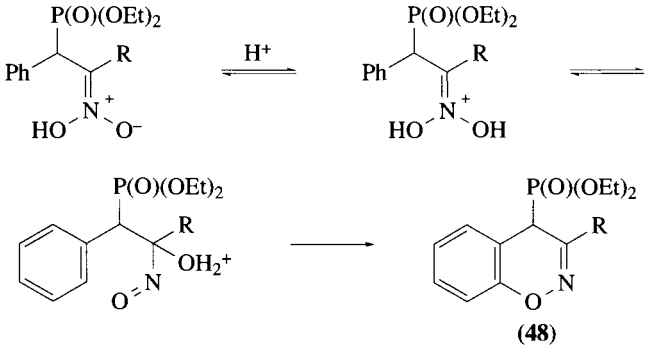
(15)



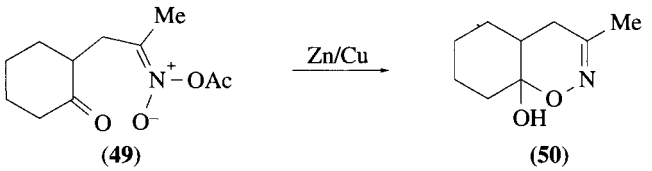
(46) (47)

(16)

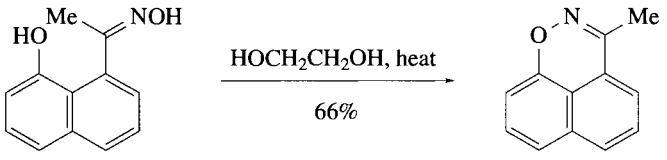
β-Nitrostyrenes have been used as precursors of benzoxazines. Conjugate addition of diethyl phosphite to the compounds $PhCH{=}C(R)NO_2$ (R = Me, Ph) gives nitronic acids which are cyclized to the benzoxazines (**48**) in moderate yield when added to 85% sulfuric acid ⟨92JOC6508⟩. A mechanism has been proposed for the reaction involving cyclization of an intermediate nitroso alcohol (Scheme 11). Other examples ⟨86JHC759, 90T7569⟩ of the cyclization of nitronic acid derivatives to 1,2-oxazines include the preparation of the 6-hydroxy-5,6-dihydro-4*H*-1,2-oxazine (**50**) (50%) by reduction of the nitronic anhydride (**49**) with zinc–copper couple (Equation (17)) ⟨90T7569⟩. Derivatives of the 1,2-benzoxazin-4-one and the naphth[1,8-*de*]-1,2-oxazine ring systems have been prepared by cyclization of oximes onto aromatic rings bearing hydroxy or methoxy groups ⟨86MI 604-01, 90AHC(51)1⟩. The process is exemplified by the preparation of 3-methylnaphth[1,8-*de*]-1,2-oxazine by heating the oxime of 8-acetyl-1-naphthol in ethylene glycol (Equation (18)) ⟨71JCS(C)747⟩.



Scheme 11



(17)



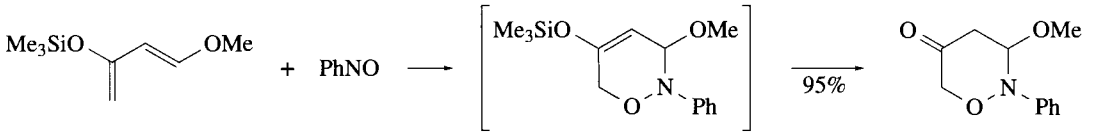
(18)

6.04.8.2 Combination of 4-Atom and 2-Atom Components

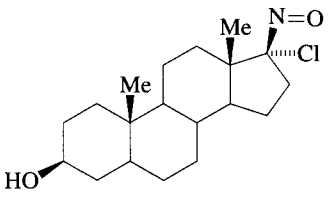
6.04.8.2.1 [4 + 2] Cycloaddition leading to 3,6-dihydro-2H-1,2-oxazines

The well-established Diels–Alder reaction between nitroso compounds and conjugated dienes has continued to be refined over the last decade. The most important advances have been in the development of chiral nitroso dienophiles useful for asymmetric synthesis and in the exploitation of the intramolecular Diels–Alder reaction in synthesis ⟨94S1107⟩.

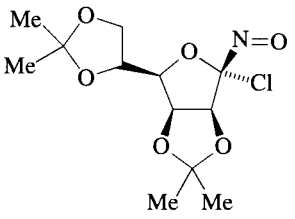
Several cycloaddition reactions of nitrosobenzenes to acyclic, electron-rich dienes have been described ⟨91JOC850, 93JA6094⟩; an example is illustrated in Scheme 12. α-Chloronitrosoalkanes are particularly useful dienophiles because the cycloadducts are easily cleaved by acid to the *N*-unsubstituted 1,2-oxazines. Two chiral α-chloronitroso compounds which have been used in Diels–Alder reactions are compounds (**51**) ⟨84TL5377⟩ and (**52**) ⟨86LA1360, 90LA267, 93LA261, 94TL5653⟩. The latter, which is derived from D-mannose, has been shown to add to several cyclic and acyclic dienes with high regioselectivity and diastereoselectivity.



Scheme 12



(**51**)

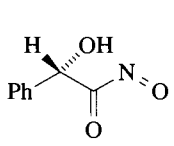


(**52**)

The more reactive acylnitroso compounds, which were originally introduced by Kirby ⟨77CSR1⟩, are now widely used in both intermolecular and intramolecular Diels–Alder reactions. These compounds are not isolable but are generated *in situ* by oxidation of the corresponding hydroxamic acids. Sodium periodate or tetraalkylammonium periodates are usually used as the oxidants but other reagents, such as oxalyl chloride/DMSO ⟨92TL3583⟩ can be used. A new route to acylnitroso compounds has also been discovered: rhodium(II)-catalyzed decomposition of the diazo compound $CF_3C(N_2)NO_2$ gave CF_3CONO which was intercepted by cycloaddition to 9,10-dimethylanthracene ⟨88TL5719⟩.

The chiral compounds (**53**)–(**58**) have been used as dienophiles in order to assess their use in asymmetric synthesis. Chiral induction is more difficult than for chiral α-chloronitroso compounds because of the greater separation between the nitroso group and the chiral substituent. It is for this reason that compounds such as (**53**), derived from mandelic acid and other hydroxy acids, have been studied, on the basis that intramolecular hydrogen bonding might improve the rigidity of the dienophile ⟨91JA5089, 93JCS(P1)1397⟩. This prediction is partly borne out by the higher diastereoselectivities achieved with dienophiles bearing a free hydroxy group compared with the analogous methyl ethers. Several dienophiles bearing chiral pyrrolidine substituents, including (**54**) ⟨90TA363⟩, (**55**) ⟨91TA1209⟩, and (**56**) ⟨92HCA109⟩ have been generated; high diastereoselectivities were achieved in the cycloadditions with compounds (**54**) and (**55**), which possess C_2 symmetry. In these, and other cycloadditions of acylnitroso compounds, the major products are formed by *endo* addition of the dienes to nitroso compounds in the *cisoid* conformation (Figure 3). The more bulky acylnitroso compounds (**57**) ⟨91TA1173⟩ and (**58**) ⟨92TL3583⟩ also react with simple dienes to give adducts in high yield and with excellent diastereoselectivity. The alternative approach, the addition of an achiral acylnitroso compound to a chiral diene, has also been explored ⟨93T2123⟩.

Several intramolecular Diels–Alder reactions of acylnitroso compounds have been investigated, particularly as steps in target synthesis ⟨88JA2341, 89JOC4088, 91TL4325, 93JOC6083⟩. When the tethering chain contains an asymmetric carbon centre, the cycloaddition results in the formation of diastereoisomers. In the case of the reaction shown in (Equation (19)), the selectivity was much higher when the reaction was carried out in water rather than in an organic solvent ⟨94TL595⟩.



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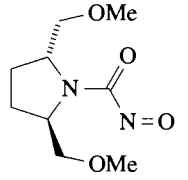

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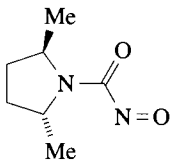

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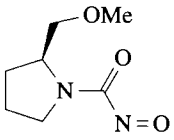

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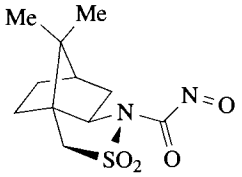

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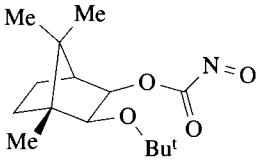

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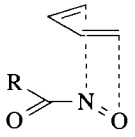
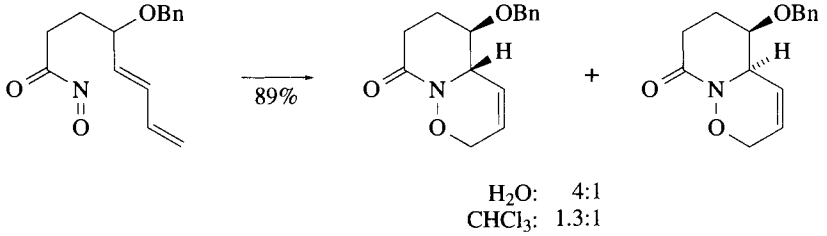


Figure 3 Preferred transition state (*endo* approach to the *cis*-acylnitroso compound) in Diels–Alder reactions with dienes.



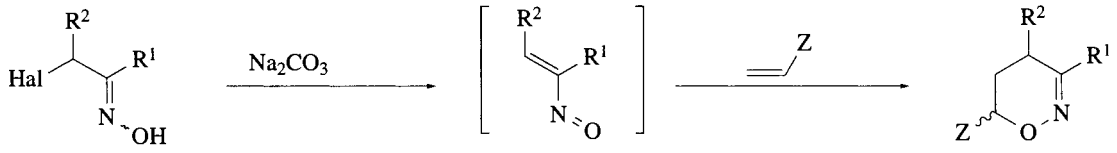
(19)

H_2O: 4:1
$CHCl_3$: 1.3:1

6.04.8.2.2 [4 + 2] Cycloaddition leading to 5,6-dihydro-4H-1,2-oxazines

Conjugated nitrosoalkenes are unlike other nitroso compounds in that they act as dienes, rather than as dienophiles, in the Diels–Alder reaction. Even with conjugated dienes such as cyclopentadiene, nitrosoalkenes normally act as the 4π components in such reactions ⟨83CSR53⟩. This Diels–Alder reaction is now the best general method for the preparation of 5,6-dihydro-4*H*-1,2-oxazines.

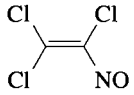
The nitrosoalkenes which are used in the reaction are transient species. They are usually generated *in situ* from an α-haloketoxime, by reaction with a heterogeneous base such as sodium carbonate in an organic solvent (dichloromethane, diethyl ether, or methyl *t*-butyl ether) at room temperature. In the presence of simple enol ethers and other electron-rich alkenes, dihydrooxazines are formed in good yield (Scheme 13). Nitrosoalkenes which have been generated and used in this way are listed in Table 2. A longer-lived nitrosoalkene, 1,2,2-trichloronitrosoethylene (**59**), also reacts with electron-rich alkenes to give dihydrooxazines ⟨87BSB51⟩. The nitrosoalkenes (**61**; R = H, Me) have been generated from the *O*-silyloximes (**60**) by reaction with fluoride, and products of intramolecular cycloaddition have been isolated (Equation (20)) ⟨84JOC4741⟩.



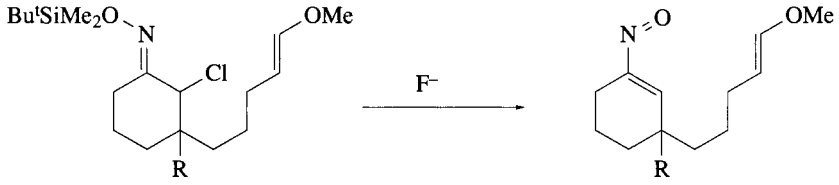
Scheme 13

Table 2 3-Substituted 5,6-dihydro-4*H*-1,2-oxazines by Diels–Alder addition of nitrosoalkenes to alkenes (Scheme 13).

R^1	R^2	*Ref.*
Ph	H	83JCS(P1)1275, 90CB2403, 90LA217, 91JCS(P1)3153
4-$O_2NC_6H_4$	H	83JCS(P1)1275
1-Adamantyl	H	84CPB1433
Bu^t	H	92MIP9209587
CF_3	H	92JOC339
CHO	H	83JCS(P1)1283
COMe	H	83JCS(P1)1283
$CH{=}CHCO_2Me$	H	92LA709
CO_2Me	H	92LA709
CO_2Et	H	83JCS(P1)1283, 86CC30, 90LA217
o-C_6H_4—CH_2—CH_2		90CB2403



(59)



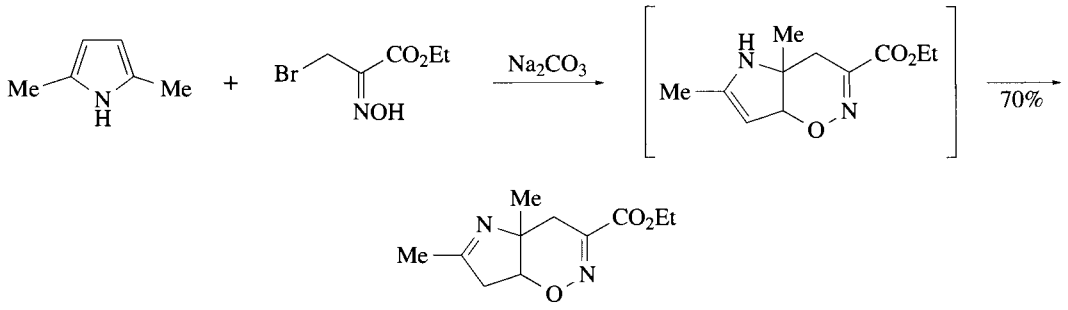
(20)

(60) (61)

Cycloaddition reactions of α-nitrosostyrene (Scheme 13; R^1 = Ph, R^2 = H) have been investigated the most. Earlier examples of these reactions have been reviewed briefly ⟨83CSR53⟩. The intermediate adds to conjugated alkenes in moderate to good yield, but not to simple alkenes ⟨83JCS(P1)1275⟩. Enol ethers give dihydrooxazines in good yield ⟨83JCS(P1)1479⟩; dihydrooxazines can also be obtained by cycloaddition to electron-rich heterocycles such as furans ⟨79JCS(P1)249⟩ and 3-substituted indoles ⟨83JCS(P1)1479⟩. In publications from the late 1980s and early 1990s examples have been published of dihydrooxazine synthesis by cycloaddition of α-nitrosostyrene to silyl enol ethers ⟨87S77, 90BCJ3595, 90CB2403, 90LA217, 90S26, 92LA709⟩, ketene trimethylsilyl acetals ⟨91JCS(P1)3153⟩, allylsilanes ⟨86CC30, 87S77, 90LA217⟩, chiral enol ethers ⟨90SL514, 92AG(E)1033⟩, enamines ⟨90BCJ3595⟩, methoxyallene ⟨91LA553⟩, and the enolate anion of ethyl cyanoacetate ⟨87AP(320)776⟩.

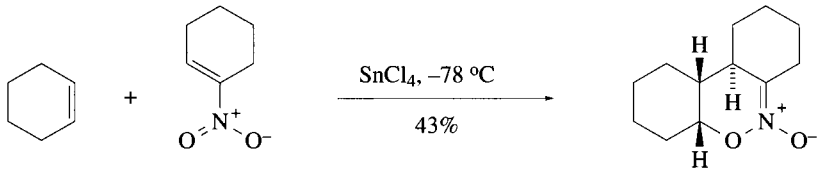
With other nitrosoalkenes there is a general trend towards greater reactivity as the α-substituent becomes more electron withdrawing in character. This is particularly so for 3-nitrosobut-3-en-2-one (Scheme 13; R^1 = COMe, R^2 = H) ⟨83JCS(P1)1283⟩ and for 1,1,1-trifluoro-2-nitrosopropene (R^1 = CF_3, R^2 = H) ⟨92JOC339⟩, but even the introduction of a *p*-nitro substituent into α-nitrosostyrene significantly improves the efficiency of the cycloaddition process ⟨83JCS(P1)1275⟩. For example, in contrast to α-nitrosostyrene, both 3-nitrosobut-3-en-2-one and 4-nitro-α-nitrosostyrene react with simple alkenes to produce dihydrooxazines in moderate yield.

The outcome of extensive investigations of the mechanism of these reactions is a consensus that they are concerted Diels–Alder reactions with inverse electron demand ⟨83JCS(P1)1275, 90CB2403, 90LA217, 91LA553, 92JOC339, 93JCS(P1)1391⟩. The cycloaddition is stereospecific with respect to the alkene component and it is usually regioselective, the more electron-rich substituent of the alkene becoming the 6-substituent of the dihydrooxazine as shown in Scheme 13. With indoles, the terminal carbon of the nitrosoalkene invariably attacks at C-3, and with furans and pyrroles, at C-2, even if these positions are blocked by substituents: this is shown in the reaction of 2,5-dimethylpyrrole with ethyl 2-nitrosopropenoate (Scheme 14) ⟨93JCS(P1)1391⟩. The cycloaddition is, however, subject to steric effects and these influence the diastereoselectivity of the process ⟨90CB2403⟩. A striking example of selectivity is provided by the reaction of α-nitrosostyrene with silyl enol ethers as (*E*)/(*Z*) mixtures: the reactivity is so much greater for the (*E*) isomers that the procedure can be used as a practicable means of separation of the (*E*) and (*Z*) isomers ⟨90S26⟩.



Scheme 14

There are two methods of preparing dihydrooxazines which are closely related to the cycloaddition of nitrosoalkenes; both were known before the 1980s but have been subject to more recent investigation. The first is the cycloaddition of nitroalkenes to alkenes. Denmark and co-workers have described both intermolecular ⟨86HCA1971, 93JOC1853, 93JOC1859⟩ and intramolecular ⟨86JA1306⟩ Lewis acid-catalyzed versions of the reaction. 1-Nitrocyclohexene reacts with cyclohexene and other cycloalkenes in the presence of tin(IV) chloride at −78 °C ⟨86HCA1971⟩. The major product of the reaction with cyclohexene is the oxazine 2-oxide (**62**) (Equation (21)) although isomeric compounds are also isolated in low yield. A stepwise mechanism with a zwitterionic intermediate has been suggested for the reaction.



(21)

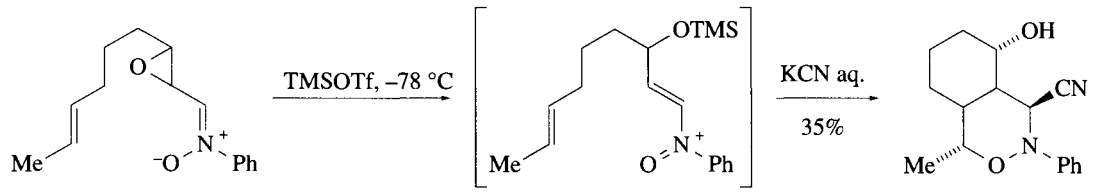
(**62**)

Cycloaddition reactions of nitroalkenes to enamines, enolate anions, and silyl enol ethers are well established. Reactions with simple enol ethers have also been described ⟨88BCJ461, 93JOC1853⟩. Chiral enol ethers have been used as partners in the cycloaddition process ⟨93JOC1859, 94JOC4576, 94JOC5672, 95JOC3221⟩. 2-Nitro-1,3-dienes have also been added to enol ethers ⟨91TL5607⟩ and to enamines (including a chiral enamine) ⟨92TL5641⟩ to give dihydrooxazine 2-oxides.

The second method related to nitrosoalkene cycloaddition is the reaction of vinylnitrosonium cations with alkenes. Several intramolecular cycloaddition reactions of this type have been described ⟨87JOC877⟩; one example is illustrated in Scheme 15.

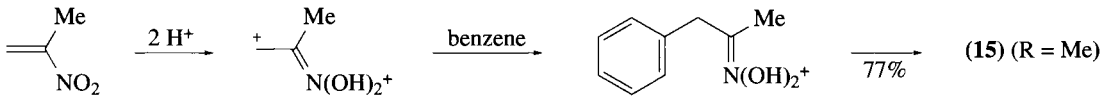
6.04.8.2.3 Other syntheses involving 4-atom and 2-atom combinations

Methods in which hydroxylamine acts as the 2-atom component have been described in Section 6.04.8.1. The reactions of nitroalkenes with enolate anions and with electron-rich alkenes (see Section 6.04.8.2.2) can also be regarded as examples of this class since some at least of these processes



Scheme 15

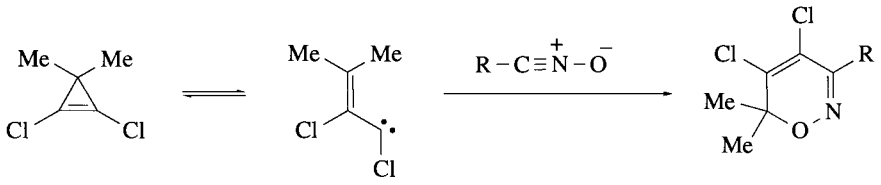
take place through detectable intermediates. There are few new methods in this category, but the synthesis of the benzoxazines (**15**) is one of this type. Compound (**15**; R = Me) was prepared in 77% yield by the reaction of 2-nitropropene with TFSA and benzene ⟨90T7539⟩. Other nitroalkenes react similarly. A mechanism was proposed in which the nitroalkene is doubly protonated and the dication is then intercepted by benzene (Scheme 16).



Scheme 16

6.04.8.3 Combination of Two 3-Atom Components

An unusual synthesis of 4,5-dichloro-6,6-dimethyl-6*H*-1,2-oxazines is provided by the reaction of nitrile oxides with 1,2-dichloro-3,3-dimethylcyclopropene ⟨93JCS(P1)2507⟩. This reaction apparently involves an acyclic vinylcarbene isomer of the cyclopropene (Scheme 17).

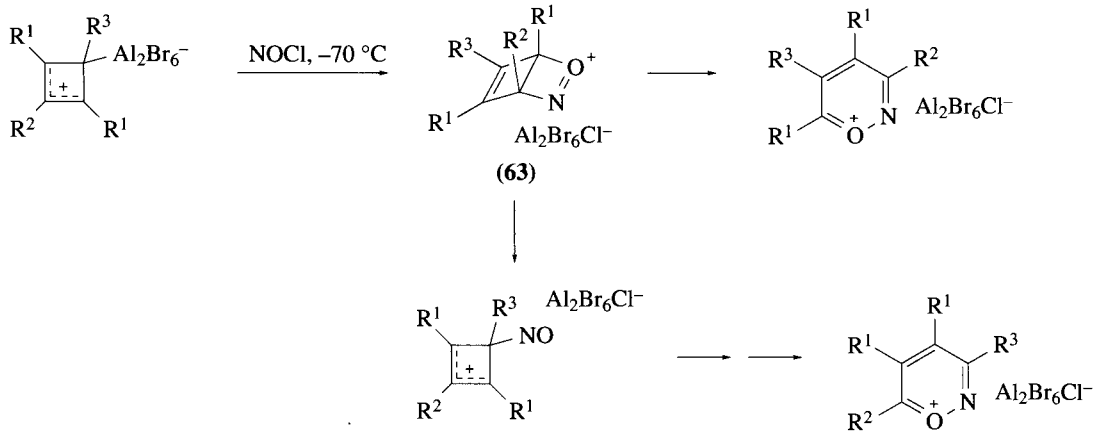


Scheme 17

6.04.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

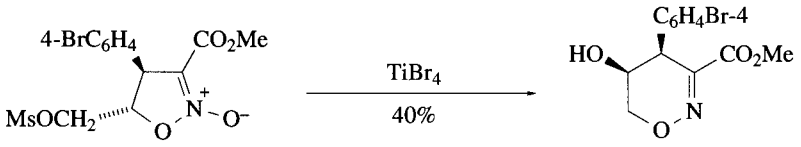
The most important synthesis in this class is that leading to the oxazinium salts such as (**3**). These compounds are formed by the reaction of nitrosyl chloride with dialuminum hexahalide σ complexes of alkyl-substituted cyclobutadienes. A mechanism has been proposed involving the formation and rearrangement of a bicyclic cation (**63**) and, since isomeric oxazinium salts are formed in some cases, further rearrangement (Scheme 18), possibly through a benzvalene type structure ⟨85JA5722, 86PAC89⟩. Calculations have been carried out on the energies of the various structures possible for a nitrosocyclobutenyl cation ⟨87ZOR717⟩.

A 5,6-dihydro-4*H*-1,2-oxazine has also been formed by the titanium bromide-catalyzed ring expansion of an isoxazoline *N*-oxide (Equation (22)) ⟨92CPB1921⟩.



(63)

Scheme 18



(22)

6.04.10 IMPORTANT COMPOUNDS AND APPLICATIONS

The main application of 1,2-oxazine derivatives has been as intermediates in synthesis. As described in Section 6.04.6, the weak N—O bond allows oxazines having a defined substitution pattern to be constructed and then cleaved. Examples include the asymmetric synthesis of mannostatin A ⟨91JA5089⟩ and of amino sugars ⟨90LA267, 94TL5653⟩ as potentially useful glycosidase enzyme inhibitors, and the target synthesis of piperidine and indolizidine alkaloids ⟨93JOC6083, 94TL595⟩. In the 5,6-dihydro-4*H*-1,2-oxazine series, the reductive cleavage reaction has been used in the synthesis of lipophilic analogues of proline; these compounds are useful as inhibitors of angiotensin converting enzyme ⟨89S265⟩. The acid-catalyzed and reductive cleavage of 6-silyloxy substituted dihydrooxazines has been used in the target synthesis of precursors to the macrolide pyrenophorin and of (*Z*)-jasmone ⟨92LA709⟩. 3-*t*-Butyl-5,6-dihydrooxazines have been prepared as potential herbicides ⟨92MIP9209587⟩.

Denmark and co-workers have developed a versatile route to pyrrolizidine alkaloids and other natural products which is based on successive [4 + 2] and [3 + 2] cycloaddition of nitroalkenes to alkenes followed by N—O bond cleavage ⟨94JOC5672, 94PAC2041, 95JOC3205, 95JOC3574, 96CRV137⟩.

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6.05
1,3-Oxazines and their Benzo Derivatives

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6.05.1 INTRODUCTION

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), oxazines and thiazines were considered together and, because the entire history of the compounds was under review, the

depth of coverage of the various types was necessarily limited. Here the 1,3-oxazines and their derivatives are given individual treatment and the shorter timescale allows more analysis and discussion of the reactions and syntheses involved.

Several informative reviews have been published since the 1970s, and include a survey by Steglich *et al.* ⟨86G361⟩ of the uses of 1,3-oxazin-6-ones as versatile intermediates in heterocyclic syntheses and a more general summary of the chemistry and uses of oxazinones covering the period 1976–1985 by Zakhs *et al.* ⟨87KGS1443⟩. More recent work is reviewed by Yamamoto and Morita ⟨92YG887⟩.

With a few notable exceptions, new information relating to the reactions of 1,3-oxazines and benzoxazines is restricted, but two aspects of their chemistry stand out as changes of emphasis. First, more has been made of the use of suitably functionalized 1,3-oxazines to provide acyclic compounds, which are difficult to obtain by other routes, and also their application in asymmetric synthesis. Secondly, there has been an upsurge in the range of methods which can be used to synthesize 1,3-oxazines and, in some measure, this has been in response to the first demand. Additionally, from a commercial point of view there has also been considerable interest in spiro-1,3-oxazines as photochromic agents ⟨90BCJ267, 90MI 605-01, 91YGK392, 92JHC1709⟩; however, in the main, this activity lies outside the scope of this chapter.

As in CHEC-I, the reactions of 1,3-oxazines will be considered before the synthetic approaches to them and, for ease of presentation, in each of the sections and subsections the compounds will be discussed in the order of decreasing number of double bonds *in* the ring. Thus, 1,3-oxazines will take precedence over dihydro-1,3-oxazines, and the latter will be considered before tetrahydro-1,3-oxazines. Furthermore, wherever possible, the summaries will begin with 2*H*- and end with 6*H*-types.

Even though there are obvious difficulties with tautomerism, which can sometimes interrelate the above rankings, carbonyl, thiocarbonyl, and imino derivatives of each type will normally be dealt with last.

6.05.2 PARENT RING SYSTEMS AND NOMENCLATURE

The nomenclature used in this chapter follows IUPAC rules as laid down in the *IUPAC Nomenclature of Organic Compounds*, 1979 edition. Thus the parent compounds and the dihydro-1,3-oxazines have the names indicated in Figure 1, where the locant for *H* (the *indicated hydrogen*) is always given the lowest number.

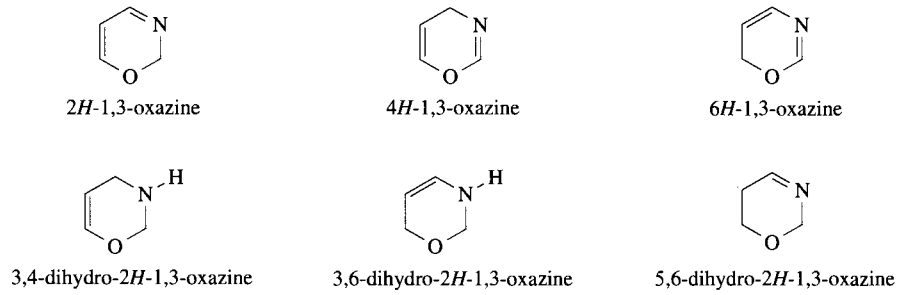
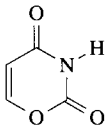


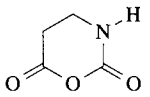
Figure 1 Nomenclature for simple 1,3-oxazines and their dihydro derivatives.

The major difficulty with the naming of 1,3-oxazines relates to oxazinones, oxazinediones, and similar compounds. Unfortunately, a variety of nonIUPAC methods have been employed to describe these compounds, which are at best confusing and at worst incorrect! The adoption of the IUPAC rule relating to ketones (C-315) provides an unambiguous solution: thus, for simple 1,3-oxazinones the carbonyl group is the primary functional group, and the name should end in -one. The maximum number of double bonds is inserted and any hydrogen that remains is denoted with a locant which should have the lowest possible number. For example, compound (**1**) has the name 1,3-oxazine-2,4(3*H*)-dione, (**2**) is called 4,5-dihydro-1,3-oxazine-2,6(3*H*)-dione, and (**3**) is 4,5-dihydro-6-thioxo-1,3-oxazin-2(3*H*)-one. In the last case, the thione group has a lower ranking than the carbonyl function and thus takes the prefix thioxo (Figure 2).



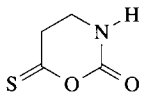
(1)

1,3-oxazine-2,4(3*H*)-dione



(2)

4,5-dihydro-1,3-oxazine-2,6(3*H*)-dione



(3)

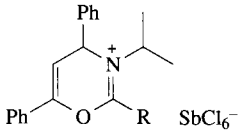
4,5-dihydro-6-thioxo-1,3-oxazine-2(3*H*)-one

Figure 2 Examples of oxazinones.

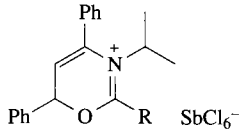
6.05.3 EXPERIMENTAL STRUCTURAL METHODS

6.05.3.1 Tautomerism, Spectra, and Crystallography

1,3-Oxazines and their derivatives present a wide range of tautomeric possibilities and prototropic rearrangements could, in principle, interconvert many of the different forms. However, both 4*H*- or 6*H*-1,3-oxazinium salts are known, and there is no evidence that these interconvert. These isomers can be easily differentiated, since in the ^{13}C NMR spectra a resonance at ca. 60 ppm (CD_3CN) is diagnostic of a saturated C-4 position, while a signal between 78 and 82 ppm characterizes saturation at C-6. For 3-*i*-propyl-4*H*-1,3-oxazinium hexachloroantimonate salts (**4**; R = Me or Ph) the ^1H NMR resonances of the diastereotopic methyl groups show a chemical shift difference of about 0.5 ppm, whereas for the 6*H*-isomers (**5**; R = Me or Ph) difference is typically less than 0.1 ppm ⟨90S763⟩.

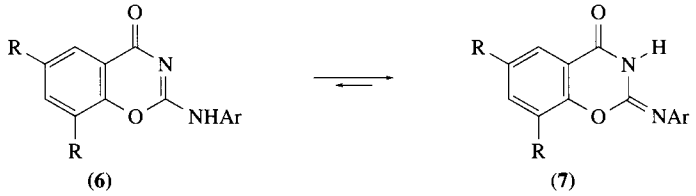


(4)



(5)

Similarly, in the absence of carbonyl and/or other unsaturated groups to increase the acidity of α-protons, equilibration of 1,3-oxazines is not generally observed. Where there is an unsaturated group, however, the situation is less secure. For example, the balance between 2-arylamino-1,3-benzoxazin-4-ones (**6**) and 2-arylimino-3*H*-1,3-benzoxazin-4-ones (**7**) seems to lie in favor of the latter, at least in solution (Scheme 1) ⟨91JHC133⟩.

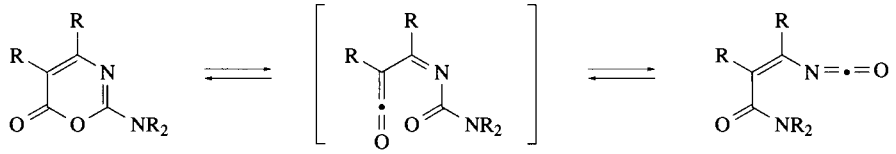


(6) (7)

Scheme 1

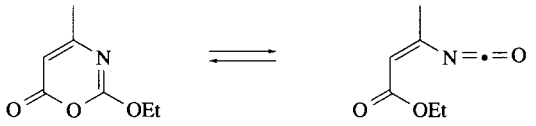
Evidence has been advanced to show that 2-(*N*,*N*-dialkylamino)-1,3-oxazin-6-ones (**8**) exist in equilibrium with vinyl isocyanates (**9**), probably through the intermediacy of an iminoketene and a [1,5]-shift of the amino substituent (Scheme 2). There is support for this since 2-ethoxy-4-methyl-1,3-oxazin-6-one (**10**) is known to exist in equilibrium with ethyl 3-isocyanatopropenoate (**11**); presumably here too a [1,5]-shift of the ethoxy group occurs (Scheme 3) ⟨72AG(E)128⟩. Indeed, many of the chemical reactions of 2-amino-1,3-oxazin-6-ones with either electrophiles or with nucleophiles can be rationalized on the basis that vinyl isocyanates are the reactive species (see Sections 6.05.2.4 and 6.05.6.2.3(iv)) ⟨87JOC3426⟩. Since vinyl isocyanates do not equilibrate with 6-amino-1,3-oxazin-2-ones, certain compounds previously claimed to be 6-amino-1,3-oxazin-2-ones are most likely to be 2-amino-1,3-oxazin-6-ones. For example, 2-amino-1,3-oxazin-6-ones, rather than 6-amino-1,3-oxazin-2-ones, may have been the substrates upon which vacuum-flash pyrolyses were conducted ⟨81JCS(P1)2878⟩.

2-Amino-1,3-oxazin-6-ones can be isolated as crystalline compounds and, for example, the structures of 2-amino-5-cyano-4-methylthio-1,3-oxazin-6-one (**12**) ⟨85HCA1155⟩, 5-ethoxycarbonyl-2-(*N*,*N*-dimethylamino)-4-phenyl-1,3-oxazin-6-one (**13**), and 4-ethoxycarbonyl-2-(*N*,*N*-dimethyl-



(8) (9)

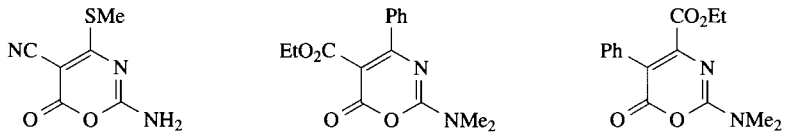
Scheme 2



(10) (11)

Scheme 3

amino)-5-phenyl-1,3-oxazin-6-one (**14**) ⟨88AX(C)1256⟩ have been established by x-ray crystallography.

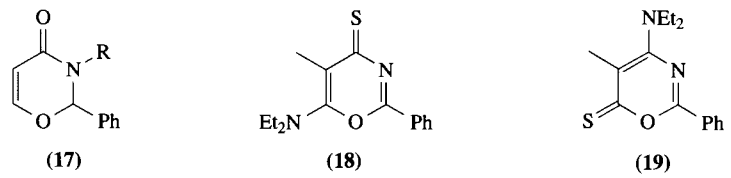


(12) (13) (14)

2-Amino-4*H*-3,1-benzoxazines (**15**) normally exist in this form rather than as the 2-imino tautomers (**16**), but the iminocyanide (**16**; R = CN) is known. In the ^{1}H NMR spectrum of (**16**; R = CN), there is a significant downfield shift of the NH resonance (11.5 ppm) compared to that of the *N*-alkylamino compounds (**15**; R = alkyl) where this signal is found at 7.1–7.5 ppm ⟨89T829⟩.

(15) (16)

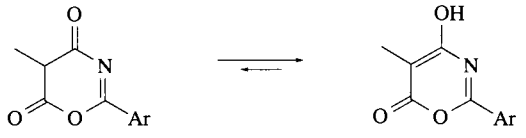
The IR spectra of 3-alkyl-2-phenyl-2*H*-1,3-oxazin-4-ones (**17**) exhibit a carbonyl band at 1650–1665 cm^{-1}, and in the ^{1}H NMR spectra the H-5 resonance appears as a singlet at about 5.3 ppm, with that of H-2 at 6.1–6.6 ppm ⟨87CPB1860⟩. Both 1,3-oxazine-4-thiones and 1,3-oxazine-6-thiones are known and the crystal structures of several representative compounds including 6-(*N*,*N*-diethylamino)-5-methyl-2-phenyl-1,3-oxazine-4-thione (**18**) and 4-(*N*,*N*-diethylamino)-5-methyl-2-phenyl-1,3-oxazine-6-thione (**19**) have been determined by x-ray diffraction ⟨86JCR(S)40⟩.



(17) (18) (19)

Physical methods show that, in either tetrahydrofuran or in dimethyl sulfoxide, 2-aryl-1,3-oxazine-4,6(5*H*)-diones (**20**) are less favored than the corresponding 4-hydroxy-1,3-oxazin-6-ones (**21**) ⟨87KGS386⟩. Similarly, 4-aryl-5-hydroxy-1,3-oxazin-6(6*H*)-ones (**23**) exist as such, rather than as the corresponding 5,6-diones (**22**). Thus their IR spectra (Nujol) show hydroxyl (3300–3350 cm^{-1}) and carbonyl bands (1690–1720 cm^{-1}), as well as imine bands (1610–1630 cm^{-1}). In the ^{1}H NMR spectra ($CDCl_3$) the hydroxyl proton signal occurs at 5.8–6.5 ppm. Confirmation of the constitution of these compounds is provided by a single crystal diffraction study of the 2,4-diphenyl derivative (**23**;

R = Ph), which shows evidence of 6-carbonyl and 5-hydroxyl groups bonded to an almost planar heterocyclic ring ⟨91H(32)1181⟩.



(20) (21)

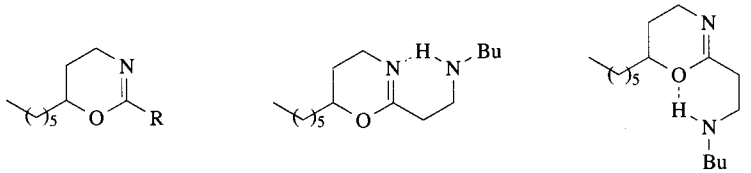
(22) (23)

Although originally described as 5-acyl-3-alkyl-2-phenyltetrahydro-1,3-oxazine-4,6-diones (**24**) ⟨87CPB1860⟩, the ^{1}H NMR spectra of these compounds show a very low field singlet at 16–17 ppm, typical of the chemical shift of the proton resonance of a chelated enol. In addition, only one carbonyl band is exhibited (or is quoted in the paper) at 1710–1735 cm^{-1} in the IR spectra. This data indicates that these compounds are better formulated as 5-hydroxmethylene-2*H*-1,3-oxazine-2,6-diones (**25**). However, it should be noted that the crystal structure of 2,3-bis(4-methoxyphenyl)-2-(4-nitrophenyl)-1,3-oxazine-4,6-dione (**26**) has been determined, and it shows the dione tautomer to occur in the solid phase. In this form a boat conformation is adopted in which C-2 and C-5 are shifted 0.0578 nm and 0.0348 nm, respectively, from the plane of the ring. In addition, the planes through O(1)—N(3)—C(4) and C(4)—C(5)—C(6) make angles of 41.9° and 26.0°, respectively, to the plane of the heterocyclic ring, and the 4-nitrophenyl group assumes a pseudoaxial position ⟨93T6575⟩.

(24) (25)

(**26**) X = C_6H_4-4-OMe; Y = C_6H_4-4-NO_2

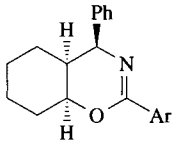
The ^{1}H NMR spectra ($CDCl_3$) of 6-hexyl-5,6-dihydro-4*H*-1,3-oxazines (**27**; R = H, Ph, or vinyl) exhibit the signal of 4-H_2 at 3.25–3.65 ppm, and 6-H at 4.05–4.22 ppm. In the case of (**27**; R = H) 2-H resonates at ca. 7.0 ppm ⟨93T3907⟩. 2-[2-(*N*-Butylamino)ethyl)-6-hexyl-5,6-dihydro-4*H*-1,3-oxazines exist as two isomers (**28**) and (**29**), the ratio of which varies slightly with a change in solvent. It is assumed that these two isomers are due to different NH hydrogen bonding loci: to oxygen in one isomer, and to nitrogen in the other.

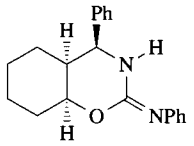


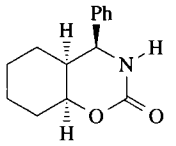
(27) (28) (29)

Typically the IR spectra of *cis*-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazines (**30**) show a C=N band at 1652–1658 cm^{-1}, but for the 2-imino analogue (**31**) the exocyclic C=N band is observed at

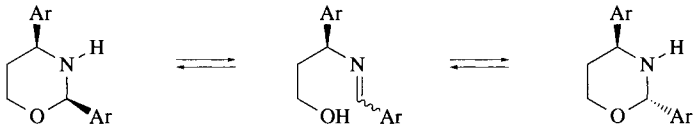
a slightly higher wavenumber (1666 cm^{-1}). The carbonyl band of the corresponding 2-ones (**32**) occurs at 1705–1717 cm^{-1} ⟨90T6859⟩.

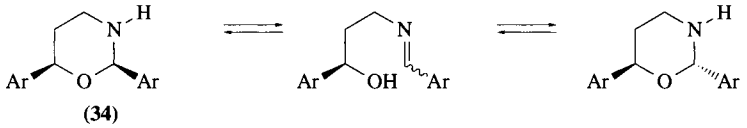

(**30**)


(**31**)


(**32**)

2,4-Diarylperhydro-1,3-oxazines (**33**) and their 2,6-diaryl isomers (**34**) exhibit ring-chain tautomerism and in deuteriochloroform solution exist as a mixture of two ring forms (biased in favor of the tautomer in which the aryl groups are equatorial) and one acyclic isomer (Scheme 4) ⟨87T1863⟩. Whereas aryl groups at C-4 and C-6 fail to exert an observable electronic influence on the ratio of the *cis* and *trans* ring tautomers of either 2,4- or 2,6-diaryl-perhydro-1,3-oxazines, aryl groups at C-2 have a discernible effect. This effect can be discussed in terms of the equation $\log k = \rho\sigma^+ + \log K_0$, where $K = [\text{ring}]/[\text{chain}]$, σ^+ is the Hammett–Brown constant of the aryl substituent, and ρ is characteristic of the oxazine system (the last value depends on the solvent and the temperature, thus for 1,3-oxazines in $CDCl_3$ and at room temperature it is 0.76 ± 0.04) ⟨93T2115⟩.


(**33**)


(**34**)

Scheme 4

6.05.3.2 Conformational Aspects

The heterocyclic ring of 3,4-dihydro-2*H*-1,3-benzoxazines (**35**) can adopt several half-chair conformations (see Figure 3). For 4-methyl derivatives (**35**; $R^1 = H$, $R^2 = Me$) there is little difference between the energies of the isomers in which the C-4 methyl group is α- or β-orientated, and the compound exists as a 54 : 46 mixture of 4-eq′ and 4-ax′ forms. However, when present, an *N*-alkyl group occupies a pseudoaxial position and this alters the balance. Thus, 3,4-dihydro-3,4-dimethyl-2*H*-benzoxazine (**35**; $R^1 = R^2 = Me$) is an 8 : 92 mixture of the 4-eq′ and 4-ax′ isomers ⟨88JCS(P2)461⟩.

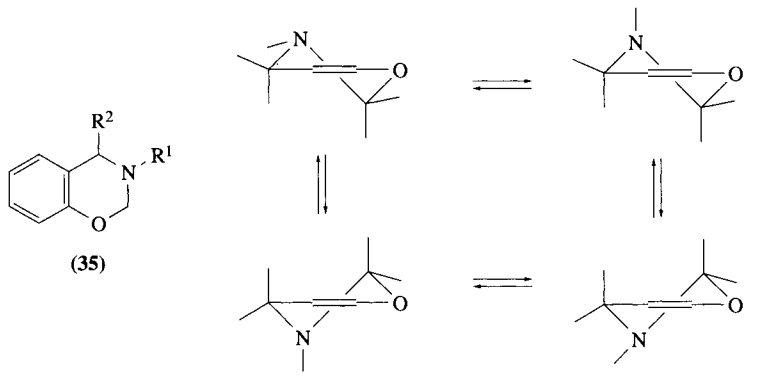
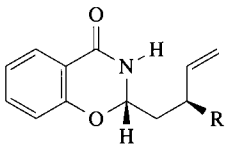
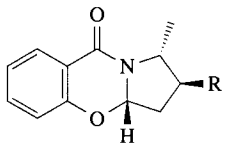

(**35**)

Figure 3 Possible conformations of substituted dihydrobenzoxazines.

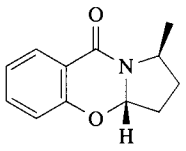
There is a surprisingly large stereodirecting effect for an alkoxy substituent (ca. 4 kcal mol^{-1}) in the amidomercuriation cyclization of the 2-(3-butenyl)-1,3-benzoxazin-4-ones (**36**). Thus, there is competition between the stereoselective effect of the aminal center and that of the allylic alkoxy group. For example, reaction of (**36**; R = OBn) with mercury(II) acetate and trifluoroacetate, followed by reduction with lithium borohydride, affords only the tricyclic compound (**37**; R = OBn), whereas similar treatment of (**36**; R = H) gives a mixture of the cycloadducts (**37**; R = H) and (**38**) in the ratio 1 : 12.4, respectively ⟨90TL6765⟩.



(**36**)



(**37**)



(**38**)

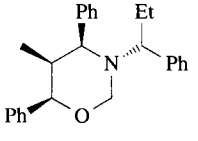
That perhydro-1,3-oxazines adopt a chair conformation is well established ⟨80JCS(P2)1739, 86MRC(24)480, 92T4979⟩. However, for *N*-alkyl derivatives the alkyl group could be sited equatorially or axially, the two conformers being related by *N*-inversion (Scheme 5). At normal temperatures this process is very rapid and the barrier to inversion is undetectable by ^{13}C NMR.

(**39**) (**40**)

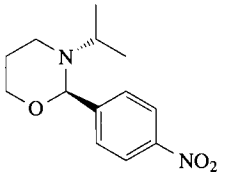
Scheme 5

Thus, five sharp singlets are observed in the fully decoupled spectrum of 3-methylperhydro-1,3-oxazine. If the sample is cooled to ca. 170 K all the resonances in the spectrum collapse. On further cooling to below 143 K clearly resolved signals due to the presence of two forms are noted, one being more abundant than the other ⟨80JCS(P2)1739⟩. In the spectrum of the favored isomer (**39**) the signals of the *N*-methyl carbon and C-5 appear at higher field than the corresponding signals of the less abundant isomer (**40**) (Scheme 5). These upfield shifts are explained by invoking the *γ-gauche* effect, which indicate that, in the preferred isomer, the *N*—Me bond is axial ($\Delta_{G\,138°}$(eq⇌ax) = −0.16 kcal mol^{-1}. This contradicts earlier conclusions based upon dipole moments and ^1H NMR spectra ⟨71JCS(B)1300, 77JCS(P2)818⟩, but fulfills the requirements of the "generalized anomeric effect" ⟨71PAC527, 72AG(E)739⟩. Thus, in (**39**) the lone pair electrons on the *N*-methyl group are antiperiplanar to the C(−1)—O bond thereby facilitating overlap between the nonbonded electrons and σ^*. This stabilizing effect is unavailable to the alternative conformer (**40**) ⟨B-94MI 605-01⟩.

Whereas the axial preference seems to be general for oxazines with small *N*-alkyl substituents, there are exceptions when larger groups are present and when the ring is multiply substituted. For example, an x-ray analysis of crystalline 5-methyl-4,6-diphenyl-3-(1-phenylpropyl)perhydro-1,3-oxazine (**41**) shows the heterocycle to be a chair with the *N*-substituent and the phenyl groups at C-4 and C-6 all in equatorial sites ⟨91S387⟩. Similarly, 3-isopropyl-2-(4-nitrophenyl)perhydro-1,3-oxazine (**42**) assumes a chair form, in which the *N*-isopropyl and 2-aryl groups are both accommodated in equatorial positions. Here, the dihedral angle between the plane of the oxazine ring and that of the aryl ring is 86° ⟨91AX(C)1994⟩.



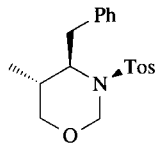
(**41**)



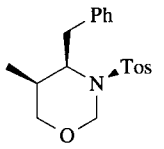
(**42**)

On a cautionary note, it might have been expected that the ^1H NMR spectrum of the *anti*-4-benzylperhydro-5-methyl-3-tosyl-1,3-oxazine (**43**) would show a larger coupling constant $J_{4,5}$ than that of the *syn* isomer (**44**). The coupling constants are different ($J_{4,5}$ 0.5 Hz and 4.6 Hz), but x-ray

diffraction studies reveal that the compound with the larger coupling constant is (**44**). In both isomers the *N*-tosyl group is located in a pseudoaxial site ⟨90JOC1359⟩.



(**43**)

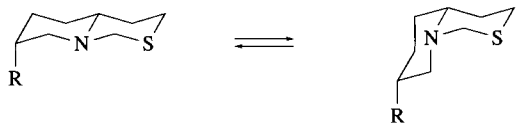


(**44**)

Proton and ^{13}C NMR techniques are much used in deducing preferred conformations of azabicyclic molecules. In particular, upfield ^{13}C NMR shifts due to γ_{ax} effects are extremely valuable as indicators of *cis*-fused systems. Such data provides support for classic conformational analyses based upon nonbonding interactions and anomeric effects ⟨67JACS6612, B-72MI 605-01⟩. Thus, it is argued that 4-methylperhydropyrido[1,3-*c*]oxazine only exists as the *trans* fused conformer (**45**; R = Me), because in the *cis* form (**46**; R = Me) severe interactions occur between the axial methyl and the C-8 methylene groups (Scheme 6). This is confirmed by NMR studies, which also show that, at 203 K, ($CDCl_3$—$CFCl_3$) the parent heterocycle exists as 97 : 3 mixture of the *trans* (**45**; R = H) and *cis* forms (**46**; R = H) ⟨B-92MI 605-02⟩. Greater flexibility is allowed in the thia analogue, which at 198 K (CS_2—THF) exists as a 64 : 36 mixture of the *trans* (**47**; R = H) and *cis* (**48**; R = H) conformers. When there is an axially bonded ethyl group at C-5, only the *cis* epimer (**48**; R = Et) is observed (Scheme 7), but for the corresponding fused oxazine the preference for the *cis* conformer (**49**) is reduced to 70% (Scheme 8) ⟨82OMR(20)239, B-92MI 605-02⟩.

(**45**) (**46**)

Scheme 6



(**47**) (**48**)

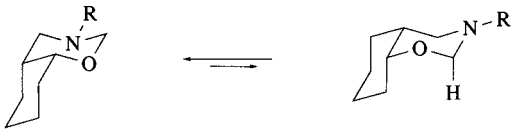
Scheme 7

(**49**)

Scheme 8

Numerous condensed 5,6-bridged 1,3-oxazines have been investigated. For *trans*-fused perhydro-1,3-benzoxazines, only one conformer (chair–chair) is accessible; however, for the *cis*-fused isomers, where the carbocycle is a chair, two nonenantiomeric assemblies (**50**) and (**51**) are possible (Scheme 9). In practice, (**50**) is strongly favored in which the oxygen atom of the oxazine ring is bonded axially to the cyclohexane unit ⟨73OMR(5)159, 80OMR(14)204, 84OMR(22)527, 89CB651⟩. A similar preference has been noted for the *N*-inside *cis*-decahydroquinolines (**52**), rather than the *N*-outside conformers (**53**) (Scheme 10), and in the absence of bulky substituents this is explained by reduced 1,3-*syn*-axial interactions ⟨73JCS(P2)842, 77JOC51, B-94MI 605-01⟩. A similar argument may apply to the oxazines; thus, the *O*-inside isomer (**50**) is energetically more favored, since an adjacent methylene group in

the carbocycle is 1,3-synaxial to a lone pair of electrons, rather than to a hydrogen atom as it is in the *O*-outside tautomer (**51**).



(**50**) *O*-inside (**51**) *O*-outside

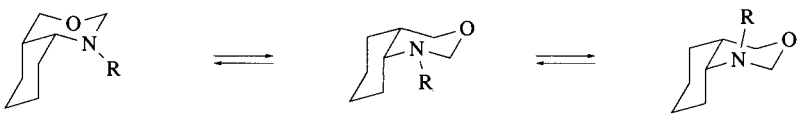
Scheme 9

(**52**) *N*-inside (**53**) *N*-outside

Scheme 10

Despite this, there is often a delicate balance between the generalized anomeric effect and non-bonded interactions, and conclusions established for one series of compounds may not necessarily hold for another. For example, *cis*-perhydro-3,1-benzoxazine (**54**; R = H), and *cis*-decahydroquinoline (**52**; R = H) both favor *N*-inside conformations, and this is also the case for *N*-methyl-*cis*-decahydroquinoline (**52**; R = Me). However, *N*-methyl-*cis*-perhydro-3,1-benzoxazine adopts the alternative *N*-outside form (**55**; R = Me). Destabilization of the *N*-inside conformer (**54**; R = Me) is considered to be due to an unfavorable anomeric effect and a gauche propylamine interaction, but there is a further subtlety to be considered, i.e. the orientation of the *N*-methyl group. The dihedral angle between the heteroatom lone pair electrons and the C—H bonds of the NCH_2O group has an important effect upon the coupling constant J_{gem}. The more negative values are observed for those conformers in which the nitrogen lone pair bisects the angle made by the adjacent CH_2 bonds, while larger values are associated with those isomers in which the lone pair and an adjacent CH bond are antiperiplanar (Figure 4) ⟨65JCP(42)1339, 66T355, 68T1997, 68T4423, 84AHC(36)1, 90AHC(49)193⟩. On this basis, the observed geminal coupling constant of *N*-methyl-*cis*-perhydro-3,1-benzoxazine ($J = -8.8$ Hz) does not tally with that expected for the NMe_{eq} conformer (**55**; R = Me) alone. To explain the coupling constant it is proposed that the NMe_{eq} form is accompanied by a substantial amount of the NMe_{ax} conformer (**56**; R = Me) (Scheme 11) ⟨B-92MI 605-02⟩.

Figure 4 Conformations of geminal protons and *N*-lone pair electrons.

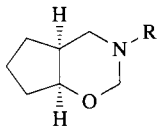


(**54**) (**55**) (**56**)

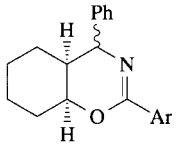
Scheme 11

Conformational analyses and NMR spectroscopy can also be used to study the equilibria of *cis*-5,6-fused cyclopenta-1,3-oxazines (**57**) and *cis*-2,4-diaryl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazines (**58**). In both types only conformers which have the oxygen atom in an axial orientation are observed ⟨90T6859⟩.

In the case of *cis*-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazines, the heterocycle is flattened out compared to the perhydro-1,3-benzoxazines, and there can be no 1,3-synaxial interaction of a hydrogen atom at C-2 with the carbocycle. The "axial" preference is insensitive to the configuration

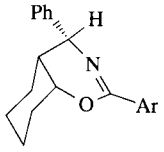


(57)



(58)

at C-4 and both diastereomers (**59**) and (**60**) are observed. An inspection of models suggests that this arises because either an α- or a β-substituent at C-4 in the alternative "equatorial" forms (**61**) and (**62**) would generate severe nonbonded interactions with the carbocyclic system.



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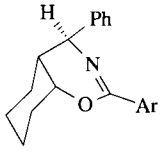

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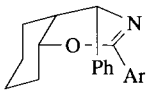

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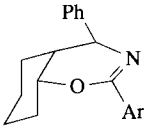


(62)

Proton NMR studies show that, when present, the C-6 substituent of perhydro-1,3-oxazin-2-ones (**63**) normally adopts a pseudoequatorial site. For example, the resonance of H-6 exhibits coupling constants of $J_{4,5} = 9.6$ and $J_{4,5} = 3$ Hz, commensurate with axial–equatorial and axial–axial spin–spin couplings, respectively to the CH_2 at C-5. MM2-Calculations indicate that, in such compounds, all the ring atoms with the exception of C-5 are coplanar: with C-5 lying about 20° out of the plane of the ring ⟨88CL87⟩.

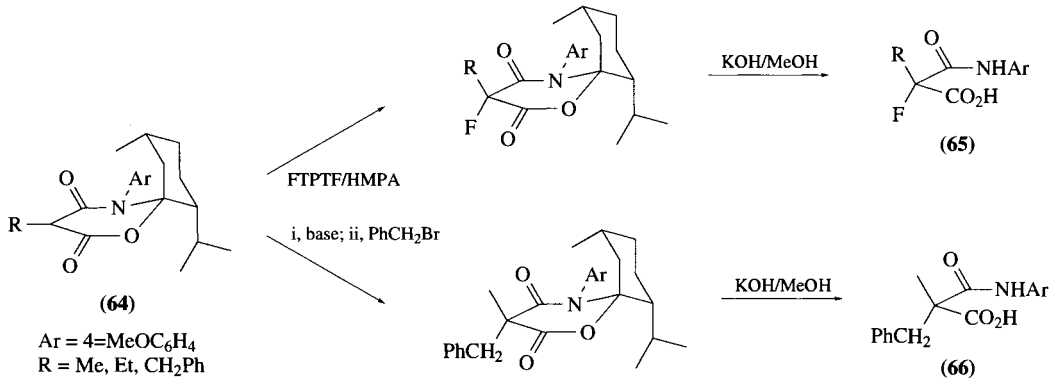
(63)

6.05.4 USE OF 1,3-OXAZINES IN STEREO-CONTROLED SYNTHESES

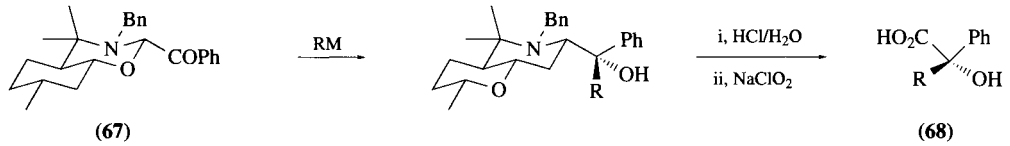
There are several illustrations of the use of oxazinones and diones for the preparation of asymmetric compounds: for example, the synthesis of chiral fluoromalonamides (**65**). These are available through the stereoselective fluorination of the 5-substituted 1,3-oxazine-4,6-diones (**64**; R = Me, Et, Bn) with 1-fluoro-2,4,6-trimethylpyridinium triflate (FTPTF) in THF and HMPA. Attack from the lower face is preferred (20 : 1) and the minor diastereomer can be removed by crystallization. After hydrolysis, with potassium hydroxide in methanol, the chiral products are obtained in high enantiomeric excess ⟨92H(33)105⟩. An extension of this work leading to alkylated malonamides (**66**), requires the initial deprotonation of the dione, prior to treatment with alkyl halides. The final step is again hydrolytic ring fission (Scheme 12) ⟨90TL3605⟩.

In another illustration, Eliel ⟨87T4979⟩ has shown that 2α-benzoyl-*N*-benzyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine (**67**), which is available in three steps from (+)-pulegone, reacts with Grignard reagents, organolithiums, or sodium borohydride in a highly selective manner. The products can be converted by hydrolysis and oxidation into chiral α-hydroxy acids (**68**) (Scheme 13). Although the yields are moderate (20–75%), the enantiomeric excesses are good (80–100%). The functionality of the template at C-2α is readily changed and methoxycarbonyl, formyl, and other acyl derivatives have been prepared. These derivatives react with nucleophiles in the same way, but often with improved product yields ⟨90JOC2114⟩.

Tetrahydro-1,3-oxazin-2-ones can be used to prepare enantiomerically pure amino alcohols. The starting materials can be prepared through the nonselective iodocyclization of homoallylic

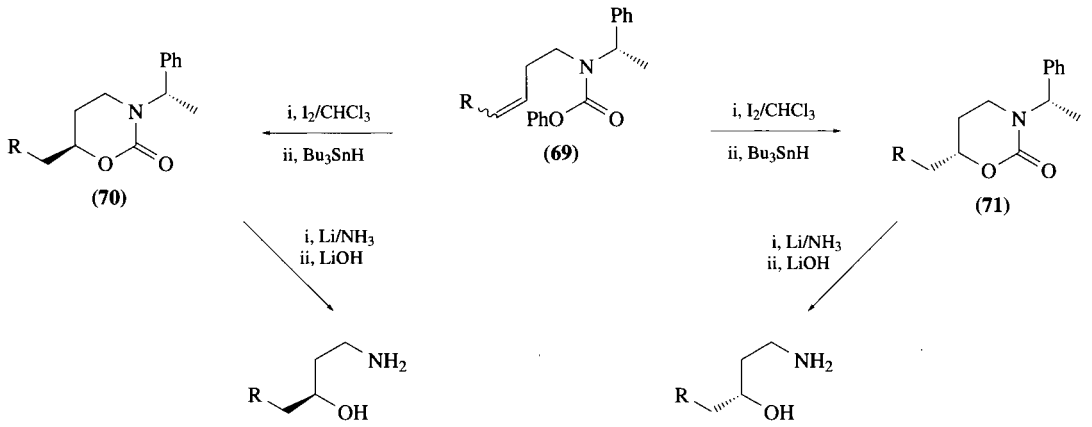


Scheme 12



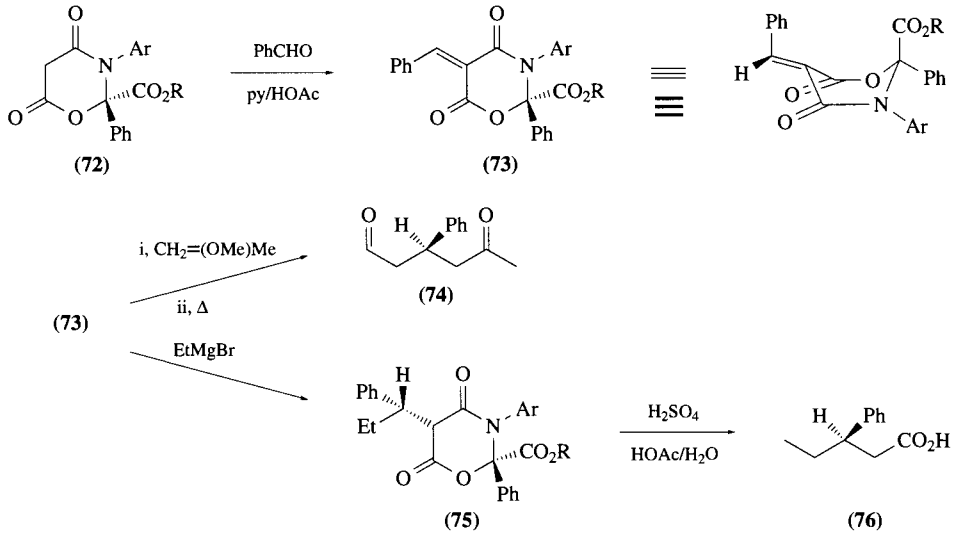
Scheme 13

carbamates (**69**), and the intermediate cyclic iodocarbamates can be reductively deiodinated by treatment with tributyltin hydride. The products are the diastereomeric oxazinones (**70**) and (**71**) (formed in the ratio 1 : 1); these can be separated by chromatography on silica and *N*-dealkylated with lithium in liquid ammonia. Ring opening is effected by treatment with lithium hydroxide, releasing the required amino alcohols (Scheme 14) ⟨88CL87⟩. The conformation and absolute configurations of the diastereomeric 1,3-oxazinones can be deduced by a combination of ^{1}H NMR data and MM2 calculations. Thus it is observed that, while C-6, O-1, C-2, N-3 and C-4 are almost coplanar, C-5 occupies a site about 20° out of the plane formed by the other atoms.



Scheme 14

The enantiomerically pure perhydro-1,3-oxazine-2,6-dione (**72**; R = menthyl; Ar = 4-methoxylphenyl) reacts with benzaldehyde to give the benzylidene derivative (**73**). This compound shows high diastereofacial selectivity (≥98%) when used as either an oxadiene, or as a Michael acceptor. For example, with 2-methoxypropene, followed by thermolysis of the adduct in boiling 1,4-dioxane, it affords the ketoaldehyde (**74**) and with ethyl magnesium bromide it gives the adduct (**75**), acidic hydrolysis of which yields the chiral acid (**76**) (Scheme 15) ⟨92CL485, 92CPB1972⟩.



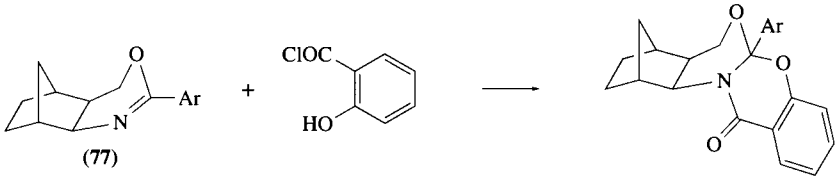
Scheme 15

6.05.5 REACTIONS

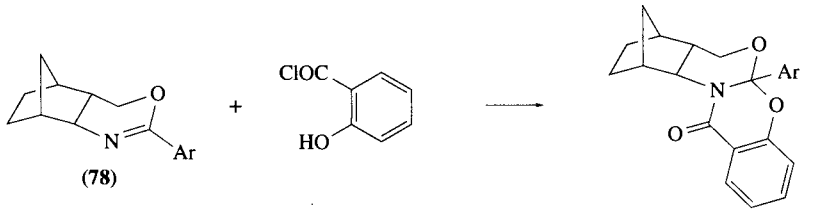
6.05.5.1 Oxidation and Reactions with Electrophiles

6.05.5.1.1 Attack at nitrogen

Norbornane-condensed 1,3-oxazines exist in both *exo* and *endo* forms (**77** and **78**, respectively), and these react with 2-hydroxybenzoyl chloride in a regioselective manner to give tetracyclic derivatives. It is assumed that the selectivity observed is determined by initial acylation of the oxazine nitrogen atom by the acid chlorides, prior to annulation (Equations (1) and (2)) ⟨91JHC753⟩.



(1)



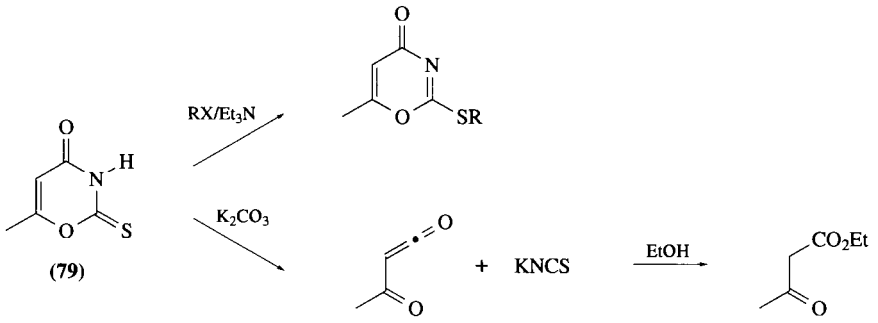
(2)

6.05.5.1.2 Attack at oxygen (oxazinones) or sulfur (oxazinethiones)

(i) 2-Thioxo-1,3-oxazin-4-ones

Whereas acylations of 2-thioxo-1,3-oxazin-4-ones (**79**) with acyl chlorides in the presence of triethylamine occur at N-3, alkyl halides alkylate the sulfur atom. However, should the latter reactions be attempted in the presence of potassium carbonate rather than triethylamine, the heterocycle is cleaved and an alkyl thiocyanate is formed. Indeed, potassium carbonate promotes a retroannulation reaction and, in the absence of an alkyl halide, forms potassium thiocyanate and

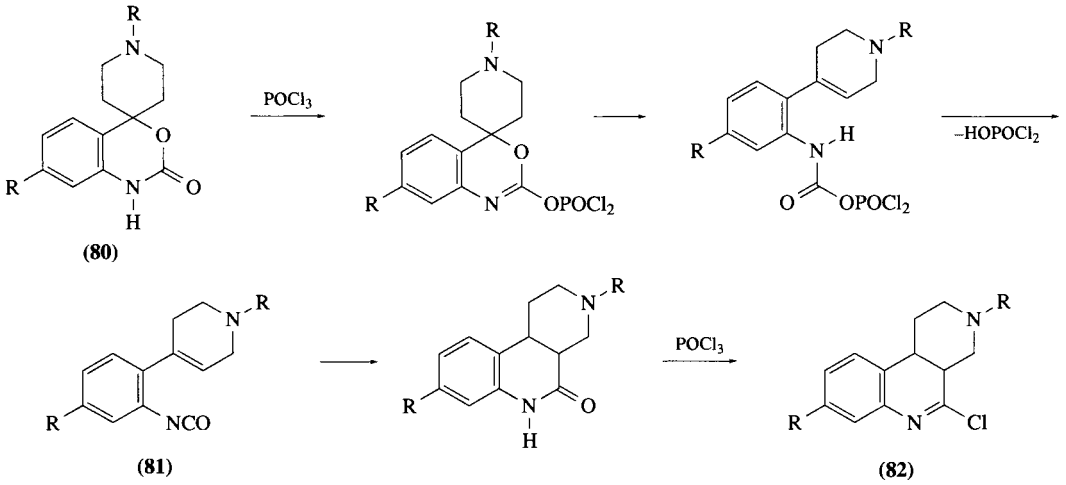
acetylketene. If ethanol is present the ketene reacts with it and ethyl acetoacetate can be isolated (Scheme 16). The corresponding 1,3-oxazinediones are stable to potassium carbonate and these compounds undergo alkylation at the nitrogen atom ⟨84CPB2957⟩.



Scheme 16

(ii) 1,4-Dihydro-3,1-benzoxazin-2-ones

Spiro[3,1-benzoxazine-4,4′-piperidine]-2(1*H*)-ones (**80**) afford 5-chloro-1,2,3,4,4a,10b-hexahydrobenzo[*c*][2,7]naphthyridines when treated with phosphorus oxychloride. The likely reaction pathway involves initial electrophilic attack at the carbonyl oxygen atom which promotes ring opening of the heterocycle and the formation of isocyanates (**81**). These undergo intramolecular [4 + 2]-cyclizations to yield quinolinones, and further reaction with excess reagent then gives the final products (**82**) (Scheme 17) ⟨86CPB1901⟩.

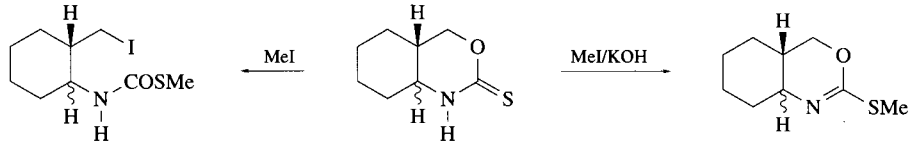


Scheme 17

(iii) Perhydro-3,1-benzoxazine-2-thiones

Perhydro-3,1-benzoxazine-2-thiones (**83**) (*cis* and *trans*) react with methyl iodide and potassium hydroxide to afford 2-methylthio derivatives (**84**), but in the absence of potassium hydroxide ring opening occurs to produce iodomethyl thiocarbamates (**85**) (Scheme 18). In the latter case it is assumed that hydrogen iodide released in the first *S*-methylation step is responsible for initiating

cleavage of the ether unit in the heterocycle and this seems to be correct since acid treatment of the *cis*-2-methylthiobenzoxazine with either hydrogen chloride or hydrogen bromide gives the corresponding ring-opened halide ⟨86T2345⟩.



(85) (83) (84)

Scheme 18

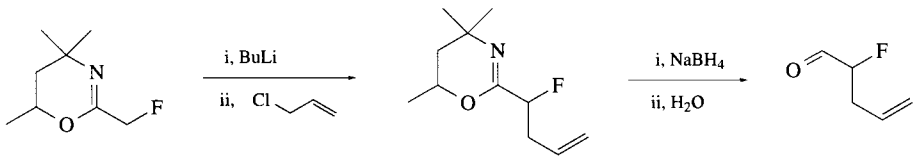
6.05.5.1.3 Reactions at carbon

1,3-Oxazine-2,4-dione is an inhibitor of *Escherichia coli* and other bacteria. It may be halogenated directly at C-5 by chlorine, bromine, or iodine monochloride ⟨76CCC2059⟩. Its derivatives undergo deuterium exchange at this site ⟨78TL1693⟩.

6.05.5.2 Reactions with Bases and Nucleophiles

6.05.5.2.1 5,6-Dihydro-4H-1,3-oxazines

5,6-Dihydro-2-fluoromethyl-4,4,6-trimethyl-4*H*-1,3-oxazine (**86**) can be deprotonated by treatment with butyllithium, and the anion then reacted with electrophiles such as alkyl halides and carbonyl compounds. Reduction and hydrolysis of the products destroy the heterocycle and releases the corresponding α-fluoroaldehydes. For example, reaction of the anion with 3-chloropropene yields the fluorobutenyl-1,3-oxazine (**87**), which on reduction and hydrolysis yields 2-fluoropent-4-enal (**88**) (Scheme 19) ⟨90TL179⟩.

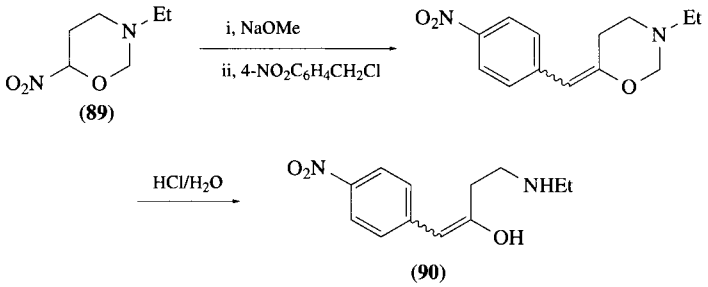


(86) (87) (88)

Scheme 19

6.05.5.2.2 Perhydro-1,3-oxazines

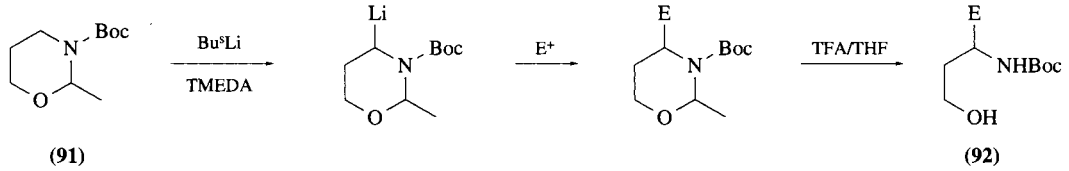
3-Ethyl-6-nitroperhydro-1,3-oxazine (**89**) can be deprotonated by the action of sodium or lithium methoxide, and the anion thus formed then alkylated with benzyl halides. Nitrous acid is eliminated from the products, affording 5-benzylidene derivatives, hydrolysis of which provides easy access to stable compounds formulated as the enols (**90**) (Scheme 20) ⟨89T5477⟩.



(89) (90)

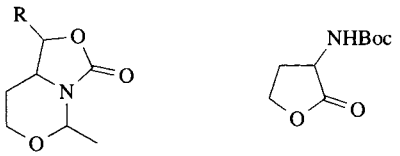
Scheme 20

Lithiation of the perhydro-2-methyl-1,3-oxazine (**91**) takes place at C-4, allowing the selective introduction of various groups at this position. Electrophiles such as alkyl, trimethylsilyl, and tributyltin halides all react with the lithiated oxazine to afford the corresponding derivatives, which can then be ring-opened to substituted 3-aminopropanols (**92**) (Scheme 21). Aldehydes give rise to the bicyclic oxazolones (**93**), whereas treatment with carbon dioxide, followed by acidic work-up, yields the 3-aminobutyrolactone (**94**) ⟨93JOC823⟩.



(**91**) (**92**)

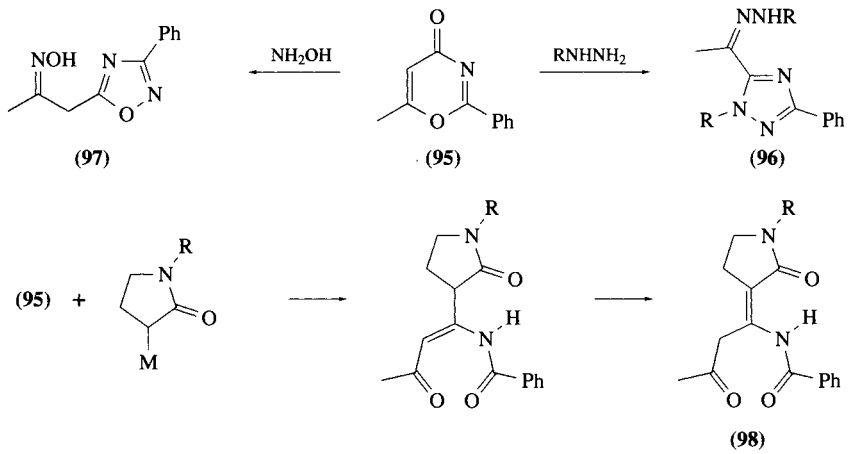
Scheme 21



(**93**) (**94**)

6.05.5.2.3 1,3-Oxazin-4-ones

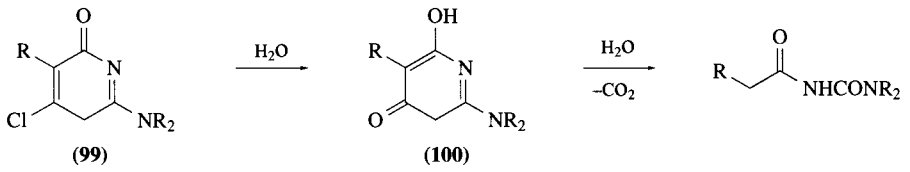
1,3-Oxazin-4-ones undergo a number of ring contraction reactions when reacted with nucleophiles, giving other heterocycles. For example, with hydrazines 6-methyl-2-phenyl-1,3-oxazin-4-one (**95**) affords triazoles (**96**) ⟨78CPB1825⟩ and hydroxylamine yields 1,2,4-oxadiazoles (**97**) ⟨78H(9)185⟩. On the other hand, carbanions, such as those from *N*-substituted pyrrolidin-2-ones, give products (e.g., **98**) in which the C5—O6 bond of the original oxazine ring is cleaved (Scheme 22) ⟨84CPB2555⟩. Similarly, ring contraction is not observed in reactions with enolate anions; in such cases initial ring-opening is followed by recyclization to afford pyridones ⟨85CPB975⟩. Hydrolysis of 6-chloro-1,3-oxazin-4-ones (**99**) leads to the diones (**100**), or their tautomers, which ring open with loss of carbon dioxide to yield imides (Scheme 23) ⟨90S167⟩.



(**97**) (**95**) (**96**)

(**98**)

Scheme 22

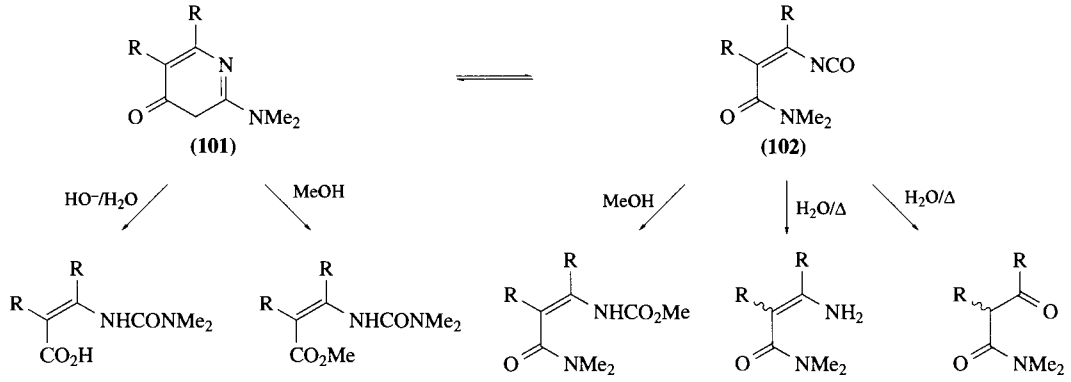


(99) (100)

Scheme 23

6.05.5.2.4 1,3-Oxazin-6-ones

2-(*N*,*N*-Dimethylamino)-1,3-oxazin-6-ones (**101**) react with hydroxide ion to give ureas, with methanol to generate ureas and carbamates, and with water to form β-ketoamides and enaminamides (Scheme 24). In all but two of these reactions the progenitors of the observed products are vinyl isocyanates (**102**), which are in equilibrium with the oxazinones (see Section 6.05.5.3) ⟨87JOC3426⟩.

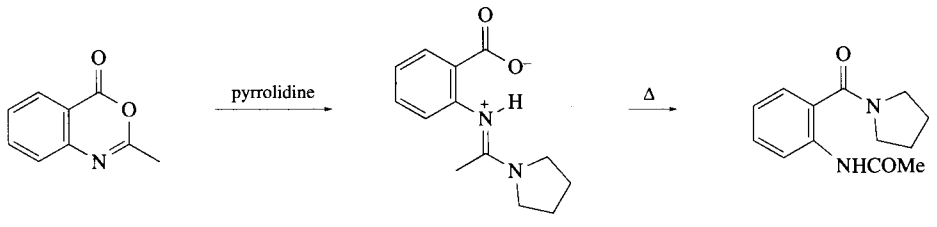


(101) (102)

Scheme 24

6.05.5.2.5 3,1-Benzoxazin-4-ones

When 2-methyl-3,1-benzoxazin-4-one (**103**) is reacted with pyrrolidine in diethyl ether, the zwitterion (**104**) is formed, together with some of the diamide (**105**) (Scheme 25). However, in boiling propanol, or when the reagents are heated without solvent, only the diamide is produced. This suggests that the zwitterion is formed first and then rearranges to the diamide on heating ⟨85ZC103⟩.

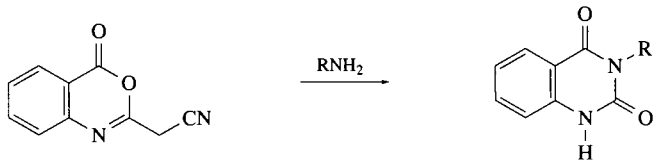


(103) (104) (105)

Scheme 25

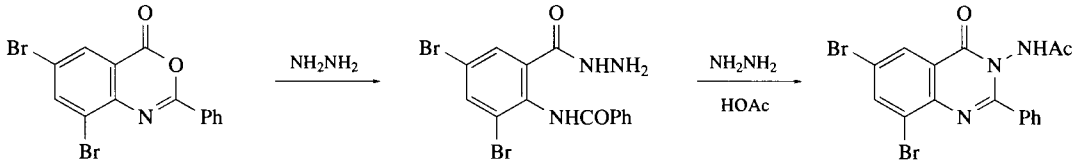
Primary amines behave in a similar way and, in the case of reactions with 2-cyanomethyl-3,1-benzoxazin-4-one (**106**), the final products are quinazoline-2,4-diones (**107**) (Equation (3)) ⟨91MI 605-01⟩. With hydrazine at room temperature the 2-phenyl analogue (**108**) affords the corresponding

2-benzoylaminobenzhydrazide (**109**), but in the presence of hot acetic acid recyclization occurs to give the 3-acetylaminoquinazolinone (**110**) (Scheme 26) ⟨89MI 605-02⟩.



(3)

(106) (107)

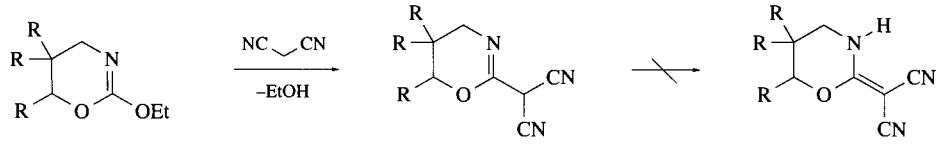


(108) (109) (110)

Scheme 26

6.05.5.2.6 Dihydro-1,3-oxazines

2-Ethoxy-5,6-dihydro-4*H*-1,3-oxazines (**111**) react with enolates and related compounds at C-2; ethanol is lost and the corresponding 2-substituted dihydro-1,3-oxazine is formed. Depending upon the nature of the substituent *endo–exo* double bond, tautomerism can be observed. Thus, a reaction with the anion of malononitrile yields the 2-alkylidene-3,4,5,6-tetrahydro-1,3-oxazine (**112**) rather than the 2-alkyl-5,6-dihydro-1,3-oxazine (**113**) (Scheme 27) ⟨86JHC701⟩.

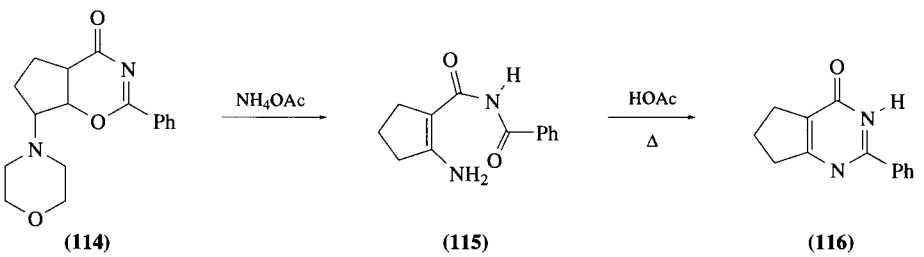


(111) (112) (113)

Scheme 27

6.05.5.2.7 5,6-Dihydro-1,3-oxazin-4-ones

2-Phenyl-5*H*-6,7-dihydrocyclopenta[*d*]pyrimidin-4(3*H*)-one (**116**) is obtained by the reaction of the 5,6-dihydro-6-(morpholin-4-yl)-1,3-oxazin-4-one (**114**) with ammonium acetate, followed by recyclization of the intermediate enaminimide (**115**) with boiling acetic acid (Scheme 28). Both stages occur consecutively if the starting material is heated with the combined reagents ⟨93JOC414⟩.

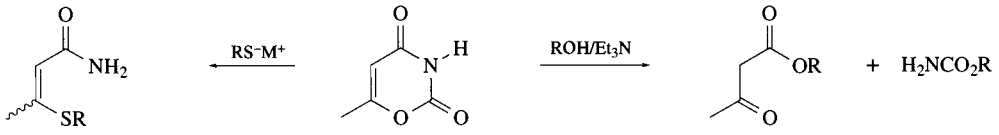


(114) (115) (116)

Scheme 28

6.05.5.2.8 1,3-Oxazine-2,4(3H)-diones

In the first edition it was noted that 1,3-oxazine-2,4(3*H*)-diones react with ammonia, amines, hydrazines, carbanions, and alcohols at C-2. This selectivity has been rationalized on the basis of the relative hardness of the three electrophilic centers (C-2 > C-4 > C-6) ⟨84JCS(P1)2097⟩. Support for this view is provided by the fact that alkanols "softened" by the presence of triethylamine react with 6-methyl-1,3-oxazine-2,4(3*H*)-dione (**117**) at C-4, causing ring cleavage and the formation of alkyl acetoacetates and carbamates ⟨85IJC(B)1201⟩. In some cases triethylamine is not required, but the rates of reaction are markedly affected by temperature, and with either ethanol, or 1-propanol at reflux the reactions fail ⟨87JCR(S)390⟩. Soft nucleophiles such as thiolates react at C-6, also causing ring scission, and in this case the products are (*E*)- and (*Z*)-3-thiobut-2-enamides (**118**) (Scheme 29) ⟨91JCS(P1)1391⟩.



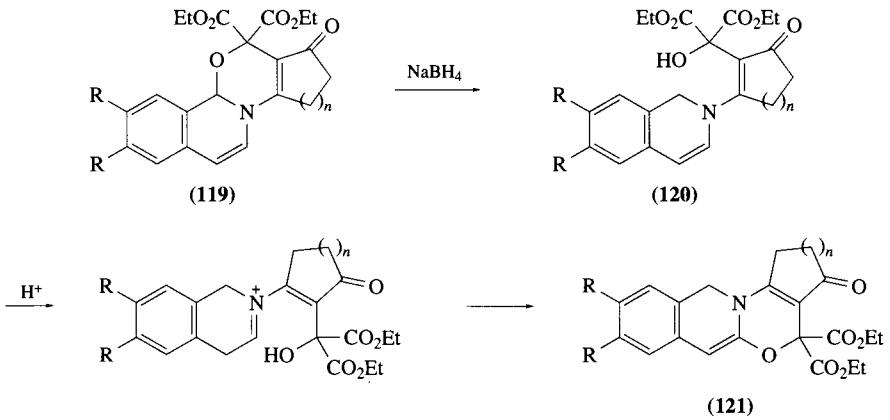
(118) (117)

Scheme 29

6.05.5.3 Reduction

6.05.5.3.1 Dihydro-1,3-oxazines and derivatives

[1,3]Oxazino[2,3-*a*]isoquinolines (**119**; $n = 2$) undergo reductive isomerization to [1,3]oxazino[3,2-*b*]isoquinolines (**121**; $n = 2$), by hydrogenolysis of the benzylic ether unit and recyclization of the protonated intermediate 1,2-dihydroisoquinoline (**120**; $n = 2$). [1,3]Oxazino[2,3-*a*]isoquinolines (**119**; $n = 1$) only afford the dihydroisoquinolines (**120**, $n = 1$) when reduced with sodium borohydride, but these can be ring-closed to the corresponding [1,3]oxazino[3,2-*b*]isoquinolines if an acid catalyst (4-$MeC_6H_4SO_3H$) is added in a follow-up step (Scheme 30) ⟨88H(27)245⟩.

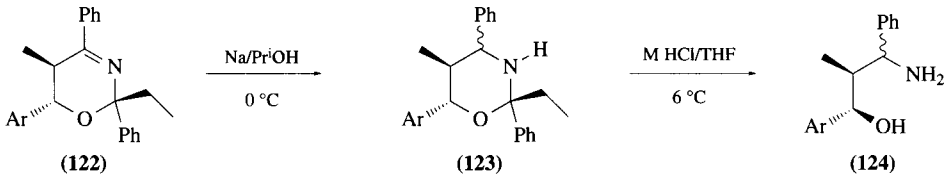


(119) (120) (121)

Scheme 30

6.05.5.3.2 5,6-Dihydro-2H-1,3-oxazines

5,6-Dihydro-2*H*-1,3-oxazines (**122**), which are available through cycloaddition reactions (see Section 6.05.6.2.2(vi)), may be reduced with sodium and 2-propanol to yield perhydro derivatives (**123**) without ring fission. These products may then be ring opened by treatment with hydrochloric acid to give the diastereomeric 3-aminopropanols (**124**) (Scheme 31) ⟨91S387⟩.

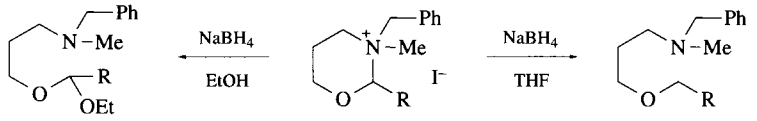


(122) (123) (124)

Scheme 31

6.05.5.3.3 *Perhydro-1,3-oxazines*

As for dihydro-1,3-oxazines, perhydro-1,3-oxazine methiodides (**125**) are ring-opened by reaction with sodium borohydride. The products obtained depend upon the conditions used; thus, in anhydrous tetrahydrofuran tertiary amines and their borane derivatives are formed, but in ethanol or methanol transesterification occurs to give the corresponding ethyl or methyl ethers (Scheme 32) ⟨90H(31)2079⟩.



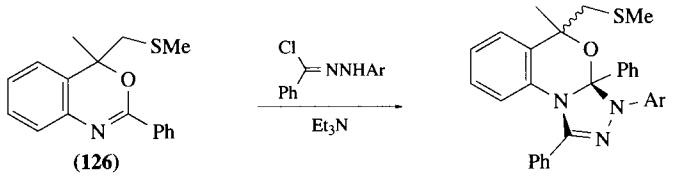
(125)

Scheme 32

6.05.5.4 Addition Reactions

6.05.5.4.1 *4H-3,1-Benzoxazines*

4*H*-3,1-Benzoxazines (**126**) undergo 1,3-dipolar cyclizations with nitrilimines formed *in situ* by the treatment of hydrazonyl chlorides with triethylamine. The addition reactions are regioselective, affording triazoline derivatives in which the nitrogen atom of the parent benzoxazine is bonded to the C-atom of the nitrilimine (Equation (4)) ⟨86JCR(S)200⟩.



(126) (4)

6.05.5.4.2 *Dihydro-1,3-oxazines*

4*H*-5,6-Dihydro-1,3-oxazines also undergo cycloaddition reactions, and with diphenylnitrilimine or benzonitrile oxide the bicyclic derivatives (**127**) give rise to the triazolines (**128**) and the oxadiazolines (**129**), respectively (Scheme 33) ⟨88MI 605-02⟩; also see ⟨87T5461⟩.

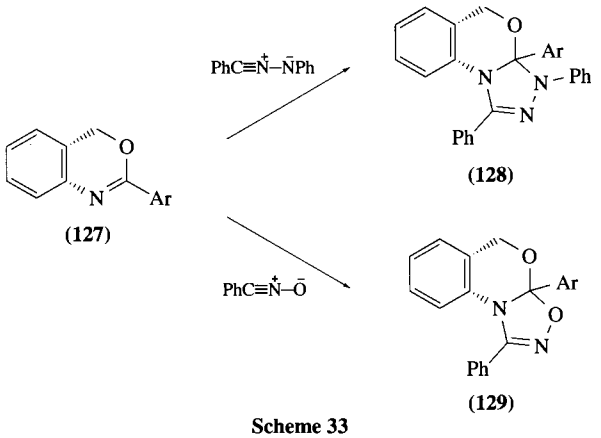
6.05.6 SYNTHESIS OF 1,3-OXAZINES, BENZOXAZINES, AND THEIR REDUCED FORMS

6.05.6.1 Introduction

Syntheses of 1,3-oxazines and their derivatives can be classified according to the number and elemental composition of the assembling units. The most common are:

[3 + 3] C—C—C + N—C—O, O—C—C + C—N—C

[4 + 2] C—C—C—N + C—O, O—C—C—C + N—C, C—C + C—N—C—O



Scheme 33

[5 + 1] C—C—C—N—C + O, O—C—C—C—N + C, C—C—N—C—O + C, C—C—C—S—C + N
[6 + 0] N—C—O—C—C—C, C—O—C—C—C—N, O—C—C—C—N—C, C—C—C—N—C—O, C—C—N—C—O—C, C—N—C—O—C—C

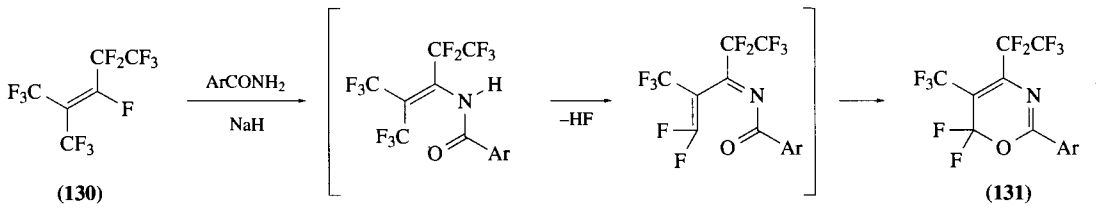
This classification will be used here, although segregation into the various subgroups of each type is not attempted. Where there are appropriate examples within type, the order of discussion will be oxazinium salts, oxazines, oxazinones and oxazinethiones, dihydro-1,3-oxazines, dihydro-1,3-oxazinones and thiones, perhydro-1,3-oxazines, and finally perhydro-1,3-oxazinones and thiones. 1,3-Benzoxazines and 3,1-benzoxazines are not treated separately, but included within this general classification and listed according to the number of *formal* double bonds in the heterocycle.

6.05.6.2 Synthesis of Oxazine Derivatives

6.05.6.2.1 [3 + 3] Types

(i) 1,3-Oxazines

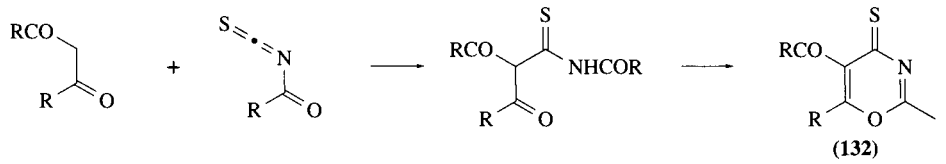
Perfluoro-6*H*-1,3-oxazines (**131**) are available through the reactions of 4-substituted benzamides and 2-trifluoromethylperfluoropent-2-ene (**130**) in contact with sodium hydride. It is probable that the deprotonated amides react through the nitrogen atom with the fluorinated alkene to form *N*-allylamides. These eliminate hydrogen fluoride and afford azadienes which then undergo intramolecular cyclization to form the oxazines (Scheme 34) ⟨86JOC569⟩.



Scheme 34

(ii) 1,3-Oxazine-4-thiones

1,3-Oxazine-4-thiones (**132**) can also be obtained by the cyclocondensation of acylisothiocyanates and 1,3-diketones, probably via the intermediacy of *N*-thioacylamides (Scheme 35) ⟨82JPR(324)915⟩.

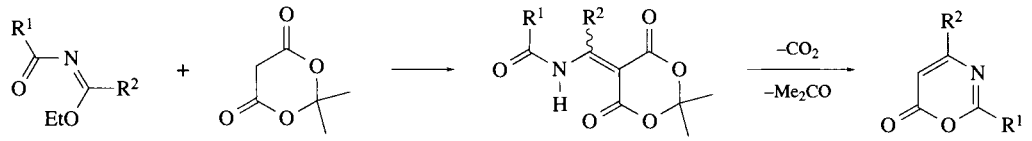


(132)

Scheme 35

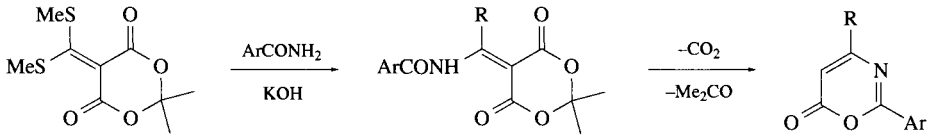
(iii) 1,3-Oxazin-6-ones

As in many other areas of 1,3-oxazine chemistry, ketenes and isocyanates generated *in situ* are often used to prepare oxazin-6-ones. For example, 2,4-disubstituted 1,3-oxazin-6-ones (**135**) are readily available through the thermolysis of 5-[(*N*-acylamino)alkylidene]-1,3-dioxane-4,6-diones (**134**). The latter are generated from the reactions of the appropriate ethyl acylimidate (**133**) and Meldrum's acid (Scheme 36) ⟨86CPB1980⟩. Similarly, the bismethylthiomethylene derivative (**136**) reacts with benzamides in the presence of potassium hydroxide to afford the methylthioacylaminomethylene derivatives (**137**; R = MeS), which can be reacted further with ammonia to give the amino compounds (**137**; R = NH_2). In turn, these products can be thermolyzed to afford the oxazinones (**138**; R = MeS) or (**138**; R = NH_2), respectively (Scheme 37) ⟨91SC1213⟩.



(133) (134) (135)

Scheme 36

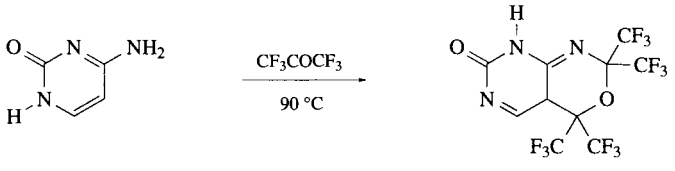


(136) (137) (138)

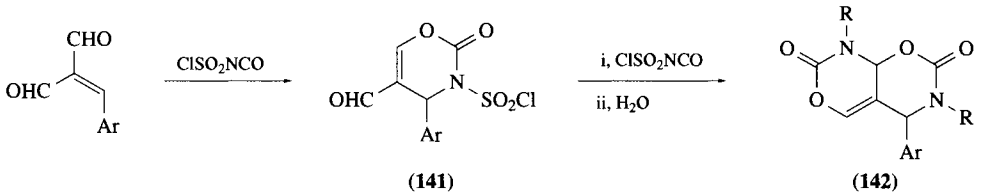
Scheme 37

(iv) Dihydro-1,3-oxazines and oxazinones

Cytosine (**139**) reacts with hexafluoropropanone at 90 °C in DMF to give the pyrimido-1,3-oxazine (**140**) (Equation (5)) ⟨88IZV1433⟩, and fused and partly reduced 1,3-oxazine-2-ones, exemplified by compounds of the type (**142**), are obtained through the reactions of arylmethylenemalonaldehydes and chlorosulfonyl isocyanate. It seems possible that the reactions occur in stages, giving firstly monocyclic oxazinones (**141**), which then react with more reagent to afford the bicycles (**142**; R = SO_2Cl). These products are hydrolyzed to (**142**; R = H) when water is added (Scheme 38) ⟨92T4551⟩.



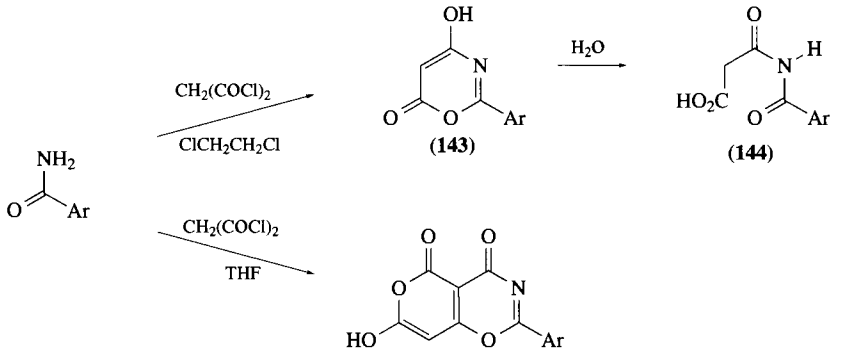
(139) (140) (5)



(141) (142)

Scheme 38

4-Hydroxy-1,3-oxazin-6-ones (**143**) are formed by the reactions of benzamides with malonyl chloride in 1,2-dichloroethane. These products can easily be hydrolyzed to the imides (**144**). Depending upon the substituent in the aromatic ring of the benzamide, the 1,3-oxazinones may also be accompanied by hydroxypyrano-1,3-oxazinediones (**145**), especially if the reactions are conducted in THF as the solvent (Scheme 39) ⟨87KGS382⟩.



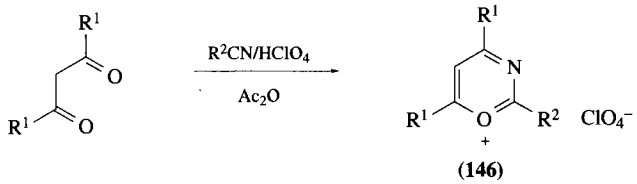
(143) (144) (145)

Scheme 39

6.05.6.2.2 [4 + 2] Types

(i) 1,3-Oxazinium salts

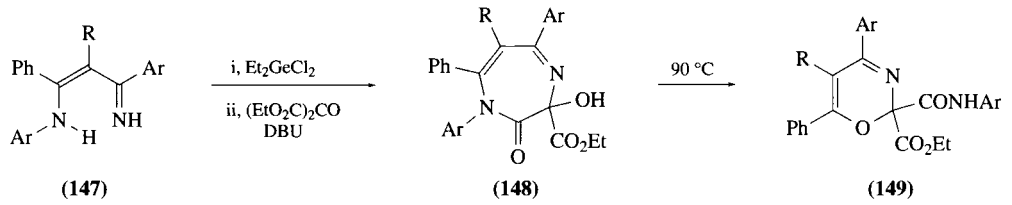
1,3-Oxazinium perchlorates (**146**) can be obtained from 1,3-diketones through reactions with benzonitrile in the presence of perchloric acid and acetic anhydride (Equation (6)) ⟨88ZOR1561, 88ZOR2232, 91ZOR1986⟩.



(146) (6)

(ii) 2H-1,3-Oxazines

1,3-Dihydro-1,4-diazepin-2-ones (**148**) are obtained when 3-iminopropenylamines (**147**) are reacted first with diethylgermanium dichloride and then with diethyl oxomalonate and DBU. If these products are heated to 90 °C in toluene, they rearrange to produce 2*H*-1,3-oxazines (**149**). The initial reactions are considered to involve diaza germana intermediates (Scheme 40) ⟨93CC217⟩.

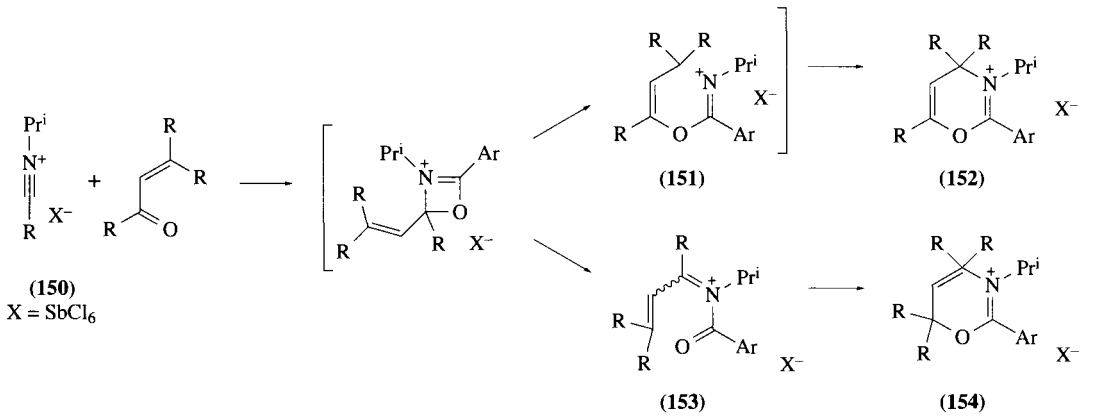


(147) (148) (149)

Scheme 40

*(iii) 4*H*-1,3-Oxazines*

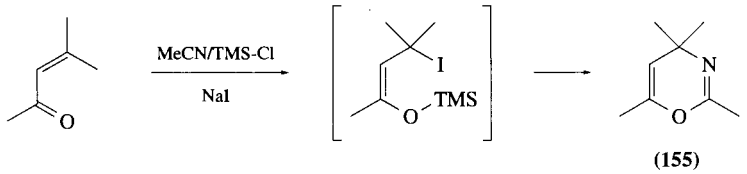
It is well known that nitriles react with β-chlorocarbonyl compounds in the presence of a Lewis acid to yield 4*H*-1,3-oxazinium salts, but now it has been shown that nitrilium salts combine with enones to give similar products. Thus enones and nitrilium hexachloroantimonates (**150**) combine to produce 4*H*-1,3-oxazinium salts (**152**), but in some cases 6*H*-1,3-oxazinium salts (**154**) are formed instead and, while tautomerism between the 4*H*- and 6*H*-forms cannot be ruled out, oxetenium salts may participate in the reactions as common intermediates. One type of bond cleavage may give the carbocations (**151**) (especially when R = Ar), which cyclize to the 4*H*-tautomers and another may lead to *N*-acyliminium salts (**153**) (Scheme 41). The latter then ring close to 6*H*-1,3-oxazines. Evidence that such reactions do occur is provided, since *N*-acyliminium salts can be isolated in some cases ⟨90S763⟩.



(150) X = $SbCl_6$ (151) (152) (153) (154)

Scheme 41

A new synthesis of 2,4,4,6-tetramethyl-4*H*-1,3-oxazine (**155**) simply involves a reductive cycloaddition of 4-methylpent-3-en-2-one and acetonitrile in the presence of trimethylsilyl chloride and sodium iodide (Scheme 42) ⟨89TL4741⟩. Other cycloaddition reactions have been used previously to synthesize 4*H*-1,3-oxazines and this methodology has been extended to include cycloadditions between alkynes and 1-oxa-3-azabuta-1,3-dienes. For example, phenylethyne and the *N*-benzoylimine (**156**) afford 4,4-bis(trifluoromethyl)-2,6-diphenyl-4*H*-1,3-oxazine (**157**). The reaction proceeds through a Michael-type addition between the alkyne and the heterodiene giving an adduct which when heated to 80–90 °C cyclizes to the oxazine (Scheme 43) ⟨83CC945, 89ZN(B)1298⟩.

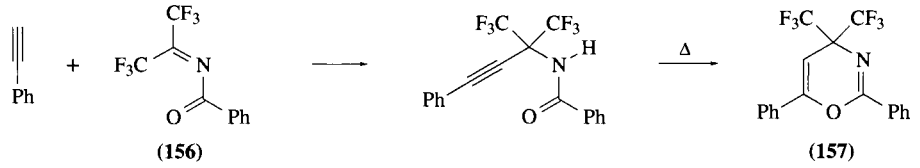


(155)

Scheme 42

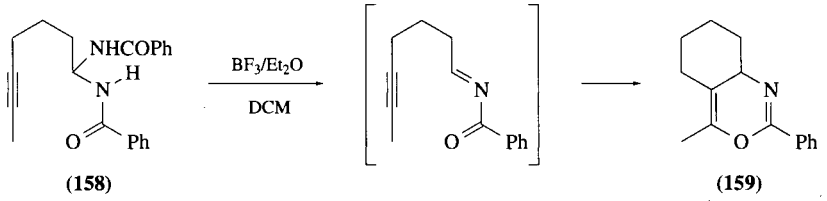
In another intramolecular cyclization of above type the cyclohexano derivative (**159**) is obtained through exposure of the alkynic amide (**158**) to boron trifluoride (Scheme 44) ⟨86JOC3248⟩.

An alternative method requires cycloadditions between dimethylcyanamide and 4-substituted arylidene malonaldehydes (**160**). Conducted in boiling benzene, such reactions afford 4-aryl-5-



(156) (157)

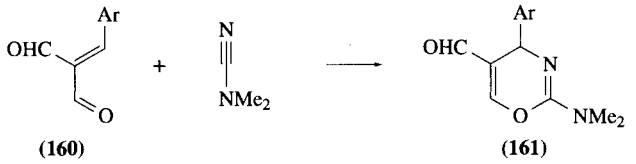
Scheme 43



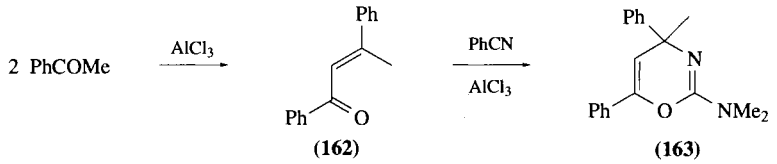
(158) (159)

Scheme 44

formyl-2-(*N*,*N*-dimethylamino)-4*H*-1,3-oxazines (**161**) (Equation (7)) ⟨85CCC2265⟩. Similarly, acetophenone in the presence of aluminum trichloride forms the chalcone (**162**), which with the co-reactant benzonitrile affords 4-methyl-2,4,6-triphenyl-4*H*-1,3-oxazine (**163**) (Scheme 45) ⟨78CL1391⟩.



(160) (161) (7)

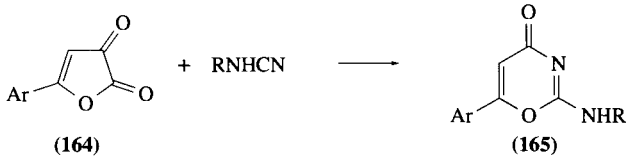


(162) (163)

Scheme 45

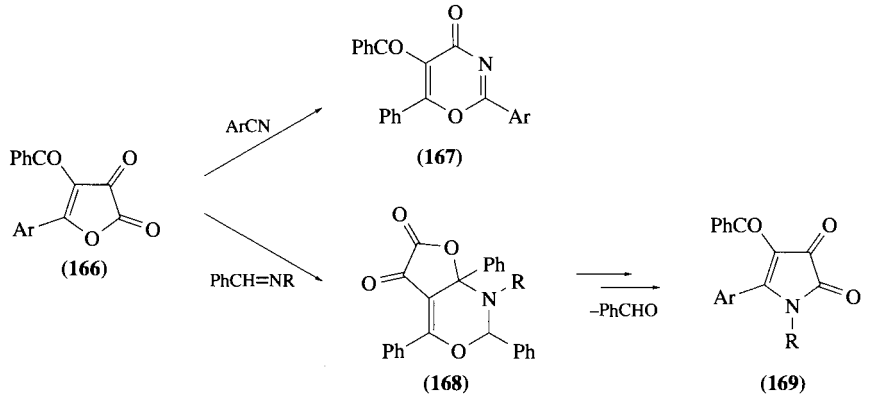
(iv) 1,3-Oxazin-4-ones and 1,3-oxazine-4-thiones

Furan-2,3-diones are a potential source of acylketenes and as a result they are commonly used as reactants in the synthesis of 1,3-oxazines. For example, when heated in the presence of 2-benzimidazoylcyanamide the furandiones (**164**) afford 2-(benzimidazo-2-yl)amino-1,3-oxazin-4-ones (**165**) (Equation (8)) ⟨88ZOR2237, 89KGS1265⟩. The benzoylfurandiones (**166**) react similarly and when heated with aryl nitriles 2-aryl-1,3-oxazin-4-ones (**167**) are obtained ⟨77LA1751⟩. With imines, furo[3,2-*e*][1,3]oxazines (**168**) are formed initially, but these products are thermally unstable. They undergo rearrangement with elimination of benzaldehyde to form 2,3-dioxopyrroles (**169**) (Scheme 46) ⟨87S176, 92ZOR779⟩.



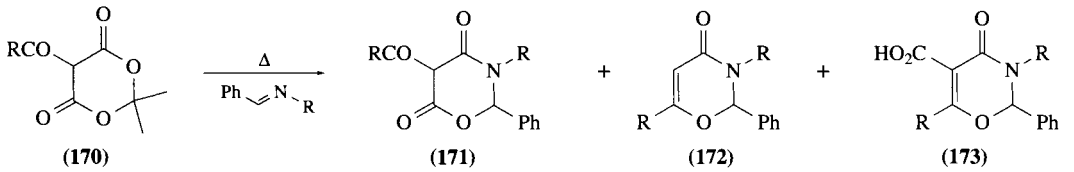
(164) (165) (8)

(R = 2-benzimidazoyl)



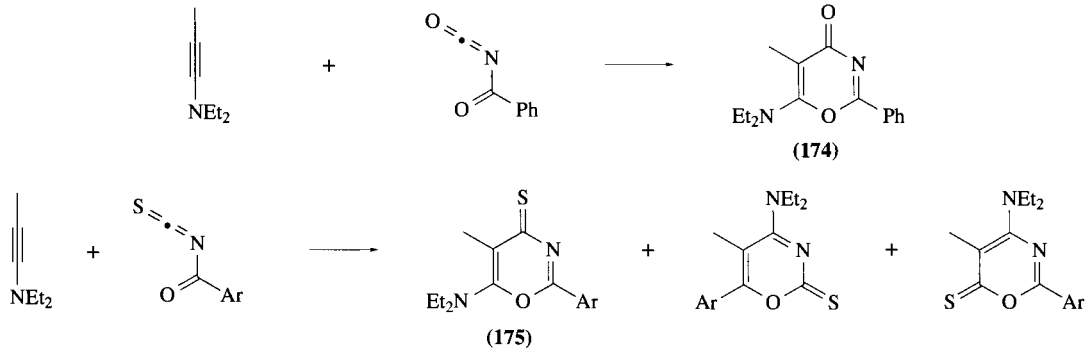
Scheme 46

Related work has shown that acylated Meldrum's acids (**170**; R = alkyl or aryl) react with imines to give a mixture of 1,3-oxazine-4,6-diones (**171**) and 2,3-dihydro-1,3-oxazin-4-ones (**172**) plus smaller amounts of the acids (**173**) (Scheme 47). The diones (**171**) are unstable and if they are heated in separate experiments they ring-open and recyclize to afford the oxazin-4-ones (**172**) ⟨87CPB1860⟩.



Scheme 47

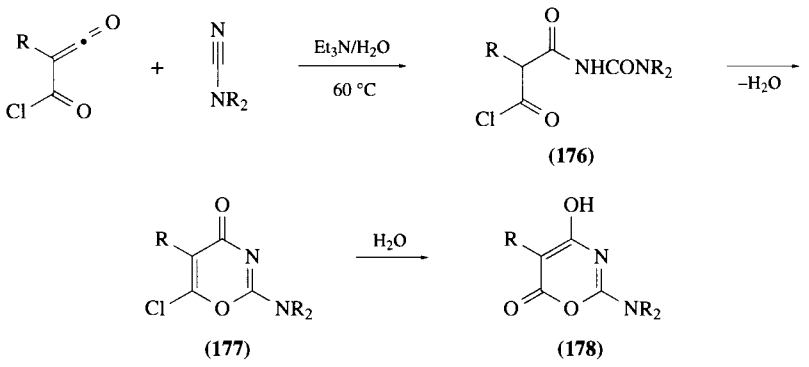
N,*N*-Diethylaminopropyne reacts with *N*-benzoylisocyanate to give the 1,3-oxazin-4-one (**174**) as the only product. However, although 1,3-oxazine-4-thiones (**175**) are available by the same route, using *N*-aroylisothiocyanates instead of *N*-benzoylisocyanate, mixtures result and the oxazine-4-thiones are accompanied by their 2- and 6-isomers (Scheme 48) ⟨86JCR(S)40⟩.



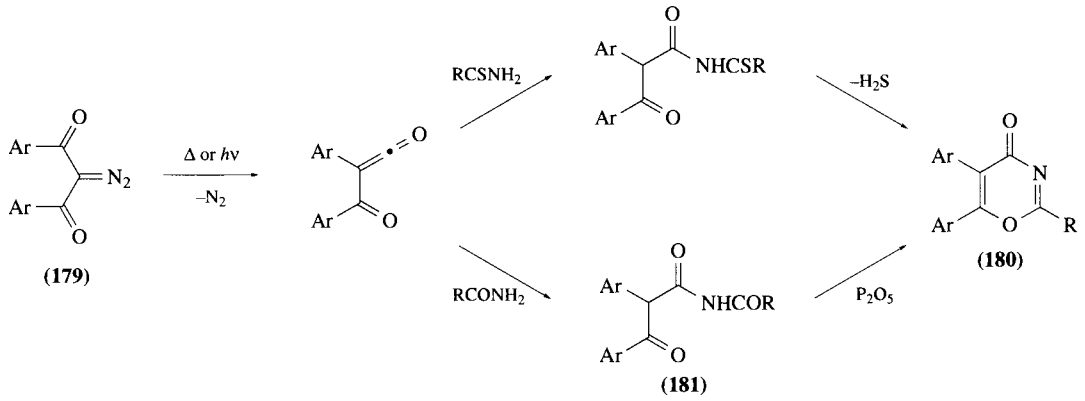
Scheme 48

A popular approach to 1,3-oxazine-4-ones involves the reactions of acylketenes with nitriles or amides: thus, cyanamide reacts with chlorocarbonylketenes to generate 6-chloro-1,3-oxazin-4-ones (**177**). *N*-Acylureas (**176**) are formed first and these undergo cyclodehydration to the heterocycles. 6-Chloro-1,3-oxazin-4-ones are easily hydrolyzed to 4-hydroxy-1,3-oxazin-6-ones (**178**), or their tautomers (Scheme 49) ⟨90S167⟩.

2-Diazo-1,3-diketones (**179**) on heating, or photolysis, generate acylketenes via the Wolff rearrangement. These can be trapped by thioamides to form intermediate *N*-acylthioamides, which are unstable and expel hydrogen sulfide to give 1,3-oxazin-4-ones (**180**). A better method, however, is to combine the acylketenes with amides and to cyclodehydrate the product *N*-acylamides (**181**) with phosphorus pentoxide (Scheme 50) ⟨90LA239⟩.



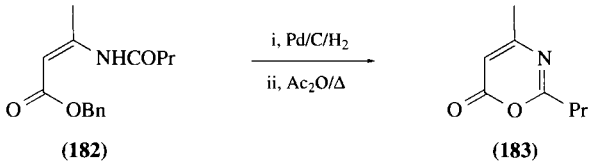
Scheme 49



Scheme 50

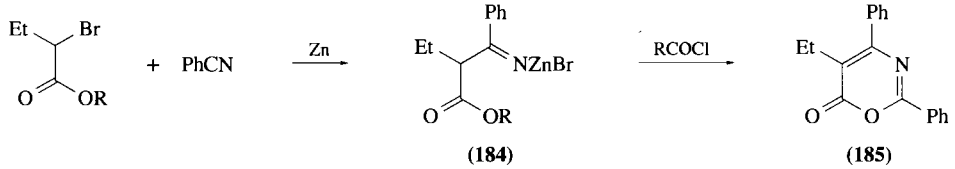
(v) 1,3-Oxazin-6-ones

4-Methyl-2-propyl-1,3-oxazin-6-one (**183**), required in the synthesis of the natural product rubrolone, was obtained from benzyl 3-(*N*-butanoylamino)but-2-enoate (**182**) by *O*-debenzylation, followed by cyclodehydration with hot acetic anhydride (Scheme 51) ⟨89JOC714⟩.



Scheme 51

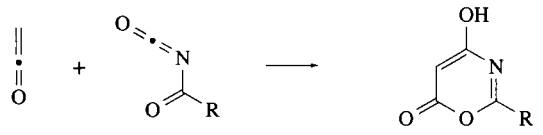
A simple two-step synthesis of 1,3-oxazin-6-ones (e.g. **185**) requires the formation of intermediate *N*-zincates (**184**) from α-bromoacetates and nitriles in contact with zinc powder. When the zincates (**184**) are treated with acyl chlorides, zinc halides are eliminated and cyclization occurs (Scheme 52) ⟨77ZOR1328⟩.



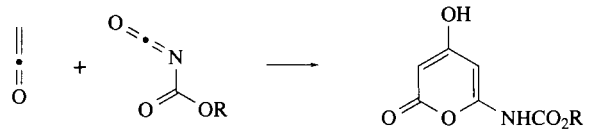
Scheme 52

Acyl isocyanates react with ketene in nonpolar solvents to give 4-hydroxy-1,3-oxazin-6-ones (**186**) (Equation (9)), but the regioselectivity of the cycloadditions is changed if the *N*-acyl substituent is

replaced by an ester unit. Thus, the corresponding *N*-carboxylates afford pyranones (**187**) (Equation (10)) ⟨91ZOR864⟩.



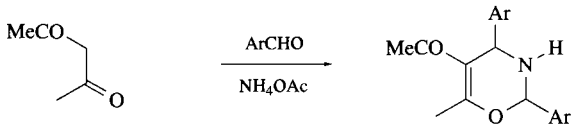
R = alkyl, or aryl (**186**) (9)



R = Me, or Et (**187**) (10)

*(vi) 3,4-Dihydro-2*H*-1,3-oxazines and 5,6-dihydro-2*H*-1,3-oxazines*

3,4-Dihydro-2*H*-1,3-oxazines (**188**) are available through a one-pot procedure in which acetylacetone is reacted with arylaldehydes and ammonium acetate (Equation (11)) ⟨92JCS(P1)2055⟩. Assuming that a benzylidene derivative is formed *in situ* and this reacts with an arylimine, this preparation is included here as a [4 + 2]-type.



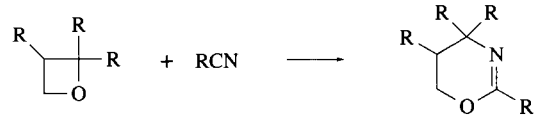
(**188**) (11)

5,6-Dihydro-2*H*-1,3-oxazines (e.g. **189**) are relatively uncommon, but they can be synthesized through the cycloadditions of 2-aza-1,3-dienes and aldehydes (Equation (12)). The relative stereochemistry of the products is dictated by the geometry of the azadiene ⟨91S387⟩.

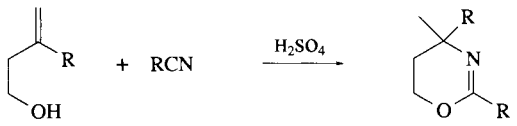
(**189**) (12)

*(vii) 5,6-Dihydro-4*H*-1,3-oxazines*

Most interest in this area centers around 5,6-dihydro-4*H*-1,3-oxazines. These compounds can be prepared in a variety of ways, for example, by the addition of nitriles to oxetanes (presumably the latter ring-open by S_N1 cleavage, prior to reaction with the nitrile (Equation (13)) ⟨81TL341, 82ZOR178⟩, or through the interaction of *β*-hydroxyalkenes with nitriles in the presence of concentrated sulfuric acid (Equation (14)) ⟨79URP649713⟩.

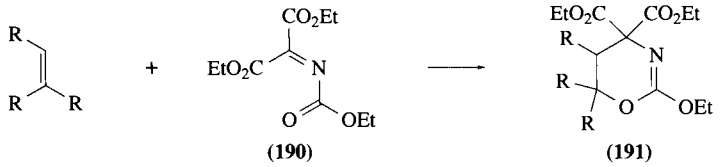


(13)



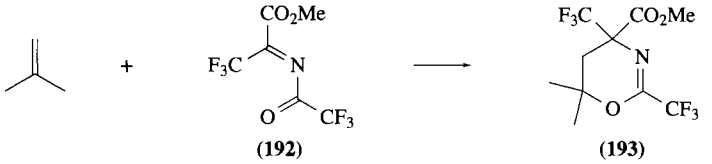
(14)

Another route involves inverse demand Diels–Alder reactions between azadienes and electron "rich" alkenes. Thus, the carbamate (**190**) combines with trisubstituted alkenes to yield adducts (**191**) (Equation (15)) ⟨84TL943⟩. Similarly, the trifluoroacetylimine (**192**) of methyl trifluoropyruvate enters into cycloaddition reactions with alkenes such as 2-methylpropene to give the corresponding 5,6-dihydro-4*H*-1,3-oxazines (**193**) (Equation (16)). In both cases the reactions are regioselective and C-6 (rather than C-5) in the products becomes the more substituted site ⟨91IZV1130⟩.



(190) (191)

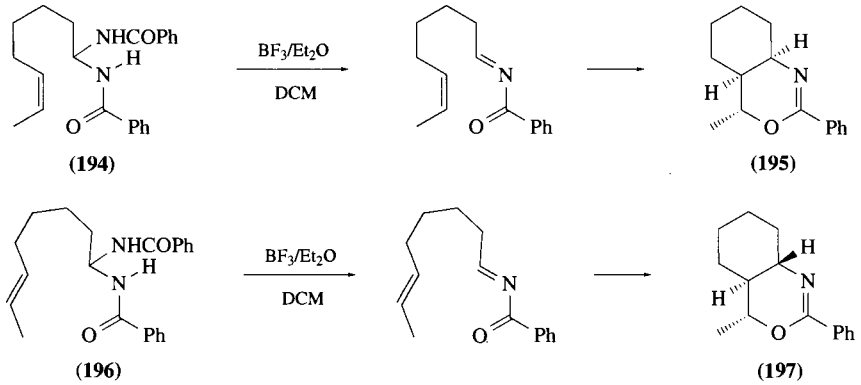
(15)



(192) (193)

(16)

An intramolecular version of this type of reaction has already been described in Section 6.05.6.2.2(iii) for the synthesis of 4*H*-1,3-oxazines, and an analogous route to dihydro-1,3-oxazines has also been reported. Thus, treatment of the (*Z*)-isomer (**194**) of 1,1-di(*N*-benzoylamino)oct-6-ene with boron trifluoride diethyl etherate in DCM affords the bicyclic 5,6-dihydro-1,3-oxazine (**195**) in 74% yield. Under similar conditions the (*E*)-isomer (**196**) gives 89% of the diastereomer (**197**). In both cases it is assumed that an *N*-acyliminium intermediate is generated which undergoes an intramolecular [4 + 2]-cycloaddition reaction (Scheme 53) ⟨86JOC3248⟩.



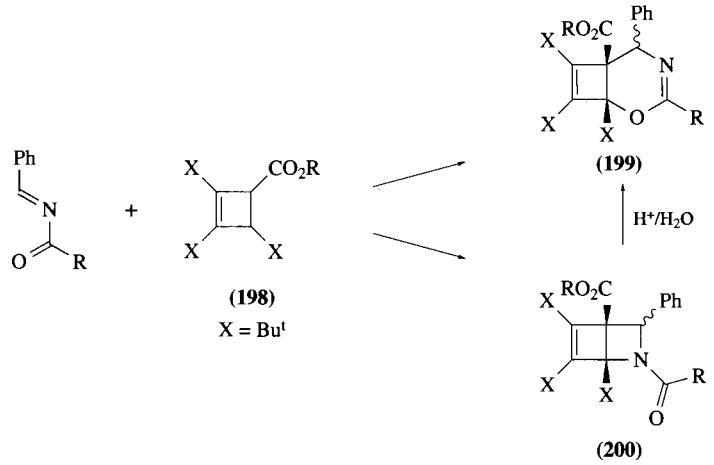
(194) (195)

(196) (197)

Scheme 53

Yet another extension of this type of procedure utilizes cyclobutadienes (**198**; R = Me, or Bu^t) as the alkene component. These react with *N*-acylimines to form azaoxabicyclo[4.2.0]octadienes (**199**) and azabicyclo[2.2.0]hexenes (**200**). When exposed to acid the latter products rearrange into the former (Scheme 54) ⟨85TL3315⟩.

The amidoalkylation of alkenes is a well-known process for the synthesis of 5,6-dihydro-4*H*-1,3-oxazines, but yields are low except when styrenes are used. In new work it has been shown that unactivated alkenes, such as octene, react with benzamide, paraformaldehyde, and trifluoroacetic acid to give the dihydro-1,3-oxazines (e.g. **201**) in 50–80% yield (Scheme 55) ⟨93T3907⟩.

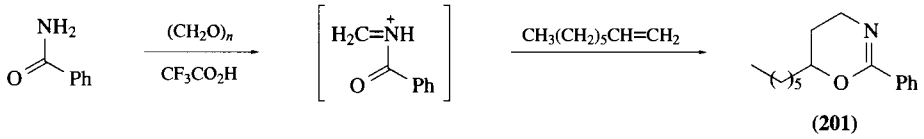


(198)
X = Bu^t

(199)

(200)

Scheme 54

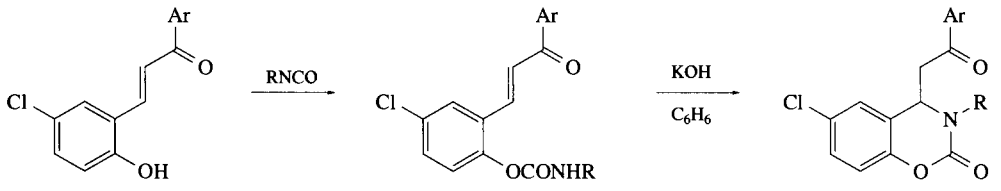


(201)

Scheme 55

(viii) 3,4-Dihydro-1,3-benzoxazin-2-ones, 2,3-dihydro-1,3-oxazin-4-ones, and 2,3-dihydro-1,3-oxazine-6-thiones

2-Hydroxychalcones (**202**) react with either alkyl or aryl isocyanates to give 3,4-dihydro-4-phenacyl-1,3-benzoxazin-2-ones (**203**). Carbamates form initially and these require heating in the presence of potassium hydroxide in order to effect cyclization to the benzoxazinones (Scheme 56). By heating a mixture of all of the reactants at once the preparation can be run as a "one-pot" reaction ⟨88S246⟩.

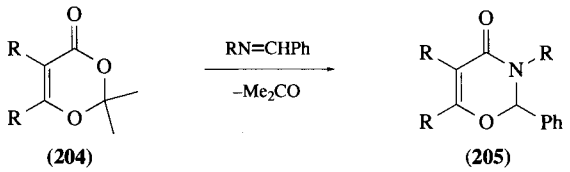


(202)

(203)

Scheme 56

Although 2,3-dihydro-1,3-oxazin-4-ones (**205**) are frequently obtained by other methods, one approach utilizes 1,3-dioxinones (**204**), which on thermolysis afford acylketenes. These undergo cycloadditions with imines *in situ* to provide the required heterocycles (Equation (17)) ⟨84CPB2602⟩.

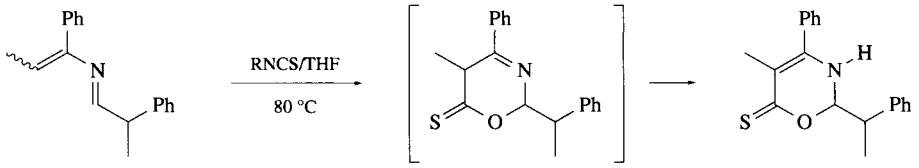


(204)

(205)

(17)

2,3-Dihydro-1,3-oxazine-6-thiones (**207**) are obtained from 2-aza-1,3-dienes through cycloaddition reactions with isothiocyanates. Presumably the initial adducts are 2,5-dihydro-1,3-oxazine-6-thiones (**206**), but these spontaneously tautomerize into the conjugated enethiones under the reaction conditions (Scheme 57) ⟨86CC1179⟩.

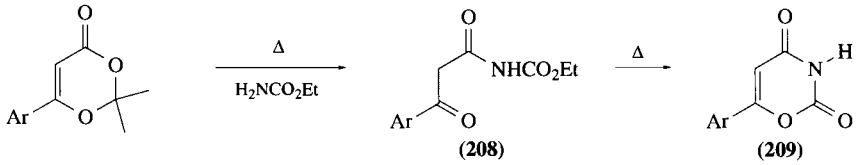


(206) (207)

Scheme 57

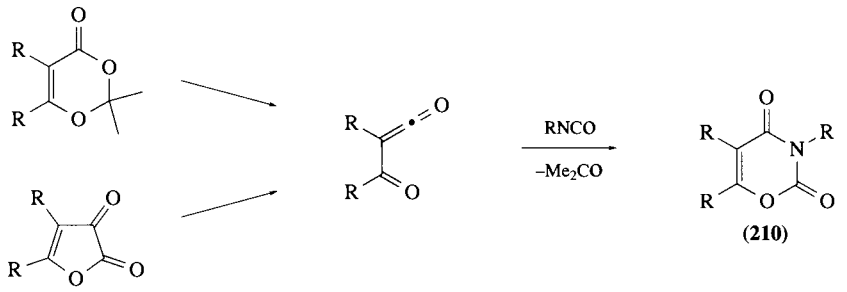
(ix) Oxazine-2,4-diones and derivatives

Hydroxy tautomers of some types of 1,3-oxazinediones have been encountered in the previous section. Here, compounds normally represented as diketo compounds are described. Thus, aroylketenes, generated through the thermolyses of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones, can be trapped by ethyl carbamate to give *N*-aroylacetylcarbamates (**208**). These products on heating give 6-aryl-1,3-oxazinediones (**209**) (Scheme 58) ⟨89ZOR2431⟩. Other syntheses utilizing 1,3-dioxinones include reactions with isocyanates to give 1,3-oxazine-2,4-diones (**210**) ⟨84CPB2602⟩. The other common source of acylketenes, furan-2,3-diones, can also be employed (Scheme 59) ⟨78KGS271⟩.



(208) (209)

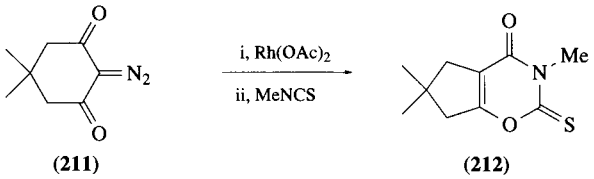
Scheme 58



(210)

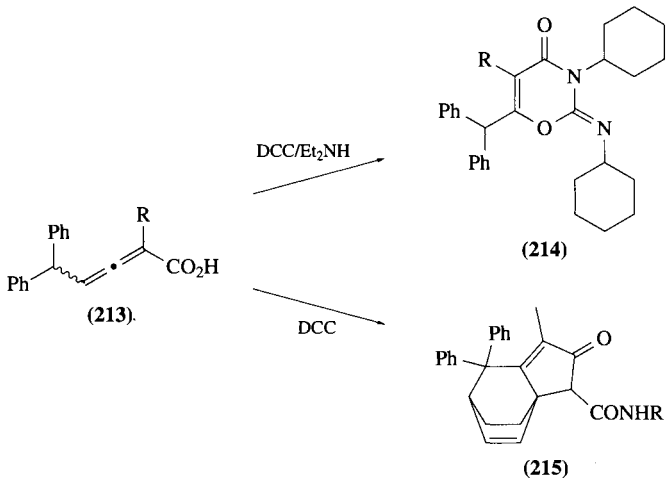
Scheme 59

Similar reactions to those used to obtain 1,3-oxazin-4-ones from diazo-1,3-diketones [Section 6.05.6.2.2(iv)] have also been employed to form 2-thioxo-1,3-oxazin-4-ones (e.g. **212**), but here diacyldiazomethanes (**211**) are treated with rhodium(II) acetate and the acylketenes released through loss of nitrogen and the Wolff rearrangement are captured by isothiocyanates (Equation (18)). The products are frequently accompanied by the corresponding 2,4-diones ⟨93BCJ238⟩.



(211) (212) (18)

Dicyclohexylcarbodiimide reacts with allenic acids (**213**) in the presence of secondary amines to afford 2-imino-1,3-oxazin-4(3*H*)-ones (e.g. **214**); however, in the absence of the amines azatricycloundecatrienones (**215**) are produced (Scheme 60) ⟨86HCA1585, 87HCA262⟩.

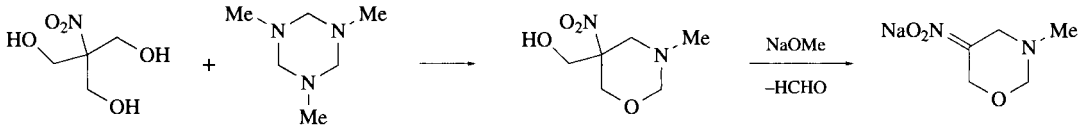


(213) (214) (215)

Scheme 60

(x) Perhydro-1,3-oxazines and oxazinones

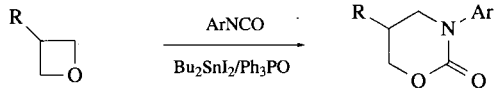
The 5-nitrotetrahydro-1,3-oxazine (**217**) is obtained from 2-hydroxymethyl-2-nitro-1,3-propanediol (**216**) by treatment with 1,3,5-trimethylhexahydro-1,3,5-triazine. When reacted with metal alkoxides, it yields the corresponding nitronate (**218**) through a retro-aldol process which proceeds with loss of formaldehyde (Scheme 61) ⟨85TL323⟩.



(216) (217) (218)

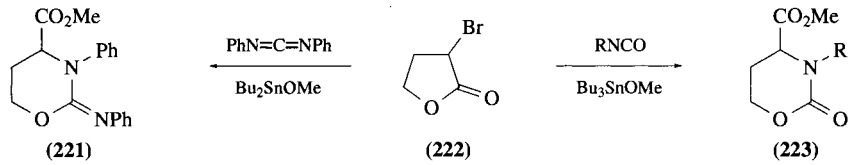
Scheme 61

A more general route to tetrahydro-1,3-oxazin-2-ones (**220**) is the addition of oxetanes (**219**) to isocyanates in the presence of dibutyltin diiodide and triphenylphosphine oxide (diphenyltin diiodide–HMPA are alternative reagents) (Equation (19)) ⟨85TL5157, 87JHC361⟩. 3-Bromo-4,5-dihydrofuran-2(3*H*)-one (**222**) can also be used as the source of three carbon atoms in a similar reaction using tributyltin methoxide as the catalyst. The products are 4-methoxycarbonyloxazin-2-ones (**223**), but the corresponding 2-imines (**221**) are formed if isocyanates are replaced by diimides (Scheme 62) ⟨88S486⟩.



(19)

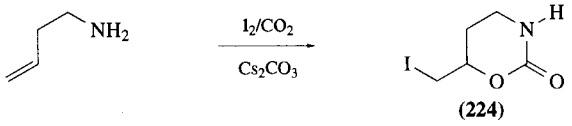
(219) (220)



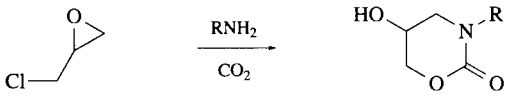
(221) (222) (223)

Scheme 62

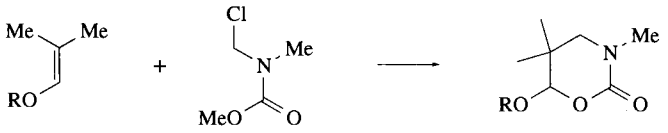
3,4,5,6-Tetrahydro-6-iodomethyl-2-one (**224**) is formed from 3-butenamine by coupling it with carbon dioxide in the presence of iodine and caesium carbonate (Equation (20)) ⟨87AG(E)334⟩ and in related chemistry 2-chloromethyloxirane (**225**) reacts with primary amines in the presence of carbon dioxide to give 5-hydroxytetrahydro-1,3-oxazin-2-ones (**226**) (Equation (21)) ⟨86NKK1196⟩. Cycloadditions with activated alkenes can also be used. Thus, 6-alkoxytetrahydro-1,3-oxazin-2-ones (**228**; R = Me, or Et) are synthesized through the reactions of alkyl vinyl ethers with *N*-chloromethylcarbamates (**227**) (Equation (22)) ⟨88ZOB1919⟩.



(224) (20)



(225) (226) (21)



(227) (228) (22)

6.05.6.2.3 [5 + 1] Types

(i) 4H-1,3-Benzoxazines and derivatives

Malononitrile and similar "active" acetonitriles combine with 3,5-bis(2,4-cyclohexadien-1-on-6-ylidene)-1,2,4-dithiazolidine (**229**) to yield dicyanomethylene-1,3-benzoxazines (**231**). Presumably intermediates (**230**) are formed through addition of the malononitrile to the exocyclic double bond at C-3 of the dithiazolidine, allowing in turn ring-opening, aromatization of the 1,2-quinonemethide ring, cyclization to the oxazine unit, and finally loss of hydrogen sulfide plus sulfur (Scheme 63) ⟨85S535⟩.

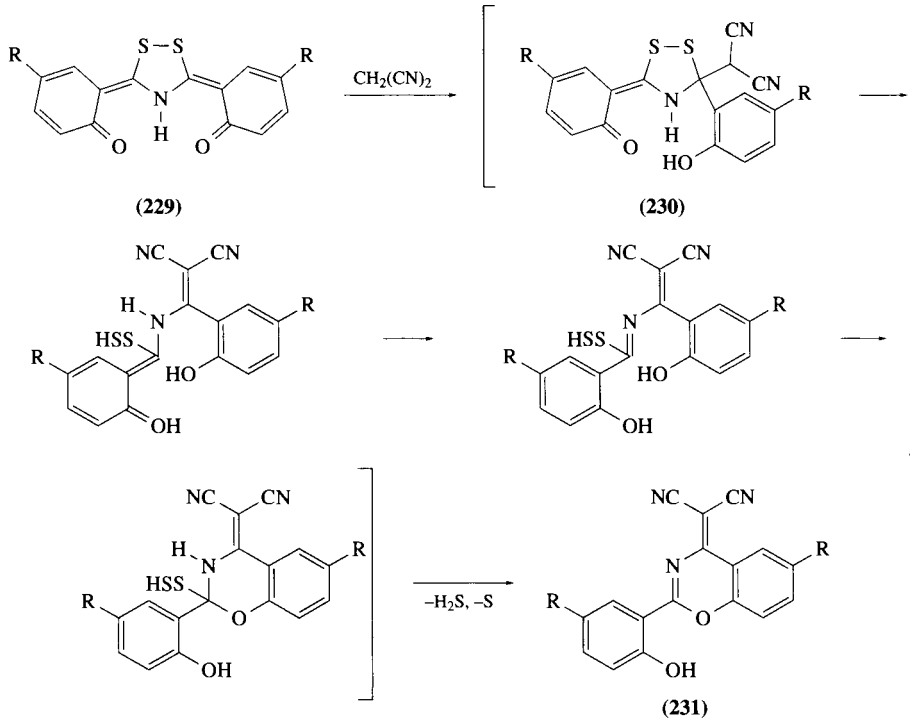
Naphtho[1,8-*de*][1,3]oxazines (**234**; R^1 = alkyl, or alkenyl) are formed from 1,8-aminonaphthol (**232**) and 1-aminoalkynes, presumably through the intermediacy of the amino adducts (**233**) which eliminate the appropriate amine under the reaction conditions (Scheme 64) ⟨91KGS532⟩.

(ii) 4H-3,1-Benzoxazines

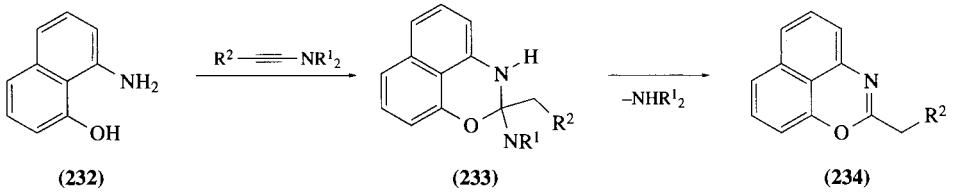
2-Aryl-4-methylene-3,1-benzoxazines (**236**) are synthesized by aza-Wittig reactions between 2-acetylphenyliminophosphoranes (**235**) and aroyl chlorides. If the aroyl chlorides are replaced by variously substituted isocyanates, a range of 2-amino derivatives (**237**) are obtained (Scheme 65) ⟨93T7599⟩.

2-Cyanamino-4*H*-3,1-benzoxazine (**239**) can be derived from its tautomer 1,4-dihydro-3,1-benzoxazine-2-cyanimine (**238**) by treatment with ammonia, or primary or secondary alkylamines. The starting material is synthesized by treating 2-aminobenzyl alcohol with diphenyl cyanocarbonimidate (Scheme 66) ⟨89T829⟩.

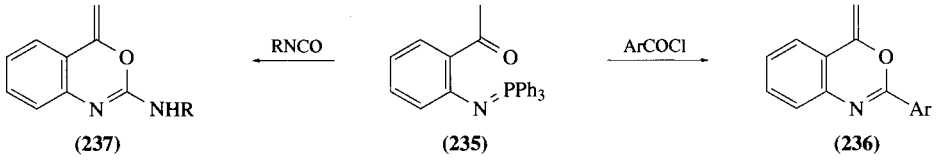
4*H*-3,1-Benzoxazines (e.g. **240** and **241**) bearing substituents at C-2 are also available through the condensations of 2-aminobenzyl alcohols with disubstituted allenic nitriles and acetylenic nitriles, respectively (Scheme 67) ⟨88JCS(P1)277⟩.



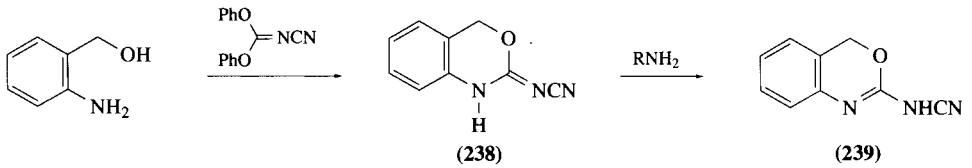
Scheme 63



Scheme 64



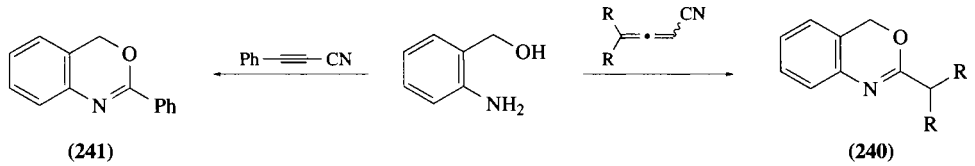
Scheme 65



Scheme 66

(iii) 1,3-Oxazin-2-ones and 2-thiones

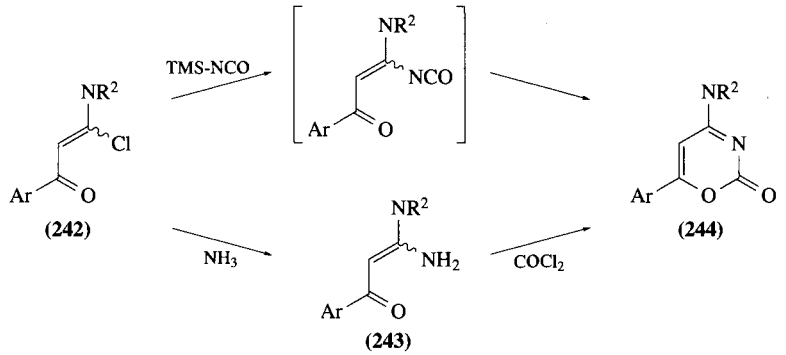
Approaches to 1,3-oxazin-2-ones (**244**) utilize acylchloroenamines (**242**), either directly by reactions with trimethylsilyl isocyanate, or in a two-step sequence in which the corresponding acylvinylamidines (**243**) are formed first by reactions with ammonia and these products are then cyclized



(241) (240)

Scheme 67

with phosgene (Scheme 68). The first procedure can also be used to synthesize the corresponding 2-thiones if trimethylsilyl isothiocyanate, or sodium isothiocyanate, replaces trimethylsilyl isocyanate ⟨87M1263⟩.

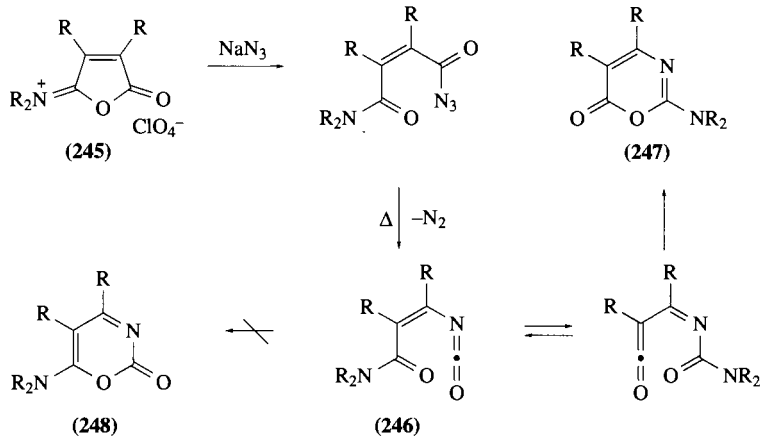


(242) (243) (244)

Scheme 68

(iv) 1,3-Oxazin-6-ones

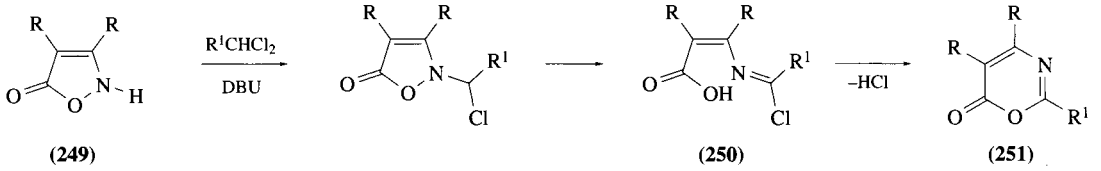
Full details of the synthesis of supposed 6-amino-1,3-oxazin-2-ones (**248**), as reported in the first edition, have been published ⟨81JCS(P1)2871⟩, but now it seems that these compounds are almost certainly 2-amino-1,3-oxazin-6-ones (**247**) (see Section 6.05.3). The method of synthesis is a two-step sequence beginning with the ring opening of furanoimidium salts (**245**), through attack at the carbonyl group by azide ion. This is followed by thermolyses of the product acyl azides to give *cis*-isocyanates (**246**) (Scheme 69). According to Beccalli and Marchesini, cyclization does not take place immediately as thought previously; instead a [1,5]-transfer of the amino substituent occurs, leading to 1,3-oxazin-6-ones (**247**) ⟨87JOC3426⟩. It should be noted that substituents at position C-4 and/or at C-3 in the furanimidium salts are necessary, otherwise azide anion may react there, rather than at the carbonyl group, leading eventually to the formation of *trans*-isocyanates which cannot undergo the [1,5]-shift required for heterocyclization.



(245) (247) (248) (246)

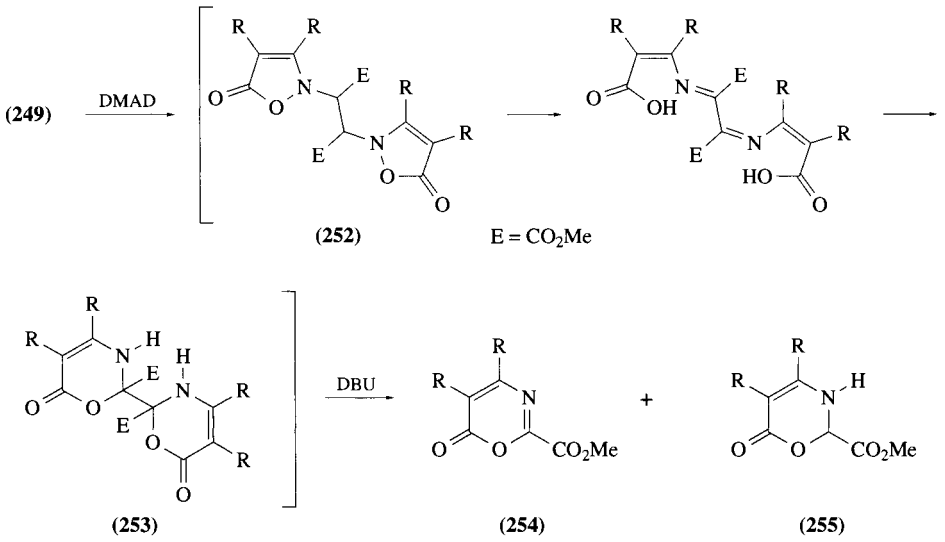
Scheme 69

Isoxazolinones (**249**) combine with dichloromethanes in the presence of a base (DBU) to afford 1,3-oxazin-6-ones (**251**). It is likely that carbenes are generated in these reactions, which attack the nitrogen atom of the isoxazolinones to form *N*-chloromethyl derivatives. Ring-chain tautomerism generates azabutadienes (**250**) and these cyclize with loss of hydrogen chloride (Scheme 70) ⟨88S630⟩. Related chemistry involves double Michael additions of dimethyl alkynedicarboxylate to the isoxazolinones; this gives adducts (**252**) which ring open and then ring-close to afford bis(oxazinyl) derivatives (**253**). Treatment of (**253**) with DBU effects fragmentation into the oxazinones (**254**) and the dihydrooxazinones (**255**) (Scheme 71) ⟨87JOC1666⟩.



(249) (250) (251)

Scheme 70



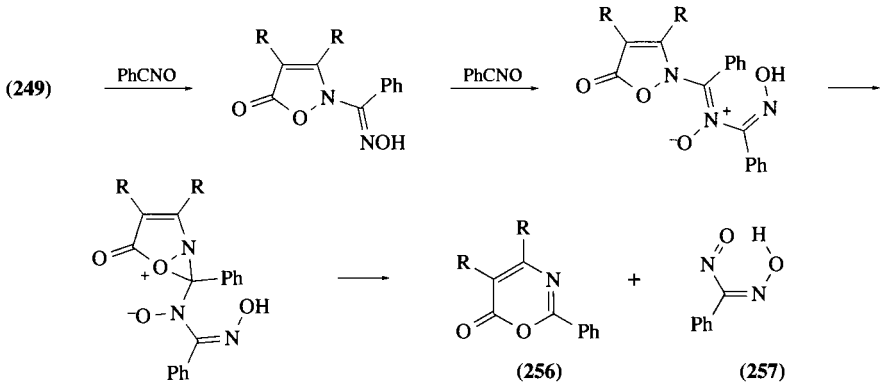
(252) E = CO_2Me

(253) (254) (255)

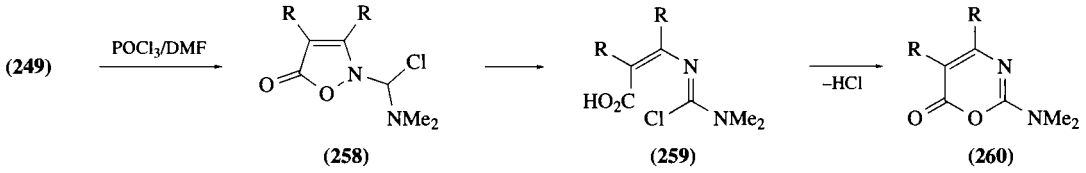
Scheme 71

When isoxazolin-5-ones (**249**) are treated with benzonitrile oxide ring-expansion to 1,3-oxazin-5-ones (**256**) occurs, but the reactions are not simple and two equivalents of the nitrile oxide are involved, perhaps as shown in Scheme 72. Certainly, the oxime (**257**) is a by-product, which decays under the reaction conditions to nitrous acid and benzonitrile ⟨79JCS(P1)1522⟩. In yet another synthesis of oxazin-6-ones, isoxazolin-5-ones are reacted with phosphorus oxychloride and DMF under Vilsmeier–Haack conditions. Two reaction pathways are noted, depending upon the substitution pattern of the isoxazolinones: thus, if the starting materials are substituted at C-4 attack of the Vilsmeier reagent occurs at the nitrogen atom, generating the adducts (**258**), which ring-open to chloroazadienes (**259**). Recyclization, followed by loss of hydrogen chloride, then affords 2-dialkylamino-1,3-oxazin-6-ones (**260**) (Scheme 73). However, when there is no substituent at C-4 the initial attack is directed to this site and 5-formyl-1,3-oxazin-6-ones (**261**) are produced, together with 5-chloro-4-formylisoxazoles (**262**) (Scheme 74) ⟨87JOC3426⟩.

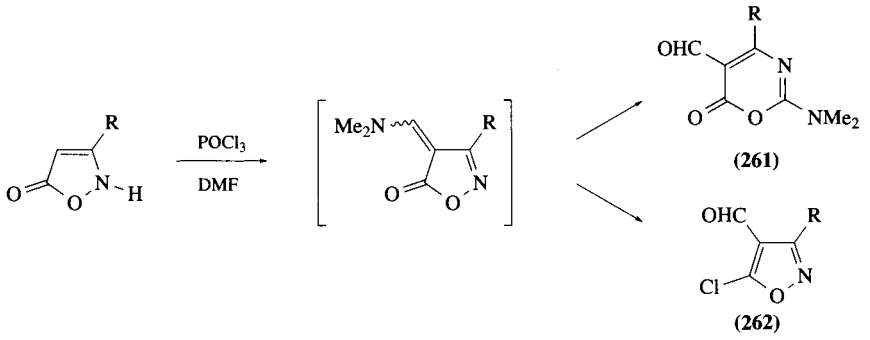
4-Chloro-5-cyano-2-(*N*,*N*-dimethylamino)-1,3-oxazin-6-one (**264**) is available through the reaction of the salts (**263**) of alkyl 2,2-dicyanoacetates and dichloromethyleninimium chloride. The chlorine atom of the oxazinone can be displaced by alkanols to give the alkoxy derivatives (**265**; R = O-alkyl). Similar treatment with primary and secondary amines yields the corresponding diamino-1,3-oxazinones (e.g. **265**; R = Et_2N, NHPh or NHBu) (Scheme 75) ⟨90S959⟩.



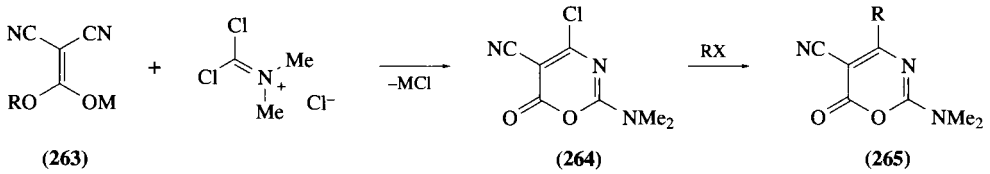
Scheme 72



Scheme 73



Scheme 74

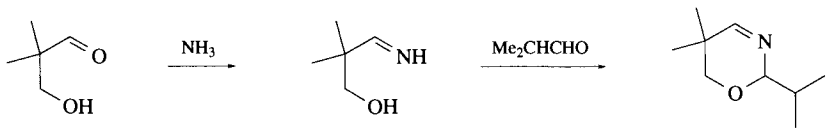


Scheme 75

*(v) 5,6-Dihydro-2*H*-1,3-oxazines, 5,6-dihydro-4*H*-1,3-oxazines, and 3,4-dihydro-2*H*-1,3-benzoxazines*

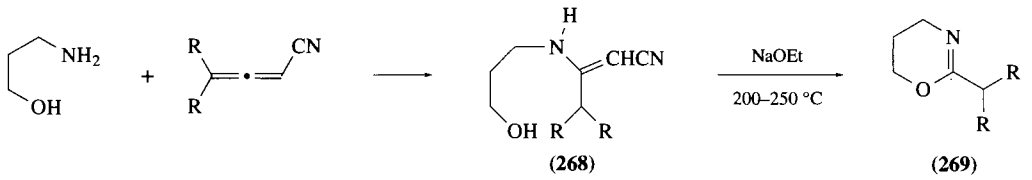
Another route to the uncommon 5,6-dihydro-2*H*-1,3-oxazines (**267**) (see Section 6.05.6.2.2(vi)) requires the reactions of 3-hydroxypropanals with alkanals (other than formaldehyde), or alkanones, in the presence of ammonia (Scheme 76) ⟨93T9495⟩. It is notable that 3-hydroxypropanones do not react in this way, and it seems that the initial step is the formation of imines (e.g. **266**); thus when hydroxypropanones are used the more electrophilic alkanals, present as co-reactants, irreversibly scavenge ammonia and the cyclization step is prevented.

5,6-Dihydro-4*H*-1,3-oxazines (**269**) can be prepared in two steps: first the addition of allenyl nitriles and 3-aminopropanol to give enamino nitriles (**268**), and then treatment of these products with a catalytic amount of sodium ethoxide at 200–250 °C (Scheme 77) ⟨81H(16)1889⟩.



(266) (267)

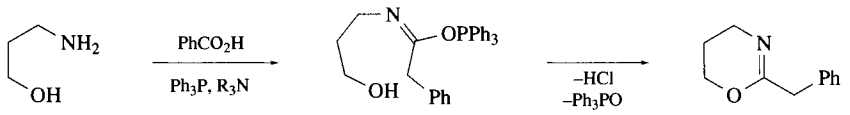
Scheme 76



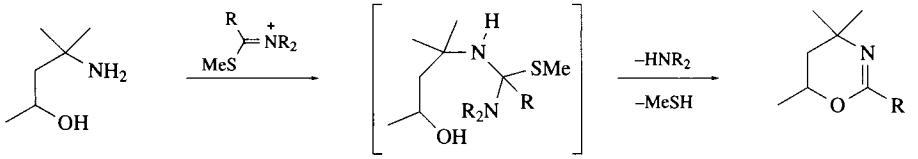
(268) (269)

Scheme 77

Other methods include (i) the cyclocondensation of carboxylic acids and 3-aminopropanols in the presence of triphenylphosphine and either pyridine in carbon tetrachloride, or triethylamine in acetonitrile (Scheme 78) ⟨81TL4471, 93T9353⟩ and (ii) the reaction of aminoalcohols with thioamide salts (Scheme 79) ⟨79CL1353⟩.



Scheme 78

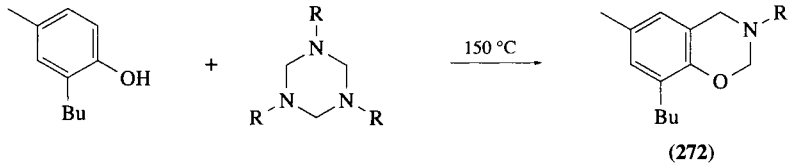


Scheme 79

A standard way of synthesizing 1,3-benzoxazines is to react 2-hydroxybenzylamines with aldehydes or ketones ⟨88JCS(P2)461⟩; this approach is exemplified by a construction of pyrazolo[2,3-*c*]benzoxazines (**271**) from 5-(2-hydroxyphenyl)pyrazoles (**270**) and acetone (Equation (23)) ⟨86MI 605-02⟩.

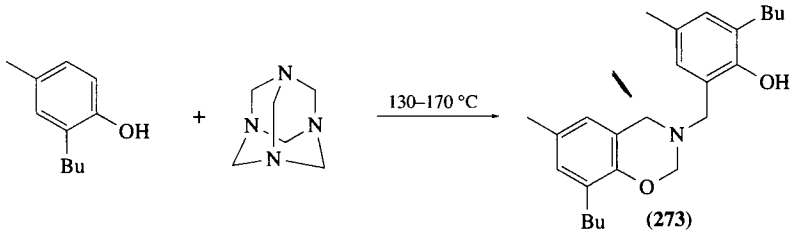
(270) (271) (23)

Reaction of phenols and hexahydro-1,3,5-triazines at 150 °C also provides access to dihydro-1,3-benzoxazines (**272**) (Equation (24)). Similar constructions use hexamethylenetetramine, rather than hexahydro-1,3,5-triazines, but now the products are 3-benzyl derivatives (e.g. **273**) (Equation (25)) ⟨85ZOR2243⟩. It seems likely that, in these reactions, the nitrogen-containing reagents act as sources of methylenimine, which convert the phenols into the corresponding benzylamines. Further reactions with more methylenimine then results in cyclization; if so these preparations are closely related to those which employ hydroxybenzylamines and carbonyl compounds.



(24)

(272)

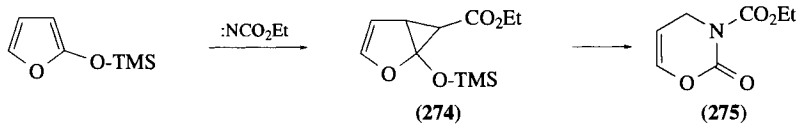


(25)

(273)

(vi) Dihydro-1,3-oxazin-2-ones and dihydro-3,1-benzoxazin-2-ones

2-Trimethylsilyloxyfuran reacts with ethoxycarbonylnitrene to give 3-ethoxycarbonyl-3,4-dihydro-1,3-oxazin-2-one (**275**). The nature of the product is unaffected by the conditions used to generate the nitrene, but it may be assumed that the nitrene reacts to form an aziridine intermediate (**274**), which then undergoes desilylation and ring opening to form the product (Scheme 80) ⟨89TL5025⟩.



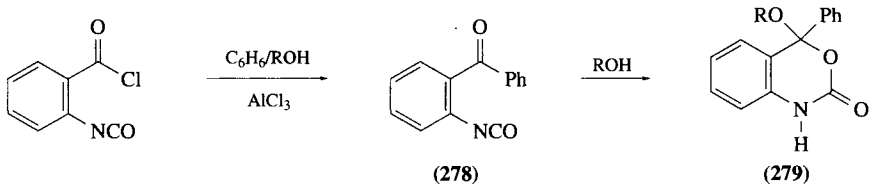
(274) (275)

Scheme 80

Spirocyclic pyrido-1,3-oxazin-2-ones (**277**) can be obtained by the reactions of 2-amino-3-(1-hydroxycycloalkanyl)pyridines (**276**) with butyllithium and diethyl carbonate (Equation (26)) ⟨89JHC113⟩, and 1,4-dihydro-3,1-benzoxazin-2-ones (**279**) are available through the reactions of 2-benzoylphenyl isocyanates (**278**) with alcohols. The former are prepared by Friedel–Crafts acylation of benzene by 2-isocyanatobenzoyl chloride in the presence of aluminum(III) chloride (Scheme 81) and the whole process can be run as a "one pot" reaction ⟨87JCR(S)96⟩.

(26)

(276) (277)



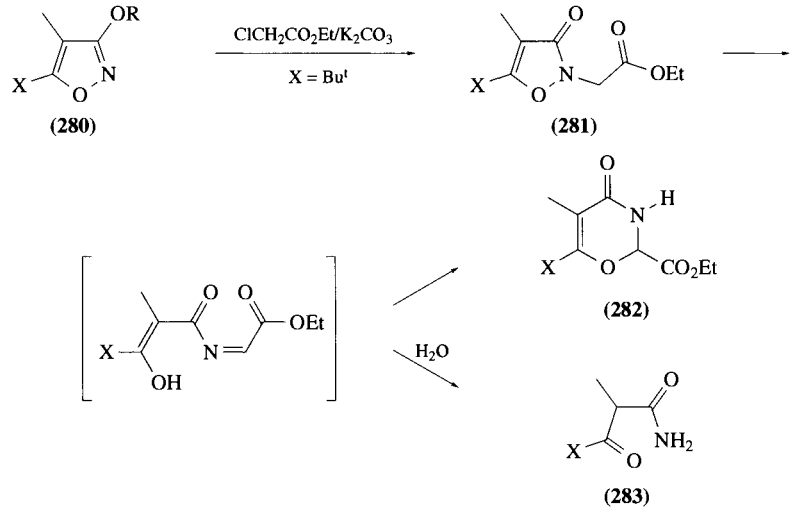
(278) (279)

Scheme 81

(vii) Dihydro-1,3-oxazin-4-ones

When the 3-hydroxyisoxazole (**280**, R = H) is reacted with ethyl chloroacetate and potassium carbonate, three products are formed: (i) the expected ester (**280**; R = CO_2Et) (27%), (ii) the 3,4-

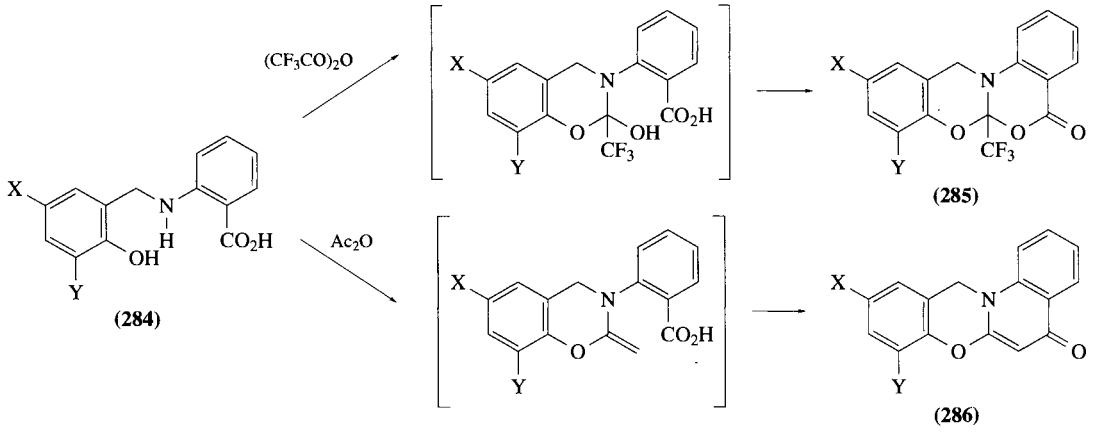
dihydro-1,3-oxazin-4(2*H*)-one (**282**) (21%); and (iii) the amide (**283**) (10%). It is suggested that the last two compounds arise through the intermediacy of the *N*-alkylated isoxazolinone (**281**) and an acylic tautomer (Scheme 82) ⟨91JCS(P1)2009⟩.



Scheme 82

(viii) Dihydro-1,3-oxazin-6-ones and 1,2-dihydro-3,1-benzoxazin-4-ones

2-Alkoxy-1,2-dihydro-3,1-benzoxazin-4-ones are often prepared from anthranilic acids by reaction with alkyl chloroformates in the presence of pyridine ⟨87PHA694⟩. More complex compounds such as the [3,1]benzoxazino[2,1-*b*][1,3]oxazin-5-ones (**285**) are synthesized through a tandem cyclization process when *N*-(2-hydroxybenzyl)anthranilic acids (**284**; X = H, Me, or Cl: Y = H, or Me) are treated with trifluoroacetic anhydride ⟨88JHC297⟩. When reacted with acetic anhydride, however, the course of the reaction is changed and quino[2,1-*b*][1,3]benzoxazines (**286**) are produced (Scheme 83) ⟨89JHC237⟩.

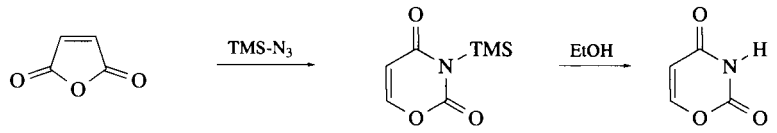


Scheme 83

*(ix) 1,3-Oxazine-2,4(3*H*)-diones, 6-thioxo-1,3-oxazin-2(3*H*)-ones, and 1,3-oxazine-2,6(4*H*)-diones*

3-Trimethylsilyl-1,3-oxazine-2,4(3*H*)-dione (**287**) is formed by reacting maleic anhydride with trimethylsilyl azide at 55–60 °C. On treatment with ethanol, the *N*-silyl bond is cleaved to give 1,3-

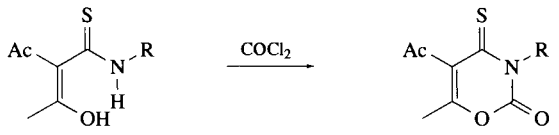
oxazine-2,4(3*H*)-dione (Scheme 84) ⟨77OPP87⟩. The reaction is probably initiated by silylation of a carbonyl oxygen atom and the relative accessibility of one carbonyl group versus the other has been used to explain the product selectivity noted when certain substituted maleic anhydrides are used as starting materials ⟨78JOC2719⟩.



(287)

Scheme 84

5-Acetyl-3,4-dihydro-6-methyl-4-thioxo-1,3-oxazin-2-ones (**289**) are formed by treating 2-acetyl-3-oxobutanoic thioamides (**288**) with phosgene (Equation (27)) ⟨88JPR(330)795⟩ and fused analogues, such as the pyrrolo-1,3-oxazine-2,6-diones (**291**), are available through acylation and cyclization of *t*-butyl 1-alkyl-2-amino-pyrrole-3-carboxylates (**290**) with phosgene (Equation (28)) ⟨85S796⟩.



(27)

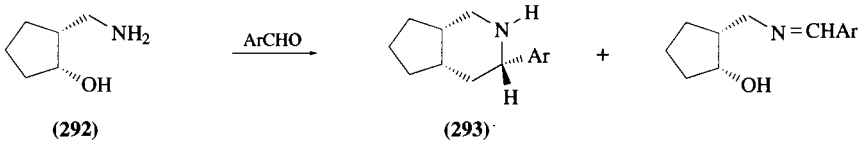
(288) (289)

(28)

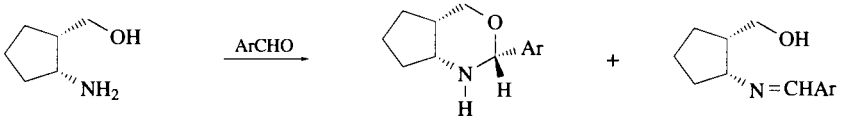
(290) R^1 = alkyl; R^2 = Bu^t (291)

(x) Perhydro-1,3-oxazines, oxazinones, and oxazinediones and derivatives

Fully reduced bicyclic 1,3-oxazines are obtained from the reactions of 2-hydroxymethylcycloalkylamines with formaldehyde ⟨85T5159⟩, and similarly araldehydes combine with either *cis*-2-hydroxymethylcyclopentylamine (**292**), or *cis*-2-aminomethylcyclopentanol (**294**) to give the corresponding bicyclic perhydro-1,3-oxazines (**293** and **295**, respectively). In each case, however, the bicycles are accompanied by the appropriate monocyclic hydroxyimines (Scheme 85) ⟨89MI 605-01⟩.



(292) (293)

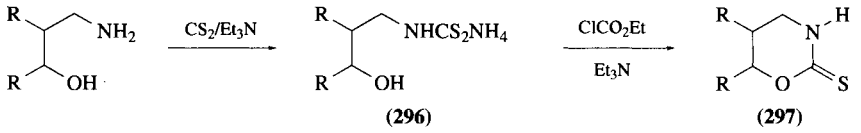


(294) (295)

Scheme 85

Tetrahydro-1,3-oxazin-2-ones may be obtained through the palladium-catalyzed carbonylation of 3-aminopropanols ⟨86JOC2977⟩, but despite these innovations more traditional methods for the syntheses of perhydro-1,3-oxazines are still used: for example, the cyclization of 3-aminopropanols with ethyl chloroformate, phosgene, or similar reagents ⟨76BAP447⟩. The preparation of the cor-

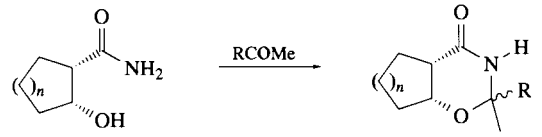
responding 2-thiones (**297**) employs the same starting materials, but thiophosgene, or carbon disulfide, is now the reagent ⟨83MI 605-01⟩. The reactions may involve more than one step; thus, when 3-aminopropanols are reacted with carbon disulfide and triethylamine intermediate dithiocarbamates (**296**) are formed. These may then be cyclized to the thiones by treatment with ethyl chloroformate and triethylamine (Scheme 86) ⟨86MI 605-01⟩.



(296) (297)

Scheme 86

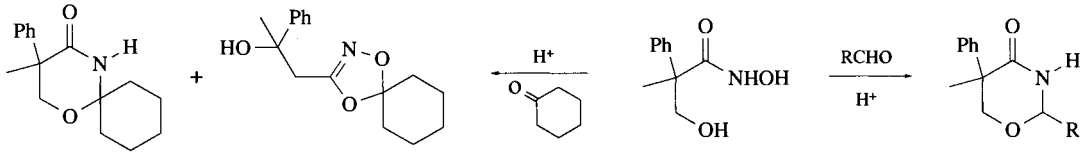
Bicyclic tetrahydro-1,3-oxazin-4-ones, such as the perhydro-1,3-oxazin-2-ones (**298**; $n = 1$, or 2), are also formed by an established method, namely the reactions of ketones with the appropriate 1,2-hydroxyamides (Equation (29)) ⟨84JCS(P1)84, 88MI 605-01⟩.



(29)

(298)

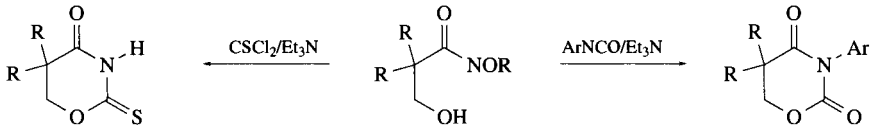
N-(Hydroxyacyl)hydroxylamines (e.g. **299**) readily yield the corresponding *N*-hydroxyperhydro-1,3-oxazin-4-ones (**300**) when treated with phenylacetaldehyde dimethylacetal and aqueous acid, or paraformaldehyde. Ketones react similarly, but in certain cases the expected products are accompanied, or even replaced, by dioxazoles. Cyclohexanone, for example, gives the spiro-oxazinone (**301**) and the dioxazole (**302**) (Scheme 87) ⟨85AP(318)895⟩.



(301) (302) (299) (300)

Scheme 87

N-Alkoxy-3-hydroxypropionamides (**303**) and aryl isocyanates cyclize in the presence of triethylamine to produce perhydro-1,3-oxazine-2,4-diones (**304**) ⟨79CB600⟩. If thiophosgene is used instead of an aryl isocyanate, the corresponding 2-thioxo-1,3-oxazin-4-ones (**305**) are obtained (Scheme 88) ⟨79CZ79⟩.



(305) (303) (304)

Scheme 88

6.05.6.2.4 [6 + 0] Types

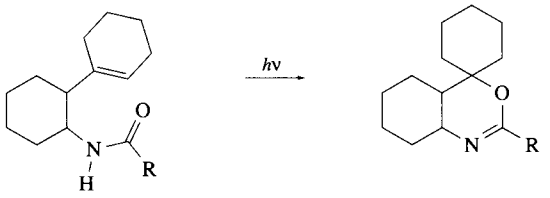
(i) 1,3-Oxazinium salts

N-Acyl-β-enamino ketones (**306**), prepared from *N*-substituted dithiocarbonimidates and the potassium enolates of methyl ketones, on treatment with perchloric acid or methanesulfonic acid, yield 1,3-oxazinium salts (**307**) (Equation (30)) ⟨83JOC623⟩.

(306) (307) (30)

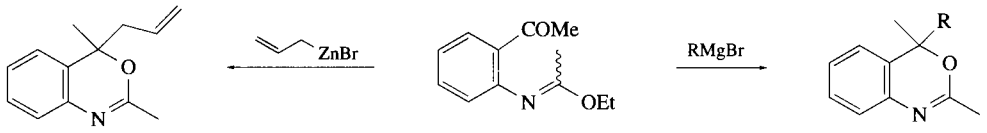
(ii) 6H-1,3-Oxazines, 4H-3,1-benzoxazines, and 1,3-benzoxazin-4-ones

Dienamides (**308**; R = Me, Ph, or 1-naphthyl) undergo spiroannelation to the 3,1-benzoxazines (**309**) when irradiated in hexane solution with ultraviolet light. A double bond in the ring to which the amide function is attached is not an essential requirement for cyclization, but aryl units may impair the reactivity of the system (Equation (31)) ⟨88T1959⟩.



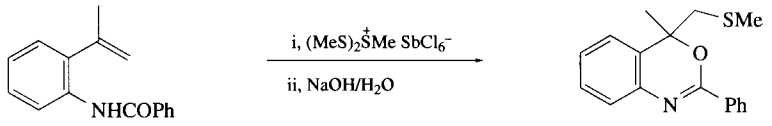
(308) (309) (31)

4*H*-3,1-Benzoxazines (**311**) or (**312**) can be synthesized by reacting imidates (**310**) with Grignard reagents and allylzinc bromide, respectively (Scheme 89) ⟨92SC295⟩. They are also formed when 2-vinylanilides (**313**) are treated with methyl bis(methylthio)sulfonium hexachloroantimonate, followed by basification of the product salts (Equation (32)) ⟨86JCR(S)200⟩.



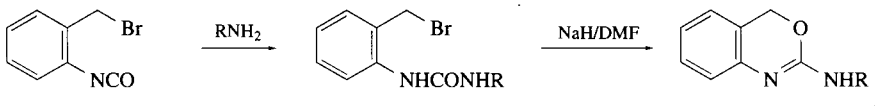
(312) (310) (311)

Scheme 89



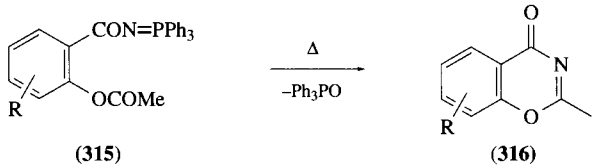
(313) (32)

Yet another approach to 3,1-benzoxazines requires the base-promoted cyclizations of 2-bromomethylphenylureas (**314**), preformed from the corresponding isocyanates by reactions with amines (Scheme 90) ⟨90CCC752⟩, and a neat construction of 1,3-benzoxazin-4-ones (**316**) requires the thermolysis of benzoyliminophosphoranes (**315**) in boiling toluene. Here an intramolecular aza-Wittig reaction occurs, during which the benzoxazinone is formed and triphenylphosphine oxide is eliminated (Equation (33)) ⟨85CB4632⟩.



(314)

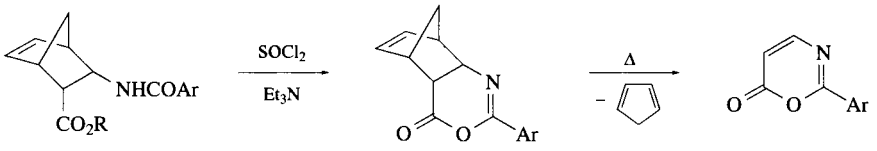
Scheme 90



(315) (316) (33)

(iii) 1,3-Oxazin-6-ones and 3,1-benzoxazin-4-ones

N-(Aroylamino)norbornene carboxylates (**317**) are cyclized by treatment with thionyl chloride and triethylamine. The tricyclic 1,3-oxazinones (**318**) thus formed undergo retro-Diels–Alder reactions when heated at 150 °C to give 2-aryl-1,3-oxazin-6-ones (**319**) and cyclopentadiene (Scheme 91) ⟨84S345⟩.

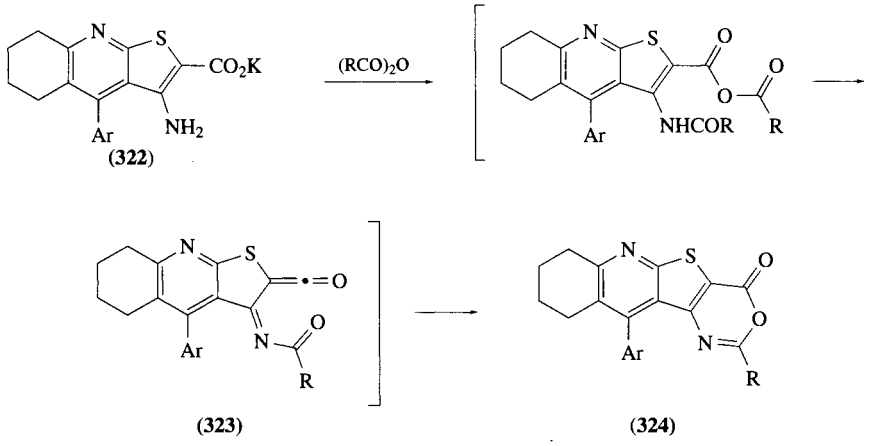


Scheme 91

The initial cyclization reaction in the previous synthesis is similar to that used in the formation of thienooxazinones (**321**) through the annulation of thiophene carboxylic acids (**320**) by thionyl chloride in the presence of DMF (Equation (34)) ⟨80KGS45⟩.

(34)

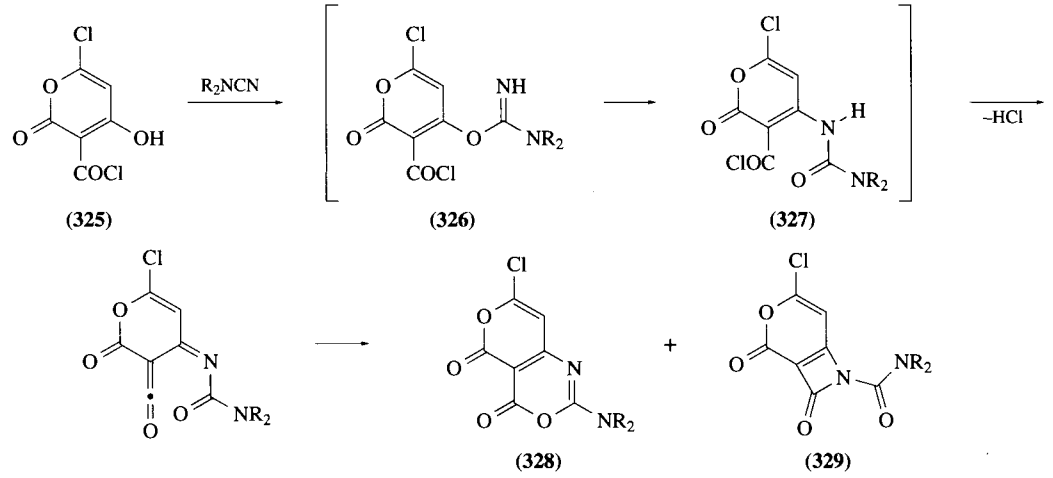
1,3-Oxazin-6-ones are formed from the potassium salts of (*Z*)-3-aminopropenoic acids by treatment with acid anhydrides. This approach has been used to prepare the tetrahydroquinolinothieno-1,3-oxazine (**324**) from the amino carboxylate (**322**) and it seems probable that in the cyclization the key step is a cycloaddition of an intermediate ketene (**323**) (Scheme 92) ⟨93PHA63⟩.



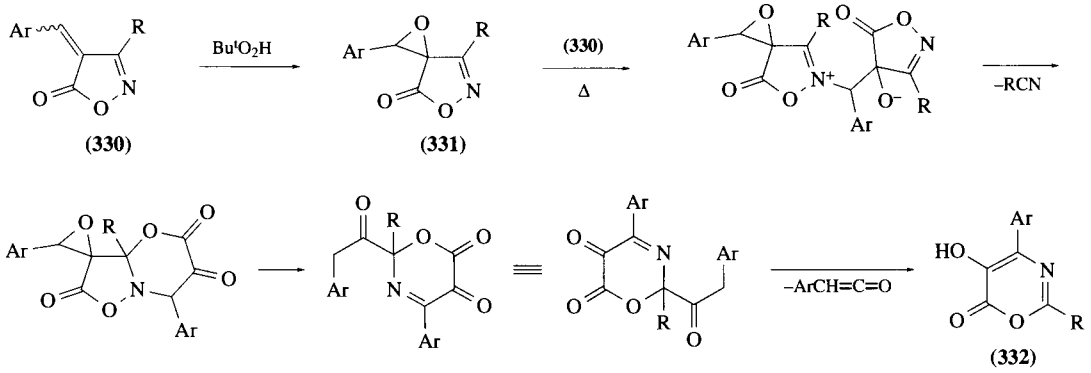
Scheme 92

Malonyl chloride enolizes and cyclizes to form a pyranone (**325**) which combines with dialkylcyanamides to yield pyrano[4,3-*b*][1,3]oxazinediones (**328**), as well as pyranoazetediones (**329**). Presumably, the first step is the formation of adducts (**326**), which undergo rearrangement to the ureas (**327**) and elimination of hydrogen chloride to yield ketenes. Alternate intramolecular cycloadditions of the ketenes afford the final products (Scheme 93) ⟨85CB4707⟩.

5-Hydroxy-1,3-oxazin-6-ones (**332**) can be synthesized by the thermal rearrangement of 6-aza-1,5-dioxaspiro[2.4]hept-6-en-4-ones (**331**) in boiling toluene. The starting compounds are available simply by the epoxidation of the appropriate 4-alkylideneisoxazolones (**330**) with *t*-butyl hydroperoxide, but the mechanism of the ring-expansion reaction is complex and may involve two molecules of the substrate as illustrated in Scheme 94 ⟨91H(32)1181⟩.

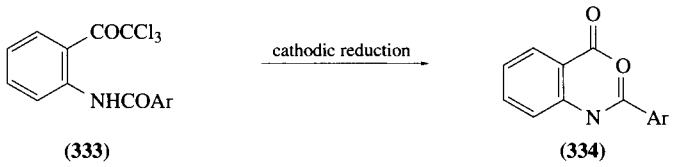


Scheme 93



Scheme 94

3,1-Benzoxazin-4-ones (**334**) are available through the electrochemical reduction of 2-trichloroacetylanilides (**333**) at a mercury pool cathode in acetonitrile plus a supporting electrolyte (Equation (35)) ⟨93TL175⟩.

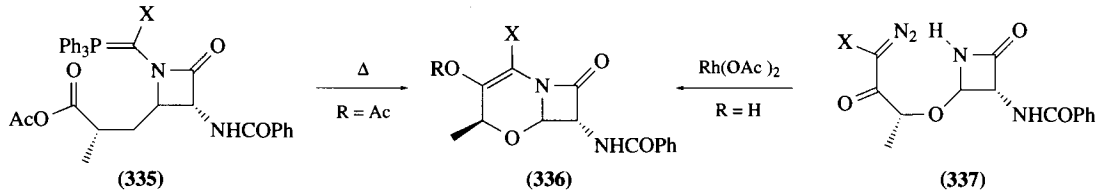


(35)

(iv) Dihydro-1,3-oxazines

Methods for the formation of the six-membered ring of oxacephalosporins (**336**) include the intramolecular Wittig cyclization of azetidinonyl ylides (**335**) and the rhodium(II) acetate generation of carbene intermediates from 4-alkoxylactams (**337**) bearing a diazoketone unit in the side chain. Once formed, the carbenes insert into the N—H bond of the lactam unit thereby effecting ring closure (Scheme 95) ⟨90H(31)791, 90H(31)797⟩.

The above products can be regarded as examples of 3,6-dihydro-2*H*-1,3-oxazines. Monocyclic representatives of 5,6-dihydro-4*H*-1,3-oxazines (**339**) are readily obtained through the acid-mediated cyclization of 3-amidopropanols (**338**) (Equation (36)) ⟨82MI 605-01⟩. Spirocyclic 2-aryl-5,6-dihydro-4*H*-1,3-oxazines (**341**) are available through the oxidative cyclization of 4-(*N*-aroylaminoethyl)phenols (**340**) by treatment with thallium(III) trifluoroacetate in trifluoroacetic acid (Equation



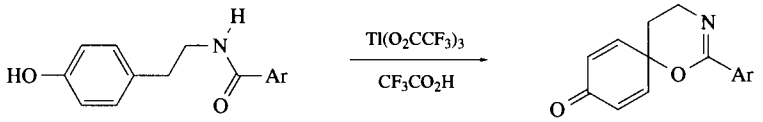
(335) (336) (337)

$X = CO_2CHPh_2$

Scheme 95

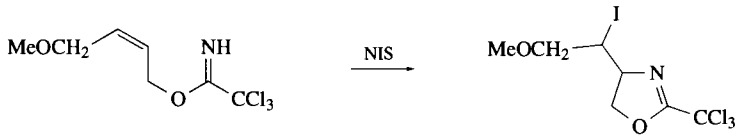
(37)). It is suggested that the reactions occur through the formation of intermediate radical cations formed by single electron abstraction from the phenolic unit by the thallium(III) cation ⟨86SC1599⟩.

(338) (339) (36)

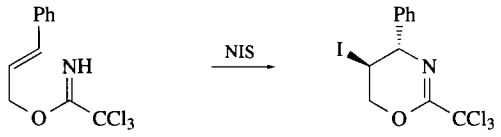


(340) (341) (37)

The iodocyclization of allylic imidates by reaction with *N*-iodosuccinimide (NIS) gives 4,5-dihydro-1,3-oxazolines (**343**) or 5,6-dihydro-4*H*-1,3-oxazines (**345**) depending upon the configuration of the double bond. Thus, the (*Z*)-isomers (**342**) ring close preferentially through the 5-*exo-trig* mode to yield oxazolines (Equation (38)), whereas (*E*)-allylic imidates (**344**) form oxazines through 6-*endo-trig* cyclizations (Equation (39)) ⟨86JOC4905⟩.

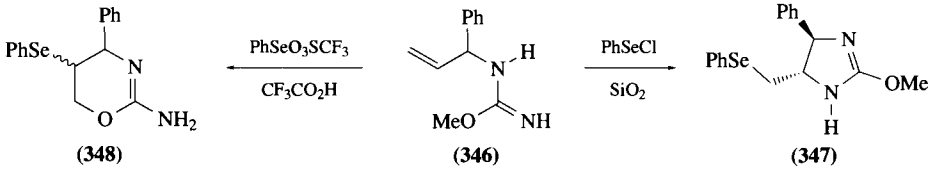


(342) (343) (38)



(344) (345) (39)

Even more subtle effects are manifest in the case of allylic *O*-methylisoureas (e.g. **346**), which are cyclized to imidazolines (**347**) by phenylselenenyl chloride in the presence of silica gel, but with trifluoromethyl phenylthioselenate and trifluoromethanesulfonic acid the products are 5,6-dihydro-4*H*-1,3-oxazines (**348**) (Scheme 96) ⟨89CC452⟩.

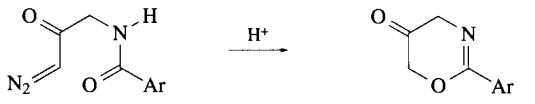


(348) (346) (347)

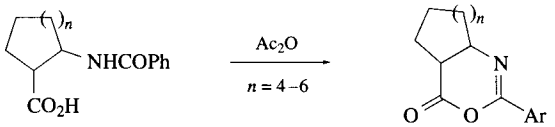
Scheme 96

(v) Dihydro-1,3-oxazinones and 1,3-oxazine-2,4-diones

4,6-Dihydro-1,3-oxazin-5-ones (e.g. **350**) are uncommon, but may be obtained by the treatment of diazoketones (**349**) with mineral acids (Equation (40)) ⟨90KGS565⟩. In contrast, there are many examples of 1,3-oxazin-6-ones and some examples of the [6 + 0] type of ring formation apply to them. For example, cyclodehydration of 3-acylaminopropionic acids normally affords the corresponding anhydrides, but should the starting material be cyclic (e.g. **351**) then 4,5-dihydro-1,3-oxazin-6-ones (e.g. **352**) are formed (Equation (41)) ⟨87MI 605-01⟩.

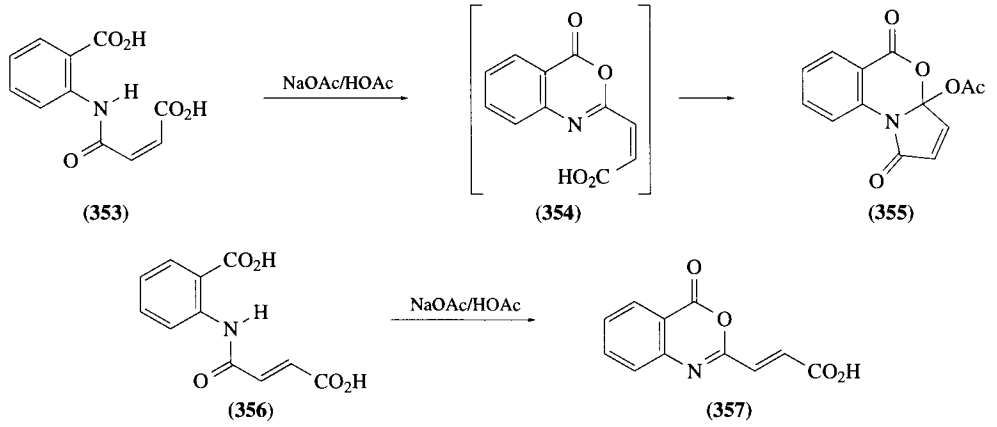


(349) (350) (40)



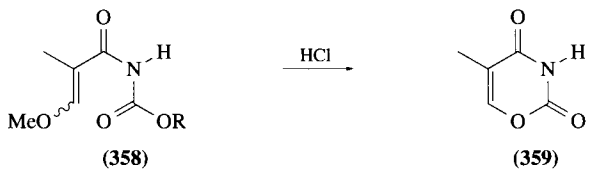
(351) (352) (41)

3,1-Benzoxazin-4-ones are very well-known compounds, sometimes called acylanthranils. Recent examples include the pyrrolo-3,1-benzoxazinone (**355**), which is synthesized through the intramolecular double cyclization of the maleanilic acid (**353**) when it is treated with sodium acetate and acetic anhydride. It seems possible that 2-[(*Z*)-carboxypropen-3-yl]-3,1-benzoxazin-4-one (**354**) is formed first, which then undergoes further ring closure and addition of acetate anion. Circumstantial evidence in support of this conclusion is provided since, under the same reaction conditions, the corresponding fumaranilic acid (**356**) affords 2-[(*E*)-carboxypropen-3-yl]-3,1-benzoxazinone (**357**) (Scheme 97) ⟨86TL2487⟩.



Scheme 97

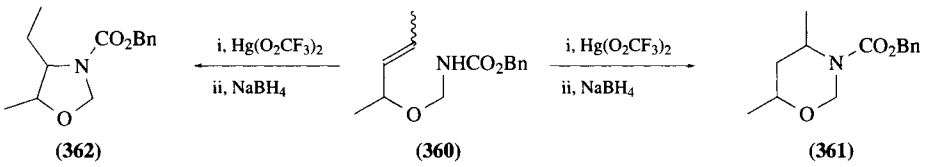
5-Methyl-1,3-oxazine-2,4-dione (**359**) is obtained by the acid-mediated cyclization of the vinyl ether (**358**) (Equation (42)) ⟨79CCC269⟩.



(358) (359) (42)

(vi) Perhydro-1,3-oxazines, perhydro-1,3-oxazinones and derivatives

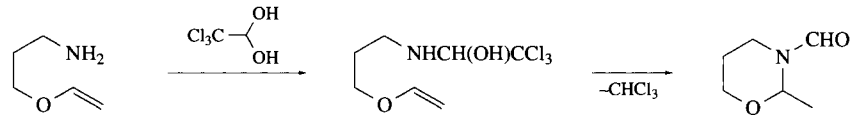
The amidomercuriation of (*E*)- or (*Z*)-allyl acylaminomethyl ethers (**360**) with mercury trifluoroacetate, followed by reduction with sodium borohydride, leads to mixtures of oxazolidines (**361**) and 1,3-oxazines (**362**), the composition of the mixtures depending upon the reaction times (Scheme 98) ⟨88TL3789⟩.



(362) (360) (361)

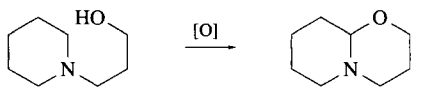
Scheme 98

A different bond-forming reaction is operative in the synthesis of the 3-formyl-2-methyl-1,3-oxazines (**364**) from 3-aminopropyl vinyl ethers (**363**), which cyclize when reacted with chloral hydrate (Scheme 99) ⟨86ZOR1556⟩. A novel synthesis of 5-oxa-1-azabicyclo[4.4.0]decane (**366**) relies upon the photosensitized single-electron oxidation of *N*-(3-hydroxypropyl)piperidine (**365**) in the presence of 1,4-dicyanonaphthalene (Equation (43)) ⟨88TL4153⟩.



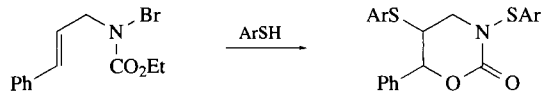
(363) (364)

Scheme 99

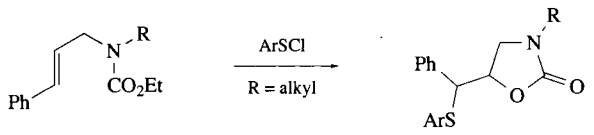


(365) (366) (43)

3,4,5,6-Tetrahydro-1,3-oxazin-2-ones (**368**) can be obtained by the reaction of arylthiols with *N*-bromo-*N*-cinnamylcarbamates (**367**). Presumably a sulfenyl bromide, or its equivalent, is formed initially which then acts as an electrophilic agent to promote the cyclization step (Equation (44)). However, should sulfenyl chlorides be reacted with *N*-alkyl-*N*-cinnamylcarbamates (**369**) then the regioselectivity is changed and oxazolidinones (**370**) are formed instead (Equation (45)) ⟨86JPR173⟩.

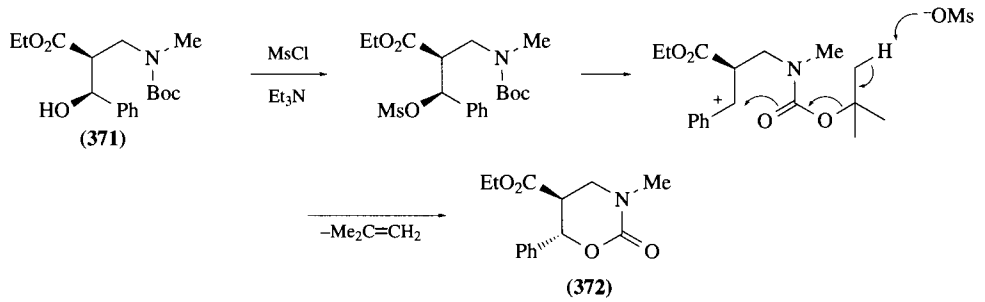


(367) (368) (44)



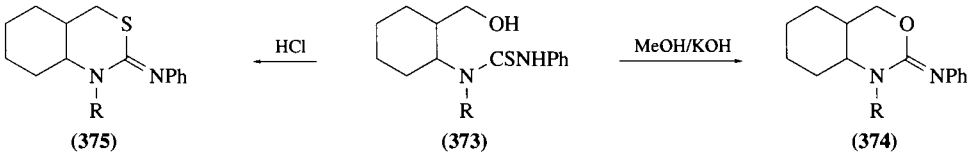
(369) (370) (45)

The tetrahydro-1,3-oxazin-2-one (**372**) is prepared through the cyclization of the *threo* form of hydroxycarbamate (**371**) in contact with mesyl chloride, conversely the *erythro* isomer is *O*-sulfinated without undergoing cyclization. The removal of an *N*-Boc group under basic conditions is unusual, and it is proposed that the selective cyclization of the *threo* isomer occurs because, in its lowest energy conformation, the proximity of the ethoxycarbonyl group and the mesyloxy unit potentiates the ionization of the latter. Once formed, the mesyloxy anion assists deprotonation of the Boc group and hence the cyclization to the oxazine (Scheme 100) ⟨87H(26)641, 88H(27)667⟩.



Scheme 100

N-(2-(Hydroxymethyl)cyclohexyl)thioureas (**373**) when treated with methanol and then potassium hydroxide yield 2-iminoperhydro-3,1-benzooxazines (**374**), but when these starting materials are treated with hydrochloric acid the related 3,1-benzothiazines (**375**) are formed (Scheme 101) ⟨88OPP73⟩.



Scheme 101

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6.06
1,2-Thiazines and their Benzo Derivatives

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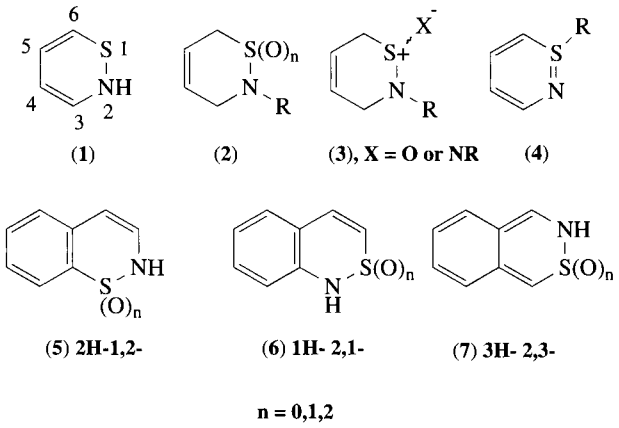
6.06.1 INTRODUCTION

1,2-Thiazines are cyclic six-membered ring compounds containing an S—N bond. The parent 1,2-thiazine (**1**) is unknown, but the corresponding *N*-aryl 1,1-dioxide is well documented ⟨84MI 606-01⟩. 3,6-Dihydrothiazines (**2**) and their derivatives have been studied in more detail, including all the oxidation states of sulfur. 3,6-Dihydrothiazine 1-oxides or imines (**3**) are the [4 + 2] cycloaddition products of *N*-sulfinylamine dienophiles and conjugated 1,3-dienes. Wichterle *et al.* were the first to study this cycloaddition and to explore 3,6-dihydro-1,2-thiazine 1-oxides ⟨54CCC282⟩. The other isomeric dihydrothiazines are known but are not very common. The cyclically conjugated 1*H*-1,2-thiazine (**4**), which is ylidic in nature, has also been studied ⟨84CPB3028⟩. Fusion of a benzene ring onto the heterocycle leads to benzothiazines, of which there are three possible regioisomers, namely 2*H*-1,2-, 1*H*-2,1-, and 3*H*-2,3-benzothiazines, (**5**), (**6**), and (**7**), respectively. 1,2-Benzothiazines (**5**) are commercially very important (*vide infra*) and have been investigated in great detail ⟨B-85MI 606-01⟩. A few tricyclic dibenzothiazines have also been investigated.



The principal emphasis of this chapter will be on work on the title compounds since the publication of *Comprehensive Heterocyclic Chemistry, First Edition* (CHEC-I) in 1984. It is obvious that, except for the arguable possibility of *p–d* π bonding from sulfur to nitrogen, the sultam systems (e.g., (**5**)–(**7**), $n = 2$) cannot have cyclic π conjugation, and so they are treated as "cyclically nonjugated" systems in this chapter.

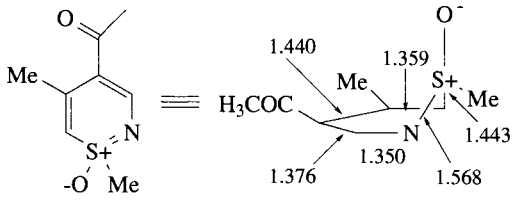
6.06.2 THEORETICAL METHODS

The application of theoretical methods to 1,2-thiazines has been nonexistent. However, FMO theory has been used to explain the stereochemical outcome of [4 + 2] cycloaddition reactions of *N*-sulfinylamine dienophiles leading to 3,6-dihydrothiazine oxides ⟨85JCS(P2)589⟩.

6.06.3 EXPERIMENTAL STRUCTURAL METHODS

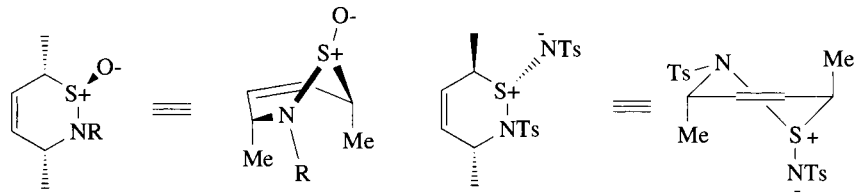
6.06.3.1 X-ray Diffraction

X-ray diffraction studies have played a major role in the structural elucidation of 1,2-thiazines and their derivatives, and such studies have confirmed the nonaromatic nature of the fully conjugated 1,2-thiazines. 4-Acetyl-1,5-dimethyl-1*H*-1,2-thiazine 1-oxide (**8**) exists in a half-boat conformation with the apex at the sulfur atom. The oxygen atom attached to sulfur occupies a quasi-axial position, and the *S*-methyl group an equatorial position. The molecule adopts a half-boat conformation to relieve angle strain caused by incorporation of the tetrahedral sulfur atom into the planar aza-pentadienyl anion system. There seems to be an appreciable $\pi\pi$–$d\pi$ contribution to the S—N bond ⟨78CC197⟩.

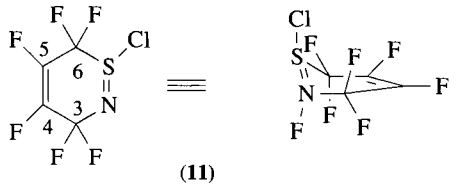


(8)

Since the mid-1980s there have been several reports on x-ray diffraction studies of 3,6-dihydrothiazine 1-oxides ⟨84JA7861, 84JA7867, 84JOC3243, 85AX(C)1514⟩. The dihydrothiazine oxide (**9**) approximates a twist boat in the crystal, presumably to minimize $A^{1,3}$ strain between the carbamate and the adjacent methyl group (the torsional angle between the two groups is 66°). The sulfur and nitrogen are displaced by −0.65 Å and −0.18 Å, respectively, out of the mean plane of the remaining part of the heterocycle. The S—O bond is quasi-axial, possibly because of an anomeric effect. The 3,6-dihydrothiazine 1-imine (**10**) also exists in a twist-boat conformation. It is noteworthy that this conformation of the thiazine (**10**) incorporates three axial substituents. X-ray analysis of a related compound (**11**) shows an envelope-type conformation in which the angle between the S–N–C-3 and C-4–C-5–C-6 planes is 33.5° and the S—Cl bond is quasi-axial ⟨92CB581⟩. There is, in fact, a general trend in all these systems in which the molecule adopts a twist-boat conformation and the sulfur–heteroatom bond is quasi-axial. There are no reports of x-ray crystallographic data for dihydrothiazines or the corresponding dioxides.

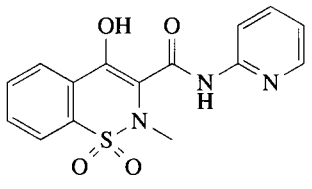


(**9**), **R** = CO_2Ph (**10**)



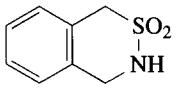
(**11**)

The molecular structure of 1,2-benzothiazines has been extensively studied by x-ray diffraction. Several crystalline forms of piroxicam (**12**) and other related anti-inflammatory drugs have thus been analyzed ⟨82AX(B)2948, 87AX(C)280, 94AX(C)791⟩. The 1,2-thiazine ring exists in a half-chair conformation. The S-1 and N-2 atoms are displaced by 0.514 Å and 0.315 Å from the plane defined by the four carbon atoms of the thiazine ring. The torsional angles in the ring are consistent with a half-chair conformation. This same conformation of the thiazine ring is also found in the zwitterionic form of piroxicam ⟨84AX(C)989⟩. Several metal complexes of piroxicam have been studied, and their molecular structures have been determined by x-ray diffraction ⟨90IC5197⟩. These studies indicate that the thiazine ring maintains a half-chair conformation. An increased contribution of the keto form in these metal complexes leads to the shortening of the C-4—O bond from 1.341 Å to 1.276 Å and lengthening of the C-3—C-4 bond to 1.396 Å from 1.369 Å.



(**12**)

There have been two structural studies on 2,3-benzothiazine systems by Rivero *et al.* ⟨91AX(C)2501, 93AX(C)544⟩. For the *S*-dioxide (**13**), a distorted tetrahedral geometry is observed about the sulfur atom, with an O–S–O angle of 118.9°, and the nitrogen atom is in a distorted pyramidal geometry. Once again, the thiazine ring is in a half-chair conformation. The S—N distance is shorter than that found in other thiazine systems, including 1,2-benzothiazines.

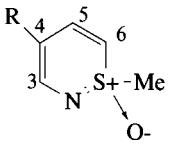


(**13**)

6.06.3.2 NMR Spectroscopy

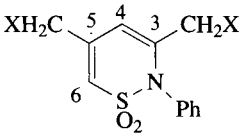
Proton and carbon-13 NMR spectroscopy have been used effectively in the structure elucidation of 1,2-thiazines and their derivatives. The nonaromatic nature of cyclically conjugated 1,2-thiazines is unequivocally indicated by ^{1}H NMR spectroscopy ⟨84CPB3028⟩. Table 1 illustrates ^{1}H and ^{13}C NMR data for two representative conjugated 1,2-thiazines. The H-4 and H-6 atoms resonate at a much higher magnetic field than H-3 and H-5. The same trend is also found in the ^{13}C NMR spectra.

Table 1 Proton and carbon-13 NMR spectral data for two thiazine-1-oxides (δ in ppm, $CDCl_3$).



R		δ			
		C-3	*C-4*	*C-5*	*C-6*
H	^{1}H	7.40	5.74	7.16	5.95
	^{13}C	146.2	100.5	137.7	96.2
CO_2Et	^{1}H	8.36	–	7.84	5.97
	^{13}C	152.9	104.7	138.5	96.1

A detailed ^{1}H and ^{13}C NMR spectroscopic investigation of 2-phenyl-1,2-thiazine 1,1-dioxides (**14**) has been carried out ⟨91JPR25⟩. In this study the influence of various substituents X in the 3 and 5 positions on the ^{1}H and ^{13}C NMR chemical shifts of the thiazine ring atoms has been studied. The chemical shifts for the parent 2-(4-methoxyphenyl)-1,2-thiazine 1,1-dioxide are shown in Table 2. The general trend of δ(CH-6) > δ(CH-4) and δ(C-5—CH_2X) > δ(C-3—CH_2X) is followed in all of these compounds.



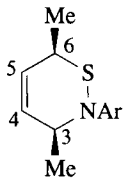
(**14**)

The ^{1}H and ^{13}C NMR spectra of 3,6-dihydrothiazines have been well documented. In the ^{1}H NMR spectrum of the 2-phenyl-3,6-dihydrothiazine (**15**) (Table 3), the C-3 methyl group resonates at a higher field than the C-6 methyl group. The same trend is seen in the corresponding methine protons. These chemical shifts can be rationalized by the greater deshielding effect of the ArN compared with the sulfur atom ⟨90JCS(P2)3225⟩. This trend in chemical shifts, where the nuclei (protons or carbons) at C-3 resonate at a higher field than the corresponding nuclei at C-6 is a

Table 2 Proton and carbon-13 NMR spectral data for 3,5-dimethyl-*N*-phenylthiazine-1,1-dioxide (**14**) (X = H) (δ in ppm, $CDCl_3$).

	δ			
	C-3	*C-4*	*C-5*	*C-6*
^1H	1.81	5.61	2.02	6.14
^{13}C	143.9	106.9	145.2	111.8

general one, and is also observed in the higher sulfur oxidation states of 3,6-dihydrothiazine 1-oxides ⟨84JA7861, 87JOC1177, 88JOC1116⟩. The spectral trends are illustrated in the ^1H and ^{13}C spectra for dihydrothiazine oxides (**16**) (Table 4) and (**17**). These spectral assignments have been confirmed by 2D (COSY) NMR experiments ⟨89JCS(P2)1855⟩.



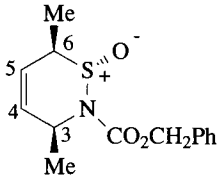
(**15**)

Table 3 Proton and carbon-13 NMR chemical shift data for (**15**).

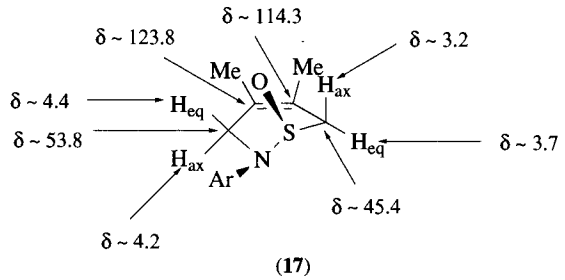
	δ			
	C-3	*C-6*	*C-3-Me*	*C-6-Me*
^1H	3.90	3.50	1.44	1.08
^{13}C	52.9	30.6	16.0	16.0

Table 4 Proton and carbon-13 NMR chemical shift data for (**16**).

	δ			
	C-3	*C-6*	*C-3-Me*	*C-6-Me*
^1H	3.23	3.44	1.34	1.48
^{13}C	48.94	53.82	16.28	21.90



(**16**)



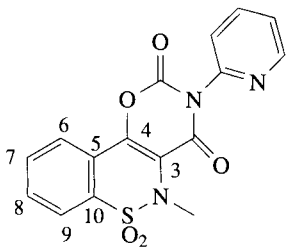
(**17**)

Proton NMR spectra of benzothiazines are not discussed in this review because most of the structures in the literature have a fully substituted thiazine ring. However, ^{13}C NMR has been very effectively used in the structure elucidation of benzothiazines. For example, the data in Table 5

illustrate the ^{13}C spectral profile of the 1,2-benzothiazine portion of droxicam (**18**) ⟨88JCS(P2)241⟩. Carbon-13 NMR of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides has been documented in some detail ⟨93JHC1051⟩. The ^{13}C chemical shifts of 1,2-benzothiazines reflect the strain in the heterocyclic ring and the shielding effects of the sulfur atom. Ring strain also plays a role in defining the $^{1}J(CH)$ coupling constants ⟨83OMR(21)187⟩. Typical chemical shift patterns of a 1,2-benzothiazin-3-one are presented in Table 6.

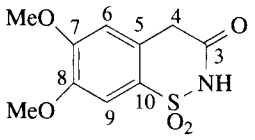
Table 5 Carbon-13 NMR spectral data for droxicam (**18**).

Carbon atom	*^{13}C chemical shift (DMSO-d_6)*	*Multiplicity*	
		Direct	*Long range*
3	117.3	s	q, $^{3}J_{CH} = 2.8$ Hz
4	148.6	s	q, $^{3}J_{CH} = 4.2$ Hz
5	123.97	s	m
6	125.6	d, $^{1}J_{CH} = 167$ Hz	m
7	134.2	d, $^{1}J_{CH} = 169$ Hz	d, $^{3}J_{CH} = 7.4$ Hz
8	133.7	d, $^{1}J_{CH} = 166$ Hz	m
9	123.6	d, $^{1}J_{CH} = 170$ Hz	m
10	134.0	s	m



(**18**)

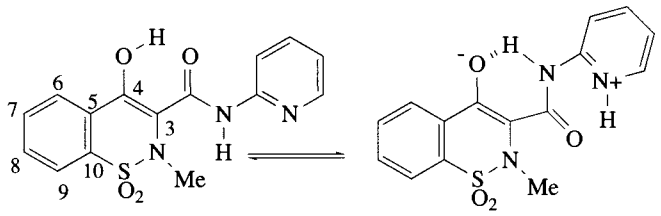
Table 6 Carbon-13 NMR chemical shift data for a 1,2-benzothiazin-3-one.



Carbon atom	*^{13}C chemical shift (DMSO-d_6)*
3	170.6
4	37.3
5	124.9
6	112.2
7	152.5
8	148.0
9	104.1
10	127.2

Carbon-13 NMR has also been used very effectively in the elucidation of the solution structure of piroxicam (**19a**). The chemical shift data of the benzothiazine nucleus in DMF-d^7 are shown in Table 7. Based on these ^{13}C NMR studies it has been estimated that the amount of the zwitterion (**19b**) is 19% ⟨89MRC(27)150⟩.

Surprisingly, there have been no detailed ^{15}N NMR studies of 1,2-thiazines, except for one report ⟨93MI 606-01⟩.



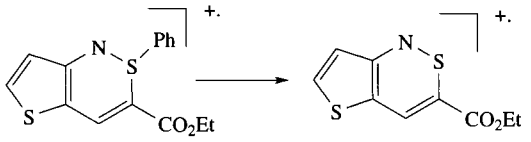
(19a) (19b)

Table 7 Carbon-13 NMR chemical shift data for neutral (δ_n) and zwitterionic (δ_z) piroxicam in DMF-d_7 at 250 K.

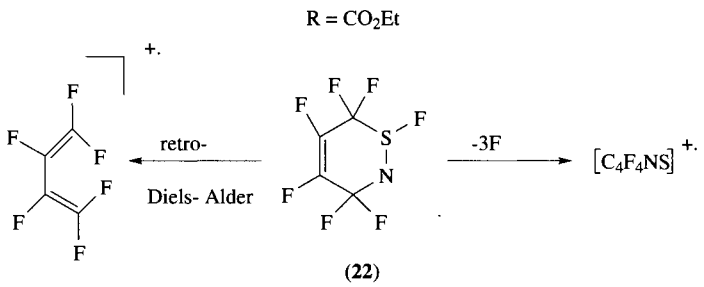
Carbon atom	δ_n	δ_z
3	111.8	109.0
4	158.8	169.7
5	128.5	135.2
6	127.1	127.9
7	134.2	133.3
8	133.9	132.1
9	125.0	123.8
10	135.2	136.3

6.06.3.3 Mass Spectrometry

Fully conjugated 1,2-thiazines such as (**20**) show a molecular ion of moderate to low abundance. Because of their ylidic nature, a common fragment of this class of compounds is (**21**) ⟨86JCS(P1)483⟩. The thiazine (**22**) also behaves in a similar fashion. However, the base peak in this case is derived from a retro-Diels–Alder reaction (Scheme 1) ⟨91MI 606-01⟩.



(**20**), $M^{+\cdot}$, m/z = 303 (**21**), m/z = 226 (100%)

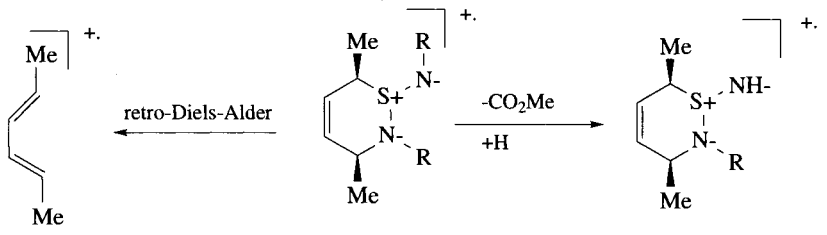


(**22**)

Scheme 1

Even though there are no mass spectral data available for unsubstituted dihydrothiazines, the corresponding oxides and imines have been investigated. The dihydrothiazine imine (**23**) shows a molecular ion of good intensity. The two significant fragmentation pathways involve cleavage of the carbomethoxy groups and a retro-Diels–Alder reaction (Scheme 2) ⟨84JA7867⟩. Dihydrothiazine 1-oxides and 1,1-dioxides behave in a similar fashion ⟨84JA7861, 87JOC1177, 91JOC373⟩.

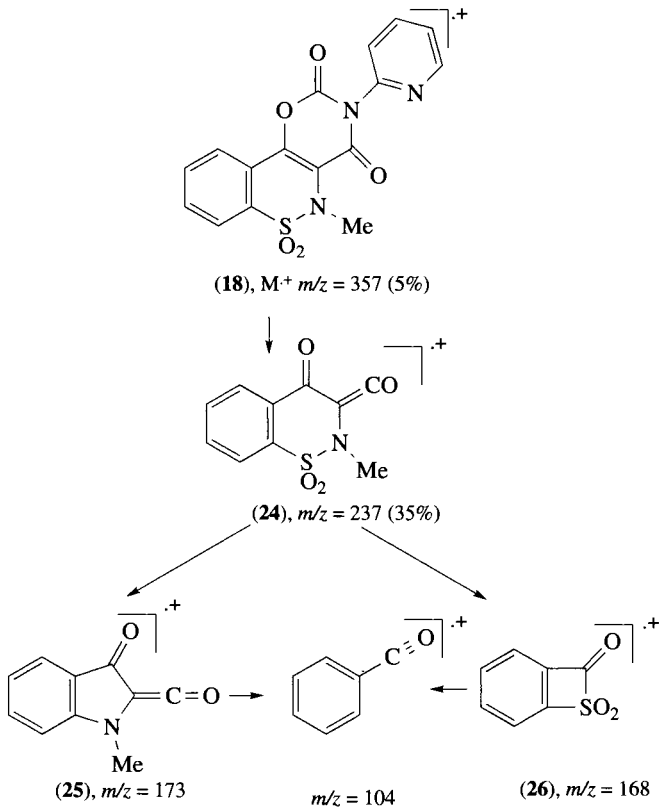
Mass spectra of 1,2-benzothiazines have been well studied because of the pharmacological importance of these compounds. The electron impact mass spectrum of droxicam (**18**) shows a molecular



m/z = 82 (100 %) (23), R = CO_2Me, $M^{+\cdot}$ = 260 (25%) m/z = 144 (93%)

Scheme 2

ion ($m/z = 357$) of moderate intensity which fragments by the elimination of 2-pyridyl isocyanate. The resulting ion (**24**) loses SO_2 to yield (**25**) ($m/z = 173$). A loss of C_3H_3NO from the ion (**24**) leads to the ion (**26**) ($m/z = 168$). Both these ions (**25**) and (**26**) can lead to the base peak ($m/z = 104$) (Scheme 3) ⟨88JCS(P2)241⟩. This fragmentation pattern is typical of 1,2-benzothiazines. For example, 2*H*-pyrido-1,2-thiazine 1,1-dioxide (**27**) shows a molecular ion ($m/z = 282$) which loses SO_2 to give the base peak (**28**) ($m/z = 218$). This ion fragments further via cleavage adjacent to the carbonyl group (Scheme 4) ⟨86FES819⟩. The 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides generally show a medium to low intensity molecular ion. Once again, the loss of SO_2 is the key fragmentation pathway. The benzothiazine dioxide (**29**) shows a very low intensity molecular ion, which loses the *N*-benzyl group followed by SO_2 leading to the ion (**30**) ($m/z = 118$). This fragmentation pattern is typical of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides (Scheme 5) ⟨90OMS(25)517⟩.



(**18**), M^{+} m/z = 357 (5%)

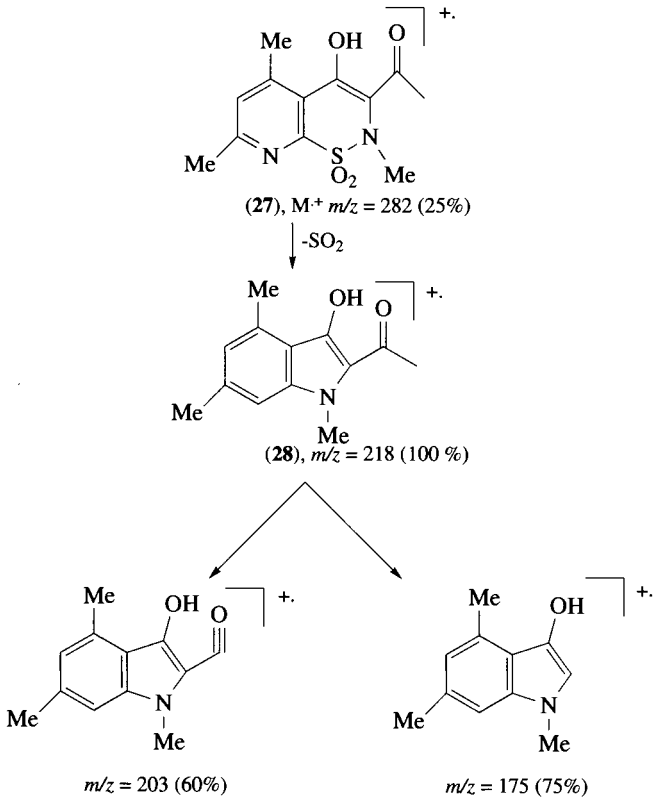
(**24**), m/z = 237 (35%)

(**25**), m/z = 173 m/z = 104 (**26**), m/z = 168

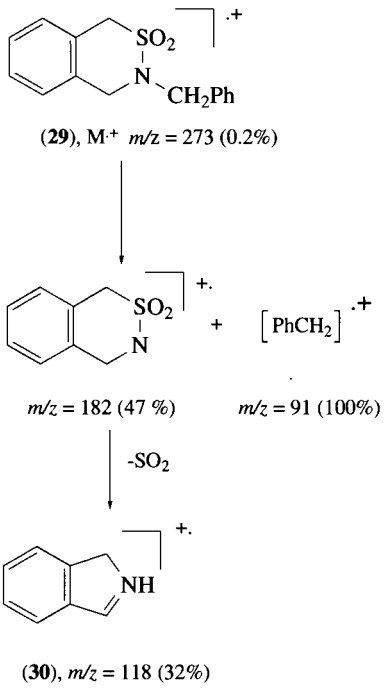
Scheme 3

6.06.3.4 Ultraviolet Spectroscopy

Ultraviolet absorption spectra have been used only very sparingly in structural studies of 1,2-thiazines, mainly because the parent chromophore is relatively weak. However, the ultraviolet



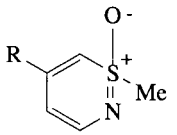
Scheme 4



Scheme 5

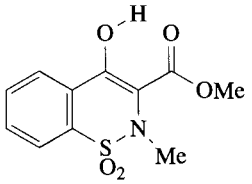
absorption spectra of 1,2-benzothiazines have been analyzed in some detail because of the pharmacological importance of the molecules.

The ultraviolet spectra of 1,2-thiazine 1-oxides (**31**; R = H, Me) show an absorption band at 310 nm (log $\varepsilon = 3.3$–3.4), which is unaffected by the addition of 6 N HCl ⟨84CPB3028⟩. The ultraviolet spectra of the benzothiazine derivatives piroxicam (**19**) and (**32**), which have been studied in several solvents ⟨88MI 606-01⟩, are similar and consist of three absorption bands at 320 nm, 290 nm, and 250 nm. The higher-energy bands do not shift with solvent changes. However, the first band at 320 nm is significantly red shifted with an increase of polarity of the solvent, showing a high molecular extinction coefficient. This shift indicates that the absorption at 320 nm originates from a strong $S_0 \rightarrow {}^1(\pi, \pi^*)$ transition.



(**31**), R = H, Me

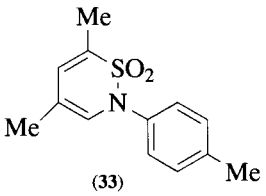
It is well established that in a nonpolar solvent, $S_0 \rightarrow {}^1(n, \pi^*)$ transitions of heterocyclic carbonyl groups are blue shifted (because of intramolecular hydrogen bonding) and are hence partially hidden by the stronger $S_0 \rightarrow {}^1(\pi, \pi^*)$ absorption. This phenomenon is also observed in the case of (**19**) and (**32**), in that the first absorption at 320 nm has a long and weak tail around 370–380 nm in nonpolar solvents which disappears in polar hydrogen-bonding solvents such as water. In strong, polar hydrogen-bonding solvents, the low-lying ${}^1(n, \pi^*)$ state is blue shifted by the disruption of the intramolecular hydrogen bond while the ${}^1(\pi, \pi^*)$ state is red shifted by the high polarity. Hence the ${}^1(\pi, \pi^*)$ transition becomes the lowest excited state (S_1) in water. The pH dependence of the ultraviolet absorption spectra of (**19**) and (**32**) and the corresponding proton transfer equilibria have also been studied ⟨88MI 606-01, 88MI 606-02⟩.



(**32**)

6.06.3.5 Infrared Spectroscopy

There is only a limited amount of infrared absorption data available for 1,2-thiazines in the literature. This paucity of information can be attributed to the increasing popularity of NMR in structure elucidation since the mid-1970s and also to the lack of any characteristic absorptions for the S—N bond of 1,2-thiazines. Some of the earlier structural work on 1,2-thiazines was carried out on the corresponding 1,1-dioxides. The 4,6-dimethyl-1,2-thiazine 1,1-dioxide (**33**) shows strong absorption bands at 1290–1270 cm^{-1} due to SO_2 stretching vibrations. This absorption is very characteristic for 1,2-thiazine 1,1-dioxides. The conjugated double bonds show the expected vibrations at 1550 cm^{-1} and 1625 cm^{-1} ⟨87MI 606-01⟩.

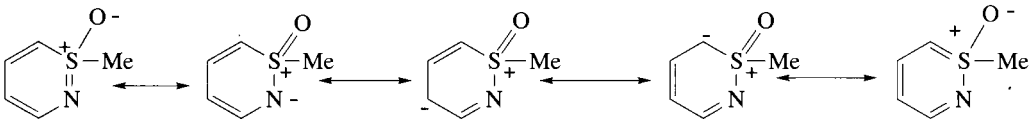


(**33**)

6.06.4 REACTIVITY

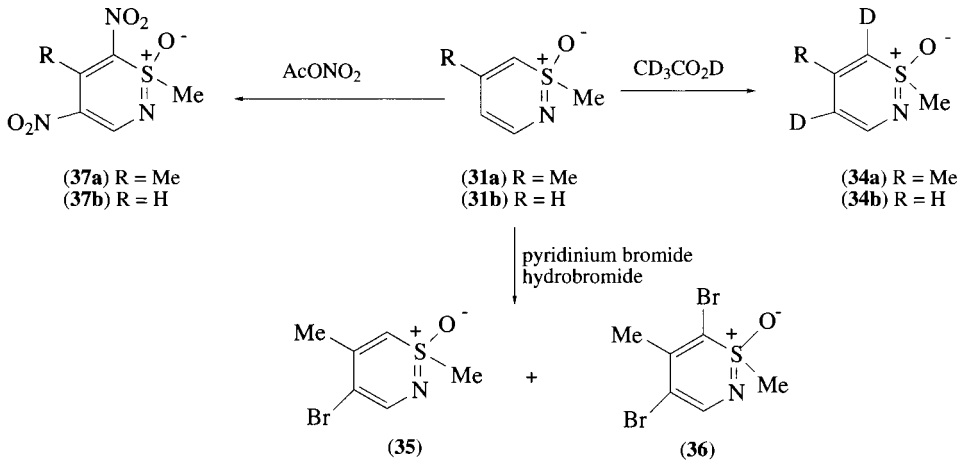
6.06.4.1 Cyclically Conjugated 1,2-Thiazines

The reactivity of cyclically conjugated 1,2-thiazines is predictable from structural studies (*vide supra*). These compounds can be regarded as sulfur ylides, whose negative charge is delocalized over the azapentadienyl portion of the molecule and the positive charge is located on the sulfur atom. The stability of these ylides can be attributed to the $\pi\pi$–$d\pi$ bonding. The higher electron density at the 4 and 6 positions as compared to the 3 and 5 positions is reflected in their reactivity, especially in electrophilic substitution reactions (Scheme 6) ⟨84CPB3028⟩.



Scheme 6

Deuteration of (**31a**; R = Me) with CD_3CO_2D occurs at the 4 and 6 positions, yielding (**34a**) ($t_{1/2}$ = 140 h). However, deuteration of (**31b**; R = H) proceeds at a much slower rate ($t_{1/2}$ = 700 h), leading to (**34b**). Electrophilic bromination of (**31a**) gives the monobromide (**35**) (48%) and the dibromide (**36**) (8%). The use of two equivalents of the brominating reagent yields exclusively the dibromide (86%). The selective bromination at the 4 position to yield (**35**) with one equivalent of the brominating reagent can be attributed to the relative steric hindrance at the 6 position. The thiazine oxide (**31b**) decomposes under these bromination conditions (Scheme 7).



(**37a**) R = Me
(**37b**) R = H

(**31a**) R = Me
(**31b**) R = H

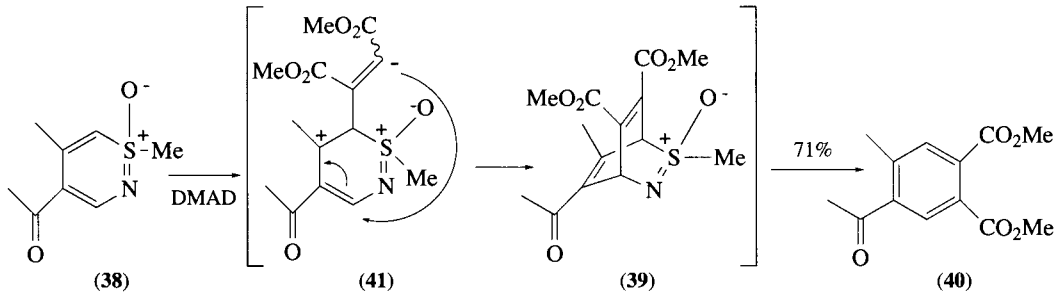
(**34a**) R = Me
(**34b**) R = H

(**35**) (**36**)

Scheme 7

The thiazine oxides (**31a**) and (**31b**) can be nitrated with an excess of acetyl nitrate to give the corresponding 4,6-dinitro derivatives (**37a**) and (**37b**), respectively. Nitration of (**31b**) is very sluggish and yields (**37b**) in only 18% yield.

The unactivated thiazine oxides (**31a**) and (**31b**) do not participate in [4 + 2] cycloaddition reactions. Thiazine oxides such as (**38**), which have an electron-withdrawing group at the 4 position, undergo cycloaddition reactions with dimethyl alkynedicarboxylate (DMAD) in refluxing bromobenzene (Scheme 8). The resulting [4 + 2] adduct (**39**) fragments, leading to the phthalate (**40**) in 71% yield. The presence of an electron-withdrawing group at the 4 position is crucial for this reaction, and an electron-donating group at the 5 position enhances reactivity. This cycloaddition reaction can also be catalyzed by a base (NaH/DMSO), and hence is ostensibly a stepwise "double Michael addition" involving intermediates such as (**41**) ⟨84CPB3028⟩.



Scheme 8

6.06.4.2 Cyclically Nonconjugated 1,2-Thiazines

6.06.4.2.1 1,2-Thiazines

(i) General considerations

In this class of 1,2-thiazines, 3,5-dimethyl-2-phenyl-1,2-thiazine 1,1-dioxide (**42**) (commonly referred to as 2,3-dimethyl-1,3-butadiene 1,4-sultam) has been completely investigated. This thiazine behaves like a highly polarized conjugated 1,3-diene, as can be expected from its ^{1}H and ^{13}C NMR spectra. This distortion causes carbons C-4 and C-6 to be highly susceptible to electrophilic attack, and the formation of disubstituted products is common. Suitably substituted 1,2-thiazines can also undergo nucleophilic attack.

(ii) Electrophilic substitution

The thiazine (**42**) can be easily deuterated at the C-4 and C-6 positions under acidic conditions. The readiness of (**42**) to undergo electrophilic attack can be further demonstrated by the conversion of the perdeuterated thiazine (**43**) to the partially deuterated thiazine (**44**) (Scheme 9) ⟨88JPR(330)79⟩. Electrophilic chlorination of (**42**) can be cleanly accomplished with *t*-butyl hypochlorite, affording the corresponding 4-chlorothiazine (**45**). Under the same conditions, sulfuryl chloride leads to a mixture of 4- and 6-chlorothiazines (**45**) and (**46**) ⟨84JPR(326)545⟩. However, electrophilic bromination (Br_2 in $CHCl_3$) of (**42**) leads to a different substitution pattern, and the order of reactivity is C-3 Me > C-6 H > C-4 H ⟨84MI 606-01⟩. The thiazine (**42**) can also be iodinated at the 6 position with iodine monochloride ⟨90MI 606-01⟩. The thiazine (**42**) can be formylated at the 6 position under the standard Vilsmeier–Haack conditions, leading to (**47**) in 30% yield ⟨84ZC403⟩.

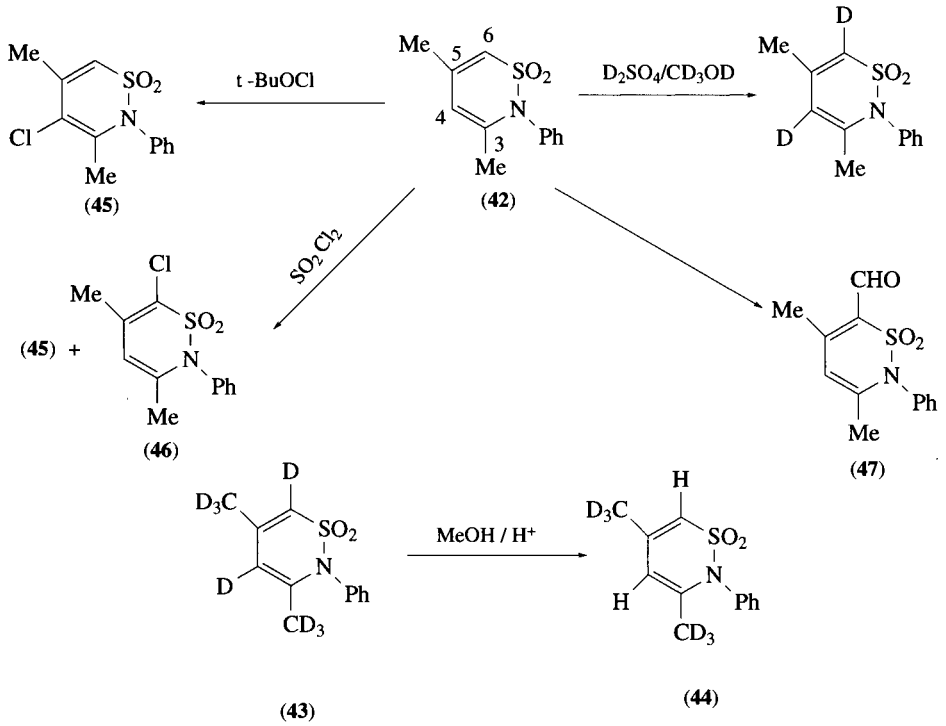
Treatment of (**42**) with potassium thiocyanate and bromine yields the 6-thiocyanatothiazine (**48**) (Scheme 10). Both the C-4 and C-6 positions are substituted when two equivalents of thiocyanate and bromine are used ⟨88JPR(330)142⟩.

(iii) Nucleophilic displacement of halogens

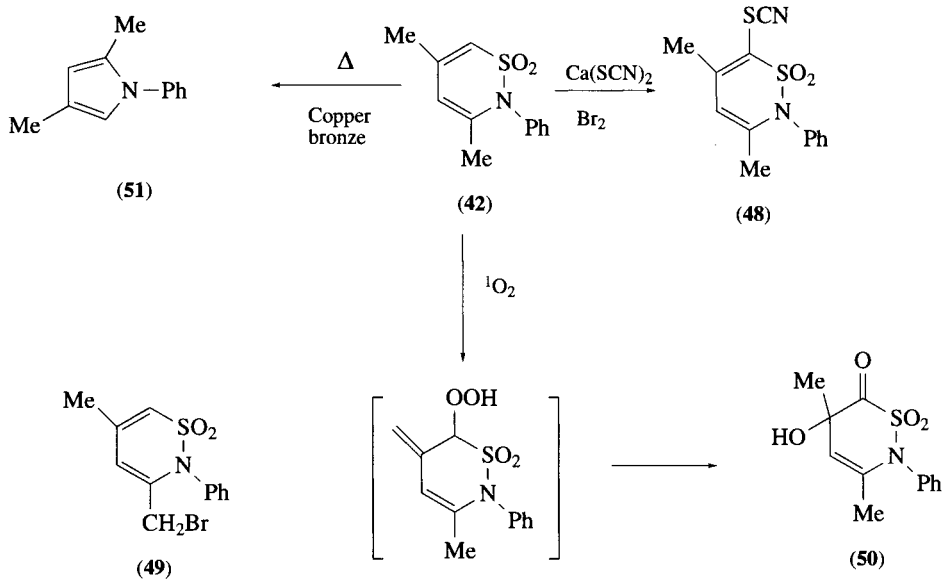
Bromomethyl groups, in (**49**) and related compounds, are readily converted into thiocyanatomethyl using KSCN in acetonitrile ⟨88JPR(330)142⟩.

(iv) Photochemical and thermal transformations

The thiazine (**42**) can be photo-oxidized in the presence of methylene blue. The major photo product (**50**) is derived via a singlet oxygen ene reaction ⟨88JPR(330)79⟩. Thiazines such as (**42**) are relatively stable to heat, but (**42**) can be thermally degraded at 180°C with copper bronze to yield the pyrrole (**51**) (Scheme 10) ⟨92MI 606-01⟩.



Scheme 9



Scheme 10

6.06.4.2.2 Dihydrothiazines

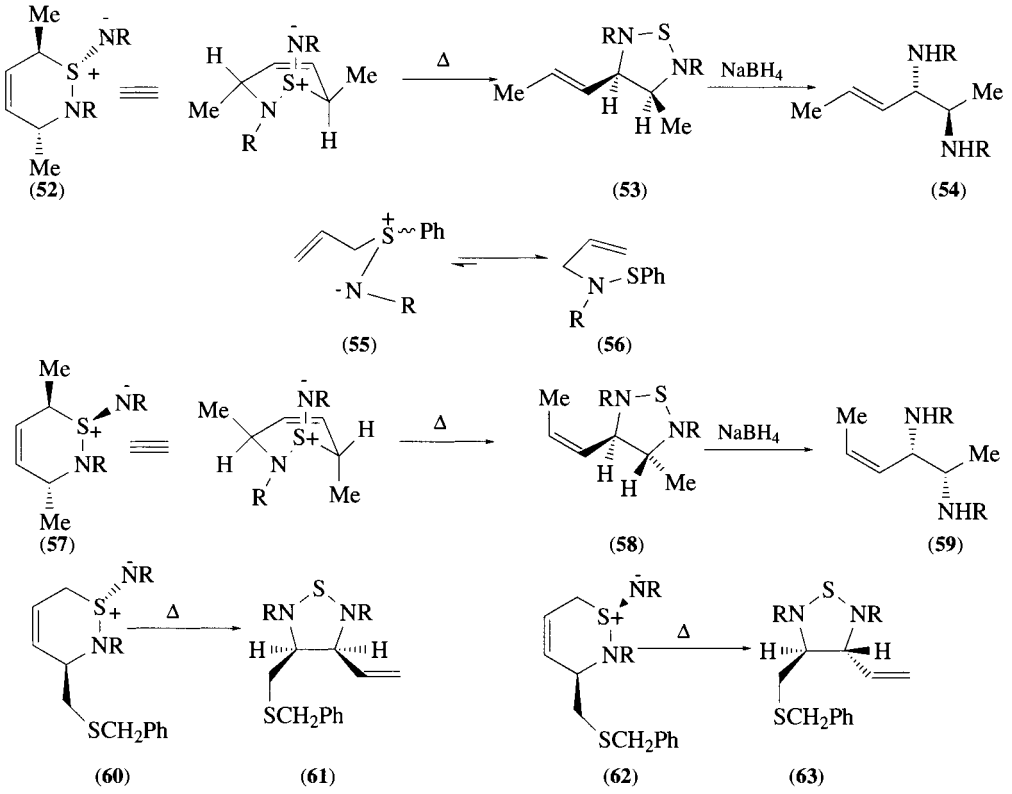
(i) General considerations

The chemistry of 3,6-dihydrothiazines such as (**2**) and (**3**) has been investigated in some detail since the mid-1980s ⟨88ACR313⟩. Before this burst of activity in this field, virtually all of the known reactions had been reported over four decades ago ⟨54CCC282⟩. Even though 3,6-dihydrothiazine 1-oxides and imines are relatively stable, the S—N bond is very scissile and can easily be cleaved. This reactivity is in fact a very important and useful aspect of 3,6-dihydrothiazine chemistry.

(ii) Thermal and photochemical reactions

Dihydrothiazines and their *S*-oxides are relatively stable to heat. However, 3,6-dihydrothiazine *S*-imines such as (**52**) undergo a very facile thermal [2,3]-sigmatropic rearrangement leading to thiadiazolidines (**53**), which can be desulfurized to the corresponding *vicinal* diamines (**54**) in high yields ⟨84JA7867, 87H(25)19, 88JOC1116⟩.

Since 3,6-dihydrothiazine 1-imines exist in conformations having a quasi-axial S—N bond, these imines are properly disposed stereoelectronically for such a pericyclic process. This reaction is essentially irreversible, similar to the equilibrium in a [2,3]-sigmatropic rearrangement of allylic sulfilimines (**55**), which lies to the side of the sulfenamide (**56**) (Scheme 11). There is a clean transfer of stereochemistry from C-6 of the dihydrothiazine (**52**) to C-4 of the thiadiazolidine (**53**), leading to the (*E*)-*erythro-vicinal* diamine derivative (**54**). In a similar fashion, thermolysis of the epimeric imine (**57**) gives the thiadiazolidine (**58**), which can be converted into the (*Z*)-*threo-vicinal* diamine (**59**). In the absence of any substituent at the C-6 position, the sulfur stereochemistry controls the stereochemical outcome of the [2,3]-sigmatropic reaction, and hence the imine (**60**) can be stereospecifically converted to the *cis*-thiadiazolidine (**61**) ⟨88JOC1116⟩. The epimeric dihydrothiazine (**62**) leads the corresponding *trans*-thiadiazolidine (**63**).

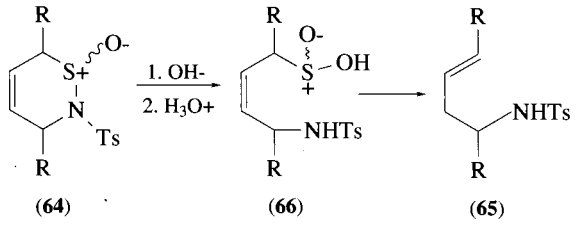


Scheme 11

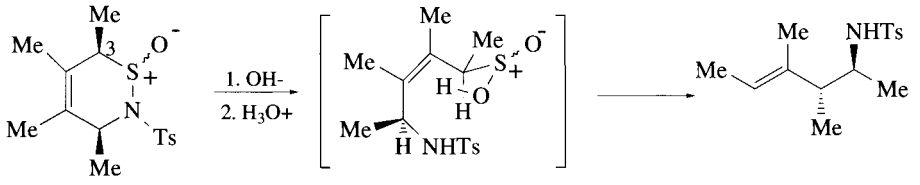
(iii) Ring cleavage and related reactions

The 3,6-dihydrothiazine 1-oxides and 1-imines are susceptible to ring cleavage with a variety of nucleophiles. Wucherpfennig investigated the S—N bond cleavage of 3,6-dihydrothiazine 1-oxides (**64**) with alkoxides and thioalkoxides in 1971, and it was discovered that these compounds can be converted to unsaturated amine derivatives (**65**) under hydrolytic conditions ⟨71LA(746)16⟩. Mock and Nugent examined the mechanism of this hydrolytic cleavage of 3,6-dihydrothiazine 1-oxides (Scheme 12) ⟨78JOC3433⟩. Based on deuterium labeling experiments, it was postulated that the conversion of (**64**) and (**65**) involves a concerted retro-ene reaction of the allylic sulfinic acid (**66**) resulting from ring opening. The mechanism of this reaction was further confirmed by Weinreb and

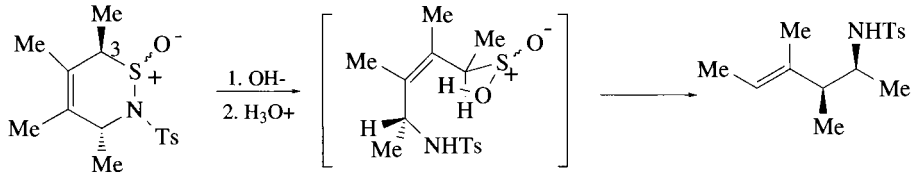
co-workers by the stereospecific conversion of the dihydrothiazine oxides (**67**) and (**68**) to the corresponding homoallylic amines (**69**) and (**70**) ⟨83TL987⟩. Hence, the S—N bond cleavage of (**67**) and (**68**) leads to sulfinic acids (**71**) and (**72**), respectively. Retro-ene reaction of these sulfinic acids via diastereomeric transition states leads to the respective homoallylic amine diastereomers (**69**) and (**70**). The noteworthy feature of this transformation is that the C-3 substituent of the dihydrothiazine oxide acts as an equatorial "anchor" and, hence, the retro-ene proton transfer occurs onto a single diastereotopic face of the double bond.



(**64**) (**66**) (**65**)



(**67**) (**71**) (**69**)



(**68**) (**72**) (**70**)

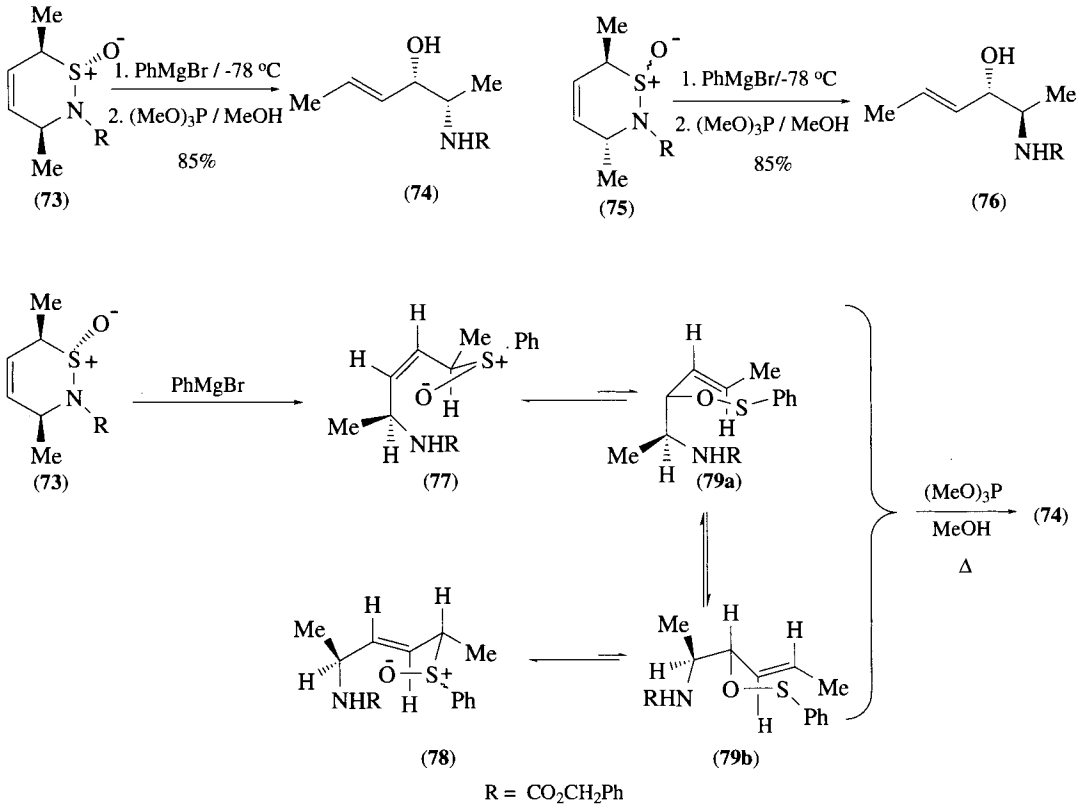
Scheme 12

These 3,6-dihydrothiazine 1-oxides also undergo clean S—N bond cleavage with a variety of carbon nucleophiles ⟨84JA7861⟩. A number of organometallic reagents have been used to implement this cleavage. The bond rupture with Grignard reagents is stereospecific and proceeds with inversion at the sulfur atom to afford (*Z*)-allylic sulfoxides. These allylic sulfoxides can undergo a number of useful synthetic transformations. For example, they undergo a reversible [2,3]-sigmatropic rearrangement to produce sulfenate esters, which upon treatment with a thiophile afford allylic alcohols.

The dihydrothiazine oxide (**73**) can be effectively converted into the (*E*)-*threo*-hydroxy carbamate (**74**) upon treatment with phenylmagnesium bromide, followed by refluxing the crude product with trimethyl phosphite in methanol (85%). In a similar fashion, the isomeric 3,6-dihydrothiazine 1-oxide (**75**) can be transformed into the (*E*)-*erythro*-carbamate (**76**) (85%) (Scheme 13). This transformation involves a complex set of equilibria between the initially formed allylic sulfoxides and sulfenate esters.

The dihydrothiazine oxide (**73**) gives the (*Z*)-allylic sulfoxide (**77**), which ($t_{1/2} = 90$ min) is slowly converted to a mixture of (*E*)-allylic sulfoxides (**78**) that are epimeric at the sulfur atom. This well-precedented transformation of (**77**) to the thermodynamically more stable (**78**) involves conformational inversion of the sulfenate ester (**79a**) to (**79b**). At any stage of this equilibrium, treatment with a thiophile such as trimethyl phosphite can stereospecifically lead to the (*E*)-hydroxy carbamate (**74**) (Scheme 13) ⟨84JA7861⟩. This versatile transformation has been applied to stereospecific *vicinal* amino alcohol synthesis.

In a similar fashion, 3,6-dihydrothiazine 1-imines can be cleaved by several alkyl and aryl organometallic reagents. Dihydrothiazine imines have more steric and electronic constraints compared to the corresponding oxides, and hence some are very resilient to ring opening by nucleophiles. Treatment of imine (**80a**) with phenylmagnesium bromide at −60°C gave a product which was



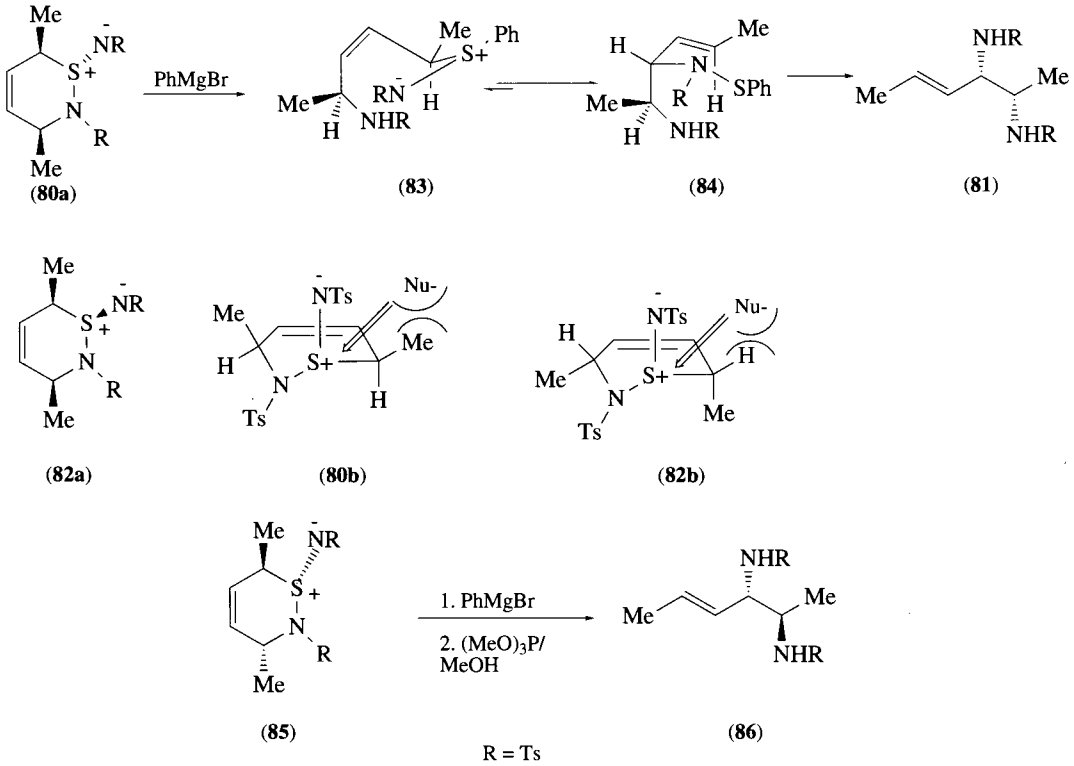
(73) (74) (75) (76) (77) (78) (79a) (79b)

Scheme 13

converted to the (*E*)-*threo-vicinal* sulfonamide (**81**) (83%). The epimeric imine (**82a**) is relatively resistant to nucleophiles and is stable to phenylmagnesium bromide at temperatures up to 0°C. However, treatment with the more reactive phenyllithium at −60°C, followed by methanolic trimethyl phosphite, yielded the same *vicinal* sulfonamide (**81**) (Scheme 14). The difference in reactivity of these sulfur epimers was rationalized by assuming that this nucleophilic cleavage is an S_N2-like process, and that the reactive conformations are (**80b**) and (**82b**). The incoming nucleophile experiences more severe torsional strain in (**80b**) as compared to (**82b**). This reactivity difference in 3,6-dihydrothiazine 1-imines epimeric at sulfur is not evident in the corresponding 1-oxides, probably because the substituent on sulfur is more electronegative and also less sterically demanding ⟨84JA7867⟩.

The second aspect which is different in the case of the 3,6-dihydrothiazine 1-imines (**80a**) and (**82a**) as compared to the 1-oxide (**73**) involves the reactivity of the resulting allylic sulfilimine (**83**). Even though the sulfilimine (**83**) undergoes a [2,3]-sigmatropic rearrangement, unlike the sulfoxide/sulfenate rearrangement the equilibrium here lies toward the sulfenamide (**84**) (Scheme 14). This difference in reactivity plays a very critical role in the stereochemical outcome in the conversion of some dihydrothiazine imines to *vicinal* diamines.

Similar to dihydrothiazine oxides, by the choice of proper stereochemistry at C-3 and C-6, it is possible to stereospecifically synthesize *vicinal* diamines. The imine (**85**), isomeric to (**80a**), yields the (*E*)-*erythro*-sulfonamide (**86**) (71%). The dihydrothiazine imines (**87**) and (**88**), which lack a C-6 substituent, upon treatment with phenylmagnesium bromide and the standard thiophile, stereospecifically lead to the diamines (**89**) and (**90**), respectively. The high stereoselectivity in this sequence of reactions was surprising. As mentioned above, the cleavage of the S—N bond proceeds with inversion at the sulfur atom, and the resulting allylic sulfilimine (**91**) rearranges irreversibly to the sulfenamide (**92**). In an envelope-type transition state, the *S*-phenyl group preferentially occupies a quasi-equatorial position, leading to the *threo*-sulfenamide (**92**). Similarly, the isomeric imine (**88**) leads to the *erythro*-diamine (**90**) (Scheme 15). However, there is no transfer of chirality from the sulfur atom in the dihydrothiazine oxide (**93**) upon S—N bond cleavage and the subsequent conversion into the corresponding amino alcohol. This difference in the stereochemical outcome

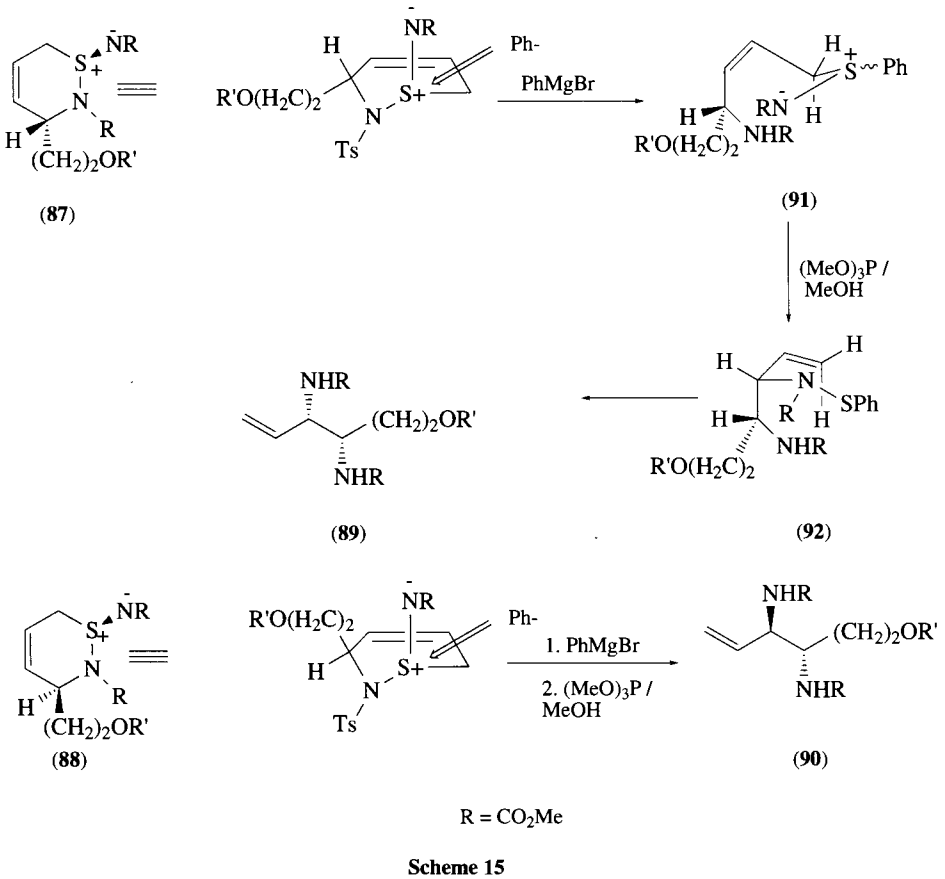


(80a) (83) (84) (81)

(82a) (80b) (82b)

(85) (86)

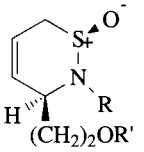
Scheme 14



(87) (91) (89) (92) (88) (90)

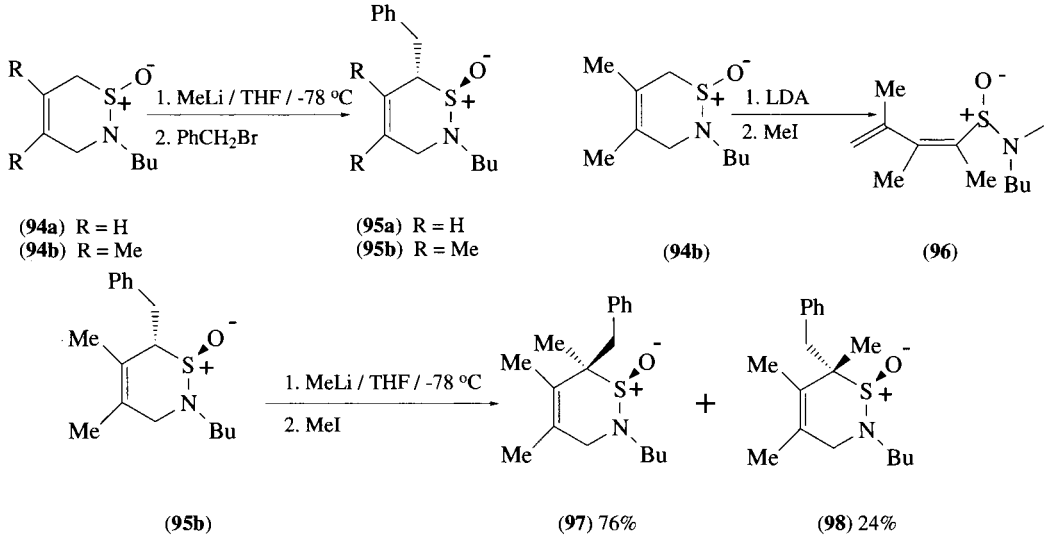
Scheme 15

between dihydrothiazine imines and oxides can be attributed to the lack of reversibility in the [2,3]-sigmatropic rearrangement of allylic sulfilimines ⟨87H(25)19⟩.



(93)

The reaction of 3,6-dihydrothiazine 1-oxides which lack an electron-withdrawing group on nitrogen can take a different course ⟨91JOC373⟩. Dihydrothiazine oxides (**94a**) and (**94b**), upon exposure to MeLi at −78 °C, undergo clean deprotonation at the C-6 position. The resulting anion can then be alkylated with a variety of alkyl halides to give predominantly the *anti*-dihydrothiazine oxides (**95a**) and (**95b**). This deprotonation can also be accomplished with LDA. At higher temperatures, these monoalkylated dihydrothiazine oxides tend to undergo ring cleavage to yield a dienic sulfenamide (**96**) (Scheme 16). The monosubstituted dihydrothiazine oxide (**95b**) can be dialkylated to afford (**97**) and (**98**). It is noteworthy that the corresponding *syn* isomer is stable to further deprotonation and can be recovered unchanged after prolonged exposure to a base. It seems likely that an oxygen *syn* to a proton on carbon significantly accelerates the rate of deprotonation.



(**94a**) R = H
(**94b**) R = Me

(**95a**) R = H
(**95b**) R = Me

(**94b**)

(**96**)

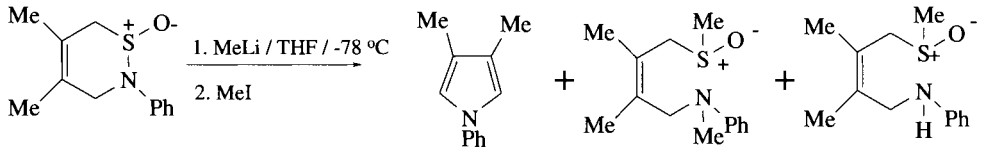
(**95b**)

(**97**) 76%

(**98**) 24%

Scheme 16

Dihydrothiazine oxides with aryl groups on the ring nitrogen do not undergo clean deprotonation, and a mixture of products derived from ring cleavage are formed. The 2-phenyl-substituted heterocycle (**99**) leads to products derived from attack of the methyllithium on the sulfur (Equation (1)) ⟨91JOC373⟩.



(**99**)

30%

47%

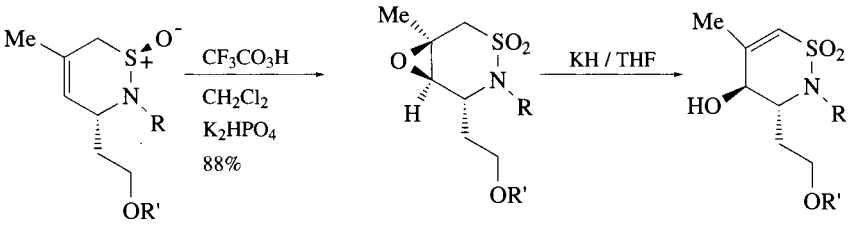
15%

(1)

(iv) Oxidation and reduction reactions

Peracids can efficiently oxidize 3,6-dihydrothiazine 1-oxides to the corresponding 3,6-dihydrothiazine 1,1-dioxides (sultams). Dihydrothiazine oxides with an unsubstituted double bond can be

selectively oxidized to the dioxide. A trisubstituted double bond is prone to undergo competing oxidation along with sulfur. The dihydrothiazine oxide (**100**) can be cleanly converted into the β-epoxy sultam (**101**) with trifluoroperacetic acid (Scheme 17). A milder oxidizing agent such as MCPBA simply yields the corresponding sultam without oxidizing the double bond. The epoxy sultam (**101**) undergoes a β-elimination upon treatment with potassium hydride, leading to the 3,4-dihydro-4-hydroxy 1,1-dioxide (**102**) ⟨87JOC1177⟩. It has been reported that 3,6-dihydrothiazine 1-oxides which have a tetrasubstituted double bond afford the epoxide without any sulfur oxidation ⟨86CB3405⟩.



(**100**) (**101**) (**102**)

R = CO_2CH_2Ph

Scheme 17

Dihydrothiazine oxides can be reduced by a wide variety of reducing agents, similar to the deoxygenation of sulfoxides, provided that the substituent on nitrogen is an aryl group. Dihydrothiazine oxides with an electron-withdrawing group on nitrogen yield only products derived from S—N bond cleavage ⟨67AG(E)149⟩.

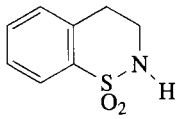
6.06.4.2.3 Benzothiazines

(i) General considerations

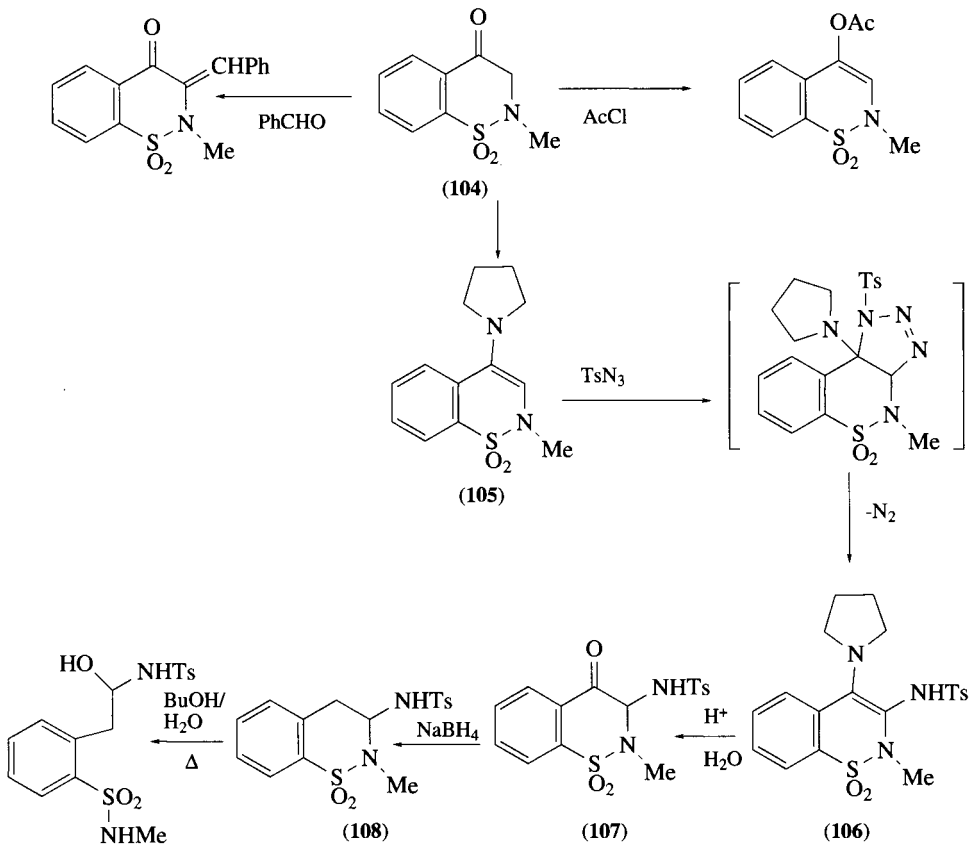
All the possible isomers of benzo-fused 1,2-thiazines are known. The chemistry of 1,2- and 2,1-benzothiazines has been extensively investigated because of their commercial importance. On the other hand, 2,3-benzothiazines have not been studied so well. The chemistry of 1,2- and 2,1-benzothiazines was thoroughly reviewed in 1981 ⟨81AHC(28)73⟩. This review is a good source of references for the research done in this area prior to 1980, which will not be covered again here.

(ii) 1,2-Benzothiazines

There have been many references to this ring system in the literature since 1980 (> 1800). However, most of these pertain to the biological aspects of piroxicam (**19**) and related compounds, and there have been no new insights into the chemical reactivity of 1,2-benzothiazines since the last review on this ring system ⟨81AHC(28)73⟩. Most 1,2-benzothiazines have been studied as the corresponding 3,4-dihydro-1,1-dioxides and, as one would expect, the nitrogen atom behaves like a typical sulfonamide nitrogen. 2*H*-1,2-Benzothiazine (**103**) can readily be *N*-alkylated with a variety of electrophiles. The 3,4-dihydro-1,2-benzothiazin-4-one (**104**) shows considerable enolic reactivity and can be cleanly converted into enol ethers and esters (Scheme 18). These compounds also condense with a variety of aryl aldehydes. The 4-pyrrolidinobenzothiazine (**105**) is relatively unreactive toward electrophiles and 1,3-dipoles but can be forced to react with *p*-toluenesulfonyl azide at 80 °C over a prolonged reaction time, yielding (**106**) as the main product ⟨90JHC427⟩. Reduction of (**107**) yields the benzothiazine (**108**), which undergoes proteolytic cleavage at the amino acetal linkage.

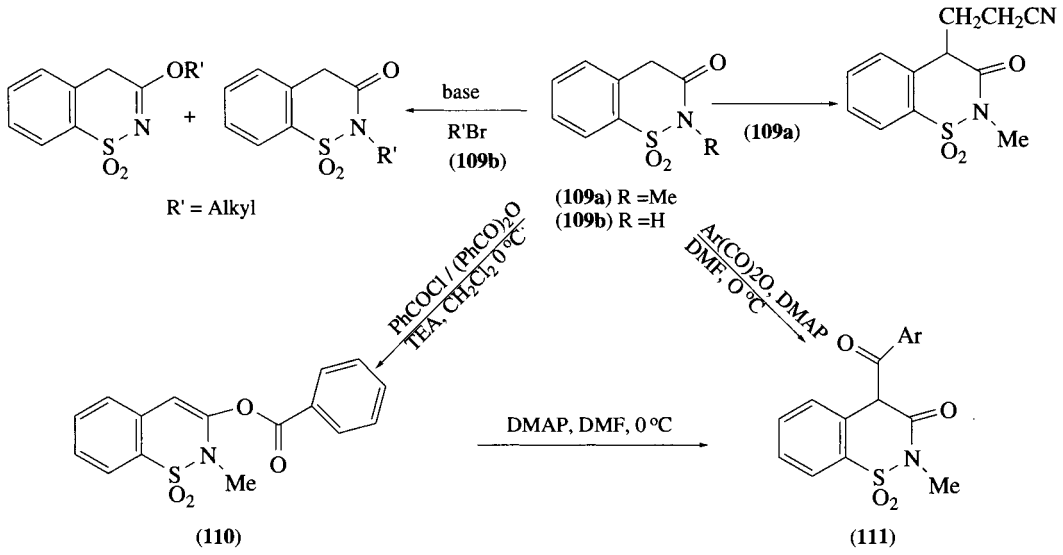


(**103**)



Scheme 18

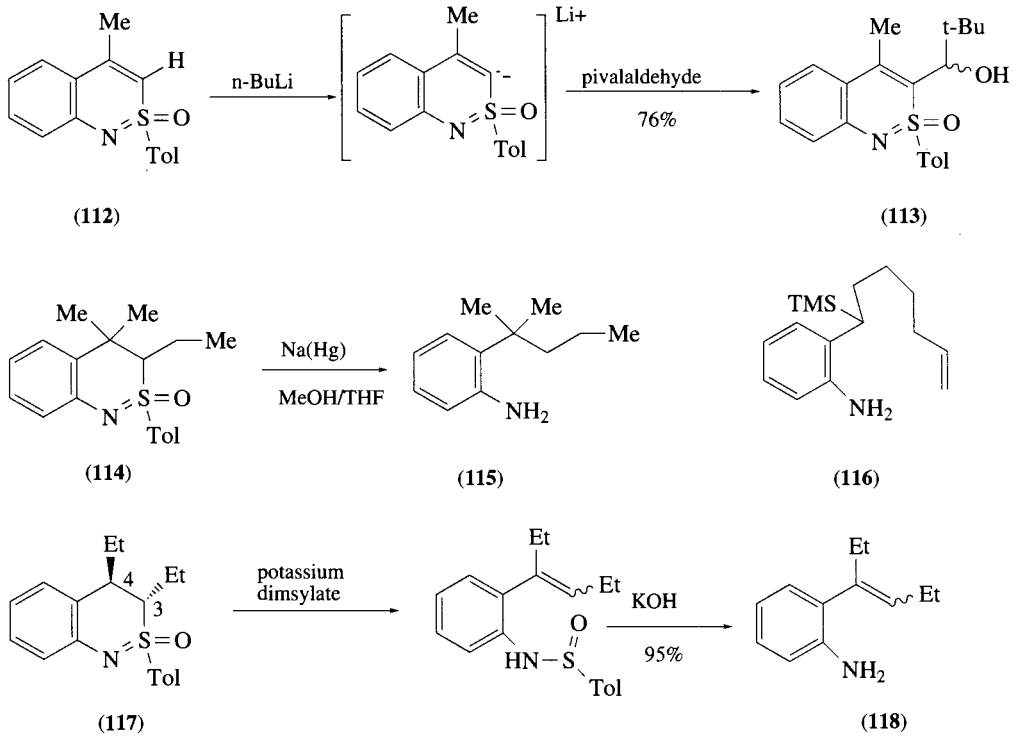
The reactive 4-methylene moiety in 2-alkyl-3,4-dihydro-1,2-benzothiazin-3-ones (**109a**) can be deprotonated and the anion can be reacted with electrophiles. Unlike the 4-oxobenzothiazines, compounds such as (**109b**) undergo either *N*- or *O*-alkylation, depending on the reaction conditions (Scheme 19) ⟨81AHC(28)73⟩. The *N*-methylbenzothiazine (**109a**) can be cleanly *O*-benzoylated under all conditions. However, in the presence of DMAP, (**109a**) can be converted into the corresponding 4-benzoyl derivative (**111**) in moderate yield. The *O*-benzoylbenzothiazine (**110**) can be transformed into the ketone (**111**) by acylation catalyzed by DMAP ⟨89JHC843⟩.



Scheme 19

(iii) 2,1-Benzothiazines

Since 1988 the chemistry of 2-aryl-2,1-benzothiazine 2-oxides has been studied in some detail. The benzothiazine oxide (**112**) can be smoothly deprotonated by n-BuLi, and the resulting sulfoximine-stabilized anion can be trapped by an assortment of electrophiles (Scheme 20). However, none of the alkylation reactions showed any diastereoselectivity (e.g., (**113**) was obtained as a 2.5/1 isomeric mixture ⟨88TL5229⟩; no allylic deprotonation was observed).



Scheme 20

The 3,4-dihydro-2,1-benzothiazines undergo some useful synthetic transformations. Treatment of the benzothiazine (**114**) with sodium amalgam yields the 2-alkylaniline (**115**) by reductive desulfonylation ⟨94S142⟩. Since benzothiazines such as (**114**) can be prepared from anilines, this reaction constitutes a regioselective *ortho*-alkylation of anilines. This reaction sequence can also be used to prepare highly substituted anilines such as (**116**). The benzothiazine (**117**) can be converted into the corresponding 2-alkenyl amine (**118**) upon treatment with potassium dimsylate followed by saponification. Even though this route to 2-alkenylanilines is general and regioselective, it is not stereoselective. The lack of stereoselectivity is probably due to the loss of stereochemical integrity at C-3 before the irreversible deprotonation of C-4 leading to ring cleavage ⟨91T8855⟩.

In the mid-1990s, a related sequence of reactions has been used for the regioselective preparation of 2-allyl and 2-alkenyl anilines from 2,1-benzothiazines ⟨95S713, 95TL4769⟩.

(iv) 2,3-Benzothiazines

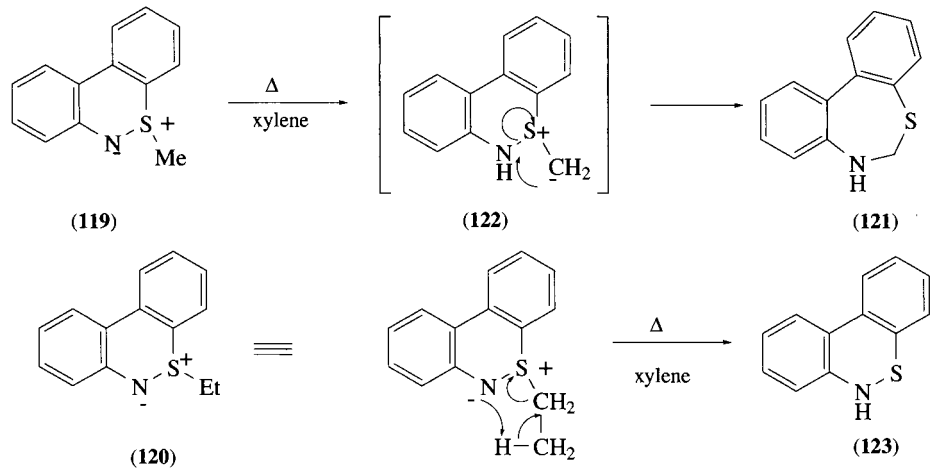
2,3-Benzothiazines have not been studied since the early 1970s, and there are only a few passing references to these compounds in the literature ⟨91LA831⟩.

6.06.4.2.4 Reactions of substituents

(i) Substituents on sulfur

The most common substituents at the 1 position of a 1,2-thiazine are oxygen and nitrogen. In general, the oxidation state of the divalent and tetravalent sulfur in a thiazine ring can easily be

altered. The hexavalent sulfur in 1,2-thiazine dioxides is, as expected, very stable. There are a few examples of carbon substitution at the 1 position of a substituted 1,2-thiazine. The aza-thiaphenanthrenes (**119**) and (**120**) are ylidic in nature, and these compounds undergo thermal rearrangements involving the carbon substituent on sulfur. The compound (**119**) undergoes a ring expansion in refluxing xylene to yield the dibenzothiazepine (**121**) via a Stevens-type rearrangement of the methylide intermediate (**122**). Under the same reaction conditions, the ethyl derivative (**119**) undergoes de-ethylation to afford (**123**) (Scheme 21) ⟨84CPB4360, 90TL7021⟩.

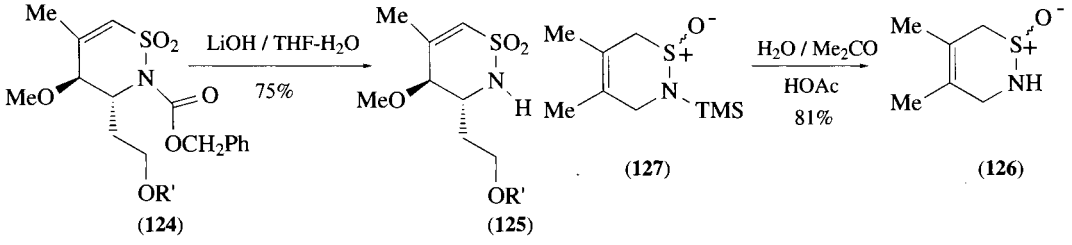


Scheme 21

There have been a few reports dealing with 1,2-thiazines bearing a halogen substituent at the 1 position ⟨91MI 606-01, 92CB581, 93CB1529⟩. The *S*-halogen bond in a 1,2-thiazine is hydrolytically labile.

(ii) Substituents on nitrogen

The most common 1,2-thiazines have either an alkyl, aryl, acyl, or a sulfonyl moiety at the 2 position. The 2-acyl-substituted 1,2-thiazine 1,1-dioxides can be hydrolytically cleaved to yield the 2-unsubstituted dioxides ⟨86TL4885, 87JOC1177⟩. The 2-carbamoyl-1,2-thiazine (**124**) can be efficiently hydrolyzed to (**125**) (Scheme 22). However, the 2-acyl-substituted 1,2-thiazine 1-oxide cannot be hydrolyzed in a similar fashion since the S—N bond is cleaved. The 2-unsubstituted-1,2-thiazine 1-oxide (**126**) can be obtained by the cleavage of the 2-TMS-substituted 1,2-thiazine (**127**) (Scheme 22) ⟨91JOC373⟩.



Scheme 22

6.06.5 SYNTHESIS

6.06.5.1 Introduction

There are some distinctive features of 1,2-thiazine and benzothiazine syntheses. Most of the principal and efficacious synthetic approaches for 1,2-thiazines use a fragment in which the S—N

bond already exists. In general, syntheses via [4 + 2] cycloadditions constitute a major part of the synthetic repertoire for this class of compound (Figure 1). There are six possible one-bond formations, of which type b is unknown.

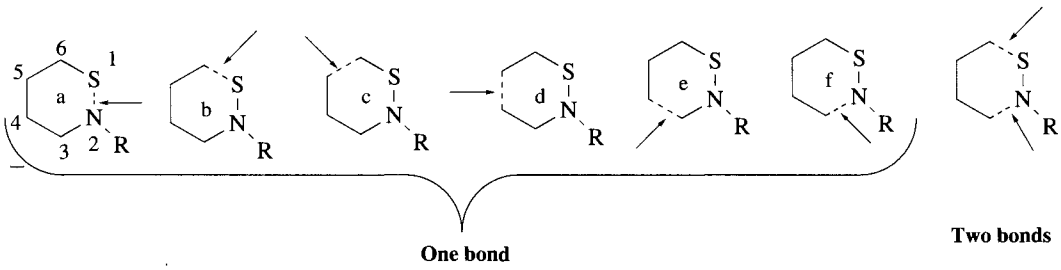
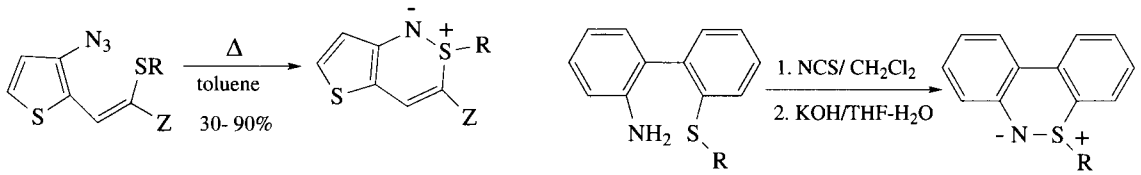


Figure 1 The possible one- and two-bond syntheses of 1,2-thiazines.

6.06.5.2 Formation of One Bond

6.06.5.2.1 Between the two heteroatoms (type a)

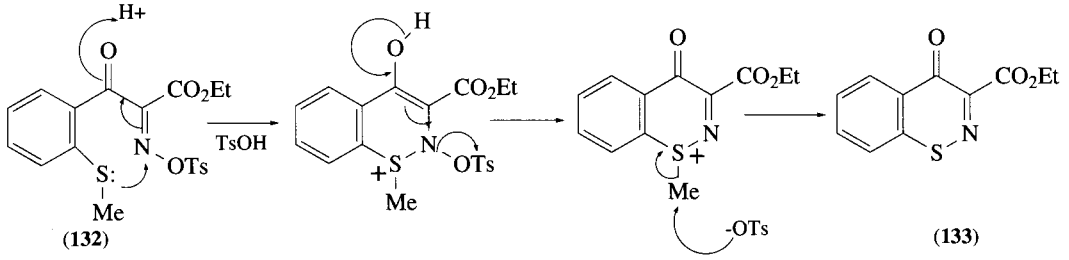
There are a few examples of 1,2-thiazine synthesis in which the creation of the S—N bond is the final step. This approach is most common in benzothiazine synthesis. The azides (**128**) can be thermolyzed in refluxing toluene to afford the expected $1\lambda^4$-1,2-thiazines (**129**) (Scheme 23) ⟨86JCS(P1)483⟩. This reaction is an intramolecular variant of the well-known acyclic sulfimide formation from azides and sulfides ⟨77CRV409⟩. The related ring skeleton (**130**) can also be prepared by the oxidative treatment of the aminosulfide (**131**) with NCS, followed by deprotonation with aqueous KOH ⟨84CPB4360, 90TL7021⟩. An efficient synthesis of 1,2-benzothiazin-4-one has been described, involving an unusual nucleophilic displacement from an oxime tosylate followed by dealkylation. The thermolysis of the oxime tosylate (**132**) at 80°C in the presence of a catalytic amount of *p*-toluenesulfonic acid yields the benzothiazinecarboxylate (**133**) (Scheme 24) ⟨90CC497⟩.



(**128**) (**129**) (**131**) (**130**)

R = Me, Et, Ph
Z = CO_2Et, CHO,CN

Scheme 23

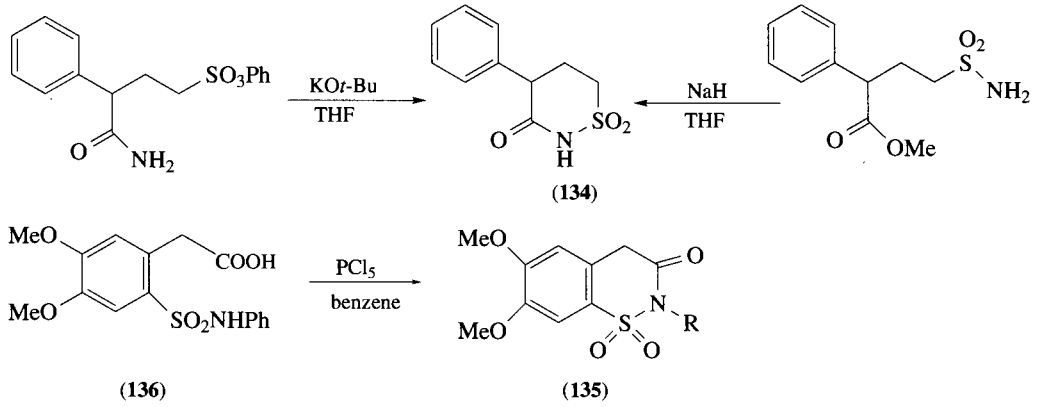


(**132**) (**133**)

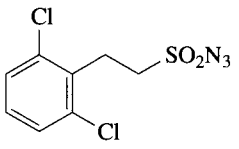
Scheme 24

6.06.5.2.2 *Adjacent to the nitrogen (type f)*

A facile base-catalyzed cyclization can be induced in γ-carboxamidosulfonates or γ-carboalkoxysulfonamides, leading to the 3-oxo-1,2-thiazine 1,1-dioxide (**134**) (Scheme 25). These cyclization reactions leading to 1,2-thiazines are relatively general ⟨91JOC3549⟩. A variation of this strategy has been successfully utilized in the synthesis of 1,2-benzothiazin-3-ones (**135**) from 2-carboxymethylbenzenesulfonamides (**136**) ⟨91DP161, 92JHC569⟩. The flash vacuum pyrolysis of 2,6-dihalo-β-phenethylsulfonyl azides (e.g., (**137**)) can afford 2,1-benzothiazine 2,2-dioxides ⟨85JOC2066⟩.



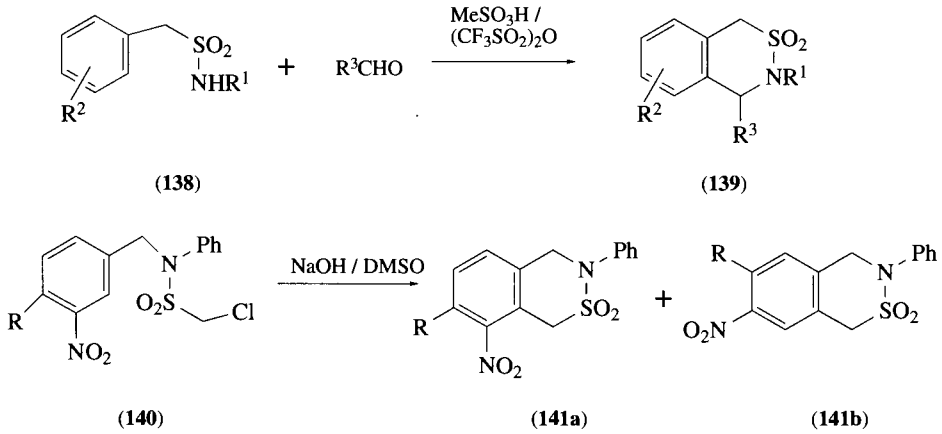
Scheme 25



(**137**)

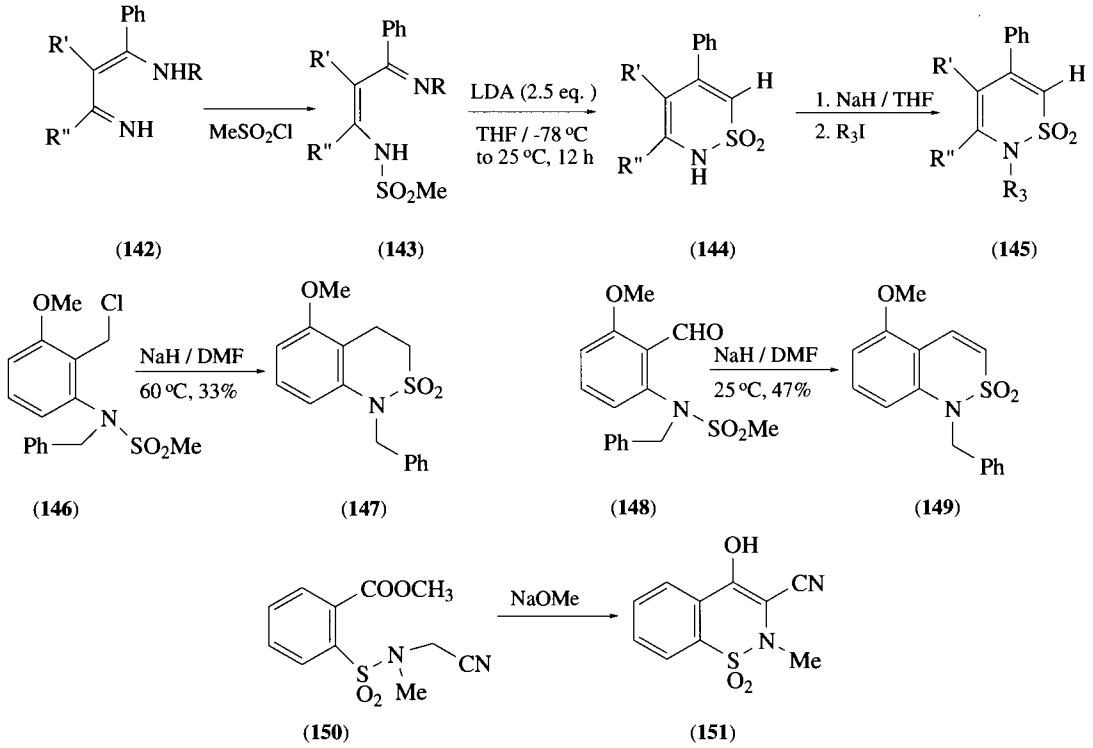
6.06.5.2.3 *β to the heteroatoms (types c and e)*

Benzylsulfonamides (**138**) and aldehydes can be combined under strongly acidic conditions to afford 2,3-benzothiazine 2,2-dioxides (**139**) via a preparative scale intramolecular sulfonamidomethylation. This highly effective procedure provides a rapid entry into the 2,3-benzothiazine ring skeleton (Scheme 26). When this reaction is carried out with weak acids or short reaction times, uncyclized intermediates can be isolated ⟨86JHC1701⟩. The treatment of 3-nitrobenzylamine derivatives (**140**) with NaOH in DMSO leads to 2,3-benzothiazines (**141a**) and (**141b**) by an intramolecular nucleophilic aromatic substitution (Scheme 26) ⟨92S571⟩.



Scheme 26

1,2-Thiazine 1,1-dioxides can be prepared by base-catalyzed ring closure of an appropriately substituted methanesulfonamide. The treatment of compounds (**142**) with methanesulfonyl chloride leads to the sulfonamides (**143**) in 85–90% yield. These sulfonamides, when reacted with LDA, afford 1,2-thiazine 1,1-dioxides (**144**) by intramolecular addition of the α-sulfonyl carbanion to the C—N double bond, followed by the loss of RNH_2. Thiazines (**144**) can be further alkylated on the nitrogen, leading to more highly substituted 1,2-thiazines (**145**) ⟨89TL4705⟩. This type of ring closure can also be used to prepare benzothiazines. The *o*-chloromethylsulfanilide (**146**) can be cyclized to the 2,1-benzothiazine (**147**), by treatment with NaH/DMF. The corresponding *o*-formylsulfanilide (**148**) also undergoes a base-induced cyclization to yield (**149**) (Scheme 27) ⟨94TL2911⟩. In a somewhat similar reaction, the 2-methoxycarbonyl-*N*-cyanomethylbenzenesulfonamide (**150**) can be cyclized by sodium methoxide to afford the 1,2-benzothiazine (**151**), which is a useful intermediate in synthesis of piroxicam (**19**) ⟨89MI 606-01⟩.

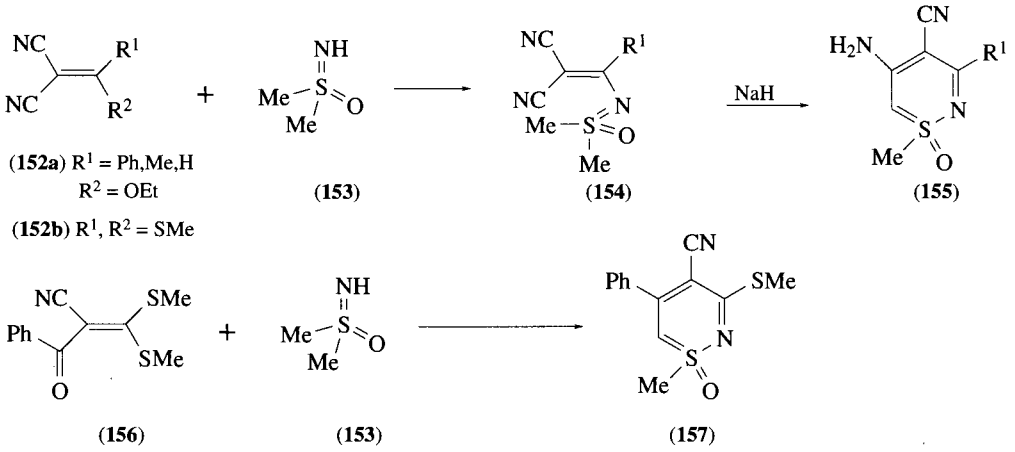


Scheme 27

A very similar process can be used in the synthesis of fully conjugated 1,2-thiazine 1-oxides. Ethoxyalkylidenemalononitriles (**152a**) or the related dithioacetal (**152b**), can be reacted with *S,S*-dimethylsulfoximide (**153**) to yield Michael adducts (**154**). These compounds undergo base-induced cyclization to afford 1,2-thiazines (**155**) ⟨88CB1005⟩. The ketene dithioacetal (**156**) reacts with the sulfoximide (**153**) at 100–150 °C to yield the thiazine (**157**) (Scheme 28) ⟨83S926⟩.

6.06.5.2.4 γ to the heteroatoms (type d)

There is one interesting example of this type of bond formation in which the bis-sulfonamide (**158**) can be cyclized with bis(triphenylphosphine)palladium(II) chloride and sodium acetate to give the dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (**159**). It is noteworthy that the monosulfonamide (**160**) is recovered unchanged under the same reaction conditions (Equation (2)) ⟨84T1919⟩.



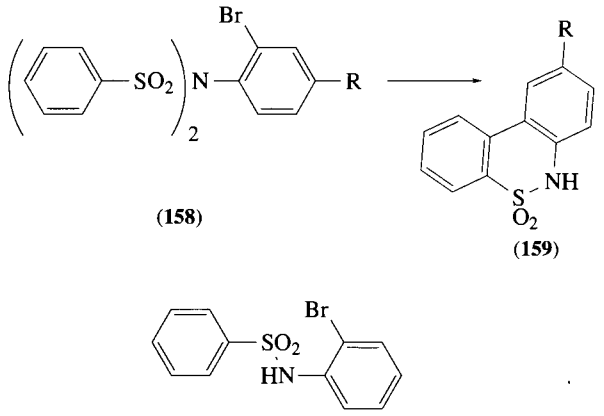
(152a) R^1 = Ph,Me,H
R^2 = OEt

(152b) R^1, R^2 = SMe

(153) (154) (155)

(156) (153) (157)

Scheme 28



(158) (159)

(160)

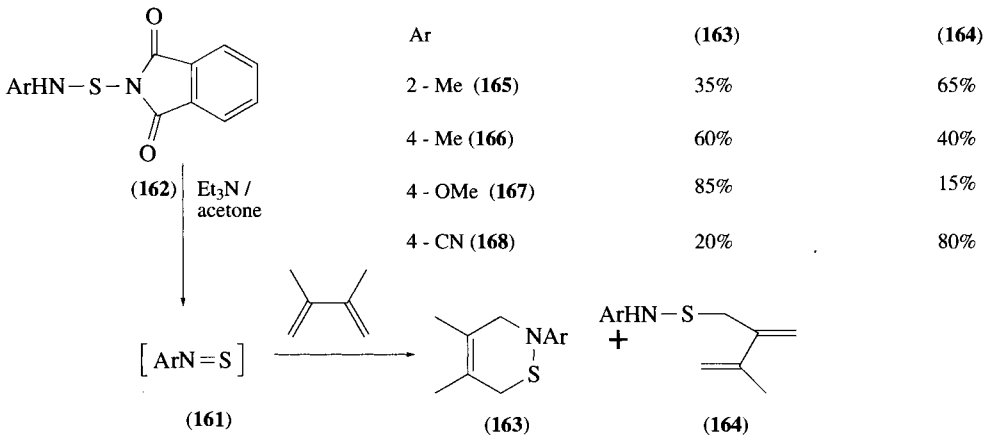
(2)

6.06.5.3 Formation of Two Bonds

6.06.5.3.1 3,6-Dihydro-1,2-thiazines

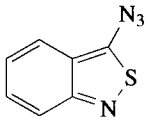
This type of bond formation includes the most versatile and preponderant synthetic approaches to numerous 1,2-thiazines. These reactions include the Diels–Alder-type [4 + 2] cycloadditions leading to 3,6-dihydro-1,2-thiazines. Transient thionitrosoarenes and alkanes can be trapped with conjugated 1,3-dienes, yielding the corresponding dihydrothiazines. There are several convenient procedures to generate these transient thionitroso species. Thionitrosoarenes (**161**) can be produced by 1,2-elimination of phthalimide from (**162**), and can be very efficiently trapped with an assortment of dienes to give the [4 + 2] cycloadducts (**163**), along with the ene adducts (**164**) (Scheme 29) ⟨90JCS(P2)3225⟩. The Diels–Alder : ene adduct ratio is highly dependent on the presence of an *ortho* substituent on the aryl ring. For instance, (**165**) affords the [4 + 2] adduct in only 35% yield, whereas in the case of (**166**) the [4 + 2] adduct can be isolated in 60% yield ⟨91TL7459⟩. The [4 + 2] adducts are also favored by electron-donating substituents at the 4 position of the aryl ring, as exemplified by (**167**). Electron-withdrawing groups favor the ene adducts (e.g., (**168**)). Thionitrosoarenes can also be generated by thermolysis or photolysis of 3-azido-2,1-benzisothiazoles (**169**) ⟨84CC374⟩.

Thionitrosoalkanes have been generated by the thermal decomposition of *N*-trimethylsilyl-*N*-chlorosulfenylalkylamines. The thermolysis of *N*-trimethylsilyl-*N*-chlorothio-*t*-butylamine (**170**) in the presence of 2,3-dimethylbutadiene affords a 65% yield of the dihydrothiazine (**171**) ⟨90JOU1799⟩. These thionitroso alkanes show good regioselectivity with unsymmetrical dienes (Scheme 30).



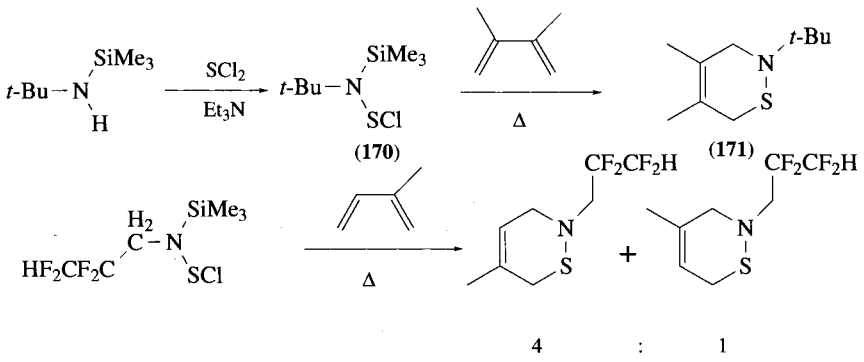
Ar	(163)	(164)
2 - Me (**165**)	35%	65%
4 - Me (**166**)	60%	40%
4 - OMe (**167**)	85%	15%
4 - CN (**168**)	20%	80%

Scheme 29



(**169**)

This regioselectivity is similar to that of *N*-sulfinylamine [4 + 2] cycloadditions ⟨92JOU1092⟩. This procedure has also been used to prepare thionitrosoarenes ⟨94TL5275⟩.

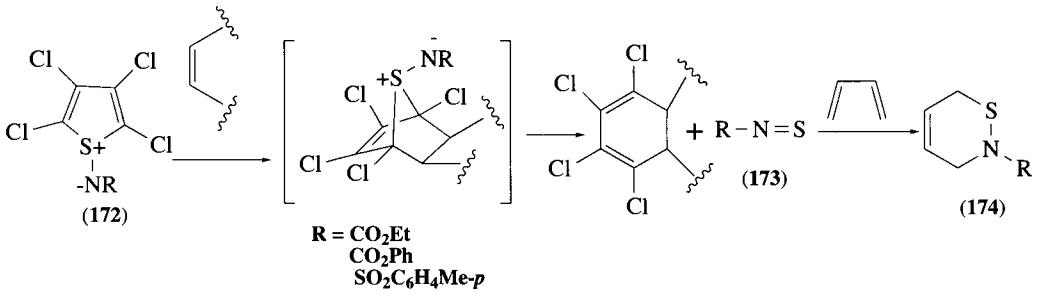


Scheme 30

Electron-deficient (i.e., acyl and sulfonyl) thionitroso compounds have also been prepared and can be used as precursors for 1,2-thiazines ⟨86JCS(P1)245⟩. The thiophene ylides (**172**) react with electron-rich alkenes such as acenaphthylene, and the resulting [4 + 2] adducts undergo a concomitant chelotropic elimination to afford the corresponding acyl or sulfonylthionitroso compounds (**173**). These highly reactive species can be trapped with 1,3-dienes to yield the appropriate 1,2-thiazines (**174**) (Scheme 31). With dienes such as isoprene and 2,3-dimethylbutadiene, the ene reaction effectively competes with the [4 + 2] cycloaddition, hence reducing the yield of 1,2-thiazines.

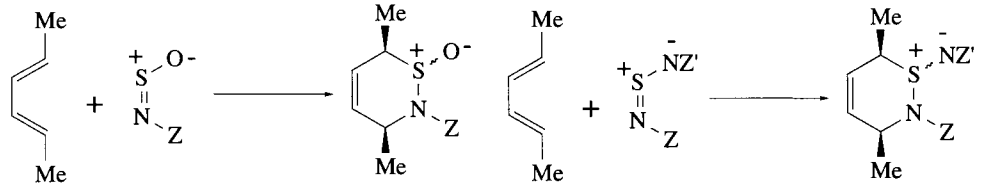
6.06.5.3.2 3,6-Dihydro-1,2-thiazine 1-oxides and 1-imines

The preparation of 3,6-dihydro-1,2-thiazine 1-oxides by [4 + 2] cycloaddition of *N*-sulfinyl compounds has been intensively studied since the mid-1980s ⟨B-87MI 606-02, 88ACR313⟩. The [4 + 2] cycloaddition of *N*-sulfinylaniline with 1,3-dienes was first reported in 1953. Since then, a number of Diels–Alder cycloadditions of *N*-sulfinyl compounds and the related sulfur diimides have been reported. These cycloadditions usually proceed expeditiously, often exothermically, at



Scheme 31

low temperatures when there is an electron-withdrawing group Z on the nitrogen atom (Scheme 32). When Z is an electron-donating group such as an alkyl group the cycloadditions often do not occur under normal conditions.

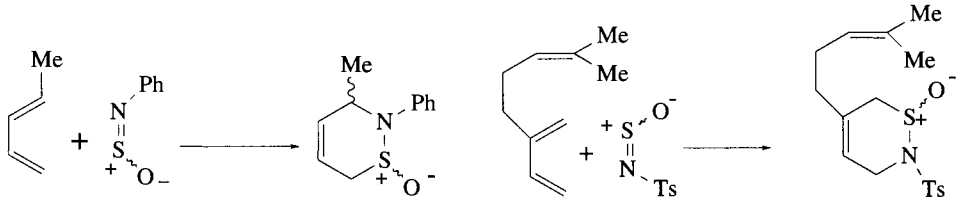


Z = Alkyl, Ar, SO_2Ar, CO_2R, COR, CN, $^+SR_2$

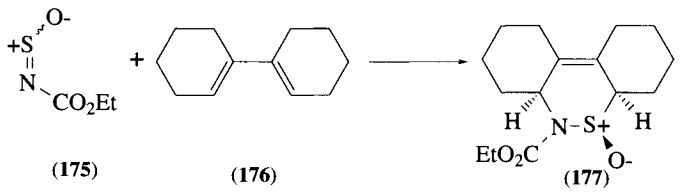
Scheme 32

A multitude of *N*-sulfinyl compounds and sulfur diimides bearing a plethora of substituents Z on the nitrogen atom(s) have been prepared and used in 1,2-thiazine synthesis. The *N*-sulfinyl dienophiles are commonly generated by the treatment of the parent NH_2 compounds with thionyl chloride/pyridine and can often be reacted with dienes without purification. Symmetrically substituted sulfur diimides are generally prepared by reacting the parent NH_2 compound with SCl_2 or S_2Cl_2 in the presence of a base. A few unsymmetrical sulfur diimides have also been prepared ⟨B-87MI 606-02⟩.

Both of the cycloadditions shown in Scheme 32 exhibit excellent regiochemical control when unsymmetrical dienes are used (Scheme 33) ⟨B-87MI 606-02, 90TL7007⟩. Since 1985 mechanistic information for these cycloaddition reactions has been provided. These regioselective reactions of *N*-sulfinyl compounds are seemingly concerted in nature. Hanson and Stockburn investigated the mechanism of the cycloaddition of *N*-sulfinyl ethyl carbamate (**175**) and 1,1′-bicyclohexenyl (**176**), which exclusively affords the dihydrothiazine oxide (**177**). The activation parameters derived from the reaction kinetics are highly characteristic of a concerted pericyclic process. The large entropy and the small enthalpy of activation attest to a highly ordered, early transition state with concerted bond making and breaking. The reaction rate was unaffected by solvent polarity, indicating minimal separation of charge in the transition state, consistent with a concerted mechanism (Equation (3)) ⟨85JCS(P2)589⟩. It was proposed that less electrophilic dienophiles, such as *N*-sulfinylanilines, also undergo cycloadditions via a concerted process.



Scheme 33



(175) (176) (177)

Activation Parameters

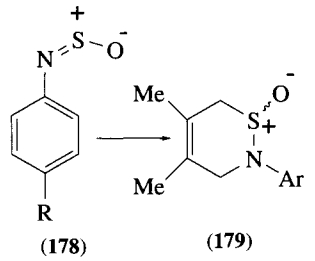
$\Delta S^{\ddagger}$ = -176.9 J K^{-1} mol^{-1}

$\Delta H^{\ddagger}$ = 30.3kJ mol^{-1}

$\Delta G^{\ddagger}$ = 83.0 kJ mol^{-1}

at 298°K (3)

However, a later study ⟨89JCS(P2)1855⟩ of *p*-substituted *N*-sulfinyl aniline cycloadditions indicates a more complicated picture. A kinetic study of the reaction of a series of *N*-sulfinyl compounds (**178**) with 2,3-dimethylbutadiene, giving the adduct (**179**), was carried out. Although the reactions were relatively slow below 350 K, activation parameters were derived from the Arrhenius data obtained at 330 K, 340 K, and 350 K (Equation (4)). These results are in good agreement with those for *N*-sulfinyl ethyl carbamate (**175**). Once again, the high negative entropy of the transition state is noteworthy. Even though this is consistent with an ordered pericyclic transition state, the substituent effects paint a significantly more complicated picture. Electron-donating groups (e.g., (**178c**)) in the *para* position enhance the reaction rate while electron-withdrawing groups (e.g., (**178f**)) inhibit it. The rates showed no linear correlation with MNDO calculated values for Δ[HOMO(diene) – LUMO (ArN=S^+—O^-)]. These studies suggested a significant resonance contribution from the *para* electron-donating substituent, resulting in a decrease in the double bond character of the N—S bond, implying nonsynchronous bond formation (cf. the transition state of (**178c**)). It was concluded that there is mechanistic continuum with a concerted pericyclic process on one end and a stepwise nucleophilic addition process on the other end, depending on the electronic nature of the N—S double bond. A similar detailed mechanistic investigation of the sulfur diimide cycloadditions has not been reported.



(178) (179)

N-Sulfinyl aniline	R
(178a)	H
(178b)	Me
(178c)	OMe
(178d)	Cl
(178e)	Br
(178f)	NO_2

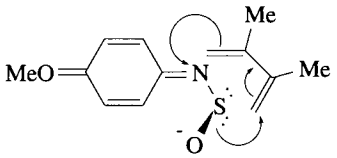
Activation Parameters for **175a** (R = H)

$\Delta S^{\ddagger}$ = -145.5 J K^{-1} mol^{-1}

$\Delta H^{\ddagger}$ =72.0 kJ mol^{-1}

$\Delta G^{\ddagger}$ =122.9 kJ mol^{-1}

at 350°K (4)



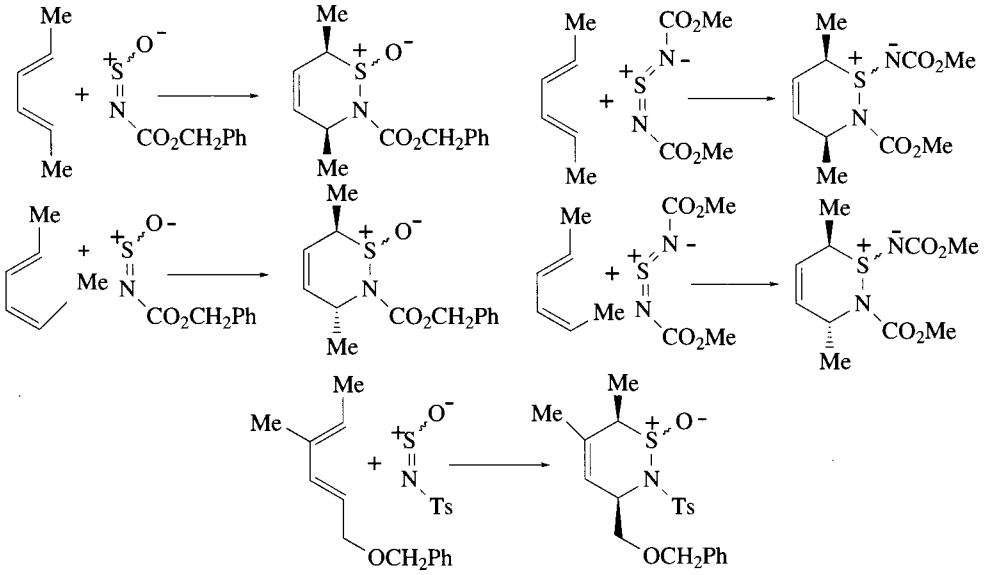
TS178C

These *N*-sulfinyl Diels–Alder reactions are also highly stereoselective, giving products of *syn* addition to the 1,3-diene. The same holds true for the sulfur diimide cycloadditions ⟨B-87MI 606-02⟩. The stereoselectivity with respect to the dienophile is not very well known because the stereochemistry of sulfur in the starting *N*-sulfinyl dienophile and in the resulting thiazine derivatives has usually not been determined. A representative sample of the stereoselective preparation of 3,6-dihydrothiazine 1-oxides and 1-imines is shown in Scheme 34 ⟨84JA7861, 84JA7867⟩.

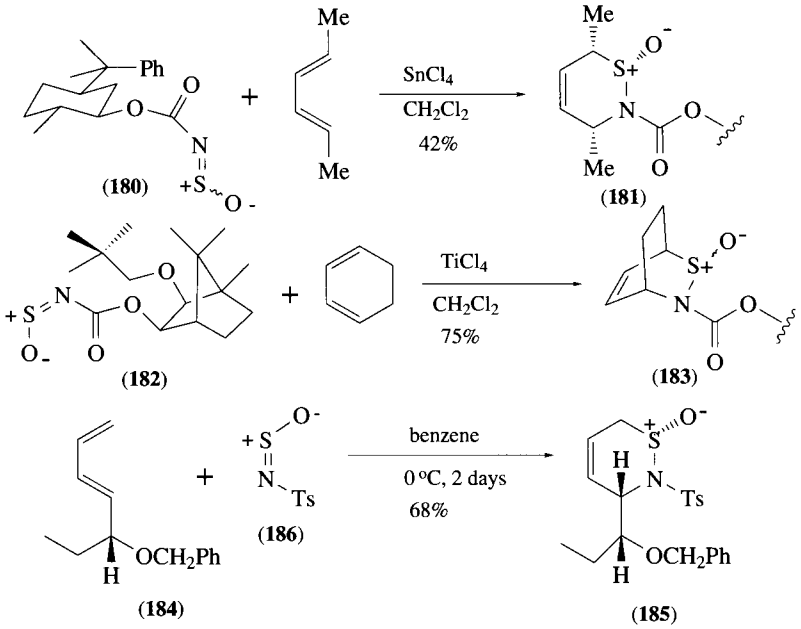
High levels of asymmetric induction at the C-3 and C-6 positions and at the sulfur atom of 3,6-dihydrothiazine 1-oxides have been achieved in a [4 + 2] cycloaddition of a chiral *N*-sulfinylcarbamate with dienes. The *N*-sulfinylcarbamate (**180**) derived from 8-phenylmenthol reacts with (*E*,*E*)-2,4-hexadiene at 0°C in the presence of $SnCl_4$ to give the diastereomeric adduct (**181**) as the exclusive product ⟨85CC1449⟩. This product may result from *endo* addition of the diene to the least congested face of the (*Z*)-*N*-sulfinyl dienophile. In a similar fashion, the dienophile (**182**) yields exclusively the diastereomer (**183**) in the presence of $TiCl_4$ ⟨86TL1853⟩. Chiral dienes can also induce asymmetry into a 3,6-dihydrothiazine ring. For example, the diene (**184**) yields (**185**) upon reaction with *N*-sulfinylsulfonamide (**186**) (Scheme 35) ⟨89TL6405⟩.

The [4 + 2] cycloadditions of *N*-sulfinyl compounds can also be carried out intramolecularly to afford highly functionalized dihydrothiazine derivatives (Scheme 36) ⟨88ACR313⟩.

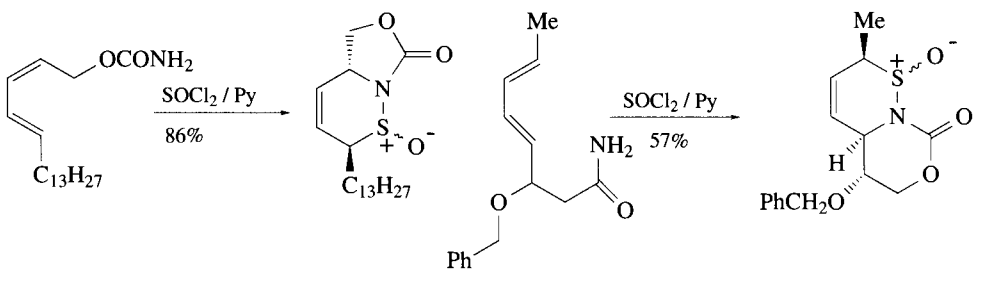
As mentioned previously, *N*-sulfinyl compounds derived from alkylamines do not easily participate in Diels–Alder-type cycloadditions with dienes. These cycloaddition reactions can, however,



Scheme 34

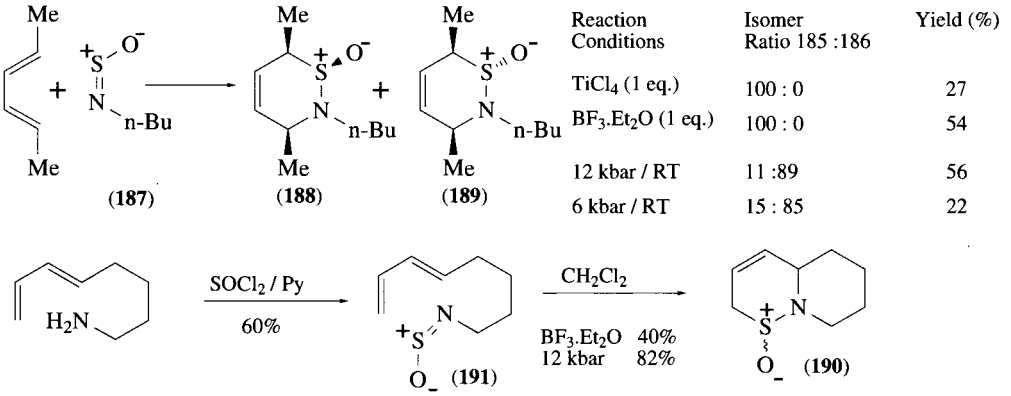


Scheme 35



Scheme 36

be successfully carried out under high-pressure conditions or under Lewis acid catalysis. The *N*-sulfinyl derivative (**187**) of *n*-butylamine reacts with (*E,E*)-2,4-hexadiene to yield the corresponding dihydrothiazine oxides (**188**) and (**189**). The variation in the isomer ratio could be due to changes in reaction mechanism (i.e., concerted versus stepwise). These reaction conditions were also effectively used in the preparation of (**190**) by the intramolecular cycloaddition of (**191**) (Scheme 37) ⟨88TL4233⟩.



Scheme 37

A [4 + 2] cycloaddition strategy has been used in the preparation of perfluorinated thiazines ⟨91MI 606-01, 92CB581⟩.

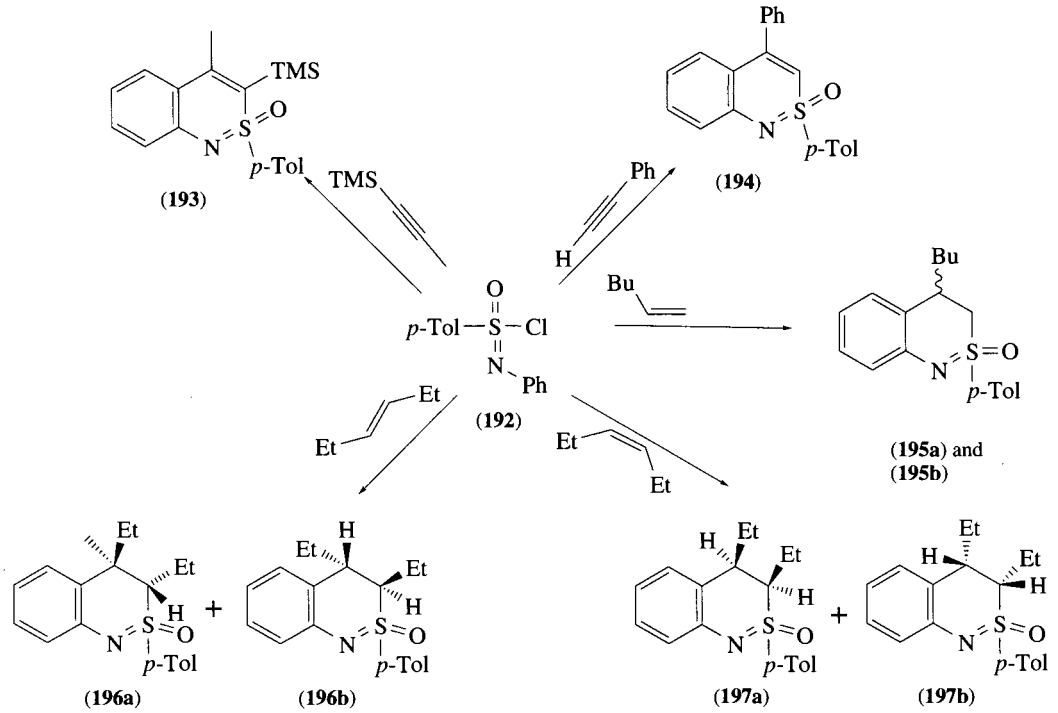
6.06.5.3.3 2,1-Benzothiazines

Several reports have appeared of Lewis acid-mediated reactions of sulfoximidoyl chlorides with alkenes and alkynes to afford 2,1-benzothiazines. *N*-Phenylsulfoximidoyl chloride (**192**) reacts with a variety of alkynes in the presence of aluminum chloride to yield 2,1-benzothiazines in high yield ⟨87TL5997⟩. 1-Trimethylsilyl-1-propyne reacts with (**192**) in the presence of an equivalent amount of $AlCl_3$ to give the benzothiazine (**193**). In a similar fashion, phenylalkyne leads to the adduct (**194**) regioselectively. This cyclization appears to be general. These sulfoximidoyl chlorides also react with alkenes to afford 3,4-dihydro-2,1-benzothiazines with high and predictable regioselectivity. 1-Hexene leads to (**195a**) and (**195b**), whereas (*E*)-3-hexene gives a 122 : 1 ratio of (**196a**) and (**196b**) (Scheme 38) ⟨91JOC5059⟩. Under the same reaction conditions (*Z*)-3-hexene affords equal amounts of the *cis*-substituted benzothiazines ((**197a**) and (**197b**)). In these two reactions, the geometry of the alkene is completely retained in the cycloaddition product. This result seems to suggest a concerted cycloaddition pathway. MNDO calculations of the iminosulfonium ion (**198**) (a model for the presumed intermediate in the cyclization) suggest a cisoid geometry similar to that of an *s-cis*-diene. If the reaction is in fact concerted, the Markovnikov regioselectivity indicates a high degree of asynchronicity in the cycloaddition with a sizable accumulation of positive charge on the more substituted carbon of the alkene.

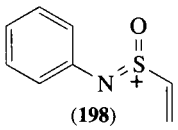
6.06.5.4 1,2-Thiazine Ring Synthesis by Transformation of Another Heterocycle

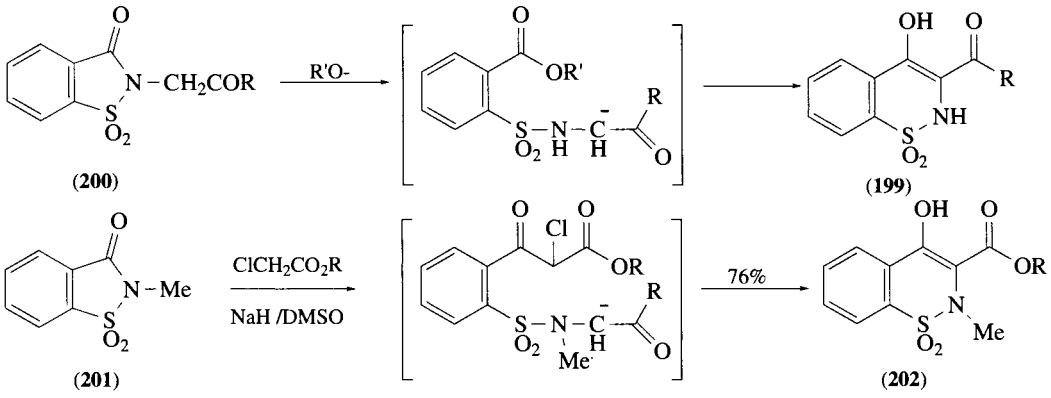
There are a few examples of 1,2-thiazine synthesis of this type which are of importance. The most noteworthy is the preparation of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**199**) from the benzisothiazolinone (**200**) ⟨81AHC(28)73⟩. This general procedure can be extended to the preparation of 2-alkyl-4-hydroxybenzothiazines. The treatment of *N*-methylsaccharin (**201**) and an alkyl chloroacetate with NaH in DMSO or DMF affords a 76% yield of the 1,2-benzothiazine (**202**) (Scheme 39) ⟨83JOC3601, 86CCC1113, 86FES819⟩.

Amines, anilines, and hydrazides react with sultones to afford the complementary 1,2-thiazines (Scheme 40). The reactions are usually carried out in a nonpolar solvent or by fusion of the reactants at high temperature ⟨87LA481, 89MI 606-02, 91RRC197, 92MI 606-01⟩, and presumably proceed by the cleavage of the carbon–oxygen bond and subsequent ring closure of the resulting sulfonic acid.

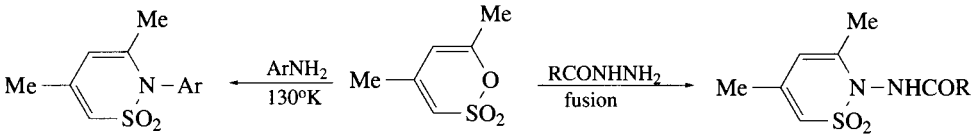


Scheme 38



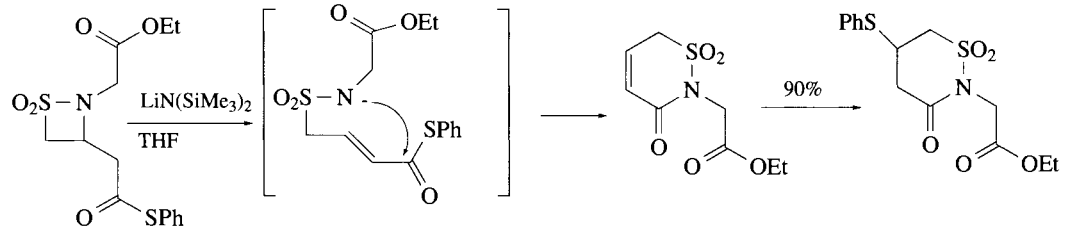


Scheme 39



Scheme 40

A novel entry into 1,2-thiazin-3-ones (**203**) can be achieved by a base-catalyzed ring expansion of the 1,2-thiazetidine 1,1-dioxide (**204**). This reaction is initiated by a retro-Michael process leading to the $\alpha\beta$-unsaturated thioester (**205**), which cyclizes to the thiazinone (**206**). Thiophenoxide addition to (**206**) gives the heterocycle (**203**) in an overall yield of 90% (Scheme 41) ⟨94LA251⟩.



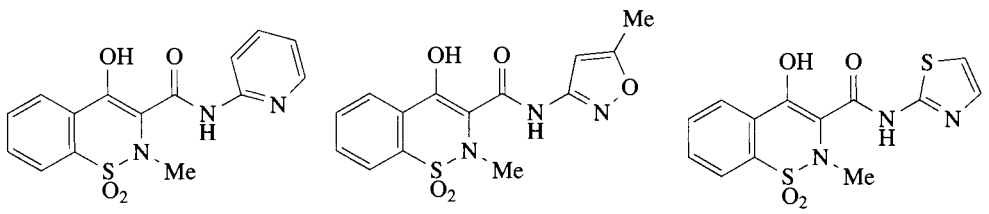
(204) (205) (206) (203)

Scheme 41

6.06.6 IMPORTANT COMPOUNDS AND APPLICATIONS

6.06.6.1 Pharmaceutical and Industrial Applications

Oxicams are a series of *N*-heterocyclic carboxamides of 1,2-benzothiazine 1,1-dioxides. Piroxicam (**207**) was the first member of this family of NSAIDs (nonsteroidal anti-inflammatory drugs), which are inhibitors of prostaglandin biosynthesis. Piroxicam and other members of this class (e.g., isoxicam (**208**) and sudoxicam (**209**)) are characterized by long-acting and often very potent antipyretic and anti-inflammatory activity ⟨B-85MI 606-01⟩. Piroxicam has been effectively used in the treatment of rheumatoid arthritis, osteoarthritis, and soft-tissue rheumatism. Unfortunately, oxicams suffer from the same side-effects shown by most other NSAIDs, such as gastrointestinal and renal toxicity.



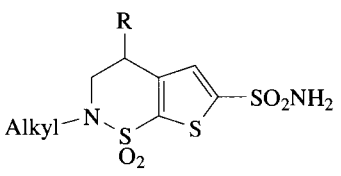
(207) (208) (209)

In 1993, several substituted benzothiazines such as (**210**) and (**211**) were reported to be very potent carbonic anhydrase inhibitors useful for treating conditions which derive from the restriction of blood flow to the brain ⟨93USP5240923⟩.

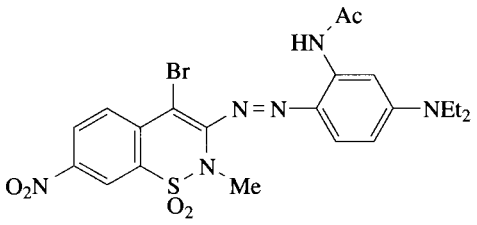
1,2-Benzothiazine derivatives have been used in the preparation of a variety of azo disperse dyes (e.g., (**212**) and (**213**)) for polyesters. The dye (**212**) produces a yellow shade and the dye (**213**) a bright red color on polyesters ⟨90DP93, 90DP161⟩. Some dyes in this class have high light and wash fastness while possessing a high tinctorial power.

6.06.6.2 Synthetic Applications

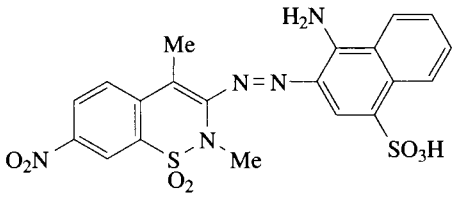
Since the late 1980s, 3,6-dihydrothiazines have been used as building blocks for stereoselective synthesis of *vicinal* amino alcohols, diamines and other highly functionalized amines ⟨86T2979, 88ACR313⟩. 3,6-Dihydrothiazine 1-oxide (**214**) has been efficiently converted to *erythro*-sphingosine (**215**) (Scheme 42). Using the same methodology, the dihydrothiazine (**216**) was used to prepare the



(210) R = OH
(211) R = NHEt

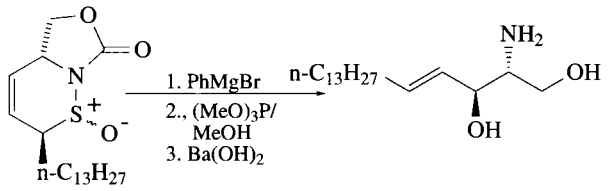


(212)

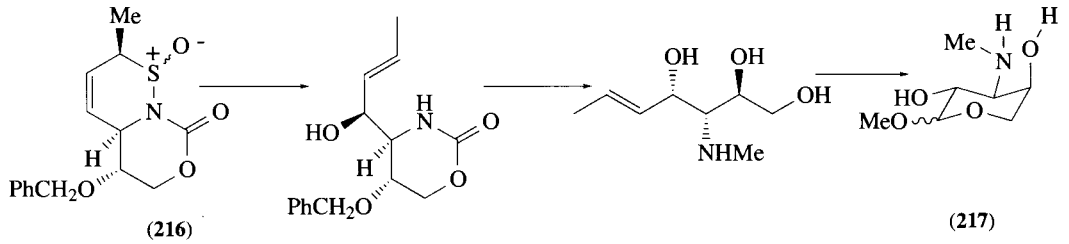


(213)

deoxyaminopentose (**217**), a component of the aminoglycoside antibiotic 66-40D ⟨85T1173⟩. This methodology has also been used in the stereoselective synthesis of complex 1,2-amino alcohol derivatives such as (**218**) ⟨93SL551⟩. As mentioned previously, 3,6-dihydrothiazine 1-imines can be used in the stereoselective preparation of *vicinal* diamines ⟨88ACR313⟩.

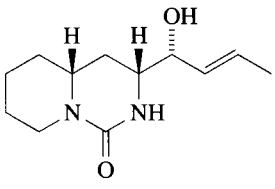


(214) (215)



(216) (217)

Scheme 42



(218)

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6.07
1,3-Thiazines and their Benzo Derivatives

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6.07.1 INTRODUCTION

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) 1,3-thiazines and 1,3-oxazines were reviewed together; indeed, much of their chemistry is similar, providing justification for this arrangement. However, there are areas in which this is not so, and in this edition the two types of heterocycle are treated separately. This allows a more focused approach, but as Quiniou and Guilloton ⟨90AHC(50)85⟩ have already pointed out, one feature which complicates any survey of 1,3-thiazines is the interrelationship of these compounds to cephalosporins. The literature dealing with cephems and related systems is vast and requires individual treatment, so here the emphasis is on the synthesis and reactions of simple 1,3-thiazines and their benzo derivatives. Other fused systems are not included unless their chemistry illustrates some important property of the 1,3-thiazine heterocycle itself.

Many new reactions of 1,3-thiazines have been uncovered since CHEC-I was published, most of which parallel known reactions of 1,3-oxazines. There have also been advances in synthetic methodology, but generally speaking this has not been such an active area. The nomenclature of 1,3-thiazines follows the same IUPAC system as adopted for 1,3-oxazines (see Chapter 6.05), and the order of coverage within each section of the following account will be based upon the number of formal double bonds in the ring, so that thiazines and benzothiazines will be dealt with before their reduced forms. Thiazinones, thiazinediones, and their derivatives will be discussed last in each subsection, even though tautomerism with enolic isomers may well mean that this is an artificial situation.

6.07.2 EXPERIMENTAL STRUCTURAL METHODS AND TAUTOMERISM

6.07.2.1 UV Spectra

Examples of both 2-amino-4*H*-1,3-thiazines and 2-amino-6*H*-1,3-thiazines are known, and in the case of 2-amino-4*H*-1,3-thiazines these seem to be favored over their imino tautomers, at least in solution. Thus, 4,4,6-trimethyl-2-(*N*-methyl-*N*-phenylamino)-4*H*-1,3-thiazine (**1**), which cannot tautomerize, absorbs at $\lambda_{max} = 264$ nm, and 4,4,6-trimethyl-2-(*N*-phenylamino)-4*H*-1,3-thiazine (**2**), which can, shows $\lambda_{max} = 263$ nm. 3,4,4-Trimethyl-2-(*N*-phenylimino)-4*H*-1,3-thiazine (**3**), which is locked into the imino form, shows a main UV band at $\lambda_{max} = 236$ nm with a shoulder at 280 nm. Many 2-amino-6*H*-1,3-thiazines are known where there is an unsaturated (acyl) group at C-5. This group serves to extend the delocalization of the chromophore, and 5-ethoxycarbonyl-2-(*N*-methylamino)-6*H*-1,3-thiazine (**4**), for example, exhibits UV bands at $\lambda_{max} = 240$ nm, 266 nm, and 330 nm (Figure 1) ⟨90AHC(50)85⟩.

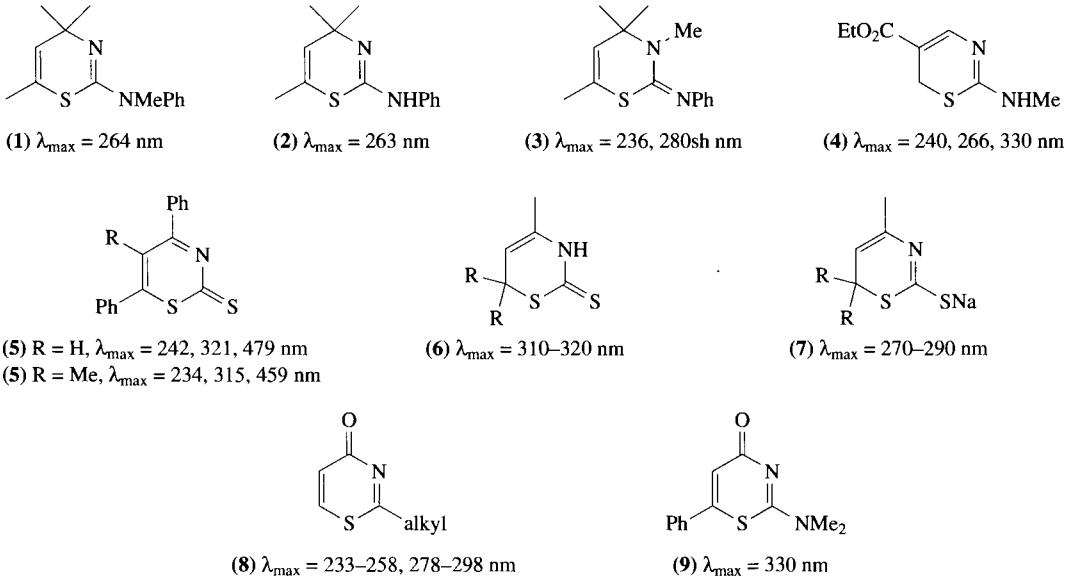


Figure 1 UV spectra of prominent 1,3-thiazine derivatives.

4,6-Diphenyl-1,3-thiazine-2-thione (**5**) (R = H) gives rise to UV bands at $\lambda_{max} = 242$ nm, 321 nm, and 479 nm; these undergo a blue shift if an alkyl group replaces H-5, and the UV spectrum of the methyl derivative (**5**) (R = Me), for example, shows bands at $\lambda_{max} = 234$ nm, 315 nm, and 459 nm ⟨82JCS(P1)2149⟩. 3,6-Dihydro-1,3-thiazine-2-thiones (**6**) give the corresponding thiolates (**7**) on exposure to sodium hydroxide, and this causes a blue shift of 40–60 nm in the absorption maximum, perhaps because there is now cross-conjugation between the electrons of the two sulfur atoms and the unsaturated unit of the heterocycle ⟨55JA2866, 64JCS4008⟩.

1,3-Thiazin-4-ones (**8**) bearing alkyl groups at C-2 exhibit two bands in their UV spectra at $\lambda_{max} = 233$–258 nm and 278–298 nm. This is altered if an electron-donating group is present at C-2 and, for example, a bathochromic shift of about 30 nm is observed in the spectrum of 2-(*N*,*N*-dimethylamino)-6-phenyl-1,3-thiazin-4-one (**9**).

6.07.2.2 IR Spectra

For some 2-amino-1,3-thiazin-4-ones, equilibration with the imino form is possible, but this isomerism is not easily studied by UV spectroscopy because the absorption bands can overlap ⟨66TL3225, 77LA1249, 78JCS(P1)1428, 82CCC3268⟩. More information is available through IR measurements; thus, 2-alkylamino-6-phenyl-1,3-thiazin-4-ones (**10**) and 2-alkylimino-6-phenyl-3*H*-1,3-thiazin-4-ones (**11**) occur together in chloroform solution (Equation (1)). The former tautomer is favored, and exhibits a carbonyl band at 1615–1620 cm^{-1} in the IR spectrum. Shoulders on this band at 1654–1696 cm^{-1} are cited as evidence of the imino tautomer, together with an NH absorption band in the region $\nu_{max} = 3377$–3408 cm^{-1}. The latter forms a satellite of the more intense NH band of the amino form at 3410–3435 cm^{-1} ⟨90AHC(50)85⟩.

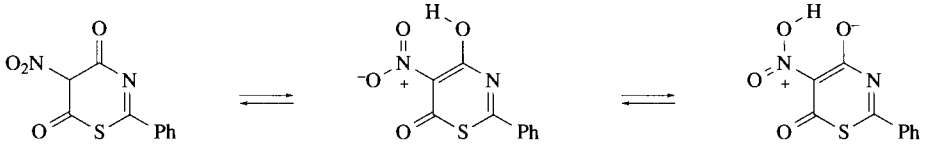
(1)

(**10**) ν_{max} = 3410–3435 (NH), 1615–1620 (CO) cm^{-1} (**11**) ν_{max} = 3377–3408 (NH), 1654–1696 (CO) cm^{-1}

2-Phenyl-1,3-thiazine-4,6(5*H*)-diones (**12**) exist in equilibrium with the enol tautomers (**13**) (Equation (2)). The dione forms show two carbonyl bands in the IR at 1690 and 1730 cm^{-1} respectively, whereas the enol isomers show only one at 1640 cm^{-1}. Unsaturated groups at C-5 favor enol forms, and 5-nitro-2-phenyl-1,3-thiazine-4,6-dione exists in $CDCl_3$ solution as a mixture of the three isomers (**14**), (**15**), and (**16**), in which the tautomer (**16**) is said to be the most abundant (Scheme 1) ⟨90AHC(50)85⟩. This result seems unexpected: possibly the *N*-H (zwitterionic) form should be considered.

(2)

(**12**) ν_{max} = 1730, 1690 cm^{-1} (**13**) ν_{max} = 1640 cm^{-1}



(**14**) 27% (**15**) 8% (**16**) 65%

Scheme 1

6.07.2.3 Proton and ^{13}C NMR Spectra

The ^{1}H NMR chemical shifts of 6*H*-1,3-thiazines (**17**) follow a pattern reflecting both the greater electronegativies of the heteroatoms, sulfur and nitrogen versus carbon, and the electron densities as predicted by the simple resonance description of the molecule. For example, the signal of H-2 "sandwiched" between sulfur and nitrogen is at lowest field (~8.3 ppm). The resonance of H-4, next to nitrogen, occurs at 6.3–6.55 ppm, and that of H-5, shielded by electron enrichment through the resonance effect, is observed at 5.35–5.4 ppm. The methylene protons resonate at 3.0–3.7 ppm.

Many compounds of this type (e.g., (**18**)) bear an acyl group at C-5; this depletes the electron density at C-4 and the attendant proton resonance is shifted downfield to 7.7–7.95 ppm (Figure 2). A similar deshielding effect is induced by the enone system of 1,3-thiazin-6-ones (**19**) (X = O). Now, H-4 resonates at 8.3–8.4 ppm, but in line with the less polar nature of the thione group the shielding is reduced in 1,3-thiazine-6-thiones (**19**) (X = S). Now, the signal for H-4 is at 7.8–7.9 ppm. The chemical shift for the resonance of H-5 in 1,3-thiazin-6-ones and in 1,3-thiazine-6-thiones is 6.1–6.3 ppm and 6.9 ppm, respectively ⟨65JOC2290, 90AHC(50)85⟩.

The combined deshielding effects of the adjacent sulfur atom and the enone chromophore ensure that H-6 of 1,3-thiazin-4-one (**20**) occurs at lower field 7.25–8.36 ppm than that of H-5 6.6–7.0 ppm ⟨66TL3225, 79JCS(P1)1428, 82CCC3268, 82JOC1090, 84JOC74⟩.

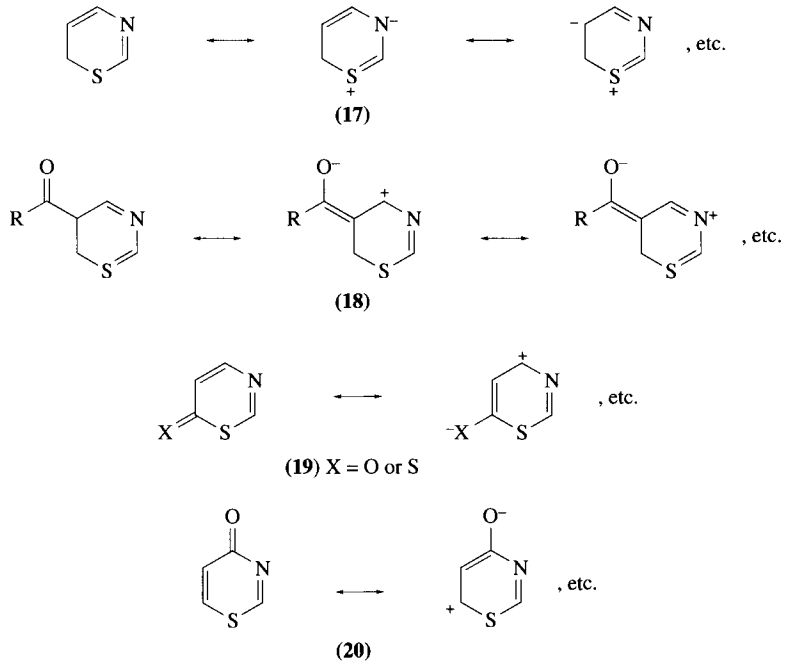
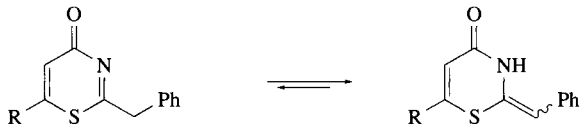


Figure 2 Resonance effects in 1,3-thiazines and derivatives.

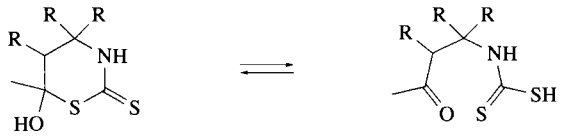
The conclusions reached regarding the chemical shifts of the proton signals are equally applicable to an understanding of the ^{13}C data. Thus, for 6*H*-1,3-thiazines C-2 is at lowest field, typically 160–175 ppm. C-4 resonates at 135–161 ppm and C-5 is in the range 84–130 ppm, depending upon the nature of the substituent at this position, and the signal of C-6 is generally between 19 ppm and 30 ppm.

For 1,3-thiazin-6-ones C-2 is at 168–179 ppm, C-5 at 108–114 ppm, and C-4 at 148–163 ppm, whereas for 1,3-thiazine-6-thiones the corresponding chemical shifts are C-2 174–189 ppm, C-5 124–125 ppm, and C-4 154–155 ppm ⟨80OMR479, 81BSB75, 85JOC1545, 86CJC597, 86PS(27)327, 87BSF149, 87SC1971⟩.

Proton and ^{13}C NMR data has proved useful in establishing that 2-benzyl-1,3-thiazin-4-ones (**21**) exist preferentially as the 2-benzylidene forms (**22**) (Equation (3)) ⟨83CPB1929⟩, and in demonstrating the existence of ring-chain tautomerism between 1,2,3,4-tetrahydro-6-hydroxy-6-methyl-1,3-thiazine-2-thiones (**23**) and acyldithiocarbamic acids (**24**) (Equation (4)), although the reasons for this are not entirely clear ⟨92KGS985⟩.



(21) (22) (3)



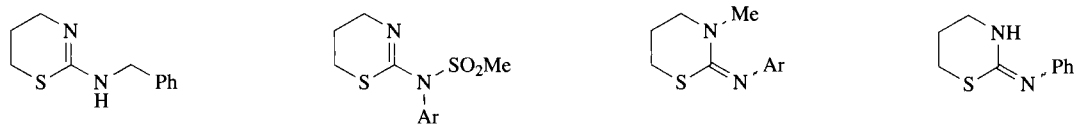
(23) (24) (4)

For aza bicyclic systems, including some 6-6 fused perhydro-1,3-thiazines, ^{13}C NMR shifts show a stereochemical dependency, which can be used to determine conformational preferences (see Chapter 6.05.4).

6.07.2.4 X-ray Studies

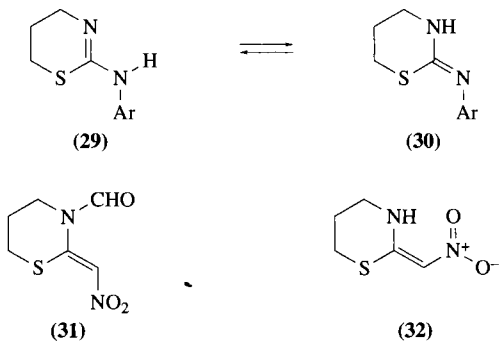
A significant number of 1,3-thiazine derivatives have been subjected to x-ray crystallographic analysis. Thus, it has been shown that the atoms of the unsaturated chromophore of simple 6*H*-1,3-thiazines lie in the same plane, with the methylene group at C-6 out of the plane ⟨86CJC597, 87BSF149⟩, and that in the solid state 4-hydroxy-1,3-thiazin-6-ones (**13**) are preferred to 4,6-diones (**12**) ⟨86MI 607-01, 93AX(C)976⟩.

2-Amino-5,6-dihydro-4*H*-1,3-thiazines and 2-iminoperhydro-1,3-thiazines form crystalline solids, and representative compounds of both types have been studied, including 2-(*N*-benzylamino)-5,6-dihydro-4*H*-1,3-thiazine (**25**) ⟨81CSC979⟩, 2-(*N*-mesyl-*N*-2,6-dimethylphenylamino)-5,6-dihydro-4*H*-1,3-thiazine (**26**) (Ar = 2,6-$Me_2C_6H_3$) ⟨77TL4237⟩, 2-(*N*-2,6-dichlorophenyl)imino-3-methyl-perhydro-1,3-thiazine (**27**) (Ar = 2,6-$Cl_2C_6H_3$) ⟨80CX(B)363⟩, and 2-(*N*-phenylimino)perhydro-1,3-thiazine (**28**) ⟨77TL4241⟩.



(25) (26) (27) (28)

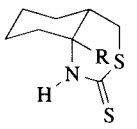
When tautomerism is possible, the imino forms are normally preferred in the solid phase and, for 2-(*N*-arylimino)perhydro-1,3-thiazines (**29**) (rather than (**30**)), the side chain tends to adopt the (*Z*) geometry. This is also the case for 3-formyl-2-nitromethyleneperhydro-1,3-thiazine (**31**), although 2-nitromethyleneperhydro-1,3-thiazine (**32**) exists in the (*E*) form, probably because of intramolecular hydrogen bonding between the NH and the nitro groups ⟨88JCS(P2)591⟩.



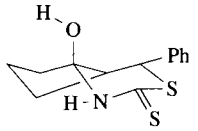
(29) (30) (31) (32)

6.07.3 CONFORMATIONAL ASPECTS

Despite greater flexibility, the perhydro-1,3-thiazines show similar conformational behavior to their 1,3-oxazine counterparts (see Chapter 6.05). In the case of *cis*-perhydro-1,3-benzothiazines, for example, the preferred conformation has the sulfur atom bonded axially to the cyclohexane ring (as a chair) ⟨84OMR597⟩. This preference extends to *cis*-perhydro-3,1-benzothiazine-2-thiones (**33**) (R = OH), where the nitrogen atom occupies the axial site. In the case of 4-aryl derivatives only one diastereomer is detected, probably because the bulky substituent is better located in an equatorial site ⟨89CB651⟩. However, in contrast to the analogous tetrahydro-1,3-oxazin-2-ones and 2-thiones ⟨85JST31, 85JST45⟩, the cyclopentane ring of the *cis*-fused perhydro-1,3-thiazines (**34**), although an almost perfect half-chair, does not shift the conformation of the heterocycle toward a C_{4a}–C_{7a} half-chair. The phenyl group occupies a pseudo-equatorial position and the hydroxy group assumes a pseudo-axial site (see (**34**)) ⟨87AX(C)324⟩. A full discussion of the subtle factors which control the stereochemistry of these and related compounds is given by Crabb ⟨B-92MI 607-01⟩.



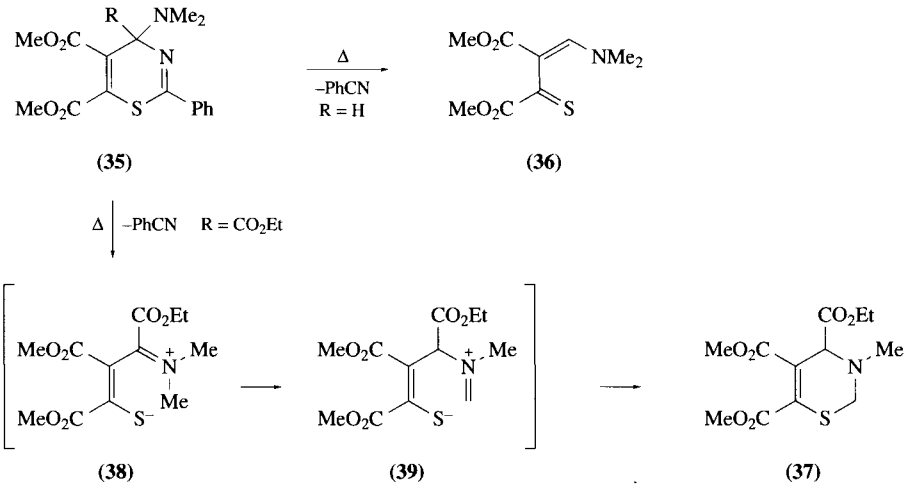
(**33**)



(**34**)

6.07.4 THERMOLYSIS

The thermolysis of 4-(*N*,*N*-dimethylamino)-4*H*-1,3-thiazines (**35**) (R = H) causes the expulsion of benzonitrile and the formation of the corresponding enaminothione (**36**) (Scheme 2). However, in the case of the ethoxycarbonyl derivative (**35**) (R = CO_2Et) the 3,4-dihydro-2*H*-1,3-thiazine (**37**) is obtained, probably through the intermediacy of the tautomers (**38**) and (**39**) ⟨86SC79⟩ (Scheme 2).



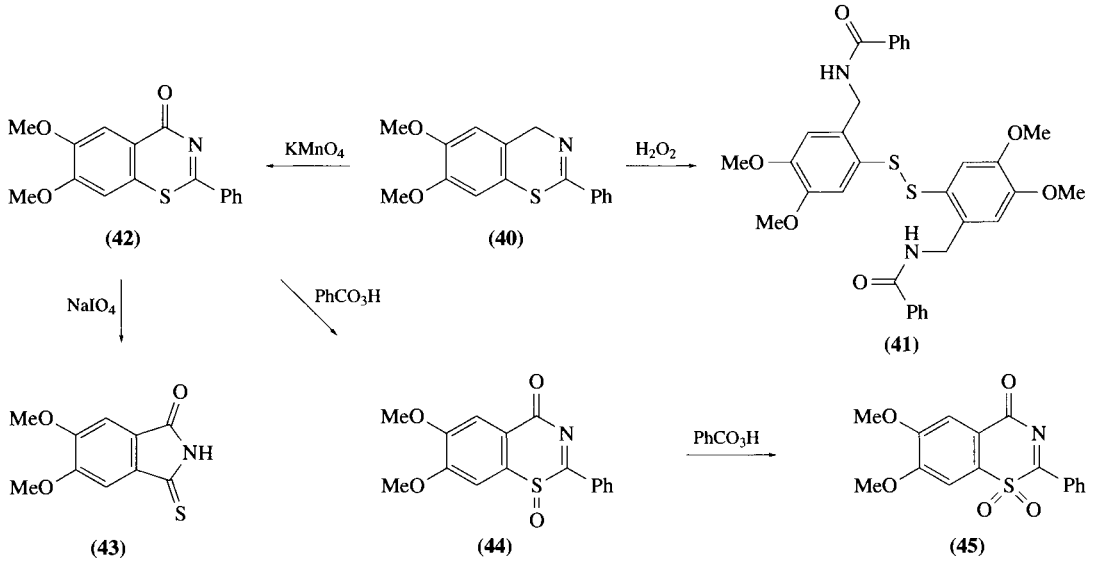
Scheme 2

6.07.5 OXIDATION AND REACTIONS WITH ELECTROPHILES

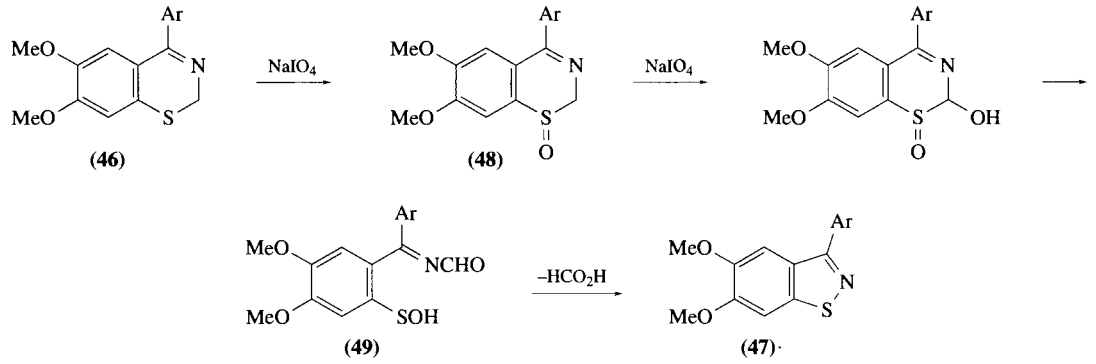
6.07.5.1 Oxidation

An investigation of the effects of different oxidants upon 1,3-benzothiazines has been conducted: thus, treatment of 6,7-dimethoxy-2-phenyl-4*H*-1,3-benzothiazine (**40**) with hydrogen peroxide gives

the disulfide (**41**), but with potassium permanganate benzylic oxidation occurs to yield the benzothiazin-4-one (**42**) (Scheme 3). The latter product when reacted with sodium periodate undergoes oxidative ring contraction to provide the 1,2-benzisothiazol-3(2*H*)-one (**43**), whereas oxidation with perbenzoic acid gives first the *S*-oxide (**44**) and then the *S*,*S*-dioxide (**45**) (Scheme 3). The 2*H*-1,3-benzothiazine (**46**) also undergoes a ring contraction when treated with sodium periodate in aqueous methanol, and in this case the product is the 1,2-benzothiazole (**47**). Here the reaction is initiated by the formation of the sulfoxide (**48**), which undergoes further oxidation and ring opening to afford the sulfenic acid (**49**), prior to recyclization to the benzothiazole (Scheme 4) ⟨88T2985⟩ (presumably the ring contraction of the benzothiazinone (**42**) to the benzoisothiazole (**43**) in Scheme 3 involves a similar reaction mechanism).

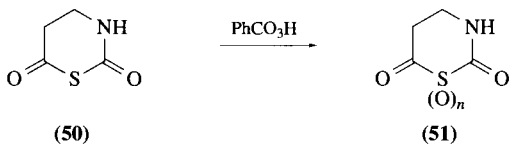


Scheme 3



Scheme 4

In the case of perhydro-1,3-thiazine-2,6-diones (**50**), oxidation with peracids gives *S*-oxides (**51**) ($n = 1$) and eventually *S*,*S*-oxides (**50**) ($n = 2$) (Equation (5)) ⟨84LA1627⟩.

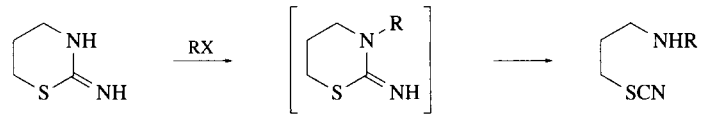


(5)

6.07.5.2 Electrophilic Attack at Nitrogen

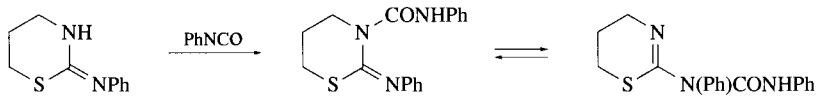
A number of examples of attack at nitrogen will be cited in the following section, together with similar reactions at sulfur, and it is clear that the factors which determine attack at one atom or at another can be subtle.

3,4,5,6-Tetrahydro-2-imino-1,3-thiazine (**52**) is attacked by 4-toluenesulfonyl chloride at the ring nitrogen atom, and subsequent opening of the heterocycle results in the formation of 3-(*N*-tosylamino)propyl isothiocyanate (**53**) (R = Ts) (Scheme 5). Other electrophiles, such as diethyl chlorophosphite, or diethyl thiochlorophosphite, behave in the same way and afford the 3-aminopropyl isothiocyanates (**53**) (R = $OP(OEt)_2$) and (**53**) (R = $SP(OEt)_2$)), respectively ⟨89H(29)841⟩. When the reagents are isocyanates the ring nitrogen is again the initial site for reaction, but the carbamoyl group which is introduced migrates to the side chain nitrogen atom with a concomitant shift of the double bond into the heterocycle. For example, 3,4,5,6-tetrahydro-2-(*N*-phenylimino)-1,3-thiazine (**54**) reacts with phenyl isocyanate to give (**55**). This then isomerizes to the tautomer (**56**), and although both products are in equilibrium with the parent thiazine and phenyl isocyanate, cross-over experiments indicate that the isomerization process operates through an intramolecular mechanism (Scheme 6) ⟨90JHC903⟩.



(52) (53)

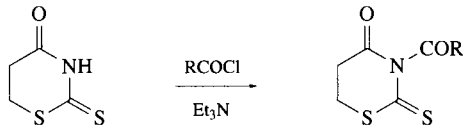
Scheme 5



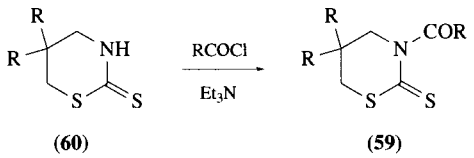
(54) (55) (56)

Scheme 6

2-Thioxo-3,4,5,6-tetrahydro-1,3-thiazin-4-ones (**57**) are *N*-acylated by acid chlorides in the presence of triethylamine to give 3-acyl-2-thioxo-3,4,5,6-tetrahydro-1,3-thiazin-4-ones (**58**) (Equation (6)) ⟨80AP833⟩, and 3-acyl-3,4,5,6-tetrahydro-1,3-thiazine-2-thiones (**59**) are formed in the same way from the parent 3,4,5,6-tetrahydro-1,3-thiazine-2-thiones (**60**) (Equation (7)) ⟨84AP74⟩. Both types of product are unstable and can be used as transacylating agents for amines and thiols. Thiocarbamoyl chlorides also react with 3,4,5,6-tetrahydro-1,3-thiazin-2-ones, but here both *N*- and *O*-thiocarbamoylation can occur ⟨86LA1140⟩.

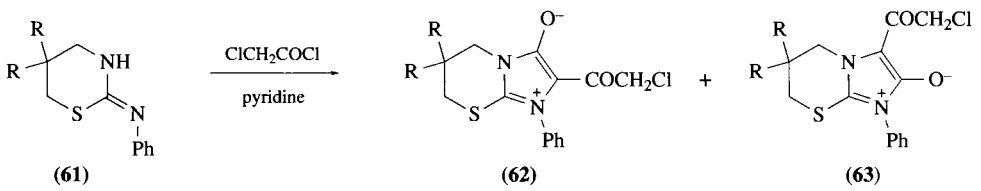


(57) (58) (6)

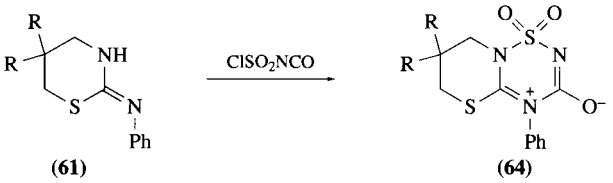


(60) (59) (7)

2-Arylimino-3,4,5,6-tetrahydro-1,3-thiazines (**61**) react with chloroacetyl chloride and pyridine to afford mixtures of the mesoionic imidazolones (**62**) and (**63**), reflecting initial electrophilic attack at either the ring or the side chain nitrogen atoms (Equation (8)), but when reacted with chlorosulfonyl isocyanate under the same reaction conditions these substrates give only the mesomeric betaine thiatriazinones (**64**) (Equation (9)) ⟨88H(27)227⟩.



(8)

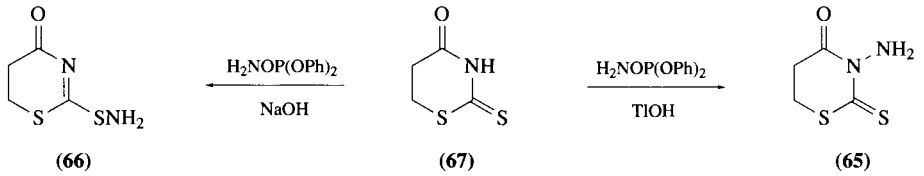


(9)

6.07.5.3 Electrophilic Attack at Sulfur, Either in the Ring, or at a Thione Group

Some reactions of this type have already been covered in Section 6.07.5.2 above.

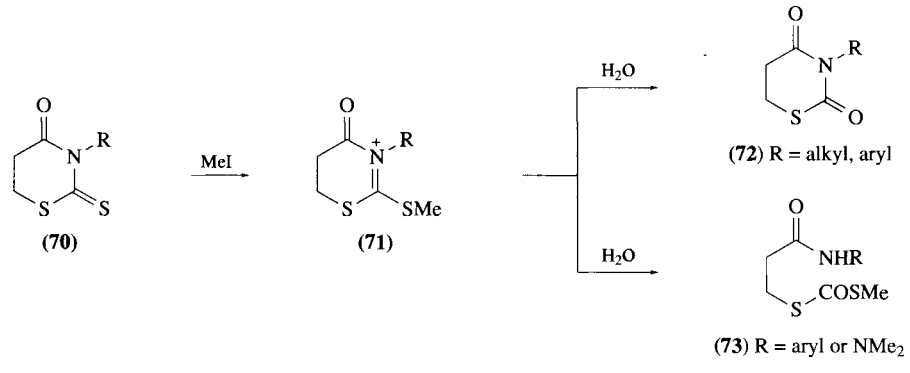
Either *N*- (**65**) or *S*-amino (**66**) products are formed if the 2-thioxothiazin-4-ones (**67**) are reacted with *O*-(diphenylphosphoryl)hydroxylamine in contact with thallium(I) hydroxide, or sodium hydride, respectively (Scheme 7) ⟨87AP(320)67⟩.



Scheme 7

When 5-cyano-4-methyl-1,3-thiazine-2,6-dithiones (**68**) react with methyl iodide, selective *S*-methylation of the 6-thiocarbonyl function occurs with concomitant loss of a proton from the methyl group at C-4 and the formation of the exocyclic methylene derivative (**69**) (Equation (10)) ⟨85BCS(J)771⟩. *S*-Methylation also occurs when *N*-substituted 5,6-dihydro-2-thioxo-1,3-thiazin-4-ones (**70**) are reacted with methyl iodide. Here the products are unstable iminium salts (**71**), which cannot be isolated and are hydrolyzed to the corresponding diones (**72**), and/or the acyclic dithiocarbonates (**73**) (Scheme 8) ⟨85MI 607-01⟩.

(10)

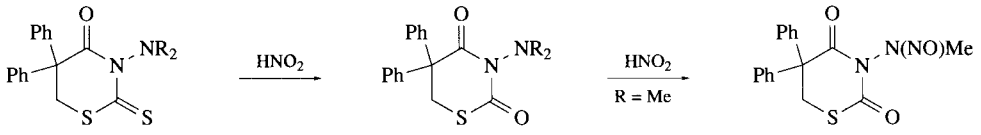


Scheme 8

Acid chlorides react at the nitrogen atom of 5,6-dihydro-2-thioxo-1,3-thiazin-4(3*H*)-ones (see Section 6.07.4.2), and the same regioselectivity is obtained if these substrates are reacted with trichloromethylsulfenyl chloride in the presence of either sodium hydride or triethylamine, but in the absence of bases attack is directed to the sulfur atom and the products are 5,6-dihydro-2-dithio-1,3-thiazin-4-ones (**74**) (Equation (11)) ⟨87AP(320)74⟩.

(74) (11)

Treatment of 3-amino-5,6-dihydro-2-thioxo-1,3-thiazin-4(3*H*)-ones (**75**) with nitrous acid results in oxidative desulfurization and the formation of the corresponding diones (**76**). However, if the *N*-amino substituent bears two methyl groups the reaction can proceed further and monodemethylation and *N*-nitrosation may take place, leading to the nitrosamine (**77**) (Scheme 9) ⟨86AP521⟩.



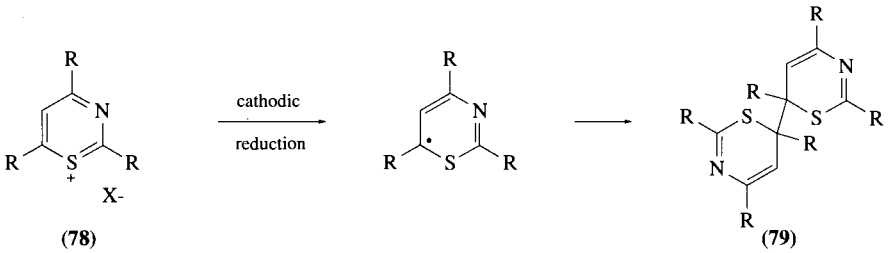
(75) (76) (77)

Scheme 9

6.07.6 REDUCTION AND REACTIONS WITH NUCLEOPHILES

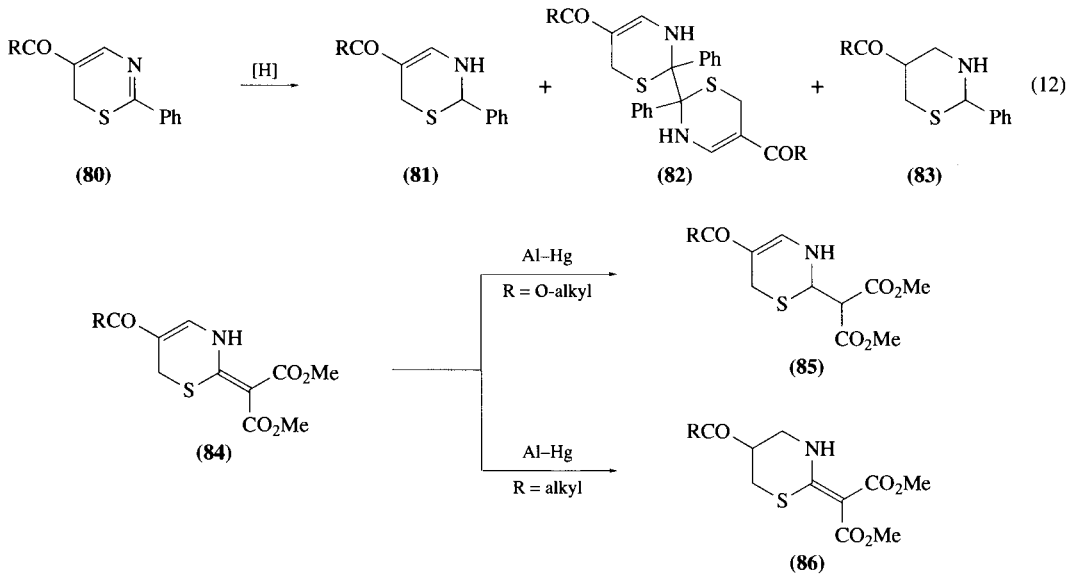
6.07.6.1 Reduction

1,3-Thiazinium salts (**78**) undergo reductive dimerization on cathodic reduction to afford 6,6′-bithiazinyls (**79**) (Scheme 10) ⟨81JPC33⟩. However, 5-acyl-2-phenyl-6*H*-1,3-thiazines (**80**) undergo electrochemical reduction under controlled conditions and at 2 °C to yield 3,6-dihydro-2*H*-1,3-thiazines (**81**) and dihydrodimers (**82**) coupled through C-2. Further reduction leads to tetrahydro-1,3-thiazines (**83**), but in none of the products is the acyl group reduced (Equation (12)). These results parallel those obtained by chemical reduction with sodium cyanoborohydride at pH 6, but when there are no substituents at either C-5 or C-6, electrochemical reduction may cause ring opening ⟨85TL745, 86MI 607-02, 87T2709⟩. 5-Acyl-6*H*-1,3-thiazines are also reduced to 3,6-dihydro-2*H*-1,3-thiazines by aluminum amalgam in ethanol, diborane, sodium cyanoborohydride, or triethylsilane in acidic media ⟨82JCR(S)72, 85TL745⟩, but in the cases of 5-alkoxycarbonyl-2-alkylidene-6*H*-1,3-thiazines (**84**), where there are two enaminone systems, the exocyclic double bond is selectively reduced by such reagents, and the products are 3,6-dihydro-2*H*-1,3-thiazines (**85**). Zinc in hydrochloric acid ⟨83PS143⟩ and aluminum amalgam in ethanol ⟨82JCR(S)72, 82TL2315, 83CJC1169⟩ behave similarly, but with the last reagent the selectivity is altered if the ester group at C-5 is replaced by an acyl group—the exocyclic double bond is retained, the ring is saturated, and 2-alkylideneperhydro-1,3-thiazines (**86**) are formed (Scheme 11) ⟨84CC157⟩.



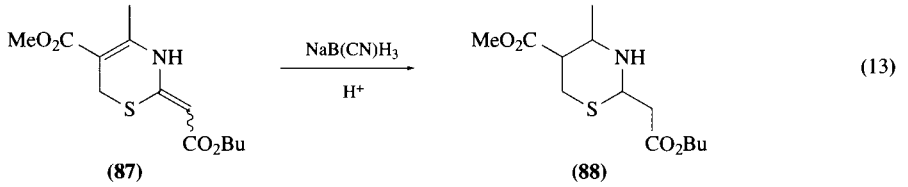
(78) (79)

Scheme 10

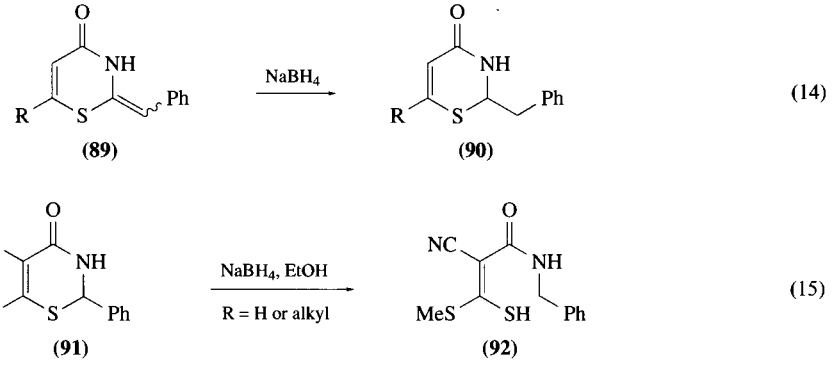


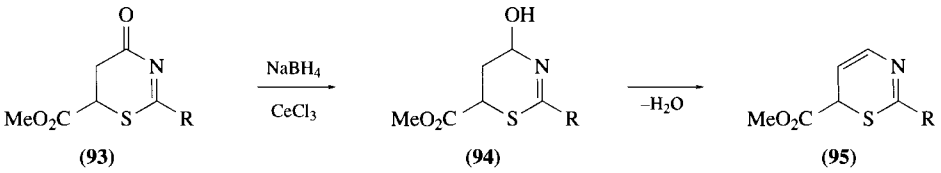
Scheme 11

Sodium cyanohydride may reduce both double bonds, and the alkylidene derivative (**87**), for example, is converted into the fully reduced 1,3-thiazine (**88**) by this reagent (Equation (13)). The presence of the 4-alkyl group seems to be important since when this is absent the reduction only proceeds as far as the 2*H*-3,6-dihydro derivative ⟨83CJC1169, 83PS143⟩.



Sodium borohydride reduces aldehyde and keto functions at C-5 to the corresponding alcohols, leaving the heterocyclic double bonds intact ⟨82JCR(S)72, 83PS143⟩, but if there is no electron-withdrawing group at C-5 then the products are perhydro-1,3-thiazines ⟨90AHC(50)85⟩. 2-Benzylidene-1,3-thiazin-4-ones (**89**) are easily reduced by sodium borohydride to 2-benzyl-2,3-dihydro-1,3-thiazin-4-ones (**90**) (Equation (14)) ⟨83CPB1929⟩. Both 1,3-thiazin-4-ones and 1,3-thiazin-6-ones are reduced by sodium borohydride, or lithium aluminum hydride, to their 2,3-dihydro derivatives ⟨82JOC1090, 83CPB1929⟩. Further reaction may cause ring scission as illustrated by the reduction of the 5-cyano-6-methylthio-1,3-thiazine-4-one (**91**), which on treatment with sodium borohydride gives the hemidithioacetal (**92**) (Equation (15)) ⟨75JCS(P1)1417⟩. None of the reagents so far described reduce ring carbonyl groups at C-2, C-4, or C-6, but when cerium(III) chloride is present, sodium borohydride can be used to reduce 1,3-thiazin-4-ones (**93**) to the corresponding hydroxy compounds (**94**). These products are readily dehydrated to afford 6*H*-1-3,-thiazines (**95**) (Scheme 12) ⟨90TL4019⟩.

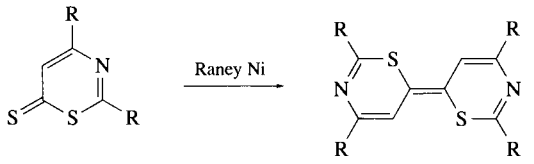




(93) (94) (95)

Scheme 12

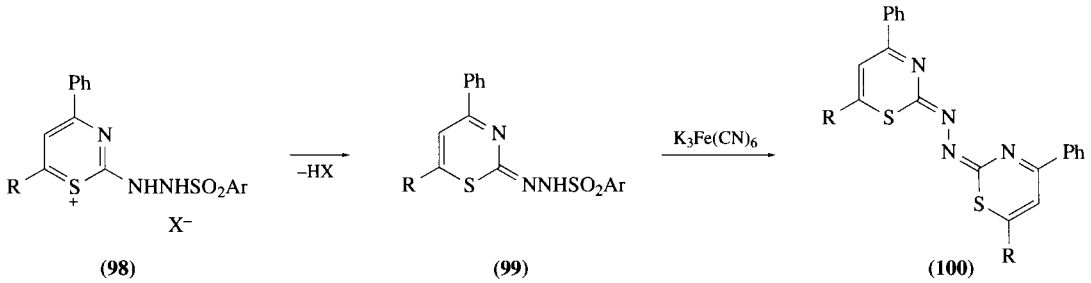
Dimers (**96**) are formed by the treatment of 2,4-disubstituted 1,3-thiazine-6-thiones (**97**) with Raney nickel in benzene (Equation (16)). Presumably radical anions, or their equivalents, are formed first, and these then couple and eliminate sulfur. The thermodynamically favored (*E*) isomers are eventually obtained, but there is evidence to show that after shorter reaction times both (*E*) and (*Z*) forms are present in the reaction mixture ⟨84SUL127⟩.



(97) (96) (16)

6.07.6.2 Reactions with Bases and Nucleophiles

When treated with bases, 2-hydrazinyl-1,3-thiazinium cations (**98**) are readily deprotonated to give a mixture of (*E*)- and (*Z*)-2-hydrazonoyl-1,3-thiazines (**99**), oxidation of which with potassium ferricyanide yields the azines (**100**) (Scheme 13) ⟨87ZC25⟩.



(98) (99) (100)

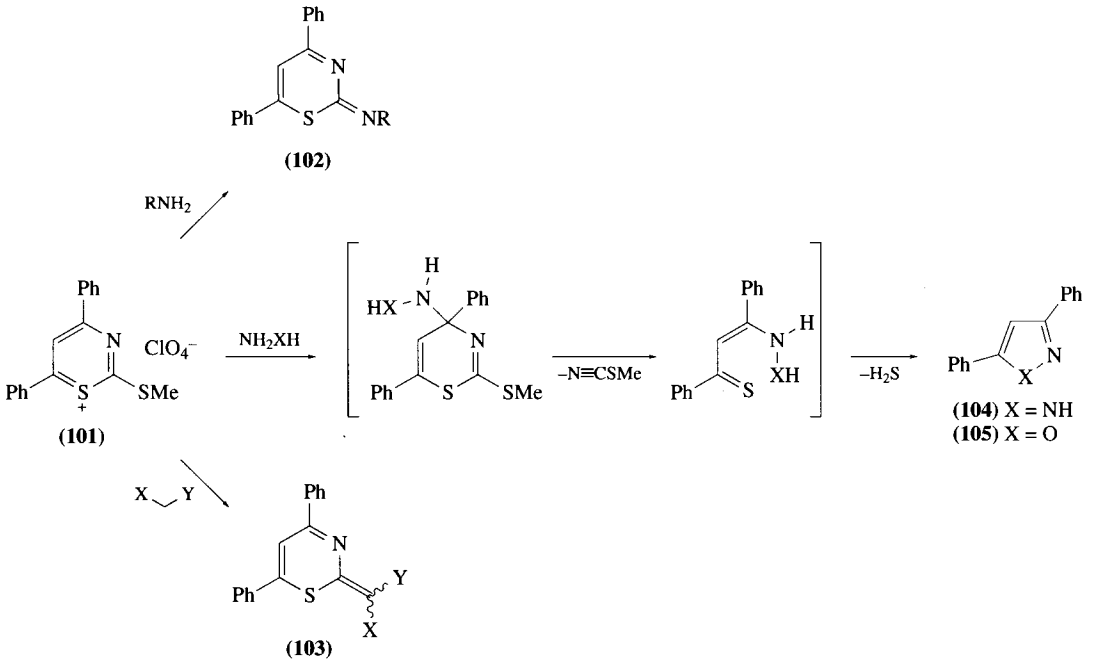
Scheme 13

2-Methylthio-4,6-diphenyl-1,3-thiazinium perchlorate (**101**) reacts with primary amines and active methylene compounds at C-2 to give the 2-imino (**102**) and the methylene derivatives (**103**), respectively. However, hydrazine and hydroxylamine give 3,5-phenylpyrazole (**104**) and 3,5-diphenylisoxazole (**105**), respectively, and it is possible that here the reactions proceed through initial nucleophilic attack at C-4 as indicated in Scheme 14 ⟨87NKK780⟩.

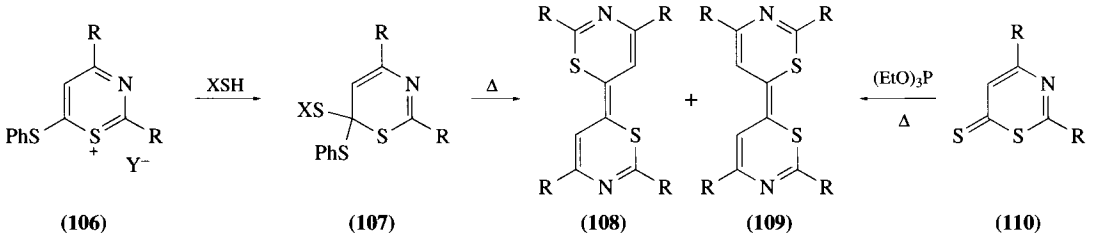
6-Thio-1,3-thiazinium salts (**106**) when reacted with thiols afford dithioacetals (**107**), which on thermolysis yield 6,6′-bi(1,3-thiazinylidenes) ((**108**) and (**109**)). The same final products are formed directly from the thiazinium salts if triethylamine is added in the first step, or if the thiones (**110**) are heated with triethyl phosphite in toluene (Scheme 15) ⟨86S916⟩.

Hydrogen sulfide reacts with 5-acyl-2-thio-6*H*-1,3-thiazines (**111**) to give thiones (**112**), and it is probable that these reactions proceed through initial attack at C-2. The appropriate thiol is then displaced from the initially formed adducts as shown in Scheme 16 ⟨83TL3713, 90AHC(50)85⟩. Amines react similarly, and with dimethylamine, for example, 5-acetyl-2-(*N*,*N*-dimethylamino)-6*H*-1,3-thiazine (**113**) is obtained (Scheme 17). However, this compound reacts with a second equivalent of the amine to give the acyclic thiourea (**114**): alternatively, the thiol generated in the first reaction may recombine with the thiazine (**113**) to afford sulfides (**115**) (Scheme 17) ⟨83TL3713⟩.

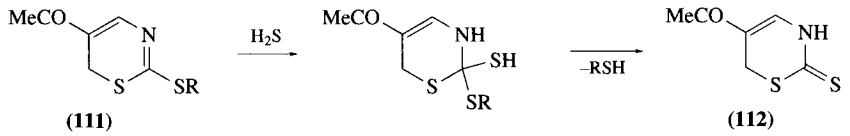
The hydrogen sulfite anion may also act as a nucleophile and react with 5-acetoxy-6*H*-1,3-thiazines (e.g., (**116**)) to yield intermediate sulfites (**117**), which on treatment with water ring open to give the acyclic thiols (**118**) (Scheme 18). The cyanide ion may also attack at C-2, and in the case



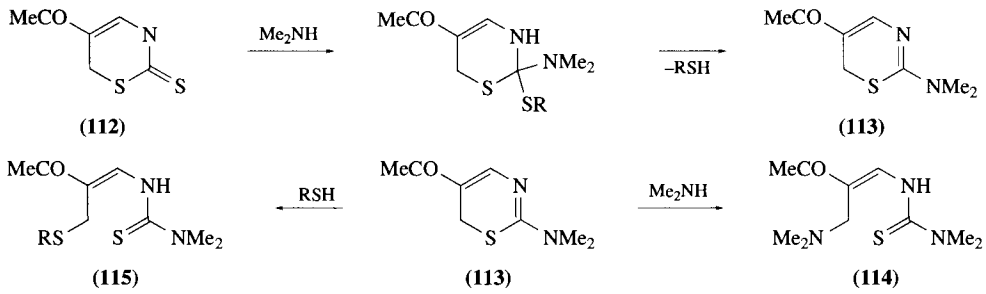
Scheme 14



Scheme 15

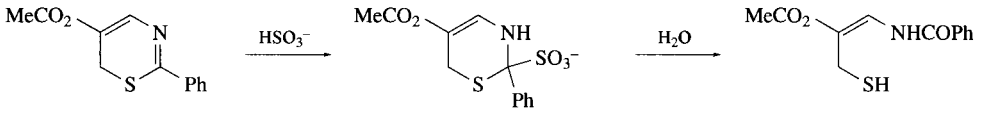


Scheme 16



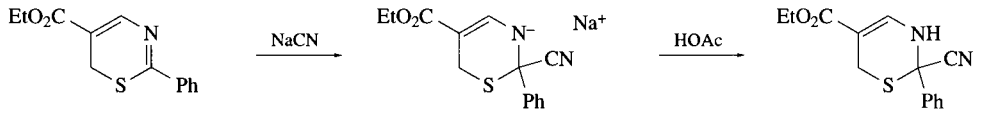
Scheme 17

of the 5-ethoxycarbonyl-2-phenyl-6*H*-1,3-thiazine (**119**) this gives (**120**) as an isolable compound, after protonation with acetic acid (Scheme 19) ⟨87SUL117⟩. Hydrolysis also causes ring opening in a variety of related substrates, but the regiochemistry of the initial nucleophilic attack depends upon the nature of the substituents ⟨87T2709⟩. However, ring scission does not always occur, and, for example, 5-methyl-2-benzylthio-6*H*-1,3-thiazine (**121**) (R = H) is hydrated in moist air to form the adduct (**122**), which then eliminates benzylthiol to afford the 3,6-dihydro-1,3-thiazin-2-one (**123**) (Scheme 20) ⟨87SUL117⟩.



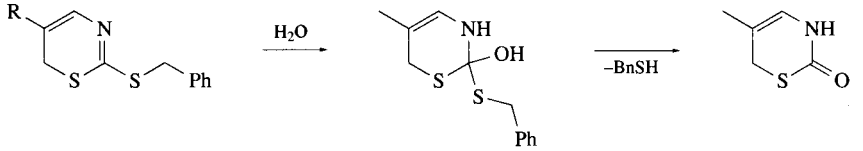
(**116**) (**117**) (**118**)

Scheme 18



(**119**) (**120**)

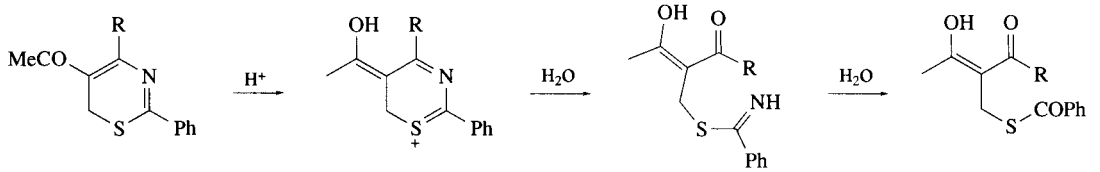
Scheme 19



(**121**) (**122**) (**123**)

Scheme 20

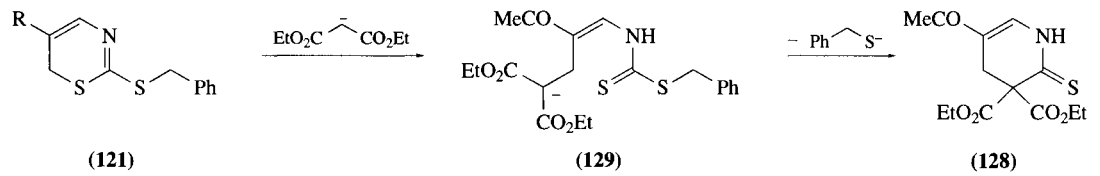
In acidic media, ester groups appended to the heterocycle are hydrolyzed without ring cleavage, but in the case of the 5-acetyl compound (**124**) the exocyclic carbonyl group is protonated and the intermediate cation (**125**), or its equivalent, is hydrated. Ring opening then takes place, generating first the imidate (**126**) and then the thiobenzoate (**127**) (Scheme 21) ⟨87T2709⟩.



(**124**) (**125**) (**126**) (**127**)

Scheme 21

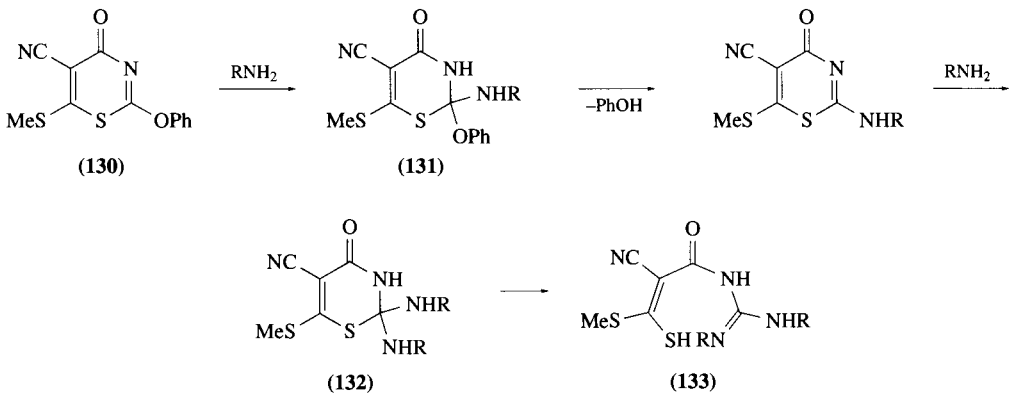
"Soft carbanions" react with 6*H*-1,3-thiazines at C-6, and this also brings about ring opening provided there is a potential leaving group at C-2. Recyclization of the acyclic product may now occur as happens in the case of the thiazine (**121**) (R = MeCO), which reacts with the anion of diethyl malonate to give the pyridinethione (**128**) via the acyclic dithiocarbamate (**129**), or its equivalent (Scheme 22) ⟨83TL3713⟩.



(**121**) (**129**) (**128**)

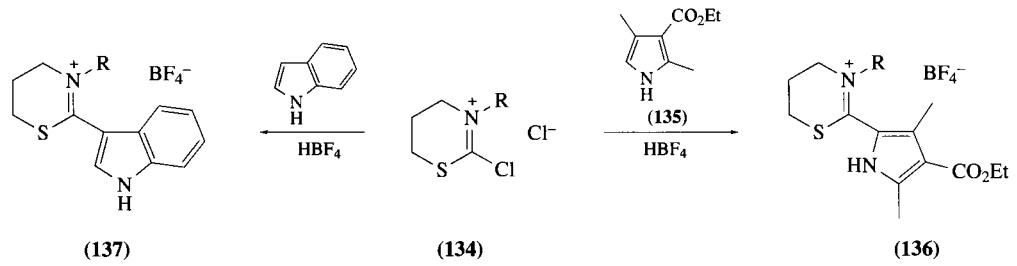
Scheme 22

The 2-phenoxy-1,3-thiazin-4-one (**130**) reacts with primary amines at C-2, but the adducts (**131**) so formed eliminate phenol, prior to the incorporation of another molar equivalent of the amine. The products (**132**) are also unstable, and ring open to give guanidines (**133**) (Scheme 23) ⟨85ZC430⟩.



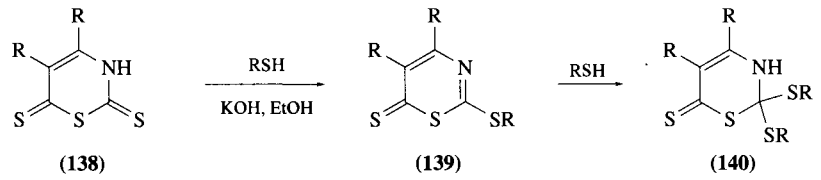
Scheme 23

2-Chloro-5,6-dihydro-4*H*-1,3-thiazinium salts (**134**) are strongly electrophilic and react with enamines and other nucleophiles by displacement of the chlorine atom as the chloride ion and the formation of 2-substituted derivatives. With the pyrrole (**135**) and indole this leads to the 2-(pyrrol-2-yl)-, or 2-(indol-3-yl)-5,6-dihydro-4*H*-1,3-thiazinium salts (**136**) and (**137**), respectively (Scheme 24) ⟨90AP869⟩.



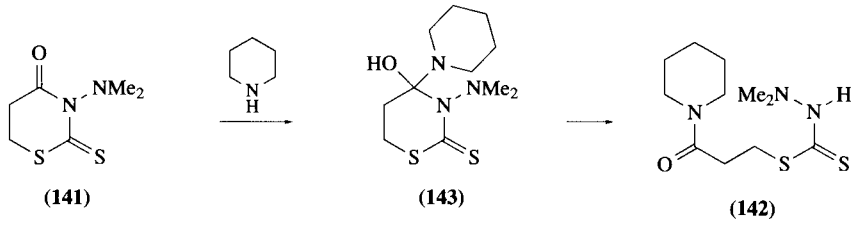
Scheme 24

The reactions of 1,3-thiazine-2,6(3*H*)-dithiones (**138**) have been well studied (e.g., ⟨84JHC953⟩). They combine with thiols in the presence of potassium hydroxide at 60°C to give the 2-thio-1,3-thiazine-6-thiones (**139**) and then, if there is an excess of the thiol, 2,2-dithio-2,3-dihydro-1,3-thiazine-6-thiones (**140**) (Scheme 25).



Scheme 25

3-(*N*,*N*-Dimethylamino)perhydro-2-thioxo-1,3-thiazin-4-one (**141**) reacts preferentially with many nucleophiles at the carbonyl group: thus with piperidine, for example, it affords the *N*-(*N*,*N*-dimethylamino)dithiocarbamate (**142**), probably via the intermediate pseudobase (**143**) (Scheme 26) ⟨85AP1080⟩.

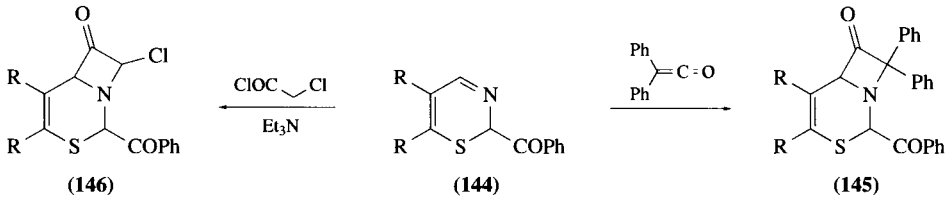


(141) (143) (142)

Scheme 26

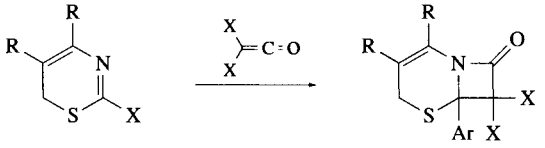
6.07.7 ADDITION REACTIONS

2-Benzoyl-2*H*-1,3-thiazines (**144**) and diphenylketene enter into [2 + 2] cycloaddition reactions via the imine bond, thereby providing access to thiazolo-β-lactams (**145**) ⟨85CS239⟩. Chloroketenes (from chloroacetyl chlorides and a tertiary amine) react in a similar manner and give chloro derivatives (**146**) (Scheme 27) ⟨85BSB149⟩. With 6*H*-1,3-thiazines (**147**) the products are the corresponding β-lactams (**148**) (Equation (17)) ⟨86CJC597⟩.



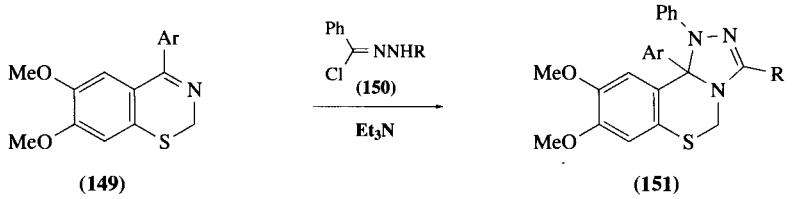
(146) (144) (145)

Scheme 27

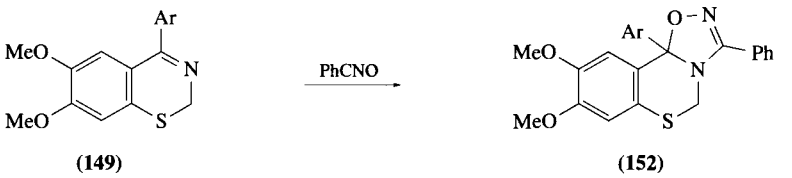


(147) (148) (17)

Dimethoxy-2*H*-1,3-benzothiazines (**149**) undergo addition reactions with nitrilimines generated through the treatment of hydrazonyl chlorides (e.g., (**150**)) with triethylamine. The [3 + 2] cycloadditions are regioselective and yield triazolobenzothiazines (**151**) (Equation (18)) ⟨92T4957⟩. Benzonitrile oxide adds to (**149**) in a similar way and gives the 1,2,4-oxadiazolobenzothiazines (**152**) (Equation (19)), but the isomeric 4*H*-1,3-benzothiazines do not react ⟨91JHC481⟩.

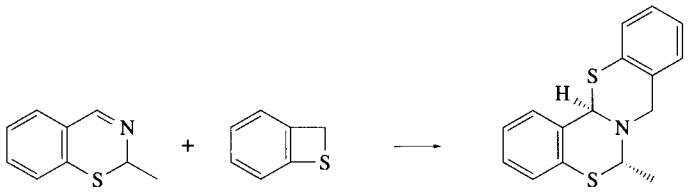


(149) (151) (18)



(149) (152) (19)

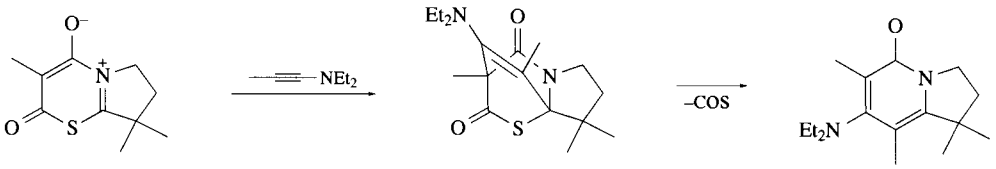
2*H*-1,3-Benzothiazines (**153**) and 4*H*-1,3-benzothiazines (**154**) also undergo cycloadditions with benzothiete (**155**), affording adducts of the type (**156**) and (**157**), respectively (Equations (20) and (21)).



(153) (155) (156) (20)

(154) (155) (157) (21)

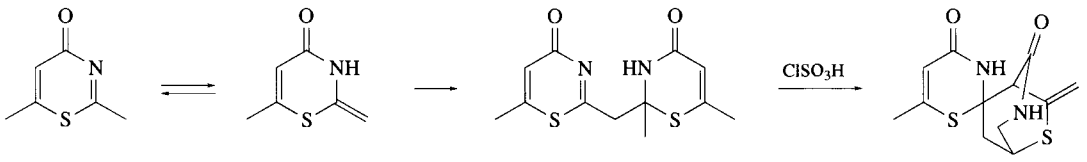
Mesomeric betaines (e.g., (**158**)) undergo 1,4-dipolar cycloadditions with various electron-rich dienophiles: thus, with 1-*N*,*N*-diethylaminopropyne, for example, the adduct (**159**) is obtained. When heated this expels carbonyl sulfide to generate α-pyridone (**160**) (Scheme 28) ⟨93TL5408⟩.



(158) (159) (160)

Scheme 28

2-Alkyl-1,3-thiazin-4-ones (**161**) undergo self-addition when allowed to stand at room temperature. This process can be considered to involve the tautomerism of the alkylthiazinone into its alkylidene isomer (**162**), which acts as an enamine and adds to the enone system of another molecule of the alkylthiazinone. The adducts (**163**) can be converted into the very unusual spiro derivatives (**164**) when they are treated with chlorosulfonic acid (Scheme 29) ⟨83CPB1936⟩.

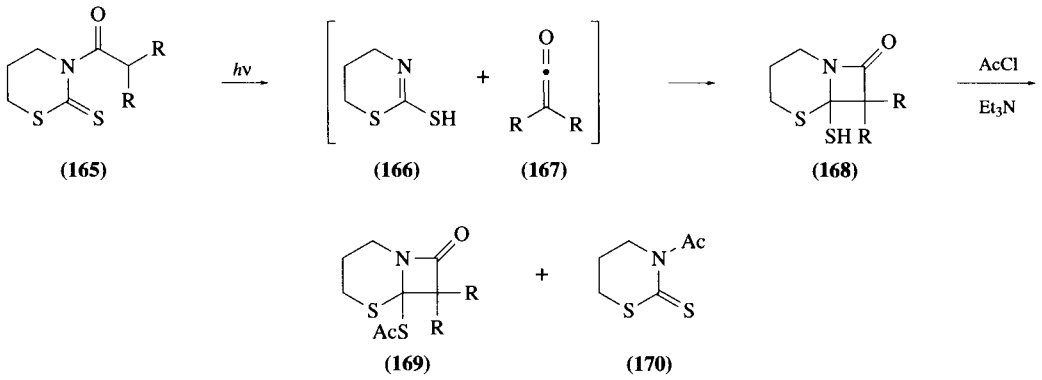


(161) (162) (163) (164)

Scheme 29

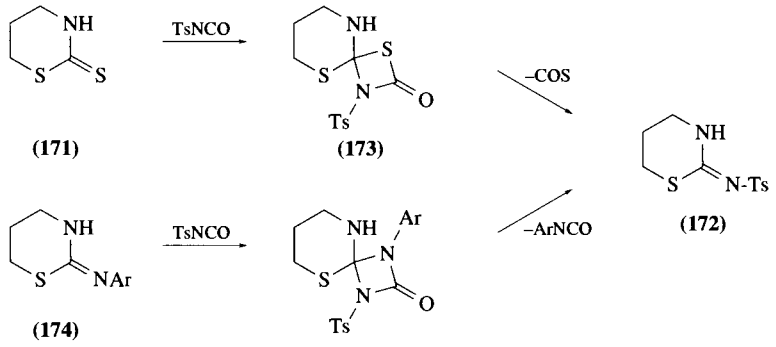
Photolysis of 3-acyltetrahydro-1,3-thiazine-2-thiones (**165**) initially gives 5,6-dihydro-4*H*-1,3-thiazine-2-thiol (**166**) and ketenes (**167**), but these products immediately recombine to form cephem thiols (**168**) as the major products (Scheme 30). Although the cephem thiols are unstable, they may be isolated as their *S*-acetyl derivatives (**169**) if acetyl chloride and triethylamine are added to the reaction mixture, prior to irradiation with light. The *N*-acetylperhydrothione (**170**) is also formed as a by-product, and this provides evidence for the suggested pathway since it probably arises through acylation of the intermediate thiol (**166**) (Scheme 30) ⟨86TL1335⟩.

When 3,4,5,6-tetrahydro-1,3-thiazine-2-thione (**171**) is treated with 4-toluenesulfonyl isocyanate 2-(4-toluenesulfonyl)imino-1,3-thiazine (**172**) is obtained, probably through the formation of the intermediate adduct (**173**), which loses carbonyl sulfide (Scheme 31). A similar reaction occurs with 2-(arylimino)perhydro-1,3-thiazine (**174**) and the same product is obtained (Scheme 31) ⟨89H(29)895⟩.



(165) (166) (167) (168) (169) (170)

Scheme 30



(171) (173) (172) (174)

Scheme 31

6.07.8 SYNTHESIS

Syntheses of 1,3-thiazines and their derivatives have been classified according to the composition of the assembling units. The most common types are:

[3 + 3] C—C—C + N—C—S
[4 + 2] C—C—C—N + C—S, S—C—C—C + N—C, C—C + C—N—C—S
[5 + 1] C—C—C—N—C + S, S—C—C—C—N + C, C—C—N—C—S + C, C—C—C—S—C + N
[6 + 0] N—C—S—C—C—C, C—S—C—C—C—N, C—C—C—N—C—S

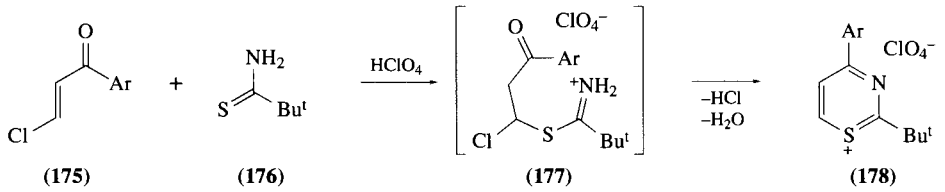
This classification will be used here and, where there are appropriate examples within each subdivision, the order of discussion will be thiazinium salts, thiazines, thiazinones and thiones, dihydrothiazines, dihydrothiazinones and thiones, perhydrothiazines and perhydrothiazinones, and thiones. 1,3-Benzothiazines and 3,1-benzothiazines are not treated separately, but are included within this general classification and listed with the appropriate thiazines according to the oxidation state of the heterocyclic ring.

6.07.8.1 [3 + 3]-type Syntheses

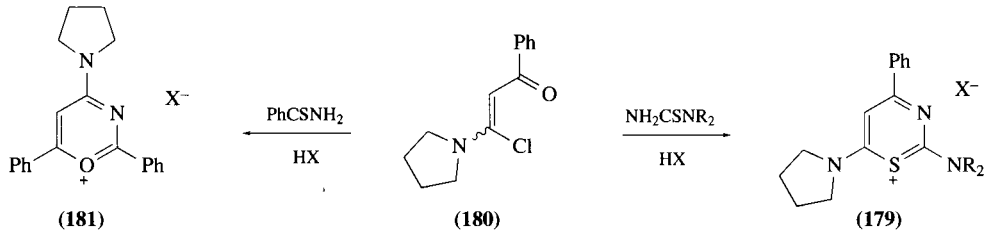
6.07.8.1.1 1,3-Thiazinium salts and 1,3-thiazin-6-ones

β-Chlorovinyl ketones (**175**) and the thioamide (**176**) in the presence of perchloric acid give rise to intermediate *S*-ketovinylthioimidium salts (**177**), which then cyclize to yield 1,3-thiazinium salts (**178**) (Scheme 32) ⟨82T937⟩.

2,6-Diamino-1,3-thiazinium salts (**179**) are obtained in a similar way from 2-acyl-1-chloroenamines (**180**) and thioureas in the presence of either perchloric or tetrafluoroboric acid (X = ClO_4 or BF_4), but if the enamines (**180**) are reacted with thiobenzamide the products are 4-amino-1,3-oxazinium salts (**181**) (Scheme 33) ⟨87M1383⟩.

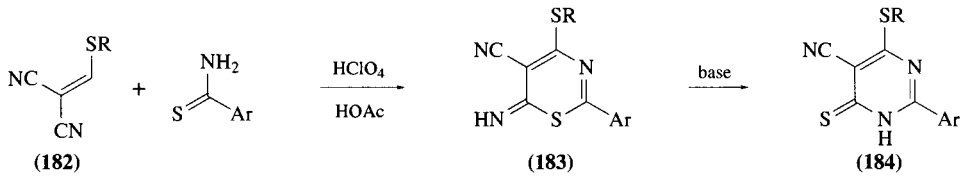


Scheme 32



Scheme 33

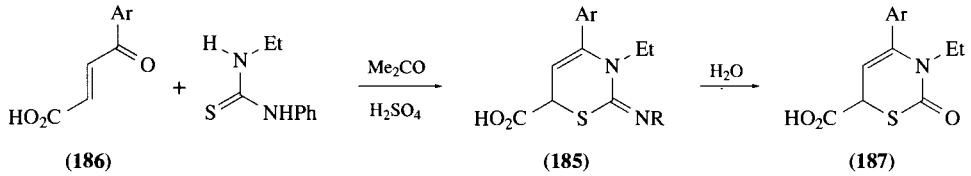
The cyclocondensation of alkylidenemalononitriles (**182**) and thiobenzamides in acetic acid solution containing perchloric acid affords 6-imino-1,3-thiazines (**183**). Dimroth rearrangement of these products in the presence of a base yields pyrimidine-4(3*H*)-thiones (**184**) (Scheme 34) ⟨88PS55⟩.



Scheme 34

6.07.8.1.2 *Dihydro-1,3-thiazines, dihydro-1,3-thiazinones, 2H-1,3-benzothiazines, 4H-1,3-benzothiazines, and related compounds*

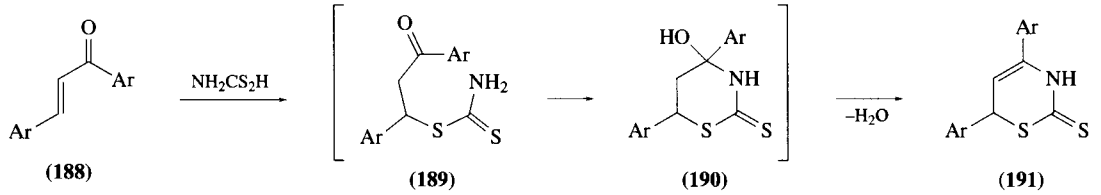
It is also common to use thioureas as one three-atom component and enones as the other in syntheses of this type, which provide a variety of dihydro-1,3-thiazine derivatives. For example, 6-carboxy-3,6-dihydro-2-imino-1,3-thiazines (**185**) are formed by the condensation of 4-aryl-4-oxobut-2-enoic acids (**186**) with thioureas in acetone solution containing some sulfuric acid; on hydrolysis these products form the corresponding thiazin-2-ones (**187**) (Scheme 35) ⟨85MI 607-01⟩.



Scheme 35

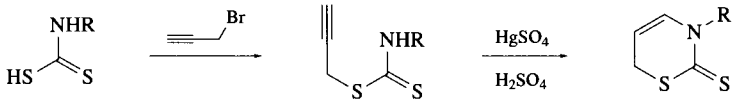
Dithiocarbamic acid undergoes acid-catalyzed β-addition to chalcones (**188**) to give adducts (**189**) and their cyclic tautomers (**190**). Dehydration of the latter yields 4,6-diaryl-3,6-dihydro-1,3-thiazine-2-thiones (**191**) (Scheme 36) ⟨86ACH119⟩. Dithiocarbamic acids (generated *in situ* from the reactions of primary amines, carbon disulfide, and sodium hydroxide) combine with propargyl bromide to give dithiocarbamates (**192**). These are said to cyclize to the thiones (**193**) when treated with mercury(II) sulfate and sulfuric acid (Scheme 37), despite the fact that this reaction is formally of the 6-*endo dig* type and would have been expected to give 5-methylenethiazolidine-2-thiones. The

products show a C=C band at 1640 cm^{-1} in the IR spectrum, but no NMR data are available ⟨84AP297⟩.



(188) (189) (190) (191)

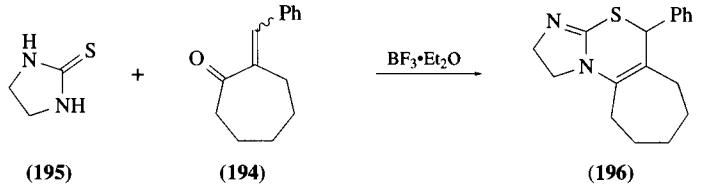
Scheme 36



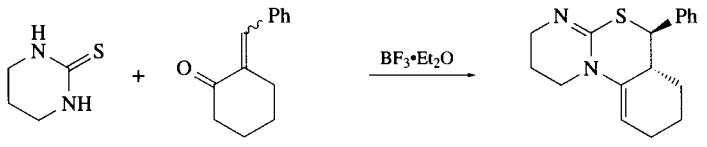
(192) (193)

Scheme 37

The boron trifluoride-promoted condensation of cyclic thioureas with enones gives tricyclic 1,3-thiazines. Thus, in the reaction between 2-benzylidenecycloheptanone (**194**) and imidazolidine-2-thione (**195**) the product is the octahydrocyclohept[*d*]imidazo[2,1-*b*][1,3]thiazine (**196**) (Equation (22)), whereas 2-benzylidenecyclohexanone (**197**) and the perhydropyrimidinethione (**198**) yield the adduct (**199**), in which both double bonds are exocyclic to the thiazine ring (Equation (23)) ⟨87CB1449⟩.

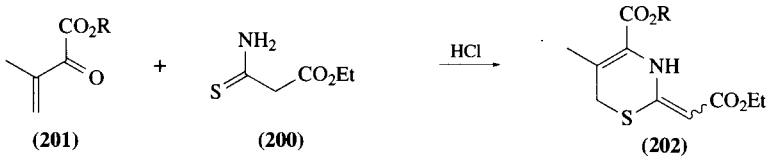


(195) (194) (196) (22)

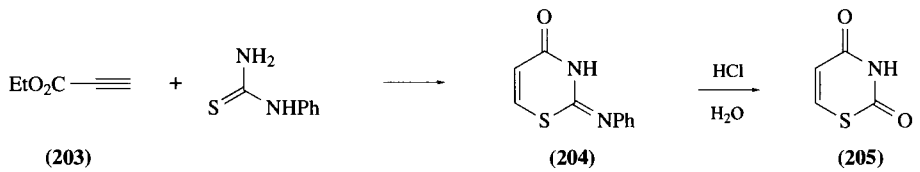


(198) (197) (199) (23)

Michael additions between the thioamido ester (**200**) and alkyl-3-methyl-2-oxobut-3-enoates (**201**) in the presence of an acid gives the thiazines (**202**) (Equation (24)) ⟨88SC1043⟩, and in yet another variation on this theme ethyl propiolate (**203**) and *N*-phenylthiourea can be cyclocondensed to yield 2-phenylimino-1,3-thiazin-4(3*H*)-one (**204**) (Scheme 38). Hydrolysis of the imine with 3% aqueous hydrochloric acid affords the dione (**205**) ⟨84KGS997⟩.



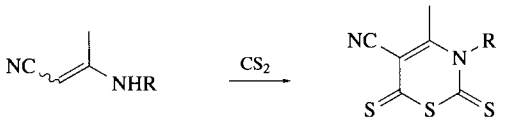
(201) (200) (202) (24)



(203) (204) (205)

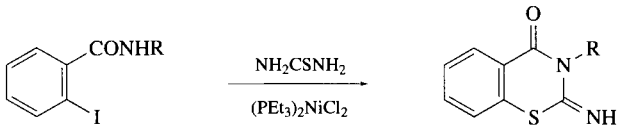
Scheme 38

Alkylenaminonitriles (**206**) add carbon disulfide in dimethylformamide solution to form 3-alkyl-5-cyano-4-methyl-1,3-thiazine-2,6(3*H*)-dithiones (**207**) (Equation (25)) ⟨85BCS(J)771⟩.

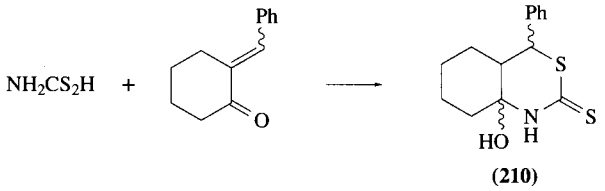


(206) (207) (25)

A novel construction of 2-imino-1,3-benzothiazin-4(3*H*)-ones (**208**) utilizes the cyclocondensation of thioureas and 2-iodobenzamides (**209**) in the presence of a nickel catalyst (Equation (26)) ⟨90CL2205⟩, and dithiocarbamic acid reacts with 2-benzylidenecyclohexanone to form stereoisomeric perhydro-3,1-benzothiazine-2-thiones (**210**) (Equation (27)) ⟨87TL571⟩.



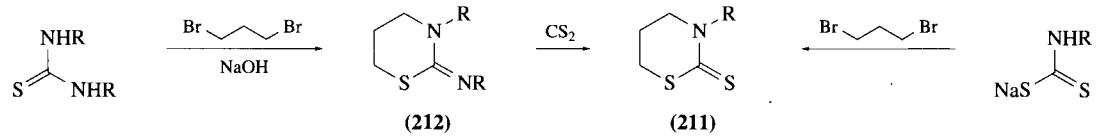
(209) (208) (26)



(210) (27)

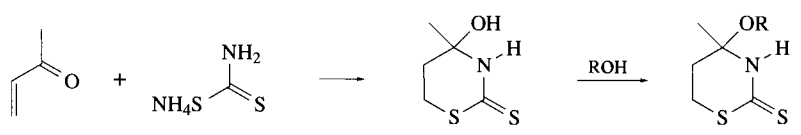
6.07.8.1.3 Perhydro-1,3-thiazinones, thiones, diones, and related compounds

Perhydro-1,3-thiazine-2-thiones (**211**) can be synthesized from thioureas and 1,3-dibromopropanes in the presence of sodium hydroxide, followed by the treatment of the product imines (**212**) with carbon disulfide (Scheme 39). Alternatively, they can be obtained directly from sodium dithiocarbamates and 1,3-dibromopropanes (Scheme 39) ⟨77AP409, 81AP413⟩. Another approach, which affords the 4-hydroxy analogues (**213**), requires the reactions of ammonium dithiocarbamate and enones (**214**). In the presence of alkanols the products are converted into the corresponding alkyl ethers (**215**) (Scheme 40) ⟨91ZOR1274⟩. On the other hand, the isomeric 2-imino derivatives (**216**) and (**217**) are obtained by the cycloadditions of propenoyl chloride and thioureas (Equation (28)) ⟨77AP273, 77MI 607-01⟩.



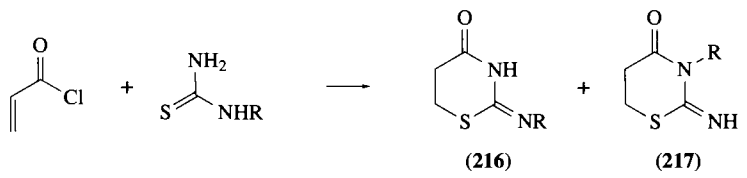
(212) (211)

Scheme 39



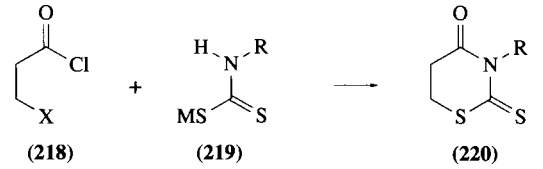
(214) (213) (215)

Scheme 40

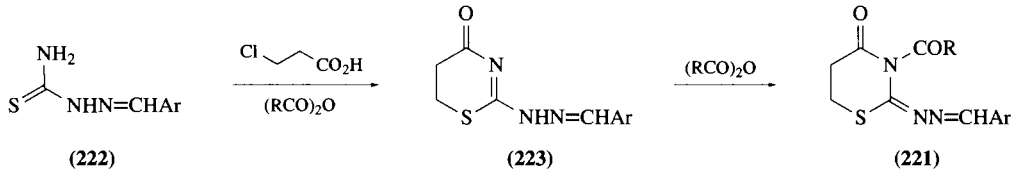


(216) (217) (28)

Reactions between 3-halogenopropanoyl chlorides (**218**) (X = Cl or Br) and sodium, or ammonium, dithiocarbamates (**219**) produce perhydro-3-alkyl-2-thioxo-1,3-thiazin-4-ones (**220**) (Equation (29)) ⟨85MI 607-01⟩. A similar procedure, leading to 3-acyl-2-hydrazono-5,6-dihydro-1,3-thiazin-4(3*H*)-ones (**221**) (R = Et), requires the treatment of hydrazones (**222**) with 3-chloropropanoic acid in the presence of propanoic anhydride containing sodium acetate (Scheme 41). If propanoic anhydride is replaced by succinic anhydride then the acid (**221**) (R = $CH_2CH_2CO_2H$) is the product, so it is likely that *N*-acylation occurs after the heterocycles (**223**) are formed (Scheme 41) ⟨85MI 607-02⟩.



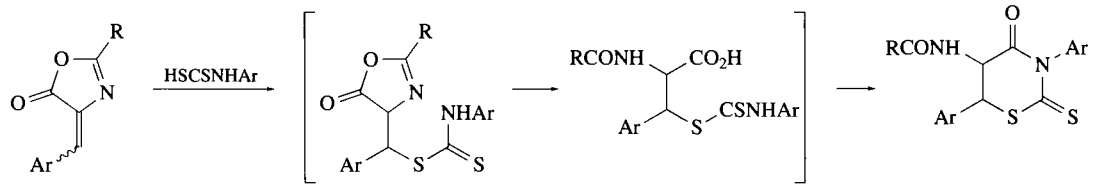
(218) (219) (220) (29)



(222) (223) (221)

Scheme 41

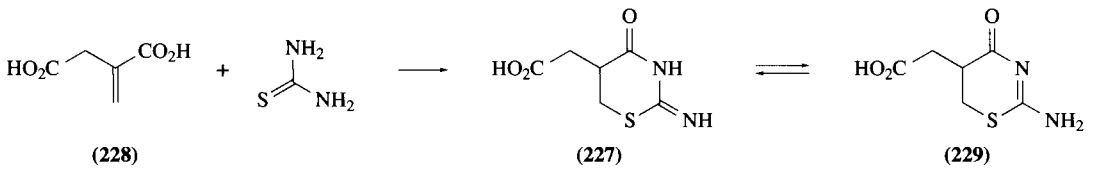
N-Aryldithiocarbamic acids enter into Michael-type additions with 4-arylidene-5-oxazolinones (**224**) to give adducts (**225**) which then ring open and rearrange to form 5-amido-5,6-dihydro-2-thioxo-1,3-thiazin-4(3*H*)-ones (**226**) (Scheme 42) ⟨92S919⟩.



(224) (225) (226)

Scheme 42

Aqueous acidic conditions favor the formation of the iminothiazinone (**227**) from the reaction of itaconic acid (**228**) and thiourea. However, if the reaction is carried out in water alone the product is the amino tautomer (**229**) (Scheme 43) ⟨91IJC(B)886⟩.



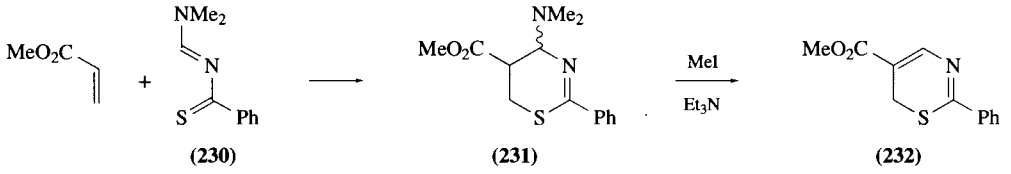
(228) (227) (229)

Scheme 43

6.07.8.2 [4 + 2]-type Syntheses

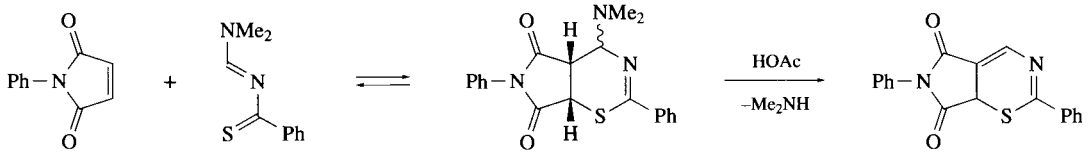
6.07.8.2.1 6H-1,3-Thiazines and 1,3-benzothiazines

The cycloaddition of methyl acrylate with *N'*-thiobenzoyl-*N,N*-dimethylformamidine (**230**) under pressure affords the 4-(*N,N*-dimethylamino)-5,6-dihydro-4*H*-1,3-thiazine (**231**). When this compound is treated with methyl iodide and triethylamine an elimination reaction ensues to give 6*H*-1,3-thiazine (**232**) (Scheme 44). This product is also obtained directly through the cycloaddition of methyl acrylate and the methiodide salt of the formamidine ⟨85JOC1545, 87SC1971⟩. The same methodology has been used to synthesize a range of other 6*H*-1,3-thiazines simply by varying the formamidines employed ⟨85SL139, 88SL205⟩, or by employing other electron-deficient cyclic dienophiles. For example, *N'*-thiobenzoyl-*N,N*-dimethylformamidine (**230**) combines with *N*-phenylmaleimide (**233**) in acetic acid to generate a mixture of the *exo* and *endo* adducts (**234**), which eliminate dimethylamine to afford the thiazine (**235**) (Scheme 45). Similarly cycloaddition with the allene (**236**) yields the diester (**237**) via the adducts (**238**), whereas cyclohexenone eventually gives the bicyclic derivative (**239**) (Scheme 45) ⟨93CPB50⟩.

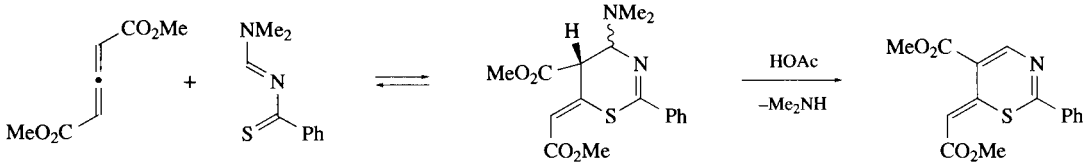


(230) (231) (232)

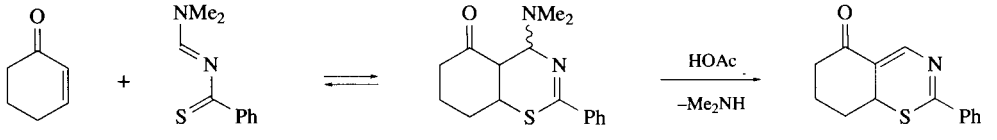
Scheme 44



(233) (230) (234) (235)



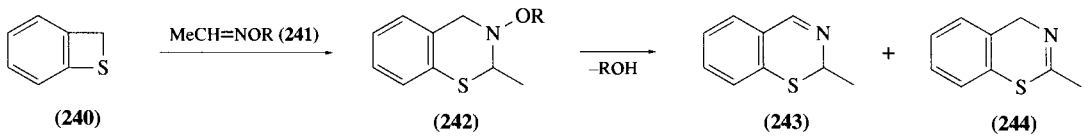
(236) (230) (238) (237)



(230) (239)

Scheme 45

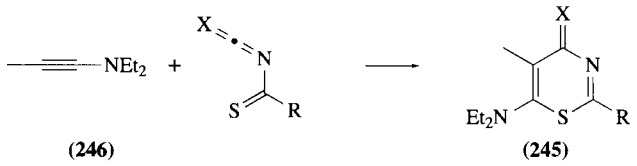
Benzothiete (**240**) reacts with oximes (**241**) (R = H), or *O*-acyloximes (**241**) (R = COR') to afford the corresponding 3,4-dihydro-2*H*-1,3-benzothiazines (**242**). If the *N*-substituent is an acyl group, then elimination occurs to give both the 2*H*- (**243**) and 4*H*-1,3-benzothiazines (**244**) (Scheme 46). Unfortunately, these products are prone to further reactions with benzothiete (see Section 6.07.7) ⟨91JHC843⟩. The synthesis is a development of similar methodology in which benzothiete reacts with *N*-arylimines to give 3-aryl-2*H*-1,3-benzothiazines ⟨86JHC1085⟩.



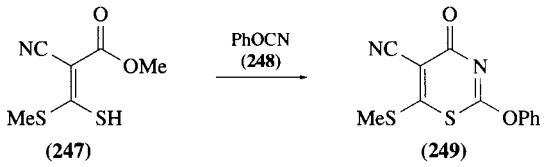
Scheme 46

6.07.8.2.2 1,3-Thiazinones, thiones, and 1,3-benzothiazinones

6-Amino-1,3-thiazin-4-ones (**245**) (X = O), or thiones (**245**) (X = S), are obtainable via the cycloadditions of 1-(*N*,*N*-diethylamino)propyne (**246**) and thioacyl isocyanates, or isothiocyanates, respectively (Equation (30)) ⟨85ZC324⟩. A less common approach utilizes nitriles as the C—N component in [4 + 2] constructions of 1,3-thiazin-4-ones: thus, the cyclization of the (*E*)-thiohemiacetal (**247**) with (**248**) gives the 2-phenoxy-1,3-thiazin-4-one (**249**) (Equation (31)) ⟨85ZC430⟩.

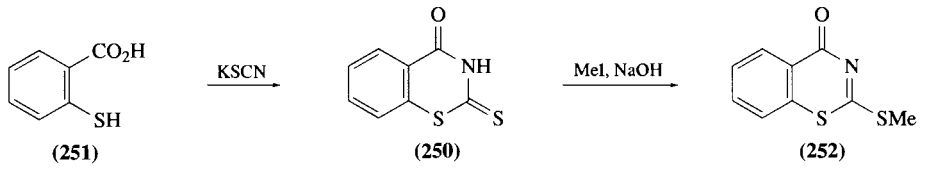


(30)



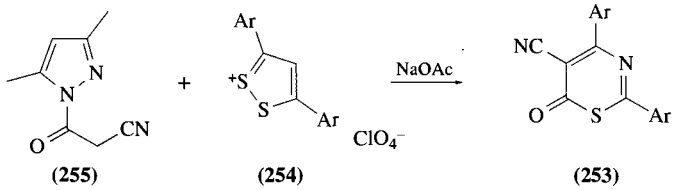
(31)

2-Thioxo-1,3-benzothiazin-4(3*H*)-one (**250**) is formed by reacting 2-thiobenzoic acid (**251**) with potassium isothiocyanate; alkylation of (**250**) with methyl iodide and sodium hydroxide yields the *S*-methyl derivative (**252**) (Scheme 47) ⟨89MI 607-01⟩.



Scheme 47

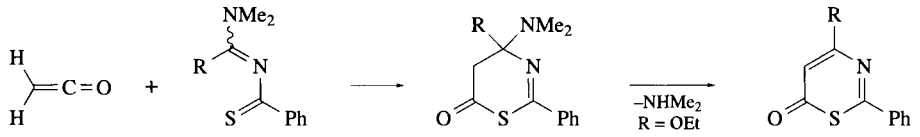
A general synthesis of 2,4-diaryl-5-cyano-1,3-thiazin-6-ones (**253**) is described in which dithiazolium perchlorates (**254**) are condensed with cyanomethyl ketones such as 1-(cyanoacetyl)-3,5-dimethylpyrazole (**255**) in the presence of a base, sodium acetate, at room temperature (Equation (32)) ⟨85AP1145, 85ZC327⟩.



(32)

When ketene reacts with the formamidine (**256**), the final products are 1,3-thiazin-6-ones (**257**), as in previous reactions of this type (see Section 6.07.8.2.1), and it may be assumed that the initial adducts (**258**) eliminate dimethylamine under the reaction conditions (Scheme 48). Unfortunately, the products are contaminated by derivatives formed by multiple additions of ketene ⟨86PS327⟩.

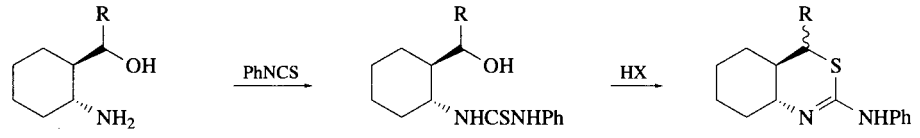
The two atoms (C + S) from an isothiocyanate can be used in a [4 + 2]-type synthesis of bicyclic 5,6-dihydro-4*H*-1,3-thiazines from 2-hydroxymethylcyclohexylamines (**259**). With phenyl isothiocyanate, for example, the initial products are thioureas (**260**), which can be cyclized to the



(256) (258) (257)

Scheme 48

thiazines (**261**) on exposure to mineral acids (Scheme 49). When R = Me the methyl group in the final product occupies an axial site, but for the corresponding phenyl compound the substituent is equatorially orientated ⟨92KGS1433⟩.

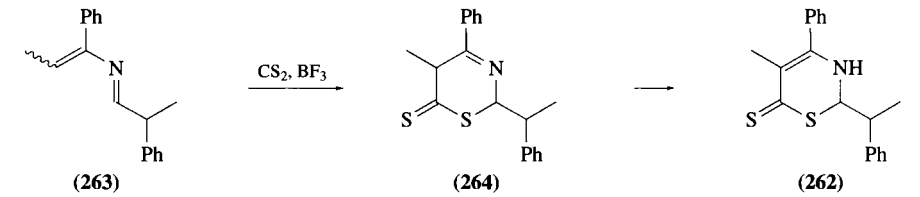


(259) (260) (261)

Scheme 49

6.07.8.2.3 Dihydro-1,3-thiazinethiones and dihydrobenzothiazinethiones

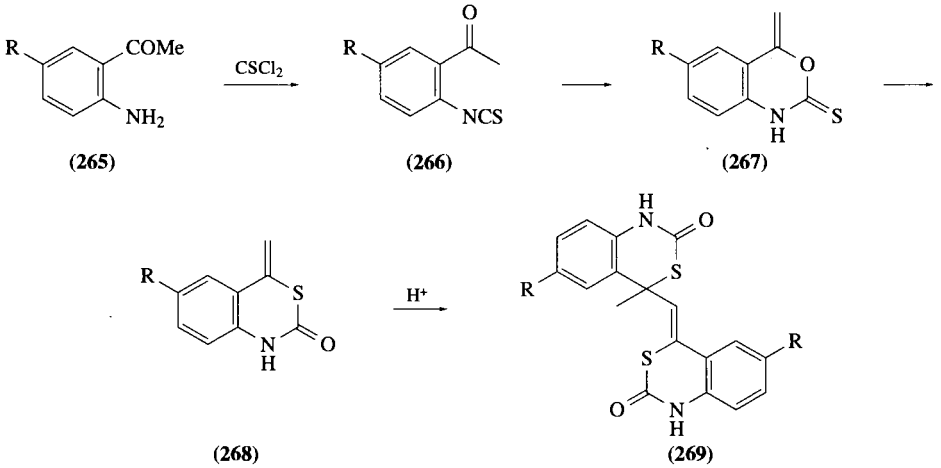
2,3-Dihydro-1,3-thiazine-6-thiones (**262**) are obtained from 2-aza-1,3-dienes (**263**) through cycloaddition reactions with carbon disulfide in the presence of a catalytic amount of boron trifluoride. It is probable that the initial adducts are 2,5-dihydro-1,3-thiazine-6-thiones (**264**), which are unstable and tautomerize to the observed products (Scheme 50) ⟨86CC1179⟩.



(263) (264) (262)

Scheme 50

2-Aminoacetophenones (**265**) when reacted with thiophosgene in a mixture of chloroform, water, and calcium carbonate form the corresponding isothiocyanates (**266**), but these spontaneously cyclize to afford 4-methylene-3,1-benzoxazine-2-thiones (**267**) which rearrange under the reaction conditions to yield 4-methylene-3,1-benzothiazin-2-ones (**268**). These products then slowly dimerize to 4-(3,1-benzothiazine-4-yl)methylene-3,1-benzothiazines (**269**) (Scheme 51) ⟨91JHC1091⟩.

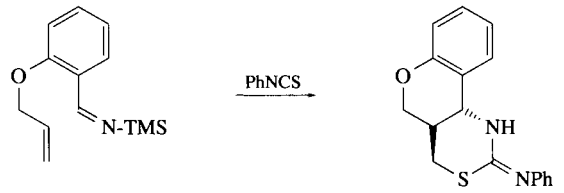


(265) (266) (267)

(268) (269)

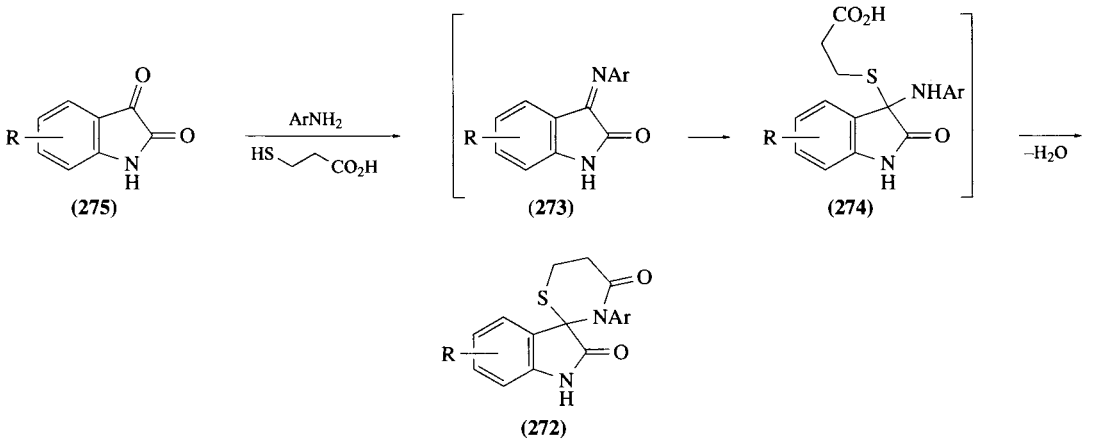
Scheme 51

Another reaction involving an isothiocyanate is employed in the synthesis of the benzopyrano-1,3-thiazines (**270**). In this case, a concerted addition of phenyl isothiocyanate to (2-allyloxybenzylidene)-*N*-trimethylsilylamine (**271**) may occur when the two chemicals are heated together in boiling toluene (Equation (33)) ⟨91JOC5680⟩.



(271) (270) (33)

An unusual construction of the thiazine nucleus is illustrated by the synthesis of a number of *spiro*-indole derivatives (**272**). Here 3-thiopropanoic acid, which provides the sulfur and three carbon atoms, reacts with 3-iminoindolin-2-ones (**273**) to give aminothiols (**274**), which then lactamize (Scheme 52). The 3-iminoindolin-2-ones are formed *in situ* by the condensation of arylamines with isatins (**275**) ⟨86H2479⟩.



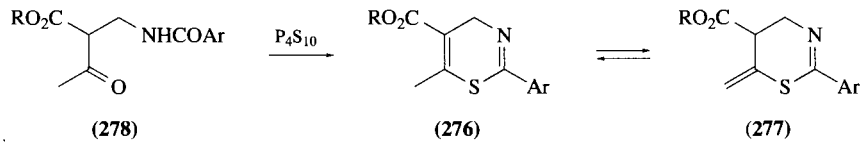
(275) (273) (274) (272)

Scheme 52

6.07.8.3 [5 + 1]-type Syntheses

6.07.8.3.1 4H-1,3-Thiazines and 1,3-thiazin-4-ones

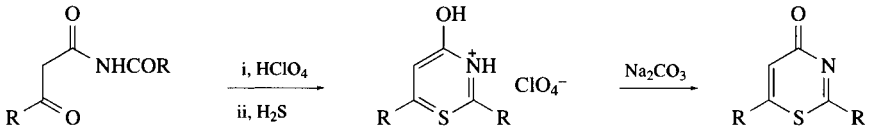
4*H*-1,3-Thiazines (**276**) or their tautomers (**277**) are available through the cyclization of amido ketones (**278**) with phosphorus(V) sulfide (Scheme 53) ⟨78JAP78-111080⟩.



(278) (276) (277)

Scheme 53

2,6-Disubstituted 1,3-thiazin-4-ones (**279**) may be synthesized by successive treatment of β-ketoimides (**280**) with perchloric acid and hydrogen sulfide, followed by the basification of the product 4-hydroxy-1,3-thiazinium salts (**281**) with sodium carbonate (Scheme 54) ⟨83CPB1929⟩.

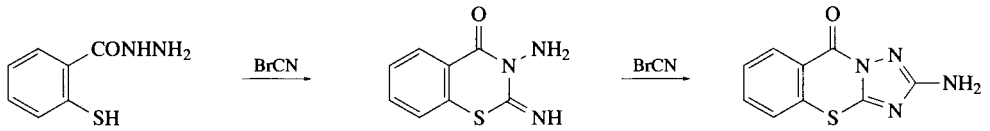


(280) (281) (279)

Scheme 54

6.07.8.3.2 Dihydro-1,3-thiazinones and 1,3-benzothiazinones

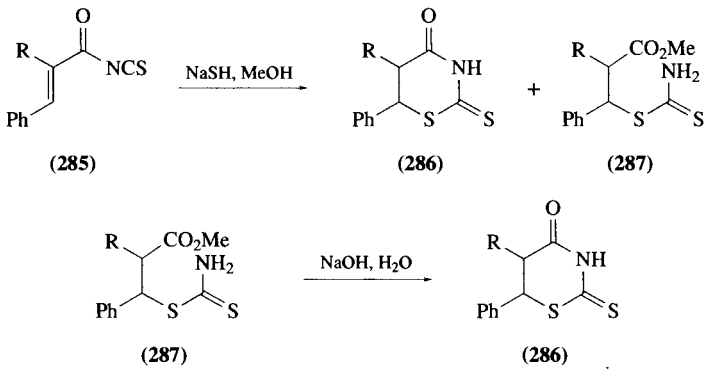
In earlier work it was shown that 2-thiobenzohydrazide (**282**) can be reacted with dicyanogen to form the biologically active 3-amino-2-iminobenzo-1,3-thiazin-4-one (**283**) ⟨75JPS1425⟩. A safer method is now recommended in which dicyanogen is replaced by cyanogen bromide; however, exposure of the product to excess of the reagent affords the tricyclic product (**284**) (Scheme 55) ⟨88JHC1215⟩.



(282) (283) (284)

Scheme 55

The reaction of 3-phenylpropenoyl isothiocyanates (**285**) with sodium hydrogen sulfide in methanol gives thiazinones (**286**) and thiocarbamates (**287**) (Scheme 56). The thiocarbamates are derived from the thiazinones through methanolysis and can be recyclized to them by treatment with aqueous sodium hydroxide in a separate step ⟨90MI 607-01⟩.



(285) (286) (287)

(287) (286)

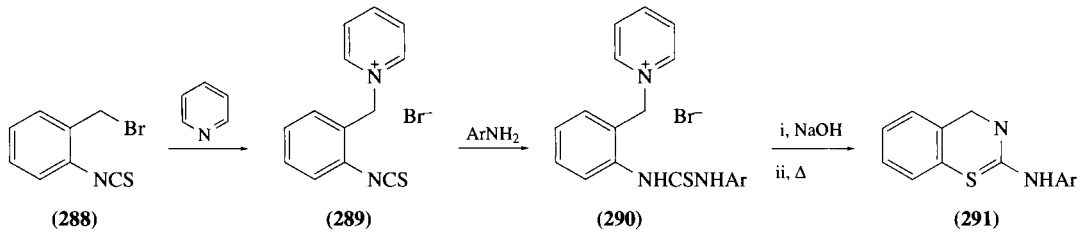
Scheme 56

6.07.8.4 [6 + 0]-type Syntheses

6.07.8.4.1 4H-3,1-Benzothiazines, 1,3-thiazin-4-ones, and related compounds

2-(Bromomethyl)phenyl isothiocyanate (**288**) reacts with pyridine to form *N*-(2-isothiocyanatobenzyl)pyridinium bromide (**289**) (Scheme 57). The treatment of this salt with arylamines

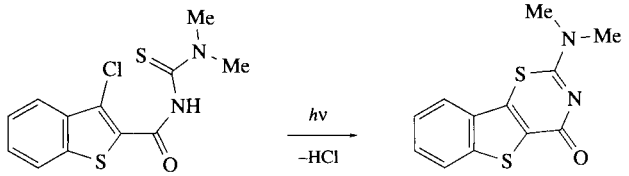
generates the corresponding 2-thioureidobenzylpyridinium bromides (**290**), which when heated with sodium hydroxide afford 2-arylamino-4*H*-3,1-benzothiazines (**291**) (Scheme 57) ⟨86CCC2810⟩.



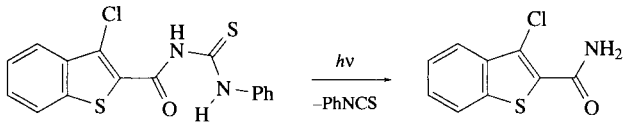
(288) (289) (290) (291)

Scheme 57

N′,*N*′-Disubstituted thioureas (e.g., (**292**)) on irradiation with ultraviolet light give rise to benzothienothiazinones (**293**) (Equation (34)). However, their *N*′-monosubstituted analogues (**294**), which adopt a different ground state conformation favored by hydrogen bonding between an amino proton and the oxygen atom of the carbonyl group, undergo an alternative reaction, affording 3-chlorobenzothiophene-2-carbonamides (**295**) and phenyl isothiocyanate (Equation (35)) ⟨86CCC2839⟩.

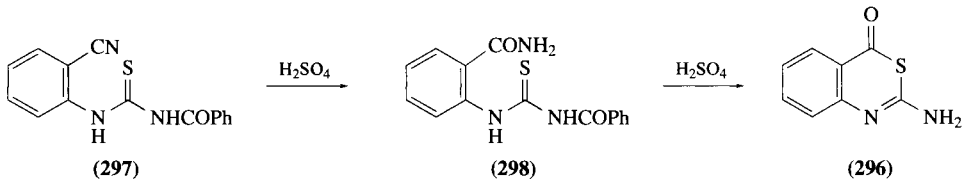


(292) (293) (34)



(294) (295) (35)

2-Amino-3,1-benzothiazin-4-one (**296**) is obtained from *N*-(2-cyanophenyl)-*N*′-benzoylthiourea (**297**) in contact with concentrated sulfuric acid over 2 d. In this reaction the nitrile group of the starting material is slowly hydrolyzed, affording the amide (**298**), which then undergoes acid-catalyzed cyclization and amide hydrolysis to give the benzothiazinone (Scheme 58) ⟨90ZC440⟩.



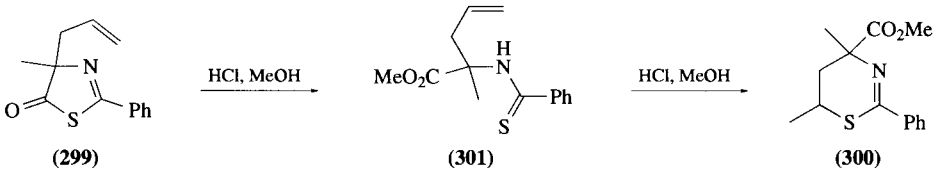
(297) (298) (296)

Scheme 58

*6.07.8.4.2 5,6-Dihydro-4*H*-1,3-thiazines*

4-Allyl-1,3-thiazolin-5-ones (**299**) can be ring expanded to 5,6-dihydro-4*H*-1,3-thiazine-4-carboxylates (**300**) by treatment with hydrochloric acid in methanol; probable intermediates are methyl *N*-(thioacyl)glycinates (**301**), which also occur as minor by-products (Scheme 59). Should 4-toluenesulfonic acid in toluene be used as the reagent, rather than hydrochloric acid in methanol,

then the 4-allyloxazoline (**302**) and the 5-allylthiooxazole (**303**) are formed in the ratio 1 : 1 ⟨89HCA1639⟩.

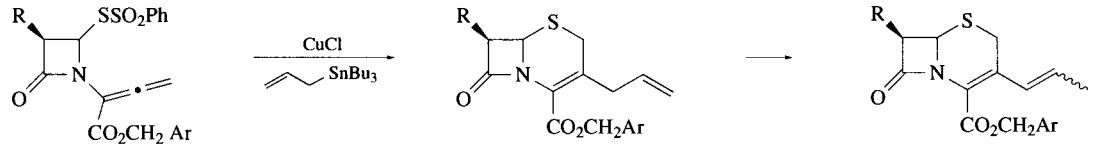


(299) (301) (300)

Scheme 59

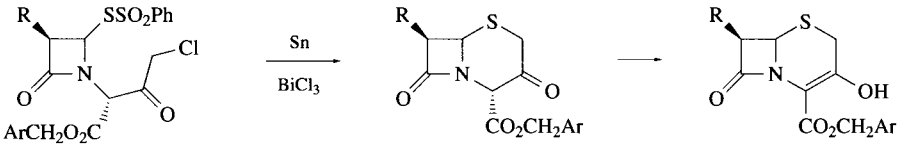
(302) (303)

No attempt has been made in this chapter to document synthetic routes to cephems, but two related routes to the dihydro-1,3-thiazine ring system of certain cephalosporins have been recommended. They also serve as illustrations of the types of construction often used in this vast area of endeavor (see also ⟨92TL3559⟩). The first is a tandem process, which requires the copper(I)-mediated fragmentation of the allenic thiosulfinate (**304**) with concomitant cyclization and capture of an allyl radical released from allyltributyltin hydride (Scheme 60). This yields the cephem (**305**), which tautomerizes to give the more conjugated isomer (**306**) ⟨92TL7029⟩. The second example also involves cleavage of an S—S bond, but this time in the thiosulfinate (**307**) (Scheme 61). The fragmentation step is promoted by contact with tin powder and bismuth(III) chloride, which sets up a bismuth(0)–(III) redox couple. A radical, or its equivalent, is generated and this then undergoes an intramolecular cyclization to afford the cephem (**308**) ⟨92SL878⟩.



(304) (305) (306)

Scheme 60



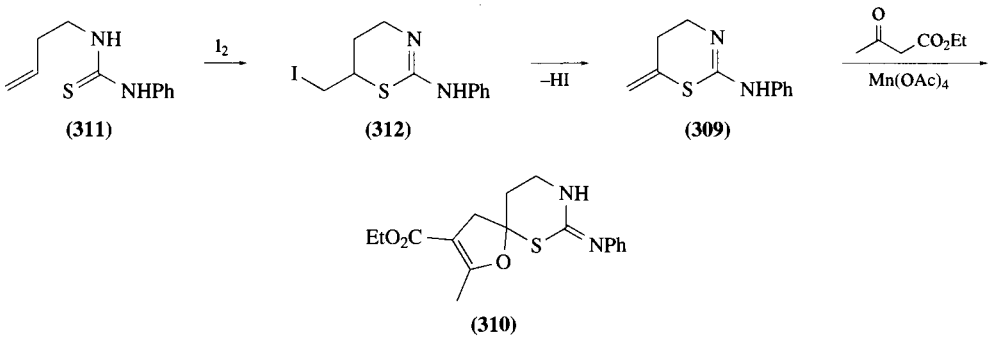
(307) (308)

Scheme 61

Ethyl acetoacetate reacts with 2-(*N*-benzylamino)-5,6-dihydro-6-methylene-4*H*-1,3-thiazine (**309**) in the presence of manganese(IV) acetate to give the spirocyclic derivative (**310**) (Scheme 62). The starting material for this reaction is obtained from the *N*-butenylthiourea (**311**) by iodocyclization and elimination of hydrogen iodide from the intermediate iodomethyl-1,3-thiazine (**312**) ⟨91TL7111⟩.

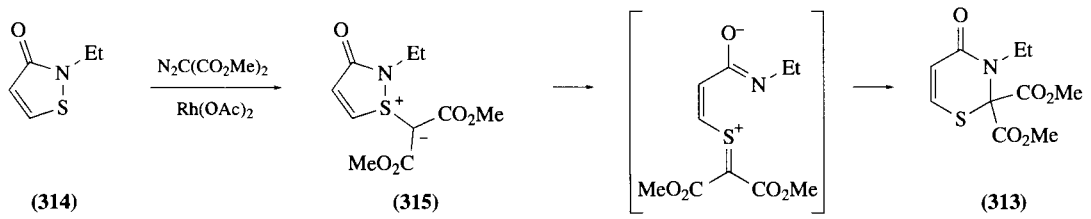
6.07.8.4.3 Dihydro-1,3-thiazinones

3,4-Dihydro-2*H*-1,3-thiazin-4-ones (**313**) are available through the ring expansion of 2-substituted isothiazolones (**314**) with dimethyl diazomalonate in the presence of rhodium(II) acetate (Scheme



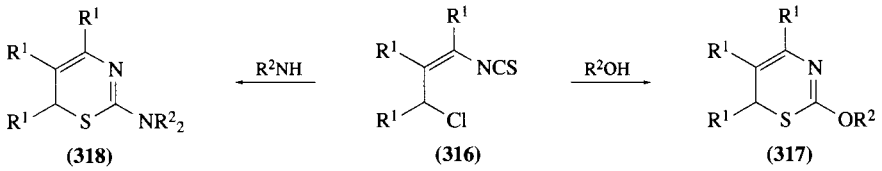
Scheme 62

63). Zwitterionic adducts (**315**) may act as reaction intermediates, ring opening and then recyclization giving the observed products (Scheme 63) ⟨83CC643⟩.



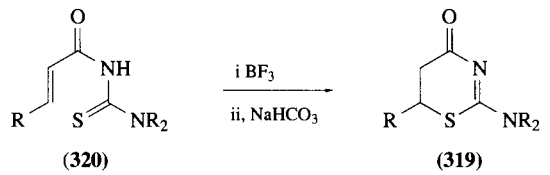
Scheme 63

3,6-Dihydro-2*H*-1,3-thiazin-2-ones and 2-imines can be synthesized in a number of ways. Thus, 3-chloroalkenyl isothiocyanates (**316**) can be cyclized to give 2-alkoxythiazines (**317**) by treatment with alcohols. If amines are used then the 2-amino compounds (**318**) are obtained (Scheme 64) ⟨84JPC101⟩.



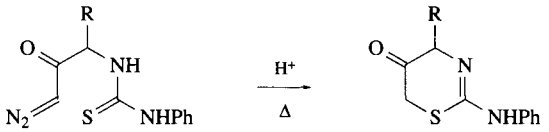
Scheme 64

2,6-Disubstituted-5,6-dihydro-1,3-thiazin-4-ones (**319**) are easily synthesized from *N*-propenoylthioureas (**320**) through their reactions with boron trifluoride etherate, followed by basification with sodium bicarbonate (Equation (36)) ⟨85S933⟩.



(36)

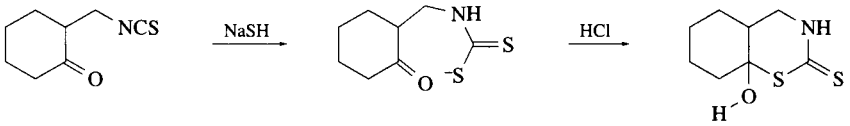
4,6-Dihydro-1,3-thiazin-5-ones (e.g., (**321**)) are uncommon, but they can be synthesized from diazoketones (**322**), which in the presence of an acid eliminate nitrogen and form the heterocycles, presumably via intermediate carbenes (Equation (37)) ⟨80KGS1327⟩.



(322) (321) (37)

6.07.8.4.4 2H-3,4,5,6-Tetrahydro-1,3-thiazines and related compounds

The perhydro-8a-hydroxy-1,3-benzothiazine-2-thione (**323**) is available through the reaction of the isothiocyanato ketone (**324**) with sodium hydrogen sulfide (Scheme 65). An intermediate dithiocarbamate (**325**) is produced, which upon treatment with a mineral acid cyclizes to the required thiazine. Analogous tetrahydro-6-hydroxy-1,3-thiazine-2-thiones were prepared in a similar fashion ⟨91KGS416⟩.



(324) (325) (323)

Scheme 65

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6.08
1,3-Dioxins, Oxathiins, Dithiins, and their Benzo Derivatives

PHILIP C BULMAN PAGE and ANDREW LUND
Loughborough University, UK

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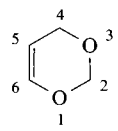
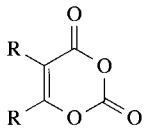
6.08.1 INTRODUCTION

This chapter discusses the chemistry of 1,3-dioxanes, -oxathianes, -dithianes, their unsaturated and benzo-fused derivatives, and their tautomers. All possible degrees of unsaturation in the six-membered ring, from zero to four sp^2-hybridized carbon atoms, are included. Following a brief treatment of theoretical, structural, and spectroscopic studies, the reactivity of the different ring systems is examined, categorized by the formal degree of unsaturation.

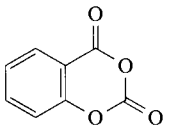
Due to the disposition of the heteroatoms in the ring, and their normal valency (2), the formal maximally-unsaturated monocyclic structure, illustrated by 2*H*,4*H*-1,3-dioxin (**1**), contains only one endocyclic double bond. Further unsaturation can of course be accommodated by exocyclic double bond formation, and in particular by the introduction of carbonyl groups. For complete cyclic conjugation in a monocyclic ring, the only structures relevant to this chapter to which considerations of aromaticity might apply are the 2*H*,4*H*-1,3-dioxin-2,4-diones (**2**). However, it seems that compounds of this type have not been synthesized. The benzologue of (**2**), 2*H*,4*H*-1,3-benzodioxin-2,4-dione (**3**), has been known for a considerable time ⟨41CR(213)355, 51JCS1357, 72JCS(P1)2007⟩. This compound is rather unstable, particularly towards hydrolysis; it behaves as a typical mixed anhydride. Analogues of (**2**) and (**3**) with one or two sulfur atoms replacing oxygen appear to be unknown. In the *peri*-naphtho-fused series, all of the various possibilities illustrated by structure (**4**) are known, although they have not attracted a great deal of attention.



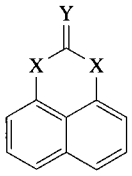
(**1**)



(**2**)



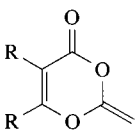
(**3**)



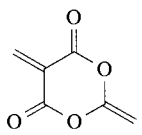
(**4**)

X = O, S
Y = O, S, H_2

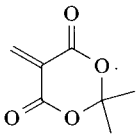
Complete cyclic conjugation is present also in derivatives of the as yet unknown 2-methylene-1,3-dioxin-4-one (**5**) and 2,5-dimethylene-1,3-dioxane-4,6-dione (**6**). These structures are cyclic acylals of ketene. Well-known and intensively studied are the 5-methylene Meldrum's acid derivatives (**7**); here the cyclic π-conjugation is blocked at C-2. The reactivity of compounds of this type is discussed in Section 6.08.5.1. The cyclic αβ-unsaturated lactones (**8**) have also been thoroughly investigated, as their thermal and photochemical reactions are of great synthetic utility. These are dealt with in Section 6.08.5.2.



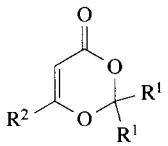
(**5**)



(**6**)



(**7**)



(**8**)

The chemistry of the more saturated systems has been the most thoroughly investigated, and these Sections (6.08.5.3 and 6.08.5.4) are correspondingly longer. It will be seen that sulfur-containing rings are usually fully reduced at carbon, although of course the sulfur itself occurs in several oxidation states. Later sections cover the reactivity of ring substituents, where that chemistry is affected by or dependent upon the presence of the heterocycle, and then methods of synthesis of the various ring types are covered. The chapter concludes with a short description of biologically active derivatives of this class of heterocycle.

6.08.2 THEORETICAL STUDIES

Since the late 1980s, there has been much interest in the conformations of oxygen and sulfur containing heterocycles (see for example ⟨89ACR357⟩), particularly with regard to studies of the anomeric effect. Although the vast majority of these studies have been carried out using NMR and x-ray crystallographic techniques, a small number have involved theoretical and semi-empirical methods, detailed below.

Several different studies of the 1,3-dioxane series have been published. These include MNDO calculations of protonation equilibria ⟨89ZOR1059⟩ and MO calculations used in HOMO determination ⟨85IZV1433⟩. The structure of the radical cation derived from 1,3-dioxane has been investigated in a semi-empirical SCF–MO study ⟨83JCS(P2)1285⟩. In a publication by Juaristi *et al.*, *ab initio* Hartree–Fock 6-31G** and other calculations were reported of variously sustituted 1,3-dioxanes, dithianes, and oxathianes in an examination of stereoelectronic interactions in each molecule ⟨94JA5796⟩.

In the early 1980s, Allinger and co-workers published the results of IDME (induced dipole moment and energy) calculations for various conformations of halogenated dioxanes and concluded that this method gave superior results which were in good agreement with experimentally determined values ⟨83JA1723⟩. MMP2 force field calculations have been used in the prediction of preferred conformations of 1,3-dioxanes substituted at C-5 with sulfoxide and sulfone units ⟨92JA2157⟩.

Other saturated heterocycles addressed in this chapter have received considerably less attention in the context of theoretical calculations. MNDO calculations on a range of 1,3-dithianes have been completed and the UV photoelectronic spectra of the compounds compared with the predicted values ⟨87JST(160)117⟩. PM3-MO calculations for 2-lithiated 1,3-dithianes have been carried out; comparison with x-ray crystallographic data showed these calculations to provide closer agreement with the experimental data than did MNDO calculations ⟨94JOC4529⟩.

In the unsaturated series, *ab initio* calculations have been performed on 1,3-dithiin ⟨90H(31)701⟩, and MM2 force field calculations have been applied to the 1,3-dioxin molecule ⟨89JA6920⟩. The origins of stereoelectronic control in the carbonyl group reduction of 1,3-dioxan-5-one and 1,3-dithian-5-one have been explored ⟨92AG(E)1019⟩.

6.08.3 EXPERIMENTAL STRUCTURAL METHODS

6.08.3.1 X-ray Diffraction

X-ray crystallography, in conjunction with NMR techniques, has been central to the study of molecular geometry in this group of compounds, and has been important in investigation of the anomeric effect, resulting in the structural determination of a large number of 2-substituted-1,3-dithianes ⟨84JOC3026, 86CJC732, 94JOC1672⟩, 1,3-dioxanes ⟨87JOC3806, 88JOC3609, 89ACR357, 89JOC5963, 90JOC33, 92JA2157⟩, and 1,3-oxathianes ⟨88TL6801, 93MI 608-01⟩.

The fully saturated compounds for the most part prefer a chair conformation, although an exception is seen in the case of some substituted 1,3-dithianes, where axial substituents can destabilize the chair conformation in favor of twist forms as a result of 1,3-diaxial interactions. ⟨74PMH(6)199⟩.

Among the most thoroughly studied compounds in this series are the fully saturated 2-aryl-1,3-disubstituted derivatives ⟨66AX4907, 70RTC313, 72AX(B)2424⟩. These show that, while chair conformations are generally adopted, the degree of puckering in the heterocyclic ring depends considerably upon the nature of the heteroatomic substituents and their positions in the ring. In 1,3-dioxane, the ring is noticeably most puckered around the heteroatoms. In contrast, in 1,3-dithiane derivatives, the S—C—S segment of the ring is the least puckered. As might therefore be expected, in 1,3-oxathianes, the ring is more puckered around the oxygen atom than around the sulfur atom.

The structures of a number of 1,3-dithiane 1-oxide and 1,3-oxathiane 3-oxide derivatives have been determined, and they invariably show chair-type conformations ⟨89JCS(P1)185, 89JCS(P1)1158, 90JCS(P1)167, 95MI 608-01⟩. Of considerable interest is that very different structures are found for the *cis* and *trans* isomers of unsubstituted 1,3-dithiane 1,3-dioxides ⟨91SL80⟩. The structure of the *trans* isomer suggests the presence of a favorable dipole–dipole interaction between the two sulfoxide groups, where the axial sulfoxide is displaced towards the equatorial sulfenyl group ⟨91JCS(P1)662⟩. Conversely, for the *cis* isomer, in the diaxial conformation, which is preferred ⟨79JOC1540, 90JCS(P2)1987⟩, the two sulfenyl groups experience mutual repulsion, increasing the S1–S3 distance by 0.135 Å over that in the *trans* isomer and the S—C—S bond angle from *ca.* 113° to *ca.* 120° ⟨90JCS(P2)1987⟩.

Not all of the compounds in this group adopt a chair conformation in the solid state. For example, 2,2-dimethyl-1,3-dioxane-4,6-dione, also known as Meldrum's acid, is known to adopt a boat conformation ⟨85JCS(P2)1547⟩. Another interesting example is 2-*t*-butyl-2,6-dimethyl-1,3-dioxin-4-one, which adopts an envelope-like conformation ⟨94JA3312⟩.

Few structures of the benzo derivatives of these compounds have been reported, but a typical example of those which have is of 1,3-benzodioxin, in which the dioxin ring adopts an envelope conformation ⟨88MI 608-01⟩.

X-ray diffraction studies have suggested that the anomeric effect operates in 2-phosphinoyl derivatives of the saturated heterocycles, where the 2-substituent has no lone electron pairs. For example, in 2-diphenylphosphinoyl-1,3-dithiane, the substituent occupies an axial position, in contrast to the 1,3-dioxane and 1,3-oxathiane derivatives, where the same substituent occupies an equatorial position ⟨84JOC3026, 88JOC3609, 88TL6801⟩.

6.08.3.2 NMR Spectroscopy

The examination of chemical shifts and coupling constants in proton and ^{13}C NMR spectra has been used extensively for determining solution conformations. These techniques are particularly appropriate to the compounds discussed in this Chapter, as the chemical shifts of the two protons at the C-2 position are substantially different, as are their ^{1}J coupling constants with the C-2 carbon atom. In 1994, the ^{1}H NMR spectrum of 2-phenyl-1,3-dithiane was analyzed precisely, including up to ^{6}J coupling data ⟨94CJC1722⟩. The data confirm the expected chair conformation.

The analysis of ^{1}H and ^{13}C data, particularly ^{1}H chemical shifts and C–H coupling constants, is indeed often used to determine C–H bond orientation. In cyclohexane, ^{1}J C–H coupling constants of equatorial C–H bonds ($^{1}J_{C\text{-}Heq}$) are greater than those of axial bonds ($^{1}J_{C\text{-}Hax}$) (the Perlin effect). This effect also operates in 1,3-dioxanes for the C-2 position protons ⟨73ACS2676⟩. In contrast, the C-5 position protons display a reverse Perlin effect when the conformation is locked by a 2-*t*-butyl substituent ⟨94JCS(P2)1151⟩. Such a reverse Perlin effect has been observed for all ring protons in 1,3-dithiane ⟨92TL1847⟩. In 1,3-oxathianes, $^{1}J_{C\text{-}Hax}$ is approximately equal to $^{1}J_{C\text{-}Heq}$ ⟨92TL6927⟩. A complete analysis of these effects in all three molecules has been reported ⟨94JA5796⟩.

The chemical shifts of ring protons in 1,3-oxathiane and dithiane sulfoxides are very sensitive to sulfoxide orientation. This is due mainly to the "*syn*-axial effect," the deshielding of a *syn*-axial proton, and the shielding of an equatorial β-proton, by an axial sulfoxide. In general, the magnitudes of the ^{2}J geminal coupling constants observed for the C-2 position depend upon the electronegativity of the two adjacent heteroatoms, the bond angle, and the relative orientation of the heteroatom pairs and the C–H bonds ⟨70T3389, 71T1917, 72T2139⟩.

Vicinal coupling constants in 1,3-oxathianes and 1,3-dithianes show a strong dependence on dihedral angle, and hence are important indicators of ring conformation. ^{3}J values in a CH_2—CH_2 fragment are also dependent on electronegativities of ring heteroatoms ⟨71ACR87⟩.

Carbon-13 data for this series of saturated heterocycles have been comprehensively reviewed and tabulated ⟨82JOC4688, 86T1253, 87JOC5185, 89JOC5191, 89JPO349, 90JOC33, 94JOC1672⟩. Methyl substitution at ring carbon atoms shows similar effects in all three systems, the α-effect leading to a downfield shift of the substituted carbon atom resonance, except where an axial C-5 substitutent is present in 1,3-dithiane, when the ^{13}C signal is shifted upfield. Conversion into the corresponding sulfoxides induces similar α-effects. Again, sulfoxide bond orientation has considerable influence over ^{13}C shifts ⟨78JOC96⟩. Detailed ^{13}C and ^{1}H data for 2-oxo-1,3-dioxane and all the methyl derivatives have been published ⟨83ACS(B)289⟩. Oxygen-17 heteronuclear NMR has been examined in 5-hydroxy- and 5-methoxy-1,3-dioxanes, the oxygen atom in the axial isomer resonating downfield of that of the equatorial isomer for both the alcohol and the ether, suggesting that hydrogen bonding is not relevant ⟨83OMR(21)179⟩. Selenium-77 NMR spectroscopy has been used in the evaluation of the anomeric effect in 2-(arylseleno)-1,3-dithianes ⟨85TL5235, 88JOC3766⟩.

6.08.3.3 Mass Spectrometry

The standard reference text on mass spectrometry which deals with these heterocycles is that by Porter and Baldas ⟨B-71MI 608-01⟩.

The mass spectra of the radical cations derived from 1,3-dioxanes shows an intense $(M\text{-}1)^{+}$ peak due to α-cleavage of the C-2 proton. This is also a feature in the mass spectra of 1,3-oxathianes.

More intense peaks are obtained from sulfur-containing ions due to the more ready loss of an electron from sulfur than from oxygen. ⟨71OMS(5)763⟩.

The mass spectra of 1,3-dithianes is more complicated. The electron impact (EI) mass spectrometry of 2-aryl and 2-alkyl-1,3-dithianes has been investigated with deuterium labeling studies and these showed the loss of S_2H to be a common feature. ⟨69OMS(2)611, 72OMS(7)317⟩. The EI mass spectra of 2-aryl-2-methyl and 2-alkyl-2-methyl 1,3-dithiane show S_2H loss as well as fragmentation by several other pathways ⟨86OMS(21)335⟩. The CI mass spectra of 2-aryl-2-methyl-1,3-dithianes also show the loss of S_2H, and a mechanism has been suggested ⟨89OMS(24)777⟩. Under FAB conditions, fragment ions formed by primary loss of S_2H are not observed. Rather, ions corresponding to C_4H_8S loss are seen ⟨89OMS(24)777⟩.

2-Aryl-1,3-oxathianes have also been examined under EI conditions and show pronounced molecular ions and fragment ions due to simple and complex fragmentation patterns ⟨73AJC2009⟩. The EI mass spectra of a variety of dithiaspiranes as well as 2-aryl-1,3-dithianes have been reported ⟨95MI 608-02⟩.

6.08.3.4 Other Methods

6.08.3.4.1 IR spectroscopy

The infrared spectra of the saturated heterocycles in this series show characteristic C—O (1300–1020 cm^{-1}) and C—S (800–600 cm^{-1}) stretching vibrations. The ν(C—O) are often found to be the stronger. In the case of 1,3-dioxane, IR has been used as a structural probe for ring conformation, and the conclusions are in agreement with those from other methods ⟨70JCP(53)376⟩.

Carbonyl frequencies occur in the expected regions, when allowance is made for the inductive effect of the oxygen atoms, if present. Thus, several 1,3-dioxan-4-ones, mostly with fused cyclobutane rings, were found to absorb in the region 1732–1755 cm^{-1} (CCl_4), somewhat higher than a normal δ-lactone ⟨94JA3312⟩. The band in 1,3-dioxan-2-one (trimethylene carbonate) is very solvent-sensitive, being found at 1753 cm^{-1} in $CHCl_3$, and 1814 cm^{-1} in the vapor phase ⟨76JCS(P2)1800⟩. Meldrum's acid shows the expected two bands, at 1794 cm^{-1} and 1770 cm^{-1} (CCl_4), or 1789 cm^{-1} and 1745 cm^{-1} (KBr) ⟨67M564⟩. The cyclic anhydride (**3**) also shows two bands, at 1812 cm^{-1}, assigned to the carbonate carbonyl, and 1756 cm^{-1}, the benzoate carbonyl ⟨72JCS(P1)2007⟩. The cyclic dithiocarbonate (**4**; X = S, Y = O) absorbs in an altogether different area, 1630 cm^{-1} ⟨86CL551⟩.

6.08.3.4.2 Electron diffraction

A gas phase electron diffraction study of 1,3-dithiane was carried out by Adams and Bartell. It suggested a chair conformation to be the most stable, in agreement with solution and solid phase studies ⟨77JST(37)261⟩.

6.08.3.4.3 Microwave spectroscopy and dipole moments

The microwave spectrum of 1,3-dioxane in the region 8 to 40 GHz has been observed. The derived data, including the dipole moment (2.06 D), were in good agreement with solution values, and suggested the expected chair conformation ⟨72CJC1690⟩. Similar studies of 1,3-dithiane ⟨83JST(96)225⟩ and 1,3-dioxan-5-ol ⟨80JA1248⟩ indicated that these molecules also both adopt the chair conformation. The dipole moments of 1,3-dioxane, 1,3-dioxan-5-ol, and 1,3-dithiane have all been derived from microwave studies. The rotational constants for the ground state and six vibrationally excited states of 1,3-dithiane were derived from the microwave spectrum in the 12 to 40 GHz range. The total dipole moment was calculated to be 2.14 D, and the data were again consistent with the ring assuming a chair conformation ⟨83JST(96)225⟩.

6.08.3.4.4 ESR spectroscopy

ESR spectroscopy has been used in the structural determinations of the radical cations derived from 1,3-dioxane ⟨84JCS(P2)511⟩ and 1,3-dithiane ⟨82TL4739⟩. An unusually high proton hyperfine

coupling constant of the methylene protons in the 1,3-dioxane system was attributed to the π-σ-π delocalized SOMO. Whereas, in the case of 1,3-dioxane, high spin density is observed at the 2-CH_2 group, in the dithiane system, a weak S–S σ-bond is present, with the unpaired electron occupying the σ^* orbital, and there is negligible spin density at the 2-position methylene group. The same spectrum has been recorded and interpreted by Williams and co-workers ⟨82JA2062⟩.

The conformations of 1,3-dioxanes with a 2-*exo*-methylenyl radical have also been investigated by ESR spectroscopy. It is interesting to note that conformation in these systems is determined largely by the C-2 substituent: lack of severe 1,3-diaxial interactions in the dioxane system allows a methyl group or even a 2-*exo*-methylenyl radical to force a 5-*t*-butyl substituent to adopt an axial orientation ⟨91JCS(P2)1893⟩. The corresponding dithianes could not be prepared as elimination to give the 2-methylidene derivative was too rapid ⟨91JCS(P2)1893⟩.

6.08.3.4.5 UV spectroscopy

An investigation into spiro-conjugation in dioxane systems has been carried out using UV spectroscopy. The UV spectrum of a spirocyclic orthocarbonate was compared with the spectra of two other nonspirocyclic dioxane-derived compounds ⟨82BCJ1106⟩.

6.08.3.4.6 Photoelectron spectroscopy

The PE spectrum of naphtho[1,8-*de*]-1,3-dithiin has been reported by Bock *et al.* ⟨81CB2622⟩.

6.08.4 THERMODYNAMIC ASPECTS

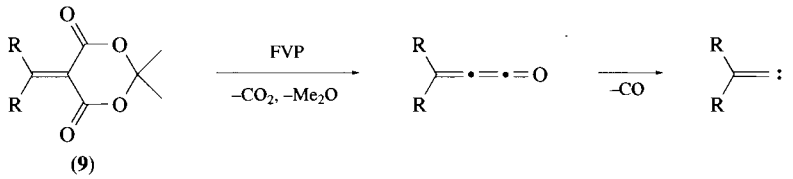
The majority of thermodynamic data examined in these heterocyclic systems has been concerned with their ring conformations and the anomeric effect. Much of this work is cited in Section 6.08.3. Other data has been obtained from 2-phosphoryl- and 2-thiophosphoryl-1,3-dithianes ⟨92TL2271, 94JOC1672⟩ and 2-phosphoryl- and 2-thiophosphoryl-1,3-dioxanes ⟨93PS(74)311⟩.

The ideal gas thermodynamic properties of 1,3-dithiane ⟨95MI 608-03⟩ and 1,3-dioxane ⟨92MI 608-01⟩ are available. Ion-pair carbon acidities, ionic acidities, and various thermodynamic parameters of 2-trimethylsilyl-1,3-dithiane and related silyl species have been measured ⟨93JOC1778⟩. The energetics of C—H bond cleavage mediated by Lewis acid, free radicals or base in 2-aryl-1,3-dithianes have also been investigated ⟨95PAC729⟩.

6.08.5 REACTIVITY OF HETEROCYCLIC RINGS

6.08.5.1 Alkylidene Dioxanediones

Pyrolysis of 5-methylene derivatives of Meldrum's acid is well known and the trapping of the reactive intermediates is well documented ⟨91H(32)529⟩. The reactive intermediates in some cases have been identified as methylene ketenes and carbenes (Scheme 1).

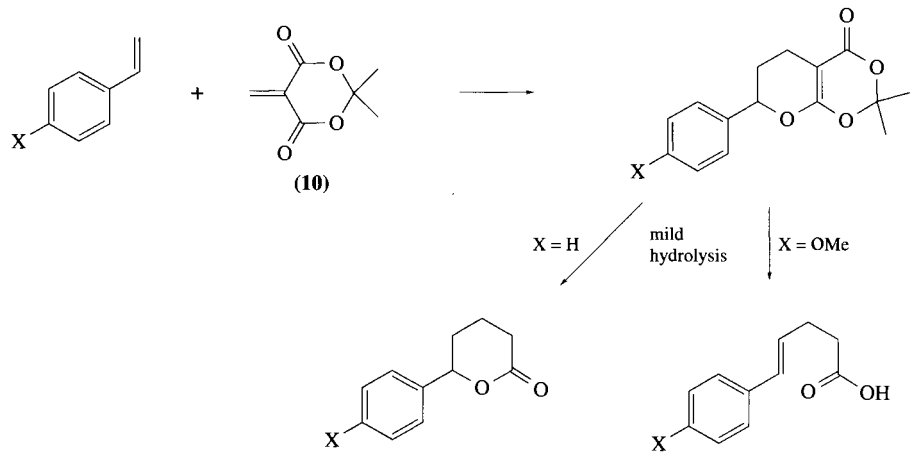


(9)

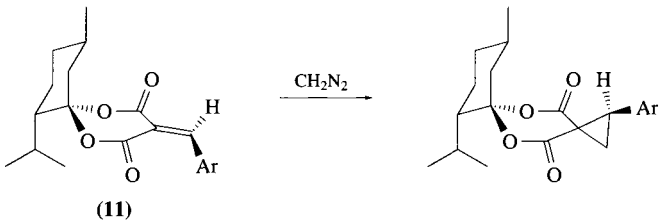
Scheme 1

Meldrum's acid derivatives possessing a 5-alkylidene group have been shown to function as useful dienophiles ⟨77TL4539, 85TL3195⟩. The same materials can also function as heterodienes in Diels–Alder reactions (Scheme 2) ⟨88H(27)1929⟩. The 5-methylene derivative (**10**) of Meldrum's acid is generated as a transient species *in situ* by oxidation of 5-methyl-5-phenylselenenyl Meldrum's acid ⟨77AJC179, 85TL3195⟩. Chiral spiro-5-alkylidene-1,3-dioxane-4,6-diones (e.g. **11**) undergo diastereo-

facially selective hetero-Diels–Alder reactions ⟨90H(31)1229⟩, and cyclopropanation (Equation (1)) ⟨89TL5281⟩.



Scheme 2

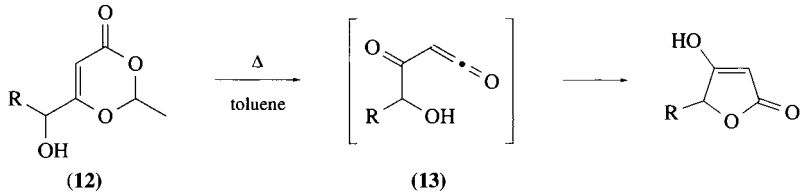


(1)

6.08.5.2 Dioxinones and Dioxanediones

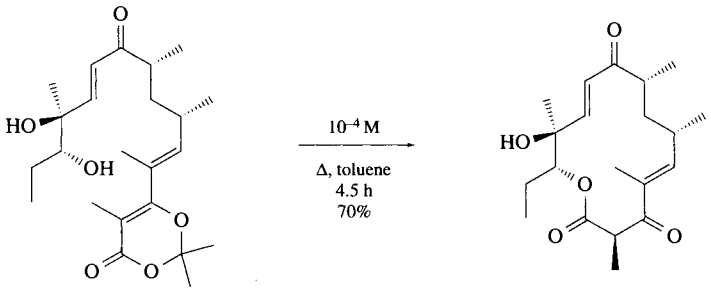
6.08.5.2.1 Unimolecular thermal and photochemical reactions

Thermal ring opening of dioxinones followed by intramolecular trapping of the resulting α-ketoketenes leads to β-hydroxybutenolides in good yield (Scheme 3) ⟨90CPB94⟩. The process has been applied to the synthesis of larger ring lactones (Equation (2)) ⟨89JA8286⟩, and macrocyclic di- and tri-lactones may also be isolated ⟨93JOC5011⟩. With an amino function as the internal nucleophile, lactams can be produced in good yields ⟨87H(26)2611⟩. This process has also been used in the synthesis of large rings (Equation (3)) ⟨86JOC5486⟩, although β-lactams (**15**) can be produced by a similar process, albeit in modest yields, by irradiation of the aminoalkyl dioxinones (**14**) at 254 nm (Equation (4)) ⟨87H(26)2611⟩.

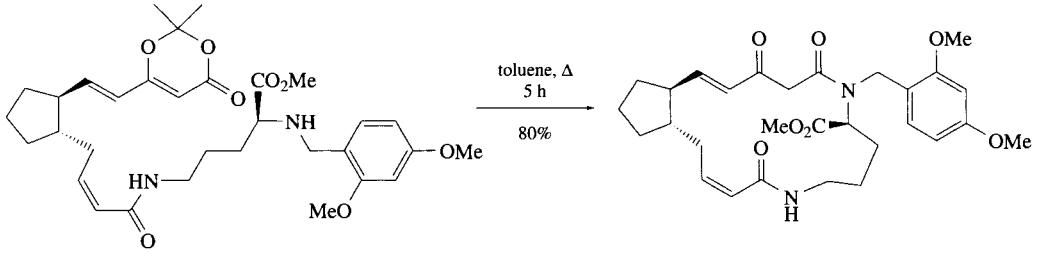


R	*Yield* (%)
H	80
Me	92

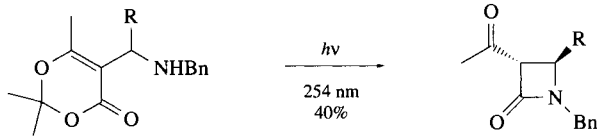
Scheme 3



(2)



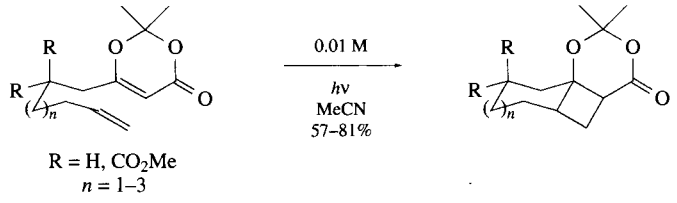
(3)



(4)

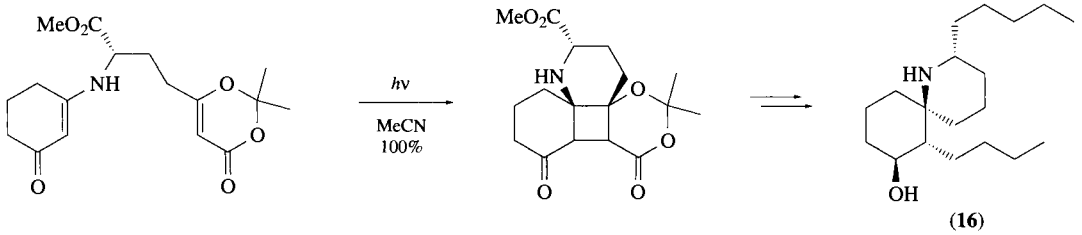
(14) R = H, Me (15)

The intramolecular [2 + 2] photocycloaddition of dioxinones has been studied extensively by Winkler *et al.*, the reaction being carried out in acetonitrile–acetone with irradiation through Pyrex glass. The procedure, together with subsequent reactions, leads to a variety of ring systems, and is particularly successful for medium sized rings (Equation (5)) ⟨87H(25)55⟩. Much of the early work in this area has been reviewed ⟨88CRV1453⟩. Later applications have involved the assembly of more complicated systems including perhydrohistrionicotoxin (**16**) (Scheme 4); those involving chiral starting materials have shown good to excellent levels of diastereoselectivity (Equation (6)) ⟨89JA4852, 91JA8839⟩.



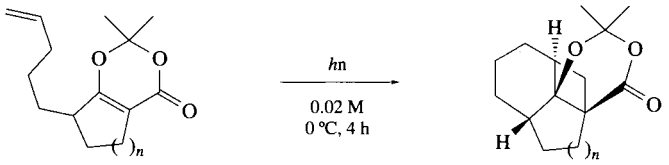
(5)

R = H, CO_2Me
n = 1–3



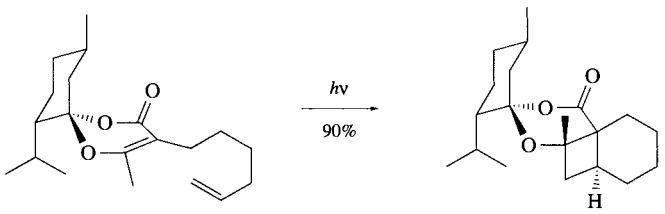
(16)

Scheme 4



(6)

[2 + 2] Photocycloadditions of dioxinones have also been reported by Sato *et al.*, particularly with chiral-2-spirocyclic dioxinones. Both inter- and intramolecular versions have shown high regio- and stereoselectivity (Equation (7)) ⟨90H(30)217, 90H(31)2115⟩.

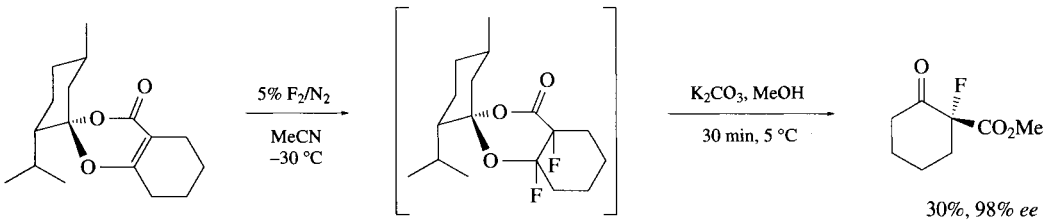


(7)

6.08.5.2.2 Reactivity towards electrophiles

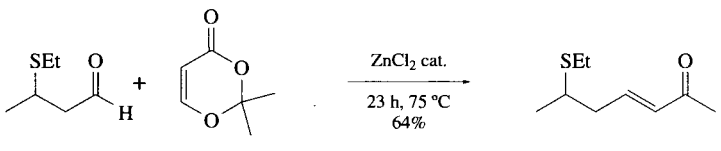
The chemistry of Meldrum's acid is dominated by electrophilic attack at the 5 position, via the anion, and by nucleophilic attack at the 4 and 6 positions. Meldrum's acid is known to react with a very wide variety of electrophiles, including alkyl halides ⟨82S452⟩, enones ⟨84S224⟩, and other electron-deficient alkenes ⟨79SC383, 83IJC(B)519⟩, Mannich bases ⟨82JOC3769⟩, O,N-acetals ⟨83H(20)985, 84CB2928, 87M1039, 87M1057⟩, and aldehydes ⟨88HCA1974⟩, among others. These and similar reactions have been reviewed ⟨91H(32)529⟩.

The unsaturated system of 1,3-dioxin-4-ones readily undergoes reaction with simple electrophiles such as molecular bromine; *N*-iodosuccinimide in acetic acid gives the corresponding 5-iodo-1,3-dioxin-4-one ⟨92JCS(P1)1393⟩. Fluorination with molecular fluorine occurs in good yields in the presence of triethylamine ⟨91CC699⟩. The potential of the difluorination of chiral 1,3-dioxin-4-ones for the enantioselective preparation of α-fluorinated-β-ketoacids has been investigated (Scheme 5) ⟨92TA1025⟩.



Scheme 5

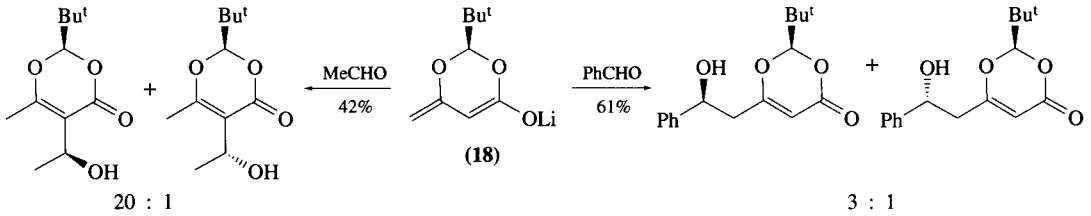
It is reported that, at 75°C in the presence of a Lewis acid catalyst, 2,2,6-trimethyl-1,3-dioxin-4-one (**17**) undergoes fragmentation to give an α-ketoketene and acetone. In the presence of 3-(ethylthio)butanal a crossed aldol reaction with the acetone (Scheme 6) takes place, rather than a hetero-Diels–Alder reaction with the α-ketoketene ⟨84USP4480132⟩.



(**17**)

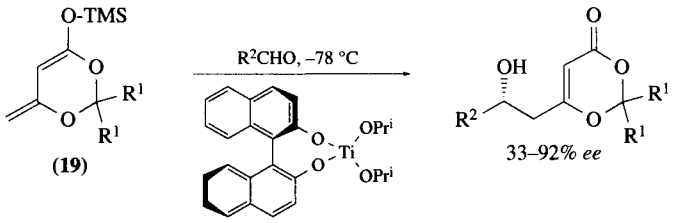
Scheme 6

Seebach and co-workers have explored the uses of enantiomerically pure dienolates (**18**) and silyl dienol ethers derived from dioxinones as chiral synthetic equivalents of the acetoacetic ester dianion. Reactions were carried out principally with aldehydes, and are regio- and diastereoselective (Scheme 7) ⟨89AG(E)472, 91CB1845⟩.



Scheme 7

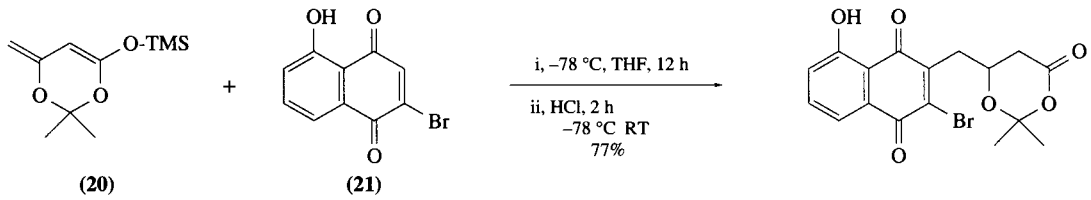
In complementary work carried out by Sato *et al.*, the aldol reactions of achiral silyl dienol ethers (**19**) with aldehydes in the presence of a chiral binaphthol–titanium complex catalyst proceeded by addition at the exocyclic substituent with good to excellent enantioselectivity (33–92% *ee*) (Scheme 8) ⟨95H(41)1435⟩.



R^1R^1 = Me, Me; $(CH_2)_5$
R^2 = Ph, Bu

Scheme 8

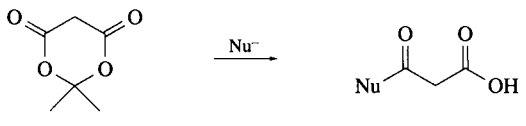
Finally, silyl dienol ethers (**20**) have been shown to react with bromonaphthoquinones (**21**) in a mode described as a formal oxidative addition process (Scheme 9) ⟨91JOC91⟩.



Scheme 9

6.08.5.2.3 Reactivity towards nucleophiles

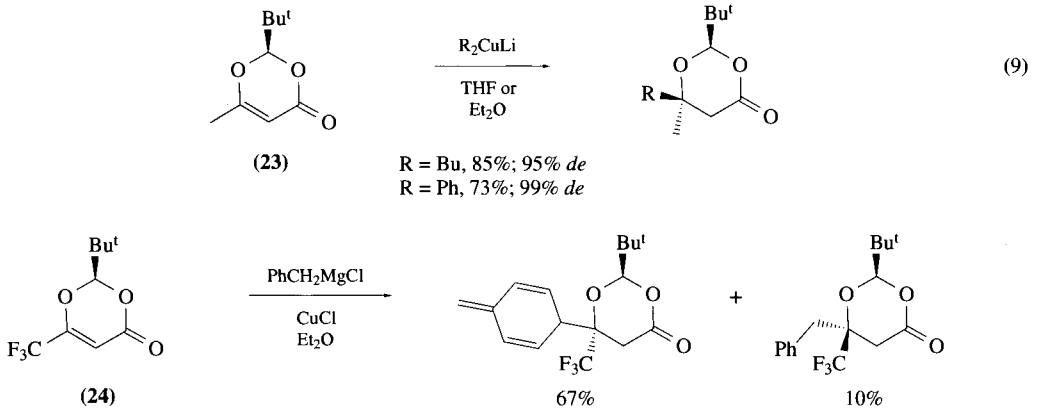
Meldrum's acid (**22**) readily undergoes nucleophilic attack at the 4 and 6 positions, accompanied by ring cleavage and hydrolysis under acidic or basic conditions to give the malonic acid derivatives (Equation (8)) ⟨08JCS598⟩.



(8)

The $\alpha\beta$-unsaturated system of dioxinones can undergo conjugate addition by organocopper

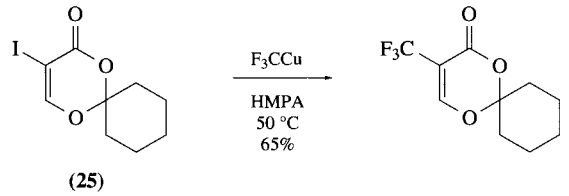
species in excellent yields ⟨88JA4763⟩. Very high diastereoselectivities have been observed in the 1,4-addition of lithium diorganocuprates to enantiomerically pure dioxinones. For example, the addition of lithium dibutylcuprate to (*R*)-2-*t*-butyl-6-methyl-4*H*-1,3-dioxin-4-one (**23**) proceeds in 85% yield with 95% diastereoselectivity ⟨86HCA1147⟩, while addition of lithium diphenylcuprate gives 99% diastereoselectivity (Equation (9)) ⟨88JA4763⟩. The copper(I) iodide catalyzed addition of benzylmagnesium chloride to the 6-trifluoromethyl derivative (**24**) proceeds through an unusual mode of attack of the Grignard reagent (Scheme 10) ⟨92AG(E)1083⟩.



(9)

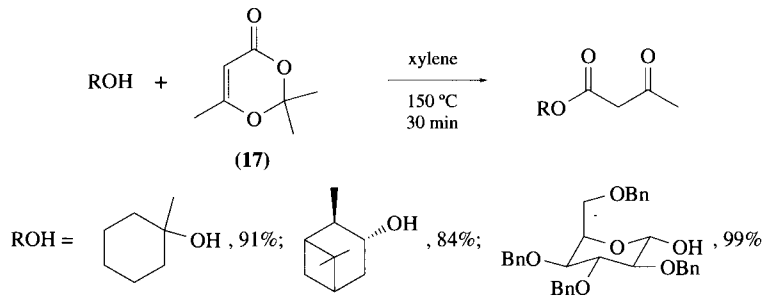
Scheme 10

Trifluoromethyl copper has been shown to react with a 5-iodo-dioxinone (**25**) in the presence of HMPA to give the corresponding 5-trifluoromethyl derivative in 65% yield through an addition–elimination pathway (Equation (10)) ⟨91CC1241⟩.



(10)

Simple alcohols are known to attack α-ketoketenes, derived from dioxinones at elevated temperatures, to give the acetoacetylated products (Equation (11)), typically in excellent yields, as are more complex alcohols such as those derived from steroids and carbohydrates ⟨85JOC2431⟩.



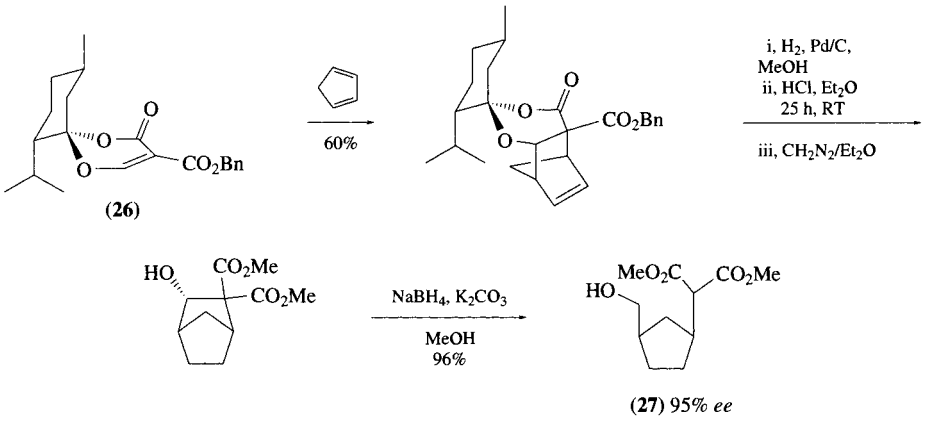
(11)

Other nucleophiles, including thiols and amines, are also acetoacetylated under similar conditions to give β-ketothioesters ⟨90CPB2262⟩ and β-ketocarboxamides respectively ⟨84CPB3848⟩. Intramolecular examples of these reactions are described above (see Section 6.08.5.2.1) ⟨93JOC5011⟩.

6.08.5.2.4 Cyclic transition state reactions

Most examples of cycloaddition reactions in this series of unsaturated heterocycles involve 1,3-dioxin-4-ones. Sato *et al.* has demonstrated that [2 + 2] (see Section 6.08.5.2.1) (Equation (7))

⟨87CPB3971⟩ and [4 + 2] ⟨89CPB2615⟩ pericyclic reactions can take place with variously substituted dioxinones with very high facial selectivities, particularly in the case of chiral 2-spirocyclic-1,3-dioxin-4-ones having a (−)-menthone unit at the 2-position (e.g. (**26**)) where exclusive selectivity is observed (Scheme 11). A mechanism has been proposed to explain the high selectivity ⟨90JCS(P1)1779⟩.



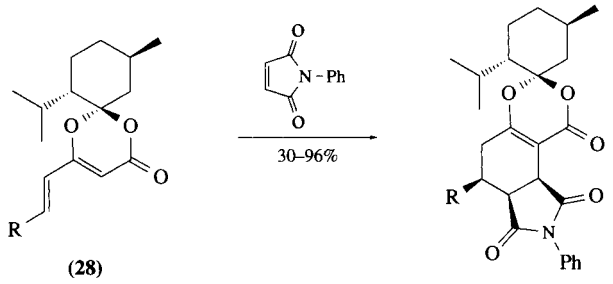
(**26**)

(**27**) 95% *ee*

Scheme 11

The Diels–Alder reaction of these chiral dioxinones with cyclopentadiene has provided a highly stereoselective route to carbocyclic C-nucleoside precursors (**27**) (Scheme 11) ⟨89CPB2615⟩. The [2 + 2] cycloaddition of the same menthone-derived dioxinone with cyclopentene has also been observed ⟨87CPB3539⟩.

The reactions of similarly derived dioxinones, but containing a 6-alkenyl substituent (**28**), with *N*-phenylmaleimide have demonstrated the complementary ability of these systems to act as chiral dienes (Scheme 12) ⟨95LA1455⟩.

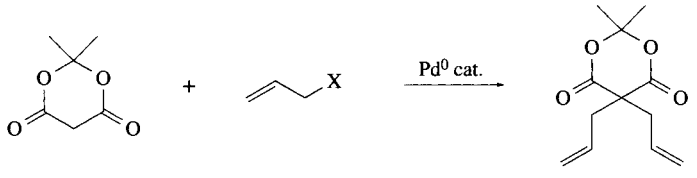


(**28**)

Scheme 12

6.08.5.2.5 Miscellaneous reactions

Meldrum's acid derivatives have been shown to react with allylpalladium complexes derived from a variety of palladium sources. Several types of allylic acetates have been used as substrates, and the major product in these reactions is the diallyl Meldrum's acid derivative (e.g. (**29**)), often formed exclusively (Equation (12)). This and other metal-mediated reactions of Meldrum's acid and its derivatives are thoroughly discussed in a review ⟨91H(32)529⟩.

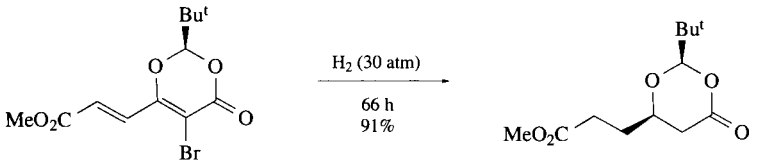


X = OAc, Cl, $OB(OR)_2$

(**29**)

(12)

Catalytic hydrogenation of the C=C double bond in optically pure dioxinone systems (e.g. (**30**)) has been observed in an investigation of the facial selectivity of the double bond towards a variety of reagents, including organocopper species ⟨88JA4763⟩. Hydrogenation has also been used during the synthesis of chiral β-hydroxycarboxylic acids by Seebach and co-workers (Equation (13)) ⟨87HCA2137⟩.



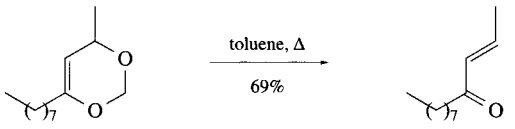
(30) (13)

6.08.5.3 Systems with one Endocyclic or Exocyclic Double Bond

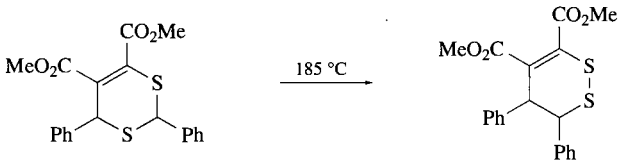
The general reactivity of the 1,3-dithiins and related species has been reviewed ⟨66CHE(21)1028, 72IJS(B)101⟩.

6.08.5.3.1 Unimolecular thermal and photochemical reactions

A thermal retro-Diels–Alder reaction has been observed in substituted dioxin systems, accounting for the production of enones (**31**) upon heating in toluene, presumably with loss of formaldehyde (Equation (14)) ⟨88JA1290, 88TL1111⟩. For 1,3-dithianes and dithiins, however, the main pyrolysis products are generated through skeletal rearrangements. A number of examples of the isomerization of 1,3-dithiins to the thermodynamically more stable 1,2-dithiins (e.g. (**32**)) are known (Equation (15)) ⟨71T5753, 81T3839⟩.



(31) (14)



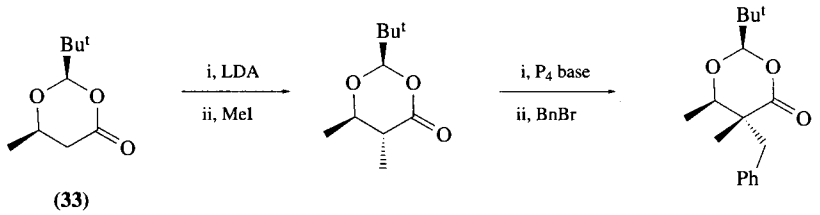
(32) (15)

6.08.5.3.2 Reactivity towards electrophiles

Deprotonation and reaction of the resulting anion with electrophiles is a relatively common process in this series of heterocycles. For example, 1,3-dioxins can be deprotonated with *sec*-butyllithium to give the allylic anion which can subsequently be alkylated ⟨88TL1111⟩.

The deprotonation and alkylation of 2-*t*-butyl-6-methyl-1,3-dioxan-4-ones has been accomplished, in a piece of work related to the aldol reactions of deprotonated 2-*t*-butyl-6-methyl-1,3-dioxin-4-ones, described above (see Section 6.08.5.2.2). Good diastereoselectivities were observed in the reaction of the enolates derived from (*R*)-2-*t*-butyl-6-methyl-1,3-dioxan-4-one (**33**)

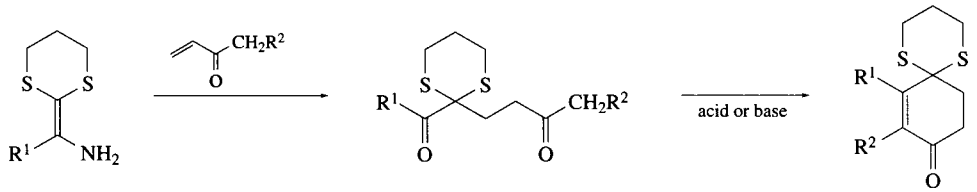
by treatment with either lithium or Schwesinger P4 bases. The anion generated using the P4 base was of higher reactivity (Scheme 13) ⟨91CB1837⟩.



(33)

Scheme 13

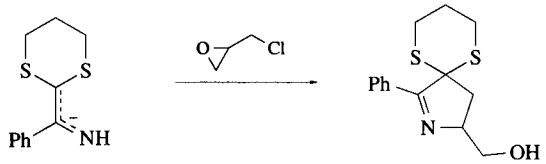
Aminoketene dithioacetals (**34**) undergo conjugate addition to $\alpha\beta$-unsaturated ketones to give δ-diketones, the 1,2,5-triketone mono-dithioacetals (**35**), upon work-up. These δ-diketones may suffer acid- or base-catalyzed cyclization to give cyclohexenedione mono-dithioacetals (**36**) in high yields (Scheme 14) (see also Section 6.08.6) ⟨87CC43, 89SC1655, 89T3819, 89TL7235, 93T10369⟩. The ambident anion (**37**) derived from an aminoketene dithioacetal reacts with epichlorohydrin to give the spiro-fused pyrroline (**38**) (Equation (16)) ⟨87CC775⟩.



(34) (35) (36)

R^1 = Ph, H
R^2 = H, Me

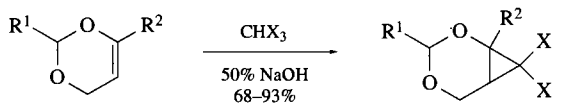
Scheme 14



(37) (38) (16)

6.08.5.3.3 *Reactivity towards carbenes*

Dioxins have been shown to react with dibromo- or dichlorocarbenes in a two-phase system in good to excellent yields to give the cyclopropanation products (**39**) (Equation (17)) ⟨80IZV1648⟩.

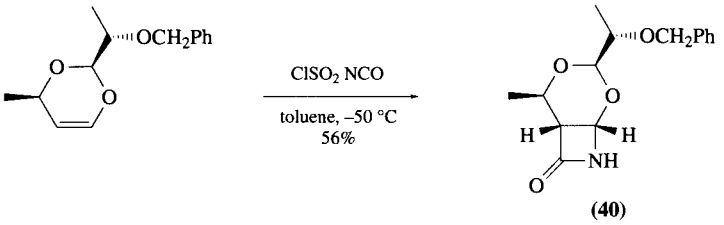


R^1 = H, Ph
R^2 = H, Me

(**39**) X = Cl, Br (17)

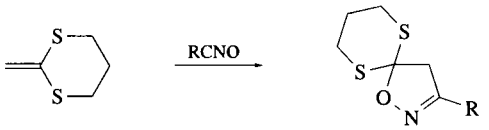
6.08.5.3.4 *Cyclic transition state reactions*

A key intermediate in carbapenem antibiotic synthesis has been prepared through a highly stereoselective [2 + 2] cycloaddition of chlorosulfonyl isocyanate with an optically pure 1,3-dioxin (**40**) derived from methyl (*R*)-3-hydroxybutyrate (Equation (18)) ⟨89TL5631⟩.



(40) (18)

1,3-Dipolar cycloadditions have been carried out by Yamamoto *et al.* using the ketene thioacetal 2-methylene-1,3-dithiane (**41**) as the dipolarophile and nitrile oxides as the 1,3-dipoles (Equation (19)) ⟨87H(26)755⟩.

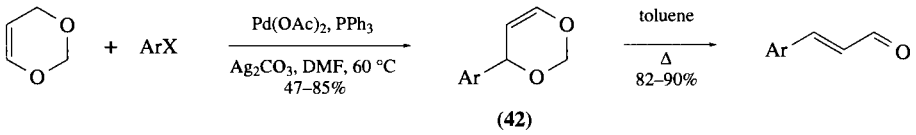


(41) (19)

R = Ph, 95%
R = Me, 87%

6.08.5.3.5 Miscellaneous reactions

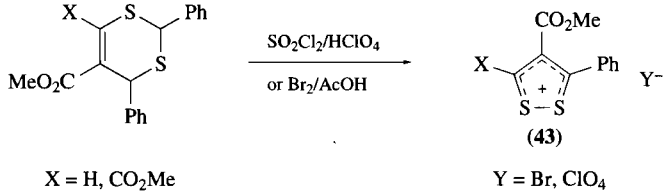
The palladium catalyzed arylation of 1,3-dioxin has been used in the preparation of 4-aryldioxins (**42**). The use of these compounds as β-formylvinyl synthons means that access to aryl derivatives, inaccessible by lithiation and alkylation, is possible (Scheme 15). Use of the asymmetric Heck reaction allowed the synthesis of optically active dioxin derivatives, albeit in modest enantiomeric excess ⟨92TL6845⟩.



(42)

Scheme 15

In the case of 1,3-dithiins, the general chemistry remains relatively unexplored, although the thermal rearrangement of the ring system to give 1,2-dithiins (Section 6.08.5.3.1), and formation of 1,2-dithiolium bromides (**43**) on treatment with bromine (Equation (20)), have been reported ⟨66CHE(21)1028, 72IJS(B)101⟩.



(43) (20)

X = H, CO_2Me Y = Br, ClO_4

6.08.5.4 Fully Saturated Systems

Most of the chemistry associated with this series of heterocycles is a consequence of the acetal moiety. For example, all three saturated systems undergo acetal hydrolysis, the dioxanes being the most acid-sensitive. The chemistry of 1,3-dithianes and 1,3-oxathianes is further dominated by the acidity of the C-2 protons, leading to the use of the derived carbanions as acyl anion equivalents, particularly in the case of 1,3-dithiane derivatives. Oxidation at sulfur is also a common process.

These reactions are indicated schematically in Figure 1. The general reactivity of the dithioacetals has been reviewed ⟨66CHE(21)998, 89T7643, B-95MI 608-04⟩.

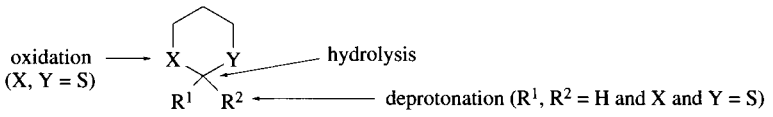
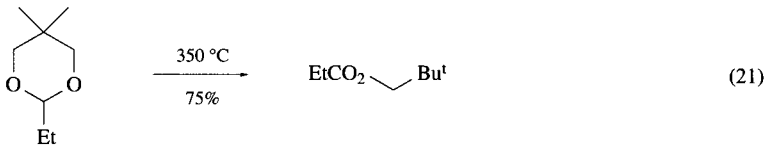


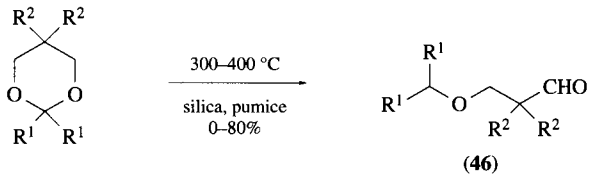
Figure 1 Reaction of 1,3-dioxanes, oxathianes, and dithianes.

6.08.5.4.1 *Thermal and photochemical reactions*

Ring cleavage is known to occur under thermolytic conditions. Rearrangement of 2-substituted 1,3-dioxanes (**44**) to the isomeric esters (**45**) occurs at 350°C (Equation (21)). Lower molecular weight products are also produced ⟨65BSF1358, 72BSF4308⟩. The participation of oxygen-stabilized free radicals appears to account for the products, which are then formed through C—H bond cleavage at the C-2 position. Pyrolysis over pumice or silica leads to isomeric products such as the alkoxyaldehydes (**46**) together with other fragmentation products (Equation (22)) ⟨62JA3307, 62JA3319⟩. 1,3-Oxathianes react in a similar manner ⟨62JA3307⟩.



(21)



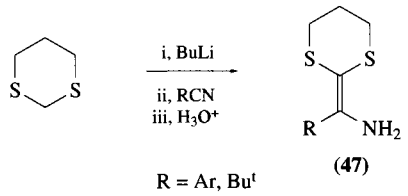
(22)

R^1, R^2 = H, Me, Et, , Ph

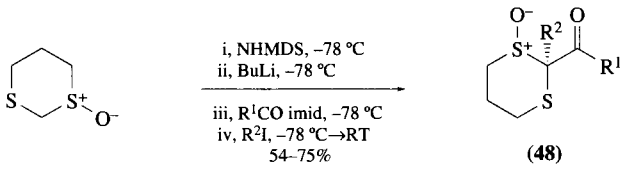
6.08.5.4.2 *Reactivity towards electrophiles*

The commonly encountered C-2 anions derived from 1,3-dithiane and 1,3-oxathiane and their derivatives can be generated by treatment with any of a wide range of bases, but typically *n*-butyllithium (for 1,3-dithianes) or *sec*-butyllithium (sometimes necessary for 1,3-oxathianes). There are many instances where the deprotonated heterocycles have been used in synthesis, usually as acyl anion equivalents ⟨89T7643, B-95MI 608-05⟩. Use of 1,3-dithiane derivatives is by far the most common, and the derived anions react with with a very wide variety of electrophiles ⟨69AG(E)639, 89T7643⟩, whether or not the dithiane system is initially substituted at C-2. For example, 2-lithio-1,3-dithianes react efficiently with alkyl, allyl, and benzyl halides to give simple alkylation products ⟨75JOC231⟩, with aldehydes to give secondary alcohols ⟨92T7265, 93JOC6902⟩, with ketones to give tertiary alcohols ⟨84JOC4912⟩, with epoxides to give primary alcohols ⟨84T2225⟩, and with carboxylic acid derivatives ⟨88JCS(P1)269⟩ including esters (to give ketones) and nonenolizable nitriles (to give primary aminoketene thioacetals (**47**) (Equation (23)) ⟨85CC742⟩, among many others ⟨77S357, 89T7643⟩. Additions to $\alpha\beta$-unsaturated carbonyl compounds are also known; reaction can take place either at the carbonyl group or by conjugate addition, depending on the structures of the reacting components, counterion, conditions, etc. ⟨89T7643, 89TL7235⟩. The addition of 2-metallated-1,3-dithianes to esters and other carboxylic acid derivatives to give 2-acyl-1,3-dithianes can be capricious, due in part to problems of substrate enolization, double addition of the anion to the substrate, and yield limitation caused by deprotonation of the (more acidic) product by the metallated dithiane starting material. The last of these is particularly troublesome in the case of 2-metallated-1,3-dithiane 1-oxides, but can largely be overcome by the use of a sodium counterion, two equivalents

of base to provide complete product deprotonation (see Equation (24): NHMDS = sodium hexamethyldisilylamide), and an *N*-acylimidazole as the electrophile ⟨93TL5159⟩. This solution is ineffective for 2-substituted 1,3-dithiane 1-oxide anions; 2-alkyl-2-acyl-1,3-dithiane 1-oxides (**48**) were prepared in a one-pot procedure by use of the above sequence coupled with a final alkylation (Equation (24)) ⟨93TL5159, 93TL6947⟩. Curiously, the procedure is also ineffective for 1,3-dithianes. Otherwise, the sulfoxide and sulfone systems generally undergo deprotonation and reaction with electrophiles under similar conditions to the 1,3-dithiane systems ⟨89JCS(P1)2441, 91JCS(P1)662, 94CC1653⟩.



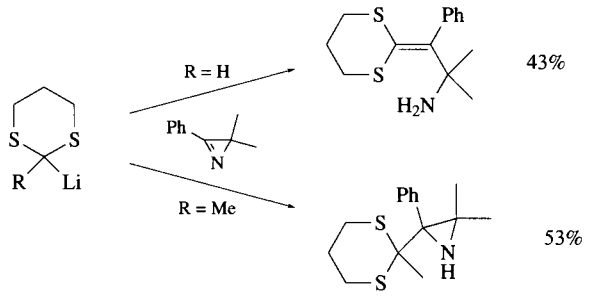
(23)



(24)

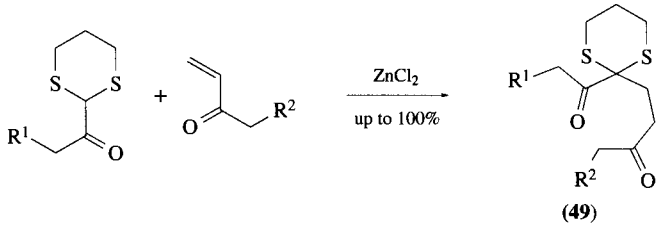
R^1 = Me, Et, Bu, Ar
R^2 = Me, Et, allyl

An interesting example of the reactivity of 2-lithio-1,3-dithiane is seen in the addition to azirines, which yields mixtures of primary allylic amine and *C*-substituted aziridine, the product distribution being influenced by both the azirine and, particularly, dithiane substitution (Scheme 16) ⟨90T5155⟩. The anion derived from 1,3-dithianes is also known to undergo conjugate addition reactions to unsaturated lactones ⟨94JCS(P1)45⟩ and to $\alpha\beta$-unsaturated ketones ⟨89T7643⟩, a reaction which has been used in a synthetic approach to compactin ⟨85JOC1190⟩.



Scheme 16

2-Acyl-1,3-dithianes undergo Lewis acid mediated conjugate addition to $\alpha\beta$-unsaturated ketones to give the 1,2,5-triketone mono-dithioacetals (**49**) (Equation (25)). These δ-diketones undergo acid- or base-catalyzed cyclization to cyclohexenedione mono-dithioacetals in high yields (see Section 6.08.6) ⟨87CC43, 89SC1655, 89T3819, 89TL7235, 93T10369⟩.

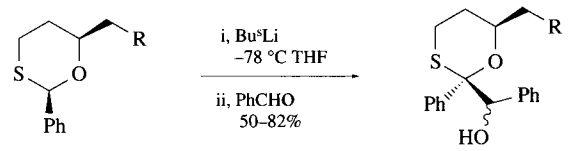


(25)

R^1 = H, Me, Et, MeO
R^2 = Me, Et, Pr, MeO

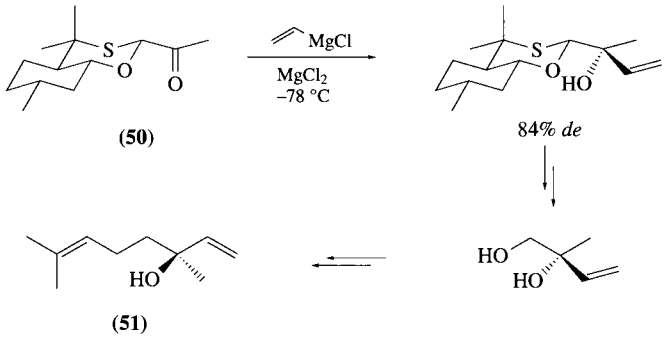
2-Lithio-2-trimethylsilyl-1,3-dithiane also adds to a range of electrophiles ⟨88JCS(P1)269⟩, including ketones and aldehydes, to give the ketene thioacetals through a Peterson elimination process ⟨89JCS(P1)1793⟩, and to nitriles to give aminoketene thioacetals ⟨85CC742⟩. The preparation of a variety of other 2-heterosubstituted-1,3-dithianes has been reported, including 2-thio, 2-stannyl, 2-silyl, 2-methoxy, 2-cyano, and 2-carboxy derivatives, together with their asymmetric sulfoxidation ⟨94SL547, 96T2125⟩.

Anions derived from 1,3-oxathianes are generally more difficult to generate than those of the corresponding 1,3-dithianes, and the use of *sec*-butyllithium is often required. In general, however, 2-acyl-1,3-oxathiane derivatives can be deprotonated with *n*-butyllithium or LDA. They have been shown to react with a range of electrophiles broadly similar to those successful with 1,3-dithiane anions ⟨75JOC231⟩, such as alkyl halides and carbonyl compounds, including a number of 2-heterosubstituted acetates. Silicon, tin, germanium, selenium, lead, sulfur, oxygen, and amino derivatives at the C-2 position have all been prepared ⟨77S357, 85JOC657, 92JOC5162⟩. Some 2-metallated-1,3-oxathianes have been alkylated diastereoselectively (Equation (26)) ⟨92TL725⟩. Reaction of the deprotonated oxathianes with primary alkyl iodides proceeds in excellent yields, while those for secondary/tertiary iodides and other halides are generally much less satisfactory ⟨85JOC657⟩. Reaction with carbonyl compounds proceeds in moderate to excellent yields, and indeed this and related reactions, with chiral oxathianes (**50**) prepared from pulegone, can be highly diastereoselective, and has formed the key step in several natural product syntheses, including enantioselective approaches to (*S*)-(+)-linalool (**51**) (Scheme 17), citramalate, malyngolide, and atrolactic acid derivatives ⟨78JA1614, 81TL2855, 84JOC576, 85TL3907, 86JOC2599⟩.



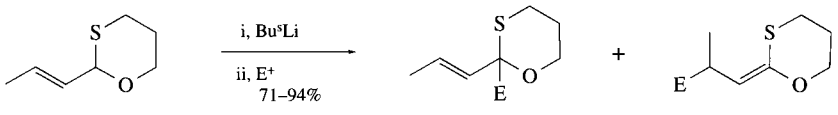
(26)

R = OMOM, NMe_2, $OSiPh_2Bu^t$



Scheme 17

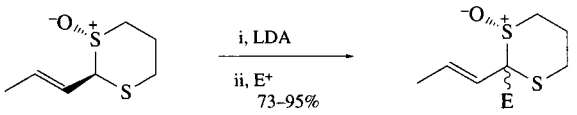
When deprotonation is effected in a 2-allyl-1,3-oxathiane with *sec*-butyllithium, the expected allylic anion is generated. Interestingly, reaction with alkyl halides leads to substitution at the α-terminus (**52**), whereas reaction with carbonyl compounds gives products of substitution at the γ-terminus (**53**) (Scheme 18) ⟨92TL2501⟩. In contrast, when the anion derived from 2-allyl-1,3-dithiane 1-oxide by reaction with LDA was allowed to react with a variety of electrophiles, the reaction proved highly regioselective at the α-position for almost all alkyl halides and aldehydes used (Equation (27)). The reaction with aldehydes is diastereofacially selective ⟨90JOC5515⟩.



(**52**) E = D, Pr, Bu, TMS

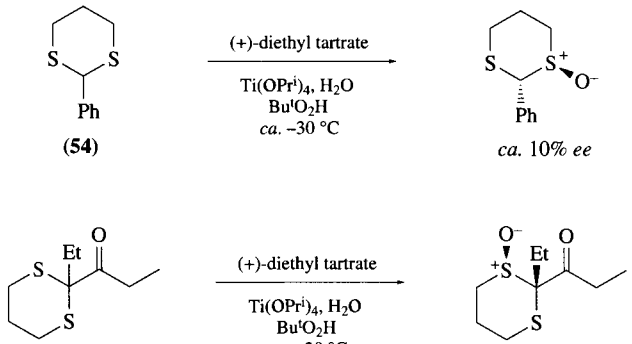
(**53**) E = PhCH(OH), PhC(OH)Me, PhC(OH)Ph

Scheme 18

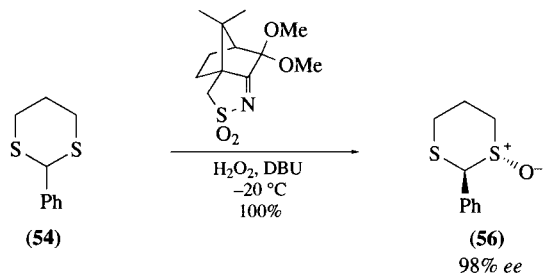


(27)

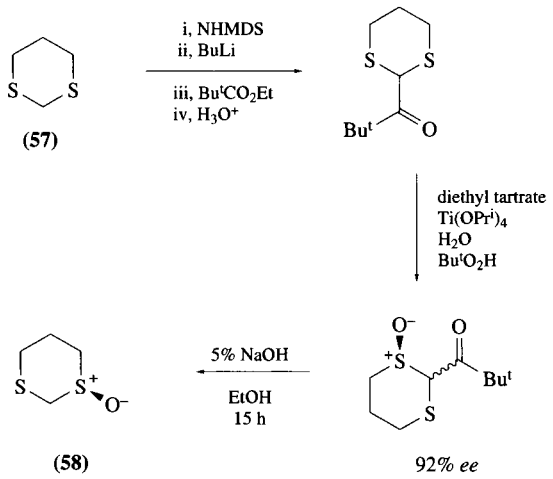
For the sulfur-containing heterocycles of this series, perhaps the most common reagents for attack by the nucleophilic sulfur atoms are electrophilic oxidants. 1,3-Dithiane 1-oxide ⟨93TL2139⟩, 1,3-dioxide, 1,1,3-trioxide ⟨91JCS(P1)662⟩, and 1,1,3,3-tetraoxide ⟨83JCS(P1)1303⟩ and many derivatives have all proved accessible through simple oxidation processes. Typical reagents include mcpba, peracetic acid, sodium periodate, and hydrogen peroxide at low pH, although many other oxidants are successful including a modification of the Payne oxidation procedure ⟨93SC1507⟩. A second oxidation in the 1,3-dithiane system occurs to give the 1,3-dioxide rather than the sulfone; most reagents give the *trans* stereochemistry, and it has been shown that the first oxidation takes place to give equatorial sulfoxide and the second, axial in a chair conformation ⟨95MI 608-01⟩. 1,3-Oxathiane and its sulfoxide and sulfone have also been prepared, along with a number of 2-alkyl derivatives ⟨70ACS2257, 86CL1655⟩. Nonracemic 2-substituted-1,3-dithiane 1-oxide derivatives have been prepared in moderate to high enantiomeric excess using enantioselective sulfoxidation processes, particularly those based upon modified Sharpless oxidation procedures. These reactions generally give disappointing enantioselectivities for oxidation of 1,3-dithiane or simple 2-alkyl derivatives, but can be very successful for substrates containing polar groups, presumably because they aid coordination to the oxidizing species ⟨89JOM(370)43, 90G165, 90SL457, 91JOC5991, 93TL2975, 95TL6537, 96SL404, 96T2125⟩. For example, 2-phenyl-1,3-dithiane (**54**) is oxidized in 10–15% *ee*, but oxidation of 2-ethyl-2-propanoyl-1,3-dithiane (**55**) under the same conditions occurs with 97% *ee* (Scheme 19) ⟨90SL457, 96T2125⟩. Hydrogen peroxide does not induce sulfoxidation directly at high pH, and this feature has been utilized in a catalytic enantioselective sulfur oxidation process driven by hydrogen peroxide, which gives 2-phenyl-1,3-dithiane 1-oxide (**56**) with better than 98% *ee* (Equation (28)) ⟨94TL9629, 95SL773⟩. Enantiomerically pure oxaziridines have also been used to good effect for asymmetric sulfur oxidation in these systems ⟨95SL773, 95TA2911⟩. The parent 1,3-dithiane 1-oxide (**58**) has been prepared in >99% *ee* by resolution via the D-(+)-camphor adduct ⟨78JOC90⟩, and, on a multigram scale, by a three-step procedure involving acylation of (**57**), enantioselective sulfoxidation, and deacylation (Scheme 20) ⟨93TA2139, 94OPPI702, 96T2125⟩, a route also used successfully for 2-alkyl-1,3-dithiane 1-oxides ⟨91SL80, 96T2125⟩. *trans*-1,3-Dithiane 1,3-dioxide has been prepared by a similar route ⟨91JCS(P1)662⟩.



Scheme 19

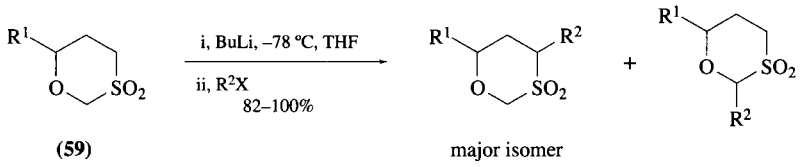


(28)



Scheme 20

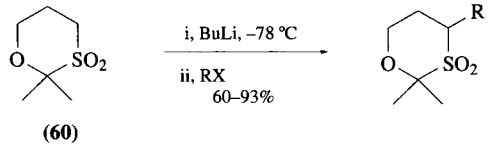
Remarkably, in contrast to the parent 1,3-oxathiane and the corresponding dithiane systems, the sulfones 1,3-oxathiane 3,3-dioxide and its 6-methyl derivative (**59**; R^1 = H, Me), obtained by reaction of the 1,3-oxathianes with *t*-butyl hydroperoxide and molybdenyl acetylacetonate, are deprotonated, and subsequently react with a variety of electrophiles, at the 4-position (Scheme 21) ⟨86CL1655⟩.



R^1 = H, Me
R^2 = D, Me, TMS

Scheme 21

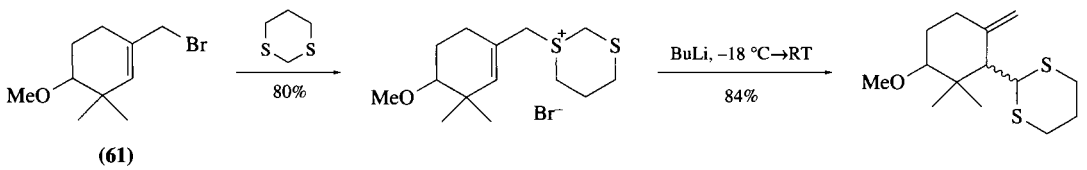
2,2-Dimethyl-1,3-oxathiane 3,3-dioxide (**60**), obtained by oxidation of the parent compound with mcpba, also undergoes efficient deprotonation and alkylation at the 4-position, so acting as a γ-hydroxylpropyl anion equivalent (Equation (29)) ⟨92S852⟩.



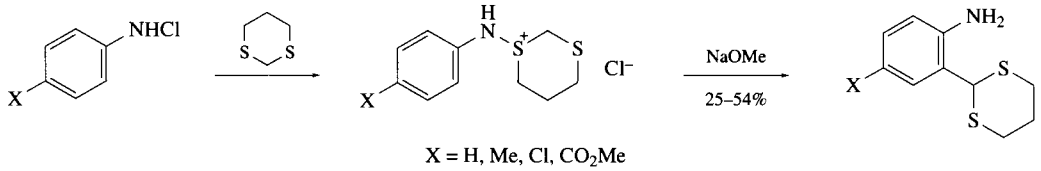
(29)

R = D, Me, Et, TMS, PhCH$_2$

An example of *S*-allylation with an allylic halide (**61**) is shown in Scheme 22. The product undergoes a subsequent [2,3] sigmatropic rearrangement ⟨81BSF(2)192⟩. A related reaction, used for *ortho*-functionalization of anilines, is observed on treatment of *N*-chloroanilines with dithiane (Scheme 23) ⟨78JA7600⟩.



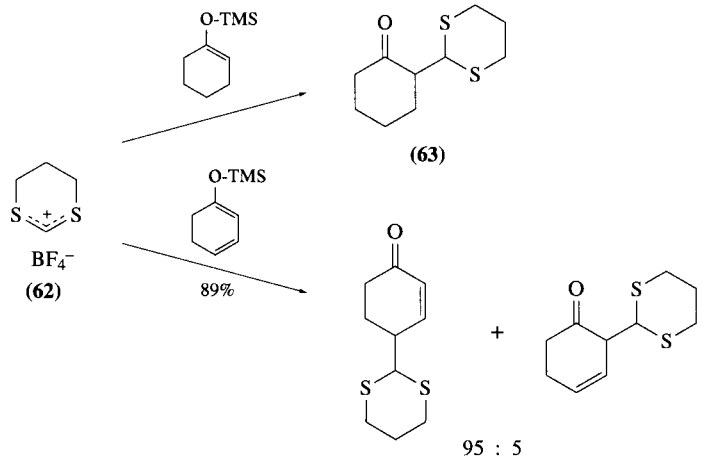
Scheme 22



X = H, Me, Cl, CO_2Me

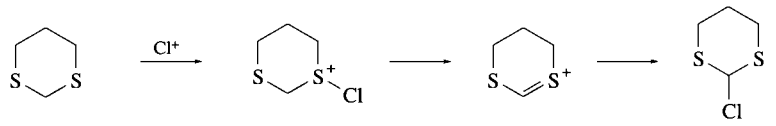
Scheme 23

Formal loss of hydride occurs readily from 1,3-dithiane at the 2-position upon reaction with trityl tetrafluoroborate, possibly through initial electrophilic attack at sulfur ⟨72JA8932⟩. It has been reported that this dithiocarbocation, 1,3-dithienium, or 1,3-dithian-2-ylium, tetrafluoroborate (**62**), is stable and easily handed ⟨85JOC1299⟩. The product reacts with silyl enol and dienol ethers and allylsilanes to give α-1,3-dithian-2-yl ketones (**63**) and enones (Scheme 24) ⟨81TL2829, 81TL2833⟩, and 2-allyl-1,3-dithianes, respectively. These last compounds can also be prepared from allylic aluminum reagents ⟨85JOC1299⟩, or, of course, by treatment of an allyl electrophile with a 1,3-dithiane 2-anion. Reaction of 2-substituted 1,3-dithienium tetrafluoroborates with *N,N*-dialkyl arylamines leads to 2,2-disubstituted products ⟨87CB135⟩. Interestingly, when 2-substituted-1,3-dithianes are treated with bromine in diethyl ether, the corresponding 2-substituted 1,3-dithian-2-ylium tribromides are formed ⟨88CB617⟩.



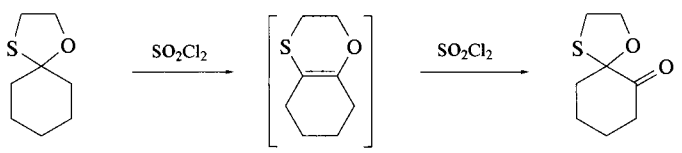
Scheme 24

Reaction of 2-substituted-1,3-dithianes with sulfuryl chloride in strictly anhydrous conditions gives 1,3-dithienium hydrogen dichlorides, which are extremely hygroscopic and hydrolysable ⟨83CB1739⟩. Chlorination of 1,3-dithianes at the C-2 position occurs with common sources of electrophilic chlorine such as sulfuryl chloride or NCS, presumably through initial chlorination at sulfur and Pummerer-type rearrangement (Scheme 25a) ⟨94JOC1672⟩.



Scheme 25a

In contrast, the treatment of the spiro-252-disubstituted 1,3-dithiolane or oxathiolane derived from cyclohexanone with sulfuryl chloride, leads to double rearrangement to the α-keto derivative of the starting material (Scheme 25b) ⟨81JCS(P1)457⟩.



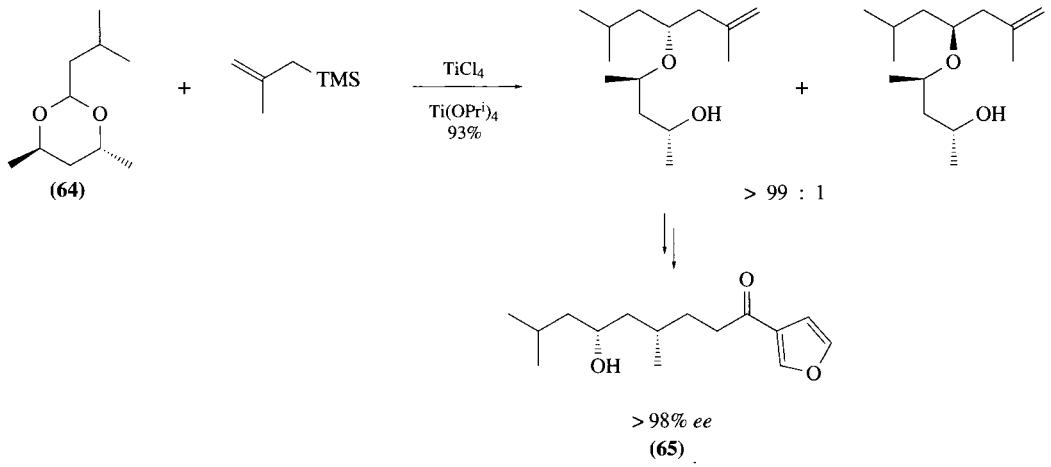
Scheme 25b

Similarly, a variety of substituted 1,3-dioxanes have been shown to react with acid chlorides in the presence of antimony pentachloride to give the corresponding 1,3-dioxan-2-ylium hexachloroantimonates ⟨83KGS464⟩.

The use of 1,3-dithiane and 1,3-oxathiane 2-carbanions as masked acyl anion equivalents of course ultimately requires efficient hydrolytic removal. The wide range of conditions suitable for the hydrolytic removal of the 1,3-dithiane and other acetal moieties have been compared and contrasted ⟨B-73MI 608-01, 82S679, 89T7643, B-91MI 608-01, B-94MI 608-01, B-95MI 608-05⟩. Hydrolysis of the corresponding sulfoxides can often be easier ⟨94TL2607, 95JCS(P1)2673⟩, as can hydrolysis of the 1,3-oxathiane unit ⟨81TL2855⟩. Reductive cleavage to give the methylene group using Raney nickel desulfurization is also possible ⟨B-95MI 608-06⟩.

6.08.5.4.3 Reactivity towards nucleophiles

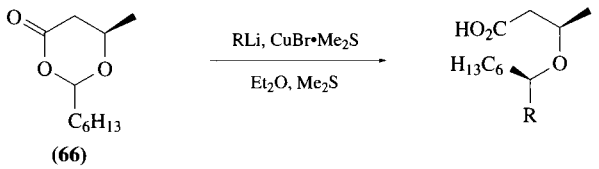
The widespread use of dioxane acetals as protecting groups is a result of their stability towards bases. Further, they do not ordinarily react with common organometallic species such as organolithium, magnesium or copper compounds. The range of reactions of C-nucleophiles with these systems is therefore limited. In the presence of strong Lewis acids, such as $TiCl_4$, however, this pattern of reactivity can be altered, presumably through initial coordination of the Lewis acid at sulfur followed by attack at C-2. Important examples include the Lewis acid-mediated attack of acetals, for example (**64**), by allyl silanes, used in a synthesis of (−)-dihydromyoporone (**65**) (Scheme 26) ⟨84TL3951⟩, silyl enol ethers, well known for acyclic acetals ⟨74CL15⟩, and organometallic reagents ⟨90TA477⟩. Thus, Grignard reagents react with acetals in the presence of $TiCl_4$ to give the monosubstituted ethers in good yields ⟨86AG(E)947⟩. Similarly, acetals react smoothly with organocuprates in the presence of BF_3 in ethereal solution ⟨84TL3075⟩. Remarkably, complex organocopper reagents derived from Grignard reagents, such as $RCu(MgBr_2)$, have been shown to add to certain cyclic acylals (**66**) at C-2, even in the absence of additional Lewis acids (Scheme 27). The carbonyl group in this case is unaffected and the reaction proceeds with complete control over stereoselectivity ⟨86TL2945⟩.



(64)

(65)

Scheme 26



(66)

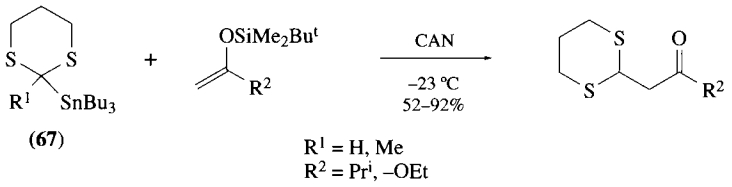
R	*Yield*(%)	*de*
Me	58	94
Ph	90	97

Scheme 27

In a related process, the reaction of 2-chloro-1,3-dithiane with a range of Grignard reagents, presumably with participation by the sulfur lone pairs, has been shown to proceed in good yields ⟨79JOC1847⟩.

6.08.5.4.4 Reactivity towards radicals

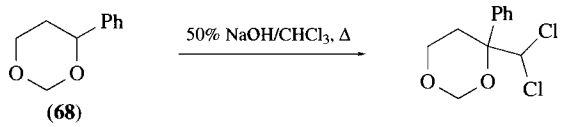
The reactivity of these heterocycles towards hydrogen atom abstraction at C-2 has been shown to increase in the expected order, from 1,3-dioxane, through 1,3-oxathiane, to 1,3-dithiane. Hydrogen atom abstraction from C-2 in 4-methyl-1,3-dioxane, 2,4-dimethyl-1,3-dioxane, and 2-ethyl-4-methyl-1,3-dioxane has also been investigated ⟨77MI 608-01⟩. The radical-mediated alkylation of 2-stannyl-1,3-dithianes (**67**) with alkenes and enol ethers has been observed (Equation (30)) ⟨92CL1229⟩.



(67) (30)

6.08.5.4.5 Reactivity towards carbenes and nitrenes

The reaction of carbenes with dioxanes can give rise to C—H insertion products. In the case of 4-phenyl-1,3-dioxane (**68**), reaction with dichlorocarbene generated *in situ* results in insertion at the C(4)-H bond (Equation (31)) ⟨87ZOR2022⟩. The same regioselectivity is observed in the reaction with chlorophenyl carbene, but in much lower yield ⟨88ZOR1790⟩. 1,3-Dithiane has been observed to react with phenyl nitrene in very low yield with much product decomposition under the reaction conditions ⟨78JA7600, 82CC763⟩.

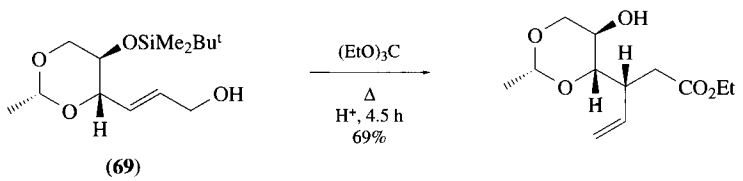


(68) (31)

6.08.5.4.6 Cyclic transition state reactions

After alkylation at sulfur with an allylic electrophile, 1,3-dithiane has been shown to undergo [2,3] sigmatropic rearrangement upon deprotonation with butyllithium (see Scheme 22) ⟨81BSF(2)192⟩. Several related reactions are known (see Scheme 23) ⟨78JA7600⟩ (Section 6.08.5.4.2).

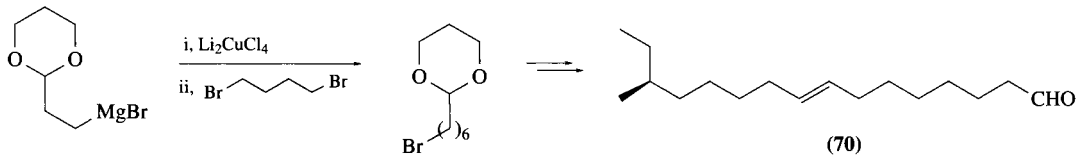
The use of sugar-derived dioxanes (e.g. (**69**)) as chiral auxiliaries in Claisen rearrangements with optically pure substrates has been investigated by Tadano *et al.* (Equation (32)) ⟨90JOC2108⟩.



(69) (32)

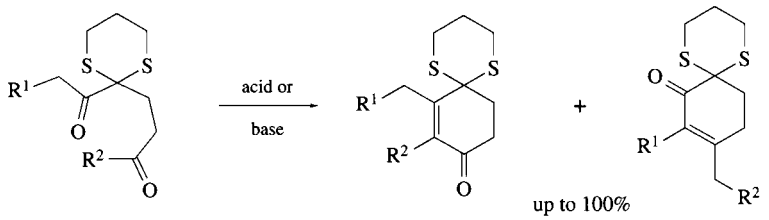
6.08.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

In general, most reactions carried out at substituents attached to carbon in these systems are predictable from general functional group chemistry, and often involve simple transformations where the heterocycle is acting merely as a masked carbonyl group ⟨88JCR(S)302⟩. For example, in the 1,3-dioxane series, acetals of 3-bromopropanal are commonly used as homoenolate equivalents, with lithium or magnesium counterions ⟨87SC385⟩, or even as cuprate reagents. The reaction has been used in the synthesis of trogodermal (**70**) (Scheme 28) ⟨82TL3587⟩.



Scheme 28

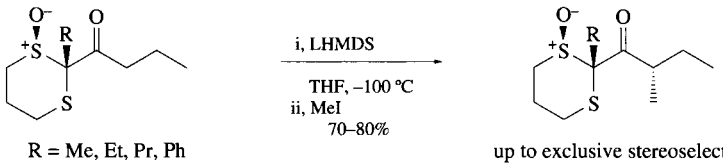
1,2,5-Triketone mono-dithioacetals, δ-diketones prepared from 2-acyl-1,3-dithianes (Section 6.08.5.4.2) or aminoketene dithioacetals (Section 6.08.5.3.2), undergo acid- or base-catalyzed cyclization to give cyclohexenedione mono-dithioacetals in high yields (Schemes 14 and 29) ⟨87CC43, 89SC1655, 89T3819, 89TL7235, 93T10369⟩. The ambident anion derived from aminoketene dithioacetals reacts with epichlorohydrin to give nitrogen heterocycles (see Equation (16)), Section 6.08.5.3.2) ⟨87CC775⟩.



Scheme 29

In some cases however, the heterocycle plays a role in the reaction at the substituent, and this can be of particular interest where the stereochemical outcome of the reaction is affected. Several chiral auxiliaries/asymmetric building blocks have been based upon this principle (e.g. Equation (32)).

Enolates derived from 2-acyl-1,3-dithiane 1-oxides undergo highly diastereoselective intermolecular ⟨89JCS(P1)185, 89JCS(P1)2441⟩ and intramolecular ⟨93TL6947⟩ alkylation, Mannich reactions ⟨93JOC6902⟩ and amination ⟨94TL2427⟩ (Equations (33)–(36)). The methodology has been used to prepare a number of biologically active α-substituted propanoic acids with high enantiomeric excesses (Scheme 30) ⟨94TL2607, 95JCS(P1)2673⟩. The observed stereoselectivity is rationalized by invoking chelated chair conformations coupled with steric control over the approach of the electrophile (Figure 2).



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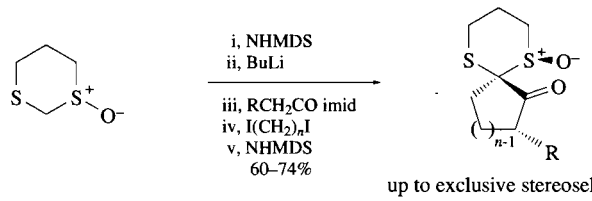

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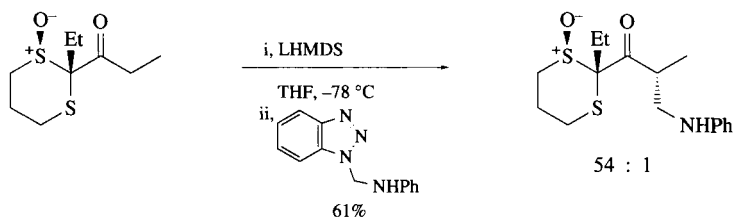

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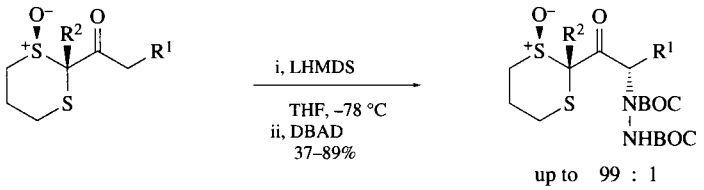

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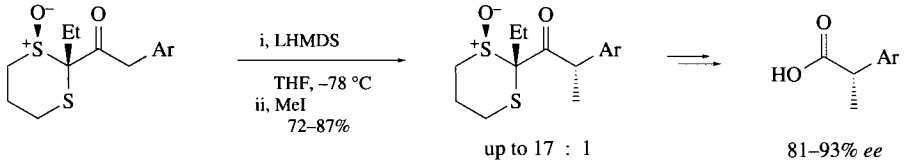


Scheme 30

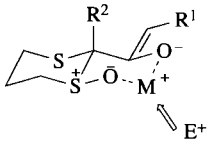
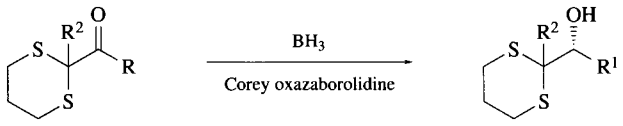


Figure 2 Conformation of enolate of 2-acyl-1,3-dithiane 1-oxide.

Only moderate diastereoselectivity is observed in enolate bromination in these systems, using *N*-bromosuccinimide as the source of halogen. In this case only, equilibration at the new asymmetric center in the products appears to take place, limiting the available stereoselectivity ⟨95T1285⟩.

Reduction of 2-acyl 1,3-dithianes and oxathianes has been carried out by several methods. The Corey oxazaborolidine gives very high enantioselectivities (up to 96% *ee*) in the reduction of a variety of 2-acyl-1,3-dithianes (**71**) (Equation (37)) ⟨90TL7415⟩. Very high diastereoselectivity has also been observed in the reduction of 2-acyl-1,3-oxathianes. Reduction with $Zn(BH_4)_2$ gave the opposite sense of asymmetric induction to that observed using $YCl_3/Zn(BH_4)_2$. High yields were obtained ⟨92CL2173⟩.

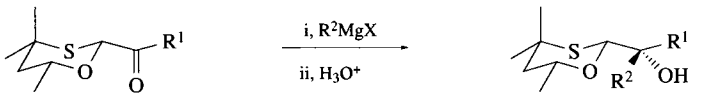


(**71**) R^1 = Me, Et; R^2 = Me, Pr, Bn, Ph — 60–96% *ee*

(37)

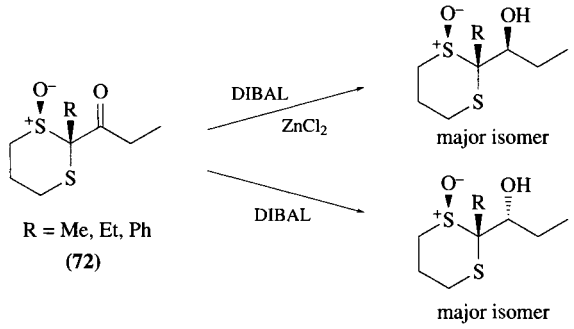
2-Acyl-1,3-dithiane 1-oxides (**72**) undergo carbonyl group reduction by DIBAL in the presence of zinc chloride with very high diastereoselectivity ⟨90SL460⟩. The observed stereoselectivity is again rationalized through chelation phenomena together with steric control over the approach of the nucleophile. Reversal of the sense of induced diastereoselectivity is usually observed in the absence of $ZnCl_2$ (Scheme 31), in accord with the work of Solladié *et al.* on β-ketosulfoxide substrates ⟨82TL5047, 85TL435⟩.

The addition of Grignard reagents to enantiomerically pure 2-acyl-1,3-oxathianes (**73**) occurs with high diastereoselectivity (Equation (38)) ⟨88JA484⟩. Similar reactions mediated by ytterbium give the opposite sense of asymmetric induction ⟨90JA8189⟩. 2-Acyl-1,3-dithiane 1-oxides also provide high diastereoselectivities on addition of Grignard reagents, and again the observed stereoselectivity is rationalized through chelation and steric approach control ⟨89JCS(P1)1158, 93T10355⟩.



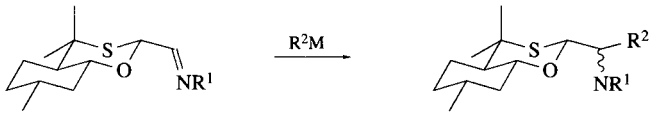
(**73**) R^1 = Me, Et, P, vinyl, Ph, Bu^t; R^2 = Me, Et, Pr, vinyl, Ph, HC≡C; X = Cl, Br, I — major isomer up to > 99 : 1

(38)



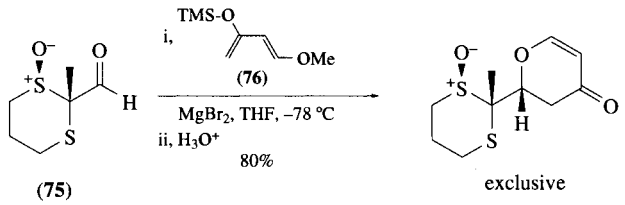
Scheme 31

The addition of a variety of organometallic reagents to imines and hydrazones (**74**) of 2-acyl-1,3-oxathianes derived from pulegone proceeds with very high diastereoselectivity (Equation (39)), the addition of lanthanide salts reversing the sense of asymmetric induction ⟨90JA8189, 94CL831⟩.



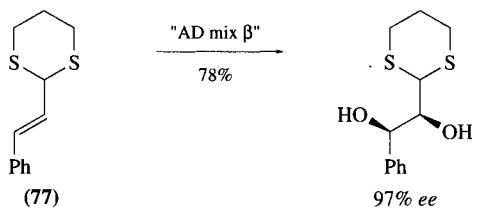
(39)

2-Formyl-2-methyl-1,3-dithiane 1-oxide (**75**) shows high diastereofacial selectivity in the hetero-Diels–Alder reaction with Danishefsky's diene (**76**) (Equation (40)). The stereoselectivity obtained was highly dependent on the Lewis acid used, only magnesium bromide providing high selectivity ⟨91SL84⟩. Conjugate addition of various organocuprate reagents to $\alpha\beta$-unsaturated 2-acyl-1,3-dithiane 1-oxides has been investigated, and stereoselectivities of up to 10:1 were observed ⟨90JCS(P1)167⟩.



(40)

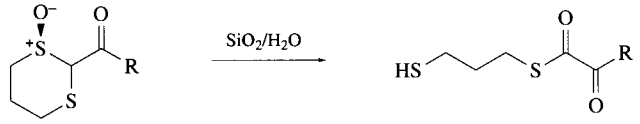
In another highly enantioselective process, asymmetric dihydroxylation of the alkene moiety of a 1,3-dithiane-protected cinnamaldehyde derivative (**77**) gave the corresponding diol in 78% yield and 97% *ee* (Equation (41)) ⟨94TL5129⟩.



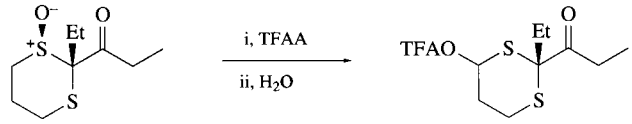
(41)

6.08.7 REACTIVITY OF SUBSTITUENTS ATTATCHED TO RING HETEROATOMS

There are no examples of reactions of substituents attatched to ring oxygen atoms. In the 1,3-dithiane-oxide series, however, Pummerer rearrangement of the sulfoxide moiety has been observed in both the mono- and disulfoxide systems (Equations (42)–(44)) ⟨94CC1653, 95S73⟩.



(42)



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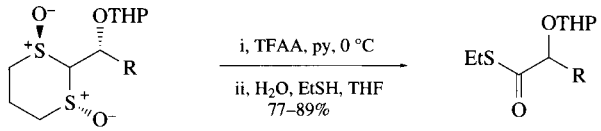


(44)

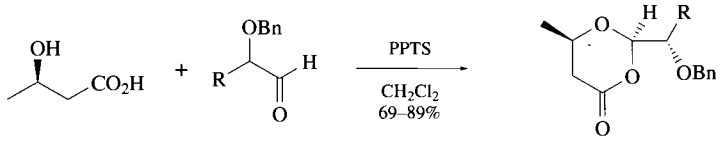
As described above (see Sections 6.08.5.4.6 and 6.08.5.4.2), alkylation of 1,3-dithiane at sulfur with an allylic electrophile can lead to [2,3] sigmatropic rearrangement (Schemes 22 and 23) ⟨78JA7600, 81BSF(2)192⟩.

6.08.8 HETEROCYCLE SYNTHESIS

6.08.8.1 Condensation of 1,3-diols and Congeners with Carbonyl Groups

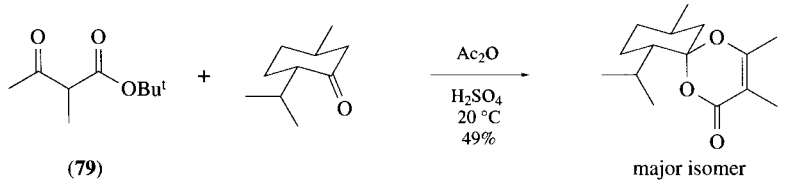
This type of reaction is by far the most common method for the synthesis of the saturated ring systems, usually involving the acid-catalyzed condensation of an aldehyde or ketone with a 1,3-diol, 1,3-hydroxythiol or 1,3-dithiol to give the 1,3-dioxane, 1,3-oxathiane or 1,3-dithiane respectively ⟨81TL2855, 89T7643, B-95MI 608-04⟩. Mineral or Lewis acids are normally used, but the reaction may also be catalyzed by phosphorus pentoxide ⟨83RCR350⟩ or ion-exchange resins including Amberlyst-15 ⟨79JCS(P1)158⟩. Silica gel treated with thionyl chloride has been shown to be a highly selective catalyst for thioacetalization. The rates of formation of the 1,3-dithiane derived from aldehydes are sufficiently higher than those for ketones to allow the selective thioacetalization of aldehydes in the presence of ketones ⟨86JOC1427⟩.

The reaction is not restricted to 1,3-diols and the sulfur analogues. The cyclization of a β-hydroxy acid or β-hydroxy ester (**78**) with a carbonyl compound or an acetal gives a dioxanone (Equation (45)), a reaction which has been used in the synthesis of a key intermediate for 1β-methyl carbapenem production ⟨87HCA448, 89TL5631, 91T5689, 92T55⟩. Similarly, β-keto esters (**79**), when reacted with carbonyl compounds, give dioxinones (Equation (46)) ⟨87TL1051, 90JHC25, 91LA283, 91T5689⟩. Meldrum's acid is typically prepared by the condensation of malonic acid and acetone in the presence of concentrated sulfuric acid, with acetic anhydride used as the solvent ⟨48JA3426⟩. An unusual, but related, method for the synthesis of this compound involves the reaction of carbon suboxide, prepared by the dehydration of malonic acid, with acetone in the presence of oxalic acid ⟨24LA(439)76⟩.



(45)

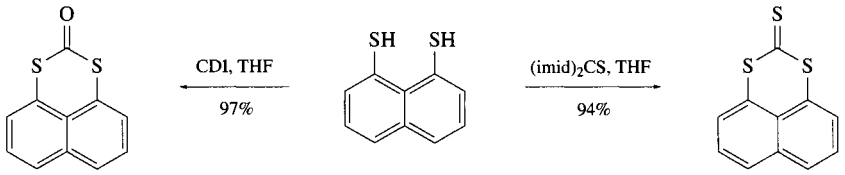
(**78**) R = H, Me — up to exclusive stereoselectivity



(46)

(**79**) — major isomer

Benzodithiins can be prepared from the appropriate dithiols and aldehydes using similar condensation reactions ⟨55AG304, 63LA(661)84⟩. A related example is the synthesis of the *peri*-naphtho-bridged thiocarbonates by reaction of the dithiol (**80**) with carbonyl or thiocarbonyl diimidazole (Scheme 32) ⟨86CL551⟩.

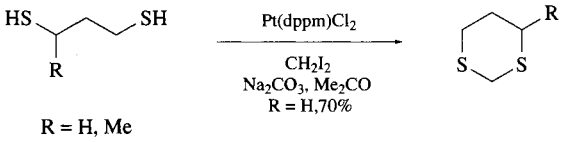


(80)

Scheme 32

trans-Thioacetalization can be used in some cases with reactive aldehydes, although the intention is usually deprotection. For example, the silicon reagents trimethylsilyl triflate and *t*-butyldimethylsilyl triflate catalyse the deprotection of dithioacetal-protected aldehydes and ketones by *trans*-thioacetalization upon heating under reflux with 4-nitrobenzaldehyde ⟨91CC1750⟩.

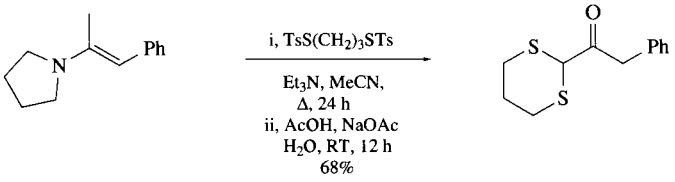
Less common methods of acetal generation involve the reaction of 1,3-diols with alkynes ⟨B-57MI 608-01⟩, and the reaction of aldehydes with 2-stanna-1,3-dithianes to give thioacetals, catalyzed by organotin triflates, in good to excellent yields. Various types of carbonyl group are differentiated ⟨93JOC4971⟩. The generation of thioacetals from dithiols and geminal dihalides is catalyzed by platinum complexes, in a reaction particularly useful for preparing thioacetals of formaldehyde (Equation (47)) ⟨88TL4477, 92T5933⟩.



R = H, Me

(47)

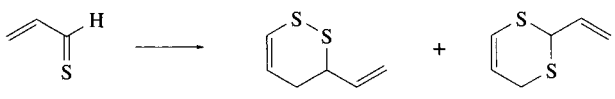
In a complementary process, the reaction of active methylene compounds, and derivatives such as the enamine shown, with ditosylated 1,3-dithiols, derived from the reaction of 1,3-dibromopropane with potassium thiotosylate, can provide unusually substituted 1,3-dithianes (Equation (48)) ⟨71JOC1137⟩.



(48)

6.08.8.2 [4 + 2] Cycloaddition

The Diels–Alder reaction has been used to prepare unsaturated ring systems in this series. A common example is the dimerization of $\alpha\beta$-unsaturated thiocarbonyl compounds (Equation (49)) ⟨86JA7045⟩. These thiocarbonyl compounds are commonly unstable at room temperature, but can be generated *in situ* in a number of ways ⟨B-78MI 608-01, B-95MI 608-07⟩. A number of examples have been observed ⟨90H(31)701⟩.

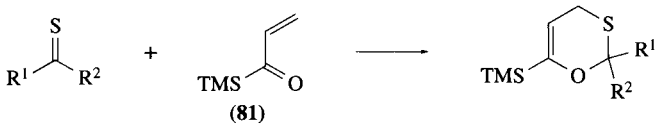


1 : 4.4

(49)

1,3-Oxathiins have also been synthesized by related cycloaddition reactions. Thioketones were treated with the acyl silane (**81**), and the adducts were obtained in good to excellent yields (Equation

(50)). The authors noted that sulfoxidation with mcpba leads to greatly increased stability of the adducts ⟨91T2971⟩.

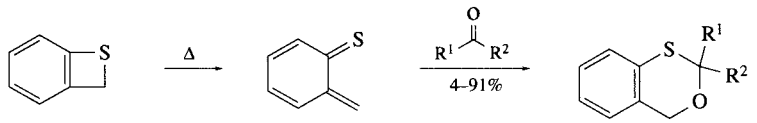


(50)

(81)

R^1	R^2	*Yield (%)*
4-tolyl	4-tolyl	100
Ph	TMS	100

A related synthesis of benzoxathiins has been reported, in which benzothiete (**82**) was ring-opened, and the unstable product (**83**) trapped with electron deficient carbonyl compounds (Scheme 33) ⟨90CB1143⟩. Yields are extremely dependent upon the nature of the carbonyl compound.



(82) (83)

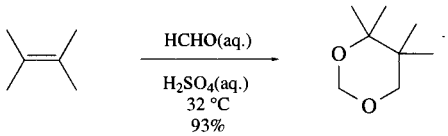
Scheme 33

Dipivaloyl ketone, generated by flash vacuum pyrolysis of a furandione, undergoes two different modes of [4 + 2] dimerization in high yields, depending upon the conditions used, to give different 1,3-dioxinone products ⟨91JA4234, 92JOC7078⟩.

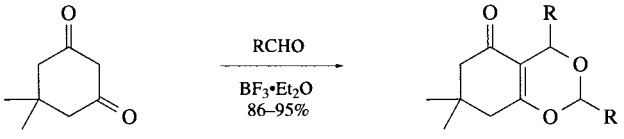
6.08.8.3 Other Syntheses

6.08.8.3.1 [2 + 2 + 2] types

The reaction of excess formaldehyde with alkenes in the presence of aqueous acid gives 1,3-dioxanes through the Prins reaction (Equation (51)). The reaction is known to be catalyzed by a variety of inorganic acids, Lewis acids and ion-exchange resins, and has been reviewed ⟨77S661⟩. In a similar process, treatment of cyclic 1,3-diketones with aliphatic aldehydes in the presence of $BF_3 \cdot OEt_2$ leads to 1,3-dioxins (Equation (52)), a reaction used in the synthesis of a plant growth regulator ⟨82AJC1411, 88JOC4314⟩. A related reaction occurs between α-silyloxypropargyl trimethylsilanes (**84**) and aliphatic aldehydes in the presence of titanium tetrachloride, to give 5-allenylidene-1,3-dioxanes (**85**) (Equation (53)) ⟨86T2501⟩; other acid-catalyzed reactions occur between aldehydes and hydroquinones to give 1,3-benzodioxin-6-ols ⟨94BCJ1371⟩. This type of reaction has also been carried out with ion-exchange resins on variously substituted hydroquinones ⟨82SC533⟩, and nitro-, formyl-, acetyl-, and carboxy-substituted benzodioxins have all been synthesized in this way ⟨84JHC517⟩.

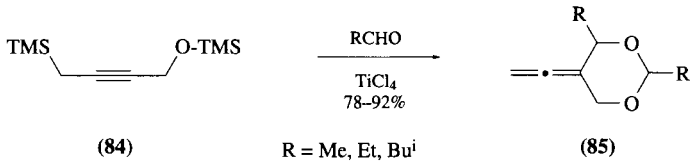


(51)



(52)

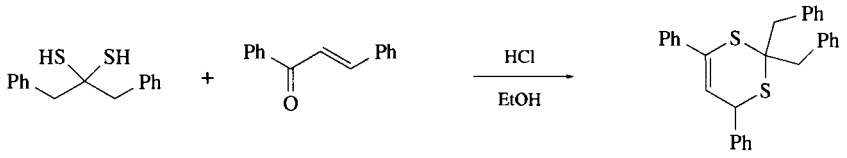
R = Et, Pr, Bu^s



(84) R = Me, Et, Bu^i (85) (53)

6.08.8.3.2 Preparation from geminal dithiols

Dithiins are produced by the reactions of geminal dithiols with enones such as chalcone and benzylidene acetophenone (Equation (54)) ⟨62JOC4488, 66BSF1920⟩. Treatment of geminal dithiols with malononitrile also gives rise to 1,3-dithiins (Equation (55)) ⟨62JPR211⟩.



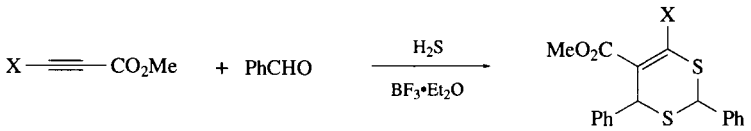
(54)

(55)

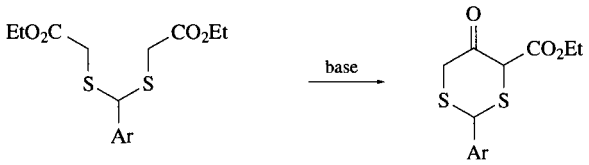
R, R = Me, Me, $-(CH_2)_4-$, $-(CH_2)_5-$

6.08.8.3.3 Miscellaneous reactions

The reaction of propargylic esters with aldehydes and hydrogen sulfide in the presence of boron trifluoride etherate leads to 1,3-dithiins (**86**) (Equation (56)) ⟨71T5753⟩. Dieckmann cyclization of suitably substituted acyclic 1,3-dithioacetals gives rise to 1,3-dithian-5-ones (**87**) (Equation (57)) ⟨59LA(624)79, 63LA(661)84⟩.

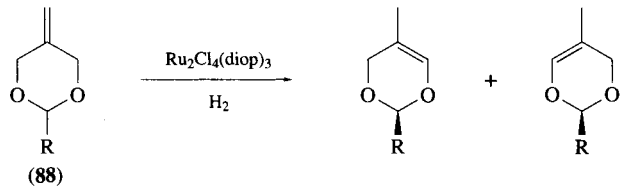


X = H, CO_2Me (86) (56)



(87) (57)

In an interesting process, the prochiral 2-substituted 5-methylidene-1,3-dioxane (**88**) was isomerized to give a mixture of the enantiomeric dioxins using a chiral ruthenium catalyst. Enantiomeric excesses ranged from 13 to 38% (Equation (58)) ⟨94SL517⟩.



(88) (58)

6.08.9 IMPORTANT COMPOUNDS AND APPLICATIONS

Dithianes substituted at the 2 and 5 positions, and their sulfoxides, are insecticidal agents. Optimum activity was observed for 5-*t*-butyl derivatives with either 2-phenyl or 2-cyano substituents ⟨92MI 608-02⟩. The mode of action is thought to be similar to that of the insecticidal 2,6,7-trioxabicyclo[2.2.2]octanes. Investigations of the oxidation, metabolism, and photoactivity of these materials have been carried out ⟨92MI 608-03, 92MI 608-04, 94JMC133⟩. In related work, 2,5-disubstituted-1,3-dithianes containing acid functionalities have proved to be potent blockers of the γ-aminobutyric acid (GABA) gated chloride ion channels, which are important in neurotransmission, particularly with regard to neurological abnormalities ⟨93BMC2671⟩.

5-*t*-Butyl-2-phenyl-1,3-dithianes and dithiane oxides have been synthesized with ^{14}C, ^{18}F, and ^{125}I labeling to act as probes of the GABA receptor complex ⟨95JMC2663⟩.

Since the early 1980s, many 2,5-disubstituted-1,3-dithianes, 1,3-oxathianes, and 1,3-dioxanes have been reported as new types of liquid crystal materials. The heterocyclic ring is almost invariably synthesized by thioacetalization processes. As well as achiral and racemic 1,3-dioxanes ⟨79JAP54160916⟩, oxathianes ⟨86BCJ1337⟩, and dithianes ⟨83EGP160061, 95CL133⟩, a number of non-racemic dithiane chiral liquid crystals have been prepared ⟨86BCJ3877, 90BCJ3063⟩.

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6.09
1,4-Dioxins, Oxathiins, Dithiins and their Benzo Derivatives

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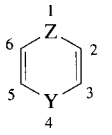
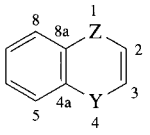
6.09.1 INTRODUCTION

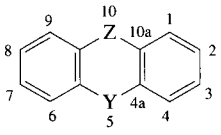
The present chapter embraces a particularly wide variety of ring systems. In the fully unsaturated compounds, the more comprehensively studied include 1,4-dioxin (**1**), first prepared in the 1930s, and 1,4-dithiin (**2**), obtained two decades later. Examples of 1,4-oxathiins are rare and indeed the parent compound (**3**) was first described only in 1980. The monobenzo-fused derivatives (**4**), (**5**), and (**6**) of all three rings have been investigated but it is the dibenzo analogues, dibenzo[*b*,*e*][1,4]dioxin or oxanthrene (**7**), thianthrene (**8**), and phenoxathiin (**9**) which are perhaps the best known. It should be noted that, although oxanthrene is now the IUPAC-recommended name for (**7**), *Chemical Abstracts* continues to use the dibenzodioxin name. Ring numbering is as shown in the formulae (**1–9**), with oxygen taking priority over sulfur, when both heteroatoms are present.



(**1**) Z = Y = O
(**2**) Z = Y = S
(**3**) Z = O, Y = S

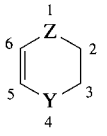


(**4**) Z = Y = O
(**5**) Z = Y = S
(**6**) Z = O, Y = S

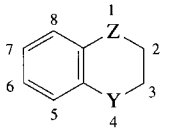


(**7**) Z = Y = O
(**8**) Z = Y = S
(**9**) Z = S, Y = O

Most partially saturated ring systems are well investigated, with 2,3-dihydro-1,4-dioxin (**10**), 2,3-dihydro-1,4-dithiin (**11**), 2,3-dihydro-1,4-oxathiin (**12**), 2,3-dihydro-1,4-benzodioxin (**13**), 2,3-dihydro-1,4-benzodithiin (**14**), and 2,3-dihydro-1,4-benzoxathiin (**15**) being first described in fairly early work.



(**10**) Z = Y = O
(**11**) Z = Y = S
(**12**) Z = O, Y = S



(**13**) Z = Y = O
(**14**) Z = Y = S
(**15**) Z = O, Y = S

Saturated ring systems have long been known. 1,4-Dioxane (**16**), frequently used as a solvent, has been known to the organic chemist for the past 85 years. 1,4-Dithiane (**17**) and 1,4-oxathiane (**18**),

the analogues of 1,4-dioxane in which both or one of the oxygen atoms are replaced by sulfur, were first prepared at the turn of the century.

(16) Z = Y = O
(17) Z = Y = S
(18) Z = O, Y = S

Earlier major reviews have appeared in both the Elderfield and the Weissberger–Taylor series. Contributions to the former deal with rings containing two oxygen atoms ⟨B-57MI 609-01, B-57MI 609-02⟩ and with their sulfur and sulfur–oxygen analogues ⟨B-57MI 609-03⟩ whilst the latter, a very comprehensive treatise, discussed all the multi-sulfur and sulfur–oxygen six-membered heterocycles known at that time ⟨66HC(21-2)611⟩.

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), published early in 1984, Cook exhaustively reviewed the six-membered rings with more than one oxygen or sulfur atom ⟨84CHEC-I(3)943⟩. In 1990, Joule in *Advances in Heterocyclic Chemistry* provided a very comprehensive discussion of the structure, physical properties, reactivity, and synthesis of thianthrenes ⟨90AHC(48)301⟩.

6.09.2 THEORETICAL METHODS

Numerous theoretical studies deal with the structural and physicochemical properties of the unsaturated series of compounds, and calculations have been performed at various levels of sophistication.

Calculations of geometry have been concerned particularly with whether the rings are planar or folded. All computational methods predict planar structures for dioxin ⟨86H(24)2757, 88JOC2127, 88JST(163)111⟩. Studies on dithiin, in contrast, are conflicting. HMO ⟨58JA5543⟩, EHT ⟨68JST(1)489⟩, and *ab initio* STO-3G basis set calculations with partial geometry optimization ⟨81JST(85)159⟩ all predict boat forms with boat-to-boat interconversion barriers of 6.4, 2.2, and 14.6 kcal mol^{-1}, respectively. *Ab initio* calculations with STO-3G basis set including gradient complete geometry optimization ⟨82JA7136⟩ and MNDO calculations ⟨82JA7136, 87MI 609-01⟩ predict planar structures. Moreover, puckered and planar conformations have been found to have comparable energies by means of the AM1 method ⟨89JST(187)325⟩. However, more detailed *ab initio* studies have been performed. Calculations using the 3-21G basis set make the boat form 3.0 kcal mol^{-1} more stable than the planar form while the 6-21G basis set reduces this energy difference to 2.6 kcal mol^{-1} ⟨85JA5323⟩. Using a 3-21G* basis set further reduces the energy difference to 2-3 kcal mol^{-1} while with the 6-31G* single point calculations the energy difference is down to 1.8 kcal mol^{-1} ⟨84JST(108)59⟩.

In summary, theoretical calculations predict that, in the gas phase, the dithiin molecule is very flexible, with the boat form being the minimum in energy. However, since the butterfly-flapping potential is extremely shallow, the conformational equilibrium can easily be modified by solvent or other effects. This is particularly true for polar solvents, since the boat form is disfavored by dipolar interactions according to molecular mechanics calculations ⟨85JA5323⟩. In the early 1990s, the structures of 1,4-dithiin in the neutral, radical cation and dication states have been investigated by *ab initio* calculations with the MIDI-4 basis set. The MIDI-4 calculations predict a folded form (energy difference 2.5 kcal mol^{-1}) for the neutral state and planar forms for the cation and dication states ⟨91JST(231)283⟩.

The EHT energies of oxanthrene and phenoxathiin, calculated as a function of the angle of fold, predict that the two molecules should adopt planar conformations ⟨78JOM(146)235⟩. However, another EHT calculation of the dihedral angle dependence of the all-valence electronic energies suggests that, whereas the former is planar, the latter is folded ⟨72BCJ1589⟩. Full geometry optimized 6-31*G calculations on 2,3,7,8-tetrachlorooxanthrene have been carried out and the authors found that a near planar structure is favored for this compound ⟨88JOC5471⟩. Thianthrene has been the subject of many theoretical studies. Molecular mechanics calculations predict an inversion barrier of 4.6 kcal mol^{-1} by the MM method ⟨85JA5323⟩, and a dihedral angle of 150° or 125° by the semiempirical PM3 calculational method ⟨93OM775⟩ or by the 4-31G basis set ⟨90JST(204)41⟩, respectively.

Ab initio molecular orbital calculations and/or molecular mechanics methods have been also employed to investigate bond lengths, bond angle electronic structure, and electrostatic potentials of 1,4-dioxin, 1,4-benzodithiin, thianthrene, and oxanthrene ⟨84JST(108)59, 85JA5323, 87CJS14, 87JA4149, 88JST(163)111, 89JCC635, 89JST(187)325, 91JST(231)283⟩. Moreover, bond lengths and bond angles of 2,3-dihydro-1,4-dioxin and 2,3-dihydro-1,4-benzodioxin have also been determined by theoretical calculations ⟨88AJC1107, 89JCC635⟩.

6.09.3 EXPERIMENTAL STRUCTURAL METHODS

6.09.3.1 X-ray Diffraction

An x-ray diffraction study of the parent compound 1,4-dithiin has revealed a boat structure in the solid state, with a dihedral angle (θ) of 137° or 141° between the two S—C=C—S planes ⟨54AX498⟩. However, discrepancies exist in the analysis owing to nonequivalent interatomic distances which should, because of symmetry, be equivalent. The crystal and molecular structure has been determined for 2,5-diphenyl-1,4-dithiin by x-ray analysis. The dithiin ring is arranged in a boat structure with a dihedral angle of 132.7° ⟨86SR123, 88JHC783⟩.

Oxanthrene, phenoxathiin, and thianthrene have each been investigated extensively by x-ray crystallography. Oxanthrene is alone in adopting a planar structure in the solid state. In contrast, phenoxathiin and thianthrene are both folded about the axis containing the two heteroatoms with dihedral angles (θ) of 138° and 128°, respectively ⟨84CHEC-I(3)94⟩. The average C—S bond length in both phenoxathiin and thianthrene is a little shorter than in 1,4-dithiin and this, coupled with the smaller angle of fold in thianthrene than in 1,4-dithiin, implies greater conjugation between the sulfur atom and the neighboring carbon atom in the fused ring derivatives.

In the case of thianthrene, a redetermination ⟨84AX(C)103⟩ at room temperature and measurement at 163 K gives values of 128.1° and 127.1°, respectively, for the fold angle. The oxides of phenoxathiin and thianthrene are also folded: the fold angle (θ) is 152° for phenoxathiin 10-oxide ⟨79JOC1989⟩, 123° for *cis*-thianthrene 5,10-dioxide ⟨63AX310⟩, 127.7° for *trans*-thianthrene 5,10-dioxide ⟨63AX310⟩, revised in ⟨66AX21⟩, recalculated in ⟨70AX(B)451⟩ and ⟨84AX(C)103⟩, and was found to be 127° for thianthrene 5,5,10,10-tetroxide ⟨63AX310⟩. However, a later determination of the tetroxide at 163 K found two crystallographically distinct molecules with fold angles (θ) of 138.0° and 144.0° in the unit cell ⟨84AX(C)1378⟩.

The solid state conformations of the *N*-(*p*-toluenesulfonyl)sulfilimines of phenoxathiin and thianthrene, determined by single-crystal x-ray diffraction, are also reported. In phenoxathiin, the ring system is slightly folded in a 'boat' conformation with the phenyl rings inclined 16.9°; the substituent is pseudoaxial. In thianthrene, the ring system is sharply folded in a "boat" conformation with the phenyl rings inclined 52.7°; the substituent is pseudoequatorial. In each structure, the substituents are asymmetrically oriented with respect to the vertical plane bisecting the central ring. In addition, the authors report briefly on the results of a theoretical (MNDO) study, which was undertaken in an attempt to shed additional light on the conformational preference of these derivatives ⟨91JOC3259⟩.

6.09.3.2 Electron Diffraction

The structure of 1,4-dioxin was first investigated by electron diffraction methods and the observed pattern was fitted to an assumed planar structure. From this study the following dimensions were obtained: C—O bond length 1.41 ± 1.03 Å; C—C bond length 1.35 ± 0.03 Å; C—O—C angle $116 \pm 4°$. The C—O bond length is only marginally less than the sum of covalent radii of the oxygen and carbon atoms ⟨84CHEC-I(3)943⟩.

6.09.3.3 Proton and Carbon-13 NMR Spectroscopy

Chemical shifts of protons in 1,4-dioxin and 1,4-dithiin fall to higher field of the "aromatic region", with the dioxin protons more shielded than those in 1,4-dithiin. The protons on the

heterocyclic ring of 1,4-benzodioxin and 1,4-benzodithiin are shifted downfield by about 0.25 ppm relative to the monocyclic series (Table 1).

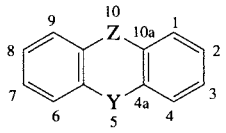
Table 1 Chemical shifts of protons bonded to unsaturated rings.

Compound	*Chemical shift (ppm)*	*Ref.*
1,4-Dioxin	5.5	84CHEC-I(3)943
1,4-Dithiin	6.19	85JPR523
1,4-Oxathiin	6.05 and 4.91	80RTC12
1,4-Benzodioxin	5.81	87JOC5616
1,4-Benzodithiin	6.42	90AHC(48)301
1,4-Benzodithiin tetroxide	8.25	84MI 609-01

Carbon-13 NMR spectra of numerous 1,4-dioxins, 1,4-oxathiins, 1,4-dithiins, and their benzo-fused and reduced derivatives have been described ⟨80RTC12, 84JOC3920, 85CB4385, 87JOC5616, 92JOC1161⟩.

The ^{13}C chemical shifts for oxanthrene, phenoxathiin, and thianthrene are listed in Table 2.

Table 2 Carbon-13 chemical shifts (ppm) for benzofused derivatives in $CDCl_3$ solution ⟨93OM775⟩.



Y	*Z*	*C-1*	*C-2*	*C-3*	*C-4*	*C-4a*	*C-10a*
O	O	116.20	123.60	12.60	116.20	142.10	142.10
O	S	126.75	124.49	127.68	117.77	120.10	152.13
S	S	128.71	127.66	127.66	128.71	135.52	135.52

In 2,3-dihydro-1,4-dioxin, -1,4-oxathiin, and -1,4-dithiin derivatives and their benzo analogues, the values of the vicinal proton coupling constant ratios and ring dihedral angles were determined and found to be consistent with half-chair conformation ⟨82OMR(18)92⟩.

Proton and ^{13}C chemical shifts for simple saturated rings are listed in Figure 1.

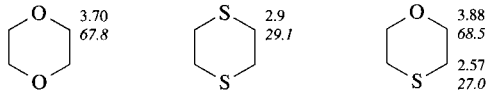


Figure 1 Proton and carbon-13 (italicized) chemical shifts (ppm) for saturated compounds.

In contrast to a thoroughly performed conformational analysis of 1,4-dioxanes and 1,4-oxathianes, the data on the conformational behavior of 1,4-dithianes are quite limited. According to NMR (^1H, ^{13}C) spectroscopy and molecular mechanics calculations, 2-alkyl-substituted 1,4-dithianes exist preferentially in the conformation with equatorially oriented substituents. For 1,4-dithianes with substituents of the CH_2X type (X = acetoxy, halogen), the predominance of axial conformers is observed originating from an intramolecular electrostatic attraction ⟨91T9455⟩.

6.09.3.4 Oxygen-17 NMR Spectroscopy

Oxygen-17 NMR spectroscopic data was obtained for several cyclic aromatic ethers, including 2,3-dihydro-1,4-benzodioxin, oxanthrene and phenoxathiin ⟨87JHC365, 90JPC7418⟩. Furthermore, ^{17}O NMR has been employed to distinguish between diastereotopic sulfonyl oxygens in substituted six-membered ring sulfones such as 1,4-dithiane or 1,4-oxathiane dioxides ⟨91JOC5589⟩.

6.09.3.5 UV Spectroscopy

The nonaromatic but fully conjugated 1,4-dioxin and its sulfur analogues show absorption at quite long wavelengths. The absorption maxima for representative compounds are given in Table 3.

Table 3 Representative UV spectra.

Compound	λ_{max} *(nm) (log ε)*	*Solvent*	*Ref.*
1,4-Dioxin	250(3.0), 307(1.6)	Hexane	84CHEC-I(3)943
1,4-Dithiin	262(3.73), 266–270s(3.65)	EtOH	84CHEC-I(3)943
2-Methyl-1,4-benzodioxin	234(3.90), 277.5(3.36), 283(3.31)	EtOH	84CHEC-I(3)943
1,4-Benzodithiin	253(4.23), 262s(3.81), 301(2.91)	EtOH	84CHEC-I(3)943
Oxanthrene	222(4.64), 228(4.73), 289(3.87)	Heptane	84CHEC-I(3)943
Phenoxathiin	238(4.50), 241(4.50), 295(3.60)	Heptane	84CHEC-I(3)943
Thianthrene	257(4.56)	EtOH	84CHEC-I(3)943
2,3-Dihydro-1,4-dioxin	224s(3.5), 307(1.3)	Hexane	46JA216
2,3-Dihydro-1,4-dithiin	282(3.64)		55JA1169

1,4-Dioxane absorbs at 180 nm and is thus transparent in the part of the UV region accessible to normal spectrometer systems. Replacement of the ring oxygen atoms by sulfur causes a bathochromic shift, and both 1,4-oxathiane and 1,4-dithiane show absorption above 200 nm.

6.09.3.6 IR and Raman Spectroscopy

Characteristic absorption in the vibrational spectra of the multi-oxygen and -sulfur heterocycles are those due to the C—O and the C—S bonds, the IR stretching frequencies for which fall in the regions 1300–1020 cm^{-1} and 800–600 cm^{-1}, respectively. The bands for the former are normally the stronger. The ν (C=C) band in 1,4-benzodioxin is at 1675 cm^{-1}, at higher frequency than 1,4-dioxin itself, 1640 cm^{-1}. In oxanthrene, very strong bands for the C—O—C asymmetric stretching mode are observed at 1299 cm^{-1} and 1287 cm^{-1}, at higher frequency than in diphenyl ether. Phenoxathiins show a characteristic band at *ca.* 1080 cm^{-1}, which remains relatively constant over a series of substituted derivatives. The spectrum of thianthrene also shows a band in this region, but the two strongest and most characteristic absorptions appear between 740 cm^{-1} and 770 cm^{-1} ⟨84CHEC-I(3)943⟩.

The far infrared and Raman spectra of several oxygen heterocycles have been recorded and analyzed ⟨89JA6920, 93JA8396⟩. In these works, the authors have determined the ring-puckering potential energy functions of 1,4-dioxin from the far infrared spectrum and the calculation of the kinetic energy expansion. This function clearly indicates that the equilibrium structure of 1,4-dioxin is planar ⟨93JA8396⟩.

6.09.3.7 Mass Spectrometry

Of the unsaturated ring systems the dibenzo-fused derivatives have attracted by far the most attention and provide a useful comparison of C—O and C—S bond reactivity under electron impact. Oxanthrene and phenoxathiin both fragment to give the dibenzofuran radical cation by extrusion of oxygen and sulfur, respectively. Loss of oxygen is unusual among oxygen heterocycles and the peak for the daughter ion, though small (2.1%), is significant. Loss of sulfur is a generally more favored process and thus the intensity of the dibenzofuran radical cation peak obtained from phenoxathiin is much higher, 21.2% ⟨84CHEC-I(3)943⟩. The principal fragmentation of thianthrene involves loss of sulfur ⟨87PS(29)377⟩. A fragmentation of oxanthrene, which clearly distinguishes it from the other dibenzo-fused compounds, is a remarkable simultaneous loss of two CO molecules to give, presumably, the naphthalene radical cation. 1,4-Benzodioxin behaves similarly to give what is believed to be the radical cation of benzene ⟨84CHEC-I(3)943⟩. Moreover, starting from 2-phenyl- or 2,3-diphenyl-1,4-benzodioxin, the loss of HCO and PhCO, respectively, cannot be considered as a simple elimination. Comparison with their benzocyclobutenyl isomers indicates hydrogen exchange between the phenyl and heterocyclic rings ⟨81OMS(16)246⟩.

In the electron impact induced fragmentation of 2,3-disubstituted 5,6-dihydro-1,4-oxathiins or

-dithiins, the most important cleavage of the heterocyclic ring occurs via the retro Diels–Alder type of reaction. The further fragmentation of the resulting radical cation gives rise to substituted carbonyl or thiocarbonyl compounds. This fragmentation favors the formation of ions in which the electron-deficient carbon–oxygen or carbon–sulfur triple bond is stabilized by an electron-releasing group. The ring fragmentation was observed to be dependent on the nature of the 3- and 2-substituents of the ring of the investigated series of 3- and 2-substituted 5,6-dihydro-1,4-oxathiins or -dithiins. The presence of the two sulfur atoms in dihydro-1,4-dithiins gives rise to more stable molecular ions than are observed in the case of the dihydro-1,4-oxathiin analogues ⟨86OMS(21)543, 87OMS(22)586⟩. In the benzo analogue series the mass spectrometric behavior of substituted 2,3-dihydro-1,4-benzodioxins and -benzoxathiins has been studied in detail ⟨78JHC777, 88H(27)1169⟩.

6.09.3.8 Photoelectron Spectroscopy

The UV photoelectron spectrum of 1,4-dioxin shows several bands in the region 8–15 eV. The separation between the band of lowest ionization energy and the second band, 2.52 eV, is significantly larger than in 1,4-cyclohexadiene, 1.00 eV, and demonstrates that the oxygen nπ-orbital is superior to the CH_2 pseudo π-orbital as a relay orbital ⟨78HCA1388⟩. The electronic structure of 1,4-dithiin has been investigated experimentally. The ionization energy of 1,4-dithiin has been measured by means of UV photoelectron spectroscopy and the molecular orbitals assigned by quantum mechanical calculations ⟨80MI 609-01⟩. The IP values calculated by X_α-SCF method, using Koopman's theorem, can be related to the experimental values by a simple linear relation such as IP(exp.) = 2.6 + IP (X_α-SCF). The lowest ionization energy observed is 8.15 eV ⟨80MI 609-01⟩. The calculations based on the X_α methodology provide the energies of the optical transitions in good agreement with the experimental spectra ⟨85JA5323⟩. Comparison of higher occupied orbital energies among the folded and planar forms of 1,4-dithiin and planar 1,4-dioxin has been calculated using the split valence basis sets MIDI 4 ⟨91JST(231)283⟩.

In the oxanthrene spectrum, the two bands of lowest ionization energy are related to electrons in antibonding π-MOs having a node along each C—O bond. The third and fourth bands, closely spaced, have been assigned to ejection of an electron from noninteracting π-phenyl orbitals with no involvement of the heteroatoms. A very similar pattern is observed in the photoelectron spectrum of phenoxathiin, and close similarity between the ionization energies of the first two bands for the two compounds has been cited as evidence for the nonplanarity of the two systems ⟨78JOM(146)235⟩. The negatives of the highest occupied molecular orbital (HOMO) energies for dibenzo-1,4-dithiin have been calculated by the VEH method and compared with the available experimental data on ionization potentials. The theoretical calculations predict that there is about 0.5 eV increase in IP from 1,4-dithiin to thianthrene, while the experimental data indicates a decrease of 0.35 eV ⟨85JA5323⟩.

The UV photoelectron spectra of the saturated compounds have attracted considerable attention and were detailed in CHEC-I ⟨84CHEC-I(3)958⟩.

6.09.4 THERMODYNAMIC ASPECTS

6.09.4.1 Intramolecular Forces

Boiling points and melting points of main compounds are shown in Table 4.

6.09.4.2 Aromaticity in the Unsaturated Series

A number of calculations have been concerned with the question of aromaticity. According to the extension of Hückel's work by Frost and by Breslow, it would be more reasonable to assume antiaromaticity for a cyclic 8π-electron system ⟨53JCP(21)572, 73ACR393⟩. Like 1,4-dioxin, 1,4-dithiin is computed to have a negative resonance energy and hence should also be antiaromatic. Indeed, Hess *et al.* have performed calculations which show a negative resonance energy of -0.017β per π-electron ⟨73JA3907⟩ and DasGupta *et al.* have reported a negative resonance energy of -0.053 eV ⟨80T2711⟩. A technique which combines perturbation theory and the graph-theoretical definition of resonance energy also predicts a negative resonance energy ⟨86SR123⟩. However, calculations at the

Table 4 Boiling and melting points[a,b] (°C).

1,4-Dioxin	77	Benzodioxin	193
1,4-Oxathiin	145	Benzoxathiin	230
1,4-Dithiin	190	Benzodithiin	310
2,3-Dihydro-1,4-dioxin	94	2,3-Dihydro-1,4-benzodioxin	213
2,3-Dihydro-1,4-oxathiin	165	2,3-Dihydro-1,4-benzoxathiin	295
2,3-Dihydro-1,4-dithiin	205	2,3-Dihydro-1,4-benzodithiin	335
1,4-Dioxan	102	Oxanthrene	**119**
1,4-Oxathian	147	Phenoxathiin	**59**
1,4-Dithian	200, **133**	Thianthrene	**158–9**

[a]Melting points above 30 °C are given in bold; melting points below 30 °C are not included. [b]Boiling points are given at atmospheric pressure to facilitate comparison; those reported at other than atmospheric pressure were converted using a nomogram ⟨57IEC125⟩.

ab initio 6-21G level of the energies of various six membered ring systems with π-electrons show that these energies are very shallow for the 1,4-dioxin and 1,4-dithiin rings and therefore they should be classified as nonaromatic rather than antiaromatic ⟨88JOC2127⟩.

6.09.4.3 Conformations

Interpretation of the far infrared spectra ⟨88JSP(129)126, 93JA8396⟩, vibrational spectra ⟨87CJS14⟩, electron diffraction data ⟨80JCR(S)111⟩, and theoretical calculations (Section 6.09.2) indicates that the structure of 1,4-dioxin is planar (D_2h symmetry) and corresponds to the parabolic potential energy function with large amplitude vibrations around the planar form. For 1,4-dithiin, the folded form has been proposed from x-ray analysis ⟨54AX498⟩ and measurement of the dipole moment ⟨82AJC2335⟩. However, conflicting results have been obtained in theoretical studies, although most of the results predict the boat-like form to be favored over the planar (Section 6.09.2).

Various experimental techniques have been used to determine bond angles for oxanthrenes and related compounds. From many of these studies, structures ranging from folded to near planar have been inferred ⟨69JCS(B)980, 78JOM(146)235, 83JCS(F2)1633, 88MI 609-01⟩.

Thianthrene has been the subject of many experimental studies. X-ray diffraction studies ⟨58AX372⟩ reveal that the molecule exists as a folded C_{2v} configuration with a dihedral angle of 128°. A dipole moment study in benzene solution gave $144 \pm 8°$ for this angle ⟨65JCS571⟩. A dielectric study in a polymer matrix gave 3.6 ± 0.7 kcal mol^{-1} for the inversion barrier ⟨70BCJ3929⟩. Electron diffraction analysis found 128–130° for the dihedral angle, and estimated that the inversion barrier should be greater than 4 kcal mol^{-1}. Theoretical calculations are presented in Section 6.09.2.

The most stable form of 2,3-dihydro-1,4-dioxin has been determined by far infrared ⟨89JA6920⟩, Raman ⟨74JCP(60)3098⟩, and microwave ⟨74JCP(60)2132⟩ spectroscopy to be the half-chair (twisted) conformation with C_2 symmetry. In all these works the potential energy surface for half-chair interconversion was also analyzed. From spectroscopic data, the bent structure (C_s symmetry) was found to have a second minimum on the potential surface. However, using molecular mechanics calculations Dodziuk *et al.* did not find a bent structure ⟨82T2811⟩. According to the improved potential energy surface ⟨89JA6920⟩, 2,3-dihydro-1,4-dioxin has energy minima corresponding to the twisted conformations, whereas the bent conformations are at the saddle points on the surface and are not energetically stable.

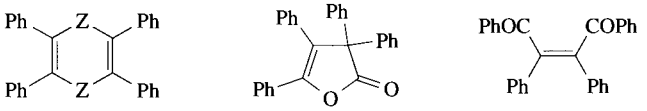
The conformational analysis of saturated multi oxygen and sulfur rings is very well developed. The survey of the area ⟨B-80MI 609-01⟩ provides an excellent coverage of the topic, updating an important earlier review ⟨B-69MI 609-01⟩.

6.09.5 REACTIVITY OF FULLY CONJUGATED RINGS

6.09.5.1 Unimolecular Thermal and Photochemical Reactions

1,4-Dioxin decomposes slowly over two to three weeks at room temperature to a polymeric material which does not melt below 250 °C. 1,4-Dithiin is more stable and can be distilled at 190 °C without decomposition, although such thermal stability is not shared by its derivatives. On heating

2,3,5,6-tetraphenyl-1,1,4-dioxin (**19**) in the absence of solvent at 250°C, the main product is the lactone (**21**) together with small quantities of *cis*-dibenzoylstilbene (**22**) ⟨77PIA(A)1⟩.

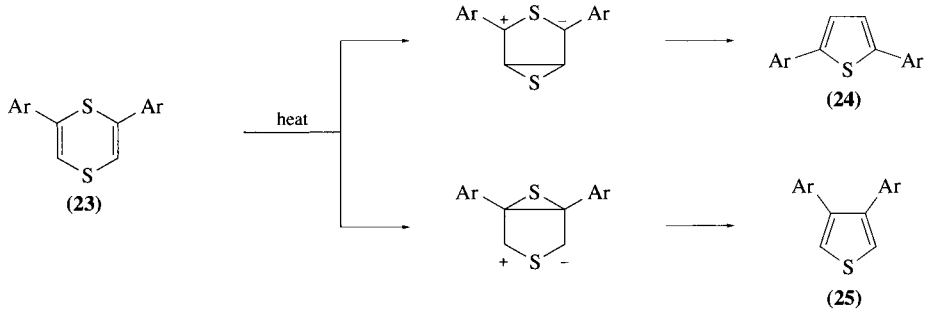


(**19**) Z = O
(**20**) Z = S

(**21**)

(**22**)

Under photolytic conditions, (**19**) gives benzil as the main product together with tolan and *trans*-dibenzoylstilbene. In contrast, the 1,4-dithiin analogue (**20**), under both thermal and photochemical conditions, is simply converted into tetraphenylthiophene. Sulfur extrusion of this type is very common with substituted 1,4-dithiins. Thus, thermolysis of 2,6-diaryl-1,4-dithiin (**23**) is found to give 2,5-diarylthiophenes (**24**) predominantly over 3,4-diarylthiophenes (**25**) in various solvents. The predominant formation of (**24**) and (**25**) provides evidence that the thermal extrusion of sulfur occurs by way of a zwitterionic thiirane structure; the major products are rationalized as arising from the thiirane compound, which is the more stabilized by the substituents (Scheme 1) ⟨85H(23)1907⟩.



(**23**)

(**24**)

(**25**)

Scheme 1

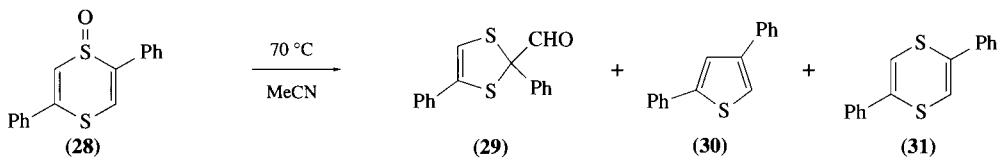
Methyl 3,5-diaryl-2,4-thiophenecarboxylates (**27**) were obtained by thermolysis of corresponding 1,4-dithiins (**26**) Equation (1) ⟨83PS(17)135⟩.

(**26**)

(**27**)

(1)

1,4-Dithiins containing sulfur in a higher oxidation state also undergo extrusion of sulfur (as an oxide) to give the corresponding thiophenes. Such thermal decomposition of oxides of 1,4-dithiin into thiophenes has been known for many years but a report shows that other very different reactions are also possible. Thus, thermolysis of 2,5-diphenyl-1,4-dithiin 1-oxide (**28**) in the liquid phase resulted in rearrangement to 2-formyl-2,4-diphenyl-1,3-dithiole (**29**) and extrusion of sulfur oxide to give 2,4-diphenylthiophene (**30**), as well as deoxygenation to 2,5-diphenyl-1,4-dithiin (**31**) (Equation (2)). Distribution among the three products depended on the initial concentration; at low concentrations the deoxygenation was suppressed (Equation (2)) ⟨85PS(25)43⟩.



(**28**)

(**29**)

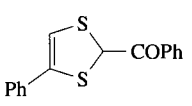
(**30**)

(**31**)

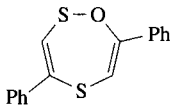
(2)

Furthermore, the photolysis of (**28**), in methanol with a 100 W high-pressure Hg lamp, afforded (**29**) and another 1,3-dithiole isomer, 2-benzoyl-4-phenyl-1,3-dithiole (**32**) ⟨85PS(25)43⟩. In dimethyl

sulfoxide, the photolysis (2537 Å) of the same compound affords the ring enlarged product, 4,7-diphenyl-1,2,5-oxadithiepin (**33**) ⟨86IJC(B)319⟩.

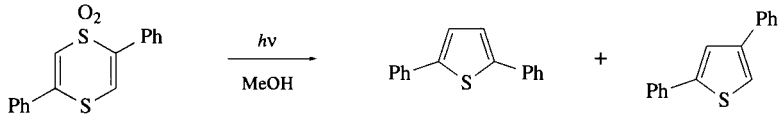


(**32**)



(**33**)

On the other hand, the photochemical behavior of 2,5-diphenyl-1,4-dithiin 1,1-dioxides (**34**) is remarkably different from that of the corresponding sulfoxides. Thus, irradiation of derivatives (**34**) gave the thiophenes (**24**) and (**30**), but in very low yields (Equation (3)) ⟨83CL61⟩.

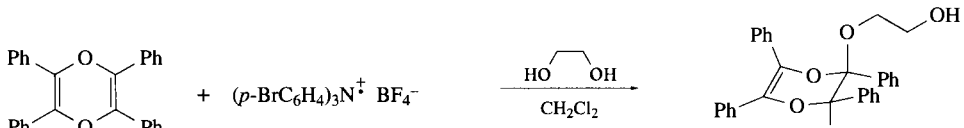


(**34**) (**24**) (**30**) (3)

6.09.5.2 Electrophilic Attack at Carbon

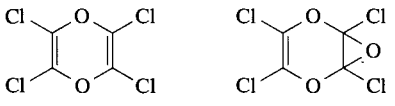
6.09.5.2.1 At carbon of the heterocyclic ring

1,4-Dioxin is considered to have a greater stability towards dilute acid than vinyl ethers or 2,3-dihydro-1,4-dioxin but otherwise it behaves as a typical unsaturated ether. The 2,3,4,5-tetraphenyl derivative (**19**) reacts with two equivalents of tris(*p*-bromophenyl)aminium tetrafluoroborate in a dichloromethane/ethylene glycol mixture to give the *trans*-diaxial bisketal addition product (**35**) (Equation (4)) ⟨87S947⟩.



(**19**) (**35**) (4)

m-Chloroperbenzoic acid oxidation, or ozonolysis, of compound (**19**) affords, in high yield, benzil as the sole product ⟨85JCS(P1)457⟩. Moreover, 2,3,5,6-tetrachlorodioxin (**36**) reacts with oxygen spontaneously and exothermically. A sample of (**36**), stirred in air until the reaction subsided and then allowed to stand in the open, gave hydrated oxalic acid as the residue. When exposed to oxygen in a controlled manner, (**36**) absorbed somewhat over 0.5 mol of oxygen to form, as the major product, the epoxide (**37**) in 60–70% yield, along with phosgene, oxalyl chloride, and several unidentified minor products ⟨91JOC3915⟩.

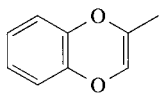


(**36**) (**37**)

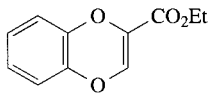
The electrophilic reactivity of the 1,4-dithiin system is dependent somewhat upon the substituents which are present. Thus, a variety of electrophilic substitution reactions of 2,5-diphenyl-1,4-dithiin (**31**) have been reported, including formylation, nitration, acetylation, and chloromercuration as well as sulfenylation ⟨86SR123⟩.

In the benzo-fused series the oxygenated ring is by far the most susceptible to electrophilic reagents. This is exemplified by results of a study of 2-methyl-1,4-benzodioxin (**38**), which is polymerized by 1% sulfuric acid after one hour. Intractable products were also generated under conditions of the Friedel–Crafts, Vilsmeier, and Mannich reactions ⟨67AJC1773⟩. However, treatment of 1,4-benzodioxin (**7**), 2-methyl-1,4-benzodioxin (**38**) or ethyl 1,4-benzodioxin-2-carboxylate (**39**)

with bromine in an inert solvent afforded the corresponding dibromo adducts in high yields ⟨67AJC1773, 94UP 609-01⟩.

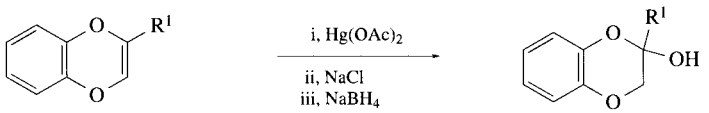


(38)



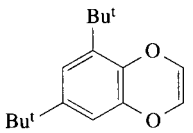
(39)

Likewise, 2-substituted-1,4-benzodioxins (**40**) react smoothly with mercuric acetate to give mercury compounds, which on treatment with sodium borohydride afford the corresponding hydrates (**41**) in good yields (Equation (5)) ⟨94UP 609-01⟩.

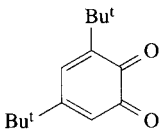


(40) R^1 = alkyl, aryl, CH_2OR^2 (41) (5)

The oxidation of 1,4-benzodioxins has been well investigated. Thus, oxidation of the 1,4-benzodioxin (**42**) by *m*-chloroperbenzonic acid afforded the 1,2-benzoquinone (**43**) in moderate yields. On the other hand, when (**42**) was oxidized by a *t*-butyl hydroperoxide–vanadium catalyst system, followed by treatment with potassium carbonate, 1,2-benzoquinone (**43**) was obtained in good yield, because of the suppression of the formation of nucleophilic by-products ⟨87JHC785⟩.

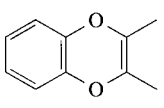


(42)

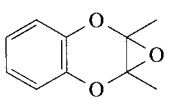


(43)

However, it is possible to generate the epoxides corresponding to benzodioxins using dimethyldioxirane. In this manner, 2,3-dimethyl-1,4-benzodioxin (**44**), with dimethyldioxirane in a mixture of dichloromethane–acetone under nitrogen, was transformed in excellent yield to its labile epoxide (**45**). Although epoxide (**45**) could be isolated in pure form by distillation of the solvent (−20 °C/0.01 torr), when left, at *ca.* 20 °C, it rearranged into the corresponding 2-acetyl-2-methyl-1,3-benzodioxole (**46**) ⟨91TL1295⟩.



(44)



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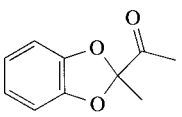


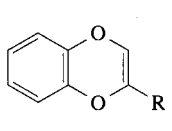
(46)

As for 1,4-benzodithiin, it reacts smoothly with various electrophiles to give 2-substituted derivatives in a range of reactions. Studies have also been done of 1,4-benzoxathiin, and its chemical properties are found to fall between those of 1,4-benzodioxin and 1,4-benzodithiin ⟨B-61MI 609-01⟩.

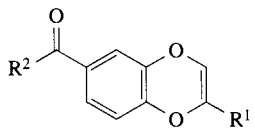
6.09.5.2.2 At carbon of an aromatic ring

As above (Section 6.09.5.2.1), the oxygenated ring of benzodioxin is relatively unstable towards electrophilic agents. However, reaction of ethyl 1,4-benzodioxin-2-carboxylate (**39**) and 1,4-benzodioxin-2-carbonitrile (**47**) with acyl chlorides in the presence of aluminum chloride in an inert solvent affords regiospecifically the corresponding acylated products (**48**) and (**49**), in excellent yields ⟨95T2619⟩.

Oxanthrene, phenoxathiin, and thianthrene are all reactive towards electrophiles. In the dibenzo series, nitration of the oxanthrene by nitric acid gives the 2-nitro product; further nitration gives a mixture of the 2,7- and 2,8-dinitro compounds, which can be separated by fractional crystallization. Nitration of 1- or 2-acylaminooxanthrenes was employed to achieve regioselective further



(47) R = CN



(48) $R^1 = CO_2Et$

(49) $R^1 = CN$

functionalization of these compounds. The choice of nitrating conditions and/or acyl substituent (CH_3CO vs CF_3CO) often dictated into which position the first nitro group was directed ⟨84JHC1073⟩.

1,3,6,8-Tetrachlorooxanthrene has been dinitrated with either nitric acid/acetic anhydride or with ammonium nitrate/trifluoroacetic anhydride to give the 2,7-dinitro compound, and dinitration of the 2,3,6,7-tetrachloro derivative was achieved with excess of nitronium tetrafluoroborate in sulfolane at 125 °C to give the 1,5-dinitro product ⟨83MI 609-01⟩.

6.09.5.3 Electrophilic Attack at Sulfur

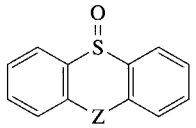
The oxidation of the sulfur atoms of 1,4-dithiin is a fascinating reaction. Depending upon the quantity of the oxidizing agent used, one or both sulfur atoms can be oxidized. Usually the monosulfoxide is unstable in comparison with the mono- or disulfone ⟨86SR123⟩. In the benzo-fused series, periodate oxidation (sodium metaperiodate) of 1,4-benzodithiin in a mixture of acetone–water affords the monosulfoxide ⟨84MI 609-02⟩. 1,4-Benzoxathiin and 1,4-benzodithiin have been oxidized with hydrogen peroxide to the monosulfone and disulfone derivatives ⟨84CHEC-I(3)943⟩. 1,4-Benzodithiins have also been oxidized to the corresponding tetroxides with hydrogen peroxide in acetic acid at reflux ⟨85H(23)1119⟩ or with *m*-chloroperbenzoic acid in dichloromethane ⟨94T7913⟩. Furthermore, thianthrene and phenoxathiin have been oxidized to all the possible oxide derivatives using an assortment of reagents which includes hydrogen peroxide, potassium permanganate, and nitric acid ⟨84CHEC-I(3)943, 90AHC(48)301⟩.

The oxidation of thioethers is also performed with *o*-iodosylbenzoic acid in acetic acid containing some sulfuric acid as catalyst. Thus, thianthrene gives the corresponding sulfoxide and thianthrene monoxide affords only the disulfoxides, mainly the *cis* isomer ⟨92SC1799⟩. Iodosobenzene in the presence of a catalytic amount of benzeneseleninic acid also oxidized thianthrene and thianthrene 5-oxide to sulfoxides in excellent yields in acetonitrile under mild conditions ⟨91TL793⟩. Thianthrene 5-oxide was also converted in good yield into the 5,5-dioxide and 5,10-dioxide by peroxo species generated from cetylpyridinium tungstophosphates and hydrogen peroxide in a catalytic cycle ⟨94CL1⟩. Tetrabutylammonium periodate is a potent oxygen atom donor to substrates in the presence of a catalytic amount of metalloporphyrin under neutral and homogeneous conditions, enabling the transformation of phenoxathiin into the corresponding sulfoxide in excellent yield ⟨83TL3631⟩. Phenoxathiin reacted also with one molar equivalent of ozone to give phenoxathiin 10-oxide quantitatively. When thianthrene was ozonized, thianthrene 5-oxide and a trace of *trans*-thianthrene 5,10-dioxide were obtained ⟨84BCJ2526⟩. Phenoxathiin and thianthrene have been readily converted in high yields to sulfoxides in the presence of dioxygen and catalytic amounts of nitrogen dioxide ⟨95JOC3172⟩.

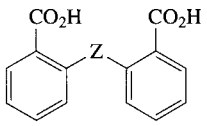
6.09.5.4 Nucleophilic Attack at Sulfur

As expected, nucleophilic attack at a heteroatom is relatively rare, but a few examples are to be found among reactions of thianthrene and the oxides of phenoxathiin and thianthrene. Reactions of methylmagnesium iodide and phenylmagnesium bromide with thianthrene in the presence of (1,3-bis(diphenylphosphino)propane)nickel dichloride (dpppNiCl$_2$) have been shown to yield, regioselectively, ring opened products in which the carbon–sulfur bonds are replaced by carbon–carbon bonds. Thus, the reaction of phenylmagnesium bromide with thianthrene in refluxing benzene in the presence of dpppNiCl$_2$ gave *o*-terphenyl ⟨85JOC3828⟩. The reaction of phenoxathiin 10-oxide (**50**) with butyllithium followed by carbon dioxide produces, besides phenoxathiin, formed by a reduction process, and its 1-carboxylic acid, generated via lithiation of the benzene ring (Section 6.09.5.5.2), also a number of ring cleavage products. These include the dicarboxylic acid (**53**),

diphenyl ether, and phenoxybenzoic acid. Thianthrene 5-oxide (**51**) under similar conditions gives dibenzothiophene and the dicarboxylic acid (**54**) as the main cleavage products, and the trioxide (**52**) behaves likewise, affording dibenzothiophene dioxide and the diacid (**55**) ⟨84CHEC-I(3)943⟩.

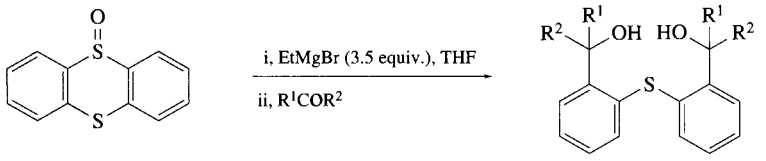


(**50**) Z = O
(**51**) Z = S
(**52**) Z = SO_2



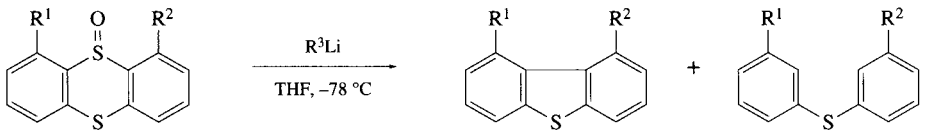
(**53**) Z = O
(**54**) Z = S
(**55**) Z = SO_2

Thianthrene 5-oxide (**51**) has been found to react with alkyl Grignard reagents and subsequently with aldehydes or ketones to form diols (**56**) (Equation (6)) ⟨90CL979⟩.



(**51**) (**56**) (6)

Furthermore, the thianthrene 5-oxides (**57**), substituted or not, react with *n*-butyllithium or phenyllithium to provide various dibenzothiophene derivatives (**58**) and diaryl sulfides (**59**) (Equation (7)) ⟨91H(32)675⟩.



(**57**) (**58**) (**59**) (7)

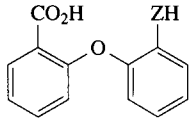
6.09.5.5 Nucleophilic Attack at Hydrogen

6.09.5.5.1 At carbon of the heterocyclic ring

An attempt to deprotonate 1,4-dioxin with potassium in refluxing ether for two days failed. About half of the starting material was recovered from the ether solution, the remainder undergoing polymerization. 1,4-Dithiin, however, is readily deprotonated with *n*-butyllithium at −110 °C in ether or THF to afford the 2-lithio derivative. At this temperature it can be trapped with electrophiles to give 2-substituted derivatives. At −60 °C, the 2-lithio derivative undergoes ring opening ⟨86SR123⟩.

1,4-Benzodioxin and its 2-substituted derivatives react, at low temperature, with *n*-butyllithium, *t*-butyllithium or lithium diisopropylamide to give (2- or) 3-lithio derivatives. The lithiated products are excellent intermediates for functionalizing the hetero-ring. Thus, treatment of these anions with various electrophiles (alkyl halides, aldehydes, ketones, epoxides, etc.) gave, in good yields, the corresponding condensation products ⟨79TL4379, 82S322, 84GEP(O)3338753, 86S337, 87JHC609, 90T921, 92CJC828⟩.

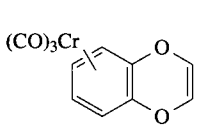
Oxanthrene is cleaved by lithium in THF at 25 °C and the product obtained by quenching the intermediate with carbon dioxide is the carboxylic acid (**60**) in 56% yield. On heating with lithium in THF for 7 h the main isolated product is catechol. Cleavage of phenoxathiin with lithium in ether occurs at C-5 to give, after carboxylation, product (**61**), analogous to those obtained from oxanthrene, and the disulfide of this same compound. However, this reaction, when run in THF at 50 °C and terminated by carboxylation, produced 2-thiolphenol and phenoxathiin-4,6-dicarboxylic acid, the product of dimetallation ⟨58JA380⟩.



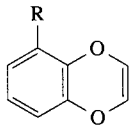
(60) Z = O
(61) Z = S

6.09.5.5.2 At carbon of the aromatic ring

Reaction of 1,4-benzodioxin with chromium hexacarbonyl gives a 41% yield of the η^6-arene chromium complex (**62**). Reaction of this complex with *n*-butyllithium forms a yellow solution of the aryllithium. Reaction of this with a range of electrophiles gives a series of 5-substituted derivatives in modest yield, which are readily decomplexed by iodine to form the useful 5-substituted 1,4-benzodioxins (**63**) ⟨89TL5519⟩.

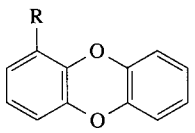


(62)

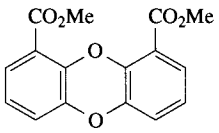


(63)

Oxanthrene, phenoxathiin, and thianthrene all react with butyllithium with proton abstraction from a benzene ring. Oxanthrene itself is not metallated at −78 °C, but can be deprotonated smoothly at −30 °C, leading to a range of 1-substituted dibenzodioxins (**64**)–(**66**) upon quenching with electrophiles such as carbon dioxide, iodomethane, or *N*,*N*-dimethylformamide ⟨88JMC707⟩. When oxanthrene was reacted with two molar equivalents of *t*-butyllithium at −30 °C, the mixture quenched with carbon dioxide and the product esterified, a good yield of the 1,9-diester (**67**) was obtained, suggesting that a 1,9-dianion might have been generated under these conditions ⟨90JOC438⟩.

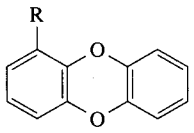


(64) R = CO_2H
(65) R = Me
(66) R = CHO

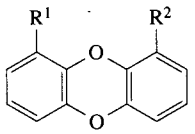


(67)

On the other hand, oxanthrene-1-carboxylic acid (**64**) reacts with two molar equivalents of *t*-butyllithium to give in good yields substituted products (**69**), following treatment with various electrophiles ⟨90JOC438, 92JMC258⟩. Furthermore, lithiation of *N*-[2-(dimethylamino)ethyl]-oxanthrene-1-carboxamide (**68**) followed by quenching with a variety of electrophiles yielded derivatives functionalized in the 9 position. This regiospecificity reflects lithiation directed by a dioxin oxygen atom and by the amide anion cooperatively to the *peri* site on the distal ring rather than simply *ortho* to the amide ⟨91JOM(420)387⟩.



(68) R = $CONH(CH_2)_2NMe_2$



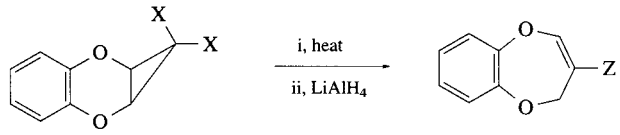
(69) R^1 = CO_2H, R^2 = CO_2H, CHO, TMS, etc...

Thianthrene is metallated at the 1-position ⟨88JMC707⟩ while lithiation of phenoxathiin occurs *ortho* to the C—O bond rather that the C—S bond, i.e. at C-4 ⟨86JA181, 89LA459, 90JOC438⟩. The lithiated products are excellent intermediates for ring functionalization. When phenoxathiin was reacted with excess of *n*-butyllithium, followed by quenching with carbon dioxide, the 4,6-diacid (substituting *ortho* to oxygen) was obtained in satisfactory yield ⟨90CB1579⟩. Finally, the phenoxa-

thiins already substituted in position four can be lithiated by reaction with *n*-butyllithium in the presence of tetramethylenediamine. Quenching with electrophiles generated 4,6-disubstituted phenoxathiins with good yields ⟨86JOC1829⟩. Unlike phenoxathiin itself, its 10-oxide and 10,10-dioxide are metallated at C-1, i.e. *ortho* to the C—S bond ⟨88JMC707, 91JMC2931⟩. Thianthrene 5-oxide and 5,5-dioxide are also metallated *ortho* to the sulfur atom in the oxidized state ⟨57JA208, 91H(32)675⟩.

6.09.5.6 Reactions with Carbenoid, Electron-deficient Species

1,4-Benzodioxin reacts with dihalocarbenes under liquid–liquid phase-transfer catalysis conditions to give the corresponding *gem*-dihalocyclopropane derivatives (**70**) and (**71**). The compounds (**70**) and (**71**), by heating at 170–185°C, afford the benzodioxepin derivatives, which were not isolated but immediately reduced with lithium aluminum hydride to give (**72**) and (**73**), respectively (Equation (8)) ⟨83AG(E)64⟩.



(8)

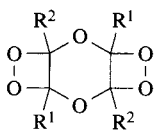
(**70**) X = Cl
(**71**) X = Br

(**72**) Z = Cl
(**73**) Z = H

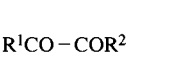
The sulfur-containing rings are obvious candidates for desulfurization reactions. Desulfurization of thianthrene was >80% effective over $MoO_3/CoO/S_2O_2/Al_2O_3$ at 350°C/H_2/85 bar. The use of MoS_3/250–400°C/25–75 kg/cm^2 was said to be 100% effective in C—S—C hydrogenolysis and the use of commercial Co/Mo/γ-Al_2O_3 catalyst worked even with 1,4,6,9-tetramethylthianthrene, a thianthrene hindered around the sulfur atoms, giving *p*-xylene cleanly ⟨90AHC(48)301⟩. The folded shape of thianthrene (and also phenoxathiin) is believed to allow easier adsorption than comparable planar aromatic sulfur-containing heterocycles, such as dibenzothiophene ⟨84BSB653⟩. Phenoxathiin and thianthrene are both partially desulfurized by high temperature catalytic hydrogenolysis over NH_4Y zeolite, presulfided Co/Mo/Al_2O_3, and Ni/W/S_2O_2/Al_2O_3. The former is cleaved to give diphenyl ether as the major product, together with phenol and benzene, indicating that sulfur removal occurs more readily than removal of oxygen. In line with this, thianthrene reacts under the same conditions to give benzene as the main product ⟨78BCJ1422⟩. Organometallic chemical reducing agents have been examined in this context: two molar equivalents of (2,2′-bipyridyl) (1,5-cyclooctadiene)nickel(0) ((bpy)(COD)Ni(0)), over 48 hours at 55°C converted thianthrene into dibenzothiophene (55%) and diphenyl sulfide (15%) and phenoxathiin into dibenzofuran (79%) and diphenyl ether (3%). Under the same conditions, $LiAlH_4$ $(THF)_n$ (bpy) Ni(0) from thianthrene gave dibenzothiophene (5%) and diphenyl sulfide (75%), and from phenoxathiin dibenzofuran (3%) and diphenyl ether (92%) ⟨86JA7763⟩. The nickel-containing complex reducing agents alone, or in the presence of 2,2′-bipyridine (NiCRA and NiCRA-bpy, respectively), are very efficient in the desulfurization of sulfur-containing compounds. Thus, phenoxathiin was converted into diphenyl ether and dibenzofuran and thianthrene into benzene, biphenyl and diphenyl sulfide ⟨89JOC4848⟩.

6.09.5.7 Cyclic Transition State Reactions with a Second Molecule

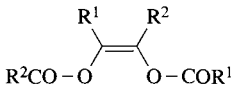
The photosensitized singlet oxygenation of 1,4-dioxins in methylene chloride at −78°C using tetraphenylporphin as sensitizer affords the corresponding bisdioxetanes (**74**). In all photooxygenations, variable amounts of the corresponding α-diketones (**75**) and enediol diesters (**76**) were formed. Thermal decomposition of the bisdioxetanes (**74**) yielded the corresponding anhydrides (**77**) essentially quantitatively ⟨85CB4385⟩.



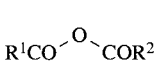
(**74**)



(**75**)



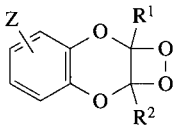
(**76**)



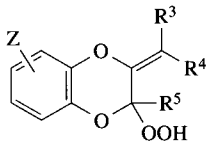
(**77**)

The photooxygenation of 2,3,5,6-tetraphenyl-1,4-dioxin (**19**) in an acetonitrile-dichloromethane mixture, using 2,4,4,6-tetrabromocyclohexa-2,5-dienone or 9,10-dicyanoanthracene as sensitizer, yields *Z*-stilbenediol benzoate together with benzil ⟨85TL4383, 86MI 609-01⟩.

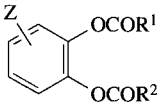
Photosensitized singlet oxygenation of benzo- and naphtho-1,4-dioxins in chloroform at −78 °C using polymer-bound Rose Bengal as sensitizer affords the corresponding 1,2-dioxetanes (**78**) in moderate to good yields. Ene products (**79**) are obtained in those cases in which the 1,4-dioxins bear alkyl substituents. Thermal decomposition of the dioxetanes (**78**) affords the corresponding diesters (**80**) essentially quantitatively ⟨84JOC3920⟩.



(**78**)

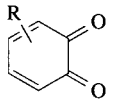


(**79**)



(**80**)

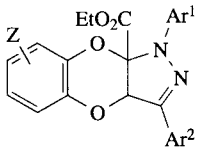
Ozonolysis of 1,4-benzodioxins followed by photolysis gave 1,2-benzoquinones (**81**) in moderate yields and catechols were formed as by-products. The yields were independent of the stability of the *o*-benzoquinones, except when a nitro group was present, when the formation of 4-nitro-*o*-benzoquinone was not detected ⟨87JOC5616⟩.



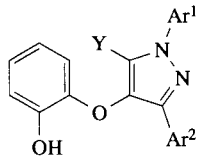
(**81**)

Thermally, dithiins may react as dienophiles in [2 + 4] cycloadditions ⟨86SR123⟩. Photochemically, they afford [2 + 2] cyclodimerization products in the absence of oxygen; in its presence, they are degraded to carbon dioxide and hydrogen sulfide among other photooxidation products ⟨82TL2651⟩.

The 1,3-dipolar cycloaddition of diarylnitrilimines to ethyl 1,4-benzodioxin-2-carboxylate (**39**) is regiospecific and gave the single cycloadducts (**82**). Treatment of each cycloadduct with a boiling mixture of acetic and hydrochloric acids led quantitatively to the esters (**83**). Saponification of each ester followed by acidification gave acids (**84**) in quantitative yield. When the acids were heated to their melting points, they lost carbon dioxide and gave the 4-*o*-hydroxyphenyloxy-1,3-diarylpyrazoles (**85**) ⟨86JCR(S)266⟩.

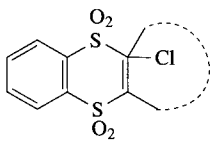


(**82**)

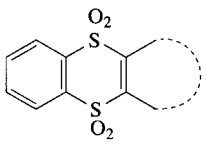


(**83**) Y = CO_2Et
(**84**) Y = CO_2H
(**85**) Y = H

1,4-Benzodithiin 1,1,4,4-tetraoxide undergoes the Diels–Alder reaction with a series of dienes under mild conditions to provide the corresponding adducts in excellent yields ⟨84MI 609-02, 85H(23)1119, 94T7913⟩. Indeed, the reaction of 2-chloro-1,4-benzodithiin 1,1,4,4-tetraoxide with dienes led to the expected Diels–Alder adducts (**86**) which were readily dehydrochlorinated with triethylamine to alkenes (**87**). The preparation of compounds (**87**) could be conveniently carried out in a "one pot" operation without isolation of cycloadduct (**86**) ⟨92CC1089⟩.



(**86**)

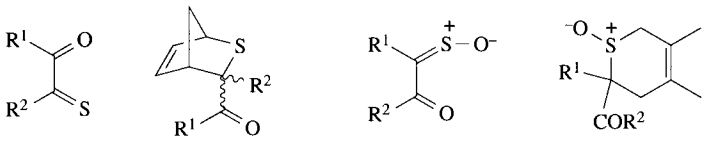


(**87**)

6.09.6 REACTIVITY OF NONCONJUGATED RINGS

6.09.6.1 Unimolecular Thermal Reactions

The thermolysis (retro-Diels–Alder reaction) of 2,3-dihydro-1,4-oxathiins led to the corresponding thioxoethanal or α-oxothiones (**88**), which were trapped by cyclopentadiene as the adducts (**89**) ⟨90JOC2596, 90TL6183⟩. Thioxoethanal *S*-oxide, as well as its mono and dimethyl derivatives (**90**) were generated under flash vacuum thermolysis conditions by the retro-Diels–Alder cleavage of the corresponding 2,3-dihydo-1,4-oxathiin *S*-oxides. The parent compound, thioxoethanal *S*-oxide, was characterized by low temperature IR, and in particular photoelectron spectroscopy. The methyl derivatives were trapped by 2,3-dimethyl-1,3-butadiene as the thiopyrans (**91**) ⟨91NJC533⟩.



(**88**) (**89**) (**90**) (**91**)

5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (**92**), known as Carboxin (a fungicide), rearranges to the enamine (**93**) when refluxed in toluene with *p*-toluenesulfonic acid. The structural assignment of (**93**) are made on the basis of crystal x-ray diffraction analysis ⟨84MI 609-02⟩.

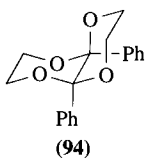
(**92**) (**93**)

6.09.6.2 Electrophilic Attack at Carbon

6.09.6.2.1 At carbon of the heterocyclic ring

The cyclic vinyl ether 2,3-dihydro-1,4-dioxin is converted into its cyclic hemiacetal hydration product, tetrahydro-2-hydroxy-1,4-dioxin, in aqueous solution by an acid-catalyzed reaction ⟨87OK2746, 89JPO43⟩. Treatment of an alcohol with excess of 2,3-dihydro-1,4-dioxin at room temperature in the presence of copper(II) bromide in tetrahydrofuran leads to the corresponding acetal. This new protective group for alcohols, which is stable towards lithium aluminum hydride and organolithium reagents, can be removed by treatment with acidified aqueous methanol ⟨85S806⟩.

The reaction of 2,3-diphenyl-5,6-dihydro-1,4-dioxin with molecular bromine or 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one in carbon tetrachloride/ethylene glycol mixture affords in high yields the *cis*-1,6-diphenyl-2,5,7,10-tetraoxabicyclo[4.4.0] decane (**94**) ⟨84S774⟩. Compound (**94**) is also prepared by treatment of 2,3-diphenyl-5,6-dihydro-1,4-dioxin with two equivalents of tris(*p*-bromophenyl)aminium tetrafluoroborate in a dichloromethane/ethylene glycol mixture. The structural and conformational assignments were made on the basis of spectroscopic and single crystal x-ray diffraction data ⟨87S947⟩. In the absence of ethylene glycol, benzil is the only isolated product ⟨85TL789⟩.

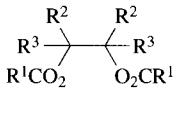


(**94**)

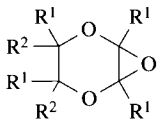
Indeed, reactions of 5,6-dihydro-2,3-dimethyl-1,4-dioxin, -1,4-oxathiin, and -1,4-dithiin with bromine in the presence of 1,2-ethanediol, 2-thiolethanol, and 1,2-ethanedithiol, respectively, afforded, in most cases, high yields of the corresponding oxa- and thiadecalins as *cis* isomers only ⟨91ACS410⟩. 2-Cyano-5,6-dihydro-1,4-dioxin reacts with bromine to afford the corresponding dibromide deriva-

tive ⟨83ZOR1097⟩. In the same way, treatment of 2,2,3,3-tetrafluoro-5,6-dichloro-2,3-dihydro-1,4-dioxin with chlorine under irradiation with a sunlamp at 80 °C served to introduce two chlorine atoms to give the octahalo-1,4-dioxane ⟨91JOC3915⟩.

Dihydrodioxins may undergo various oxidation reactions. Thus, the *m*-chloroperbenzoic acid oxidation of dihydrodioxins affords, in high yields, ethylene glycol dibenzoates (**95**) via unstable epoxy diethers (**96**). These elusive intermediates have been characterized chemically and by ^{1}H NMR spectroscopy ⟨85JCS(P1)457⟩.



(95)



(96)

6.09.6.2.2 *At carbon of the aromatic ring*

The sulfonation of 2,3-dihydro-1,4-benzodioxin (**13**) in concentrated sulfuric acid, and with sulphur trioxide in nitromethane or dichloromethane, has been studied ⟨89RTC395, 92RTC183⟩. Nitration of (**13**) employing an excess of concentrated nitric acid at 20–30 °C furnished the respective 5- and 6-nitro derivatives in the relative ratio 2 : 98 (global yield 98%). Nitration of 6-nitro-2,3-dihydro-1,4-benzodioxin gave the 5,6-, 5,7, and 6,7-dinitro derivatives in the relative ratio 7.7 : 3.3 : 89. Nitration of the isomeric 5-nitro-2,3-dihydro-1,4-benzodioxin afforded the 5,6- and 5,7-dinitro products in the relative ratio 80 : 20 ⟨91JHC625⟩. Direct nitration of the acetate of 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin was reported to give exclusively the 7-nitro derivative. In fact, ^{13}C NMR spectra of the product readily showed that nearly equal amounts of the 6- and 7-nitro isomer had been formed ⟨81JOC3846⟩. The reaction of (**13**) with *N*-chlorodialkylamines in the presence of iron(II) sulfate gave 5-dialkylamino-2,3-dihydro-1,4-benzodioxin. Several electrophilic substitution reactions (acylation, formylation, halogenation, chlorosulfonation) of substituted 2,3-dihydro-1,4-benzodioxins have been reported ⟨88CPB3404, 89EJM619, 90EJM45, 92MI 609-01, 93JMC4121⟩.

1,4-Benzodithians afford in satisfactory yields their corresponding monobromo derivatives by treatment with an equimolar amount of bromine at room temperature in anhydrous chloroform (whether the reaction is carried out in light or in the dark). The substitution of bromine on the aromatic ring is rigorously regioselective, the bromine atom being invariably at one of the ring positions *ortho* to the sulfur atoms. Where the *ortho* positions are not equivalent, one of them is exclusively preferred. By the use of quantum mechanical semiempirical calculations, the reaction is shown to proceed most likely via a "vicarious nucleophilic substitution of hydrogen." That means, in this context, prior electrophilic addition of Br^+ to sulfur, followed by addition of Br^- to the neighboring carbon and loss of HBr ⟨93T11383⟩.

6.09.6.3 Nucleophilic Attack at Hydrogen

6.09.6.3.1 *At hydrogen of the heterocyclic ring*

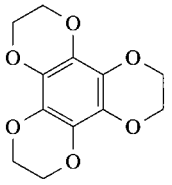
Treatment of 2,3-dihydro-1,4-dioxin (**10**) with *t*-butyllithium at −40 °C affords 5-lithio-2,3-dihydro-1,4-dioxin, which slowly reacts with aldehydes or ketones in tetrahydrofuran, leading to alcohols in good to moderate yields ⟨85TL3453, 88JOC5672⟩. This anion reacts with other electrophiles such as deuterium oxide, iodomethane or chlorotrialkyltin to give the corresponding 5-substituted products ⟨82SC579, 90S755⟩. Furthermore, some Fischer-type carbenes have been prepared from dihydrodioxinyllithium and chromium hexacarbonyl. They react normally with acetylenes to give substituted benzoquinones ⟨84JOC2294⟩.

Elsewhere, it is reported that metallation of 5-substituted or 5,6-disubstituted 2,3-dihydrodioxins with strong lithiating agents leads to ring-opened products ⟨84JCS(P1)1949, 91SC563⟩.

The treatment of one equivalent of 5-lithio-2,3-dihydro-1,4-dioxin with 0.5 equivalent of copper(I) cyanide solubilized as its lithium chloride (0.5 equiv.) complex at −15 °C affords the corresponding cyanocuprate. The reactivity of this cuprate was assessed by its conjugate addition to cyclic enones, and by nucleophilic epoxide opening; the presence of boron trifluoride etherate led to enhancement

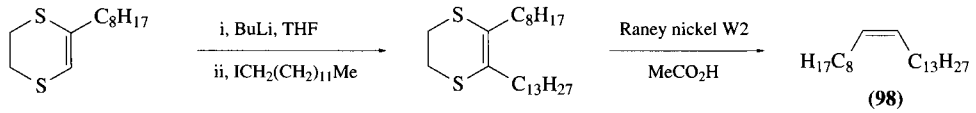
in product yields relative to those observed in its absence. Thus, reaction of cyanocuprate with acyclic epoxides gave the expected alcohols, and condensation with cyclohexenone gave the adduct in high yield ⟨92TL8087⟩.

1,4-Dioxacyclohexyne (5,6-didehydro-2,3-dihydro-1,4-dioxin) has been generated at low temperature in tetrahydrofuran solution from 5,6-dibromo-2,3-dihydro-1,4-dioxin, via 5-bromo-6-lithio-2,3-dihydro-1,4-dioxin, and isolated as the corresponding cyclotrimer (**97**) ⟨88CC942⟩.



(**97**)

2,3-Dihydro-1,4-dithiins can be converted by *n*-butyllithium in anhydrous THF at −78 °C into their corresponding sulfur stabilized carbanions. The reactions of the latter with electrophiles (alkyl halides, acyl halides) may then afford various coupling products that are characterized by the presence of a *cis*-substituted double bond tied up by the sulfur-containing dihydrodithiin ring ⟨92SC1345⟩. Furthermore, coupling of lithiated 5,6-dihydro-1,4-dithiins with aldehydes can be performed in excellent yields in the presence of titanium(IV) isopropoxide as catalyst ⟨94SC1223, 95SC1517⟩. The chemo- and stereoselective desulfurization of the 5,6-dihydro-1,4-dithiins was effected by using Raney nickel W2 in glacial acetic acid for a few minutes at room temperature. Under these conditions, 2,3-diphenyl-5,6-dihydro-1,4-dithiin is stereoselectively converted into *cis*-stilbene in satisfactory yield and without traces of the *trans* isomer and/or 1,2-diphenylethane. To demonstrate the utility of the dithiin approach for producing *cis* configured double bonds, the sex pheromone muscalure, (*Z*)-9-tricosene (**98**), from the common house fly *Musca domestica*, was prepared by a short synthesis in which the 5,6-dihydro-1,4-dithiin moiety serves as the penultimate alkene precursor (Scheme 2) ⟨94T7265⟩.



(**98**)

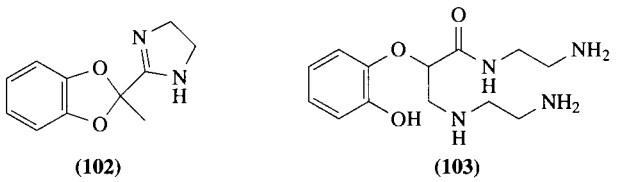
Scheme 2

Reaction of 2-cyano-or 2-carboxy-2,3-dihydro-1,4-benzodioxin with base results in abstraction of the proton at C-2 leading to immediate ring opening ⟨87JMC49, 90S755⟩. Thus, the reaction of the nitrile with, for example, sodium hydride and methyl iodide gave the unsaturated product (**99**). In the absence of an alkylation agent, the unstable phenol (**100**) was obtained, which quickly recyclized to give the imino structure (**101**) ⟨84JHC77⟩.

(**99**) R = Me
(**100**) R = H

(**101**)

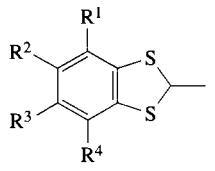
The reaction between ethylenediamine and 2-carboxy-2,3-dihydro-1,4-benzodioxin yielded four detectable products. The two major products were shown to be the dioxole (**102**) (45%) and catechol (29%). An analytical investigation of this process has revealed that, prior to the final distillation, the reaction gave a major product (**103**) which was different from the four mentioned above ⟨84JHC77⟩.



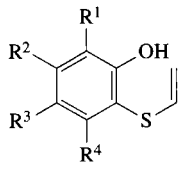
(**102**)

(**103**)

2,3-Dihydro-1,4-benzodithiins and 2,3-dihydro-1,4-benzoxathiins react with sodium methoxide in dimethylacetamide to give 1,3-benzodithioles (**104**) and 2-(vinylthio)phenols (**105**), respectively ⟨89CL2111⟩.

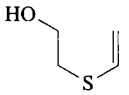


(**104**)

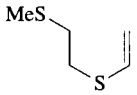


(**105**)

When oxathiane was treated with lithium diisopropylamide at 0 °C and iodomethane was added, 2-vinylthioethanol (**106**) was formed in good yield. However, the treatment of dithiane with lithium diisopropylamide in THF at 0 °C provided the ring opened product (**107**) after iodomethane quench ⟨84JCS(P1)1949⟩.



(**106**)



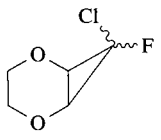
(**107**)

6.09.6.3.2 At hydrogen of the aromatic ring

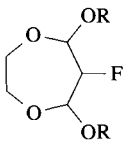
6-Methoxy and 6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxin can be lithiated by butyllithium in tetrahydrofuran, at −50 °C, to give intermediate lithio derivatives which react with various electrophiles to afford, after hydrolysis, 5-substituted-6-methoxy and 6-hydroxy-2,3-dihydro-1,4-benzodioxins ⟨93T1421⟩.

6.09.6.4 Reactions with Carbenoid, Electron-deficient Species

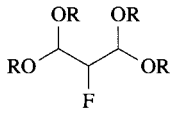
Various examples are available of reactions of the double bonds with carbenoids to give bicyclo[4.1.0]diheteroheptanes ⟨81JHC1637, 82CB229, 89MI 609-01⟩. Thus, condensation of 2,3-dihydro-1,4-dioxin with chlorofluorocarbene generated from dichlorofluoromethane under phase-transfer conditions led to 7-chloro-7-fluoro-2,5-dioxabicyclo[4.1.0]heptane (**108**) in 91% isolated yield. The thermal decomposition of this adduct was performed in refluxing alcohol and gave a mixture of two acetals (**109**) and (**110**) ⟨89JOC5618⟩.



(**108**)

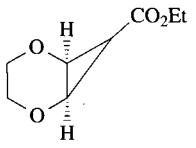


(**109**)

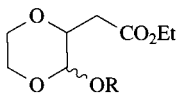


(**110**)

Metal-assisted decompositions of α-diazocarbonyl compounds in 1,2-dialkoxy-1-alkenes give dialkoxycyclopropylcarbonyl systems. Thus, reaction of 2,3-dihydro-1,4-dioxin with ethyl diazoacetate at 80 °C over copper bronze yielded the cyclopropane (**111**); acid catalyzed solvolysis of this with water, and with ethanol, gave hemiacetal and acetal esters (**112**) and (**113**), respectively ⟨85JOC4681⟩.

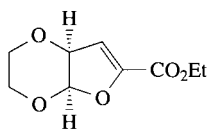


(**111**)

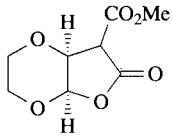


(**112**) R = H
(**113**) R = Et

Reaction of 2,3-dihydro-1,4-dioxin with ethyl diazopyruvate over (trimethylphosphino)copper(I) chloride produces dihydrofuroic ester (**114**) and a similar reaction with dimethyl diazomalonate, followed by acid hydrolysis, afforded the lactone ester (**115**) ⟨85JOC4681⟩.



(**114**)



(**115**)

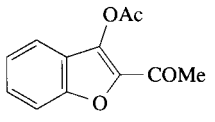
6.09.6.5 Cyclic Transition State with a Second Molecule

2,4,4,6-Tetrabromocyclohexa-2,5-dienone sensitizes the photooxidation of 5,6-diaryl-2,3-dihydrodioxins by electron transfer to yield ethane-1,2-diol dibenzoates, together with small quantities of the corresponding α-diketones. A preliminary investigation of the physical properties of the dienone supports a radical cation chain mechanism in which the active oxygen species involved is molecular oxygen ⟨86MI 609-01⟩. The 9,10-dicyanoanthracene-sensitized photooxidation of 5,6-diphenyl-2,3-dihydro-1,4-dioxin also produces ethylene glycol dibenzoate and small amounts of epoxide. Most of the diester is formed from singlet oxygen via the dioxetane, and only a small amount by electron transfer. The epoxide is a primary electron-transfer product ⟨91JA7672⟩. The photooxidation of 5,6-diaryl-2,3-dihydro-1,4-dioxins with singlet oxygen promoted by an anionic photosensitizer also affords ethane-1,2-diol dibenzoates ⟨82TL2943, 87JOC3501⟩. This sequence is also possible with 5,6-diphenyl-2,3-dihydro-1,4-oxathiin and -1,4-dithiin ⟨85TL3183⟩.

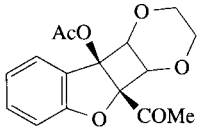
5,6-Diphenyl-2,3-dihydro-1,4-dioxin reacts with chromium(VI) or molybdenum(VI) oxide diperoxides in chloroform in the absence of oxygen, affording ethane-1,2-diol dibenzoate and benzil as reaction products ⟨88TL3145⟩.

Paterno–Büchi cycloaddition of 2,3-dihydro-1,4-dioxin to carbonyl compounds yields the expected compounds but these adducts have not yet been examined further ⟨85JA3819⟩.

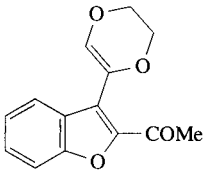
Various examples are available of reactions of the double bond with alkenes in [2 + 2] cycloadditions. Thus, photochemical cycloaddition of 2,3-dihydro-1,4-dioxin to 3-methylcyclohex-2-en-1-one leads to a mixture of four 11-methyl-1,4-dioxatricyclo[6.4.0.0.^{6,11}]dodecan-7-one isomers whose structures have been established by x-ray diffraction and ^{13}C NMR, and their conformational properties have been studied by force field calculations ⟨87JOC1993⟩. Analogous adducts (**117**) were obtained by photochemical addition of 2,3-dihydro-1,4-dioxin to the enol acetate (**116**). Acid hydrolysis of the 1,4-dioxin adduct, however, did not give the expected benzoxepin but a red crystalline compound which was assigned the benzofuran structure (**118**) ⟨83CC501⟩.



(**116**)

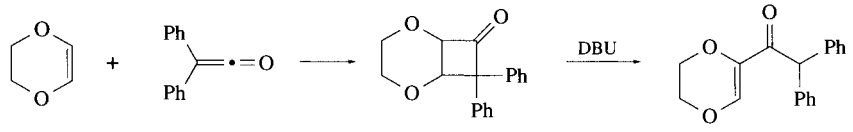


(**117**)



(**118**)

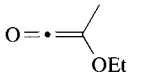
Cycloaddition of diphenylketene to 2,3-dihydro-1,4-dioxin (**10**) has been described. The resulting cyclobutanone (**119**) is transformed almost quantitatively to a ketone (**120**) on heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 3) ⟨89H(28)521⟩.



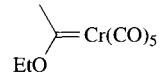
(**10**) (**119**) (**120**)

Scheme 3

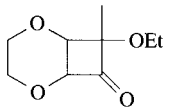
The preparation of cyclobutanone (**123**) via the [2 + 2] cycloaddition of ketene (**121**), and the photolytic reaction of chromium carbene complex (**122**) with 2,3-dihydro-1,4-dioxin (**10**), has also been described ⟨92TL927⟩.



(**121**)

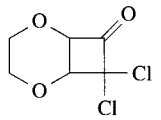


(**122**)

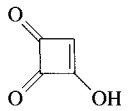


(**123**)

Cycloaddition of 2,3-dihydro-1,4-dioxin (**10**) to 1,1-dichloroketene, generated from zinc and trichloroacetyl chloride by sonication, leads to 7,7-dichloro-2,5-dioxabicyclo[4.2.0]octan-8-one (**124**), which upon acid hydrolysis affords semisquaric acid (**125**) ⟨90S583⟩.



(**124**)

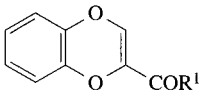


(**125**)

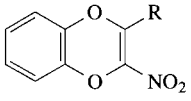
6.09.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

6.09.7.1 Fully Conjugated Rings

2-Trimethylsilyl-1,4-benzodioxin, readily prepared by metallation of 1,4-benzodioxin with *n*-butyllithium in tetrahydrofuran followed by addition of chlorotrimethylsilane, reacts efficiently in the presence of aluminum chloride with a range of aliphatic and aromatic acid chlorides. In each case, the corresponding 2-acylbenzodioxin (**126**) was obtained rapidly with satisfactory yields ⟨86S337⟩. 2-Trimethylstannyl-1,4-benzodioxin and its 3-methyl analogue are easily converted into the corresponding nitro derivatives (**127**) by treatment with tetranitromethane in dimethyl sulfoxide ⟨84TH 609-01⟩.

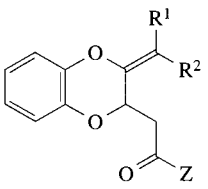


(**126**)

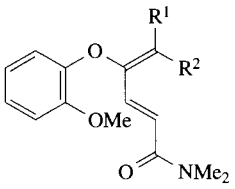


(**127**)

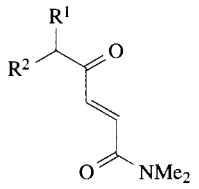
Allylic benzodioxin alcohols, prepared from 1,4-benzodioxin (**13**), when submitted to the acid-catalyzed orthoester Claisen rearrangement or the related Eschenmoser procedure lead respectively to derivatives (**128**) and (**129**). After treatment of compounds (**129**) at 0 °C with potassium *t*-butoxide then methylation with iodomethane, dienes (**130**) were isolated in good yields. The dienes (**130**) were also accessible by prolonged heating, in refluxing xylene, of allylic benzodioxin alcohols in the presence of *N*,*N*-dimethylacetamide dimethylacetal ⟨91TL5525⟩. The derivatives (**129**) were suggested to constitute versatile intermediates for the preparation of *N*,*N*-dimethyl-4-oxo-2-(*E*)-alkenamides (**131**). Indeed, when the compounds (**130**) were submitted to a basic elimination reaction, immediately followed by acidic hydrolysis with 10% aqueous trifluoroacetic acid, the corresponding expected alkenamides (**131**) were obtained in high yields ⟨94SC1781⟩.



(**128**) Z = OMe
(**129**) Z = NMe_2

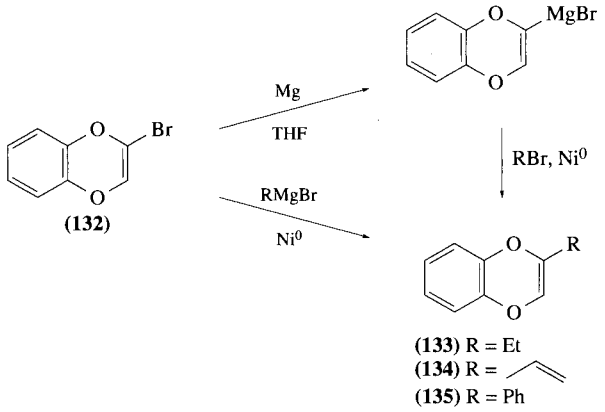


(**130**)



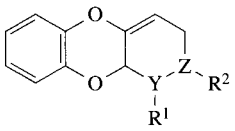
(**131**)

2-Bromo-1,4-benzodioxin (**132**) can readily be obtained by basic treatment of 2,3-dibromo-2,3-dihydro-1,4-benzodioxin, using potassium *t*-butoxide in diethyl ether ⟨90T921⟩. Two complementary methods were used for the synthesis of 2-substituted benzodioxins from the bromide (**132**). The first involves the reaction of alkenyl Grignard reagents in the presence of a catalytic amount (1 mol%) of (1,3-bis(diphenylphosphino)propane)nickel(II) chloride, resulting in the formation of the coupled products (**133**)–(**135**). The second method reverses the nature of the reagents by coupling the Grignard reagent derived from the bromide (**132**) with the necessary alkenyl halides, using the same catalyst (Scheme 4) ⟨89S208, 90T921⟩.



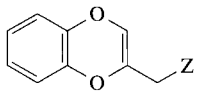
Scheme 4

In order to construct tricyclic systems containing the benzodioxin group, cycloaddition reactions of the diene (**134**) were studied. Reaction of (**134**) with reactive dienophiles such as maleic anhydride, dimethyl acetylenedicarboxylate, dialkyl azodicarboxylates, and tetracyanoethene gave in good yields a range of tricyclic adducts (**136**). The stereochemical outcome of the reactions follows the conventional pattern, giving the *endo* adducts in each case ⟨89SL30, 90T921⟩.

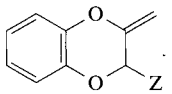


(**136**)

2-Hydroxymethyl-1,4-benzodioxin (**137**) obtained in 80% yield by reduction of ethyl 1,4-benzodioxin-2-carboxylate (**39**) with lithium aluminum hydride in refluxing ether ⟨91TL5525⟩ reacted with zinc azide bis-pyridine complex under Mitsunobu conditions (triphenylphosphine, diisopropyl azodicarboxylate) to yield exclusively compound (**138**) in 75% yield. Otherwise, (**137**) was first reacted with zinc iodide under the same conditions until complete transformation of the starting material into the mixture of regioisomers (**139**) and (**140**); excess of dry piperidine was then added to the crude reaction medium to yield the alkenic analogue (**141**) of Piperoxan ⟨89TL1637⟩.



(**137**) Z = OH
(**139**) Z = I
(**141**) Z = N

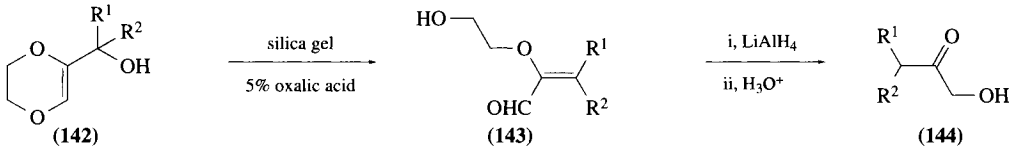


(**138**) Z = N_3
(**140**) Z = I

6.09.7.2 Saturated and Partially Saturated Compounds

The alcohols (**142**), easily obtained from 2,3-dihydro-1,4-dioxin (**10**) (Section 6.09.6.3.1), form the intermediates (**143**) by allylic rearrangement under mild conditions. Treatment of crude (**143**)

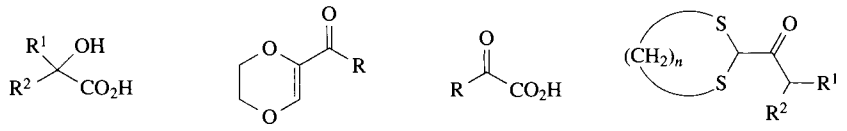
with lithium aluminum hydride, followed by hydrolysis of the enol ether, gives hydroxymethyl ketones (**144**) (Scheme 5) ⟨85TL3453⟩.



(142) (143) (144)

Scheme 5

The same allylic alcohols (**142**) undergo regiospecific oxidative cleavage with pyridinium chlorochromate at the ethylenic bond to give, after saponification, α-hydroxyacids (**145**). Extension of this reaction to αβ-unsaturated ketones (**146**), obtained by oxidation of secondary alcohols with silver carbonate on celite, affords α-ketoacids (**147**) ⟨88TL6261⟩.

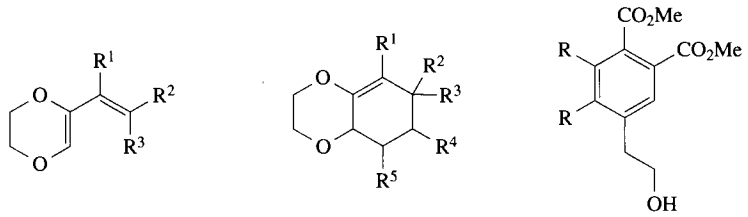


(145) (146) (147) (148) $n = 2$ (149) $n = 3$

The 5-acyl-2,3-dihydro-1,4-dioxins (**146**) directly produced by the alcohol oxidation can be also obtained by the following pathway. 5-Tributylstannyl-2,3-dihydro-1,4-dioxin, readily obtained from 5-lithio-2,3-dihydro-1,4-dioxin and chlorotributyltin (Section 6.09.6.3.1), smoothly undergoes palladium-catalyzed coupling reactions with aliphatic, aromatic, and heterocyclic acyl chlorides, affording the acyl compounds (**146**) in high yields. These compounds (**146**) were oxidized with pyridinium chlorochromate to the corresponding α-oxo esters, which were hydrolyzed to α-oxo acids (**147**) ⟨90S755⟩. The tertiary allylic alcohols (**142**) react with 1,2-ethanedithiol or 1,3-propanedithiol in dichloromethane in the presence of catalytic amounts of boron trifluoride etherate to give, after acid hydrolysis, 2-acyl-1,3-dithiolanes (**148**) or 2-acyl-1,3-dithianes (**149**), respectively ⟨87S503⟩.

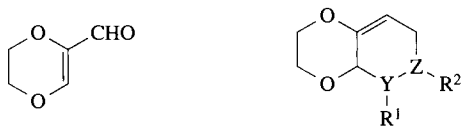
In a new synthesis of KDO, D-mannose, which has all of the asymmetric carbons, was effectively elongated by a two-carbon unit by condensation of its 6-di-*O*-isopropylidene furanose derivative with 5-lithio-2,3-dihydro-1,4-dioxin as a key step ⟨89MI 609-02⟩.

Substituted 5-vinyl-2,3-dihydro-1,4-dioxins (**150**), prepared by dehydration of allylic alcohols (**142**) with mesyl chloride–triethylamine or thionyl chloride–pyridine, undergo [4 + 2] cycloaddition reactions with various dienophiles to give the adducts (**151**). Exposure of (**151**), obtained by Diels–Alder reaction with dimethyl alkynedicarboxylate, to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by acidic hydrolysis affords the highly functionalized diesters (**152**) ⟨88JOC5672⟩.



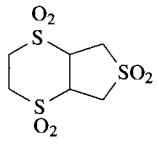
(150) (151) (152)

5-Vinyl-2,3-dihydro-1,4-dioxin (**150**; $R^1 = R^2 = R^3 = H$) was also prepared by Wittig alkenylation of the aldehyde (**153**). Cycloaddition with dienophiles such as tetracyanoethene, β-nitrostyrene, diethyl azodicarboxylate, phenyltriazolinedione, and diethyl mesoxalate gives the fused dioxins (**154**) ⟨86CB3204⟩.

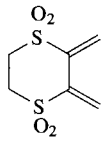


(153) (154)

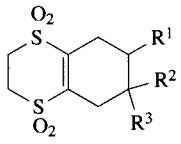
In the dithiin series, 2,3-(ethylenedisulfonyl)-1,3-butadiene (**156**) may be prepared readily by thermolysis of its stable 3-sulfolene precursor (**155**) in the presence of pyridine. The disulfone (**156**) is a very reactive diene and, although electron-deficient, readily reacts with both electron-rich and electron-poor dienophiles to afford the cycloadducts (**157**) ⟨92CB499⟩.



(**155**)

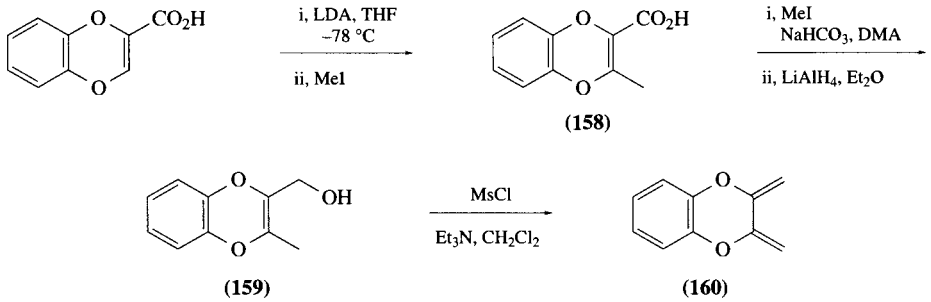


(**156**)



(**157**)

In the benzo-fused series, 2,3-dihydro-2,3-dimethylene-1,4-benzodioxin (**160**) was obtained by the route outlined in Scheme 6. The 3-methyl substituted acid (**158**), obtained by methylation of the dianion of 2-carboxy-1,4-benzodioxin, was esterified and then reduced with lithium aluminum hydride to afford the allylic alcohol (**159**). The treatment of (**159**) with mesyl chloride at −70°C in the presence of triethylamine afforded the required diene (**160**) in 80% overall yield. The Diels–Alder cycloaddition of the diene (**160**) with range of dienophiles (dimethyl alkynedicarboxylate, acrylonitrile, diisopropyl azodicarboxylate, methyl vinyl ketone, 2-vinylpyridine, 1,4-benzoquinone) gave, in good yields, the corresponding tricyclic adducts ⟨92TL2965⟩.



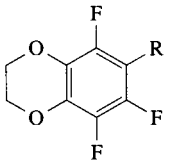
(**158**)

(**159**)

(**160**)

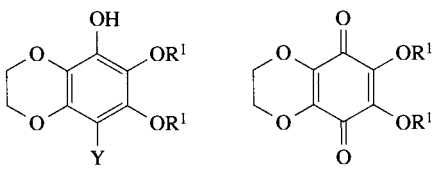
Scheme 6

As an illustrative example of the reactivity of aromatic substituents, light-catalyzed bromination of the methyl derivative (**161**) provided, in very good yield, the bromomethyl compound (**162**) which was converted into the acetamido derivative (**163**) by nucleophilic substitution ⟨81JFC(18)483⟩.



(**161**) R = Me
(**162**) R = CH_2Br
(**163**) R = $CH_2C(CO_2Et)_2NHCOMe$

Treatment of 6,7-dimethoxy and 6,7-methylenedioxy-5-hydroxy or 5,8-dihydroxy-2,3-dihydro-1,4-benzodioxins (**164**) with potassium nitrosodisulfonate in acetone easily affords the corresponding quinones (**165**) ⟨87CZ193⟩.



(**164**) Y = H or OH (**165**)

R^1 = Me or R^1–R^1 = $-CH_2-$

6.09.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO A RING HETEROATOM

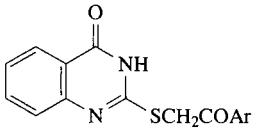
In the ring containing sulfur, sulfoxides of phenoxathiin and thianthrene are reduced to the corresponding sulfides in excellent yields with the aluminum chloride/sodium iodide ⟨88IJC(B)259⟩ or zinc dust/1,4-dibromobutane systems ⟨87CPB4351⟩.

6.09.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

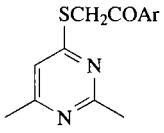
6.09.9.1 Fully Unsaturated Compounds

6.09.9.1.1 Nonbenzo-fused ring systems

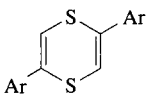
1,4-Dioxins and 1,4-dithiins have often been prepared by elimination reactions of appropriately substituted saturated analogues. However, in the more recent literature a number of examples of syntheses of 1,4-dithiins are described. Of the several methods developed over the past decades, methods involving condensation or cycloaddition are of greater synthetic importance. Thus, the synthesis of 2,5-diphenyl-1,4-dithiin involves the formation of the Bunte salt from phenacyl halides with sodium thiosulfate, followed by cyclization under acidic conditions. This procedure is widely applicable to the preparation of 2,5-diaryl-1,4-dithiins ⟨86SR123⟩. Modifications of this method have been reported; the treatment of the phenacylthio derivatives (**166**) and (**167**) with hydrochloric or perchloric acid affords 2,5-diaryl-1,4-dithiins (**168**), the pyrimidine and quinazoline rings having functioned as protecting groups for the thiol ⟨84T4941⟩.



(166)

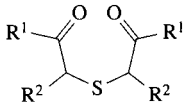


(167)

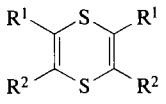


(168)

The construction of the 1,4-dithiin ring system via Bunte salt formation is severely limited. This difficulty is, however, overcome by using β,β′-dioxodialkyl sulfides and phosphorus pentasulfide or Lawesson's reagent. Thus, treatment of the sulfides (**169**), readily obtainable from α-haloketones and sodium sulfide, with phosphorus pentasulfide or Lawesson's reagent in refluxing toluene or benzene affords a variety of 1,4-dithiins (**170**) in good yields ⟨84H(22)1527, 89H(29)391, 91PS(57)227⟩. In the same manner, hydrothiation of (**169**; $R^1 = Ph$, $R^2 = H$) by hydrogen sulfide in methanol containing hydrochloric acid gives 2,6-diphenyl-1,4-dithiin in 93% yield ⟨87KGS419⟩.



(169)

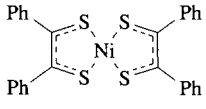


(170)

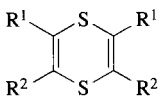
1,4-Dithiins can also be generated by cyclization of a five-atom fragment and a one-atom unit. 1-Alkynylethynyl sulfides react with sodium sulfide in methanol to afford monosubstituted 1,4-dithiins ⟨86SR123⟩. Likewise, dipropynyl sulfone is transformed conveniently into 3,5-dimethyl-1,4-oxathiin 1,1-dioxide during chromatography on alumina in the presence of a protic acid ⟨91SUL133⟩.

Another approach is based on cyclization between a two-atom and a four-atom fragment. This involves treating alkynes (**171**) with nickel bisdiphenyldithiolene (**172**) in refluxing chlorobenzene in the presence of pyridine. Pyridine appears to be essential in order to avoid further transformation of 1,4-dithiins (**173**) to thiophenes ⟨87SC1683⟩.

(171)



(172)

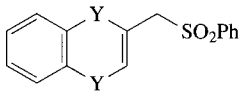


(173)

6.09.9.1.2 Benzo-fused ring systems

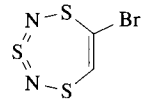
The monobenzo-fused derivatives of 1,4-dioxin, 1,4-oxathiin, and 1,4-dithiin can all be prepared by routes in which the first step is a base-catalyzed reaction between the appropriate 1,2-disubstituted benzene and an α-haloketal. The product is a 2-alkoxy-2,3-dihydro derivative from which the unsaturated heterocycle is obtained in one or more steps ⟨84CHEC-I(3)943⟩.

A direct synthesis of 1,4-benzodioxin (**174**) is feasible by treatment of catechol with (*E*)-2,3-diodo-1-phenylsulfonyl-1-propene in the presence of pyridine or potassium carbonate. Similarly, 1,2-benzenedithiol cleanly afforded (**175**) in high yield ⟨92JOC1161⟩.

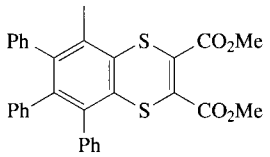


(**174**) Y = O
(**175**) Y = S

In the benzodithiin series, direct synthesis is also possible by condensation of 1,2-benzenedithiol with dichloroalkenes. Thus, reaction of the disodium salt of 1,2-benzenedithiol with trichloroethylene provides quantitative yields of 2-chloro-1,4-benzodithiin ⟨92CC1089⟩. These derivatives can also be obtained by an acidic procedure: the treatment of 1,2-benzenedithiol with an α-bromo ketone in the presence of *p*-toluenesulfonic acid affords the corresponding benzodithiins with excellent yields ⟨94T7913⟩. A special case is that of 6-bromotrithiadiazepine (**176**), which when treated with 2-methyl-3,4,5-triphenylcyclopentadienone and dimethyl alkynedicarboxylate in the presence of Hünig's base gives the 1,4-benzodithiin (**177**) in relatively modest yields ⟨91JCS(P1)317⟩.



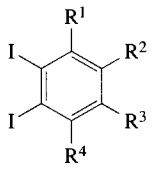
(**176**)



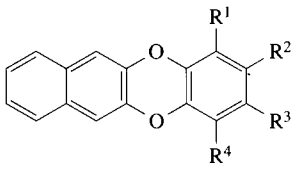
(**177**)

With one or two exceptions, dibenzo-fused derivatives require quite different synthetic strategies to those above. Oxanthrene (**7**) is nowadays frequently prepared in 10–20% yield by heating a mixture of 2-chlorophenol, potassium carbonate, and copper powder to 170–180 °C ⟨57JA1439⟩. The disodium salt of catechol can also be used as a precursor, by reacting it with an aromatic ring containing two displaceable substituents. Reactions of the unactivated 1,2-dichlorobenzene with this anion in HMPA gave only trace amounts (< 1%) of the parent oxanthrene. However, 2-chloronitrobenzene gave a 71% yield and 1,2-dinitrobenzene an 87% yield under the same conditions ⟨90JCS(P1)1071⟩.

The synthesis of a series of new alkoxylated annulated dioxins has been described from 2,3-dihydroxynaphthalene. For example, the readily available diiodinated substrates (**178**) were reacted with the dianion of 2,3-dihydroxynaphthalene in the presence of copper(I) iodide in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone as solvent. By this procedure, new fused dioxins (**179**) were isolated in modest yields after chromatography ⟨94TL1769⟩.



(**178**)



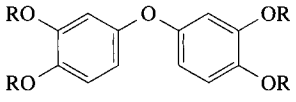
(**179**)

These various approaches, however, require vigorous experimental conditions which may not be appropriate for the synthesis of polyfunctional oxanthrenes. Moreover, the formation of a mixture of regioisomeric products (often very difficult to separate) when each of the coupling partners is unsymmetrical presents an additional problem. Activation of 1,2-dichlorobenzene by complexation with tricarbonylchromium solves the former problem. Thus, the reaction of this activated dichlorobenzene with an excess of the potassium salt of the catechol gave a good yield of the oxanthrene at relatively low temperature ⟨86ZOR157⟩. An alternative method, which uses a cationic (cyclo-

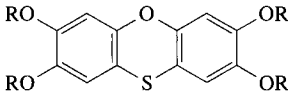
pentadienyl)iron complex to activate 1,2-dichlorobenzene towards nucleophilic substitution, has been reported ⟨88H(25)1911, 91JOM(420)387⟩.

In the thianthrene series, *o*-diodo- and *o*-bromochloro derivatives react under photostimulation by the $S_{RN}1$ mechanism with 3,4-toluenedithiolate anion to give good yields of the cyclic substituted compound, 2-methylthianthrene ⟨87JOC1089⟩.

A particularly valuable route to phenoxathiin utilizes the long-known reactions of diphenyl ether with sulfur in the presence of aluminum chloride. Thianthrene was similarly prepared from sulfur and benzene. These harsh conditions would not be suitable for the preparation of electron-rich alkoxylated dibenzo compounds (**181**). For the construction of compounds (**181**), a strategy involving electrophilic ring closure of preformed alkoxylated diaryl chalcogenides (**180**) was used. Thus, treatment of compounds (**180**) with sulfur dichloride in dry chloroform provided the derived phenoxathiins (**181**) in satisfactory yields ⟨88JCS(P1)2095⟩.

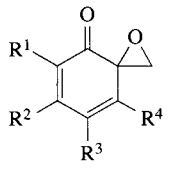


(**180**)

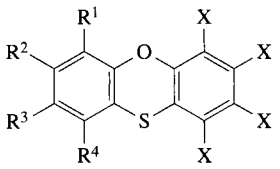


(**181**)

A series of halogenated phenoxathiins (**183**) has been prepared satisfactorily by the reaction between 1-oxaspiro[2.5]octa-5,7-dien-4-ones (**182**) and the appropriate pentahalogenated thiophenolate anion. The reaction sequence appears to be initiated by nucleophilic attack by the thiolate anion at the quaternary carbon of the spiroepoxide ring system with concomitant cleavage of a carbon–oxygen bond of the epoxide ring to produce a presumed intermediate. Rearrangement of this intermediate to a phenolate occurs with elimination of formaldehyde. The phenolate then leads to formation of the phenoxathiin by a secondary intramolecular nucleophilic substitution of an *o*-halo group ⟨84AJC2537⟩.



(**182**)



(**183**) X = Cl or F

6.09.9.2 Saturated and Partially Saturated Compounds

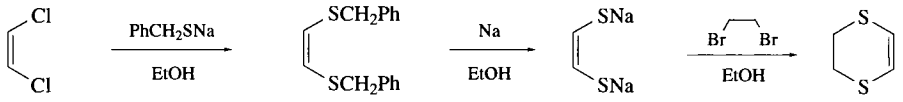
The chemistry of almost all of the numerous syntheses of 1,4-dioxanes, 1,4-oxathianes, and 1,4-dithianes utilizes the nucleophilicity of negatively charged or neutral oxygen and sulfur atoms. In CHEC-I, this subject is expounded in detail ⟨84CHEC-I(3)943⟩.

More general routes to rings containing one double bond utilize elimination of an alcohol from a 2-alkoxy derivative of the saturated ring system or elimination of water, which frequently occurs under cyclization conditions. Thus, acid-catalyzed reactions of α-hydroxy ketones with ethylene glycol, 2-thiolethanol, and 1,2-ethanedithiol furnish, in most cases, the corresponding dihydro-1,4-dioxin, dihydro-1,4-oxathiin, and dihydro-1,4-dithiin derivatives respectively, in high yields ⟨85TL3183, 91ACS410⟩. Likewise, the treatment of 2-haloketones or 2-haloesters with 2-thiolethanol and 1,2-ethanedithiol gives the dihydro-1,4-oxathiins and the dihydro-1,4-dithiins respectively ⟨88MI 609-02, 90ACS591⟩.

Another approach applicable to 2,3-dihydro-1,4-dioxins involves the reaction of benzoin with monoethylene glycol ditosylates in the presence of an alkali metal hydroxide in homogeneous or heterogeneous solutions ⟨85JOC5151⟩.

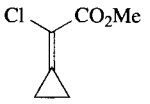
An alternative synthesis of 2,3-dihydro-1,4-dithiin employs an unsaturated dithiolate ion. Thus, *cis*-1,2-ethylenedithiolate, generated from 1,2-dichloroethylene as shown, reacts with 1,2-dibromoethane to give the desired compound (Scheme 7) ⟨91SM2093⟩.

In the 2,3-dihydro-1,4-benzodioxin series, several approaches are available. One of the most usual is to substitute the dianion of the catechol or its derivative with a dihalogenated derivative ⟨54JCS18, 55JA5373, 93JMC1520⟩ or with an α-chloronitrile or ester ⟨74JOC1808⟩. Thus, methyl 2-chloro-2-cyclopropylideneacetate (**184**) reacts with the dianion of catechol in a heterogeneous system of potassium

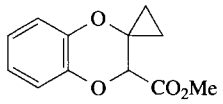


Scheme 7

hydroxide and dichloromethane under phase-transfer catalysis to give spirocyclopropane annelated heterocyclic carboxylate (**185**) ⟨89T2957⟩.

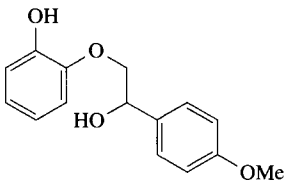


(**184**)

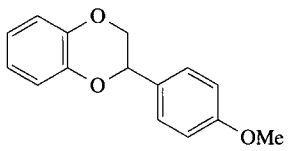


(**185**)

Another approach uses the reaction of catechol dianion derivatives with epichlorohydrin and yields 2,3-dihydro-1,4-benzodioxins substituted in the 2-position by a hydroxymethyl group ⟨81JOC3846, 86CC1432⟩. A third route is a cyclization reaction between the two hydroxyl functions of an *o*-hydroxyalkyloxyphenol. For example, cyclization of diol (**186**) to 2,3-dihydro-1,4-benzodioxin (**187**) was accomplished by brief heating in toluene with the strongly acidic ion exchanger Amberlyst 15 as a catalyst ⟨86MI 609-03⟩. The cyclization by polyphosphoric acid was also possible ⟨89ABC1557⟩.



(**186**)

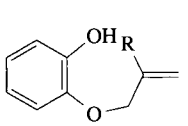


(**187**)

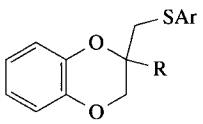
The method using Amberlyst 15 can also be applied to the 2,3-dihydro-1,4-benzoxathiin and 2,3-dihydro-1,4-benzodithiin series ⟨93JCS(P1)1359⟩.

The cyclodehydration reactions of hydroxyalkyloxyphenols using a tosylate ⟨88MI 609-03⟩ or imidate ester ⟨93TL7483⟩ as leaving group are also available.

Another route uses alkyloxyphenols (**188**) which, when treated with various arylsulfenyl chlorides yield the corresponding 2,3-dihydro-1,4-benzodioxin derivatives (**189**) by intramolecular cyclization ⟨86JPR137⟩.

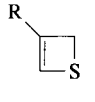


(**188**) R = H or Me

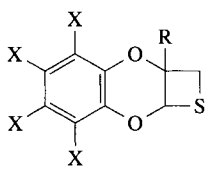


(**189**) R = H or Me

Thietes (thiacyclobutenes) (**190**) give substituted 2,3-dihydro-1,4-benzodioxins (**191**), when treated in dichloromethane at reflux with *o*-chloranil or *o*-bromanil ⟨87H(26)969⟩.



(**190**)

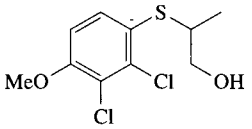


(**191**)

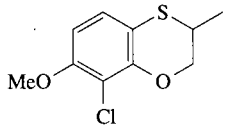
The 2,3-dihydro-1,4-benzodioxin ring system has aroused increasing interest, owing to its presence in a large number of structures of important therapeutic agents, the activity of which is considerably influenced by the chirality of the heterocyclic unit. Most of the syntheses of optically pure 2-substituted-2,3-dihydro-1,4-benzodioxins start from 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin in chiral form; this latter compound can be obtained from D-mannitol ⟨76CC921⟩, by direct con-

densation of catechol with chiral glycidol ⟨88TL3671⟩ or epichlorohydrin ⟨86T447⟩, by Sharpless epoxidation of a 1-aryloxy-4-hydroxy-2-butene substrate ⟨85H(23)2005⟩ or by enzymatic ⟨92TL6283, 93TA339⟩ or chemical resolution ⟨94TA538⟩ of the racemic compound. Furthermore, 2-vinyl-2,3-dihydro-1,4-benzodioxin was obtained with *ee* up to 45% by condensation of catechol and (*Z*)-2-butene-1,4-diylbis(methylcarbonate) in the presence of a catalytic amount of palladium(0) in association with a chiral ligand such as (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine) ⟨94TL6093⟩.

The monobenzo-fused 1,4-dithiin and 1,4-oxathiin derivatives were originally prepared via base-catalyzed nucleophilic substitution reactions using 1,2-benzenedithiol or *o*-thiolphenol. Although an improved method, starting from more readily available materials such as thiophenol or phenol, has been devised ⟨75S451⟩, the preparation of these compounds is still not easy. 2,3-Dihydro-1,4-benzodithiins and 2,3-dihydro-1,4-benzoxathiins have been prepared in good yields by a one-pot procedure from the reaction of cyclohexanone derivatives with ethane-1,2-dithiol or 2-thiolethanol using *N*-bromosuccinimide in dichloromethane at 0 °C ⟨93H(36)1783⟩. 2,3-Dihydro-1,4-benzodithiin is also accessible by reaction of the readily available 7-oxabicyclo[2.2.1]hept-5-en-2-one with 1,2-ethanedithiol in acetic acid in the presence of boron trifluoride etherate ⟨86H(24)141⟩. Another approach to the dihydrobenzoxathiin nucleus was devised via an intramolecular alkoxide induced chloride displacement. Thus, for example, when diglyme was employed as solvent, clean cyclization of the 2-arylthiopropanol (**192**) to the 3-methyl-2,3-dihydro-1,4-benzoxathiin (**193**) resulted in 63% yield ⟨83JHC867⟩.



(192)



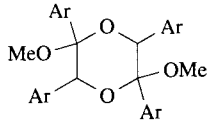
(193)

6.09.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

6.09.10.1 Fully Unsaturated Compounds

6.09.10.1.1 Nonbenzo-fused ring systems

1,4-Dioxins, 1,4-oxathiins, and 1,4-dithiins have often been prepared by elimination reactions of appropriately substituted saturated analogues. Thus, for example, by elimination of methanol from 2,5-dimethoxy-1,4-dioxans (**194**) and 2,3-dihydro-2-methoxy-1,4-dioxins (**195**) with *p*-toluenesulfonic acid in acetic anhydride, tetra(4-methoxyphenyl)-, tetra(4-chlorophenyl)-, and tetra-*p*-tolyl-1,4-dioxins (**196**) were prepared in good yields ⟨85CB4385⟩.



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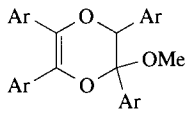
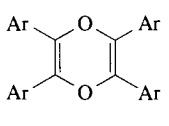
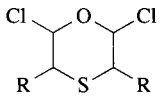


(195)



(196)

The dechlorination of 2,3,5,6-tetrachloro-2,3-difluoro-2,3-dihydro-1,4-dioxin with zinc in dimethylformamide afforded 2,3-dichloro-5,6-difluoro-1,4-dioxin as a distillate contamination with dimethylformamide ⟨91JOC3915⟩. In the oxathiin series, sulfur dichloride added to vinylic ethers gave 2,6-dichloro-1,4-oxathianes (**197**). Dehydrohalogenation of these products by potassium *t*-butoxide gives the fully unsaturated compounds 1,4-oxathiin and 3,5-dimethyl-1,4-oxathiin (**198**) in moderate to reasonable yields ⟨80RTC12⟩.



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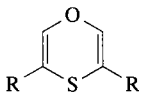
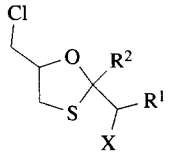
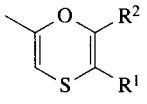


(198)

1,4-Oxathiins can also be obtained by rearrangement of another heterocyclic ring. Thus, 1,4-oxathiins are obtained by ring expansion of 1,3-oxathiolanes (**199**). These compounds are synthesized from 1-thiol-3-chloro-2-propanol and the appropriate α-halo-ketone in good yields. Elimination and rearrangement of the 1,3-oxathiolanes by means of potassium *t*-butoxide in dimethyl sulfoxide at room temperature yields 1,4-oxathiins (**200**) in at least 80% yield, provided that bromide is the leaving group. The yields decrease markedly if the chloro counterparts (X = Cl) are used ⟨86JOC1894⟩.

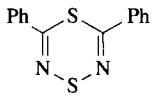


(**199**)

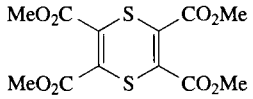


(**200**)

Synthetic routes to 1,4-dithiins have been explored more thoroughly than those to the 1,4-dioxin and 1,4-oxathiin ring systems. The parent compound is obtained in 47–60% yield by vapour-phase dealkoxylation of 2,5-dialkoxy-1,4-dithianes over alumina at 260–265 °C, and this type of approach can also be used to prepare 2,5-dimethyl-1,4-dithiin. Such cleavages can be brought about either photochemically or by thermal reactions. 1,4-Dithiins can also be derived as cleavage products of other heterocyclic rings ⟨86SR123⟩. Thus, dithiadiazine (**201**) reacts with dimethyl alkynedicarboxylate in boiling *o*-dichlorobenzene to give dithiin tetracarboxylate (**202**), both possible molecules of benzonitrile having been eliminated ⟨87JCS(P1)207⟩.



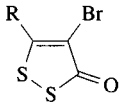
(**201**)



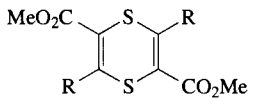
(**202**)

4-Bromo-3*H*-1,2-dithiol-3-ones (**203**) containing aryl substituents in the 5-position react with methanolic methylate solution to give dimethyl 1,4-dithiin-2,5-dicarboxylates (**204**) with aryl substituents in the 3- and 6-positions ⟨83PS(17)135⟩.

The synthesis of dithiins may proceed via 1,2-dithiete intermediates. In these cases, yields of dithiins are usually low but the chemistry is interesting ⟨93BCJ623⟩.



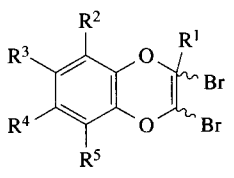
(**203**)



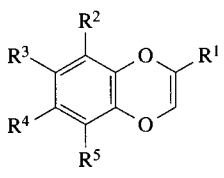
(**204**)

6.09.10.1.2 Benzo-fused ring systems

A general route to 1,4-benzodioxins starts from the corresponding dihydro compounds. Thus, treatment of 2,3-dihydro-1,4-benzodioxin derivatives with *N*-bromosuccinimide gives the corresponding 2,3-dibromo-2,3-dihydrobenzodioxins (**205**). The bromination step with *N*-bromosuccinimide is particularly critical, since electrophilic substitution of the benzo ring constitutes an undesirable side reaction. Then, the dibromo compounds undergo debromination on reaction with an excess of sodium iodide in acetone, affording the desired products (**206**) in very good overall yields ⟨78TL1059, 84JOC3920, 84MI 609-03, 87JOC5616, 89JHC193⟩.



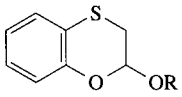
(**205**)



(**206**)

2-Aryl-1,4-benzodioxins have been prepared by dehydration of 2,3-dihydro-2-hydroxy-2-aryl-1,4-benzodioxins with thionyl chloride in pyridine at elevated temperatures ⟨84JOC3920⟩ or with copper(II) sulfate in toluene at reflux ⟨91JCS(P2)1399⟩.

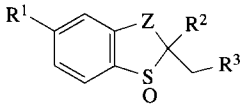
In the 1,4-benzoxathiin series, neither dehydration of the hydroxy compound (**207**) nor elimination of ethanol from (**208**) gives a very satisfactory yield of (**6**), and once again the best yield (76%) is obtained by pyrolysis of the 2-acetoxy derivative (**209**). 3-Methyl-1,4-benzoxathiin is obtained by an analogous route ⟨66HC(21-2)852⟩.



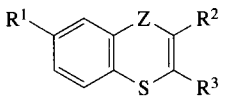
(**207**) R = H
(**208**) R = Et
(**209**) R = COMe

In contrast to the difficulty experienced in eliminating ethanol from (**208**), the corresponding elimination reaction in 2-ethoxy-2,3-dihydro-1,4-benzodithiin occurs remarkably well. The best conditions involve the use of phosphorus pentoxide at 170–175°C, to give 1,4-benzodithiin in 75% yield ⟨66HC(21-2)1143⟩. 1,4-Benzodithiin can also be obtained by the dehydrogenation of 2,3-dihydro-1,4-benzodithiin. Thus, exposure of 2,3-dihydro-1,4-benzodithiin to an oxidation (sodium meta-periodate)-dehydration (acetic anhydride) treatment yielded the desired product in 49% yield ⟨84MI 609-01⟩.

Benzoxathiin and benzodithiin derivatives can also be derived as rearrangement products of other heterocyclic rings. Thus, nonstereospecific ring expansion reactions of 1,3-benzoxathiole sulfoxides (**210**) and 1,3-benzodithiole sulfoxides (**211**) with acetic anhydride or *p*-toluenesulfonic acid afford the corresponding 1,4-benzoxathiins or 1,4-benzodithiins (**212**) and (**213**) in satisfactory yields ⟨84TL757, 94T7913⟩.

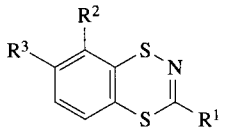


(**210**) Z = O
(**211**) Z = S

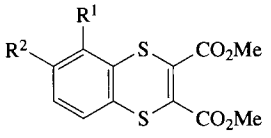


(**212**) Z = O
(**213**) Z = S

Benzodithiazines (**214**) reacted with dimethyl alkynedicarboxylate in boiling *o*-dichlorobenzene to give 2,3-bis(methoxycarbonyl)-1,4-benzodithiins (**215**) in good yields with elimination of hydrogen cyanide or a nitrile ⟨82CC612⟩.

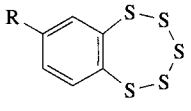


(**214**)

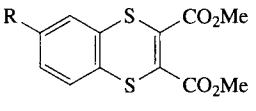


(**215**)

The reaction of benzopentathiepins (**216**) and dimethyl alkynedicarboxylate in the presence of triphenylphosphine or triethylamine gives 1,4-benzodithiins (**217**) in good to excellent yields ⟨85JA3871, 90SUL233⟩.



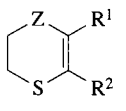
(**216**)



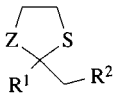
(**217**)

6.09.10.2 Saturated and Partially Saturated Compounds

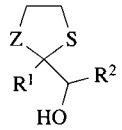
5,6-Dihydro-1,4-oxathiins (**218**) and 5,6-dihydro-1,4-dithiins (**219**) can be obtained easily in moderate to excellent yields from 1,3-oxathiolanes (**220**) and 1,3-dithiolanes (**221**), respectively, by treatment with bromine ⟨91S223⟩, *N*-bromosuccinimide ⟨94T7265⟩, chlorine ⟨87JOC5374, 91S223⟩, sulfuryl chloride ⟨88JCR(M)1401⟩, or tellurium tetrachloride ⟨90CL1323⟩. Treatment of the 2-(1-hydroxyalkyl)-1,3-oxathiolanes (**222**) and dithiolanes (**233**) with tosyl chloride in pyridine, mesyl chloride in the presence of triethylamine, sulfuryl chloride, hydrobromic acid or *p*-toluenesulfonic acid resulted in ring expansion, again forming the 2,3-dihydro-1,4-oxathiins (**218**) and the 2,4-dihydro-1,4-dithiins (**219**) respectively, in good yields ⟨89JOC2455, 90ACS591, 91S575, 95H(41)921⟩. Moreover, thermolysis of α-alkylthio substituted *N*-aziridinylimines (**224**) and (**225**) in refluxing toluene gave, in high yields, compounds containing heterocyclic rings such as 1,4-oxathiins (**218**) and 1,4-dithiins (**219**), respectively ⟨94H(38)1971⟩. Finally, elimination and rearrangement of 1,3-oxathiolanes (**226**) by means of potassium *t*-butoxide in dimethyl sulfoxide at room temperature yields 5,6-dihydro-1,4-oxathiins (**218**) in excellent yields ⟨86JOC1894⟩.



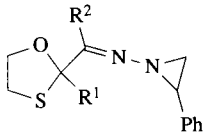
(**218**) Z = O
(**219**) Z = S



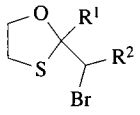
(**220**) Z = O
(**221**) Z = S



(**222**) Z = O
(**223**) Z = S



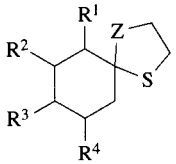
(**224**) Z = O
(**225**) Z = S



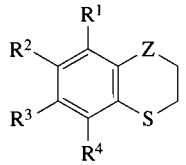
(**226**)

The ring expansion of appropriately substituted 1,3-oxathiolane sulfoxides and 1,3-dithiolane sulfoxides can be performed under acidic or neutral conditions. This sequence gives, in good yields, the corresponding substituted 2,3-dihydro-1,4-oxathiins and 2,3-dihydro-1,4-dithiins ⟨84TL757, 86JOC2789, 91T8091⟩.

For the benzo-fused series, the ethylene monothioacetals (**227**) and dithioacetals (**228**) of alkylcyclohexanones react with copper(II) bromide in diglyme at 110 °C to give, in satisfactory yields, 2,3-dihydro-1,4-benzoxathiin (**229**) and 2,3-dihydro-1,4-benzodithiin (**230**) derivatives, respectively ⟨85CC1645⟩.



(**227**) Z = O
(**228**) Z = S



(**229**) Z = O
(**230**) Z = S

Ethylene dithioacetal derivatives of cyclohexanone and substituted cyclohexanones are also reported to be rapidly and smoothly converted into 2,3-dihydro-1,4-benzodithiins by simple treatment with bromine in anhydrous chloroform at room temperature ⟨91T4187⟩.

1,4-Dithiins can also be derived from the decomposition of other heterocyclic systems. Thus, the reactions of benzopentathiepin with norbornene, norbornadiene, and acrylonitrile in the presence of triethylamine afforded the corresponding 2,3-dihydro-1,4-benzodithiins, in satisfactory yields ⟨90SUL233⟩. The reaction of 2,3-dimethyl-2-butene with benzopentathiepin in the presence of boron trifluoride etherate give 2,2,3,3-tetramethyl-2,3-dihydro-1,4-benzodithiin in 89% yield ⟨89CL2111⟩.

6.09.11 IMPORTANT COMPOUNDS AND APPLICATIONS

Few chemicals have acquired as much notoriety as 2,3,7,8-tetrachlorooxanthrene, or -dibenzo[*b*,*e*][1,4]dioxin. The compound, commonly referred to as TCDD, or simply but misleading as dioxin, is formed as a by-product in the commercial preparation of 2,4,5-trichlorophenol, an intermediate in the manufacture of the bactericide hexachlorophene and the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The commercial production of 2,4,5-trichlorophenol, during which TCDD is generated, involves the reaction of 1,2,4,5-tetrachlorobenzene with base; TCDD is formed if the product reacts further.

TCDD is extraordinarily toxic (for rats the LD_{50} is 45 $\mu g\ kg^{-1}$) and is also a teratogen, i.e. an agent causing birth defects. Typical symptoms resulting from occupational exposure include chloracne, a very severe form of acne, and liver damage. Disquiet has arisen principally in connection with the compound's impact on the environment and the attendant health hazards, problems which became particularly apparent during the defoliation programme in Vietnam which utilized a formulation based partly on 2,4,5-T containing TCDD as contaminant. Public awareness of its toxicity was heightened after an explosion at Seveso in northern Italy (July 1976), where an estimated 2.5 kg of TCDD was released over the adjacent area ⟨76MI 609-01, B-79MI 609-01⟩.

Most other oxanthrene are relatively nontoxic and potential applications for the ring system have been sought within medicinal chemistry. Thus, the oxanthrene-1-carboxamides are active against wild-type P388 leukemia *in vitro* and *in vivo*, with structure–activity relationships resembling those for both the acridine-4-carboxamide and phenazine-1-carboxamide series of DNA-intercalating antitumor agents ⟨92JMC258⟩.

Phenoxathiins have found quite a range of applications ⟨66HC(21-2)867⟩. Included among these are the use of phenoxathiin itself as an insecticide against aphids, termites, houseflies, rice weevils, etc. 1-Ethylphenoxathiin 10,10-dioxide (1370 U 87) is a potent monoamine oxidase inhibitor selective for MAO A. This compound gives positive results in standard antidepressant tests in rats and in a personality disorder paradigm in Rhesus monkeys ⟨91JMC2931⟩.

Thianthrene derivatives have been patented for a variety of uses including an early treatment of skin infections caused by mites, as a solvent and plasticizer for PVC, and as a stabilizer in coolant moderator fluids for nuclear reactors. Furthermore, 2,7-dimethylthianthrene is an ingredient in shampoos and soaps used to control scabies, seborrhea and pruritus ⟨84JAP(K)59230100⟩ and, in admixture with ditoluene disulfide, it is used as a skin cosmetic for the removal of freckles ⟨81JAP(K)55151507⟩.

(Piperazinomethyl)benzodioxins are useful as psychotropics ⟨83EUP84993⟩ and 2-benzodioxinylaminoethanol derivatives demonstrated a β-blocking activity of a competitive type and antihypertensive properties ⟨81JMC994⟩. Benzoxathiins are prepared as lypoxygenase inhibitors ⟨87GEP(O)3532279⟩.

1,4-Dithiin rings substituted with cyano groups at the 2- and 3-positions, and fused to rings such as naphthoquinones, chloropyridazines, and pyrazines, have been shown to have good fungicidal and bacteriological properties for agricultural use.

Among the saturated or partially saturated compounds, 1,4-dioxane is of well proven industrial importance. It is an excellent solvent for a range of materials including cellulose acetate, oils, greases, waxes and resins, and finds use as a solvent in the manufacture of paints, varnishes and polishes, and as a wetting agent and dispersing agent in textile processing. It has also been used in dye baths and in printing and polishing compositions.

Numerous derivatives of 2,3-dihydro-1,4-benzodioxin have been studied in the field of medicinal chemistry as: selective α_1-adrenoreceptor antagonist (WB4101) ⟨87EJM23⟩, (Doxazosin) ⟨87JMC49⟩, (Phendioxan) ⟨90JMC2946⟩, selective α_2-adrenoreceptor antagonist (Idazoxan) ⟨83JMC823⟩, selective 5-HT_{1A} receptor agonist (Spiroxatrine) ⟨88JMC1965⟩, (MDL72832) ⟨88JMC1087⟩, (Flesinoxan) ⟨88MI 609-04⟩, 5-HT_{1B} receptor agonist (Eltoprazine) ⟨86JAP(K)61152655⟩, 5-HT_4 receptor antagonist (SB 204070A) ⟨93JMC4121⟩. The pharmacological activity of the above-mentioned compounds varies greatly, depending on their specific observed affinities. Thus, these derivatives can be antihypertensive agents, antidepressant agents, anxiolytic agents, serenic agents, etc.

Among the 2-phenyl-2,3-dihydro-1,4-benzodioxins, one of them, 2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-1,4-benzodioxin, is 450 times sweeter than sucrose, with an aftertaste similar to that of Phyllodulcin ⟨91JCS(P2)1399⟩.

The 2,3-dihydro-1,4-benzodioxin framework has often been found in biologically active lignans. Silybin ⟨75CB1482⟩ and Americanin A ⟨78TL3239⟩ are antihepatotoxic, and Haedoxan ⟨89ABC631⟩ has insecticidal activity.

In the 2,3-dihydro-1,4-benzoxathiin series, the 2,2-(2,6-dimethoxyphenoxy)ethylamino methyl-

2,3-dihydro-1,4-benzoxathiin (Benoxathian) is a potent and selective α_1-adrenoreceptor antagonist ⟨84JMC1535⟩.

Derivatives of 2,3-dihydro-1,4-oxathiin have been patented as agrochemicals. Thus, 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide or Carboxin is a well-known systemic fungicide used for seed treatment ⟨B-77MI 609-01⟩. The ring substituents are apparently very important; various analogues of Carboxin such as the free acid, simple esters and *N*-alkylated amides show considerably less fungicidal activity or are quite inactive.

Some 2,3-dihydro-1,4-dithiin derivatives have also attracted attention as chemicals for agricultural use ⟨77USP4062969⟩. Pyrimidine nucleoside analogues, in which the group attached at *N*-1 is a six-membered ring containing two heteroatoms (1,4-dioxane, 1,4-dithiane and 1,4-oxathiane), have been synthesized and show relative activity on the growth of a variety of tumor cells in tissue culture ⟨82JMC522⟩.

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6.10
1,2,3-Triazines and their Benzo Derivatives

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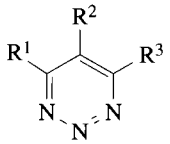
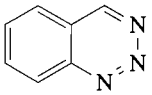
6.10.1 INTRODUCTION

Among the three triazine isomers, the 1,2,3-triazines (**1**) are the least studied compounds in comparison with their 1,3,5- and 1,2,4-isomers, because the ring system is the least stable of the three. Since the first report of 1,2,3-benzotriazin-4-one in 1887 ⟨1887JPR262⟩, monocyclic 1,2,3-triazines which were synthesized before 1979 were limited to 4,5,6-trisubstituted examples, because the only and general method for their synthesis was by the rearrangement of trisubstituted cyclopropenyl azides. Study of the reactivity and stability of the unsubstituted ring system has been possible only since 1981, when the first synthesis of the parent monocyclic 1,2,3-triazine was reported. Thus the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(3)369⟩ described only a few examples of the chemistry of monocyclic 1,2,3-triazines. In this chapter, studies on the chemistry of monocyclic and benzo-fuzed 1,2,3-triazines (**2**) after 1981 are described, together with the fundamental aspects reported before 1980. Several reviews on the chemistry of 1,2,3-triazines

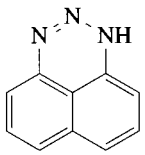
have been published ⟨56HC(10)1, B-61MI 610-01, 74MI 610-01, 76AHC(19)215, 76TCA183, 78HC(33)3⟩, besides CHEC-I. The chemistry of naphtho[1,8-*de*]-1,2,3-triazines (**3**) was covered in the earlier edition ⟨84CHEC-I(3)369⟩, and no recent developments in this area have been reported.



(1)



(2)



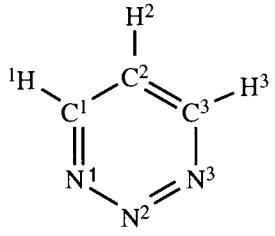
(3)

6.10.2 THEORETICAL AND EXPERIMENTAL STRUCTURAL METHODS

4,5,6-Tris(4-methoxyphenyl)-1,2,3-triazine was the first monocyclic triazine to be studied by x-ray crystallographic analysis ⟨72CB3704⟩. This work showed the planarity of the triazine ring, but the C—C bond length in the ring was a little longer than that of the parent triazine (**1a**), probably because of repulsive interaction of the substituents.

The first attempts at a crystallographic analysis of the parent 1,2,3-triazine (**1a**) were unsuccessful, and the crystal was thought to be unstable under x-ray irradiation ⟨81CC1174⟩. However, careful examination revealed that the instability was caused by the adhesive used to mount the crystal. Subsequently, the x-ray analysis was performed by two groups ⟨83CPB3762, 85LA1732⟩ and the results were fully in accord with the planar and aromatic nature of the ring system. The fully optimized geometry of (**1a**) by *ab initio* molecular orbital calculations were in good agreement with the experimental results (Table 1) ⟨93JSP388⟩.

Table 1 Experimental and calculated geometry of 1,2,3-triazine (**1a**).



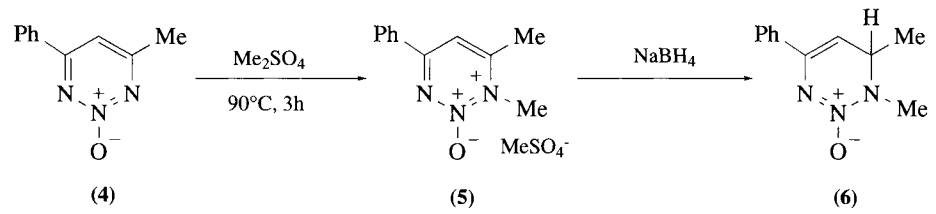
(1a)

	*HF/6-31G**[a]	*MP2/6-31G**[a]	*Exptl.*[b]
N^1—N^2 (Å)	1.292	1.341	1.326
N^1—C^1 (Å)	1.322	1.346	1.346
C^1—C^2 (Å)	1.375	1.388	1.382
C^1—H^1 (Å)	1.074	1.087	1.085
C^2—H^2 (Å)	1.073	1.086	1.085
N^1—N^2—N^3 (°)	121.8	121.1	121.6
C^1—N^1—N^2 (°)	120.4[c]	119.7[c]	119.6
C^2—C^1—N^1 (°)	121.3[c]	122.1[c]	121.8
C^1—C^2—C^3 (°)	114.8	115.3	115.4
C^2—C^1—H^1 (°)	122.7	122.7	124.5
C^1—C^2—H^2 (°)	122.9	122.4	120.2

[a]⟨93JSP388⟩. [b]⟨85LA1732⟩. [c]Data not given in ref. a)

X-ray crystallographic analyses of other 1,2,3-triazine derivatives have been reported (Table 2) ⟨90AX(C)2177, 92AX(C)964⟩. Alkyl and aryl substituents only slightly affect the ring geometry (Table 2, **a**,**b**). N—N Bond lengths vary with the introduction of a substituent at N-2; they are longer in triazine 2-oxides (Table 2, **c**,**d**), but shorter in the 2-methyltriazinium salt (Table 2, **f**), than in the parent (**1a**). The N—O bond length of 2-oxides are shorter than those of pyridine *N*-oxides ⟨71AX(B)432⟩, which suggests a strong back donation effect of the oxygen lone pair. This assumption

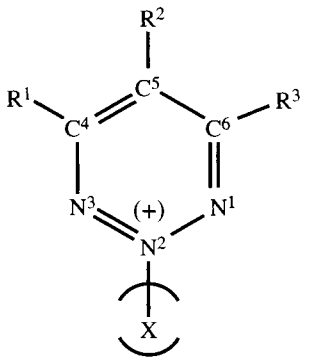
is supported by the fact that the oxygen atom of triazine 2-oxides is inert to electrophilic reagents. For example, triazine 2-oxide (**4**) underwent methylation at the N-1(3) position, not at oxygen, to give (**5**), whose structure was confirmed by an x-ray crystallographic analysis of the dihydro derivative (**6**) (Scheme 1) ⟨86CPB109⟩. The structures of some other 1,2,3-triazine derivatives have also been investigated by x-ray crystallography ⟨93MI 610-01, 94MI 610-01⟩.



(4) (5) (6)

Scheme 1

Table 2 Experimental bond lengths (Å) and bond angles (°) of various triazine derivatives.



(a) R^1=Me, R^2=H, R^3=Ph
(b) R^1=R^2= $(CH_2)_4$, R^3=Ph
(c) R^1=Me, R^2=H, R^3=Ph, X=O^-
(d) R^1=R^3=Me, R^2=H, X=O^-
(e) R^1=R^2=R^3=Me, X=NH^-
(f) R^1=R^3=Ph, R^2=H, X=CH_3

Compound	*a*	*b*	*c*	*d*	*e*	*f*
N^1—N^2	1.317(4)	1.329(3)	1.330(2)	1.327(4)	1.352(4)	1.300(4)
N^2—N^3	1.327(4)	1.324(3)	1.340(2)	1.334(5)	1.357(4)	1.300(4)
N^3—C^4	1.337(3)	1.345(3)	1.337(2)	1.334(5)	1.333(5)	1.358(6)
C^4—C^5	1.373(4)	1.382(3)	1.380(2)	1.370(5)	1.389(5)	1.378(6)
C^5—C^6	1.374(3)	1.391(3)	1.380(2)	1.368(6)	1.380(5)	1.378(6)
C^6—N^1	1.351(4)	1.345(3)	1.341(2)	1.338(5)	1.334(5)	1.358(6)
N^2—X	–	–	1.247(2)	1.251(4)	1.286(5)	1.469(10)
N^1—N^2—N^3	122.3(2)	121.8(1)	126.1(1)	126.3(2)	124.4(3)	129.0(6)
N^2—N^3—C^4	119.1(2)	119.4(1)	115.6(1)	116.0(2)	117.0(2)	115.5(3)
N^3—C^4—C^5	121.0(2)	121.9(2)	122.6(1)	122.2(3)	122.9(3)	118.8(4)
C^4—C^5—C^6	117.7(2)	115.6(1)	117.1(1)	117.1(3)	115.1(3)	120.4(7)
C^5—C^6—N^1	119.7(2)	121.1(1)	121.2(1)	122.3(3)	124.4(3)	118.8(4)
C^6—N^1—N^2	119.9(2)	119.9(1)	117.0(1)	115.9(3)	115.8(2)	115.5(3)

The standard deviations in the last figure are given in parentheses. ⟨90AX(C)2177⟩ (compounds **a**–**e**). ⟨92AX(C)964⟩ (compound **f**).

Gleiter *et al.* measured the He(Iα) photoelectron (PE) spectra of the parent heterocycle and its five mono-, di-, and tri-methyl derivatives, and assigned the PE bands by comparison with the results of MO calculations ⟨83CPL(97)94⟩. They showed that the spectral assignment was consistent with the results of four very different theoretical procedures (HMO, EWMO, HAM/3, and LCGO MB). Recently, it has been reported that the PE spectra were reproduced well by the Outer-Valence Green Function approach with PM3 ⟨91JCS(P2)1865⟩ (see Table 3).

The proton affinity of (**1a**) has been calculated using STO3-21G+G, MNDO, and AM1 methods, and the results suggested that (**1a**) has almost the same basicity as pyrazine and 1,2,4-triazine, and is more basic than 1,3,5-triazine ⟨88MI 610-01⟩.

The melting points and ^{1}H-NMR data of various 1,2,3-triazines are given in Table 4. The low-field chemical shifts of ring protons are consistent with deshielding by a ring current of π-electrons;

Table 3 Experimental and theoretically estimated ionization energies (eV) for (**1a**)[a].

Band	*Expt.*	*Orbital assignment*	*Calcd.*				
			HMO	*EWMO*	*HAM/3*	*LCGO MB*	*OVGF(PM3)*[b]
1	10.0	$7a_1(n)$	10.1	10.1	9.6	10.1	9.87
2	10.4	$5b_2(n)$	10.4	10.5	10.3	10.6	10.21
3	11.6	$2b_1(p)$	11.9	11.7	11.6	11.1	11.51
4	12.0	$1a_2(p)$	11.9	11.8	11.7	11.2	11.53
5	13.1	$6a_1(n)$	13.0	13.3	13.3	13.6	12.46

[a]⟨83CPL(97)94⟩. [b]⟨91JCS(P2)1865⟩.

thus the triazine ring is, on this criterion, aromatic. The relatively high melting point of (**1a**) suggests the tight stacking of unsubstituted triazine rings, which was shown in x-ray data ⟨83CPB3762⟩.

Table 4 Physical and ^{1}H NMR data of 1,2,3-triazines.

Entry	*Substituent*	*Ref.*	*mp* (°C)	*^{1}H-NMR ($CDCl_3$)*
(**1a**)	$R^1 = R^2 = R^3 = H$	81CC1174	70–71	9.06 (2H, d, J = 6.0 Hz), 7.45 (1H, t, J = 6.0 Hz)
(**1b**)	R^1 = Me, $R^2 = R^3 = H$	85JOC5520	30–31	8.92 (1H, d, J = 6.0 Hz), 7.33 (1H, d, J = 6.0 Hz), 2.70 (3H, s)
(**1c**)	$R^1 = R^3 = H$, R^2 = Me	85JOC5520	67–68	8.93 (2H, s), 2.40 (3H, s)
(**1d**)	$R^1 = R^2$ = Me, $R^3 = H$	85JOC5520	28	8.78 (1H, s), 2.68 (3H, s), 2.37 (3H, s)
(**1e**)	$R^1 = R^3$ = Me, $R^2 = H$	80CC1182	87–88	7.11 (1H, s), 2.68 (6H, s)
(**1f**)	$R^1 = R^2 = R^3$ = Me	72JOC1051	146–147	2.62 (6H, s), 2.28 (3H, s)
(**1g**)	R^1 = Ph, $R^2 = R^3 = H$	85JOC5520	110–111	9.05 (1H, d, J = 6.0 Hz), 8.17–8.30 (2H, m), 7.72 (1H, d, J = 6.0 Hz), 7.40–7.70 (3H, m)
(**1h**)	$R^1 = R^3$ = Ph, $R^2 = H$	85JOC5520	171–172	8.17–8.35 (4H, m), 8.01 (1H, s), 7.50–7.70 (6H, m)
(**1i**)	R^1 = Me, $R^2 = H$, R^3 = Ph	85JOC5520	158–159	8.16–8.30 (2H, m), 7.46–7.67 (4H, m), 2.76 (3H, s)
(**1j**)	R^1 = Me, $R^2 = H$, R^3 = Et	91T4317	oil	7.07 (1H, s), 2.95 (2H, q, J = 7.0 Hz), 2.67 (3H, s), 1.38 (3H, t, J = 7.0 Hz)
(**1k**)	$R^1 = R^3$ = Et, $R^2 = H$	91T4317	oil	7.04 (1H, s), 2.85 (4H, q, J = 7.0 Hz), 1.38 (6H, t, J = 7.0 Hz)
(**1l**)	$R^1 = R^3 = H$, $R^2 = CO_2Me$	93LA367	47	9.53 (2H, s), 4.13 (3H, s)
(**1m**)	$R^1 = CO_2Me$, $R^2 = R^3 = H$	93LA367	116	9.35 (1H, d, J = 6.0 Hz), 8.06 (1H, d, J = 6.0 Hz), 4.13 (3H, s)
(**1n**)	$R^1 = CO_2Me$, R^2 = Me, $R^3 = H$	93LA367	85	9.13 (1H, s), 4.10 (3H, s), 2.67 (3H, s)
(**1o**)	R^1 = Me, $R^2 = CO_2Me$, $R^3 = H$	93LA367	oil	9.27 (1H, s), 4.03 (3H, s), 3.00 (3H, s)
(**1p**)	$R^1 = R^3 = H$, R^2 = Br	88CPB3838	125–126	9.22 (2H, s)
(**1q**)	$R^1 = R^3$ = Me, R^2 = Br	88CPB3838	104–105	2.79 (6H, s)
(**1r**)	R^1 = Me, R^2 = Br, R^3 = Ph	88CPB3838	138–140	7.80–7.90 (2H, m), 7.52–7.58 (3H, m), 2.89 (3H, s)
(**1s**)	$R^1 = R^3$ = Me, R^2 = OH	91T4317	206	2.28 (6H, s), 1.90 (1H, bs)
(**1t**)	R^1 = Me, R^2 = OH, R^3 = Ph	91T4317	182	8.12–8.25 (2H, m), 7.31–7.41 (3H, m), 2.41 (3H, s), 2.17 (1H, bs)
(**1u**)	$R^1 = R^3$ = Me, $R^2 = CONH_2$	91H(32)2015	210	6.60 (2H, bs), 2.72 (6H, s)
(**1v**)	$R^1 = R^3$ = Ph, $R^2 = CONH_2$	91H(32)2015	230	7.80–7.93 (4H, m), 7.43–7.56 (6H, m)
(**1w**)	$R^1 = R^3$ = Me, $R^2 = CH_2SO_2Ph$	93CPB1644	135–137	7.36–7.92 (5H, m), 4.44 (2H, s), 2.52 (6H, s)
(**1x**)	$R^1 = R^3$ = Et, $R^2 = CH_2SO_2Ph$	93CPB1644	137–138	7.35–7.80 (5H, m), 4.43 (2H, s), 2.83 (4H, q, J = 7.0 Hz), 1.33 (6H, t, J = 7.0 Hz)

The reported ^{13}C-NMR data for triazine and its derivatives is summarized in Table 5, and this also shows the aromatic nature of the triazine ring. The large $^1J_{CH}$ couplings (J_{C5H} 175 Hz, J_{C4H} 187.5 Hz) suggest the π-electron deficiency of the ring.

Nitrogen-15 NMR spectra of 1,2,3-triazines have been reported in several papers ⟨85LA1732, 86JCS(P1)1249, 88JCS(P1)1509⟩, and the data are listed in Table 6. The N-2 positions show larger downfield shifts than ^{15}N-NMR signals of pyridazine (δ = +20.3) or 1,2,4-triazine (N-1: δ = +62; shifts downfield of external nitromethane).

Table 5 Carbon-13 NMR data of 1,2,3-triazines.

Entry	*Substituent*	*Ref.*	*^{13}C-NMR ($CDCl_3$)*
(1a)	$R^1 = R^2 = R^3 = H$	81CC1174	117.9 (J_{CH} 175.0 Hz), 149.7 (J_{CH} 187.5 Hz)
(1b)	$R^1 = Me$, $R^2 = R^3 = H$	86CPB109	21.4, 117.8, 148.8, 159.7
(1c)	$R^1 = R^3 = H$, $R^2 = Me$	86CPB109	17.4, 123.5, 137.4, 146.9
(1e)	$R^1 = R^3 = Me$, $R^2 = H$	86CPB109	21.1, 117.6, 158.8
(1j)	$R^1 = Me$, $R^2 = H$, $R^3 = Et$	91T4317	12.4, 21.7, 28.6, 116.5, 159.4, 163.7
(1k)	$R^1 = R^3 = Et$, $R^2 = H$	91T4317	12.4, 28.7, 115.3, 163.9
(1s)	$R^1 = R^3 = Me$, $R^2 = OH$	91T4317	15.6, 152.7, 165.6
(1t)	$R^1 = Me$, $R^2 = OH$, $R^3 = Ph$	91T4317	15.5, 127.7, 127.9, 129.5, 132.3, 147.7, 156.4, 164.1
(1u)	$R^1 = R^3 = Me$, $R^2 = CONH_2$	91H(32)2015	17.5, 126.5, 154.8, 166.1
(1v)	$R^1 = R^3 = Ph$, $R^2 = CONH_2$	91H(32)2015	123.4, 127.7, 128.3, 130.0, 133.1, 155.0, 166.3
(1w)	$R^1 = R^3 = Me$, $R^2 = CH_2SO_2Ph$	93CPB1644	19.6, 54.9, 118.8, 128.2, 129.9, 134.9, 138.2, 159.6
(1x)	$R^1 = R^3 = Et$, $R^2 = CH_2SO_2Ph$	93CPB1644	12.1, 25.6, 53.6, 117.2, 128.2, 129.8, 134.9, 138.2, 163.1

Table 6 Nitrogen-15 chemical shifts (δ) relative to external nitromethane ($\delta = 0$) of 1,2,3-triazines, benzotriazines, and benzotriazine *N*-oxides.

1,2,3-Triazine	*Ref.*	*^{15}N-NMR* (ppm)		
		N-1	N-2	N-3
1,2,3-triazine (**1a**)	85LA1732	+13.7 (J = 9.5 Hz)	+80.8	+13.7
4-methyl- (**1b**)	86JCS(P1)1249	+12.5	+79.9	+3.6
4,6-dimethyl- (**1e**)	*ibid.*	+3.8	+78.6	+3.8
4-methylbenzo-	*ibid.*	+15.9	+66.6	−16.1
4-methoxybenzo-	*ibid.*	+5.1	+61.2	−66.3
4-methylbenzotriazine 3-oxide	88JCS(P1)1509	+18.5	+39.1	−51.8
4-methylbenzotriazine 2-oxide	*ibid.*	−49.5	−48.1	−75.6
4-methoxybenzotriazine 2-oxide	*ibid.*	−85.0	−54.4	−95.5

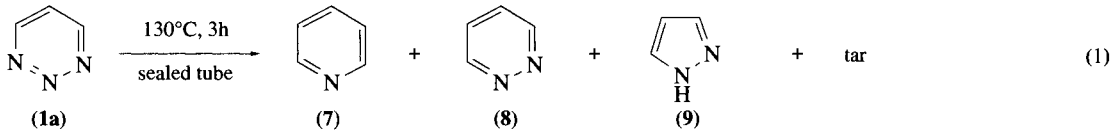
Mass spectrometry of 1,2,3-triazine affords a characteristic fragmentation. The general fragmentation pattern of monocyclic 1,2,3-triazines shows peaks for $[M^+-N_2]$, and for an acetylene and a nitrile, which is in accordance with the results of thermolysis and photolysis. The mass spectrum of the parent triazine (**1a**) showed peaks as follows: 81 (M^+, 47%), 53 (M^+-N_2, 69%), 27 (HCN, 13%), and 26 (C_2H_2, 100%) ⟨81CC1174⟩. The presence of alkyl and/or aryl substituents diminishes the molecular ion peak. Mass spectral fragmentation data were used for the structural elucidation of monocyclic triazine *N*-oxides. In the cases of triazine 1-oxides, molecular ion peaks are absent or very weak, whereas the peaks at $[M^+-N_3O]$ and $[M^+-N_2]$ are strong. On the other hand, triazine 2-oxides have strong molecular ion peaks accompanied by peaks of $[M^+-N_3O]$ with moderate intensities ⟨86CPB109⟩. Benzotriazine 2-oxides showed prominent molecular ion peaks, and strong fragments arising from $[M^+-NO]$, while benzotriazine 3-oxides showed weak $[M^+]$ and strong $[M^+-N_2]$ ions ⟨88JCS(P1)1509⟩.

6.10.3 THERMODYNAMIC ASPECTS

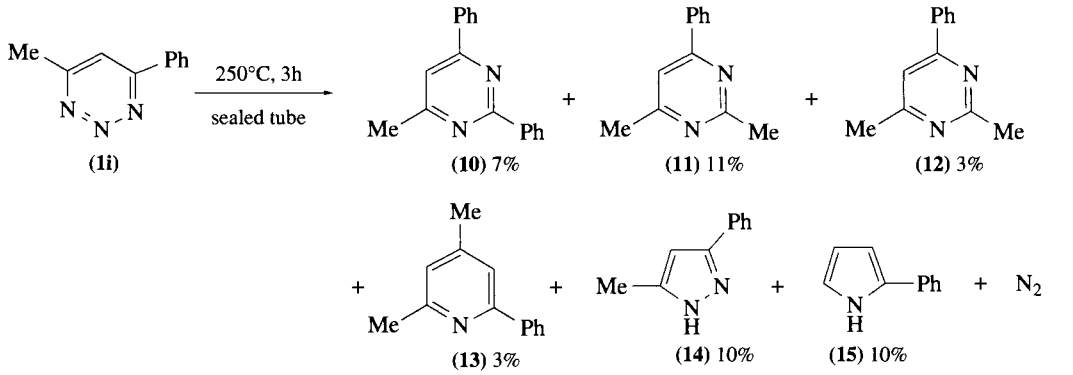
Melting points of monocyclic triazines are given in Table 4. Basicity estimated by the theoretical method is also given in the previous section. The observed pK_as of 4,6-dimethyl- (**1e**), 4-methyl-6-phenyl- (**1i**), and 4,5,6-trimethyltriazine (**1f**) are −0.58, −0.79, and 0.07, respectively. The data were obtained from measurement of the UV absorption in sulfuric acid at room temperature using Hammett's acidity function values ⟨89UP 613-01⟩. The pK_a determination of the parent triazine (**1a**) failed because of its instability in acidic media.

The aromatic nature of 1,2,3-triazines is suggested by various spectral data, which are given in Section 6.10.2. In terms of tautomerism, there is little information concerning the monocyclic series. "5-Hydroxy" derivatives have been isolated and appear to exist in the oxo forms (see Section 6.10.6). Benzotriazin-4-one ("4-hydroxybenzotriazine") has long been known to exist in the 3*H* form, and its 1- and 2-oxides are likewise 3*H* structures. The p*K* values have been determined for all of these compounds, and for 3-hydroxybenzotriazin-4-one ⟨89JCS(P1)543⟩.

The parent 1,2,3-triazine (**1a**) can be obtained as colorless plates (m.p. 70–71 °C) from ether, and it is stable for several months when stored under vacuum in a freezer. When (**1a**) is heated to 130 °C in a sealed tube, however, it decomposes to tar accompanied by small amounts of pyridine (**7**), pyridazine (**8**), and pyrazole (**9**) (Equation (1)). Higher temperatures are needed for the degradation when (**1**) has bulky substituents; of the products obtained, (**10**), (**11**), (**12**), (**13**), (**18**), and (**20**) in Equations (2) and (3) are postulated to be formed by intermolecular Diels–Alder reactions, while (**14**), (**15**), (**16**), (**17**), and (**19**) arise from unimolecular decompositions ⟨92H(34)1183⟩. The reaction patterns are quite different in the case of triaryltriazines. These compounds do not easily undergo intermolecular reactions on account of their bulky substituents, and decompose mainly to the indenone imines (**22**) on thermolysis (Equation (4)) ⟨73TL219⟩.



(1)



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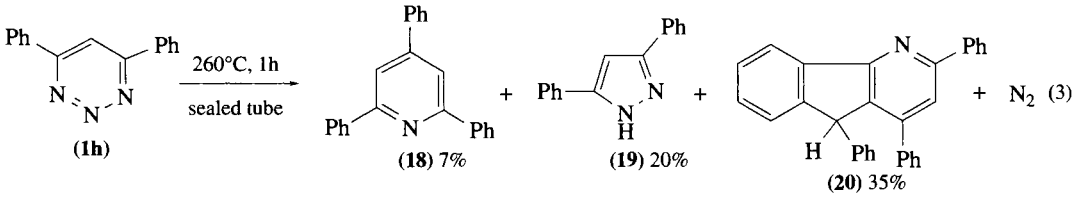

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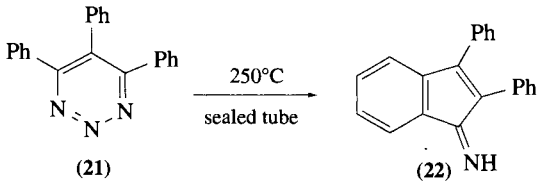


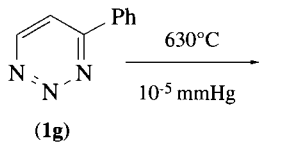
(4)

6.10.4 REACTIVITY OF FULLY CONJUGATED RINGS

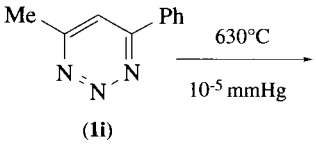
6.10.4.1 Unimolecular Thermal and Photochemical Reactions

Flash vacuum thermolysis (FVT) was applied to (**1**) in order to prevent intermolecular reactions, when it was found that (**1**) was readily thermolyzed to an alkyne, a nitrile, and nitrogen in high yields (Equations (5) and (6)). This tends to suggest that 1,2,3-triazine has only weak aromaticity, since pyridine and pyridazine rings are stable under the same conditions. Two sets of products were

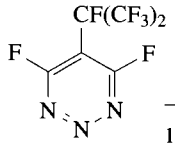
expected in the case of unsymmetrically substituted triazines as FVT substrates, and it was found that fragmentation proceeded selectively. The results indicated that a bulky substituent at C-4(6) made the adjacent C—N bond break more easily than the opposite C—N bond. The FVT method was applied to the synthesis of the fluorinated alkynes, perfluoro-3-methyl-1-butyne (**25**) and difluoroethyne (**27**) (Equations (7) and (8)) ⟨89CC1657, 91CC456⟩. The results of neat thermolysis are given in the previous section.



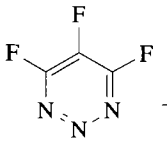
(1g) $\xrightarrow[10^{-5}\text{ mmHg}]{630°C}$ Ph-C≡N (**16**) 4% + Ph-C≡C-H (**17**) 72% + N_2 (5)



(1i) $\xrightarrow[10^{-5}\text{ mmHg}]{630°C}$ Ph-C≡N (**16**) 18% + Ph-C≡C-H (**17**) 77% + Me-C≡N (**23**) 70% + N_2 (6)

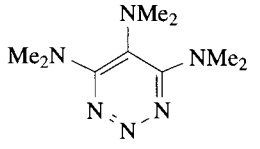


(**24**) $\xrightarrow[10^{-2}\text{ mmHg}]{700°C}$ $(CF_3)_2CF$-C≡C-F (**25**) (7)

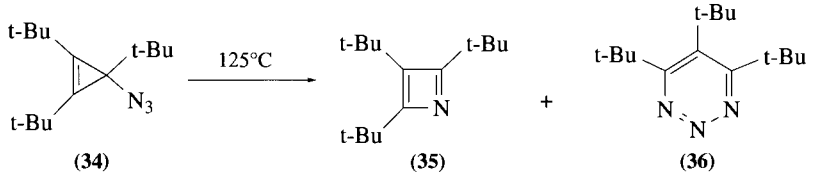


(**26**) $\xrightarrow[10^{-2}\text{ mmHg}]{700°C}$ F-C≡C-F (**27**) + F-C≡N (**28**) (8)

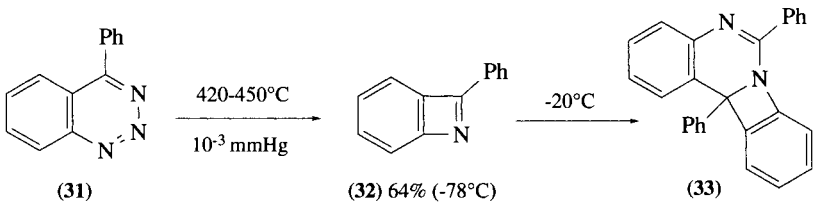
The pioneering work of Seybold *et al.* led to the first isolable unfused azete (**30**) by the FVT of tris(dimethylamino)triazine (**29**) (Equation (9)) ⟨73AG(E)847⟩. The FVT of 4-phenylbenzotriazine (**31**) was performed by Rees, Storr, and co-workers, and the formation of the benzazete (**32**) was confirmed at low temperature; it dimerizes to (**33**) on warming (Scheme 2) ⟨73CC19, 75CC740, 75JCS(P1)45, 76CC125, 76CC411, 76TL4647⟩. Werstiuk *et al.* reported that the FVT product of benzotriazine (**2**) gave the HeI photoelectron spectrum of benzazete, which correlated with ionization energies calculated with HAM/3 using an equilibrium geometry obtained by the *ab initio* HF/6-31G** method ⟨95CJC146⟩. The stable azete (**35**) was obtained using the method for synthesizing trisubstituted triazines ⟨86AG(E)842, 88AG(E)272, 88AG(E)1559⟩. In this case, only a small amount of triazine (**36**) was formed, probably because the steric repulsion is more severe in the six-membered triazine than in the azete (Equation (10)).



(**29**) $\xrightarrow[10^{-4}\text{ mmHg}]{527°C}$ (**30**) 31% (9)



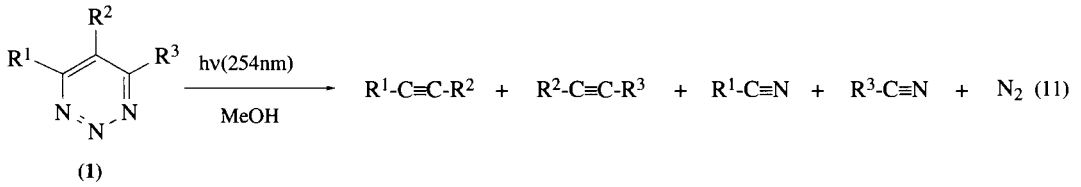
(**34**) $\xrightarrow{125°C}$ (**35**) + (**36**) (10)



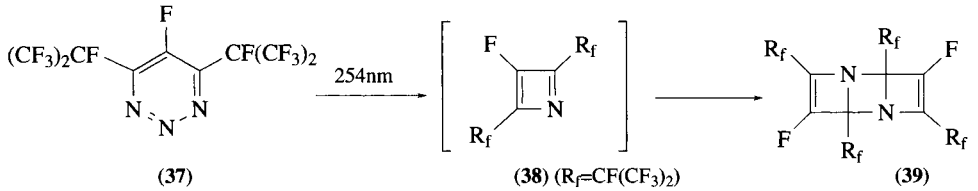
(31) (32) 64% (-78°C) (33)

Scheme 2

The photolysis of monocyclic triazines has been studied by several groups ⟨60TL19, 72JOC1051, 73JOC176, 74JOC940, 80LA798⟩. The rings readily fragment to nitrogen, nitrile, and alkyne as under FVT conditions. In contrast to the FVT, however, unsymmetrical triazines gave two sets of products in almost the same yields (Equation (11)) ⟨77H(8)319⟩. Using fluoro and perfluoroalkyl groups as small-ring stabilizer, Chambers *et al.* performed the photolysis of fluorotriazines. They found that when perfluoro-4,6-diisopropyltriazine (**37**) was photolyzed, an intermediate azete (**38**) was formed, which gave the dimeric compound (**39**) (Scheme 3) ⟨87CC1699, 90JCS(P1)975⟩. Although several substrates (e.g. (**40**) and (**42**)) have been tested as potential precursors to novel alkyne compounds by triazine photolysis, the reactions simply resulted in formation of strain-free alkynic nitriles (e.g. (**41**) and (**43**)) (Equations (12) and (13)) ⟨77H(8)319⟩.

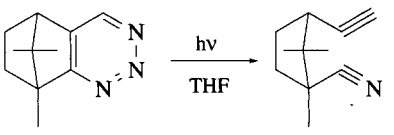


(1)

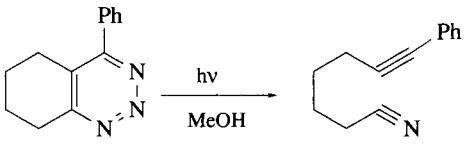


(37) (38) (R_f=$CF(CF_3)_2$) (39)

Scheme 3



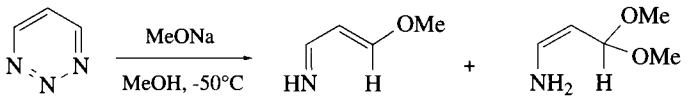
(40) (41) (12)



(42) (43) (13)

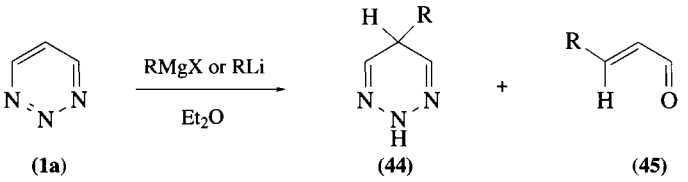
6.10.4.2 Reactions with Nucleophiles

1,2,3-Triazine (**1**) is highly π-electron deficient and readily attacked by nucleophiles. The parent triazine (**1a**) slowly decomposed in methanol at room temperature, which suggested that nucleophilic attack of methanol occurred in the solution. The NMR spectrum of (**1a**) in CD_3OD measured at $-50\,^{\circ}C$ in the presence of a base indicated that attack of methoxide ion on the 4-position was succeeded by ring-opening accompanied by the elimination of nitrogen (Equation (14)) ⟨92H(33)631⟩. All attempts failed to oxidize the intermediate 1,4-dihydro adducts to form 4-substituted triazines.



(1a) (14)

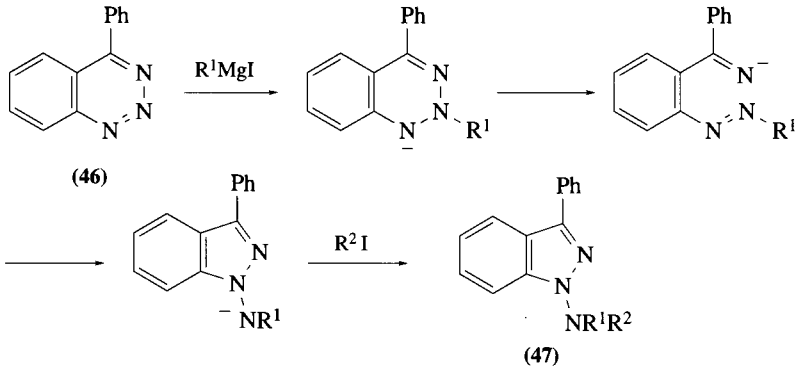
Nucleophilic addition using organometallics showed that the C-4 position of (**1a**) is a hard reaction site, whereas the C-5 position has soft reactivity (Equation (15)) ⟨85CC1370⟩. These results are in accord with those from MO calculations. Softer nucleophiles such as organocopper reagents underwent a redox reaction with triazine to give 2,5-dihydro derivatives without ring substitution.



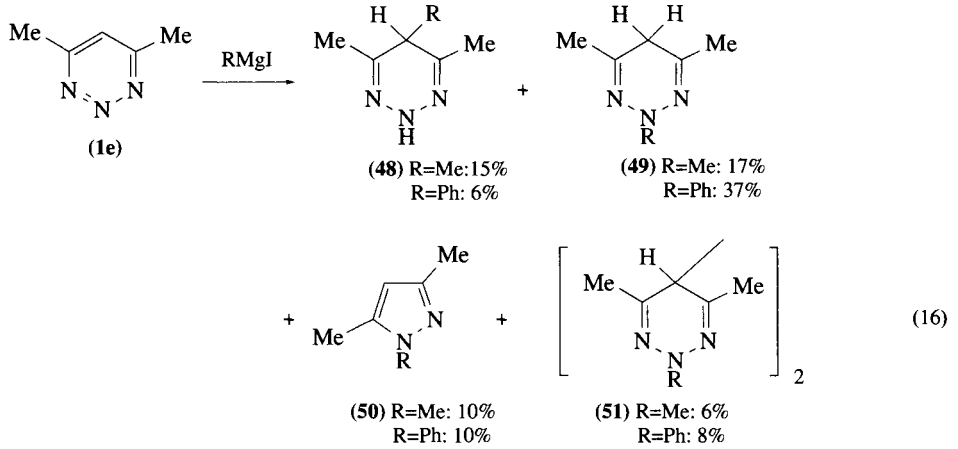
(1a) (44) (45) (15)

Reagent	*Yield* (44)	(45)
MeMgI	42%	trace
PhMgBr	13%	52%
PhLi	0	49%

Storr *et al.* reported that the attack of alkyl Grignard reagents on 4-substituted 1,2,3-benzotriazines (**46**) occurred at the N-2 position, in spite of the existence at that site of a pair of unshared electrons, to form (**47**) (Scheme 4) ⟨83CC1344⟩. This unusual reactivity was also shown when 4,6-dimethyltriazine (**1e**) was treated with Grignard reagents. The steric effect of the 4,6-substituents was suggested to change the reaction site from C-4(6) to the C-5 and N-2 positions to give (**49**), (**50**), and (**51**) other than normal adducts (**48**) (Equation (16)) ⟨92H(33)631⟩. These facts suggested the extremely weak basicity of the nitrogen at position 2.

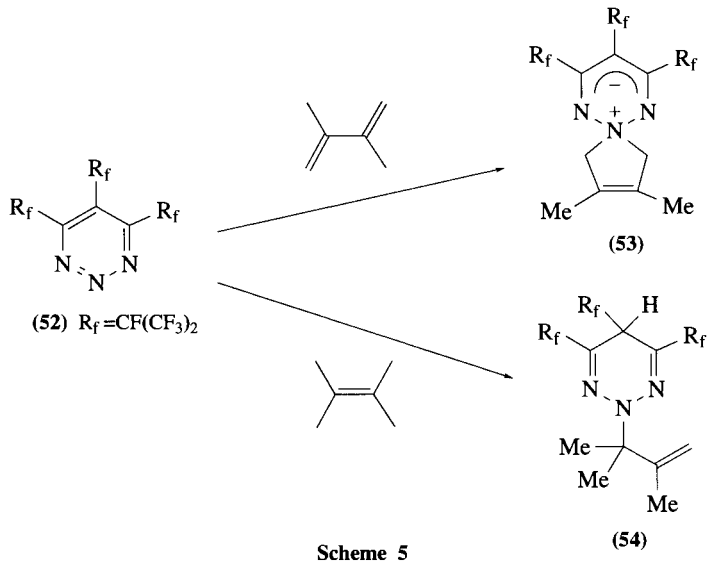


Scheme 4



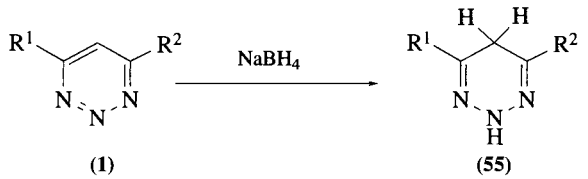
(16)

A related attack on ring nitrogen also occurred with 4,5,6-tris(perfluoroisopropyl)-1,2,3-triazine (**52**) ⟨87CC1697, 90JCS(P1)2379⟩. When (**52**) was treated with a large excess of 2,3-dimethylbutadiene at 70°C, a spirotriazinium zwitterion (**53**) was obtained whose structure was confirmed by x-ray crystallography. The reaction with 2,3-dimethylbut-2-ene resulted in a 2-substituted 2,5-dihydro derivative (**54**) (Scheme 5).



Scheme 5

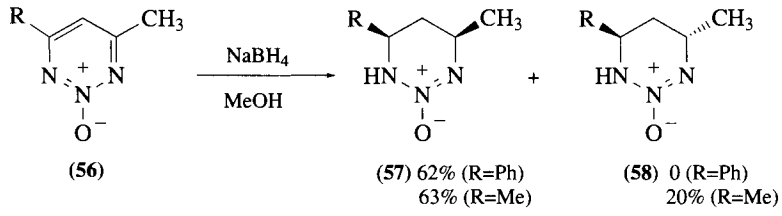
Sodium borohydride reduction of 4,6-disubstituted triazines in methanol afforded 2,5-dihydrotriazines (**55**) in good yields (Equation (17)) ⟨80CC1182, 85YZ1122⟩. Experiments using $NaBD_4$ showed that the hydrogen of the dihydro adduct at C-5 was derived from the reductant. Therefore the hydride anion of borohydride attacks at C-5, not at N-2, irrespective of the presence of 4,6-substituents. The parent triazine (**1a**) slowly decomposed under the same conditions, and the 2,5-dihydro adduct was not detected in the reaction mixture. 4,5,6-Triaryltriazines were reduced with $LiAlH_4$ in ether to also give 2,5-dihydro adducts in moderate yields ⟨85LA1732⟩.



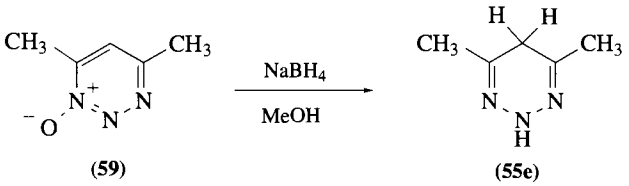
(17)

Monocyclic triazine 2-oxides are quite stable and unreactive toward reagents such as Grignard reagents, alkyl- and aryllithiums, and other organometallics. Reduction of the 2-oxides (**56**) with $NaBH_4$, however, gave the tetrahydro derivatives (**57**) and (**58**) in good yields (Equation (18))

⟨82H(17)317⟩. Using $NaBD_4$/MeOH and $NaBH_4$/MeOD as reduction systems, it was found that reduction was initiated by the attack of hydride ion on a C-4(6) position. Reduction of the triazine 1-oxide (**59**) afforded 2,5-dihydrotriazine (**55e**). These facts suggested that the *N*-oxide moiety back-donates electrons to the triazine ring, thus making the α- and γ-positions less reactive toward nucleophiles (Equation (19)).



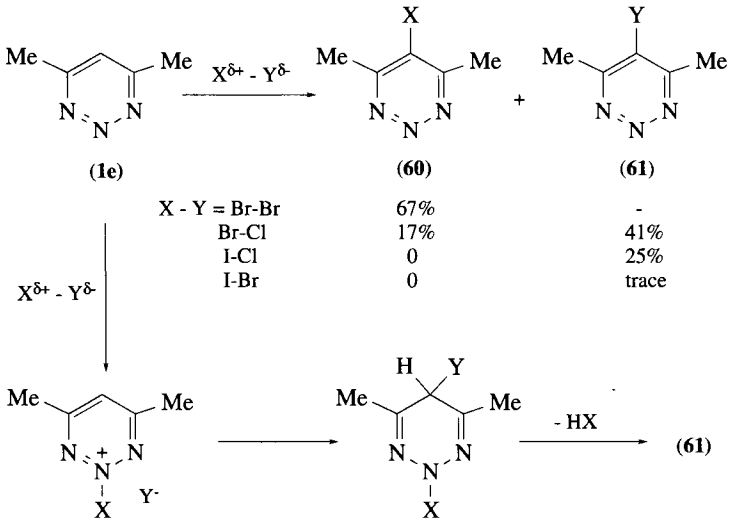
(18)



(19)

6.10.4.3 Reactions with Electrophiles at Nitrogen

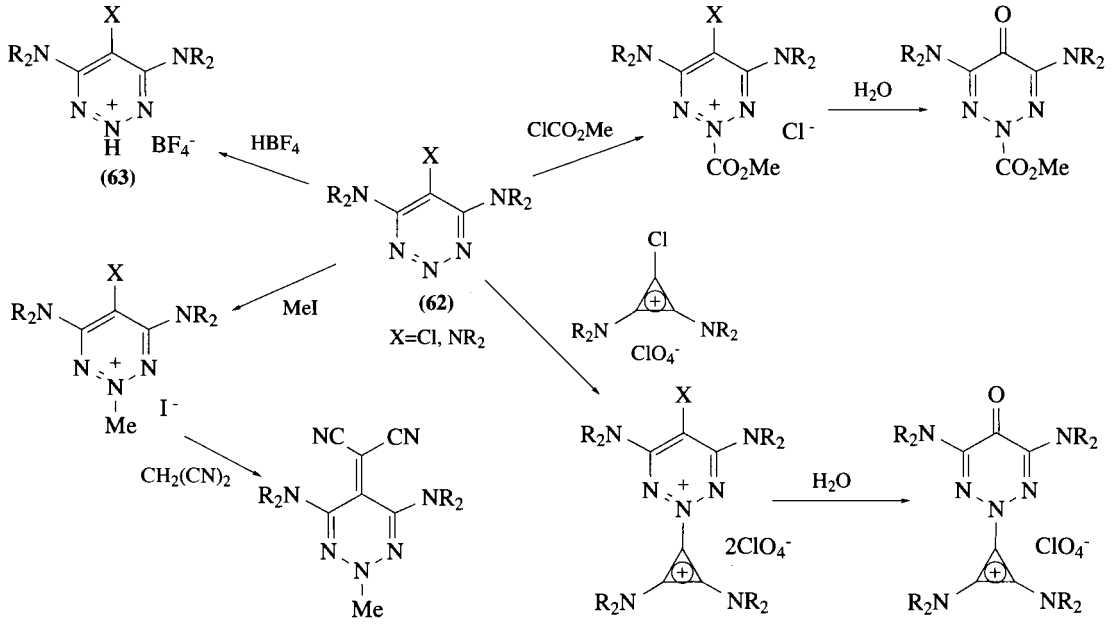
Electrophilic reactions on ring carbon of (**1**) never proceed because of the intense π-electron deficiency of the ring system. An exceptional, apparently electrophilic substitution occurs when halogenating reagents react with (**1**) to afford 5-halotriazines (**60**) and (**61**). The use of interhalogen reagents affords 5-halotriazines derived completely or mainly from the more electronegative halogen. These results suggest that the reaction is initiated by the quaternization of (**1**) with cationic halogen, followed by nucleophilic addition of halide ion and elimination of hydrogen halide (Scheme 6) ⟨86CPB4432⟩.



Scheme 6

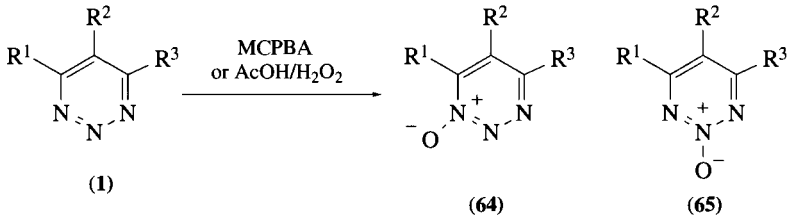
Protonation on ring nitrogen does not seem to proceed in alkyl and/or aryl substituted monocyclic triazines due to their low basicity. 4,6-Diamino- and 4,5,6-triaminotriazines (**62**) have relatively high nucleophilicity at N-2, and have been found to undergo various kinds of reactions with electrophiles ⟨79CB1535⟩. The triazinium tetrafluoroborate salts (**63**) showed symmetrical NMR spectra, indi-

cating protonation to occur at the N-2 position. These and other reactions of (**62**) are shown in Scheme 7.



Scheme 7

Other electrophilic reactions proceeded on the ring nitrogen of (**1**), although the reaction rates were much slower than those of pyridines or pyridazines. When monocyclic 1,2,3-triazines were treated with MCPBA or $AcOH/H_2O_2$, 1- and/or 2-oxides (**64**) and/or (**65**) were obtained. A report claimed 4,5,6-triaryltriazine oxides as 1-oxides ⟨85LA1732⟩, but further research showed by x-ray crystallography that the 2-oxides (**65**) were the exclusive products ⟨86CPB109, 91AX(C)2193, 91CPB2117⟩. Triazines with bulky aryl groups on C-4 and C-6 were suggested to give 2-oxides (**65**) dominantly, whereas 4- and/or 6-alkyl groups allow 1-oxides (**64**) to form. There are no reported 1(3)-oxides without an adjacent substituent at carbon. Equation (20) summarizes results in this area.

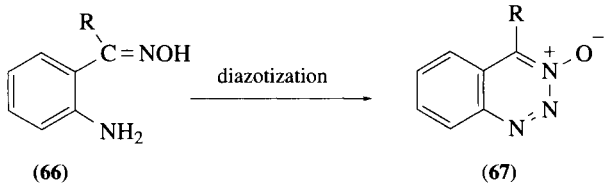


(1) → (64) + (65) (20)

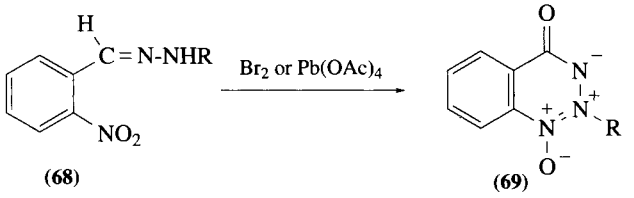
	(64)	(65)
$R^1=R^2=R^3=Ph$	0	53%
$R^1=R^3=Ph$, $R^2=H$	0	81%
$R^1=Me$, $R^2=H$, $R^3=Ph$	29%	60%
$R^1=R^3=Me$, $R^2=H$	20%	48%
$R^1=Me$, $R^2=R^3=H$	15%	32%

There are three possible series of *N*-oxides of 1,2,3-benzotriazines. The longest known isomers are the 3-oxides (**67**), which are formed by diazotization of 2-aminophenyl ketoximes (**66**) (Equation (21)) ⟨1898JPR(58)333, 01CB1309, 27CB1736, 59JOC272⟩. (The earliest references to these compounds wrongly assigned the structures as indazolone oximes.) 1-Oxides, previously reported only as mesomeric betaines (**69**) (Equation (22)) ⟨25JCS2407, 27JCS323, 72JOC1587, 74JOC2710⟩, have been obtained in the 4-oxo derivatives (**72**) using the approach involving attachment and removal of a suitable protective group at N-3 (Scheme 8) ⟨89JCS(P1)543⟩. The synthesis of benzotriazine 2-oxides (**75**) was also reported using MCPBA (Scheme 9) ⟨88JCS(P1)1509⟩. Although formation of a small amount of the 3-oxide was reported, in the case of 4-methyl-1,2,3-benzotriazine, in general 1,2,3-

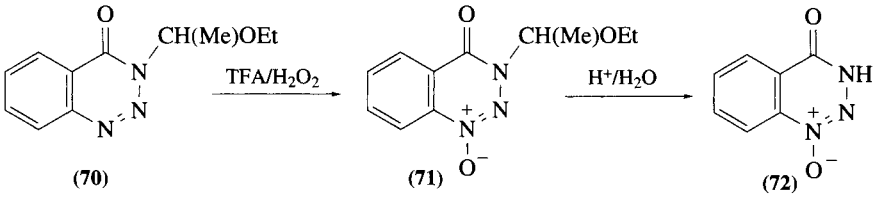
benzotriazines in which all three nitrogen atoms are dicoordinate are almost exclusively oxidized at N-2. By hydrolysis of the 4-methoxy 2-oxide (**74**; R = OMe), 1,2,3-benzotriazin-4-one 2-oxide (**75**) was obtained (Scheme 9) ⟨88JCS(P1)1509⟩. An alternative approach to some compounds in this series had been observed earlier: a suitably substituted 2-aminobenzonitrile (**76**) can be converted by a nitrating medium into a benzotriazinone 2-oxide (**77**), via the intermediate nitramine (Equation (23)) ⟨83GEP(O)3222960, 88S517⟩.



(66) (67) (21)

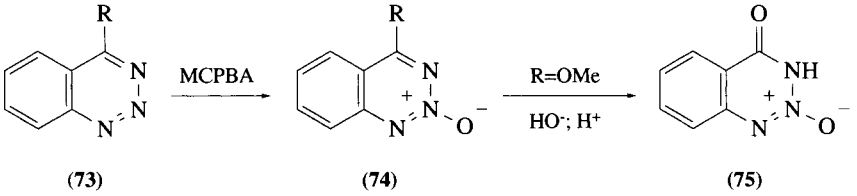


(68) (69) (22)



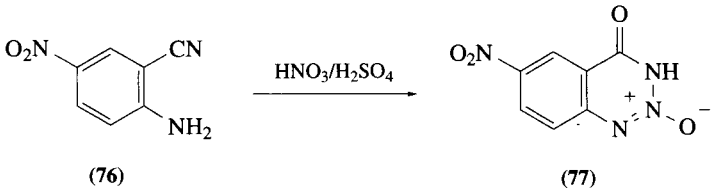
(70) (71) (72)

Scheme 8



(73) (74) (75)

Scheme 9

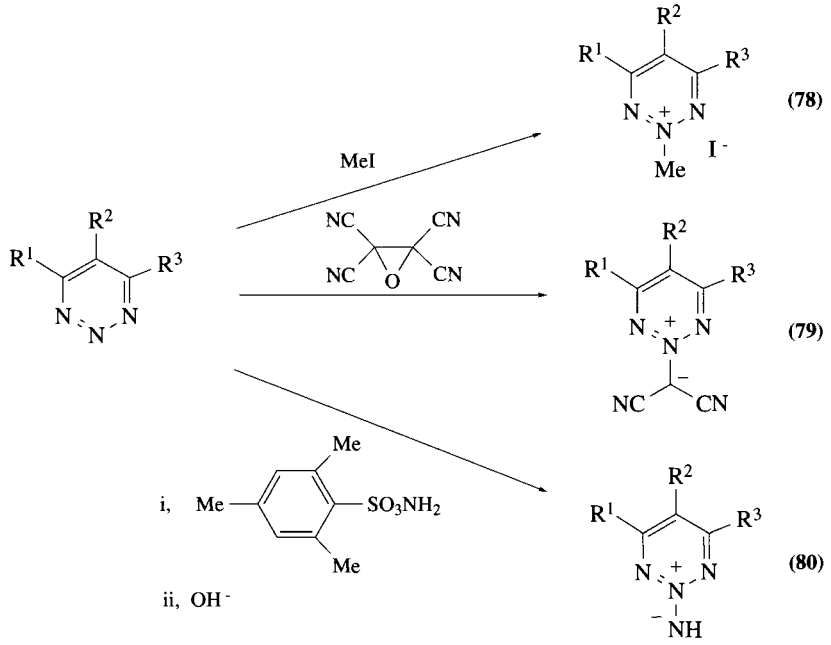


(76) (77) (23)

N-Alkylation was first reported using triaminotriazine derivatives ⟨79CB1535⟩, and thereafter, alkyl and aryl triazines were methylated by MeI to give (**78**) ⟨85YZ1122⟩. Methylation occurred exclusively at the N-2 position, and the substrates were limited to those which have 4- and 6-substituents. The alkylation of 1,2,3-benzotriazin-4-ones was investigated by several groups. In most cases, alkylation was reported to occur at N-3, accompanied by minor *O*-alkylated products ⟨68PHA629, 71JHC785⟩. McKillop and Kobylecki showed that methylation of benzotriazin-4-one in alkali with Me_2SO_4 gave 71% of the 2-methyl derivative, whose structure was confirmed by an alternative synthesis ⟨74JOC2710⟩. The synthesis of the first 1-methyl derivative has been reported by quaternizing the substrate whose 3-position was protected by a 1-ethoxyethyl substituent,

followed by removal of the protecting group ⟨88CC631⟩. There has been no report concerning the alkylation of benzotriazine itself.

N-Amination and *N*-ylidation of monocyclic triazines also occurs and the corresponding 2-substituted isomers are obtained in good yields ⟨81H(16)163, 91H(32)2015⟩. Triazine *N*-imines (**80**) were obtained from the reaction with *O*-mesitylenesulfonylhydroxylamine (MSH), followed by a neutralization with potassium carbonate. As with the alkylation, available substrates were 4,6-disubstituted, and regio isomers (attack on N-1(3)) were not isolated. *N*-Dicyanomethylidation, using tetracyanoethylene oxide (TCNEO), afforded the stable triazinium 2-dicyanomethylides (**79**). In this case, the parent triazine (**1a**) was also transformed to the corresponding 2-substituted derivative (Scheme 10).



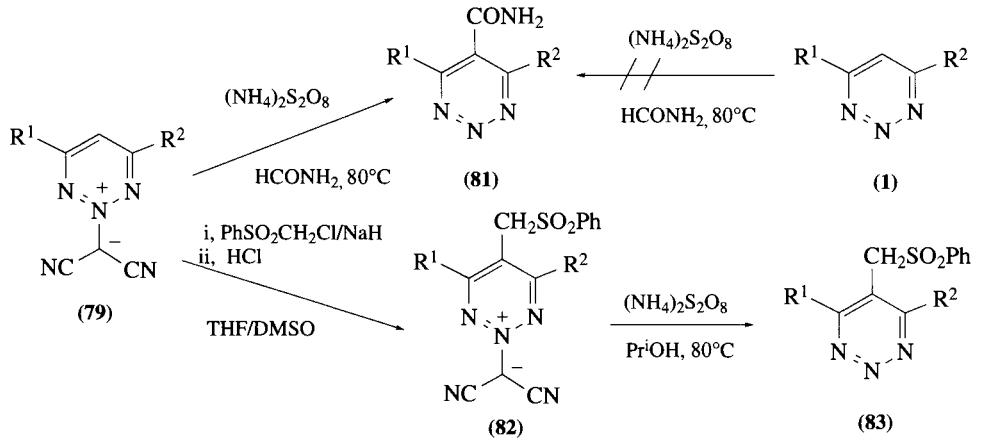
Scheme 10

The reaction of 4,5,6-triphenyltriazine with nonacarbonyldiiron afforded 3,4,5-triphenylpyrazole in 80% yield, probably through the initial *n*-donor complexation of the triazine to iron carbonyl ⟨87BCJ3062⟩.

6.10.4.4 Substitution at Carbon by Indirect Methods

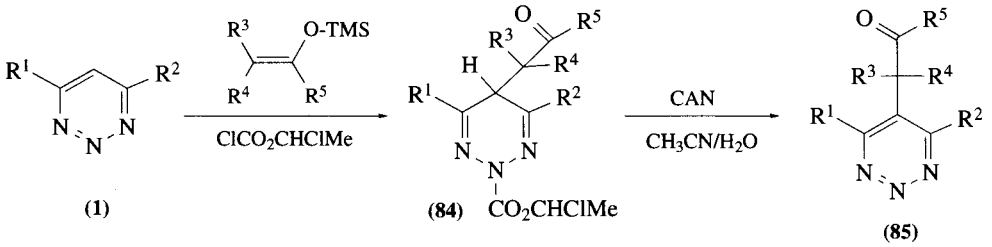
The instability of the ring system has prompted the use of indirect methodology for substitution, and it was found that triazinium dicyanomethylides (**79**) are useful compounds for the introduction of substituents into the C-5 position (Scheme 11). Radical nucleophilic carbamoylation, which was developed by Minisci *et al.* ⟨90JHC79⟩, was applied to triazinium dicyanomethylides to form 5-carbamoyl-1,2,3-triazines (**81**) in good yields ⟨91H(32)855, 91H(32)2015⟩. Direct radical reaction on the triazines afforded the products only in low yields; thus the dicyanomethylene group was revealed to be a good activator, whose removal was simultaneously effected under the reaction conditions. The vicarious nucleophilic substitution of hydrogen, a method developed by Makosza *et al.* ⟨91S103⟩, can also be applied to dicyanomethylides (**79**), and the 5-substituted derivatives (**82**) transformed into 5-benzenesulfonylmethyltriazines (**83**) by a radical reaction ⟨93H(35)581, 93CPB1644⟩.

2-Alkoxycarbonyl-1,2,3-triazinium salts, which were postulated to be formed *in situ* in low concentration from triazines and chloroformates, have been trapped by carrying out reactions in the presence of a ketene silyl acetal or a silyl enol ether, which gives 2-alkoxycarbonyl-5-substituted 2,5-dihydrotriazines (**84**). The dihydro adducts were oxidized by ceric ammonium nitrate (CAN) to 5-substituted triazines (**85**) (Scheme 12) ⟨95CPB881⟩. The use of ethyl or methyl chloroformate



Scheme 11

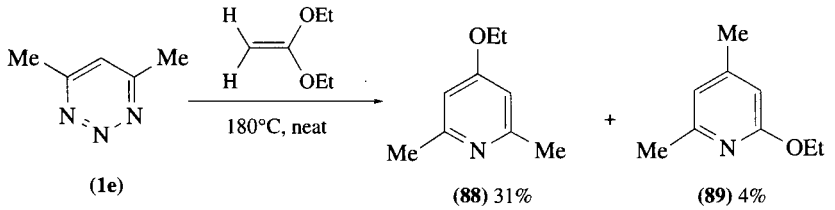
resulted in the recovery of starting material, which suggests that they were not sufficiently electrophilic to form the intermediate quaternary salts. This method provides a synthesis of triazines with a β-ketoalkyl functional group at C-5.



Scheme 12

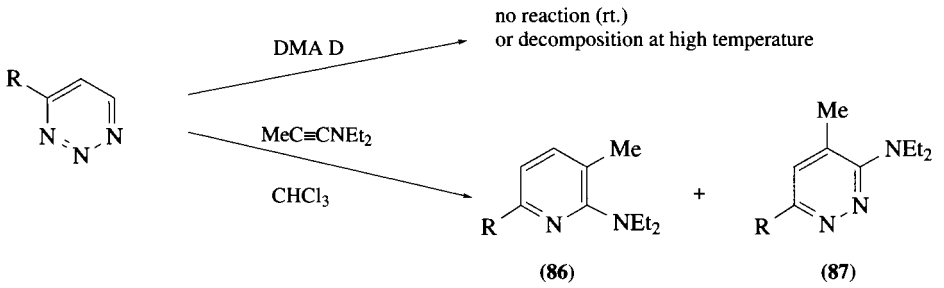
6.10.4.5 Cycloaddition Reactions

1,2,3-Triazines behave as electron deficient dienes, although their reactivity is not as high as that of 1,2,4-triazines. It has been shown that the inverse electron-demand Diels–Alder reaction of (**1**) proceeds when an electron rich dienophile such as an enamine is used ⟨85LA1732, 90CPB2108⟩. Molecular orbital calculations indicated that the LUMO coefficients are large at the N-2 and C-5 positions of (**1**), whereas C-4 (and N-1) are electron deficient, so the dominant formation of pyridine rings (**86**) seemed to involve a nonconcerted ionic reaction (Scheme 13). In the case of 4,6-dimethyltriazine, the above reaction did not proceed even under xylene reflux; heating with the dienophile in a sealed tube without solvent afforded pyridine derivatives, one of which (**88**) was postulated to be formed via an azete intermediate (Equation (24)) ⟨85CPB3050⟩.



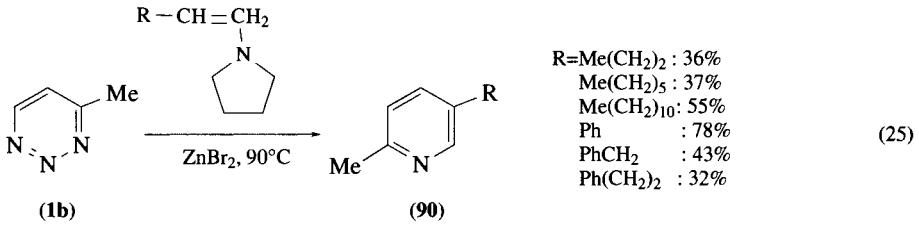
(24)

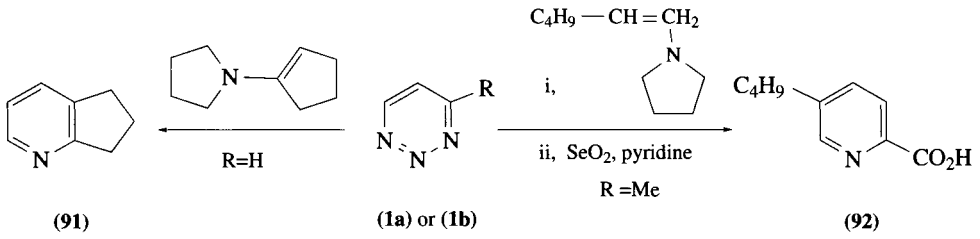
Koyama *et al.* reported that various kinds of enamines react with the parent or 4-substituted triazines to afford many pyridine derivatives (**90**) via Diels–Alder reactions (Equation (25)), and the approach was applied to the total syntheses of pyridine alkaloids such as fabianine (**91**) and fusaric acid (**92**) (Scheme 14) ⟨85H(23)2789, 86H(24)29, 89H(29)1809, 92MI 610-01, 94H(38)1595⟩.



R	Reaction time	Yield of (86)	Yield of (87)
H	5 h	52%	trace
Me	7 h	31%	3%
Ph	92 h	21%	24%

Scheme 13



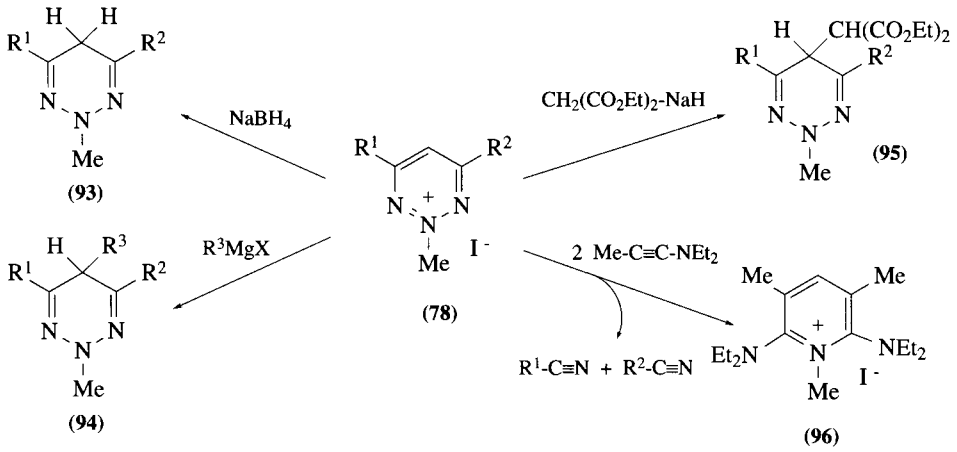


Scheme 14

6.10.4.6 Reactions of Triazinium Salts

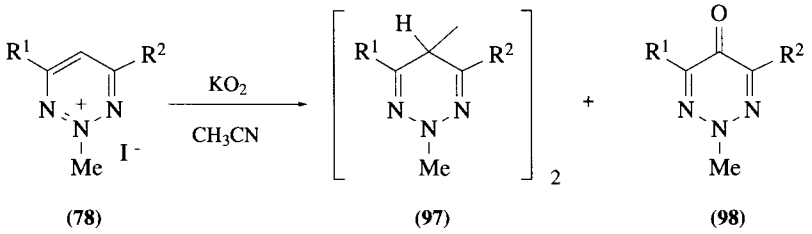
2-Methyltriazinium quaternary salts (**78**), which are obtained by the reaction of (**1**) with methyl iodide for several days, are highly reactive to nucleophiles; the reactive site is the 5-position, giving 2,5-dihydro derivatives ⟨92CPB2283⟩. Thus, reduction with $NaBH_4$ gives 2,5-dihydrotriazines (**93**) ⟨85YZ1122⟩, and reaction with Grignard reagents gives 5-alkyl- or 5-aryl-2,5-dihydrotriazines (**94**) in moderate yields. Other nucleophiles such as diethyl malonate anion and silyl enol ethers also afford the corresponding dihydro adducts (**95**). The unique reactivity of the salts was shown when they were treated with an ynamine to form an *N*-methylpyridinium salt (**96**) ⟨90CPB2108⟩. The results are summarized in Scheme 15.

The reaction of triazinium salts (**78**) with superoxide gave 5,5′-bi(2-methyl-2,5-dihydrotriazinyls) (**97**), which were formed by one electron reduction with superoxide followed by dimerization, accompanied by small amounts of 5-oxo-2,5-dihydrotriazines (**98**) (Equation (26)). The product



Scheme 15

ratio did not change significantly even in the presence of oxygen, which suggested that the dimerization process is quite fast ⟨90TL7193, 92CPB2283⟩.

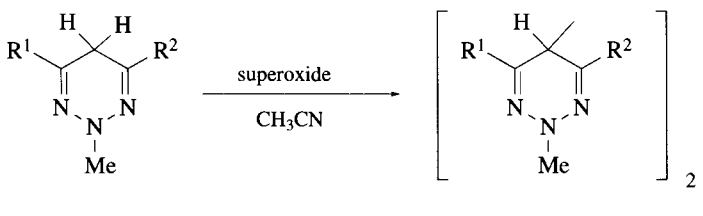


(26)

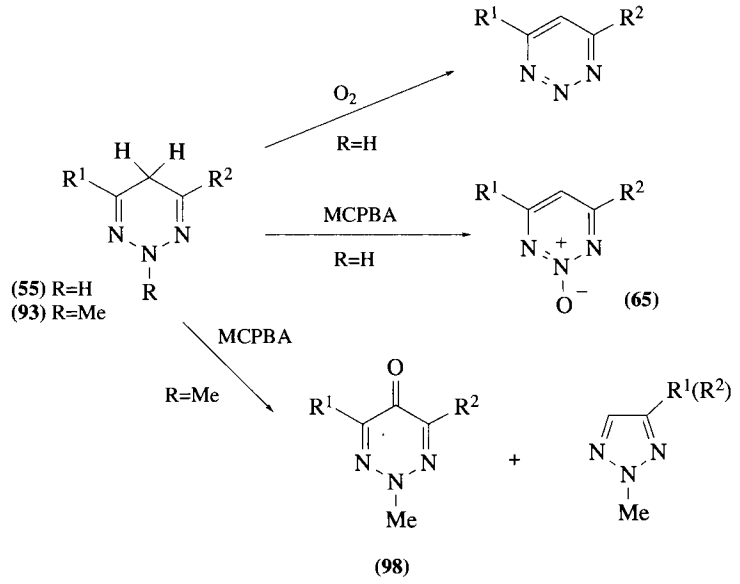
	Yield under Ar (97)	(98)	Yield under O_2 (97)	(98)
R^1=R^2=Me:	52%	12%	58%	7%
R^1=Me, R^2=Ph:	54%	6%	61%	11%
R^1=R^2=Ph:	57%	13%	65%	13%

6.10.5 REACTIVITY OF NONCONJUGATED RINGS

The reactions of nonconjugated rings have rarely been reported because such derivatives of (**1**) are scarcely known. A report ⟨86H(24)33⟩ was concerned with the oxidation of 2,5-dihydrotriazines, which afforded the results shown in Scheme 16 and Equation (27). The 2,5-dihydrotriazines (**55**) were slowly oxidized in air to the corresponding triazines (*ca.* 20–30% yields in chloroform after 3 days) ⟨85YZ1122⟩, whereas oxidation with MCPBA afforded 2-oxides (**65**) exclusively. The fact that 1-oxides were not formed means that the triazine is not an intermediate. *N*-Methyl derivatives (**93**) were partly ring contracted to the corresponding triazoles with MCPBA, and were oxidized by superoxide in a different manner to afford the dimeric products (**97**) ⟨90TL7193⟩. In these cases, hydrogen abstraction of C—H at the 5-position prevailed. The results are summarized in Scheme 16 and Equation (27).



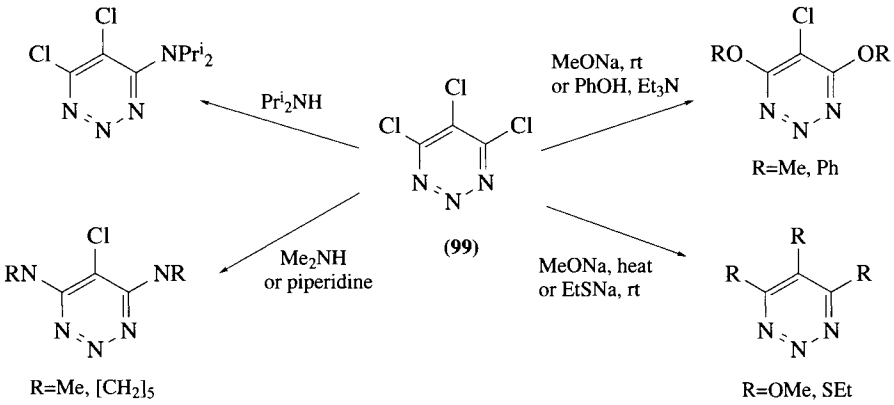
(27)



Scheme 16

6.10.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

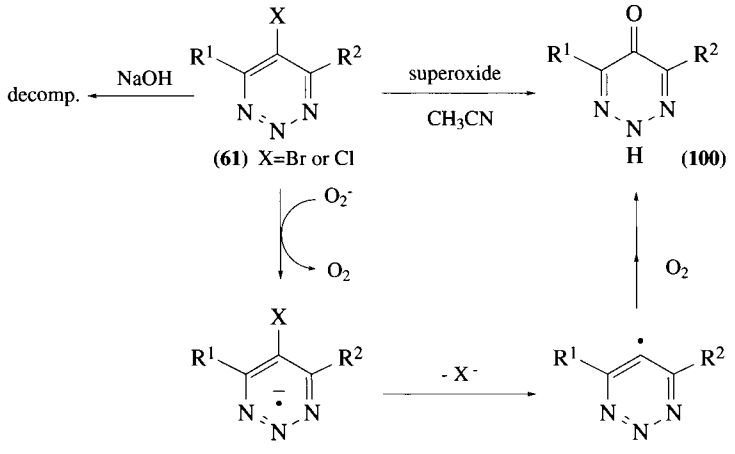
Since the triazines obtained until 1995 have had mainly alkyl or aryl substituents, or been benzo-fused derivatives, reports concerning the reactivity of substituents have been relatively few. Gompper *et al.* reported that 4,5,6-trichlorotriazine (**99**) undergoes substitution reactions with amines and alcohols ⟨79CB1535⟩. The first reaction site was the C-4 position, and successive displacement(s) occurred depending on the nature of the nucleophile (Scheme 17).



Scheme 17

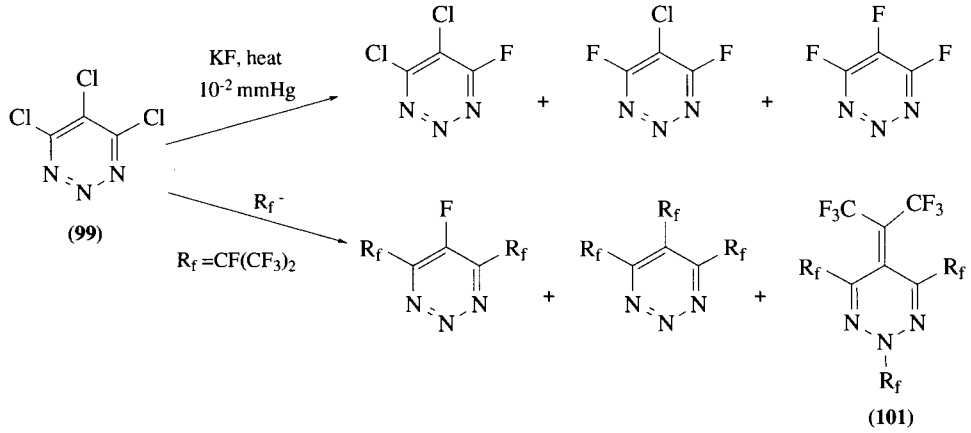
It has been shown that 5-halo-1,2,3-triazines (**61**) react with superoxide to give 1,2,3-triazin-5(2*H*)-ones (**100**) ⟨90TL2429⟩. Hydroxide ion attacked at the C-4(6) position, even in the absence of the leaving group, and resulted in ring-opening. Electrochemical methods revealed that the reaction was initiated by a one electron transfer from superoxide to (**61**) (Scheme 18) ⟨91T4317⟩. 5-Triazinones (**100**) thus formed showed intense molecular ion peaks in EI–MS, in contrast to other triazines. The 5-oxo forms are therefore believed to predominate rather than 5-hydroxy tautomers.

4,5,6-Trichlorotriazine (**99**) has been used for the syntheses of trifluoro and perfluoroisopropyl derivatives. Chambers *et al.* reported that reaction of trichlorotriazine with potassium fluoride at elevated temperature gave trifluorotriazine and the corresponding chlorofluoro derivatives ⟨88T2583⟩. In the case of fluoride ion and hexafluoropropene as reagents, the perfluoroisopropyl



Scheme 18

group was introduced. In this case, a compound (**101**) was obtained which was derived from nucleophilic attack at N-2 (Scheme 19).



Scheme 19

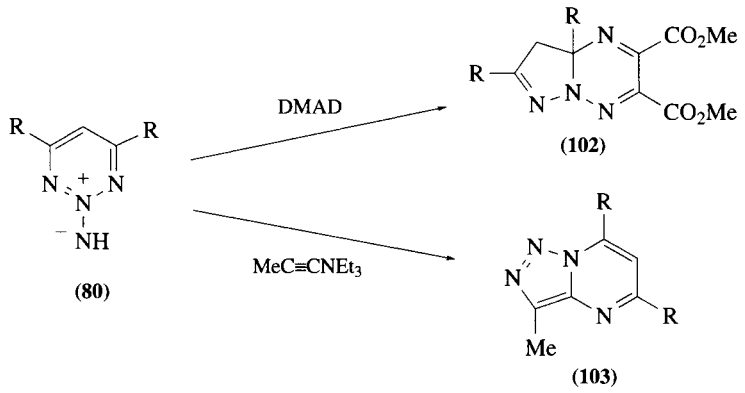
6.10.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN ATOMS

Triazine *N*-imines (**80**) react with dimethyl ethynedicarboxylate to give the products (**102**) which are derived from the primary 1,3-dipolar cycloadducts via a ring transformation ⟨83CPB3759⟩. An electron-rich dienophile, *N*,*N*-diethylamino-1-propyne, with (**80**) formed a different ring system (**103**), which was also postulated to arise by cycloaddition followed by a ring opening and re-cyclization (Scheme 20) ⟨90CPB2108⟩.

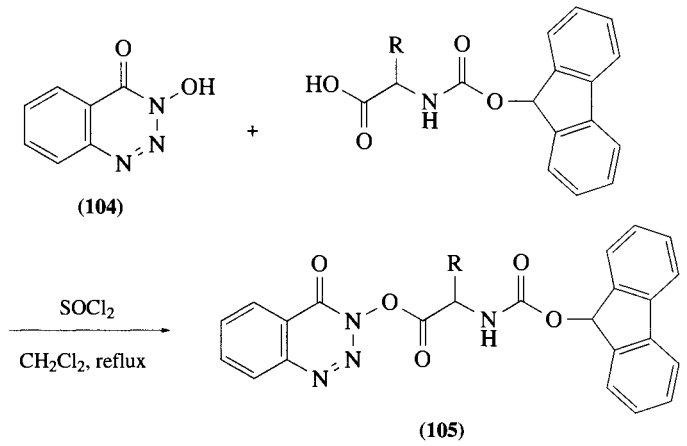
There are few reports on the reactivity of 1,2,3-triazine *N*-oxides. Thermolysis of 4-phenyl-1,2,3-benzotriazine 3-oxide gave 3-phenylbenzisoxazole, 3-phenylindazole, and acridin-9-one ⟨75JCS(P1)45⟩, whereas its photolysis afforded 3-phenylindazole as the major product ⟨73JA2390⟩. Photo and thermal reactions of monocyclic triazine *N*-oxides have not been reported.

3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one (Dhbt—OH) (**104**) is an advantageous additive in the synthesis of peptides using either the carbodiimide or the active ester method. This compound was recognized to suppress racemization, and Fmoc amino acid derivatives of Dhbt—OH (**105**) have been used for peptide synthesis (Equation (28)) ⟨70CB2024, 70CB2034, 86CC1763, 87CC270, 88JCS(P1)2895,

91TL6199〉. A new synthetic method for Dhbt—OH analogues (**106**) from substituted anthranilic acids has been reported 〈90S1008〉 (Equation (29)).



Scheme 20



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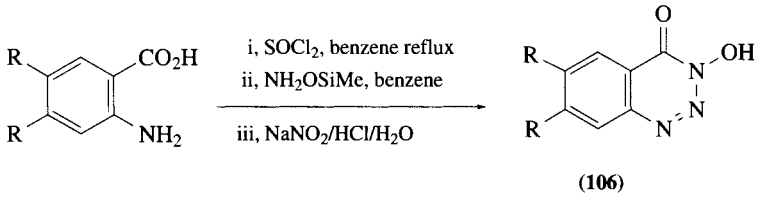
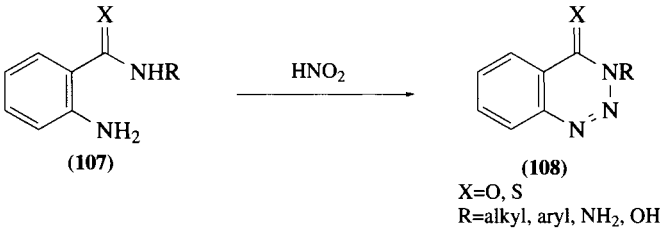


(29)

6.10.8 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

For the synthesis of benzotriazine derivatives, ring closure by the [5 + 1] atom fragment method has been the most frequently used, in which N-2 is supplied as the one-atom fragment. The source of N-2 is nitrous acid, and 1,2,3-benzotriazin-4-ones (**108**; X = O) 〈78HC(33)17〉, benzotriazine-4-thiones (**108**; X = S) 〈71JHC785〉, 3-aminobenzotriazin-4-ones (**108**; X = O, R = amino) 〈78HC(33)17〉, 3-hydroxybenzotriazin-4-ones (**108**; X = O, R = OH) 〈75JHC199, 78HC(33)17〉, benzotriazine 3-oxides (**110**) 〈78HC(33)84〉, and 4-aminobenzotriazines (**113**) 〈70JCS(C)2308〉 have been synthesized from

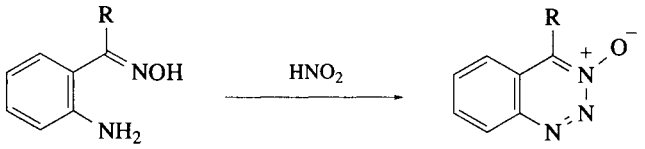
2-aminobenzamides (**107**; X = O), 2-aminothiobenzamides (**107**; X = S), 2-aminobenzohydrazides (**107**; X = O, R = amino), 2-aminobenzohydroxamic acids (**107**; X = O, R = OH), 2-aminophenylaldoximes or ketoximes (**109**), and 2-aminobenzamidines (**111**), respectively. 3,4-Dihydrobenzotriazines have been obtained in the same manner using 2-aminobenzylamines or 2-aminobenzylhydrazines ⟨78HC(33)91⟩ (Equations (30)–(32)).



(107) (108)

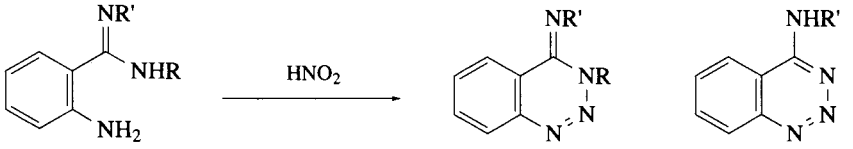
X=O, S
R=alkyl, aryl, NH_2, OH

(30)



(109) (110)

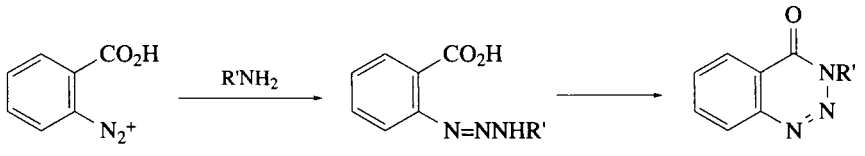
(31)



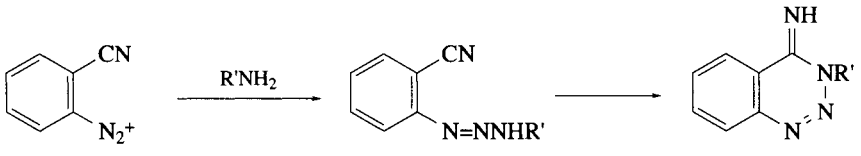
(111) (112) (113) (R=H)

(32)

The second method involves the N-3 nitrogen as the one-atom fragment, and the general approaches are shown in Schemes 21 and 22 ⟨78HC(33)17, 78HC(33)72, 78TL5041⟩.

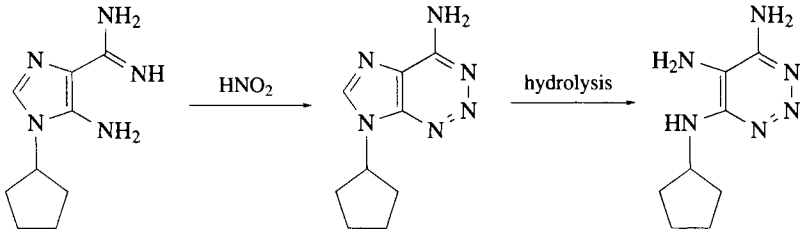


Scheme 21



Scheme 22

The ring synthesis of monocyclic triazines by the addition of components is practically unknown. The general method shown in Equation (32) for (**111**)→(**113**) was used in an indirect synthesis of the monocyclic triazine (**114**) (Scheme 23) ⟨72JMC182⟩.

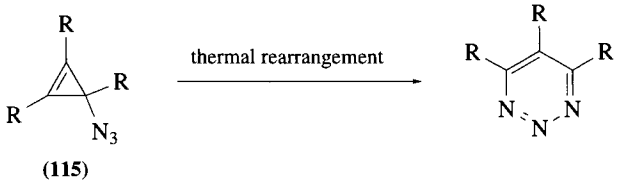


(114)

Scheme 23

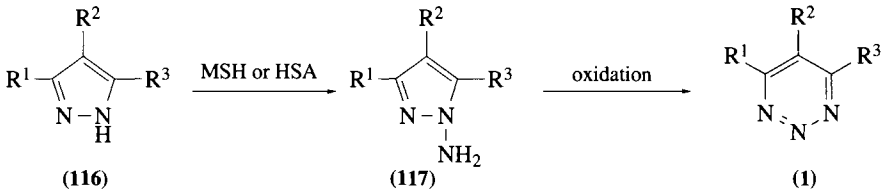
6.10.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

There are two general synthetic methods for 1,2,3-triazines which belong to this section. The first, reported in 1960 ⟨60TL19⟩, is the thermal rearrangement of a cyclopropenyl azide (**115**) (Equation (33)) ⟨72CB3695, 72JOC1051, 72TL3293, 73AG(E)847, 73JOC3149, 79CB1514, 79CB1529⟩. This method is limited to the synthesis of trisubstituted triazines, because only trisubstituted cyclopropenyl azides were rearranged. 4,5-Diphenyltriazine was obtained by an analogous method based on rearrangement of a aziridinyl diazomethane ⟨81TL2909⟩. The second, and more general method involves the oxidation of *N*-aminopyrazoles (**117**). This method was used at first by Rees *et al.* for the synthesis of benzotriazine ⟨71CC828, 75JCS(P1)31⟩, and was later applied to monocyclic compounds including the parent triazine ⟨80CC1182, 81CC1174, 85JOC5520, 85LA1732⟩. By this method, various mono-, di-, and trisubstituted alkyl- and aryltriazines were synthesized. The amino nitrogen is incorporated into the triazine ring as the central nitrogen N-2, probably via insertion of the nitrene moiety to the N—N bond of the pyrazole ring ⟨86JCS(P1)1249⟩. The method has been further applied to the synthesis of 1,2,3-triazinecarboxylates ⟨93LA367⟩. Until now, the best method for the synthesis of the parent monocyclic triazine has been the oxidation of 1-aminopyrazole (**117**; $R^1 = R^2 = R^3 = H$) with sodium perchlorate, which gives (**1a**) in 46% yield ⟨89H(29)1809⟩ (Scheme 24).



(115)

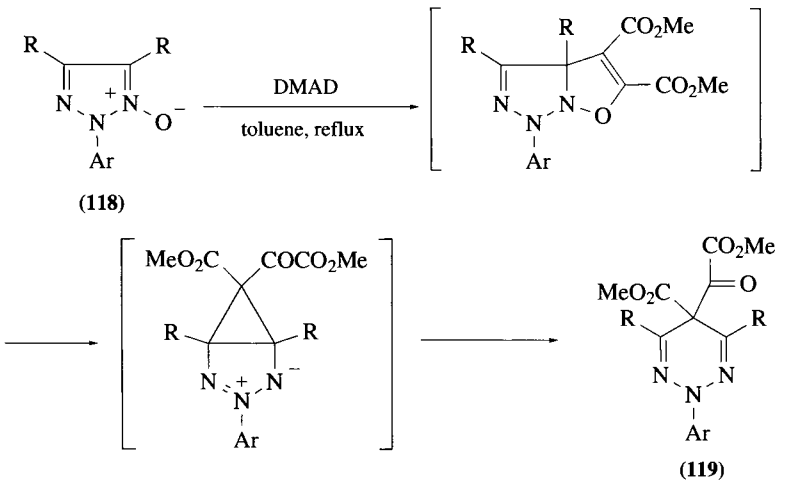
(33)



(116) (117) (1)

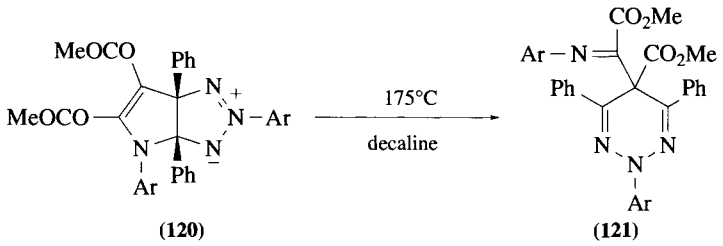
Scheme 24

Butler *et al.* reported that 2,5-dihydro-1,2,3-triazine derivatives (**119**) are obtained by the 1,3-dipolar cycloaddition of 1,2,3-triazole *N*-oxides (**118**) with DMAD (Scheme 25) ⟨87CC706, 90JCS(P1)3321⟩. The reaction was suggested to proceed through the sequence of cyclization and two rearrangements. One of the structures of the products was elucidated by x-ray crystallographic analysis. A recent report from the same group revealed that pyrrolo[2,3-*d*]-1,2,3-triazoles (**120**) thermally rearranged to 2,5-dihydro derivatives (**121**) ⟨93JCR(S)78⟩ (Equation (34)).



(118) **(119)**

Scheme 25



(120) **(121)** (34)

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6.11
1,2,4-Triazines and their Benzo Derivatives

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Technische Hochshule Darmstadt, Germany

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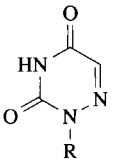
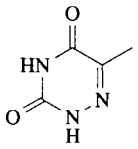
6.11.1 INTRODUCTION

1,2,4-Triazines were already a well-known class of heterocyclic compound when the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) was published in 1984 ⟨84CHEC-I(3)369⟩. Since that time about 4000 papers, dealing with all aspects (chemical, physical, spectroscopic, analytical, biological, biochemical, agrochemical, environmental, etc.) of 1,2,4-triazines and their benzo derivatives have been published. However, more than 50% of these papers deal with the properties of only a few compounds, used as agrochemicals, as drugs, or as ligands for metal ion complexation (see Section 6.11.11).

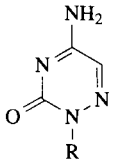
Since 1,2,4-triazines can be considered as azapyrimidines, a great number of 6-azapyrimidine nucleotides and nucleosides have been prepared and their properties intensively studied, for instance 6-azauracil (**1**), 6-azauridine (**2**), 6-azathymine (**3**), 6-azacytosine (**4**), and 6-azacytidine (**5**).



(**1,2**)

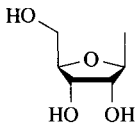


(**3**)



(**4,5**)

1,4; R = H **2,5**; R =

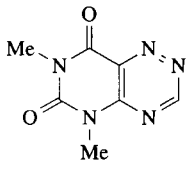


Finally, many papers have been concerned with the use of 1,2,4-triazines in cycloaddition reactions and especially in Diels–Alder reactions with inverse electron demand (see Section 6.11.5.11).

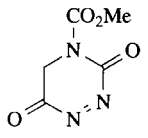
Few additional synthetic methods to 1,2,4-triazines have been published since 1984. Most possible 1,2,4-triazine structures are known, and their physical and chemical properties have been extensively studied and well documented. Most important spectral and structural data were summarized in CHEC-I, Chapter 2.19, and the best synthetic methods and reactions of various 1,2,4-triazines were discussed in that article.

Only a few 1,2,4-triazines have been isolated from natural sources. Most are fused examples, such as the pyrimido[5,4-*e*]-1,2,4-triazine fervenulin (**6**). In 1988 the very surprising monocyclic 4,5-dihydro-1,2,4-triazine-3,6-dione structure (**7**) was reported to be isolated from the seeds of *Butea monosperma* ⟨88MI 611-01⟩.

Since 1982 a number of reviews have been published on different aspects of 1,2,4-triazines. These



(**6**)



(**7**)

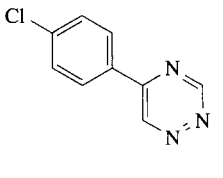
are; progress in the synthesis and reactions of 1,2,3- and 1,2,4-triazines ⟨84OPP199⟩, advances in the chemistry of dihydroazines ⟨85AHC(38)1⟩, behavior of monocyclic 1,2,4-triazines in reactions with C-, N-, and S-nucleophiles ⟨89AHC(46)73⟩, advances in the chemistry of *as*-triazinium salts ⟨92H(33)931⟩, hetero Diels–Alder methodology ⟨B-87MI 611-01⟩, metribuzin ⟨91MI 611-01⟩, lamotrigine ⟨86MI 611-01, 91MI 611-02⟩, effects on DNA of bioreducible nitroimidazoles and benzotriazine drugs ⟨90MI 611-01⟩, bioreductive antineoplastic agents ⟨90MI 611-02⟩, azapyrimidine nucleosides: metabolism and inhibitor mechanism ⟨85MI 611-01⟩, azapyrimidine nucleosides ⟨84MI 611-01⟩, and synthesis and pesticidal activity of heterocyclic compounds containing nitrogen and sulfur ⟨86YGK939⟩.

6.11.2 THEORETICAL METHODS

Semiempirical and *ab initio* molecular orbital methods have been used to calculate various aspects of 1,2,4-triazine chemistry. The Hückel method was used to calculate the π-electron energies ⟨85MI 611-02, 85MI 611-03⟩, the electronic excitation energies and intensities were calculated by the RPAC molar-properties program ⟨89MI 611-01⟩, and the ionization energies were calculated by the following methods: SCF(AM1), SCF(PM3), HAM/3, OVGF (AM1) and OVGF(PM3): the last method gave the best results ⟨91JCS(P2)1865⟩.

The performance of the MNDO method, as far as the energy of 1,2,4-triazines is concerned, is critically evaluated after comparing its results with some *ab initio* calculations at the 4-31G level and with experimental data. The lone-pair electronic repulsion between the neighboring pyridine-like nitrogens is systematically underestimated by MNDO. When corrections are introduced, the relative stabilities are predicted with reasonable accuracy ⟨85JOC4894⟩. The energy levels for the LUMOs of the parent 1,2,4-triazine (−0.77553 eV) and of 3-phenyl-1,2,4-triazine (−1.038 eV) were calculated by the AM1 method ⟨93LA583⟩.

The structure, protonation energies, isomer stabilities, and vertical ionization potentials of 1,2,4-triazine and its three protonated cations were investigated by *ab initio* calculations using different basis sets. Minimal basis tends to overestimate N—N bond lengths, C—N and C—C bond lengths are also overestimated, but to a lesser degree. In general 6-31G structures are very close to the experimental ones while the 3-21G basis does not always correct the deficiencies of the minimal basis ⟨87JST135⟩. We compare the calculated bond lengths with the experimental values in 5-(4-chlorophenyl)-1,2,4-triazine (**8**) ⟨74JHC743⟩: N1—N2: 1.327 calc./1.335 exp.; N2—C3: 1.311/1.314; C3—N4: 1.353/1.339; N4—C5: 1.310/1.317; C5—C6: 1.409/1.401; C6—N1: 1.312/1.317 Å. The bond angles show greater deviations from the experimental values: C6$\widehat{N1}$N2: 125.2°/118.8°; N1$\widehat{N2}$C3: 116.1°/117.1°; N2$\widehat{C3}$N4: 123.4°/127.2°; C3$\widehat{N4}$C5: 119.2°/115.9°; N4$\widehat{C5}$C6: 119.4°/118.4°; C5$\widehat{C6}$N1: 116.7°/122.5°.



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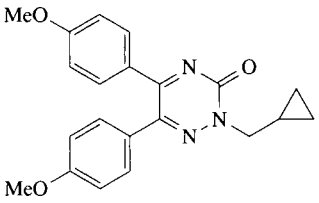


(9)

Bond lengths and bond angles of the algicidal compound Diazatrifone, 2-cyclopropylmethyl-5,6-bis(4-methoxyphenyl)-1,2,4-triazin-3(2*H*)-one (**9**), were calculated by the CNDO/2 quantum method ⟨87JST(35)379⟩. The calculated values for 6-azacytidine (**5**) are not always in agreement with the experimental values ⟨74JA1239⟩.

The CNDO/2 method has been used for the calculation of the sites of the protonation and alkylation of 1,2,4-triazines ⟨88KGS525⟩. It was also applied to calculate the two-photon tensor invariants proportional to two-photon absorptivities for transitions to the lowest singlet states, L_b^- (B_{2u}^-) and L_a^+ (B_{1u}^+) ⟨84CPL(107)125⟩.

The acidities and basicities of 1,2,4-triazines have been calculated by the MOSP method. The pK_a values correlate satisfactorily with the total ($\sigma + \pi$) atomic charges of the proton-accepting atom and the ionization potential ⟨92RRC819⟩. The proton affinities of 1,2,4-triazines were calculated by the 3-21 + G, 3-21G, MNDO, and AM1 methods ⟨88MI 611-02⟩, and the tautomeric equilibrium by the AM1 and MNDO-PM3 methods ⟨91MI 611-03⟩ and the lithium-triazine binding energies by the 6-31G* method ⟨90TCA1⟩. Calculation of the [2 + 2]-cycloaddition of alkenes to the C=N bond of

1,2,4-triazine-3,5-diones were carried out by the EHMO, INDO/S and *ab initio* methods ⟨86MI 611-02, 85ZN(A)279⟩. The calculations are in agreement with the observed regioselectivities.

Frequencies and intensities of bands in the IR spectra of 1,2,4-triazines have been calculated by the 4-31G method ⟨93JST(101)97⟩ and by *ab initio* Hartee–Fock methods at the 6-31G, 6-31G**, U-9, and 3-21G levels ⟨91SA(A)595⟩. Calculations on the conformations of 1,2,4-triazines by the molecular mechanics method using the MM285 field of Allinger *et al.* ⟨91JST(245)53⟩, the heats of formation by molecular mechanics calculations ⟨91MI 611-04⟩, the nature of distant heteroatom lone-pair effects on direct ^{13}C-^{1}H spin coupling constants by the AM1 method ⟨91IZV582⟩ and nuclear shielding tensors of ^{15}N and ^{13}C nuclei by the SOLO (second-order corrected localized orbital-local origin) *ab initio* method ⟨92CPL(197)55⟩, have been reported.

6.11.3 EXPERIMENTAL STRUCTURAL METHODS

Because of the considerable interest in 1,2,4-triazine chemistry since the 1960s, most of the structural data could be discussed in CHEC-I ⟨84CHEC-I(3)369⟩. General information on the structures of different types of 1,2,4-triazines, based on x-ray crystallographic analysis, IR, UV, NMR, mass spectra, and photoelectron spectra can be found in that article. In the following sections a few additional details are presented.

6.11.3.1 X-ray Crystallography

The simplest 1,2,4-triazine of which the structure has been determined by x-ray crystallography is still the 5-(4-chlorophenyl)-1,2,4-triazine (**8**) ⟨74JHC743⟩. Wilson and Wadsworth, with 1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1**) (6-azauracil), have shown that it is possible to solve crystal structures of simple organic molecules from very poor x-ray powder diffraction data. ⟨90AX(A)258⟩

For the following monocyclic 1,2,4-triazine and 1,2,4-benzotriazine derivatives x-ray crystallographic data has been published;

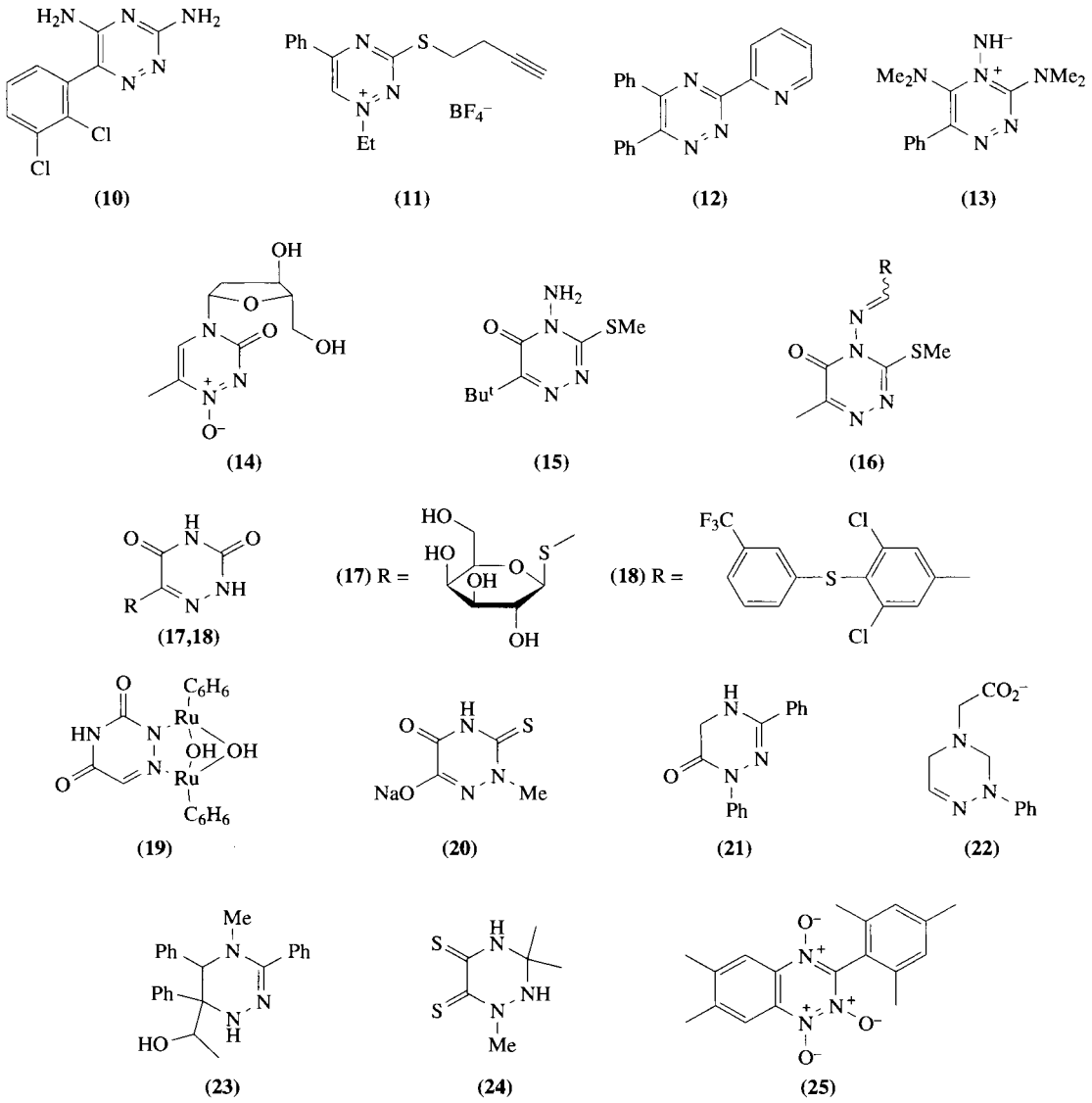
3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (Lamotrigine (**10**) as methanol solvate) ⟨89CSC129⟩, 3-(but-3-ynylthio)-1-ethyl-5-phenyl-1,2,4-triazinium tetrafluoroborate (**11**) ⟨89T6499⟩, 5,6-diphenyl-3-(2-pyridyl)-1,2,4-triazine ((**12**) as Et_2SnCl_2 complex) ⟨83ICA(68)45⟩, 3,5-bis-(dimethylamino)-6-phenyl-1,2,4-triazine 4-imine (**13**) ⟨90CSC1487⟩, 6-methyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (6-azathymine (**3**) as hemihydrate) ⟨85MI 611-04⟩, 4-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-1,2,4-triazin-3(4*H*)-one 1-oxide (**14**) ⟨82JOC913⟩, 4-amino-6-*t*-butyl-3-methylthio-1,2,4-triazin-3(4*H*)-one (**15**) (Sencor, Metribuzin) ⟨89MI 611-02⟩, 4-(alkylideneamino)-6-methyl-3-methylthio-1,2,4-triazin-5(4*H*)-ones (**16**) ⟨89JA355, 89JOC1264, 90JCS(P2)1859⟩, 6-(galactopyranosylthio)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**17**) ⟨82DOK(263)345⟩, 6-[3,5-dichloro-4-(3-trifluoromethylphenylthio)-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**18**) ⟨93DOK(329)603⟩, the (η^6-benzene)ruthenium complex of 1,2,4-triazine-3,5(2*H*,4*H*)-dione (**19**) ⟨91JOM(410)73⟩, the sodium salt of 6-hydroxy-2-methyl-3-thioxo-2,3-dihydro-1,2,4-triazin-5(4*H*)-one (**20**) ⟨93CSC241⟩, 1,3-diphenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**21**) ⟨88CSC1440⟩, the copper complex of 2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazin-4-ylacetate (**22**) ⟨86JCS(D)553⟩, 6-(1-hydroxyethyl)-4-methyl-3,5,6-triphenyl-1,4,5,6-tetrahydro-1,2,4-triazine (**23**) ⟨88JCS(P1)3267⟩, the silver complex of 1,3,3-trimethyl-3,4-dihydro-1,2,4-triazine-5,6-dithione (**24**) ⟨94JPR53⟩, 3-mesityl-6,7-dimethyl-1,2,4-benzotriazine 1,2,4-trioxide (**25**) ⟨89CC986⟩.

6.11.3.2 NMR Spectroscopy

NMR spectra of 1,2,4-triazines are well documented, not only the ^{1}H and ^{13}C but also the ^{15}N spectra, which have been studied intensively between 1985 and 1995.

6.11.3.2.1 Proton spectra

The parent 1,2,4-triazine shows three signals in the ^{1}H NMR spectrum, as expected, the shifts depending on the solvent as shown in Table 1. In liquid ammonia a σ-complex is formed. The signal of H-6 is a doublet of doublets, while the signals for H-3 and H-5 are simple doublets. Since to our



knowledge coupling between H-3 and H-5 is never observed in simple 1,2,4-triazines, ^{1}H NMR spectroscopy provides a simple method to distinguish between isomeric monosubstituted derivatives.

Table 1 Proton NMR shifts (δ values) of 1,2,4-triazine in different solvents and predicted chemical shifts.

Solvent	*H-3*	*H-5*	*H-6*	*Ref.*
$CDCl_3$	9.88	8.84	9.48	66JOC1720
	9.73	8.70	9.34	78RTC273
CCl_4	9.63	8.53	9.24	69TL3147
CD_3OD	9.86	8.93	9.52	69TL3147
DMSO-d_6	9.75	8.88	9.42	69TL3147
C_6D_6	9.45	7.92	8.68	69TL3147
NH_3	7.40	4.15	6.65	78RTC273
Predicted shifts	9.74	8.74	8.98	68CC1028

From the data it is seen that the shifts for H-5 (7.92–8.98) and H-6 (8.68–9.52) are more influenced by the solvent than the shifts for H-3 (9.45–9.88).

The influence of *N*-oxidation on the ^{1}H NMR spectra of 1,2,4-triazines has been studied by

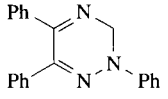
various groups. Comparison of the spectrum of a 1,2,4-triazine with those of its 1-oxide and 2-oxide (Table 2) shows that on oxidation at N-1 the proton at the 6-position is shielded by about 1.4 ppm, that at the 5-position by about 0.3 ppm, and that at the 3-position by about 0.9 ppm. Oxidation at N-2 leads to a shielding of H-3 by about 1.1 ppm, of H-5 by about 0.8 ppm, and of H-6 by about 1.1 ppm ⟨71JOC787, 77JOC546⟩. *N*-4-oxidation in 6-methyl-1,2,4-triazine results in a small shielding (0.27 ppm (H-3) and 0.33 ppm (H-5)) of both ring protons ⟨71LA(750)12⟩. It is noteworthy that in 6-substituted 1,2,4-triazine 4-oxides the H-3 and H-5 signals are doublets, while in 6-substituted 1,2,4-triazines they are singlets.

Table 2 Influence of N-oxidation on the ^{1}H NMR shifts (δ values) of 1,2,4-triazines.

1,2,4-Triazine	*H-3*	*H-5*	*H-6*	*Ref.*
1,2,4-Triazine	9.88	8.84	9.48	66JOC1720
1-oxide	9.00	8.57	8.05	71JOC787
2-oxide	8.82	8.00	8.42	77JOC546
3-Methoxy-1,2,4-triazine	–	8.56	9.00	78RTC273
1-oxide	–	8.37	7.83	71JOC787
2-oxide	–	7.76	8.12	77JOC546
6-Methyl-1,2,4-triazine	9.55	8.55	–	71LA(750)12
4-oxide	9.28	8.22	–	71LA(750)12

3-Amino-1,2,4-triazine gives two resonances in the ^{1}H NMR spectrum, both doublets, at $\delta = 8.5$ ppm and 8.3 ppm, assigned to the protons at the five and six positions respectively ⟨93JOC2001⟩.

During the last decade data on the ^{1}H NMR spectra of dihydro-1,2,4-triazines have become available. In 2,5,6-triphenyl-2,3-dihydro-1,2,4-triazine (**26**) the signal for the 3-CH_2 group is observed at $\delta = 5.26$ ppm ($CDCl_3$) ⟨92JCS(P1)147⟩. The CH_2 group in 6-duryl-3,4-diphenyl-4,5-dihydro-1,2,4-triazine (**27**) gives a signal at $\delta = 4.00$ ($CDCl_3$), which is shifted in trifluoroacetic acid. For the CH_2 group in 3-benzhydryl-6-phenyl-2,5-dihydro-1,2,4-triazine (**28**) a signal at $\delta = 4.32$ ppm is observed ⟨73JOC3466⟩. In 1-alkyl-4,5-dihydro-1,2,4-triazinium salts the CH_2 group in the 5-position absorbs between $\delta = 4.72$ and 5.24 ⟨74ZOR2429⟩.



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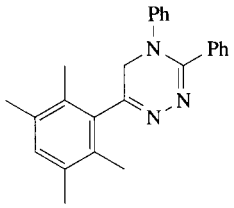

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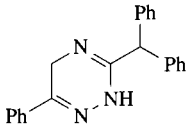

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The sodium salt of 1,2,4-triazin-3(2*H*)-one gave two signals, at $\delta = 8.36$ (H-6) and 8.28 (H-5) (DMSO-d_6); the signal for H-6 in 5-methyl-1,2,4-triazin-3(2*H*)-one is observed at $\delta = 7.93$ ⟨71JOC3921⟩. In the ^{1}H NMR spectrum of 1,2,4-triazin-5(2*H*)-one two signals were found, at $\delta = 8.72$ (H-3) and 7.74 (H-6) ⟨72JHC995⟩.

2,4,6-Triaryl-2,3,4,5-tetrahydro-1,2,4-triazines show the expected methylene group signals in the region $\delta = 4.2$–4.6 ppm ⟨78LA2033⟩.

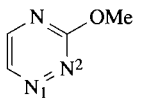
The following ^{1}H NMR spectrum is reported for 1,2,4-trimethylhexahydro-1,2,4-triazine at 34°C: $\delta = 2.16$ (s; 4-Me), 2.46 (s; 1-Me), 2.51 (s; 2-Me), 2.74 (bm; CH_2CH_2) and 3.42 (s; CH_2) ⟨79JCS(P2)984⟩. A study of the effect of temperature on the spectrum of this compound and also of the 3-methyl analogue provided information on their conformational equilibria.

6.11.3.2.2 Carbon-13 spectra

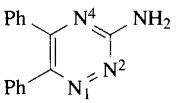
The ^{13}C NMR spectra of the parent 1,2,4-triazine and its three monomethyl derivatives, and of two dimethyl derivatives and the trimethyl compound, were recorded by Braun and Frey ⟨75OMR(7)194⟩. The parent 1,2,4-triazine shows the following absorptions and coupling constants: $\delta = 158.1$ (C-3), 149.6 (C-5), and 150.8 ppm (C-6); $J = 207.1$ Hz (C-3/H-3), 9.1 Hz (C-3/H-5), 1.3 Hz (C-3/H-6), 188.0 Hz (C-5/H-5), 7.5 Hz (C-5/H-3), 9.0 Hz (C-5/H-6), 187.5 Hz (C-6/H-6), 9.5 Hz

(C-6/H-5), and 2.0 Hz (C-6/H-3). Substitution of the heterocyclic ring with methyl groups shifts the signals of the ring carbons to lower fields, as is shown for 3,5,6-trimethyl-1,2,4-triazine: $\delta = 164.7$ (C-3), 158.3 (C-5) and 155.0 (C-6).

1,2,4-Triazine 1-oxide has the signals for the three carbon atoms at $\delta = 158.5$ (C-3), 152.7 (C-5), and 129.7 (C-6) ⟨86H(24)951⟩, and the three signals for 1,2,4-triazine 2-oxide have been variously reported at $\delta = 132$ (C-3), 143 (C-5), and 143 ppm (C-6) ⟨77JOC546⟩, or at 143.5 (C-3), 132.5 (C-5), and 146.0 (C-6) ⟨86H(24)951⟩. To compare the influence of oxidation at N-1 and N-2 on the ^{13}C spectra of 1,2,4-triazines the values are given for 3-methoxy-1,2,4-triazine (**29**) ⟨78RTC273⟩ and its 1-oxide and 2-oxide ⟨77JOC546⟩. From the data (Table 3) it follows that oxidation at N-1 has a large influence on C-6 (−19 ppm) and a small influence on C-5 (2.4 ppm) and C-3 (0.4 ppm), while oxidation at N-2 affects all three carbon atoms, but especially C-3 (−13.6 ppm) and C-5 (−21.6 ppm). Comparison of the ^{13}C spectra of the unsubstituted 1,2,4-triazine and its 2-oxide gives different results since the largest influence is observed on C-3 and the effects on C-5 and C-6 are smaller. The ^{13}C spectra of a 1,2,4-triazine and its 4-oxide show that there is a large influence on C-3 (−10.4 ppm) and C-5 (−15.8 ppm) while the effect on C-6 is smaller (3.0 ppm) ⟨79JHC1389⟩. Table 3 also presents the ring carbon chemical shifts for 3-amino-5,6-dimethyl-1,2,4-triazine (**30**) and its 1-, 2-, and 4-oxides ⟨86H(24)951⟩.



(**29**)



(**30**)

Table 3 Carbon-13 chemical shifts of ring carbon atoms of 1,2,4-triazines.

Compound	*C-3*	*C-5*	*C-6*
3-methoxy (**29**)	166.1	161.6	145.5
1-oxide	166.5	154	124.5
2-oxide	152.5	130	135.5
3-amino (**30**)	162.1	158.9	147.1
1-oxide	164.3	162.1	127.6
2-oxide	148.9	140.2	144.2
4-oxide	154.4	143.0	148.7

In the ^{13}C NMR spectrum of 3-fluoro-1,2,4-triazine 2-oxide the signals for the three carbon atoms were recorded at 149.8 (C-3), 122.1 (C-5), and 131.5 ppm (C-6) while the resonances in 3-fluoro-5,6-diphenyl-1,2,4-triazine 2-oxide were observed at 145.6 (C-3), 136.3 (C-5), and 127.6 ppm (C-6) with the following C—F coupling constants: C-3/F: 218 Hz, C-5/F: 42 Hz and C-6/F: 14 Hz ⟨85H(23)1969⟩.

The shifts of the ^{13}C NMR signals of 3,5,6-trichloro-1,2,4-triazine have been compared with the calculated values obtained by first and second order SCS methods: $\delta = 160.8$ (C-3; 157.7, 163.4), 157.0 (C-5; 155.8, 153.0) and 154.7 (C-6; 140.8, 151.9) ⟨80OMR(13)363⟩.

The three carbon atoms of the 1,2,4-triazine ring in 1,2,4-triazine-5-carbaldehyde oxime absorb at $\delta = 157.4$ (C-3), 151.4 (C-5), and 146.4 ppm (C-6) ⟨93JHC413⟩. In 3-amino-1,2,4-triazine the signals were observed at $\delta = 163.3$ (C-3), 153.3 (C-5), and 141.0 ppm (C-6) which were shifted in the 5,6-dimethyl derivative to 162.3 (C-3), 159.2 (C-5), and 147.3 ppm (C-6) ⟨79JHC53⟩.

The ^{13}C NMR spectrum of 1,2,4-triazine-3,5-dione shows three signals at $\delta = 149.5$ (C-3), 158.1 (C-5), and 137.1 ppm (C-6) ⟨79OMR(12)612⟩. The 2-(β-D-ribofuranosyl)-1,2,4-triazine-3,5-dione has very similar values ⟨73JA4761⟩.

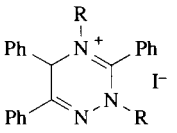
In the ^{13}C NMR spectrum of 2,5,6-triphenyl-2,3-dihydro-1,2,4-triazine the following signals were observed: $\delta = 61.7$ (C-3), 159.0 (C-5), and 144.0 (C-6) ⟨92JCS(P1)147⟩.

For 4,5-dihydro-1,2,4-triazin-6(1*H*)-one resonances were recorded at $\delta = 137.5$ (C-3), 42.1 (C-5), and 160.5 ppm (C-6) ⟨83T3419⟩.

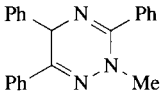
In the ^{13}C NMR spectrum of 3,5,6-triphenyl-2,5-dihydro-1,2,4-triazinium iodide (**31**) the following signals were observed: 154.47 (C-3), 50.49 (C-5), and 153.05 ppm (C-6); for the 2-methyl derivative (**32**) signals were found at $\delta = 143.4$ (C-3), 56.7 (C-5), and 154.0 ppm (C-6). 2,4-Dimethyl-3,5,6-triphenyl-2,5-dihydro-1,2,4-triazinium iodide (**33**) showed resonances at $\delta = 150.2$ (C-3), 57.2 (C-5),

and 154.8 ppm (C-6), and for 1-methyl-3,5,6-triphenyl-1,6-dihydro-1,2,4-triazine (**34**) signals at 145.9 (C-3), 153.1 (C-5), and 56.2 ppm (C-6) were recorded ⟨93JCS(P1)661⟩.

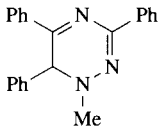
The three ring carbon atoms in 1,2,4-trimethylhexahydro-1,2,4-triazine resonate at 77.1 (C-3), 54.5 (C-5), and 46.4 ppm (C-6) ⟨79JCS(P2)984⟩.



(**31**) R = H
(**33**) R = Me



(**32**)



(**34**)

6.11.3.2.3 Nitrogen-15 spectra

To assist comparison of data, both within this chapter and elsewhere in the volume, all nitrogen chemical shifts are expressed on the δ scale with respect to nitromethane ($\delta = 0$ ppm).

The ^{15}N NMR spectrum of the parent 1,2,4-triazine has been measured in a range of solvents, and the observed shifts provide insight into solvent-induced, site-orientated electric charge redistributions and solvent–solute hydrogen bonding effects in the molecule. A sharp contrast is observed in the solvent effects on the nitrogen atoms in positions one and two with respect to that at position four. The former pair exhibit a remarkable affinity to, and sensitivity towards, hydrogen-bond donor solvents. Their electron densities appear to be significantly dependent upon the solvent polarity. In contrast, N-4 appears to be relatively uninfluenced by solvent effects ⟨92JMR(98)109⟩. The measured values are given in Table 4.

Table 4 Solvent effects on the nitrogen NMR shielding of 1,2,4-triazines.

Solvent	*Chemical shifts* (δ)[a]		
	N-1	*N-2*	*N-4*
CF_3CH_2OH	+18.48	−21.63	−85.51
H_2O	+21.24	−22.65	−84.63
MeOH	+33.87	−11.29	−80.03
EtOH	+36.65	−8.80	−79.51
DMSO	+39.24	−4.89	−80.34
CH_2Cl_2	+41.64	−2.47	−80.60
$CHCl_3$	+42.12	−2.41	−80.24
acetone	+42.23	−2.33	−80.43
dioxan	+43.42	+0.76	−80.94
benzene	+45.40	+1.26	−80.98
Et_2O	+47.59	+2.67	−80.22
CCl_4	+48.37	+3.82	−79.95
cyclohexane	+51.16	+6.84	−79.95

[a]Solute concentration 0.25 M, temperature 35 °C; shieldings corrected for bulk susceptibility effects.

Table 5 lists the ^{15}N chemical shifts of a number of 1,2,4-triazines and their *N*-oxides.

For 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one the following ^{15}N shifts were recorded; $\delta = -219.0$ (N-1), −155.9 (N-2), and −312.9 ppm (N-4) ⟨83T3419⟩.

The ^{15}N–^{13}C coupling constants have been measured for ^{15}N-labelled 3-methyl- and 3,5,6-trimethyl-1,2,4-triazine ⟨76OMR(8)273⟩, they are in the same range as is found in other azines. The ^{14}N–^{13}C spin-spin coupling constants were recorded for some 1,2,4-triazines and their 1- or 2-oxides ⟨86H(24)951⟩.

6.11.3.3 Mass Spectrometry

The mass spectra of 1,2,4-triazines have been studied extensively since they can be used for structure determination. The fragmentation pattern depends on the structure (aromatic, quinoid,

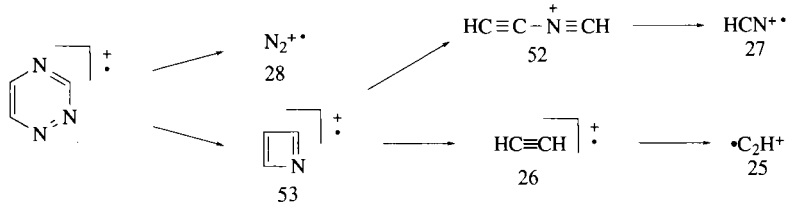
Table 5 Nitrogen-15 NMR spectra of some 1,2,4-triazines.

Compound	*N-1*	*N-2*	*N-4*	*Ref.*
unsubstituted	+40.0	+2.0	−62.0	84SA(A)637
3-amino	+35.7	−61.0	−130.0	84SA(A)637
3-methoxy	+36.0	−58.0	−124.4	84SA(A)637
3-methylthio	+32.0	−29.0	−98.0	84SA(A)637
1-oxide	−43			84SA(A)637
3-amino 1-oxide	−51.1	−107.0	−152.0	84SA(A)637
3-methoxy 1-oxide	−50.0	−97.1	−148.0	84SA(A)637
3-amino 2-oxide	−39.0	−137.0	−153.0	84SA(A)637
3-bromo 2-oxide	−28.6	−71.0	−74	84SA(A)637
3-phenyl 5-carbaldoxime	+36.8	−18.9	−98.6	93JHC413
1,2,4-benzotriazine	+68.3	+23.4	−98.1	84OMR(22)201

[a] δ-values (CH_3NO_2) in d_6-DMSO with $Cr(acac)_3$.

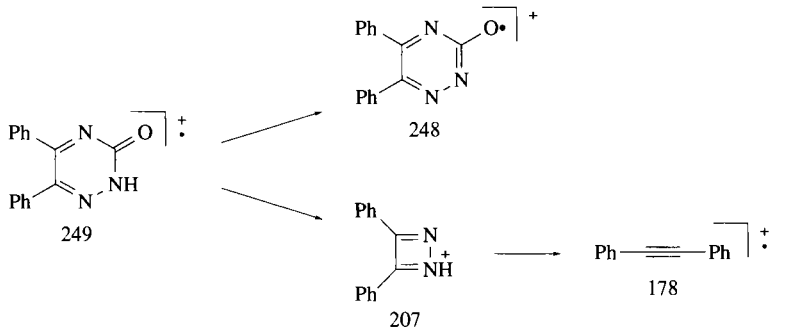
alicyclic) of the 1,2,4-triazine system and on the substituents; no general underlying system is observed.

The mass spectrum of the unsubstituted 1,2,4-triazine shows peaks at 81, 53, 52, 51, 40, 39, 38, 28, 27, 26, and 25 Da, being accounted for in part by the fragmentation pattern given in Scheme 1. This was confirmed by the mass spectrum of 1,2,4-triazine-d_3 ⟨67JHC224⟩. [4-^{15}N]-3-Methyl-1,2,4-triazine shows a similar fragmentation pattern ⟨72LA(760)102⟩. From these data it follows that the fragmentation starts with loss of nitrogen.



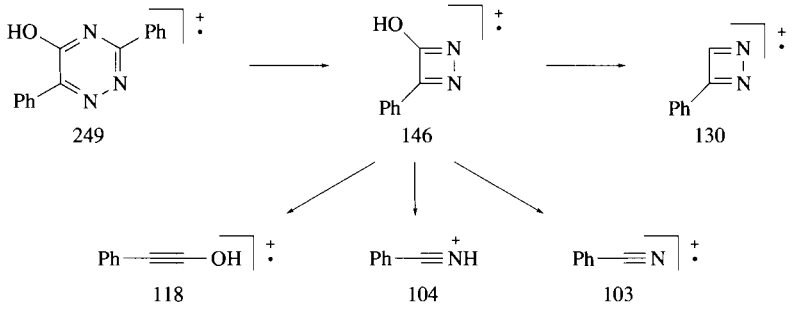
Scheme 1

The suggested pattern for 5,6-diphenyl-1,2,4-triazin-3-one is quite different from that of the parent 1,2,4-triazine. The first fragmentation step is the loss, not of nitrogen, but of an NCO moiety, as shown in Scheme 2 ⟨71OMS(5)1085⟩. Similarly, in the mass spectrum of 3,6-diphenyl-1,2,4-triazin-5-one, the first step is not the elimination of nitrogen but of benzonitrile. From the observed data the fragmentation pattern of Scheme 3 is suggested ⟨70JPR669⟩. On the other hand, 3,5-diphenyl-1,2,4-triazin-6-one starts with loss of nitrogen, as with the simple 1,2,4-triazines. The main fragmentation pattern is given in Scheme 4 ⟨70JPR669, 92LA1271⟩. For ethyl 3-methylthio-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylate the fragmentation starts with the loss of N_2H, but the general pattern is the same as for the 5,6-diphenyl derivative ⟨85JOC2293⟩.

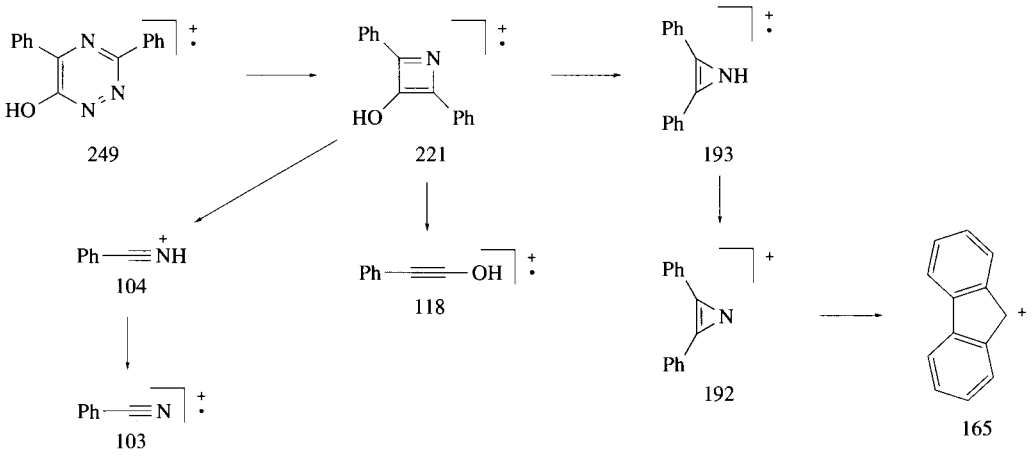


Scheme 2

Mass spectrometric fragmentation of 1,2,4-triazin-5-ones, 2-methyl-1,2,4-triazin-5-ones, 4-methyl-1,2,4-triazin-5-ones, 5-methoxy-1,2,4-triazines and a few deuterated derivatives, was studied



Scheme 3



Scheme 4

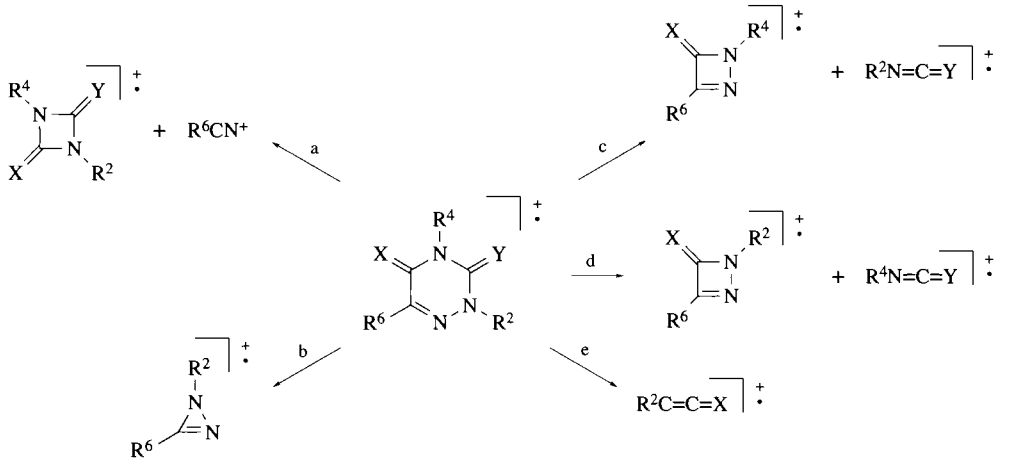
in the course of an investigation into tautomeric equilibria. It was found that the equilibria are dependent upon the nature of the substituents in the 3- and 6-positions ⟨81OMS(16)347⟩.

An extensive investigation on 1,2,4-triazines substituted with oxygen or sulfur in the 3- and 5-positions has been made. The following systems were studied: 1,2,4-triazine-3,5-diones, 1,2,4-triazine-3,5-dithiones, 3-thioxo-1,2,4-triazin-5-ones, 3-methoxy-1,2,4-triazin-5-ones, 3-methylthio-1,2,4-triazin-5-ones, 3-methylthio-1,2,4-triazine-5-thiones, 5-methyloxy-3-methylthio-1,2,4-triazines, and 3,5-bis(methylthio)-1,2,4-triazines. Five distinct fragmentation patterns were observed upon electron impact, but none involve initial loss of nitrogen. The observed fragmentations start with rupture of the N(1)—N(2) and C(5)—C(6) bonds and loss of a nitrile (a), with rupture of the N(2)—C(3) and C(5)—C(6) bonds (b), with the rupture of the N(1)—N(2) and C(3)—C(4) bonds (c), with the rupture of the N(2)—C(3) and N(4)—C(5) bonds (d), or with the rupture of the N(1)—C(6) and N(4)—C(5) bonds (e), as shown in Scheme 5. ⟨76OMS(11)1002⟩

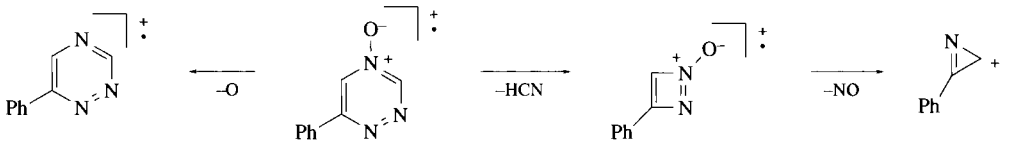
Also in the mass spectrum of 3-hydrazino-5,6-diphenyl-1,2,4-triazine the elimination of nitrogen from the molecular ion could not be detected. The dominant process in this case is the fragmentation of the molecular ion into the diphenylethyne radical ion at m/z 178 Da ⟨71OMS(5)1085⟩.

Paudler and his group have studied the fragmentation of 1,2,4-triazine 1-oxides and 2-oxides. The mass spectrum of unsubstituted 1,2,4-triazine 2-oxide has an intense molecular ion, which is the base peak, and others at $(M-16)^+$ and $(M-30)^+$. Comparison of the mass spectra of 1,2,4-triazine 1- and 2-oxides shows that the patterns are very similar, with the relative peak intensities varying with the type of substituent present. For 1,2,4-triazine 1-oxides without a substituent in the 6-position the fragmentation starts with loss of oxygen, nitric oxide or nitrous oxide, and the same was found with the 2-oxides. A substituent in the 6-position of 1,2,4-triazine 1-oxides leads to elimination of OH, as does a substituent in the 3-position of 1,2,4-triazine 2-oxides, as proven by deuterium labelling ⟨71JHC317, 77JHC1389⟩.

The mass spectra of 1,2,4-triazine 4-oxides show very intense molecular ion peaks and very weak peaks for $(M-16)^+$ (Scheme 6) ⟨71LA(750)12⟩.



Scheme 5



157 173 146 116

Scheme 6

Mass spectra of dihydro-1,2,4-triazines have been measured by Nagy *et al.*, but they were not discussed in detail ⟨93JCS(P1)661⟩.

6.11.3.4 UV/vis Spectroscopy

The UV/vis spectra of 1,2,4-triazines were discussed in detail in the previous reviews ⟨78HC(33)189, 84CHEC-I(3)369⟩. Only a few additional data have been published during the following decade.

The parent 1,2,4-triazine has two absorption bands in methanol, at 374 ($\varepsilon = 400$) and 247.8 nm (3020). In 0.1N HCl/methanol only one band is observed, at 230 nm ($\varepsilon = 4460$), while in 0.1N NaOH/methanol bands at 382 nm (380) and 249.5 nm (3430) were found ⟨68CB3952⟩. In the gas phase this compound has several bands in the region between 420 nm and 380 nm ⟨75TH 611-01⟩. Alkyl-substituted 1,2,4-triazines show similar electronic spectra ⟨59JCS1240, 59JCS1247⟩.

Ultraviolet spectra have been used to identify the predominant tautomeric forms of 1,2,4-triazinones, 1,2,4-triazinethiones, and amino-1,2,4-triazines.

1,2,4-Triazin-3-ones exist predominantly in the 2*H*-form, as shown by comparison of the following UV spectra: 5,6-diphenyl-1,2,4-triazin-3-one: 335 ($\varepsilon = 4170$), 295 (6550), and 252 nm (14880); 2-methyl-5,6-diphenyl-1,2,4-triazin-3-one: 338 (4970), 290 (6160), and 254 nm (14300); 4-methyl-5,6-diphenyl-1,2,4-triazin-3-one: 292 (10720), 230 (10920), and 215 nm (15440); and 3-methoxy 5,6-diphenyl-1,2,4-triazine: 328 (8000) and 257 nm (13000) ⟨66JOC3914, 71JOC3921⟩. 5,6-Diamino-1,2,4-triazin-3-one shows the following bands in methanol: 307.5 ($\varepsilon = 2800$), 249.5 (6080), and 225.5 nm (10170) ⟨83JOC1271⟩. For 5,6-dialkylthio-1,2,4-triazin-3-ones in ethanol only one band at 293 nm ($\log \varepsilon = 3.8$) is reported ⟨89RRC1321⟩.

In a similar way, 1,2,4-triazin-5-ones were found to exist in solution predominantly in the 2*H* form; however, in the solid it seems that the 5-hydroxy tautomer predominates, at least in the 3,6-diphenyl derivative ⟨74T3171⟩. The UV-spectra (ethanol): 3,6-dimethyl-1,2,4-triazin-5-one: 260 ($\varepsilon = 4530$), 232 nm (8900); 2,3,6-trimethyl-1,2,4-triazin-5-one: 255 (7290) and 243 nm (10000); 3,4,6-trimethyl-1,2,4-triazin-5-one: 273 (5190) and 218 nm (5190); 5-methoxy-3,6-dimethyl-1,2,4-triazine: 318 (340), 262 (5160), and 212 nm (6710) ⟨72JHC995⟩.

1,2,4-Triazin-6-ones exist predominantly in the 1*H*-form, as was found by comparison of the UV spectra of 3-methyl-5-phenyl-1,2,4-triazin-6-one (315 ($\log \varepsilon = 3.35$), 263 (4.32)) and 5-methyl-3-

phenyl-1,2,4-triazin-6-one (333 (3.98), 277 (3.75), 226 (3.78)) with the spectra of their 1-methyl analogues (320 (3.48), 265 (4.33) and 337 (4.13), 278 (3.87), 225 (3.92), respectively) ⟨78JHC1271⟩.

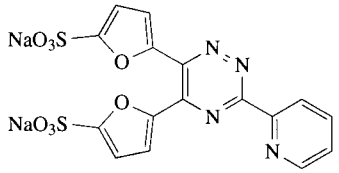
1,2,4-Triazine-3,5-diones show an absorption maximum in the UV at 261 nm (ethanol, dioxan) or 259 nm ($\varepsilon = 5100$) (H_2O; pH = 3) ⟨61CCC2155⟩. Methylation at N-2 shifts the maximum to 273 nm while methylation at N-4 causes a hypsochromic shift (to 258 nm). Dimethylation leads to a band which is given by additive contributions of the individual methyl group effects.

Similar results were obtained for 1,2,4-triazine-3-thiones, -5-thiones and -3,5-dithiones. The last show two absorption maxima around 320 and 280 nm ⟨62CCC1886⟩.

3-Amino-1,2,4-triazine has two absorption maxima, at 394 ($\varepsilon = 505$) and 310 nm (2730). The first is attributed to an $n \rightarrow \pi^*$ and the second to a $\pi \rightarrow \pi^*$ transition ⟨59JCS1247⟩.

Ultraviolet spectra of 1,2,4-triazines substituted with different hetero substituents (amino, oxo, thioxo) are also published ⟨83JOC1271, 86JHC33, 89RRC1321⟩.

Ferene (5,6-di-(2-furyl)-3-(2-pyridyl)-1,2,4-triazine 5′,5″-disulfonate (**35**) forms a stable tris-complex with iron(II) ions, which exhibits a single sharp peak with a maximum absorption at 593 nm and a molar absorptivity of 34500 L cm^{-1} mol^{-1}. Ferene is one of the most sensitive colorimetric reagents for iron(II) yet reported ⟨84CJC721⟩.



(35)

For 1,2,4-benzotriazine in cyclohexane two absorption maxima are reported: 458 ($\varepsilon = 400$) and 296 (3750) ⟨62JCS493⟩. 3-Benzyl-1,2,4-benzotriazine shows four bands in ethanol: 331 ($\log \varepsilon = 3.49$), 302 (3.66), 234 (4.65), and 208 (4.36) ⟨67JCS(C)1279⟩, while for 3-phenyl-1,2,4-benzotriazine the following two bands were seen: 352 ($\varepsilon = 910$) and 261 (12500) ⟨82BCJ859⟩.

Only a few data on the UV spectra of 1,2,4-triazine N-oxides are to be found in the literature. It seems to us that these spectra should allow a determination of the position of the *N*-oxide function. For instance, 3-amino-5,6-diphenyl-1,2,4-triazine 1-oxide has two absorption bands at 298 ($\log \varepsilon = 4.20$), and 231 nm (4.44) ⟨65CPB1168⟩, while the 2-oxide shows three bands, at 365 (3.82), 257 (4.31), and 222 nm (4.25, infl.) ⟨66JOC3914⟩. For 5,6-diphenyl-1,2,4-triazin-3(4*H*)-one 2-oxide two bands at 354 ($\log \varepsilon = 3.78$) and 255 nm (4.17) were reported. The 4-methyl derivative shows a similar UV spectrum with two bands at 365 ($\log \varepsilon = 3.79$) and 252 nm (4.11) ⟨66JOC3914⟩. For 3-methoxy-5,6-diphenyl-1,2,4-triazine 2-oxide two bands were observed, at 346 ($\log \varepsilon = 3.89$) and 252 nm (4.21) ⟨66JOC3914⟩. For 1,2,4-triazine 4-oxides a band at about 270 nm and an inflection in the 300 nm region have been noted ⟨71LA(750)12⟩.

Further information on the UV spectra of the different 1,2,4-triazines can be found in the 1978 review ⟨78HC(33)189⟩.

6.11.3.5 IR Spectroscopy

IR spectral data for most known 1,2,4-triazines has been published and a detailed discussion can be found in CHEC-I. Only a little additional information has been published up to 1995, most dealing with the carbonyl frequencies in 1,2,4-triazinones.

The absorptions of 1,2,4-triazines in the IR region are as expected for this system. The IR spectrum of the parent compound shows three absorption bands for the C—H stretching vibrations, at 3090, 3060, and 3030 cm^{-1}, five bands for C=N and C=C stretching vibrations, at 1560, 1529, 1435, 1380, and 1295 cm^{-1}, three for the C—H in-plane deformations at 1163, 1135, and 1113 cm^{-1}, two for the characteristic ring skeleton vibrations at 1050 and 995 cm^{-1}, and three bands for the C—H out-of-plane deformation vibrations at 875, 768, and 713 cm^{-1} ⟨68CB3952⟩. Alkyl and aryl derivatives show similar absorptions from the framework, with additional bands from the substituents.

The N—O stretching vibration in 1,2,4-triazine 1-oxide is observed at 1370 cm^{-1}, and the corresponding band in 1,2,4-triazine 2-oxide is at 1330 cm^{-1} ⟨85SA(A)1135⟩. 1,2,4-Triazine 4-oxides show a band for the N—O stretching vibration in the 1280 cm^{-1} region ⟨71LA(750)12⟩.

1,2,4-Triazin-3-ones show a strong carbonyl absorption around 1685 cm^{-1} which is observed both in KBr and in chloroform ⟨62CJC1053⟩, and a weak peak for the N—H stretching vibration at 3450 cm^{-1} (KBr) or 3350 cm^{-1} ($CHCl_3$). The C=O stretching vibration for 1,2,4-triazin-5-ones occurs at 1640–1670 cm^{-1} for the 2*H*-form and 1675–1690 cm^{-1} for the 4*H*-form. The N—H stretching vibration is observed at ca. 3170 cm^{-1}. In 2-amino-1,2,4-triazin-5-ones the carbonyl absorption is found at 1620–1625 cm^{-1} ⟨83JHC1671⟩. 1,2,4-Triazin-6-ones have a strong C=O stretching vibration at 1665 cm^{-1} ⟨85JHC409⟩ and the dihydro-1,2,4-triazin-6-ones absorb at similar frequencies ⟨82SA(A)133⟩.

The infrared absorption spectra of 1,2,4-triazine-3,5-diones show two ν(N—H) vibrations in the region 3450–3350 cm^{-1} ⟨65CCC1792⟩, which were assigned to H-4 and H-2 by comparison with the 2-methyl (3374 cm^{-1} ⟨63CCC3392⟩) and 4-methyl (3424 cm^{-1} ⟨65CCC1792⟩ derivatives. Also two bands in the carbonyl region were observed at 1730 cm^{-1} and 1700 cm^{-1}. The first band is shifted to 1723–1720 cm^{-1} if N-2 is alkylated, and the second to 1687–1680 cm^{-1} when N-4 is alkylated. IR spectroscopy can therefore be used to determine the position of substituents in 1,2,4-triazine-3,5-diones ⟨61CCC1680⟩. The IR absorption spectra of the unsubstituted 1,2,4-triazine-3,5-dione isolated in low-temperature N_2 and Ar matrices are also reported. Within the limits of accuracy of spectroscopic measurements the compound appears to exist in these matrices exclusively in the dioxo tautomeric form. An assignment of the observed bands was proposed, based on the comparison of experimental frequencies and intensities with those calculated theoretically at *ab initio* Hartree–Fock level with 6-31G** basis set. The carbonyl absorptions in 2-amino-1,2,4-triazine-3,5-diones were observed at 1640–1680 and 1680–1720 cm^{-1} ⟨83JHC1671⟩.

Further information on the IR spectra of 1,2,4-triazines can be found in a 1978 review ⟨78HC(33)189⟩.

6.11.3.6 Photoelectron Spectroscopy

Photoelectron spectra of unsubstituted 1,2,4-triazine, its three monomethyl, two dimethyl and the trimethyl derivatives have been measured by Gleiter ⟨77CPL(46)231⟩. The He(I) photoelectron spectrum of the parent 1,2,4-triazine is characterized by a single band at 9.6 eV followed by a complicated system of several overlapping peaks between 11 and 13 eV. A further composite band is found at 15 eV. Methyl substitution seems to help in the resolution of the peaks. The experimental PE spectra were interpreted by comparison with the results of MO calculations and empirical correlation procedures. In Figure 1 the correlations of the first five bands of 1,2,4-triazine and its three monomethyl derivatives are given.

The PE spectrum of 1,2,4-trimethylhexahydro-1,2,4-triazine was measured, as part of an investigation into the conformation of this compound in the gas phase ⟨80JCS(P2)91⟩.

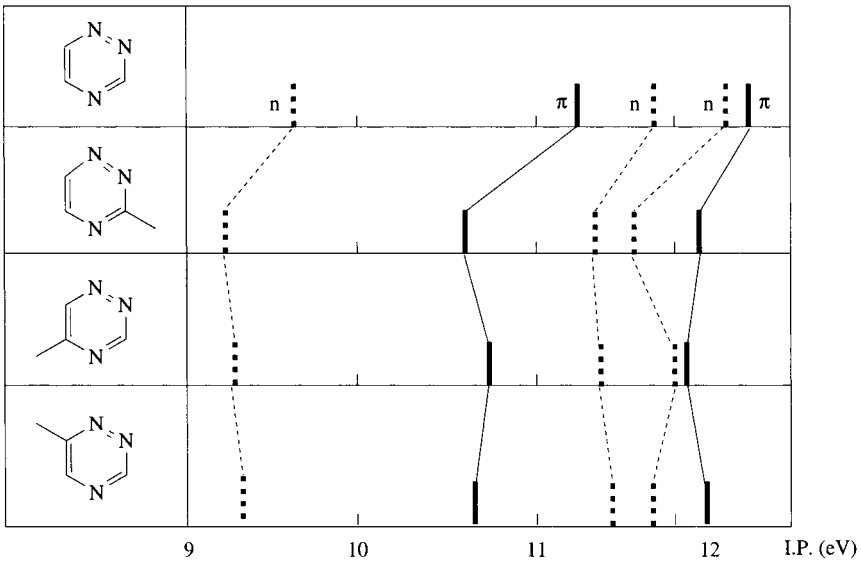


Figure 1 Correlation of the first five bands in the PE spectra of 1,2,4-triazine and its three monomethyl derivatives.

6.11.3.7 ESR Spectroscopy

Irradiation of single crystals of *N*-deuterated and undeuterated 6-methyl-1,2,4-triazine-3,5-dione with γ- or x-rays afforded radicals by loss of hydrogen from the methyl group. The EPR spectra of these were recorded by Herak and Schoffa ⟨71MP379⟩. The 19-line spectrum of the deuterated radical indicates interaction of the unpaired electron with two apparently equivalent protons and two nonequivalent nitrogen atoms. The spectrum of the undeuterated 6-methyl derivative shows an additional proton coupling. The two equivalent proton couplings are 14.2 Gauss in both crystals. The nitrogen couplings are also the same in both crystals: 24.0 and 5.0 Gauss.

The ESR spectra of radicals produced by one-electron loss from 1,2,4-triazine-3,5-dione, 6-methyl-1,2,4-triazine-3,5-dione and 5-amino-1,2,4-triazin-3-one have been measured at 77 K. That from 1,2,4-triazine-3,5-dione is found to be a σ-radical whose ESR spectrum shows large couplings (ca. 30 G) to the nitrogens at positions one and two. The 6-methyl-1,2,4-triazine-3,5-dione cation radical gives an ESR spectrum characteristic of a π-radical. This spectrum shows couplings to the 6-methyl group (14.7 G) and the nitrogen at position two (ca. 9.6 G). 5-Amino-1,2,4-triazin-3-one forms a σ-radical with nitrogen couplings within 1 Gauss of those found for the 1,2,4-triazine-3,5-dione; however this radical decays to a new radical species whose ESR spectrum is suggestive of a π-radical. ⟨82JPC1751⟩.

The ESR spectra of metastable triplet states of 6-methyl-1,2,4-triazine-3,5-dione in ethylene glycol/water glass at $-196\,^{\circ}C$ were recorded by Shulman and Rahn ⟨66JCP(45)2940⟩. It was found that the lowest triplet state is a $\pi \rightarrow \pi^*$ state.

The ESR spectra of 1,3-diphenyl- and 3-t-butyl-1-phenyl-1,4-dihydro-1,2,4-benzotriazinyl radicals, and of the corresponding radical cations, were studied. In the uncharged species the spin density at N-4 apparently determines the ^1H HFC pattern in the 1,2,4-benzotriazinyl compound. In the radical cation, on the other hand, it is N-1, with an unusually high splitting of 9.9 G, is the position of highest spin density, which controls the ^1H HFC pattern ⟨88MRC595⟩.

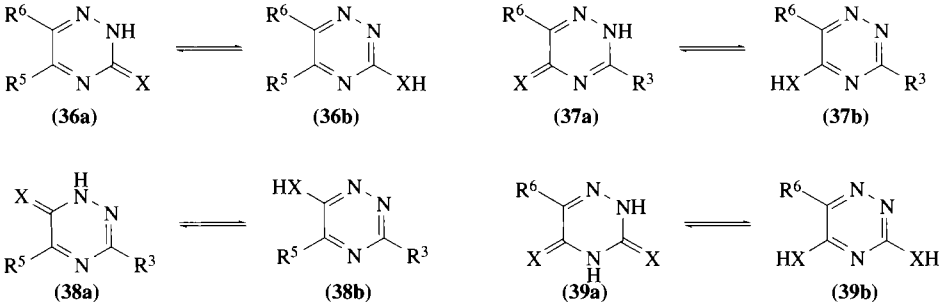
6.11.4 THERMODYNAMIC PROPERTIES

Most 1,2,4-triazines are crystalline compounds, the melting points depending on the structure and the substituents present. Alkyl-substituted 1,2,4-triazines are yellow and melt at low temperatures, or in a few cases they are liquids at room temperature; but they are reasonably stable. They can be stored at $0\,^{\circ}C$ or lower, but in time they become dark. They can usually be distilled under reduced pressure, and can be purified by vapor-phase chromatography, by which isomeric alkyl-1,2,4-triazines can be separated. Aryl-substituted 1,2,4-triazines have melting points around $100\,^{\circ}C$, while all heterosubstituted (oxo, thioxo, amino, etc.) 1,2,4-triazines have melting points in the $200\,^{\circ}C$ region. These compounds are usually very stable.

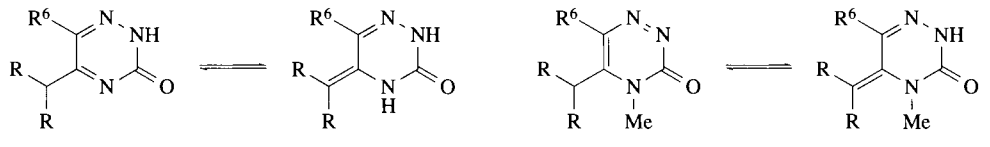
Alkyl- and aryl-substituted 1,2,4-triazines are soluble in most organic solvents, while hetero-substituted 1,2,4-triazines need highly polar solvents for solution. In most cases there are no problems in purifying 1,2,4-triazines by chromatography on silica gel.

The aromaticity of 1,2,4-triazine has been calculated by various methods, which all show that, in agreement with their structures determined by x-ray crystallographic analysis, these molecules show some degree of delocalization.

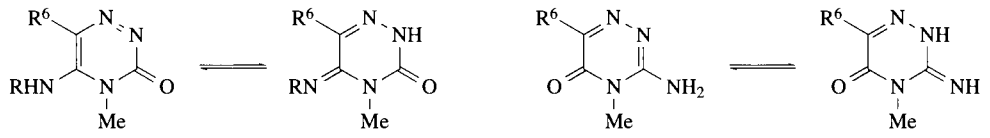
The tautomeric problem in 1,2,4-triazinones/hydroxy-1,2,4-triazines or 1,2,4-triazinethiones/thio-1,2,4-triazines was discussed in CHEC-I ⟨84CHEC-I389⟩ and further results are given in Section 6.11.3.4. In this section, the principal results are summarized. It was found that in general for oxygen (X = O) or sulfur (X = S) substituted 1,2,4-triazines the oxo- or thioxo form (**36a–39a**) predominates while in nitrogen substituted 1,2,4-triazines (X = NH) the amino form (**36b–39b**) predominates.



5-Alkyl-1,2,4-triazin-3-ones (**40**) with a proton at C-1 of the alkyl group can occur in two tautomeric forms: the alkyl form (**40a**) and the structure (**40b**) with an alkylidene group. The ratio of the two tautomers depends on the solvent, and in a few cases both have been isolated. 5-Alkyl-4-methyl-1,2,4-triazin-3-ones (**41**) form predominantly the 5-alkylidene tautomers (**41b**). This is explained by the fact that structures with a formal N=N double bond are energetically unfavourable; they are destabilized and so tend to be avoided. 5-Amino-4-methyl-1,2,4-triazin-3-ones (**42**) were shown to exist predominantly in the 5-imino forms (**42b**) due to the destabilization of the amino tautomer (**42a**) by the formal N=N double bond. On the other hand, for 3-amino-4,6-dimethyl-1,2,4-triazin-5-one (**43a**) the predominance of the amino tautomer was proven and no imino tautomer (**43b**) could be detected.



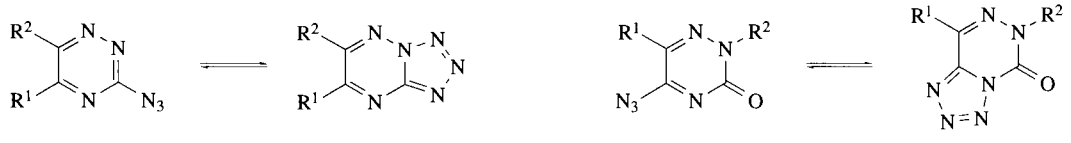
(**40a**) (**40b**) (**41a**) (**41b**)



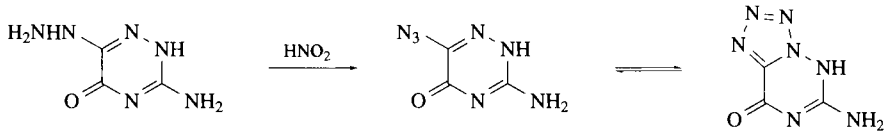
(**42a**) (**42b**) (**43a**) (**43b**)

Tautomerism in the gas phase, determined by mass spectrometry, can differ from that in solution or in the solid state ⟨81OMS(16)347⟩.

Azido-1,2,4-triazines may exist either as such or as tetrazolo-fused tautomers ⟨84CHEC-I(3)369⟩. 3-Azido-1,2,4-triazines (**44**) spontaneously cyclize to give the tetrazolo[1,5-*b*][1,2,4]triazines (**45**), if cyclization to N-2 is possible; no cyclization to N-4 was observed. 5-Azido-2*H*-1,2,4-triazin-3-ones (**46**) also cyclize to give the tetrazolo[5,1-*d*][1,2,4]triazin-5-ones (**47**). Nitrosation of 3-amino-6-hydrazino-1,2,4-triazin-5-one (**48**) affords a compound which exhibits the intense absorption of the 6-azido tautomer (**49**) at 2140 cm^{-1}. When this compound was stirred for a few minutes in a polar solvent it was quantitatively transformed into the tetrazole tautomer (**50**).



(**44**) (**45**) (**46**) (**47**)

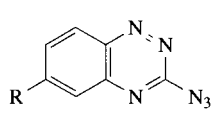


(**48**) (**49**) (**50**)

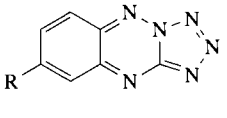
Ring-chain tautomerism was also studied in the system azido-1,2,4-benzotriazine (**51**)/tetrazolo[5,1-*c*][1,2,4]benzotriazine (**52**)/tetrazolo[1,5-*b*][1,2,4]benzotriazine (**53**). It was found that electron-donating groups and polar solvents stabilize the tetrazole tautomers over the azide forms. A 7-methyl group favours the angular tetrazole tautomer (**53**), while a 7-methoxy group changes the equilibrium to the linear isomer (**52**), in acetone and dimethyl sulfoxide ⟨82JOC3886⟩.

2-Phenyl-1,2,4-benzotriazin-3-one 1-oxide (**54**), which exists as such in the crystal, gives in solution the 2-isocyanato-azoxybenzene (**55**) ⟨85JCS(P1)1471⟩.

For 2-aryl-6-thia-2,3,8-triazabicyclo[3.2.1]oct-3-ene-4-carboxylic esters (**56**) in solution there is an equilibrium with the 2-aryl-2,3-dihydro-3-thiomethyl-1,2,4-triazine-6-carboxylic esters (**57**) ⟨82CB26⟩.



(51)



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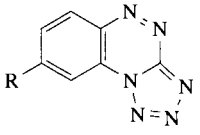
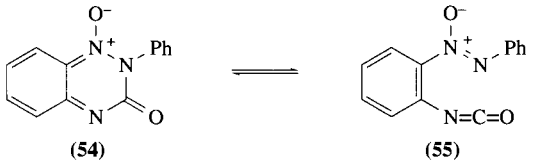
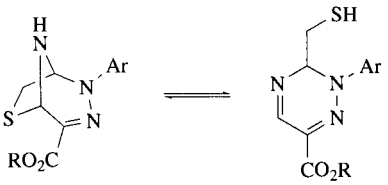


(53)



(54) (55)



(56) (57)

6.11.5 REACTIVITY OF FULLY AROMATIC RINGS

6.11.5.1 Introduction

1,2,4-Triazinones which can exist in fully aromatic hydroxy forms are covered in Section 6.11.6. Their aromaticity in the oxo forms is reduced, and although in some reactions there are similarities with those of the fully conjugated (aromatic) rings, the differences are often more apparent.

Most 1,2,4-triazines are thermally very stable. The unsubstituted and the lower alkyl-1,2,4-triazines can be distilled under reduced pressure or purified by gas chromatography. Aryl-1,2,4-triazines can be heated up to 200°C and higher without decomposition.

Addition of water (covalent hydration) in acidic media has been observed; addition of base regenerates the aromatic system ⟨84CHEC-I(3)369⟩.

Addition of ammonia to aromatic 1,2,4-triazines was reported by van der Plas and his group ⟨84CHEC-I(3)369⟩. Reaction of 1,2,4-triazines with potassium cyanide, sodium methoxide, or potassium in liquid ammonia, leading mainly to bi-1,2,4-triazin-5-yls, is also reported ⟨84CHEC-I(3)369⟩. H/D exchange has been observed in neutral or basic media ⟨73T2495, 74UP 611-01⟩. Most 1,2,4-triazines are less stable towards bases than towards acids. 1,2,4-Triazine 4-oxides can be hydrolyzed by bases ⟨76LA153⟩. In 1,2,4-benzotriazines the heterocyclic ring is destroyed by bases.

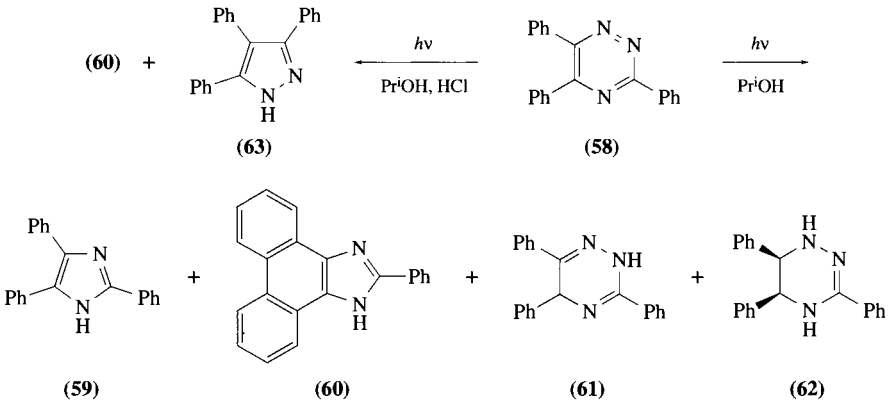
Most fully aromatic 1,2,4-triazines are stable toward acids, but prolonged treatment with concentrated acids at elevated temperatures leads to the destruction of the heterocyclic ring. Many 1,2,4-triazines are soluble in acids and are recovered unchanged on addition of water or bases. Aryl-substituted 1,2,4-triazines form deep red solutions in concentrated sulfuric acid from which they are reprecipitated on addition of water. Salts of 1,2,4-triazines with mineral acids have been isolated.

Alkylation and acylation of 1,2,4-triazines is possible, leading to the red 1- or the colorless 2-substituted 1,2,4-triazinium salts ⟨84CHEC-I(3)369⟩.

6.11.5.2 Photochemistry

The photochemistry of 1,2,4-triazines has not yet been studied systematically. Irradiation of 3,5,6-triphenyl-1,2,4-triazine (**58**) in isopropanol leads to the isolation of 2,4,5-triphenylimidazole (**59**) (14.5%), 2-phenylphenanthro[9,10-*d*]imidazole (**60**) (3%), 2,5-dihydro-3,5,6-triphenyl-1,2,4-triazine (**61**) (25%) and 1,4,5,6-tetrahydro-3,5,6-triphenyl-1,2,4-triazine (**62**) (41%). Irradiation in the pres-

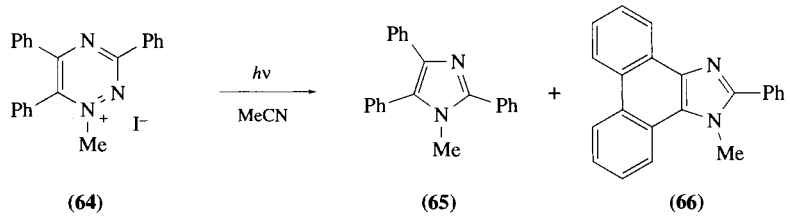
ence of an equimolar amount of HCl afforded 3,4,5-triphenylpyrazole (**63**) and the phenanthroimidazole (**60**) in 4 : 1 ratio (79%) (Scheme 7) ⟨93JCS(P1)661⟩.



Scheme 7

1-Methyl-3,5,6-triphenyl-1,2,4-triazinium iodide (**64**) was irradiated in acetonitrile for 84 hours. After work-up 1-methyl-2,4,5-triphenylimidazole (**65**) (32%) and 1-methyl-2-phenylphenanthro[9,10-*e*][1,2,4]-triazine (**66**) (34%) were isolated (Equation (1)).

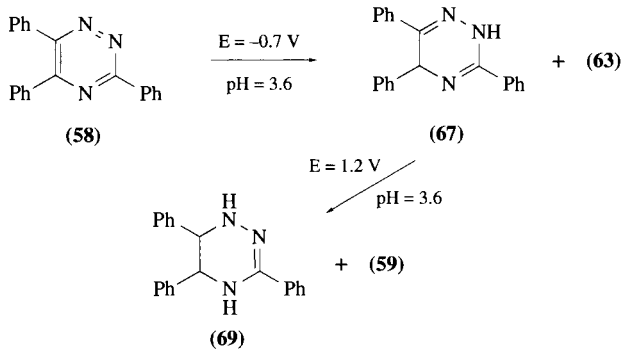
Further information on 1,2,4-triazine photochemistry is found in Section 6.11.6.1.



(1)

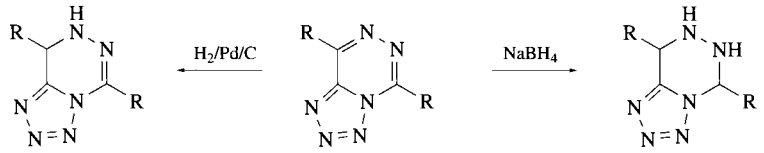
6.11.5.3 Reduction

Electrochemical reduction of 3,5,6-triphenyl-1,2,4-triazine (**58**) on the first plateau at pH 3.6 (E − 0.70 V) furnished 3,5,6-triphenyl-2,5-dihydro-1,2,4-triazine (**67**) and 3,4,5-triphenylpyrazole (**63**) ⟨93JCS(P1)661⟩. No 1,2-dihydro-3,5,6-triphenyl-1,2,4-triazine (**68**) could be detected, as had been reported earlier ⟨72CJC1581⟩. In a second step (pH 3.6; E − 1.20 V) the dihydro-1,2,4-triazine (**67**) was reduced to give *cis*-3,5,6-triphenyl-1,4,5,6-tetrahydro-1,2,4-triazine (**69**) and 2,4,5-triphenylimidazole (**59**) ⟨93JCS(P1)661⟩.



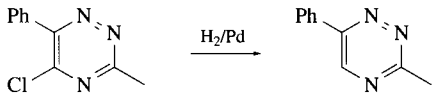
Hydrogenation of tetrazolo[1,5-*b*][1,2,4]triazines (**70**) over a Pd/C catalyst consistently stopped after the absorption of 1 mol of hydrogen and the 7,8-dihydro-derivatives (**71**) were isolated.

Reduction of the tetrazolo-triazines (**70**) with sodium borohydride in methanol afforded the 5,6,7,8-tetrahydro derivatives (**72**) ⟨88JOC5371⟩.



(71) (70) (72)

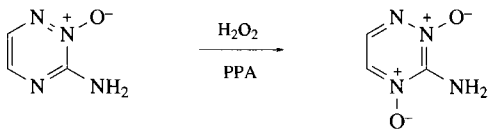
Hydrogenation of 5-chloro-3-methyl-6-phenyl-1,2,4-triazine (**73**) in benzene over palladium in the presence of triethylamine afforded the dechlorinated product (**74**) ⟨85H(23)2807⟩. The reduction of chloro-1,2,4-triazines, mainly by catalytic means, has been used for the synthesis of a variety of 1,2,4-triazines ⟨76CB1113⟩.



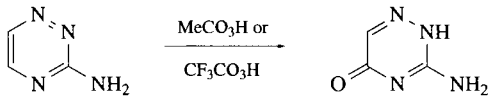
(73) (74)

6.11.5.4 Oxidation

The oxidation of 1,2,4-triazines was discussed in the first edition ⟨84CHEC-I(3)369⟩. Oxidation of 3-amino-1,2,4-triazine 2-oxide (**75**) with H_2O_2 in polyphosphoric acid at 24°C affords 3-amino-1,2,4-triazine 2,4-dioxide (**76**), the first monosubstituted 1,2,4-triazine di-*N*-oxide (Equation (2)). However, 3-amino-1,2,4-triazine (**77**) with peracetic or peroxytrifluoroacetic acid at 60°C formed only 3-amino-1,2,4-triazin-5(2*H*)-one (**78**) (Equation (3)) ⟨86H(24)951⟩.

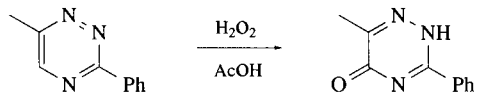


(75) (76) (2)



(77) (78) (3)

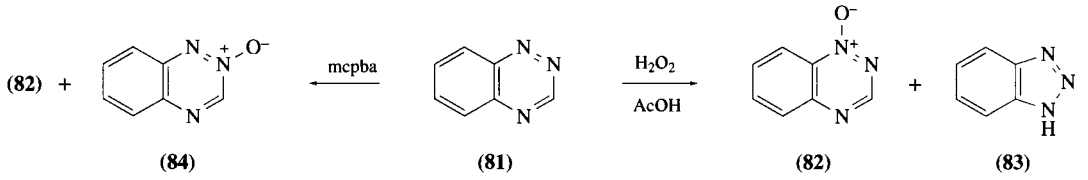
Oxidation of 6-methyl-3-phenyl-1,2,4-triazine (**79**) with H_2O_2 in acetic acid at room temperature gave 6-methyl-3-phenyl-1,2,4-triazin-5-one (**80**) in 82% yield (Equation (4)) ⟨87CPB1378⟩.



(79) (80) (4)

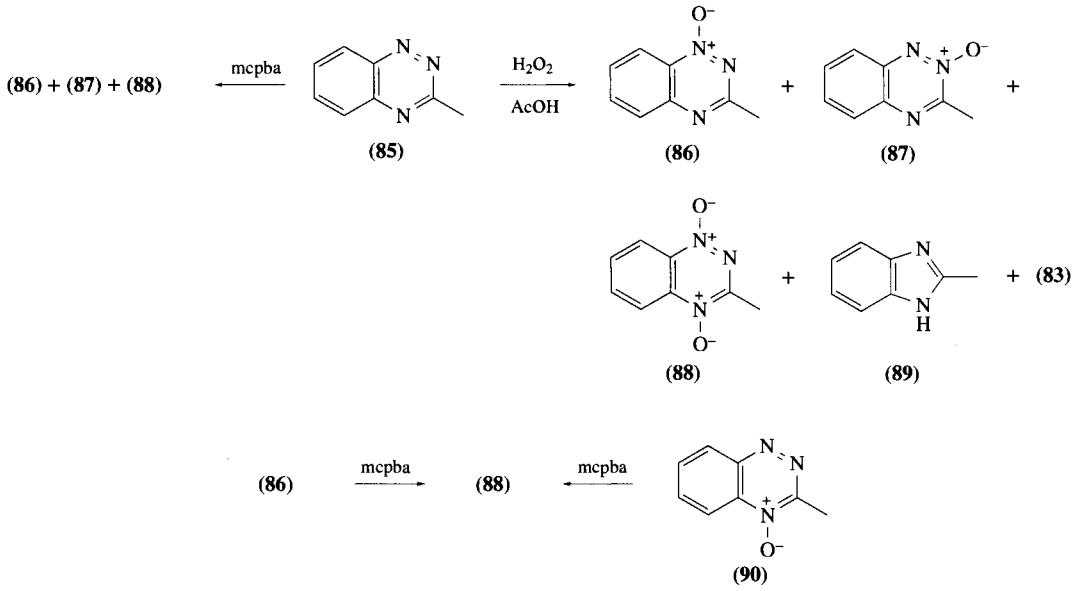
With hydrogen peroxide in acetic acid 1,2,4-benzotriazine (**81**) gave 1,2,4-benzotriazine 1-oxide (**82**) and benzotriazole (**83**), but oxidation with 3-chloroperbenzoic acid afforded the 1-oxide (**82**) and the 2-oxide (**84**) (Scheme 8) ⟨82T1793⟩. Oxidation of 3-methyl-1,2,4-benzotriazine (**85**) with hydrogen peroxide in acetic acid for four days at room temperature gives five products: 3-methyl-1,2,4-benzotriazine 1-oxide (**86**), the 2-oxide (**87**), 3-methyl-1,2,4-benzotriazine 1,4-dioxide (**88**), benzotriazole (**83**) and 2-methylbenzimidazole (**89**). Treatment of the same 1,2,4-benzotriazine (**85**) with 3-chloroperbenzoic acid in benzene at room temperature for four days led to the isolation of

the two monoxides (**86**), (**87**), and the dioxide (**88**). Oxidation of either 3-methyl-1,2,4-benzotriazine 1-oxide (**86**) or the 4-oxide (**90**) with 3-chloroperbenzoic acid in benzene yielded 3-methyl-1,2,4-benzotriazine 1,4-dioxide (**88**) (Scheme 9) ⟨82T1793⟩.



(84) (81) (82) (83)

Scheme 8



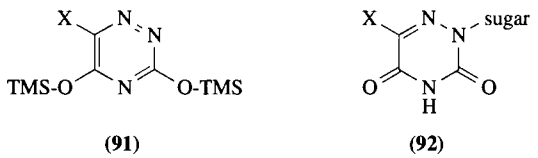
(85) (86) (87) (88) (89) (90)

Scheme 9

6.11.5.5 Electrophilic Attack at Nitrogen

Protonation, alkylation, and acylation of 1,2,4-triazines were discussed in detail in CHEC-I ⟨84CHEC-I(3)369⟩, and *N*-oxidation was dealt with in Section 6.11.5.4. In this section some additional information is presented.

Treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose with trimethylchlorosilane and anhydrous sodium iodide in dry acetonitrile followed by reaction with 3,5-bis-trimethylsilyloxy-1,2,4-triazine (**91a**) or its 6-bromo- (**91b**) or 6-benzylthio- derivative (**91c**) afforded only the *N*(2)-glycosides (**92a-c**) in good yields ⟨83RRC989, 85RRC117, 87RRC329⟩.

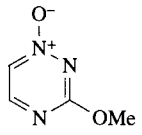


(91) (92)

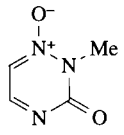
a: X = H
b: X = Br
c: X = SCH_2Ar

3-Methoxy-1,2,4-triazine 1-oxide (**93**) with methyl iodide in methanol at room temperature for 10 days produced 2-methyl-1,2,4-triazin-3-one 1-oxide (**94**). 3-Methoxy-1,2,4-triazine 2-oxide (**95**)

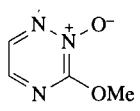
afforded 2-methoxy-1,2,4-triazin-3-one (**96**) under the same conditions. 3-Amino-1,2,4-triazine 1-oxide (**97**) yielded 3-methylamino-1,2,4-triazine 1-oxide (**98**) when rapidly stirred into the non-polar solvent CH_2Cl_2/hexane containing methyl iodide in an immiscible aqueous bicarbonate solution, but gave the 3-imino-2-methyl-1,2,4-triazine 1-oxide (**99**) in the polar solvent methanol. 3-Methylamino-1,2,4-triazine 1-oxide (**98**) was not further methylated, but simply rearranged to the imine (**99**) on treatment with methyl iodide in methanol at room temperature for 10 days ⟨84TL1677⟩.



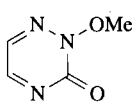
(**93**)



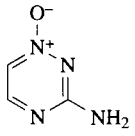
(**94**)



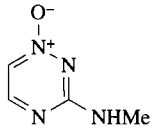
(**95**)



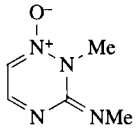
(**96**)



(**97**)

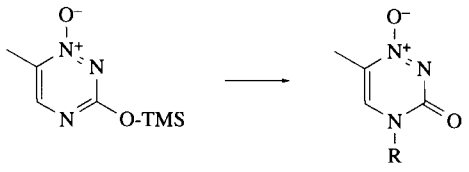


(**98**)

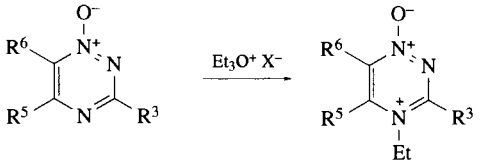


(**99**)

Reaction of 6-methyl-3-trimethylsilyloxy-1,2,4-triazine 1-oxide (**100**) with alkylating agents gives, after aqueous work-up, 4-alkyl-6-methyl-1,2,4-triazin-3-one 1-oxides (**101**) (Equation (5)) ⟨86JHC1613⟩. Alkylation of the 1,2,4-triazine 1-oxides (**102a–c**) with triethyloxonium salts yielded 4-alkyl-1-oxy-1,2,4-triazinium salts (**103a–c**) (Equation (6)) ⟨95UP 611-01⟩.



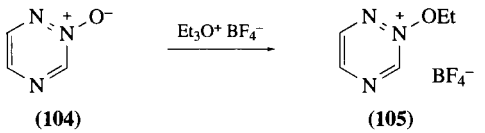
(**100**) (**101**) (5)



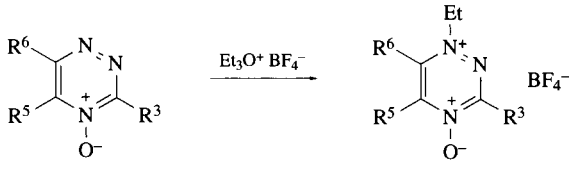
(6)

(**102**) **a**; $R^3 = R^5 = R^6 = H$ (**103**)
b: $R^3 = OMe$, $R^5 = R^6 = H$
c: $R^3 = R^5 = R^6 = Ph$

Alkylation of 1,2,4-triazine 2-oxide (**104**) with triethyloxonium tetrafluoroborate afforded the *O*-alkylated product (**105**) (Equation (7)), while alkylation of 1,2,4-triazine 4-oxides (**106**) with triethyloxonium tetrafluoroborate led to the 1-alkylated triazinium salts (**107**) (Equation (8)) ⟨95UP 611-01⟩.



(**104**) (**105**) (7)



(**106**) (**107**) (8)

6.11.5.6 Electrophilic Attack at Carbon

To our knowledge no electrophilic attack on a carbon atom of a fully aromatic 1,2,4-triazine has been reported so far. Attempted nitration of the 3-methoxy-, 1-oxide, and the 3-amino-1- and 2-oxides, resulted only in the 3-oxo products ⟨84TL1677⟩.

6.11.5.7 Nucleophilic Attack at Carbon

Nucleophilic attack on the carbon atoms of the 1,2,4-triazine ring is well-known and was discussed in detail in the previous review ⟨84CHEC-I(3)369⟩.

There are four different types of reaction which are to be considered:

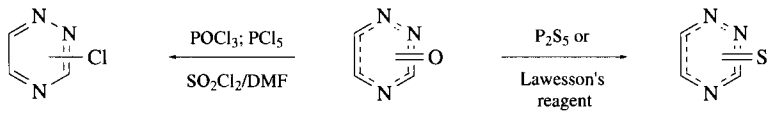
(a) exchange of a heterosubstituent in the 3-, 5-, or 6-position by another heterosubstituent;

(b) exchange of a heterosubstituent by a carbon nucleophile;

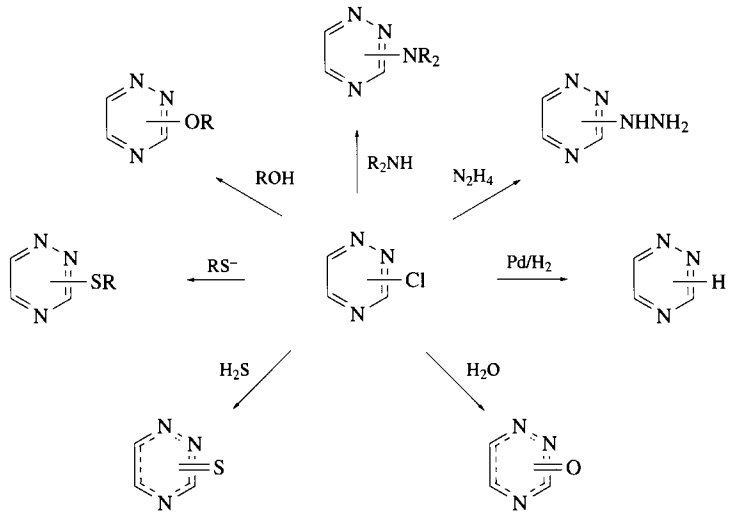
(c) addition of a nucleophile, preferentially in the 5-position, and oxidation of the dihydro-1,2,4-triazine formed; and

(d) vicarious nucleophilic substitution.

(i) Hetero-substituent exchange. This reaction was discussed in detail in the previous review ⟨84CHEC-I(3)369⟩. All reactions mentioned there have been used during the past ten years to synthesize heterosubstituted 1,2,4-triazines, such as the transformation of an oxo-/hydroxy group into a thio or chloro group, while the chlorine substituent has been replaced by hydroxy/oxo, alkoxy, amino, thio, hydrazino, or iodo groups. The thioxo or alkylthio group can be substituted by hydrazines, alkoxides, amines, hydroxylamine and water. Even more reactive than alkylthio is the alkylsulfonyl group, which can be replaced by alkoxy and amino groups. Schemes 10–13 summarize the reactions.



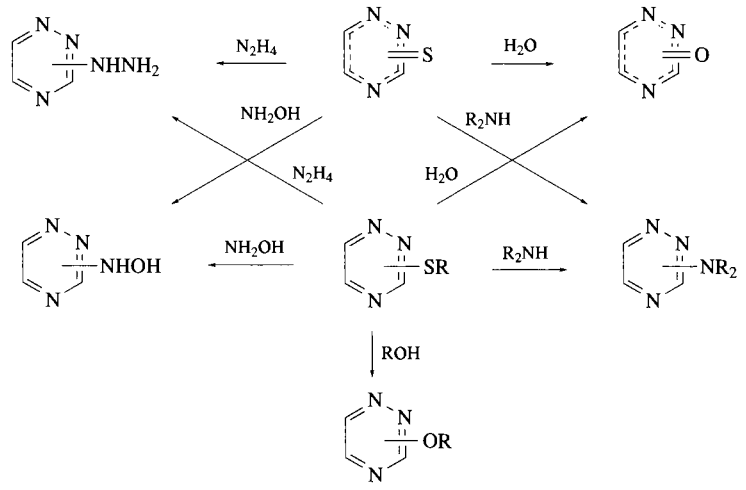
Scheme 10



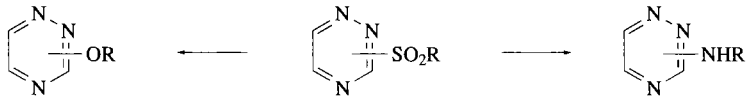
Scheme 11

The substitution of chlorine by amino groups using potassium amide in liquid ammonia was studied by Rykowsky and van der Plas ⟨80JOC881, 82JHC653, 84JHC433⟩. Both ANRORC and S_N(*ipso*) mechanisms were found to operate, except with 3-chloro-1,2,4-benzotriazine, which followed *ipso* attack practically exclusively.

The exchange of one heterosubstituent by another has been widely used for the preparation of 3-, 5- or 6-alkynyloxy-, -alkynylthio- and -alkynylamino-1,2,4-triazines which undergo intramolecular



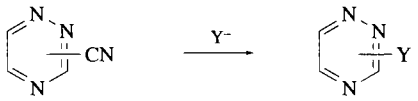
Scheme 12



Scheme 13

Diels–Alder reactions with inverse electron demand (see Section 6.11.5.11) ⟨86TL431, 86TL2747, 87T5145, 90CB133, 91JOC1807⟩.

A special heterosubstituent is the cyano group, which is easily substituted by other nucleophiles (Equation (9)) ⟨85JOC2293, 91CPB486⟩, particularly in the 5-position; for 3-cyano- and 6-cyano-1,2,4-triazines addition of a nucleophile to the cyano group is also observed ⟨91CPB486⟩.



(9)

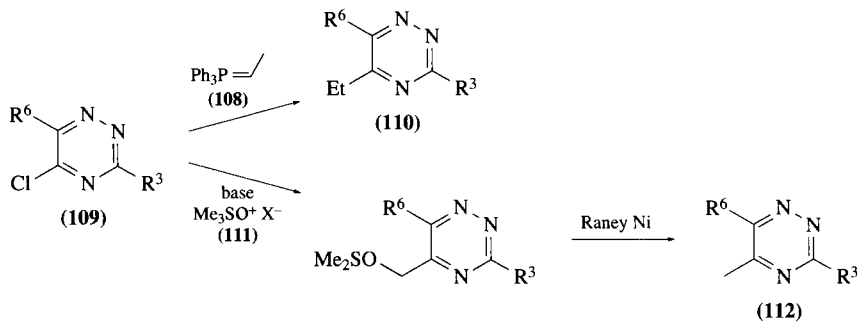
The substitution of the 3-trichloromethyl group by a hydrazino, *n*-butylamino, ethoxy or hydroxy group has been reported (Equation (10)) ⟨82H(19)1865⟩.

(10)

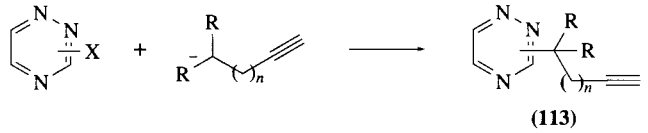
Y = OH, OEt, NHBu, $NHNH_2$

(ii) Heterosubstituent displacement by carbon nucleophiles. Most leaving groups in the 3-, 5-, and 6-positions of 1,2,4-triazines can be substituted by carbon nucleophiles, prepared from benzaldehyde and 1,3-dimethylbenzimidazolium iodide, which generates an ylid catalyst ⟨86H(24)1243⟩, and from malonates, acetonitriles, malonodinitrile, and other C—H acidic compounds and a base ⟨87H(26)3259, 90H(31)895, 91CPB486, 92YZ729⟩. Ethylidenetriphenylphosphorane (**108**) reacts with 5-chloro-1,2,4-triazines (**109**), leading to 5-ethyl-1,2,4-triazines (**110**) after aqueous work-up, and 5-methyl-1,2,4-triazines (**112**) were obtained from the reaction of 5-chloro-1,2,4-triazines (**109**) with trimethylsulfoxonium halide (**111**) and a base, followed by work-up with deactivated Raney nickel (Scheme 14) ⟨84H(22)2241⟩.

The exchange of a heterosubstituent by a carbon nucleophile was used for the preparation of ω-alkynyl-1,2,4-triazines (**113**) (Equation (11)), which can undergo intramolecular Diels–Alder reaction with inverse electron demand ⟨91JOC1807⟩.

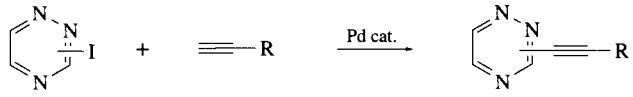


Scheme 14



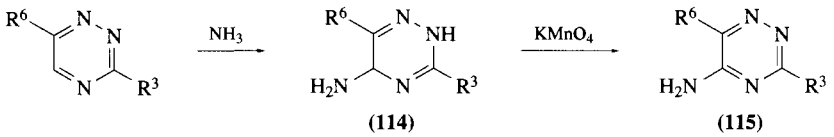
(11)

The Heck reaction of iodo-1,2,4-triazines with acetylenes has been reported (Equation (12)) ⟨84H(22)2245, 93LA583⟩.



(12)

(iii) Addition of nucleophile followed by oxidative rearomatization. Many nucleophiles add to 1,2,4-triazines, preferentially to the 5-position which is in general the most electrophilic. A nucleophile much studied in these reactions is ammonia, which affords the 5-amino-2,5-dihydro-1,2,4-triazines (**114**) which can be oxidized by potassium permanganate to the 5-amino-1,2,4-triazines (**115**) when the 5-position in the starting 1,2,4-triazine is unsubstituted (Scheme 15) ⟨85S884, 87JHC1657⟩.



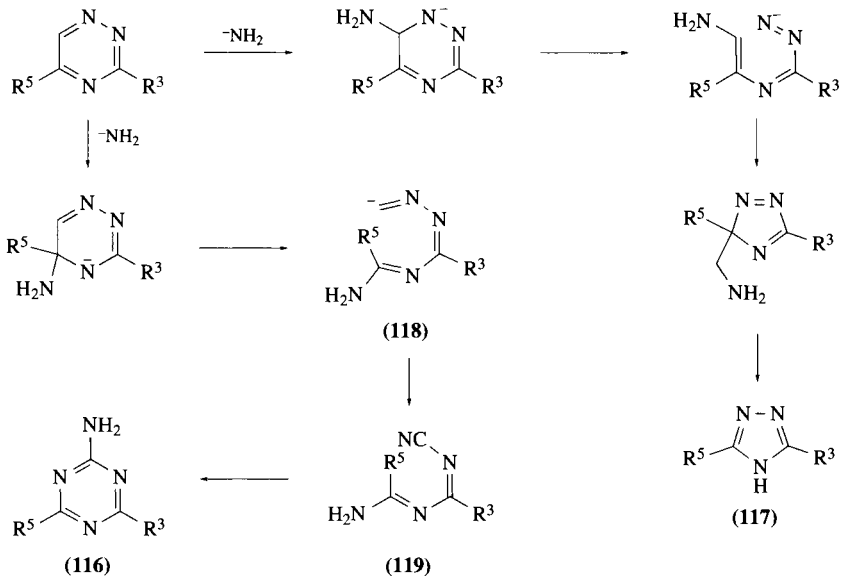
Scheme 15

In the cases where the 5-position is substituted, rearranged products, like 1,3,5-triazines (**116**) and 1,2,4-triazoles (**117**) are isolated. The contraction of the 1,2,4-triazine ring to the triazole was explained by an initial addition of the amide ion to C-6, ring opening by fission of the N(1)—C(6) bond and ring closure (ANRORC-mechanism), and loss of methylenimine (retro-Mannich reaction). The transformation into the 1,3,5-triazine ring was studied by ^{15}N labelling experiments. On this basis it was proposed that the reaction starts with addition of the amide ion to C-5, ring-opening between C-5 and C-6, a dehydrogenative rearrangement of the open-chain intermediate 1-amino-2,4,5-triazahexatriene (**118**) to 1-amino-4-cyano-2,4-diaza-1,3-butadiene (**119**), and ring closure (Scheme 16) ⟨87JOC71⟩.

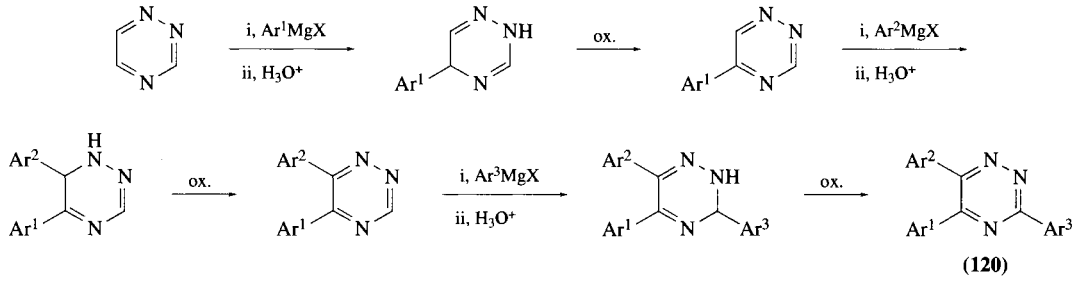
Grignard reagents also add to 1,2,4-triazines. Initial attack at the 5-position is again favored; if this position is substituted the nucleophile adds to the 6-position, and finally to the 3-position. Starting from the parent 1,2,4-triazine, 3,5,6-triaryl-1,2,4-triazines (**120**) have been prepared by successive addition of Grignard reagents to the ring and oxidation of the dihydro-1,2,4-triazine so formed (Scheme 17) ⟨85H(23)2807, 87H(26)3111, 87CPB1378, 92YZ729⟩.

Addition of carbanions other than from Grignard reagents to 1,2,4-triazines with an unsubstituted 5-position, followed by oxidation with oxygen, has been investigated ⟨87CPB1378⟩.

Addition of hydrogen cyanide to 5-unsubstituted 1,2,4-triazines (**121**) is also reported; the formation of the 5-cyano-1,2,4-triazines (**123**) was explained by oxidation of the intermediates (**122**) with air. The same compounds (**123**) were isolated when the triazines (**121**) were reacted with sulfur

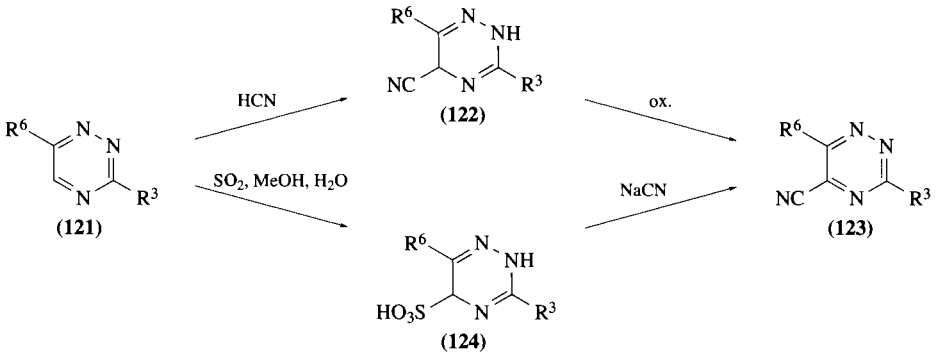


Scheme 16



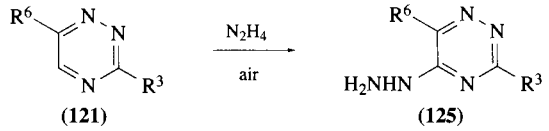
Scheme 17

dioxide in aqueous methanol and the dihydro-1,2,4-triazinesulfonic acids (**124**) treated with sodium cyanide (Scheme 18). ⟨86H(24)1243, 87CPB1378⟩.



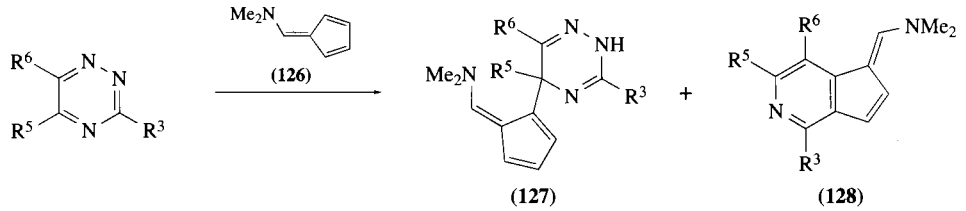
Scheme 18

Formation of 5-hydrazino-1,2,4-triazines (**125**) is observed from 5-unsubstituted 1,2,4-triazines (**121**) and hydrazine (Equation (13)) ⟨87CPB1378⟩.



(121) (125) (13)

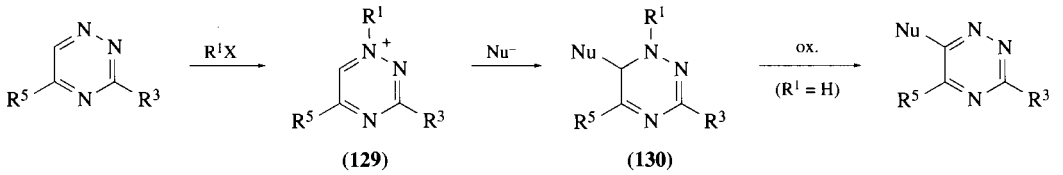
6-(Dimethylamino)pentafulvene (**126**) reacts with 1,2,4-triazines either by addition to C-5 of the 1,2,4-triazines, forming the 2,5-dihydro-pentafulvenyltriazines (**127**), or via a [4 + 2]cycloaddition reaction across atoms C(3)—C(6), to give the 2-pyrindines (**128**) (Scheme 19) ⟨85LA1263⟩.



(126) (127) (128)

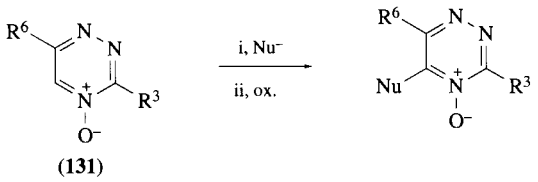
Scheme 19

Addition of electron-rich aromatic systems to the 1,2,4-triazine ring can easily be achieved by preliminary activation of the heterocyclic system by protonation or alkylation. Addition of the following nucleophiles to the 1,2,4-triazinium ion (**129**) has been observed: indoles, pyrroles, anilines, phenols, and aminothiazoles. The 1,6-dihydro-1,2,4-triazines (**130**) can be isolated in most cases and oxidized in a second step to the aromatic 1,2,4-triazine system (Scheme 20). 1,2,4-Triazin-5(2*H*)-ones also undergo this reaction. 5-Unsubstituted 1,2,4-triazine 4-oxides (**131**) can be transformed into 5-substituted 1,2,4-triazine 4-oxides (Equation (14)) ⟨86KGS1535, 92H(33)931, 95UP 611-01⟩.



(129) (130)

Scheme 20

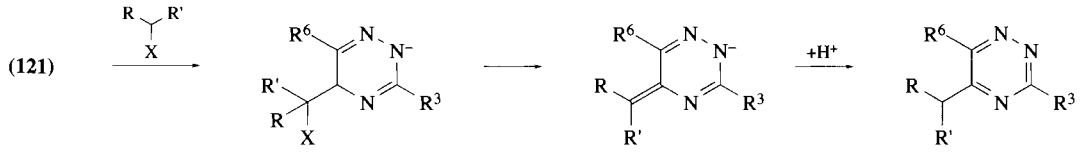


(131) (14)

(iv) Vicarious nucleophilic substitution. Carbanions containing leaving groups at the carbanionic centers react with 1,2,4-triazines by replacement of hydrogen atoms in the 5-, 3-, and 6-position with the carbanionic moiety and loss of the leaving group. The reactivity of the various positions decreases in the order 5 > 3 > 6, which differs from that towards Grignard reagents. This reaction provides an efficient way for the introduction of functionalized alkyl substituents into the triazine ring. Carbanions of the following compounds have been used in this reaction: nitroalkanes, chloromethyl phenyl sulfones, chloromethane sulfonmorpholides, and acetonitriles ⟨83TL3277, 84TL4795, 88LA627, 92PJC3, 93JHC413⟩. This reaction is shown in Scheme 21 for 5-unsubstituted 1,2,4-triazines (**121**).

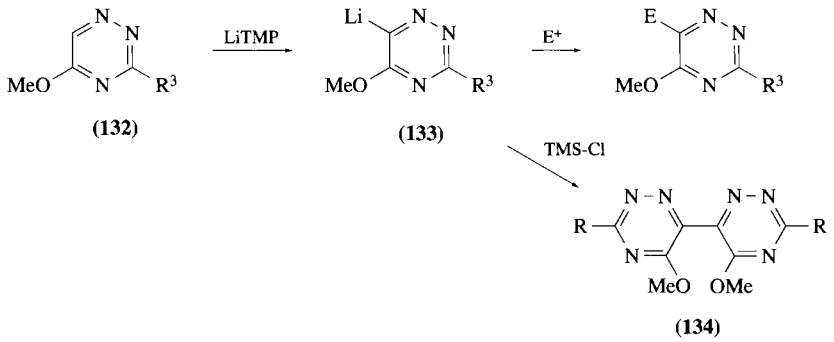
6.11.5.8 Nucleophilic Attack at Hydrogen

6-Unsubstituted 5-methoxy-1,2,4-triazines (**132**) can be lithiated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and the 6-lithio derivatives (**133**) trapped with electrophiles (Scheme 22)



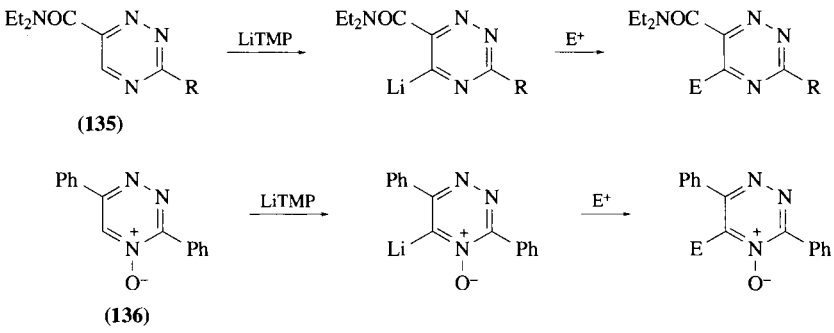
Scheme 21

⟨93LA583⟩. Addition of trimethylchlorosilane to (**133**) led to the isolation of bi-1,2,4-triazin-6,6′-yls (**134**) ⟨95UP 611-02⟩.



Scheme 22

Lithiation at the 5-position of 1,2,4-triazines was observed in the reactions of 1,2,4-triazine-6-carboxamides (**135**) and of 3,6-diphenyl-1,2,4-triazine 4-oxide (**136**) with LiTMP. 5-Lithio-1,2,4-triazines can also be trapped by electrophiles. (Scheme 23) ⟨95UP 611-02⟩.



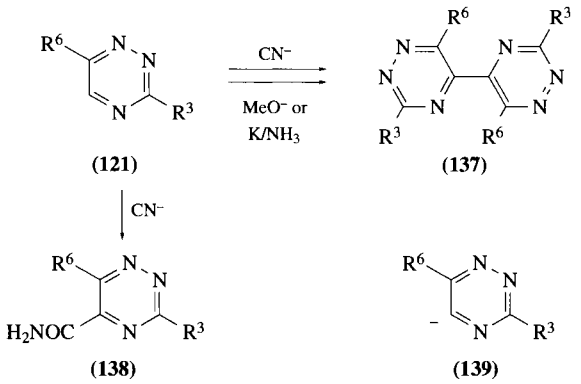
Scheme 23

6.11.5.9 Radical Reactions

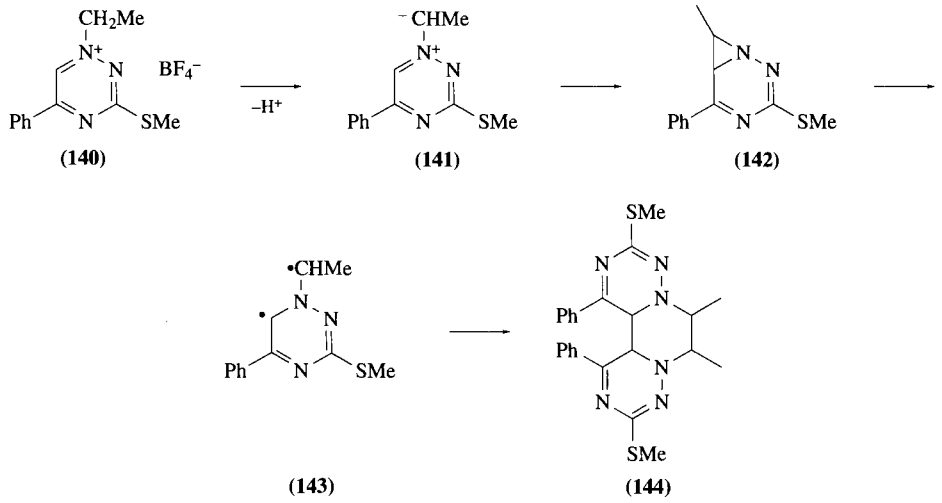
No study of the reaction of 1,2,4-triazines with radicals has been published up to 1995. There are three reactions which can be explained by intermediate formation of 1,2,4-triazinyl radicals.

The first example is the reaction of 5-unsubstituted 1,2,4-triazines (**121**) with cyanide ions, which affords bi-1,2,4-triazin-5,5′-yls (**137**) and 1,2,4-triazine-5-carboxamides (**138**) ⟨84CHEC-I(3)369, 87CPB1378⟩. Bi-1,2,4-triazin-5-yls (**137**) were also isolated when (**121**) was treated with sodium methoxide or potassium in liquid ammonia. (Scheme 24) It is suggested that the methoxide-induced dehydro-dimerization proceeds via an anionic intermediate (**139**), while the reaction with potassium in liquid ammonia occurs by a free radical process.

3-Alkylthio-1-ethyl-5-phenyl-1,2,4-triazinium tetrafluoroborates (**140**) were found to undergo an unusual dimerization on treatment with triethylamine in methanol or ethanol ⟨90TL7665⟩. This was explained by the following mechanism: deprotonation of the ethyl group affords the ylide (**141**), which cyclizes to the azirino[2,1-*f*][1,2,4]triazine (**142**). Opening of the three-membered ring leads to the diradical (**143**), which dimerizes in a head-to-head fashion to give the 4a,4b,9,10-tetrahydro-1,3,6,8,8a,10a-hexaazaphenanthrenes (**144**) (Scheme 25).



Scheme 24



Scheme 25

The third example is the reaction of lithio-1,2,4-triazines with chlorotrimethylsilane, which affords bi-1,2,4-triazinyls irrespective of the position of lithiation.

6.11.5.10 Reactions with Electron-deficient Species

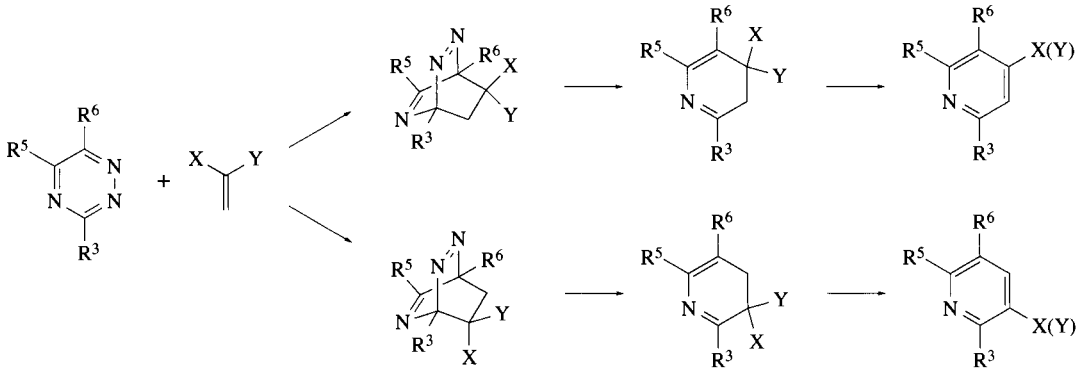
We could not find any report on the reaction of 1,2,4-triazines with carbenes or nitrenes.

6.11.5.11 Cycloaddition Reactions

The most extensively studied reaction of 1,2,4-triazines is the Diels–Alder reaction with inverse electron demand, in which the triazines behave as reactive electron-deficient dienes. Electron-rich alkenes and acetylenes have been most often used as dienophiles but alkenes with strained double bonds and nitriles can also react. Besides intermolecular Diels–Alder reactions, which were discussed in detail in CHEC-I, intramolecular cycloadditions have been studied widely and used in the synthesis of condensed heterocyclic systems. A review on intermolecular Diels–Alder reactions was published by Boger and Weinreb in 1987 ⟨B-87MI 611-01⟩, Sauer published an account of his studies in 1992 ⟨92BSB521⟩, and a summary by Taylor of his own work on intramolecular Diels–Alder reactions was published in 1988 ⟨88BSB599⟩.

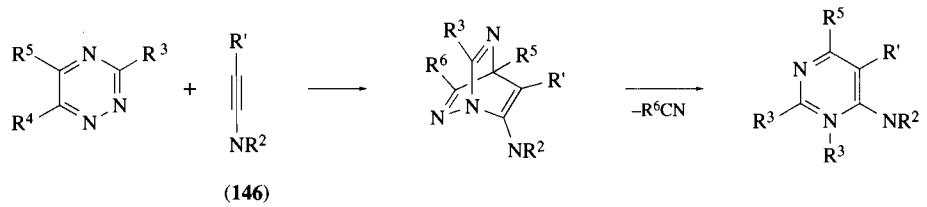
6.11.5.11.1 Intermolecular cycloadditions

In most cases of intermolecular Diels–Alder reactions it has been found that the dienophile addition occurs across the 3- and 6-positions of the 1,2,4-triazine ring, but acetylenes can also add across the 2- and 5-positions. The general form of these reactions is outlined in Scheme 26, in which the dienophile is a ketene acetal, aminal, or related derivative (**145**), and Scheme 27, where the reactant is an ynamine (**146**).



a, X, Y = OR
b, X = OR, Y = NR_2
c, X, Y = NR_2
d, X = SR, Y = NR_2

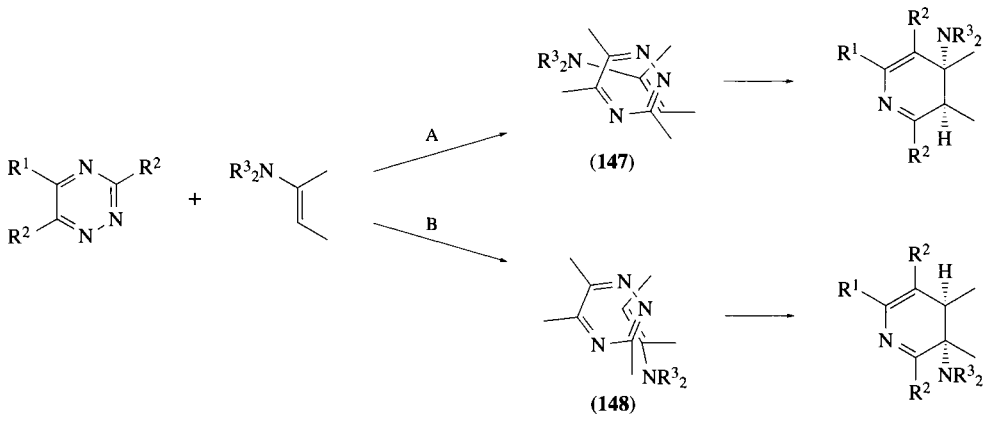
Scheme 26



(**146**)

Scheme 27

Since the 1,2,4-triazines and also most dienophiles are unsymmetrical, two orientations in the transition state have to be considered, as (**147**) and (**148**) in Scheme 28.



(**147**)

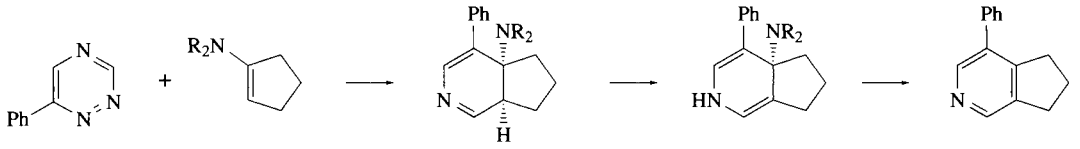
(**148**)

Scheme 28

Detailed studies by Neunhoeffer and Sauer have shown that secondary orbital interactions dominate the orientation if these interactions are possible. As a result of these, in the transition state, the substituent with lone-pair electrons of the dienophile is always on the same side as

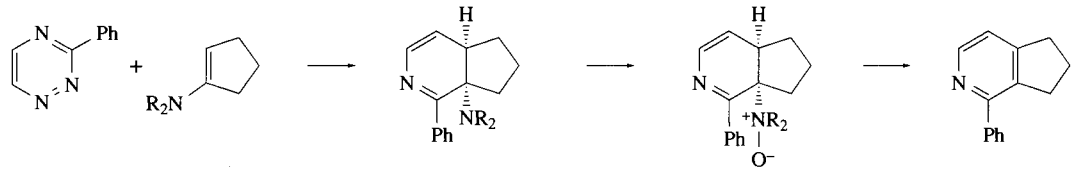
substituents with π-bonds on the triazine. Only in this orientation can secondary orbital interactions occur between the lone pair in the dienophile and the π-electrons of the substituent. The orientations can also be explained using the frontier-orbital method.

The reaction can become more complicated when cyclic dienophiles are used. Depending on the orientation (determined by the substrate), the two dihydopyridines (**149**) and (**150**) can be formed. For rearomatization, elimination of the two *cis*-oriented substituents is necessary. If (**149**) is formed there is no problem since there the *cis*-oriented proton can shift to the nitrogen to form the 1,4-dihydropyridines (**151**) from which HNR_2 can be eliminated (Scheme 29). If a product of type (**150**) is formed no tautomerism is possible. As a result of this, in a few cases the dihydropyridine (**150**) has been isolated ⟨83LA1476, 88JOC5175⟩. Oxidation of the intermediate (**150**) to the *N*-oxide (**152**) and Cope elimination affords the condensed pyridines (**153**) (Scheme 30) ⟨83LA1476, 88JOC5175⟩. In many cases the elimination of the *cis* oriented groups was observed under the reaction conditions used.



(149) (151)

Scheme 29



(150) (152)

Scheme 30

The following dienophiles have been used during the ten years from 1985 to 1995 (this listing is not complete): enamines ⟨82JOC895, 82JOC3763, 83JOC621, 85TL2415, 85JA5745, 89JOC1249, 93H(35)1089⟩, enaminones ⟨89JOC1249⟩, vinyl silyl ethers ⟨85JA5745, 90JCS(P1)1887⟩, vinyl thioethers ⟨85JA5745⟩, cyclic ketene N,O-acetals ⟨86CB3600⟩, N-phenylmaleimide ⟨87CPB4705⟩, 6-dimethylaminopentafulvene ⟨85LA1263⟩, 2-alkylidene-imidazolidines (cyclic ketene aminals) ⟨87TL6027⟩, cyclic vinyl ethers ⟨93T5277⟩, arynes ⟨92T6821⟩, benzocyclopropene ⟨84JOC1040⟩, acetylenes ⟨82JOC3761, 82JCS(P1)1245⟩ and alkenes like ethylene ⟨82JCS(P1)1245⟩, (Z)-but-2-ene, cyclopentene, cyclooctene and bicyclo[2.2.1]hept-2-ene ⟨82JCS(P1)1245⟩, hexa-1,5-diene, cycloocta-1,5-diene, diallyl ether, cyclododeca-1,5,9-triene ⟨92TL4653,83TL4087, 88CC1482, 90JCS(P1)1887⟩, di-(3-methylcyclopropen-3-yl) ⟨83TL4087⟩, and norbornadiene ⟨82JCS(P1)1245, 89H(29)2249, 93YZ40⟩.

It was shown by Neunhoeffer ⟨83LA1476⟩ and Boger ⟨82JOC895, 85JA5745⟩ that oxo-compounds and catalytic amounts of amines can be used instead of the enamines, but the water which is formed can lead to side reactions.

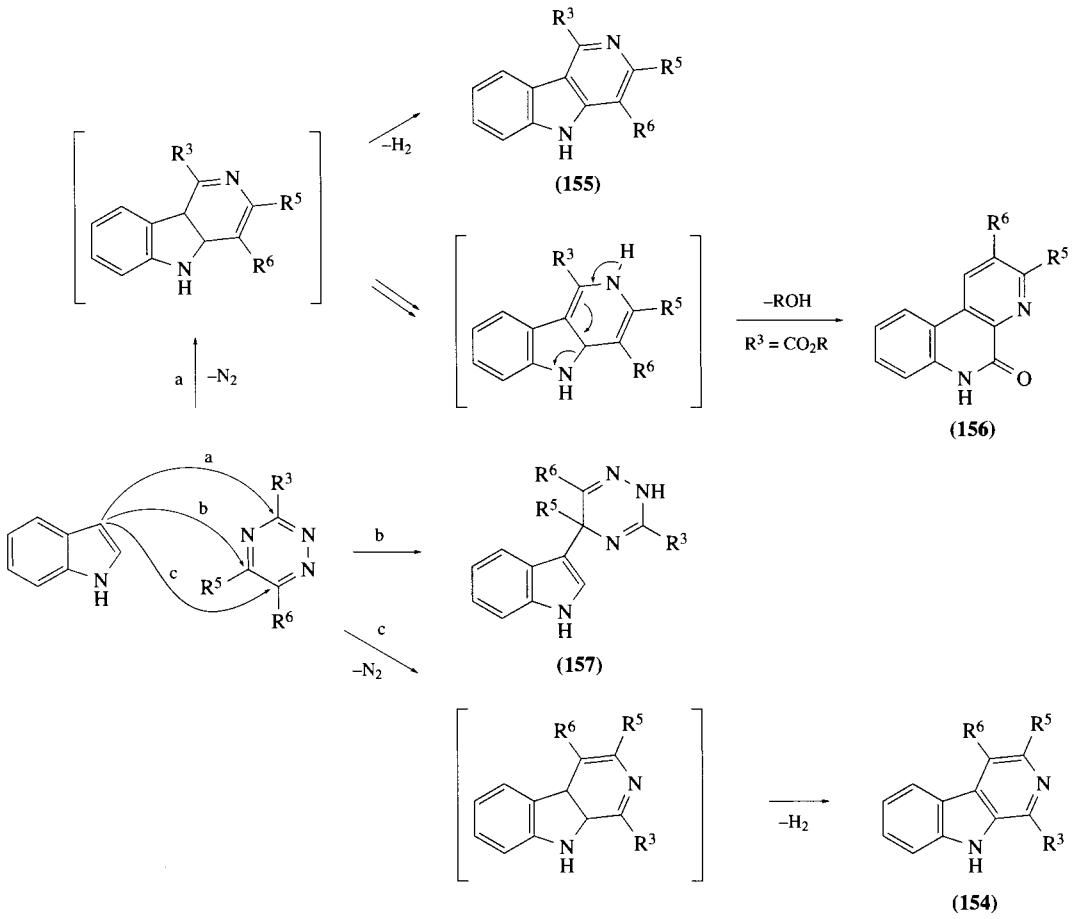
The reactivity of 1,2,4-triazines depends very much on the substituents bound to the heterocyclic system. Only 1,2,4-triazines with strongly electron-accepting substituents react with simple olefins such as ethylene, or unactivated acetylenes.

Indole has also been used as a dienophile in cycloadditions with 1,2,4-triazines ⟨90JOC3257⟩. Depending on the substituents in the triazine ring, β- (**154**) or γ-carbolines (**155**), benzo[*f*][1,7]naphthyridines (**156**) or 3-(dihydrotriazin-4-yl)indoles (**157**) have been isolated (Scheme 31).

Studies on the kinetics, mechanism and regioselectivity of Diels–Alder reactions with inverse electron demand have been published by Sauer and his group ⟨83TL1481, 84TL2541, 92BSB521⟩. They found that the rate of cycloaddition of cyclooctyne to a number of 1,2,4-triazines can be correlated with the reduction potential of these dienes provided that steric effects are approximately equal.

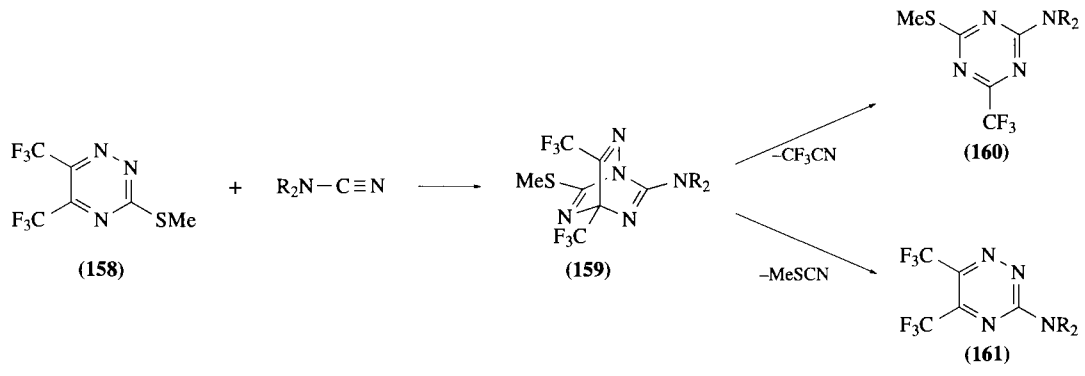
These cycloadditions are not limited to the monocyclic triazines. Taylor has shown that also pyrimido[4,5-*e*]-1,2,4-triazines react with enamines in a Diels–Alder reaction with inverse electron demand, leading to pyrido[2,3-*d*]pyrimidines (5-deazapteridines) ⟨87TL1977⟩.

N-Substituted cyanamides cycloadd exclusively across C-5 and N-2 of the 1,2,4-triazine nucleus



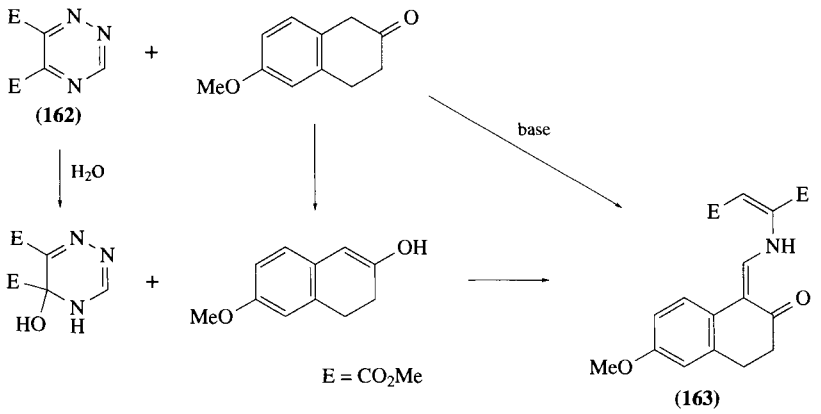
Scheme 31

in 3-methylthio-5,6-bis(trifluoromethyl)-1,2,4-triazine (**158**), forming the bicyclic compound (**159**) as an unisolated intermediate. Elimination of trifluoroacetonitrile affords 1,3,5-triazines (**160**), while elimination of methyl thiocyanate gives 1,2,4-triazines (**161**) (Scheme 32) ⟨89CB1381⟩.



Scheme 32

Cycloaddition of dimethyl 1,2,4-triazine-5,6-dicarboxylate (**162**) with 6-methoxy-2-tetralone in the presence of a base afforded a product (**163**), which was explained by the intermediate formation of the triazine hydrate and its Diels–Alder reaction with the enol form of the tetralone (Scheme 33) ⟨83LA1476⟩.



Scheme 33

6.11.5.11.2 *Intramolecular cycloadditions*

Besides the intermolecular Diels–Alder reactions, intramolecular Diels–Alder reactions have been studied and used for the synthesis of condensed pyridines and pyrimidines. In these cases mostly ω-alkynyl- (**164**; X = CH_2 or CR_2), ⟨86TL2107, 91JOC1807⟩ ω-alkynyloxy- (X = O), ⟨85TL4355, 86TL431, 86TL2747, 87T5145⟩ ω-alkynylthio- (X = S), ⟨85TL2419, 85TL4355, 86TL2747, 87JOC4280, 88CZ243, 89JOC4984⟩ ω-alkynylsulfinyl- (X = SO), ⟨85TL2419, 87JOC4280, 89JOC4984⟩ ω-alkynylsulfonyl-(X = SO_2) ⟨85TL2419, 87JOC4280, 89JOC4984⟩, and ω-alkynylamino-1,2,4-triazines (X = NR) ⟨86TL2747, 87TL379, 87T5145, 89CZ252, 90CB133⟩ ω-alkynyl esters (X = COO) ⟨90H(30)1009⟩ and ω-alkynyl amides (X = CONH) ⟨90CZ381⟩ have been used, with the substituent in the 3- as well as the 5- and 6-positions. Instead of the ω-C≡C bond, a C≡N bond (**165**) can be used in intramolecular cycloadditions.

(164) (165)

Reactivity studies have shown that the alkynylsulfinyl compounds are more reactive than all others ⟨85TL2419⟩.

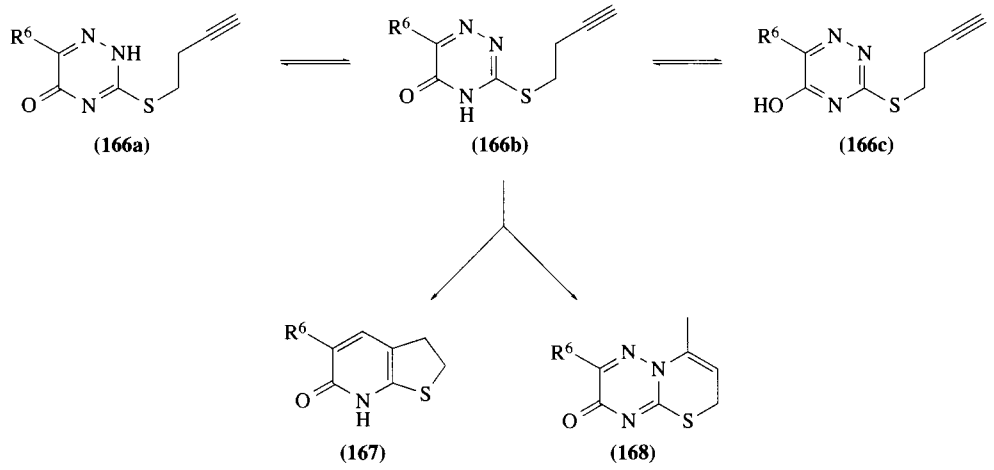
The Thorpe–Ingold effect assists the intramolecular Diels–Alder reaction with inverse electron demand ⟨86TL2107⟩.

1,2,4-Triazines with C-5-tethered dienophilic side chains are sterically constrained to undergo intramolecular Diels–Alder reactions across the N-2/C-5 triazine positions; elimination from the intermediate adduct (N-1 and C-6 of the starting triazine) leads to condensed pyrimidines. The reactivity of 5-(alkynyl-substituted)-1,2,4-triazines in the intramolecular Diels–Alder process is highly dependent on the steric and electronic disposition in the dienophilic side chain. Cycloaddition is hindered when an electron-donating atom (N, O) is used to link the side chain to the nucleus, while the introduction of bulky groups into the side chain facilitates the process by the Thorpe–Ingold effect ⟨87JOC4287⟩.

Intramolecular cycloaddition reactions of 1,2,4-triazines with the C=C double bond of pyrrole ⟨93JOC516⟩ or indole ⟨92JOC5285⟩ have also been observed.

Besides monocyclic 1,2,4-triazines, condensed systems such as pyrimido[4,5-*e*]1,2,4-triazines ⟨87T5159⟩, benzofuro[3,2-*e*]-1,2,4-triazines and benzothieno[3,2-*e*]-1,2,4-triazines ⟨89CB2177⟩ can be used in intramolecular Diels–Alder reactions.

The fully aromatic system is not necessary for the intramolecular Diels–Alder reaction to take place. 3-Butynylthio-1,2,4-triazin-5(2*H*)-ones (**166a**) undergo intramolecular Diels–Alder reaction in competition with an intramolecular cycloamination process, providing 2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-ones (**167**) and 1,3-thiazino[3,2-*b*]-1,2,4-triazin-3-ones (**168**). The Diels–Alder reaction probably proceeds via an alternative tautomer, (**166b**) or (**166c**) (Scheme 34) ⟨88JHC1733, 88JOC5093⟩.

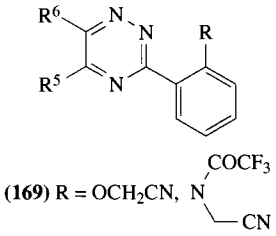


(166a) (166b) (166c)

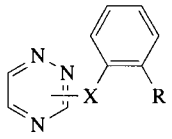
(167) (168)

Scheme 34

The dienophilic group can also be linked to the triazine system through an aryl ⟨87T5159, 89JOC1245⟩, an aryloxy ⟨87T5159, 90H(30)1009⟩ or arylthio group ⟨89CB2177⟩, or an aryl ester function ⟨90H(30)1009⟩ **(169)**, **(170)**.



(169) R = OCH_2CN, $N(COCF_3)CN$



(170) X = O, S, COO
R = C≡C–Bu
C≡C–TMS
C≡C–Ph
$(CH_2)_nC{\equiv}CH$
CN
CH=NOMe

6.11.6 REACTIVITY OF NON-CONJUGATED COMPOUNDS

Dihydro-1,2,4-triazines with two double bonds in the ring and no tautomeric aromatic structure are well-known compounds ⟨78HC(33)189⟩. The x-ray crystal structure of 2-methyl-3-methylthio-5,6-diphenyl-2,5-dihydro-1,2,4-triazine has been published ⟨81BCJ41, 84CHEC-I(3)369⟩. However, only a few studies on the reactivity of dihydro-1,2,4-triazines have been reported during the last decade. On the other hand, many papers on the reactions of 1,2,4-triazinones with a tautomeric aromatic structure can be found in the literature of the same period.

6.11.6.1 Reactivity of Dihydro-1,2,4-triazines

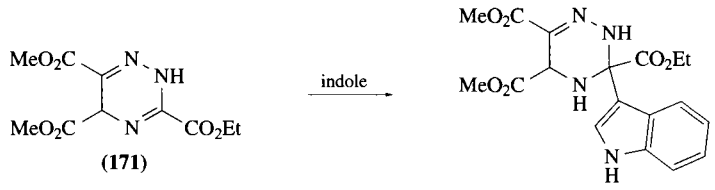
Most dihydro-1,2,4-triazines have been prepared by addition of nucleophiles to 1,2,4-triazines, but in general the dihydro-1,2,4-triazines were not isolated but oxidized back to the fully aromatic systems. Section 6.11.5.7.(iii) covers these reactions, from the aspect of the reactivity of the fully aromatic compounds. A summary of the main features, and some additional information is presented in this Section.

The reactions studied are: Addition of ammonia to 1,2,4-triazines and oxidation of the amino-dihydro compounds with potassium permanganate to amino-1,2,4-triazines (Scheme 15); addition of Grignard reagents or other carbanions to 1,2,4-triazines and oxidation of the dihydro adducts with potassium permanganate or potassium hexacyanoferrate(III) (Scheme 17); and addition of

HCN or SO_2 in aqueous methanol (Scheme 18) or of hydrazine (Equation (13)) and oxidation of the intermediate dihydro-triazines.

In all cases the predominant site of addition of the nucleophile is in the 5-position of the heterocyclic ring, leading to 2,5-dihydro-1,2,4-triazines, but addition to other sites occurs when position five is not available. These reactions were discussed in detail in the Section 6.11.5.7.

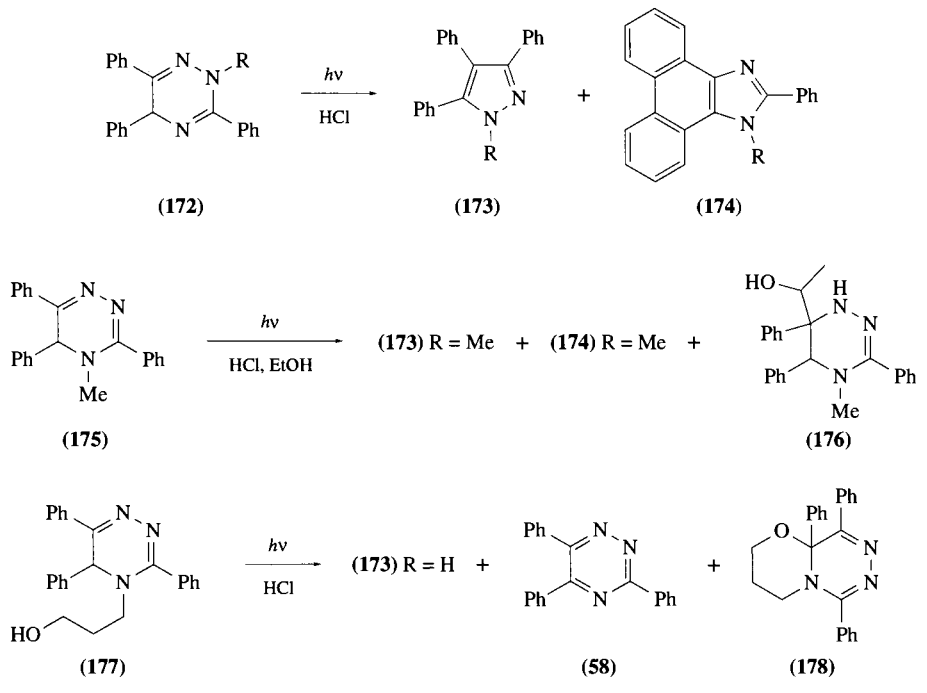
Besides the fully aromatic system, dihydro-triazines can also add nucleophiles. The addition of indole to the 2,5-dihydro derivative (**171**) forms the 3-adduct (Equation (15)) ⟨90JOC3257⟩.



(171) (15)

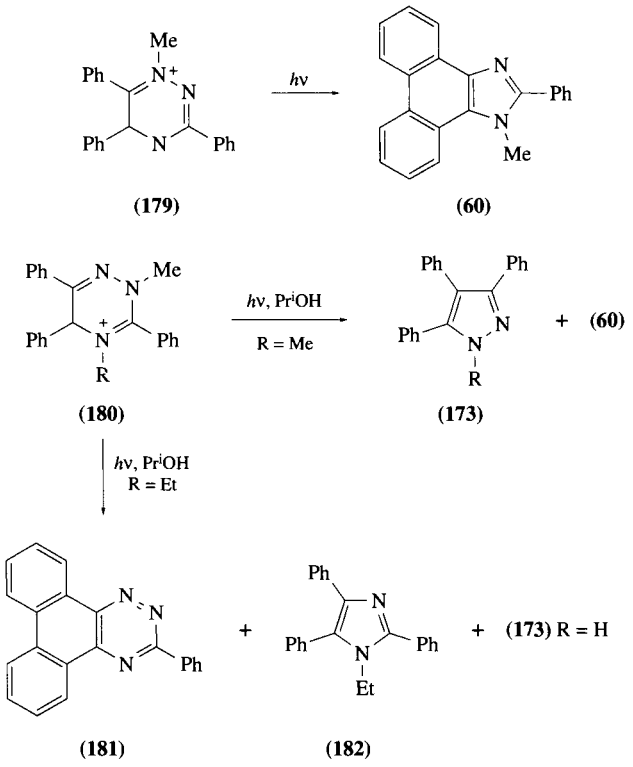
In addition, the photochemical behaviour of dihydro-1,2,4-triazines has received attention. The results from the fully unsaturated compounds (see Section 6.11.5.2) may be relevant here, because of the prevalence of photo-oxidation, -dehydrogenation, and -reduction.

2,5-Dihydro- and 4,5-dihydro-1,2,4-triazines in ethanolic solution were found to be stable to irradiation with a high-pressure mercury lamp ($\lambda \geqslant 300$ nm). In contrast, the hydrochloride salts of the 2,5-dihydrotriazines (**172**; R = H, Me) gave, under the same conditions, the corresponding pyrazoles (**173**) as the main products, via a novel photochemical ring contraction rather than an aza-di-π-methane rearrangement. From the 4,5-dihydrotriazine (**175**), besides the pyrazole and phenanthroimidazole (**173**) and (**174**; R = Me), the 6-(1-hydroxyethyl) adduct (**176**) were formed. The 4-(3-hydroxypropyl) analogue (**177**) gave the pyrazole (**173**; R = H), the aromatic 1,2,4-triazine (**58**), by dealkylation, and the [1,3]oxazino[3,2-*d*][1,2,4]triazine (**178**) (Scheme 35). Mechanisms for the formation of the various products were suggested. ⟨88JCS(P1)3267, 90ACH733, 93JCS(P1)661⟩



Scheme 35

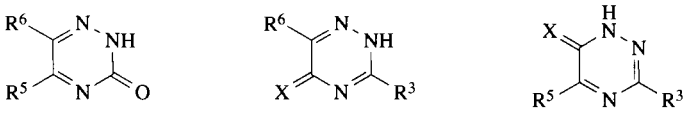
1,4-Dimethyl-3,5,6-triphenyl-4,5-dihydro-1,2,4-triazinium iodide (**179**) gave 1-methyl-2-phenylphenanthro[9,10-*d*]imidazole (**60**) in 90% yield. 2,4-Dimethyl-3,5,6-triphenyl-2,5-dihydro-1,2,4-triazinium iodide (**180**; R = Me) after irradiation for 96 hours in isopropanol afforded 1-methyl-3,4,5-triphenylpyrazole (**173**; R = Me) (34%), the phenanthroimidazole (**60**) (10%), and starting material (28%). The 4-ethyl analogue (**180**; R = Et) under similar conditions provided starting material (48%), 3-phenylphenanthro[9,10-*e*]-1,2,4-triazine (**181**) (24%), 1-ethyl-2,4,5-triphenylimidazole (**182**) (15%), and 3,4,5-triphenylpyrazole (**173**; R = H) (7%) (Scheme 36) ⟨93JCS(P1)661⟩.



Scheme 36

6.11.6.2 Reactivity of 1,2,4-Triazinones and 1,2,4-Triazinethiones with an Aromatic Tautomeric Structure

All three possible 1,2,4-triazinones (**183**)–(**185**) and 1,2,4-triazinethiones (**186**)–(**188**) are known. In all cases the predominant tautomeric form is as shown, but derivatives of the other possible tautomers are also known. Some of their reactions are already discussed in Section 6.11.5.7.



(**183**) X = O
(**186**) X = S

(**184**) X = O
(**187**) X = S

(**185**) X = O
(**188**) X = S

All 1,2,4-triazinones (**183**)–(**185**) can be transformed into the corresponding thiones (**186**)–(**188**) by reaction with phosphorus pentasulfide or Lawesson's reagent, and into chloro-1,2,4-triazines by $POCl_3$, PCl_5, or $SOCl_2$ ⟨84H(22)2241, 84LA283, 85H(23)2807, 85JOC2293, 85LA640, 85TL2415, 87CPB1378, 87H(26)3259, 87JOC4287, 88CPB3354, 88S877, 89H(29)2279, 89JOC1249, 89JOC4984, 90LA631⟩. In one instance the Lawesson reagent has been reported also to replace an amino group by thione (Equation (16)) ⟨88S877⟩.

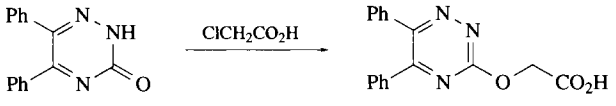
(16)

1,2,4-Triazinones can be alkylated to give mixtures of *O*- and *N*-alkylated products, the ratio of which depends on the alkylation reagent and the conditions used ⟨83H(20)51, 86JHC1613, 88CPB3354, 88JOC5093, 88S877, 93LA583⟩. Silylation of 1,2,4-triazinones leads exclusively to *O*-silylated products.

Triazinethiones (**186**)–(**188**) can be hydrolyzed to give the appropriate triazinones (**183**)–(**185**). They react with hydrazines, ammonia, and amines by substituent exchange ⟨88S778, 88S877,

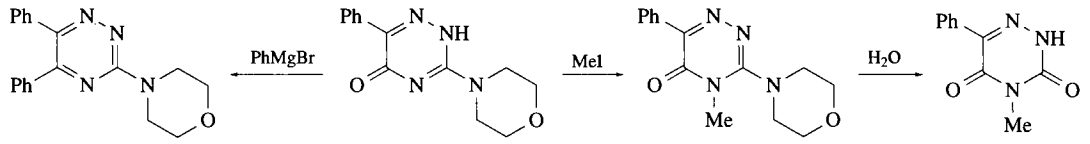
89H(29)2249〉 and can be alkylated, mainly to *S*-alkyl aromatic 1,2,4-triazines but in a few cases to *N*-alkyl-1,2,4-triazinethiones 〈85TL2415, 85TL2419, 87JOC4280, 87JOC4287, 89H(29)2279, 89JOC1245, 89JOC1249, 89JOC4984〉. Silylation gives trialkylsilylthio-1,2,4-triazines.

Reaction of 5,6-diphenyl-1,2,4-triazin-3(2*H*)-one with ethyl chloroacetate and potassium carbonate in dry acetone gives ethyl (5,6-diphenyl-1,2,4-triazin-3-yloxy)acetic acid (**189**) (Equation (17)) 〈83JHC507〉.



(189) (17)

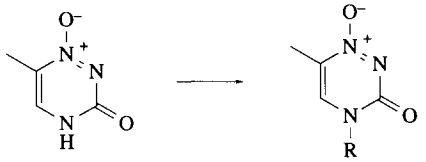
3-Morpholino-6-phenyl-1,2,4-triazin-5(2*H*)-one (**190**) afforded the 4-methyl derivative (**191**) upon treatment with methyl iodide, which with water gave 4-methyl-6-phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**192**). 3-Morpholino-5,6-diphenyl-1,2,4-triazine (**193**) was isolated from the reaction of (**190**) with phenylmagnesium bromide (Scheme 37) 〈88LA141〉.



(193) (190) (191) (192)

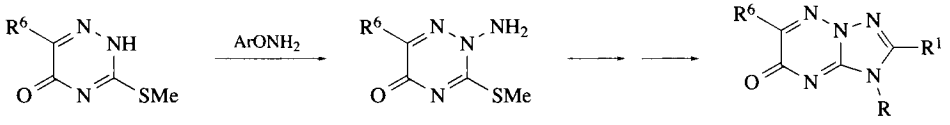
Scheme 37

Alkylation of 6-methyl-1,2,4-triazin-3(4*H*)-one 1-oxide in basic media afforded the 4-alkylated derivatives (Equation (18)) 〈86JHC1613〉.



(18)

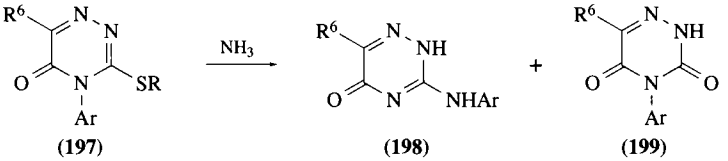
3-Methylthio-1,2,4-triazin-5(2*H*)-ones (**194**) can be aminated regioselectively with *O*-(2,4-dinitrophenyl)hydroxylamine as an amino-transfer reagent to give 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones (**195**) (Scheme 38). Reaction of the products (**195**) with amines followed by ring closure with aliphatic acids provided [1,2,4]triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-ones (**196**) 〈82JHC1583, 83JHC1671〉.



(194) (195) (196)

Scheme 38

Some substituent replacements in this area follow pathways incorporating a Dimroth rearrangement. Thus, 3-alkylthio-4-aryl-1,2,4-triazin-5(4*H*)-one derivatives (**197**) react with ammonium acetate in acetic acid under reflux for 4 hours to give mainly the 3-arylamino-1,2,4-triazin-5(2*H*)-ones (**198**); 4-aryl-1,2,4-triazine-3,5(2*H*,4*H*)-diones (**199**) are minor products (Equation (19)) 〈83H(20)51〉.

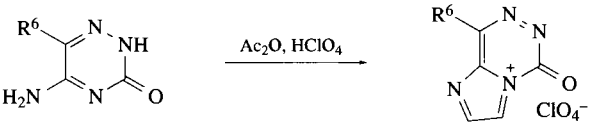


(197) (198) (199) (19)

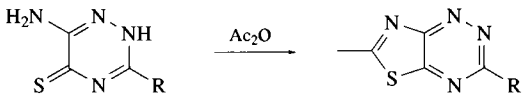
Reaction of 6-benzyl-3-methylthio-4-phenyl-1,2,4-triazines (**200**) with hydrazine gave the 4-amino-3-anilino-1,2,4-triazin-5(4*H*)-ones (**201**) (Equation (20)) ⟨88JHC279⟩.

(200) (201) (20)

In a very unusual reaction, the 5-amino-1,2,4-triazin-3-ones (**202**) are cyclized by perchloric acid and acetic anhydride to give 5-oxoimidazo[1,2-*d*][1,2,4]triazin-4-ium salts (**203**) as crystalline solids in good yields (Equation (21)) ⟨86S635⟩. A more conventional cyclization occurs with the 6-amino-1,2,4-triazine-5(2*H*)-thiones (**204**), which give thiazolo[5,4-*e*]-1,2,4-triazines (**205**) with acetic anhydride (Equation (22)) ⟨84LA283⟩.

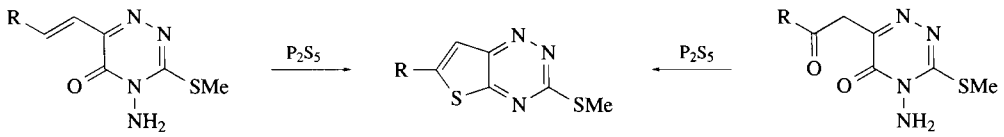


(202) (203) (21)



(204) (205) (22)

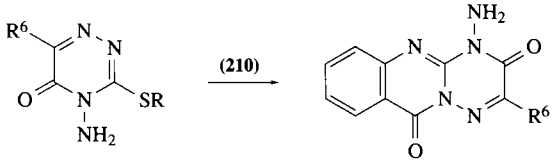
The action of phosphorus pentasulfide on 6-alkenyl-4-amino-3-methylthio- (**206**) and 4-amino-6-(2-oxoalkyl)-3-methylthio-1,2,4-triazin-5-ones (**208**) gave the thieno[2,3-*e*]-1,2,4-triazines (**207**) (Scheme 39) Besides the deamination, demethylation of the 3-methylthio group was often observed ⟨83JHC1709⟩.



(206) (207) (208)

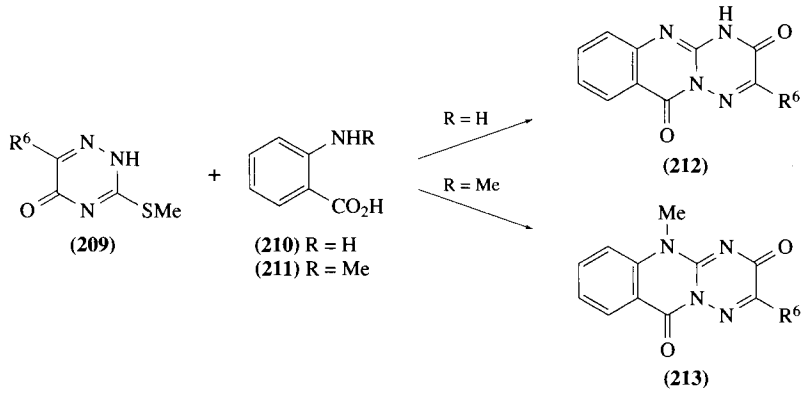
Scheme 39

3-Methylthio-1,2,4-triazin-5(2*H*)-ones (**209**) have been converted into 3*H*-[1,2,4]triazino[3,2-*b*]quinoxaline-3,10(4*H*)-diones (**212**) upon cyclocondensation with anthranilic acid (**210**) (Scheme 40). *N*-Methylanthranilic acid (**211**) with (**209**) afforded the 5-methyl-3*H*-[1,2,4]triazino[3,2-*b*]quinazoline-3,10(5*H*)-diones (**213**) (Scheme 40). Reaction of 2-methyl-3-methylthio-6-phenyl-1,2,4-triazin-5(2*H*)-one (**214**) with anthranilic acid (**210**) gave 1-methyl-3-phenyl-4*H*-[1,2,4]triazino[3,4-*b*]quinazoline-4,6(1*H*)-dione (**216**) via the intermediate (**215**) (Scheme 41) ⟨84CB1077, 84CB1083⟩. 3-Alkylthio-4-amino-1,2,4-triazin-5(4*H*)-ones (**217**) with anthranilic acid formed 1-amino-3*H*-[1,2,4]triazino[3,2-*b*]quinoxaline-3,10(4*H*)-diones (**218**) (Equation (23)) ⟨84CB1083⟩.



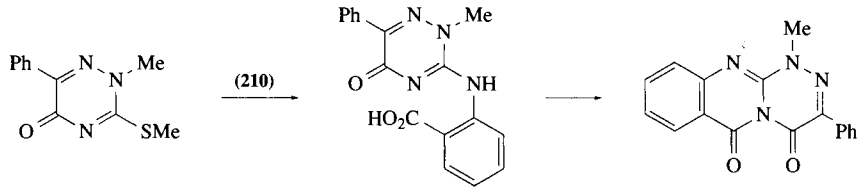
(217) (218) (23)

3-(Allylthio)-1,2,4-triazin-5(2*H*)-ones (**219**) rearrange by palladium(II) catalysis, depending on the substitution pattern of the allylic moiety to 2- (**220**) or 4-allyl-3-thioxo-3,4-dihydro-1,2,4-triazin-



(209) (210) R = H (211) R = Me (212) (213)

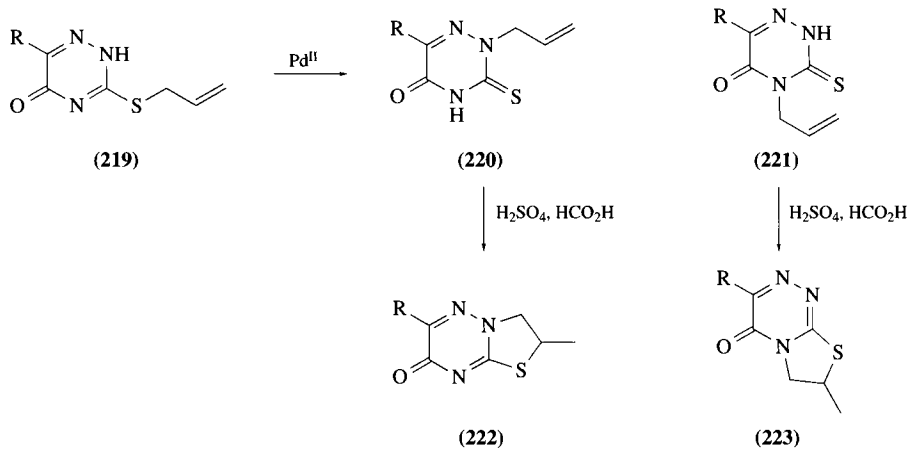
Scheme 40



(214) (215) (216)

Scheme 41

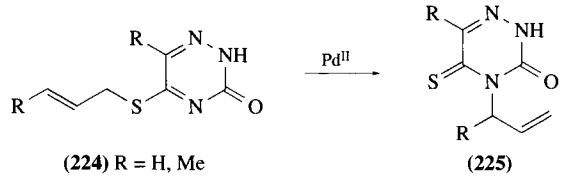
5-ones (**221**). Treatment of these with sulfuric acid in refluxing formic acid yields the dihydro-thiazolo-triazinones (**222**) and (**223**) respectively (Scheme 42) ⟨83JOC4585⟩.



(219) (220) (221) (222) (223)

Scheme 42

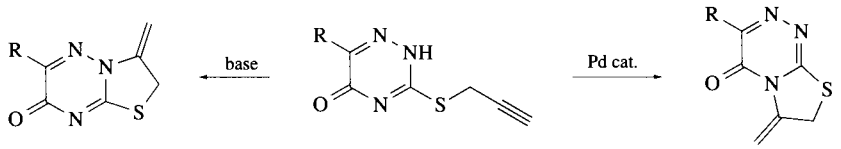
5-Allylthio-1,2,4-triazin-3(2*H*)-ones (**224**) can be rearranged by palladium(II) catalysis; only 4-allyl-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones (**225**) were obtained, with (in cases in which R^6 = H in (**224**)) none of the C-6-alkylated products (Equation (24)) ⟨85T5289⟩.



(24)

(224) R = H, Me (225)

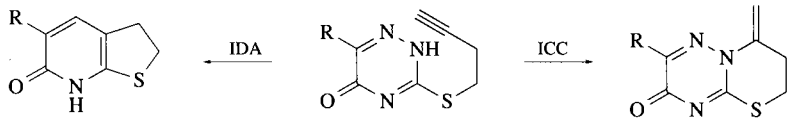
Palladium-catalyzed cyclization of 3-propargylthio-1,2,4-triazin-5(2*H*)-ones (**226**) leads mainly to 6-methylene-6,7-dihydro-4*H*-thiazolo[2,3-*c*][1,2,4]triazin-4-ones (**227**), while base-catalyzed cyclization gives the isomeric 3-methylene-2,3-dihydro-7*H*-thiazolo[3,2-*b*][1,2,4]triazin-7-ones (**228**) (Scheme 43) ⟨85TL1237, 86T305⟩.



(228) (226) (227)

Scheme 43

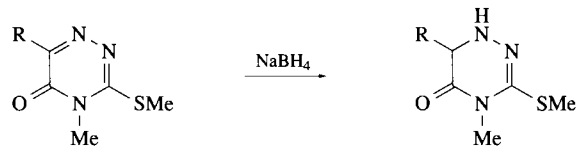
3-(But-3-ynylthio)-1,2,4-triazin-5(2*H*)-ones (**229**) undergo competitive intramolecular Diels–Alder reactions (IDA) and intramolecular coplanar cycloamination processes (ICC), to provide 2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-ones (**230**) and 8-methylene-7,8-dihydro-3*H*,6*H*-[1,3]thiazino-[3,2-*b*][1,2,4]triazin-3-ones (**231**), respectively (Scheme 44). In a relatively inert aromatic solvent system, the ratio of IDA to ICC products is markedly dependent on the electronic character of the substituent R of the precursor 1,2,4-triazine. Furthermore, when R is electron-withdrawing (CO_2Et), the ratio of IDA to ICC product formation is very sensitive to reaction temperature, with higher temperatures favoring the IDA process. However, this sensitivity to reaction temperature is not observed with the 6-methyl derivative. Ethanol as the reaction solvent in the presence of triethylamine generally facilitates the ICC vs. the IDA process. Without triethylamine, the amount of ICC product is diminished relative to other competitively-formed materials. Use of deuteriated DMSO as the solvent leads to completely reversed trends in reactivity and almost exclusive formation of IDA products ⟨88JOC5093⟩.



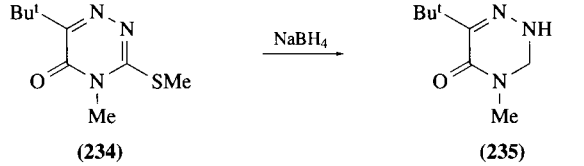
(230) (229) (231)

Scheme 44

Reduction of 4-methyl-3-methylthio-1,2,4-triazin-5(4*H*)-ones (**232**) with sodium borohydride usually afforded the 1,6-dihydro products (**233**) selectively (Equation (25)), but the 6-*t*-butyl compound (**234**) gave mainly the 2,3-dihydro compound (**235**) (Equation (26)). The influence of the steric and electronic effects of the substituents at the 3- and 6-positions upon the product ratio was studied ⟨84JHC639⟩.



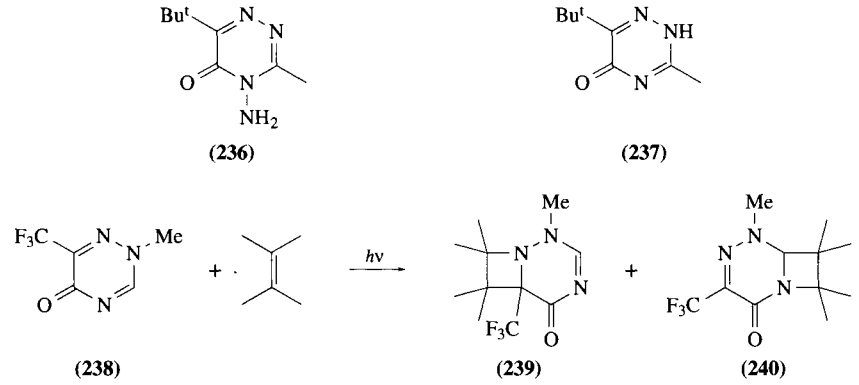
(232) (233) (25)



(234) (235) (26)

The photochemical degradation of 4-amino-6-*t*-butyl-3-methyl-1,2,4-triazin-5(4*H*)-ones (**236**) to 6-*t*-butyl-3-methyl-1,2,4-triazin-5(2*H*)-ones (**237**) is influenced by oxygen and water. The photochemical deamination in solution at 290 nm appears to be an intermolecular process ⟨82CZ373⟩. Irradiation of 2-methyl-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (**238**) in methanol containing ole-

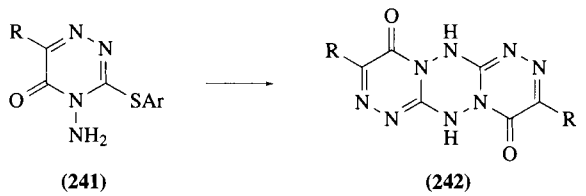
fins at ⩾300 nm (high-pressure mercury lamp with a Pyrex filter) gave products obviously formed by [2 + 2]cycloadditions across both the N1—C6 and C3—N4 bonds, irrespective of the nature of the alkene (Scheme 45). The primary products (**239**), (**240**) are transformed in the course of the reaction into the isolated products either by methanolysis or cycloreversion ⟨88CPB3354⟩.



(236) (237) (238) (239) (240)

Scheme 45

Heating 4-amino-3-arylthio-1,2,4-triazin-5(4*H*)-ones (**241**) in toluene afforded the tricyclic compounds (**242**) (Equation (27)) ⟨87S1134⟩.

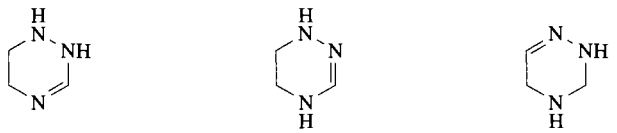


(241) (242) (27)

6.11.6.3 Reactivity of Tetrahydro-1,2,4-triazines, Triazine-diones and -dithiones, and Thioxodihydrotriazinones

In this section all 1,2,4-triazines are discussed which have one double bond in the ring, irrespective of whether one can draw tautomeric forms with two or three endocyclic double bonds.

Of the six possible tetrahydro-1,2,4-triazines without a possible tautomeric structure with more than one double bond in the ring only three are known, the 1,2,5,6- (**243**), 1,4,5,6- (**244**), and 2,3,4,5-tetrahydro-1,2,4-triazines (**245**). Most of the chemistry of these systems was covered in the 1978 review ⟨78HC(33)189⟩.



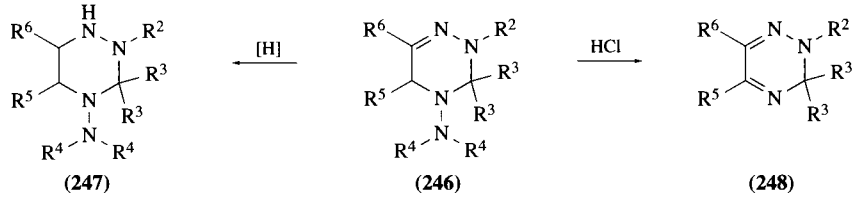
(243) (244) (245)

Much more is known about tetrahydro-1,2,4-tetrazines which can form tautomeric structures with more than one double bond in the ring. These include the tetrahydro-oxo(thioxo)-1,2,4-triazines and tetrahydro-dioxo(thioxo)-1,2,4-triazines, which, in the absence of a principal group of higher priority, are more usually named as dihydro-1,2,4-triazinones and dihydro-1,2,4-triazinethiones. Still better known are the tetrahydro-dioxo-1,2,4-triazines and their mono- and dithiooxo analogues, because the 3,5-isomers [1,2,4-triazine-3,5(2*H*,4*H*)-diones, 1,2,4-triazine-3,5(2*H*,4*H*)-dithiones, and dihydro-3/5-thioxo-1,2,4-triazin-5/3-ones] are aza-uracil derivatives.

The chemistry of the tetrahydro-1,2,4-triazines has not yet been studied systematically.

4-Amino-2,3,4,5-tetrahydro-1,2,4-triazines (**246**) can be reduced to the 4-amino-hexahydro-1,2,4-

triazines (**247**), while treatment with HCl converts them into the 2,3-dihydro-1,2,4-triazines (**248**) by elimination of amine (Scheme 46) ⟨78HC(33)189⟩.



(247) (246) (248)

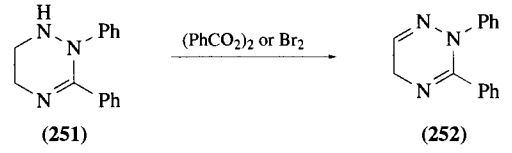
Scheme 46

Oxidation of 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines (**249**) afforded the 1,2,4-triazine 4-oxides (**250**) (Equation (28)) ⟨73KGS134⟩.

(28)

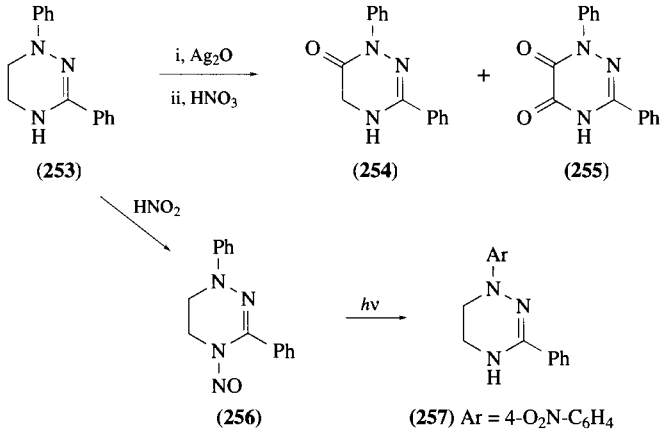
(249) (250)

Oxidation of 2,3-diphenyl-1,2,5,6-tetrahydro-1,2,4-triazine (**251**) with dibenzoyl peroxide or bromine gives the 2,5-dihydro derivative (**252**) (Equation (29)). 1,3-Diphenyl-1,2,5,6-tetrahydro-1,2,4-triazine (**253**) forms a silver complex with silver oxide, which is oxidized by dilute nitric acid to the 2,5-dihydro-1,2,4-triazin-6(1*H*)-one (**254**) and the 5,6-dione (**255**). Treatment of (**253**) with nitrous acid afforded the 4-nitroso derivative (**256**), which was transformed photochemically into the 1-(4-nitrophenyl) compound (**257**) (Scheme 47) ⟨89CB1983⟩.



(29)

(251) (252)

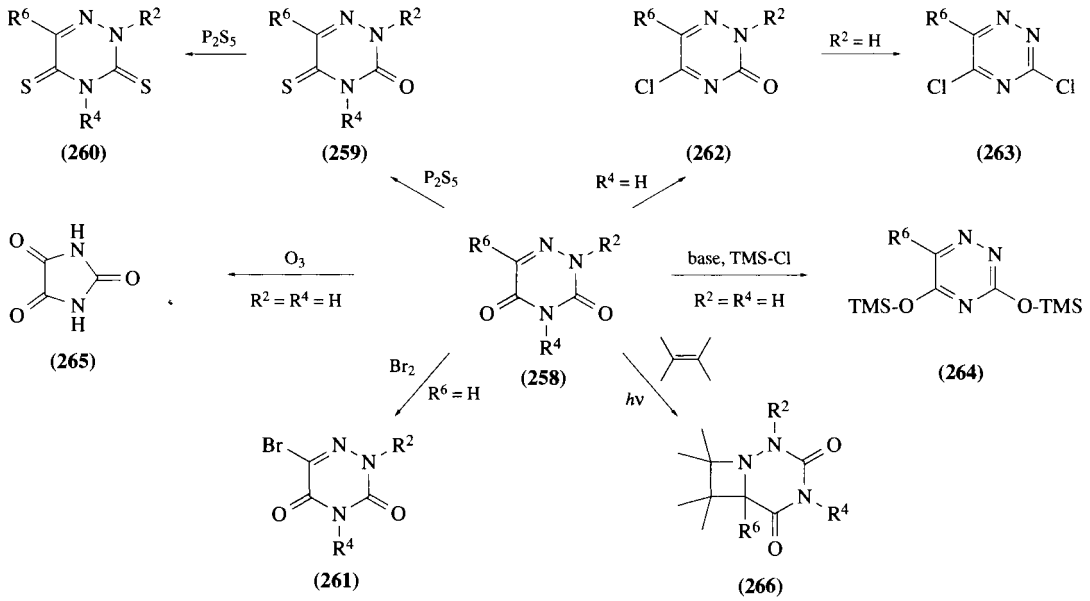


(253) (254) (255) (256) (257) Ar = 4-O_2N-C_6H_4

Scheme 47

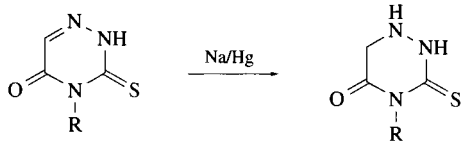
Most dihydro-1,2,4-triazinones can be converted into the corresponding thiones, and into chlorodihydrotriazines, and they can be alkylated by the usual methods. These reactions are also known for the diones. As was mentioned earlier, in these reactions the 5-position is the most reactive. Treatment of 1,2,4-triazine-3,5-diones (**258**) with phosphorus pentasulfide leads firstly to the 5-thioxo-4,5-dihydro-1,2,4-triazin-3-ones (**259**), and then to the 1,2,4-triazine-3,5-dithiones (**260**). Further reactions reported for 1,2,4-triazine-3,5-diones (**258**) are bromination in the 6-position to give (**261**), replacement of one (**262**) or both oxygens by chlorine (**263**) on reaction with $SOCl_2$,

$SOCl_2$/DMF, or $POCl_3/NEt_3$, alkylation and acylation, predominantly at N-2 ⟨88CPB3354, 91CPB2597⟩, formation of 3,5-bis-(trimethylsilyloxy)-1,2,4-triazines (**264**) ⟨83RRC989, 85RRC117⟩, with subsequent amination ⟨84CB1523⟩, and oxidation with ozone ($R^2 = R^4 = H$) to form parabanic acid (**265**) ⟨89BCJ2939⟩ (Scheme 48); also inter- and intra-molecular photochemical [2 + 2]-cycloadditions with alkenes across the C6—N1 bond to give products of type (**266**) ⟨83AG(E)161, 84H(22)67, 84H(22)1363, 88CPB3354⟩.



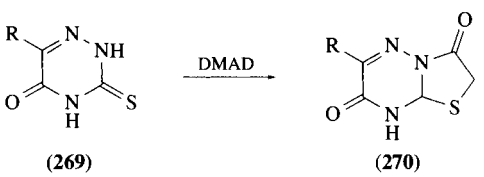
Scheme 48

Reduction of 4-amino- or 4-methyl-dihydro-3-thioxo-1,2,4-triazin-5-ones (**267**) with sodium amalgam afforded the tetrahydro derivatives (**268**) (Equation (30)) ⟨85JHC11⟩.



(30)

With DMAD, the 3-thioxo-1,2,4-triazin-5-ones (**269**) formed thiazolo[3,2-*b*][1,2,4]triazine-3,7-diones (**270**) (Equation (31)) ⟨84JCS(P1)2707⟩.

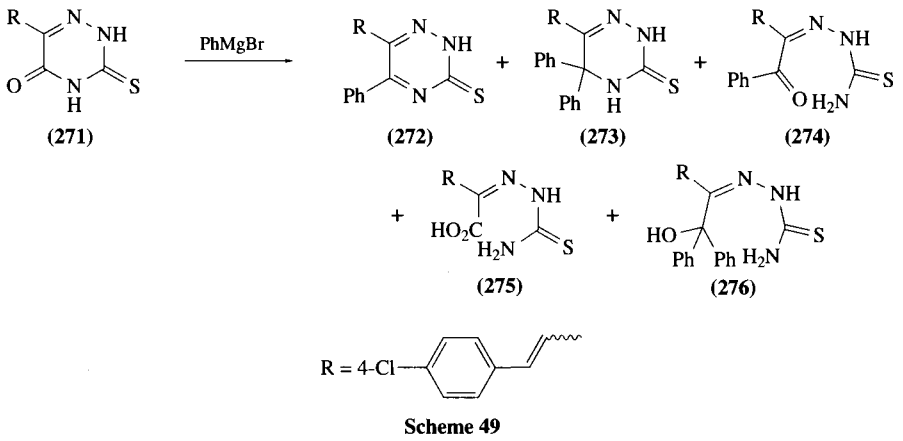


(31)

From the reaction of 6-*p*-chlorostyryl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**271**) with phenylmagnesium bromide a mixture of seven products was isolated. These were separated and identified as 6-*p*-chlorostyryl-5-phenyl-1,2,4-triazine-3(2*H*)-thione (**272**), 6-*p*-chlorostyryl-5,5-diphenyl-4,5-dihydro-1,2,4-triazine-3(2*H*)-thione (**273**), the open-chain compounds (**274**)–(**276**), thiosemicarbazide and sulfur (Scheme 49). Mechanisms for the formation of these products were suggested ⟨84JHC905⟩

6.11.6.4 Reactivity of Hexahydro-1,2,4-triazines and Tetrahydro-triazinones

Very few reactions of hexahydro-1,2,4-triazines and tetrahydro-1,2,4-triazinones are known ⟨78HC(33)189⟩.



Scheme 49

Tetrahydro-1,2,4-triazin-3-ones can be treated as cyclic azapetides (Figure 2). The 2-benzyl group in (**277**) can be removed by catalytic hydrogenation and the product (**278**) can be re-alkylated at N-2 to give (**279**). 2-Alkyl-tetrahydro-1,2,4-triazin-3-ones (**280**) can be acylated at N-1 and alkylated at N-4. This allows the use of tetrahydro-1,2,4-triazin-3-ones as building blocks in the synthesis of modified peptides ⟨94JOC6487, 95UP 611-03⟩.

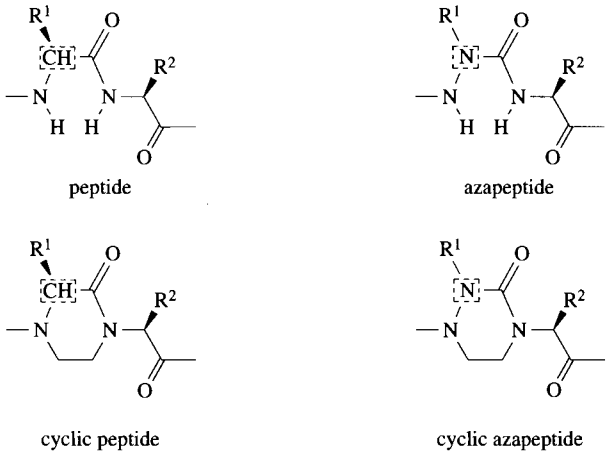
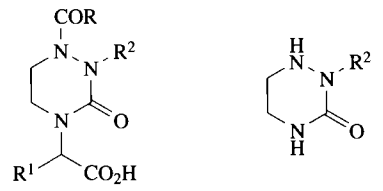


Figure 2 Peptides, azapeptides, and their cyclic forms.



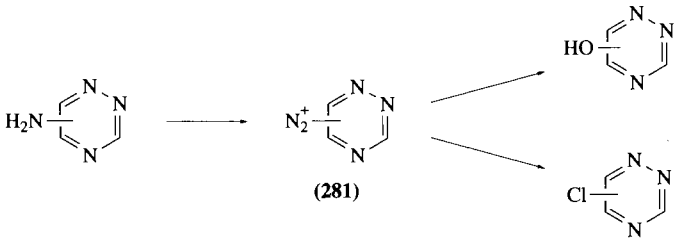
(**277**) R^2 = Bn
(**278**) R^2 = H
(**279**) R^2 = alkyl

(**280**)

6.11.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

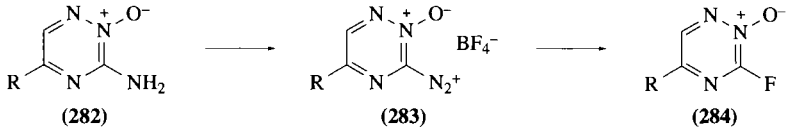
Substituents on carbon atoms of the 1,2,4-triazine nucleus in general show the expected reactivity of groups attached to a strongly electron-withdrawing ring. Oxygen, nitrogen, and sulfur substituents with actual or potential (by tautomerism) acidic hydrogen atoms can be alkylated and silylated.

An amino group can also be acylated ⟨84JHC697, 86JHC935⟩; it reacts with sulfonyl chlorides and aryl isocyanates ⟨86JHC935⟩, and also with nitrous acid to give, via the diazonium salt (**281**), either the triazinone by reaction with water or the chloro-triazine by reaction with chloride ions (Scheme 50). Nitrosation of 3-amino-1,2,4-triazine 2-oxides (**282**) and subsequent thermolysis of the diazonium tetrafluoroborate salts (**283**) afforded 3-fluoro-1,2,4-triazine 2-oxides (**284**) (Scheme 51). In one instance the diazonium tetrafluoroborate was isolated ⟨85H(23)1969⟩.



(281)

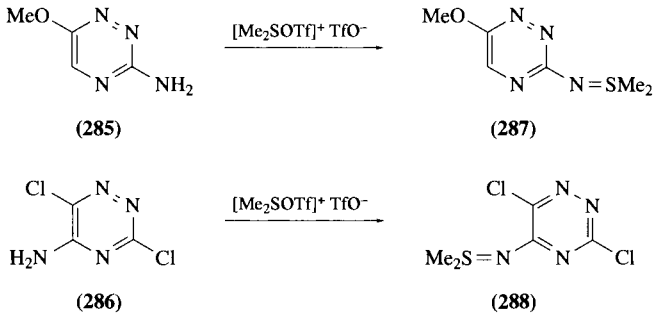
Scheme 50



(282) (283) (284)

Scheme 51

3-Amino-6-methoxy- (**285**) and 5-amino-3,6-dichloro-1,2,4-triazine (**286**) afforded the iminosulfuranes (**287**) and (**288**) by reaction with dimethyl(triflyloxy)sulfonium triflate (Scheme 52) ⟨83TL1011⟩.



(285) (287)

(286) (288)

Scheme 52

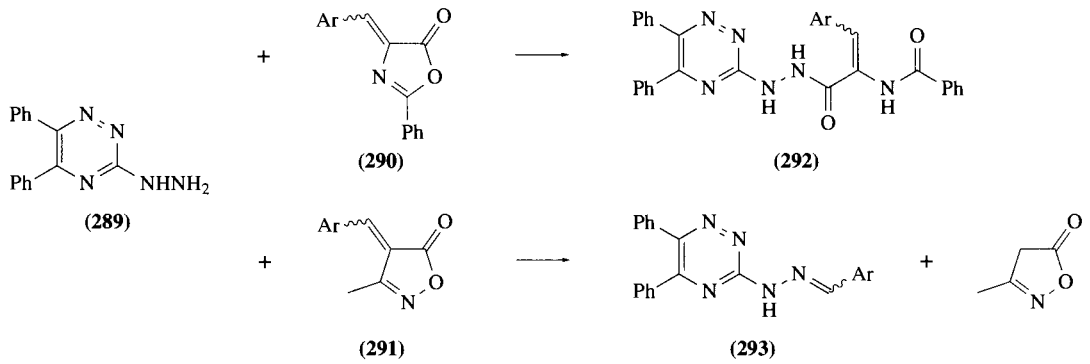
Hydrazino groups form azido groups with nitrous acid. These generally cyclize to the valence-isomeric tetrazolo-1,2,4-triazines, depending on the site of substitution (see Section 6.11.4).

3-Hydrazino-5,6-diphenyl-1,2,4-triazine (**289**) reacts with 4-benzylidene-2-phenyl-5(4*H*)-oxazolones (**290**) and 4-benzylidene-3-methyl-5(4*H*)-isoxazolones (**291**) in toluene to products (**292**), (**293**) substituted in the hydrazino group, the first by acylation by the oxazolone, the second by arylmethylidene group transfer (Scheme 53) ⟨88JHC1813⟩.

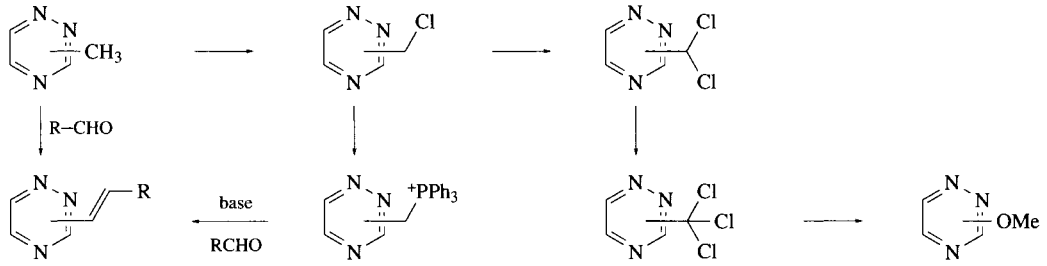
Alkylthio groups can be oxidized to alkylsulfinyl and alkylsulfonyl groups ⟨85TL2419, 88YZ142, 89JOC1249, 89JOC4984⟩

Only little is known about reactions of carbon substituents on carbon atoms of the 1,2,4-triazine nucleus. Methyl groups can react with chlorine or phosphorus pentachloride to give chloro-, dichloro-, and trichloromethyl-1,2,4-triazines ⟨82H(19)1865, 82H(19)1869, 88CPB1721, 90H(31)1933, 90LA631⟩. The chlorine can be substituted by other nucleophiles such as ethanol/sodium ethoxide ⟨82H(19)1865, 90H(31)1933⟩, but the 5-trichloromethyl group can also be displaced by methanol/sodium methoxide to give the 5-methoxy compound (Scheme 54) ⟨90H(31)1933⟩.

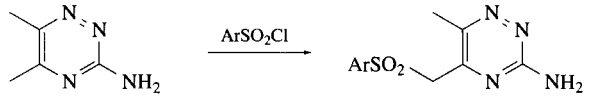
3-Amino-5,6-dimethyl-1,2,4-triazine (**294**) reacted with arenesulfonyl chlorides to give (perhaps unexpectedly) the 5-(arylsulfonylmethyl)-1,2,4-triazines (**295**) (Equation (32)) ⟨86JHC935⟩.



Scheme 53



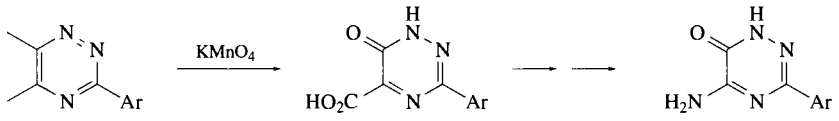
Scheme 54



(32)

(294) **(295)**

Oxidation of 3-aryl-5,6-dimethyl-1,2,4-triazines (**296**) with potassium permanganate yielded 3-aryl-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylic acids (**297**), which were transformed into 5-amino-3-aryl-1,2,4-triazin-6(1*H*)-ones (**298**) via the carbonyl azides and Curtius rearrangement (Scheme 55) ⟨90H(31)2163⟩.



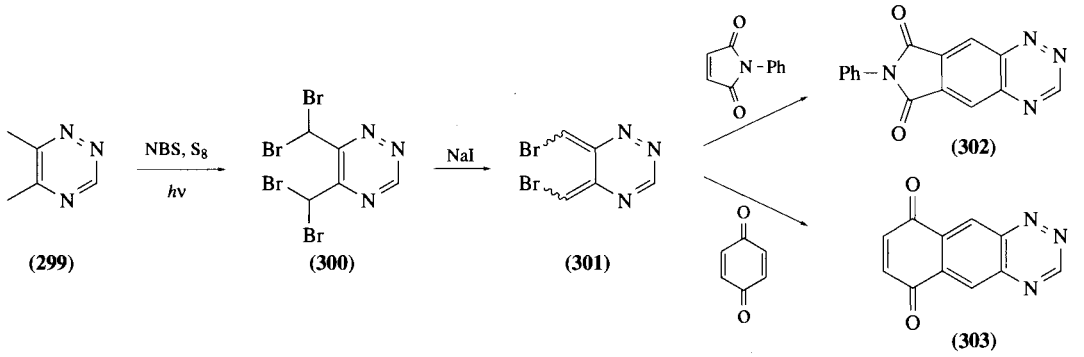
(296) **(297)** **(298)**

Scheme 55

Photo-induced bromination of 5,6-dimethyl-1,2,4-triazine (**299**) with NBS and sulfur in carbon tetrachloride for 24 hours gave 5,6-bis-(dibromomethyl)-1,2,4-triazine (**300**) (24%). Treatment of the tetrabromide (**300**) with sodium iodide gave the quinodimethane (**301**), which was trapped by reaction with *N*-phenylmaleimide or benzoquinone; reductive elimination of Br_2 led to the isolated products (**302**), (**303**) (Scheme 56) ⟨86JCS(P1)1495⟩.

The methyl groups in 1,2,4-triazines react with aldehydes to give the alkenyl-1,2,4-triazines; in this reaction too the 5-methyl group is the most reactive ⟨86JHC935⟩. Alkenyl-1,2,4-triazines can also be obtained by reaction of chloromethyl-1,2,4-triazines with triphenylphosphine and subsequent reaction with aldehydes (Scheme 54) ⟨82H(19)1869, 88CPB1721⟩.

Ethynyl groups react with water to give the acylmethyl-1,2,4-triazines (**304**). (Equation (33))



(299) (300) (301) (302) (303)

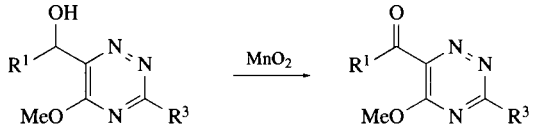
Scheme 56

Amines and ethanol can also be added. 3/5-Trimethylsilylethynyl derivatives are hydrated to form the corresponding acetyl compounds ⟨84H(22)2245⟩.

(33)

(304)

6-Hydroxyalkyl-1,2,4-triazines (**305**) can be oxidized by manganese dioxide to afford 6-acyl-1,2,4-triazines (**306**) (Equation (34)) ⟨93LA583⟩.

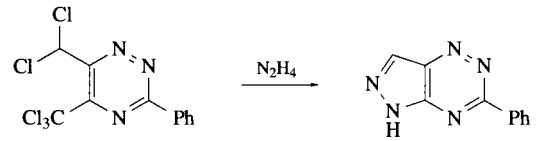


(34)

(305) (306)

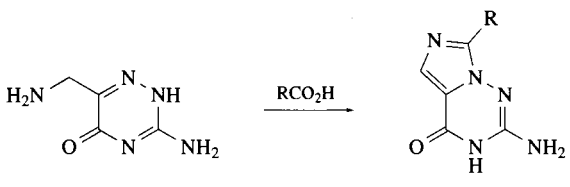
Condensed 1,2,4-triazines have been prepared in a number of reactions in which substituents at carbon atoms are involved (see also Section 6.11.6.2):

6-Dichloromethyl-5-trichloromethyl-3-phenyl-1,2,4-triazine (**307**) reacts with hydrazine to give 3-phenylpyrazolo[3,4-*e*]-1,2,4-triazine (**308**) (Equation (35)) ⟨90H(31)1933⟩. 3-Amino-6-aminomethyl-1,2,4-triazin-5-one (**309**) was cyclized by carboxylic acids to imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones (**310**) (Equation (36)) ⟨84JHC697⟩. Similarly, 3-Amino-6-hydrazino-1,2,4-triazin-5-ones (**311**) condense with carboxylic acids to give 1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-ones (**312**) (Equation (37)) ⟨84JHC697⟩.



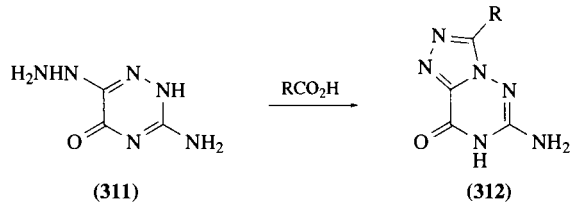
(35)

(307) (308)



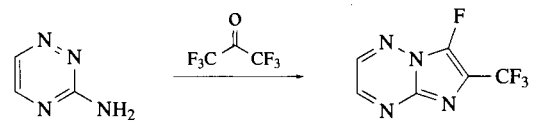
(36)

(309) (310)



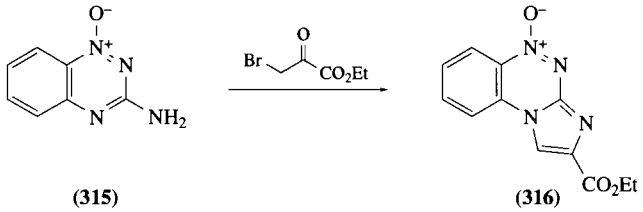
(311) (312) (37)

When 3-amino-1,2,4-triazine (**313**) was heated with hexafluoroacetone and tin(II) chloride in xylene/THF at 100–120°C 7-fluoro-6-trifluoromethylimidazo[1,2-*b*]-1,2,4-triazine (**314**) was isolated (28%) (Equation (38)) ⟨88S199⟩.



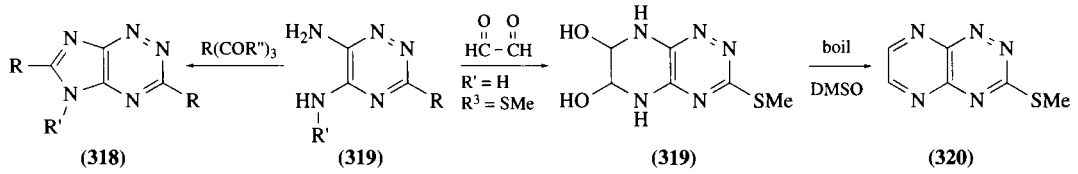
(313) (314) (38)

Condensation of 3-amino-1,2,4-benzotriazine 1-oxide (**315**) with ethyl bromopyruvate in THF at reflux in the presence of ethanol furnished the imidazo[1,2-*c*][1,2,4]benzotriazine-2-carboxylate 5-oxide (**316**) (Equation (39)), which can be reduced to the 5-deoxygenated analogue ⟨84JHC1081⟩.



(315) (316) (39)

5,6-Diamino-1,2,4-triazines (**317**) and ortho-esters afforded imidazo[4,5-*e*]-1,2,4-triazines (6-azapurines) (**318**) ⟨86JCS(P2)931, 90LA631⟩. With glyoxal and substituted glyoxals in methanol dihydro- and tetrahydro-pyrazino[2,3-*e*]-1,2,4-triazines (**319**) (azapteridine systems) were obtained. In one case the pyrazino[2,3-*e*]-1,2,4-triazine (**320**) was obtained, by dehydration of the dihydroxy-tetrahydro intermediate (Scheme 57) ⟨83JHC1123, 86JHC33, 93H(36)2577⟩.

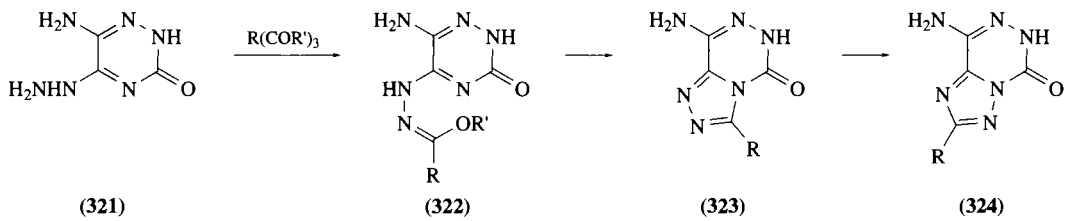


(318) (319) (319) (320)

Scheme 57

Reaction of 6-amino-5-hydrazino-1,2,4-triazin-3-one (**321**) with orthocarboxylates affords the [1,2,4]triazolo[5,1-*d*][1,2,4]triazin-5(6*H*)-ones (**324**) via open-chain derivatives (**322**) by a regiospecific ring closure to N-4 and subsequent Dimroth rearrangement of the initially formed 1,2,4-triazolo[4,3-*d*][1,2,4]triazin-5(6*H*)-ones (**323**) (Scheme 58) ⟨82JHC1345⟩.

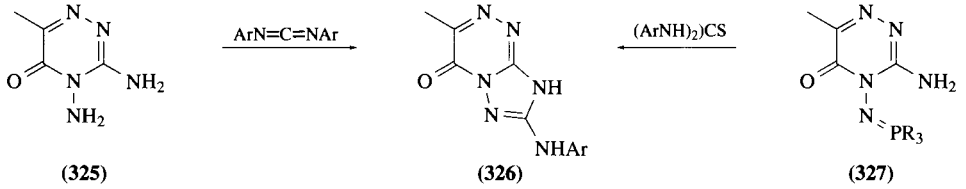
3,4-Diamino-1,2,4-triazin-5-one (**325**) affords 1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (**326**) by



(321) (322) (323) (324)

Scheme 58

reaction with carbodiimides, and the same system was obtained by reaction of the 3-amino-4-iminophosphoranes (**327**) with *N,N'*-diarylthioureas (Scheme 59) ⟨89H(29)1607⟩.

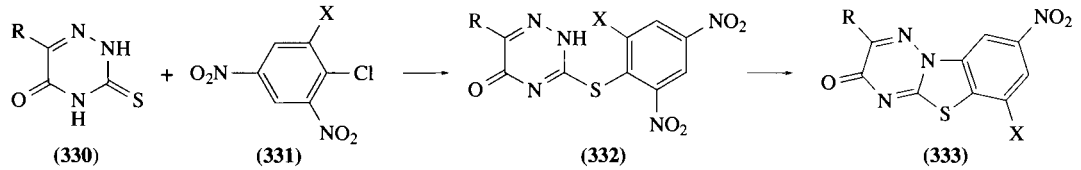


Scheme 59

Reaction of 6-amino-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**328**) with haloacetophenones provides the 7-aryl-2,8-dihydro-3*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3-ones (**329**) (Equation (40)) ⟨93JHC293⟩.

(40)

3-Thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-ones (**330**) and 2,4-dinitro- or 2,4,6-trinitro-chlorobenzene (**331**) afford [1,2,4]triazino[3,2-*b*]benzothiazol-3-ones (**333**) or the *S*-arylated intermediates (**332**), depending on the reaction temperature (Scheme 60) ⟨88LA1089⟩.

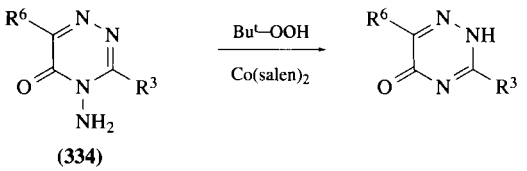


Scheme 60

6.11.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN ATOMS

In this section there are only reactions of the 4-amino group in 4-amino-1,2,4-triazin-5-ones to be considered. This group shows all reactions to be expected from an amino group bound to a heterocyclic system via a nitrogen atom. Thus, it can be alkylated ⟨85JHC11⟩ and acylated ⟨86H(24)1031⟩, and it reacts with aldehydes and ketones ⟨89JCS(P1)247⟩, carbodiimides ⟨86H(24)3363, 88H(27)161⟩, and isothiocyanates in DMF ⟨83S759⟩. It can be removed by oxidation ⟨82TL2499⟩. The general chemistry of 4-amino-1,2,4-triazines is discussed in detail in the 1978 review ⟨78HC(33)189⟩.

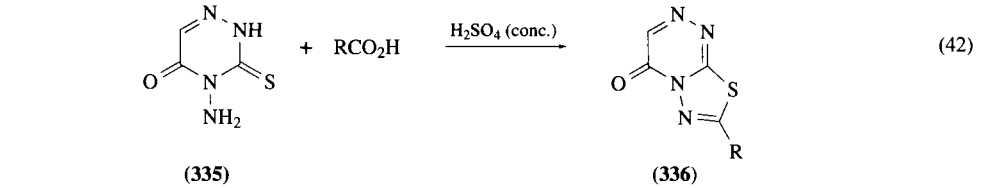
The oxidation of 4-amino-1,2,4-triazine herbicides (**334**) with *t*-butyl hydroperoxide catalyzed by $Co(salen)_2$ resulted in the specific deamination of the 4-amino group (Equation (41)), providing a chemical model for the metabolism of these herbicides ⟨82TL2499⟩. Other ways to remove a 4-amino group include treatment with HNO_2 ⟨64CB2647⟩ or P_2S_5 (Scheme 39), and photochemically (Scheme 45).



(41)

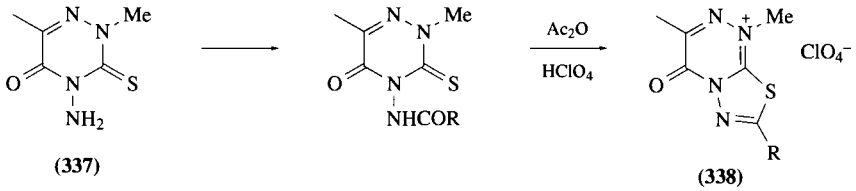
A wide variety of fused 1,2,4-triazines has been prepared starting from the 4-amino derivatives, and in particular from 4-amino-3-thioxo compounds. Thus, 4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-ones (**336**) are formed from 4-amino-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one

(**335**) with a variety of carboxylic acids in the presence of concentrated sulfuric acid (Equation (42)) ⟨82JHC1577⟩. In a variant of this reaction, the 2,6-dimethyl analogue (**337**) was first acylated at the 4-amino group and then cyclized ($Ac_2O/HClO_4$) to give 7-substituted 1,3-dimethyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazinium perchlorates (**338**) (Scheme 61) ⟨86H(24)1031⟩.



(42)

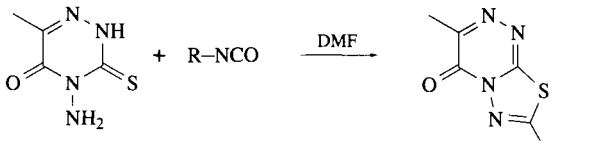
(**335**) (**336**)



(**337**) (**338**)

Scheme 61

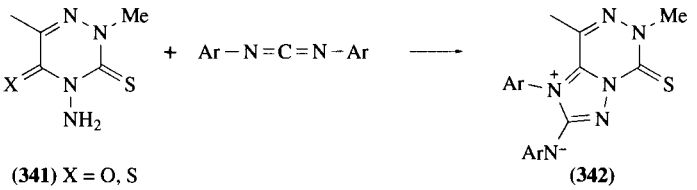
Reaction of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5-one (**339**) with isocyanates in DMF yields 4*H*-1,3,4-thiadiazolo[2,3-*c*]1,2,4-triazin-4-one derivatives (**340**) (Equation (43)) ⟨83S759⟩.



(43)

(**339**) (**340**)

Reaction of the 2,6-dimethyl derivative (**337**), or of the analogous 3,5-dithiones (**341**), with diaryl carbodiimides affords the mesoionic [1,2,4]triazolo[1,5-*d*][1,2,4]triazines (**342**) (Equation (44)) ⟨88H(27)161⟩.

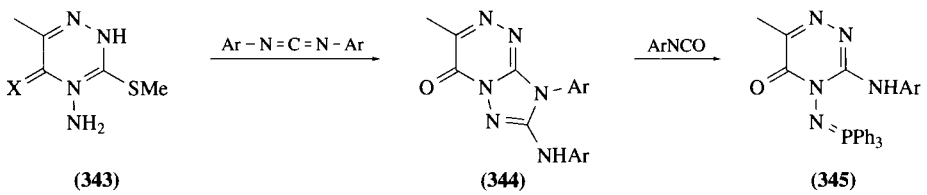


(44)

(**341**) X = O, S (**342**)

4-Amino-6-methyl-3-methylthio-1,2,4-triazin-5(2*H*)-one (**343**) reacts with diarylcarbodiimides to form 8-aryl-7-arylamino-3-methyl[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-4(8*H*)-ones (**344**), and the same products are formed from the iminophosphoranes (**345**) with isocyanates (Scheme 62) ⟨86H(24)3363⟩. The iminophosphoranes are prepared from the corresponding amines with triphenylphosphine dibromide.

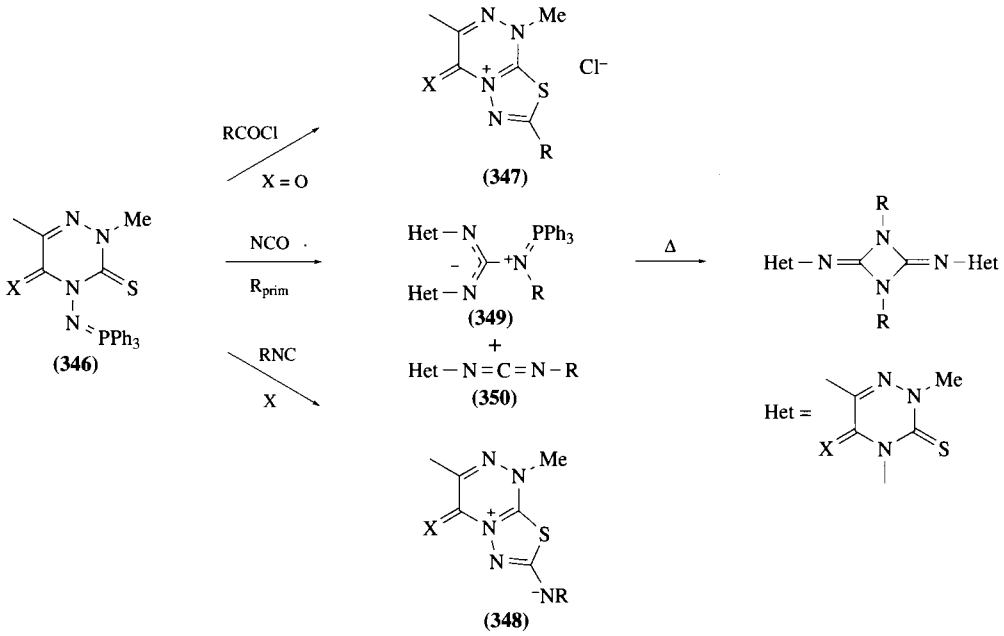
The iminophosphorane (**346**) (X = O) was cyclized with acyl chlorides to give the 4-oxo-



(**343**) (**344**) (**345**)

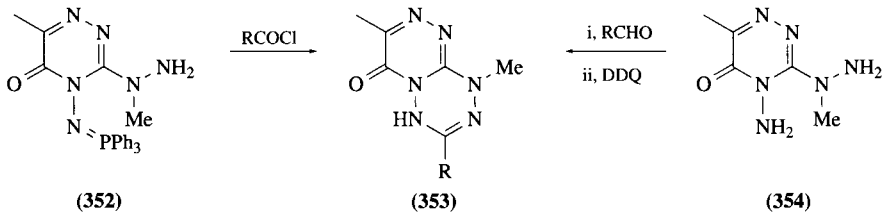
Scheme 62

[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazinium salts (**347**) ⟨88H(27)1935⟩. Reaction of (**346**) (X = O or S) with isocyanates or isothiocyanates formed the [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazines (**348**) ⟨84S983, 91T6747⟩, but with primary alkyl isocyanates the betaines (**349**) or the carbodiimides (**350**) were formed. Thermolysis of the betaines (**349**) afforded diazetidines (**351**), the dimers of the carbodiimides (**350**) (Scheme 63) ⟨86JCS(P1)2037, 92JCS(P1)199⟩



Scheme 63

The iminophosphorane (**352**) reacts with acyl chlorides to give the corresponding 3-substituted 1,7-dimethyl-1,4-dihydro-6*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazin-6-ones (**353**). The same compounds were obtained by reaction of the amino-hydrazine (**354**) with aldehydes and dehydrogenation of the 1,2,3,4-tetrahydro products with DDQ (Scheme 64) ⟨88T2249⟩.



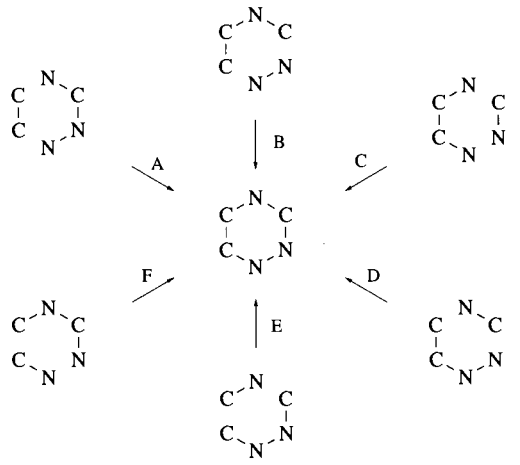
Scheme 64

6.11.9 RING SYNTHESIS

6.11.9.1 [4 + 2]Atom Combinations

The most frequently-used methods of forming six-membered rings, and those most applicable to the synthesis of 1,2,4-triazines, are those which proceed from [4 + 2] atom fragments. Examples of five of the six possible [4 + 2] atom fragment combinations for 1,2,4-triazines were discussed in the previous review ⟨84CHEC-I(3)369⟩. These are the following: N(1)N(2)C(3)N(4) + C(5)C(6) (A), C(3)N(4)C(5)C(6) + N(1)N(2) (B), N(4)C(5)C(6)N(1) + N(2)C(3) (C), C(5)C(6)N(1)N(2) + C(3)N(4) (D) and C(6)N(1)N(2)C(3) + N(4)C(5) (E). Most of these methods have been used during

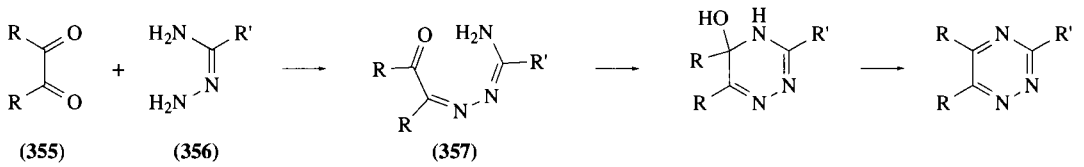
the last ten years also. We have not been able to find an example of the last possible combination: N(2)C(3)N(4)C(5) + C(6)N(1) (F) (Scheme 65). Of the five known methods, the first (A) is the one most frequently used, followed by method (B).



Scheme 65

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

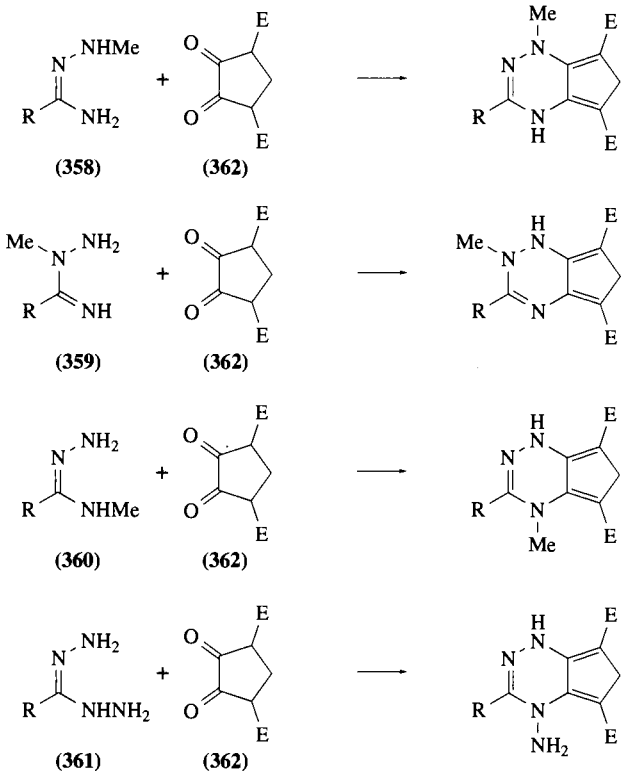
The reaction of 1,2-dicarbonyl compounds (**355**) with amidrazones (**356**) is still the best method for the synthesis of alkyl, aryl or heteroaryl substituted 1,2,4-triazines (Scheme 66) ⟨78HC(33)189, 82JHC1201, 82JOC3761, 83LA1476, 84CHEC-I(3)369, 84H(22)2241, 88OS(66)142, 89H(29)2249, 90JOC3257, 92S519⟩. No limitation on this synthetic principle is reported, except that it is, of course, preferable for the dione to be symmetrical. The best reaction procedure is to add the dicarbonyl compound to a solution of the free amidrazone, or amidrazonium salt in the presence of one mole of base, and allow a reaction time of about 12 hours. Since the first step of this reaction, the condensation of the hydrazono group with one carbonyl group, is fast, while the second, the condensation of the amide group with the other, is often slow, the intermediate (**357**) has been isolated in a few cases. This method has been used for the synthesis of all types of 1,2,4-triazines, including condensed 1,2,4-triazines by starting with cyclic 1,2-dicarbonyl compounds.



Scheme 66

N-1, *N*-2- and *N*-4-substituted amidrazones (**358**)–(**360**) can be used for the synthesis of 1-, 2-, or 4-substituted dihydro-1,2,4-triazines ⟨82CB2807⟩. Reactions of 1,2-dicarbonyl compounds with hydrazidines (**361**) have been used for the synthesis of 4-amino-dihydro-1,2,4-triazines ⟨85LA78⟩. The examples shown (Scheme 67), employing the cyclopentanedione (**362**), result in a variety of reduced cyclopenta[*e*]-1,2,4-triazines.

When semicarbazide (**363a**), thiosemicarbazide (**363b**), selenosemicarbazide (**363c**), or aminoguanidine (**369a**) are used instead of the amidrazones, the corresponding 1,2,4-triazin-3-ones (**366a**) ⟨78HC(33)189, 84CHEC-I(3)369⟩ -3-thiones (**366b**) ⟨78HC(33)189, 84CHEC-I(3)369, 87JOC4280, 87YZ301⟩, -3-selones (**366c**) ⟨78HC(33)189, 84CHEC-I(3)369⟩ (Scheme 68) and the 3-amino-1,2,4-triazines (**371a**) (Scheme 69) are prepared ⟨84JHC697, 93JOC2001⟩. Similarly, N-2- and N-4-substituted semicarbazides can be used for the synthesis of 2- (**367a**) or 4-substituted 1,2,4-triazin-3-ones (**368a**) and -3-thiones (**367b**), (**368b**), and use of substituted aminoguanidines (**369b**) leads to 3-(substituted amino)-1,2,4-



(358) (362)

(359) (362)

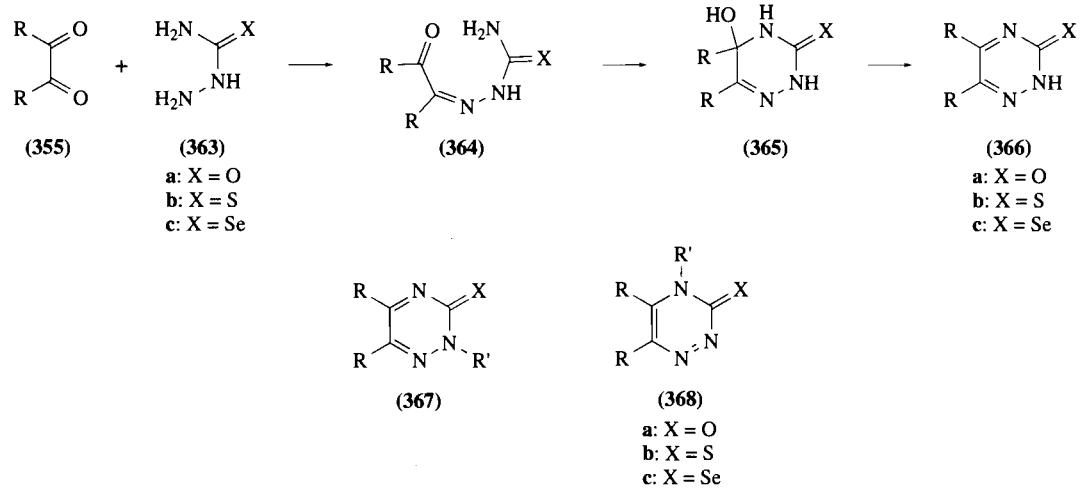
(360) (362)

(361) (362)

E = CO_2Me

Scheme 67

triazines (**371b**). Reaction of *S*-methylthiosemicarbazide (**369c**) with (**355**) affords 3-methylthio-1,2,4-triazines (**371c**) ⟨86TL2747, 87JOC4280, 88CZ243, 88JHC1733, 88YZ142, 93YZ40⟩.



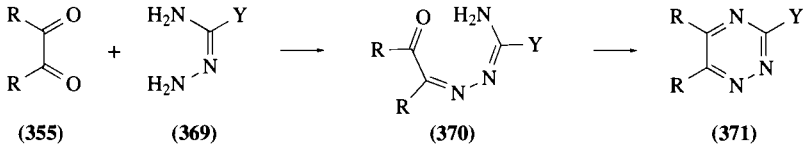
(355) (363) a: X = O b: X = S c: X = Se (364) (365) (366) a: X = O b: X = S c: X = Se

(367) (368) a: X = O b: X = S c: X = Se

Scheme 68

The hydrazones (**364**), (**370**) initially formed can in most cases be isolated, and cyclized in a second step, but this is not necessary, as direct cyclization usually takes place readily. Intermediates of type (**365**) could be isolated, but in only a few cases.

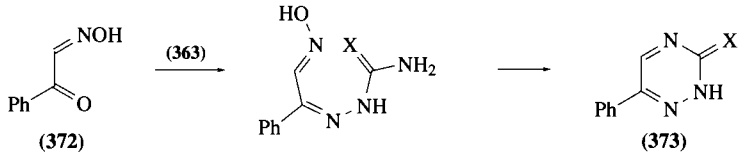
Semicarbazides (**363a**) and thiosemicarbazides (**363b**) also react with 1,2-dicarbonyl monoximes, leading to 1,2,4-triazin-3-ones and -3-thiones (**366a**), (**366b**). This method is of preparative value for the synthesis of 6-substituted 1,2,4-triazin-3-ones or -3-thiones (e.g. (**373a**), (**373b**) from (**372**)



(355) (369) (370) (371)
a: X = NH_2
b: X = NHR
c: X = SMe

Scheme 69

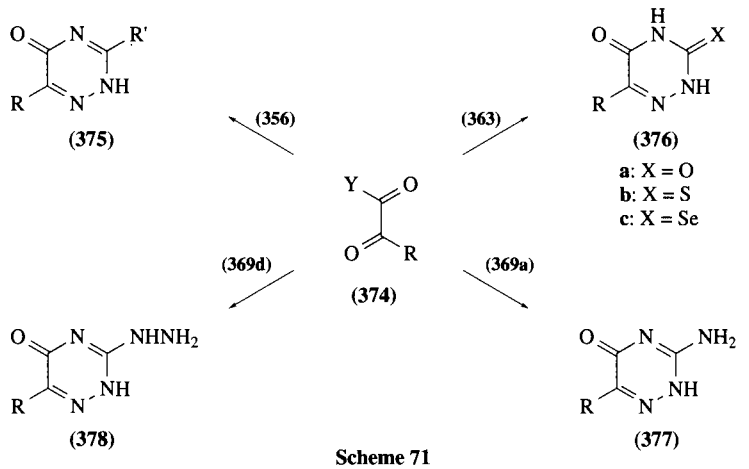
(Scheme 70)); these are formed in only minor amounts when a substituted glyoxal reacts with semicarbazide or thiosemicarbazide.



(372) (373)
a: X = O
b: X = S

Scheme 70

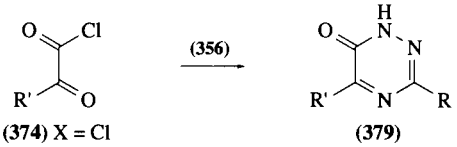
The use of α-ketocarboxylic acids or their esters (**374**; Y = OH, OR) instead of 1,2-dicarbonyl compounds is the general method for the synthesis of 1,2,4-triazin-5-ones ⟨84CHEC-I(3)369, 84H(22)2241, 85JOC2293, 86BSF944, 90LA631⟩. Compounds (**374**) react with amidrazones (**356**), semicarbazide, thiosemicarbazide and selenosemicarbazide (**363a–c**), aminoguanidine (**369a**), and diaminoguanidine (**369d**) to yield 1,2,4-triazin-5-ones (**375**) ⟨78HC(33)189⟩, 1,2,4-triazine-3,5-diones (**376a**) ⟨78HC(33)189⟩, 3-thioxo-1,2,4-triazin-5-ones (**376b**) ⟨78HC(33)430⟩, 3-selenoxo-1,2,4-triazin-5-ones (**376c**) ⟨78HC(33)189⟩, 3-amino-1,2,4-triazin-5-ones (**377**) ⟨78HC(33)475⟩ and 3-hydrazino-1,2,4-triazin-5-ones (**378**) ⟨78HC(33)494⟩ (Scheme 71).



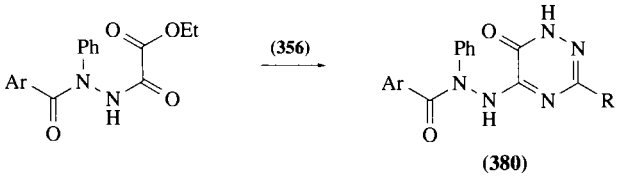
(375) (376) (374) (378) (377)
(376): a: X = O; b: X = S; c: X = Se

Scheme 71

Reaction of α-ketoacid chlorides (**374**; Y = Cl) with amidrazones (**356**) leads preferentially to 1,2,4-triazin-6-ones (**379**) (Equation (45)) ⟨86S635, 92JHC1161, 92LA1271⟩. In this case the more reactive hydrazono group of the amidrazone reacts with the carbonyl chloride instead of the keto group. *N*-Aroyl-*N'*-ethoxalylphenylhydrazines react with amidrazones to form the 5-hydrazino-1,2,4-triazin-6-ones (**380**) (Equation (46)) ⟨87S128⟩.



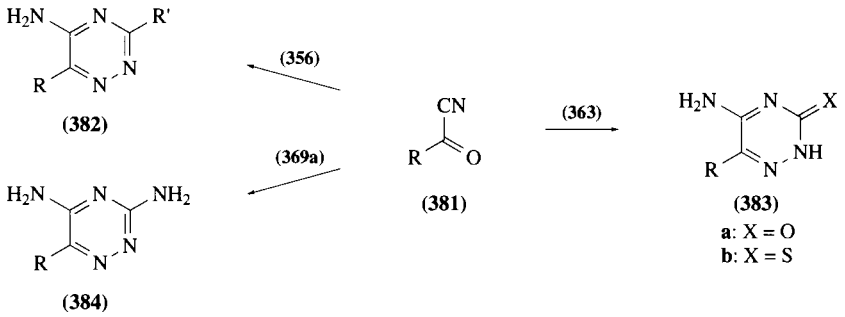
(374) X = Cl (379) (45)



(46)

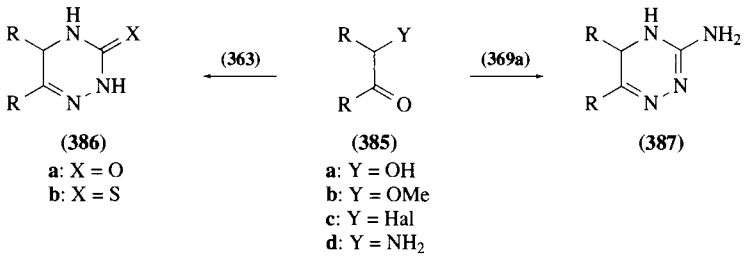
Substituted amidrazones also react with α-keto-acids or their esters, leading to *N*-substituted compounds of the types discussed. The amidrazone can also be part of a heterocyclic system; in these cases condensed 1,2,4-triazines are formed.

Reaction of acyl cyanides (**381**) with amidrazones (**356**), semicarbazide (**363a**), thiosemicarbazide (**363b**), and aminoguanidine (**369a**) provides syntheses of 5-amino-1,2,4-triazines (**382**), 5-amino-3-ones (**383a**) and -3-thiones (**383b**), and 3,5-diamino-1,2,4-triazines (**384**) respectively (Scheme 72) ⟨78HC(33)189⟩.



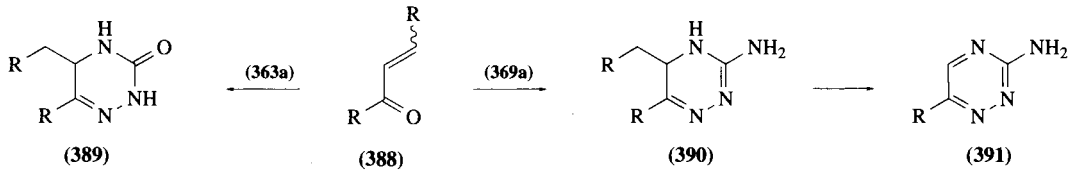
Scheme 72

The reactions of α-hydroxy- (**385a**), α-methoxy- (**385b**), α-halo- (**385c**), α-amino- (**385d**), and αβ-unsaturated (**388**) ketones with semicarbazide (**363a**) are used for the synthesis of dihydro-1,2,4-triazin-3-ones (**386a**), (**389**) (Schemes 73, 74) ⟨78HC(33)189⟩. Similarly, α-hydroxy- and α-bromo-ketones with thiosemicarbazide (**363b**) have been shown to give the corresponding thiones (**386b**) ⟨78HC(33)189⟩. The reaction of α-halo ketones of αβ-unsaturated ketones with aminoguanidine (**369a**) gives the 3-aminodihydro-1,2,4-triazines (**387**), (**390**) ⟨78HC(33)189⟩. When the dihydro-1,2,4-triazines (**390**) are treated with a base, RCH_3 may be eliminated, to give the 5-substituted 3-amino-1,2,4-triazines (**391**) (Scheme 74). The reaction of α-aminoketones(**385d**) with thiosemicarbazide yields a mixture of 3-aminodihydrotriazines (**387**) and dihydro-1,2,4-triazine-3-thiones (**386b**) ⟨78HC(33)189⟩. The participation of α-aminoketones in these reactions is mentioned here because of their relationship to the other α-substituted ketones. It is, however, apparent that this reaction forms a [3 + 3] atom fragment sequence rather than a [4 + 2], since the amino group of the α-aminoketone and not the amino group of semicarbazide, thiosemicarbazide or aminoguanidine becomes N-4 of the 1,2,4-triazine ring.



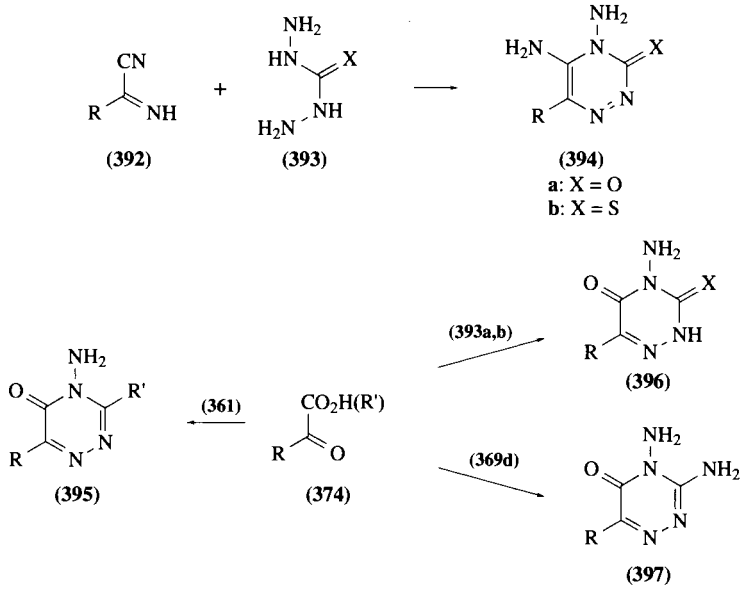
Scheme 73

4,5-Diamino-1,2,4-triazin-3-ones (**394a**) and the 3-thiones (**394b**) were obtained by treatment of α-iminonitriles (**392**) with carbonohydrazide or thiocarbonohydrazide (**393a**), (**393b**), respectively ⟨78HC(33)189⟩. Reaction of hydrazidines (**361**) with α-ketocarboxylic acids or their derivatives (**374**) is a straightforward route to 4-amino-1,2,4-triazin-5-ones (**395**) (Scheme 75) ⟨84CHEC-1(3)369, 85LA78, 92LA115⟩. Similarly, carbonohydrazide (**393a**) and thiocarbonohydrazide (**393b**) with (**374**) afford the 4-amino-3,5-diones (**396a**) and 4-amino-3-thioxo-5-ones (**396b**) ⟨78HC(33)189⟩. Diaminoguanidine



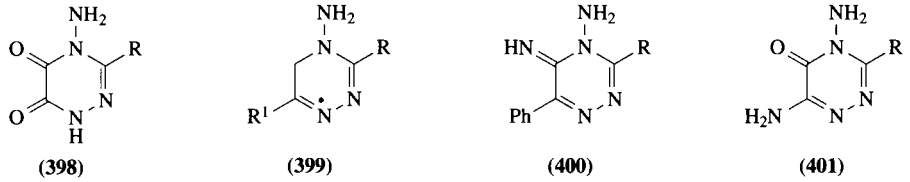
Scheme 74

(**369d**) and α-ketocarboxylates yield 3,4-diamino-1,2,4-triazin-5-ones (**397**) (Scheme 75) ⟨78HC(33)189⟩.

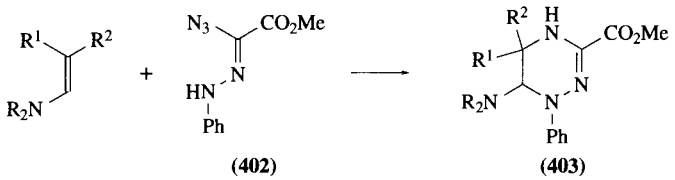


Scheme 75

4-Amino-1,2,4-triazine-5,6-diones (**398**), 4-amino-4,5-dihydro-1,2,4-triazines (**399**), 4-amino-5-imino-1,2,4-triazines (**400**) and 4,6-diamino-1,2,4-triazin-5-ones (**401**) were prepared from hydrazidines (**361**) by reaction with oxalates, α-bromo-ketones (**385**; Y = Br), acyl cyanides (**381**) and thiooxamides, respectively ⟨85LA78, 92LA115⟩.



The reaction of methyl azido(phenylhydrazono)acetate (**402**) with enamines leads to various types of ring-closed products, one of them being the 1,4,5,6-tetrahydro-1,2,4-triazines (**403**) (Equation (47)) ⟨84JCS(P1)1427, 85JCS(P1)1903⟩.

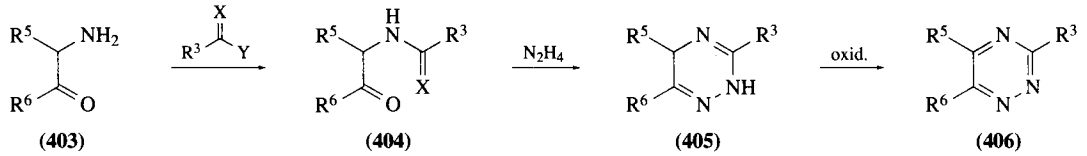


(47)

Cycloaddition of diazo-diazoles and -triazoles with electron-rich dipolarophiles such as 1-diethylaminopropyne affords azolo-1,2,4-triazines. However, these fused products lie outside the scope of this chapter.

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

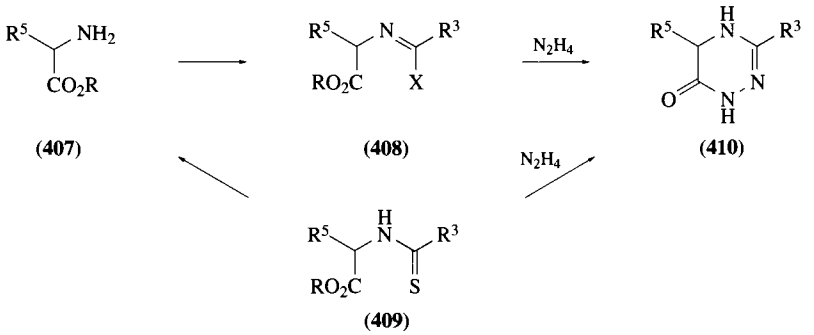
The combination of C(3)N(4)C(5)C(6) with N(1)N(2) is another frequently-used method for the synthesis of 1,2,4-triazines. In many cases it is a question of convenience whether one takes the C(3)N(4)C(5)C(6) fragment as the starting material or considers it as a combination of [3 + 1] atom fragments. For instance, α-acylamino ketones and α-thioacylamino ketones (**404**; X = O, S) react with hydrazine to give dihydro-1,2,4-triazines (**405**) which can be oxidized to the 1,2,4-triazines (**406**) (Scheme 76) ⟨78HC(33)189⟩. Since α-acylamino ketones (**404**; X = O) are usually prepared by acylation of α-amino ketones (**403**), one may also call this triazine synthesis a [3 + 2 + 1] atom fragment sequence.



(**403**) (**404**) (**405**) (**406**)

Scheme 76

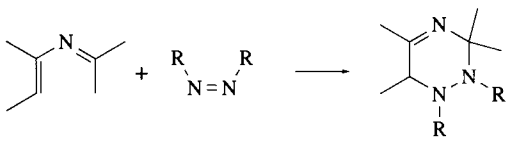
Besides α-acylamino ketones, derivatives of α-acylaminoacids have been used as the C(3)N(4)C(5)C(6) atom fragment. For instance, α-aminoacid esters (**407**) were transformed into the imidates (**408**; X = OR) ⟨82SA(A)133⟩, amidines (**408**; X = NR_2) ⟨85JHC409, 90H(30)393, 91JHC1715, 94JOC507⟩, chloroformamidines (**408**; X = Cl) ⟨88LA141⟩, or thioacylaminoacids (**409**) ⟨83T3419⟩, and these derivatives reacted with hydrazine or substituted hydrazines to give in most cases the 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones (**410**) (Scheme 77).



(**407**) (**408**) (**410**) (**409**)

Scheme 77

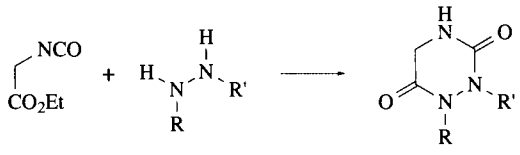
Another route to the 1,2,4-triazine ring is the cycloaddition of 2-azabutadienes (**411**) with azo compounds (**412**) leading to 1,2,3,6-tetrahydro-1,2,4-triazines (**413**) (Equation (48)) ⟨86CC1179, 87HCA1255, 90TL397, 91JOC4459⟩. In a few cases of these reactions diastereofacial selectivity has been observed.



(48)

(**411**) (**412**) (**413**)

Reaction of ethyl isocyanatoacetate (**414**) with hydrazines affords tetrahydro-1,2,4-triazine-3,6-diones (**415**) (Equation (49)) ⟨83JHC547⟩.



(49)

(**414**) (**415**)

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

This combination is widely found in 1,2,4-benzotriazine syntheses ⟨84CHEC-I(3)369⟩, but it does not seem to have been applied in the monocyclic series. No significant advances in syntheses by these methods have been reported since the publication of CHEC-I.

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

No unfused 1,2,4-triazines seem to have been made by this atom combination. Mesomeric betaines containing the bicyclic pyrido[2,1-*f*][1,2,4]triazine system have been prepared by reaction of 2-alkoxycarbonyl pyridinium *N*-imines with phenyl isocyanate or isothiocyanate ⟨93T3185⟩, but discussion of these reactions lies within the scope of another Volume.

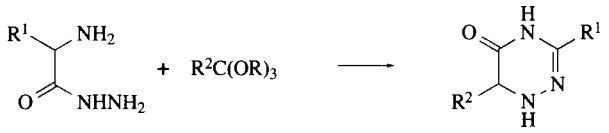
6.11.9.2 [5 + 1] Atom Combinations

Of the six possible [5 + 1] atom fragment combinations for synthesizing 1,2,4-triazines, only two are found in the literature; in these C-3 and N-4 are the one-atom fragments. Both were discussed in detail in CHEC-I ⟨84CHEC-I(3)369⟩.

Many of the methods discussed in this section can also be treated as combinations of more than two fragments. For instance, in the cyclization of *C,N*-diaryl hydrazones (**425**) with ammonia described in Section 6.11.9.2.2 the α-acylamino-hydrazones are treated as a five-atom fragment, but since these compounds were prepared from methylene ketones (**424**) via diazo group transfer and acylation of the α-hydrazono-ketones, the entire reaction sequence may be described as a [2 + 2 + 1 + 1] combination.

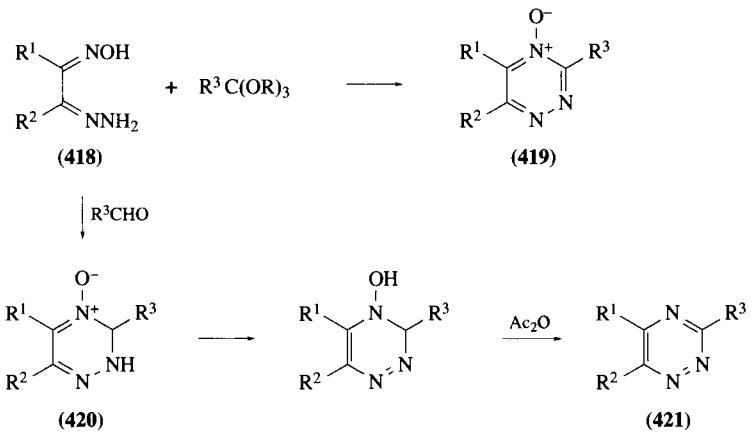
6.11.9.2.1 C-3 as the One-atom fragment

The cyclization of α-aminoacid hydrazides (**416**) with ortho-esters is a way to prepare 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones (**417**) (Equation (50)) ⟨92LA1271⟩.



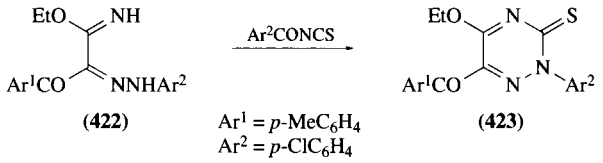
(416) (417) (50)

The cyclization of α-hydrazono oximes (**418**) with orthocarboxylates is an excellent way of preparing 1,2,4-triazine 4-oxides (**419**) ⟨84CHEC-I(3)369⟩. Using aldehydes instead of the ortho-carboxylates provides the 2,3-dihydro derivatives (**420**) ⟨75S794, 89LA1071⟩, which can be transformed by acetic anhydride into 1,2,4-triazines (**421**) (Scheme 78) ⟨89LA1071⟩.



Scheme 78

Reaction of an α-hydrazono-imidate (**422**) with an aroyl isothiocyanate afforded, in one instance, the 5-alkoxy-1,2,4-triazine-3(2*H*)-thione (**423**) (Equation (51)) ⟨92T9295⟩.

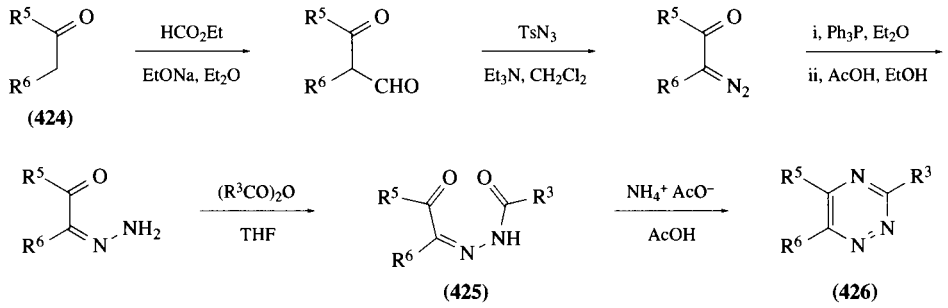


(422) $Ar^1 = p\text{-}MeC_6H_4$, $Ar^2 = p\text{-}ClC_6H_4$ (423) (51)

There are also a number of hetero-fused 1,2,4-triazine syntheses which involve this atom combination.

6.11.9.2.2 N-4 as the One-atom fragment

α-Acylhydrazono-ketones (**425**) react with ammonia to give 1,2,4-triazines (**426**) in good yields (Scheme 79) ⟨84CHEC-I(3)369, 92H(33)893, 92T651, 92T5227⟩. The sequence of Scheme 79 was used for the regioselective introduction of substituents in the 5- and/or 6-positions of the triazine ring.



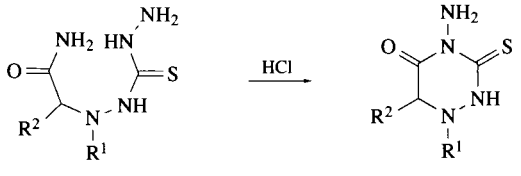
(424) (425) (426)

Scheme 79

6.11.9.3 [6 + 0] Atom Combinations

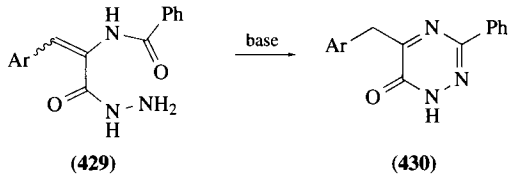
Most of the unimolecular cyclizations discussed in this section can be treated as syntheses of 1,2,4-triazines from more than one fragment.

Cyclization of 2-(thiocarbohydrazido)carboxylic acid amides (**427**) in hydrochloric acid under reflux gave 4-amino-3-thioxo-1,2,3,6-tetrahydro-1,2,4-triazin-5(4*H*)-ones (**428**) (Equation (52)) ⟨85JHC11⟩.



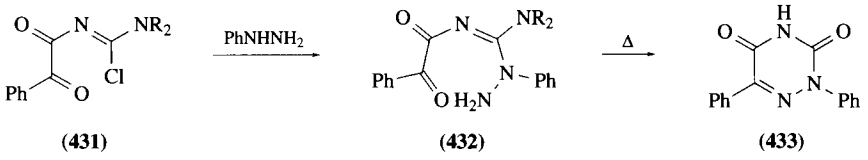
(427) (428) (52)

1,2,4-Triazin-6(1*H*)-ones (**430**) were obtained by cyclization of the α-acylaminocinnamoyl hydrazides (**429**) under basic conditions (Equation (53)). The structures of the products were deduced spectroscopically ⟨89H(29)2279⟩.



(429) (430) (53)

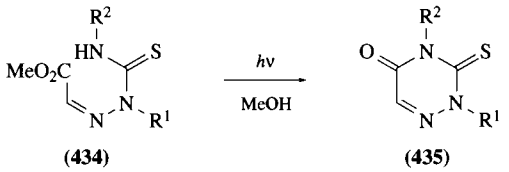
Reaction of the chloroformamidines (**431**) with phenylhydrazine afforded the aminoguanidines (**432**) which gave the 1,2,4-triazine-3,5-dione (**433**) on heating (Scheme 80) ⟨88LA141⟩.



(431) (432) (433)

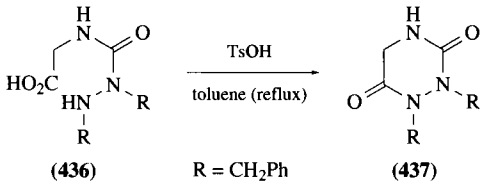
Scheme 80

Thiosemicarbazones (**434**) of methyl glyoxylate formed 3-thioxo-1,2,4-triazin-5-ones (**435**) by photochemical cyclization (254 nm, in methanol) (Equation (54)) ⟨92JHC233⟩.



(434) (435) (54)

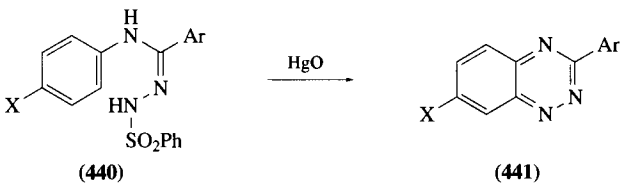
N-(1,2-Dibenzylhydrazinocarbonyl)glycine (**436**) was cyclized to 1,2-dibenzyltetrahydro-1,2,4-triazine-3,6-dione (**437**) by *p*-toluenesulfonic acid in refluxing toluene (Equation (55)) ⟨83JHC547⟩. Similarly, heating ethyl N^1-(2-nitrophenyl)-N^4-(ethoxalyl)-oxamidrazonate (**438**) in the presence of triethylamine in dimethylformamide gave ethyl 1-(2-nitrophenyl)-5,6-dioxo-1,4,5,6-tetrahydro-1,2,4-triazine-3-carboxylate (**439**) (63%) as the main product (Equation (56)) ⟨92JHC1161⟩.



(436) R = CH_2Ph (437) (55)

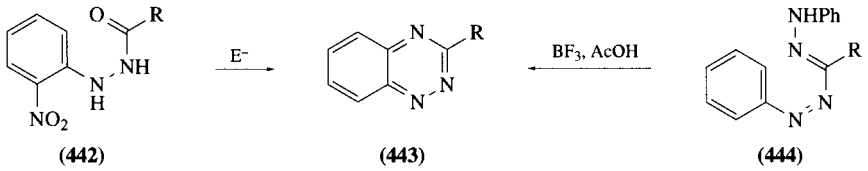
(438) Ar = *o*-$C_6H_4NO_2$ (439) (56)

3-Aryl-1,2,4-benzotriazines (**441**) were obtained in moderate to good yields by the mercury(II) oxide oxidation of N^1-benzenesulfonyl-N^4-arylbenzamidrazones (**440**) (Equation (57)) ⟨82BCJ859⟩.



(440) (441) (57)

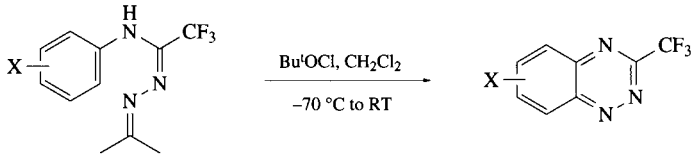
Electrochemical reduction of *o*-nitrophenylhydrazides (**442**) led to the isolation of 3-substituted 1,2,4-benzotriazines (**443**) ⟨92BSF343⟩. Good yields of 3-substituted 1,2,4-benzotriazines (**443**) were realized by a modification of the Bamberger synthesis. It was found that the use of BF_3/AcOH in place of concentrated sulfuric acid resulted in a more effective cyclization of the formazan precursor (**444**) (Scheme 81) ⟨82T1793⟩.



(**442**) (**443**) (**444**)

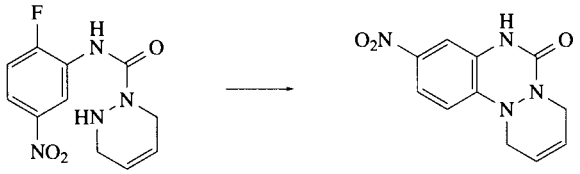
Scheme 81

N^1-Isopropylidene-N^3-aryl-amidrazones (**445**) cyclize on reaction with *t*-butyl hypochlorite in methylene chloride to give 1,2,4-benzotriazines (**446**) (Equation (58)). A mechanism for this reaction was proposed ⟨92JOC6014⟩.



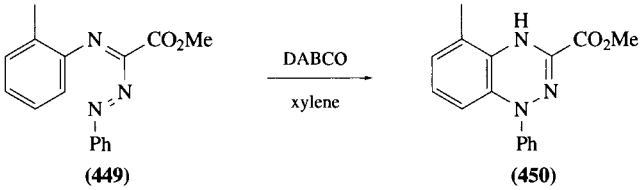
(**445**) (**446**) (58)

The semicarbazide derivative (**447**) with potassium carbonate in DMF at 90°C was smoothly cyclized to the fused benzotriazinone (**448**) (76% yield) (Equation (59)) ⟨93JHC45⟩.



(**447**) (**448**) (59)

When the azo-imine (**449**) was heated in refluxing xylene in the presence of a catalytic amount of DABCO methyl 5-methyl-1-phenyl-1,4-dihydro-1,2,4-benztriazine-3-carboxylate (**450**) was isolated as the main product (Equation (60)) ⟨86JHC1795⟩.

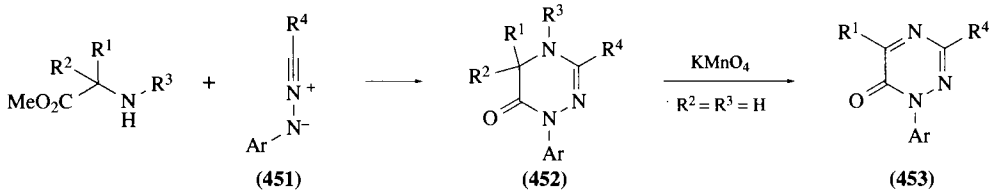


(**449**) (**450**) (60)

6.11.9.4 [3 + 3] Atom Combinations

Only a few reactions are known which can be treated as synthetic methods for 1,2,4-triazines from two three-atom fragments ⟨84CHEC-I(3)369⟩.

Reaction of nitrilimines (**451**) with α-aminoesters produces 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones (**452**), which can be oxidized ($KMnO_4$), if appropriately unsubstituted ($R^4 = R^2 = H$) to the corresponding 1,2,4-triazin-6(1*H*)-ones (**453**) (Scheme 82) ⟨91H(32)1879⟩.

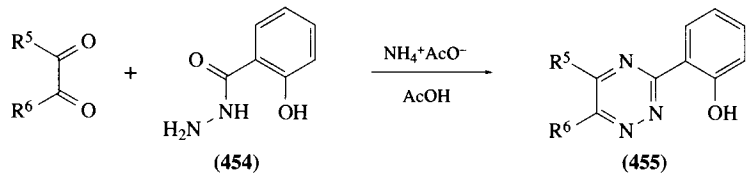


(451) (452) (453)

Scheme 82

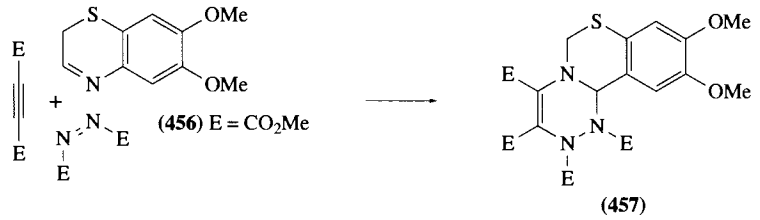
6.11.9.5 Synthesis from More than Two Fragments

In the previous sections a number of reactions were mentioned which could be treated as methods for the preparation of 1,2,4-triazines from more than two fragments since one of the starting materials is prepared from two or three compounds. A further example (a [3 + 2 + 1] combination; otherwise a [5 + 1]) is seen when salicylhydrazide (**454**), ammonium acetate, and a 1,2-dicarbonyl compound are heated at reflux in acetic acid; 3-(2′-hydroxyphenyl)-1,2,4-triazines (**455**) are formed (Equation (61) cf. (**425**) → (**426**) in Scheme 79) ⟨89JOC1245⟩.



(454) (455) (61)

A hetero-fused 1,2,4-triazine (**457**) has been prepared by reaction of 6,7-dimethoxy-2*H*-1,3-benzothiazine (**456**) with dimethyl acetylenedicarboxylate and dimethyl azodicarboxylate (Equation (62))—a [2 + 2 + 2] combination ⟨82H(19)489⟩.

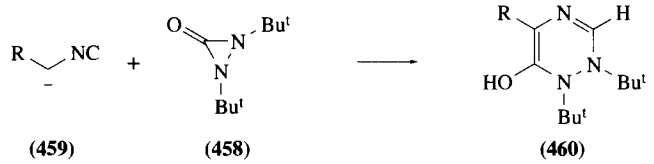


(456) E = CO_2Me (457) (62)

6.11.9.6 Synthesis by Transformation of Another Ring

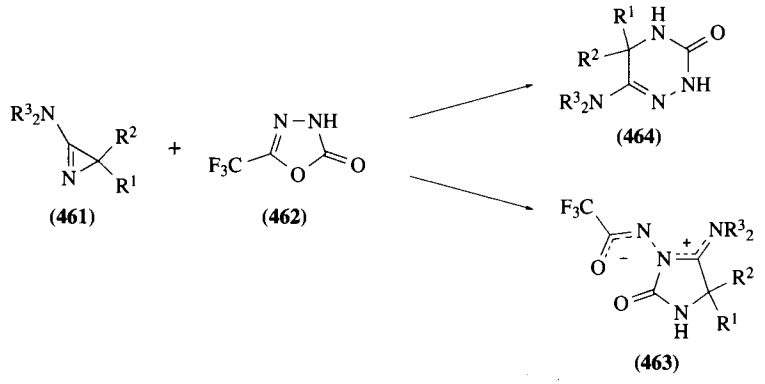
6.11.9.6.1 Synthesis from three-membered rings

Treatment of 1,2-di-*t*-butyldiaziridinone (**458**) with α-metallated isocyanides (**459**) at room temperature gives 5-substituted 1,2-di-*t*-butyl-1,2-dihydro-6-hydroxy-1,2,4-triazines (**460**) (Equation (63)) ⟨83S477⟩.



(459) (458) (460) (63)

The sterically crowded 3-amino-2*H*-aziridines (**461**) react with 5-trifluoromethyl-1,3,4-oxadiazol-2(3*H*)-one (**462**) to give 1 : 1 adducts of type (**463**); 6-amino-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones (**464**) are formed as minor products (5–31%) (Scheme 83) ⟨90HCA492⟩.

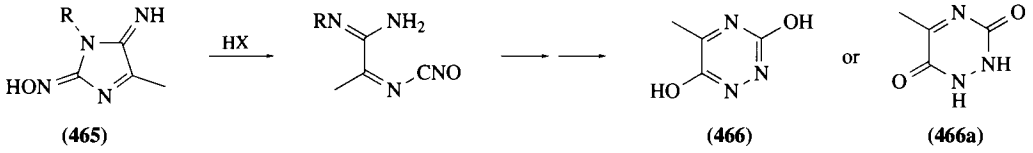


Scheme 83

6.11.9.6.2 *Synthesis from five-membered rings*

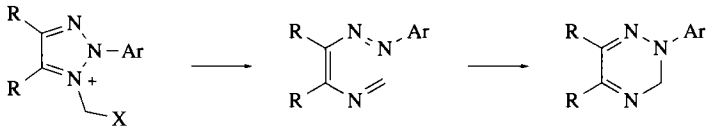
The reaction above (Scheme 83) is relevant also to this section.

Refluxing the oximino-imidazolimine (**465**) with concentrated hydrochloric or hydrobromic acid reportedly afforded the 3,6-dihydroxy-1,2,4-triazine (**466**) (probably the dione (**466a**)) (73%) (Scheme 84) ⟨84CPB2863⟩.



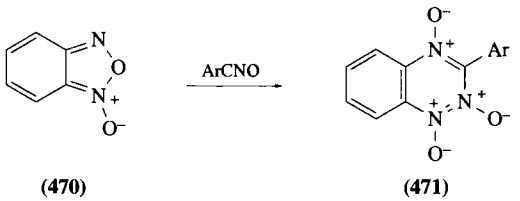
Scheme 84

Treatment of 1-methyl- or 1-(trimethylsilylmethyl)-1,2,3-triazolium salts (**467**) with ethoxide or cesium fluoride, respectively, gave substituted 2,3-dihydro-1,2,4-triazines (**469**) via 1,2,5-triazahexa-1,3,5-trienes (**468**) (Scheme 85) ⟨90CC882, 92JCS(P1)147⟩.



Scheme 85

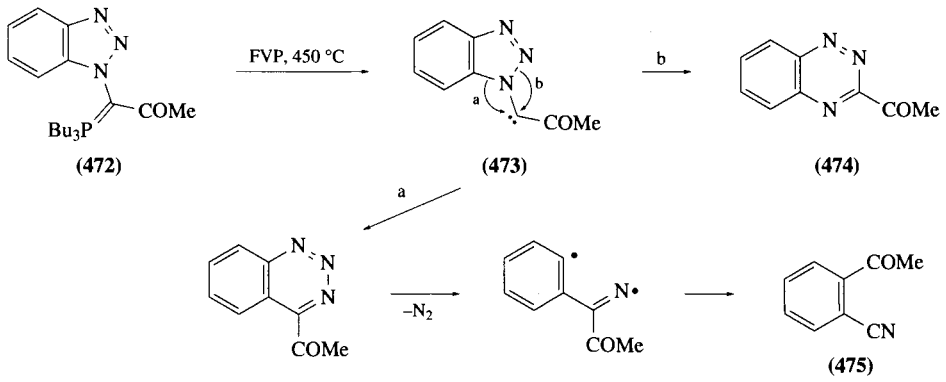
Reaction of benzofuroxan (**470**) with nitrile oxides in refluxing dichloromethane affords 1,2,4-benzotriazine 1,2,4-trioxides (**471**) (Equation (64)) ⟨89CC986⟩. The reaction has also been applied to the formation of 1,2,4-triazino[5,6-*b*]quinoxaline trioxides ⟨91S83⟩.



(64)

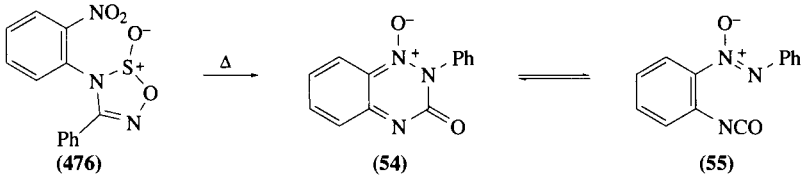
Flash vacuum pyrolysis of α-benzotriazolyl-β-oxo phosphorus ylids (**472**) results in 3-acetyl-1,2,4-benzotriazine (**474**) and *o*-cyanoacetophenone (**475**), products apparently derived from rearrange-

ment of the initially formed acetyl benzotriazolyl carbene (**473**). The formation of (**475**) involves a novel 1,3-acetyl migration process. (Scheme 86) ⟨93CC1517⟩.



Scheme 86

Careful thermolysis of 3-(*o*-nitrophenyl)-4-phenyl-1,2,3,5-oxathiadiazole 2-oxide (**476**) in toluene led to the isolation of 2-phenyl-1,2,4-benzotriazin-3(2*H*)-one 1-oxide (**54**). In solution a reversible equilibrium of (**54**) with the ring-opened o-isocyanato-azoxybenzene (**55**) is observed (Scheme 87) ⟨85JCS(P1)1471⟩.

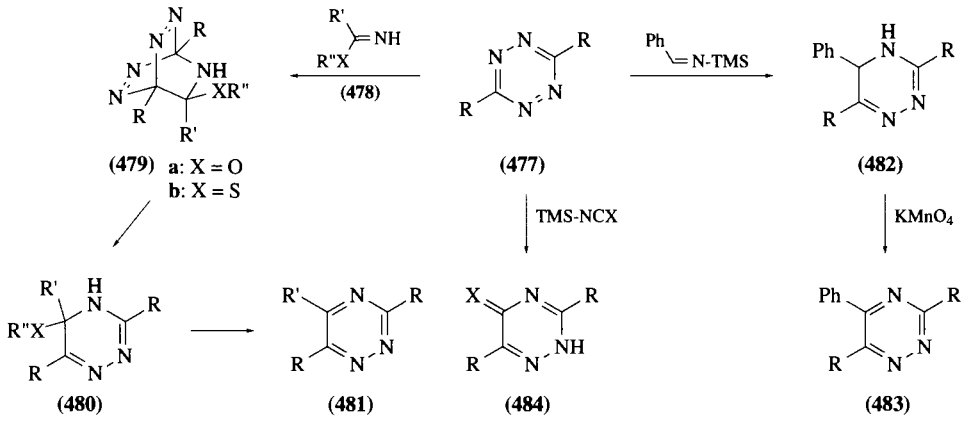


Scheme 87

6.11.9.6.3 Synthesis from six-membered rings

In most of the examples relevant to this section the six-membered starting materials are 1,2,4,5-tetrazines, reacting with dienophiles with CN double or triple bonds.

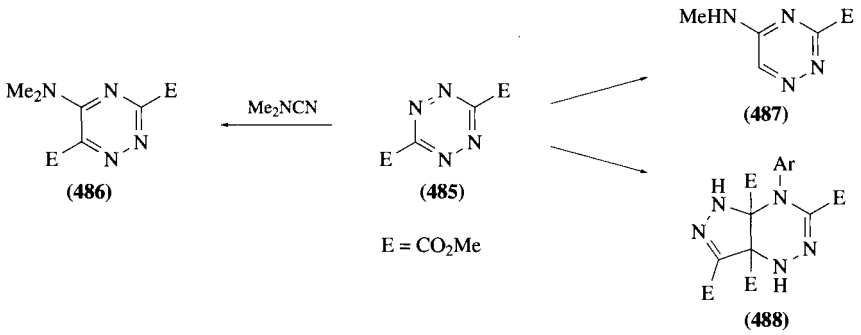
As early as 1969 Roffey and Verge reported the reaction of 1,2,4,5-tetrazines (**477**) with imidates (**478a**) to afford 1,2,4-triazines (**481**) by a [4 + 2]cycloaddition reaction via the bicyclic intermediates (**479**) and the dihydro-1,2,4-triazines (**480**) ⟨69JHC497⟩. Later studies showed that much better yields could be obtained using thioimidates (**478b**) as the dienophiles (Scheme 88) ⟨83JOC621, 83TL4511, 85JA5745⟩.



Scheme 88

N-(Trimethylsilyl)benzaldimine reacts with tetrazines (**477**) to give 2,5-dihydro-1,2,4-triazines (**482**), which can be oxidized by potassium permanganate to the triazines (**483**) ⟨89H(29)1379⟩. The formation of 1,2,4-triazin-5-ones (**484a**) and 5-thiones (**484b**) was observed when 3,6-disubstituted 1,2,4,5-tetrazines (**477**) were treated with trimethylsilyl isocyanate and isothiocyanate in DMF (Scheme 88) ⟨88CL817⟩.

Dimethylcyanamide reacts with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**485**) to give dimethyl 5-dimethylamino-1,2,4-triazine-3,6-dicarboxylate (**486**) ⟨90JOC3257⟩. The diester (**485**) with dimethylamine yields methyl 5-methylamino-1,2,4-triazine-3-carboxylate (**487**) and its reaction with arylamines gives pyrazolo[3,4-*e*]1,2,4-triazine derivatives (**488**). (Scheme 89). Mechanisms for the formation of (**487**) and (**488**) were suggested ⟨89CB1381⟩.

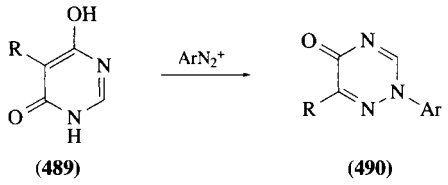


Scheme 89

N-Substituted cyanamides cycloadd exclusively across N-2/C-5 of the 1,2,4-triazine nucleus of (**158**), yielding 1,3,5-triazines as the main products, via cycloaddition and elimination of trifluoroacetonitrile, but 1,2,4-triazines are also formed, by loss of methyl thiocyanate (Scheme 32) ⟨89CB1381⟩.

Intramolecular cycloaddition reactions of 1,2,4,5-tetrazines with a cyano group are also reported, giving rise to condensed 1,2,4-triazines ⟨89CB2177⟩. The cycloadditions of 1,2,4,5-tetrazines are considered in detail in Chapter 6.24.

The reaction of arenediazonium salts with 5-methyl- and 5-ethylpyrimidine-4,6-diones (**489**) gives 6-alkyl-2-aryl-1,2,4-triazin-5(2*H*)-ones (**490**) (Equation (65)) ⟨89TL3719⟩.



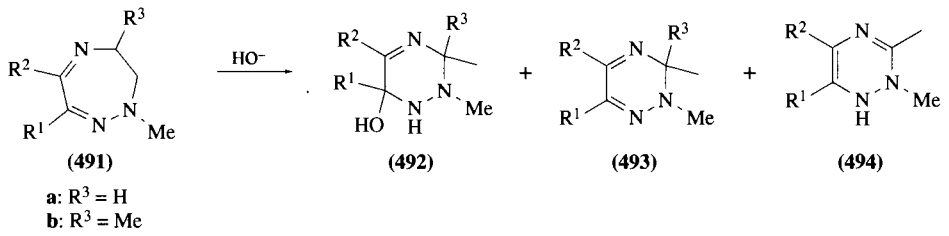
(65)

6.11.9.6.4 Synthesis from seven-membered rings

6,7-Dihydro-1-methyl-1*H*-1,2,5-triazepines (**491a**) in ethanolic sodium hydroxide were converted into one or two compounds of the following types, in which the extra methyl group is formed from the ring C-7-methylene: 6-hydroxy-1,2,3,6-tetrahydro-1,2,4-triazines (**492**), 2,3-dihydro-1,2,4-triazines (**493**), and 1,2-dihydro-1,2,4-triazines (**494**). It was shown that (**492**) are precursors to (**493**). The 1,6-dimethyl analogs (**491b**) were converted simply into the corresponding 2,3,3-trimethyl-2,3-dihydro-1,2,4-triazines (**493b**). Mechanisms for these reactions were suggested (Scheme 90) ⟨92JCS(P1)3233⟩.

6.11.10 SYNTHESIS OF SPECIAL CLASSES

The preceding Section (6.11.9) summarized the available synthetic methods to 1,2,4-triazines, emphasizing the developments of the 12 years since 1984. Alkyl, aryl, amino, oxo, thioxo, carboxy,



(491)
a: R^3 = H
b: R^3 = Me

(492) (493) (494)

Scheme 90

and other substituted derivatives are normally prepared by ring synthesis, although substitution of other functional groups is frequently applied to the synthesis of amino (via chloro or thioxo) and thioxo (via oxo) derivatives. Halo derivatives are almost invariably obtained by substitution of oxo groups. These substitution reactions are covered in Sections 6.11.5.7 and 6.11.6.2. For the synthesis of specific compounds the earlier reviews, in particular ⟨56HC(10)44, 78HC(33)189⟩, should be consulted.

In this section we bring together information on the synthesis of some special classes of 1,2,4-triazine derivatives which do not fall into any particular earlier section by virtue of the methods applied to their preparations.

6.11.10.1 *N*-Oxides

The two main approaches to *N*-oxides of 1,2,4-triazines are (a) *N*-oxidation (Section 6.11.5.4), and (b) ring synthesis by closure to an oxime group (Scheme 78). See also Equation (25). Other methods can be applied to 1,2,4-benzotriazine oxides, including the rather spectacular trioxide synthesis (Equation (60)).

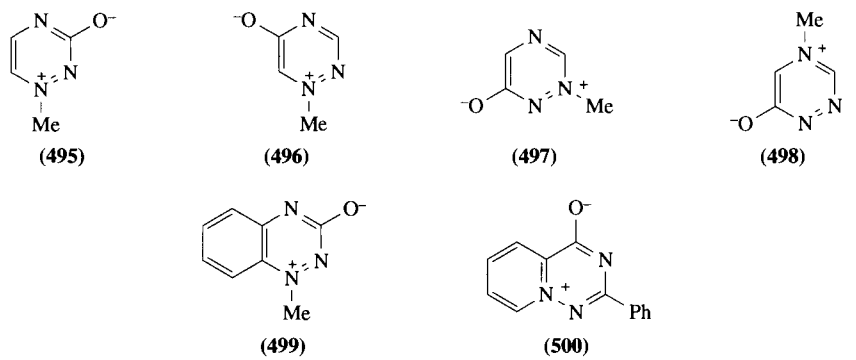
6.11.10.2 *N*-Amino Compounds and *N*-Imines

The best-known *N*-amino derivatives are the 4-amino-1,2,4-triazin-3-ones and -5-ones. These are prepared by standard ring closures in which the N—N bond is already present (see Section 6.11.9.1). *N*-Amination provides an entry to the less well-known 2-amino-1,2,4-triazin-5-ones (Scheme 38).

Few *N*-imines have been investigated; one example (**11**) has been examined by x-ray crystallography.

6.11.10.3 Mesomeric Betaines

There are many possibilities for mesomeric betaine formation in the 1,2,4-triazine series, illustrated by the *N*-methyl-oxo compounds in structures (**495**)–(**498**), and in the benzotriazine series by (**499**). These compounds seem not to have been investigated, however, and the closest example we have found is the pyrido-fused system (**500**) ⟨77JOC443⟩. See also Section 6.11.9.1.4.

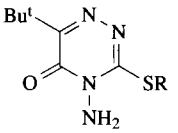


(495) (496) (497) (498)

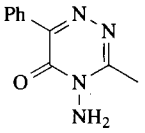
(499) (500)

6.11.11 IMPORTANT COMPOUNDS AND APPLICATIONS

1,2,4-Triazines are biologically very active compounds. Many have been tested for use in agrochemistry or medicine. 1,2,4-Triazines used as agrochemicals are 4-amino-6-*t*-butyl-3-methylthio-1,2,4-triazin-5(4*H*)-one (**501a**) (Sencor or Metribuzin), 4-amino-6-*t*-butyl-3-ethylthio-1,2,4-triazin-5(4*H*)-one (**501b**) (Ethyl metribuzin or SMY 1500) and 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one (**502**) (Goltix or Metamitron). 2-Cyclopropylmethyl-5,6-bis(4-methoxyphenyl)-1,2,4-triazin-3(2*H*)-one (**9**) (Diazatrifone) shows algicidal properties.



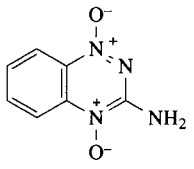
(**501**)
a: R = Me
b: R = Et



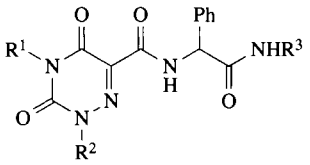
(**502**)

A number of other 1,2,4-triazines have been suggested for use as agrochemicals but apparently they are not yet used or only to a limited extent.

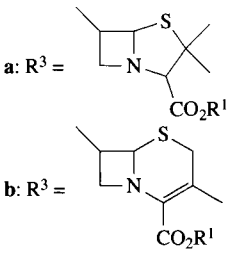
1,2,4-Triazines used as drugs are 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (**10**) (trade names Lamotrigine, LTG, BW430C or 430C78), 3-amino-1,2,4-benzotriazine 1,4-dioxide (**503**) (SR4233) and the penicillin and cephalosporin derivatives of types (**504a**) and (**504b**), respectively.



(**503**)



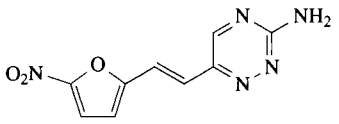
(**504**)



a: R^3 =

b: R^3 =

3-Amino-6-[(5-nitro-2-furyl)vinyl]-1,2,4-triazine (**505**) (Panfuran) shows antibacterial and tuberculostatic activity.



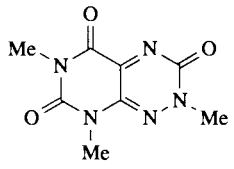
(**505**)

Since 1,2,4-triazines can be considered as azapyrimidines, a great number of 6-azapyrimidine nucleotides and nucleosides have been prepared and their properties intensively studied. Most significant amongst these are 6-azauracil (**1**), 6-azauridine (**2**), 6-azathymine (**3**), 6-azacytosine (**4**) and 6-azacytidine (**5**).

Many other 1,2,4-triazines have been tested and biological activity claimed, but there seems to be no broad application for another 1,2,4-triazine in medicine.

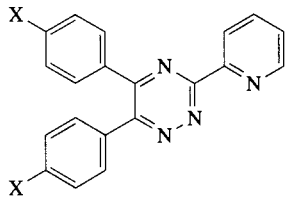
A number of pyrimido[5,4-*e*]-1,2,4-triazine derivatives (fervenulin or planomycin (**6**), toxoflavin or xanthothricin, reumycin, MSD 92 (**506**)) have powerful antibiotic properties, but owing to their toxicity they have not found use in medicine.

1,2,4-Triazines with appropriate substituents form stable complexes with metal ions and can therefore be used for their determination. 5,6-Diphenyl-3-(2-pyridyl)-1,2,4-triazine, or PDT (**507a**) and its 4′,4″-disulfonate FerroZine (**507b**) are mainly used for the determination of iron(II) ions,

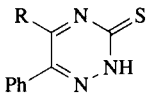


(506)

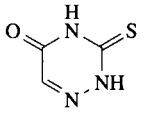
but cobalt(II), nickel(II), zinc(II), ruthenium(II), silver(I), and copper(I) ions can also be determined. Disodium 5,6-di-(2-furyl)-3-(2-pyridyl)-1,2,4-triazine-5′,5″-disulfonate (**35**) (Ferene S) is even more effective than FerroZine. 6-Phenyl- (**508a**) and 5,6-diphenyl-1,2,4-triazine-3(2H)-thione (**508b**; DDTT) are used for the determination of thallium and palladium ions, and osmium can be analyzed using 3-thioxo-3,4-dihydro-1,2,4-triazin-5-one (**509**).



(507)
a: X = H
b: X = SO_3Na



(508)
a: R = H
b: R = Ph



(509)

1,2,4-Triazines are reactive dienes in Diels–Alder reactions with inverse electron demand. An account of their use in the synthesis of pyridines and pyrimidines was presented in Section 6.11.5.11. The most reactive compounds in these reactions are trimethyl 1,2,4-triazine-3,5,6-tricarboxylate and 3,5,6-tris-(trifluoromethyl)-1,2,4-triazine, both of which form pyridines on reaction with enamines. Reaction of 1,2,4-triazines with acetylenes can afford pyrimidines or pyridines. Wide use has been made of both intermolecular and intramolecular cycloadditions in heterocyclic synthesis. Figure 3 is a chart showing the various fused ring systems which have been prepared by this method.

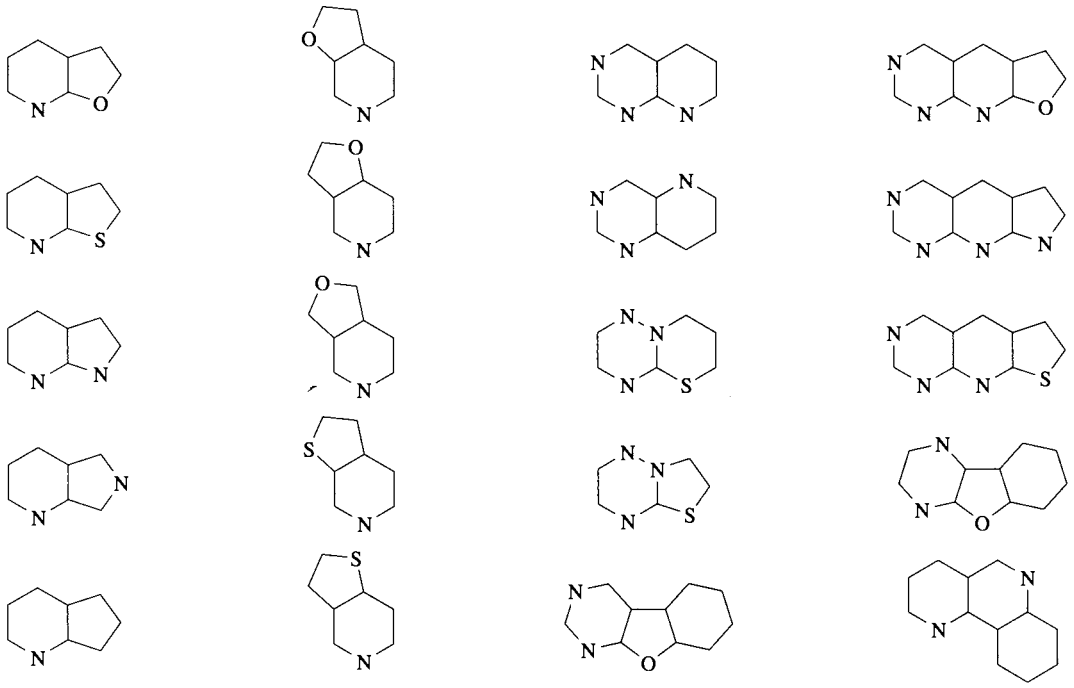


Figure 3 Ring systems from cycloaddition reactions of 1,2,4-triazines.

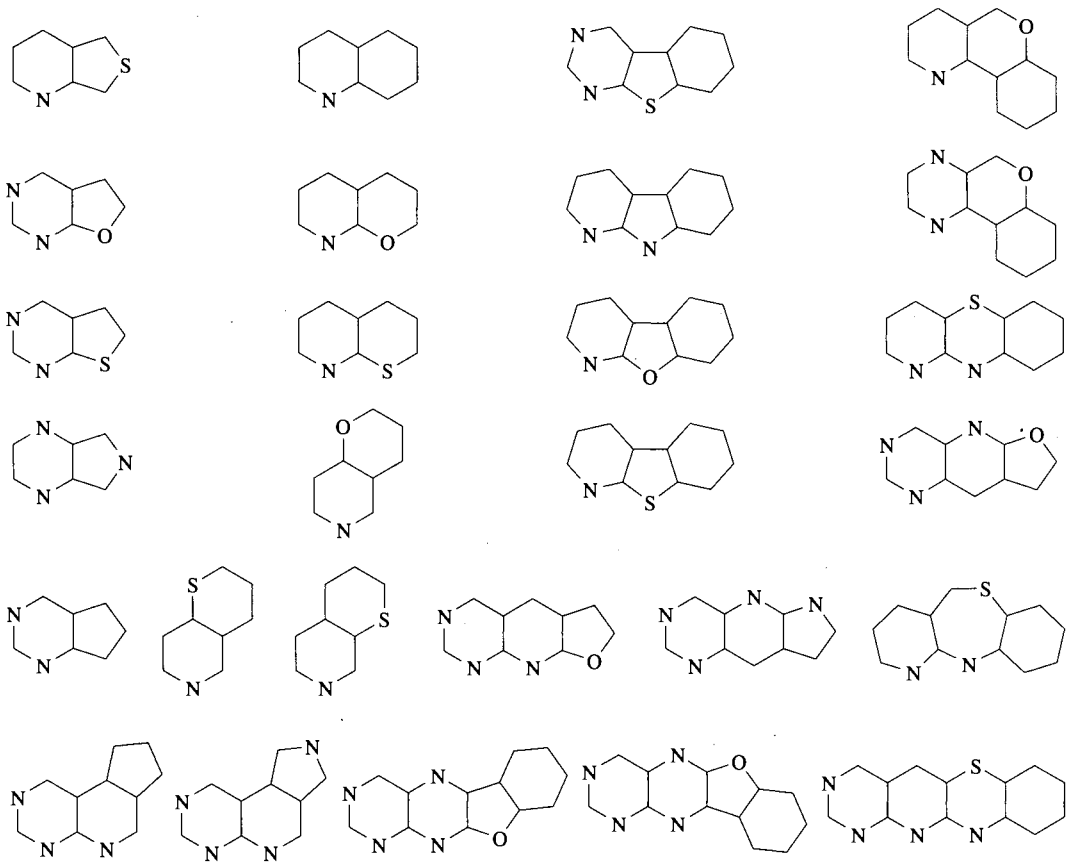


Figure 3 (continued)

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6.12
1,3,5-Triazines

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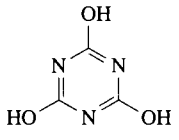
6.12.1 INTRODUCTION

1,3,5-Triazines, formerly symmetric or *s*-triazines, have been known for almost 200 years, and are, like many heterocyclic compounds, often referred to by trivial names. Common trivial names used include cyanuric acid (2,4,6-trihydroxy-1,3,5-triazine (**1**)), cyanurates (2,4,6-trialkoxy-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**)), and melamine (2,4,6-triamino-1,3,5-triazine (**5**)). Heterocycles are numbered, by convention, to begin at a heteroatom, hence 1,3,5-triazine (**6**).

In 1793, Scheele, naturally unaware of the structure, first mentioned cyanuric acid. 1,3,5-Triazine was first isolated in 1895 by Nef ⟨1895LA(287)333⟩. An incorrect molecular weight determination led Nef to assign the wrong structure; it was regarded as a dimer of hydrocyanic acid. This incorrect assignment was accepted by other workers, but in 1954 a correct cryoscopic molecular weight determination established the structure of (**6**) ⟨54JA632⟩.

The chemistry of 1,3,5-triazines, cyanuric acid, and cyanuric halides has been reviewed by Bann and Miller ⟨58CRV131⟩, by Matsui ⟨59YGK528⟩, and extensively by Smolin and Rapoport ⟨B-59MI 612-01⟩. Syntheses of 1,3,5-triazine and substituted 1,3,5-triazines have been reviewed by Bredereck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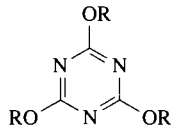
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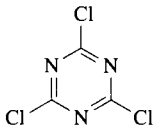
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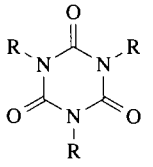
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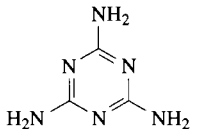
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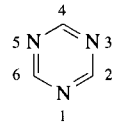

(6)

et al. ⟨63AG(E)655⟩. Syntheses with 1,3,5-triazine have been reviewed by Grundmann ⟨63AG(E)309⟩, and another review includes the molecular structure of 1,3,5-triazine and its derivatives by Finkel'shtein and Boitsov, who determined interatomic distances, vibrational and electronic spectra ⟨62RCR712⟩. 1,3,5-Triazines have also been reviewed by Shepherd and Fedrick ⟨65AHC(4)296⟩, Forrest ⟨B-71MI 612-01⟩, and extensively in the comprehensive review by Quirke in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(3)457⟩. A short review has since appeared by Watanabe ⟨83MI 612-01⟩, and Alekseeva and Yakhontov have reported on the reactions of 1,3,5-triazines with nucleophiles ⟨90UK888⟩.

Several chapters in *Advances in Heterocyclic Chemistry* deal with aspects of 1,3,5-triazine chemistry: reactions of ring nitrogen atoms with electrophiles ⟨88AHC(43)127⟩; dihydro-1,3,5-triazines ⟨85AHC(38)91⟩; halogenation of 1,3,5-triazines ⟨93AHC(58)323⟩; conformation of hexahydro-1,3,5-triazines ⟨84AHC(36)160⟩.

6.12.2 THEORETICAL METHODS

Ab initio methods are applied to *N*-heterocycles to determine useful models that give calculated results which correlate with known experimental data. A molecular orbital based molecular mechanics approach, the Allinger MM2 program, has been extended to calculate conjugated systems which include *N*-heteroatoms. A C—N bond length of 1.356 Å and CNC bond angle of 113.8° were obtained for 1,3,5-triazine ⟨85TL2403⟩. MNDO 4-31G calculations on a series of *N*-heterocycles gave $\Delta H_f^\circ = 40.8$ kcal mol^{-1}, which is much smaller than the experimental value of 54.0 kcal mol^{-1} for 1,3,5-triazine ⟨85JOC4894⟩. A more realistic result was derived from the molecular orbital based molecular mechanics (MOMM) method which gave $\Delta H_f^\circ = 53.82$ kcal mol^{-1} for 1,3,5-triazine ⟨88MI 612-01⟩.

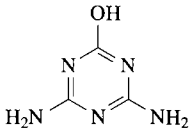
The molecular structure of 1,3,5-triazine in the gas phase was determined from electron diffraction, infrared and Raman data and 4-21G force field calculations: C—N bond length = 1.338 Å, C—H = 1.106 Å, CNC bond angle = 113.9°, NCN = 126.1°, and HCN = 116.9° ⟨86JST(147)321⟩. The geometries of 1,3,5-triazine and its protonated form, along with other azines, have been fully optimized at the STO-3G, 3-21G and 6-31G levels ⟨87JST(35)135⟩.

Wiberg *et al.* carried out a theoretical study of π-electron delocalization. Delocalization energies, resonance energies, enthalpies of formation, dissociation energies, and structural parameters were studied via 6-31G* and 6-31G** basis sets. The energies of reduction and hydrogen transfer were also considered. The calculated energies for the addition of one equivalent of hydrogen suggest that 1,3,5-triazine has lower resonance energy than benzene, pyridine, pyrazine, and pyrimidine, which have essentially the same resonance energy ⟨89JA4178⟩.

Ab initio studies on the structural effects of fluorine substitution in 1,3,5-triazine have been reported ⟨84JHC1801⟩. An *ab initio* SCF computational approach was used to study 1,3,5-triazine and its mononitro derivative ⟨89JST(56)95⟩. Creuzet and Langlet employed *ab initio* and semiempirical calculations in a comparative study of the structural parameters for 1,3,5-triazine and amino derivatives ⟨93CPL(208)511⟩. 6-31G and D95 basis sets were used to compare results from simple SCF, addition of polarization functions, and MP2 treatment of structural parameter determinations. The results were compared with AM1 calculations, 6-31G and 6-31G**, at the SCF and SCF/MIP levels and showed that the introduction of amino groups at the 2 and 4 positions did not distort the ring. AM1 revealed that 2- and 4-amino-substituents affected the bond lengths but the bond angle alternation (CNC < NCN) remained. Bond lengths and angles of 1,3,5-triazine, 2,4-diamino- and

2,4-bis(methylamino)-1,3,5-triazine and atrazine (i.e., 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine) were compared with experimental values from x-ray data.

Pittman and co-workers investigated the structure and properties of 2,4-diamino-6-hydroxy-1,3,5-triazine, 2,4,6-triamino-1,3,5-triazine, and 2,4-diamino-1,3,5-triazine by *ab initio* calculations at the SCF level with several different basis sets. The hydroxy tautomer of 4,6-diamino-2-hydroxy-1,3,5-triazine (**7**) was predicted to be 4.82 kcal mol^{-1} more stable than its 1*H*-carbonyl tautomer (**8**), and 23.8 kcal mol^{-1} more stable than the 4*H*-tautomer (**9**) in the gas phase. Protonation was also studied. 2,4-Diamino-6-hydroxy-1,3,5-triazine is protonated only at the three ring nitrogens. The hydroxy group is more acidic than that of phenol ⟨93JOC3085⟩.



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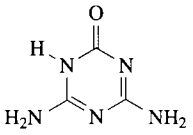

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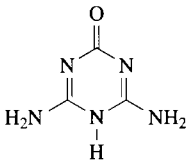


(9)

Optimized geometries, ionization potentials, and total energies for basis sets 6-31G**, 4-21G*, and STO-3G for each compound are reported. Results for 2,4-diamino-1,3,5-triazine can be compared with those of Creuzet at the 6-31G** levels. Creuzet's bond lengths are longer and AM1 bond lengths are always found to be higher than experimental results.

A CNDO/2 method has been applied to calculate structural parameters of 5-azauracil ⟨82ACH351⟩. *Ab initio* and x-ray deformation densities have been compared in cyanuryl chloride; the basis sets examined range over STO-3G, 3-21G, 4-31G, 6-31G, and 6-31G*. Good agreements were found when a polarization basis set was employed in the calculation of the electronic structure ⟨89JST(202)111⟩.

The conformations of 1,3,5-trinitrohexahydro-1,3,5-triazine were determined by SCF/4-21G *ab initio* gradient optimization. The conformation *aaa* was identified as the most stable, in agreement with gas phase and solution studies of the compound ⟨91JST(251)219⟩. Hexahydro-1,3,5-triazines, the parent compound and its derivatives 1,3,5-trisubstituted by Me, Et, Pr^i, and Bu^n, were studied by the Allinger MM2 method. 1,3,5-Tri-*n*-butyl-1,3,5-hexahydrotriazine, due to steric bulk, has the *aae* form as the most stable conformer, but in agreement with experiment the *aee* form still predominates in the equilibrium mixture ⟨89JST(195)89⟩.

Ab initio calculations of the electronic spectra of 1,3,5-triazine have been determined via the complete active space method (CASSCF). This describes the major features in the electronic structure of the excited state of 1,3,5-triazine ⟨92JPC9204⟩. Nowack and co-workers undertook a theoretical study of 5-azauracil ⟨91SA(A)595⟩. The predicted IR spectrum at the HF/6-31G** level gave an accurate reproduction of the experimental spectrum; on the other hand *ab initio* HF/3-21G calculations gave limited correlation with the observed data. Osamura *et al.* undertook a theoretical study of the photo-decomposition of 1,3,5-triazine ⟨87JA1370⟩. The reaction mechanism was examined by the *ab initio* molecular orbital method with STO-3G, 3-21G, 6-31G, and 6-31G** basis sets. The decomposition to three equivalent HCN molecules is a symmetry-allowed reaction in the ground state, and the symmetric transition state is a true one. The activation energy was estimated to be about 100 kcal mol^{-1} ⟨91SA(A)595⟩.

6.12.3 EXPERIMENTAL STRUCTURAL METHODS

6.12.3.1 X-ray Analysis

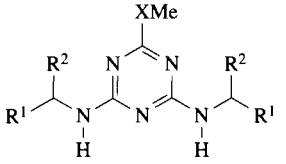
Several x-ray crystallographic studies have been used to obtain the molecular dimensions of 1,3,5-triazines. The C—N bond length was reported as 1.319 Å with CNC and NCN bond angles of 113.2° and 126.8° respectively. The presence of substituents has little effect on the bond length or bond angles ⟨72JCS(P2)642⟩.

Cyanuric acid has C—N, C—O, and N—H bond lengths of 1.37 Å, 1.22 Å, and 0.9 Å respectively. The CNC and NCN bond angles were reported to be 124.6° and 115.4°. X-ray analysis confirms the predominance of the keto form as a hydrogen bonded dimer with hydrogen bond length of 2.77–2.80 Å.

Cyanuryl chloride crystallizes as slippery, colorless plates. A layered structural lattice of the π-

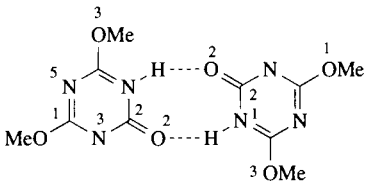
stacked planar array with an interplanar separation of 3.26 Å was found by x-ray ⟨92TL4707⟩. The triazine ring is planar and equilateral (bond length is 1.325 Å). The triazine is not a regular hexagon, as the mean NCN bond angle is 127.4° and CNC angle is only 112.7°; this distortion is similar to that found in 1,3,5-triazine itself ⟨55AX224⟩.

Comparative geometrical data for four triazine herbicides ((**10**), (**11**), (**12**), and (**13**)) have been determined by x-ray analysis. Within the triazine ring all C=N bond distances are similar (1.339 Å) and as usual NCN bond angles are large (126.8°) and CNC bond angles are small (113.1°). C(1)OMe bond angles (117.7°) and C(1)SMe bond angles (102.7°) are consistent with ether and thioether systems ⟨85AX(C)938⟩.



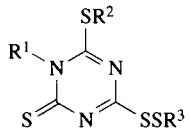
(**10**) Prometryn, $R^2 = R^1 = Me$, X = S
(**11**) Simetryne, $R^2 = H$, $R^1 = Me$, X = S
(**12**) Simetone, $R^2 = H$, $R^1 = Me$, X = O
(**13**) Prometone, $R^2 = R^1 = Me$, X = O

4,6-Dimethoxy-1,3,5-triazin-2(1*H*)-one exists in the keto form and forms a dimer (**14**) in the crystalline state via two N—H···O (keto) hydrogen bonds with N—O distances of 2.82 Å and 2.79 Å. The *p*-atomic orbitals at the OMe and N(1) atoms overlap with the π-systems of the C=O and C=N bonds as evidenced by shortened O(1)—C(4), O(3)—C(6), N(1)—C(6), and N(1)—C(2) bonds to 1.33 Å, 1.32 Å, 1.35 Å, and 1.38 Å respectively, with coplanarity of the methoxy groups with the 1,3,5-triazine ring ⟨87AX(C)149⟩.



(**14**)

Various reaction products have been identified by x-ray analysis when spectroscopic methods gave insufficient structural data. 1,2-Dihydro-4-methyldithio-2-thioxo-1,3,5-triazines (**15**) were obtained from reaction of isothiocyanates with sulfenyl thiocyanate. Structural assignments were based on spectral data and confirmed by x-ray analysis ⟨86JOC4043⟩.

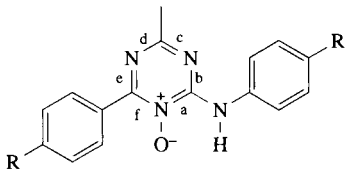


(**15**)

Reaction of amidoximes with ethyl orthoacetate and acid catalyst gave the 1,3,5-triazine-*N*-oxides (**16**), via a Beckmann rearrangement. X-ray analysis confirmed the structure to be an *N*-oxide ⟨93JHC497⟩.

Tetraphenyldihydro-1,3,5-triazines can exist in the 2,3-dihydro or the 2,5-dihydro form (see Section 6.12.4.5). X-ray analysis has found the hydrogen atom bound to N(3) and not N(5); therefore tetraphenyldihydro-1,3,5-triazine was shown to exist solely in the 1,2-dihydro form ⟨88BCJ2487, 89BCJ3171⟩. Unusual enol acylenamine tautomerism was observed for hydroxyalkenyl-1,3,5-triazines (see Section 6.12.4.5, compounds (**49**), (**50**), and (**51**)). X-ray examination revealed a preferred hexahydro-1,3,5-triazine tautomeric structure for (**51**) with three acylenediamine units. All substituents have the same orientation, as in (**51**). Three strong intramolecular hydrogen bonds between N—H and aldehyde oxygen are present.

X-ray crystallographic studies have shown *eaa* chair conformations are preferred for 1,3,5-triarylhexahydro-1,3,5-triazines (see Section 6.12.4.4) ⟨89JCS(P2)583⟩.



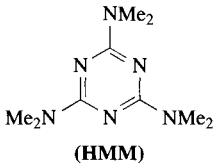
(16)

Bond lengths: (Å) a = 1.398, b = 1.323, c = 1.337, d = 1.326, e = 1.338, f = 1.358, (N—O) = 1.316. Bond angles: (°) ab = 121.7, bc = 116.2, cd = 125.6, de = 117.6, ef = 120.8, fa = 117.6.

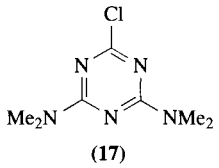
6.12.3.2 NMR Spectra

A sharply defined line for the proton signal, not broadened by nitrogen quadrupolar relaxation, is seen for 1,3,5-triazine at 9.18 ppm, which is well downfield of the chemical shift of the benzene proton. The presence of electron-releasing substituents gives slight upfield shifts for ring protons of substituted 1,3,5-triazines. Chemical shifts of 8.8 ppm, 8.51 ppm, and 8.19 ppm are seen for 2,4-dimethyl-1,3,5-triazine, 2,4-dimethoxy-1,3,5-triazine, and 2,4-di(diethylamino)-1,3,5-triazine respectively as the electron release of the substituents increases from methyl to methoxy to dimethylamino ⟨65BSB119⟩. Isocyanurates show NH protons with shifts in the range 11.0–13.5 ppm ⟨76TH 612-01, 81CB2075⟩.

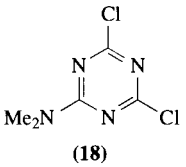
^{1}H NMR spectra of 1,3,5-triazines are otherwise straightforward. The chemical shifts of substituents appear as expected and are readily assigned from known published data. In this context aspects of ^{1}H NMR applied to 1,3,5-triazines are discussed rather than listings of chemical shifts of substituents attached to 1,3,5-triazines. An investigation of the possible impurities in hexamethylmelamine (2,4,6-tris(dimethylamino)-1,3,5-triazine, HMM) involved a ^{1}H NMR analysis of HMM, cyanuric acid (**1**), and several potential impurities, namely 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (**17**); 4,6-dichloro-2-dimethylamino-1,3,5-triazine (**18**); 4,6-bis(dimethylamino)-1,3,5-triazin-2(1*H*)-one (**19**); 4-chloro-6-dimethylamino-1,3,5-triazine-2(1*H*)-one (**20**), and 6-dimethylamino-1,3,5-triazine-2,4-(1*H*,3*H*)-dione (**21**). The spectra of these compounds gave the dimethylamino protons as singlets at 3.09–3.17 ppm. NH protons of the oxotriazines ((**1**), (**19**), and (**21**)) appeared as broad singlets (10.5–11.4 ppm); (**20**) shows no NH peak (amide protons are usually seen at 6–8 ppm). The downfield shifts and broad peaks of (**1**), (**19**), and (**21**) are due to intermolecular hydrogen bonding, confirmed by upfield shifts and sharpened NH peaks on dilution. Based on substituent-induced chemical shifts, the NH protons of (**21**) were assigned as the signals at 10.88 ppm for N(3)H adjacent to two carbonyls and at 10.55 ppm for N(1)H adjacent to a carbonyl and a C=N group. Cyanuric acid (**1**) and (**20**) show broad singlets at 11.5 ppm and 11.33 ppm respectively. Compound (**19**) does not show an NH peak, probably due to an exchange process. This information along with other analytical data was used to identify impurities in HMM prepared from cyanuryl chloride and dimethylamine ⟨92JHC979⟩.



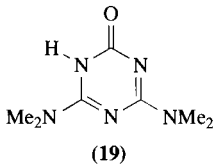
(HMM)



(17)



(18)



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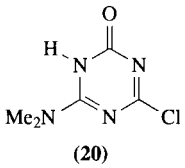
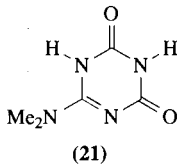


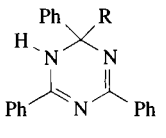
(20)



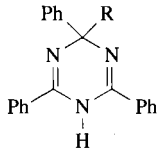
(21)

^{1}H NMR of the dihydrotriazines (**22**) has been used to examine the position of the NH protons and to establish the existence of the two possible 1,2-dihydro (**22a**) and 1,4-dihydro (**22b**) tautomeric forms. Spectra at 25 °C gave broad NH signals at 6.15 ppm and phenyl protons at 6.7–8.5 ppm. At −40 °C, the NH signal shifted to 6.37 ppm with another signal at 7.99 ppm (hidden in the aromatic protons signal at 25 °C). The signals at 6.37 ppm and 7.99 ppm both exchanged with D_2O, indicative

of two kinds of NH protons. The signal at 6.37 ppm was assigned to the 1,2-dihydro form (**22a**) and that at 7.99 ppm to the 1,4-dihydro form (**22b**). Relative concentration of the two kinds of NH proton was estimated to be ca. 2 : 1 in favor of the 1,2-dihydro form. Different NH protons in (**23**) could not be found but signals from two ethyl groups were observed. The 1,2-dihydro form was assigned peaks at 2.20 ppm (CH_2) and 0.97 ppm (Me), and the 1,4-dihydro form assigned as 2.17 ppm (CH_2) and 1.01 ppm (Me). The concentration ratio of the two kinds of ethyl signals in (**23**) was in the ratio ca. 5 : 3 in favor of (**23a**) (see Section 6.12.4.5) ⟨85JCS(P2)887⟩.

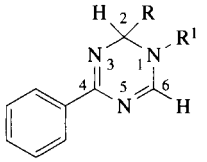


(**22a**) R = Ph
(**23a**) R = Et



(**22b**) R = Ph
(**23b**) R = Et

1,2-Dihydro-1,3,5-triazines (**24**) have been prepared (the 1,4-dihydro form is not seen) and showed transannular coupling of the C(2) and C(6) protons. When H(2) was replaced by a methyl group H(6) showed as a singlet at 7.78 ppm ⟨86CB3737⟩.



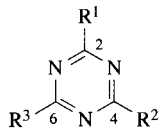
(**24**)

R	R^1	*H(2) ppm*	*H(6) ppm*	*J (Hz)*
Me	Bu^t	5.34 (dq)	7.66 (d)	2
C_6H_5	Pr^i	6.14 (d)	7.78 (d)	1.5
C_6H_5	Bu^i	6.27 (d)	8.00 (d)	2
C_6H_5	C_6H_5	6.56 (d)	8.04 (d)	2

The Dimroth rearrangement of 4,6-diamino-1-aryl-2,2-dimethyl-1,2-dihydro-1,3,5-triazines, e.g. (**79**)→(**80**) (see Section 6.12.6.1) has been monitored by ^1H NMR. Restricted rotation about the pivotal inter-ring bond in (**79**) makes the methyl groups diastereotopic and they appear as equal intensity singlets at 1.24 ppm and 1.60 ppm. A singlet for the 2-methyl groups at 1.48 ppm appears in the Dimroth product (**80**); data are given for 12 triazines and rearrangement products ⟨93JHC849⟩.

^{13}C NMR has become more prominent over the last decade and details are now widely quoted in publications. Ring carbon chemical shifts ($CDCl_3$) for 1,3,5-triazine and some substituted 1,3,5-triazines are shown in Table 1 (ring carbon with $CONH_2$ recorded in $(CD_3)_2SO$) ⟨75OMR(7)194, 78JHC1055, 92JHC979⟩.

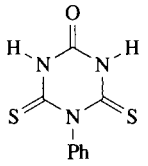
Table 1 Ring carbon ^{13}C chemical shifts for 1,3,5-triazines (ppm).



R^1	R^2	R^3	*C(2)*	*C(4)*	*C(6)*
H	H	H	166.1	166.1	166.1
Me	Me	Me	175.9	175.9	175.9
Ph	Ph	Ph	171.7	171.7	171.7
Cl	Cl	Cl	172.5	172.5	172.5
OMe	OMe	OMe	173.3	173.3	173.3
CN	Ph	Ph	153.6	171.7	171.7
$CONH_2$	Ph	Ph	166.4	171.7	171.7

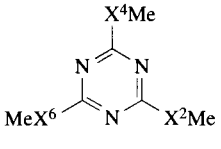
The ^{13}C NMR spectra of 3,4,5,6-tetrahydro-5-phenyl-3,5-dithioxo-1,3,5-triazin-2-one (**25**) contained peaks at 143.6 ppm and 177.8 ppm which were assigned to the C=O and C=S carbons respectively. Tosato carried out a systematic analysis of substituent effects on ^{13}C chemical shifts of the ring carbons in trimethylcyanurates and thiocyanurates. The 69 chemical shifts of the ring carbons, distributed over a 43 ppm range, were assigned after classification into four main groups

dependent on structural characteristics. The structures of the trimethyl-cyanurates and -thiocyanurates and their chemical shift data are shown in Table 2. This provides a useful reference paper for chemical assignments in these types of compounds ⟨84JCS(P2)1593⟩.

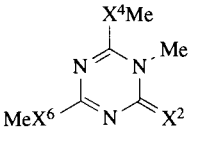


(25)

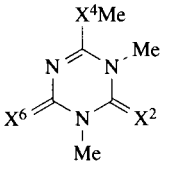
Table 2 The trimethyl-cyanurates and -thiocyanurates and their ^{13}C chemical shifts.



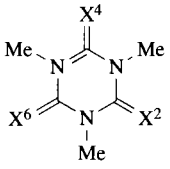
(a–d)



(e–l)



(m–t)



(u–x)

Compounds				*Ring carbons*			*^{13}C Chemical shifts*[a] *X-Methyl carbons*			N-*Methyl carbons*		
X^2	X^4	X^6		C-2	C-4	C-6	X^2Me	X^4Me	X^6Me	N^1Me	N^3Me	N^5Me
S	S	S	(a)	179.5	179.5	179.5	13.4	13.4	13.4			
S	O	S	(b)	182.5	167.8	182.5	13.2	54.7	13.2			
O	O	S	(c)	170.7	170.7	185.1	55.0	55.0	13.3			
O	O	O	(d)	173.3	173.3	173.3	54.7	54.7	54.7			
S	S	S	(e)	183.0	170.2	173.3		15.0	14.2		38.0	
S	O	S	(f)	184.7	159.1	174.4		57.0	14.2		34.9	
O	S	S	(g)	152.6	171.2	180.1		14.7	14.0		31.3	
O	O	S	(h)	154.1	160.6	181.8		56.5	14.0		28.4	
O	O	O	(i)	156.4	163.2	169.0		56.5	55.4		28.5	
S	S	O	(j)[b]	186.0	173.0	163.0						
O	O	O	(k)	187.4	162.2	164.2		57.1	56.1		35.0	
O	S	O	(l)	155.7	174.6	167.6		14.7	55.5		31.4	
S	S	S	(m)	175.5	162.4	180.5		15.3		43.3	38.7	
S	O	S	(n)	176.1	151.5	183.4		57.4		43.7	36.4	
S	S	O	(o)	177.0	169.2	149.2		15.7		36.6	38.1	
S	O	O	(p)	178.7	158.1	152.0		57.0		36.2[c]	35.8[d]	
O	S	O	(q)	150.0	170.0	152.5		15.0		28.8	31.8	
O	O	O	(r)	150.7	159.0	154.0		56.7		29.1[c]	28.9[d]	
O	S	S	(s)	147.5	164.1	183.6		15.1		35.4	31.6	
O	O	S	(t)	148.8	153.6	185.8		57.3		35.6	29.6	
O	O	S	(u)	146.7	146.7	177.3				36.5	29.8	36.5
O	O	O	(v)	148.0	148.0	148.0				29.0	29.0	29.0
S	S	S	(w)	171.9	171.9	171.9				45.0	45.0	45.0
S	O	S	(x)	175.1	145.0	175.1				44.6	37.0	37.0

[a]In ppm from Me_4Si in $CDCl_3$ solution. [b]Compound (j) has not been synthesized; ring carbon chemical shifts are predicted values. [c]This signal could be assigned to the corresponding N^3Me carbons. [d]This signal could be assigned to the corresponding N^1Me carbon.

The ring carbons of cyanuryl chloride (**3**) occur at 172.5 ppm and in cyanuric acid (**1**) they are at 149.8 ppm. The ^{13}C NMR of the other impurities (**17**)–(**21**) found in the preparation of HMM are also reported. Proton decoupled ^{13}C NMR of (**19**) showed two broad signals at 165.52 ppm and 157.19 ppm with a sharp peak at 160.09 ppm. These results were said to be indicative of a keto–enol tautomeric exchange process. The two broad peaks were assigned to C(2) and the signal at 160.09 ppm to C(4) and C(6) ⟨92JHC979⟩.

1-Alkyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones have ring carbons ($(CD_3)_2SO$) at 148.3 ppm for the carbonyl with two adjacent NH groups and signals at 149.8 ppm (alkyl = Me), 149.4 ppm (alkyl = Et), 149.7 ppm (alkyl = $PhCH_2$), and 149.3 ppm (alkyl replaced by 4-bromophenyl) for the other two ring carbons ⟨86CB83⟩. 1-Acyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones show ^{13}C chemical shifts at 149.3 ppm (acyl = MeCO), 148.4 ppm (acyl = EtCO), and 148.6 ppm (acyl = PhCO) for

the carbonyl with two adjacent NH groups and 149.3 ppm (acyl = MeCO), 148.4 ppm (acyl = EtCO), and 148.6 ppm (acyl = PhCO) for the other ring carbons. When the acyl group is replaced by Ph_2NCO— the ring carbon signal at 147.8 ppm is assigned to the one with two adjacent NH groups and 147.1 ppm to the other two ring carbons. Similar chemical shifts are observed for 1-arenesulfonyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones, with 146 ppm for C(4) and 147.5 ppm for C(2) and C(6) ⟨86CB669⟩. Spirotriazines (**186**) (see Section 6.12.9.5.2) have the spiro carbon at 85.7–87.6 ppm and the triazine carbonyls between 149.6 ppm and 150.4 ppm ⟨85CB3959⟩.

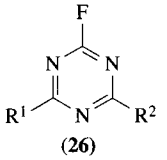
Dihydro-1,3,5-triazines (**24**) show ring carbon signals for C(2) at 63.7 ppm, C(4) at 159.8 ppm, and C(6) at 151.7 ppm when $R^1 = Bu^t$; C(2) at 74.2 ppm, C(4) at 158.1 ppm, and C(6) at 153.4 ppm when $R^1 = Pr^i$; and C(2) at 76.2 ppm, C(4) at 158.7 ppm, and C(6) at 154.9 ppm when R^1 = phenyl ⟨86CB3737⟩.

^{13}C NMR spectra support the peroxide structure (**71**); ring carbons occur at 176 ppm as in 2,4,6-trimethoxy-1,3,5-triazine, far removed from 149 ppm for C=O in cyanuric acid ⟨81JCS(P2)1512⟩.

4,6-Difluoro-2-(pyrrol-2-yl)-1,3,5-triazine, 6-fluoro-2-(pyrrol-2-yl)-4-perfluoroisopropyl-1,3,5-triazine, and 4,6-di(perfluoroisopropyl)-2-(pyrrol-2-yl)-1,3,5-triazine have chemical shifts for the ring carbons that carry the fluorine substituent between 170.3 ppm and 172.3 ppm, ring carbons with the perfluoroisopropyls from 165.5 ppm to 169.2 ppm, and the ring carbon with the pyrrole substituent from 166.5 ppm to 170.4 ppm ⟨92T7939⟩.

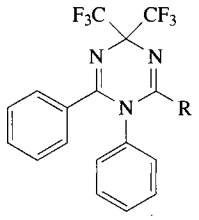
Contrary to Quirke's prediction ⟨84CHEC-I(3)457⟩, ^{14}N NMR has not evolved as a valuable spectrometric technique for 1,3,5-triazines, and there have been few application over the past 10 years. Solvent effects on the nitrogen shielding in 1,3,5-triazine have been reported. Chemical shifts vary over about 11 ppm, from 95.36 ppm in cyclohexane to 106.27 ppm in water relative to $MeNO_2$ ⟨91JMR(91)289⟩.

^{19}F NMR spectra of some fluorinated 1,3,5-triazines (**26**) ⟨92T7939⟩, and also of some trifluoromethylated dihydro-1,3,5-triazines (**27**) and (**28**) ⟨84CZ205⟩, have been reported. Comparison of chemical shift data in (**26**) shows chemical shifts to higher field for the ring fluorines (−33 to −40 ppm on average), indicative of charge separation present in (**26**; R = 4-$Me_2NC_6H_4$- or R = 4-$Et_2NC_6H_4$-).

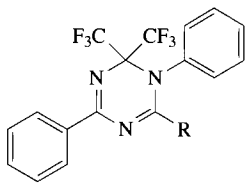


(**26**)

$R^1 = R^2 = F$	−33 (from $CFCl_3$)
$R^1 = F$, $R^2 = CF(CF_3)_2$	−32, −183 (CF) −74 (CF_3)
$R^1 = F$, $R^2 = 4\text{-}Me_2NC_6H_4$	−40
$R^1 = CF(CF_3)_2$, $R^2 = 4\text{-}Me_2NC_6H_4$	−37, −184 (CF) −74 (CF_3)
$R^1 = CF(CF_3)_2$, $R^2 = 4\text{-}Et_2NC_6H_4$	−43, −188 (CF) −78 (CF_3)



(**27**)



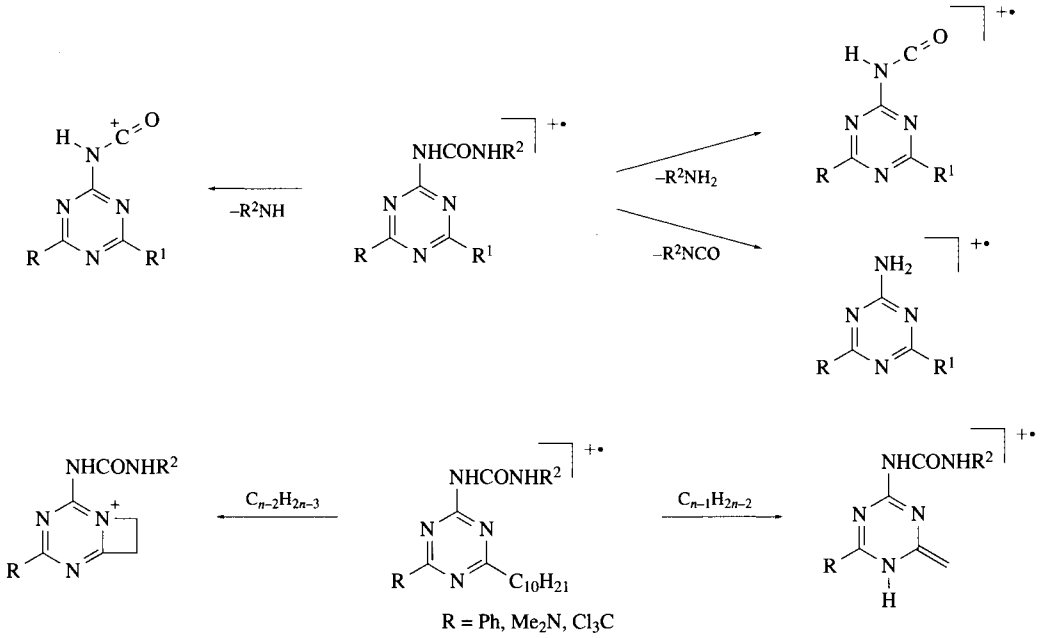
(**28**)

6.12.3.3 Mass Spectra

1,3,5-Triazine fragments by the stepwise loss of HCN from the molecular ion (m/z 81 M^+, 54 and 27). 2,4,6-Triaryl-1,3,5-triazines show molecular ions with base peaks of the aryl cyanide ions ⟨85S95⟩. 2-Alkoxy-4,6-diaryl-1,3,5-triazines also show the aryl cyanide as the base peak ⟨93S33⟩. 2-Amino-4-methoxy-6-methyl-1,3,5-triazine shows fragments of m/z 140 (M^+), 111 ($MeOC_3N_3H_2^+$), 110 ($MeOC_3N_3H^+$), 69 ($C_2N_3H_3^+$/$MeCNCNH_2^+$), 68 ($C_2N_3H_2^+$), 58 ($MeOCNH^+$), 43 (H_2NCNH^+), and 42 (H_2NCN^+); m/z 43 and 42 are typical of amino-substituted 1,3,5-triazines ⟨B-91MI 612-01⟩.

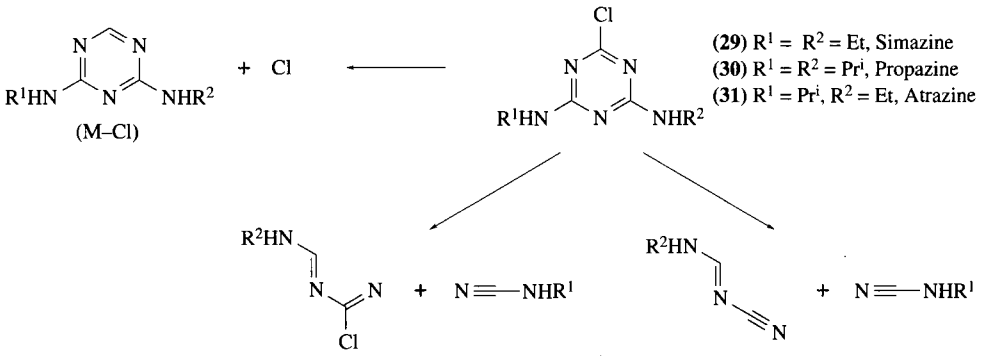
Mass spectra of (alkylamino)triazines have been studied extensively by Kreutzberger *et al.* ⟨85JHC1441, 86CZ16, 87JHC1697, 88JHC1645⟩. Cleavage of the side-chain by McLafferty rearrangements was frequently found. Kelarev *et al.* have shown that urea side chains $R^2NHCONH$- attached to 1,3,5-triazines (R^2 = H or C_6H_5) fragment by loss of R^2NH and R^2NH_2 or R^2NCO. They also

showed that long chain alkyl groups of general formula C_nH_{2n+1} attached to these ureido triazines fragment by loss of $C_{n-1}H_{2n-2}$ or $C_{n-2}H_{2n-3}$ (Scheme 1) ⟨87KGS356⟩.



Scheme 1

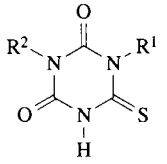
Chlorodiaminotriazines have been studied by laser photolysis. The products formed from the herbicides Simazine (**29**), Atrazine (**30**), and Propazine (**31**) were investigated by time-of-flight mass spectroscopy (laser microprobe analysis, LAMMA). It is proposed that all the triazines undergo a retro-Diels–Alder type [4 + 2] ring opening, with or without initial loss of chlorine, where two systems, one with four π-electrons and the other with two π-electrons, are involved (Scheme 2). The fragment ion $NCNHR^1$ occurs as a common two-π fragment. The main process of fragmentation competes with cluster formation ⟨91OMS(26)779⟩.



Scheme 2

HMM and triazines (**1**), (**19**), and (**21**) show peaks (M^+), $(M\text{-}Me)^+$, $(M\text{-}NHCH_2)^+$, $(MeNHCH_2)^+$, whereas triazines (**17**), (**18**), and (**20**) show the same peaks as well as $(M\text{-}Cl)^+$. All the compounds have m/z 71 (69) from the fragment Me_2NCN^+, which gains or loses a hydrogen atom via a rearrangement process ⟨92JHC979⟩.

Mass spectra of 6-thioxo-1,3,5-triazine-2,4-diones (**32**) involve loss of R^2NCO, of SH (M − 33) and of HNCS (M − 59) in preference to loss of R^1NCS (R^1 = Me) ⟨92JCS(P1)1139⟩.



(**32**)

1,3,5-Tris-(3′,4′,5′-trimethoxyphenethyl)-hexahydro-1,3,5-triazine, which is typical of hexahydrotriazines, did not give a molecular ion (EI or CI). The spectra gave peaks at m/z 223, 211, 181 (base peak), 148, and 136. Californium-252 plasma mass spectra gave the molecular ion of m/z 669 ⟨89H(29)1179⟩.

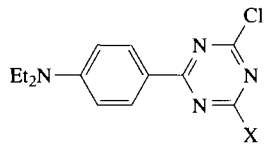
Methane-enhanced negative-ion chemical ionization mass spectra of 22 triazine herbicides have been examined. Major ions observed are (M-Cl-RH), (M-HCl), (M-Cl), (M − 2), (M − 1), (M), (M + 1), (M + 2), (M + 14), (M + 28), and (M + 37) for 2-chloro-1,3,5-triazines. For 2-methylthio-1,3,5-triazines the ions are (M-HSMe), (M-SMe), (M), (M-Me), (M + 1), (M + 13), and (M + 25) ⟨89MI 612-01⟩.

6.12.3.4 UV Spectra

The UV spectrum of 1,3,5-triazine has been reported in a review by Finkel'shtein and Boitsov; two bands for n-π^* (272 nm) and π-π^* (222 nm) are shown. The UV spectra and extinction coefficients were also reported for a series of symmetrically substituted 1,3,5-triazines ⟨62RCR712⟩.

The UV absorption spectra of 1,3,5-triazine derivatives which contain π-electron donors (Cl, O, OH, and OMe) have been studied ⟨91MI 612-02⟩. Together with calculations of the electronic excitation energies and their intensities by CNDO/S method, the structure of cyanuryl chloride hydrolysis products have been determined. Conjugation of substituents with the 1,3,5-triazine ring leads to a bathochromic shift ⟨61RTC158⟩. Cyanuric acid absorbs in the far UV with a weak band at 280 nm and a hypsochromic shift was reported as the pH was lowered ⟨64SA397⟩.

UV absorption and fluorescence characteristics of new optical probes based on the 1,3,5-triazinylaniline chromophore have been reported ⟨91JCS(P2)1495⟩. Compounds (**33**), where X = OR, NRR^1, that possess this chromophore, show an intense absorption maximum at 360–370 nm, with strong fluorescence in low polarity solvents at 400–420 nm. These absorptions are due to an intramolecular π-π^* charge transfer transition. The transfer is from the HOMO of the phenyl ring and exocyclic nitrogen to the LUMO located on the triazine ring. The triazine LUMO energy is raised by replacement of Cl by a conjugating electron donor substituent. The π-electron acceptor character of the triazine is lowered and the absorption-fluorescence band is shifted to the blue by about 30 nm for the NRR^1 substituent. Chambers *et al.* reported formation of an immediate blue coloration on addition of *N*,*N*-dimethylaniline to 2,4,6-trifluoro-1,3,5-triazine, which they attributed to a charge transfer complex ⟨92T7939⟩.

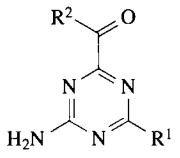


(**33**)
X = OR, Cl, NMe_2, N(Me)Bu^n, N(Me)octadecyl

The prototropic tautomerism of tri- and tetraphenyl 1,2-(or 1,4)-dihydro-1,3,5-triazines has been examined by UV in methanol. Absorption maxima were expected to differ due to the extended conjugation in the 1,2-dihydro form, which is not present in the 1,4-dihydro form. No differences were found, however, and the UV did not distinguish between the tautomers of (**22**) and (**23**) ⟨85JCS(P2)887⟩.

6.12.3.5 IR/Raman Spectra

IR spectra of 1,3,5-triazines give spectra which are typical of the substituents. 4-Amino-1,3,5-triazin-2-yl ketones (**34**) have characteristic amine bands at 3170–3497 cm^{-1} and 1696 cm^{-1} for the ketone carbonyl (KBr).



(**34**)

The IR spectra of compounds formed by systematic replacement of chlorine in cyanuryl chloride by various fluorinated anilines show bands at 3460–3380 cm^{-1} (NH), 1265–1240 cm^{-1} and 1100–1120 cm^{-1} (ArF and CF_3 bands), and C-Cl at 705–805 cm^{-1}, with the triazine at 810–830 cm^{-1} ⟨88JFC(39)117, 90RRC1025⟩. 2-(2-Cyanoethyl)amino substituents show the cyanide bond at 2260 cm^{-1} (KBr) ⟨87JHC1697⟩; the C=C bond in diallylamino substituents is at 1640–1650 cm^{-1} ⟨88JHC1645⟩.

4,6-Bis(dimethylamino)-1,3,5-triazin-2(1*H*)-one has its carbonyl absorption at 1680–1700 cm^{-1} ⟨85JCS(P1)1533⟩. 6-Methylthio-1,3,5-triazine-2,4 (1*H*,3*H*)-diones show bands at 1680 cm^{-1} and 1710–1720 cm^{-1} ⟨84S770⟩. The carbonyl stretching frequencies of the amide moiety in cyanuric acid and compounds (**19**)–(**21**) have a strong absorption at 1677–1730 cm^{-1} (KBr) with ring C=N stretching absorptions at 1608–1302 cm^{-1} ⟨92JHC979⟩. 1,3,5-Tri(isocyanatocarbonyl)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione has carbonyls at 1835 cm^{-1}, 1785 cm^{-1}, and 1750 cm^{-1} and an isocyanate band at 2250 cm^{-1} in sulfolane. 1-Methyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione has peaks (KBr) at 3210 cm^{-1} and 3100 cm^{-1} for NH and 1805 cm^{-1}, 1750 cm^{-1}, 1690 cm^{-1}, and 1665 cm^{-1} for C=O as strong evidence for the preferred keto form ⟨86CB83⟩.

1,3,5-Triacylhexahydro-1,3,5-triazines ⟨86S643⟩ have carbonyl frequencies at 1620–1645 cm^{-1} (KBr). 1,3,5-Trisubstituted 1,3,5-hexahydrotriazin-2-ones have carbonyl absorption at ca. 1644 cm^{-1} (film) ⟨90TL2109⟩.

Prototropic tautomerism of 1,2- and 1,4-dihydro-1,3,5-triazines (**22**) has been examined by IR (KBr and $CHCl_3$). Peaks at 1605–1620 cm^{-1} for the 1,2-dihydro form and 1645–1690 cm^{-1} for the 1,4-dihydro tautomer showed the existence of an equilibrium mixture of the two forms ⟨85JCS(P2)887⟩. This corresponds to peaks at 1608–1642 cm^{-1} found in *N*-substituted 1,2-dihydrotriazines (**24**) and 1675–1685 cm^{-1} for the 1,4-dihydro forms ⟨84CZ205⟩.

A combination of IR and Raman spectroscopy has confirmed that the ring atoms and substituents in 2-amino-4-methoxy-6-methyl-1,3,5-triazine are exactly planar ⟨B-91MI 612-01⟩. IR/Raman spectroscopy was applied to triazinyl peroxides (see Section 6.12.5.1.4) and the results were analyzed by a frequency calculation model due to Bleckman ⟨74ZN(A)1485⟩.

6.12.3.6 Photoelectron Spectroscopy

The photoelectron spectrum of 1,3,5-triazine has been recorded ⟨84JA2805⟩. The assignments remain unchanged from those previously reported ⟨72HCA255⟩. Investigation of the vapors over heated 1,3,5-triphenylhexahydro-1,3,5-triazine, by UV photoelectron and electron transmission spectral techniques, found them to consist mainly of monomeric *N*-methyleneaniline ⟨85JCS(P2)1623⟩.

6.12.3.7 Electron Spin Resonance

ESR spectroscopy has been used to observe the radical cation of 1,3,5-triazine. The cation was formed by γ irradiation of a dilute solution of 1,3,5-triazine in fluorotrichloromethane at 77 K and a distorted structure was found, with the unpaired electron localized on one of the nitrogens in a nonbonding σ orbital, as found for the radical cations of pyrimidine and pyridine ⟨89JCR(S)76⟩.

The photolysis of triazinyl peroxides (see Section 6.12.5.1.4) has been studied. Triazinyloxy radicals could not be observed, but the adducts formed with ethylene and trimethyl phosphite were detected and claimed as evidence for the peroxide structures ⟨81JCS(P2)1512⟩.

6.12.3.8 Dipole Moments

Dipole moments of six 1,3,5-triphenylhexahydro-1,3,5-triazines have been determined. The moment decreased with +I substituents and increased with −I substituents in the 4-position of the phenyl ring. The dipole moment data support the existence of conformational isomerism in these compounds ⟨87MI 612-01⟩.

6.12.4 THERMODYNAMIC ASPECTS

6.12.4.1 Boiling Points and Melting Points

The majority of 1,3,5-triazine derivatives are solids, and liquids are seen with the introduction of fluorine into the ring or with other highly fluorinated substituents. Cyanuric fluoride has b.p. 73–74 °C; cyanuryl chloride is a solid, m.p. 146 °C. Cyanuric acid, thiocyanuric acid and melamine have m.p. >300 °C because of strong intermolecular hydrogen bonding. 4,6-Dimethoxy-1,3,5-triazin-2(1*H*)-one (**14**) forms a dimer via hydrogen bonding (see Section 6.12.3.1) and also has a high m.p. (222 °C). Methylation of (**14**) to give 4,6-dimethoxy-1-methyl-1,3,5-triazin-2(1*H*)-one, which cannot dimerize by hydrogen bonding, lowers the m.p. to 148 °C ⟨68JHC533⟩. 1,3,5-Tribenzylhexahydro-1,3,5-triazine has m.p. 50 °C, which suggests that lattice forces are not particularly strong in hexahydrotriazines ⟨87CC1118⟩.

6.12.4.2 Solubilities and Chromatography

Water solubility [30 mg l^{-1} for 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine, 5 mg l^{-1} for 2-chloro-4,6-bis(ethylamino)-1,3,5-triazine, and 33 g l^{-1} for 3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (Hexazinone) at 25 °C ⟨B-91MI 612-01⟩], hydrolysis and adsorptivity are properties of the triazine herbicides which allow for potential contamination of water and soils ⟨90AKZ733⟩. The increased water solubility of Hexazinone is probably due to hydrogen bonding interactions of the carbonyl oxygens with water. Also, the crystal lattice in Hexazinone is expected to be less compact (lower lattice energy) than in the 2-chloro-4,6-bis(alkylamino)-1,3,5-triazines so that more surface area is exposed to the solvent with a resultant increase in solubility. The lower lattice energy of Hexazinone is demonstrated by its lower m.p. (115 °C) compared with the m.p. (225 °C) of 2-chloro-4,6-bis(ethylamino)-1,3,5-triazine. Analysis for these triazine herbicides is therefore important and chromatography is widely used and developed.

6.12.4.2.1 Thin layer chromatography

1,3,5-Triazine herbicides have been separated by TLC on Kieselgel 60G, Kieselgel DSF5, and Silufol W254. Hexane/acetone (3 : 2) or hexane/chloroform/acetone (8 : 4 : 1) were used as the mobile phase ⟨89MI 612-02, 91AP(324)173⟩. Separation was also obtained by adsorption TLC on Silufol when eluted with hexane/acetone (19 : 5) followed by distribution TLC on silica gel LS 5/50 μ impregnated with vaseline oil and eluted with ethanol/water (1 : 1). The R_f value was found to be dependent on the substituent in the 2-position of the triazine herbicide, MeS < Cl < MeO ⟨87ZAK2048⟩.

Reverse phase (RP) TLC with various solvents miscible with water (29 systems reported) has been examined for the separation of 17 triazine herbicides on DC-Alufolien Kieselgel 60F_{254} (Merck) plates after overnight impregnation with 5% paraffin oil in *n*-hexane. R_f values for all systems studied were determined and recorded ⟨84JC131⟩.

After development on TLC plates, amino-substituted 1,3,5-triazines can be revealed by use of the chloro-toluidine reaction ⟨83JC97⟩. This is a sensitive method developed for the detection of amino and imino compounds on paper chromatograms. The method depends on the formation of chloramines which are then detected by liberation of iodine from a starch–potassium iodide reagent.

The chromatogram is lightly sprayed with 2% aqueous potassium hypochlorite and left for 1–1.5 h at room temperature. It is then sprayed with a saturated solution of 2-toluidine in 2% acetic acid and 0.85% aqueous potassium iodide ⟨60NAT310⟩.

6.12.4.2.2 High pressure liquid chromatography

HPLC is directly applicable to 1,3,5-triazines and their degradation products. Hydroxy derivatives have been separated in RP systems with acidic and weakly alkaline mobile phases. The chromatographic behavior of 18 1,3,5-triazines has been studied in a RP system with a separon SLC 18 stationary phase and a mobile phase of aqueous sodium dihydrogen phosphate and methanol ⟨88JC147⟩.

HPLC separation of potential impurities of HMM has been studied. A Waters HPLC system was used with a 5 μm ultrasphere C_{18} column with mixtures of water and acetonitrile as mobile phase ⟨91JLC2331⟩.

An HPLC method has been developed for the determination of Hexazinone residues in soil and water ⟨83AKZ207⟩.

6.12.4.2.3 Gas chromatography

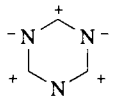
GC has high sensitivity and a good separation efficiency down to very low levels for 1,3,5-triazines. They can be determined by a thermoionization detector ⟨88MI 612-02⟩. GC with an atomic emission detector can also be used ⟨90JC131⟩.

GC/MS in the selected ion monitoring (SIM) mode can identify 1,3,5-triazines ⟨83MI 612-02⟩. In an attempt to simplify this method for routine analysis, separation on a fused silica capillary column coated with SE-54, of 70000 theoretical plates was investigated. The result was complete separation of the herbicides Propazine, Atrazine, and Simazine, but the analysis time was high. Low surface area graphitized carbon black coated with 0.26% SP100, a polar acidic phase, gave complete separation in 3 minutes. Simazine has the highest retention time; Propazine was eluted first ⟨84JOC85⟩.

6.12.4.3 Aromaticity

1,3,5-Triazine is known to be aromatic, and Bird has developed an aromaticity index (I_6) where 1,3,5-triazine ($I_6 = 100$) has a value identical to that of benzene ⟨92T335⟩. Jug has used a bond order approach to ring current and aromaticity and determined a ring current index of 1.724 for 1,3,5-triazine compared with 1.751 for benzene ⟨83JOC1344⟩.

The resonance energy of 1,3,5-triazine has been calculated from experimental heats of formation by a Laidler bond energy scheme which gave a value for 1,3,5-triazine of 44.9 Kcal compared with 45.8 Kcal for benzene ⟨92T335⟩. The delocalization energy of 1,3,5-triazine (121 kJ mol^{-1}) has been derived from valence bond calculations and compared with benzene (172 kJ mol^{-1}). This lower value for 1,3,5-triazine is due to the increase in the polarity of the C=N bonds as more π-electrons are partially located on the ring nitrogens. Charge distribution on nitrogen compared with carbon is 1.517 and 0.483 respectively and (**35**) becomes a major contributor to the structure of 1,3,5-triazine and explains its reactivity towards nucleophiles ⟨46JCS670⟩.



(35)

The Cotton–Mouton effect, magnetic anisotropy, and charge localization of 2,4,6-tris(dimethylamino)-1,3,5-triazine compared with 1,3,5-triazine have been examined ⟨91JST(248)201⟩. Dilute solution Kerr and Cotton–Mouton constants were measured for both 1,3,5-triazine and 2,4,6-tris(dimethylamino)-1,3,5-triazine. These constants were then used to derive experimental values for the optical-frequency polarizability anisotropies, and more importantly the magnetic anisotropies of

the two compounds. The conclusions are that replacement of three CH groups of benzene with N atoms, as in 1,3,5-triazine, substantially localizes electronic charge on the nitrogen atoms and reduces the delocalization to perhaps only one tenth of that in benzene. 1,3,5-Triazine does not exhibit the typical electrophilic substitution reactions of benzene, but readily undergoes nucleophilic addition. The presence of three dimethylamino substituents in 1,3,5-triazine significantly increases the charge localization on the nitrogen atoms. Due to the extended π-electron system, the extent of delocalization is increased to at least half of that in benzene, which may explain the inertness to nucleophilic substitution of 2,4,6-tris(dimethylamino)-1,3,5-triazine ⟨82JCS(P1)1821⟩.

6.12.4.4 Conformation

In 1,3,5-trimethylhexahydro-1,3,5-triazine the *eea* conformation predominates. The *eea* conformation is much more stable than the *eee* or the *eaa* conformations ⟨74JA1591, 78JCS(P2)377⟩. This preference continues as the substituent methyl groups are replaced by higher homologues—triethyl, triisopropyl, and even tri-*n*-butyl ⟨70JCS(B)135, 73JCS(P2)2109, 78JCS(P2)377⟩.

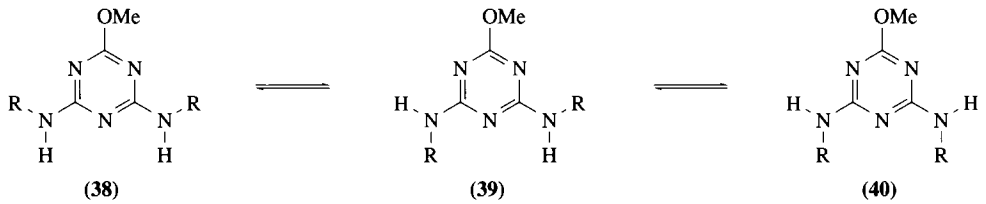
Sim has studied the conformation of crystalline 1,3,5-tribenzylhexahydro-1,3,5-triazine by x-ray analysis at various temperatures. Conformational isomerization occurs even in the crystalline material. At temperatures below 250 K all the molecules are in the *eea* conformation, but then the *eaa* conformation becomes more populated as the temperature is increased. At 293 K the *eaa* population reaches ca. 46%. These conformational changes take place in the crystal without upsetting the crystal structure ⟨87CC1118⟩.

Sim and co-workers have also studied the conformation of 1,3,5-triarylhexahydro-1,3,5-triazines. X-ray analysis of 1,3,5-tris(*o*-, *m*-, and *p*-fluorophenyl)hexahydro-1,3,5-triazines shows that the *eaa* conformation is adopted, as is also found in 1,3,5-triphenylhexahydro-1,3,5-triazine; the two rings are virtually coplanar in the *p*-fluorophenylhexahydro-1,3,5-triazine as in the 1,3,5-triphenylhexahydro-1,3,5-triazine. The two rings move from coplanarity as the fluorine moves from the *para* to *meta* to *ortho* positions. The *p*-fluoro compound has an angle between the phenyl ring and the symmetry plane of the hexahydrotriazine ring of 90°; it is 54.7° for the *m*-fluoro and 22.5° for the *o*-fluoro compound ⟨89JCS(P2)583⟩.

2,4,6-Tris(cyclohexylamino)-1,3,5-triazine exists in solution in two different conformers (**36**) and (**37**) (Equation (1)); the activation energy for the interconversion is 14.55 kcal mol^{-1}. At room temperature rapid exchange between the conformers occurs. The two forms are detectable by ^{13}C and ^{1}H NMR at reduced temperature. These results confirm that the amino groups in melamine resonate with the ring about as strongly as they do in amides ⟨93JPO29⟩.

(36) (37) (1)

2,6-Bis(cyclohexylamino)-4-methoxy-1,3,5-triazine exists in three rapidly equilibrating conformations (**38**), (**39**), and (**40**) at room temperature (Scheme 3). At 270 K, the three distinct forms are observed by ^{13}C and ^{1}H NMR ⟨93JPO29⟩.



(38) (39) (40)

Scheme 3

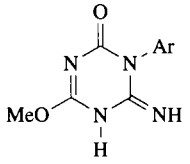
6.12.4.5 Tautomerism

The prototropic tautomerism of 1,3,5-triazinones, 1,3,5-triazinethiones, and amino-1,3,5-triazines has been discussed in detail ⟨B-76MI 612-01⟩. Cyanuric acid was shown to exist as the trioxo structure by UV and x-ray data. 1-Methyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione has the trioxo form as preferred tautomer (see Section 6.12.3.5) ⟨86CB83⟩. Compounds (**19**), (**20**) and (**21**) were also shown by IR spectroscopy to show the oxo forms as preferred tautomers; carbonyl bands were found at 1677–1730 cm^{-1}.

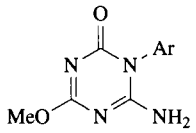
4,6-Bis(dimethylamino)-1,3,5-triazin-2(1*H*)-one and 6-methylthio-1,3,5-triazine-2,4(1*H*,3*H*)-dione exist as the keto tautomers (see Section 6.12.3.5). IR spectra also indicate the dioxo form in the solid state for 5-azauracil (1,3,5-triazine-2,4-(1*H*,3*H*)-dione) ⟨62CCC2754⟩. However, in a ^1H NMR study it was concluded that it exists in the monoenolic form in solution, as the spectra showed a nonexchangeable singlet for the 6-hydrogen substituent at 8.18 ppm ⟨76OMR(8)224⟩. The hydroxy tautomer of 2,4-diamino-6-hydroxy-1,3,5-triazine was found to predominate in the gas phase. *Ab initio* calculations (see Section 6.12.2.1) found the hydroxy tautomer to be 4.82 kcal mol^{-1} lower in energy than the carbonyl tautomer ⟨93JOC3085⟩.

Trithiocyanuric acid exists mainly in the trithione tautomeric structure. IR bands at 1115 cm^{-1}, 1330 cm^{-1}, and 1540 cm^{-1} were assigned to —N—C=S and bands at 2900 cm^{-1} and 3200 cm^{-1} to NH ⟨66JCS(C)909⟩. The work of Tosato (see Section 6.12.3.2, Table 1) has provided ^{13}C NMR data for the many possible fixed forms of cyanurates and thiocyanurates.

Melamine exists in the triamino form but various *N*-arylamino-1,3,5-triazines have been shown to exist in an imino-oxo form (**41**) rather than the amino form (**42**) ⟨66JOC784⟩.

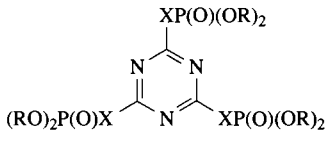


(**41**)

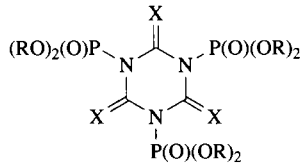


(**42**)

^{31}P NMR results have shown that triazines (**43**) and (**44**) undergo tautomeric transformation by migration of the phosphorus moiety from oxygen or sulfur to ring nitrogen to give (**45**) and (**46**). An intramolecular mechanism was demonstrated by tautomeric transformation reactions of mixtures. All four forms (X = O or S) were demonstrated to be present in equilibrium mixtures starting from a mixture of (**43**) and (**44**) ⟨86DOK(287)865, 86ZOB756⟩.



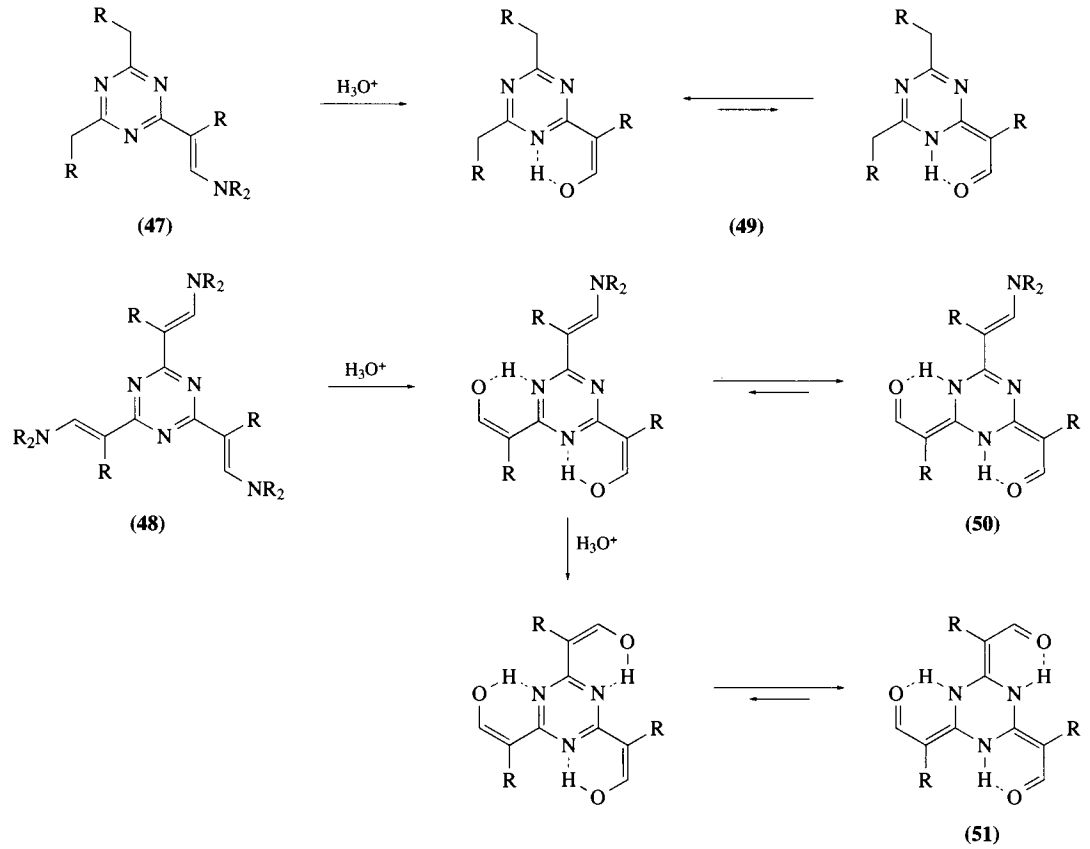
(**43**) X = S
(**44**) X = O



(**45**) X = S
(**46**) X = O

Spectroscopic studies [IR (Section 6.12.3.5) and NMR (Section 6.12.3.2)] show 2,2,4,6-tetraphenyldihydro-1,3,5-triazines (**22**; R^1 = H) to exist in an equilibrium mixture of the 1,2- (**22a**) and the 1,4-dihydro (**22b**) forms. The 1,2-dihydro form was found to be the preferred form in solution and in the solid state. Ritter and Anderson isolated two *N*-methyl derivatives which showed different m.p.s. (191 °C and 210 °C); they assigned the structures as 3-methyl-2,2,4,6-tetraphenyl-1,2-dihydro-1,3,5-triazine (**22a**; R^1 = Me) and 5-methyl-2,2,4,6-tetraphenyl-1,4-dihydro-1,3,5-triazine (**22b**; R^1 = Me) respectively, based on UV data. When compound (**22**) had R^1 substituted by a bulky group a single isomer (**22b**) of the 2,5-dihydro form predominated ⟨85JCS(P2)887⟩. Goerdeler and Eggers also synthesized a series of 2,3-dihydro-1,3,5-triazines (see Section 6.12.3.2) where the 2,5-dihydro form was not seen ⟨86CB3737⟩.

Aminoalkenyltriazines (e.g. (**47**) and (**48**)) are partially or fully hydrolyzed to formyl products ((**49**), (**50**), and (**51**)). Enol or unusual acylenamine tautomeric structures are found and confirmed by x-ray. Compound (**49**) was found to exist in the enol tautomeric form but all other cases reported had predominance of the aldehydo forms (e.g. (**50**) and (**51**)) (Scheme 4) ⟨92JHC1125⟩.



Scheme 4

Azidotriazines (**52**) exist alongside small proportions of tetrazole tautomer (**53**) (Equation (2)). In CD_3COCD_3 the azido–tetrazole ratio is 100–96 : 0–4 ⟨88IZV491⟩.

(2)

6.12.5 REACTIVITY OF FULLY CONJUGATED RINGS

6.12.5.1 Reactivity of 1,3,5-Triazines

6.12.5.1.1 Unimolecular thermal and photochemical reactions

Above 600 °C 1,3,5-triazine decomposes to three molecules of hydrogen cyanide but it is thermally stable below this temperature. This breakdown is also observed in the mass spectrum of 1,3,5-triazine (see Section 6.12.3.3). Photodecomposition of 1,3,5-triazine to three molecules of HCN is also known and a theoretical study of this process has been carried out by Osamura *et al.* (see Section 6.12.2.1).

Thermal isomerization of cyanurates to isocyanurates, and thiocyanurates to isothiocyanurates,

has been investigated by Tosato and Soccorsi, and rules for methyl migration established ⟨82JCS(P2)1321⟩. The conversion of triallyl cyanurates into triallyl isocyanurates via thermal rearrangement has also been reported ⟨88KGS376⟩.

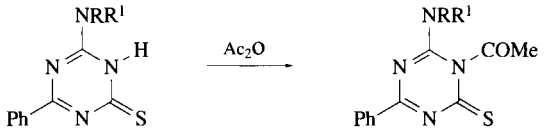
6.12.5.1.2 Electrophilic attack at carbon

1,3,5-Triazines are resistant to electrophilic attack at carbon.

6.12.5.1.3 Electrophilic attack at nitrogen

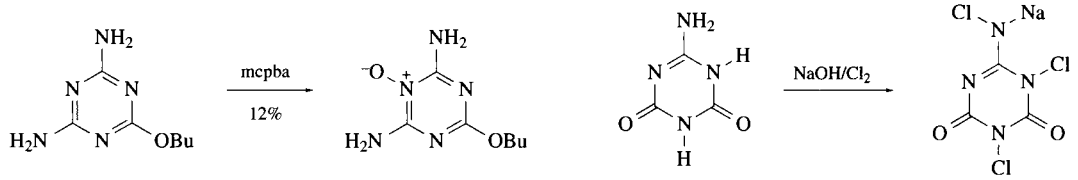
N-Alkylation of 1,3-disubstituted 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones in the 5-position is well exemplified ⟨84JAP5925379, 85FRP2560874, 87GEP3618662, 91GEP4000624⟩. Cyanuric acid reacts with electrophiles with replacement of all three imido hydrogens. Electrophiles include allyl chloride ⟨82JAP57200371⟩, epoxides ⟨82JAP57212173⟩, and Michael reagents ⟨85AKZ300, 87AKZ261, 87MI 612-02⟩. Strict control of pH (pH = 9) and temperature (15 °C) allows monoformylation on nitrogen of cyanuric acid; diformylation occurs at 40 °C. Aminomethylation of cyanuric acid (formaldehyde and piperidine) gave mono- and di-substituted products ⟨90FRP2636328⟩.

Acylation occurs at N-1 of 6-(dimethylamino)-4-phenyl-1,3,5-triazine-2(1*H*)-thione as shown in Scheme 5 ⟨89AKZ407⟩.



Scheme 5

Oxidation of 6-butoxy-1,3,5-triazine-2,4-diamine with MCPBA in ethanol gave an *N*-oxide (**54**), but in only 12% yield ⟨91MIP9119701⟩. Chlorination of 6-amino-triazine-2,4(1*H*,3*H*)dione in NaOH solution gave (**55**), with chlorination on the exocyclic nitrogen as well as on the ring (Scheme 6) ⟨83USP4386202⟩.



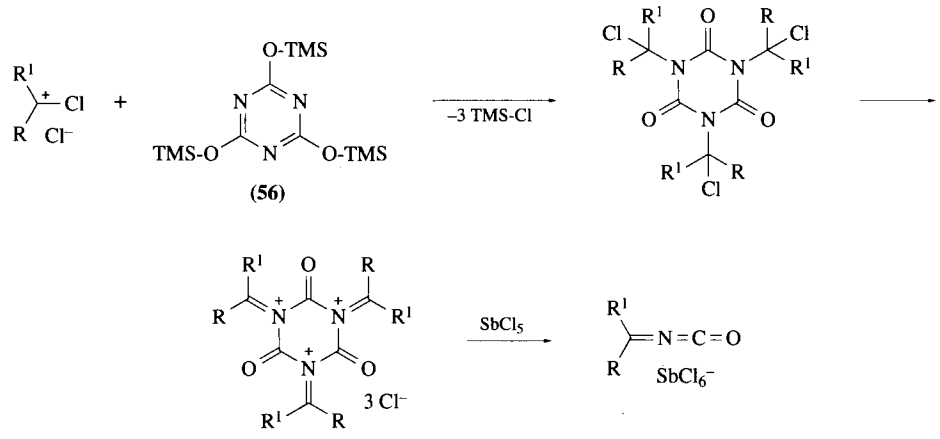
Scheme 6

Chlorocarbenium salts (Vilsmeier–Arnold type) are reported to react with silylated cyanurate (**56**) to give 1-oxa-3-azoniabutatriene salts as shown in Scheme 7. This could be regarded as an electrophilic attack at nitrogen with breakdown of the triazine ring ⟨86T6645⟩.

6.12.5.1.4 Nucleophilic attack at carbon

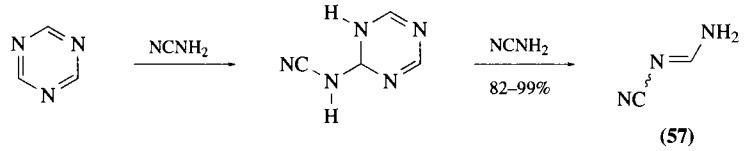
Nucleophilic attack at the fully conjugated 1,3,5-triazine usually results in ring cleavage. Ring degenerate transformations with KNH_2-NH_3 of 1,3,5-triazines, at low temperature, via an ANRORC (addition of the nucleophile, ring opening and ring closure) mechanism have been reviewed ⟨85T237⟩. A S_N ANRORC ring transformation of 1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione on reaction with fluoroacetamide gives a simple method for the preparation of 5-fluorouracil. LDA was required as base; NaOEt fails in the reaction ⟨83JHC457⟩.

Aminomethylenation reactions have been carried out, in the presence of a secondary amine, as a three-component reaction ⟨84AP(317)417⟩. The products are classed as dehydro-*N*-Mannich bases,



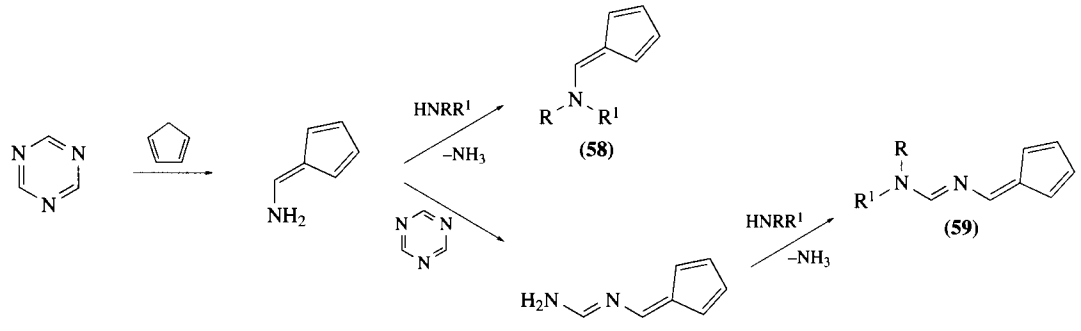
Scheme 7

e.g. (**57**) via aminomethylenation of cyanamide (Scheme 8). Kreutzberger *et al.* have also described the coupling of a 2-aminothiazole with pyrrolidine in a three-component reaction ⟨82JHC753⟩.



Scheme 8

Active methylene compounds also react with 1,3,5-triazine in aminomethylenation reactions. A three-component reaction of cyclopentadiene with 1,3,5-triazine and a secondary amine leads to *N,N*-disubstituted pentafulven-6-amines (**58**) and *N,N*-disubstituted-N^2-(6-pentafulvenyl)-formamidines (**59**) (Scheme 9) ⟨86LA374⟩.

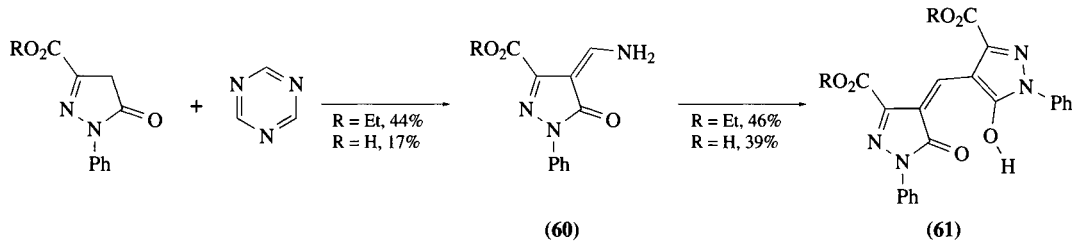


Scheme 9

Aminomethylenation reactions of active methylene compounds with 1,3,5-triazine have also been described by Kreutzberger *et al.* ⟨85AP(318)89, 85AP(318)821⟩. A second equivalent of the active methylene compound can react as the third component to give =CH—linked heterocycles, e.g. (**61**) from initial product (**60**) (Scheme 10) ⟨86AP(319)18⟩.

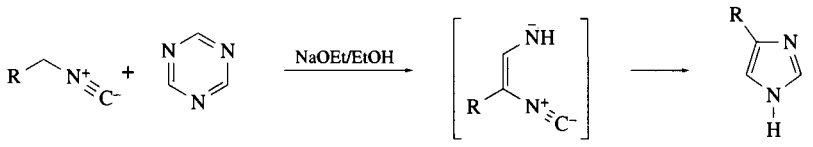
Aminomethylenation of benzyl isocyanides with 1,3,5-triazine forms 4-substituted imidazoles in yields of 28–57% (Scheme 11) ⟨86CZ256⟩.

1,6-Naphthyridines (**63**) were synthesized by aminomethylenation of 1,4-dihydropyridines (**62**) in the presence of base (Equation (3)) ⟨86GEP3502742, 86S859⟩.

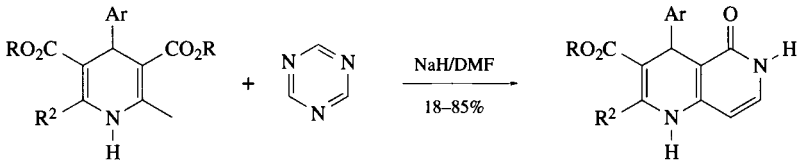


(60) (61)

Scheme 10

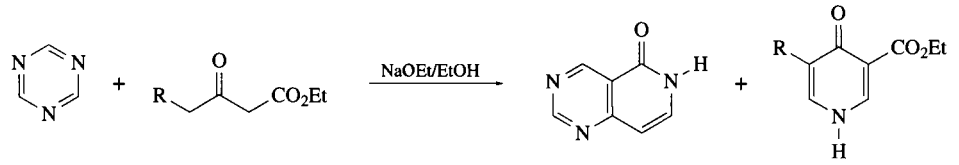


Scheme 11



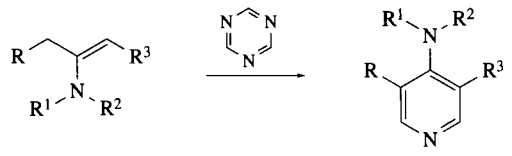
(62) (63) (3)

Pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (**64**) was prepared, along with the expected ethyl 4-oxo-1,4-dihydro-3-pyridinecarboxylate (**65**), by reaction of a β-ketoester with 1,3,5-triazine and sodium ethoxide in ethanol (Equation (4)) ⟨80JHC359⟩. This reaction was extended to the synthesis of the 1,6-naphthyridin-5(6*H*)-one, of which the reaction illustrated in Equation (3) is a dihydropyridine example ⟨89JHC1755⟩.



(**64**) 11.8% (**65**) 21.7% (4)

Aminomethylation of enamines (**66**) with 1,3,5-triazine in MeCN at reflux temperature gives derivatives of 4-aminopyridine (**67**) (Equation (5)) ⟨82URP1049484⟩.

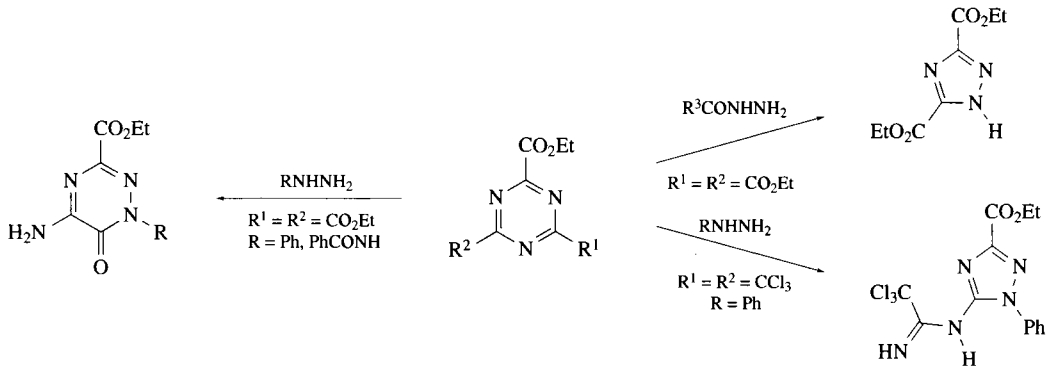


(**66**) (**67**) (5)

In another example of a reaction of an enamine with 1,3,5-triazine a mixture of products was obtained. The main product was the pyrimidine (**68**) and a minor product was the pyridine (**69**) (Equation (6)) ⟨92KGS1243⟩.

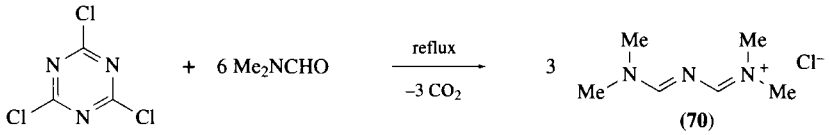
R = H, Me; R^1 = CO_2Et, COMe (**68**) 35–66% (**69**) 6–8% (6)

Alekseeva *et al.* have reported on the recyclization of trisubstituted 1,3,5-triazines (Scheme 12) on reaction with hydrazines ⟨83KGS702, 84ZOR893, 85KGS700, 89KGS1529, 90KGS1655⟩; the topic has been reviewed ⟨90MI 612-01⟩.



Scheme 12

Cyanuryl chloride is ring cleaved with DMF to form [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (Gold's reagent) (**70**), a general β-dimethylaminomethylenating agent, in 95% yield (Equation (7)) ⟨86OS(64)85⟩. Cyanuryl chloride and derivatives are the most commonly used 1,3,5-triazine substrates for reaction with nucleophiles. Chlorine has been replaced by carbon, hydrogen, fluorine, nitrogen, oxygen, phosphorus, and sulfur nucleophiles ⟨88AHC(44)243⟩.

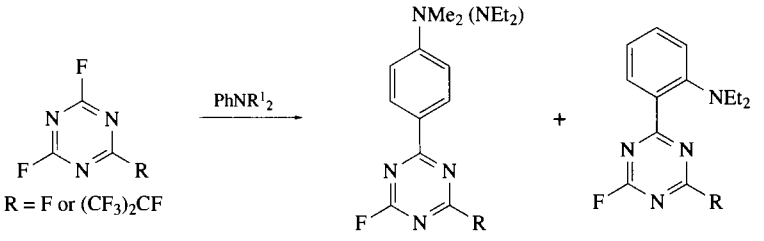


(7)

Silyl enol ethers (CH_2 = $CROSiMe_3$) react with cyanuryl chloride and replace only one chlorine with a carbon substituent (CH_2COR; R = cyclopropyl, 70%, R = Ph, 90%). Friedel–Crafts arylation ⟨83KGS1125, 92EUP497734⟩, the Ullmann reaction of 2-iodo-1,3,5-triazine to form 2,2′-bis-1,3,5-triazine ⟨82NKK1425⟩, and a palladium-catalyzed cross-coupling reaction of 2-substituted 4,6-dichloro-1,3,5-triazine with phenylboronic acid ⟨93S33⟩ have been described for the introduction of carbon substituents.

Triaryl cyanurates have been prepared from cyanuryl chloride (80–98%) by aryloxylation with Amberlite IRA-400 supported aryloxide ions ⟨88AKZ407⟩. Silylation of cyanuric acid on oxygen followed by amination has been described ⟨84CB1523⟩ to give 2,4,6-triaminotriazines, but in practice it is much easier to aminate cyanuric chloride. Use of *S,S*-dialkyl dithiocarbonates avoids that of low boiling alkanethiols for introduction of thiols ⟨86CI(L)671⟩. A thiol exchange reaction where a methylmercapto group was replaced by cyclohexanethiol in 94% yield has been reported ⟨87S1134⟩. Methylmercapto groups are also displaced by methoxide ⟨82JCS(P2)1321⟩.

Aromatic *t*-amines can act as carbon nucleophiles in reaction with perfluorinated 1,3,5-triazines. Amines used are 1-methylpyrrole, 1-methylindole, 1,8-bis(dimethylamino)naphthalene (proton sponge), *N,N*-dimethyl- and *N,N*-diethyl-aniline. All the amines reacted at the expected position in the ring except *N,N*-diethylaniline which also gave some *ortho*-product not seen with *N,N*-dimethylaniline (Equation (8)) ⟨92T7939⟩.

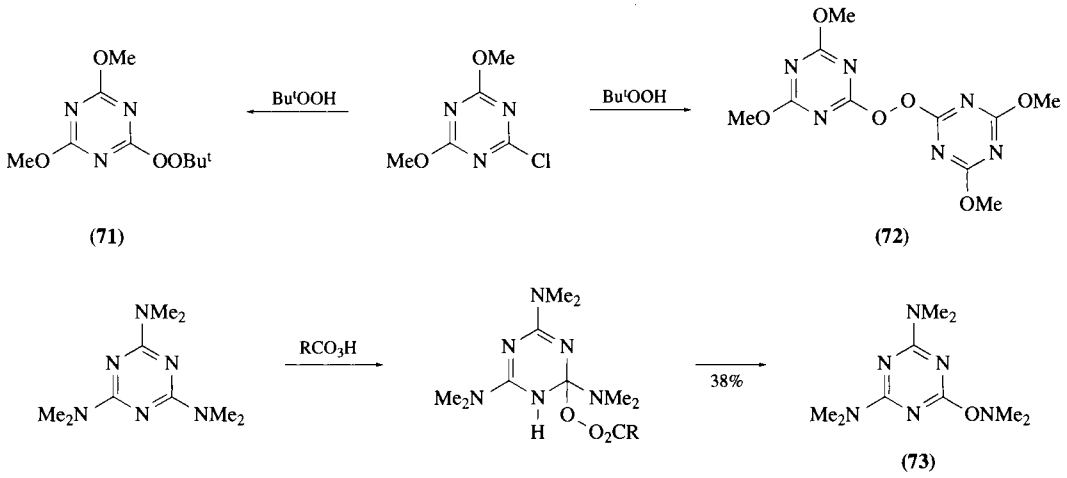


(8)

Allyloxy and aryloxy groups have been displaced by nitrogen and oxygen nucleophiles, and

methylmercapto groups have been replaced by methoxy groups. Trichloromethyl groups have been replaced by alkoxides ⟨84KGS1674⟩ and by amines ⟨85KGS1557⟩ and guanidines ⟨89AKZ576⟩, while the trimethylammonium group has been replaced by nitrogen and oxygen nucleophiles ⟨85KGS1125, 88AKZ407⟩. The synthetic application of the trimethylammonium leaving group was demonstrated by reaction of glucosamine with 2,4,6-tris(dimethylamino)-1,3,5-triazine monohydrochloride salt in alkali to form 2-amino-*N*-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-2-deoxy-D-glucopyranose ⟨82JCS(P1)1821⟩.

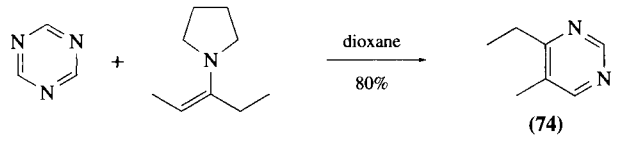
t-Butyl hydroperoxide replaces chlorine in chloro-1,3,5-triazines to give (**71**) and (**72**) ⟨81JCS(P2)1512⟩. HMM undergoes an unusual acyl hydroperoxide oxidative transformation to 2,4-bis(dimethylamino)-6-[(dimethylamino)oxy]-1,3,5-triazine (**73**). Various peracid reagents gave acceptable yields (MCPBA/$CHCl_3$: 38%) (Scheme 13) ⟨85TL5247⟩.



Scheme 13

6.12.5.1.5 Cycloaddition reactions

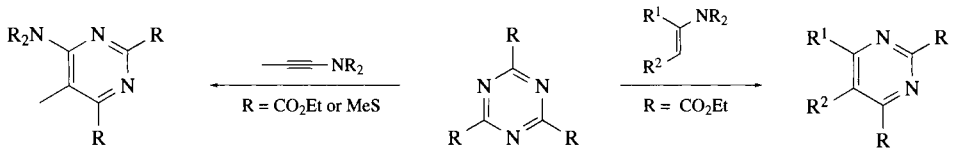
1,3,5-Triazine undergoes a regiospecific inverse electron demand cycloaddition reaction with pyrrolidine enamines to give pyrimidine products (e.g. (**74**)) (Equation (9)) ⟨82JOC2673, 82TL4559⟩.



(9)

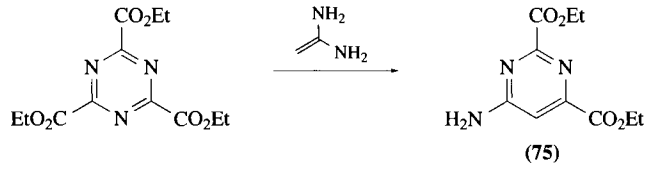
2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine reacts with ynamines and enamines in [4 + 2] cycloadditions followed by a retro-Diels–Alder reaction; 2,4,6-tris-(methylthio)-1,3,5-triazine reacts only with ynamines (Scheme 14) ⟨88T3379⟩.

1,1-Diaminoethene, produced *in situ* by reversible tautomerism of acetamidine hydrochloride,



Scheme 14

participates in [4 + 2] reactions with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine to form pyrimidine (**75**) (Equation (10)) ⟨92JOC1631, 93AG(E)273⟩.



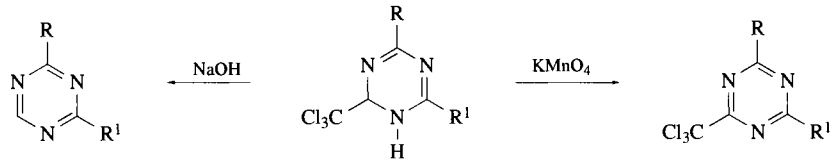
(10)

(**75**)

6.12.6 REACTIVITY OF NONCONJUGATED RINGS

6.12.6.1 Dihydro-1,3,5-triazines

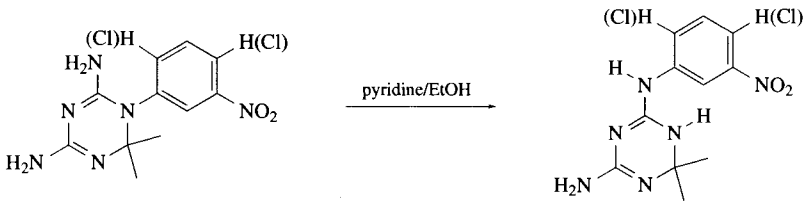
Dihydro-1,3,5-triazines have been reviewed elsewhere ⟨85AHC(38)91⟩. The dihydro-1,3,5-triazines (**76**) react with alcoholic NaOH to give triazine (**77**) by elimination of chloroform and are aromatized to triazine (**78**) on oxidation with permanganate (Scheme 15) ⟨87ZOR2443⟩.



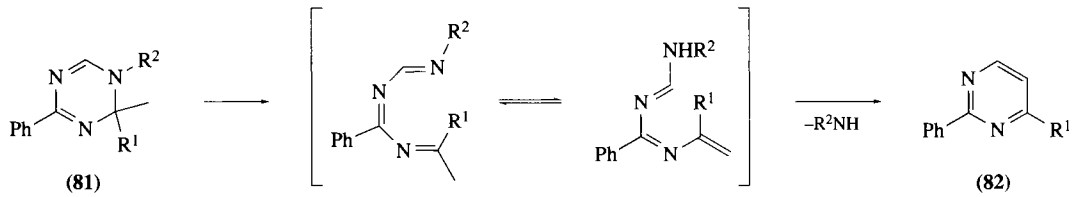
(**77**) (**76**) (**78**)

Scheme 15

Dimroth rearrangement in ethanolic pyridine at reflux temperature converts (**79**) into (**80**) ⟨93JHC849⟩. Dihydrotriazines (**81**) eliminate primary amine on thermal rearrangement to pyrimidines (**82**) (Scheme 16) ⟨86CB3737⟩.



(**79**) (**80**)

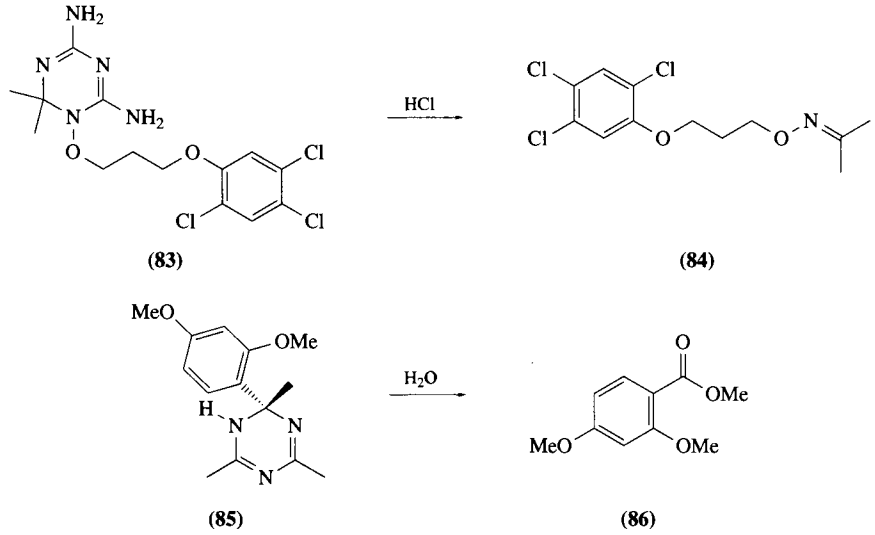


(**81**) (**82**)

Scheme 16

Dihydrotriazine (**83**) on acid hydrolysis gives the oxime degradation product (**84**) ⟨83H(20)839⟩ and the dihydrotriazine (**85**) decomposes when heated in water to give the ketone (**86**), acetamide (2.5%) and diacetamide (5%) (Scheme 17) ⟨83JCS(P1)1075⟩.

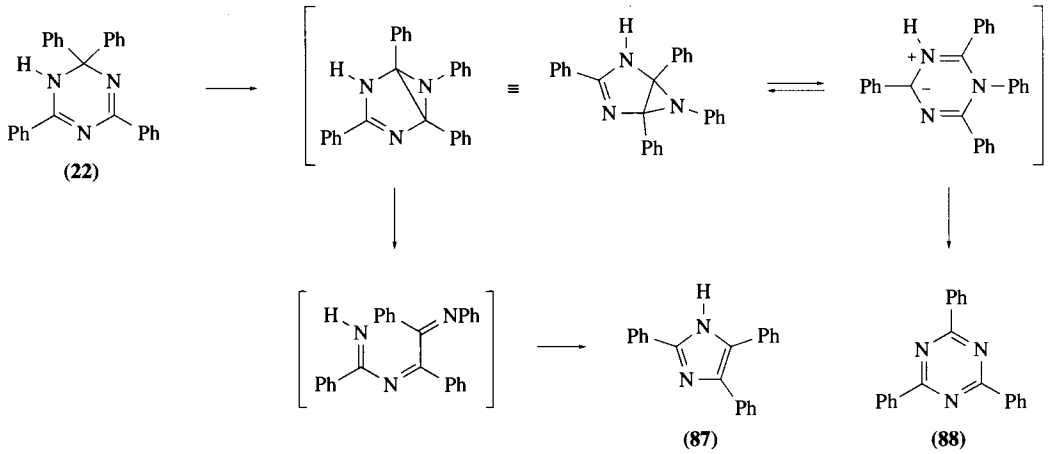
2,2,4,6-Tetraphenyldihydro-1,3,5-triazine (**22**) has been found to undergo photochemical reactions. Photolysis was carried out in benzene for 5 h and six products were isolated by chromatography. The products (**87**) and (**88**) were separated and identified; Scheme 18 is proposed to account for their formation ⟨88BCJ2487, 89BCJ3171⟩.



(83) (84)

(85) (86)

Scheme 17



(22) (87) (88)

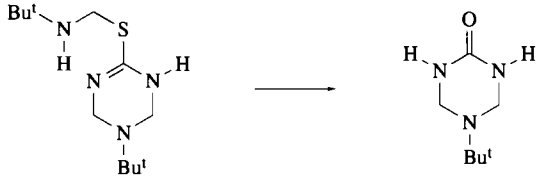
Scheme 18

6.12.6.2 Tetrahydro-1,3,5-triazines

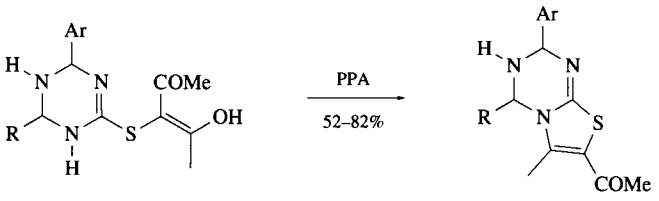
Alkaline hydrolysis of the triazine (**89**) gives the triazinone (**90**) ⟨90ZOB1436⟩. 4,6-Diaryl-3,4,5,6-tetrahydro-2-(2,4-dioxopent-3-ylthio)-1,3,5-triazines (**91**) were converted into the thiazolo[3,2-*a*]-1,3,5-triazines (**92**) on treatment with polyphosphoric acid (Scheme 19) ⟨84JCED99⟩.

6.12.6.3 Hexahydro-1,3,5-triazines

The chemistry of hexamethylenetetramine (hexamine) has been reviewed ⟨79S161⟩. Reaction of hexamine with nitrous acid in hydrochloric acid at pH 1 gives 1,3,5-trinitrosohexahydro-1,3,5-triazine. In acetic acid and ammonium nitrate 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX) is formed ⟨59GP1004618⟩. 1,3,5-Trinitrosohexahydro-1,3,5-triazine is oxidized to RDX in 74% yield with hydrogen peroxide in nitric acid at low temperatures (−40°C to 30°C) ⟨49MI 612-01⟩. Hexahydro-1,3,5-triazines are readily hydrolyzed in acid; thus 2,4-diketohexahydro-1,3,5-triazine gave 1-nitrobiuret with 70% nitric acid ⟨86EGP276864⟩. Sikorski *et al.* prepared *N,N*-methylenebis[*N*-(diaryloxyphosphinyl)methyl]glycine esters as herbicides from (**93**) (Equation (11)) ⟨86USP4601744⟩.



(89) (90)



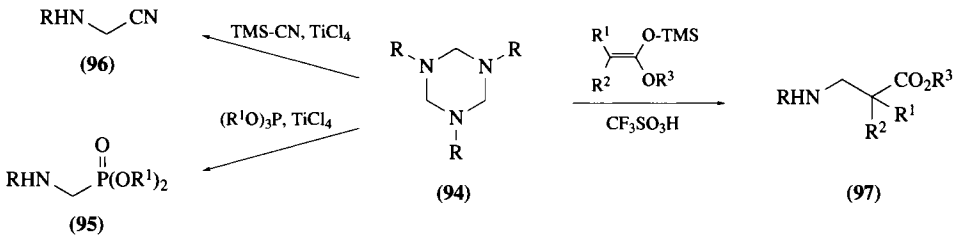
(91) (92)

Scheme 19

(93)

R = alkyl, aryl; Ar = substituted phenyl (11)

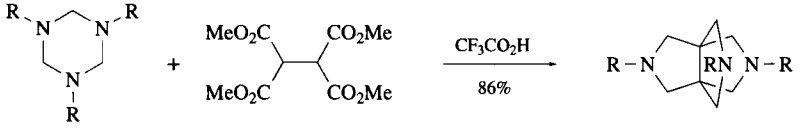
Lewis acid was used to produce *N*-methyleneamine equivalents from (**94**) which react with trialkyl phosphites to give (**95**) and with TMS-CN to give aminoacetonitriles (**96**) ⟨90MI 612-04, 91SC155⟩. Ketene silyl acetals react with (**94**) to give aminoesters (**97**) in the presence of triflic acid (Scheme 20) ⟨85CPB1579⟩.



(96) (95) (94) (97)

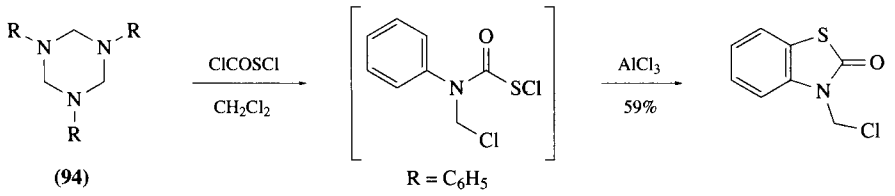
Scheme 20

Use of trifluoroacetic acid as catalyst in the reaction of (**94**) with tetramethyl ethane-1,1,2,2-tetracarboxylate gave the propellane (**98**) (Equation (12)) ⟨85HCA610⟩.



(94) R = CH_2Ph (98) (12)

3-Chloromethyl-2(3*H*)-benzothiazolones were prepared from (**94**) and chlorocarbonylsulfenyl chloride (Scheme 21) ⟨88S482⟩.



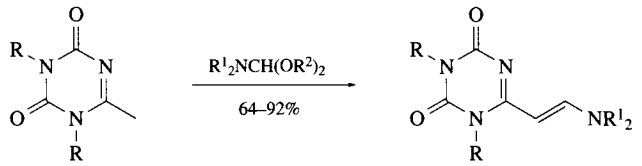
Scheme 21

6.12.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

6.12.7.1 Reactivity of Carbon Substituents

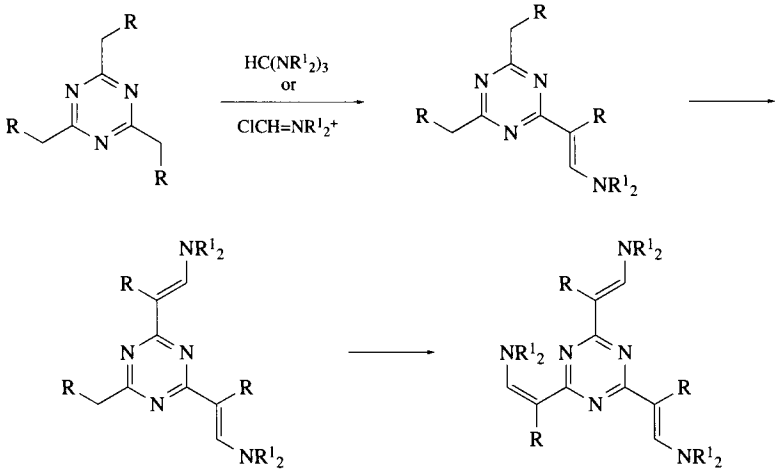
Alkyl groups attached to carbon of a 1,3,5-triazine ring are α to two ring nitrogens and therefore are activated to react with electrophilic species under basic or acidic conditions.

2,4-Diamino-6-methyl-1,3,5-triazine has been shown to react with aldehydes in the presence of potassium hydroxide or methanesulfonic acid ⟨91CPB3180⟩. Equation (13) shows a similar type of reaction in which formamide (or lactam) acetals condense with the active methyl group of a 1,3,5-triazinedione ⟨85LA65⟩.



(13)

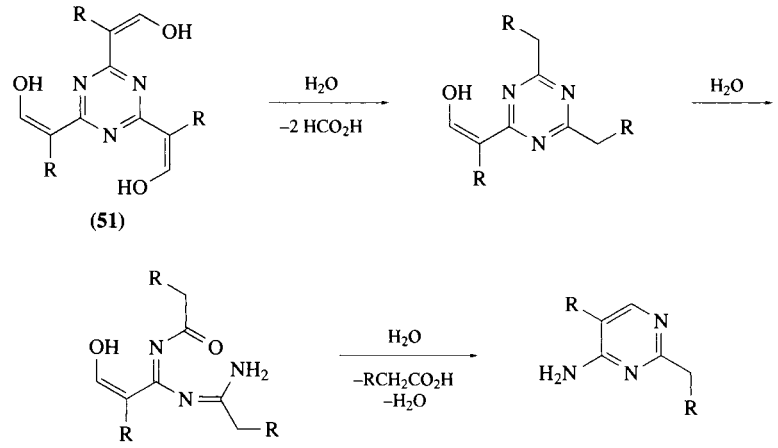
Liebscher and co-workers attempted the multiple iminoformylation of 2,4,6-trialkyl-1,3,5-triazines (Scheme 22) ⟨92JHC1125⟩. Tris(arylmethyl)triazines react with trismorpholinomethane in toluene at reflux temperature to give 2-(arylmethyl)-4,6-bis(aminoalkenyl)-1,3,5-triazines via bis-iminoformylation. A fusion reaction (no solvent) gave threefold iminoformylation. Mono-iminoformylation was achieved with the use of chloromethylene iminium salt when heated for 2 min in an excess of the corresponding formamide as solvent, for R = Et only. Prolonged heating at 70 °C in formamide gave threefold iminoformylation in all examples of R substituents. Aqueous workup gave hydrolysis products which can exist in unusual tautomeric forms (see Section 6.12.4.5).



Scheme 22

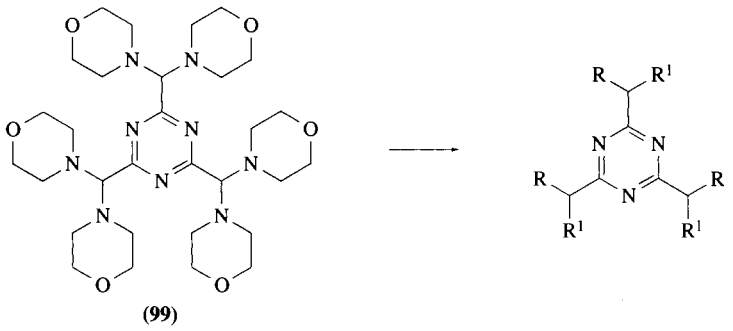
Acid hydrolysis of 2,4,6-tris(aminoalkenyl)-1,3,5-triazines (**48**) has now been shown to give 1-amino-5-aryl-2-benzylpyrimidines via the trisenol tautomer (**51**) (Scheme 23) (see Section 6.12.4.5) ⟨92LA411⟩.

2,4,6-Tris(dimorpholinomethyl)-1,3,5-triazine (**99**) has been found to behave as a synthetic equivalent of the still unknown 1,3,5-triazinetricarbaldehyde. Trisphenylhydrazones, trioximes, tri-



Scheme 23

semicarbazones, and tris[bis(*N*,*N*-dimethylamino-4-phenyl)methyl]-1,3,5-triazines have been obtained from (**99**) (Equation (14)) ⟨87JHC793⟩.



(14)

(**99**)

R, R^1 = $NNHCONH_2$, 98%; R, R^1 = $C_6H_4NMe_2$-4, 45%
R, R^1 = $NNHC_6H_5$, 90%; R, R^1 = NOH, 79%; R, R^1 = $NNHC_6H_3(NO_2)_2$-2,4, 99%

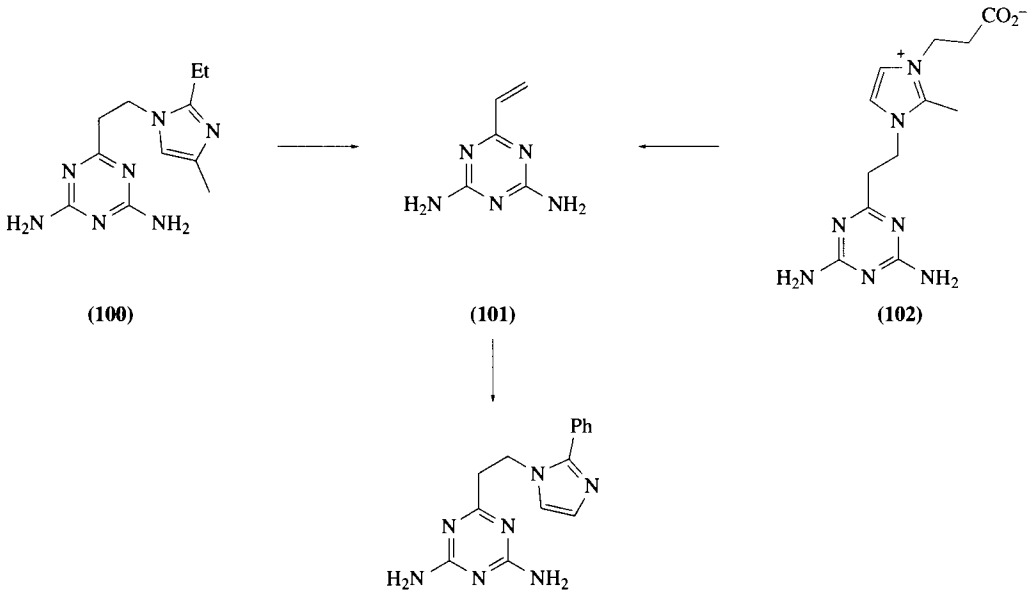
The 2,4-diamino-1,3,5-triazine (**100**) when heated in the presence of polymerization inhibitors, under reduced pressure, formed the vinyltriazine (**101**); 2-ethyl-4-methylimidazole was eliminated ⟨85JAP60181077⟩. The same product (**101**) was obtained from (**102**) with aqueous sodium hydroxide ⟨85JAP59216879⟩. The reaction can be reversed, in that vinyltriazine (**101**) reacts with 2-phenylimidazole to form the diaminotriazine (**103**) equivalent to (**100**) (Scheme 24) ⟨85JAP6084283⟩.

The expected reactions of the cyano group attached to triazine ring carbon with amine, alcohol, and azide nucleophiles have been described ⟨90NKK396⟩. Reduction of ketone to alcohol with sodium borohydride ⟨88HCA712⟩ and trichloromethyl groups to methyls with lithium aluminum hydride are also reported ⟨86MI 612-02⟩.

6.12.7.2 Reactivity of Nitrogen Substituents

An *N*-acetylcysteine-melamine adduct (**105**) has been described as shown in Scheme 25. The mechanism probably involves a methyleneiminium ion (**104**). *N*-Hydroxymethyl compounds are produced by the metabolism of materials which contain *N*-methyl groups by preparations of murine liver. Hexamethylmelamine (HMM) is hydroxylated by this route, which involves cytochrome P450. As electrophiles, these *N*-hydroxymethyl compounds may be excreted as glutathione conjugates, hence (**105**) and other *N*-acetylcysteine and glutathione derivatives were prepared as part of a study of possible biochemical mechanisms ⟨85JCS(P1)75⟩.

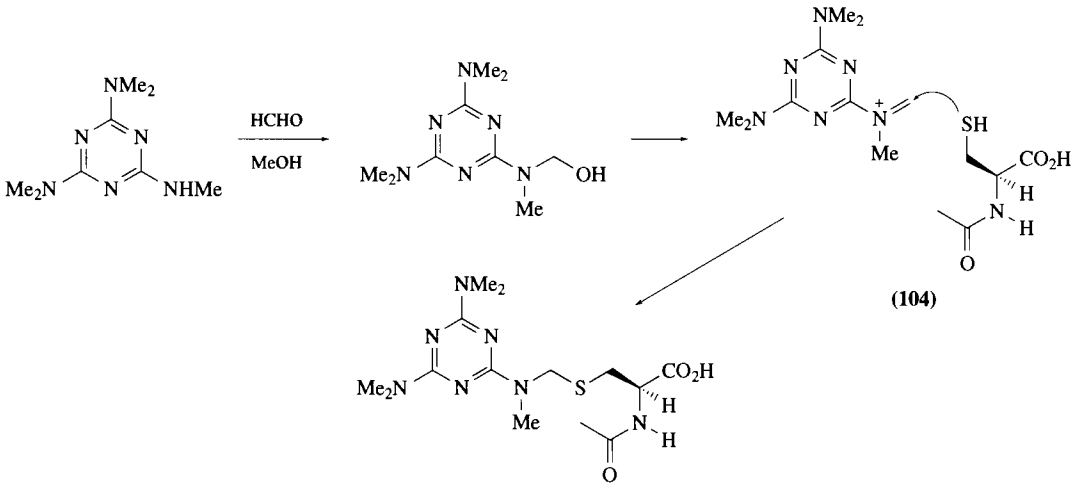
Highly reactive electrophilic thiocarboxylating reagents (e.g. trichloromethanesulfenyl chloride) react with alkylamino-1,3,5-triazines at the least sterically hindered exocyclic nitrogen ⟨88JHC193⟩. Dimethyl sulfide ditriflate is an effective reagent for the conversion of melamine into the corresponding tris(sulfilimine) ⟨86S490⟩. Numerous patents have described the conversion of amino-



(100) (101) (102)

(103)

Scheme 24



(104)

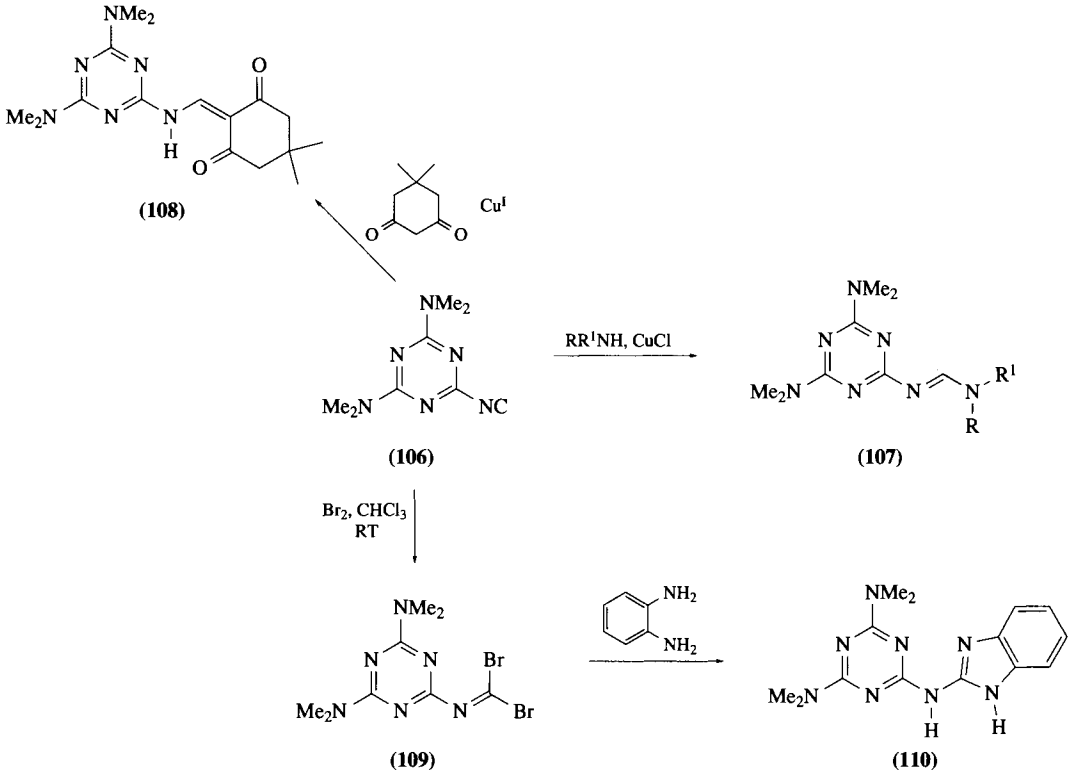
(105)

Scheme 25

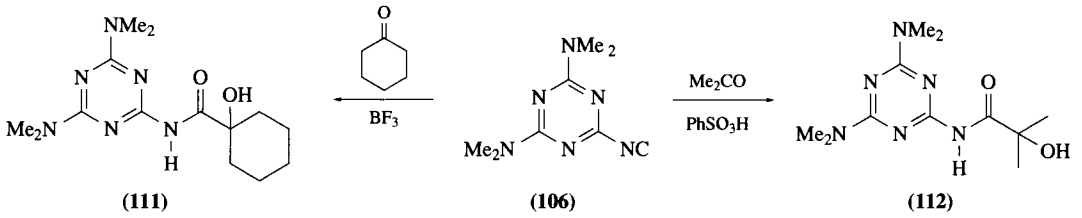
triazines into sulfonyl ureas by reaction with sulfonyl isocyanates, e.g. ⟨83EUP71958, 88CP1243676, 90MIP9113880⟩.

2-Amino-4,6-bis(dimethylamino)-1,3,5-triazine has been converted by the Hofmann carbylamine reaction under phase-transfer conditions into 4,6-bis(dimethylamino)-2-isocyano-1,3,5-triazine (**106**), which reacts with amines in the presence of copper salts to form triazinylformamidines (**107**). Reaction with active methylene compounds in the presence of base also occurred to give, e.g. (**108**), which illustrates the high electrophilic reactivity of (**106**) compared with simple alkyl isocyanides. The reactions of (**106**) with electrophiles such as bromine gave (**109**), which was not isolated but converted into (**110**) with *o*-phenylenediamine and base (Scheme 26) ⟨89JHC901⟩.

Reaction of (**106**) with cyclohexanone and acetone, activated by Lewis acid or strong protonic acid, was sluggish, but afforded the corresponding 2-hydroxyamides (**111**) and (**112**) respectively (Scheme 27).

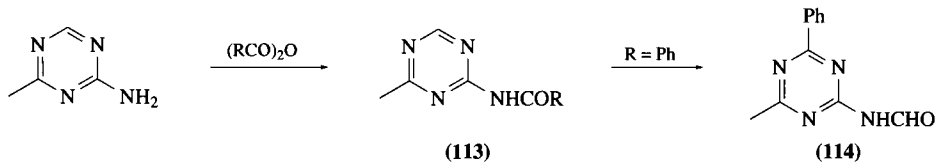


Scheme 26



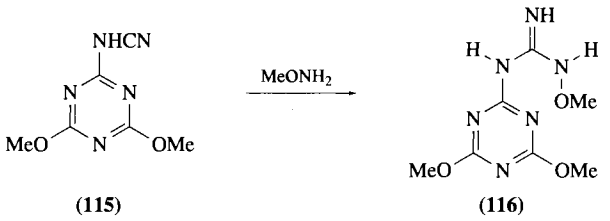
Scheme 27

Aminotriazines are acylated with acid anhydrides ⟨91CZ186⟩ and the products can undergo Dimroth rearrangement, e.g., (**113**) to (**114**) (Scheme 28) ⟨87AKZ749, 87MI 612-02⟩.



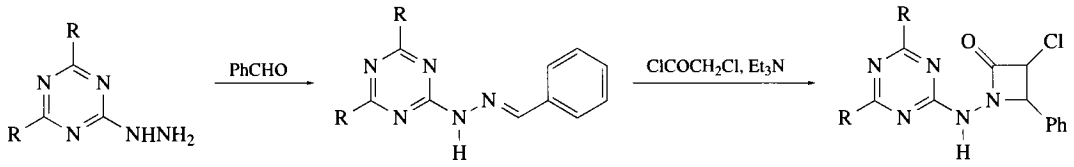
Scheme 28

Cyanoamino-1,3,5-triazines are known ⟨86GEP3507749, 86GEP3507750⟩ and the cyano group is readily transformed by known reactions. Hydration with ethanolic HCl gives triazinyl ureas ⟨84BCJ2009⟩, sodium alkoxide forms *O*-alkyltriazinyl isoureas ⟨82AKZ799⟩, and hydrogen sulfide and aqueous ammonia the thioureas ⟨85EGP228548⟩. 2-Chloro-4,6-dimethoxy-1,3,5-triazine reacted with sodium cyanamide to form the cyanoamine (**115**) which reacts with *O*-methylhydroxylamine to give the guanidine (**116**) (Equation (15)) ⟨87GEP3528099⟩.



(115) (116) (15)

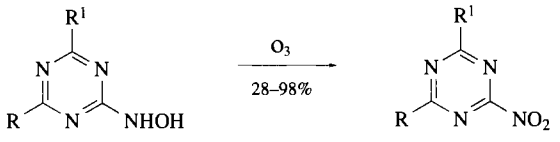
N-Cyano-*N*-(methoxycarbonylalkyl)amino groups attached to 1,3,5-triazines have been reacted with hydrazine to give imidazolyltriazines ⟨89AKZ192⟩. The same author also reacted an aminonitrile with a chloroacetamide to give the same imidazolyltriazine structure with a phenyl substituent. Hydrazones (**117**) are available from hydrazinotriazines on reaction with benzaldehyde and have been converted into β-lactams (**118**) by reaction with chloroacetyl chloride and base (Scheme 29) ⟨91MI 612-03⟩.



R = NHMe (117) (118)

Scheme 29

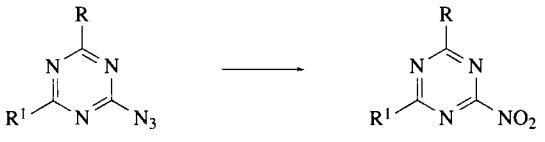
Ozonolysis of 2-hydroxylamino-1,3,5-triazines (**119**) gave 2-nitro-1,3,5-triazines (**120**) (Equation (16)) ⟨90KGS657⟩.



(119) (120) (16)

R = Ph, Me, NMe_2; R^1 = Ph, Me, 4-FC_6H_4, NMe_2

Nitrotriazines are reported to be formed by photolysis of azido-1,3,5-triazines (**121**) in $CHCl_3$ or MeCN in the presence of air (Equation (17)) ⟨87IZV1196⟩.



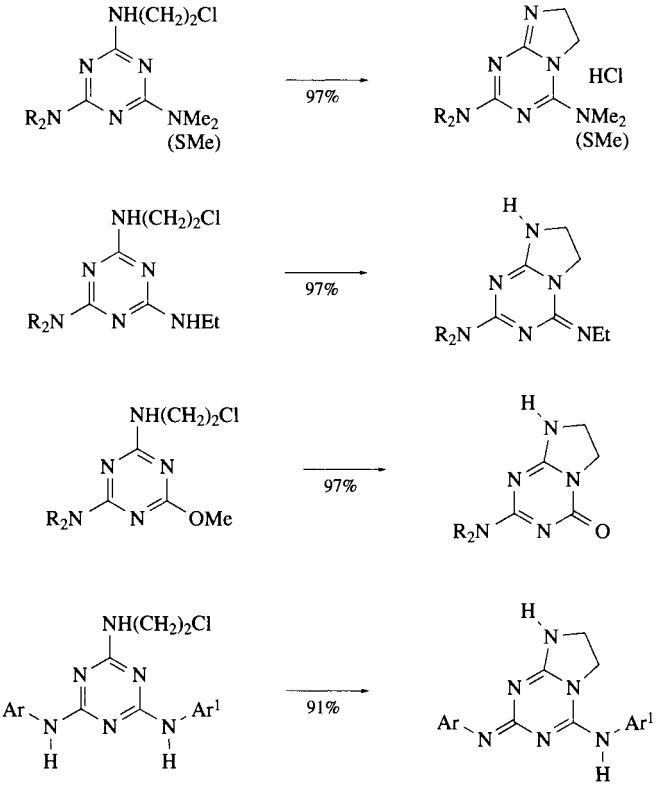
(121) R = Me_2N, MeO; R^1 = Me_2N (17)

Bicyclic products are obtained by intramolecular nucleophilic displacements by the ring nitrogen. Thermolysis of 2[(2-chloroethyl)amino]-1,3,5-triazines for example, gave various types of bicyclic products (Scheme 30) ⟨87NKK40, 92KGS228⟩.

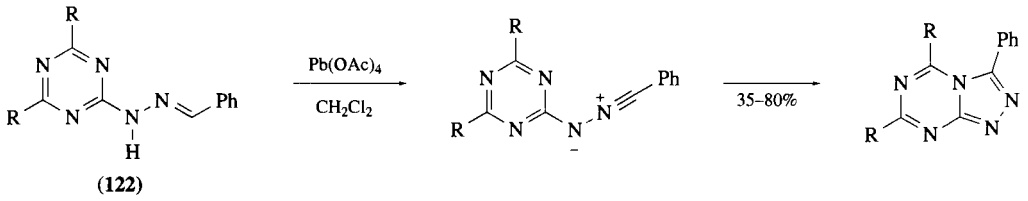
Treatment of triazines (**122**) with lead tetraacetate in dichloromethane was reported by Stevens and co-workers to give the bicyclic products shown in Scheme 31 ⟨84JCS(P1)993⟩.

6.12.7.3 Reactivity of Oxygen Substituents

Claisen rearrangements of 2,4-di(*N*-arylamino)-1,3,5-triazin-6-ylprop-2-ynyl ethers (**123**) have been investigated. The thermal rearrangement of (**123**) yields either 6-methylenimidazo[1,2-*a*]-1,3,5-triazin-4-one (**124**) or isomer (**125**) dependent upon reaction time. Under the influence of mercuric trifluoroacetate at room temperature, the triazine (**123**) was rearranged to (**124**) only; allyl ethers



Scheme 30



(122)

Scheme 31

were found not to rearrange (Scheme 32) ⟨80TL4731, 85T111⟩. A possible mechanism has been proposed to explain this novel transformation (Scheme 33) based on the fact that 2,4-di(*N*-arylamino)-1,3,5-triazinyl-6-yl allyl ethers did not undergo Claisen rearrangement when heated in 1,2-dichlorobenzene.

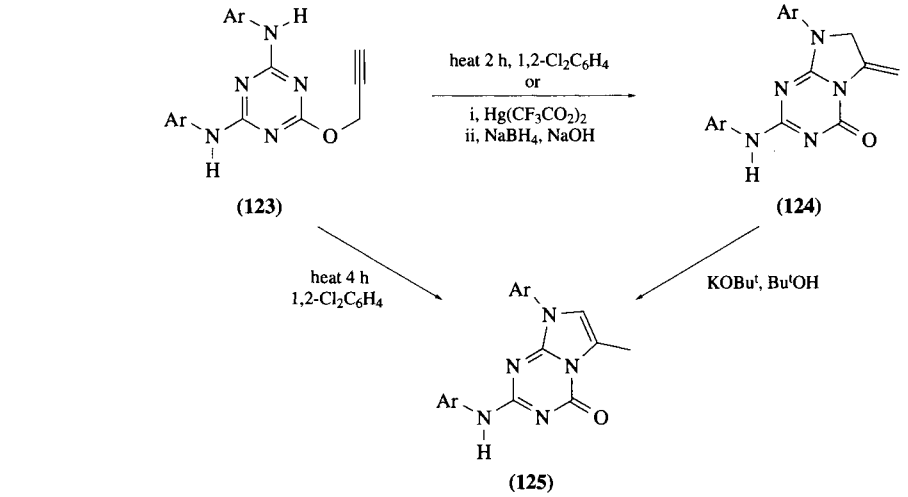
Cyanurate–isocyanurate rearrangements are well known ⟨83IZV2369⟩. An application of the thermal rearrangement (230 °C) to an amine synthesis has been utilized in the preparation of 2-(2-thienyl)ethylamine from 2-(2-thienyl)ethanol in 77% overall yield. A mechanism for the tetrabutylphosphonium bromide-catalyzed rearrangement was proposed (Scheme 34) ⟨93SC1307⟩.

Amino-oxy-triazines condense with aldehydes and ketones, isocyanates, chloroformates, and sulfonyl halides in the normal way ⟨87AKZ749⟩.

Internal nucleophilic displacement reactions of (**126**) to give bicyclic products (**127**) have been reported (Scheme 35) ⟨92KGS228⟩.

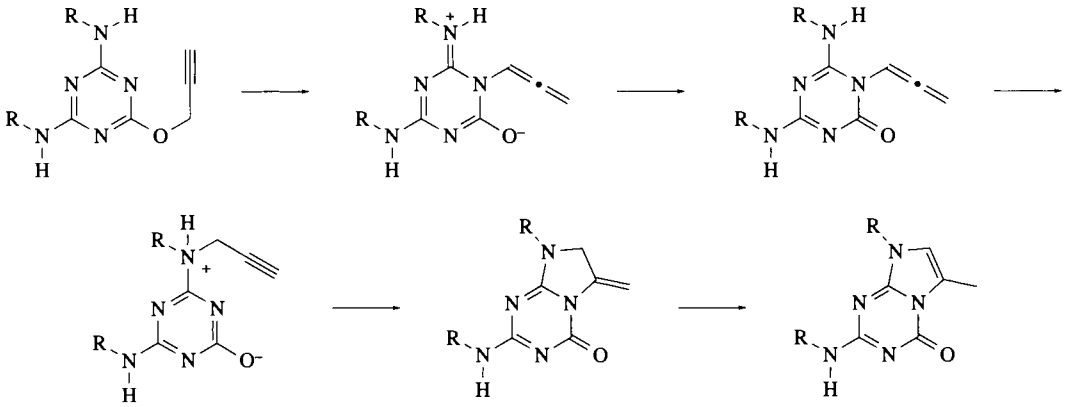
6.12.7.4 Reactivity of Phosphorus Substituents

Reactions of groups attached to 1,3,5-triazine through phosphorus are uncommon. There is a report on the preparation of triazinylphosphonic acids and their use in fire-resistant polymeric compositions. The acids are prepared by hydrolysis of the corresponding esters by generation



(123) (124) (125)

Scheme 32



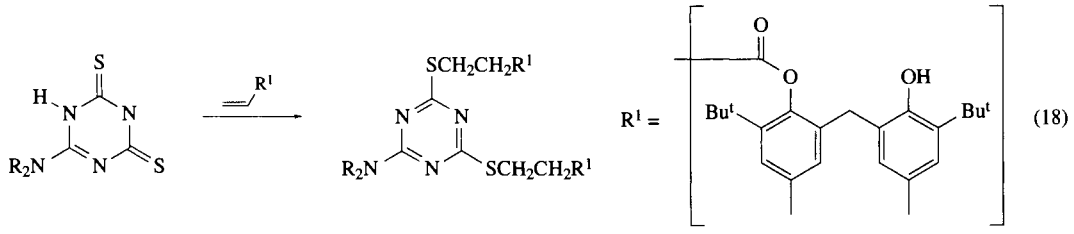
Scheme 33

of the bis(trimethylsilyl)phosphonate, followed by reaction with methanol or water (Scheme 36) ⟨93EUP547714⟩. The esters were prepared via an Arbusov reaction from the relevant chlorotriazine ⟨57JOC444⟩.

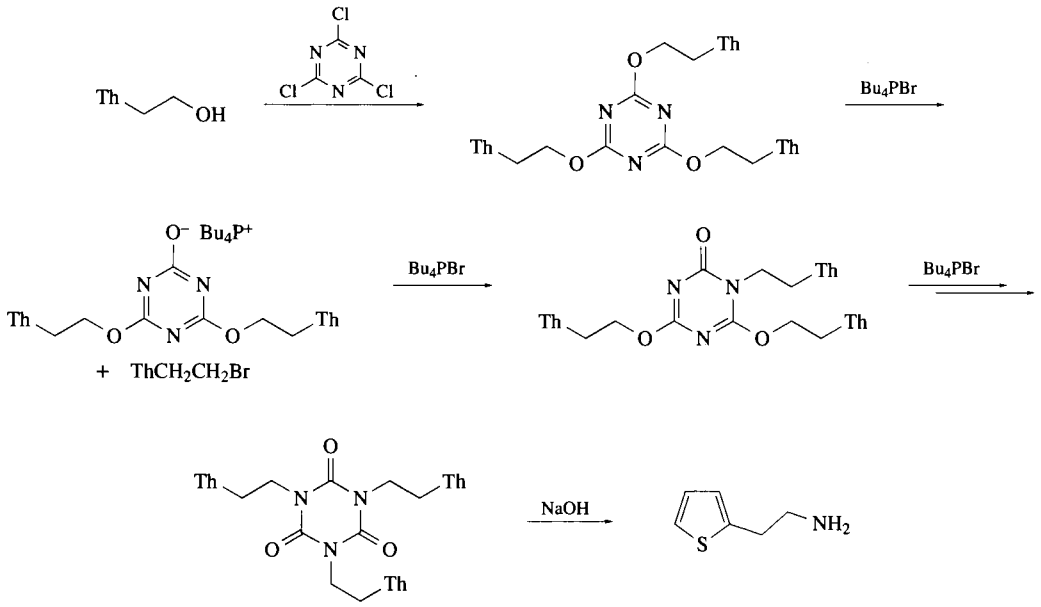
6.12.7.5 Reactivity of Sulfur Substituents

Alkylation of 1,3,5-triazinethiones occurs on sulfur (Scheme 37) ⟨84JCED99, 89MI 612-03, 91AKZ173⟩.

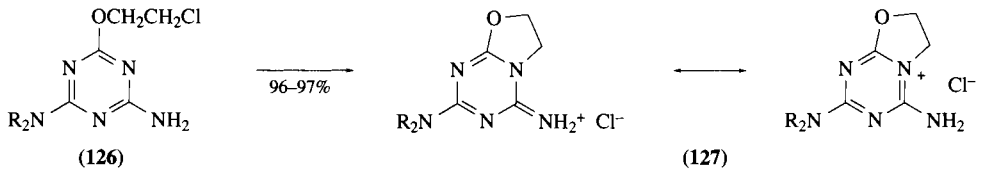
Michael reactions have also been reported, e.g. with acrylonitrile, as expected ⟨89MI 612-03⟩, and with acrylates to give useful antioxidants for polybutadiene gum (Equation (18)) ⟨83JAP58103375⟩. Iodine in aqueous potassium hydroxide has been shown to oxidize triazinethiones to the appropriate disulfides ⟨86IZV1437⟩.



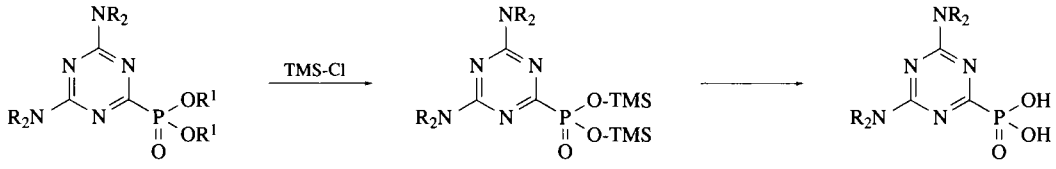
(18)



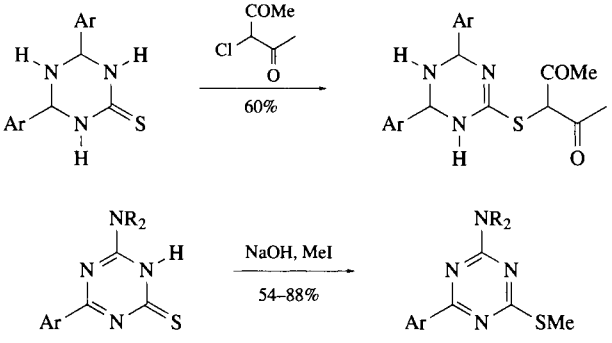
Scheme 34



Scheme 35



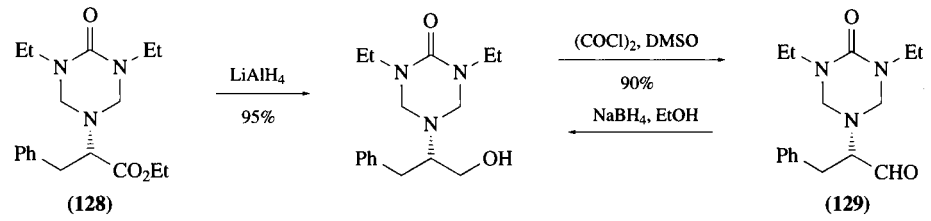
Scheme 36



Scheme 37

6.12.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN ATOMS

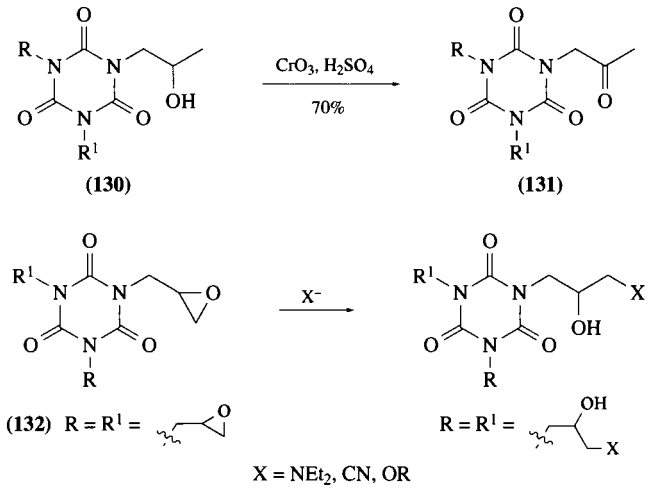
Tris(3-aminophenyl)isocyanurates were obtained on hydrogenation (Pt/C catalyst in dioxan at 70 °C, 3 kg cm^2 pressure, 4 h) of the corresponding nitro compounds ⟨87JAP62205064⟩. *N*-Aminopropyl-hexahydro-1,3,5-triazine-2,4-diones were obtained by hydrogenation of the corresponding nitriles over nickel catalyst at elevated temperatures ⟨90EGP284288⟩. *N*-(α-Ethoxycarbonyl) phenethyltriazinones (**128**) were converted by lithium aluminum hydride reduction and Swern oxidation into the corresponding α-aldehydes (**129**) without racemization (Scheme 38) ⟨90TL2109⟩.



(128) (129)

Scheme 38

Secondary alcohols (**130**) were oxidized to ketones (**131**) with chromium trioxide in sulfuric acid ⟨84JAP5993064⟩. Epoxide (**132**) was opened by amines ⟨91AKZ173⟩, by cyanide ⟨83JAP5818371⟩, and by alcohols ⟨90AKZ733⟩ as illustrated in Scheme 39.

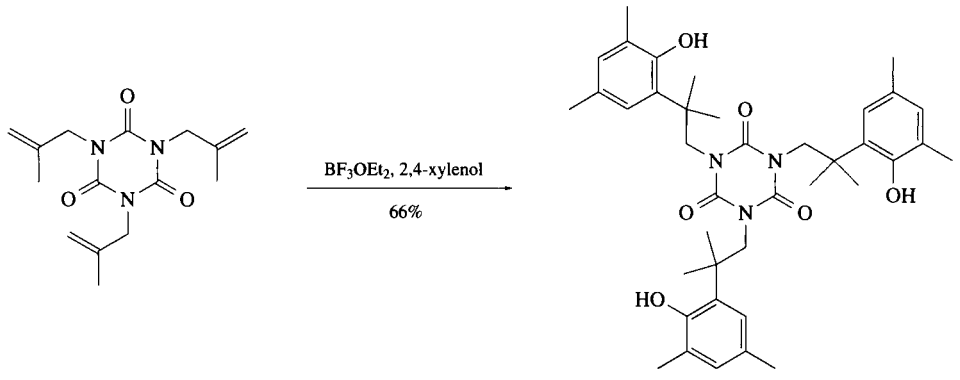


(130) (131)

(132) R = R¹ = R = R¹ =

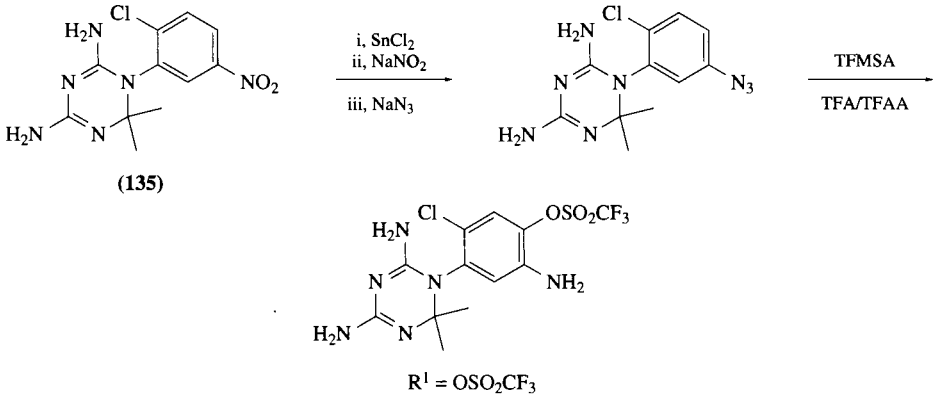
Scheme 39

Silylated substituents on the nitrogen atoms of isocyanurates have been manipulated in a variety of ways to produce 4-hydroxy-, -acyloxy-, and -carboxy-phenyl derivatives ⟨93JOC1932⟩, and trismethallyl isocyanurate (**133**) has been condensed with 2,4-xylenol to obtain (**134**), a potential polymer stabilizer (Equation (19)) ⟨89USP4826983⟩.



(133) (134) (19)

Sterically hindered positions of 1-aryl-4,6-diamino-1,3,5-dihydrotriazines (**135**) have been substituted by the triflate group. As shown in Scheme 40, reduction of nitro groups and diazotization–azidation reactions in the benzene ring are straightforward ⟨93JHC849⟩.



(135)

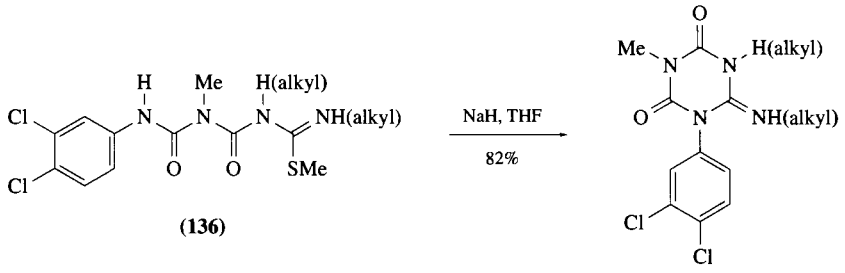
Scheme 40

6.12.9 SYNTHESES

The nucleophilic, stepwise displacement of chlorine from cyanuric chloride is usually the first method considered for preparation of 1,3,5-triazine derivatives (see Section 6.12.5.1.4). When this approach is not applicable, construction of the 1,3,5-triazine ring from various subunits by formation of carbon–nitrogen bonds is the alternative approach. No new synthetic strategies have emerged over the past decade and synthetic routes are based on the same fundamental principles described in previous reviews.

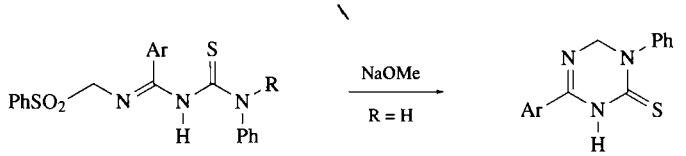
6.12.9.1 Synthesis by Formation of One Carbon–Nitrogen Bond

6-Imino-dihydro-1,3,5-triazine-2,4-diones have been prepared by ring closure of the biuret (**136**) with sodium hydride in tetrahydrofuran (Equation (20)) ⟨84EGP211111⟩.



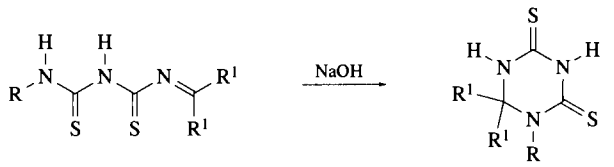
(136) (20)

Regioselective heterocyclization of the thiourea derivative (**137**) with sodium methoxide gave the dihydrotriazinethione (**138**). If the R substituent was other than hydrogen, thiadiazines were formed (Equation (21)) ⟨90DOK31⟩.



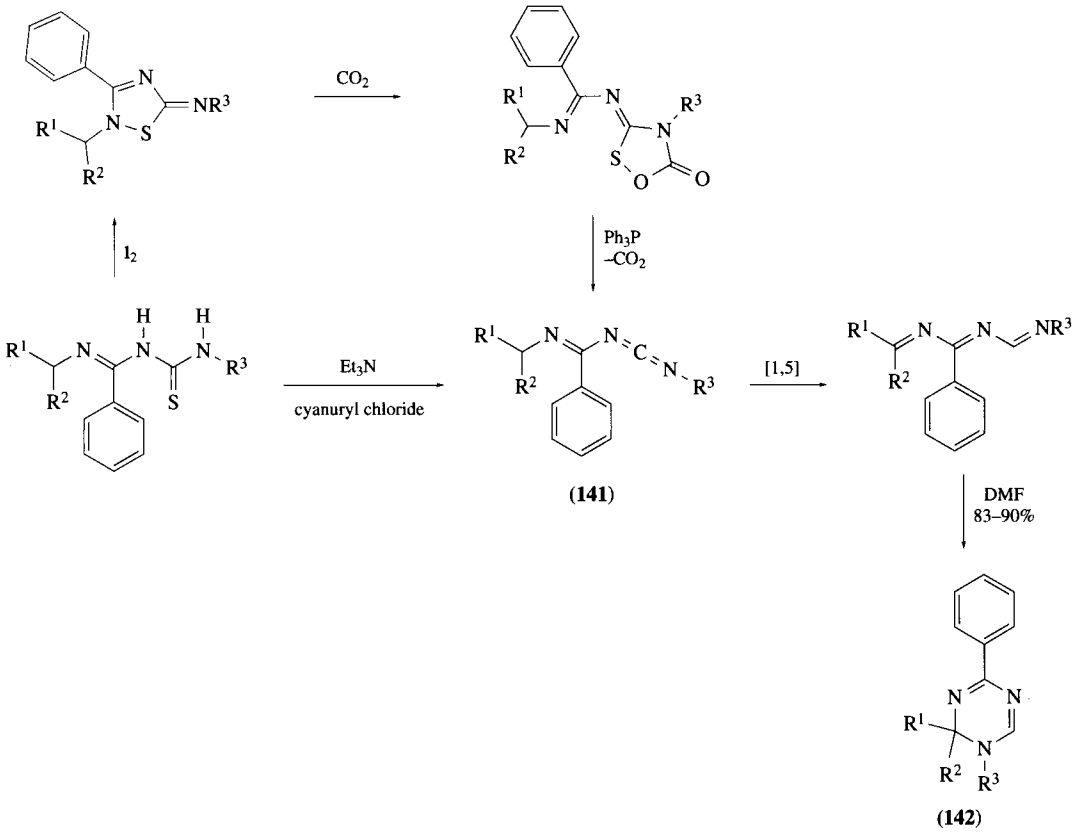
(137) (138) Ar = C_6H_5, 4-MeC_6H_4 (21)

1-Alkylidene-2,4-dithiobiurets (**139**) when warmed in aqueous sodium hydroxide were cyclized to 1-alkyl/aryl-6,6-dialkyl-dihydro-1,3,5-triazine-2,4-dithiones (**140**) (Equation (22)) ⟨90JIC849⟩.



(139) (140) (22)

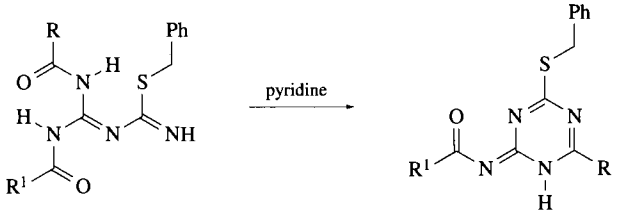
Goerdeler and Eggers have described the synthesis of dihydro-1,3,5-triazines (**142**) by rearrangement of carbodiimides (**141**). The mechanism was shown to be a [1,5] sigmatropic shift of a hydrogen atom of the carbodiimide, followed by electrocyclic ring closure to form the dihydro-1,3,5-triazine (**142**) (Scheme 41) ⟨86CB3737⟩.



(141) (142)

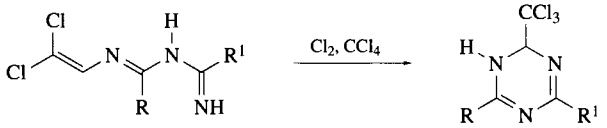
Scheme 41

The guanidine (**143**) cyclizes in pyridine to the triazine (**144**) (Equation (23)) ⟨88IJC(B)269⟩.



(143) (144) (23)

The dihydrotriazine (**146**) was prepared by cyclization of the amidine derivative (**145**) with chlorine in carbon tetrachloride (Equation (24)) ⟨87ZOR2443⟩.



(145) (146)

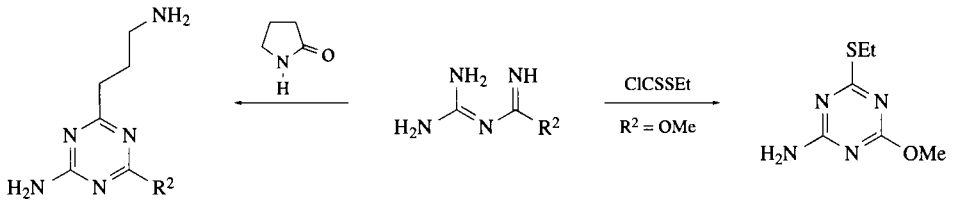
(24)

6.12.9.2 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [5 + 1] Atom Fragments

Biguanides are the most frequently used five-atom fragment in the synthesis of 1,3,5-triazines. Some new one-atom fragments have been used and an amine as the one-atom fragment has been described.

6.12.9.2.1 Synthesis with biguanides as the five-atom fragment

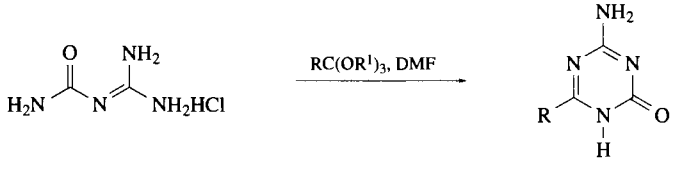
γ-Butyrolactam and ethyl chlorodithioformate are used as one-atom fragments to introduce the 3-aminopropyl and mercapto groups into the 1,3,5-triazine ring respectively (Scheme 42) ⟨87MI 612-03, 90ZAAC(585)151⟩.



Scheme 42

6.12.9.2.2 Synthesis from other five-atom fragments

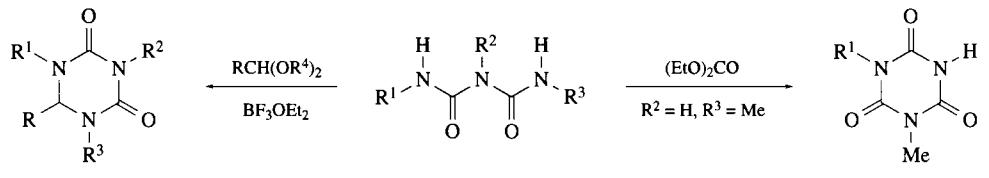
Triazinones (**147**) were synthesized by the cyclocondensation of the *N*-carbamoylguandine hydrochloride with an orthoester in DMF at 100 °C (Equation (25)) ⟨90CZP269077⟩. Triazinones (**147**) are also available (51–93%) from biguanides and diethyl azodicarboxylate with an improvement in yield compared with the use of ethylene carbonate (47%) ⟨90JHC1213⟩.



(147)

(25)

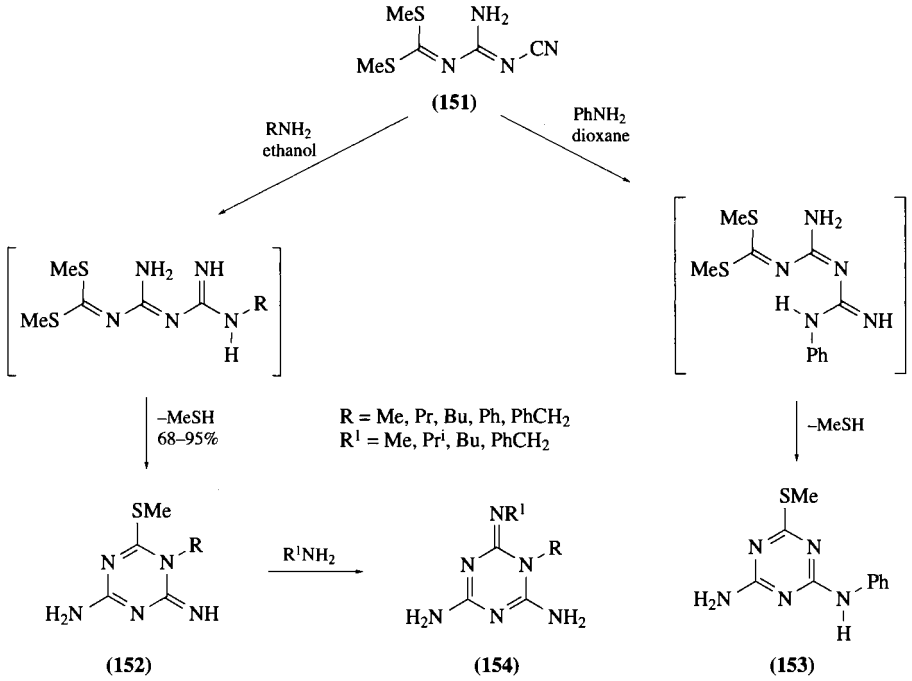
Dihydrotriazinediones (**149**) were prepared when biurets (**148**) cyclocondensed with aldehyde acetals in the presence of boron trifluoride etherate ⟨82JAP57145864⟩. Triazinetriones (**150**) were obtained if the biuret (**148**) was cyclized with diethyl carbonate (Scheme 43) ⟨86GEP3516632⟩.



(149) (148) (150)

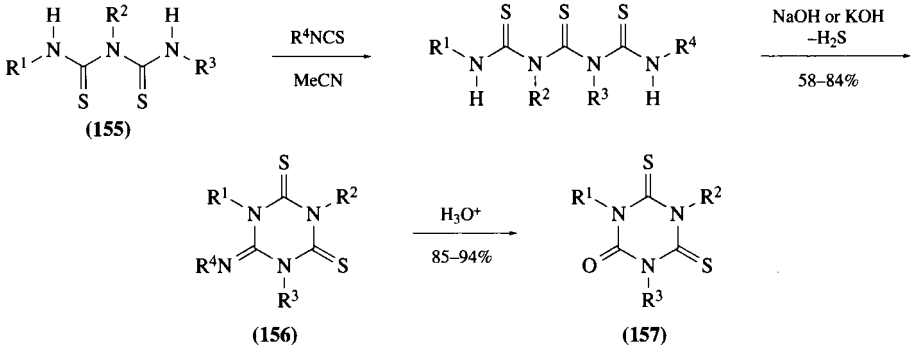
Scheme 43

Amines can be employed as the one-atom fragment. When primary amines were heated (30°C) with the cyanoguanidine (**151**) in ethanol, 1,3,5-triazinimines (**152**) were formed in good yield ⟨82EGP156810⟩. A change in solvent from ethanol to dioxane gave 2-amino-4-methylthio-6-phenylamino-1,3,5-triazine (**153**) as the product. The 1,3,5-triazinimine (**152**) reacted with amines to produce the isomelamine (**154**) (Scheme 44) ⟨90NKK173⟩.



Scheme 44

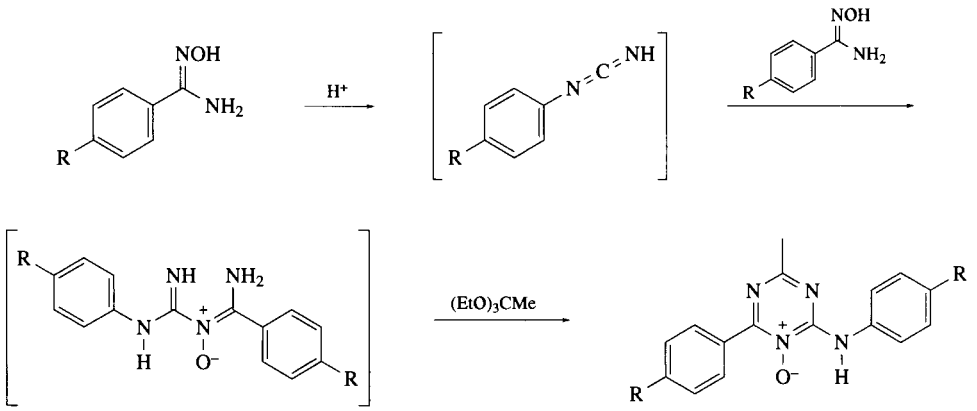
Reaction of isothiocyanates with 1,3,5-trisubstituted 2,4-dithiobiurets (**155**) in the presence of powdered sodium or potassium hydroxide in a polar solvent gave 1,3,5-trisubstituted 6-(substituted-imino)-1,3,5-triazine-2,4-dithiones (**156**). Condensation of the isothiocyanate did not occur on a nitrogen bearing an aryl substituent. Other modes of cyclization may be envisaged, but only (**156**) was found. Triazines (**156**) were sensitive to acid and readily hydrolyzed to 4,6-dithioxotetrahydro-1,3,5-triazin-2-ones (**157**) (Scheme 45) ⟨82S1070⟩.



Scheme 45

Kaugars and Watt have described a Beckmann rearrangement of an amidoxime to a carbodiimide

(or cyanamide) which reacts with more amidoxime followed by ring closure with orthoacetate to form a 1,3,5-triazine *N*-oxide (Scheme 46) ⟨93JHC497⟩.

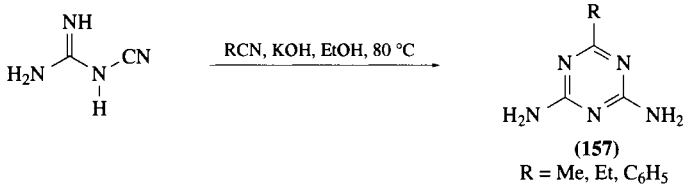


Scheme 46

6.12.9.3 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [4 + 2] Atom Fragments

6.12.9.3.1 Synthesis from dicyandiamide

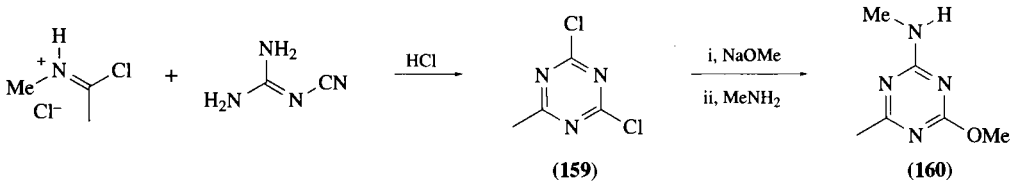
2,4-Diamino-1,3,5-triazines are prepared from dicyandiamide and a nitrile. The condensations are catalyzed by potassium hydroxide and subjected to temperatures between 82 °C and 150 °C for 1.5–44 h dependent on the nitrile used ⟨85JAP60166671, 87CZP246648, 88JAP0190174, 89JAP01294666, 91JAP03145476, 92MIP11247⟩. Acetonitrile, propionitrile, and benzonitrile condensed with dicyandiamide in ethanol with KOH at 80 °C for 24–44 h to give the triazines (**158**) in 85%, 52%, and 72% yield respectively (Equation (26)) ⟨82JHC493⟩.



(26)

(**157**)
R = Me, Et, C_6H_5

Chiang has developed a process for the preparation of 2-methyl-4-methylamino-6-methoxy-1,3,5-triazine (**160**) as an intermediate in the manufacture of sulfonylurea herbicides. Thus, cyclocondensation of dicyandiamide in the presence of HCl with the halomethyleneiminium salt formed from *N*-methylacetamide and phosphorus oxychloride gave the dichlorotriazine (**159**), which was treated with sodium methoxide and methylamine to give (**160**) (Scheme 47) ⟨92USP5095113⟩.

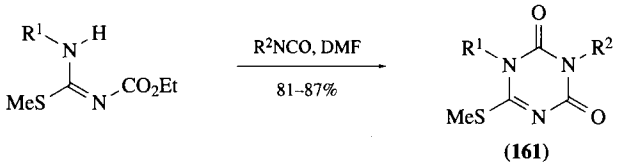


Scheme 47

6.12.9.3.2 Synthesis from other four-atom fragments

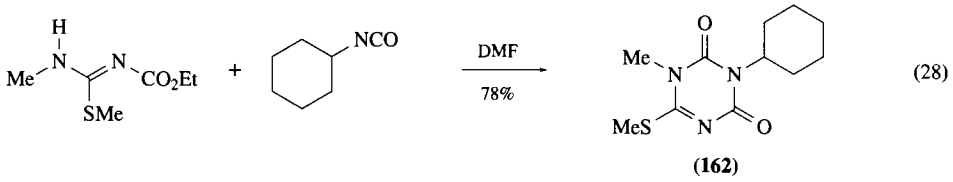
1,3,5-Triazine-2,4(1*H*,3*H*)-diones are of particular interest as potential herbicides. The standard synthetic approach is the reaction of an isocyanate with a urea or thiourea derivative.

N-Ethoxycarbonyl-*S*-methylisothioureas react with isocyanates in DMF at room temperature to give the triazinediones (**161**) (Equation (27)) ⟨84S770⟩.

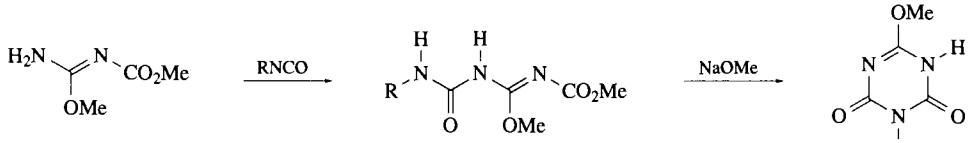


(161) (27)

Reaction of *N*-ethoxycarbonyl-*N*^{1},*S*-dimethylisothiourea with cyclohexyl isocyanate at room temperature gave the 1,3,5-triazine-2,4(1*H*,3*H*)-dione (**162**) in 78% yield (Equation (28)) ⟨85JAP60166672⟩. *N*-Methoxycarbonyl-*O*-methylisoureas (**163**) also react with isocyanates, and the intermediate (**163**) can be cyclized in methoxide/methanol at reflux temperature to the 1,3,5-triazine-2,4-dione (**164**) (Scheme 48) ⟨86GEP3516631⟩. Imino derivatives can be used instead of isocyanates for reaction with *N*-alkoxycarbonylisoureas and isothioureas. The 1,3,5 triazin-2(1*H*)-one derivatives (**165**), which are useful as diuretics, as antibacterial and antiinflammatory agents, and as analgesics, were prepared this way (Equation (29)) ⟨82JAP57144269⟩.

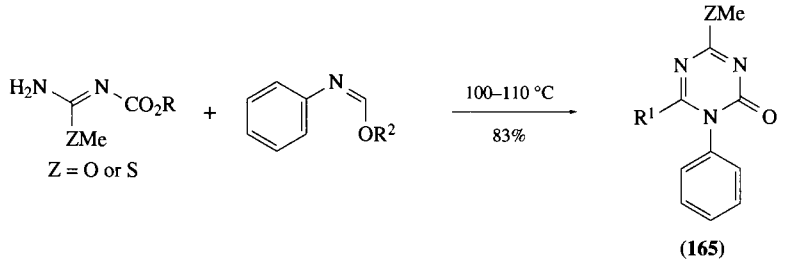


(162) (28)



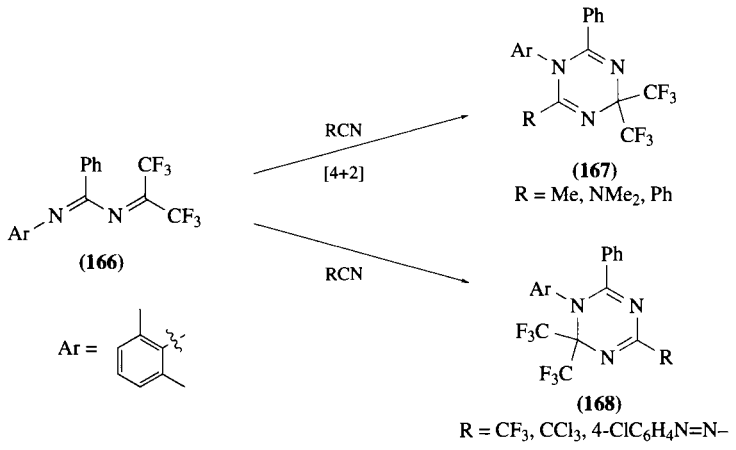
(163) (164)

Scheme 48



(165) (29)

Hexafluoropropylidenebenzamidines (**166**) react with cyanamides and with acetonitrile and benzonitrile to give [4 + 2] cycloadducts (**167**). When trifluoroacetonitrile, trichloroacetonitrile, or 4-chlorophenylazocyanide were used, unexpected reactions were observed; 1,3,5-triazines (**168**) were formed with reorganization of the diene skeleton (Scheme 49) ⟨84CZ205⟩.



Scheme 49

6.12.9.4 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [3 + 3] Atom Fragments

6.12.9.4.1 Synthesis from amidines

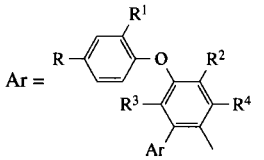
Amidines react with various three-atom fragments as illustrated in Scheme 50 ⟨84CC1105, 89ZOB1766, 91USP5075443, 92UKZ585, 93EUP529468⟩.

6.12.9.4.2 Synthesis from urea, thiourea, and guanidine derivatives

Triazinethiones (**169**) are synthesized from *S*-alkylisothioureas and acyl isothiocyanates ⟨87MI 612-04, 91PS(62)275⟩. *N*-Aminotriazinedione derivatives (**170**) are obtained when *S*-alkylisothiosemicarbazones are condensed with diphenyl dicarbimidate (Scheme 51). The dicarbimidate was produced by reaction of chlorocarbonyl isocyanate with phenol ⟨84GEP3409065⟩.

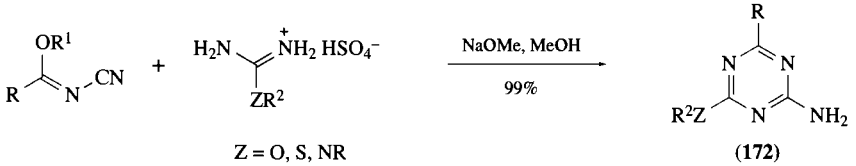
Chlorocarbonyl isocyanate reacts directly with ureas in toluene at reflux temperature to form triazinetriones (**171**), which are useful as herbicides (Equation (30)) ⟨83GEP3147879, 84GEP3314739⟩.

(30)



R = CF_3CH_2S, $R^1 = R^4 = H$, $R^2 = R^3 = Cl$, $R^5 = Me$, 87%
R = CF_3, $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = NO_2$, $R^5 = Me$, 83%

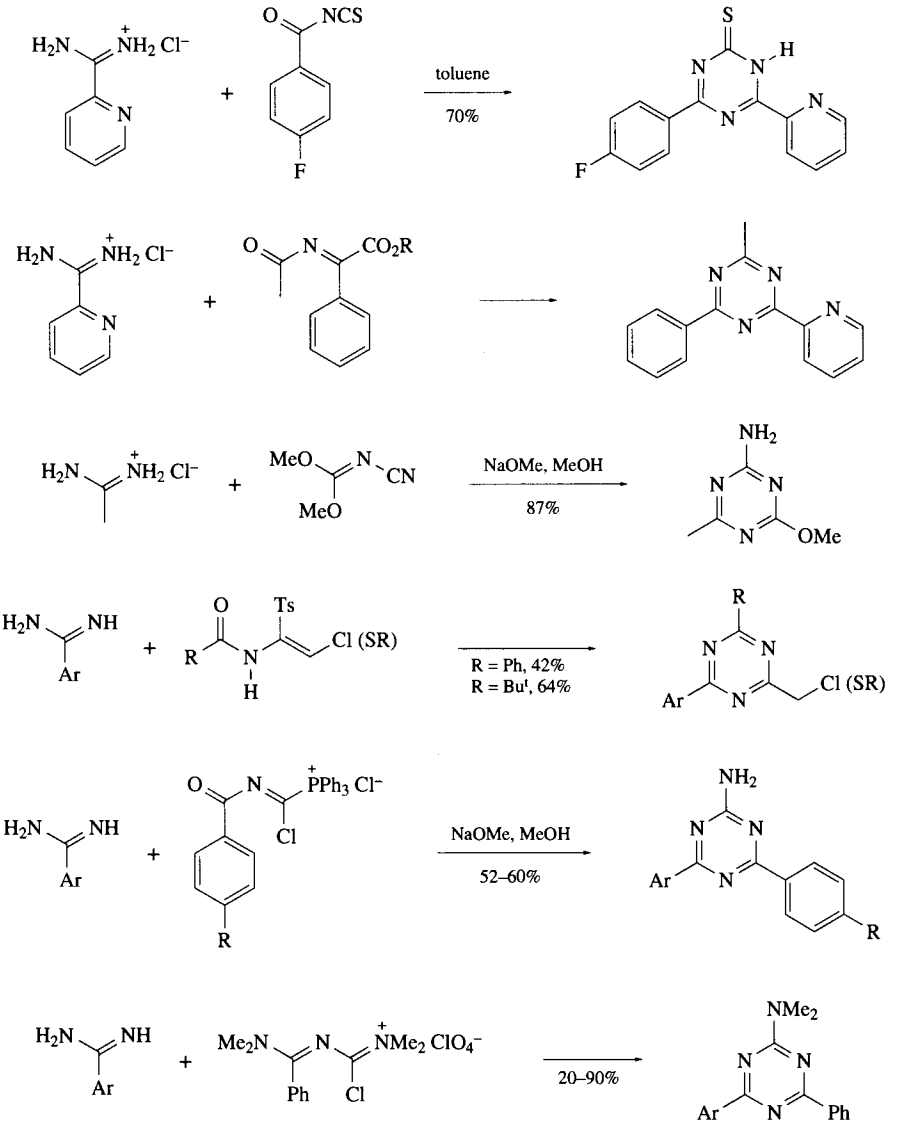
Almost quantitative yields of (**172**) are claimed for the reaction of cyanoimidates with salts of *O*-alkylisourea, *S*-alkylisothiourea, and guanidines (Equation (31)) ⟨84GEP3411202⟩. Alkoxycarbonylimidates are used in a similar manner to cyanoimidates to generate the triazin-2(1*H*)-ones (**173**) (Equation (32)) ⟨82JAP57144268⟩.



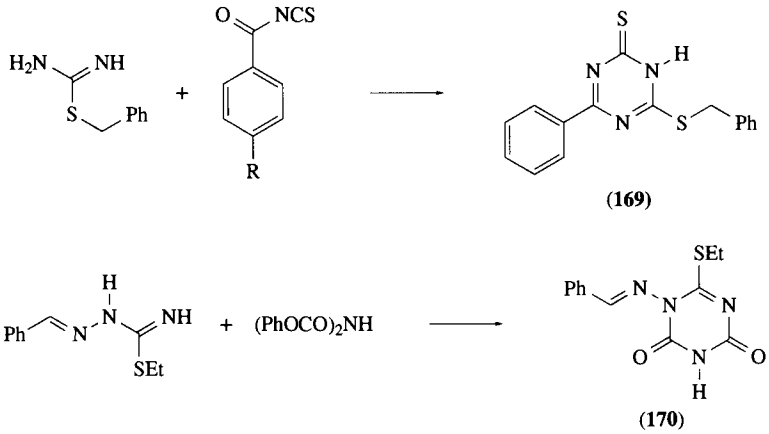
Z = O, S, NR

(172)

(31)



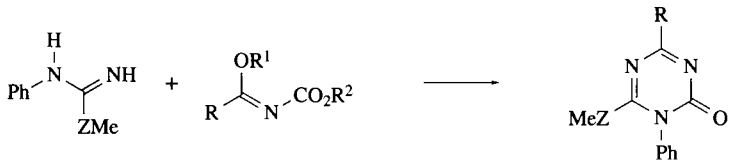
Scheme 50



(169)

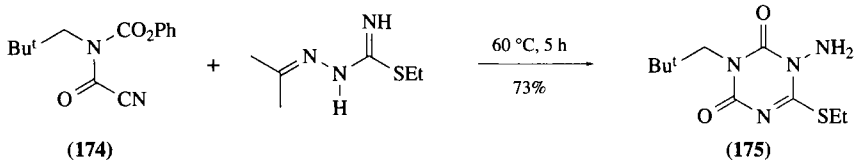
(170)

Scheme 51



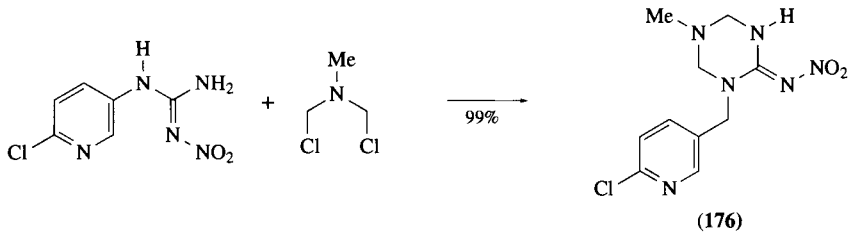
R = H, Z = S $R^1 = R^2$ = alkyl (173) (32)

The 1-amino-1,3,5-triazine-2,4-(1*H*,3*H*)-dione (**175**) was obtained in 73% yield when the carbamate (**174**) was heated at 60 °C with an isothiosemicarbazone (Equation (33)) ⟨83GEP3147735⟩.



(174) (175) (33)

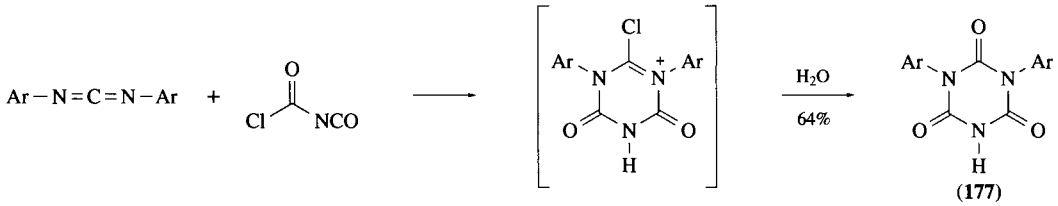
Hexahydrotriazines such as (**176**), which are useful as insecticides, are synthesized from nitroguanidine derivatives and *N*-methyl-*N*-bis(chloromethyl)amine (Equation (34)) ⟨91EUP428941⟩.



(176) (34)

6.12.9.4.3 Synthesis from carbodiimides

Akteries and Jochims reported the synthesis of 1,4-bis(4-methoxyphenyl)-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**177**) when chlorocarbonyl isocyanate was reacted with di-(4-methoxyphenyl)carbodiimide. The chloro intermediate was not isolated but hydrolyzed with water to give (**177**) (Scheme 52) ⟨86CB1133⟩. Products similar to (**177**) (e.g. (**171**)) are available by the condensation of chlorocarbonyl isocyanate directly with ureas.



(177)

Scheme 52

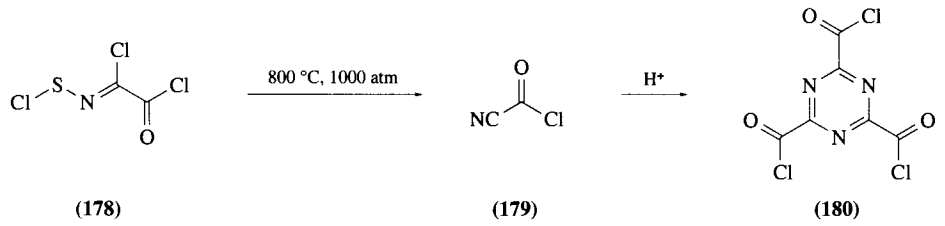
6.12.9.5 Synthesis of Symmetrical 1,3,5-Triazines by Formation of Three Carbon–Nitrogen Bonds from [2 + 2 + 2] Atom Fragments

Cyclotrimerization of nitriles, isocyanates, isothiocyanates, imidates, and carbodiimides all lead to symmetrical 1,3,5-triazines. New catalysts have been introduced in some cases to carry out these transformations with increased yields and under relatively milder reaction conditions. The cyclotrimerization of monocyanamides has been reviewed ⟨89RCR879⟩.

6.12.9.5.1 Synthesis from nitriles

Extreme pressure (above 1000 atm) and high temperatures are required for the preparation of trisubstituted 1,3,5-triazines from nitriles. Strong acids or bases can be used as an alternative.

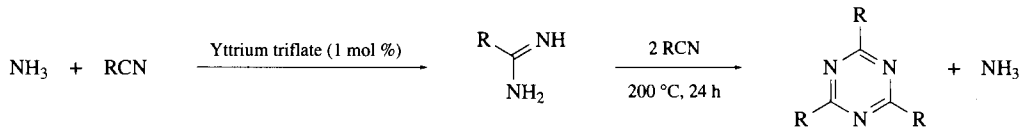
Thermolysis of the acid chloride (**178**) at 800 °C gives cyanocarbonyl chloride (**179**) which reacts with acid to give the triazine (**180**) (Scheme 53) ⟨83AG(E)785⟩.



(178) (179) (180)

Scheme 53

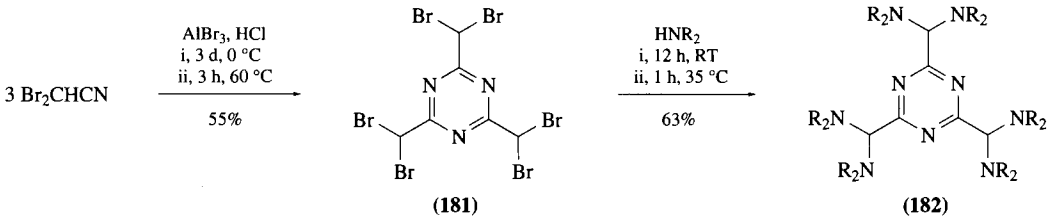
2,4,6-Triphenyl-1,3,5-triazine was prepared by the cyclotrimerization of benzonitrile at 300–320 °C in the presence of 0.5–1.0 parts of iodine per one part benzonitrile ⟨91URP1657499⟩. Dry acetonitrile when added to freshly distilled triflic acid at 0 °C under nitrogen and then stirred for 23 h at room temperature gave 2,4,6-trimethyl-1,3,5-triazine, after neutralization with pyridine. Isobutyronitrile and triflic acid when stirred together at room temperature for 20 h and neutralized with ammonia gave 2,4,6-tri-isopropyl-1,3,5-triazine (67%). 2,4,6-Triphenyl-1,3,5-triazine (95%) was obtained from benzonitrile and triflic acid. The reagents were stirred at room temperature for 4 days and then added to water to precipitate the product ⟨83JCS(P1)1075⟩. Procedures have been developed for the cyclotrimerization of nitriles which use lanthanide trifluoromethanesulfonates and ammonia as cocatalysts. This is claimed as an improved procedure for the preparation of symmetrically substituted 1,3,5-triazines. Increased yields and relatively mild reaction conditions are involved, in particular for aromatic nitriles (Scheme 54) ⟨88JHC767⟩.



Scheme 54

Yields % for R = C_6H_8 100, Me 62, cyclopropyl 88, $4ClC_6H_4$ 99, 4-pyridyl 91, 2-pyridyl 100, 2-thienyl 69.

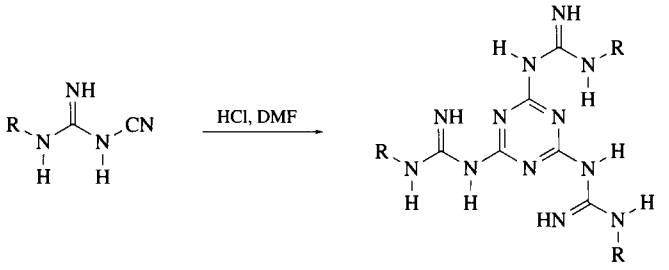
A synthetic equivalent of 2,4,6-triformyl-1,3,5-triazine has been prepared by cyclotrimerization of dibromoacetonitrile with aluminum tribromide and hydrogen chloride. 2,4,6-Tris(dibromomethyl)-1,3,5-triazine (**181**), thus formed, underwent displacement of each bromine with morpholine (R^2NH) to give the trisaminal (**182**) (Scheme 55) ⟨87JHC793⟩ (see Section 6.12.7.1).



(181) (182)

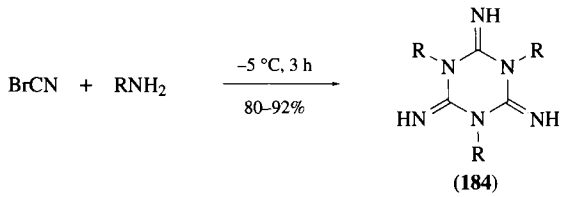
Scheme 55

2,4,6-Triguanidino-1,3,5-triazine and 2,4,6-tris(3-methylguanidino)-1,3,5-triazines (**183**) have been obtained by the cyclotrimerization of cyanoguanidine and 1-methyl-3-cyanoguanidine. The reactions were carried out in DMF with hydrogen chloride (Equation (35)) ⟨85BCJ2735⟩.



R = H, Me (183) (35)

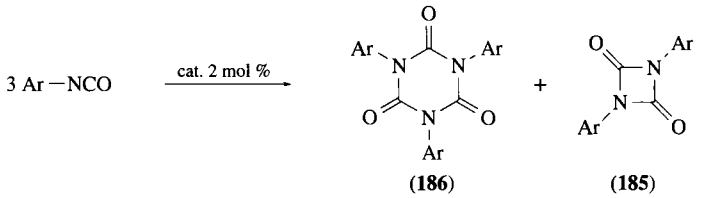
Amines can also be used to catalyze the cyclotrimerization of nitriles. Amines and cyanogen bromide, in isopropyl ether at −5°C for 3 h, are reported to give ring *N*-substituted trisaminotriazines (**184**; R = Et, 2-furylmethyl, 2-thienylmethyl, and 3-pyridylmethyl) (Equation (36)) ⟨86JAP62226970, 91JAP0368571⟩.



(184) (36)

6.12.9.5.2 Synthesis from isocyanates

Numerous catalysts have been reported for the trimerization of isocyanates, including various metal salts of carboxylic acids, tertiary amines, metal alkoxides, epoxides/pyridine, and metal oxides, but all have limitations. Fluoride catalyzed selective trimerization of isocyanates, reported by Nambu and Endo, is an improvement. Trimerization of phenyl isocyanate has been performed with caesium fluoride under heterogeneous conditions or with tetrabutylammonium fluoride (tbaf) under homogeneous conditions. Reaction with CsF as catalyst at room temperature for 20 min resulted in formation of 8.8% of the dimer (**185**). On the other hand, use of tbaf as catalyst with a reaction time of only 1 min at room temperature gave 12.7% of the dimer (**185**). A reaction time of 5 min at 130°C gave 90.5% of triazine (**186**) with the CsF catalyst and 5 min at room temperature with tbaf as catalyst gave 98.8% of (**186**); no dimer was detected in either case (Equation (37)) ⟨93JOC1932⟩. CsF or tbaf have also been used as catalysts to trimerize aromatic isocyanates with reactive substituent groups. Reaction times of 1 min at 70°C or 10 min with temperatures of 130°C for CsF and tbaf respectively were required, and yields varied from 65.5% to 100% ⟨93JOC1932⟩.



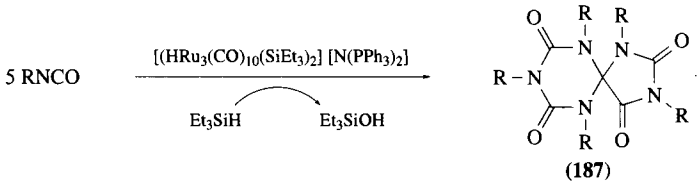
(186) (185) (37)

Trimerization of phenyl isocyanate with triethylamine as catalyst has also been reported and patented. Reactions were carried out at 8000 kg cm^{-2} and 40°C for 20 h to give 78% of (**186**) ⟨91JAP03109382⟩. This contrasts poorly with the 98.8% yield at room temperature in 5 min when tbaf is used.

Carelli *et al.* devised another procedure for the preparation of isocyanurates from isocyanates. The trimerization reaction was promoted by an anionic species obtained *in situ* by electrochemical reduction of catalytic quantities of α-bromoesters in dipolar aprotic solvents. Phenyl and 1-naphthyl isocyanate were trimerized in 90% and 85% yield respectively ⟨85SC249⟩.

[4,5] Spiroheterocycles (**187**) of alternating C=O and NR building units were constructed by the

trimerization of alkyl isocyanates in the presence of triethylsilane and catalytic amounts of a ruthenium catalyst (Equation (38)) ⟨85CB3959⟩.



(38)

(187)

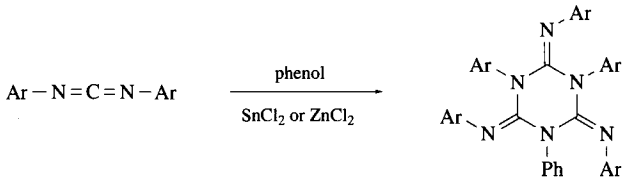
R = Me, 41%; Et, 43%; Pr^n, 69%; Pr^i, 22%; Bu^n, 51%

6.12.9.5.3 Synthesis from isothiocyanates, imidates, and carbodiimides

Alkyl and aryl isothiocyanates are trimerized at high pressure with triethylamine as catalyst ⟨92JAP04169575⟩; methyl isothiocyanate trimerized in 76% yield.

Imino esters, catalyzed by trifluoroacetic acid, are trimerized in 81–85% yield with loss of alcohol. The iminoester hydrochloride salt gave the corresponding triazines in 72–78% yield in the presence of sodium acetate ⟨92ZOR1750⟩.

Diphenylcarbodiimides are reported not to trimerize with Lewis acids and base or ($SnCl_2$ or $ZnCl_2$, Et_3N or quinuclidine). However, on the addition of phenol as a promoter to $SnCl_2$ or $ZnCl_2$, the triazine (**188**) was formed in 89% and 90% yield respectively (Equation (39)) ⟨81MI 612-01⟩.

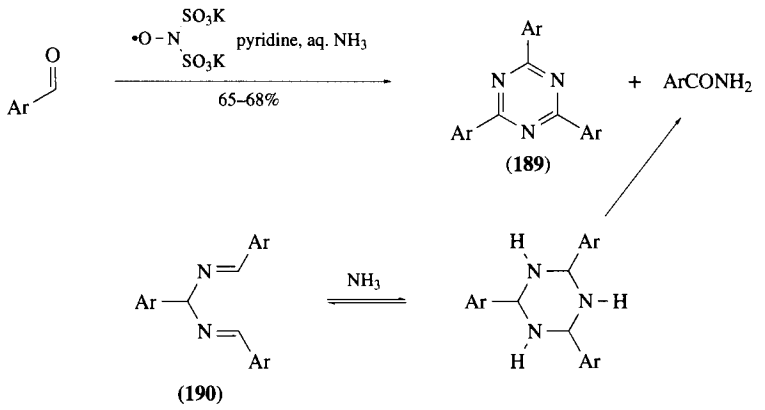


(39)

(188)

6.12.9.5.4 Synthesis of symmetrical 1,3,5-triazines from aldehydes and ammonia or amines

A new, mild and general method for the synthesis of aryl-substituted-1,3,5-triazines from aromatic aldehydes and ammonia has been found. Treatment of a 1 : 1 pyridine, concentrated ammonia solution of aromatic aldehyde with excess of Frémy's salt at room temperature gave a readily separable mixture of a primary amide and 1,3,5-triazine (**189**). *N,N*-Dibenzylidenephenylmethanediamine (**190**) on similar treatment produced almost identical results (Scheme 56) ⟨85S95⟩. Extension of the reaction to aliphatic aldehydes does not appear to be possible as attempts to oxidize 2,4,6-trimethyl-hexahydro-1,3,5-triazine with Frémy's salt gave rise to complex mixtures, in low yield.



(189)

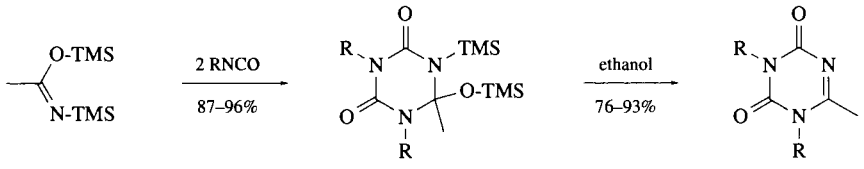
(190)

Scheme 56

6.12.9.6 Synthesis of Unsymmetrical 1,3,5-Triazines by Formation of Three Carbon–Nitrogen Bonds from [2 + 2 + 2] Atom Fragments

6.12.9.6.1 Synthesis from imino derivatives

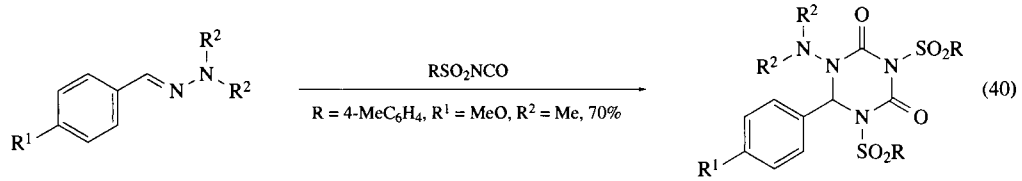
Kantlehner *et al.* have extended the reaction of *N,O*-bis(trimethylsilyl)acetimidate (**191**) with methyl isocyanate ⟨78LA512⟩ to a range of aromatic and aliphatic isocyanates to give the triazine-2,4-diones (**193**) ⟨85LA65⟩. The intermediates (**192**) were isolated when R = Ar or Me but on alcoholysis were desilylated to yield the triazine-2,4-diones (**193**) (Scheme 57) ⟨78LA512, 85LA65⟩.



(**191**) (**192**) R = Me, 86%; R = Ar, 87–96% (**193**)

Scheme 57

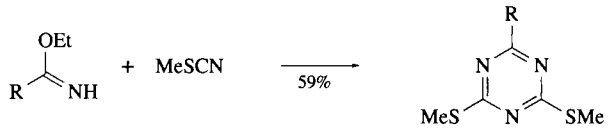
N-Amino-1,3,5-triazine-2,4-diones (**195**) were prepared by reaction of *N,N*-dialkylhydrazones of aromatic aldehydes (**194**) with sulfonyl isocyanates (Equation (40)) ⟨85EGP220956, 87JPR246⟩.



(40)

(**194**) (**195**)

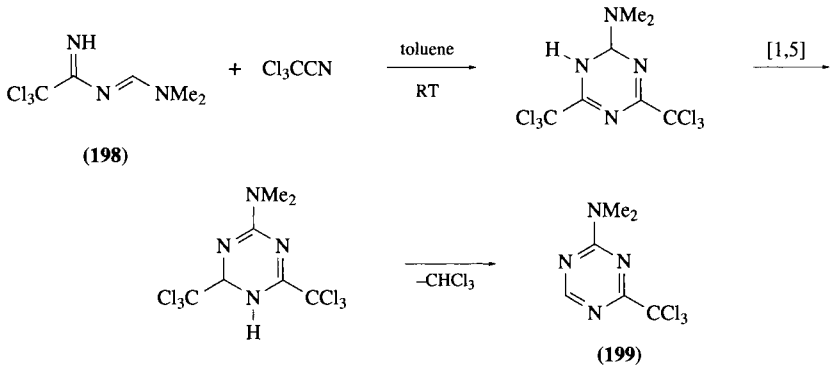
Imidates (**196**) cyclocondense with methyl thiocyanate to give the bis(methylmercapto)-1,3,5-triazines (**197**) (Equation (41)) ⟨92ZOR1750⟩.



(41)

(**196**) (**197**)

Muchowski and co-workers reported the synthesis of 2-dimethylamino-4-trichloromethyl-1,3,5-triazine (**199**) in over 80% yield. 4-Dimethylamino-2-trichloromethyl-1,3-diaza-1,3-butadiene (**198**) reacts with two equivalents of trichloroacetonitrile at room temperature, followed by a [1,5] hydrogen shift and loss of chloroform to give the triazine (**199**) (Scheme 58) ⟨92TL3449⟩.

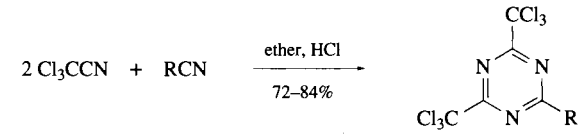


(**198**) (**199**)

Scheme 58

6.12.9.6.2 Synthesis by cotrimerization of nitriles

Two equivalents of trichloroacetonitrile and one equivalent of an alkyl cyanide give only one product ⟨74JOC2591⟩ and this selective reaction has been employed with a number of nitriles (Equation (42)) ⟨85ZOR1306, 86MI 612-01⟩. Acetonitrile can be treated with chlorine and the chlorination product reacted with acetonitrile to give 2-methyl-4,6-bis(trichloromethyl)-1,3,5-triazine, essentially the cotrimerization of trichloroacetonitrile and acetonitrile ⟨83MIP80831⟩.

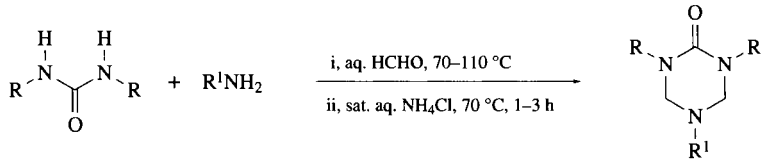


(42)

R = $ClCH_2CH_2$, FCH_2CH_2, $MeOCH_2CH_2$, $EtOCH_2CH_2$, $PrOCH_2CH_2$, pentyl, decyl, undecyl, dodecyl, pentadecyl, heptadecyl

6.12.9.7 Synthesis by Formation of Four Carbon–Nitrogen Bonds

Syntheses of this type are from urea, thiourea, and amidine and guanidine derivatives. Ureas give tetrahydro-1,3,5-triazin-2-ones on reaction with a primary amine (1 equiv.) and aqueous formaldehyde (2–30 equiv.). In general, alkyl and aryl amines, unsaturated amines, amino alcohols, and α-amino esters form triazinone derivatives (Equation (43)). Methyl and benzyl have proven to be the most useful urea substituents with respect to high yields and product solubility. *N,N'*-Dicyclohexyl- and *N,N'*-diphenyl-urea gave poor yields of triazinone ⟨90TL2109⟩.

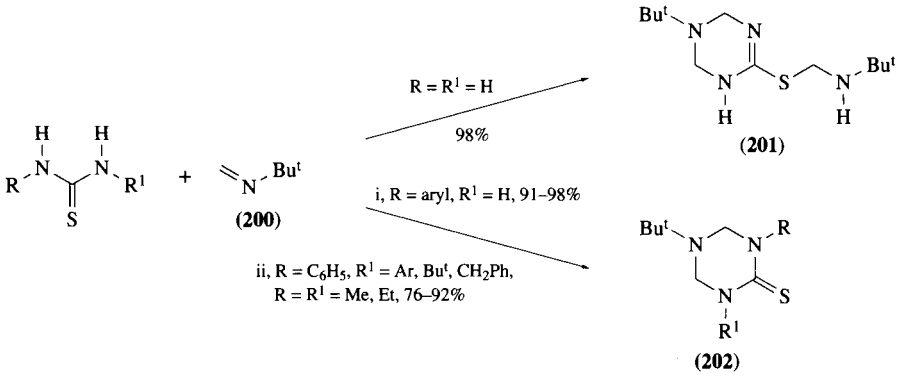


(43)

R = R^1, 90%; R = Me, R^1 = CH(Ph)Me, 98%; R = Et, R^1 = $CH_2CO_2Bu^t$, 69%

Treatment of urea with azomethines and 30% formalin gave quantitative yields of tetrahydro-1,3,5-triazin-2-ones. Amidines and guanidines can be used instead of ureas ⟨91ZOR2074⟩.

Kovalenko *et al.* have described the aminomethylenation of thioureas with *N*-methylene-*t*-butylamine (**200**). Thiourea with (**200**) gave a 98% yield of the (alkylthio)triazines (**201**). Mono- and disubstituted thioureas gave the triazines (**202**) in 76–92% yield (Scheme 59) ⟨91ZOB1867, 91ZOB1870⟩.



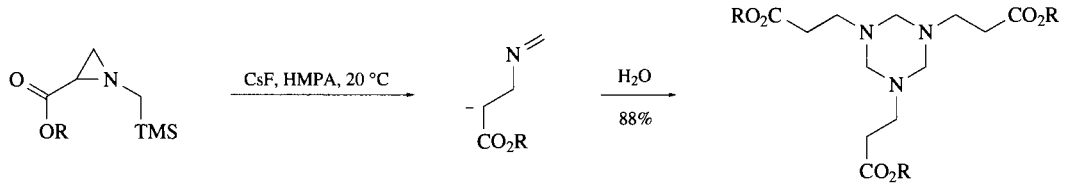
Scheme 59

6.12.10 SYNTHESIS OF 1,3,5-TRIAZINES BY TRANSFORMATION OF OTHER HETEROCYCLES

Triazines can be formed from three-, four-, five-, and six-membered heterocycles. The transformation of pyrimidines and 1,2,4-triazines into 1,3,5-triazines has received most attention.

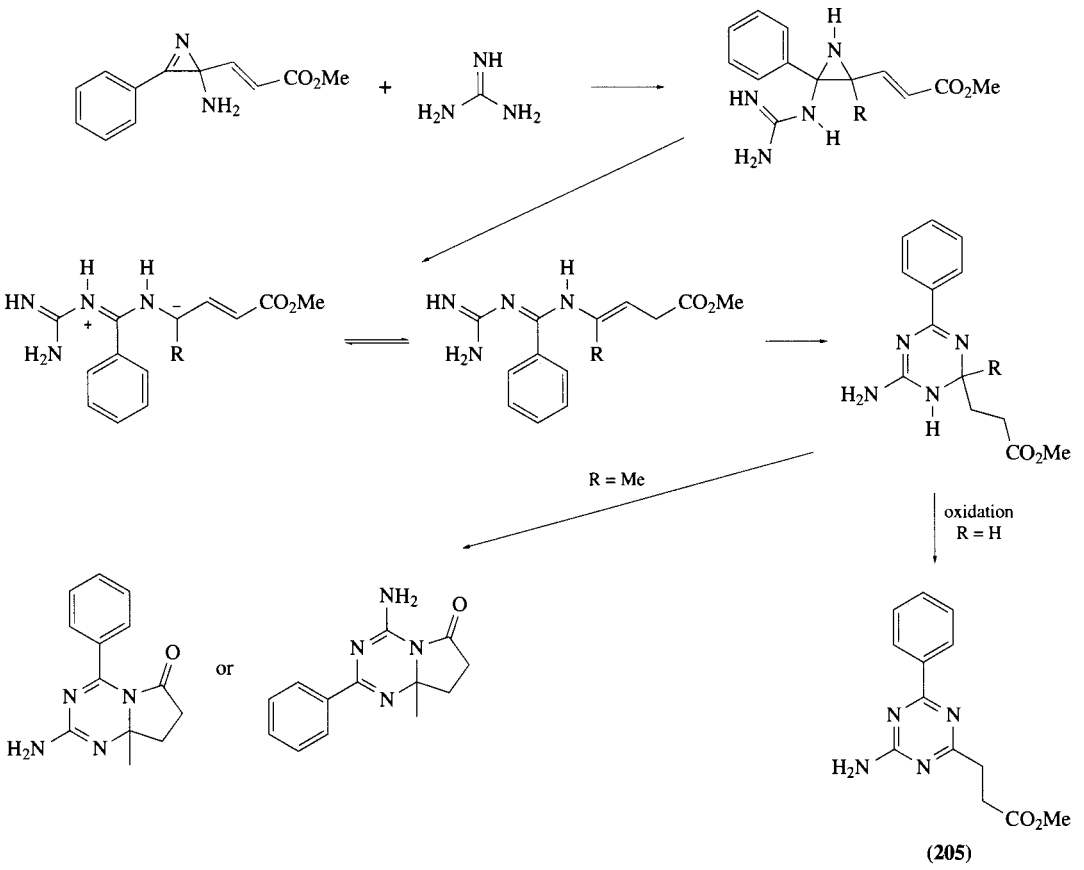
6.12.10.1 Synthesis from a Three-membered Ring

Aziridines (**203**) are ring opened on treatment with caesium fluoride and HMPA at 20 °C and treatment of the intermediates so formed with water results in trimerization to form the triazines (**204**) (Scheme 60). If a diester is used (rather than a monoester) then cleavage of the aziridine occurs to give an enamine ⟨84H(22)1955⟩.



Scheme 60

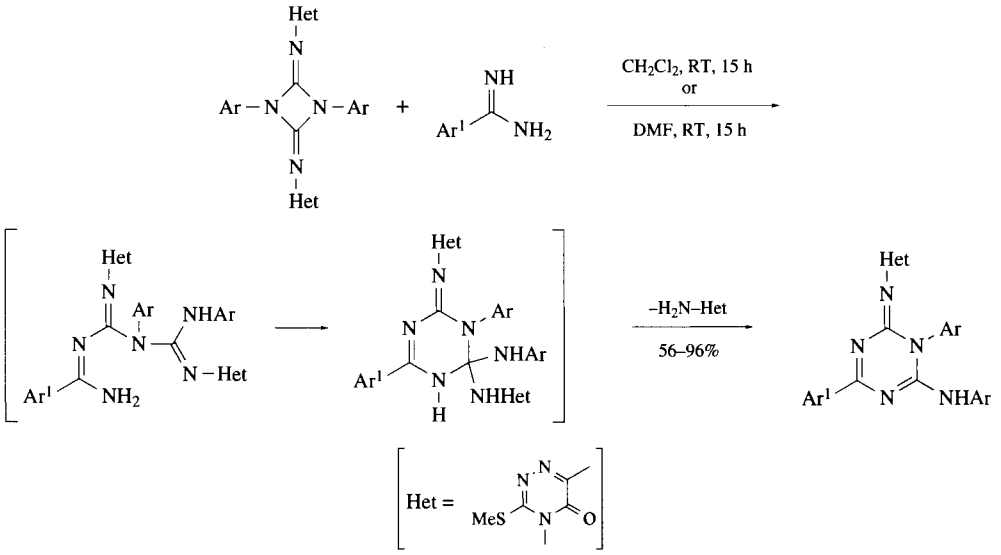
1,3,5-Triazines (**205**) are formed from the reaction of guanidine and methyl (*E*)-3-amino-2-phenyl-1-azirine-3-acrylate in 35% yield. The mechanistic pathway is shown in Scheme 61. Under the same reaction conditions formamidine gives a pyrimidine ⟨91JOC7⟩.



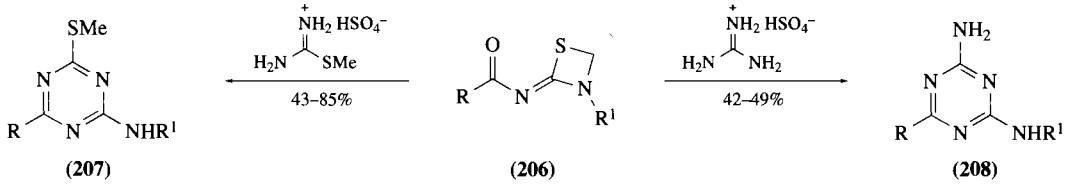
Scheme 61

6.12.10.2 Synthesis from a Four-membered Ring

A new synthesis of 6-arylamino-2-heteroarylimino-1,2-dihydro-1,3,5-triazines from 2,4-bis-(heteroarylimino)-1,3-diazetidines and amidines has been developed by Molina *et al.* The formation of the triazines was explained as an initial addition of the imino nitrogen of the amidine to the exocyclic C=N bond, followed by formation of an open chain intermediate. This intermediate cyclized, followed by elimination of 4-amino-6-methyl-3-methylthio-1,2,4-triazin-5(4*H*)-one to give the triazine product (Scheme 62) ⟨87S150⟩. 1,3,5-Triazines (**207**) and (**208**) have been prepared from 2-acylimino-1,3-thiazetidines (**204**) by treatment with isothioureas or guanidines respectively (Scheme 63) ⟨91JHC177⟩.



Scheme 62

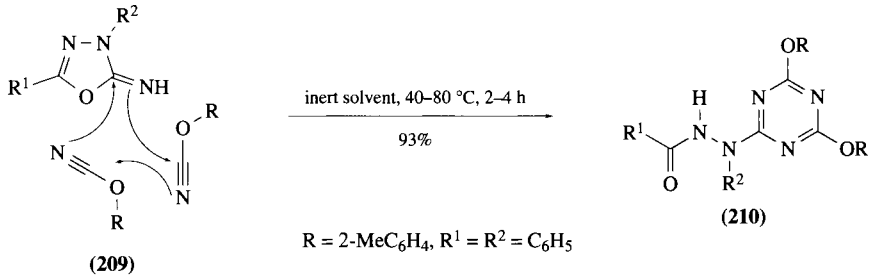


(207) (206) (208)

Scheme 63

6.12.10.3 Synthesis from a Five-membered Ring

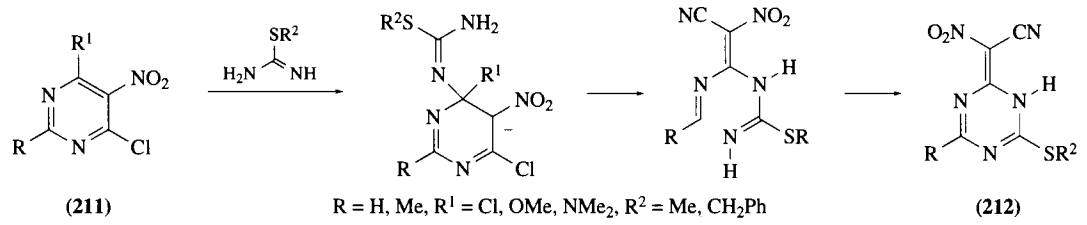
1,3,4-Oxadiazoles of the type (**209**) condense with aryl cyanates (ArOCN) to give 1,3,5-triazines (**210**), probably by the mechanism shown in Equation (44) ⟨83EGP220603⟩.



(209) (210) (44)

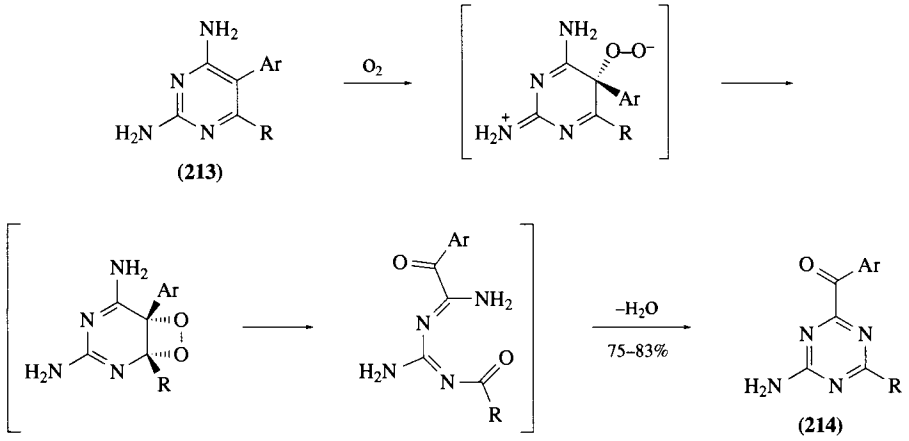
6.12.10.4 Synthesis from a Six-membered Ring

Isothioureas react with pyrimidines (**211**) to give 1,3,5-triazines (**212**) (Scheme 64), together with small amounts of (alkylthio)pyrimidine by-products ⟨91KGS999⟩.



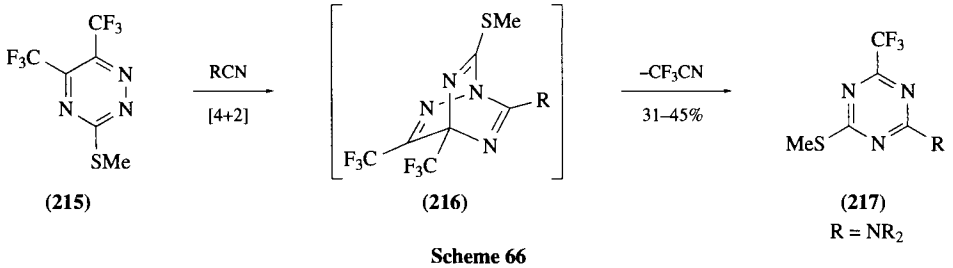
Scheme 64

4-Amino-1,3,5-triazin-2-yl ketones (**214**) were formed in high yield by the photosensitized oxygenation of 5-aryl-2,4-diaminopyrimidines (**213**) in protic solvents (Scheme 65) ⟨88HCA712⟩.



Scheme 65

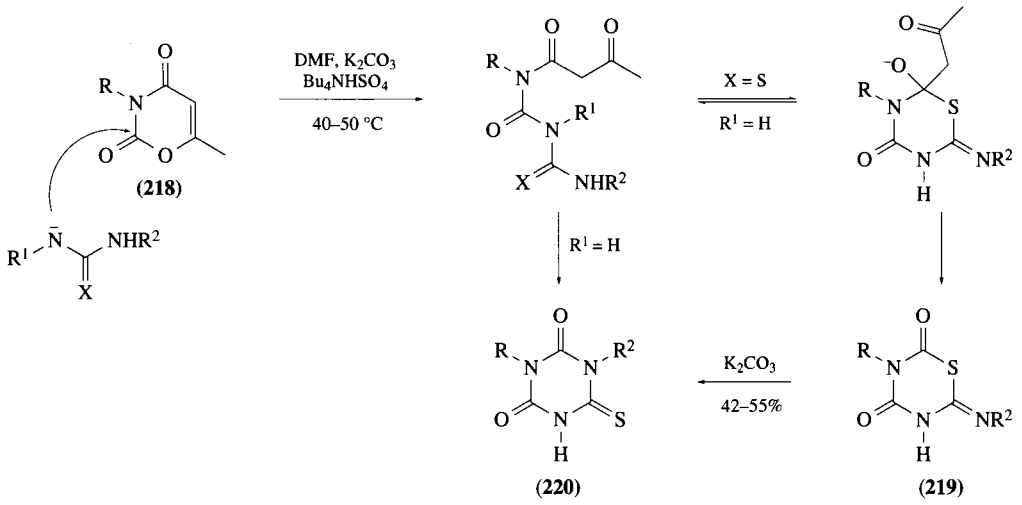
[4 + 2] Cycloaddition of cyanamides across the C5—N2 atoms of the 1,2,4-triazine (**215**) nucleus gave the bicyclo intermediate (**216**), which was not isolated. [4 + 2] Cycloreversion with elimination of trifluoroacetonitrile led to 1,3,5-triazines (**217**) (Scheme 66) ⟨89CB1381⟩.



Scheme 66

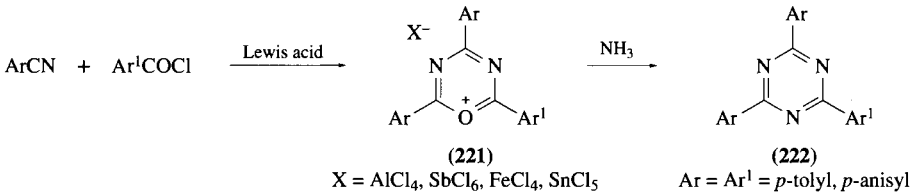
6-Methyl-1,3-oxazine-2,4(3*H*)-diones (**218**) combine with ureas or thioureas under phase-transfer catalytic conditions to give 1,3,5-triazines. Unfortunately the yields in the reactions with ureas were very low and therefore not synthetically useful. However, reaction with thioureas provided 5,6-dihydro-6-thioxo-1,3,5-triazine-2,4(1*H*,3*H*)-diones (**220**) in better yields. Two pathways are possible for the formation of (**220**), either directly to (**220**) or via the intermediate (**219**) which implies the involvement of sulfur. The failure of *S*-methylisothiourea to react with (**218**) and the absence of this mode of cyclization in the reactions with biprotic ureas supported the pathway via (**219**). The participation of sulfur is therefore invoked, followed by loss of acetone (detected as its 2,4-DNPH

(dinitrophenyl hydrazine) derivative) to give (**219**), which with excess of base (K_2CO_3) could undergo Dimroth rearrangement to (**220**) (Scheme 67) ⟨92JCS(P1)1139⟩.



Scheme 67

Ammonolysis of 1,3,5-oxadiazinium salts gives 1,3,5-triazines. Stable oxadiazinium salts can be formed by reaction of an aryl nitrile with an aromatic acid chloride and Lewis acid ($AlCl_3$, $SbCl_5$, $FeCl_3$, or $SnCl_4$). Electron-withdrawing groups in the aromatic rings render the salts unstable, and they are difficult to isolate. The salts (**221**) were isolated and converted with ammonia into the triazines (**222**) (Scheme 68) ⟨86MI 612-02⟩.

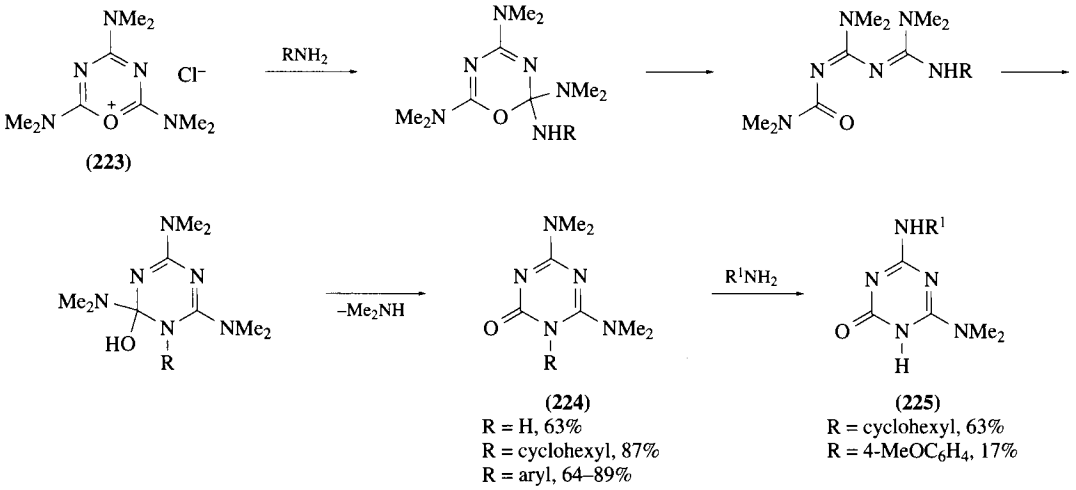


Scheme 68

2,4,6-Tris(dimethylamino)-1,3,5-oxadiazinium chloride (**223**) was obtained when dimethylcyanamide and dimethylcarbamoyl chloride were heated together at 170°C for 20 min. When the salt (**223**) was heated with concentrated ammonia the 1,3,5-triazin-2-one (**224**; R = H) was the product. The suggested mechanism follows the ANRORC pathway. The triazine product (**224**) can also be prepared more simply by hydrolysis of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine by 1M hydrochloric acid at boiling point for 3 h (Scheme 69) ⟨85JCS(P1)1533⟩ and 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine is available from cyanuric chloride and dimethylamine. The salt (**223**) was also converted into 1,3,5-triazin-2-ones with cyclohexylamine and aromatic amines. Under more forcing conditions triazines (**225**) were obtained where one of the dimethylamino groups was displaced by another molecule of amine.

Benzoxazonium cation (**227**) is obtained when disalicylimide (**226**) is treated with 70% perchloric acid and gives on reaction with guanidines or isothioureas 1,3,5-triazines (**228**) (Scheme 70) ⟨83KGS406⟩.

1,3,5-Thiadiazines (**229**) are rearranged into triazines (**230**) and (**231**) on treatment with sodium hydroxide and amines respectively (Scheme 71) ⟨91NKK1655, 92NKK1450⟩ while the 1,3,5-thiadiazinetrithiones (**232**), which were prepared by the reaction of thioureas with ethyl chloroformate in the presence of pyridine, react with anilines to give the 1,3,5-triazines (**233**) or (**234**) (Scheme 72) ⟨88PIA53⟩.

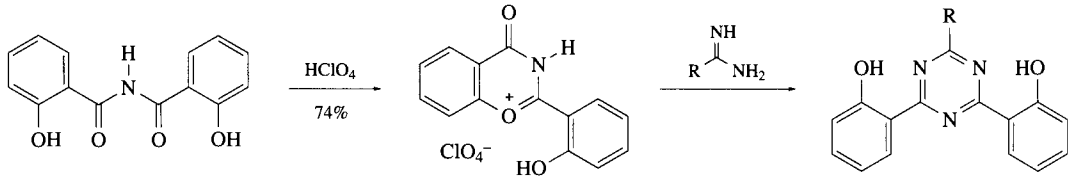


(223)

(224)
R = H, 63%
R = cyclohexyl, 87%
R = aryl, 64–89%

(225)
R = cyclohexyl, 63%
R = 4-MeOC$_6$H$_4$, 17%

Scheme 69

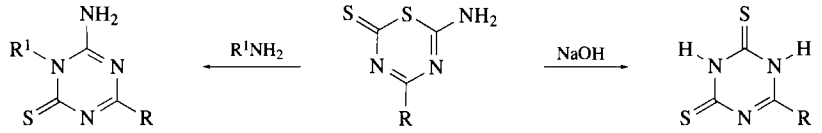


(226)

(227)

(228)
R = NH$_2$, MeNH, MeS

Scheme 70

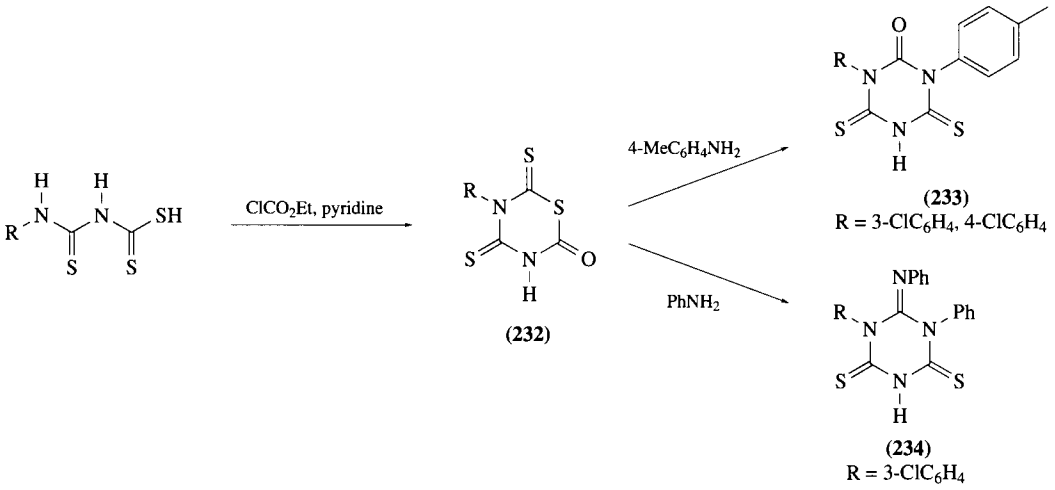


(231)

(229)

(230)

Scheme 71



(232)

(233)
R = 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$

(234)
R = 3-ClC$_6$H$_4$

Scheme 72

6.12.11 AN ASSESSMENT OF THE SYNTHETIC ROUTES TO 1,3,5-TRIAZINES

6.12.11.1 Synthesis of 1,3,5-Triazine

No new preparations of the parent 1,3,5-triazine have appeared since the mid 1980s. The synthesis due to Maier and Bredereck which involves the reaction of ammonium acetate with triethyl orthoformate remains the best route ⟨79S690⟩.

6.12.11.2 Synthesis of Monosubstituted 1,3,5-Triazines

No new synthetic routes to monosubstituted 1,3,5-triazines have been reported. The reaction of 1,3,5-triazine with imidates gives monoalkyl- or aryl-1,3,5-triazines ⟨61JOC2784⟩. 2-Amino-1,3,5-triazines are best prepared by reaction of triformidomethane with a formyl guanidine ⟨63AG(E)655⟩.

6.12.11.3 Synthesis of 2,4-Disubstituted 1,3,5-Triazines

General synthetic approaches to 2,4-disubstituted 1,3,5-triazines have not been described. Muchowski reported a specific route for the efficient synthesis of 2-dimethylamino-4-(trichloromethyl)-1,3,5-triazine from trichloroacetonitrile and *N*,*N*-dimethylformamidine in over 80% yield (see Section 6.12.9.6.1).

Moderate yields (30–48%) are claimed for the disubstituted 1,3,5-triazine formed on elimination of chloroform from dihydrotriazine (**146**), on treatment with sodium hydroxide (see Section 6.12.9.3.1).

6.12.11.4 Synthesis of Trisubstituted 1,3,5-Triazines

Nucleophilic displacement of chlorine, in a stepwise manner, from cyanuric chloride leads to triazines with heteroatom substituents (see Section 6.12.5.2.4) in symmetrical or unsymmetrical substitution patterns. New reactions for introduction of carbon nucleophiles are useful for the preparation of unsymmetrical 2,4,6-trisubstituted 1,3,5-triazines. The reaction of silyl enol ethers with cyanuric chloride replaces only one of the chlorine atoms and the remaining chlorines can be subjected to further nucleophilic substitution, but the ketone produced from the silyl enol ether reaction may need protection or transformation first. Palladium-catalyzed cross-coupling of 2-substituted 4,6-dichloro-1,3,5-triazine with phenylboronic acid gives 2,4-diaryl-6-substituted 1,3,5-triazines ⟨93S33⟩. Cyanuric fluoride can be used in a similar manner to cyanuric chloride but has the added advantage of the reactions with aromatic amines, which react as carbon nucleophiles. New 2,4,6-trisubstituted 1,3,5-triazines are therefore available with aryl or heteroaryl and fluoro substituents (see Section 6.12.5.2.4).

Trimerization of nitriles, isocyanates, isothiocyanates, imidates, and carbodiimides all lead to symmetrical 2,4,6-trisubstituted 1,3,5-triazines (see Section 6.12.9.5). The use of lanthanide trifluoromethanesulfonate and ammonia as cocatalysts is claimed as a big improvement. The trisaminal of 2,4,6-triformyl-1,3,5-triazine is also useful for further derivatization to unusual structures (see Section 6.12.7.1). Treatment of a 1 : 1 pyridine/conc. ammonia solution of an aromatic aldehyde with excess Frémy's salt is another development. Separation of the amide coproduct was claimed to be easy. The synthesis fails with aliphatic aldehydes (see Section 6.12.9.5.4). Aminolysis of 2,4,6-triaryl-1,3,5-oxadiazinium salts gives symmetrical 1,3,5-triazines but the reactions are limited in that electron-withdrawing groups in the aromatic rings lead to instability and difficulty in separation of products (see Section 6.12.10.4).

Unsymmetrical 1,3,5-triazines are available by the general method of preparation from biguanides with γ-butyrolactam or ClCSSR (see Section 6.12.9.2.1). Substituted cyanoguanidines with aromatic amines in dioxan is a useful approach (see Section 6.12.9.2.2). Dicyandiamide is a useful starting material for reaction with a variety of nitriles; 2,4-diamino-6-substituted 1,3,5-triazines are readily formed (see Section 6.12.9.3.1). Section 6.12.9.4.1 reports the numerous alternatives available for the cyclization of amidines with 1,3-bifunctional reagents. Quantitative yields are claimed for the condensation of cyanoimidates with salts of *O*-alkylisoureas, *S*-alkylisothioureas, and guanidines (see Section 6.12.9.4.2).

2,4-Diaryl-6-substituted 1,3,5-triazines are obtained from reaction of a benzoxazonium cation with amidines and perchloric acid in acceptable yields (see Section 6.12.10.4). Aryl cyanates with 1,3,4-oxadiazoles give diaryloxy-1,3,5-triazines in good yields (see Section 6.12.10.3).

6.12.11.5 Synthesis of 1,3,5-Triazin-2(1*H*)-ones

1,3,5-Triazin-2(1*H*)-ones are prepared from amidinoureas or 1,4-dimethylbiurets with orthoformates. This general approach has seen the introduction of diethyl azodicarboxylate in place of orthoformates. Improved yields are seen compared with the alternative use of ethylene carbonate (see Section 6.12.9.2.2). Imino derivatives with *N*-alkoxycarbonyl isoureas or isothioureas give triazinones (see Section 6.12.9.3.2), as do alkoxycarbonyl imidates with isothioureas (see Section 6.12.9.4.2).

6.12.11.6 Synthesis of 1,3,5-Triazine-2,4(1*H*,3*H*)-diones

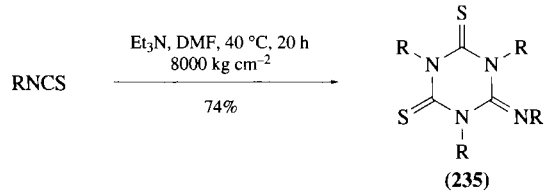
1,3,5-Triazine-2,4(1*H*,3*H*)-diones are prepared by the well-known condensation of biurets with acetaldehyde acetals (see Section 6.12.9.2.2). The reaction of carbomethoxy *O*-methylisoureas with isocyanates is a good general route to triazinediones (see Section 6.12.9.3.2). Kantlehner's reaction of a range of aromatic and aliphatic isocyanates with *N*,*O*-bis(trimethylsilyl)acetamidate constitutes a good general preparation, in high yields, after desilylation with alcohol (see Section 6.12.9.6).

6.12.11.7 Synthesis of 1,3,5-Triazine-2,4,6(1*H*,3*H*,5*H*)-triones

1,3,5-Triazine-2,4,6(1*H*,3*H*,5*H*)-triones are best prepared by the cyclotrimerization of isocyanates with CsF or tbaf catalysts. The electrochemical approach of Carelli *et al.* may also prove useful (see Section 6.12.9.5.2) ⟨85SC249⟩.

6.12.11.8 Synthesis of 1,3,5-Triazinethiones

Routes to triazinethiones are less common, and involve thiourea derivatives as in the cyclization of (**137**) with sodium methoxide and the cyclization of dithiobiuret with base (see Section 6.12.9.1). Reactions of isothiocyanates with dithiobiurets and isothioureas were also used to give good yields of triazinetrithiones. High pressures are required to trimerize isothiocyanates, usually in the presence of triethylamine, but yields of triazinetrithiones are generally high (76%) (see Section 6.12.9.3). When the pressure was increased tenfold an unexpected triazine product (**235**) was formed (Equation (45)) ⟨92JAP04169575⟩.



(45)

(**235**)

6.12.11.9 Synthesis of Reduced 1,3,5-Triazines

2,4-Disubstituted-dihydrotriazines, with the two substituents the same or different and the third 6-substituent as trichloromethyl, can be prepared by an efficient synthesis. An amidine derivative is cyclized with chlorine in carbon tetrachloride (see Section 6.12.9.1). The route gives scope for numerous derivatives of dihydrotriazines which can easily be aromatized on oxidation with permanganate to give trisubstituted triazines in which the trichloromethyl group may be displaced with nucleophiles. Hexafluoroisopropylidenebenzamidines react with cyanamides or nitriles to give [4 + 2] cycloadducts or rearranged products (see Section 6.12.9.3.2). This is a useful synthesis but

always gives dihydrotriazines with bis(trifluoromethyl) substitution on the same carbon. Acid-catalyzed ring closure of biguanides with ketones is an alternative to give alkyl or aryl substituents on the same carbon ⟨84CHEC-I(3)457⟩ and this route is also applicable to the synthesis of *N*-oxydihydrotriazines ⟨B-84MI 612-01⟩.

Kavalenko reported the synthesis of tetrahydrotriazines by the aminomethylenation of thiourea with *N*-methylene-*t*-butylamine (see Section 6.12.9.7). The reaction is limited in that it only gives the tetrahydrotriazine with thiourea itself; mono- and disubstituted thioureas give hexahydrotriazines in excellent yields.

N,*N*-Bis(chloromethyl)methylamine looks to be a useful reagent for the synthesis of hexahydrotriazines (see Section 6.12.9.4.2). Reaction of ureas with aqueous formaldehyde and amines is a common and much used approach to tetrahydrotriazinones (see Section 6.12.9.7). Aziridines (see Section 6.12.10.1) are converted into hexahydrotriazines with CsF and HMPA in good yield, but HMPA is highly toxic and not recommended for general use.

6.12.11.10 Synthesis of Triazinetriimines

Syntheses of triazinetriimines are reported; isomelamines are prepared in 68–95% yield (see Section 6.12.9.2.2). A more general route is the cotrimerization of amines with cyanogen bromide; high yields are recorded from readily available starting materials (see Section 6.12.9.5.1). Diphenylcarbodiimide is trimerized by Lewis acids with phenol as promoter but the method is specific to diphenylcarbodiimide and not of general use.

6.12.11.11 Synthesis of *N*-Aminotriazines

N-Aminotriazines are readily synthesized from *S*-alkylisothiosemicarbazones (see Section 6.12.9.4.2) and by reaction of a sulfenyl isocyanate with hydrazones of aromatic aldehydes (see Section 6.12.9.6.1). *N*-Amination reactions have not been reported.

6.12.11.12 Synthesis of Triazine *N*-oxides

Shaw has described the oxidation of triazines with peracetic acid (very poor to high yields) and the preparation of 2,6-diamino-4-methyl-1,3,5-triazine *N*-oxides from potassium dicyanoacetamide and hydroxylamine (24–69% yield) ⟨62JOC3890⟩. Kaugars and Watt reported the formation of triazine *N*-oxides from two equivalents of an amidoxime with ethyl orthoacetate, but only in low to moderate yields (13–48%) (see Section 6.12.9.2.2).

6.12.12 IMPORTANT COMPOUNDS AND APPLICATIONS

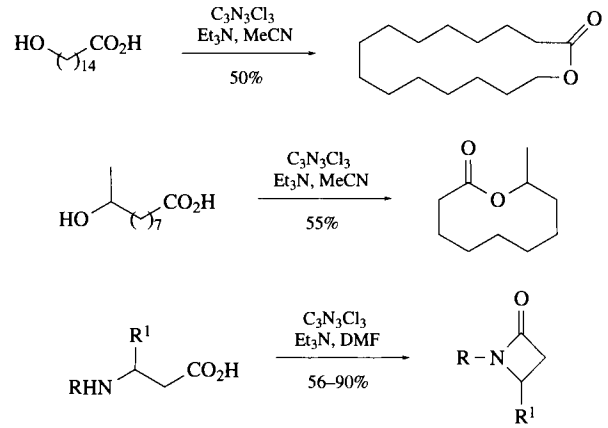
6.12.12.1 1,3,5-Triazines as Reagents in Organic Chemistry

1,3,5-Triazine is very useful in aminomethylenation reactions for the preparation of Mannich bases and numerous heterocycles. For example, 4-aminopyridines are obtained on reaction with enamines (see Section 6.12.5.1.4). Hexahydrotriazines are also useful aminomethylenating reagents (see Section 6.12.6.6).

The 1,3,5-triazine system undergoes cycloaddition reactions of the [4 + 2] type (see Section 6.12.5.1.5). Addition of electron-withdrawing substituents, as in 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine, increases the rate of participation in Diels–Alder reactions. 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine has proved useful in the first stage of the total synthesis of pyrimidoblamic acid, the heteroaromatic segment of bleomycin A_2 ⟨92JOC1631, 93AG(E)273⟩.

Cyanuric chloride is a valuable reagent in organic chemistry. Not only is it used to synthesize

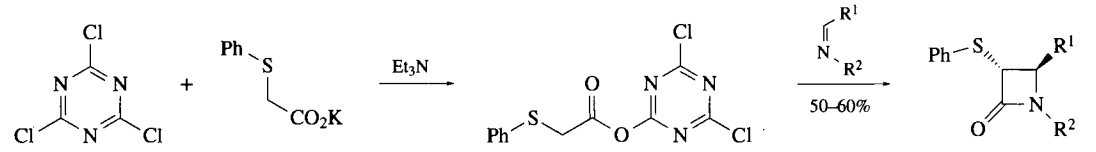
many of the 1,3,5-triazine derivatives, but it also acts as a coupling reagent in the formation of macrocyclic lactones ⟨86TL2369⟩ and β-lactams ⟨87MI 612-05⟩ (Scheme 73).



R = $PhCH_2$, Bu, *n*-pentyl, *n*-hexyl, cyclohexyl; R^1 = Me, Ph

Scheme 73

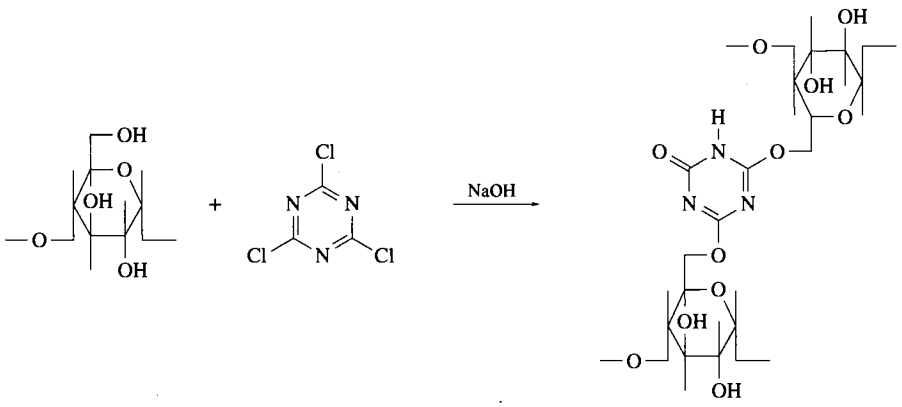
The potassium salt of phenylthioglycolic acid reacts with cyanuric chloride and base elimination of the cyanuric moiety liberates a ketene which undergoes [2 + 2] cycloaddition with a Schiff's base to give β-lactams. The active ester intermediate plays the same role as an acid chloride (Scheme 74) ⟨84TL4733, 89JOC5758⟩.



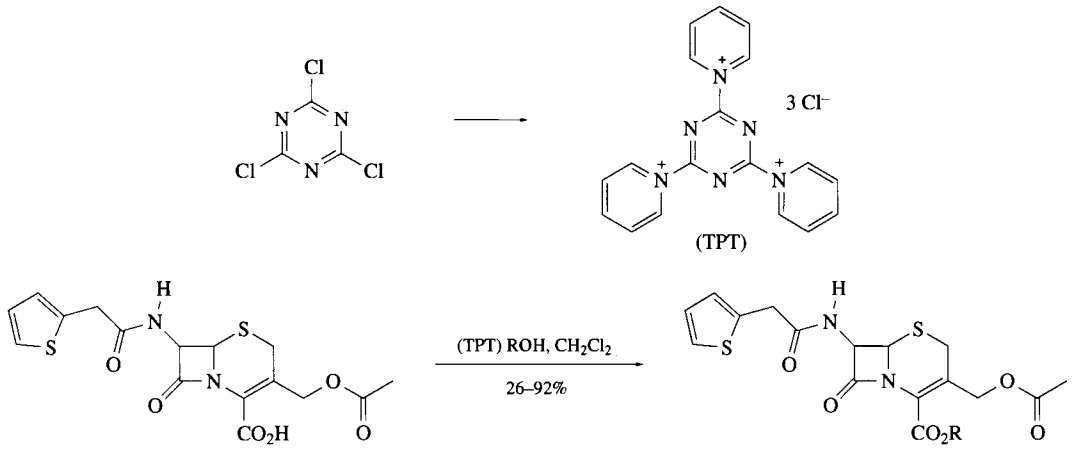
Scheme 74

Reaction of cyanuric chloride with three equivalents of pyridine gives 2,4,6-tripyridinio-1,3,5-triazine (TPT), a new and mild esterification agent for the preparation of penicillin and cephalosporin esters (Scheme 75) ⟨90H(31)2055⟩. This esterification procedure has been successfully applied to the industrial production of diphenylmethyl 6β-(4-toluamido)penicillate, an important intermediate for the production of Shionogi β-lactam antiobiotics Latamoxef, Flomoxef, and Ceftibuten. The use of cyanuric chloride with pyridine is safer and more economical on a large scale, with better product yield than other known esterification procedures.

A template synthesis, by the cross link of water soluble starch with cyanuric chloride in a two-phase system (Equation (46)) provides a potential method for 'tailor-made cyclodextrins'. Tailor-made cyclodextrins are believed to be applicable, more precisely and successfully, to many novel phenomena attained in the past by the use of cyclodextrin ⟨83TL3501⟩.

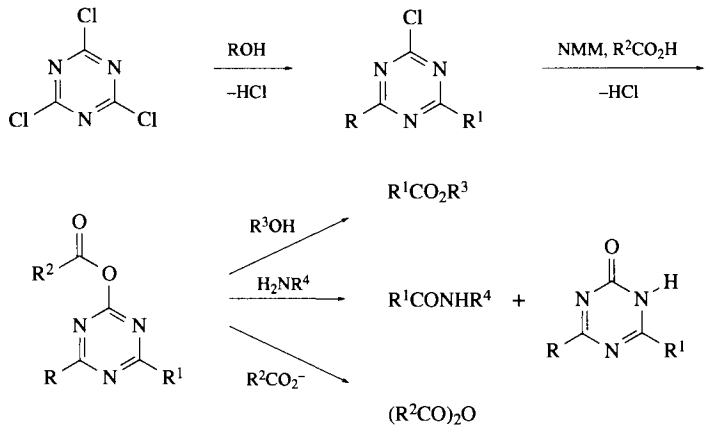


(46)



Scheme 75

Partial substitution of the chlorine atoms of cyanuric chloride by methoxy or phenoxy groups changes the course of reaction with carboxylic acids. The reaction between 2-chloro-4,6-disubstituted-1,3,5-triazines and carboxylic acids gave highly reactive intermediates. Treatment of these intermediates with alcohols, amines, and carboxylic acids, gave appropriate esters, amides, and acid anhydrides respectively (Scheme 76). Substituents attached to the triazine ring affect the acylation ability of the 2-chloro-4,6-disubstituted-1,3,5-triazines. The reactivity decreases in the order 2,4-dichloro-6-methoxy-1,3,5-triazine > 2-chloro-4,6-dimethoxy-1,3,5-triazine > 2-chloro-4,6-diphenoxy-1,3,5-triazine. The most reactive gave esters, amides, and acid anhydrides. 2-Chloro-4,6-diphenoxy-1,3,5-triazine was limited to the acylation of amines only ⟨85TL2901⟩.



R = Cl, R¹ = OMe; R = R¹ = OMe; R = R¹ = OC_6H_5

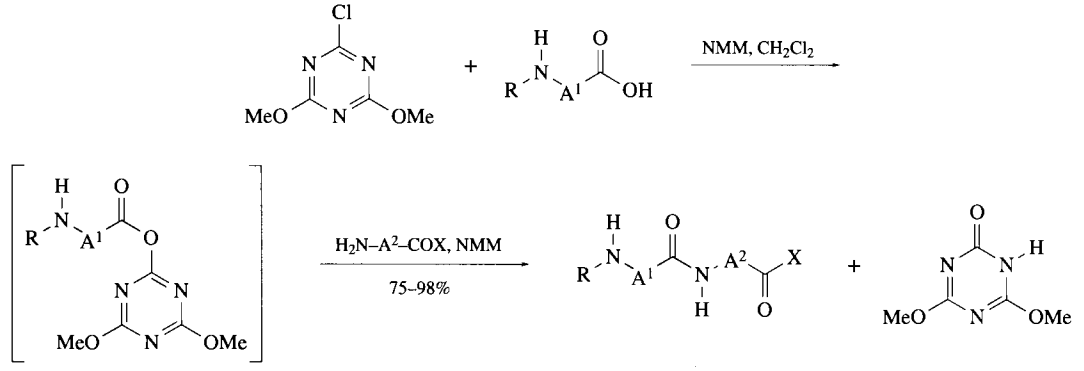
Scheme 76

2-Chloro-4,6-dimethoxy-1,3,5-triazine is a potent coupling reagent for the synthesis of peptides. It has the advantage of high product yield under mild conditions with easy removal of any excess of reagent. No racemization occurs during the reaction (Scheme 77) ⟨87S917, 91JOC5716⟩.

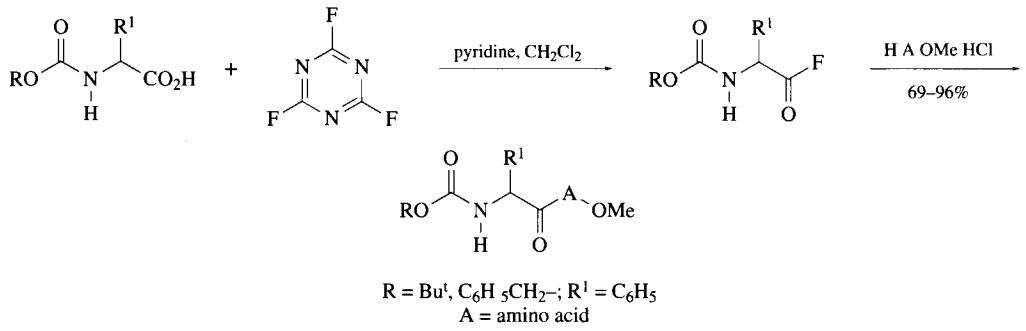
Cyanuric fluoride behaves much the same as cyanuric chloride but its higher reactivity leads to nucleophilic reactions with aromatic amines, which act as carbon nucleophiles. This is a useful advantage for cyanuric fluoride, as a synthetic reagent, for the synthesis of these triazine derivatives with carbon substituents.

α-BOC (tertiary butoxycarbonyl) and *Z*-amino acid fluorides are prepared as reactive peptide coupling reagents by reaction of the protected amino acid with cyanuric fluoride (Scheme 78) ⟨91JOC2611, 91TL1303, 92JOC6371, 93JOC4162⟩.

Trichloroisocyanuric acid (TCC) has proved useful in the side chain chlorination of *N*-heterocyclic compounds. 2-Methylpyridines (**236**), 2-methylquinolines, and 2-methylquinoxalines react with



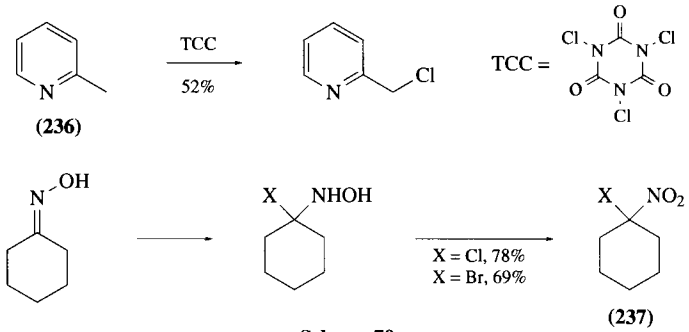
Scheme 77



R = Bu^t, $C_6H_5CH_2$–; $R^1 = C_6H_5$
A = amino acid

Scheme 78

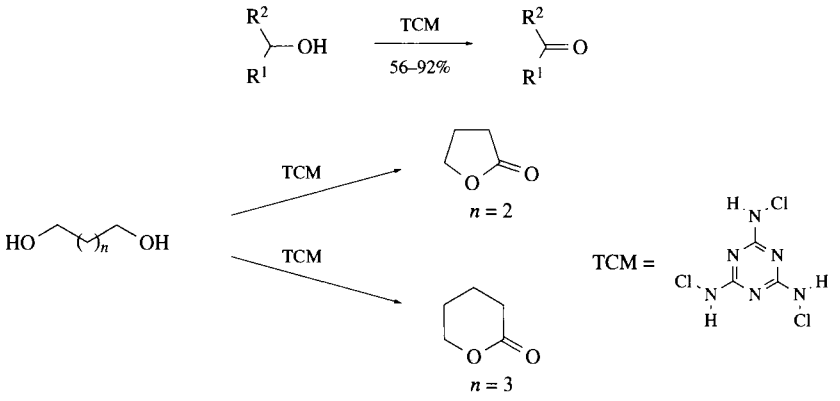
TCC, without initiator, to give the corresponding chloromethyl compounds (Scheme 79) ⟨87CB649⟩. Triazine derivatives 1-sodio-3,5-dichloro-1,3,5-triazine- and 1,3-dibromo-1,3,5-triazine-2,4,6 (1*H*,3*H*,5*H*)-trione are useful combination halogenation–oxidation reagents. Oximes are converted into *gem*-halonitro compounds (e.g. (**237**)). The three triazine derivatives may also be used in conjunction with ozone to accomplish the transformation in a stepwise manner (Scheme 79) ⟨91JOC316⟩.



Scheme 79

Trichloromelamine (TCM), because of the simple procedure, mild conditions, high selectivity, and low cost, is a useful reagent for the selective oxidation of alcohols to the corresponding carbonyl compounds. Oxidation of diols to lactones with two equivalents of TCM in dichloromethane is also reported. Lactones of five- and six-membered rings only were obtained in 87% and 95% yield respectively; four- and seven-membered ring lactonization did not occur (Scheme 80) ⟨93JOC5003⟩.

Melamine-hydrogen fluoride solution (14:86 w/w %) is claimed to be superior to other amine-hydrogen fluoride solutions, such as Olah's reagent, for the hydrofluorination of alkenes ⟨83CL1135⟩. Melamine-HF solution has the advantages of ease of preparation and handling, stability, and high hydrofluorination activity. To obtain hydrofluorination products it is necessary to quench the reaction with large quantities of water followed by neutralization with sodium bicarbonate and



Scheme 80

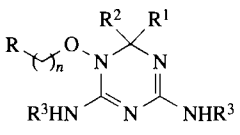
subsequent loss of the reagent. This disadvantage is overcome by the use of pentane or carbon tetrachloride cosolvent. The reagent with a cosolvent forms a liquid–liquid two-phase system for the continuous hydrofluorination of alkenes ⟨84CL1241⟩.

Cyanuric chloride on monosubstitution with nucleophiles such as methanol or 4-amino-azobenzene followed by displacement of a second chlorine with alanine amide gave compounds which are used for precolumn derivatization of amino acids. The diastereoisomers formed are resolved by reverse-phase HPLC ⟨92MI 612-01⟩. Enantiomeric amino acids are separated by HPLC on bis[carbamoyl(alkyl)methylamino]-6-chloro-1,3,5-triazine derived stationary phases ⟨93JC277⟩.

Doubly and triply bridged polyoxapolyazaheterophanes developed from cyanuric chloride are available which can complex alkali cations and therefore act as catalysts in nucleophilic aliphatic substitutions under phase-transfer conditions ⟨84JOC4197⟩.

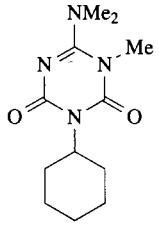
6.12.12.2 Agricultural Chemicals

1,3,5-Triazines have found application as fungicides, insecticides, and herbicides. These applications are represented by Anilazine (fungicide), Menazon (insecticide), and the wide range of herbicides of which Simazine and Atrazine are the most important. These are all old, well-established products but only the two herbicides are still of importance. Numerous patents have appeared over the last decade but no significant advances have been made with triazine fungicides or insecticides, although a recent patent does claim *N*-oxydihydrotriazines (**238**) as potential insecticides ⟨94USP5300503⟩.

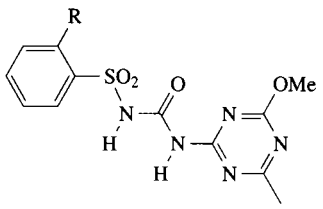


(238)

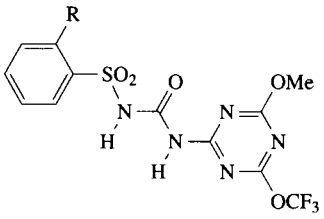
Hexazinone has been introduced by Du Pont as a post emergent herbicide, effective against annual and biennial weeds for selective control in lucerne, pineapple, sugar cane, and some coniferous species. Its primary use is the control of undesirable hardwood trees in pine stands and its application has expanded rapidly since the use of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) was banned. Du Pont have also developed Chlorsulfuron and Metsulfuron, which are sulfonyl urea herbicides, for pre- and postemergence application against broadleaf weeds in cereals ⟨79MIP7903261, 79USP4127405⟩. Numerous patents from other companies, with variations of structure, have followed on the sulfonyl ureas since disclosure of the compounds by Du-Pont, e.g. (**239**) and (**240**) ⟨84EUP116518, 92GEP4024755⟩.



Hexazinone



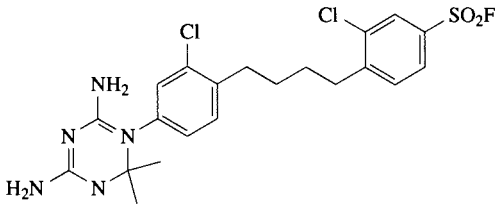
R = Cl (Chlorsulfuron)
R = CO_2Me (Metsulfuron)
(**239**) R = $NHCO(CH_2)_3Cl$



(**240**)

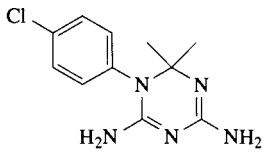
6.12.12.3 Pharmaceuticals

1,3,5-Triazines as drugs have been reviewed ⟨81KFZ27⟩ and are claimed as antibacterial, antineoplastic, antimalarial, antiprotozoal, antispasmodic, antitrypanosomal, and antiulcerative agents, and as diuretics. Antineoplastic agents (anticancer, dihydrofolate reductase inhibitors) have been thoroughly investigated (Baker triazines (**241**)) and are the subject of an excellent review by Hansch and co-workers ⟨84CRV333⟩.

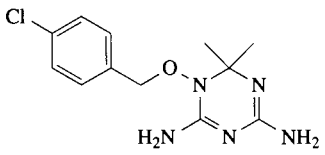


(**241**)

An extensive range of 1-aryl substituted 2,4-diamino-1,2-dihydro-2,2-dimethyl-1,3,5-triazines have also shown potent antimalarial activity (e.g. Cycloguanil (**242**)). The emergence of resistant strains of *Plasmodium falciparum* has restricted the widespread clinical use of cycloguanil. *N*-Oxydihydrotriazines such as Clociguanil (**243**), which do not show cross resistance with cycloguanil against triazine resistant strains of *P. berghei* and are also active against *P. falciparum*, have been developed. The chemistry and antimalarial activity of these compounds has been extensively reviewed by Mamalis and Werbel ⟨B-84MI 612-01⟩. *N*-Oxydihydrotriazines (arylmethoxy-, aryloxy-, and arylalkoxy-dihydrotriazines) were thoroughly investigated as antimalarial agents but triazine research has been replaced by work on quinoline- and phenanthrenemethanols. However, interest in *N*-oxydihydrotriazines as potential insecticides has been recently revived (see Section 6.12.12.2).



(**242**)



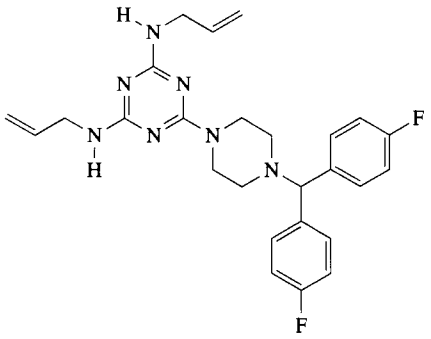
(**243**)

Almitrine (**244**), which is used to treat respiratory problems, was used as a lead compound to develop triazine derivatives as potent modulators of multidrug resistance in cancer therapy ⟨92JMC2481⟩. Triazine (**245**) was selected as the best candidate for development and is currently in phase 1 clinical trials.

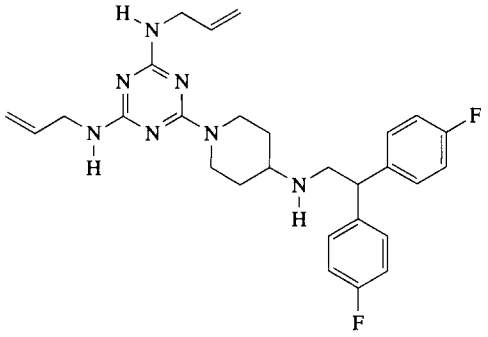
Triazine derivatives (**246**) and (**247**) have been established as suitable lead compounds for the possible development of new antiulcer drugs ⟨91CPB3180⟩.

6.12.12.4 Miscellaneous Applications

1,3,5-Triazines are well known and established as fiber-reactive dyes, optical brighteners, explosives, resins, and polymers ⟨B-84MI 612-01⟩. Pogosyan and Zaplishnyi have reviewed polymers which contain 1,3,5-triazine ⟨83AKZ207⟩.



(244)
Almitrine



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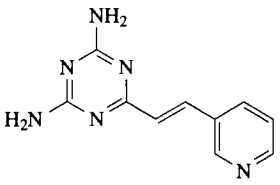

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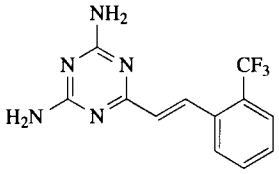

(247)

Rapreno is a process whereby cyanuric acid is injected into exhaust fumes which contain nitrogen oxides. Cyanuric acid when heated is decomposed into isocyanic acid, which reacts with the nitrogen oxides to remove them from the exhaust gases. The process has been applied to a single-cylinder diesel engine to demonstrate its practical feasibility ⟨86NAT657⟩.

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6.13 1,2,3-Oxadiazines and 1,2,3-Thiadiazines

ROBERT K. SMALLEY
University of Salford, UK

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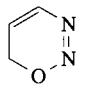
6.13.1 INTRODUCTION

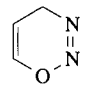
In all sections of this chapter, and in the following five chapters (see 6.14, 6.15, 6.16, 6.17 and 6.18, the heterocyclic systems are dealt with in the order, oxadiazines and their benzo derivatives, followed by thiadiazines and their benzo derivatives in which sulfur is divalent, then thiadiazines in which sulfur exhibits a valency of four.

The 1,2,3-oxadiazines (**1**) and the isomeric 4*H*- (**2**) and 2*H*- derivatives (**3**) remain elusive ring systems, although 2,3-dihydro derivatives of system (**1**) are now available (see Section 6.13.7.2.1) ⟨93SC107⟩. Likewise, the fully conjugated 1-oxonia derivatives, which would be expected to be 6π-heteroaromatic systems, are unknown. Whereas 4*H*- (**4**) and 2*H*-1,2,3-benzoxadiazines (**5**) are still

unknown, there is some spectroscopic evidence to support the existence of the isomeric 4*H*-3,1,2-benzoxadiazine system (**6**) (see Section 6.13.4) ⟨87JOU99⟩.



(1)



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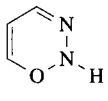

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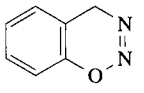

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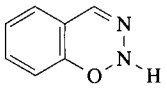

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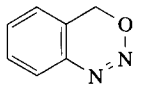
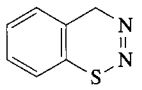


(6)

The earlier claims to the preparation of 1,2,3-oxadiazines, mentioned in the first edition ⟨84CHEC-I(3)1039⟩, remain unsubstantiated.

The 1,2,3-thiadiazines (**7**) are still uncommon and are known mainly as the *S*,*S*-dioxides of their hydro derivatives; likewise for the 2*H*- and 4*H*-1,2,3-benzothiadiazine systems (**8**). 2*H*-1,2,3-Benzothiadiazines (**8**) are now accessible as the 3,4-dihydro derivatives by thermally induced [4 + 2] cycloadditions of azodicarboxylates to benzothietes (see Section 6.13.7.2.2) ⟨86TL5703⟩, whereas 4*H*-3,1,2-benzothiadiazines (**9**) are unknown. 1,2,3-Thiadiazines in which sulfur is four-valent do not appear to have been prepared, nor do 1-thionia systems. The chemistry of 1,2,3-thiadiazines and 1,2,3-benzothiadiazines has been reviewed ⟨90AHC(50)255⟩.

(7)



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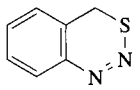


(9)

6.13.2 THEORETICAL METHODS

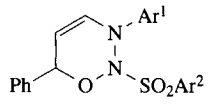
Theoretical calculations and studies do not appear to have been carried out on any of these ring systems. However, the instability of 3,1,2-benzoxadiazines has been discussed in terms of their formulation as examples of cyclic *syn*-diazoethers ⟨88IJC(B)653⟩.

6.13.3 EXPERIMENTAL STRUCTURAL METHODS

6.13.3.1 Spectroscopic Studies

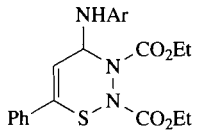
6.13.3.1.1 NMR spectra

In the proton magnetic resonance (PMR) spectrum, the C-4 alkene proton of the 3,6-dihydro-2*H*-1,2,3-oxadiazine (**10**; $Ar^1 = 4\text{-}MeOC_6H_4$, $Ar^2 = 4\text{-}MeC_6H_4$) appears as a doublet (no *J* value cited) at 9.2 δ, with the C-5 proton signal contained within the aromatic resonances at 7.2–8.3 δ ⟨93SC107⟩. The C-6 proton is assigned as a doublet at 6.9 δ (again, no *J* value is cited).

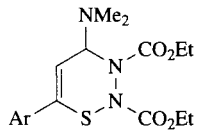


(10)

A comparative study of the PMR spectra of the 4-arylamino- (**11**) and 4-dimethylamino-3,4-dihydro-2*H*-1,2,3-thiadiazines (**12**) reveals that, in the former, H-4 occupies an equatorial position ($J_{4,5} \simeq 6$ Hz), whereas in the latter H-4 is in an axial position ($J_{4,5} \simeq 3$ Hz) ⟨89S631⟩.



(**11**)



(**12**)

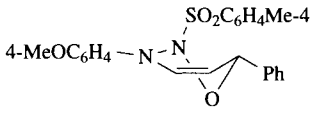
Carbon-13 NMR resonances of 61.51 δ, 113.88 δ and 139.29 δ have been recorded for C-4, C-5 and C-6, respectively, of diethyl 6-phenyl-4-phenylamino-3,4-dihydro-2*H*-1,2,3-thiadiazine-2,3-dicarboxylate (**11**; Ar = Ph) ⟨89S631⟩.

6.13.3.1.2 Mass spectra

The mass spectrum of the 1,2,3-oxadiazine (**10**; Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4) shows no molecular ion, rather a base peak at m/z 236 corresponding to 1-(4-methoxyphenyl)-4-phenyl-1-aza-1,3-butadienium ion, the product of a retro-Diels–Alder reaction ⟨93SC107⟩. Similarly, the 1,2,3-thiadiazines (**11**) and (**12**), in general, show no, or only weak, molecular ions, but strong (M^+—S) and (M^+—CO_2Et) fragments ⟨89S631⟩.

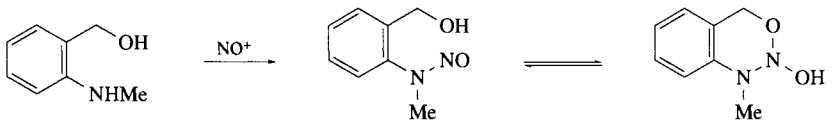
6.13.4 THERMODYNAMIC ASPECTS

Little information has been published regarding the detailed structure, general stability, and tautomeric nature of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems. X-ray data is lacking, although the conformation of the 3,6-dihydro-2*H*-1,2,3-oxadiazine (**10**; Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4) has been assigned tentatively as Structure (**13**), on the basis of ^{1}H NMR measurements in conjunction with a Dreiding model ⟨93SC107⟩.



(**13**)

Nitrosation of 2-methylaminobenzyl alcohol (**14**) produces the *N*-nitroso compound (**15**), a ring–chain tautomer of 2-hydroxy-1-methyl-1,2-dihydro-4*H*-3,1,2-benzoxadiazine (**16**) (Scheme 1) ⟨88IJC(B)653⟩. However, no chemical or spectroscopic evidence for the heterocyclic tautomer (**16**) was found.

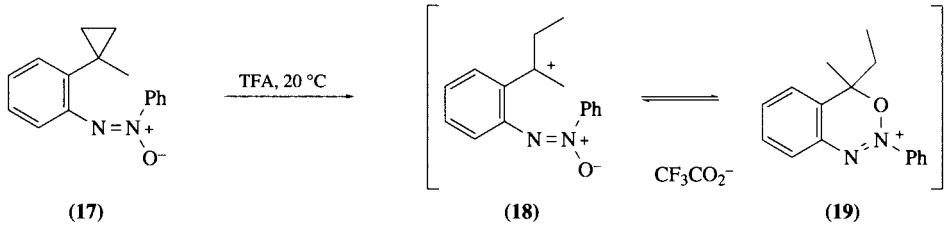


(**14**) (**15**) (**16**)

Scheme 1

Carbon-13 NMR spectroscopic evidence has been presented for the formation of 4*H*-3,1,2-benzoxadiazinium ions on treatment of the 2-cyclopropylazoxybenzene (**17**) with trifluoroethanoic acid (Scheme 2) ⟨87JOU99⟩. PMR studies failed to differentiate between the open-chain carbocation

(**18**) and the cyclic oxadiazinium ion (**19**). However, a single line resonance for C-4 at 94.55 δ in the ^{13}C NMR spectrum is indicative of the cyclic structure (**19**) rather than the tertiary carbocation (**18**) for which, from model compounds, a C-4 resonance in the region of 170–200 δ is to be expected.



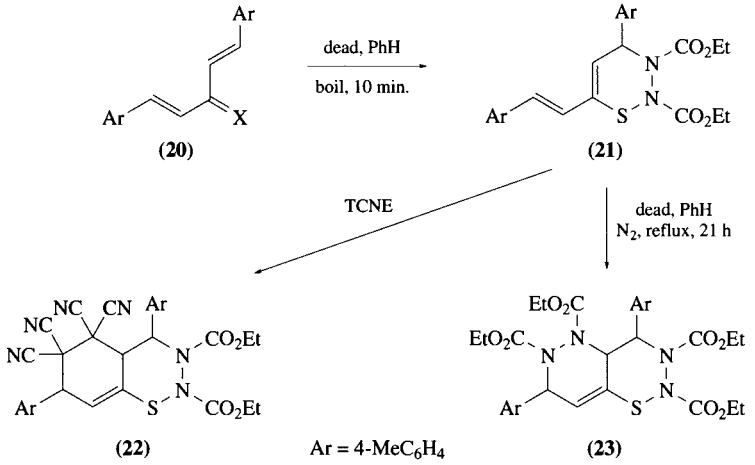
(**17**) (**18**) (**19**)

Scheme 2

6.13.5 REACTIVITY OF FULLY CONJUGATED AND NONCONJUGATED RINGS

6.13.5.1 Cycloaddition Reactions

The cross-conjugated thione (**20**; X = S), prepared from the corresponding ketone (**20**; X = O) with phosphorus pentasulfide, participates in a diene-transmissive Diels–Alder reaction with diethyl azodicarboxylate ⟨90BCJ284⟩. The 3,4-dihydro-2*H*-1,2,3-thiadiazine (**21**) so formed is isolable (see Section 6.13.7.2.2) and on prolonged heating with diethyl azodicarboxylate undergoes further cycloaddition to yield the pyridazino[3,4-*e*]-1,2,3-thiadiazine derivative (**23**) in 74% yield (Scheme 3). Cycloaddition of the thiadiazine (**21**) with tetracyanoethene is much more rapid (10 min) and affords a high yield (73%) of cycloadduct (**22**). In contrast, cycloadditions with maleic anhydride and with *N*-(4-methoxyphenyl)maleimide are much slower (40 h) and the yields inferior (52% and 47%, respectively). Surprisingly, only trace amounts of adduct are obtained with dimethyl ethynedicarboxylate as the dienophile.



(**20**) (**21**) (**22**) Ar = 4-MeC$_6$H$_4$ (**23**)

Scheme 3

6.13.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING CARBON ATOMS AND TO THE RING NITROGEN AND SULFUR ATOMS

Since the first edition of Comprehensive Heterocyclic Chemistry ⟨84CHEC-I(3)1039⟩ there have been no developments in the chemistry concerning reactions at the ring atoms of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems.

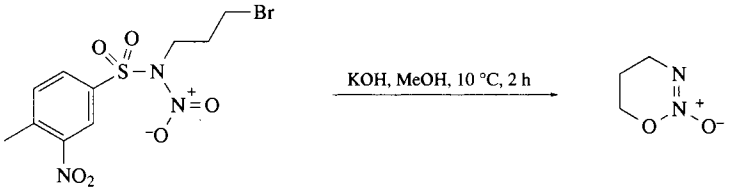
6.13.7 RING SYNTHESIS

As in the first edition ⟨84CHEC-I(3)1039⟩, synthetic methods are classified according to the size and number of fragments involved in ring formation and according to the nature of the bond, or bonds, formed during the ring closure.

6.13.7.1 Formation of One Bond

6.13.7.1.1 Between C and O

The product from the base-induced cyclization of the *N*-(3-bromopropyl)-*N*-nitroarene-sulfonamide (**24**) has been formulated as the 5,6-dihydro-4*H*-1,2,3-oxadiazine 2-oxide (**25**) (Equation (1)) ⟨83IZV667⟩.

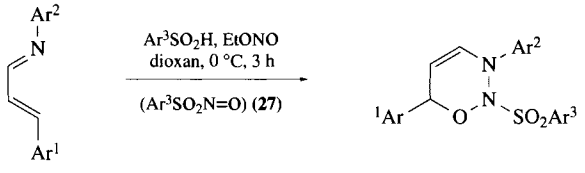


(24) (25) (1)

6.13.7.2 Formation of Two Bonds

6.13.7.2.1 From C—C—C—N and N—O fragments

A significant development in 1,2,3-oxadiazine chemistry is the preparation, in moderate yields (30–55%), of the 3,6-diaryl-2-arylsulfonyl-2,3-dihydro-6*H*-derivatives (**28**) by a [4 + 2] regiospecific cycloaddition of 1,4-diaryl-1-aza-1,3-butadienes (**26**) with arenesulfonyl nitrosites (**27**; Ar^3 = Ph or 4-MeC_6H_4), generated *in situ* from ethyl nitrite and an arenesulfinic acid (Equation (2)). Electron-withdrawing and electron-donating substituents on the *C*-aryl and *N*-aryl rings have only a marginal effect on the yield of oxadiazine, but the reaction fails with the *N*-(2-hydroxyphenyl)azabutadiene (**26**; Ar^1 = Ph, Ar^2 = 2-HOC_6H_4). Steric inhibition to the approach of the two reactants by the 2-hydroxy group is cited as a possible explanation for this failure ⟨93SC107⟩.

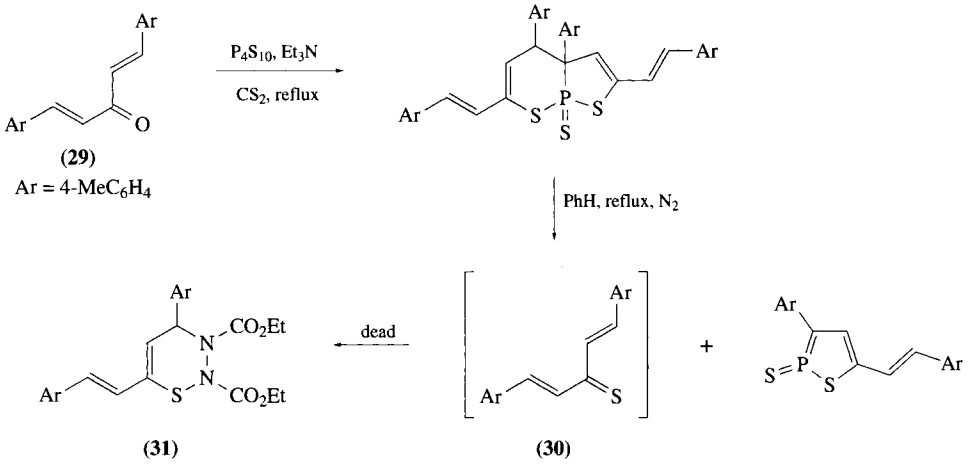


(26) (28) (2)

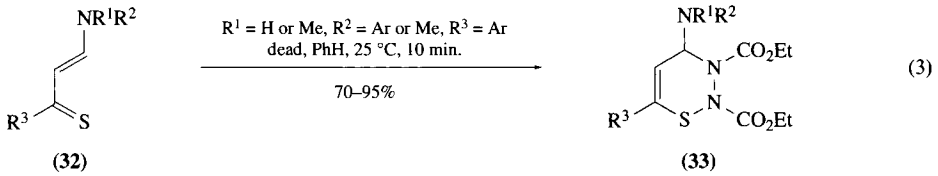
6.13.7.2.2 From C—C—C—S and N—N fragments

A new synthesis of a 3,4-dihydro-2*H*-1,2,3-thiadiazine (**31**) (43% yield) has been described ⟨88CL717, 92BCJ923⟩ in which the cross-conjugated thione (**30**), prepared from the ketone (**29**) as indicated in Scheme 4, is trapped as the Diels–Alder [4 + 2] cycloadduct with diethyl azodicarboxylate. The thiadiazine (**31**) also functions as a diene and undergoes further cycloaddition with the azadienophile (see Section 6.13.5.1). The enaminothiones (**32**) also undergo [4 + 2] cycloadditions

with diethyl azodicarboxylate to furnish 4-amino-3,4-dihydro-2*H*-1,2,3-thiadiazine-2,3-dicarboxylates (**33**) in excellent yields (Equation (3)) ⟨89S631⟩.

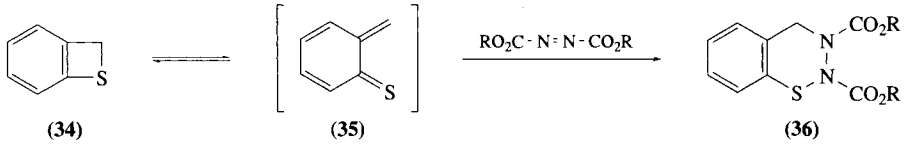


Scheme 4



(3)

An elegant new synthesis of 3,4-dihydro-2*H*-1,2,3-benzothiadiazine-2,3-dicarboxylates involving benzothiete (**34**) has been described ⟨86TL5703⟩. In boiling toluene the strained thiete ring undergoes electrocyclic ring opening to the *o*-quinonoid valence tautomer (**35**), which has a high energy HOMO (−8.96 eV) and enters readily into [4 + 2] cycloadditions with azo dicarboxylates to give the dihydro-1,2,3-benzothiadiazines (**36**) in high yields (Scheme 5).



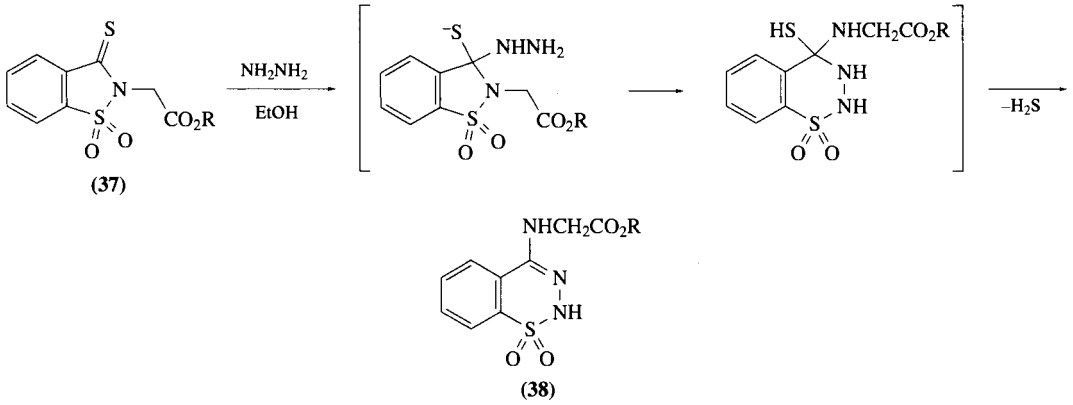
Yields: (**36**); R = CO_2Et, 77%; R = CO_2CH_2Ph, 90%; R = CO_2Bu^t, 73%; R = CO_2Ph, 84%

Scheme 5

6.13.8 RING SYNTHESIS BY TRANSFORMATIONS OF ANOTHER RING

1,2-Benzothiazole-3-thione 1,1-dioxides (**37**), unlike the 3-ones which yield hydrazones, on treatment with hydrazine hydrate undergo ring expansion to 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (**38**) ⟨88IJC(B)109⟩. A mechanistic rationale (Scheme 6), which involves initial attack by hydrazine at the thiocarbonyl group followed by intramolecular nucleophilic attack at the ring sulfur by the terminal nitrogen of the hydrazine so formed accompanied by loss of hydrogen sulfide, is proposed. Attack by hydrazine at the ester carbonyl centre is discounted as the methyl and ethyl esters (**37**; R = Me or Et) yield different products, both of which show the appropriate alkyl resonances in

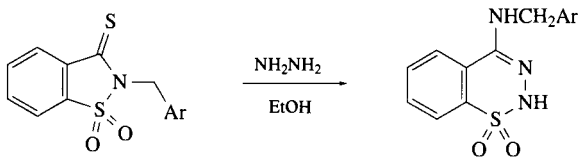
their PMR spectra. Analogous reactions occur with *N*-benzyl-1,2-benzothiazol-3-thione 1,1-dioxides (**39**) (Equation (4)) ⟨90IJC(B)598⟩.



(**37**)

(**38**)

Scheme 6

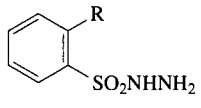


(**39**) (4)

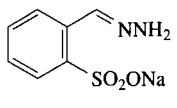
6.13.9 SUMMARY OF SYNTHETIC METHODS

The synthesis of 1,2,3-oxadiazines is limited to the cycloaddition of arenesulfonyl nitrosites to 1-aza-1,3-butadienes ⟨93SC107⟩. Similarly, access to 1,2,3-thiadiazines, as their 3,4-dihydro-derivatives, is confined to the cycloaddition of azodicarboxylates to cross-conjugated thiones ⟨92BCJ923⟩ and, to a lesser degree, by addition of sulfines to 1,2-diaza-1,3-butadienes ⟨81JCS(P1)2322, 84CHEC-I(3)1039⟩.

Unlike 2*H*-1,2,3-benzoxadiazine, which remains an unknown system, 2*H*-1,2,3-benzothiadiazines are prepared readily, as their *S*,*S*-dioxides, by cyclization of *ortho*-substituted arenesulfonyl hydrazides (**40**; R = CN ⟨63FRP2166⟩, R = CO_2R ⟨62JOC1703⟩) and by ring closure of hydrazone (**41**) with phosphorus pentachloride ⟨69CC33⟩. In 1990 the *S*,*S*-dioxides were synthesized by ring expansion of *N*-substituted-1,2-benzothiazole 1,1-dioxides in the presence of hydrazine ⟨90IJC(B)598⟩. 3,4-Dihydro-2*H*-1,2,3-benzothiadiazine-2,3-dicarboxylates are accessible by [4 + 2] cycloaddition of dialkyl azodicarboxylates with the open-chain valence tautomer of benzothiete ⟨86TL5703⟩.

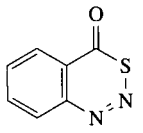


(**40**)



(**41**)

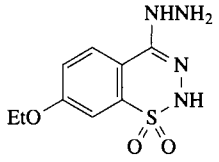
Uniquely, 3,1,2-benzothiadiazin-4-one (**42**) can be obtained by diazotization of thioanthranilic acid under aprotic conditions ⟨72JA8505⟩.



(**42**)

6.13.10 IMPORTANT COMPOUNDS AND APPLICATIONS

The only compound of note is the 4-hydrazino-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**43**) which, like the 1,2,4-thiadiazine 1,1-dioxides (see Chapter 6.14), is reported to have diuretic and antihypertensive activity ⟨62HCA996⟩.



(43)

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6.14
1,2,4-Oxadiazines and 1,2,4-Thiadiazines

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University of Salford, UK

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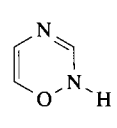
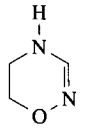
6.14.1 INTRODUCTION

2*H*-1,2,4-Oxadiazines (**1**) and their 4*H*- and 6*H*-isomers are known mainly as the 5,6-dihydro- (**2**) and tetrahydro- derivatives. 1,2,4-Benzoxadiazines are uncommon systems but have been reported as both the 2*H*-(**3**) and 4*H*-(**4**) isomers.


(1)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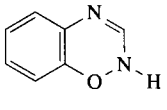
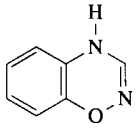
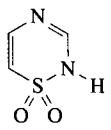

(3)


(4)

Although 2*H*- and 4*H*-1,2,4-thiadiazines with divalent sulfur are virtually unknown, both isomers have been prepared as the 1-oxides and, more commonly, as the 1,1-dioxides (**5**) and (**6**). Likewise, 2*H*- and 4*H*-1,2,4-benzothiadiazines are known mainly as the mono- and disulfoxides, for example, (**7**).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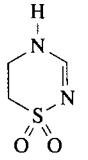
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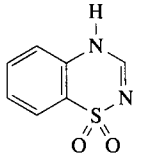
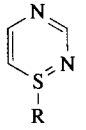

(7)

1,2,4-Thiadiazines and their benzologues, in which sulfur forms four classical covalent bonds, are designated as 1λ^4,2,4-thiadiazines ⟨84CHEC-I(1)32⟩. In addition to the simple derivatives (**8**) (see Section 6.14.9.1.2), examples of the cyclic sulfoximides (**9**; X = O) (see Section 6.14.9.2.3(ii)) and the cyclic sulfimides (**9**; X = NH), which are referred to in the original paper ⟨88CB1689⟩ as 1λ^6,2,4-thiadiazines (see Section 6.14.9.1.2) have also been prepared. Throughout this chapter such derivatives are represented as the conjugated systems (**9**) rather than the dipolar forms (**10**) (see Section 6.14.5).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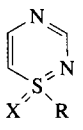
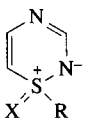

(9)

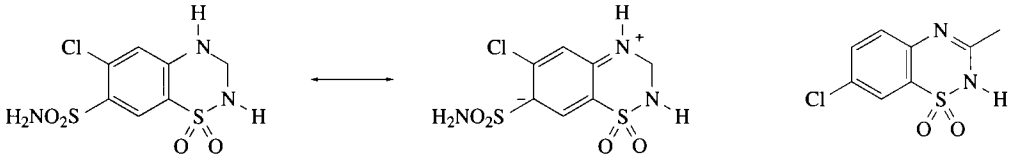

(10)

As with the 1,2,3-oxadiazines and 1,2,3-thiadiazines discussed in Chapter 6.13 there appear to be no examples of the fully conjugated 1-oxonia-(**11**; X = O) and 1-thionia-(**11**; X = S) systems. The chemistry of 1,2,4-thiadiazines and 1,2,4-benzothiadiazines has been reviewed ⟨90AHC(50)255⟩.

(**11**)

6.14.2 THEORETICAL METHODS

Theoretical studies on the title compounds and their benzo derivatives are confined to a structure–activity relationship study on the 1,2,4-benzothiadiazine 1,1-dioxide diuretics. From a consideration of van der Waals volumes and hydrophobic parameters it is concluded that the diuretic activity of hydrochlorothiazide (**12**), and related derivatives, is closely linked to the van der Waals volume of the 6-substituent ⟨83AF688⟩. It has been indicated by CNDO/2 calculations that these diuretics are electron accepting and that the presence of the 7-sulfonamide group confers a formal negative charge at C-7 as represented by mesomer (**13**), and the significant contribution of this mesomer is in accord with earlier x-ray crystallographic data ⟨72AX(B)2340⟩. In contrast, a 7-chloro substituent, such as is present in the related antihypertensive, but nondiuretic, 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (e.g., (**14**) diazoxide), has the opposite electronic effect.



(**12**) (**13**) (**14**)

6.14.3 EXPERIMENTAL STRUCTURAL METHODS

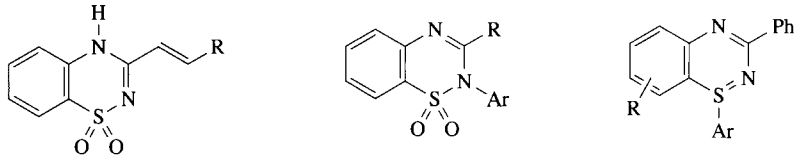
6.14.3.1 Spectroscopic Studies

6.14.3.1.1 Ultraviolet and infrared spectra

The UV spectra of the major 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide diuretics (e.g., (**12**)) have been recorded as 10% solutions in methanol. All show absorptions at 220–235 and 271–281 nm ⟨82PHA150⟩.

The differences in the UV spectra of 3-(alkenyl)-(**15**) and 3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides are not due to the presence of the 2*H*-tautomer, but rather to the cross-conjugated system present in the former ⟨84CHE735⟩. 3-Alkyl-2-aryl-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**16**) in methanol solution show three absorption maxima, at 250–260, 260–275, and 280–300 nm ⟨86JOC1967⟩.

1-Alkyl- and 1-aryl-1λ^4,2,4-benzothiadiazines (**17**) exhibit characteristic infrared absorption maxima at around 1450, 1300, 830, and 700 cm^{-1}, whereas the 1-morpholino-derivatives have maxima near 1460, 1320, 1290, 1100, and 900 cm^{-1} ⟨83JCS(P1)49⟩.



(**15**) (**16**) (**17**)

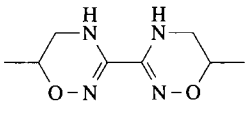
6.14.3.1.2 NMR spectra

The isomeric 3,3-bis(6- and 5-methyl-5,6-dihydro-4*H*-1,2,4-oxadiazines) (**18**) and (**19**) (see Section 6.14.10) have been characterized by their ^1H and ^{13}C NMR spectra, details of which are ⟨82CHE369⟩:

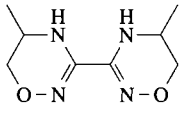
(**20**); ^1H ($CDCl_3$, δ); Me, 1.29; H-5, 3.12, 3.35; H-6, 3.69; NH, 5.7; ^{13}C ($CDCl_3$, δ); Me, 17.9; C-5, 44.1; C-6, 69.4; C-3, 144.9;

(**21**); ^1H ($CDCl_3$, δ); Me, 1.17; H-5, 3.39; H-6, 3.39, 3.96; NH, 5.6; ^{13}C ($CDCl_3$, δ); Me, 16.9; C-5, 44.9; C-6, 68.2; C-3, 144.7.

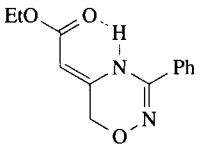
In each isomer the coupling between the tertiary hydrogen and the nonequivalent geminal protons of the adjacent CH_2 group indicates a pseudoequatorial orientation of the methyl group and the nonplanar oxadiazine ring.



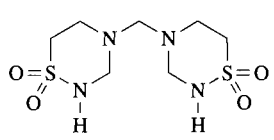
(**18**)



(**19**)



(**20**)

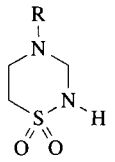


(**21**)

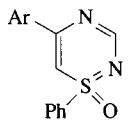
The (*Z*)- and (*E*)-5-(ethoxycarbonylmethylene)-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazines (see Section 6.14.9.2.2(i)) are readily distinguished by the low field intramolecularly hydrogen bonded NH of the (*Z*)-isomer (**20**) at 10.9 ppm. The (*E*)-isomer has NH resonance at 7.6 ppm ⟨82CPB3987⟩. A detailed ^1H and ^{13}C NMR spectroscopic study of the stability and equilibria in aqueous solution of the important antibacterial agents Taurolidine (**21**), and the related Taurultam (**22**; R = H) (see Section 6.14.12) reveals, in each case, the presence of the 4-(hydroxymethyl) derivative (**22**; R = CH_2OH), which is believed to be the active bactericide ⟨82TAL953⟩.

The C-3 and C-6 protons of 1,5-diaryl-1λ^4,2,4-thiadiazine 1-oxides (**23**) (see Section 6.14.9.2.3(ii)) show characteristic PMR signals at 8.2–8.3 δ and 6.2 δ ($J_{3,6}$ 1.5–1.8 Hz), respectively ⟨90JCS(P1)447⟩. The high field ^{13}C chemical shift of C-6 (89.0 δ), compared with C-3 (at 156.5 δ) of the 1,5-diphenyl derivative (**23**; Ar = Ph), is indicative of a high electron density at the 6-position, and is in accord with electrophilic substitution studies on this system (see Section 6.14.6.3.3).

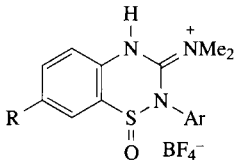
Data from ^1H and ^{13}C NMR for the 1,2,4-benzothiadiazine 1-oxide tetrafluoroborate (**24**; R = H, Ar = Ph) (see Section 6.14.9.2.3(iv)) have been published ⟨84LA904⟩. The CH_3 proton resonances appear at 3.07 δ, and the CH_3 and C-3 carbon resonances at 41.05 and 149.83 respectively; both spectra were measured in acetonitrile solution.



(**22**)



(**23**)



(**24**)

6.14.3.1.3 ESR spectra

The ESR spectrum of the tetrachloro-1,2,4-benzothiadiazinyl radical (**91**) (see Section 6.14.6.3.4) appears as a quintet with intensity ratios of 1 : 2 : 3 : 2 : 1, and a hyperfine splitting constant of 0.52 mT ⟨89JOU550⟩.

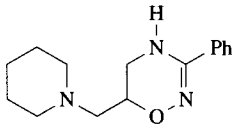
6.14.3.1.4 Mass spectra

Electron impact (EI) mass spectral fragmentation patterns of 5,6-dihydro-4*H*-1,2,4-oxadiazines are complex, and in some instances (e.g., (**25**)) display no molecular ion ⟨83IJM419⟩. Similarly, no regular fragmentation pattern is discernible in the EI mass spectra of 4*H*-1,2,4-oxadiazin-5(6*H*)-ones, and -5(6*H*)-thiones (**26**; X = O and S, respectively) ⟨92OMS(27)833⟩. In fact, in several cases the molecular ion is the base peak, a feature which suggests that the 1,2,4-oxadiazine system is relatively

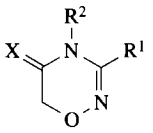
stable. In contrast, 4*H*-1,2,4-oxadiazine-6(5*H*)-ones (**27**) show an intense base peak corresponding to a nitrile oxide ion, formed by successive loss of CO and RCH—NH from the molecular ion ⟨84JHC455⟩.

Detailed analyses of the EI ⟨87MI 614-01⟩ and negative ion ⟨92RCM349⟩ mass spectra of the major 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide diuretics (e.g., (**12**)) have been reported. The characteristic, and unexpected, base peak at *m/z* 303 noted for several of these compounds in their CI (ammonia) mass spectra is thought to be due to formation of the complex ion $(M + NH_4NH_3)^+$, which loses an $RCHNH_2$ fragment consisting of a ring-nitrogen and C-3 with its substituent *R* ⟨88RCM25⟩.

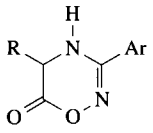
1λ^4,2,4-Benzothiadiazines (**28**) display molecular ions and base peaks corresponding to $(M)^+$-loss of the *S*-substituent in their EI mass spectra ⟨83JCS(P1)49⟩.



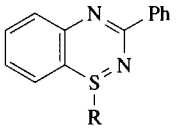
(25)



(26)



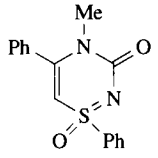
(27)



(28)

6.14.3.1.5 X-ray crystallography

An x-ray crystal structure of the major product from the methylation of 1,5-diphenyl-1λ^4,2,4-thiadiazin-3(4*H*)-one 1-oxide (see Section 6.14.7.5) shows it to be the *N*-methyl derivative (**29**) rather than the methyl ether ⟨90JCS(P1)447⟩.

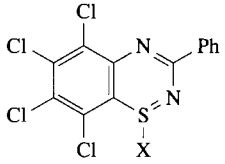


(29)

Using x-ray crystallography a monoclinic form for the 1 : 1 complex of hydrochlorothiazide (**12**) with 18-crown-6 has been revealed ⟨90K682⟩. A monoclinic structure, with space grouping $P2_1/b$, is also noted for 1-(4-morpholino)-3-phenyl-5,6,7,8-tetrachloro-1λ^4,2,4-benzothiadiazine (**30**; X = 4-morpholino) ⟨91MI 614-01⟩. Almost planar orthorhombic crystal structures with the SO_2 group perpendicular to the plane of the ring have been determined for the 4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**31**) and (**32**) ⟨90MI 614-01⟩. The 3-methyl derivative (**32**), in the crystal state, exists solely as the 4*H*-tautomer, whereas the 3-(aminomethyl)-derivative (**31**) is found to be a mixture of the 2*H*- and 4*H*-tautomers. In contrast, the 3-amino derivative (**33**) is rhombohedral ⟨90AX(C)1988⟩, and not monoclinic as reported originally ⟨89AX(C)1905⟩. Furthermore, the x-ray data support unequivocally the 4*H*-tautomer and indicate a significant amidine resonance (**34**) involving the 3-amino group and C-3 and N-2 of the ring in preference to an N(2)—C(3)—N(4) resonance ⟨89AX(C)1905⟩.

The characterization of several commercially important diuretics including hydrochlorothiazide (**35**; X = Cl, R = H), altizide (**35**; X = Cl, $R = CH_2SCH_2CH{=}CH_2$), hydroflumethiazide (**35**; $X = CF_3$, R = H), and trichlormethiazide (**35**; X = Cl, $R = CHCl_2$) by x-ray powder diffraction techniques has been reported ⟨92JCED187⟩. An orthorhombic crystal structure, in which the molecules are linked by N—H···O hydrogen bonds, has been determined for the 3-(cyclopentylmethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**35**; X = Cl, $R = CH_2C_5H_9$) using the heavy atom method ⟨89MI 614-01⟩. The x-ray crystal structure of 1,5,6,7,8-pentachloro-3-phenyl-1λ^4,2,4-benzothiadiazine (**30**; X = Cl) (see Section 6.14.7.1) reveals an almost planar structure with an unionized, but elongated (by 0.16–0.17 Å) S—Cl bond ⟨89JOU550⟩.

The structures of the 2-aryl-3-(*N*,*N*-dimethyliminium)-1,2,4-benzothiadiazine 1-oxide tetrafluoroborates (see Section 6.14.9.2.3(iv)) have been confirmed by an x-ray analysis of the dimethoxy-derivative (**24**; R = MeO, Ar = 4-$MeOC_6H_4$) ⟨84LA904⟩.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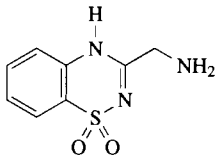
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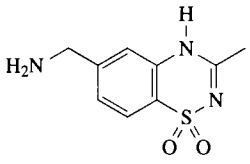
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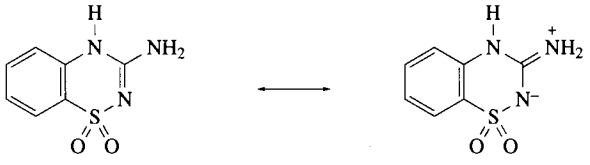
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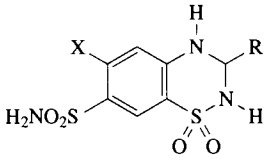
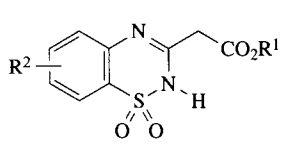

(35)

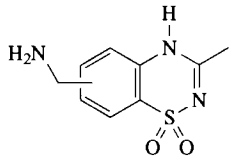
6.14.4 THERMODYNAMIC ASPECTS

There is no PMR spectroscopic evidence to support the existence of the 2*H*-isomers of 4*H*-1,2,4-oxadiazin-6(5*H*)-ones ⟨84JHC455⟩.

The racemic, anticonvulsant 2-acyl-3,4-dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones (see Section 6.14.12) have been resolved via the diastereoisomeric esters of their 4-(hydroxymethyl) derivatives with (*S*)-phenylalanine ⟨89JHC133⟩.

A careful study has been made of the pK_a values of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide diuretics (e.g., (**12**)) ⟨84CPB2380, 86TAL119⟩ and their partition coefficients in a 1 : 1 octanol–water mixture. Two pK_a values are noted: the first, in the range 6.8–8.8, is attributed to ionization of the 2-NH function, whereas the second, at 9.5–10.5, is typical of a primary sulfonamide group ⟨84CPB2380⟩. Ionization constants for a series of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**36**) have been determined potentiometrically in 60% aqueous dioxan at 25°C ⟨85MI 614-01⟩. Values of pK_a (in Me_2SO-H_2O) of 8.5 and 10.1, and 8.2 and 10.0 have been measured for the 6- and 8-(aminomethyl)-derivatives (**37**), respectively, of 3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide. The lower values are assigned tentatively to the N-4 protons, the higher values to deprotonation of the primary amine groups ⟨82JMC113⟩.


(36)


(37)

The Mitsunobu cyclizations of 3-(ω-hydroxyalkyl)-1,2,4-thiadiazine 1,1-dioxides to the angular, rather than to the linear fused thiadiazine systems (see Section 6.14.7.5), are cited as chemical evidence in support of the earlier theoretical and spectroscopic data for the 4*H*- rather than the 2*H*-tautomeric form of these heterocycles ⟨91PS(59)529, 91S159⟩.

The HPLC characterization of the major 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide diuretics has been discussed in detail ⟨85JC395⟩, and their racemic mixtures have been resolved into the pure enantiomers by liquid chromatography on a variety of stationary phases including chiral polyacrylamides (1 : 1 toluene–dioxan as eluant) ⟨85JPS438⟩, (*R*)(+)-camphanic acid and *N*-(1*S*)-

camphanoyl-(*R*)-phenylglycine covalently bound to aminopropyl-silica (3 : 2 hexane-2-propanol as eluant) ⟨89AP(322)405⟩, and immobilized bovine serum albumin ⟨89MI 614-02⟩. Racemization of the optically pure forms in aqueous solution is a function of pH and follows first order kinetics. Racemization and epimerization of the dihydro-2*H*-1,2,4-thiadiazine dioxides have been noted in the presence of human serum albumin ⟨90CPB180⟩.

6.14.5 REACTIVITY OF FULLY CONJUGATED RINGS

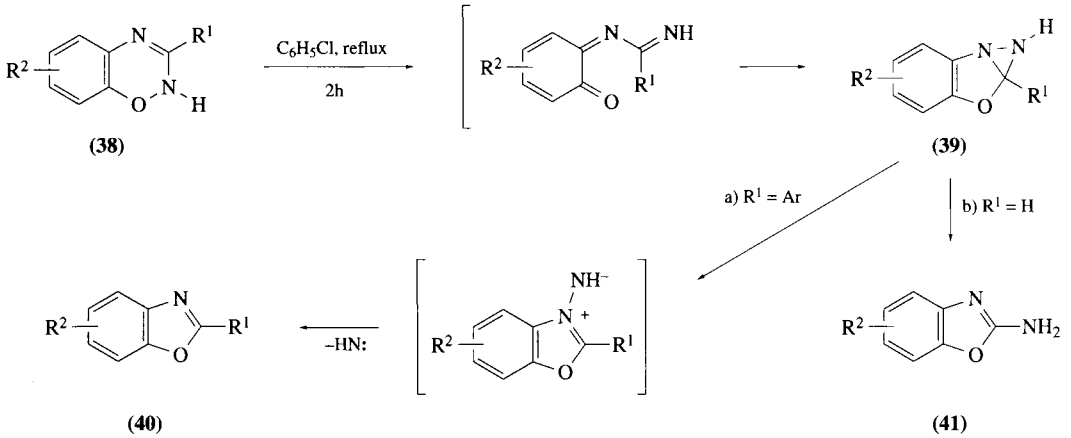
None of the heterocyclic systems covered in this chapter possesses aromatic character. $1\lambda^4$,2,4-thiadiazines (**9**) and their benzologues, which are drawn throughout this chapter as fully conjugated systems, exist as the dipolar forms (e.g., (**10**)) ⟨75CSR189⟩, and as such their chemistry is considered in Section 6.14.6.

6.14.6 REACTIVITY OF NONCONJUGATED RINGS

6.14.6.1 1,2,4-Oxadiazines and 1,2,4-Benzoxadiazines

6.14.6.1.1 Thermal and photochemical unimolecular reactions

In boiling chlorobenzene, 2*H*-1,2,4-benzoxadiazines (**38**) undergo a formal thermal extrusion of nitrene (:NH, subsequently detected as ammonia and nitrogen) and ring-contraction to 1,3-benzoxazoles (**40**) (path a) ⟨75CC962, 88JCS(P1)2169⟩. A mechanistic rationale (Scheme 1) based on substantial supporting evidence is proposed. Of particular interest are the 3-ethoxycarbonyl derivatives (**38**; $R^1 = CO_2Et$, R^2 = 7-H, 7-Cl, or 7-NO_2) which, on mild basic hydrolysis, undergo decarboxylation and rearrangement to the 2-amino-1,3-benzoxazoles (**41**; R^2 = H, Cl, or NO_2) via the fused diaziridine intermediates (**39**; R = H), which can aromatize by hydrogen migration (path b) rather than by C—N bond fission and loss of nitrene.



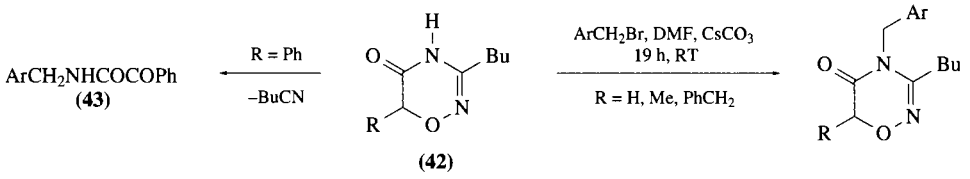
(38) (39) (40) (41)

Scheme 1

6.14.6.1.2 Electrophilic attack at nitrogen

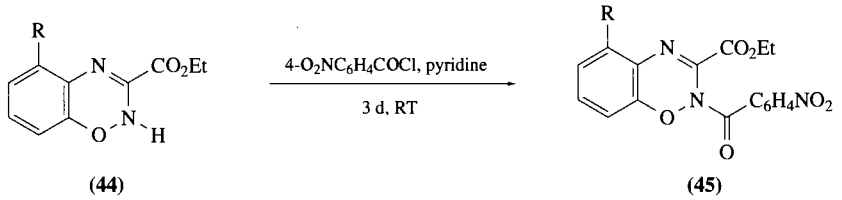
Contrary to an earlier statement ⟨B-61MI 614-01⟩, regioselective alkylation of 4*H*-1,2,4-oxadiazin-5(6*H*)-ones (**42**; R = alkyl) can be achieved at N-4 in good yields (55–81%) with benzyl bromides in dimethylformamide in the presence of potassium or caesium carbonate ⟨93H(36)1027⟩. Inexplicably,

however, the 6-phenyl derivative (**42**; R = Ph) suffers ring cleavage to furnish the α-keto-amides (**43**; ≈75%) as the sole products (Scheme 2).



Scheme 2

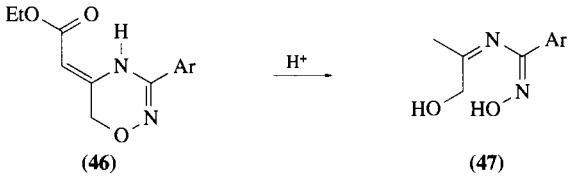
2*H*-1,2,4-benzoxadiazines appear to be weak nucleophiles and are acylated at nitrogen with difficulty. However, acylation of the 5-bromo-derivative (**44**; R = Br) with 4-nitrobenzoyl chloride in pyridine takes place slowly over three days to give what is deemed to be the sterically less hindered 2-acyl derivative (**45**; R = Br) (Equation (1)). In contrast, acylation of the 1,2,4-benzoxadiazine (**44**; R = H), which lacks a 5-substituent, furnishes a mixture of the 2- and 4-(4-nitrobenzoyl)-derivatives ⟨88JCS(P1)2169⟩.



(1)

6.14.6.1.3 Electrophilic attack at oxygen

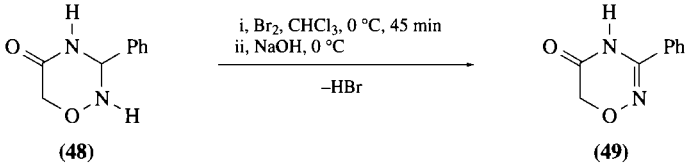
Whereas alkaline hydrolysis of (*Z*)-5-(ethoxycarbonylmethylene)-3-*p*-tolyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**46**; Ar = 4-MeC$_6$H$_4$) (see Section 6.14.9.2.2(i)) results in complete fragmentation of the molecule to yield 4-methylbenzamide, in hot dilute hydrochloric acid initial N—O bond fission is followed by ester hydrolysis and elimination of CO_2 to give the amidoxime derivative (**47**) (Equation 2) ⟨82CPB3987⟩.



(2)

6.14.6.1.4 Electrophilic attack at carbon

Bromination of 3,4-dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-one (**48**) at the benzylic 3-position, followed by dehydrobromination with sodium hydroxide, affords 3-phenyl-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**49**) in 42% yield (Equation (3)) ⟨89JHC129⟩.

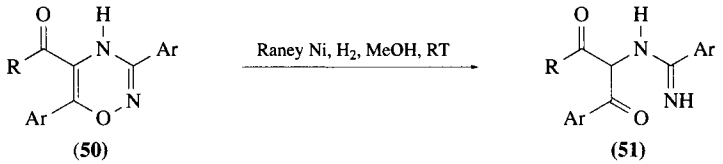


(3)

6.14.6.1.5 Reduction

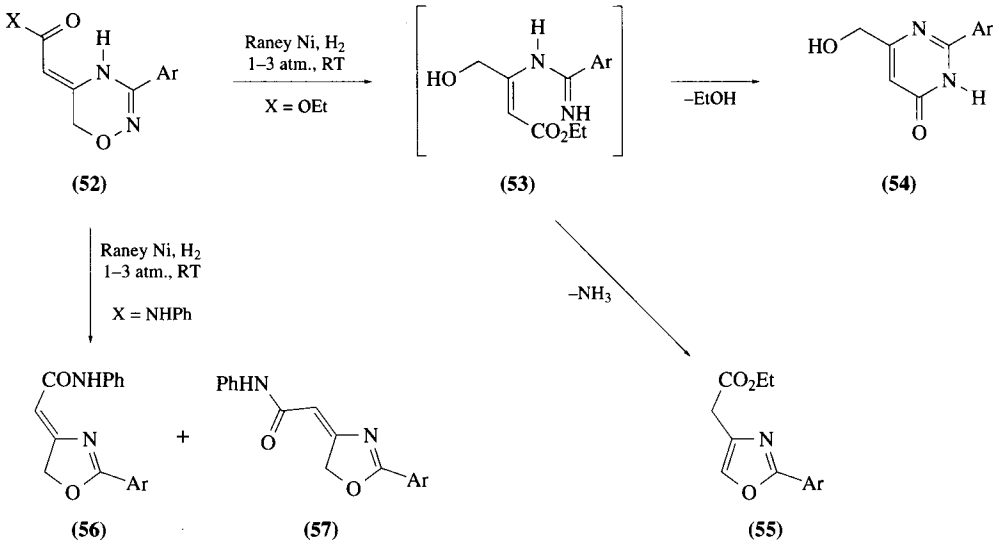
Predictably, in the majority of cases catalytic reduction of 1,2,4-oxadiazines proceeds initially via cleavage of the N—O bond. For example, reduction of 5-acyl-4*H*-1,2,4-oxadiazines (**50**) (see Section

6.14.10) with Raney nickel and hydrogen at room temperature results in ring scission to the amidines (**51**) (Equation (4)) ⟨82CL1711⟩.



(**50**) (**51**) (4)

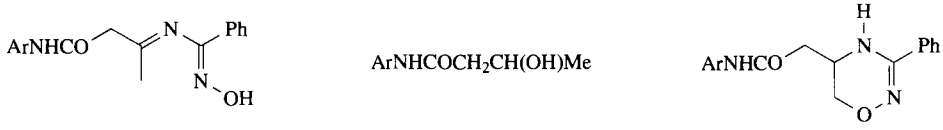
Catalytic reduction of (*Z*)-5-(ethoxycarbonylmethylene)-3-aryl-5,6-dihydro-4*H*-1,2,4-oxadiazines (**52**; X = OEt) in the presence of Raney nickel and low hydrogen pressures (1–3 atm) gives rise to 2-arylpyrimidin-4(3*H*)-ones (**54**; 58–77%), accompanied by lesser amounts (1.5–22%) of the oxazoles (**55**) ⟨85JHC569⟩, via cyclization of the initially formed amidine-esters (**53**) as indicated in Scheme 3. Reduction of the anilide (**52**; X = NHPh, Ar = Ph), however, is more complex and yields a mixture of the (*E*)-(22%)- and (*Z*)-(46%)-oxazolines (**56**) and (**57**) together with a small amount (4.6%) of the oxazole (**55**).



(**52**) (**53**) (**54**) (**56**) (**57**) (**55**)

Scheme 3

In contrast, reductions of the esters (**52**; X = OEt) and anilides (**52**; X = NHAr) with platinum oxide and hydrogen in THF at NTP, although slow and incomplete (35–50% starting material recovered), provide rare examples of the reductive cleavage of the C—O rather than the N—O bond of the 1,2,4-oxadiazine ring. The esters yield, as major products, the benzamidoximes (**58**; 19–25%) along with, in some cases, the pyrimidin-4(3*H*)-ones (**54**) (5%) ⟨85JHC1409⟩, whereas reductions of the anilides are again more complex and, in addition to the benzamidoximes (**58**; 19%) and the *N*-arylamides (**59**; 20%), furnish the 5,6-dihydro-4*H*-1,2,4-oxadiazines (**60**) in which hydrogenation has occurred at the exocyclic double bond ⟨85JHC1409⟩.



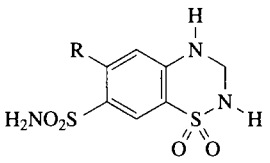
(**58**) (**59**) (**60**)

6.14.6.2 1,2,4-Thiadiazines and 1,2,4-Benzothiadiazines

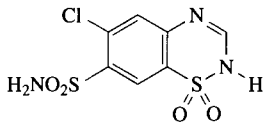
6.14.6.2.1 Thermal and photochemical unimolecular reactions

Possible side effects such as skin photosensitization associated with the diuretic hydrochlorothiazide (**61**; R = Cl) may be linked to photoactivation of the chloro group ⟨87MI 614-02⟩. Irradiation

of the thiadiazine in methanol produces a mixture of the substitution (**61**; R = OMe) and hydrolysis (**61**; R = OH) products together with the hydro-dechlorinated product (**61**; R = H). The latter is thought to proceed via a radical anion, whereas the former are radical cation processes ⟨83JPS180, 89MI 614-03⟩. In contrast, chlorothiazide (**62**) under similar photolytic conditions suffers loss of the sulfonamide group via a singlet, rather than a triplet, excited state ⟨89MI 614-03⟩.

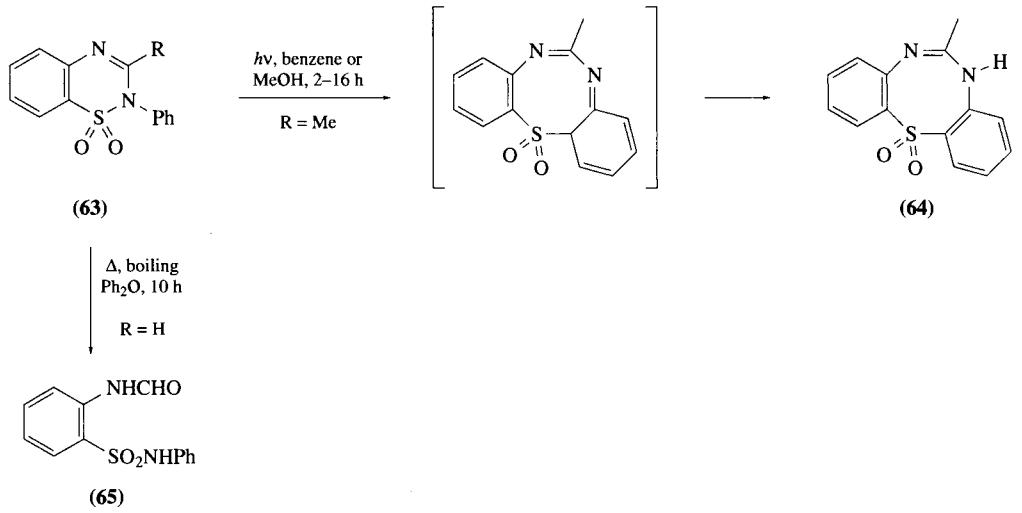


(**61**)



(**62**)

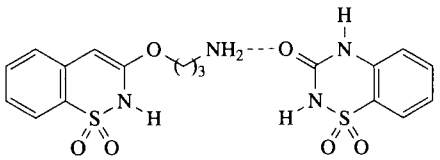
Under steady state or laser flash photolysis conditions, 3-substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**63**) undergo ring expansion to 5*H*-dibenzo[*b*,*g*][1,4,6]-thiadiazocine 12,12-dioxides (**64**) via a concerted or stepwise diradical pathway. Yields are variable (14–70%) ⟨86JOC1967⟩. In contrast, the 3-substituted benzothiadiazine 1,1-dioxides (**63**) are recovered unchanged after prolonged (9 h) heating at 255 °C, whereas, in the absence of the 3-substituent (**63**; R = H), an 87% yield of the sulfonamide (**65**) is obtained (Scheme 4).



(**63**) (**64**) (**65**)

Scheme 4

Attempts to crystallize the amine hydrochloride of 3-(3-aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide in hot ethanol leads to the formation of a 1 : 1 complex, the x-ray structure of which reveals it to be the product (**66**) consisting of the benzothiadiazine and the deaminoalkylated 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one held together by intermolecular hydrogen bonds ⟨90JHC1909⟩.

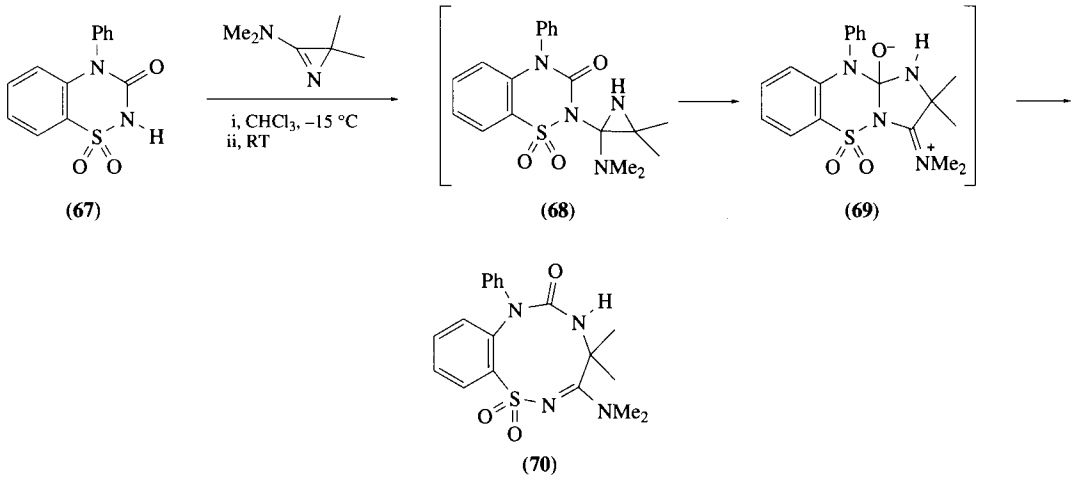


(**66**)

6.14.6.2.2 Electrophilic attack at nitrogen

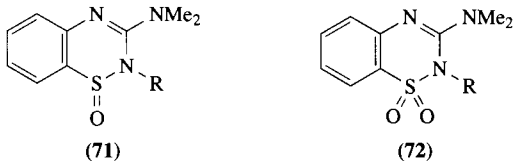
An intriguing ring expansion results on treating 4-phenyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one (**67**) with 2,2-dimethyl-3-dimethylamino-2*H*-azirine (Scheme 5) ⟨84H(22)1667⟩. Addition of the benzo-

thiadiazine to the reactive imine bond of the azirine is followed, successively, by ring opening of the aziridine (**68**) so formed, then ring closure at the carbonyl carbon center, and ring expansion of the resulting tricycle (**69**) to yield, ultimately, 4,5,6,7-tetrahydro-1,2,5,7-benzothiatriazonin-6-one 1,1-dioxide (**70**), the structure of which has been confirmed by x-ray analysis.



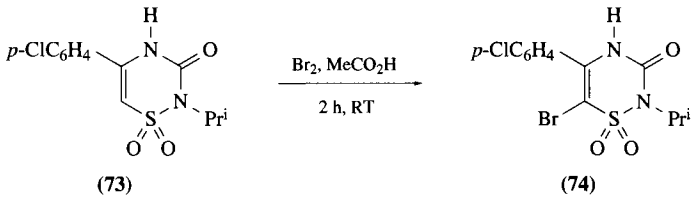
Scheme 5

1,2,4-Benzothiadiazine 1,1-dioxides (e.g., (**72**)) are generally prepared directly from 2-substituted benzenesulfonamides, or related derivatives (see Section 6.14.9.2.3(ii)), and only rarely by peroxide oxidation of 1,2,4-benzothiadiazine 1-oxides (e.g., (**71**) ⟨87PS(29)41⟩. The 1,2,4-benzothiadiazine 1-oxides (**71**) form salts with the Lewis acids $SbCl_5$, $AlCl_3$, and $SnCl_4$ ⟨87PS(29)41⟩.



6.14.6.2.3 Electrophilic attack at carbon

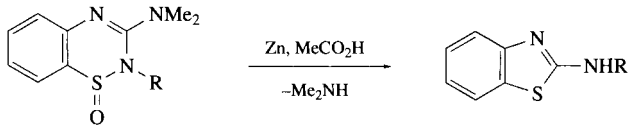
A rare example of the substitution of a thiadiazine ring is noted with 5-(4-chlorophenyl)-2-isopropyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide (**73**), which with bromine in acetic acid at room temperature undergoes rapid bromination to the 6-bromo-derivative (**74**) in high yield (83%), presumably by an addition–dehydrobromination process (Equation (5)) ⟨88S733⟩.



(5)

6.14.6.2.4 Reduction

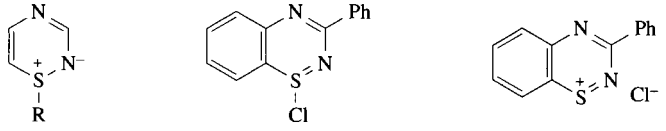
Remarkably, reduction of 3-dimethylamino-2*H*-1,2,4-benzothiadiazine 1-oxides (**75**) with zinc and acetic acid is accompanied by loss of dimethylamine and ring contraction to the benzothiazoles (**76**) in 75–95% yield (Equation (6)) ⟨87PS(29)41⟩.



(75) (76) (6)

6.14.6.3 $1\lambda^4$,2,4-Thiadiazines and $1\lambda^4$,2,4-Benzothiadiazines

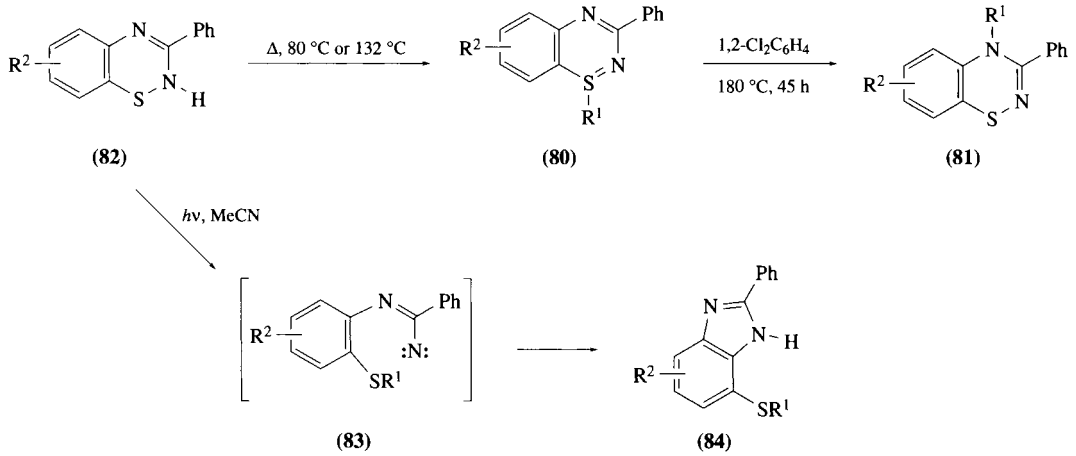
As mentioned in Section 6.14.4.5 these systems are formally fully conjugated but in practice behave as cyclic dipolar species, for example, (**77**). The suggestion ⟨81JOU2338⟩ that the *S*-chloro derivative (**78**) is in equilibrium with the ionic form (**79**) has been withdrawn since x-ray data on the 1,5,6,7,8-pentachloro derivative (**95**) (see Section 6.14.7.1) reveal an almost planar structure with an elongated (2.178 Å) but unionized S—Cl bond ⟨89JOU550⟩.



(77) (78) (79)

6.14.6.3.1 Thermal and photochemical unimolecular reactions

1-Aryl-3-phenyl-$1\lambda^4$,2,4-benzothiadiazines (**80**; R^1 = Ph or 4-MeC_6H_4) when heated at 180°C rearrange to the 4-aryl-3-phenyl-4*H*-1,2,4-thiadiazines (**81**) via a [1,4]-sigmatropic shift ⟨83JCS(P1)55⟩. In contrast, at lower temperature (80°C) the 1-methyl-derivative (**80**; R^1 = Me, R^2 = H) suffers loss of the methyl group to form 3-phenyl-2*H*-1,2,4-benzothiadiazine (**82**; R^2 = H; 52%). At intermediate temperatures (132°C), the 1-morpholino derivatives (**80**; R^1 = morpholino) lose morpholine to give 2*H*-1,2,4-benzothiadiazines (**82**) as the major products (42–76%) accompanied by minor amounts (4–20%) of benzothiazoles (Scheme 6). These latter products appear to be artefacts from the 2*H*-1,2,4-thiadiazines rather than from the unsaturated systems (**80**). Loss of the 1-substituent may involve a *β*-elimination (when such a path is possible) or a free radical process. In contrast, the 1-alkyl- and 1-aryl-$1\lambda^4$,2,4-benzothiadiazines (**80**), on photolysis, behave in a like manner to acyclic sulfimides and undergo cleavage of the S—N bond to yield imidoyl nitrenes (**83**) which, in the absence of a 5-substituent, cyclize to the 7-alkylthio- or 7-arylthio-benzimidazoles (**84**), the former in inferior yields ⟨83JCS(P1)55⟩. In the presence of a 5-substituent the imidoyl nitrene is again formed, and can be trapped intermolecularly as the sulfoximide with dimethyl sulfoxide. However, in the absence of an external trap the nitrene is promptly recaptured by the adjacent sulfur centre to reform the benzothiadiazine.

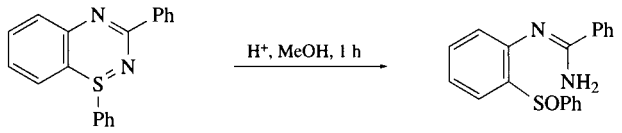


(82) (80) (81) (83) (84)

Scheme 6

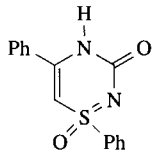
6.14.6.3.2 Electrophilic attack at a ring heteroatom

The dipolar character of $1\lambda^4$,2,4-benzothiadiazines is demonstrated in the ease of hydrolysis of the 1,3-diphenyl derivative (**85**) in methanolic sulfuric acid to the amidine sulfoxide (**86**; 78%) (Equation (7)) ⟨83JCS(P1)49⟩.



(85) (86) (7)

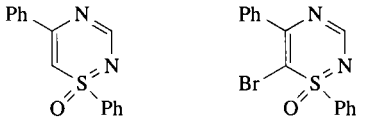
The *O*- vs. *N*-alkylation of 1,5-diphenyl-$1\lambda^4$,2,4-thiadiazin-3(4*H*)-one 1-oxide (**87**) appears to be dependent on the steric requirement of the alkylating agent ⟨90JCS(P1)447⟩ (see Section 6.14.7.5).



(87)

6.14.6.3.3 Electrophilic attack at carbon

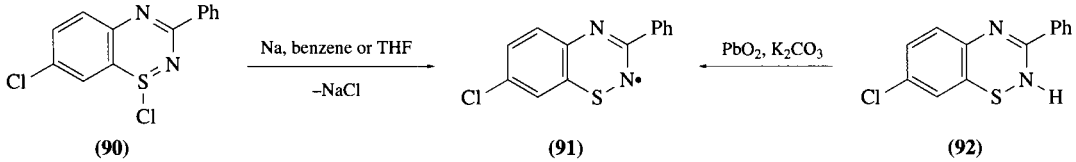
As expected from its ^{13}C NMR spectrum (see Section 6.14.3.1.2), which is indicative of a high electron density at C-6, bromination of 1,5-diphenyl-$1\lambda^4$,2,4-thiadiazine 1-oxide (**88**) in chloroform solution furnishes the 6-bromo-derivative (**89**) in good yield (60%) ⟨90JCS(P1)447⟩. The 1,5-diphenyl-$1\lambda^4$,2,4-thiadiazin-3(4*H*)-one (**87**) behaves in a similar manner. In contrast, the $1\lambda^4$,2,4-thiadiazine (**88**) is inert towards acetyl nitrate, whereas nitration with mixed acids effects nitration at the 3-position of the 5-phenyl group in 70% yield. It is likely that, under the strong acid conditions, the protonated thiadiazine ring is behaving as a *meta*-directing substituent towards the phenyl nucleus.



(88) (89)

6.14.6.3.4 Other reactions

It has been shown that 1,7-dichloro-3-phenyl-$1\lambda^4$,2,4-benzothiadiazine (**90**) (see Section 6.14.9.1.2) on oxidation with powdered sodium in benzene or in THF, yields the 1,2,4-benzothiadiazinyl (**91**) a new type of relatively stable (24 h in solution) free radical ⟨81JOU2338⟩. The same radical is also generated by oxidizing 7-chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine (**92**) with lead dioxide (Scheme 7).



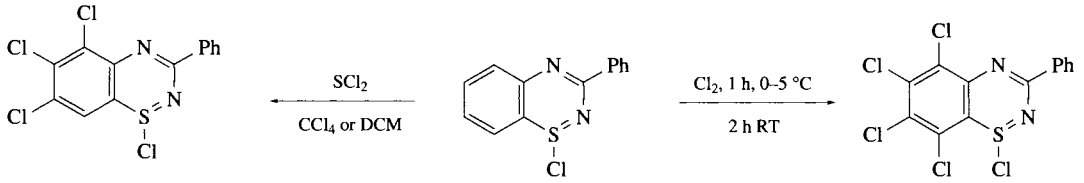
(90) (91) (92)

Scheme 7

6.14.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON CENTRES

6.14.7.1 Unsubstituted Benzenoid Rings

The ease of polychlorination of 1-chloro-3-phenyl-1λ^4,2,4-benzothiadiazine (**93**)→(**94**) at the carbocyclic ring rather than at the 3-phenyl substituent is indicative of the activating effect of a fused 1λ^4,2,4-thiadiazine ring on the benzene nucleus ⟨89JOU550⟩, a result in direct contrast to the electrophilic substitution of 1λ^4,2,4-thiadiazine 1-oxides under strong acid conditions (see Section 6.14.6.3.3). With sulfur dichloride at 80 °C, the 1-chloro derivative (**93**) undergoes trichlorination at the carbocyclic ring to give what, on the basis of PMR spectroscopic evidence, is thought to be the 1,5,6,7-tetrachloro derivative (**95**) (70%) (Scheme 8) ⟨84JOU176⟩.

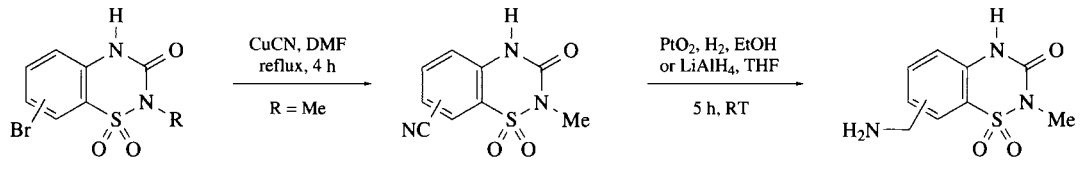


(**95**) (**93**) (**94**)

Scheme 8

6.14.7.2 Substituted Benzenoid Rings

Whereas attempts to replace bromine from 6- or 8-bromo-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one (**96**; R = H) with cuprous cyanide in DMF have failed, the reaction is successful with the 2-methyl derivative (**96**; R = Me), and with 6- and 8-bromo 3-methyl-4*H*-1,2,4-benzothiadiazines ⟨82JMC113, 90FES631⟩. Reduction of the resulting nitriles (**97**) with hydrogen and a platinum oxide catalyst ⟨82JMC113⟩, or with lithium aluminum hydride in THF ⟨90FES631⟩, yields the aminomethyl derivatives (**98**) without deoxygenation at sulfur or disruption of the thiadiazine ring (Scheme 9).

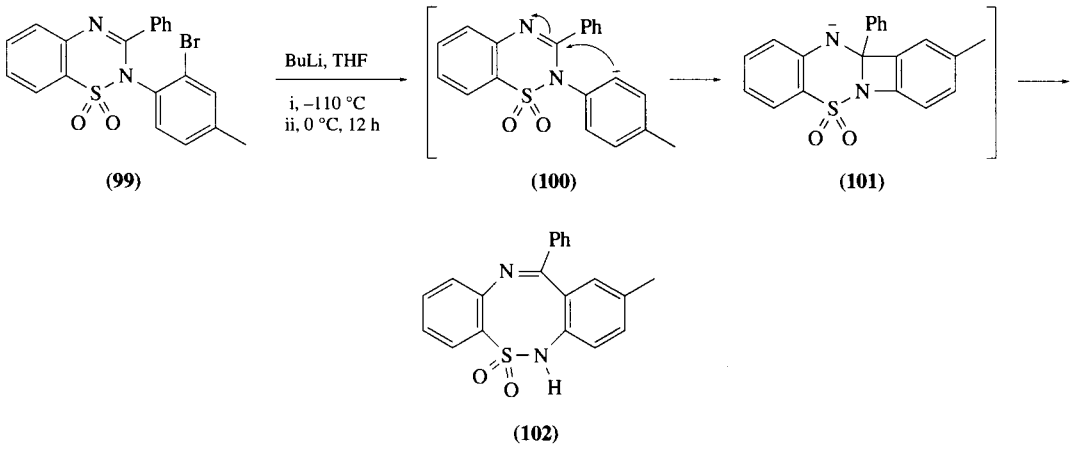


(**96**) (**97**) (**98**)

Scheme 9

6.14.7.3 Aryl Groups

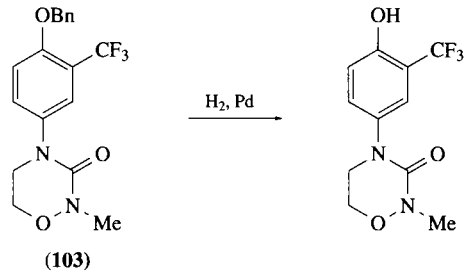
Metal–halogen exchange of 2-(2-bromo-4-methylphenyl)-3-phenyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**99**) results in an unusual ring expansion via the carbanion (**100**) and the tetracyclic intermediate (**101**) to the 5*H*-dibenzo[*c*,*g*][1,2,6]thiadiazocine 6,6-dioxide (**102**) in 85% yield (Scheme 10) ⟨83T2073⟩.



(99) (100) (101) (102)

Scheme 10

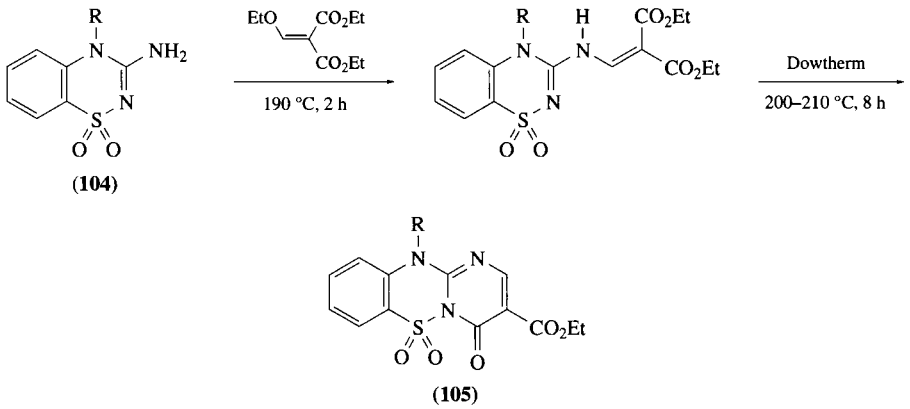
Benzyl ethers (e.g., (**103**)) can be debenzylated under standard conditions with hydrogen and palladium without cleavage of the oxadiazinone ring (Equation (8)) ⟨91FRP2660307⟩.



(103) (8)

6.14.7.4 Amino and Other Nitrogen Groups

Condensation of 3-amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**104**) with diethyl ethoxymethylenemalonate, followed by heating in "Dowtherm" at 200°C, brings about cyclization to the pyrimido[1,2-*b*][1,2,4]benzothiadiazine dioxides (**105**) in good yields (70–75%) (Scheme 11) ⟨89JHC473⟩.

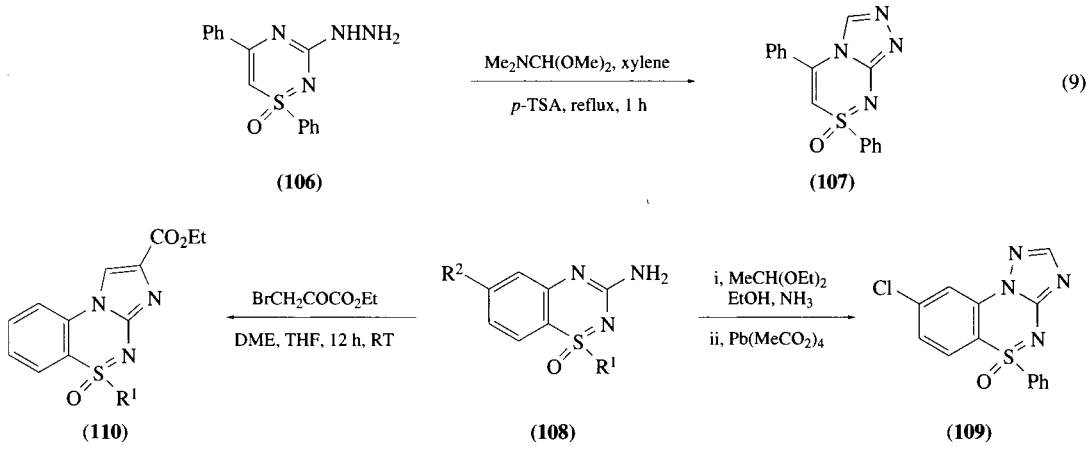


(104) (105)

Scheme 11

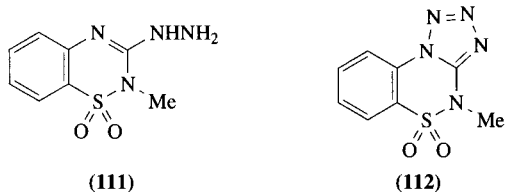
The hydrazino derivative (**106**), obtained from the chloro-compound (**123**) (see Section 6.14.7.5) by reaction with ethanolic hydrazine hydrate, reacts with DMF-dimethyl acetal in hot xylene to give 5,7-diphenyl-7λ^4-[1,2,4]triazolo[3,4-*c*][1,2,4]thiadiazine 7-oxide (**107**; 72%) (Equation (9))

⟨90JCS(P1)447⟩. Related reactions are the oxidative cyclization of 3-amino-6-chloro-1-phenyl-1λ^4,2,4-benzothiadiazine 1-oxide (**108**; R^1 = Ph, R^2 = Cl) to the 5λ^4-1,2,4-triazolo[5,1-*c*][1,2,4]-benzothiadiazine 5-oxide (**109**) with triethyl orthoacetate in the presence of alcoholic ammonia and lead tetraacetate ⟨86GEP3433307⟩, and the ring closures of the amines (**108**; R^1 = Me, Ph; R^2 = H) to 5λ^4-imidazo[1,2-*c*][1,2,4]benzothiadiazine *S*-oxides (**110**; R^1 = Me, Ph) with ethyl bromopyruvate (Scheme 12) ⟨88JMC1098⟩.



Scheme 12

Diazotization of 2-methyl-3-hydrazino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**111**) produces the tetrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide (**112**), an agricultural bactericide ⟨85JAP(K)6078990⟩.

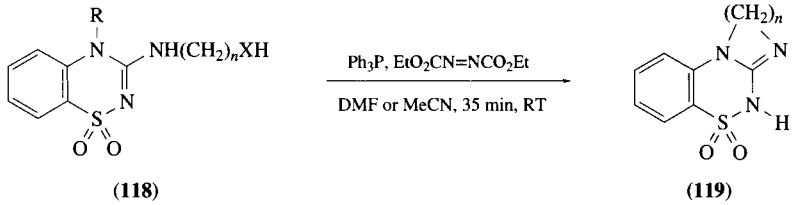


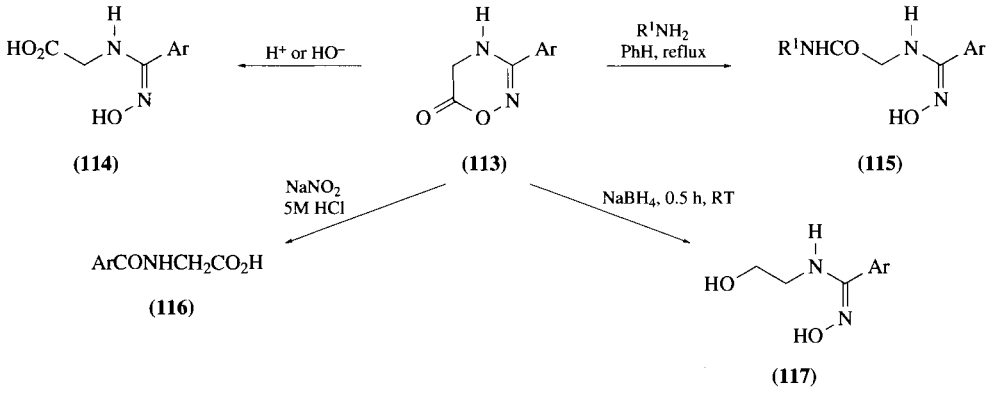
6.14.7.5 Hydroxy and Oxo Groups

6*H*-1,2,4-oxadiazin-5(4*H*)-ones are converted into the corresponding 5(4*H*)-thiones in moderate yields (43–62%) by phosphorus pentasulfide in boiling xylene ⟨86EUP178176, 92SC209⟩.

The lactone character of 4*H*-1,2,4-oxadiazin-6(5*H*)-ones (**113**) is revealed in the ease with which they undergo hydrolysis to amidoximes (**114**) with aqueous alkali or acid, and ring opening to amides (**115**) with amines ⟨84CB2999, 84JHC455⟩; with aqueous nitrous acid *N*-acylglycines (**116**) are produced ⟨84CB2999⟩. Reductive cleavage of the oxadiazin-6-ones with sodium borohydride yields the alcohols (**117**) (Scheme 13) ⟨84JHC455⟩.

Under Mitsunobo conditions, 3-(ω-hydroxyalkylamino)-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**118**; X = O, n = 2 or 3) undergo cyclodehydration at N-4, rather than at N-2, to produce the angular tricyclic benzothiadiazines (**119**) (Equation (10)) ⟨91PS(59)529, 91S159⟩. In contrast, the thio-analogues (**118**; X = S), under the same conditions, yield only bis[(4*H*-1,2,4-benzothiadiazin-3-ylamino)alkyl] disulfides.

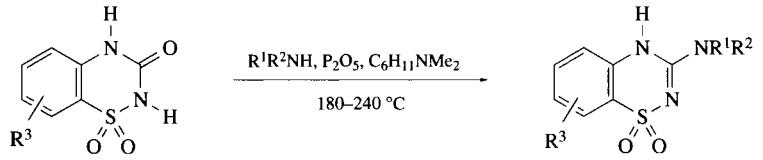




(114) (113) (115) (116) (117)

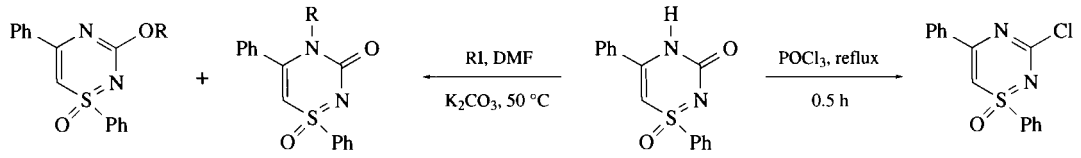
Scheme 13

Amino-dehydroxylation of 4*H*-1,2,4-benzothiadiazin-3(2*H*)-one 1,1-dioxides (**120**) → (**121**) can be achieved in variable yields (37–80%) with phosphorus pentoxide and a secondary aliphatic, or alicyclic amine (Equation (11)) ⟨82CS248⟩.



(120) (121) (11)

As expected, treatment of 1,5-diphenyl-1λ^4,2,4-thiadiazin-3(4*H*)-one 1-oxide (**122**) with phosphorus oxychloride yields the 3-chloro derivative (**123**) (Scheme 14) which under aqueous alkaline conditions reverts to the 3(4*H*)-one ⟨90JCS(P1)447⟩.



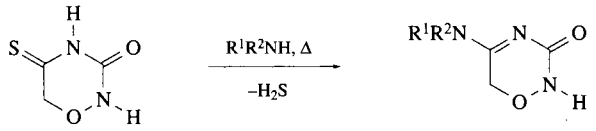
(125) (124) (122) (123)

Scheme 14

The *O*- vs. *N*-alkylation of the 1-oxide (**122**) appears to be dependent on the steric requirement of the alkylating agent. For example, with iodomethane and potassium carbonate in dimethylformamide the *N*-methyl derivative (**124**; R = Me) dominates (96 : 4) (Scheme 14), whereas with 2-iodoethane the *N* : *O* alkylation ratio is 2 : 3, and with 2-iodopropane only the *O*-alkylated product (**125**; R = $CH(Me)_2$) is obtained. The *O*-alkylation appears to be the kinetically controlled product since the *O*-allyl derivative (**125**; R = $CH_2CH{=}CH_2$), on heating at 200 °C in the presence of palladium acetylacetonate, rearranges quantitatively to the *N*-allyl isomer (**124**; R = $CH_2CH{=}CH_2$) ⟨90JCS(P1)447⟩.

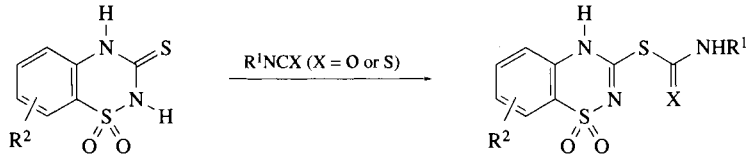
6.14.7.6 Sulfur Linked Groups

5-Amino-6*H*-1,2,4-oxadiazin-3(2*H*)-ones (**127**) are accessible by regioselective amine attack at the thione carbon center of 5,6-dihydro-5-thioxo-2*H*-1,2,4-oxadiazin-3(4*H*)-ones (**126**) (Equation (12)) ⟨84USP4459403⟩.



(126) (127) (12)

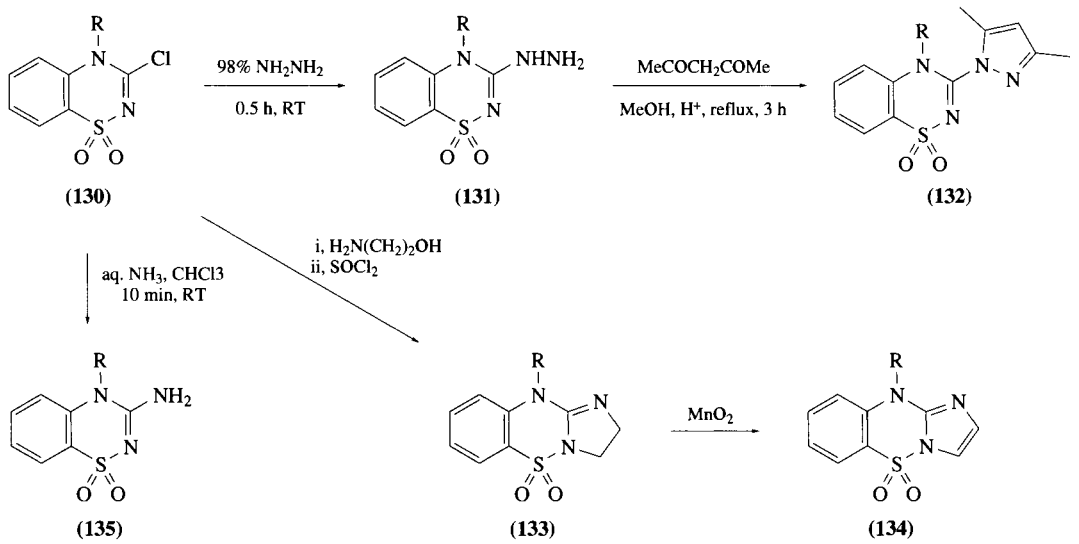
It has been shown that 2*H*-1,2,4-benzothiadiazin-3(4*H*)-thiones (**128**) add to isocyanates and isothiocyanates at sulfur rather than the ring NH, to give thio- and dithiocarbamates (**129**) (Equation (13)) ⟨83FES466⟩.



(128) (129) (13)

6.14.7.7 Halogen Atoms

3-Chloro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**130**), formed by the action of phosphorus pentachloride on the corresponding benzothiadiazin-3(2*H*)-ones, are versatile precursors for the production of other 3-substituted 1,2,4-benzothiadiazines and for fused ring systems. Halogen displacement with hydrazine gives the 3-hydrazino derivatives (**131**) which, on treatment with a variety of 1,3-dicarbonyl compounds, yield pyrazole derivatives (e.g., (**132**)) ⟨85IJC(B)1295⟩. Condensation of the 4-substituted chloro compounds (**130**; R = Me or Et) with ethanolamine, followed by ring closure of the 3-(hydroxyethylamino) derivative so formed with thionyl chloride, produces the dihydroimidazobenzothiadiazine *S*,*S*-dioxides (**133**), oxidation of which yields the anti-inflammatory imidazo[1,2-*b*][1,2,4]benzothiadiazine *S*,*S*-dioxides (**134**) (Scheme 15) ⟨87EJM157⟩.

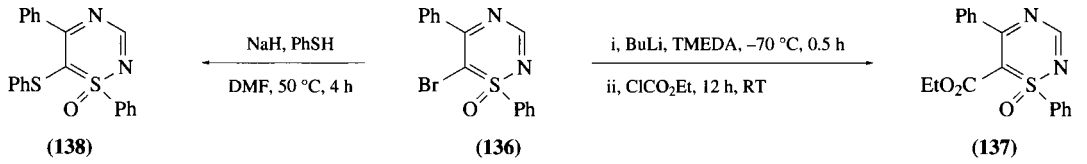


(130) (131) (132) (135) (133) (134)

Scheme 15

A superior synthesis of 3-amino-4-alkyl- and 3-amino-4-aryl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**135**), involving the amino-dechlorination of chloro compounds (**130**; R = alkyl or aryl) with aqueous ammonia in chloroform has been reported ⟨86S864⟩; yields are excellent (86–94%). It has been shown that 1,5-diphenyl-6-bromo-1λ^4,2,4-thiadiazine 1-oxide (**136**) (see Section 6.14.6.3.3) undergoes metal exchange with butyllithium and, on quenching the mixture with ethyl chloroformate, the 6-ethoxycarbonyl derivative (**137**) is obtained in moderate yield (31%). Displacement

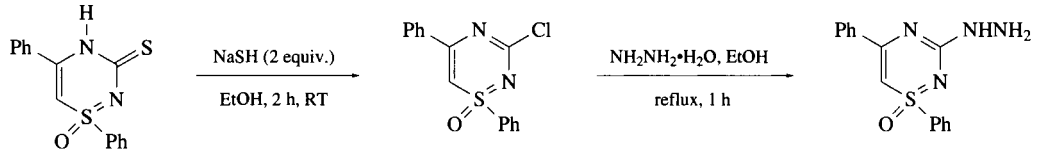
of the bromo substituent with sodium thiophenoxide in DMF produces the 6-phenylthio derivative (**138**; 71%) (Scheme 16) ⟨90JCS(P1)447⟩.



(138) (136) (137)

Scheme 16

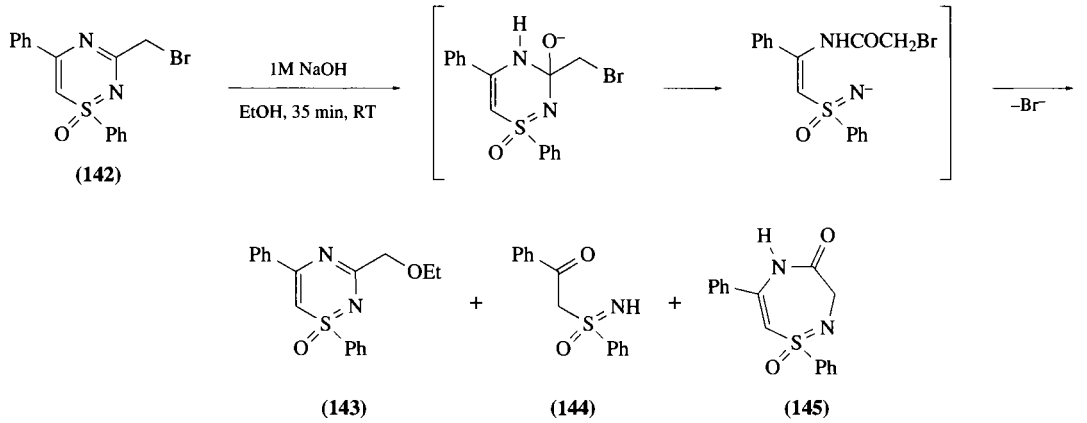
The imino-chloride character of 3-chloro-1,5-diphenyl-1λ^4,2,4-thiadiazine 1-oxide (**139**) has been exploited and displacements of the halogen by oxygen and sulfur nucleophiles, and by hydrazine, to give 3-alkoxy-, 3-alkylthio-, and 3-hydrazino- (**140**) 1λ^4,2,4-thiadiazine 1-oxides have been carried out. On the basis of PMR spectroscopic evidence the product from the reaction with sodium hydrogen sulfide appears to be the 3(4*H*)-thione (**141**) rather than the tautomeric 3-thiol (Scheme 17) ⟨90JCS(P1)447⟩.



(141) (139) (140)

Scheme 17

The benzylic nature of the 3-bromomethyl substituent of the 1λ^4,2,4-thiadiazine (**142**) is reflected in the ease with which it undergoes bromine displacement with a range of nitrogen and sulfur nucleophiles ⟨90JCS(P1)447⟩. However, with sodium hydroxide in aqueous ethanol, in addition to the substitution and ring cleavage products (**143**) and (**144**), ring-expansion to the 3*H*-1λ^4,2,5-thiadiazepin-4(5*H*)-one 1-oxide (**145**) (Scheme 18) is noted, albeit in low yield (24%). Under the same conditions the 3-chloromethyl-derivative yields only the keto sulfoximide (**144**) ⟨90JCS(P1)447⟩.



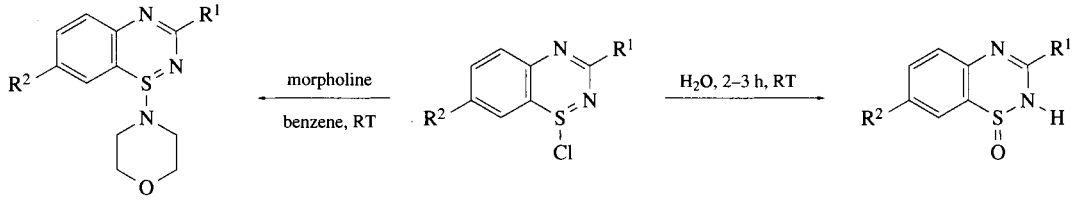
(142) (143) (144) (145)

Scheme 18

6.14.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The chlorine atom of 1-chloro-1λ^4,2,4-benzothiadiazines (**146**) is labile towards nucleophiles. For example, rapid hydrolysis to the 1-oxide (**147**) occurs in water at room temperature, and displacement

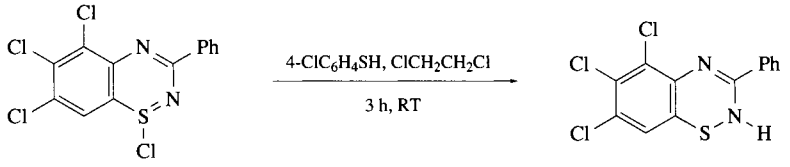
with morpholine under mild conditions yields the 1-morpholino derivative (**148**) (Scheme 19) ⟨84JOU176⟩.



(148) (146) (147)

Scheme 19

Reductive *S*-dechlorination of 3-phenyl-1,5,6,7-tetrachloro-1λ^4,2,4-benzothiadiazine (**149**) to the trichloro-2*H*-1,2,4-benzothiadiazine (**150**) is achieved with *p*-chlorothiophenol in dichloroethane (Equation (14)) ⟨84JOU176⟩.



(149) (150) (14)

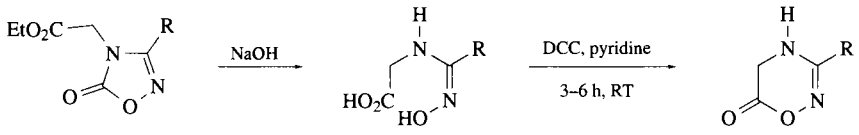
4-Hydroxy-2,3-dihydro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (see Section 6.14.9.1.3) undergo quantitative dehydroxylation with triphenylphosphine ⟨93H(36)1091⟩.

6.14.9 RING SYNTHESIS

6.14.9.1 By Formation of One Bond

6.14.9.1.1 Between carbon and oxygen

Two routes to the previously unknown 1,2,4-oxadiazin-6(5*H*)-ones have been described. The first involves hydrolytic ring opening of 4-ethoxycarbonylmethyl-1,2,4-oxadiazol-5(4*H*)-ones (**151**; R = Ph, $PhCH_2$, $Ph(CH_2)_2$) to the amidoxime derivatives (**152**), which on treatment with dicyclohexylcarbodiimide undergo cyclodehydration to the 4*H*-1,2,4-oxadiazin-6(5*H*)-ones (**153**) in moderate yields (50–71%) (Scheme 20) ⟨84CB2999⟩.

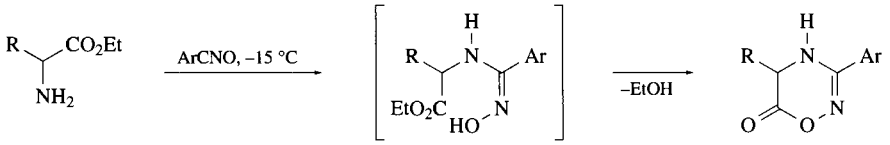


(151) (152) (153)

Scheme 20

In the second route, the amidoxime esters (**154**), formed *in situ* by addition of α-substituted ethyl glycinates to arylcarbonitrile oxides, are reported to cyclize spontaneously to the 3-aryl-4*H*-1,2,4-oxadiazin-6(5*H*)-ones (**155**) (Scheme 21). Yields range from 12–73% ⟨84JHC455⟩.

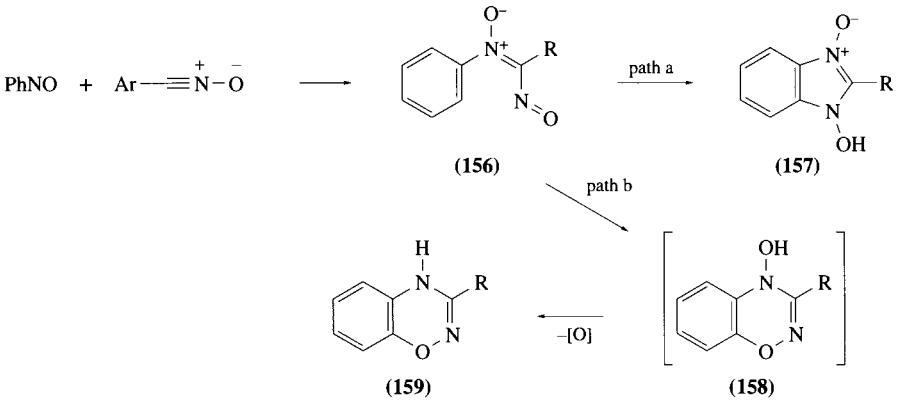
N-aryl-*C*-nitrosoimines are known to undergo cyclization to 1,2,4-benzoxadiazines ⟨76JCS(P1)2161⟩, whereas the isolable α-nitroso nitrone (**156**; R = Ph) is reported to give 1-hydroxy-2-phenylbenzimidazole 3-oxide (**157**; R = Ph) ⟨63TL785⟩. A reinvestigation of this latter reaction confirms that, in dichloromethane at room temperature, the unstable, but isolable, α-nitroso nitrones (**156**; R = Ph and 4-MeC_6H_4), formed by the reaction of the corresponding arylcarbonitrile oxides with nitrosobenzene (Scheme 22), undergo rapid rearrangement (path a) to the 1-hydroxy-2-arylbenzimidazole *N*-oxides (**157**) ⟨88JCR(S)148⟩. However, in a mixture of nitromethane and diethyl



(154) (155)

Scheme 21

ether at −20 °C, 3-aryl-4*H*-1,2,4-benzoxadiazines (**159**; R = Ph and 4-MeC_6H_4) are also formed in 12–23% yield by a competing electrocyclic reaction (path b). Interestingly, the 4-hydroxy-4*H*-1,2,4-benzoxadiazines (**158**), the initial products expected from an electrocyclic ring closure of the nitroso nitrone, are not detected. The ethoxycarbonyl nitroso nitrone (**156**; R = CO_2Et), which is not isolable, furnishes the 3-ethoxycarbonyl-4*H*-1,2,4-benzoxadiazine (**157**; R = CO_2Et) directly in 35% yield. In contrast, all attempts to effect cyclization of the crystalline nitroso nitrones derived from 2,4,6-trimethylnitrosobenzene and arylcarbonitrile oxides have failed.

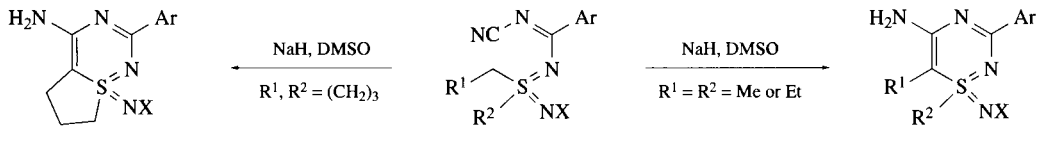


(156) (157) (159) (158)

Scheme 22

6.14.9.1.2 *Between carbon and sulfur*

It has been shown that *N*-acyl- and *N*-sulfonyl-*N'*-cyanoimidoyl *S,S*-dialkylsulfur diimides (**160**; X = COR, or SO_2R; $R^1 = R^2$ = Me, and R^1 = Me, R^2 = Et), formed by the condensation of *S,S*-dialkylsulfur diimides with *N*-cyanoimidates followed by *N*-acylation or *N*-sulfonylation at the free sulfimide group, under strong basic conditions, cyclize to 1λ^4,2,4-thiadiazines (**161**; R^1 = Me or Et) albeit in poor yields (Scheme 23) ⟨88CB1689⟩. However, when $R^1 = R^2$ = trimethylene, the corresponding tetrahydrothieno[2,1-*f*][1λ^4,2,4]thiadiazines (**162**) are formed in improved yields (20–55%).

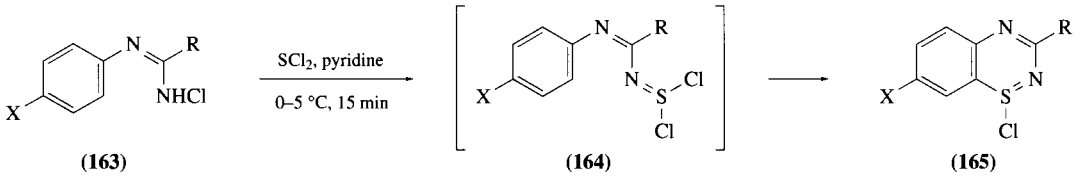


(162) (160) (161)

Scheme 23

With sulfur dichloride in the presence of pyridine, *N*-chloro-*N'*-arylbenzamidines (**163**) yield the thermally unstable, orange–red crystalline 1-chloro-1λ^4,2,4-benzothiadiazines (**165**); 74–90%), most probably via cyclization of the nonisolable dichlorosulfimides (**164**) (Scheme 24) ⟨84JOU176⟩. In

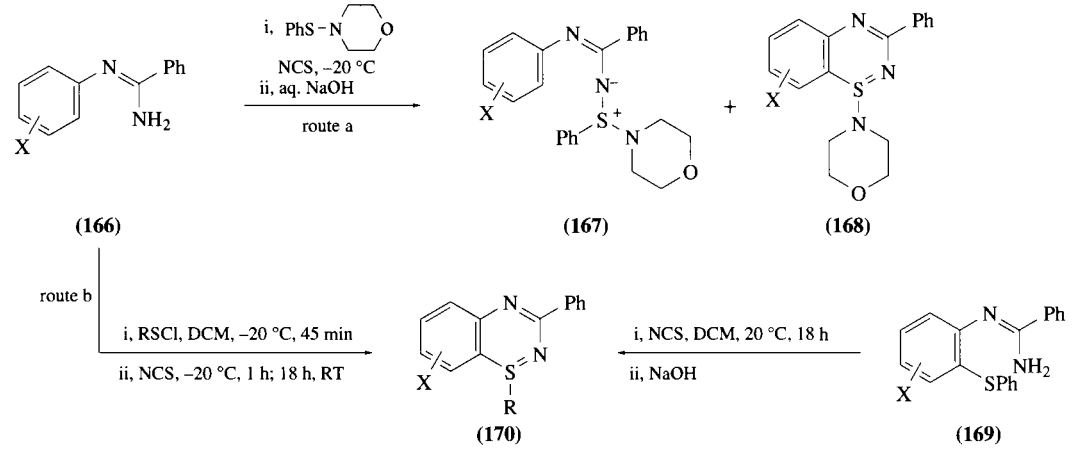
the absence of pyridine the reaction is incomplete and benzothiadiazines contaminated by the corresponding benzamidine hydrochlorides result.



(163) (164) (165)

Scheme 24

1λ^4,2,4-Benzothiadiazines (**168**) are obtained as minor products, along with open-chain sulfimides (**167**), by treating *N*-arylbenzamidines (**166**) with *N*-phenylthiomorpholine (Scheme 25; route a). The yields of benzothiadiazine are improved (43–60%) with 4,4′-thiobismorpholine as the sulfur carrier, and are optimized (30–86%) by using sulfenyl chlorides (Scheme 25; route b) in place of the sulfenamides. Corroborative evidence for the structure of 1,3-diphenyl-1λ^4,2,4-benzothiadiazine (**170**; R = Ph, X = H) was obtained by an alternative synthesis (in 98% yield) involving successive treatment of the amidine (**169**) with *N*-chlorosuccinimide and sodium hydroxide ⟨83JCS(P1)49⟩.



(166) (167) (168) (170) (169)

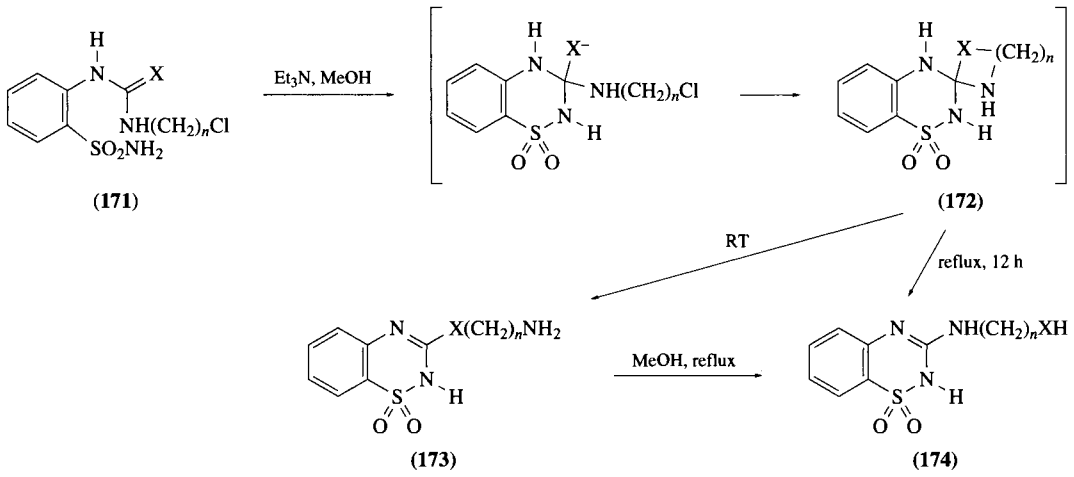
Scheme 25

6.14.9.1.3 Between carbon and nitrogen

N-(ω-haloalkyl)-*N*′-2-sulfamoylphenylthioureas (**171**), formed by condensation of ω-haloalkyl isothiocyanates with 2-aminobenzenesulfonamides in 2-propanol, can cyclize to two different products depending on the reaction conditions. Treatment with triethylamine in methanol at room temperature furnishes the γ-aminoalkylthio-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**173**; X = S; *n* = 2,3) in quantitative yields, whereas with triethylamine in hot methanol the isomeric 3-(γ-thiolalkylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**174**; X = S; *n* = 2,3) are obtained in 65 and 88% yield, respectively. In hot methanol the aminoalkylthio compounds (**173**) isomerize to the thiols (**174**) via, it is thought, a Smiles-type rearrangement of a spiro-intermediate (**172**) (Scheme 26) ⟨90JHC1485⟩. Similar reaction sequences are noted with ω-chloroalkyl isocyanates which in boiling propanol, or in boiling propanol in the presence of triethylamine, yield the corresponding 3-(γ-aminoalkoxy)- and 3-(γ-hydroxyalkylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**173**) and (**174**) (X = O; *n* = 2,3), respectively, in 79–87% yield ⟨90JHC1909⟩.

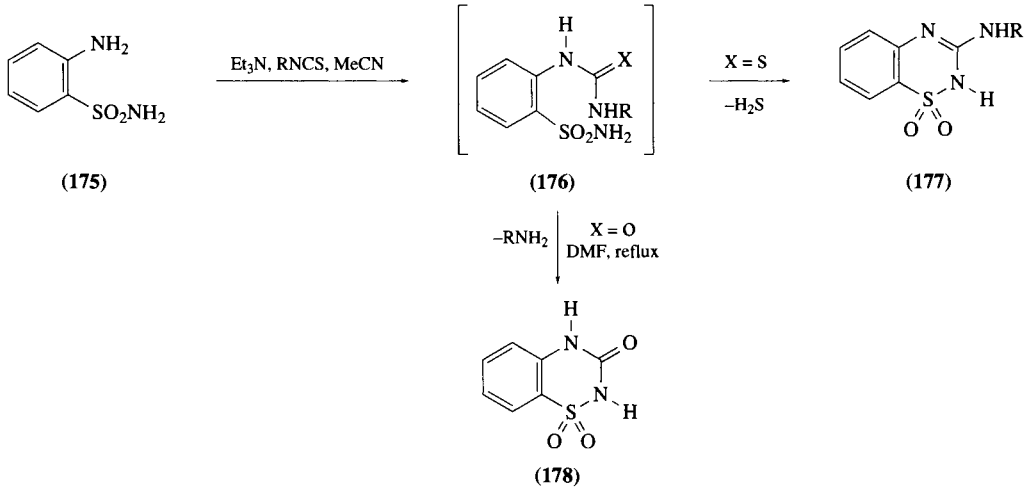
Condensation of 2-aminobenzenesulfonamide (**175**) with an alkyl or acyl isothiocyanate in the presence of triethylamine affords a 3-alkylamino- or 3-acylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**177**) via cyclization of a thiourea intermediate (**176**; X = S) (Scheme 27) ⟨90MI 614-04⟩. In contrast, the corresponding ureas (**176**; X = O) in hot DMF suffer elimination of the alkylamine residue to form 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one (**178**) in 90% yield ⟨90JHC1909⟩.

Treatment of 5-aminotetrazole with 2-nitrobenzenesulfonyl chloride (**179**) does not yield the



(171) (172) (173) (174)

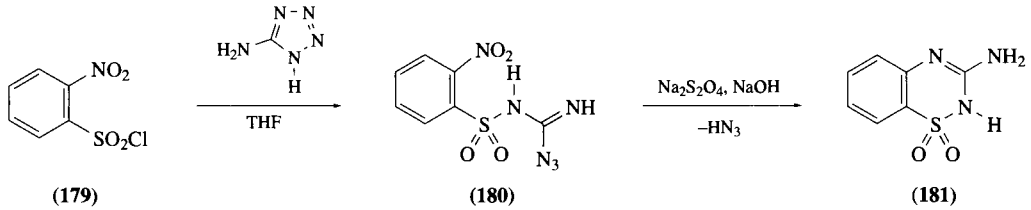
Scheme 26



(175) (176) (177) (178)

Scheme 27

expected *N*-sulfonylaminotetrazole, but gives the ring-chain tautomer, the imidoyl azide (**180**). Reduction of the nitro group of (**180**) with sodium dithionite results in ring-closure to 3-amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**181**) in quantitative yield (Scheme 28) ⟨87JHC1531⟩.

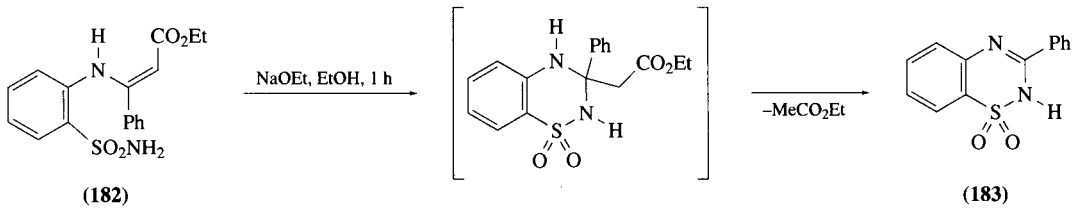


(179) (180) (181)

Scheme 28

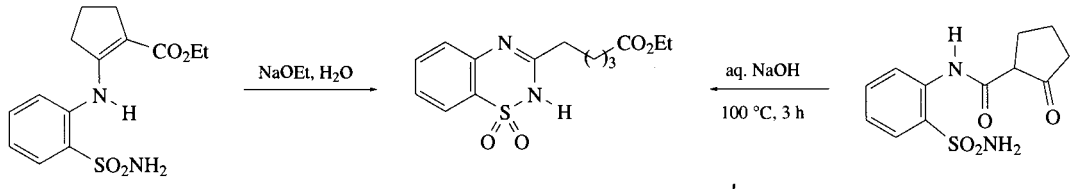
Acid-catalyzed condensation of ethyl benzoylacetate with 2-aminobenzenesulfonamide yields the enamine (**182**), which, under basic conditions, is cyclized to 3-phenyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**183**) in 65% yield (Scheme 29) ⟨84JOU534, 84URP1074873, 87EJM157⟩.

Cyclization of the related enamine (**184**) under similar conditions is accompanied by cleavage of the carbocyclic ring to form the carboxylic acid (**185**; 71%), which is also obtained, in 63% yield, by treating the keto-amide (**186**) with aqueous sodium hydroxide (Scheme 30) ⟨84JOU534⟩.



(182) (183)

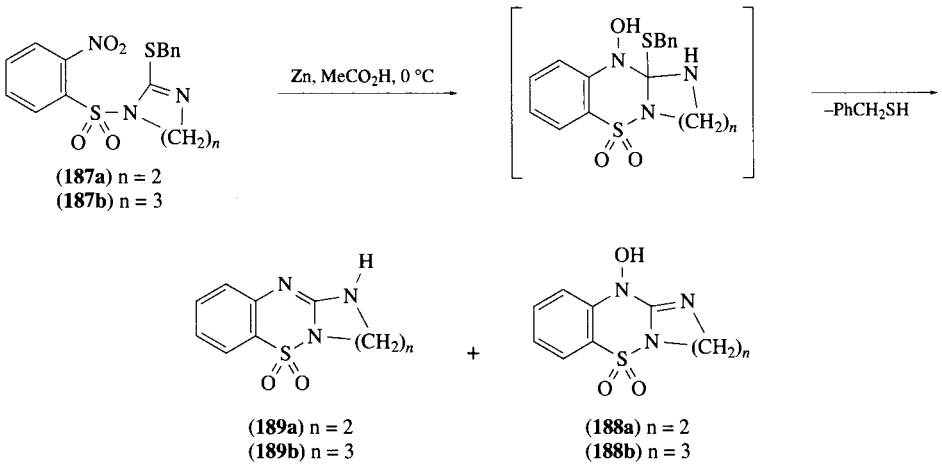
Scheme 29



(184) (185) (186)

Scheme 30

Intramolecular capture of the arylhydroxylamine intermediate formed during reduction of the 1-(2-nitrobenzenesulfonyl)imidazole (**187a**) with zinc and acetic acid at 0 °C leads to formation of the 4-hydroxyimidazo[1,2-*b*][1,2,4]benzothiadiazine *S*,*S*-dioxide (**188a**) in 79% yield, together with a small amount of the dehydroxylated derivative (**189a**) ⟨93H(36)1091⟩. The tetrahydropyrimidine derivative (**187b**) behaves similarly and yields the pyrimido[1,2-*b*][1,2,4]benzothiadiazine dioxides (**188b**) and (**189b**) in 30% and 10% yield, respectively. If the latter reduction is carried out at room temperature during 2 days then the dehydroxylated material (**189b**) is formed exclusively in 80% yield (Scheme 31).



(**187a**) n = 2
(**187b**) n = 3

(**189a**) n = 2
(**189b**) n = 3

(**188a**) n = 2
(**188b**) n = 3

Scheme 31

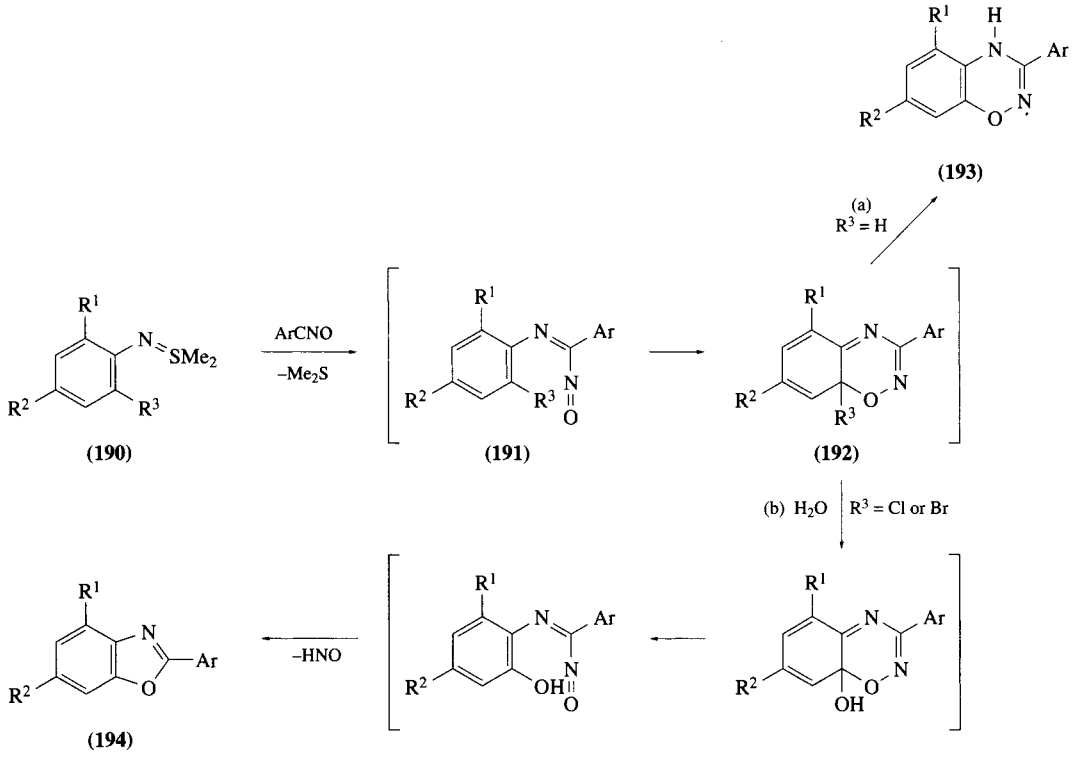
6.14.9.2 Formation of Two Bonds

6.14.9.2.1 [3 + 3] fragments

(i) From C-C-N and C-N-O fragments

The formation of 4*H*-1,2,4-benzoxadiazines by the action of nitrile oxides on *N*-aryl-*S*,*S*-dialkylsulfimides (**190**) is a well-established procedure ⟨76JCS(P1)2161, 78BCJ563⟩. Results in 1983, however, demonstrate that the reaction is sensitive to the nature of the substituents on the aryl ring of the sulfimide ⟨83BCJ1514⟩. Thus, whereas the reactions of *N*-(4-bromophenyl)-*S*,*S*-dimethylsulfimide

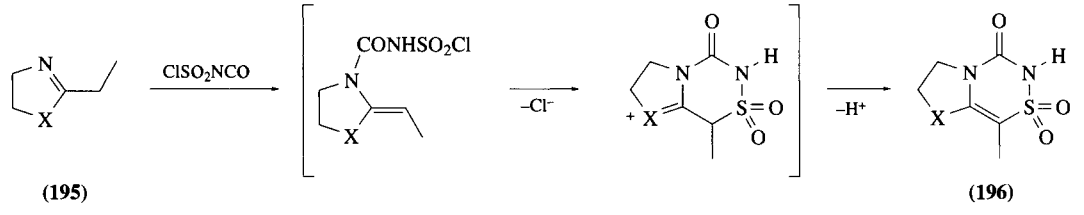
(**190**; $R^1 = R^3 = H$, $R^2 = Br$) and *N*-(2,4-dibromophenyl)-*S*,*S*-dimethylsulfimide (**190**; $R^1 = R^2 = Br$, $R^3 = H$) with arylcarbonitrile oxides ($ArC{\equiv}N^+{-}O^-$) furnish the expected 3-aryl-4*H*-1,2,4-benzoxadiazines (**193**; $R^1 = H$, $R^2 = Br$; and $R^1 = R^2 = Br$), respectively, in high yields (80–92%) (path a), the corresponding *N*-(2,4,6-tribromophenyl)- and *N*-(2,4,6-trichlorophenyl)sulfimides (**190**; $R^1 = R^2 = R^3 = Br$ or Cl) give only moderate amounts (37–57%) of 2-aryl-4,6-dihalogeno-1,3-benzoxazoles (**194**) $R^1 = R^2 = Br$ or Cl). A mechanistic rationale is offered involving cyclization of a nitrosoimine intermediate (**191**), the product (**192**) from which, in the case of the trihalogeno derivatives (path b), suffers nucleophilic displacement of the bridgehead halogen by extraneous water, followed by a ring-opening and ring-closure sequence to give ultimately the benzoxazole (**194**) (Scheme 32).



Scheme 32

(ii) From C-C-N and C-N-S fragments

4-Substituted 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxides are available by a one-pot intramolecular Friedel–Crafts reaction involving the action of chlorosulfonyl isocyanate on a secondary aromatic amine in the presence of aluminum chloride ⟨85IJC(B)1295⟩. Chlorosulfonyl isocyanate is also employed in the synthesis of oxazolo- and thiazolo[2,3-*d*][1,2,4]-thiadiazin-3(2*H*)-ones (**196**; X = O and S) from 2-ethyloxazolines (**195**; X = O) and 2-ethylthiazolines (**195**; X = S) respectively (Scheme 33) ⟨93SC121⟩.

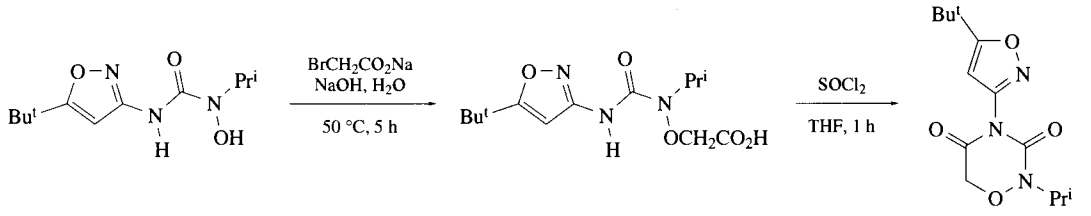


Scheme 33

6.14.9.2.2 [4 + 2] fragments

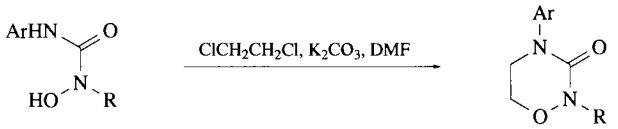
(i) From N-C-N-O and C-C fragments

N,N'-disubstituted 2*H*-1,2,4-oxadiazin-3,5(4*H*,6*H*)-diones (e.g. (**199**)) can be synthesized by condensing sodium bromoacetate with an *N*-hydroxyurea (e.g. (**197**)), followed by cyclization of the resulting oxyacetic acid (**198**) with thionyl chloride in THF (Scheme 34) ⟨89JAP(K)01186882⟩. Likewise, *N*-aryl-*N'*-alkyl-*N'*-hydroxyureas (**200**), prepared by the addition of an alkylhydroxylamine (RNHOH) to an aryl isocyanate (ArNCO), are precursors of 2-alkyl-4-aryl-5,6-dihydro-2*H*-1,2,4-oxadiazin-3(4*H*)-ones (**201**), the two carbon fragment in this instance being provided by 1,2-dichloroethane (Equation (15)) ⟨91FRP2660158⟩.



(**197**) (**198**) (**199**)

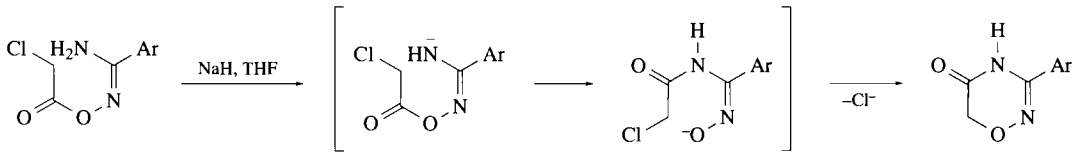
Scheme 34



(15)

(**200**) (**201**)

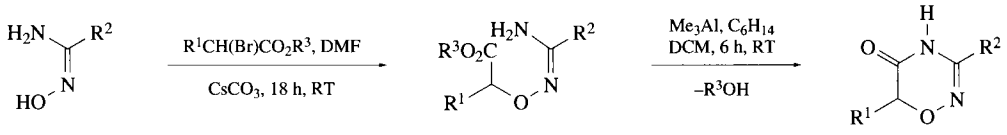
Attempts to prepare 4*H*-1,2,4-oxadiazin-6(5*H*)-ones by base (NaH in THF)-induced condensation of amidoximes with chloroethanoyl chlorides have failed; only the isomeric 5(6*H*)-ones (**205**) are obtained ⟨87H(26)163, 92SC209⟩. The reaction is of mechanistic interest in that the *O*-acylated oximes (**202**), the likely precursors of the 6(5*H*)-ones, can be isolated, but on treatment with sodium hydride yield the isomeric 5(6*H*)-ones ⟨87H(26)163⟩. A mechanistic rationale involving an intramolecular rearrangement of the anion (**203**) to the *N*-acyl derivative of the more stable oxyanion (**204**) followed by cyclization as indicated in Scheme 35, is proposed ⟨87H(26)163⟩. Under thermal conditions the *O*-acyl derivatives (**202**) ring-close to 1,2,4-oxadiazoles.



(**202**) (**203**) (**204**) (**205**)

Scheme 35

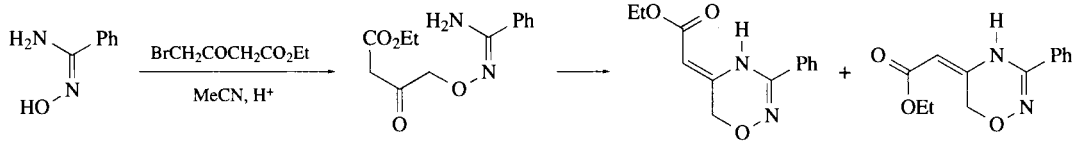
An improved procedure for the preparation of 4*H*-1,2,4-oxadiazin-5(6*H*)-ones (**208**) involving *O*-acylation of amidoximes (**206**) with α-bromoesters and potassium or caesium carbonate in DMF followed by a trimethylaluminum mediated ring closure of the crude esters (**207**), has been reported (Scheme 36) ⟨93H(36)1027⟩.



(**206**) (**207**) (**208**)

Scheme 36

Condensation of ethyl γ-bromoacetoacetate with benzamidoxime (**209**) under acid catalyzed conditions furnishes a mixture of (*Z*)- and (*E*)-5-ethoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazines (**211**) and (**212**) via cyclization of the *O*-alkylated amidoxime (**210**). The yields, which vary from 18 to 77%, depend on the acid catalyst, solvent, and reaction temperature, and are optimal with *p*-toluenesulfonic acid as the catalyst in boiling acetonitrile (Scheme 37) ⟨82CPB3987, 82H(19)2061⟩. Separation by flash and high pressure liquid chromatography on silica gives the intramolecularly hydrogen bonded (*Z*)-isomer (**211**) as the major product (71%). The reaction is equally successful with nuclear substituted benzamidoximes and γ-bromoacetoacetanilides (yields 60–71%). However, 6-ethoxycarbonylmethylene-4*H*-1,2,4-oxadiazines, the products which would result from dehydration of the isomeric *N*-alkylated amidoximes, are not formed.

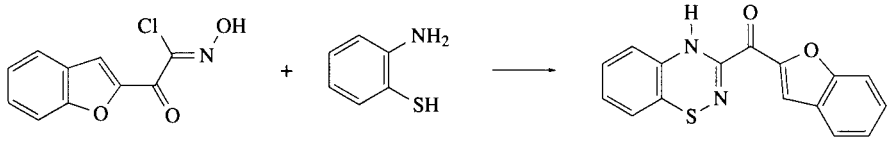


(**209**) (**210**) (**211**) (**212**)

Scheme 37

(ii) From N-C-C-S and C-N fragments

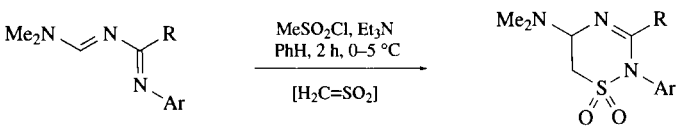
Examples of 1,2,4-benzothiadiazines lacking an SO or SO_2 grouping are uncommon. One such derivative, the 3-acyl-4*H*-1,2,4-benzothiadiazine (**214**) is claimed to be formed in 73% yield by the condensation of 2-aminothiophenol with the 2-benzofuroyl α-chloroxime (**213**) (Equation (16)) ⟨88AP(321)913⟩.



(**213**) (**214**) (16)

(iii) From fragments N-C-N-C and C-S

There is an isolated report on the synthesis of 2,3-diaryl-5,6-dihydro-2*H*-1,2,4-thiadiazine 1,1-dioxides (**216**; R = Ph), in yields of 60–70%, by [4 + 2] cycloaddition of sulfene ($CH_2{=}SO_2$; generated *in situ*) to 4-amino-1,3-diaza-1,3-butadienes (**215**; R = Ph) (Equation (17)). Superior yields (80–94%) of the thiadiazines (**216**; R = SMe) are obtained with 2-(methylthio)-1,3-diazabutadienes (**215**; R = SMe) ⟨87TL2641⟩.

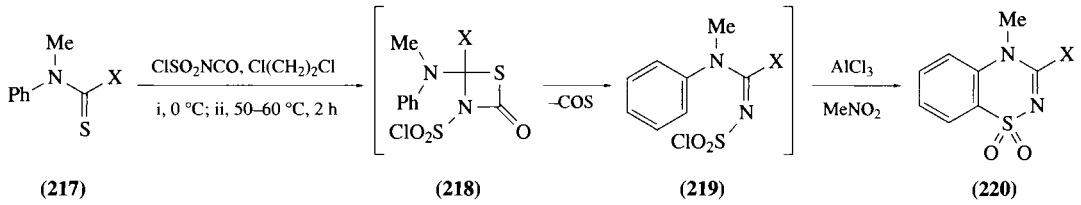


(**215**) (**216**) (17)

(iv) From fragments C-C-N-C and N-S

A new one-pot, but low yielding (5–27%), synthesis of 3-(alkylthio)-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**220**; X = SR) involving the [2 + 2] cycloaddition of chlorosulfonyl isocyanate and

dithiocarbamates (**217**; X = SR) has been developed (Scheme 38) ⟨90CPB1075⟩. Loss of COS from the cycloadducts (**218**) yields the *N*-chlorosulfonylisothioureas (**219**; X = SR), which, under Friedel–Crafts conditions, are cyclized to the 1,2,4-benzothiadiazines (**220**). A similar reaction sequence on the thiocarbamates (**217**; X = OR) furnishes the 3-alkoxy derivatives (**220**; X = OR) in much better yield (75%) ⟨91CPB1939⟩. However, an attempt to extend the synthesis to the 3-dimethylamino-1,2,4-benzothiadiazine 1,1-dioxide (**220**; X = NMe_2) by cyclization of *N*,*N*-dimethyl-*N'*-arylthiourea (**217**; X = NMe_2) failed ⟨91CPB1939⟩.

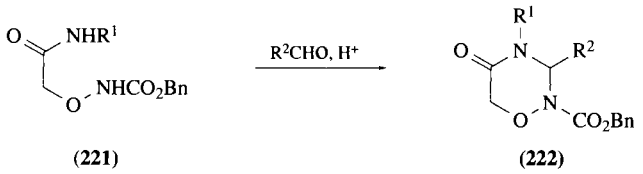


Scheme 38

6.14.9.2.3 [5 + 1] fragments

(i) From fragments N-C-C-O-N and C

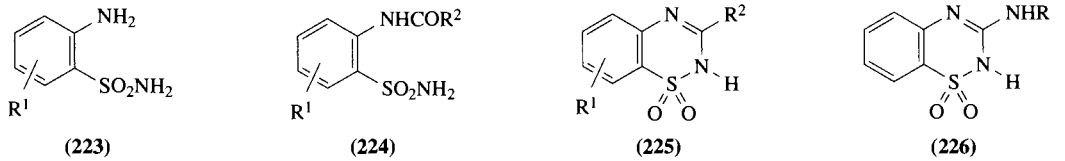
3,4-Dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones (**222**) are synthesized in 50–80% yield by acid-catalyzed condensation of arylaldehydes with *O*-alkyl-*N*-acylhydroxylamines (e.g., (**221**)) (Equation (18)) ⟨82EUP55484, 89JHC129⟩. The benzyloxycarbonyl group is removable by careful hydrogenation in the presence of a palladium catalyst ⟨89JHC129⟩.



(18)

(ii) From fragments N-C-C-S-N and C

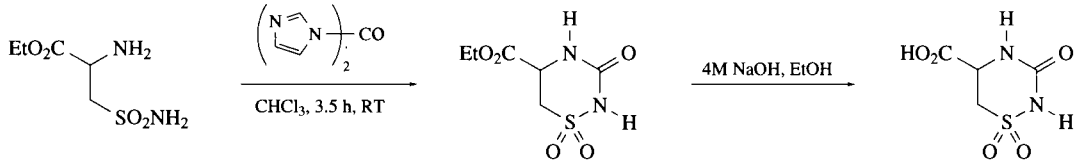
The one-carbon ring closure of 2-aminobenzenesulfonamides (**223**) continues to be an obvious and popular route to 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**225**). The one-carbon fragment is provided by a number of reagents, including trialkyl and triaryl orthoesters ⟨83T2073, 86JOC1967⟩, alkanoic acids ⟨83MI 614-01⟩, α,β-unsaturated acids and acyl halides ⟨84CHE735, 90JMC1721⟩, trifluoroethanoic acid ⟨86BSF871⟩, trifluoropyruvic acid dihydrate ⟨86BSF944⟩, 6-bromohexanal ⟨87USP4634689⟩, and ketals ⟨90JMC1600, 90JMC1606⟩. In the instances in which the intermediate *N*-acylaminoarenesulfonamides (**224**) are isolated, cyclization to the benzothiadiazine 1,1-dioxides (**225**) is accomplished, generally in high yield, with sodium methoxide in methanol ⟨84CHE735, 86MI 614-01⟩, or with aqueous sodium hydroxide ⟨85AP(318)903⟩. The 3-ethoxycarbonyl derivatives (**225**; $R^2 = CO_2Et$) are formed from 2-aminoarenesulfonamides with diethyl oxalate and sodium methoxide ⟨83MI 614-02⟩, or with ethyl ethoxy-carbonylformimidate in boiling ethanol ⟨86T2625⟩.



Condensation of 2-aminobenzenesulfonamide with an isothiocyanate in the presence of triethylamine results in the formation of a 3-amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**226**), the

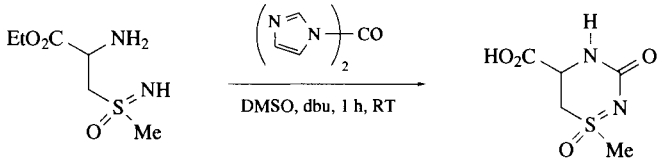
PMR spectra of which support the 3-amino rather than the 3-imino tautomers. In the absence of base only uncyclized thioureas are obtained ⟨90MI 614-05⟩.

Cyclization of 2-aminoarenesulfonamides with carbonyldiimidazole in dioxan affords 2*H*-1,2,4-benzothiadiazin-3(4*H*)-ones ⟨88EUP268990⟩. An interesting adaptation of this method involves the carbonylation of β-aminosulfonamide (**227**) with carbonyldiimidazole to yield the 5,6-dihydro-2*H*-1,2,4-thiadiazine-3(4*H*)-one 1,1-dioxide (**228**; 86%), which on hydrolysis furnishes the 5-carboxylic acid (**229**), a sulfur analogue of dihydroorotic acid (Scheme 39) ⟨84JMC228⟩. Cyclization of the aminosulfonamide (**227**) can also be effected, but less efficiently, with phosgene and with 4-nitrophenyl chloroformate. In a similar manner, the treatment of *S*-methylcysteine sulfoximide (**230**), obtained by the action of sodium azide in sulfuric acid on the corresponding sulfoxide, with carbonyldiimidazole in DBU produces 1-methyl-5,6-dihydro-1λ^4,2,4-thiadiazin-3(4*H*)-one-5-carboxylic acid 1-oxide (**231**) (Equation (19)) ⟨84JMC228⟩.



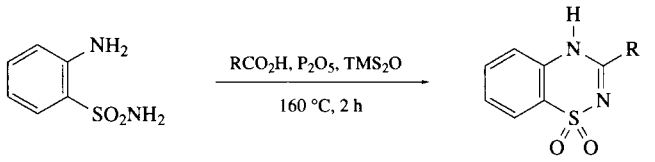
(227) (228) (229)

Scheme 39



(230) (231) (19)

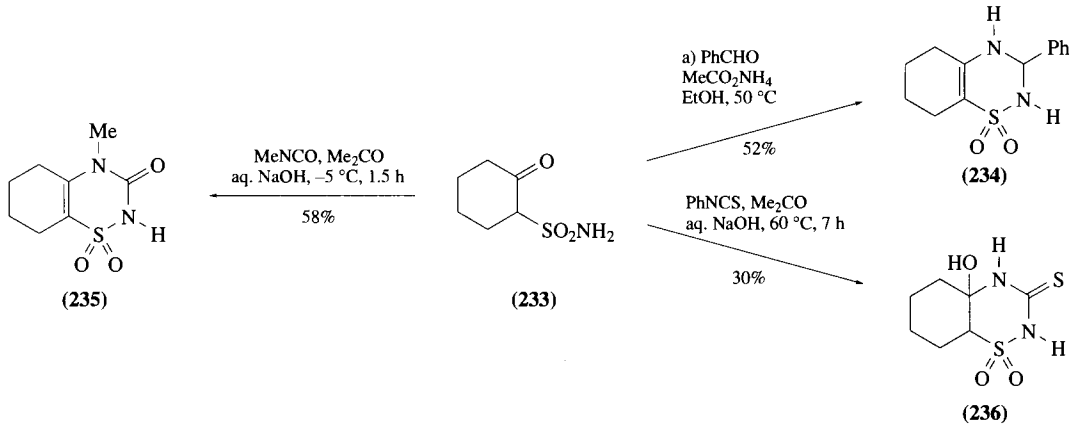
A significant improvement for the direct ring closure of 2-aminobenzenesulfonamides to 4*H*-1,2,4-benzothiadiazine 1,1-dioxides with a variety of carboxylic acids, employing polyphosphoric acid trimethylsilyl ester as the cyclization agent, has been described (Equation (20)) ⟨83S851, 85JAP(K)6025984, 90JMC1721⟩. The reagent, which is prepared readily from phosphorus pentoxide and hexamethyldisiloxane, is a milder and more efficient cyclo-dehydrating agent than polyphosphoric acid and furnishes 3-alkyl- and 3-aryl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**232**), in most cases, in 75–96% yield.



(232) (20)

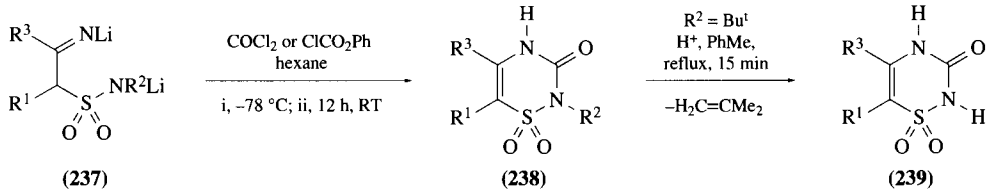
The 2-oxosulfonamides (e.g., (**233**)) are versatile reagents and with carbonyl compounds can serve as synthons for a variety of heterocyclic systems including 3,4-dihydro-2*H*-1,2,4-thiadiazine 1,1-dioxides (**234**), as exemplified in Scheme 40 ⟨85LA579⟩. Reaction of the oxosulfonamide with methyl isocyanate produces the 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide (**235**), whereas with phenyl isothiocyanate the 5-hydroxy-5,6-dihydro-2*H*-1,2,4-thiadiazin-3(4*H*)-thione 1,1-dioxide (**236**) is obtained.

Access to the little known 2*H*-1,2,4-thiadiazine-3(4*H*)-one 1,1-dioxides (**238**) is now possible in moderate yields (29–45%) by carbonylation of the dilithio derivatives (**237**), prepared by the low temperature addition of nitriles to alkylsulfonamide dianions, with phosgene or with phenyl chloroformate (Scheme 41) ⟨88S733⟩. The reaction is successful with a range of nitriles, with the notable exception of acetonitrile, which gives the thiadiazinones (**238**; R^3 = Me) in unspecified low yields.



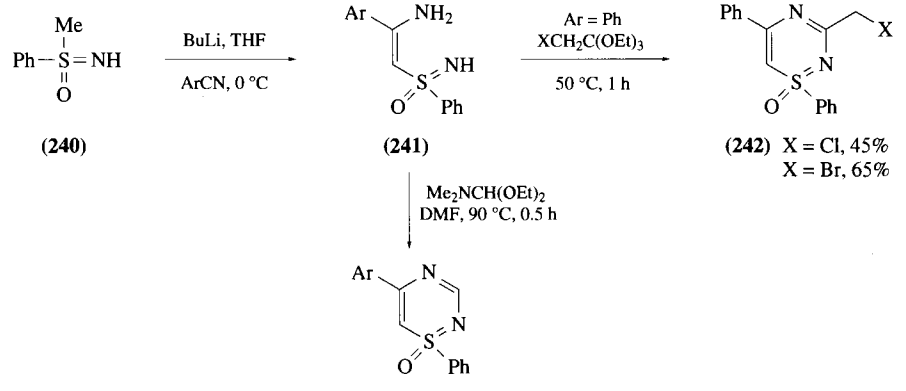
Scheme 40

The 2-*t*-butyl-derivatives (**238**; $R^2 = CMe_3$) are particularly useful, since on heating in toluene with a catalytic amount of acid they undergo loss of butylene to form the 2,4-unsubstituted 1,2,4-thiadiazinones (**239**).

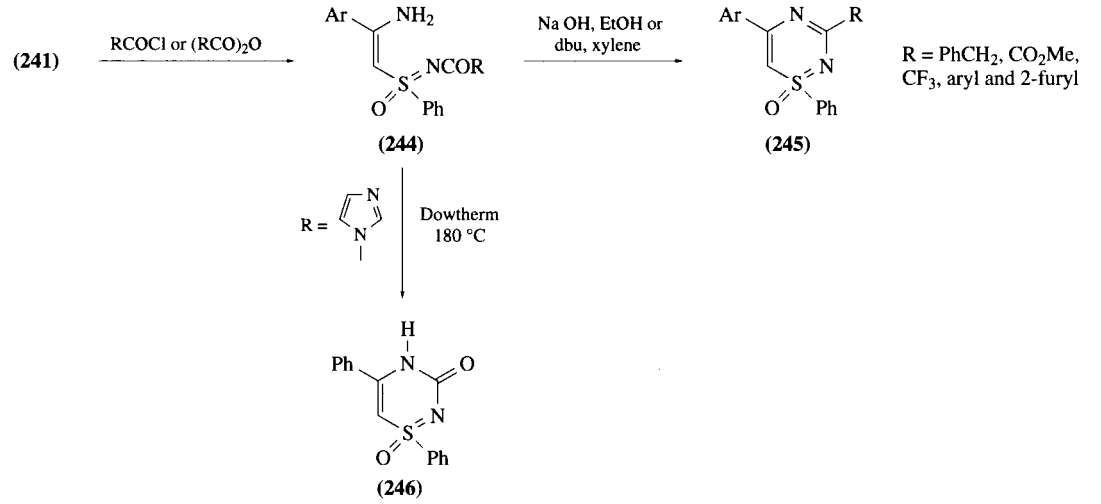


Scheme 41

The dianion of *S*-methyl-*S*-phenylsulfoximide (**240**) reacts with aryl carbonitriles to yield 2-enaminosulfoximides (**241**), which are useful precursors of $1\lambda^4$,2,4-thiadiazine 1-oxides ⟨85EUP161143, 90JCS(P1)447⟩; a system which was known previously only as the 5-oxo and 3,5-dioxo derivatives ⟨77JOC952⟩. Examples (**242**) and (**243**) are illustrated in Scheme 42. If optically pure *S*-methyl-*S*-phenylsulfoximide is employed then the (*R*) and (*S*) enantiomers of the $1\lambda^4$,2,4-thiadiazine 1-oxide (**243**; Ar = Ph) are produced with optical rotations of −120.7 and +119.4 respectively ⟨90JCS(P1)447⟩. Acylation of the enamines (**241**) occurs preferentially at the more nucleophilic sulfoximide nitrogen, and the resulting acyl derivatives (**244**) on treatment with sodium hydroxide in ethanol or, better, with DBU in boiling xylene, undergo ring closure to 3-substituted-1,5-diaryl-$1\lambda^4$,2,4-thiadiazine 1-oxides (**245**). Cyclization of the acyl derivative (**244**; R = 1*H*-imidazol-1-yl; Ar = Ph) in Dowtherm at 180°C produces 1,5-diphenyl-$1\lambda^4$,2,4-thiadiazin-3(4*H*)-one 1-oxide (**246**) in 87% yield (Scheme 43) ⟨90JCS(P1)447⟩.

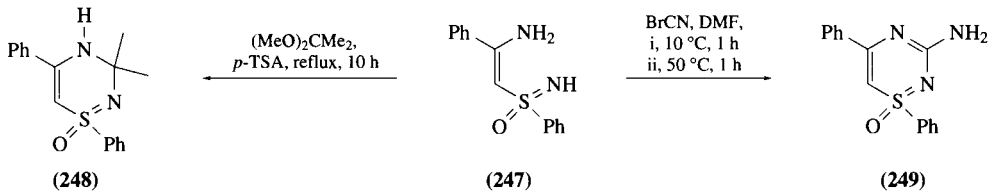


Scheme 42



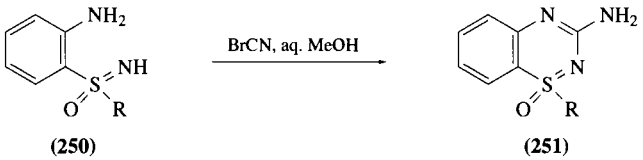
Scheme 43

Treatment of the sulfoximide (**247**) with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid yields 3,3-dimethyl-1,5-diphenyl-3,4-dihydro-1λ^4,2,4-thiadiazine 1-oxide (**248**), whereas the 3-amino derivative (**249**) is accessible, although only in low yield (21%), by reaction of the enamine (**247**) with cyanogen bromide in DMF (Scheme 44).



Scheme 44

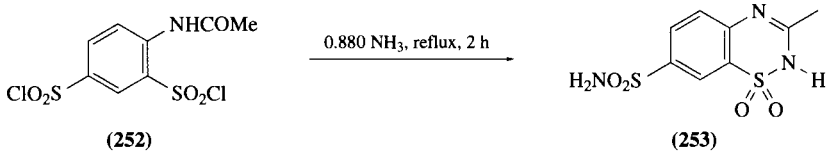
In a similar manner, treatment of the *S*-(2-aminophenyl)sulfoximides (**250**; R = Me or Ph) with cyanogen bromide in aqueous methanol gives 1-substituted 3-amino-1λ^4,2,4-benzothiadiazine 1-oxides (**251**) (Equation (21)) ⟨88JMC1098⟩.



(21)

(iii) From fragments C-N-C-C-S and N

An infrequently used route to 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (e.g., (**253**)) is by ring closure of 2-acylaminoarenesulfonyl chlorides (e.g., (**252**)) with concentrated aqueous ammonia (Equation (22)) ⟨84MI 614-01⟩.

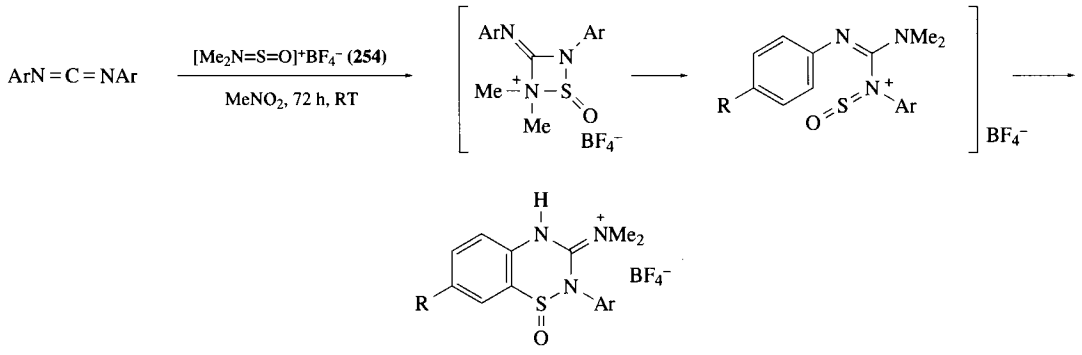


(22)

(iv) From fragments C-C-N-C-N and S

1,2,4-Benzothiadiazine 1-oxides are less common than the 1,1-dioxides. Noteworthy, therefore, is their formation as the 3-(*N*,*N*-dimethyliminium) tetrafluoroborates (**255**) via a complex reaction

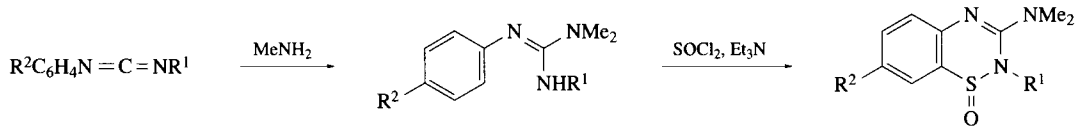
involving cycloaddition of diarylcarbodiimides with *N,N*-dimethylsulfinylaminium tetrafluoroborate (**254**) (Scheme 45). The 1-oxide structure has been confirmed by x-ray analysis of the dimethoxy derivative (**255**; R = MeO; Ar = 4-$MeOC_6H_4$) ⟨84LA904⟩.



(255)

Scheme 45

Also, 1,2,4-benzothiadiazine 1-oxides (**258**) are produced by addition of dimethylamine to the carbodiimides (**256**) followed by cyclization of the guanidines (**257**), so formed with thionyl chloride in triethylamine (Scheme 46) ⟨87PS(29)41⟩.

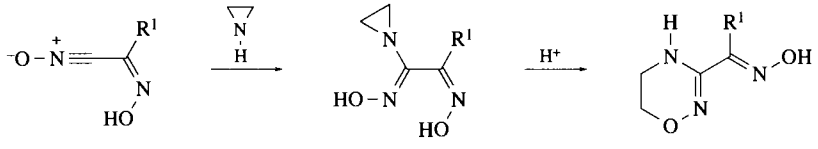


(256) (257) (258)

Scheme 46

6.14.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

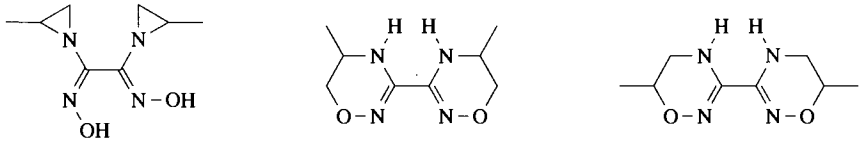
Aziridino dioximes (**260**) derived by addition of aziridines to the oximinocarbonitrile oxides (**259**), on treatment with acid rearrange to 5,6-dihydro-4*H*-1,2,4-oxadiazines (**261**) (Scheme 47) ⟨82CHE369⟩.



(259) (260) (261)

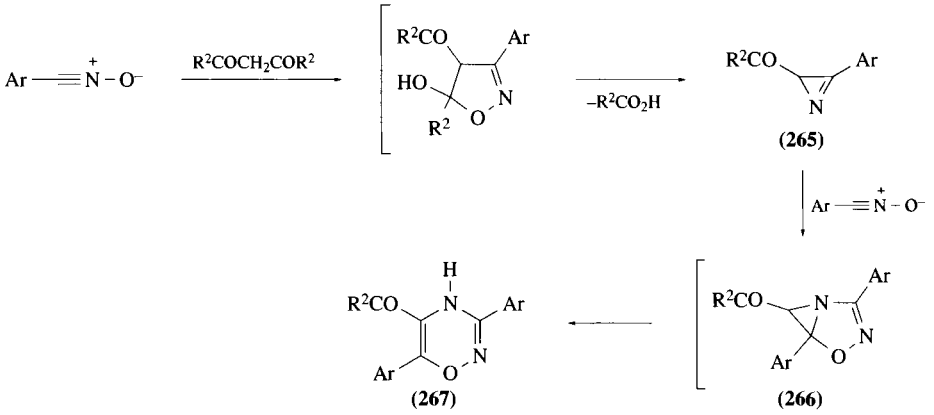
Scheme 47

Under S_N1 conditions, regioselective ring opening of an unsymmetrically substituted aziridine to give the more stable carbocation is to be expected. However, with the bis-(2-methylaziridino)dioxime (**262**) a mixture (separable by TLC) of the 5,5′-dimethyl- and 6,6′-dimethyl 3,3′-bis(5,6-dihydro-4*H*-1,2,4-oxadiazines) (**263**) and (**264**) resulting from C_1—N and C_2—N bond cleavage of the aziridine ring, is formed.



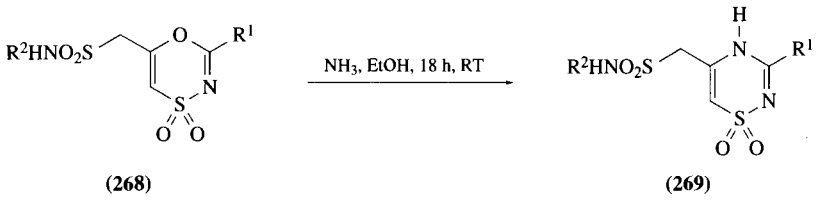
(262) (263) (264)

It is known that 2*H*-azirines can react with carbonitrile oxides to yield carbodiimides ⟨71TL4831⟩. It has been found, however, that the 2-acyl-2*H*-azirines (**265**), formed *in situ* by the addition of carbonitrile oxides to the enol tautomers of β-diketones, are trapped by an excess of nitrile oxide at the bicyclic 1,3-dipolar cycloadducts (**266**), which promptly undergo ring expansion to 5-acyl-4*H*-1,2,4-oxadiazines (**267**) as outlined in Scheme 48 ⟨82CL1711⟩. Support for this reaction pathway comes from trial experiments in which isolable 2-acyl-2*H*-azirines were found to react directly with carbonitrile oxides to yield 1,2,4-oxadiazines.



Scheme 48

The conversion of a 1,4,3-oxathiazine 4,4-dioxide (**268**) by ethanolic ammonia into a 4*H*-1,2,4-thiadiazine 1,1-dioxide (**269**) is a rare example of the formation of a 1,2,4-thiadiazine by ring transformation from another six-membered heterocyclic system (Equation (23)) ⟨88S521⟩.



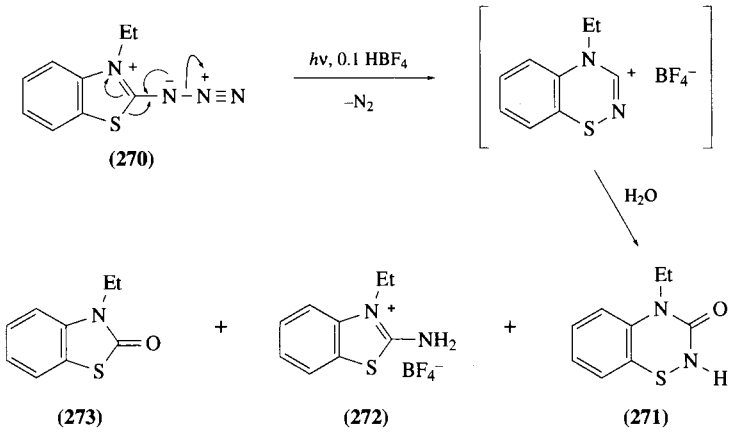
(23)

A novel synthesis of 4-ethyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one (**271**; 60%), which employs a photoinduced Curtius-type rearrangement of 2-azido-3-ethylbenzothiazolium tetrafluoroborate (**270**) in 0.1 M tetrafluoroboric acid, has been reported ⟨87HCA2045⟩. The by-products are 2-amino-3-ethylbenzothiazolium tetrafluoroborate (**272**; 12%) and 3-ethylbenzothiazol-2(3*H*)-one (**273**; 4.4%) (Scheme 49). An acidic medium appears to be necessary for successful ring expansion since photolysis in methanol solution yields only the benzothiazolone (**273**) and the 2-amino derivative (**272**) in 8% and 89% yield, respectively.

6.14.11 GENERAL SYNTHETIC METHODS

6.14.11.1 1,2,4-Oxadiazines

Formation of 1,2,4-oxadiazines occurs by acid-catalyzed ring expansion of α-aziridino oximes and dioximes, and by 1,3-dipolar cycloaddition of arylcarbonitrile oxides and 2-acyl-2*H*-azirines (Section 6.14.10). Preparation of 1,2,4-oxadiazin-5-ones can be achieved by ring closure of *N*-carboxymethyl and *N*-alkoxycarbonylmethyl amidoximes (Section 6.14.9.1.1), by the acid-catalyzed condensation of arylaldehydes with *O*-alkyl-*N*-acylhydroxylamines (Section 6.14.9.2.3.1), and by reaction of *N*-hydroxyureas or amidoximes with a two-carbon fragment such as an α-halo ester or an acyl halide (Section 6.14.9.2.2.1).



Scheme 49

6.14.11.2 1,2,4-Benzoxadiazines

1,2,4-Benzoxadiazines are obtained by the ring closure of α-nitrosonitrones (Section 6.14.9.1.1) and by the action of nitrile oxides on *N*-aryl-*S*,*S*-dialkylsulfimides (Section 6.14.9.1.3).

6.14.11.3 1,2,4-Thiadiazines

The formation of 1,2,4-thiadiazine 1,1-dioxides occurs by the addition of carbonitriles to alkylsulfonamide dianions followed by carbonylation with phosgene or phenyl chloroformate (Section 6.14.9.2.3(ii)), and by the [4 + 2] cycloaddition of 1,3-diaza-1,3-butadienes with sulfene (Section 6.14.9.2.2(iii)).

$1\lambda^4$,2,4-Thiadiazine 1-oxides are now accessible by the one-carbon ring-closure of 2-enaminosulfoximides with a variety of reagents (Section 6.14.9.2.3(ii)).

6.14.11.4 1,2,4-Benzothiadiazines

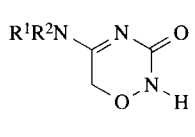
The most popular route to 1,2,4-benzothiadiazine 1,1-dioxides is by one-carbon ring closure of 2-aminoarenesulfonamides (Section 6.14.9.2.3(ii)). Other methods include the base-induced ring closure of *N*-(2-sulfamoylphenyl)-*N'*-(γ-chloroalkyl)ureas and -thioureas (Section 6.14.9.1.3), by intramolecular Friedel–Crafts reaction involving chlorosulfonyl isocyanate and a secondary aromatic amine (Section 6.14.9.2.1(ii)), and by [2 + 2]cycloadditions of chlorosulfonyl isocyanate with thio- and dithiocarbamates (Section 6.14.9.2.2(iv)).

The formation of $1\lambda^4$,2,4-benzothiadiazines result from treatment of *N*-chloro-*N'*-arylamidines with thionyl chloride in pyridine, and by ring closure of *N*-arylbenzamidines with sulfenyl chlorides and *N*-chlorosuccinimide (Section 6.14.9.1.2).

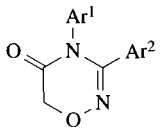
6.14.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Since the mid-1980s there has been a good deal of activity in the patent literature on the use of 1,2,4-oxadiazin-3(2*H*)-ones and related structures such as agrochemicals. Herbicidal, fungicidal, and bactericidal activities are claimed for 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-ones (**274**) ⟨84USP4459403⟩. Pronounced herbicidal activity is also noted for *N*,*N*-disubstituted 2*H*-1,2,4-oxadiazin-3,5(4*H*,6*H*)-diones (e.g., (**199**)) ⟨89JAP(K)01186882⟩ and for *N*,*N*-disubstituted 5,6-dihydro-1,2,4-oxadiazin-3(2*H*)-ones ⟨91FRP2660158, 91FRP2660308⟩, while 3,4-diaryl-4*H*-1,2,4-oxadiazin-5(6*H*)-ones (**275**) have use as agrochemical microbiocides ⟨91JAP(K)03148267⟩. The 2-acyl-3-aryl-3,4-dihydro-2*H*-1,2,4-oxadiazin-

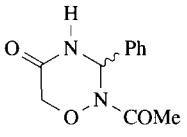
5(6*H*)-ones (e.g. (**276**)) are reported to possess remarkable anticonvulsant activity ⟨B-84MI 614-02, 89JHC129, 89JHC133⟩.



(**274**)

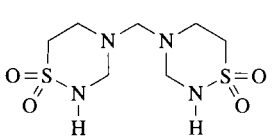


(**275**)



(**276**)

Bis[4-(1,1-dioxo-3,4,5,6-tetrahydro-2*H*-1,2,4-thiadiazinyl)methane (**277**) (Taurolidine) is an important antibacterial agent of long standing ⟨66FRP1458701⟩. The basic ring system (**278**) (Taurultam) also displays powerful antibacterial and antifungal activity. The pharmacology and toxicology of these systems have been reviewed ⟨B-85MI 614-01, B-85MI 614-02⟩. It has been reported that 2-dithiophosphonic acid and dithiophosphoric acid derivatives (e.g. (**279**)) of 3-alkyl-5,6-dihydro-2*H*-1,2,4-thiadiazine 1,1-dioxides have fungicidal, acaracidal, nematocidal, and insecticidal activity ⟨83GEP3208187⟩.



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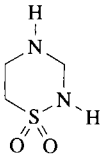
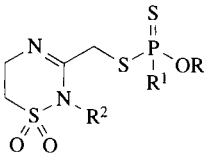
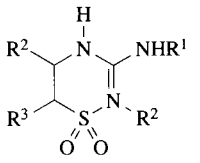


(**278**)

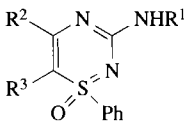


(**279**)

Antihistamine and anxiolytic properties are claimed for 3-alkylamino-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-dioxides (**280**) ⟨85JAP(K)60112781⟩, and for 1-phenyl-1λ^4,2,4-thiadiazine 1-oxides (**281**) ⟨85EUP161143⟩.

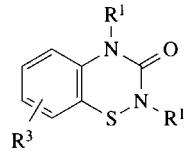


(**280**)



(**281**)

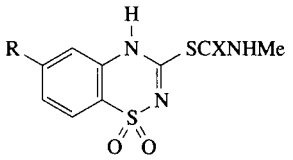
In addition to the long-standing and well-known diuretic activity of 2,3-dihydro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides such as hydrochlorothiazide (**12**) and chlorothiazide (**62**) ⟨89MI 614-04⟩, derivatives of this system bearing peptide side-chains at the 3-position, or on the sulfonamide function, are found to be antiglaucoma agents ⟨85USP4559340, 87USP4634689, 87USP4634698⟩. They also have angiotensin converting enzyme inhibitory action ⟨83EUP95584, 85EUP153755, 85USP4536501, 85USP4556655, 86GEP3427309, 87USP4666906, 88GEP3632544, 89BRP2207130, 89USP4826826, 90JMC1600⟩. Therapeutic and prophylactic action for osteoporosis has been claimed for 2,4-disubstituted 2*H*-benzothiadiazin-3(4*H*)-ones (**282**) ⟨89JAP(K)01238529⟩.



(**282**)

Moderate antitumor activity is reported for the thio- and dithiocarbamate derivatives (**283**; X = O or S; R = H or Cl) ⟨90MI 614-02⟩, while significant antihypertensive effects and diuretic activity are noted for 3-perfluoroalkyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (e.g. (**284**)) ⟨86BSF871, 87JAP62195371⟩. Patents claiming antibacterial ⟨85JAP(K)6025984⟩ and fungicidal activity ⟨85JAP(K)6097970⟩, respectively, for 3-aryl- and 3-alkylthio-2*H*-1,2,4-benzothiadiazine 1,1-dioxides

have been filed. Antiviral action, particularly against HIV-1 reverse transcriptase, have been attributed to 2*H*-1,2,4-benzothiadiazin-3(4*H*)-thiones (e.g., (**285**)) ⟨92GEP4036571⟩.



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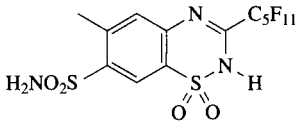

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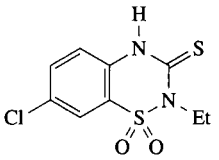
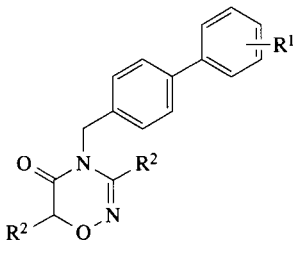


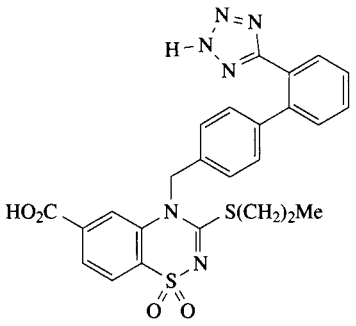
(**285**)

In vitro aldose reductase inhibitory action and antiinflammatory activity is shown by 3-carboxyalkylamino- and 3-carboxyalkylthio-4*H*-benzothiadiazine 1,1-dioxides ⟨87MI 614-03, 89MI 614-05, 90MI 614-03, 93MI 614-01⟩ and by their 2*H*-3(4*H*)-one derivatives ⟨87EUP218999⟩. Patents claiming 1,2,4-benzothiadiazine 1,1-dioxides as histamine H_2-receptor antagonists ⟨84EUP105732⟩, and as psychotropic ⟨85JAP(K)60156680⟩, cardiovascular ⟨88PHA37⟩, and antiulcer ⟨85JAP(K)6092278⟩ agents have also appeared.

Results reveal that 4-biphenylylmethyl-4*H*-1,2,4-oxadiazin-5(6*H*)-ones (**286**) are potent angiotensin-II receptor antagonists ⟨93H(36)1027, 93USP5225408⟩. The 4-heteroarylmethyl derivatives display similar activity ⟨93USP5236916⟩, as do 4-biphenylylmethyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (e.g. (**287**)) ⟨92BMC1115⟩. It is found for the latter systems that their stability is dependent on the nature of the 3-substituent, whereas their potency is related to the nature of the substituents on the carbocyclic ring.



(**286**)



(**287**)

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6.15 1,2,5-Oxadiazines and 1,2,5-Thiadiazines

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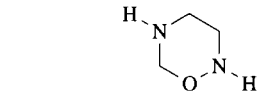
6.15.1 INTRODUCTION

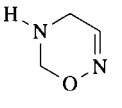
Despite reports to the contrary ⟨84CHEC-I(3)1039⟩, it is now known that 1,2,5-oxadiazines are not "extremely common systems." Reports on their synthesis by self-condensation of ketoaldehyde monoximes in concentrated mineral acid ⟨1897CB1292, 07CB4052⟩, and by the condensation of 2,3-butanedione monoxime with aldoximes ⟨05CB3357⟩, have been shown to be incorrect (see Section 6.15.6.2.2.2). On account of this confusion some of the early chemistry (i.e., prior to 1982) of these systems is included in this chapter.

Fully saturated (**1**) (see Section 6.15.6.2.1.1) and 5,6-dihydro-4*H*-1,2,5-oxadiazines (**2**) (see Section 6.15.6.2.2.2) have been reported, whereas the 2*H*- and 4*H*-1,2,5-oxadiazines (**3**) are still unknown. Also rare are the 1*H*-2,1,4-benzoxadiazines (**4**) (see Section 6.15.7), the 1,2,5-thiadiazines, which are known only as the 5,6-dihydro-4*H*-derivatives (**5**) (see Section 6.15.7), and the 1*H*-2,1,4-benzothiadiazines (**6**) (see Section 6.15.6.1). There are no examples of fully conjugated 1-oxonia- (**7**; X = O) or 1-thionia- (**7**; X = S) systems.

The chemistry of 1,2,5-thiadiazines and 2,1,4-benzothiadiazines has been reviewed ⟨90AHC(50)255⟩.



(**1**)



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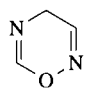

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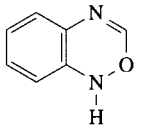

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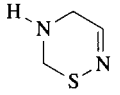

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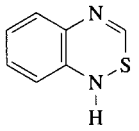


(**6**)

(**7**)

6.15.2 THEORETICAL AND EXPERIMENTAL STRUCTURAL METHODS

There have been no theoretical studies carried out on 1,2,5-oxadiazines or 1,2,5-thiadiazines and their benzologues.

6.15.2.1 Spectroscopic Studies

6.15.2.1.1 Ultraviolet, infrared, and mass spectra

Detailed spectroscopic studies on these ring systems are meagre. Infrared absorptions at 1605, 1680 and 3170 and 3190 cm^{-1} for the 5,6-dihydro-2*H*-1,2,5-oxadiazin-4(3*H*)-one (**8**; Ar = 2-$O_2NC_6H_4$) are assigned to ν(C=C), ν(C=O), and ν(NH), respectively ⟨87HCA1255⟩.

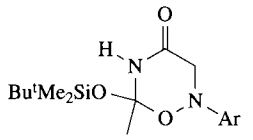
The 3*H*-2,1,4-benzoxadiazine 4-oxide (**9**) has UV absorptions (λ_{max}, MeOH) at 228 nm and 405 nm and, in its EI mass spectrum, it shows peaks at *m/z* 173 and 159 corresponding to (M^+—O) and (M^+—NO), respectively ⟨78JOC76⟩.

6.15.2.1.2 NMR spectra

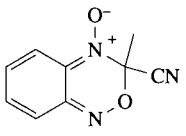
The ^{1}H NMR spectrum (δ, $CDCl_3$) of the oxadiazinone (**8**; Ar = 2-$O_2NC_6H_4$) shows ring proton resonances at 3.85–4.13 (dd, 3-CH_2), and 7.81 (5-NH); the 6-Me group absorbs at δ 1.75 ⟨87HCA1255⟩. Ring proton resonances for 3,6-diphenyl-6-(*N*-methylanilino)-5,6-dihydro-4*H*-1,2,5-oxadiazine (**10**) are at δ 5.19 (2*H*, *d*, 4-CH_2 *J* 6 Hz) and 6.5–6.7 (1*H*, m, 5-NH) ⟨83CL341⟩.

Proton-decoupled ^{13}C NMR spectroscopy was instrumental in determining the structure of the 3*H*-2,1,4-benzoxadiazine 4-oxide (**9**) and the isomeric 2*H*-benzimidazole 1,3-dioxide (**11**) ⟨78JOC76⟩ (see Section 6.15.7). The unsymmetrical benzoxadiazine displays a nine-line spectrum consisting of the cyano resonance at 113.5 ppm, six aromatic carbons (4 × CH at 130.6, 130.1, 123.5, and 117.3 ppm, and 2 × C at 150.8, and 129.1 ppm), the Me group at 19.1 ppm, and C-3 at 86.1 ppm.

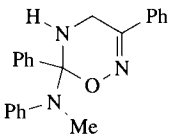
The proton at C-3 in the 4,6-diimino-1,2,5-thiadiazine (**12**) (see Section 6.15.7) is found at low field (8.8 δ) in the ^{1}H NMR spectrum ⟨79TL1281⟩. The methyl group at the exocyclic sp^2 nitrogen and the methyl group at N-5 are reported as a six-proton singlet at 3.57 δ. In contrast, the methyl signals in the methoxycarbonylmethylene derivative (**13**) appear at 3.34 (NMe), 3.4 (C=NMe) and 3.7 (OMe). The exocyclic alkene proton is at 5.1 δ whereas H-3 is again at low field (8.37 δ).



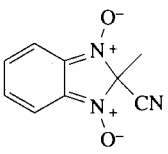
(8)



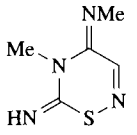
(9)



(10)



(11)



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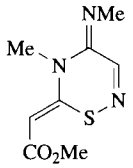
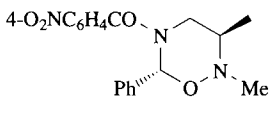


(13)

6.15.2.1.3 X-ray crystallography

Unequivocal evidence for a 1,2,5-oxadiazine ring comes from the x-ray crystallographic analysis of 5-(4-nitrobenzoyl)-2,3-dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-oxadiazine (**14**) ⟨93CC169⟩. The structure of the 4*H*-1,2,5-thiadiazin-6(5*H*)-thione (**15**), one of the few examples of this rare ring system (see Section 6.15.7), has been confirmed by x-ray analysis ⟨87CHE1026⟩. The molecule has a boat conformation in which the ring sulfur and C-4 are at angles of 13.3° and 34.6°, respectively, to the plane of the ring generated by N(2), C(3), N(5), and C(6). The crystal structure of the 5,6-dihydro-2*H*-1,2,5-oxadiazin-4(3*H*)-one (**8**; Ar = 2-$O_2NC_6H_4$) (Section 6.15.6.2.2.1) has also been determined ⟨87HCA1255⟩.



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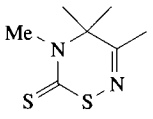


(15)

6.15.3 THERMODYNAMIC ASPECTS AND REACTIVITY OF FULLY CONJUGATED RINGS

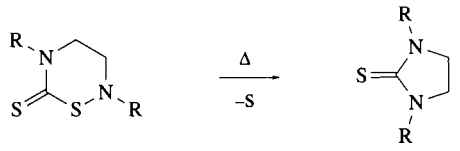
None of the systems considered in this chapter is aromatic, and only a few unsaturated derivatives have been reported. In addition, there appear to be no recent (i.e., since the mid-1980s) conformational studies on 1,2,5-oxadiazine or 1,2,5-thiadiazine rings, nor are there any data concerning tautomeric equilibria of the basic ring systems or of their oxo derivatives (see, however, Section 6.15.6.2.3.1).

6.15.4 REACTIVITY OF NONCONJUGATED RINGS

6.15.4.1 Thermal and Photochemical Unimolecular Reactions

2,5-Dialkyl-3,4-dihydro-2*H*-1,2,5-thiadiazin-6(5*H*)-thiones (**16**) (see Section 6.15.6.1) extrude the ring sulfur on gentle heating (temperature not cited) to yield 1,3-dialkyl-4,5-dihydro-1*H*-imidazolin-2(3*H*)-thiones (**17**) (Equation (1)) ⟨49JOC946⟩. The thermal stability of the thiadiazinethiones is dependent on the size of the alkyl substituent, with bulky substituents imparting enhanced stability. For example, the dicyclohexyl compound (**16**; R = cyclohexyl) can be stored for several weeks

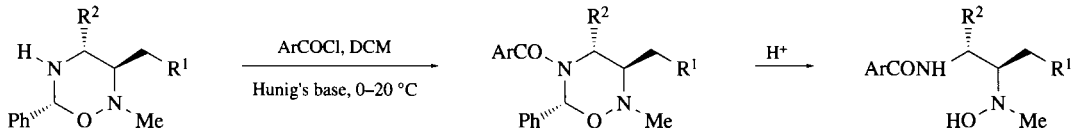
without decomposition, whereas the diethyl compound (**16**; R = Et) decomposes readily at room temperature. The imidazolethione (**17**; R = Et) and sulfur are the main decomposition products.



(16) (17) (1)

6.15.4.2 Electrophilic Attack at Ring Nitrogen, Sulfur, or Carbon

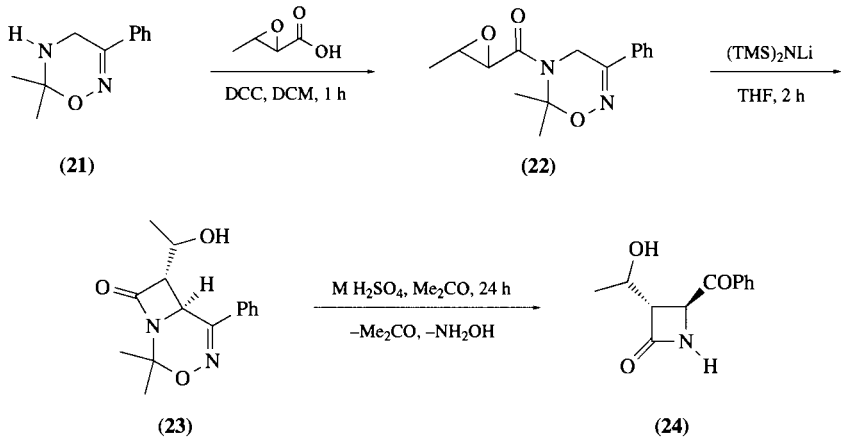
Only a few examples of direct electrophilic attack at the oxadiazine or thiadiazine ring have been reported. The tetrahydro-2*H*-1,2,5-oxadiazines (**18**) can be acylated at low temperatures (1–4 °C) in dichloromethane to give the 5-acyl derivatives (**19**) in 65–70% yield (Scheme 1) ⟨93CC169⟩. However, the oxadiazines (**18**) and, to a lesser extent, their 5-acyl derivatives are acid sensitive (the former even during purification by chromatography) and with 2 M hydrochloric acid undergo ring opening to the amido hydroxylamines (**20**) in almost quantitative yields (>95%).



(18) (19) (20)

Scheme 1

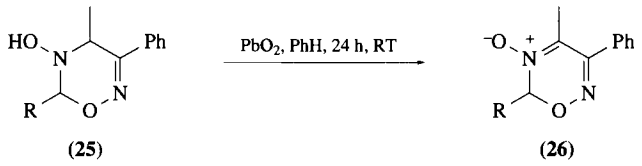
5,6-Dihydro-4*H*-1,2,5-oxadiazines (**21**) (see Section 6.15.6.2.3.1) have been used as masked acyl groups for the stereoselective synthesis of 3(α)-(1-hydroxyethyl)-4(β)-benzoyl-β-lactams (**24**) (Scheme 2) ⟨88EUP265169⟩. Condensation of the oxadiazine (**21**) with (2*R*,3*R*)-epoxy-butanoic acid in the presence of dicyclohexylcarbodiimide yields the *N*-acyl derivative (**22**), which on treatment with lithium bis(trimethylsilyl)amide in THF undergoes stereoselective ring closure to the fused azetidinone (**23**). Hydrolysis with 1 M sulfuric acid in acetone ruptures the oxadiazine ring and forms the β-lactam (**24**).



(21) (22) (23) (24)

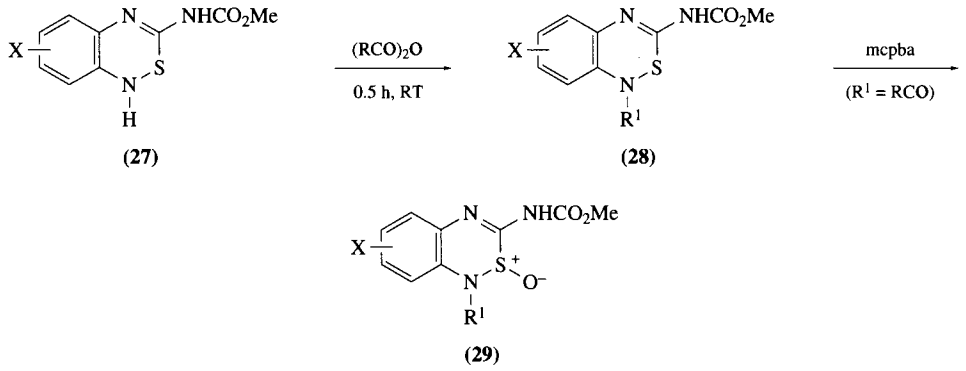
Scheme 2

There is an unconfirmed report of the oxidation of 5-hydroxy-5,6-dihydro-4*H*-1,2,5-oxadiazines (**25**; R = H or Me) to 6*H*-1,2,5-oxadiazine-5-oxides (**26**) with lead dioxide in benzene at room temperature (Equation (2)) ⟨70CHE1180⟩.



(25) (26) (2)

1*H*-2,1,4-Benzothiadiazines (**27**) (see Section 6.15.6.1) are acylated at N-1 in acetic anhydride (Scheme 3) ⟨71GEP2108461, 72GEP2215733⟩.



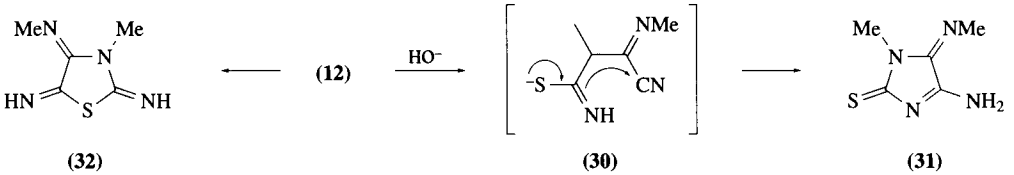
(27) (28) (29)

Scheme 3

1*H*-2,1,4-Benzothiadiazine 2-oxides (**29**; R^1 = H or COR) result from the oxidation of 1*H*-2,1,4-benzothiadiazines (**28**; R^1 = H), or their 1-acyl derivatives (**28**; R^1 = COR), with *m*-chloroperbenzoic acid (Scheme 3) ⟨71GEP2108461, 72GEP2215733⟩.

6.15.4.3 Nucleophilic Attack at Ring Carbon

The ring-contraction of the 4,6-diimino-5*H*-1,2,5-thiadiazine (**12**) (see Section 6.15.7) in the presence of a trace of hydroxide or cyanide ion involves a rare example of a nucleophilic attack on the 1,2,5-oxadiazine or 1,2,5-thiadiazine ring systems ⟨79TL1281⟩. The product, which is also formed on treating 3-methylamino-2-methyl-1,2,5-thiadiazolium chloride ((**91**) see Section 6.15.7) with an excess of cyanide ion, is thought to be the imidazoline-2-thione (**31**) formed as indicated in Scheme 4, although an alternative cyclization of intermediate (**30**) to give the isomeric 2,4,5-tri-iminothiazolidine (**32**) is not discounted.

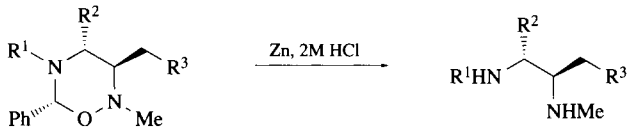


(32) (30) (31)

Scheme 4

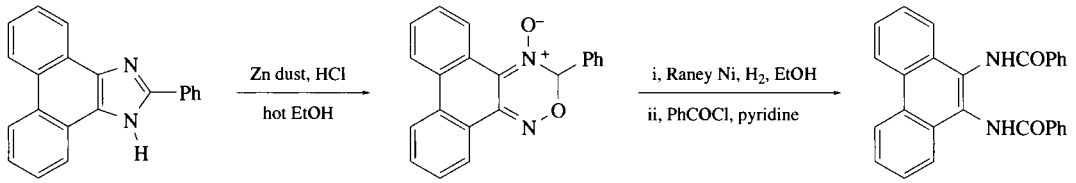
6.15.4.4 Reduction

Reduction of 5-aryl- and 5-alkyl-tetrahydro-2*H*-1,2,5-oxadiazines (**33**) (see Section 6.15.6.2.1.1) with zinc and hydrochloric acid yields the diamines (**34**) (Equation (3)) ⟨93CC169⟩.



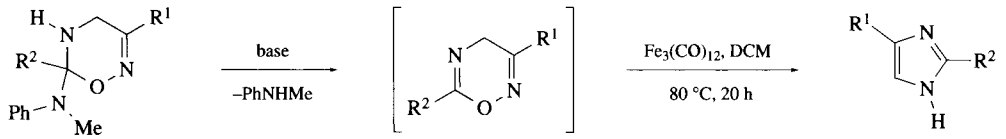
(3)

Catalytic reduction of the phenanthro[9,10-*c*][1,2,5]oxadiazine-4-oxide (**35**) (see Section 6.15.6.2.2.2) with Raney nickel and hydrogen affords benzyl alcohol (85%) and 9,10-diaminophenanthrene, characterized as the dibenzoyl derivative (**36**) ⟨69CB4177⟩. In contrast, reduction with zinc and hydrochloric acid yields 2-phenyl-1*H*-phenanthro[9,10-*d*]imidazole (**37**) (59%) as the hydrochloride (Scheme 5).



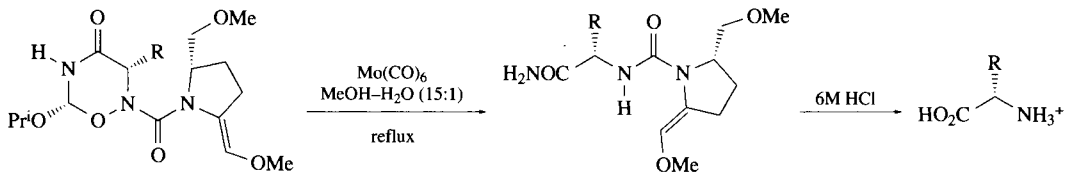
Scheme 5

Treatment of 5,6-dihydro-4*H*-1,2,5-oxadiazines (**38**) with an iron carbonyl complex results in deoxygenation and ring contraction to the 2,4-disubstituted imidazoles (**40**) in 31–93% yield ⟨83CL341⟩. The effectiveness of the iron carbonyl decreases in the order $Fe_3(CO)_{12} > Fe_2(CO)_9 > Fe(CO)_5$. A reaction sequence involving base catalysed loss of *N*-methylphenylamine to give the nonisolable 4*H*-1,2,5-oxadiazine intermediate (**39**) followed by an iron carbonyl-mediated deoxygenation, is proposed (Scheme 6).



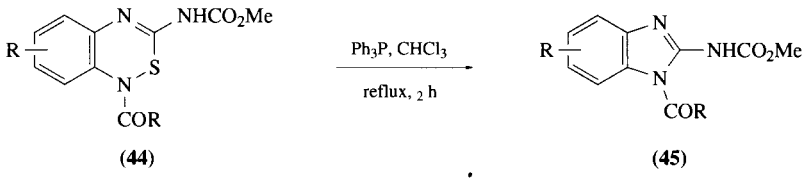
Scheme 6

In a similar manner, the optically pure 5,6-dihydro-2*H*-1,2,5-oxadiazin-4(3*H*)-ones (**41**) (see Section 6.15.6.2.2.1) on treatment with $Mo(CO)_6$ in aqueous acetonitrile undergo ring-contraction to the protected amino acids (**42**; 73–78%), which on hydrolytic removal of the chiral auxiliary with 6 M hydrochloric acid furnish α-amino acids (**43**) of >98% *ee* in 71–78% yield (Scheme 7) ⟨91TL5349⟩.



Scheme 7

Reductive desulfurization and ring contraction of *N*-(1-acyl-1*H*-2,1,4-benzothiadiazin-3-yl)carbamates (**44**) to 1-acyl-2-methoxycarbonylaminobenzimidazoles (e.g., **45**; R = OMe) can be effected with triphenylphosphine in hot chloroform (Equation (4)) ⟨75GEP2332486, 88IJC(B)672⟩.



(44) (45) (4)

6.15.5 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON AND TO RING HETEROATOMS

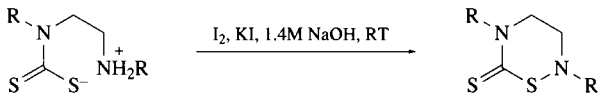
Since the mid-1980s there has been no chemistry to report under this heading.

6.15.6 RING SYNTHESIS

6.15.6.1 By Formation of One Bond–Between N and S

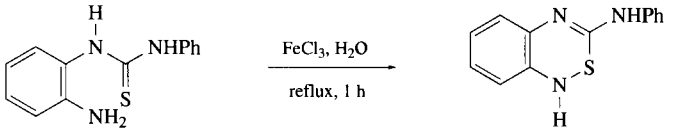
Methods involving the formation of one bond are rare and are limited to the preparation of 1,2,5-thiadiazines and their benzologues.

The 1,2,5-thiadiazine ring system was first prepared by oxidative cyclization of a zwitterionic *N*-alkyl-*N*-(β-alkylaminoethyl)dithiocarbamic acid (**46**) ⟨49JOC946, 50USP2514200, 51USP2537633⟩. These inner salts, which are formed by the action of carbon disulfide on bis-1,2-alkylaminoethanes, on oxidation with iodine in aqueous sodium hydroxide furnish the 2,5-dialkyl-3,4-dihydro-2*H*-1,2,5-thiadiazine-6(5*H*)-thiones (**47**) in ca. 70% yield (Equation (5)). With bulky substituents (e.g., R = cyclohexyl or isopropyl) yields are good (70%), whereas the diethyl compound (**48**; R = Et) (see Section 6.15.4.1) is obtained in an unspecified low yield.

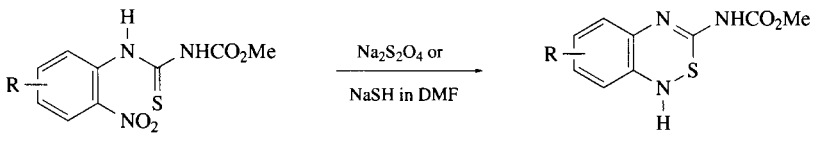


(46) (47) (5)

The first recorded example of a 2,1,4-benzothiadiazine appears to be the 3-phenylamino-1*H*-derivative (**49**) which was obtained as a yellow crystalline solid by oxidative ring-closure of *N*-(2-aminophenyl)-*N*′-phenylthiourea (**48**) with aqueous ferric chloride (Equation (6)) ⟨29JIC181⟩. In a related manner, reduction of the *N*-(2-nitroaryl)-*N*′-(methoxycarbonyl)thioureas (**50**) with sodium dithionite ⟨71GEP2108461, 88IJC(B)672⟩ or with sodium hydrosulfide in DMF ⟨72GEP2215733⟩ affords the 3-methoxycarbonylamino-1*H*-2,1,4-benzothiadiazines (**51**) (Equation (7)), the *S*-oxides of which (see Section 6.15.4.2) are useful anthelmintics (see Section 6.15.9).



(48) (49) (6)



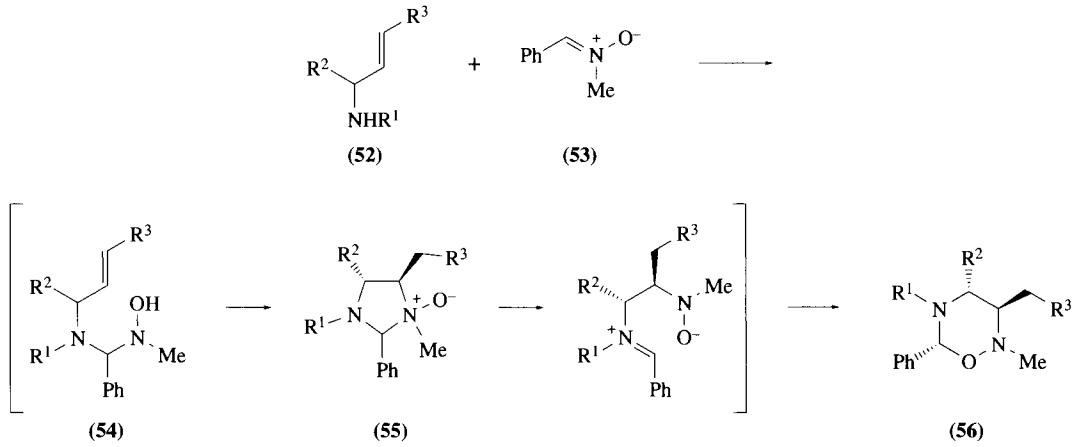
(50) (51) (7)

6.15.6.2 By Formation of Two Bonds

6.15.6.2.1 [3 + 3] fragments

(i) From C—C—N and C—N—O fragments

3,4,5,6-Tetrahydro-2*H*-1,2,5-oxadiazines (**56**) are obtained stereospecifically in an intriguing reaction of allylamines (**52**) with *C*-phenyl-*N*-methylnitrone (**53**) ⟨93CC169⟩. With allylamine (**52**; $R^1 = R^2 = R^3 = H$), the reaction proceeds slowly (7 days) in chloroform at room temperature, but more rapidly (36 h) and quantitatively at 45 °C. Under more vigorous conditions (boiling toluene for 17 h) oxadiazine (**56**; $R^1 = R^2 = R^3 = H$) (80%) is accompanied by the imine ($PHCH{=}N\text{-}CH_2CH{=}CH_2$; 20%). Imines are the major products with substituted primary allylamines, for example, (*E*)-cinnamylamine, and also with more sterically hindered nitrones such as *N*-benzyl and *N*-*t*-butyl-*C*-phenylnitrone. A mechanistic rationale has been proposed to account for oxadiazine formation which involves initial addition of the allylamine, to the nitrone followed by proton transfer and formation of the imidazolidine *N*-oxide (**55**) by a retro-Cope elimination as indicated in Scheme 8. Reaction is completed by a ring-expansion of the *N*-oxide to the oxadiazine via a Meisenheimer rearrangement. The imine probably arises by a competing allylamine–hydroxylamine exchange in the initial adduct (**54**). Imine formation can be eliminated by using secondary rather than primary allylamines, in which case the 1,2,5-oxadiazines are obtained, generally in excellent yields (80–100%). The stereospecificity of these reactions is confirmed by nOe. measurements and by the coupling constants of the ring protons in the trimethyl- (**56**; $R^1 = R^2 = Me$, $R^3 = H$) and 5-butyl-4-phenyl- (**56**; $R^1 = Bu$, $R^2 = Ph$, $R^3 = H$) derivatives, both of which have the oxadiazine ring in the chair conformation with the phenyl, R^2, and R^3CH_2 groups occupying equatorial positions.



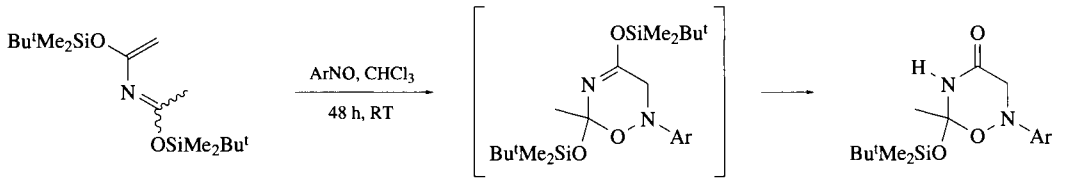
Scheme 8

6.15.6.2.2 [4 + 2] fragments

(i) From C—C—N—C and N—O fragments

The 2-aza-1,3-butadiene (**57**), prepared by the action of *t*-butyldimethylsilyl triflate on diacetimide (MeCONHCOMe), undergoes Diels–Alder cycloaddition with nitrosoarenes to yield 2-aryl-6-(*t*-butyldimethyl)silyloxy-6-methyl-5,6-dihydro-2*H*-1,2,5-oxadiazin-4(3*H*)-ones (**58a**) and (**58b**) (Scheme 9) ⟨87HCA1255⟩. The yield is moderate (53%) with 2-nitronitrosobenzene but poor (13%) with the 4-chloro nitroso-compound.

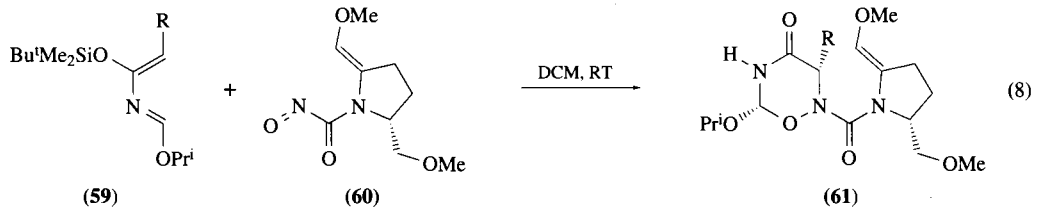
Another application of the reaction employing the chiral acylnitroso compound (**60**) and dienes (**59**) leads to regiospecific cycloaddition with high (>90%) facial selectivity to yield, after flash chromatography and recrystallization, the enantiomerically pure 5,6-dihydro-2*H*-1,2,5-oxadiazin-4(3*H*)-ones (**61**; R = Me, Ph or $PhCH_2$) (Equation (8)) ⟨91TL5349⟩.



(57)

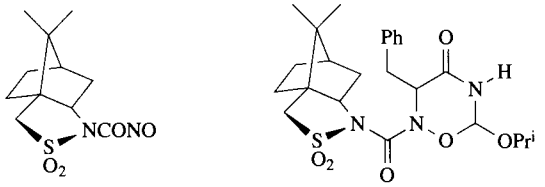
(58a) Ar = 2-$O_2NC_6H_4$
(58b) Ar = 4-ClC_6H_4

Scheme 9



(59) (60) (61) (8)

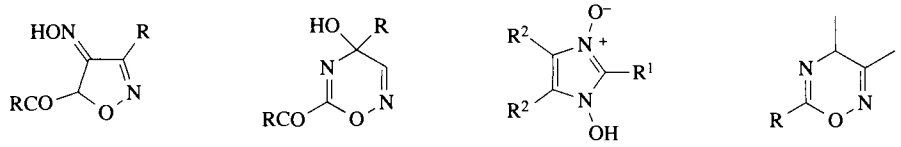
In contrast, with the acylnitroso compound (**62**) derived from the commercially available sultam as chiral auxiliary, the 1,2,5-oxadiazin-4(3*H*)-one (**63**) is obtained in low yield (25%), and could not be separated from the many reaction products ⟨91TA1173⟩.



(62) (63)

(ii) From C—C—N—O and C—N fragments

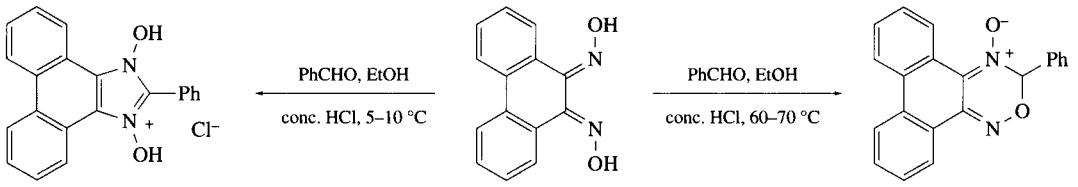
Originally, the products from the acid-catalyzed self-condensation of ketoaldehyde monoximes were formulated as 5-acyl-4-hydroxyimino-4,5-dihydroisoxazolines (**64**) ⟨1897CB1292⟩, structures which later were revised to 6-acyl-4-hydroxy-4*H*-1,2,5-oxadiazines (**64**) ⟨23G311, 26G713⟩. However, Polish workers, on the basis of chemical and spectroscopic evidence together with pK_a measurements, have proposed that the supposed 6-acyl-4-hydroxy-4*H*-oxadiazines are in fact 2-acyl-1-hydroxyimidazole 3-oxides (**66**; R^1 = acyl) ⟨74RZC345⟩. Likewise, the products obtained from the condensation of 2,3-butanedione monoxime with aldoximes (RCH=NOH), which have been represented as 6-alkyl-3,4-dimethyl-4*H*-1,2,5-oxadiazines (**67**) ⟨05CB3357, 64AC(R)1364⟩ have been reformulated, again on the basis of chemical and ^{1}H NMR spectroscopic evidence, as 1-hydroxy-2,4,5-trialkylimidazole 3-oxides (**66**; $R^1 = R^2$ = alkyl) ⟨64JOC1620, 65AP(298)293⟩.



(64) (65) (66) (67)

The formation of 1-hydroxyimidazole 3-oxides had been reported in the mid 1940s in a closely related reaction involving the condensation of dimethylglyoxime with benzaldehyde ⟨45G216⟩. In contrast, the products formed from the condensation of phenanthraquinone dioxime (**68**) with benzaldehyde have been shown to be temperature dependent ⟨69CB4177⟩. At low temperature (5°C) the phenanthro[9,10-*d*]imidazole *N*-oxide is obtained as the hydrochloride (**69**) in 85% yield.

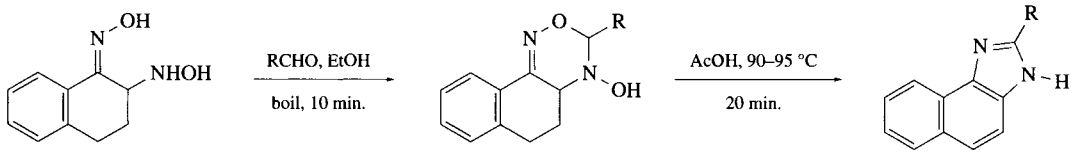
However, if the condensation is carried out in hot ethanol at 60–70 °C, 3-phenyl-3*H*-phenanthro[9,10-*c*][1,2,5]oxadiazine 4-oxide (**70**) is obtained as the major product (85%; m.p. 184–188 °C) along with the hydroxyimidazole *N*-oxide (**69**; 8%) (Scheme 10).



(69) (68) (70)

Scheme 10

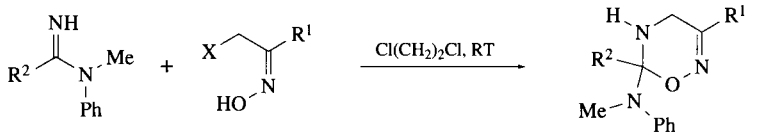
Similarly, the products formed by condensation of aldehydes with the tetrahydronaphthalene (**71**) have been formulated as the 3-hydroxytetrahydronaphtho[1,2-*c*][1,2,5]oxadiazines (**72**; R = H, Me and Et) (63–70%) which, in hot glacial acetic acid, are converted into the 2-alkyl-naphtho[1,2-*d*]imidazoles (**73**) supposedly via naphtho[1,2-*d*]imidazole *N*-oxides (Scheme 11) ⟨64JOU227⟩. Ring-contractions of 1,2,5-oxadiazines to imidazole 1-oxides have also been reported ⟨37JPR1, 70CHE1180⟩.



(71) (72) (73)

Scheme 11

Condensation of an α-haloketoxime (**75**) and an excess (5 equiv.) of an amidine (**74**) at room temperature produces a 5,6-dihydro-4*H*-1,2,5-oxadiazine (**76**) in moderate yield (50%) (Equation (9)) ⟨83CL341⟩.

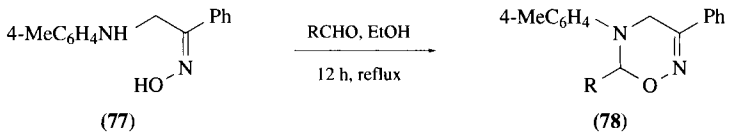


(74) (75) (76) (9)

6.15.6.2.3 [5 + 1] fragments

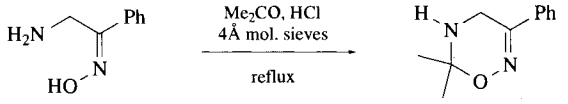
(i) From N—C—C—N—O and C fragments

In view of the revision of the structures of the supposed 1,2,5-oxadiazines discussed in the previous Section, it would now appear that the condensation of the (*E*)-oxime of an *N*-phenacylarylamine (e.g., **77**) with benzaldehyde to give a 3,5,6-triaryl-5,6-dihydro-4*H*-1,2,5-oxadiazine (e.g., **78**; R = Ph) (Equation (10)) constitutes the first successful synthesis of this ring-system ⟨30CB649, 37JPR(150)1, 66CHE591⟩. The 6-benzoyl derivative (**78**; R = PhCO) has also been obtained by using phenyl glyoxal (PhCOCHO) in place of benzaldehyde ⟨81CB3170⟩, whereas with methanal the 3,5-diaryl-derivative (**78**; R = H) is produced ⟨37JPR(150)1⟩. Interestingly, the (*Z*)-oximes undergo ring-closure to yield 1,4-diaryl-1,5-dihydro-2*H*-imidazoline 3-oxides ⟨74ZN(B)234⟩.



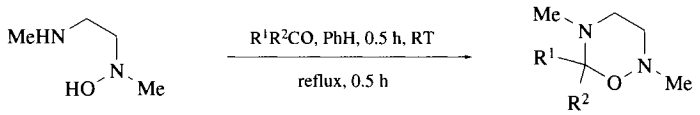
(77) (78) (10)

A variation of the high-yielding reaction (**77**) → (**78**) involves the acid catalyzed condensation of acetone with α-aminoacetophenone oxide (**79**) to yield 6,6-dimethyl-3-phenyl-5,6-dihydro-4*H*-1,2,5-oxadiazine (**80**) (Equation (11)) ⟨88EUP265169⟩ which is used as a masked acyl group in the stereoselective synthesis of 3-α-(hydroxyethyl)-4-β-acyl-β-lactams (see Section 6.15.4.2).



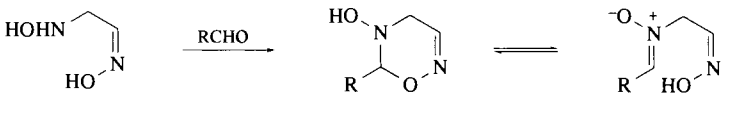
(79) (80) (11)

Fully saturated 1,2,5-oxadiazines (**82**) are accessible as stable colourless oils from condensation of aldehydes and ketones with the β-aminoethylhydroxylamine (**81**) (Equation (12)) which is derived by ring opening of 1-methylaziridine with *N*-methylhydroxylamine ⟨79JCS(P2)993⟩. Yields are excellent (80–90%) with aldehydes ($R^1 = R^2 = H$; and $R^1 = H$, $R^2 = Me$) but only moderate (43%) with acetone ($R^1 = R^2 = Me$).



(81) (82) (12)

If β-hydroxyiminoethylhydroxylamines (e.g., **83**) are used in place of the β-aminoethyl compound (**81**) then 5-hydroxy-5,6-dihydro-4*H*-1,2,5-oxadiazines (**84**) are produced which, on the basis of their PMR spectra, appear to be in equilibrium in solution with the open chain nitrone tautomers (**85**) (Equation (13)) ⟨69JOU341⟩.

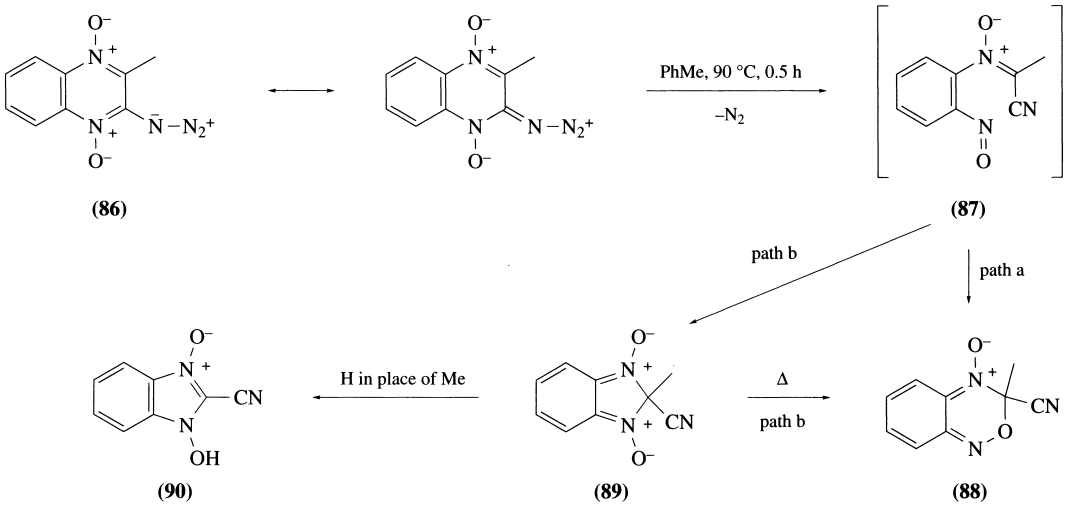


(83) (84) (85) (13)

6.15.7 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

3-Cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-oxide (**88**), formed in 94% yield by thermal decomposition of 2-azido-3-methylquinoxaline 1,4-dioxide (**86**) in boiling toluene, appears to be the only example of the 2,1,4-benzoxadiazine ring system ⟨78JOC76⟩. Thermolysis of the azide for a short time (10 min) in boiling benzene followed by careful chromatographic separation of the products on silica gel affords a mixture of the 2,1,4-benzoxadiazine oxide (**88**; 41%) and the violet 2*H*-benzimidazole 1,3-dioxide (**89**; 45%). A mechanistic rationale (Scheme 12) is proposed in which the 1,2,5-benzoxadiazine 4-oxide is formed either directly from the nitroso nitrone intermediate (**87**; path a), or, as is more likely, by rearrangement of the 2*H*-benzimidazole dioxide (**89**). The benzimidazole dioxide rearranges to the 2*H*-benzoxadiazine on further heating in benzene, although attempts to effect an analogous rearrangement of 2,2-dimethyl-2*H*-benzimidazole 1,3-dioxide have failed. Not surprisingly, in the absence of the 3-methyl substituent in the quinoxaline dioxide (**86**) neither the 2,1,4-benzoxadiazine oxide nor the 2*H*-benzimidazole dioxide are isolated, as the 2*H*-benzimidazole dioxide (**89**; H in place of methyl) can now aromatize to the more stable 2-cyano-1-hydroxy-1*H*-benzimidazole 3-oxide (**90**).

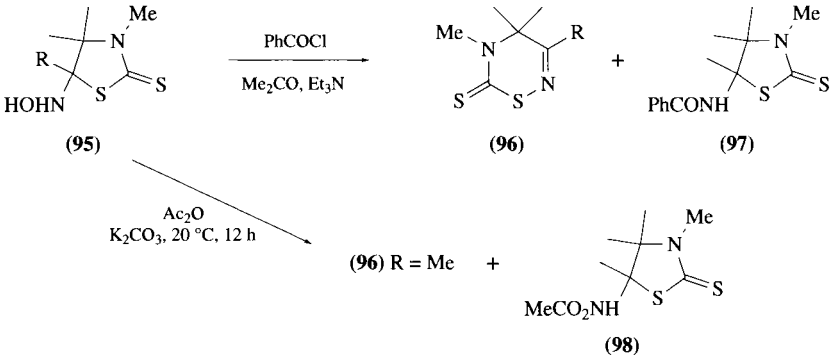
The rare 1,2,5-thiadiazine ring system (see Section 6.15.1) is accessible by two routes, both of which involve the ring expansion of a five-membered heterocycle. In the earlier synthesis, treatment of the 1,2,5-thiadiazolium chloride (**91**) with an equivalent of cyanide ion results in nucleophilic



(86) (87) (88) (89) (90)

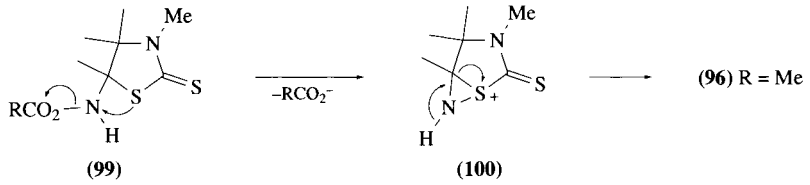
Scheme 12

attack at sulfur to yield the open chain amidino iminothiocyanate (**92**), which promptly ring closes



Scheme 14

this ring-transformation is not yet clear an interesting possibility is via the thiaziridinium intermediate (**100**) formed by intramolecular sulfur attack at the developing nitrenium ion centre (**99**) as outlined in Scheme 15.



Scheme 15

6.15.8 GENERAL SYNTHETIC METHODS

6.15.8.1 1,2,5-Oxadiazines and 2,1,4-Benzoxadiazines

The 1,2,5-oxadiazine ring-system is prepared by the addition of allylamines to nitrones (see Section 6.15.6.2.1.1), by [4 + 2] cycloaddition of 2-aza-1,3-butadienes with nitrosoarenes (see Section 6.15.6.2.2.1), and by condensation of α-haloketoximes with amidines (see Section 6.15.6.2.2.2). High yields of 1,2,5-oxadiazines are also obtained by condensation of the (*E*)-oximes of *N*-phenacylarylamines with aldehydes and ketones (see Section 6.15.6.2.3.1).

The thermal decomposition of 2-azido-3-methylquinoxaline 1,4-dioxide appears to be the only route so far to the 2,1,4-benzoxadiazine system (see Section 6.15.7).

6.15.8.2 1,2,5-Thiadiazines and 2,1,4-Benzothiadiazines

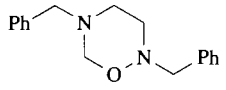
1,2,5-Thiadiazin-6-thiones are prepared by oxidative cyclization of *N*-acyl-*N'*-(β-alkylaminoethyl)-dithiocarbamic acids (see Section 6.15.6.1), by ring expansion of 5-hydroxy-aminothiazolidine-2-thiones under acylating conditions (see Section 6.15.7), and by the ring-expansion of 1,2,5-thiadiazolium salts in the presence of cyanide ion (see Section 6.15.7).

2,1,4-Benzothiadiazines are accessible by oxidative cyclization of *N*-(2-aminophenyl)-*N'*-phenylthioureas (see Section 6.15.6.1) and by reduction of *N*-(2-nitroaryl)-*N'*-methoxy-carbonylthioureas (see Section 6.15.6.1).

6.15.9 IMPORTANT COMPOUNDS AND APPLICATIONS

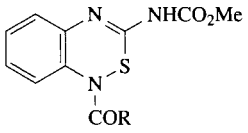
Only a few applications of these ring systems have been reported.

2,5-Dibenzyl-3,4,5,6-tetrahydro-2*H*-1,2,5-oxadiazine (**101**) has been used as a fading preventative in color photography ⟨88JAP(K)63149642⟩.



(101)

N-(1-Acyl-1*H*-2,1,4-benzothiadiazine-3-yl)carbamates (**102**) (see Section 6.15.6.1) and their 2-oxides are reported to have fungicidal and acaricidal activity ⟨71GEP2108461⟩, whereas the 7-acyl (**103**; X = RCO) ⟨72GEP2215733, 75GEP2332486⟩, 7-arylsulfonyloxy (**103**; X = $ArSO_2O$) ⟨77GEP2541742⟩, and 7-arylthio (**103**; X = ArS) ⟨76GEP2438099⟩ derivatives are notable anthelmintics.



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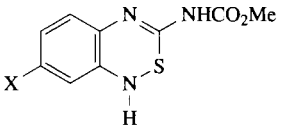

(103)

2,5-Dialkyl-3,4-dihydro-2*H*-thiadiazine-6(5*H*)-thiones (see Section 6.15.6.1) have been used in the vulcanization of rubber ⟨50USP2514200, 51USP2537633⟩ and as insecticides and agricultural fungicides ⟨51USP2537633⟩.

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6.16
1,2,6-Oxadiazines and 1,2,6-Thiadiazines

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University of Salford UK

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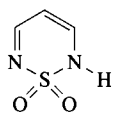
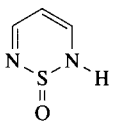
6.16.1 INTRODUCTION

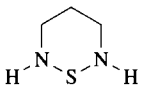
The most common of the systems discussed in this Chapter are the 1,2,6-thiadiazine 1,1-dioxides which are known mainly as the 2*H*-derivatives (**1**). 2*H*-1,2,6-Thiadiazine 1,1-dioxide (**1**) itself is noncrystalline ⟨82JOC536⟩ but is readily purified via the crystalline potassium salt ⟨90ACS726⟩. Much less common are the monoxides (**2**) and the nonoxygenated compounds (**3**), the latter having been prepared only as the hydroderivatives (Sections 6.16.9.2.1.1 and 6.16.9.2.3.1).



(**1**)



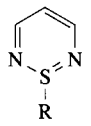
(**2**)



(**3**)

Examples of the $1\lambda^4$,2,6-thiadiazines (**4**) (Section 6.16.9.2) (see also ⟨69TL4117, 76CB2442⟩) and $1\lambda^6$,2,6-thiadiazines have been described, the latter as the 1,1-dialkyl-3-one derivatives (**5**) (Section 6.16.9.2.1.1). Of the benzologues, the 2,1,3-benzothiadiazine 2,2-dioxides are well documented, particularly the 4(3*H*)-one derivative (**6**; R = $CHMe_2$) which is of commercial importance (Section 6.16.12). Less common are the monoxides (**7**), and the $2\lambda^6$,1,3-benzothiadiazines which, like the monocycles, are known as the 2,2-dialkyl-4-one derivatives (**8**) (Section 6.16.9.1.2). No examples of aromatic oxonia- (**9**; X = O) and thionia- (**9**; X = S) systems have been reported.

Peri-fused systems, e.g. (**10**), are known; they have been reviewed ⟨90AHC(51)1⟩, but no work seems to have been reported on them since the early 1990s.



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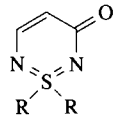

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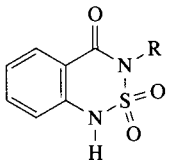

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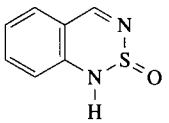

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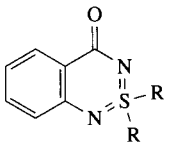
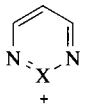


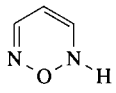
(**8**)



(**9**)

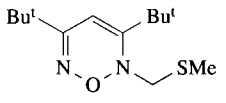
(**10**)

The 1,2,6-oxadiazine ring system (**11**) is much less common. Some reports concerning this system are incorrect, while others are unsubstantiated (see Section 6.16.9.1.3).



(**11**)

2-(Methylthiomethyl)-3,5-di-*t*-butyl-2*H*-1,2,6-oxadiazine (**12**) has been identified tentatively as one of the many impurities in a technical grade sample of the insecticide Thiofanox ⟨85MI 616-01⟩. 2,1,3-Benzoxadiazines (**13**) appear to be unknown.



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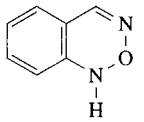
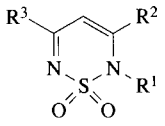


(13)

The chemistry of 1,2,6-thiadiazine 1,1-dioxides, and other heterocycles containing the sulfamide (—$NHSO_2NH$—) fragment, have been reviewed by Spanish workers who have been extremely active in this field ⟨88AHC(44)81⟩. 1,2,6-Thiadiazines, and their benzologues, other than the S,S-dioxides have also been reviewed ⟨90AHC(50)255⟩. The herbicidal activity of 3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (Bentazone; **6**, R = $CHMe_2$), an important commercial product has been appraised ⟨89CI(M)30⟩.

6.16.2 THEORETICAL METHODS

Few theoretical studies on the title compounds have been carried out. A CNDO/2 method for estimating dipole moments, which is successful for a variety of heterocyclic systems, produces calculated dipole moments for 2*H*-1,2,6-thiadiazine 1,1-dioxides (**14**) which are consistently higher (by 2–2.5 units) than experimentally determined values in dioxan solution ⟨82JOC536⟩. In contrast, dipole moments calculated by classical vectorial methods are much more in agreement with experimental values. The error in the CNDO/2 derived values probably arises from lone pair repulsions between N-6 and the SO_2 group, which are not described adequately by the CNDO/2 method.



(14)

Comparison of the experimentally determined dipole (6.42 D) for tautomeric 5-methyl-1,2,6-thiadiazine 1,1-dioxide with the vectorially calculated values for individual tautomers (**15**) and (**16**) has been used to determine the equilibrium position of this tautomeric system ⟨82JOC536⟩ (Section 6.16.4.2).

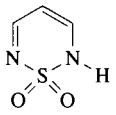
(15) (16)

A rough correlation between experimentally determined ^{13}C NMR chemical shifts and total charge densities, as calculated by the CNDO/2 method, has been proposed for 1,2,6-thiadiazine 1,1-dioxides ⟨82JOC536⟩.

A detailed comparative study of the chemistry of 1,2,6-thiadiazine 1,1-dioxides and related pyrazoles has been carried out ⟨82JOC536⟩. Useful comparisons can be made regarding tautomeric equilibria, ^{13}C NMR chemical shifts, and the general reactivity of the 4-positions. As expected however, the lack of aromaticity of the 1,2,6-thiadiazine 1,1-dioxide system (Section 6.16.4.1) imparts substantial differences to their general chemistry.

Ab initio calculations on the three tautomeric forms of 2*H*-1,2,6-thiadiazine 1,1-dioxide reveals that for the 2*H*- (**17**) and 4*H*- (**20**) tautomers the planar conformers are less stable than the nonplanar boat conformers by 2.7 and 1.2 kcal mol^{-1}, respectively. For the 3,5-dimethyl- derivative there is reasonable agreement between the calculated bond angles and those obtained by x-ray crystallographic measurements ⟨90JPO470⟩. In contrast, for the fully conjugated tautomer (**18**) theoretical calculations reveal that the planar form is the more stable and that aromatic character is to be

expected. However, more refined calculations reveal that this tautomer, for which only one example has been reported (Section 6.16.4.1), is best represented as a delocalised ylide (**19**) containing S—N single bonds.



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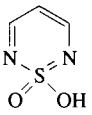

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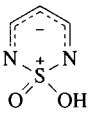

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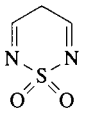


(20)

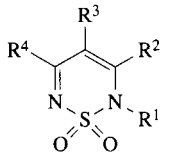
6.16.3 EXPERIMENTAL STRUCTURAL METHODS

6.16.3.1 Spectroscopic Studies

6.16.3.1.1 Ultraviolet and infrared spectra

UV Spectroscopy has been instrumental in determining not only the tautomeric nature of 1,2,6-thiadiazine 1,1-dioxides and their oxo-derivatives, but also the site of alkylation and glycosylation of these systems and of 1,2,6-thiadiazine 1,1-dioxides fused to other heterocyclic rings, for example pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides. A detailed account of these studies is available ⟨88AHC(44)81⟩, as is a brief review on the UV spectra of 1,2,6-thiadiazine 1,1-dioxides ⟨70CRV593⟩.

As expected, fully saturated 1,2,6-thiadiazine 1,1-dioxides are UV transparent in the region 200–400 nm ⟨82H(17)401⟩. 2*H*-1,2,6-thiadiazine 1,1-dioxides (**21**) ⟨65CI(L)182⟩ and 4*H*-1,2,6-thiadiazine 1,1-dioxides (**22**) ⟨81JHC27⟩ display UV absorptions at 250 nm and 323 nm, and at 250 nm and 290 nm, respectively. 5-Amino-2*H*-1,2,6-thiadiazine 1,1-dioxides (**21**; $R^4 = NH_2$) show two maxima at 243 nm and 290 nm ⟨79JOC4191⟩, whereas the 5-alkoxy-derivatives (**21**; R^4 = O-alkyl) show only one absorption at 290 nm ⟨82H(17)401, 88JCR(S)94⟩. Detailed UV data is also available on 6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxides (**23**) ⟨82H(17)401, 88JCR(S)94⟩ and on 4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxides (**24**) ⟨87CJC298⟩. 3,4-Dihydro-2*H*-1,2,6-thiadiazine 1,1,6-trioxides (**25**) (Section 6.16.9.2.3.1) are reported to have absorption maxima at 228–240 nm ⟨90LA775⟩.



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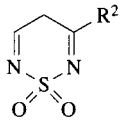

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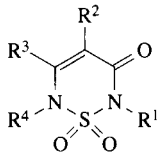

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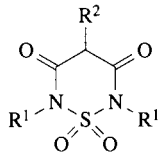

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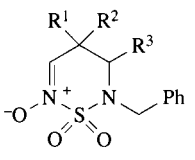
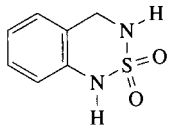


(25)

The spectroscopically determined pK_a value (3.92 ± 0.04) for 4-butyl-2,6-diphenyl-4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxide (**24**; R^1 = Ph, R^2 = Bu) is significantly and unexpectedly different from those of the 2,6-dicyclohexyl derivatives (**24**; $R^1 = C_6H_{11}$, R^2 = H; pK_a 6.04 ± 0.11) and (**24**; $R^1 = C_6H_{11}$, R^2 = Bu; pK_a 6.18 ± 0.06) ⟨87CJC298⟩.

Cyclic sulfamides, like the corresponding cyclic sulfonamides ⟨79JCS(P1)1043⟩ appear to be substantially more acidic than their acyclic counterparts as witnessed by their pK_a values which, on average, are some 2.5 units greater ⟨84JCS(P2)1851⟩. For example, the 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (**26**) has a pK_a of 8.79 compared to *N*-phenyl-N^1-cyclohexylsulfamide (pK_a 11.4) and *N*-(*p*-tolyl)-N^1-butylsulfamide (pK_a 11.34). No explanation of this discrepancy is offered although it is suggested tentatively that the increased acidity of the cyclic compounds is due to overlap of the sulphur *d*-orbitals with the lone pair on nitrogen.



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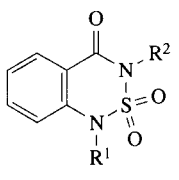


(27)

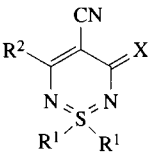
The highly acidic 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (**27**; $R^1 = R^2 = H$) in ethanol solution has UV absorption maxima at 312 and 345 nm ⟨62JA1994⟩. The 3-methyl derivative (**27**; $R^1 = H$, $R^2 = Me$) behaves similarly, whereas with the 1,3-dimethyl derivative (**27**; $R^1 = R^2 = Me$) a hypsochromic shift occurs and a single absorption maximum at 305 nm is observed.

1,2,6-Thiadiazines absorb at 277 nm ⟨69TL4117⟩ and in conjugation with other chromophoric groups result in deeply coloured heterocyclic systems ⟨79PS(7)61⟩.

There are no particular distinguishing features present in the IR spectra of 1,2,6-thiadiazine 1,1-dioxides. The (S=O) stretching vibrations appear at 1310–1360 cm^{-1} and 1150–1180 cm^{-1} ⟨88AHC(44)81⟩. The N=S=N moiety in 1λ^4,2,6-thiadiazines absorbs at 1020 cm^{-1} and 1135 cm^{-1} corresponding to ν(sym) and ν(asym), respectively ⟨69TL4117⟩.

1,1-Dialkyl-1λ^6,2,6-thiadiazin-3-ones (**28**; X = O) (Section 6.16.9.2.1.1) have ν(C=C) and ν(C=O) at 3020–3060 cm^{-1} and at 1600–1630 cm^{-1}, respectively ⟨85CB2561⟩, while the imines (**28**; X = NH) display ν(NH) at 3230–3275 cm^{-1} ⟨87CB1455⟩

Detailed infrared data is available for 1-alkyl-3-amino-4-cyano-1λ^4,2,6-thiadiazines (**29**) and for 1-alkyl-4-cyano-5-methylthio-1λ^4,2,6-thiadiazin-3(2*H*)-ones (**30**) (Section 6.16.9.2.1.1) ⟨87CB1455⟩.



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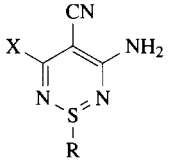

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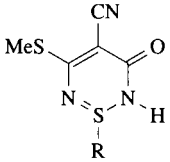
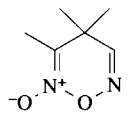


(30)

6.16.3.1.2 NMR spectra

(i) Proton NMR spectra

The pair of isomeric 1,2,6-oxadiazine N-oxides (**31**) and (**32**) (Section 6.16.9.1.3) have been identified tentatively on the basis of the ^1H NMR spectrum of the isomer mixture ⟨85JHC293⟩. The 2 singlets at 1.91 δ and 1.93 δ are assigned to the 3- and 5-methyl groups, respectively, whereas the singlets at 5.67 δ and 5.73 δ are identified with the C-3 and C-5 protons.



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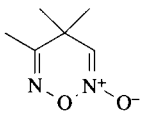
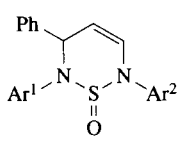


(32)

The C-3 proton of the 2,3,6-triaryl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1-oxide (**33**) lies in the deshielding zone of the sulfoxide group and hence appears as a low field doublet at 9.0 δ ⟨88IJC(B)843⟩. The C-4 proton is merged in the aromatic multiplet, whereas the proton at C-5 is a doublet (J 9.0 Hz) at 6.9 δ. In contrast, the C-3 protons in the 5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide dicarboxylates (**34**) appear as singlets at 7.3–7.5 δ, with the C-5 protons as multiplets at 4.5–4.8 δ ⟨90JHC2107⟩.

The proton and ^{13}C resonances for 2*H*-1,2,6-thiadiazine 1,1-dioxide accompany diagram (**35**) ⟨82JOC536⟩.



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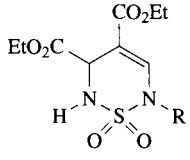

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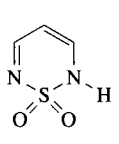


(35)

δCDCl$_3$ (d$_6$-DMSO)				δd$_6$-DMSO		
H-2	H-3	H-4	H-5	C-3	C-4	C-5
3.54	7.28	5.85	7.94	155.0	98.7	155.0
(~8.8)	(7.88)	(5.94)	(7.88)			

$J_{3,4} = J_{4,5} = 5.65$ Hz

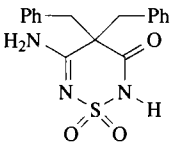
The ring protons of substituted 2*H*-1,2,6-thiadiazine 1,1-dioxides located at sp^2 carbon centers have chemical shifts in the region 4.7–8.5 δ and vicinal coupling constants across the C=C bond of $J_{3,4} = 7.0$–7.4 Hz ⟨82JOC536, 85T3105⟩. In *N*-unsubstituted 1,2,6-thiadiazine 1,1-dioxides, protons at

C-3 and C-5 are equivalent as a consequence of prototropic exchange between N-2 and N-6 ⟨82JOC536⟩. Hydrogens located at sp^3 carbon centers of saturated or partially saturated 1,2,6-thiadiazine 1,1-dioxides appear at 2.4–3.5 δ and have J values of 4.5–4.9 Hz ⟨64JOC1865⟩.

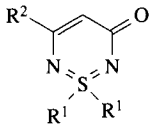
There is evidence to suggest that the isomeric N-2 and N-6 monomethyl derivatives of 1,2,6-thiadiazin-3-ones (**23**) can be distinguished by means of the chemical shifts of the *N*-Me groups. The 2-methyl compounds (**23**; R^1 = Me, R^4 = H) absorb at 3.1 δ ⟨81JHC459, 82H(17)401⟩, whereas the 6-Me isomers (**23**; R^1 = H, R^4 = Me) absorb downfield at 3.6 δ. There are however, exceptions, notably the 2,6-dimethyl derivatives (**23**; $R^1 = R^4$ = Me) in which the difference in chemical shift of the two methyl groups is only 0.1 ppm ⟨82H(17)401, 86EJM531⟩. For *N*-substituted 1,2,6-thiadiazine 1,1-dioxides, coupling between adjacent ring-protons is always $J_{3,4} > J_{4,5}$. ⟨82JOC536⟩.

The 4-methylene group in 4*H*-1,2,6-thiadiazine-3,5 (2*H*,6*H*)-dione 1,1-dioxides (**24**; R^2 = H) is seen generally as a singlet at 3.0–4.15 ppm ⟨86JCS(P1)643⟩ except for *N*-nucleoside derivatives, in which case the methylene protons appear as doublets with geminal coupling of −18Hz ⟨87MI 616-03⟩.

Proton NMR spectroscopic and dipole moment measurements indicate that the heterocyclic ring of 5-amino-4,4-dibenzyl-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**36**) has the same planar structure in solution as in the solid state ⟨88CJC2477⟩.



(**36**)

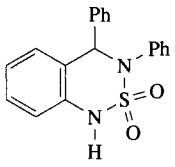


(**37**)

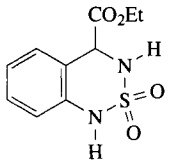
The comprehensive review by Arán *et al* ⟨88AHC(44)81⟩ should be consulted for details of other PMR data on 1,2,6-thiadiazine 1,1-dioxides and on 1,2,6-thiadiazine 1,1-dioxide systems fused to other heterocyclic rings.

In d^6-DMSO solution the C-4 protons of 1,1-dialkyl-1λ^6,2,6-thiadiazin-3-ones (**37**) resonate at 4–4.9 δ ⟨85CB2561⟩.

There are no detailed studies on the PMR spectra of 2,1,3-benzothiadiazines. A chemical shift of 6.93 δ has been reported for the C-4 proton of 3,4-diaryl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides (**38**) ⟨85TL2813⟩. Coupling of 7.7 Hz is noted between the C-4 proton (5.35 δ) and the proton on N-3 (7.9 δ) for ethyl 3,4-dihydro-1*H*-2,1,3-benzothiadiazine-4-carboxylate 2,2-dioxide (**39**). ⟨90JOC6098⟩. The proton at N-1 appears as a singlet at 10.35 δ.



(**38**)



(**39**)

(ii) ^{13}C NMR spectra

The 5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide dicarboxylates (**34**) display distinctive ^{13}C NMR resonances for C-3 and C-4 at 140–142 and 100–106 δ. ⟨90JHC2107⟩. In d^6-DMSO solution the C-5, C-4 and C-3 positions of 2*H*-1,2,6-thiadiazine 1,1-dioxides (**21**) have ^{13}C nuclear magnetic resonances in the range 160–178 δ, 69–105 δ and 148–164 δ, respectively ⟨82JOC536, 86EJM531, 86FES862, 88JCS(P1)1271⟩. For N-2 unsubstituted derivatives the signals for C-3 and C-5 often appear as broad peaks due to annular prototropic tautomerism. As expected, this broadening decreases with an increase in temperature ⟨82JOC536⟩.

Identification of pairs of isomers is possible by consideration of ^{13}C chemical shifts of an *N*-methyl group. In 3-substituted derivatives (e.g. **21**; $R^1 = R^2$ = Me, $R^3 = R^4$ = H) the C-13 signal for the *N*-Me group is seen at 31 δ whereas in the absence of the 3-substituent (e.g. **21**; R^1 = Me, $R^2 = R^3 = R^4$ = H) the signal shifts upfield to 35 δ ⟨82JOC536⟩. In addition, a Me group at C-5 appears at ~24.5 δ whereas the C-3 methyl group absorbs at ~20 δ.

The ^{13}C resonances for C-3 in 2,6-disubstituted 3-oxo derivatives (**23**) that are unable to form a lactim tautomer, occur at 155–162 δ, with C-5 and C-4 appearing at 150–153.5 and 98–105 δ, respectively. Not surprisingly, the actual position of these resonances is dependent on the relative electron donating or electron withdrawing ability of the ring substituents ⟨86MRC444, 88JCR(S)94⟩.

The ^{13}C chemical shifts for C-3 in 2,6-disubstituted 1,2,6-thiadiazine-3,5(2*H*,6*H*)-diones (**24**) are at 163–167 δ with the signal for the sp^3 carbon at position 4 appearing at 42–54 δ ⟨87CJC298⟩.

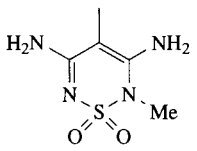
Detailed ^{13}C NMR spectroscopic data for a range of fused 1,2,6-thiadiazine 1,1-dioxides has also been reported ⟨88AHC(44)81⟩.

^{13}C NMR data is available for 5-substituted-1-alkyl-3-amino-4-cyano-1λ^4,2,6-thiadiazines (**29**) and for 5-substituted 1,1-dialkyl-3-imino-4-cyano-1λ^6,2,6-thiadiazines (**28**; X = NH) ⟨87CB1455⟩. For the former, the C-3, C-4, and C-5 resonances in d^6-DMSO occur at 173–176 δ, 68–70 δ, and 163–164 δ, respectively, except for the 5-phenyl derivative (**29**; X = Ph), in which the C-3 resonance is downfield (165.6 δ) of C-5, appearing at 173.3 δ. Presumably the upfield chemical shift of C-4 in these systems reflects the delocalisation of the negative charge at N-5 of the ylide form of the S=N linkage, to the C-4 position. Likewise, for the dicyano-3-imino-derivative (**28**; R^1 = Me; R^2 = CN, X = NH), C-4 appears at 52.08 δ, with C-3 and C-5 at 163.50 δ and 174.15 δ, respectively.

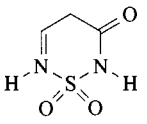
(iii) ^{15}N NMR spectra

(All ^{15}N resonance values cited in this Section refer to an increase in shielding with respect to nitromethane as external standard.)

The natural abundance ^{15}N NMR spectra of several 1,2,6-thiadiazine 1,1-dioxides have been measured and *J* values determined ⟨86MRC444, 88AQ89, 88JCS(P2)859⟩. For mononuclear 1,2,6-thiadiazine 1,1-dioxides (**35**), N-6 (the pyridine-like nitrogen) is seen at +130–165 δ, whereas N-2 (the pyrrole-like nitrogen) absorbs at +240–260 δ, except in the case of 3,5-diamino-2,4-dimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**40**) for which N-2 and N-6 appear at +261.9 δ and +214.7 δ, respectively. The amino resonances are seen at +290.6 (5-NH_2) and 302.6 (3-NH_2) with J_{N-H} coupling of 89.3 Hz and 89.7 Hz ⟨86MRC444⟩.



(40)



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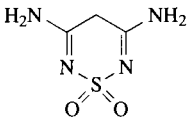


(42)

The ^{15}N resonance for N-2 adjacent to the carbonyl function in 6*H*-1,2,6-thiadiazin-3(2*H*)-one (**41**) is seen as a broad signal at +176.5 δ, whereas N-6 appears at 242.7 δ. In N-2 substituted 1,2,6-thiadiazin-3-ones the amide nitrogen resonance is generally seen at 204–245 δ ⟨86MRC444, 88JCS(P2)859⟩.

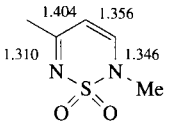
Significantly, the ^{15}N NMR spectrum of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**42**) ⟨86MRC444⟩ contains only two signals, at +164.9 δ and +277.6 δ ($J_{N,H}$ 90.3 Hz) corresponding to N-2, N-6, and the 3-NH_2 and 5-NH_2 groups, respectively. This result has led the authors to conclude that the molecule exists as the symmetrical 4*H*-tautomer (**42**) and not as the 6*H*-tautomer as suggested earlier on the basis of ^1H NMR data ⟨76JHC793⟩.

For the use of ^{15}N NMR spectroscopy in studying tautomerism of 1,2,6-thiadiazines and 1,2,6-thiadiazin-3-ones see Section 6.16.4.2.

6.16.3.1.3 X-Ray crystallography

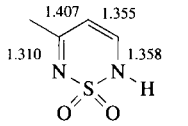
An 'envelope' conformation is indicated for 2,5-dimethyl- (**14**; $R^1 = R^3$ = Me, R^2 = H) and for 3,5-dimethyl- (**14**; R^1 = H, $R^2 = R^3$ = Me) 2*H*-1,2,6-thiadiazine 1,1-dioxide with the SO_2 group out of the plane of the ring and acting as the "flap" ⟨82JOC536⟩. Unlike the heteroaromatic pyrazoles with which they have been compared, and as expected for a nonaromatic structure, there are

significant differences in the C—C and S—N bond lengths of the heterocyclic ring (see diagrams (**43**) and (**44**)) ⟨82JOC536, 77AX(B)910, 79JOC4191⟩.



$S–N_2$ 1.672; $S–N_6$ 1.583

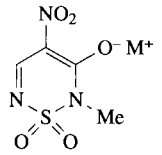
(**43**)



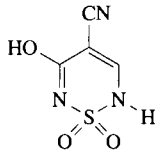
$S–N_2$ 1.591; $S–N_6$ 1.640

(**44**)

X-Ray crystal structures of the sodium and potassium salts of 3-hydroxy-2-methyl-4-nitro-2*H*-1,2,6-thiadiazine 1,1-dioxide (**45**; M = Na or K) ⟨83AX(C)440⟩, and of 4-cyano-5-hydroxy-2*H*-1,2,6-thiadiazine 1,1-dioxide (**46**) ⟨82AX(B)1128⟩ have been determined. X-Ray analysis of 5-hydroxy-4-nitro-2*H*-1,2,6-thiadiazine 1,1-dioxide (**46**; NO_2 in place of CN) confirms unequivocally the presence of the 5-hydroxy form in the solid state, and indicates the presence of strong intramolecular hydrogen bonding with the adjacent nitro group ⟨82AX(B)1124, 82AX(B)1340⟩.



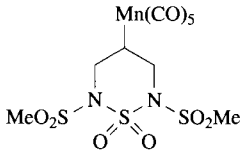
(**45**)



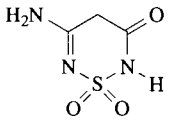
(**46**)

The structure of the 2,6-dimesyl-3,4,5,6-tetrahydro-2*H*-1,2,6-thiadiazine manganese pentacarbonyl complex (**47**) (Section 6.16.9.2.1.1) has been confirmed by x-ray analysis ⟨86OM846⟩. The thiadiazine ring is in the chair conformation and the S—N_2 and S—N_6 bond lengths lie between the normal S—N single and double bond values.

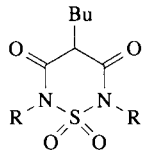
5-Amino-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**48**) has a monoclinic crystal structure with a flattened boat conformation. The SO_2 "prow" and the 4-CH_2 'stern' subtend angles of 27.5° and 25.3°, respectively, with the planar "hull" as defined by N_2—C_3—C_5—N_6 ⟨86AX(C)892⟩. Boat conformations have also been determined for 4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxides (**49**; R = cycloC_6H_{11} or Ph) ⟨87CJC298⟩.



(**47**)



(**48**)

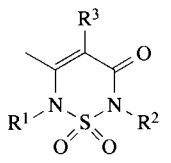


(**49**)

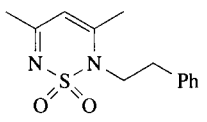
X-ray studies on 4-(4-chlorophenyl)-4,5-dihydro-3H-1λ^4,2,6-thiadiazine reveal that the ring is in a half-boat conformation with the aryl group occupying an equatorial position. The ring nitrogens are sp^2 hydridized, the N—S bond length is 1.534 Å, and the N=S=N bond angle is 118.5° ⟨76AG(E)782⟩.

In contrast, the orthorhombic 6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxides (**50**; R^1 = Me, R^2 = Ph, R^3 = H; R^1 = Ph, R^2 = Me, R^3 = H; and R^1 = Me, R^2 = Ph, R^3 = Br) are in the envelope conformation with the sulfur atom out of the plane of the other ring atoms ⟨88JCR(S)94⟩. 3,5-Dimethyl-2-phenethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**51**), which forms monoclinic crystals, adopts a quasi-planar conformation in the solid state, possibly caused by the bulky substituent at N-2 ⟨89AX(C)495⟩.

The x-ray analysis of 5-amino-4,4-dibenzyl-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide shows not

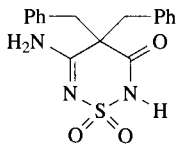


(**50**)



(**51**)

only that the molecule exists in the solid state as the amino-tautomer (**52**), but also that the heterocyclic ring is planar rather than in the more usual boat conformation. ⟨88CJC2477⟩.



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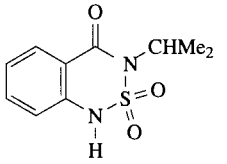

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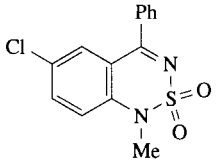


(54)

An x-ray crystallographic analysis of monoclinic 3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (Bentazone) (**53**), a long-established commercially important herbicide ⟨81AG(E)151⟩ (see Section 6.16.12), reveals that N-1 and C-4 are almost coplanar with the benzene ring whereas the sulfur atom is displaced from the plane of the ring by 0.7 Å ⟨86AX(C)1785⟩. The S—N-1 bond (1.666 Å) is longer that the S—N-3 bond (1.603 Å), a result in accord with the involvement of N-3 in amide resonance with the carbonyl function at C-4.

An x-ray crystallographic analysis of the unexpected byproduct formed in the synthesis of 6-chloro-1-methyl-4-phenylquinazolin-2(1*H*)-one ⟨80SC799⟩ reveals it to be 6-chloro-1-methyl-4-phenyl-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (**54**) ⟨83AX(C)358⟩. The x-ray data indicates that the sulfur is tetrahedral and that the phenyl ring is at an angle of 55° to the plane of the heterocyclic ring.

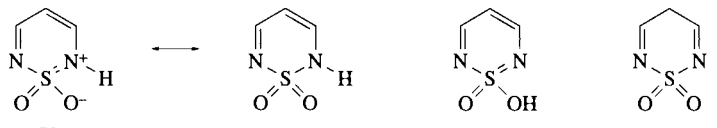
6.16.3.1.4 Mass spectra

No detailed mass spectral studies on 1,2,6-thiadiazine 1,1-dioxides have appeared since an earlier definitive report on their complex fragmentation patterns ⟨80JHC977⟩. However, the major fragmentations of 3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides and of 5-amino-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxides have been recorded ⟨88JCS(P1)1271⟩.

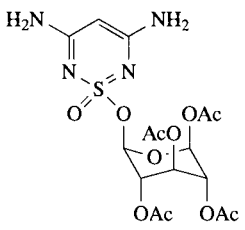
6.16.4 THERMODYNAMIC ASPECTS

6.16.4.1 Aromaticity

The possibility of aromaticity associated with the three tautomeric forms (**55**)–(**57**) of 1,2,6-thiadiazine 1,1-dioxide has been considered ⟨88AHC(44)81⟩. The 4*H*-tautomer (**57**) is nonaromatic, whereas *ab initio* calculations for the conjugated *S*-hydroxy form (**56**), which has not been observed experimentally other than as the *O*-(*β*)-D-glucopyranosyloxy tetraacetate (**59**) ⟨81JHC27⟩, indicate a delocalized ylide structure (**19**; see Section 6.16.2) ⟨90JPO470⟩ Aromatic resonance forms can be envisaged for the 2*H*-tautomer (e.g. **58**), but all physical and spectroscopic measurements, particularly PMR and x-ray studies, indicate nonplanar structures with localized double bonds ⟨82JOC536⟩. Although there is no evidence for sulfonamide resonance as required in mesomer (**58**), there is definite conjugation in the N2—C3=C4—C5—N6 fragment of the ring.



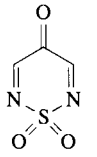
(58) (55) (56) (57)



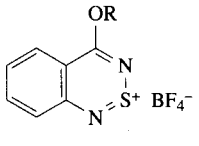
(59)

The existence of imino-tautomers (which are rarely seen with heteroaromatic amines) of 5-amino-1,2,6-thiadiazine 1,1-dioxides (see Section 6.16.4.2) has been attributed to the nonaromatic character of these systems ⟨82JOC536⟩.

In contrast, on the basis of a new aromaticity index (I_6) for six-membered heterocycles, 1,2,6-thiadiazin-4-one 1,1-dioxide (**60**) has been assigned an I_6 value of 54.2 (benzene $I_6 = 100$) and is reckoned to have moderate to low aromatic character and is deemed to be more aromatic than pyranones but less aromatic than 4-pyridones ⟨86T89⟩.



(60)



(61)

O-Alkylations of $2\lambda^4$,1,3-benzothiadiazin-4-ones with Meerwein's reagents ($R_3O^+BF_4^-$; R = Me or Et) yield 4-alkoxy-2, 1,3-benzothiadiazinium tetrafluoroborates (**61**) as crystalline solids which, on the basis mainly of resonance energies calculated on an Hückel molecular orbital model, have a resonance energy (0.313 β) comparable to that of naphthalene (0.389 β) and are deemed to be heteroaromatic ⟨77AG(E)780⟩. In addition, the strong deshielding (+15.5 ppm) of C-6 in the ^{13}C NMR spectrum is comparable to that of the diazonium group, and is indicative of a degree of π-electron delocalization in the system involving the strongly electron-withdrawing N=S$^+$—N function.

6.16.4.2 Tautomerism

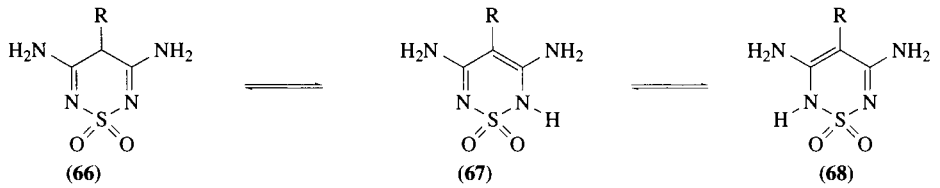
The prototropic annular and substituent tautomerism of 1,2,6-thiadiazine 1,1-dioxides and their 3-one derivatives have been investigated in great detail by Spanish workers ⟨88AHC(44)81⟩. On the basis of ^{13}C NMR chemical shifts and ^1H NMR coupling constants, 2*H*-1,2,6-thiadiazine 1,1-dioxides are shown to be in equilibrium (**62**)⇌(**63**) in dimethyl sulfoxide solution, the equilibrium being shifted in favor of the 2*H*-tautomer (**62**) with the less bulky substituent at the 3-position. ⟨82JOC536⟩. The tautomeric composition of 5-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide has been estimated to be 65% in favor of the 5-methyl-2*H*-tautomer (**62**; R^1 = Me, R^2 = H) by four different methods based on the ring proton coupling constants, and ^{13}C chemical shifts of the methyl group and ring carbons C-3 and C-5. In contrast, a comparison of the experimentally determined dipole moment (6.42 D) with the vectorially calculated value for the individual tautomers (**62**; 6.24 D) and (**63**; 6.52 D) indicates only 36% of the 5-methyl-2*H*-tautomer. However, as the authors point out, this discrepancy could be caused by a error of only 0.1 D in the experimentally determined moment.

(62) (63)

X-Ray crystallographic studies have shown that 5-amino-2*H*-1,2,6-thiadiazine 1,1-dioxide is present in the solid state as the amino-2*H*-tautomer (**64**) ⟨79JOC4191⟩. A comparison of $J_{H3,H4}$ (7.47) for the amino compound with other model compounds indicates that the same tautomer is also the favored form in solution ⟨82JOC536⟩. However, the vectorially calculated dipole moment for the 5-amino-1,2,6-thiadiazine 1,1-dioxide differs considerably (6.19 D) from the experimentally determined value (7.18 D) for the supposed tautomer (**64**). This result, together with the fact that the calculated charge densities do not correlate well with the ^{13}C chemical shifts, has led the authors to propose involvement of the imino-tautomer (**65**) in the equilibrium mixture ⟨82JOC536, 86EJM531⟩.

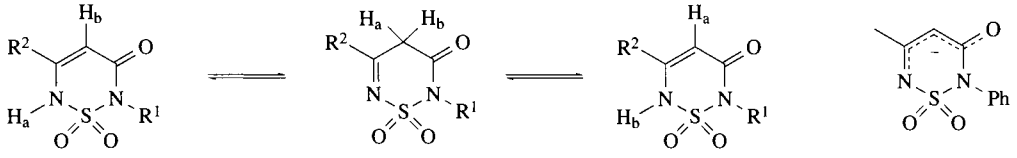
(64) (65)

Proton, ^{13}C, and ^{15}N NMR spectroscopic studies on 3,5-diamino-1,2,6-thiadiazine 1,1-dioxides in d^6-DMSO solution demonstrate that they exist mainly as the 4*H*-tautomers (**66**; R = H) ⟨76JHC793, 86MRC444⟩. However, the situation is more complex with 4-substituted 3,5-diamino derivatives. With R = NH_2, NO_2, $NHCOCF_3$ or $NHSO_2C_6H_4$-*p*-Me, the thiadiazine-1,1-dioxides are found to be equimolar mixtures of the degenerate 2*H*- (**67**) and 6*H*- (**68**) tautomers, whereas with R = NHCOMe or NHCOPh, the ^{13}C NMR spectra suggest an equilibrium between the 2*H*- and 6*H*-tautomers and the 4*H*-tautomer (**66**) ⟨86FES862⟩.



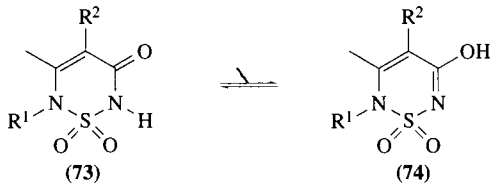
(**66**) (**67**) (**68**)

The tautomeric equilibria present in 2,5-disubstituted 1,2,6-thiadiazin-3-one 1,1-dioxides has been studied extensively in a variety of solvents ⟨88JCS(P2)859⟩. In d^6-DMSO solution the ^{15}N NMR spectra of the dioxides (**69**; R^1 = Ph, R^2 = Me; R^1 = Bu^n, R^2 = Me) display only two signals between 210 δ and 245 δ characteristic of 'pyrrole-type' nitrogen centers that indicate >95% of the 6*H*-3(2*H*)-one tautomer (**69**). A similar result is deduced for the 2,5-dimethyl compound (**69**; $R^1 = R^2$ = Me) from ^{13}C (C-3, 162.1; C-4, 98.6 br; C-5, 151.8 br δ) and ^{15}N (N-2, +209.6; N-6, +241.6 δ) chemical shifts. In order to account for the broadening of the C-4 and C-5 signals a temperature dependent dynamic equilibrium involving trace amounts of the 4*H*-tautomer (**70**) and which does not effect the proportions of tautomers (**69**) and (**71**) is proposed. In contrast, the 5-amino-2-butyl derivative exists solely as the 4*H*-tautomer (**70**; R^1 = Bu, R^2 = NH_2) with C-4 appearing as a singlet at 3.75 δ, and the C-3, C-4, and C-5 resonances at 163.7 (s) δ, 36.2 (t) δ, and 165.3 (s) δ, respectively ⟨88JCS(P2)859⟩. In pyridine solution, the ^{13}C NMR spectrum reveals that the 2-phenyl-5-methyl derivative (**69**; R^1 = Ph, R^2 = Me) exists as the resonance stabilized anion (**72**), whereas the proton magnetic resonance spectra of 2-phenyl-5-methyl- and 2-butyl-5-methyl- 1,2,6-thiadiazin-3(2*H*)-ones in $CDCl_3$ solution indicate 55% and 30% respectively of the 4*H*-tautomers (**70**; R^1 = Ph, R^2 = Me; and R^1 = Bu, R^2 = Me), the remainder being the 6*H*-tautomers (**69**). Interestingly, the 5-amino-2-butyl derivative is present only as the 4*H*-tautomer (**70**; R^1 = Bu, R^2 = NH_2). In methanol solution, UV spectroscopic measurements are consistent with the 6-NH tautomers being the dominant forms, except for the 5-amino-2-butyl compound, which from ^{13}C NMR data is once again in the 4*H*-form.



(**69**) (**70**) (**71**) (**72**)

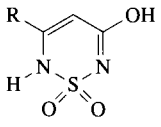
Extension of these studies to 4,5,6-trisubstituted-1,2,6-thiadiazin-3-one 1,1-dioxides (**73**; R^1 = C_6H_{11}, Bu or Ph; R^2 = H or Br) reveals that in d^6-DMSO, pyridine, chloroform and methanol solution the hydroxy tautomer (**74**) is dominant. ⟨88JCS(P2)859⟩, except for the 5-methyl-6-phenyl derivative which is a mixture of the amide and hydroxy forms (**73** and **74**; R^1 = Ph, R^2 = H).



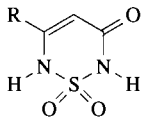
(**73**) (**74**)

Spectroscopic studies on the tautomerism of 6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**75**; R = H) and its 5-methyl derivative (**75**; R = Me), are hampered by their low solubility in the standard solvents. However, from a comparison of ^{13}C NMR data, obtained in d^6-DMSO solution, with model compounds, it is concluded that they exist mainly as the 3-hydroxy-6*H*-tautomers (**75**). In

contrast, in methanol solution an equilibrium between tautomers (**75**) and (**76**) is likely ⟨88JCS(P2)859⟩.

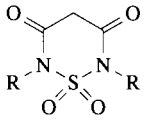


(**75**)

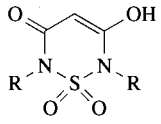


(**76**)

1,2,6-Thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxides, for which a keto–enol tautomeric equilibrium (**77**⇌**78**) is possible, exist solely as the 4*H*-tautomers (**77**) ⟨86MRC444⟩.

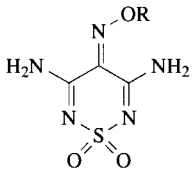


(**77**)

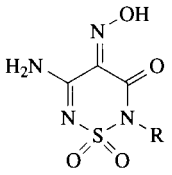


(**78**)

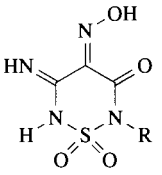
Studies on the tautomeric equilibria of 3,5-diamino-4-hydroxyimino-1,2,6-thiadiazine 1,1-dioxides (**79**; R = H) and 5-amino-4-hydroxyimino-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxides (**80**) are also available ⟨88MI 616-01⟩. On the basis of ^{1}H, ^{13}C, and ^{15}N NMR studies it is concluded that in all instances, the oxime tautomers are preferred over the 4-nitroso- forms, and that the 3-ones exist as the lactams rather than the 3-hydroxy tautomers. In addition, for the diamino-oxime (**79**; R = H) and its *O*-methyl ether (**79**; R = Me), the amino rather than the imino tautomer is dominant. In contrast, with the 5-amino-1,2,6-thiadiazinone 1,1-dioxides (**80**; R = H or $PhCH_2$) there appear to be unquantified amounts of the imino tautomers (**81**) present.



(**79**)



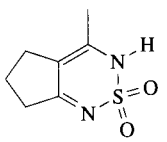
(**80**)



(**81**)

At room temperature in d^6-DMSO solution both (*E*)- and (*Z*)- forms of the oxime (**80**) are present, the latter being the more abundant.

A careful comparison of PMR and ^{13}C NMR spectroscopic data, including COSY and HETCOR experiments, on cycloalkano-1,2,6-thiadiazine 1,1-dioxides and their *N*-methyl derivatives has confirmed theoretical predictions regarding the tautomeric equilibria of the *N*-unsubstituted systems. In solution, and in the solid state, the cyclopentano derivative exists as the 3-NH tautomer (**82**), whereas the cyclohexano derivative adopts the 1-NH tautomeric form (**83**) ⟨94JCS(P2)1561⟩.



(**82**)

(**83**)

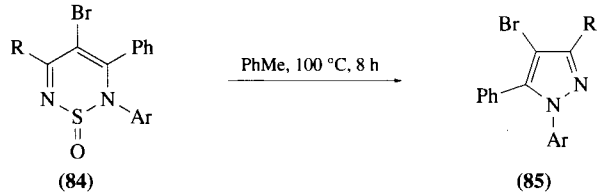
6.16.5 REACTIVITY OF FULLY CONJUGATED RINGS

Although there is some theoretical evidence for heteroaromaticity in the tetrafluoroborate salts of 4-alkoxy-2,1,3-benzothiadiazines (**61**; Section 6.16.4.1), none of the monocyclic systems covered in this chapter possesses aromatic character. Hence, the chemistry of these systems, along with that of $1\lambda^4$,2,6- and $1\lambda^6$,2,6-thiadiazines and their benzologues, is considered in the following Section.

6.16.6 REACTIVITY OF NONCONJUGATED RINGS

6.16.6.1 Thermal and Photochemical Unimolecular Reactions

2,5-Disubstituted 4-bromo-3-phenyl-2*H*-1,2,6-thiadiazine 1-oxides (**84**; R = aryl or cyclohexyl) (Section 6.16.9.2.3(i)) on heating in toluene at 100 °C extrude sulfur monoxide to give 4-bromo-5-phenylpyrazoles (**85**) in high yields (73–84%) (Equation (1)) ⟨81JCS(P1)1891, 83JCS(P1)2273⟩.



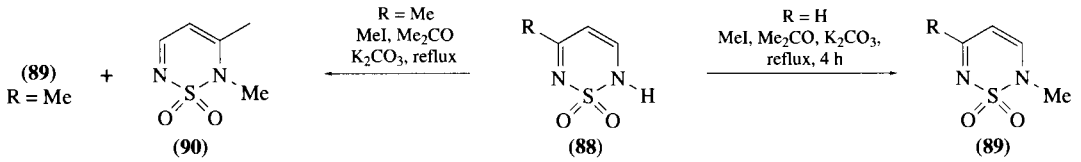
(84) (85) (1)

Pyrazoles (**87**) are also formed, by extrusion of SO_2, on submitting 2-alkyl-3,5-dimethyl-1,2,6-thiadiazine 1,1-dioxides (**86**; R = Me or $PhCH_2$) to flash vacuum pyrolysis at 700 °C (Equation (2)) ⟨93CJC410⟩. With 2-unsubstituted thiadiazine 1,1-dioxides (**86**; R = H) no pyrazoles are formed, whereas with the 2-cyclohexyl derivative (**86**; R = cyclohexyl) the reaction is more complex and yields, in addition to starting material, pyrazole (**87**; R = cyclohexyl; 50%), the decycloalkylated thiadiazine 1,1-dioxide (**86**; R = H; 35%), and cyclohexene. The last two products most probably arise by a retro-ene reaction.

(86) (87) (2)

6.16.6.2 Electrophilic Attack at Nitrogen

A detailed comparison of the chemistry of pyrazoles and 2*H*-1,2,6-thiadiazine 1,1-dioxides has been carried out ⟨82JOC536⟩. In general, the thiadiazine 1,1-dioxides are found to be less basic and more acidic than the corresponding pyrazoles, with N-2 behaving as the acidic NH of a pyrrole system and N-6 as the basic pyridine-like center. The parent 2*H*-1,2,6-thiadiazine 1,1-dioxide (**88**; R = H) with methyl iodide in acetone furnishes the 2-methyl derivative (**89**; R = H) in 70% yield ⟨82JOC536⟩. Under the same conditions, 5-methyl-2*H*-1,2,6-thiadiazine 1,1,dioxide (**88**; R = Me) affords a mixture of the 2,5-dimethyl (**89**; R = Me) (82% yield) and the 2,3-dimethyl derivative (**90**) (18% yield), from which the 2,5-dimethyl isomer can be isolated by crystallisation of the mixture from ethanol (Scheme 1). A similar yield of products (79% yield and 21% yield) is obtained using dimethyl sulfate as the methylating agent, whereas with diazomethane more of the 2,3-dimethyl isomer is produced (34% yield).

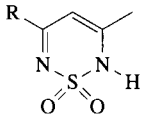


(90) (88) (89)

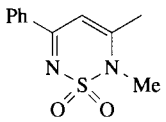
Scheme 1

In contrast to the 5-methyl derivative (**88**; R = Me), reaction of 3-methyl-5-phenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**91**; R = Ph) with methyl iodide yields mainly the 2,3-dimethyl derivative (**92**) (70% yield) along with the 2,5-dimethyl-3-phenyl derivative (**93**) (30% yield). In this case,

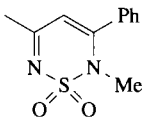
however, both isomers can be separated and characterized, the former by crystallization and the latter by thin layer chromatography of the residue after crystallization of the 2,3-dimethyl isomer.



(91)



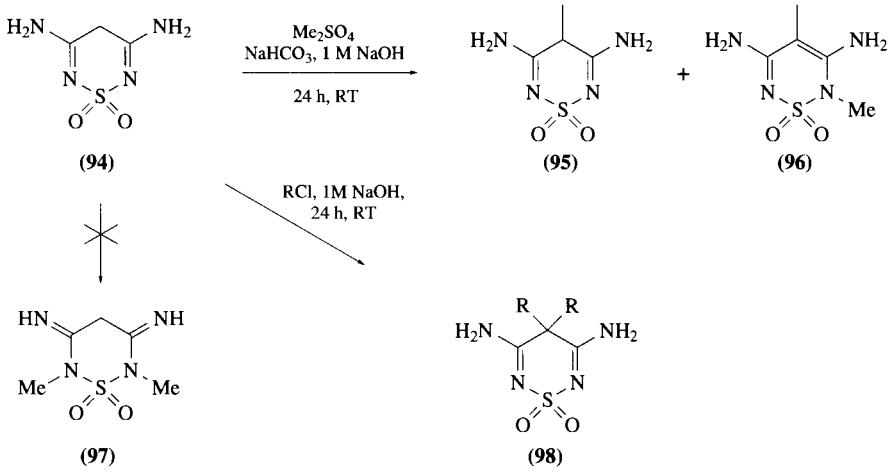
(92)



(93)

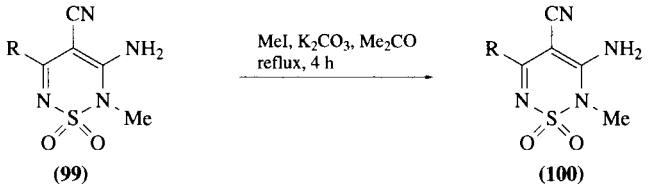
Initial attempts to effect *N*-alkylation under phase-transfer conditions failed, seemingly on account of the high solubility of the sodium salts of 1,2,6-thiadiazine 1,1,dioxides in water. Apparently, however, such reactions have since been carried out successfully ⟨88AHC(44)81⟩.

Alkylation of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**94**) with dimethyl sulfate furnishes a 2 : 1 mixture of the *C*-methylated (**95**) and *C*,*N*-dimethylated (**96**) derivatives ⟨81JHC27⟩ and not, as had been reported previously ⟨70UKZ77⟩, the 2,6-dimethyl-3,5-diimino compound (**97**). Alkylations with benzyl chloride and with allyl chloride yield only the 4,4-dialkyl derivatives (**98**; R = $PhCH_2$; 44%) and (**98**; CH_2=$CHCH_2$; 40%), respectively (Scheme 2) ⟨81JHC27⟩.



Scheme 2

Regioselective N-2 methylation of 5-phenoxy- and 5-dialkylamino- 3-amino-4-cyano-2*H*-1,2,6-thiadiazine 1,1-dioxides (**99**; R = OPh or NR'_2) (Section 6.16.9.1.2) has been noted (Equation (3)) ⟨91S753⟩.

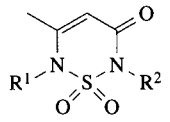


(3)

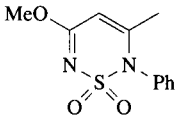
Similarly, 5-amino-2*H*-1,2,6-thiadiazine 1,1-dioxide with methyl iodide yields only the 2-methyl derivative, and in high yield (84%) ⟨82JOC536⟩.

Methylation of 5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**101**; R^2 = Ph, R^1 = H) with methyl iodide in hot acetone furnishes a mixture of the 5,6-dimethyl (**101**; R^1 = Me. R^2 = Ph; 49% yield) and 2,5-dimethyl (**101**; R^1 = Ph, R^2 = Me; 39% yield) derivatives ⟨87MI 616-01, 88JCR(S)94⟩. In contrast, methylation of the isomeric 5-methyl-6-phenyl-2*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**101**; R^1 = Ph, R^2 = H) produces a mixture of the 2,5-dimethyl compound (**101**; R^1 = Ph, R^2 = Me; 40% yield) and 5-methoxy-3-methyl-2-phenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**102**), a rare example of an alkoxy-1,2,6-thiadiazine 1,1-dioxide ⟨88JCR(S)94⟩.

Methylation of 4-bromo-5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**103**) is unusual in that methylation at N-6 is accompanied by methylation and debromination at C-4

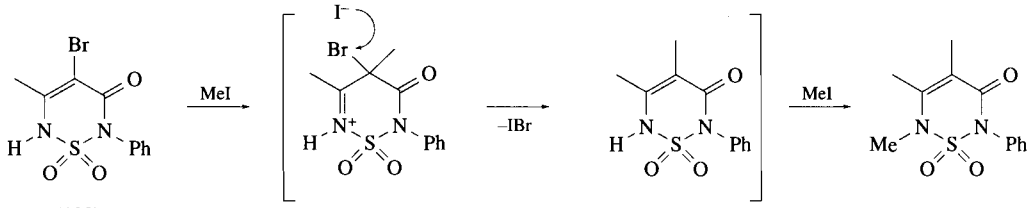


(101)



(102)

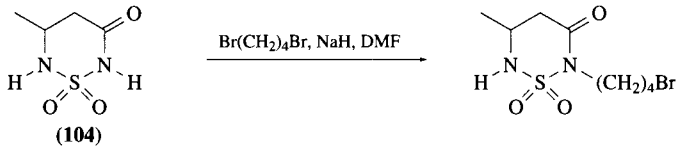
⟨88JCR(S)94⟩. Debromination is thought to occur via initial methylation at C-4 followed by loss of iodine bromide and methylation at N-6 as indicated in Scheme 3.



(103)

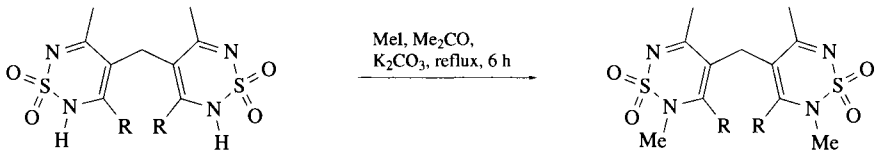
Scheme 3

Alkylation of 5-methyl-5,6-dihydro-2*H*-1,2,6-thiadiazin-3(4*H*)-one 1,1-dioxide (**104**) in the presence of strong base proceeds as expected at the "amide" nitrogen center N-2 (Equation (4)) ⟨89JMC1024⟩.



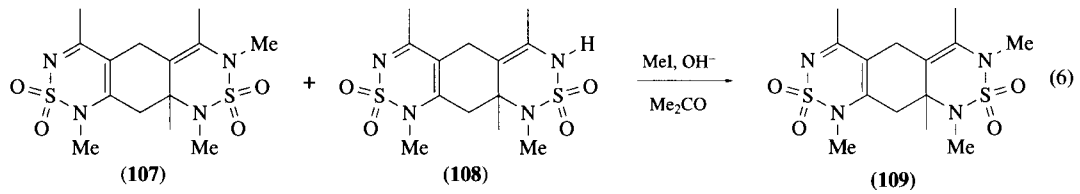
(104) (4)

Attempts to methylate the bis(1,2,6-thiadiazin-4-yl)methanes (**105**; R = H or Me) (Section 6.16.6.3.2) with dimethyl sulfate have failed, whereas with methyl iodide in hot anhydrous acetone containing potassium carbonate, dimethylation occurs to produce the bis-2,5-dimethyl and bis-2,3,5-trimethyl derivatives (**106**; R = H and Me) in 30% and 44% yield, respectively (Equation (5)) ⟨85T3105⟩.



(105) (106) (5)

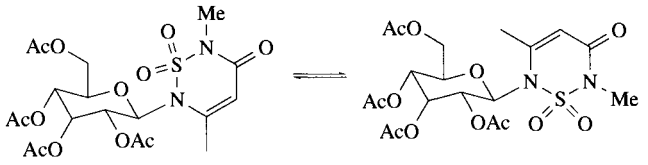
Methylation of the mixture of [1,2,6]thiadiazino[4,3-*g*][2,1,3]benzothiadiazine tetraoxides (**107**) and (**108**) (see Section 6.16.6.5.3) yields the hexamethyl derivative (**109**) (65% yield), the structure of which has been confirmed by x-ray crystallographic analysis (Equation (6)) ⟨85T3105⟩.



(107) (108) (109) (6)

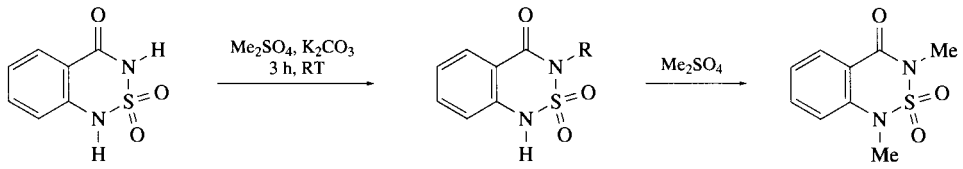
N-Glycosylation of 5-methyl-6H-1,2,6-thiadiazin-3(2*H*)-one via the N-6 trimethylsilyl derivative followed by *N*-methylation with methyl iodide yields the 2,5-dimethylated glycoside, which on the

basis of ^{1}H NMR measurements, appears to exist in solution at room temperature as an equilibrium mixture of the *syn*- (**110**) and *anti*- (**111**) rotamers ⟨87MI 616-02, 90JCS(P2)783⟩.



(**110**) (**111**)

Methylation of the highly acidic 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (**112**) at N-3 is readily achieved in 62% yield with dimethyl sulfate at room temperature ⟨62JA1994⟩; with an excess of reagent the 1,3-dimethyl derivative (**114**) is obtained in the same yield (Scheme 4).



(**112**) (**113**) (**114**)

Scheme 4

N-1 Alkylation of 3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (**113**; R = $CHMe_2$) (Bentazone) is possible in high yields (69–89%) with an alkyl halide and potassium carbonate in acetonitrile ⟨90CCC2787⟩, and chlorocarbonylation at the same position can be effected with trichloromethyl chloroformate ⟨85JAP(K)6016986⟩. Metal salts of the 2,1,3-benzothiadiazinone (**113**; R = $CHMe_2$; BTD) of general formula $M(BTD)_2 \cdot nH_2O$ (M = Mn, Co, Ni or Zn) have been prepared, whereas with copper(II) salts, a hydroxy complex $[Cu(BTD)_2(H_2O)_2(OH)_2]$ is formed ⟨91JGU415⟩.

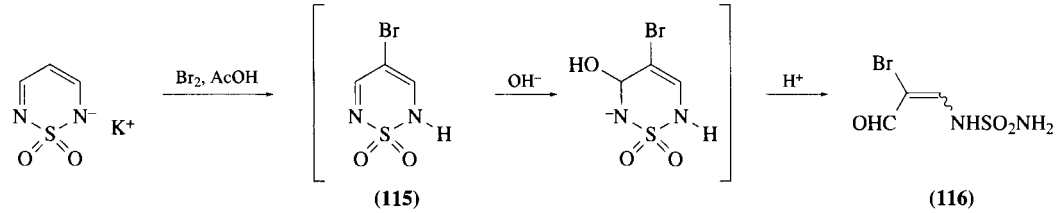
6.16.6.3 Electrophilic Attack at Carbon

6.16.6.3.1 Halogenation

Reports of electrophilic substitution at carbon are limited to the 1,2,6-thiadiazine system and always take place at the 4-position ⟨74JCS(P1)2050, 80JHC977⟩.

Attempts to brominate 2*H*-1,2,6-thiadiazine 1,1-dioxide, as the potassium salt, with bromine in acetic acid result in ring-opening to the substituted acrylaldehyde (**116**), probably by nucleophilic attack of water at the highly electrophilic 3(5)-position of the initially formed 4-bromo derivative (**115**) (Scheme 5) ⟨90ACS726⟩.

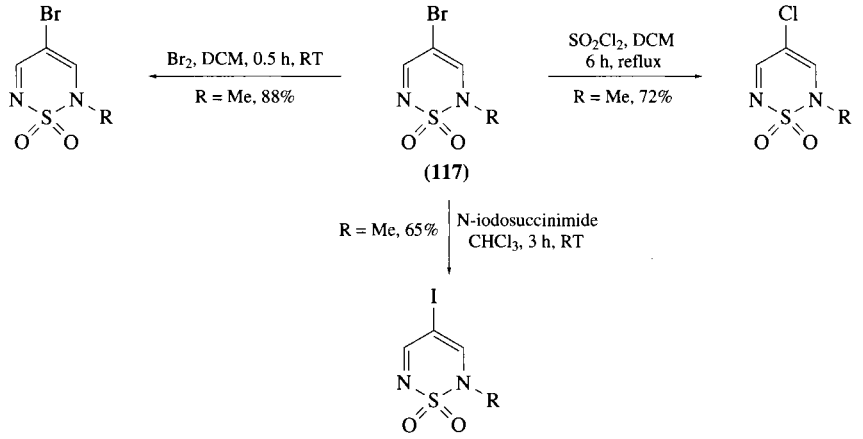
The *N*-alkyl derivatives (**117**) are halogenated successfully at C-4 by a variety of reagents as



(**115**) (**116**)

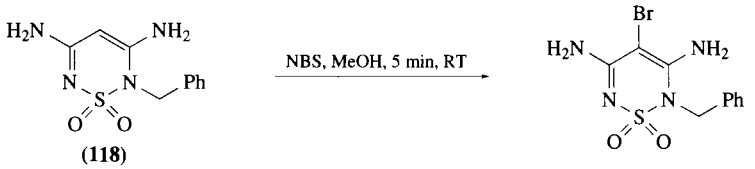
Scheme 5

exemplified in Scheme 6. *N*-Chloro- and *N*-bromosuccinimide have also been used but, in general, proved to be inferior to the reagents shown.

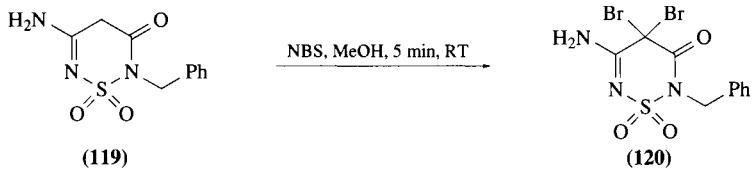


Scheme 6

However, 2-benzyl-3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**118**) is brominated at C-4 in high yield (83%) by *N*-bromosuccinimide in methanol (Equation (7)) ⟨91AF264⟩. Under similar conditions 5-amino-2-benzyl-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**119**) yields the 4,4-dibromo derivative (**120**) (Equation (8)).

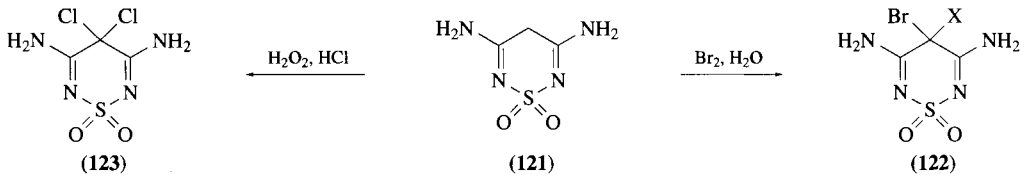


(118) (7)



(119) (120) (8)

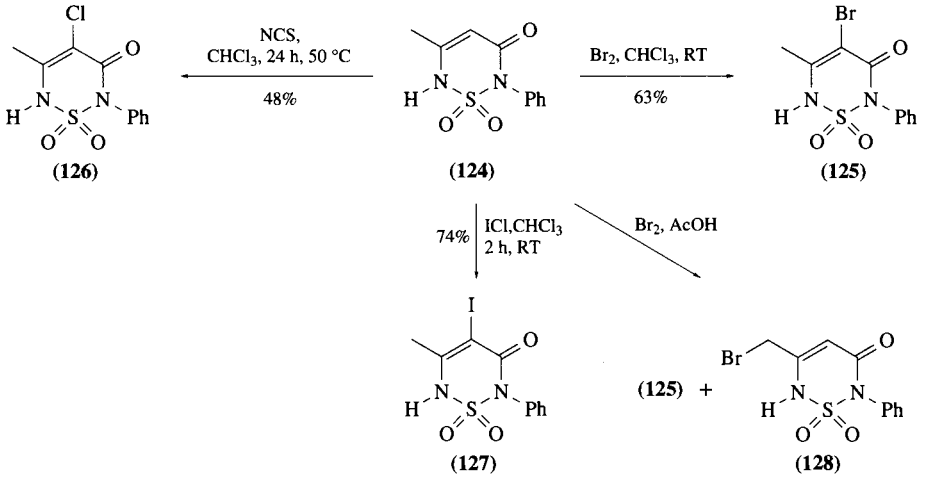
Bromination of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**121**) with bromine water yields a mixture of the 4-bromo (**122**; X = H) and 4,4-dibromo derivatives (**122**; X = Br). The 4,4-dichloro derivative (**123**) is obtained by treating the diamino compound (**121**) with a mixture of hydrogen peroxide and hydrochloric acid (Scheme 7) ⟨86FES862⟩.



(123) (121) (122)

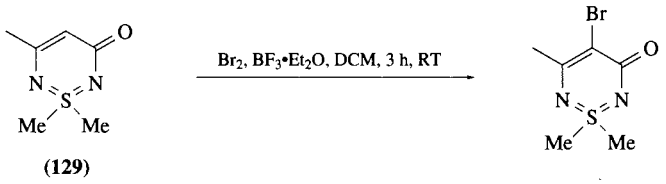
Scheme 7

Halogenation of 5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**124**) in chloroform solution, as shown in Scheme 8, furnishes the 4-halogeno-derivatives (**125**–**127**) ⟨87MI 616-01, 88JCR(S)94⟩. However, with bromine in hot acetic acid a mixture (50%) of the 4-bromo (**125**) and the 5-(bromomethyl) (**128**) derivatives is produced (Section 6.16.7.2) ⟨88JCR(S)94⟩.



Scheme 8

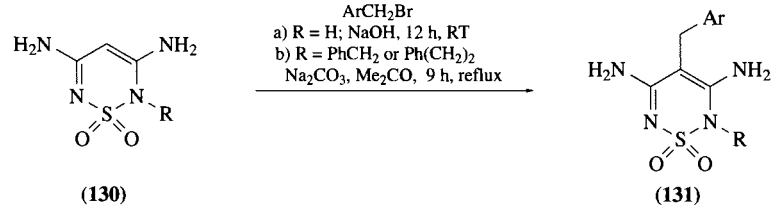
1,1,5-Trimethyl-1λ^6,2,6-thiadiazin-3-one (**129**) with bromine in the presence of boron trifluoride etherate is brominated at the 4-position in 64% yield (Equation (9)) ⟨85CB2561⟩.



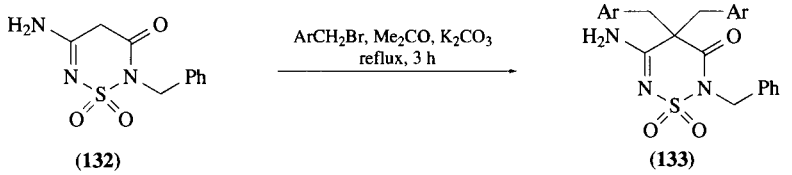
(9)

6.16.6.3.2 *Alkylation and acylation*

2-Alkyl-3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides (**130**) with benzyl bromides in the presence of sodium hydroxide or sodium carbonate undergo regioselective benzylation to give the 4-benzyl derivatives (**131**) in 43–63% yield (Equation (10)) ⟨91AF264⟩. In contrast, 5-amino-2-benzyl-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**132**) yields only the 4,4-dibenzylated product (**133**) (Equation (11)).



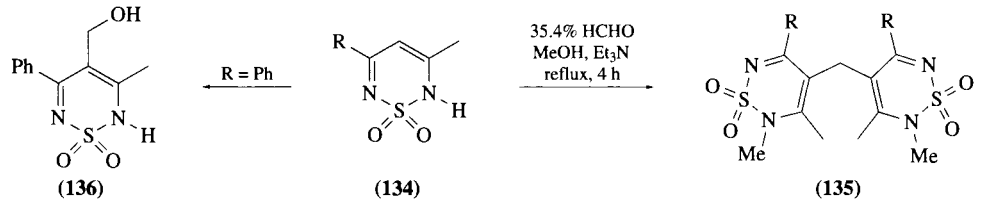
(10)



(11)

Bis(1,2,6-thiadiazin-4-yl)methanes (e.g. **135**) result in high yields (83–94%) on treating 2H-1,2,6-thiadiazine 1,1-dioxides (e.g. **134**) with methanal in aqueous methanol in the presence of triethylamine ⟨85T3105, 89EJM497⟩. However, with the 5-phenyl derivative (**134**; R = Ph), the 4-

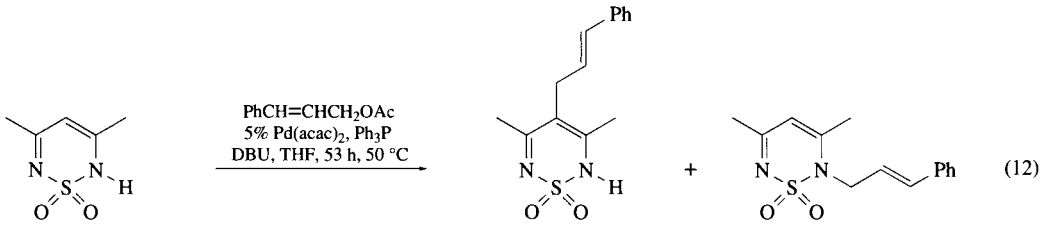
(hydroxymethyl)- compound (**136**) is obtained as the main product (19% yield) (Scheme 9). Interestingly, 2-alkyl- and 2-aryl-1,2,6-thiadiazine 1,1-dioxides fail to react.



(136) (134) (135)

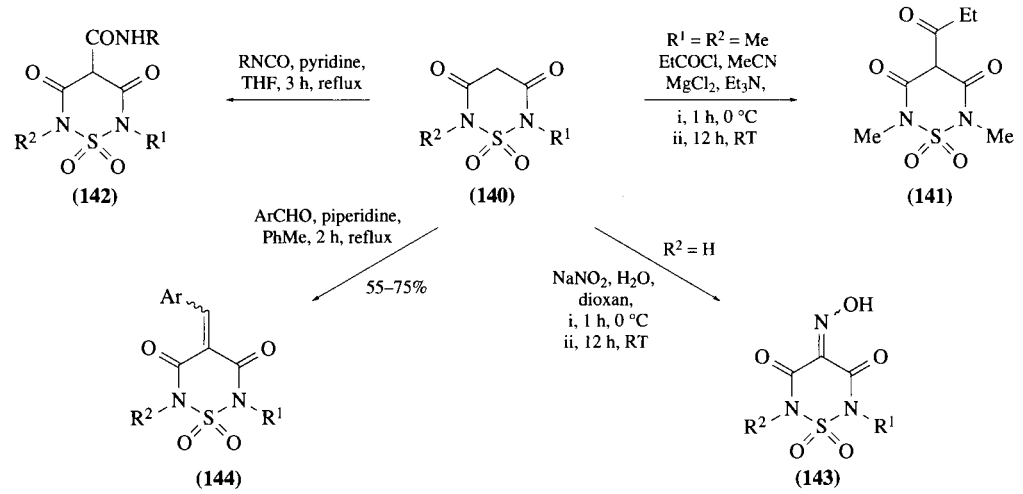
Scheme 9

An attempt to effect palladium catalysed *C*-allylation of 3,5-dimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**137**) is only moderately successful, as allylation at C-4 to give the cinnamyl-derivative (**138**; 13% yield) is accompanied by equal amounts of the *N*-cinnamyl derivative (**139**) (Equation (12)) ⟨88T7205⟩.



(137) (138) (139) (12)

Examples of *C*- or *N*- acylations of the 1,2,6-thiadiazine 1,1-dioxide nucleus are rare. However, acylation of 2,6-dimethyl-4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxide (**140**; $R^1 = Me$) with propionyl chloride in acetonitrile in the presence of triethylamine and magnesium chloride affords the 4-propanoyl derivative (**141**) (Scheme 10) ⟨89BRP2213145⟩.



(142) (140) (141)

(144) (143)

Scheme 10

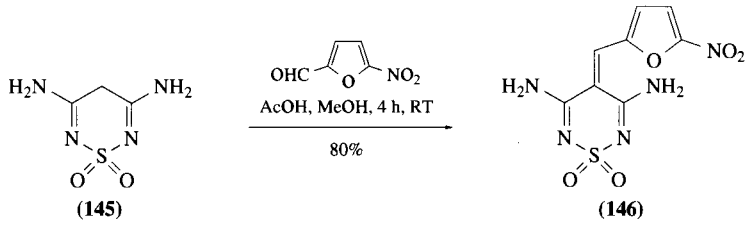
The thiadiazinediones (**140**) also react readily with isocyanates in the presence of pyridine to yield 4-amidocarbonyl derivatives (**142**) which have some use as endoparasiticides ⟨84GEP3230332, 84GEP3230923, 88GEP3623532⟩.

6.16.6.3.3 Nitrosation

Nitrosation of 4*H*-1,2,6-thiadiazine-3,5-diones (**140**) with sodium nitrite in aqueous dioxan affords the 4-hydroxyimino derivatives (**143**; 72–78%) which in some cases (e.g. **143**; $R^1 = Ph(CH_2)_2$ or cycloC_6H_{11}) can be isolated as the monohydrated sodium salts (Scheme 10) ⟨86JCS(P1)643⟩. Likewise, diamine (**121**) undergoes oximation at C-4 with nitrous acid ⟨76MI 616-01⟩.

6.16.6.3.4 Reaction with aldehydes

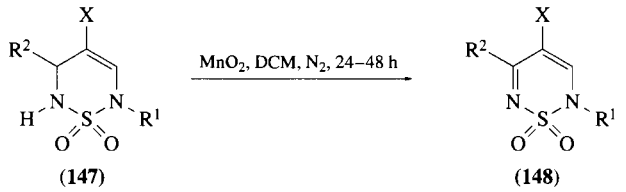
2,6-Disubstituted 4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-diones (**140**) in the presence of piperidine readily undergo Knoevenagel type condensation with a variety of aldehydes to yield the 4-arylidene derivatives (**144**) (Scheme 10) ⟨92AP(325)509⟩. In contrast, however, the corresponding base-catalysed condensation with 3,5-diamino-4*H*-1,2,6-thiadiazine-1,1-dioxide (**145**) is successful only with 5-nitrofuran-2-carbaldehyde (**145**) → (**146**) (Equation (13)).



(13)

6.16.6.3.5 Oxidation

Dehydrogenation of 5-alkyl-4-halogeno-5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides (**147**; R^1 = Me or $PhCH_2$; R^2 = Ph or Me; X = Cl or Br) (Section 6.16.6.5.3) to 5-alkyl-4-halogeno-2*H*-1,2,6-thiadiazine 1,1-dioxides (**148**) is effected with manganese dioxide at room temperature (Equation (14)) ⟨90ACS726⟩. Yields are good (70%) with the 5-phenyl derivatives (**147**; R^2 = Ph) but poor (11–15%) with the 5-methyl-compounds (**147**; R^2 = Me).



(14)

6.16.6.4 Electrophilic Attack at Sulfur

There are only a few examples of the oxidation of the divalent ring sulfur atom in 1,2,6-thiadiazines to the *S*-mono- and *S*,*S*-dioxides. Oxidation of 1,2,6-thiadiazines and their 1-oxides to the 1,1-dioxides can be effected in high yields (71–75%) with *m*-chloroperbenzoic acid in chloroform solution at room temperature ⟨81JCS(P1)1891, 93JOC700⟩. In contrast, similar oxidations of 3-aryl-4,5-dihydro-1*H*-2,1,3-benzothiadiazine 1-oxides (Section 6.16.9.2.2.2) yield only uncharacterized oily products ⟨85TL2813⟩.

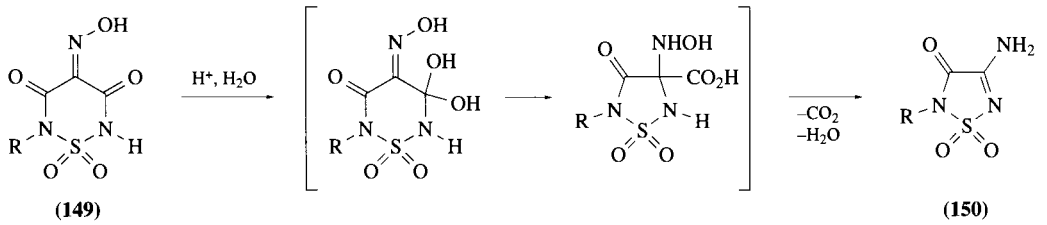
6.16.6.5 Nucleophilic Attack at Carbon

6.16.6.5.1 By oxygen nucleophiles

4-Hydroxyimino-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxides (**149**) (Section 6.16.6.3.3) on treatment with dilute hydrochloric acid undergo ring contraction to 4-amino-1,2,5-thiadiazole-3(2*H*)-one 1,1-dioxides (**150**), generally in high yields (R^1 = $PhCH_2$, 75%; R^1 = $Ph(CH_2)_2$, 76%; R^1 = cyclohexyl, 71%) ⟨86JCS(P1)643⟩. A mechanistic rationale involving initial nucleophilic attack at the protonated 3-carbonyl group as outlined in Scheme 11 is proposed.

The cyclohexyl (**149**; R = C_6H_{11}) and phenethyl [**149**; R = $Ph(CH_2)_2$] derivatives rearrange rapidly and completely in boiling dilute acid, whereas under the same conditions the benzyl compound (**149**; R = $PhCH_2$) suffers hydrolytic cleavage of the thiadiazine ring and formation of the parent sulfamide ($PhCH_2NHSO_2NH_2$). Successful ring contraction of the benzyl derivative, however, is accomplished by allowing the reaction mixture to stand at room temperature for several days.

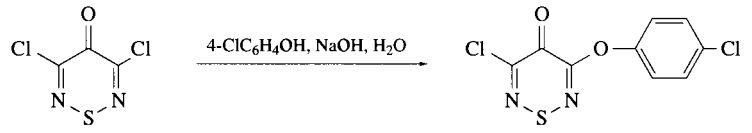
Instances of nucleophilic displacement of halogen from halogeno-1,2,6-thiadiazine systems are



(149) (150)

Scheme 11

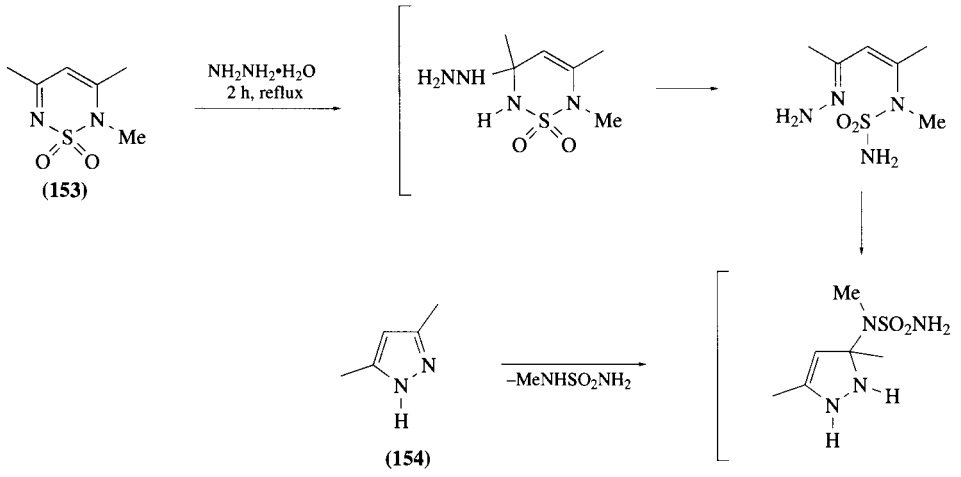
rare. However, 3,5-dichloro-1,2,6-thiadiazin-4-one (**151**) suffers nucleophilic displacement of chlorine by *p*-chlorophenoxide ion to yield 5-chloro-3-(4-chlorophenoxy)-1,2,6-thiadiazine (**152**) (Equation (15)), a useful plant disease control agent against, for example, apple scab ⟨85USP4497807⟩.



(151) (152) (15)

6.16.6.5.2 By nitrogen nucleophiles

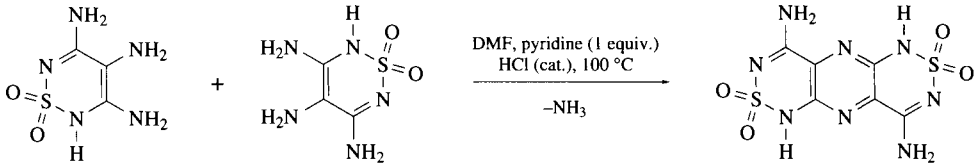
In boiling aqueous hydrazine 2,3,5-trimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**153**) undergoes loss of *N*-methylsulfamide and ring-contraction to 3,5-dimethylpyrazole (**154**; 65% yield) as outlined in Scheme 12 ⟨89H(29)245⟩.



(153) (154)

Scheme 12

Attempts to condense 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**155**) with methyl chloroformate in dimethylformamide solution gives not the expected 6-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2,2-dioxide but the unexpected tricyclic compound (**156**) ⟨90T1679⟩. The same product is also obtained in good yield (54%) by heating the triamine in DMF with one equivalent of pyridine and a few drops of hydrochloric acid. In the absence of pyridine only trace amounts of the tricycle are formed, whereas in the absence of acid there is no reaction. ^{15}N labelling studies demonstrate that the reaction proceeds via intermolecular nucleophilic attack at the electron-deficient 3-position of the thiadiazine ring by the 4-amino-group (most nucleophilic) of another thiadiazine molecule as outlined in Scheme 13.

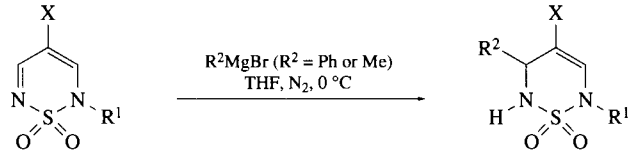


(155) (156)

Scheme 13

6.16.6.5.3 *By carbon nucleophiles*

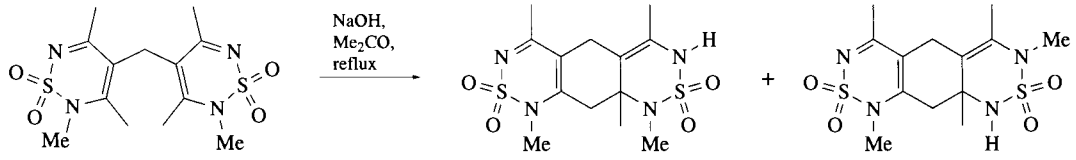
The reactivity of 1,2,6-thiadiazine 1,1-dioxides towards electrophiles and nucleophiles has been likened to that of the corresponding pyrimidones ⟨88AHC(44)81⟩. However, unlike pyrimidones 4-halogeno-2*H*-1,2,6-thiadiazine 1,1-dioxides (**157**; X = Cl or Br) with Grignard reagents undergo regiospecific addition to yield 5-alkyl-4-halogeno-5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides (**158**) (65–75%) (Equation (16)) ⟨90ACS726⟩. The 5-phenyl derivatives (**158**; R^2 = Ph) are sufficiently stable to allow purification, but not so the 5-methyl compounds (**158**; R^2 = Me), which are used as the crude materials in subsequent reactions (Section 6.16.6.3.5).



(157) (158) (16)

The presence of the 4-halogeno- substituent, which is inert under the reaction conditions, appears to be necessary for addition to take place, as trial experiments indicate that 2-benzyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**157**; R^1 = $PhCH_2$; X = H) fails to react with Grignard reagents.

The bis-(2,3,5-trimethyl-1,2,6-thiadiazin-4-yl)methane (**159**) (Section 6.16.6.3.2) on treatment with sodium hydroxide in boiling acetone undergoes ring closure to a mixture of the isomeric 1,2,6-thiadiazino[4,3-*g*][2,1,3]benzothiadiazine tetraoxides (**160**) and (**161**) ⟨85T3105⟩. The former product is isolable in 20% yield, whereas the presence of the latter isomer is deduced from the ^{1}H NMR spectrum of the mixture. The isomers are thought to arise by an intramolecular attack of the carbanion, generated from the 3-methyl group, at C-3 or at C-5, of the adjacent 1,2,6-thiadiazine ring as outlined in Scheme 14.

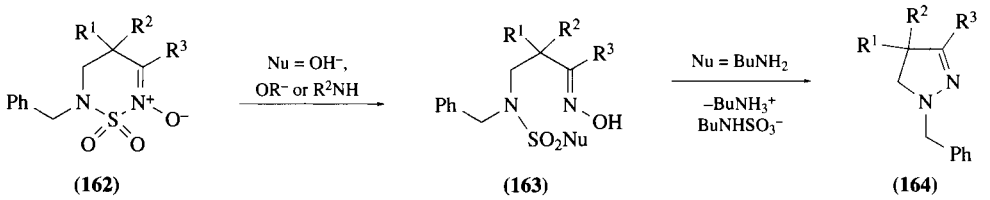


(159) (160) (161)

Scheme 14

6.16.6.6 Nucleophilic Attack at Sulfur

The 5,6-dihydro-4*H*-1,2,6-thiadiazine 1,1,2-trioxides (**162**) described in Section 6.16.9.2.3.1 are susceptible to nucleophilic attack at sulfur, which promotes heterolytic cleavage of the heterocyclic ring and formation of β-hydroxyaminosulfamic acid derivatives (**163**) as outlined in Scheme 15 ⟨90LA775⟩. However, with a primary amine as the attacking nucleophile the sulfamides (**163**) so formed undergo base-catalysed ring closure to the 4,5-dihydropyrazoles (**164**) in yields of 72–90%.

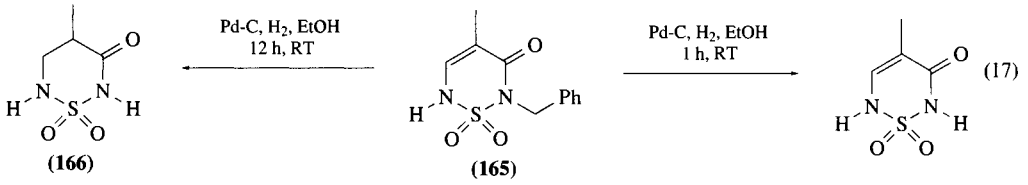


(162) (163) (164)

Scheme 15

6.16.6.7 Reduction

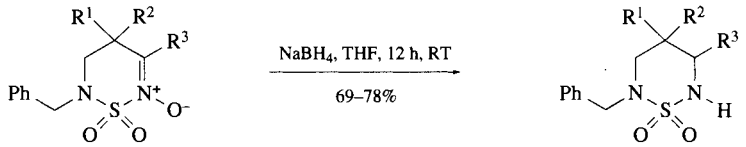
Catalytic debenzylation of 2-benzyl-4-methyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**165**) is effected in high yield (86%) with palladium–charcoal and hydrogen over a short period (1 h) ⟨84CCC840⟩. However, on prolonged treatment (12 h) debenzylation is followed by reduction of the C-4—C-5 double bond and formation of 4-methyl-5,6-dihydro-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**166**) (Equation (17)).



(166) (165) (17)

Debenzylations of 2-benzyl-3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxide and of 2-benzyl-5-amino-4*H*-1,2,6-thiadiazin-3(2*H*)-one are successful with 10% palladium charcoal in methanol at room temperature ⟨88JCS(P1)1271⟩.

The tetrahydro-2*H*-thiadiazine 1,1-dioxides (**168**) are accessible by reduction and regioselective deoxygenation of 4,5-dihydro-6*H*-1,2,6-thiadiazine 1,1,2-trioxides (**167**) (Section 6.16.9.2.3.1) with sodium borohydride (Equation (18)) ⟨90LA775⟩.



(167) (168) (18)

Reduction of 3-aryl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2-oxides (Section 6.16.9.2.2.2) with lithium aluminum hydride yields only complex mixtures of uncharacterized products ⟨85TL2813⟩.

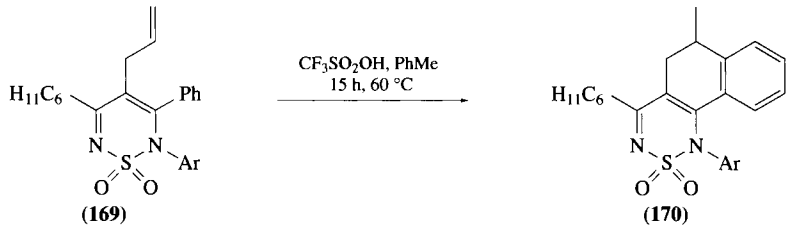
6.16.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Other than the condensations of aminothiadiazine 1,1-dioxides with various mono- and dicarbonyl compounds (Section 6.16.7.3), surprisingly little work has been published on the reactivity of substituents attached to the thiadiazine nucleus.

6.16.7.1 Aryl Groups

The 4-allyl-3-phenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**169**), on treatment with trifluoromethanesulfonic acid, undergoes an intramolecular Friedel–Crafts alkylation to yield the 4-cyclohexyl-5,6-

dihydro-6-methyl-1-*p*-tolyl-1*H*-naphtho[1,2-*c*][1,2,6]thiadiazine 2,2-dioxide (**170**; Ar = 4-MeC_6H_4) in 90% yield (Equation (19)) ⟨93JOC700⟩.



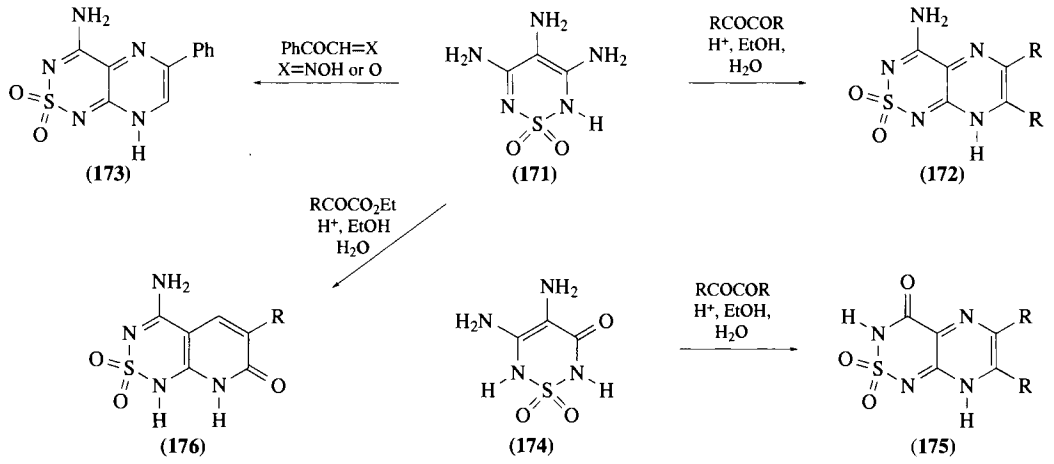
(169) (170) (19)

6.16.7.2 Alkyl Groups

Bromination of 5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide in hot acetic acid yields a mixture of the 4-bromo derivative (**125**) and 5-(bromomethyl)-2-phenyl-6*H*-thiadiazin-3(2*H*)-one 1,1-dioxide (**128**) (50% yield) (see Section 6.16.6.3.1) ⟨88JCR(S)94⟩. The yield of the bromomethyl compound increases with increasing reaction temperature but is unaffected by the presence of dibenzoyl peroxide or by ultraviolet light.

6.16.7.3 Amino Groups

3,4,5-Triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**171**) undergoes condensation with α-diketones via the 3- and 4-amino groups to yield 4-amino-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides (**172**; R = H, Me, or Ph) in good yields (57–69%) ⟨84JHC861, 85MI 616-02⟩. Condensation with phenyl glyoxal, or its oxime, is regioselective and affords only 4-amino-6-phenyl-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**173**) ⟨90MI 616-05⟩. Likewise, with 4,5-diamino-6*H*-1,2,6-thiadiazin-3(2*H*)-one (**174**), 8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxides (**175**) are produced. (Scheme 16) ⟨84JHC861⟩.



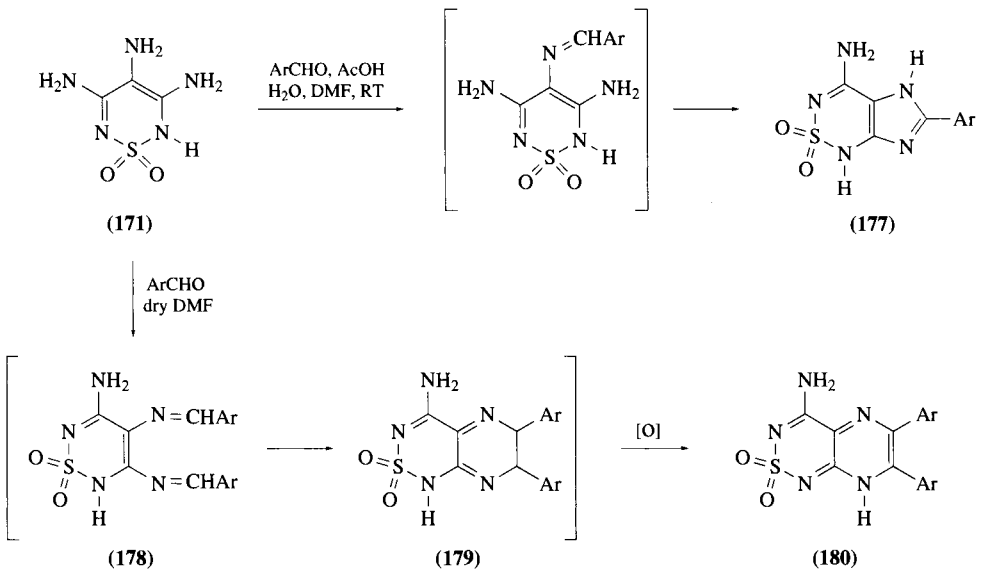
(173) (171) (172) (176) (174) (175)

Scheme 16

With α-keto-esters, 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**171**) yields only the 4-amino-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-7(8*H*)-one 2,2-dioxides (**176**), as a result of regioselective attack of the more nucleophilic 4-aminosubstituent at the ketone carbonyl centre ⟨88LA121⟩.

Condensation of triamine (**171**) with arylaldehydes in dimethylformamide at room temperature affords 4-amino-6-aryl-1,5-dihydroimidazo[4,5-*c*][1,2,6]thiadiazine 2,2-dioxides (**177**) in 63–95% yield. The reaction is also successful with ethanal, but proceeds in lower yield (45%) ⟨87H(26)3123⟩. Studies in the late 1980s, revealed that under anhydrous conditions and with electron rich aldehydes, mixtures of the imidazo[4,5-*c*]-thiadiazine dioxides (**177**) and pyrazino[2,3-*c*]thiadiazine dioxides (**180**) are produced ⟨88JHC891, 89MI 616-01⟩. The latter products arise by electrocyclization of the bis-anils (**178**), formed by condensation of the triamine with two equivalents of aldehyde, followed by

air oxidation of the 6,7-dihydro intermediates (**179**) which, if the reaction is carried out under nitrogen, can be detected by ^{1}H NMR spectroscopy (Scheme 17). Fusion of the triamine with an aldehyde at 180 °C yields only the pyrazino[2,3-*c*]thiadiazine dioxide ⟨88JHC891, 89MI 616-01⟩, whereas in solution with arylaldehydes and heteroarylaldehydes bearing electron-withdrawing groups, imidazothiadiazines are produced selectively ⟨88JHC891⟩.

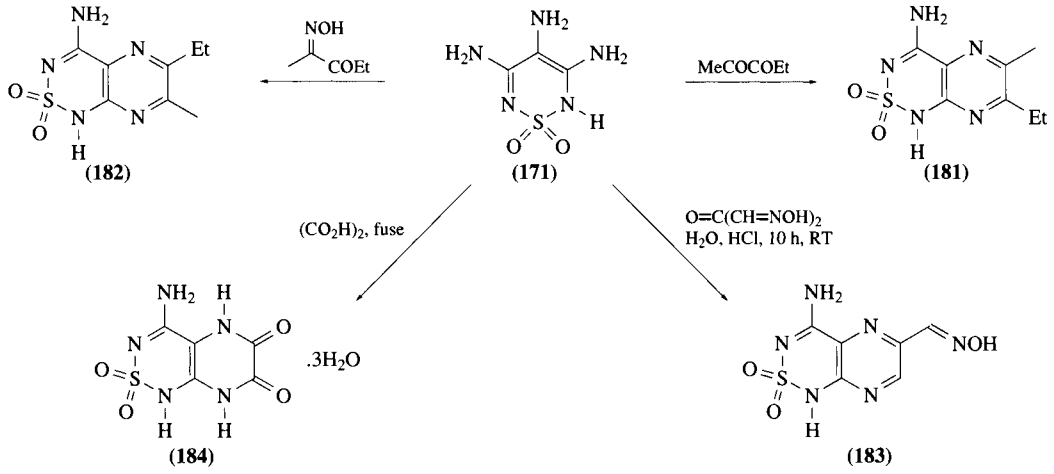


(171) (177) (178) (179) (180)

Scheme 17

Optimum conditions for the preparation of imidazothiadiazine dioxides (**177**) have been determined by carrying out a 2^4 factorial design study, involving solvent, ratio of reactants, temperature, and reaction time, on the condensation between triamine (**171**) and 4-chlorobenzaldehyde ⟨88CS415⟩. With a three-fold excess of aldehyde in aqueous acetic acid at 30 °C for 10 hours, a 92% yield of the imidazothiadiazine (**177**; Ar = 4-ClC$_6$H$_4$) is obtained.

Remarkable regioselectivity is noted in the condensation of pentane-2,3-dione and its 2-oxime with triamine (**171**). The diketone yields exclusively the 7-ethyl-6-methylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**181**) whereas the monoxime affords only the regioisomeric 6-ethyl-7-methyl derivative (**182**) ⟨92JMC3977⟩. With propanetrione 1,3-dioxime, the triamine furnishes 4-amino-6-(hydroxyiminomethyl)-1*H*-pyrazino [2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**183**) in 88% yield (Scheme 18) ⟨91H279⟩.



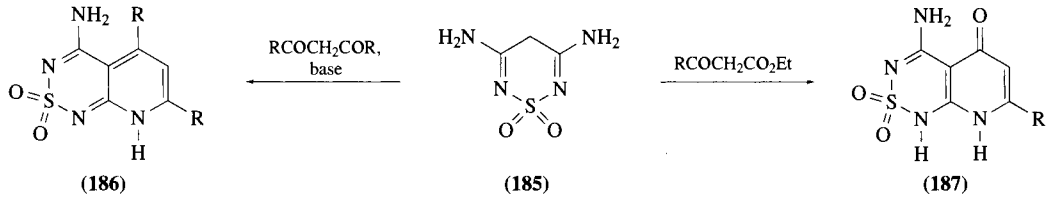
(182) (171) (181) (184) (183)

Scheme 18

On fusing the triamine with oxalic acid, 4-amino-5,8-dihydro-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine-6,7-dione 2,2-dioxide, a strong acid of pK_a 1.31, is obtained as the trihydrate (**184**) in 46%

yield (Scheme 18). However, attempts to prepare the dione by condensing triamine (**171**) with oxalyl chloride, diethyl oxalate or oxalic acid in solution failed ⟨88JST423⟩.

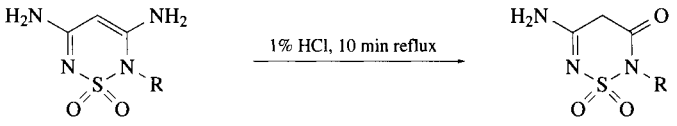
3,5-Diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**185**) undergoes base-catalysed condensations with β-diketones to yield 4-aminopyrido[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides (**186**) ⟨86CS607⟩, and Conrad–Limpach type cyclization with β-keto esters to yield 4-amino-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-5(8*H*)-one 2,2-dioxides (**187**) (Scheme 19) ⟨88AQ89⟩.



(186) (185) (187)

Scheme 19

The enaminic character of the 3-amino group in 2-alkyl-3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides (**188**) is apparent in their ease of hydrolysis under mild conditions to the corresponding 5-amino-4*H*-1,2,6-thiadiazin-3(2*H*)-ones (**189**) in excellent yields (84–91%) (Equation (20)) ⟨88JCS(P1)1271⟩. The 5-amino group, which is involved in amidine resonance with N-6, is unaffected.

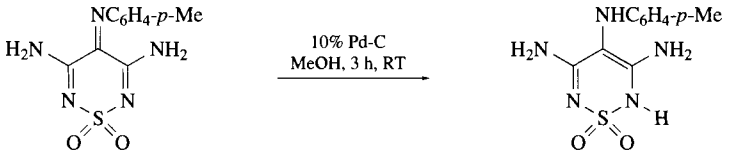


(188) (189) (20)

6.16.7.4 Other Nitrogen-linked Substituents

The polarographic reduction of 4-arylazo-2*H*-1,2,6-thiadiazine 1,1-dioxides (Section 6.16.9.2.1.1) at 30°C in methanol–1M aqueous potassium chloride solution proceeds via a single two-electron transfer process corresponding to reduction of the azo group ⟨83IJC(A)331⟩.

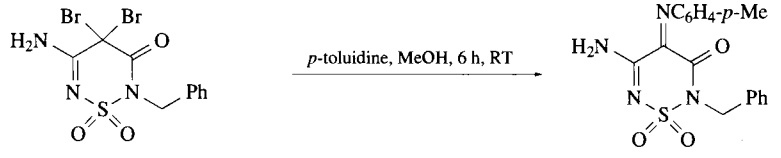
Catalytic reduction of imine (**190**) yields 3,5-diamino-4-*p*-toluidino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**191**; 53% yield) (Equation (21)) ⟨91AF264⟩.



(190) (191) (21)

6.16.7.5 Halogen Atoms

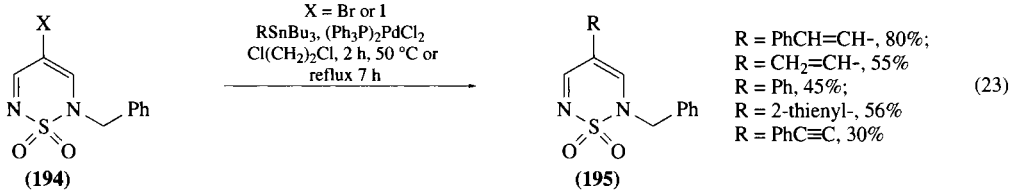
5-Amino-2-benzyl-4,4-dibromo-4*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**192**) (Section 6.16.6.3.1) condenses with *p*-toluidine to yield the imino derivative (**193**) (Equation (22)). Likewise, 4,4-dibromo-3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide yields the imine (**190**) ⟨91AF264⟩.



(192) (193) (22)

4-Bromo- and 4-iodo- 2-benzyl-2*H*-1,2,6-thiadiazine 1,1-dioxides (**194**) (Section 6.16.6.3.1)

undergo palladium catalysed coupling with organostannanes to yield 4-substituted 2*H*-1,2,6-thiadiazine 1,1-dioxides (**195**) in the yields indicated (Equation (23)) ⟨90ACS726⟩.

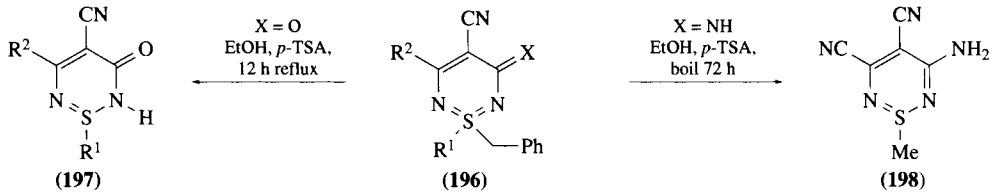


(194) (195) (23)

6.16.8 REACTION OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Reactions of this type are confined to debenzylations of *N*-benzylated derivatives. Catalytic debenzylations of 1-benzyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxides are readily effected with palladium charcoal and hydrogen ⟨84CCC840⟩. However, care is needed as prolonged reaction times result in reduction of the thiadiazine ring (Section 6.16.6.7).

Under acid conditions, 1-alkyl-1-benzyl-4-cyano-5-methylthio-1λ^6,2,6-thiadiazin-3-ones (**196**; R^1 = Me or Et, R^2 = MeS, X = O) (Section 6.16.9.2.1.1) undergo debenzylation to form the corresponding 1λ^4,2,6-thiadiazin-3-ones (**197**) in high yields (80%) (Scheme 20) ⟨87CB1455⟩. The 3-imino compound (**196**; R^1 = Me, R^2 = CN, X = NH) behaves similarly to yield 3-amino-4,5-dicyano-1-methyl-1λ^4,2,6-thiadiazine (**198**).



(197) (196) (198)

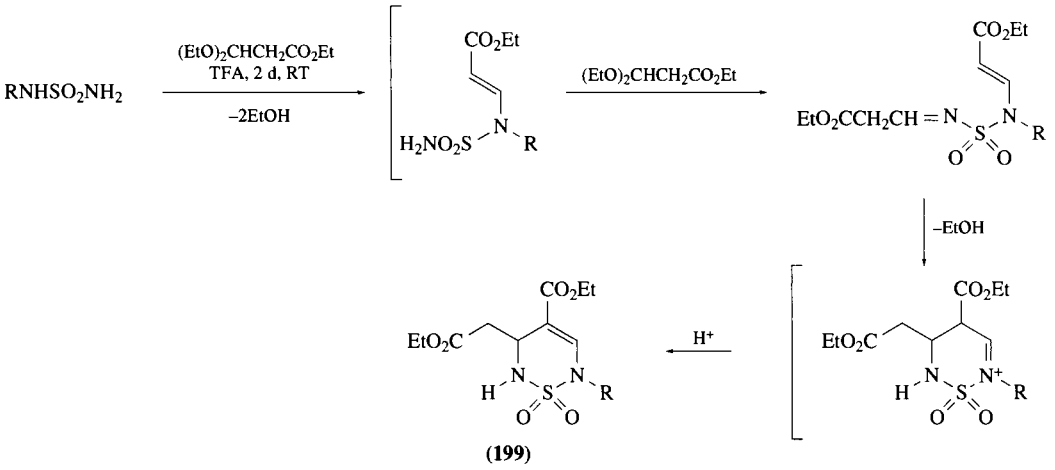
Scheme 20

6.16.9 RING SYNTHESIS

6.16.9.1 By Formation of One Bond

6.16.9.1.1 Between carbon and carbon

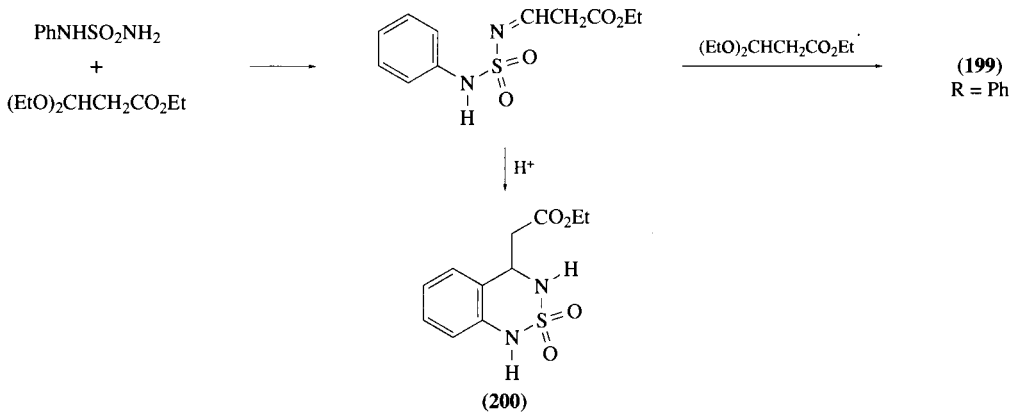
Treatment of sulfamides and *N*-alkyl sulfamides with two equivalents of ethyl 3,3-diethoxypropionate in trifluoroacetic acid furnishes the 5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide dicarboxylates (**199**) as viscous oils (30–79%) ⟨90JHC2107⟩. A mechanistic rationale (Scheme 21) involving stepwise addition of two equivalents of the acetal to the sulfamide is proposed.



(199)

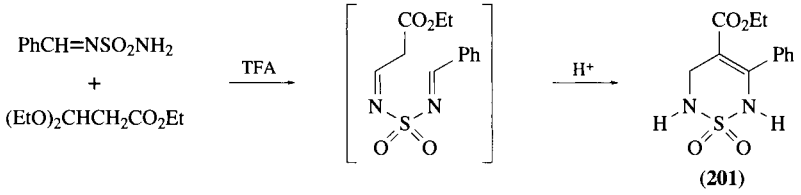
Scheme 21

With the *N*-phenylsulfamide, formation of the dihydrothiadiazine 1,1-dioxide (**199**; R = Ph) (42% yield) is accompanied by 4-(ethoxycarbonylmethyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (**200**) (41% yield), an intramolecular α-sulfamidoalkylation product (Scheme 22).



Scheme 22

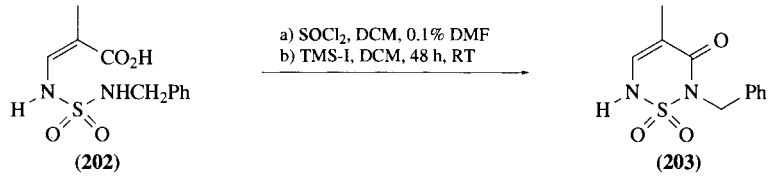
Corroborative evidence for this process is obtained by treating *N*-benzylidenesulfamide with ethyl 3,3-diethoxypropionate in trifluoroacetic acid, whereupon ethyl 3-phenyl-5,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (**201**) is produced in 42% yield (Equation (24)) ⟨90JHC2107⟩.



(24)

6.16.9.1.2 Between carbon and nitrogen

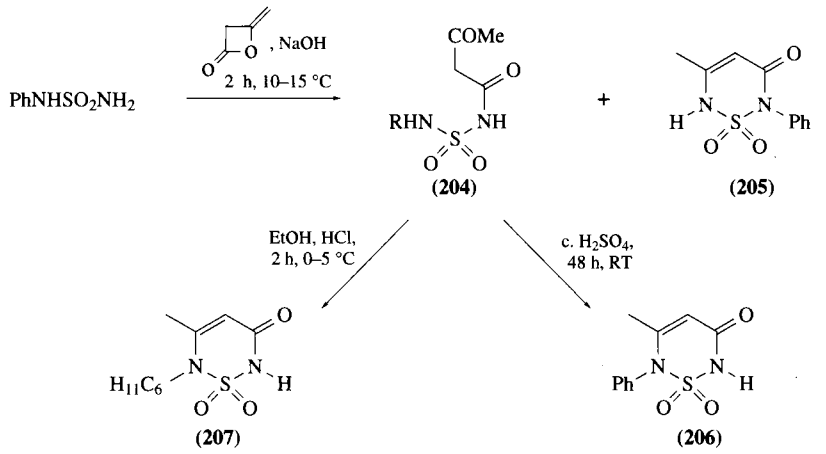
2-Benzyl-4-methyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**203**) is obtained in poor yield (22%) by cyclization of the sulfamide (**202**) with thionyl chloride in dichloromethane containing a catalytic amount of dimethylformamide. Yields are much improved (61%), however, with trimethylsilyl iodide as the cyclization agent (Equation (25)) ⟨84CCC840⟩.



(25)

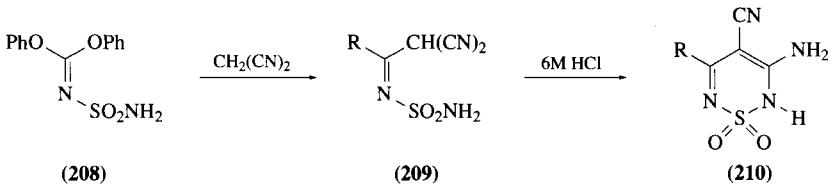
Acetoacetylation of *N*-phenylsulfamide with diketene in base solution affords a mixture of the *N*,*N*-disubstituted sulfamide (**204**; R = Ph; 78% yield) along with a small amount of 5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**205**). However, acid-catalysed ring-closure of the sulfamide produces the isomeric 5-methyl-6-phenyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one (**206**) in 63% yield ⟨87MI 616-01, 88JCR(S)94, 89EJM497⟩. In contrast, *N*-cyclohexylsulfamide and diketene produce only the *N*-acetoacetylated sulfamide (**204**; R = C_6H_{11}), which in ethanolic hydrochloric acid undergoes ring closure to 5-methyl-6-cyclohexyl-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**207**) in 41% yield (Scheme 23).

Diphenyl *N*-sulfamoyl carbonimidate (**208**), prepared by the action of sulfamide on dichlorodiphenoxymethane [$Cl_2C(OPh)_2$], on treatment with malononitrile yields the isolable *N*-(dicyanomethyl) derivative (**209**; R = PhO), which in 6M hydrochloric acid, ring closes to 3-amino-4-cyano-5-phenoxy-2*H*-1,2,6-thiadiazine 1,1-dioxide (**210**; R = PhO) (Scheme 24) ⟨91S753⟩. In a similar



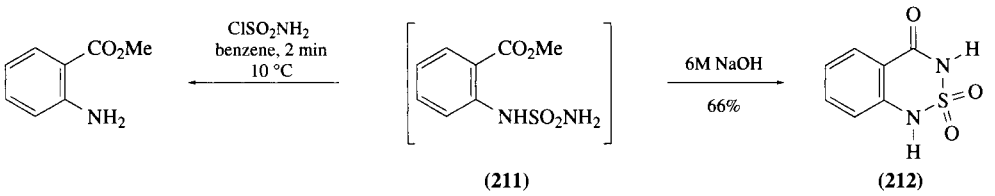
Scheme 23

manner, the 3,5-diamino derivatives (**210**; $R = NR^1_2$) are available from the dialkylamine intermediates (**209**; $R = NR^1_2$).



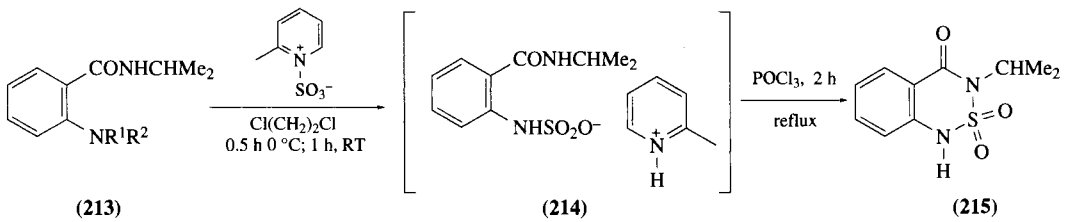
Scheme 24

The treatment of methyl anthranilate with sulfamoyl chloride represents the original synthetic route to 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxides (**212**; Scheme 25) ⟨62JA1994⟩. The intermediate *N*-arylsulfamides (e.g. **211**) are difficult to purify and are generally cyclized *in situ* with 5–6 M sodium hydroxide.



Scheme 25

A modified synthetic route to 3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (**215**) (Bentazon) (Section 6.16.12) involving sulfonylation of the 2-aminobenzamide (**213**; $R^1 = R^2 = H$) at the amine function with 2-methylpyridine-sulfur trioxide complex, followed by cyclization of the resulting 2-methylpyridinium sulfonate salt (**214**) with hot phosphorus oxychloride has been patented (Scheme 26) ⟨89CZP257059, 91CZP270529⟩. The reaction kinetics, particularly the cyclization of the 2-methylpyridinium salt (**214**), have been subjected to a detailed investigation ⟨89MI 616-02⟩.



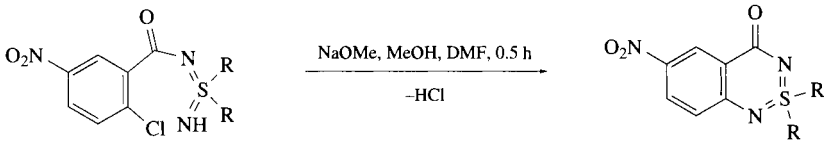
Scheme 26

The reaction kinetics of the base-catalysed cyclizations of the *N*-methyl-N^1-arylsulfamides (**213**; $R^1 = H$, $R^2 = SO_2NHMe$) ⟨91CCC1701⟩ and of N,N^1-dimethylsulfamide (**213**; $R^1 = Me$, $R^2 = SO_2NHMe$) ⟨92CCC1282⟩ to the corresponding 2,1,3-benzothiadiazin-4(3*H*)-one 1,1-dioxides have also been determined.

4-Amino-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (**217**) is readily obtained, although in moderate yield, by ring-closure of *N*-(2-cyanophenyl)sulfamide (**216**) in aqueous sodium hydroxide ⟨84AP(317)777⟩. The cyclization is also successful with the corresponding *N*-(3-cyano-5,6,7,8-tetrahydrobenzothien-2-yl)sulfamide, but fails with N^1-substituted *N*-(2-cyanophenyl)sulfamides ⟨84AP(317)777, 85MI 616-03⟩ (Equation (26)).

(216) (217) (26)

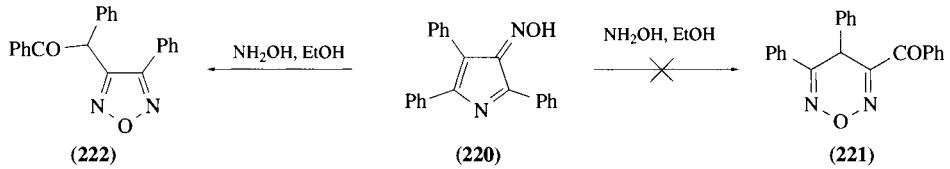
N-Aroyl-*S*,*S*-dialkylsulfur diimides (**218**), prepared by aroylation of *S*,*S*-dialkylsulfur diimides, in which the halogen of the aryl halide is activated towards nucleophilic substitution by the *p*-nitro group, undergo base-catalysed cyclization with sodium methoxide in dimethylformamide to yield 6-nitro-2,2-dialkyl-2λ^6,1,3-benzothiadiazin-4-ones (**219**) in 73–88% yield (Equation (27)) ⟨84CB2779⟩.



(218) (219) (27)

6.16.9.1.3 Between nitrogen and oxygen

There is some confusion regarding reports on the formation of 1,2,6-oxadiazines. 1,2,6-Oxadiazine (**221**) formed supposedly by the action of hydroxylamine hydrochloride on 3-hydroxyimino-2,4,5-triphenyl-3*H*-pyrrole (**220**) ⟨35G176, 84CHEC-I(3)1039⟩ is the 1,2,5-oxadiazole (**222**) (Scheme 27) ⟨37G55⟩.

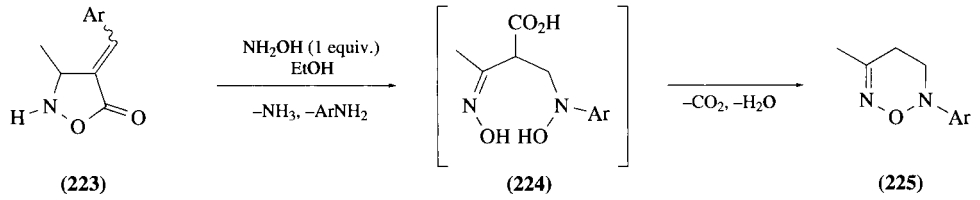


(222) (220) (221)

Scheme 27

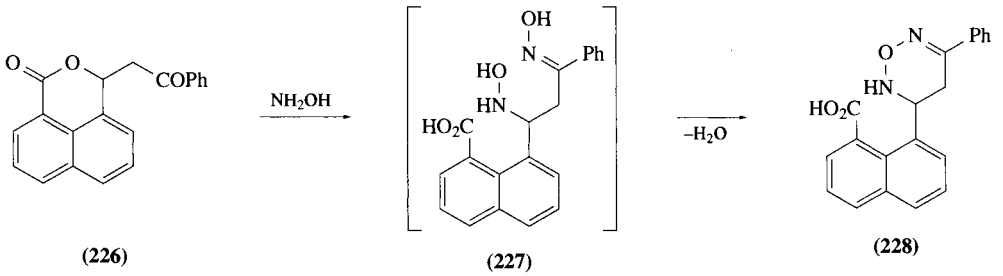
The 1952 example of this rare heterocyclic system, produced by the action of hydroxylamine on the isoxazolidone (**223**; Ar = 4-MeC_6H_4) remains unsubstantiated ⟨52JCS3428⟩. No evidence for the 5-methyl-2-*p*-tolyl-3,4-dihydro-2*H*-1,2,6-oxadiazine structure (**225**) is presented other than an elemental analysis, and a comparison with a similar, but equally unsubstantiated, reaction involving the action of hydroxylamine on the lactone (**226**), which is deemed to give the 3,4-dihydro-2*H*-1,2,6-oxadiazine (**228**) ⟨01M813⟩. If these structures are correct, then they represent the earliest examples of the 1,2,6-oxadiazine system and their production must involve formation of an N—O bond presumably by cyclization of oxime-hydroxylamine intermediates of the type (**224**) and (**227**) as indicated in Schemes 28 and 29.

More recently, in the mid-1980s, a pair of isomeric 4*H*-1,2,6-oxadiazine *N*-oxides (**230**) and (**231**), together with the isoxazolidine (**232**; 25%), have been isolated from the oxidation of the dioxime (**229**) with lead tetraacetate (Equation (28)) ⟨85JHC293⟩. The *N*-oxides, which are formed in 26%



(223) (224) (225)

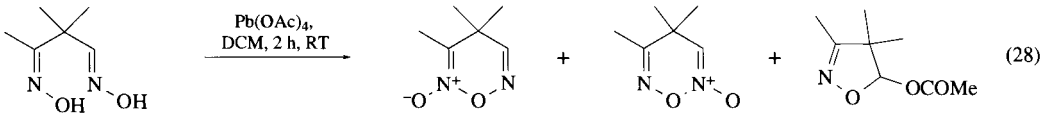
Scheme 28



(226) (227) (228)

Scheme 29

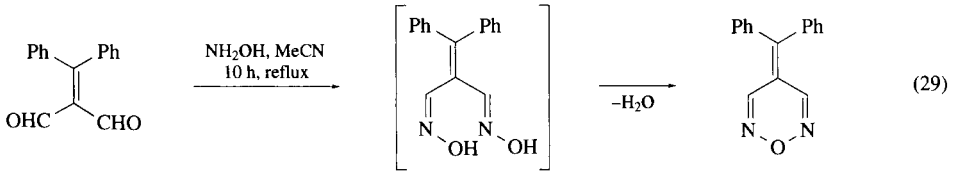
combined yield, were not separated but identified tentatively on the basis of the ^{1}H NMR spectrum of the isomeric mixture (see Section 6.193.1.2.1).



(28)

(229) (230) (231) (232)

The 4-(diphenylmethylene)-1,2,6-oxadiazine (**235**) is formed in 74% yield by treating diphenylmethylene)malonaldehyde (**233**) with hydroxylamine in boiling acetonitrile (Equation (29)) ⟨89CCC2721⟩. Presumably the product arises by cyclodehydration of the initially formed dioxime (**234**).



(29)

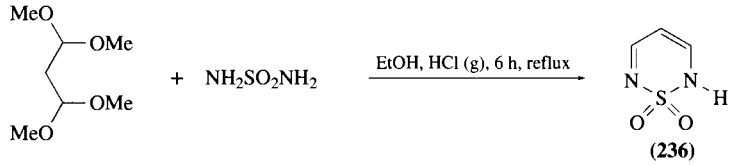
(233) (234) (235)

6.16.9.2 Formation of Two Bonds

6.16.9.2.1 [3 + 3] Fragments

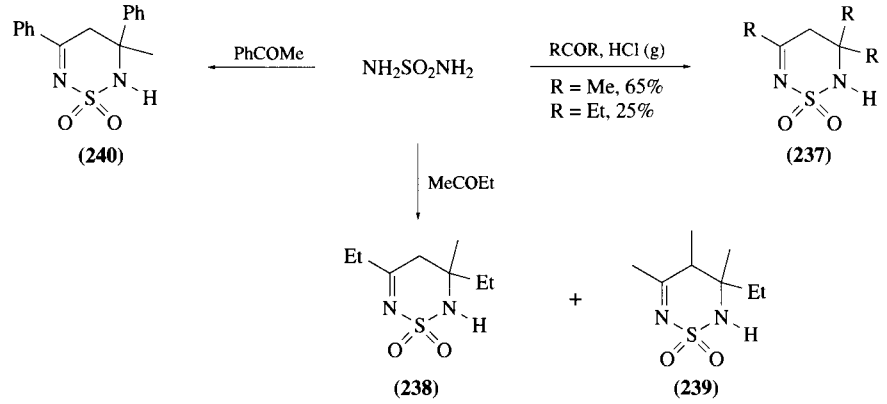
(i) From C—C—C— and N—S—N fragments

The condensation of sulfamides with malonyl derivatives continues to be a reliable synthetic route to 1,2,6-thiadiazine 1,1-dioxides. The parent system, 2*H*-1,2,6-thiadiazine 1,1-dioxide (**236**) is prepared in unspecified yield by condensing sulfamide with malonaldehyde tetramethyl acetal (Equation (30)) ⟨82JOC536⟩. The product, which resists purification by column chromatography, is isolated as a syrup, and is characterized satisfactorily on the basis of ^{1}H and ^{13}C NMR spectral data.



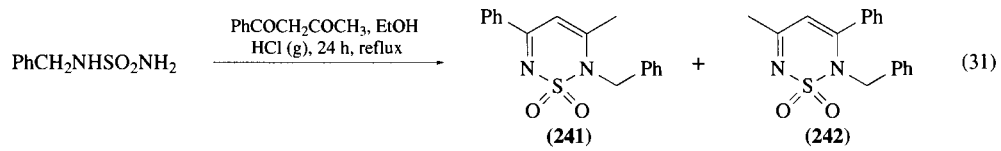
(30)

The condensation of β-diketones with sulfamide is a well-established route to 3,5-disubstituted 2*H*-1,2,6-thiadiazine 1,1-dioxides ⟨52JOC339⟩. A less used route is the formation of 3,3-disubstituted-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides (**237**) by acid-catalysed condensation of sulfamide with two equivalents of a ketone (Scheme 30) ⟨64JOC1865⟩. With unsymmetrical ketones, for example butanone, a mixture (41%) of isomers (**238**) and (**239**) is obtained, whereas with acetophenone the 3-methyl-3,5-diphenyl derivative (**240**) results in 21% yield.



Scheme 30

Condensation of an *N*-monosubstituted sulfamide with an unsymmetrical β-diketone gives rise to two isomeric products. In the case of *N*-benzylsulfamide and benzoylacetone the mixture of isomers (**241**) and (**242**) is produced in 90% yield, from which pure 2-benzyl-3-methyl-5-phenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**241**) is obtained in 60% yield by crystallization from ethanol (Equation (31)). Purification of the residue by TLC yields the 2-benzyl-5-methyl-3-phenyl isomer (**242**) ⟨82JOC536⟩.

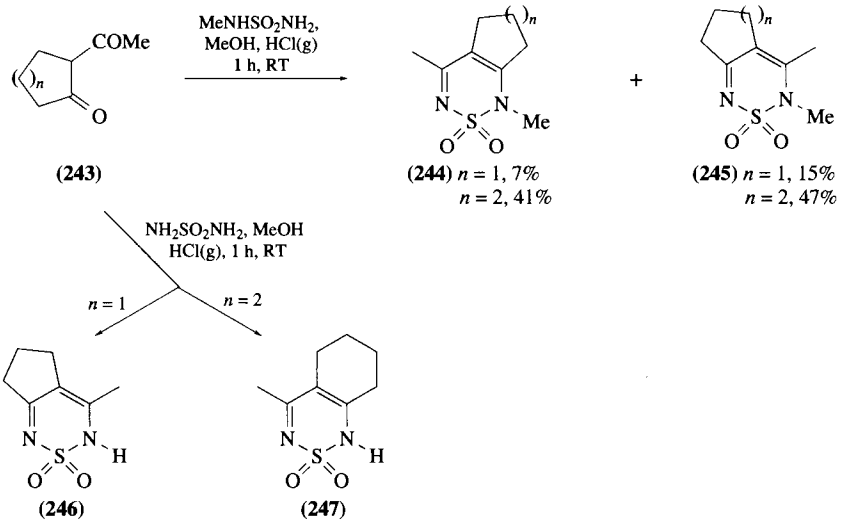


(31)

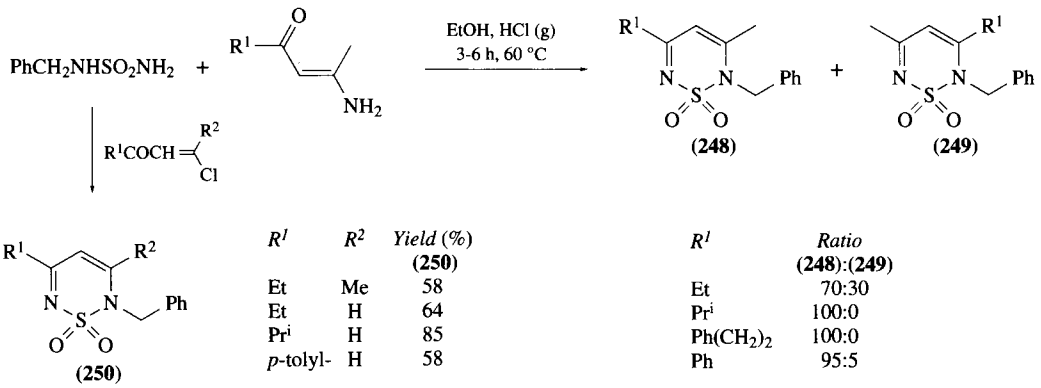
Likewise, *N*-methylsulfamide and 2-acetylcycloalkanones (**243**; $n = 1$ or 2) yield mixtures of the isomeric cycloalkano[1,2,6]thiadiazine 1,1-dioxides (**244**) and (**245**). However, with sulfamide the condensations are regioselective and with 2-acetylcyclopentanone (**243**; $n = 1$) yield exclusively the 2*H*-3-methyl derivative (**246**), whereas with 2-acetylcyclohexanone (**243**; $n = 2$) the 2*H*-5-methyl derivative (**247**) is the sole product (Scheme 31) ⟨94JCS(P2)1561⟩. The structures of these products have been confirmed by detailed NMR spectroscopic data (see Section 6.16.4.2).

It has been reported that β-amino- and β-chloro-αβ-unsaturated ketones undergo condensation with sulfamide to yield 2*H*-1,2,6-thiadiazine 1,1-dioxides in superior yields to those obtained using β-diketones ⟨91S355⟩. With unsymmetrically substituted sulfamides enhanced yields and regioselectivity are noted, particularly with the β-chloro compounds (see Scheme 32).

2,6-Disubstituted-4*H*-1,2,6-thiadiazin-3,5(2*H*,6*H*)-dione 1,1-dioxides (**251**) arise by condensation of N,N^1-disubstituted sulfamides with malonic acids ⟨84MI 616-01⟩ or with malonyl chlorides (Equation (32)) ⟨84GEP3230332, 84GEP3230923, 86JCS(P1)643, 87CJC298, 89BRP2213145, 92AP(325)509⟩.



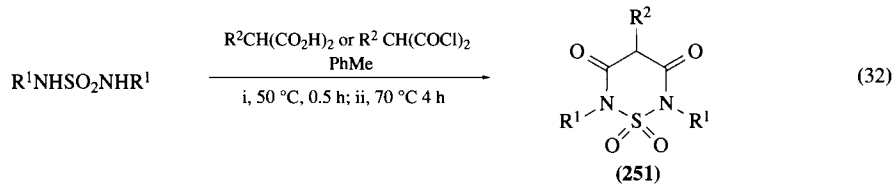
Scheme 31



R^1	R^2	*Yield* (%) (250)
Et	Me	58
Et	H	64
Pr^i	H	85
p-tolyl-	H	58

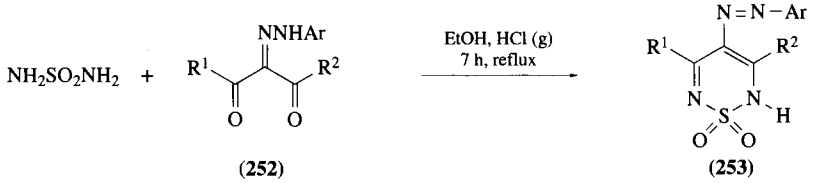
R^1	*Ratio* (248):(249)
Et	70:30
Pr^i	100:0
$Ph(CH_2)_2$	100:0
Ph	95:5

Scheme 32



(32)

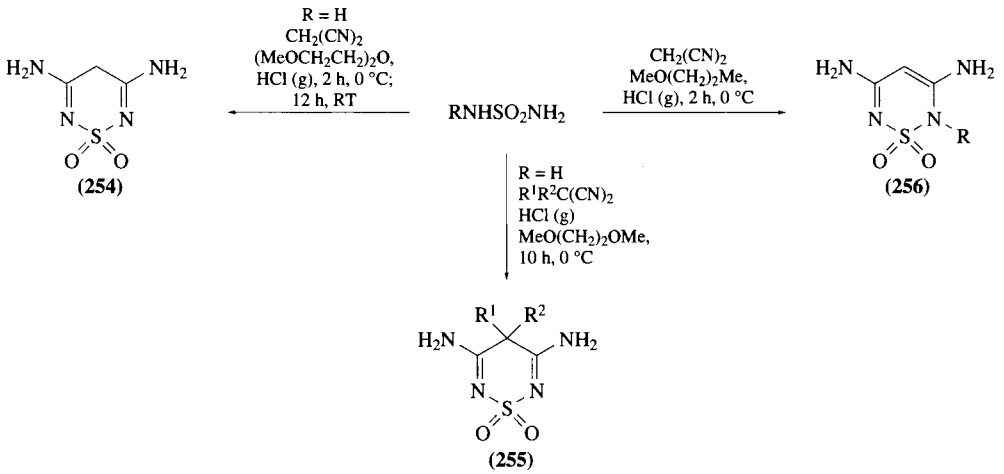
Tricarbonyl monohydrazones (e.g. (**252**)), prepared by classical Japp–Klingermann coupling of aryl diazonium salts with β-dicarbonyl compounds, undergo condensation with sulfamide to yield 4-arylazo-2*H*-1,2,6-thiadiazine 1,1-dioxides (**253**) rather than the tautomeric 4*H*-hydrazones (Equation (33)) ⟨83IJC(A)331, 89MI 616-03⟩.



(33)

Attempts in the late 1980s ⟨88JCS(P1)1271⟩, to repeat an earlier preparation ⟨48USP2454262⟩ of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**254**) by reaction of sulfamide with malononitrile in alcohol have failed. As a result, a modified procedure involving the acid-catalysed condensation of

malononitrile with sulfamide in diglyme or 1,2-dimethoxyethane was developed (Scheme (33)). This procedure has also been used to prepare 4,4-disubstituted-3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxides (**255**) from disubstituted malononitriles ⟨86MI 616-01⟩ and 2-substituted-3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides (**256**) in excellent yields (91–94%) from *N*-substituted sulfamides ⟨88JCS(P1)1271⟩.

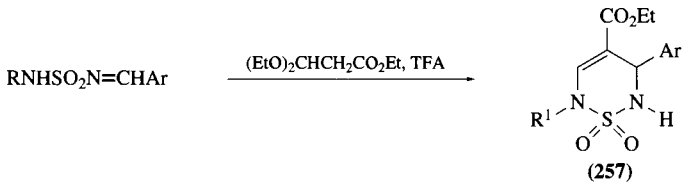


Scheme 33

Condensation of methylsulfamide, a useful byproduct from the ring contraction of 2,3,5-trimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (Section 6.16.6.5.2), with malononitrile in 1,2-dimethoxyethane yields 3,5-diamino-2-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**256**; R = Me), a product which is not available (Section 6.16.6.2) by direct methylation of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**254**) (Scheme 33) ⟨89H(29)245⟩.

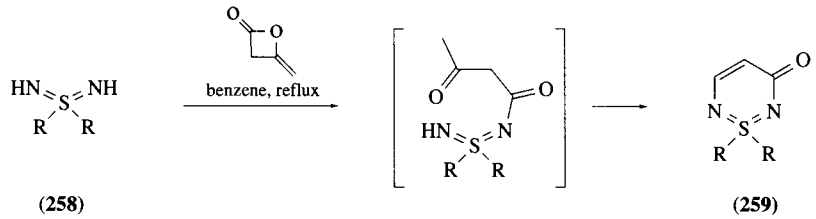
Condensation of ethoxymethylenemalononitrile [EtOCH=C(CN)$_2$] with sulfamide furnishes 5-amino-4-cyano-2*H*-1,2,6-thiadiazine 1,1-dioxide which is identical to the product formed by ring-transformation of 1,2,4,6-thiatriazine 1,1-dioxide with malononitrile anion (Section 6.16.10) ⟨84H(22)471⟩.

Ethyl 3-aryl-2,3-dihydro-6*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxides (**257**) are produced by condensation of alkylidenesulfamides with ethyl 3,3-diethoxypropionate in trifluoroacetic acid (Equation (34)) ⟨92MI 616-01⟩.



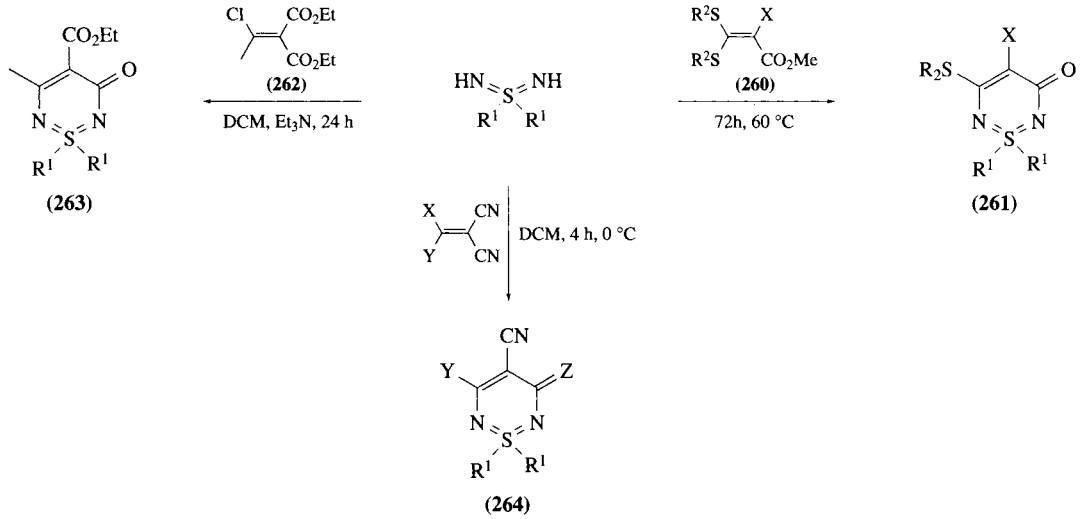
(34)

Condensation of *S*,*S*-dialkylsulfur diimides (**258**) with diketene provides convenient access to 1,1-dialkyl-1λ^6,2,6-thiadiazin-3-ones (**259**) in high yields (61–83%) (Equation (35)) ⟨85CB2561⟩. The same products are also obtained in lesser yields by using ethyl acetoacetate in place of diketene. Other β-keto esters react in a similar manner.



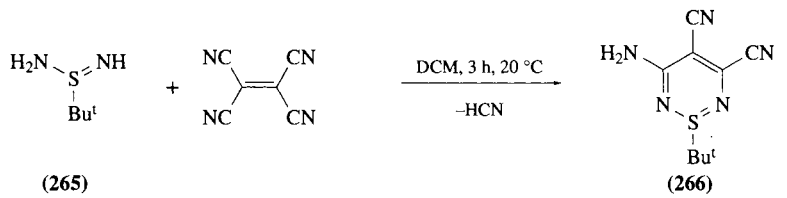
(35)

Related reactions are the condensations of thioketene *S,S*-acetals (**260**) which, with dialkylsulfur diimides, afford 5-alkylthio-1,1-dialkyl-1λ^6,2,6-thiadiazin-3-ones (**261**) generally in high yields (>80%) ⟨86CB1745⟩. In a similar manner, the chloroethylenomalonate (**262**) undergoes condensation with 1,1-dialkylsulfur diimides to give ethyl 1,1-dialkyl-5-methyl-1λ^6,2,6-thiadiazin-3-one-4-carboxylates (**263**), albeit in poor yields (15–35%) ⟨86CB1745⟩, whereas with malononitriles ($XYC{=}C(CN)_2$; X = MeO, EtO, MeS; Y = Me, Ph, or MeS) 1,1-dialkyl-4-cyano-1λ^6,2,6-thiadiazine derivatives (**264**; Z = O or NH) are obtained in variable yields (20–98%) (Scheme 34) ⟨87CB1455⟩.



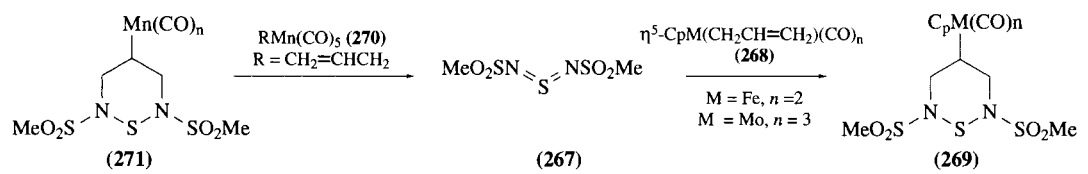
Scheme 34

5-Amino-3,4-dicyano-1-t-butyl-1λ^4,2,6-thiadiazine (**266**) is prepared in almost quantitative yield (95%) by condensation of t-butylsulfinimidamide (**265**) with tetracyanoethylene (Equation (36)) ⟨92ZAAC(615)49⟩.



(36)

η^1-Allyl η^5-cyclopentadienyl complexes (**268**; M = Fe or Mo) on treatment with bis(N,N^1-dimesyl)sulfinimide (**267**) yield the 2,3,5,6-tetrahydro-4*H*-1,2,6-thiadiazine complexes (**269**) in 60–75% yields ⟨86OM846⟩. The manganese pentacarbonyl-π-allyl complex (**270**) behaves similarly and the structure of the resulting product (**271**) was confirmed by x-ray crystallography (Scheme 35) ⟨86OM846⟩. The products appear to be derived by a [3 + 3] cycloaddition of the N=S=N moiety to C_1-C_3 of the η^1-allyl ligand of the metal carbonyl complex followed by a 1,2-metal migration.

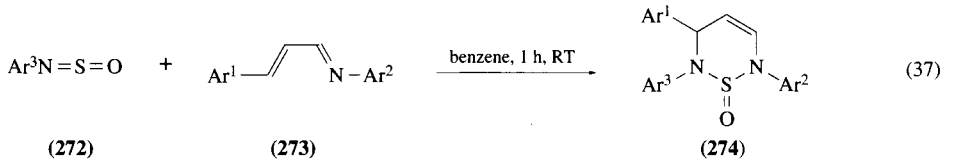


Scheme 35

6.16.9.2.2 [4 + 2] Fragments

(i) From C—C—C—N and N—S fragments

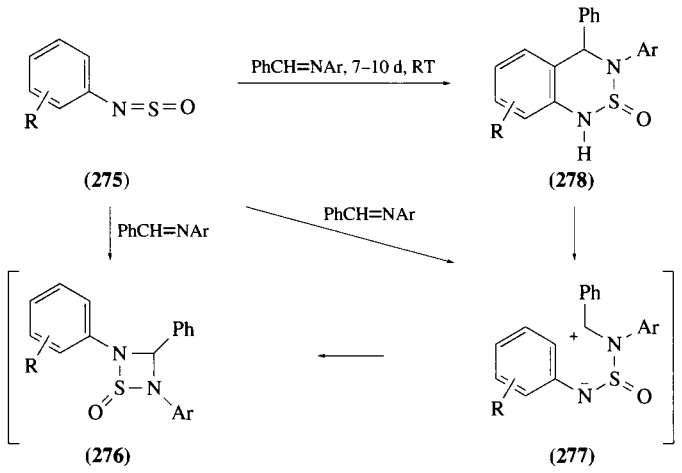
There is a solitary report on the synthesis of 2,5,6-triaryl-5,6-dihydro-2*H*-1,2,6-thiadiazine 1-oxides (**275**) by Diels–Alder [4 + 2] cycloaddition of 1,4-diaryl-1-aza-1,3-butadienes (**273**) with arylsulfinylamines (**272**) (Equation (37)). Yields are in the range of 60–80% ⟨88IJC(B)843⟩.



(272) (273) (274) (37)

(ii) From C—C—N—S and C—N fragments

Prolonged (7–10 d) stirring of equimolar amounts of arylsulfinylamines (**275**; R = H, 3-Me or 4-Me) and benzylideneanilines (PhCH=NAr; Ar = Ph, 3-MeC_6H_4 or 4-MeC_6H_4) at room temperature leads to the formation of 3,4-diaryl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2-oxides (**278**) in almost quantitative yields. ⟨85TL2813⟩. Interestingly, the 3-(methylphenyl)sulfinylamine (**275**; R = 3-Me) yields only the 7-methylbenzothiadiazine 2-oxide (**278**; R = 7-Me, Ar = 3-MeC_6H_4). The reaction is described as a cycloaddition with the sulfinylamine acting as the diene. However, equally feasible is a [2 + 2] cycloaddition to give the 1,2,4-thiadiazetidine 1-oxide (**276**) followed by ring opening and then ring closure of the polar intermediate (**277**), which can also be formed directly from the sulfinylamine by a polar addition as outlined in Scheme 36. In fact, *N*-alkylanils on treatment with phenylsulfinylamine yield benzylideneaniline (PhCH=NPh), via a cycloreversion of the initially formed [2 + 2]cycloadduct (**276**; Et in place of Ar), rather than a benzothiadiazine.



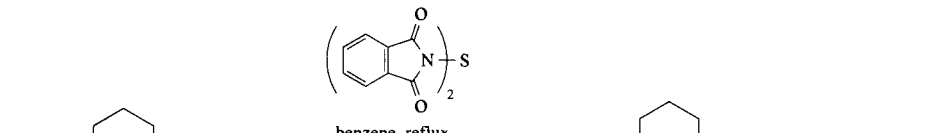
(275) (278) (276) (277)

Scheme 36

6.16.9.2.3 [5 + 1] Fragments

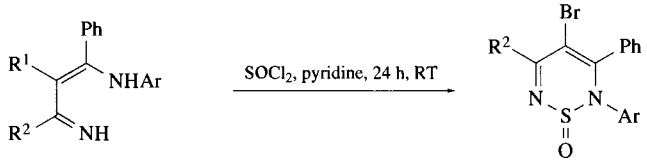
(i) From N—C—C—C—N and sulfur fragments

Rare examples of a perhydro-1,2,6-thiadiazine have been reported from the reaction of piperidyl sulfenyl chloride ⟨84JCS(P1)2591⟩ or, better and in superior yield (70–91% yield compared with 30% yield), by the action of *N*,*N*-thiobisphthalimide on *N*,*N*¹-dialkyl-1,3-diaminopropanes (**279**) (Equation (38)) ⟨72TL1481, 89SC2229⟩. Attempts to obtain the 1,2,6-thiadiazines (**280**) by condensing diaminopropanes with sulfur dichloride failed.



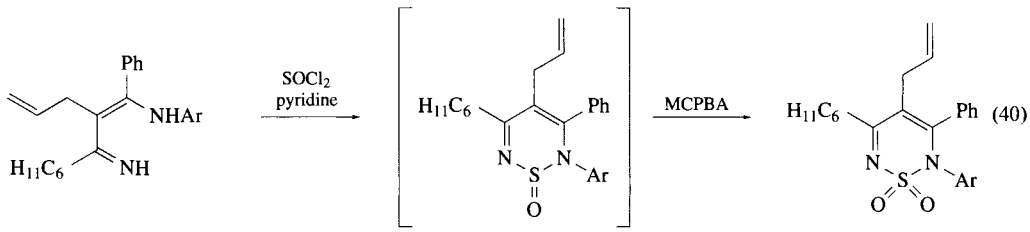
(279) (280) (38)

4-Arylamino-3-bromo-1-aza-1,3-butadienes (**281**; R^1 = Br), prepared by the action of *N*-bromosuccinimide on the 1-azadienes (**281**; R^1 = H), on treatment with thionyl chloride in cold pyridine furnish the 4-bromo-1,2,6-thiadiazine 1-oxides (**282**) in high yields (72–82%) (Equation (39)) ⟨83JCS(P1)2273⟩. In contrast, the 3-chloro-azabutadiene (**281**; R^1 = Cl) remains unchanged with thionyl chloride at room temperature, whereas at 70 °C the enamino ketone (**281**; C=O in place of C=NH) is formed rather than the chlorothiadiazine 1-oxide. At higher temperatures (100 °C) the bromo- and chloro-1-azadienes yield 4-chloropyrazoles by thermal extrusion of sulfur monoxide from the initially formed 1,2,6-thiadiazine 1-oxides (Section 6.16.6.1).



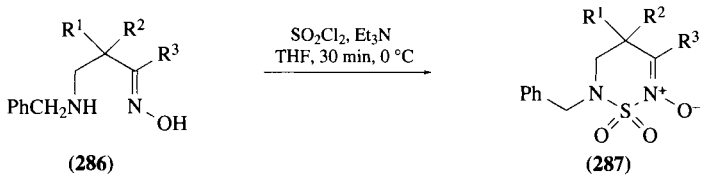
(281) (282) (39)

Ring-closure of the 3-allyl-4-arylamino-1-aza-1,3-butadiene (**283**; Ar = 4-MeC_6H_4) with thionyl chloride produces the fully substituted 1,2,6-thiadiazine 1-oxide (**284**), which is not isolated but is oxidised *in situ* with *m*-chloroperbenzoic acid (Section 6.16.6.4) to furnish the 1,1-dioxide (**285**) in 91% yield overall (Equation (40)) ⟨93JOC700⟩.



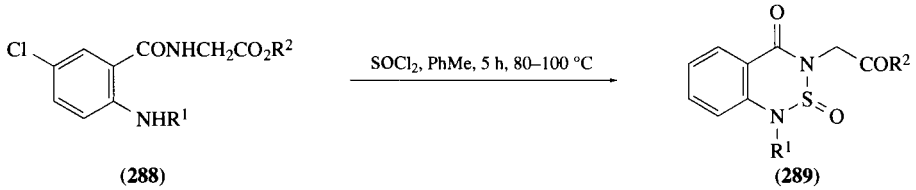
(283) (284) (285) (40)

A new, but low-yielding (7–26%), route to 5,6-dihydro-4*H*-1,2,6-thiadiazine 1,1,2-trioxides (**287**), involving the cyclization of *anti*-β-benzylamino-oximes (**286**) with sulfuryl chloride, has been developed during the early 1990s (Equation (41)) ⟨90LA775⟩. Under similar conditions the *syn*-β-benzylamino-oximes yield only pyrazoles.



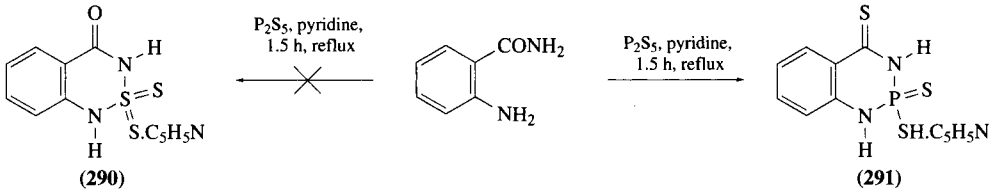
(286) (287) (41)

Ring-closure of 2-aminobenzamides (**288**) with thionyl chloride yields the 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 1-oxides (**289**) (Equation (42)) ⟨91JMC1492⟩.



(288) (289) (42)

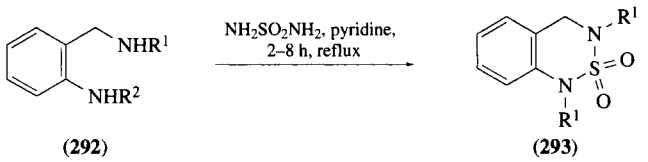
The novel and surprisingly stable 1*H*-2,1,3-benzothiadiazine-4-(3*H*)thione 2,2-disulphide was reported as yellow crystals of the 1 : 1 pyridine complex $C_7H_6N_2S_4 \cdot C_5H_5N$ (**290**; 56%; m.p. 189–190 °C; M^+ 246 ($C_7H_6N_2S_4$)) by treating 2-aminobenzamide with phosphorus pentasulfide in boiling pyridine ⟨83CC1002⟩. Curiously, however, and despite a supporting x-ray crystal structure for (**290**), repetition of the synthesis by other workers ⟨85HCA900⟩ resulted in the structure of the product being reassigned, mainly on the basis of high resolution MS, as the pyridine salt of 1,2,3,4-tetrahydro-4-thioxo-2,1,3-phosphadiazine-2-thiol 2-sulfide (**291**; m.p. 222–24 °C; 70%; M^+ found 245.9509; $C_7H_7N_2PS_3$ calc. 245.9512; M^+ calc. for $C_7H_6N_2S_4$ 245.9414) (Scheme 37).



(290) (291)

Scheme 37

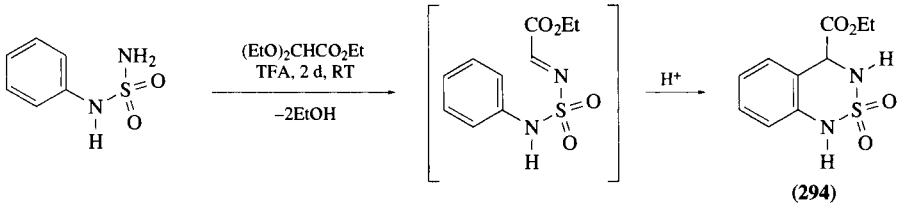
The use of sulfamide as a source of the SO_2 unit in the synthesis of 1,2,6-thiadiazine 1,1-dioxides has been realized in the reaction of 2-aminobenzylamines (**292**) in hot pyridine ⟨85CPB1104⟩. The 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides (**293**) are obtained in 66–73% yield (Equation (43)).



(292) (293) (43)

(iii) From C—C—N—S—N and carbon fragments

Ethyl 3,4-dihydro-1*H*-2,1,3-benzothiadiazine-4-carboxylate 2,2-dioxide (**294**) is prepared in moderate yield (50%) by intramolecular α-sulfamidoalkylation of *N*-phenylsulfamide using ethyl 2,2-diethoxyethanoate as the source of the one carbon fragment (Scheme 38) ⟨90JOC6098⟩.



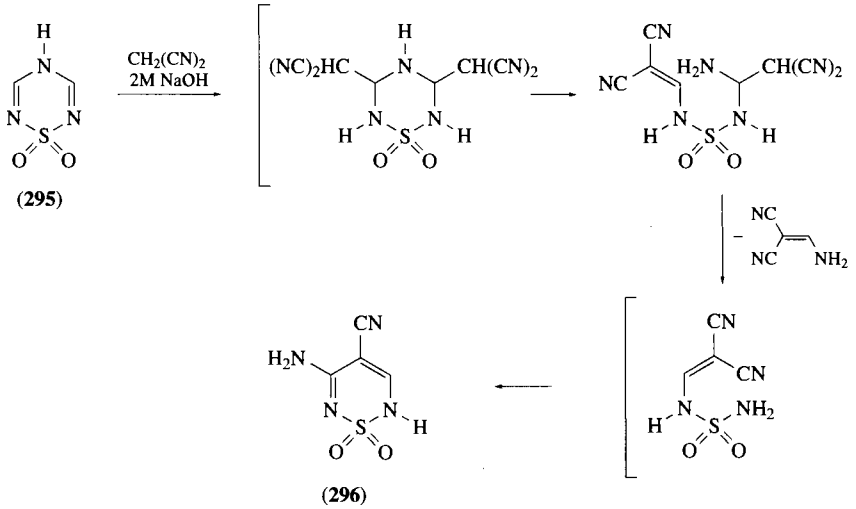
(294)

Scheme 38

6.16.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Treatment of 4*H*-1,2,4,6-thiatriazine 1,1-dioxide (**295**) with malononitrile anion leads to the formation of 5-amino-4-cyano-2*H*-1,2,6-thiadiazine 1,1-dioxide (**296**; R = NH_2) in 60% yield (see also Section 6.16.9.2.1.1) ⟨84H(22)471⟩. This ring transformation is proposed to go by a double carbanion addition at the 2,3- and 5,6- imine bonds followed by ring-opening and ring-closure, with

loss of 1-amino-2,2-dicyanoethene, of the intermediates so formed (Scheme 39). The reaction fails with the carbanions derived from malonamide and diethyl malonate, but with ethyl cyanoacetate 4-cyano-5-hydroxy-2*H*-1,2,6-thiadiazine 1,1-dioxide (**296**; OH in place of NH_2) is obtained.



(**295**)

(**296**)

Scheme 39

6.16.11 GENERAL SYNTHETIC METHODS

6.16.11.1 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. A solitary example of the 1,2,6-oxadiazine system has been prepared by the action of hydroxylamine on (diphenylmethylene)-malonaldehyde (Section 6.16.9.1.3), and 1,2,6-oxadiazine *N*-oxides are reported to be formed by oxidation of the dioximes of butane-1,3-dione with lead tetraacetate (Section 6.16.9.1.3).

6.16.11.2 1,2,6-Thiadiazines

There are many methods for the preparation of 1,2,6-thiadiazine 1,1-dioxides, the most common representatives of this ring system. The most obvious and most commonly applied route involves condensation of malonic acid and its derivatives, β-diketones, or β-keto esters with sulfamides (Section 6.16.9.2.1.1). An improvement using β-amino- and β-chloro- αβ-unsaturated ketones in place of β-diketones has been reported (Section 6.16.9.2.1.1). The use of malononitrile rather than the acid or its derivatives gives rise to 3,5-diamino-1,2,6-thiadiazine 1,1-dioxides (Section 6.16.9.2.1.1).

1,2,6-Thiadiazine 1,1-dioxides are also accessible by condensation of sulfamides with ethyl 3,3-diethoxypropionate in trifluoroacetic acid (Section 6.16.9.1.1), and by acid catalysed ring-closure of *N*-acetoacetylsulfamides (Section 6.16.9.1.2). Amino derivatives are obtained by acid-catalysed ring closure of *N*-(2,2-dicyanoethylidene)-sulfamide (Section 6.16.9.1.2) and by ring-contraction of 4*H*-1,2,4,6-thiatriazine 1,1-dioxides in the presence of malononitrile or ethyl cyanoacetate anions (Section 6.16.10).

The *N*-oxides of 1,2,6-thiadiazine 1,1-dioxides are obtainable by cyclization of *anti*-β-benzylamino-oximes with sulfuryl chloride (Section 6.16.9.2.3.1).

1,2,6-Thiadiazines lacking the *S*,*S*-dioxide function are much less common. They have been prepared by reaction of η^1-allylmetal complexes with *N*,*N*^{1}-dimesylsulfamide (Section 6.16.9.2.1.1), by treatment of 1,3-diaminopropanes with *N*,*N*-thiobisphthalimide (Section 6.16.9.2.3.1), and, in high yield, by cyclization of 4-arylamino-3-bromo-1-aza-1,3-butadienes with thionyl chloride in cold pyridine (Section 6.16.9.2.3.1).

Equally rare are 1,2,6-thiadiazine 1-oxides, however, they are available by cycloaddition of 1,4-diaryl-1-aza-1,3-butadienes with arylsulfinylamines (Section 6.16.9.2.2.1).

The uncommon 1λ^6,2,6-thiadiazine system is accessible as the 3-one derivatives, by the action of diketene on *S,S*-dialkylsulfur diimides. Similar products are also obtained by reaction of the diimides with thioketene *S,S*-diacetals and with chloroethylenemalonate (Section 6.16.9.2.1.1).

1λ^6,2,6-Thiadiazines lacking the carbonyl function are much rarer. One example has been reported from the condensation of a sulfinimidamide with tetracyanoethene (Section 6.16.9.2.1.1).

6.16.11.3 2,1,3-Benzothiadiazines

Cyclization of 2-aminobenzamide derivatives constitute the main synthetic approach to the 2,1,3-benzothiadiazine nucleus. 2,1,3-Benzothiadiazin-4(3*H*)-one 2,2-dioxides are available by the action of sulfamoyl chloride on methyl anthranilate, by treatment of 2-methylpyridinium salts of 2-sulfamoylbenzamides with phosphorus oxychloride (Section 6.16.9.1.2), by base-catalysed cyclization of *N*-(2-aminocarbonyl)sulfamides (Section 6.16.9.1.2), and by cyclization of 2-aminobenzamides with thionyl chloride (Section 6.16.2.3.1).

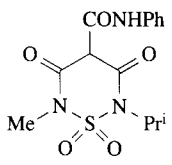
The less common 1*H*-2,1,3-benzothiadiazine 2,2-dioxides have been prepared by cyclization of 2-aminobenzylamines with sulfamide (Section 6.16.9.2.3.1) and their 4-amino derivatives, by ring closure of *N*-(2-cyanophenyl)sulfamides with aqueous sodium hydroxide (Section 6.16.9.1.2). The equally uncommon 2,1,3-benzothiadiazine 1-oxides are available in almost quantitative yields, by addition of arylsulfinylamines with benzylideneanilines (Section 6.16.9.2.2.2).

Examples of 2λ^6,1,3-benzothiadiazin-4(3*H*)-ones have been synthesized by base-catalysed cyclization of *N*-(2-chloro-4-nitrobenzoyl)-*S,S*,dialkylsulfur diimides (Section 6.16.9.1.2).

6.16.12 IMPORTANT COMPOUNDS AND APPLICATIONS

1,2,6-Thiadiazine 1,1-dioxides have been incorporated in silver halide photographic materials as development inhibitor releasing couplers ⟨87JAP(K)62291645⟩. Cephalosporins incorporating a 1,2,6-thiadiazin-2-yl 1,1-dioxide unit at the exomethylene side chain of the β-lactam have been prepared ⟨88USP4728733⟩. The corresponding 4-oxo-1*H*-2,1,3-benzothiadiazin-3-yl derivatives have also been prepared and are found to possess potent antibacterial activity ⟨86JAN380⟩. The 2,6-dialkyl-4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione-4-carboxyamide 1,1-dioxide (**297**) is a good fungicide ⟨84GEP3230332, 84GEP3230923⟩. Antiprotozoal activity has also been noted for these dialkyl diones and for 3,5-diamino-4-(5-nitro-2-furylidene)-4*H*-1,2,6-thiadiazine 1,1-dioxide (**146**) (Section 6.16.3.4) ⟨92AP(325)509⟩. 4-Hydroxy-5,6-dihydro-2*H*-1,2,6-thiadiazine-3-carboxyamide 1,1-dioxides (**298**) have antiinflammatory, analgesic, and antipyretic activity ⟨93GEP4141218⟩.

3,5-Diamino-4-arylazo-2*H*-1,2,6-thiadiazine 1,1-dioxides have been used as yellow–orange dyestuffs for paper ⟨92GEP4208535⟩. Antitrichomonal and antitrypanosomal activity of 1,2,6-thiadiazine 1,1-dioxides has been noted ⟨92MI 616-02⟩.



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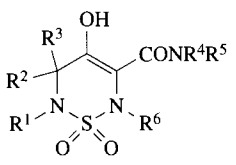
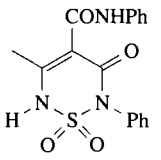


(298)

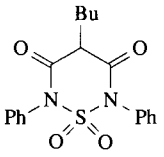
The anilide of 5-methyl-2-phenyl-6*H*-1,2,6-thiadiazin-3(4*H*)-one-4-carboxylic acid 1,1-dioxide (**299**) ⟨89EJM497⟩ and 2,6-diphenyl-4-butyl-4*H*-1,2,6-thiadiazine-3,5(2*H*,6*H*)-dione 1,1-dioxide (**300**) ⟨87CJC298⟩ are reported to have antiinflammatory activity comparable to that of phenylbutazone.

5-Chloro-3-(*p*-chlorophenoxy)-1,2,6-thiadiazin-4-one (**301**; R = 4-ClC$_6$H$_4$O) is used in low concentration (80 ppm) for the control of apple scab ⟨85USP4497807⟩, while 3,6-dichloro-1,2,6-thiadiazin-4-one (**301**; R = Cl) is an effective biocide against algae and fungus on wood and artificial materials ⟨90EUP363316⟩.

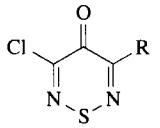
The *O*-allyl oxime (**302**), prepared from 2,6-dimethyl-4-propionyl-4*H*-1,2,6-thiadiazine-3,5 (2*H*,6*H*)-dione 1,1-dioxide (Section 6.16.6.3.2) has pronounced herbicidal activity ⟨89BRP2213145⟩.



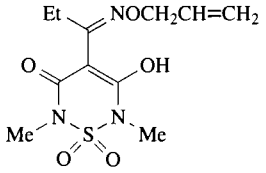
(**299**)



(**300**)

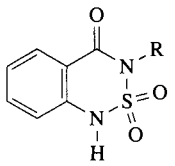


(**301**)

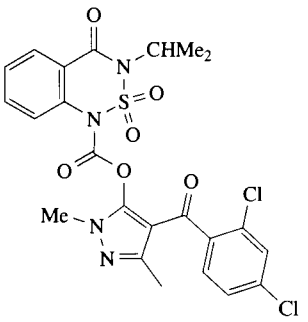


(**302**)

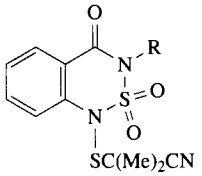
Commercially, the most important compound containing the 1,2,6-thiadiazine system is the benzologue, 3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (Bentazone) (**303**), which is a well-known, highly active and selective herbicide of long-standing ⟨81AG(E)151, 89CI(M)30⟩. More recently, in the mid-1980s, related compounds, for example the fluoroalkyl derivative [**303**; R = $CH(CH_2F)_2$] ⟨86GEP3429048⟩ and the pyrazolyl carbamate (**304**) ⟨85JAP(K)6016986⟩ have been reported to have significant herbicidal activity, whereas 1-(alkylthio) derivatives (e.g. **305**) have wheat root growth promoting properties ⟨82MI 8107612⟩.



(**303**)



(**304**)



(**305**)

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6.17
1,3,4-Oxadiazines and 1,3,4-Thiadiazines

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University of Salford, UK

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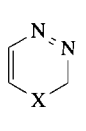
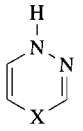
6.17.1 INTRODUCTION

Both 1,3,4-oxadiazines and 1,3,4-thiadiazines are well-known heterocyclic systems ⟨B-61MI 617-01, 62HC(17)447, 79COC(4)1051⟩. 2*H*- (**1**; X = O), 4*H*- (**2**; X = O), and 6*H*- (**3**; X = O) 1,3,4-oxadiazines are common, whereas the thiadiazines have been reported mainly as the 6*H*-derivatives (**3**; X = S). 1,3,4-Oxadiazin-2-ones, -5-ones, and -6-ones, and their thiadiazine analogues (e.g. **4**; X = O or S), are all known and for the hydro-derivatives in which lactam–lactim tautomerism is possible (e.g. **5**) they appear to exist as the lactam tautomer.


(1)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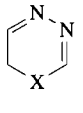
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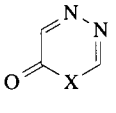
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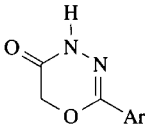
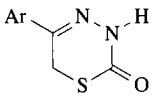

(5)

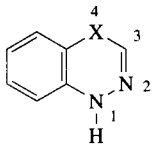
1,3,4-Oxadiazin-6-ones (**4**; X = O) function as 2,3-diazabutadienes in inverse electron-demand Diels–Alder cycloadditions (Section 6.17.5.9), and a review of the pioneering work in this field has appeared ⟨86G1⟩. Activity in the patent literature has testified to the importance of 2-aryl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones (**5**) and 5-aryl- and 5-heteroaryl-3,6-dihydro-2*H*-1,3,4-thiadiazin-2-ones (**6**) as effective cardiotonics (Sections 6.17.10.1 and 6.17.10.2).


(6)

Little chemistry has been carried out on the thiadiazine systems, which are much less stable than their oxygen analogues, and readily undergo ring contraction to pyrazoles and/or thiazolines under a variety of reaction conditions (Sections 6.17.5.1 and 6.17.5.2). There are no reports on the preparation of $1\lambda^4$,3,4-thiadiazines and only isolated examples of 1,3,4-thiadiazine *S*,*S*-dioxides have been synthesized. Also unknown are examples of the fully conjugated 1,3,4-oxonia- and 1,3,4-thionia-systems (**7**; X = O and S, respectively).

(7)

In contrast to the monocyclic systems in which numbering of the ring commences at the oxygen or sulfur atom, for the benzo-fused systems the numbering of the ring is as indicated in (**8**).



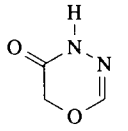
(**8**)

Surprisingly, there are only a few reports concerning the chemistry of 4,1,2-benzoxadiazines (**8**; X = O) and 4,1,2-benzothiadiazines (**8**; X = S).

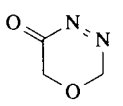
An excellent review of the early, and sometimes confusing, chemistry of 1,3,4-oxadiazines and 1,3,4-thiadiazines is available ⟨B-61MI 617-01⟩, and reviews of the chemistry of 1,3,4-thiadiazines have appeared ⟨69ZC361, 91CHE1159⟩.

6.17.2 THEORETICAL METHODS

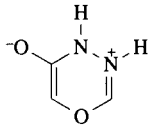
MNDO calculations have been used to determine the relative stabilities of the tautomeric 1,3,4-oxadiazin-5-ones (**9**) and (**10**) and the dipolar form (**11**), and also of the three isomeric 1,3,4-oxadiazin-2-ones (**12**)–(**14**) ⟨88CB887⟩. Calculated ΔH_f values are appended to the diagrams.



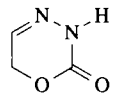
(**9**) –47.3 kcal mol^{-1}



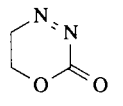
(**10**) –38.7 kcal mol–1



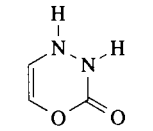
(**11**) –3.7 kcal mol–1



(**12**) –48.6 kcal mol^{-1}

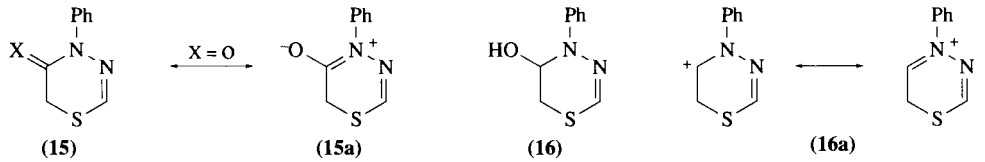


(**13**) –45.4 kcal mol^{-1}



(**14**) –37.5 kcal mol–1

The striking difference in reactivity and stability of the 4*H*-1,3,4-thiadiazin-5(6*H*)-one (**15**; X = O) and the 5-ol (**16**) have been discussed in terms of resonance stabilization based on spectral data and extended Hückel MO calculations ⟨87NKZ1312⟩. The lactam exhibits typical amide resonance (**15**↔**15a**) and is resistant to attack by electrophiles, nucleophiles, and free radicals, whereas the reactivity of the 5-ol (**16**) towards displacement of the hydroxy group by nucleophiles is attributed to resonance stabilization of the thiadiazinium cation (**16a**) formed by heterolysis of the C—OH bond. Extended Hückel MO calculations on the thione analogue of the thiadiazinone, coupled with spectroscopic data, indicate that this system is best represented as the thione (**15**; X = S) ⟨89CE797⟩.



(**15**) (**15a**) (**16**) (**16a**)

6.17.3 EXPERIMENTAL STRUCTURAL METHODS

6.17.3.1 Spectroscopic Studies

No detailed spectroscopic analyses of the 1,3,4-oxadiazine and 1,3,4-thiadiazine systems have been reported, and all spectral data recorded is of a routine nature.

6.17.3.1.1 Ultraviolet and infrared spectra

1,3,4-Oxadiazin-6-ones are colored oils which absorb at 274–475 nm ⟨86G1⟩.

4-Phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**15**; X = O) exhibits absorption maxima at 240 (ε_{max} 12 000) and 300 (ε_{max} 2800) nm, whereas for the 5-ol (**16**) λ_{max} occur at 250 (ε_{max} 10 200) nd 285 (ε_{max} 14 640) nm ⟨85PS(22)41⟩.

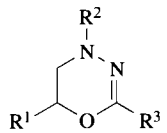
From UV studies it is concluded that 5-phenyl-6*H*-1,3,4-thiadiazine-2(3*H*)-thione prefers the thione rather than the 2-thiol form ⟨85H(23)3099⟩.

The carbonyl stretching frequency for thiadiazinone (**15**; X = O) is seen at 1640–1660 cm^{-1} ⟨84CPB1590⟩.

6.17.3.1.2 NMR spectra

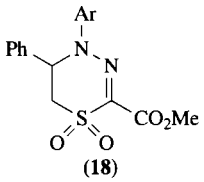
(i) Proton NMR spectra

The C-5 and C-6 methylene protons of 5,6-dihydro-4*H*-1,3,4-oxadiazines (**17**; R^1 = H) appear in the ranges 3.7–4.0 δ and 4.4–4.6 δ, respectively ⟨84JOU651, 86HCA333, 92JHC1081⟩. The methylene group at C-5 in 6-substituted 2-phenyl-4-benzyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (**17**; R^2 = $PhCH_2$, R^3 = Ph) appears as a pair of double doublets at 4.7–4.8 and 3.7 δ with J_{ab} = 13 Hz, J_{ax} = 3 Hz, and J_{bx} = 9 Hz. The proton at C-6 is found as a multiplet at 5.6–6.2 δ ⟨85JCS(P2)1759⟩.



(**17**)

4-Aryl-4*H*-1,3,4-thiadiazin-5(6*H*)-ones (e.g. **15**; X = O) exhibit proton resonances at 7.7–7.8 δ (2-*H*), and 3.5–3.75 δ (6-CH_2) ⟨84CPB1590, 85PS(22)41⟩, whereas the 5,6-dihydro-4*H*-1,3,4-thiadiazin-5-ol (**16**) and the 5-alkoxy-, 5-alkylthio-, and 5-alkylamino-derivatives (**16**; RO-, RS-, and RNH-, respectively, in place of OH) have CH_2 resonances, which in the case of the alkylthio- and alkylamino compounds occur as multiplets, at 3.1–3.8 δ, with the C-5 proton appearing at 5.0–5.5 δ ⟨85PS(22)41⟩. The protons at C-5 and C-6 of the 4,5-diaryl-5,6-dihydro-4*H*-1,3,4-thiadiazine 1,1-dioxides (**18**; Ar = Ph) absorb at 5.97 δ (t) and 3.74 δ (d), respectively (J = 5 Hz) ⟨90H(31)1537⟩. The tautomeric 2-amino-6*H*- and 2-amino-4*H*-1,3,4-thiadiazines are readily distinguished by means of their PMR spectra. The C-6 protons of the 6*H*-tautomers resonate as 2-proton singlets at 3.6–3.9 δ, whereas the C-6 protons of the 4*H*-tautomers are seen downfield as one-proton singlets around 5.6 δ ⟨78CPB3017, 85OPP206⟩.

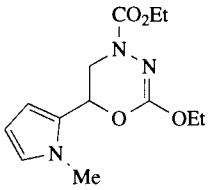


(**18**)

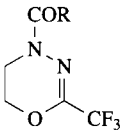
(ii) Carbon-13 NMR spectra

Carbon-13 NMR spectroscopy has been instrumental in determining the structures of the 1,3,4-oxadiazines (e.g. **19**), that are formed as major products in the cycloaddition of 1-methyl-2-vinylpyrroles with diethyl azodicarboxylate (Section 6.17.7.2.2.1); C-5 is noted at 53.6 δ whereas C-6 appears at 72.9 δ ⟨85JCR(S)12⟩. Carbon resonances for 4-acyl-2-(trifluoromethyl)-5,6-dihydro-4*H*-

1,3,4-oxadiazines (**20**) occur at 134.9–137.6 δ (C-2), 39.5–40.7 δ (C-5), and 64.0–65.6 δ (C-6), respectively, while the trifluoromethyl carbon appears at 116–118 δ ⟨86HCA333⟩.



(19)



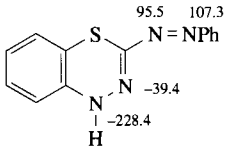
(20)

The carbon resonances for the 4*H*-1,3,4-thiadiazin-5(6*H*)-one (**15**; X = O) are at 27 δ (C-6), 136 δ (C-2), and 153 δ (C-5) compared with 29 δ (C-6), 124 δ (C-2), and 71 δ (C-5) for the 5-ol (**16**) ⟨85PS(22)41⟩.

Carbon resonances at 24.76 (C-6), 187.69 (C-2), and 147.85 (C-5) δ have been reported for 5-phenyl-6*H*-1,3,4-thiadiazine-2(3*H*)-thione (**6**; Ar = Ph) ⟨85H(23)3099⟩.

(iii) Nitrogen-15 NMR spectra

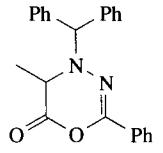
Other than a detailed analysis of the ^{15}N NMR spectrum of 3-phenylazo-1*H*-4,1,2-benzothiadiazine (**21**) (Section 6.17.7.2.2.2) no other ^{15}N NMR spectral data for 1,3,4-oxadiazines or their thio-analogues appear to have been published. Nitrogen-15 chemical shift data (with respect to CH_3NO_2) for azo-compound (**21**) are appended to (**21**) ⟨90MRC1027⟩.



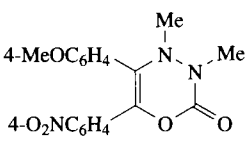
(21)

6.17.3.2 X-ray Crystallography

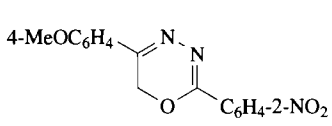
X-ray crystal structures for 4-(diphenylmethyl)-5-methyl-2-phenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one (**22**) ⟨84JOC2204⟩, 3,4-dimethyl-5-(4-methoxyphenyl)-6-(4-nitrophenyl)-4*H*-1,3,4-oxadiazin-2(3*H*)-one (**23**) ⟨88CB887⟩, 2-(2-nitrophenyl)-5-(4-methoxyphenyl)-6*H*-1,3,4-oxadiazine (**24**) ⟨85CB4026⟩, and 2-phenyl-5-(benzoylhydrazono)-5,6-dihydro-4*H*-1,3,4-oxadiazine (**25**) ⟨85CB4026⟩ have been recorded.



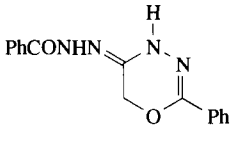
(22)



(23)



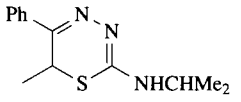
(24)



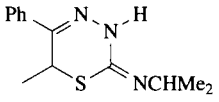
(25)

X-ray studies reveal that the unit cell of the monoclinic 4-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazin-5-ol (**16**) is built of pairs of the (*S*)- and (*R*)-enantiomers, and that the S—C2—N3—N4 atoms are coplanar ⟨85PS(22)41⟩. The x-ray crystal structure of 2-(isopropylamino)-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine has been determined and from a careful consideration of the C2—N3 and C2—NHPr^i bond lengths (1.297 and 1.350 Å, respectively), it is concluded that, in the solid state,

the amine tautomer (**26**) rather than the 2-imino form (**27**) is preferred ⟨93ACS302⟩. In contrast, x-ray data for the corresponding 1,3,4-selenadiazine are consistent with the imine tautomer.

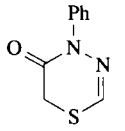


(**26**)



(**27**)

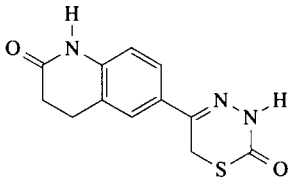
As a result of an x-ray crystal structure determination, the product obtained by the action of triethylamine on (methoxycarbonyl)methyl-*N*-(phenylamino)thioformimidate (Section 6.17.7.1.2) has been assigned as 4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**28**) ⟨83PS(16)89⟩.



(**28**)

A redetermination of the structure of the commonly encountered oxidation product of the metal complexing agent "dithizone" (PhN=NC(S)NHNHPh) has confirmed it to be 3-phenylazo-1*H*-4,1,2-benzothiadiazine (**21**) ⟨69CC392, 82AJC2157⟩. The crystals of the azo-compound are orthorhombic and the substantially planar molecule is present as the 1*H*-tautomer in the solid state.

The crystal structure of the β-form of the valuable cardiotonic (**29**), obtained by heating the α-form under reflux in aqueous ethanol, has been determined ⟨90JAP(K)02279685⟩.



(**29**)

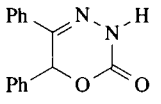
6.17.4 THERMODYNAMIC ASPECTS

6.17.4.1 Aromaticity, Tautomerism, and Ring Conformation

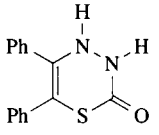
None of the 1,3,4-oxadiazines or 1,3,4-thiadiazines mentioned in this chapter exhibits aromaticity, and only a few isolated studies have been made concerning the existence of tautomerism in these systems.

Treatment of 5,6-diphenyl-6*H*-1,3,4-oxadiazin-2(3*H*)-one (**30**; mp 192°C) with strong base (Ph_3C^-) brings about isomerization to a higher-melting (217°C) product to which the 4*H*-1,3,4-oxadiazin-2(3*H*)-one structure (**31**) has been assigned ⟨88CB887⟩.

There have been no further reports on the conformation of 1,3,4-oxadiazine and 1,3,4-thiadiazine systems since the early studies on tetrahydro-3,4-dimethyl-1,3,4-oxadiazine ⟨76JCS(P2)1861, 77JCS(P2)1816⟩ and the corresponding dimethyl 1,3,4-thiadiazines ⟨78CHE1281, 80JCS(P2)279⟩.



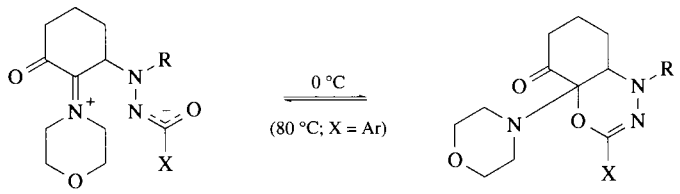
(**30**)



(**31**)

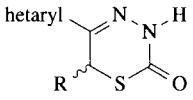
Ring-chain tautomerism (**32** ⇌ **33**), which is well established for tetrahydro-1,3,4-oxadiazines ⟨73CHE830⟩ and for tetrahydro-1,3,4-thiadiazines ⟨79CHE1314⟩, has been observed on heating the bicyclic 1,3,4-oxadiazines (**33**; R = CO_2Et or COAr) (Section 6.17.7.2.2.1) in boiling benzene ⟨82G335,

83JHC305〉. In contrast, the diaryl derivatives (**33**; R = X = Ar) are stable as solids and in solution at room temperature.



(**32**) (**33**)

An effective process for the resolution of racemic 5-heteroaryl-6*H*-1,3,4-thiadiazin-2(3*H*)-ones (**34**), effective cardiotonics (Section 6.17.10.2), has been developed which involves *N*-acylation of the racemic mixture with chiral camphoric acid chloride followed by kinetic cleavage of the resulting diastereomeric amides with an amine 〈93GEP4129062〉.



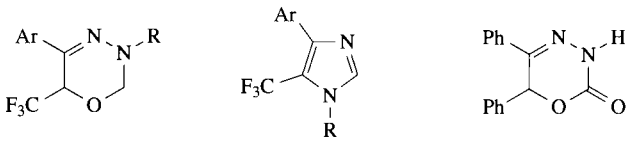
(**34**)

There is some spectroscopic evidence (PMR and IR) to suggest that 2-amino-1,3,4-thiadiazines exist as mixtures of the 4*H*- and 6*H*-tautomers. The former dominate in solution and the latter in the solid state 〈67YZ539, 77ZC173, 84EGP209196, 85OPP206〉. (See also Section 6.17.7.2.2.2.)

6.17.5 REACTIVITY OF NONCONJUGATED RINGS

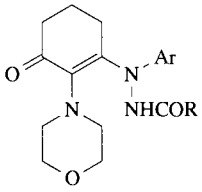
6.17.5.1 Thermal and Photochemical Unimolecular Reactions

5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines (**35**) (Section 6.17.7.1.1) in boiling toluene undergo slow ring-contraction and rearrangement to 4-aryl-5-(trifluoromethyl)-imidazoles (**36**) 〈90JHC487〉. 5,6-Diphenyl-6*H*-1,3,4-oxadiazin-2(3*H*)-one (**37**), however, on thermolysis in benzene at 180°C suffers stepwise loss of CO_2 and N_2 to form a mixture of *cis*- and *trans*-stilbene 〈65JA5716〉.



(**35**) (**36**) (**37**)

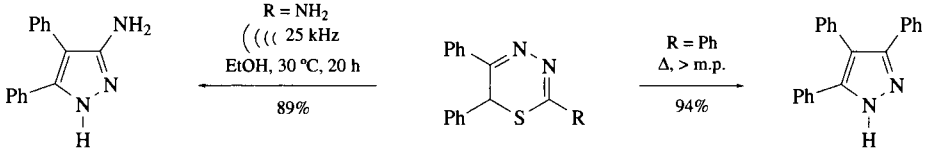
1,3-Diaryl-4a,5,6,7,8,8a-hexahydro-1*H*-4,1,2-benzoxazin-5-ones (**33**; R = X = Ar) on prolonged heating (16 h) in benzene undergo isomerization to the acylhydrazides (**38**) 〈82G335〉. In contrast, the 1-acyl-3-aryl-derivatives (**33**; X = Ar, R = CO_2Et, or COAr) are unstable at room temperature and exist in equilibrium with the open-chain enamine tautomers (Section 6.17.4.1).



(**38**)

In contrast to the 1,3,4-oxadiazines (**35**), 6*H*-1,3,4-thiadiazines (**39**) on heating at temperatures above their melting points 〈74JAP(K)74100080, 86EGP235640, 91EGP293348〉, or on prolonged boiling in nonpolar organic solvents 〈75JAP(K)75130760, 76JPR(318)971, 76ZC80〉 undergo rearrangement to

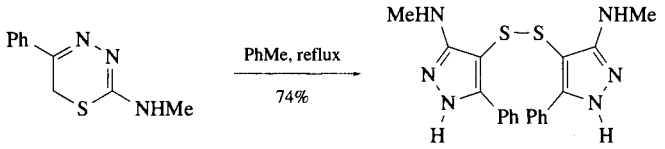
pyrazoles (**40**), accompanied by extrusion of sulfur, (see also Sections 6.17.5.2 and 6.17.5.7). More recently similar reactions (e.g. **39**→**41**) have been effected in excellent yields using ultrasound (Scheme 1) ⟨87ZC296, 88EGP253030⟩.



(41) (39) (40)

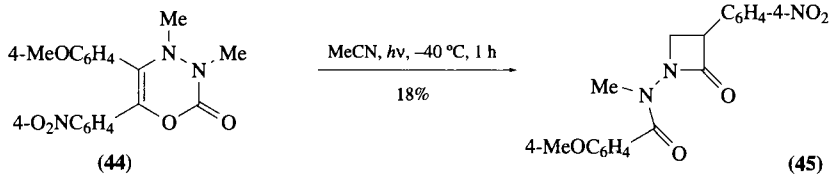
Scheme 1

Occasionally, bis-(pyrazol-4-yl) disulfides (e.g. **43**) are formed either on heating the 1,3,4-thiadiazine (e.g. **42**) at 180°C ⟨74JAP(K)74100080⟩ or under reflux in toluene (Equation (1)) ⟨91EGP288824⟩.



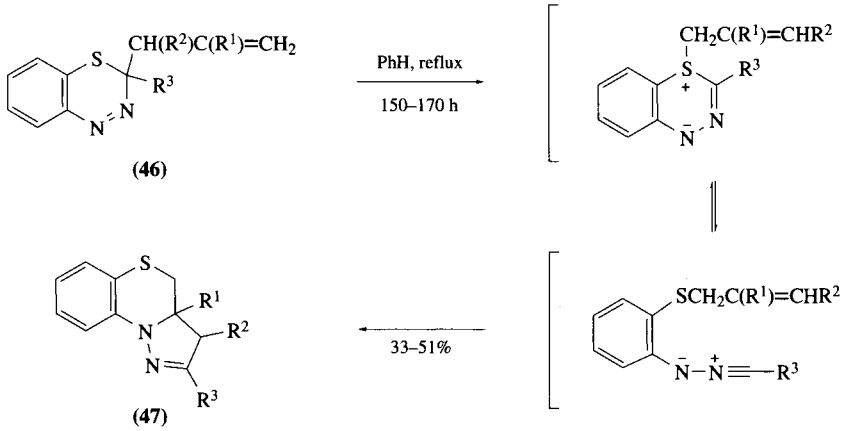
(42) (43) (1)

Few photochemical reactions of 1,3,4-oxadiazines and 1,3,4-thiadiazines have been reported. However, the 5,6-diaryl-4*H*-1,3,4-oxadiazin-2(3*H*)-one (**44**) on photolysis in acetonitrile undergoes ring contraction to the azetidinone (**45**), albeit in low yield (Equation (2)) ⟨88CB887⟩. In contrast, 5,6-diphenyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one on photolysis undergoes loss of CO_2 to yield a mixture of (*E*)- and (*Z*)-stilbene ⟨68JA1061⟩.



(44) (45) (2)

3,3-Disubstituted-3*H*-4,1,2-benzothiadiazines (**46**) (Section 6.17.7.1.3) possess varying degrees of thermal stability. The esters (**46**; $R^3 = CO_2Et$) are stable in boiling benzene, whereas the 3-(4-nitrophenyl)-derivatives (**46**; $R^3 = 4\text{-}NO_2C_6H_4$) on prolonged heating rearrange to the dihydropyrazolo[3,2-*c*][1,4]benzothiazines (**47**) as illustrated in Scheme 2 ⟨84JCS(P1)2535⟩.

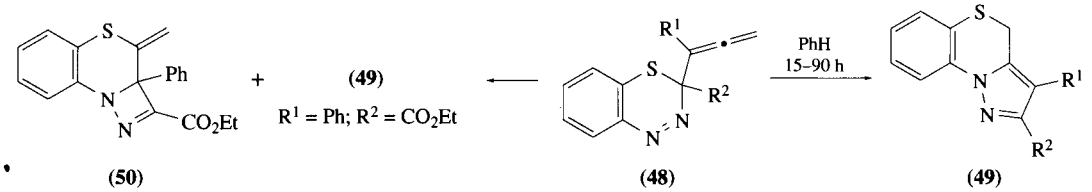


(46) (47)

Scheme 2

Likewise, the 3-allenyl-derivatives (**48**) yield the corresponding pyrazolo[3,2-*c*][1,4]-benzothiazines (**49**). However, in the case of the 3-(1-phenylallyl)-4,1,2-benzothiadiazine-3-carboxylate (**48**;

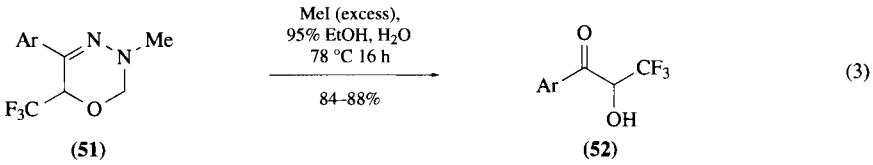
R^1 = Ph, R^2 = CO_2Et) formation of the pyrazolo-1,4-benzothiazine (**49**) is accompanied by the novel diazeto[2,3-*c*][1,4]benzothiazine (**50**; 13%), for which an x-ray crystal structure has been obtained ⟨84AX(C)1476⟩.



Scheme 3

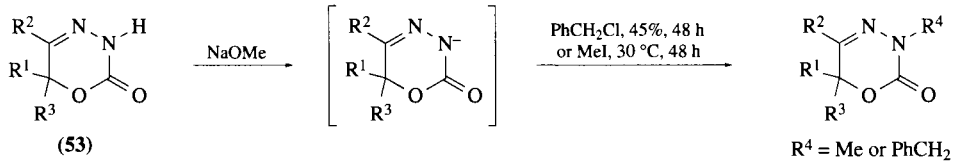
6.17.5.2 Electrophilic Attack at Nitrogen

6-Trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines (**51**) with an excess of iodomethane in hot ethanol undergo ring scission to the 2-hydroxy-ketones (**52**) in high yields (Equation (3)) ⟨88S208⟩.



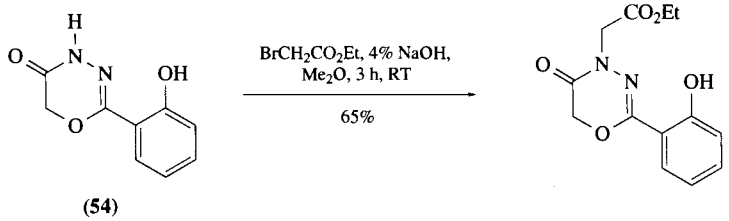
(3)

In contrast, 3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones (**53**) in the presence of sodium methoxide are methylated and benzylated exclusively at N-3 in high yields (60–85%) (Scheme 4) ⟨86EJM403⟩.



Scheme 4

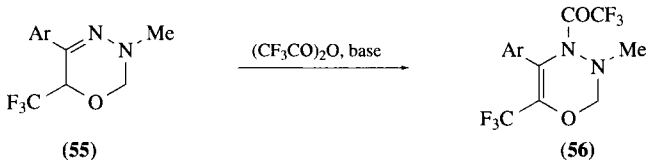
Surprisingly, treatment of 2-(2-hydroxyphenyl)-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**54**) with ethyl bromoacetate in aqueous alkali results in regioselective alkylation at N-4 rather than at the phenolic hydroxy-group (Equation (4)) ⟨91JIC574⟩.



(4)

5,6-Diphenyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**37**), in the presence of sodium hydride, is tosylated at N-3 ⟨83TL4635⟩.

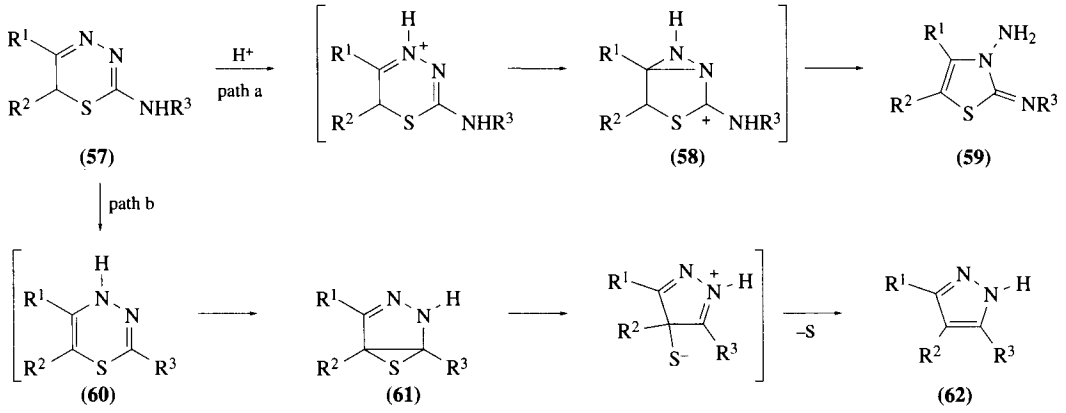
Trifluoroacetylation of 5-aryl-3-methyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazine (**55**) with trifluoroacetic anhydride in the presence of an organic base yields the 4-(trifluoroacetyl)-2*H*-3,4-dihydro derivative (**56**) (Equation (5)). In the absence of base only small amounts of product (**56**) are formed along with large amounts of unidentified materials ⟨90TL1183⟩.



(55) (56) (5)

4,1,2-Benzoxazine-5,8-diones (e.g. **101**; Section 6.17.5.8) undergo acetylation at N-1 in acetic anhydride ⟨85IJC(B)307⟩.

The acid-catalyzed rearrangement of 2-amino-6*H*-1,3,4-thiadiazines (**57**) to 3-amino-2-imino-thiazolidines (**59**) has long been known, and was the cause of some confusion in the early literature ⟨B-61MI 617-01⟩. Kinetic studies have since shown that the rate of rearrangement increases with increasing acid concentration and reaction temperature, and is dependent on the nature of the 5-substituent (R^1); decreasing in the order 5-alkyl > 5-benzyl > 5-aryl. Some 2-amino-5-aryl-6*H*-1,3,4-thiadiazines (**57**; R^1 = Ar) resist rearrangement while others do so only in boiling concentrated acid ⟨80JCS(P2)890, 91JHC1365⟩ and, in some cases, accompanied by extrusion of sulfur and formation of pyrazoles ⟨69ZC361, 78ZC65, 87ZC296, 88MI 617-01⟩. In fact, in strong acid solution desulfurization and rearrangement to a 5-amino-4-arylpyrazole (**62**; R^2 = Ar, R^3 = NHR) can become the dominant reaction ⟨70LA(741)45, 77ZC173, 85EGP228248⟩. A mechanistic rationale (path a) for the 1,3,4-thiadiazine–thiazolidine rearrangement involving the bicyclic diaziridine intermediate (**58**), produced by a transannular reaction as shown in Scheme 5, has been proposed ⟨80JCS(P2)890⟩. An alternative mechanism involving hydrolytic cleavage of the N4—C5 bond has also been considered ⟨69ZC361, 88MI 617-01⟩.



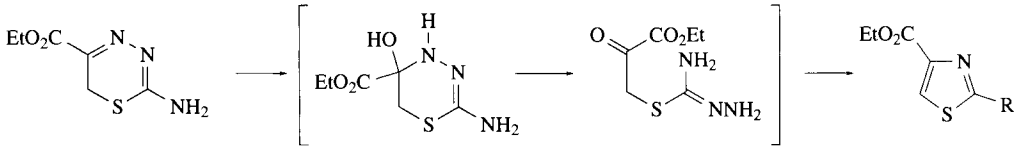
Scheme 5

It was found for 5-alkyl-2-amino-6*H*-1,3,4-thiadiazines (**57**; R^1 = alkyl) that the rate of rearrangement decreases in the order Me > Et > Pr^i > Bu^t, i.e. in accordance with an S_N2 type mechanism for diaziridine ring-formation, whereas for the 5-aryl derivatives an S_N1 process is envisaged. In the absence of a 5-substituent, rearrangement is slowed markedly, whereas 6,6-disubstituted and N-3 substituted derivatives fail to rearrange. MNDO calculations suggest that a neighboring group effect by sulfur is operating during rearrangement of the 5-alkyl derivatives ⟨89DIS(B)157⟩.

The means by which sulfur is lost has not been elucidated fully, but isomerization of the 6*H*-1,3,4-thiadiazine to the less stable 8π 4*H*-tautomer (**60**) followed by elimination of sulfur from a bicyclic thiirane (**61**) as outlined in Scheme 5 (path b) seems likely ⟨91CHE1159⟩. Alternatively, loss of sulfur may occur from a bis-(pyrazol-4-yl)disulfide (**43**).

There is one report, however, that in hot acid, ethyl 2-amino-6*H*-1,3,4-thiadiazine-5-carboxylate (**63**), unlike the 5-alkyl-2-amino derivatives, fails to give the 2-imino-3-aminothiazoline, but rather ethyl 2-hydrazinothiazole-4-carboxylate (**64**; R = $NHNH_2$) by hydrolytic cleavage of the N4—C5 bond and recyclization as outlined in Scheme 6 ⟨91CHE442⟩. The ring contraction also takes place in boiling nitric acid whereupon ethyl 2-azidothiazole-4-carboxylate (**64**; R = N_3) is obtained (34%) by diazotization of the 2-hydrazino-compound (**64**; R = $NHNH_2$) with nitrous acid formed *in situ* by a redox reaction between the hydrazine and nitric acid.

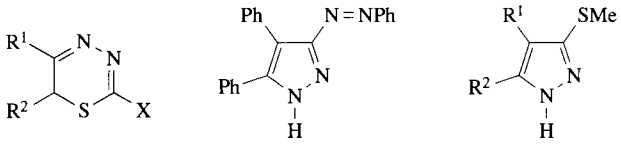
The rearrangement of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines (**57**; R^1 = Ar) in hot acetic acid has some merit as a synthetic route to 5-amino-3-arylpyrazoles (**62**; R^1 = Ar) ⟨87MI 617-01⟩. The yields of pyrazole increase markedly relative to those obtained from the 6-unsubstituted thiadiazine (**57**;



(63) (64)

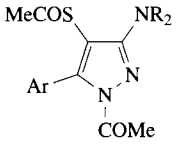
Scheme 6

R^2 = H) if an aryl, acyl, or alkoxy group is present at the 6-position ⟨69ZC361, 76JPR(318)971, 77S196, 77ZC173, 77ZC218, 78CCC1227, 78ZC65, 84CPB152⟩. The 2-(phenylhydrazino)-6*H*-1,3,4-thiadiazine (**65**; X = PhNHNH, $R^1 = R^2$ = Ph) rearranges smoothly in hot acetic acid to 4,5-diphenyl-3-phenylazopyrazole (**66**; 74%) ⟨89ZC288⟩. Likewise, 3-methylthio-derivatives (**67**) are formed from 2-methylthio-6*H*-1,3,4-thiadiazines (**65**; X = SMe) ⟨84CPB152⟩.



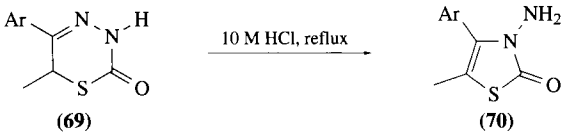
(65) (66) (67)

Ring contraction of 1,3,4-thiadiazines to pyrazoles also takes place in boiling acetic anhydride but in this case the sulfur fragment is retained in the final product as an acetylthio derivative (**68**) ⟨69ZC361, 70LA(741)45, 76ZC80⟩.



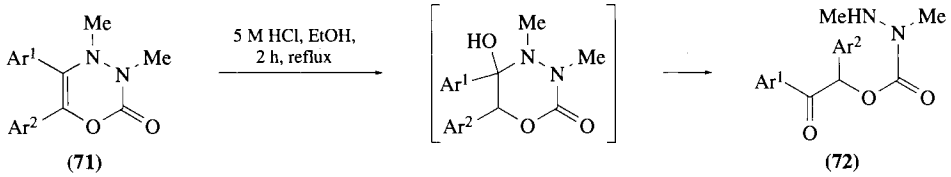
(68)

Whereas 1,3,4-thiadiazin-5-ones are resistant to rearrangement in acid solution ⟨91CHE1159⟩, in boiling concentrated hydrochloric acid, the 3,6-dihydro-2*H*-1,3,4-thiadiazin-2-one (**69**) undergoes rearrangement to the 3-aminothiazolidin-2-one (**70**) (Equation (6)) ⟨91JHC1365⟩.



(69) (70) (6)

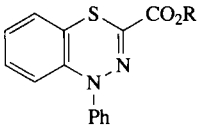
Although 5,6-diaryl 3,4-dihydro-2*H*-1,3,4-oxadiazin-2-ones (**71**) are stable in dilute acid, under more forcing conditions they yield carbazates (**72**) by hydrolysis of the N4—C5=C6 enamine system as outlined in Scheme 7 ⟨88CB887⟩.



(71) (72)

Scheme 7

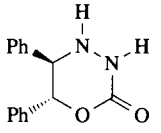
1*H*-4,1,2-Benzothiadiazines (**73**) are alkylated at N-1 under phase-transfer catalyst conditions ⟨83JCR(S)64⟩.



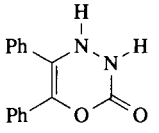
(73)

6.17.5.3 Electrophilic Attack at Carbon

Electrophilic attack at carbon is a rare event, and generally involves an oxidative process. For example, 5,6-diphenyl-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (**74**) (Section 6.17.7.2.1.1) is inert towards oxidation by HgO, whereas with lead tetraacetate *trans*-stilbene is produced in 89% yield ⟨65JA5716⟩. In contrast, under the same conditions, the dehydro-derivative (**75**) is oxidized more slowly and in much lower yield (14%) to diphenylethyne.



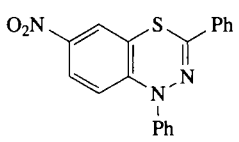
(74)



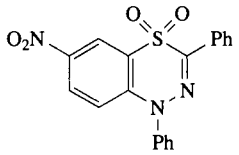
(75)

6.17.5.4 Electrophilic Attack at Sulfur

Peracid oxidation of 1,3-diphenyl-6-nitro-1*H*-4,1,2-benzothiadiazine (**76**) produces the 4,4-dioxide (**77**; 60%) ⟨80JOC3677⟩.



(76)

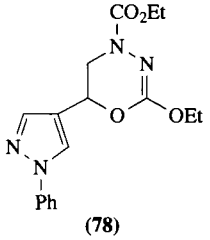


(77)

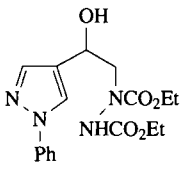
6.17.5.5 Nucleophilic Attack at Carbon

Not surprisingly, the 2-ethoxy-5,6-dihydro-4*H*-1,3,4-oxadiazine (**78**) (Section 6.17.7.2.2.1) is very susceptible to hydrolysis and ring-opens to the bis-1,2-(ethoxycarbonyl)hydrazine (**79**) during column chromatography on silica or on crystallization from "wet" solvents ⟨84JCS(P1)1423⟩.

2-(Alkylimino)-3,4-dimethyl-3,4-dihydro-2*H*-1,3,4-thiadiazin-5(6*H*)-ones (**80**) in ethanolic

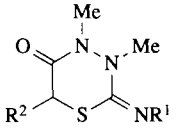


(78)



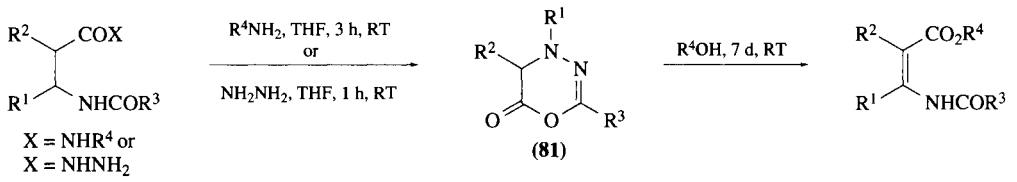
(79)

sodium hydroxide undergo hydrolytic ring-cleavage to trisubstituted semicarbazides ($R^1NHCON(Me)NHMe$) ⟨86H(24)885⟩.



(80)

4*H*-1,3,4-oxadiazin-6(5*H*)-ones (**81**) resemble azalactones in that they behave as acylating agents towards a variety of nucleophiles (Scheme 8), and have been used to effect *N*-acylation of 7-aminocephalosporanic acid in good yields (> 70%) ⟨83JHC979⟩.

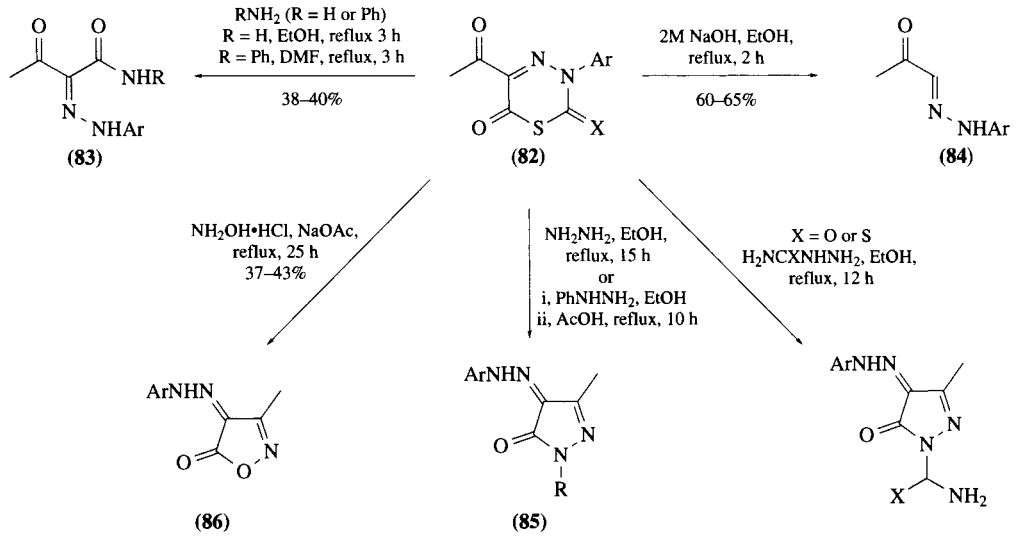


Scheme 8

Analogous ring-opening reactions are noted with 1,3,4-oxadiazin-6-ones and a $t_{1/2}$ of 1 h has been measured for 2,5-diphenyl-1,3,4-oxadiazin-6-one in a mixture of carbon tetrachloride and methanol at 20 °C ⟨85CB2940⟩.

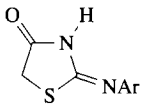
The 2,3-dihydro-2-thioxo-6*H*-1,3,4-thiadiazin-6-ones (**82**; X = S) and the corresponding 2-phenylimino-derivatives (**82**; X = NPh) are susceptible to nucleophilic attack at C-6 ⟨90IJC(B)1044⟩. Ring scission is accompanied by loss of CS_2, or phenyl isocyanate, and with ammonia or aniline results in formation of the β-keto-amide 2-hydrazones (**83**); with dilute sodium hydroxide, fragmentation to hydrazone (**84**) is noted. The thiones (**82**; X = S) with hydrazine in hot ethanol as the attacking nucleophile yield 4-(arylhydrazono)-3-methyl-pyrazolin-5-ones (**85**). Under the same conditions phenyl hydrazine forms the phenyl hydrazones of the 5-acetyl-1,3,4-thiadiazines (**82**) which ring-contract to the pyrazolin-2-ones (**85**) on heating under reflux in acetic acid. Ring-transformations are noted also with hydroxylamine (e.g. **82** → **86**), semicarbazide and thiosemicarbazide (Scheme 9).

In contrast to the corresponding 4-aryl-dihydro thiadiazinols (**16**), 4-aryl-4*H*-1,3,4-thiadiazin-



Scheme 9

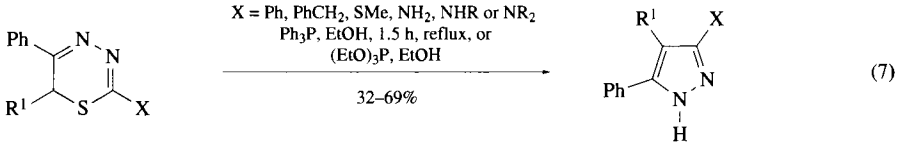
5(6*H*)-ones (**15**; X = O) are surprisingly resistant to attack by electrophiles and nucleophiles ⟨87NKZ1312⟩. However, with sodium ethoxide, ring-contractions to 2-arylimino-1,3-thiazolidin-4-ones (**87**) occur quantitatively ⟨85CPB3009⟩.



(**87**)

6.17.5.6 Nucleophilic Attack at Sulfur

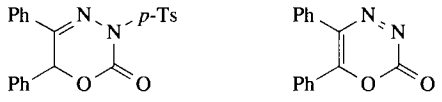
The ring contraction of 6*H*-1,3,4-thiadiazines (**88**) to pyrazoles (**89**) (Equation (7)) in the presence of a trivalent phosphorus reagent is thought to involve a valence isomerization, via the 4*H*-tautomer to the thiirane (**61**) as outlined in Scheme 5 (Section 6.17.5.2) which then undergoes desulfurization by the phosphorus reagent ⟨77S485, 85EGP228248⟩.



(**88**) (**89**) (7)

6.17.5.7 Nucleophilic Attack at Hydrogen (Proton Abstraction)

5,6-Diphenyl-3-*p*-tosyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**90**) (Section 6.17.5.2) on treatment with *t*-butyllithium at −78 °C undergoes an orbital symmetry controlled ring collapse of the resulting unstable 1,3,4-oxadiazin-2-one (**91**) to 1,2-diphenylethyne ⟨83TL4635⟩.

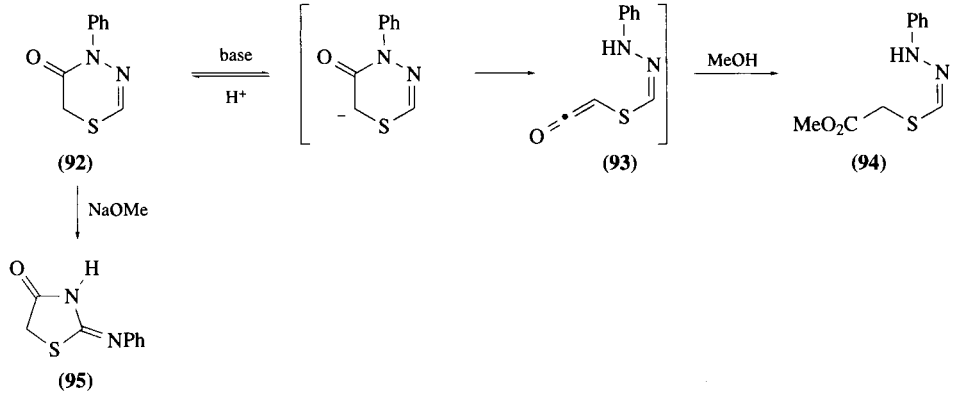


(**90**) (**91**)

Base-induced ring contraction and desulfurization of 6*H*-1,3,4-thiadiazines (**57**) to pyrazoles are known. Potassium *t*-butoxide ⟨82ZC137⟩, sodium ethoxide ⟨77S196⟩, and an excess of aqueous sodium hydroxide ⟨84EGP211343⟩ have been employed, but the rearrangement proceeds more rapidly with butyllithium in benzene at room temperature ⟨75TL33, 82ZC137⟩ and with lithium diisopropylamide in THF at −110 °C ⟨75TL33⟩. A mechanistic rationale involving the anion of the 4*H*-1,3,4-thiadiazine (**60**; Scheme 5, Section 6.17.5.2) which collapses to the bicyclic thiirane (**61**) followed by loss of sulfur, is proposed.

The base-induced rearrangement of 4*H*-1,3,4-thiadiazin-5(6*H*)-ones is dependent on the strength of the base used. HPLC and PMR spectroscopic analysis reveal that, in the presence of triethylamine, 4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**92**) exists in equilibrium with (methoxycarbonyl)methyl *N*-(phenylamino)formimidate (**94**) ⟨83PS(16)89⟩. Equilibration is thought to involve the ketene intermediate (**93**). In the presence of a stronger base (NaOMe) rearrangement of the thiadiazinone (**92**) to 2-phenylimino-1,3-thiazolidin-4(5*H*)-one (**95**) is noted (Scheme 10).

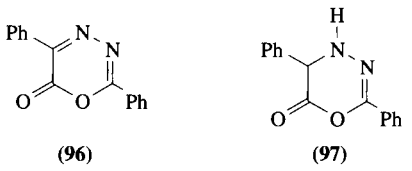
A kinetic study of the cleavage of the N—N bond during the quantitative ring contraction of 4-aryl-4*H*-1,3,4-thiadiazin-5(6*H*)-ones to 2-arylimino-1,3-thiazolidin-4(5*H*)-ones in the presence of methanolic sodium hydroxide has been carried out ⟨91YZ672⟩.



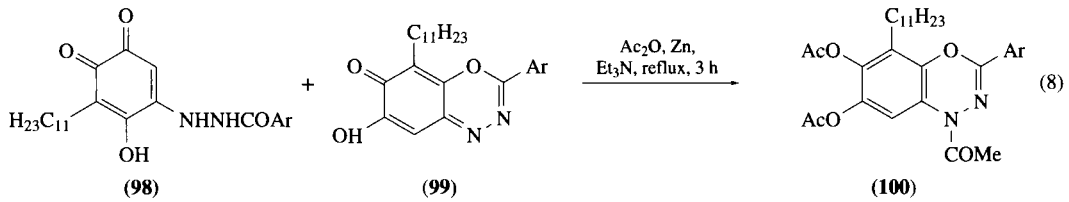
Scheme 10

6.17.5.8 Reduction

2,5-Diphenyl-1,3,4-oxadiazin-6-one (**96**) is reduced to the 4,5-dihydro-derivative (**97**) by zinc and acetic acid ⟨83JHC979⟩.

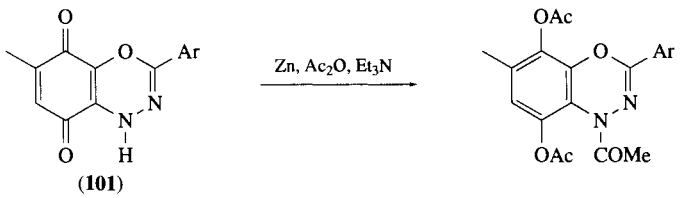


Reduction of the mixture of products (**98**) and (**99**), obtained by the action of an acylhydrazide on 2,5-dihydroxy-6-undecyl-1,4-benzoquinone, with zinc and acetic acid furnishes 1-acetyl-3-aryl-6,7-diacetoxy-5-undecyl-1*H*-4,1,2-benzoxadiazines (**100**) albeit in moderate yields (29–40%) (Equation (8)) ⟨84IJC(B)874⟩.



(8)

Further examples of the surprisingly uncommon 4,1,2-benzoxazine ring system are obtained by a similar reduction of 4,1,2-benzoxadiazine-5,8-diones (**101**) (Equation (9)) ⟨85IJC(B)307⟩.

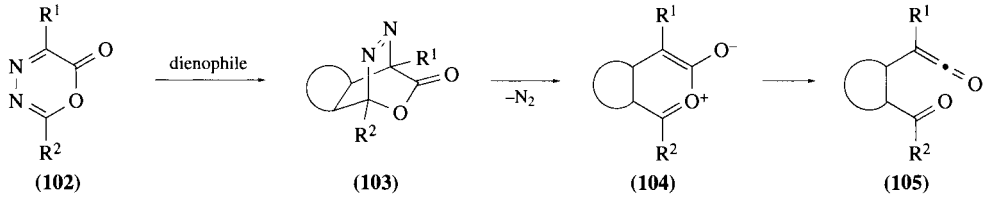


(9)

6.17.5.9 Cycloadditions

The most significant advance in the chemistry of 1,3,4-oxadiazines was the use of 3,5-disubstituted-1,3,4-oxadiazin-6-ones (**102**) as 2,3-diaza-1,3-butadienes in inverse-electron-demand Diels–Alder [4 + 2]π cycloadditions with a wide range of electron-rich dienophiles ⟨86GI⟩. In general, the initial

cycloadducts (**103**) are unstable and undergo loss of nitrogen, rather than CO_2, to yield, via the pyrylium-2-olate (**104**) a γ-ketoketene (**105**) (Scheme 11) from which a variety of final products can be obtained, as illustrated in the following sections.

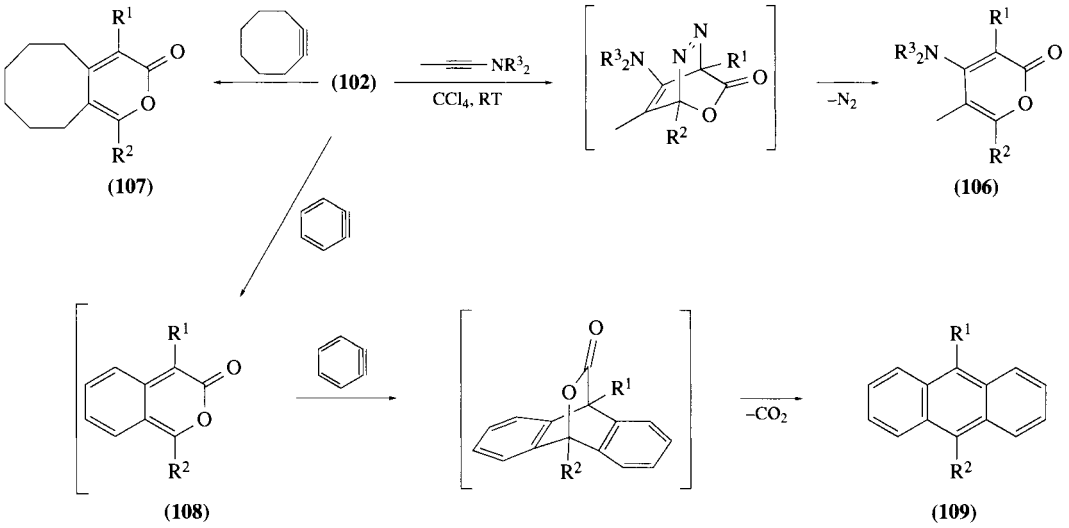


(102) (103) (104) (105)

Scheme 11

6.17.5.9.1 With alkynes and arynes

Cycloadditions with ynamines proceed readily at room temperature in carbon tetrachloride solution to yield α-pyrones (**106**) ⟨77S252⟩. Likewise, α-pyrones (**107**) are also formed with cyclooctyne ⟨83TL1481⟩, whereas with benzyne the α-benzopyrone (**108**), produced initially, enters into a second [4 + 2] cycloaddition with benzyne to give ultimately the 9,10-disubstituted anthracene (**109**) (Scheme 12) ⟨77S252⟩.



(107) (106) (108) (109)

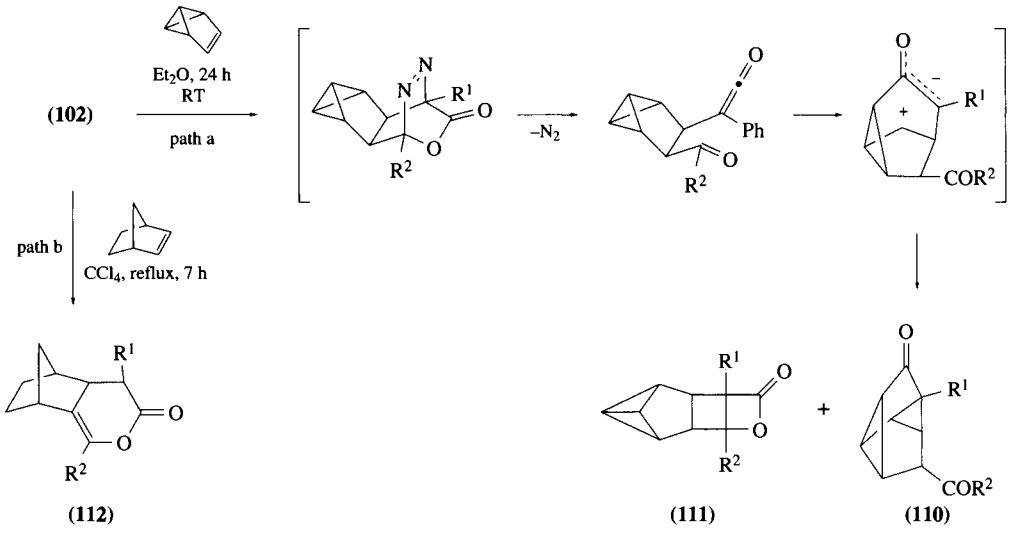
Scheme 12

6.17.5.9.2 With alkenes

Systematic studies of the cycloaddition of 1,3,4-oxadiazin-6-ones with a variety of alkenes have been carried out. With benzvalene the tetracyclic ketone (**110**) is the major product (75%) accompanied in some instances (R^1 = Ph, $R^2 = CO_2Me$) by a small amount of the fused β-lactone (**111**) (Scheme 13—path a). Cycloaddition with the less reactive norbornene (Scheme 13—path b) yields ultimately the reduced α-pyrone (**112**), an enol-lactone ⟨81AG(E)674, 85CB2940, 85JHC61, 90CB2031⟩. The enol-lactone is found to be produced more quickly and at a lower temperature if cycloaddition is carried out in the presence of trifluoroacetic acid.

As expected, 2-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazin-6-one (**102**; R^1 = Ph, $R^2 = CO_2Et$) shows enhanced diene reactivity over the 2,5-diphenyl compound (**102**; $R^1 = R^2$ = Ph) and will react with norbornadiene at room temperature. Additionally, in some cases (e.g. with norbornene) the initial cycloadducts (**103**; R^1 = Ph, $R^2 = CO_2Et$) are isolable ⟨85AG(E)886, 90CB2031⟩.

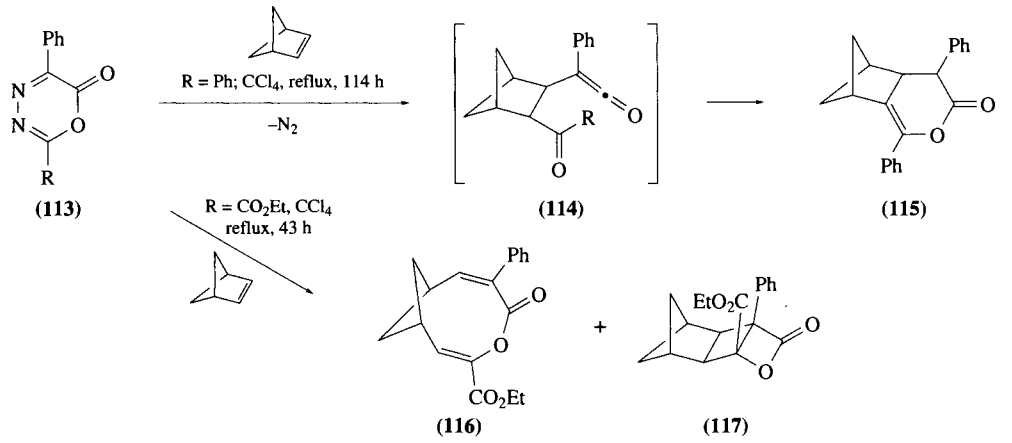
Cycloadditions with norbornadiene, cyclopentene, cyclopentadiene, *trans*-cyclooctene, and sty-



(102) (112) (111) (110)

Scheme 13

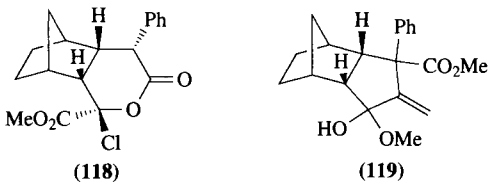
rene proceed slowly in hot carbon tetrachloride (more quickly with TFA present) to give isolable γ-ketoketenes (**105**) ⟨85CB2940, 87TL6429, 90CB2031⟩. 2,5-Diphenyl-1,3,4-oxadiazin-6-one (**113**; R = Ph) and bicyclo[2.1.1]hexene in hot carbon tetrachloride yield the dihydro-α-pyrone (**115**). The 1,3,4-oxadiazine (**113**; R = CO_2Et), however, reacts more rapidly to yield a mixture of the isolable αβ-unsaturated enol-lactone (**116**; 38%) and the β-lactone (**117**; 4%), the former by electrocyclic ring-expansion of γ-ketoketene intermediate (**114**; R = CO_2Et), the latter by an intramolecular [2 + 2] cycloaddition (Scheme 14) ⟨87TL6433, 91CB1435⟩.



(113) (114) (115) (116) (117)

Scheme 14

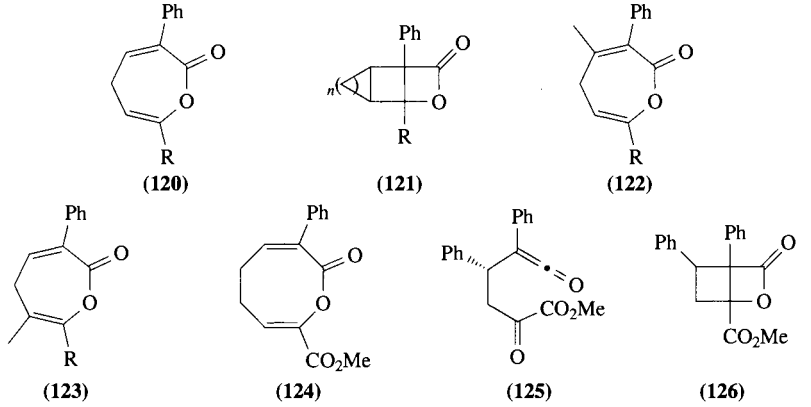
If cycloaddition to the ester (**113**; R = CO_2Et) is followed directly by treating the reaction mixture with hydrogen chloride, then δ-chloro-δ-lactones (e.g. **118**) are produced by ring closure of the γ-ketoketene ⟨92CB1913⟩, while quenching the reaction mixture with methanol results in formation of a hemiacetal (e.g. **119**) ⟨93CB797⟩.



(118) (119)

Cycloadditions of the 1,3,4-oxadiazin-6-ones (**113**; R = Ph or CO_2Me) with cyclopropenes proceed at 0 °C in THF to yield bicyclic pyrylium-2-olates (**104**) by loss of N_2 from the initial adducts,

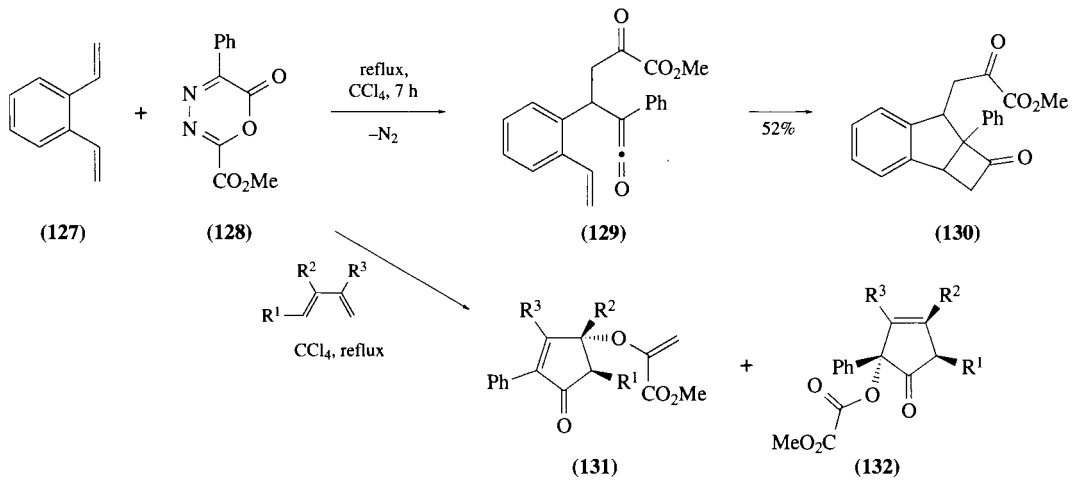
which promptly undergo an electrocyclic ring expansion to the valence isomeric oxepinones (**120**) (53–97%) accompanied by minor amounts (≈4%) of the tricyclic β-lactones (**121**; $n = 1$) ⟨83TL353, 85CB2940, 90CB2031⟩. With 3,3-dimethylcyclopropene much higher temperatures (110–120°C) are required to effect cycloaddition, whereas with 1-methylcyclopropene the reaction proceeds at 20°C to afford mixtures of the regioisomeric oxepinones (**122**) and (**123**) ⟨90CB2031⟩. An analogous reaction takes place with cyclobutene, to yield the 4,5-dihydro-8-oxo-oxocin-2-carboxylate (**124**; 59%) together with a small amount of the tricyclic lactone (**121**; $n = 2$); with styrene the γ-ketoketene (**125**) and bicyclic lactone (**126**) result ⟨93CB797⟩.



6.17.5.9.3 With dienes

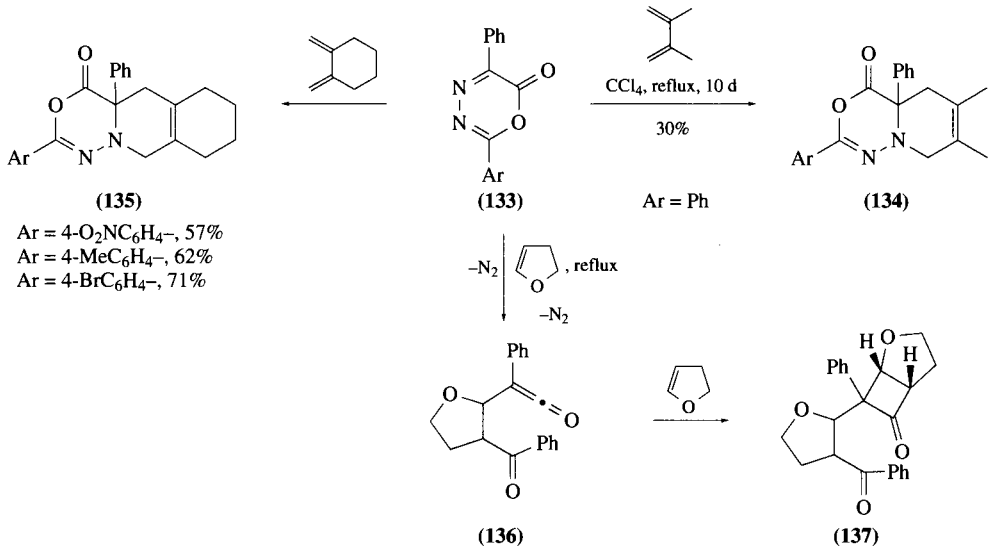
Annelated cyclobutanones (e.g. **130**) are the final products from the cycloaddition of 1,3,4-oxadiazin-6-ones (e.g. **128**) with *cis*- and *trans*-1,5-cyclooctadiene and with 1,2-di(vinyl)benzene ⟨85CB2940⟩. In each case, the γ-ketoketene intermediate (e.g. **129**) undergoes intramolecular [2 + 2] cycloaddition with the pendant vinyl group as exemplified in Scheme 15 for 1,2-divinylbenzene (**127**) ⟨93CB1743⟩. Mixtures of conjugated (**131**) and nonconjugated (**132**) cyclopentenones have been obtained by reaction of methyl 5-phenyl-1,3,4-oxadiazin-6-one-2-carboxylate (**128**) with 1,3-butadienes in hot carbon tetrachloride. A mechanistic rationale is proposed ⟨88AG(E)931⟩.

In marked contrast, however, the less reactive 2,5-diaryl-1,3,4-oxadiazin-6-ones (**133**) behave as



Scheme 15

the dienophile component towards 2,3-dimethylbutadiene and 1,2-dimethylenecyclohexane, and undergo regioselective [2 + 4] cycloaddition at the 5,6-position to give pyrido[1,2-*d*] and isoquino[1,2-*d*][1,3,4]oxadiazinones (**134**) and (**135**), respectively (Scheme 16) ⟨93CB1743⟩.



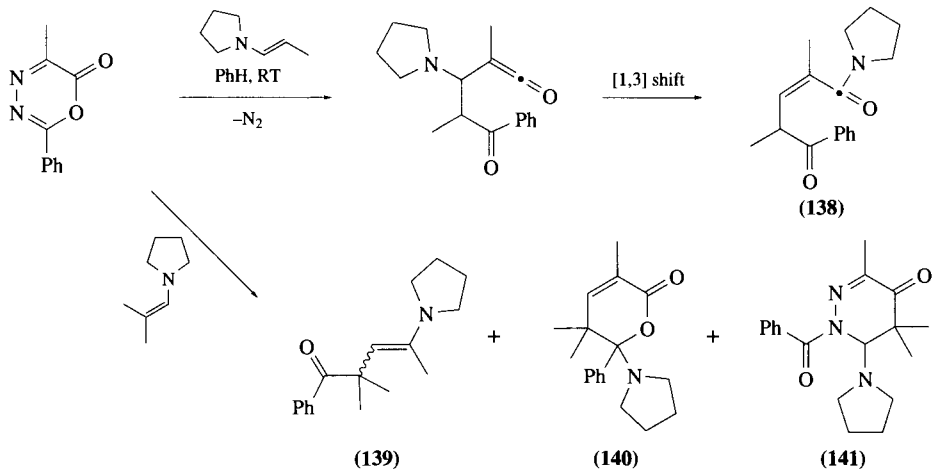
Scheme 16

6.17.5.9.4 With enol ethers

Reaction of 2,3-dihydrofuran with 2,5-diphenyl-1,3,4-oxadiazin-6-one results in trapping of the γ-ketoketene (**136**) by an excess of dihydrofuran and production of diastereoisomeric cyclobutanones (**137**) in 62% yield ⟨85T283⟩.

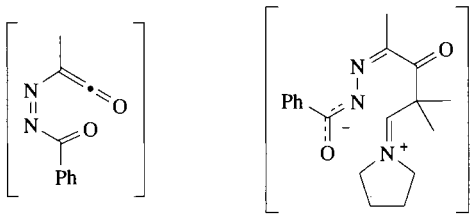
6.17.5.9.5 With enamines

[4 + 2] Cycloadditions of 1,3,4-oxadiazin-6-ones with enamines are more complex than expected and rearranged products (e.g. **138**–**141**) as outlined in Scheme 17, are common. Mechanistic explanations have been advanced ⟨85T283, 86G1⟩.



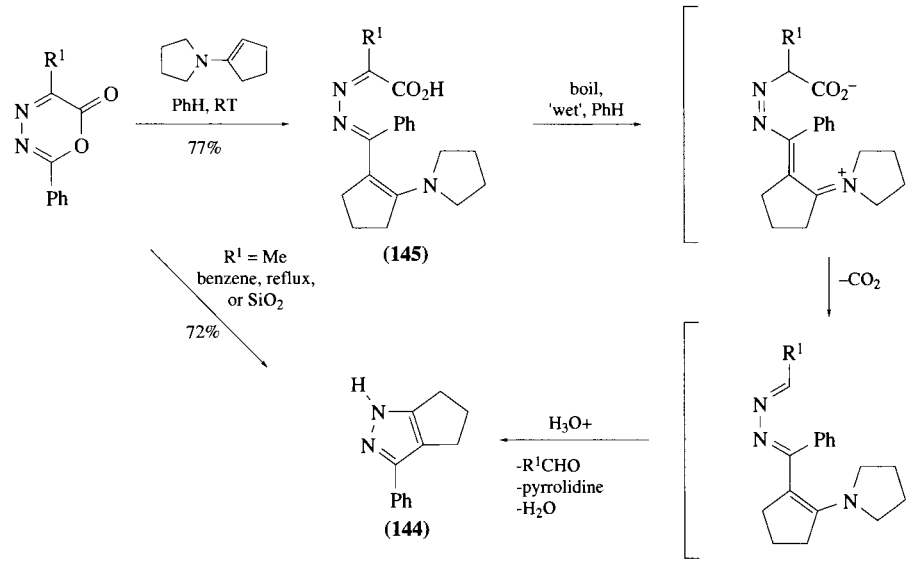
Scheme 17

Of particular interest is the tetrahydropyridazinone (**141**) which is suggested to be formed by electrocyclic ring opening of the 1,3,4-oxadiazinone followed by either a [4 + 2] cycloaddition of the resulting 1,2-diaza-1,3-butadiene (**142**) with the enamine ⟨84TL5489, 85T283⟩, or by collapse of the zwitterion (**143**) produced by direct attack of the enamine at the carbonyl carbon of the oxadiazinone ⟨86G1⟩.



(**142**) (**143**)

2,5-Diphenyl and 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one with 1-pyrrolidinylcyclopentene in boiling benzene followed by chromatography on silica gel yield, in each case, benzaldehyde and the tetrahydrocyclopenta[*c*]pyrazole (**144**) ⟨85T283⟩. However, with the diphenyl-oxadiazinone in benzene at room temperature the diazatriene (**145**; R^1 = Ph) is formed (77%), which on heating in "wet" solvent forms benzaldehyde and the pyrazole (**144**) (Scheme 18). A mechanistic rationale is proposed.



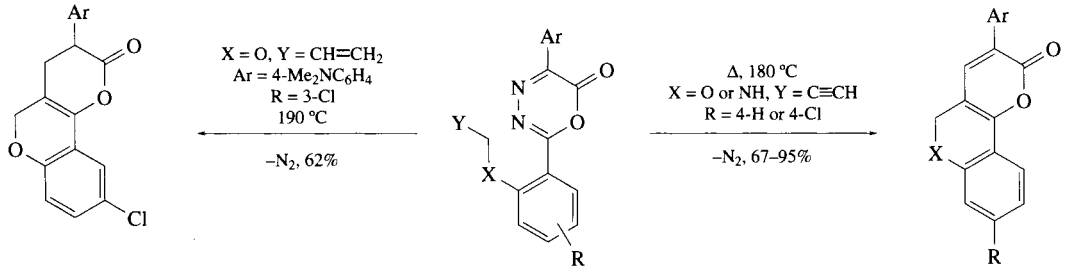
Scheme 18

6.17.5.9.6 Intramolecular cycloadditions

High yield intramolecular inverse-electron-demand [4 + 2] cycloadditions have been noted for 2,5-diaryl-1,3,4-oxadiazin-6-ones (**146**) in which the 2-aryl group bears an *ortho*-propargyloxy, propargylamino, or allyloxy side chain (Scheme 19) ⟨86G1⟩.

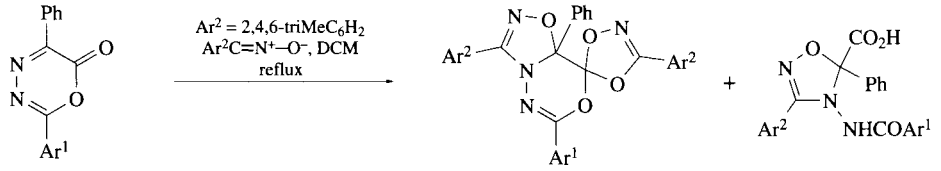
6.17.5.9.7 With 1,3-dipoles

2,5-Diaryl-1,3,4-oxadiazin-6-ones (**147**) undergo a stepwise 1,3-dipolar cycloaddition with 2,4,6-trimethylbenzonitrile oxide to yield the bis-adducts (**148**) together with varying amounts of the hydrolysis products (**149**) (Scheme 20) ⟨90JHC1425⟩. The adducts, whose structures are confirmed by x-ray analysis, arise by sequential addition of the nitrile oxide at the N4—C5 imine bond and the carbonyl group.



(146)

Scheme 19

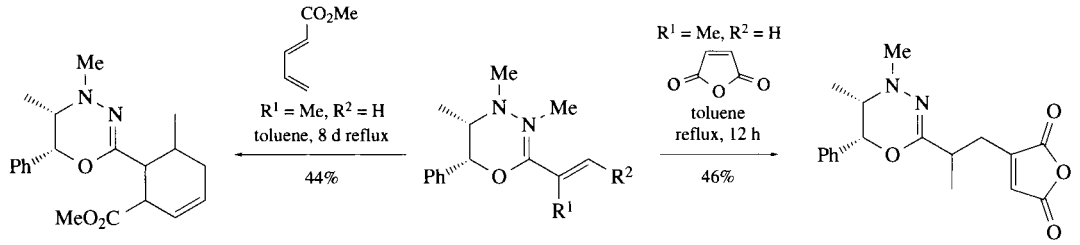


(147) (148) (149)

Scheme 20

6.17.5.9.8 Other cycloadditions

The 1-azadiene and the dienophilic character of 2-alkenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (**150**; Section 6.17.6.2) have been explored (Scheme 21) ⟨93TL457⟩. Attempts to effect cycloaddition with DMAD, dimethyl fumarate, and acrylonitrile failed, whereas with maleic anhydride and *N*-methylmaleimide unexpected noncyclic adducts (e.g. **151**) are obtained. The alkenyl oxadiazines also fail to give cycloadducts with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene with or without the presence of a Lewis acid catalyst. However, with methyl penta-2,4-dienoate mixtures of diastereoisomeric products (e.g. **152**) are formed, albeit slowly, by [4 + 2] cycloaddition at the alkenyl side chain, rather than at the C2—N3 imine bond.



(152) (150) (151)

Scheme 21

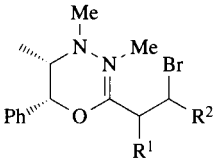
6.17.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

6.17.6.1 Substituted Benzene Rings

3,4-Dihydro-6-(4-nitrophenyl)-2*H*-1,3,4-oxadiazin-2-one can be reduced to the 4-aminophenyl derivative in low yield (37%) with hydrogen and palladium-charcoal in acetone at room temperature ⟨88CB887⟩. Likewise, reduction of 3,6-dihydro-5-(4-nitrophenyl)-2*H*-1,3,4-thiadiazin-2-one to the 4-aminophenyl compound is possible with tin(II) chloride in a mixture of hydrochloric and acetic acids ⟨91JAP(K)03261773⟩.

6.17.6.2 Alkyl Groups

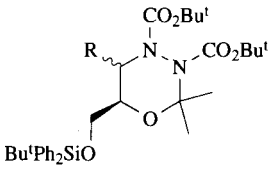
2-(β-Bromoalkyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines (**153**) (Section 6.17.7.1.1) on treatment with DBU in acetonitrile suffer dehydrobromination to the 2-alkenyl derivatives (**150**; R^1 = Me, R^2 = H, 61%; R^1 = H, R^2 = Me, 69%) ⟨93TL457⟩.



(153)

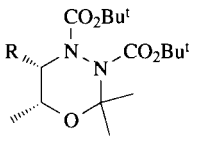
6.17.6.3 Carbonyl Groups

Reductions of *cis*- and *trans*-oxadiazine-5-carboxylates (**154**; R = CO_2Me) (Section 6.17.7.2.3.1) with calcium borohydride in THF–ethanol proceed in high yields (90%) without epimerization. Swern oxidation of the resulting alcohols (**154**; R = CH_2OH) yields the stereoisomeric aldehydes (**154**; R = CHO) ⟨89TL5507⟩.

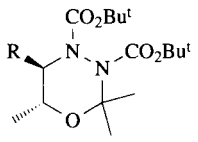


(154)

In a similar manner, the isomeric oxadiazine carbaldehydes (**155**; R = CHO) and (**156**; R = CHO), which are synthetic equivalents of 2,4-deoxy-2-amino-L-erythrose and 2,4-deoxy-2-amino-L-threose, respectively, have been prepared from the oxadiazine-5-carboxylates (**155**; R = CO_2Et) and (**156**; R = CO_2Et) ⟨89TL5511⟩.



(155)



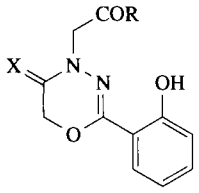
(156)

Reaction of the aldehydes (**155**) and (**156**; R = CHO) with lithium enolate (CH_2 = C(OBu^t)OLi) in THF yields mainly the products of *anti*-addition to the aldehyde in the ratios of 87 : 13 and 91 : 9, respectively. Likewise, the *trans*-aldehyde (**156**; R = CHO) with allyl magnesium halides, ethylmagnesium bromide, and lithium trimethylsilylethyne yields predominantly the *anti*-addition products regardless of the solvent used. In contrast, addition to the *cis*-aldehyde (**155**; R = CHO) is solvent and reagent dependent. With ethylmagnesium bromide or the alkyne lithium in THF, *syn*-adducts dominate in the ratio of 2–3 : 1. However, with allyl magnesium halides in THF or THF–HMPA, and with ethyl magnesium bromide in THF–HMPA, the *anti*-adducts are the major products ⟨89TL5511⟩.

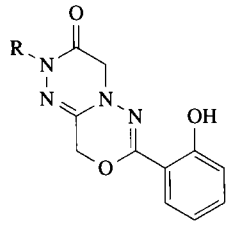
In the early 1990s, the *cis*-aldehyde was used in the stereoselective syntheses of *N*-acetyl-L-tolyposamine ⟨92TL2221⟩ and 4-amino-2,4,6-trideoxy-L-ribohexose ⟨92SL311⟩ from ethyl (*S*)-β-hydroxybutyrate.

Treatment of the 4-(ethoxycarbonylmethyl)-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**157**; X = O, R = OEt) with hydrazine hydrate in boiling ethanol yields only the hydrazide (**157**; X = O, R = $NHNH_2$). In contrast, similar treatment of the 5(6*H*)-thione (**157**; X = S) with hydrazine or

phenylhydrazine in hot ethanol results in ring closure to the 1,2,4-triazino[3,4-*d*][1,3,4]-oxadiazines (**158**; R = H, 95%; R = Ph, 78%) ⟨91JIC574⟩.

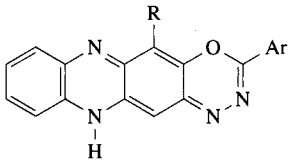


(157)



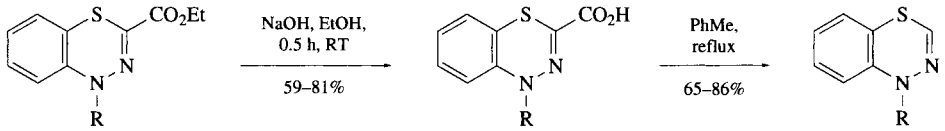
(158)

Condensations of the 3-aryl-7-hydroxy-4,1,2-benzoxadiazin-6-ones (**99**) (Section 6.17.5.8) with *o*-phenylenediamine yield the 11*H*-[1,3,4]oxadiazino[5,6-*b*]phenazines (**159**) in 50–75% yield ⟨84IJC(B)874⟩.



(159)

1*H*-4,1,2-Benzothiadiazines (**162**) unsubstituted at C-3 are accessible by the stepwise hydrolysis and decarboxylation of the 1-alkyl-3-ethoxycarbonyl derivatives (**160**) as indicated in Scheme 22 ⟨83JCR(S)64⟩. The carboxylate anions are surprisingly stable, and the anion derived from the parent acid (**161**; R = H) is recovered unchanged after 20 hours in boiling ethanolic sodium ethoxide.

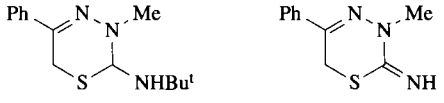


(160) (161) (162)

Scheme 22

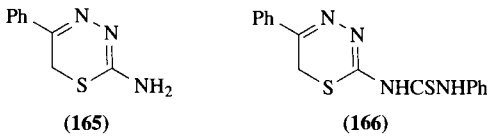
6.17.6.4 Amino Groups

3-Methyl-5-phenyl-3,6-dihydro-2*H*-1,3,4-thiadiazin-2-imine (**164**) is available in excellent yield by de-*t*-butylation of the 2-(*t*-butylamino)-derivative (**163**) with 48% HBr ⟨90EGP280760⟩. Deallylation is achieved in a similar manner. Curiously, in both instances, ring contraction to a pyrazole (Section 6.17.5.2) does not appear to occur.



(163) (164)

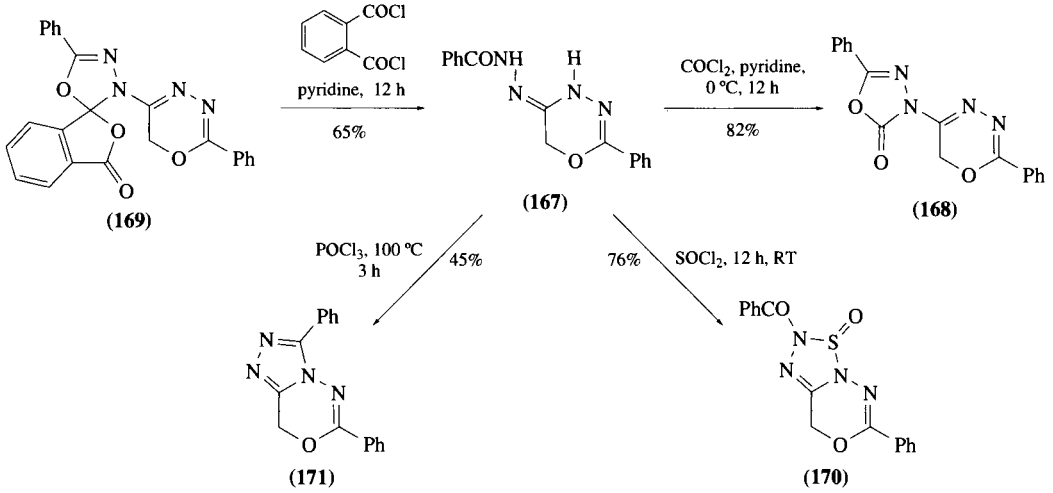
2-Amino-6*H*-1,3,4-thiadiazines (e.g. **165**) condense with isothiocyanates to yield thioureas (e.g. **166**), by reaction at the exocyclic amino-group rather than at N-3 ⟨91EGP293351⟩.



(165) (166)

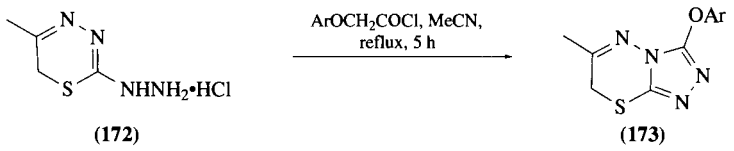
6.17.6.5 Other Nitrogen Groups

The 5-(acylhydrazono)-5,6-dihydro-4*H*-1,3,4-oxadiazine (**167**) on treatment with phosgene yields the 1,3,4-oxadiazolyl-6*H*-1,3,4-oxadiazine (**168**), while with phthaloyl chloride, under similar conditions, the spiro compound (**169**) is produced. However, with thionyl chloride and with phosphorus oxychloride, ring formation involving N-3 is observed to yield the thiatriazolo[5,4-*d*][1,3,4]-oxadiazine 3-oxide (**170**) and the 1,2,4-triazolo[4,5-*d*][1,3,4]oxadiazine (**171**), respectively (Scheme 23) ⟨89ZN(B)587⟩.



Scheme 23

In boiling acetonitrile, 2-hydrazino-5-methyl-6*H*-1,3,4-thiadiazine hydrochloride (**172**) undergoes condensation with aryloxyacetyl chlorides to yield 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazines (**173**) (Equation (10)) ⟨87JAP(K)61260085⟩.



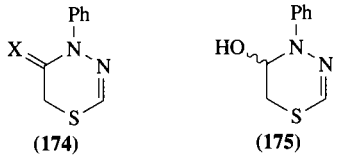
(10)

Oxidation of 2-(phenylhydrazino)-5,6-diphenyl-6*H*-1,3,4-thiadiazine with 30% hydrogen peroxide furnishes the 2-phenylazo compound in 65% yield ⟨89ZC288⟩.

6.17.6.6 Hydroxy and Oxo Groups

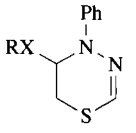
Phosphorus pentasulfide in boiling dioxan ⟨91JIC574⟩ or in hot (60 °C) pyridine ⟨93JMC1157⟩ or benzene ⟨89CE797⟩, has been used for the conversion of 4*H*-1,3,4-oxadiazin-5(6*H*)-ones into the -5(6*H*)-thiones, e.g. (**174**; X = S).

5-Hydroxy-4-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine (**175**; 93%) is obtained as a thermally unstable racemic mixture by reduction of 4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**174**; X = O) with lithium aluminum hydride in THF at −10 °C ⟨85PS(22)41⟩.



The hydroxy-group of 5-hydroxy-4-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine (**175**) is uncommonly susceptible towards nucleophilic displacement and with alcohols, thiols, and amines readily

furnishes the corresponding 5-alkoxy-, 5-alkylthio-, and 5-alkylamino-1,3,4-thiadiazines (**176**; X = O, S, and NH) in almost quantitative yields ⟨85PS(22)41⟩, via the resonance stabilized cation (**16a**) (Section 6.17.2) ⟨87NKZ1312⟩.



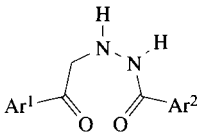
(176)

6.17.7 RING SYNTHESIS

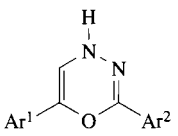
6.17.7.1 By Formation of One Bond

6.17.7.1.1 Between carbon and oxygen

The cyclodehydration of readily available *N*-phenacyl-*N'*-acylhydrazines (**177**) and related compounds, continues to provide a versatile entry to the 1,3,4-oxadiazine ring-system. Cyclodehydration, which usually yields the 4*H*-derivatives (**178**) can be effected with polyphosphoric acid and acetic acid at 140°C ⟨83MI 617-01⟩, or, as in the case of the benzoin *N*-acyl hydrazones (**179**; X = OH), in good yields (75–80%) with polyphosphoric acid at 160°C ⟨85IJC(B)979⟩. The 5,6-diphenyl-4*H*-1,3,4-oxadiazines (**180**) resulting from this latter reaction are also available, but in lesser yields (50–60%), by condensation of desyl halides (**179**; X = Cl or Br) with an acylhydrazide ($RCONHNH_2$) followed by cyclization in hot ethanolic potassium hydroxide.



(177)



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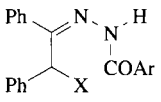
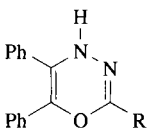
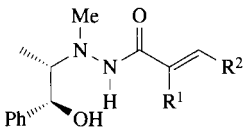


(179)



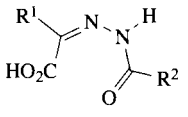
(180)

In 1993 the 2-(β-bromoalkyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines (**153**; Section 6.17.6.3) have been obtained by cyclization of *N*-(β-hydroxyalkyl)-*N*^{1}-acryloylhydrazides (**181**) with HBr in acetic acid ⟨93TL457⟩. If phosphoric acid is used as the cyclodehydrating agent then the 2-alkenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (**150**; Section 6.17.5.9.8) are formed albeit in low yields (R^1 = Me, R^2 = H, 20%; R^1 = H, R^2 = Me, 41%).

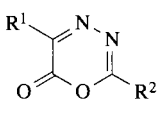


(181)

1,3,4-Oxadiazin-6-ones (**183**), which in the last decade, between 1985 and 1995, have assumed importance as electron-deficient 2,3-diaza-1,3-butadienes (see Section 6.17.5.9), are easily prepared by cyclodehydration of α-ketoacid *N*-acyl hydrazones (**182**) with dicyclohexylcarbodiimide in THF at room temperature ⟨77S252, 86G1, 90CB2031⟩. Trifluoroacetic anhydride, acetic anhydride, methane sulfonyl chloride, and *p*-toluene sulfonyl chloride have also been employed as cyclization agents ⟨86G1⟩.



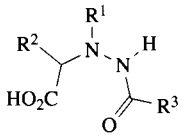
(182)



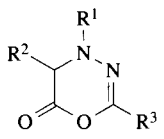
(183)

Substituent R^1 is generally aryl and only occasionally alkyl ⟨85JHC61, 85T283⟩, and examples of R^2 = aryl, heteroaryl, alkyl, and alkoxycarbonyl have been reported ⟨83TL353, 85AG(E)886, 85JHC61, 90CB2031⟩.

The little-known 4,5-dihydro-6*H*-1,3,4-oxadiazin-6-ones (**185**) are prepared in 54–88% yield by cyclization of the α-(acylhydrazino)carboxylic acids (**184**) with either dicyclohexylcarbodiimide in THF at 25 °C or warm (40 °C) acetic anhydride ⟨83JHC979⟩.

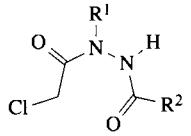


(184)



(185)

4*H*-1,3,4-Oxadiazin-5(6*H*)-ones (**187**) are obtainable by base-induced (NaH or K_2CO_3 in DMF; K_2CO_3 in MEK; Na_2CO_3 in EtOH) ring-closure of 2-chloroacetylhydrazides (**186**) ⟨85USP4508718, 86FRP2580643, 91JIC574, 91MI 617-01, 93JMC1157⟩.



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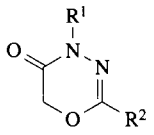
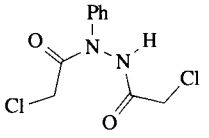


(187)

By application of this method to bis(*N*,*N*′-chloroacetyl)phenylhydrazine (**188**), 2-(chloromethyl)-4-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**189**), a useful intermediate for the preparation of organophosphothioates (Section 6.17.10.1), is obtained ⟨91USP5010068⟩.



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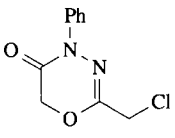
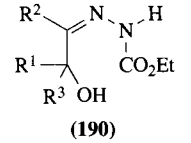


(189)

Base-induced cyclization of *N*-(α-hydroxyalkyl)-*N*′-(alkoxycarbonyl)hydrazones (**190**) is a popular route to 3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones (**191**). A variety of bases have been used including 50% aqueous sodium hydroxide in ethanol ⟨84JAP(K)5962578⟩, potassium carbonate in boiling benzene ⟨79USP4158094⟩, aqueous ammonia in ethanol ⟨87IZV181, 87IZV194⟩ and sodium ethoxide in ethanol ⟨92JMC163⟩. However, optimum yields appear to be achieved with potassium *t*-butoxide in *t*-butanol, as used originally ⟨63JA3874⟩, or in *t*-butanol–benzene mixture ⟨86EJM403⟩.



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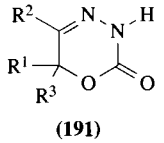
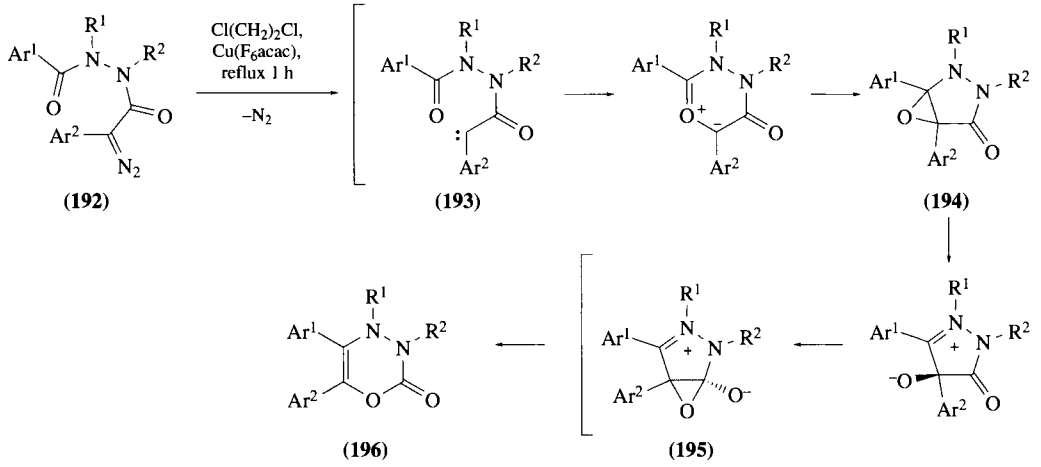


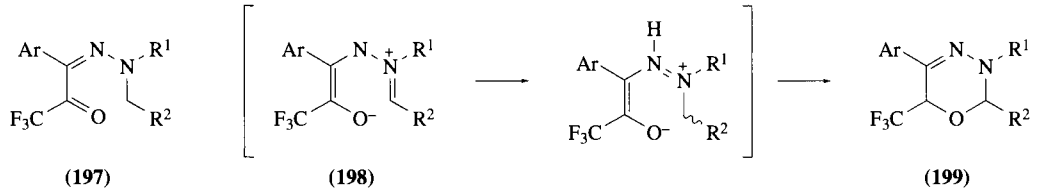
(191)

6-Aryl-3,4-dihydro-2*H*-1,3,4-oxadiazin-2-ones (**196**) have been prepared for the first time by metal-catalyzed decomposition of *N*-acyl-*N*′-(α-diazoacyl)hydrazines (**192**) ⟨88CB887⟩. A mechanistic rationale involving a carbene intermediate (**193**) followed by a rearrangement to, and then ring expansion of, oxiranopyrazole intermediates, (**194**) and (**195**) is proposed (Scheme 24).

α-(Trifluoroacetyl)arylaldehyde *N*,*N*-dialkylhydrazones (**197**), formed by trifluoroacetylation of the *N*,*N*-dialkylhydrazones in pyridine at room temperature, on adsorption onto silica gel undergo slow (several days) cyclization to 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines (**199**) in variable yields ⟨88S208⟩. Subsequently, it was shown that the hydrazones (**197**), on heating in carbon tetrachloride form mixtures of the 5-aryl-6-trifluoromethyl oxadiazines (**199**) and the regioisomeric trifluoromethylimidazoles (**200**) and (**201**) ⟨88JOC129⟩. The oxadiazines are formed as outlined in Scheme 25, while the imidazoles are thought to be produced in a manner analogous to the formation of 4,5-diphenylimidazole from benzil hydrazone ⟨85TL1595⟩.



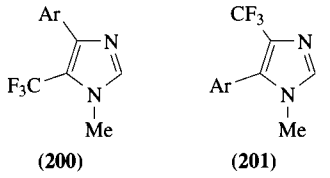
Scheme 24



Scheme 25

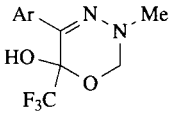
1,3,4-Oxadiazines are also produced, but more slowly (20 days), from the *N*-methyl-*N*-*t*-butylhydrazone (**197**; $R^1 = Bu^t$, $R^2 = H$), with the *N*-methyl-*N*-ethylhydrazone (**197**; $R^1 = Et$, $R^2 = H$), the 3-ethyl-6-trifluoromethyl-1,3,4-oxadiazine (**199**; $R^1 = Et$, $R^2 = H$) (34%) is accompanied by a small amount (4%) of the isomeric 2,3-dimethyloxadiazine (**199**; $R^1 = R^2 = Me$), derived by cyclization at the methylene group of the ethyl substituent ⟨88S208⟩.

A detailed systematic study of the reaction conditions revealed that the ratio of 1,3,4-oxadiazine : imidazole formed is dependent on the solvent, and on the acid or base catalyst employed ⟨90JHC487⟩. Yields of 1,3,4-oxadiazine are optimal (60–70%) in boiling carbon tetrachloride or in *n*-heptane, whereas in acetonitrile, 1,2-dimethoxyethane, or toluene only the isomeric imidazoles (**200**) and (**201**) are produced. Acid catalysis (*p*-TSA or acetic acid) in hot carbon tetrachloride favors the 1,3,4-oxadiazine (80%), but with silica in boiling carbon tetrachloride imidazoles are the sole products.



Latterly a superior method for producing the (trifluoromethyl)-1,3,4-oxadiazines (**199**) rapidly (6 h), and in high yields (72–97%), has been found which involves treating the α-(trifluoroacetyl)hydrazones (**197**) with trifluoroacetic acid at room temperature ⟨90S493⟩. The reaction is successful with a range of *N*-mono- (**197**; $R^1 = Bu^t$, $R^2 = Me$) and *N*,*N*-dialkylated hydrazones, with the exception of the *N*-*t*-butyl-hydrazone which suffers de-*t*-butylation. However, cyclization of the *t*-butyl derivative is possible in warm (50 °C) acetic acid; higher temperatures have to be avoided in order to prevent imidazole formation.

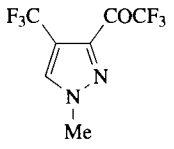
An attempt to oxidize the dimethylhydrazone (**197**; $R^1 = Me$, $R^2 = H$, Ar = Ph) to the 1,2-diketone with sodium periodate furnished 3-methyl-6-hydroxy-5-phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazine (**202**; Ar = Ph) as the major product (30%) ⟨88JOC129⟩. Attempts to oxidize the 6-(trifluoromethyl)-1,3,4-oxadiazine (**199**; $R^1 = Me$, $R^2 = H$, Ar = Ph) to the hydroxy compound under similar conditions failed.



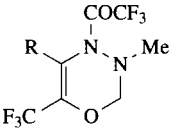
(202)

A detailed study of this oxidative cyclization revealed that 6-hydroxy-6-trifluoromethyl-1,3,4-oxadiazines are produced in good yields (52–72%) if the oxidation is carried out with sodium periodate at 25°C in a 2:3 THF–H_2O mixture. In 2:1 THF–H_2O solution, the reaction is much slower (5 days) and in some cases (**197**; Ar = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, R^1 = Me, R^2 = H) considerable quantities of the dehydroxylated products (**199**) are obtained ⟨91H(32)1693⟩.

A more complex reaction is noted with the *N,N*-dimethylhydrazone of methanal, which with trifluoroacetic anhydride in the presence of 2,6-dimethylpyridine and chloroform affords a mixture of products including 1-methyl-3-trifluoroacetyl-4-(trifluoromethyl)pyrazole (**203**; 14%) and 3-methyl-6-trifluoromethyl-4-trifluoroacetyl-3,4-dihydro-2*H*-1,3,4-oxadiazine (**204**; R = H, 33%) ⟨88JOC519⟩. In the absence of base, however, the oxadiazine is obtained in quantitative yield. A systematic investigation of the reaction showed that the 1,3,4-oxadiazine arises via *N*-(trifluoroacetylation) of the initially formed *C*-trifluoroacetyl derivative (**197**), and then cyclization by a route analogous to that indicated in Scheme 25, whereas the pyrazole is derived by a separate pathway involving *O*-trifluoroacetylation of the intermediate (**198**).

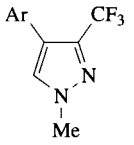


(203)



(204)

A similar situation prevails with *C*-trifluoroacetylated arylaldehyde *N,N*-dimethyl-hydrazones (**197**; R^1 = Me, R^2 = H) which in trifluoroacetic anhydride and pyridine yield only 1-alkyl-4-aryl-3-(trifluoromethyl)pyrazoles (**205**) ⟨88TL5281⟩, while in the absence of pyridine the isomeric 5-aryl-3-methyl-4-(trifluoroacetyl)-6-trifluoromethyl-3,4-dihydro-2*H*-oxadiazines (**204**; R = Ar) are formed in 40–76% yield ⟨90TL1183⟩.

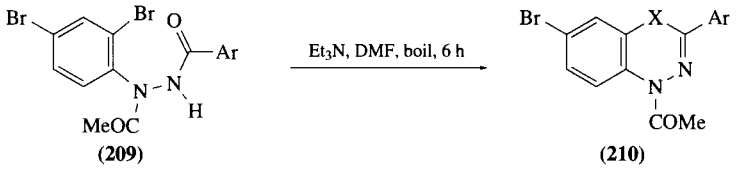


(205)

In trifluoroacetic acid at room temperature the *N'*-allyl-*N'*-methyl hydrazones (**206**; R = —CH=CH_2, —C(Me)=CH_2, or —CH=CHMe) yield not the expected 3-allyl-6-trifluoromethyl-1,3,4-oxadiazines but the novel 2,6-ethylene bridged 1,3,4-oxadiazines (**207**), which in the case of R^1 = Me, R^2 = H, and R^1 = H, R^2 = Me are produced as a mixture of the *endo-* and *exo-*isomers ⟨92H(34)237⟩. The proposed route is exemplified in Scheme 26 for the *N*-allylhydrazone (**206**; R = —CR^1=CHR^2).

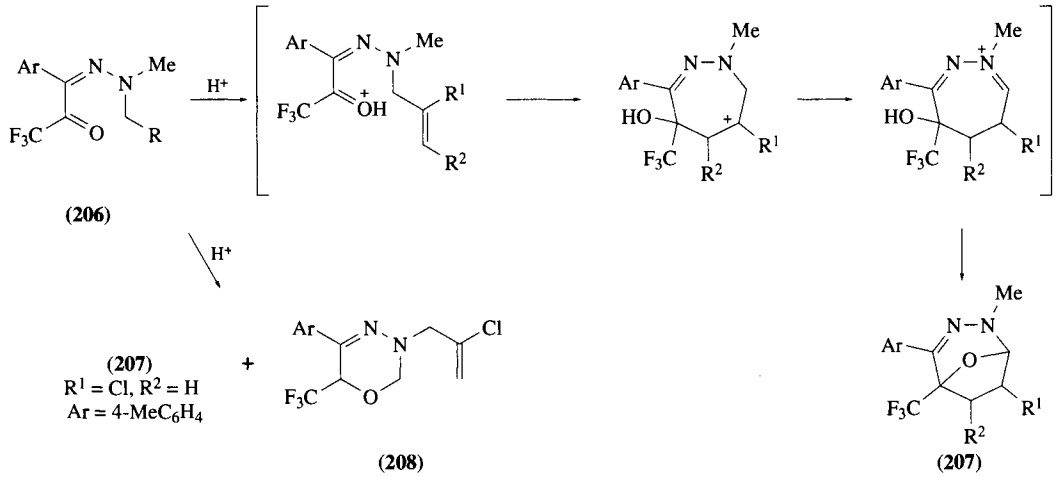
In the case of the (chloropropenyl)-derivative (**206**; R = —C(Cl)=CH_2), the bridged oxadiazine (**207**; R^1 = Cl, R^2 = H, Ar = 4-MeC_6H_4) is formed (36%) along with the expected 3-(2-chloroprop-1-ene-3-yl)-3,6-dihydro-2*H*-1,3,4-oxadiazine (35%) (**208**).

Derivatives (**210**) of the surprisingly uncommon 4,1,2-benzoxadiazine system are reported to be obtained by cyclization of *N'*-acetyl-*N'*-(2,4-dibromophenyl)acyl hydrazides (**209**; X = O) in hot DMF (Equation (11)) (see also Section 6.17.7.2.2(i)) ⟨91EUP410834⟩.



(209) (210)

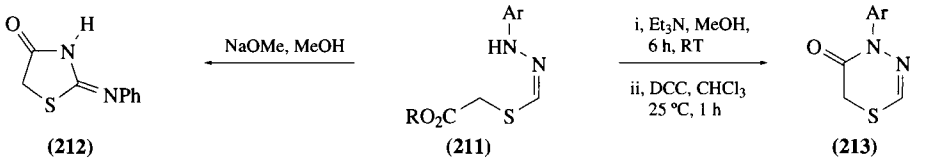
(11)



Scheme 26

6.17.7.1.2 *Between carbon and nitrogen*

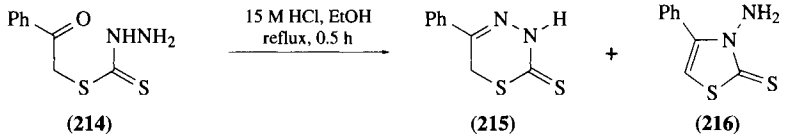
A reinvestigation of the cyclization of (methoxcarbonylmethyl)-*N*-(phenylamino)thioformimidate (**211**; Ar = Ph; R = Me) with sodium methoxide has shown that the product (mp 181 °C) is not 4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**213**; Ar = Ph) ⟨54YZ821⟩ but 2-phenylimino-1,3-thiazolidin-4(5*H*)-one (**212**). Cyclization to the 4-phenylthiadiazinone (mp 77–78 °C) can, however, be accomplished by using triethylamine in methanol in place of the sodium methoxide (Scheme 27) ⟨83PS(16)89⟩.



Scheme 27

4-Aryl-4*H*-1,3,4-thiadiazin-5(6*H*)-ones (**213**) are also obtained in high yields (73–82%) by ring-closure of the (arylhydrazonoalkylthio)acetic acids (**211**; R = H) with DCC in chloroform ⟨84CPB1590⟩.

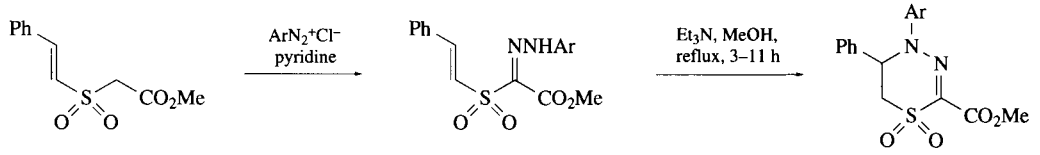
3,6-Dihydro-5-phenyl-2*H*-1,3,4-thiadiazine-2-thione (**215**) is obtained as a by-product (29%) from the cyclization of the phenacyl dithiocarbazate (**214**) under strong acid conditions (Scheme 28). The major product, 3-amino-4-phenylthiazoline-2(3*H*)-thione (**216**; 48%), becomes the sole product if the reaction time (0.5 h) is extended ⟨85H(23)3099⟩.



Scheme 28

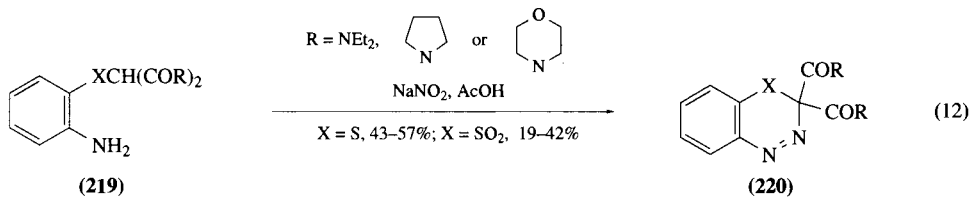
The first examples of 5,6-dihydro-4*H*-1,3,4-thiadiazine 1,1-dioxides (**218**) have been synthesized by cyclization of (β-styrylsulfonyl)glyoxalate aryl hydrazones (**217**), which are prepared as indicated in Scheme 29 ⟨90H(31)1537⟩.

Ready access to 3*H*-4,1,2-benzothiadiazine-3,3-dicarboxamides (**220**; X = S) and to the 3*H*-4,1,2-benzothiadiazine 4,4-dioxides (**220**; X = SO_2) is possible by diazotization of α-(2-amino-phenylsulfenyl)- and α-(2-aminophenylsulfonyl)-malonamides (**219**; X = S and SO_2, respectively) (Equation (12)) ⟨91JHC1633⟩.



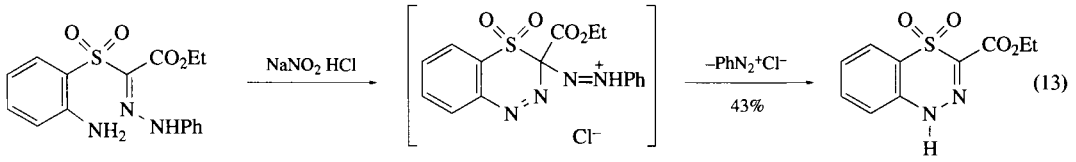
(217) (218)

Scheme 29



(219) (220) (12)

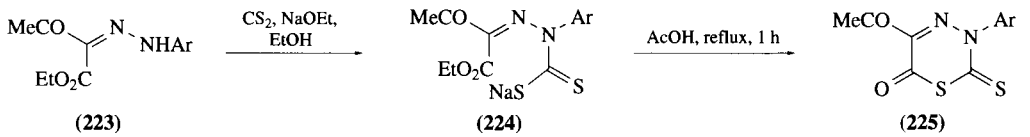
Previously, ethyl 1*H*-4,1,2-benzothiadiazine-3-carboxylate 4,4-dioxide (**222**) had been obtained unexpectedly by diazotization of the (2-aminophenyl)sulfonylhydrazone (**221**) (Equation (13)) ⟨78JCS(P1)539⟩.



(221) (222) (13)

6.17.7.1.3 Between carbon and sulfur

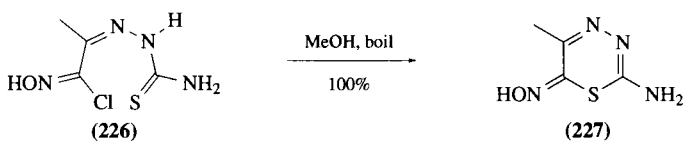
Dithiocarbazates (**224**), formed by the action of CS_2 on the hydrazones (**223**), ring-close in hot acetic acid to 5-acyl-3-aryl-2-thioxo-1,3,4-thiadiazin-6(3*H*)-ones (**225**) in moderate yields (30–38%) (Scheme 30) ⟨90IJC(B)1044⟩. The same products are also obtained directly, by treating the hydrazones with CS_2 and triethylamine in hot DMF–ethanol.



(223) (224) (225)

Scheme 30

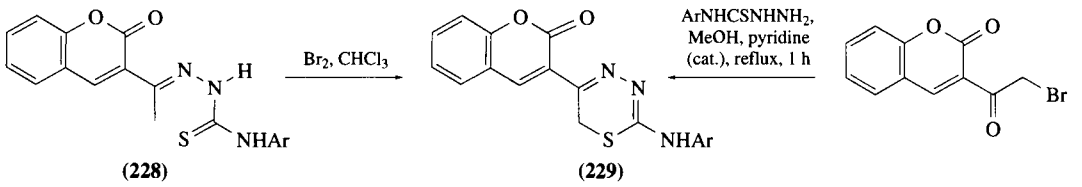
The chloro-oximinosemicarbazone (**226**) in boiling methanol is cyclized in quantitative yield to 2-amino-6-hydroxyimino-5-methyl-6*H*-1,3,4-thiadiazine (**227**) (Equation (14)) ⟨84IZV56⟩.



(226) (227) (14)

Bromination of the thiosemicarbazide derivatives (**228**) results in ring-closure to the 2-arylamino-5-(coumarin-3-yl)-6*H*-1,3,4-thiadiazines (**229**) in 60–80% yield ⟨90JIC81⟩. The same products can be

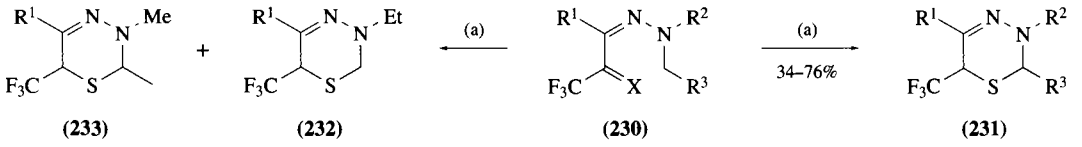
obtained by condensing 3-(bromoacetyl)coumarin with thiosemicarbazides in hot methanol (Scheme 31) ⟨85OPP206, 90JIC81⟩.



(228) (229)

Scheme 31

A synthetic route to 6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-thiadiazines analogous to that described in Section 6.17.7.1.1 for the corresponding 1,3,4-oxadiazines, has been developed ⟨90S491⟩. Conversion of the trifluoroacetylhydrazones (**230**; X = O) into the corresponding thioacetyl compounds (**230**; X = S) with Lawesson's reagent in boiling toluene is followed by cyclization to the 3,6-dihydro-2*H*-1,3,4-thiadiazines (**231**) (Scheme 32). Unlike the α-(trifluoroacetyl)-*N*-methyl-*N*-ethyl hydrazones (**230**; $R^2 = R^3 = Me$, X = O), which cyclize almost exclusively at the *N*-methyl group, the corresponding trifluorothioacetyl hydrazone (**230**; X = S, R^2 = Et, R^3 = H) yields a 56 : 44 mixture of the isomeric thiadiazines (**232**) and (**233**), the result of cyclization at the N—Me and N—Et groups, respectively.



(233) (232) (230) (231)

R^1 = 4-MeC_6H_4

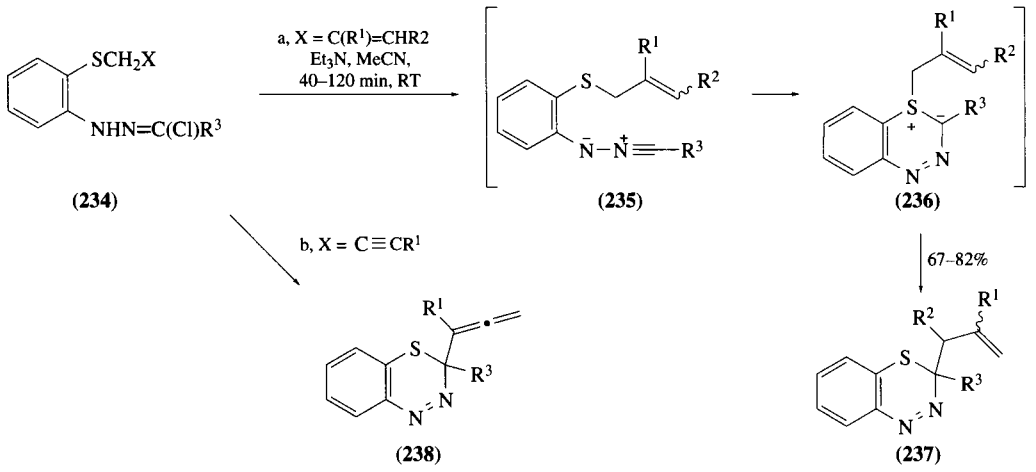
(a) Lawesson's reagent, PhH, reflux, 15–24 h

R^1 = 4-MeC_6H_4,
R^2 = Me, Et, Pr^i or Bu^t
R^3 = H, Me, or Me_2

Scheme 32

Similarly, Lawesson's reagent in boiling benzene effects cyclization of benzil monodimethylhydrazone to 5,6-diphenyl-3-methyl-3,6-dihydro-2*H*-1,3,4-thiadiazine (46%) ⟨90S491⟩.

N-Arylnitrilimines (**235**) bearing an *ortho*-alkenylthio function undergo intramolecular nucleophilic attack by sulfur at the cationic carbon center of the nitrilimine followed by a [2,3] sigmatropic shift of the 5-allyl group in the resulting ylides (**236**) to yield the 3,3-disubstituted 3*H*-4,1,2-benzothiadiazines (**237**) as outlined in Scheme 33 (path a). In a similar manner (2-alkynylthio)-nitrilimines yield 3-(allenyl)-3*H*-4,1,2-benzothiadiazines (**238**) (Scheme 33; path b) ⟨81JCS(P1)2245, 84JCS(P1)2535⟩.

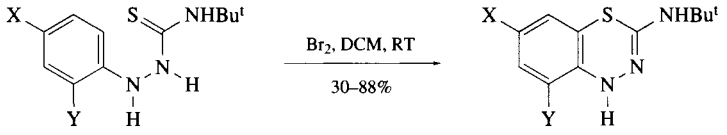


(234) (235) (236) (238) (237)

Scheme 33

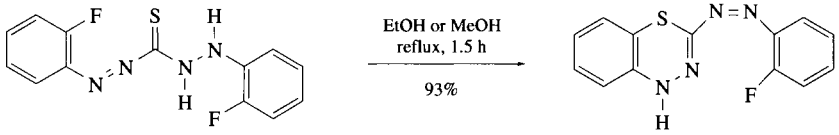
The 3-allyl-3*H*-4,1,2-benzothiadiazines (**237**) are also formed as major by-products during the azido-dechlorination of the α-chlorohydrazones (**234**) with sodium azide in the presence of a phase-transfer catalyst ⟨84JCR(S)364⟩.

Bromine in dichloromethane effects cyclization of the thiosemicarbazides (**239**) to 3-*t*-(butylamino)-1*H*-4,1,2-benzothiadiazines (**240**) via an intramolecular electrophilic substitution of the benzene ring by the initially formed sulfenyl bromides (Equation (15)) ⟨89JAP(K)0150873, 90JHC1517⟩.



(239) (240) (15)

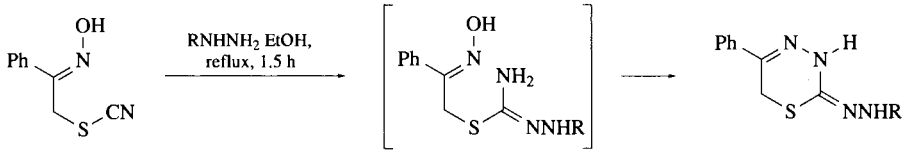
The difluoro-substituted "dithizone" (**241**) on heating in alcohol solution ring-closes in almost quantitative yield to 3-(2-fluorophenylazo)-1*H*-4,1,2-benzothiadiazine (**242**) (Equation (16)) ⟨77JCS(P2)1118⟩ (see also Section 6.17.7.2.2.2).



(241) (242) (16)

6.17.7.1.4 Between nitrogen and nitrogen

Syntheses of 1,3,4-oxadiazines or 1,3,4-thiadiazines by N—N bond formation are rare. However, the oxime (**243**) of α-thiocyanatoacetophenone, formed by the action of potassium thiocyanate on phenacyl bromide oxime, on treatment with hydrazine or phenylhydrazine, undergoes cyclization to the 2-hydrazono-3,6-dihydro-2*H*-thiadiazines (**244**; R = H, 65%; R = Ph, 72%), respectively, as outlined in Scheme 34 ⟨87AP(320)776⟩.



(243) (244)

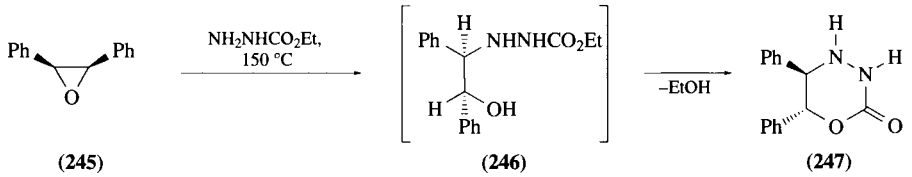
Scheme 34

6.17.7.2 By Formation of Two Bonds

6.17.7.2.1 [3 + 3] fragments

(i) From C—C—O and C—N—N fragments

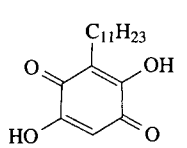
cis-1,2-Diphenyloxirane (**245**) on heating with ethyl carbazate yields directly *trans*-5,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxazin-2(3*H*)-one (**247**) via cyclization of the intermediate carbazate (**246**) (Scheme 35) ⟨65JA5716⟩.



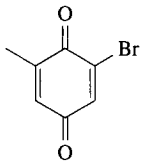
(245) (246) (247)

Scheme 35

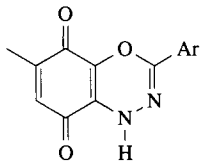
Condensation of 3,6-dihydroxy-2-undecyl-1,4-benzoquinone (**248**) with an acylhydrazide in hot ethanol produces a mixture of the 4,1,2-benzoxadiazin-6-one (**99**) and the 4-hydroxy-5-acylhydrazino-1,2-benzoquinone (**98**) (Equation (8) Section 6.17.5.8) ⟨84IJC(B)874⟩. The benzoxadiazinones are isolated in good yields (60–80%) as their *O*-acetyl derivatives. Later work revealed that 3-aryl-6-methyl-1*H*-4,1,2-benzothiadiazine-5,8-diones (**250**) can be obtained in good yields (57–62%) by condensing acylhydrazides with 2-bromo-6-methyl-1,4-benzoquinone (**249**) ⟨85IJC(B)307⟩.



(**248**)



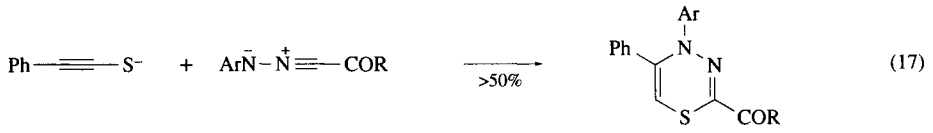
(**249**)



(**250**)

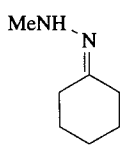
(ii) From C—C—S and C—N—N fragments

2-Acyl-4*H*-1,3,4-thiadiazines (**253**) are reported to be formed by cycloaddition of phenyl-ethynethiolates (**251**) with *C*-acylnitrilimines (**252**) (Equation (17)) ⟨89RRC901⟩.

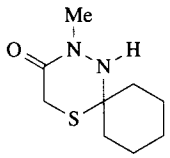


(**251**) (**252**) (**253**) (17)

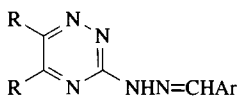
Tetrahydro-1,3,4-thiadiazin-5-ones (**255**) containing a spiro-carbon center at C-2 are accessible by condensing thioglycolic acid with cyclohexanone *N*-alkylhydrazones (e.g. **254**) ⟨91JAP(K)0383972⟩. In a similar manner condensation of the 1,2,4-triazine hydrazone (**256**; Ar = 2,4-diHOC_6H_3) with thioglycolic acid in boiling benzene furnishes the corresponding 4-(1,2,4-triazin-3-yl)-3,4-dihydro-2*H*-1,3,4-thiadiazin-5(6*H*)-one (**257**) in 60% yield ⟨86IJC(B)815⟩.



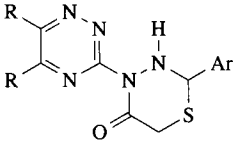
(**254**)



(**255**)

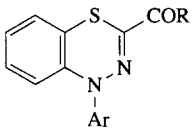


(**256**)



(**257**)

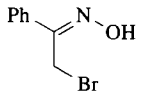
Surprisingly, α-chloro-α-acylphenylhydrazones (RCOC(Cl)=NNHAr) condense with 2-aminothiophenol in boiling ethanol in the presence of triethylamine to yield 3-acyl-1-aryl-1*H*-4,1,2-benzothiadiazines (**258**) ⟨88IJC(B)836⟩. Attempts to prepare 2-acyl-4*H*-1,3,4-thiadiazin-5(6*H*)-ones by condensation of the α-chloroacylhydrazones with thioglycolic acid have failed.



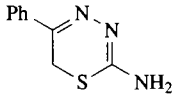
(**258**)

(iii) From C—N—N and N—C—S fragments

Thiourea and the oxime (**259**) of phenacyl bromide undergo condensation in aqueous solution at 60 °C to give 2-amino-5-phenyl-6*H*-1,3,4-thiadiazine (**260**) in 75% yield ⟨87AP(320)776⟩.



(259)

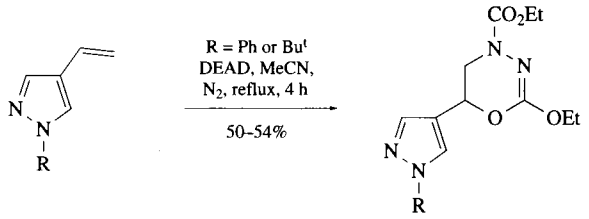


(260)

6.17.7.2.2 [4 + 2] fragments

(i) From N—N—C—O and C—C fragments

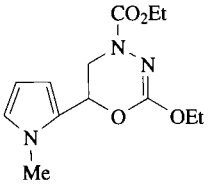
1-Substituted-4-vinylpyrazoles (**261**), unlike the vinylpyrroles, fail to undergo [4 + 2] cycloaddition with alkenes and alkynes. Surprisingly, however, with diethyl azodicarboxylate under anhydrous conditions, ethyl 2-ethoxy-6-(pyrazol-4-yl)-5,6-dihydro-4*H*-1,3,4-oxadiazine-4-carboxylates (**262**), are obtained by addition of the azodicarboxylate, as the diene component, to the vinyl side chain (Equation (18)) ⟨84JCS(P1)1423, 89M1113⟩. The regiochemistry of the cycloaddition is confirmed by an x-ray crystal structure of the 1,2-bis-ethoxycarbonyl hydrazine obtained by hydrolysis of the oxadiazine. Analogous cycloadditions of the dibenzoylazo compound (PhCON=NCOPh) with electron-rich ethenes have also been reported ⟨85JCS(P2)1759⟩.



(18)

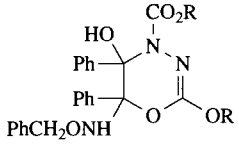
(261) (262)

Likewise, the major product (amongst many), from the addition of diethyl azodicarboxylate with 1-methyl-2-vinylpyrrole has been shown, mainly on the basis of ^1H and ^{13}C NMR spectral evidence, to be the 2-ethoxy-6-(1-methylpyrrol-2-yl)-5,6-dihydro-4*H*-1,3,4-oxadiazine (**263**) ⟨85JCR(S)12⟩.



(263)

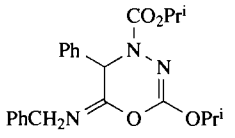
The highly substituted 5,6-dihydro-4*H*-1,3,4-oxadiazine (**264**; R = Pr^i) is formed as a by-product (20%) along with benzil monoxime (40%) on subjecting the *O*-benzylated monoxime of benzoin (PhCH(OH)C(Ph)=NOCH$_2$Ph) to a Mitsunobu reaction (Ph$_3$P and diisopropyl azodicarboxylate) ⟨87JOC4978⟩. Substitution of the diisopropyl by the diethyl ester raises the yield of oxadiazine (**264**; R = Et) to 50%.



(264)

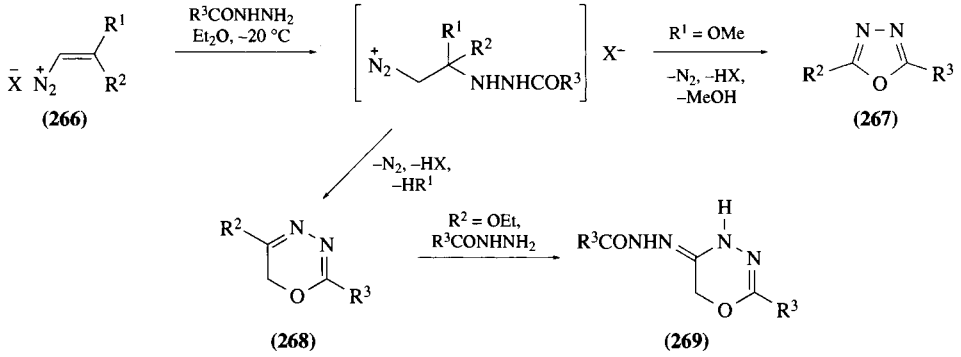
Similarly, with an excess of the diisopropyl ester and triphenylphosphine, the benzylamide of mandelic acid (PhCH(OH)CONHCH$_2$Ph) furnishes the 6-benzylimino-5,6-dihydro-4*H*-1,3,4-oxa-

diazine-4-carboxylate (**265**) in 21% yield, along with the ketoamide ($PhCOCONHCH_2Ph$) as the major product (35%).



(**265**)

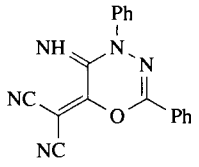
The products from the reaction of alkene diazonium salts (**266**; X = $SbCl_6$ or BF_4) with acyl hydrazides are dependent on the nature of the substituents (R^1 and R^2) on the alkene ⟨85CB4026, 89ZN(B)587⟩. With the 4-methoxystyryl derivative (**266**; R^1 = OMe, R^2 = 4-$MeOC_6H_4$) only 1,3,4-oxadiazoles (**267**) are produced (17–40%), whereas with ketene acetals (**266**; R^1 = OMe, R^2 = OEt) 5-(acylhydrazono)-5,6-dihydro-4*H*-1,3,4-oxadiazines (**269**) result in 17–36% yield (as mixtures of the (*Z*)- and (*E*)-isomers), via nucleophilic displacement of the 5-ethoxy group of the initially formed 5-ethoxy-6*H*-1,3,4-oxadiazine (**268**) by an excess of acylhydrazide (Scheme 36).



(**266**) (**267**) (**268**) (**269**)

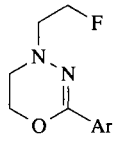
Scheme 36

N'-Benzoylphenylhydrazine (PhNHNHCOPh) is reported to undergo condensation with tetracyanoethene to yield 2,4-diphenyl-5-imino-6-(dicyanomethyleno)-5,6-dihydro-4*H*-1,3,4-oxadiazine (**270**) ⟨90MI 617-01⟩.



(**270**)

In 1993, acylhydrazides were used for the synthesis of 2-aryl-4-(2-fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines (**271**), with 1-bromo-2-fluoroethane supplying the C5-C6 fragment in addition to the fluoroethyl side chain ⟨93MI 617-01⟩.



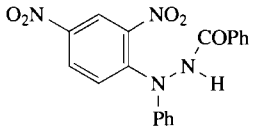
(**271**)

4a,7,8,8a-Tetrahydro-1*H*-4,1,2-benzoxadiazin-5(6*H*)-ones (**33**) result from cycloaddition of morpholine cyclohexenamines and azo-carbonyl compounds (X—N=N—COR) ⟨82G335, 83JHC305⟩. The 1,3-diaryl derivatives (**33**; R = X = Ar) are isolated in high yields (80–95%) as stable yellow–orange products, while the ethoxycarbonyl and acyl derivatives (**33**; R = Ar, X = CO_2Et or COAr) exist as equilibrium mixtures with the open-chain enamine tautomers (**32**) (Section 6.17.4.1).

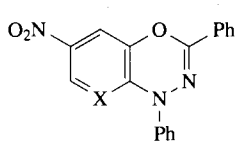
In contrast, the corresponding pyrrolidine enamines in all cases yield a mixture of 4,1,2-benzoxadiazine and the enamine-tautomer, the former always as the major component.

N'-Benzoylphenylhydrazine (PhCONHNHPh) can function as a useful bidentate nucleophile and in acetonitrile at room temperature undergoes condensation with 2,4-dinitrofluorobenzene to give the disubstituted benzohydrazide (**272**), which with sodium hydroxide in boiling DMF undergoes cyclization to 1,3-diphenyl-6-nitro-1*H*-4,1,2-benzoxadiazine (**273**; X = CH) in excellent yield ⟨75CJC1484, 80JOC3677⟩. The reaction fails with 2-chloro-3-nitro-pyridine, but with 2-chloro-3,5-dinitropyridine the nitropyrido[3,2-*e*][1,3,4]oxadiazine (**273**; X = N) is formed. Pyrimido-, pyrazino-, and quinazolino-[1,3,4]oxadiazines are prepared in a similar manner from the corresponding 2-chloro-nitroazines ⟨80JOC3677⟩.

4,1,2-Benzothiadiazines are formed in a similar way from the thiohydrazides (see Section 6.17.7.2.2).



(**272**)

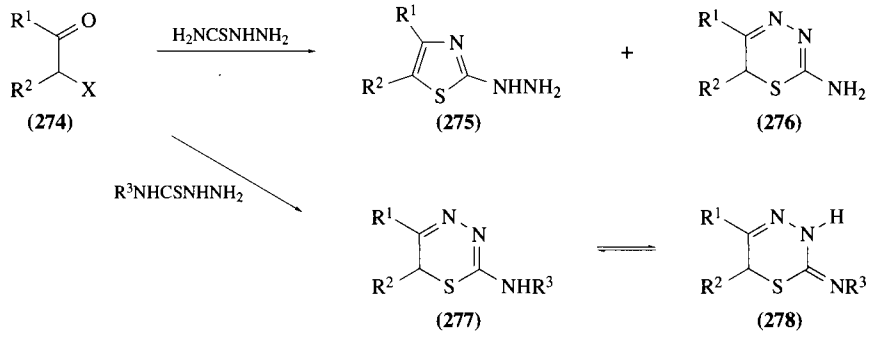


(**273**)

(ii) From N—N—C—S and C—C fragments

The synthesis of 2-amino-6*H*-1,3,4-thiadiazines (**276**) by condensation of α-haloketones (**274**) with thiosemicarbazides, as first reported by Bose ⟨25JIC51, 25JIC95⟩ continues to be used as a reliable route to this system. The reaction, however, can be complex and the products are dependent on the nature of the substituents in each of the reactants, the polarity of the solvent used, and the reaction temperature ⟨91CHE666⟩; common by-products are 2-hydrazinothiazoles (**275**) and 3-aminothiazolines (see Section 6.17.5.2). An excellent review of the confusing and sometimes erroneous pioneering work on these reactions is available ⟨B-61MI 617-01⟩.

Results indicate that in strong acid solution (pH 1–2) 2-amino-6*H*-1,3,4-thiadiazines (**276**) are produced ⟨91CHE666⟩, whereas in ethanol and acetic acid (2 : 1), mixtures of thiadiazine and thiazole (**275**) are formed. However, exceptions occur, notably with 2-(bromoacetyl)pyridine (**274**; X = Br, R^1 = 2-pyridyl, R^2 = H) which, unlike the isomeric 3- and 4-bromoacetyl compounds, condenses with thiosemicarbazide in either 48% or 2M hydrobromic acid to give solely the 2-hydrazinothiazole (**275**; R^1 = 2-pyridyl, R^2 = H) in 60% and 90% yield, respectively (Scheme 37).



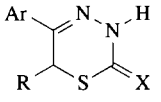
Scheme 37

N'-Substituted thiosemicarbazides ($R^3NHCSNHNH_2$) yield the correspondingly *N*-substituted 1,3,4-thiadiazines (**277**) ⟨70LA(741)45, 83EGP204092, 84EGP209196, 84USP4436549, 85JAP(K)60239420, 89S518, 90JHC707, 92CCC656⟩ of which the 2-alkyl-amino derivatives are of particular interest in that they exist as tautomeric mixtures of the amino (**277**) and imino (**278**) forms ⟨93ACS302, 94PHA401⟩.

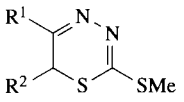
Instances of catalysis of the reaction by TFA have been noted and in some cases the presence of the acid catalyst is vital, otherwise only 1-amino-2-imino-1,3-thiazoles are produced ⟨91JHC1365⟩.

If ammonium thiocarbazate or alkyl thiocarbazates are used in place of the thiosemicarbazides, then 6*H*-1,3,4-thiadiazin-2(3*H*)-ones (**279**; X = O) are obtained ⟨83EUP85227, 84USP4489074, 91JHC1365, 91JHC1525, 92JMC163, 93GEP4134893⟩, the 5-aryl derivatives of which are valuable cardiotonics (Section

6.17.10.2). With methyl dithiocarbazate as the reactant 2-methylthio-6*H*-1,3,4-thiadiazines (**280**) result ⟨59CB2593, 62ACS2395, 84CPB152⟩.

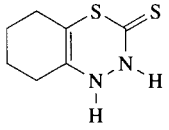


(**279**)



(**280**)

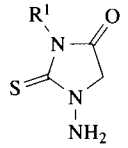
α-Chlorocyclohexanone condenses with potassium dithiocarbazate to give a moderate yield of the acid- and base-sensitive 1,2,5,6,7,8-hexahydro-3*H*-4,1,2-benzothiadiazine-3-thione (**281**). The thiol tautomer is discounted on the basis of PMR and IR spectral data ⟨86JHC105⟩. In contrast, phenacyl bromide and the potassium salt in boiling ethanol yield a mixture of 3-amino-4-phenyl-1,3-thiazoline-2(3*H*)-thione (48%) and 3,6-dihydro-5-phenyl-2*H*-1,3,4-thiadiazine-2-thione (**279**; R = H, Ar = Ph, X = S) (29%) ⟨85H(23)3099⟩.



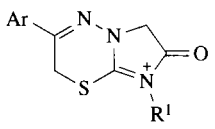
(**281**)

N^1,N^2,N^3-Trisubstituted thiosemicarbazides (MeNHN(Me)CSNHR^1) also react readily with α-haloacyl halides (R^{2}CH(X)COX; X = Cl or Br) to give 2-alkylimino-3,4-dihydro-2*H*-1,3,4-thiadiazin-5(6*H*)-ones (**80**) in 52–81% yield ⟨86H(24)885, 87JCR(S)254⟩. The formation of the isomeric 1,3,4-thiadiazin-6(5*H*)-ones was considered but discounted on the basis of spectral data and on the alkaline hydrolysis of the products to identifiable semicarbazides (Section 6.17.5.5).

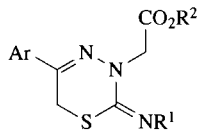
An adaptation of this reaction is the transformation of 3-substituted 1-amino-4-oxo-imidazoline-2-thiones (**282**) into 2-alkylimino-5-aryl-3,6-dihydro-2*H*-1,3,4-thiadiazine-3-acetic esters, involving ring-scission of an imidazo[1,2-*b*]thiadiazine intermediate (**283**), occurs on treating the imidazoline thiones with a phenacyl bromide in hot alcohol solution ⟨89S518⟩. The free bases (**284**) are liberated on heating the hydrobromides under reflux with triethylamine in ethanol. The thiadiazines (**284**) can also be synthesized independently from the *N*-(alkoxycarbonylmethyl) semicarbazides (R^{1}NHCSN(NH$_2$)CH$_2$CO$_2$Et) and phenacyl bromide.



(**282**)

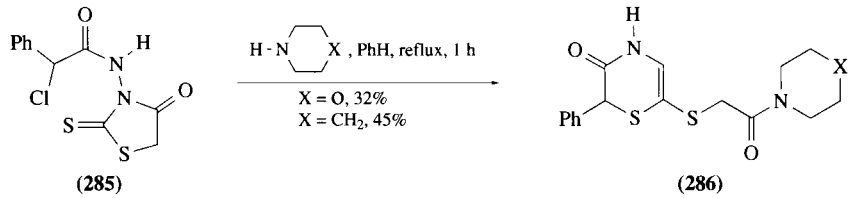


(**283**)



(**284**)

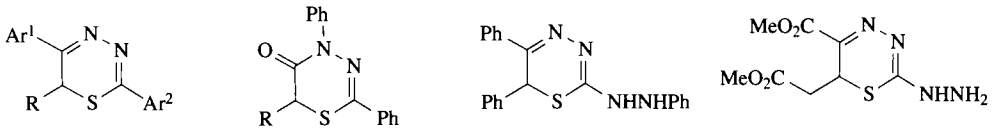
A similar reaction is noted on treating the 3-(α-haloacylamino)-rhodamine (**285**) with a secondary alkylamine. Nucleophilic attack at the ring-carbonyl, with concomitant opening of the thiazolidine ring, rather than amino-dehalogenation at the acyl-side-chain, is followed by ring closure to the 4*H*-1,3,4-thiadiazin-5(6*H*)-one (**286**) (Equation (19)) ⟨93AP(326)249⟩.



(**285**) (**286**) (19)

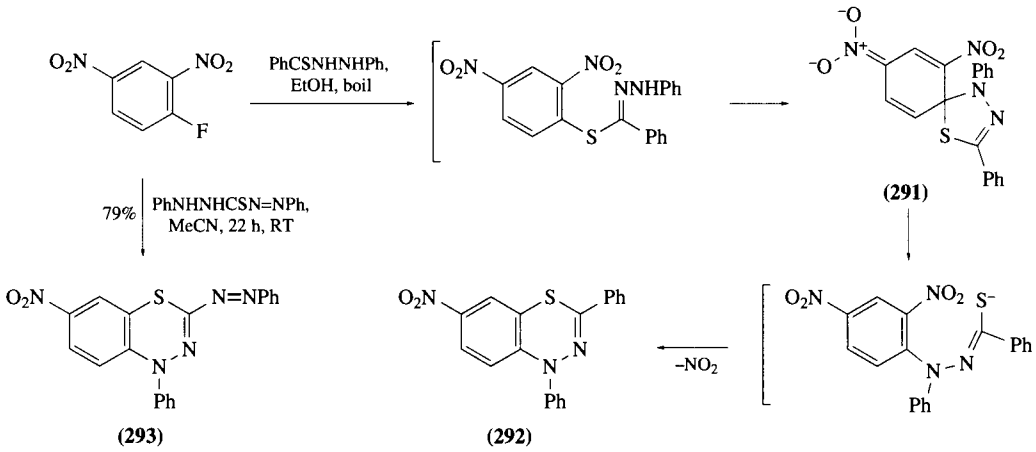
Condensation of a phenacyl halide with an arylthiohydrazide (ArCSNHNH$_2$) gives rise to a 2,5-diaryl-6*H*-1,3,4-thiadiazine (**287**) ⟨76JPR(318)971, 86JCS(P1)1499⟩. Variations on this reaction are the condensations of *N'*-phenylthiobenzohydrazide (PhNHNHCSPh) with bromoacetic acid ⟨91CE411⟩, to give 2,4-diphenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (**288**; 90%) and of the thiocarbohydrazide (PhNHNHCSNHNH$_2$) with desyl bromide to form 5,6-diphenyl-2-(phenylhydrazino)-6*H*-1,3,4-thiadiazine (**289**; 87%) ⟨89ZC288⟩. Likewise, dimethyl 2-bromo-1-oxoglutarate and thio-

carbohydrazide ($(H_2NHN)_2CS$) in boiling methanol yield the 2-hydrazino-6*H*-1,3,4-thiadiazine-5-carboxylate (**290**) (23%) as the hydrobromide ⟨93JPR176⟩.



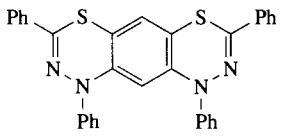
(**287**) (**288**) (**289**) (**290**)

1,3-Diphenyl-6-nitro-1*H*-4,1,2-benzothiadiazine (**292**) is available by condensation of 2,4-dinitrofluorobenzene and the thioacylhydrazide PhCSNHNHPh in a similar manner to that described for 4,1,2-benzoxadiazines in Section 6.17.7.2.2.1. In this case, however, initial substitution of fluorine is thought to be by sulfur, followed by rearrangement to the product via the spiro-intermediate (**291**), as indicated in Scheme 38 ⟨80JOC3677⟩.



Scheme 38

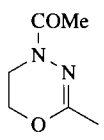
If 1,5-difluoro-2,4-dinitrobenzene is used as the "activated halogen" compound, then in boiling DMF solution a double ring-closure to the tetraphenyl-1*H*,9*H*-benzo[1,2-*e*:5,4-*e*′]bis[1,3,4]thiadiazine (**294**) (14%) is noted. 2,4-Dinitrofluorobenzene also undergoes reaction with "dithizone" (PhN=NCSNHNHPh) in acetonitrile at 25°C to yield 6-nitro-1-phenyl-3-phenylazo-1*H*-4,1,2-benzothiadiazine (**293**) as purple needles in 79% yield (see also Section 6.17.7.1.3).



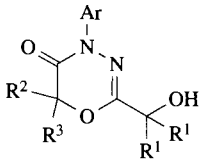
(**294**)

(iii) From C—C—N—N and C—O fragments

4-Acetyl-2-methyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (**295**) is obtained in low yield (20%) by heating (β-hydroxyethyl)hydrazine with an excess of acetic anhydride ⟨84JOU651⟩. 4*H*-1,3,4-Oxadiazin-5(6*H*)-ones (**296**) are prepared in variable yields (31–80%) by condensing *N*′-(α-hydroxyacyl)aryl hydrazines ($ArNHNHCOCR^1_2OH$) with α-haloacyl halides ($R^2R^3CXCOCl$) in hot benzene ⟨84CHE726⟩.



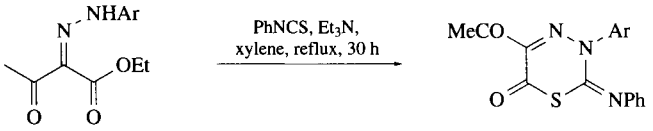
(295)



(296)

(iv) From C—C—N—N and C—S fragments

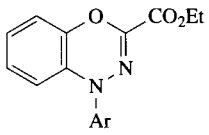
β-Keto-ester arylhydrazones (**297**) condense with arylisothiocyanates in boiling xylene to give 5-acyl-3-aryl-2-arylimino-2,3-dihydro-1,3,4-thiadiazin-6-ones (**298**) rather than 1,2,4-triazine-2-thiones (Equation (20)) ⟨90IJC(B)1044⟩.



(297) (298) (20)

(v) From N—C—C—O and C—N fragments

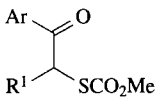
Remarkably, 1-aryl-1*H*-4,1,2-benzoxadiazine-3-carboxylates (**299**) are formed by condensation of 2-aminophenol with arylhydrazones of ethyl chloroglyoxylate in hot DMF ⟨88JIC194⟩. An alternative initial condensation of the chlorohydrazone at nitrogen followed by cyclization to a triazine was discounted on the basis of the nonidentity of the products with those formed by condensing the chlorohydrazones with *o*-phenylenediamine.



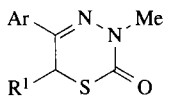
(299)

(vi) C—C—S—C and N—N fragments

α-(Methoxycarbonyl)sulfenyl ketones (**300**), prepared by condensation of methoxycarbonylsulfenyl chloride with an alkyl aryl ketone in chloroform at room temperature, on treatment with methylhydrazine give 3,6-dihydro-3-methyl-2*H*-1,3,4-thiadiazin-2-ones (**301**) in moderate yields (38–58%) ⟨92JOC1053⟩.



(300)



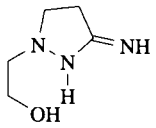
(301)

6.17.7.2.3 [5 + 1] fragments

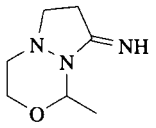
(i) N—N—C—C—O and C fragments

Cyclocondensation of the iminotetrahydropyrazole (**302**) with ethanal yields the bicyclic 1,3,4-oxadiazine (**303**) in 52% yield ⟨86JOU2038⟩. In a similar manner, ring-closure of the *N*-(β-hydroxy-

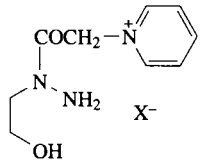
ethyl)hydrazine (**304**) with 4-nitrobenzaldehyde in hot methanol yields the 4-acyl-2-aryl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine (**305**; Ar = 4-$NO_2C_6H_4$) ⟨86JOU1195⟩.



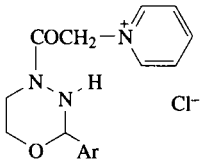
(**302**)



(**303**)

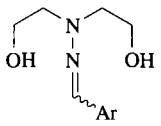


(**304**)

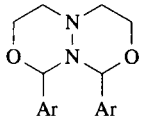


(**305**)

Acid-catalyzed condensation of 1,1-bis-(β-hydroxyethyl)hydrazine with 4-nitrobenzaldehyde in hot methanal yields mainly the hydrazone (**306**) (48%) together with a small amount (6.5%) of the hydro-1,3,4-oxadiazino[3,4-*c*][1,3,4]oxadiazine (**307**). However, with a two-fold excess of aldehyde, the yield of the fused oxadiazine increases to 17% ⟨85JOU832⟩.

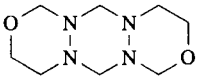


(**306**)



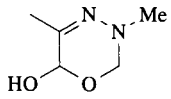
(**307**)

4-(Hydroxyethyl)-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine, a by-product in the synthesis of oxazolidines by the action of paraformaldehyde on (β-hydroxyethyl hydrazones, dimerizes *in situ* to give the bisoxadiazinotetrazine (**308**) in 20% yield ⟨84JOU460⟩.



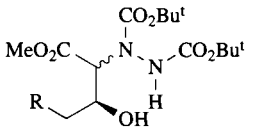
(**308**)

3,5-Dimethyl-6-hydroxy-3,6-dihydro-2*H*-1,3,4-oxadiazine (**309**), a cyclic hemiacetal, is formed by reaction of 2-methylhydrazonopropanal (MeNHN=C(Me)CHO) with aqueous methanal ⟨85JCS(P1)81⟩.

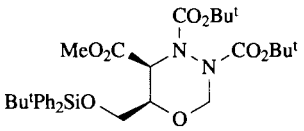


(**309**)

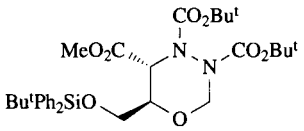
The *cis*- and *trans*-1,3,4-oxadiazine-5-carboxylates (**311**; 71%) and (**312**; 57%) are prepared by ring-closure of the *erythro*- and *threo*-isomers of the diBOC protected hydrazine (**310**; R = Bu^tPh_2SiO) with 2-methoxypropene ⟨89TL5507⟩. The more stable *trans*-isomer (**312**) is also available in 75% yield by base-mediated equilibration of the *cis*-isomer (**311**).



(**310**)



(**311**)



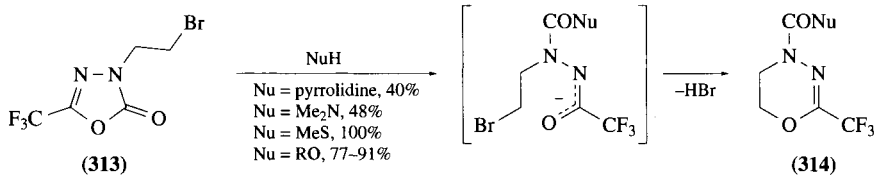
(**312**)

The isomeric 6-methyl-tetrahydro-2*H*-1,3,4-oxadiazine-5-carboxylates (**155** and **156**; R = CO_2Me) (Section 6.17.6.3) are prepared in a similar manner from the isomeric hydrazines (**310**; R = H) with 2,2-dimethoxypropane providing the C-2 fragment ⟨89TL5511⟩.

6.17.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

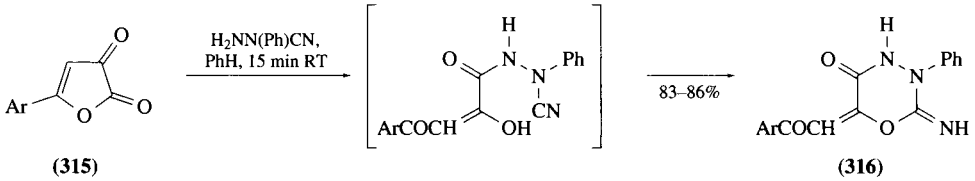
6.17.8.1 1,3,4-Oxadiazines

Treatment of 3-(2-bromoethyl)-5-trifluoromethyl-1,3,4-oxadiazolin-2(3*H*)-one (**313**) with nucleophiles brings about ring expansion to 2-trifluoromethyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (**314**) by an intramolecular S_N2 process (Scheme 39). Yields are moderate with secondary amines, quantitative with methanethiol ⟨86HCA333⟩, and excellent with alkoxides ⟨92JHC1081⟩.



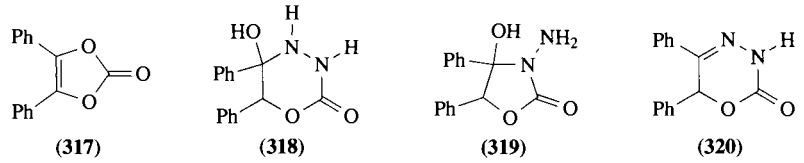
Scheme 39

2-Imino-6-phenacylidene-3,4-dihydro-2*H*-1,3,4-oxadiazin-5(6*H*)-ones (**316**), rather than the expected 2-amino-5-phenacylidene-1,3-oxazolidin-4-ones, are formed in excellent yields by treating 5-arylfuran-2,3-diones (**315**; Ar = 4-Me- or 4-EtO—C_6H_4) with *N*-cyano-*N*-phenylhydrazine (Scheme 40) ⟨85JOU620⟩.

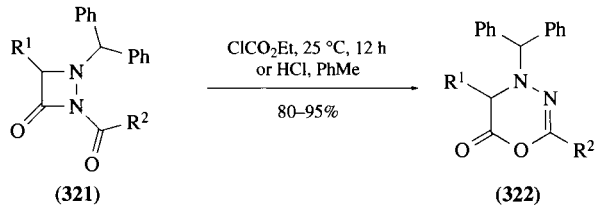


Scheme 40

The mixture of 5,6-diphenyl-5-hydroxy-5,6-dihydro-4*H*-1,3,4-oxadiazin-2(3*H*)-one (**318**) and the 3-amino-4-hydroxyoxazolin-2(3*H*)-one (**319**), formed by the action of hydrazine on diphenylethylene carbonate (**317**), undergoes dehydration in the presence of phosphorus pentoxide to yield 5,6-diphenyl-6*H*-1,3,4-oxadiazin-2(3*H*)-one (**320**; 46%) and 4,5-diphenyl-3-aminooxazol-2(3*H*)-one (45%), which are separable by column chromatography on silica ⟨83TL4635⟩.



In the presence of ethyl chloroformate or hydrogen chloride in toluene, 2-acylated 1-(diphenylmethyl)-1,2-diazetidin-3-ones (**321**) undergo a novel ring expansion to 4*H*-1,3,4-oxadiazin-6(5*H*)-ones (**322**) in excellent yields (Equation (21)) ⟨84JOC2204⟩.

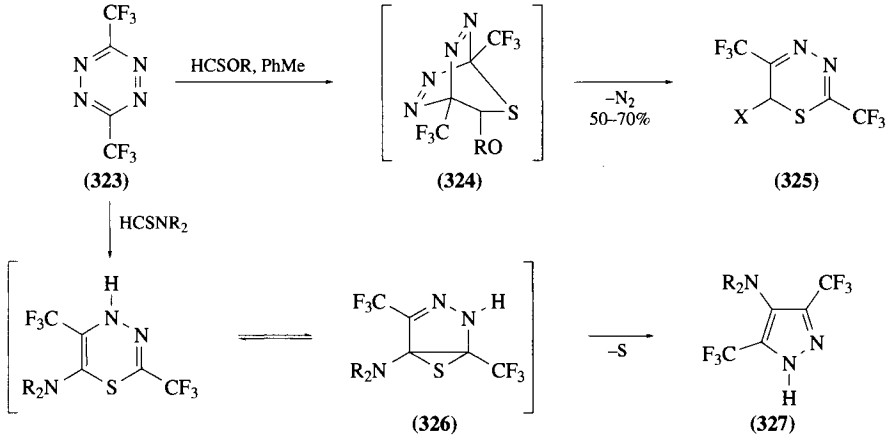


(21)

6.17.8.2 1,3,4-Thiadiazines

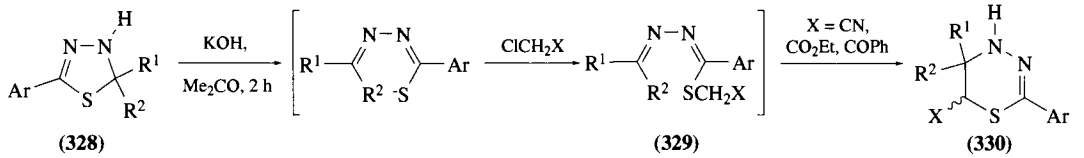
The excellent dienophilic character shown by thiocarbonyl compounds in inverse-electron demand Diels–Alder cycloadditions has been utilized in the synthesis of 1,3,4-thiadiazines (Scheme 41)

⟨84AG(E)890⟩. Addition of ethyl or propyl thioformate to 3,6-bis-(trifluoromethyl)-1,2,4,5-tetrazine (**323**) yields the 6-alkoxy-6*H*-1,3,4-thiadiazines (**325**; X = OEt or OPr) by loss of nitrogen from the nonisolable [4 + 2] cycloadducts (**324**). In contrast, with thioamides only 4-amino-3,5-bis(trifluoromethyl)pyrazoles (**327**) are formed by extrusion of sulfur from the valence isomer (**326**) of the initially formed, but unstable 6-amino-6*H*-1,3,4-thiadiazine (**325**; X = NR_2). Likewise, with thiobenzaldehyde, only the pyrazole (**327**; Ph in place of NR_2) is obtained.



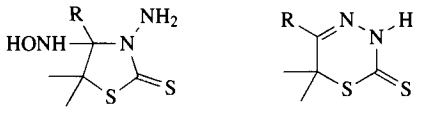
Scheme 41

Attempts to alkylate 4,5-dihydro-1,3,4-thiadiazoles (**328**) with iodomethane, in the presence of a variety of bases, results in ring opening and *S*-alkylation to yield 1-(alkylthio)-2,3-diazabutadienes (**329**). However, if the alkylating agent ($ClCH_2X$) contains an electron-withdrawing group (X = CN, CO_2Et, or COPh) then ring closure of the alkylthiodiene (**329**) to a *cis–trans*-mixture of 5,6-dihydro-4*H*-1,3,4-thiadiazines (**330**) takes place in 60–70% yield as outlined in Scheme 42. Benzylation of the thiadiazole (**328**; R^2 = Ar = 4-$MeOC_6H_4$; R^1 = H) with benzyl chloride and sodium hydride in DMF is much slower (18 h) and furnishes the 6-phenyl-5,6-dihydro-4*H*-thiadiazine (**331**; X = Ph; R^2 = Ar = 4-$MeOC_6H_4$; R^1 = H) in 70% yield. However, if the reaction is stopped after 1 h, then the *S*-benzylated azine (**329**; X = Ph) can be isolated in 80% yield ⟨84CC1444⟩.



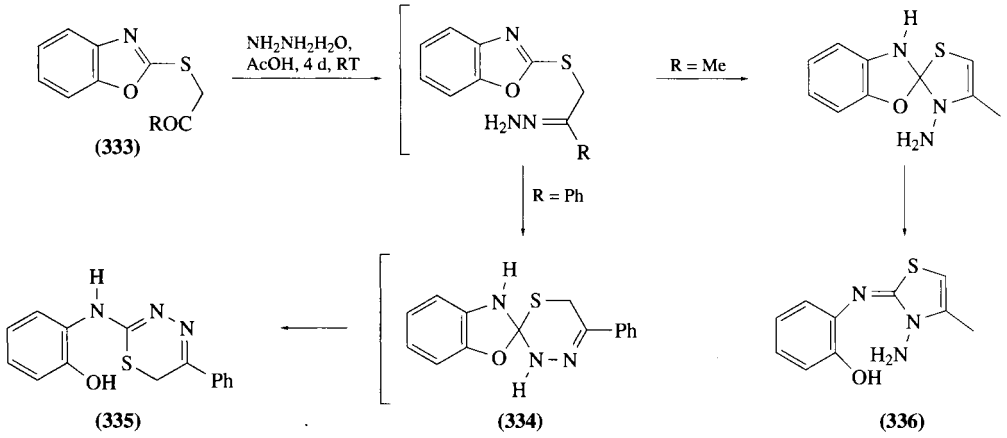
Scheme 42

3-Amino-4-hydroxyaminothiazoline-2-thiones (**331**), formed by the action of potassium dithiocarbazate on dimeric nitrosoalkyl chlorides, undergo ring expansion in dilute acid to give 5-substituted-6,6-dimethyl-3,6-dihydro-1,3,4-thiadiazine-2-thiones (**332**) ⟨78EGP127811, 79JPR959, 87CHE463⟩.



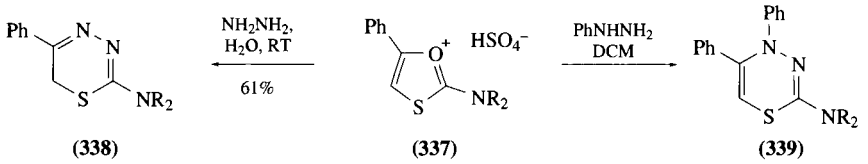
Treatment of 2-(phenacylthio)benzoxazole (**333**; R = Ph) with hydrazine hydrate results in cleavage of the oxazole ring and rearrangement via the spiro-intermediate (**334**) to the 6*H*-1,3,4-thiadiazine (**335**) (Scheme 43). In contrast, the methyl analogue (**333**; R = Me) yields only the *N*-aminothiazole (**336**; 86%) ⟨82H(19)2119⟩.

5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines (**199**) (Section 6.17.7.1.1) are converted into the corresponding 1,3,4-thiadiazines in high yields (> 80%) with Lawesson's reagent in boiling benzene ⟨90S491⟩.



Scheme 43

Aqueous hydrazine at room temperature effects ring expansion of 2-alkylamino-1,3-oxathiolium salts (**337**) to 2-alkylamino-6*H*-1,3,4-thiadiazines (**338**) in excellent yields (>90%); with phenylhydrazine the 4,5-diphenyl-4*H*-derivatives (**339**) are obtained (Scheme 44) ⟨78CPB3017⟩.



Scheme 44

6.17.9 GENERAL SYNTHETIC METHODS

6.17.9.1 1,3,4-Oxadiazines

4*H*-1,3,4-Oxadiazines are prepared by cyclodehydration of *N*-phenacyl-*N'*-acylhydrazines under acid conditions (Section 6.17.7.1.1). 5,6-Dihydro-4*H*-1,3,4-oxadiazines are available by [4 + 2] cycloaddition of vinyl heterocycles with azodicarboxylates (Section 6.17.7.2.2(i)) and by ring expansion of 3-(2-bromoethyl)-1,3,4-oxadiazolin-2(3*H*)-ones in the presence of a nucleophile (Section 6.17.8.1).

5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines result from the trifluoroacetylation of arylaldehyde *N*,*N*-dialkylhydrazones, while oxidation of the hydrazones with sodium periodate yields the 6-hydroxy-6-trifluoromethyl derivatives (Section 6.17.7.1.1).

4-(2-Fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazines are accessible by ring closure of acylhydrazides with 1-bromo-2-fluoroethane (6.17.7.2.2.1) and fully saturated 1,3,4-oxadiazines arise by condensation of (β-hydroxyethyl)hydrazines with aldehydes (6.17.7.2.3.1).

3,6-Dihydro-2*H*-1,3,4-oxadiazin-2-ones are prepared by base-induced cyclization of *N*-(α-hydroxyalkyl)-*N'*-(alkoxycarbonyl)hydrazines, and by copper-catalyzed decomposition of *N*-acyl-*N'*-(α-diazoacyl)hydrazones (Section 6.17.7.1.1). 4*H*-1,3,4-Oxadiazin-5(6*H*)-ones are accessible by base-induced ring closure of 2-chloroacetylhydrazides (Section 6.17.7.1.1), by condensing *N'*-(α-hydroxyacyl)arylhydrazines with α-haloacylhalides (Section 6.17.7.2.2(iii)), while the ring expansion of furan-2,3-diones by reaction with *N*-cyano-*N*-phenylhydrazine forms 3-aryl-2-imino-6-phenacylidene derivatives (Section 6.17.8.1). Cyclodehydrations of the *N*-acylhydrazones of α-ketoacids and of α-(acylhydrazono)-carboxylic acids with dicyclohexylcarbodiimide provide routes to 1,3,4-oxadiazin-6-ones and their 4,5-dihydro derivatives, respectively (Section 6.17.7.1.1). 4,5-Dihydro-6*H*-1,3,4-oxadiazin-6-ones are also available in high yield by a novel ring expansion of 2-acylated-1,2-diazetidin-3-ones (Section 6.17.8.1).

6.17.9.2 4,1,2-Benzoxadiazines

The uncommon 4,1,2-benzoxadiazine ring-system is accessible by condensation of 2,4-dinitrofluorobenzene with *N'*-benzoylphenylhydrazine (Section 6.17.7.2.2(i)) and as the 6-ones by condensation of 2,5-dihydroxy-1,4-benzoquinones with acylhydrazides (Section 6.17.7.2.1(i)).

6.17.9.3 1,3,4-Thiadiazines

A major route to 2-amino-6*H*-1,3,4-thiadiazines is by the condensation of α-haloketones with thiosemicarbazides (Section 6.17.7.2.2(ii)). Replacement of the thiosemicarbazide by a thiocarbamic acid or by a thiocarbazide results in formation of 3,6-dihydro-2*H*-1,3,4-thiadiazin-2-ones. Likewise, replacement with an *N'*-arylthiohydrazide yields a 4*H*-1,3,4-thiadiazin-5(6*H*)-one (Section 6.17.7.2.2(ii)). 3,6-Dihydro-2*H*-thiadiazin-2-ones are also available by the condensation of alkylhydrazines with α-(methoxycarbonylsulfenyl)alkylaryl ketones (Section 6.17.7.2.2(vi)), while the ring closure of (arylhydrazonoalkylthio)acetic acids with dicyclohexylcarbodiimide provides an alternative route to 4*H*-1,3,4-thiadiazin-5(6*H*)-ones (Section 6.17.7.1.2). 2-Phenylimino-3-aryl-2,3-dihydro-1,3,5-thiadiazin-6-ones result from treatment of α-hydrazono-β-ketoesters with arylisothiocyanates (Section 6.17.7.2.2(iv)).

3,6-Dihydro-2*H*-1,3,4-thiadiazines are formed by the action of Lawesson's reagent on α-trifluoroacetyl)aryl aldehyde *N,N*-dialkylhydrazones (Section 6.17.7.1.3), while alkylation of dihydro-1,3,4-thiadiazoles yields 5,6-dihydro-4*H*-1,3,4-thiazines (Section 6.17.8.2). The transformation of 1,3,4-oxadiazines to 1,3,4-thiadiazines with Lawesson's reagent has been reported (Section 6.17.8.2), and 6*H*-1,3,4-thiadiazines are available by [4 + 2] cycloaddition of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazines with thioesters (Section 6.17.8.2).

Rare examples of the synthesis of the 1,3,4-thiadiazine system by N—N bond formation are noted in the cyclization of α-thiocyanatoacetophenone oxime with hydrazine or phenylhydrazine (Section 6.17.7.1(ii)).

6.17.9.4 4,1,2-Benzothiadiazines

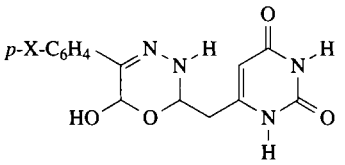
3*H*-4,1,2-Benzothiadiazines and their 4,4-dioxides are obtained by diazotization of α-(2-aminosulfenyl) and α-(2-aminosulfonyl)-malonamides, respectively (Section 6.17.7.1.2). 4,1,2-Benzothiadiazines are also formed by ring closure of *N*-arylnitrilimines bearing an *ortho*-alkenylthio-, or an *ortho*-alkynylthio substituent (Section 6.17.7.1.3), and by the condensation of 2,4-dinitrofluorobenzene with thioacylhydrazides (Section 6.17.7.2.2.2).

6.17.10 IMPORTANT COMPOUNDS AND APPLICATIONS

6.17.10.1 1,3,4-Oxadiazines

A wide range of applications have been reported for 1,3,4-oxadiazines and 1,3,4-thiadiazines.

Antiviral activity has been noted for 6-substituted 1,3,4-oxadiazines ⟨84MI 617-01, 84MI 617-02, 84MI 617-03⟩ and for 6-(5-aryl-6-hydroxy-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ylmethyl) uracils (**339**; X = Cl or Br) ⟨90MI 617-02, 91MI 617-02, 92MI 617-01, 92MI 617-02, 92MI 617-03⟩.



(**339**)

2,6-Diaryl-4*H*-1,3,4-oxadiazines are antibacterial agents ⟨83MI 617-01⟩, and excellent acaricidal and insecticidal activities have been reported for 4-(fluoroalkyl)-2-(haloaryl)-5,6-dihydro-4*H*-1,3,4-oxadiazines (**271**) (Section 6.17.7.2.2(i)) ⟨93MI 617-01, 94MI 617-01⟩.

2,4-Diaryl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones have useful acaricide and nematocide activity ⟨86FRP2580643, 87USP4670555⟩ and a quantitative structure–activity relationship for their acaracidal activity is available ⟨91MI 617-01⟩. Organophosphothioate derivatives of 2-alkyl-4-aryl-4*H*-oxadiazin-5(6*H*)-ones are effective insecticides, nematocides, and acaricides ⟨91USP5010068⟩. Cardiotonic and antihypertensive activities are shown by 2-substituted 4*H*-1,3,4-oxadiazin-5(6*H*)-ones ⟨83JAP(K)58131973, 85USP4508718, 87EUP220044, 90JMC2870⟩; enzyme (monoamine oxidase) inhibitory action has also been reported ⟨88EJM441⟩.

Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones ⟨89EUP299449⟩ and 1-acyl-3-aryl-1*H*-4,1,2-benzoxadiazines exhibit lipoxygenase inhibition ⟨91EUP410834⟩; the latter compounds are also cycloxygenase inhibitors.

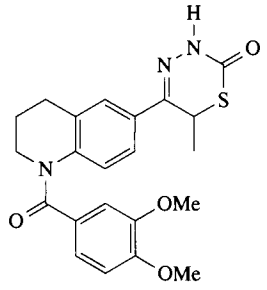
CNS activity has been attributed to 3-alkyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones ⟨86EJM403⟩, and 5-aryl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones ⟨93JAP(K)05148250⟩ are blood platelet aggregation inhibitors.

5-Phenyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones are used as blowing agents for formaldehyde-polyether resins ⟨85USP4543368⟩, for polycarbonates ⟨79USP4158094, 85USP4544677, 86USP4587272, 89CP1250087⟩ and for polypropylene ether resins ⟨87USP4684669, 90USP4904702⟩.

Tetrahydro-2*H*-1,3,4-oxadiazines have been patented as photofading preventatives for color film ⟨88JAP(K)63256951⟩.

6.17.10.2 1,3,4-Thiadiazines

5-Aryl- and 5-heteroaryl-3,6-dihydro-2*H*-1,3,4-thiadiazin-2-ones display important cardiotonic and antihypertensive activity and are the subject of many patents ⟨83EUP80296, 86EUP180158, 88EGP294647, 89EUP303418, 90BRP2228004, 90EUP351213, 90JAP(K)02279685, 91JAP(K)03261773, 92EUP466952, 92GEP4041074⟩ and several papers ⟨89BJP409, 91JHC1365, 91JHC1525, 91MI 617-03⟩. A kinetic resolution of the enantiomeric 3,6-dihydro-2*H*-1,3,4-thiadiazin-2-one (**340**), a new cardiotonic with calcium sensitizing activity, has been carried out. Subsequent tests revealed that the calcium sensitizing effects reside only in the (+)-enantiomer; the (−)-enantiomer is a PDE inhibitor ⟨92BMC589, 93MI 617-02⟩. 5-(Heteroaryl)-3,6-dihydro-2*H*-1,3,4-thiadiazin-2-ones and the corresponding 2-thiones are phosphodiesterase inhibitors ⟨90EUP381374⟩.



(340)

Cardiotonic and spasmolytic activity are present in 2-(alkylimino)-3,4-dihydro-2*H*-1,3,4-thiadiazines ⟨83EGP204092, 84EGP209196, 85EGP220311, 90EGP280760⟩, antineoplastic effects have also been claimed ⟨85JAP(K)60239420⟩.

2-Imino-3,4-dihydro-2*H*-1,3,4-thiadiazin-5(6*H*)-ones induce and promote the differentiation of Friend leukemia cells ⟨86ABC1757⟩, 5-aryl-2-dialkylamino-6*H*-1,3,4-thiadiazines possess analgesic and 5-lipoxygenase inhibitory, activity, and are antioxidants ⟨88GEP3702756⟩. Spiro-3,4-dihydro-2*H*-1,3,4-thiadiazin-5(6*H*)-ones (**255**; Section 6.17.7.2.1(ii)) have been patented as agrochemical microbicides ⟨91JAP(K)0383972⟩, and 3-(*t*-butylamino)-1*H*-4,1,2-benzothiadiazines as plant fungicides ⟨89JAP(K)0150873⟩.

2-Morpholino-5-(2-pyridyl)-6*H*-1,3,4-thiadiazine is a reagent for the photometric determination of iron ⟨85URP1189862⟩, and 2-dialkylamino-2*H*-1,3,4-thiadiazines are insect oviposition inhibitors ⟨92JAP(K)04297468⟩.

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6.18
1,3,5-Oxadiazines and 1,3,5-Thiadiazines

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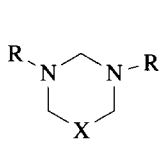
6.18.1 INTRODUCTION

1,3,5-Oxadiazines and 1,3,5-thiadiazines are common ring systems ⟨B-61MI 618-01, 62HC(17)447, 79COC(4)1051⟩ and several derivatives, especially the 1,3,5-oxadiazine-2,4-diones and the 1,3,5-thiadiazin-4(3*H*)-ones, are important insecticides (see Sections 6.18.13.1 and 6.18.13.2). Fully reduced compounds (**1**; X = O or S) have been characterized, as have a variety of 2*H*- and 4*H*-1,3,5-oxadiazines (**2** and **3**; X = O). 2*H*-1,3,5-Thiadiazines (**2**; X = S) however, unlike the 4*H*-isomers (**3**; X = S), are uncommon.



(1)

(2)

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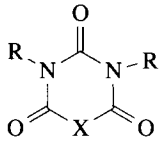

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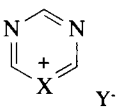


(5)

Also widely known are the 2- and 4-ones and their thione analogues. Examples of virtually all possible mono-, di- and triones, together with their thione equivalents, of the partially and fully reduced ring systems have been prepared, and 1,3,5-oxadiazinetriones (**4**; X = O) are essential components of several polymer formulations (see Section 6.18.13.1). Of particular interest are the fully conjugated 1,3,5-oxonia- and 1,3,5-thionia systems (**5**; X = O and S), which in the primary literature, and throughout this chapter, are referred to as 1,3,5-oxadiazinium and 1,3,5-thiadiazinium salts, respectively. These 6π systems are characterized mainly as their hexachloroantimonate or perchlorate salts, and exhibit a moderate degree of aromaticity (see Section 6.18.4.1). However, and as expected, they resemble pyrylium salts and are very susceptible to nucleophilic attack at C-2(6) (see Section 6.18.5).

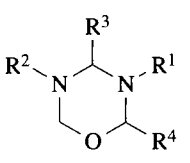
There appears to be only one report dealing with the synthesis of 1,3,5-thiadiazine mono- and di-*S*-oxides (see Section 6.18.7.2) and, curiously, 1λ^4- and 1λ^6-derivatives of this system are unknown.

There have been no reviews since the mid-1980s of the general chemistry of 1,3,5-oxadiazines and 1,3,5-thiadiazines. However, the synthesis of 1,3,5-oxadiazinium salts is included in a review on the use of acylium salts for the synthesis of heterocycles ⟨90OPP3⟩, and reviews on the synthesis and biological activity of 1,3,5-thiadiazines are available ⟨83MI 618-01, 87PAC1027⟩.

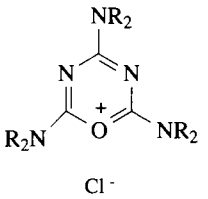
6.18.2 THEORETICAL METHODS

A molecular mechanics force field based on *ab initio* calculations developed for systems containing the N—C—O unit has been applied to fully saturated 1,3,5-oxadiazine derivatives ⟨90JST(206)29, 91MI 618-01⟩. Results indicate that for perhydro-1,3,5-oxadiazine (**6**; $R^1 = R^2 = R^3 = R^4 = H$) the conformer with the NH hydrogens in the axial positions (AA) is more stable than the (AE) and

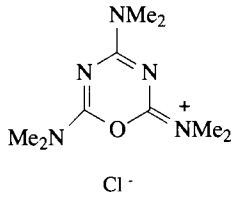
(EE) conformers by 5.5 and 15.1 kcal mol^{-1}, respectively ⟨90JST(206)29⟩, whereas for the 3,5-dimethyl derivative (**6**; $R^1 = R^2 = Me$; $R^3 = R^4 = H$), the (AA) and (AE) conformers are the more stable, the latter by 4.5 kcal mol^{-1} over that of the (EE) conformer ⟨78JCS(P2)377, 91MI 618-01⟩. Likewise, for the 2-methyl (**6**; $R^1 = R^2 = R^3 = H$, $R^4 = Me$), the 4-methyl (**6**; $R^1 = R^2 = R^4 = H$, $R^3 = Me$), and the 2,4-dimethyl (**6**; $R^1 = R^2 = H$, $R^3 = R^4 = Me$) derivatives, the equatorial conformers are the least stable ⟨91MI 618-01⟩. The stability of the (AA) conformers is attributed to anomeric interactions involving the *trans*-arrangement of the C—N and C—O bonds with respect to the lone pairs on the heteroatoms. Detailed information on bond lengths, bond angles and torsional angles for the 1,3,5-oxadiazine nucleus has been presented.



(**6**)



(**7**)



(**8**)

6.18.3 EXPERIMENTAL STRUCTURAL METHODS

6.18.3.1 Spectroscopic Studies

6.18.3.1.1 Ultraviolet and infrared spectra

UV and IR spectroscopic data for 1,3,5-oxadiazines and 1,3,5-thiadiazines are scattered throughout the literature, and are of no particular diagnostic value. 6-Aryl-2,4-dialkylamino-1,3,5-oxadiazinium perchlorates exhibit UV absorption maxima at 220–246 and 284–364 nm, and the corresponding 1,3,5-thiadiazinium perchlorates show absorptions at 225–240, 270–325, and 358–396 nm ⟨85T5371⟩.

The strong infrared absorption band noted for the 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me) at 1720 cm^{-1} is attributed to $\nu(C{=}\overset{+}{N}Me_2)$ and is indicative of major contributions from mesomers of type (**8**) ⟨85JCS(P1)1533⟩. The $\nu(C{=}O)$ for 6-substituted 1,3,5-thiadiazin-2-ones appears at 1680 cm^{-1} ⟨86ZC132⟩.

For the use of IR spectroscopy in the study of tautomeric equilibria in 1,3,5-oxadiazines and 1,3,5-thiadiazines see Section 6.18.4.3.

6.18.3.1.2 NMR spectra

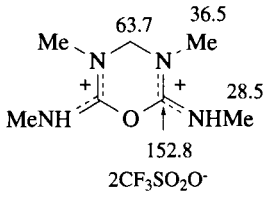
(i) ^1H NMR spectra

In the PMR spectra ($CDCl_3$) of the tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me), the 4-dimethylamino-group appears as a sharp singlet at 3.4 δ, while the 2- and 6-dimethylamino groups are equivalent and appear as a doublet at 3.3 δ. This is consistent with the importance of mesomers of type (**8**), for which severe restriction of rotation about the C—N bonds is expected ⟨85JCS(P1)1533⟩.

3,5-Dimethyl-2,6-di(methylimino)-tetrahydro-2*H*-1,3,5-oxadiazine bis(hydrogen trifluoromethanesulfonate) (**9**) in CD_3CN solution has the NH resonance at 8.77 δ, and the 4-CH_2 resonance at 4.89 δ ⟨85JHC907⟩.

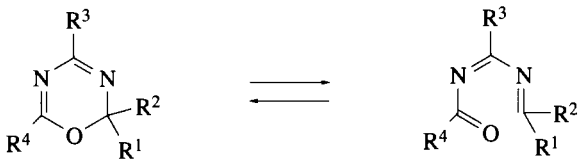
Variable temperature ^1H NMR studies have been used to determine the free enthalpy of activation of 2*H*-1,3,5-oxadiazine–oxadiazatriene ring-chain tautomeric systems (**10**)⇋(**11**) (see Section 6.18.4.3) ⟨93CB957⟩. A major difference in the proton resonances of the two forms is noted with a phenyl group at C-2 or C-4, the *ortho* protons of which appear at 8.1–8.4 δ in the oxadiazines in comparison with 7.8–7.9 δ for the open-chain tautomers.

In $CDCl_3$ solution the C-4 proton of 2,4,6-triaryl-4*H*-1,3,5-thiadiazines is found at 5.33–5.46 δ;



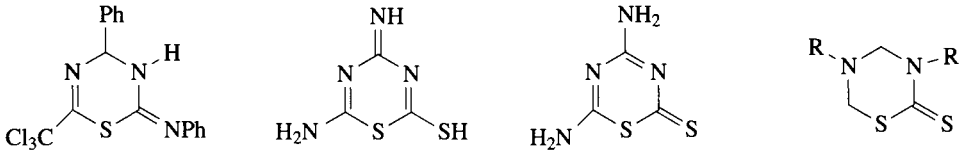
(9)

for the 2,6-diphenyl- and the 4-methyl-2,6-diphenyl derivatives the H-4 resonance is seen, for the former, as a 2H singlet at 5.52 δ, and for the latter, as a quartet (J 6.6 Hz) at 4.57 δ ⟨75S266⟩.



(10) (11)

Chemical shifts of 5.9 and 6.8 δ ($CDCl_3$) have been noted for the C-4 and C-5 protons of 2-imino-3,4-dihydro-1,3,5-thiadiazines (**12**) ⟨91SL93⟩. In d^6-DMSO solution, 4,6-diamino-1,3,5-thiadiazine-2-thione is said to exhibit ^{1}H NMR signals at 8.72 (NH_2), 8.25 (SH) and 8.12 (NH), indicative of the imino–thiol tautomer (**13**) rather than the diaminothione (**14**) ⟨83ZAAC(502)11⟩. However, other spectral data were compatible with the diamino form (**14**), and this conclusion should be treated with caution.



(12) (13) (14) (15)

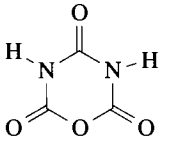
A detailed ^{1}H and ^{13}C NMR study of 3,5-dialkyl-5,6-dihydro-4*H*-1,3,5-thiadiazine-2(3*H*)-thiones (**15**) has been reported ⟨85ACH7⟩. The axial and equatorial protons at H-4 and H-6 appear either as two closely spaced (**15**; R = Me, Et, Pr^n, Bu^i, Bu^n), or overlapping (**15**; R = Pr^i, Me_2CHCH_2) singlets at 4.4–4.45 and 4.37–4.45 δ, in $CDCl_3$, and at 3.7–3.95, 3.42–3.95 δ in C_6D_6, indicative of a rapid ring-inversion process. The lower field signals are assigned tentatively to H-4, which, in accord with corresponding ^{13}C NMR signals (see Section 6.18.3.1.2.ii), and on the basis of Dreiding models, appear to be more deshielded by the anisotropic effect of the thione group than the C-6 protons.

(ii) ^{13}C NMR spectra

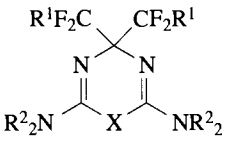
Chemical shifts in d^6-acetone at 148.3 δ (C-4) and 145.4 δ (C-2, C-6) have been recorded for 2*H*-1,3,5-oxadiazine-2,4,6(3*H*,5*H*)-trione (**16**) ⟨86CB83⟩.

In $CDCl_3$ solution the C-4 resonance signals for 2,6-diamino-4,4-bis(trifluoromethyl)- and 2,6-diamino-4,4-bis(chlorodifluoromethyl)-4*H*-1,3,5-oxadiazines (**17**; X = O, R^1 = F or Cl) appear at 75.5–76.9 and 81.5–82.9 δ, respectively ⟨84LA982⟩.

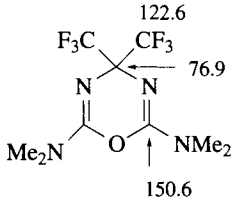
^{13}C NMR chemical shifts for 2,6-bis(dimethylamino)-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine are annotated to diagram (**18**). The C-4 septet has $J_{C,F} = 29$ Hz ⟨83S237⟩.



(**16**)



(**17**)

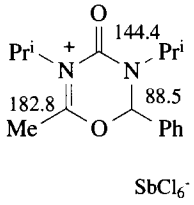


(**18**)

Significant and diagnostic differences are noted in the ^{13}C NMR spectra of the ring-chain tautomers (**10**)⇆(**11**) ⟨93CB957⟩. For the oxadiazine (**10**), the sp^3-carbon centre at C-2 appears at ≃ 100 δ (depending on substituents R^1,R^2), compared to 160–185 δ for the sp^2 carbon centre in the oxadiazatriene (**11**). Not unexpectedly, the C-6 signal, which in the oxadiazine appears at 162–176 δ is found at substantially lower field (180–196 δ) in the oxadiazatriene, a change which reflects the transition of C-6 from an imine carbon to a carbonyl carbon centre. The C-4 signal does not change appreciably and is found at 150–175 δ in each tautomer, depending on the nature of substituent R^3.

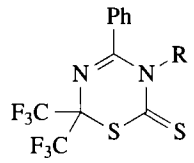
^{13}C NMR data on 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me), like the ^1H NMR data, is in accord with a dominant mesomeric contribution (**8**), and signals at 159.58 (C-4), 155.64 (C-2 and C-6), and at 37.81 δ (4-NMe_2) are noted along with absorbances at 37.28 and 37.15 δ for the nonequivalent *N*-methyl groups at C-2 and C-6 ⟨85JCS(P1)1533⟩. Three carbon resonances at 156, 158, and 164–169 δ are noted for 6-alkyl- and 6-aryl-2,4-dialkylamino-1,3,5-oxadiazinium hexachloroantimonates (see Section 6.18.10.3.1.i) ⟨85CB1304⟩ at 165–168, 165–169, and 172–173.6 δ for the hexachloroantimonate salts of 2-alkyl-4,6-diaryl-1,3,5-oxadiazines ⟨91JPR303⟩, and at 165.5, 172.7, and 182.2 δ for the corresponding salts of 2-phenoxy-4,6-diaryl-1,3,5-oxadiazines ⟨93S426⟩.

^{13}C Chemical shifts (in CD_3CN) for the salt (**9**) ⟨85JHC907⟩, and for 3,5-diisopropyl-6-methyl-4-oxo-2-phenyl-3,4-dihydro-2*H*-1,3,5-oxadiazin-5-ium hexachloroantimonate ⟨91T205⟩ are appended to diagrams (**9**) and (**19**), respectively.



(**19**)

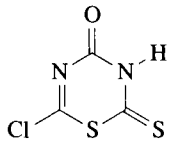
4,4-Bis(trifluoromethyl)-2,6-dialkylamino-4*H*-1,3,5-thiadiazines (**17**; R^1 = F, X = S) (see Section 6.18.10.3.1.i), in $CDCl_3$, exhibit a characteristic C-4 resonance at 83–84 δ, which appears as a septet with $J_{C-F} = 28$–30 Hz. The C-2 and C-4 resonances are seen at around 152 δ ⟨84LA982⟩. In contrast, the C-6 resonance signal for 6,6-bis(trifluoromethyl)-4-phenyl-6*H*-1,3,5-thiadiazine-2(3*H*)-thiones (**20**) appears at 72.6 δ (J_{C-F} 30 Hz) with the C-2 and C-4 carbons absorbing at 186.6 and 155.4 δ, respectively ⟨84ZN(B)1442⟩.



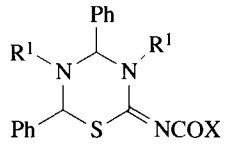
(**20**)

^{13}C resonances at 150.6 (C-4), 168.0 (C-6), and 190.3 (C-2) δ (d^6-acetone) have been observed for 6-chloro-2-thioxo-1,3,5-thiadiazin-4(3*H*)-one (**21**) ⟨82CB3587⟩ and at 61.2–62.7 (C-6), 75–84 (C-4),

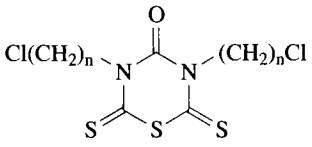
and 159–161.5 (C-2) δ ($CDCl_3$) for the 2-iminoperhydro derivatives (**22**) ⟨83CB1297, 85CB4196⟩. 2,6-Dithioxo-1,3,5-thiadiazin-4-ones (**23**; $n = 1$ or 2) (see Section 6.18.10.1.2) exhibit two signals for the ring carbons at 189.5 δ (C=S) and at 145.6–145.8 δ (C=O) ⟨91LA1095⟩.



(**21**)



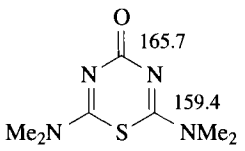
(**22**)



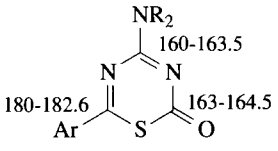
(**23**)

In contrast to the PMR data on 3,5-dialkylperhydro-1,3,5-thiadiazine-2-thiones (**15**) of which only tentative assignments for H-4 and H-6 were made, ^{13}C NMR resonances at 190.8–192.6, 61.7–73, and 54.3–60.2 δ, have been assigned unequivocally to C-2, C-4, and C-6 of the thiadiazine ring ⟨85ACH7⟩. ^{13}C Chemical shifts for 2,6-bis(dimethylamino)-1,3,5-thiadiazin-4-one ⟨91CL1229⟩, and for 6-aryl-4-dialkylamino-1,3,5-thiadiazin-2-ones ⟨87MRC688, 89LA931⟩ are appended to diagrams (**24**) and (**25**).

For the use of ^{13}C and ^{1}H NMR spectroscopy in conformational and tautomeric studies of 1,3,5-oxadiazines and 1,3,5-thiadiazines see Section 6.18.4.



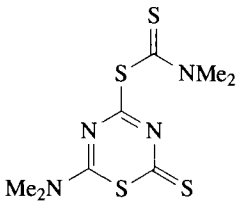
(**24**)



(**25**)

6.18.3.1.3 X-ray crystallography

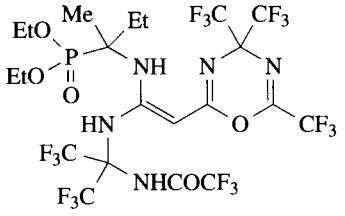
The structure of 3,5-dimethyl-5,6-dihydro-2*H*-1,3,5-oxadiazine-4(3*H*)-thione, an unexpected by-product in the oxidation of *N*,*N*^{1}-dimethylthiourea with singlet oxygen, has been confirmed by x-ray analysis ⟨92MI 618-01⟩. In a similar manner, the product formed by the action of potassium thiocyanate on *N*,*N*-dimethylthiocarbamoyl chloride (Me_2NCSCl) has been shown to be the 1,3,5-thiadiazine-2-thione dithiocarbamate (**26**) ⟨89IZV909⟩.



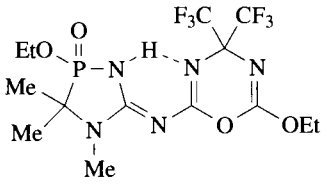
(**26**)

The structure of the 2,4,4-tris(trifluoromethyl)-4*H*-1,3,5-oxadiazine formed by condensation of *O*,*O*-diethyl-1-(2-cyanoguanidino)-1-methylpropyl phosphonate with 2-(acylimino)hexafluoropropanone has been assigned unequivocally on the basis of an x-ray crystal structure of the trifluoroacetyl derivative (**27**) ⟨88DOK(302)107⟩. A crystal structure of the related diazaphospholidene derivative (**28**) reveals that the 1,3,5-oxadiazine ring adopts a markedly flattened chair conformation with O_1 and C_4 at 3.8° and −4.5°, respectively, out of the plane formed by C_2—N_3—N_5—C_6

⟨90JGU1552⟩. Stabilization of this conformer is attributed to intramolecular hydrogen bonding as indicated in diagram (**28**).

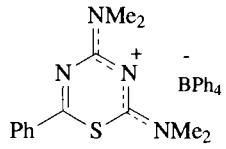


(**27**)



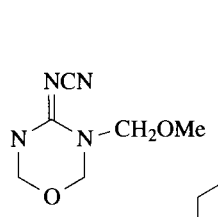
(**28**)

An x-ray structure of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me) reveals a planar structure with extensive delocalization of the positive charge and major contributions from mesomers of type (**8**) ⟨83AX(C)476, 85JCS(P1)1533⟩. Likewise, an almost planar structure is found for the monoclinic 2,4-bis(dimethylamino)-6-phenyl-1,3,5-thiadiazinium tetraphenylborate, whose crystal structure indicates a delocalization of the positive charge involving the dimethylamino groups, as shown in diagram (**29**), rather than the S—C=N moiety of the thiadiazine ring ⟨85AX(C)1260⟩.

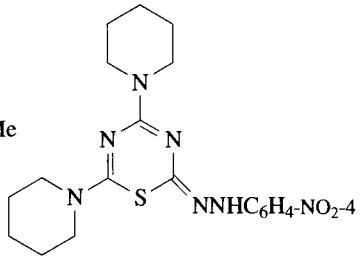


(**29**)

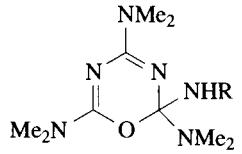
Crystal structures of 2,6-dipiperidino-4*H*-1,3,5-thiadiazin-4-one ⟨91CL1229⟩ (see Section 6.18.10.2.2.iii), the triclinic 4-cyanoimino-1,3,5-oxadiazine (**30**) ⟨84BCJ275⟩ (see Section 6.18.10.1.1), and the monoclinic 4,6-dipiperidino-2*H*-1,3,5-thiadiazin-2-one arylhydrazone (**31**) ⟨93PS(84)83⟩ (see Section 6.18.11.2) are available.



(**30**)



(**31**)



(**32**)

6.18.3.1.4 Mass spectra

Mass spectral fragmentation patterns have been used to determine the structures of the adducts formed by reaction of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me) with primary alkylamines ⟨85JCS(P1)1533⟩. Loss of Me_2N, and H, followed by a prominent alkylisocyanate ion favors strongly the 2-amino (**32**) rather than the isomeric 4-amino adducts.

6.18.4 THERMODYNAMIC ASPECTS

6.18.4.1 Aromaticity

An aromaticity index (I) based on "a statistical evaluation of the deviations in peripheral bond orders" derived from experimentally determined bond lengths, has been calculated for the 1,3,5-thiadiazinium cation (**33**) ⟨86T89⟩. A value of I_6 (relative to benzene $I_6 = 100$) of 53.1 has been estimated, which is substantially lower than the value obtained for the pyrylium cation ($I_6 = 65.8$) and marginally lower than that of 1,2,6-thiadiazin-4-one ($I_6 = 54.2$) (see Chapter 6.16). X-ray crystal structures for the 1,3,5-oxadiazinium chloride (**7**; R = Me) (see Section 6.18.2) and the 1,3,5-thiadiazinium tetraphenylborate (**29**) (see Section 6.18.3.1.3) reveal a planar heterocyclic ring. However, in each case bond lengths indicate substantial delocalization of the positive charge over the dimethylamino groups rather than over the whole ring system (see (**29**)). So far only trisubstituted 1,3,5-oxadiazinium and 1,3,5-thiadiazinium salts, in which the substituents are electron donors (i.e. Ar, SMe, NMe_2, OPh) have been prepared (see Section 6.18.10), and, as expected for a "3,5-diazapyrylium" salt, ring-scission and/or rearrangement occurs readily in the presence of nucleophiles (see Section 6.18.5).

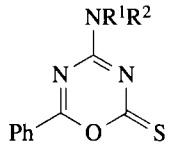
(**33**)

6.18.4.2 Conformation Studies

In contrast to the perhydro-3,5-dialkyl-1,3,5-thiadiazines, for which ring-inversion barriers of 9–12 kcal mol^{-1} have been determined from low temperature PMR spectroscopy studies ⟨72JCS(P2)674⟩, perhydro-3,5-dialkyl-1,3,5-thiadiazine-2-thiones (**15**) fail to show any line broadening of the proton signals even at 195 K ⟨85ACH7⟩. From these results, the authors conclude that ring conversion for the thiones about carbons C-4 and C-6 is fast, with a barrier to inversion of <9 kcal mol^{-1}.

Theoretical calculations on axial/equatorial preferences of methyl groups on perhydro-1,3,5-oxadiazine rings have been mentioned in Section 6.18.2.

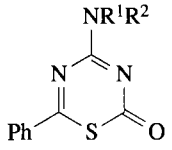
Rotational energy barriers (ΔG_c^*) about exocyclic partial double bonds for 4-dialkylamino-6-phenyl-1,3,5-oxadiazine-2-thiones and for 4-dialkylamino-6-phenyl-1,3,5-thiadiazin-2-ones have been determined using ^{13}C and ^1H NMR spectroscopic data, and are appended to diagrams (**34**) and (**35**) ⟨87MRC688⟩.



(**34**)

$R^1R^2 = (CH_2)_4$ 20.1 kcal mol^{-1}

$R^1 = R^2 = Me$ 19.6 kcal mol^{-1}



(**35**)

22.5 kcal mol^{-1}

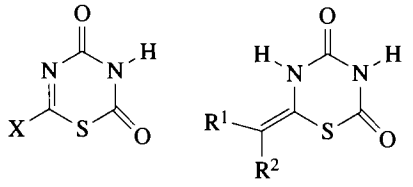
22.1 kcal mol^{-1}

6.18.4.3 Tautomerism

The ring-chain tautomeric equilibria of 1-oxa-3,5-diaza-1,3,5-hexatrienes and 2*H*-1,3,5-oxadiazines (see Section 6.18.3.1.2.i) have been studied extensively by spectroscopic (^1H and ^{13}C NMR, IR, and UV) methods, and by quantum mechanical *ab initio* calculations ⟨93CB957⟩. It is found that

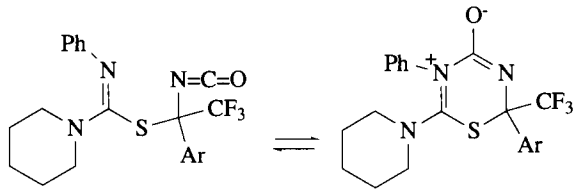
the equilibrium position is dependent on the nature of the substituent at C-6. Aryl groups (e.g. (**11**; $R^1 = R^2 = R^3 = R^4 = Ph$)) favor the acyclic form, whereas 6-*t*-butyl derivatives (e.g. $R^1 = R^3 = Ph$, $R^2 = R^4 = Bu^t$) exist exclusively as the oxadiazine (**10**). A free enthalpy of activation of 12.5 kcal mol^{-1} for the *t*-butyltriphenyl derivative, which exists as a 3:1 mixture of (**11**) and (**10**; $R^1 = R^2 = R^4 = Ph$, $R^3 = Bu^t$), has been determined by variable temperature NMR studies, a coalescence temperature of $-10°C$ being noted. *Ab initio* calculations on the model compounds (**10**) and (**11**; $R^1 = R^2 = R^3 = R^4 = H$) reveal that the oxadiazine tautomer is some 6 kcal mol^{-1} lower in energy than the acyclic form.

As expected, 6-aryl- and 6-heteroaryl-2*H*-1,3,5-thiadiazine-2,4(3*H*)-diones (**36**; X = Ar) have IR absorptions at 3040 and 3140 cm^{-1} ν(NH), 1690–1675 and 1660–1690 cm^{-1} ν(C=O), and 1540–1570 cm^{-1} ν(C=N). However, for the 6-alkyl derivatives (**36**; X = Me_2CH, $PhCH_2$ or RCH_2) the 1540–1570 cm^{-1} absorption band is replaced by a ν(C=C) absorption at 1625 cm^{-1}, indicative of a 2-methylene group as required by the tautomers (**37**) ⟨82JMC481⟩. Confirmation of these exocyclic methylene structures is obtained from the PMR spectrum of the isopropyl compound (**37**; $R^1 = R^2 = Me$), which exhibits two distinct methyl resonances at 1.72 and 1.79 δ, and the appearance of vinyl proton resonances for those structures in which R^1 or $R^2 = H$.



(**36**) (**37**)

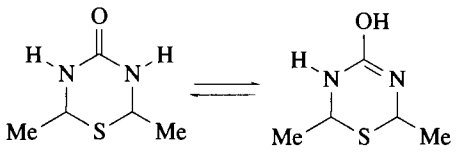
In polar solvents (e.g. Me_2CO, $CHCl_3$ or CH_3CN) *S*-(1-isocyanatoalkyl)isothioureas (e.g. (**38**)) exist in tautomeric equilibria with the polar ring tautomers (**39**), as indicated by strong IR absorptions at 2265, 1685, and 1620 cm^{-1}, corresponding to ν(N=C=O), ν(C=O), and ν(C=N), respectively. In contrast, in the solid state or in nonpolar solvents (e.g. PhH, or CCl_4) the mesomeric betaine 2*H*-1,3,5-thiadiazinium-4-olates (**39**) are favored ⟨90CHE959⟩.



(**38**) (**39**)

The strong IR absorptions at 3430 ν(OH), 3230 ν(NH), and 1520 cm^{-1} ν(C=N) and the weak ν(C=O) at 1630 cm^{-1}, have been suggested to indicate that in the solid state 2,6-dimethyl-5,6-dihydro-2*H*-1,3,5-thiadiazin-4(3*H*)-one exists mainly as the lactim form (**41**). However, from the symmetry of the PMR spectrum in d^6-DMSO, which shows a solitary doublet methyl resonance at 1.13 δ, H-2 and H-6 as a singlet quartet at 4.8 δ (*J* 5.5 Hz), and the NH protons at 8.5 δ, it was concluded that in solution the lactam structure (**40**) is the dominant form ⟨82CHE491⟩.

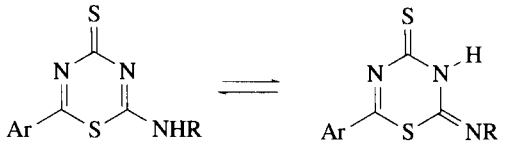
The presence of two ν(NH) absorptions at 3445–3495 and 3390–3395 cm^{-1} has been cited as



(**40**) (**41**)

evidence for an imine–amine tautomeric equilibrium (**42**)⇋(**43**) in 2-alkylamino-6-aryl-4*H*-1,3,5-thiadiazine-4-thiones ⟨84JCR(S)266⟩.

The PMR evidence (see Section 6.18.3.1.2.i) suggesting that 4,6-diamino-1,3,5-thiadiazine-2-thione (**13**) exists as the 2-thiol (**12**) in d^6-DMSO solution has been referred to earlier ⟨83ZAAC(502)11⟩.



(**42**) (**43**)

6.18.5 REACTIVITY OF FULLY CONJUGATED CATIONIC RINGS

6.18.5.1 Thermal and Photochemical Unimolecular Reactions

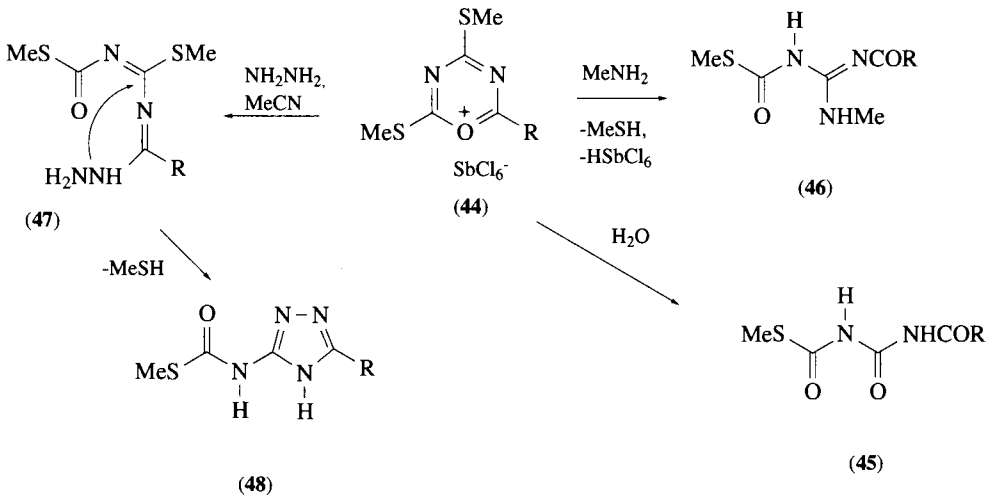
Compared to the 1,3,4-systems (see Chapter 6.20) unimolecular reactions of 1,3,5-oxadiazines and 1,3,5-thiadiazines are uncommon.

4,6-Bis(dimethylamino)-2-phenyl-1,3,5-oxadiazinium chloride is known to undergo thermal decomposition to yield benzonitrile, dimethylcyanamide and dimethylcarbamoyl chloride ⟨66CB2454⟩.

6.18.5.2 Reactions with Oxygen, Nitrogen, and Sulfur Nucleophiles

1,3,5-Oxadiazinium and 1,3,5-thiadiazinium salts are very susceptible to attack by nucleophiles, generally at C-2, or C-6 to give a variety of acyclic and/or ring-transformation products.

2-Substituted-4,6-bis(methylthio)-1,3,5-oxadiazinium hexachloroantimonates (**44**) in the presence of water or methylamine yield the ring-opened products (**45**) and (**46**) in 37–57% and 26–49% yield, respectively. With hydrazine, however, the initially formed acyclic products (**47**) undergo ring-closure to the 1,3,4-triazoles (**48**), albeit in low yields (19–27%) (Scheme 1) ⟨85LA1874⟩. Analogous reactions have been noted previously between 2,4,6-triphenyl-1,3,5-oxadiazinium perchlorate and *N*-substituted hydrazines ⟨65CB334, 83RTC453⟩.

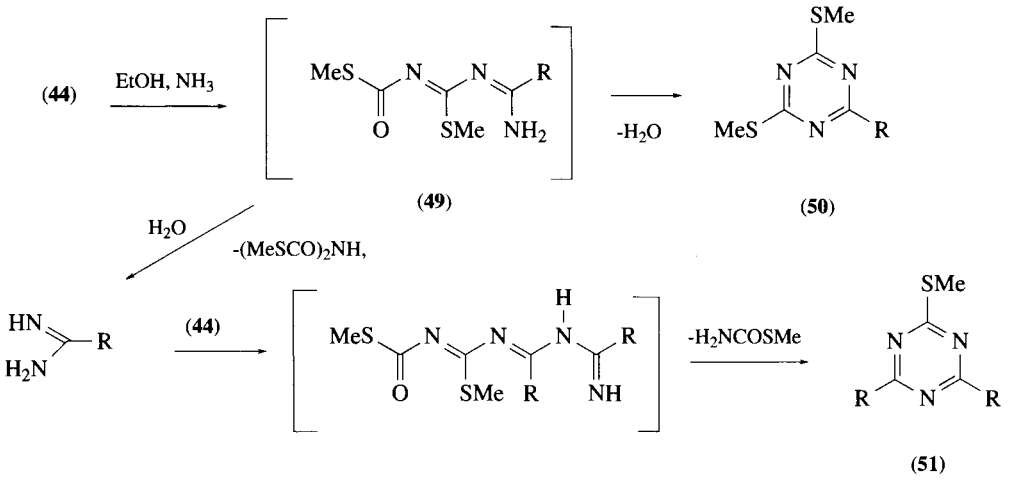


(**47**) (**44**) (**46**) (**48**) (**45**)

Scheme 1

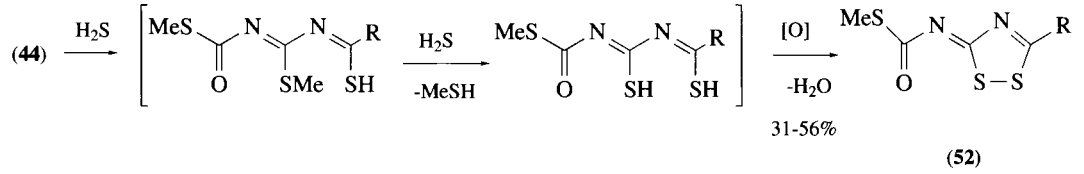
The reactions of oxadiazinium salts (**44**) with ethanolic ammonia, however, are more complex and yield mixtures of the 1,3,5-triazines (**50**) and (**51**). The former, which are minor products (10–

15%), arise by cyclization of the initially formed amidines (**49**), whereas the latter products are formed in 40–50% yields via the process outlined in Scheme 2. 2,6-Diaryl-1,3,5-triazines (**51**; R = Ar) are obtained directly by treating the 1,3,5-oxadiazinium salts with arylamidines ⟨85LA1874⟩.



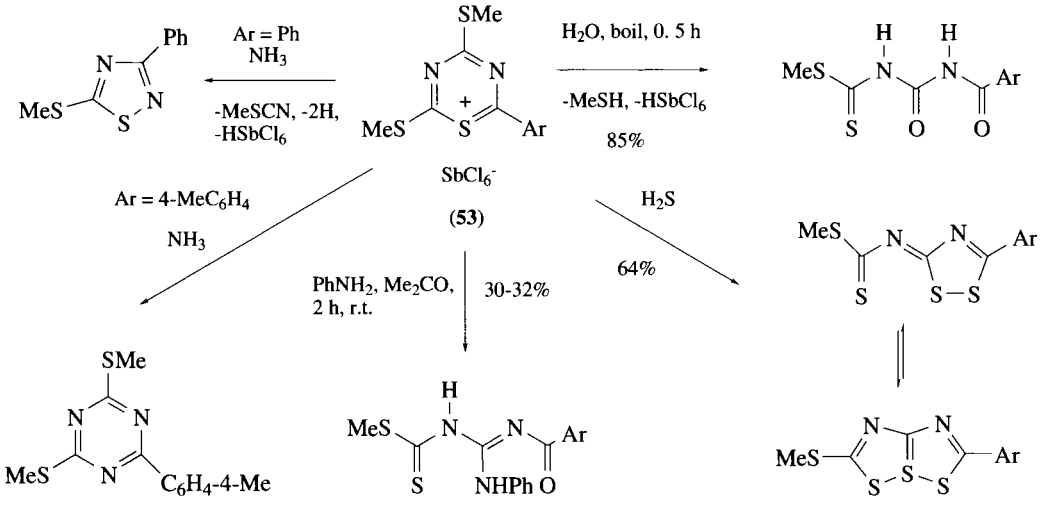
Scheme 2

Equally complex are the reactions of the oxadiazinium salts (**44**) with hydrogen sulfide, to yield 3*H*-1,2,4-dithiazolidines (**52**) (Scheme 3) ⟨85LA1874⟩.



Scheme 3

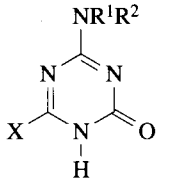
A similar series of reactions is undergone by 2-aryl-4,6-bis(methylthio)-1,3,5-thiadiazinium salts (**53**), as exemplified in Scheme 4 ⟨88LA729⟩.



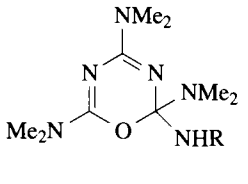
Scheme 4

In contrast to the bis(methylthio) salts (**44**), 2-aryl-4,6-bis(dialkylamino)-1,3,5-oxadiazinium perchlorates on treatment with 0.88 ammonia solution yield 6-aryl-4-dialkylamino-1,3,5-triazin-2(1*H*)-

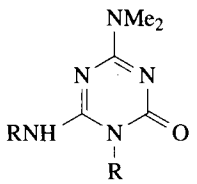
ones (**54**; X = Ar) ⟨85T5371, 86ZC95⟩ and not 6-aryl-2,4-diamino-1,3,5-triazines as obtained previously in similar reactions ⟨66CB2454⟩. Likewise, with 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me) the 4,6-bis(dimethylamino)-1,3,5-triazin-2(1*H*)-one (**54**; X = NMe_2, $R^1 = R^2 = Me$) is formed ⟨85JCS(P1)1533⟩. Interestingly, with primary aliphatic amines in DCM the stable 2*H*-1,3,5-oxadiazines (**55**) can be isolated in 26–78% yield, whereas with primary aromatic amines 1-aryl-6-bis(dimethylamino)-1,3,5-triazin-2(1*H*)-ones are formed as the major (31–89%) products. Under more forcing conditions (reflux 1 h) mixtures of triazinones, identified tentatively as the isomeric 4- and 6-dimethylamino 1-substituted 1,3,5-triazin-2(1*H*)-ones (**56**) and (**57**; R = alkyl or aryl) are produced.



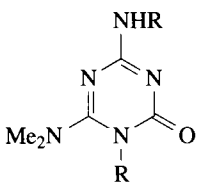
(**54**)



(**55**)

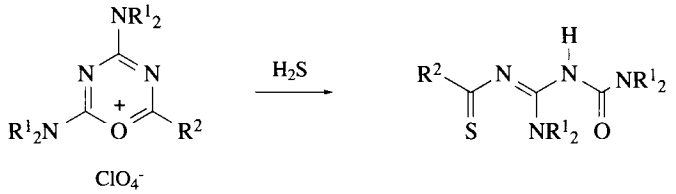


(**56**)



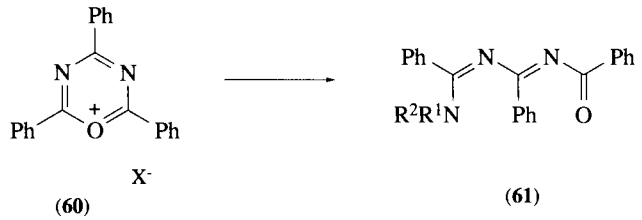
(**57**)

The 4,6-bis(dialkylamino)-1,3,5-oxadiazinium salts (**58**) undergo a more simple reaction with H_2S than that noted for the 4,6-bis(methylthio)-derivatives (**53**; Scheme 4) in that *N*-(thioacyl)guanidines (**59**) are produced in 67–75% yield (Equation (1)) ⟨86ZC132⟩.



(**58**) (**59**) (1)

2,4,6-Triphenyl-1,3,5-oxadiazinium salts (**60**; X = $SnCl_5$ or ClO_4) with dialkylamines yield only the benzamidines derivatives (**61**) (50–75%) (Equation (2)) ⟨77S788, 86ZC295⟩. With ammonia 2,4,6-triaryl-1,3,5-triazines are formed ⟨86MI 618-01⟩.



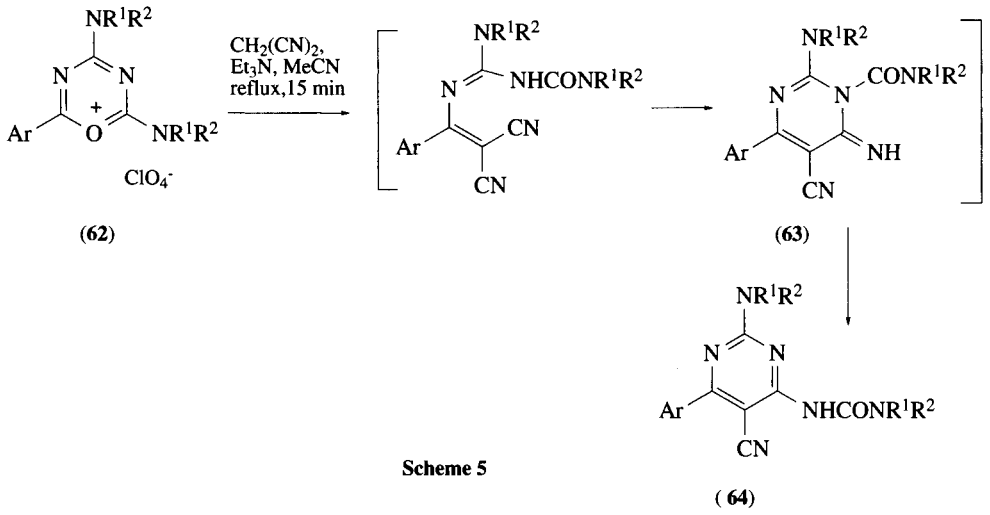
(**60**) (**61**) (2)

6.18.5.3 Reactions with Carbon Nucleophiles

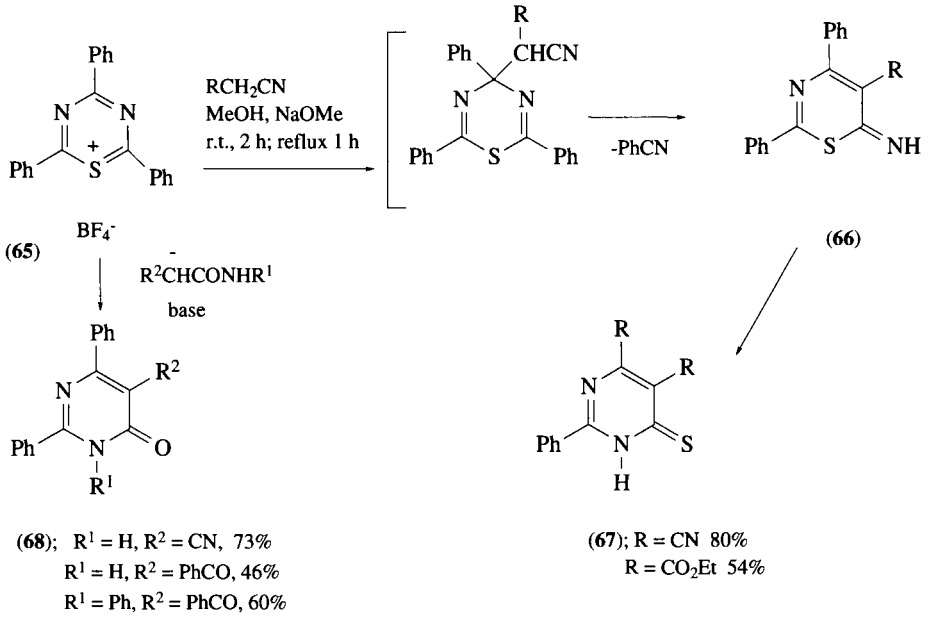
6-Aryl-2,6-bis(dialkylamino)-1,3,5-oxadiazinium perchlorates (**62**) undergo attack by malononitrile anion at C-6 to give ultimately 2-amino-6-aryl-5-cyano-4-ureidopyrimidines (**64**) by rearrangement of intermediates (**63**) (Scheme 5) ⟨85T5371⟩.

In contrast, attack of cyanocarbanions ($R\bar{C}HCN$) on 2,4,6-triphenyl-1,3,5-thiadiazinium tetrafluoroborates (**65**) takes place at C-4 to give ultimately the pyrimidine-4-thiones (**67**) via acid-catalyzed rearrangement of the initially formed 6-imino-1,3-thiazines (**66**) as outlined in Scheme 6 ⟨82BCJ2158⟩. In a similar manner, with carboxyamide stabilized carbanions, 5-substituted-pyrimidin-4(3*H*)-ones (**68**) are produced.

However, with nitro-substituted carbanions, attack occurs at C-2 to give the stable adducts (**69**) (Scheme 7), the structures of which have been assigned on the basis of their mass spectral fragmentation patterns. With acyl carbanions the oxadiazinium salts undergo an ANRORC process



Scheme 5



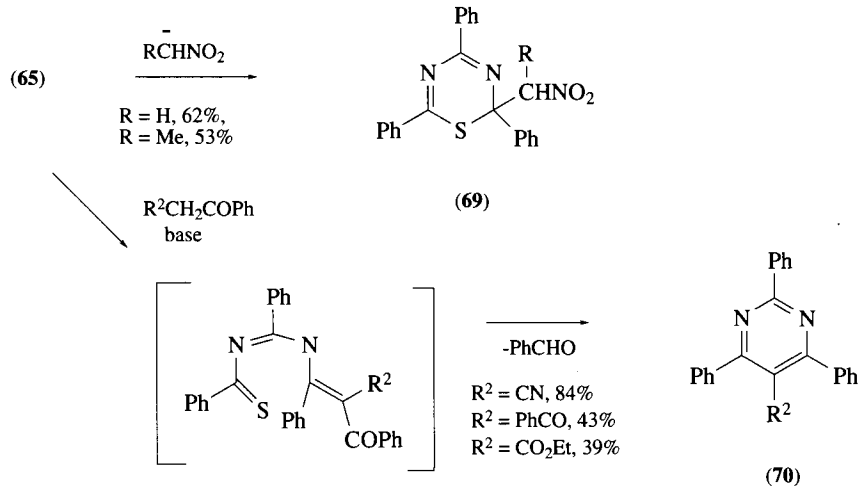
Scheme 6

accompanied by loss of the sulfur function (as PhCOSH) to give 5-substituted-2,4,6-triphenylpyrimidines (**70**) (Scheme 7) ⟨82BCJ2158⟩.

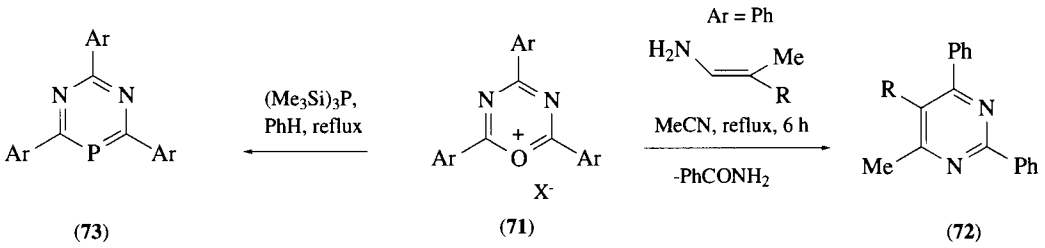
2,4,6-Triphenyl-1,3,5-oxadiazinium pentachlorostannates (**71**; X = $SnCl_5$) are reported to react with primary enamines in boiling acetonitrile to yield 5-substituted 2,4-diphenyl-6-methylpyrimidines (**72**; R = CO_2Et, 80%; R = COMe, 60%) (Scheme 8) ⟨92CHE1054⟩.

6.18.5.4 Reactions with Phosphorus Nucleophiles

2,4,6-Triaryl-1,3,5-oxadiazinium salts (**71**; X = $SnCl_5$, PF_6, I, ClO_4 or BF_4), unlike 2,4,6-triarylpyrylium salts, fail to undergo oxygen–phosphorus exchange on treatment with PH_3, $P(CH_2OH)_3$ or $P(TMS)_3$ in acetonitrile. However, with tris(trimethylsilyl)phosphine in boiling benzene the tetrafluoroborate salts (**71**; X = BF_4) afford 2,4,6-triaryl-1,3,5-diazaphosphazines (**73**) albeit in low yields (5–6%) (Scheme 8) ⟨91AG(E)106⟩.



Scheme 7



Scheme 8

6.18.6 REACTIVITY OF FULLY CONJUGATED RINGS CONTAINING OXO, THIOXO, AND IMINO GROUPS

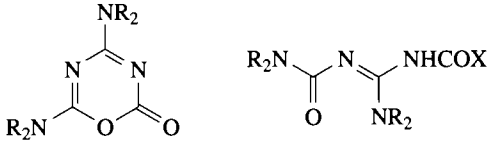
6.18.6.1 Electrophilic Attack at Nitrogen

Alkylation and alkynylation of 2-thioxo-1,3,5-thiadiazin-4(3*H*)-ones at N-3 can be effected in THF solution at room temperature with diazomethane, and with iodoalkynes in the presence of triethylamine, respectively ⟨85GEP3333659, 87GEP3607624⟩.

1,3,5-Oxadiazine-2,4(3*H*)-diones undergo acetylation at N-3 in moderate yields (31–58%) with acetyl chloride and triethylamine ⟨86CB669⟩.

6.18.6.2 Nucleophilic Attack at Carbon

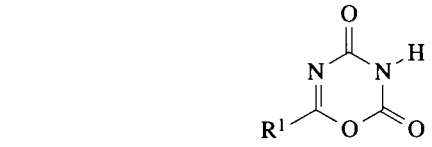
As expected, 1,3,5-oxadiazin-2-ones and their 1,3,5-thiadiazine analogues are susceptible to nucleophilic attack at C-2, generally under mild conditions, to give ring-opened products. For example, the 2,4-bis(dialkylamino)-1,3,5-oxadiazin-2-ones (**74**) undergo ring cleavage with methanol at room temperature, and with morpholine and ethyl magnesium bromide in boiling benzene, to give acyclic products (**75a–c**) ⟨75S522⟩.



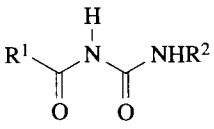
(74)

(75) a) X = OMe
b) X = Et
c) X = N O

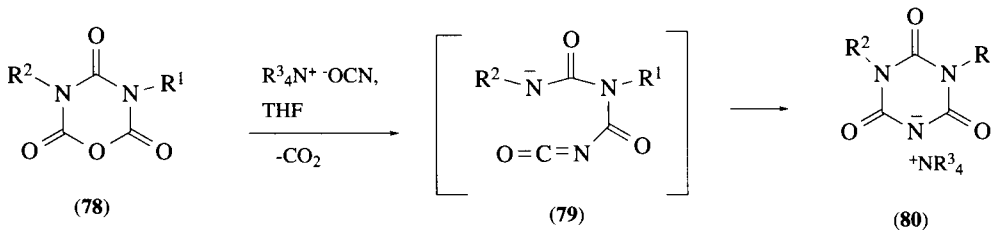
Likewise, hydrolysis, alcoholysis, and aminolysis of 6-substituted 1,3,5-oxadiazine-2,4(3*H*)-diones (**76**) proceed readily to yield *N*,*N*^{1}-disubstituted ureas (**77**; R^2 = H, CO_2 alkyl, $CONR^3R^4$) ⟨86CB669⟩. More interesting is the action of tetralkylammonium cyanates on 1,3,5-oxadiazine-2,4,6(3*H*,5*H*)-triones (**78**), which results in nucleophilic attack by cyanate ion at C-2 followed by loss of CO_2 and cyclization of the ureidoisocyanate (**79**) so formed to yield a 1,3,5-triazine-2,4,6(3*H*,5*H*)-trione salt (**80**) as indicated in Scheme 9 ⟨84EUP98006⟩.



(76)



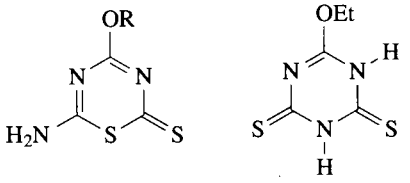
(77)



(78) (79) (80)

Scheme 9

The products of nucleophilic attack on 4-alkoxy-6-amino-1,3,5-thiadiazine-2-thiones (**81**) depend on the nature of the attacking nucleophile. Primary amines bring about amino-dealkoxylation, whereas on hydrolysis, initial attack at C-4 is accompanied by ring opening to give an *N*-(alkoxycarbonyl)thiourea. In contrast, in the presence of ethanolic sodium hydroxide an ANRORC process (Dimroth-type rearrangement) takes place to yield 6-ethoxy-1,3,5-triazine-2,4(1*H*,3*H*)-dithione (**82**) ⟨92NKK1450⟩.



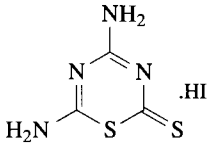
(81) (82)

Analogous ring transformations have also been reported with 4,6-diamino-1,3,5-thiadiazine-2-thione hydroiodides (**83**) which in boiling water or with amines (R^2NH_2) at room temperature yield 1,3,5-triazin-2(1*H*)-ones (**84**; R^1 = SH, R^2 = H, and R^1 = NH_2, R^2 = H, respectively) ⟨91NKK1655, 91NKK1684⟩, and with the 2,6-diimino-1,3,5-thiadiazin-4(3*H*)-ones (**85**), which in warm ethanol furnish the 4-imino-6-thioxo-1,3,5-triazin-2-ones (**86**) ⟨84JIC68⟩. However, all attempts to effect similar rearrangements of the *S*- and *N*-(tetra-*O*-acetyl-D-glucosopyranosyl) derivatives (**87**) and (**88**; R^2 = tetra-*O*-Ac-D-glucopyranosyl) failed; only ring-scission products were isolated ⟨84JIC781, 84JIC883⟩. Rearrangements are also noted with 5-aryl-1,3,5-thiadiazine-2,4,6(3*H*,5*H*)-trithiones (**89**) which in the presence of aniline yield 1-phenyl-6-phenylimino-1,3,5-triazine-2,4(1*H*,3*H*)-dithiones (**90**) ⟨88PIA53⟩.

6.18.7 REACTIVITY OF NONCONJUGATED RINGS

6.18.7.1 Thermal and Photochemical Unimolecular Reactions

The thermally induced rearrangements with loss of dimethylamine, of 2-alkylamino-2,4,6-tris(dimethylamino)-2*H*-1,3,5-oxadiazines (**55**) to 4,6-bis(dimethylamino)-1,3,5-triazin-2(1*H*)-ones (**57**) have been reported ⟨85JCS(P1)1533⟩.



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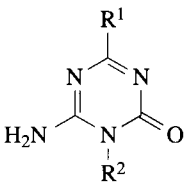

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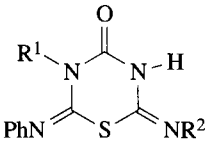

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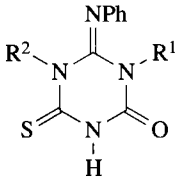

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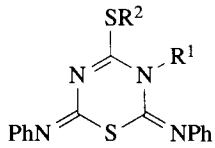

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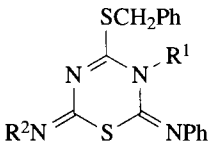

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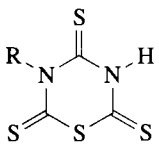

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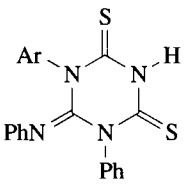
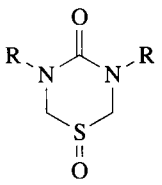


(90)

6.18.7.2 Electrophilic Attack at Sulfur

Oxidation of 3,5-dialkyl tetrahydro-4*H*-1,3,5-thiadiazin-4-ones with one equivalent of MCPBA in chloroform at room temperature yields the 1-oxides (**91**) in 31–60% yield. With an excess of oxidant, the 1,1-dioxides (**92**) are produced ⟨72JHC231⟩.



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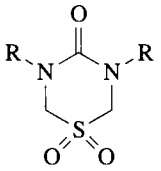
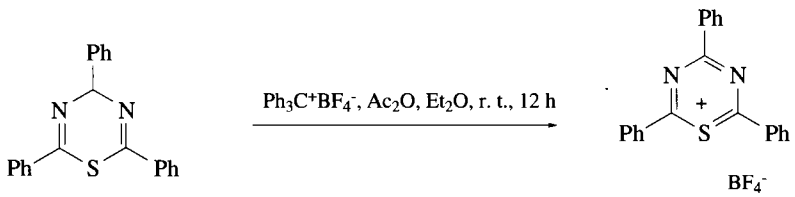


(92)

6.18.7.3 Electrophilic Attack at Hydrogen (Abstraction of Hydride Ion)

The synthesis of 2,4,6-triaryl-1,3,5-thiadiazinium tetrafluoroborates (e.g. (**94**)) by abstraction of hydride ion from 2,4,6-triaryl-4*H*-1,3,5-thiadiazines (e.g. (**93**)) with triphenylcarbenium tetrafluoroborate has been reported (Equation (3)) ⟨73BCJ3902, 80BCJ3369, 81JAP(K)5657778, 81JAP(K)5657779⟩.



(93)

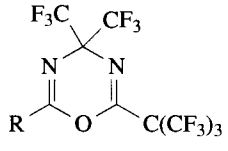
(94)

(3)

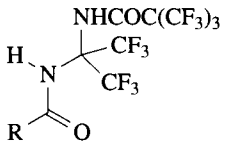
6.18.7.4 Nucleophilic Attack at Carbon

Acid hydrolysis of the bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (**95**; R = Me) produces the diamide (**96**; R = Me, 57.5%) ⟨84IZV2736⟩. Careful hydrolysis of the dihydro-4*H*-1,3,5-oxadiazine-2,6-

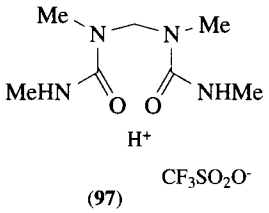
diylium bistriflate (**9**) yields the triflate salt (**97**), the structure of which has been confirmed by x-ray analysis ⟨85JHC907⟩. In contrast, 4,4,6-tris(trifluoromethyl)-2-perfluoroalkyl-4*H*-1,3,5-oxadiazines (**95**; R = CF_3) are reported to be unaffected by mineral or Lewis acids, whereas in base solution at room temperature they undergo ring opening to amides (e.g. (**96**; R = CF_3)) ⟨89JOU578⟩. Ring opening also occurs with amines and alcohols which, in the case of unsymmetrically 2,6-disubstituted derivatives, takes place regioselectively at the C—O bond bearing the CF_3 substituent.



(**95**)



(**96**)

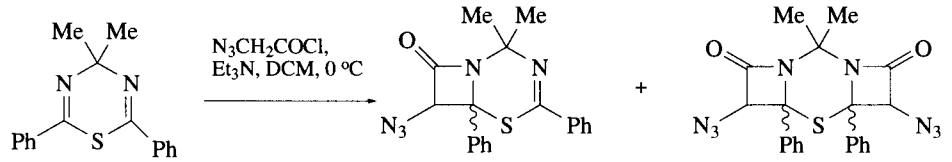


(**97**)

6.18.7.5 Cycloadditions

Cycloadditions involving 1,3,5-oxadiazines and 1,3,5-thiadiazines are rare.

[2 + 2]Cycloaddition of 4,4-dimethyl-2,6-diphenyl-4*H*-1,3,5-thiadiazine (**98**) with one equivalent of azidoketene yields the 5-thia-1,3-diazabicyclo[4.2.0]oct-3-ene (**99**) in 75% yield together with a lesser amount (15%) of the bis-adduct (**100**) (Equation (4)) ⟨82JIC536⟩.



(**98**) (**99**) (**100**) (4)

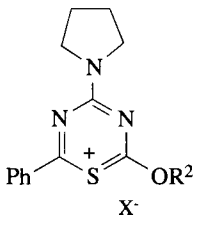
6.18.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON

6.18.8.1 Alkenyl Groups

Oxidation of the 4-alkenyl-2,6-diphenyl-4*H*-1,3,5-thiadiazine (**186**) (see Section 6.18.10.2.2.iii) with potassium permanganate yields 2,6-diphenyl-1,3,5-thiadiazin-4-one ⟨85LA2305⟩.

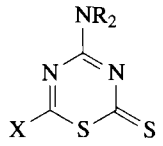
6.18.8.2 Oxo- and Hydroxy Groups

O-Methylation of 1,3,5-thiadiazin-2-ones with dimethyl sulfate, followed by treatment with 70% perchloric acid, affords 1,3,5-thiadiazinium perchlorates (e.g. (**101**; R^2 = Me, X = ClO_4)) in good yields ⟨86ZC132⟩. Likewise, ethylation with Meerwein's reagent produces the 2-ethoxy-1,3,5-thiadiazinium tetrafluoroborates (e.g. (**101**; R^2 = Et, X = BF_4; 81%)). Meerwein's reagent has also been used for the synthesis of 4,6-bis(dialkylamino)-2-ethoxy-1,3,5-oxadiazinium salts from 4,6-bis(dialkylamino)-1,3,5-oxadiazin-2-ones ⟨75S522⟩.

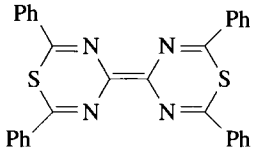


(**101**)

Conversion of 1,3,4-thiadiazin-2-ones into the corresponding thiadiazine-2-thiones (**102**; X = Ar) is accomplished with Lawesson's reagent in boiling benzene ⟨86ZC132⟩. Treatment of 2,5-diphenyl-1,3,5-thiadiazin-4-one with Lawesson's reagent, however, yields not the 4-thione, but the 4,4-bis(1,3,5-thiadiazinylidene) (**103**) which, with iodine, forms an electrical conducting charge-transfer complex ⟨84SUL127⟩.



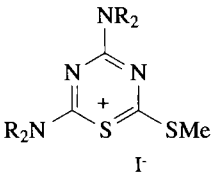
(**102**)



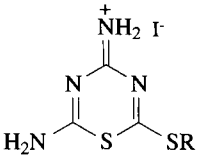
(**103**)

6.18.8.3 Sulfur-linked Groups

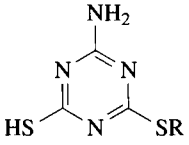
Methylation of 4,6-diamino-1,3,5-thiadiazine-2-thiones (**102**; X = NR_2) with methyl iodide in boiling acetone affords the 2-methylthio-1,3,5-thiadiazinium iodides (**104**) in variable yields (45–81%) ⟨71JHC1087, 88JPR241⟩. 2,4-Diamino-1,3,5-thiadiazine-2-thione hydriodide (**83**; Section 6.18.6.2) on treatment with an alkyl iodide yields a 2-alkylthio-6-amino-4-imino-4*H*-1,3,5-thiadiazinium iodide (**105**; R = Me or Et). Attempts to liberate the free bases brings about immediate rearrangement to the 2-alkylthio-4-amino-1,3,5-triazine-6-thiols (**106**; R = Me or Et) ⟨91NKK1684⟩.



(**104**)



(**105**)



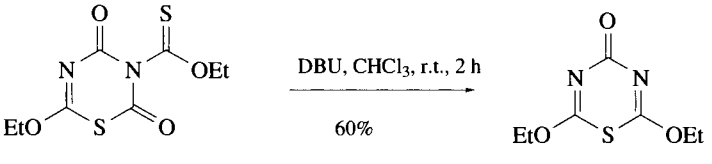
(**106**)

6.18.8.4 Halogen Atoms

In contrast to the 1,3,5-thiadiazine-2-thiones noted in Section 6.18.6.2, 6-chloro-2-thioxo-1,3,5-thiadiazin-4(3*H*)-one (**21**) with ethanol in cold THF undergoes ethoxy-dechlorination rather than a ring opening or ring transformation ⟨82CB3587⟩.

6.18.9 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN

The 1,3,5-thiadiazinedione-3-thiocarboxylic acid *O*-ethyl ester (**107**) on treatment with DBU in chloroform undergoes loss of COS and rearrangement to yield 2,6-diethoxy-1,3,5-thiadiazin-4-one (**108**) (Equation (5)) ⟨82CB1252⟩.



(5)

(**107**) (**108**)

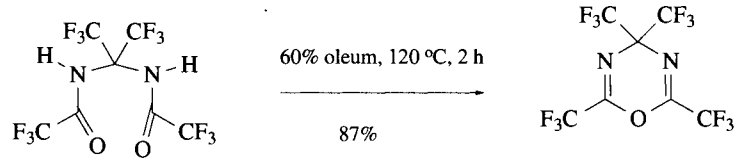
Hot (80°C) 0.1M hydrochloric acid effects rapid (20 min) regioselective hydrolysis of 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**30**) (see Section 6.18.10.1.1) to 4-cyanoiminoperhydro-1,3,5-oxadiazine in 72% yield ⟨83BCJ3319⟩.

6.18.10 RING SYNTHESIS

6.18.10.1 Formation of One Bond

6.18.10.1.1 Between carbon and oxygen

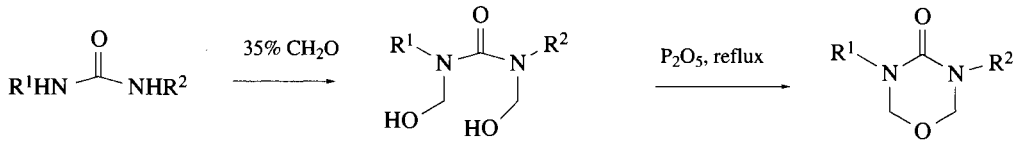
2,4,4,6-Tetrakis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (**110**) is formed by cyclodehydration of the 2,2-diacylaminohexafluoropropane (**109**) with 60% oleum (Equation (6)) ⟨86JOU206⟩.



(6)

(**109**) (**110**)

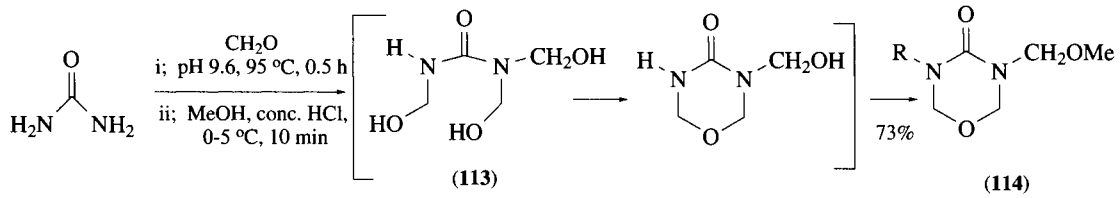
Treatment of N^1,N^2-disubstituted ureas with methanal followed by cyclodehydration of the resulting N^1,N^2-bis(hydroxymethyl) ureas (**111**) with P_2O_5 furnishes 3,5-dialkyl-5,6-dihydro-2*H*-1,3,5-oxadiazin-4(3*H*)-ones (**112**) in high yields (>90%) (Scheme 10) ⟨85JAP(K)6067471, 85JAP(K)6067472, 85JAP(K)60104075, 85JAP(K)60104076⟩.



(**111**) (**112**)

Scheme 10

The formation of 3,5-bis(methoxymethyl)-5,6-dihydro-2*H*-1,3,5-oxadiazin-4(3*H*)-one (**114**; R = $MeOCH_2$) by reaction of urea with methanal under carefully controlled acidic methanolic conditions has been shown to proceed via cyclization of the tris(hydroxyethyl) urea (**113**) as outlined in Scheme 11 ⟨89BCJ1930⟩, rather than via a tetrakis(hydroxymethyl)urea or a perhydro-1,3,5-oxadiazin-4-one as suggested originally ⟨36BCJ248⟩. *N*-Methylurea under the same conditions gives the 3-methoxymethyl-5-methyl derivative (**114**; R = Me) but in only 27% yield.



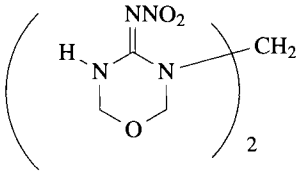
(**113**) (**114**)

Scheme 11

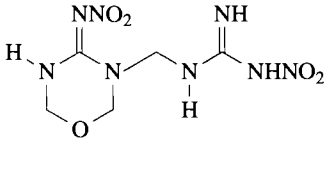
The formation of the 4-cyanoimino-3-(methoxymethyl)perhydro-1,3,5-oxadiazine (**30**; 42%) from 2-cyanoguanidine and methanal follows a similar reaction pathway ⟨89BCJ3721⟩, and the same

product is also obtained in 51% yield by treating 1,3-bis(methoxymethyl)-2-cyanoguanidine with 37% aqueous methanal at pH 8.8 and 80°C ⟨83BCJ3319⟩.

A variety of products including the explosive *N*-(nitroimino)-1,3,5-oxadiazines (**115**) and (**116**) are formed from the condensation of bis(nitroguanidino)methane with methanal ⟨89MI 618-01⟩.

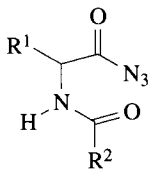


(**115**)

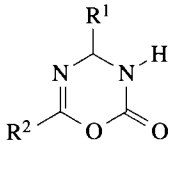


(**116**)

4*H*-1,3,5-Oxadiazin-2(3*H*)-ones (**118**) are produced by Curtius rearrangement of α-acylaminoacyl azides (**117**) in boiling benzene followed by cyclization of the resulting isocyanates ⟨82IJC(B)773, 92JSC407⟩. The 1,3,5-oxadiazine-2,6-diylium bistriflate (**9**) (see Section 6.18.11.1) has been synthesized independently by ring-closure of the bis-ureidomethane $[MeNHCONMe]_2CH_2$ with triflic anhydride ⟨85JHC907⟩.

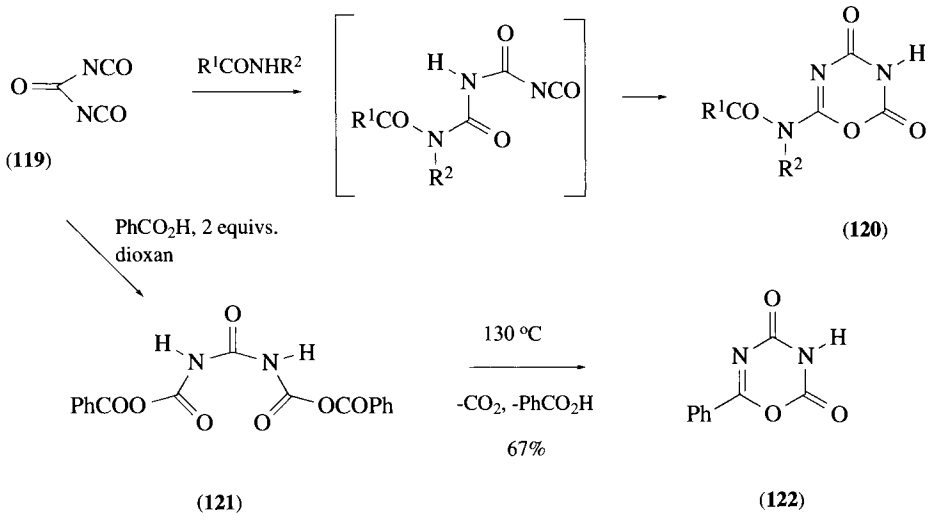


(**117**)



(**118**)

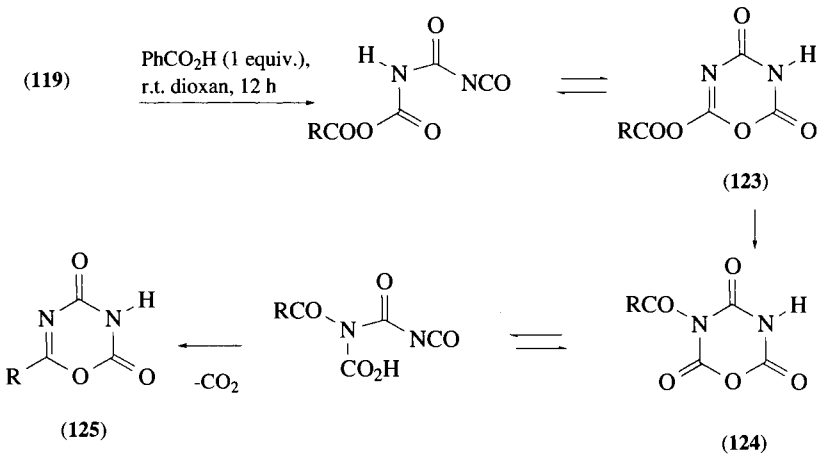
Carbonyl diisocyanate (**119**) adds to *N*-substituted amides to yield the unstable but isolable 1,3,5-oxadiazine-2,4(3*H*)-diones (**120**). However, with primary amides the resulting 1,3,5-oxadiazinediones (**120**; R^2 = H) undergo a Dimroth rearrangement to the isomeric 1,3,5-triazine-2,4,6-triones (see Section 6.18.6.2) ⟨86CB669⟩. Reaction of the diisocyanate with 2 equivalents of benzoic acid yields the bis-anhydride (**121**) which on heating at 130°C undergoes ring closure to 6-phenyl-1,3,5-oxadiazine-2,4(3*H*)-dione (**122**) (Scheme 12).



Scheme 12

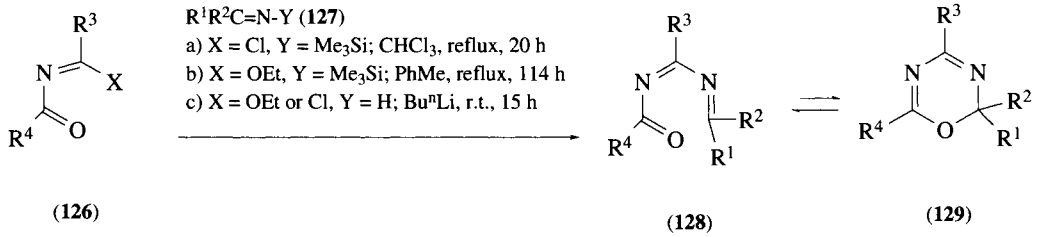
However, with 1 equivalent of benzoic acid at room temperature, a slow cyclization to the 1,3,5-oxadiazine-2,4(3*H*)-dione (**125**; R = Ph) takes place via a Chapman rearrangement (**123**) → (**124**) of the 6-benzoyloxy-1,3,5-oxadiazine-2,4(3*H*)-dione (**123**; R = Ph) as outlined in Scheme 13 ⟨86CB669⟩. Other aryl carboxylic acids yield only complex mixtures, whereas with alkyl carboxylic acids and with trichloroacetic acid, 1,3,5-oxadiazine-2,4(3*H*)-diones (**125**; R = alkyl and H, respectively) are

obtained in good yields (55–90%). Hydrolysis of carbonyl diisocyanate in wet diethyl ether at 0 °C affords 1,3,5-oxadiazine-2,4,6-trione (**124**; H in place of RCO) in 88% yield ⟨86CB83⟩.



Scheme 13

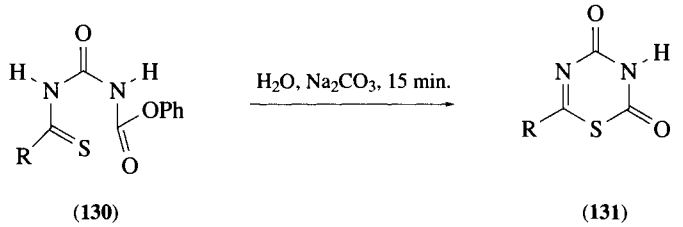
1-Oxa-3,5-diaza-1,3,5-hexatrienes (**128**), obtained either by reaction of *N*-lithio- or *N*-trimethylsilyl substituted imines (**127**; Y = Li or Me_3Si) with *N*-acylimidates (**126**; X = OEt) or with *N*-acylimidoyl chlorides (**126**; X = Cl), exist in equilibrium with their ring-chain tautomers (see Section 6.18.4.3), the 2*H*-1,3,5-oxadiazines (**129**). Generally, with aryl groups at C-6 the open-chain tautomers (**128**) dominate, whereas with the 6-*t*-butyl derivatives the oxadiazines (**129**) are formed exclusively (Scheme 14) ⟨93CB957⟩.



Scheme 14

6.18.10.1.2 Between carbon and sulfur

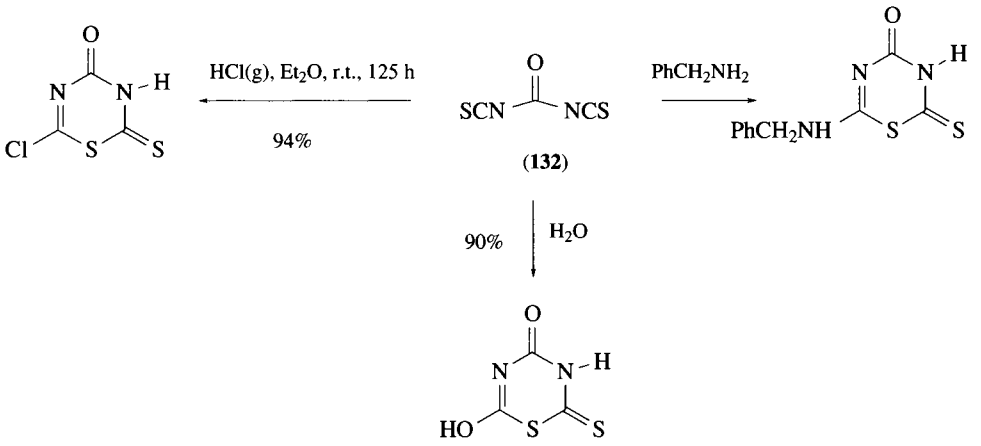
N^1-Phenoxycarbonyl-N^2-thioacylureas (**130**), formed by addition of thioamides to phenoxycarbonyl isocyanate, in aqueous sodium carbonate undergo rapid cyclization to 6-substituted-1,3,5-thiadiazine-2,4(3*H*)-diones (**131**) in high yields (≃90%) (Equation (7)). Cyclization can also be achieved, although in inferior yields (50–60%), by prolonged heating of the thioacylurea with pyridine in xylene ⟨82JMC481⟩.



(7)

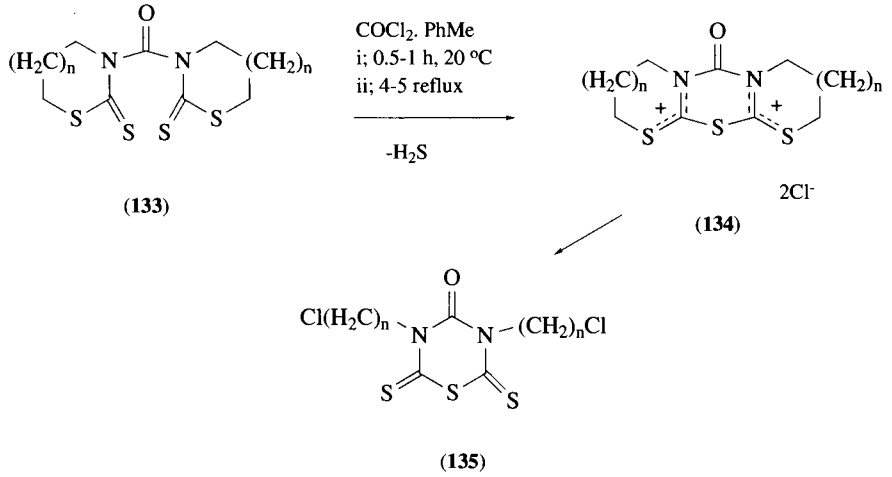
Carbonyl diisothiocyanate (**132**), prepared readily from carbonyl bromide or chloride and

ammonium thiocyanate in liquid SO_2 at $-22°C$, is a useful precursor for the synthesis of a variety of 2-thioxo-1,3,5-thiadiazin-4-ones (Scheme 15) ⟨81GEP3010204, 81GEP3010238, 82CB3587⟩.



Scheme 15

Treatment of di(perhydro-2-thioxo-1,3-thiazin-3-yl)methanone (**133**; $n = 1$) with phosgene brings about cyclization to the tricyclic salt (**134**; $n = 1$) which on isolation forms its covalent isomer, 3,5-bis(3-chloropropyl)-2,6-dithioxoperhydro-1,3,5-thiadiazin-4-one (**135**; $n = 3$; 36%). A similar reaction on the bis(2-thioxothiazolidin-3-yl)methanone (**133**; $n = 0$) yields the 3,5-bis(2-chloroethyl) derivative (**135**; $n = 2$, 56%) (Scheme 16) ⟨91LA1095⟩.



Scheme 16

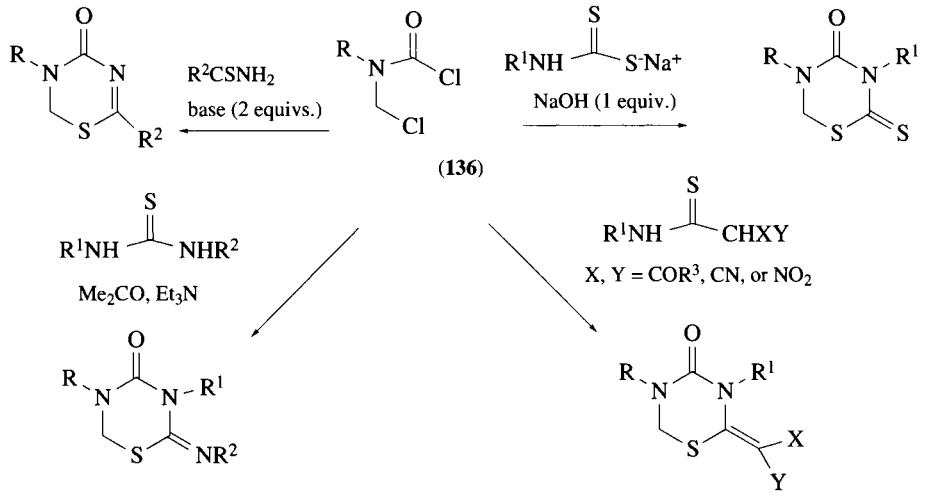
6.18.10.2 Formation of Two Bonds

6.18.10.2.1 [3 + 3] Fragments

(i) From C—N—C and N—C—S Fragments

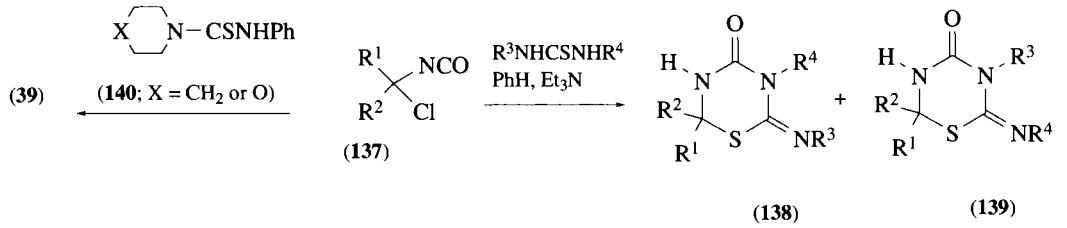
N-Substituted *N*-chloromethylcarbamoyl chlorides (**136**) react with sodium dithiocarbamates and with thioamides in the presence of base to give a variety of 1,3,5-thiadiazin-4-ones as exemplified in Scheme 17 ⟨86MI 618-02⟩. Likewise, with N^1,N^2-disubstituted thioureas, 2-alkylimino-5,6-di-

hydro-2*H*-1,3,5-thiadiazin-4(3*H*)-ones are formed ⟨83GEP3232346, 86JAP(K)61140577, 87PAC1027, 90JAP(K)02101069, 91JAP(K)03197473⟩.



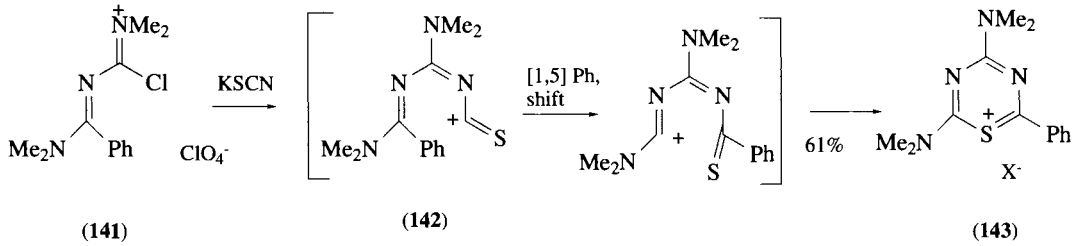
Scheme 17

Cyclocondensations of α-chloroalkylisocyanates (**137**) with N^1,N^2-disubstituted thioureas yield mixtures of isomeric 2-imino-5,6-dihydro-1,3,5-thiadiazin-4(3*H*)-ones (**138**) and (**139**) ⟨92MI 618-02, 92UKZ54⟩. Under similar conditions α-chloro-α-trifluoromethylbenzyl isocyanates (**137**; $R^1 = CF_3$, R^2 = Ar) and thioureas (**140**) condense to yield 2*H*-1,3,5-thiadiazinium-4-olates (e.g. (**39**)) (Scheme 18) which in polar solvents exist in equilibrium with their ring-chain tautomers (see Section 6.18.4.3) ⟨90CHE959, 91UKZ1316⟩.



Scheme 18

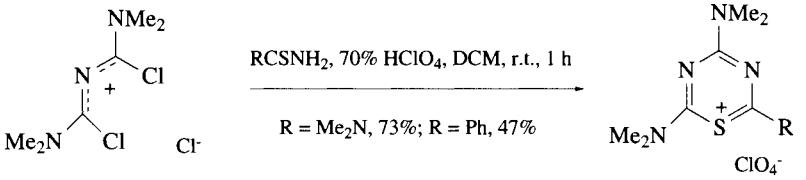
The formation of the 4,6-bis(dimethylamino)-2-phenyl-1,3,5-thiadiazinium salt (**143**) (isolated as the tetraphenylborate (X = BPh_4)) by treatment of 1-chloro-1,3-bis(dimethylamino)-3-phenyl-2-azapropenylium perchlorate (**141**) with potassium thiocyanate most probably involves a 1,5-sigmatropic shift of the phenyl group in the initially formed isothiocyanate cation (**142**) (Scheme 19) ⟨84CC1105⟩.



Scheme 19

1,3,5-Thiadiazinium salts (**145**) are also available by related reactions involving the condensation of 1,3-bis(dimethylamino)-1,3-dichloro-2-azapropenylium chlorides (**144**) and *N*-acylimidoyl chlor-

ides with thioamides in the presence of perchloric acid or tetrafluoroboric acid (e.g. Equation (8)) ⟨75ZC438, 80BCJ3369, 81JAP(K)5657778, 81JAP(K)5657780, 87BCJ2686⟩.



(8)

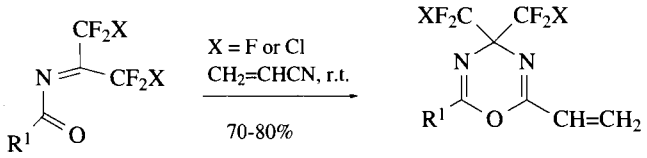
(144)

(145); R = NMe_2, 73%
R = Ph, 47%

6.18.10.2.2 [4 + 2] Fragments

(i) From C—N—C—O and C—N Fragments

4,4-Bis(trihaloalkyl)-3-aza-1-oxa-1,3-butadienes (**146**) undergo regioselective [4 + 2] π cycloaddition with αβ-unsaturated carbonitriles to yield 2-alkenyl-4,4-bis(trihaloalkyl)-4*H*-1,3,5-oxadiazines (e.g. (**147**)) (Equation (9)) ⟨82JOU1638, 83JFC(22)99⟩. Cycloadditions of the isolable highly electron-deficient oxazadiene (**146**; X = F, $R^1 = C(CF_3)_3$) with acetonitrile and benzonitrile have been reported ⟨84IZV2736, 85IZV2533, 88IZV132⟩, and cycloadditions of the oxazadienes (**146**; R^1 = Ph or Bu^t) with electron-deficient carbonitriles (e.g. CF_3CN, Cl_3CCN) have also been noted ⟨86CZ79⟩.

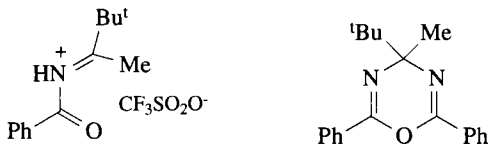


(9)

(146)

(147)

4-*t*-Butyl-2,6-diphenyl-4-methyl-4*H*-1,3,5-oxadiazine (**149**) is produced by treating the triflate salt (**148**), formed by slow (5 d) reaction of pinacolone with benzonitrile in triflic acid at room temperature, with an excess of benzonitrile at 100 °C followed by basification. In the absence of benzonitrile the salt (**148**) undergoes rearrangement and cyclization to 2-phenyl-4,4,5,5-tetramethyl-4,5-dihydro-1,3-oxazole ⟨88JOU207⟩.



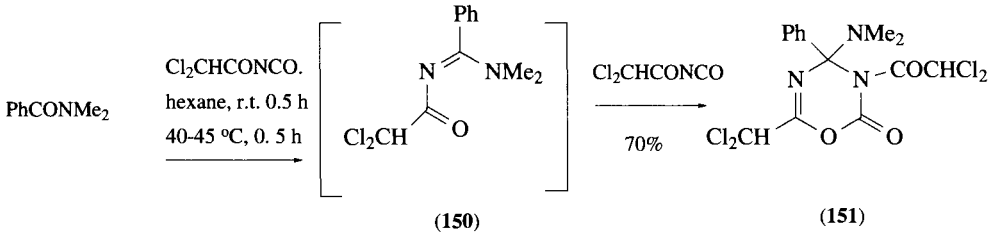
(148)

(149)

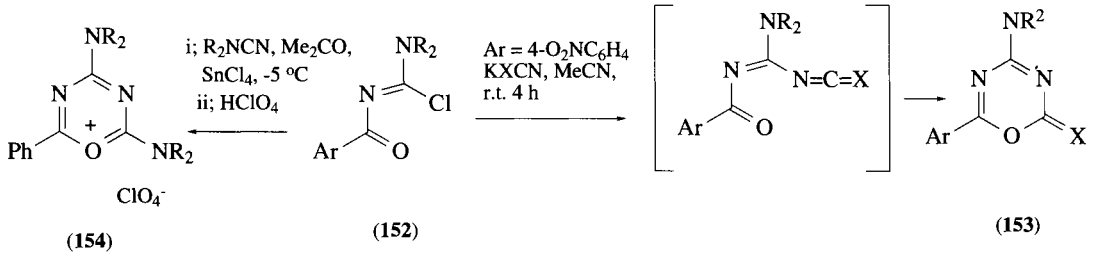
The *N*-acylimine (**150**), formed *in situ* by reaction of *N*,*N*-dimethylbenzamide with dichloroacetyl isocyanate, undergoes cycloaddition with a second equivalent of the isocyanate to yield the 4*H*-1,3,5-oxadiazin-2(3*H*)-one (**151**) (Scheme 20). A similar reaction occurs with *N*,*N*-dimethylacetamide but in inferior yield (15%) ⟨87JGU1848⟩.

Acid-sensitive 4-alkylamino-1,3,5-oxadiazine-2-thiones (**153**; X = S) are obtained readily in (56–83%) yield by treating *N*-acylchloroformamidines (**152**) with potassium thiocyanate in acetonitrile. Likewise, with potassium selenocyanate the 1,3,5-oxadiazine-2-selones (**153**; X = Se; 57–67%) are produced (Scheme 21) ⟨82LA201, 89LA931⟩. The formamidines also undergo cyclocondensation with cyanamides in the presence of stannic chloride to give 6-aryl-2,4-dialkylamino-1,3,5-oxadiazinium salts (**154**) ⟨86ZC94⟩.

The *N*-acylketenimine (**156**; R = Ph)), obtained by heating the chloro-*N*-trimethylsilylcarbamate

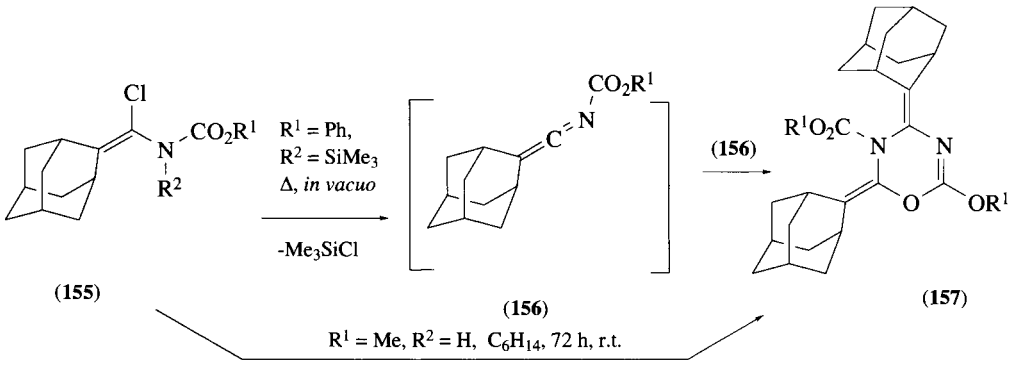


Scheme 20



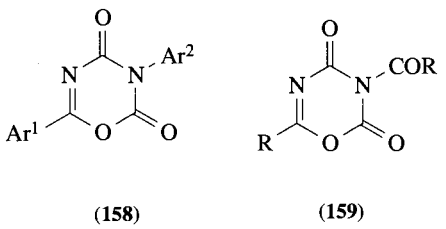
Scheme 21

(**155**; R^1 = Ph, R^2 = TMS) *in vacuo*, undergoes spontaneous dimerization to the 3-acyl 2,4-diadamantylidene-3,4-dihydro-2*H*-1,3,5-oxadiazine (**157**; R^1 = Ph). The methyl analogue (**157**; R^1 = Me) arises on prolonged heating of the chlorocarbamate (**155**; R^1 = Me, R^2 = H) with triethylamine ⟨90CB2339⟩ (Scheme 22).

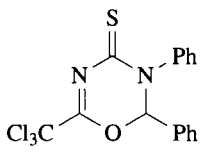


Scheme 22

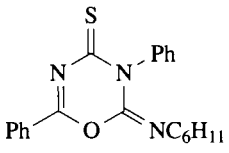
Base-catalyzed (Et_3N) cyclocondensations of aryl isocyanates with aroyl isocyanates afford 3,6-diaryl-1,3,5-oxadiazine-2,4-(3*H*)-diones (**158**) in practicable yields (60–92%) ⟨83GEP3200196, 85BRP2145068, 87GEP3627161, 89EUP318882⟩. Tributyltin isocyanate reacts in a similar manner with aroyl isocyanates, and in lesser yields with alkanoyl isocyanates, to give 3-acyl-1,3,5-oxadiazine-2,4(3*H*)-diones (**159**; R = aryl or alkyl) ⟨86CB83⟩.



2,3-Diphenyl-6-trichloromethyl-2*H*-1,3,5-oxadiazine-4(3*H*)-thione (**160**) is formed as an orange oil in 87% yield by cycloaddition of trichloroacetyl isothiocyanate with benzylideneaniline in DCM at room temperature ⟨84AJC2073⟩. In a like manner, benzoyl isothiocyanate and N^1-phenyl-N^2-cyclohexylcarbodiimide yield 3,6-diphenyl-2-cyclohexylimino-2*H*-1,3,4-thiadiazine-4(3*H*)-thione (**161**) ⟨81MI 618-01⟩. An analogous reaction had been noted earlier with aroyl isocyanates ⟨79BSF(2)499⟩.

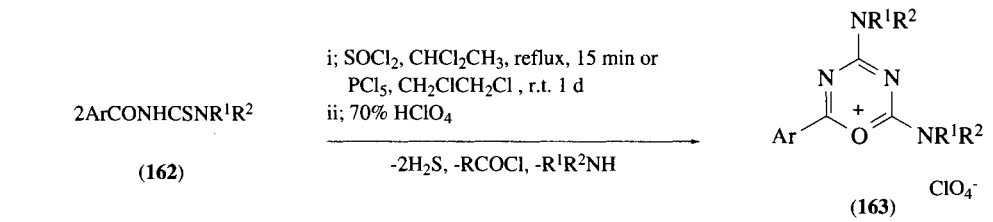


(**160**)



(**161**)

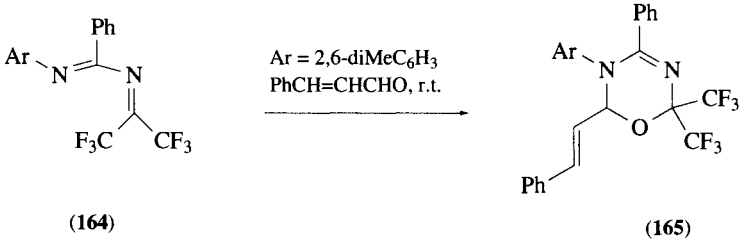
2,4-Bis(dialkylamino)-1,3,5-oxadiazinium salts (**163**) result from an unusual condensation involving two equivalents of an N^1,N^1-disubstituted-N^2-acylthiourea (**162**) with thionyl chloride, or (but in lesser yield) with phosphorus pentachloride in 1,2-dichloroethane (Equation (10)) ⟨85T5371, 92ZN(B)183⟩. A mechanistic rationale involving initial attack of the acid halide at sulfur followed by condensation with a second molecule of the acylthiourea is proposed. With phosphorus oxychloride in place of PCl_5 or $SOCl_2$, 1,3,5-thiadiazinium salts are obtained via initial attack of the phosphorus halide at the acyl oxygen (see Section 6.18.10.2.2.iii).



(10)

(ii) From C—N—C—N and C—O Fragments

The bis(trifluoromethyl)-2,4-diazadiene (**164**) undergoes regioselective [4 + 2] cycloaddition with cinnamaldehyde to give the 2,2-bis(trifluoromethyl)-5,6-dihydro-2*H*-1,3,5-oxadiazine (**165**) in 66% yield (Equation (11)) ⟨82ZN(B)1669⟩. Additions to simple ketones have also been reported ⟨78S524⟩.



(**164**) (**165**)

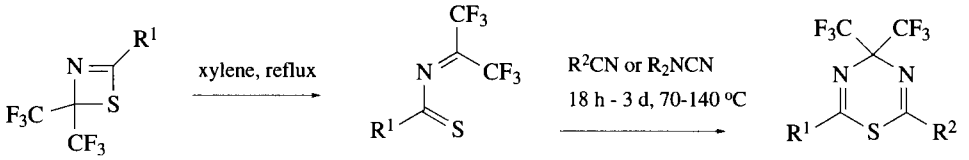
(11)

(iii) From C—N—C—S and C—N Fragments

[4 + 2] Cycloadditions of *N*-thioacylimines with carbonitriles and with imines constitute well-established and popular routes to the 1,3,5-thiadiazine system ⟨70CB3393, 72BCJ2877⟩.

On thermolysis in hot xylene, 1,3-thiazetines (**166**), obtained by [2 + 2] cycloaddition of perfluorothiopropanone and a carbonitrile, undergo electrocyclic ring-opening to the *N*-thioacylimines (**167**), which in the presence of a carbonitrile or an *N*,*N*-dialkylcyanamide yield 4,4-bis(trifluoromethyl)-

4*H*-1,3,5-thiadiazines (**168**; R^1 = alkyl or NR_2) as outlined in Scheme 23 ⟨86CZ79⟩ (see also Section 6.18.10.3.1.ii).

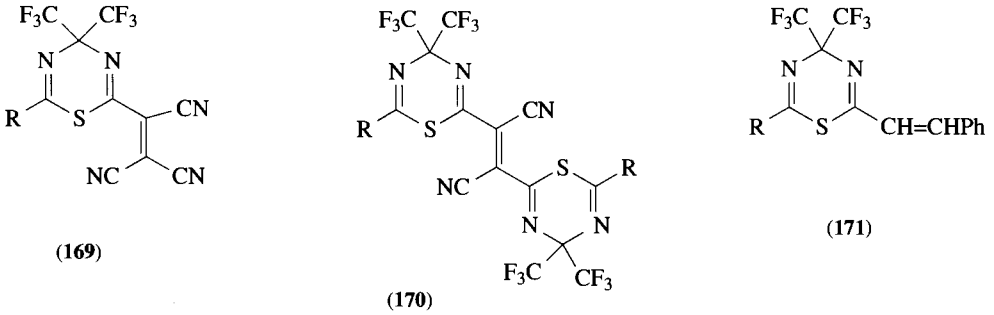


(**166**) (**167**) (**168**)

Scheme 23

With tetracyanoethene as the carbonitrile component the monoadducts (**169**) are formed (51–60%) accompanied by small amounts (≃7%) of the bis-adducts (**170**) ⟨82T287⟩.

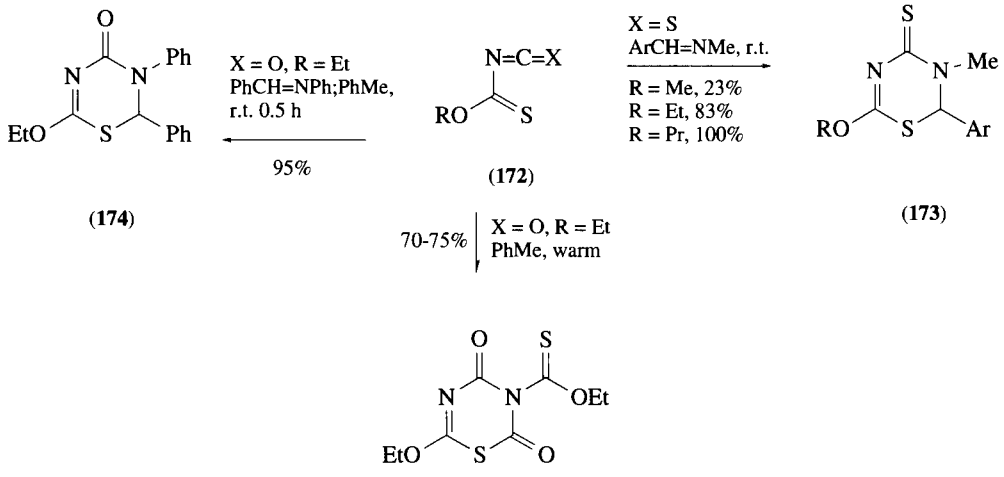
In a similar manner to the bis(trifluoromethyl)-2,4-dienes (**164**) mentioned in the previous section, addition of the thioacylimines (**167**) to αβ-unsaturated nitriles takes place exclusively at the hetero-multiple bond to give 4*H*-1,3,5-thiadiazines (e.g. (**171**; 75%)) ⟨81CZ380⟩.



(**169**) (**170**) (**171**)

Alkoxythiocarbonyl isothiocyanates (**172**; X = S) are also useful 4π components and with imines at room temperature furnish 6-alkoxy-2*H*-1,3,5-thiadiazine-4(3*H*)-thiones (**173**) albeit in variable yields ⟨83CB2044⟩. In a similar manner ethoxythiocarbonyl isocyanate (**172**; R = Et, X = O) and benzylideneaniline produce 2,3-diphenyl-6-ethoxy-2*H*-1,3,5-thiadiazin-4(3*H*)-one (**174**) ⟨82CB1252⟩. In warm toluene the ethoxythiocarbonyl isocyanate dimerizes to give the *O*-ethyl ester (**175**) of 6-ethoxy-3,4-dihydro-2,4-dioxo-2*H*-1,3,5-thiadiazine-3-thiocarboxylic acid (Scheme 24).

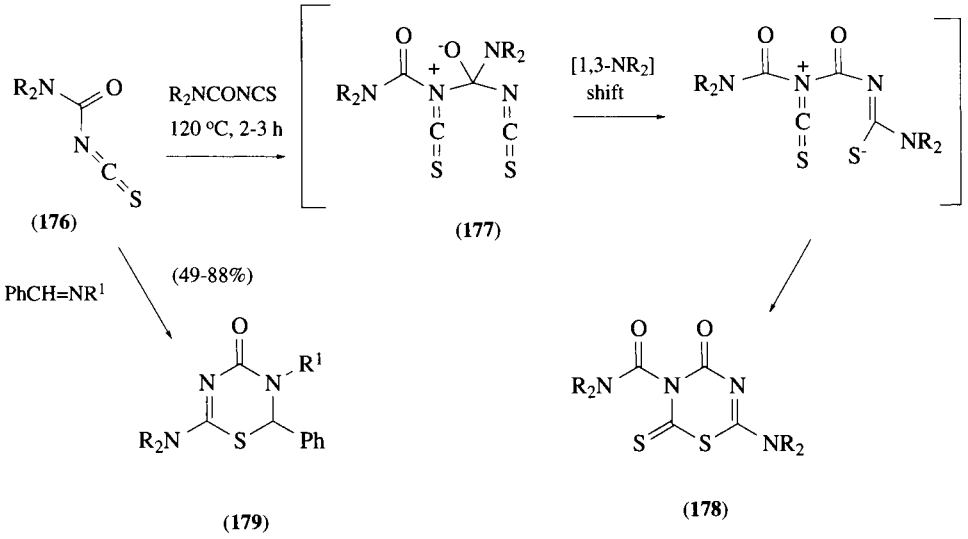
In contrast, under similar conditions, or on long standing (4 weeks–6 months) at room tempera-



(**174**) (**172**) (**173**) (**175**)

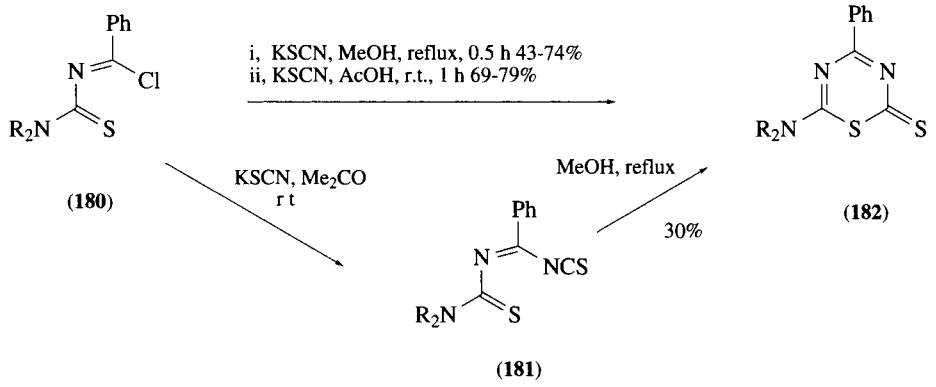
Scheme 24

ture, carbamoyl isothiocyanates (**176**) yield 2-thioxo-1,3,5-thiadiazin-4(3*H*)-ones (**178**) rather than 1,3,5-thiadiazine-2,4-diones. These unexpected products, which formally are cycloadducts of the carbamoyl isothiocyanate and the isomeric thiocarbamoyl isocyanate, arise via a [1,3] sigmatropic shift of the R_2N group in the polar intermediate (**177**) as outlined in Scheme 25 ⟨85CB4196⟩. A similar reaction sequence is noted during addition of the carbamoyl isothiocyanate to imines ($PhCH{=}NR^1$) whereby 6-dialkylamino-2-phenyl-2*H*-1,3,5-thiadiazin-4(3*H*)-ones (**179**) are produced in practicable yields ⟨85CB4196⟩.



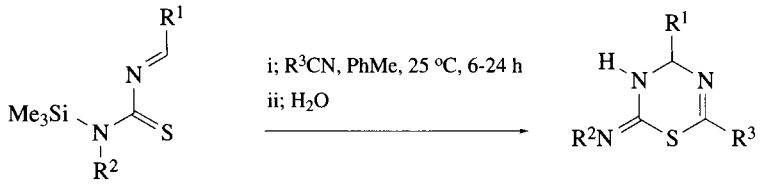
Scheme 25

Treatment of an *N*-(aminothiocarbonyl)benzimidoyl chloride (**180**) with potassium thiocyanate in methanol, or better, in acetic acid, results in cyclization of the initially formed benzimidoyl isothiocyanate (**181**) to a 1,3,5-thiadiazine-2-thione (**182**) (Scheme 26). The isocyanates can be isolated if the reaction is carried out in acetone at room temperature, but ring close to the thiones in boiling methanol ⟨88JPR241, 89EGP263768⟩.



Scheme 26

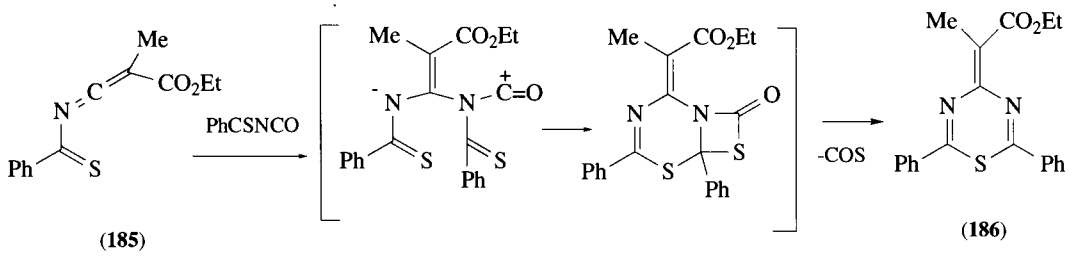
If *N*-(trimethylsilylaminothiocarbonyl) derivatives (**183**) are used as the 4π components then cycloadditions with a carbonitrile followed by mild aqueous hydrolysis afford 2-imino-3,4-dihydro-2*H*-1,3,5-thiadiazines (**184**) in excellent yields (80–91%) (Equation (11a)) ⟨91SL93⟩.



(11a)

(183) (184)

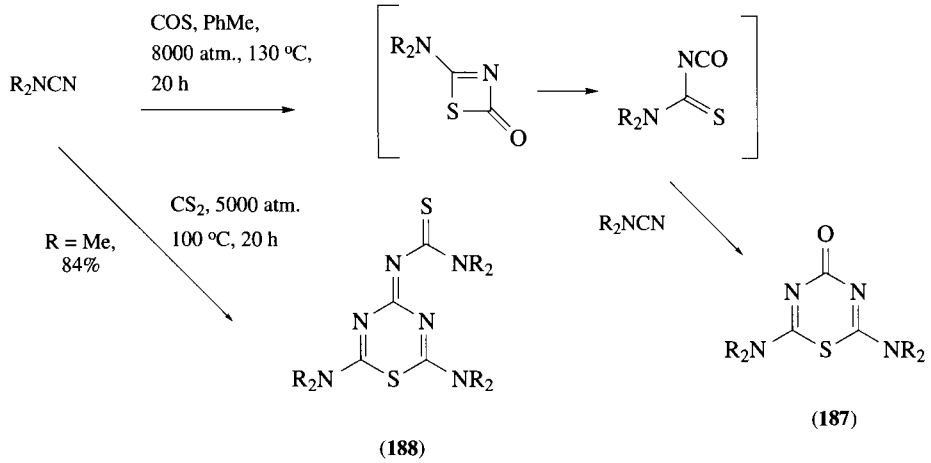
Addition of thiobenzoyl isocyanate to the *N*-thiobenzoylketenimine (**185**) is accompanied by loss of COS and forms the violet 4-alkylidene-4*H*-1,3,5-thiadiazine (**186**) possibly as outlined in Scheme 27 ⟨85LA2305⟩.



(185) (186)

Scheme 27

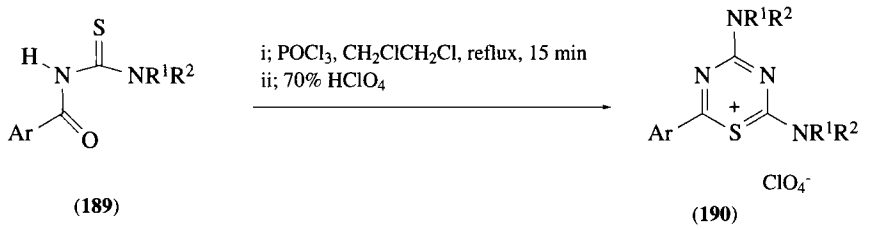
2,6-Bis(dialkylamino)-1,3,5-thiadiazin-4-ones (**187**) are produced in high yields (74–94%) by heating dialkylaminocyanamides under high pressure (8000 atm) with COS in toluene (Scheme 28). The reaction, however, is very susceptible to variations in temperature and pressure. For example, at 130 °C and 4000 atm, the yield of the bis(dimethylamino) derivative (**187**; R = Me) decreases from 92% to 33%, whereas maintaining the pressure at 8000 atm but lowering the temperature to 100 °C brings about a further decrease in yield of the product to 14% ⟨91CL1229, 92EUP486041⟩. Replacement of COS by CS_2 results in the formation of 2,6-bis(dialkylamino)-4-(thiocarbamoyl)imino-4*H*-1,3,5-thiadiazines (**188**) in excellent yields ⟨90EUP391078⟩.



(188) (187)

Scheme 28

In contrast to their reactions with $SOCl_2$ and PCl_5 (see Section 6.18.10.2.2.i), N^1-acyl-N^2,N^2-disubstituted thioureas (**189**), on treatment with $POCl_3$ in boiling 1,2-dichloroethane followed by addition of perchloric acid, afford 1,3,5-thiadiazinium perchlorates (**190**) in 50–98% yield (Equation (12)) ⟨85T5371⟩.

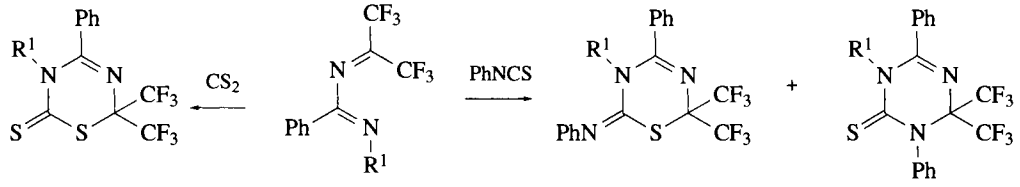


(189) (190) (12)

(iv) From C—N—C—N and C—S Fragments

In contrast to the 1,3,5-oxadiazines discussed in the previous section, the formation of 1,3,5-thiadiazines by cycloadditions involving a 1,3-diazadiene system is uncommon.

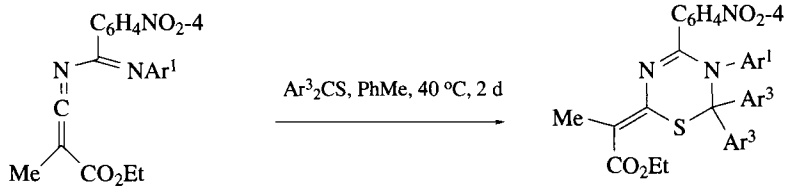
N-(Benzimidoyl)imines (**191**; $R^1 = 2,4,6\text{-}Me_3C_6H_2$) undergo cycloaddition with CS_2 to yield 3,6-dihydro-6,6-bis(trifluoromethyl)-2*H*-1,3,5-thiadiazine-2-thiones (**192**). Addition to phenyl isothiocyanate, however, is nonregioselective and produces a mixture of the 6-phenylimino-2*H*-1,3,5-thiadiazine (**193**; 51%) and the isomeric 3,6-dihydro-2*H*-1,3,5-triazine-2(1*H*)-thione (**194**; 28%) (Scheme 29) ⟨84ZN(B)1442⟩.



(192) (191) (193) (194)

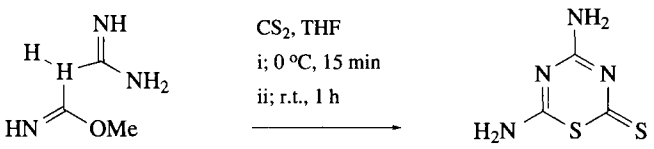
Scheme 29

6-Alkylidene-2,3-dihydro-1,3,5-thiadiazines (**196**) are produced slowly in [4 + 2] cycloadditions of *N*-imidoyl ketenimines (**195**) with diarylthioketones in warm toluene (Equation (13)) ⟨85LA2305⟩.



(195) (196) (13)

4,6-Diamino-1,3,5-thiadiazine-2-thione (**198**) is formed in 30% yield by cyclocondensation of *N*-(methoxycarbimidoyl)guanidine (**197**) with CS_2 (Equation (14)) ⟨90ZAAC(584)143⟩.

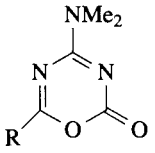


(197) (198) (14)

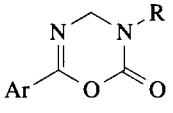
6.18.10.2.3 [5 + 1] Fragments

(i) From N—C—N—C—O and C Fragments

N-Acylguanidines and *N*-(alkylaminomethyl)benzamides cyclize on treatment with phosgene to give 1,3,4-oxadiazin-2-ones (**199**) ⟨76S38⟩ and 3,4-dihydro-2*H*-1,3,5-oxadiazin-2-ones (**200**) ⟨82SZP630245⟩, respectively.

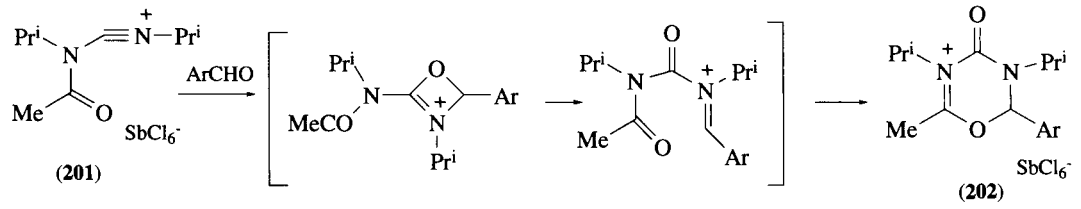


(**199**)



(**200**)

The acetyl-N^1,N^2-diisopropylcyanamidinium salt (**201**) undergoes reaction with arylaldehydes under mild conditions to yield 6-aryl-3,5-diisopropyl-5,6-dihydro-4-oxo-1,3,5-oxadiazin-3-ium hexachloroantimonates (**202**) as outlined in Scheme 30 ⟨91T205⟩.



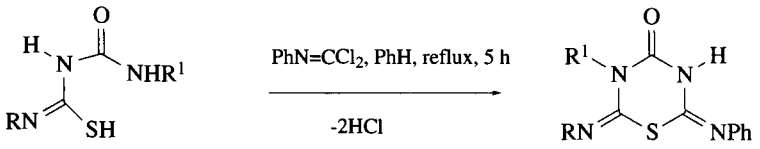
(**201**)

(**202**)

Scheme 30

(ii) From N—C—N—C—S and C Fragments

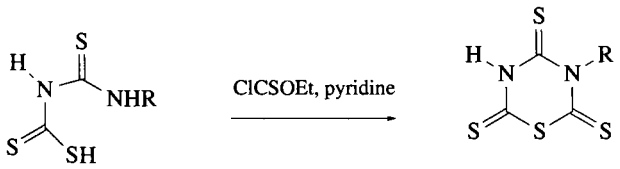
Phenylisocyanodichloride (PhN=CCl_2) has been used as the one-carbon component in the synthesis of a number of 2,6-diimino-5,6-dihydro-2*H*-1,3,5-thiadiazin-4(3*H*)-ones (**203**) (Equation (15)) ⟨84JIC68, 84JIC781, 84JIC883⟩.



(15)

(**203**)

1,3,5-Thiadiazine-2,4,6-trithiones (**205**) are reported to be formed by condensation of *N*-(aminothiocarbonyl)dithiocarbamates (**204**) with ethyl chlorothioformate in pyridine (Equation (16)) ⟨88PIA53⟩. In a similar manner, the ring closure of *N*-thioacylamidines with thiophosgene yields 4,6-diamino-1,3,5-thiadiazine-2-thiones ⟨71JHC1087⟩.



(16)

(**204**)

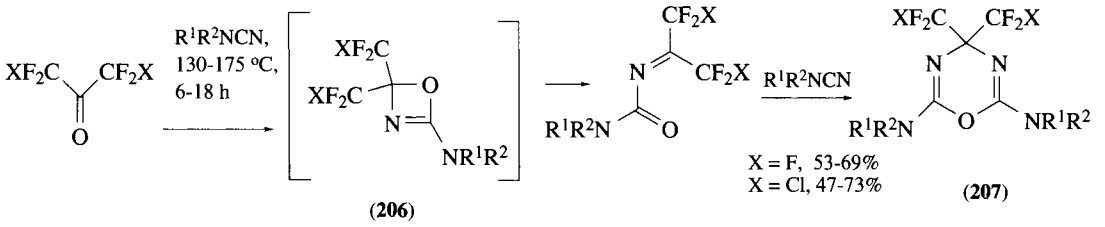
(**205**)

6.18.10.3 Formation of 3 Bonds

6.18.10.3.1 [2 + 2 + 2] Fragments

(i) From C—N, C—N and C—O Fragments

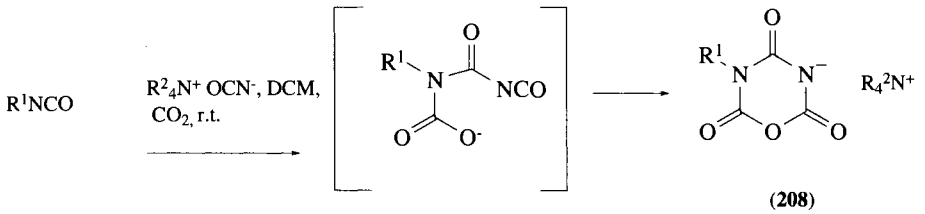
The 1 : 2 cycloadducts formed from hexahalogenopropanones and dialkylcyanamides, which previously were thought to be 2*H*-1,3,5-oxadiazines ⟨66JOC2568, 67USP3310554⟩ have been reformulated as the isomeric 4*H*-derivatives (**207**) ⟨83S237, 84LA982⟩. A two-stage process involving an oxazete intermediate (**206**) is proposed for their formation (Scheme 31). Analogous reactions occur with cyanoguanidines ⟨84LA982, 89IZV2815⟩.



(206) (207)

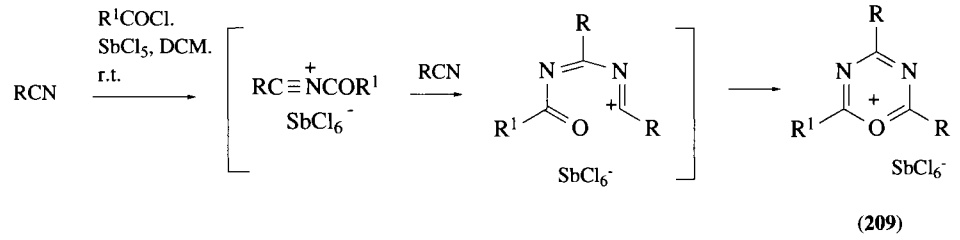
Scheme 31

1,3,5-Oxadiazine-2,4,6-triones are produced as the tetraalkylammonium salts (**208**) in a three-component reaction involving the condensation of an alkyl isocyanate with a tetralkylammonium cyanate in the presence of CO_2 (Equation (17)) ⟨84EUP98005⟩. Tetraalkyl phosphonium and arsonium cyanates have also been used.



(208) (17)

Great interest has been shown in the synthesis of 1,3,5-oxadiazinium salts (**209**) by the reaction of an aryl carbonitrile (2 equivs.) with an acyl halide (1 equiv.) in the presence of a Lewis acid, generally antimony pentachloride (Scheme 32). Stannic chloride, aluminum chloride and ferric chloride have also been employed but are less effective catalysts ⟨1892CB2266, 56CB209, 65CB334, 67CB3736, 86MI 618-01⟩.

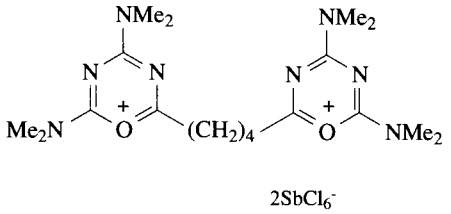


(209)

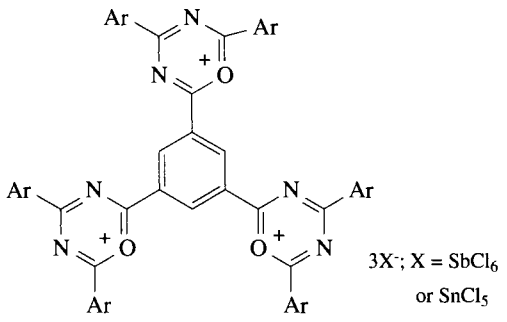
Scheme 32

The reaction proceeds equally well with an aryl cyanate, a cyanamide or an alkyl thiocyanate in place of the carbonitrile, to yield 2,4-diaryloxy-, (**209**; R = OAr) ⟨67CB3736⟩, 2,4-bis(dialkylamino)- (e.g. (**209**; R = NMe_2)) ⟨85CB1304, 85CB1887, 85EGP224590, 86ZC94, 88IJC(B)934⟩, and 2,4-dialkylthio- (e.g. (**209**; R = SMe)) ⟨81LA1198, 85LA1874⟩ 1,3,5-oxadiazinium hexachloroantimonates, respectively. Replacement of the acyl chloride by dimethylcarbamoyl chloride (Me_2NCOCl) in the reaction with *N*,*N*-dimethylcyanamide results in formation of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (**7**; R = Me), although in this case a higher temperature (170 °C) is required ⟨85JCS(P1)1533⟩.

With diacid chlorides, cyanamides form bis(2,2-oxadiazin-1-ylium) salts (e.g. (**210**; $n = 4$)) generally in high yields (>70%) ⟨87TL353, 88JHC1023⟩. Analogous reactions with arylcarbonitriles ⟨91JPR303, 92JPR151⟩ and with methyl thiocyanate ⟨90LA307⟩ yield the corresponding 2,4-diaryl- and 2,4-bis(methylthio)-derivatives (**210**; Ar and MeS in place of NMe_2), the latter in excellent yields (>85%). 1,3,5-Tris(2-oxadiazin-1-ylium)benzenes (**211**) result in high yields from the condensation of 1,3,5-(trichlorocarbonyl)benzene with aryl carbonitriles in the presence of antimony pentachloride or stannic chloride ⟨91JPR303⟩.

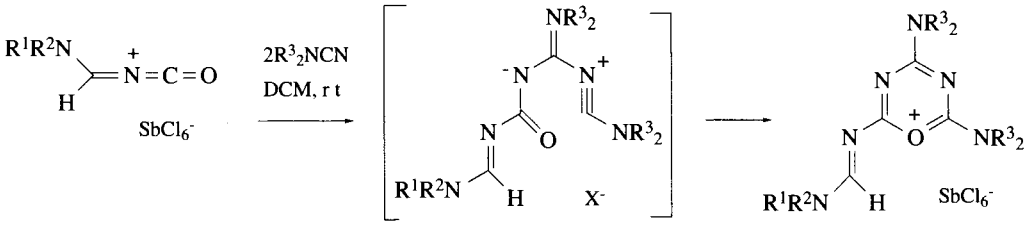


(**210**)



(**211**)

1-Oxa-3-azabutatrienium salts (**212**) condense with 2 equivalents of a cyanamide to give 2-amidino-4,6-dialkylamino-1,3,5-oxadiazinium hexachloroantimonates (**213**; 71–94%) (Scheme 33) ⟨88JCED388⟩.



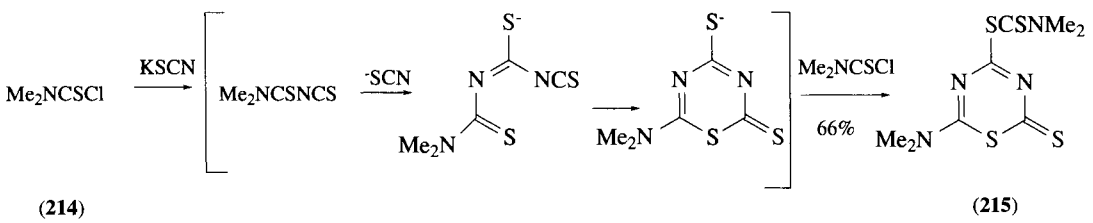
(**212**) (**213**)

Scheme 33

4,6-Diaryl-2-phenoxy-1,3,5-oxadiazinium hexachloroantimonates have been prepared in high yield (76–84%) from aryl carbonitriles (2 equivs.) and phenyl chloroformate (1 equiv.) under reflux in DCM in the presence of $SbCl_5$ ⟨93S426⟩.

(ii) From C—N, C—N and C—S Fragments

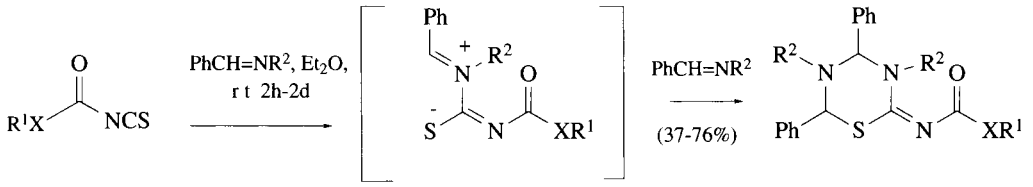
Treatment of *N,N*-dimethylthiocarbamoyl chloride (**214**) with potassium thiocyanate affords the 6-dimethylamino-1,3,5-thiadiazine-2-thione derivative (**215**; Scheme 34), the structure of which has been confirmed by x-ray analysis (see Section 6.18.3.1.3) ⟨89IZV909⟩.



(**214**) (**215**)

Scheme 34

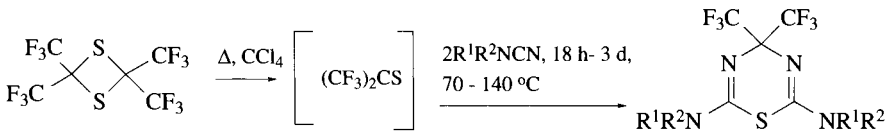
Alkoxycarbonyl isocyanates and isothiocyanates (**216**; X = O or S) in the presence of an excess of a benzylideneamine yield 2-acyliminoperhydro-1,3,5-thiadiazines (**218**). A two-stage process involving addition of the imine to the initially formed 1,4-dipolar 1 : 1-adduct (**217**), which in some instances is isolated as the ring-closed 1,3-thiazetidine, is likely (Scheme 35) ⟨83CB1297, 85CB4196⟩.



(**216**) (**217**) (**218**)

Scheme 35

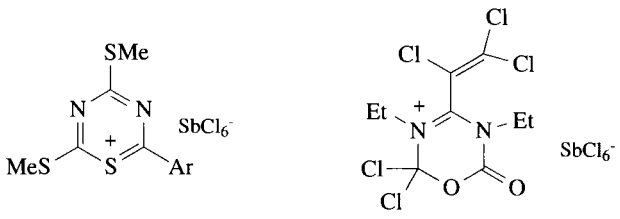
Hexafluorothiopropanone, generated *in situ* from the stable 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (**219**), reacts in an analogous manner to that described for hexafluoropropanone (Scheme 31; see Section 6.18.10.3.1.i) with an excess of dialkyl cyanamides to give 2,6-bis(dialkylamino)-4,4-bis(trifluoromethyl)-4*H*-1,3,5-thiadiazines (**220**) (Scheme 36) ⟨84LA982⟩.



(**219**) (**220**)

Scheme 36

In a reaction similar to that described for the preparation of 1,3,5-oxadiazinium salts (**209**) (Scheme 32; see Section 6.18.10.3.1.i) methyl thiocyanate in the presence of $SbCl_5$ undergoes cyclocondensations with arylthiocarbonyl chlorides to give 2-aryl-4,6-bis(methylthio)-1,3,5-thiadiazinium hexachloroantimonates (**221**) (39–46%) ⟨88LA729⟩.



(**221**) (**222**)

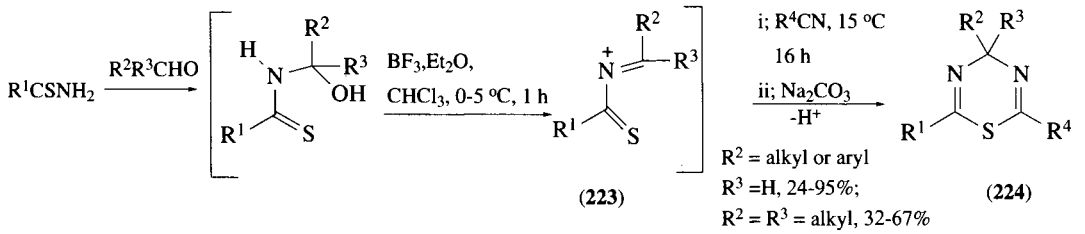
6.18.10.3.2 [3 + 2 + 1] Fragments

(i) From N—C—O, N—C and C Fragments

On the basis of an x-ray analysis the structure of the product obtained by reaction of ethyl isocyanate (2 equivs.) with hexachloropropene in the presence of antimony pentachloride has been formulated as 6,6-dichloro-3,5-diethyl-4(trichlorovinyl)-6*H*-1,3,5-oxadiazin-2(3*H*)-on-5-ium hexachloroantimonate (**222**) ⟨92JPR669⟩.

(ii) From N—C—S, N—C and C Fragments

4-Alkyl- and 4-aryl-4*H*-1,3,5-thiadiazines (**224**) are readily accessible by a one-pot BF_3-etherate-catalyzed condensation of an aldehyde, a carbonitrile and a thioamide ⟨75S266, 81JAP(K)5657779⟩. The reaction is also successful with dialkyl ketones but not with diaryl ketones ⟨77S476⟩. A mechanistic rationale involving initial addition of the thioamide to the aldehyde (or ketone) followed by 1,4-polar cycloaddition of the derived cation (**223**) to the nitrile is proposed (Scheme 37) ⟨75S266⟩.



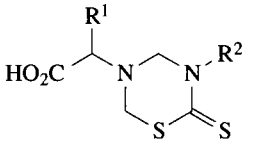
(223) (224)

Scheme 37

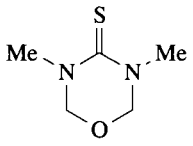
6.18.10.4 Miscellaneous Syntheses

3,5-Disubstituted perhydro-1,3,5-thiadiazine-2-thiones (**225**) are prepared by sequential condensation of an alkylamine (RCH_2NH_2) with carbon disulfide, methanol, and an α-amino-acid ⟨91AF1182, 92AF160⟩.

3,5-Dimethyl-5,6-dihydro-2*H*-1,3,5-oxadiazine-4(3*H*)-thione (**226**) has been isolated as an unexpected major by-product (21%) from the oxidation of N^1,N^2-dimethylthiourea with photochemically generated singlet oxygen ⟨92MI 618-01⟩. The mechanism of this reaction, which fails with N^1N^2-diethyl- and N^1,N^2-diphenylthiourea, and, in particular, the origin of the CH_2OCH_2 fragment, is not clear.



(225)

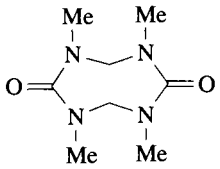


(226)

6.18.11 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

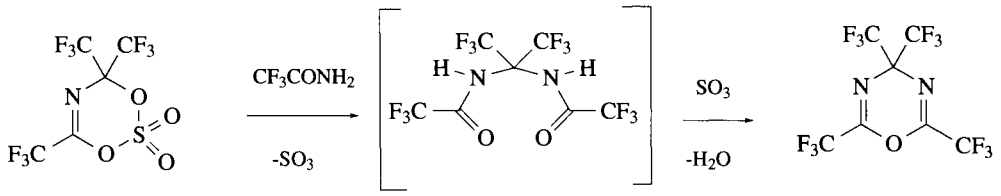
6.18.11.1 To Give 1,3,5-Oxadiazines

The monocyclic bis-urea (**227**) on treatment with triflic anhydride yields, unexpectedly, the 2,6-di(methylamino)-3,5-dihydro-4*H*-1,3,5-oxadiazine-2,6-diylium bistriflate (**9**; 66%) (see Section 6.18.3.1.2.i), the structure of which has been confirmed by an alternative synthesis (see Section 6.18.10.1.1) and by x-ray analysis of its hydrolysis product (**97**) (see Section 6.18.7.4) ⟨85JHC907⟩.



(227)

The tris(trifluoromethyl)-1,3,2,5-dioxathiazine 2,2-dioxide (**228**), obtained by the action of SO_3 on *N*-[bis(trifluoromethyl)hydroxymethyl]trifluoroacetamide, on treatment with trifluoroacetamide undergoes ring scission accompanied by loss of SO_3, which acts as a cyclodehydrating agent on the bis-amide (**229**) so-formed, to yield 2,4,4,6-tetrakis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (**230**) (Scheme 38) ⟨84JOU1213, 89JOU578⟩.

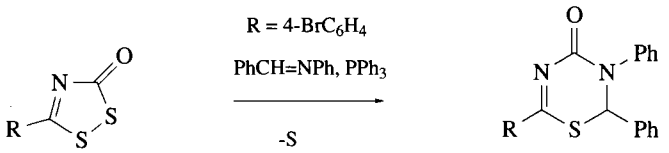


(**228**) (**229**) (**230**)

Scheme 38

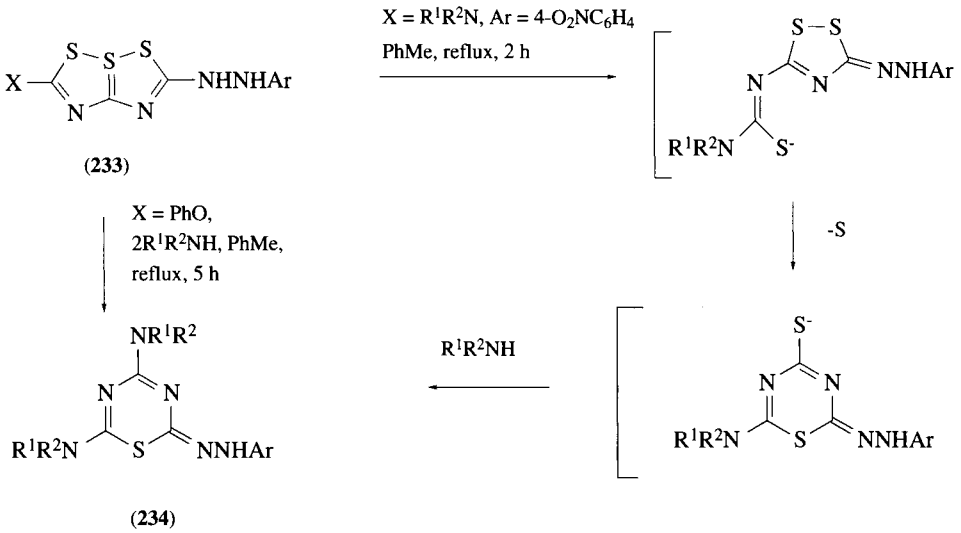
6.18.11.2 To Give 1,3,5-Thiadiazines

1,2,4-Dithiazol-3-ones (**231**), prepared by the action of chlorocarbonyl sulfenyl chloride on thioamides, undergo loss of sulfur and ring expansion to 2,3,6-triaryl-2*H*-1,3,5-thiadiazin-4(3*H*)-ones (**232**) on treatment with benzylideneaniline and triphenylphosphine (Equation (18)) ⟨83MI 618-02⟩.



(**231**) (**232**) (18)

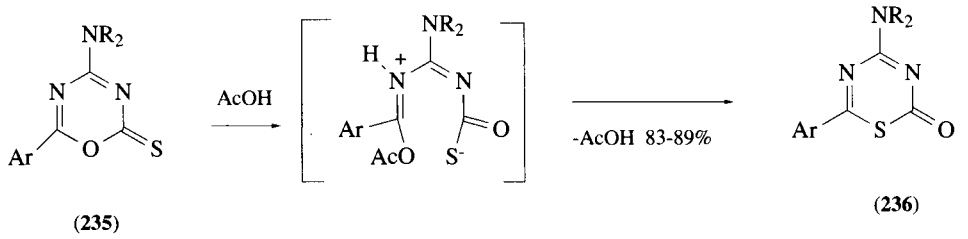
5-Amino-2-hydrazino-1,6,6aλ^4-trithia-3,4-diazapentalenes (**233**) in boiling toluene in the presence of a secondary amine suffer ring expansion to 4,6-diamino-2-hydrazono-2*H*-1,3,5-thiadiazines (**234**) as exemplified in Scheme 39 ⟨93PS(84)83⟩. The 2*H*-1,3,5-thiadiazines are also formed by heating the 5-phenoxytrithiadiazapentalenes (**233**; X = OPh) with two equivalents of a secondary amine.



(**234**)

Scheme 39

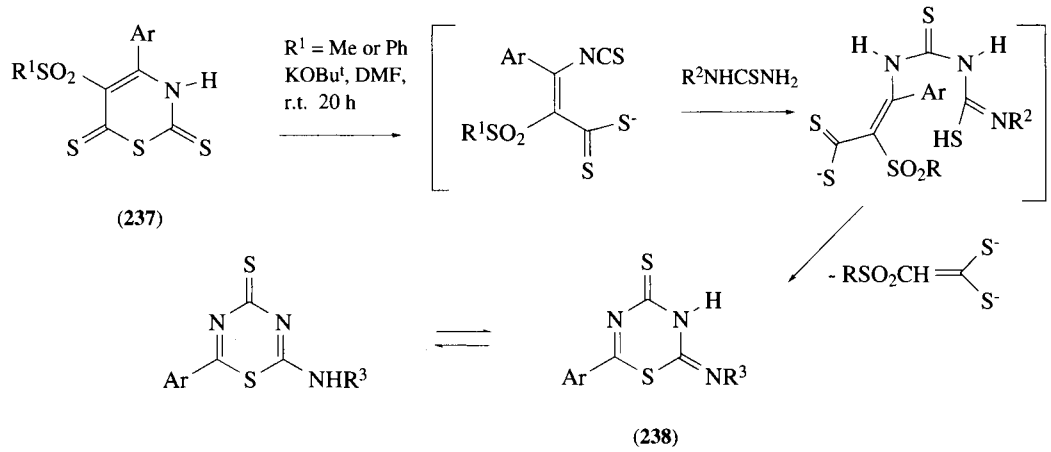
The acid-sensitive 4-alkylamino-6-aryl-1,3,5-oxadiazine-2-thiones (**235**) undergo a rapid Dimroth-type rearrangement in boiling acetic acid to the isomeric 1,3,5-thiadiazin-2-ones (**236**) (Scheme 40) ⟨86ZC132, 89LA931⟩.



(235) (236)

Scheme 40

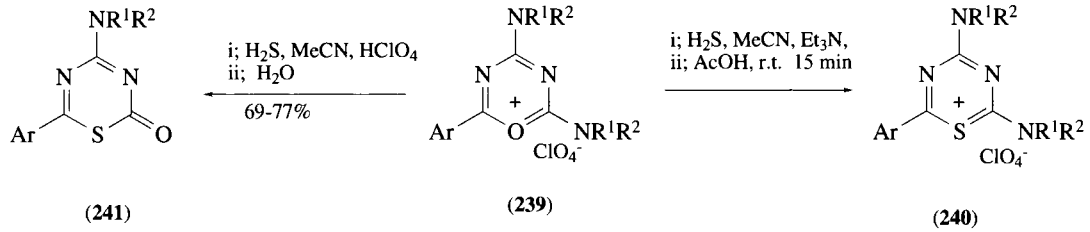
The first 1,3,5-thiadiazine-4-thiones (**238**) have been prepared by base-catalyzed reaction of 4*H*-1,3-thiazine-2,6(3*H*)-dithiones (**237**) with a thiourea in DMF ⟨84JCR(S)266⟩. A mechanistic rationale has been proposed (Scheme 41).



(237) (238)

Scheme 41

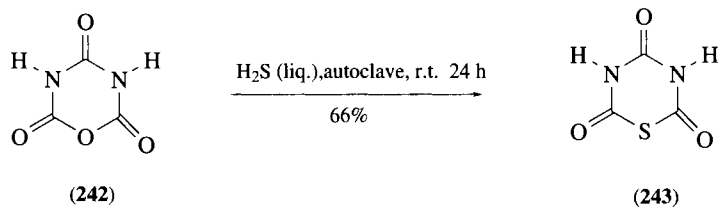
6-Aryl-2,4-dialkylamino-1,3,5-oxadiazinium perchlorates (**239**) are converted into the corresponding 1,3,5-thiadiazinium salts (**240**) by H_2S in acetonitrile in the presence of triethylamine. In contrast, in acid solution ring transformation is accompanied by elimination of the dialkylamino residue and formation of a 1,3,5-thiadiazin-2-one (**241**) (Scheme 42) ⟨85T5371, 86ZC132⟩.



(241) (239) (240)

Scheme 42

Hydrogen sulfide has also been used to effect the conversion of 1,3,5-oxadiazine-2,4,6(3*H*,5*H*)-trione (**242**) into 1,3,5-thiadiazine-2,4,6(3*H*,5*H*)-trione (**243**) (Equation (19)) ⟨86CB83⟩.



(242) (243)

(19)

6.18.12 GENERAL SYNTHETIC METHODS

6.18.12.1 1,3,5-Oxadiazines

A variety of methods are available for preparing the 1,3,5-oxadiazine system. Perhydro-1,3,5-oxadiazines are accessible by cyclodehydration of N^1,N^2-bis(hydroxymethyl)ureas and by Curtius rearrangement of α-acylaminoacylazides (see Section 6.18.10.1.1). 1,3,5-Oxadiazin-2-thiones are formed by treatment of *N*-acylchloroformamidines with potassium thiocyanate (see Section 6.18.10.2.2.i). 1,3,5-Oxadiazin-2-ones are obtained by ring-closure of *N*-(alkylaminomethyl)-benzamides with phosgene (see Section 6.18.10.2.3.i) and by ring closure of *N*-acylguanidines with phosgene (see Section 6.18.10.2.3.i).

Treatment of carbonyl diisocyanate with *N*-substituted amides or with alkyl carboxylic acids produces 1,3,5-oxadiazine-2,4-diones (see Section 6.18.10.1.1), which are also prepared by base-catalyzed cyclocondensation of aroyl isocyanates with aryl isocyanates (see Section 6.18.10.2.2.i). 1,3,5-Oxadiazine-2,4,6-trione is formed on treatment of carbonyl diisocyanate with water (see Section 6.18.10.1.2).

Electrocyclic ring closure of 1-oxa-3,5-diaza-1,3,5-hexatrienes forms 2*H*-1,3,5-oxadiazines (see Section 6.18.10.1.1), while 4*H*-1,3,5-oxadiazines arise by (4 + 2)π cycloaddition of electron-deficient 1-oxa-3-aza-1,3-dienes with carbonitriles (see Section 6.18.10.2.2.i) and by cycloaddition of hexahalogenopropanones (1 equiv.) with dialkylcyanamides (2 equivs.) (see Section 6.18.10.3.1.i).

Lewis acid-catalyzed condensation of an aryl carbonitrile (2 equivs.) with an acyl halide (1 equiv.) is a well-established and popular route to 1,3,5-oxadiazinium salts (see Section 6.18.10.3.1.i). The carbonitrile can be replaced successfully by aryl cyanates, cyanamides, and alkylthiocyanates, and examples using carbamoyl chlorides rather than the acyl halide have also been reported. The 1,3,5-oxadiazinium salts are also accessible by cyclocondensation of *N*-acylchloroformamidines with cyanamides in the presence of stannic chloride (see Section 6.18.10.2.2.1.i) and by condensation of N^1N^1-disubstituted-N^2-acylthioureas (2 equivs.) with thionyl chloride or phosphorus pentachloride (see Section 6.18.10.2.2.i).

6.18.12.2 1,3,5-Thiadiazines

Whereas there appear to be no general synthetic routes to 2*H*-1,3,5-thiadiazines, the 2-thiones and the 2,4-dione derivatives are accessible by Dimroth rearrangement of 1,3,5-oxadiazine-2-thiones (see Section 6.18.11.2) and by base-catalyzed cyclization of N^1-acyl-N^2-thioacylureas (see Section 6.18.10.1.2), respectively. The 2,4-diones have also been prepared by condensation of *N*-chloromethylcarbamoyl chlorides with sodium dithiocarbamates and with thioamides (see Section 6.18.10.2.1.i). A variety of 2-thioxo-1,3,5-oxadiazin-4-ones are available by condensation of carbonyl diisothiocyanate with a range of nucleophiles (see Section 6.18.10.1.2).

4*H*-1,3,5-Thiadiazines are prepared readily by (4 + 2) cycloaddition of *N*-thioacylimines with carbonitriles or cyanamides (see Section 6.18.10.2.2.iii). Analogous cycloadditions with alkoxythiocarbonyl isocyanates produce 2*H*-1,3,5-thiadiazine-4(3*H*)-thiones (see Section 6.18.10.2.2.iii). The boron-trifluoride etherate-catalyzed condensation of an aldehyde (or dialkyl ketone), a carbonitrile and a thioamide is also a versatile route to 4*H*-1,3,5-thiadiazines (see Section 6.18.10.3.2.2). 4,4-Bis(trifluoromethyl)-4*H*-1,3,5-thiadiazines arise by condensation of an excess of a dialkyl cyanamide with hexafluorothiopropanone (see Section 6.18.10.3.1.ii).

1,3,5-Thiadiazin-4-ones are obtained by heating dialkylaminocyanamides with COS under high pressure (see Section 6.18.10.2.2.iii), and the corresponding 4-thiones are formed by base-catalyzed ring-transformation of 1,3-thiazine-2,6(3*H*)-dithiones in the presence of thiourea (see Section 6.18.11.2).

1,3,5-Thiadiazine-2,4,6-triones can be prepared by ring closure of *N*-(aminothiocarbonyl)-dithiocarbamates with ethyl chlorothioformate (see Section 6.18.10.2.3.ii), and by treating 1,3,5-oxadiazine-2,4,6-trione with hydrogen sulfide (see Section 6.18.11.2). Condensation of 1-chloro- or 1,3-dichloro-2-azapropenylium salts with potassium thiocyanate or with thiourea produces 1,3,5-thiadiazinium salts (see Section 6.18.10.2.1.i). These salts are also obtained by heating N^1,N^2-disubstituted thioureas with phosphorus oxychloride (see Section 6.18.10.2.2.iii), by condensing arylthiocarbonyl chlorides with methyl thiocyanate in the presence of antimony pentachloride (see Section 6.18.10.3.1.ii), and by thionation of 1,3,5-oxadiazinium perchlorates with H_2S in the presence of triethylamine (see Section 6.18.11.2).

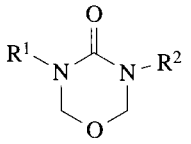
6.18.13 IMPORTANT COMPOUNDS AND APPLICATIONS

6.18.13.1 1,3,5-Oxadiazines

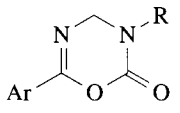
3,6-(Halodiaryl)-1,3,5-oxadiazine-2,4-diones are effective insecticides ⟨83GEP3200196, 85BRP2145068, 85EUP138772, 86EUP180547, 87GEP3627161, 89EUP318882⟩. Insecticidal and acaricidal activity is also present in 3,6-disubstituted-4*H*-1,3,5-oxadiazin-2(3*H*)-ones ⟨87EUP225854, 87EUP230863⟩.

3,5-Dialkyl-5,6-dihydro-2*H*-1,3,5-oxadiazin-4(3*H*)-ones possess high dielectric constants (e.g. (**244**; R^1 = Me, R^2 = CH_2CHMe_2, 17.6)) and are useful media for the formulation of high-speed jet inks ⟨85JAP(K)6067471, 85JAP(K)6067472, 85JAP(K)60104075, 85JAP(K)60104076⟩.

3-Alkyl-6-aryl-4*H*-1,3,5-oxadiazin-2(3*H*)-ones (**245**) have been used as weight promoters in animal feedstuffs ⟨82SZP630245⟩.

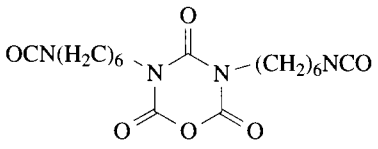


(**244**)



(**245**)

The 3,5-bis(ω-isocyanatohexyl)-1,3,5-oxadiazine-2,4,6-trione (**246**) is an important industrial reagent and is used in formulations for offset printed pressure-sensitive copying paper ⟨81EUP37477, 81GEP3011708, 81GEP3011709, 83USP4404251⟩, pressure-sensitive adhesives ⟨83EUP81103, 83EUP81693⟩, primers for polyalkene resins ⟨84JAP(K)59124937⟩, polyamide thermoplastics ⟨84JAP(K)59124938⟩, and polyurethane resins ⟨85EUP142838, 85EUP144841, 86MI 618-03⟩. It has also been used as a primer to improve the adhesion of adhesives to metal coatings ⟨84JAP(K)59124921, 85MI 618-01⟩, and in the late 1980s, its uses in insulating polymers for solid rocket propellants ⟨88GEP3706368⟩ and in polymeric resins in magnetic recording media ⟨88GEP3643458⟩ have been patented.



(**246**)

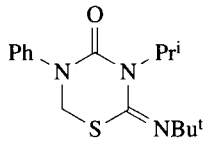
3,5-Disubstituted 5,6-dihydro-2*H*-1,3,5-oxadiazine-4(3*H*)-thiones have been used as ozone-induced colour fading preventatives ⟨88JAP(K)63205652, 88USP4737155⟩ and as antiozonants for rubber ⟨88EUP278890⟩. The corresponding 4(3*H*)-ones are one of the active ingredients for the removal of sulfur compound impurities from gaseous hydrocarbon mixtures ⟨92GEP4027300⟩, and are used as electrolytes in electrolytic capacitors ⟨90JAP(K)02194610⟩ and electrochromic light controlling devices ⟨88JAP(K)6356591⟩.

1,3,5-Oxadiazinium hexachlorantimonates are reported to stimulate the dissolution of aluminum in acetonitrile ⟨91MI 618-02⟩, but to inhibit that of copper in nitric acid ⟨89MI 521-02⟩.

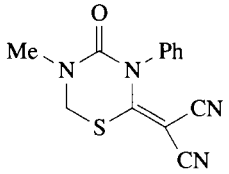
6.18.13.2 1,3,5-Thiadiazines

2-*t*-Butylimino-3-isopropyl-5-phenyl-5,6-dihydro-2*H*-1,3,5-thiadiazin-4(3*H*)-one (**247**; Buprofezin) is an important insect growth regulator with potent insecticidal and acaricidal activity ⟨82JAP(K)5758602, 82JAP(K)5785306, 82JAP(K)57169405, 82MI 618-01, 87PAC1027, 89MI 618-03⟩. Likewise, other 3-alkyl-2-alkylimino-5-aryl derivatives show similar properties ⟨82JAP(K)5731603, 82JAP(K)57169407,

83GEP3232346, 86JAP(K)61140577, 90JAP(K)02101069〉 as do the reported 5-aryl-3-arylmethyl-2-fluoroalkylimino derivatives 〈89EUP308961, 90EUP354297, 90JAP(K)0222269, 91JAP(K)0372472, 91JAP(K)03197474, 91JAP(K)03215478, 91USP5021412, 92JAP(K)0477478〉. 3,5-Disubstituted 2-cyanomethylene-5,6-dihydro-2*H*-1,3,5-thiadiazin-4(3*H*)-ones (e.g. (**248**)) are stated to have herbicidal activity 〈85JAP(K)6011482〉.

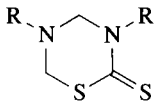


(**247**)

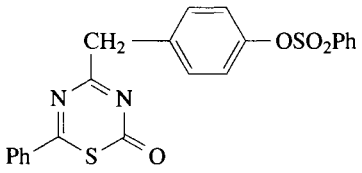


(**248**)

3,5-Dimethyl-5,6-dihydro-4*H*-1,3,5-thiadiazine-2(3*H*)-thione (**249**; R = Me; Dazomet) is an important pesticide, bactericide, and fungicide and is used in combination with a variety of other compounds as a soil disinfectant 〈81USP4301162, 82JAP(K)5799502, 82JAP(K)5799503, 82JAP(K)57114502, 82JAP(K)57165303, 84EUP98410, 84JAP(K)59210073, 89EGP273154〉. Antifungal activity is also displayed by 5-(carboxymethyl)-1,3,5-thiadiazine-2-thiones (**225**) 〈86MI 618-04, 86MI 618-05, 91AF1182, 92AF160〉, and by 6-phenyl-4-benzyl-1,3,5-thiadiazin-2-ones (e.g. (**250**)) 〈94MI 618-01〉.



(**249**)

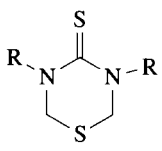


(**250**)

Hypolipemic activity has been noted for the 3,5-dibenzylperhydro-1,3,5-thiadiazine-2-thiones (**249**; R = CH_2Ph) 〈85JAP(K)60156616, 87JAP(K)6236319〉, while 4,6-diaryl-3,5-dimethyl-5,6-dihydro-4*H*-1,3,5-thiadiazine-2(3*H*)-thiones are reported to be antiatherosclerotic agents 〈85EUP135109, 86EUP183173, 87JAP(K)62195377〉.

3,5-Dialkylperhydro-1,3,5-thiadiazine-2-thiones have also been used in the manufacture of photographic paper 〈88JAP(K)63296042, 92JAP(K)04180059〉, and have been incorporated into the 7-amido side chain of penam and cepham antibiotics 〈90AP(323)605, 90AF790, 90AF1246, 91AP(324)449〉.

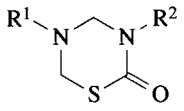
Inclusion of 1,2-bis(1,3,5-thiadiazin-3-yl)- and 1,2-bis(1,3,5-thiadiazin-5-yl)-ethanes is reported to improve the stability of thermal recording materials 〈86JAP(K)61202885〉. 3,5-Dialkyl-5,6-dihydro-2*H*-1,3,5-thiadiazine-4(3*H*)-thiones (**251**) have been used as rubber antiozonants 〈88EUP278890〉.



(**251**)

3,5-Dialkyl-5,6-dihydro-4*H*-1,3,5-thiadiazin-2(3*H*)-ones (**252**) in combination with polyethylenepolyamines have been employed as corrosion inhibitors for metals 〈82JAP(K)5779181〉, and 5-benzyl-3-(β-hydroxyethyl)-5,6-dihydro-4*H*-1,3,5-thiadiazin-2(3*H*)-one (**252**; $R^1 = PhCH_2$, R = CH_2CH_2OH) is effective at low concentration for the control of dandruff 〈81GEP3022799〉. 2,4,6-Trimethylperhydro-1,3,5-thiadiazine, along with other related heterocycles (e.g. dithiazines) has

been detected as a volatile component in dried roast squid, and probably arises by combination *in situ* of ethanal with hydrogen sulfide and ammonia ⟨91MI 618-03⟩.



(252)

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6.19
Dioxazines, Oxathiazines, and Dithiazines

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University of St. Andrews, UK

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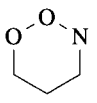
6.19.1 INTRODUCTION

This chapter covers those systems containing one nitrogen and two other heteroatoms which may be either oxygen or sulfur. In spite of these fairly narrow limits, there are still 22 different parent ring systems that fall into this category, six each for the dioxazines and dithiazines as well as 10 oxathiazines. Of these, 18 are known, to some extent at least, the four systems which appear unknown being the 1,2,3-dioxazines (**1**) and the 1,2,6-, 1,3,2- and 1,3,4-oxathiazines (**2**)–(**4**). A good tabular survey of the known systems was presented in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(3)1039⟩. Indeed, the current chapter serves the purpose, as far as possible, of updating and expanding the coverage of these heterocyclic rings from work published since that edition, avoiding duplication of this material.



[1,2,3]

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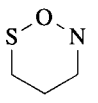

[1,2,6]

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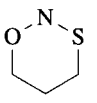

[1,3,2,]

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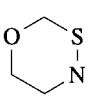
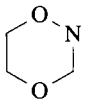


[1,3,4]

(4)

Evidently, given the number and variety of heterocycles that are described by the title of this chapter, an exhaustive treatment of each system individually is not practicable here. Therefore we present a comparative assessment of the various ring systems, with particular attention being paid to the trends and differences (where they are known) in properties, structure and reactivity, as well as in synthetic methodology. The coverage is necessarily biased toward those systems which have

been given the most attention in the literature. These most common systems are the 1,4,2-dioxazines (**5**), the 1,2,3- (**6**), 1,3,5- (**7**) and 1,4,3-oxathiazines (**8**) and, in addition, the 1,3,5- (**9**) and 1,4,2-dithiazines (**10**) ⟨84CHEC-I(3)1039⟩.



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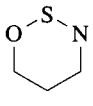

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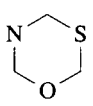

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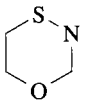

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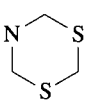

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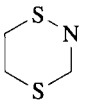
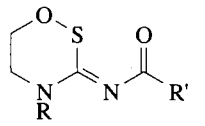


(10)

6.19.2 THEORETICAL METHODS

Despite their increasing use, theoretical calculations have not been widely carried out on dioxazines, oxathiazines or dithiazines. Extended Hückel MO theory explained the short (1.84–2.68 Å) nonbonded S···O interaction found in 3-(acylimino)-1,2,4-oxathiazines (**11**). The calculations indicated coupling between the O lone-pair to the S atom of an adjacent molecule by way of the O—S antibonding orbital ⟨84JCS(P2)191, 86MI 619-01⟩. AM1-MO calculations predict the stabilization of cationic and radical intermediates derived from 1,4,2-dioxazines (**12b, d**) via delocalization and accommodation of positive charge or the unpaired electron ⟨91MI 619-01⟩. The mechanisms by which these occur are conjugation, hyperconjugation and field effects. The same study noted that the corresponding carbanions are less planar but nevertheless can still achieve stabilization through delocalization. Molecular mechanics calculations have been used to ascertain the minimum energy conformations of the 1,3,5-dithiazines (**13a, b**). In both cases the chair was the favored conformation with the *N*-substituent in the axial position, even when this was a bulky *t*-butyl group ⟨93PS(81)111⟩.



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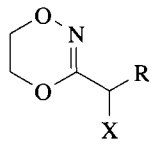
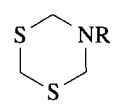


(12) **a** R = Me; X = H
b R = Me; X = Br
c R = Ph; X = H
d R = Ph; X = Br



(13) **a** R = Me; **b** R = *t*-Bu; **c** R = *i*-Pr

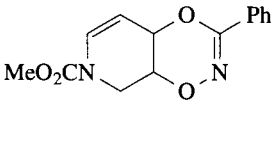
6.19.3 EXPERIMENTAL STRUCTURAL METHODS

6.19.3.1 X-ray Crystallography

Many of the systems falling within this chapter have been studied by x-ray diffraction techniques, primarily as a means for determination or confirmation of the structure. In general the results are unexceptional, with bond angles and lengths possessing typical values for each particular unit ⟨87JCS(P2)S1⟩. Some useful information on conformation in the solid state has emerged and some important examples are presented below.

The bicyclic dioxazine (**14**) with a *cis* ring junction has its dioxazine ring in a half chair form with the phenyl ring coplanar with the O—C=N plane ⟨85AX(C)456⟩. Compound (**15**) exists in a chair conformation where the ethyl and *p*-nitrophenyl substituents adopt equatorial positions ⟨89AX(C)1655⟩. The intramolecular distance between the carbonyl oxygen and the ring sulfur atom in (**16**) is 2.24 Å (i.e. less than the sum of the van der Waals' radii) due to σ-interactions between the O *p*- and the S *p*- and *d*-orbitals ⟨84JCS(P2)191⟩. This is in good agreement with theoretical calculations on such systems (see Section 6.19.2). The oxathiazinone (**17**) exists in a half chair arrangement with the sulfone group above the plane of the ring. Interestingly, the system exists solely in a hydrogen bonded amide form (**17a**) when crystallized from chloroform, but exclusively in the imino form (**17b**) when it is crystallized in the presence of Ph_3PO. This is because a very strong hydrogen bond is formed between the hydroxyl proton of (**17b**) and the oxygen in Ph_3PO

⟨86JOC5405⟩. The oxathiazine ring in (**18**) is in a half chair conformation ⟨85AX(C)1084⟩ and the novel system (**19**) is similarly arranged ⟨85TL2131⟩. The boat form is found in (**20**) where all substituents are pseudoequatorial. Notably the S—N bond is longer (1.709 Å) than is normal in a C=N—SR unit, indicating essentially single bond character ⟨92CC478⟩.



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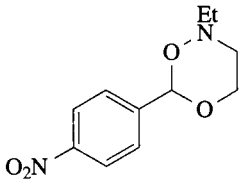

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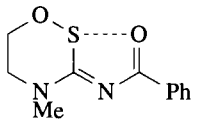

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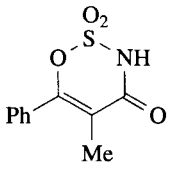
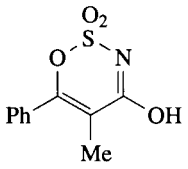


(17a)



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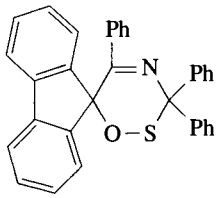

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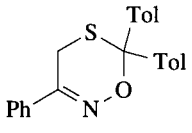

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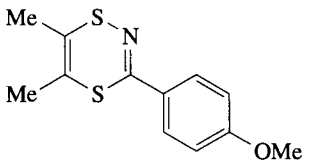
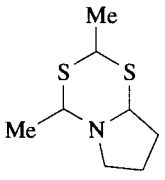


(20)

Dithiazines (**21**) and (**22**) have chair arrangements in the solid state. In (**21**) the methyl groups adopt equatorial positions and the bridgehead *N*-substituent is axial ⟨91MI 619-02⟩; likewise, (**13a**) has an axial *N*-substituent ⟨93PS(81)111⟩ and this is in good agreement with MO calculations for this system (see Section 6.19.2).



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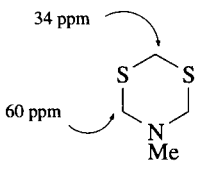
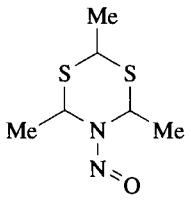


(13a)



(22)

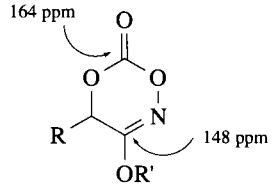
6.19.3.2 NMR Spectroscopy

^{1}H and ^{13}C NMR have been extensively employed in the characterization of most, if not all, the heterocycles covered by this chapter. However, ^{15}N and the quadrupolar ^{14}N, ^{17}O and ^{33}S nuclei have scarcely been investigated for these compounds. In the last case the lines are generally extremely broad and consequently often not observable, owing to quadrupolar interactions. In the main the

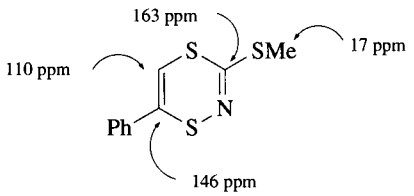
data are much as would be expected for nonaromatic sp^2 and sp^3 carbon atoms and their associated hydrogens, and the same holds true for the chemical shifts of the ring substituents.

More usefully, NMR methods have been of great service in the study of tautomerism and conformation of various rings in the solution phase (see Section 6.19.4 for consideration of the results). The shielding or deshielding effect of a nitrogen lone pair causes a difference in chemical shift between the axial and equatorial positions (Δ_{ae}) of a group in the α-position ⟨84AHC(36)1⟩. Kinetic parameters such as the energy barriers for nitrogen inversion, ring flip and side group rotation have also been measured using variable temperature dynamic NMR methods which, along with nuclear Overhauser effect (nOe) experiments, have proven to be invaluable tools for conformational analysis. The barrier to rotation about the N—N bond in (**22**) was found to be unusually low (17.2 kcal mol^{-1}) because of steric crowding and the electronegativity of the two sulfur atoms ⟨81T4143⟩.

The methylene protons of (**13a**) have chemical shift values of 4.05 (H-2) and 4.39 (H-4 and H-6) ⟨93PS(81)111⟩ and those of (**23a**) resonate at 4.77 ppm ⟨88AP(321)51⟩. The methine protons in (**24**) resonate at 6.27 ppm; the chemical shifts for the carbon atoms are shown beside their structures ⟨81JPR121⟩.



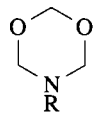
(**23**) **a** R = H; R' = Et
b R = Ph; R' = CH_2Ph



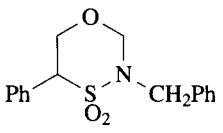
(**24**)

6.19.3.3 Mass Spectrometry

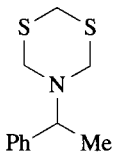
The only systematic study reported in this area which assigns a fragmentation pathway was carried out on the *N*-sulfonyl-1,3,5-dioxazines (**25**) ⟨81OMS(16)495⟩. Two distinct pathways were identified. The first involves loss of the substituent, the second involves initial loss of a hydrogen atom from the ring. The behavior of other rings has received less attention, although many common features such as loss of CO, CO_2, CH_2O, S, SO_2 and other small stable fragments are apparent. Compound (**26**), for example, shows (in addition to the molecular ion) peaks corresponding to [M-SO_2], [M-SO_2-CH_2O] as well as [M-benzyl] ⟨91SL800⟩. Dithiazane (**27**) loses CH_2S, then sulfur, from the molecular ion and this subsequently fragments into aziridinyl and substituted benzyl moieties ⟨94TA633⟩.



(**25**) R = SO_2X
X = alkyl or benzyl



(**26**)

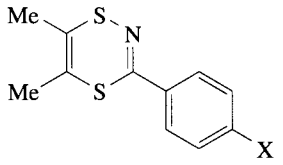


(**27**)

6.19.3.4 UV Spectroscopy

Because the majority of dioxazines, oxathiazines and dithiazines contain no chromophores few accounts of their UV/VIS spectra have appeared. Even in the few instances where the systems are

colored, in the majority of cases no UV/VIS data are given amongst the other spectral properties listed. The orange dithiazines (**28a–d**) have λ_{max} values in the range 382–432 nm depending upon the nature of the aromatic substituent (electron-withdrawing groups produce a red shift) ⟨92CC478⟩.



(**28**) **a** X = MeO, λ_{max} 382 nm
b X = H, λ_{max} 389 nm
c X = Br, λ_{max} 393 nm
d X = NO_2, λ_{max} 432 nm

6.19.3.5 IR Spectroscopy

IR spectroscopy has scarcely ever been employed other than for characterization purposes. As the rings are not fully conjugated the bands observed generally correspond closely with the various functional groups present, i.e. C=O, C=N or SO_2 moieties. Carbonyl stretching frequencies occur in the range 1600–1800 cm^{-1}, depending on whether the C=O forms part of a cyclic carbonate, amide, carbamate, etc., whilst —SO_2— symmetrical stretching frequencies appear in the normal range 1120–1180 cm^{-1}.

6.19.3.6 Photoelectron Spectroscopy and ESR

Neither of these techniques has been much used to study the heterocycles falling within the remit of this chapter. In a rare example, the photoelectron spectrum of (**13a**), in which no bands exhibited any splitting, showed a lowest ionization potential of 8.55 eV (i.e. virtually identical to 1,3,5-trithianes) ⟨89JA6745⟩. The absence of splitting means that the nitrogen lone pair does not interact with those on the sulfur atoms. This constitutes additional evidence that the *N*-methyl group adopts an axial orientation in order to avoid lone pair–lone pair repulsion and possibly allow favorable η_N–$\sigma^*_{C\text{-}S}$ interactions.

6.19.4 THERMODYNAMIC ASPECTS

6.19.4.1 Boiling and Melting Points

The various ring systems reviewed in this chapter exhibit a broad range of physical characteristics, from liquids to high melting solids. General trends exist, as they do for any class of organic compounds. Dithiazines tend to be more volatile and it is perhaps not surprising that many important flavors and aromas contain such compounds (see Section 6.19.11). Molecules that have unsaturation in the ring, and hence are more rigid, tend to be higher melting than the corresponding unsaturated rings. Rigid substituents such as aromatic groups on the ring also increase the melting points whilst bulky, flexible alkyl chains have the opposite effect. In sulfur-containing systems, those with strongly polar —SO_2— units are higher melting than the nonoxidized compounds. Melting or boiling points of a representative sample of each class are presented in Table 1. The solvent used for crystallization or chromatography is included in each case to give the reader an impression of the polarity of each system.

6.19.4.2 Aromaticity

Six-membered rings which contain one nitrogen and two other oxygen and/or sulfur(II) atoms do not have fully delocalized π-systems, and hence are not aromatic. In compounds (e.g. (**36a**)) where the sulfur is in a higher oxidation state it is possible to represent the structure (on paper) by

Table 1 Some physical properties of various dioxa-, oxathia- and dithiazines.

Compound number	*m.p.* (°C)	*or b.p.* (°C) (mmHg)	*Solvent for crystallization/ chromatography*	*Ref.*
(12a)		78(22)	$CHCl_3$–hexane	90CC327
(12b)		75(2)	$CHCl_3$–hexane	90CC327
(12c)		110(1)	$CHCl_3$–hexane	90CC327
(12d)		110(0.01)	$CHCl_3$–hexane	90CC327
(13a)	61		DCM–hexane	93PS(81)111
(13b)	44		DCM–hexane	93PS(81)111
(13c)		120(13)		94TA633
(14)	128		ether	85AX(C)456
(21)	40		ether	91MI 619-02
(23a)	34		DCM–petrol	88AP(321)51
(23b)	106		DCM–petrol	88AP(321)51
(24)	42			81JPR121
(26)	135		cyclohexane	91SL800
(28b)		oil		92CC478
(28d)	128			92CC478
(29a)	30		ether–petrol	82AP(315)802
(29b)	92		ether–petrol	82AP(315)802
(30a)	75		DCM	85TL2131
(30b)	218		DCM	85TL2131
(30c)	125		DCM	85TL2131
(31a)	109		ethanol	88G435
(31b)	160		ethanol	88G435
(32)	259		ether–petrol	85AX(C)1084
(33a)	79		hexane	93H(36)733
(33b)	135		hexane	93H(36)733
(34a)	180		EtOAc–ethanol	83IJC(B)627
(34b)	240		EtOAc–ethanol	83IJC(B)627
(35)	200(d.)		water	90S405
(36a)	143		ethanol	88S521
(36b)	187		ethanol	88S521
(37)	221		hexane–EtOAc	86JCR(S)388

drawing several canonical forms which delocalize 8 π-electrons over the whole ring (Figure 1). Such canonical forms do not imply aromaticity according to Hückel's rule and so the rings systems should not be aromatic. All the evidence agrees with this conclusion. For example, x-ray crystallography has shown that they are not planar (see Section 6.19.3.1). The dithiazines (**28**) reversibly undergo two successive single-electron oxidations, generating the 6-π dication species (**38**) which is formally aromatic. This species coproportionates by electron transfer from the neutral species to form the corresponding radical monocation.

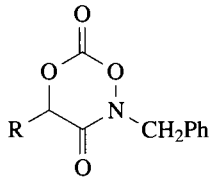
6.19.4.3 Conformation

The conformational equilibria of fully saturated six-membered heterocyclic rings in solution have been extensively investigated, especially through proton and carbon NMR, and comprehensive reviews of this work have been published ⟨B-80MI 619-01, 84AHC(36)1⟩. Details of experimental techniques or measurements will not be considered here, the emphasis being placed on the results obtained. Some of the general features found in the solution conformations of six-membered rings are applicable to the systems covered in this chapter:

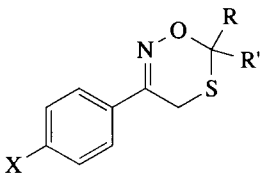
(i) Inclusion of a sulfur atom lowers the barrier to ring inversion on account of the longer C—S bond and smaller C—S—C angle.

(ii) Oxygen-containing rings also have a lower ring inversion barrier than their nitrogen analogues. For the series (**39**) the ring inversion barrier decreases from left to right along the series X = CH_2, NMe, O, S ⟨80JCS(P2)279⟩.

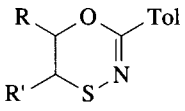
(iii) A sulfoxide group preferentially occupies an axial position.



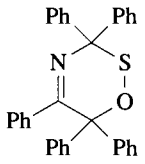
(29)a R = *i*-Pr
b R = Ph



(30) a R = Ph, R' = TMS; X = H
b R = R' = *p*-$NO_2C_6H_4$; X = NO_2



(31) a R = Ph, R' = H
b R = R' = -$(CH_2)_4$-



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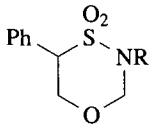
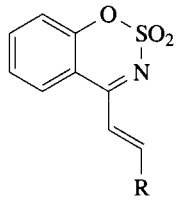
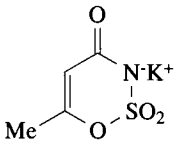


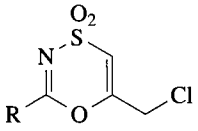
(33) a R = *n*-Bu
b R = CH_2Ph



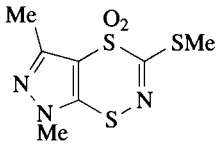
(34) a R = Ph
b R = *p*-ClC_6H_4



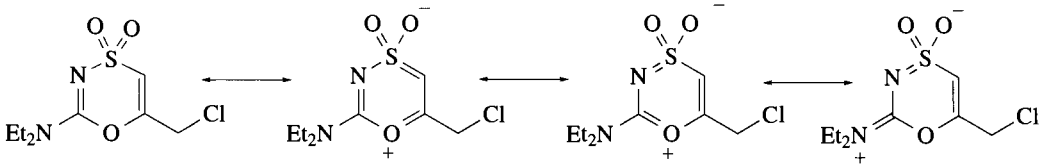
(35)



(36) a R = NEt_2
b R = 4-morpholino

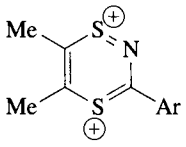


(37)



(36a)

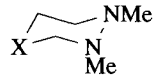
Figure 1 Resonance forms of (**36a**).



(38)

(iv) Systems containing nitrogen can undergo conformational change through ring inversion or umbrella inversion at the nitrogen center. The latter process is usually that of lower energy.

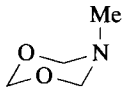
(v) α-Heteroatom substitution on nitrogen raises the barrier to nitrogen inversion whilst β-heteroatom substitution slightly lowers it.



(39)

6.19.4.3.1 Dioxazines

Detailed study of the ^{1}H NMR of (**40**) revealed that the major conformer has the *N*-methyl group axial with $\Delta G‡ = 10.5$ kcal mol^{-1} (at -58°C) for ring inversion ⟨78JCS(P2)377⟩. The fact that no change could be seen in the ^{13}C NMR spectrum over the temperature range $+34$ to -145°C indicated that only this conformer is populated. In (**41a, b**) at low temperature (-82°C) the *N*-substituents prefer the equatorial position ⟨74JCS(P2)1561⟩. It was later established that ring inversion (11.0 kcal mol^{-1}) has a slightly lower energy barrier ⟨78T1415⟩ than nitrogen inversion (11.5 kcal mol^{-1}) and that it is slightly easier (ca. 0.06 kcal mol^{-1}) for an *N*-ethyl group to be axial than an *N*-methyl group. The unusual system (**42**) has a chair conformation with the *N*-hydrogen atom in an equatorial position (as determined by ^{1}H, ^{13}C and ^{15}N NMR) ⟨88KGS396⟩. When C-4 bears a methyl group the molecule adopts a 2,4-diequatorial conformation.



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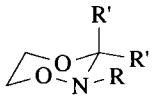
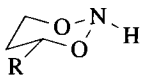


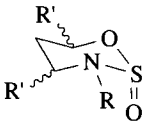
(41)**a** R = Me or Et; R' = H
b R = R' = Me



(42) R = H or Me

6.19.4.3.2 Oxathiazines

Proton NMR revealed that when substituents at C-4 and C-6 are absent (**43**) exists in the chair form with the sulfoxide group axial. When substituents are present at C-4 or C-6 the conformation is dependent upon their orientation relative to the sulfoxide group, which itself remains axial. When substituents are *trans* to the sulfoxide function the chair form is still favored but when they are *cis* either the chair or a twist form (about a 1,4 axis) can exist ⟨79OMR(12)481⟩.

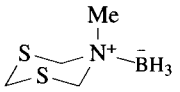


(43) R = Ph; R' = H, Me or *t*-Bu

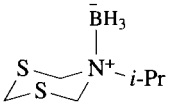
6.19.4.3.3 Dithiazines

Dipole moment and proton NMR data indicate that the predominant conformer of *N*-substituted dithiazines (**13a–c**) is that with the axially oriented substituent, even when it is an unconstrained *t*-butyl group ⟨72JCS(P2)674⟩. This agrees with theoretical predictions (see Section 6.19.2). Ring inversion barriers decrease in these compounds as the size of the *N*-substituent increases. For the borane adducts of some dithiazines the conformational equilibria are strongly biased at room temperature and these were investigated using ^{11}B, ^{13}C and ^{1}H NMR. The adduct (**44**), which has

the borane group in an equatorial position, is chemically quite stable and can be isolated ⟨91T6903, 93CB863⟩, whereas for the adduct (**45**), which is a much less stable compound, the opposite arrangement is found ⟨94TA633⟩.



(**44**)

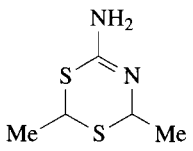


(**45**)

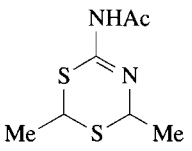
6.19.4.4 Tautomerism

6.19.4.4.1 Prototropic tautomerism

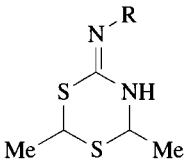
Tautomerism may occur in those systems containing amide or amidine functionality within the ring. In such cases the behavior normally mirrors that of other heterocyclic systems. The dithiazine (**46**) exists in the amino form (i.e. with an endocyclic double bond) ⟨82KGS652, 83KGS333⟩. However, when acylated on nitrogen either tautomer may be favored; depending upon the electron-acceptor properties of the acyl group either the amido form (**47**) or the acylimino tautomer (**48**) predominates ⟨82KGS622⟩. These findings were supported by IR ⟨81KGS1050⟩, UV ⟨82KGS622⟩ and NMR ⟨81KGS485⟩ data.



(**46**)

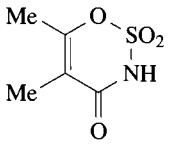


(**47**)



(**48**) R = $COCH_2Cl$, Tos

The 1,2,3-oxathiazin-4-ones offer the possibility of tautomerism. They exist in the amide form with intermolecular hydrogen bonding present ⟨86JOC5405⟩. The addition of Ph_3PO to (**17**) causes the equilibrium to shift in favor of the enol form as a result of very strong hydrogen bonding between the enolic hydrogen and the P=O group. A similar situation exists for (**49**). This compound, when treated with diazomethane, yields a 4.25:1 mixture of *N*- and *O*-methylated products ⟨73AG(E)869⟩.



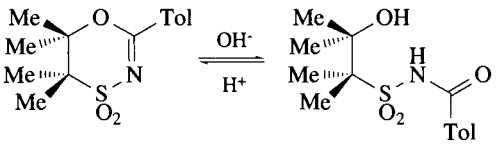
(**49**)

6.19.4.4.2 Ring–chain tautomerism

Ring–chain tautomerism is a common phenomenon in 1,3-oxazines and thiazines, but it appears seldom to have been observed in the systems presently described. An example is seen in the dithiazine (**50**) (Equation (1)) ⟨72BCJ1567⟩. Reversible ring–chain hydrolysis occurs in the oxathiazine system (**51**) (Equation (2)). The equilibrium is pH dependent, with low pH favoring the ring-closed form ⟨88G435⟩.

(1)

(50) R = Ph, 4-ClC_6H_4 or 4-MeC_6H_4; X = SH or NH_2



(2)

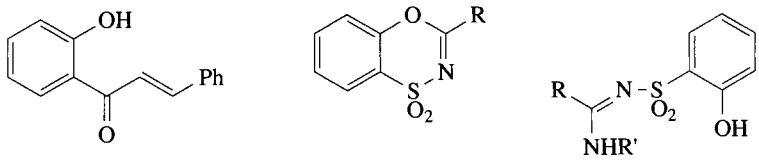
(51)

6.19.5 REACTIVITY OF FULLY CONJUGATED RINGS

The fully conjugated ring systems (those containing no sp^3 hybridized carbon or nitrogen atoms) under consideration are not aromatic and consequently do not exhibit the typical reactions, e.g. electrophilic aromatic substitution, of such rings (see, for example, Chapter 5.02 on pyridines). A simplistic appreciation of the reactivity of a particular ring may be gained by consideration of the functional groups within that system, e.g. rings containing the —$NHSO_2$— unit display typical reactions of sulfonamides. In a similar fashion to the first edition (CHEC-I, chapter 2.28), individual ring systems will not be treated separately and the different reactivity of the various functionalities common within these rings will be presented. Because fully conjugated derivatives of six-membered rings with one nitrogen and two other oxygen and/or sulfur heteroatoms are rare, the reactivity will be classified according to the nature of the species involved (i.e. electrophiles, nucleophiles, etc.). No subdivision according to the site at which reaction occurs (carbon, nitrogen or sulfur) will be made.

6.19.5.1 Reaction with Nucleophiles

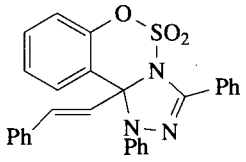
The 1,2,3-benzoxathiazine 2,2-dioxides (**34**) undergo reduction of the C=N bond upon treatment with lithium aluminum hydride ⟨83IJC(B)627⟩. Treatment of (**34a**) with aqueous sodium hydroxide results in degradation (saponification) to the corresponding 2′-hydroxychalcone (**52**). 1,4,3-Benzoxathiazine 4,4-dioxides (**53**) are readily hydrolyzed to the parent *N*-acylsulfonamides ⟨79COC(4)1051⟩ and with amines give the expected *o*-hydroxybenzenesulfonylamines (**54**).



(52) **(53)** **(54)**

6.19.5.2 Cycloaddition Reactions

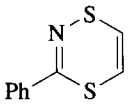
The novel tricyclic system (**55**) was prepared by the 1,3-dipolar cycloaddition of 1,3-diphenylnitrilimine to the C=N double bond of (**34a**) ⟨83IJC(B)627⟩.



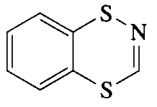
(55)

6.19.5.3 Ring Contraction

Dithiazine (**56**) extrudes sulfur at the 4-position, prolonged heating giving the isothiazole (Equation (3)). The benzo derivative (**57**), however, undergoes an isomerization reaction under similar conditions to give the imine (**58**) (Equation (4)) ⟨83TL3729⟩. The bicyclic system (**59**) also undergoes thermal extrusion of sulfur but under photochemical conditions it fragments into methyl thiocyanate and cyclohexane-1,2-dithione ⟨73ZC431⟩.

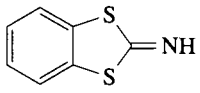


(56)



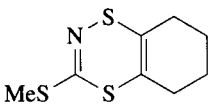
(57)

(3)



(58)

(4)



(59)

6.19.6 REACTIVITY OF NONCONJUGATED RINGS

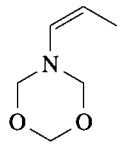
The vast majority of the heterocycles that fall within the brief of this chapter are nonconjugated rings. The reactions of each system are generally governed by the nature of the functional groups contained within the ring.

6.19.6.1 Reactivity at Nitrogen

6.19.6.1.1 Acid–base properties

No detailed study of the acid–base properties of these six-membered heterocycles has been carried out, but the behavior is fairly predictable. Fully reduced systems behave as typical secondary amines

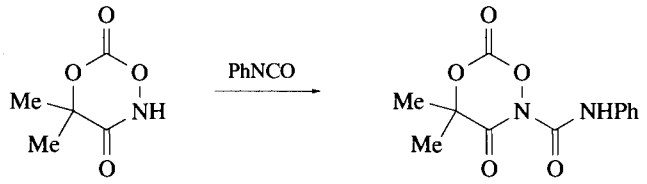
although the inductive effect due to any heteroatoms in α- or β-positions reduces the basicity. In contrast with the much more reactive morpholino and pyrrolidino analogues the *cis* enamine (**60**) shows no tendency towards acid catalyzed isomerization to the *trans* form because of the significantly reduced conjugation between the nitrogen lone pair and the alkenic π-system in the *cis* form, as a result of conformational effects ⟨80JCS(P1)2383⟩.



(**60**)

6.19.6.1.2 Reaction with electrophiles

Surprisingly, this type of reaction has not been well documented, as most systems bearing a nitrogen substituent are prepared via routes in which the substituent is incorporated prior to the cyclization stage. Hence processes such as *N*-acylation are not well described. However, the dioxazine (**61**) reacts readily with phenyl isocyanate to generate the substituted urethane (**62**) (Equation (5)) ⟨88LA35⟩.



(**61**) (**62**) (5)

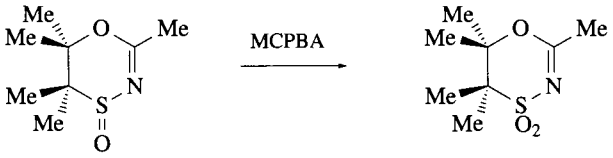
6.19.6.1.3 Reactions with nucleophiles

Predictably, nucleophilic attack on nitrogen is virtually unknown in these systems given that the nitrogen center is a relatively electron-rich one.

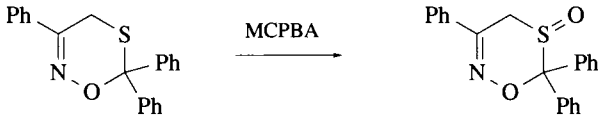
6.19.6.2 Reactivity at Sulfur

6.19.6.2.1 Reaction with electrophiles

The sulfur(II) atom is readily oxidized to sulfoxides and sulfones by treatment with MCPBA, however, there are relatively few reported syntheses of *S*-oxides or *S,S*-dioxides via oxidative methods because compounds containing these groups are generally prepared with the sulfur atom already at the desired level of oxidation. The sulfone (**64**) was obtained through oxidation of the corresponding sulfoxide (**63**) with MCPBA (Equation (6)) ⟨82G469, 88G435⟩. Oxidation of (**65**) using one equivalent of the same reagent afforded the thermally unstable (decomposition above 0 °C) sulfoxide (**66**) (Equation (7)) ⟨85TL2131⟩.



(63) (64) (6)



(65) (66) (7)

There are few examples, besides oxidation, of electrophilic attack at sulfur(II) in these systems.

6.19.6.2.2 Reaction with nucleophiles

Nucleophilic attack at sulfur is not a common process in the nonconjugated heterocycles treated in this chapter. Systems containing a cyclic sulfinate unit are known to undergo hydrolytic ring opening in aqueous base via attack at the sulfur(IV) center ⟨84CHEC-I(6)872⟩. In general, however, the sulfur centers of oxathiazines and dithiazines, even when they are at higher oxidation levels, are not susceptible to nucleophilic attack.

6.19.6.3 Reactivity at Carbon

6.19.6.3.1 Reaction with electrophiles

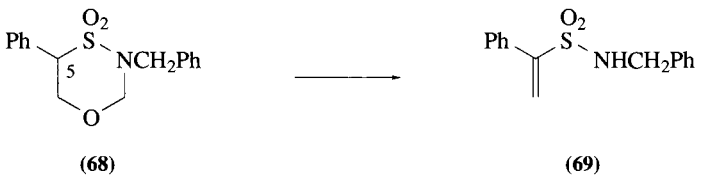
The six-membered rings discussed herein, being nonaromatic, do not participate in the typical reactions of aromatic systems with electrophiles like electrophilic aromatic substitution. In fact direct reaction with electrophilic species is unusual, though this is not altogether unexpected as the carbon centers are in the main electron deficient themselves.

6.19.6.3.2 Reaction with bases

Rings containing hydrogen atoms adjacent to a sulfur atom may be deprotonated with strong bases. 1,3,5-Dithiazanes have long been known to act as umpolung reagents in exactly the same manner as 1,3-dithianes; that is to say they undergo deprotonation then subsequent reaction with an electrophile at the 2-position ⟨89JA6745⟩.

1,4,3-Oxathiazine 4,4-dioxide (**31c**) is deprotonated at position 5 on treatment with sodium hydroxide or potassium *t*-butoxide. The resulting carbanion cannot be isolated but instead undergoes an E_2-like eliminative ring opening (Equation (8)) to give the alkenic sulfonamide (**67**) ⟨88G435⟩. The related system (**68**) is deprotonated, using sodium hydride or *n*-butyllithium, at the same position in the ring, giving, via loss of formaldehyde, the corresponding ethenesulfonamide (**69**) (Equation (9)) ⟨93H(36)733⟩.

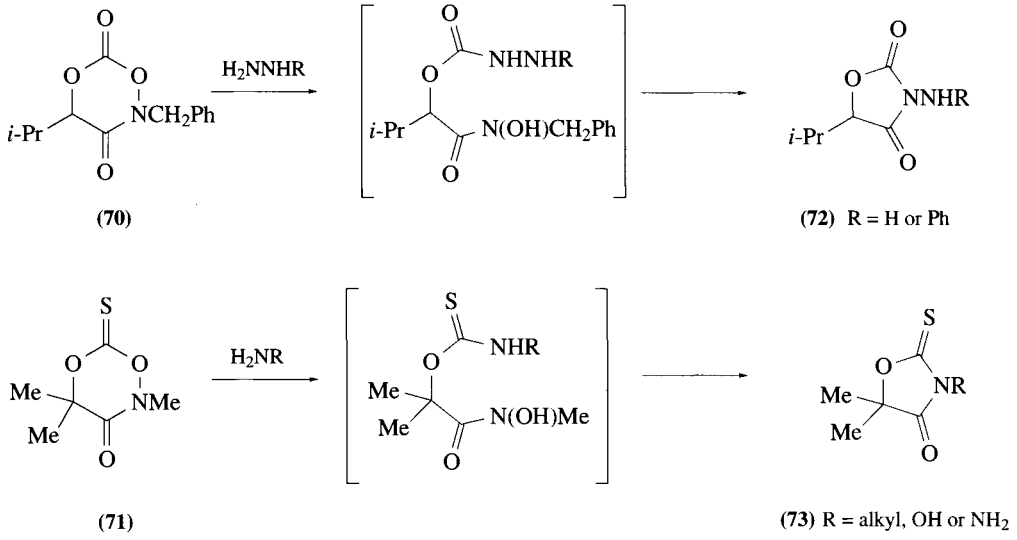
(31c) (67) (8)



(68) (69) (9)

6.19.6.3.3 Reaction with nucleophiles

Nucleophilic attack at a ring carbon is a very common reaction of the various heterocycles covered in this chapter, and usually results in ring opening. The most common sites for attack are carbonyl or imine sp^2 carbons, with the susceptibility of the ring to attack dependent upon the nature of the sp^2 center. Hence it is the carbonate and thiocarbonate type carbons (rather than the amidic carbons) in (**70**) ⟨82AP(315)802⟩ and (**71**) ⟨83ZN(B)1008⟩ respectively that are attacked by amines, resulting in ring opening. In both cases the newly formed open chain secondary amides undergo intramolecular recyclization to yield the corresponding oxazolidines (**72**) and (**73**) with concomitant displacement of the substituted hydroxylamines (Scheme 1).

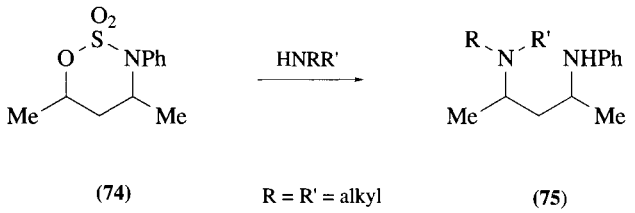


(70) (72) R = H or Ph

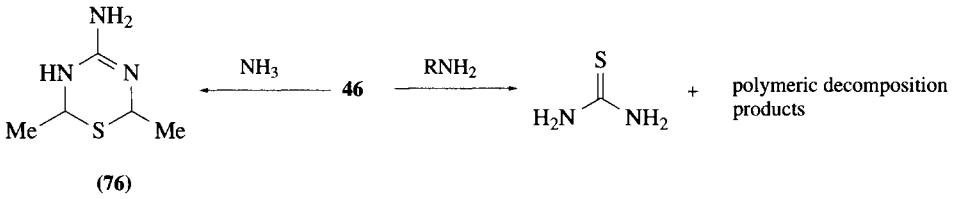
(71) (73) R = alkyl, OH or NH_2

Scheme 1

The 1,2,3-oxathiazine (**74**) is attacked at C-6 by amines resulting in formation of the 1,3-diamines (**75**) (Equation (10)) ⟨85EGP219185⟩. The C=N double bond in (**46**) is attacked by ammonia which results in opening of the ring; reclosure with loss of sulfur gives the thiadiazine system (**76**). If other amines are used instead of ammonia, only thiourea and complex decomposition products are observed (Scheme 2) ⟨82KGS652⟩. Dioxazinone (**77**) is ring-opened through nucleophilic attack at the carbonyl carbon by methanol or benzylamine. This results in the formation of the open-chain carbamate (**78**) or carbonate (**79**), neither of which recyclizes (Scheme 3) ⟨88AP(321)51⟩.

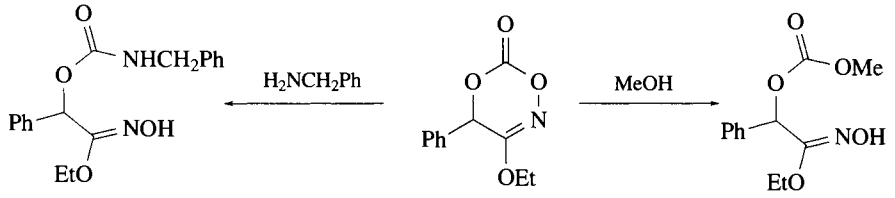


(74) R = R' = alkyl (75) (10)



(76)

Scheme 2



(78) (77) (79)

Scheme 3

6.19.6.4 Cycloaddition Reactions

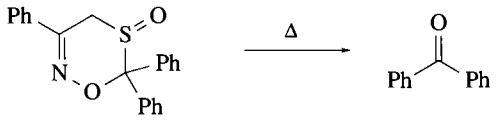
While many of the heterocyclic systems under discussion contain C=O, C=S or C=N double bonds, and these functions are capable of acting directly as, or forming part of, 2π or 4π components in cycloaddition reactions, no examples have been reported.

6.19.6.5 Ring Cleavage and Contraction

Reactions in which the ring is cleaved or fragmented are quite common in these systems and some of them have already been dealt with in Section 6.19.6.3.3 (nucleophilic attack at carbon). Contraction of the ring to form four- or five-membered rings is also fairly common, especially where sulfur or carbon dioxide can be extruded.

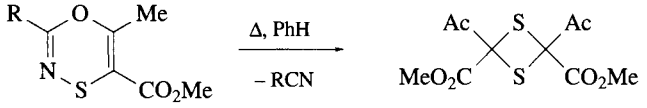
6.19.6.5.1 Thermal reactions

As mentioned in Section 6.19.6.2.1, *S*-oxidation of the 1,5,2-oxathiazine system (**65**) yields (**66**), which thermally decomposes above 0 °C to give, amongst other unidentified products, benzophenone (Equation (11)) ⟨85TL2131⟩. The 1,4,3-oxathiazine (**80**) eliminates *p*-methoxybenzonitrile upon heating at 80 °C to give the dithietane (**81**) derived from methyl α-thioxoacetoacetate (Equation (12)) ⟨90JCR(S)343⟩.



(11)

(66)

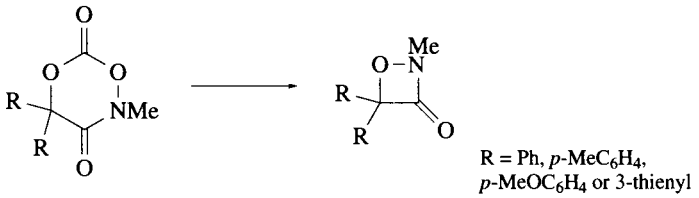


(12)

(80) (81)

6.19.6.5.2 Ring contraction

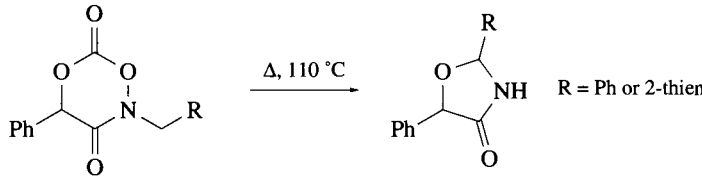
The 1,3,4-dioxazine-2,5-diones (**82**) thermally extrude CO_2 at temperatures above 110°C ⟨82CZ442⟩, or in the presence of molecular sieves at room temperature ⟨86LA1478⟩, to furnish the 1,2-oxazetidin-3-ones (**83**) (Equation (13)). In contrast, the closely related system (**84**) when heated loses CO_2 but forms the oxazolidinone (**85**) (Equation (14)) ⟨83ZN(B)531⟩ and not the four-membered ring.



R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$ or 3-thienyl

(13)

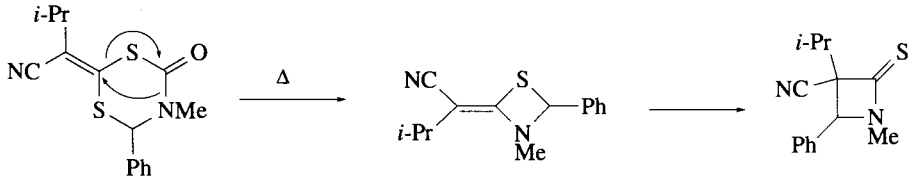
(82) (83)



(14)

(84) (85)

Dithiazine (**86**) gives the β-thiolactam (**87**) after concerted thermal elimination of carbon oxysulfide followed by further rearrangement of the ensuing 1,3-thiazetidine (Scheme 4) ⟨84CB2205⟩.

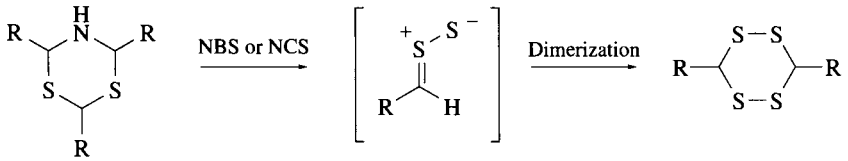


(86) (87)

Scheme 4

6.19.6.5.3 Ring cleavage

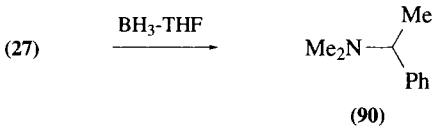
Many of the reactions which result in ring cleavage have been described in Section 6.19.6.3.3. This section is reserved for those reactions which do not involve nucleophilic attack at a ring carbon. The 1,3,5-dithiazine (**88**) is cleaved by *N*-bromo- or *N*-chlorosuccinimide to produce the reactive thial *S*-sulfide species which dimerizes to the tetrathiane (**89**) (Scheme 5) ⟨88CL1517⟩. Compound (**27**) is reductively cleaved by borane, giving the tertiary amine (**90**) in good yield (Equation (15)) ⟨94TA633⟩.



(88) (89)

R = Me, Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$

Scheme 5



(15)

6.19.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

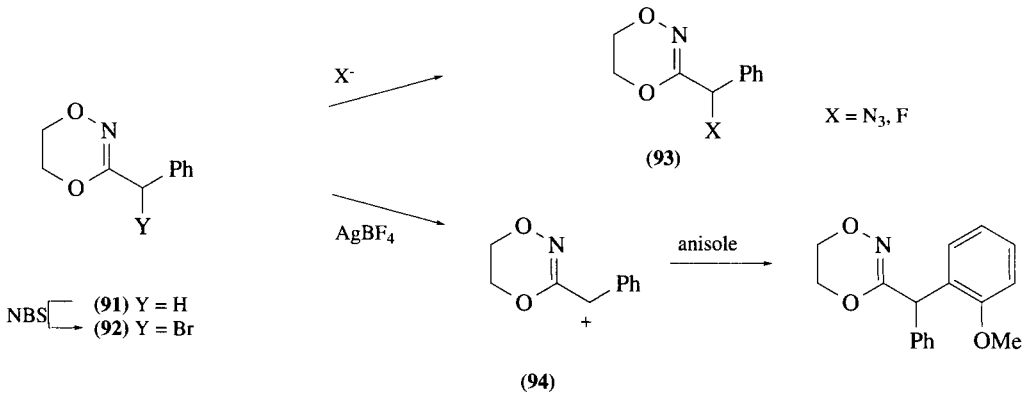
Substituents of dioxazines, oxathiazines or dithiazines are generally close to, or attached to, a heteroatom. Consequently the reactivity of any substituents is influenced by the adjacent heteroatoms. For example, halogens bonded to a carbon α to a heteroatom are readily displaced. The substituent reactivity is usually predictable on the basis of the chemistry of the functional groups of which they are comprised.

6.19.7.1 Fused Benzene Rings

Because the heterocyclic systems are not aromatic, it is appropriate to consider them as substituents on the fused benzene ring. The reactivity of the benzene ring is predictable, as being a consequence of the electron-releasing or -withdrawing properties of the substituents which go to form the heterocyclic moiety.

6.19.7.2 C-linked Substituents

The halogen atom in the chloromethyl substituent of (**36**) is easily displaced by nitrogen and sulfur nucleophiles ⟨88S521⟩. The methylene group in the side chain of (**91**) undergoes radical bromination to form (**92**) ⟨90CC327, 92LA997⟩. The halogen can be displaced by nucleophiles to produce the substituted derivatives (**93**) (Scheme 6). In the presence of silver(I) the C—Br bond is heterolytically broken to give the carbocation (**94**) which may then take part in electrophilic aromatic substitution reactions.

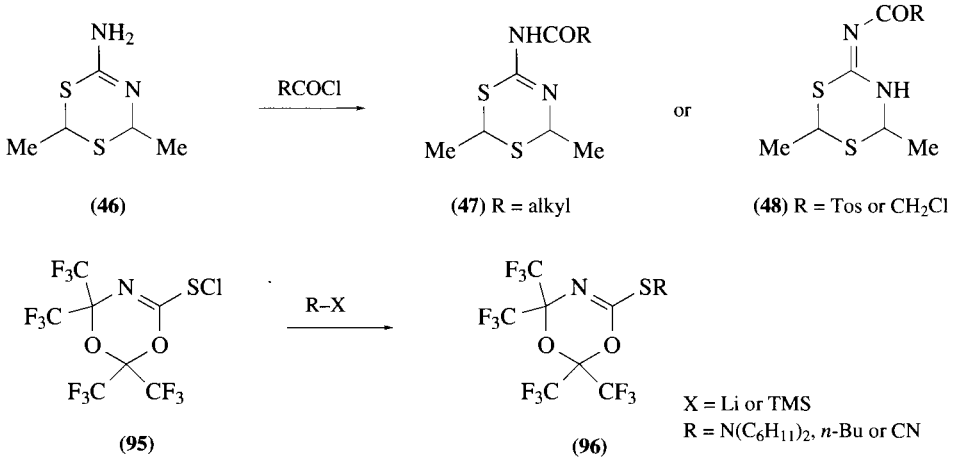


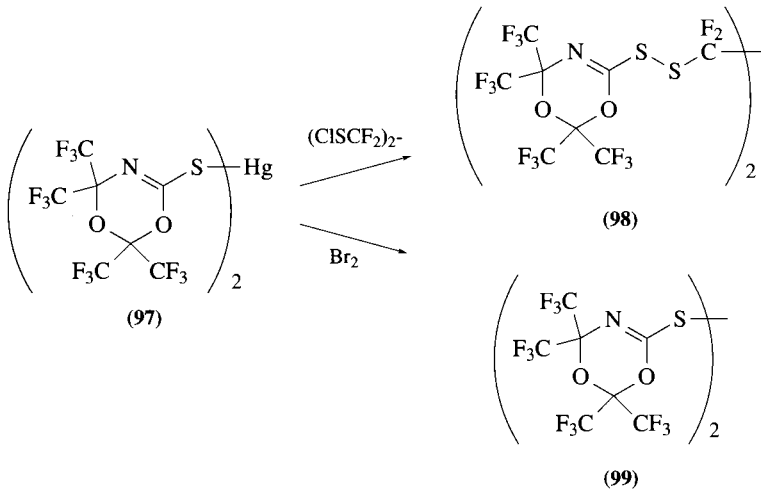
Scheme 6

6.19.7.3 N- and S-linked Substituents

The amino-substituted 1,3,5-dithiazine (**46**) can be acylated on nitrogen quite readily. The tautomeric nature of the product depends upon the electronic characteristics of the acylating agent used (see Section 6.19.4.4.1): electron-withdrawing reagents give the *exo* tautomers (**48**) whilst the *endo* tautomers (**47**) are obtained when less strongly electron-withdrawing agents are used (Equation (16)) ⟨81KGS485, 82KGS622, 83KGS333⟩. The electrophilic sulfur center in the sulfenyl chloride subunit

of 1,3,5-dioxazine (**95**) is attacked by various nucleophiles resulting in formation of the derivatives (**96**) (Equation (17)) ⟨86ZAAC(532)131⟩. The closely related mercury(II) compound (**97**) possesses a nucleophilic sulfur substituent on C-4. This reacts either with electrophilic species giving, for example, (**98**) or dimerizes to (**99**) in the presence of bromine (Scheme 7) ⟨86CB2687⟩.

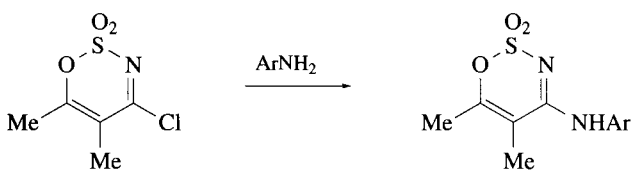


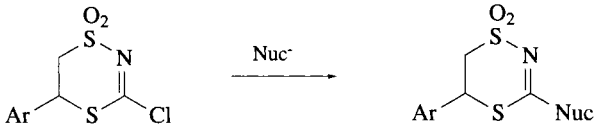


Scheme 7

6.19.7.4 Halogen Substituents

Halogen substituents in these ring systems tend to be susceptible to nucleophilic displacement. The most common arrangement is a chlorine substituent on the carbon of a C=N group, and this behaves like a cyclic imidoyl chloride. Thus, the chlorine atom in (**100**) is displaced by amines (Equation (18)) ⟨73AG(E)869⟩. Similarly (**101**) contains a chlorine reactive towards nucleophilic displacement (Equation (19)) ⟨72BCJ1567⟩.

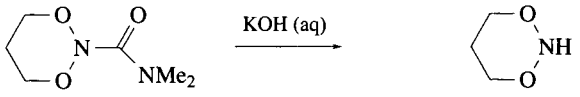




(101) (19)

6.19.8 REACTIVITY OF SUBSTITUENTS ON RING HETEROATOMS

Only nitrogen commonly bears a substituent group in these systems (apart from sulfur in sulfone and sulfoxide groups) and their reactions are not well reported. Substitution on a ring oxygen or sulfur(II) leads to a positively charged species and as such they tend to be transient and short-lived or undergo rearrangement. The *N*-substituent of the 1,3,2-dioxazine (**102**) is removed via alkaline hydrolysis, a typical reaction of ureas (Equation (20)) ⟨85IZV1685, 87IZV1556⟩.



(102) (20)

6.19.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

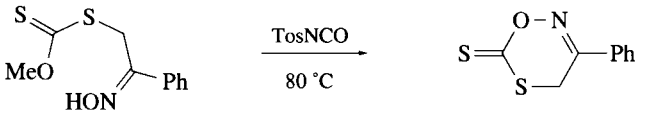
The spectrum of methodologies that have been devised for synthesizing the various dioxazines, oxathiazines and dithiazines is as diverse as the range of ring systems themselves. This chapter covers 22 different parent heterocycles, of which 18 have been prepared by at least one route. Here the synthetic methods are classified according to the size and number of the fragments which when coupled together form the six-membered ring, and according to the nature of the bond or bonds formed during the ring closure. Individual ring systems do not receive individual treatment. For those interested in the preparation of a particular heterocyclic ring the different systems have been arranged in Table 2 along with a reference to a published synthetic procedure for each. The survey of known systems in chapter 2.28 of CHEC-I will also be of use for this purpose. For certain ring systems, notably 1,2,4-dioxa- and dithiazines as well as 1,2,5- and 1,4,2-oxathiazines, there is a distinct lack of preparative methods available.

Table 2 Examples of synthetic routes to dioxa-, oxathia- and dithiazine systems.

Dioxazine	*Oxathiazine*	*Dithiazine*	*Ref.*
1,2,4-			76CC608
1,3,2-			81IZV2539
1,3,5-			82ZN(B)1669
1,4,2-			92LA997
1,5,2-			88AP(321)51
	1,2,3-		90S405
	1,2,4-		85AX(C)1084
	1,2,5-		69IZV2059
	1,3,5-		82CZ303
	1,4,2-		72TL5267
	1,4,3-		90JCR(S)343
	1,5,2-		85TL2131
		1,2,3-	89BSF433
		1,2,4-	63JCS2097
		1,3,2-	83CJC1161
		1,3,5-	91MI 619-02
		1,4,2-	86JCR(S)388
		1,5,2-	84CC1084

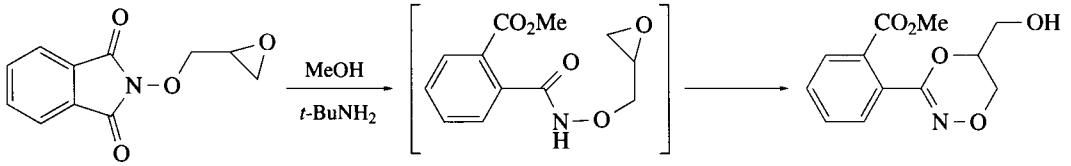
6.19.9.1 Formation of One Bond

The majority of the reactions of this type that lead to the heterocyclic systems discussed in this chapter involve formation of a bond between a carbon and a heteroatom. Intramolecular nucleophilic attack by the oxime oxygen on the dithiocarbonate thiocarbonyl group in (**103**) gives the 1,5,2-oxathiazinethione (**104**) in reasonable yield (Equation (21)) ⟨87S349⟩. The reaction is performed in the presence of tosyl isocyanate in order to remove the methanol formed during cyclization that might otherwise lead to ring cleavage. *N*-Glycidyloxyphthalimide (**105**) affords the phthalamic ester (**106**) upon exposure to methanol and this spontaneously cyclizes to the 1,4,2-dioxazine (**107**) via base-induced nucleophilic attack of the carbonyl oxygen in the hydroxamic ester functionality at C-2 of the epoxide ring (Scheme 8) ⟨82JOC517⟩.



(21)

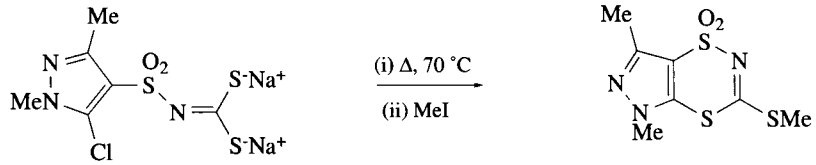
(**103**) (**104**)



(**105**) (**106**) (**107**)

Scheme 8

Intramolecular nucleophilic displacement of chloride occurs readily when the dithiolate species (**108**), obtained from CS_2 and the corresponding sulfonamide, is heated ⟨86JCR(S)388⟩. The resultant monosodium salt was not isolated but alkylated *in situ* to form the pyrazolo-fused 1,4,2-dithiazine derivative (**109**) in good yield (Equation (22)). The action of methylmagnesium iodide on the ester (**110**) produces the expected tertiary alcohol (**111**), and this undergoes cyclization through attack on the C=N bond to give the 1,4,2-dioxazine (**112**) (Scheme 9) ⟨92SC1985⟩. *N*-(Acetoacetyl)sulfamic acid (**113**) takes part in an intramolecular cyclization when treated with SO_3 to form the 1,2,3-oxathiazinone (**114**) ⟨87GEP(O)3527070, 90S405⟩. This is easily converted to its potassium salt, acesulfame K (**35**), with KOH (Scheme 9).



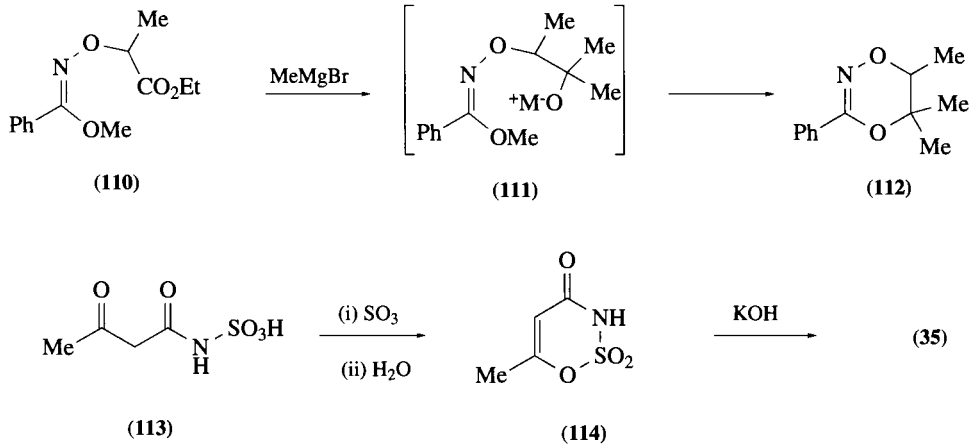
(22)

(**108**) (**109**)

6.19.9.2 Formation of Two Bonds

6.19.9.2.1 From [5 + 1] atom fragments

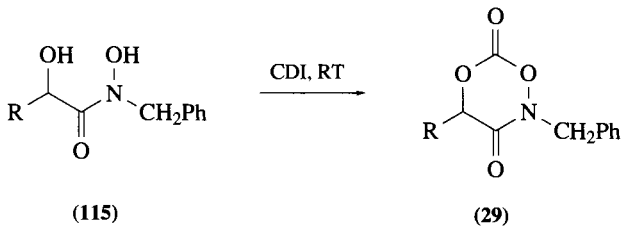
Methods that involve formation of two bonds from [5 + 1] atom fragments are important in the synthesis of dioxa-, oxathia- and dithiazines, and particularly those systems which contain a carbonyl group as part of the ring. The one-atom fragment is most commonly an electrophilic carbon though



Scheme 9

it can also be a nitrogen. When the one-atom fragment contains a C=O group the synthon employed is normally phosgene or carbonyl diimidazole (CDI).

The reaction between CDI and the *N*-alkylhydroxamic acids (**115**) occurs very rapidly (ca. 60 s for complete reaction) to give the 1,5,2-dioxazinones (**29**) (Equation (23)) ⟨80AP(313)377, 82AP(315)802⟩. The related hydroximate esters (**116**) behave in a similar manner, forming 1,5,2-dioxazinones (**117**) when treated with diphosgene (trichloromethyl chloroformate) (Equation (24)) ⟨87AP(320)884, 88AP(321)51⟩. The nucleophilic hydroxyl and nitrogen moieties in the sulfoximine (**118**) react with phosgene to give the 1,4,3-oxathiazinone derivative (**119**) (Equation (25)) ⟨87JOC3435⟩. The five-atom component is easily prepared from the anion of phenyl methyl sulfoximine and the appropriate aldehyde.



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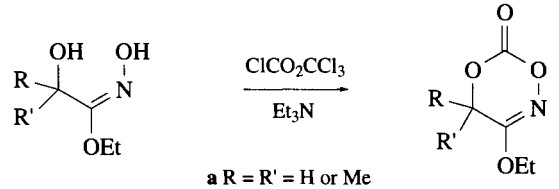

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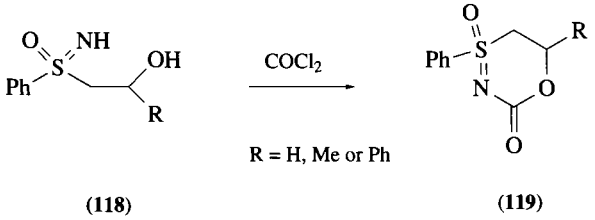
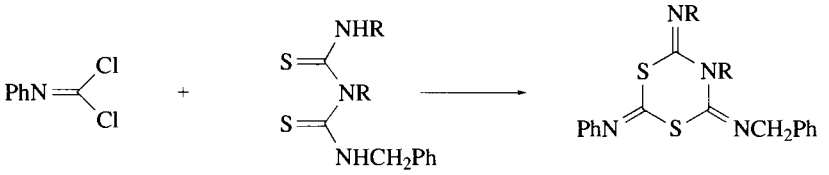


(25)

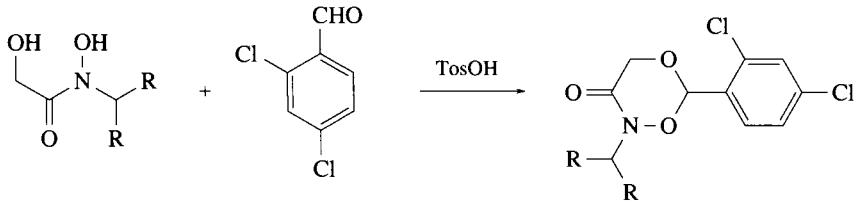
The interaction of phenyl isocyanodichloride (**120**) with 2,4-dithiobiurets (**121**) affords the 2,4,6-triimino-1,3,5-dithiazines (**122**) (Equation (26)) ⟨84JIC149⟩. The hydroxamic acid derivatives (**123**) are capable of forming cyclic acetals with an aldehyde, thus giving rise to the 1,5,2-dioxazinone

systems (**124**) (Equation (27)) ⟨89CZ348⟩. The unusual 1,3,2-dioxazine ring (**127**) was prepared from the 1,3-diol (**126**) and the *N,N*-di(methoxy)amino compound (**125**) though a transketalization-like process (Equation (28)) ⟨81IZV2539⟩. The chemistry of this system, and of related compounds with the O—N—O structural element, has been reviewed ⟨93CRV725⟩.

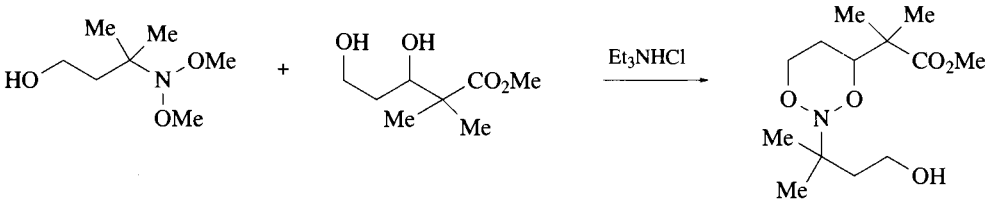


(120) (121) (122) (26)

R = Ph or *m*-ClC_6H_4



(123) (124) (27)

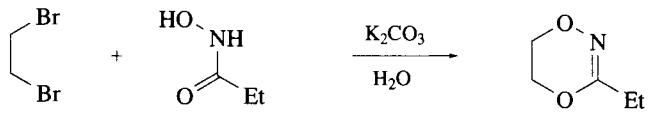


(125) (126) (127) (28)

6.19.9.2.2 From [4 + 2] atom fragments

Condensation and cycloaddition reactions involving [4 + 2] atom fragments are very important processes for the synthesis of six-membered rings. The systems covered by this chapter are no exception to this statement, with by far the majority of synthetic procedures falling into this category. The examples presented herein have been organized according to the nature of the two-atom fragment: C—C, C—N, C—O, C—S and N—S.

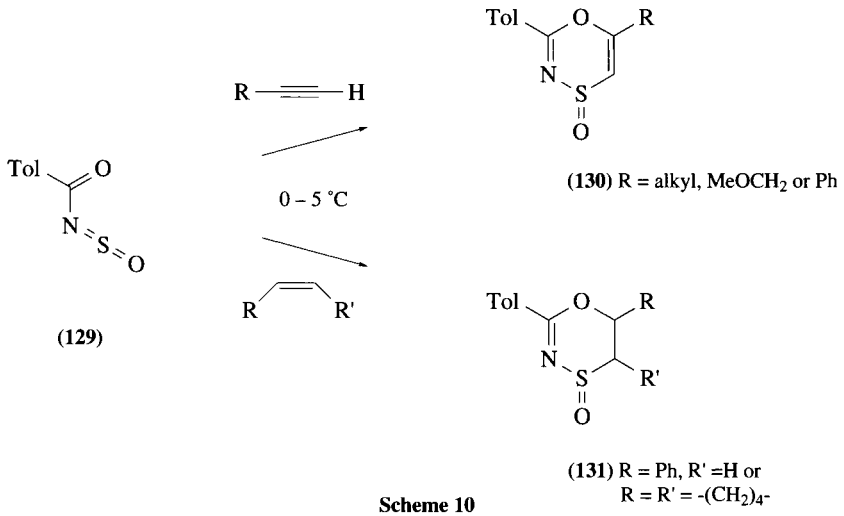
Di-*O*-alkylation of the hydroxamic acids (**128**) with 1,2-dibromoethane furnishes the 1,4,2-dioxazines (**12a**) in good yield (Equation (29)) ⟨90CC327, 92LA997⟩. Alkylation initially takes place on the hydroxyl group before a second deprotonation at the NH group induces alkylation on the carbonyl oxygen.



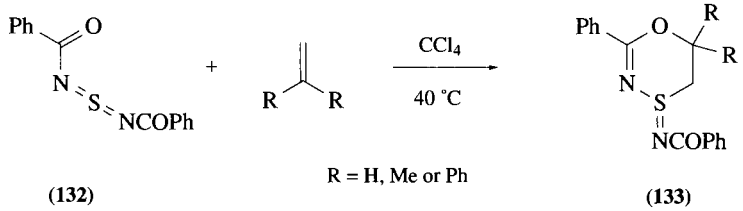
(128) (12a) (29)

N-Sulfinyl-*p*-toluamide (**129**) acts as an OCNS diene unit in the Diels–Alder reaction. When the dienophile is alkynic in nature the products are the fully conjugated 1,4,3-oxathiazine-4-oxides (**130**) ⟨85G265⟩. The reaction works equally well with alkenes as dienophiles to give the dihydro-1,4,3-oxathiazine-4-oxides (**131**) (Scheme 10). The sulfoxide group in (**131**) is readily oxidized with MCPBA to the sulfone, forming (**31a, b**) ⟨88G435⟩. *N,N'*-Dibenzoyl sulfurdiimide (**132**) has also been used as an OCNS diene in [4 + 2] cycloaddition reactions with alkenes ⟨84ZOR519⟩. The reaction

proceeds under mild conditions to give an almost quantitative yield of the 1,4,3-oxathiazine 4-imides (**133**) (Equation (30)).

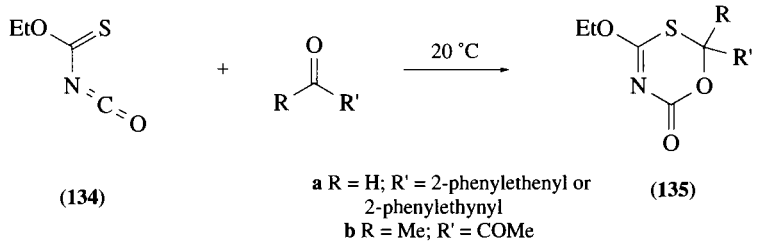


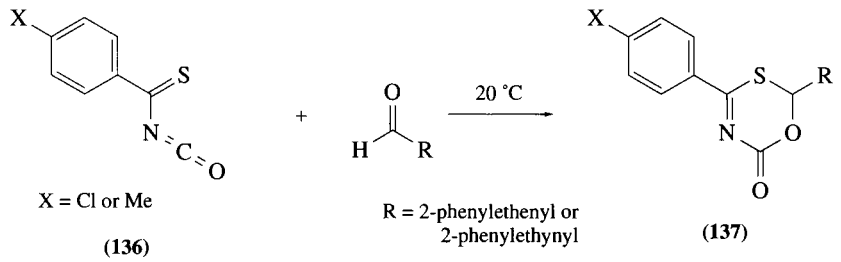
Scheme 10



(30)

The 1,3,5-oxathiazine ring system can be obtained by the [4 + 2] cycloaddition reaction of *N*-(thiocarbonyl)isocyanates with oxygen containing dienophiles. The reaction has been carried out using ethoxythiocarbonyl isocyanate (**134**) with aldehydes and ketones ⟨82CB3063⟩ and also using the substituted thiobenzoyl isocyanates (**136**) with aldehydes ⟨82CZ303⟩. The products ((**135a**, **b**) and (**137**) respectively) are obtained in good yield after reaction at room temperature (Scheme 11).

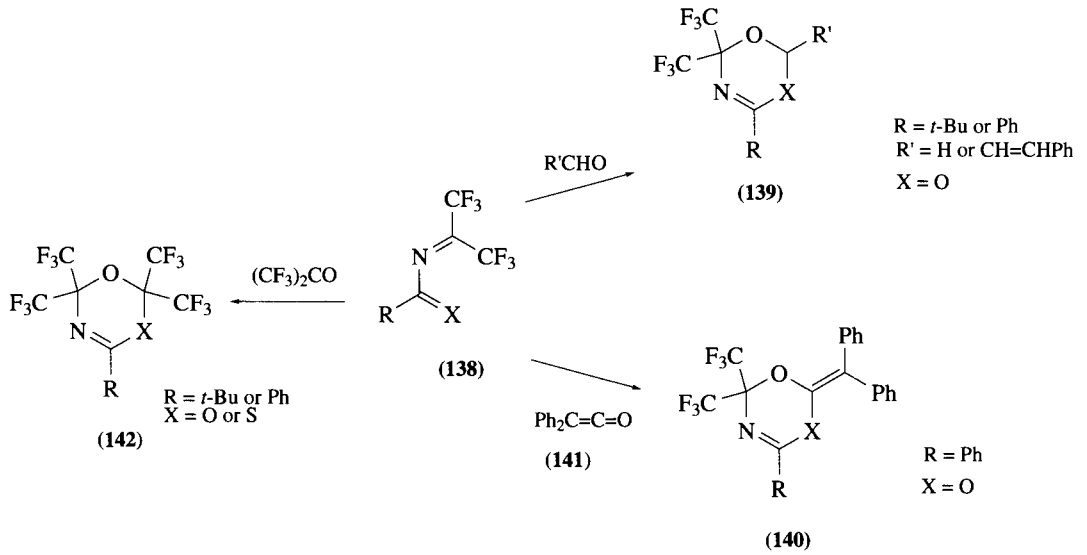




Scheme 11

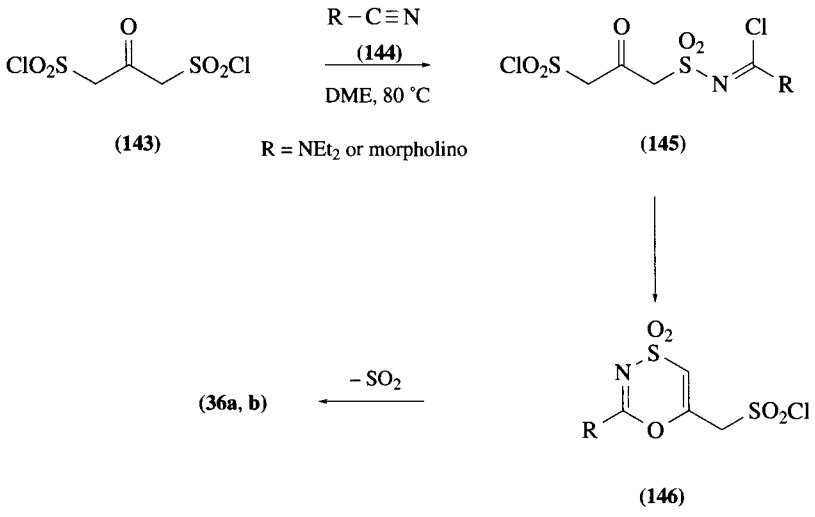
N-Acyl- and *N*-thioacylimino compounds are useful CNCO and CNCS heterodienes in [4 + 2] cycloaddition reactions with carbonyl compounds, which result in the formation of 1,3,5-dioxazines

and -oxathiazines. The hexafluoroisopropylidenimino derivatives (**138**) react either with aldehydes ⟨82ZN(B)1669⟩ or with diphenylketene (**141**) ⟨86CZ83⟩ to yield the 1,3,5-heterosubstituted six-membered rings (**139**) or (**140**), respectively, and with hexafluoroacetone (HFA) to give (**142**) (Scheme 12) ⟨86CZ79⟩.



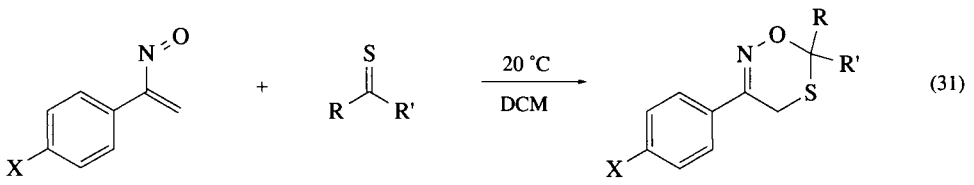
Scheme 12

1,4,3-Oxathiazine 4,4-dioxides (**36a, b**) are prepared in good yield from 1,3-bis(chlorosulfonyl)acetone (**143**) and dialkylcyanamides (**144**) ⟨88S521⟩. The reaction goes through the *N*-sulfonylcarbimidoyl chloride (**145**) which cyclizes with loss of HCl to form the sulfonyl chloride (**146**). This spontaneously expels SO_2 at the temperature of the reaction to give the chloromethyl derivatives (**36a, b**) (Scheme 13).



Scheme 13

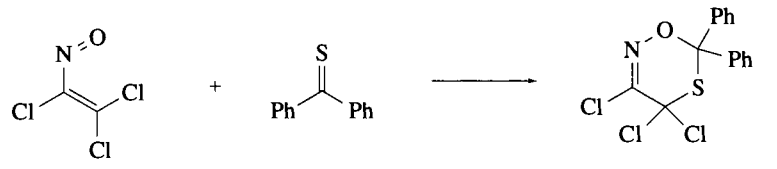
The Diels–Alder reaction of α-nitrosostyrenes (**147**) with various thiocarbonyl compounds (**148**) has provided a high-yielding synthesis of the previously unknown 1,5,2-oxathiazine ring system (**30a–c**) (Equation (31)) ⟨85TL2131, 87JCS(P1)2647⟩. A subsequent synthesis of this ring system employed essentially the same method except that the diene was the nitrosoethylene derivative (**149**) (Equation (32)) ⟨87BSB51⟩. As in the earlier examples, the nitrosoalkene was generated *in situ* by base-induced elimination of HCl from the corresponding α-halo oxime.



(31)

(147) (148)

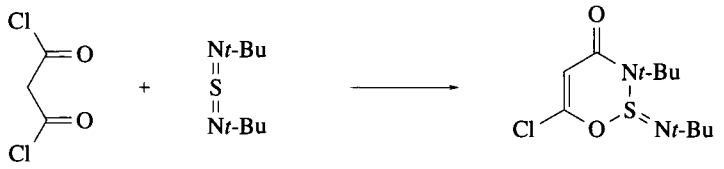
(30) **a** R = Ph; R' = TMS; X = H
b R = R' = *p*-$NO_2C_6H_4$; X = NO_2
c R= R' = SPh; X = H



(32)

(149)

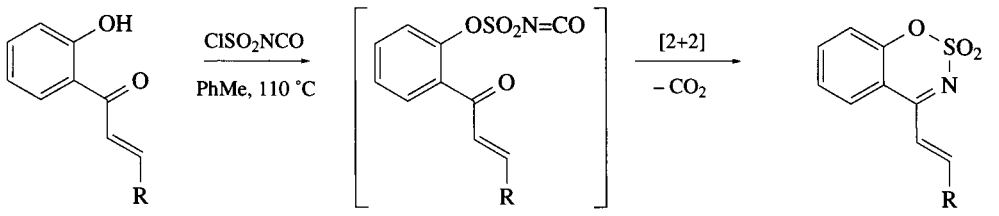
Di-*tert*-butyl sulfurdiimide (**150**), in the presence of base, undergoes a cyclization reaction across one of the S=N bonds with malonyl dichloride ⟨85SUL11⟩. The first stage is nucleophilic attack by one of the diimide nitrogens on a carbonyl group. The intermediate thus formed is deprotonated before cyclization occurs to afford the 1,2,3-oxathiazin-4-one (**151**) in near quantitative yield (Equation (33)).



(33)

(150) (151)

In another synthesis of 1,2,3-oxathiazine derivatives, 2′-hydroxychalcones (**152**) are heated with chlorosulfonyl isocyanate (CSI) to form the intermediate aryloxysulfonyl isocyanates (**153**). This was suggested to undergo a [2 + 2] cycloaddition of the keto carbonyl to the C=N bond forming a 1,3-oxazetidinone which rapidly eliminates CO_2 to give the observed products (**34a, b**) (Scheme 14) ⟨83IJC(B)627⟩.



(152) (153)

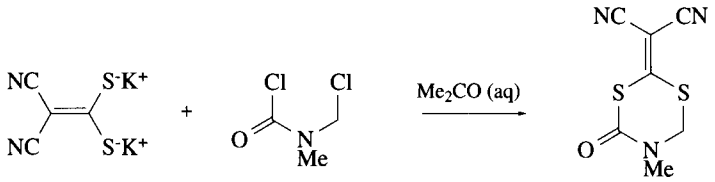
(34) **a** R = Ph
b R = *p*-ClC_6H_4

Scheme 14

6.19.9.2.3 From [3 + 3] atom fragments

Synthetic routes to dioxa-, oxathia- and dithiazines from [3 + 3] atom fragments are little used compared with those using [4 + 2] methods. Nevertheless an example is the reaction between the

ketene dithioacetal derivative (**154**) and the chloroformamide (**155**) ⟨85JAP(K)6004177⟩. This produces the 1,3,5-dithiazinone (**156**) in moderate yield (Equation (34)).



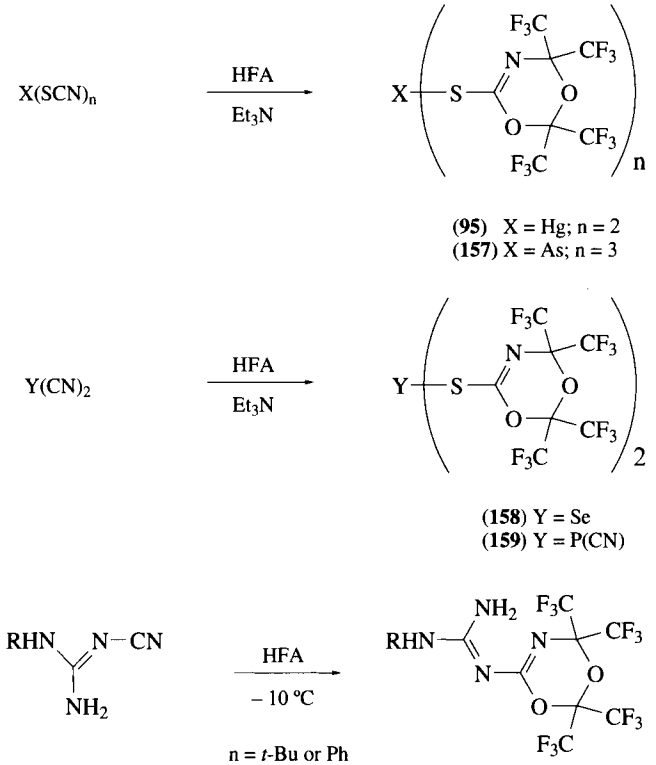
(**154**) (**155**) (**156**) (34)

6.19.9.3 Formation of Three or More Bonds

Synthetic methods involving formation of three or more bonds and leading to six-membered ring systems that contain one nitrogen and two other oxygen and/or sulfur atoms are well known. They are frequently of the [2 + 2 + 2] type though it is also common for formaldehyde and sulfur (in the form of H_2S or SH^-) to act as one-atom fragments.

6.19.9.3.1 From [2 + 2 + 2] atom fragments

1,3,5-Dioxazines ((**95**) and (**157**)–(**160**)) are readily available through the cyclization of two equivalents of HFA with main group cyano or thiocyanato compounds under basic conditions ⟨83PS(18)69, 85CB2396, 86CB2687, 86ZAAC(532)131⟩. The mechanism can be rationalized by attack of the nucleophilic nitrile nitrogen on the carbonyl group of an HFA molecule. A second HFA molecule is then attacked and it is this intermediate which cyclizes to yield the observed products. The analogous process can be carried out using the cyanoguanidines (**161**) (Scheme 15) ⟨89ZOB1397⟩.



(**95**) X = Hg; n = 2
(**157**) X = As; n = 3

(**158**) Y = Se
(**159**) Y = P(CN)

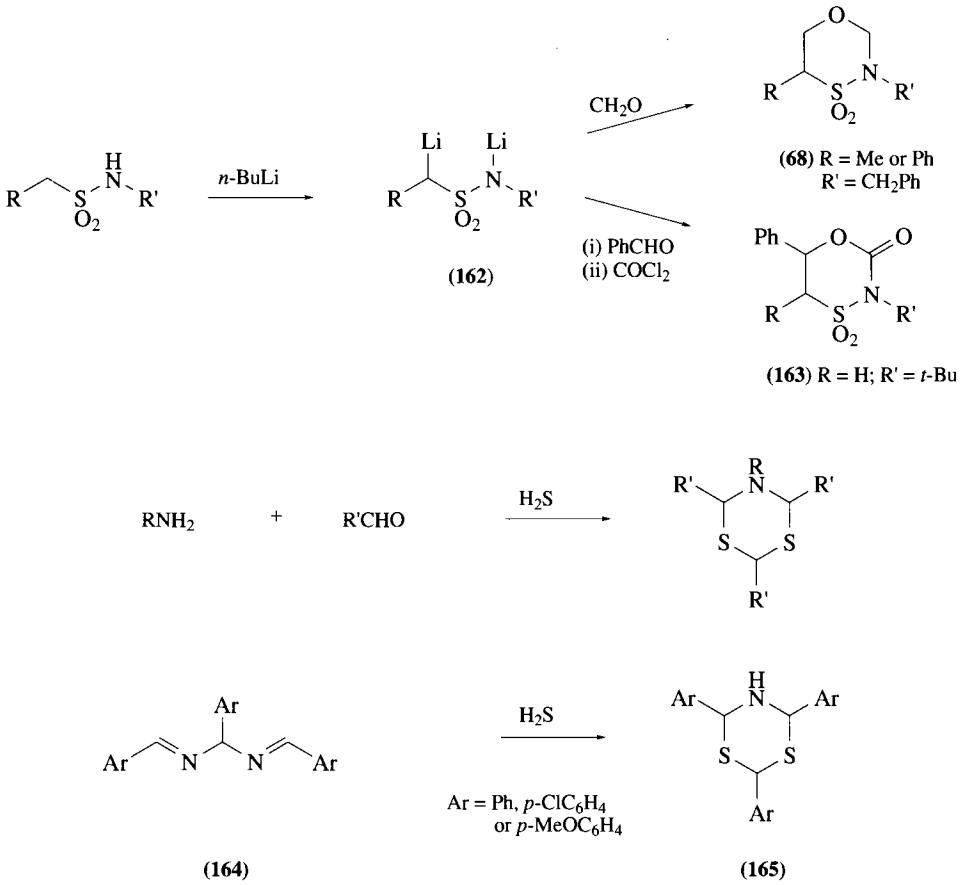
n = *t*-Bu or Ph

(**161**) (**160**)

Scheme 15

6.19.9.3.2 Other reactions

The one-pot dialkylation of alkylsulfonamide α,*N*-dianions (**162**) with (gaseous) formaldehyde or benzaldehyde leads to formation of the 1,4,3-oxathiazine 4,4-dioxides (**68**) ⟨91SL800, 93H(36)733⟩ or (**163**) ⟨88S733⟩ (Scheme 16). The most commonly used method for the preparation of 1,3,5-dithiazines is the reaction of ammonia (or a primary amine) and an aldehyde with H_2S (or SH^-). This has been widely used to make a broad range of 1,3,5-dithiazines (e.g. (**13a–c**), (**21**) and (**27**)) ⟨89JA6745, 91MI 619-02, 93PS(81)111, 94TA633⟩. A variant of this procedure, whereby the amino and aldehydic components have been precondensed, entails the treatment of (**164**) with H_2S ⟨85S92⟩. The corresponding 1,3,5-dithiazines (**165**) are obtained in good yield.



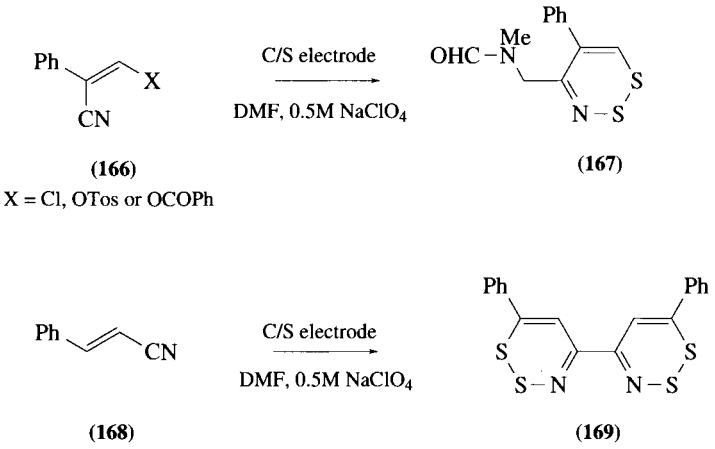
Scheme 16

The rare 1,2,3-dithiazine ring system was prepared by the relatively unusual method of electrochemical synthesis ⟨89BSF433, 90BSF427⟩. The electrolysis is performed using a carbon–sulfur cathode, which acts as a rich source of highly nucleophilic sulfur radical anions. These attack the substrate α,β-unsaturated nitriles (**166**) or (**168**) to give radical intermediates which lead to the 1,2,3-dithiazine products by attack on the solvent (**167**) or by dimerization (**169**) (Scheme 17).

6.19.9.4 Ring Synthesis by Transformation of Another Ring

There are several significant preparative procedures for dioxazines, oxathiazines and diathiazines that are based on transformation of other heterocyclic systems. Most, but not all, involve ring expansion of five- or, less frequently, four-membered systems. The synthetic methods employed in the preparation of the precursor heterocycles are not covered in this section as they are dealt with in the appropriate chapters elsewhere in this edition.

Oxazolidine *N*-oxides (**170**) with an aryl group at the 2-position rearrange thermally to give the



(166)
X = Cl, OTos or OCOPh

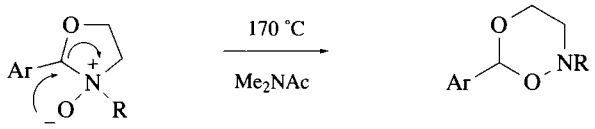
(167)

(168)

(169)

Scheme 17

corresponding 1,5,2-dioxazines (**171**) in good yield (Equation (35)) ⟨90S921⟩. The addition of a carbene to the sulfur atom of oxathiazolone (**172**) forms the sulfonium ylide (**173**). This intermediate is then presumed to suffer thermal elimination of CO_2 before ring closure occurs to give the 1,4,3-oxathiazine (**80**) (Scheme 18) ⟨90JCR(S)343⟩.

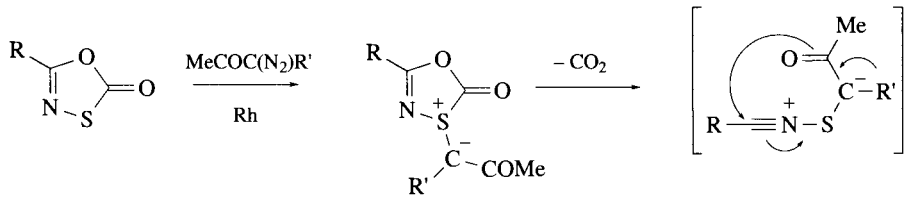


(35)

(170)

R = Me or Et
Ar = Ph or *p*-MeC_6H_4

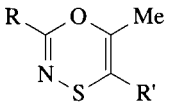
(171)



(172)

(173)

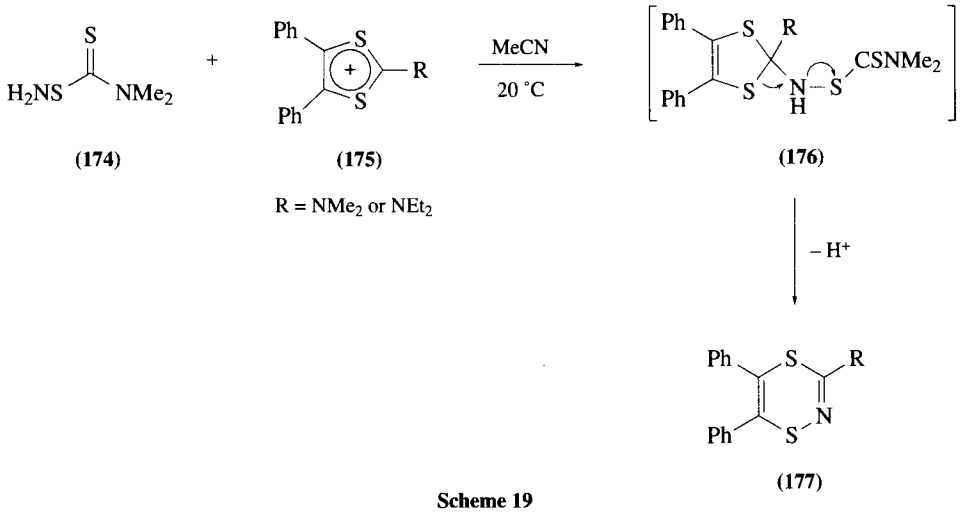
R = *p*-$MeOC_6H_4$
R' = CO_2Me



Scheme 18

(80)

The susceptibility of 1,3-dithiolium cations to nucleophilic attack at C-2 has been exploited in the development of a useful route to 1,4,2-dithiazines where amino compounds are used as nucleophiles. The adducts (**176**), formed by the action of the dithiocarbamate derivative (**174**) on dithiolium rings (**175**), readily experience ring expansion (a sulfur *C* to *N* bond migration with concomitant displacement of the dithiocarbamate) at ambient temperature to afford the 1,4,2-dithiazines (**177**) (Scheme 19) ⟨88BCJ2232⟩. An almost identical process, using NH_3/I_2 as the nucleophilic species, has been used to make the 1,4,2-dithiazines (**28a–d**); the same mechanism is thought to be involved ⟨92CC478⟩.

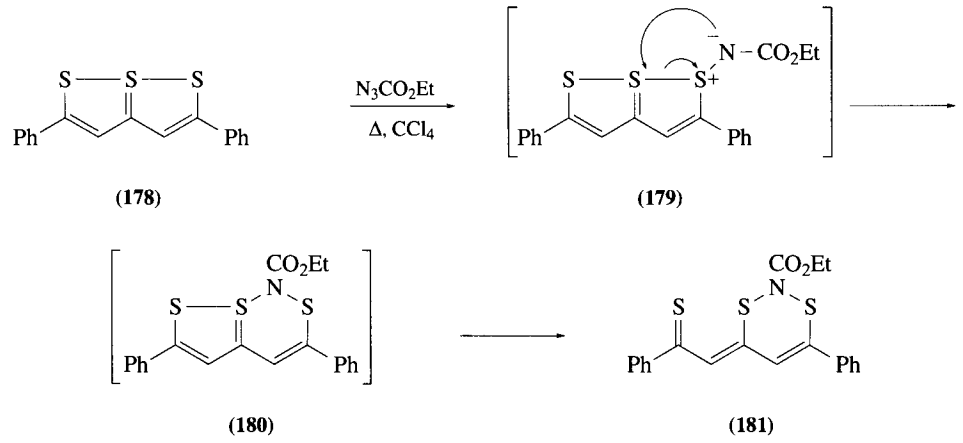


(174) (175) (176) (177)

R = NMe_2 or NEt_2

Scheme 19

The 1,6,6a-λ^4-trithiapentalene system (**178**) reacts with ethoxycarbonyl-nitrene to give, after ring expansion, the little-known 1,3,2-dithiazine derivative (**181**) (Scheme 20) ⟨83CJC1161⟩. The mechanism is believed to proceed by attack of the nitrene at the nucleophilic S_1 position to give intermediate (**179**) which then is subject to insertion of the nitrogen into the S_1—S_{6a} bond. The final product is obtained after cleavage of the S_6—S_{6a} bond in (**180**).



(178) (179) (180) (181)

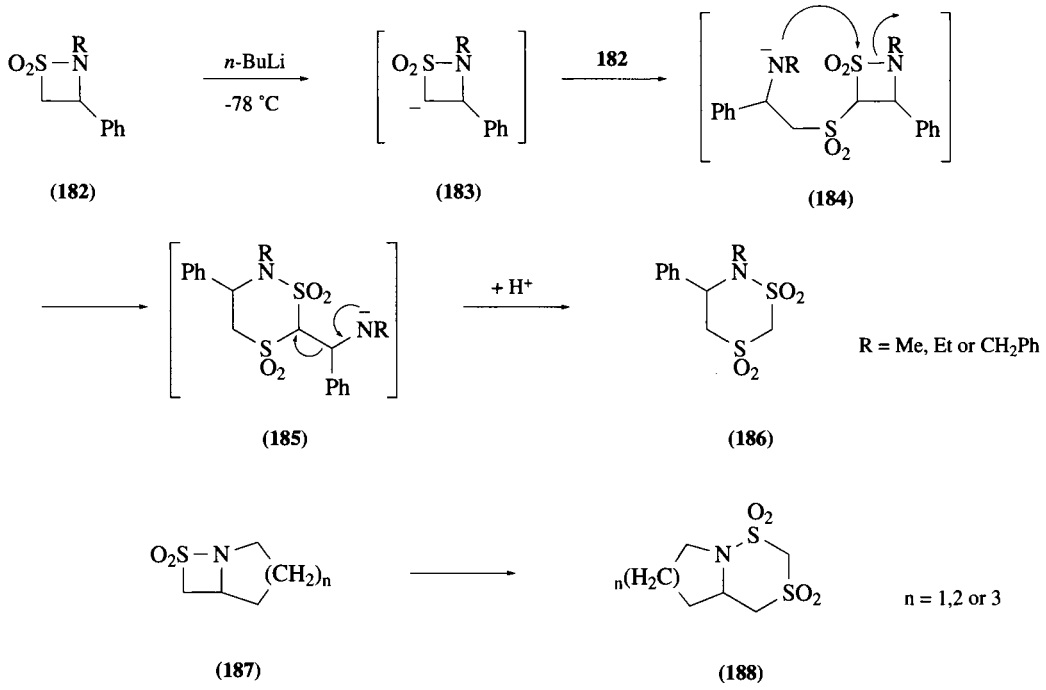
Scheme 20

The 1,2-thiazetidine (**182**) gives the 1,5,2-dithiazine 1,1,5,5-tetroxide (**186**) upon treatment with strong base (Scheme 21) ⟨84CC1084⟩. The formation of (**186**), which at first sight seems rather unexpected, can be rationalized through reaction of the α-sulfonyl carbanion (**183**) with a second molecule of (**182**) to give initially (**184**) and then the 1,5,2-dithiazine (**185**). Elimination of the *N*-alkyl benzylideneimine gives the final product. Similarly the bicyclic derivatives (**187**) give (**188**) ⟨89AP(322)17⟩.

The thermal elimination of SO_3 from 1,3,2,4,5-dioxadithiazine 2,2,4,4-tetroxides (**189**) occurs very readily at 0 °C, generating the *N*-sulfonylamides (**190**). These then act as SNCO heterodienes in [4 + 2] cycloaddition reactions with alkynes ⟨88ZOR1978⟩ and alkenes ⟨85TL5689⟩, to give either the fully unsaturated oxathiazines (**191**) or the dihydro systems (**192**) (Scheme 22). Some of the products resulting from [2 + 2] cycloaddition (across the S=N bond) were observed in each case.

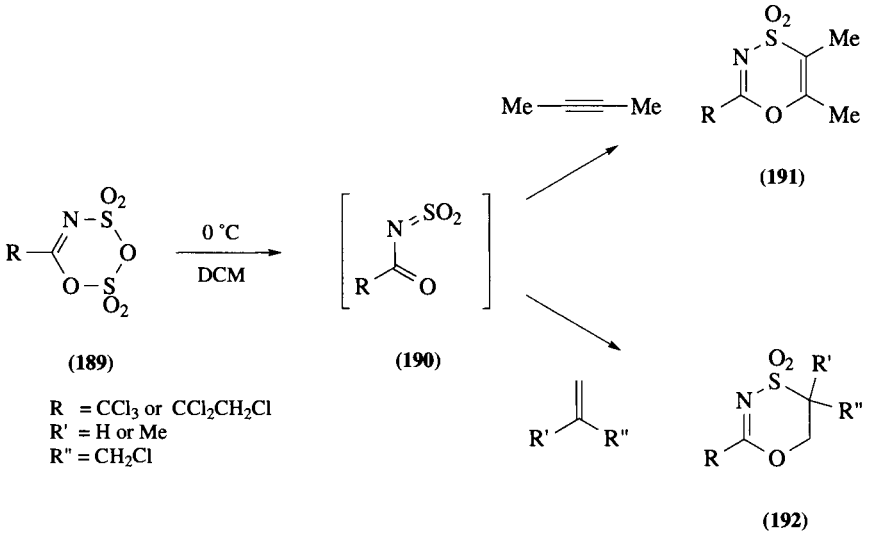
6.19.10 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUND, AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

A list giving examples of preparative methods for each individual system covered by this chapter has been presented in Table 2 and this may be augmented by the tabular survey of known systems



(182) (183) (184) (185) (186) (187) (188)

Scheme 21



(189) (190) (191) (192)

Scheme 22

given in the first edition ⟨84CHEC-I(3)1039⟩. In several cases (notably 1,2,4- and 1,3,2-dioxazines; 1,2,5- and 1,4,2-oxathiazines; 1,2,3-, 1,2,4- and 1,3,2-dithiazines) these appear to represent the only preparative methods currently at the disposal of the synthetic chemist and therefore critical comparison is obviously not warranted. The most important factors which determine the overall efficacy and generality of a route are (i) availability/ease of preparation of precursors, (ii) how readily substituents can be varied, and (iii) yield. Comparisons drawn along these lines are summarized below for the common heterocyclic systems in this chapter.

6.19.10.1 Dioxazines

6.19.10.1.1 1,3,2-Systems

The dialkoxyamine exchange method exemplified in Equation (28), and related reactions employing *N*-chloro-*N*-alkoxyamines is still the only approach to rings of this type.

6.19.10.1.2 1,3,5-Systems

This ring system can be prepared in any of the following ways: (i) reaction of nitriles or thiocyanates with hexafluoroacetone (Scheme 15), (ii) cycloaddition of *N*-acylimines to aldehydes and ketones (Scheme 12), and (iii) cycloaddition of *N*-acylimines to ketenes (Scheme 12). All of these methods are somewhat limited, in that hexafluoroacetone is used in the synthesis of starting-materials or in the cyclization step. All three methods give comparable yields of the dioxazines. An example cited in CHEC-I lacking trifluoromethyl groups (synthesis of 5-chlorosulfonyl-2,6-diphenyl-1,3,5-oxadiazin-4-one from $ClSO_2NCO$ and benzaldehyde) forms an apparently very unstable product ⟨74LA561⟩.

6.19.10.1.3 1,4,2-Systems

The principal routes to heterocycles of this type are: (i) di-*O*-alkylation of hydroxamic acids with 1,2-dihaloalkanes (Equation (29)), (ii) cyclization of *O*-(ethoxycarbonylalkyl)hydroxamates using Grignard reagents (Scheme 9), and (iii) condensation of *O*-(α-hydroxyacyl)hydroxylamines with carbonyldiimidazole ⟨80AP(313)377⟩. The first procedure is probably the most versatile because the substituent in the hydroxamic acid is easily varied. The other two routes involve construction of six- and five-atom fragment precursors respectively, and whilst there is a degree of flexibility in the range of substituents that may be incorporated, the increased number of steps inevitably means lower yields of the final product. The first two procedures give rise to 5,6-dihydro-1,4,2-dioxazines, the third to the 3,6-dione system.

6.19.10.1.4 1,5,2-Systems

The most significant synthetic route to these compounds is the condensation of *N*-(α-hydroxyacyl)hydroxamic acids with carbonyldiimidazole (Equation (23)) or aromatic aldehydes (Equation (27)). Yields are generally good and various substituents can be introduced via the hydroxamic acid portion.

6.19.10.2 Oxathiazines

6.19.10.2.1 1,2,3-Systems

Several synthetic methods for 1,2,3-oxathiazines have been developed over the years: (i) reaction of ketones with CSI ⟨76CRV389⟩, (ii) reaction of alkynes with CSI ⟨72JOC196⟩, and (iii) reaction of sulfurdiimides with malonyl dichloride (Equation (33)). Methods (i) and (ii) offer the greatest scope for the preparation of many derivatives as a wide range of alkynes or ketones may be utilized. The third method gives a near quantitative yield of the product but is limited in scope. Many other high-yielding methods (e.g. see Scheme 9) for synthesizing the sweetener acesulfame K (**35**) have been patented or published but as these are particular to this compound they have been mentioned only in passing.

6.19.10.2.2 1,3,5-Systems

Two strategies have appeared which afford this type of compound: (i) cycloaddition of *N*-thioacylimines to ketones (Scheme 12), and (ii) cycloaddition of thioacyl isocyanates to ketones

(Scheme 11). Both these procedures are high-yielding processes and offer scope for analogue preparation through the many different carbonyl compounds that may be employed. One slight drawback is obtaining the reactive cumulenes required for the cycloaddition.

6.19.10.2.3 1,4,3-Systems

Heterocycles of this type can be made using the following methods: (i) condensation of β-hydroxyalkylsulfoximines with phosgene (Equation (25)), (ii) cycloaddition of *N*-sulfinyltoluamide to alkenes or alkynes (Scheme 10), (iii) cycloaddition of *N,N'*-diacylthiodiimides to alkenes (Equation (30)), and (iv) di-deprotonation of *N*-(methylsulfonyl)amines followed by reaction with aldehydes (Scheme 16). The two methods involving cycloaddition are fairly general (as numerous differently substituted alkenes or alkynes can be used) but subject to the need to obtain the cumulene systems. The first method can be used to make many derivatives as the precursor (**118**) is made from the corresponding methyl derivative (protected on nitrogen) and an aldehyde. In the last procedure various aldehydes can be used, which makes a wide range of products possible.

6.19.10.2.4 1,5,2-Systems

There are two methods for synthesizing this system in spite of the fact that it is the newest of the oxathiazines: (i) cyclocondensation of *S*-[β-(hydroxyimino)alkyl]dithiocarbonates using tosyl isocyanate (Equation (21)), and (ii) cycloaddition of α-nitrosoalkenes to thiocarbonyl compounds (Equations (31) and (32)). The scope of method (i) is limited and gives only moderate yields. Method (ii) on the other hand is high yielding and preparation of the α-nitrosoalkenes is more straightforward than that of the six-atom fragment in (i).

6.19.10.3 Dithiazines

6.19.10.3.1 1,3,5-Systems

The vast majority of the compounds of this type are prepared through condensation of aldehydes, primary amines and H_2S or variants thereof (Scheme 16). Although other methods exist, e.g., the reaction of 1,3-dithietan-2-ones with aldimines to give systems like (**86**) ⟨84CB2205⟩, they have found little general use because the three compounds in the condensation process are so simple. This reaction is extremely simply carried out in one pot to furnish the 1,3,5-dithiazine in acceptable yield.

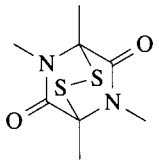
6.19.10.3.2 1,4,2-Systems

The most important means of obtaining a 1,4,2-dithiazine is through ring expansion of a 1,3-dithiolium cation via nitrogen insertion (Scheme 19). A number of methods based on this technique have appeared and the yields vary widely according to the substituents and conditions employed ⟨92CC478⟩.

6.19.11 IMPORTANT COMPOUNDS AND APPLICATIONS

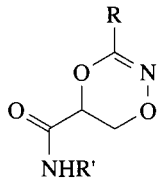
Dioxazine, oxathiazine or dithiazine ring systems are seldom found in natural products. One exception is the 1,2,4-dithiazine system, bridged derivatives of which occur in the epithiodiketopiperazine antibiotics. The subunit (**193**) is common to several metabolites, such as sirodesmin

⟨77JCS(P1)180⟩, chaetomin ⟨76JA6741⟩ and emestrin ⟨86JCS(P1)109⟩, and seems to play an important role in their potent antiviral, antibiotic and antifungal properties.



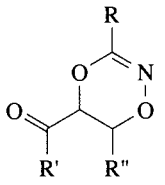
(193)

Synthetic members of the three classes of heterocycle falling within the definitions of this chapter have been widely screened for biological activity. Those compounds which display activity do so almost exclusively in the agrochemical rather than the pharmaceutical area. Several 1,4,2-dioxazines (for instance **(194)** ⟨90JAP(K)02134373⟩ and **(195)** ⟨91JAP(K)0327368⟩) and 1,3,5-dithiazines (such as **(196)** ⟨85JAP(K)60161972⟩) possess powerful herbicidal and fungicidal properties. The 1,4,2-oxathiazine derivatives **(197)** were also found to be effective as herbicides and fungicides ⟨84EUP104940⟩. A series of compounds which have a biological effect on humans are derivatives of the 1,3,5-dithiazine **(46)**. These are orally active radioprotective agents against γ-rays even at low dosage levels ⟨90MI 619-01⟩.



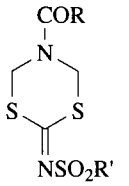
(194)

R = alkyl, haloalkyl, alkoxyphenyl
R' = H, alkyl, benzyl



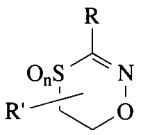
(195)

R = H, alkyl
R' = H, alkyl, aryl
R" = OH, Oalkyl, Salkyl



(196)

R = H, alkyl, alkenyl
R' = H, alkyl, benzyl

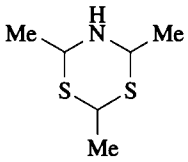


(197) n = 0, 1, 2

R = naphthyl, pyridyl, thienyl
R' = H, alkyl, benzyl

1,3,5-Dithiazines are very important, though often overlooked, components of the flavor and aroma of various cooked meats, e.g. beef and prawns ⟨92MI 619-01⟩. In most cases they exhibit interesting organoleptic properties and have low flavor thresholds. The majority of the compounds are simple alkyl substituted systems of which thialdine **(198)** is probably the best-known example. The synthetic compound **(199)** is used, at a concentration of only 6 ppb, to flavor instant coffee preparations ⟨92EUP482448⟩, its addition providing an improved fresh roasted coffee aroma.

It has long been known that certain 1,2,3-oxathiazines are excellent artificial sweetening agents. A great deal of work has been carried out in this area ⟨73AG(E)869⟩ and the most significant compound is undoubtedly acesulfame K **(35)** ⟨85MI 619-01, 92MI 619-02⟩ which is 130 times sweeter than cane sugar. It is therefore as powerful a sweetener as saccharin and five times sweeter than cyclamate (*N*-cyclohexylsulfamic acid), two well-known older sugar substitutes.



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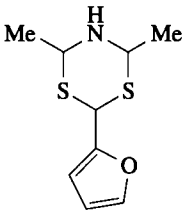

(199)

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6.20
Six-membered Rings with 1,2,4-Oxygen or Sulfur Atoms

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6.20.1 INTRODUCTION

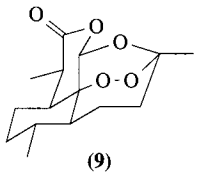
There are eight possible ways of substituting oxygen and sulfur atoms at the 1-, 2-, and 4-positions within a cyclohexane ring (**1**)–(**8**). However, nearly all compounds reported are derivatives of 1,2,4-trioxane (**1**). About two dozen 1,2,4-trithianes are known, which are mostly simple alkylated derivatives of (**2**). Less than 30 compounds have been described for the remaining arrangements,

namely for derivatives of 1,4,2- and 1,5,2-dioxathiane (**3**) and (**4**), 1,3,4-, 1,2,4- and 1,2,5-oxadithiane (**6**), (**7**), and (**8**). Derivatives of 1,2,4-dioxathiane (**5**) are unknown.

(**1**) (**2**) (**3**) (**4**)

(**5**) (**6**) (**7**) (**8**)

In comparison with their lower homologues, the 1,2,4-trioxolanes or secondary ozonides, trioxanes have received considerably less attention. No mention was made of them in the literature before 1957 ⟨57JOC1682⟩. Thereafter, in the period 1957–1982, citations were sporadic. However, with the discovery in 1979 that a naturally occurring tetracyclic 1,2,4-trioxane, qinghaosu, or artemisinin (**9**), possesses potent antimalarial activity ⟨79MI 620-01⟩ the development of synthetic methods for preparing derivatives of (**1**) and (**9**) has grown dramatically. Contrary to expectation, most trioxanes are thermally stable, thereby permitting studies on their chemical and physical properties to be undertaken. The synthesis and chemistry of (**9**) ⟨91H(32)1593, 94ACR211⟩ and of structurally simpler trioxanes ⟨88HOU(E13)720, 95COS225⟩ have been reviewed. Accounts of (**9**) and its importance as an antimalarial have appeared ⟨85SCI1049, 87MI 620-01, 92CSR85⟩. The mechanistic principles underlying syntheses of bicyclic 1,2,4-trioxanes have also been reviewed ⟨B-86MI 620-01, B-91MI 620-01, 93CSR59⟩.



(**9**)

Less has been reported on (**2**). The first instance of an accidental synthesis of a 3,3-spirocyclic 1,2,4-trithiane was noted in 1970 ⟨70JOC2102⟩. Since then, 3-alkyl derivatives of (**2**) have been identified as some of the exiguous ingredients responsible for the flavor of cooked meat ⟨93MI 620-01⟩. Artificial foodstuff flavors, for example, those concocted by heating cysteine with sugar, contain the same derivatives ⟨81MI 620-01⟩. The role of 1,2,4-trithianes and other heterocycles as flavor principles in processed foodstuffs has been reviewed ⟨78H(11)663, B-78MI 620-01⟩.

Allusions to mixed heterocycles (**3**)–(**8**) have been surprisingly few since the discovery that β-naphtha-1-thioquinone exists as the dimer, the first example of a 1,3,4-oxadithiane ⟨30JCS1740⟩.

Although theoretical considerations and physical measurements came after the molecules were prepared, the material in this chapter is presented in the usual format. However, there are some inevitable exceptions which spring from the fact that practically all the compounds discussed are fully saturated, nonnitrogen containing heterocycles. In other words, there is none of the traditional reactivity pertaining to unsaturated compounds, or fused benzene rings. Benzo derivatives are encountered only because of the particular method of preparation. Moreover, there are no substituents attached to ring heteroatoms and no attendant reactivity. Synthesis is necessarily confined to the different ways in which the six-membered ring may be assembled. In other words, the chemistry of these heterocycles is reminiscent of that of alicyclic compounds, but evidently dominated by the peroxidic functionality. Furthermore, the present chapter did not feature in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and is therefore new in substance and, to a certain extent, new in style.

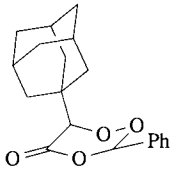
6.20.2 THEORETICAL METHODS

6.20.2.1 Comparison of Calculated and Experimental Parameters

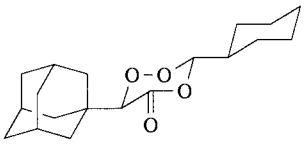
Theoretical methods have been used to compute geometries, heats of formation, conformational energies, and molecular electrostatic potentials (MEPs) of certain derivatives of (**1**) and (**9**). Deriva-

tives of (**2**)–(**8**) have not received such attention. Calculation is often performed in the context of testing the accuracy of a particular method or in association with a physical measurement.

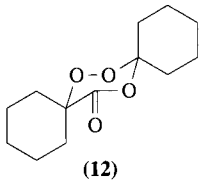
1,2,4-Trioxan-5-ones provide an illustration. Despite appearances, such molecules are thermally stable. The *cis*- and *trans*-3,6 disubstituted (**10**) and (**11**) and the doubly spirocyclic (**12**) derivatives are crystalline substances, the structures of which have been determined by x-ray ⟨91AX(C)388⟩. Their experimental geometries have been used as yardsticks for evaluating the accuracy of molecular mechanics (MM2) and semiempirical (AM1, PM3) methods ⟨95JST(337)31⟩. X-ray analysis shows that the trioxane ring exists as an envelope in (**10**) and as half-chair conformations in (**11**) and (**12**) ⟨91AX(C)388⟩.



(**10**)



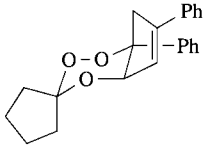
(**11**)



(**12**)

All three computational methods give global minima corresponding to half-chair conformations for all three trioxanones. Calculated and measured bond lengths, bond angles and dihedral angles of the trioxanone portion have been compared. As expected, the greatest discrepancies are observed for the O—O bond. PM3 overestimates and AM1 underestimates its length, whereas MM2 gives a result little different from the actual value. All three methods predict the other C—O and C—C bond lengths with the same degree of high accuracy. Calculation performs best for (**10**) and (**11**). Although the conformation of (**10**) is not that predicted by MM2, calculated bond angles for (**10**)–(**12**) could be usefully compared. The angles O(1)-O(2)-C(3) and O(4)-C(5)-C(6) are too wide when calculated by AM1 and PM3. All three methods poorly predict the O(4)-C(5)-O(7) angle. Excepting (**10**), calculated and experimental values for the dihedral angles in (**11**) and (**12**) are in good agreement. Overall, MM2 is found to be the most accurate calculation method, with PM3 being slightly more accurate than AM1.

Calculations have also been carried out on the cyclopentene-fused 1,2,4-trioxane (**13**) ⟨95HCA647⟩. The potential energy surface of (**13**) has been explored. Full geometry optimization was performed with the CHEM-X and MOPAC programs by using the PM3 method. The global minimum is computed to have a heat of formation of 0.9 kcal mol^{-1} and a flattened, twisted chair conformation (Figure 1, TC). Two local minima are found nearby, one in which the trioxane ring exists as a twist-boat (TB) and another as a twist-chair conformer (TC′). Passage between TC and TB is easy, requiring 9.8 kcal mol^{-1} to reach the transition structure (ts-1). Similarly, transit from TB through ts-2 to TC′ is even easier, needing only 2.3 kcal mol^{-1}.



(**13**)

The aforementioned theoretical conformational mobility of the *cis*-fused bicyclic entity is confirmed by line shape analysis of the NMR spectrum of (**13**) in the temperature range 223–273 K. The observed activation parameters, $\Delta H_{223}^{\#} = 15.2$ kcal mol^{-1}, $\Delta S^{\#} = 6.6$ cal mol^{-1} K^{-1} and $\Delta G_{273}^{\#} = 13.4$ kcal mol^{-1}, are consonant with the equilibrium between conformers resembling TC and TB or TC′. The crystal structure of (**13**) confirms that the ground state is similar to TC. The 1,2,4-trioxane ring adopts a slightly flattened chair conformation bearing the angular phenyl substituent in the axial position ⟨95HCA647⟩.

Semi-empirical and *ab initio* calculations have been performed on 5-hydroxymethyl-3,5,6,6-tetramethyl-1,2,4-trioxane (**14**) ⟨91IJQ231⟩. A comparison of the AM1, PM3, 3-21G, and 6-31G optimized geometries, all of which are chair conformations, are in excellent agreement with the x-ray structure. Similar comparisons have been made for artemisinin (**9**) ⟨94IJQ11⟩. Agreement between the *ab initio* 3-21G and 6-31G* calculations is excellent; both give O(1)—O(2) bond lengths close to the value determined by x-ray. The trioxane ring assumes a twist-boat conformation and the O1—O2 bond length calculated by 3-21G (1.462 Å) lies close to the experimental value (1.478 Å). This result shows

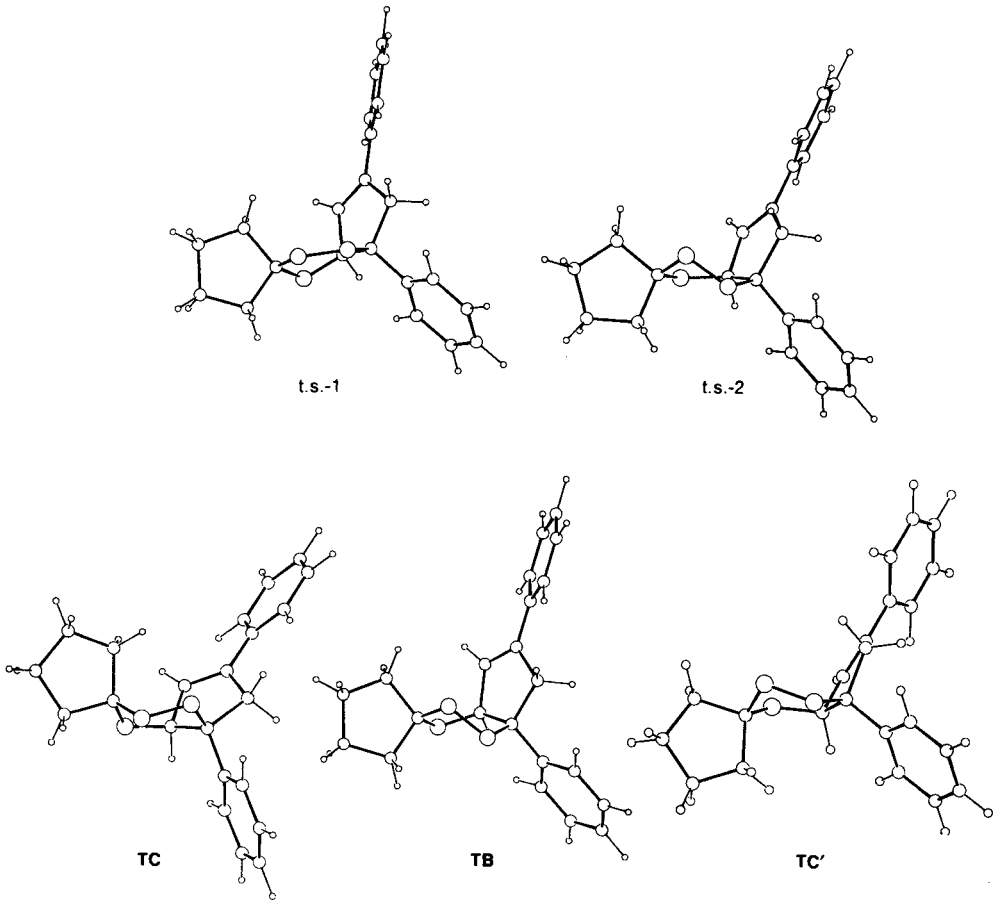
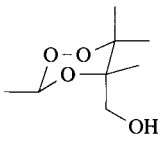
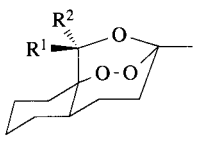


Figure 1 Perspective views of the PM3-optimized geometries of conformers TC, TB, and TC′ and of the transition-state structures ts-1 and ts-2 of (**13**).

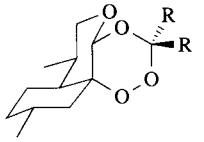
that 6-31G* optimizations are superfluous and that 3-21G is adequate for calculating the properties of (**9**) and structurally related trioxanes, such as the pair of tricyclic epimers (**15**) and (**16**). The error in the bond lengths is <0.02 Å, the bond angles fall within 2° and torsion angles are of the correct magnitude and size. Calculations suggest that the trioxane ring in the tricyclic analogues (**17**) and (**18**), as in artemisinin (**9**), adopts a boat conformation. However, the x-ray of (**17**) reveals a chair-like conformation ⟨88HCA2042⟩.



(**14**)



(**15**) R^1 = OMe, R^2 = H
(**16**) R^1 = H, R^2 = OMe

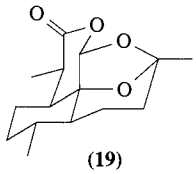


(**17**) R = Me
(**18**) R ,R = $(CH_2)_4$

6.20.2.2 Calculated Molecular Parameters as an Index of Antimalarial Activity

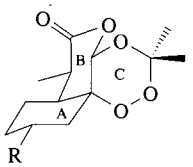
MEPs have been calculated for (**9**), (**15**)–(**17**), and deoxyartemisinin (**19**) in an attempt to correlate structure with antimalarial activity. All molecules, except (**19**), have high activity and display an area of negative potential over the peroxide bond, although less so for (**9**). Unequivocal conclusions concerning the relation between MEPs and antimalarial activity could not be drawn.

The minimum energy conformations of the secoartemisinin analogues (**20**)–(**22**) have been determined by a combination of x-ray crystallography, NMR spectroscopy and computational analysis using MM2 ⟨94T957⟩. Two major conformations of (**20**) and (**21**) are found: one in which the A, B,

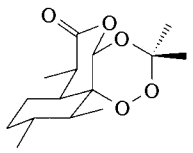


(19)

and C rings are all disposed as chairs, just like the x-ray structure of (**20**) and the other having the three rings as chair, twist-boat, and twist-boat, respectively. Computations suggest that (**22**) in solution comprises three conformations of equal energy, namely one having rings A, B, and C as boat, twist-boat, chair; a second with chair, twist-boat, twist-boat, and the third containing chair, chair, twist-boat forms. The antimalarial activities of these flexible analogues are found to be less than that of (**9**).

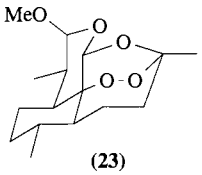


(**20**) R = H
(**21**) R = Me



(**22**)

The antimalarial activity of (**9**) involves its interaction with heme or hemin in the parasitized erythrocyte. Molecular modeling techniques have been used to investigate how the two molecules dock, the one on the other ⟨95MI 620-01⟩. The x-ray structures of artemether (**23**) and hemin have been taken and modeled with the SYBYL software. It is found that, in the optimum interaction, the peroxide bridge lies close to the central iron atom of heme or hemin. It will be seen in Section 6.20.5.6 that such contiguity is a *sine qua non* for single electron transfer (SET), the first step towards parasiticidal action.



(**23**)

6.20.3 EXPERIMENTAL STRUCTURAL METHODS

6.20.3.1 Crystal Structures

Unlike the volatile 1,2,4-trithianes, 1,2,4-trioxanes usually give crystals suitable for x-ray analysis. This particularity is fortunate, because structural information from ^{1}H and ^{13}C NMR spectroscopy is meagre owing to the three heteroatoms within the ring. Consequently, x-ray analysis is the method of choice. In most cases, it is the only unambiguous method for determining constitution, configuration and conformation. Up to 1996, the crystal structures of at least 41 1,2,4-trioxanes, one 1,5,2-dioxathiane and one 1,3,4-oxadithiane have been determined. The intracyclic dimensions, namely the interatomic distances, are normal and deserve no particular comment. The bond and dihedral angles depend on the ring fusion or the substituents attached to the trioxane ring. In general, like cyclohexane, 1,2,4-trioxane prefers the chair conformation. However, as already observed with (**13**), a five-membered ring fused *cis* to the parent trioxane introduces a propensity towards the boat conformation, especially in solution. Nonetheless in the crystal, *cis*-fused cyclopenteno and dihydronaphtho derivatives (e.g. (**292**)) stay predominantly in the chair conformation ⟨82AX(C)829⟩. Additional constraints, such as bridging across the C(3)–C(6) positions, as is the case for artemisinin (**9**) and its lactol derivatives (e.g. (**23**)), force the trioxane ring into a boat conformation.

The structures can be classified as (i) monocyclic, bearing substituents or even spirocyclic groups at C(3) or C(6), (ii) bicyclic, with another ring fused at the C(4)–C(5) positions, (iii) tricyclic,

possessing, in addition to a ring at C(4)–C(5), a spirocyclic attachment at C(6), (iv) bridged tricyclic, having a spirocyclic attachment at C(6) with bridging across the C(3)–C(6) positions, and (v) tetracyclic or artemisinin-like. For convenience, these classes are designated as M, B, T, BT, and A. A comparison of the experimental interatomic distances for trioxanes representative of the five classes reveals no significant deviations (Table 1).

Table 1 Experimental interatomic distances between adjacent ring atoms in some trioxanes (Values in Å, numbering based on parent 1,2,4-trioxane ring).

Compound (Class)	*Ref.*	*O1-O2* (Å)	*O2-C3* (Å)	*C3-O4* (Å)	*O4-C5* (Å)	*C5-C6* (Å)	*C6-O1* (Å)
(**257**) (M)	77AX(B)3564	1.469	1.423	1.411	1.441	1.533	1.458
(**13**) (B)	95HCA647	1.477	1.439	1.413	1.446	1.548	1.447
(**17**) (T)	88HCA2042	1.477	1.412	1.447	1.403	1.528	1.472
(**15**) (BT)	93HCA2775	1.473	1.417	1.424	1.427	1.525	1.473
(**9**) (A)	80MI 620-01	1.462	1.441	1.436	1.408	1.529	1.477

For the sake of completeness, all literature references to crystallographic data, although most are cited elsewhere in the chapter, are listed below by class and identified by molecular formula.

Class M: $C_{19}H_{22}O_4$, $C_{19}H_{28}O_4$, $C_{13}H_{20}O_4$ ⟨91AX(C)388⟩; $C_{18}H_{23}NO_3$ ⟨77AX(B)3564⟩; $C_{17}H_{28}O_4$ ⟨85T2081⟩; $C_{14}H_{20}ClNO_3$ ⟨83CL1841⟩; $C_{15}H_{26}O_6$ ⟨88CC372⟩.

Class B: $C_{22}H_{22}O_3$, $C_{32}H_{34}O_7$, $C_{32}H_{32}O_7F_2$ ⟨95HCA647⟩; $C_{13}H_{16}O_3$ ⟨93MI 620-02⟩; $C_{26}H_{28}O_3$, $C_{27}H_{32}O_3$ ⟨91TL7243⟩; $C_{13}H_{14}O_6$ ⟨88JOC4986⟩; $C_{18}H_{16}O_5$, $C_{20}H_{20}O_6$, $C_{20}H_{20}O_3$ ⟨86HCA941, 87AX(C)701⟩; $C_{20}H_{20}O_3$, $C_{16}H_{18}O_5$ ⟨86AX(C)829⟩; $C_{19}H_{17}ClO_4$ ⟨84HCA2254⟩; $C_{12}H_{15}NO_3$ ⟨84HCA1104⟩; $C_{14}H_{11}BrO_4$ ⟨74JA2955⟩.

Class T: $C_{13}H_{20}O_5$ ⟨94T957⟩; $C_{14}H_{24}O_4$ ⟨88HCA2042⟩; $C_{15}H_{24}O_5$ ⟨90CC1487⟩; $C_{13}H_{20}O_5$ ⟨88CC372⟩.

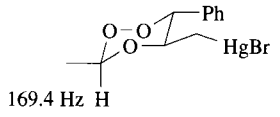
Class BT: $C_{12}H_{20}O_4$, $C_{12}H_{20}O_4$ ⟨89TL4485, 93HCA2775⟩; $C_{14}H_{14}O_3$ ⟨86HCA1778⟩.

Class A: $C_{24}H_{31}NO_9$, $C_{26}H_{35}NO_9$ ⟨95AX(B)1063⟩; $C_{15}H_{22}O_6$ ⟨90MI 620-01⟩; $C_{20}H_{27}BrN_2O_4$ ⟨90JMC2610⟩; $C_{15}H_{22}O_5$ ⟨90MI 620-02⟩; $C_{15}H_{24}O_5$ ⟨80MI 620-01, 88MI 620-01⟩; $C_{15}H_{20}O_6$ ⟨93JMC2552⟩; $C_{17}H_{28}O_5$ ⟨92MI 620-01⟩; $C_{19}H_{28}O_8$ ⟨86MI 620-02⟩; $C_{15}H_{22}O_5$ ⟨93MI 620-03⟩; $C_{16}H_{26}O_5$, $C_{15}H_{24}O_5$ ⟨84HCA1515⟩.

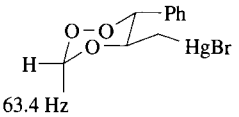
Others: $C_{28}H_{24}O_3S$ ⟨91CJC185⟩; $C_{20}H_{12}O_2S$ ⟨78AX(B)2907⟩.

6.20.3.2 NMR Spectroscopy

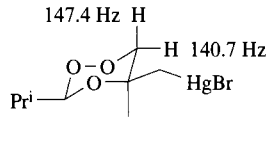
For obvious reasons, vicinal coupling constants in trioxanes offer less NMR spectral information on configuration than those in cyclohexane. However, one-bond ^{13}C—H coupling constants ($^1J_{C-H}$) are a useful index of the equatorial or axial configuration of a substituent attached to the ring. The epimeric pair of monocyclic trioxanes (**24**) and (**25**), disposed as chair conformations, display characteristic values of $^1J_{C-H}$ for the critical C(3) atom ⟨92CC1689⟩. The values are 169.4 Hz for (**24**) and 163.5 Hz for (**25**). The difference, 6 Hz, is diagnostic for the C(3) configuration. It is ascribable to a homoanomeric effect by the lone pair on the oxygen atom furthest away from the equatorial C—H bond. The relative magnitude of the $^1J_{C-H}$ value, bigger for the axial H atom, is the opposite of that usually seen in cyclohexanes and pyranosides; for that reason it has been termed a reversed Perlin effect. Similar differential effects operate on the C(6) position. In the chair conformer (**26**), the equatorial and axial protons at C(6) are clearly distinguishable by the corresponding values of 140.7 Hz and 147.4 Hz.



(**24**)



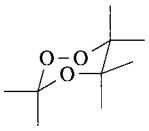
(**25**)



(**26**)

Crystallographic evidence amply demonstrates that the trioxane ring is similar in shape and conformational preference to cyclohexane. The barrier for chair-to-chair interconversion, a hitherto unknown quantity, has been determined by a dynamic NMR spectral study ⟨93JCS(P1)1927⟩. The behavior of 3,3,5,5,6,6-hexamethyl-1,2,4-trioxane (**27**) is typical. Despite the high degree of substitution, MM3 calculations show that it exists as a chair in the ground state. The value determined

for ring inversion, 12.3 kcal mol^{-1} at the coalescence temperature of $-5°C$, is higher than that observed for comparably substituted 1,3-dioxanes (6.5–10.1 kcal mol^{-1}). The difference is attributed to the higher barrier to rotation about the O—O bond in the trioxane compared with the C—O and C—C bonds in the dioxane.



(27)

Definitive ^{1}H and ^{13}C NMR assignments have been reported for artemisinin (**9**) ⟨85CJC3070, 88MI 620-02⟩.

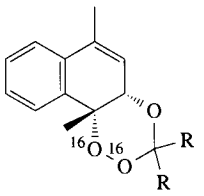
The ^{13}C NMR spectral data of α- and β-dihydroartemisinin (**65**) have been compared with those reported for 11α- and 11β-hydroxy-11-epidihydroartemisinin (**112**), α-arteether (**95**), β-artemether (**23**) and (**9**) ⟨95IJC(B)992⟩.

The structures of (**9**), (**65**), (**23**) and artesunic acid have been elucidated by ^{1}H NMR spectroscopy and supported by x-ray data obtained for (**65**) and (**23**) ⟨84HCA1515⟩.

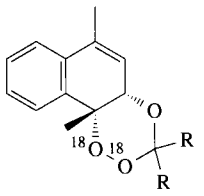
Differential shielding effects on the proton chemical shifts of ethyl (3*R*)-(*p*-nitrophenyl)-3-(10β-dihydroartemininoxy)propionate and its (3*S*) diastereomer are correlated with crystal structure. In the two isomers, the phenyl substituent adopts markedly different conformations with respect to the nearby methine protons on the dihydropyran moiety thereby producing sizable differences in chemical shift ⟨95AX(B)1063⟩.

6.20.3.3 Raman Spectroscopy

The vibrational spectrum of (**9**) has been determined by laser Raman and IR spectroscopy. It is concluded that the peroxide group contained therein is characterized by a frequency of 722 cm^{-1} and not 881 cm^{-1} ⟨84MI 620-01⟩. However, a subsequent study on the pair of isotopically different parent *cis*-fused naphthaleno-trioxanes (**28**) and (**29**) and their *gem*-dimethyl derivatives (**30**) and (**31**) reveals strong Raman bands at 816 cm^{-1} and 897 cm^{-1} for (**28**), and at 802 cm^{-1} and 885 cm^{-1} for (**30**) ⟨88HCA992⟩. These frequencies are attributed to the coupled C—O and O—O stretching modes of the C—O—O element. The strong Raman bands at 789 cm^{-1} and 876 cm^{-1} observed for (**9**) characterize the same element. Consequently, the frequency at 722 cm^{-1} must be of nontrioxane origin. In general, bands at 780 ± 20 cm^{-1} and 880 ± 10 cm^{-1} can be regarded as the 'fingerprint' of 1,2,4-trioxanes.



(**28**) R = H
(**30**) R = Me



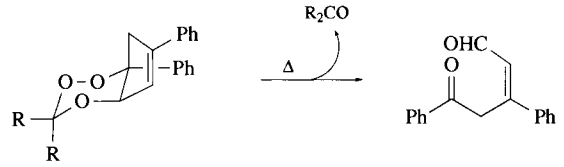
(**29**) R = H
(**31**) R = Me

6.20.4 THERMODYNAMIC ASPECTS

6.20.4.1 Thermal Stability

Intuitively, chemists might believe that trioxanes are thermally unstable because of the peroxide bond. Generally, this expectation is not borne out experimentally. Artemisinin (**9**) has to be heated to 190°C before it decomposes ⟨85H(23)881, 85JOC4504⟩. The same resilience is noted for simpler bicyclic trioxanes (**32**)–(**34**) ⟨91MI 620-02⟩. Thermogravimetric analysis reveals that melting occurs in the range 114–180°C resulting in gradual decomposition to the ketone centered on C(3) and the

diphenyl keto-aldehyde (**35**) (Equation (1)). All three trioxanes conserve their initial weight beyond their melting points. Similar enthalpies of fusion (21.7 kJ mol^{-1} and 22.1 kJ mol^{-1}), determined by differential scanning calorimetry, are observed for (**32**) and (**33**). The lower value seen for (**34**) (16.6 kJ mol^{-1}) probably reflects greater steric congestion at C(3).



(1)

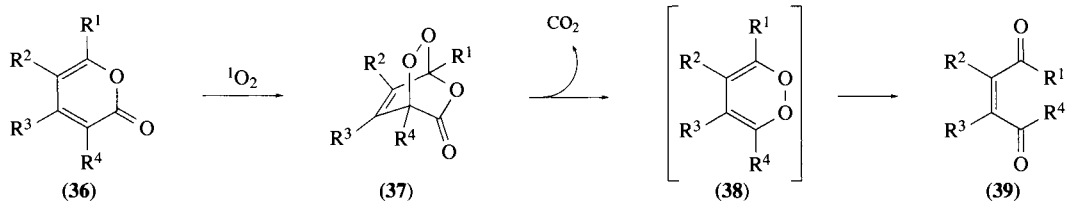
(**32**) R = H
(**33**) R = Me
(**34**) R,R = Me, Pr

(**35**)

6.20.5 REACTIVITY

6.20.5.1 Thermolysis Reactions

As a notable exception, the bridged bicyclic 1,2,4-trioxan-5-ones (**37**), obtained by the addition of a molecule of singlet oxygen to the 2*H*-pyran-2-ones (**36**), are indeed unstable. At 25 °C they undergo decarboxylation to the enediones (**39**) with emission of light of low intensity (Scheme 1) ⟨79JA5692⟩. No evidence for the 1,4-dioxins (**38**) is found.



(**36**) (**37**) (**38**) (**39**)

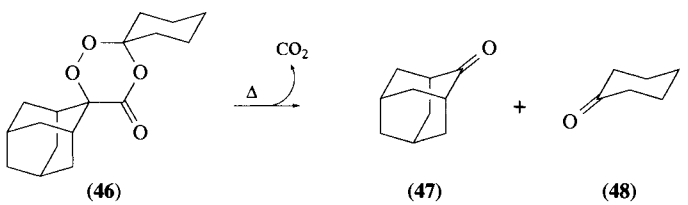
$R^1 = R^2 = R^3 = R^4$ = H or Ph
$R^1 = R^3 = R^4$ = H, R^2 = CO_2H or CO_2Me

Scheme 1

In contrast, the adduct (**41**) obtained from singlet oxygen and 1,4-diphenyl-3*H*-2-benzopyran-3-one (**40**) is a stable, crystalline solid (Scheme 2) ⟨78JA2564⟩. Nonetheless, (**41**) decomposes in boiling benzene giving *o*-dibenzoylbenzene (**43**) and phenyl *o*-benzoylbenzoate (**45**) in 85% and 5% yield respectively. No luminescence is detected. The major reaction course is decarboxylation to the intermediate *o*-xylylene peroxide (**42**), which can be trapped as its Diels–Alder adduct with maleic anhydride. The ester (**45**) could have arisen directly from (**41**) by decarbonylation and concomitant 1,2-migration of the phenyl group or stepwise through the 1,2,4-trioxolane intermediate (**44**).

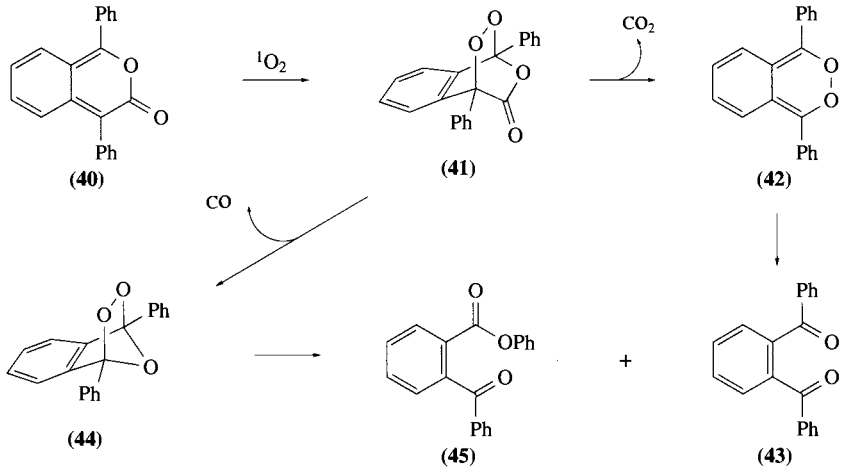
When (**37**) and (**41**) are thermolyzed in the presence of rubrene, luminescence is enhanced as fluorescence. It is deduced that the acceptor in the electron-exchange process for (**37**) is the trioxane ring, and (**42**) in the case of (**41**).

3,6-Substituted 1,2,4-trioxan-5-ones also show high thermal stability ⟨93H(35)725⟩. Typically, the flash vacuum thermolysis of (**46**) goes to completion at temperatures of 350–400 °C giving adamantanone (**47**), cyclohexanone (**48**) and carbon dioxide (Equation (2)).



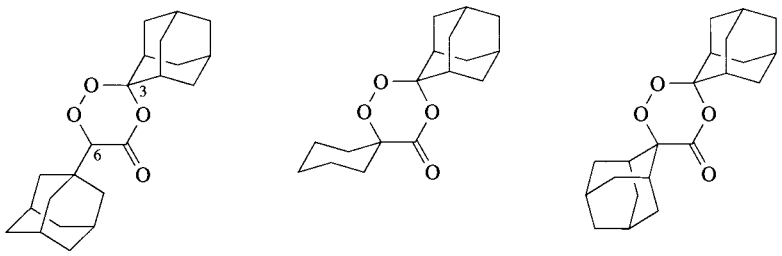
(2)

(**46**) (**47**) (**48**)

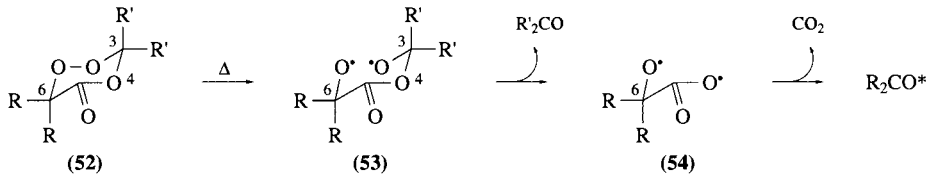


Scheme 2

Further studies have been conducted with (**46**), (**49**)–(**51**) in 1-phenyldecane at high temperatures (170–220 °C) ⟨94HCA1851⟩. On heating, the trioxanones decompose unimolecularly to give electronically excited singlet ketones with an efficiency of ca. 0.2%. The chemiluminescence quantum yields depend on the nature of the substituents at C(6) and increase linearly with temperature. The rate of decay of chemiluminescence affords the Arrhenius activation energies, which are found to be 35.6, 22.9, 30.4, and 34.2 kcal mol^{-1} respectively.

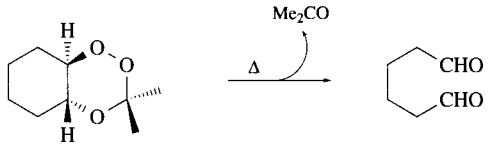


Thermolysis of (**46**), (**50**) and (**51**) proceeds through initial homolysis of the O—O bond, exemplified by (**52**). Excision of ketone (R'_2CO) occurs from the C(3) end of the oxy diradical (**53**) giving the carboxyl diradical (**54**), which by loss of carbon dioxide liberates the light-emitting ketone, R_2CO^*, from the C(6) terminus (Scheme 3).



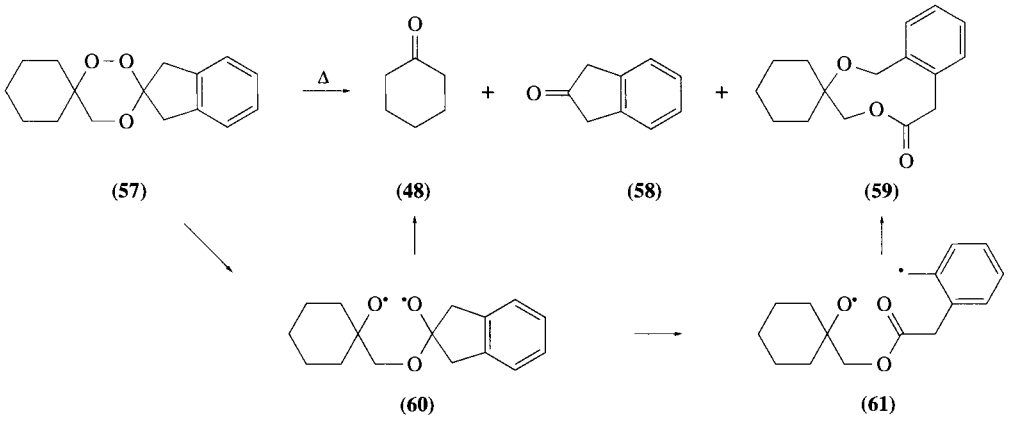
Scheme 3

Thermolysis of *trans*-4,4-dimethyl-2,3,5-trioxabicyclo[4.4.0]decane (**55**) in octane or diphenyl ether at temperatures of 160–189 °C gives adipaldehyde (**56**) and acetone (Equation (3)) ⟨78JOC521⟩. Chemiluminescence is not observed. The kinetics are consistent with a unimolecular process and yield 39.9 ± 1.4 kcal mol^{-1} for $\Delta G^{\#}$ at 175 °C. Cleavage is undoubtedly triggered by homolytic rupture of the O—O bond.



(55) (56) (3)

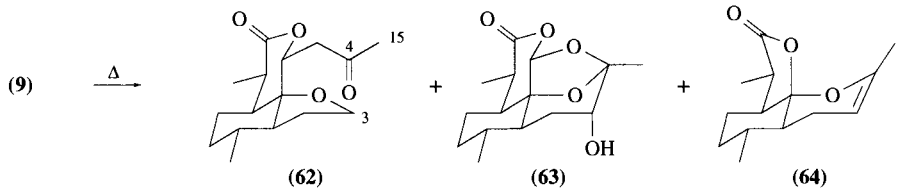
Thermolysis of the dispiro-trioxane (**57**) in decane at 190°C affords cyclohexanone (**48**), indan-2-one (**58**) and a more or less equal amount of the nine-membered ring lactone (**59**) (Scheme 4) ⟨85CC590⟩. This result can be rationalized in terms of the initial formation of the oxy diradical (**60**) which by extrusion of formaldehyde would account for (**48**) and (**58**). Rearrangement of (**60**) to the C-centered radical (**61**) competes with fragmentation due to the thermodynamic stability accruing from formation of the ester group. Intramolecular union of the radical centers in (**61**) then gives the lactone (**59**). Further results are accountable by the foregoing radical mechanism ⟨93CC1076⟩.



(57) (48) (58) (59) (60) (61)

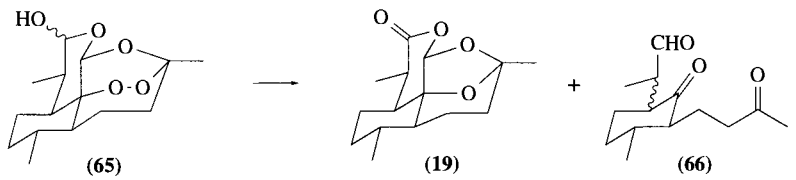
Scheme 4

The thermolytic course for artemisinin (**9**) parallels the mechanistic dichotomy observed for (**57**) ⟨85JOC4504⟩. When heated to 150°C in neutral solvents, (**9**) remains unchanged. On heating neat in a flask at 190°C for 10 min three products, (**62**)–(**64**), are obtained in yields of 12, 10, and 4% (Equation (4)). Evidently, homolysis of the O—O bond gives oxy radicals that evolve differently to (**62**) and (**63**). Elimination of formic acid accounts for (**64**). The same products are found on heating (**9**) in boiling xylene for 22 hours, except that (**64**) is not detected ⟨85H(23)881⟩.



(9) (62) (63) (64) (4)

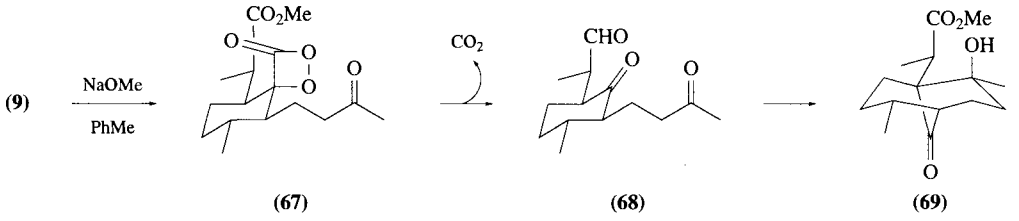
Heating dihydroartemisinin (**65**) for 190°C gives deoxyartemisinin (**19**) and an epimeric mixture of the aldehydes (**66**) in yields of 30% and 50% respectively (Equation (5)) ⟨86T2181⟩. Dehydration accounts for the formation of (**19**) and loss of formic acid for (**66**). Ionic and radical mechanisms can possibly explain the different reaction courses.



(65) (19) (66) (5)

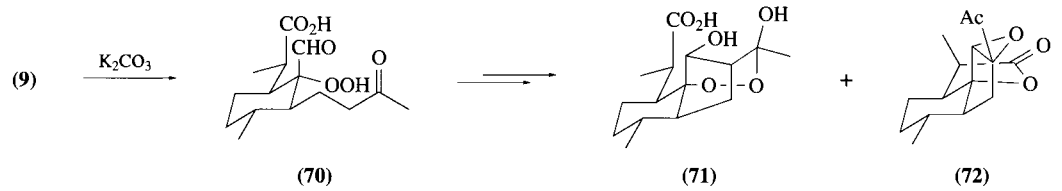
6.20.5.2 Reactions with Base

The action of methanol-free sodium methoxide on (**9**) in toluene at 100 °C for 10 min results in 11% conversion to the bicyclo[3.3.1]nonanone (**69**) as a single product with brief emission of chemiluminescence (Scheme 5) ⟨85CJC3070⟩. The dioxetanone (**67**) may be the light emitter which by scission and base condensation gives the cyclohexanone (**68**) and its condensation product (**69**).



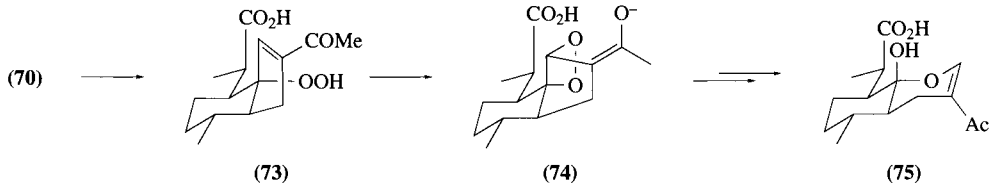
Scheme 5

The treatment of (**9**) with potassium carbonate in aqueous methanol at 25 °C unravels the lactone and trioxane rings. The first formed hydroperoxide (**70**) then reacts further to furnish the peroxide (**71**) and the epoxide (**72**) in 20% yield (Scheme 6) ⟨86T4437⟩.



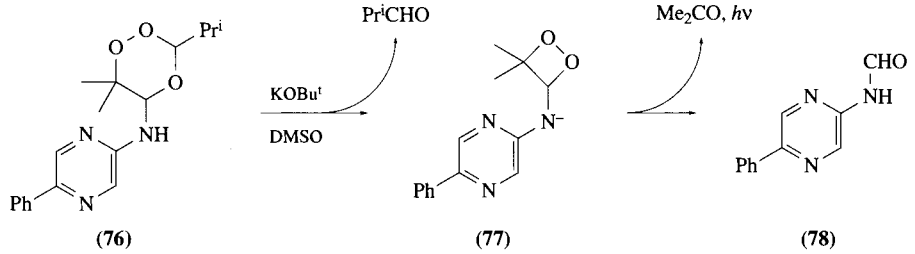
Scheme 6

In a related study, (**9**) under the same conditions gives (**72**) as before, but accompanied by the bicyclic acid (**75**) (Scheme 7) ⟨89H(28)421⟩. Its origin has been ascribed to intramolecular condensation of (**70**) to the hydroperoxide (**73**). Closure to the dioxetane (**74**) followed by cleavage and cyclization accounts for the formation of (**75**).



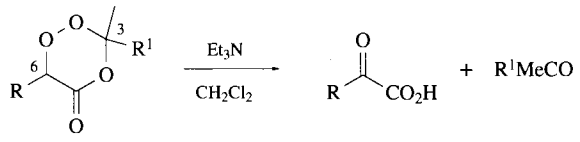
Scheme 7

The treatment of the 5-amino-trioxane (**76**) with potassium *t*-butoxide in dimethyl sulfoxide gives the amide (**78**) with light emission (Scheme 8) ⟨76TL4627⟩. Deprotonation of the amine initiates the reaction thereby eliminating isopropanal and producing the dioxetane (**77**). Scission of the latter produces (**78**), acetone, and light.



Scheme 8

6-Monosubstituted 1,2,4-trioxan-5-ones readily undergo base-catalyzed O—O cleavage to give α-keto acids ⟨86CC1701⟩. Typically, a solution of 6-(1-adamantyl)trioxanone (**79**) in triethylamine and methylene chloride on standing for 16 hours at 25 °C gives the α-keto acid (**80**) in 82% yield on evaporating the solution and acetone so formed (Equation (6)). The keto group in (**79**) confers acidity on the hydrogen atom at C(6) clearly overriding any steric hindrance. Even in (**81**), where the hydrogen atom at C(3) is sterically favored, base-induced elimination of acetaldehyde proceeds in the same sense as before to deliver the α-keto acid (**82**) in 87% yield after three hours. Proof that the C(6) position must bear a hydrogen substituent is attested by the complete inertness of 3,3,6,6-tetrasubstituted trioxanones towards triethylamine.

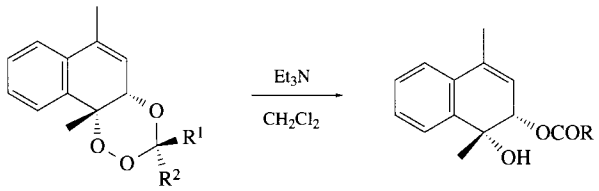


(6)

(**79**) R = 1-adamantyl, R^1 = Me
(**81**) R = Bu^t, R^1 = H

(**80**)
(**82**)

1,2,4-Trioxanes bearing a hydrogen substituent at C(3) are also cleaved by base, but more slowly. Exposure of the *cis*-fused bicyclic trioxanes (**83**) and (**85**) to triethylamine in methylene chloride for 9 days at 25 °C affords the 1,2-diol monoesters (**84**) and (**86**) in 67–78% yield (Equation (7)) ⟨85CC1783⟩. The resulting diol has the *cis*-configuration, the same as that of the starting trioxane. 3,3-Unsubstituted 1,2,4-trioxanes behave similarly ⟨87CC1593⟩.

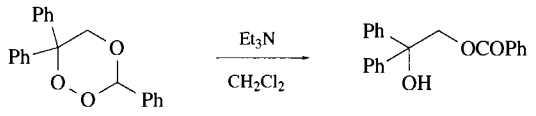


(7)

(**83**) R^1 = Ph, R^2 = H
(**85**) R^1 = H, R^2 = Me

(**84**) R = Ph
(**86**) R = Me

Monocyclic trioxanes, such as (**87**), are also efficiently cleaved by triethylamine to the 1,2-diol esters (**88**) (Equation (8)) ⟨89JCS(P1)1031⟩. Sodium ethoxide in ethanol is equally efficacious in generating the diols. Analogous reaction courses are observed with lithium diisopropylamide, phenyl lithium and alkylmagnesium halides.



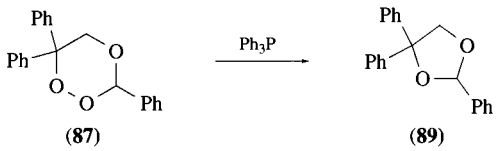
(8)

(**87**) (**88**)

The mechanism of these reactions is unknown, although it has been supposed that base abstracts a proton from C(3) to initiate cleavage. However, donation of a single electron by the base to the O—O antibonding orbital is another possibility. The resulting radical anion would undergo 1,5 hydrogen atom shift finally returning the borrowed electron to the donor and thereby creating the diol monoester. Such a scheme has been proposed for the ferrous ion-catalyzed rearrangement of simple trioxanes ⟨95TL7551⟩.

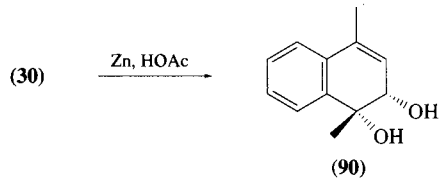
6.20.5.3 Deoxygenation

Deoxygenation of trioxanes can be affected with the oxophilic reagents triphenylphosphine and zinc dissolving in acetic acid. Trioxane (**87**) on heating with triphenylphosphine in benzene for 24 hours gives the corresponding 1,3-dioxolane (**89**) (Equation (9)) ⟨89JCS(P1)1031⟩.

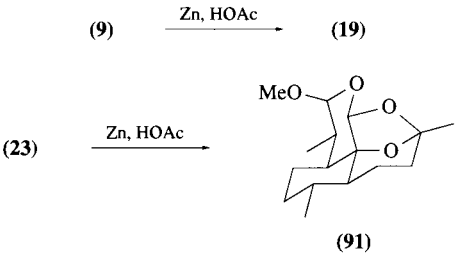


(87) (89) (9)

Cis-fused trioxanes, exemplified by (**30**), are readily deoxygenated by zinc and acetic acid (Equation (10)) ⟨89H(28)673⟩. The *cis*-1,2-diol (**90**) is formed. Formally, zinc is converted into zinc oxide and subsequently zinc acetate by solution in the acid. Artemisinin (**9**) and β-artemether (**23**) are similarly deoxygenated to deoxyartemisinin (**19**) and deoxy-β-artemether (**91**) by dissolving zinc (Scheme 9) ⟨96HCA1475⟩.



(90) (10)



(91)

Scheme 9

6.20.5.4 Reduction and Hydrogenation

LAH reduces trioxanes to diols as the first event. Trioxane (**87**) furnishes a mixture of the diol (**92**), diphenylmethanol and benzyl alcohol (Scheme 10) ⟨89JCS(P1)1031⟩. These products are explicable through the intermediacy of the primary diol (**93**). Hydrolysis of the latter accounts for (**92**); benzyl alcohol arises by reduction of the benzoic acid so liberated. The formation of small amounts of diphenylmethanol is due to fragmentation of (**87**) by SET from LAH to the peroxide bond. Further reduction of diphenyl ketone accounts for the diphenylmethanol.

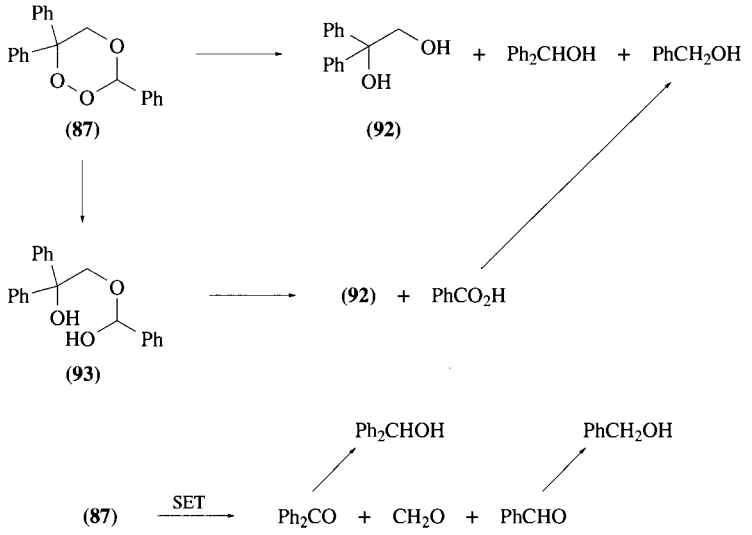
Surprisingly, lithium aluminum deuteride (LAD) gives none of the expected diol (**92**), but only deuterated diphenylmethanol and benzyl alcohol. Thus, SET-initiated fragmentation is the exclusive course of reaction.

The peroxide bond in artemisinin (**9**) resists reduction with sodium borohydride, yielding a mixture of the epimeric lactols or dihydroartemisinins (**65**) ⟨82MI 620-01⟩. On the other hand, hydrogenation of (**9**) over $Pd/CaCO_3$ converts it into deoxyartemisinin (**19**), presumably by spontaneous dehydration of the intermediate diol (**94**) (Scheme 11) ⟨88JMC645⟩.

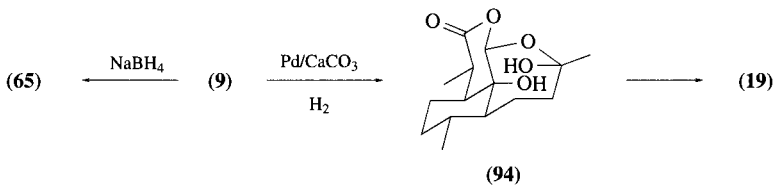
Sodium dithionite ($Na_2S_2O_4$) in neutral medium reduces arteether (**95**) to the ring-opened diol (**96**). In alkaline medium, reduction is more profound, giving the dihydropyran (**97**) (Scheme 12) ⟨90T1871⟩.

6.20.5.5 Reaction with Acid

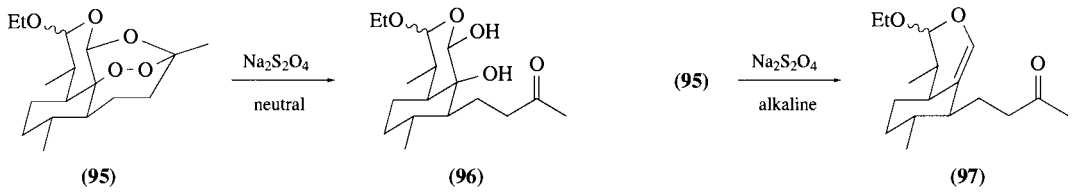
The action of acid on artemisinin (**9**) and its derivatives gives rise to complex mixtures of products, which are often difficult to analyze. Arteether (**95**) undergoes deep-seated rearrangement when



Scheme 10

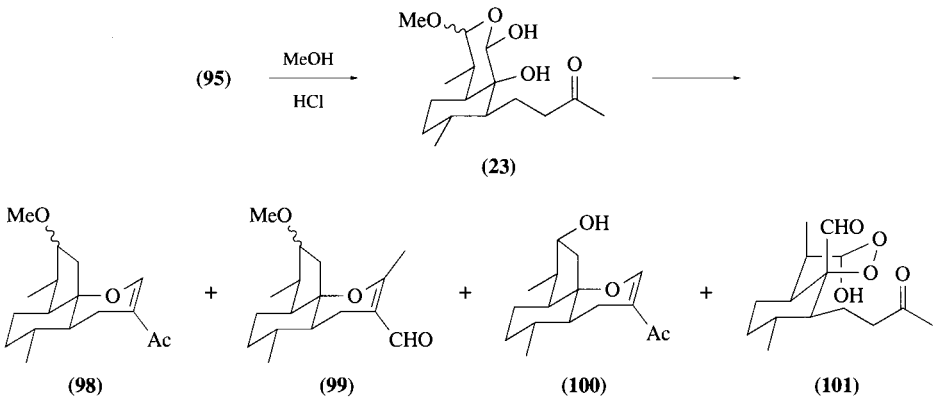


Scheme 11



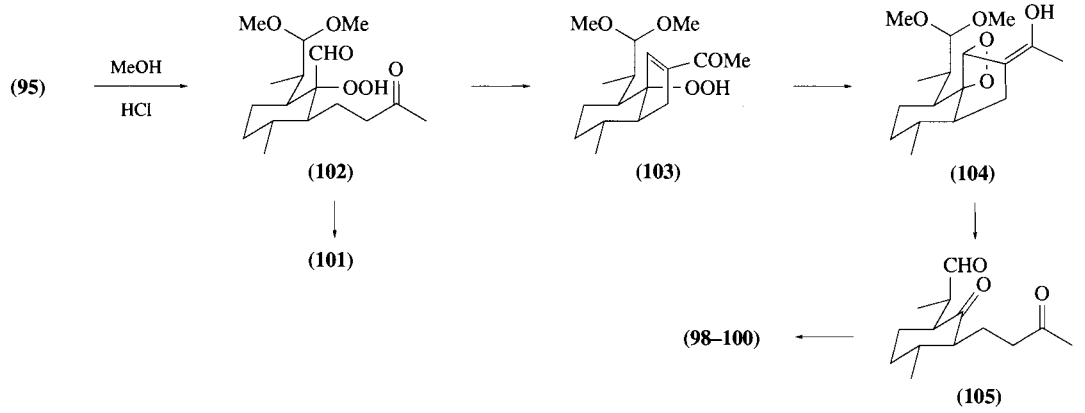
Scheme 12

treated with aqueous hydrochloric acid in methanol for 15 min at 53 °C (Scheme 13) ⟨94H(38)1497⟩. Apart from the primary products, α- and β-artemethers (**23**), the secondary products are the tricyclic dihydropyrans (**98**)–(**100**). The peroxide (**101**) is also formed and this offers a clue to the mechanism of rearrangement, which is reminiscent of the base-promoted reaction of (**9**).



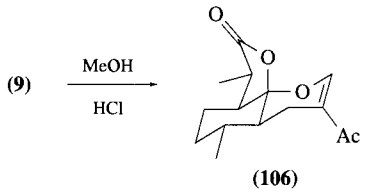
Scheme 13

Protonation in methanol first unravels three of the rings to generate the hydroperoxy acetal (**102**) (Scheme 14). Condensation to (**103**) followed by cyclization to the dioxetane (**104**) and cleavage furnishes the pivotal intermediate (**105**). The latter has the chance to undergo acid-catalyzed bicyclization either through the aldehyde or acetyl function to give the two sets of dihydropyrans (**98**)–(**100**). The hydroperoxide (**102**), in view of its strong nucleophilicity, pre-empts aldolization to a certain extent by reacting with the conveniently placed acetal group to give the cyclic peroxide (**101**). The foregoing results are a correction of those reported earlier ⟨90T1871⟩. The essence of these findings has been further confirmed ⟨95H(41)95⟩.



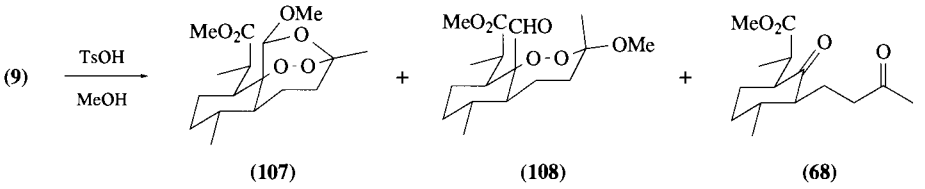
Scheme 14

Artemisinin (**9**) under the same conditions behaves analogously and is reported to give the lactone-pyran (**106**) (Equation (11)) ⟨89H(28)421⟩.



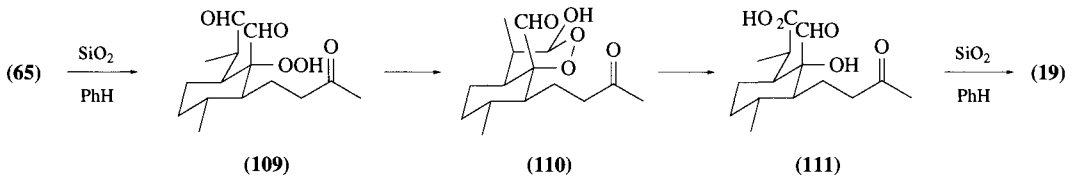
(11)

Submission of (**9**) to *p*-toluenesulfonic acid monohydrate in anhydrous methanol gives the methyl esters (**107**), (**108**) and (**68**), in which the ring system is successively demolished (Equation (12)) ⟨90H(31)1011⟩. The corresponding ethyl esters are obtained by acid catalysis in ethanol.



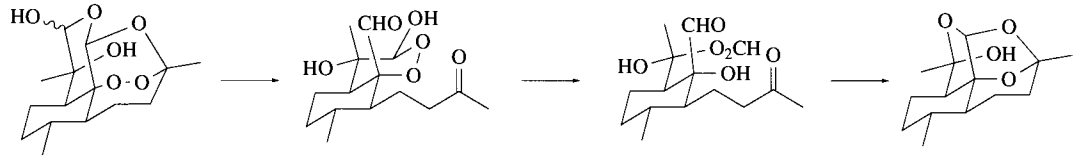
(12)

Dihydroartemisinin (**65**) on treatment with silica gel in benzene rearranges with loss of water to deoxyartemisinin (**19**) in 29% yield (Scheme 15) ⟨94JCS(P1)843⟩. The process entails the ring-opened tautomer (**109**) which by internal oxidation and reduction of the endoperoxide (**110**) forms the hydroxy acid (**111**). The latter finally leads to (**19**) by lactonization.



Scheme 15

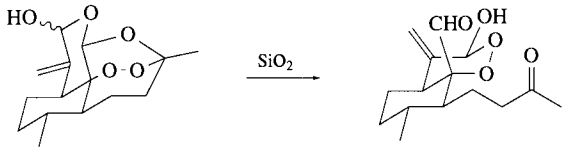
In related fashion, 11β-hydroxy-11-epidihydroartemisinin (**112**) evolves to the hydroxytetrahydrofuran (**115**) (Scheme 16). The presumed intermediate peroxide (**113**) then undergoes Baeyer–Villiger rearrangement to the formate (**114**). Acetalization by elimination of formic acid produces (**115**).



(112) (113) (114) (115)

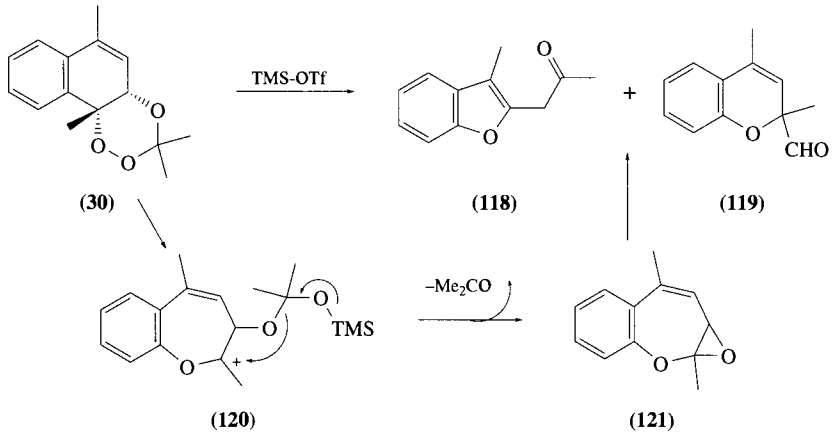
Scheme 16

The foregoing mechanistic considerations, especially the intermediacy of the peroxides (**110**) and (**113**), are supported by the finding that silica converts dihydroartemisitene (**116**) to the peroxide (**117**) (Equation (13)) ⟨90MI 620-02⟩. Moreover, (**110**) has been isolated by treating (**65**) with ethanolic aqueous hydrochloric acid ⟨93MI 620-04⟩.



(116) (117) (13)

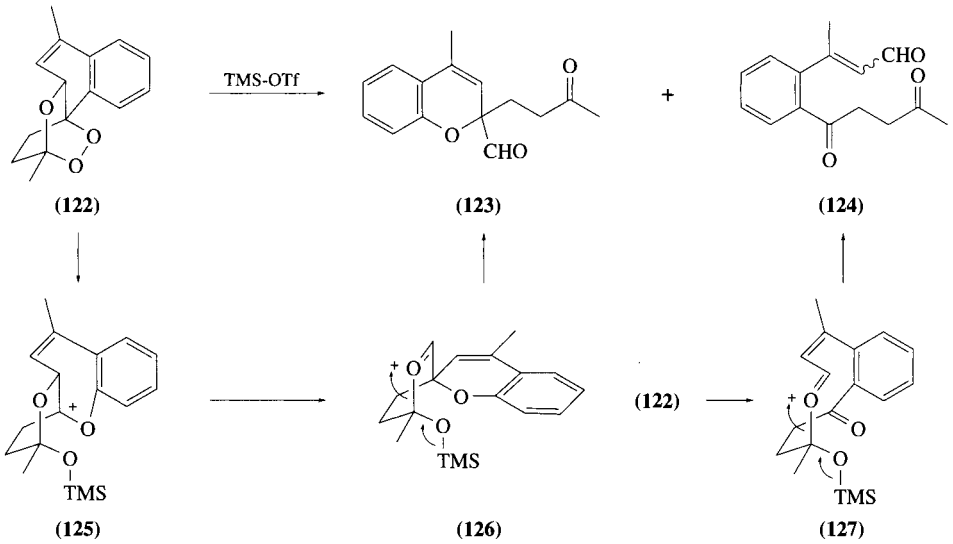
Simple 1,2,4-trioxanes also can be induced to undergo far-reaching rearrangement. Examples are the *cis*- and *trans*-fused bicyclic derivatives (**30**) and (**122**). Exposure of (**30**) to an excess of trimethylsilyl trifluoromethanesulfonate (TMSOTf) for 10 min at 24 °C produces the benzofuran (**118**) in quantitative yield (Scheme 17) ⟨87CC713⟩. Repetition of the experiment with 0.07 equiv. of TMSOTf affords (**118**) in lesser yield, but compensated by the benzopyran isomer (**119**). This result is explicable in terms of rupture of the peroxide bond by the trimethylsilyl cation and subsequent ring enlargement to the benzohomopyrylium cation (**120**). Elimination of acetone gives the epoxide (**121**) that later evolves to (**118**) and (**119**). The *trans*-fused trioxane (**122**) under the same conditions is converted into the benzopyran (**123**) and the fully unravelled ketonic aldehyde (**124**) in high yield (Scheme 18). This time, the geometry of the bridged bicyclic trioxane (**122**) is well disposed for 1,2-migration of the phenyl and vinyl groups to the developing oxenium center to generate the cations (**125**) and (**126**). Desilylation and cleavage afford (**123**). A competing pathway is offered by direct cleavage to the oxonium cation (**127**) and thence to (**124**).



(30) (118) (119) (120) (121)

Scheme 17

Monocyclic trioxanes such as (**87**) are decomposed by Lewis acids ⟨89JCS(P1)1031⟩. Benzaldehyde, phenol and hydroxyacetophenone are obtained from the $TiCl_4$-mediated reaction of (**87**).



Scheme 18

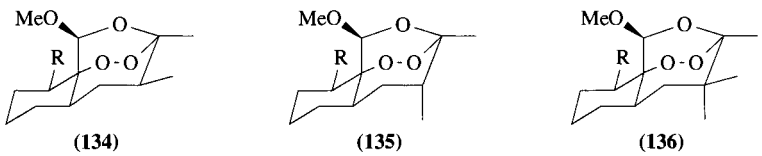
6.20.5.6 Reaction with Ferrous Ion, Ferric Ion, Heme, and Hemin

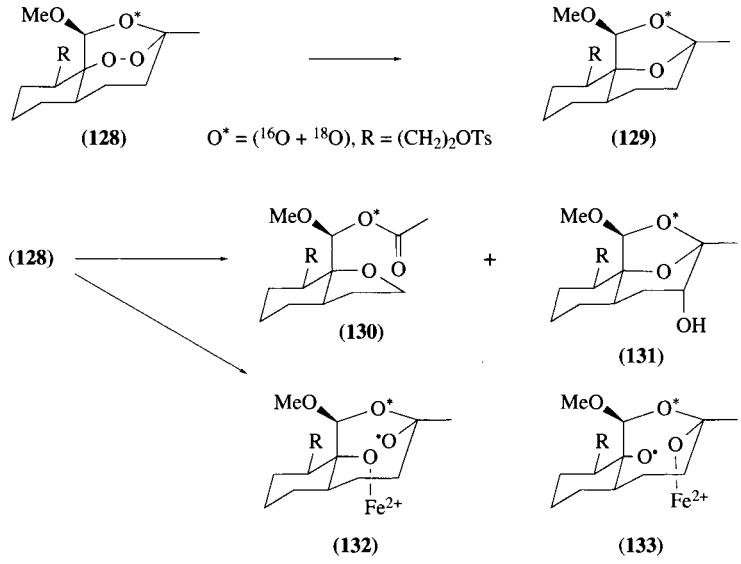
Artemisinin (**9**) and several synthetic trioxanes are endowed with potent antimalarial activity ⟨85SCI1049, B-93MI 620-05, 96MI 620-01⟩. The mode of action is thought to involve the interaction of (**9**) with heme that is produced as a by-product from the digestion of hemoglobin by the malarial parasite, *Plasmodium*, after it has invaded the red blood cell in the host. Accordingly, many model studies have been devoted to delineating the nature of the intermediates that might be responsible for the parasiticidal effect.

Artemisinin (**9**) is reported to form an adduct with heme and hemin ⟨91MI 620-03, 94MI 620-01⟩. Solutions of ferrous ammonium sulfate and (**9**) generate in the presence of a spin trap an unspecified free radical ⟨93AAC1108⟩. Hemin, and particularly intraerythrocytic heme, is thought to activate (**9**) and engender radicals that kill the parasite by alkylating specific membrane-associated proteins.

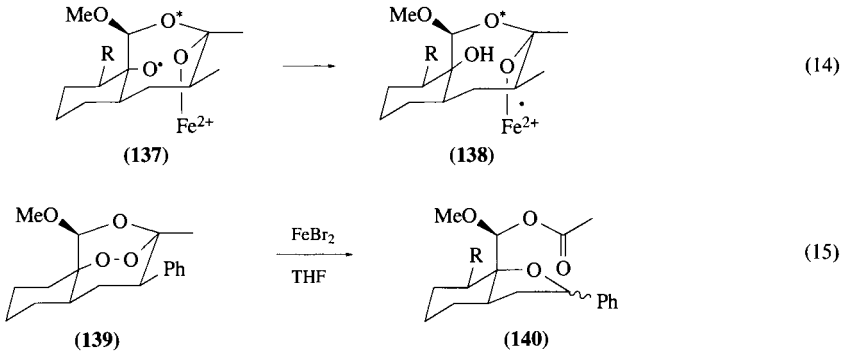
The first chemical test of the aforementioned idea comes from experiments with the ^{18}O-labeled tricyclic trioxane (**128**) (Scheme 19) ⟨92JA8328⟩. Samarium diiodide, dissolving zinc in acetic acid, and similar agents, bring about deoxygenation to 1,3-dioxolane (**129**). On the other hand, ferrous bromide in THF and hemin plus phenylmercaptan, taken as models for intraerythrocytic heme, isomerize (**128**) to the tetrahydrofuran (**130**) and the hydroxy-dioxolane (**131**). This result is explained in terms of the pair of oxy radicals, (**132**) and (**133**), that arise from ferrous ion-induced cleavage of the peroxide bond. It is believed that (**132**) yields (**130**) by C—C bond cleavage, and that (**133**) by 1,5-hydrogen atom shift leads to (**131**).

The antimalarial activity of the 4-methyl, (**134**) and (**135**), and 4,4-dimethyl (**136**) derivatives reveals the relevance of the 1,5-shift ⟨94JMC1256⟩. Of the three, only (**134**) shows significant *in vitro* activity against *P. falciparum*. The other two, (**135**) and (**136**), are inactive because 1,5 hydrogen atom shift is not possible. Thus, (**134**) complexes with the ferrous ion of heme giving first the oxy radical (**137**) and then the C-centered radical (**138**) that is deemed to be toxic to the parasite (Equation (14)). However, if a strongly stabilizing group such as phenyl is placed at the C(4)-β position, as exemplified by (**139**), then antimalarial activity is lost ⟨95JMC2273⟩. The exclusive isomerization of (**139**) by ferrous bromide in THF to the phenyltetrahydrofuran (**140**) reinforces the notion that the lethal agent must be a C(4)-centered radical (Equation (15)). Further studies support the iron–oxene mechanism ⟨96JA3537⟩.

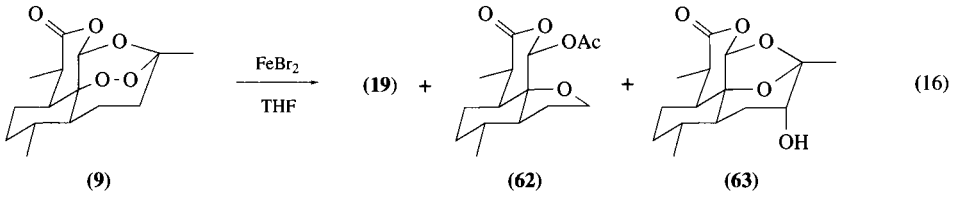




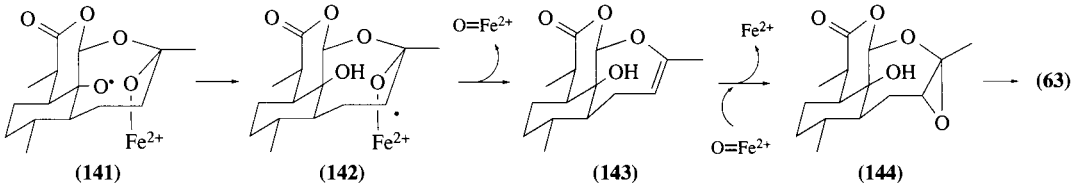
Scheme 19



An amplification of the above mechanistic rationale is offered by the behavior of artemisinin (**9**) towards ferrous bromide in THF (Equation (16)) ⟨95JA5885⟩. On reaction at 0 °C for 45 min, deoxygenation and rearrangement occur to give a 98% yield of (**19**), (**62**) and (**63**), in a ratio of 6 : 3 : 1. The main event is explained by the successive formation of the oxy radical (**141**), deoxyartemisinin (**19**) and Fe(IV)=O. Some 1,5 hydrogen atom shift supervenes; the C-centered radical (**142**) so obtained splits to the hypothetical olefin (**143**) and Fe(IV)=O. The latter oxidant then selectively epoxidizes (**143**) to (**144**), which, after rearranging, accounts for (**63**) (Scheme 20). Repetition of the procedure in the presence of increasing amounts of 1,4-cyclohexadiene proportionally increases the yield of (**19**). This result is attributed to the capture of the radical (**142**). However, reduction of (**9**) to (**19**) is another possibility. Conducting the experiment in the presence of hexamethyl Dewar benzene, tetrahydronaphthalene and methyl phenyl mercaptan, results in aromatization and oxygenation to the sulfoxide and is regarded as evidence for Fe(IV)=O.



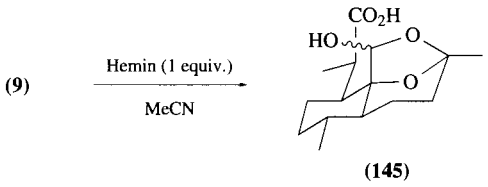
Hemin (1 equiv.) in aqueous acetonitrile, buffered to pH 7.8 to mimic physiological conditions, after 10 days at room temperature deoxygenates artemisinin (**9**) giving (**145**) in 23% yield (Equation (17)) ⟨96TL253⟩. Hemin in the presence of cysteine (1 equiv.) accelerates the formation of (**145**); a similar yield being obtained in 10 min. Hemin and *N*-acetylcysteine (1 equiv.) in THF after 7 h give



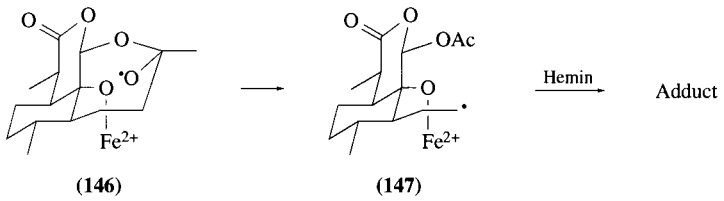
(141) (142) (143) (144)

Scheme 20

deoxyartemisinin (**19**), (**145**), (**62**) and (**63**) in yields of 6, 2, 5 and 2% respectively. Besides these products, an unidentified adduct between (**9**) and hemin appears to form. In contrast, tetraphenylporphin iron(III) chloride (TPPFeCl) converts (**9**) into (**62**) and (**63**) as major and minor products in 74% yield in just 45 min. It is inferred from these results that the C-centered radical (**147**) derived from the initial oxy radical (**146**) may alkylate hemin (Scheme 21). The genesis of the minor product (**63**) from hemin through (**142**) is not considered to be of biological significance.



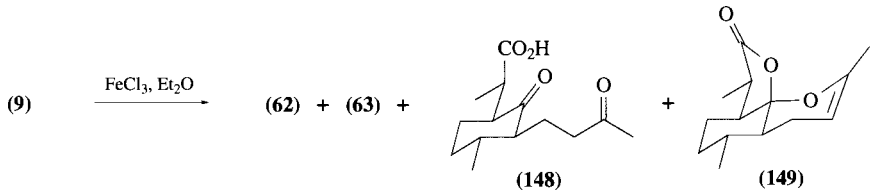
(17)



(146) (147)

Scheme 21

Artemisinin (**9**) reacts with ferrous and ferric salts in aprotic solvents to give similar products ⟨96TL257⟩. Ferrous chloride in the presence of imidazole in MeCN converts (**9**) quantitatively into a mixture of (**62**), (**63**) and (**145**) in a ratio of 78 : 16 : 6. Ferric chloride (0.1 equiv.) in ether under N_2 on reaction for 1.5 hours gives (**62**), (**63**) and the diketo acid (**148**) in 52, 8 and 34% yield respectively (Equation (18)). With an equivalent of $FeCl_3$, reaction is complete in 30 min forming (**62**), (**63**), and the dihydropyran (**149**) in 18, 4 and 68% yield.

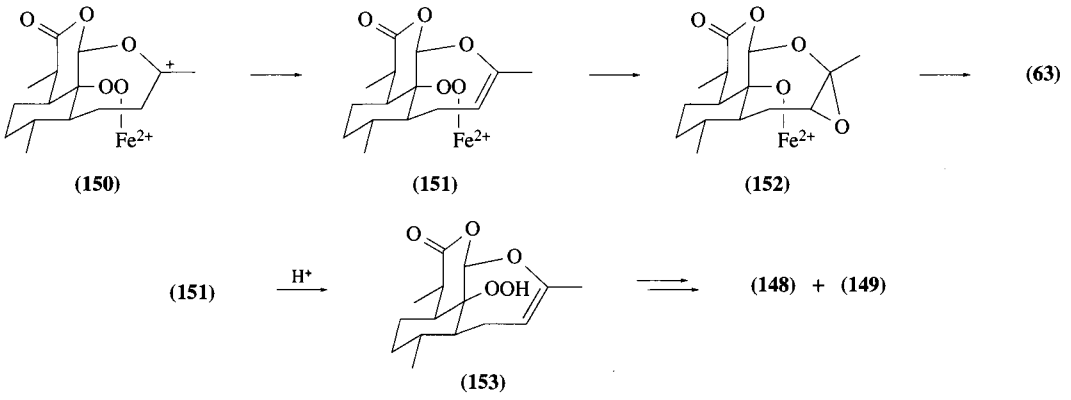


(148) (149)

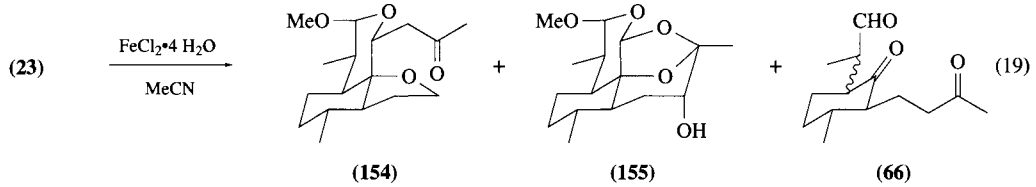
(18)

It is concluded that (**62**) arises by a radical pathway as already postulated, but that (**63**) and (**145**) spring from an ionic process. Lewis acid complexation of (**9**) by $FeCl_3$ is believed to create successively the tertiary cation (**150**) and the alkene (**151**) by selective deprotonation (Scheme 22). Next, intramolecular epoxidation to (**152**) followed by rearrangement delivers (**63**). The alkene (**151**) is also assumed to be the precursor to the dihydropyran (**149**). Protonation of (**151**) produces the hydroperoxide (**153**) that evolves stepwise to (**148**) and (**149**). The antimalarial activity of (**9**) is ascribed to (**153**).

β-Artemether (**23**) displays the same propensity as (**9**) to isomerization when treated with $FeCl_2 \cdot 4H_2O$ in MeCN (Equation (19)) ⟨96HCA1475⟩. Only the tetrahydrofuran (**154**), and the hydroxy-1,3-dioxolane (**155**) together with an epimeric mixture of (**66**) are formed, in 32, 23 and 16% yield respectively. Performing the experiment in the presence of cyclohexene reveals no epoxidation, thereby making the intervention of a Fe(IV)=O species unlikely.

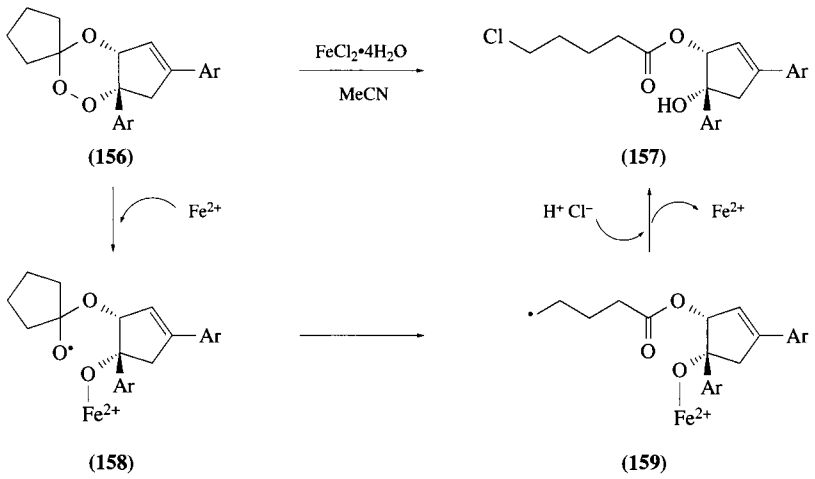


Scheme 22



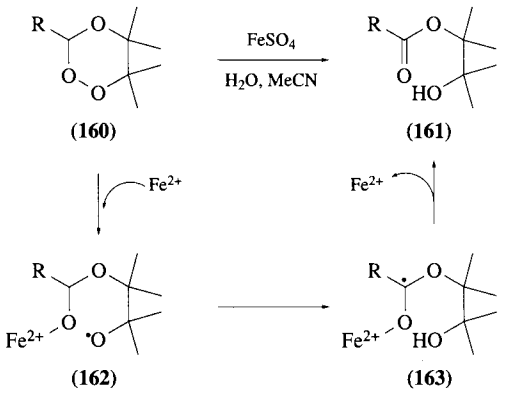
β-Arteether (**95**) on treatment with ferric chloride in methylene chloride at 0 °C is equilibrated to a 1 : 1 mixture of the α- and β-epimers ⟨94IJC(B)613⟩.

Cis-fused cyclopenteno-1,2,4-trioxanes are also sensitive to $FeCl_2$-catalyzed rearrangement ⟨95HCA452⟩. The action of a stoichiometric amount of $FeCl_2 \cdot 4H_2O$ in MeCN on (**156**) leads to (**157**). An oxy radical (**158**) is engendered by adjunction of Fe^{2+} which collapses to the C-centered radical (**159**) thanks to ester formation. Finally (**159**) is captured by chloride ion giving (**157**) (Scheme 23) ⟨96HCA1475⟩.



Scheme 23

Monocyclic trioxanes (**160**) having a hydrogen substituent at C(3) are isomerized to 1,2-diol monoesters (**161**) on treatment with ferrous sulfate in aqueous MeCN (Scheme 24) ⟨95TL7551⟩. Coordination of Fe^{2+} to (**160**) generates the oxy radical (**162**) which by 1,5-hydrogen shift and ejection of Fe^{2+} from the resulting C-centered radical (**163**) accounts for (**161**). The foregoing avenue of rearrangement explains why trioxanes like (**156**), but only having a single alkyl substituent at C(3), do not display antimalarial activity.

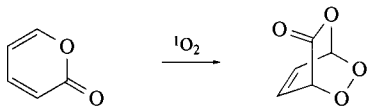


Scheme 24

6.20.6 SYNTHESIS

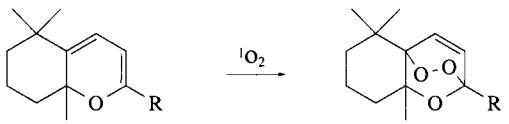
6.20.6.1 Addition of Singlet Oxygen to α-Pyrans and α-Pyrones

Dye-sensitized photooxygenation of α-pyrones and α-pyrans offers the simplest access to 1,2,4-trioxanes. Examples are the conversions of (**36**) to (**37**), and (**40**) to (**41**). The photooxygenation of α-pyran (**164**) in methylene chloride at 0 °C using tetraphenylporphin as sensitizer and a 400 W sodium lamp gives (**165**) (Equation (20)) ⟨78AG(E)211⟩.



(**164**) (**165**) (20)

Singlet oxygen adds readily to tetrahydrobenzopyrans (**166**) derived from the photoisomerization of β-ionone ⟨73ABC2241⟩ and its derivatives, for example (**167**) ⟨88JMC713⟩, to afford the corresponding trioxanes (**168**) and (**169**) (Equation (21)). The saturated derivatives are obtainable by reduction with diimide in the case of (**165**) and (**169**), and by hydrogenation over Pt for (**168**).

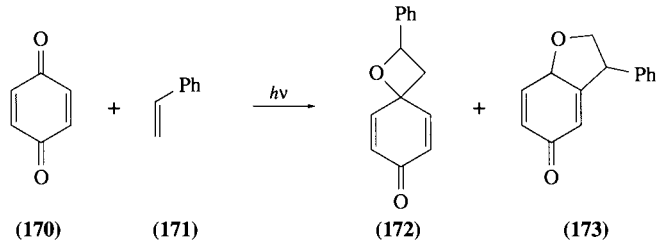


(**166**) R = Me
(**167**) R = $CH_2CH(OH)Me$

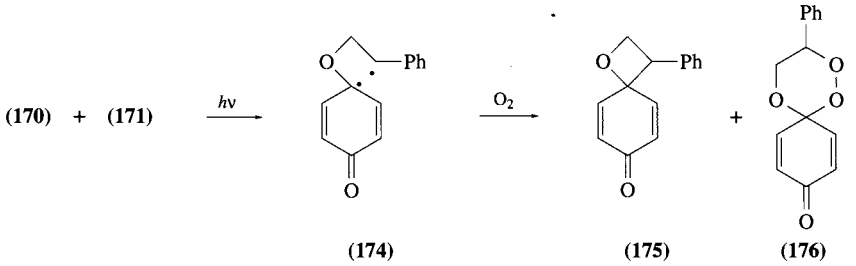
(**168**)
(**169**) (21)

6.20.6.2 Addition of Triplet Oxygen to 1,4-Diradicals

1,2,4-Trioxanes can be formed by the laser excitation of electron deficient ketones, such as *p*-benzoquinone (**170**), and olefins under an atmosphere of triplet oxygen. The irradiation of (**170**) in the presence of styrene (**171**) is inefficient and leads to cycloadducts (**172**) and (**173**) (Equation (22)) ⟨74CC461⟩. However, under 11 atm of oxygen pressure the trioxane (**176**) is the sole product (Scheme 25). The reaction is a variant of the Paternó–Büchi reaction for preparing oxetanes. The excited ketone adds to the alkene to give the triplet 1,4-diradical (**174**) which, instead of closing to (**175**), captures oxygen. 1,1-Diphenylethylene and *t*-butylethylene can be similarly transformed to trioxanes.



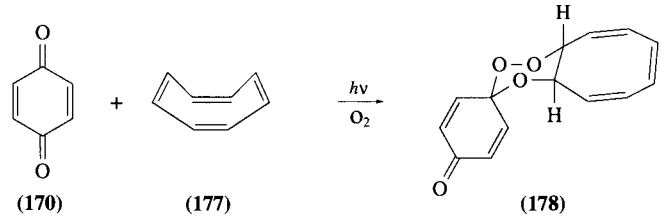
(170) (171) (172) (173) (22)



(170) + (171) (174) (175) (176)

Scheme 25

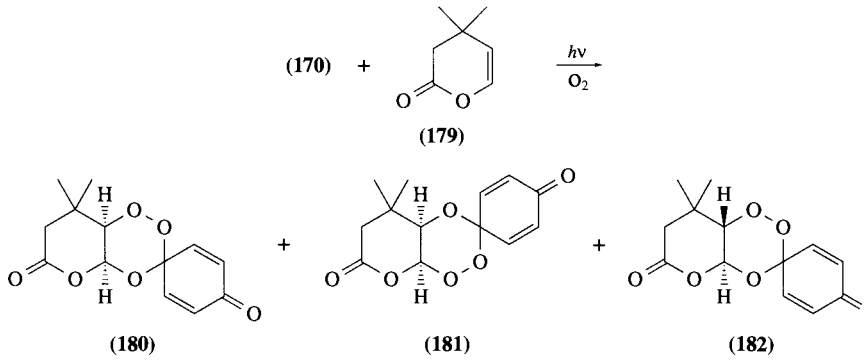
The stereochemistry of addition has been elucidated by irradiating (**170**) under aerobic conditions with cyclooctatetraene (**177**). The *trans*-fused trioxane (**178**) is formed as evidenced by x-ray crystallography (Equation (23)) ⟨74JA2955⟩. Norbornene under the same conditions also gives a *trans*-fused trioxane ⟨82JA4429⟩.



(170) (177) (178) (23)

The procedure works well when cyclohexene, cyclooctene, 2,2-dimethyl-3-(trimethylsiloxy)-3-butene and 1-phenyl-1-(trimethylsiloxy)ethylene are used as the olefin partner. Incorporation of oxygen gives the trioxanes in yields of 45–80%.

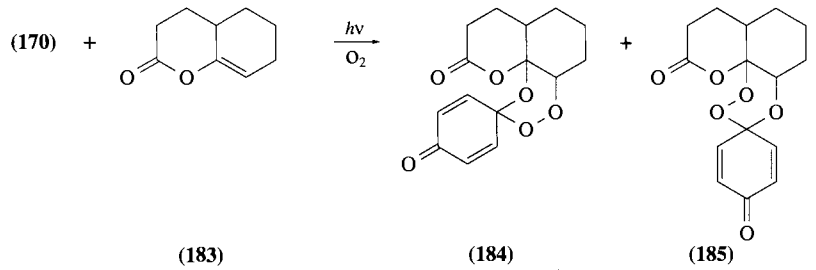
The 1,2,4-trioxane lactone structural unit that is part of artemisinin (**9**) has been synthesized by the laser irradiation of benzoquinone (**170**) and dihydro-4,4-dimethyl-2*H*-pyran-2-one (**179**) under oxygen (Equation (24)) ⟨88JOC4986⟩. Two regioisomeric *cis*-fused trioxanes, (**180**) and (**181**), and the *trans*-fused isomer (**182**) are obtained besides the pair of less and more hindered oxetanes in a ratio of 9 : 18 : 28 : 17 : 28 and yields of ca. 65%.



(170) + (179) (180) (181) (182) (24)

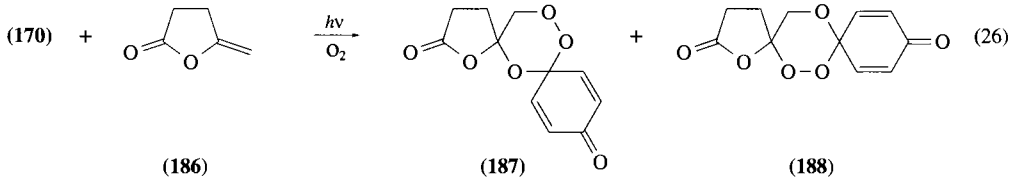
Further examples of the aerobic Paternó–Büchi reaction furnish trioxanes, but with little regio- and stereocontrol. All four possible trioxanes, *cis* and *trans* for each regioisomer, (**184**) and (**185**),

are obtained from the combination of (**170**), the bicyclic ene-lactone (**183**) and oxygen (Equation (25)) ⟨88JPR391⟩.



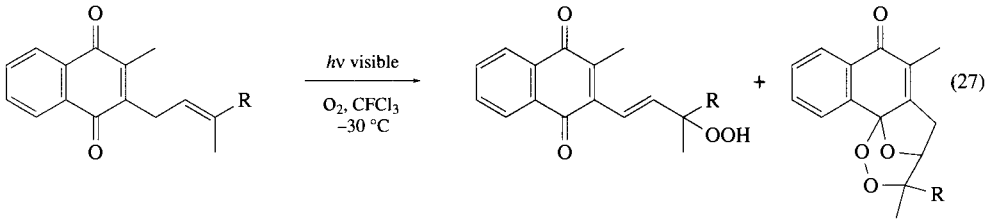
(**183**) (**184**) (**185**) (25)

4-Penten-4-olide (**186**) combines in the same oxygenative fashion with (**170**) to assemble the trioxanes (**187**) and (**188**) (Equation (26)) ⟨88LA869⟩.



(**186**) (**187**) (**188**) (26)

Several intramolecular examples of the above reaction are known. Menaquinone-1 (**189**) forms an allylic hydroperoxide (**191**) (34% yield) of nonsinglet oxygen origin and a stable trioxane (**192**) (31% yield) when irradiated under oxygen (Equation (27)) ⟨80TL3459⟩. Phylloquinone (**190**) follows the same course giving a pair of epimeric trioxanes (**193**).

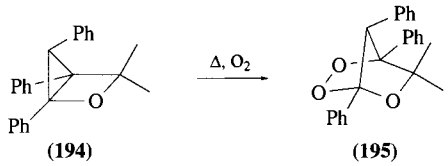


(**189**) R = Me
(**190**) R = $CH_2(CH_2CH_2CH(Me)CH_2)_3H$

(**191**) (**192**) (**193**) (27)

The near-UV irradiation of plastoquinone-1 in benzene under oxygen gives several products including a bridged bicyclic trioxane ⟨71JA502⟩.

Thermolysis of the oxetane (**194**) in the presence of oxygen yields the 1,2,4-trioxane (**195**) in 90% yield (Equation (28)) ⟨79JOC4021⟩.



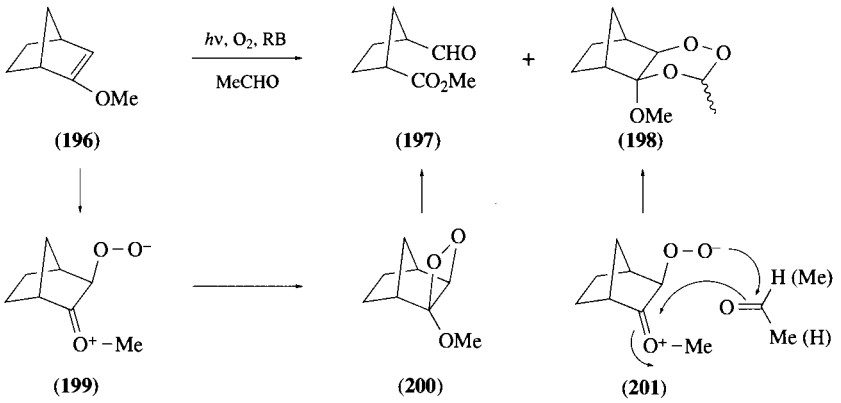
(**194**) (**195**) (28)

6.20.6.3 Addition of Singlet Oxygen to Monoalkenes in the Presence of Aldehydes

The reaction of singlet oxygen with alkenes constitutes an important chapter in organic chemistry. The discovery that certain enol ethers from zwitterionic peroxides as the primary event has led to the development of new methods for preparing a variety of 1,2,4-trioxanes ⟨B-91MI 620-01, 93CSR59⟩.

The rose bengal-sensitized photooxygenation of 2-methoxynorbornene (**196**) in acetaldehyde at −78 °C is the archetype (Scheme 26) ⟨83JA6498, 84MI 620-02⟩. The aldehydic ester, (**197**) (31% yield), and the pair of *cis*-fused epimeric trioxanes (**198**) (13% yield) are obtained. The result is interpreted

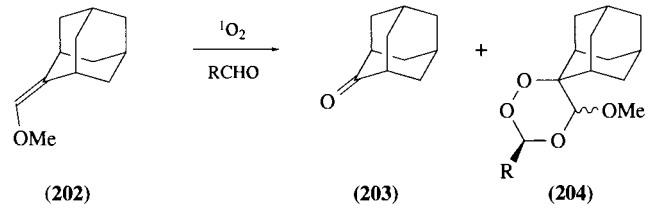
by attack of a molecule of singlet oxygen on the *exo* face of (**196**) to give the zwitterion (**199**), which normally closes to the 1,2-dioxetane (**200**) and thence to (**197**) by fission. However, a molecule of acetaldehyde can intercept (**199**) in *syn* and *anti* arrangements (**201**) canceling the charges by cyclization in *cis* fashion to the parent ring to form (**198**).



(196) (197) (198) (199) (200) (201)

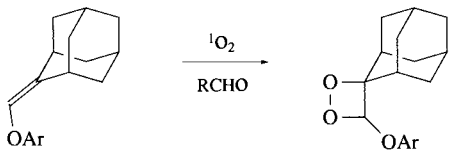
Scheme 26

2-(Methoxymethylidene)adamantane (**202**) on photooxygenation in acetaldehyde, propanal and pivalaldehyde (RCHO) gives, apart from some adamantanone (**203**), the epimeric trioxanes (**204**) (Equation (29)) ⟨85T2081⟩. The structures follow from the x-ray structure of the *cis*-epimer of (**204**) (R = Bu^t).

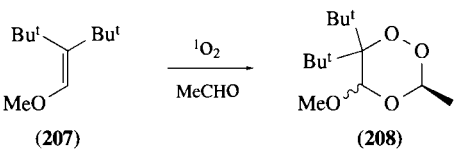


(202) (203) (204) (29)

It is worth noting that only 1,2-dioxetanes (**206**) are obtained by photooxygenating 2-(phenoxymethylidene)adamantanes (**205**) in acetaldehyde as solvent (Equation (30)). However, these dioxetanes can be expanded to trioxanes at a later stage (see Section 6.20.6.4). Acyclic enol ethers behave in the same way. 1,1-Di-*t*-butyl-2-methoxyethylene (**207**), singlet oxygen and acetaldehyde cyclize to the *cis* and *trans* trioxanes (**208**) in 31% yield (Equation (31)).

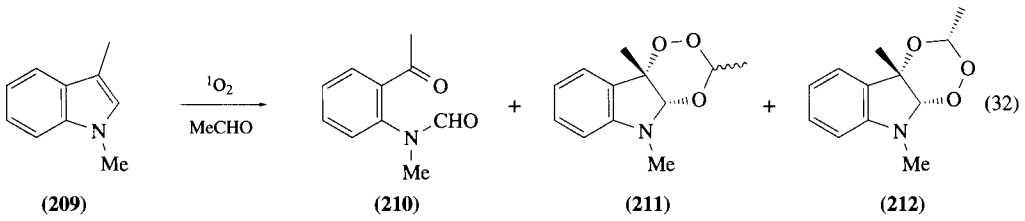


(205) (206) (30)



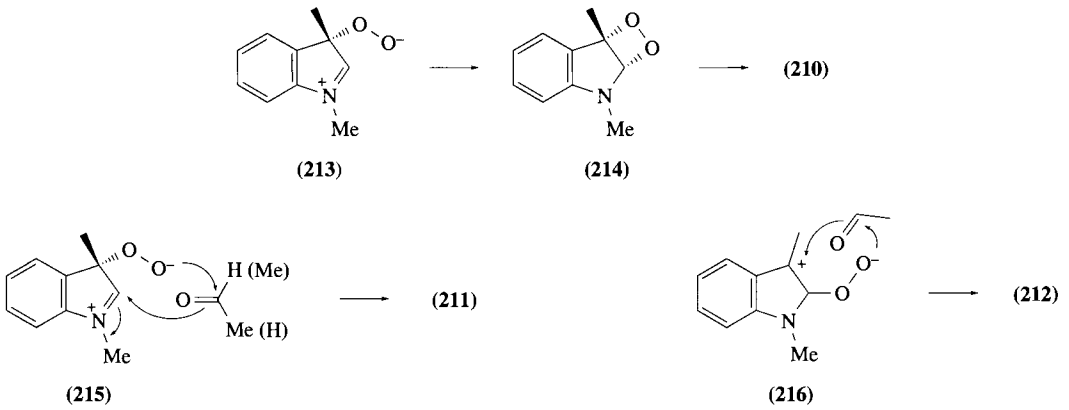
(207) (208) (31)

Zwitterionic peroxides are likely intermediates in the addition of singlet oxygen to indoles ⟨77ACR346⟩. The behavior of 1,3-dimethyl indole (**209**) confirms this expectation. Photooxygenation of (**209**) in CCl_4 containing tetraphenylporphin (TPP) as sensitizer and a molar excess of acetaldehyde gives rise to the expected *N*-formyl ketone (**210**) (10% yield) and the trioxanes (**211**) and (**212**) in 50–60% yield (Equation (32)) ⟨84HCA1104⟩.



(209) (210) (211) (212)

Clearly, the zwitterionic peroxide (**213**) is implicated (Scheme 27). Closure to the dioxetane (**214**) and scission to (**210**) is a minor event. Capture of (**213**) by aldehyde predominates. The epimeric *cis*-fused trioxanes (**211**) arise from the *syn* or *anti* arrangement (**215**). The major epimer, identified by x-ray, has the C3 methyl group disposed *cis* with respect to the indole ring. The *trans* epimer is unstable and cannot be isolated. The structure of the minor position isomer (**212**) follows from its NMR spectrum. It probably derives from the addition of the alternative benzylic zwitterionic peroxide (**216**) to acetaldehyde.

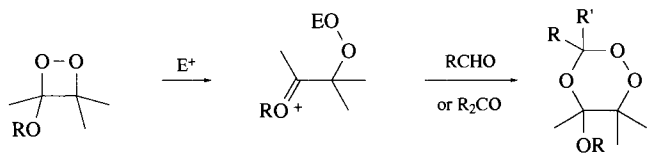


Scheme 27

The synthetic utility of this method is confined to those alkenes which give trappable zwitterionic peroxides and only works for aldehydes. The less electrophilic ketones fail to give trioxanes.

6.20.6.4 Addition of 1,2-Dioxetanes to Carbonyl Partners

The number of reactions that 1,2-dioxetanes can undergo is limited. Usually the O—O bond is broken followed by attack of the reagent. However, when an alkoxy or phenoxy is attached at C(3), as exemplified by (**217**), the endocyclic C(3)—O bond can be induced to break by an electrophile (E^+). The resulting peroxy alkoxonium or phenoxonium ion (**218**) can then incorporate an aldehyde (RCHO) or ketone (R_2CO) to make a 3-substituted 1,2,4-trioxane ring (**219**) (Scheme 28).

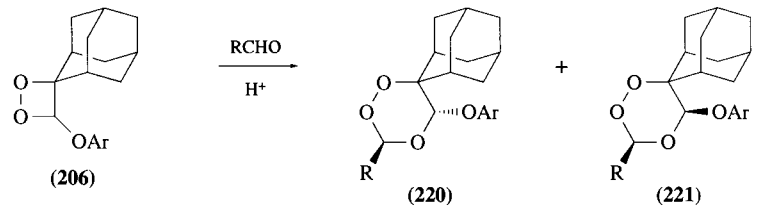


(**217**) R = alkyl or aryl (**218**) (**219**) R' = H or R

Scheme 28

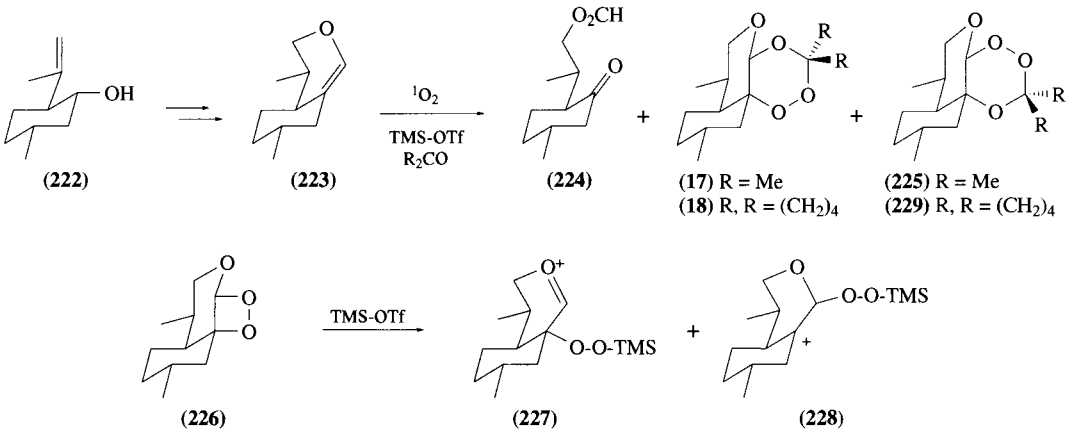
The 1,2-dioxetanes of 2-(phenoxymethylidene)adamantanes (**206**) when mixed with excess acetaldehyde in methylene chloride containing a catalytic amount of Amberlyst-15 give the *erythro* and *threo* diastereomers (**220**) and (**221**) in a ratio of ca. 2:1 and yields of 45–75% (Equation (33)) ⟨83HCA2615⟩. *p*-Chloro- and *p*-methoxyphenoxy-substituted dioxetanes give the highest yields. Trioxane formation is less efficient with propanal and the *p*-chloro and *p*-nitro derivatives of

benzaldehyde, yields of 17–34% being obtained. In all cases, small amounts of adamantanone accompany the trioxane product.



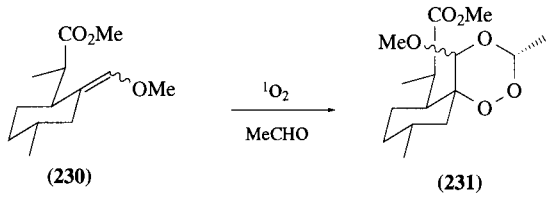
(33)

The 1,2-dioxetanes of indene and 1,2-dihydronaphthalene on catalysis with trifluoroacetic acid incorporate acetaldehyde so forming the corresponding *cis*-fused bicyclic trioxanes in yields of 95% and 75% respectively ⟨92C114⟩. An application of the preceding reaction is the preparation of trioxanes possessing part of the artemisinin skeleton (Scheme 29) ⟨88HCA2042⟩. (−)-Isopulegol (**222**) is transformed in a few steps to the pyran (**223**). Photooxygenation of (**223**) is carried out by using methylene blue (MB) as sensitizer in methylene chloride at −78 °C. Addition of excess acetone and TMSOTf to the cold solution leads to the formation of the formate (**224**) (11% yield), the desired trioxane (**17**) (59% yield), and the regioisomeric trioxane (**225**) (5% yield). The structure of (**17**), determined by x-ray, has the same configuration as the corresponding part of artemisinin (**9**). The precursor is the dioxetane (**226**) resulting from the selective addition of singlet oxygen to the *exo* face of the double bond of (**223**). The electrophilic agent, TMSOTf, opens (**226**) mainly to the peroxy cation (**227**) which captures acetone to give (**17**). However, a small amount of the regioisomeric peroxy cation (**228**) must also be formed, thereby accounting for the formation of the 'wrong' trioxane (**225**). Cyclopentanone reacts the same way, giving the spirocyclic trioxanes (**18**) (61% yield) and (**229**) (8% yield).

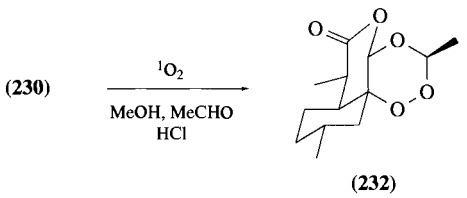


Scheme 29

The enol ether (**230**) has features in common with (**223**) in that they both encompass part of the artemisinin skeleton. Rose bengal-sensitized photooxygenation of (**230**) in THF containing acetaldehyde is reported to give the pair of (3*S*) 3-methyl trioxanes (**231**) (35% yield) which are epimeric at C5 (Equation (34)) ⟨88CC372⟩. Paradoxically, when photooxygenation is carried out in methanol followed by acid hydrolysis, the secoartemisinin derivative (**232**) (15% yield) is formed in which the C(3) methyl substituent has the 3*R* configuration (Equation (35)). The structures of the 3*S*,5*S* epimer of (**231**), and (**232**) are established by x-ray.

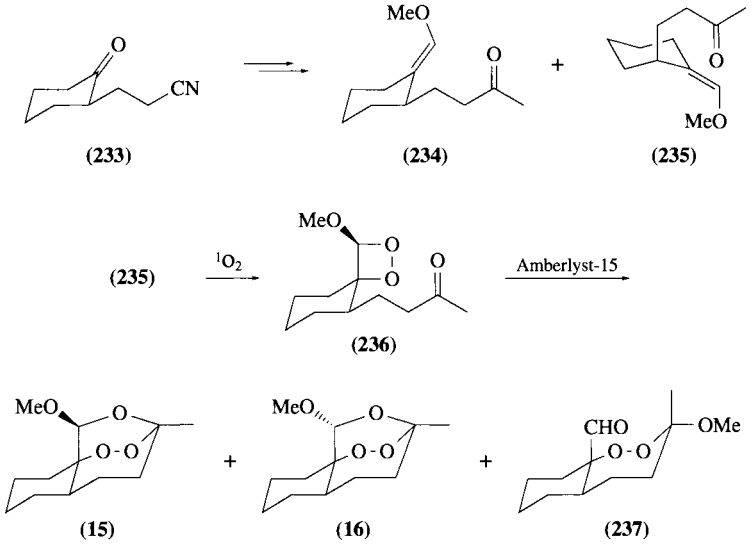


(34)



(35)

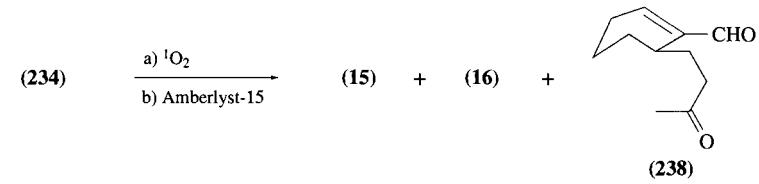
An intramolecular version of the preceding reaction enables an artemisinin-like ABC-tricyclic trioxane to be constructed. The *E*- and *Z*-2-(methoxymethylidene)cyclohexanones, (**234**) and (**235**), are first prepared from the 2-(cyanoethyl)cyclohexanone (**233**) (Equation (36)) ⟨93HCA2775⟩. Photooxygenation of a solution of (**235**) containing MB in methylene chloride at −78°C followed by addition of Amberlyst-15 gives the *endo* and *exo* methoxy-1,2,4-trioxanes (**15**) and (**16**) together with the peroxide (**237**) in yields of 48, 19 and 30% respectively (Scheme 30). All compounds are crystalline solids, the structures of which are elucidated by x-ray. The products are explicable by addition of singlet oxygen to the less hindered face of (**235**) to give the dioxetane (**236**), which on acid catalysis isomerizes first to the *endo* trioxane (**15**). As the latter is an acetal it readily loses methanol by protonation thereby equilibrating to the more stable *exo* epimer (**16**) and finally undergoes ring cleavage to the peroxide (**237**).



(36)

Scheme 30

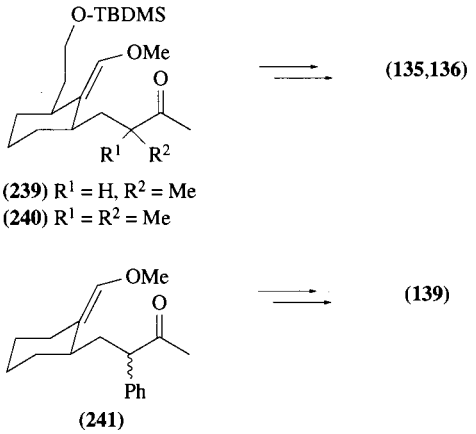
The foregoing sequence is less effective with the *E*-isomer (**234**), the total yield of product being 65%. The reason lies in the availability of axially disposed allylic hydrogen atoms on the side of the molecule that is sterically accessible to singlet oxygen. In other words, allylic hydroperoxidation pre-empts cycloaddition to the dioxetane. Consequently, although (**15**), (**16**) and (**237**) (17, 17 and 14% yield respectively) are formed as before, the cyclohexenecarboxaldehyde (**238**) is the major product (30% yield) (Equation (37)).



(37)

The aforementioned route has been used to prepare the 4-substituted tricyclic trioxanes (**135**), and (**136**) from the *E*-2-(methoxymethylidene)cyclohexanones (**239**) and (**240**), and (**139**) from the *Z*-methoxymethylidene derivative (**241**) (Scheme 31) ⟨92JA8328, 92JMC2459, 94JMC1256, 95JMC2273⟩. In all these cases, only the *endo* methoxy epimers are reported. No mention is made of equilibration

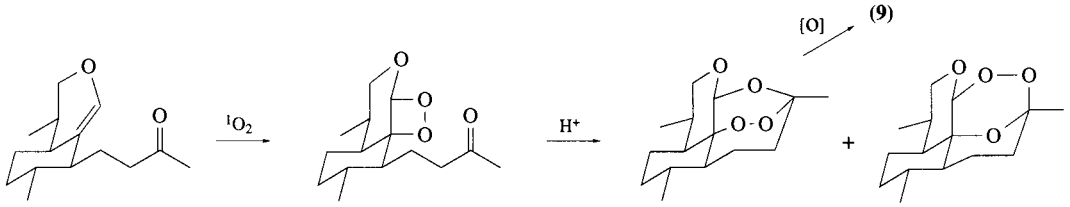
to *exo* epimers or to peroxides resembling (**237**). An analogous synthetic procedure makes use of triethylsilyl hydrotrioxide ($Et_3SiOOOH$), for preparing the intermediate 1,2-dioxetane ⟨95HAC105⟩.



(**239**) $R^1 = H$, $R^2 = Me$
(**240**) $R^1 = R^2 = Me$
(**241**)

Scheme 31

A synthesis of artemisinin (**9**) has exploited the intramolecular variant of the sequence (**223**)–(**17**) ⟨90CC726⟩. MB-sensitized photooxygenation of the pyran (**242**) affords the 1,2-dioxetane (**243**) (Scheme 32) which on acid catalysis opens to the analogue of (**227**). Its capture gives the deoxoartemisinin (**244**) that can easily be oxidized to artemisinin (**9**). The other trioxane (**245**), having the 'wrong' arrangement of oxygen atoms, is also formed via the other zwitterionic peroxide analogous to (**228**). 4-Demethyl- and 4-demethyl-4-ethyldeoxoartemisinin have been prepared by using the same key steps, namely the photooxygenation of a pyran intermediate and intramolecular condensation of the resulting dioxetane ⟨93JCS(P1)2147⟩. The same technology has been exploited for the preparation of a steroidal 1,2,4-trioxane ⟨93JCS(P1)2149⟩.



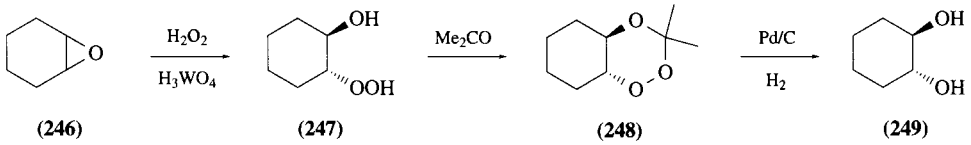
(**242**) (**243**) (**244**) (**245**)

Scheme 32

6.20.6.5 Addition of Hydroperoxides to Carbonyl Partners

The first recorded preparation of a 1,2,4-trioxane springs from a study of the reaction of 1,2-epoxycyclohexane (**246**) with hydrogen peroxide ⟨57JOC1682⟩. The addition of (**246**) to a mixture of tungstic acid (H_3WO_4), acetone and hydrogen peroxide gives a 20% yield of the *trans*-bicyclic trioxane (**248**). Hydrogenation of (**248**) over 10% palladium-on-charcoal gives *trans*-1,2-cyclohexanediol (**249**) thereby showing the ring fusion to be *trans*. In a separate experiment the *trans*-1,2-hydroperoxy alcohol (**247**) intermediate and acetone are shown to give (**248**).

The preceding reaction turns out to be general. Epoxides on treatment with hydrogen peroxide



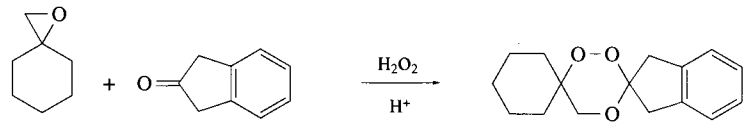
(**246**) (**247**) (**248**) (**249**)

Scheme 33

can be opened to the hydroperoxy alcohols and transformed into trioxanes by condensation with a carbonyl partner. The simplest example is provided by ethylene oxide; 3,3-dimethyl-1,2,4-trioxane is obtainable from the intermediate hydroperoxy alcohol and acetone in the presence of copper sulfate ⟨B-72MI 602-01⟩.

The perhydrolysis of other epoxides and subsequent condensation follow the same reaction course. Styrene epoxide affords 3,6-diphenyl-1,2,4-trioxane ⟨76CC508⟩. Other simple epoxides, for example those obtained from ispropene and 1,1-diphenylethylene, are also similarly convertible into trioxanes ⟨71CC822⟩.

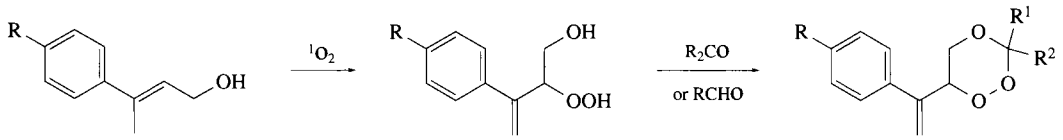
The acid-catalyzed condensation of methylidenecyclohexane epoxide (**250**), hydrogen peroxide and 2-indanone (**58**) affords (**57**) (Equation (38)) ⟨85CC590⟩.



(250) (58) (57) (38)

An equivalent process is the tungsten oxide-catalyzed interaction of epoxides and peracetals ⟨89JCS(P1)1031⟩. An example is the condensation of styrene epoxide and the peracetal of benzaldehyde to give 3,6-diphenyl-1,2,4-trioxane.

The dye-sensitized photooxygenation of 3-aryl-2-butenols (**251**) provides several 1,2-hydroperoxy alcohols (**252**) (Scheme 34) ⟨90T6901⟩. The latter condense easily with aldehydes and ketones to the trioxanes (**253**) and (**254**).

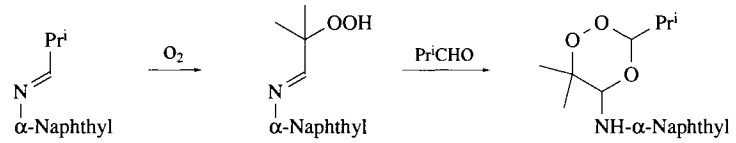


(**251**) R = H, Me, OMe, F, Cl (**252**) (**253**) $R^1 = R^2 = Me$; (**254**) $R^1 = H$, $R^2 = C_6H_4OMe$-*p*

Scheme 34

The same reaction is observed between *trans*-1-hydroxy-2-hydroperoxy-1,2,3,4-tetrahydronaphthalene and aldehydes or ketones in the presence of catalytic amounts of Amberlyst-15 or trimethylsilyl trifluoromethanesulfonate; the *trans*-fused trioxanes being formed in 75–95% yield ⟨92C114⟩.

Imines, formed *in situ* from primary amines and aldehydes having a hydrogen atom available at the α-position, are easily autoxidized to the allylic hydroperoxides. The latter can then condense with the excess aldehyde present to form trioxanes in yields varying from 11% to 66%. A pertinent example is the imine (**255**), derived from α-naphthylamine and isobutyraldehyde ⟨80JCS(P1)2300⟩. The hydroperoxide (**256**) formed from (**255**) condenses with another molecule of isobutyraldehyde to give the *cis* and *trans* 3,5-disubstituted trioxanes (**257**), the structures of which are elucidated by x-ray (Scheme 35).

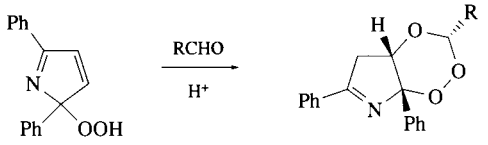


(**255**) (**256**) (**257**)

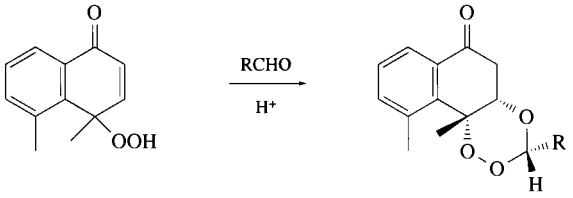
Scheme 35

In analogous fashion, acetaldehyde or pivalaldehyde add to 2-hydroperoxy-2,5-diphenyl-2*H*-pyrrole (**258**) to form the *cis*-fused 3-methyl and *t*-butyltrioxanes (**259**) in 24% and 20% yields (Equation (39)) ⟨84HCA2254⟩. The Amberlyst-15-catalyzed adjunction of acetaldehyde, pivalaldehyde, benzaldehyde or *p*-chlorobenzaldehyde to the hydroperoxynapthalenone (**260**) is far more

efficient. Just the *cis*-3-substituted trioxanes (**261**) are formed in 80–95% yields (Equation (40)). The new ring junction is *cis*-fused as attested by the x-ray of the *p*-chlorophenyl derivative. The methyl group at the *peri* position sterically prevents the formation of the *trans* C(3)-substituted epimer. Nevertheless, the addition of acetone to (**260**) is unhampered, the trioxane being obtained in 64% yield.

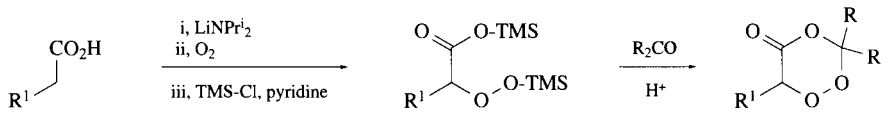


(258) (259) R = Me, Bu^t (39)



(260) (261) R = Me, Bu^t, Ph, C_6H_4-Cl-*p* (40)

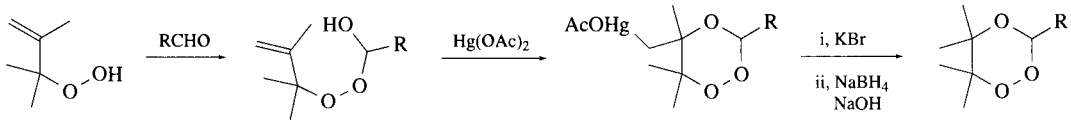
Yet another variant of the preceding theme provides a simple synthesis of 1,2,4-trioxan-5-ones, a formerly unknown chemical species. The oxygenation of the dianion of acetic acid derivatives (**262**) followed by quenching with trimethylsilyl chloride produces the silylated peroxy esters (**263**) (Scheme 36) ⟨83CC1064, 91HCA1239⟩. Catalyzed condensation of aldehydes and ketones, exemplified by R_2CO, proceeds with elimination of $Me_3SiOSiMe_3$ giving, despite appearances, a thermally stable variety of 3,6-substituted trioxanones (**264**). Their structures are confirmed by x-ray.



(262) (263) (264)

Scheme 36

Oxymercuriation has also been used to trigger cyclization of peracetals ⟨91CC947, 92CC428, 94TL8057⟩. The peracetal (**266**), obtainable from the allylic hydroperoxide (**265**), adds to the double bond to give the mercuric acetate (**267**) (Scheme 37). Anion exchange and reduction afford the 3-substituted trimethyltrioxanes (**268**) in yields of 35–62%. Cyclization of (**266**) can also be effected with *N*-bromosuccinimide ⟨93TL6643⟩. Other electrophiles can be used for activating unsaturated hydroperoxides to bring about ring closure ⟨96TL463⟩.



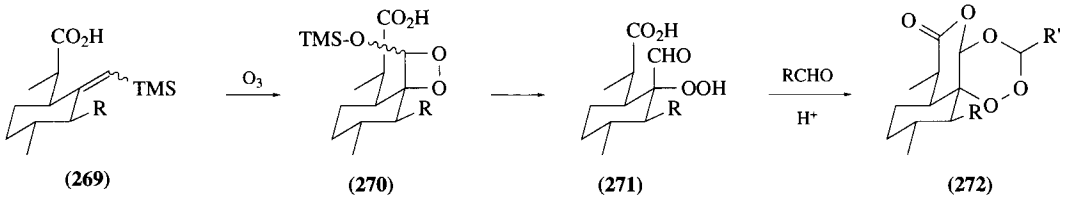
(265) (266) (267) (268)

Scheme 37

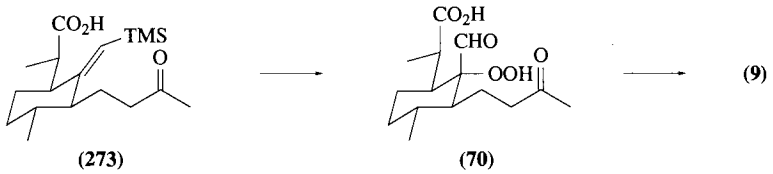
Several secoartemisinins, illustrated by (**272**), have been assembled from vinylsilane (**269**) (Scheme 38) ⟨90CC1487⟩. Ozonation and treatment with Amberlyst-15 generate successively the dioxetane (**270**) and the hydroperoxy-aldehyde (**271**). Condensation of the latter with acetaldehyde, followed by lactonization, affords (**272**).

Artemisinin (**9**) has been synthesized from the vinylsilane (**273**) by repetition of the preceding sequence (Scheme 39) ⟨92JA974⟩. The crucial intermediate is the hydroperoxyaldehyde (**70**) that cyclizes to (**9**). 6,9-Desdimethylartemisinin has been prepared by applying the same methodology ⟨89JOC1792⟩.

The intermediate (**70**) can also be conveniently obtained from artemisinic acid (**274**), the biogenetic

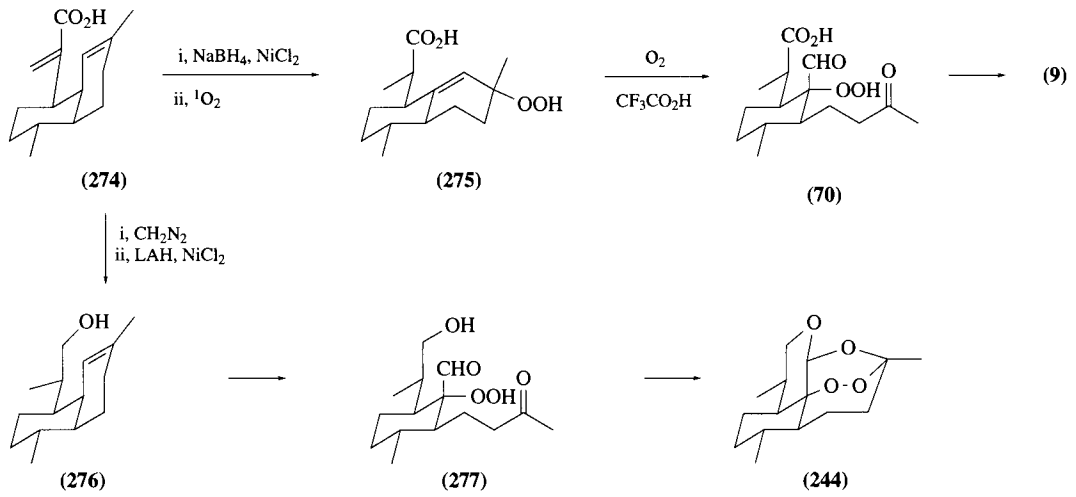


Scheme 38



Scheme 39

precursor to (**9**). Since (**274**) is some ten times more abundant than (**9**) in the plant, *Artemisia annua*, ways of converting it to (**9**) are clearly worthwhile. A chemical mimic of the natural process starts with the reduction and photooxygenation of (**274**). The resulting allylic hydroperoxide (**275**) on aerial oxygenation in the presence of a little trifluoroacetic acid is converted first to (**70**) and thereafter into (**9**) in a yield of 30% (Scheme 40) ⟨89MI 620-01, 92JOC3610⟩. In like fashion (**274**) is convertible into deoxoartemisinin (**244**) via the alcohol (**276**) and the hydroperoxide (**277**) ⟨89TL5973, 94TL5489⟩. The preparation of the 12-butyl derivative of (**244**) has been achieved by a modification of the same sequence ⟨90SL743, 94MI 620-02⟩.

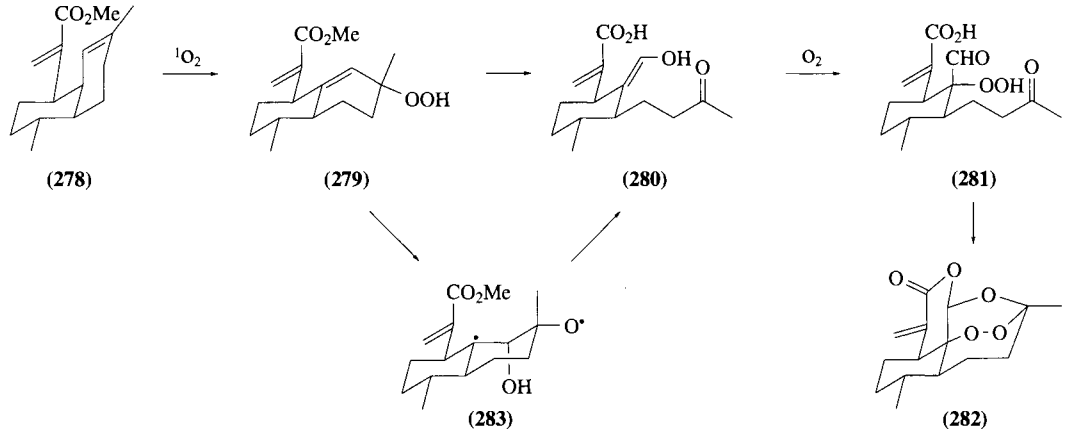


Scheme 40

A variant of the preceding pathway has been described in which the methyl ester of (**275**) on treatment with a small amount of cupric trifluoromethanesulfonate in methylene chloride under oxygen for several hours affords (**9**) ⟨90CC451⟩. The yields of (**9**) are similar to those previously obtained by acid catalysis which suggests that adventitious acid, rather than cupric salt, may have been responsible for the result.

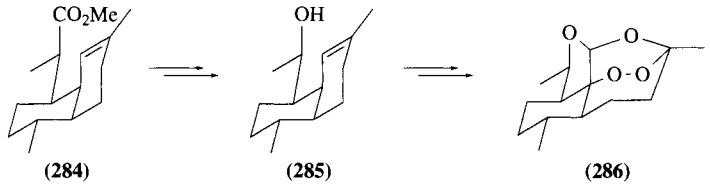
Further studies carried out on methyl artemisinate (**278**) confirm that the hydroperoxide (**279**) rearranges to the enol (**280**) which is subsequently autoxidized to (**281**) and thence to artemisitene (**282**) under catalysis with acid or copper trifluoromethanesulfonate (Scheme 41) ⟨95JA11098⟩. It is likely that (**279**) rearranges by homolysis to the 1,4-diradical (**283**) which then cleaves to (**280**). In

the same way, the hydroperoxide (**275**) gives the corresponding enol, thereby accounting for the formation of (**70**).



Scheme 41

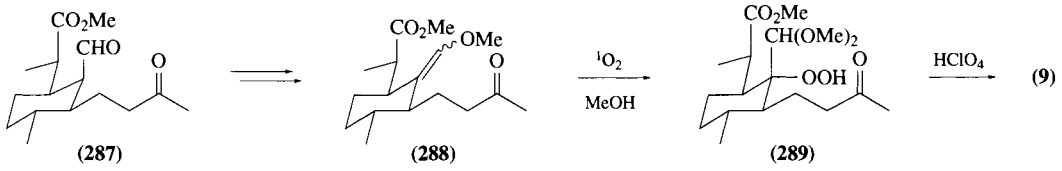
Ring-contracted artemisinins, exemplified by (**286**), are accessible from methyl dihydroartemisinate (**284**) via the alcohol (**285**) (Scheme 42) ⟨95TL4641⟩.



Scheme 42

Dihydroartemisinic acid corresponding to the ester (**284**) has been synthesized from (−)-isopulegol (**222**) and converted by the abovementioned procedure of hydroperoxidation, oxygenation and acid catalysis to (**9**) ⟨66SC321⟩. The unnatural *trans*-fused isomer of (**284**) submitted to the same sequence of reactions affords (**9**) ⟨93TL4435⟩. In a related application of the same trioxane ring-forming methodology, a Diels–Alder adduct precursor is elaborated into racemic 6,9-desdimethylartemisinin through *trans*-fused desdimethyldihydroartemisinic acid ⟨94JOC4743⟩.

An early synthesis of (**9**) starts with the ozonolysis of (**284**) ⟨83ASIN574⟩. The resulting ketone-aldehyde (**287**) is converted to the enol ether (**288**); photooxygenation in methanol affords the hydroperoxy acetal (**289**) which on treatment with strong acid gives (**9**) in 28% yield (Scheme 43)



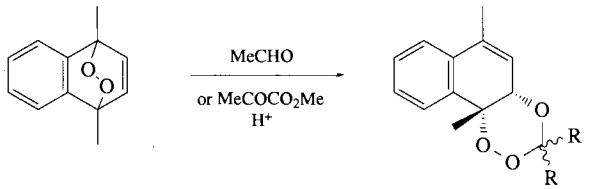
Scheme 43

The hydroperoxidation and acid-catalyzed condensation steps have been employed many times for building the trioxane ring of (**9**) ⟨83JA624, 86T819, 90TL755, 92TL1029, 94ACR211⟩. The acid-catalyzed intramoleclar closure of certain hydroperoxy-cyclic acetals leads to bridged bicyclic trioxanes ⟨92BMC632, 93BMC1707⟩.

6.20.6.6 Addition of Endoperoxides to Carbonyl Partners

Endoperoxides are easily formed by Diels–Alder addition of singlet oxygen to 1,3-dienes. On acid catalysis these endoperoxides behave like 1,2-dioxetanes combining efficiently with aldehydes and

ketones. The 1,4-endoperoxide of 1,4-dimethylnaphthalene (**290**) is typical. It reacts with acetaldehyde and methyl pyruvate giving pairs of the diastereomeric trioxanes (**291**) and (**292**) (Equation (41)) ⟨83JA6497⟩. Reactions of (**290**) with ketones, such as cyclohexanone, proceed normally to the trioxanes ⟨89H(28)673⟩.

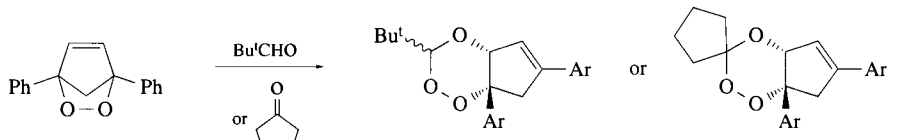


(41)

(**290**)

(**291**) R = H
(**292**) R = CO_2Me

The endoperoxide of 1,4-diaryl-1,3-cyclopentadiene (**293**) reacts in precisely the same way with pivalaldehyde and cyclopentanone affording the *cis* and *trans* *t*-butyltrioxanes (**294**), and the spirocyclic derivative (**156**) (Equation (42)) ⟨95HCA647⟩. In all cases, x-ray reveals that the newly formed trioxane ring is *cis*-fused to the original ring. 1,3-Cyclohexadiene peroxides also react with aldehydes and ketones to give *cis*-fused bicyclic trioxanes.

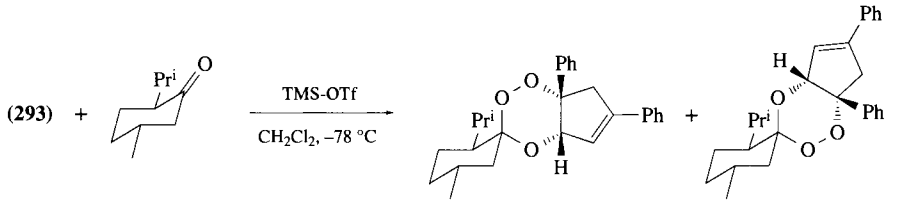


(42)

(**293**) (**294**) (**156**)

Enantiomerically pure samples of (**156**) are obtainable by chromatographic separation on a chiral column or by kinetically resolving the racemic mixture by catalytic asymmetric dihydroxylation ⟨94TL6275, 95CC1501⟩.

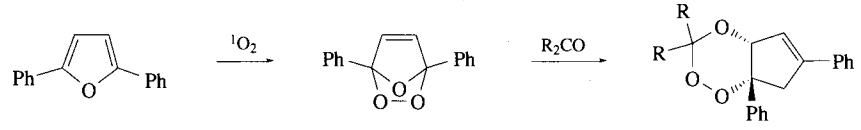
The endoperoxide (**293**) on catalysis with trimethylsilyl trifluoromethanesulfonate combines with chiral ketones in a highly diastereoselective manner. The behavior of (−)-menthone (**295**) provides an apt illustration (Equation (43)) ⟨91TL7243⟩. Only two of the four possible trioxanes are formed in a yield of 21%, the *cis*-fused 3*S*,5*S*,6*S* and 3*R*,5*R*,6*R* isomers, (**296**) and (**297**), in a 1 : 1 ratio. Other chiral ketones, such as (+)-nopinone and (−)-carvone react with (**293**) analogously.



(43)

(**295**) (**296**) (**297**)

The unstable endoperoxide (**299**) obtained by the MB-sensitized photooxygenation of 2,5-diphenylfuran (**298**) at −30 °C on catalysis with trimethylsilyl trifluoromethanesulfonate reacts poorly with aldehydes, but reasonably well with acetone and cyclohexanone to furnish the dimethyl (**300**) and spirocyclic (**301**) trioxanes as crystals in 27% and 14% yield (Scheme 44). Their constitution and structure follow from x-ray ⟨96H(44)367⟩.

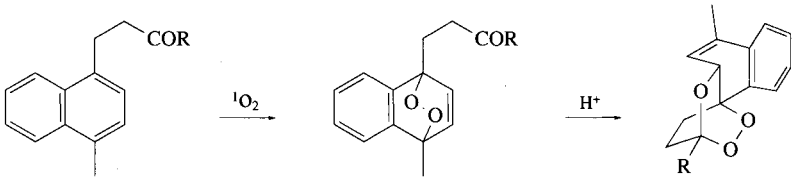


(**298**) (**299**)

(**300**) R = Me
(**301**) R,R = $(CH_2)_5$

Scheme 44

Examples of the intramolecular capture of an endoperoxide are provided by the pendent carbonyl derivatives of naphthalene (**302**) (Scheme 45) ⟨86HCA1778⟩. MB-sensitized photooxygenation in methylene chloride proceeds quantitatively. The resulting endoperoxides (**303**) when treated *in situ* with Amberlyst-15 at −15°C isomerize to the bridged bicyclic 1,2,4-trioxanes (**304**) in high yield. Although two cyclization modes are feasible, x-ray analysis of the parent (**304**; R = H) reveals that the *trans*-fused isomer is uniquely formed. Evidently, the tethered carbonyl group, unlike the intermolecular case, is constrained so that the new trioxane ring becomes fixed *trans* to the original naphthalene moiety.



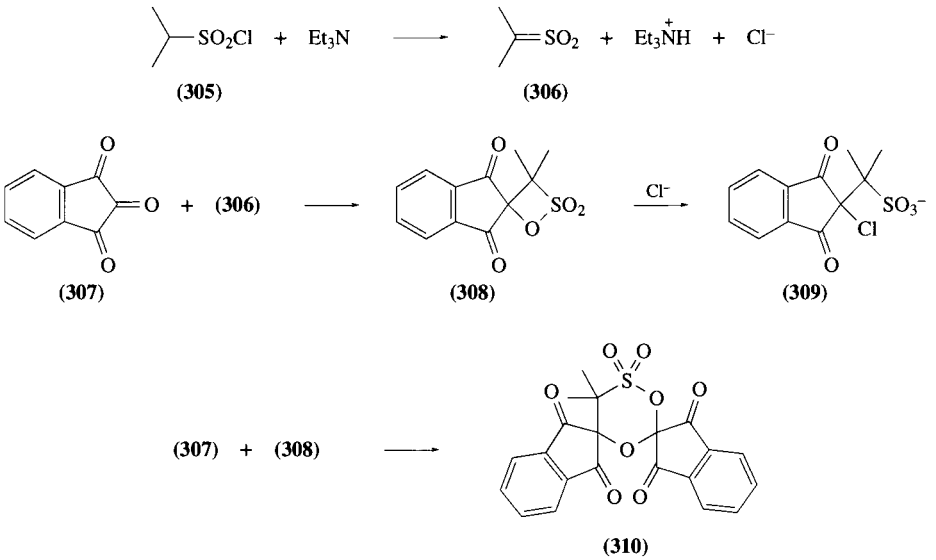
(**302**) (**303**) (**304**)

R = H, Me, Bu, Ph

Scheme 45

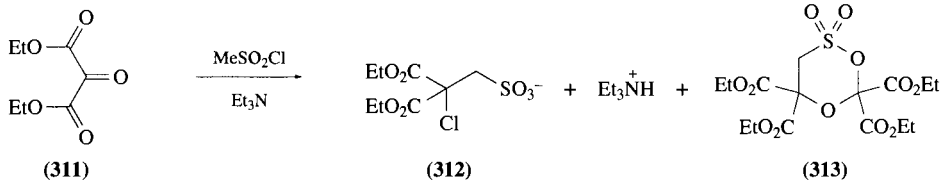
6.20.6.7 Cycloaddition and Dimerization

Sulfenes when generated in the presence of tricarbonyl partners give rise to 1,3,4-dioxathiane *S,S*-dioxides ⟨82AP(315)57⟩. Typically, the treatment of propane-2-sulfonyl chloride (**305**) with triethylamine in the presence of 1,2,3-indanetrione (**307**) gives initially the β-sultone (**308**) that arises by cycloaddition of the intermediate sulfene (**306**). Thereafter, attack by chloride ion on (**308**) furnishes the β-chlorosulfonate (**309**). At the same time, further cycloaddition occurs with excess of (**307**) to generate the doubly spirocyclic 1,3,4-dioxathiane dioxide (**310**) (Scheme 46).



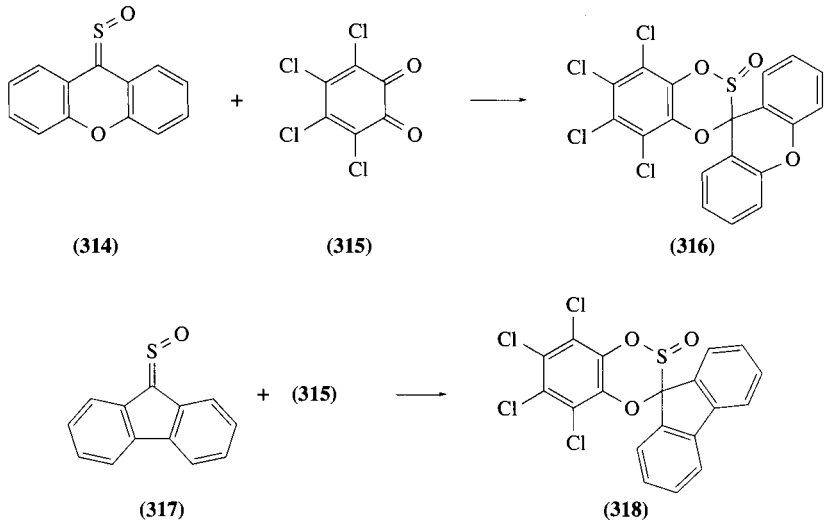
Scheme 46

The reaction of a two-molar amount of diethyl mesoxalate (**311**) with the sulfene arising from methanesulfonyl chloride and base gives a nearly quantitative yield of the sulfonate (**312**), but disappointingly little of the dioxathiane (**313**), which is only formed in 9% yield (Equation (44)) ⟨88AP(321)85⟩.



(311) (312) (313) (44)

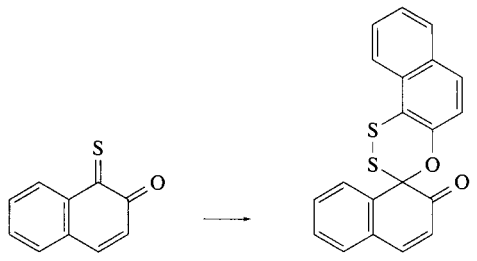
Sulfines, although not so reactive as sulfenes, have the advantage of being able to participate in Diels–Alder reactions. Xanthenethione *S*-oxide (**314**) and thiofluorenone *S*-oxide (**317**) undergo [4 + 2] cycloaddition with the diene equivalent, tetrachloro-*o*-benzoquinone (**315**), to form the 1,4,2-dioxathiane *S*-oxides (**316**) and (**318**) (Scheme 47) ⟨67RTC641⟩.



(314) (315) (316) (317) (315) (318)

Scheme 47

α-Ketothioketones display dienophilic properties as well as being diene equivalents. They therefore have a propensity to dimerize to 1,3,4-oxadithianes. Indeed, attempts to prepare β-naphtho-1-thioquinone (**319**) resulted in the formation of dehydro-2-naphthol 1-disulfide (**320**) (Equation (45)) ⟨30JCS1740⟩. The spirocyclic structure is confirmed by x-ray ⟨78AX(B)2907⟩.

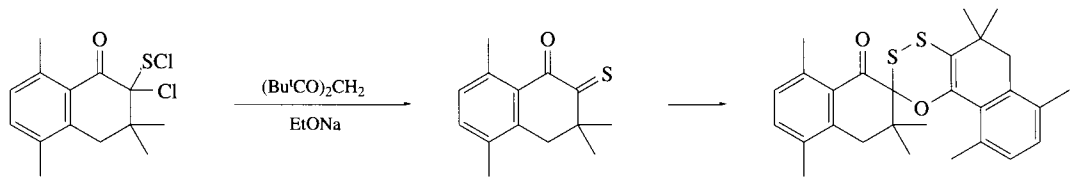


(319) (320) (45)

The α-chloro-β-oxosulfenyl chloride (**321**) on treatment with dipivaloylmethane and sodium ethoxide affords the intermediate α-ketothione (**322**) by reductive elimination of chlorine. Dimerization to (**323**) is spontaneous (Scheme 48) ⟨77ACS(B)890⟩.

6.20.6.8 Miscellaneous Methods

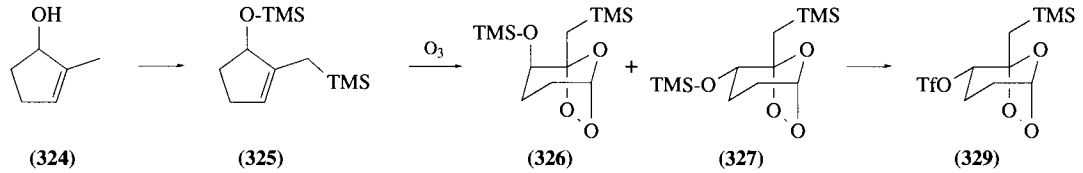
1,2,4-Trioxanes are homologues of 1,2,4-trioxolanes or secondary ozonides. Consequently a leaving group positioned outside and adjacent to the trioxolane ring offers an entry to trioxanes by 1,2-rearrangement. Such an idea has been realized by recourse to 2-methyl-2-cyclopent-1-ol (**324**) as a suitable test-molecule (Scheme 49) ⟨91JA8168⟩. The dianion from (**324**) on quenching with



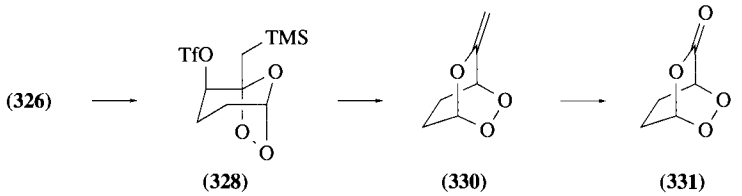
(321) (322) (323)

Scheme 48

trimethylsilyl chloride affords the bis-silyl derivative (**325**). Ozonolysis of the latter gives a modest yield (53%) of the diastereomeric *exo* and *endo* ozonides (**326**) and (**327**) in a 14 : 1 ratio. Conversion to the trifluoromethanesulfonates (**328**) and (**329**) readies them for rearrangement. Simply stirring (**328**) in acetonitrile buffered with aqueous sodium bicarbonate triggers eliminative solvolysis to the bridged bicyclic trioxane (**330**). The identity of (**330**) follows from its ozonolysis to the known lactone (**331**). The minor ozonide (**329**) is inert under the solvolysis conditions; a result to be expected as the peroxy bridge is not placed *trans*- and *peri*-planar to the leaving group.



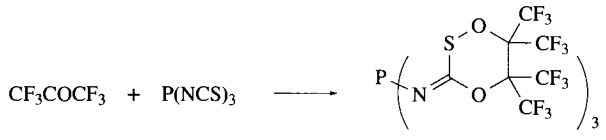
(324) (325) (326) (327) (329)



(328) (330) (331)

Scheme 49

An unusual reaction has been briefly reported for hexafluoroacetone and phosphorus triisothiocyanate (P(NCS)$_3$). Base-catalysis produces the 1,4,3-dioxathiane derivative (**332**) (Equation (46)) ⟨83PS(18)69⟩.

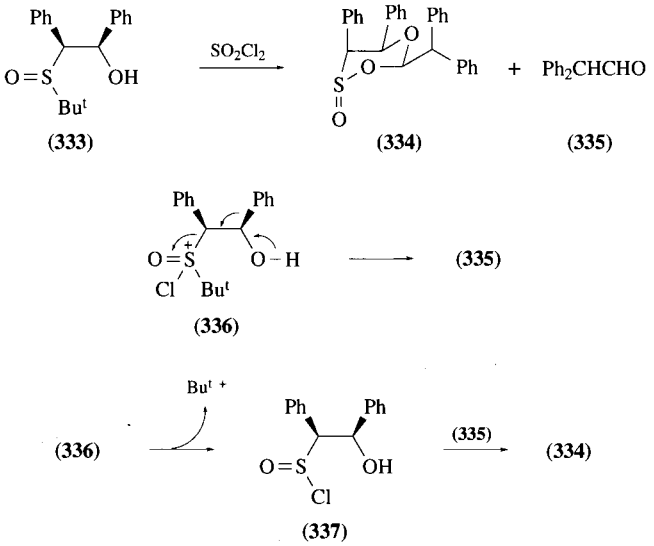


(46)

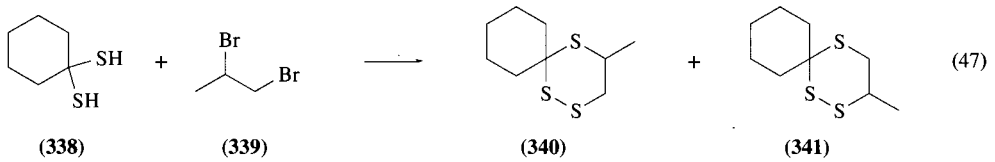
(332)

An unexpected outcome attends the reaction of 1,2-diphenyl-2-*t*-butylsulfinylethanol (**333**) with sulfuryl chloride (SO_2Cl_2) at −78 °C (Scheme 50) ⟨91CJC185⟩. The 1,3,4-dioxathiane *S*-oxide (**334**) and diphenylacetaldehyde (**335**) are formed in about 60% and 35% yield respectively. A plausible mechanism starts with the formation of the chlorosulfoxonium cation (**336**). A semipinacol-type rearrangement accounts for (**335**). A second avenue of reaction available to (**336**) is loss of *t*-butyl cation. The resulting sulfinyl chloride (**337**) then condenses with (**335**). The product (**334**), as x-ray attests, conserves the configuration of the starting material (**333**) in keeping with the proposed mechanism.

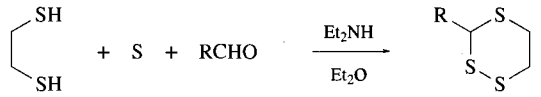
1,2,4-Trithianes are rare and elusive entities. Few syntheses have been reported. The reaction between cyclohexane-1,1-dithiol (**338**) and 1,2-dibromopropane (**339**) in alkaline medium gives a mixture of the 5- and 6-methyl-3,3-spirocyclic 1,2,4-trithianes, (**340**) and (**341**) (Equation (47)) ⟨70JOC2102⟩. The extra atom of sulfur is supposed to come from another molecule of (**338**).



Scheme 50



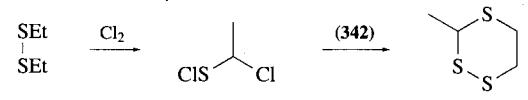
3-Alkyl-1,2,4-trithianes (**343**) are conveniently prepared by treating a mixture of 1,2-ethanethiol (**342**), sulfur and the aldehyde with diethylamine in ethyl ether for 4 h (Equation (48)) ⟨JAP01102075⟩. Hexanal gives the 3-pentyl derivative in 56% yield.



(48)

(342) (343)

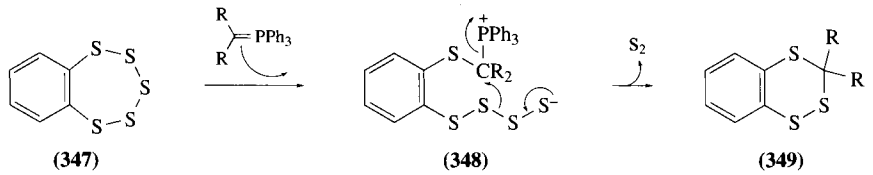
3-Methyl-1,2,4-trithiane (**346**) can be prepared by chlorinating diethyl disulfide (**344**) to the dichloride (**345**) and letting it react with (**342**) (Scheme 51) ⟨74MI 620-01⟩. The reaction of acetaldehyde, hydrogen sulfide and (**342**) also affords (**346**) ⟨B-92MI 620-02⟩.



Scheme 51

1,2,4-Benzotrithiins (**349**) are accessible by the reaction of benzopentathiepin (**347**) with alkylidenephosphoranes (Scheme 52) ⟨91TL6345⟩. Intramolecular nucleophilic addition in the dipolar intermediate (**348**) followed by extrusion of elemental sulfur accounts for the reaction course. Other nucleophiles, such as the anion derived from ethyl α-chloropropionate, also react with (**347**) in the same way ⟨89H(29)2097⟩.

Although they are not methods of preparative value in a chemical sense, cysteine, cystine, *N*-acetylcysteine, 4-thiazolidinecarboxylic acid and cysteine methyl ester when heated in soybean oil at 200°C produce many sulfur-containing heterocycles among which are found vanishingly small amounts of various 1,2,4-trithianes ⟨76MI 620-01⟩. The reaction is termed the Maillard reaction and is widely employed in laboratories in the flavor industry.



(347) (348) (349)

Scheme 52

Heating L-cysteine and propanol at 170°C yields a complex volatile mixture containing 1,2,4-trithianes ⟨91ABC2931⟩. It is also reported that heating cysteine and ribose with or without the addition of phosphatidylcholine under dry or moist conditions generates a complex mixture of volatile products, including 3-methyl-1,2,4-trithiane (**346**) as a major component ⟨95MI 620-02⟩.

Studies on the volatile extract obtained from the steam distillation of roasted sesame seeds reveals that some 146 compounds are present including (**346**) in trace amounts ⟨89ABC1891⟩.

The only other relevant benzo derivatives apart from (**349**) are obtained by pyrolysis of benzenesulfonate salts. Lithium *o*-(trifluoromethylthio)benzenesulfonate (**350**) on heating at 360°C *in vacuo* loses lithium fluoride and cyclizes to 3,3-difluoro-2-oxa-1,4-dithia-naphthalene 1,1-dioxide (**351**) in 70% yield (Equation (49)). Pyrolysis of the *o*-trifluoromethoxy analogue (**352**) at 260°C is less efficient, giving the 1,3,4-dioxathiane (**353**) in 17% yield ⟨72ZOR1023⟩.

(49)

(**350**) Z = S
(**352**) Z = O

(**351**) Z = S
(**353**) Z = O

6.20.7 IMPORTANT COMPOUNDS AND APPLICATIONS

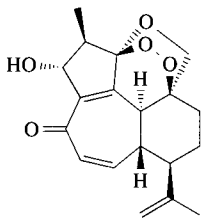
The bicyclic trioxane (**248**) is important simply by being the first to be described. It is claimed to improve the octane rating of certain diesel fuels and to be effective at promoting the polymerization of diallyl phthalate and dienes such as butadiene and methylpentadienes ⟨58USP2853494⟩. These claims presage the biological role found for the trioxane antimalarials.

Artemisinin (**9**) is clearly the most important member of the class of compounds presented in this chapter. As an antimalarial remedy, it and its first-generation derivatives such as artemether (**23**) must be regarded as prototypes for structurally simpler and more synthetically accessible derivatives, which will be ultimately developed. Thus, a new chapter in antimalarial chemotherapy has opened up. Trioxanes are unusual as therapeutic agents in that they do not contain nitrogen, unlike many drugs in today's pharmacopoeia. An effective antimalarial must be as cheap to produce and easy to manufacture as chloroquine. Some of the synthetic methods outlined above will need to be simplified or further utilized to prepare new, simple trioxanes which fulfil the mechanistic criteria for antimalarial activity. In any event, as resistance grows in the malarial parasite to the conventional quinoline-based drugs, the chances of a synthetic trioxane surrogate replacing chloroquine becomes correspondingly greater. Therefore, the synthesis and antimalarial testing of first-generation artemisinin derivatives continues apace ⟨95EJM697, 95JMC764, 95JMC4120, 95JMC5050⟩.

It is no surprise that other therapeutic areas are being explored as well. Artemisinin (**9**) and derivatives have been evaluated for activity against *Toxoplasma gondii* ⟨90AAC1961⟩, *Schistosoma japonicum* ⟨92MI 620-03⟩, and for cytotoxicity ⟨93MI 620-07⟩. A new approach to cancer therapy is based on the production of radicals from dihydroartemisinin (**65**) when treated with ferrous sulfate ⟨95MI 620-03⟩. The combination of the two retards growth of implanted fibrosarcoma in the rat. Ferrous sulfate or (**65**) alone is ineffective. Further examples could be given, but this sampling of the recent literature is sufficiently illustrative. Synthetic trioxanes are expected to display similar activity and will be worth screening for signs of therapeutic potential. It has already been shown that *cis*-fused cyclopenteno-1,2,4-trioxanes exert an effect *in vitro* on *Toxoplasma gondii* ⟨89AAC1748⟩.

It is worth noting that 1,2,4-trioxanes are essentially unknown as naturally occurring organic products. Just four have been reported so far. The best known are (**9**) and artemisitene (**282**), which

are found as sesquiterpene constituents of the shrub *Artemisia annua* ⟨85MI 620-01, 85SCI1049⟩. The other two are the diterpenes, caniojane (**354**) and its 1,11-epimer, isolated from the roots of *Jatropha grossidenta*, a plant growing in central Paraguay which is used for shamanic practices ⟨88P2997⟩. The structure of (**354**) suggests that it may have antimalarial properties.



(354)

Finally, the synthetic 1,2,4-trioxanes already constitute a significant chapter in organic chemistry and further development is expected. The 1,2,4-trithianes are obviously appreciated for their contribution to the pleasures of the table. However, the present synthetic methodology needs to be exploited further and extended so that a wider variety of structures may be prepared.

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6.21
1,2,4,5-Tetrazines

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6.21.1 INTRODUCTION

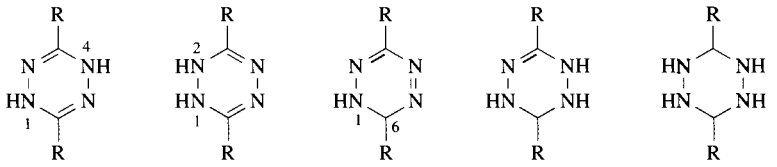
There are three possible tetrazine isomers. By far the best-known class are the 1,2,4,5-tetrazines (**1**), for which two degenerate Kekulé structures can be drawn (**1a**)⇔(**1b**). The parent compound (**1**; R = H) was first synthesized by Hantzsch and Lehmann in 1900 ⟨00CB3668⟩. The old-fashioned name *s*-tetrazine is still frequently used.

(**1a**) (**1b**)

The interest of physical organic chemists in the physical and spectroscopic properties of 1,2,4,5-tetrazines, and of preparative organic chemists in the high reactivity of tetrazines as dienes in (4 + 2) cycloaddition reactions in particular, is still increasing. Therefore there are many methods known for the synthesis of 1,2,4,5-tetrazines (**1**) in very good yields, including the parent compound (see Section 6.21.8).

The literature on 1,2,4,5-tetrazines was well documented in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) in Neunhoeffer's contribution which surveyed the field up to 1981 to 1982 ⟨84CHEC-I(3)531⟩. Since that time several excellent reviews have been published ⟨82T3087, 83T2869, 86CRV781, B-87MI 621-01, 89PHC263, 90PHC(2)203, 91PHC(3)223, 92BSB521, 92PHC(4)204, 93PHC(5)239, 94MI 621-01, 94PHC(6)221, 95CHE1279, 95PHC(7)244, 96MI 621-01⟩. Mechanistic aspects of Diels–Alder reactions have been reviewed by Sauer and Sustmann ⟨80AG(E)779⟩ including normal, neutral, and inverse (4 + 2) cycloaddition reactions. Finally, a *Chemical Abstracts* search between 1980 and the end of 1995 revealed about 750 relevant publications which were critically screened for inclusion in this chapter.

In addition to the aromatic tetrazine system (**1**), dihydro-1,2,4,5-tetrazines, tetrahydro-1,2,4,5-tetrazines, and hexahydro-1,2,4,5-tetrazines are known. In almost all the cases which have been studied by x-ray diffraction the dihydro derivatives are best described as 1,4-dihydro isomers (**2**); structures such as 1,2- and 1,6-dihydro isomers, (**3**) and (**4**) respectively, are very rare. Tetrahydro and hexahydro tetrazines, such as (**5**) and (**6**), are also known.



(**2**) (**3**) (**4**) (**5**) (**6**)

This chapter will mainly describe new developments in the area of theoretical methods and experimental structural methods, and in the rapidly growing field of inter- and intramolecular Diels–Alder reactions of these electron-poor azadienes. Quantitative data for the reactivity of dienes and dienophiles in these (4 + 2) cycloadditions with inverse electron demand will be discussed. The synthesis and reactions of dihydro, tetrahydro, and hexahydro tetrazines cannot be discussed broadly beyond the scope of ⟨84CHEC-I(3)531⟩. Verdazyls, a well-known class of compound, cannot be treated in detail within the frame of this contribution (see Section 6.21.5.9).

6.21.2 THEORETICAL METHODS

This chapter necessarily can offer only a short survey on theoretical methods. A separation into *ab initio* and semiempirical methods does not seem practical, because in many cases there is an overlap in the same publication. Furthermore there will be much overlap with Section 6.21.3, as many publications on calculations also deal with spectroscopic techniques.

The 1,2,4,5-tetrazine system is the only stable isomer of three possible tetrazines. Interestingly, according to *ab initio* calculations the 1,2,3,5-isomer is more stable by 8.5 kcal mol^{-1}, while the 1,2,3,4-isomer is 13.7 kcal mol^{-1} less stable than the 1,2,4,5-isomer ⟨91JOC539⟩.

Most papers dealing with the bonding of 1,2,4,5-tetrazine (often also the structural isomers) make a comparison with other five- and six-membered aromatic heterocyclic systems. A quantitative CNDO/2 and INDO analysis of the through-space and through-bond interactions between lone-pairs and *s*-frames compares *s*-triazine and *s*-tetrazine ⟨81T297⟩. A comparison of MNDO and *ab initio* calculations at the 4-31G level for azoles and azines, and also with experimental data, shows that the lone-pair electronic repulsion between neighboring pyridine-like nitrogens is systematically underestimated by MNDO ⟨85JOC4894⟩. MNDO-calculated heats of formation and dipole moments for all of the tetrazines are given. The question of aromaticity is discussed in a number of papers. An aromaticity index for six-membered heterocycles has been defined by Bird ⟨86T89⟩.

Wiberg *et al.* compared the π-electron delocalization in benzene and the azines via analysis of the first $\pi \rightarrow \pi^*$ transition, via calculation of hydrogenation energies, and via an analysis of the wave functions ⟨89JA4178⟩. Resonance energies, dissociation energies (1,2,4,5-tetrazine $\rightarrow$ 2 HCN + N_2), enthalpies of formation, and group equivalent energies of reduction, hydrogen-transfer energies, bond properties, and bond angles are given for benzene and all azines at the 6-31G* and 6-31G** level. While the resonance energies of benzene (36 kcal mol^{-1}), pyridine (34 kcal mol^{-1}), pyrazine (32 kcal mol^{-1}), and pyrimidine (33 kcal mol^{-1}) are quite similar, those for pyridazine (26 kcal mol^{-1}), 1,3,5-triazine (25 kcal mol^{-1}), and 1,2,4,5-tetrazines (16 kcal mol^{-1}) are somewhat lower.

Another detailed treatment for pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4,5-tetrazine, and a number of five-membered aromatic heterocycles is based on AM1 semiempirical calculations ⟨89H(28)1135⟩. Dewar and Holder's values for the aromatic energies are all lower than Wiberg's: benzene (28.3 kcal mol^{-1}), pyridine (25.6 kcal mol^{-1}), pyridazine (22.7 kcal mol^{-1}), pyrimidine (25.0 kcal mol^{-1}), pyrazine (24.6 kcal mol^{-1}), and 1,2,4,5-tetrazine (12.4 kcal mol^{-1}); again the tetrazine system seems to be least stabilized.

Jug and Köster have introduced a new σ–π separability criterion to divide the total energy of planar ring systems into two parts, a σ-part and a π-part ⟨90JA6772⟩.

In a series of papers on 'aromaticity as a quantitative concept' Katritzky and Barczynski subjected a set of 23 monoheterocycles to AM1 calculations and concluded that pyridine-like nitrogen atoms have relatively little effect on classical aromaticity ⟨90JPR885⟩.

The MM3 force field has been extended by Allinger and co-workers to cover aromatic heterocycles of the pyridine and pyrrole types ⟨93JA11906⟩. Structures (32 compounds), dipole moments (35 compounds), heats of formation (35 compounds), and vibrational spectra (11 compounds) were examined. The results are good for structure and fair for the other items; resonance energies were reported for the series benzene (17.79 kcal mol^{-1}), pyridine (17.02 kcal mol^{-1}), pyridazine (14.35 kcal mol^{-1}), pyrazine (17.01 kcal mol^{-1}), pyrimidine (15.60 kcal mol^{-1}), 1,3,5-triazine (13.51 kcal mol^{-1}), and 1,2,4,5-tetrazine (17.72 kcal mol^{-1}). Finally, *ab initio* studies of the dipole polarizabilities of conjugated molecules have been reported in which monocyclic azines (pyridine, pyridazine, pyrimidine, pyrazine, *s*-triazine, and *s*-tetrazine) are compared ⟨94JST(304)109⟩.

A Fock space multireference coupled cluster method was described by Rittby and Bartlett ⟨91TCA469⟩, applied to the calculation of ionization potentials and excitation energies of 1,2,4,5-tetrazines, and compared with conventional *ab initio* calculations and experimental results.

Hartree–Fock calculations with the 6-31G* basis have been performed to investigate the structure and the Li^+ binding energies of the complexes between Li and diazines, triazines, and tetrazines ⟨90TCA1⟩. The correlations between calculated Li^+ binding energies and proton affinities are compared.

In a conformational study on nonfused biheterocycles, phenyltetrazines and bitetrazines were compared by *ab initio* STO-3G and semiempirical AM1 calculations ⟨92MI 621-01⟩. Phenyltetrazines apparently prefer a planar conformation, while in bitetrazines, because of dominant lone pair–lone pair interactions, a nonplanar conformation prevails. For 6,6′-diphenyl-3,3′-bi-1,2,4,5-tetrazine a planar arrangement could be proven for the solid state by x-ray diffraction ⟨96AX(C)936⟩.

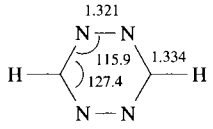
Finally, there are some reports on calculations of photoelectron spectra of 1,2,4,5-tetrazines by Gleiter *et al.* ⟨88JOC5757⟩, Cederbaum and co-workers ⟨90JA94⟩, and Danovich and Apeloig ⟨91JCS(P2)1865⟩. The principal problem is the relative ordering of n and π ionizations. Gleiter used HAM/3 calculations, Cederbaum the UVGF and ADC(3) method, and Apeloig the OVGF technique, using as the zeroth order approximation the wave functions obtained with semiempirical AM1 and PM3 approximations. According to Apeloig, in many cases SCF (AM1), SCF (PM3), HAM/3, and OVGF (AM1) methods fail to reproduce correctly the ordering of the ionization energies.

6.21.3 EXPERIMENTAL STRUCTURAL METHODS

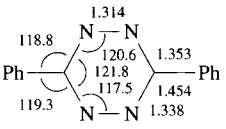
In Neunhoeffer's contribution to CHEC-I a large body of detailed data was compiled, for x-ray diffraction, ^{1}H and ^{13}C NMR, ESR, UV/VIS, fluorescence, phosphorescence, and photoelectron spectroscopy ⟨84CHEC-I(3)531⟩. It is not possible within the limited space of this contribution to go back to the roots. There are many individual reports of spectral data on a variety of tetrazine derivatives, but it would be inappropriate to tabulate them here. The principal aspects of different types of spectroscopy have been well described by Neunhoeffer in ⟨CHEC-I(3)531⟩. A few new results are presented in this chapter.

6.21.3.1 X-ray Diffraction

Bond angles and bond lengths for the parent 1,2,4,5-tetrazine (**7**) ⟨56AX510⟩ and its diphenyl derivative (**8**) ⟨72AX(B)739⟩ are shown by the structures. The observed bond distances and angles are similar for the diphenyl and the parent compound. In both cases the heterocyclic ring is planar as expected for an aromatic system with electron delocalization.



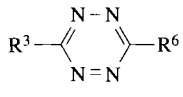
(**7**)



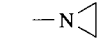
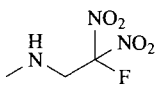
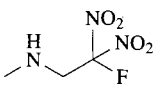
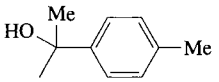
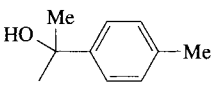
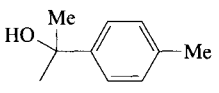
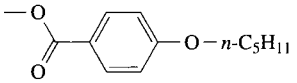
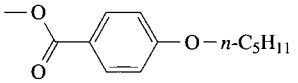
(**8**)

Detailed tables with bond distances and bond angles were presented in ⟨CHEC-I(3)531⟩. Many papers published since then have reported that bond lengths and angles lie within the expected ranges.

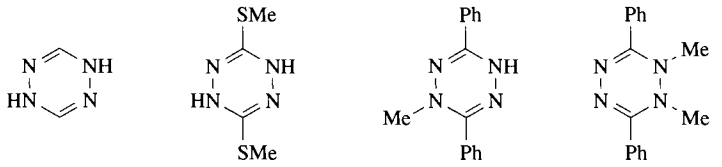
3,6-Diamino-1,2,4,5-tetrazine (**9a**) shows an intermolecular hydrogen-bonded network where amino groups act as proton donors, forming intermolecular hydrogen bonds with adjacent N atoms of neighboring tetrazine rings, leading to planar molecular layers separated from each other ⟨87AX(C)1320⟩. In (**9b**) and (**9c**) the bonds to the substituents (C—O = 1.328 Å; C—N = 1.385 Å) are remarkably short, in accordance with a conjugative interaction of the substituents as weak π-donors with the electron-deficient tetrazine system ⟨87AX(C)1412⟩. The x-ray for (**9d**) shows normal values, and the center of the heterocyclic ring is also a center of symmetry ⟨88AX(C)1686⟩. Tetrazine (**9e**) was analyzed as the racemate ⟨89AX(C)1167⟩ while (**9f**) was studied as the (*R*,*R*)-(+)-isomer ⟨86AX(C)1621⟩. Tetrazine (**9g**) was analyzed in the solid state; it forms a nematic mesophase in the range 336–341 K ⟨84AX(C)482⟩. An x-ray analysis was also reported for the first bitetrazine ⟨94TL7935, 96AX(C)936⟩ (see Section 6.21.5.5).



(**9**)

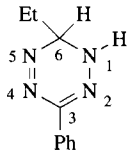
	R^3	R^6
a	$-NH_2$	$-NH_2$
b	–OMe	–OMe
c		
d		
e	–Ph	
f		
g		

For the dihydrotetrazines (**10**)–(**12**) the 1,4-dihydro structure was proven by x-ray diffraction in the solid state; in (**13**) only the 1,2-dihydro isomer is possible ⟨83CB2261⟩. N(2), C(3), N(5), and C(6) in (**10**) are practically coplanar, with N(1) and N(4) lying above the plane (32°), i.e. a boat, which seems to be typical for 1,4-dihydrotetrazines.



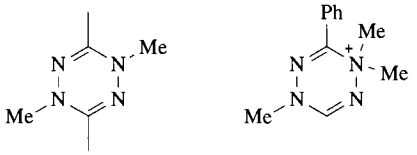
(**10**) (**11**) (**12**) (**13**)

An interesting case was reported by van der Plas and co-workers with 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**14**), a possible homoaromatic system ⟨82JOC2856⟩. A boat conformation, with C(6) and C(3) pointing upward with dihedral angles of 49.3° and 26.7° respectively, was found. N(1) was sp^2 hybridized, and the bond lengths N(1) to N(5) of the ring were found to be between single and double bond lengths, in agreement with the expected electron delocalization. A second investigation, of 1-acetyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine and 1-hydroxymethyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine with the help of ^{1}H NMR spectroscopy and x-ray analysis, came to the conclusion that, despite the nonplanarity of the five atoms N(1)–N(5) and the relatively large separation between N(1) and N(5) (2.29 Å and 2.35 Å), a case can be made for the operation of a homoaromatic ring current in these systems ⟨86JOC3043⟩.



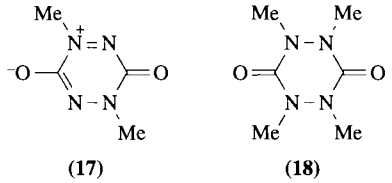
(**14**)

1,3,4,6-Tetramethyl-1,4-dihydro-1,2,4,5-tetrazine (**15**) ⟨84AX(C)2076⟩ and the 1,1,4-trimethyl-6-phenyl-1,4-dihydro-1,2,4,5-tetrazinium cation (**16**) ⟨82JOC2858⟩ likewise were analyzed by x-ray diffraction to identify possible homoaromatic structures.



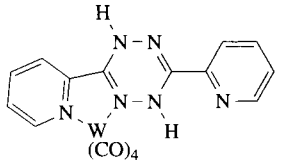
(**15**) (**16**)

Further reports on 1,4-dihydro-1,2,4,5-tetrazine structures by x-ray diffraction are found for the 3-(*p*-chlorophenyl)-6-trifluoromethyl derivative ⟨85JHC643⟩, 1,3,6-triphenyl-1,4-dihydro-1,2,4,5-tetrazine ⟨90JCS(P1)2527⟩, 6-bromo-1,4-dihydro-1,4-di(*o*-tolyl)-1,2,4,5-tetrazin-3(2*H*)-one, and 3,6-dibromo-1,4-dihydro-1,4-bis(*p*-methoxyphenyl)-1,2,4,5-tetrazine ⟨94AX(C)1781⟩. Finally, there are reports on the crystal structures of the heterocyclic betaine 1,4-dimethyl-6-oxo-1,2,4,5-tetrazin-1-ium-3-olate (**17**) ⟨84TL629⟩ and tetramethyl-*p*-urazine (**18**), from which cation radicals could be formed ⟨91JOC1045⟩.



(**17**) (**18**)

Metal complexes of tetrazines attracted some interest during the last decade (see Section 6.21.5.8); an x-ray analysis was published for tetracarbonyl [3,6-bis(pyridin-2-yl)-2,5-dihydro-1,2,4,5-tetrazine]-tungsten(0) (**19**) ⟨91AX(C)2448⟩.



(**19**)

6.21.3.2 NMR Spectroscopy

Typical chemical shifts for protons at the tetrazine nucleus were presented in CHEC-I ⟨CHEC-I(3)531⟩. Two theoretical papers should be mentioned with regard to ^{13}C and ^{15}N chemical shifts of heterocycles. Second-order magnetic properties, i.e. magnetic susceptibility and chemical shift tensors, of some five- and six-membered heterocycles containing nitrogen were calculated by means of the IGLO method. Good agreement was found between calculation and experiment, but the calculated NMR shifts of nitrogen atoms involved in NN multiple bonds are too paramagnetic (deshielded) ⟨88MRC394⟩. *Ab initio* calculations using the second-order correlated localized orbital–local origin method (SOLO) were presented for the nuclear shielding tensor of ^{15}N and ^{13}C nuclei in benzene and six-membered aromatic heterocycles from pyridine to *s*-tetrazine ⟨92CPL(197)59⟩.

6.21.3.3 Mass Spectrometry

Mass spectra of 1,2,4,5-tetrazines are quite simple ⟨CHEC-I(3)531⟩. The molecular ion loses N_2 quickly with formation of ions of nitrile structure sometimes accompanied with $(RCN + H^+)$ and $(RCN - H^+)$ions. Diaryl tetrazines also show $(M + 2)^+$ ions, probably by formation of 1,4-dihydro derivatives in the ion source. MS data of individual tetrazines are somewhat scattered in the experimental parts of publications dealing with 1,2,4,5-tetrazines and their reactions.

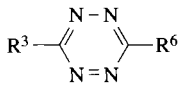
6.21.3.4 UV/VIS Spectroscopy

UV/VIS spectroscopy is a playground for spectroscopists. Neunhoeffer ⟨CHEC-I(3)531⟩ cited a number of leading references. This may be continued with a number of publications dealing with absorption, fluorescence, and phosphorescence spectroscopy as well as vibrational fine structure of the ground state and excited electronic states.

1,2,4,5-Tetrazines are strongly colored compounds, the color ranging from red to violet, red–violet, or blue. The color is caused by the typical $n \rightarrow \pi^*$ absorption which is usually found between 520–570 nm, with molar extinction coefficients 10^2–10^3. In addition, strongly depending on the structure of substituents in the 3- and 6-positions, a $\pi \rightarrow \pi^*$ absorption band is found between 250–350 nm with ε-values of 2×10^3 to 4×10^3. Detailed data for different tetrazines are found in ⟨CHEC-I(3)531⟩ and in many publications dealing with tetrazines. Table 1 shows the values for the $n \rightarrow \pi^*$ transitions for a number of mono- and disubstituted 1,2,4,5-tetrazines ⟨94UP 621-01⟩. Transannular interaction in (**20**) leads to a hypsochromic shift of the first $n \rightarrow \pi^*$ absorption ⟨86TL5367⟩.

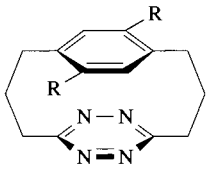
1,2,4,5-Tetrazine-d_0 and -d_2 have been studied in solution, in matrices, and in the vapor phase, and there are contributions on: Franck–Condon analysis of visible absorption of *s*-tetrazine vapor ⟨81CPH439⟩, single vibronic level fluorescence, and relaxation spectra of *s*-tetrazine-d_0 and -d_2 vapors ⟨81CPH413⟩, *s*-tetrazine—coupling of the S_0 and S_1 electronic state by two out-of-plane B_{3u} vibrations ⟨82JCP(76)2100⟩, new S_1 vibronic level assignments for *s*-tetrazine vapor—polarization and lifetime ⟨82JSP(94)316⟩, the electronic state of *s*-tetrazine—structure and vibrational frequencies of the ground and excited electronic states ⟨87JCP(87)3539⟩, approximate energy of the $^1A_u(\pi^* \leftarrow n)$ electronic state of *s*-tetrazine ⟨88JSP(129)140⟩, MRINDO/S-CI calculation on the electron spectra of higher azines (*s*-triazine, *s*-tetrazine, pentazine) ⟨90TCA343⟩, measurements of static polarizabilities on *s*-tetrazine ⟨91JCP(95)7952⟩, solvatochromic shifts of azabenzenes studied by SCRF theory ⟨92CPH211⟩, radiative lifetimes of triplet spin sublevels of the azabenzenes ⟨94CPH291⟩, and mechanism of spectral shift and inhomogeneous broadening of the $n \rightarrow \pi^*$ transition of 1,2,4,5-tetrazine in polymer glass ⟨95JA7493⟩.

Table 1 UV/VIS-absorptions ($n \rightarrow \pi$) for mono- and disubstituted 1,2,4,5-tetrazines: λ[nm]/ξ[1/mol cm]; solvent; acetonitrile.



No	$R^3 = R^6$	λ/ε	*No*	R^3	R^6	λ/ε
1[a]	H	528/706	43	4-Pyridyl	R^3	537/452
2[a]	Me	543/620	44	4-Pyridazinyl	R^3	528/444
3[a]	CO_2Me	520/568	45	Pyrazinyl	R^3	532/431
4[a]	CF_3	500/660	46[c]	NMe_2	R^3	525 sh/–
5	Ph	538/432	47[c]	OMe	R^3	528/580
6	*p*-MeC_6H_4	543/467	48[c]	SMe	R^3	535/521
7	*m*-MeC_6H_4	538/443	49[c]	NMe_2	OMe	540/489
8	*o*-MeC_6H_4	538/425	50[c]	NMe_2	SMe	540/494
9	*p*-$MeOC_6H_4$	544/438	51[c]	OMe	SMe	530/497
10	*m*-$MeOC_6H_4$	542/427	52[c]	Ph	NMe_2	545/480
11	*o*-$MeOC_6H_4$	532/414	53[c]	Ph	OMe	536/494
12	*p*-ClC_6H_4	541/494	54[c]	Ph	SMe	545/491
13	*m*-ClC_6H_4	538/433	55	3,5-Dimethyl-1-pyrazolyl	OEt	521/443
14	*o*-ClC_6H_4	528/443	56[d]	Ph	H	540/579
15	*p*-$CF_3C_6H_4$	539/288	57	*p*-MeC_6H_4	H	528/486
16	*m*-$CF_3C_6H_4$	538/533	58[d]	*p*-$MeOC_6H_4$	H	541/594
17	*p*-$NMe_2C_6H_4$	390/69200[e]	59	*m*-$MeOC_6H_4$	H	526/504
18[a]	*p*-$NO_2C_6H_4$	538/494	60[d]	*p*-ClC_6H_4	H	536/603
19[a]	*m*-$NO_2C_6H_4$	540/500	61	*m*-ClC_6H_4	H	523/533
20	2-Pyrrolyl	520 sh/–	62[d]	*m*-$CF_3C_6H_4$	H	539/600
21	*N*-Methyl-2-pyrrolyl	525 sh/285	63[d]	*p*-$NMe_2C_6H_4$	H	540/500
22	2-Furyl	518/518	64	2-Pyrrolyl	H	524/547
23	3-Furyl	525/524	65	*N*-Methyl-2-pyrrolyl	H	530/514
24	2-Thienyl	526/483	66	2-Furyl	H	522/585
25	3-Thienyl	536/486	67	3-Furyl	H	526/522
26	2-Thiazolyl	520/475	68	2-Thienyl	H	525/721
27	4-Thiazolyl	530/481	69	3-Thienyl	H	528/575
28	4-Isothiazolyl	526/491	70	2-Thiazolyl	H	526/523
29	1-Methyl-5-imidazolyl	550/456	71	4-Thiazolyl	H	530/525
30	1-Methyl-2-imidazolyl	538/414	72	4-Isothiazolyl	H	528/564
31	3,5-Dimethyl-1-pyrazolyl	523/500	73	2-Pyridyl	H	529/500
32	1-Methyl-5-pyrazolyl	528/453	74	3-Pyridyl	H	528/538
33	1-Methyl-3-pyrazolyl	532/517	75	4-Pyridyl	H	529/668
34[b]	1-Methyl-4-[1,2,3-triazol]-yl	534/1161	76	Pyrazinyl	H	529/520
35	1-Methyl-5-[1,2,4-triazol]-yl	526/461				
36	5-Tetrazolyl	517/517				
37	2-Methyl-5-tetrazolyl	522/514				
38	2-Methyl-5-oxadiazolyl	524/528				
39	2-Phenyl-5-oxadiazolyl	508/487				
40	2-[2′-Thienyl]-5-oxadiazolyl	506/–				
41	2-Pyridyl	535/424				
42	3-Pyridyl	537/445				

[a]Solvent: 1,4-dioxane. [b]Solvent: DMSO. [c]Solvent: *n*-hexane. [d]Solvent: trichloromethane. [e]$n \rightarrow \pi^*$ superposed by $\pi \rightarrow \pi^*$.



(20)

a: R = H
b: R = OMe

3-Methyl-, 3,6-dimethyl-, 3,6-dimethoxy-, 3,6-dimethylthio-, and 3,6-diphenyltetrazines were included in these experimental and theoretical investigations: dimethyl-*s*-tetrazine vapor—visible absorption, laser-excited fluorescence, and photophysics ⟨80JSP(83)266⟩; excitation spectra of dimethyl-*s*-tetrazine by fixed-frequency recording ⟨84JSP(103)495⟩; the fluorescence lifetimes of methyl- and dimethyl-*s*-tetrazine ⟨84JCP(81)5216⟩; fluorescence line narrowing spectroscopy of dimethyl-*s*-tetrazine in glycerol in liquid and glassy states ⟨92JCP(96)8750⟩; very long (10^7 s) spin conversion times for dimethyl-*s*-tetrazine in durene ⟨93CPH433⟩; lowest triplet states of *s*-tetrazines [H_2, Me_2, $(MeO)_2$, $(MeS)_2$] ⟨92CPH217⟩; and $S_1(n\pi^*)$, $T_1(n\pi^*)$, and $S_2(n\pi^*)$ emissions in 3,6-diphenyl-*s*-tetrazine ⟨82CPL233⟩.

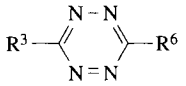
The field of UV/VIS spectroscopy of 1,2,4,5-tetrazines is a broad one; the above references are illustrative of various areas of interest.

6.21.3.5 IR Spectroscopy

The IR spectra of tetrazines are found to be as expected for this system; literature leading to data on simple derivatives is found in ⟨84CHEC-I(3)531⟩. Some more recent literature can be found: for the diode laser spectrum and analysis of the 882 cm^{-1} band of *s*-tetrazine ⟨84JSP(107)373⟩, the diode laser spectrum and analysis of the 1103 cm^{-1} band of *s*-tetrazine ⟨85JSP(112)340⟩, and the comparative study by Wiberg of azines—the effect of basis set on the calculated vibrational frequences, infrared, and Raman intensities ⟨90JST(244)61⟩.

6.21.3.6 Photoelectron Spectroscopy

The fundamental experiments in the field of photoelectron spectroscopy of tetrazines are due to Gleiter *et al.* ⟨88JOC5757⟩, who studied a large number of donor-substituted tetrazines in order to find out the influence of π-electron donating and accepting groups on the ionization energies and the level ordering for the tetrazines (**9**) which were included in the investigation. These PE measurements were combined with an electrochemical study ($E_{1/2}$) and HAM/3 calculations to assign PE bands and calculate the HAM/3 electron affinities. It was indicated in Section 6.21.2 that the principal problem is to assign the measured bands to the relative ordering of *n*- and π-ionization. Some more recent contributions by the groups of Cederbaum ⟨90JA94⟩ and Apeloig ⟨91JCS(P2)1865⟩ deal competently with this problem.



(**9**)

R^3	NHMe	NMe_2		NHMe	NMe_2	
R^6	OMe	OMe	OMe	SMe	SMe	SMe

$R^3 = R^6$ = H, Me, Ph, OMe, SMe, NH_2, NHMe, NMe_2, , , , CO_2Me, Cl, F, CN, CF_3

Kaim reports on the photoelectron spectroscopy and cyclic voltammetry of 1,4-dihydro-1,2,4,5-tetrazine, the parent compound as well as its 1,4-dimethyl- and 1,4-bis(trimethylsilyl) derivatives ⟨85JCS(P2)1633⟩.

6.21.3.7 ESR Spectroscopy

Section 6.21.5.9 on redox reactions discusses the formation of radical cations and radical anions from tetrazines, dihydrotetrazines, and tetrahydrotetrazines. The literature cited there offers all information on relevant ESR investigations in this field. Earlier literature is to be found in Neunhoeffer's review ⟨84CHEC-I(3)540⟩.

6.21.3.8 Supersonic Jet Investigations—van der Waals Clusters

Neunhoeffer, in ⟨CHEC-I(3)531⟩, briefly mentioned that van der Waals (vdW) complexes between 1,2,4,5-tetrazine and a number of light gases (He, Ar, H_2) have been observed and characterized by laser spectroscopy studies of free supersonic jet expansion of the tetrazine in the carrier gas ⟨84CHEC-I(3)531⟩. Complexes with one equivalent of noble gas were analyzed as having C_{2v} symmetry, the gases sitting on top of the aromatic π-system of the heterocycle. This field has considerably expanded, with 1,2,4,5-tetrazine, its 3-methyl, and 3,6-dimethyl derivative as well as aminotetrazine being used as heterocycles, and the noble gases, water, HCl, benzene, and acetylene, for instance, playing the role of the second partner. Dimers of 1,2,4,5-tetrazines and mixed 'dimers' of tetrazine with benzene have also been studied by this technique.

Some leading references to investigations on 1,2,4,5-tetrazines again may be cited to open the field for spectroscopists: electronic spectra of mixed complexes of *s*-tetrazine with He and Ar ⟨84JCP(80)2256⟩, vibrational predissociation and intramolecular vibrational relaxation in electronically excited *s*-tetrazine-Ar vdW complex ⟨83JCP(78)3415⟩, time-resolved mode-to-mode vibrational energy flow in the *s*-tetrazine-Ar complex ⟨85JCP(83)5341⟩, vdW rovibrational states of benzene-Ar and tetrazine-Ar complexes ⟨86JCP(85)3411⟩, application of the indirect dephasing model to resonance, and dispersed fluorescence in the isolated molecular complex ⟨87JCP(86)2510⟩, vibrational predissociation of *s*-tetrazine-Ar vdW clusters ⟨86JPC5164⟩, intramolecular vibrational relaxation in S_1 tetrazine-Ar—a perturbation theory analysis ⟨88JPC5470⟩, intramolecular vibrational relaxation in the S_0 state of *s*-tetrazine-X (X = Ar, Kr, Xe) ⟨88JCP(88)6120⟩, vdW bond stretch and bend frequencies in the molecules tetrazine-X (X = Ar, Kr, Xe) ⟨88JCP(88)6082⟩, vibrationally excited jet-cooled tetrazine-X complexes (X = Ar, Kr, Xe) ⟨88JCP(88)6107⟩, vdW bound states and intermolecular bend/stretch coupling in tetrazine-Ar ⟨89CPH67⟩ and calculations on the vdW spectrum of tetrazine-Ar ⟨90JCP(92)5875⟩.

Similar investigations have been reported for the 3,6-dimethyl-1,2,4,5-tetrazine-Ar vdW complex ⟨92JCP(97)2276⟩. In the early 1990s 1 : 1 and 1 : 2 vdW complexes of 3-amino-1,2,4,5-tetrazine and Ar were detected and their spectroscopy and structure as well as predissociation were studied ⟨90JCS(F1)2503, 91JCP(94)1673, 92JCP(96)2522⟩.

vdW Complexes of 1,2,4,5-tetrazine and HCl or H_2O are both planar species, the hydrogen of HCl H-bonded to the lone pair of the tetrazine nitrogen, and H_2O being on the edge of the tetrazine ring, again hydrogen-bridged to the ring nitrogen ⟨87JPC2519, 87JPC2526⟩.

Acetylene forms three vdW complexes with *s*-tetrazine in total, two planar ones in a 1 : 1 ratio and a distorted T-shape structure with two equivalents of acetylene. The 1 : 1 vdW complexes both carry acetylene on top of the tetrazine ring; in one with the protons of the acetylene molecule forming hydrogen bonds with the nitrogen lone pair, in the second complex the acetylene molecule lies flat above the *s*-tetrazine with its molecular axis bisecting the N—N bonds of the ring ⟨88JCP(89)1867⟩. The photophysics and photochemistry of these complexes have been investigated ⟨91JCP(95)1518⟩.

With the same technique dimers of 1,2,4,5-tetrazine ⟨83JCP(79)1581, 83JCP(79)1592, 86JCS(F2)1107⟩, of its 3,6-dimethyl derivative ⟨84JCP(81)2282⟩, and mixed 'dimers' benzene/1,2,4,5-tetrazine ⟨84JPC1726, 87JCS(P2)943⟩ have been detected and their electronic spectra, structure, photophysics, and photochemistry have been studied. For the 1,2,4,5-tetrazine dimer and the mixed benzene/1,2,4,5-tetrazine cluster two geometries are in accord with the data, a planar one having the six-membered rings side-by-side with a center-to-center ring separation of 5.6 Å for the tetrazine dimer. The second cluster has a T-shaped conformation. In the dimer of 3,6-dimethyltetrazine the two rings are arranged stacked and parallel with one ring slipped with respect to the other.

Finally, the supersonic jet technique has been applied to study spectroscopic details of 3-methyltetrazine ⟨83JPC2091, 84CPL141⟩, 3,6-dimethyltetrazine ⟨84JCP(81)2270⟩, and 3-amino-*s*-tetrazine and its 6-methyl derivative ⟨91JCP(94)2475⟩.

6.21.3.9 Spectral Hole Burning

Many tetrazines undergo an irreversible photochemical fragmentation with reasonable quantum yield even at very low temperatures. This fact has been used in several applications of the new spectroscopic technique of photochemical hole burning (HB). In the following sections brief descriptions of the principles of this method with references to applications to tetrazines, especially 3,6-dimethyl-1,2,4,5-tetrazine are given.

The large band width of electronic transitions observed in condensed phase UV/VIS spectra results from the many fluctuating perturbations exerted upon the chromophore by the surrounding

solvent molecules. At very low temperatures most of these fluctuations can be frozen out. Each individual molecule then has a narrow absorption line with a homogeneous line width given by the inverse of the excited state lifetime (typically 10^{-3} cm^{-1} for S_1). However, the individual transition frequencies are inhomogeneously distributed over a spectral region with a typical width of 100 cm^{-1}, leading to a broad structureless bandshape. Irradiation with a narrow-bandwidth laser, however, excites only a small homogeneous subensemble of molecules. If these molecules decay to a different ground state, e.g. through decomposition by a photochemical reaction, their contribution to the absorption spectrum is removed. Hence the absorption spectrum will display narrow 'holes' which correspond to the homogeneous spectrum of the originally excited subensemble. For review articles and the theory of HB see ⟨80JCP(72)1851, 82MI 621-01, 84AG(E)113, B-88MI 621-01⟩.

In several applications the mechanism of spectral HB is not the photochemical decomposition but a transition in the nuclear-spin wave function of the methyl group in the electronically excited state. The corresponding transition in the electronic ground state is very slow. This 'reaction' leads only to a small but well-defined shift of the transition frequency. The 'photoproduct' hence appears as Lorentzian 'antiholes' in the spectrum ⟨92JPC2080⟩. These can be used to study the temperature dependence of the spin conversion rate ⟨92JCP(96)6335, 93JCP(99)1⟩.

With the development of ultrafast lasers it has become possible to study spectral holes even at room temperature in liquid solutions ⟨90CPL(174)476, 92JCP(96)8741, 93CPL(201)437, 93JCP(98)7773, 93JCP(99)8552⟩.

The topics of papers relevant to *s*-tetrazine HB studies, arranged chronologically, are as follows: photophysical and photochemical molecular HB theory ⟨80JCP(72)1851⟩, photochemical HB of gas phase *s*-tetrazine ⟨86JCP(85)6983⟩, dispersive relaxation and spectral diffusion in doped alcohol glasses ⟨87CPL263⟩, rapid solvation of a nonpolar solution measured by ultrafast transient HB ⟨90CPL476⟩, optical dephasing of organic glassy systems studied by HB—relation with excited-state lifetime ⟨91CPL387⟩, ultrafast transient and permanent HB in glycerol ⟨92JCP(96)8741⟩, temperature dependence of nuclear spin conversion rate ⟨92JCP(96)6335⟩, pressure tuning of spectral holes in organic crystalline materials ⟨92JCP(97)5403⟩, Lorentzian antihole formation through optically induced spin conversion in doped *n*-octane crystals ⟨92JPC2080⟩, dephasing effects on ultrafast transient HB of nonpolar solute and solvent molecules ⟨93CPL437⟩, molecular interactions and correlation phenomena between pressure shift and solvent shift—a spectral HB study ⟨93JPC6902⟩, spin conversion relaxation in 3,6-dimethyl-*s*-tetrazine doped *n*-octane ⟨93JCP(99)1⟩, temperature-dependent ultrafast solvation dynamics in *n*-butylbenzene ⟨93JCP(98)7773⟩ and time-resolved nonpolar solvation dynamics in supercooled and low viscosity *n*-butylbenzene ⟨93JCP(99)8552⟩.

6.21.4 THERMODYNAMIC ASPECTS

A number of thermodynamic data have been investigated by experiment and theory. Section 6.21.2 contains references to investigations on enthalpies of formation, hydrogenation energies, hydrogen transfer energies, resonance energies, dissociation energies, bond energies, bond angles, ionization potentials, dipole moments, and conformations of tetrazine and its derivatives.

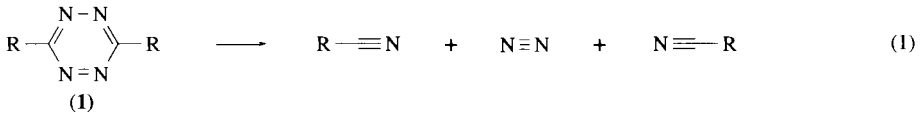
Prototropic tautomerism of the dihydrotetrazines is mentioned in Section 6.21.3.1, and ring–chain tautomerism of the tetrahydro and hexahydro derivatives in Section 6.21.9.1.

6.21.5 REACTIVITY OF FULLY CONJUGATED RINGS

Neunhoeffer's contribution on the reactions of 1,2,4,5-tetrazines in CHEC-I broadly covered most of the principal reactions: instability to acids and bases, acidic hydrolysis, basic hydrolysis, thermal rearrangements, attack of various nucleophiles at the 3- or 6-position, oxidation, and reduction reactions by various reagents, thermolysis and photolysis ⟨84CHEC-I(3)531⟩. There is little progress to be reported in these fields. A brief survey is presented in Sections 6.21.6 and 6.21.9. Still rapidly growing is the field of (4 + 2) cycloaddition reactions of 1,2,4,5-tetrazines, upon which we shall concentrate in Sections 6.21.5.4 and 6.21.5.5.

6.21.5.1 Thermal and Photochemical Unimolecular Reactions

CHEC-I reports that tetrazines (**1**) decompose thermally and photochemically to yield nitrogen and two equivalents of nitrile (Equation (1)) ⟨84CHEC-I(3)531⟩. Diphenyltetrazine thermally decomposes at temperatures above 250 °C, so tetrazines are normally stable enough for all reactions to be studied.



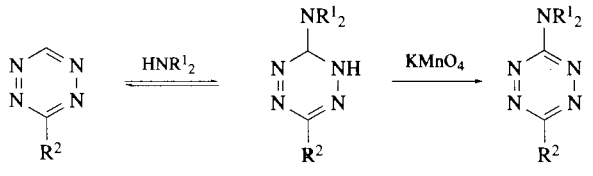
(1)

The photochemical fission of the tetrazine nucleus has been accomplished in the UV (260 nm) and visible (530 nm) range as well as by synchroton radiation (9–22 eV). The principal question, which is still under experimental and theoretical examination, is: is the excited species a vibrationally excited ground state or a photochemically excited state, and is the breakdown a stepwise mechanism or a concerted triple dissociation to two equivalents of RCN and nitrogen? Most experimental effort has been devoted to the parent compound. Leading papers offer entry to this interesting field of spectroscopy: ultraviolet and visible photodissociation of *s*-tetrazine ⟨80CPL(71)429⟩, laser-induced photodissociation ⟨92JCP(96)3628⟩, mechanism of photodissociation of *s*-tetrazine—a unimolecular triple dissociation ⟨86JA8160⟩, FTIR spectroscopy of fragments of photodissociation ⟨87MI 621-02⟩, synchroton radiation selected *s*-tetrazine ion chemistry ⟨88JA1093⟩, unimolecular photodissociation of *s*-tetrazines and derivatives ⟨88JPC5366⟩, concerted unimolecular triple dissociation of *s*-tetrazines ⟨90JPC5552⟩, and concerted triple dissociation—the photochemistry of *s*-tetrazine ⟨89JCP(90)5527⟩ are headings which illustrate the problem.

6.21.5.2 Addition Reactions

Due to the four electronegative nitrogen atoms the 1,2,4,5-tetrazine ring system is quite electron deficient. The high oxidizing power of tetrazines (see Section 6.21.5.9) leads to an easy addition of electrons to the tetrazine nucleus and to the expectation that nucleophiles should add to the carbons at the 3- and 6-positions. The addition of a nucleophile in combination with the presence of a good leaving group in the site of addition is the perequisite for nucleophilic aromatic substitution at the tetrazine ring, which will be treated in Section 6.21.5.3. Complete separation between addition and substitution reactions is not always possible.

Dissolving 3-aryl(alkyl)-1,2,4,5-tetrazines (**21**) in liquid ammonia or primary aliphatic amines at −35°C to −40°C, followed by addition of potassium permanganate, gives 6-alkylamino-3-aryl-(alkyl)-1,2,4,5-tetrazines (**23**) in reasonable to excellent yields. This shows that, under the reaction conditions, addition of *N*-nucleophiles to the tetrazine ring must have occurred (Scheme 1) ⟨81JHC123⟩. The presumption of a 1,6-dihydro intermediate (**22**) rests on the experimental result that tetrazines can be transformed by sodium borohydride into the isolable 1,6-dihydro-1,2,4,5-tetrazines, which can be considered as neutral homoaromatic systems ⟨81JOC2138⟩.



(21) (22) (23)

R^1 = alkyl
R^2 = alkyl, aryl

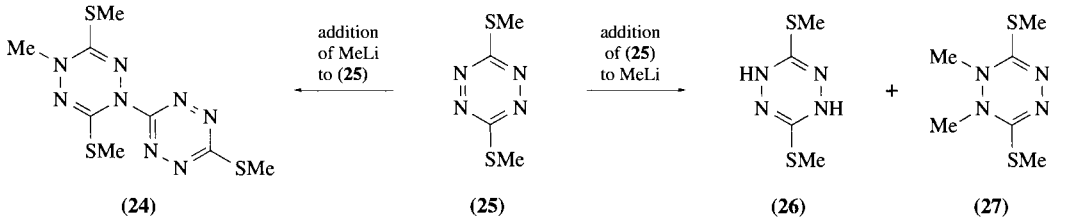
Scheme 1

The expectation would be that substitution reactions on tetrazines occur without rearrangement. However, van der Plas and co-workers, in an elegant tracer study, could show that the hydrazination of 3-alkyl(aryl)-1,2,4,5-tetrazines occurs with rearrangement according to the S_N(ANRORC) mechanism: addition of a nucleophile is followed by a ring opening and ring closure ⟨81JOC5102, 83JHC1259⟩.

Tetrazinedicarboxylic ester is quite sensitive to protic solvents (H_2O, ROH) especially in the presence of base, as well as to ammonia and secondary amines. A thorough study by Seitz and co-workers showed that the primary step is the addition of the nucleophile, with subsequent loss of nitrogen and ring opening ⟨82CB683⟩. A more detailed discussion of other addition reactions is found in ⟨84CHEC-I(3)531⟩.

3,6-Bismethylthio-1,2,4,5-tetrazine (**25**) is an appropriate starting compound for substitution reactions (see Section 6.21.5.3); *N*-nucleophiles displace one or two sulfur functions. By contrast,

methyllithium in THF at −78 °C gave (**26**) and a trace of (**27**) in an "azaphilic addition" (Scheme 2) ⟨91JHC1163⟩. Inverse addition of CH_3Li to the tetrazine solution yielded (**24**). Grignard compounds also show "azaphilic addition."



(24) (25) (26) (27)

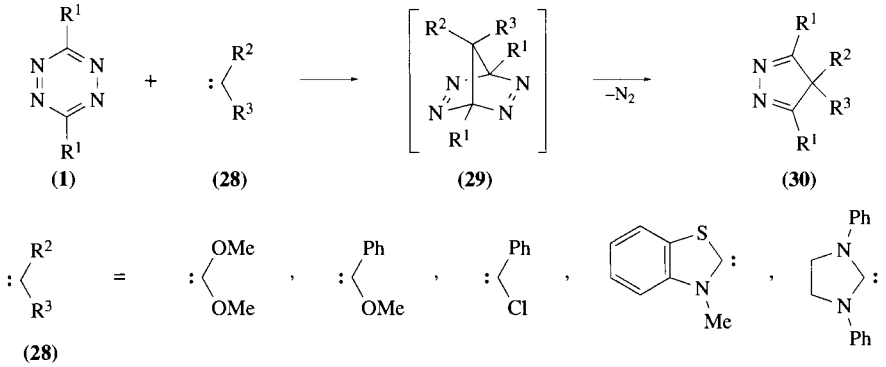
Scheme 2

6.21.5.3 Substitution Reactions

In Section 6.21.5.6 a number of intramolecular (4 + 2) cycloaddition reactions of 1,2,4,5-tetrazines carrying an appropriate side-chain with a 2π-system will be discussed. In all these examples the side-chain is introduced in a nucleophilic aromatic substitution reaction; *C*-, *N*-, *O*-, and *S*-nucleophiles are used. As leaving groups, halogens, SMe, SOMe, and SO_2Me groups in the 3- or 6-position are effective ⟨84CZ331, 85TL4355, 86TL2747, 87CZ16, 88CZ243, 89CZ254, 91AP(324)803, 91CZ367, 92AP(325)559⟩. A large number of interesting bicyclic pyridazine heterocycles are available by the sequence S_N reaction–intramolecular (4 + 2) cycloaddition.

6.21.5.4 (4 + 1) Cycloaddition Reactions

Various donor-substituted carbenes (**28**) can be trapped in good yields by 1,2,4,5-tetrazines in (4 + 1) cycloaddition reactions (Scheme 3); in a subsequent cycloreversion step nitrogen is lost from the intermediate (**29**) with formation of stable isopyrazoles (**30**). As carbene precursors, orthoformic acid derivatives ⟨93CB733, 93H(35)299, 95LA1313⟩, diazirines ⟨91TL2743⟩, and 'Wanzlick's alkene' ⟨87CZ9, 94CB1803⟩ can be used, leading to the electron-rich carbenes shown in Scheme 3. Substituents R in the tetrazine (**1**) may be CF_3, CO_2Me, Ph, SMe, SO_2Me/NMe_2, and SMe/NMe_2. The isopyrazoles (**30**; $R^1 = CF_3$; $R^2 = R^3 = OMe$) turned out to be reactive 2,3-diazacyclopentadienes, especially towards angle-strained 2π-components (norbornene, norbornadiene, 1,3-cyclopentadiene, *trans*-cyclooctene, cyclooctyne) in a (4 + 2) fashion ⟨93CB733⟩. The *N*-methyl derivative of (**30**), a 4*H*-pyrazolium salt, proved to be a still more reactive 4π-system in (4 + 2) cycloaddition reactions ⟨95LA1313⟩.



(1) (28) (29) (30)

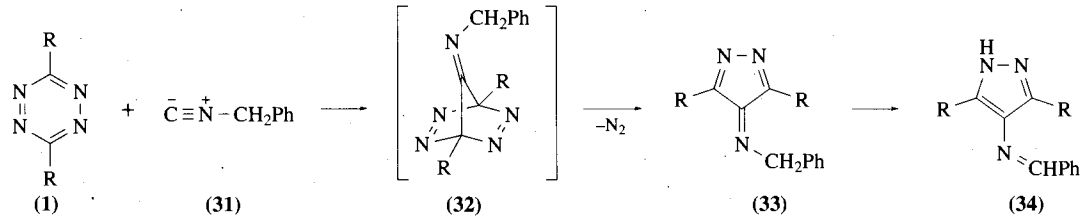
(28) = OMe/OMe, Ph/OMe, Ph/Cl, S/N/Me, Ph/N/N/Ph

R^1 = CO_2Me, CF_3, Ph, SMe and others

Scheme 3

Isonitriles often show carbenoid reactivity, so it is not surprising that benzyl isocyanide (**31**) adds readily to 1,2,4,5-tetrazines (Scheme 4). Again the (4 + 1) cycloaddition step to (**32**) is followed by

a cycloreversion step to (**33**) with nitrogen loss, and a final 1,5-*H*-shift to give (**34**) allows the system to avoid the antiaromatic character of (**33**) ⟨82AG(E)284, 86AP(319)798, 90AP(324)923⟩. Again R may be CO_2Me, CF_3, and Ph as well as SMe and NMe_2/SMe, OMe, and SO_2Me.



(1) (31) (32) (33) (34)

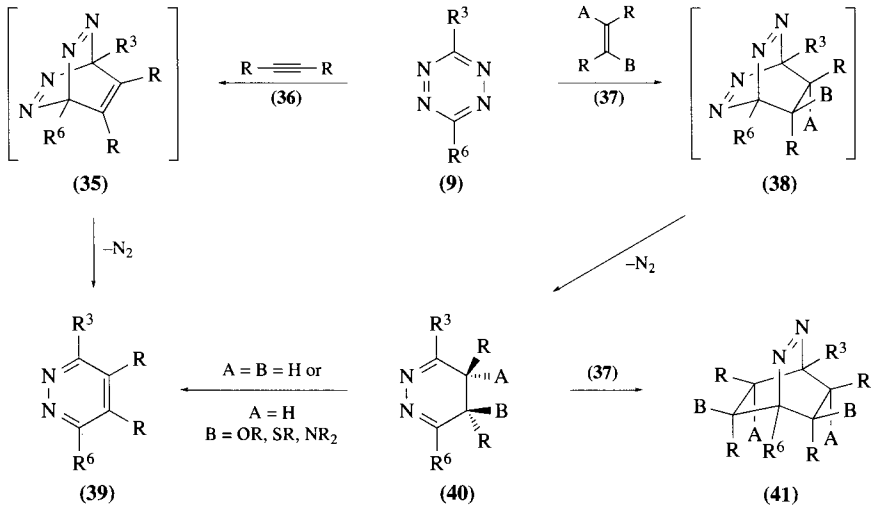
R^1 = CO_2Me, CF_3, Ph, SMe and others

Scheme 4

6.21.5.5 (4 + 2) Cycloaddition Reactions

As early as 1959 Carboni and Lindsey reported the surprising result that aromatic fluoroalkyl 1,2,4,5-tetrazines react with simple alkenes and alkynes under quite mild thermal conditions to form 1 : 1 adducts with loss of nitrogen ⟨59JA4342⟩. With electron-attracting substituents ($R^3 = R^6 = CO_2Me$) the reactivity of tetrazines is particularly high, so Nenitzescu and co-workers proposed the use of the tetrazine diester as a titrating agent to determine the purity of liquid alkenes ⟨62CB2248⟩.

The reactions can be described as Diels–Alder reactions with inverse electron demand, according to early kinetic measurements by Sauer (Scheme 5) ⟨62AG353, 66TL4979⟩. (4 + 2) Cycloaddition reactions of electron-poor tetrazines (**9**) with electron-rich alkenes (**37**) or alkynes (**36**) form unisolable bicyclic adducts (**38**) or (**35**) in the rate-determining step, which extremely rapidly lose nitrogen to yield 4,5-dihydropyridazines (**40**) or pyridazines (**39**) ⟨65CB1435⟩; (**40**) can readily be oxidized to (**39**). Aromatization also occurs easily if alcohol, thiol, or amine can be eliminated from a *trans*-arrangement of substituents. The cycloaddition step is especially fast if ketene aminals, enamines, enol ethers, enol esters, or trimethylsilyloxyalkenes are used as 2π-compounds. The reaction enthalpy ΔH for the cycloaddition of 1,3-cyclopentadiene or 1-hexene to dimethyl tetrazinedicarboxylate is in the range of 60–70 kcal mol^{-1} ⟨93ZOR1719⟩.

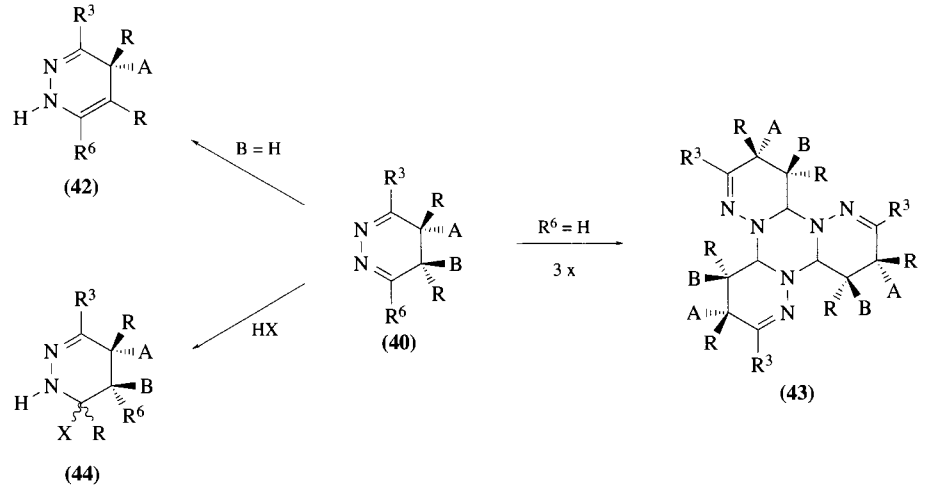


(35) (36) (9) (37) (38) (39) (40) (41)

Scheme 5

Other modes of sometimes unwanted side reactions of (**40**) are the formation of 2 : 1 adducts (**41**) with alkenes (**37**), the tautomerization to stable 1,4-dihydropyridazines (**42**), the addition of compounds of type HX (water, alcohol, amine, hydrogen cyanide) to a CN double bond in (**40**) to yield the (1 : 1) adducts (**44**), and the extremely rapid trimerization to (**43**), for the case where R^3

and/or R^6 are hydrogen (Scheme 6). The trimers are usually isolated as mixtures of stereoisomers with regard to the central 1,3,5-triazane ring system, as shown by the extensive investigations of Sauer ⟨92BSB521⟩.



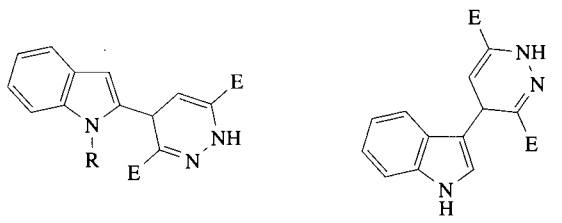
(42) (40) (43) (44)

Scheme 6

As long as acceptors are used for R^3 and R^6 in tetrazines (**9**) and donors for R or A and B in dienophiles (**36**) and (**37**) the cycloadditions in Scheme 5 are quite fast and can in fact approach diffusion-controlled reactions, as kinetic data prove. The great variability of substituents in both reaction partners, 1,2,4,5-tetrazines and dienophiles, is responsible for the increasing importance of the reactions outlined in Scheme 5. A systematic treatment of the dienophile (simple alkenes and alkynes, more complicated alkenes, donor-substituted alkenes and alkynes, hetero 2π-systems, aromatic systems, heteroaromatic dienophiles; stereospecificity, regiospecificity, and reactivity data) demonstrates this. The variation of the 1,2,4,5-tetrazine partner is included in this discussion.

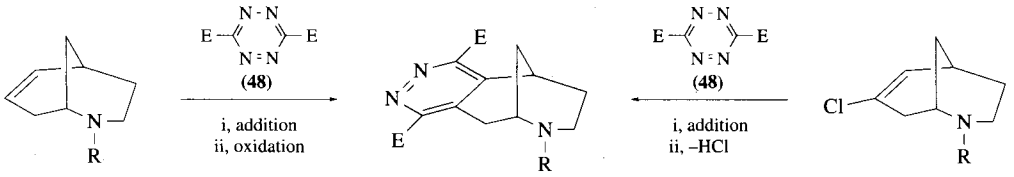
6.21.5.5.1 Simple alkenes and alkynes as dienophiles

The most reactive 1,2,4,5-tetrazines (**9**) (R^3, $R^6 = CF_3$, CO_2Me) react with ethylene and acetylene rapidly at room temperature, the 1,4-dihydropyridazines (**42**) or pyridazines (**39**) being the first isolable products. A large number of mono- and disubstituted ethylenes and alkynes react in a similar way, and examples are collected in many tables in Boger's excellent reviews ⟨83T2869, 86CRV781, B-87MI 621-01⟩. The 4,5-dihydro intermediate (**40**) usually cannot be isolated. Timberlake and co-workers reported a 78 : 22 ratio of the isomer mixture of 1,4- versus 4,5-dihydro forms in the reaction of diphenyltetrazine with isobutylene in $CHCl_3$ solution ⟨83JHC855⟩. Styrene reacts in CCl_4 with bis(trifluoromethyl)tetrazine to yield the 4,5-dihydropyridazine derivative (**40**) exclusively; this is transformed into the isolable 1,4-dihydro isomer (**42**) with $t_{1/2}$ of about 100 min ⟨89TH 621-02⟩. 2- and 3-Vinyl indoles have been used as dienophiles in the reaction with tetrazine diester to yield compounds (**45**) and (**46**) in good yields ⟨87C125, 88TL3927⟩. Annelation of a pyridazine ring onto the morphan ring system (**47**) or (**50**) readily occurs using the highly reactive tetrazine diester (**48**) (Scheme 7) ⟨84BCJ806⟩.



(45) (46)

R = H, Me
E = CO_2Me



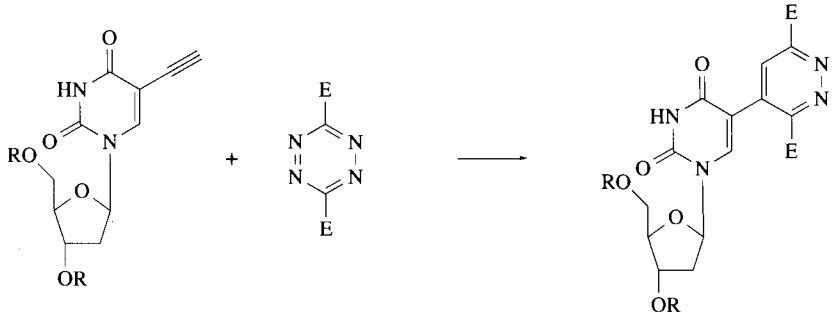
(47) (49) (50)

R = SO_2Ph, E = CO_2Me

Scheme 7

The easily accessible cyclooctyne, because of its high ring strain, proved to be a reactive test dienophile to measure the diene quality of 1,2,4,5-tetrazines, 1,2,4-triazines, 3,4-diazanorcaradienes, and other electron-poor cyclic azadienes ⟨83TL1481, 86TH 621-01, 92TH 621-01⟩.

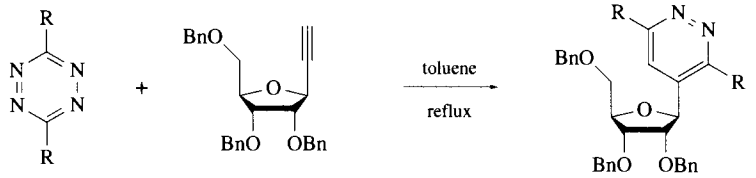
A simple approach to pyridazine-substituted pyrimidine nucleosides (**52**) in the reaction of alkyne derivatives (**51**) with tetrazine diester (**48**) was reported by Maggiora and Mertes (Equation (2)) ⟨86JOC950⟩; use of the 1,2,4-triazine triester as diene yields the corresponding pyridine derivatives. A new route to the novel *C*-nucleosides (**55**) with substituted pyridazines as aglycones by the reaction of tetrazines (**48**) and (**53**) with the sugar alkyne (**54**) has been described (Equation (3)) ⟨94AP(327)365⟩.



(51) (48) (52)

R = H, Ac; E = CO_2Me

(2)



(53) R = CF_3
(48) R = CO_2Me

(54)
Bn = benzyl

(55)
R = CF_3, 77%
R = CO_2Me, 76%

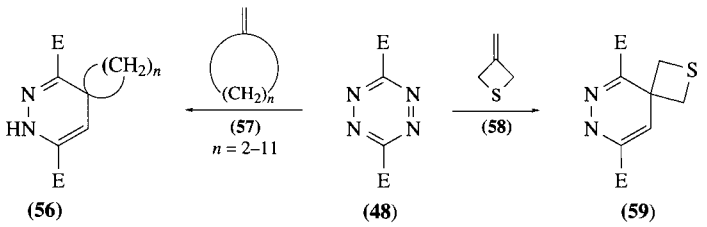
(3)

6.21.5.5.2 *More complex alkenes and alkynes*

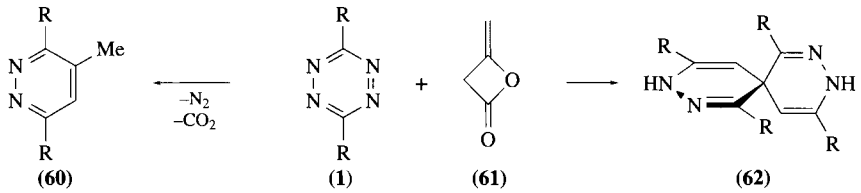
Varying the dienophile in Scheme 5 allows scope for synthesizing complex heterocyclic compounds, polycyclic azo compounds, and even complex carbocyclic systems by thermal or photochemical extrusion of nitrogen. The examples selected in this chapter follow and extend Neunhoeffer's treatment in ⟨84CHEC-I(3)531⟩.

Exomethylene cycloalkanes (**57**) and hetero derivatives such as (**58**) offer an easy entrance to spiro-1,4-dihydropyridazines (**56**) and (**59**) (Scheme 8) ⟨75AP(308)237, 94TH 621-01⟩. Using diketene (**61**) as dienophile a spiro-bisdihydropyridazine (**62**) is obtained in a series of steps as the main product besides small amounts of (**60**) (Scheme 9) ⟨83CZ172⟩.

Benzvalene (**63**) is an interesting compound, as extensive studies by Christl have shown ⟨81AG(E)529⟩. The high ring strain causes high dienophilic reactivity as shown by the fast formation of 4,5-dihydropyridazine derivatives (**64**), which quickly add 2π-components at the diazadiene

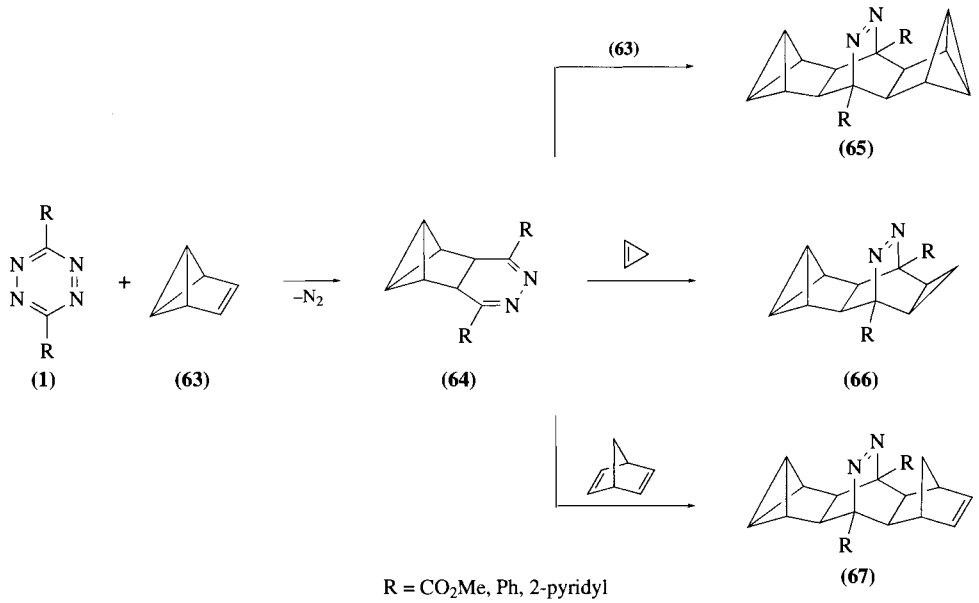


Scheme 8



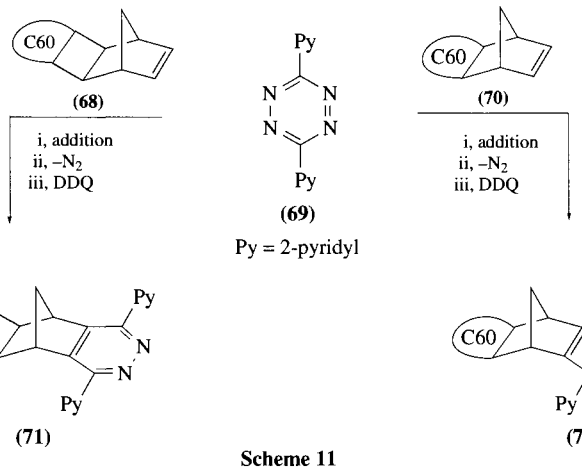
Scheme 9

system to form so-called 'bisadducts' (**65**)–(**67**) (Scheme 10) ⟨88CB1675, 88JA3263⟩, which by nitrogen elimination open the way to a new field of carbocyclic chemistry.

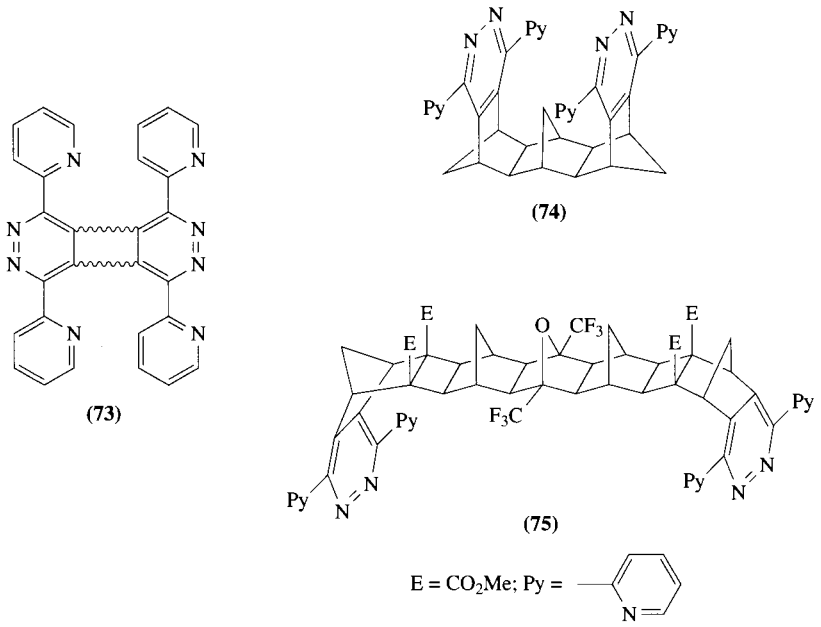


Scheme 10

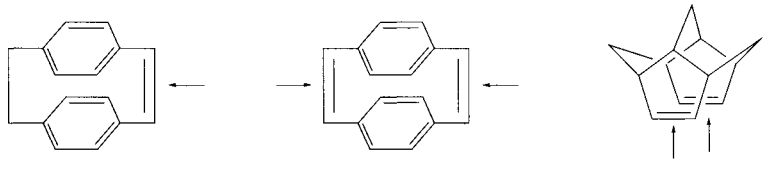
Norbornene derivatives have been widely used as reactive angle-strained 2π-systems. Scheme 11 illustrates this for the reaction of fullerene derivatives (**68**) and (**70**) in the (4 + 2) cycloaddition with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**69**) to form new chelating agents attached to [60]fullerene ⟨95CC1417⟩. The preparation of space-separated chelating agents of type (**73**) rests on the same reaction type ⟨94TL6745⟩; compounds (**74**) and (**75**) are representative examples. The synthesis of inward-facing pyridazine ligands fused to rigid molecular racks has been reported ⟨96TL2825⟩. A cycloaddition–cycloreversion sequence for the combination of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine and an oxanorbornadiene derivative was used to obtain complex furan derivatives ⟨95AJC593⟩. Unsaturated bicyclic endoperoxides reacted with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to yield bicyclic endoperoxides containing pyridazine rings after oxidation ⟨96TL921⟩.



Scheme 11



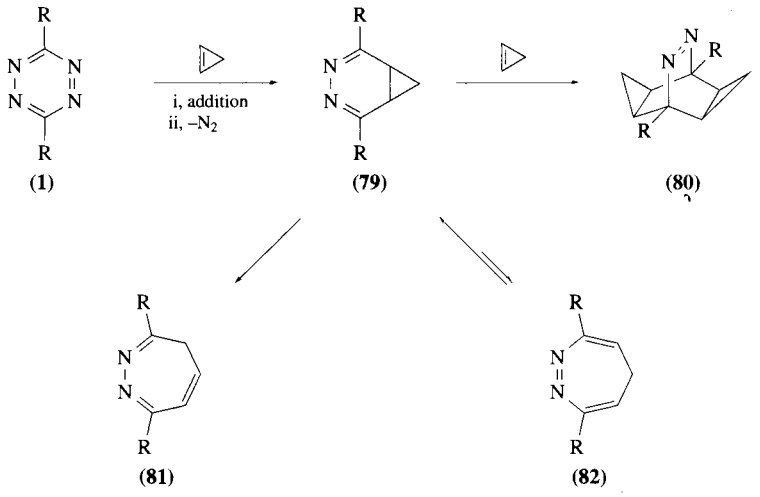
Angle strain is again responsible for the smooth reactions of [2.2]paracyclophan-1-ene (**76**) and [2.2]paracyclophane-1,9-diene (**77**) with tetrazines at the marked double bonds to give the expected (1 : 1) and (1 : 2) adducts, which can be oxidized to the pyridazine derivatives ⟨92HCA901⟩. In a similar way pentaasterane derivatives (**78**) react at the marked double bonds with tetrazine diester ⟨88CB327⟩. Tetradehydrodianthracene ⟨94AG(E)993, 95LA1283, 96AG(E)417⟩, a remarkable angle strained alkadiene, adds 1 equiv. (and under forcing conditions (5 kbar) 2 equiv.) of tetrazine (**9**); the addition rate is purely controlled by steric effects ⟨96LA⟩.



(**76**) (**77**) (**78**)

Cyclopropene and its derivatives show high reactivity as dienophiles; the broad range of subsequent reactions makes it understandable that this type of cycloaddition has been studied extensively. Scheme 12 illustrates the reactions possible in principle for the parent compound

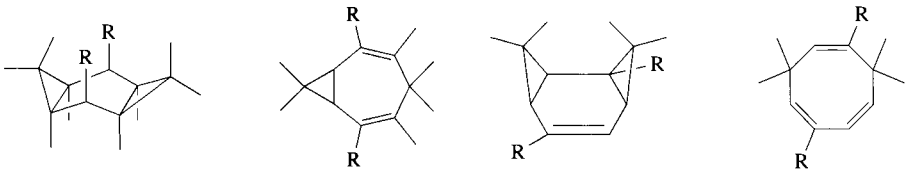
cyclopropene; many substituted cyclopropenes have been used in these reaction sequences. A wide variety of substituents R in tetrazines (**1**) is possible (CO_2Me, CF_3, Ph, Me, SMe, OMe, heteroaryl) ⟨92BSB521, 94MI 621-01, 95CHE1279⟩. Cycloaddition with subsequent N_2-elimination leads to 3,4-diazanorcaradienes (**79**), which undergo rapid valence isomerization to 5*H*-1,2-diazepines (**82**) as D-NMR investigations prove ⟨72JA2770⟩. Thermal and photochemical sigmatropic reactions lead to 4*H*-azepines (**81**) ⟨77TL4393⟩ with subsequent photochemical rearrangement to 6*H*-1,4-diazepines ⟨77TL4389, 84TH 621-01⟩.



(1) (79) (80) (81) (82)

Scheme 12

Many 'bisadducts' (**80**) have been synthesized because of their interesting thermal and photochemical reactions with loss of nitrogen ⟨92BSB521, 94TL7935⟩. Bis(homo-Dewar benzenes) (**83**), homotropilidenes (**84**) ⟨78TL3903, 78TL3907, 79TL1295⟩, *syn*- and *anti*-bis(homobenzenes) (**85**), and 1,3,6-cyclooctatrienes (**86**) ⟨79TL1299, 94TH 621-06⟩ can be obtained in great variety and have been studied extensively. For the formation of compounds of type (**85**) the geminal dimethyl groups in the cyclopropene are essential.



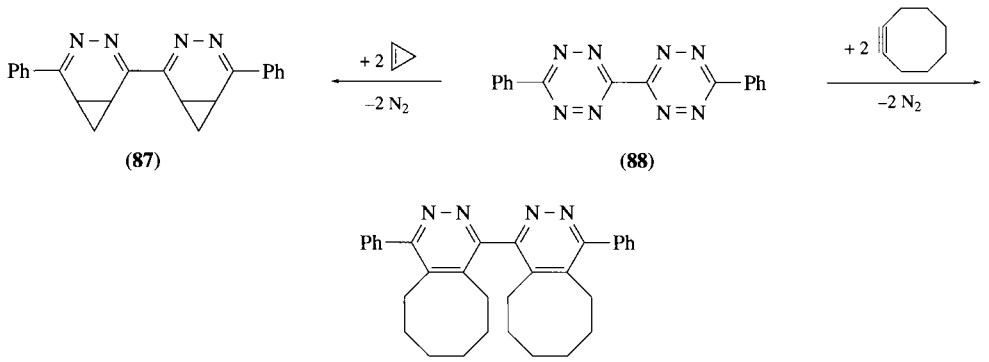
(83) (84) (85) (86)

The first bitetrazine (**88**) to be synthesized reacted readily with cyclopropene and cyclooctyne to yield "bisadducts" (**87**) and (**89**) in good yields (Scheme 13) ⟨94TH 621-02, 94TL7935⟩.

The reactions of 1,2,4,5-tetrazines with the bifunctional dimethylbicyclopropenyl (**90**) to form semibullvalenes (**93**) occur via the proven sequence: *anti*-diazanorcaradienes (**91**) → *syn*-diazanorcaradienes (**92**) → diazasnoutenes (**94**) (Scheme 14); only the *anti*-isomer (**91**) and the stable semibullvalene derivatives (**93**) are isolable ⟨80AG(E)456, 83CB3751, 83TL1485, 84TL749⟩.

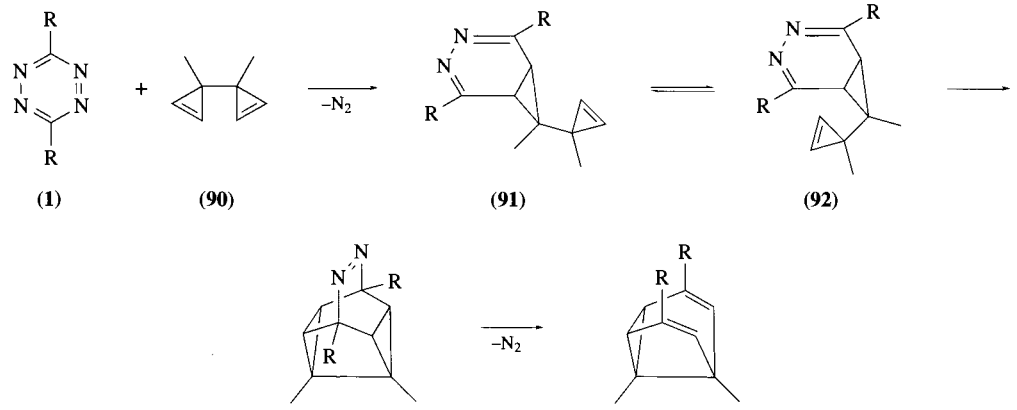
The reaction of bicyclopropylidene (**95**) with the parent compound 1,2,4,5-tetrazine occurs readily at room temperature in CH_2Cl_2, but instead of the expected bisspiro compound (**96**) its trimer (**97**) was isolated by de Meijere *et al.* (Scheme 15) ⟨88JOC152, 93JOC502⟩. The result is in analogy to the trimer formation of the parent compound 3,4-diazanorcaradiene ⟨68CB1354⟩; several isomers of these trimers (**98**; R = H), which can be separated and analyzed by x-ray diffraction, differ in stereochemistry at the central 1,3,5-triazane ring with regard to *cis*- or *trans*-substitution ⟨83TH 621-01, 89TH 621-01⟩. Also monosubstituted 1,2,4,5-tetrazines react with cyclic alkenes (cyclopropene to cyclooctene) to yield trimers of the expected diazabicyclo[4.*n*.0]alkanes (**99**) ⟨89TH 621-01, 94TH 621-02⟩.

Cyclobutene is a reactive dienophile and makes available the diazabicyclo[4.2.0] system (**100**) by its reaction with 1,2,4,5-tetrazines ⟨85TH 621-01, 92BSB521⟩; this bicyclic diazadiene is still a reactive



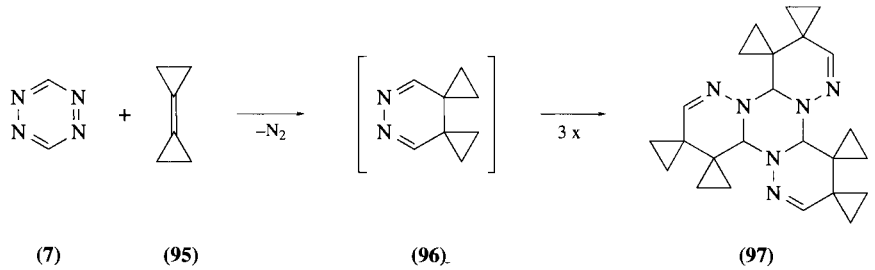
(87) **(88)** **(89)**

Scheme 13



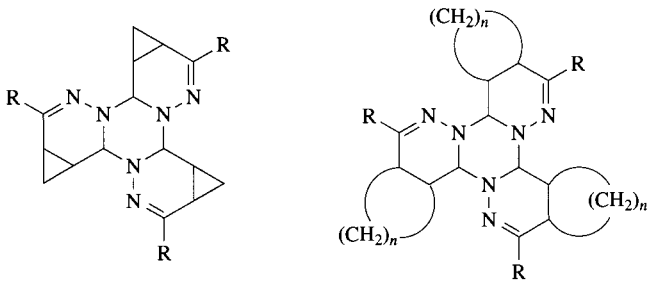
(1) **(90)** **(91)** **(92)** **(94)** **(93)**

Scheme 14



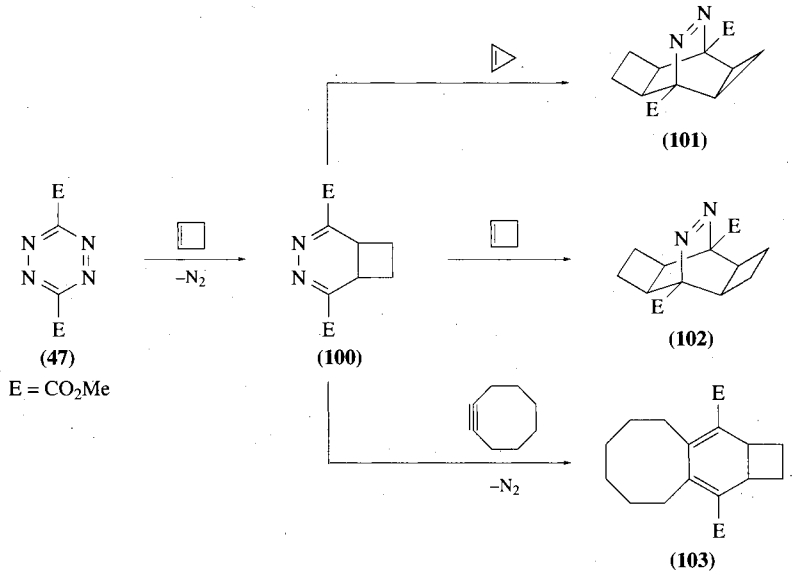
(7) **(95)** **(96)** **(97)**

Scheme 15



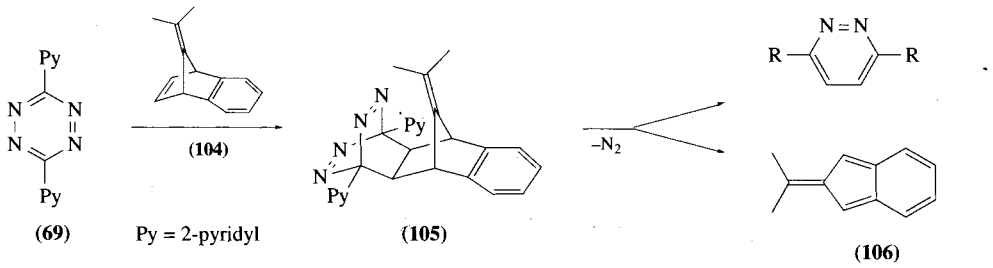
(98) **(99)** $n = 2–6$

electron-poor diene and reacts with a variety of angle-strained and electron-rich 2π-components to form adducts (**101**)–(**103**) (Scheme 16).



Scheme 16

Norbornadiene derivatives are not only angle-strained reactive 2π-systems, but the cycloaddition adducts with 1,2,4,5-tetrazine very often undergo cycloreversion to give interesting π-systems. Some examples may be added to Neunhoeffer's report ⟨84CHEC-I(3)531⟩. Scheme 17 shows the sequence by which 7-isopropylidenebenzonorbornadiene (**104**) is transformed into the isobenzofulvene (**106**) by reaction with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**69**) in a cycloaddition and two cycloreversion steps ⟨81TL2579⟩. An analogous reaction sequence was used for the conversions (**107**)→(**110**) ⟨81JOC2021⟩, (**108**)→(**111**) ⟨86T6713⟩, and (**109**)→(**112**) ⟨86TL3045⟩ (Scheme 18).

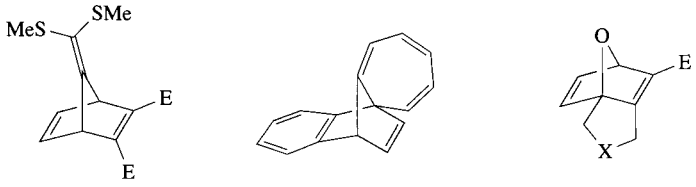


Scheme 17

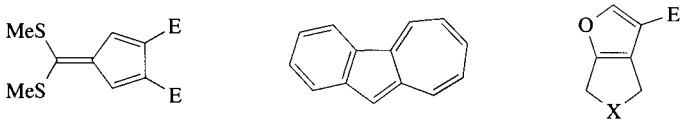
Tetrahydromethanonaphthalenes (**113**) have also been used as dienophiles ⟨88CB685, 91AJC555⟩. The reaction to form the 1,4-dihydropyridazine derivative (**115**) via (**114**) is normal (Scheme 19); (**115**) can be transformed into the methanopyridazin[10]annulene (**118**). In the presence of protons apparently a small equilibrium concentration of the 4,5-dihydro isomer (**114**; $R^1 = CO_2Me$, $R^2 = Cl$) undergoes an intramolecular (4 + 2) cycloaddition to the cage compound (**117**) which is photolyzed to the nitrogen-free cage (**116**) ⟨83TL4087⟩.

Cycloheptatriene derivatives (**119**) were studied by Seitz and co-workers (Scheme 20) ⟨92CB171⟩. With electron acceptors R the tricyclic 1,4-dihydropyridazines (**120**) are obtained which can be oxidized to (**121**). Donor substituted cycloheptatrienes give the same product in addition to those (**122**), (**123**) which result from the addition to the 3,4-double bond of the cycloheptatriene.

Cyclooctatetraene (**124**) reacts normally as a cyclic alkene to give a 1,4-dihydropyridazine derivative (**125**), which undergoes further rearrangement reactions (Equation (4)) ⟨91TL5949, 95LA661⟩.



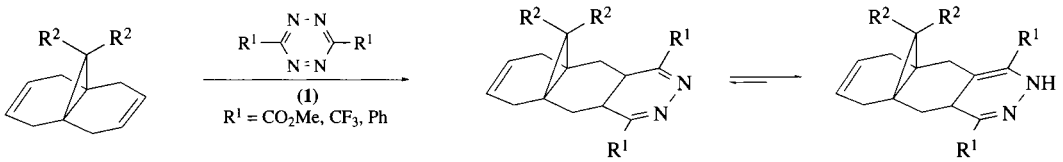
(107) **(108)** **(109)**



(110) **(111)** **(112)**

E = CO_2Me X = O, S; E = CO_2Me

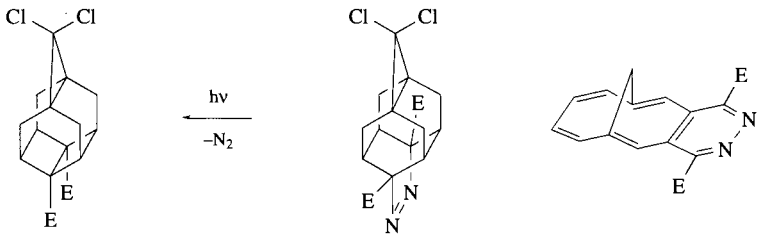
Scheme 18



(113) **(1)** **(114)** **(115)**

R^1 = CO_2Me, CF_3, Ph

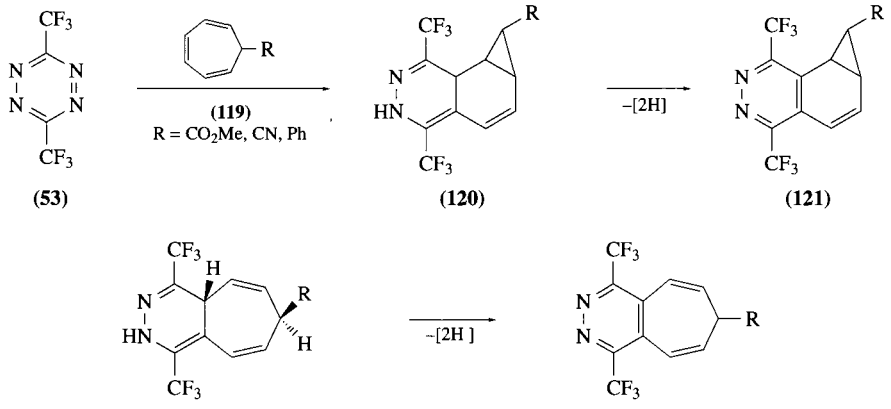
R^2 = H, Cl



(116) **(117)** **(118)**

E = CO_2Me

Scheme 19



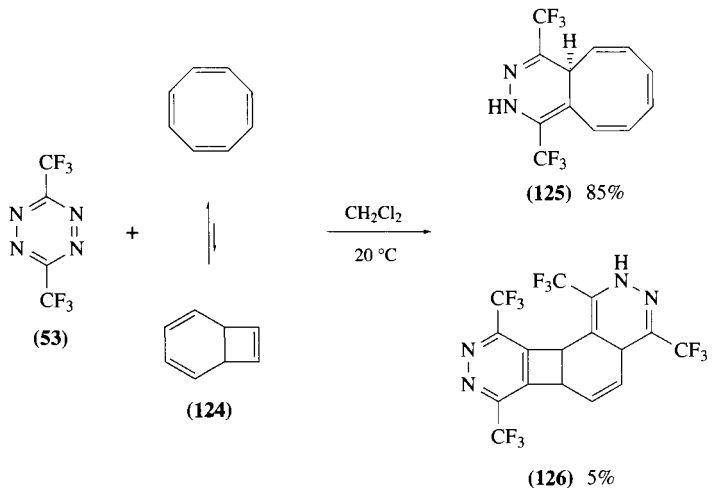
(53) **(119)** **(120)** **(121)**

R = CO_2Me, CN, Ph

(122) **(123)**

R = CMe_3, Me, $CH(OMe)_2$

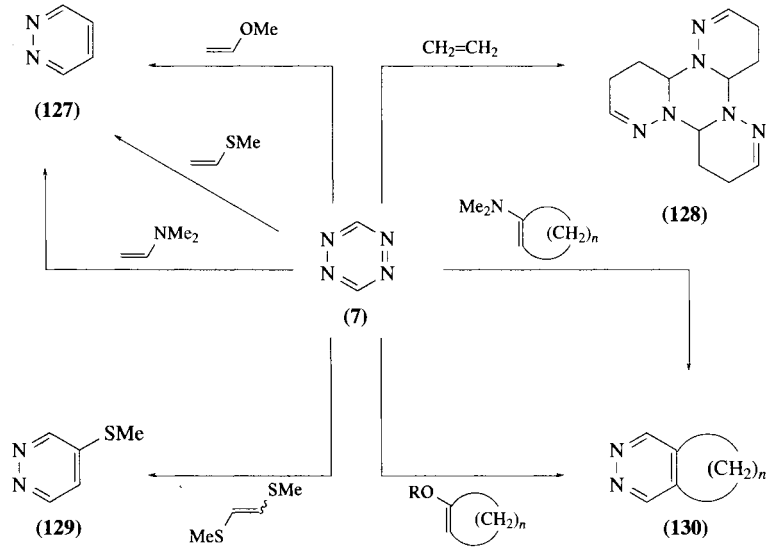
Scheme 20



(4)

6.21.5.5.3 *Donor-substituted alkenes and alkynes*

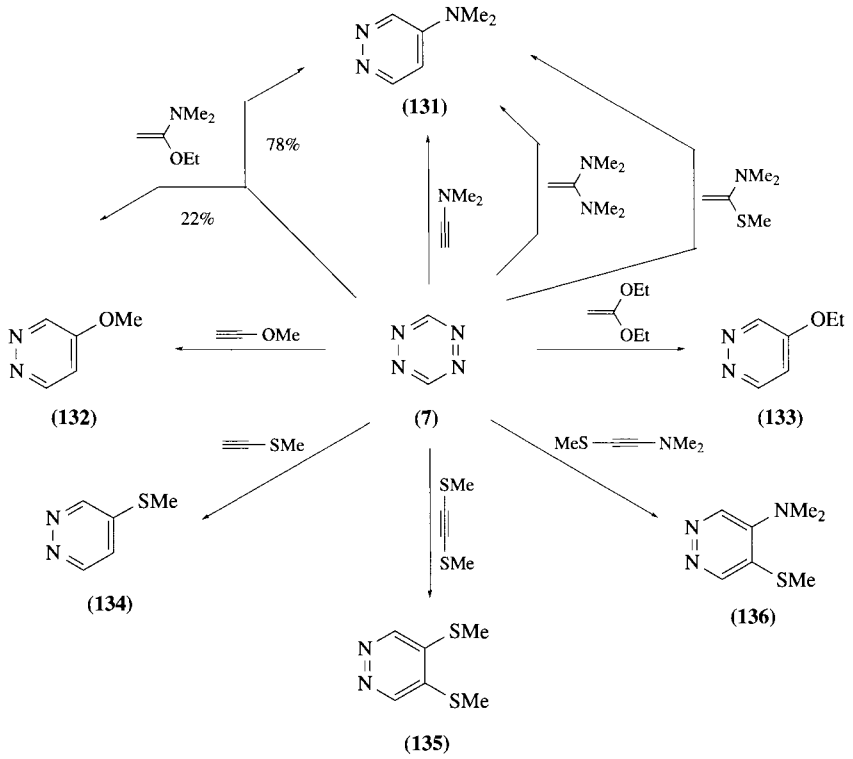
Donor substituents such as NR_2, OR, SR, and $OSiR_3$ increase the electron density of dienophiles and also their reactivity in cycloadditions with 1,2,4,5-tetrazines. Schemes 21 and 22 ⟨89TH 621-01⟩ show typical (4 + 2) cycloaddition reactions for the parent compound (**7**) with donor substituted alkenes and alkynes, which make available a large number of simple donor substituted pyridazines (**127**)–(**136**).



R = Me, TMS; n = 5–8

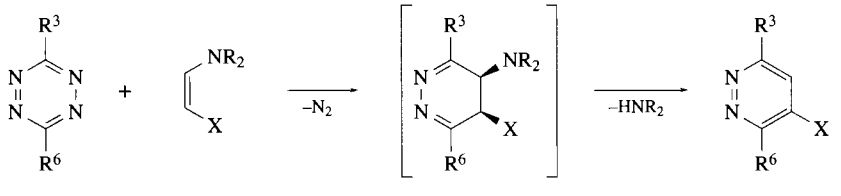
Scheme 21

It was recognized as early as 1965 by Sauer *et al.*, that enol ethers, enol esters, enamines, and ketene aminals cycloadd to 1,2,4,5-tetrazines in a normal way according to Scheme 5; HOR, HO_2CR, HSR, and HNR_2 elimination leads to the aromatic systems ⟨65CB1435⟩. Roffey and Verge added a number of further examples for open-chain and cyclic enol ethers, enol esters, and enamines ⟨69JHC497⟩, as did Boger *et al.* with tetrazine diester ⟨84JOC4405⟩, and 3,6-bis(methylthio)-1,2,4,5-tetrazine ⟨88JOC1415⟩. Acyclic dienamines ⟨87H(26)337⟩, 1-morpholinocycloalkenes ⟨89JHC717⟩, and enamines of steroids ⟨93TA393⟩ reacted with 1,2,4,5-tetrazines in the expected mode. The activating effect of dialkylamino groups overcompensates the deactivating effect of nitro or cyano groups, so nitro- and cyanopyridazines (**139**) can be obtained from the combination of 1,2,4,5-tetrazines (**9**)

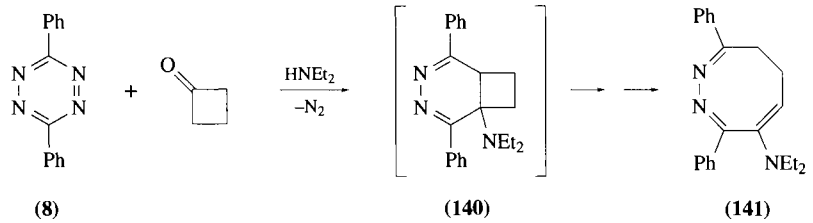


Scheme 22

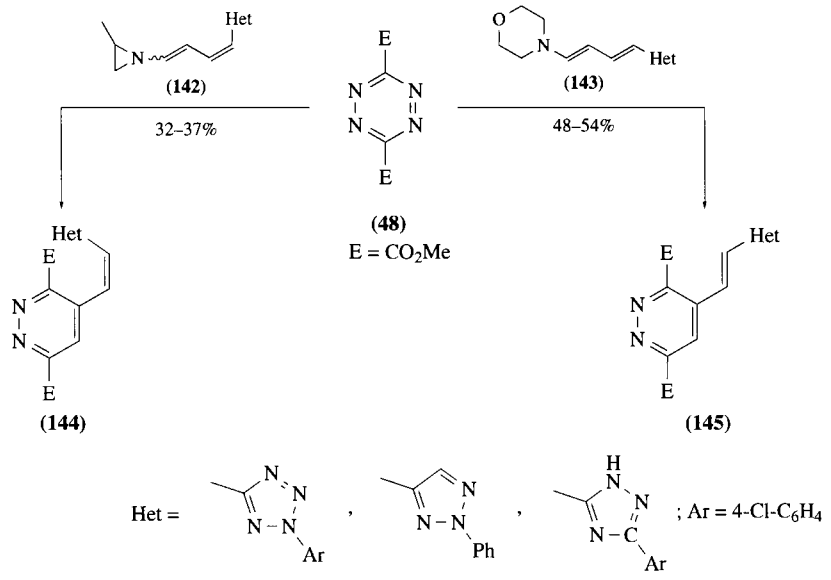
with push–pull systems (**137**) as Scheme 23 shows ⟨85H(23)683, 90TL6855⟩. Enamines do not need to be isolated, a mixture of ketone and secondary amine can sometimes be used as an equivalent, as was shown for the combination of cyclobutanone and diethylamine in the reaction with 3,6-diphenyl-1,2,4,5-tetrazine (**8**) to (**141**), through (**140**) (Scheme 24) ⟨84TL2577⟩. 1,4-Dihydropyridines have also been used as enamines ⟨87JOC2026⟩. Heteroaryl substituted dienamines (**142**) and (**143**) of different geometry reacted as enamines selectively when treated with tetrazine (**48**) to yield pyridazines (**144**) and (**145**) (Scheme 25) ⟨95JOC4919⟩.



Scheme 23

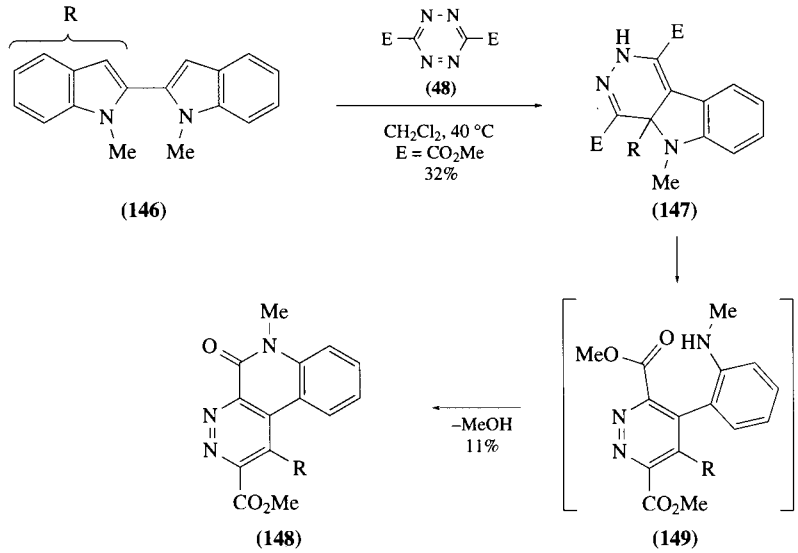


Scheme 24



Scheme 25

Di-*N*-methyl-2,2′-biindole (**146**) when combined with tetrazine dicarboxylate (**48**) uses only one heterocyclic ring as an enamine function to form (**147**) and by a subsequent ring opening ring closure via intermediate (**149**) the tricyclic compound (**148**) is formed (Scheme 26) ⟨94H(38)2267⟩.



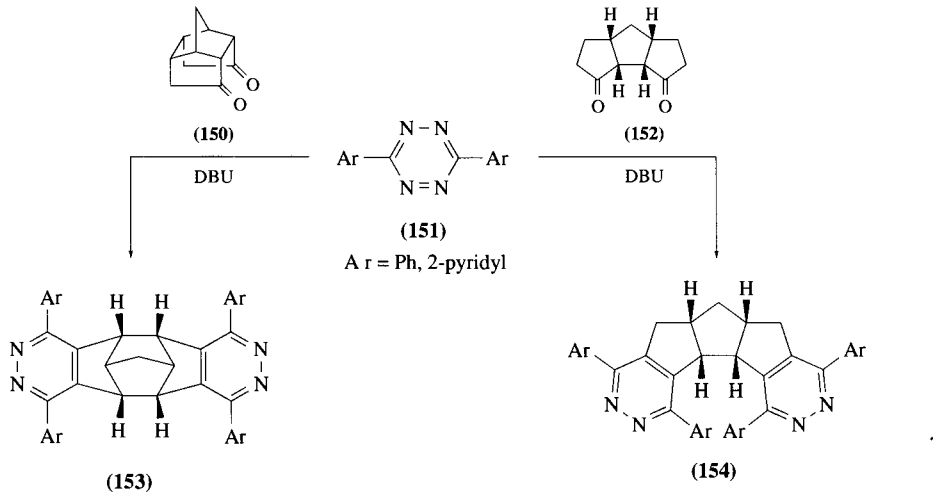
Scheme 26

3,6-Diaryl-1,2,4,5-tetrazines react with diethylamine or triethylamine in the presence of oxidizing agents to form 3,6-diarylpyridazines ⟨90KGS1545, 91ZOR1123⟩; apparently an enamine is formed as an intermediate which reacts in the normal way with the tetrazine in a (4 + 2) cycloaddition.

A larger number of silyl enol ethers have been studied by kinetic measurements with regard to their synthetic value as dienophiles and their reactivity; the readily accessible silyl enol ethers proved to be enol equivalents ⟨92TL8019⟩. Synthesis of novel heterocyclic clefts such as (**153**) and (**154**) can be achieved by (4 + 2) cycloaddition reactions of 1,2,4,5-tetrazines (**151**) with polycyclic diketones (**150**) and (**152**) in the presence of base; apparently the enolates (or enols) are the dienophiles (Scheme 27) ⟨94H(37)869⟩.

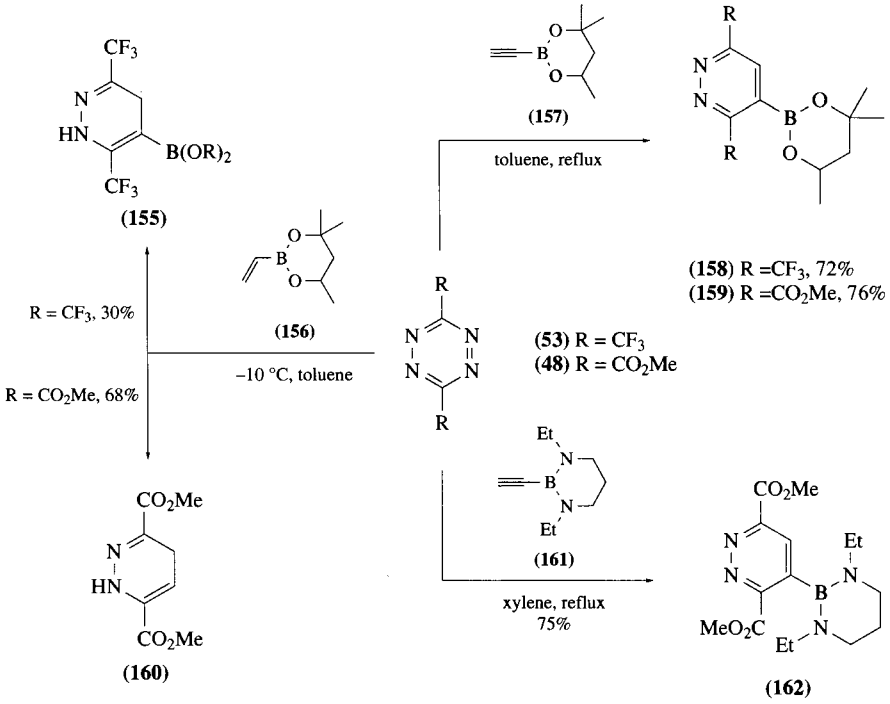
1,5-Anhydrohex-1-enitol (anhydro sugars) behave as enol ethers and give the expected products with tetrazine diester ⟨85LA628⟩.

Finally, there are reports that silyl and stannyl alkynes can be used as alkynes with various



Scheme 27

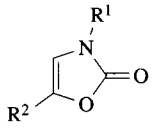
tetrazines ⟨68LA(716)29, 74JOM(74)C1, 78JCS(P1)378, 82CB2574, 91H(32)1387⟩; electrophilic substitution reactions at the pyridazine derivatives with removal of Si and Sn are interesting synthetic goals. While vinylboranes such as (**156**) react already at −10 °C with tetrazines (**48**) and (**53**) to form (**155**) and (**160**), ethynylboranes (**157**) and (**161**) need boiling toluene and xylene as solvent to yield the expected pyridazines (**158**), (**159**), and (**162**) (Scheme 28) ⟨94AP(327)673⟩.



Scheme 28

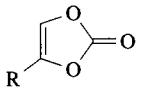
With an increasing number of donor substituents in the dienophile component its reactivity normally increases, so 1,2- and especially the unsymmetrical 1,1-donor substituted 2π-components have proved to be valuable dienophiles. After initial reports ⟨65CB1435, 69JHC497⟩, Deyrup and Gingrich introduced 4-oxazolin-2-ones (**163**) and vinylene carbonate (**164**) as cyclic bifunctional dienophiles, making possible the introduction of hydroxy and amino groups in the pyridazines ⟨77TH 621-01, 77TL3115⟩.

Ketene aminals in all variations have stood the test as record dienophiles in these Diels–Alder



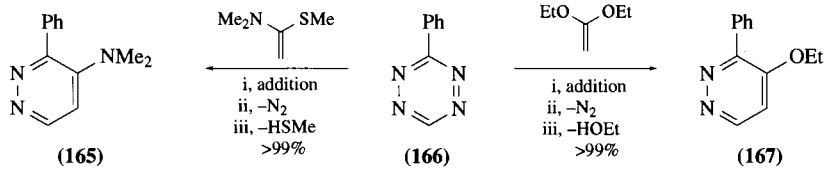
(163)

$R^1 = R^2 = H$
$R^1 = CO_2Me$, $R^2 = H$
$R^1 = H$, $R^2 = Ph$
$R^1 = CO_2Me$, $R^2 = Ph$



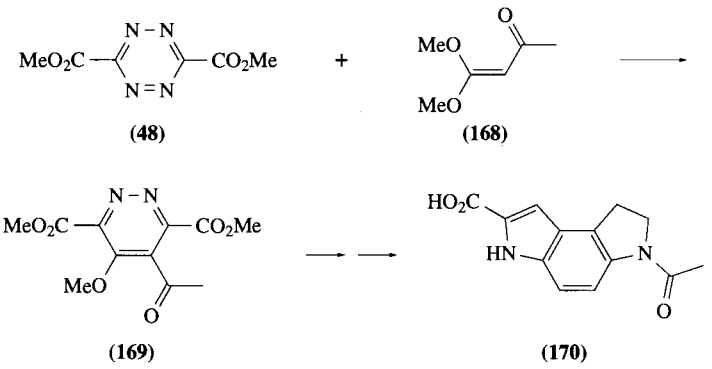
(164)

reactions with inverse electron demand; 1,2,4,5-tetrazines and 1,2,4-triazines were used as 4π-partners ⟨84TL2541⟩. A sequence of 4π cycloaddition → N_2 elimination → HX elimination with aromatization leads directly to the aromatic pyridazine system with introduction of a donor substituent (Scheme 29). With unsymmetrically substituted tetrazines a strict regiochemistry is usually obeyed, as the almost exclusive formation of (**165**) and (**167**) shows. Highlights in this field are Boger and Coleman's elegant total synthesis of natural products—PDE-II methyl ester (**170**) (Scheme 30) ⟨86JOC3250⟩, prodigiosin (**174**) (Scheme 31) ⟨87TL2499⟩, and isochrysohermidin (**177**) (Scheme 32) ⟨93JA11418⟩ are interesting examples: in all reaction sequences the (4 + 2) cycloaddition step of a ketene acetal (**168**), (**171**), or (**175**) to a tetrazine derivative was the introductory step; another key step was the reductive ring transformation of a pyridazine to a pyrrole (**169**) → (**170**), (**172**) → (**173**), or (**176**) → (**177**).



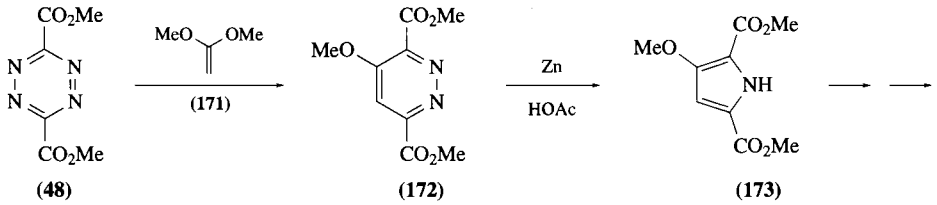
(165) (166) (167)

Scheme 29

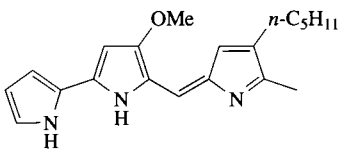


(48) (168) (169) (170)

Scheme 30

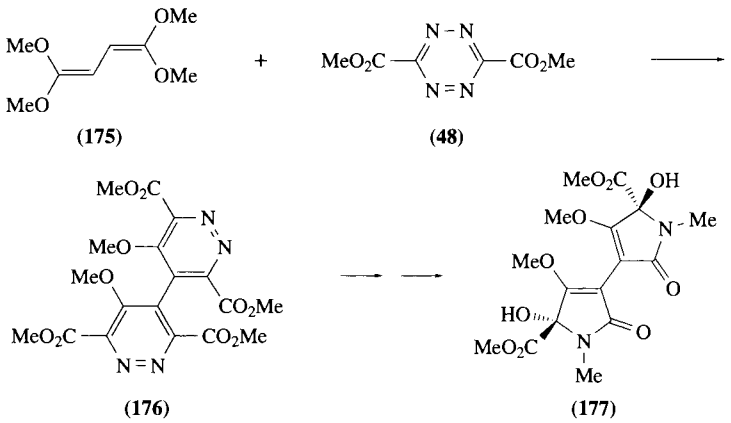


(48) (172) (173)



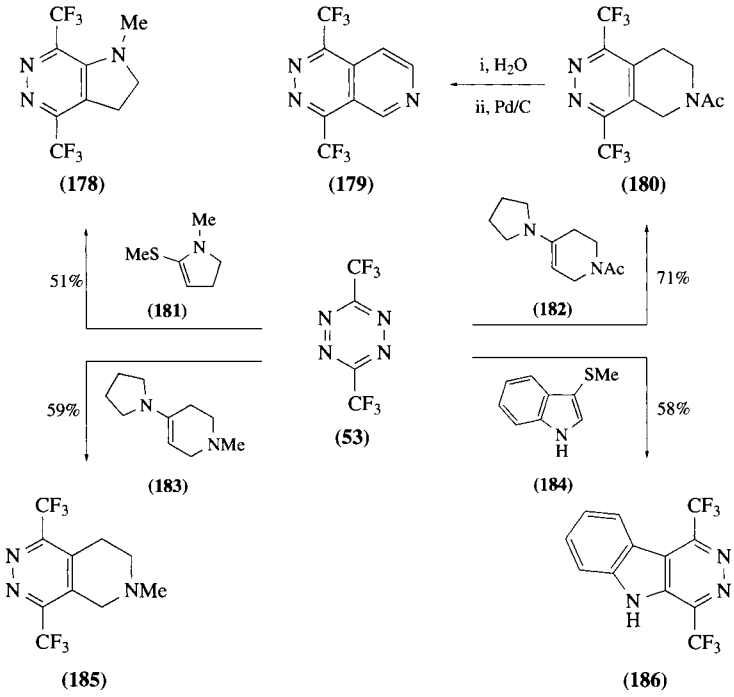
(174)

Scheme 31



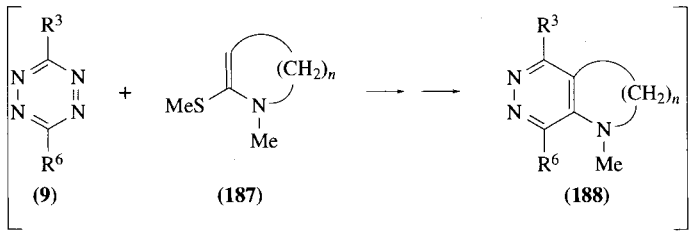
Scheme 32

Haider's approach to alkaloid precursors includes reactions of tetrazine (**53**) with the cyclic *N,S*-aminal (**181**) and with the heterocyclic enamines (**182**), (**183**), and (**184**); compounds (**180**), (**185**), (**186**), and (**178**) are the expected reaction products (Scheme 33) ⟨94H(38)1805, 94H(38)1845⟩.



Scheme 33

Cyclic ketene *N,S*-aminals (**187**) with different ring sizes were used by Marcelis and van der Plas to form (**188**) (Equation (5)) ⟨87JHC545⟩. Cyclic lactim ethers (**189**) and donor substituted 2,5-dihydropyrazines (**191**) react in their tautomeric ketene *O,N*-aminal forms (**190**) and (**192**); (**194**) and (**193**) are accessible as has been shown in a number of examples (Scheme 34) ⟨77AP(310)936, 90AP(323)89⟩. The sulfur analogue reacts in the same way. Finally, lactam acetals (**195**) can be used as an *in situ* source of cyclic ketene *O,N*-aminals (**196**) and form pyridazines (**197**) on reaction with (**8**) (Scheme 35) ⟨86CB3600⟩; 1,2,4,5-tetrazines and 1,2,4-triazines were the 4π-partners.

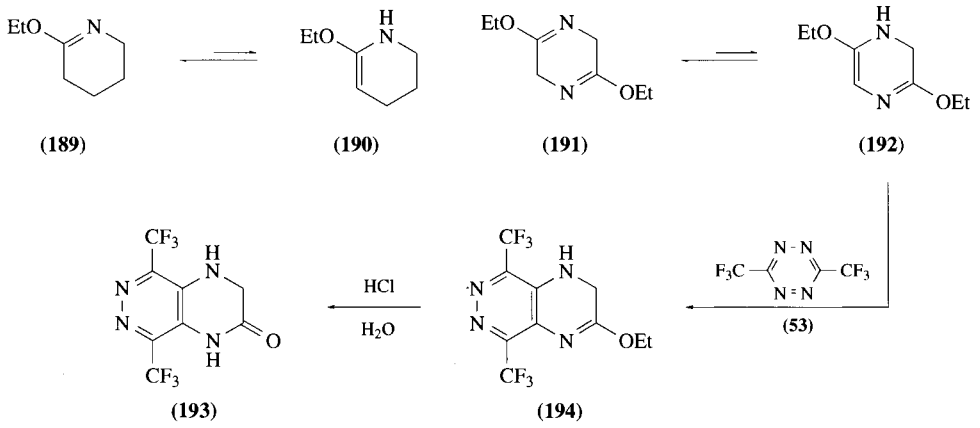


(9) (187) (188)

$R^3 = R^6$ = Ph, 2-pyridyl, H

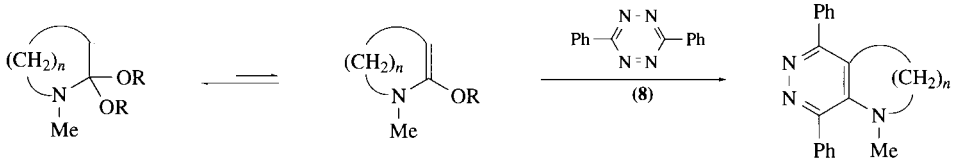
R^3 = H, R^6 = Ph; n = 2, 3

(5)



(189) (190) (191) (192) (193) (194) (53)

Scheme 34



(195) (196) (197) (8)

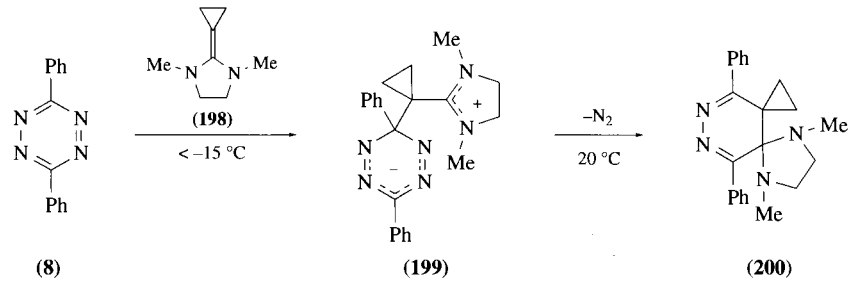
R = Me, Et

n = 2–4

+ HOR

Scheme 35

A two-step (4 + 2) cycloaddition mode was proposed by Hartmann and Heuschmann for the reaction of the cyclic ketene aminal (**198**) with 3,6-diphenyltetrazine (**8**), as a crystalline zwitterionic intermediate (**199**) could be isolated, which ring-closed in a second step to form (**200**) (Scheme 36) ⟨89AG(E)1267⟩.



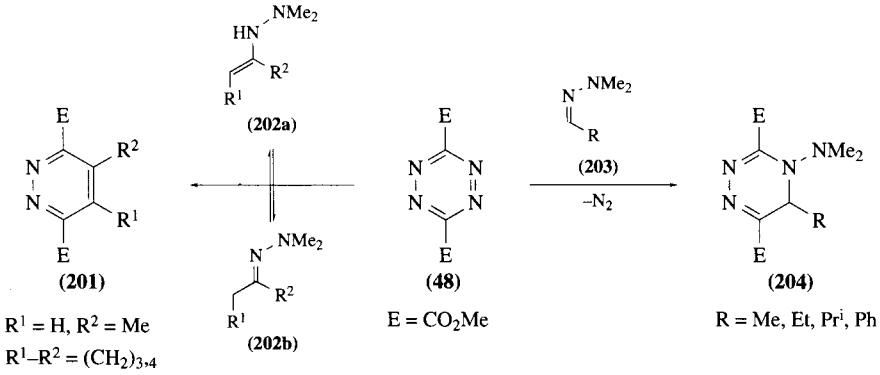
(8) (198) (199) (200)

Scheme 36

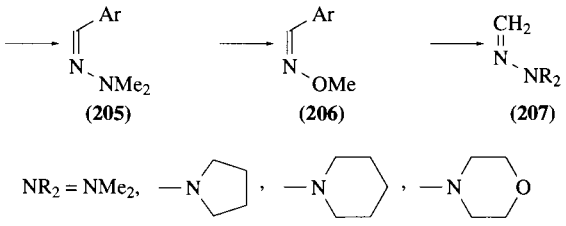
6.21.5.5.4 *Hetero 2π-systems as dienophiles*

The results with lactim ethers, discussed in Section 6.21.5.5.3 indicate that —CH—C=N— double bonds are much less reactive than the tautomeric —C=C—NH— unit. The reactivity

of Schiff bases was studied with electron-rich hydrazones (Scheme 37) ⟨79AP(312)452⟩. Aldehyde hydrazones (**203**) accepted the tetrazine diester (**48**) at the hetero double bond to form 1,2,4-triazine derivatives (**204**), while ketone hydrazones (**202b**) formed pyridazine derivatives (**201**) via the enehydrazine tautomer (**202a**). In a similar way the C=N— derivatives (**205**)–(**207**) reacted as shown at the hetero 2π-bond indicated ⟨82CZ100, 83AP(315)472, 86AP(319)690⟩. Oxazolines, thiazolines, and pyrazolines likewise proved to be reactive hetero 2π-systems ⟨84AP(317)237⟩. A number of tetrazines reacted readily with *N*-(trimethylsilyl)benzaldimine ⟨89H(29)1379⟩.

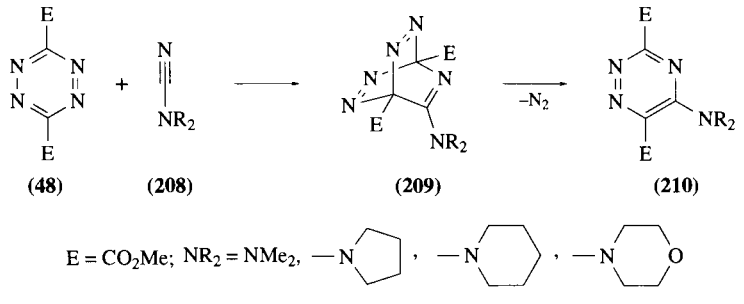


Scheme 37



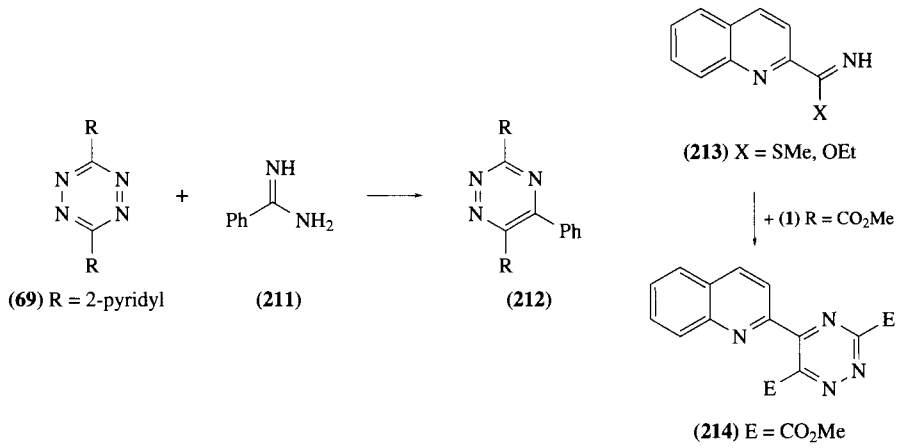
The *N*,*N*-dimethylhydrazone of β-R-substituted acroleins allow an interesting comparison to be made of the reactivity of the C=C and C=N double bonds as dienophiles ⟨81AP(314)376⟩. With R = Me only addition at the C=C double bond occurs, while when R = Ph an 84 : 16 mixture of CN and CC addition is observed, probably the result of a subtle competition of electronic and steric effects.

Even the C≡N triple bond in electron-rich cyanamides (**208**) reacts as a dienophile to give (**210**) via (**209**) (Scheme 38) ⟨79CZ230⟩; the 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine was also used as a diene ⟨85CZ348⟩ and is so reactive that it even combined with donor substituted benzonitriles.



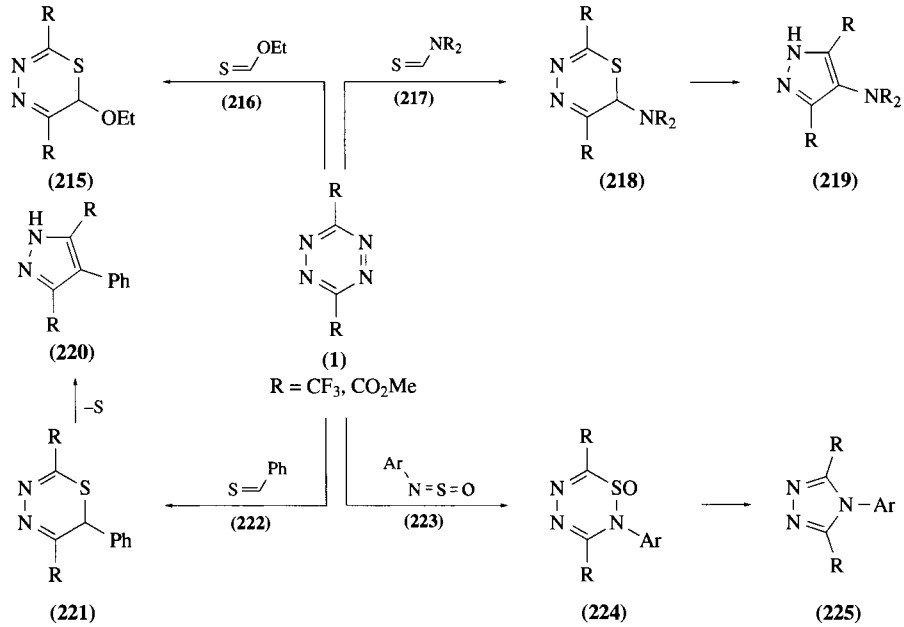
Scheme 38

CN double bonds in amidines (**211**), imidates, and thioimidates (**213**) as dienophiles were studied by Figeys *et al.* ⟨79BSB905, 81SC655, 81TL1393⟩, Boger and Panek ⟨83TL4511⟩, and Seitz and co-workers ⟨89CZ188⟩. Scheme 39 illustrates the possible reactions with a few examples; 1,2,4-triazine derivatives (**212**) and (**214**) are formed.



Scheme 39

Thioketones have been found to be excellent dienophiles ⟨94TL4767⟩. Kinetic measurements indicate that thioketones can behave as electrophiles and nucleophiles, so it is not surprising that C=S and N=S heterodienophiles can also act as 2π-components (Scheme 40) ⟨77AP(310)269, 82AP(315)428, 84AG(E)890⟩. Thiobenzaldehyde (**222**) was formed *in situ* by cycloreversion from its anthracene adduct and trapped by tetrazines. Stable thioformic acid derivatives (**216**) and (**217**) as well as thionylimines (**223**) reacted at room temperature to form the sulfur-containing six-membered heterocycles (**221**), (**218**), (**215**), and (**224**) which sometimes extruded sulfur with ring contraction to pyrazoles (**219**), (**220**), and triazoles (**225**).

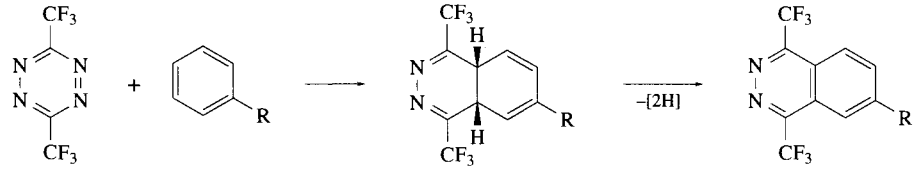


Scheme 40

6.21.5.5.5 Aromatic compounds as dienophiles

In normal Diels–Alder reactions benzene and naphthalene usually prove to be quite inert as dienes; anthracene adds reactive dienophiles at the central ring. These results are entirely as expected on the basis of the aromaticity of the systems. By contrast, tetrazine diester and 3,6-bistrifluoromethyltetrazine, due to their low-lying LUMOs and lower resonance energy, will react even with aromatic compounds as dienophiles (Scheme 41): benzene, toluene, anisole, *N*,*N*-dimethylaniline, and methylthiobenzene (**226**) react at 140°C ⟨81CZ342, 87AG(E)332⟩. In monosubstituted benzene

derivatives the main path is addition to the 3,4-double bond which, according to MNDO calculations, shows the highest electron density, followed by the 1,2-position; derivatives (**227**) and (**228**) are formed. *o*-, *m*-, and *p*-Dimethoxybenzenes are also reactive dienophiles, using the double bond with the highest orbital coefficient ⟨92LA1153⟩.

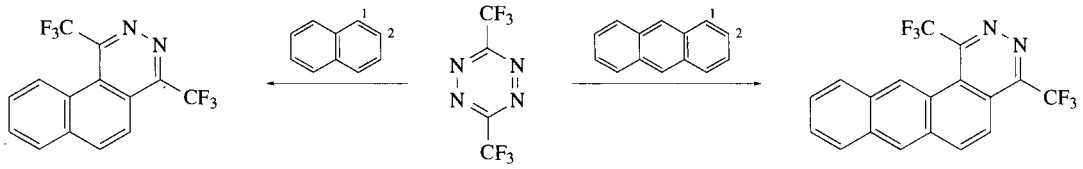


(**53**) (**226**) (**227**) (**228**)

R = H, Me, OMe, SMe, NMe_2

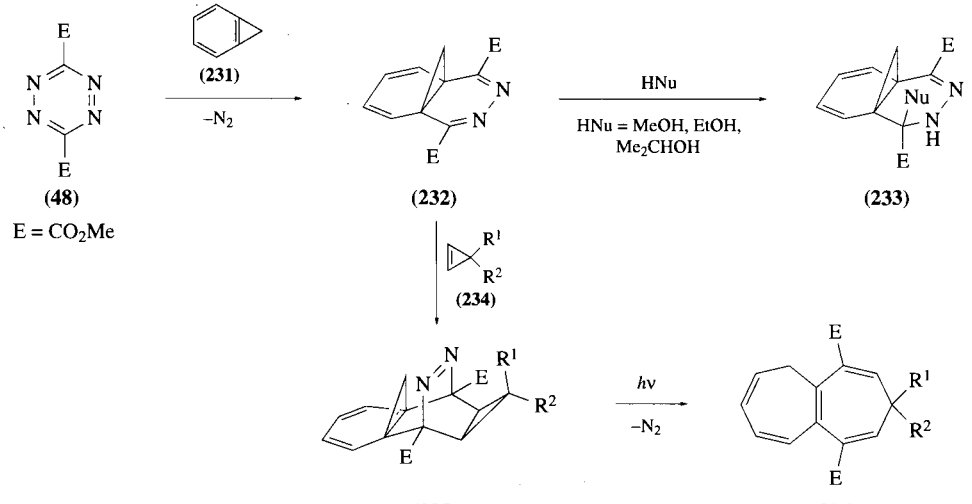
Scheme 41

Naphthalene and anthracene show dienophilic activity at the 1,2-bonds (Scheme 42) to give (**229**) and (**230**) ⟨87AG(E)332⟩. In 1-methoxy- and 1-*N*,*N*-dimethylaminonaphthalene the 3,4-double bond is attacked ⟨88AP(321)889⟩. The high angle strain is probably responsible for 1*H*-cyclopropabenzene (**231**) reacting with the tetrazine diester (**48**) at room temperature ⟨69TH 621-01, 87TH 621-01, 88HCA249⟩ to yield the tricyclic dihydropyridazine derivative (**232**) (Scheme 43), which adds not only nucleophiles at the electron-poor CN double bond to form (**233**) but also cyclopropenes (**234**) to give tetracyclic azo compounds (**235**). The products (**235**) are readily transformed in a multistep sequence to dihydroheptalenes (**236**): N_2 elimination and cyclopropane ring opening form the 'right-hand' seven-membered ring, and sigmatropic shift followed by a valence isomerization completes the 'left-hand' seven-membered unit ⟨87TH 621-01⟩. Substituted benzocyclopropenes behave in the same way as the parent compound ⟨87TH 621-01⟩. 3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine (**53**) reacts with benzocyclopropene to form the tricyclic fused pyridazine analogous to (**232**), opening the way to further interesting cycloaddition reactions ⟨96LA645⟩.



(**229**) (**53**) (**230**)

Scheme 42



(**48**) (**232**) (**233**)

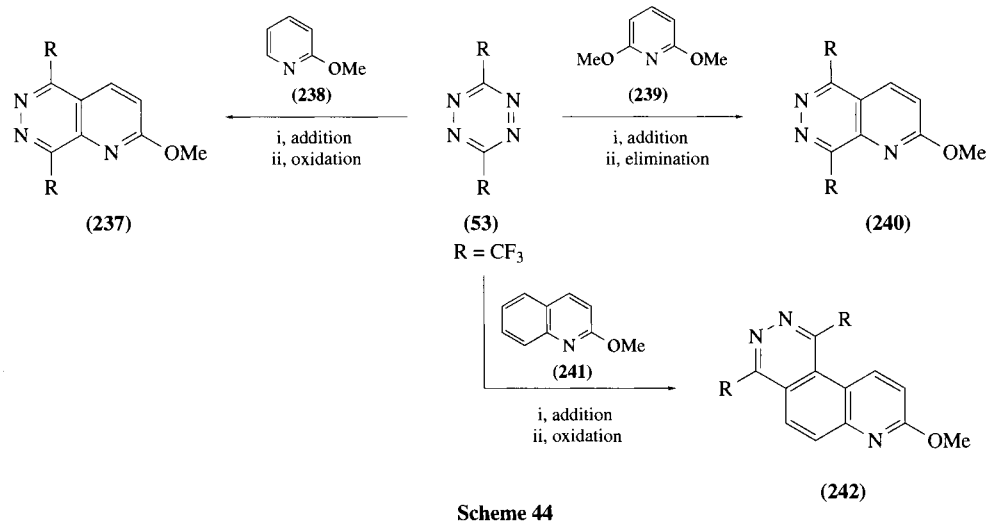
E = CO_2Me

(**231**) (**234**) (**235**) (**236**)

R^1, R^2 = H, Me

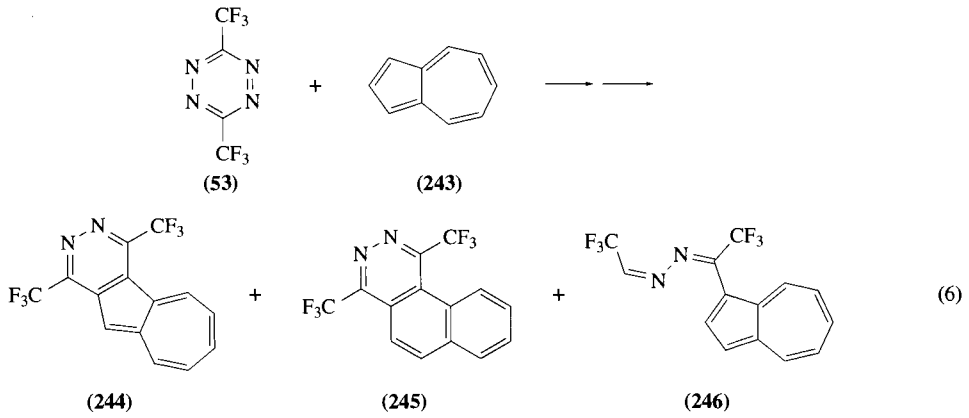
Scheme 43

Even the electron-poor pyridine and quinoline systems carrying donor substituents (**238**), (**239**), and (**241**) undergo (4 + 2) cycloadditions at 130 °C and extended reaction times (12–14 hours) (Scheme 44) ⟨93AP(326)427⟩ to yield pyridopyridazines (**237**) as well as the pyridazinoquinoline (**242**); the latter results from the reaction of the electron-rich 1,2-naphthalene double bond.



Scheme 44

Azulene (**243**) yields a product mixture of (**244**), (**245**), and (**246**) (Equation (6)) possibly by way of a two-step mechanism via a dipolar species ⟨93AP(326)29, 93CB441, 93CB2143⟩. Substituted azulenes as well as thia- and azaazulenes react in a similar way.

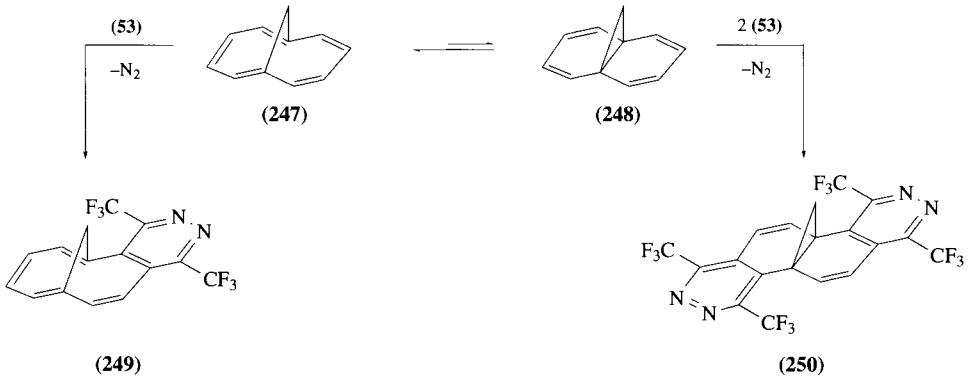


(6)

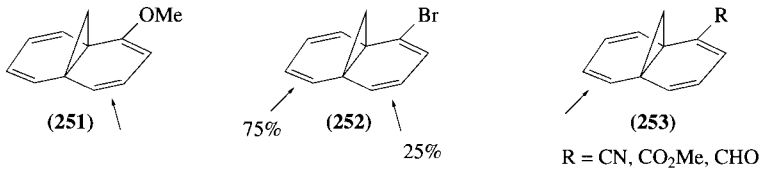
1,6-Methano[10]annulene (**247**) ⟨69TH 621-01⟩, again studied by Seitz's group, offers an interesting interplay of substituent influence, reactivity, and regiochemistry ⟨93JPR152⟩. The reaction probably starts from the tricyclic valence tautomer (**248**) which can accept one or two tetrazine equivalents (Scheme 45) to give (**249**) or (**250**). The methoxy derivative (**251**) yields only the product from attack at the double bond (of the valence tautomer) marked by an arrow. The bromomethano[10]annulene (**252**) gives a 75 : 25 mixture of two regioisomers, and the annulenes (**253**) carrying acceptor groups are attacked only at the double bond remote from the substituent.

6.21.5.5.6 Five-membered heterocyclic aromatic systems as dienophiles

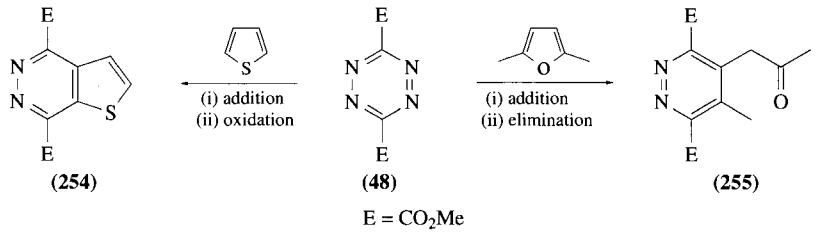
Early examples for this reaction type were cited in CHEC-I by Neunhoeffer: thiophene, 1-methylimidazole, benzofuran, benzothiophene, *N*-methylindole, and pyrrolopyridine reacted as enol ethers, ene thioethers, and enamines, as shown for two typical examples in Scheme 46 ⟨84CHEC-I(3)531⟩. Thiophene adds as a dienophile, and the thienopyridazine (**254**) is isolated after nitrogen elimination and oxidation. In contrast, 2,5-dimethylfuran, after addition and nitrogen loss, under-



Scheme 45

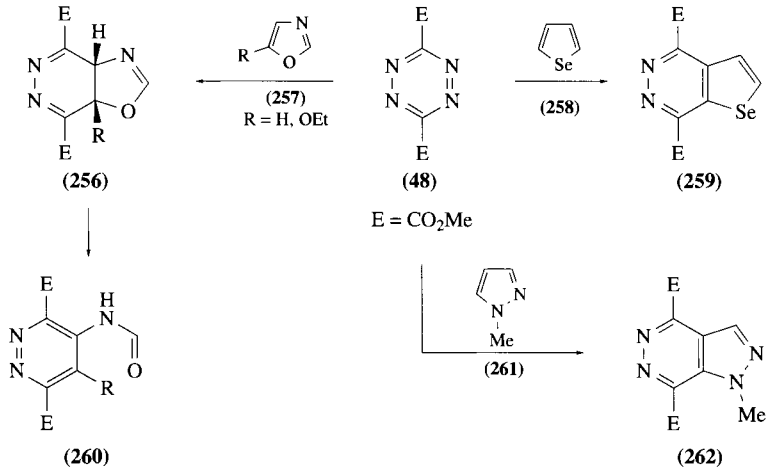


goes an aromatization with ring opening to form (**255**); this reaction parallels the addition of enol ethers and enamines.



Scheme 46

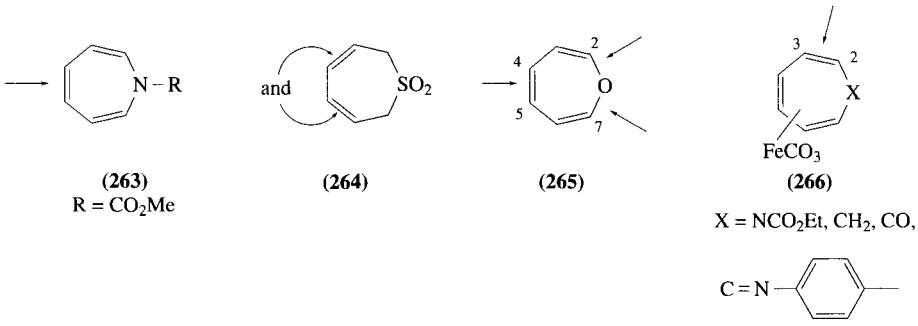
Further examples have accumulated. The reactions of oxazoles (**257**), selenophene (**258**), and *N*-methylpyrazole (**261**) with tetrazine (**48**) form (**256**) and (**260**), (**259**), and (**262**) respectively, partly after oxidation (Scheme 47) ⟨88CZ17⟩. The reactions of 3,6-bis(trifluoromethyl)tetrazine with imidazoles, oxazoles, pyrazoles ⟨89AP(322)415⟩, indole, and benzo[*b*]thiophene ⟨87CZ81, 87JOC4610⟩ have also been studied.



Scheme 47

6.21.5.5.7 *Seven-membered ring dienes and trienes as dienophiles*

Neunhoeffer reported on reactions of 1*H*-azepines and oxepins with 1,2,4,5-tetrazines. Among additional examples are: tetrazine diester with 1*H*-diazepines and with 2-diethylamino-3*H*-azepine ⟨78AP(311)786⟩ and the structure proof by x-ray analysis ⟨84AX(C)1934⟩; with 2,7-dihydrothiepin 1,1-dioxide ⟨81AP(314)892⟩; with oxepins ⟨83CB97⟩; and with tricarbonyliron complexes of *N*-ethoxycarbonylazepine, cycloheptatriene, tropone, and azaheptafulvene derivatives ⟨82JOC110⟩. The dienophilic components are shown in structures (**263**)–(**266**); the arrows mark the 2π-systems which undergo the cycloaddition with the tetrazine component. Oxepin (**265**) shows a competition between a (4 + 2) cycloaddition reaction at the 4,5-double bond and a (6 + 4) cycloaddition at the 2- and 7-positions of the oxepin system. By complex formation in (**266**) two π-bonds are masked, and only the 2,3-double bond is available for the cycloaddition.



(**263**)
R = CO_2Me

(**264**)

(**265**)

(**266**)
X = NCO_2Et, CH_2, CO,

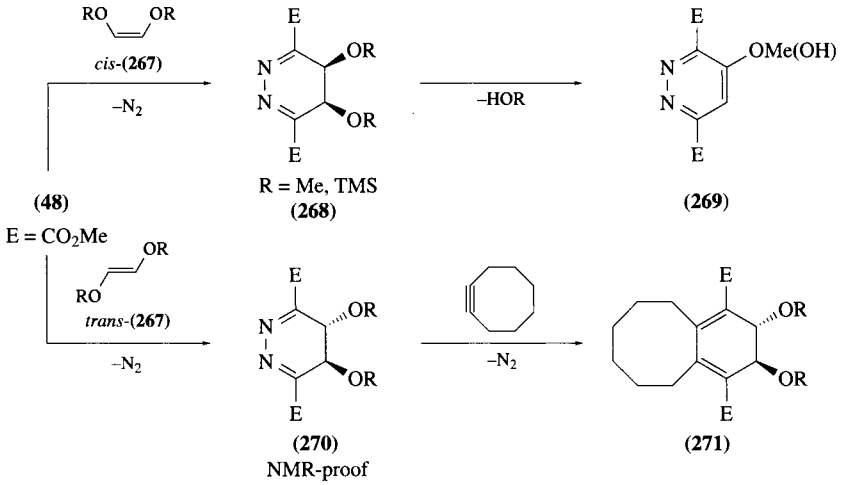
6.21.5.5.8 *Stereochemistry and regiochemistry of the cycloadditions of 1,2,4,5-tetrazines*

The synthetic importance of normal Diels–Alder reactions rests on the great variability of the diene and dienophile components. Almost all additions occur in a stereospecific way. There are only a few examples which show a nonstereospecific reaction mode ⟨91TH 621-01, 94TH 621-03⟩. Furthermore, in many cases Diels–Alder reactions are highly regioselective, 1-substituted and 2-substituted 1,3-dienes adding to monosubstituted alkenes and alkynes to yield so-called '*ortho*-' and '*meta*-' adducts.

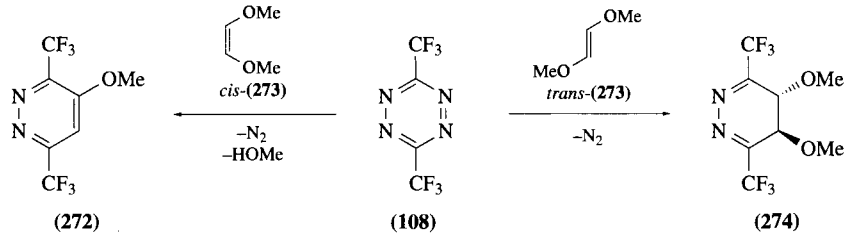
Investigations to elucidate the stereochemistry of the tetrazine cycloadditions are rendered more difficult because the initially formed Diels–Alder adduct is not isolable, but loses nitrogen extremely rapidly (Scheme 5) and the 4,5-dihydropyridazine derivative formed undergoes either a rapid tautomerization to the 1,4-dihydro isomer or a β-elimination reaction to form aromatic compounds (Scheme 6). In both cases the stereochemical centers, by which the stereochemical course of the reaction could be followed, are destroyed.

For stereochemical investigations of the reaction type mentioned above *cis–trans* isomeric dienophiles (or dienes) are normally used. For the tetrazine reactions in question electron-rich dienophiles are necessary, such as *cis–trans*-isomeric enamines or enol ethers. *Cis*-enamines are extremely sensitive, isomerizing to the more stable *trans* isomers very quickly ⟨69CB1917⟩. Hence, it is not surprising that only very few examples are available to prove that the (4 + 2) cycloaddition reactions of 1,2,4,5-tetrazines are stereospecific, in accord with concerted bond making. *Cis–trans* isomeric 1,2-dimethoxyethylenes (**267**) and 1,2-bis(trimethylsilyloxy)ethylenes (**273**) were used as dienophiles ⟨94UP 621-02⟩. Schemes 48 and 49 show that the 4,5-dihydropyridazines (**268**) formed from the *cis*-dienophile apparently lose HX (HOMe, HO-TMS) quite rapidly in a *trans*-1,2-elimination while the diastereoisomer (**270**) can be trapped as (**271**) by the highly reactive cyclooctyne or, in the case of (**274**), can even be distilled ⟨89TH 621-01⟩.

The reaction of 3-phenyl-1,2,4,5-tetrazine (**166**) with phenylalkyne (**276**) corresponds to the Diels–Alder addition of a 1-substituted diene with a monosubstituted alkyne, and the *ortho* adduct is expected. Scheme 50 shows that the addition is highly regioselective, leading to the *ortho* product (**275**) and *meta* product (**277**) in a 95 : 5 (acetonitrile) or 92 : 8 ratio (dioxane) ⟨93JA1353⟩. In a similar way, *N*,*N*-dimethylaminoalkyne (**278**), methylthioalkyne (**279**), and methoxyalkyne (**280**) add to 3-phenyl-1,2,4,5-tetrazine (**166**) in acetonitrile to give predominantly the *ortho* product (> 90%); there is a distinct solvent effect, nonpolar solvents favoring the *meta* isomer ⟨94TH 621-04⟩. *Ab initio*

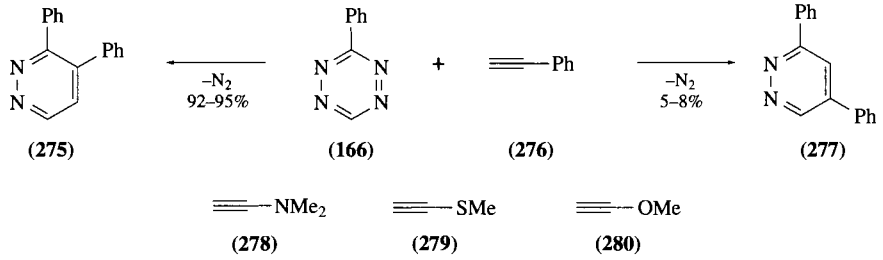


Scheme 48



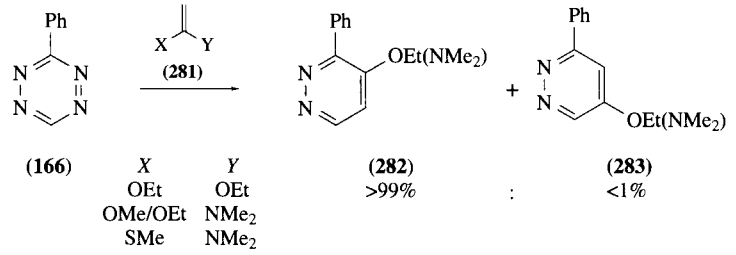
Scheme 49

quantum mechanical calculations show that considerable attractive dispersion interactions are responsible for the high *ortho* orientation ⟨93JA1353⟩.



Scheme 50

Ketene *O,O*-, *N,O*-, and *N,S*-aminals (**281**) are reactive dienophiles which likewise add to 3-phenyl-1,2,4,5-tetrazine (**166**) in a highly regioselective way: more than 99% of the *ortho*-isomeric pyridazines (**282**) and only a trace of the *meta*-isomers (**283**) are formed, and the regiochemistry is not influenced by solvents (Equation (7)). By contrast, the isomer ratio is highly solvent dependent in the reaction of (**166**) with ketene *N,N*-aminals, polar solvents favoring the *meta*-isomer (**289**) (Table 2). Similar orientation phenomena have been observed for the reactions of 1,3,4-triazines with ketene *N,N*-aminal (**287**) in which CO_2Me, Ph, and H compete as directing substituents ⟨91TH 621-02⟩. 1-Donor substituted styrenes, acrylonitriles, and acrylic esters (**284**) likewise add to 3-phenyl-1,2,4,5-tetrazine (**166**) with preferred *ortho*-orientation (Equation (8)) ⟨90TL6855⟩. It is highly probable that, in contrast to a concerted reaction which is followed in most of the cases studied, the reactions of the *N,N*-aminals proceed by a different mechanism.

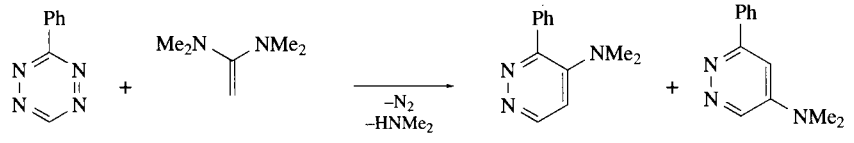


(7)

(166) (282) (283)

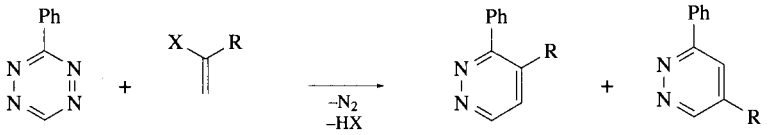
X	Y	(282)		(283)
OEt	OEt	>99%	:	<1%
OMe/OEt	NMe_2			
SMe	NMe_2			

Table 2 Solvent influence on the regiospecificity for the reaction of 3-phenyl-1,2,4,5-tetrazine (**166**) with the ketene-*N*,*N*-aminal (**287**).



(166) (287) (288) (289)

Solvent	(288) : (289)
n-Hexane	78 : 22
Toluene	41 : 59
Tetrahydrofuran	20 : 80
Methylacetate	14 : 86
Acetone	7 : 93
Pyridine	4 : 96
Dichloromethane	3 : 97
Acetonitrile	3 : 97



(8)

(166) (284) (285) (286)

X	*R*	*Yield* (%)	*Yield* (%)
NMe_2	CN, Ph, CO_2Me	>99	<1
OMe	Ph	>99	<1
OMe, SMe	CO_2Me	>99	<1

6.21.5.5.9 Reactivity data for (4 + 2) cycloadditions of 1,2,4,5-tetrazines

The cycloadditions described so far are $LUMO_{diene}$-$HOMO_{phil}$ controlled reactions. It is to be expected that acceptor substituents in the tetrazine component and donor substituents in the dienophile accelerate the reaction. Many kinetic data have already been published by Sauer and co-workers which corroborate these expectations ⟨83TL1481, 84TL2541, 90TL6851⟩. Some kinetic data are presented here along with unpublished data ⟨89TH 621-02, 94TH 621-01, 94TH 621-02, 94TH 621-04, 94TH 621-05, 94TH 621-06, 94TH 621-08⟩, to give an impression of how large the substituent effects in the tetrazine and dienophile component are. The most reactive systems are sometimes too fast to be measured by the stopped-flow apparatus available ($k_2 > 10^6$ l mol^{-1} s^{-1}).

(i) Reactivity of dienophiles

Figure 1 presents a collection of rate constants for cyclic dienophiles in the reaction with tetrazine diester (**48**).

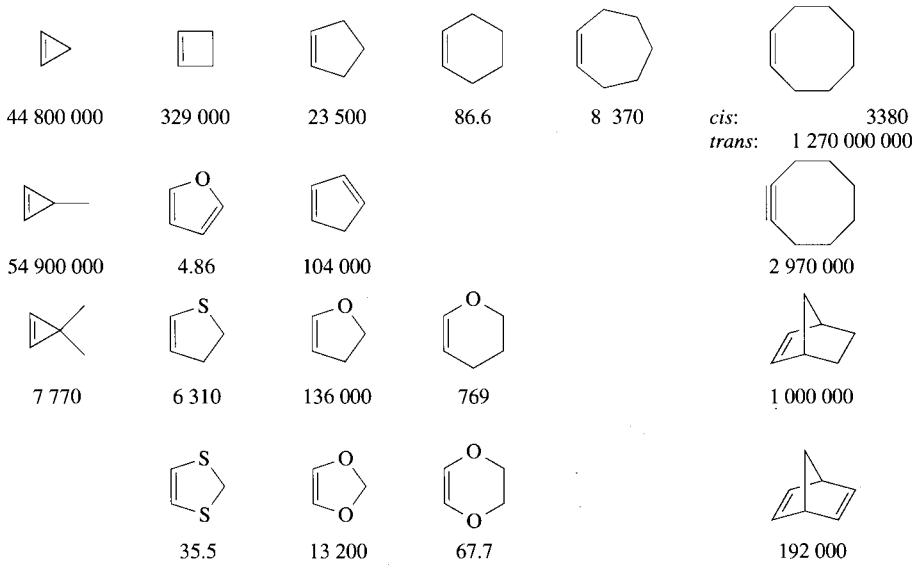


Figure 1 Rate constants ($10^5 k_2$ l mol^{-1} s^{-1}, 20 °C, dioxan) for the reaction of different cyclic dienophiles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**48**).

The following details are evident:

(i) The rate constants span a range of nearly a factor of 10^7, in spite of the fact that the functional groups are not very different (simple alkenes and alkynes, enol ethers, and enol thioethers).

(ii) The relief of strain, when angle strained dienophiles are used, is responsible for the tremendous rate differences. *Trans*-cyclooctene is the fastest dienophile, with a rate ratio for *trans*-/*cis*-cyclooctene of 375000. The decreasing angle strain in the series cyclopropene to cyclohexene parallels the decreasing rate constants. The rate minimum for cyclohexene is typical for all cycloaddition reactions of cyclic olefins, as Figure 2 illustrates for a number of systems (all *cis* isomers; ring size 5–8-membered).

(iii) A number of other angle strained cyclic alkenes and alkynes, frequently used in cycloaddition reactions, likewise show large rate constants (cyclooctyne, norbornene, norbornadiene, 1,3-cyclopentadiene).

(iv) Steric factors play an important role as the series cyclopropene, 3-methylcyclopropene, and 3,3-dimethylcyclopropene proves. The first methyl group as a donor increases the rate constant further in spite of the fact that one face of the double bond is screened. This screening effect is well seen when a second methyl group is introduced: 3,3-dimethylcyclopropene is less reactive than cyclopropene by a factor of 5700.

(v) The donor function in the cyclic enol ether increases the rate by a factor of 5–6, the second donor in 1,2-arrangement at the double bond reduces the rate below the value of the unsubstituted cyclopentene.

(vi) Furan is the slowest dienophile in the whole series. A drop in the rate constant of more than 28000 compared with dihydrofuran shows that in the case of furan the aromatic character must be partially sacrificed in the transition state.

Figure 3 shows rate data for cycloaddition reactions of cyclic dienophiles with the parent compound 1,2,4,5-tetrazine (**7**) ⟨94TH 621-01⟩. The reactivity of MeO- and TMSO-substituted cycloalkenes is lower than that of the unsubstituted alkenes; the mild electron donating effect of the oxygen donor groups is more than cancelled out by the impeding steric effect of the substituents. By contrast, the cyclic enamines are more reactive than the cyclic alkenes by a factor between 2000 and 8000. The high donating power of the NMe_2 group now more than compensates for the hindering steric substituent effect.

Figure 4 presents rate data for unsymmetrically disubstituted electron-rich acyclic alkenes and monosubstituted alkynes, again in reaction with (**7**) ⟨94TH 621-01⟩. The impeding steric substituent effect of OMe, OEt, and SMe is apparent when the rate constants for mono- and disubstituted alkenes and alkynes are compared with those for ethylene and acetylene. Even the introduction of two SR or OR groups in an unsymmetrical 1,1-fashion shows no accelerating effect. The high donor activity of NMe_2 groups in ynamines and ketene aminals pushes the rate constants well above the

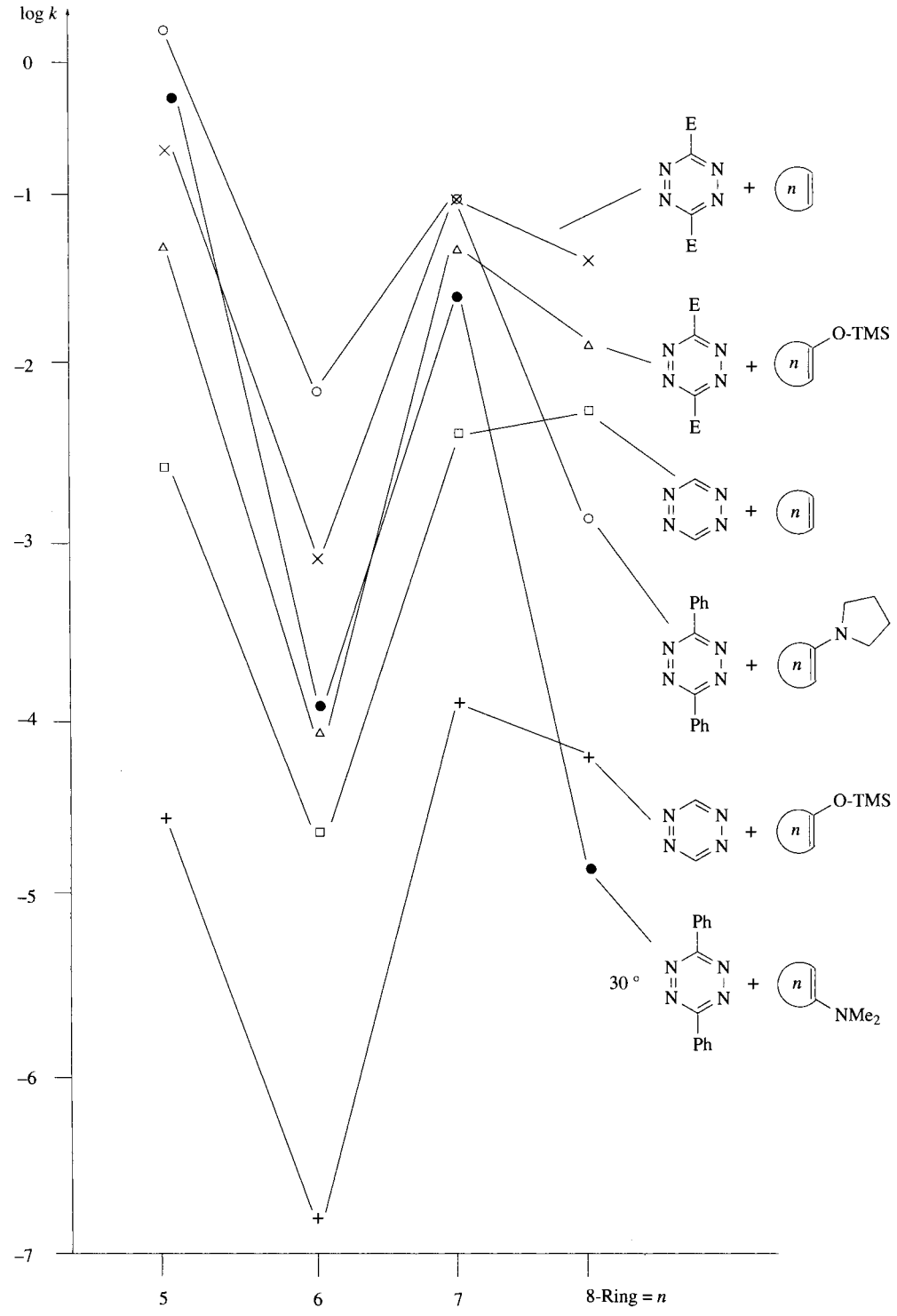


Figure 2 Plot of log k [l mol^{-1} s^{-1}], 20°C, dioxane, for (4 + 2) cycloaddition reactions of 1,2,4,5-tetrazines with cyclic dienophiles against n, number of ring carbons.

values for ethylene and alkyne. Alkyne derivatives are always less reactive than similarly substituted alkenes.

The high activating power of NR_2 groups allows substituent effects in enamines in reactions with 3,6-diphenyl-1,2,4,5-tetrazine (**8**) as 4π-component to be studied (Figure 5) ⟨94TH 621-05⟩. There is

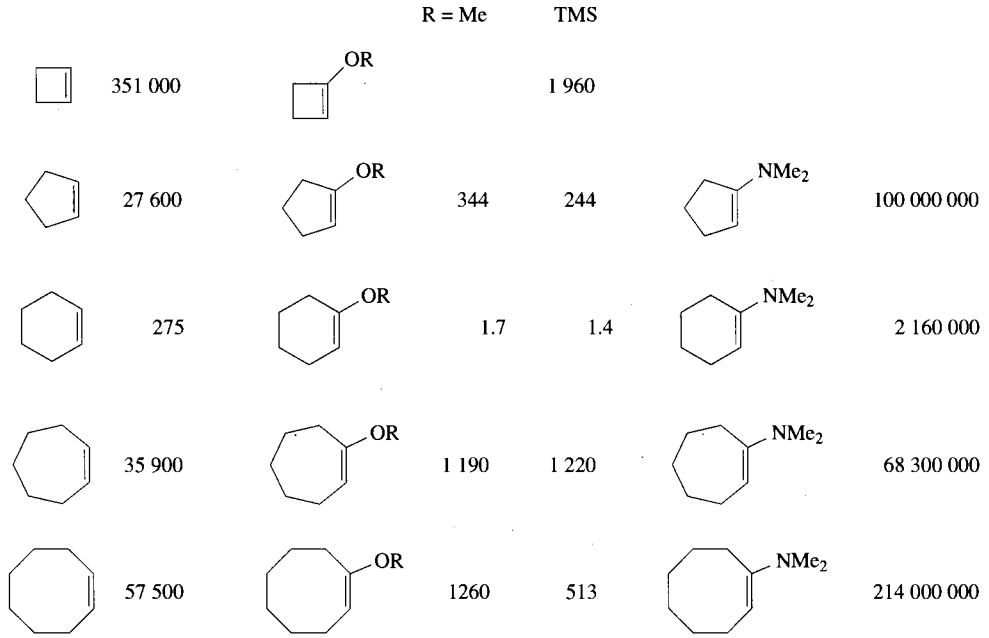


Figure 3 Rate constants ($10^7 k_2$ l mol^{-1} s^{-1}, 20 °C, dioxan) for the reaction of cyclic dienophiles with 1,2,4,5-tetrazine (**7**).

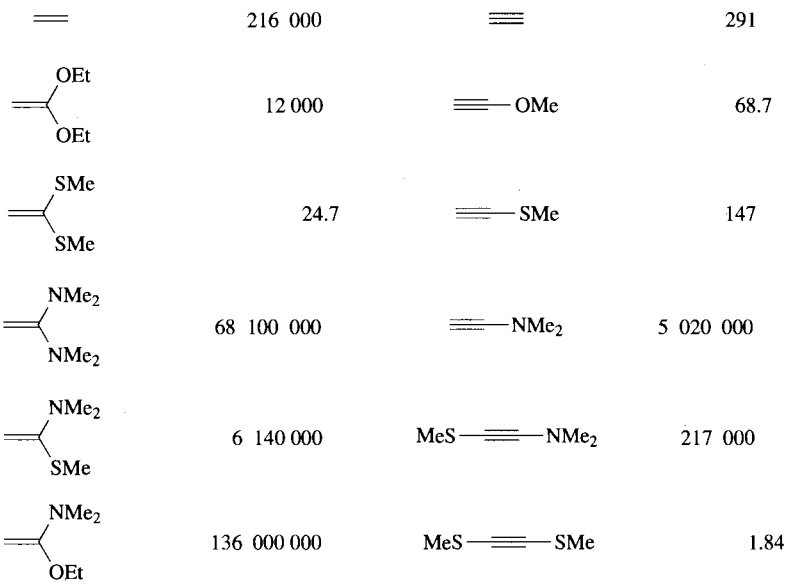


Figure 4 Rate constants ($10^7 k_2$ l mol^{-1} s^{-1}, 20 °C, dioxan) for the reaction of donor substituted open chain alkenes and alkynes with 1,2,4,5-tetrazine (**7**).

an interesting steric interplay of substituents in the α- and β-positions; with increasing substituent size the rate constants drop considerably. Data for cyclic enamines are added for comparison.

(ii) Reactivity of 1,2,4,5-tetrazines

The prediction that electron-withdrawing substituents in tetrazines accelerate, and electron donors decrease the reaction rate was demonstrated by ρ values of +1.24 and +2.51 for the combination of 3,6-disubstituted 1,2,4,5-tetrazines with styrene and α-methylstyrene respectively ⟨80MI 621-01⟩ and was also confirmed using cyclooctyne as dienophile ⟨83TL1481⟩ for a number of nitrogen

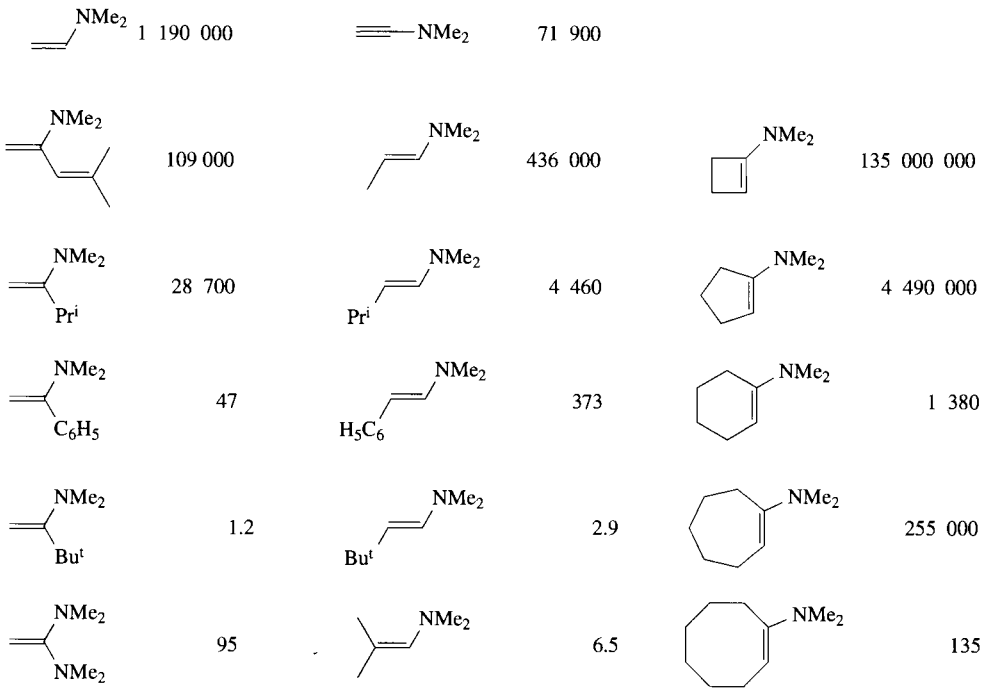


Figure 5 Rate constants (10^7 k_2 l mol^{-1} s^{-1}, 20°C, dioxan) for the reaction of enamines with 3,6-diphenyl-1,2,4,5-tetrazine (**8**).

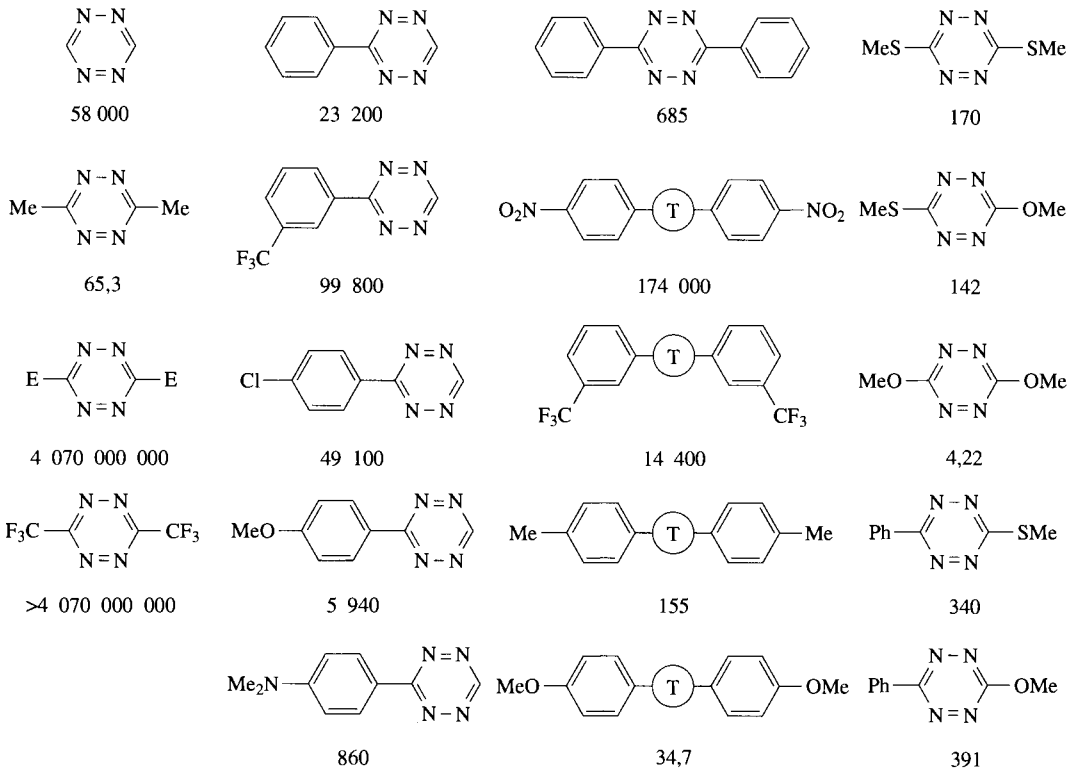


Figure 6 Rate constants (10^4 k_2 l mol^{-1} s^{-1}, 20°C, nitrobenzene) for the reaction of 1-*N*,*N*-dimethylaminopropyne with various 1,2,4,5-tetrazines.

heterocycles. Data are also available for 1-*N*,*N*-dimethylaminopropyne ⟨90TH 621-01, 94TH 621-02, 94TH 621-06⟩ and 1-*N*-pyrrolidinocyclopentene ⟨94TH 621-05⟩ as dienophiles. After this introduction the data of Figure 6 are almost self-explanatory. The parent compound 1,2,4,5-tetrazine (**7**) serves as the standard. Dimethyltetrazine is less reactive; tetrazine diester and the bistrifluoromethyl derivative are much more reactive. Phenyl-substituted tetrazines show nice Hammett plots (ρ values range between 1 and 2). The donor substituted tetrazines are at the lower end of the reactivity scale.

Figure 7 offers a collection of *k*-values for the same dienophile in the reaction with 1,2,4,5-tetrazines carrying heterocycles as substituents in the 3- and 6-positions ⟨94TH 621-02, 94TH621-05, 94TH 621-06, 94TH 621-08⟩. These data offer not only information for preparative work, because heteroaryl-substituted tetrazines have often been used in synthesis, but also the possibility to derive σ values for heterocyclic substituents.

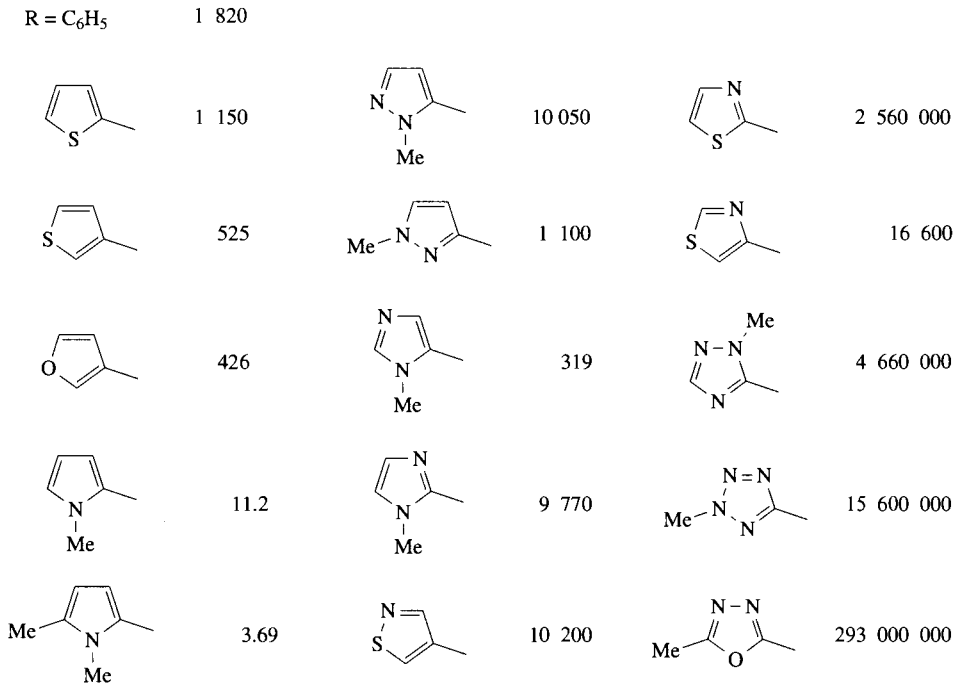


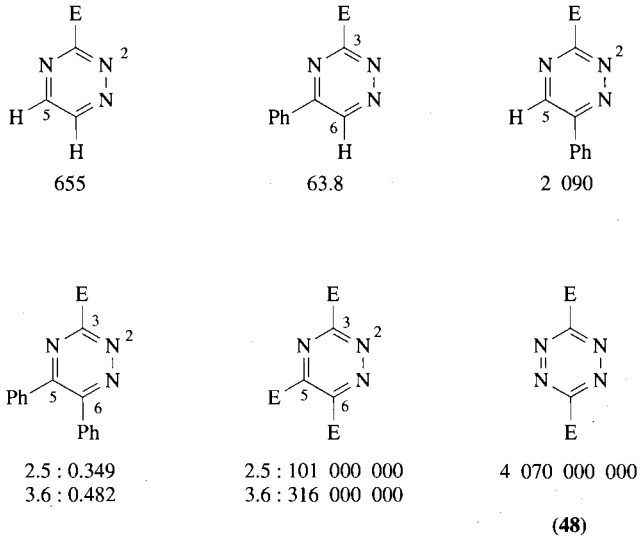
Figure 7 Rate constants (10^4 k_2 1 mol^{-1} s^{-1}, 20°C, acetonitrile) for the reaction of 1-*N*,*N*-dimethylaminopropyne with heteroaryl 3,6-disubstituted 1,2,4,5-tetrazines.

Figure 8 connects the kinetic data obtained in the tetrazine series with those measured for 1,2,4-triazines ⟨90TH 621-01⟩. The numbers at the triazine nucleus show the diene system which is involved in these cycloaddition reactions; the dimethylamino group of the ynamine always orients to the CO_2Me substituents in the addition step. The triazine triester with a total rate constant of $10^4k_2 = 4.17 \times 10^8$ comes close in rate to the tetrazine diester. In general, triazines are less reactive than tetrazines by some powers of ten.

Finally, kinetic data for the reaction of an enamine are collected in Figure 9 ⟨94TH 621-05⟩. The *k*-values parallel those obtained with 1-*N*,*N*-dimethylaminopropyne and cyclooctyne as dienophiles. As long as steric effects are the same the kinetic data with different dienophiles can be correlated with satisfactory *r*-values (0.96–0.99). The correlation coefficients for a plot of $E_{1/2}$ (half wave reduction potential of the tetrazine used; see Section 6.21.5.9) against the log *k* values of the corresponding cycloadditions are somewhat lower ($r = 0.87$–0.94), while an attempt to connect $1/(E_{\text{LUMO-diene}} - E_{\text{HOMO-phil}})$ with the log *k* values showed only a rough correlation ($r = 0.7$–0.8). Nevertheless, all these cycloaddition reactions are $\text{LUMO}_{\text{diene}}$-$\text{HOMO}_{\text{phil}}$ controlled reactions.

(iii) Influence of solvent polarity on rate

For synthetic purposes a large number of solvents have been used in cycloadditions. In general the polarity of solvents does not greatly influence the rate ⟨80AG(E)779⟩. This observation is true for all types of Diels–Alder reactions, normal, neutral, and inverse type ones. Table 3 contains data for



(48)

Figure 8 Rate constants (10^4 k_2 l mol^{-1} s^{-1}, 20°C, nitrobenzene) for the reaction of 1-*N*,*N*-dimethylaminopropyne with 1,2,4-triazine derivatives.

the reaction of one particular tetrazine with cyclooctyne and with an ynamine ⟨84TH 621-01⟩. The cycloaddition with the nonpolar cyclooctyne shows only a very slight solvent influence, higher solvent polarity favoring the reaction. Apparently the reaction with the ynamine has a more polar transition state, because here the solvent effect is more pronounced.

The solvent influence on rate has been studied in the system di(2-pyridyl)-1,2,4,5-tetrazine (**69**) and substituted styrenes. The second-order rate constants increase dramatically in water-rich media ⟨96JOC2001⟩.

6.21.5.5.10 The mechanism of (4 + 2) cycloadditions of 1,2,4,5-tetrazines

Do (4 + 2) cycloaddition reactions of tetrazines follow a one-step mechanism with concerted bond making? Stereospecificity, regiospecificity, structure-rate correlations, solvent dependence, and activation entropies ⟨80AG(E)779⟩ are all in accord with the assumption that they do.

A possible borderline case is observed in the reactions of tetrazines with cyclic ketene *N*,*N*-aminals (Scheme 51) ⟨89AG(E)1267⟩. Hartmann and Heuschmann offered some evidence that the dipolar intermediate (**199**) isolable in their system might be a true intermediate in a two-step (4 + 2) cycloaddition. There are a few examples ⟨90TH 621-02, 93UP 621-01⟩ which contradict their assumption. Tetrazine (**166**) and aminal (**290**) react to form the dipole (**291**), which can be protonated to (**292**) (NMR); but the cycloaddition forms (**294**), the product with *meta*-orientation, via (**293**).

Mixing a 3-substituted 1,2,4,5-tetrazine with one equivalent of a ketene *N*,*N*-aminal is followed by the formation of a heavy yellow-orange precipitate which unfortunately could not be crystallized, so x-ray diffraction was not possible. Adding CF_3CO_2H at low temperature transforms the yellow compound to a protonated species analogous to (**292**) which could be analyzed by ^1H and ^{13}C NMR spectroscopy and shown to be the proton adduct of the dipolar yellow compound (**295**) (Scheme 52). In solution the (4 + 2) cycloaddition leads to the pyridazine derivatives (**300**) and (**301**), which proves that the yellow compound (**295**) must dissociate before the cycloaddition step.

If this is the case, then crossing experiments should be successful in trapping the free components tetrazine and dienophile. This expectation is fully met. As Scheme 52 shows, both fragments of the yellow compound (**295**) obtained from 3-*p*-anisyl-1,2,4,5-tetrazine and ketene *N*,*N*-aminal (**287**) could be trapped by 3-*p*-chlorophenyl-1,2,4,5-tetrazine (**297**) to give a mixture of pyridazines (**298**)–(**301**). In a similar competition experiment, dipole (**295**) reacted in the presence of 9.5 equivalents of cyclooctyne to yield a 92 : 8 mixture of (**300**) and (**301**) besides the cycloaddition product of tetrazine and cyclooctyne. These crossing experiments prove beyond doubt that the yellow compound (**295**) in this system cannot be an intermediate in the cycloaddition reactions. Furthermore, all yellow dipolar species isolated dissolve with the typical violet color of tetrazines and yield the

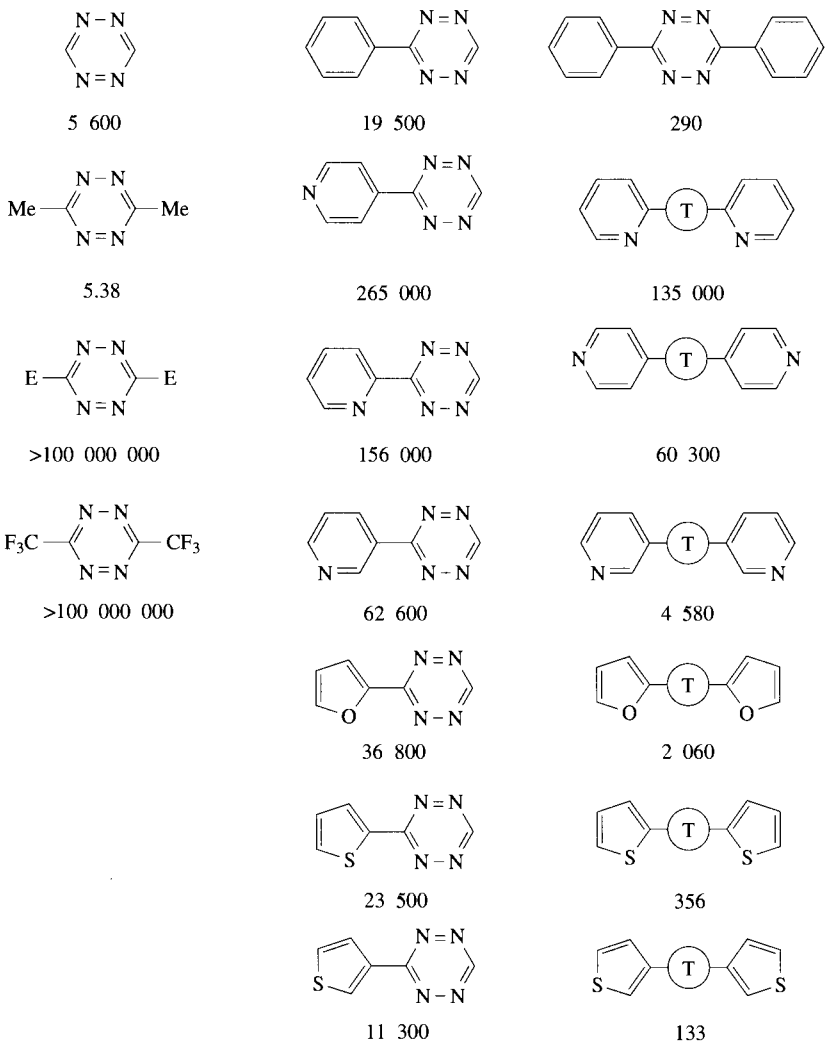


Figure 9 Rate constants ($10^2 k_2$ l mol^{-1} s^{-1}, 20 °C, acetonitrile) for the reaction of 1-*N*-pyrrolidinocyclopentene with various 1,2,4,5-tetrazines.

expected product mixture corresponding to the solvent polarity (Table 2). Similar but colorless intermediates could be observed by NMR in mixtures of 1,2,4-triazines and ketene *N,N*-aminals ⟨91TH 621-02, 93UP 621-01⟩.

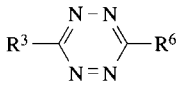
6.21.5.6 Intramolecular Cycloaddition Reactions

Intramolecular Diels–Alder reactions are of great preparative importance as routes to often very complicated bicyclic and polycyclic compounds in one-pot reactions. It was to be expected that intramolecular (4 + 2) cycloadditions of tetrazines would also be successful ⟨83TL4087⟩. There is ample analogy in the 1,2,4-triazine field.

The synthetic strategy is simple: by way of a nucleophilic aromatic substitution—normally using *C*-, *O*-, *S*-, or *N*-nucleophiles (**303**)—a chain with the 2π-unit is anchored to the tetrazine ring (**302**). The subsequent intramolecular (4 + 2) cycloaddition (**304**) → (**305**) follows the normal course of Scheme 53. In most cases alkyne units have been used as the 2π-component, forming bicyclic pyridazines (**305**) directly.

A series of papers from Seitz's group, which also deals with examples in the 1,2,4-triazine field, describes routes to bicyclic pyridazines and pyridines. Instead of the terminal alkyne group the cyanamide unit can be used, leading to bicyclic 1,2,4-triazines. Scheme 54 offers the general reaction sequence (**306**) → (**307**) and a selection of typical systems (**308**)–(**310**), which can be synthesized by

Table 3 Half wave reduction potentials $E_{1/2}$ of mono- and disubstituted 1,2,4,5-tetrazines measured in acetonitrile, 20°C, reference electrode: $Ag/AgNO_3$ (0.1 N), $Prop_4NBF_4$ (0.1 N).



No	$R^3 = R^6$	$-E_{1/2}$(V)	*No*	R^3	R^6	$-E_{1/2}$(V)
1	H	1.20	40	2-Phenyl-5-oxadiazolyl	R^3	0.79
2	Me	1.36	41	2-[2′-Thienyl]-5-oxadiazolyl	R^3	0.74
3	CO_2Me	0.83	42	2-Pyridyl	R^3	1.19
4	CF_3	0.50	43	3-Pyridyl	R^3	1.11
5	Ph	1.24	44	4-Pyridyl	R^3	1.05
6	*p*-MeC_6H_4	1.27	45	4-Pyridazinyl	R^3	0.89
7	*m*-MeC_6H_4	1.25	46	4-Pyrimidinyl	R^3	0.98
8	*o*-MeC_6H_4	1.26	47	Pyrazinyl	R^3	1.03
9	*p*-$MeOC_6H_4$	1.30	48	NMe_2	R^3	1.60
10	*m*-$MeOC_6H_4$	1.22	49	OMe	R^3	1.17
11	*o*-$MeOC_6H_4$	1.28	50	SMe	R^3	1.08
12	*m*-FC_6H_4	1.15	51	NMe_2	OMe	1.40
13	*p*-ClC_6H_4	1.15	52	NMe_2	SMe	1.38
14	*m*-ClC_6H_4	1.13	53	OMe	SMe	1.12
15	*o*-ClC_6H_4	1.13	54	Ph	NMe_2	1.48
16	*p*-$CF_3C_6H_4$	1.10	55	Ph	OMe	1.22
17	*m*-$CF_3C_6H_4$	1.09	56	Ph	SMe	1.17
18	*p*-$NME_2C_6H_4$	1.43	57	3,5-Dimethyl-1-pyrazolyl	OEt	1.06
19	*p*-$NO_2C_6H_4$	1.01	58	Ph	H	1.22
20	*m*-$NO_2C_6H_4$	1.03	59	*p*-MeC_6H_4	H	1.25
21	2-Pyrrolyl	1.30	60	*p*-$MeOC_6H_4$	H	1.25
22	*N*-Methyl-2-pyrrolyl	1.34	61	*m*-$MeOC_6H_4$	H	1.22
23	2-Furyl	1.16	62	*p*-ClC_6H_4	H	1.17
24	3-Furyl	1.23	63	*m*-ClC_6H_4	H	1.16
25	2-Thienyl	1.17	64	*m*-$CF_3C_6H_4$	H	1.14
26	3-Thienyl	1.24	65	*p*-$NMe_2C_6H_4$	H	1.32
27	2-Thiazolyl	0.96	66	2-Pyrrolyl	H	1.27
28	4-Thiazolyl	1.18	67	*N*-Methyl-2-pyrrolyl	H	1.28
29	4-Isothiazolyl	1.08	68	2-Furyl	H	1.19
30	1-Methyl-5-imidazolyl	1.18	69	3-Furyl	H	1.22
31	1-Methyl-2-imidazolyl	1.14	70	2-Thienyl	H	1.19
32	3,5-Dimethyl-1-pyrazolyl	0.95	71	3-Thienyl	H	1.23
33	1-Methyl-5-pyrazolyl	0.98	72	2-Thiazolyl	H	1.08
34	1-Methyl-3-pyrazolyl	1.32	73	4-Thiazolyl	H	1.19
35	1-Methyl-4-[1,2,3-triazol]-yl	1.07	74	4-Isothiazolyl	H	1.15
36	1-Methyl-5-[1,2,4-triazol]-yl	0.80	75	2-Pyridyl	H	1.19
37[a]	5-Tetrazolyl	0.74	76	3-Pyridyl	H	1.15
38	2-Methyl-5-tetrazolyl	0.83	77	4-Pyridyl	H	1.11
39	2-Methyl-5-oxadiazolyl	0.77	78	Pyrazinyl	H	1.12

[a] Reference electrode: $Pt/Pt(NO_3)_2$ (0.1 m), $Prop_4NBF_4$(0.1 m), value not directly comparable.

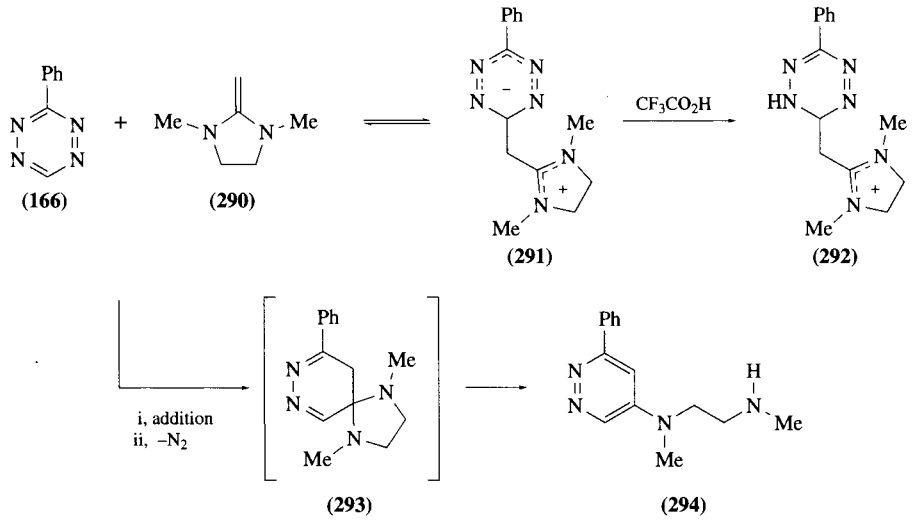
these intramolecular cycloadditions ⟨84CZ331, 85TL4355, 86TL2747, 87CZ16, 88CZ243, 89CZ254, 91AP(324)803, 91CZ367, 92AP(325)349, 92AP(325)559, 92AP(325)563⟩. The dotted circles in (**307**) and the products (**308**)–(**310**) indicate the strategy of the intramolecular Diels–Alder reactions with inverse electron demand.

6.21.5.7 Rearrangements

The fully conjugated tetrazine nucleus in principle cannot undergo rearrangement reactions. Ring transformations of dihydro, tetrahydro, and hexahydro 1,2,4,5-tetrazines under acidic and basic conditions (partial hydrolysis) are well known and were competently and extensively treated by Neunhoeffer ⟨84CHEC-I(3)531⟩. Short surveys can be found in Sections 6.21.6 and 6.21.9. No new aspects seem to be worthy of discussion here.

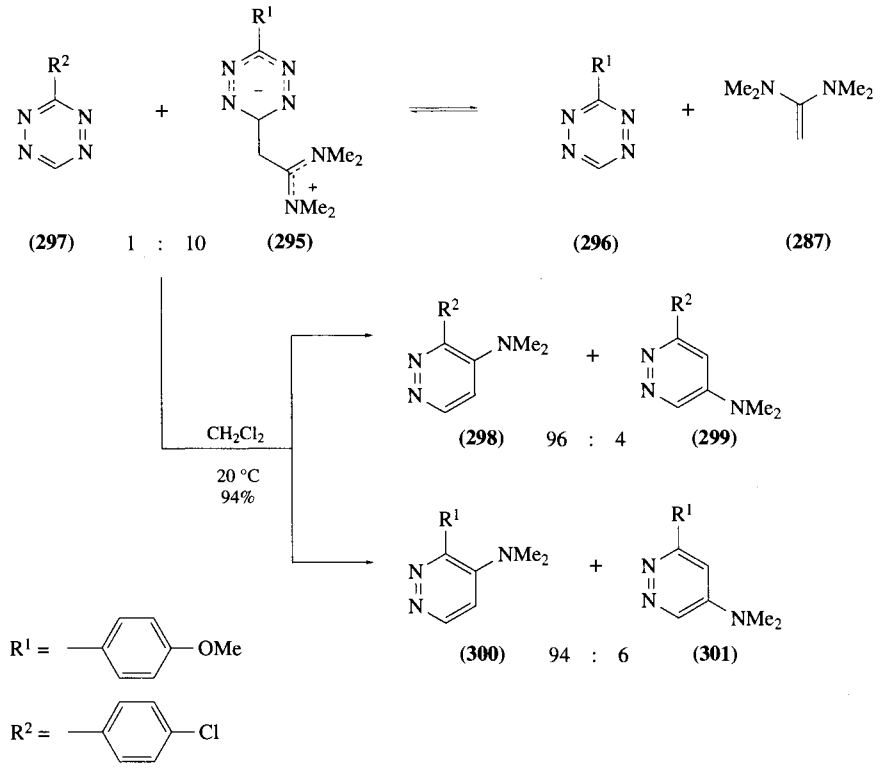
6.21.5.8 Metal Complexes—Charge Transfer Complexes

Two different approaches to tetrazine metal complexes have been reported.



(166) (290) (291) (292) (293) (294)

Scheme 51



(297) 1 : 10 (295) (296) (287)

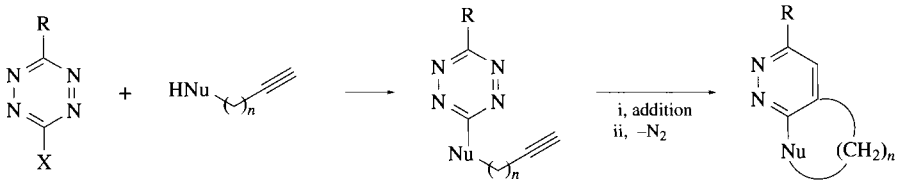
(298) 96 : 4 (299)

(300) 94 : 6 (301)

Scheme 52

Stacked transition metal macrocycles $[MacM(L)]_n$ with M = Fe, Ru, Os, Co, Mn, or Rh, and Mac = phthalocyanine (Pc), 1,2-, or 2,3-naphthalocyanine (1,2-, 2,3-Nc) have been synthesized by Hanack's group. Pyridazino (pyz) and especially *s*-tetrazine (tz), the parent compound, were used as bridging ligands ⟨83AG(E)784, 91MCLC75, 91SM59, 92IC1542, 92MCLC197, 92SM241, 94AM(6)819, 94IC3201⟩. The tetrazine-bridged metal complexes (**311**) showed interesting semiconducting properties, which depend strongly on the fragments from which they are composed. Electrical and physical properties, especially the UV and Mössbauer spectra, were studied and discussed with respect to the intrinsic semiconducting properties of these compounds.

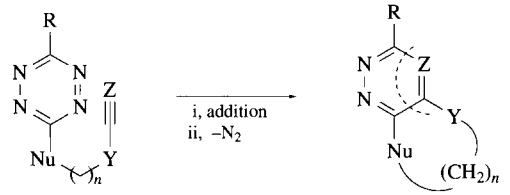
Another line of interest follows the synthesis and spectroscopic investigation of metal complexes (**312**) with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine or the corresponding pyrimidyl tetrazine (**313**) as a



(302) (303) (304) (305)

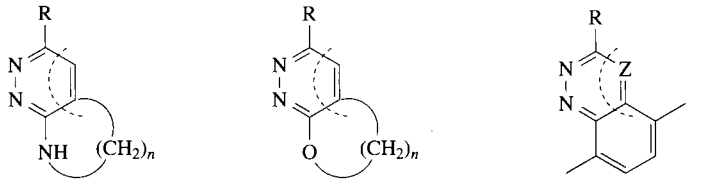
X = nucleofuge; HNu = nucleophile; n = 2–5

Scheme 53



(306) (307)

Z = CH, N; Y = CH_2, NMe

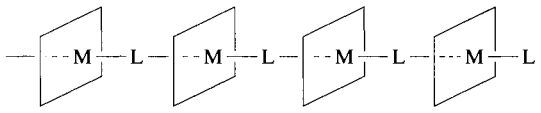


(308)
R = SMe, SOMe, SO_2Me
n = 2–5

(309)
R = SMe, NMe_2, Ph
n = 2–4

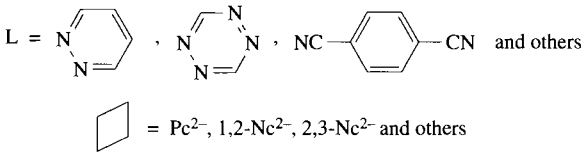
(310)
R = SMe, SCH_2Ph, Ph
Z = CH, N

Scheme 54



(311)

M = Fe^{2+}, Fe^{3+}, Co^{2+}, Co^{3+}, Ru^{2+}, Mn^{2+}, Mn^{3+}, Cr^{3+} and others

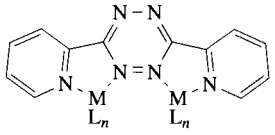


L = , , NC—⟨⟩—CN and others

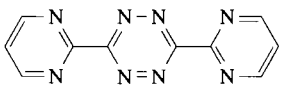
= Pc^{2-}, 1,2-Nc^{2-}, 2,3-Nc^{2-} and others

complex partner. A wide variety of metals M and ligands L_n were used to synthesize for instance complexes (**312**) from which UV/VIS spectra, NMR, and ESR spectra were measured and compared with HMO calculations ⟨85CPL431, 86IC3442, 86ICA63, 86POL445, 87IC68, 88ICA125, 88ICA131, 89ICA193, 89JCS(F1)4047, 91ICA73, 93IC2640, 95ZN123⟩. Binuclear complexes (**314**) with symmetrical bridging with pyrazine, 4,4′-bipyridine, and 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine have been studied ⟨95IC663⟩.

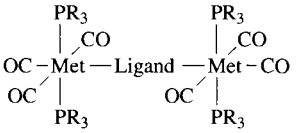
Finally, there are a few reports on conducting charge transfer complexes in which for instance 3,6-dicyano-1,2,4,5-tetrazine was combined as an acceptor with tetrathiafulvalene (TTF) ⟨86CC1579, 87SM415⟩, or 3,6-bis(2′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine served as a donor with TCNQ as acceptor ⟨88SM219, 91SM1723⟩.



(312)



(313)

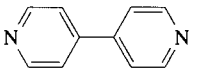


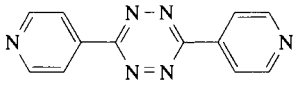
(314)

R = Pr^i; Met = W, Mo

Ligand

(a)

(b) 

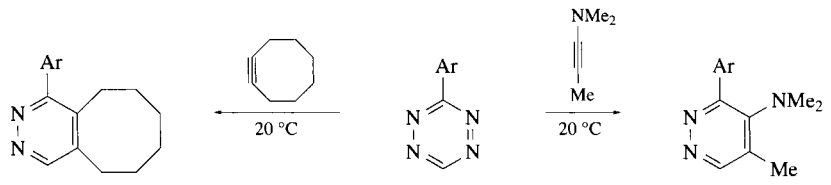
(c) 

6.21.5.9 *N*-Oxidation and Redox Reactions

The N(1) atom of 3-aryl-1,2,4,5-tetrazines is oxidized regioselectively by methyl(trifluoromethyl)dioxirane to give the hitherto unknown *N*(1)-oxides ⟨96T2377⟩.

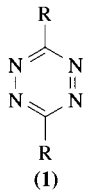
1,2,4,5-Tetrazines can be reduced very easily by many reagents; the oxidation potentials of tetrazines are quite high, so in cycloaddition reactions of 1,2,4,5-tetrazines with alkenes (see Section 6.21.5.5) the dihydropyridazines formed initially are very often oxidized by excess of the tetrazine to form pyridazine and dihydrotetrazine derivatives. There is a report on the systematic influence of substituents in the 3- and 6-positions of the tetrazine on its half wave reduction potentials $E_{1/2}$ ⟨82MI 621-02⟩. These data and many others unpublished ⟨94UP 621-01⟩ are collected in Table 4. $E_{1/2}$ parallels the LUMO energies of tetrazines and, as long as steric factors are constant, correlate log k values for cycloaddition reactions in a satisfactory way (see Section 6.21.5.5).

Table 4 Relative rate constants for the reaction of 3-[*p*-chlorophenyl]-1,2,4,5-tetrazine with cyclooctyne and 1-*N*,*N*-dimethylaminopropyne at 20 °C in various solvents.

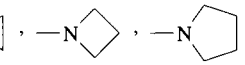


Solvent	k_{rel}	Me—≡—NMe k_{rel}
n-C_6H_{14}	1.22	≡1.00
Et_2O	≡1.00	2.17
Dioxane	1.05	2.93
C_6H_6	1.76	3.83
$MeCO_2Me$	1.29	6.11
Me_2CO	1.99	19.4
PhCN	2.33	27.2
MeCN	2.26	31.1
DMF	2.31	32.2
CH_2Cl_2	2.77	32.7
DMSO	3.46	63.1
MeOH	4.01	
EtOH	4.85	

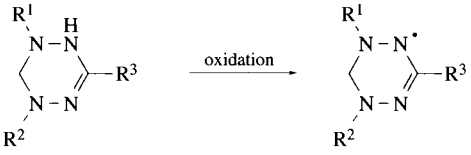
Radical cations and anions of 1,2,4,5-tetrazines (**1**) have been studied extensively by Neugebauer and co-workers ⟨86CC837, 88JCS(P2)413⟩. Exposure of (**1**) to ^{60}Co γ-rays in dilute solutions of $FeCl_3$ at 77 K gave the corresponding radical cations, identified by their ESR spectra. Two distinct types of spectra were obtained, a $n(\sigma)$-radical cation, and for tetrazines with NR_2 groups, a π-radical cation. Reversible behavior of the tetrazines was found in their cyclic voltammograms for the second group. The radical anions were studied both in liquid and solid solutions. Total spin densities were estimated for both types of radical cation and for the radical anions, and in all cases the total is in the 1.05–1.2 range, the deviation from unity being interpreted in terms of spin polarization giving rise to considerable negative spin densities.



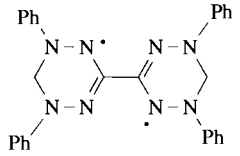
(**1**)

R = H, Me, Ph, Cl, OMe, SMe, NH_2, NHMe, NMe_2, 

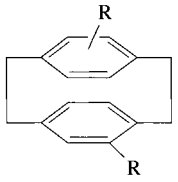
Continuing interest is also shown for verdazyl radicals (**316**) a class of quite stable radicals, which can be easily analyzed by ESR spectroscopy. A bisverdazyl (**317**) was synthesized by Neugebauer *et al.* ⟨80CB2049⟩, and mono and bisverdazyls (**318**) of [2.2]paracyclophanes were studied by NMR ⟨81T1391⟩ and ESR spectroscopy ⟨81JCS(P2)896⟩ as well as 3-oxo- and 3-thioxoverdazyls (**319**) for which redox reactions, EPR, ENDOR, and ^2H NMR spectra are recorded ⟨88CB815, 93JCS(P2)535, 94JHC319⟩. A stable radical (**320**) with a functional group, part of a study on ferromagnetic organic compounds, has been reported ⟨93LA201⟩. Finally, radical cations of 1,4-dihydrotetrazines (**321**)–(**323**) have been easily obtained by oxidation, for instance with bis(4-methylphenyl)aminyl, and ESR as well as ENDOR spectra have been reported ⟨85CB2157, 85JCS(P2)1633, 90ZC133, 94HCA86, 94LA1049⟩.



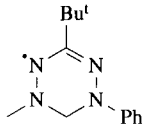
(**315**) (**316**) (9)

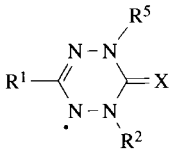


(**317**)

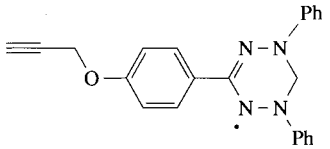


(**318**)

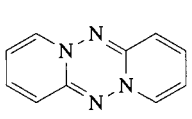
R = 



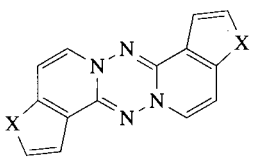
(**319**)
X = O, S



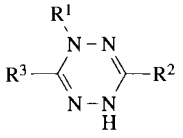
(**320**)



(**321**)



(**322**)
X = O, S, NMe

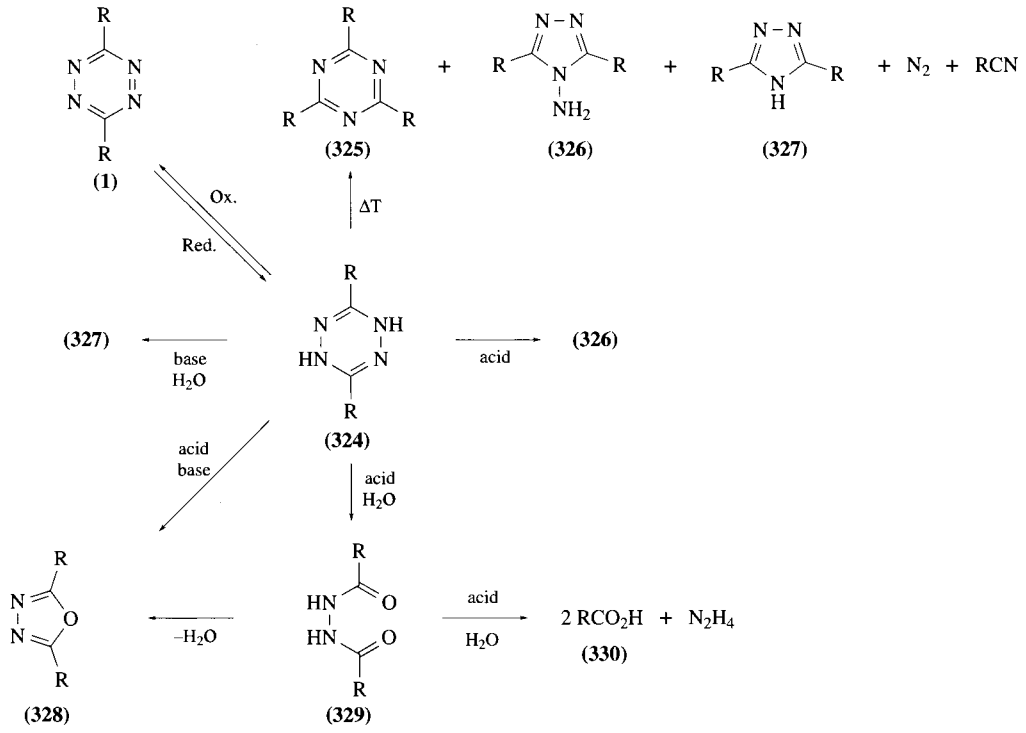


(**323**)
R^1, R^2, R^3 = alkyl, aryl

6.21.6 REACTIVITY OF NONCONJUGATED RINGS

As mentioned earlier, the main interest of this chapter lies in the new aspects of the fully conjugated tetrazine system. In CHEC-I a detailed discussion of all fundamental reactions of dihydro to hexahydro tetrazines can be found ⟨84CHEC-I(3)531⟩; no significant new aspects have since been reported.

A few typical reactions of 1,4-dihydro-1,2,4,5-tetrazines are listed in Scheme 55. 1,4-Dihydrotetrazines (**2**) are easily oxidized to 1,2,4,5-tetrazines (**1**) by nitrous acid, nitric acid, oxygen, halogens, iron(III) chloride, hydrogen peroxide, and lead tetraacetate ⟨78HC(33)1077⟩. In contrast, 1,2,4,5-tetrazines are strong oxidants, as the half wave reduction potentials of Table 4 show. The redox system is quite mobile.



Scheme 55

In boiling mesitylene, and faster in the neat material at its melting point, 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (**324**; R = Ph) decomposes to a complex mixture of triphenyl-1,3,5-triazine (**325**), 3,5-diphenyl-4-amino-1,2,4-triazole (**326**), 3,5-diphenyl-1,2,4-triazole (**327**), benzonitrile, and ammonia; apparently a redox reaction is implicated ⟨62LA(654)146⟩.

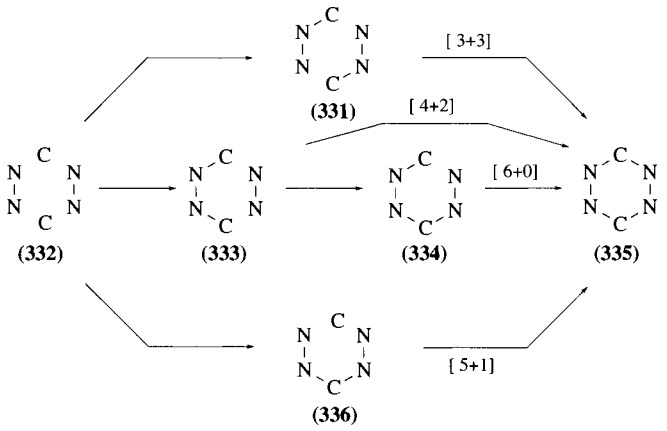
Under anhydrous conditions 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine isomerizes to the 4-amino-1,2,4-triazole derivative (**326**). Hydrolysis under the influence of acids or bases transforms the 1,4-dihydro-1,2,4,5-tetrazine system to diacylhydrazines (**329**), carboxylic acids (**330**), and hydrazine, 1,3,4-oxadiazoles (**328**), or 1,2,4-triazoles (**327**) depending on the reaction conditions ⟨78HC(33)1077⟩.

6.21.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Most tetrazines used in the literature have one or two substituents in the 3- and/or 6-position: alkyl, aryl, heteroaryl, CO_2R, CF_3, NR_2, OR, SR, Hal, SOR, SO_2R, and others. All these substituents show their normal reactivity, quantitatively modified by the tetrazine system, a strongly electron-attracting group. Substituents which are good leaving groups, such as Hal, SR, SOR, and SO_2R are readily substituted by reactive nucleophiles (see Section 6.21.5.3). A number of these nucleophilic aromatic substitution reactions form the initial step of the intramolecular (4 + 2) cycloaddition reactions described in Section 6.21.5.6.

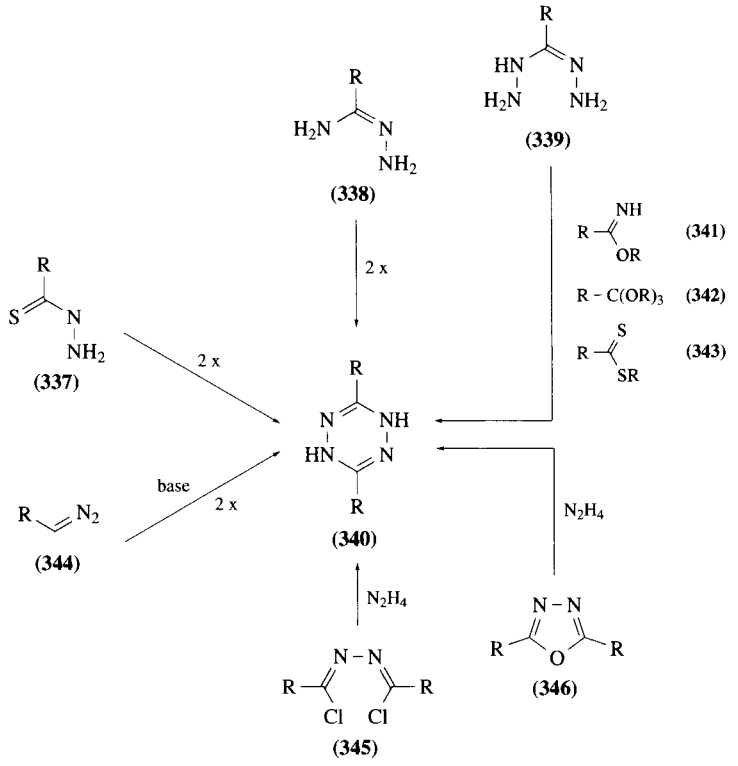
6.21.8 RING SYNTHESIS BY NUMBER OF RING ATOMS IN EACH COMPONENT

The principal problem in the synthesis of 1,2,4,5-tetrazines is the selection of the fragments to build up the heterocyclic skeleton of the tetraaza ring system. Scheme 56 shows different approaches in a more formal way. In almost all attempts to synthesize the heterocyclic system hydrazine is used to incorporate the neighboring nitrogens into the ring system. In many cases the synthesis starts with a [1 + 2 + 1 + 2] combination (**332**). Depending on the method by which the bonds between the fragments are formed, arrangements (**331**), (**333**), or (**336**) can be obtained. The final ring closure from these intermediates to (**335**) represents a [3 + 3], [4 + 2], [5 + 1], or [6 + 0] addition. There is no report of a ring transformation to build the 1,2,4,5-tetrazine ring.



Scheme 56

In Neunhoeffer's contribution to CHEC-I a detailed and very competent discussion is found of the synthesis of the tetrazine system ⟨84CHEC-I(3)531⟩. All principal synthetic ways are described there, and no new method has been published in the meantime, especially for the fully conjugated system. Therefore the discussion in this contribution is limited to Scheme 57, which summarizes the most successful ways to the heterocyclic ring system via the dihydro compounds.



Scheme 57

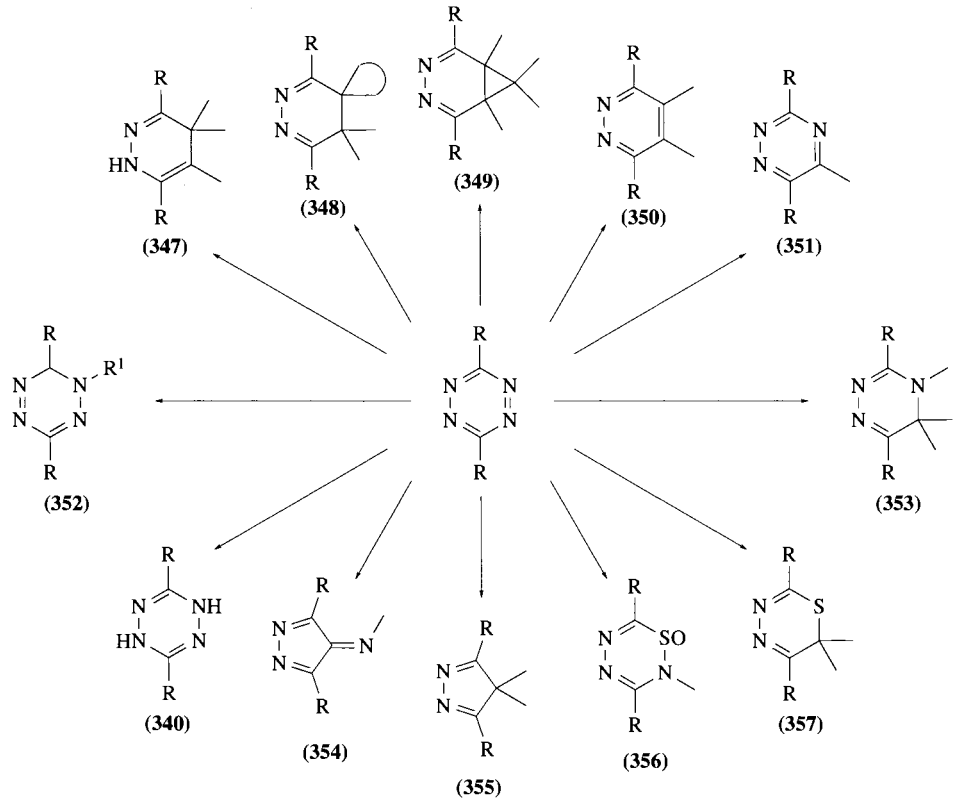
1,4-Dihydrotetrazines (**340**), which can easily be oxidized to 1,2,4,5-tetrazines, can be formed by dimerization of thiohydrazides (**337**) or amidrazones (**338**). The ring closure of hydrazidines (**339**) in a [5 + 1] fashion proceeds well with activated carboxylic acid derivatives such as imidates (**341**), orthocarboxylates (**342**) or dithiocarboxylates (**343**). The [4 + 2] procedure is found in the transformation of 1,3,4-oxadiazoles (**346**) or 1,4-dichloroazines (**345**) with hydrazine. Finally diazoalkanes (**344**) can be dimerized in a [3 + 3] manner under the influence of a base; the dimerization of diazoacetic ester is an early example, leading to 3,6-tetrazinedicarboxylate (**48**), which is frequently used in (4 + 2) cycloaddition reactions with inverse electron demand. Nitrile imines, reactive intermediates which are formed from many precursors, can dimerize in a [3 + 3] fashion to form 1,3,4,6-tetrasubstituted 1,4-dihydrotetrazines. These reactions are summarized in Scheme 57.

Many detailed procedures for the synthesis of specific compounds can be extracted from the schemes presented above and the corresponding literature of these contributions. A review describes tetrazine synthesis using carboxylic iminoesters ⟨95RCR317⟩.

6.21.9 APPLICATIONS AND IMPORTANT COMPOUNDS

6.21.9.1 Ring Transformations of 1,2,4,5-Tetrazines

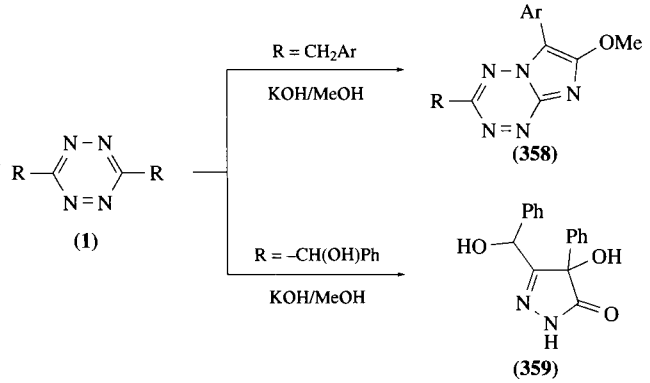
1,2,4,5-Tetrazines are the starting point for numerous ring transformations in the synthesis of five- and six-membered heterocyclic ring systems. Scheme 58 presents a schematic survey of a larger number of examples scattered over the present chapter, mainly in Sections 6.21.5.4 and 6.21.5.5 dealing with cycloaddition reactions.



Scheme 58

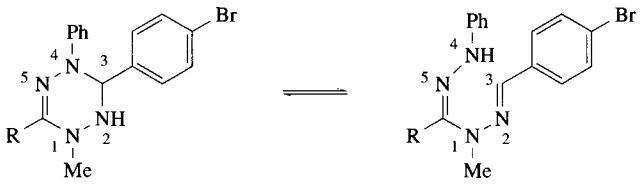
Alkenes lead to 1,4-dihydropyridazines (**347**) or the spiro derivatives (**348**). Cyclic alkenes, such as cyclopropenes give rise to diazanorcaradienes (**349**) or higher homologues, and reaction with alkynes yields pyridazines (**350**). Hetero-2π-systems such as nitriles, imines, thioketones, and *N*-sulfinylamines open the way to heterocyclic six-membered systems (**351**), (**353**), (**357**), and (**356**). (4 + 1) Addition reactions of isocyanides and carbenes make isopyrazoles (**354**) and (**355**) available. Reduction processes lead to 1,4- or 1,6-dihydrotetrazines (**340**) or (**352**). The reactions of 1,4-dihydrotetrazines (**340**) were briefly collected in Scheme 57.

In the presence of nucleophiles, 3,6-disubstituted 1,2,4,5-tetrazines (**1**) are transformed to imidazo[1,2-*b*]-1,2,4,5-tetrazines (**358**) or pyrazolin-5-one derivatives (**359**) as one of the main products, depending on the nature of the substituents R, as extensive investigations by Neilson and co-workers have shown (Scheme 59) ⟨81JCS(P1)1371, 82JCS(P1)1165, 83JCS(P1)1601, 84JCS(P1)2779, 85JCS(P1)1081, 85JCS(P1)2709, 88JCS(P1)1439⟩. Cyanotrimethylsilane reacts with 3,6-disubstituted tetrazines in boiling toluene or xylene to form 3,5-disubstituted 4-amino-3-cyano-3*H*-pyrazoles, 4-amino-1-arylmethyl-1*H*-pyrazoles, or 4-amino-1*H*-pyrazoles by ring contraction ⟨87TL2139⟩.



Scheme 59

1,2,3,4-Tetrahydro-1,2,4,5-tetrazines (**360**) are in equilibrium with the noncyclic hydrazidines (**361**) by ring–chain tautomerism (Equation (10)) ⟨88H(27)917, 89H(29)1163, 91H(32)1063, 91JPR61⟩. The extent of the ring–chain equilibrium in solution varies widely depending both on steric and electronic effects of substituents at the tetrazine ring. X-ray diffraction proved that compounds showing a high ratio (>80%) of the ring tautomer in solution are cyclic in solid state; when the ratio of the chain tautomer in solution exceeds 50% the noncyclic structure is found in the solid state (Equation (10)) ⟨94JHC505⟩.

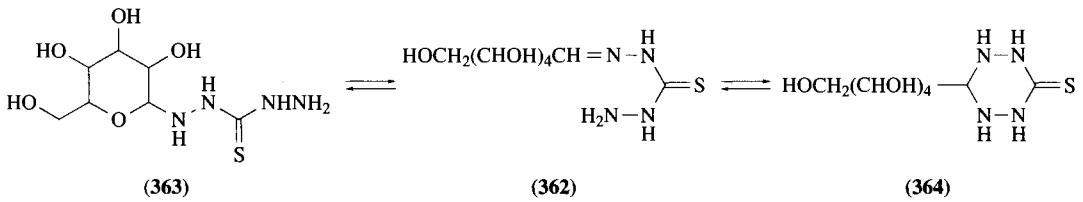


(**360**)
Solid state 100%
for R = Ph

(**361**)
Solid state 100%
for R = COMe

(10)

Finally in the case of thiosemicarbazones of mannose, galactose, and glucose in DMSO solutions a ring–chain equilibrium (**363**)⇌(**362**)⇌(**364**) is reported (Scheme 60) in which a hydroxyl group of the sugar component competes with the free amino group in (**362**); either the pyranose form (**363**) or the heterocyclic ring (**364**) is formed, depending on the sugar component ⟨93MC168⟩.



(**363**) (**362**) (**364**)

Sugar	(**362**)	: (**363**)	: (**364**)
Mannose	5	0	95
Galactose	10	30	60
Glucose	5	35	60

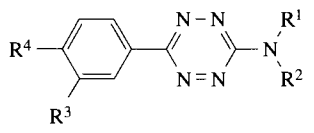
Scheme 60

6.21.9.2 Applications of 1,2,4,5-Tetrazines

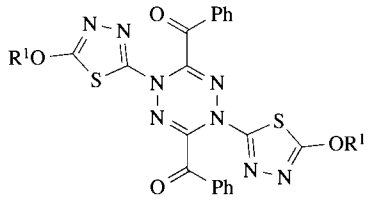
In CHEC-I, Neunhoeffer briefly indicated that the use of compounds containing the 1,2,4,5-tetrazine skeleton had been claimed for use as pesticides, pharmaceuticals, explosives and rocket propellants, photographic dyes and additives to photographic layers, reducing agents, inhibitors of steel corrosion, and fuel additives ⟨84CHEC-I(3)531⟩. Neunhoeffer mentioned "that most claims must be taken with a pinch of salt and it seems doubtful that any compound is of significant value."

Most reports are published in patents, and only a few in scientific journals. Nevertheless a few remarks may be made on the use of tetrazine derivatives or their hydrogenated forms as pharmaceuticals, pesticides, liquid crystals, explosives, and propellants.

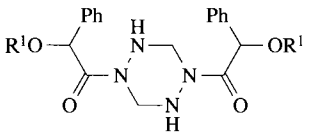
The easily accessible 3-amino-6-aryl-1,2,4,5-tetrazines (**365**) showed modest antimalarial activity ⟨79JHC881⟩, while for the 1,4-dihydrotetrazine derivative (**366**) pronounced antiviral activity is reported against animal and plant viruses (e.g. tobacco mosaic virus) ⟨86MI 621-01⟩. The hexahydrotetrazine (**367**) proved to have useful analgesic and antiinflammatory activity, and (**368**) is recommended as an antitumor agent ⟨79JAP54163579, 80URP686336⟩. Finally the 1,4-dihydrotetrazine derivative (**369**) possesses some abortifacient and antiimplantation activity in rats ⟨86MI 621-02⟩.



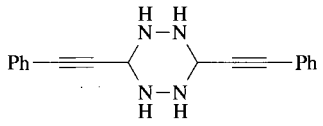
(**365**)



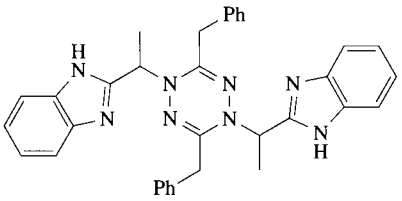
(**366**)



(**367**)

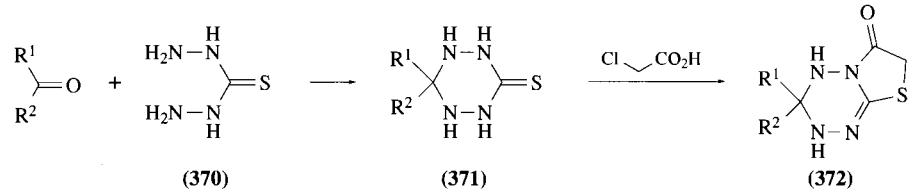


(**368**)



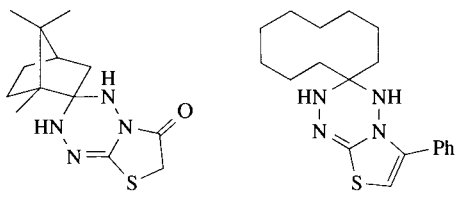
(**369**)

Scheme 61 summarizes a general synthetic sequence using ketones and thiocarbohydrazide (**370**) to form (mostly spiro) hexahydrotetrazinethiones (**371**) and, by reaction with chloroacetic acid or α-haloketones, bicyclic derivatives, e.g. (**372**). For compound (**373**) the antibacterial and antifungal activities have been evaluated. A sequence of papers from an Indian research group deals with similar reactions using for instance cyclodecanone (forming (**374**)) ⟨86IJC(B)812⟩, bicyclo[3.2.1]nonanone ⟨92OPP523⟩, anthrone ⟨91JIC252⟩, isatin ⟨86JHC97, 91IJC(B)508⟩, indanones ⟨88IJC(B)912⟩, and substituted cyclic ketones (6–8-membered rings) ⟨85IJC(B)1227, 87IJC(B)473⟩.



(**370**) (**371**) (**372**)

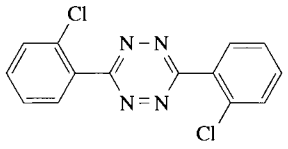
Scheme 61



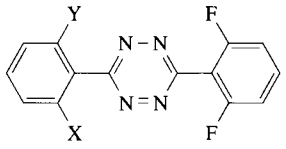
(**373**) (**374**)

Tetrazine derivatives do not seem to be very toxic. For 3,6-diamino-1,2,4,5-tetrazine an acute oral LD30/50 value (LD for 50% of the animals within 30 days after compound administration) was found (836 mg kg^{-1} in rats) which classified this compound as slightly to moderately toxic for rats ⟨93MI 621-01⟩.

Also in the field of pesticides, some recent results are documented, mainly in patents. Compounds (**375**)–(**379**) show some leading structural elements. Clofentezine (**375**) and (**376**; X = F, Cl, Br; Y = H, F) were screened for acaricidal activity; the compounds were shown to be highly active mite ovicides ⟨87MI 621-03, 89JAP01279810, 95EUP635499⟩. Generally, 3,6-diaryl-1,2,4,5-tetrazines with alkyl groups and halogens seem to be active as pesticides, bactericides, and antiinflammatory agents ⟨91MIP269604⟩.



(**375**)



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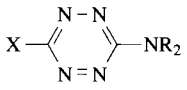

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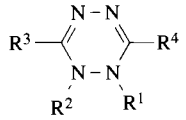
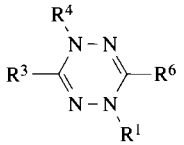


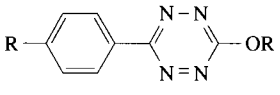
(**378**)



(**379**)

Tetrazine derivatives (**377**; X = Cl, NR_2) were prepared and proposed as herbicides ⟨86GEP3508214⟩. Mixtures of (**378**) and (**379**) (R^1, R^2, R^4 = alkyl, alkenyl, or alkynyl groups; R^3 = variously substituted alkyl, cycloalkyl, aryl, or phenylalkyl groups; R^5 = Hal-C_6H_4) were used as acaricides; they are effective against adults, larvae, and eggs ⟨80MI 621-02, 83MI 621-01⟩.

1,2,4,5-Tetrazine derivatives seem to be of considerable interest in the field of liquid crystals and their application in display devices. Compounds (**380**)–(**388**) represent a selection of different structural types which have been tested; in all cases R is a long-chain alkyl or alkoxy group; X may be oxygen or nitrogen. For (*E*,*E*)-3,6-bis(2-arylethenyl)-1,2,4,5-tetrazines (**384**) the photolysis (λ = 366 nm) is described which results in breakdown to nitrogen and cinnamonitriles ⟨95JPR641⟩. Most of the compounds are described in patents; the literature may be cited without further comment chronologically for each type of structure: (**380**) ⟨91EGP295837⟩, (**381**) ⟨87EGP245897⟩, (**382**) ⟨80MI 621-03, 81EGP151950z, 81JAP56062874, 81JAP56083481, 81JAP56090072, 82JAP56116775, 82USP4348298⟩, (**383**) ⟨82USP4358589⟩, (**385**) ⟨84BRP2138838⟩, (**386**) ⟨90JAP02311467⟩, (**387**) ⟨81JAP56018675, 82JAP57014584, 83MI 621-01⟩, (**388**) ⟨81JAP56092879⟩.



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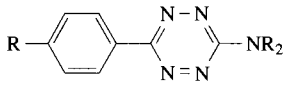

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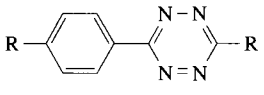

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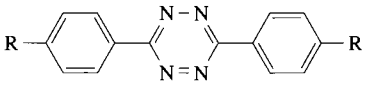
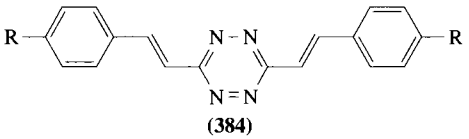
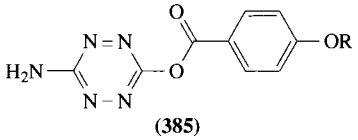


(**383**)



(**384**)



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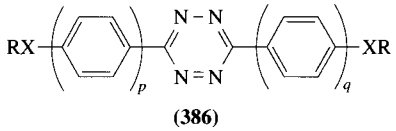

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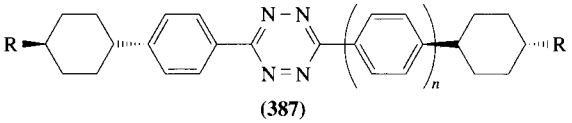

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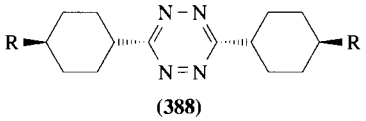
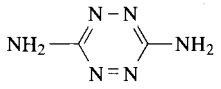


(**388**)

There are a few reports which indicate that, along with other nitrogen-containing heterocycles, tetrazine derivatives might be used as explosives and propellants. 3,6-Diamino-1,2,4,5-tetrazine (**9a**) ⟨94MI 621-02⟩, its 2,5-dioxide (**389**) ⟨93JHC1593, 95MI 621-01⟩, or amino-nitro-triazole derivatives (**390**) of 1,2,4,5-tetrazines ⟨91JEM415, 94JEM223⟩ have been proposed as suitable compounds. Molecular mechanics calculations have been performed to derive group increments in order to predict the properties of explosives ⟨91MI 621-01, 93MI 621-02⟩. Propellants and explosives of high energy and low vulnerability are the aim of these studies.



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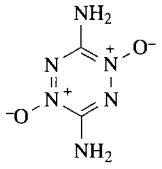

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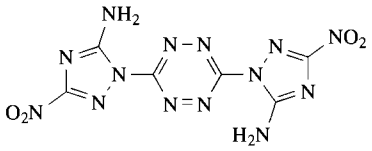

(390)

3,6-Diaryl-substituted 1,4-dihydrotetrazines showed good charge transporting properties in electrophotographic photoreceptors ⟨85JAP60195550, 90JAP02010365, 90JAP02010366⟩; CT calculations have also been performed in this field ⟨87MI 621-04⟩. Finally, there is an interesting report on the photofragmentation of 3,6-diphenyl-1,2,4,5-tetrazine in the solid state, observed by atomic force microscopy (AFM). The photolysis yields nanostructures in the form of very regularly shaped craters even though the product benzonitrile is a liquid ⟨95MCLC252⟩.

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6.22
Other Tetrazines and Pentazines

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Kingston University, UK

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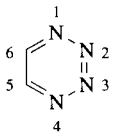
6.22.1 INTRODUCTION

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) the tetrazines, including 1,2,4,5-tetrazine and pentazine, were considered in one chapter ⟨84CHEC-I(3)531⟩. Here, only the 1,2,3,4-tetrazine (**1**), 1,2,3,5-tetrazine (**2**), 1,2,3,4-benzotetrazine (**3**), pentazine (**4**), and hexazine (**5**) systems will be covered, 1,2,4,5-tetrazine being assigned to a separate chapter. Fused systems with ring-junction nitrogen atoms are considered in another volume.



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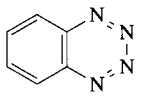
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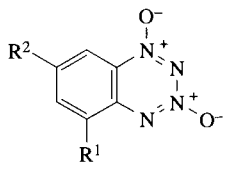
In CHEC-I there were 27 references to the subject matter of this chapter. Since 1982, only about 30 further references have been collected for consideration here with a further 20 for hexazines. Thus, although published work in this area remains relatively sparse, and most of this is of a theoretical nature, there has been an increased rate of publication since the early 1980s. Since the appearance of CHEC-I the tetrazines have been reviewed ⟨B-89MI 622-01⟩, and there have also been brief annual accounts of work in this field in the series *Progress in Heterocyclic Chemistry*.

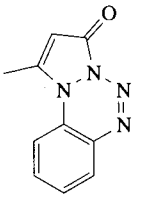
General reviews of relevance to the topics covered in this chapter include that of the concept of aromaticity in heterocyclic chemistry ⟨93AHC(56)303⟩, of a bond order approach to ring current and aromaticity ⟨83JOC1344⟩, polarizability, and hyperpolarizability, of azines ⟨85JCP(82)1435⟩, π-electron delocalization ⟨89JA4178⟩, semiempirical methods for aromatic energies of azines ⟨89H(28)1135⟩, and of the influence of σ and π electrons on aromaticity ⟨90JA6772⟩.

In 1995, no aromatic monocyclic 1,2,3,4-tetrazine has been prepared. However, 1,2,3,4-benzotetrazine, referred to as "benzotetrazine" later in this chapter, has been obtained as its 1,3-dioxide (**6**) ⟨90IZV718, 91MC101⟩, and, more recently, a dibromo derivative of the 1-oxide has been isolated ⟨94MC122⟩. A fused benzotetrazine, 1-methyl-3*H*-pyrazolo[1,2-*a*]benzotetrazin-3-one (**7**), has been made ⟨85CC204⟩, and so, too, has the 1,2,3-triazolo[4,5-*e*][1,2,3,4]tetrazine (**8**) ⟨88CC1608, 92AX(C)1237⟩.



(6)

R^1, R^2 = H, NO_2; R^1 = H, R^2 = NO_2; R^1 = NO_2, R^2 = H; R^1, R^2 = Br



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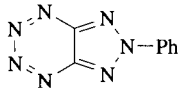
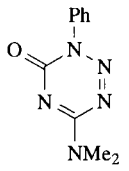


(8)

Except for the tetrazinone (**9**), no aromatic monocyclic 1,2,3,5-tetrazines have been reported, although some nonaromatic examples have been obtained ⟨88CC232, 90JCS(P1)2527⟩, and an imidazo-fused derivative, Temazolomide (**10**), has been developed and is applied in cancer chemotherapy ⟨93MI 622-01⟩.



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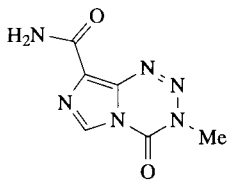


(10)

No simple pentazines have been made, although the sodium salt of a mesoionic tetrazolylpentazine has been reported ⟨93CHE395⟩. Pentazine itself is said to be unstable, and to decompose into hydrogen cyanide and dinitrogen ⟨93AHC(56)303⟩.

Hexazine is reported to have been isolated in a matrix at low temperatures by photolysis of the complex *cis*-$(Pt(N_3)_2(PPh_3)_2)$ ⟨80AG(E)717⟩; however, it has been suggested that this result requires verification ⟨83JST(14)351⟩.

Due to the paucity of references to each type of system, this chapter has not been subdivided to consider each ring system separately.

6.22.2 STRUCTURE, SPECTRA, AND THEORETICAL STUDIES

A general study of the MO patterns and HOMO energies of structurally related azaarenes has shown that the approach of S,T isomers ⟨82JST(84)361⟩ gives values in agreement with other methods, and is a suitable means to derive predictions concerning these systems ⟨83MI 622-01⟩.

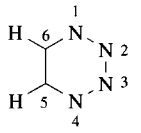
The MNDO calculated energies of 1,2,3,4-tetrazine are ΔH_f° 71.3, relative energy 7.4 kcal mol^{-1}, and the dipole moment 4.32 D. The values for 1,2,3,5-tetrazine are ΔH_f° 63.9, relative energy 0 kcal mol^{-1}, and dipole moment 2.56 D. However, it was felt that these values, although correct in relation to each other, might be too low ⟨85JOC4894⟩.

Thomas *et al.* have carried out extensive calculations on the two unknown, unsubstituted, tetrazines, as well as on 1,2,4,5-tetrazine. SCF calculations including double zeta (DZ), and DZ plus polarization (DZP) basis sets, as well as single and double excitation configuration interaction (CSID) levels of theory were used. They have calculated relative energies (ΔE) by these methods, the results being given in Table 1 ⟨91JOC539⟩.

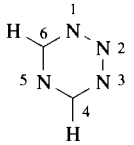
Table 1 Calculated relative energies for tetrazines.

METHOD	*ΔE (kcal mol^{-1})*	
	1,2,3,4-tetrazine	*1,2,3,5-tetrazine*
SCF/DZ	22.0	0.0
SCF/DZP	25.4	0.0
CSID(+Q)/DZ	19.3 (17.9)	0.0
CSID(+Q)/DZP	23.5 (22.2)	0.0

The geometrical structures predicted for these two heterocycles in this work are given in Figure 1. Theoretically predicted harmonic vibrational frequencies and infrared intensities were also proposed.



Angles			Bond lengths		
	C6-N1-N2	118.3		N2-N3	1.297
	N1-N2-N3	112.9		N3-N4	1.330
	C5-C6-N1	119.8		N4-C5	1.314
	C5-C6-H	123.0		C5-C6	1.396
				C5-H	1.080



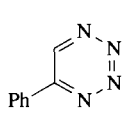
Angles			Bond lengths		
	C6-N1-N2	118.2		N2-N3	1.311
	N1-N2-N3	120.5		N3-C4	1.333
	N5-C6-N1	125.3		C4-H	1.081
	N5-C6-N1	118.5		C4-N5	1.323

Figure 1 Bond angles (°) and bond lengths (Å) for 1,2,3,4- and 1,2,3,5-tetrazines.

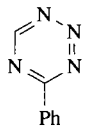
A surprising result of this work is that the calculations show that 1,2,3,5-tetrazine is the lowest energy tetrazine isomer at all levels of *ab initio* theory, although 1,2,4,5-tetrazine is the only one which has been characterized.

New calculations of aromaticity which involve dividing the total energy into a σ-part and a π-part have been applied to a number of cyclic systems, including 1,2,3,5-tetrazine and pentazine. The results show that in all cases σ electrons dominate over π electrons, and that in all compounds the behavior of the σ and the π electrons is qualitatively the same as in benzene ⟨90JA6772⟩.

Ab initio STO-3G, and advanced semiempirical AM1 calculations, have been presented for 5-phenyl-1,2,3,4-tetrazine (**11**), 4-phenyl-1,2,3,5-tetrazine (**12**), and for bitetrazines (all, so far, unknown compounds). These show that the preferred conformation of these systems is planar for compound (**11**) and for the bi(1,2,3,4-tetrazine), but nonplanar for (**12**) and for bi(1,2,3,5-tetrazine). With bi-(1,2,3,4-tetrazine) the (*anti*-)planar conformation is favored ⟨92MI 622-01⟩.

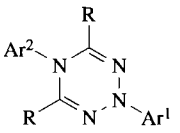


(**11**)

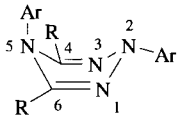


(**12**)

The dihydro-1,2,3,5-tetrazine (**13**) has been prepared and the crystal structure has been determined. This shows that the 8-π tetrazine ring is boat-shaped, with the 5-aryl group axial and the 2-aryl group equatorial to the average plane. The properties and bond lengths indicate that the ring is essentially composed of two isolated amidine groups, with no overall aromaticity. The bond lengths for (**13**) are shown in Figure 2 ⟨88CC232, 90JCS(P1)2527⟩.



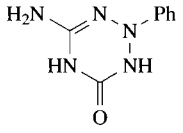
(**13**)



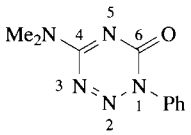
Bond lengths (Å)		
	N1–N2	1.39
	N3=C4	1.28
	C4–N5	1.43

Figure 2 Structure of compound (**13**).

The crystal structures of 1,2,3,5-tetrazinones have been determined and show some surprising features. 6-Amino-2,3-dihydro-2-phenyl-1,2,3,5-tetrazin-4(5*H*)-one (**14**) is monoclinic, of space group $P2_1/n$ [*a* 12.880(1) *b* 9.427(1) *c* 7.166(1) Å; b 100.95(1)° d.(calc.) 1.471 for $Z = 4$] and the tetrazinone ring is planar ⟨90AX(C)261⟩. 6-Dimethylamino-3-phenyl-1,2,3,5-tetrazin-4(3*H*)-one (**9**) is *ortho*-rhombic, and of space group *Pbca* [*a* 23.510(1) *b* 11.169(1) *c* 7.777(1) Å; $d_c = 1.413$ for $Z = 8$]. The x-ray crystal analysis of this phenyl derivative has shown that in this case the tetrazinone ring is slightly puckered into a boat conformation with a mirror plane bisecting *N*-1 and *C*-4. The dimensions of the compound are shown in Figure 3 ⟨85AX(C)1669, 85JCS(P1)415⟩.



(14)



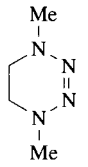
Bond lengths (Å): N1-Ph 1.440(5), N1-N2 1.339(4), N2=N3 1.277(4), N3-C4 1.407(5), C4-NMe_2 1.338(5), C4=N5 1.313(5), N5=C6 1.355(5), C6=O 1.214(5), C6-N1 1.418(5)

Bond angles (°): N1-N2-N3 120.2(3), N2-N3-C4 116.8(3), N3-C4-N5 125.5(4), C4-N5-C6 117.6(4), N5-C6-N1 115.9(4), Ph-N1-N2 114.4(3), N3-C4-NMe_2 114.4(4), Me_2N-C4-C5 120.0(4), N5-C6-O 124.8(4), O-C6-N1 119.3(4), C6-N1-Ph 122.2(3)

Figure 3 Structure of compound (**14**).

The crystal structures of several other tetrazine derivatives have also been determined. These include benzotetrazine 1,3-dioxide (**6**; $R^1 = R^2 = H$) (space group *Pcba*, with *a* 13.602(1), *b* 14.477(2), and *c* 6.969(1) Å; $Z = 8$, $d_c = 1.589$). The benzotetrazine ring is seen to be planar, indicating extensive π-electron delocalization, and shortened, semipolar, N—O bonds are observed (N(2)—O(5) = 1.255(4) and N(4)—O(6) = 1.238(4) Å) ⟨92AX(C)1237⟩. The 5,7-dibromobenzotetrazine 1-oxide has also been characterized by x-ray crystallography ⟨94MC122⟩.

1,4-Dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine (**15**), first prepared by Nelsen and Fibiger ⟨72JA8497⟩, has been investigated by photoelectron spectroscopy, and the structure has been studied using MNDO calculations ⟨B-80MI 622-01⟩. The results show that (**15**) exists in a rigid boat conformation with equatorial methyl groups.



(15)

Semiempirical MO calculations have been carried out on 1,2,3,4-tetrazine for the potential energy surfaces for degradation to ethyne and nitrogen, or to hydrogen cyanide and nitrogen ⟨90CPB3191⟩.

AM1 calculations of aromaticity have also been applied to a number of heterocycles, including the subjects of this chapter, the results being in agreement with earlier calculations ⟨90JPR885⟩. MRINDO/S-C1 calculations have also been carried out for pentazine which indicate the importance of outer (Rydberg) atomic orbitals ⟨90TCA343⟩.

Theoretical calculations of proton affinities, relative basicities, and preferred protonation sites of azines have been carried out by two groups ⟨87JST(35)135, 88MI 622-01⟩. As expected, all of the methods predict that the introduction of additional nitrogens decreases the overall absolute basicity. Furthermore, comparison of the relative basicities of isomers, and of the preferred protonation site for each isomer, indicates that nitrogen atoms with only one α-N, and without a γ-N, are more basic than any others. The results, using different methods, illustrate the necessity for using fully optimised structures to obtain reliable proton affinities.

Hartree–Fock calculations, with the 6-31G basis, have been carried out for the azines with respect to their lithium ion binding energies. As the number of nitrogen atoms in the ring is increased, a roughly additive model is followed ⟨90TCA1⟩.

Hexazine has been reported to be formed by the low temperature photolysis of a platinum complex ⟨80AG(E)717⟩, although its existence has been questioned ⟨83JST(14)351⟩. However, thorough theoretical studies of the system have been made.

Shaik and co-workers have predicted, using valence bond correlation, that N_6 in D_{6h} symmetry is unstable, and that it easily distorts from this symmetry ⟨87JA363, 88IC2219⟩. This result is supported, using σ-π separability criteria, by Jug and Koester ⟨90JA6772⟩. This study predicts that, in N_6, the π-electrons have a much higher tendency to localize than in benzene. Consequently the potential curve for N_6 is quite flat, and little energy is needed to distort it. Thus, N_6 is only metastable on the potential surface, and easily dissociates into $3N_2$.

Lauderdale *et al.* have used MBPT (many-body perturbation theory) and *ab initio* SCF methods to show, unambiguously, that although the N_6 benzene analogue is a local minimum at the SCF level, at the correlated level it is a second-order saddle point on the N_6 surface ⟨92JPC1173⟩.

Engelke has carried out extensive studies of the N_6 system, using *ab initio* correlated calculations, and concludes that there are five stable points on the energy hypersurface for N_6 corresponding to the benzene, Dewar benzene, benzvalene, triprismane, and *trans*-3,3-bi(cyclopropenyl) analogues. The first five structures are higher in energy than $3N_2$ by between 243 and 382 kcal mol^{-1} using the RHF/4-31G* model. However, correlation at the MP2 level alters the situation, showing that it is unsafe to draw conclusions about the stability of such molecules from calculations done on an RHF hypersurface ⟨89JPC5722, 92JPC10789⟩.

Schaefer and co-workers have addressed the hexazine problem by SCF theory using double zeta and (DZ + polarization) basis sets. This study yielded the prediction that, contrary to the previous belief that benzene-like N_6 was not a minimum on the N_6 potential energy hypersurface, this structure is a transition state connecting the two alternate N_6 equilibrating geometries, and corresponds to a very shallow minimum on the potential energy surface ⟨83JA1760, 89JST(59)591⟩.

Huber *et al.*, using *ab initio* SCF calculations both by FOGO (floating orbital geometry optimization) and LCAO–MO methods, have shown that the postulated N_6 molecule should spontaneously decay into $3N_2$, although the possibility of stabilization by solvation cannot be ruled out, and that open-chain N_6 in C_2 symmetry is more stable than cyclic N_6 in D_6h symmetry by 100 kJ mol^{-1} ⟨82AG(E)64, 83JST(14)351⟩.

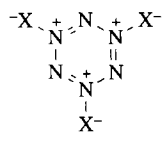
Theoretical studies of hexazine have also been carried out by Simkin *et al.* (⟨93AHC(56)303⟩ and references therein). These workers have predicted that hexazine should possess an even greater aromaticity than benzene. The ring current index indicates a value of 1.792 for hexazine, and 1.751 for benzene. Dewar resonance energies (28.2, compared to 20.0 kcal mol^{-1} for benzene) ⟨88ZOR24⟩ and quantum mechanical resonance energies (102.5 for hexazine, 85.2 for benzene) ⟨88IC2219⟩ also indicate a greater level of aromaticity for hexazine.

The instability of hexazine relative to benzene is associated with the specificity of its σ-electronic system, with the absence of the stabilizing effect of the C—H bonds which usually characterizes aromatic hydrocarbons ⟨88ZOR24⟩.

The ΔH_{diss} of hexazine has been calculated to be -213.2 kcal mol^{-1}, for benzene it is 153 ⟨89JA4178⟩. Also, relative to benzene, the π and σ components of hexazine contribute about 80% and 50–60% respectively to the stability ⟨87JA3234⟩.

Electronic structure calculations for 1,4-dihydrohexazine indicate a contraction of bonds in the six-membered ring upon consecutive replacement of CH by N, accompanied by increasing deviation from planarity, and decreasing π-electron conjugation ⟨85JCS(P2)1633⟩.

The main reason for the destabilization of the N—N bonds in polyazines is the presence, on each side of these bonds, of both geminal and vicinal sp^2 lone pairs of electrons. MNDO calculations have shown that the destabilization of hexazine is substantially reduced in structures of type (**16**) ⟨87IZV1675, 88KGS250, 88ZOR2486⟩.



(16)

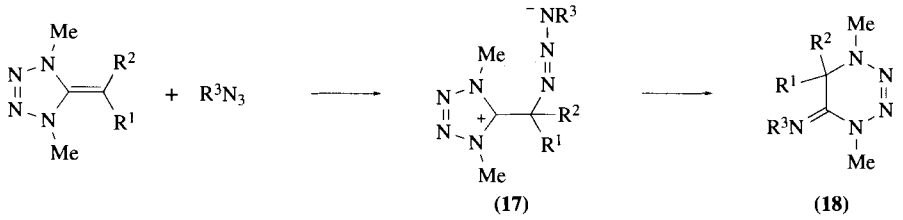
X = O, NH, CH_2

Two classes of acceptor substituents have been studied for the possibility of stabilizing N_6: substituents with vacant σ-orbitals, but with no electron pairs capable of interacting with the π-system (i.e. H^+, Lewis acids), and substituents with both vacant σ-orbitals and potentially interacting π-systems (i.e. carbenes and nitrenes). The former class destabilize the N_6 ring, rendering the three separate monomers (e.g. HN_2^+) more stable; the latter stabilize the ring relative to the separate monomers ⟨88DOK(302)1384⟩.

The structure, potential barrier, heat of dissociation, and total effective atomic charges have been calculated for hexazine 1,3,5-trioxide (a N_2O trimer) using MINDO/3, MNDO, and AM1 methods. These calculations show that the trimer is 17-155 kcal mol^{-1} higher than for the three monomeric units, but that the structure is kinetically stable ⟨90DOK(313)118⟩.

6.22.3 SYNTHESIS

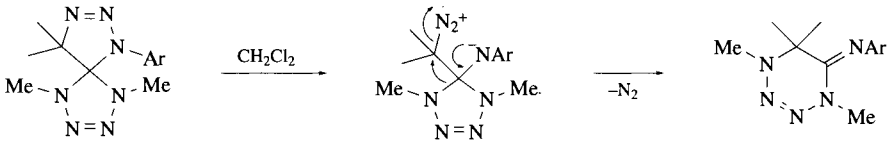
The tetrazines (**18**) are obtained when alkylidene–dihydrotetrazoles react with azides to give the zwitterions (**17**). These undergo intramolecular cyclization in chloroform to yield the iminotetrazines (Scheme 1).



(**17**) (**18**)

Scheme 1

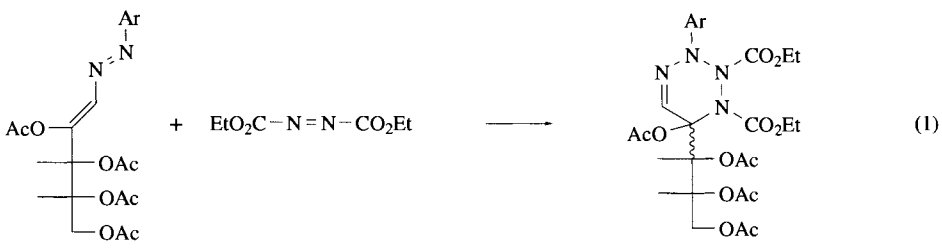
The formation of the tetrazine is interpreted in terms of an initial [3 + 2] cycloaddition leading to unstable spiro compounds. Ring opening of the dihydro-1,2,3-triazole ring generates the zwitterions (**17**) which lose molecular nitrogen with concomitant ring expansion of the dihydrotetrazole ring by a nitrogen 1,2-shift ⟨90AG(E)695, 91LA409⟩. In later studies of the same group, it was found that thermolysis of 1,2,3,4,6,7,8-heptaazaspiro[4,4]nona-2,7-dienes (**19**) gives, amongst other products, related iminotetrahydrotetrazines (**20**) via extrusion of molecular nitrogen from the triazole ring with concomitant 1,2-shift of nitrogen (Scheme 2) ⟨92CB2749⟩.



(**19**) (**20**)

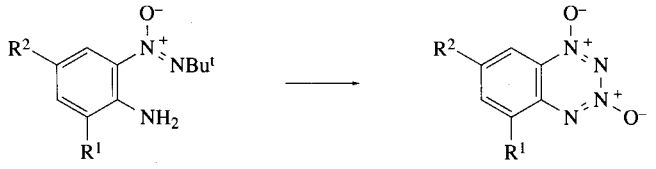
Scheme 2

(*E*,*E*)-1-Aryl-4-[(1′,2′,3′,4′-tetra-*O*-acetyl)-D-*arabino*-tetritol-1-yl]-1,2-diaza-1,3-butadienes (**21**) have been prepared. These undergo the Diels–Alder reaction with diethyl azodicarboxylate in anhydrous benzene at room temperature to yield the tetrazines (**22**) (Equation (1)). The diastereomeric ratio of (*S*) to (*R*) isomers at the 1′ position is 85 : 15 ⟨91TL2513⟩.



(**21**) Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4 (**22**) (1)

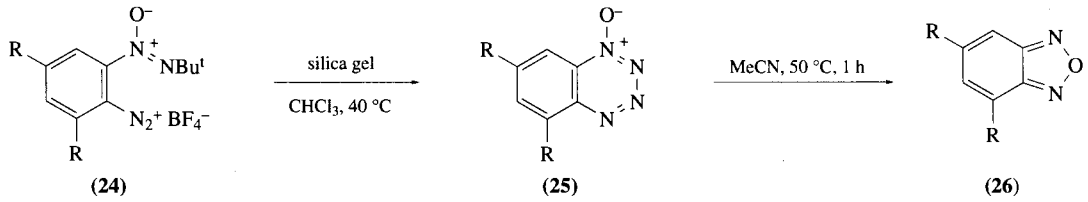
An example of a 1,2-fused benzotetrazine was reported in 1963, but without details of its chemistry ⟨63YZ373⟩. A pyrazolo[1,2-*a*]benzotetrazinone (**7**) was reported later ⟨85CC204⟩. The first example of the parent benzotetrazine ring system to be isolated was the 1,3-dioxide (**6**) ⟨90IZV718, 91MC101⟩. Treatment of the azoxy compound (**23**) with nitrosyl fluoroborate in acetonitrile, followed by *m*-chloroperoxybenzoic acid in pyridine, gives a 55–65% yield of the product (Equation (2)) ⟨90IZV718⟩. The use of dinitrogen pentoxide gives the same product. Nitration of the parent azoxy compound (**6**; $R^1 = R^2 = H$) using nitric acid in sulfuric acid yields a mixture of the nitro products ⟨91MC101⟩. Further substituted analogues of this system have been obtained, and their vibrational spectra studied ⟨94IZV1771, 95MC100⟩.



(2)

(**23**) (**6**)

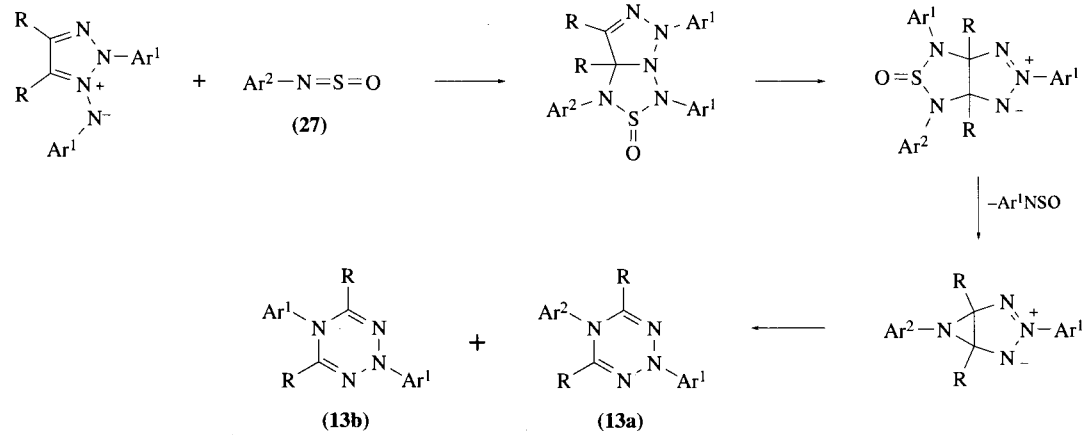
5,7-Dibromo-benzotetrazine 1-oxide (**25**; R = Br) has been isolated from the intramolecular cyclization of the dibromo-*o*-(t-butylazoxy)benzene diazonium tetrafluoroborate (**24**). The product was characterized by ^1H NMR spectroscopy and x-ray crystallography and by its thermal transformation into the benzofurazan (**26**; R = Br) (Scheme 3). The parent compound (**25**; R = H) was not obtained; the only product to be isolated was benzofurazan (**26**; R = H) ⟨94MC122⟩.



(**24**) (**25**) (**26**)

Scheme 3

• 2,5-Dihydro-1,2,3,5-tetrazines (**13**) have been obtained by 1,3-dipolar cycloadditions of *N*-sulfinylimines with substituted triazolium imides (**27**), followed by rearrangement and sulfinylimine elimination. When $Ar^1 \neq Ar^2$, both expected products (**13a**) and (**13b**) were produced (Scheme 4) ⟨88CC232, 90JCS(P1)2527⟩.



(**27**)

(**13b**) (**13a**)

R = Ph; Ar^1 = Ph, *p*-$O_2NC_6H_4$; Ar^2 = Ph, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$, 5-methylisoxazol-3-yl

Scheme 4

The reaction of phosgene with 1,1-dialkyl-2-arylazoguanidines (**28**) yields 6-dialkylamino-3-aryl-1,2,3,5-tetrazin-4-ones (**29**) (Equation (3)). These products decompose on heating at 120 °C to give nitrogen, dialkylcyanamides, and aryl isocyanates. The tetrazinones decompose in the same way

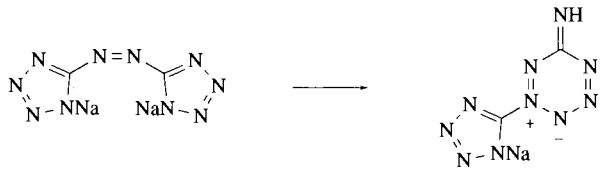
over one week in cold dichloromethane, on attempted protonation using trifluoroacetic acid, attempted alkylation with methyl trifluorosulfonate, and on attempted cycloalkylation with *N*-phenylmaleimide or with other reagents. The yields in this synthesis are variable and erratic, the best obtained being 43% ⟨85JCS(P1)415⟩. The tetrazinones are pale yellow solids which absorb in the range 1700–1712 cm^{-1}. The x-ray crystal analysis of the phenyl derivative indicates that the heterocyclic ring is slightly puckered into a boat conformation with the dimensions shown in Figure 3 ⟨82CC225⟩.

(3)

(28) (29)

R = Me; Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4; R = $(CH_2)_4$; Ar = 4-C_6H_4, 4-$MeOC_6H_4$
Conditions: $COCl_2$, toluene, excess pyridine, –70 °C

The sodium salt of the pentazine derivative (**31**) can be obtained by treatment of the azotetrazole salt (**30**) with acid. This reaction has also been used to make some ^{15}N analogues of (**31**) (Equation (4)). The mesoionic product is unstable and readily loses nitrogen in solution or decomposes, explosively, on heating ⟨93CHE395⟩.

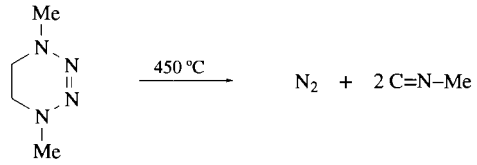


(4)

(30) (31)

6.22.4 REACTIONS

The pyrolysis of 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine (**15**) leads to loss of molecular nitrogen and formation of the imine (**32**) ⟨86T2511⟩.



(5)

(15) (32)

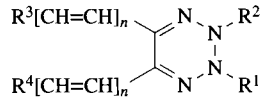
The 1,2,3,5-tetrazin-4-ones (**29**) decompose at about 120 °C to give nitrogen, dimethylcyanamide and aryl isocyanates ⟨85JCS(P1)415⟩. The thermal (sometimes spontaneous) decomposition of many of the compounds whose preparations are described in the previous section (6.22.3) has already been mentioned.

At the time of writing these are the only reactions of simple tetrazines to have been reported since the publication of CHEC-I.

6.22.5 APPLICATIONS

References to 2,3-dihydro-1,2,3,4-tetrazines appeared quite frequently in the early literature ⟨84CHEC-I(3)531⟩ and all were subsequently shown to be incorrect. However, patent from 1990 reports that the tetrazine derivatives (**33**) show photoreceptor activity with good electrophotographic

properties ⟨90JAP(K)207062⟩. A critical reinvestigation of these photoreceptors may also show the suggested structures to be in error.



(33)

$R^1 = R^2$ = Ar, aralkyl; R^3, R^4 = Ar, heterocyclic; n = 0, 1

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6.23
Other Six-membered Rings with Four or Five Nitrogen, Oxygen, or Sulfur Atoms

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Kingston University, UK

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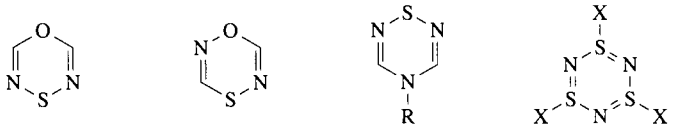
6.23.1 INTRODUCTION

The ring systems covered in this chapter appeared in two chapters in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(3)943, 84CHEC-I(3)1039⟩. The most common

systems were reported to be 1,4,3,5-oxathiadiazine (**1**), 1,4,2,5-dioxadiazine (**2**), and 1,2,4,6-thiatriazine (**3**). The 1,3,5,2,4,6-trithiatriazine system (**4**) is also very common and is extensively covered in inorganic literature. Other systems were reported to be rare. In a few cases there were only single examples cited, whilst others were unknown, although in several cases MO calculations had been reported for them. However, there were relatively few references to such compounds. These chapters did, none the less, summarize the information available at that time on syntheses of a number of oxatriazines, thiatriazines, dithiatriazines, oxathiatriazines, dithiadiazines, trithiadiazines, dioxadiazines, oxathiadiazines, tetraoxanes, dioxadithianes, and tetrathianes. Also covered were the reactions of several of these systems, including ring contraction of thiatriazines, alkylation of dithiatriazines, retro [4 + 2] cycloaddition and photolysis of oxathiadiazines, ring contraction and desulfurization of dithiadiazines, and thermal fragmentation of dioxadithiazines.

Since 1984 there has been continuing interest in many of these compounds, particularly in the *N,S* ring systems.

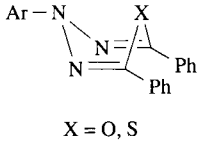


(1) (2) (3) (4)

6.23.2 THEORETICAL, EXPERIMENTAL STRUCTURAL METHODS, AND THERMODYNAMICS

6.23.2.1 Oxa- and Thiatriazines

The 1,3,4,5-oxa- and 1,3,4,5-thiatriazine ring systems (and also the 1,2,3,5-tetrazines) are 8π six-atom rings and thus do not obey the Hückel 6π electron rule for aromaticity. Both ring systems adopt a boat-shaped conformation with the substituents on the N-4 atom taking up equatorial positions (Figure 1).



X = O, S

Figure 1 Conformation of 1,3,4,5-oxa- and -thiatriazines.

The bond lengths for the tetrazines are given as N^1—N^2 1.39 Å; N^3—C^4 1.28 Å; C^4—N^5 1.43 Å. These values are similar to those for the comparable bonds in the oxatriazines and thiatriazines. When compared with the values for single and double N—N, C—N, and C—C bonds, this suggests conjugation in the ring half-plane ⟨88CC232⟩. In the case of the thiatriazines the CSC bond angle is 93.4° (similar to that in thiophene), and the C—S bond length is 1.783 Å, which is longer than the normal C(sp^2)—S(divalent) bond length of 1.751 Å, and shorter than the single C—S bond length of 1.82 Å, such as that in dimethyl sulfide, which also suggests the presence of conjugation.

These rings may thus be considered as two isolated hydrazide, or thiohydrazine units, with the 1-*O*/*S* and 4-*N* atoms common. This necessitates the boat structure as there would be a severe loss of planarity in the thiohydrazine units if a chair conformation were adopted.

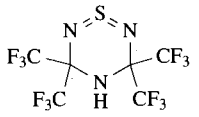
The crystal structure of the oxatriazine is *ortho*-rhombic of the space group P_{nma}, and for the thiatriazine it is monoclinic of space group $P2_1/a^a$.

The ^{13}C NMR chemical shift for C-2 in these compounds is 146 ppm, which is where aromatic Cs are to be expected ⟨87CC1090, 89JCS(P1)371, 90JCS(P1)2527⟩.

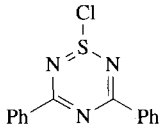
The 1,2,4,6-thiatriazine-3,3,5,5-tetrakis(trifluoromethyl)-4*H*-1λ^4,2,4,6-thiatriazine (**5**) has a planar ring, to within 0.016 Å, and the *N*-4 bonding is also planar, within experimental error. The average values for the C—NH and C—NS bond lengths correspond to single bonds and the S—N lengths (1.517 Å) are close to that expected for S^{IV}=*N*. The *N*-4 stereochemistry is unusual since it is planar but is not engaged in π-bonding, and the C—NH—C angle is very wide (128.3°), probably due to a

crowding effect. The IR and mass spectra are consistent with expected data ⟨86C99⟩. Compounds such as 1-chloro-3,5-diphenyl-1,2,4,6-thiatriazine (**6**) are also planar, and this, on dechlorination, yields the 3,5-diphenyl-1,2,4,6-thiatriazinyl radical. In the solid state this forms a cofacial dimer having a dihedral angle of 14° between the respective mean planes of the rings, the closest distance between the two S atoms being 2.666 Å ⟨84CC1021, 85JA1346⟩. A similar situation exists in the case of the selenium analogue ⟨87JA7745⟩.

The crystal structure of the thiatriazinyl radical dimer is triclinic, space group P1 ⟨85JA1346⟩.



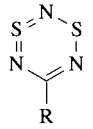
(5)



(6)

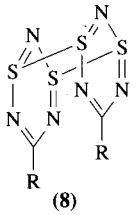
6.23.2.2 Dithiatriazines

The 1,3,2,4,6-dithiatriazines (**7**) are also formally 8π electron systems, and are thus antiaromatic. The formation of the dimer on reducing the dichloro compounds is attributed to the coupling of the triplet states of (**7**) to achieve a singlet ground state ⟨85JA7710, 92IC1417⟩.



(7)

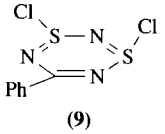
Ab initio calculations indicate that the ground state of (**7**; R = H) is a distorted singlet species with C_s symmetry. The properties of the simple 5-substituted derivatives of (**7**) indicate that, in the solid state, they do not exist as monomers but as cofacial dimers (**8**) ⟨85CC929, 86AX(C)508, 87CC63, 88CJC2279⟩.



(8)

Attempts have been made to carry out structural calculations of the ring system ⟨85JST(133)1⟩, and another report stated that single ground-state determinants could not be obtained for the planar 1,3,2,4,6-dithiatriazine ring system ⟨86IC2119⟩.

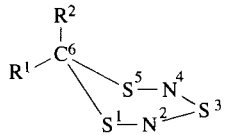
In the case of 1,3-dichloro-5-phenyl-1λ^4,3λ^4,2,4,6-dithiatriazine (**9**) the heterocyclic ring has been shown to have a planar SNCNS part (within 0.06 Å) with the third *N* displaced from this by 0.336 Å on the opposite side to the chlorine atoms. The crystal structure is triclinic, space group P1 ⟨85AX(C)1835⟩.



(9)

6.23.2.3 Trithiadiazines

The 1,3$\lambda^4\delta^2$,5,2,4-trithiadiazines (**10**) have a ring system which is almost planar, but which has a slightly puckered envelope conformation, the details of which are shown in Figure 2 ⟨87CC1546⟩. The structure is similar to that of tetrasulfur dinitride. The C-6 aryl substituent is equatorial, and virtually orthogonal (88°) to the trithiazadiazine ring, thus minimizing steric interaction ⟨83JA1186⟩.



(**10**)

Bond lengths (nm) $R^1 = R^2 = H$		Bond angles	
S^1–N^2	16.71(3)	C^6–S^1–N^2	104.8(2)
N^2–S^3	15.49(3)	S^1–N^2–S^3	125.6(2)
S^3–N^4	15.60(3)	N^2–S^3–N^4	120.8(2)
N^4–S^5	16.68(3)	S^3–N^4–S^5	125.7(2)
S^5–C^6	17.96(4)	N^4–S^5–C^6	1.4.5(2)
C^6–S^1	17.98(4)	S^5–C^6–S^1	116.8(2)

Figure 2 Structural details of compound (**10**).

For the S-1 oxide of (**10**) the *S*=*O* bond is in an equatorial orientation, and the bond lengths, and bond angles, are similar to the parent system. The main structural differences are a slight contraction of the ring angles at C and at the oxidized S and an expansion at the adjacent N ⟨87CC1546⟩.

6.23.2.4 Dithiadiazines

The crystallographic data for 3,5-diphenyl-1,4,2,6-dithiadiazine (**11**) ⟨84CC57⟩ is shown in Figure 3, together with those for the two authentic derivatives of the 1,3,2,4-dithiadiazine system so far obtained, namely the 1,3$\lambda^4\delta^2$,2,4-benzodithiadiazine (**12**) ⟨83CC73, 86IC1137⟩, and the perfluorinated compound ⟨92POL1137⟩.

The compound (**11**) has a heterocyclic ring which is not planar but which adopts a boat conformation. It has an "open book" conformation with the atoms in the two halves of the molecule coplanar within 0.1 Å. The dihedral angle between the two halves is 128.6°.

The benzo parent compound (**12a**) is essentially planar but in the case of the perfluorinated benzothiadiazine (**12b**) the carbocyclic ring is planar but the heterocyclic ring is not. The atoms *S*-1, and *N*-2 deviate considerably from the plane (0.132 Å and 0.165 Å, respectively). As a result the heterocycle is twisted along the S(1)–N(2) line by 5.5°. Neither the spectral nor the structural data show any indication of possible antiaromaticity ⟨86IC1137⟩.

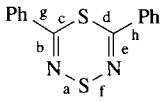
The crystal structure for the fluoro compound is monoclinic, space group $P2_1/n$, and for the parent it is monoclinic, space group *Pc*. The molecule has been best described as "two weakly coupled subunits, i.e. a benzene nucleus, and an NSNS fragment" ⟨86IC1137⟩.

6.23.2.6 Oxathiadiazines

The crystal structure of the 1,2,3,5-oxathiadiazine 2,2-dioxide (**13**) has been reported to be triclinic with the space group P1 with $z = 2$ ⟨91JOU759⟩.

6.23.2.5 Trioxazines

The trioxazinanes (**14**) adopt a chair conformation with the N—Me axial. The bond lengths are normal for aliphatic single bonds, and bond angles unremarkable ⟨89JA6884⟩.

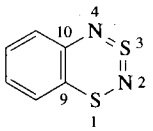


Triclinic, a = 3.951(1), b = 12.527(6), c = 12.950(5) Å

α = 77.29(4), β = 82.61(3), γ = 85.37(3)°, V = 619 Å^3

Z = 2, M = 270.4, D_c = 1.46 g cm^{-3}, Space group $P\bar{1}$

Bond lengths (Å): a 1.668(3), b 1.274(4), c 1.792(3), d 1.798(3), e 1.274(4), f 1.664(2), g 1.477(4), h 1.478(3)

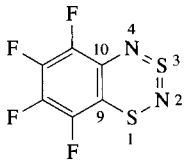


Monoclinic, a = 5.616(1), b = 3.8961 (1), c = 15.434(3) Å

β = 102.23(2)°, V = 330(1) Å^3, D_c = 1.69 g cm^{-3}, Space group Pc

Bond lengths (Å): *S*1–*N*2 1.693(3), *S*1–*C* 1.796(4), *S*3–*N*2 1.547(4), *S*3–*N*4 1.544(4), *N*4–*C* 1.423(5), *C*9–*C*10 1.394(5)

Bond angles (°): *N*2–*S*1–*C*9 105.8(2), *N*4–*S*3–*N*2 119.9(2), *S*1–*N*2–*S*3 122.7(2), *S*3–*N*4–C10 122.5(3), *S*1–*C*9–*C*10 124.3(3), *N*4–*C*10–*C*9 124.6(3)



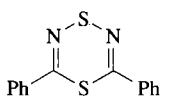
Monoclinic, a = 10.987(3), b = 5.832(2), c = 12.285(3) Å

β = 99.39(2)°, V = 776.6(4) Å^3, Z = 4, D_c = 2.05 g cm^{-3}, Space group $P\,2_1/n$

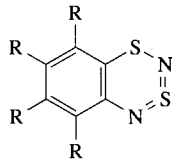
Bond lengths (Å): *S*1–*N*2 1.651(4), *N*2–*S*3 1.553(4), *S*3–*N*4 1.513(3), *N*4–*C*10 1.432(4), *C*9–*C*10 1.400(5), *C*9–*S*1 1.781(5)

Bond angles (°): *C*9–*S*1–*N*2 104.8(2), *S*1–*N*2–*S*3 125.1(2), *N*2–*S*3–*N*4 118.9(2), *S*3–*N*4–*C*10 121.7(2), *N*4–*C*10–*C*9 125.1(3), *C*10–*C*9–S1 124.1(3)

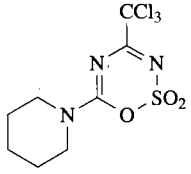
Figure 3 Crystallographic data for dithiadiazine.



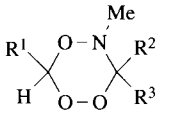
(11)



(12a) R = H
(12b) R = F



(13)



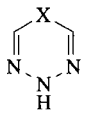
(14) Rs = various alkyl, aryl, H

No unusual spectral, or other properties, have been reported for these ring systems.

6.23.3 REACTIVITY OF RINGS AND RING SUBSTITUENTS

6.23.3.1 Oxatriazines

The 1,3,4,5-oxatriazines (**15**; X = O) are crystalline solids which are remarkably stable towards acids such as acetic acid and TFA, and to oxidizing agents such as Pb^{IV}. They do not react with 4π-systems such as 2,3-dimethylbutadiene or benzonitrile *N*-*p*-nitrophenylimide. However, they are susceptible to nucleophilic attack at C-2 by aniline, giving benzanilide, and by sodium hydroxide, giving sodium benzoate, the only other products being uncharacterized gums ⟨90JCS(P1)2527⟩.



(15)
X = O, S

1,3,4,5-Oxatriazines have been rarely reported, although an x-ray crystal structure of the only example quoted in CHEC-I has been recorded ⟨80AJC2447⟩.

6.23.3.2 Thiatriazines

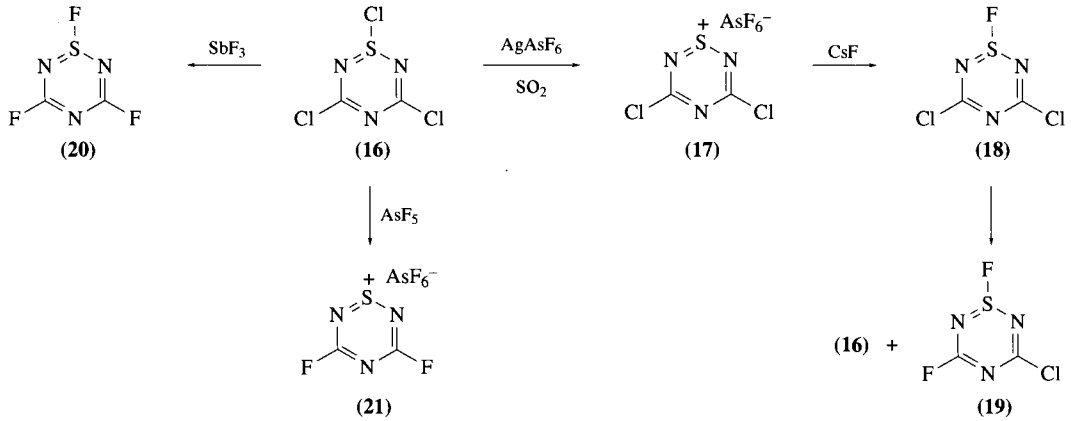
The notable feature of the 1,3,4,5-thiatriazines (**15**; X = S) is their ready desulfurization with ring contraction, to yield 1,2,3-triazoles. Even chromatography on alumina is sufficient to cause desulfurization, but MCPBA is more effective ⟨90JCS(P1)2527⟩.

The 1,2,4,6-thiatriazine ring system is very common and has been known since 1962 ⟨62CB147⟩. Reports in CHEC-I include an x-ray crystal structure for some derivatives of the system which show it to be nonplanar with the sulfur atom as a distorted trigonal bipyramid ⟨79AX(B)860, 80JOC1662⟩ and reports of the nucleophilic displacement of halogens ⟨75ZC19, 76CB2107, 80JOU1303⟩.

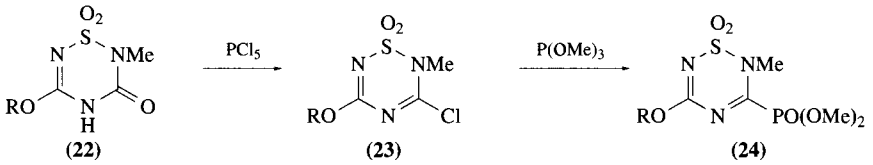
1-Chloro-1,2,4,6-thiatriazines (**16**) readily form the thiatriazinyl radical, for example, on treatment with triphenylantimony. These radicals associate in the solid state to form cofacial dimers ⟨80JOU1303, 85JA1346⟩. Persistent thiatriazinyl radicals have also been produced by treating chlorothiatriazines with sodium or with triphenylverdazyl ⟨83SUL143⟩.

1,3,5-Trichloro-1λ^4,2,4,6-thiatriazine (**16**) reacts with $AgAsF_6$ in liquid sulfur dioxide to give the salt (**17**) in quantitative yield. This reacts with CsF to give 3,5-dichloro-1-fluoro-1λ^4,2,4,6-thiatriazine (**18**), which slowly dismutates at room temperature to give a mixture of products including (**16**) and 5-chloro-1,3-difluoro-1λ^4,2,4,6-thiatriazine (**19**). Fluorination of (**16**) using SbF_3 gives the 1,3,5-trifluoro product (**20**), whilst the use of AsF_5 gives the salt (**21**). This product yields the corresponding chloro and bromo compounds when treated with NOCl or NOBr (Scheme 1) ⟨91CB1347⟩.

2*H*-1,2,4,6-Thiatriazin-3(4*H*)-one 1,1-dioxides (**22**) can be converted into the corresponding 3-chloro compounds (**23**) by phosphorus pentachloride. These products react with a variety of nucleophilic reagents to yield a range of substituted thiatriazinone dioxides. The 3-chloro compounds undergo an Arbusov-type reaction with trimethyl phosphite to yield (**24**) which are reported to be active herbicides (Scheme 2) ⟨85MIP8505105, 88LA317⟩.



Scheme 1



Scheme 2

6.23.3.3 Dioxa- and oxathiatriazines

MO Calculations on dioxatriazines were reported in CHEC-I ⟨72MI 623-01⟩ but there were no reports of either synthesis or reactions of the system.

There have been no further references to reactions of dioxa- or oxathiatriazines since 1984.

6.23.3.4 Dithiatriazines

The main reactions of the dithiatriazine system are those of dithiatriazinyl radical dimerization, and reactions of S-chlorine atoms.

Dechlorination of 1,3-dichloro-5-trifluoromethyl-1,3,2,4,6-dithiatriazine (**25**; R = CF_3) using zinc in liquid sulfur dioxide yields 5-trifluoromethyl-1,3,2,4,6-dithiatriazinyl dimer, or trifluoromethyldithiazolyl dimer, depending on the reaction conditions ⟨84ZN(B)1389⟩. Reduction of (**25**; R = Ph) with triphenylstibine also gives the dithiatriazine (as its dimer). These dimers are readily reconverted to the dichloro compounds from which they are prepared on treatment with chlorine ⟨85CC929, 87CC63⟩.

Thermolysis of (**25**; R = CCl_3, Bu^t, NMe_2, NEt_2, NPr^i_2) gives high yields of 1,2,3,5-dithiazolium chlorides (**26**) ⟨89CC96⟩.

Reaction of the dihalides (**25**) with Lewis acids such as BCl_3, $SbCl_5$, $SnCl_4$, gives salts of the monocations (**27**) ⟨86IC2119⟩.

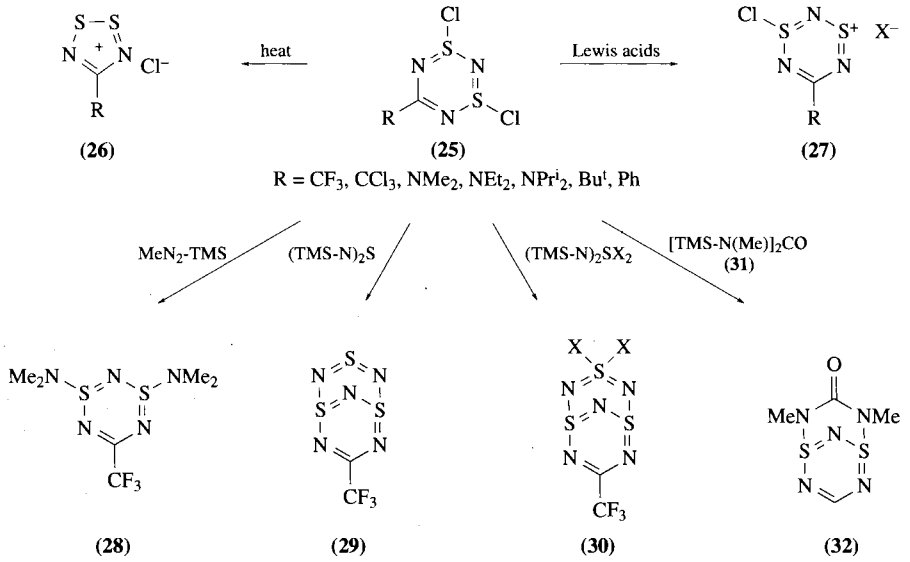
Compound (**25**; R = CF_3) reacts with dimethyl(trimethylsilyl)amine to yield (**28**). The use of N,N^1-bistrimethylsilylated sulfur diimides ($(TMS\text{-}N)_2S$ and $(TMS\text{-}N)_2SX_2$; X = Et or $X_2 = (CH_2)_4$) gives (**29**) and (**30**), whilst the urea derivative (**31**) yields (**32**) (Scheme 3) ⟨88CB1881⟩.

The reactions of the non-*S*-chlorinated 1,3,2,4,6-dithiatriazines are, in fact, reactions of the dimers. These undergo addition reactions with alkenes to give adducts ⟨85CC929, 85MCLC447, 86IC47, 86IC2119, 91CB39⟩.

Similar adducts have been obtained from 1,3,5,2,4,6-trithiatriazinium tetrachloroaluminate and norbornene ⟨91IC1392⟩.

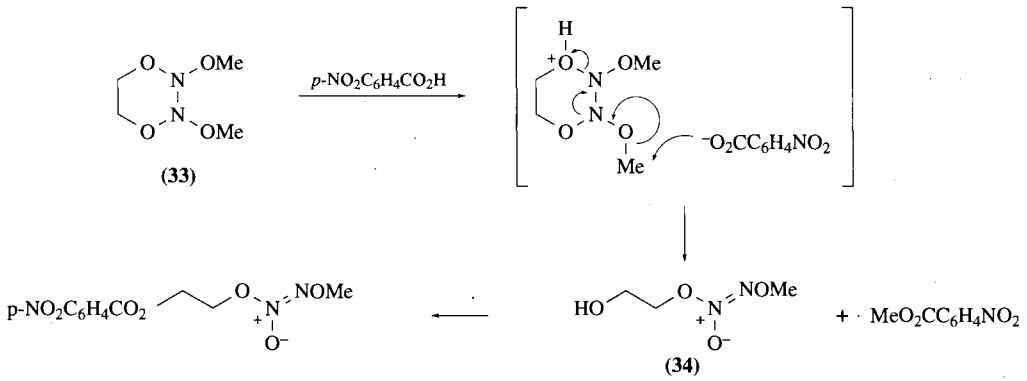
6.23.3.5 Dioxadiazines

2,3-Dimethoxy-1,4,2,3-dioxadiazinane (**33**) has been obtained as a mixture of *cis* and *trans* isomers. The compound is not very stable and decomposes on heating in toluene for a short time,



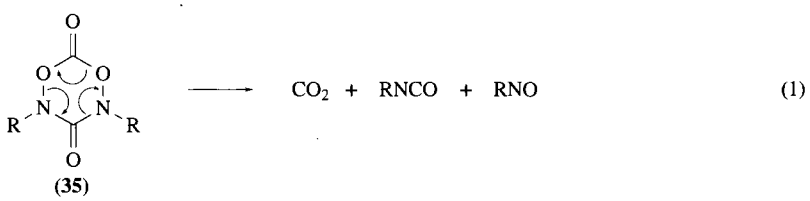
Scheme 3

on dissolving in methanol, or when subjected to chromatography, either on alumina, or on silica gel. It reacts with 4-nitrobenzoic acid to give (*E*)-(2-hydroxyethyloxy)methoxydiazene oxide (**34**) and methyl 4-nitrobenzoate via a regio- and stereospecific reaction proceeding by a synchronous mechanism (Scheme 4) ⟨92MC50⟩.



Scheme 4

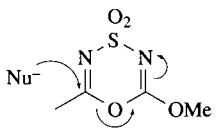
The 1,5,2,4-dioxazadiazinedione system (**35**) has been prepared. However, these compounds decompose very readily. Thermal decomposition leads to carbon dioxide loss with the formation of isocyanates and nitrosoalkanes (Equation (1)). The compounds are stable to water, but are attacked by organic soluble nucleophiles, and reagents such as phenylmagnesium bromide, to yield products which arise from attack of the nucleophile at the carbonate carbonyl, followed by fragmentation (Equation (1)). Catalytic reduction of (**35**) leads to ureas ⟨86JOC3355⟩.



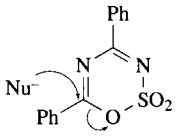
(1)

6.23.3.6 Oxathiadiazines

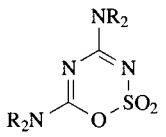
1,4,3,5- (**36**) and 1,2,3,5-Oxathiadiazines (**37**) undergo ring opening by nucleophilic attack at the sp^2 carbon atom ⟨73TL2783, 77ZC222⟩, whilst the photolysis of 4,6-diphenyl-1,2,3,5-oxathiadiazine 2,2-dioxide (**38**) in the presence of ethanol leads to a quinazolone ⟨79JOC4435⟩. These reactions were reported in CHEC-I, but there seem to have been no further references to these ring systems.



(**36**)



(**37**)



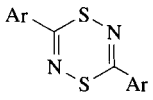
(**38**)

6.23.3.7 Dithiadiazines

3,5-Diphenyl-1,4,2,6-dithiadiazine (**39**) has been prepared and is reported to be quite stable thermally. It decomposes only slowly in boiling decalin, giving the thiadiazole (**40**) (10% after 6 h), but it readily decomposes on photolysis (Equation (2)) ⟨84CC57⟩. 3-Aryl-6-(disubstituted)amino-1,4,2,5-dithiadiazines (**41**) gradually decompose to give colorless oils when allowed to stand in air at room temperature. On melting the decomposition is rapid. In this case also sulfur is extruded to yield the thiadiazole (**42**) (Equation (3)). The 3,6-diaryl-1,4,2,5-dithiadiazines (**43**) are very much more stable under similar conditions ⟨84CC1386, 89BCJ2407⟩.

(**39**) (**40**) (2)

(**41**) (**42**) (3)



(**43**)

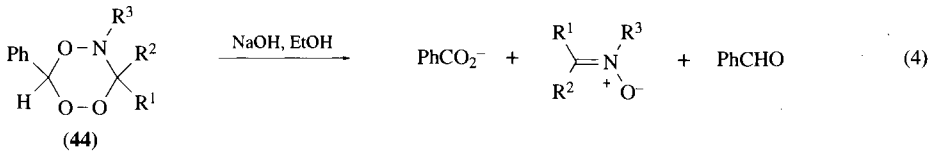
6.23.3.8 Trithiazines

There have been no reports of reactions of trithiazines nor were there any references to them in CHEC-I.

6.23.3.9 Trioxazines

The 1,2,4,5-trioxazinane ring system (**44**) has been synthesized. The only reactions which are reported for this system are ring-opening processes. Thermolysis results in fragmentation to yield

aldehydes and oximes, whilst the action of ethanolic sodium ethoxide gives benzoates, nitrones, and aldehydes (Equation (4)) ⟨89JA6884⟩.

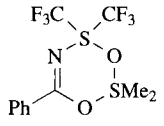


(44)

(4)

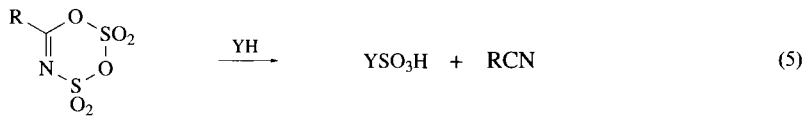
6.23.3.10 Dioxathiazines and dioxadithiazines

The thermal fragmentation of 2,2-dimethyl-4,4-*bis*(trifluoromethyl)-6-phenyl-1,3,2,4,5-dioxadithiazine (**45**) yields DMSO, benzonitrile and *bis*(trifluromethyl) sulfoxide ⟨78JA985⟩.



(45)

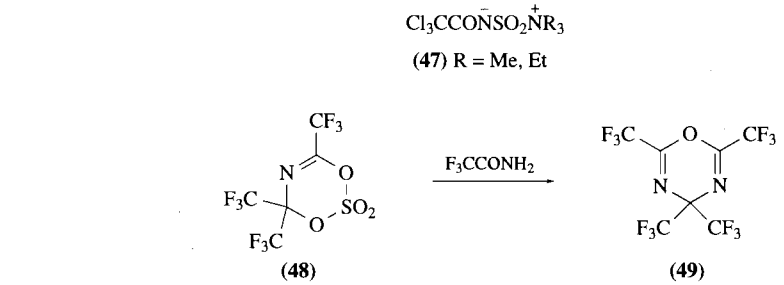
1,3,2,4,5-Dioxadithiazine 2,2,4,4-tetraoxides (**46**), in the presence of base, react with alkenes to yield other heterocyclic systems via sulfonylimidates. Thus (**46**), with alkenes, yield both 1,2-thiazetidine 1,1-dioxides and/or 1,4,5-oxathiazine 4,4-dioxides. With nitriles 1,4,3,5-oxathiadiazine-4,4-dioxides are formed ⟨75JOU2247, 75JOU2512, 83DOK1399⟩, and cyanamides, under the same conditions, yield 1,2,3,5-oxathiadiazine 2,2-dioxides ⟨85TL5689, 86JOU63, 88JOU1783, 91JOU759⟩. The ring opening of (**46**) with reagents having an active hydrogen, YH, depends on the nature of the substituent R on (**46**). When R is strongly electron-withdrawing, the ring opens with retention of the C—O bond. When R is weakly electron-withdrawing, the products are nitriles (Equation (5)) ⟨84JOU1872⟩.



(46)

(5)

The action of trialkylamines on 1,3,2,4,5-dioxadithiazines (**46**) at −40 °C in dichloromethane gives amidosulfonylammonium compounds (**47**) in quantitative yield ⟨88JOU602⟩, whilst the 1,3,2,5-dioxathiazine (**48**) reacts with trifluoroacetamide to yield the oxadiazine (**49**) (Equation (6)) ⟨89JOU578⟩.



(47) R = Me, Et

(48) (49)

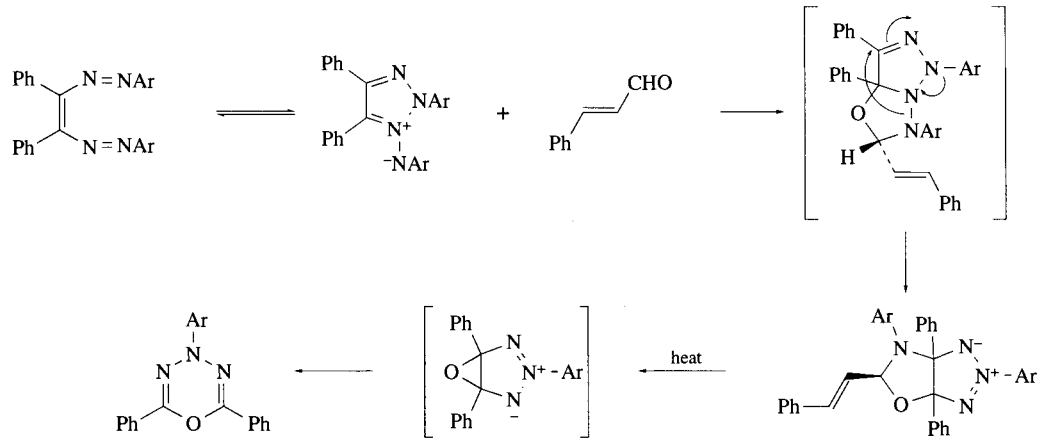
(6)

6.23.4 RING SYNTHESES

6.23.4.1 Oxatriazines

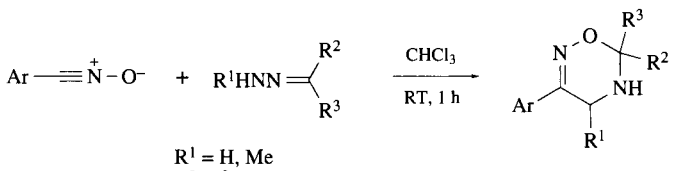
Oxatriazine systems seem to have been little studied. A synthesis of the 2*H*-1,3,4,5-oxatriazine system was first reported in 1980 ⟨80AJC2447⟩. 1,3,4,5-Oxatriazines have been obtained by the

reaction of 1,2,3-triazolium-1-imides with (*E*)-cinnamaldehyde via tandem cycloaddition and sigmatropic rearrangement. The use of methyl cyanodithioformate and aryl *N*-sulfinylamines in such reactions leads to 1,2,3,5-thiatriazines and 1,2,3,5-tetrazines, respectively. Each of these systems has an 8π six-atom ring (Scheme 5) ⟨87CC1090, 89JCS(P1)371, 90JCS(P1)2527⟩.



Scheme 5

The 1,2,4,5-oxatriazine system has been synthesized conveniently by reacting nitrile oxides, prepared *in situ* from the corresponding hydroxamoyl chloride and triethylamine in chloroform at 0 °C, with hydrazones ⟨87H(26)2199, 91CHE216⟩. The reaction involves a "6-*endo-trig*" cyclization of the initially formed (*Z*)-hydrazidoxime, and gives the products, usually as fairly stable crystalline solids, in 45–65% yield (Equation (7)).



R^1 = H, Me
R^2, R^3 = $(CH_2)_5$; Me_2CH, H; Ph, H; Ar

(7)

6.23.4.2 Thiatriazines

Of the thiatriazines, the 1,2,4,6-system has been the most studied. There has been particular interest in *N*-alkyl-1,2,4,6-thiatriazine 1,1-dioxides because of their herbicidal, fungicidal, and histamine H_2-antagonist activity ⟨86TL123, 87S170⟩.

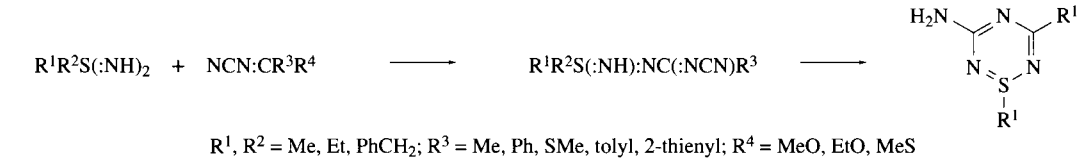
The preparation of 1-chloro-1,2,4,6-thiatriazines (**51**) by reaction of imidoylamidines (**50**) with excess of sulfur dichloride was reported in 1980 ⟨80JOU1303⟩.

(**50**) (**51**)

(8)

A convenient and versatile reaction leading to aryl derivatives of these compounds involves heating an arylamidine with $S_3N_3Cl_3$ in refluxing acetonitrile ⟨85JA1346⟩. An older reaction which leads to 1,2,4,6-thiatriazines is that of *N*-halo-amidines with thiolates, or with *N*-sulfenylamidines.

This reaction provides a wide range of 1-, 3-, and 5-substituted products ⟨54CB1079, 62CB147⟩. A newer synthesis of $1\lambda^4$,2,4,6-thiatriazines is that shown in Scheme 6 ⟨88CB386⟩.

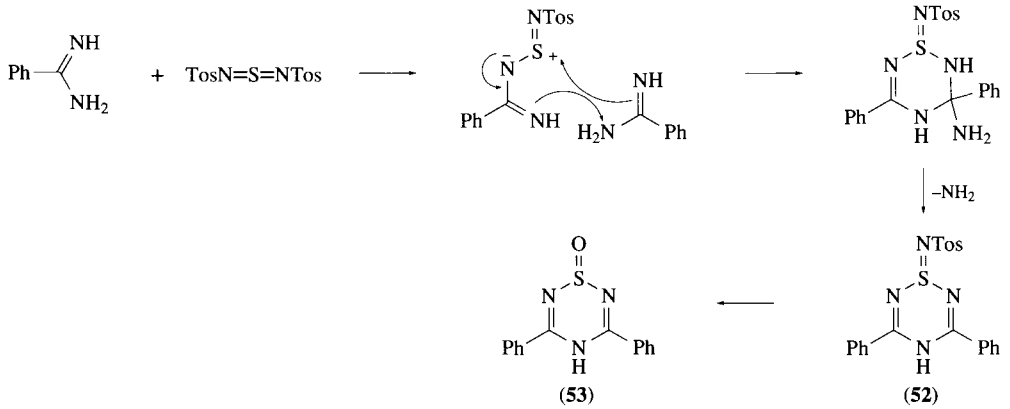


R^1, R^2 = Me, Et, $PhCH_2$; R^3 = Me, Ph, SMe, tolyl, 2-thienyl; R^4 = MeO, EtO, MeS

Scheme 6

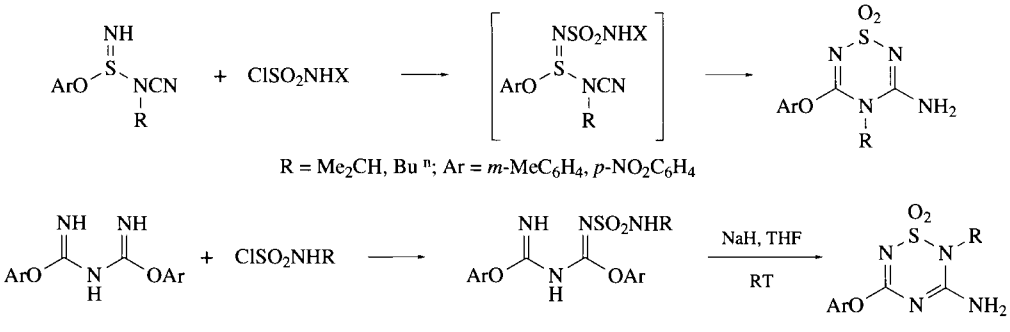
The reaction of sodium dicyanamide and thionyl chloride to give the fully chlorinated 1,3,5-trichloro-1,2,4,6-thiatriazine (**16**) is another example of the synthesis of this ring system ⟨74ZC471, 75ZC19, 76ZC358⟩.

The reaction of benzamidine with bis(*p*-toluenesulfonyl)sulfur diimide and bis(phthalimido) sulfide gives, amongst other products, 3,5-diphenyl-1-(*p*-toluenesulfonylimino)-1,2,4,6-thiatriazine (**52**), and its hydrolysis product (**53**) (Scheme 7) ⟨90JCS(P1)2495⟩.



Scheme 7

The interest in the biological activity of certain 1,2,4,6-thiatriazine 1,1-dioxides has led to the development of synthetic routes to a variety of 2-alkyl-, 2,4-dialkyl- and 4*H*-derivatives (Scheme 8) ⟨85TL1101, 85TL1105, 85TL4149, 86TL123, 87S170⟩.



R = Me_2CH, Bu^n; Ar = *m*-MeC_6H_4, *p*-$NO_2C_6H_4$

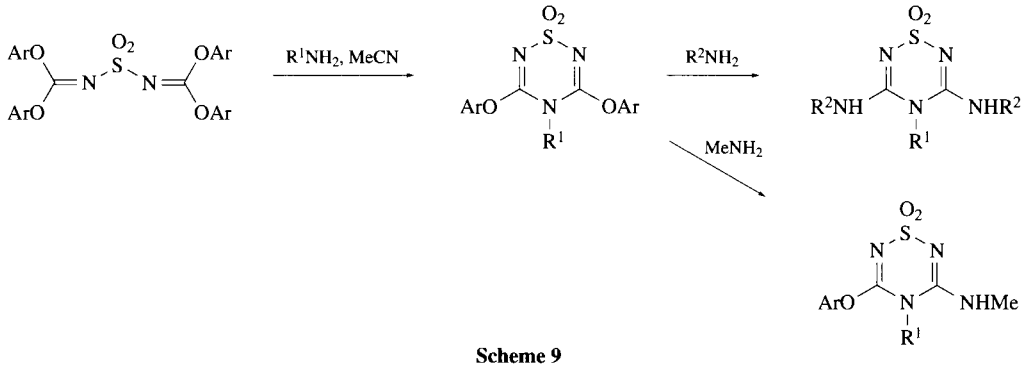
R = Me, Me_2CH, Bu^n, cyclohexyl; Ar = *m*-MeC_6H_4

Scheme 8

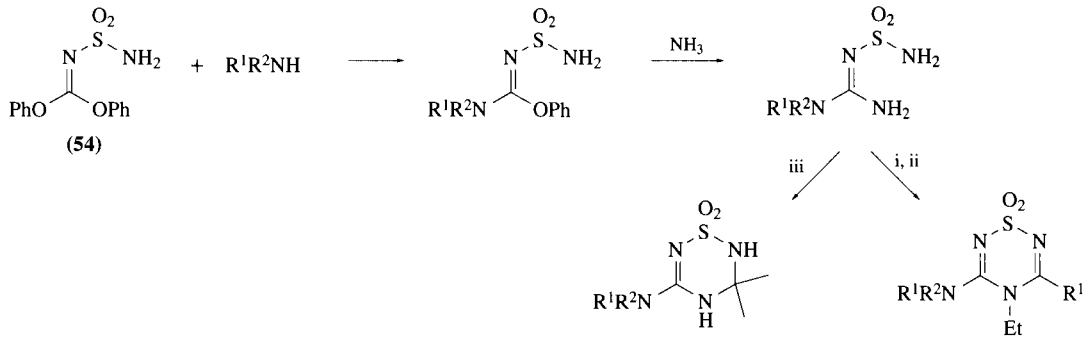
A simple, efficient synthesis of 4-substituted 1,2,4,6-thiatriazine 1,1-dioxides involves reacting *O*,O^1-diaryl carbonimidates with thionyl chloride and triethylamine to give sulfoxides which are oxidized with MCPBA. The resulting sulfamides are then reacted with primary amines to give the required products (Scheme 9) ⟨87S170⟩.

Diphenyl *N*-sulfamoylcarbonimidate (**54**) is a useful reagent for the synthesis of heterocyclic *S*-oxides, including 1,2,4,6-thiatriazine 1,1-dioxides (Scheme 10) ⟨91S753⟩.

The reaction of lithium bis(trifluoromethyl)carbonimidate with $S_3N_3Cl_3$ in boiling carbon tetra-



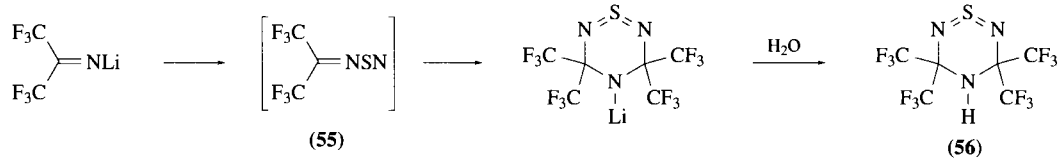
Scheme 9



i, $HC(OEt)_3$, Ac_2O, DMF, heat, 6–10 h; ii, $Me(OEt)_3$, TsOH, heat, 4–10 h; iii, Me_2CO, TsOH, heat, 20 h

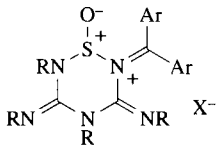
Scheme 10

chloride initially gives (**55**) which, with excess of the imidate, subsequently yields 3,3,5,5-tetrakis-(trifluoromethyl)-4*H*-1λ^4,2,4,6-thiatriazine (**56**) in the presence of water (Scheme 11) ⟨86C99⟩.



Scheme 11

N-Chlorosulfinyl diarylketimines react with Lewis acids, for example $SbCl_5$, to give orange precipitates of 1-oxa-2-thia-3-azabutatrienium salts which readily react with two equivalents of dialkylcarbodiimides to afford good yields of 1-oxo-1,2,4,6-thiatriazinium salts (**57**) ⟨89RTC117⟩.

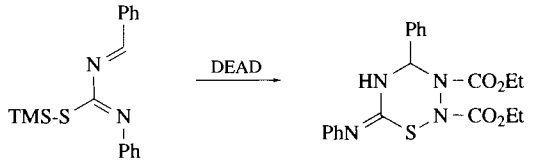


(**57**) R = Me_2CH, cycloalkyl

1,2,4,6-Thiatriazine-3,5-diones (**58**) are prepared by cyclocondensation of biurets with sulfur chlorides ZCl_2 (Z = S, SO). The products are claimed to be effective fungicides ⟨85JAP(K)6048980⟩.

(**58**)

Reports of 1,2,3,5-thiatriazines are rare. However, the cycloaddition of a thiodiazabutadiene (**59**) with DEAD yields such a product (**60**) in 90% yield (Equation (9)) ⟨89TL6923⟩.



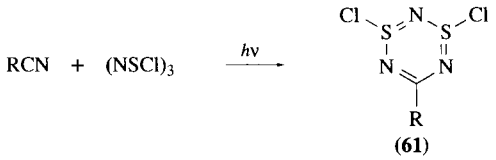
(59) (60) (9)

6.23.4.3 Dioxa- and oxathiatriazines

There were no reports of dioxa- and oxathiatriazines in CHEC-I and no examples of these two ring systems have appeared since then.

6.23.4.4 Dithiatriazines

Reaction of nitriles with $S_3N_3Cl_3$ under UV irradiation (250 watt sunlamp) in an inert atmosphere at 23 °C gives 1,3-dichloro-1,3,2,4,6-dithiatriazines (**61**) (Equation (10)) ⟨84ZN(B)1389, 86IC47, 89CC96⟩.



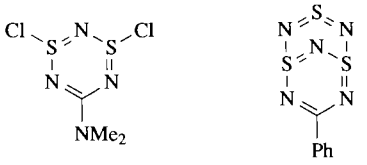
(61) (10)

R = Bu^t, CCl_3, Me_2N, Et_2N, NPr^i_2

1,3,2,4,6-Dithiatriazines are also obtained by reacting $S_3N_3Cl_3$ with amidine salts. For example, reaction with *N,N*-dimethylguanidinium hydrochloride provides 5-dimethylamino-1,3-dichloro-1,3,2,4,6-dithiatriazine (**62**) in low yield ⟨83ZN(B)347⟩.

Trichlorotrithiatriazine and cyanogen chloride gives 1,3,5-trichloro-1,3,2,4,6-dithiatriazine (26% yield). This reacts slowly with excess cyanogen chloride to give 1,3,5-trichloro-1,2,4,6-thiatriazine and trichloro-1,3,5-triazine ⟨93CB2601⟩.

A bicyclic 5-phenyl-1,3,2,4,6-dithiatriazine derivative (**63**) is obtained by the slow addition of a solution of *N,N,N*^{1}-tris(trimethylsilyl)benzamidine in dichloromethane to $S_3N_3Cl_3$ in dichloromethane at 0 °C ⟨85JA7710⟩.



(62) (63)

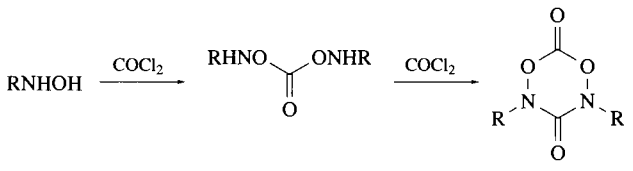
6.23.4.5 Dioxadiazines

Syntheses of 1,2,3,4- ⟨60G1165⟩, 1,2,4,5- ⟨60LA(635)73⟩, 1,4,2,3- ⟨83TL4393⟩, and 1,4,2,5-dioxadiazines ⟨56CB2159⟩ have been described previously. In 1992, it was reported that the oxidation of 1,2-bis(methoxyaminooxy)ethane with lead dioxide yields 2,3-dimethoxy-1,4,2,3-dioxadiazine (**64**) as a mixture of *trans* and *cis* isomers in the ratio of 55:45 (Equation (11)) ⟨92MC50⟩. 2,3-Dicarbalkoxy derivatives of this ring system have been described, but attempts to make 2,3-dialkyl derivatives have been reported to fail ⟨84JOC4969⟩.

(11)

(64)

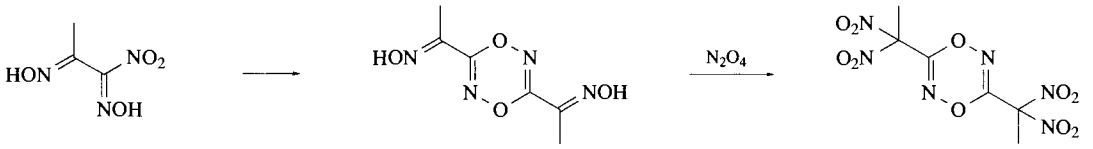
The first examples of the 1,5,2,4-dioxadiazine ring system to be prepared have been the 2,4-dialkyl-2*H*-1,5,2,4-dioxadiazine-3,6(4*H*)-diones (**65**). The synthesis involves a two-stage reaction of an *N*-alkylhydroxylamine with two equivalents of phosgene (Scheme 12) ⟨86JOC3355⟩.



R = Bu^t, $CMe_2CH_2CMe_3$ (65)

Scheme 12

A reinvestigation of a compound first described in 1893 from the reaction of (**66**) with aqueous sodium bicarbonate has shown it to be a 1,4,2,5-dioxadiazine (**67**). Further reaction of this product with nitrogen dioxide gives the bisdinitroethyl compound (**68**) (Scheme 13) ⟨88LA1017⟩.

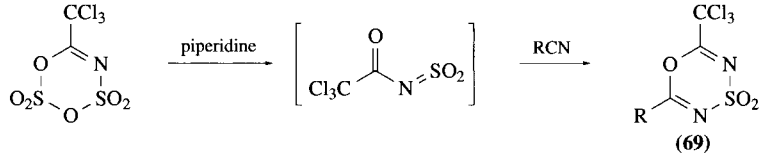


(66) (67) (68)

Scheme 13

6.23.4.6 Oxathiadiazines

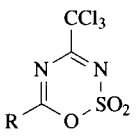
It is known that the 1,3,2,4,5-dioxadithiazine 2,2,4,4-tetraoxide plus base system reacts via sulfonylimidates with nitriles to give 1,4,3,5-oxathiadiazine-4,4-dioxides (**69**) (Scheme 14) ⟨89CRV1947⟩.



(69)

Scheme 14

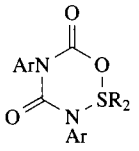
Under the same conditions reaction with cyanamides affords 1,2,3,5-oxathiadiazine-2,2-dioxides (**70**) in high yield ⟨91JOU759⟩.



(70)

R = piperidino, morpholino, Et_2N

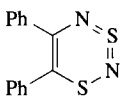
Treatment of isocyanates with sulfoxides at 80°C for 60 hours gives mainly dimers, with some oxathiadiazines (**71**), but treatment for 40 h at 25°C yields mainly the oxathiadiazines ⟨83ZOB2405, 84ZOB2120⟩.



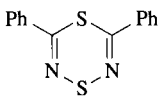
(71)

6.23.4.7 Dithiadiazines

A synthesis of the 1,4,2,3-dithiadiazine system by reacting 1,2-hydrazine-dicarboxylates with 1,2-disulfenyl chlorides was reported in CHEC-I ⟨71AG(E)407, 74CB771⟩. The 1,2,4,5-, 1,3,2,4-, 1,3,2,5-, 1,4,2,5-, and 1,4,2,6-dithiadiazine systems are also known. Earlier reports ⟨76H(4)1243, 79JHC1009⟩ indicating that the minor product obtained from reaction of S_4N_4 with diphenylalkyne in boiling toluene is 5,6-diphenyl-1,3$\lambda^4\delta^2$,2,4-dithiadiazine (**72**), which was also reported to be formed from S_4N_4 and benzil bishydrazone ⟨76H(4)1243⟩, have been shown to be erroneous, the product actually being 3,5-diphenyl-1,4,2,6-dithiadiazine (**73**) ⟨84CC57⟩. The major product from this reaction was confirmed to be 3,4-diphenyl-1,2,5-thiadiazole (**74**).



(72)



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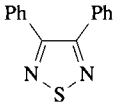
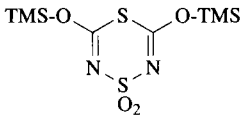


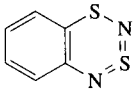
(74)

The dithiadiazine (**73**) was obtained in slightly higher yield (8%) by reacting thiobenzamide, sulfur dichloride and triethylamine in ether, and the structure of the crystalline product was confirmed by x-ray crystallography. The only previous reference to the 1,4,2,6-dithiadiazine system reports 3,5-bis(trimethylsilyloxy)-1,4,2,6-dithiadiazine 1,1-dioxide (**75**) ⟨77ZN(B)1390⟩.



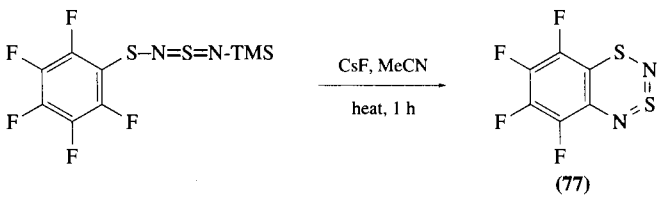
(75)

The first authentic derivative of 1,3,2,4-dithiadiazine to be reported is benzo-1,3$\lambda^4\delta^2$,2,4-dithiadiazine (**76**) ⟨83CC73, 87JCS(P1)207⟩.



(76)

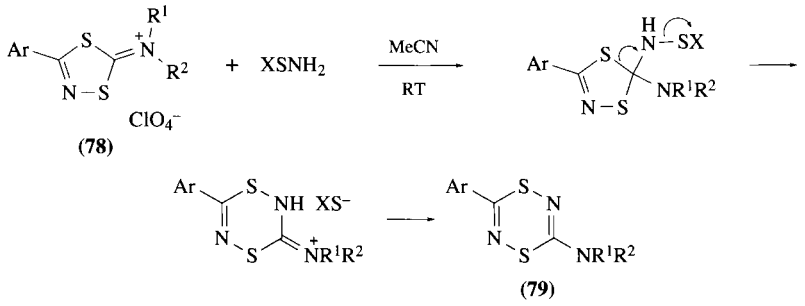
In 1992 it was shown that 5,6,7,8-tetrafluoro-1,3,2,4-benzodithiadiazine (**77**) is obtained in 54% yield by cyclization of *N*-(pentafluorophenylthio)-*N*^{1}-trimethylsilylsulfur diimide using CsF in acetonitrile (Equation (12)) ⟨92POL1137⟩.



(77)

(12)

1,4,2,5-Dithiadiazines (**79**) may be obtained by reacting 1,4,2-dithiazolium salts (**78**) with sulfenamides (Scheme 15) ⟨88BCJ2232⟩.



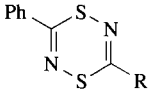
(**78**)

(**79**)

X = Me_2NCS, Pr^i_2NCS, etc., R^1R^2 = Et_2, Me_2, and others

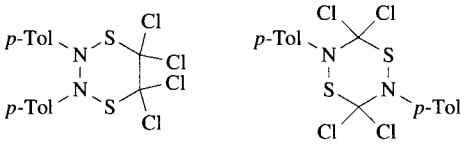
Scheme 15

Attempts to obtain 1,4,2,5-dithiadiazines using the reagents sodium azide and *S,S*-diphenylsulfilimine have been unsuccessful, but the use of iodine/ammonium hydroxide has been successful in the synthesis of (**80**) ⟨89CL89⟩.



(**80**) R = Ph, NEt_2

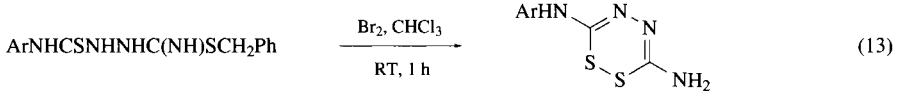
N-(*p*-Tolyl)trichloromethane sulfenamide, when treated with potassium hydroxide in an ether/ethanol mixture, yields a transient thione *S*-imide, which undergoes head-to-head dimerization to give 5,5,6,6-tetrachloro-2,3-di-*p*-tolyl-1,4,2,3-dithiadiazine (**81**). This structure was confirmed by x-ray crystallography ⟨91JHC1637⟩. The original report of the reaction ⟨34JCS822, 35JCS679⟩ gave the product as (**82**). This result suggests that other reactions of this type, reported to give products analogous to (**82**), should be reinvestigated.



(**81**) (**82**)

Nielsen and Senning have confirmed the results of Potts and Baum and have also shown that (**81**) reacts with hydrochloric acid to yield 1,1,2,2-tetrachloro-1,2-ethanedisulfenyl dichloride and di-*p*-tolylhydrazine chloride ⟨93TL2973⟩.

1,2,4,5-Dithiadiazines (**84**) are obtained by reacting *S*-benzyl-isothiosemicarbazide with aryl isothiocyanates to yield the intermediate 5-*S*-benzylthio-1-phenyl-2-thiohydrazodicarbonamides (**83**), which are oxidatively cyclized with bromine (Equation (13)) ⟨88H(27)2373⟩.

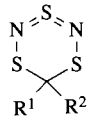


(**83**) (**84**) (13)

6.23.4.8 Trithiadiazines

Diazoalkanes react with tetrasulfur tetranitride to give red crystalline $1,3\lambda^4\delta^2,5,2,4$-trithiadiazines (**85**), a new ring system with an almost planar ring. Thus, addition of ethereal diazomethane to S_4N_4 in dichloromethane at room temperature affords, after 0.5 h, the 1,3,5,2,4-trithiadiazine in 37% yield. Similar reaction of S_4N_4 with aryldiazomethanes gives open chain compounds as major

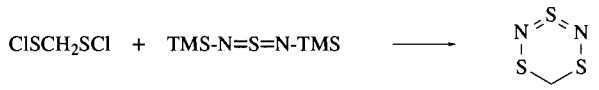
products, but low yields of the cyclic compounds are also obtained. The parent compound was also independently synthesized from methane bis(sulfenyl chloride) and sulfur bis(trimethylsilyl)diimide (Equation (14)) ⟨87CC1546, 89JCS(P1)2503⟩.



(85)

R^1 = H, Me, Ph, CO_2Et

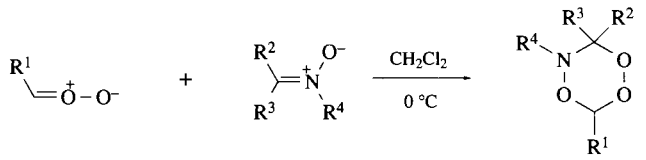
R^2 = H, Me, Ph, $PhCH_2$, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$, CO_2Et



(14)

6.23.4.9 Trioxazines

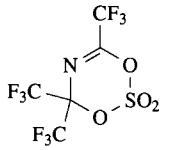
The 1,2,4,5-trioxazine ring system has been obtained by a [3 + 3] cycloaddition of carbonyl oxides, generated *in situ* from vinyl ethers and ozone, and nitrones (Equation (15)) ⟨89JA6884⟩. The products have stability similar to that of 1,2,4,5-tetraoxanes.



(15)

6.23.4.10 Dioxathiazines

The adduct of hexafluoroacetone with trifluoroacetamide reacts with oleum to give a 1,3,2,5-dioxathiazine (**86**) ⟨84JOU1213⟩.

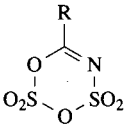


(86)

An earlier report of this system, referred to in CHEC-I, describes its synthesis by the reaction of DMSO with benzoyl isocyanate in the presence of boron trifluoride etherate ⟨75IZV1206⟩.

6.23.4.11 Dioxadithiazines

1,3,2,4,5-Dioxadithiazine 2,2,4,4-tetraoxides (**87**) have been obtained in high yield (92–97%) by the careful reaction of nitriles with sulfur trioxide in liquid sulfur dioxide at −75 to −85°C for 1 h. The structures of the products were established by x-ray crystallography ⟨84JOU1872⟩.



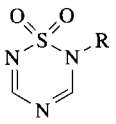
(87)

R = CCl_3, C_6H_5, Me, Et, Bu^t, $CHCl_2$, *p*-$NO_2C_6H_4$, *iso*-propenyl

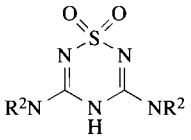
6.23.5 APPLICATIONS AND IMPORTANT COMPOUNDS

In CHEC-I the only systems of relevance to this chapter which were reported to possess commercially useful properties were the 1,2,3,5-oxathiadiazines and their 1,4,3,5-isomers. These were reported to be of interest as acid-hardening resins ⟨76GEP2524475⟩ and plant protection agents respectively ⟨72GEP2036312⟩. Certain 1,2,4,6-thiatriazines were reported to have herbicidal and fungicidal activity ⟨75GEP2508832⟩. It has been reported that N^2-alkyl-1,2,4,6-thiatriazine 1,1-dioxides (**88**) are of interest because of their herbicidal, fungicidal, and histamine H_2-antagonist activity ⟨85LA2363, 86TL123⟩.

Some derivatives of 3,5-diamino-1,2,4,6-thiatriazine 1,1-dioxide (**89**) also have potent histamine H_2-antagonist activity ⟨84BRP2129426⟩.



(88)



(89)

A number of other compounds of this type have been patented as herbicides ⟨83JAP(K)58219171, 84EUP104611, 84GEP(O)3231394, 84JAP(K)59128380, 84JAP(K)5998077, 85JAP(K)6048980⟩.

Some 2*H*-1,2,4,6-thiatriazine-3,5(4*H*,6*H*)-dione 1-oxides have been shown to have useful antifungal activity which depends on the presence of the sulfinyl function ⟨87ABC3173⟩.

Benzothiadiazine 1,1-dioxides have been shown to be useful antihypertensive agents and diuretics and many such compounds have been prepared ⟨62AG(E)235⟩.

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6.24
Six-membered Rings with Two or More Heteroatoms with at least one Selenium or Tellurium

MALCOLM SAINSBURY
University of Bath, UK

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6.24.1 INTRODUCTION

This chapter is concerned with those six-membered rings containing at least two selenium or tellurium atoms, along with their benzo analogues and other six-membered heterocycles containing a selenium or a tellurium atom, and other heteroatoms–nitrogen, oxygen, or sulfur–which have been dealt with earlier in this volume. Discussion of systems containing other elements is deferred to later chapters. These topics were not covered specifically in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), so an effort has been made to cover all the significant work in the area. It should be noted, however, that many types of such heterocycles are not represented in the literature and interest has focused on a limited number of ring systems. Some systems, like selenanthrene, have a long history, while others such as the selenadiazines, are of much more recent origin. In the case of 1,3-diselenanes, the chemistry resembles that of 1,3-dithianes and similar analogies can be made between the 1,4-selenazines and the 1,4-thiazines. However, coordination numbers vary in the group 16 elements (chalcogens), and selenium and tellurium in particular, have a propensity to increase their valency shells from the normal octet to decet and even dodecet states. The compounds involved do not obey the strict Lewis "octet rule" and can be regarded as hypervalent types ⟨B-86MI 624-01⟩. In the decet state, for example, the arrangement at the chalcogen is bipyramidal with three coplanar (equatorial) bonds and two axial bonds at 90° to the plane of the other three ⟨76JA1647, 84AG(E)272, 90JA1434⟩. In addition, molecular compounds are formed in some cases and these have generated much interest, particularly if they demonstrate semiconducting and related properties.

Nomenclature in this area, when hypervalent elements are involved, can be confusing, with both additive (e.g., 1,4-oxatellurane dichloride) and substitutive (e.g., 4,4-dichloro-1,4-oxatellurane) names being in common use. Throughout this chapter, the general name "dichalcogenine" is written with a final "e", to avoid the "genin" ending commonly used in natural product chemistry.

It is convenient to subdivide the review so that compounds containing only chalcogens are separated from those containing nitrogen and chalcogen atoms. However, it should be pointed out that the chemical behavior of the chalcogen atom(s) tends to dominate the general reactivity in both groups. There are no reviews up to 1995, which encompass the whole subject; however, the chemistry of the tellurium compounds has been well surveyed ⟨93AHC(58)47⟩, and earlier work on selenium and tellurium heterocycles has been collated ⟨66CHE1272, B-86MI 624-02⟩.

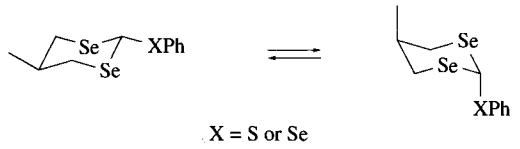
6.24.2 DISELENANES, DITELLURANES, PHENOXASELENINS, PHENOXATELLURINS, PHENOTHIASELENINS, AND ALLIED COMPOUNDS

6.24.2.1 Physical Properties

6.24.2.1.1 Conformation and NMR spectra

There is a considerable body of x-ray and NMR evidence to support the view that both in the solid state and in solution, the known 1,3-dichalcogenanes favor chair conformations. However,

ready conformational equilibration occurs for both *trans*-5-methyl-2-phenylthio-1,3-diselenane and *trans*-5-methyl-2-phenylseleno-1,3-diselenane with $\Delta G^{\circ}_{147K} = -1.20$ (0.04) kcal mol^{-1} and -9.6 (0.04) kcal mol^{-1}, respectively (Scheme 1). Since for 2-methyl-1,3-diselenane, $\Delta G^{\circ}_{147K} = +1.04$ (0.01) kcal mol^{-1}, this is taken as evidence that significant Se—C—S and Se—C—Se effects are operating in these two compounds. The equilibria of the *cis*-isomers are heavily biased and the spectra from only one conformer (PhSe group axial) were detected (Scheme 2) ⟨89H(28)389⟩.



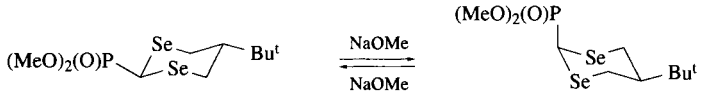
X = S or Se

Scheme 1

X = S or Se

Scheme 2

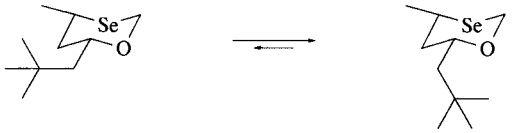
2-Phosphoryl-1,3-diselenanes are conformationally labile and *cis*- and *trans*-5-*t*-butyl derivatives equilibrate in the presence of sodium methoxide (Scheme 3). Calculations show that there is an anomeric effect of $\Delta G^{\circ}_{AE} = 10$ kJ mol^{-1} operating in the Se—C—P segment and data from crystal structure determinations support this view. It is proposed that there is a repulsive interaction between the phosphoryl oxygen atom and a lone pair of electrons on the endocyclic selenium atom which tends to destabilize the *trans*-isomer ⟨91TL4189⟩.



Scheme 3

The NMR spectra of *trans*-6-alkyl-4-methyl-1,3-oxaselenanes in carbon tetrachloride are temperature dependent, an effect associated with ring inversion. As expected, if the 6-alkyl substituent is larger than methyl, it is best accommodated in the equatorial site (Scheme 4). For *cis*-6-neopentyl-4-methyl-1,3-oxaselenane there is high rotameric preference with the *t*-butyl unit best orientated away from the C-5 methylene group ⟨72T1097⟩ (Scheme 5).

Scheme 4



Scheme 5

In common with the other heterocycles in this group, 1,4-diselenanes adopt chair conformations ⟨51JA1106, 55AX91, 60AX727, 69T539⟩. This same preference exists in the hypervalent halide derivatives and, for example, the ring of 1,1,4,4-tetrachloro-1,4-diselenane is chair-like, but the bonding arrangement about each selenium atom is trigonal bipyramidal with Cl—Se—Cl angles of ca. 180°. Only four of the five apexes of the trigonal bipyramid are occupied, two by chlorines and two by carbon atoms ⟨64IC1199⟩. A similar spatial arrangement exists for 4,4-diiodo-1,4-oxatellurane, which in the

solid state also assumes a basic chair conformation with a C—Te—C angle of 94°. The I—Te—I angle is 177°; thus, as in the previous example, the two halogen atoms occupy "axial" sites. In this case the bonding about tellurium is octahedral, but the rest of the octahedral environment is completed by intermolecular associations with two other molecules via an iodine atom in each case (Te—I distances of 3.814 Å and 3.692 Å) ⟨73IC2665⟩. X-ray crystal structural analyses have also been completed for 1,4-thiatellurane diiodide and the corresponding dibromide ⟨70IC797, 72IC3026⟩. Both compounds are distorted chairs with Hal—Te—Hal angles of 174.9° and 176.3°, respectively. Interestingly, two molecules of iodine form a molecular complex with 1,4-diselenane, rather than a covalently bonded compound. The iodine molecules are axially orientated at each selenium ⟨61AX940⟩, although in a similar compound, formed between 1,4-dithiane and iodine, the iodine units are accommodated equatorially ⟨60AX727⟩.

The ^{1}H NMR spectrum of 1,4-oxaselenane at 155 K consists of ABCD multiplets, but these coalesce as the temperature of the experiment is raised, eventually leading to an AA′BB′ system, when ring inversion is faster than the timescale of the NMR experiment ($\Delta G^{\neq} = 42.6$ kJ mol^{-1}). However, even at 155 K the spectrum of 1,4-oxatellurane appears as AA′BB′ multiplets, slightly broadened. In this molecule the greater ring flexibility is considered to be a reflection of the increased bond lengths (C—Te vs. C—Se) ⟨75JCS(P2)1354⟩.

Heteronuclear NMR spectroscopy is possible with selenium and tellurium: ^{77}Se and ^{125}Te both have nuclear spin quantum number $I = \frac{1}{2}$. However, applications to the compounds described in this chapter have been few.

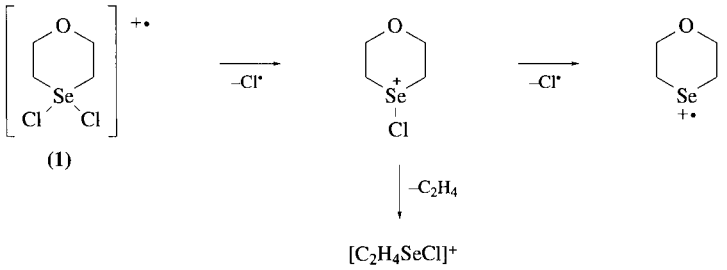
6.24.2.1.2 Tautomerism

Scattered data on the tautomerism of the various systems discussed in this chapter are available. These are discussed as they arise, since no coherent picture of the whole area can be expected from such disparate compounds.

6.24.2.1.3 Mass spectra

Both selenium and tellurium have a variety of naturally abundant isotopes, and therefore ions containing these elements show complex but characteristic patterns in the mass spectra. The abundance ratios, relative to the most abundant isotope of each element, are as follows: for selenium, 74 (1.8), 76 (18.1), 77 (15.3), 78 (47.2), 80 (100), 82 (18.5); for tellurium, 120 (0.35), 122 (7.25), 123 (4.6), 125 (20.3), 126 (54.2), 128 (91.9), 130 (100).

The mass spectra of 1,4-oxaselenane, 1,4-oxatellurane, and 1,4-diselenane are dominated by the molecular ion peaks, but in the case of 1,4-oxaselenane dichloride (**1**) (and of the dichloride of 1,4-oxatellurane) major fragmentations involve the stepwise loss of two chlorine atoms, or loss of Cl· followed by loss of ethene (Scheme 6) ⟨80JHC929⟩.



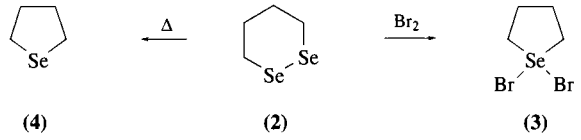
Scheme 6

6.24.2.2 Reactions

6.24.2.2.1 Oxidation and reactions with electrophiles

All the known heterocycles of this group react with halogens to form dihalides and, in the case of diselenanes and ditelluranes, tetrahalides ⟨54JA3091⟩. The formation of these compounds also

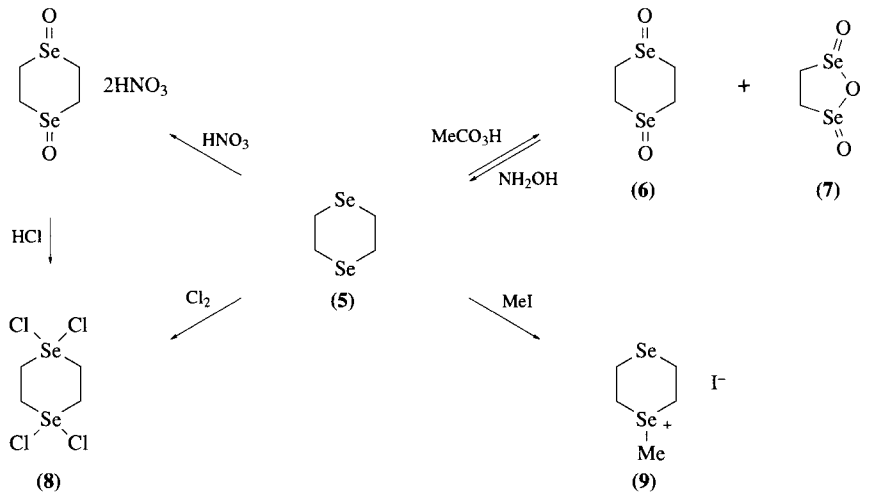
occurs during certain ring syntheses which utilize selenium or tellurium tetrahalides as reagents to introduce the chalcogen atoms (see Section 6.24.4.2.3). In the case of 1,2-diselenane (**2**), bromination in chloroform affords the 1,1,2,2-tetrabromide, but this rapidly degrades to 1,1-dibromotetrahydroselenophene (**3**). This last product is also formed when the bromination is carried out in boiling chloroform, and presumably 1,1,2,2-tetrabromo-1,2-diselenane is the reaction intermediate. The parent heterocycle is also thermally unstable and eliminates selenium to form tetrahydroselenophene (**4**) (Scheme 7) ⟨29JCS1096⟩.



Scheme 7

The tetrahalides of 1,4-diselenanes are more stable and are solids: the tetrachloride is colourless, but the tetrabromide and the tetraiodide are yellow and red, respectively. They are formed by reacting the heterocycles in carbon tetrachloride with halogens and they readily undergo halogen exchange ⟨51JA1105, 54JA3091⟩. 1,4-Diselenane (**5**) on oxidation with 30–40% peracetic acid at 0 °C is converted into the 1,4-dioxide (**6**), along with *trans*-ethane-1,2-diseleninic anhydride (**7**) (Scheme 8). 1,4-Diselenane 1,4-dioxide is water soluble and unstable above 80 °C. It reverts to 1,4-diselenane when reacted with hydroxylamine. Treatment of 1,4-diselenane with conc. nitric acid at 0 °C forms a compound considered to be a dihydroxydinitrate, which with hydrochloric acid yields 1,4-diselenane 1,1,4,4-tetrachloride (**8**) ⟨56JA5161, 56JA5825⟩.

1,4-Diselenane, like 1,4-oxatellurane and the other compounds of the group, is alkylated by treatment with methyl iodide to give a methiodide (**9**) (Scheme 8) ⟨45JCS11, 56JA5825, 65IC862, 87SR359⟩.

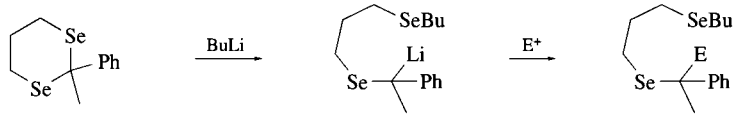


Scheme 8

6.24.2.2.2 Nucleophilic ring opening

In general, 1,3-diselenanes, for example (**10**), are resistant to attack by Grignard reagents ⟨85T4793⟩, but undergo ring opening with butyllithium at −78 °C. Once opened, the acyclic lithiated products can be quenched with electrophiles to afford selenoethers (**11**) (Scheme 9) ⟨93TL8517⟩.

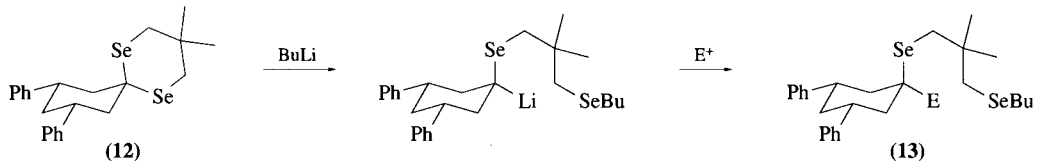
In the case of the spiroselenoacetal (**12**), attack by *t*-butyllithium occurs preferentially at the equatorial site and, after quenching with an electrophile, this favors the formation of the equatorial product (**13**) (97 : 3) (Scheme 10). This is not the case in the selenoacetal (**14**); here lithiation at the axial position is strongly favored, leading to the corresponding product (**15**) rather than (**16**) (92 : 8). This discrepancy can be explained if stereoelectronic factors promote initial lithiation at the axial selenium atom in compound (**14**), leading to the normally more hindered axial substituent. It is



(10) (11)

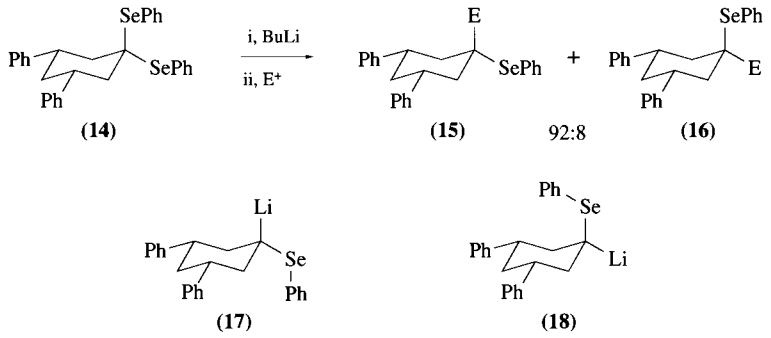
Scheme 9

considered that this effect arises in the lithiated intermediate (**17**) because the lone pair electrons in the carbanion intermediate and the Se—Ph bond are antiperiplanar, allowing optimum (n-σ^*) hyperconjugation. In the alternative intermediate there are severe steric interactions in the conformation (**18**) in which n-σ^* interaction is most effective (Scheme 11). It should be added that, from a kinetic viewpoint, the ability of the phenyl groups to stabilize a developing α-carbanion might also explain the lability of the axial phenylselenyl bond. Since there is no *anti*-conformation available in the spiroacetal, butyllithium simply cleaves at the more accessible equatorial site ⟨90JA8994⟩.



(12) (13)

Scheme 10

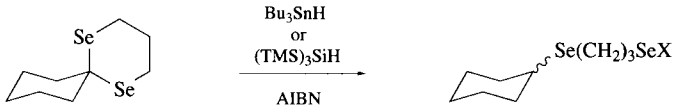


(14) (15) 92:8 (16)

(17) (18)

Scheme 11

Similar results have been noted by other workers, but when the selenoacetals (**19**) are treated with either tributyltin hydride, or tris(trimethylsilyl)silicon hydride, in the presence of AIBN, nonselective ring opening occurs (Equation (1)). Some preference for equatorial attack is observed for the silicon hydride, but this most likely reflects the large size of the reagent ⟨93TL8517⟩.

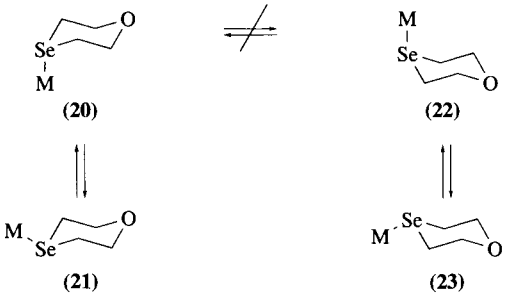


(19) X = $SnBu_3$ or $Si(TMS)_3$ (1)

6.24.2.2.3 Complexation with metal salts and carbonyls

1,4-Diselenane shows selective donor properties and forms complexes with Cd(II), Pd(II), and Hg(II) chlorides, but fails to complex with the chlorides of Fe(II), Cu(II), Co(II), or Cr(III) ⟨56JA5825⟩. It complexes with rhodium(III) chloride to give a compound $[RhCl_3(C_4H_8OSe)_3]$ and with platinum(IV) bromide to give a crystalline complex $[PtBr_2(C_4H_8OSe)_2]$ ⟨77JCS(D)458, 90POL1141⟩. In the case of the latter complex each Pt—Se bond is axially oriented with respect to the ring.

However, the ^{1}H NMR spectrum of this compound, and that of a similar palladium complex, shows temperature dependence, which is considered to reflect site inversion about the selenium atom, rather than ring inversion (i.e. **(20)**⇋**(21)** and **(22)**⇋**(23)** (Scheme 12) ⟨76JCS(D)1227⟩.



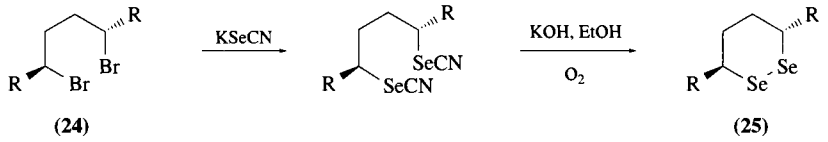
M = $PtX_2SeC_4H_8O$; X = Cl or Br
or
M = $PdX_2SeC_4H_8O$; X = Cl or Br

Scheme 12

6.24.2.3 Synthesis

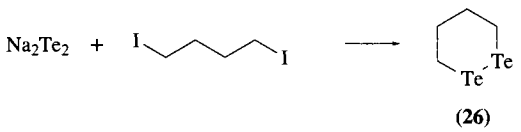
6.24.2.3.1 1,2-Dichalcogenanes

1,2-Diselenane (**25**; R = H), a low-weight polymer (monomeric in solution), is available from 1,4-dibromobutane in two steps: first conversion into the 1,4-diselenocyanate (**24**; R = H), and then treatment of this product with alcoholic potassium hydroxide in the presence of oxygen (Scheme 13) ⟨29JCS1096⟩. The 1,2-diselenane-3,6-dicarboxylic acid (**25**; R = CO_2H) can be synthesized in a similar way from meso-2,5-di(selenocyanato)adipic acid ⟨33AK(27)6⟩.



Scheme 13

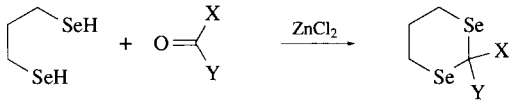
1,2-Ditellurane (**26**) is formed in 11–15% yield from 1,4-diiodobutane and freshly prepared disodium ditelluride in a water–benzene system containing a phase transfer agent (Equation (2)). Unfortunately, the yield is low and the product is accompanied by a polymer $[Te_2(CH_2)_4]_n$ ⟨88JOM(338)9⟩.



(2)

6.24.2.3.2 1,3-Dichalcogenanes

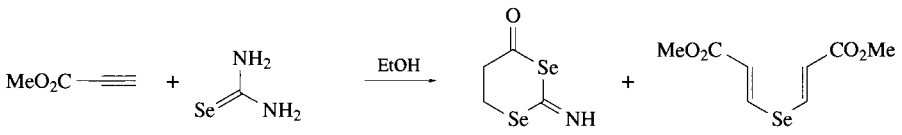
1,3-Diselenanes (**27**) are available through the reactions of 1,3-propanediselenols with aldehydes and ketones in the presence of a Lewis acid such as zinc(II) chloride (Equation (3)) ⟨85T4793, 93TL8517⟩. The diselenols are normally synthesized from the corresponding diselenocyanates by reduction with, for example, sodium borohydride, or with sodium in liquid ammonia ⟨71BSB639⟩.



(3)

(27)

Selenourea reacts with methyl propynoate to form 2-imino-1,3-diselenan-4-one (**28**), or the hydroxy tautomer, and bis(methoxycarbonylethenyl)selenide (**29**) (Equation (4)) ⟨69ZOR621⟩.

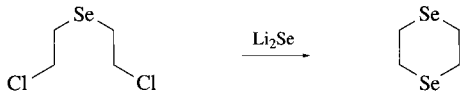


(4)

(28) (29)

6.24.2.3.3 1,4-Dichalcogenanes

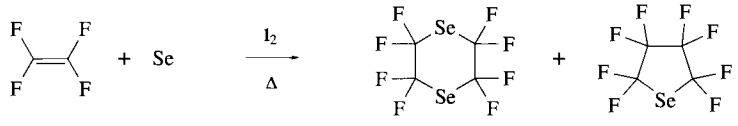
1,4-Diselenane (**31**) was first obtained in very low yield by the reaction of lithium selenide and bis(2-chlorodiethyl)selenide (**30**) in acetone (Equation (5)) ⟨51JA1105⟩. A better approach is to heat a mixture of aluminum selenide and 1,2-dibromoethane at 80–140 °C over some hours. Even using this method, the yield is only 10% ⟨56JA5825⟩.



(5)

(30) (31)

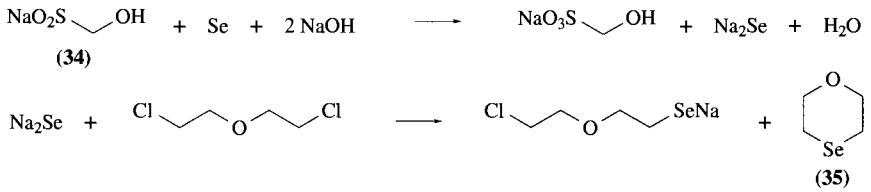
Perfluoro-1,4-diselenane (**32**) is a minor product formed when tetrafluoroethene is heated under pressure with selenium and a catalytic amount of iodine at 250 °C; the major product formed is perfluoroselenolane (**33**) (Equation (6)) ⟨60USP2931803⟩.



(6)

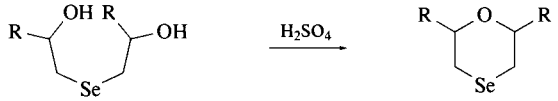
(32) (33)

1,4-Oxaselenane (**35**) was first obtained by reacting bis(2-chloroethyl)ether with aqueous sodium selenide, treating the reaction mixture with bromine and then reducing the intermediate dibromide with sodium bisulfite. 1,4-Thiaselenane can be similarly prepared from the corresponding thioether, followed by steam distillation ⟨31JCS266⟩. Sodium formaldehydesulfoxylate (rongalite) (**34**), selenium powder, and sodium hydroxide in combination can be used as a convenient source of sodium selenide (Scheme 14) ⟨66IC150⟩. An alternative route utilizes the cyclodehydration of bis(2-hydroxyethyl)selenides (**36**) by a catalytic amount of conc. sulfuric acid at 140–160 °C under a nitrogen atmosphere (Equation (7)) ⟨82URP1162803⟩.



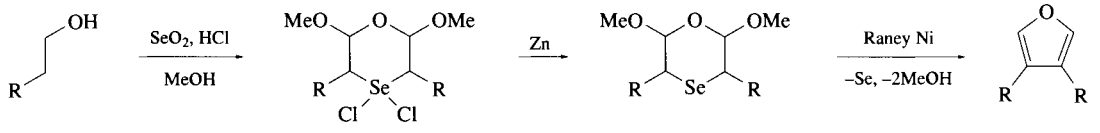
(34) (35)

Scheme 14



(36) (7)

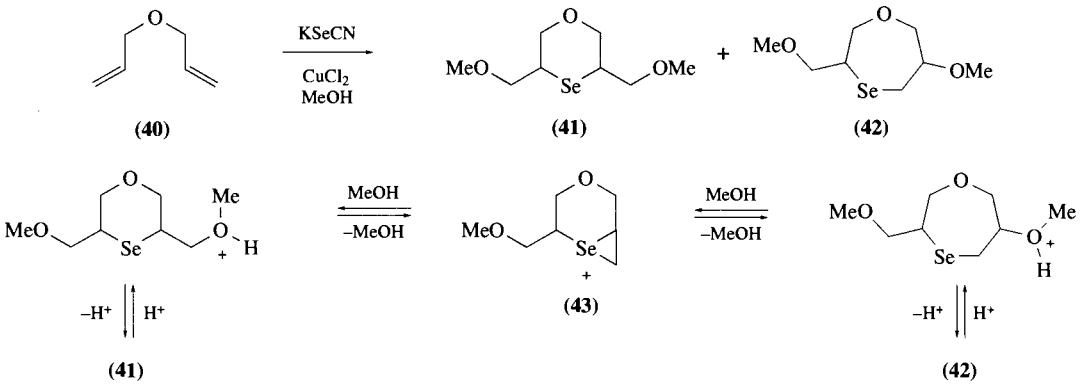
2,6-Dialkoxy-3,5-dialkyl-1,4-oxaselenane 4,4-dichlorides (**37**) are formed simply by reacting alkanols containing aqueous hydrochloric acid with selenium dioxide. These products can be dehalogenated by treatment with sulfite ion or with zinc in ethanol to give the corresponding oxaselenanes (**38**). On treatment with Raney nickel the oxaselenanes lose selenium and aromatize to 3,4-dialkylfurans (**39**) (Scheme 15) ⟨85H(23)37, 86ACS(B)715⟩.



(37) (38) (39)

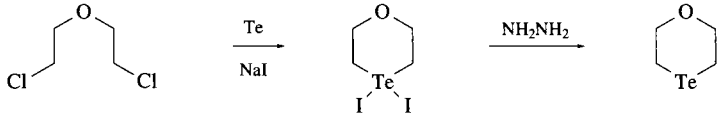
Scheme 15

When diallyl ether (**40**) is reacted with potassium selenocyanate, copper(II) chloride, and methanol a mixture of 3,5-bis(methoxymethyl)-1,4-oxaselenane (**41**) and 3-methoxymethyl-6-methyl-1,4-oxaselenepane (**42**) is formed. The amount of the selenane increases with reaction time and the ratio of products is also affected by variations in temperature. These facts suggest that an equilibrium exists, linking the products through an intermediate episelenonium cation (**43**) (Scheme 16) ⟨79JCS(P1)1206⟩.



Scheme 16

1,4-Oxatellurane (**46**) is available by heating bis(2-chloroethyl)ether (**44**) with sodium telluride (from rongalite, tellurium, and aqueous sodium hydroxide) in ethanol, chlorinating the product and reducing the resultant dichloride with potassium metabisulfite to give a foul smelling yellow solid ⟨45JCS11⟩. An alternative method uses the same chloroether in a reaction with tellurium powder and sodium iodide in 2-butoxyethanol. The product diiodide (**45**) is then deiodinated by hydrazine in hot methanol (Scheme 17) ⟨87ICA139⟩.

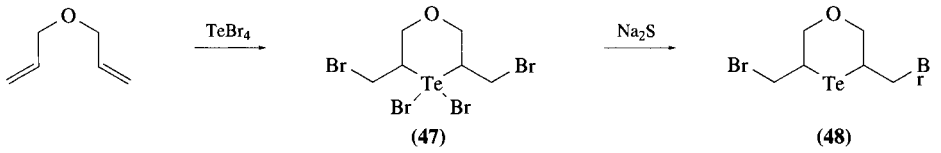


Scheme 17

3,5-Di(halogenomethyl)-4,4-dihalogeno-1,4-oxatelluranes (**47**) are formed by the reactions of diallyl ethers with tellurium tetrahalides in diethyl ether, and these products can be reduced by sodium sulfide to the di(halomethyl) derivatives (**48**) (Scheme 18). By using the corresponding thioethers the analogous 1,4-thiatelluranes are obtained ⟨77KGS58, 78KGS1212⟩. This is a very general approach to heterocycles of this type and if selenium tetrachloride is used with the ether, or the

thioether, then the products are the corresponding dichloro-1,4-oxaselenanes, or -thiaselenanes, respectively.

1,4-Thiatellurane can be synthesized through the reaction of bis(2-chloroethyl)sulfide with sodium telluride ⟨65IC862⟩.

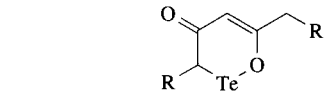


Scheme 18

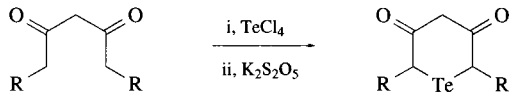
6.24.3 OXASELENINS, OXATELLURINS, DISELENINS, AND DITELLURINS

6.24.3.1 1,2-Dichalcogenines

The compounds formed when alkyl β-diketones are heated in chloroform with tellurium tetrachloride were investigated by Morgan and co-workers in the early 1920s ⟨20JCS1456, 22JCS922, 24JCS754, 24JCS760⟩. 1,2-Oxatellurin-4(3*H*)-one dichloride structures were assigned. These were reduced by metabisulfite to the dechlorinated systems designated as (**49**). However, later work by the same group showed that these structures were untenable, and the alternative tellurane-3,5-dione formulae (**50**) were proposed (Equation (8)) ⟨24JCS1601, 25JCS797⟩. This revision was apparently overlooked by Breslow and Skolnik, who reviewed the area in 1966 ⟨B-66MI 624-02⟩. Other work (NMR, x-ray crystallography) has confirmed the correctness of the revised structures (**50**) ⟨64JCS688, 76JCS(D)2307, 78OMR(11)449⟩. No genuine 1,2-oxatellurin derivative seems to have been prepared.



(**49**)



(**50**)

(8)

6.24.3.2 1,3-Dichalcogenines

The 1,3-dichalcogenines contain at most one double bond: however, no derivatives of these systems containing selenium or tellurium appear to have been reported.

6.24.3.3 1,4-Dichalcogenines and Monobenzo Derivatives

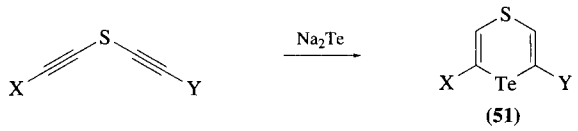
6.24.3.3.1 Metal complexes

Iron pentacarbonyl complexes of cycloalkano-1,4-diselenins have been described ⟨85OM1580⟩.

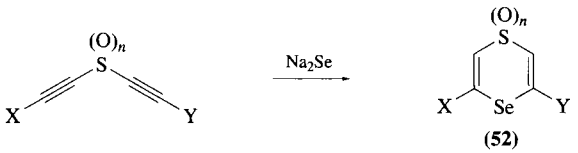
6.24.3.3.2 Synthesis

A general route to 1,4-dichalogenines (**51**) involves the cyclization of dialkynyl sulfides, selenides, or tellurides, with either sodium selenide or sodium telluride (Equation (9)). It is also possible to

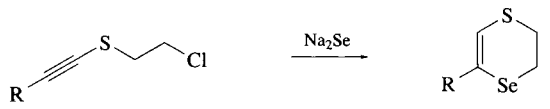
cyclize dialkynyl sulfoxides and sulfones in this way, affording the corresponding heterocyclic 1-oxides and 1,1-dioxides (**52**) (Equation (10)) ⟨73RTC1326, 75RTC163, 78RTC244⟩. In a variant of this type of reaction 2,3-dihydro-1,4-thiaselenins (**53**) can be prepared through the reactions of alkynyl 2-chloroethyl sulfides with sodium selenide (Equation (11)). 1,4-Thiatellurins are formed in the same manner using sodium telluride as the cyclization reagent ⟨81RTC369⟩.



(51) (9)

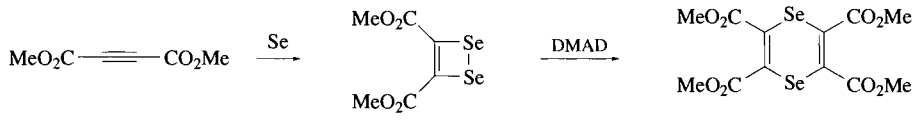


(52) (10)



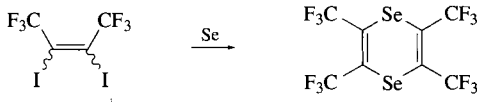
(53) (11)

1,4-Diselenin is formed by the reaction of alkynes with selenium; thus, the 2,5-diphenyl derivative is formed by heating phenylethyne and selenium ⟨43USP2332433, 72T187⟩. Tetramethyl 1,4-diselenin-2,3,5,6-tetracarboxylate (**55**) is the product of the reaction of dimethyl acetylenedicarboxylate with selenium in boiling 1,2-dichlorobenzene ⟨87NKK1424⟩. In the second example the initial product is dimethyl 1,2-diselenete-3,4-dicarboxylate (**54**), which undergoes cycloaddition with a second molecule of the alkyne (Scheme 19). Similarly, 2,3,5,6-tetrakis(trifluoromethyl)-1,4-diselenin (**57**) is obtained when 2,3-diiodohexafluorobut-2-ene (**56**) and selenium are heated together at 180 °C under pressure (Equation (12)) ⟨61JA3434⟩.



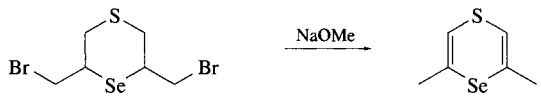
(54) (55)

Scheme 19



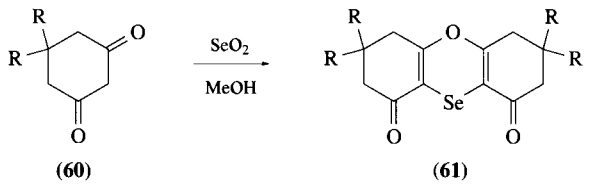
(56) (57) (12)

3,5-Dimethyl-1,4-thiaselenin (**59**) is synthesized by the dehydrobromination of 3,5-di(bromomethyl)-1,4-thiaselenane (**58**) by sodium methoxide (Equation (13)). This method can also be applied to the synthesis of other 3,5-dialkyl-1,4-dichalcogenines, which are obtained from diallyl ethers or thioethers (see Scheme 18) ⟨77KGS58⟩.



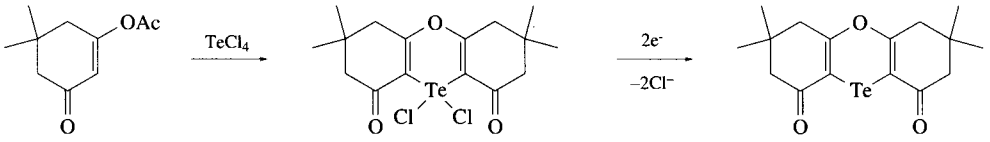
(58) (59) (13)

As early as 1933, it was known that dimedone (**60**; R = Me) reacts with selenium dioxide to afford the tricyclic 1,4-oxaselenin (**61**; R = Me) ⟨33CB1558, 40CB839⟩. 1,3-Cyclohexanedione (**60**; R = H) behaves similarly, giving (**61**; R = H) (Equation (14)) ⟨49JCS274⟩. This work has been extended to 1,4-oxatellurins, and dimedone enol acetate (**62**) for example, reacts with tellurium tetrachloride in hot acetic acid to give the dichloride (**63**). This product can be reductively dechlorinated to the parent heterocycle (**64**) (Scheme 20) ⟨85KGS769⟩.



(14)

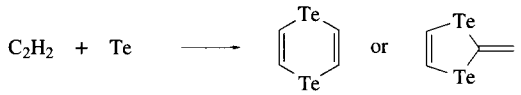
(60) (61)



(62) (63) (64)

Scheme 20

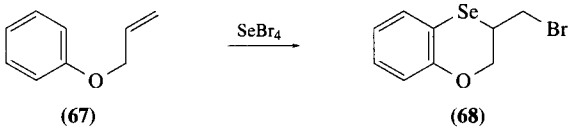
1,4-Ditellurin (**65**) and/or 2-methylene-1,3-tellurole (**66**) are formed when tellurium metal is reacted with ethyne in the presence of either hydrazine or tin dichloride (Equation (15)). Unlike the corresponding reactions in the 1,4-diselenin series, this process is unreliable, and which compound is obtained depends upon the reaction conditions ⟨91SUL143⟩.



(15)

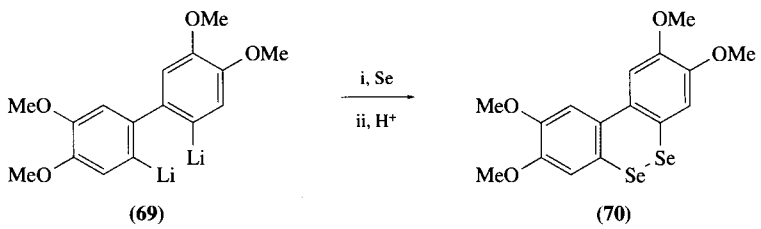
(65) (66)

Monobenzo derivatives in this series are rare, but 3-bromomethyl-2,3-dihydro-1,4-benzoxaselenin (**68**) is obtained through the cyclization of allyl phenyl ether (**67**) with selenium tetrabromide (Equation (16)) ⟨82KGS911⟩. In addition, a number of polycyclic derivatives are known, including dibenzo-1,2-diselenin (**70**), formed by reacting the dilithiobiphenyl (**69**) with selenium (Equation (17)) ⟨84JHC413⟩. Compounds of the tetraselenofulvalene type, e.g., (**71**), have been prepared, and are of interest in the production of semiconducting materials ⟨83CC235⟩.



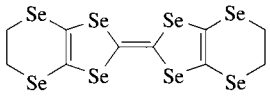
(16)

(67) (68)



(17)

(69) (70)



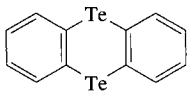
(71)

6.24.4 SELENANTHRENES, TELLURANTHRENES, PHENOXASELENINS, PHENOXATELLURINS, PHENOTHIASELENINS, AND ALLIED COMPOUNDS

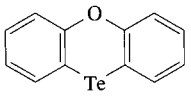
6.24.4.1 Physical Properties

6.24.4.1.1 Structures from crystallography and other methods

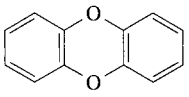
The crystal structures of selenanthrenes and telluranthrenes have been determined by several groups ⟨80JFC(16)245, 81CSC1359, 83MI 624-01, 86JOM(308)207, 87PS(38)257, 91JCR(S)314⟩. In all the various chalcogenanthrenes the heterocyclic ring exists as a boat and thus the molecule is folded about the line joining the two heteroatoms. The dihedral, or fold, angle varies depending upon which heteroatoms are present and telluranthrene (**72**), for example, shows a dihedral angle of 124° ⟨81CSC1359⟩ in the solid state, whereas that of phenoxatellurin (**73**) is 145° ⟨73JHC527⟩.



(72)



(73)



(74)

Dihedral angles in solution have been computed from dipole measurements ⟨78JOM(146)235, 87PS(38)281⟩ and in general the values are 20–30° higher than in the solid phase, perhaps because of enhanced butterfly-like motions. Selenanthrene, for example, appears to be considerably less sharply folded in benzene solution ⟨83JCS(P2)1109⟩.

6.24.4.1.2 Molecular calculations and NMR spectra

Information on the spatial environments of these tricyclic compounds is available from detailed quantum mechanical PM3 calculations and from NMR studies. For all the 5,10-dichalcogenanthrenes containing O,O; S,S; Se,Se; and Te,Te heteroatoms the ^{1}H NMR spectra exhibit AA′BB′ spin-spin splitting patterns, but for the O,Se; S,Se; and Se,Te analogues ABXY systems are observed. All of these systems with the exception of phenoxathiin and phenoxatellurin exhibit first-order spectra ⟨93OM775⟩.

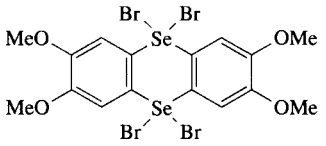
Detailed ^{13}C NMR studies have also been carried out ⟨79JOM(181)329, 81JOM(212)141, 89H(28)1007⟩. Thus, when one of the oxygen atoms in oxanthrene (**74**) is replaced in turn by sulfur, selenium, or tellurium there is a marked upfield shift in the *ipso* C-10a signal from 142.1 to 119.1 → 116.1 → 102.0 ppm, whereas that of C-4a changes much less: from 142.1 to 161.9 → 152.9 → 155.6 ppm. ⟨79JOM(181)329, 81JOM(212)141⟩.

^{13}C NMR data relating to selenanthrene, oxaselenin, and oxatellurin halides is given in Section 6.24.4.2.1.

6.24.4.1.3 Electronic properties

2,3,7,8-Tetramethoxyselenanthrene dibromide (**75**) is nearly planar and forms a self-stacking array, which acts as a semiconductor with an energy gap $E_g = 1.07$ eV ⟨86JCR(S)326, 90SM93⟩.

The nature of the lowest electronic states of the chalcogenanthrenes has been studied, as have singlet-triplet transitions in the excited states ⟨89MI 624-01⟩. In the latter case singlet-triplet radiative transitions are influenced by the nature of the heteroatoms present, and nonradiative processes are dominated by the degree of folding ⟨77JCPB1177⟩.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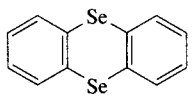
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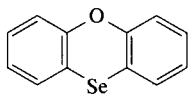
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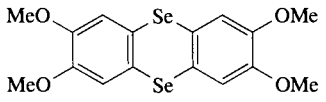
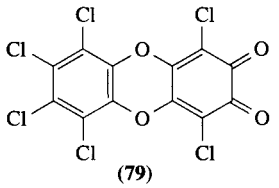

(78)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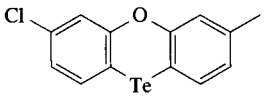
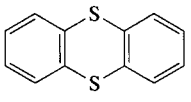

(80)

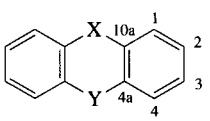
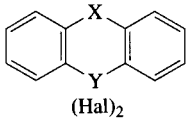

(81)

6.24.4.2 Complexation and Reactions

6.24.4.2.1 Halogenation

NMR techniques have been used to determine the nature of the compounds formed between dichalogenanthrenes and halogens. For example, the formation of hypervalent trigonal bipyramidal (TB) complexes causes large downfield shifts of the resonances of the selenium and tellurium atoms (> 100 ppm) relative to those in the parent tricycles, whereas in the ^{13}C NMR spectra upfield shifts of the resonance of the carbon *ipso* to the halogenated chalcogen atom characterize molecular compounds (MC) ⟨90JPO358, 90JPO369⟩. Selenanthrene (**76**) yields molecular complexes with bromine and iodine, whereas the chlorine, bromine, and iodine adducts of phenoxatellurin are all considered to be TB types, as are the chlorine and bromine complexes of phenoxaselenin (**77**). The iodine complex is, however, a molecular compound (Table 1). So far, there is no satisfactory explanation of what subtle factors control the relative stabilities of the two types of complex in solution.

Table 1 ^{13}C NMR Chemical shifts ($CDCl_3$) for various chalcogenanthrenes and dihalides.



$(Hal)_2$

Compound	*C10a*	*C1*	*C2*	*C3*	*C4*	*C4a*	*Type*
X = Y = Se	134.4	131.1	127.9				
Hal = Br	−2.1	−0.2	1.9				MC
Hal = I	0.5	0.1	0.3				MC
X = O, Y = Se	116.2	129.3	124.9	128.1	118.3	152.9	
Hal = Cl	4.4	−0.1	0.8	6.2	1.3	−5.3	TB
Hal = Br	0.7	0.5	1.1	6.0	1.3	−4.8	TB
Hal = I	−0.9	0.1	0.1	0.5	0.1	−0.3	MC
X = O, Y = Te	103.9	135.1	125.2	128.7	118.9	155.2	
Hal = Cl	15.3	−1.3	−0.7	4.5	0	−4.1	TB
Hal = Br	11.3	−0.7	−0.5	4.5	−0.1	−3.7	TB
Hal = I	5.5	0.2	−0.3	4.5	−0.2	−2.8	TB

6.24.4.2.2 Complexation with metal salts and acceptor molecules

The dichalcogenanthrenes and their allies exhibit marked electron-donor properties and form complexes with certain salts and metal carbonyls ⟨62CB2027, 82DOK(266)1164, 86JCR(S)326⟩. Tetramethoxyselenanthrene (**78**), for instance, forms a complex with mercury(II) chloride in which the selenium atoms are both bonded to the mercury atom, which is approximately tetrahedral in its coordination. The heterocyclic system as a result takes up a more sharply bent conformation than it normally adopts in the free state ⟨86JCR(S)326⟩.

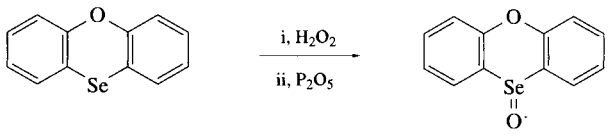
In addition, the dichalcogenanthrenes form complexes with a range of acceptor molecules, including 1,3,5-trinitrobenzene (TNB), tetracyanoethene (TCNE), and tetracyanobenzoquinone (TCNQ) ⟨69BAP1, 70RZC1713, 73RRC531, 74CJC3814, 80CJC1133, 84JCS(D)1267⟩. Frequently the products are stable 1 : 1 charge-transfer complexes and for the heteroatom combinations O,Se and O,Te the locus of the electron donation is a lone pair of electrons on the heavier atom (σ-types). For O,S however a 1 : 1 TNB complex is produced in which the π-system of the acceptor lies parallel to one of the benzenoid rings (π-type) ⟨69BAP333⟩. Similarly, 2,3,7,8-tetramethoxyselenanthrene (**78**) forms a dark blue complex with TCNQ, in which one of the benzenoid rings of the folded selenanthrene unit is coplanar with the TCNQ molecule ⟨76JA3926, 82JCR(S)336, 87SM357⟩. More than one donor molecule can be accommodated and compound (**78**) affords a 2 : 1 complex with TCNE in which the acceptor molecule is inserted into the cavity formed by two of the folded, oppositely arranged, selenanthrene units, thereby maximizing HOMO–LUMO overlap ⟨89ZN(B)211, 92MI 624-01⟩. With hexachlorooxanthrene-2,3-dione (**79**), however, a 3 : 1 dark blue adduct forms ⟨86ZN(B)1133⟩.

Phenoxatellurins exhibit both donor and acceptor properties and, for example, phenoxatellurin forms a 1 : 1 addition complex with 7-chloro-3-methylphenoxatellurin (**80**) ⟨27JCS116, 28JCS506⟩.

6.24.4.2.3 Oxidation and reactions with electrophiles

In common with the much-studied oxidation behavior of thianthrene (**81**) (⟨94JOC3553⟩ and references cited therein), radical cations are generated from chalcogenanthrenes by the action of a variety of oxidants, and reactions with nitric acid, for example, are commonly characterized by the development of a blue colour, which may indicate the formation of the radical cation. The generation of radical cations can be authenticated by cyclic voltammetry, and it has been observed that the radical cation of phenoxatellurin ($POT^{\cdot +}$) undergoes dimerization and reaction with an un-ionized molecule of the substrate (POT) to generate a complex cation $POT(POT^{\cdot +})_2$ ⟨66BSF2510, 73BSF2870⟩. 2,3,7,8-Tetramethoxyselenanthrene (**78**) is oxidized through single electron transfers at +0.9 V and at +1.21 V (vs. SCE) ⟨77CJC766, 85ZN(B)774⟩. First oxidation potentials for the other 2,3,7,8-tetramethoxyanthrenes have been measured in an attempt to relate oxidizability to the dihedral angle between the two benzenoid rings and hence the degree of π-delocalization. However, apart from phenoxaselenin (**77**) (+0.79 V), all the others are oxidized at about the same potential as selenanthrene (ca. +0.9 V) ⟨88JCS(P1)2095⟩.

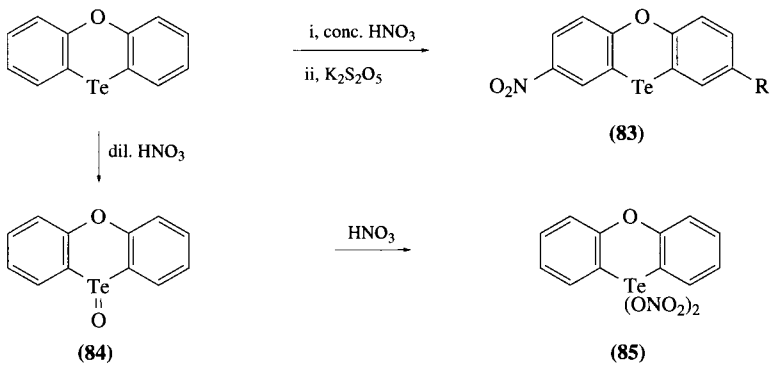
Phenoxaselenin, when oxidized with hydrogen peroxide in acetic acid, forms a dihydroxide, which on treatment with phosphorus pentoxide gives the 10-oxide (**82**) (Equation (18)) ⟨28JCS511⟩.



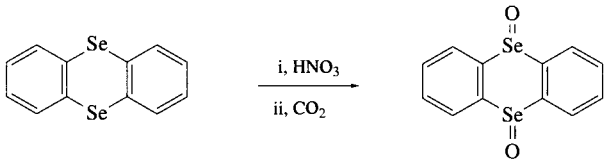
(77) (82) (18)

Phenoxatellurin is nitrated by conc. nitric acid affording 2-nitro- (**83**; R = H) and 2,8-dinitrophenoxatellurin (**83**; R = NO_2), as their 10,10-dinitrates. Reduction with $K_2S_2O_5$ affords the free nitro compounds. Dilute nitric acid yields the 10-oxide (**84**) and further reaction leads to the 10,10-dinitrato derivative (**85**) (Scheme 21) ⟨27JCS116⟩.

Selenanthrene dissolves in conc. nitric acid to give a blue solution, the color of which disappears when the solution is diluted. It also forms a crystalline dinitrate, which when heated quickly bursts into flames. When the dinitrate is treated with sodium hydroxide and then neutralized with carbon dioxide selenanthrene-5,10-dioxide (**86**) is obtained. The last compound can also be obtained from the parent by the action of hydrogen peroxide (Equation (19)) ⟨51JCS237⟩.

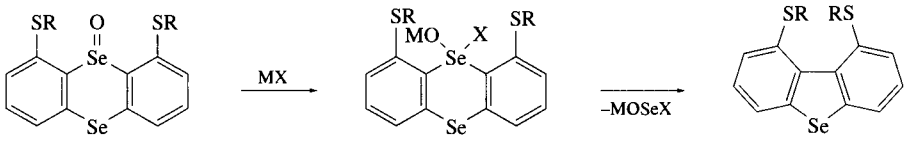


Scheme 21



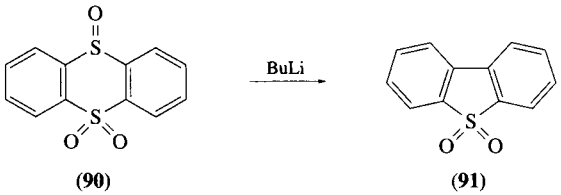
(19)

Selenanthrene monoxides (**87**) undergo ring contraction to dibenzoselenophenes (**89**) when reacted with Grignard reagents or alkyllithiums. Ligand coupling is considered to be the first step, affording intermediate selenuranes (**88**) (Scheme 22) ⟨93HAC243⟩. These reactions parallel a process which occurs between thianthrene-5,5,10-trioxide (**90**) and butyllithium, giving dibenzothiophene-5,5-dioxide (**91**) (Equation (20)) ⟨57JA208⟩.



R = Me, Ph; M = MgBr, Li

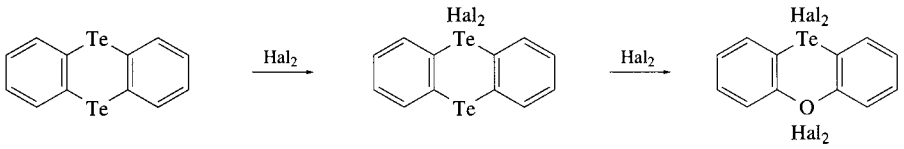
Scheme 22



(20)

As with the monocyclic dichalcogenanes, a variety of halogenating agents including the halogens themselves react oxidatively at the selenium or tellurium atoms to form halides. Tellurium-containing tricyclic systems, for example, react with sulfuryl chloride to give dichlorides. For telluranthrenes halogenation can proceed further. Thus, with either bromine or iodine in chloroform at room temperature, telluranthrene affords the corresponding 5,5-dihalides (**92**), but if the solvent is heated to its boiling point 5,5,10,10-tetrahalides (**93**) are obtained (Scheme 23) ⟨91KGS1424⟩.

Selenanthrene reacts with bromine in carbon disulfide to form a dibromide; this reverts to selenanthrene on treatment with sodium hydroxide standing in moist air or on heating. Sulfuryl chloride in boiling benzene affords the 5,5,10,10-tetrachloride, which on treatment with aqueous sodium bicarbonate yields the 5,10-dioxide ⟨57ACS580⟩. Halogens attached to the heavy atom are easily exchanged and 10,10-diiodophenoxatellurin, for example, is converted into the corresponding dichloride by reaction with either chlorine or sulfuryl chloride. With moist silver oxide, or aqueous



(92) (93)

Scheme 23

alkali, phenoxatellurin 10,10-dihalides yield the 10-oxide ⟨34JCS1790, 70MI 624-01, 85KGS757⟩. The x-ray crystal structure of phenoxatellurin diiodide has been reported ⟨73IC2665⟩.

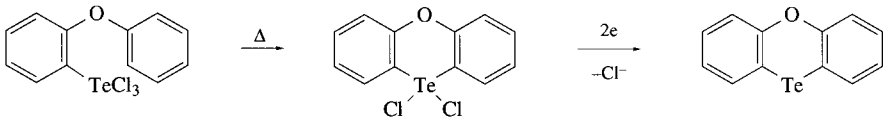
Alkylation of phenoxatellurin with methyl iodide requires heating in a sealed tube to give the corresponding 10-methyltelluronium salt (**94**). This product is an alkylating agent in its own right and in DMSO solution an equilibrium is established between the salt, phenoxatellurin, and trimethylsulfoxonium iodide (**95**) (Scheme 24) ⟨84JHC413⟩.

(94) (95)

Scheme 24

6.24.4.3 Synthesis

Phenoxatellurins can be obtained through the intramolecular thermal cyclization of 2-trichlorotelluroaryl aryl ethers (**96**), available from either the corresponding arylmercuric chlorides or aryltrimethylsilanes, and tellurium tetrachloride ⟨26JCS223⟩ and reductive dechlorination of the intermediate 10,10-dichlorophenoxatellurins (**97**) (Scheme 25). A number of reducing agents are effective for the last step, including $K_2S_2O_5$, K_2SO_3, Na_2S, and N_2H_4.

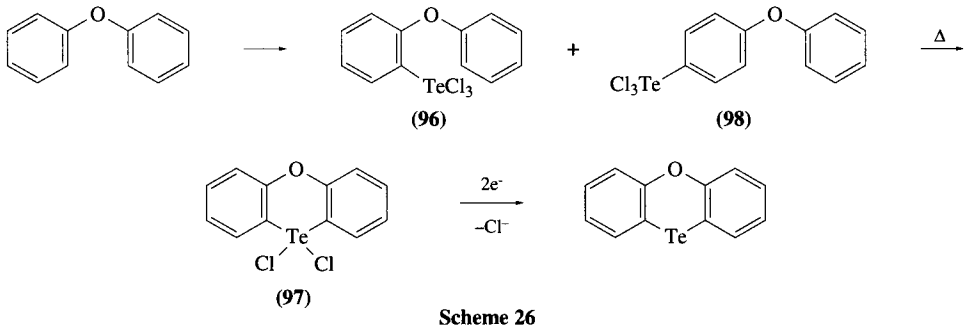


(96) (97)

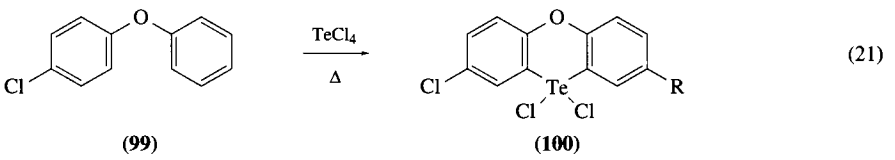
Scheme 25

When diphenyl ether is reacted with tellurium tetrachloride a mixture of the isomeric 2- and 4-trichlorotellurides (**96**) and (**98**) is formed; however, on heating only 10,10-dichlorophenoxatellurin (**97**) is obtained, suggesting that a migration of the tellurium substituent occurs in the *para*-isomer (Scheme 26). This is corroborated since, when heated at ca. 160 °C, the *para*-isomer (**98**) rearranges to 2-trichlorotellurophenyl phenyl ether (**96**). Thus the whole reaction can be run as a single operation. This approach has limitations when applied to other 10,10-dichlorophenoxatellurins, since electron-withdrawing groups inhibit the cyclization and problems arise when electron-donating substituents are present in the diphenyl ether. Now heating with tellurium tetrachloride can lead to the introduction of chlorine atoms into the aryl nuclei. For example, in the case of 4-chlorophenyl phenyl ether (**99**) the products are the mono- and dichloro phenoxatellurin dichlorides (**100**; R = H) and (**100**; R = Cl) (Equation (21)) ⟨76RRC739⟩. The problem of chlorination becomes more acute in the case of selenium tetrachloride and this reagent cannot be used to synthesize phenoxaselenins from diaryl ethers. Phenoxaselenin can be obtained, however, by heating phenoxatellurin with selenium (Equation (22)) ⟨28JCS511⟩ and phenoxaselenins (**102**) are also obtained through the

cyclodehydration of diaryl ethers (**101**) containing a 2-seleninic acid substituent and reduction with potassium metasulfite (Equation (23)) ⟨38JCS29⟩.



Scheme 26



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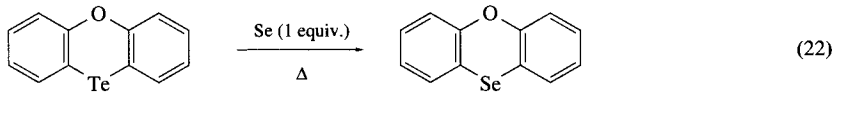

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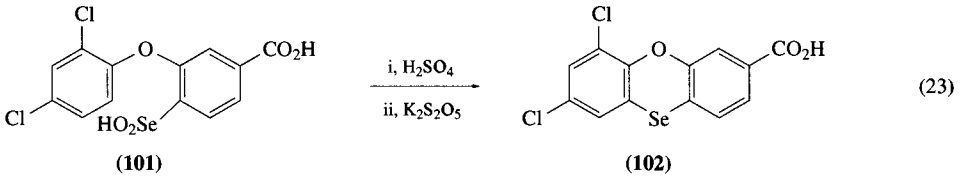
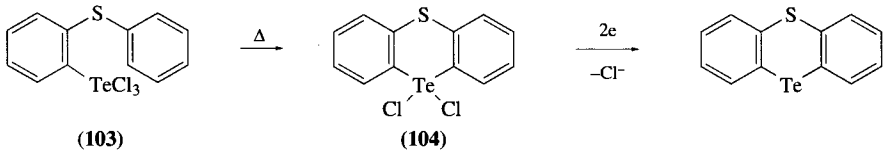


(23)

Methods for forming the oxaselenin ring fused to two aromatic rings by nucleophilic cyclizations involving selenolate anions are known, but they have been applied to the synthesis of 1,4-oxaseleninodipyridines, which are outside the scope of this chapter.

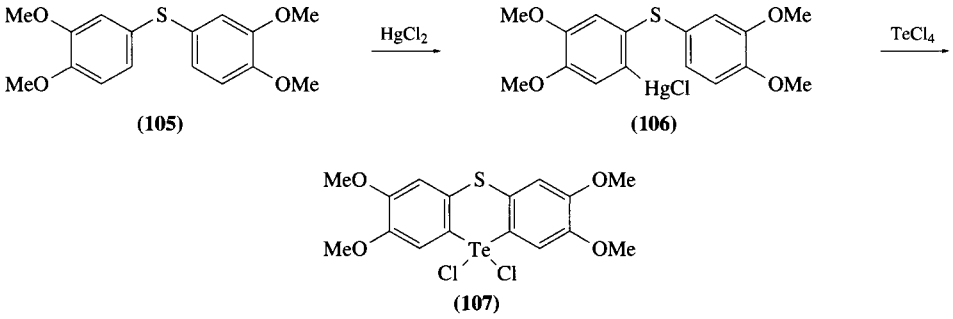
Phenothiatellurins are synthesized by heating 2-trichlorotellurophenyl phenyl sulfides; thus, phenothiatellurin is obtained when 2-trichlorotellurophenyl phenyl thioether (**103**) is heated at 240–250°C and the intermediate (**104**) is dechlorinated by reduction with sodium sulfide (Scheme 27) ⟨60T15⟩.



Scheme 27

Tetramethoxyphenothiatellurin-5,5-dichloride (**107**) is prepared by reacting bis(3,4-dimethoxyphenyl)sulfide (**105**) with mercuric chloride in trichloroacetic acid and then treating the intermediate (**106**) with tellurium tetrachloride (Scheme 28) ⟨87PS(29)377⟩.

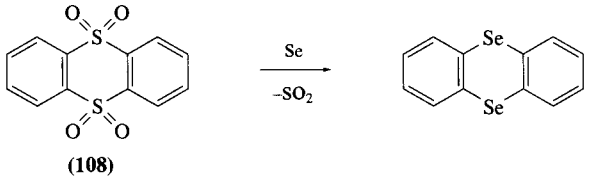
Selenanthrene has a long pedigree; it was first prepared in 1896 by heating thianthrene 5,5,10,10-tetraoxide (**108**) with selenium in an inert atmosphere (Equation (24)). The yield was 64% ⟨1896CB443⟩. A variety of other methods are available for the synthesis of selenanthrene, for example, through the reaction of diphenyl selenide and potassium amide in liquid ammonia (the yield depends on the amount of KNH_2 used) ⟨67AG(E)1071⟩. 2,3,7,8-Bis(methylenedioxy)selenanthrene was prepared by heating 1,3-benzodioxole with selenium dioxide ⟨86JCR(S)326⟩, and 2,3,7,8-tetramethoxyselenanthrene can be synthesized similarly from 1,2-dimethoxybenzene ⟨87JCR(S)248⟩. The



(105) (106) (107)

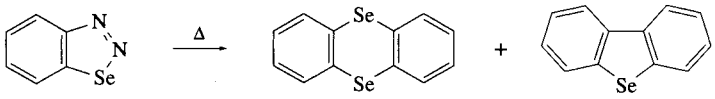
Scheme 28

parent compound and symmetrically substituted derivatives can be obtained by the thermolysis of 1,2,3-benzoselenadiazoles (**109**), although dibenzoselenophenes (**110**) are also formed (Equation (25)). In another example of this type, 2,3,7,8-tetramethoxyselenanthrene (**113**) can be synthesized by heating the selenadiazole (**112**) in acetic acid. The starting material is prepared by diazotizing 2-amino-4,5-dimethoxyselenophenol (**111**) (Scheme 29) ⟨72JHC1411, 75JHC801, 76CB1650⟩.



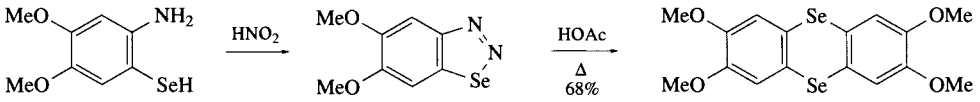
(24)

(108)



(25)

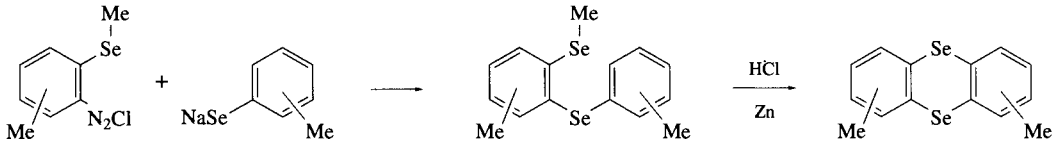
(109) (110)



(111) (112) (113)

Scheme 29

Methylselenanthrenes (**117**) (various positions) are formed by the coupling of the appropriate sodium selenophenates (**115**) and 2-(methylseleno)benzenediazonium halides (**114**), followed by the cyclization of the intermediate aryl 2-(methylseleno)aryl selenides (**116**) with conc. hydrochloric acid and zinc (Scheme 30) ⟨36YZ869, 37YZ190⟩.

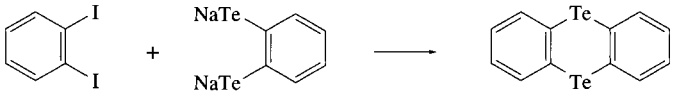


(114) (115) (116) (117)

Scheme 30

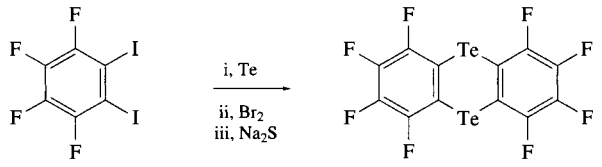
Halogenoselenanthrenes are obtained by heating tetrahalophenylenemercurials with selenium, and this approach can be adapted to prepare the corresponding halogenothianthrenes and halogenotelluranthrenes ⟨87JOM(319)59⟩. Telluranthrenes cannot be made by the reaction of diaryltellurides and tellurium tetrachloride, since this forms diaryltellurium dichlorides, which are inert to further attack.

Telluranthrene itself is available through the reaction of poly(2-phenylenemercury) with tellurium powder at a temperature not exceeding 250 °C. Although the yield was 70%, the starting material is rather inaccessible, and a more convenient, though somewhat less efficient, route is through the coupling of disodium benzene-1,2-ditellurate (**119**) with 1,2-diiodobenzene (**118**) (Equation (26)) ⟨81JOM(212)141⟩. Alternatively, poly(*ortho*-phenyleneditelluride) can be treated with sodium borohydride in DMF and then with 1,2-diiodobenzene to give telluranthrene in 50–62% yield. The direct reaction of poly(*ortho*-phenyleneditelluride) with butyllithium in diethyl ether produces the same product, but in only 26% yield ⟨91KGS1424⟩.



(118) (119) (26)

Other starting materials include 1,2-bis(trichlorotelluro)benzene, which when heated with 1,2-bis(trimethylsilyl)benzene gives telluranthrene-5,5,10,10-tetrachloride. This can be reduced to the parent heterocycle by treatment with zinc ⟨91KGS1424⟩. An early report, from the mid-1960s, claimed that this heterocycle could be prepared through the reaction of tetraphenyltin and tellurium ⟨64ZN(B)74⟩; however, the product was described as an unstable brown powder, m.p. 198–199 °C, whereas it is now known to be a stable pale yellow solid, m.p. 169–170 °C (CCl_4).



(27)

Octafluorotelluranthrene is formed when 3,4,5,6-tetrafluoro-1,2-diiodobenzene is heated with tellurium at 300 °C and the product is treated with bromine. This yields the 5,5,10,10-tetrabromide intermediate, subsequent reduction of which is achieved (although in only 20% yield) using sodium sulfide (Equation (27)) ⟨80JFC(16)245⟩.

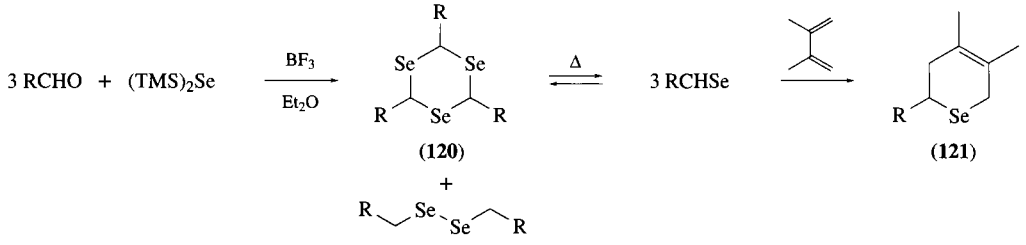
6.24.5 TRISELENANES AND TRITELLURANES

6.24.5.1 Complexation, Stability, and Reactions

Although 1,3,5-triselenane (**120**; R = H) is unstable, the heterocycle and its oligomers form relatively stable complexes with silver salts. With silver hexafluoroarsenate in sulfur dioxide, for example, 1,3,5-triselenane affords a complex $[[(CH_2Se)_3]_2Ag]AsF_6$ in which the silver atom is equidistant from all the selenium atoms in both heterocyclic subunits ⟨83JOM(249)97⟩.

1,3,5-Triselenane is decomposed by the action of chlorine in carbon tetrachloride into bis(chloromethyl)selenide, chloromethylselenium chloride, and bis(chloromethyl)diselenide ⟨50JCS1351⟩.

The cyclotrimerization of selenoaldehydes is reversible ⟨82ZAAC(488)99⟩. Thus, when aldehydes react with bis(trimethylsilyl)selenide in the presence of boron trifluoride etherate, triselenanes (**120**) are produced. These can be used as sources of selenoaldehydes, which undergo cycloaddition with 1,3-dienes affording dihydroselenins (**121**) (Scheme 31) ⟨89TL6047⟩.



Scheme 31

6.24.5.2 Synthesis

1,3,5-Triselenane is one of three oligomeric products formed by treating a solution of formaldehyde in hydrochloric acid with hydrogen selenide ⟨50JCS1351⟩. Alternatively, it is produced when bis(chloromethyl)selenide is heated with either aqueous boric acid or sodium bicarbonate ⟨82ZAAC(488)60, 83PS(14)241⟩, or when dichloromethane is treated with sodium selenide ⟨66ZN(B)622⟩. 1,3,5-Tritellurane is formed similarly ⟨35JA4329⟩ and both it, and 1,3,5-triselenane respectively, are obtained when diazomethane is thermolyzed over a tellurium or selenium mirror ⟨68CC459⟩.

6.24.6 SELENAZINES

6.24.6.1 Dihydro-1,2-selenazines

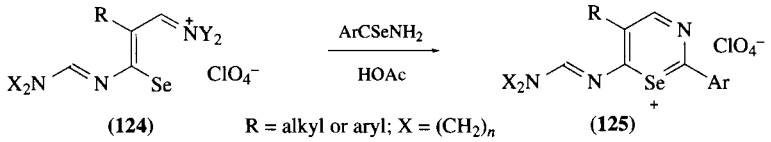
1,2-Selenazines are very poorly represented in the chemical literature, but the 3,6-dihydro-2*H*-1,2-selenazine 1-imines (**123**) are available through cycloaddition of *N*,*N*′-diarenesulfonylselenium-diimides (**122**) to 1,3-dienes (Equation (28)) ⟨86ZOR1189⟩).

(28)

(122) (123)

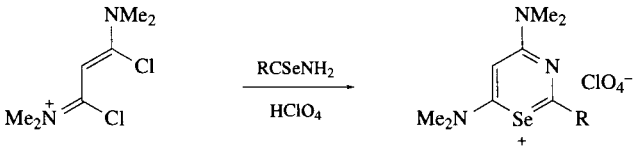
6.24.6.2 1,3-Selenazines, 1,3- and 3,1-Benzoselenazines, and Allied Compounds

A general synthesis of 6-imino-1,3-selenazinium salts (**125**) uses the condensation of 1,5,7-triazahepta-1,3,5-trienium perchlorates (**124**) and arylcarboselenoamides in acetic acid (Equation (29)) ⟨78EGP131647⟩. Alternatively, 1,3-bis(dimethylamino)-1,3-dichloropropenylium chloride (**126**) can be reacted with selenoamides and perchloric acid in DCM to afford the 4,6-diamino analogues (**127**) (Equation (30)) ⟨87BCJ2686⟩.



(29)

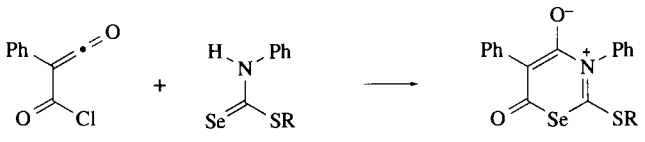
(124) R = alkyl or aryl; X = $(CH_2)_n$ (125)



(30)

(126) R = NMe_2, Ph, pyrrolidin-1-yl (127)

The 4-oxido-6-oxo-1,3-selenazinium mesomeric betaines (**130**) can be obtained through the reaction of chlorocarbonylphenylketene (**128**) and *S*-alkyl-*N*-phenylselenothiocarbamate (**129**) (Equation (31)) ⟨77JOC1644⟩.

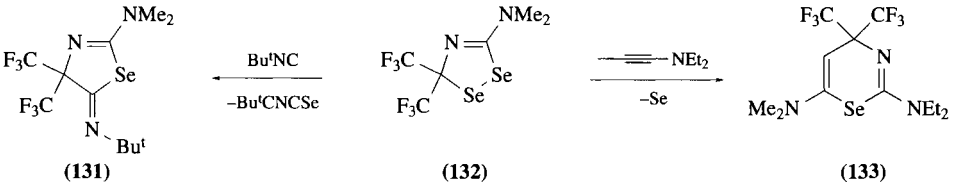


(31)

(128) (129) (130)

The 2,6-diamino-4*H*-1,3-selenazine (**133**) is synthesized by heating the 1,2,4-diselenazole (**132**) with *N*,*N*-diethylaminopropyne at 50–70 °C. Under these conditions ring expansion occurs with

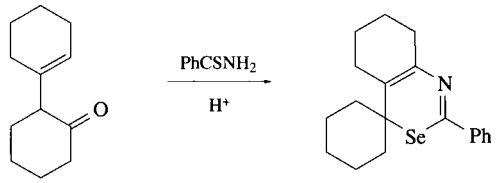
elimination of elemental selenium. If the diselenazole is heated with an alkyl isocyanide a selanazol-5(4*H*)-imine (**131**) is formed; this time an alkyl isoselenocyanate is lost (Scheme 32) ⟨78TL973⟩.



(131) (132) (133)

Scheme 32

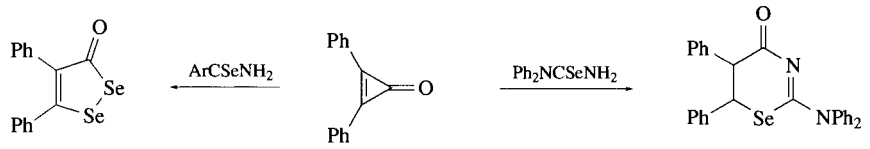
The spiro-3,1-benzoselenazine (**135**) can be synthesized very simply by heating 2-cyclohexenylcyclohexanone (**134**) with selenobenzamide in an acidic medium (Equation (32)) ⟨89AX(B)276⟩.



(32)

(134) (135)

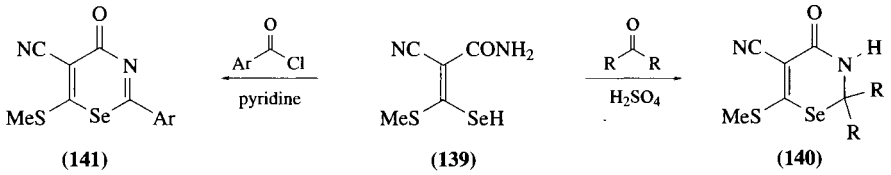
Unexpectedly, diphenylcyclopropenone (**136**) reacts with selenoamides to form the 1,2-diselenol-3-one (**138**), but with *N*,*N*-diphenylselenourea 5,6-dihydro-5,6-diphenyl-2-(*N*,*N*-diphenylamino)-1,3-selenazin-4-one (**137**) is the product (Scheme 33) ⟨80H(14)1921⟩.



(138) (136) (137)

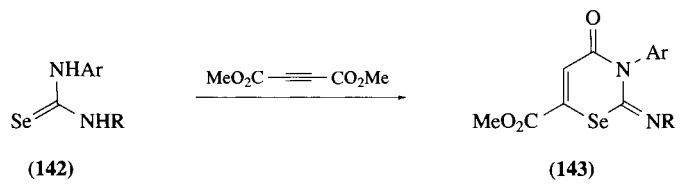
Scheme 33

2-Cyano-3-hydroseleno-3-(methylthio)acrylamide (**139**) reacts with ketones, catalyzed by sulfuric acid, to give 2,3-dihydro-1,3-selenazin-4-ones (**140**) in moderate yields. Aroyl chlorides react with the same substrate in the presence of pyridine to afford 1,3-selenazin-4-ones (**141**) (Scheme 34) ⟨86BCJ2909⟩. Another approach to 1,3-selenazin-4-ones (**143**) involves the cycloadditions of selenoureas (**142**) with DMAD in methanol at room temperature (Equation (33)) ⟨78JHC39⟩.



(141) (139) (140)

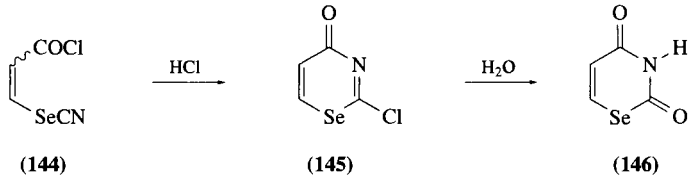
Scheme 34



(33)

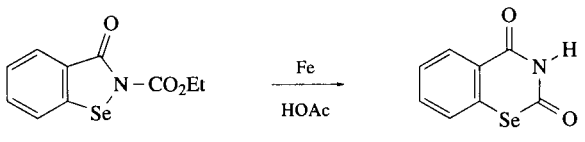
(142) (143)

2-Chloro-1,3-selenazin-4-one (**145**) can be prepared by reacting 2-selenocyanatopropenoyl chloride (**144**) with hydrogen chloride. On heating (**145**) with water hydrolysis affords the dione (**146**) (Scheme 35) ⟨77LA1249⟩.



Scheme 35

The benzo analogue (**148**) of the above dione is available through the reductive ring opening and recyclization of the 1,2-benzoselenazolone (**147**) (Equation (34)) ⟨89BSB395⟩, and the related 2-chloro (**150**) and 2-(*N*,*N*-dimethylamino) (**151**) derivatives are formed by the cyclization of 2-selenocyanatobenzoyl chloride (**149**) in the presence of hydrochloric acid, then treatment with dimethylamine (Scheme 36) ⟨70CB413⟩. 2-Pyridinoselenazinones have been prepared in a similar way ⟨83CCC3567⟩.



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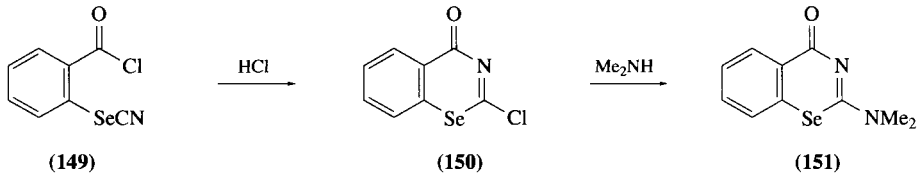
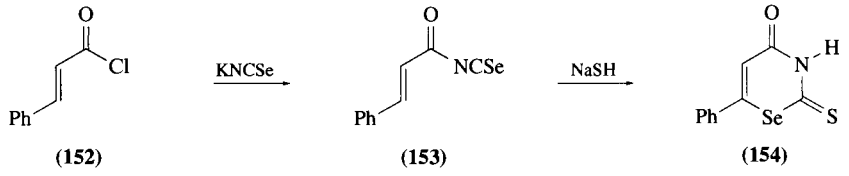
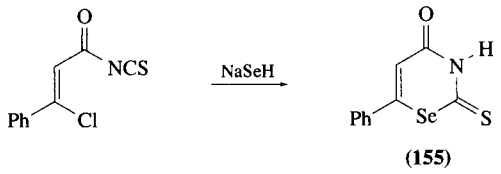


Scheme 36

6-Phenyl-2-thioxo-1,3-selenazin-4-one (**154**) is prepared by reacting cinnamoyl isoselenocyanate (**153**) with sodium hydrogen sulfide in water. The starting selenocyanate is obtained from cinnamoyl chloride (**152**) and potassium selenocyanate (Scheme 37) ⟨76CCC1388⟩. The action of sodium hydrogen selenide on 3-chloro-3-phenylpropenoyl isothiocyanate leads to the unsaturated thione (**155**) (Equation (35)) ⟨79CZ792, 82CCC3268⟩.

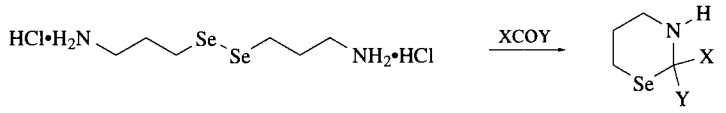


Scheme 37



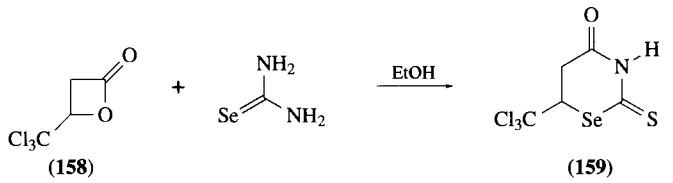
(35)

A range of 1,3-selenazanes (**157**) has been synthesized through the reactions of aldehydes and ketones with the dihydrochloride of bis(3-aminopropyl)diselenide (**156**) (Equation (36)), itself synthesized from bis(3-phthalimidopropyl) diselenide by treatment with hydrazine hydrochloride ⟨72CR(C)1637⟩.



(156) (157) X = H; Y = Me, Ar; X,Y = $(CH_2)_5$ (36)

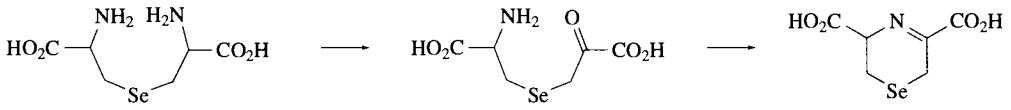
6-Trichloromethyl-2-iminotetrahydro-1,3-selenazin-4-one (**159**) has been synthesized from trichloromethylpropiolactone (**158**) and selenourea (Equation (37)) ⟨69ZOR1844⟩.



(158) (159) (37)

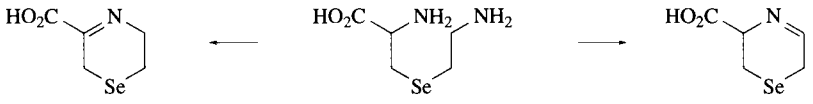
6.24.6.3 1,4-Selenazines, 1,4-Selenazanes, and Benzo Derivatives

5,6-Dihydro-2*H*-1,4-selenazine-3,5-dicarboxylic acid (**162**) is formed via the α-keto acid (**161**), which is obtained by the the deamination of selenolanthionine (**160**) with snake venom L-amino acid oxidase (Scheme 38) ⟨90MI 624-01⟩. The mono acid (**164**) is formed from the similar treatment of L-selenolysine (**163**), but its isomer (**165**) is the result of replacing the snake venom with diamine oxidase from pea seedlings (Scheme 39) ⟨81MI 624-01⟩.



(160) (161) (162)

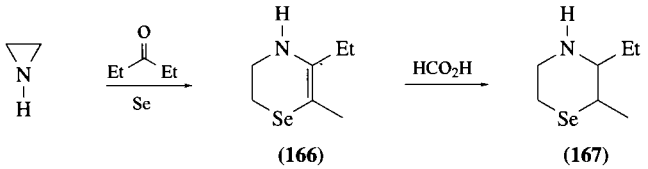
Scheme 38



(165) (163) (164)

Scheme 39

Aziridine, when reacted with selenium and pentan-3-one, affords 3-ethyl-5,6-dihydro-2-methyl-4*H*-1,4-selenazine (**166**), which is reduced to the corresponding selenazane (**167**) by formic acid (Scheme 40) ⟨68M2084⟩.

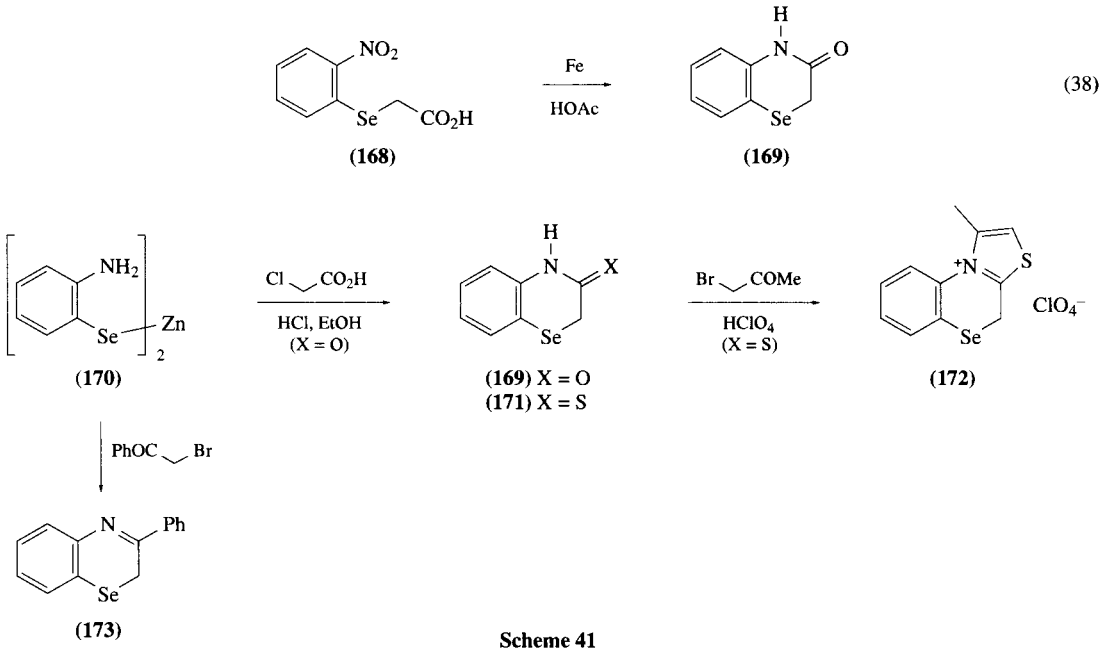


(166) (167)

Scheme 40

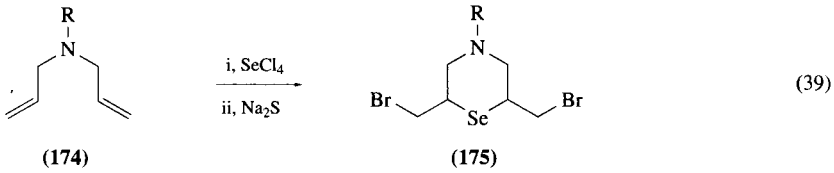
The reductive cyclization of 2-nitrophenylselenoacetic acid (**168**) with iron and acetic acid yields 2*H*-1,4-benzoselenazin-3(4*H*)-one (**169**) (Equation (38)) ⟨30JPR336⟩. This product is also available by the annulation of zinc di(2-aminophenyl)selenide (**170**) through reaction with chloroacetic acid and hydrogen chloride in ethanol. When treated with phosphorus pentasulfide the corresponding thione (**171**) is formed, and this, with bromoacetone and perchloric acid, affords 1-methylthiazolo[2,3-*c*]-1,4-benzoselenazium perchlorate (**172**), the basis of some cyanine dyestuffs

〈67ZOR1097〉. When the zinc selenide (**170**) is reacted with phenacyl bromide 3-phenyl-2*H*-1,4-benzoselenazine (**173**) is produced (Scheme 41). This compound is unstable and undergoes oxidative dimerization 〈B-86MI 624-02〉.



Scheme 41

An approach to 2,6-di(bromomethyl)-1,4-selenazanes (**175**) requires the reaction of diallylamines (**174**; R = H or Et) and selenium tetrabromide, followed by reductive debromination with sodium sulfide (Equation (39)) 〈77KGS58〉. This procedure parallels that used to prepare 1,4-dichalcogenanes (Section 6.24.3.2), and if *N*-arenesulfonyldiallylamines (**174**; R = SO_2Ar) are used, tellurium tetrabromide gives the corresponding 1,4-tellurazines as the dibromides 〈89KGS564〉.



6.24.7 PHENOSELENAZINES, PHENOTELLURAZINES, AND ALLIED COMPOUNDS

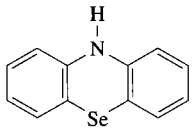
6.24.7.1 Physical Properties

The structures of the phenoselenazines and the phenotellurazines are folded and in this they resemble those of the dichalcogenanthrenes, for example, a crystal structure of phenoselenazine (**176**) shows that the molecule has a dihedral fold angle of 149.4° 〈74AX(B)1332, 75MI 624-01〉, while the angle in 10-ethyl-3,7-dimethylphenotellurazine (**177**) is 137.7° 〈85MI 624-01〉.

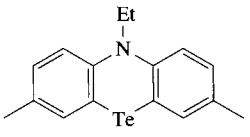
6.24.7.2 Reactions

6.24.7.2.1 Oxidation and reactions with electrophiles

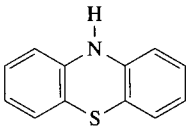
Phenothiazine (**178**) when oxidized with bromine forms a radical cation bromide (**179**) which reacts with phenoselenazine to give a complex cation radical salt involving both ring systems 〈75BCJ3747〉. Phenoselenazines initially form cation radicals on oxidation which then undergo dimerization reactions 〈75BCJ1043〉. Similarly, oxidation of phenoselenazine with dimethyl sulfoxide



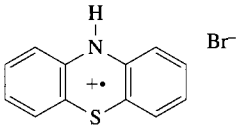
(176)



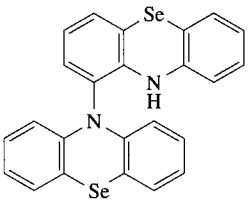
(177)



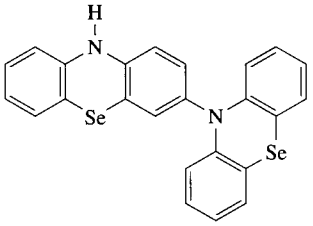
(178)



(179)



(180)

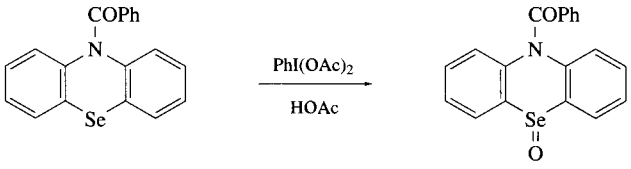


(181)

in acetic anhydride is assumed to form the neutral phenoselenazinyl radical, but the ESR signal is too weak to measure. Dehydro-dimers, linked 1,10′ (**180**) and 3,10′ (**181**), are formed after the oxidation, along with polymeric products ⟨68TL4111⟩. Surprisingly, oxidation with iodine in dimethyl sulfoxide gives only the 3,10′-dimer (**181**) in 65% yield ⟨69TL763, 75BCJ1043⟩.

Radical cations also form when phenotellurazines are oxidized by lead dioxide in trifluoroacetic acid; these are stable and their ESR spectra are well resolved, showing extensive delocalization of the unpaired electron ⟨85KGS757⟩.

When 10-benzoylphenoselenazine (**182**) is shaken with a solution of phenyl iodosodiacetate in acetic acid the 5-oxide (**183**) is produced (Equation (40)) ⟨72CCA411⟩.



(182) (183)

(40)

Oxidation of the chalcogen atom to the hypervalent state is effected by treatment with many oxidants including halogens. Thus, phenotellurazines are oxidized to the corresponding 5,5-dihalides by treatment with chlorine, bromine, or iodine, or by sulfuryl chloride ⟨82DOK(266)1164, 82KGS707, 85KGS757, 89H(28)1007⟩. Further halogenation is then directed to C-3 and C-7, positions *para* to the nitrogen atom. Thus, bromination of *N*-ethylphenotellurazine in the presence of iodine gives the 3,5,5,7-tetrabromo derivative. Similarly, nitration of *N*-ethylphenotellurazine affords the corresponding 3-, 3,7-di-, and 1,3,7,9-tetranitrophenotellurazine 5,5-nitrates, the extent of the reaction depending on the severity of the nitrating conditions ⟨85KGS757⟩.

N-Alkylphenoselenazines can be synthesized by adding alkyl halides, or less effectively dialkyl sulfates, to phenoselenazine in liquid ammonia containing sodium amide, and *N*-aroyl derivatives are obtained by reactions of the parent heterocycles with aroyl halides ⟨66MI 624-01⟩. *N*-Methylphenotellurazines are similarly prepared ⟨83JOM(251)223⟩.

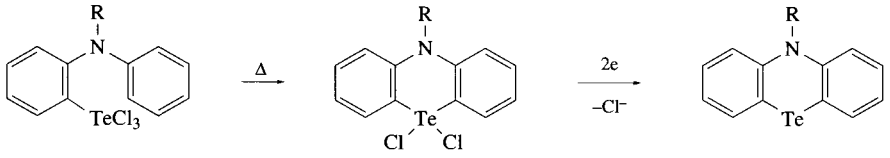
6.24.7.2.2 Complexation reactions

N-Alkylphenotellurazines form 1 : 1 molecular complexes with mercury(II) halides and with silver nitrate or silver perchlorate ⟨85KGS757⟩. Bis(benzonitrile)palladium(II) chloride reacts to form a 2 : 1 adduct and rhodium carbonyls also complex with phenotellurazines ⟨82DOK(266)1164⟩.

6.24.7.3 Synthesis

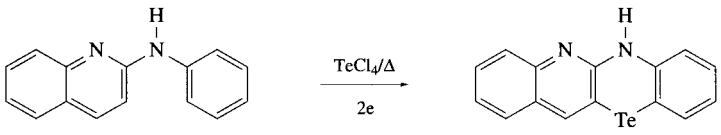
Phenotellurazines (**186**) are synthesized by heating the *N*-phenyl-*N*-(2-trichlorotellurodiphenyl)-amines (**184**) with tellurium tetrachloride, followed by reductive dechlorination of the intermediate

dichlorides (**185**) (Scheme 42) ⟨60T15, 85KGS757⟩. Simply heating the parent amines with tellurium tetrachloride is normally unsatisfactory, but when 2-(*N*-phenylamino)quinoline (**187**) is heated under these conditions and the intermediate dechlorinated by treatment with sodium bisulfite, the tetracycle (**188**) is obtained (Equation (41)) ⟨77MI 624-01⟩.



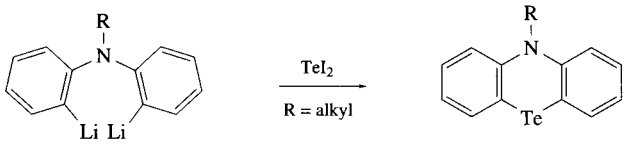
(**184**) (**185**) (**186**)

Scheme 42



(**187**) (**188**) (41)

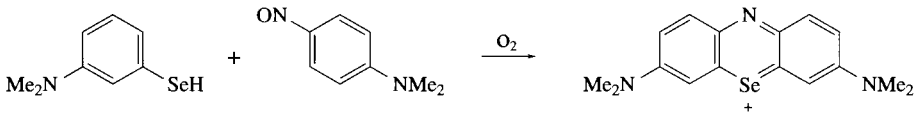
A more versatile method to phenotellurazines involves the reaction of *N*,*N*-di(2-lithioaryl)-alkylamines (**189**) with tellurium diiodide (Equation (42)) ⟨82DOK(266)1164, 82KGS707, 85KGS757⟩. Yields are ca. 50%, but are reduced if tellurium tetrachloride is used; indeed, now an extra step is introduced since the initial products are 10,10-dichlorides (**185**) which require reductive dechlorination ⟨83JOM(251)223⟩.



(**189**) (**186**) (42)

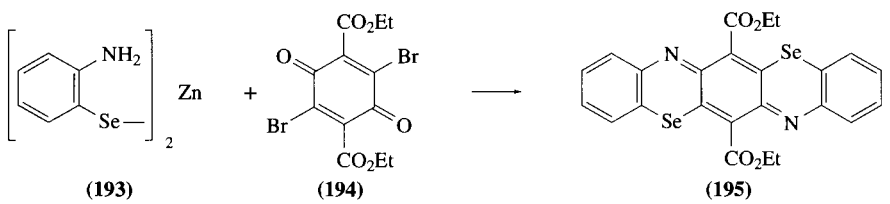
Phenoselenazines can be synthesized from diarylamines by direct reaction with diselenium dichloride in chloroform ⟨70CCA61⟩; phenoselenazine itself (**176**) is obtained in this way from diphenylamine ⟨59JOC37⟩. *N*-Alkyl phenoselenazines can be prepared in a similar way from *N*-alkyldiphenylamines, or by *N*-alkylation of phenoselenazine (see Section 6.24.7.2.1).

Selenamethylene blue (**192**) can be synthesized by treating 3-(*N*,*N*-dimethylamino)selenophenol (**190**) with 4-(*N*,*N*-dimethylamino)nitrosobenzene (**191**) under oxidative conditions (Equation (43)). When this compound bears a ^{75}Se label it is useful for the visualization of parathyroid gland adenomas ⟨83EGP3125296⟩.

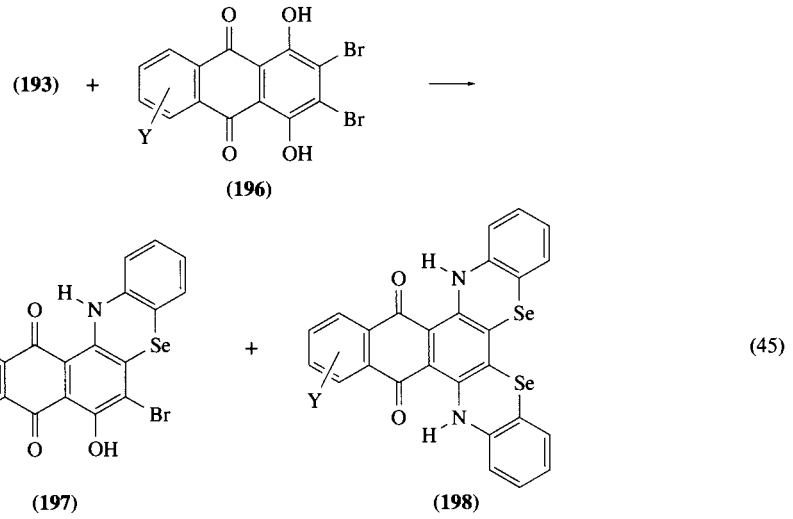


(**190**) (**191**) (**192**) (43)

A pentacyclic analogue (**195**) is formed by the condensation of zinc 2-aminobenzeneselenolate (**193**) and 3,6-dibromo-2,5-ethoxycarbonyl-1,4-benzoquinone (**194**) (Equation (44)) ⟨86NKK1329⟩. 2,3-Dibromoquinizarins (**196**) react in the same way to give the fused phenoselenazine quinones (**197**) and (**198**) (Equation (45)). These compounds are useful as infrared dyestuffs ⟨85CL1351⟩.

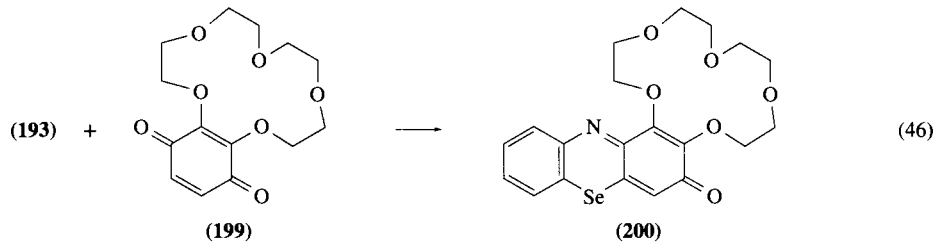


(**193**) (**194**) (**195**) (44)



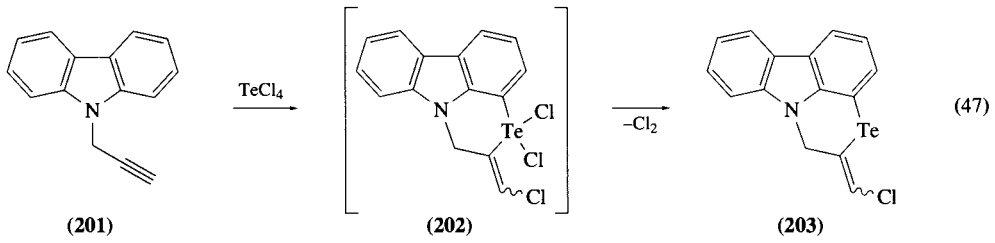
(193) + (196) → (197) + (198) (45)

In a variant on the above theme, crown-fused phenoselenazin-3-ones (**200**) are obtained by reacting zinc 2-aminobenzeneselenolates with the 1,4-benzoquinono[15]crown-5 (**199**) (Equation (46)) ⟨92M849⟩.



(193) + (199) → (200) (46)

If *N*-propargylcarbazole (**201**) is reacted with tellurium tetrachloride cyclization occurs to afford the tetracycle (**203**). The annulation process is interesting since cyclization and dehalogenation of the presumed intermediate (**202**) occur concomitantly (Equation (47)). An analogous reaction occurs if tellurium tetrabromide is the reagent ⟨90KGS126⟩.



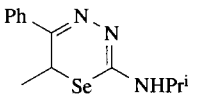
(201) → (202) → (203) (47)

6.24.8 SELENADIAZINES AND SELENATRIAZINES

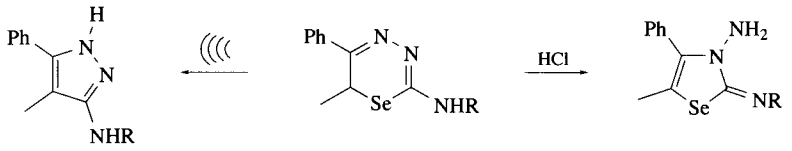
6.24.8.1 1,3,4-Selenadiazines

6.24.8.1.1 Physical properties and reactions

The structure of 2-isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-selenadiazine (**204**) has been established by x-ray crystallography ⟨93ACS302⟩. Related compounds rearrange when heated in aqueous acids to give 3-aminoselenazolin-2-imines (**205**), but on sonication selenium is extruded and pyrazoles (**206**) are formed (Scheme 43) ⟨88EGP294790, 88MI 624-01, 88UKZ538, 93PHA732⟩.



(204)

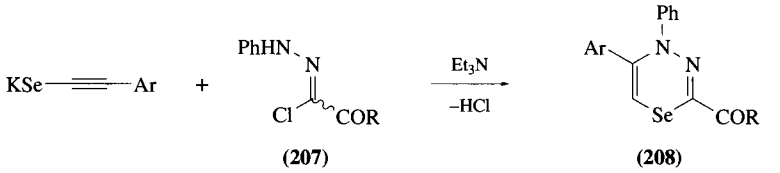


(206) (205)

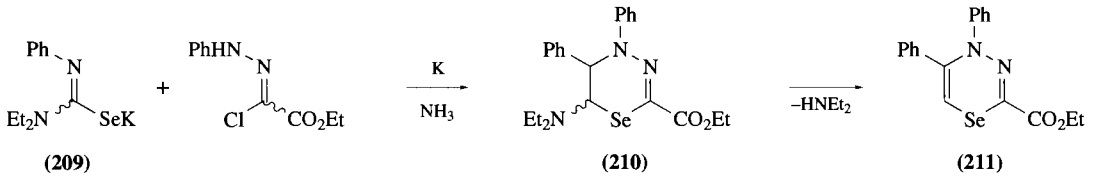
Scheme 43

6.24.8.1.2 Synthesis

4*H*-1,3,4-Selenadiazines (**208**) are normally prepared by the 1,3-dipolar additions of nitrilimines to potassium phenylethynylselenide. The nitrilimines are formed *in situ* from hydrazonyl chlorides (**207**) by treatment with triethylamine in benzene (Equation (48)) ⟨88UKZ538, 89RRC901⟩. Dihydro compounds (**210**) are available by reacting *N*,*N*-diethyl-2-phenylselenoacetamide enolates (**209**) with hydrazonyl chlorides in liquid ammonia containing potassium amide. The products readily undergo elimination of diethylamine, thereby yielding the parent selenadiazines (**211**) in two steps (Scheme 44) ⟨82ZOR224, 89ZOR199⟩.



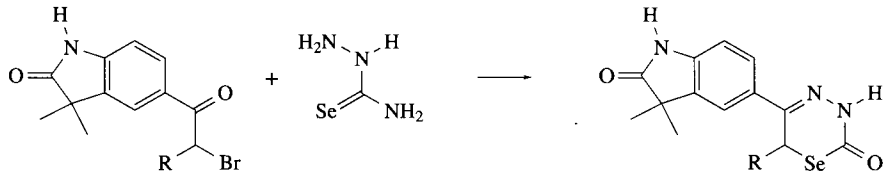
(207) (208) (48)



(209) (210) (211)

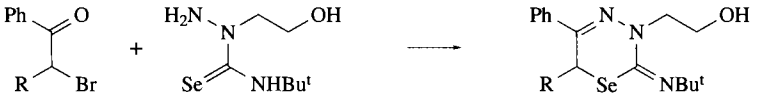
Scheme 44

5-(Indolin-2-on-5-yl)-1,3,4-selenadiazin-2-ones (**213**) have been tested as cardiotonic drugs; they are prepared by the cyclocondensation of indolinones (**212**) with selenosemicarbazide (Equation (49)) ⟨91JHC1365, 92JMC163⟩.



(212) (213) (49)

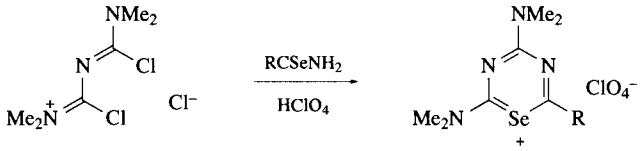
Other compounds in this group, viz. 3-alkyl-2,3-dihydro-6*H*-1,3,4-selenadiazines (**215**), are useful as spasmolytic agents. They can be synthesized by the cyclocondensation of 2-halogenoalkanones with selenosemicarbazides (**214**) (Equation (50)) ⟨90EGP281582, 91CZ361⟩.



(214) (215) (50)

6.24.8.2 1,3,5-Selenadiazines and Related Compounds

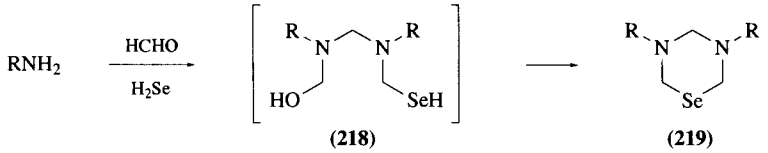
The addition of selenoamides to 1,3-bis(dimethylamino)-1,3-dichloropropenylium chloride together with perchloric acid leads to 1,3-selenazinium salts (see Section 6.24.6.2). If the aza equivalent (**216**) of the propenylium chloride is used as starting material then 1,3,5-selenadiazinium salts (**217**) are produced (Equation (51)) ⟨87BCJ2686⟩.



(51)

(**216**) R = NMe_2, Ph, pyrrolidin-1-yl (**217**)

Perhydro-1,3,5-selenadiazines (**219**) are formed by reacting primary alkylamines with formaldehyde in the presence of hydrogen selenide. It is possible that the acyclic hydroselenides (**218**) are intermediates in these reactions (Scheme 45) ⟨72CR(C)1700⟩.

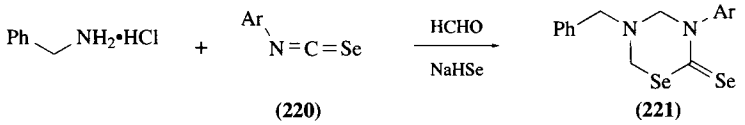


(**218**) (**219**)

R = alkyl

Scheme 45

A similar approach utilizing the reaction of aryl isoselenocyanates (**220**), the salt of a primary amine such as benzylamine, formaldehyde, and sodium hydrogen selenide yields tetrahydro-1,3,5-selenadiazine-2-selones (**221**) (Equation (52)) ⟨82MI 624-01⟩.

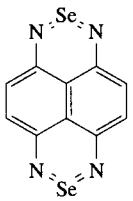


(52)

(**220**) (**221**)

6.24.8.3 1,2,6-Selenadiazines

An example of this type of compound is naphtho[1,8-*cd*][4,5-*c'd'*]bis-1,2,6-selenadiazine (**222**), prepared in the search for a potential synthetic metal ⟨82JA2691⟩.

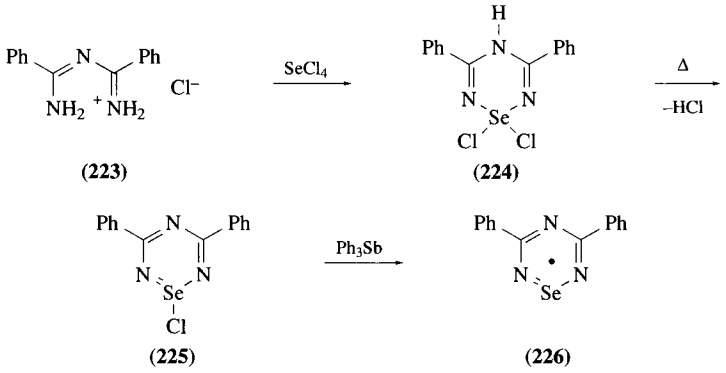


(**222**)

6.24.8.4 1,2,4,6-Selenatriazines

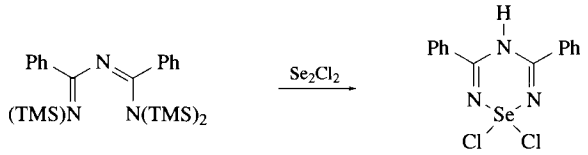
A representative of the 1,2,4,6-selenatriazine group is 1,1-dichloro-1,4-dihydro-3,5-diphenyl-1,2,4,6-selenatriazine (**224**). This compound is of interest because on heating it eliminates hydrogen chloride and the product (**225**) can be reduced (Ph_3Sb) to the 3,5-diphenyl-1,2,4,6-selenatriazenyl radical (**226**). This radical associates in solution to form a diamagnetic dimer bonded through the

selenium atoms, and in which the individual pairs of selenatriazinyl units are cofacially aligned with Se—Se distances of 2.792 Å ⟨87JA7745, 90JA2249⟩. The parent dichloride (**224**) is obtained through the reaction of *N*-benzimidoylbenzamidine hydrochloride (**223**) and selenium tetrachloride (Scheme 46), or as a minor product from the interaction of *N*,*N*′,*N*′-tris(trimethylsilyl)-*N*-benzimidoylbenzamidine (**227**) and Se_2Cl_2 (Equation (53)). Compound (**224**) exists as a dimer in the solid state, bridged via Se—Cl···Se interactions ⟨89ZN(B)857⟩.



(223) (224) (225) (226)

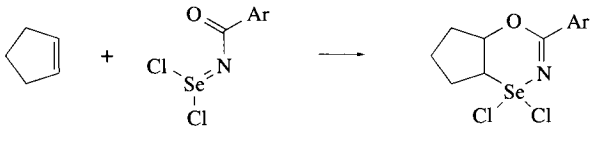
Scheme 46



(227) (224) (53)

6.24.9 OXASELENAZINES AND THIASELENAZINES

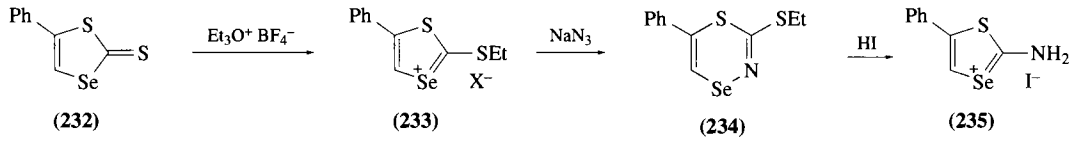
There are very few illustrations of 1,4,3-oxaselenazines, e.g. (**229**), but some can be prepared by the cycloaddition of *N*-aroyliminoselenyl dichlorides (**228**) (from selenium and the appropriate *N*,*N*-dichlorobenzamides) and alkenes (Equation (54)) ⟨84ZOB2377⟩. Imino derivatives (**231**) are similarly formed by the cycloaddition of aroylselenodiimides (**230**) and alkenes (Equation (55)) ⟨83ZOB1622⟩.



(228) (229) (54)

(230) (231) (55)

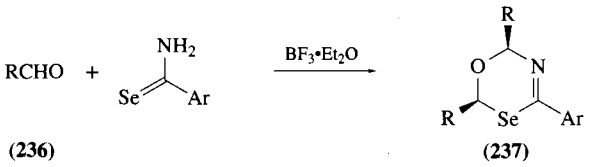
Ethylation of 1,3-thiaselenole-2-thiones (**232**) with triethyloxonium tetrafluoroborate affords the corresponding thiaselenolium salts (**233**), which ring expand when reacted with sodium azide to give the first known examples of 1,4,3-thiaselenazines (**234**). Ring contraction of these compounds takes place when they are treated with hydrogen iodide and 2-aminothiaselenolium iodides (**235**) are formed (Scheme 47) ⟨84S667⟩.



(232) (233) (234) (235)

Scheme 47

Cis-2,6-dialkyl-2*H*,6*H*-1,3,5-oxaselenazines (**237**) are synthesized from selenoamides, aldehydes (**236**; R = methyl, heptyl, or *t*-butyl), and boron trifluoride etherate (Equation (56)) ⟨90CL913⟩.



(56)

(236) (237)

6.24.10 1,3,5-OXADISELENANES AND 1,3,5-DIOXASELENANES

There are a number of six-membered heterocycles which contain selenium or tellurium, and two other heteroatoms other than nitrogen, for example, the reaction of formaldehyde and hydrogen selenide gives 1,3,5-oxadiselenane (**238**) and 1,3,5-dioxaselenane (**239**; R = Me) ⟨82ZAAC(488)60⟩. Similarly, acetaldehyde in aqueous acidic solution reacts with hydrogen selenide to afford 2,4,6-trimethyl-1,3,5-dioxaselenane (**239**; R = Me) ⟨67JCS(B)117⟩.

(238) (239)

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6.25
Six-membered Rings with Two or More Heteroatoms with at least One Phosphorus

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Universität Regensburg, Germany

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6.25.1 INTRODUCTION

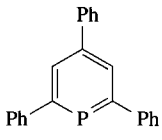
A. Michaelis (1847–1916) and A. E. Arbuzov (1877–1968), in the last decades of the nineteenth century and the first few decades of the twentieth century, laid the foundations of phosphorus

chemistry, which soon acquired a reputation for evil smells and, later, for drastic—often lethal—physiological effects.

The first comprehensive compilation of organic phosphorus compounds was that by Kosolapoff ⟨B-50MI 625-01⟩. "Kosolapoff" was the standard book in the field for many years, and the second edition, "Kosolapoff–Maier" ⟨B-72MI 625-01⟩, had expanded to eight volumes, indicating the enormous development in phosphorus chemistry in the period since 1950.

F. G. Mann, working in the field since 1935, is undoubtedly the father of phosphorus as well as arsenic heterocyclic chemistry. Most of his work, mainly on saturated and benzo-annellated ring systems, is summarized in his monograph ⟨B-70MI 625-01⟩. Other important early contributions to the synthesis of phosphorus heterocycles were made by K. Issleib and by B. A. Arbuzov, the son of A. E. Arbuzov.

After the first synthesis of a λ^3-phosphinin derivative, the 2,4,6-triphenyl compound (**1**) ⟨66AG(E)846⟩, and the isolation of the unsubstituted phosphinin (**2**) ⟨71JA3293⟩, a dramatic development and an avalanche of publications followed.

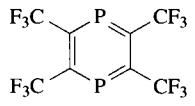


(**1**)

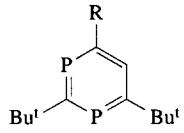
(**2**)

The question of the possible existence of λ^3-phosphinin containing more than one heteroatom, e.g. N, P, with Hückel-aromatic character, has provided the impetus for much experimental and theoretical activity in the field since 1966. Early reviews, by Berlin and Hellwege ⟨B-69MI 625-01⟩ and Quin ⟨B-81MI 625-01⟩ took into account these new developments, but they dealt only with rings containing P and C. The most comprehensive survey of heterocyclic phosphorus chemistry is that in Houben-Weyl ⟨63HOU(12)203, 82HOU(E1/2)⟩. The six-membered heterocycles are treated by Maerkl (λ^3-phosphorus) ⟨82HOU(E1)72⟩ and Dimroth (λ^5-phosphorus) ⟨82HOU(E1)783⟩. In the first edition of *Comprehensive Heterocyclic Chemistry*, the entire field of phosphorus heterocycles was covered by Dimroth ⟨82CHEC-I(1)493⟩. More recent work was reviewed in a 1990 monograph ⟨B-90MI 625-01⟩.

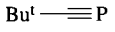
The 1,4-diphosphinin (**3**) was described as early as 1976 ⟨76TL3715⟩, but it took another 29 years for the first 1,3-diphosphinins (**4**) to be obtained ⟨95AG(E)81⟩ (Section 6.25.4.2.2). The key building-block for the synthesis of (**4**) was *t*-butylphosphaethyne (**5**) ⟨81ZN(B)16⟩, the preparation of which was certainly another milestone in phosphorus heterocyclic chemistry, as it also enabled the synthesis of 2,4,6-tri-*t*-butyl-1,3,5-triphosphinin (**6**) in 1995.



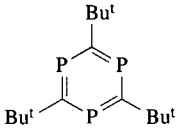
(**3**)



(**4**)

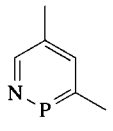


(**5**)

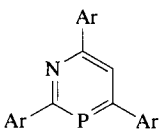


(**6**)

Aromatic six-membered phosphorus heterocycles containing nitrogen include derivatives of all the three isomeric azaphosphinines (**7**)–(**9**) and the 1,3,5-diazaphosphinines (**10**). They are all 6π-aromatic Hückel systems, although the 1,2- and the 1,4-azaphosphinines are highly reactive towards nucleophiles as a result of the N/P electronegativity difference.



(**7**)



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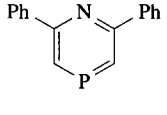
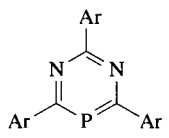


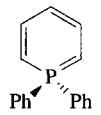
(**9**)



(**10**)

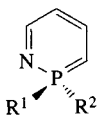
An even longer chapter of six-membered phosphorus heterocycles with more than one heteroatom is represented by those with $\lambda^5\sigma^4$-phosphorus. The first synthesis of a λ^5-phosphinin, the 1,1-diphenyl compound (**11**) was described in 1963 ⟨63AG(E)479⟩. Because of the ready availability of

λ^3-phosphinins, and the realization that these can be transformed into λ^5-phosphinins via anionic, cationic and radical intermediates, the chemistry of λ^5-phosphinins has expanded rapidly.



(11)

Several independent synthetic approaches to $1,2\lambda^5$-, $1,3\lambda^5$- and $1,4\lambda^5$-azaphosphinines (**12**)–(**14**), as well as $1\lambda^5,3\lambda^5$-diphosphinins (**15**) and $1\lambda^5,3\lambda^5,5\lambda^5$-triphosphinins (**16**), have been published. Synthetic work on polyhalogenated aza-λ^5-phosphinines, e.g. (**17**), has been carried out, mainly by Russian research groups.



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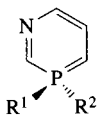
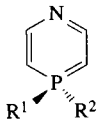


(13)



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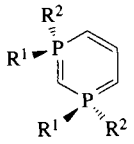

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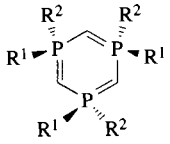

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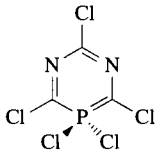
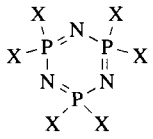


(17)

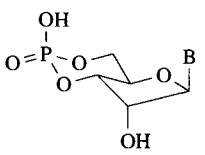
The chemistry of λ^5-phosphinins culminates in the six-membered cyclotriphosphazenes, for instance the so-called phosphonitrilic halides (**18**), which are not discussed in this review, except in connection with the polyheteroatom systems to which they may give rise.



(18)

Although a detailed review on phosphinins appears in Chapter 5.12, it is not possible to discuss the chemistry of the systems with more than one heteroatom without occasional reference to the monoheteroatom systems. Nevertheless, Chapter 5.12 should be consulted as appropriate.

Saturated ring systems containing only phosphorus and nitrogen, besides carbon, have not been investigated to any great extent. The situation is very different when the rings contain phosphorus and oxygen. A computer search for 1,3,2-dioxaphosphinanes produced over 50000 hits, including more than 12000 different structures. These include, of course, the cyclic phosphates, phosphites, phosphonates, and so on, the importance of which is based on the biological role of ribonucleotide 3′,5′-cyclic phosphates [*c*-AMP (**19**), *c*-GMP] in the synthesis of polyribonucleotides, and as second messengers for cellular enzymes. Cyclic phosphonates with 1,4,2-dioxaphosphinane structure based on a nucleoside framework, e.g. (**20**), have been found to be effective virus inhibitors.



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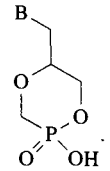


(20)

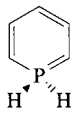
Reviews on the role of phosphorus in biochemistry by Westheimer ⟨B-92MI 625-01⟩ and on cyclic oxophosphoranes by Holmes *et al.* ⟨B-92MI 625-02⟩ have appeared.

The chemistry described in this chapter is organized into two main sections. Since the oxygen-containing ring systems are for the most part saturated, their chemistry bears little or no relation to that of the unsaturated P/N-containing rings, and it is convenient to deal with them separately.

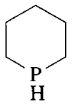
This volume normally treats reactivity and synthesis in separate sections. However, such an arrangement of the present chapter would result in separation of material which it is more appropriate, for considerations of space, to discuss together. Reactivity and synthetic methods are therefore dealt with in the same section.

6.25.2 NOMENCLATURE

Nomenclature in phosphorus chemistry is in a somewhat confused state, and for this reason information retrieval is not a straightforward matter. The saturated heterocyclic systems, particularly the oxygen-containing compounds, are for the most part cyclic phosphonate, phosphate or phosphite esters or amides, and the names may be formed from the open-chain structures from which they are derived. In this chapter we follow the IUPAC recommendations of 1983 ⟨83PAC410⟩. The fully unsaturated six-membered ring (**2**), with phosphorus in its normal (trivalent) state, is therefore named "phosphinine." When a ring contains "hypervalent" phosphorus, this is denoted using the λ convention: (**21**) is λ^5-phosphinine. Optionally, λ^3 may be used, when it is wished to emphasize that it is the P(III) valence state of phosphorus coordination number 2 that is being discussed, but in compound names this is understood unless specified otherwise. *Chemical Abstracts* perseveres with the rules which applied before 1983 ⟨B-69MI 625-02⟩, whereby the ring in (**2**) is named as "phosphorin," and derivatives of (**21**) are called 1,1-dihydrophosphorins. The saturated ring (**22**) is "phosphinane" (formerly phosphorinane). "Replacement nomenclature" is also used widely in the primary literature: (**2**) by this method is called "phosphabenzene."



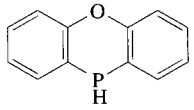
(**21**)



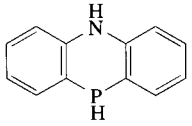
(**22**)

The ring systems described in the present chapter contain other heteroatoms, and the normal Hantzsch–Widman rules are applied. Compounds (**10**) are therefore "diazaphosphinines." The order of precedence in heteroatom numbering should be noted: oxygen > sulfur > nitrogen > phosphorus. In this chapter we normally place the P atom at the bottom of the ring, but this is seldom position 1, when other heteroatoms are present.

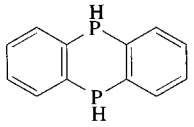
The three tricyclic ring systems (**23**)–(**25**) are usually trivially named, as indicated below the structures.



Phenoxaphosphine
(**23**)



5,10-Dihydrophenophosphazine
(**24**)



5,10-Dihydrophosphanthrene
(**25**)

6.25.3 THEORETICAL STUDIES AND AROMATICITY

For the most part, theoretical methods have been applied to the question of the aromaticity of the various phosphorus-containing ring systems, and this question is relevant only to systems with complete cyclic π-conjugation. Applications to other areas have been rare.

The Hückel aromaticity of the λ^3-phosphinins was supported by x-ray crystal structure analysis combined with:

(i) PE spectral studies of λ^3-phosphinin ⟨73JA928, 76HCA1944, 78ACR153⟩, 2,4,6-tri-*t*-butyl-λ^3-phosphinin ⟨71AG(E)656⟩, 3-methyl-2-phosphanaphthalene ⟨75JES91⟩ and 10-methyl-9-phosphaanthracene ⟨75T2931⟩;

(ii) *ab initio* calculations using an STO-3G basis set ⟨70JCP(52)2769⟩, CNDO/2 calculations ⟨67JCP(47)158⟩ and a CNDO/S-method ⟨74TCA19⟩;

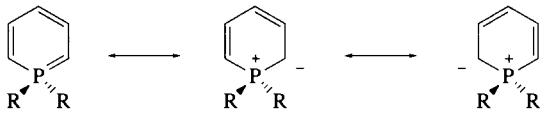
(iii) the derived resonance energies using the perturbation graph theory and PE experimental vertical π ionization potentials ⟨78T3419⟩.

While all cyclic, conjugated six-membered phosphorus heterocycles with $\lambda^3\sigma^2$-phosphorus are clearly Hückel-aromatic systems, the bonding situation in the cyclic conjugated six-membered systems containing $\lambda^5\sigma^4$-phosphorus has been discussed rather controversially. Schweig and coworkers, for example, discussed a mixture of Hückel and Möbius aromaticity and ylide character

⟨76JA4410⟩. Bird has used the bond lengths reported for 14 phosphorus-containing rings, including seven with more than one heteroatom, to provide estimates of the bond order variation about the ring, and thence an index (I_6) of the aromaticity of the ring ⟨90T5697⟩. Perhaps the most surprising feature of the figures he derives is the fact that rings with λ^5-phosphorus appear to be, on this criterion, scarcely less aromatic than those with λ^3.

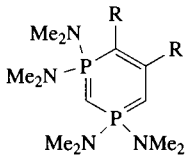
The correlation of the bonding situation with the PE spectra has been discussed ⟨95JST(347)57⟩. Dewar and Holder compared the aromatic energies of 1,2-, 1,3- and 1,4-diphosphinins according to their heats of formation obtained from AM1 semiempirical methods ⟨89H(28)1135⟩. HMO calculations of phosphorus heterocycles with $\lambda^5\sigma^4$-phosphorus were reported as early as 1968 ⟨68RRC1623⟩.

Although the molecular geometries of λ^3- and λ^5-phosphinins are nearly identical (no significant deviations from planarity or bond alternation are observed with either system), the λ^5-phosphinines as well as the mono-, di-, tri- and tetra-aza-λ^5-phosphinines, the λ^5,λ^5-diphosphinines and the $\lambda^5,\lambda^5,\lambda^5$-triphosphinines are certainly not Hückel-aromatic systems. Their description as cyclic phosphorus ylides with ionic resonance structures (**26**) is probably close to the truth. The ^1H and ^{13}C NMR evidence is particularly strong on this point.



(**26**)

The PE spectra of the $1\lambda^5,3\lambda^5$-diphosphinines of type (**27**) as well as the MO calculations (MNDO) have been reported ⟨91CB2071⟩. The calculations predict, in agreement with the P-ylide character of the $1\lambda^5,3\lambda^5$-diphosphinines, a strong negative charge for the ring carbon atoms and a strong positive net charge for the P-atoms ⟨91CB2071⟩.



(**27**)

According to calculations, the parent 1,3,5-triphosphinine is 25 kcal mol^{-1} more stable than its Dewar (triphosphabicyclo[2.2.0]hexadiene) isomer ⟨95UP 625-01⟩.

In a calculation applied to saturated systems, the CNDO/S method has been used to investigate the influence of orbital interactions on the conformational behavior of 1,3,2- and 1,3,5-dioxaphosphinanes ⟨84ZOB2532⟩.

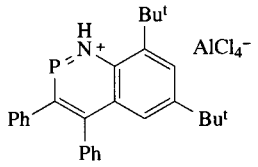
6.25.4 RING SYSTEMS WITH NITROGEN AND/OR PHOSPHORUS ATOMS

6.25.4.1 Experimental Structural Methods

6.25.4.1.1 X-ray crystallography

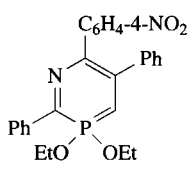
X-ray crystallography has become a routine tool for structure determination since the 1970s, and many instances of its application to phosphorus-containing six-membered heterocyclic compounds have been reported. The data from a number of determinations carried out before 1990 have been collected and discussed ⟨90T5697⟩.

The crystal structure of the unusual 1,2-benzazaphosphinine salt (**28**) has been reported ⟨92TL2335⟩—one of the few systems with λ^3-phosphorus and further heteroatoms to have been subjected to x-ray analysis. The P—N bond distance (163 pm) is slightly shorter than the P—C (175 pm), as would be expected; the C-P-N angle is 100°.



(28)

X-ray data are available for the $1,3\lambda^5$- and $1,4\lambda^5$-azaphosphinines (**29**) ⟨88ZOB526⟩ and (**30**) ⟨94JA8087⟩. P—C bond lengths are fairly similar to those that obtain with the λ^3-P systems: in (**30**) the mean distance is 172.6 pm; the C-P-C angle is 105.8°.



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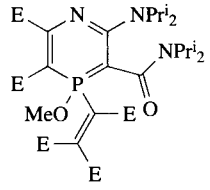
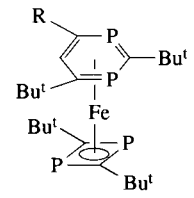
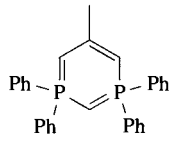


(30) E = CO_2Me

The $1\lambda^3,3\lambda^3$-diphosphinines so far synthesized are oily liquids, but the sandwich complex (**31**) is a stable solid and amenable to crystallography ⟨95AG(E)198⟩. The crystal structures of a number of $1\lambda^5,3\lambda^5$-diphosphinines have been measured, e.g. (**32**) ⟨90AG(E)516⟩, (**33**) ⟨91ZN(B)202⟩ and the $NiCl_2$ complex (**34**) ⟨94ZAAC(620)483⟩. The triphosphinine (**35**), with two λ^5 and one λ^3 P atoms, is an interesting case. According to the x-ray analysis the ring system is slightly puckered, the P(5)—C(4) and P(5)—C(6) distances (170.9 pm (2), 170.0 pm (2)) are very close to the values of normal λ^3-phosphinines, and P(1) and P(3) are more or less ylide phosphorus atoms with polar P—C bonds ⟨86AG(E)1002, 87ZN(B)1213⟩. The triphosphinine (**36**), with all P atoms λ^5, is strongly ylidic in character, with an almost planar ring system, C—P bond lengths 168.7–169.7 pm; P-C-P angles 126.6–127.0°, and C-P-C angles 113.0–113.4° ⟨90JCS(P1)1223⟩.



(31)



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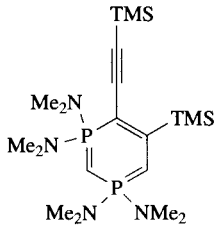
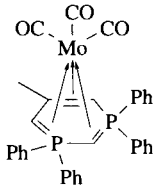


(33)



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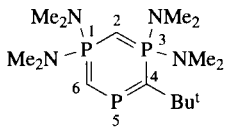

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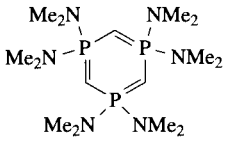
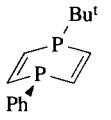


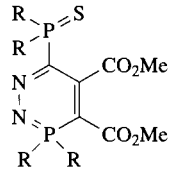
(36)

A number of six-membered rings with $\lambda^3\sigma^3$-phosphorus are known, and some have been submitted to x-ray structure determination. The 1,4-dihydro-1,4-diphosphinine (**37**) revealed a folded structure, with the P-substituents *cis*-diequatorial ⟨85CB2365⟩.



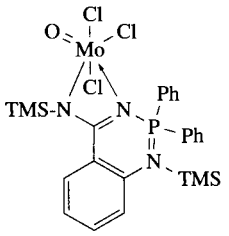
(37)

In the 1,2,3λ^5-diazaphosphinine (**38**) an ylide-like structure is consistent with the bond length data, and with the NMR measurements ⟨90AG(E)1123⟩. A later paper reports a number of crystal structures of other di- and tri-aza-λ^5-phosphinines ⟨94JA8087⟩.

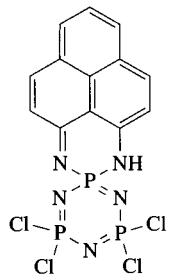


(**38**) R = NPr^i_2

Data on two fused 1,3,2λ^5-diazaphosphinines have been reported. The structures of the molybdenum complex (**39**) ⟨88ZN(B)937⟩ and the spiro-fused cyclotriphosphazine (**40**) ⟨88IC1911⟩ were confirmed by x-ray crystallography.



(**39**)



(**40**)

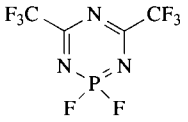
Table 1 lists (not comprehensively) references to crystal structure data of monocyclic ring systems covered in the present chapter. Ring carbon substituents are not indicated in the columns.

Table 1 X-ray crystal structures for ring systems with nitrogen and phosphorus.

Atom						*Ref.*
1	*2*	*3*	*4*	*5*	*6*	
N		λ^5P(OEt)$_2$				88ZOB526
λ^3P		λ^3P				95AG(E)198
λ^5P(NR$_2$)$_2$		λ^5P(NR$_2$)$_2$				91ZN(B)202
λ^5PPh$_2$		λ^5PPh$_2$				90AG(E)516, 91CB1525
N			λ^5P(OMe)R			94JA8087
NH			λ^5P(=O)Ph			71TL4749
$\lambda^3\sigma^3$PPH			$\lambda^3\sigma^3$P*t*-Bu			85CB2365
λ^5P(=S)Ph			λ^5P(=S)Ph			92PS(71)245
N	N	λ^5P(NR$_2$)$_2$				90AG(E)1123
N	N		λ^5PPh$_2$			90AG(E)314
N	λ^5PMe$_2$			N		90HCA1888
N	λ^5PMe$_2$			NH	C=O	94JA8087
N	λ^5PPh$_2$				λ^5PPh$_2$	91CB1525
N	λ^5P(NR$_2$)$_2$		λ^5P(NR$_2$)$_2$			91PS(56)49
λ^5P(NR$_2$)$_2$		λ^5P(NR$_2$)$_2$		λ^3P		87ZN(B)1213
λ^5P(NR$_2$)$_2$		λ^5P(NR$_2$)$_2$		λ^5P(NR$_2$)$_2$		90JCS(P1)1223
N	N	N	λ^5P(NR$_2$)$_2$			94JA8087
N	λ^5P(NR$_2$)$_2$	N		N		87ZOB1980, 90ZOB1975
N	λ^5PMe$_2$	N	λ^5PMe(R)		λ^5PMe$_2$	77CJC2534

6.25.4.1.2 Other diffraction methods

Electron diffraction has been used to investigate the vapor phase structure of the fluorinated 1,3,5,2λ^5-triazaphosphinine (**41**) ⟨88ZN(B)1010⟩.



(41)

6.25.4.1.3 Spectroscopic methods

(i) Photoelectron spectroscopy

PE spectra have been measured for some $1\lambda^5,3\lambda^5$-diphosphinines, and also for the triphosphinine (**36**), and assigned with the help of MO (MNDO) calculations (see Section 6.25.2.2.ii).

(ii) NMR spectroscopy

The conclusion referred to earlier, that rings containing only λ^3-phosphorus are Hückel 6π-aromatic systems, while those with λ^5-phosphorus are to be regarded as nonaromatic and ylidic in character, is drawn largely from the NMR data, which differ greatly for the two types of system. The ring carbon atoms of λ^3-phosphinines absorb in typically aromatic regions of the spectrum. Data by the structures in Figure 1 show ^{1}H NMR chemical shifts and, where relevant ^2J, ^3J and $^4J_{(P\text{-}H)}$ coupling constants.

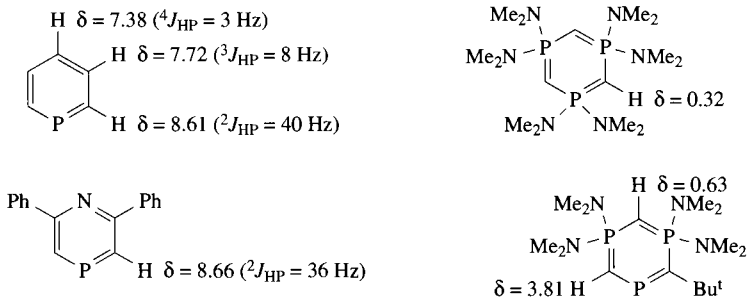


Figure 1 ^{1}H Chemical shifts and $^nJ_{HP}$ coupling constants.

The ^{13}C signals are, typically, strongly deshielded, particularly those of C atoms adjacent to phosphorus. The $^1J_{(P\text{-}C)}$ coupling constant values are unusually large. The ^{31}P signals are also at very low field. Figure 2 shows data from the spectra of some representative compounds.

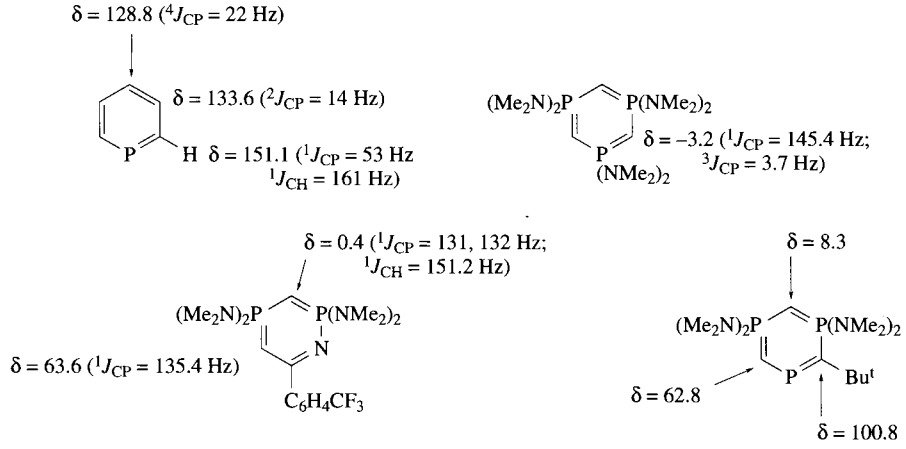


Figure 2 ^{13}C Chemical shifts and $^nJ_{CP}$ coupling constants.

It is noteworthy that the ^{31}P chemical shifts of the $1,3\lambda^3$-azaphosphinines and the $1,3,5\lambda^3$-diazaphosphinines are found at somewhat higher field (less deshielded values) than those for the

corresponding phosphinines. The weaker deshielding is attributed to the electronegative effect of the nitrogen atom ⟨87TL1093⟩. The 1,2- and 1,4-azaphosphinines, however, absorb at considerably lower fields.

The NMR data from six-membered rings containing $\lambda^5\sigma^4$-phosphorus are entirely different. Both ^1H and ^{13}C signals are shifted up-field on account of the negative charge concentrated there, arising from the ylide-like character of the molecules. When one or more nitrogen atoms is present to stabilize the negative charge, any remaining ylide-type C-H groups appear near to the normal olefinic region of the spectrum. The ^{13}C absorptions of carbon atoms adjacent to one $\lambda^5\sigma^4$-P appear in the region δ 50–60 ppm, and when adjacent to two such atoms they are so shielded as to be found at δ 10–0 ppm, and occasionally at negative values. The ^{31}P signals are also found at high field, in the region normally associated with phosphonium phosphorus. Illustrative examples are shown in Figures 1–3.

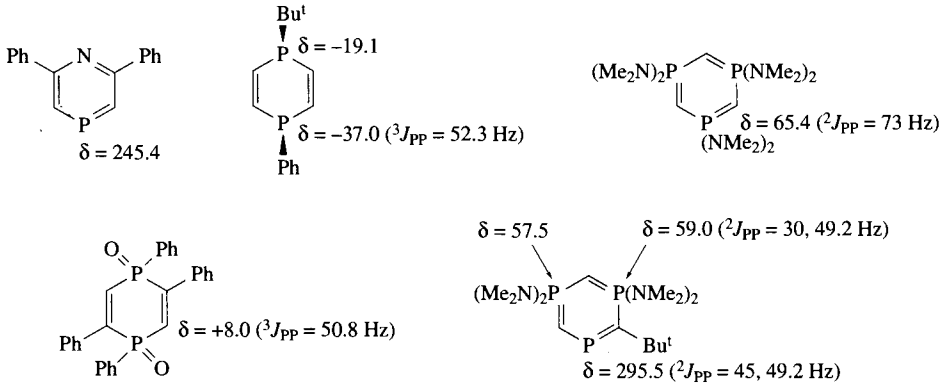


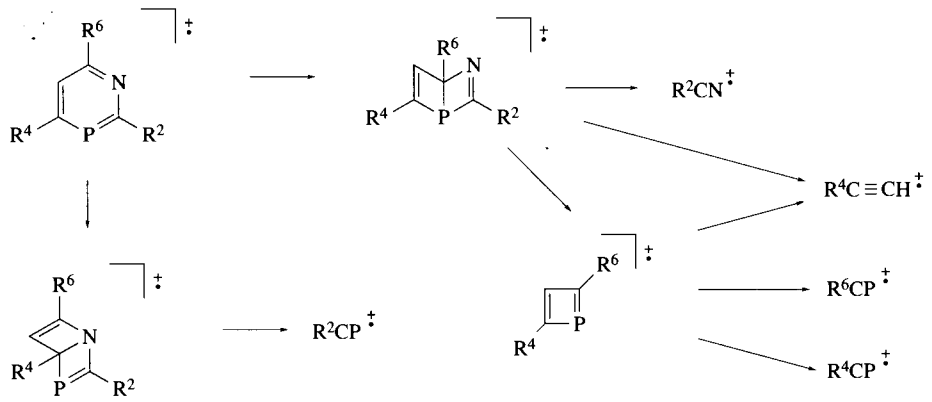
Figure 3 ^{31}P Chemical shifts (ppm; $\delta_{H_3PO_4} = 0$) and $^nJ_{PP}$ coupling constants.

Two useful reviews by Fluck and Heckmann on the NMR spectra of cyclic phosphorus compounds should be noted ⟨94RHA65, 95RHA121⟩.

^{35}Cl Nuclear quadrupole resonance spectroscopy has been applied to a number of chlorinated diazaphosphinines ⟨94ZN(B)171⟩.

6.25.4.1.4 Mass spectrometry

The mass spectra of phosphorus-containing heterocycles has frequently been applied for characterization and identification. Parent ions are frequently intense. Fragmentation patterns occasionally give a clue to the reactions taking place in the gas phase. 2,4,6-Triaryl-1,3-azaphosphinines show fragment ions as indicated in Figure 4, which are simply explained on the basis of cycloreversion reactions of the intermediate 3-aza-1-phosphabicyclo[2.2.0]hexadienes (azaphospha-Dewar benzenes).



R^2, R^4, R^6 = Aryl groups

Figure 4 Electron impact (EI) MS of triaryl-1,3-azaphosphinines.

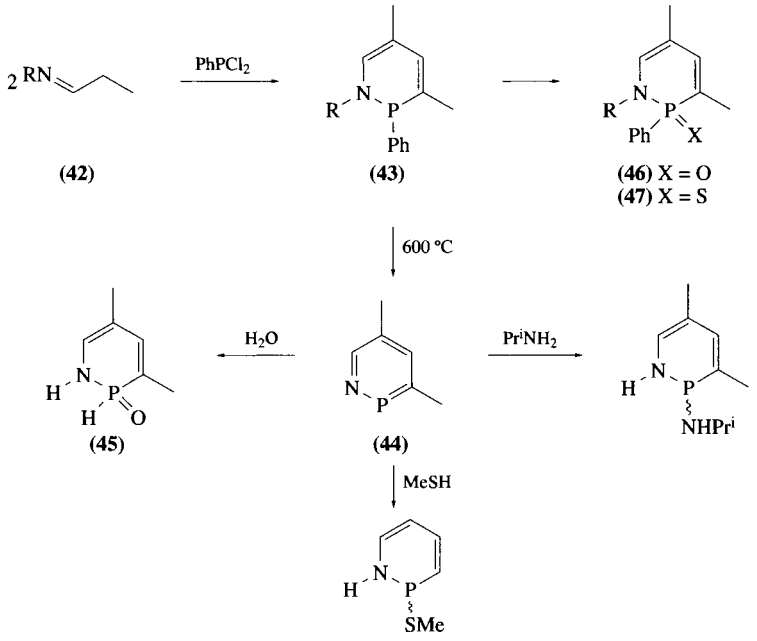
6.25.4.2 Reactivity and Syntheses

6.25.4.2.1 Six-membered rings with one phosphorus and one nitrogen atom

All of the fully conjugated six-membered ring systems with one nitrogen and one phosphorus atom—the 1,2-, 1,3- and 1,4-azaphosphinines—are known, and all may have λ^3- or λ^5-phosphorus. With λ^3-phosphorus, the 1,3-arrangement is the most stable; when λ^5-phosphorus is present, the nitrogen has a better stabilizing influence when at the 2- or 4-position.

(i) 1,2-Azaphosphinines

The first example of a fully unsaturated 1,2λ^3-azaphosphinine was reported in 1987 by Foucaud and co-workers ⟨87TL4673⟩. Two moles of an aliphatic imine (**42**) with a bulky substituent R react with one mole of dichlorophenylphosphine to give mainly the 1,2-dihydro-1,2-azaphosphinines (**43**) ⟨86TL4725, 90T6715⟩. Pyrolysis results in loss of benzene and an alkene, and formation of the azaphosphinine (**44**). Nucleophiles add readily to compound (**44**), reforming the 1,2-dihydro system, with λ^5-phosphorus in the case of the water adduct (**45**) ⟨87TL4673⟩. The dihydro-azaphosphinines (**43**) are converted into the 2-oxides (**46**) (O_2) and 2-sulfides (**47**) (S_8/*N*-methylimidazole) (Scheme 1) ⟨90T6715⟩.



Scheme 1

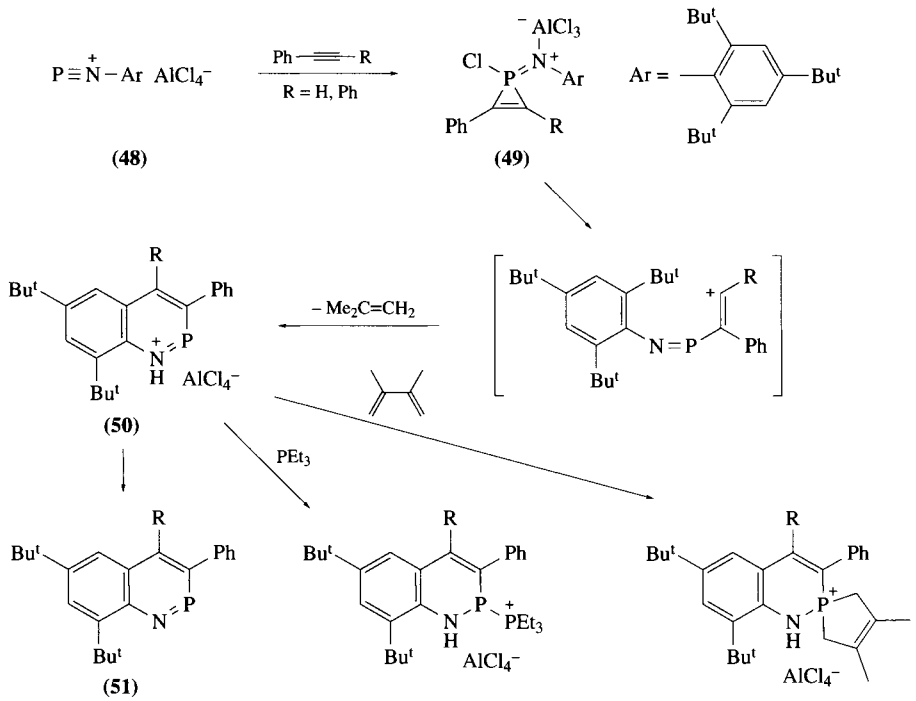
The 1,2-benzazaphosphinine system (**51**) arose in an unusual rearrangement of the phosphirenes (**49**) ⟨92TL2335⟩, which are formed by cycloaddition of the phosphanetriylammonium ion (**48**) ⟨88AG(E)1715⟩ to phenyl- or diphenyl-acetylene (Scheme 2). Triethylphosphine and 2,3-dimethylbutadiene were found to add to the tetrachloroaluminate salt (**50**) at the P atom, but, apart from spectroscopic data, no chemistry of (**51**) is yet reported.

The synthesis of the 5,6-dihydrodibenz[*c*,*e*][1,2]azaphosphinines (9,10-dihydro-9-aza-10-phosphaphenanthrenes (**52**)) was known in 1960 ⟨60JA5685, 60JA5034⟩; for an account of their chemistry the reviews cited should be consulted.

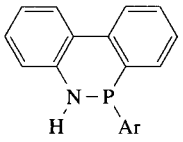
Several methods for the synthesis of 1,2λ^5-azaphosphinines are described in the literature.

(i) Thermolysis of the methiodides (**53**) of 1-*t*-butyl-1,2-dihydro compounds, which are available from aliphatic imines as shown in Scheme 1 ⟨86TL4725, 90T6715⟩. Basification forms (**54**) (Scheme 3). On exposure to moisture and air they are degraded to the phosphine oxides (**55**) ⟨91TL2619⟩.

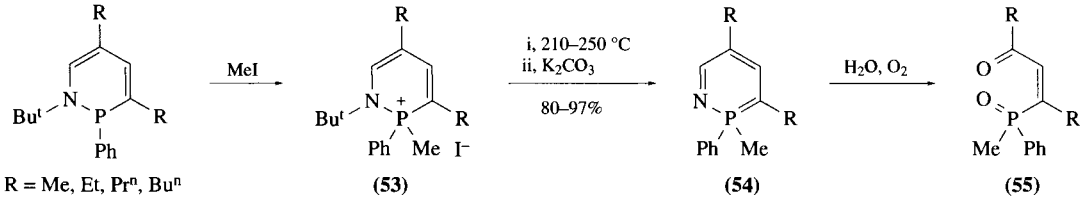
(ii) *N*-Vinyliminotrimethoxyphosphorane (**56**), easily prepared by the Staudinger reaction of α-azidostyrene with trimethyl phosphite at room temperature, reacts with electron-deficient acetylenes



Scheme 2



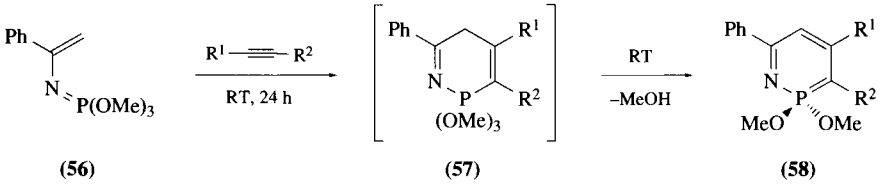
(52)



Scheme 3

in a formal (4 + 2)-cycloaddition reaction to give the cyclic phosphoranes (**57**). The 1,2λ^5-azaphosphinines (**58**) are formed by the spontaneous elimination of methanol (Scheme 4) ⟨85CL1459⟩.

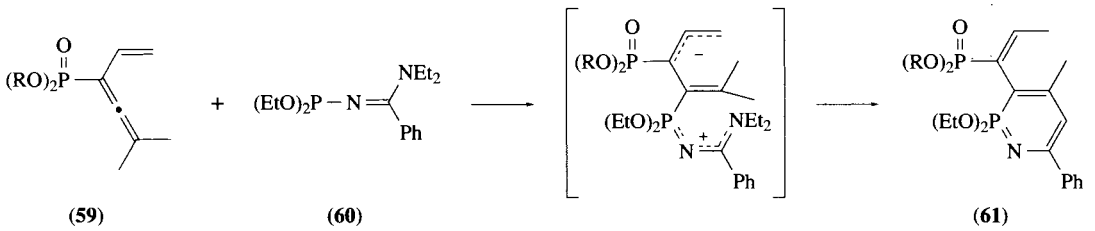
(iii) Dialkyl (3-methyl-1-vinyl-1,2-butadienyl)phosphonates (**59**) undergo a cyclocondensation



(a) R^1, R^2 = CO_2Me
(b) R^1, R^2 = COPh
(c) R^1 = H, R^2 = CO_2Me

Scheme 4

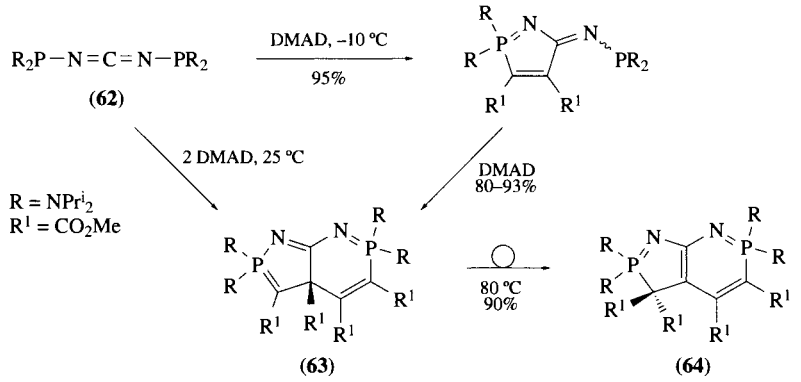
with the phosphoramidite (**60**) with formation of the substituted 1,2λ^5-azaphosphinines (**61**) (Scheme 5) ⟨85ZOB1710⟩. Similar reactions had been described earlier ⟨76ZOB51, 81ZOB767, 82ZOB789, 83ZOB930⟩. The structure of (**61**) was confirmed by ^{1}H and ^{13}C NMR and MS data.



(**59**) (**60**) (**61**)

Scheme 5

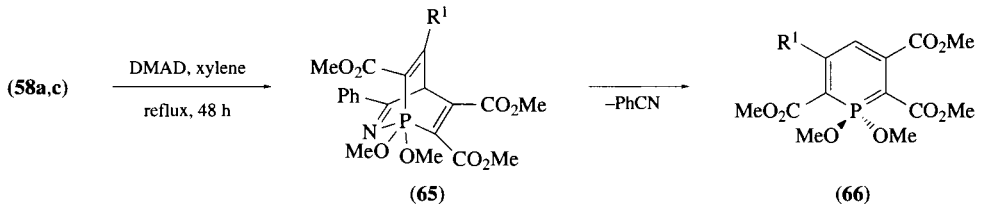
(iv) A fourth route to 1,2λ^5-azaphosphinines was reported by Bertrand's group ⟨94JOC5927⟩. The *N*,*N*′-bis[(diisopropylamino)phosphino]carbodiimide (**62**) adds two moles of DMAD in a stepwise fashion as shown, to form the intermediate (**63**), which rearranges on heating by methoxycarbonyl group migration to form the fused compound (**64**) (Scheme 6).



(**62**) (**63**) (**64**)

Scheme 6

The 1,2λ^5-azaphosphinines (**58a–c**) react with DMAD to form λ^5-phosphinines (**66**), presumably via the phosphabarrelene intermediate (**65**) (Scheme 7) ⟨85CL1459⟩.

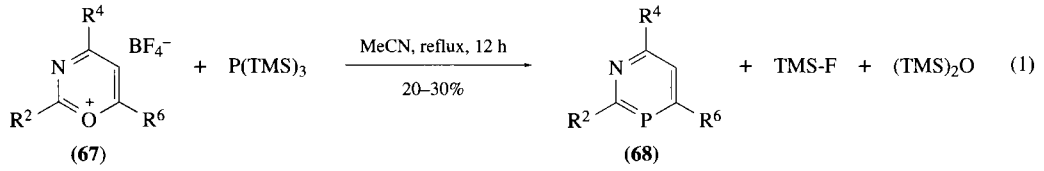


(**58a,c**) (**65**) (**66**)

Scheme 7

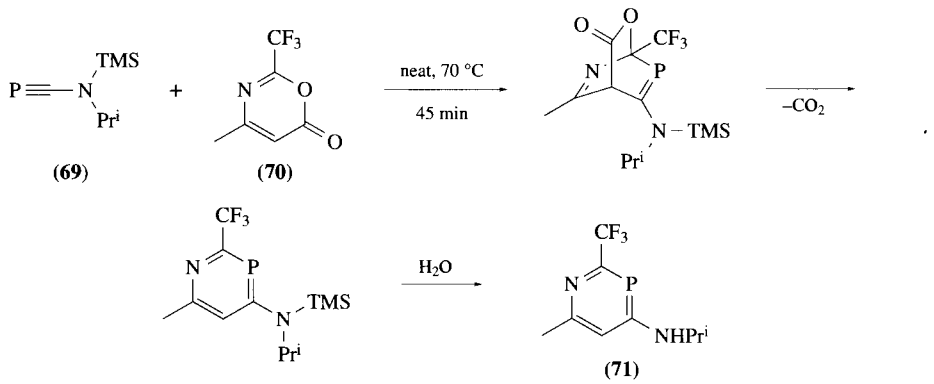
(ii) 1,3-Azaphosphinines

A very straightforward synthesis of 2,4,6-triaryl-1,3λ^3-azaphosphinines was published by Maerkl and Dorfmeister ⟨87TL1093⟩. The readily available triaryl-1,3-oxazinium salts (**67**) undergo a smooth O/P exchange reaction with tris(trimethylsilyl)phosphine to give the 1,3-azaphosphinines (**68**) in yields of 20–30% (Equation (1)).



(67) (68)

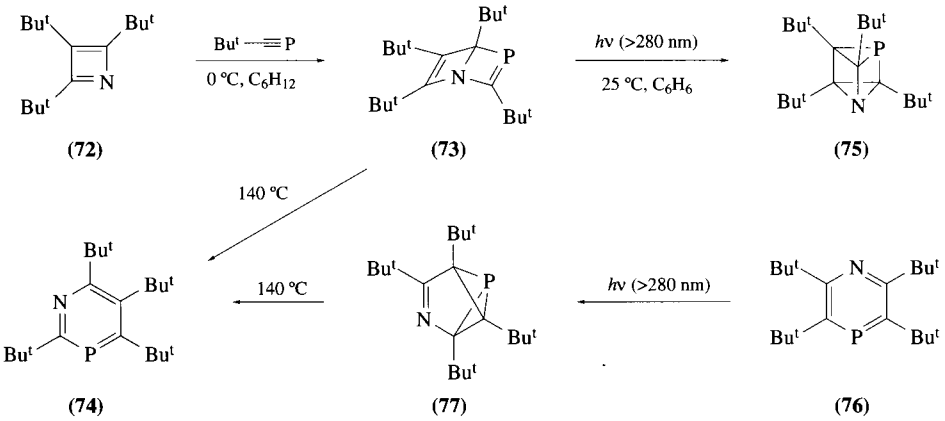
Appel and Poppe prepared the 4-amino-1,3-azaphosphinine (**71**) as a yellow oil by cycloaddition of the phospha-ynamine (**69**) to the 1,3-oxazin-6-one (**70**), followed by loss of carbon dioxide and hydrolysis (Scheme 8) ⟨89AG(E)53⟩.



(69) (70) (71)

Scheme 8

A fascinating entry to the 1,3-azaphosphinines starts from tri-*t*-butylazete (**72**), which undergoes facile cycloaddition to *t*-butylphosphaethyne in a sterically controlled reaction to yield the 1,3-Dewar azaphosphabenzene (**73**) [$\delta(^{31}P) = 202$] ⟨88AG(E)272⟩. This substance undergoes thermal valence isomerization to the 1,3-azaphosphinine (**74**) [$\delta(^{31}P) = 147$]. An alternative route to (**74**) is the photochemical valence isomerization of (**73**) to the prismane (**75**) [$\delta(^{31}P) = -111$], which at room temperature slowly rearranges to the 1,4-azaphosphinine (**76**) [$\delta(^{31}P) = 228$]. On irradiation, (**76**) is converted into the azaphosphabenzvalene (**77**) [$\delta(^{31}P) = -50$], which undergoes aromatization to (**74**) at 140°C (Scheme 9) ⟨B-90MI 625-01⟩.

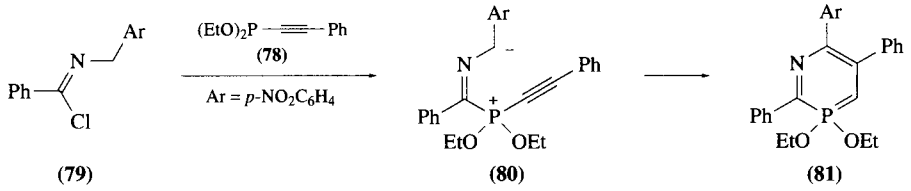


(72) (73) (75) (74) (77) (76)

Scheme 9

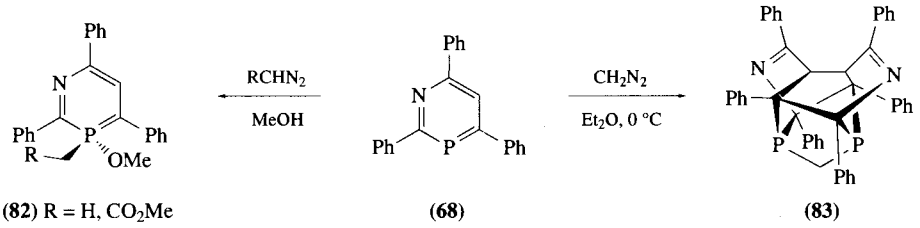
A 1,3λ^5-azaphosphinine was prepared by condensation of diethyl phenylethynylphosphonite (**78**) with the nitrile ylide formed by deprotonation and chloride ion loss from (**79**). Cyclization and prototropic isomerization of an intermediate ethynyl-1,4-dipole (**80**) led to the product (**81**) (Scheme 10), the structure of which was confirmed by x-ray, ^{31}P NMR and MS data ⟨86ZOB1661⟩.

1,3λ^5-Azaphosphinines can also be prepared from the 1,3λ^3 compounds. Addition of an alkyllithium, followed by alkylation, which works in the case of the phosphinines, fails with the triaryl-1,3-azaphosphinines because the initial RLi adduct at P extrudes R-P and forms a triarylpyrrolyl anion ⟨92TH 625-01⟩. However, the reaction with diazoalkanes in the presence of alcohols forms the



Scheme 10

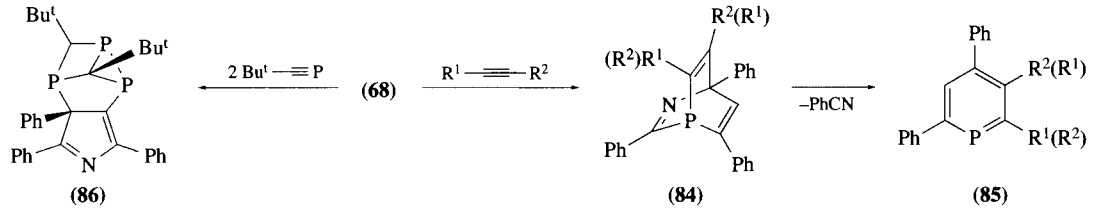
1-alkoxy-1-alkyl adducts (**82**) ⟨92TH 625-01⟩. In the absence of alcohol, diazomethane forms unusual 1 : 2 compounds (**83**) known as diaza-diphospha-chiropteradienes (Scheme 11) ⟨90TL6999⟩.



Scheme 11

The cycloadditions of alkynes to triaryl-1,3-azaphosphinines has been extensively investigated. Addition occurs across P/C-6, to form an unstable azaphosphabarrelene (**84**) which decomposes under the reaction conditions, forming the aryl carbonitrile and the phosphinine (**85**) (Scheme 12). Acetylenic esters, alkynyldiphenylphosphine oxides, and alkynyldiphenylphosphines all undergo the reaction, the last requiring heating under pressure ⟨87TL1093, 89TH 625-01, 90TL4589, 92TH 625-01, 93TH 625-01⟩.

t-Butylphosphaethyne reacts in a completely different way, forming a 2 : 1 adduct (**86**) with far-reaching rearrangement of the ring skeleton ⟨88AG(E)389⟩.



Scheme 12

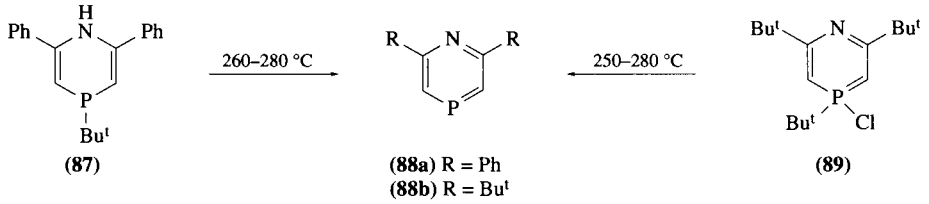
(iii) 1,4-Azaphosphinines

The 1,4-azaphosphinines include the long-known phenophosphazine system, the chemistry of which is somewhat different from that of the monocyclic compounds. Therefore phenophosphazines will be discussed in the following section.

The first, and for a long time the only, 1,4λ^3-azaphosphinine derivatives (**88a,b**) were synthesized in 1972 by thermolysis of 4-*t*-butyl-1,4-dihydro-1,4-azaphosphinine (**87**) and the 4-*t*-butyl-4-chloro-1,4λ^5-azaphosphinine (**89**), respectively (Scheme 13) ⟨72AG(E)1019, 74TH 625-01⟩. The spectral data, and particularly the very low-field ^{31}P chemical shift (see Section 6.25.4.1.3.ii) are consistent with the Hückel aromatic structure (**88**).

In Scheme 9 Regitz's preparation of the tetra-*t*-butyl-1,4-azaphosphinine (**76**) from the azaphosphaprismane (**75**) was mentioned.

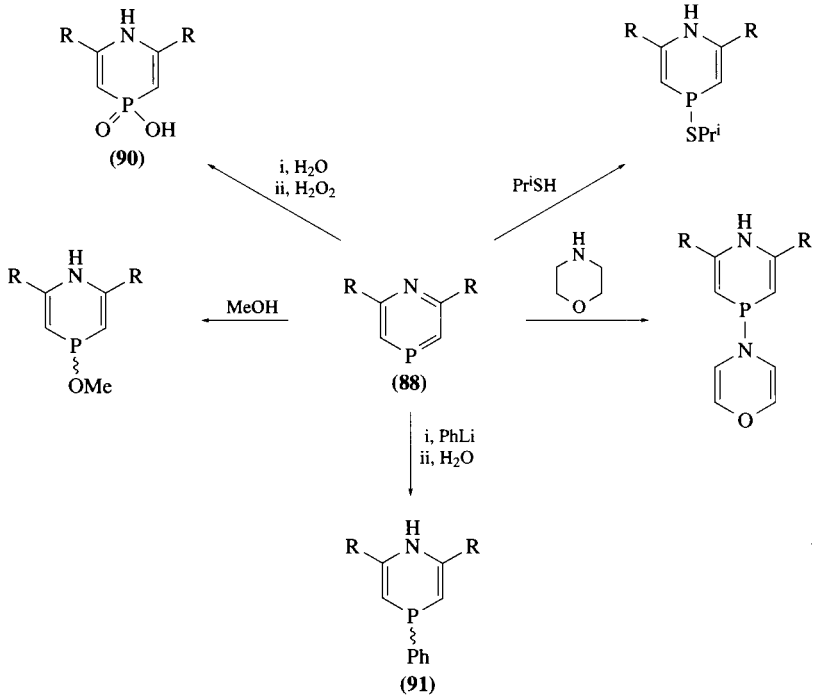
The electronegativity difference between nitrogen and phosphorus renders the 1,4-azaphosphinines (**88**) very reactive towards nucleophiles. Protic reagents H-X add the X to phosphorus, and the proton to nitrogen. Water, followed by peroxide oxidation, gives the phosphinic acid (**90**).



(87) (88a) R = Ph (88b) R = Bu^t (89)

Scheme 13

Aprotic species (PhLi) attack the P; on neutralization the N is protonated (**91**). Scheme 14 summarizes these reactions.

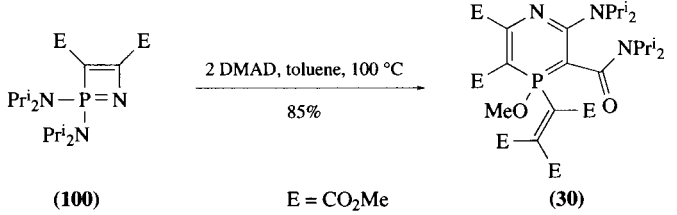


(90) (88) (91)

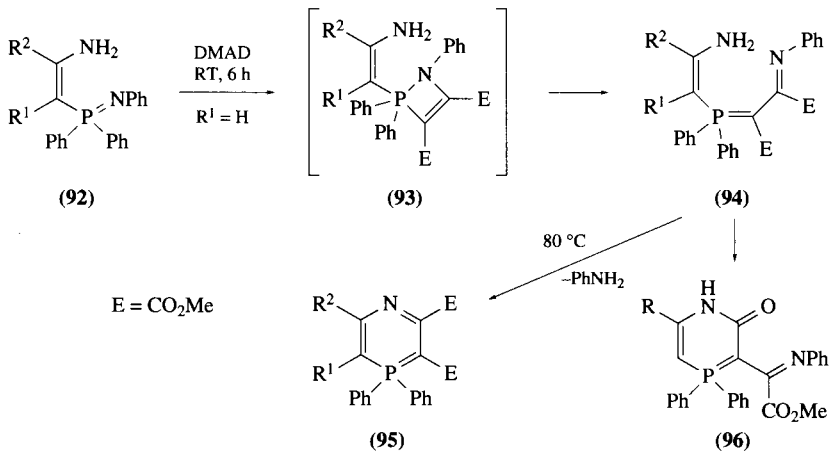
Scheme 14

The 1,4λ^5-azaphosphinines are available by a variety of methods. Cyclocondensation of the λ^5-phosphazenes (phosphinimines) (**92**) with DMAD in acetonitrile proceeds, probably via the dihydrophosphazete (**93**), with insertion of the acetylenic moiety into the P—N bond. The enamino-phosphorane products (**94**) cyclize on warming, losing aniline and forming the azaphosphinines (**95**) ⟨85CC1681⟩. With butyllithium the enamino-phosphoranes cyclize to give 1,4λ^5-azaphosphinin-2(1*H*)-ones (**96**) (Scheme 15) ⟨89JCS(P1)2273⟩. Azaphosphinin-2-ones (**99**) are also the outcome of the condensation of the phosphinimines (**97**) with acetylenic esters, followed by cyclization of the ylides (**98**) with KH (Scheme 16) ⟨90JOM(382)61⟩.

A quite extraordinary cycloaddition route to a 1,4λ^5-azaphosphinine was described by Bertrand and co-workers ⟨94JA8087⟩. The 1,2λ^5-azaphosphete (**100**) reacts with DMAD to give the azaphosphinine (**30**) (Equation (2)), as shown by x-ray crystallography.

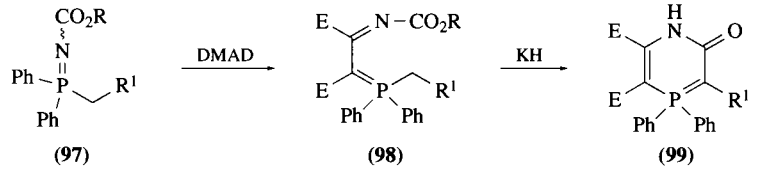


(100) E = CO_2Me (30) (2)



(92) (93) (94) (95) (96)

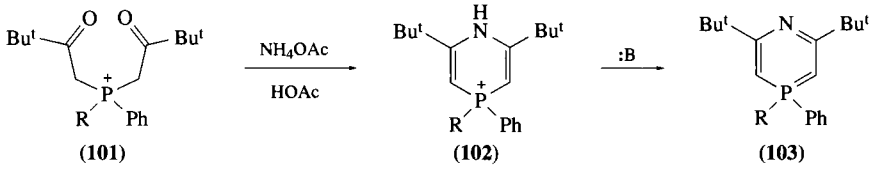
Scheme 15



(97) (98) (99)

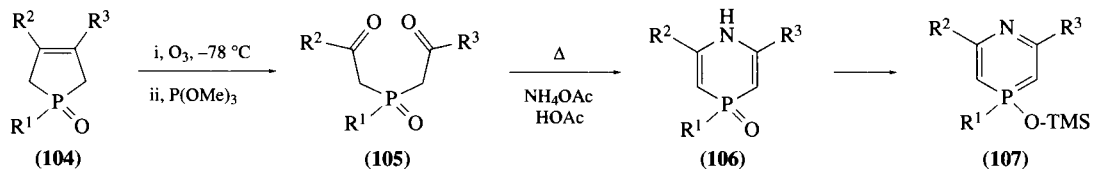
Scheme 16

By a number of related methods Simalty and others have produced di-(β-oxoalkyl)phosphonium salts (**101**) (Scheme 17). These are readily converted into the cyclic dienimines—the 1,4λ^5-azaphosphininium salts (**102**)—by reaction with ammonium acetate in refluxing acetic acid ⟨84PS(19)159⟩. Deprotonation (NaH/DMSO ⟨72TL4363⟩ or KOH/EtOH) gives the 1,4λ^5-azaphosphinines (**103**) ⟨70TL4371, 71TL4749, 72CR(274C)2206, 72JHC347, 72T3343, 79S109⟩. Quin *et al.* have shown that di-(β-oxoalkyl)phosphine oxides (**105**) can be prepared from phospholene oxides (**104**) by ozonolysis and reductive work-up ⟨84S1074⟩. These cyclize under similar conditions (NH_4OAc/AcOH) to form 1,4-dihydro-1,4-azaphosphinine 4-oxides (**106**). Silylation (bistrimethylsilyl trifluoroacetamide or Et_3SiBr) occurs to form the 4-silyloxy-1,4λ^5-azaphosphinines (**107**) (Scheme 18) (silylation at the nitrogen atom could not completely be ruled out) ⟨90PS(54)1⟩.



(101) (102) (103)

Scheme 17



(104) (105) (106) (107)

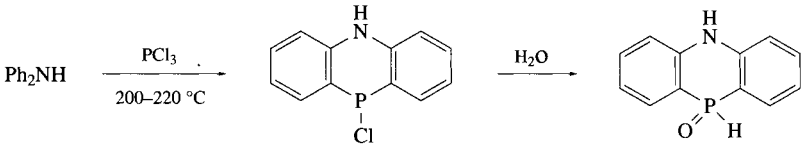
R^1, R^2, R^3 = Ph, Me; R^1 = Ph, R^2 = Me, R^3 = H; R^1, R^2 = Me, R^3 = H

Scheme 18

(iv) Phenophosphazines

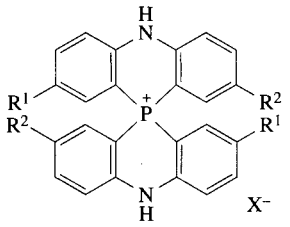
Fully unsaturated phenophosphazines (dibenzo[1,4]azaphosphinines) are unknown, but the 5,10-dihydro compounds are very well known, having first been prepared well over a century ago. Diphenylamines form the starting materials for all their syntheses. The reactivity of the 1,5-dihydrophenophosphazines is mainly classical phosphorus chemistry; it has been reviewed by Freedman and Freeman ⟨87CRV289⟩.

When diphenylamine is strongly heated with PCl_3 the chlorophenophosphazine (**108**) is formed. Aqueous work-up produces the dihydrophenophosphazine oxide (**109**) (Scheme 19) ⟨1888CB1497⟩. The structure of (**109**) was finally confirmed in 1960 ⟨60HCA1826⟩. The reaction was extended by Freedman and co-workers to substituted arylamines ⟨75JOC766, 81PS(9)269⟩. The spiro compounds (**110**) have also been detected in the reaction ⟨71JCS(A)1213⟩.



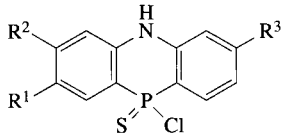
(**108**) (**109**)

Scheme 19



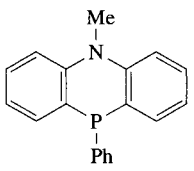
(**110**)
R^1, R^2 = Me
R^1 = Me, R^2 = H

When diphenylamines are heated with $PSCl_3$ at 200 °C in an autoclave the 10-sulfides (**111**) are formed ⟨61BRP860629, 81ZOB2222⟩. These products are available by other routes ⟨60HCA1826⟩.

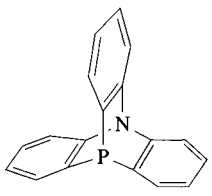


(**111a**) R^1, R^2, R^3 = H
(**111b**) R^1 = H, R^2, R^3 = Me
(**111c**) R^1 = Me, R^2, R^3 = H
(**111d**) R^1 = Cl, R^2, R^3 = H

A second, versatile method for the synthesis of dihydrophenophosphazines (**112**) involves the reaction of 2,2′-dilithiodiphenylamines with phenyldichlorophosphine or diaryl phenylphosphonites ⟨64JOC3410⟩. When trilithiotriphenylamine reacts with triaryl phosphites, the azaphosphatriptycene (**113**) is formed ⟨69AG(E)987, 78CB1798⟩.



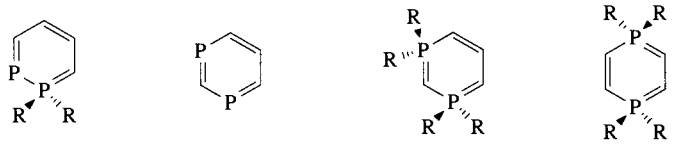
(**112**)



(**113**)

6.25.4.2.2 Six-membered rings with two phosphorus atoms

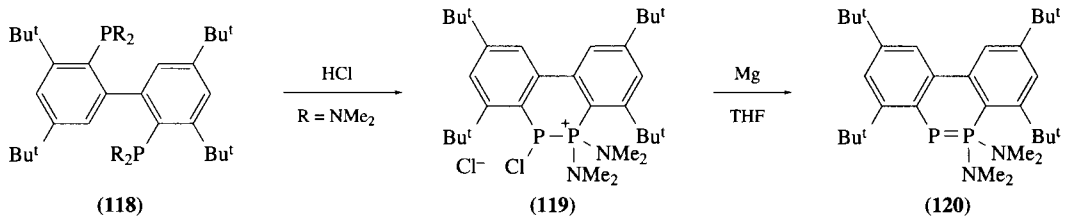
Of all the possible diphosphinines (permuting λ^3-P and λ^5-P over the 1,2-, 1,3- and 1,4-orientations gives a total of nine), only a very few are known, and some of those are too unstable to isolate. Representatives of four systems (**114**)–(**117**) have been studied. In addition, the 1,4-dihydro-1,4-diphosphinines have been known, with their dibenzo compounds (5,10-dihydrophosphanthrenes), since the early 1960s.



(**114**) (**115**) (**116**) (**117**)

(i) 1,2-Diphosphinines

Although diphosphenes (R-P=P-R) ⟨81JA4587⟩, and also five-membered rings with P=P bonds ⟨88TL5867⟩, are known, only one attempt, by Bickelhaupt and co-workers, at the synthesis of a 1,2-diphosphinine has been reported. 2,2′-Bis(bis(dimethylamino)phosphino)-3,3′,5,5′-tetra-*t*-butylbiphenyl (**118**; R = NMe_2) on treatment with hydrogen chloride was not converted into the expected bisdichlorophosphine derivative (**118**; R = Cl) but formed (**119**) by cyclization. Dehalogenation of (**119**) with Mg produced the orange λ^3,λ^5-diphosphaphenanthrene (**120**), which could not be purified. However, the ^{31}P NMR data confirmed the structure [$\delta(^{31}P) = 94.5$ (d), -129.0 (d), $^1J_{(PP)} = 469$ Hz] (Scheme 20) ⟨91HAC17⟩.



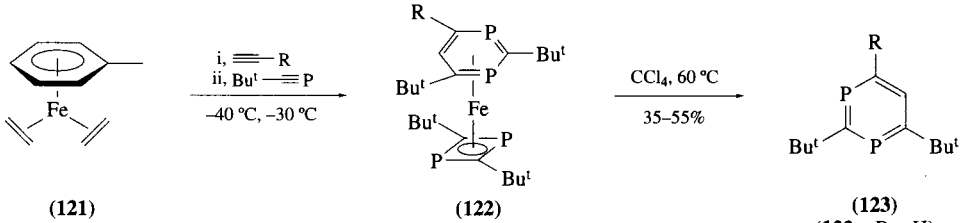
(**118**) (**119**) (**120**)

Scheme 20

(ii) 1,3-Diphosphinines

The behavior of *t*-butylphosphaethyne in the coordination sphere of transition metals opens up an entirely new field of phosphorus compounds with unusual structures ⟨88AG(E)1485, 88CRV1327⟩.

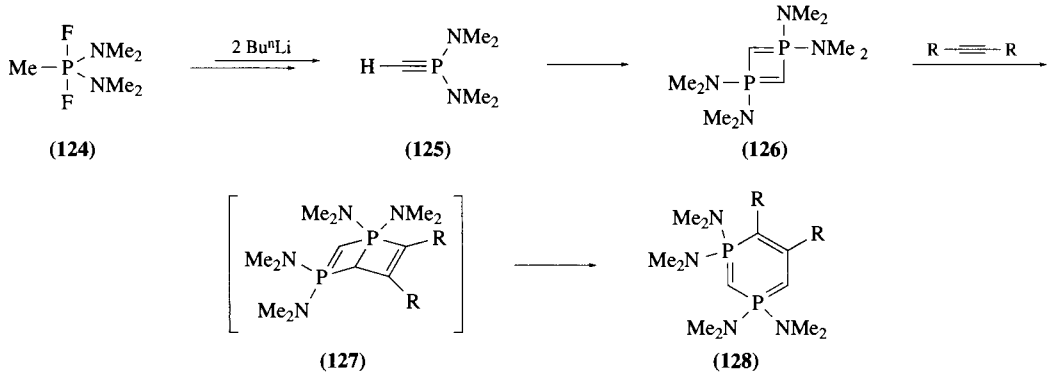
When bis(η^2-ethene)(η^6-toluene)iron(0) (**121**) ⟨86AG(E)831⟩ was reacted at $-40\,^\circ C$ with alkyne or at $-30\,^\circ C$ with terminal alkynes and subsequently with excess of *t*-butylphosphaethyne, the stable sandwich complexes (**122**) with diphosphinine and diphosphet ligands could be isolated in 35–55% yield. By oxidative decomplexation with CCl_4 the first free 1,3-diphosphinines (**123**) were obtained as yellow oils (Scheme 21). The spectroscopic data of (**123**) are in agreement with the expected Hückel aromatic 6π system: (**123a**), $\delta(^{31}P) = 220.2$ (d) 237.9 (d), $J_{(PP)} = 24.7$ Hz; ^1H NMR, δ (H-5) = 8.78 (ddd, $J_{(HP)} = 41.8$, $J_{(HP)} = 4.3$, $J_{(HH)} = 11.1$ Hz), δ (H-4) = 8.06 (ddd, $J_{(HP)} = 11.1$, $J_{(HP')} = 6.8$, $J_{(HH)} = 11.1$ Hz). The structure of (**122**) was confirmed by an x-ray analysis ⟨95AG(E)198⟩.



(**121**) (**122**) (**123**)
(**123a**; R = H)

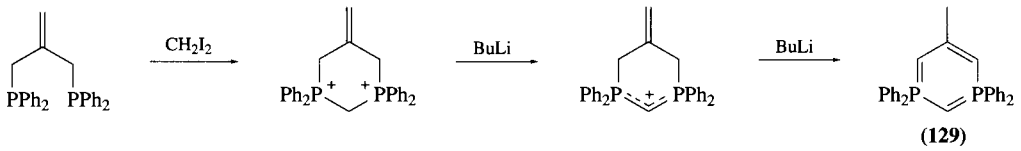
Scheme 21

With the synthesis of 1,1,3,3-tetrakis(dimethylamino)-1λ^5,3λ^5-diphosphete (**126**) by treatment of methyl(bisdimethylamino)difluorophosphorane (**124**) with *n*-butyllithium via the transient λ^5-phosphaalkyne (**125**) ⟨85ZN(B)1258, 86PS(29)23⟩, Fluck and co-workers obtained a highly reactive compound which undergoes at least formal Diels–Alder reactions with alkynes at room temperature, forming 1λ^5,3λ^5-diphosphinines (**128**) in fair to good yields. The transient Dewar isomer intermediates (**127**) were not detected. Symmetrical and some unsymmetrical alkynes give single regioisomers; other unsymmetrical alkynes form mixtures of regioisomeric products (Scheme 22) ⟨87CZ309, 89NJC383, 90ZAAC(588)181, 91ZN(B)202, 94ZAAC(620)483⟩. Photoelectron spectra and MO (MNDO) calculations on some of the products from this study have been reported ⟨91CB2071⟩.



Scheme 22

Schmidbaur's synthesis of 5-methyl-1,1,3,3-tetraphenyl-1λ^5,3λ^5-diphosphinine (**129**) (Scheme 23) ⟨90AG(E)569⟩ is reminiscent of an early approach by Maerkl to the same ring system ⟨63ZN(B)1136⟩. The exocyclic double bond moves into the ring on ylide formation, thus providing full cyclic conjugation. The saturated six-membered cyclic diphosphonium salt (**130**) behaves differently on deprotonation; a 1,2-didehydro-1,4,5,6-tetrahydro-1λ^5,3λ^5-diphosphinine (**131**) with a carbodiphosphorane structural element is produced (Scheme 24) ⟨81CB3063⟩.

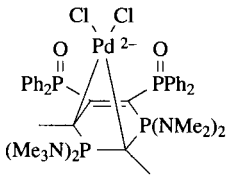


Scheme 23

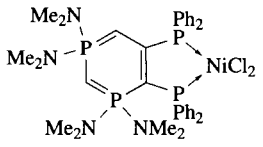
Scheme 24

The chemistry of the 1λ^5,3λ^5-diphosphinines known up to now is practically restricted to the various ways in which they can form metal complexes. Structures (**132**)–(**134**) illustrate bridging across ylide carbon atoms ⟨93JOM(459)73⟩, between two substituents ⟨94ZAAC(620)483⟩, and apparent η^6-arene bonding to a transition metal ⟨92OM2863⟩, respectively. The ligand of (**132**) is produced by air oxidation of that of (**133**).

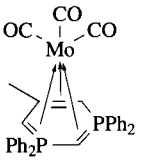
The fully saturated systems (1,3-diphosphinanes) have also received attention. A double Arbuzov reaction on the bis-phosphonite (**135**) forms the cyclic diphosphinate (**136**), which can be reduced to the diphosphine (**137**) (Scheme 25) ⟨89PS(41)113⟩. The synthesis and stereochemistry of the 1,3-diphenyl analogue (**138**) have also been reported ⟨89PS(44)235⟩.



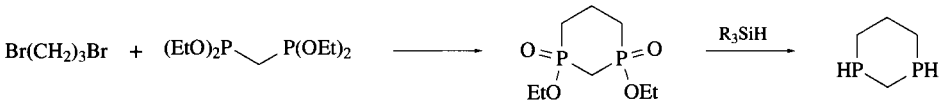
(132)



(133)



(134)



(135) (136) (137)

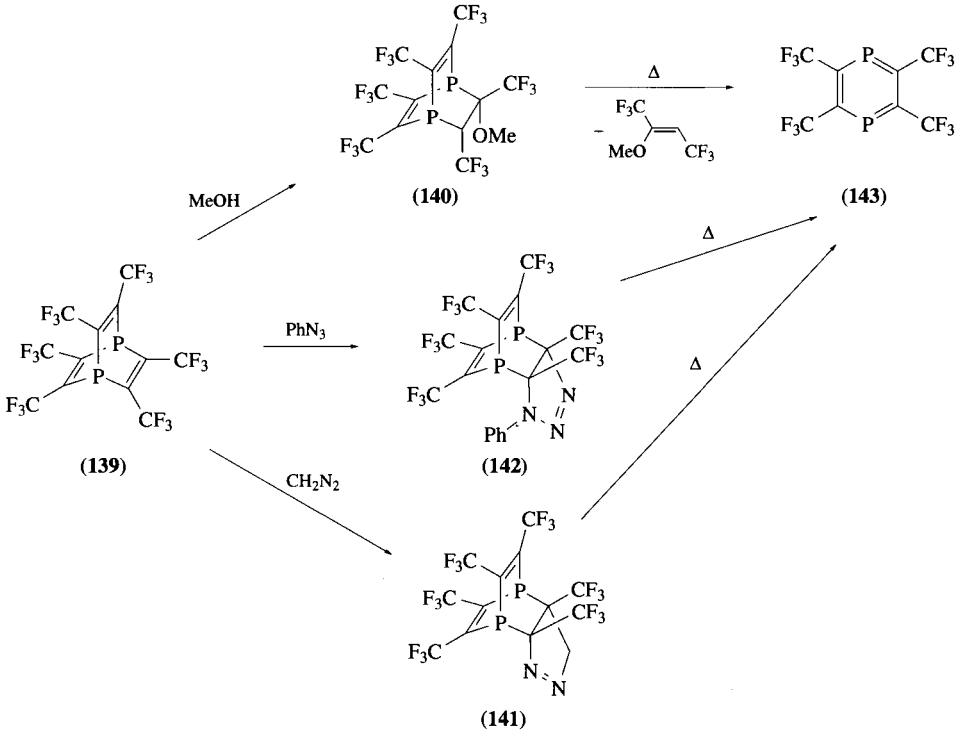
Scheme 25

(138)

(iii) 1,4-Diphosphinines, phosphanthrenes

The tetrakistrifluoromethyl compound (**143**) is the only known fully unsaturated derivative with λ^3-phosphorus. It has not been isolated, being handled only in hexane solution, and even there it is somewhat unstable. It is formed from the diphosphabarrelene (**139**) ⟨60JA1515, 61JA3432⟩, which forms adducts with methanol (**140**), diazomethane (**141**) and phenyl azide (**142**). These all thermally decompose by cycloreversion to produce the diphosphinine (**143**), along with the appropriate enol ether, pyrazole and triazole fragments, respectively (Scheme 26) ⟨76TL3715, 77TL867⟩.

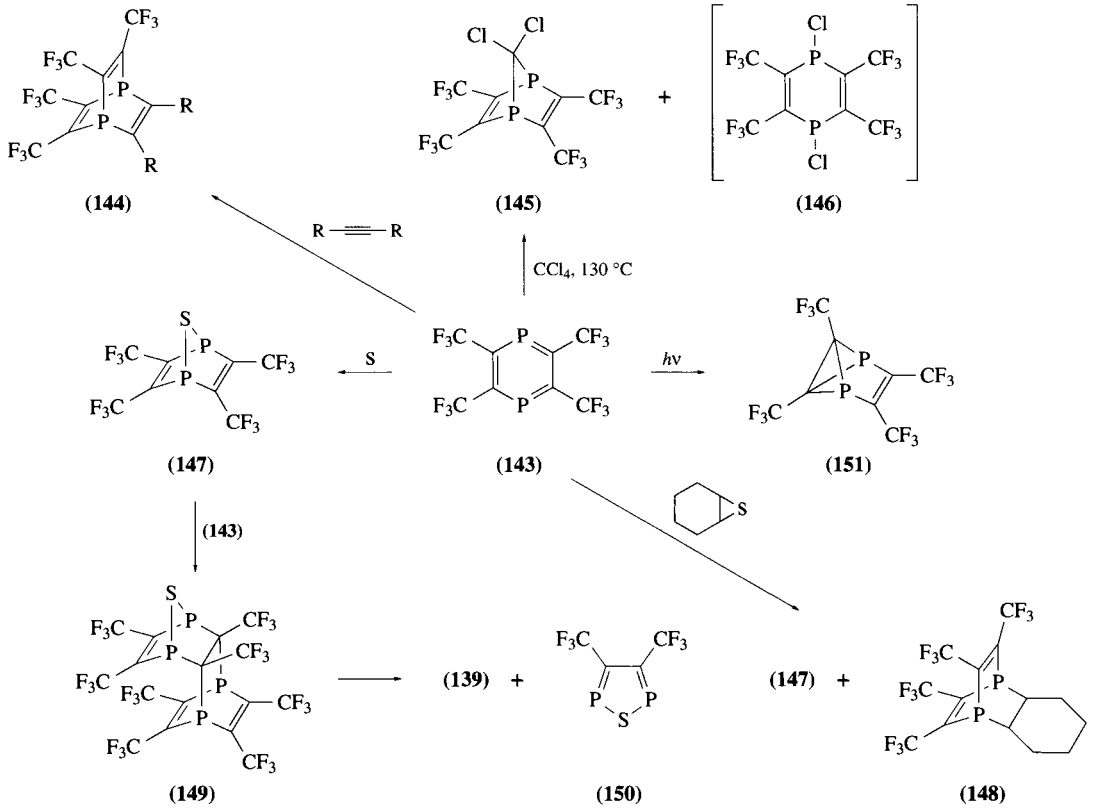
The chemistry of (**143**) is mainly characterized by (4 + 2) and (4 + 1) cycloadditions. It reacts



(139) (140) (141) (142) (143)

Scheme 26

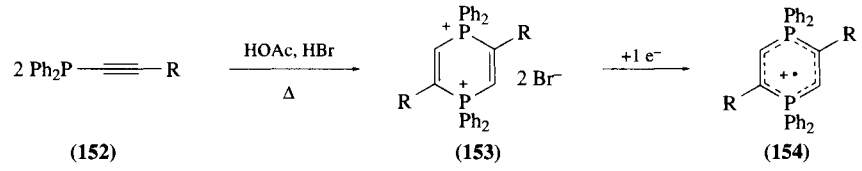
with alkynes to form the 1,4-diphosphabarrelenes (**144**) ⟨76TL3715⟩. By heating with CCl_4 in a sealed tube 7,7-dichloro-1,4-diphosphabicyclo[2.2.1]heptadiene (**145**) is isolated, besides the 1,4-dichloro-1,4-dihydro-1,4-diphosphinine (**146**), which is observed only in solution ⟨68CC1350, 77TL867, 77TL3057⟩. Elemental sulfur adds to (**143**); 7-thia-1,4-diphosphabicyclo[2.2.1]heptadiene (**147**) is obtained, and this is also formed in the reaction with 7-thiabicyclo[4.1.0]heptane, along with the cyclohexene (4 + 2)-cycloadduct (**148**) ⟨81JA2465⟩. The epithio derivative (**147**) reacts with (**143**) further to give the noninterceptible (4 + 2)-cycloadduct (**149**), which suffers a (4 + 2)-cycloreversion reaction, forming the barrelene (**139**) and the thiadiphosphole (**150**) (Scheme 27) ⟨81JA2465⟩.



Scheme 27

Irradiation of (**143**) in octafluoropentane with a high-pressure Hg lamp in a sealed tube causes valence isomerization to the 1,4-diphosphabenzvalene (**151**) (Scheme 27), which readily forms (4 + 2)-cycloadducts across the remaining double bond, with, e.g. 2,3-dimethylbutadiene or furan ⟨80JOC4683⟩.

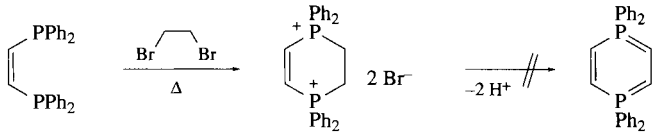
The existence of $1\lambda^5,4\lambda^5$-diphosphinines has not been firmly established. In 1967 Aguiar *et al.* published the acid-catalyzed dimerization of alkynyldiphenylphosphines (**152**) to the bis-phosphonium salts (**153**) ⟨67JA3067, 67JA4235, 69JOC2681⟩. However, according to electrochemical studies only the formation of the radical cations (**154**) by one-electron transfer can be observed, and the neutral $1\lambda^5,4\lambda^5$-diphosphinine species is not obtained (Scheme 28) ⟨77JA6656⟩.



Scheme 28

In another attempt the bis-phosphonium salt (**155**) was treated with butyl and phenyl lithium, but ring opening rather than simple di-deprotonation was observed (Scheme 29) ⟨66JA4090⟩.

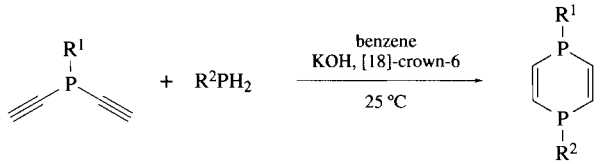
1,4-Dihydro-1,4-diphosphinines (**157**) are simply obtained by phase-transfer KOH-catalyzed



(155)

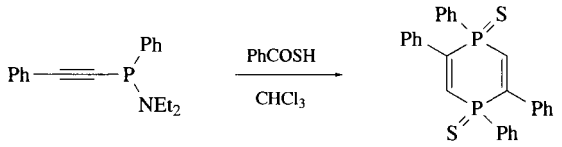
Scheme 29

addition of primary phosphines to dialkynyl phosphines (**156**) (Equation (3)) ⟨75TL3171, 77S842, 85CB2365⟩. Because of the configurational stability of phosphorus, the products (**157**) are formed as mixtures of *cis* and *trans* isomers, the *cis* predominant.

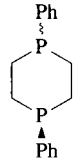


(156) (157) (3)

Fluck's group has reported the synthesis, x-ray crystal structure, and NMR spectrum of the 1,4-disulfide (**158**) (Equation (4)) ⟨92PS(71)245, 95MRC553⟩. 1,4-Diphenyl-1,4-diphosphinanes (**159**) have also been prepared and studied ⟨89PS(44)235⟩.

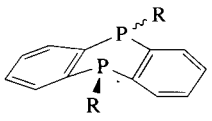


(158) (4)

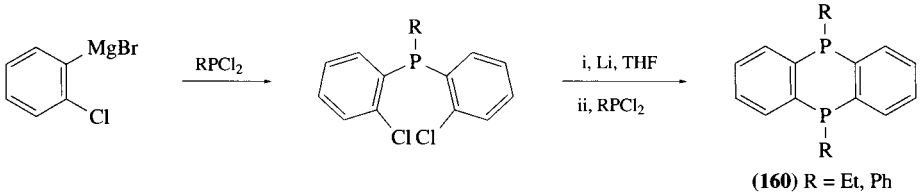


(159)

5,10-Dihydrophosphanthrenes (**160**) were synthesized by Davis and Mann via the route shown in Scheme 30 ⟨62CI(L)1539, 64JCS3770⟩. Like the monocyclic compounds (**157**), they show *cis/trans* isomerism of the substituents on P. The central ring is folded, as with the phenoxaphosphines and the dihydrophenophosphazines.



(160)

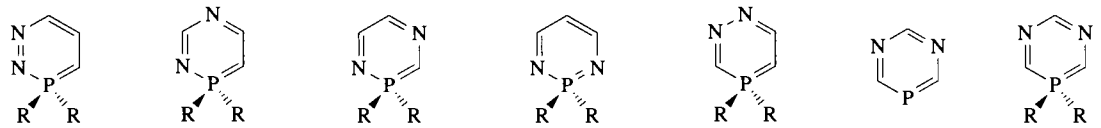


(160) R = Et, Ph

Scheme 30

6.25.4.2.3 Six-membered rings with one phosphorus and two nitrogen atoms

All (six) possible patterns of diaza–phospha substitution in a benzene ring are known. Derivatives of structures (**161**)–(**167**) can be found in the literature. With two nitrogen atoms present, $\lambda^3\sigma^2$-phosphorus is, so far, represented only in the 1,3,5-diazaphosphinine system (**166**).

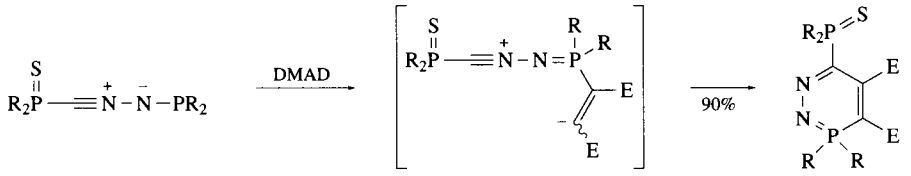


(**161**) (**162**) (**163**) (**164**) (**165**) (**166**) (**167**)

(i) 1,2,3-Diazaphosphinines

The *N*-phosphino-*C*-thiophosphinoyl-nitrilimine (**168**) is a surprisingly stable compound (m.p. 100°C). In cycloaddition reactions it can behave as a formal 1,4-dipole as well as a 1,3-dipole. With DMAD the 1,4-dipolar mode operates; cycloaddition takes place across C and P to give the 1,2,3λ^5-diazaphosphinine (**169**) as the first example of this ring system (orange crystals, m.p. 147°C) (Scheme 31). The spectroscopic data, especially the $\delta(^{31}P)$ values (+68.6, +14.5 ppm) and the high field shift of C-4 in the ^{13}C NMR [$\delta = 92.2$ (dd, $J(PC) = 107.5$ and 11.7 Hz)], attest the ylide-like character of (**169**). An x-ray crystal structure determination has been carried out ⟨90AG(E)1123, 94JA8087⟩.

The synthesis is restricted to very electron-poor alkynes; even with propiolic acid 1,3-dipolar addition forms the expected pyrazole.

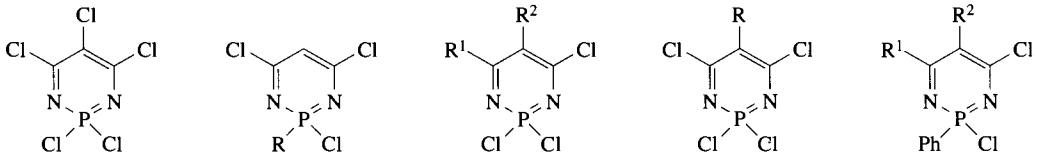


(**168**) R = NPr^i_2 (**169**)

Scheme 31

(ii) 1,3,2-Diazaphosphinines

A large number of papers from Russian laboratories dealing with the synthesis of 2,2-dichloro-1,3,2λ^5-diazaphosphinines by reaction of malononitrile, derivatives of malononitrile, and other monosubstituted nitriles with PCl_5 were published between 1966 and 1980. A brief overview of this work is given in Figure 5.



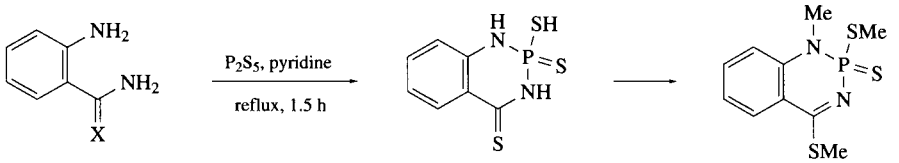
66ZOB735 66ZOB1254 71ZOB988,71ZOB2390, 73ZOB261, 74ZOB1247, 76ZOB2217, 81ZOB517 R = H, alkyl 77ZOB2522 78ZOB799

Figure 5 Halogenated 1,3,2λ^5-diazaphosphinines.

Reactions at the PCl_2 group, such as aminolysis and alcoholysis, have also been described ⟨70ZOB1466, 73ZOB16, 76ZOB1482, 77ZOB2199, 80ZOB1313⟩. Attempts to reduce the chlorine atoms away, to produce a 1,3,2λ^3-diazaphosphinine, have so far met with failure ⟨94UP 625-01⟩.

A variety of benzo-annellated 1,3,2-diazaphosphinines are known. The reaction of anthranilamide (**170**; X = O) or anthranilthioamide (X = S) with P_2S_5 in refluxing pyridine gave the pyridinium salt of (**171**), from which by treatment with base or SiO_2 (**171**) could be isolated (Scheme 32) ⟨85HCA900⟩.

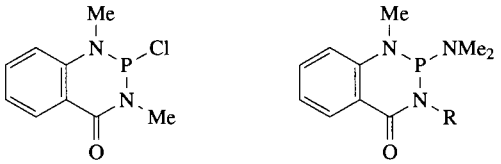
Treatment of (**171**) with aqueous alkali and dimethyl sulfate gave the trimethyl derivative (**172**). The structures of (**171**) and (**172**) were proved by x-ray analysis ⟨85JCS(P2)1913⟩; see also ⟨87JOM(325)153, 90IJC(B)711⟩. These products and others prepared from substituted anthranilamides were synthesized with a view to the development of antiparasitic compounds ⟨82MI 625-01⟩.



(**170**) (**171**) (**172**)

Scheme 32

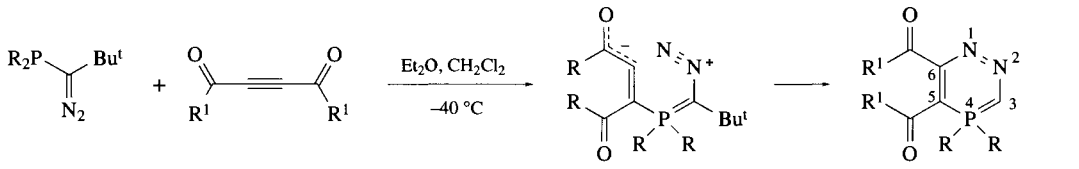
Schmutzler's group has investigated P(III) analogues of these compounds, e.g. (**173**) and (**174**) ⟨93ZN(B)333, 95PS(106)65, 95PS(107)69⟩. Structures (**39**) ⟨88ZN(B)937⟩ and (**40**) ⟨88IC1911⟩ (see Section 6.25.4.1.1) are also relevant to this section.



(**173**) (**174**)

(iii) 1,2,4-Diazaphosphinines

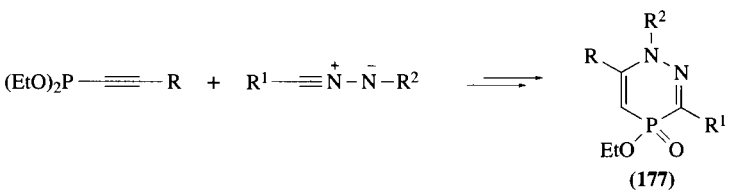
(4 + 2) Cycloaddition of phosphinodiazoalkanes (**175**) to electrophilic alkynes, probably by the two-step process indicated in Scheme 33, produces the 1,2,4λ^5-diazaphosphinines (**176**). The NMR spectra of compounds (**176**) are consistent with their ylide character ⟨90AG(E)314⟩. The 1,4-dihydro-1,2,4λ^5-diazaphosphinine oxides (**177**) are formed in a similar cycloaddition of nitrilimines to acetylenic phosphonites (Equation (5)) ⟨73ZOB2178⟩.



(**175**)

(**176a**) R = R^1 = OMe [δ(^{31}P) 1.5]
(**176b**) R = OMe, R^1 = Ph [0.3]
(**176c**) R = Ph, R^1 = OMe [−27.4]
(**176d**) R = R^1 = Ph [−32.0]

Scheme 33

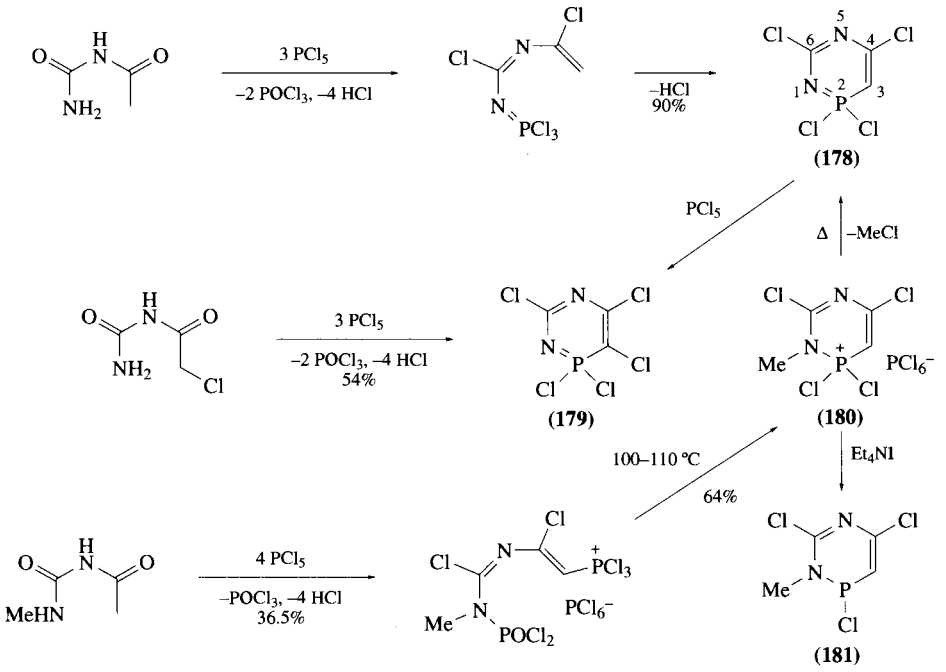


(**177**) (5)

(iv) 1,5,2-Diazaphosphinines

The reaction of acetylurea with PCl_5 leads to 2,2,4,6-tetrachloro-1,5,2λ^5-diazaphosphinine (**178**) (m.p. 79–80 °C) by a sequence of phosphorylation and chlorination steps ⟨87ZOB228, 91ZOB643,

93ZOB1976〉. Chloroacetylurea with PCl_5 produces 2,2,3,4,6-pentachloro-1,5,2λ^5-diazaphosphinine (**179**) (m.p. 91–93 °C) in a similar reaction sequence 〈91ZOB643〉. *N*-Acetyl-*N'*-methylurea with PCl_5 forms the salt (**180**), which can be reduced to (**181**), and thermally decomposed with loss of methyl chloride to form (**178**) (Scheme 34) 〈90ZOB462, 92ZOB306〉.



Scheme 34

The spectroscopic properties of all of the compounds described in this section have been thoroughly examined, including ^{35}Cl NQR and ^{31}P, ^{1}H and ^{13}C NMR.

The halogenated diaza- and particularly the triaza-λ^5-phosphinines and -diphosphinines can be considered as chimeras of cyanuric chloride, for the carbon-containing portion of the ring, and cyclotriphosphazene hexachloride—phosphonitrilic chloride—for the phosphorus-containing part. Their chemistry is understandable when this is borne in mind. With only two nitrogen atoms present, as in the compounds discussed in the present section, the *P*-halogen atoms are the more reactive, and their replacement by nucleophiles, hydrolysis and so on, can occur while the *C*-halogens are retained. When three nitrogen atoms are present the *C*-halogens are more reactive (see Sections 6.25.4.2.6.iii and 6.25.4.2.8). The references cited, and 〈94ZN(B)171〉, cover the principal features of the chemistry of the polyhalogenated 1,5,2λ^5-diazaphosphinines.

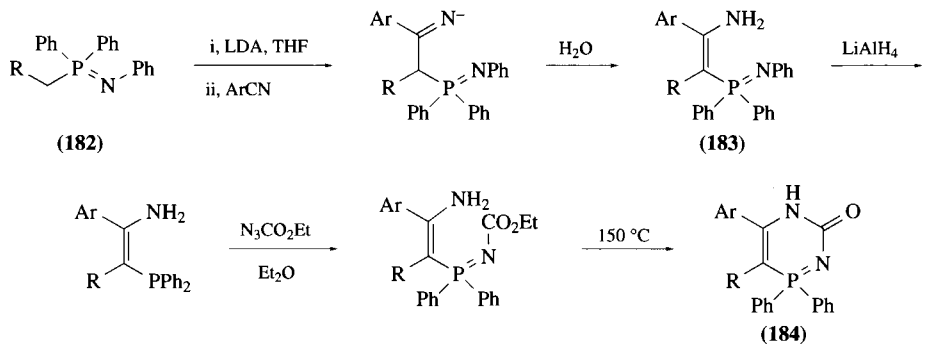
Barluenga and co-workers have reported the synthesis of 1,5,2λ^5-diazaphosphinin-6-ones (**184**) by cyclization of the enamino-phosphinimines (**183**). These are prepared from the alkyldiphenylphosphinimines (**182**) as indicated in Scheme 35 〈87TL2875, 89JCS(P1)615〉.

Another very unusual synthesis of the 6-ones and the corresponding thiones was published by Bertrand and co-workers 〈93JA7880, 94JA8087〉. The 1,2λ^5-azaphosphetes (**185**) (see Section 6.25.4.2.6.i) react with isocyanates and isothiocyanates forming the 6-oxo(thioxo)-1,5,2λ^5-diazaphosphinines (**186**) and (**187**) (Scheme 36).

Other 1,5,2λ^5-diazaphosphinines and 1,5,2λ^5-diazaphosphinin-6-ones have been reported, including some imidazo-fused derivatives which are analogous to the purine nucleosides 〈78MI 625-01〉, and some with arylazo substituents at C-6 〈90HCA1888〉.

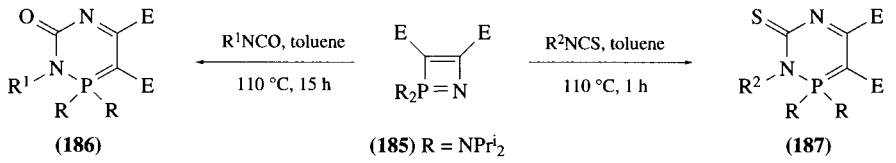
(v) 1,3,5-Diazaphosphinines, 1,3,5-diazaphosphinanes

The triaryl-1,3,5λ^3-diazaphosphinines (**189**) are prepared in a similar way to the 1,3λ^3-azaphosphinines of Section 6.25.4.2.1.ii. It is necessary to use the oxadiazinium tetrafluoroborates (**188**), and even then the yields are poor (3–5%) (Equation (6)) 〈91AG(E)106〉.



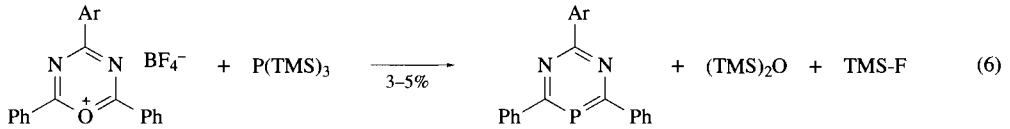
(182) (183) (184)

Scheme 35



(186) (185) R = NPr^i_2 (187)

Scheme 36

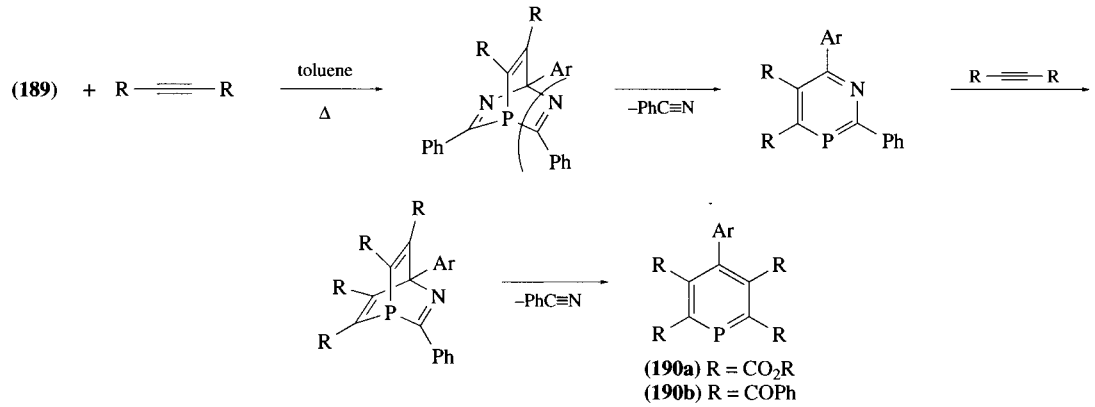


(6)

(188) (189)

^{31}P Chemical shifts of compounds (**189**) are in the region δ 135–141 ppm, depending upon the substituent group Ar.

The 1,3,5λ^3-diazaphosphinines react with alkynes in a cascade of (4 + 2)-cycloaddition and cycloreversion reactions, giving the substituted λ^3-phosphinines (**190**) (Scheme 37) ⟨91AG(E)106, 92TH 625-01⟩. With diynes the cycloadditions yield oligomeric phosphinines, and finally polymers with λ^3-phosphinine units ⟨96TH 625-01⟩.

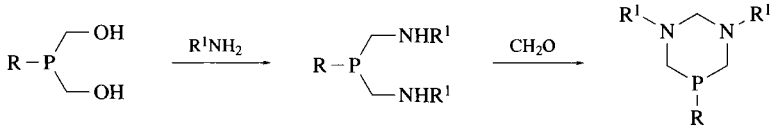


(190a) R = CO_2R
(190b) R = COPh

Scheme 37

The fully reduced 1,3,5-diazaphosphinanes (**191**) have been established in the literature since the early 1980s. Their synthesis is as outlined in Scheme 38. Their *P*-oxides and *P*-sulfides are the only formal representatives of the 1,3,5λ^5-diazaphosphinines (**166**) to have been described. The following

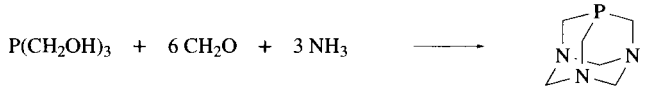
references are the main ones to cover the area ⟨80IZV721, 80IZV952, 80IZV1438, 81IZV1539, 81PS(10)207, 81TL229, 82IZV127⟩.



(191)

Scheme 38

1,3,5-Triaza-7-phosphaadamantane (TPA) (**192**) may be mentioned here, as a bridged 1,3,5-diazaphosphinane. Its synthesis has been described by several groups (Equation (7)) [$\delta(^{31}P) = -102$ ppm] ⟨74JHC407, 75CZ246, 75JHC579, 77ZN(B)499, 90PS(48)37⟩.



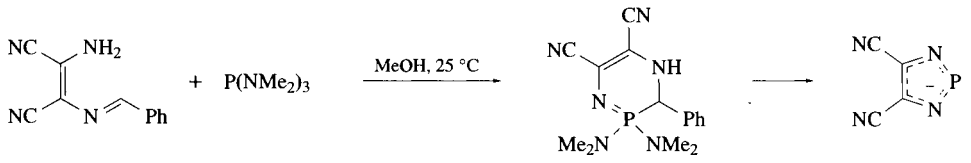
(192)

(7)

The interest in TPA arises from its capacity to form metal complexes with mercury ($TPA \cdot HgX_2$, X = Cl, Br, I, SCN, CN, NO_3) ⟨89CJC1319⟩, ruthenium and rhodium ($RuCl_2(TPA)_4$, $RuCl_2(TPA)_4 \cdot 2HCl$, $RhCl(TPA)_3$) ⟨92OM1990⟩ salts. The water-soluble complex $RuCl_2(TPA)_4$ is catalytically active in the reduction of unsaturated aldehydes to unsaturated alcohols. $RhCl(TPA)_3$ catalyzes olefin hydrogenation ⟨95JOM(488)99⟩. There is considerable recent interest in the gold(I) complexes of TPA ⟨95IC75⟩. TPA with $(Me_2S)AuCl$ in $CHCl_3$ affords the complex (TPA)AuCl in high yield. TPA·HCl in MeOH/MeCN with (tetrahydrothiophene)AuCl gives the protonated complex (TPA·HCl)AuCl. Both complexes have photoluminescence properties. The HCl-free complex in the solid state luminesces intensely red (674 nm at 78 K), the HCl complex yellow (596 nm at 78 K). This different behavior is clearly a consequence of the change in the aureophilic Au···Au interaction (3.092 Å vs. 3.322 Å). It should be pointed out that the aggregation of Au(I) complexes through the forces originating from Au···Au contacts is emerging as an element in the design of supramolecular frameworks. The Au···Au forces are similar in energy to those of hydrogen bonds. Another interesting luminescent gold(I) complex with TPA is $[(MeTPA)_3AuI]I_3$ ⟨95OM4194⟩; see also ⟨94CC431⟩.

(vi) 1,4,2-Diazaphosphinines

The only known example of this ring system is the 3,4-dihydro-2λ^5-compound (**193**) which was reported to be formed by the action of tris(dimethylamino)phosphine on monobenzylidene diaminomaleonitrile. On standing in acetonitrile it undergoes an unusual ring contraction: benzylidene bisdimethylaminoaminal and a proton are eliminated and the anion of dicyano-1,3,2-diazaphosphole is formed (Scheme 39) ⟨84CC183⟩.

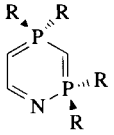


(193)

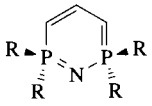
Scheme 39

6.25.4.2.4 Six-membered rings with two phosphorus atoms and one nitrogen atom

Of the possible azadiphosphinine systems only derivatives of the 1,2λ^5,4λ^5- (**194**) and 1,2λ^5,6λ^5-azadiphosphinine (**195**) systems have been reported. No azadiphosphinine with λ^3-phosphorus is yet described.



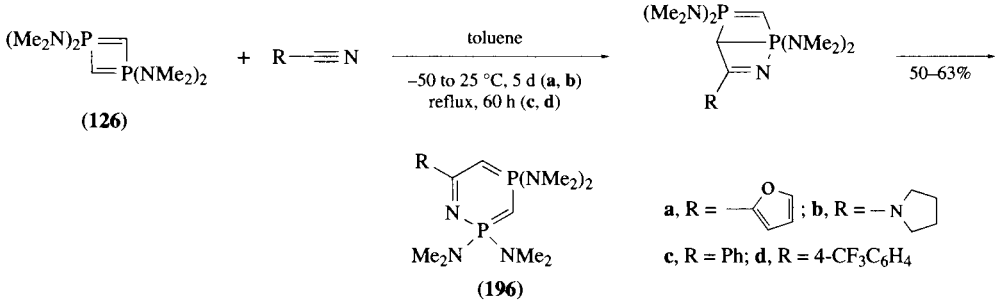
(194)



(195)

(i) 1,2,4-Azadiphosphinines

The diphosphete (**126**), which added alkynes in a synthesis of $1\lambda^5,3\lambda^5$-diphosphinines (Section 6.25.4.2.2.i), also smoothly adds to a wide variety of carbonitriles, to form $1,2\lambda^5,4\lambda^5$-azadiphosphinines (**196**) ⟨91PS(56)49, 91ZN(B)762⟩. NMR and an x-ray structure determination on (**196**; R = 4-$F_3C \cdot C_6H_4$) confirmed the structures of the products, which are very likely formed by valence isomerization via the Dewar intermediate shown (Scheme 40).



(126)

(196)

a, R = ; **b**, R =

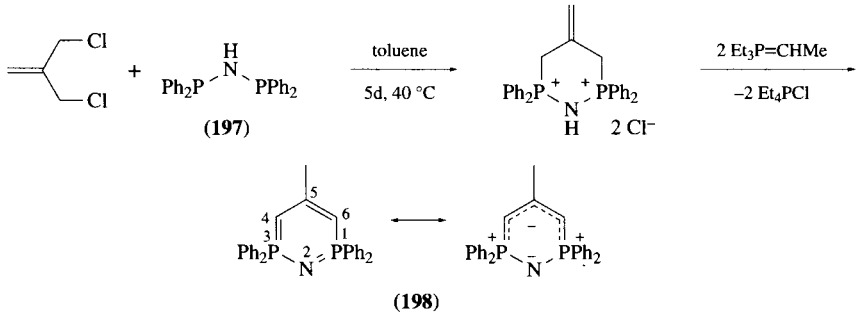
c, R = Ph; **d**, R = 4-$CF_3C_6H_4$

Scheme 40

(ii) 1,2,6-Azadiphosphinines

The preparation of these compounds is similar to that of the 1,3-diphosphinines (**129**) of Schmidbaur, described in Section 6.25.4.2.2.ii. The initial quaternization is carried out on the diphosphazane (**197**) ⟨76JA4410⟩, and deprotonation and tautomerization are brought about by triethyl(ethylidene)phosphorane (Scheme 41) ⟨91CB1525⟩.

The ^{31}P and ^{13}C NMR [δ (C-3/5) = 53.5, $^1J_{(PC)}$ = 111.7 Hz] demonstrate the ylide character of (**198**). An x-ray crystal structure determination has been carried out.



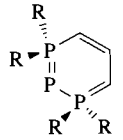
(197)

(198)

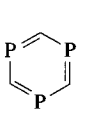
Scheme 41

6.25.4.2.5 Six-membered rings with three phosphorus atoms

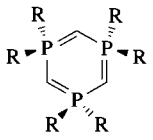
Only two arrangements of heteroatoms are known, the 1,2,3- and the 1,3,5-triphosphinines. The 1,2,3-series are known only with mixed-valence phosphorus ($1\lambda^5,3\lambda^5,2\lambda^3$) (**199**), the 1,3,5- with both all-λ^3 (**200**) and all-λ^5 (**201**), and with mixed valencies (**202**). The fully saturated 1,3,5-triphosphinanes are also known.



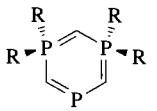
(199)



(200)



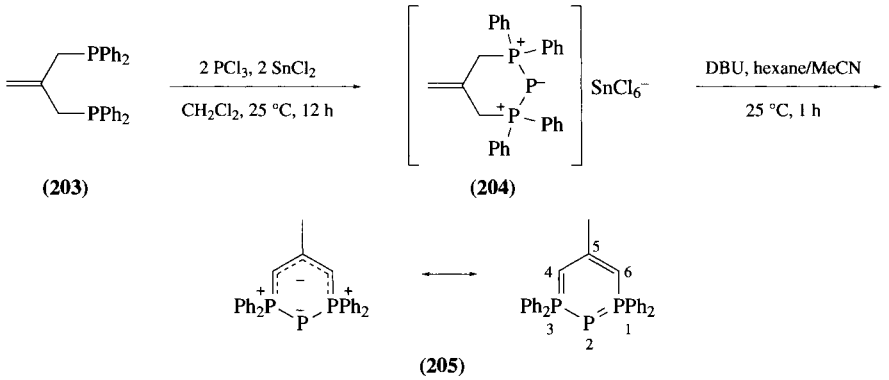
(201)



(202)

(i) 1,2,3-Triphosphinines

Treatment of 1,1-bis[(diphenylphosphonyl)methyl]ethane (**203**) with an equimolar quantity of PCl_3 in the presence of $SnCl_2$ affords the cyclic triphosphenium salt (**204**). The $SnCl_2$ acts as a reducing agent, being oxidized to $SnCl_4$ which acts as a Cl^- acceptor to give the $(SnCl_6)^{2-}$ counterion (Scheme 42) ⟨93CB601⟩. The Ph_2P—P—PPh_2 structural element in (**204**) is unusual; it is to some extent analogous to the carbodiphosphoranes $R_3P{=}C{=}PR_3$. Deprotonation accompanied by tautomerization to (**205**) could be achieved by dbu as base in the two-phase system acetonitrile/hexane, giving the product as a yellow, air-sensitive microcrystalline solid.



(203) (204) (205)

Scheme 42

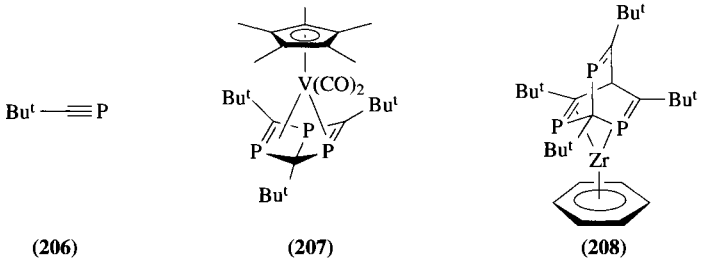
The spectral data (^{31}P NMR (C_6D_6) $\delta = +16.1$ (d, P-1, P-3), -232.94 (t, P-2), $^1J(PP) = 374.5$ Hz) are consistent with the structure.

This synthesis is closely related to that of the $1\lambda^5,3\lambda^5$-diphosphinine (**129**) (Section 6.25.4.2.2.ii) and the $1,2\lambda^5,6\lambda^5$-azadiphosphinine (**198**) (Section 6.25.4.2.4.ii).

(ii) 1,3,5-Triphosphinines, 1,3,5-triphosphinanes

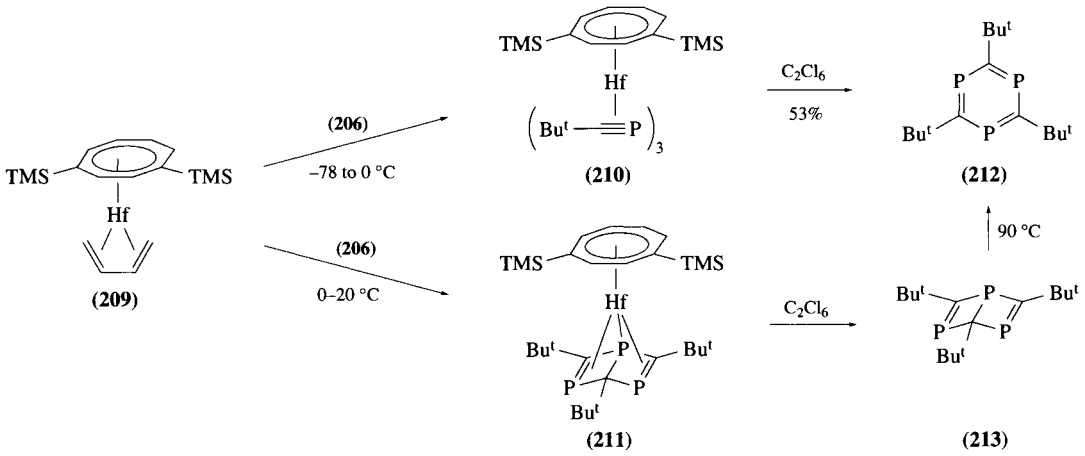
The synthesis of tri-*t*-butyl-$1\lambda^3,3\lambda^3,5\lambda^3$-triphosphinine arose from studies of the behavior of *t*-butylphosphaethyne (**206**) in the coordination sphere of transition metals. The first indication of the transition metal template catalyzed trimerization of (**206**) was the isolation of the vanadium-complexed 1,3,5-triphospha-Dewar benzene (**207**) ⟨87AG(E)908⟩. The formation of the tetraphosphabarrelene complexed to zirconium (**208**) implied the intermediate formation of the complexed tri-*t*-butyltriphosphinine derivative. The free barrelene could be obtained by oxidative decomplexation using C_2Cl_6 ⟨95AG(E)81⟩.

Shortly afterwards Binger, in a fascinating study, reported that the reaction of the hafnium



(206) (207) (208)

complex (**209**) with (**206**) is temperature dependent. At −78 to 0 °C the complex (**210**) is formed, in which three molecules of (**206**) are bound to the metal atom. At 0–20 °C the reaction with (**206**) remains at the stage of the cyclotrimer complex (**211**). By reaction of the complex (**210**) with hexachloroethane at 25 °C the first derivative of a $1\lambda^3,3\lambda^3,5\lambda^3$-triphosphinine (**212**) was obtained as a yellow, microcrystalline powder (Scheme 43). The 1,3,5-triphospha-Dewar benzene hafnium complex (**211**) releases the Dewar benzene (**213**) by oxidation with C_2Cl_6. The valence-isomerization (**213**) → (**212**) can be achieved by heating to 90 °C ⟨95AG(E)2227⟩.

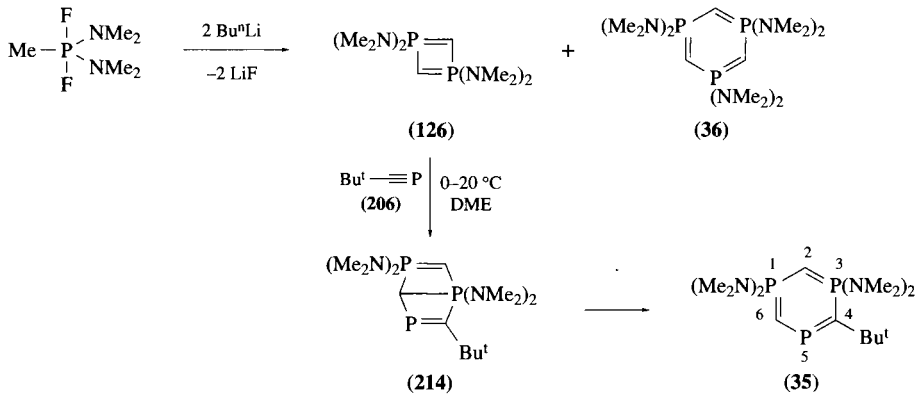


Scheme 43

The spectral data of (**212**) unambiguously establish the structure [δ (^{31}P) = 232.6 (s); the ring carbon atoms give rise to one signal in the ^{13}C NMR, δ = 211.8 (X component of an A_2BX spin system); $^1J_{(PC)}$ = 77.0 Hz].

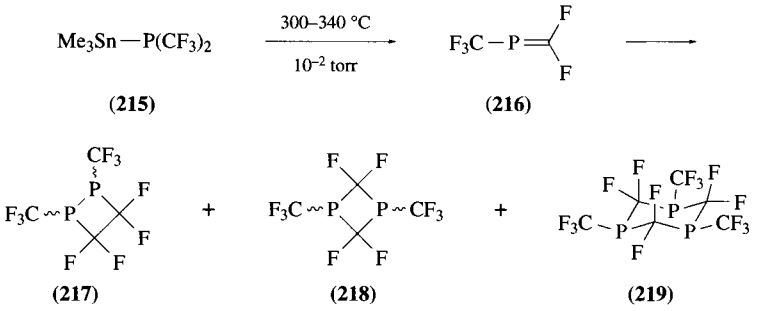
The tetrakis(dimethylamino)-1,3-diphosphete (**126**) provides access to 1,3,5-triphosphinines with λ^5-phosphorus. Its synthesis is given in Scheme 22. In 1990 one of the by-products of this reaction (3–8% yield) was identified as $1,1,3,3,5,5$-hexakis(dimethylamino)-$1\lambda^5,3\lambda^5,5\lambda^5$-triphosphinine (**36**) ⟨90JCS(P1)1223⟩. The spectroscopic and x-ray structural data have been discussed in Section 6.25.4.1. The PE spectrum of (**36**) has been reported ⟨91CB2071⟩.

Cycloaddition of (**126**) to *t*-butylphosphaethyne (**206**) forms the mixed-P-valence triphosphinine (**35**), probably via the triphospha-Dewar benzene (**214**), which was not isolated (Scheme 44) ⟨86AG(E)1002, 87ZN(B)1213⟩.



Scheme 44

Difluoromethylene(trifluoromethyl)phosphane (**216**), available most conveniently by thermolysis of the stannylphosphane (**215**), dimerizes and trimerizes on warming from a cold trap to give the 1,2- and 1,3-diphosphetanes (**217**) and (**218**) and, in yields of up to 12%, the 1,3,5-triphosphinane (**219**) (Scheme 45) ⟨83IC2573, 84AG(E)710⟩. The structures of the products were mainly elucidated by ^{19}F NMR spectroscopy.



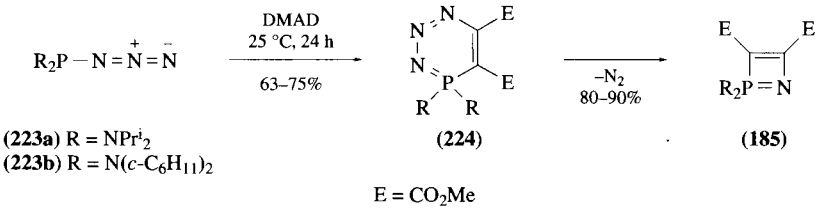
Scheme 45

6.25.4.2.6 Rings with one phosphorus and three nitrogen atoms

Of the possible triazaphosphinine isomers only derivatives of the 1,2,3,4λ^5- (**220**), 1,2,4,3λ^5- (**221**) and 1,3,5,2λ^5-triazaphosphinines (**222**) have been reported. Triazaphosphinines with $\lambda^3\sigma^2$-phosphorus are not yet known.

(i) 1,2,3,4-Triazaphosphinines

Bertrand and co-workers studied the reaction of the azidophosphines (**223a,b**) with DMAD, and found that, as with other instances of phosphino-1,3-dipoles, the (4 + 2) mode of cycloaddition was favored. In this way the 1,2,3,4λ^5-triazaphosphinine diesters (**224**) were obtained as yellow crystalline materials (Scheme 46). The NMR spectra [(**224a**): δ (^{31}P) 5.74; δ (^{13}C) 81.77 d, $^1J_{(PC)}$ 113.2 Hz; C-5; 150.4 d, $^2J_{(PC)}$ 2.4 Hz] are consistent with the P ylide/phosphinimine character of the ring, and the x-ray data are in agreement with this. The products (**224**) on heating in toluene lose nitrogen and form the 1,2-azaphosphetes (**185**), which undergo a versatile selection of cycloaddition reactions, providing phosphorus-containing six-membered rings (see Sections 6.25.4.2.1.iii and 6.25.4.2.3.iv) ⟨93JA7880, 94JA8087⟩.

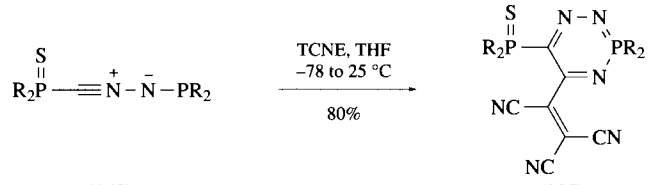


Scheme 46

(ii) 1,2,4,3-Triazaphosphinines

The *N*-phosphino-*C*-thiophosphinoylnitrilimine (**168**) has already been seen (Section 6.25.4.2.3.i) in a (4 + 2)-cycloaddition reaction with DMAD. With TCNE the same mode of addition takes

place across one of the cyano groups, giving the triazaphosphinine (**225**) (Equation (8)) [^{31}P NMR ($CDCl_3$): $\delta = 50.7$ (P-3), 22.4 $^4J_{(PP)} < 1$ Hz] ⟨91CB1739⟩.



(168) (225) (8)

(iii) 1,3,5,2-Triazaphosphinines

1,3,5,2λ^5-Triazaphosphinines with halogen and amino substituents have been investigated extensively, mainly between 1970 and 1980. The principal workers in the area were Glemser, Schmidpeter, Kornuta and Kukhar. Figure 6 provides references to six important compounds or groups of compounds studied at that time. Their syntheses are mostly based on the treatment of dicyanimides, *N*-cyanobenzamidines, *N*-cyanocarboxamides or imidoguanidines with PCl_5.

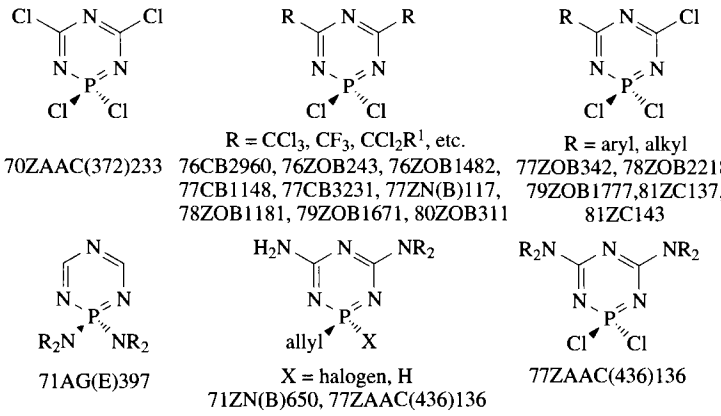
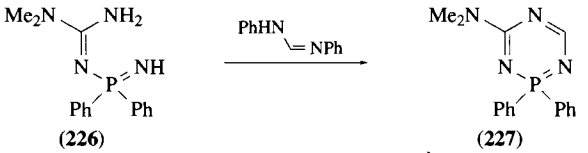


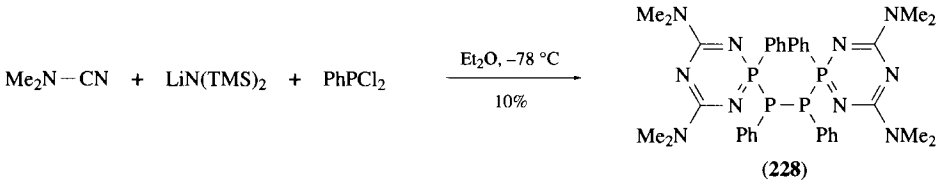
Figure 6 1,3,5,2λ^5-Triazaphosphinines.

N,*N*′-diphenylformamidine provided the C-6 for cyclization of the diphenylphosphoguanidine (**226**) in Schmidpeter and Ebeling's synthesis of the 2,2-diphenyl-1,3,5,2λ^5-triazaphosphinine (**227**) (Equation (9)) ⟨67AG(E)565⟩.



(226) (227) (9)

Only one synthesis in this area has been reported since 1983. When Me_2NCN reacts with $LiN(SiMe_3)_2$ and then with $PhPCl_2$ in CH_2Cl_2 at −78 °C an unusual product (**228**) (m.p. 228 °C) can be isolated, in which two 4,6-bis(dimethylamino)-2-phenyl-1,3,5,2λ^5-triazaphosphinine rings are connected by a —P_2Ph_2— bridge (Equation (10)) ⟨88CB1681⟩.

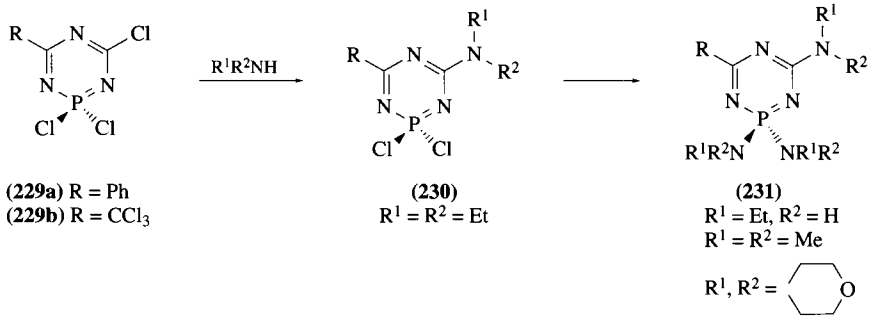


(228) (10)

The presence of $\lambda^5\sigma^4$- and $\lambda^3\sigma^3$-phosphorus atoms is evident from the ^{31}P NMR spectrum of (**228**) [δ (^{31}P) = 46.3 and −41.6, AA′XX′ spin system].

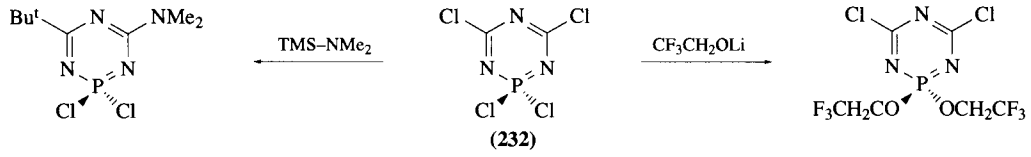
X-ray crystal structure data are available for two 1,3,5,2λ^5-triazaphosphinines with *P*-amino substitution (see Section 6.25.4.1.1). Dipole moment measurements ⟨83ZOB559⟩ and conformational studies ⟨85ZOB162⟩ have also been carried out.

The chlorine atoms in the 1,3,5,2λ^5-triazaphosphinines have acid chloride character and are readily replaced by nucleophiles. In the 2,2,4-trichloro compounds (**229**) the reaction with amines occurs selectively. At a molar ratio of (**229**) to amine of 1 : 2 only the C-4 chlorine is replaced. With excess of amine (dimethylamine, morpholine, ethylamine) the triamino derivatives (**231**) are formed, even at 20 °C. The reaction with diethylamine stops at the stage of the monoamino derivative (**230**) for steric reasons (Scheme 47) ⟨79ZOB1777⟩.



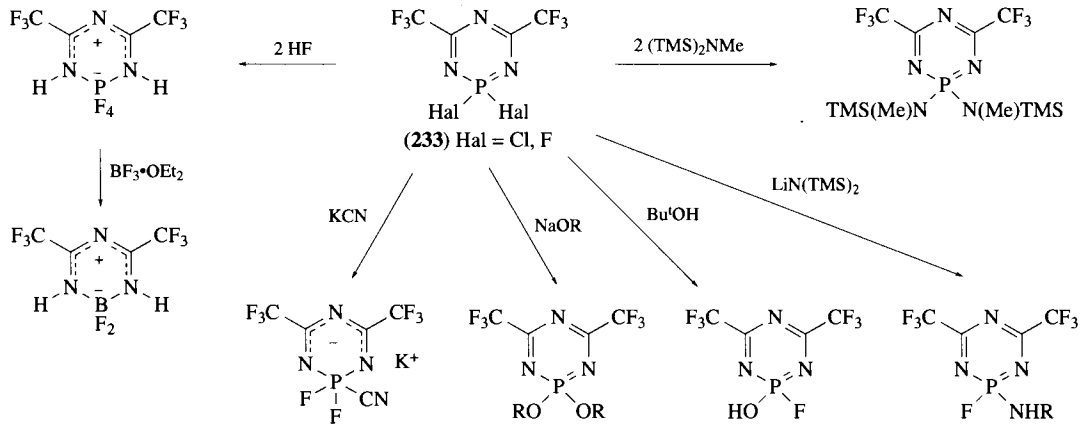
Scheme 47

In (**229a**) with sodium benzothiolate (ratio 1 : 1) only the halogen at C-4 is replaced. With sodium methoxide and sodium phenoxide (ratio 1 : 1) a mixture of monosubstitution products at C-6 and at the phosphorus atom is formed ⟨82ZOB590⟩. Roesky and Mainz confirmed this substitution pattern ⟨86ZAAC(540/1)212⟩. In the tetrachloro-triazaphosphinine (**232**), with Me_3SiNMe_2 the halogens in the 4- and 6-positions, and with CF_3CH_2OLi only the P-halogen atoms, are substituted (Scheme 48). The tetrakis(dimethylamino) substitution product can be prepared from (**232**).



Scheme 48

The 2,2-dihalo-4,6-bis(trifluoromethyl) compounds (**233**) undergo an interesting variety of substitution and addition reactions (Scheme 49) which have been studied by Klingebiel and co-workers ⟨88CB627, 88CB1119, 88ZN(B)1010⟩ and others ⟨74ZOB2104, 76CB2960, 82ZOB2742, 87ZOB1980⟩.

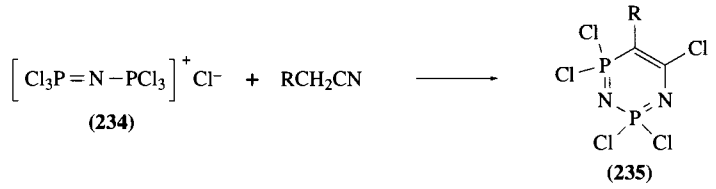


Scheme 49

6.25.4.2.7 Rings with two phosphorus and two nitrogen atoms

To date the only monocyclic compounds under the present heading are derivatives of 1,3,2λ^5,4λ^5-diazadiphosphinines. Fused ring systems containing the 2,5-dihydro-1,3,2,5-diazadiphosphinine moiety are also known.

Hexachlorodiphosphazenium chloride (**234**) reacts with a variety of carbonitriles to form 2,2,4,4,6-pentachloro-1,3,2λ^5,4λ^5-diazadiphosphinines (**235**) (Equation (11)) ⟨77PS(3)209, 77ZAAC(433)229, 77ZAAC(434)95⟩.

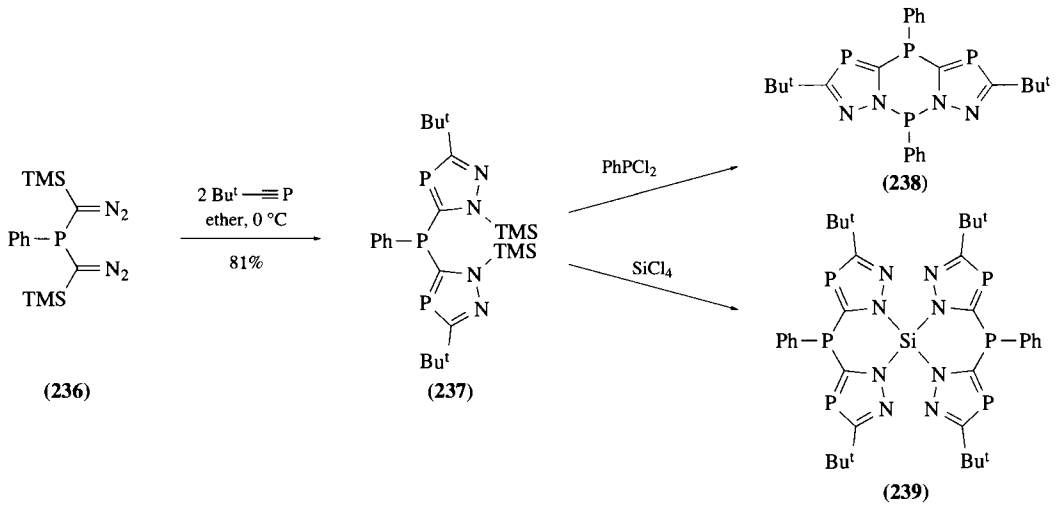


(11)

(234) (235)

a, R = Cl; **b**, R = CH_2Cl ($CHCl_2$, CCl_3); **c**, R = H; **d**, R = Ph; **e**, R = CN

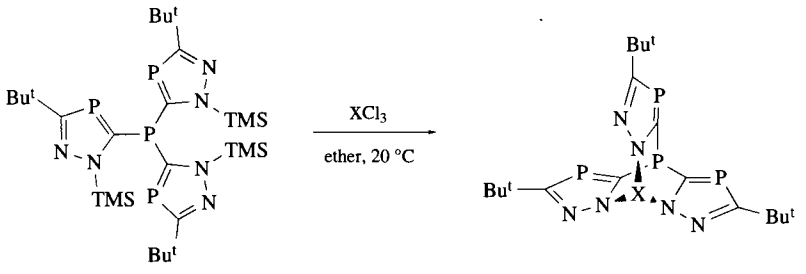
The regiospecific (3 + 2) cycloaddition of the bis(diazomethyl)phosphane (**236**) with *t*-butylphosphaalkyne gives the phosphine (**237**), substituted by 1,2,4-diazaphosphole units. With dichlorophenylphosphine (**237**) condenses smoothly to furnish compound (**238**), with a 1,3,2,5-diazadiphosphinine unit. An analogous condensation with $SiCl_4$ results in the spiro-linked silicon heterocycle (**239**) with a 1,3,5,2-diazaphosphasilabenzene structural unit (Scheme 50) ⟨88TL925⟩.



(236) (237) (238) (239)

Scheme 50

A comparable reaction sequence gives access to the tris(1,2,4-diazaphospholyl)phosphane (**240**), which was converted into the heavily heterosubstituted triptycene analogues (**241a–d**) (Equation (12)) ⟨88TL925⟩.



(12)

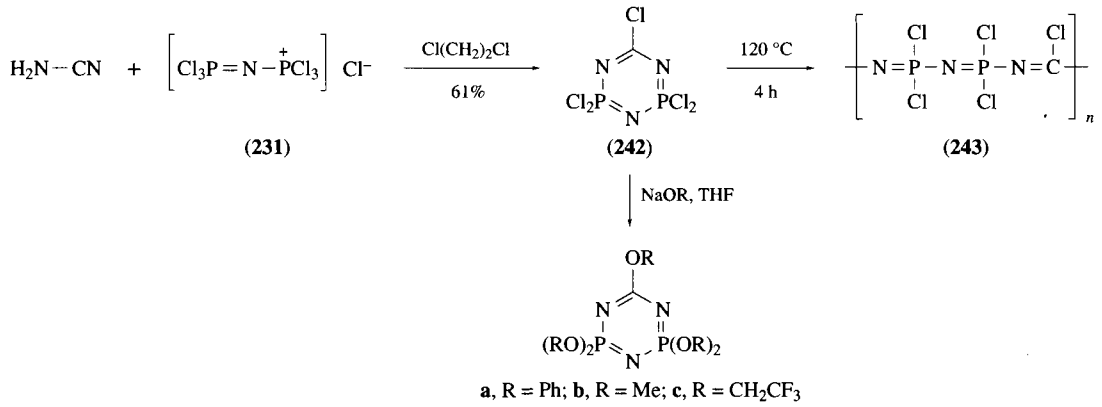
(240)

(**241a**) X = P
(**241b**) X = As
(**241c**) X = Sb
(**241d**) X = SiMe

6.25.4.2.8 Rings with two phosphorus and three nitrogen atoms

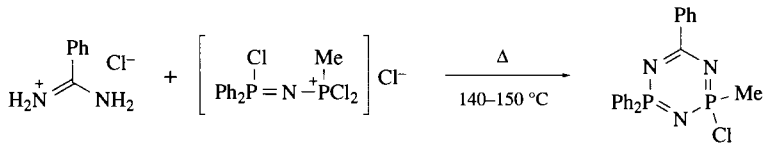
The only triazadiphosphinines known are derivatives of 1,3,5,2λ^5,4λ^5-triazadiphosphinine, which have been prepared by a variety of methods.

The pentachloro compound (**242**) was reported in 1975 to be formed by the action of cyanamide on hexachlorodiphosphazenium chloride (**234**) (Scheme 51) ⟨75ZN(B)808⟩, and its reactions have been well studied since that date. The chlorine atoms are easily replaced by amines ⟨77ZN(B)254⟩, alkoxides including trifluoroethoxide, and aryloxides ⟨93IC5088⟩. On heating to 120 °C a polychloropolycarbophosphazene (**243**) is formed, which, like its monomer, readily undergoes nucleophilic displacement of the chlorine atoms ⟨93IC5088⟩.



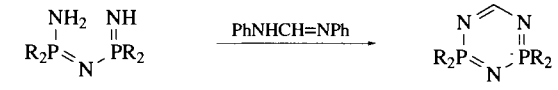
Scheme 51

A detailed six-step procedure for the synthesis of 2-chloro-2-methyl-4,4,6-triphenyl-1,3,5,2λ^5,4λ^5-triazadiphosphinine (**246**) by thermal cyclocondensation of benzamidinium chloride (**244**) with the diphosphazene (**245**) (Equation (13)) under 10^{-2} torr vacuum at 140–150 °C has been described ⟨89IS24⟩.

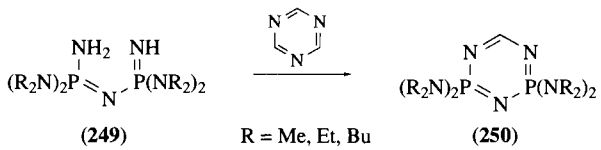


(13)

Derivatives with the 6-position unsubstituted were described by Schmidpeter and Ebeling. The 2,2,4,4-tetraphenyl and -tetramethyl compounds (**247**) were prepared using *N*,*N*′-diphenylformamidine and the aminodiphosphadiazenes (**248**) (Equation (14)) ⟨67AG(E)565⟩. The tetrakisdialkylamino compounds (**250**) were formed from the corresponding aminodiphosphazenes (**249**) using 1,3,5-triazine as the one-carbon source (Equation (15)) ⟨71AG(E)397⟩.

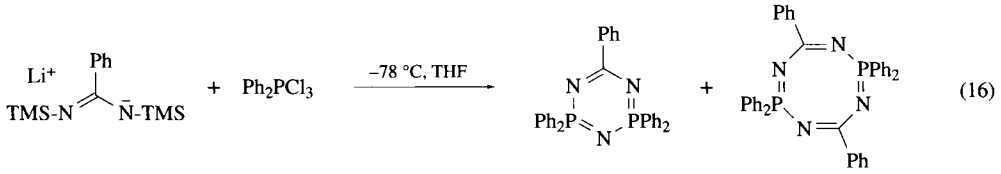


(14)



(15)

The lithium disilylbenzamidine salt (**251**) with Ph_2PCl_3 forms the pentaphenyl compound (**252**) and in addition the eight-membered ring system (**253**) (Equation (16)) ⟨91IC3402⟩.

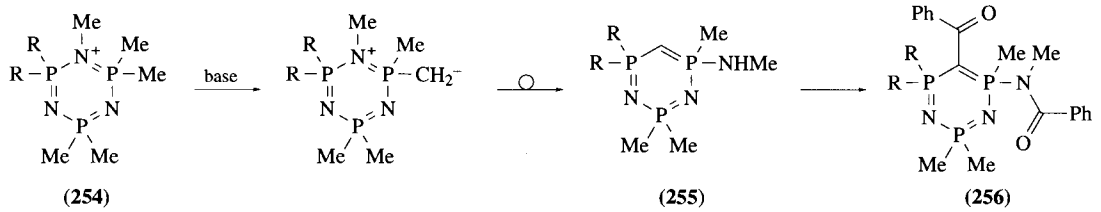


(251) (252) (253) (16)

A series of dumb-bell compounds with two tetraphenyl-1,3,5,2λ^5,4λ^5-triazadiphosphinine rings connected by a polyfluorinated chain has been described ⟨79JFC(13)189, 79JFC(13)199, 80JFC(15)327⟩.

6.25.4.2.9 Rings with three phosphorus and two nitrogen atoms

Of the possible isomers only derivatives of the 1,3,2λ^5,4λ^5,6λ^5-diazatriphosphinines are described in the literature. These were prepared by rearrangement of the heptamethylcyclotriphosphazenium salt (**254**) under the action of base (sodium hexamethyldisilazane). The authors propose a four-center mechanism, with the ylide carbon at P-2 attacking P-6 and displacing the ring N-atom carrying the methyl group. The ring carbon in the product (**255**) has strong ylide character; hydrolysis and protonation proceed as shown, and in the NMR the *C*-H signal is exchange-broadened and detectable only under favorable conditions. Benzoylation occurs both at C and exocyclic N, forming the derivative (**256**), the structure of which was solved by x-ray crystallography (Scheme 52) ⟨75CC454, 77CJC2534, 77CJC3651⟩.

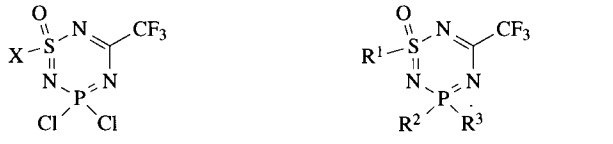


(254) (255) (256)

Scheme 52

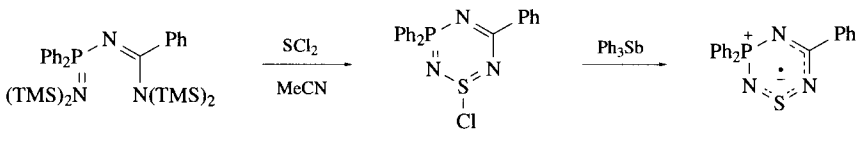
6.25.4.2.10 Rings with three phosphorus atoms, one nitrogen, and one sulfur or selenium atom

The trifluoromethyl-substituted 1λ^6,2,4,6,3λ^5-thiatriazaphosphinines (**257**) and (**258**) have been known since 1978 ⟨78CB731, 78CB737, 78CB745⟩. Reaction of SCl_2 with the phosphazenylamidine (**259**) affords the 1λ^4,2,4,6,3λ^5-system (**260**), which is reduced by triphenylstibine to the corresponding radical (**261**) (Scheme 53). The ESR spectrum revealed a spin distribution heavily localized over the P-N-S region ⟨89CC710⟩. The corresponding selenatriazaphosphininyl radical has also been described ⟨90JA2249⟩.



(257) (258)

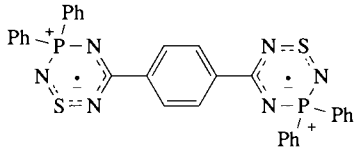
R^1 = F; R^2 = Cl, F; R^3 = NMe_2, NEt_2



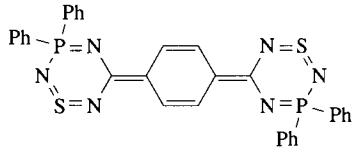
(259) (260) (261)

Scheme 53

Oakley and co-workers have synthesized the related 1,4-phenylene-bridged bis-1λ^4,2,4,6,3λ^5-thia(selena)triazaphosphinines and studied the spin distribution in the diradicals (**262**) ⟨92IC442⟩. The closed shell quinoidal ground state (**263**) evidently does not prevail.



(**262**)



(**263**)

6.25.5 RING SYSTEMS CONTAINING OXYGEN AND PHOSPHORUS ATOMS

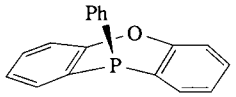
Although the majority of the ring systems considered in this section are fully saturated, a number conform to the mancude (maximum noncumulated double bond) structure, and some of these possess full cyclic conjugation and so merit consideration for the description "aromatic." The 4,4-diaryl-1,4-oxaphosphininium salts (**264a**) are occasionally drawn with $\lambda^5\delta^4$-phosphorus (**264b**), emphasizing their relationship to the 1,4λ^5-azaphosphinines ⟨72CR(274C)2206⟩. However, the Bird aromaticity index ($I_6 = 27$) of the 2,4,4,6-tetraphenyl salt seems to imply negligible aromaticity in these compounds ⟨90T5697⟩.

(**264a**) (**264b**)

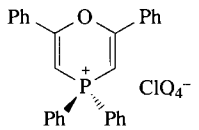
6.25.5.1 Experimental Structural Methods

6.25.5.1.1 X-ray crystallography

X-ray crystal structure determinations have been carried out on a limited number of P/O heterocycles. 10-Phenylphenoxaphosphine (**265**) was confirmed to be nonplanar by this method; the molecule is folded along the P···O axis, and the phosphorus atom is nonplanar ⟨76JCS(P2)1383⟩. The cation of 2,4,4,6-tetraphenyl-1,4-oxaphosphininium perchlorate (**266**) is described as "quasi-planar," although a small degree of folding is evident ⟨74CSC227⟩.



(**265**)



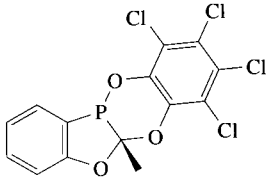
(**266**)

A crystal structure of 4-phenyl-1,4-oxaphosphinane 4-oxide confirmed the findings from solution phase NMR (see Section 6.25.5.1.2), that the ring exists in the chair conformation with the phenyl group equatorial ⟨88IZV2625⟩.

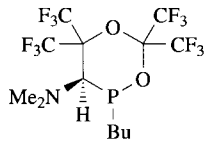
The structures of 1,3,2-dioxaphosphinanes of biochemical significance to have been solved by x-ray crystallography are numerous; the phenyl ester of thymidine 3′,5′-cyclic phosphate is an example ⟨75PNA(72)1335, 87JA4058⟩. In the 1,3,5-dioxaphosphinane series, conformational studies by NMR have been supported by x-ray crystal structures ⟨87IZV418⟩.

The structures of a number of other dioxaphosphinane molecules have been established or

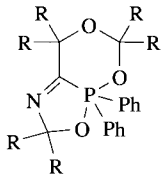
confirmed by x-ray measurements. The 1,4,2-benzodioxaphosphinine (**267**) ⟨84ZN(B)628⟩ (Section 6.25.5.2.1.v) and the four 1,5,2-dioxaphosphinine structures (**268**) ⟨95CB499⟩, (**269**) ⟨86CB2687⟩, (**270**) ⟨78CB726⟩ and (**271**) ⟨71JA5236⟩ (see Section 6.25.5.2.1.vi) are illustrative.



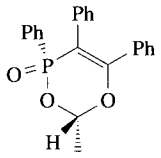
(**267**)



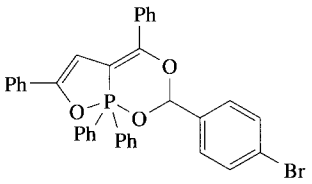
(**268**)



(**269**) R = CF_3



(**270**)



(**271**)

6.25.5.1.2 NMR spectroscopy

NMR spectral measurements have been applied to the investigation of conformational equilibria in many saturated systems. Because of the sensitivity of the ^{31}P nucleus to NMR detection, ^{31}P NMR is of great practical importance, providing valuable information supporting the ^{1}H and ^{13}C spectral measurements.

Phosphorus-31 NMR, coupled with 2D methods, was used to study diastereoisomeric exchange in η^3-allyl-Pd complexes of 2,3-diphenyl-1,3-oxaphosphinanes ⟨81JOM(222)353, 82ZAAC(494)189, 84JOM(269)209⟩. Uncomplexed 1,3-oxaphosphinanes exist in chair–chair conformational equilibria ⟨78PS(5)81, 86DOK(291)154⟩. Because of the (nonplanar) configurational stability of phosphorus(III), the 2,3-disubstituted compounds exist in two diastereomeric pairs. The $^{2}J_{P\text{-}C\text{-}H}$ couplings assisted the configurational assignments ⟨73ZC310⟩.

NMR (^{1}H, ^{31}P) and dipole moment measurements also established the conformation of 4-phenyl-1,4-oxaphosphinane 4-oxide as the chair form with Ph equatorial ⟨91ZOB2562⟩. The same methods applied to 5-phenyl-1,3,5-dioxaphosphazine, and its oxide and sulfide pointed to the conclusion that the Ph group took the axial position in all of these compounds, but in other derivatives equatorial Ph was found. This system has been investigated extensively; references can be found in Section 6.25.5.2.2.iii.

Phosphorus-31 chemical shifts have been studied in the phenoxaphosphines and their congeners with S and N instead of O, demonstrating the transmission of electronic effects through the phenylene rings ⟨91ZOB2194⟩.

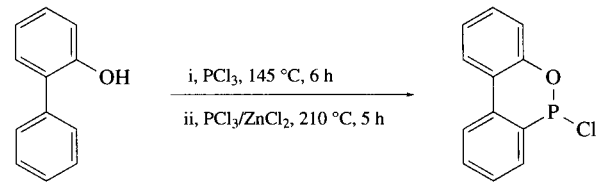
6.25.5.2 Reactivity and Syntheses

6.25.5.2.1 Rings with one phosphorus and one oxygen atom

(i) 1,2-Oxaphosphinines, 1,2-oxaphosphinanes

The fully unsaturated system is known only in the dibenzo series, where claims have been made in the patent literature for a wealth of valuable properties. These are mentioned in Section 6.25.6.

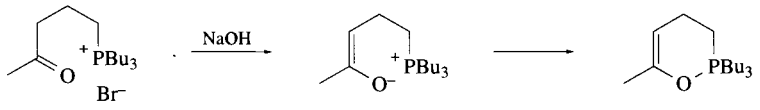
The main synthetic approach is through 2-hydroxybiphenyl. This, on heating with $PCl_3/ZnCl_2$, forms the cyclic phosphochloridite (**272**) (Equation (17)), which is a versatile intermediate for the preparation of a range of compounds with the phosphorus in both P(III) and P(V) valence forms, and at a variety of levels of oxidation, by the standard methods of phosphorus chemistry.



(17)

(272)

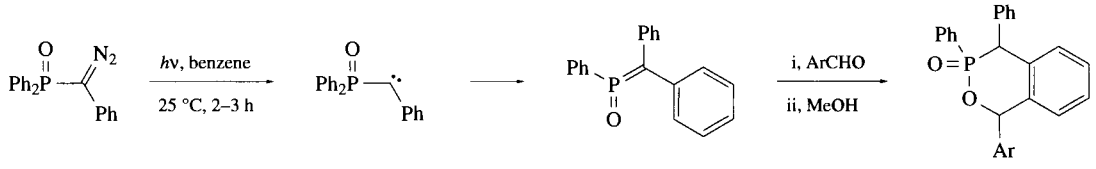
Two partially saturated systems should be considered here. Treatment of the phosphonium salt (**273**) with base forms the enolate, which cyclizes to give the 3,4-dihydro-2*H*-1,2λ^5-oxaphosphinane (**274**) (Scheme 54) ⟨68ZOB2091⟩.



(**273**) (**274**)

Scheme 54

When (diphenylphosphinyl)phenyldiazomethane (**275**) is irradiated in benzene in the presence of aromatic aldehydes a complex reaction mixture is obtained. Treatment with MeOH affords the 1-aryl-3,4-diphenyl-3,4-dihydro-1*H*-2,3-benzoxaphosphinine 3-oxide (**278**). The phosphonylcarbene (**276**) undergoes a Wolff-like rearrangement with aryl shift to give the highly reactive intermediate (**277**). In a Diels–Alder-like (4 + 2) cycloaddition followed by a 1–3 H-shift the benzoxaphosphinine is formed (Scheme 55) ⟨91BCJ713⟩. Originally (**278**) was formulated as a 1,2-oxaphosphetane ⟨73AG(E)1010, 80CB3303⟩.

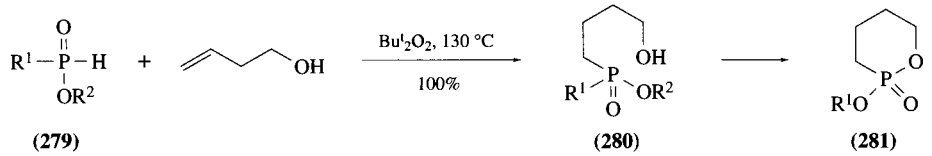


(**275**) (**276**) (**277**) (**278**)

Scheme 55

The fully saturated 1,2-oxaphosphinanes have received a great deal of attention, because their structural similarity to cyclic phosphates is of biological importance. A number of synthetic methods are available. In most of these the C—P bond is formed first, in a radical reaction or by alkylation at phosphorus, and the ring is closed by P—O bond formation.

(a) Cyclization by intramolecular transesterification. The required hydroxyalkyl phosphorus acid can be prepared by a variety of routes. Radical addition of but-3-en-1-ol to the phosphinic ester (**279**) forms the 4-hydroxybutyl phosphinate (**280**), which loses isobutanol on formation of the cyclic ester (**281**) (Scheme 56) ⟨76GEP(O)2514871⟩. Sodium hypophosphite (NaH_2PO_2) undergoes a similar radical hydroxyalkylation, finally yielding (**281**; R^1 = H) ⟨53USP2648695⟩.



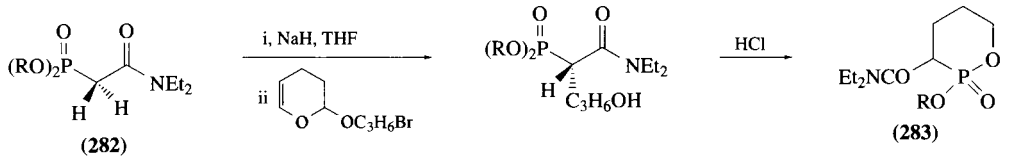
(**279**) (**280**) (**281**)

R^1 = Me, R^2 = CH_2Pr^i

Scheme 56

α-Alkylation of activated phosphonic esters provides a route to the required δ-hydroxy derivatives. Tetrahydropyranyl-protected 3-bromopropanol was used to alkylate the carbamoylmethanephos-

phonate (**282**); cyclization formed the 2-alkoxy-3-carbamoyl-1,2-oxaphosphinane oxide (**283**) (Scheme 57) ⟨93ICA213⟩.



(**282**) (**283**)

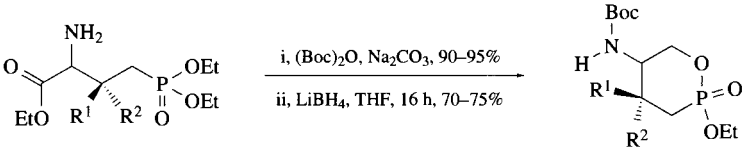
Scheme 57

Aminophosphonylation of a γ-hydroxyketone leads to phosphonic analogues of α-methyl-homoserine, which can be cyclized to the 2-alkoxy-3-amino-1,2-oxaphosphinane oxides (**284**) (Equation (18)) ⟨93PS(81)17⟩.

(18)

(**284**)

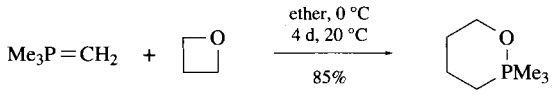
An alternative route to a hydroxyalkyl phosphonate is by $LiBH_4$ reduction of the *N*-protected ester (**285**); spontaneous cyclization to the cyclic phosphonate (**286**) occurs (Equation (19)) ⟨94TL3273⟩.



(19)

(**285**) (**286**)

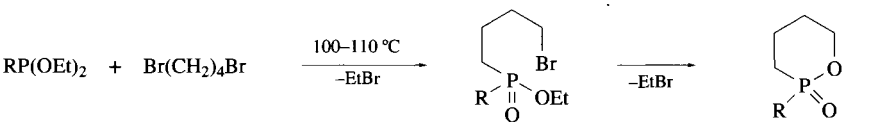
The formation of the $1,2\lambda^5$-oxaphosphinane (**287**) by reaction of methylene-trimethylphosphorane with oxetane undoubtedly proceeds by nucleophilic attack of the ylide carbon atom on the oxetane, followed by O-P cyclization (Equation (20)) ⟨79CB501⟩.



(20)

(**287**)

(b) Cyclization by intramolecular nucleophilic substitution. The intramolecular nucleophilic substitution here forms the C(6)—O bond. The C—P bond may conveniently be formed in an Arbuzov reaction; when 1,4-dibromobutane reacts with diethyl benzenephosphonite (**288**; R = Ph) the initially formed bromobutylphosphinate ester (**289**) loses another molecule of EtBr, with cyclization to give the 2-phenyl-1,2-oxaphosphinane oxide (**290**) (Scheme 58) ⟨65JA253⟩. Triethyl phosphite with 1,2-dibromobutane similarly forms the 2-ethyl ester (**291**), and analogues have been prepared using substituted dibromobutanes ⟨60USP2953591, 67ACS1587⟩.

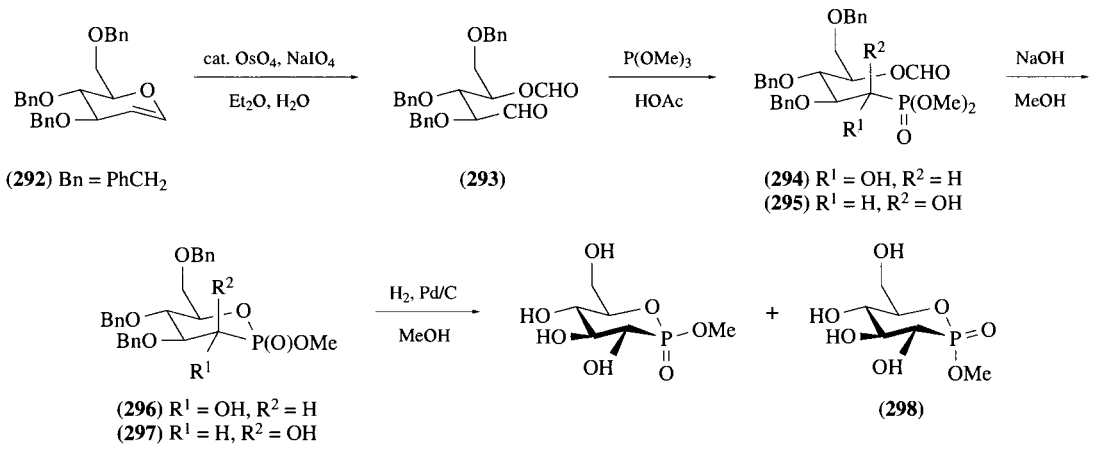


(**288**) (**289**) (**290**) R = Ph (**291**) R = OEt

Scheme 58

Cyclic analogues of D-glucopyranose and D-mannopyranose have been prepared in which the anomeric carbon has been replaced with a phosphorus atom. These ring systems possess 1,2-oxaphosphinane skeletons ⟨94JOC2976⟩. One example may suffice to illustrate a synthetic approach to these cyclic phosphonates. Tri-*O*-benzyl-D-glucal (**292**) was oxidized with $OsO_4/NaIO_4$ yielding

the protected D-arabinose (**293**) by cleavage of the C=C bond. With $P(OMe)_3$ this formed a 1 : 1 mixture of the diastereomeric phosphonates (**294**) and (**295**). The mixture was treated with NaOMe/MeOH to cleave the formate ester, and the alcohol group formed cyclized *in situ* to form the pyranose analogues (**296**) and (**297**) which could be separated by chromatography on silica gel. Debenzylation by catalytic hydrogenolysis in methanol formed an epimeric mixture of isomers (**298**) at the phosphorus atom (Scheme 59).



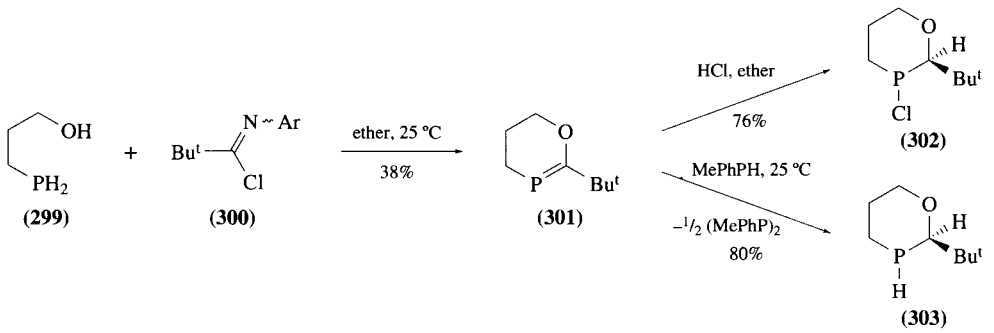
Scheme 59

The phosphorus-containing sugar analogues are recognized as having possible medical applications. The literature since 1980 is cited ⟨94JOC2976⟩.

Since alkylphosphonate esters of nucleosides are generally more stable to nucleases and have greater cell permeability, 5′-deoxyphosphonate nucleotide analogues with 1,2-oxaphosphinane structures have been synthesized ⟨95JOC2563⟩.

(ii) 1,3-Oxaphosphinines, 1,3-oxaphosphinanes

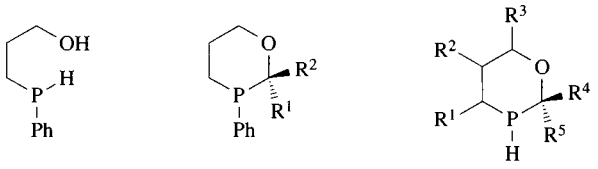
The 1,3-oxaphosphinines are represented by the dihydro derivatives (**301**), which are formed from 3-hydroxypropylphosphine (**299**) by reaction with *N*-arylpivalimidoyl chlorides (**300**). The P=C bond in (**301**) is highly reactive; it adds HCl to give the chlorophosphine (**302**), and is reduced by methylphenylphosphine forming 2-*t*-butyl-1,3-oxaphosphinane (**303**) (Scheme 60) ⟨91CB493⟩.



Scheme 60

1,3-Oxaphosphinanes (**305**) have been prepared by acid-catalyzed condensation of 3-hydroxypropylphenylphosphine (**304**) with aldehydes and ketones. The secondary phosphine is easily available by radical addition of phenylphosphine to allylic alcohols ⟨59DOK(127)1217, 63IZV502, 72SRI223⟩. Primary hydroxypropylphosphines condense similarly, forming 3-unsubstituted 1,3-oxaphosphinanes (**306**) ⟨73ZC291, 78PS(5)81⟩.

The 1,3-oxaphosphinan-2-ones (**307**) are accessible by AIBN-initiated intramolecular radical cyclization of the P—H bond to the double bond of allyloxycarbonyl phosphines (Equation (21))



(304) (305) (306)

〈82ZN(B)965〉. The tervalent phosphorus in (**307**) reacts as in normal phosphines; sulfides and phosphonium salts can be prepared.

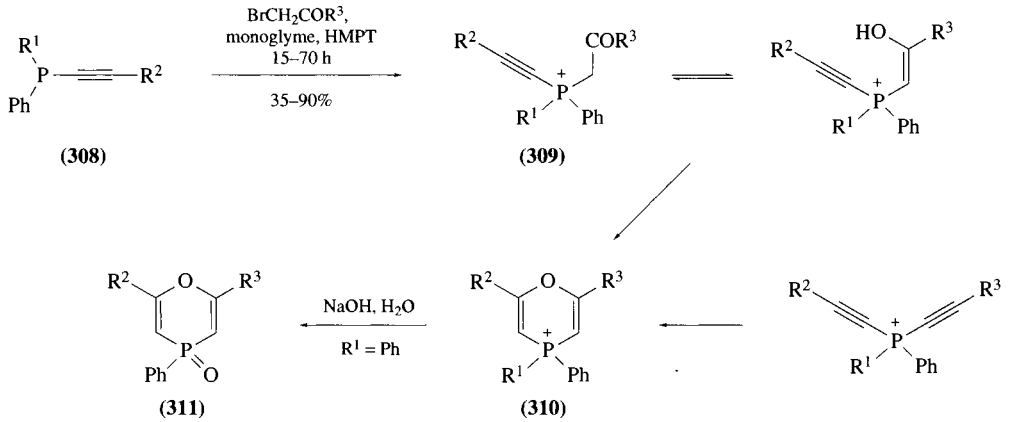
(307) (21)

Work on the configuration and conformation of 1,3-oxaphosphinanes using NMR measurements has been mentioned in Section 6.25.5.1.2.

(iii) 1,4-Oxaphosphinines, 1,4-oxaphosphinanes

The 1,4-oxaphosphinine system is represented by the 4*H*-1,4-oxaphosphininium salts, described mainly by Simalty and co-workers, and the 4-alkyl-, -aryl-, -alkoxy- and -hydroxy-1,4-oxaphosphinine 4-oxides, studied by a number of Russian groups. The dibenzo analogues—the phenoxaphosphines—are discussed in the next section.

A very general method for the synthesis of 1,4-oxaphosphininium salts (**310**) is by reaction of acetylenic phosphines (**308**) with bromomethyl ketones to give the intermediate phosphonium salts (**309**), which readily cyclize (Scheme 61) 〈68BSF4938, 72BSF3532, 72T3343, 84PS(19)159〉. Alternatively, dialkynyl phosphonium salts can be cyclized, using ammonium acetate in acetic acid 〈72TL4363, 80TL3037, 84PS(19)159〉.

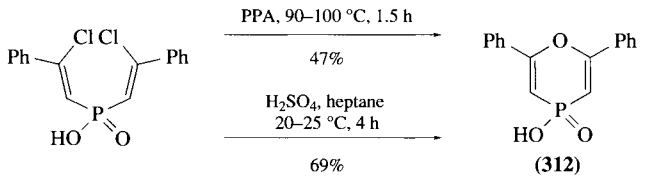


(308) (309) (311) (310)

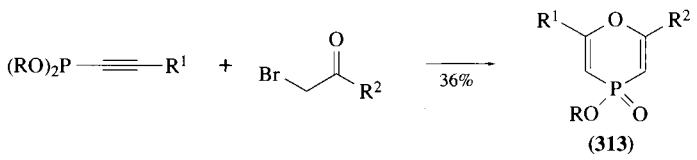
Scheme 61

A *P*-phenyl group can be removed from the phosphonium salts by the action of aqueous NaOH, to form the oxaphosphinine 4-oxides (**311**) 〈72T3343, 84PS(19)159〉. The oxides are also formed directly, by cyclization of dialkynyl phosphine oxides 〈71TL4749, 74TL4385〉.

The cyclic phosphinic acids, the 4-hydroxy-1,4-oxaphosphinine 4-oxides (**312**), may be made by acid-promoted cyclization of bis-(β-chlorostyryl)-phosphinic acids (Equation (22)) 〈84ZOB1481, 85ZOB780〉, and their esters (**313**) result from the reaction of bromomethyl ketones with dialkyl alkynylphosphonites (Equation (23)) 〈89DOK(304)625〉.

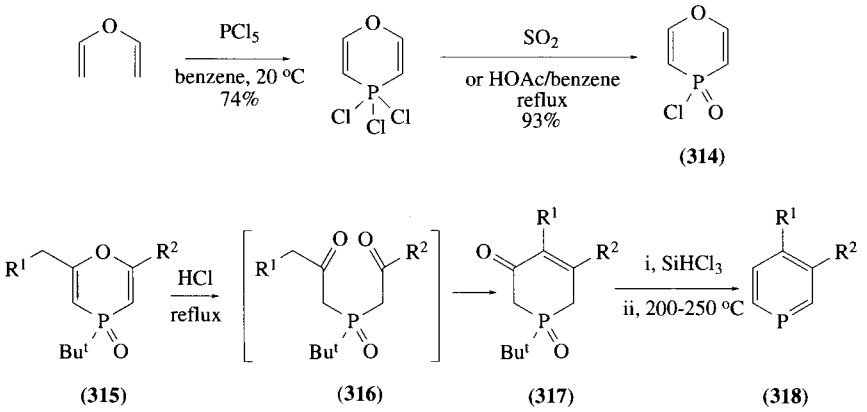


(22)



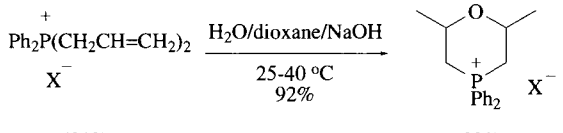
(23)

The action of PCl_5 on divinyl ether, followed by partial hydrolysis of the product, forms the 4-chloro-1,4-oxaphosphinine 4-oxide (**314**) ⟨87ZOB954, 87ZOB1518⟩. The 4-*t*-butyl-1,4-oxaphosphinine oxides (**315**) are of considerable synthetic value. Their acid-catalyzed cleavage yields the 1,5-diketones (**316**), which cannot be isolated; intramolecular aldol condensation gives rise to the enones (**317**). Reduction of (**317**) with $SiHCl_3$ and thermolysis at 200–250 °C opens a useful route to the λ^3-phosphinines (**318**) (R^1 = H, Me; R^2 = Me, Bu^t, Ph, 4-MeC_6H_4, 4-ClC_6H_4, α-furyl) (Scheme 62) ⟨74TL4385, 83CB445, 83CB1756⟩. The synthesis of 3-hydroxyphosphinines also starts from the phospha-enones (**317**) ⟨77TL3445⟩.



Scheme 62

The 1,4-oxaphosphinane system was not known until 1974, when Samaan reported the synthesis of the quaternary 1,4-oxaphosphinanes (e.g. (**320**)), 1,4-thiaphosphinanes and 1,4-azaphosphinanes by base-induced addition of H_2O, H_2S and $MeNH_2$ to the diallyldiphenylphosphonium salts (**319**) (Equation (24)) ⟨74TL3927, 78CB579⟩.

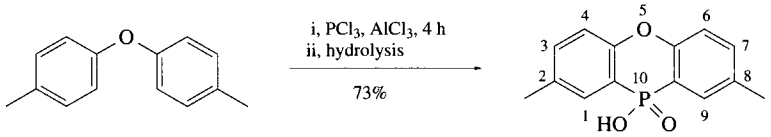


(24)

Since that time a number of other preparations have appeared, relying both on C—O and C—P bond formation for the cyclization ⟨87IZV2397, 89ZOB1047⟩. Sugar analogues have also been reported in this series.

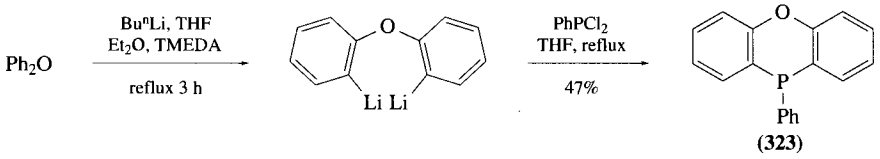
(iv) Phenoxaphosphines

In contrast to the synthesis of 10-chlorophenoxarsines (Chapter 6.26, Section 4.1.3.1), the reaction of diphenyl ether with $PCl_3/AlCl_3$ occurs exclusively in the 4-position. However, di-*p*-tolyl ether (**321**) reacts with refluxing $PCl_3/AlCl_3$ (4 h), and after hydrolysis the 2,8-dimethylphenoxaphosphinic acid (**322**) can be isolated (Equation (25)) ⟨61JOC284, 65CB1681, 68JOC474, 74URP515754⟩. The directive effects of substituents in this reaction have been studied ⟨83JHC1601, 88PS(35)215⟩.



(321) (322) (25)

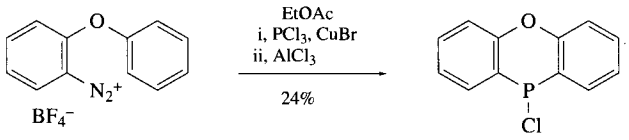
An elegant synthesis of phenoxaphosphines is by the dilithiation of diphenyl ether in the *o,o'*-positions and reaction with $PhPCl_2$ to give 10-phenylphenoxaphosphine (**323**) (Scheme 63) ⟨57JA339, 86USP4698447, 87ZOB716, 90ZOB1257⟩.



(323)

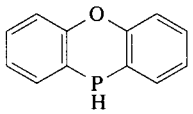
Scheme 63

In a third method the *o*-phenoxybenzenediazonium salt (**324**) is refluxed with $PCl_3/CuBr/EtOAc$ and then with $AlCl_3$; distillation of the reaction mixture yields (**325**) (Equation (26)). Use of $PhPCl_2$ instead of PCl_3 provides the phenoxaphosphine (**323**) in 26% yield ⟨51JA5658, 52JA2884, 74IJ779⟩.



(324) (325) (26)

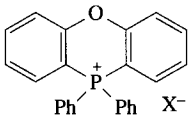
The stability of the phenoxaphosphine ring system is demonstrated by the fact that $KMnO_4$ only oxidizes methyl groups on the flanking rings to give the carboxylic acids in methyl-substituted phenoxaphosphinic acids and 10-phenylphenoxaphosphine 10-oxides; the heterocyclic nucleus is unattacked ⟨65CB1681, 80PP160, 81JAP(K)8157796⟩. Under vigorous reduction conditions (Ph_2SiH_2, 250 °C) 2,8-dimethylphenoxaphosphinic acid (**322**) forms the secondary phosphine (**326**) ⟨65CB1681⟩. Esterification of phenoxaphosphinic acids can be carried out, e.g. by treating the potassium salts with alkyl halides ⟨68IJ651⟩.



(326)

Phenoxaphosphines with P(III), e.g. the 10-phenyl compound (**323**), are much slower in their reaction with alkylating agents than triphenylphosphine ⟨79PS(7)309⟩. On the other hand, arylation can be achieved ($PhBr/AlCl_3$, 210 °C, 2 h), giving the 10,10-diphenyl phosphonium salt (**327**) (isolated as the iodide) ⟨40JCS1192, 53JCS3746⟩.

Transition metal complexes ML_2Cl_2 have been described for (**323**) with M = Ni, Pd and Pt ⟨91ZOB1641⟩.



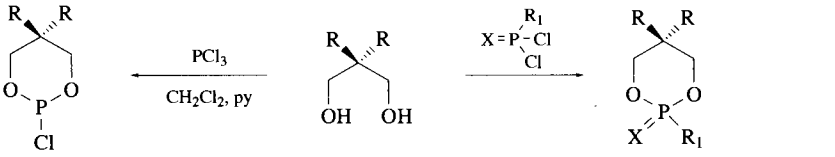
(327)

6.25.5.2.2 *Rings with one phosphorus atom and two oxygen atoms*

(i) 1,3,2-Dioxaphosphinanes

The literature on the 1,3,2-dioxaphosphinane ring system is enormous, and no more than a brief general review of the most important synthetic approaches is possible within the confines of this chapter. Most of the published papers are concerned with nucleotides with 1,3,2-dioxaphosphinane structures, isolated or synthesized with a view to an investigation of their biological properties.

Most synthetic approaches to simple 1,3,2-dioxaphosphinane systems are based on the reaction of 1,3-diols with dihalogenophosphorus compounds, as outlined in Scheme 64. With pentaerythritol the expected spiro compounds are formed ⟨63BEP628795⟩.

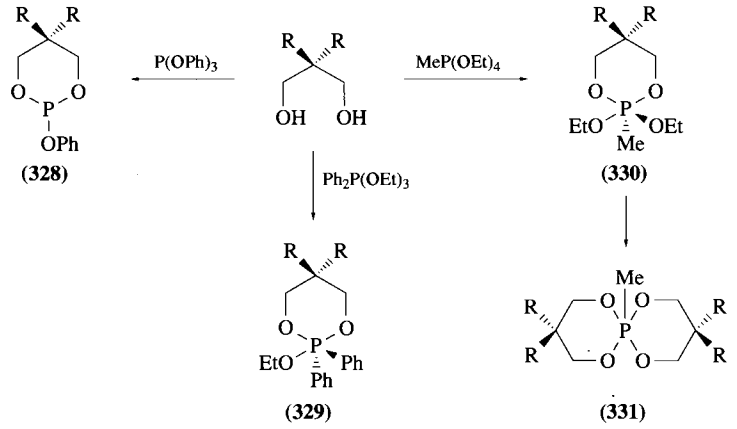


R = H, 50JA5491
R = Me, 63JCS6059

X = O, R^1 = Cl, 50JA5491, 59JOC630
X = S, R^1 = Cl, 64T2781
X = O, R^1 = OPh, 63JCS6059

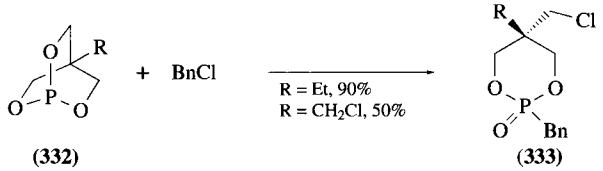
Scheme 64

Transesterification reactions with phosphites and alkoxyphosphoranes allow the synthesis of 1,3,2-dioxaphosphinanes with $\lambda^3\sigma^3$- and $\lambda^5\sigma^5$-phosphorus (**328**)–(**330**), and of spiro-systems (**331**) fused at the $2\lambda^5$ position (Scheme 65) ⟨57JCS1109, 71JA4004⟩.



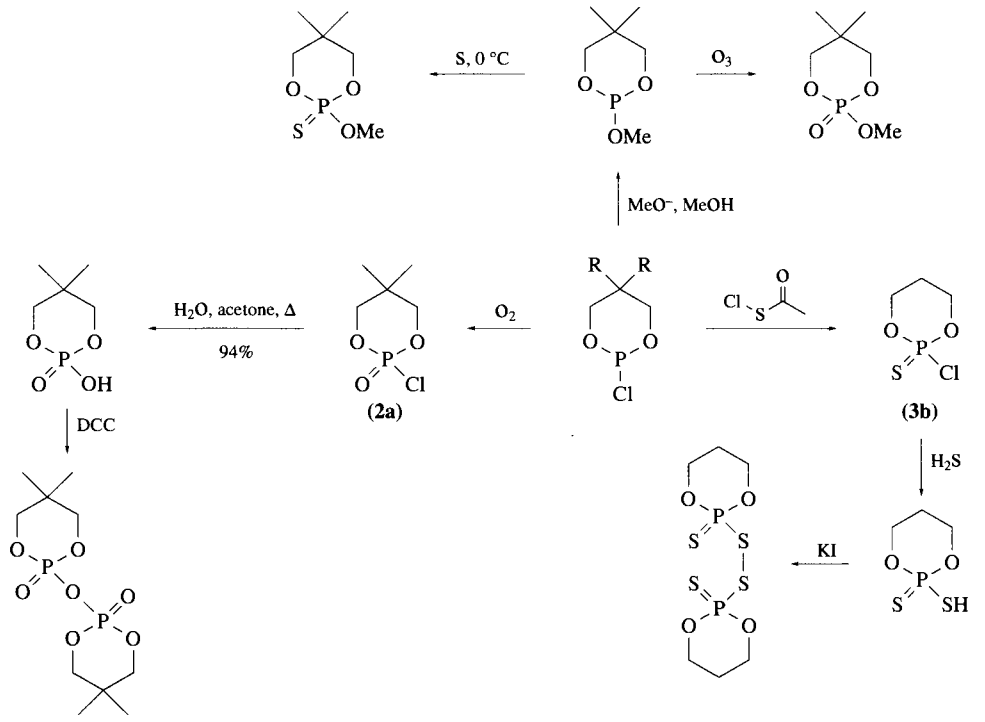
Scheme 65

An interesting synthesis of 2-alkyl-1,3,2-dioxaphosphinane oxides (**333**) results from an Arbuzov reaction of the bicyclic phosphite (**332**) with alkyl halides, e.g. $PhCH_2Cl$ (Equation (27)) ⟨62JA610⟩.

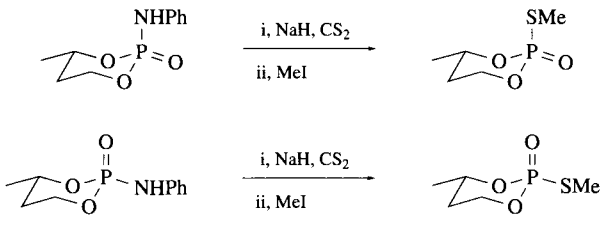


(27)

By standard methods of phosphorus chemistry, substituents at the phosphorus atom of 1,3,2-dioxaphosphinanes can be added and exchanged, with chlorine and amino or anilino as convenient leaving groups in both P(III) and P(V) systems, and with oxygen, sulfur and selenium both singly and doubly bonded to phosphorus. Scheme 66 shows a few of the possibilities that are available ⟨65T2379, 74ZOB1697, 83ACR411⟩. The stereochemistry of these interconversions is of interest: the reactions shown in Scheme 67 demonstrate that retention of configuration at the phosphorus atom operates in this case ⟨75JCS(P1)1828⟩.



Scheme 66



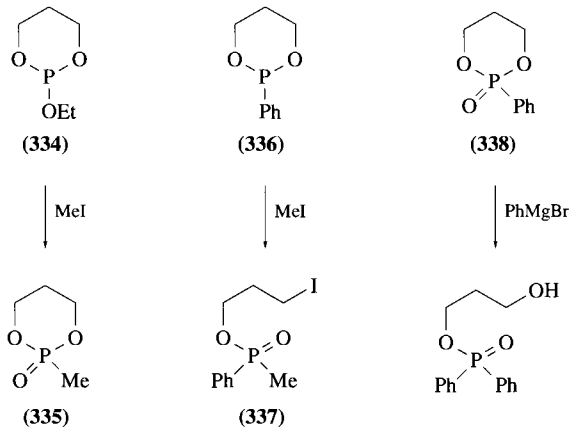
Scheme 67

For further examples and applications of these and other methods Stec's review may be consulted ⟨83ACR411⟩.

The dioxaphosphinane ring is preserved on reaction of the cyclic phosphite (**334**) with methyl iodide; the methanephosphonate diester (**335**) is the only product ⟨64T2781⟩. Similar treatment of the 2-phenyl derivative (**336**), a cyclic phosphonite, does cleave the ring, to form the iodopropyl phosphinate (**337**) with C—O fission ⟨79JOC1060⟩. The ring is also opened when the cyclic phosphonate ester (**338**) reacts with PhMgBr; here the P—O bond is broken (Scheme 68) ⟨67T283⟩.

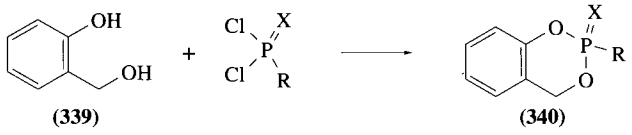
(ii) 1,3,2-Benzodioxaphosphinines

Reaction of various dichloro-phosphorus reagents with salicyl alcohol (**339**) leads to the benzo-fused analogues (**340**) of the 1,3,2-dioxaphosphinane system (Equation (28)) ⟨65ABC243, 66NKK315,



Scheme 68

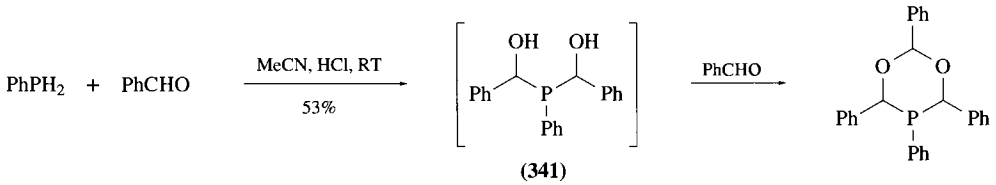
69MI 625-03, 70JAP7028183〉. Their chemistry, so far as it has been investigated, is very similar to that of the monocyclic derivatives of the previous section.



(28)

(iii) 1,3,5-Dioxaphosphinanes

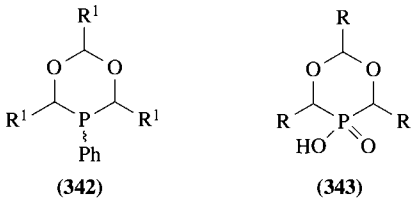
Epstein and Buckler discovered the acid-catalyzed reaction of phenylphosphine with benzaldehyde, giving 2,4,5,6-tetraphenyl-1,3,5-dioxaphosphinane. The 1,3-glycol (**341**), formed by the addition of two moles of benzaldehyde to the phosphine, is a probable intermediate, and the ring closure is an acetalation of the third mole of benzaldehyde by (**341**) (Scheme 69) 〈62T1231〉.

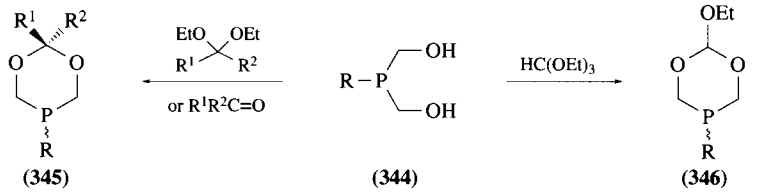


Scheme 69

This reaction proved to be very versatile. Most of the more recent work has been done by B. A. Arbuzov's group.

Extension to aliphatic aldehydes leads to the 2,4,6-trialkyl-5-phenyl derivatives (**342**). When H_3PO_2 is refluxed in toluene with benzaldehyde or isobutyraldehyde the phosphinic acids (**343**; R = Ph, Pr^i) are formed 〈68IZV397, 92EUP463994〉. Di(hydroxymethyl)phosphines (**344**) react with aldehydes, ketones and acetals to form the 2-mono- or 2,2-disubstituted 1,3,5-dioxaphosphinanes (**345**) 〈86IZV2506, 86ZOB2256〉. With triethyl orthoformate the 2-ethoxy derivatives (**346**) are obtained (Scheme 70) 〈86IZV418, 86IZV640〉.

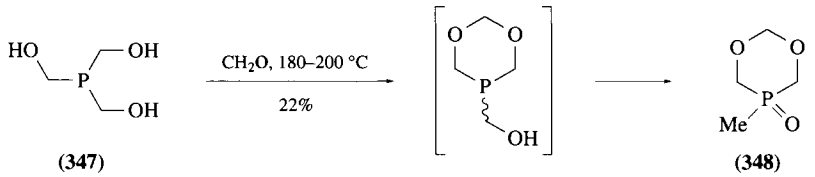




(345) (344) (346)

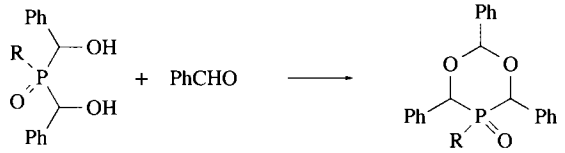
Scheme 70

When tri(hydroxymethyl)phosphine (**347**) reacts at 180–200 °C with formaldehyde 5-methyl-1,3,5-dioxaphosphinane 5-oxide (**348**) is formed. The initial 5-hydroxymethyl compound undergoes a thermal Buckler–Trippett reaction under the reaction conditions (Scheme 71) ⟨78ZOB97, 78ZOB2653⟩. 5-Oxides are also formed directly, from α,α′-dihydroxydialkylphosphine oxides (Equation (29)) ⟨75JOC2056⟩. The 5-sulfides are formed in a similar way (Equation (30)) ⟨86IZV640, 87IZV418⟩.

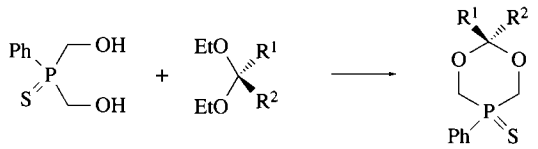


(347) (348)

Scheme 71



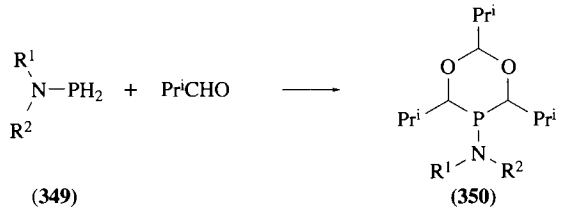
(29)



(30)

The synthesis of the unsubstituted 1,3,5-dioxaphosphinane was achieved simply by thermolysis of the phosphonium salt $[PhP(CH_2OH)_3]^+ Cl^-$ ⟨80IZV1626⟩.

5-Amino-substituted 1,3,5-dioxaphosphinanes (**350**) could be synthesized by the reaction of aminophosphines (**349**) with aldehydes, e.g. isobutyraldehyde (Equation (31)) ⟨83IZV2550⟩.



(349) (350)

$R^1 = H, R^2 = Ph; R^1, R^2 = Et_2, -(CH_2)_5-, -(CH_2)_2O(CH_2)_2-$

(31)

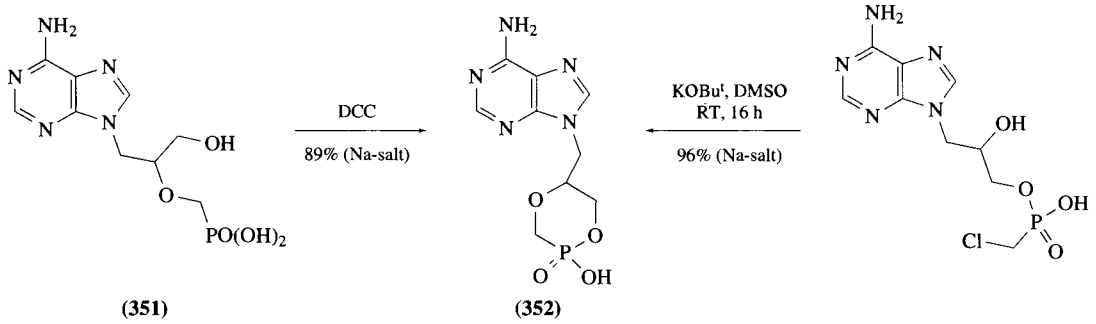
The *P*-oxides, -sulfides and -selenides are also produced from the P(III) compounds by action of H_2O_2 or ozone, sulfur and selenium ⟨80IZV1626, 86IZV640, 86ZOB2256⟩. Imines (phenylimines, for instance) are readily obtained by Staudinger reactions using azides ⟨83IZV2550⟩.

The conformations of 1,3,5-dioxaphosphinines have been studied extensively, normally by a combination of NMR and dipole moment measurements, but x-ray evidence is also available. Ring-chair conformations are the general rule. With P(III) at the 5-position, substituents (Ph has been most fully investigated) tend to occupy the axial position, but this does not hold universally. 5-Phenyl-1,3,5-dioxaphosphinane has predominantly axial Ph, as does its 5-oxide, but both stereoisomers of the 2-ethoxy-5-phenyl compound have the Ph predominantly equatorial ⟨86IZV418⟩. The

5-sulfides and 5-selenides of these compounds have the Ph axial, notwithstanding the anomeric effect which should apply at position 2 and favor OEt-axial conformers ⟨86IZV640⟩. References to conformational studies on 1,3,5-dioxaphosphinanes, widely scattered through the Russian literature, include those above and the following ⟨78DOK(240)331, 80IZV1626, 82IZV127, 82IZV594, 84IZV1056, 85IZV1296, 86ZOB2256⟩. Calculations by the CNDO/S method relating to the conformations of 1,3,5-dioxaphosphinanes have been reported ⟨84ZOB2532⟩.

(iv) 1,4,2-Dioxaphosphinanes

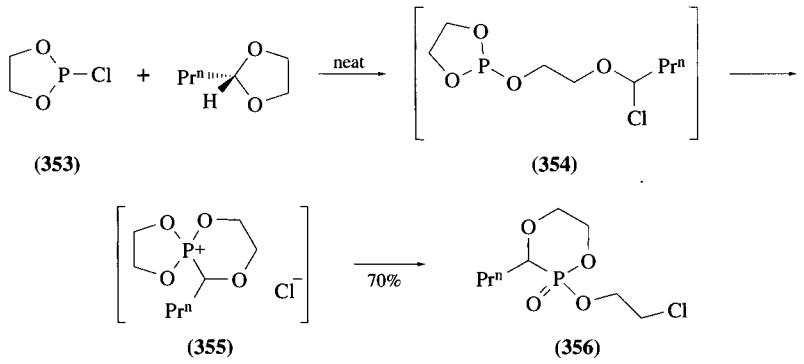
This system has been actively investigated in the search for effective antiviral agents, and useful activity has been reported for a number of derivatives. Analogues attached to nucleic acid bases have received the most attention, and an example from this area is illustrated (Scheme 72) ⟨87CCC2775, 87CCC2792⟩. The product, (*S*)-cyclo-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine [(*S*)-cHPMPA] (**352**), and its precursor [(*S*)-HPMPA] (**351**), are active against a wide screen of human and animal viruses ⟨87MI 625-01, 87MI 625-02⟩.



(**351**) (**352**)

Scheme 72

2-Chloro-1,3,2-dioxaphospholane (**353**) reacts with 1,3-dioxolanes by nucleophilic attack of the dioxolane oxygen on the phosphorus atom and ring opening to give (**354**). Intramolecular alkylation of the phosphite forms the spiro-phosphonium salt (**355**), and this is followed by ring opening by nucleophilic attack of Cl^- at the 1,3,2-dioxaphospholane carbon as in an Arbuzov rearrangement. The products finally isolated from this exothermic reaction sequence are the 1,4,2-dioxaphosphinanes (**356**) (Scheme 73) ⟨81ZOB782, 83ZOB1525⟩.

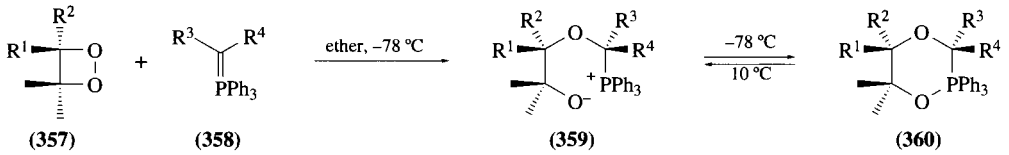


(**353**) (**354**) (**355**) (**356**)

Scheme 73

An interesting approach to 1,4,2λ^5-dioxaphosphinanes has been reported. Methyl-substituted 1,2-dioxetans (**357**) react with triphenylalkylidenephosphoranes (**358**) by nucleophilic attack of the ylide carbon at the peroxide bond of (**357**); the 2,2,2-triphenyl-1,4,2λ^5-dioxaphosphinanes (**360**) are

formed, which are in equilibrium with the dipolar phosphonium-alkoxides (**359**) (Scheme 74). At −40 °C the 1,4,2λ^5-dioxaphosphinanes persist, but upon standing at room temperature for several days only the open-chain betaines (**359**) can be detected ⟨94JA7581⟩.



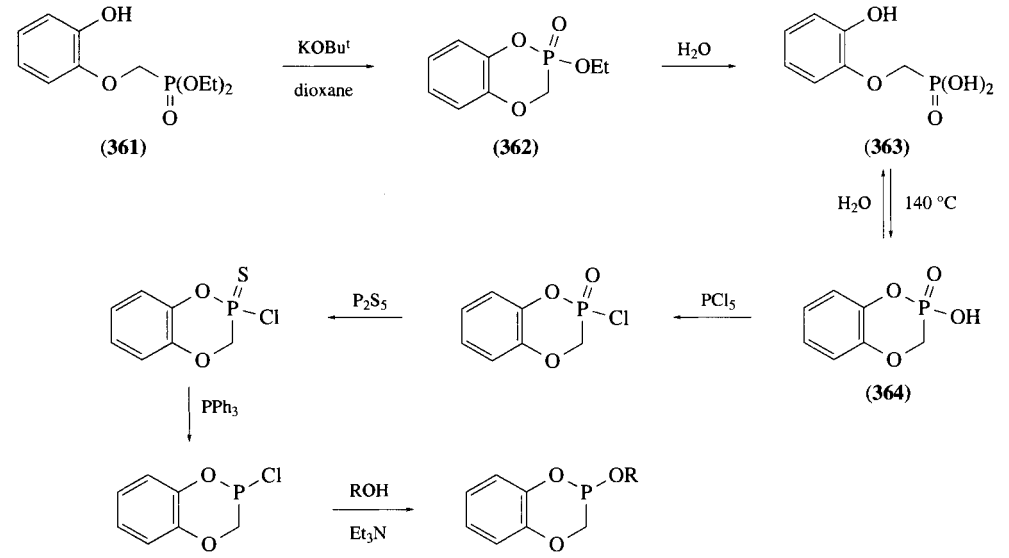
(**357**) (**358**) (**359**) (**360**)

Scheme 74

(v) 1,4,2-Benzodioxaphosphinines

A number of 1,4,2-benzodioxaphosphinines have been synthesized, all at the formal 2,3-dihydro level of oxidation. Synthetic approaches vary from the straightforward (base-induced catechol cyclization with chloromethyl phosphonyl or phosphinyl chlorides) to the exotic (cycloadditions of phosphaalkenes to *o*-quinones).

Cyclization of diethyl *o*-hydroxyphenoxymethanephosphonate (**361**) by base forms the trans-esterified product (**362**) ⟨87ZOB82⟩. Hydrolysis forms the ring-opened phosphonic acid (**363**), which can be recyclized thermally to (**364**) ⟨86ZOB2542⟩. Further manipulation of (**364**) by standard methods of phosphorus chemistry leads to a wide variety of structures (Scheme 75) with potential for further extension ⟨88ZOB2226⟩.

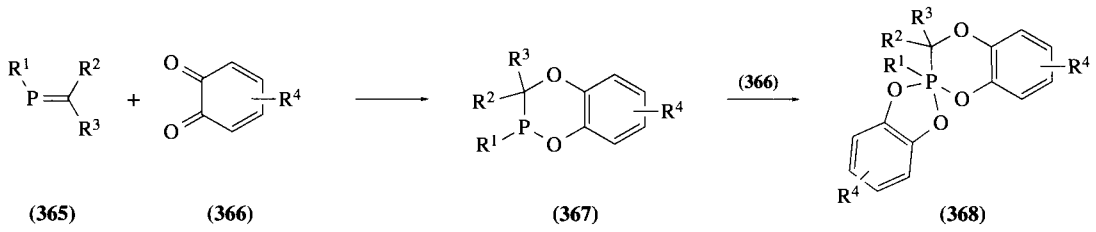


(**361**) (**362**) (**363**) (**364**)

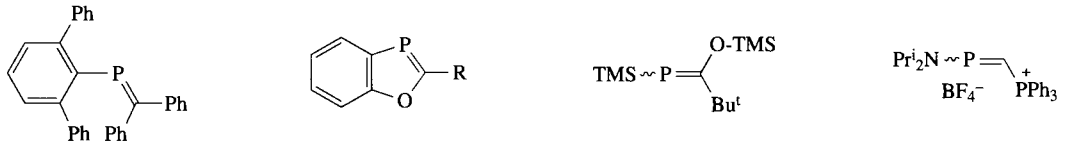
Scheme 75

The reactions of phosphaalkenes (**365**) with *o*-quinones (**366**) have been studied by several groups of workers. The initial reaction is a (4 + 2) cycloaddition, and in some cases this forms the final product. Frequently, however, a (4 + 1) cycloaddition to the phosphorus (Ramirez reaction) follows, leading to 1 : 2 adducts (**368**); isolation of the intermediates (**367**) in these cases may not be possible (Scheme 76).

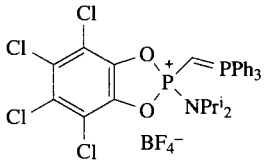
o-Quinones used in these reactions include 3,5-di-*t*-butyl-, tetrabromo- and tetrachloro-*o*-benzoquinone, and phenanthraquinone. As phosphaalkenes, compounds (**365a**) ⟨83T3189⟩, (**365b**) ⟨83TL5481⟩, (**365c**) ⟨85ZN(B)1077⟩ and (**365d**) ⟨90T2381⟩ have been used. In the reaction of tetrachloro-*o*-benzoquinone with the 2-phosphoniophosphaalkene (**365d**), the 1 : 1 adduct (**367**) is formed under $BF_3.Et_2O$ catalysis; without the catalyst the quinone forms a (4 + 1)-cycloadduct (**369**) at the P(III) atom ⟨90T2381⟩.



(365) (366) (367) (368)



(365a) (365b) R = Me, Bu^t (365c) (365d)

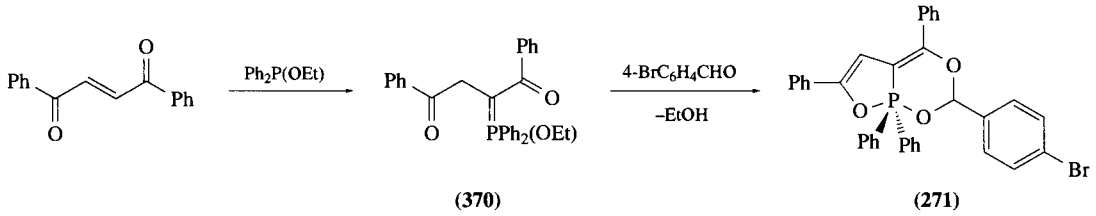


(369)

Scheme 76

(vi) 1,5,2-Dioxaphosphinines, 1,5,2-dioxaphosphinanes

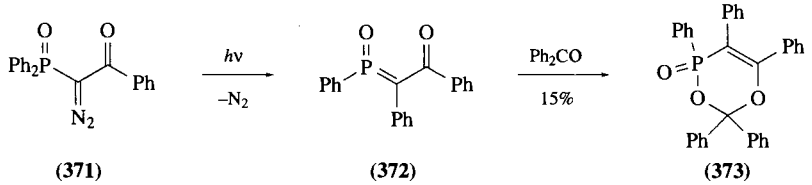
Ramirez *et al.* reported the reaction of 1,2-dibenzoylethylene with ethyl diphenylphosphinite to give the crystalline phosphorane (**370**). *p*-Bromobenzaldehyde adds to (**370**) forming the stable bicyclic dioxyphosphorane (**271**) (Scheme 77). The structure of the product was confirmed by x-ray crystallography; the phosphorus atom formed a trigonal bipyramid with the two oxygens apical and the carbon atoms equatorial ⟨64JA5339, 71JA5236⟩.



(370) (271)

Scheme 77

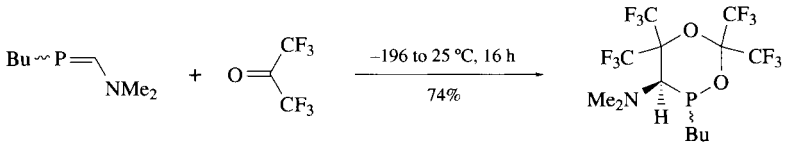
Regitz *et al.* studied the chemistry of the benzoylphosphene (**372**), generated photochemically from the diazo-compound (**371**). Benzophenone adds in a (4 + 2)-cycloaddition process, to form the pentaphenyl-2*H*,6*H*-1,5,2-oxaphosphinine 1-oxide (**373**) (Scheme 78). Other aromatic and aliphatic aldehydes and ketones cycloadd in a similar fashion ⟨73AG(E)1010, 78CB705, 78CB726⟩.



(371) (372) (373)

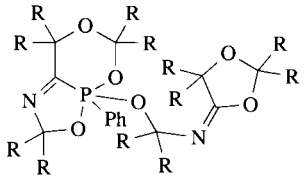
Scheme 78

Schmutzler and co-workers have reported the reaction of the phospha-enamine (**374**) with hexafluoroacetone to give (**268**), possibly the result of an ionic (2 + 2 + 2) cycloaddition (Equation (32)) ⟨95CB499⟩. The structure was confirmed by an x-ray crystal structure analysis.



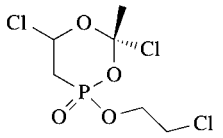
(374) (268) (32)

Roesky *et al.* discovered unusual products arising from reactions of some phosphorus(III) cyanides, or P(III) halides and mercuric cyanide, with hexafluoroacetone ⟨86CB2687⟩. Two of these have fused 1,5,2-dioxaphosphinine structures, (**269**) and (**375**).



(**375**) R = CF_3

A singular, but simple, synthesis of a 1,5,2-dioxaphosphinane (**376**) is by reaction of vinyl acetate with PCl_5 followed by treatment with ethylene oxide ⟨79IZV1162⟩.



(**376**)

6.25.6 APPLICATIONS

The uses claimed for the P-N heterocyclic systems described in this chapter have been few. The phosphorylated anthranilamide derivatives described in Section 6.25.4.2.3.iii were developed in a search for antiparasitic agents ⟨82MI 625-01⟩. The catalytic activity of complexes of 1,3,5-triaza-7-phosphaadamantane ⟨95JOM(488)99⟩ and the interesting luminescence properties of its gold complexes ⟨95OM4194, 94CC431, 95IC75⟩ have been mentioned in Section 6.25.4.2.3.v.

In contrast, multifarious uses have been proposed for P-O heterocyclic systems. It is convenient to divide them into biological and medicinal uses, and others.

6.25.6.1 Biological and Medicinal Uses

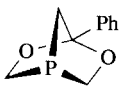
Phosphorus-containing sugar analogues have possible medicinal application in the treatment of obesity and diabetes, and also in the formulation of antiviral, antibiotic and antitumor agents (Section 6.25.5.2.1.ii) ⟨94JOC2976⟩.

Cyclonucleotides containing the 1,3,2-dioxaphosphinane ring system (Section 6.25.5.2.2.i) play an important role in cellular metabolism ⟨B-92MI 625-01⟩.

The antiviral activities of certain nucleotide-like derivatives of 1,4,2-dioxaphosphinanes were mentioned in Section 6.25.5.2.2.iv. (*S*)-cHMPA is reported to be an effective inhibitor of herpes simplex virus type 1 and type 2, varicella zoster virus, cytomegalovirus, adenovirus, African swine fever virus and vaccinia virus ⟨87MI 625-01, 87MI 625-02⟩. Activity has been claimed for analogues of other bases too ⟨89CCC2470, 89EUP319228, 91EUP405748, 91MI 625-01, 91MI 625-02, 92MI 625-03, 93MIP 625-01, 94MI 625-01, 94AAC2387, 95MI 625-01, 95MIP625-01⟩. The stability of the cyclic phosphonate esters to ribonucleases ⟨85CCC1507⟩ is probably important to their activity.

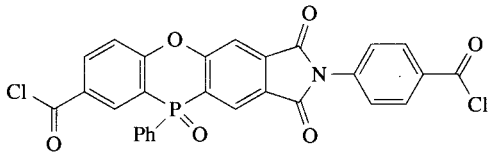
6.25.6.2 Other Uses

The insecticidal properties of the 1,3,5-dioxaphosphinane derivative (**377**), against rice weevils, houseflies and aphids, have been reported ⟨77MI 625-01⟩. 2,4,6-Triisopropyl-1,3,5-trioxaphosphinane (TTP) has been incorporated into a number of catalytic formulations, such as the ternary system $Co_2(CO)_8/R_3N/TTP$ for hydroformylation of olefins ⟨72USP3644529⟩, and in other combinations for diene alkylation and alkenylation ⟨69GEP1300695, 70GEP(O)1965047, 70USP3524896, 71USP3567792⟩.



(**377**)

The dibenzo[1,2]dioxaphosphinines (Section 6.25.5.2.1.i) have been described in the patent literature as having applications for stabilization of organic polymers, as flame retardants, and as polymerization promoters ⟨72USP3702878, 89EUP304782, 94EUP582957, 94JAP(K)06145182, 95EUP632050⟩. Phenoxaphosphines (Section 6.25.5.2.1.v) are also effective flame retardants. Polyesters formed from the di-acid chloride (**378**) by interfacial copolymerization with bisphenols have been described in numerous reports and patents, e.g. ⟨81JAP(K)81150098, 84MI 625-01⟩. Good thermal stability is reported for benzimidazole and benzoxazole polymers containing phenoxaphosphine rings ⟨80PP160⟩.



(**378**)

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6.26
Six-membered Rings with Two or More Heteroatoms with at least One Arsenic

GOTTFRIED MAERKL and PETER KREITMEIER
Universität Regensburg, Germany

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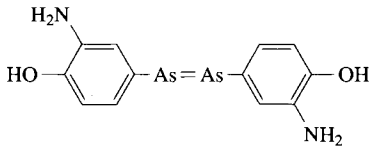
6.26.1 INTRODUCTION

Arsenic compounds became important much earlier than did phosphorus compounds. Since Ehrlich (1854–1915, Nobel laureate 1908 and creator of modern chemotherapy) together with Hata prepared salvarsan (**1**) (Ehrlich–Hata 606), the first trypanocidal compound against syphilis, an early boom in arsenic chemistry began. The formula (**1**) of salvarsan is in fact incorrect; salvarsan is an oligmeric compound. Systems with true As=As double bonds were described only as late as 1983 ⟨83TL3625⟩.



(**1**)

The importance of organic arsenic compounds as antiprotozoals faded with the development of penicillin. Because of the toxicity of arsenic compounds this branch of chemistry lost its importance for the next 40 years.

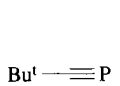
Since 1965 arsenic chemistry and especially the chemistry of heterocyclic arsenic compounds has become revitalized because of the synthesis of the first six-membered, cyclic conjugated, Hückel-aromatic phosphabenzenes (**2**) and arsabenzenes (**3**) ⟨71JA3293⟩. Then, 50 years after the salvarsan period, a second boom in arsenic chemistry, especially in heterocyclic, unsaturated arsenic compounds began.

(**2**)

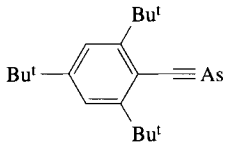
(**3**)

For several reasons the development of the chemistry of 6π heteroaromatic arsenic systems, for example arsinine (**3**), was much less vigorous than that of the phosphinines. While *t*-butylphosphaethyne (**4**) and several other phosphaethynes are important building blocks for the synthesis of six-membered aromatic phosphorus heterocycles with more than one heteroatom, only one compound with a C≡As triple bond, the 2,4,6-tri-*t*-butylphenyl derivative (**5**), has been described ⟨86AG(E)264⟩, and this has not been thoroughly studied. The only six-membered As-heteroaromatic system with more than one heteroatom is the 1,3λ^3-azarsinine (**6**) ⟨88TL535⟩. Since pentavalent

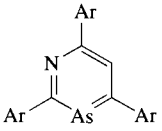
arsenic compounds like the λ^5-arsinines (**7**) are less stable than the corresponding λ^5-phosphinines, this chemistry is less developed, too.



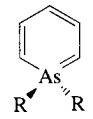
(**4**)



(**5**)



(**6**)



(**7**)

For all these reasons, the chemistry of six-membered arsenic heterocycles with more than one arsenic atom is mainly restricted to oxa-, dioxa-, and aza-phospharsinanes and diarsinanes. Since the detection of a highly active arsenolipid, the so-called octadecylphosphoarsenocholin D-21805, as an anticancer compound by the German company Asta Medica, one may expect a renaissance in organoarsenic chemistry, more than 80 years after the discovery of salvarsan. This development certainly will advance heterocyclic arsenic chemistry also.

The first monograph dealing with heterocyclic arsenic compounds was that by Mann ⟨B-50MI 626-01⟩. Six-membered arsenic heterocycles with two and more heteroatoms are discussed also by Cullen ⟨66AOC(4)144⟩ (see also ⟨B-58MI 626-01, B-61MI 626-01⟩). The most important monograph dealing with arsenic heterocycles, covering the literature up to 1976, was written by Tzschach and Heinicke ⟨B-78MI 626-01⟩. Annual reviews were published by Doak and Freedman between 1968 and 1975 ⟨68MI 626-01⟩.

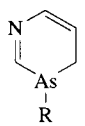
6.26.2 NOMENCLATURE OF SIX-MEMBERED HETEROCYCLES CONTAINING ARSENIC

The problems of nomenclature of arsenic compounds and the confusion connected with them, mainly a result of incorrect translations, are comparable to the situation in phosphorus chemistry. In principle, the nomenclature of arsenic compounds is similar to that of phosphorus compounds.

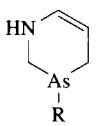
The IUPAC name for the six-membered, cyclic conjugated, Hückel-aromatic arsabenzene (**3**) was for some time "arsenin". Since 1983 the IUPAC nomenclature has been "arsinin" ⟨83PAC409⟩. If one wants to point out that the arsenic atom is tervalent, coordination number 2, it is written as λ^3-arsinin. Derivatives of (**3**) with pentavalent arsenic, coordination number 4 (**7**) are defined as λ^5-arsinines (*Chemical Abstracts*: 1,1-dihydroarsenins).

In the case of further heteroatoms in (**1**) the Widman substitution nomenclature is used, for example for (**8**) 1,3-azarsinin or 1,3λ^3-azarsinin. Consequently (**9**) is a 3,4-dihydro-1,3-azarsinine, (**10**) is a 1,2,3,4-tetrahydro-1,3-azarsinin, and the name of (**11**) is 1,3-azarsinan (before 1983 (**11**) was called 1,3-azarsenan). It has to be remembered that *Chemical Abstracts* keeps the old arsenin and arsenan nomenclature. Although normally an As atom is placed at the lowest point in the ring in the present chapter, arsenic takes lower priority than most of the other heteroatoms when rings are numbered. Consequently, in the heterocycles discussed here the As atom seldom takes position 1.

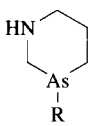
(**8**)



(**9**)



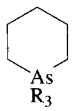
(**10**)



(**11**)

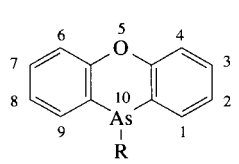
Generically, pentavalent arsenic compounds (**12**) and (**13**) are called arsoranes. Systematically, compounds (**13**) are λ^5-arsinanes, or (*Chemical Abstracts*) 1,1-dihydroarsenanes.

(**12**)

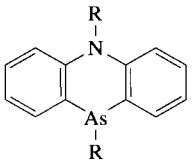


(**13**)

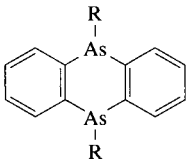
The trivial nomenclature for the dibenzannelated tetrahydro-1,4-oxarsinanes and the corresponding nitrogen and arsenic derivatives (**14**)–(**16**) has been maintained, too. Oxygenated λ^5As analogues of (**14**) are called phenoxarsinic acids (**17**). Phenoxarsines, phenazarsines and arsanthrenes are all numbered regularly.



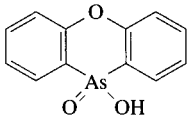
(**14**)
phenoxarsines



(**15**)
5,10-dihydrophenarsazines



(**16**)
5,10-dihydroarsanthrenes

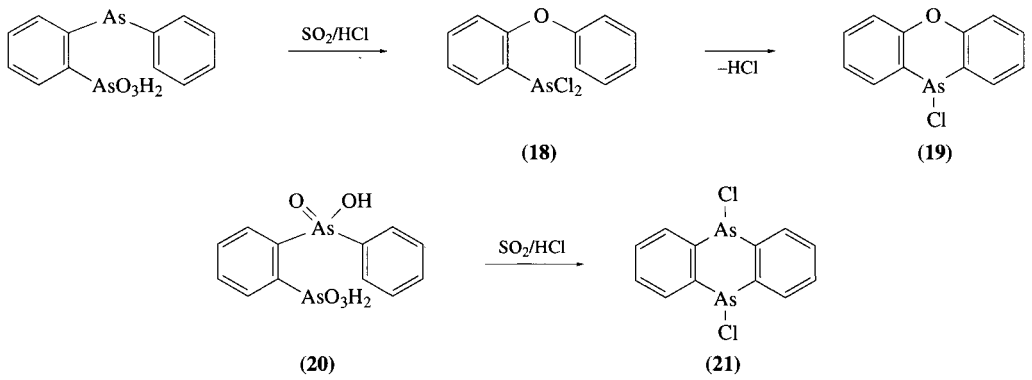


(**17**)
phenoxarsinic acid

6.26.3 SYNTHESIS OF SIX-MEMBERED ARSENIC HETEROCYCLES WITH AT LEAST TWO HETEROATOMS

In some respects the chemistry of arsenic compounds differs only slightly, but in others significantly, from phosphorus chemistry.

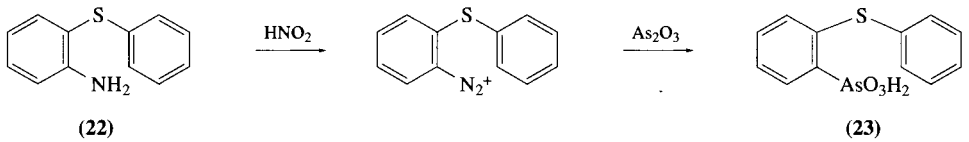
Like As_2O_3 itself, arsonic as well as arsinic acids are easily reduced by SO_2/HCl to give the chloroarsines, which can undergo ring closure by an electrophilic aromatic substitution reaction, for example (**18**)→(**19**) (Section 6.26.4.1.3.i) or (**20**)→(**21**) (Section 6.26.4.3.2.ii) (Scheme 1).



(**18**) (**19**) (**20**) (**21**)

Scheme 1

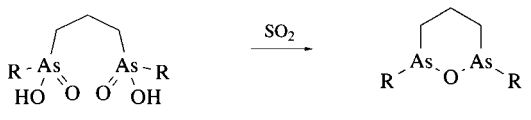
The synthesis of arsonic acids by the Bart reaction is a domain of classical arsenic chemistry (Section 6.26.4.1.3.1.1), for example (**22**)→(**23**) (Scheme 2) ⟨22LA(429)55⟩ (see also ⟨1863CR(56)1172, 21CB438, 25BRP261026⟩).



(**22**) (**23**)

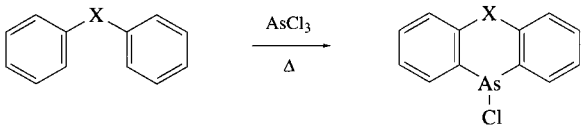
Scheme 2

If the reduction of arsonic and arsinic acids with SO_2 is carried out in the absence of HCl, cyclic arsine oxides are obtained, (**24**)→(**25**) (Equation (1)) (Section 6.26.5.5.1.i).

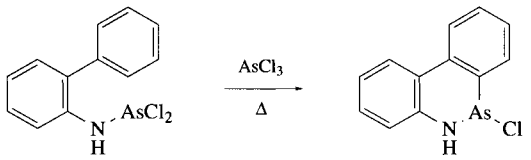


(**24**) (**25**) (1)

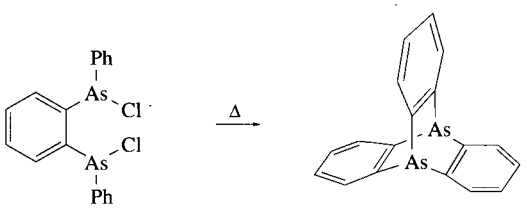
The electrophilic aromatic substitution by $AsCl_3$ (the Wieland–Rheinheimer reaction ⟨21LA(423)1⟩) proceeds more easily than the corresponding reaction with PCl_3, for example (**26**) → (**27**) (Equation (2)) (Sections 6.26.4.1.3.i and 6.26.4.2.4.i), (**28**) → (**29**) (Equation (3)) (Section 6.26.4.2.1). The thermal formation of the diarsatriptycene (**31**) from (**30**) occurs by the same mechanism (Equation (4)) (Section 6.26.4.3.2.ii).



(26) X = O, NH (27) (2)

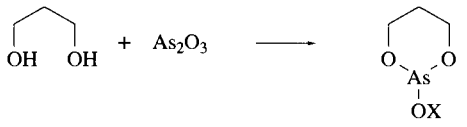


(28) (29) (3)

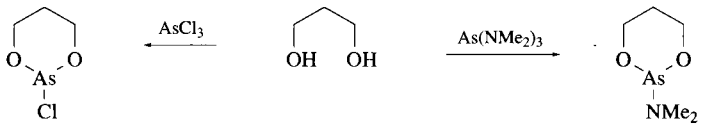


(30) (31) (4)

The esterification of As_2O_3 with alcohols is a very straightforward method for the synthesis of heterocyclic arsenite esters, i.e. (**32**) → (**33**) (Equation (5)). However, a more general approach to the synthesis of 1,3,2-dioxarsinanes is the reaction of 1,3-diols with $AsCl_3$ or with $As(NMe_2)_3$, for example (**34**) and (**35**) (Scheme 3) (Section 6.26.5.1.1.i).



(32) (33) (5)



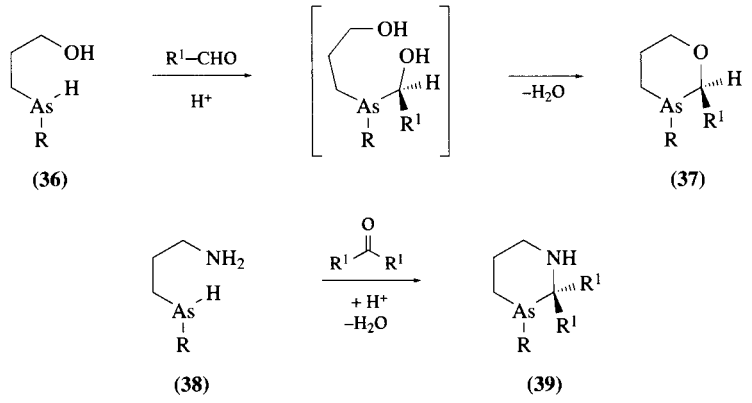
(34) (35)

Scheme 3

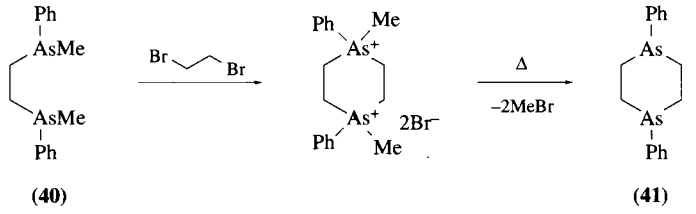
Another very characteristic cyclization reaction is the acetalation of aldehydes and ketones, for example (**36**) → (**37**) (Section 6.26.4.1.2) and (**38**) → (**39**) (Section 6.26.4.2.3) (Scheme 4).

Quaternary alkylarsonium salts are thermally much less stable than the corresponding phosphonium salts, as in the synthesis of (**41**) from (**40**) (Scheme 5) (Section 6.26.4.3.2.iii).

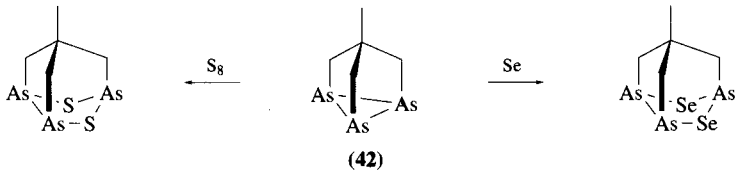
Oxygen, sulfur and selenium can be inserted into As—As bonds, for example in (**42**) (Scheme 6) (Section 6.26.5.5.1 and 6.26.5.7.1.ii).



Scheme 4

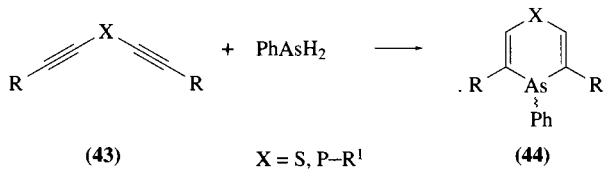


Scheme 5



Scheme 6

The base-catalyzed or radical-initiated cyclizations of primary arsines to dialkynes, for example (**43**) → (**44**) (Equation (6)) (Sections 6.26.4.1.4 and 6.26.4.4.2), are closely related to the corresponding reactions of primary phosphines (see Chapter 6.25).

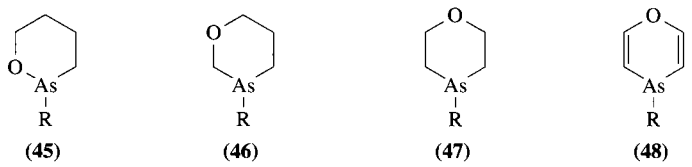


(6)

6.26.4 SIX-MEMBERED RINGS WITH TWO HETEROATOMS

6.26.4.1 Rings with One Arsenic and One Oxygen or Sulfur Atom

Derivatives of all possible oxarsinanes (**45**)–(**47**) and also of the 4*H*-1,4-oxarsinines (**48**) are described in the literature. While only a few derivatives of (**45**) and (**46**) have appeared, a flood of papers on derivatives of (**47**) and (**48**) has been published.

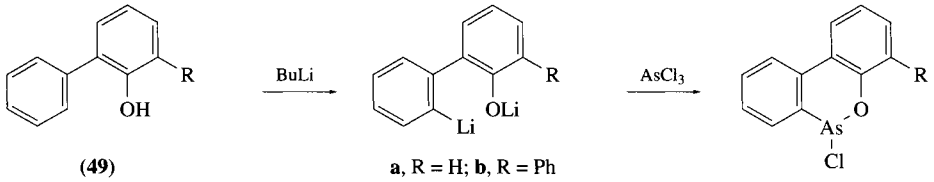


(45) (46) (47) (48)

6.26.4.1.1 1,2-Oxarsinines and 1,2-oxarsinanes

(i) 2H-1,2-Oxarsinines

Lithiated 2-hydroxybiphenyl and 2′-hydroxy-*m*-terphenyl (**49a,b**) react with $AsCl_3$ yielding the dibenz[1,2]oxarsinines (**50a,b**) (Scheme 7) ⟨94PS(90)235⟩. The synthesis of (**50a**) is possible also by heating (**49a**) with $AsCl_3$ in refluxing benzene and then distilling *in vacuo* (60% yield) ⟨75CI(L)400⟩.

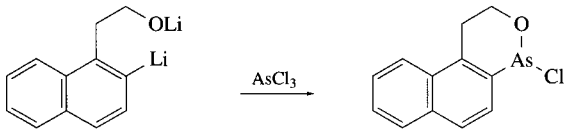


(49) **a**, R = H; **b**, R = Ph (50)

Scheme 7

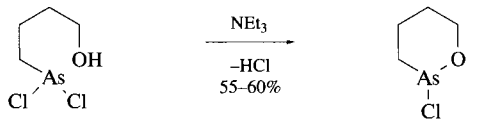
(ii) Dihydro-1,2-oxarsinines and 1,2-oxarsinanes

Metallation of 1-(β-hydroxyethyl)naphthalene and subsequent treatment with $AsCl_3$ yields the 1,4-dihydro-2*H*-naphth[2,1-*c*][1,2]oxarsinine (**51**) (Equation (7)) ⟨77CI(L)402, 77IJC(B)1145⟩. 2-Chloro-1,2-oxarsinane (**52**) results from the reaction of 4-hydroxybutyl-dichloroarsine with triethylamine (Equation (8)) ⟨70ZAAC(375)101⟩.



(7)

(51)

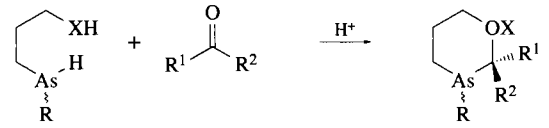


(8)

(52)

6.26.4.1.2 1,3-Oxarsinanes

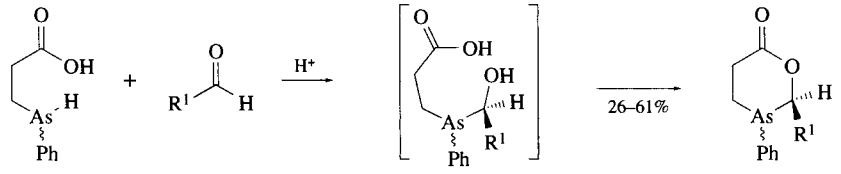
1,3-Oxarsinanes (**53**), which may be considered as O,As-acetals of aldehydes and ketones, are easily accessible by the acid-catalyzed reaction of 3-hydroxypropylarsines with aldehydes and ketones ⟨77TH 626-01⟩. The 1,3-thiarsinanes (**54**) are obtained in a similar way starting from 3-mercaptopropylarsines (Equation (9)) ⟨76TH 626-01, 77TH 626-01⟩.



(9)

(53) X = O
(54) X = S

Secondary arsinepropionic acids (**55**) undergo acid-catalyzed addition to aldehydes, yielding the δ-hydroxycarboxylic acids (**56**), which further lactonize to give the 1,3-oxarsinan-6-ones (**57**) (Scheme 8) ⟨78JOM(155)195⟩.



(55) (56) (57)

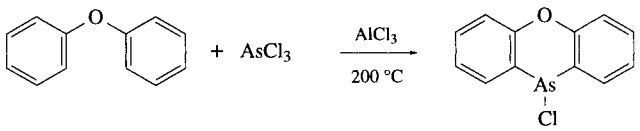
R^1 = H, Me, Pr^i, Ph

Scheme 8

6.26.4.1.3 1,4-Oxarsinines and 1,4-oxarsinanes

*(i) 10*H*-Dibenz[*b,e*][1,4]oxarsinines (phenoxarsines)*

(a) Synthesis. Similar to the synthesis of the 5,10-dihydrophenarsazines (Section 6.26.4.2.4.i), the most general and efficient synthesis of 10-chlorophenoxarsines (**59**) is the reaction, discovered in the 1920s, of diphenyl ethers (**58**) with $AsCl_3$ at 200 °C and $AlCl_3$ as catalyst (Equation (10)) ⟨21JA891, 25JCS544, 36JCS1236, 68USP3371105, 70USP3532727, 74RTC251⟩. Intermediates and further arsenated by-products have been detected by Gavrilov *et al.* ⟨91ZOB2213⟩. 10-Aryl- or -alkyl-phenoxarsines cannot be prepared from the corresponding dichloroarsine and diphenyl ethers, but they are readily obtained from (**59**) (see Section 6.26.4.1.3.i).

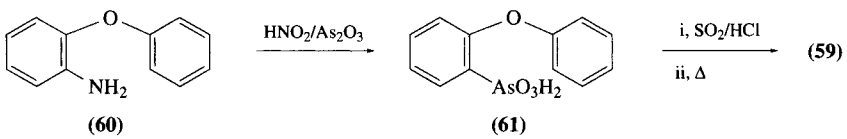


(10)

(58) (59)

A second method for the synthesis of phenoxarsines starts from *o*-phenoxyanilines (**60**). The *o*-phenoxyarsonic acids (**61**), accessible from (**60**) via the Bart reaction, are reduced to give the dichloroarsines, which then cyclize thermally yielding (**59**) (Scheme 9) ⟨25JCS544, 34JCS1170, 36JCS1236, 39JCS1720⟩.

Closely related is the synthesis of benzanellated phenoxarsines. Condensation of phenols with 1-

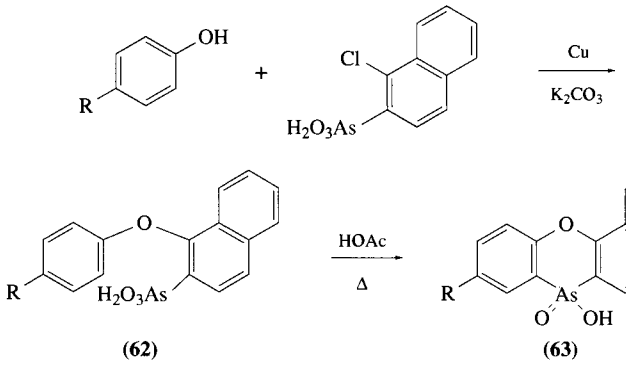


(59)

(60) (61)

Scheme 9

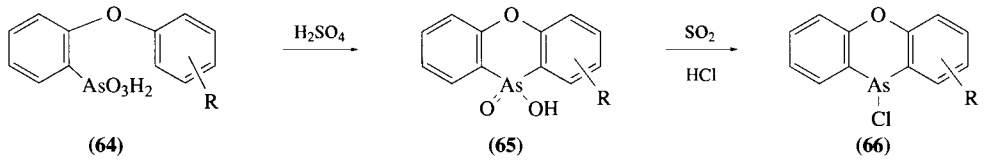
chloronaphthalene-2-arsonic acids yields (**62**), which can be cyclized to the benzo[*c*]phenoxarsinic acids (**63**) (Scheme 10) ⟨36JA1573⟩.



(**62**) (**63**)

Scheme 10

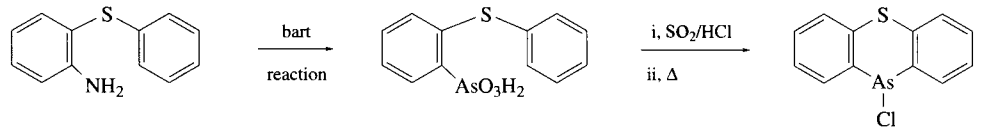
Substituted *o*-phenoxyphenylarsonic acids (**64**) can be cyclized to give the phenoxarsinic acids (**65**) and by reduction with SO_2/HCl the substituted 10-chlorophenoxarsines (**66**) are formed (Scheme 11) ⟨25JCS2004, 34JCS1170⟩.



(**64**) (**65**) (**66**)

Scheme 11

Phenothiarsines (**69**) can be prepared by the same procedure. 2-Nitro-diphenylthioether is reduced to the amine (**67**). The arsonic acid (**68**), obtained by a Bart reaction, is transformed into the dichloroarsine and cyclized to (**69**) at 200 °C (Scheme 12) ⟨26JCS1207⟩.



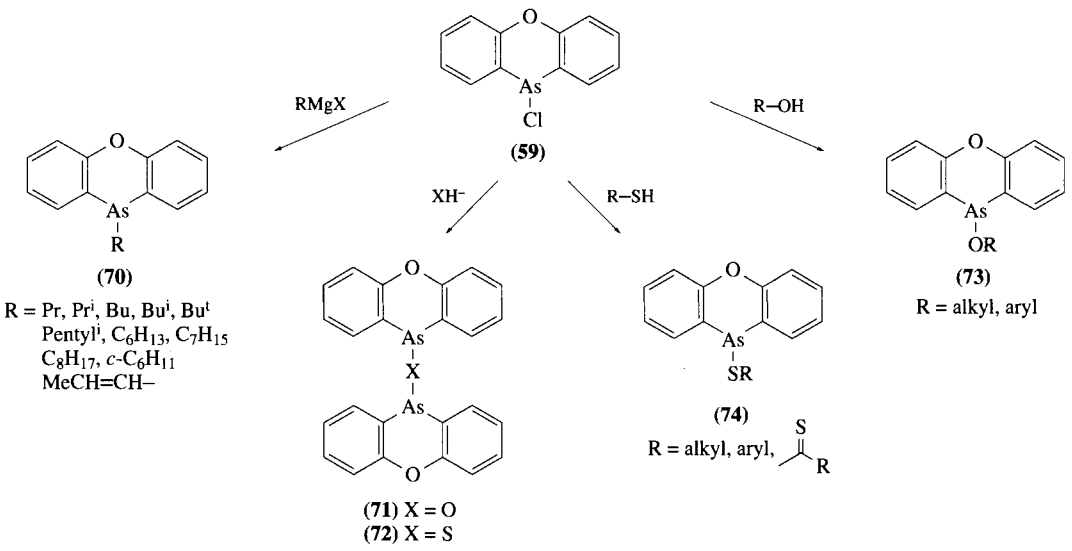
(**67**) (**68**) (**69**)

Scheme 12

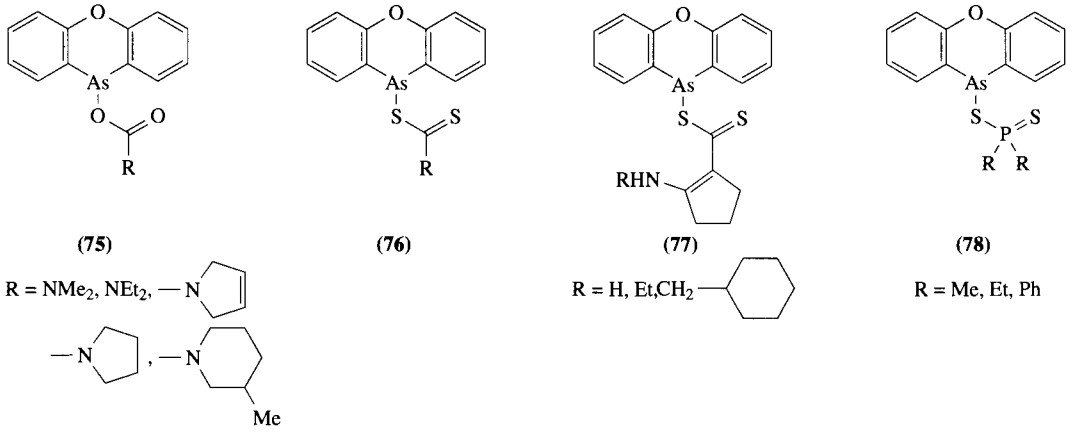
(b) Reactivity. 10-Alkyl- and -aryl-phenoxarsines (**70**) can be prepared by reaction of 10-chlorophenoxarsines (**59**) with organometallic compounds (Scheme 13). Grignard reagents ⟨25JCS811, 27JCS413, 34JCS1170, 35JCS1051, 35JCS1268, 36JCS730, 49JCS1183, 72ZOB1963, 73MI 626-01⟩, sodium acetylides ⟨72ZOB1963⟩, aryllithiums ⟨74ZOB256⟩ and tetraethyllead ⟨74ZOB2506⟩ have been used. With aqueous alkali hydroxides, (**59**) is hydrolyzed to give the 10,10′-oxydiphenoxarsines (**71**), and with H_2S the corresponding 10,10′-thiodiphenoxarsine (**72**) is precipitated from an ethanolic solution of (**59**) ⟨21JA891⟩. 10-Alkoxy-, 10-aryloxy- (**73**), 10-thioalkoxy- and 10-thiophenoxy-derivatives (**74**) have also been described.

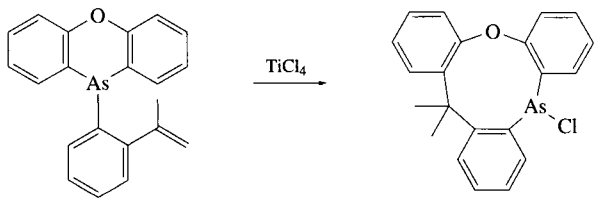
By reaction of the oxydiphenoxarsine (**71**) with various mono- and dibasic acids the esters (**75**) were synthesized ⟨92ZOB1294⟩. The synthesis of phenoxarsin-10-yl dithiocarbamates (**76**) by reaction of (**59**) with sodium dithiocarbamates (reaction in MeOH/water, 4 h, 25 °C) has been described ⟨95JOM(493)61⟩. Also the phenoxarsin-10-yl carbodithioates (**77**) have been described ⟨95MI 626-01⟩. Some phenoxarsin-10-yl diorganodithiophosphinates (**78**) were prepared by reaction of (**59**) with salts of the corresponding dithio compounds ⟨94JCS(D)2191⟩.

Interesting rearrangements of phenoxarsine derivatives have been investigated by Hellwinkel *et al.* ⟨90AG(E)689⟩. 10-(2-Isopropenylphenyl)-10*H*-phenoxarsine (**79**) on treatment with $TiCl_4$ in cyclohexane undergoes a ring-enlargement reaction to give the nine-membered ring system (**80**) (Equation (11)). Treatment of (**81**) with formic acid yields (**82**) (Equation (12)).

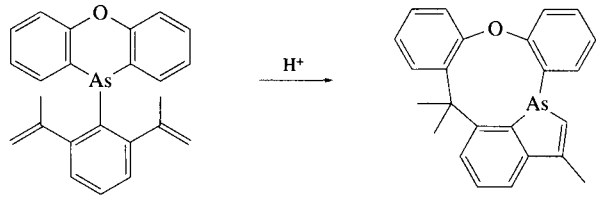


Scheme 13





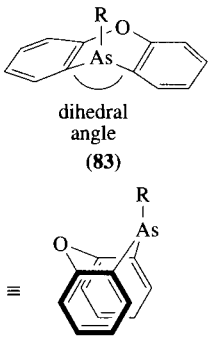
(11)



(12)

Studies on the effect of solvent on the decomposition rate of 10-methyl-10-phenylphenoxarsonium iodide have been reported ⟨85ZOB413, 86ZOB1291⟩.

(c) Spectroscopy and structure. Several x-ray structural analyses of phenoxarsines have been published. The main feature is the "butterfly" structure (**83**) similar to the 5,10-dichloro-5,10-dihydroarsanthrenes (Section 6.26.4.3.2.ii) and the 10-chloro-5,10-dihydrophenarsazines (Section 6.26.4.2.4.i). These molecules are folded along the As···O axis with dihedral angles of about 155°. As the data in Figure 1 show, the dihedral angle is fairly independent of the substituents at the arsenic atom.



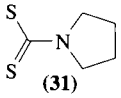
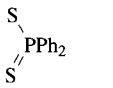
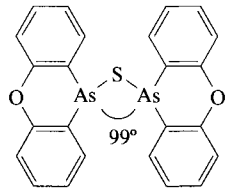
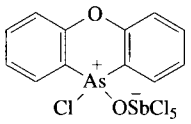
R	*dihedral angle*	*ref.*
Cl (**59**)	156.3	72IC1849
Me	154.1	86JHC1131
3-$MeOC_6H_4$	164.6	85JHC1237
 (**31**)	155.2	95JOM(493)61
	154.4	94JCS(D)2191

Figure 1 Crystal structures of phenoxarsines.

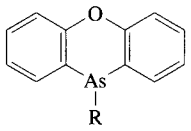
In contrast to these observations, the phenoxarsine rings in the 10,10′-thiodiphenoxarsine (**72**) are nearly flat (dihedral angles 175.2° and 178.5°); the value of the As-S-As angle is 99° ⟨72IC1846⟩.



(**72**)



(**84**)



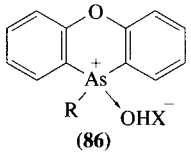
(**85**)

In the $OSbCl_5$ adduct (**84**), which was isolated by the reaction of (**59**) with $SbCl_5$ in the presence of oxygen, the molecule is flattened; the dihedral angle is spread to 167.7° ⟨72IC1849⟩.

The configurational stability of the arsenic atom in phenoxarsines was early demonstrated by the optical resolution of several 10-substituted 2-carboxylic acids (**85**), and of 10-(*p*-carboxyphenyl)-2-chlorophenoxarsines ⟨34JCS1170, 35JCS1268, 36JCS730, 38JCS1001⟩.

The mass spectra of phenoxarsines have been reported. In almost all cases the $O(C_6H_4)_2As^+$ ion is the base peak.

The spectra of the adducts (**86**) of some 10-alkyl- and 10-aryl-phenoxarsine 10-oxides with HCl, HBr and $HClO_4$ have been studied in detail ⟨76ZOB72⟩.



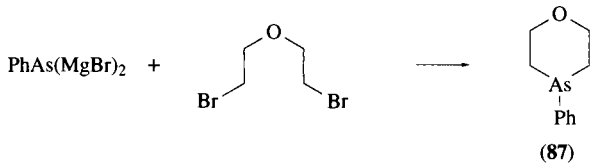
(**86**)

R = Et, Pr, Bz, Ph, 4-$MeOC_6H_4$, 4-$HalC_6H_4$ (Hal = F, Cl, Br)
X = Cl, Br, ClO_4

(ii) 1,4-Oxarsinanes

The bulk of the work on 1,4-oxarsinanes was published before 1974, and therefore only a short summary will be given. Phenylarsinebis(magnesiumbromide) reacts with 2,2′-dibromodiethyl ether

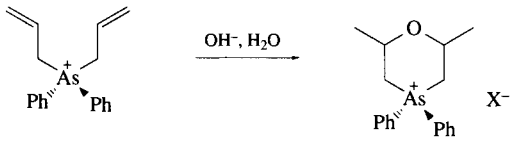
mainly with the formation of polymers; the 4-phenyl-1,4-oxarsinane (**87**) can be isolated only in 19% yield (Equation (13)) ⟨51JCS886⟩.



(13)

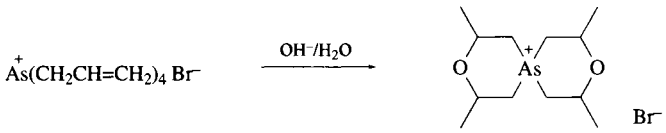
(**87**)

Diphenyl-diallylarsonium bromide reacts with dilute aqueous NaOH to give the 2,6-dimethyl-4,4-diphenyl-1,4-oxarsinanium salt (**88**) (Equation (14)), and tetraallylarsonium bromide yields the spiro-compound (**89**) by the same method (Equation (15)) ⟨73MI 626-03, 74MI 626-01⟩. X-ray structural analysis of (**88**; X = Br, NO_3) has been reported ⟨75JOM(94)383, 76ZAAC(421)174⟩.



(14)

(**88**)

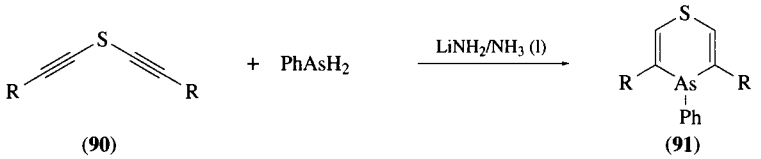


(15)

(**89**)

6.26.4.1.4 *1,4-Thiarsinines and phenothiarsines*

Bis-alkynyl sulfides (**90**) react in a base-catalyzed (lithium amide/liquid ammonia) cyclizing addition reaction with phenylarsine to give the only known monocyclic 1,4-thiaarsinines (**91**) (Equation (16)) ⟨74RTC241⟩.



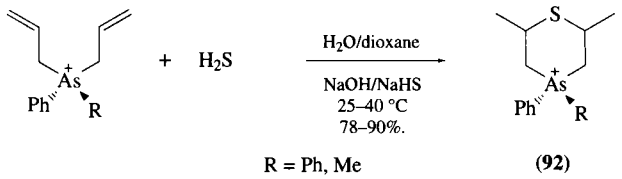
(16)

(**90**) (**91**)

The synthesis of phenothiarsine by ring closure of *o*-(phenylthio)benzenearsonic acid via the dichloroarsine has been noted earlier (Scheme 12) ⟨26JCS1207⟩.

6.26.4.1.5 *1,4-Thiarsinanes*

The 1,4-thiarsinanium salts (**92**) were prepared by Samaan by methods similar to those which provided the corresponding oxarsinanium salts from the same substrates (Equation (17)) ⟨74TL3927⟩.

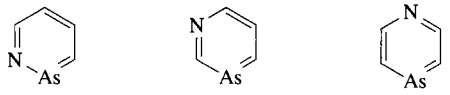


(17)

R = Ph, Me (**92**)

6.26.4.2 Rings with One Arsenic and One Nitrogen Atom

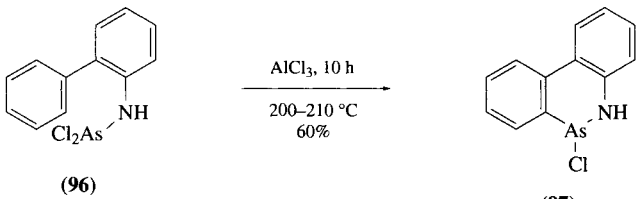
Of the three azarsinines (**93**)–(**95**), heteroaromatic derivatives of only the 1,3-azarsinine (**94**) are known. Isomers (**93**) and (**95**) hitherto have been described only as di- and tetrahydro derivatives.



(93) (94) (95)

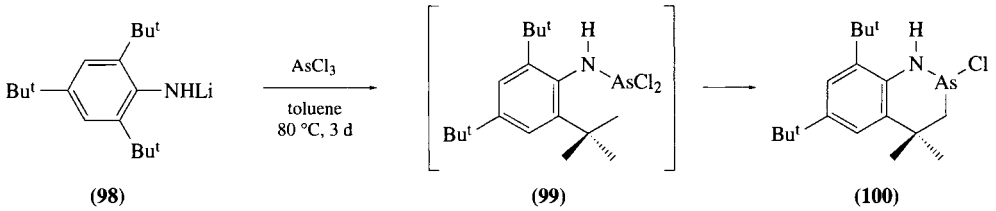
6.26.4.2.1 1,2-Azarsinines

Only a few representatives of this class of compound have been published. The first derivative of the 1,2-dihydro-1,2-azarsinines was the dihydro-heterophenanthrene (**97**), obtained by heating $AsCl_3$ with 2-aminobiphenyl to give the aminoarsine dichloride (**96**), which then was cyclized by heating with a catalytic amount of anhydrous $AlCl_3$ (Equation (18)) ⟨76IJC(B)902⟩. This synthesis is closely related to the numerous syntheses of phenarsazines (see Section 6.26.4.2.4.i).



(96) (97) (18)

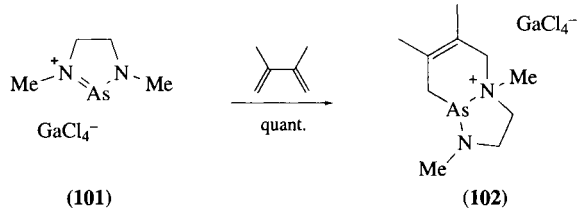
The synthesis of a tetrahydro-1,2-benzazarsinine is somewhat similar. Lithio-2,4,6-tris-*t*-butylanilide (**98**) in refluxing toluene reacts with $AsCl_3$ yielding (**100**). The intermediate aminoarsine dichloride (**99**) cyclizes by an insertion into a CH_3 group of the *t*-Bu (Scheme 14) ⟨86CC1634⟩.



(98) (99) (100)

Scheme 14

An entirely different approach to a tetrahydro-1,2-azarsininium salt (**102**) is represented by the (4 + 2) cycloaddition of 2,3-dimethylbutadiene to the As=N$^+$ bond of the arsenium ions (**101**) (Equation (19)) ⟨92CJC703, 92JA8147⟩. The structure of (**102**) was proven by the ^{1}H NMR and IR data and by x-ray analysis ⟨94AG(E)1267⟩.



(101) (102) (19)

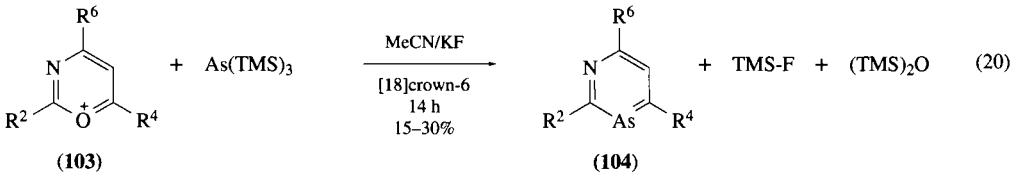
The corresponding phosphenium ion reacts quite differently. With dimethylbutadiene, a spirocyclic phosphonium salt is the only product ⟨83JA7443, 83JA7444, 86IC740⟩.

6.26.4.2.2 1,3-Azarsinines

(i) Synthesis

The 1,3-azarsinines (**104**) are so far the only known 6π Hückel aromatic six-membered ring system with two or more heteroatoms containing at least one arsenic atom.

The synthetic approach is very similar to the synthesis of 1,3-azaphosphinines ⟨87TL1093⟩. 1,3-Oxazinium salts (**103**) react in refluxing acetonitrile with tris(trimethylsilyl)arsine ⟨80ZAAC(462)113⟩ by an oxygen–arsenic exchange reaction, to give the 1,3-azarsinines (**104**) (Equation (20)), which can be isolated as crystalline, fairly stable compounds ⟨88TL535⟩.



(**103**) (**104**)

a, R^2, R^4, R^6 = Ph; **b**, R^2, R^4 = Ph, R^6 = 4-Me-C_6H_4; **c**, R^4, R^6 = Ph, R^2 = 4-Me-C_6H_4; **d**, R^2, R^4 = 4-Me_6H_4, R^6 = Ph

(ii) Spectroscopy and structure

The spectroscopic data of (**104**) confirm the Hückel aromaticity of this system ⟨88TL535⟩. The ^1H NMR data of H-5 are comparable with those of phosphinines and nearly identical to those of the corresponding 1,3-azaphosphinines (Table 1) ⟨87TL1093⟩.

Table 1 NMR and UV/VIS data for 1,3-azaarsinines.

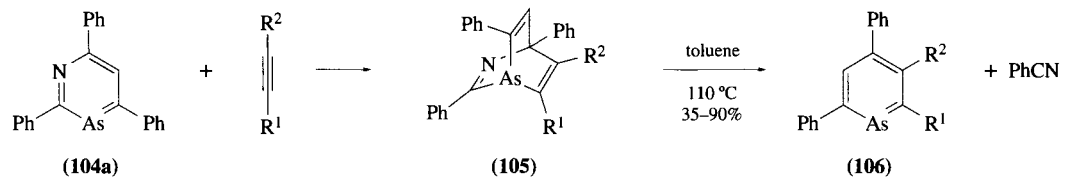
Compound	*^1H NMR* (250 MHz), *$CDCl_3$* δ (H-5) ppm	*^{13}C NMR ($CDCl_3$)* δ (ppm) *(C-2)*	*(C-4)*	*(C-5)*	*(C-6)*	*UV/VIS (hexane)* λ(nm) (ε)	
(104a)	8.04 (s)	204.7	155.7	118.7	193.5	300 (37000)	370 (sh) (9600)
(104b)	8.04 (s)	204.6	155.7	118.4	193.3	303 (27000)	370 (sh) (6400)
(104c)	8.03 (s)	204.5	155.6	118.6	193.3	303 (27900)	375 (sh) (62000)
Ph_3-1,3-azaphosphinine	8.14 (d)	191.5	157.1	119.8	180.5	289 (28000)	344 (sh) (4900)

In the mass spectra the base peak is the molecular ion M^+. The fragmentation pattern is determined by the fragments $[M\text{-}C_6H_5CN]^+$ and [M-*p*-tolyl]$^+$. In general the number of fragments is rather small, pointing to the stability of the system.

The x-ray analysis of (**104a**) is in agreement with expectation for an aromatic system (C-2/As 1.88 Å; As/C-4 1.90 Å; C-4/C-5 1.39 Å; C-5/C-6 1.41 Å; C-6/N 1.40 Å; N/C-2 1.38 Å).

(iii) Reactivity

Like the 1,3-azaphosphinines, the 1,3-azarsinines (**104a**) react as dienes with alkyne dienophiles yielding the azaarsabarrelenes (**105**), which are not stable under the reaction conditions. By a retro-Diels–Alder reaction ArCN is eliminated, yielding the arsinines (**106**) with the substituents of the alkyne used (Scheme 15) ⟨88TL539⟩.

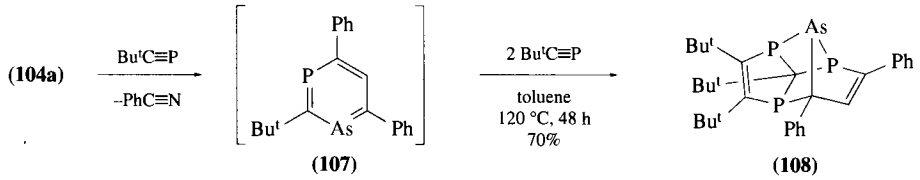


(**104a**) (**105**) (**106**)

R^1 = H, R^2 = Ph; R^1 = CHO, R^2 = Ph; R^1 = Ph; R^2 = COMe; R^1 = H, R^2 = CO_2R

Scheme 15

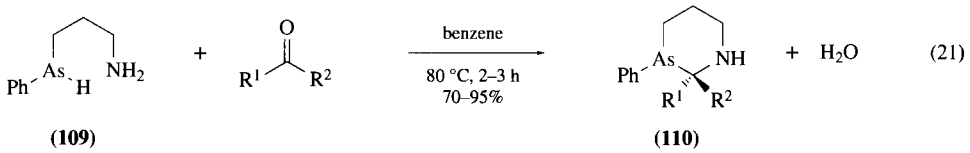
In an unusual sequence of cycloaddition reactions the 1,3-azarsinine (**104a**) reacts with three moles of *t*-butylphosphaethyne to give the pentacyclic product (**108**), demonstrated by an x-ray structural analysis ⟨88AG(E)709⟩. The first reaction step is undoubtedly a (4 + 2) cycloaddition to give the 1,3-phospharsinine (**107**) (Scheme 16).



Scheme 16

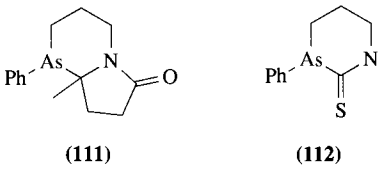
6.26.4.2.3 1,3-Azarsinanes

The reaction of PhAs(Na)H (prepared from $PhAsH_2$ by metallation using $NaNH_2/NH_3$) with $ClCH_2CH_2CH_2NH_2$ yields the secondary 3-aminopropylarsines (**109**), which form the 1,3-azarsinanes (**110**) by reaction with aldehydes and ketones (Equation (21)) ⟨74JOM(81)187, 74TH 626-01⟩. The reaction water is removed by azeotropic distillation. With ethyl levulinate (**111**) is formed by an intramolecular lactonization. Carbon disulfide also reacts smoothly, to give the thiolactam (**112**).



(21)

R^1 = Me, R^2 = H; R^1 = Prop^n, R^2 = H; R^1 = Ph, R^2 = H; R^1 = Me, R^2 = Et; R^1 = Bu^i, R^2 = Me; R^1, R^2 = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$



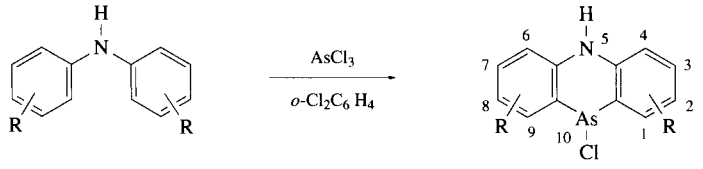
Despite the fact that 1,3-azarsinanes (**110**) may be considered as N,As-acetals, they are rather stable to hydrolysis. Alkyl halides react to form the 1,3-azarsinanium salts, and with sulfur the sulfides of (**110**) are obtained.

6.26.4.2.4 1,4-Azarsinines

(i) 5,10-Dihydrophenarsazines

(a) Synthesis. The 5,10-dihydrodibenz[*b*,*e*][1,4]azarsinines (**113**) (5,10-dihydrophenarsazines) are the most extensively studied azarsinine systems. Nearly all the work was published in two periods, between 1920 and 1930 and between 1950 and 1970, and only a short summary is given here.

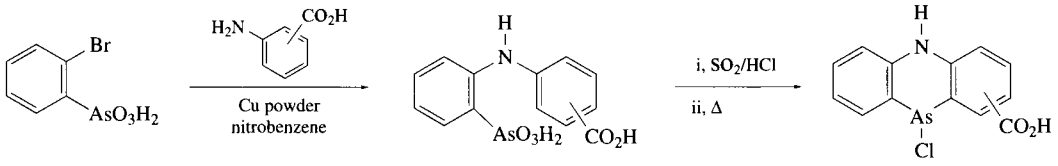
The best general synthesis is the reaction of diphenylamine and substituted diphenylamines with $AsCl_3$ (the Wieland–Rheinheimer synthesis; Equation (22)) ⟨21LA(423)1, 24JCS2275, 25JA2546, 26JCS450, 26JCS464, 26JCS2241, 27JCS413, 28CB1821, 29CB1208, 29CB2186, 29JCS1473, 30JA4164, 31JCS294, 49CR(228)868, 64JHC28, 67JCS(C)662, 68BSF627, 68ZOB1569, 71JCS(C)2428, 75JOC2684, 83JHC527⟩.



(22)

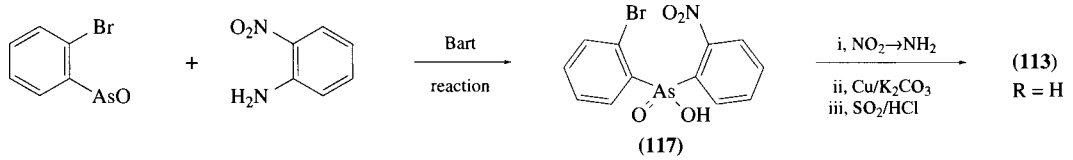
(113)

Two further synthetic approaches had also been published by the 1930s. *o*-Bromoarsonic acids (**114**) were transformed into the diphenylamine derivatives (**115**) by Ullmann condensation with aminobenzoic acids. After reduction of the arsonic acid to the dichloroarsine with SO_2/HCl, reflux in glacial acetic acid causes ring closure to form (**116**) (Scheme 17) ⟨27JCS247, 27JCS2499, 28JCS2204, 29JCS767, 29JCS1229, 29JCS2743, 31JCS294, 31JCS2381, 31JCS3270⟩. In the second method the diphenylarsinic acid (**117**) is prepared first by a Bart reaction, and the ring closure is achieved by an Ullmann reaction (Scheme 18) ⟨26JCS450, 30JCS1124⟩.



(**114**) (**115**) (**116**)

Scheme 17



(**117**)

Scheme 18

Many 5,10-dihydrophenarsazines have been prepared following the most simple and general synthesis, the condensation of diarylamines with $AsCl_3$. Figure 2 exemplifies the large variety of phenarsazines and related systems with further ring fusion described in the literature over a period of 50 years.

While *C*-alkyl-substituted derivatives of (**113**) can be prepared by the $AsCl_3$ method, *N*-alkylated and -arylated 5,10-dihydrophenarsazines are not accessible from *N*-substituted diarylamines. Dichloroarsines $RAsCl_2$ (R = alkyl, aryl) do not undergo the reaction either ⟨26JCS464, 27JCS2499, 30JA4164, 31JA376, 73MI 626-01, 75JOC2684, 75ZOB2524⟩. Ways to circumvent these problems, and to prepare *N*- and As-substituted 5,10-dihydrophenarsazines, are described in the following section.

(b) Reactivity. The chemistry of the 5,10-dihydrophenarsazines (**113**) and the various benzanellated analogues is determined by the reactivity of the As—Cl bond. In Scheme 19 the most significant reactions are summarized ⟨21LA(423)1, 30RTC1006, 46JA1860, 49CR(228)868, 67ZOB1402, 68ZOB1569, 70IZV1092, 70ZAAC(376)150, 72ZOB1530, 85JHC1237, 86JHC1131, 87ZOB350⟩. For more details see ⟨B-78MI 626-01⟩.

By vacuum thermolysis of (**118**; X = OCHO, OMe, NR_2 or Cl) the expected phenarsazine (**119**) (dibenz[1,4]azarsinine) could not be detected; the orange–red product turned out to be the dihydrodimer (**120**) (Scheme 20) ⟨75T2529⟩. The simple dehydrochlorination of (**113**) with dbu was not successful in providing (**119**) either.

The *N*-substituted 5,10-dihydrophenarsazines (**122**) and (**123**) are not accessible from *N*-substituted diarylamines by the Wieland–Rheinheimer method, and therefore they have to be prepared via the anions of (**121**) (Scheme 21). Thus, Gavrilov has described the alkylation of the MgBr salt of (**121**), yielding (**122**) ⟨87ZOB347⟩, while the 5,10-diphenyl compound (**123**) was obtained for the first time by the reaction of bromobenzene with the sodium salt of (**121**; R = Ph) in liquid ammonia ⟨88JHC1555⟩.

By heating the 10-(*o*-chlorophenyl)-5,10-dihydrophenarsazine (**121**; $R^1 = o\text{-}C_6H_4Cl$) with lithium

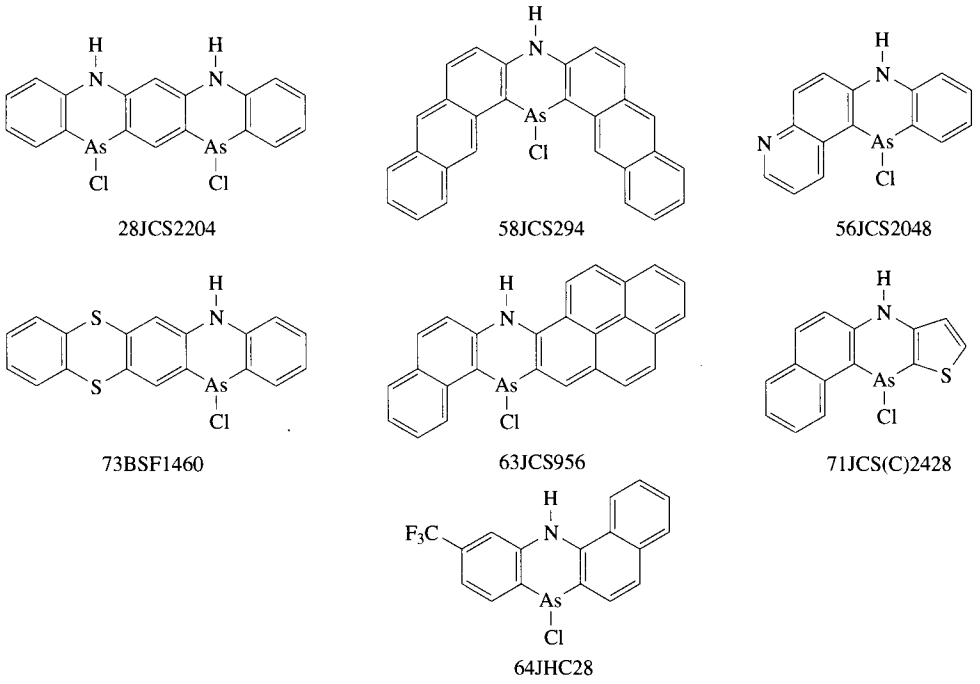
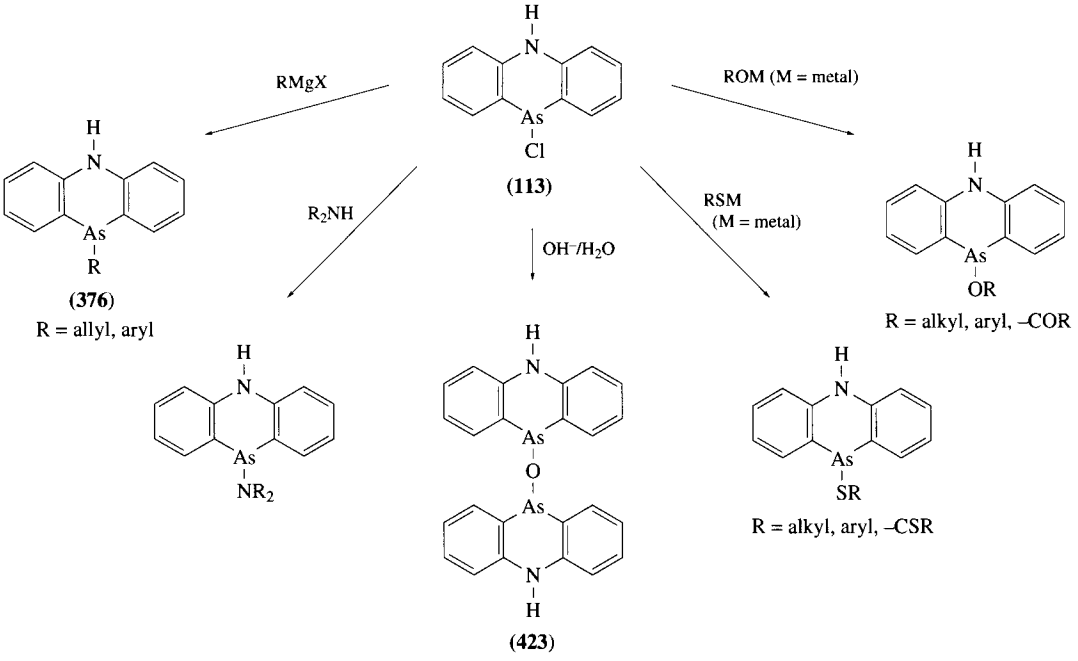


Figure 2 Fused 5,10-dihydrophenarsazine analogues.



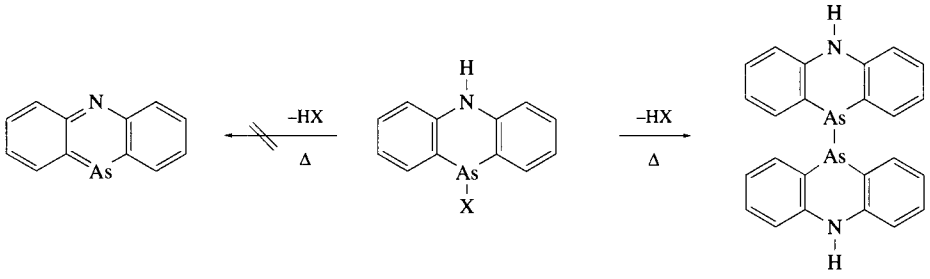
Scheme 19

diethylamide the azaarsatriptycene (**124**) was obtained as result of dehydrochlorination reaction via an aryne mechanism ⟨70CC158⟩.

Studies on the dependence of the basicity of 10-alkyl-5,10-dihydrophenarsazines on the nature of the substituents have been reported ⟨85ZOB413⟩.

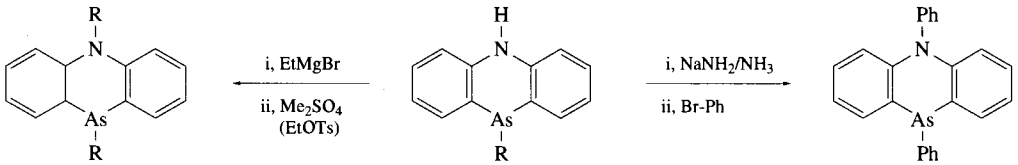
(c) Structure. The x-ray crystal structures of various 5,10-dihydrophenarsazines (**125**)–(**128**) have been determined (Figure 3).

The tricyclic ring system is folded, with the central ring in a flattened boat conformation. The folding angles between the least-squares planes of the two benzo rings are 169.2° (**125**), 164.6° (**126**),



(119) **(118)** **(120)**

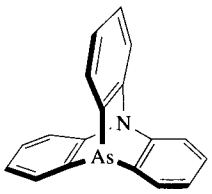
Scheme 20



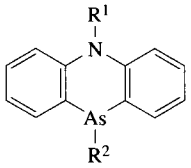
(122) **(121)** **(123)**

R^1 = Et, Pr^i, Ph, 4-$MeOC_6H_4$, 4-Hal-C_6H_4,4-$Me_2NC_6H_4$
R^2 = Me, Et, Bu

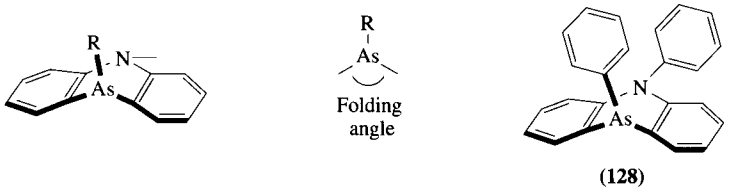
Scheme 21



(124)



(125) R^1 =H, R^2 = Cl; 65JCS730
(126) R^1 = H, R^2 = *m*-$MeOC_6H_4$; 85JHC1237
(127) R^1 = H, R^2 = Me; 86JHC1131
(128) R^1 = R^2 = Ph; 88JHC1555



(128)

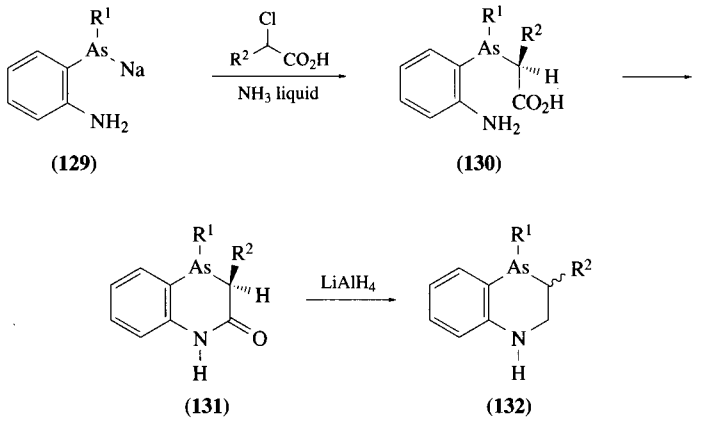
Figure 3 5,10-dihydrophenarsazine crystal structures.

154.1° (**127**) and 151.7° (**128**). The folding angle in (**128**) (*N*-phenyl) indicates that this ring system is much more puckered than (**125**)–(**127**), with *N*-H groups, and the planes of the aryl rings are nearly perpendicular to each other. The similar boat conformations of the phenoxarsines are discussed in Section 6.26.4.1.3.1.i.

(ii) 1,4-Azarsinanes

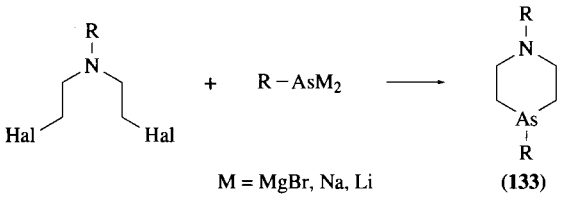
A few synthetic approaches to these ring systems were published in the years between 1950 and 1977.

The tetrahydro-1,4-benzazarsinines (**132**) are synthesized by reaction of the metalated secondary *o*-aminophenylarsines (**129**) with α-halocarboxylic acids in liquid ammonia to give (**130**). Ring closure by dehydration to give (**131**) and reduction of the lactam with $LiAlH_4$ affords (**132**) (Scheme 22) ⟨77JOM(133)293⟩.

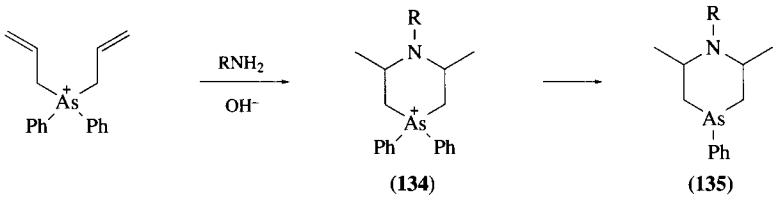


Scheme 22

1,4-Azarsinanes (**133**) are obtained by reaction of metallated primary arsines with tertiary bis-(β-halogenoethyl)amines (Equation (23)) ⟨51JCS886⟩. A second approach is the addition of primary amines to bis(allyl)arsonium salts yielding (**134**) and electrochemical or $LiAlH_4$ reduction to give the 1,4-azarsinane (**135**) (Scheme 23) ⟨73MI 626-01, 74TL3927⟩.



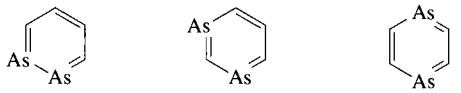
(23)



Scheme 23

6.26.4.3 Rings with Two Arsenic Atoms

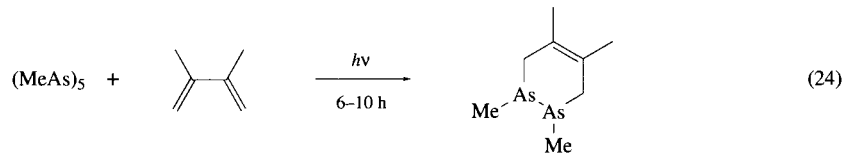
The cyclic conjugated diarsinine systems (**136**)–(**138**) are not known. Only di- and tetrahydro derivatives of (**136**) and (**138**) have been described in the literature, although there are indications for the transient formation of a derivative of (**138**) (Section 6.26.4.3.2.i).



(136) (137) (138)

6.26.4.3.1 Tetrahydro-1,2-diarsinines

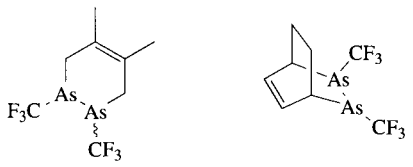
Nearly all synthetic approaches to this ring system are the result of (4 + 2)-cycloaddition reactions with diarsenes as reactive intermediates. Pentamethylcyclopentaarsane (**139**) and 2,3-dimethylbutadiene yield the tetrahydro-1,2-diarsinine (**140**) on irradiation with a normal electric light bulb (Equation (24)) ⟨68CB1381⟩.



(24)

(139) (140)

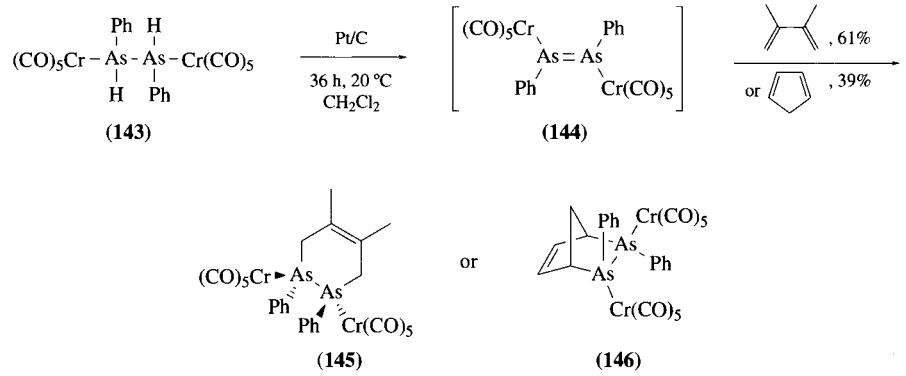
The photochemically-induced cleavage (high pressure Hg lamp) of the trifluoromethyl-substituted cyclopenta- and cyclotetra-arsanes in the presence of 1,3-dienes yields the (4 + 2) cycloadducts (**141**) and (**142**) ⟨95ZN(B)189⟩. These results underline the intermediate formation of the bistrifluoromethyl diarsene.



(141) (142)

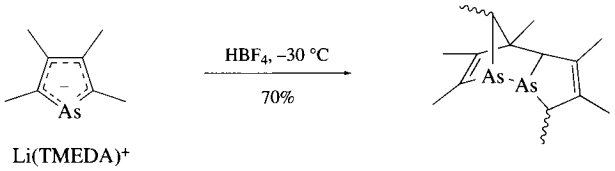
Huttner and Jibril described the dehydrogenation of the diarsane chromium complex (**143**) by Pt/C to give the diarsene complex (**144**), which can be isolated by ligand exchange as the stable $(CO)_4CrP(OMe)_3$ complex or intercepted as Diels–Alder adducts with 2,3-dimethylbutadiene or cyclopentadiene to give the tetrahydro-1,2-diarsinines (**145**) or (**146**) (Scheme 24) ⟨84AG(E)739⟩. The structure of (**146**) was demonstrated by x-ray analysis ⟨90JOM(393)213⟩.

An unusual formation of a product with a tetrahydro-1,2-diarsinine structural unit was described



Scheme 24

by Theopold and co-workers. The permethylated arsolyl anion (**147**) on protonation with $HBF_4 \cdot Et_2O$ forms the 2*H*-arsole dimer (**148**) (Equation (25)) ⟨91CB2453⟩.



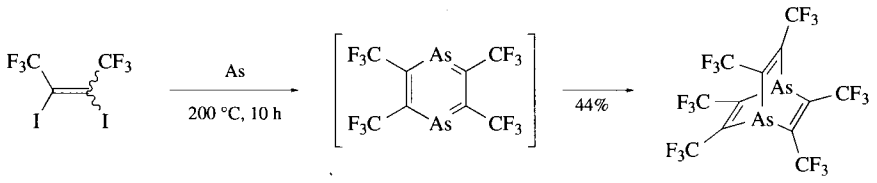
Li(TMEDA)$^+$

(**147**) (**148**) (25)

6.26.4.3.2 1,4-Diarsinines

(i) 1,4-Dihydro-1,4-diarsinines

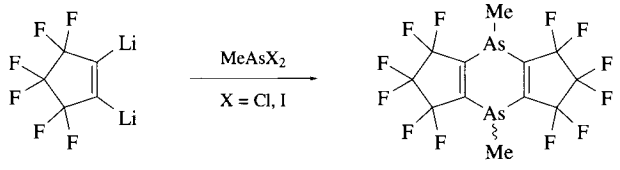
The first derivative of a 1,4-dihydro-1,4-diarsinine was described by Krespan ⟨61JA3432⟩. From the reaction mixture of the bis(trifluoromethyl)diiodoethene (**149**) with metallic arsenic at 200 °C the 1,4-diarsabarrelene (**151**) (m.p. 139–140 °C) was isolated. The intermediate formation of the 1,4-diarsinine (**150**) is very likely (Scheme 25).



(**149**) (**150**) (**151**)

Scheme 25

The dilithioperfluorocyclopentene (**152**) reacts with $MeAsX_2$ (X = Cl, I) to give the 1,4-dihydro-1,4-dimethyl-1,4-diarsinine (**153**) (Equation (26)) ⟨73MI 626-02, 74USP3787461⟩.



(**152**) (**153**) (26)

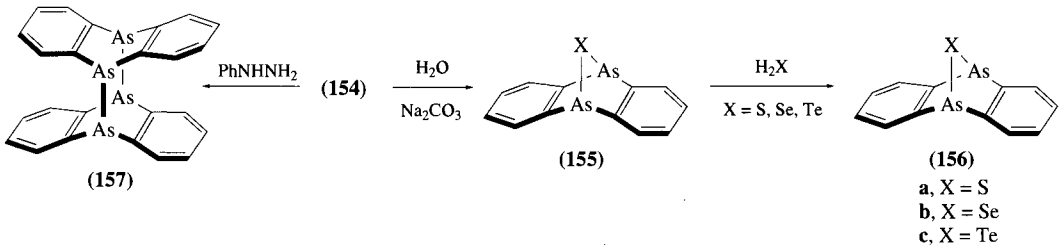
(ii) Arsanthrenes

The dibenzo compound (**154**), 5,10-dichloro-5,10-dihydroarsanthrene, was synthesized from the arsonyl-diphenylarsinic acid via reduction and cyclization (Equation (27)) ⟨21LA(423)39, 40JCS1184⟩.

(**154**) (27)

Compound (**154**) is a very valuable educt for the synthesis of many arsanthrene derivatives ⟨21LA(423)1, 40JCS1184, 48JCS2208, 55JCS411, 70JCS(C)810⟩. The stereochemistry of these 1,4-dihydrodiarsinines has also been studied thoroughly ⟨63JCS4266, 68CC269⟩.

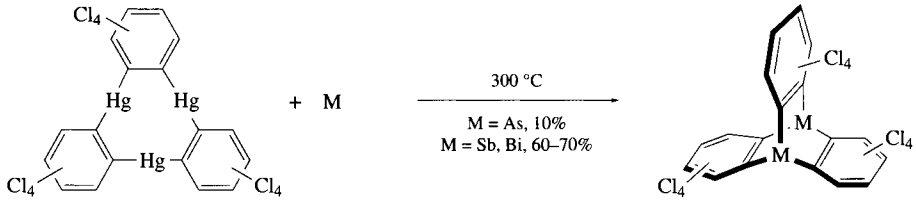
The dichloro-dihydroarsanthrene (**154**) reacts with H_2O/Na_2CO_3 yielding (**155**), which with H_2S, H_2Se and H_2Te can be transformed into the bridged compounds (**156**) (Scheme 26) ⟨70JCS(C)810, 71JCS(C)1511⟩. By reduction of (**154**) with phenylhydrazine the dimeric "arsanthrene" (**157**) is formed ⟨21LA(423)1⟩.



Scheme 26

The synthesis of dihydroarsanthrene derivatives can also be achieved via organometallic intermediates. By reaction of $NaAsMe_2$ with *o*-$Cl_2C_6H_4$ 5,10-dimethyl-5,10-dihydroarsanthrene could be isolated, besides several other products ⟨71JOM(33)347⟩. Perfluorinated dibenzo-1,4-dihydro-1,4-diarsinines have been synthesized by reaction of *o*-dilithiotetrafluorobenzene with diiodoarsines $RAsI_2$ ⟨76JFC(8)183⟩.

The phenylenemercury compound (**158**) reacts with finely powdered metallic arsenic, antimony and bismuth at temperatures above 300 °C to give the diarsa-, distiba- and dibisma-triptycenes (**159**) (Equation (28)). The characterization of compounds (**159**) was based mainly on MS data ⟨87JOM(319)59⟩. The same compounds are accessible also by heating the metal powders with 3,4,5,6-tetrachloro-1,2-diiodobenzene at 260 °C.

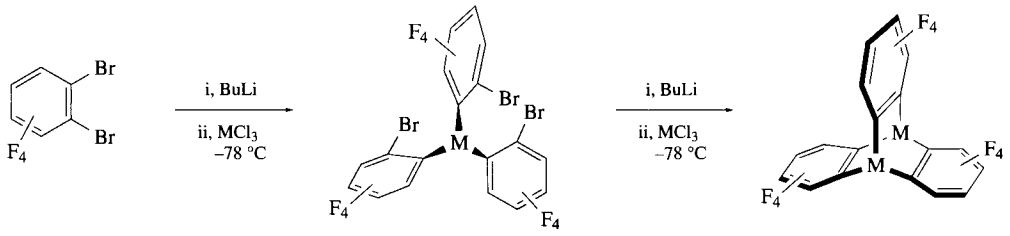


(28)

(**158**)

(**159**)
a, M = As
b, M = Sb
c, M = Bi

The stepwise synthesis of the perfluorinated 1,6-diphospha-, diarsa-, distiba- and dibisma-triptycenes (**160**), starting from 1,2-dibromotetrafluorobenzene via the dilithio-compounds, has also been described (Scheme 27) ⟨85JOM(287)57⟩.

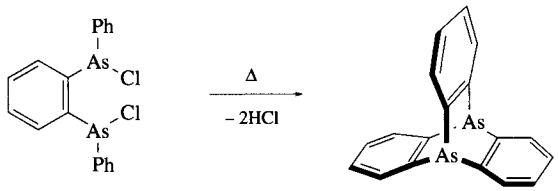


M = P, As, Sb, Bi

(**160**)

Scheme 27

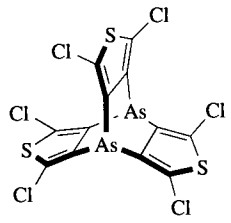
Comparable to these syntheses is the long-known formation of the unsubstituted diarsatriptycene (**162**) simply by thermal dehydrochlorination of the bis-chloroarsine (**161**) (Equation (29)) ⟨27JCS2753⟩.



(29)

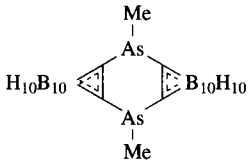
(161) **(162)**

Massey and co-workers have also synthesized the hexachlorinated diarsatriptycene thiophene derivative (**163**) ⟨88MI 626-01⟩.



(163)

The bis(dimethylarsino)-*o*-carborane (**164**) has been known since 1969 ⟨69IC678⟩.

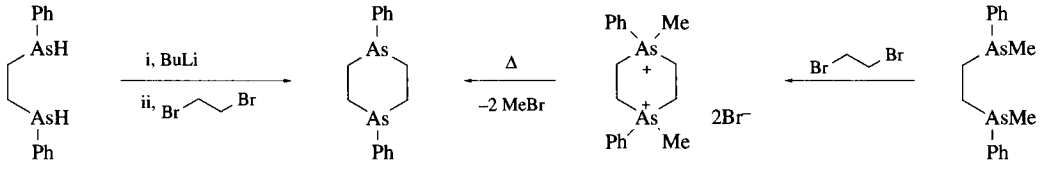


(164)

(iii) 1,4-Diarsinanes

The synthesis and the chemistry of 1,4-diarsinanes were investigated mainly between 1950 and 1970.

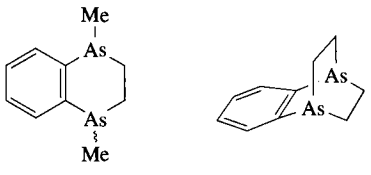
1,4-Diarsinanes like (**166**) can be prepared via the reaction of the lithiated 1,2-bis(phenylarsinyl)ethane (**165**) with 1,2-dibromoethane, or by thermolysis of the 1,4-dimethyl-1,4-diarsinanium dibromide (**167**) (Scheme 28) ⟨55JCS411⟩.



(165) **(166)** **(167)**

Scheme 28

The tetrahydro-1,4-benzodiarsinine (**168**) and the bridged derivative (**169**) were also synthesized by thermolysis of the intermediate bis-methylarsonium salts ⟨50JCS682, 52JCS4142, 55JCS411⟩.



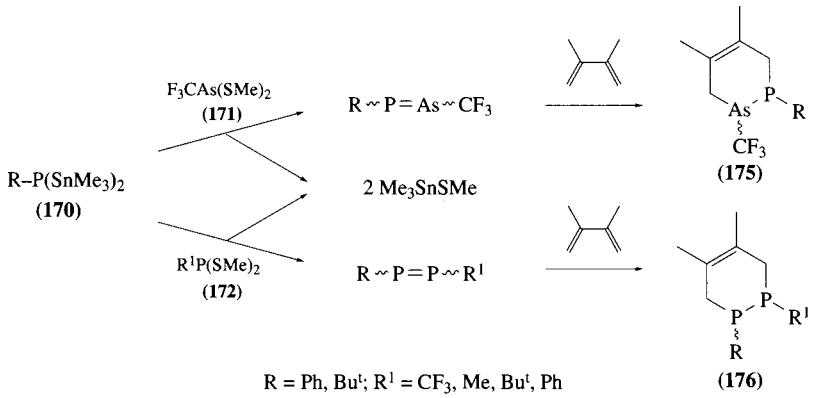
(168) **(169)**

The 1,4-diphenyl-1,4-diarsinane (**166**) undergoes an interesting "commutation" reaction with $AsCl_3$ at 260°C, with formation of 1,4-dichloro-1,4-diarsinane and phenyldichloroarsine ⟨71ZAAC(383)136⟩.

6.26.4.4 Rings with One Arsenic and One Phosphorus Atom

6.26.4.4.1 Tetrahydro-1,2-phosphaarsinines

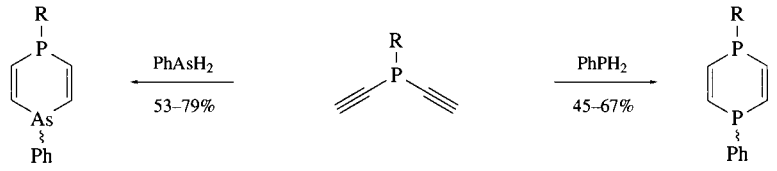
Unsymmetrically substituted phosphaarsenes (**173**) and diphosphenes (**174**) can be generated *in situ* by reacting the bis(trimethylstannyl)phosphines (**170**) with bis(methylthio)trifluoromethylarsine (**171**) and bis(methylthio)phosphines (**172**). Spectroscopic evidence for the phosphaarsenes (**173**) and the diphosphenes (**174**) was not obtained, but they could be trapped as (4 + 2) cycloadducts with 2,3-dimethyl-1,3-butadiene, yielding the tetrahydro-1,2-phospharsinines (**175**) and the tetrahydro-1,2-diphosphinines (**176**), and with isoprene, when the reactions between (**170**) and (**171**) or (**172**) were carried out in the presence of the diene (Scheme 29). The cycloaddition products were characterized by MS, and by ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy ⟨89ZAAC(579)35⟩.



Scheme 29

6.26.4.4.2 1,4-Dihydro-1,4-phospharsinines

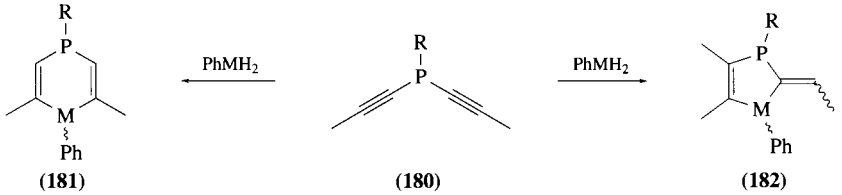
The formation of 1,4-dihydro-1,4-phospharsinines (**178**) and 1,4-dihydro-1,4-diphosphinines (**179**), by cyclizing addition of phenylarsine or phenylphosphine to various diethynylphosphines (**177**), has been reported (Scheme 30). The reaction is base-catalyzed ($NaNH_2$, $LiNH_2/NH_3$; KOH/18-crown-6), but a radical cyclization initiated by AIBN is also effective. The cyclization products (**178**) and (**179**) are formed as mixtures of *cis/trans* isomers with the *cis*-isomers with (*e,e*)-conformation prevailing. The cyclizing addition of primary alkyl (*t*-butyl, benzyl) phosphines and arsines is possible only by KOH/18-crown-6 catalysis ⟨75TL3171, 77S842, 85CB2365⟩.



Scheme 30

The radical-induced cyclization reaction of phenylarsine and phenylphosphine to the bis-(1-propynyl)phosphines (**180**) and arsines yields a mixture of the 3,5-dimethyl substituted 1,4-

dihydrophospharsinines and 1,4-dihydrodiphosphinines (**181**) and the five-membered cyclization products (**182**), which usually predominate (Scheme 31) ⟨85CB2365⟩.

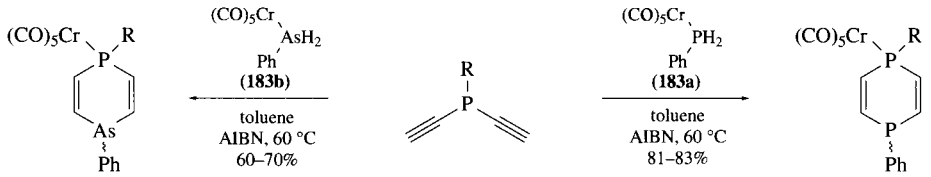


(**181**) (**180**) (**182**)

M = P, As; R = Bu^t, CH_2Ph

Scheme 31

The phenylphosphine and phenylarsine complexes (**183a,b**) react with bis-ethynylphosphine (**177**) by insertion to give the 1,4-dihydro-1,4-disphosphinine complexes (**184a**) and the 1,4-phospharsinine complexes (**184b**) (Scheme 32) ⟨93JOM(444)53⟩.

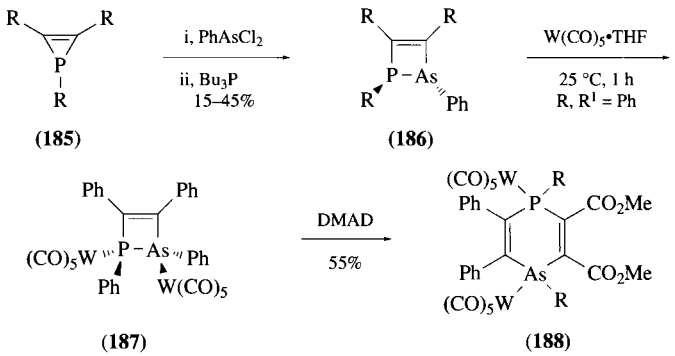


(**184b**) (**177**) (**184a**)

R = Bu^t, CH_2Ph

Scheme 32

1,2-Dihydrotetraphenyl-1,2-phospharset (**186**), obtained by ring expansion of the phosphirenes (**185**) with phenyldichloroarsine, reacts as its $[W(CO)_5]_2$ complex (**187**) with dimethyl acetylenedicarboxylate. The isolated 1,4-dihydro-1,4-phospharsinine complex (**188**) is probably the result of a (4 + 2)-cycloaddition reaction with the 1-phospha-4-arsabutadiene formed by valence isomerization of (**187**) (Scheme 33) ⟨93BSF521⟩.



(**185**) (**186**)

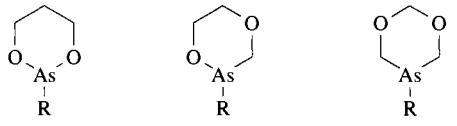
(**187**) (**188**)

Scheme 33

6.26.5 SIX-MEMBERED RINGS WITH THREE HETEROATOMS

6.26.5.1 Rings with One Arsenic and Two Oxygen Atoms

Of all the possible isomeric dioxarsinanes only derivatives of the 1,3,2- (**189**), the 1,4,2- (**190**) and the 1,3,5-dioxarsinanes (**191**) are known. The best-studied isomer is the 1,3,2-dioxarsinane ring system.



(189) (190) (191)

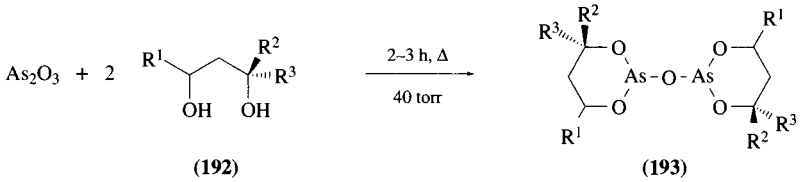
6.26.5.1.1 1,3,2-Dioxarsinanes

(i) Synthesis

This ring system has been studied thoroughly since the 1950s, but the basic syntheses were published in the years 1950 to 1953 by Russian groups. Since this work provides the starting materials for the subsequent studies carried out, a brief summary of this early work will be given.

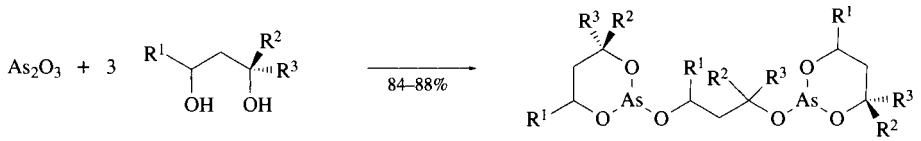
The 1,3,2-dioxarsinanes (**189**) with the R an *O*-substituent are formally cyclic arsenites, and therefore they are easily accessible by the reaction of 1,3-diols with As_2O_3 ⟨53DOK(89)1015, 53ZOB1323, 56ZOB2468, 58MI 626-02, 63DOK(151)853⟩.

Arsenic trioxide reacts with two moles of the diol (**192**) with continuous removal of the reaction water to give the 2,2′-oxybis-1,3,2-dioxarsinanes (**193**) as viscous but distillable products. With three moles of the diol the 2,2′-alkylenedioxybis(1,3,2-dioxarsinanes) (**194**) are obtained in 84–88% yields (Scheme 34) ⟨77SRI421⟩.



(192) (193)

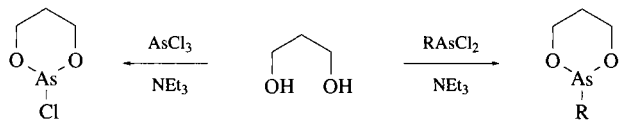
R^1, R^2, R^3 = H (80%); R^1 = Me, R^2, R^3 = H(84%); R^1, R^2, R^3 = Me (57%)



(192) (194)

Scheme 34

The most general method, applicable also to cyclic arsonites, is the reaction of 1,3-diols with $AsCl_3$ and $RAsCl_2$ to give (**195**) and (**196**) respectively (Scheme 35) ⟨51DOK(81)837, 52IZV908, 79ACS(A)413, 79ACS(A)753⟩.

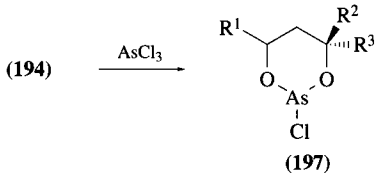


(195) (196)

Scheme 35

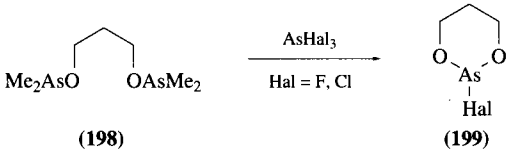
A wide variety of 1,3,2-dioxarsinanes, with alkyl and/or phenyl substituents at C4–C6 and chlorine, methoxy or phenoxy at position 2, have been synthesized by Aksnes *et al.* using the $AsCl_3$ method ⟨75ACS(A)376, 76ACS(A)327, 79ACS(A)413⟩.

The bis-dioxarsenanes (**194**) react exothermically with $AsCl_3$ giving the 2-chloro-dioxarsenanes (**197**) (Equation (30)) ⟨77SRI421⟩. The propanediol bisdimethylarsinites (**198**) react with $AsCl_3$ and AsF_3 by cleavage of the As—O bonds to give the corresponding 2-halo-1,3,2-dioxarsinanes (**199**) (Equation (31)) ⟨75ZAAC(416)57⟩.



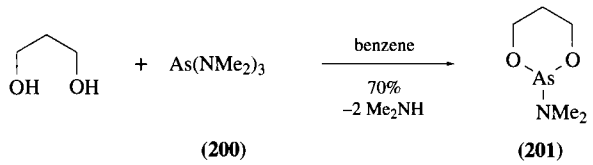
(30)

R^1 = Me, R^2, R^3 = H (88%); R^1, R^2, R^3 = H (83%); R^1, R^2, R^3 = Me (85%)

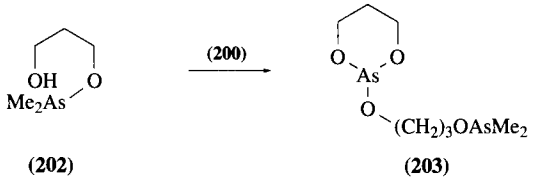


(31)

Aminoarsines such as tris(dimethylamino)arsine (**200**) react with 1,3-diols to give 2-amino-1,3,2-dioxarsinanes (**201**) (Equation (32)). The As—NMe_2 bond is easily cleaved by protic reagents ⟨70CC425, 75ZAAC(416)57, 75ZAAC(416)152⟩. In an unusual reaction the propanediol monoarsinite (**202**) reacts with (**200**) yielding (**203**) (Equation (33)) ⟨76ZN(B)190⟩. The dimethylaminoarsine $[Me_2AsO(CH_2)_3O]_2AsNMe_2$ is an intermediate.

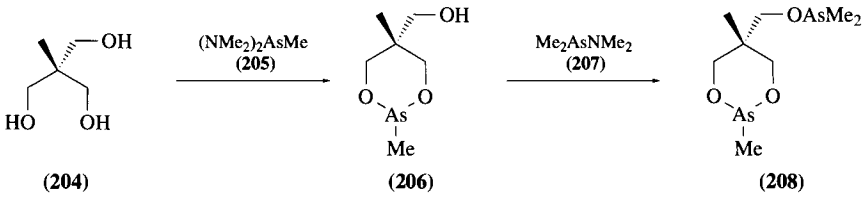


(32)



(33)

1,1,1-Tris(hydroxymethyl)ethane (**204**) reacts with bis(dimethylamino)-methylarsine (**205**) to form 5-hydroxymethyl-2,5-dimethyl-1,3,2-dioxarsinane (**206**). With (dimethylamino)dimethylarsine (**207**), (**206**) goes on to give (**208**) (Scheme 36) ⟨76ZN(B)307⟩.



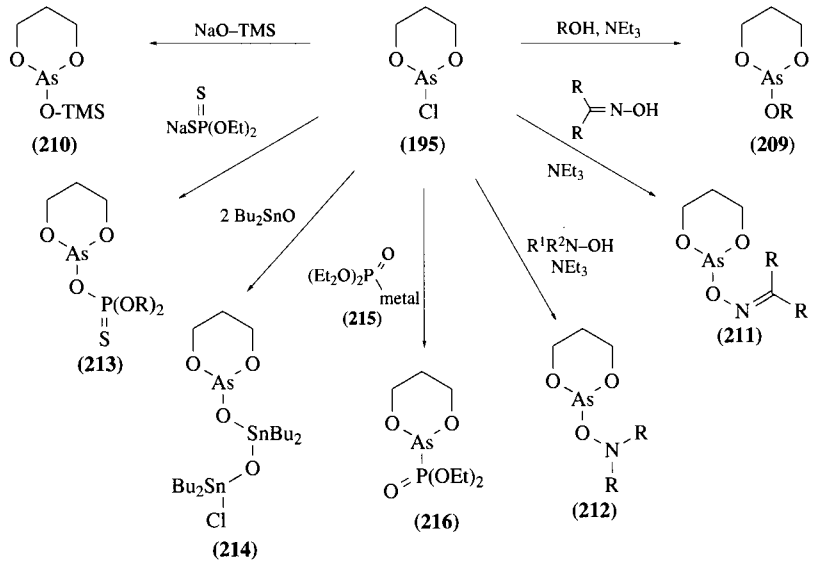
Scheme 36

(ii) Reactivity

Although 1,3,2-dioxarsinanes are cyclic esters, the ring system is rather stable to hydrolysis. All kinds of exchange reactions at the arsenic atom are therefore possible.

Treatment of 2-chloro-1,3,2-dioxarsinanes (**195**) with alcohols and phenols in diethyl ether in the presence of excess of triethylamine yields the corresponding alkoxy and phenoxy derivatives (**209**; R = alkyl, aryl) ⟨76CB493, 76ZN(B)190⟩. Aksnes *et al.* reported the preparation of several 2-methoxy- and 2-phenoxy-substituted 1,3,2-dioxarsinanes in this way (Scheme 37) ⟨75ACS(A)376, 76ACS(A)327⟩. As a result of the configurational stability at the arsenic atom, nonequilibrium mixtures of two

geometrical isomers are usually formed when there are substituents present in the ring at C(3)–C(5) ⟨76ACS(A)327⟩ (see Section 6.26.5.1.1.iii). The 2-chloro-1,3,2-dioxarsinanes (**195**) are the most important starting materials for the preparation of various 2-substituted derivatives. Some representative examples are shown in Scheme 37.



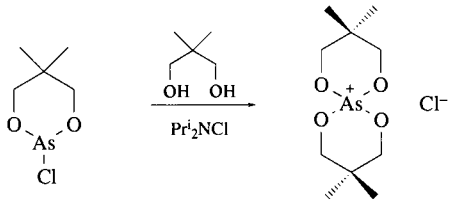
Scheme 37

The reaction with sodium silanolate yields the silyloxy derivatives (**210**) with the structural unit As—O—Si ⟨90CZ71⟩. Reaction with oximes gives the iminoxy (**211**), and with disubstituted hydroxylamines the aminoxy derivatives (**212**) ⟨76SRI179⟩. With sodium, lead and ammonium salts of di-*O*-alkyl dithiophosphates the dialkyldithiophosphates (**213**) are obtained ⟨81SRI565, 93PS(80)141⟩. With dibutyltin oxide the chloroarsine (**195**) forms the 1-chloro-3-arsenoxy-tetrabutyldistannoxanes (**214**) ⟨86ICA185⟩. Dialkylphosphonate (dialkyl phosphite) salts (**215**) react with (**195**) yielding the dialkyl 1,3,2-dioxarsinine-2-phosphonates (**216**) ⟨82SRI749⟩.

Surprisingly, almost nothing has been reported on the reactions of 2-halo-1,3,2-dioxarsinanes with Grignard reagents and other organometallic compounds.

The exchange reactions of 2-methyl-1,3,2-dioxarsinane with $AsCl_3$ and AsF_3 to give the 2-chloro- and 2-fluoro-derivatives is undoubtedly the result of ring opening–reclosure reactions, involving exchange of the As atoms ⟨75JOM(101)57⟩.

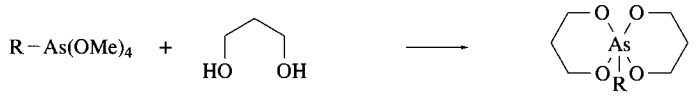
2-Chloro-5,5′-dimethyl-1,3,2-dioxarsinane reacts with 2,2-dimethyl-1,3-propanediol and *N*-chlorodiisopropylamine with formation of the arsorane (**217**) (Equation (34)) ⟨94T6989⟩.



(34)

(**217**)

The exchange reaction of acyclic oxyarsoranes (**218**) with 1,3-propanediols leads to the formation of covalent cyclic oxyarsoranes. With two moles of the 1,3-propanediol the spiroarsoranes (**219**), 2,2′-spiro-bi-(1,3,2λ^5-dioxarsinanes), are formed (Equation (35)), since they are thermodynamically more stable than the monocyclic compounds ⟨73ZOB1937, 75ACS(B)741, 75ZOB1498⟩.

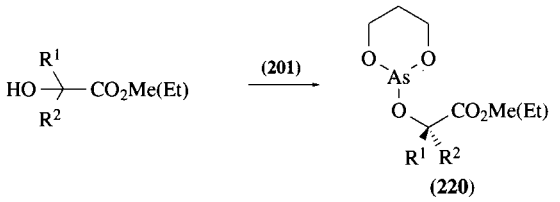


(35)

(**218**) R = OMe, Me, CH_2Ph, Ph (**219**)

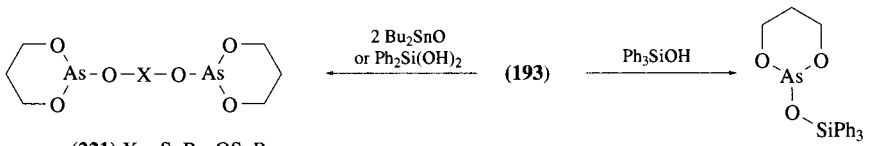
2-Dialkylamino-1,3,2-dioxarsines (e.g. (**201**)) as well as 2,2′-oxybis-1,3,2-dioxarsinanes (**193**) are very often used as starting materials for the synthesis of derivatives of 2-substituted 1,3,2-dioxarsinanes.

2-Dimethylamino-1,3,2-dioxarsinanes react with α-hydroxy-esters to give the dioxarsinanyloxy-carboxylic esters (**220**) (Equation (36)) ⟨89CZ177⟩. The 2,2′-oxybis-1,3,2-dioxarsinanes (**193**) form the 1,3-bis(arsenoxy)-tetrabutyldistannoxanes (**221**) in quantitative yields by the insertion of two moles of dibutyltin oxide into the exocyclic As—O bond ⟨88ICA259⟩. Triphenylsilyloxy- and diphenylsilanedioxy-substituted 1,3,2-dioxarsinanes (**222**) and (**223**) were prepared by treating Ph_3SiOH and $Ph_2Si(OH)_2$ with (**193**) (Scheme 38) ⟨86MI 626-01⟩.



(220) (36)

R^1, R^2 = Me; R^1 = H, R^2 = Me
R^1 = H, R^2 = Ph
R^1, R^2 = *o*-C_6H_4; *p*-C_6H_4



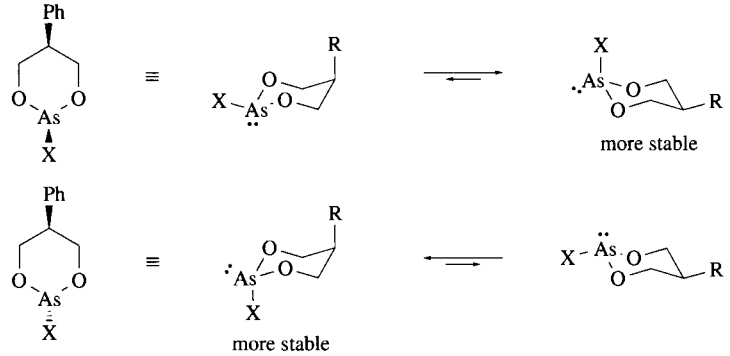
(**221**) X = $SnBu_2OSnBu_2$
(**223**) X = $SiPh_2$

(**222**)

Scheme 38

(iii) Spectroscopy and structure

The ^1H NMR spectra (100 MHz) of a number of 2-chloro-, 2-phenoxy- and 2-methoxy-1,3,2-dioxarsinanes have been studied by Aksnes *et al.* ⟨75ACS(A)376, 75ACS(B)741, 76ACS(A)327, 77ACS(A)845, 77ACS(B)599, 79ACS(A)413, 79ACS(A)753⟩. Because of the configurational stability of tertiary arsines (inversion barrier 25–42 kcal mol^{-1} ⟨70CC999, 71ACR87⟩) substituted 1,3,2-dioxarsinanes exist as *cis* and *trans* isomers, with the substituents X occupying the axial or the equatorial position (Scheme 39).



Scheme 39

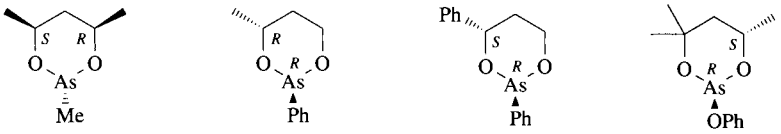
The ^1H NMR spectra of 2-chloro-1,3,2-dioxarsinane, both of its 4,6-dimethyl analogues, and the 4,4,6-trimethyl compound, show the presence of only one isomer. The coupling constant data were consistent with chair conformations. The thermodynamically more stable conformation of each

molecule is probably the chair form with the substituent X in an axial position. Nonequilibrium mixtures of two geometrical isomers were observed for the methoxy compounds. The conformer $(\mathbf{224})_{ax}$ is thermodynamically more stable than $(\mathbf{224})_{eq}$ (Equation (37)).

(37)

$(\mathbf{224})_{ax}$ $(\mathbf{224})_{eq}$

The relative stereochemistries of some thermodynamically stable 1,3,2-dioxarsinanes are presented in structures (**225**)–(**228**) ⟨79ACS(A)413⟩.



(**225**) (**226**) (**227**) (**228**)

The ^{13}C NMR spectra of the 1,3,2-dioxarsinanes (**195**) and (**224**) have been reported ⟨77ACS(A)845⟩.

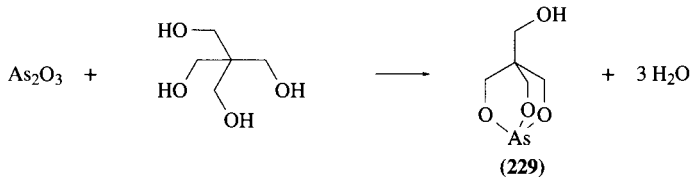
Based on dipole moments and Kerr constants, Arbusov and co-workers showed that the experimental and calculated data on 2-chloro-4-methyl-1,3,2-dioxarsinane are consistent with a chair conformation with axial chlorine and equatorial methyl ⟨74MI 626-02, 75IZV1757⟩.

Variable-temperature NMR measurements on compounds of type (**219**) at −100 °C to 30 °C were interpreted in terms of pseudorotation ⟨75ACS(B)741⟩.

6.26.5.1.2 2,6,7-Trioxa-1-arsabicyclo[2.2.2]octanes

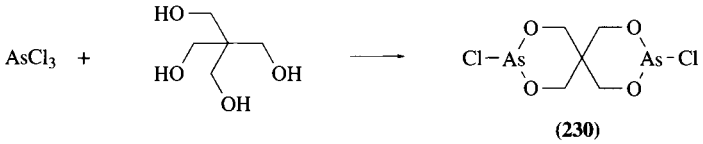
(i) Synthesis

In 1930 Eglund described the reaction of pentaerythritol with As_2O_3. After distillation *in vacuo* he isolated a crystalline compound, m.p. 106–107 °C, for which he proposed the structure (**229**) (Equation (38)) ⟨30JPR191⟩. This formula was supported by the esterification of the CH_2OH group ⟨59JOC1715⟩ (see Section 6.26.5.1.2.ii). By reaction of pentaerythritol with excess of $AsCl_3$ the spiro-compound (**230**) was obtained (Equation (39)) ⟨66IZV1543, 76IZV2707⟩. Later, a very general method for the preparation of 4-substituted 2,6,7-trioxa-1-arsabicyclo[2.2.2]octanes (**231**) was described, namely the reaction of As_2O_3 with $R\text{-}C(CH_2OH)_3$ in toluene, using a Dean–Stark separator to collect the reaction water (Equation (40)) ⟨71USP3621044, 72USP3706836⟩.



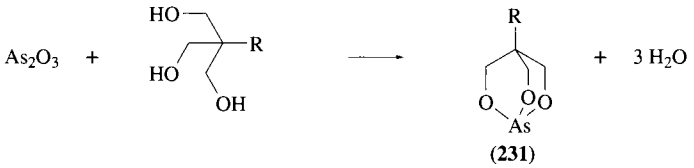
(38)

(**229**)



(39)

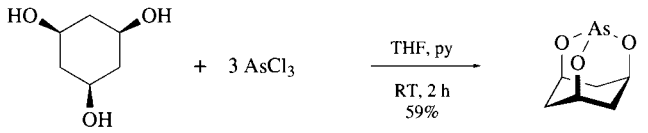
(**230**)



(40)

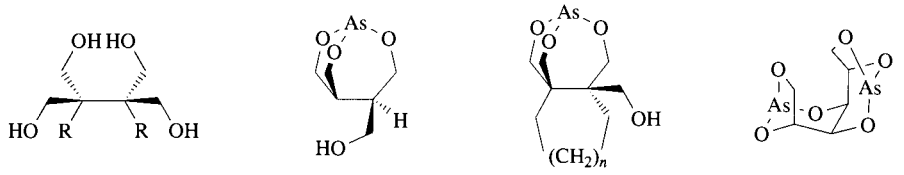
R = NO_2, NH_2, Me, Pr, CH_2OH

The reaction of R-C(CH_2OH)$_3$ with As(NMe_2)$_3$ by cleavage of the As—N bond leads to the bicyclic arsenite esters (**231**; R = CH_2OH, Me) in yields of 75–90% ⟨76ZN(B)307⟩. *cis*-Cyclohexane-1,3,5-triol reacts with $AsCl_3$ in the presence of pyridine to give the 2,8,9-trioxa-1-arsaadamantane (**232**) (Equation (41)). Compound (**232**) is more unstable than most 1,3,2-dioxarsinanes, being immediately hydrolyzed by water ⟨60JOC663, 64IC884, 70JA2702, 84IC3378⟩.



(41)

The tetrahydric alcohols (**233**) react with As(NMe_2)$_3$ in THF yielding the cage compounds (**234**)–(**236**) ⟨90IC4983⟩. In the presence of pyridine, D-mannitol and galactitol react with $AsCl_3$ to give tetracyclic 1,2,4:3,5,6-bis(arsenites), for example (**237**). According to the crystal structures they represent heterocyclic doubly bridged *cis*-decalin ring systems ⟨79CAR(68)C1⟩.



(**233**)
a, R = H
b, RR = $(CH_2)_4$
c, RR = $(CH_2)_5$

(**234**)

(**235**) *n* = 2
(**236**) *n* = 3

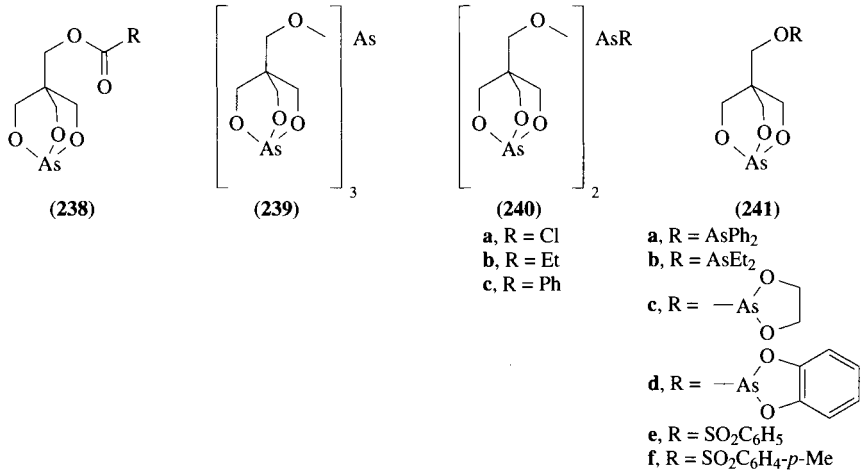
(**237**)

(ii) Reactivity

The 4-hydroxymethyl derivative (**229**) was esterified by reaction with acid chlorides (propionic, butyric, benzoic, 3-nitrobenzoic) in pyridine ⟨59JOC1715⟩. Subsequently, a large number of esters (**238**) were synthesized by the same method because of their potential against insect and plant pests. The following acid residues have been incorporated: R = 2,6-dichlorophenyl, 2,3,6-trichlorophenyl ⟨67USP3351649, 68USP3411895⟩; R = phenylacetic, 4-nitrophenylacetic, chrysanthemic ⟨71USP3621044, 72USP3706836, 74USP3787465⟩; and R = oleic and other saturated fatty acids ⟨66IZV1543, 76MI 626-01⟩. Further, esters of (**229**) with several arsenic acids ⟨66IZV1543, 76IZV2707⟩ and sulfonic acids ⟨74USP3787465⟩ have been described (**239**)–(**241**).

6.26.5.1.3 1,4,2-Dioxarsinanes

Only one derivative of the 1,4,2-dioxarsinane ring system has been described. Heinicke and Tzschach studied the (4 + 2) cycloadditions of 1,3-benzoxaphospholes and 1,3-benzoxarsoles with

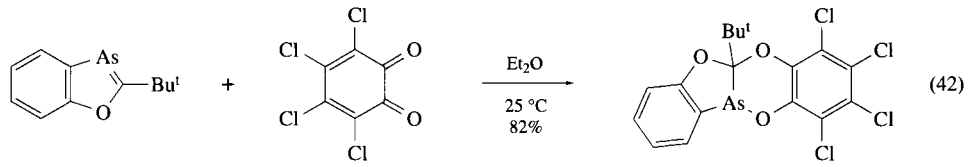


(238) (239) (240) (241)

(240): **a**, R = Cl; **b**, R = Et; **c**, R = Ph

(241): **a**, R = $AsPh_2$; **b**, R = $AsEt_2$; **c**, R = ; **d**, R = ; **e**, R = $SO_2C_6H_5$; **f**, R = $SO_2C_6H_4$-*p*-Me

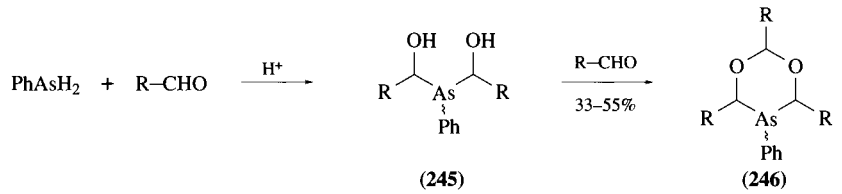
tetrachloro-*o*-benzoquinone (**243**). With 2-*t*-butyl-1,3-benzoxarsole (**242**) the cycloadduct (**244**) was obtained (Equation (42)) ⟨83TL5481⟩. The product is very sensitive to moisture.



(242) (243) (244) (42)

6.26.5.1.4 1,3,5-Dioxarsinanes

The synthesis of 1,3,5-dioxarsinanes goes in the same way as that of the corresponding 1,3,5-dioxaphosphinanes. According to Busse and Irgolic, phenylarsine reacts with aliphatic aldehydes in the presence of hydrochloric acid to give the 1,3,5-dioxarsinanes (**246**). The bishydroxyalkylarsine (**245**) is an intermediate, and the final ring closure is a normal acetalation of the third mole of aldehyde (Scheme 40) ⟨75JOM(93)107⟩. The structure of (**246**) was confirmed by ^{1}H NMR, IR and MS data. The ^{1}H NMR spectrum of (**246a**) was consistent with the chair conformation.



(245) (246)

a, R = Me; **b**, R = Et; **c**, R = Ph

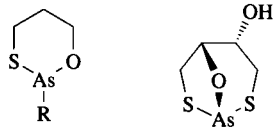
Scheme 40

6.26.5.2 Rings with One Arsenic, One Oxygen and One Sulfur Atom

6.26.5.2.1 1,3,2-Oxathiaarsinanes

The 1,3,2-oxathiarsinane system (**247**) is the only representative of the many possible C_3AsOS rings. Few examples have been described. The reaction of thietane with arsenoxides $(R\text{-}AsO)_n$ is

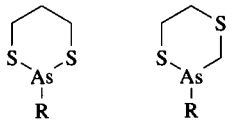
reported to form the 2-substituted derivatives (**247**) ⟨69ZAAC(370)227⟩. Bridged derivatives, for example (**248**), are produced in the reactions between dithioerythritol and dithiothreitol and As_2O_3. The structure of the latter product was determined by x-ray crystallography ⟨72AX(B)1325⟩.



(**247**) (**248**)

6.26.5.3 Rings with One Arsenic and Two Sulfur Atoms

Of the possible isomers of the dithiarsinanes only derivatives of the 1,3,2- (**249**) and the 1,4,2-series (**250**) have been described.

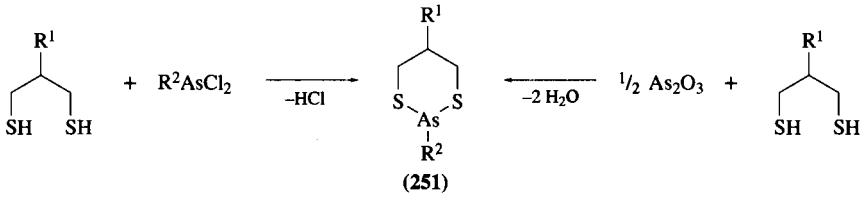


(**249**) (**250**)

6.26.5.3.1 Monocyclic and bridged 1,3,2-dithiarsinanes

(i) Synthesis

The 1,3,2-dithiarsinanes (**251**) have been synthesized by methods analogous to the synthesis of the 1,3,2-dioxarsinanes, namely by reaction of 1,3-dimercaptoalkanes with arsine halides or arsine oxides (Scheme 41) ⟨47JCS592⟩.

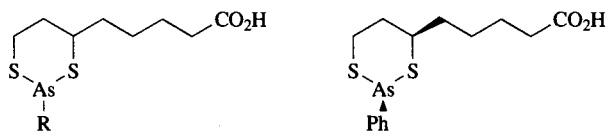


(**251**)

Scheme 41

Most of the few known derivatives of (**251**) were described between 1950 and 1960 in the patent literature, because of their potential as insecticides, acaricides, and nematocides ⟨51BRP655435, 53USP2659723, 56USP2772303, 68JBC(243)716⟩. The 1-phenyl-5-dimethylamino derivative (**251**; $R^1 = NMe_2$, $R^2 = Ph$) was synthesized as a control agent for insect pests ⟨74JAP7428980⟩.

For biological reasons also the reactions of methylarsonic acid with, for example, dithiothreitol (see Section 6.26.5.2.1) and dihydrolipoic acid have been studied. With dihydrolipoic acid the 1,3,2-dithiarsinane (**252a**) was obtained ⟨84MI 626-01⟩. The relative stereochemistry of the phenyldichloroarsine adduct (**252b**) was determined by NMR spectroscopy ⟨89MI 626-01⟩.

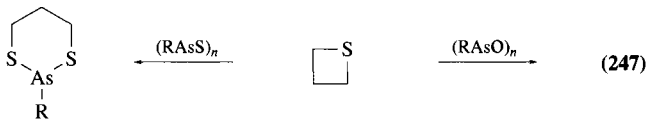


(**252**)
a, R = Me
b, R = Ph

(**252b**)

The benzyl ester of (**252b**) is a suitable derivative for gas chromatography; this method was also used for other dithiols ⟨80JC171⟩.

Rather interesting reactions of thietane (**253**) with arsine sulfides give (**254**) and with arsine oxides give (**247**) (Scheme 42) ⟨69ZAAC(370)227⟩.

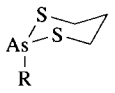


(**254**) (**253**)

Scheme 42

(ii) Spectroscopy and structure

The ^{1}H NMR spectra of (**255a, b**) have been fully analyzed ⟨72ACS(A)4170, 74ACS(A)1175⟩. The ring-torsion angles were calculated from the vicinal coupling constants using the R-value method. The NMR data are consistent with the presence of a dominant chair conformation with an axial position of the substituent R (see also ⟨89MI 626-01⟩).

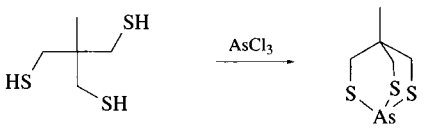


(**255**)

a, R = Ph
b, R = Cl

(iii) 2,6,7-Trithia-1-arsabicyclo[2.2.2]octanes

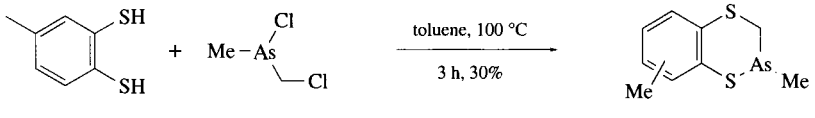
In 1968 Verkade and co-workers described what is to our knowledge the only 2,6,7-trithia-1-arsabicyclo[2.2.2]octane (**257**), by reaction of 2-(thiomethyl)-2-methyl-1,3-propanedithiol (**256**) with $AsCl_3$ (Equation (43)) ⟨68IC1469⟩.



(**256**) (**257**) (43)

6.26.5.3.2 1,4,2-Dithiarsinines

Only one derivative of this ring system has been described. Chloro(chloromethyl)-methylarsine (**259**) reacts with toluene-3,4-dithiol (**258**) in toluene to give a mixture of 2,6- and 2,7-dimethyl-tetrahydro-1,4,2-benzodithiaarsinines (**260**) (Equation (44)) ⟨73CB2742⟩.

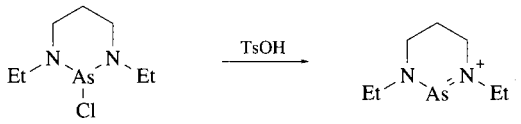


(**258**) (**259**) (**260**) (44)

6.26.5.4 Rings with One Arsenic, One Oxygen and One Nitrogen, or One Arsenic and Two Nitrogen Atoms

6.26.5.4.1 1,3,2-Diazarsinanes

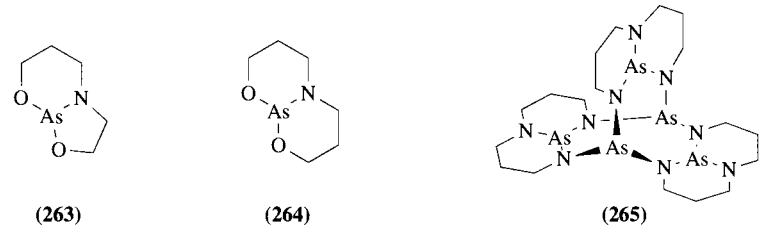
Only one monocyclic derivative of this ring system, the 2-chloro-1,3-diethyl-1,3,2-diazarsinane (**261**) has been described in the literature, formed by reaction of N,N′-diethyl-1,3-diaminopropane with $AsCl_3$. In trifluoromethanesulfonic acid the cyclic arsenium cations (**262**) are formed (Equation (45)) ⟨92HAC157⟩.



(261) (262) (45)

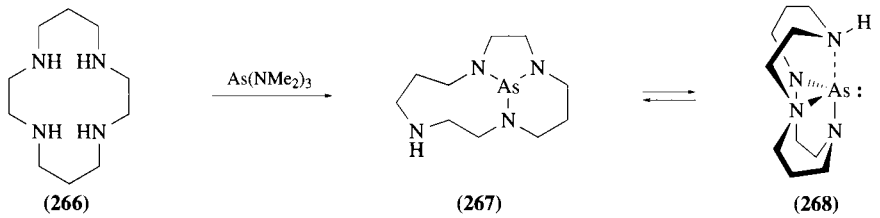
6.26.5.4.2 Polycyclic 1,3,2-oxazarsinanes and 1,3,2-diazarsinanes

Sommer *et al.* published the synthesis of the polycyclic 1,3,2-oxazarsinanes (**263**) and (**264**) by the reaction of 3-hydroxypropyl-2-hydroxyethylamine and bis(3-hydroxypropyl)amine with $As(NMe_2)_3$. With bis(3-aminopropyl)amine a more complex product (**265**) was formed, with five arsenic atoms to three of the triamine ⟨70ZAAC(379)48⟩.



(263) (264) (265)

The reaction of the 14-membered tetraaza-macrocycle (**266**) with $As(NMe_2)_3$ yields (**267**), which forms a mobile equilibrium in which the remaining NH group forms a transannular As—N bond. The stereochemistry at As can be described as a distorted trigonal bipyramid with two nitrogens and the As lone pair of electrons at the equatorial positions and two nitrogens at the axial sites (**268**) (Scheme 43) ⟨92OM3748⟩.

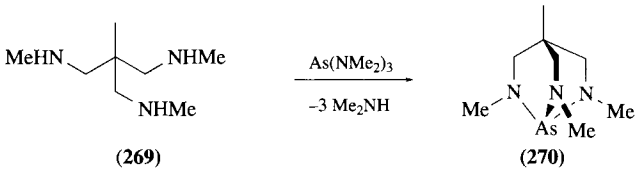


(266) (267) (268)

Scheme 43

6.26.5.4.3 2,6,7-Triaza-1-arsabicyclo[2.2.2]octanes

1,1,1-Tris(methylaminomethyl)ethane (**269**) and $As(NMe_2)_3$ react at elevated temperature to give the bicyclo[2.2.2]octane derivative (**270**) (Equation (46)) ⟨67IC173⟩.



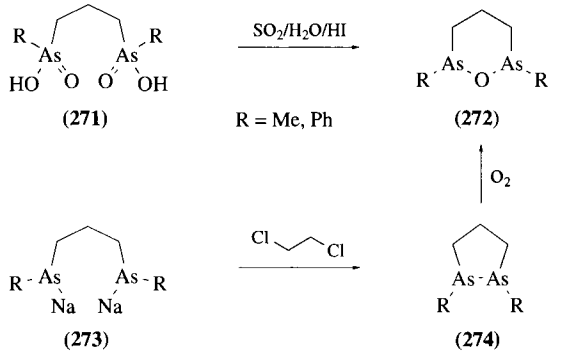
(269) (270) (46)

6.26.5.5 Rings with Two Arsenic Atoms and One Oxygen or Sulfur Atom

6.26.5.5.1 1,2,6-Oxadiarsinanes and trioxatriarsaadamantanes

(i) Synthesis

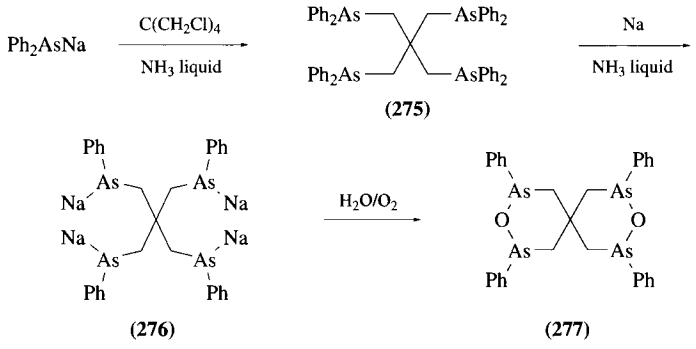
The 1,3-propanebisarsinous acids (**271**) can be reduced by SO_2 with traces of HI and H_2O in ethanol, yielding the propanebisarsenoxides (1,2,6-oxadiarsinanes) (**272**). Alternatively, the diarsenides (**273**) with 1,2-dichloroethane give the 1,2-diarsacyclopentanes (**274**), which are oxidized by air to the 1,2,6-oxadiarsinanes (**272**) (Scheme 44) ⟨70ZAAC(377)278⟩.



(271) (272) (273) (274)

Scheme 44

Sodium diphenylarsenide in liquid ammonia reacts with tetra(chloromethyl)methane to form tetrakis(diphenylarsinomethyl)methane (**275**). The tetra-sodium arsenide (**276**), obtained by cleavage of (**275**) with sodium in liquid ammonia, on hydrolysis and oxidation by air yields the spiro-system (**277**) (Scheme 45) ⟨70ZAAC(378)303⟩.

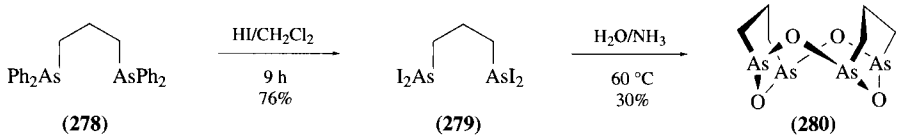


(275) (276) (277)

Scheme 45

Treatment of the diarsine (**278**) with HI gives the tetraiodide (**279**), which with aqueous ammonia forms the tricyclic compound (**280**) with 1,2,6-oxadiarsinane structural units (Scheme 46). The structure of (**280**) was proved by x-ray analysis ⟨86JCS(D)997⟩.

In a series of papers Ellermann and co-workers described As-cage compounds with hetero-noradamantane and hetero-adamantane structures ⟨74AG(E)601, 78AG(E)135, 81ZN(B)1532⟩. 1,1,1-Tris(diiodoarsinomethyl)ethane (**281**) ⟨78ZN(B)603⟩ on treatment with H_2O or H_2S results in the formation of the heteroadamantanes (**282**) and (**283**) (Scheme 47) ⟨78ICA411, 79ZN(B)975, 80ZN(B)1514,

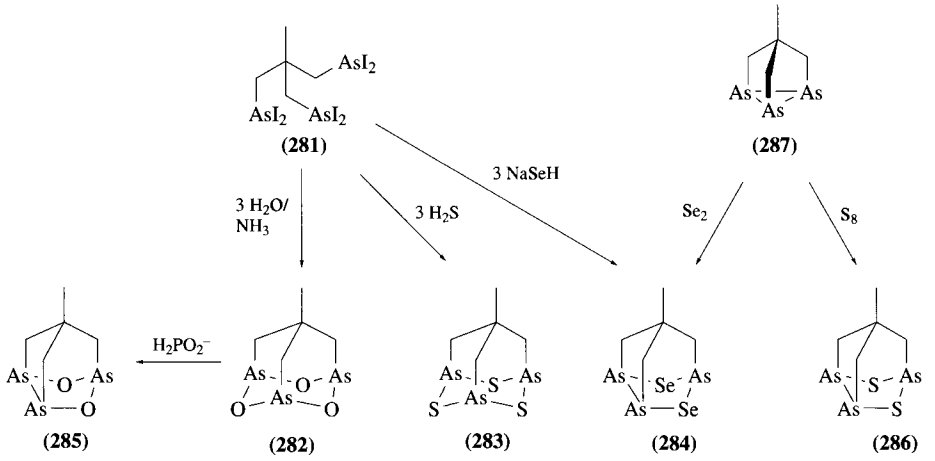


(278) (279) (280)

Scheme 46

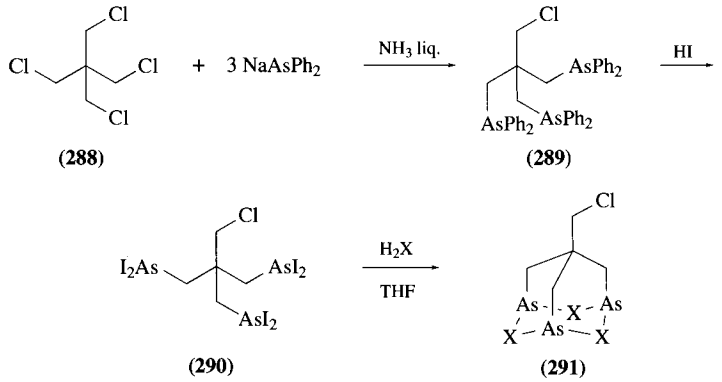
81JOM(215)165, 82ZN(B)73〉. The structure of the trithiatriarsaadamantane (**283**) was confirmed by an x-ray analysis 〈79ZN(B)975〉.

With sodium selenide the hexaiodide (**281**) forms the noradamantane (**284**). The structure of (**284**) was also confirmed by x-ray 〈80ZN(B)1514, 84CB2675, 84ZN(B)1344〉. The reduction of (**282**) with alkaline hypophosphite leads to the noradamantane (**285**) 〈84CB2675〉. The noradamantanes (**284**) and (**286**) result from melting the 4-methyl-1,2,6-triarsatricyclo[2.2.1.$0^{2,6}$]heptane (**287**) with elemental sulfur or selenium (Scheme 47) 〈84CB2675〉.



Scheme 47

Similar chemistry starting out from tetrakis(chloromethyl)methane (**288**) was published by Ellermann and Brehm. Treatment with $NaAsPh_2$ in liquid ammonia gives the tertiary arsine (**289**). Reaction of (**289**) with gaseous HI forms the trisdiiodoarsane (**290**). The hetero-adamantanes (**291a, b**) are obtained on solvolysis of (**290**) with H_2O/NH_3 and H_2S (Scheme 48) 〈85CB4794〉.

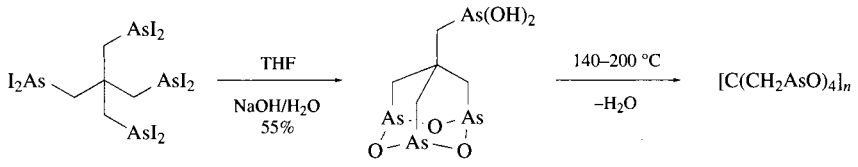


a, X = O 91.5%
b, X = S, 52%

Scheme 48

Tetrakis(diiodoarsinomethyl)methane (**292**) 〈86ZN(B)863〉 on hydrolysis gives the arsonous acid (**293**) of the trioxatriarsaadamantane 〈87JOM(336)323〉. The crystal structure of the deuterated derivative (-As(OD)$_2$) was solved by x-ray diffraction analysis. There is evidence for the existence of two

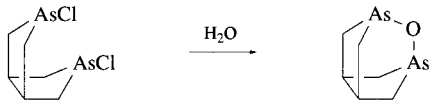
different intermolecular AsOD···O bonding systems. At temperatures between 140–200 °C (**293**) condenses to give an insoluble polymer (Scheme 49).



(**292**) (**293**)

Scheme 49

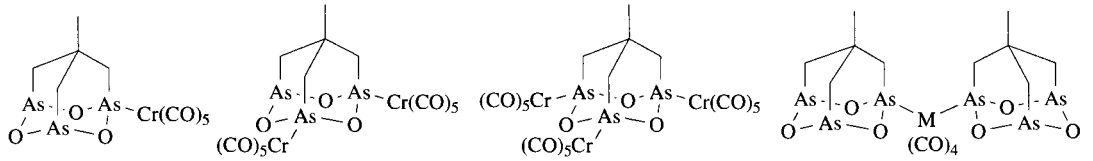
The noradamantane (**295**) was postulated as a product of the hydrolysis of 3,7-dichlorodiarsabicyclo[3.3.0]octane (**294**) (Equation (47)) ⟨70ZAAC(378)303, 71ZAAC(383)136⟩; the structure was not proven, however.



(**294**) (**295**) (47)

(ii) Reactivity

The adamantane (**282**) reacts on UV irradiation with $Cr(CO)_6$ depending on the stoichiometry to give the complexes (**296**)–(**298**), where (**282**) behaves as a mono-, di-, and tri-dentate ligand ⟨81JOM(222)105⟩. With $Mo(CO)_6$ and $W(CO)_6$ the binuclear tetracarbonyl complexes (**299**) can be isolated. The structure assignment was based mainly on the vibrational spectra.



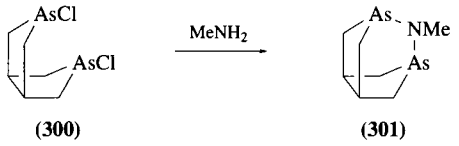
(**296**) (**297**) (**298**) (**299**)

6.26.5.6 Six-membered Rings with Two Arsenic Atoms and One Nitrogen Atom

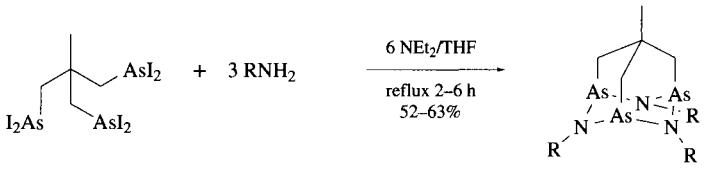
6.26.5.6.1 1,2,6-Azadiarsinanes and triazatriarsaadamantanes

(i) Synthesis

The first 1,2,6-azadiarsinane described in the literature was the cage compound 9-methyl-9-aza-1,5-diarsatricyclo[3.3.1.$0^{3,7}$]nonane (**301**), obtained by the reaction of methylamine on (**300**) (Equation (48)). However, (**301**) was not fully characterized ⟨71ZAAC(383)136⟩. The reaction of 1,1,1-tris(diiodoarsinomethyl)ethane (**281**) ⟨78ZN(B)603⟩ with aliphatic and aromatic primary amines in the presence of NEt_3 gives the adamantane-cage compounds (**302**) (Equation (49)), which can be considered as 1,2,6-azadiarsinane derivatives. The adamantane (**302**; R = 4-MeC_6H_4) can be prepared also by transamination of (**302**; R = Me) with *p*-toluidine. All the adamantanes were characterized by MS, and IR, Raman and ^{1}H NMR spectroscopy ⟨79ZN(B)975, 81JOM(215)165⟩.



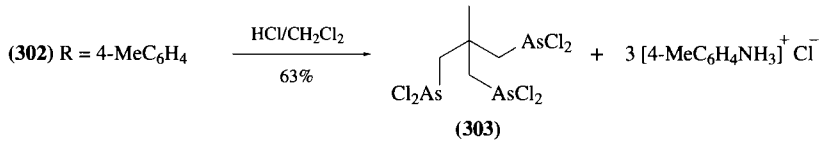
(300) (301) (48)



(281) R = Pr^i, Bu^n, Ph, 4-MeC$_6$H$_4$, TMS (302) (49)

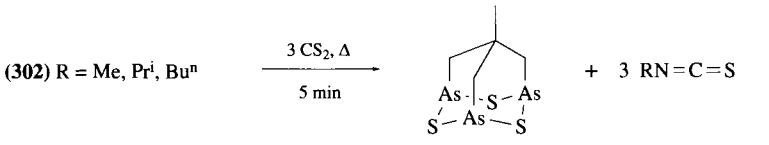
(ii) Reactivity

The heteroadamantane (**302**; R = 4-MeC$_6$H$_4$) reacts with dry, gaseous HCl by cleavage of the As—N bonds and formation of 1,1,1-tris(dichloroarsinomethyl)ethane (**303**) (Equation (50)) ⟨82ZN(B)73⟩.



(303) (50)

The alkyl-substituted adamantanes (**302**; R = alkyl) react with CS_2 under very mild conditions, yielding the 2,4,9-trithia-1,3,5-triarsaadamantane (**283**) (Equation (51)) ⟨81JOM(218)C45⟩.



(283) (51)

6.26.5.7 Rings with Three Arsenic Atoms

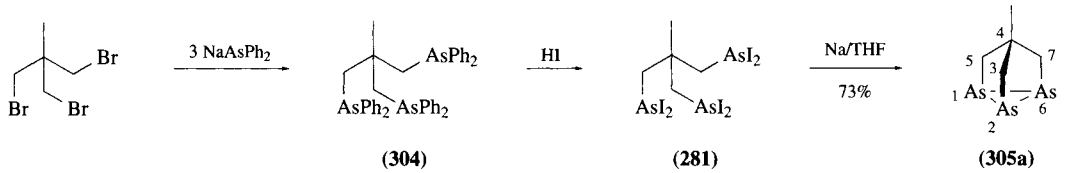
This section is devoted mainly to the synthesis and chemistry of the triarsanortricyclanes, which may be regarded as doubly bridged (As(1)–As(3) and As(2)–C(5)) 1,2,3-triarsinanes. The corresponding compounds with other elements from the same group are included in the discussion where appropriate.

6.26.5.7.1 1,2,6-Triarsatricyclo[2.2.1.0^{2,6}]heptanes (Triarsanortricyclanes)

(i) Synthesis

In 1974 Ellermann and Schössner described the first synthesis of a 1,2,6-triarsatricyclo[2.2.1.0^{2,6}]-heptane. 1,1,1-Tris(diphenylarsinomethyl)ethane (**304**), prepared by the reaction of 1,1,1-tris-(bromomethyl)ethane on sodium diphenylarsenide, can be transformed into the 1,1,1-tris(diiodo-

arsinomethyl)ethane (**281**) by cleavage of the As—C bonds with gaseous HI. Treatment of (**281**) in THF with metallic sodium yields (**305a**) as colorless crystals, m.p. 159 °C (Scheme 50) ⟨74AG(E)601⟩.

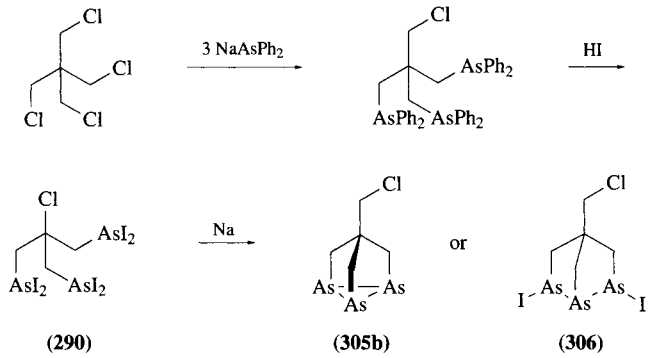


(304) (281) (305a)

Scheme 50

The structure of (**305a**) was confirmed by an x-ray analysis ⟨78AG(E)135⟩. The As—As distances in the three-membered ring are nearly equal (240.5–242.2 pm) and practically identical with the values in As_4.

The 4-chloromethyl derivative (**305b**) was prepared very similarly. 2-Chloro-1,1,1-tris(diiodoarsinomethyl)ethane (**290**) when reduced by sodium in THF under mild conditions yielded the bicyclic compound (**306**), while reduction in boiling THF formed the chloromethyl-substituted nortricyclane (**305b**) (Scheme 51) ⟨85CB4794⟩.

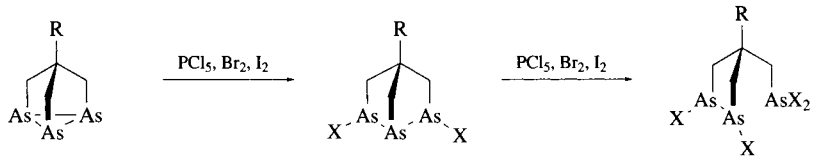


(290) (305b) (306)

Scheme 51

(ii) Reactivity

The triarsanortricyclanes (**305**) react with PCl_5, Br_2, I_2 by cleavage of one As—As bond to give the 2,6-dihalogeno-1,2,6-triarsabicyclo[2.2.1]heptanes (**306**). With excess of halogen the bicyclic ring system reacts further by halogenolysis and formation of the 1,2-diarsolane derivatives (**307**) (Scheme 52) ⟨85CB4794, 86ZAAC(539)50⟩.



(305) (306) (307)

(306) X = Cl ⟷ (305) + (307) X = Cl

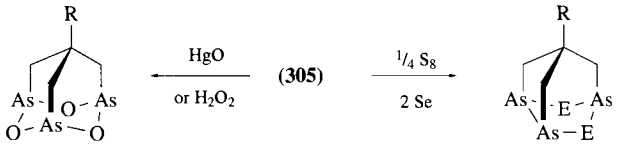
Scheme 52

In $CDCl_3$ or CS_2 (**306**; X = Cl) disproportionates, leading to an equilibrium mixture of (**305**) and (**307**).

The most interesting reactions of (**305**) are the thermal insertion reactions of S_8 and Se_2 into the As—As bonds of the As_3 rings, and the formation of transition metal complexes.

The noradamantanes (**308**) result from heating of (**305**) with elemental sulfur or selenium in a

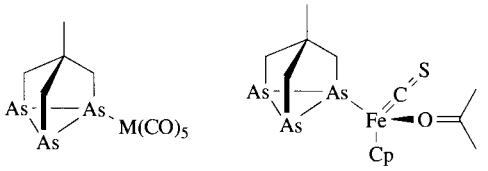
molar ratio of 1 : 2. Oxidation of (**305**) with HgO or aqueous H_2O_2 forms the heteroadamantane (**309**), rather than (**308**; E = O) (Scheme 53) ⟨84CB2675⟩.



(**309**) (**308**) E = S, Se

Scheme 53

The triarsanortricyclane (**305a**) reacts with equimolar amounts of $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$ on ultraviolet irradiation to give the yellow complexes (**310**; **a**, M = Cr, 67%; **b**, M = Mo, 40%; **c**, M = W, 72%), in which the cyclotriarsine is behaving as a monodentate ligand. The crystal structure of (**310a**) was determined by x-ray crystallography ⟨76JOM(118)C69, 78ZN(B)1386, 79JOM(172)39⟩.



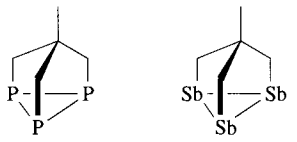
(**310**) (**311**)

Irradiation of (**305a**) with $M(CO)_6$ (M = Cr, Mo, W) in a molar ratio of 1 : 2 yields microcrystalline complexes $[(\mathbf{305a})_2 \cdot M(CO)_4]_n$; M = Cr, W, and $[(\mathbf{305a})_3 \cdot Mo(CO)_4]_n$, $n > 2$, which are insoluble in all organic solvents. Probably the complexes are polymeric. The structures were discussed on the basis of their mass, infrared, far infrared and Raman spectra.

Irradiation of $[\eta^5\text{-}C_5H_5)Fe(CO)_2(CS)][PF_6]$ with (**305a**) in acetone yields the iron complex (**311**) ⟨81JOM(213)C4⟩. With $Ru_3(CO)_{12}$ the cyclotriarsine (**305a**) reacts to give the presumably polymeric $[Ru(CO)_4 \cdot (\mathbf{305a})]_n$. With $Os_3(CO)_{11} \cdot MeCN$ (**305a**) forms the complex $[Os_6(CO)_{21} \cdot (\mathbf{305a})]$, and with $Co_2(CO)_8$ it yields $[Co_2(CO)_6 \cdot (\mathbf{305a})]_n$. $Pt(PPh_3)_3$ reacts with (**305a**) to give $[Pt(PPh_3)(\mathbf{305a})]_2 \cdot THF$ ⟨82ZAAC(485)36⟩.

(iii) Spectroscopy and structure

The He(I) photoelectron spectra of the cage compounds (**305a**), (**312**) and (**313**) ⟨82AG(E)375, 84AG(E)805⟩ have been recorded ⟨85IC4020⟩. The assignment of the first five bands in the PE spectra was based on model calculations (MINDO/3), correlation with related species, and a band shape analysis. The highest occupied MOs of all three nortricyclanes are the E and A_1 linear combinations of the lone pairs centered at the As_3, P_3, and Sb_3 units.



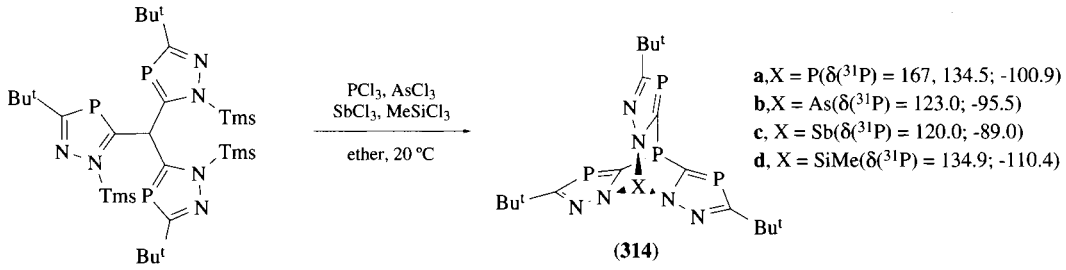
(**312**) (**313**)

6.26.6 SIX-MEMBERED RINGS WITH FOUR HETEROATOMS

6.26.6.1 Rings with Arsenic and Phosphorus, Antimony or Nitrogen Atoms

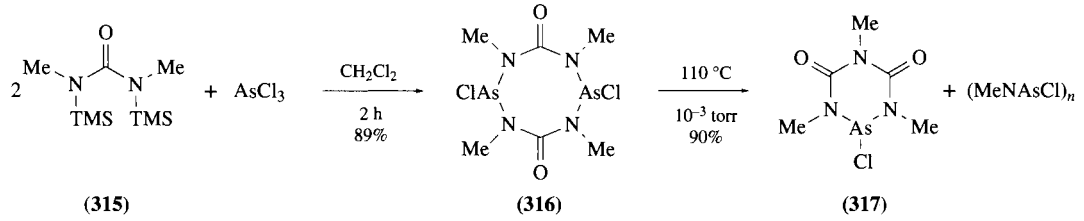
6.26.6.1.1 1,3,5,2-Diazaphosphaarsinines

The hetero-substituted tris(diazaphosphole) triptycene derivatives with bridgehead phosphorus, arsenic, antimony and silicon (**314a–d**) were synthesized as outlined in Scheme 54. The products were characterized by NMR data; the ^{31}P chemical shifts are reported in Scheme 54 ⟨88TL925⟩.



Scheme 54

An approach to a 1,3,5,2-triazarsinane starts from the reaction of the N,N′-bis(trimethylsilyl)urea (**315**) with $AsCl_3$, which forms the eight-membered heterocycle (**316**), the structure of which was established by x-ray. Thermolysis of (**316**) at 140–150 °C yields the crystalline 2-chloro-1,3,5-trimethyl-1,3,5,2-triazarsinane-4,6-dione (**317**) (Scheme 55) ⟨80CB3821⟩. Compound (**317**) can also be obtained by reaction of N,N′,N″-trimethyl-N,N″-bistrimethylsilylbiuret with $AsCl_3$ ⟨78ZN(B)756⟩.

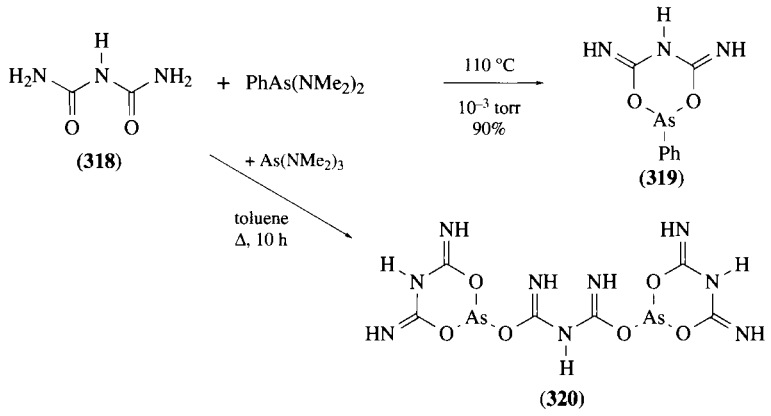


Scheme 55

6.26.6.2 Rings with Arsenic, Oxygen and Nitrogen Atoms

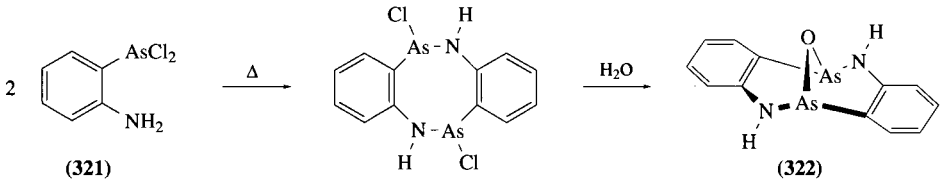
6.26.6.2.1 1,3,5,2-Dioxazarsinanes and 1,3,2,6-oxazadiarsinanes

The transamidation reaction of biuret (**318**) with bis(dimethylamino)phenylarsine produces the 4,6-diimino-2-phenyl-1,3,5,2-dioxazaarsinane (**319**). The related compound (**320**) is formed using trisdimethylaminoarsine (Scheme 56) ⟨70ZAAC(378)310⟩.



Scheme 56

The 5*H*,11*H*-6,12-epoxydibenzo[*c*,*g*][1,5,2,6]diazadiarsocine (**322**) can be considered as a derivative of tetrahydro-1,3,2,6-oxazadiarsinine. It is formed by the thermal dimerization of *o*-aminophenyldichloroarsine (**321**) followed by hydrolysis of the As—Cl groups (Scheme 57) ⟨70JPR751⟩.



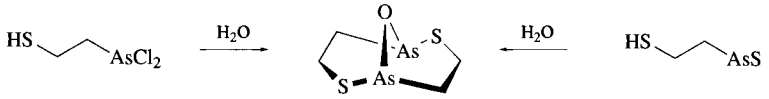
(321) (322)

Scheme 57

6.26.6.3 Rings with Arsenic, and Phosphorus, Oxygen and/or Sulfur Atoms

6.26.6.3.1 2,6,9-Trioxa- (2,6,9-trithia-, 9,2,6-oxadithia-)1,5-diarsabicyclo[2.2.1]nonanes

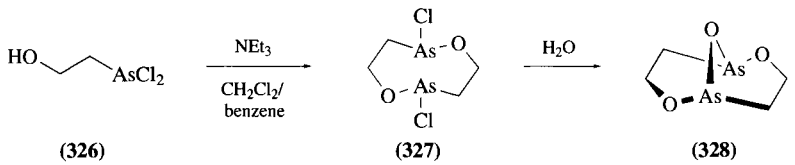
Hydrolysis of 2-mercaptoethyldichloroarsine (**323**) or 2-mercaptoethylarsine sulfide (**324**) with dilute aqueous ammonia formed a colorless product which was assigned the 9-oxa-2,6-dithia-1,5-diarsabicyclo[3.3.1]nonane structure (**325**) (Scheme 58).



(323) (325) (324)

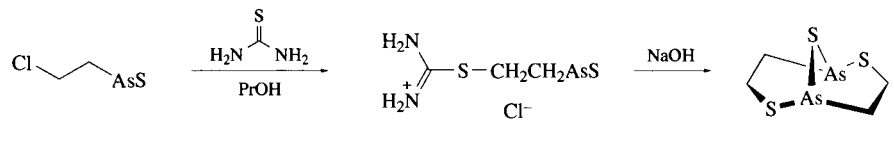
Scheme 58

Elimination of HCl from 2-hydroxyethyldichloroarsine (**326**) using triethylamine yielded the eight-membered intermediate (**327**) which with water formed the 2,6,9-trioxa derivative (**328**) (Scheme 59). The thiouronium salt (**330**), obtained by reaction of chloroethylarsine sulfide (**329**) with thiourea, on treatment with dilute sodium hydroxide is decomposed to form the 2,6,9-trithia-derivative (**325**) (Scheme 60) ⟨70ZAAC(377)128, 70ZAAC(377)273⟩. An alternative approach to (**325**) starts out from the chloroethyldichloroarsine via the isothiourea and subsequent hydrolysis ⟨70ZAAC(377)128⟩.



(326) (327) (328)

Scheme 59



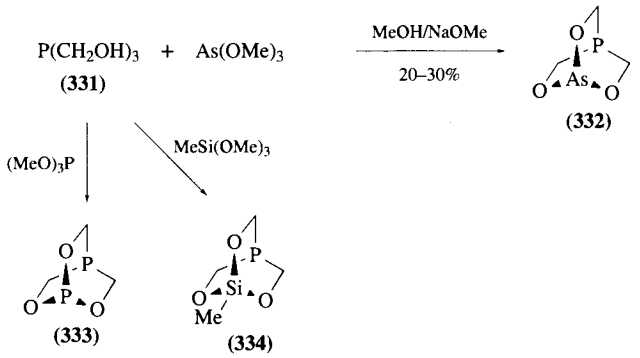
(329) (330) (325)

Scheme 60

6.26.6.3.2 1,3,5,2-Dioxaphosphaarsinanes

Verkade and co-workers reported the formation of 2,6,7-trioxa-4-phospha-1-arsabicyclo[2.2.2]-octane (**332**) by the transesterification of trimethyl arsenite with trishydroxymethylphosphine (**331**) (Scheme 61). Using $P(OMe)_3$ and $MeSi(OMe)_3$ the corresponding 1,4-diphospha- and 4-phospha-1-sila-derivatives (**333**) (30% yield) and (**334**) (42% yield) were obtained ⟨70JOC2310⟩.

Nickel carbonyl complexes of (**332**) and (**334**) [$NiL(CO)_3$; $NiL_2(CO)_2$] have been prepared ⟨73MI 626-03⟩.



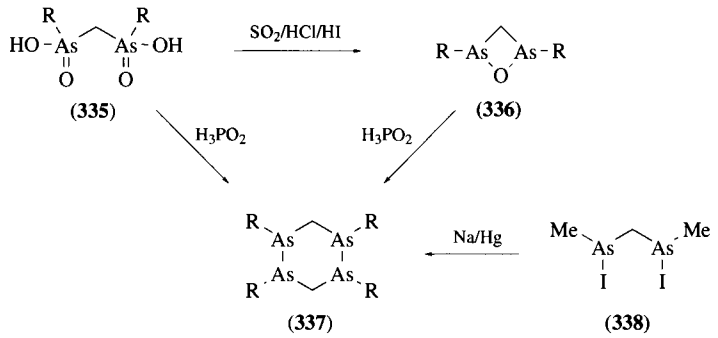
Scheme 61

6.26.6.4 Rings with Four Arsenic Atoms

6.26.6.4.1 1,2,4,5-Tetraarsinanes

The methylene-bis-arsinous acids (**335**) are reduced to the 1,2,4-oxadiarsetanes (**336**) by SO_2/HCl/HI. Reduction of either (**335**) or (**336**) with hypophosphorous acid provides a route to the 1,2,4,5-tetrarsinane system (**337**) (Scheme 62) ⟨70ZAAC(377)278⟩.

The tetramethyl derivative (**337**; R = Me) was also obtained by treatment of the diiodide (**338**) with sodium amalgam ⟨75ZAAC(412)202⟩.



R = Me, Ph

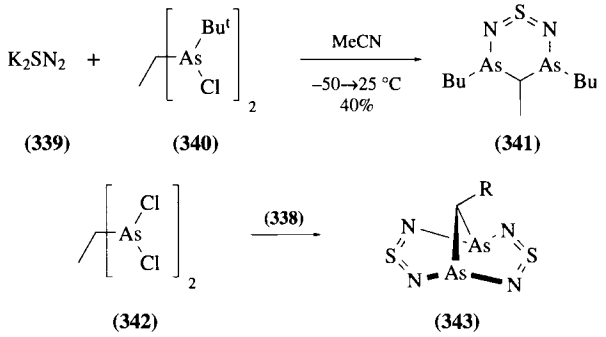
Scheme 62

6.26.7 SIX-MEMBERED RINGS WITH FIVE HETEROATOMS

6.26.7.1 Rings with Two Arsenic, One Sulfur and Two Nitrogen Atoms

6.26.7.1.1 Cyclic sulfurdiimides

The reaction of the bifunctional bis(chloroarsines) (**340**) and (**342**) with the dipotassium salt of sulfur diimide (**339**) ⟨82AG(E)633⟩ leads to rings (**341**) and cages (**343**) containing arsino-substituted sulfur diimide units (Scheme 63) ⟨87ZN(B)118⟩.

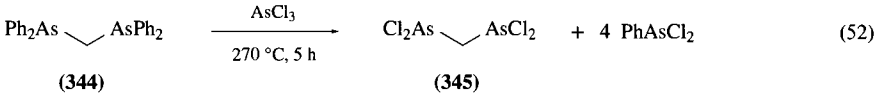


Scheme 63

6.26.7.2 Rings with Three Arsenic and Two Oxygen, Sulfur or Nitrogen Atoms

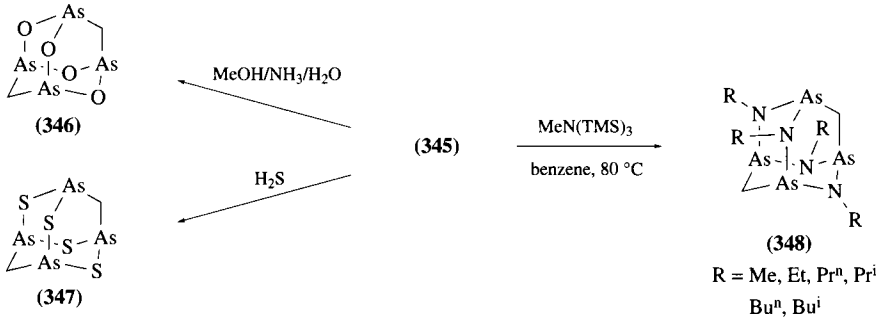
6.26.7.2.1 1,3-Dioxa-, 1,3-dithia, 1,3-diaza-2,4,6-triarsinanes with adamantane structures

Bis-diphenylarsino-methane (**344**) reacts with $AsCl_3$ to give the methane-bisdichloroarsine (**345**) (Equation (52)), which is the starting point for the synthesis of all the arsaadamantanes described here ⟨49CB152, 70ZAAC(377)120⟩.



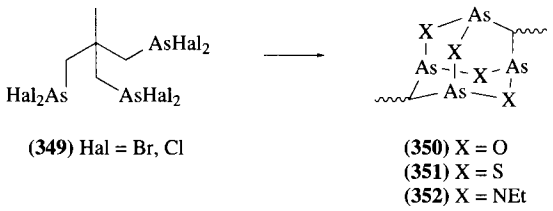
(52)

Hydrolysis of (**345**) yields a colorless, sublimable compound $(CH_2)_2As_4O_4$ which has the adamantane structure (**346**). Reaction with H_2S yields (**347**) which is insoluble in all common organic solvents, and so no structure proof has yet been possible. With methylamine or methyl-(bistrimethylsilyl)amine (**345**) reacts to give the 2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5,7-tetra-arsaadamantane (**348**; R = Me) (Scheme 64) ⟨70ZAAC(377)120⟩. Several other *N*-substituted derivatives of (**348**) have been described ⟨75JOM(94)393⟩.



Scheme 64

The *C*-methyl derivatives (**350**) and (**351**) have been synthesized by hydrolysis and thiolysis of ethylidene bis(dibromoarsine) (**349**) (Equation (53)). The adamantane (**350**) was also synthesized simply by heating potassium arsenite with propionic acid in propionic anhydride ⟨69ZAAC(370)31⟩. The tetra-*N*-ethyl compound (**352**) was obtained from (**349**; Hal = Cl) by the same method as described for the synthesis of (**348**).



(53)

The crystal and molecular structure of the 2,4,6,8-tetraoxa-1,3,5,7-tetraarsaadamantane (**346**) has been determined ⟨80ICA67⟩. It can be considered as being structurally related to As_4O_6, in which the four arsenic atoms are at the corners of a tetrahedron, with the six oxygen atoms forming an octahedron.

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6.27
Six-membered Rings With Two or More Heteroatoms with at least One Silicon to Lead

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6.27.1 INTRODUCTION

A search of the literature since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) revealed that there are about 250 different ring systems that come under the title of this chapter. A relatively small number were considered in the first edition and there is no

equivalent chapter. Two reviews of heterocyclic rings containing silicon or other unusual heteroatoms have appeared elsewhere ⟨B-82COMC-I(2)205, B-89MI 627-01⟩. It is clearly 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 will be 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 of them 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 only be found in the various tables in Sections 6.27.2.1 and 6.27.3.1. 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.

6.27.2 MONOCYCLIC COMPOUNDS

This chapter has been split into two main sections. The first deals with monocyclic compounds and the second deals with compounds containing more than one ring, mainly benzo-fused ring systems.

6.27.2.1 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 in Table 1, to five in Table 4. In many cases the only references to a ring in this chapter will be found in these tables.

6.27.2.2 Theoretical Studies

All three of the isomers of disilabenzene have been studied by *ab initio* methods. Using the 3-21G/STO-2G level of theory all of the isomers show some delocalization with the 1,3-isomer being the most stable ⟨84JOM(271)369⟩. Further *ab initio* calculations on the 1,4-isomer show that the disilabenzene, its Dewar form, and one of its silylene isomers all have similar thermodynamic stabilities ⟨85JOM(289)51⟩. Calculations on aromaticity in disilabenzenes and other group 14 containing heterocycles are also discussed in a review ⟨93AHC(56)303⟩.

MM2 calculations on 1,2-dimethyl-1,2-disilacyclohexane show that the geometry of the ring is very different from that of cyclohexane and that the lowest energy conformation has the two methyl group *trans* to each other and in axial positions, the ring having a twist chair conformation with endocyclic angles ranging from 103–116° ⟨89MI 627-02⟩. MNDO calculations on 1,3-dioxa-2-silacyclohexanes show that they have similar chair conformations to 1,3-dioxanes ⟨88JGU94⟩.

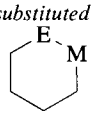
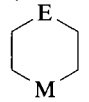
6.27.2.3 Experimental Structural Methods

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 the relatively small number of compounds that have been fully structurally characterized, mainly by x-ray crystallography.

6.27.2.3.1 Rings containing two heteroatoms

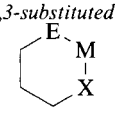
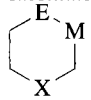
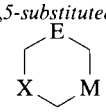
The x-ray structure of (**1**) shows that the heterocyclic ring is nearly planar (only the CPh carbon deviating from the plane of the other atoms in the ring) and that the angles at the ring oxygen and the ring silicon are both opened from their usual values to 145.62° and 126.99° respectively, presumably because of the repulsions between the sterically demanding substituents ⟨91OM2758⟩. The ring system (**2**) also shows significant deviations from normal values for bond angles and lengths, again presumably due to the bulky groups present. The exocyclic angles are relatively

Table 1 Rings containing two heteroatoms.[a]

Ring type	*Ref.*
1,2-substituted rings 	
E = N, M = Si	83NJC645
E = P, M = Si, hex-4-ene	91CB93
E = O, M = Si	90CL1055, 90JA8175, 90TL1531, 90TL6059, 92JOM(436)277, 93HCA804
hex-3-ene	85T3257, 87OM2590, 88T3997
hex-5-ene	91JOC91, 91OM2752
hexa-3,5-diene	89JOM(364)301, 90JA3642
E = S, M = Si	84NJC279
E = Se, M = Si, hex-4-ene	89AG(E)1518
E = Si, M = Si	83JOC5228, 92JA6596, 92JOM(439)115, 93JOM(452)41
hex-4-ene	83OM1484
hexa-3,5-diene	92JA6596
E = O, M = Ge	93CL1751
hex-3-ene	93CL1751
E = S, M = Ge, hex-4-ene	93JA8855, 95H(40)127
E = Ge, M = Ge	92JOM(439)115
hex-4-ene	89CC770, 92OM2752
E = S, M = Sn, hex-4-ene	93OM2573
hexa-3,5-diene	93OM2573
1,3-substituted rings	
E = P, M = Si	82PS(13)153
E = O, M = Si	92TL6743
hex-5-ene	91OM2752, 91OM2758
E = S, M = Si	83JOM(243)271, 93TL3889
E = Si, M = Si	85JOM(292)189, 87TL1293, 90JA6601, 92OM1626, 94ZN(B)1818
disilabenzene	84JOM(271)369, 88CPL(151)249
E = N, M = Ge	88JOM(346)1
E = Sn, M = Sn	85BSB299
1,4-substituted rings 	
E = N, M = Si	82ZN(B)657
biological activity	88AF1075
E = P, M = Si	87IZV451
E = O, M = Si	92JOM(427)289
E = S, M = Si	83JOM(243)271, 85JOM(288)27
E = M = Si	89JOM(377)C45, 91CB2033, 93CL985, 93JA6625
hex-2-ene	93CL985
hexa-2,5-diene	83OM974, 92OM602, 93TL6541, 95OM530
disilabenzene	87JOM(325)105
calculations	84JOM(271)369, 85JOM(289)51
E = Pt, M = Si, hexa-2,5-diene	92OM3227
E = Si, M = Sn, hexa-2,5-diene	82TL543, 90CC428
E = Ge, M = Ge, hex-2-ene	84JOM(267)93, 90ICA141, 92ICA461
hexa-2,5-diene	88TL5245, 91SL431, 92OM2069
E = P, M = Sn	89BSB1, 93OM4097
E = Sn, M = Sn	88AG(E)404, 89JOM(377)C45
hexa-2,5-diene	86CC1170

[a] Unless otherwise stated, all rings are saturated.

Table 2 Rings containing three heteroatoms.[a]

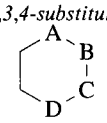
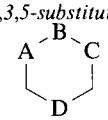
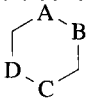
Ring type	*Ref.*
1,2,3-substituted rings 	
E = X = N, M = Si	85JOC5469, 85JOM(294)7, 92S106
hexa-3,5-diene	93MI 627-01
E = X = O, M = Si	82TL4871, 83JOM(244)C5, 92JOM(428)315
hex-4-ene	93JOM(446)139, 93TL711
E = X = S, M = Si	84ZAAC(508)201, 86TL6305
E = O, X = N, M = Si, hex-5-ene	82ZN(B)423, 91ZN(B)709
E = Si, X = N, M = O	89T1929
E = Si, X = O, M = S	93EGP4135170
E = X = Si, M = N	94ZN(B)1818
E = X = Si, M = O	94ZN(B)1818
E = X = Si, M = S	83MI 627-01
E = X = Si, M = Sn	88CPB2342, 93MM407, 93OM413
E = X = M = Si	85JOM(292)167
E = X = N, M = Ge, hexa-3,5-diene	92OM2348
E = X = O, M = Ge	84JGU1019, 86JGU306, 86JGU2445, 92JGU592
E = X = S, M = Ge	83JOM(246)227
E = X = Se, M = Ge	89CC1304
E = O, X = P, M = Ge, hex-4-ene	93OM1674
E = X = N, M = Sn	94ICA51
E = X = O, M = Sn	83JA3815, 85SRI907
E = X = S, M = Sn	88TL3971, 93JOC4971
E = O, X = N, M = Sn, hex-4-ene	93CB2247
E = O, X = S, M = Sn, biological effects	90ICA141, 93G583, 93MI 627-02
E = S, X = Sn, M = O	91ZAAC(603)41
E = X = O, M = Pb	87MI 627-03
1,2,4-substituted rings 	
E = X = O, M = Si	89BAU2405
M = X = O, E = Si	89BAU2405, 89JAP0133543
E = O, X = N, M = Si	84JGU1016, 86JGU1911
M = O, X = P, E = Si	90AG(E)1436
E = N, X = M = Si, hex-5-ene	81CB3518, 90OM2677
M = O, X = E = Si	93CL985
hex-3-ene	82JOM(235)7, 83JOM(243)393
M = X = O, E = Ge	83JOM(246)227
M = O, X = P, E = Ge	82OM1261
1,3,5-substituted rings 	
E = P, M = X = Si	84OM1199
E = X = M = Si	B-86MI 627-01, 93JOM(443)25
trisilabenzene	92TCA57
E = X = M = Ge	85JOM(288)13, 88ZN(B)727, 89ZN(B)285
trigermabenzene	92TCA57
E = X = M = Sn	85JOM(288)13

[a] Unless otherwise stated, all rings are saturated.

large while the endocyclic angles, e.g. that at silicon, 95.90(26)°, are small and the Si—C(adam) bond length is unusually long, 1.942(6) Å ⟨91OM2752⟩.

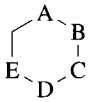
The structures of several 1-phospha-4-stannacyclohexanes have been determined and they show that there is a distorted tetrahedral geometry at phosphorus and a distorted trigonal–bipyramidal environment around the tin due to intermolecular interactions ⟨93OM4097⟩. X-ray crystallography shows that chair forms are preferred to twist conformers in 1,4-disilaradialenes ⟨89JOM(377)C45⟩.

Table 3 Rings containing four heteroatoms.[a]

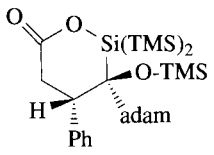
Ring type	*Ref.*
1,2,3,4-substituted rings	
	
A = D = N, B = C = Si	91JOM(407)31
A = D = O, B = C = Si	87JGU323
A = D = Si, B = C = O	92TL8015
hex-5-ene	91TL6605, 92T3283
A = C = O, B = D = Si	87CL237, 93JOM(446)183, 95OM4064
A = C = S, B = D = Si	90OM2205
B = C = Si, A = O, D = N	93JOM(454)35
A = C = D = Si, B = O	82OM1288
hex-5-ene	90CB589, 95JOM(499)99
A = P, B = C = Si, D = S	90ZAAC(588)133
A = B = C = D = Si	85JOM(292)167
hex-5-ene	86JOM(308)177, 87CE623
hex-5-yne	92OM1009, 93OM803
A = C = Ge, B = D = P	82OM1261, 82PS(12)265
A = D = Ge, B = C = O	92CC458
A = D = O, B = Ge, C = P	95OM1954
A = D = S, B = C = Ge	84JOM(277)323
A = O, B = Ge, C = D = N	86JCR(S)434, 87JCS(D)501
A = D = O, B = Sn, C = P	95OM1954
1,2,3,5-substituted rings	
	
A = C = D = N, B = Si	83ZN(B)71, 88JGU81
A = C = O, B = Si, D = N, hex-4-ene	83BAU1373, 83JGU1851
A = C = O, B = Si, D = P	84JGU1549, 87JGU475
A = C = Si, B = D = N	86JGU1155
A = C = Si, B = D = O	84BAU1734
A = C = O, B = D = Si	87DOK(292)64
A = C = Si, B = O, D = S	90JGU113
A = C = Si, B = O, D = Se	90JGU113
A = C = Si, B = O, D = Te	91JOM(410)309
A = C = Si, B = O, D = Ge	90JOM(387)65, 90SRI1373
A = C = Si, B = S, D = Ge	90JOM(387)65, 90SRI1373
A = C = N, B = D = Si, hexa-3,6-diene	86JOM(314)25
A = C = Si, B = O, D = N	91MI 627-04, 94ZOB1222
A = C = Si, B = O, D = Sn	89MI 627-04
A = C = D = Si, B = N	92OM3464
A = C = D = Si, B = O	84DOK(274)56, 84JOM(271)191
A = C = D = Si, B = S	84JOM(271)191
A = B = C = S, D = Ge	84SRI21, 88JOM(345)39
A = C = Ge, B = O, D = N	88JOM(339)259, 88JOM(346)1
A = C = Ge, B = S, D = N	88JOM(339)259
A = C = Ge, B = D = S	84SRI21
A = C = D = Ge, B = O	87OM659, 90IC1674, 90JOM(395)27, 91JOM(406)123
A = C = D = Ge, B = S	85JOM(282)315, 87OM659
A = C = D = O, B = Sn	86JAP61278864
1,2,4,5-substituted rings	
	
A = B = N, C = O, D = Si	88JOM(356)23
A = D = O, B = Si, C = Ge	90JOM(387)65
A = C = N, B = D = Si	86JGU1155, 86JOM(314)25
hexa-3,6-diene	86JOM(314)25
A = C = O, B = D = Si	83ZN(B)190
A = C = S, B = D = Si	89AG(E)762
A = B = C = D = Si	85JOM(292)189, 93JA3794
A = C = O, B = D = Ge	82JOM(232)123, 87OM659, 89OM1585
A = C = S, B = D = Ge	88JOM(345)39
A = B = C = D = Sn	83JOM(252)289, 84OM1917, 92JOM(437)127

[a] Unless otherwise stated, all rings are saturated.

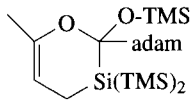
Table 4 Rings containing five heteroatoms.[a]

Ring type	*Ref.*
	
A = C = E = Si, B = O, D = S	84JOM(271)191
A = C = E = Si, B = D = O	84JOM(264)119, 88JOM(340)283
A = E = N, B = D = Si, C = O	83ZN(B)71, 88JGU81
A = E = S, B = D = O, C = Si	94ZN(B)309
A = C = E = Si, B = D = S	84DOK(274)56, 84JOM(271)191
A = B = C = D = E = Si	91JA8899, 91MI 627-03, 93JA2534
A = C = Ge, B = D = O, E = Si	90JOM(387)65
A = C = Ge, B = D = S, E = Si	90JOM(387)65, 90SRI1373
A = B = C = E = S, D = Ge	91TL6143, 95OM1008
A = B = D = E = S, C = Ge	91TL6143, 95OM1008
A = C = E = Ge, B = D = O	87OM659, 89OM1585, 90IC1674
A = C = E = Ge, B = D = S	87OM659, 89OM1585
A = B = D = E = S, C = Sn	93OM2573
A = B = C = E = S, D = Sn	93OM2573
A = B = D = E = Se, C = Sn	93OM2573

[a]All rings are saturated.



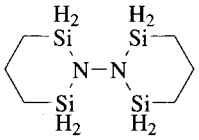
(1)



(2)

6.27.2.3.2 Rings containing three heteroatoms

The x-ray structure of (**3**) shows, as is the case for other silylamines, a trigonal planar arrangement at nitrogen and a large Si—N—Si angle (134.05°) with the two rings being orthogonal ⟨93OM413⟩.



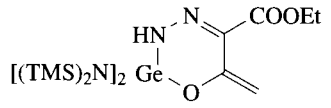
(3)

The heterocyclic ring in 2,2,5,5-tetramethyl-1,3-diselena-2-germacyclohexane has been shown to have a twist boat conformation in both the solid state and in solution with a high barrier to inversion ⟨89CC1304⟩. The x-ray structure of 1,3,5-trigermacyclohexane shows the ring to have a chair conformation and Ge—C—Ge and C—Ge—C bond angles slightly larger than the tetrahedral value ⟨88ZN(B)727⟩. The structure of 2,3-dibutyl-1,3,2-dioxastannacyclohexane is polymeric in the solid state with molecules linked by four-membered $(SnO)_2$ rings. In $CDCl_3$ solution, however, the polymer breaks down to give a mixture of dimers, trimers, and tetramers ⟨92CJC197, 92CJC205⟩.

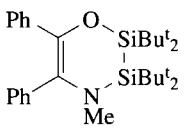
6.27.2.3.3 Rings containing four or five heteroatoms

The structure of (**4**) shows that the two nitrogen atoms and the two ring carbon atoms are coplanar and that the heterocyclic ring has an overall envelope conformation ⟨86JCR(S)434⟩. The structure of (**5**) reveals that the heterocyclic ring adopts a half chair conformation in the solid state which minimizes repulsions between the four Bu^t groups and which causes little lengthening of the Si—Si bond ⟨93JOM(454)35⟩. The structure of (**6**) shows the ring to be almost planar with somewhat

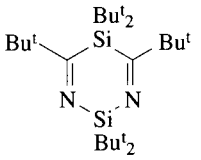
short Si—N bonds (1.712(2) Å) and long Si—C distances (≈1.95–2.00 Å) while the heterocyclic ring in (**7**) contains a long Si—Si bond (2.469(1) Å) ⟨91JOM(407)31⟩. The structure of (**8**) shows the ring to have a distorted boat conformation and there to be weak intermolecular Te···I interactions (Te···I distances 3.769 Å and 3.806 Å) ⟨91JOM(410)309⟩. The structure of 2,5-dimethyl-2,5-diphenyl-1,4-dioxa-2,5-disilacyclohexane has a chair conformation with the Ph rings *trans* to each other ⟨83ZN(B)190⟩. The gas-phase electron diffraction structure of (**9**) shows the ring to have a chair conformation and that repulsions between the axial methyl groups cause the $SiMe_2$ groups to be repelled by each other ⟨89MI 627-04⟩.



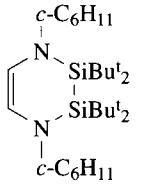
(**4**)



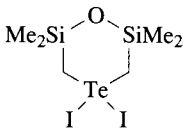
(**5**)



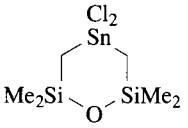
(**6**)



(**7**)



(**8**)

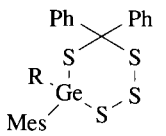


(**9**)

The solid-state structures of two 1,3-dioxa-5-phospha-2-silacyclohexane derivatives have been determined. Both have a chair conformation as was suggested by earlier solution-state work ⟨83DOK(270)208, 85DOK(278)301⟩. A bis-ferrocenyl derivative of a 1,3-dioxa-2,5-disilacyclohexane has been shown to have a distorted chair conformation in the solid state ⟨87DOK(292)64⟩. The structure of 4-phenyl-1,2-dioxa-3,6-digermacyclohex-4-ene reveals that in the solid state the $C_2O_2Ge_2$ ring is nonplanar and that the O—O bond of 1.42 Å is significantly shorter than in organic peroxides ⟨92CC458⟩.

The structure of 1,1,2,2,4,4,5,5-octaphenyl-1,2,4,5,-tetrastannacyclohexane shows the C_2Sn_4 ring to have a flattened chair conformation ⟨83JOM(252)289⟩. The structure of 1,1,2,2,3,4,4,5,5,6-decamethyl-1,2,4,5-tetrastannacyclohexane shows the compound to be the *cis* isomer in the solid state with a boat conformation rather than the chair structure of the related octaphenyl derivative ⟨84AX(C)370⟩.

Solid-state structural studies of compounds containing five heteroatoms are rare but the x-ray structure of (**10**) has been determined and shows the CS_4Ge ring to have a flattened chair conformation and to have a large S—Ge—S angle (121.0(2)°) ⟨91TL6143⟩.



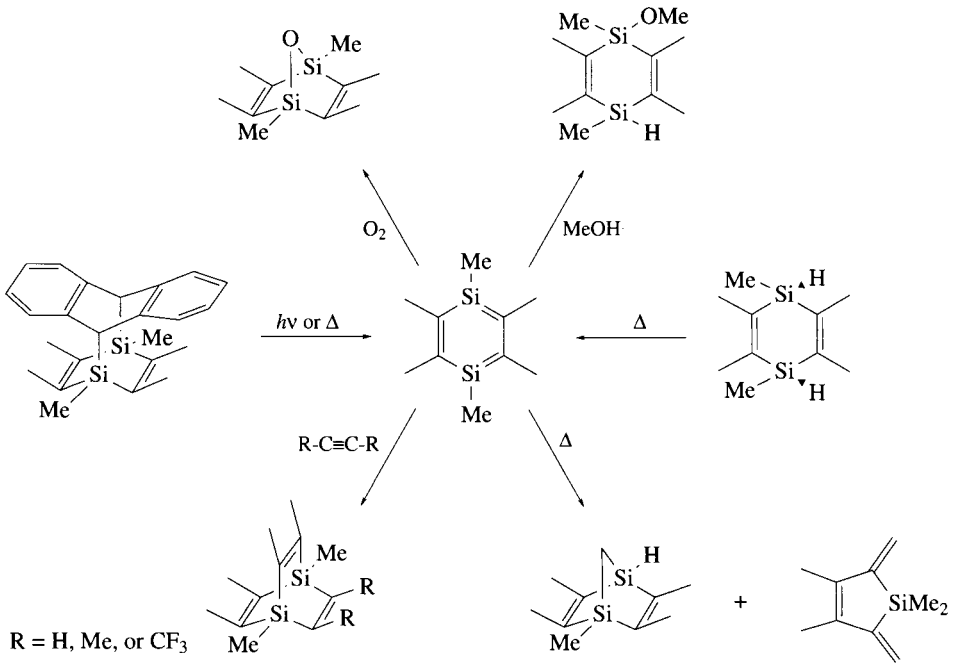
R = 2,4,6-$[(TMS)_2CH]_3C_6H_2$

(**10**)

6.27.2.4 Reactivity of Conjugated Rings

Very few of the rings in this chapter are fully conjugated because of the presence of an sp^3 hybridized Si, Ge, Sn, or Pb atom in the ring. Those rings that may be considered fully conjugated, such as the disilabenzenes, are highly reactive and have only a fleeting existence. Most of their

reactions have, therefore, been trapping studies with various protic species and with unsaturated compounds. The addition reactions of hexamethyl-1,4-disilabenzene have been studied in some detail and they often give rise to new ring systems (Scheme 1) ⟨87JOM(325)105⟩.



Scheme 1

6.27.2.5 Reactivity of Nonconjugated Rings

As mentioned in Section 6.27.2.4, most of the rings described in this chapter are nonconjugated because of the involvement of sp^3 hybridized Si, Ge, Sn, or Pb in the ring. The reactions of such rings are dominated by the substitution reactions occurring at these heteroatoms and they are generally as expected by analogy to related acyclic systems. Such reactions will not, therefore, be described in detail as the ring often has little effect. Two important reaction types that are described are those that involve stabilization of an anionic charge on a ring carbon and those that involve substitution of the group 14 heteroatom from the ring by another heteroatom (details of the latter reaction type are given in the ring syntheses section (Section 6.27.2.6) to avoid repetition).

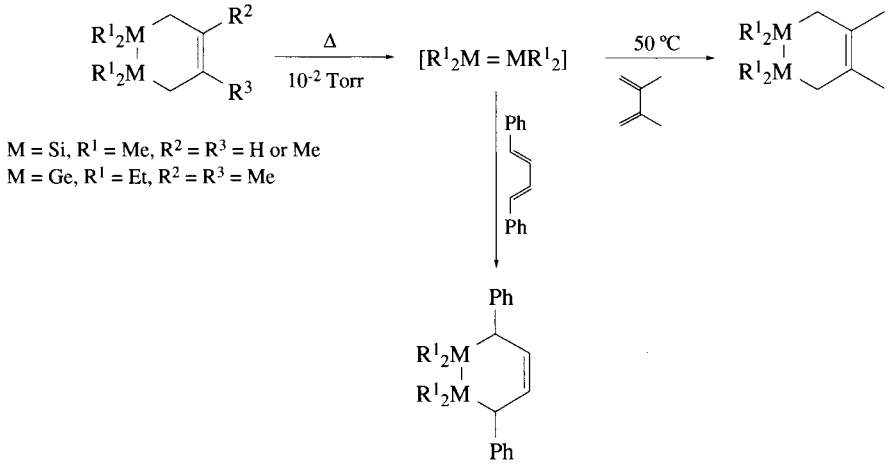
Thermolysis of disila- or digermacyclohex-4-enes gives rise to ring cleavage and formation of $R_2M{=}MR_2$ (M = Si or Ge) species which may be trapped by a variety of reagents. Several of these reactions lead to the formation of other rings as shown in Scheme 2 ⟨84JOM(267)93⟩.

The 1,3-diphospha-2,4-dimetallacyclohexanes (metal = Si, Ge, or Sn) are useful, high yield thermal precursors to R_2M: species ⟨82PS(12)265⟩.

2-Stanna-1,3-dithiacyclohexanes are useful as they react with aldehydes or acetals in the presence of $Bu^n_2Sn(OTf)_2$ to give good yields of 1,3-dithianes ⟨88TL3971, 93JOC4971⟩. The stabilizing effect on α-anions of the silicon heteroatoms in 1,3,5-trisilacyclohexanes allows them to be readily metallated by, for example, Bu^nLi/TMEDA, at a ring carbon to give lithium reagents that enable the heterocycle to be attached to a variety of other systems ⟨92OM3464, 93JOM(443)25⟩.

6.27.2.6 Ring Syntheses

The diversity of rings covered in this chapter means that there are a wide range of syntheses that have been applied to their production. The syntheses described below are some of the more general, such as intra- or intermolecular hydrometallations, and reactions of highly reactive unsaturated



Scheme 2

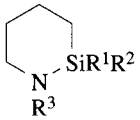
species such as R_2M: and $R_2M{=}MR_2$ (M = Si, Ge, Sn, or Pb) which are often not applicable to the synthesis of more common ring systems. References to the synthesis of most of the rings in this chapter can be found in Tables 1–4.

6.27.2.6.1 Rings containing two heteroatoms

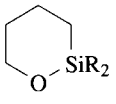
Many different rings containing two heteroatoms are known; references to many more of them than can be described in detail in the following sections, are given in Table 1.

(i) 1,2-Heteroatoms

Photolysis of cyclic silyl azides leads to loss of N_2, ring expansion, and formation of a transient silaimine which, in the presence of Bu^tOH or $(MeO)_3SiMe$, gives 1-aza-2-silacyclohexanes (**11**; $R^1 = Ph$, $R^2 = Bu^tO$, $R^3 = H$; $R^1 = Bu^t$, $R^2 = (MeO)_2MeSi$, $R^3 = H$, etc.) ⟨83NJC645⟩. Rearrangements of tetrahydrofurylsilanes are catalyzed by a variety of Pd, Pt, Rh, etc. complexes to give 1-oxa-2-silacyclohexanes (**12**) in good yield ⟨84H(22)987, 92JOM(436)277⟩. Such rings may also be formed by radical cyclization of (*E*)-1-((bromomethyl)dimethylsilyloxy)-2-methylhept-2-ene ⟨93HCA804⟩ or 1-dimethylsilyloxybut-4-ene ⟨84JA3802⟩ and, along with their benzo-fused derivatives (see Section 6.27.3), by trapping reactive 1-sila-1,3-butadienes with ketones ⟨81JOM(219)153⟩. They may also be formed from cycloadditions of bulky silenes (Si=C containing species) with α,β-unsaturated esters ⟨91OM2758⟩, base-catalyzed reaction of silacyclobutanes or benzocyclobutanes with aldehydes ⟨90TL6059⟩, and by AIBN promoted radical cyclizations of β-chloroethyldimethylsilyl enol ethers ⟨90CL1055, 90TL1531⟩. 1-Oxa-2-germacyclohexanes and 1-oxa-2-germacyclohex-3-enes may be prepared by Et_3B induced intramolecular hydrogermylation of homoallylic alcohols and alkynic alcohols respectively ⟨93CL1751⟩.



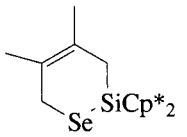
(**11**)



(**12**)

The trapping of reactive, unsaturated species is also a useful route to 1,2-heteroatom containing rings. For example, cycloaddition of 2,3-dimethylbutadiene with a reactive Ge=S containing species gives the 1-thia-2-germacyclohex-4-ene ring system ⟨93JA8855⟩ and a similar reaction between an Sn=S containing species gives the analogous 1-thia-2-stannacyclohexa-4-ene ring system ⟨93OM2573⟩. Trapping of the transient silaselone $Cp^*_2Si{=}Se$ by 2,3-dimethylbutadiene affords the

1-seleno-2-silacyclohex-4-ene ring compound (**13**) ⟨89AG(E)1518⟩ and the cycloaddition of butadiene with the reactive phosphasilene $Bu^t_2Si{=}PSiBu^t_3$ gives a 1-phospha-2-silacyclohex-4-ene ring product ⟨91CB93⟩.

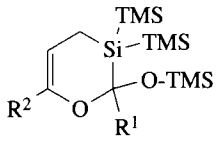


(**13**)

Reaction between 1,4-dibromo-2,3-bis(bromomethyl)-2-butene and $(ClMe_2M)_2$ (M = Si or Ge) in the presence of activated zinc gives 1,2-dimetallacyclohexanes ⟨91JOM(406)119, 92JOM(439)115, 92SRI1183⟩.

(ii) 1,3-Heteroatoms

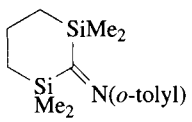
Reaction of $Me_2Si(CH_2Cl)(CH_2CH{=}CH_2)$ with H_2S leads to initial addition to the double bond followed by elimination of HCl and ring closure to give a 1-thia-3-silacyclohexane ring ⟨83JOM(243)271⟩. Intramolecular cyclization of $EtN(CH_2CH{=}CH_2)(CH_2GeHMe_2)$ promoted by AIBN gives 1-aza-3-germacyclohexane derivatives ⟨88JOM(346)1⟩. Intramolecular addition and cyclization also occurs if $Me(CH_2{=}CHCH_2)_2SiCH_2PH_2$ is heated to give a 1-phospha-3-silacyclohexane ⟨82PS(13)153⟩. As in the case of the 1,2-substituted rings described above, reactive group 14 intermediates may also be useful precursors to 1,3-substituted rings. For example, reaction of bulky silenes with α,β-unsaturated aldehydes, esters, or ketones gives 1-oxa-3-sila-cyclohex-5-ene derivatives (**14**) ⟨91OM2752, 91OM2758⟩.



R^1 = Bu^t or $C_{10}H_{15}$
R^2 = H, Me, OMe, OBu^t, etc.

(**14**)

Isocyanides undergo palladium catalyzed insertion into the Si—Si bond of disilanes, and, in the case of 1,1,2,2-tetramethyl-1,2-disilacyclopentane, ring expansion occurs and the 1,3-disilacyclohexane (**15**) results ⟨87TL1293⟩. A 1,3-disilacyclohexane may also result from the photolysis of a 1,4-disilacyclohept-2-ene ⟨90JA6601⟩ and 1,3-distannacyclohexanes are formed in the reaction of $(NaR_2Sn)_2CH_2$ (where R = Me or Ph) with $Cl(CH_2)_3Cl$ ⟨85BSB299⟩.

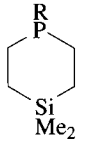


(**15**)

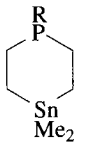
(iii) 1,4-Heteroatoms

A good method for the preparation of 1,4-hetero substituted rings involves a double hydrometallation reaction of a divinyl species with an MH_2 group. For example, $Me_2Si(CH{=}CH_2)_2$ reacts with RPH_2 species (R = TMS or Ph) in the presence of AIBN or under UV irradiation to give 1-phospha-4-silacyclohexanes (**16**) ⟨87IZV451, 89JOM(359)C36⟩, H_2S reacts with $Me_2Si(CH{=}CH_2)_2$ to

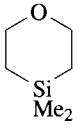
give the 1-thia-4-silacyclohexane ⟨83JOM(243)271⟩, and 1-aza-4-silacyclohexanes may be prepared from $Ph_2Si(CH{=}CH_2)_2$ by reaction with primary amines RNH_2 (R = Me, Pr^i, Bu^t, or $PhCH_2$) ⟨82ZN(B)657⟩. Similarly Me_2SnH_2 reacts with $RP(CH{=}CH_2)_2$ (R = Ph or Bu^t) to give 1-phospha-4-stannacyclohexanes (**17**) ⟨89BSB1⟩. Intramolecular hydrosilylation catalyzed by H_2PtCl_6 of $HMe_2SiCH_2CH_2OCH{=}CH_2$ affords the 1-oxa-4-silacyclohexane (**18**), but the corresponding diethylsilyl compound gives only a cyclopentane derivative ⟨92JOM(427)289⟩. 1-Aza-4-silacyclohexanes (**19**) are isolated in good yield as *cis/trans* mixtures from the intramolecular aminomercuriation of 2-aminopropyldimethylallylsilanes followed by reduction with $NaBH_4$ ⟨82S414⟩.



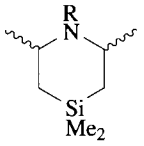
(**16**)



(**17**)



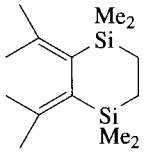
(**18**)



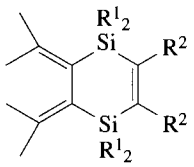
R = Ph, *o*-tolyl or *p*-tolyl

(**19**)

Ring opening of 3,4-bis(alkylidene)-1,2-disilacyclobutanes in the presence of 2,3-dimethylbutadiene or an alkyne affords the 1,4-disilacyclohexane (**20**) and 1,4-disilacyclohex-2-enes (**21**) respectively ⟨93CL985⟩. Reaction of 3,4-dilithio-2,5-dimethylhexa-2,4-diene with Me_2SnCl_2 affords a dimeric product containing the 1,4-distannacyclohexane ring ⟨89JOM(377)C45⟩. Similar reactions with chlorosilanes afford 1,4-disilacyclohexanes ⟨89JOM(377)C45⟩. Again, low coordination or unsaturated group 14 reactive intermediates are good precursors to rings via trapping reactions and addition of 2,3-dimethylbutadiene to digermenes gives the 1,2-digermacyclohex-4-enes (**22**) ⟨84JOM(264)193, 89CC770, 92OM2752⟩ while addition of Me_2Ge: to alkynes gives rise to 1,4-digermacyclohexa-2,5-dienes (**23**) ⟨92OM2069⟩. The highly reactive transient hexamethyl-1,4-disilabenzene may be formed by photolysis or thermolysis of a 9,10-bridged anthracene adduct of a substituted disilacyclohexadiene (see Scheme 1) ⟨87JOM(325)105⟩.

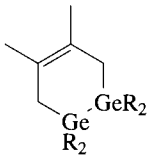


(**20**)



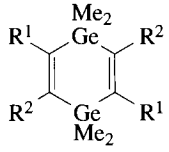
(**21**)

R^1 = Me or Et
R^2 = Ph, CO_2Me, etc.



(**22**)

R = Et, Pr^i or mesityl



(**23**)

R^1 = H, R^2 = Ph, Bu^t or cyclohexenyl
$R^1 = R^2 = CH_2OMe$, etc.

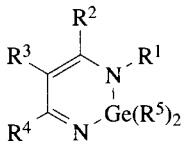
6.27.2.6.2 Rings containing three heteroatoms

There are 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.

(i) 1,2,3-Substituted rings

1,3-Diaza-2-silacyclohexanes may be prepared from the reaction between silylamides $R^1R^2Si(NR^3_2)_2$ and $MeHN(CH_2)_3NHMe$ (R^1,R^2 = Me or Ph; R^3 = Me or Et) ⟨85JOM(294)7, 86JOM(304)87⟩. The same ring system may also be obtained from the reaction between $MeSi(NMe_2)_3$

with $EtNH(CH_2)_3NHEt$ ⟨91HAC575⟩ and 1,3-diaza-2-silacyclohexa-4,6-dienes may be obtained from the reaction between 4-amino-1-azadienes and Ph_2SiCl_2 ⟨92S106⟩. The reaction of 4-amino-1-aza-butadienes with R_2GeCl_2 (R = Et or Ph) affords 1,3-diaza-2-germacyclohexa-3,5-dienes (**24**) which may be characterized by NMR spectroscopy but which do not seem to have been isolated ⟨92OM2348⟩. Reaction of a silacyclopropane with nitrones may give rise to formation of 1-oxa-2-aza-6-silacyclohexanes ⟨89T1929⟩.

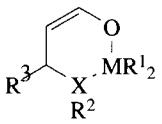


R^1 = *p*-tolyl, $R^2 = R^4$ = Ph, R^5 = Et
R^1 = *p*-tolyl, $R^2 = R^4 = R^5$ = Ph, R^3 = Me, etc.

(**24**)

The 1,3-dioxa-2-silacyclohexane and 1,3-dioxa-2-silacyclohex-4-ene ring systems are common as they are formed in the silylation of 1,3-diols, β-diketones, or β-hydroxy esters when using difunctional silylating agents. A variety of reagents such as Pr^i_2SiHCl ⟨92JA2745⟩, Me_2SiCl_2 or Ph_2SiCl_2 ⟨83JOM(244)C5⟩, $Me_2Si(CN)_2$ ⟨93TL711⟩, a silane $RPhSiH_2$ (R = Me or Ph) in the presence of Cp_2TiCl_2/Bu^nLi ⟨92JOM(428)315⟩, or, more commonly, $Bu^t_2SiCl_2$ ⟨81TL4999⟩ or $Bu^t_2Si(OTf)_2$ ⟨82TL4871, 92TL2847, 93TL5347⟩ may be used. The reaction of 1,3-diols with $(EtO)_4Si$ also gives 1,3-dioxa-2-silacyclohexanes ⟨84JGU1013⟩ and the reaction of 1,3-bis(chlorosilyl)propanes with H_2S affords 1-thia-2,6-disilacyclohexanes in good yield ⟨83AX(C)712⟩.

Addition of CH_2=CHCHO to an Sn=N containing species leads to [2 + 4] cycloaddition and formation of 1-oxa-3-aza-2-stannacyclohex-5-enes (**25**) ⟨93CB2247⟩. Similarly the reaction of a Ge=P containing species with α,β-unsaturated aldehydes or ketones affords 1-oxa-3-phospha-2-germacyclohex-4-enes (**26**) ⟨93OM1674⟩.



(**25**) M = Sn, X = N, $R^1 = N(TMS)_2$, $R^2 = 2,6\text{-}Pr^i_2C_6H_3$, R^3 = H
(**26**) M = Ge, X = P, R^1 = mesityl, $R^2 = 2,4,6\text{-}Pr^i_3C_6H_2$, R^3 = H, Me, etc.

(ii) 1,2,4-Substituted rings

The reaction between a C-lithiated 1,3-disilacyclobutane and either PhCOCl or PhCN affords the 1-oxa-2,4-disilacyclohex-5-ene and 1-aza-2,4-disilacyclohex-5-ene rings respectively ⟨90OM2677⟩. The aza ring is also formed in the reaction between $(TMS)_2C$=$SiMe_2$ and PhCN ⟨81CB3518⟩. Reaction of a 1,2-disilacyclobutane with PhCHO in the presence of $Pt(CH_2$=$CH_2)(PPh_3)_2$ causes ring expansion and formation of a 1-oxa-2,5-disilacyclohexane ring ⟨93CL985⟩. The analogous 1-oxa-2,5-disilacyclohex-3-enes may be formed from the reaction between a 1,2-disilacyclobut-3-ene and aldehydes or ketones ⟨82JOM(235)7, 83JOM(243)393⟩. Reaction between a 1,2-phosphagermetane and an aldehyde or ketone causes ring expansion and formation of a 1-oxa-2-germa-5-phospha-cyclohexane ⟨82OM1261⟩.

(iii) 1,3,5-Substituted rings

A wide range of 1,3,5-trisilacyclohexanes are known and much of the work on them has been reviewed ⟨B-86MI 627-01⟩. They may be made in a variety of ways; for example, they result from the pyrolysis of Me_4Si, from direct synthesis reactions using silicon, from organometallic syntheses using Grignard or organolithium reagents ⟨B-86MI 627-01⟩, and from the cyclotrimerization of

$(RO)_3SiCH_2MgCl$ compounds (R = Me or Et) ⟨93TL2111⟩. Mass spectrometry indicates that the reaction of metals ions or organometallic fragments such as Fe^+ or $[CpNi]^+$ in the gas phase with 1,3,5-trisilacyclohexane leads to dehydrogenation and formation of 1,3,5-trisilabenzene as a transient ligand ⟨92AG(E)1633⟩.

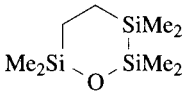
Reaction of $CH_2(MgBr)_2$ with Me_2MCl_2 (M = Ge or Sn) affords mixtures of products, the main one in each case being the 1,3,5-trimetallacyclohexane ⟨85JOM(288)13⟩. The reaction between CH_2Cl_2 and germanium powder at 350°C catalyzed by copper gives a mixture of products among which is $(Cl_2GeCH_2)_3$ which may be reduced by $LiAlH_4$ to give 1,3,5-trigermacyclohexane ⟨88ZN(B)727⟩.

6.27.2.6.3 Rings containing four heteroatoms

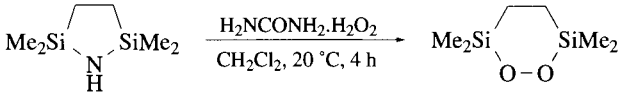
References to many rings containing four heteroatoms are given in Table 3. Their syntheses are often similar to those for the three-heteroatom cases, i.e. by trapping of low coordinate or unsaturated group 14 species, or by insertion into group 14 M—M bonds.

(i) 1,2,3,4-Substituted rings

Gentle heating of hexamethylsilirane in THF solution leads to extrusion of Me_2Si: which, in the presence of 2,2,5,5-tetramethyl-2,5-disila-1-oxacyclopentane, undergoes an insertion reaction to give the 1-oxa-2,3,6-trisilacyclohexane derivative (**27**) ⟨82OM1288⟩. Insertion of $Me_2Si{=}O$ into the Si—O bond of 2,2-dimethyl-4-vinyl-2-siloxetane causes ring expansion and formation of a 1,3-dioxa-2,4-disilacyclohexane product ⟨87CL237⟩. Photosensitized oxygenation of a 1,2-disilacyclobut-3-ene causes ring expansion via insertion into the Si—Si bond and formation of a 1,2-dioxa-3,6-disilacyclohex-4-ene derivative ⟨92T3283⟩. The saturated 1,2-dioxa-3,6-disilacyclohexane ring system (**28**) may be prepared by oxidation of a cyclic five-membered disilazane by H_2O_2·urea (Equation (1)) ⟨92TL8015⟩.

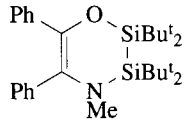


(**27**)



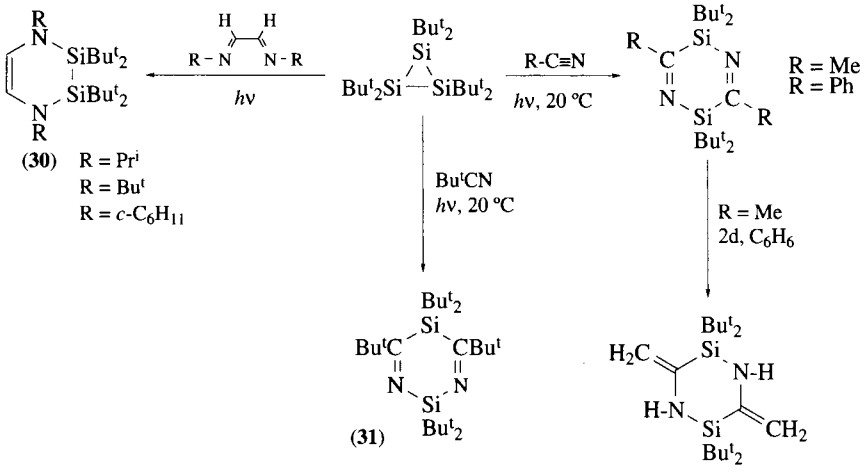
(**28**) (1)

Reaction of α-ketoimine PhC(O)CPh(=NMe) with disilene $Bu^t_2Si{=}SiBu^t_2$ leads to a [4 + 2] cycloaddition and formation of the 1-oxa-4-aza-2,3-disilacyclohex-5-ene (**29**) in 33% yield as a colorless crystalline product ⟨93JOM(454)35⟩. The 1,4-diaza-2,3-disilacyclohex-5-ene ring species (**30**) may be formed as shown in Scheme 3 ⟨91JOM(407)31⟩.



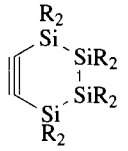
(**29**)

Ring opening of $(Bu^tc\text{-}C_6H_{11}Si)_4$ with lithium in the presence of PhC≡CH gives a 1,2,3,4-tetrasilacyclohexane product ⟨86JOM(308)177⟩ as does the condensation reaction between $(ClMe_2SiCH_2)_2$ and Cl_2MeSi-TMS ⟨85JOM(292)167⟩. A low yield of a 1,2,3,4-tetrasilacyclohex-5-ene product is obtained in the reaction between photochemically generated Me_2Si: and Bu^nC≡CH in



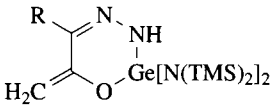
Scheme 3

the presence of $PdCl_2(PEt_3)_2$ ⟨87CE623⟩. The novel cyclic alkyne 1,2,3,4-tetrasilacyclohex-5-ynes (**32**) can be prepared in a similar way from BrMgC≡CMgBr and $Cl(SiR_2)_4Cl$ (R = Me or Et) ⟨92OM1009, 93OM803⟩.



(**32**)

The reaction of the germylene $((TMS)_2N)_2Ge$ with diazo compounds $MeC(O)C(N_2)R$ (R = CO_2Et, $SO_2C_6H_4Me$-*p*, COPh, etc.) gives 1-oxa-3,4-diaza-2-germacyclohex-4-ene products (**33**) ⟨87JCS(D)501⟩. Calculations on the mechanism and formation of these compounds have also been carried out ⟨90MI 627-06, 90MI 627-07⟩. Reaction of the unsaturated transient species $Me_2Ge{=}PPh$ with a 1,2-phosphagermetane gives a 1,3-diphospha-2,4-digermacyclohexane in good yield ⟨82OM1261⟩. Photosensitized oxygen insertion into the Ge—Ge bond in a 1,2-digermacyclobutene gives a 1,2-dioxa-3,6-digermacyclohex-4-ene derivative in 80% yield ⟨92CC458⟩. Reaction between digermane $((Et_2N)Me_2Ge)_2$ and $(HSCH_2)_2$ leads to loss of Et_2NH and cyclization giving the 1,4-dithia-2,3-digermacyclohexane ring ⟨84JOM(277)323⟩.



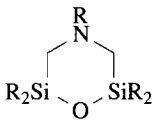
R = CO_2Et, tosyl
COPh, etc.

(**33**)

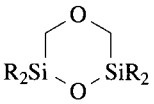
(ii) 1,2,3,5-Substituted rings

The reaction between *N,N'*-disubstituted ureas with $SiCl_4$ causes elimination of HCl and ring closure giving 1,3,5-triaza-2-silacyclohexanediones ⟨83ZN(B)71⟩. Formation of the 1,3-diaza-2,5-disilacyclohexa-3,6-diene ring compound (**31**) is shown in Scheme 3 ⟨86JOM(314)25⟩. Treatment of $(ClCH_2MeEtSi)_2O$ with primary amines RNH_2 (R = Me, Et, or $CH_2CH{=}CH_2$) affords 1-oxa-4-aza-2,6-disilacyclohexanes (**34**) in good yield ⟨91MI 627-04⟩. Reaction of $Me_2Si(C_6F_5)_2$ with $(MeC(O))_2NH$ in the presence of a catalytic amount of KCN/18-crown-6 gives rise to formation of

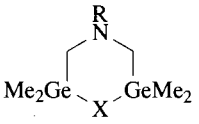
a 1,3-dioxa-5-aza-2-silacyclohexane ring ⟨83JGU1851⟩. Heating diol $(HOCH_2Me_2Si)_2O$ at 140 °C in the presence of $Cd(OAc)_2$ leads to an intramolecular dehydration and formation of the 1,4-dioxa-2,6-disilacyclohexane (**35**) ⟨84BAU1734⟩. Treatment of $MeC(O)N(CH_2GeClMe_2)_2$ with KOH/MeOH causes intramolecular ring closure and formation of a 1-oxa-4-aza-2,6-digermacyclohexane ring (**36**; E = O) ⟨88JOM(346)1⟩. Ring system (**36**; X = O) is also formed in the reaction of $(ClCH_2GeMe_2)_2O$ and a primary amine, and, if the ring is subsequently treated with H_2S, the corresponding 1-thia-4-aza-2,6-digermacyclohexane ring (**36**; X = S) is formed ⟨88JOM(339)259⟩.



(**34**)



(**35**)

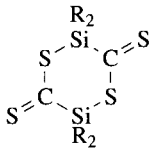


X = O or S

(**36**)

(iii) 1,2,4,5-Substituted rings

Dimerization of $R^1R^2HSiCH_2OH$ species (where $R^1R^2 = Me_2$, MePh, or Ph_2) is promoted by Bu^nLi and gives 1,4-dioxa-2,5-disilacyclohexanes as products ⟨83ZN(B)190⟩. Reaction of the highly reactive divalent silicon complex Cp^*_2Si with CS_2 affords a product (**37**) containing the related 1,4-dithia-2,5-disilacyclohexane ring ⟨89AG(E)762⟩. The analogous 1,4-diaza-2,5-disilacyclohexa-3,6-diene and 1,4-diaza-2,5-disilacyclohexane nitrogen containing rings are formed in the reaction between the cyclotrisilane $(Bu^t_2Si)_3$ and various unsaturated nitrogen containing compounds. These arise from formation of Bu^t_2Si: and $Bu^t_2Si{=}SiBu^t_2$ as intermediates (Scheme 3) ⟨86JOM(314)25⟩. The condensation of $(BrPh_2Sn)_2CH_2$ with Na/liquid NH_3 affords the expected 1,2,4,5-tetrastannacyclohexane product ⟨82JOM(236)69⟩.



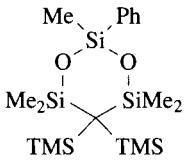
(**37**)

6.27.2.6.4 Rings containing five heteroatoms

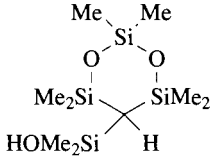
Relatively few six-membered rings containing a carbon and five heteroatoms have been prepared and those that have have often resulted as unexpected products from reactions of unstable intermediates. Examples of heterocycles in which all of the atoms in the six-membered ring are different appear to be extremely rare. References to five-heteroatom rings are given in Table 4.

Treatment of the dilithium reagent $(TMS)_2C(SiMe_2OLi)_2$ with $MePhSiF_2$ affords the 1,3-dioxa-2,4,6-trisilacyclohexane product (**38**) ⟨88JOM(340)283⟩. A similar ring (**39**) is formed in a complicated thermal or base induced rearrangement of $(HOMe_2Si)_4C$ ⟨84JOM(264)119⟩. Hydrolysis of a mixture of $(ClMe_2Ge)_2CH_2$ and Me_2GeCl_2 in benzene affords an analogous 1,3-dioxa-2,4,6-trigermacyclohexane derivative ⟨87OM659, 89OM1585⟩ while thermolysis of (**40**) gives the 1,3-dithia-2,4,6-trigermacyclo-hexane analogue (**41**) (Equation (2)) ⟨87OM659⟩ which may also be obtained from the vapor-phase thermolysis of a 1-germa-3-thiacyclobutane ⟨88JOM(345)39⟩. Similar reactions give rise to formation of the 1,3-dithia-2,4,6-trisilacyclohexane and the 1-oxa-3-thia-2,4,6-trisilacyclohexane ring systems ⟨84DOK(274)56, 84JOM(271)191⟩. Reaction of $(RHN)_2C{=}O$ (R = Me or Et) with

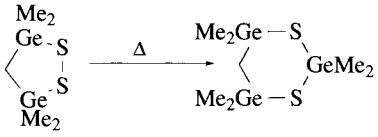
$Me_2Si(NEt_2)_2$ gives a mixture of cyclic compounds including a 1-oxa-3,5-diaza-2,6-disilacyclohexane derivative ⟨83ZN(B)71⟩.



(38)



(39)



(2)

(40) (41)

A 1,2,3,4,5-pentasilacyclohexane derivative has been found to be one of the many products formed in the pyrolysis of polydimethylsilane ⟨91MI 627-03⟩. Palladium catalyzed insertion of an arylisocyanide into a cyclopentasilane also gives the same ring system ⟨91JA8899⟩ as does the thermally induced isomerization of a pentasilacycloallene derivative ⟨93JA2534⟩.

Insertion of thermally generated Ph_2C: into a 1,2,3,4-tetrathia-5-germacyclopentane ring gives two isomeric six-membered ring products, a 1,3,4,5-tetrathia-2-germacyclohexane and a 1,2,4,5-tetrathia-3-germacyclohexane in 38% and 18% yields respectively ⟨91TL6143⟩. Similar reactions with tin and selenium containing heterocycles give 1,2,3,5-tetrathia-4-stannacyclohexane, 1,2,4,5-tetrathia-3-stannacyclohexane, and 1,2,4,5-tetraselena-3-stannacyclohexane products ⟨93OM2573⟩.

6.27.3 BICYCLIC AND LARGER RING SYSTEMS

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.

6.27.3.1 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 subject of other volumes in this series. Tables 5–7 list the various parent ring systems found, being arranged with increasing numbers of rings and heteroatoms, with unusual systems completing the section. In many cases the only references to a ring system will be found in these tables.

6.27.3.2 Bicyclic Systems

6.27.3.2.1 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

Table 5 Bicyclic compounds.

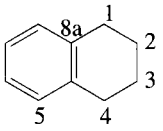
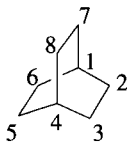
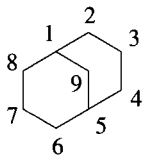
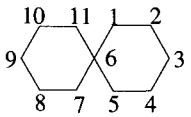
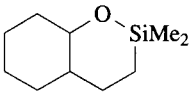
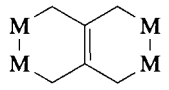
Ring system	*Heteroatoms*[a]	*Ref.*
Benzo-fused rings		
Containing two heteroatoms		
3,1-Benazasiline	E = N, M = Si	Prep. ⟨91MI 627-01⟩; prep. & pharmaceutical use ⟨92EUP511073, 92FRP2675801⟩
2,3-Benzazasiline	E = N, M = Si	Prep. ⟨81CB3518, 86JOM(315)9, 87ZN(B)1055, 89CB409, 93OM3666⟩
2*H*-1,2-Benzoxasilin	E = O, M = Si	Prep. ⟨81T2459⟩; MS ⟨81JGU1955⟩; prep. & x-ray ⟨82MI 627-03⟩; prep. ⟨93JOC6961⟩; catalytic activity ⟨91MAC2857⟩
1*H*-2,1-Benzoxasilin	E = O, M = Si	Prep. ⟨84MI 627-01⟩; prep. ⟨90TL6059⟩
1*H*-2,3-Benzoxasilin	E = O, M = Si	Prep. ⟨84MI 627-01, 87OM1246, 87ZN(B)1062, 88ZN(B)1468, 93CC1691, 93OM4085⟩
2*H*-1,3-Benzothiasilin	E = S, M = Si	Prep. ⟨89JOM(366)1⟩
1,2-Disilanaphthalene	E = Si, M = Si	Prep. ⟨85JA7706, 92JOM(439)19⟩; spectroscopy ⟨90JPC1837⟩
1,3-Disilanaphthalene	E = Si, M = Si	Prep. ⟨83JA7776, 86JA7417, 86OM1518, 89OM2050, 90JOM(399)205, 95OM1204⟩
1,4-Disilanaphthalene	E = Si, M = Si	Prep. ⟨86JA1323, 87OM1869, 88JOM(356)325, 91OM16, 91OM3173, 92JOM(428)1, 92JOM(439)19, 93BSF667, 93CC744, 93JOM(458)167, 93OM4987, 94OM4994⟩; prep. & use ⟨94JAP06128272⟩
3,1-Benazagermine	E = N, M = Ge	Prep. ⟨88JOM(339)259⟩
2*H*-1,2-Benzoxagermanin	E = O, M = Ge	Prep. ⟨81T2459⟩
1*H*-2,3-Benzoxagermanin	E = O, M = Ge	Prep. ⟨86CB2980⟩
2*H*-1,3-Benzothiastannin	E = S, M = Sn	Prep. ⟨89JOM(366)1⟩
Containing three heteroatoms		
2,3,1-Benzodiazasiline	E = N, E = N, M = Si	Prep. ⟨88JOM(341)95⟩
1,2,3-Benzodiazasiline	E = N, E = N, M = Si	Prep. ⟨81CB3518⟩
4*H*-1,3,2-Benzodioxasilin	E = O, E = O, M = Si	Prep. ⟨81MI 627-01, 81MI 627-02, 83JOM(244)C5, 83TL1273, 86JOC3545, 87MI 627-01, 90JOM(399)11, 91TL1145⟩; reactions of ⟨84TL1813⟩; GC & MS ⟨84JC119, 85MI 627-01, 88JC13⟩; ^{29}Si NMR ⟨88MI 627-01⟩
1,4,2-Benzodioxasilin	E = O, E = O, M = Si	Reactions of ⟨86IZV712⟩
2*H*-3,1,2-Benzoxazasiline	E = N, E = O, M = Si	Prep. ⟨83TL1273⟩; GC & MS ⟨85MI 627-01⟩
2*H*-1,3,2-Benzoxazasiline	E = O, E = N, M = Si	Prep. & x-ray ⟨85MI 627-02, 85MI 627-03⟩; ^{29}Si NMR ⟨88MI 627-01⟩
2*H*-1,2,4-Benzothiazasiline	E = S, E = N, M = Si	Prep. & pharmaceutical use ⟨92EUP511073, 92FRP2675801⟩
4*H*-3,1,2-Benzoxathiasilin	E = S, E = O, M = Si	Prep. ⟨83TL1273⟩
2,1,4-Benazadisiline	E = N, M = Si, M = Si	Prep. ⟨92CL45, 93JAP05178866⟩
1*H*-2,1,3-Benzoxadisilin	E = O, M = Si, M = Si	Prep. ⟨91BCJ3280⟩
2*H*-3,1,2-Benzoxadisilin	E = O, M = Si, M = Si	Prep. ⟨93OM2177⟩
1*H*-2,1,4-Benzoxadisilin	E = O, M = Si, M = Si	Prep. ⟨91JAP03258792, 91OM3173, 92JOM(439)19, 92OM2580, 93OM87, 93OM4987, 94OM4994⟩; prep. & x-ray ⟨92OM2639⟩
4*H*-1,3,2-Benzodioxagermin	E = O, E = O, M = Ge	Prep. & thermal decomp. ⟨91PS(63)341⟩
4*H*-3,1,2-Benzoxathiagermin	E = S, E = O, M = Ge	Prep. ⟨91PS(63)341⟩
4*H*-1,3,2-Benzodioxastannin	E = O, E = O, M = Sn	Prep. ⟨82IJC(A)726, 87JOM(328)61⟩; prep. & biol. activity ⟨88BSB873, 88ICA21, 89MI 627-03, 90MI 627-01⟩
2*H*-3,1,2-Benzoxazastannine	E = N, E = O, M = Sn	Prep. & biol. activity ⟨88ICA21⟩
2*H*-1,3,2-Benzoxazastannine	E = O, E = N, M = Sn	Prep. ⟨89MI 627-05⟩

Table 5 Continued.

Ring system	*Heteroatoms*[a]	*Ref.*
4*H*-3,1,2-Benzoxathiastannin	E = S, E = O, M = Sn	Prep & x-ray ⟨84OM750⟩; prep. ⟨89JOM(365)207⟩; prep. & biol. activity ⟨91HAC447, 92ICA25⟩; IR & Mössbauer spec. ⟨93G583⟩
4*H*-1,3,2-Benzodithiastannin	E = S, E = S, M = Sn	Prep. ⟨93SUL5⟩
Containing four heteroatoms		
2*H*-1,3,4,2-Benzoxazaphosphasiline	E = O, E = N, E = P, M = Si	Prep. ⟨92HAC163, 92JGU1255⟩
2*H*-1,4,2,3-Benzodioxadisilin	E = O, E = O, M = Si, M = Si	Prep. & reaction of ⟨86JGU773⟩
1,2,3,4-Tetrasilanaphthalene	M = Si, M = Si, M = Si, M = Si	Prep. & x-ray ⟨90NKK536⟩; prep. ⟨92JA4920, 92OM1009, 93OM803⟩
2*H*-1,3,4,2-Benzoxadiazagermine	E = O, E = N, E = N, M = Ge	Prep. ⟨87JCS(D)501⟩
1,4,2,3-Benzodioxazagermine	E = O, E = N, E = O, M = Ge	Prep. & thermal decomp. ⟨88JOM(358)77⟩; prep. & ring contraction of ⟨92JOM(431)17⟩
	E = O, E = O, E = P, M = Ge	Prep. ⟨95OM1954⟩
	E = O, E = O, E = P, M = Sn	Prep. ⟨95OM1954⟩
Bicyclo[a.b.c]anes and bicyclo[a.b.c]enes		
		
		
2-Oxa-3-silabicyclo[2.2.2]oct-5-ene		Prep. ⟨83JA6726, 90JA3642⟩
2-Oxa-3-silabicyclo[3.3.1]nonane		Prep. ⟨89JA4984⟩
2,3-Disilabicyclo[2.2.2]oct-5-ene		Prep. & spectra ⟨82JOM(226)21⟩
2,3-Disilabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic acid		Prep. ⟨83NJC225⟩
2,3-Disilabicyclo[2.2.2]octa-5,7-diene		Prep., reactions & thermolysis of ⟨93JA11460⟩; prep. & polym. ⟨93PP218⟩
2,3,4,6,7,8-Hexasilabicyclo[3.3.1]nona-1(9),5(9)-diene		PM3 MO calcns. ⟨93JA3111⟩
Spiro[5.5]undecanes		
		
3-Oxa-8,10-diaza-2,4-disilaspiro[5.5]undecane		Prep. & x-ray ⟨81MI 627-04⟩
1,5,7,11-Tetraoxa-2,4,8,10-tetrasilaspiro[5.5]undecane		Prep. & use of ⟨92JAP04169592⟩
2,4,8,10-Tetraoxa-3,9-disilaspiro[5.5]undecane		X-ray ⟨86MI 627-04, 88JGU94⟩
1,3,5,7,9,11-Hexasilaspiro[5.5]undecane		Prep. ⟨81ZAAC(481)60⟩
2,4,8,10-Tetraoxa-3,9-distannaspiro[5.5]undecane		Prep. & reaction of ⟨92PP1111⟩
Cyclohexyl-fused rings		
		
1,2-Oxasilacyclohexane		Prep. ⟨90TL1531, 92TL6603⟩
Substituted naphthalene ring systems		
		
2,3,6,7-Tetrasilanaphthalene	M = Si	Prep. ⟨92JOM(439)115⟩
[1,2]Digermo[4,5-*d*][1,2]digermin	M = Ge	Prep. ⟨92JOM(439)115⟩

[a]The ordering of the heteroatoms is as indicated in the ring system name.

Table 6 Tricyclic compounds.

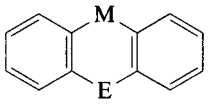
Ring system	*Heteroatoms*[a]	*Ref.*
Dibenzo-fused rings		
Phenazasiline	E = N, M = Si	Prep. ⟨81LA1285, 88ZN(B)104⟩; prep., x-ray & pharmacol. activity ⟨88LA241⟩; prep. &/or reaction of ⟨83TL5709, 84OM1051, 86JOM(304)93, 90JOM(399)221⟩; electrochem. ⟨90MI 627-02, 91AC(R)95, 92AC(R)161⟩; O_2 complex ⟨82JGU783⟩; x-ray ⟨81CSC1419, 82JGU2109, 83JOM(258)283, 85K492⟩; NMR ⟨86JGU1153, 91JGU688, 92JGU2039, 92MI 627-01⟩; MS ⟨82JGU2110⟩; UV spectra & conjugation in ⟨90JGU2240⟩; spectroscopy & MO ⟨82MI 627-02, 85MI 627-04, 87MI 627-02, 88MI 627-03, 89MI 627-06, 91MI 627-02⟩; MO ⟨81MI 627-03⟩
Phenophosphasilin	E = P, M = Si	X-ray ⟨90MI 627-03⟩; NMR ⟨91JGU688, 92MI 627-01⟩
1*H*-Phenoxasilin	E = O, M = Si	Prep. ⟨84MI 627-02, 87JGU632⟩; prep. & reactions ⟨82MI 627-01⟩; reactions ⟨84OM1051⟩; O_2 complex ⟨82JGU783⟩; x-ray ⟨83JOM(258)283, 84K386, 84MI 627-04⟩; spectroscopy & MO ⟨82JGU2015, 82MI 627-02, 86MI 627-03, 88MI 627-03, 91MI 627-02⟩; MO ⟨86H(24)2757⟩; NMR ⟨82JGU2109, 86JGU1153, 91JGU688, 92MI 627-01, 93JGU168⟩; MS ⟨82JGU2110⟩
1*H*-Phenothiasilin	E = S, M = Si	Prep. ⟨83JA6155⟩; O_2 complex ⟨82JGU783⟩; electrochem. ⟨91AC(R)95, 92AC(R)161⟩; x-ray ⟨81IZV2436, 81MI 627-05, 83JOM(258)283, 84K260, 84K386, 84K613, 84MI 627-04⟩; spectroscopy ⟨81JGU1099⟩; MO ⟨86H(24)2757⟩; spectroscopy & MO ⟨88MI 627-03, 91MI 627-02⟩; NMR ⟨86JGU1153, 91JGU688⟩; MS ⟨82JGU2110⟩
Silanthrene	E = Si, M = Si	Review ⟨85JGU1283⟩; prep. ⟨82JGU1903, 84JOM(271)319, 93MI 627-03, 95OM114⟩; Prep. & x-ray ⟨84OM255, 84OM1755, 88MI 627-02⟩; prep. & reactions ⟨87OM1393, 88JGU1432, 89JGU757, 90MI 627-04, 91JGU686, 95OM3625⟩; reactions ⟨87JGU2253, 94CC1703⟩; NMR ⟨86JGU1153, 87JGU1372, 91JGU688⟩; spectroscopy ⟨81JGU1099⟩; MO ⟨86H(24)2757⟩; thermochem. ⟨90JGU128⟩
Phenosilagermanin	E = Ge, M = Si	Prep. & x-ray ⟨84OM255⟩
Phenosilastannin	E = Sn, M = Si	Prep. & x-ray ⟨84OM255⟩
Phenosilaplumbin	E = Pb, M = Si	Prep. ⟨84OM255⟩
Phenazagermine	E = N, M = Ge	X-ray ⟨83JOM(258)283, 85K304⟩; MS ⟨82JGU2110⟩; O_2 complex ⟨82JGU783⟩; electrochem. ⟨92AC(R)161⟩; MO ⟨84MI 627-03⟩; spectroscopy & MO ⟨87MI 627-02, 88MI 627-03, 91MI 627-02⟩
1*H*-Phenoxagermin	E = O, M = Ge	X-ray ⟨83JOM(258)283, 85K304⟩; MS ⟨82JGU2110⟩; O_2 complex ⟨82JGU783⟩; MO ⟨83MI 627-02, 84MI 627-03⟩; spectroscopy & MO ⟨88MI 627-03, 91MI 627-02⟩

Table 6 Continued.

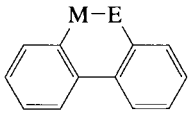
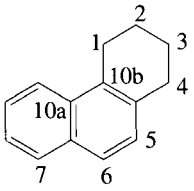
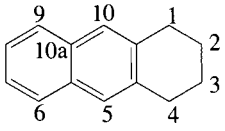
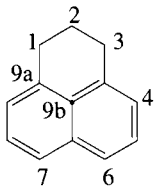
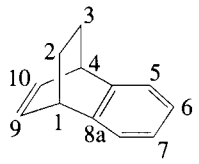
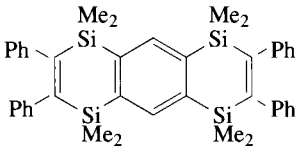
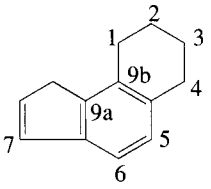
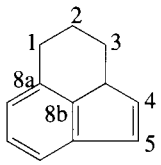
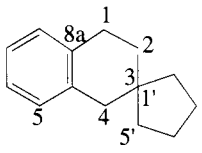
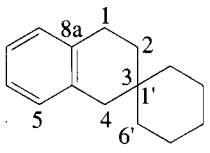
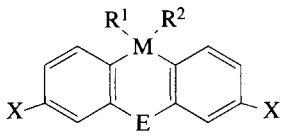
Ring system	*Heteroatoms*[a]	*Ref.*
1*H*-Phenothiagermin	E = S, M = Ge	MS ⟨82JGU2110⟩; O_2 complex ⟨82JGU783⟩; MO ⟨83MI 627-02⟩; spectroscopy & MO ⟨88MI 627-03, 91MI 627-02⟩
Phenazastannine	E = N, M = Sn	X-ray ⟨82JGU2109, 83JOM(258)283, 85K297⟩; MS ⟨82JGU2110⟩; MO ⟨84MI 627-03⟩; spectroscopy & MO ⟨87MI 627-02, 91MI 627-02⟩
1*H*-Phenoxastannin	E = O, M = Sn	O_2 complex ⟨82JGU783⟩; spectroscopy & MO ⟨91MI 627-02⟩
1*H*-Phenothiastannin	E = S, M = Sn	X-ray ⟨83AX(C)712⟩; O_2 complex ⟨82JGU783⟩; spectroscopy & MO ⟨91MI 627-02⟩
		
9,10-Disilaphenanthrene	E = Si, M = Si	Prep. ⟨82JOM(226)21⟩; prep. & photolysis ⟨83JAP5821684⟩; photolysis ⟨83JA7469, 84CL1213, 87CL983⟩; reactions ⟨87CL1075⟩
Dibenzo[*c*,*e*][1,2]digermanin	E = Ge, M = Ge	Prep. ⟨84CL1379⟩; photolysis ⟨83JA7469⟩
Naphtho-fused rings		
		
1*H*-Naphth[2,1-*d*][1,2]oxasilin	E = O, M = Si	Prep. ⟨90ZN(B)909⟩
1*H*-Naphtho[2,1-*d*][1,3,2]dioxasilin	E = O, E = O, M = Si	MS ⟨88JC13⟩
4*H*-Naphtho[1,2-*d*]-1,3,2-dioxastannin	E = O, E = O, M = Sn	Prep. ⟨93CAT229⟩
	E = O, E = O, E = P, M = Ge	Prep. ⟨95OM1954⟩
	E = O, E = O, E = P, M = Sn	Prep. ⟨95OM1954⟩
		
4*H*-Naphtho[2,3-*d*]-1,3,2-dioxasilin	E = O, E = O, M = Si	MS ⟨88JC13⟩
1*H*-Naphth[2,3-*c*][1,2,6]oxadisilin	E = O, M = Si, M = Si	Prep. & x-ray ⟨92T89⟩
1,2,3-Trisilaanthracene	M = Si, M = Si, M = Si	Prep. ⟨90TL4185, 92T89⟩
4*H*-Naphtho[2,3-*d*]-1,3,2-dioxastannin	E = O, E = O, M = Sn	Prep. ⟨93CAT229⟩
		
1*H*-Naphth[1,8-*cd*][1,2]azasiline	E = N, M = Si	Prep. & oxidn. ⟨91AG(E)1130⟩
Naphth[1,8-*de*]-1,2-oxasilin	E = O, M = Si	Prep. & oxidn. ⟨92TL2977⟩
Naphth[1,8-*de*]-1,3,2-dioxasilin	E = O, E = O, M = Si	Prep. ⟨81TL4999, 86MI 627-02⟩
Naphth[1,8-*de*]-1,3,2-dioxastannin	E = O, E = O, M = Sn	Use of for electrophotog. developers ⟨87JAP6275550⟩

Table 6 Continued.

Ring system	*Heteroatoms*[a]	*Ref.*
		
1,4-Ethano-1*H*-2,3-benzoxasilin	E = O, M = Si	Prep. ⟨91JOC3564⟩
1,4-Etheno-2,3-disilanaphthalene	M = Si, M = Si	Prep. & pyrolysis ⟨83OM1464⟩; pyrolysis ⟨85CL643⟩
1,4-Etheno-2,3-benzodigermin	M = Ge, M = Ge	Prep. & thermolysis ⟨82CL1855, 84TL2467⟩; thermolysis & reaction ⟨92OM2069⟩
5,8-Etheno-1,2,6,7-tetrasilanaphthalene		Prep., x-ray & reaction ⟨91CC341⟩
Miscellaneous rings		
		
1,4,5,8-Tetrasilaanthracene	M = Si, M = Si, M = Si, M = Si	Prep. & x-ray ⟨93CC744⟩
		
Indeno[5,4-*d*][1,2]oxasilin	E = O, M = Si	Prep. ⟨91HCA146⟩
		
4*H*-Indeno[1,7-*de*]-1,3,2-dioxasilin	E = O, E = O, M = Si	Prep. ⟨83TL1273⟩
		
Spiro[3*H*-2,1-benzoxasilin-3,1′-cyclopentane]		Prep. ⟨84MI 627-01⟩
		
Spiro[3*H*-2,1-benzoxasilin-3,1′-cyclohexane]		Prep. ⟨84MI 627-01⟩

[a] The ordering of the heteroatoms is as indicated in the ring system name.

Table 7 Dibenzo-fused tricyclic rings characterized by x-ray crystallography.

E	*M*	R^1	R^2	*X*	α (°)	*Ref.*
						
NEt	Si	Me	Me	H	157.3	81IZV2436
NEt	Si	Me	Me	Br	138.8	81IZV2436
NEt	Si	Ph	Ph	Me		83JOM(258)283, 85K492
NEt	Si	Ph	Ph	Br		83JOM(258)283
NEt	Si	OMe	*o*-tol	Br		83JOM(258)283, 85K492
NEt	Ge	Cl	Cl	Me		83JOM(258)283
NEt	Ge	Cl	Ph	Me	146.6	85K175
NEt	Ge	Ph	Ph	H	156.1	83JOM(258)283, 85K175
NEt	Ge	Ph	Ph	Br	138.2	83JOM(258)283, 85K175
NEt	Ge	Ph	Ph	H, Ph		83JOM(258)283
NEt	Sn	*o*-tol	*o*-tol	H	129.6	83JOM(258)283, 85K171
NEt	Sn	*o*-tol	*o*-tol	Me	124.4	83JOM(258)283, 85K171
NEt	Sn	*o*-tol	*o*-tol	Br	133.3	83JOM(258)283, 85K171
NEt	Sn	Ph	Ph	Br	125.2	83JOM(258)283, 85K171
O	Si	Me	Me	H	175.6	84MI 627-04
O	Si	Ph	Ph	H	165.9	83JOM(258)283, 84K232
O	Ge	Ph	Ph	H	165.8	83JOM(258)283, 85K175
S	Si	H	*p*-ClC_6H_4	H	141.1 & 143.8[a]	84K260
S	Si	H	*p*-MeC_6H_4	H	144.2 & 141.6[a]	84K260
S	Si	H	*p*-$OMeC_6H_4$	H	133.0	84K260
S	Si	OEt	*p*-$OMeC_6H_4$	H	156.7	84K613
S	Si	Me	Me	H	148.0	81MI 627-05, 84MI 627-04
S	Si	Me	CH_2Cl	H	141.3	81IZV2436, 81MI 627-05
S	Si	Ph	Ph	H	150.4	83JOM(258)283, 84K232
SO_2	Si	Me	Me	H	143.0 & 134.1[a]	81MI 627-05
S	Sn	Me	Me	H		83AX(C)712
PPh	Si	Me	Me	H		90MI 627-03
PPhO	Si	Me	Me	H		90MI 627-03
PMeO	Si	Me	Me	H		90MI 627-03
PPhS	Si	Me	Me	H		90MI 627-03
PMe_2[b]	Si	Me	Me	H		90MI 627-03

[a]Two independent molecules. [b]Ionic with I^- as the counterion.

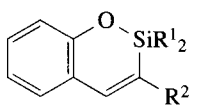
from the heterocycle and/or the aromatic ring. In addition, the heterocyclic ring may be partially conjugated. This is true for all the polycyclic compounds described and, due to the great number, the derivatives are not generally mentioned by name but can be found in the references cited.

(i) Experimental structural methods

The compounds described in this section have all been characterized by a variety of techniques such as NMR, IR, or electronic spectroscopy, or mass spectrometry amongst others. A few have been the subject of x-ray diffraction studies; for example, two derivatives (**42**) of 2*H*-1,2-benzoxasilin have been found to be analogues of naphthalene, differing in that an aromatic C—C has been replaced by an Si—O bond ⟨82MI 627-03⟩. Both molecules have planar conformations with unexceptional geometric parameters. In contrast, the heterocyclic ring in (**43**) has a flattened boat conformation with the fused aromatic ring having the normal planar conformation ⟨92OM2639⟩.

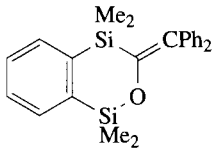
(ii) Reactivity of rings

Ring cleavage reactions are typified by the addition of TMS-OH or Et_3SiOH to a 1,4,2-benzodioxasilin resulting in *o*-$R_3SiOSiMe_2CH_2OC_6H_4OH$ ⟨86IZV712⟩. The oxidation of 1,4,2,3-benzo-



$R^1 = Ph, R^2 = H$
$R^1 = Cl, R^2 = SiCl_3$

(42)



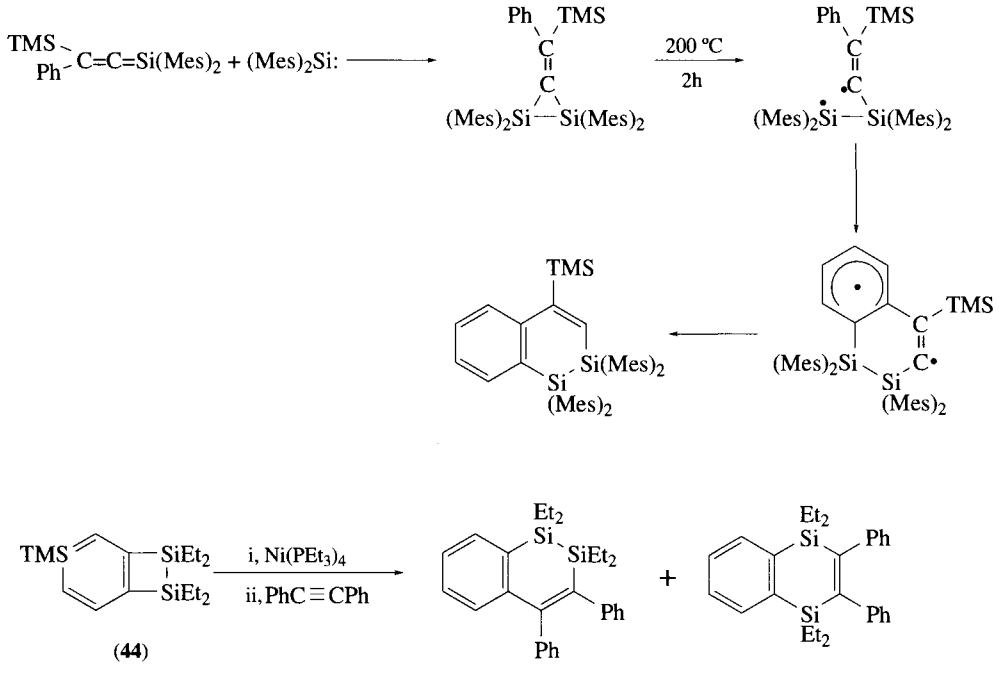
(43)

dioxadisilin with peroxybenzoic acid in benzene is practically simultaneous with mixing of the reactants resulting in a ring-expanded 1,3,5,2,4-benzotrioxadisilepin ⟨86JGU773⟩. The same reaction with atmospheric oxygen is much slower.

(iii) Synthesis of rings

Due to the great number of ring systems covered in this chapter, few of the synthetic routes employed in their preparation can be described in detail. Some of the more general synthetic methods will be briefly discussed and the tables provide more comprehensive references which should be consulted for further information.

A wide range of disilanaphthalenes are known and much of the work on them has centered on their syntheses. 1,2-Disilanaphthalenes can be prepared by either of the two routes shown in Scheme 4. The earliest method involves a radical mechanism ⟨85JA7706⟩. Another procedure involves the nickel-catalyzed reaction of cyclic disilane (**44**) with diphenylalkyne which also produces a 1,4-disilanaphthalene ⟨92JOM(439)19, 95JOM(499)35⟩.

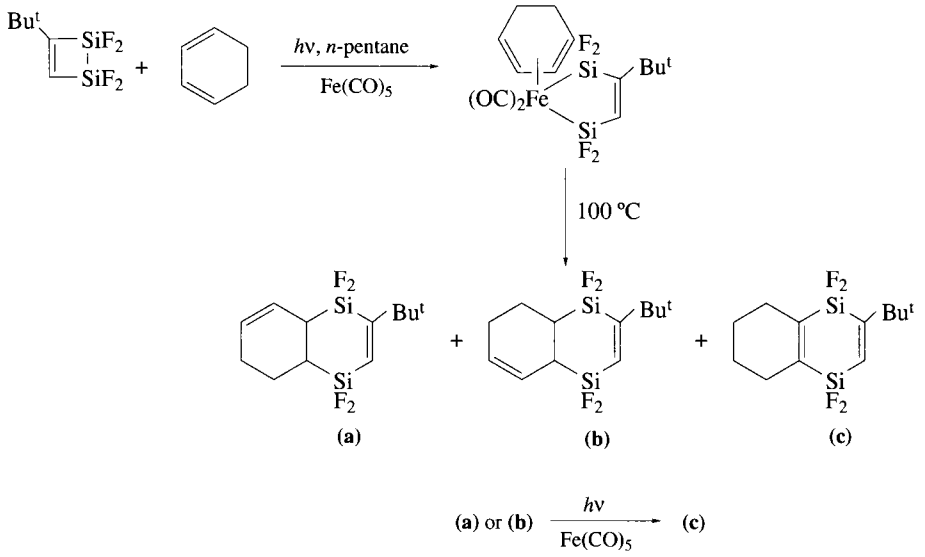


Scheme 4

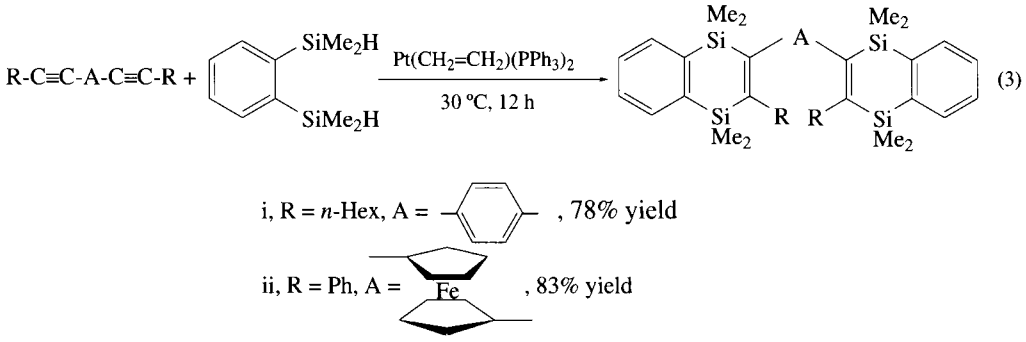
1,3-Disilanaphthalenes can be prepared by the thermolysis of a disilacyclopropane in deuteriated benzene; the reaction may be monitored by NMR spectroscopy ⟨83JA7776⟩. A mechanism of formation is proposed which involves Si—Si bond rupture followed by C—Si bond formation via a silyl radical. Thermolysis of 2-(mesityl)-2-(phenylethynyl)hexamethyltrisilane also results in two isomeric 1,3-disilanaphthalenes ⟨86OM1518⟩ but better yields are achieved if the reaction (either thermally or photochemically) is catalyzed by a nickel complex ⟨86JA7417, 89OM2050⟩. Nickel-

catalyzed thermolysis of 2-(*o*-tolyl)-2-(phenylethylnyl)-hexamethyltrisilane also affords a 1,3-disilanaphthalene ⟨90JOM(399)205⟩.

Thermolysis of (**44**) in the presence of alkynes results in 1,4-disilanaphthalenes ⟨91OM3173⟩. As already mentioned, they can be formed in higher yields during the nickel ⟨92JOM(439)19⟩ and platinum catalyzed reactions ⟨93OM4987⟩ of the (**44**) with diphenylalkyne and ethene respectively. Platinum-complex catalyzed dehydrogenative double silylation of alkynes, alkenes, and dienes with *o*-bis(dimethylsilyl)benzene ⟨91OM16, 92JOM(428)1, 93BSF667⟩ and transition-metal carbonyl mediated cycloadditions of cyclohexadiene with 1,1,2,2-tetrafluoro-1,2-disilacyclobut-3-ene ⟨86JA1323, 87OM1869, 88JOM(356)325, 93JOM(458)167⟩ also provide routes to hexahydro-1,4-disilanaphthalenes. These last reactions can give rise to three different isomeric products (Scheme 5). Isomers (**a**) and (**b**) can be photochemically converted into isomer (**c**) in the presence of an excess of $Fe(CO)_5$ ⟨86JA1323⟩. A further reaction of interest is the platinum-catalyzed polycondensation of *o*-bis(dimethylsilyl)benzene with diynes which results in compounds containing two 1,4-disilanaphthalene rings (Equation (3)) ⟨93CC744⟩.



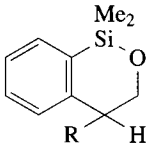
Scheme 5



Pyrolysis of certain compounds leads to heterocyclic rings, for example, when PhOM-$Me_2CH{=}CH_2$ is heated slowly to 320 °C (M = Si) or 290 °C (M = Ge), a 2*H*-1,2-benzoxasilin or a 2*H*-1,2-benzoxagermanin compound respectively results by Claisen rearrangement followed by intramolecular cycloaddition ⟨81T2459⟩. Also, thermal decomposition of a chlorotriphenyltin benzil semicarbazone complex results in the formation of a 2*H*-1,3,2-benzoxazastannine derivative ⟨89MI 627-05⟩.

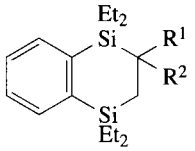
Photolysis of 1-silabenzocyclobutenes in the presence of various aldehydes and ketones yields 1*H*-2,1-benzoxasilins (**45**) and 1*H*-2,3-benzoxasilins as [2 + 4] cycloaddition products in 25–82% yields ⟨84MI 627-01⟩. Furthermore, if 1,1-dimethyl-1-hydro-1-silabenzocyclobutene reacts with PhCHO or Bu^{t}CHO in the presence of Bu^{t}OK, 1*H*-2,1-benzoxasilins (**45**) result in 84% and 85%

yields respectively ⟨90TL6059⟩. Photolysis and thermolysis of (**44**) in the presence of carbonyl compounds such as benzaldehyde, formaldehyde, and methylphenylketone afford 2*H*-2,1,4-benzoxadisilins (**46**) ⟨91OM3173, 92OM2580⟩.



R = Ph or Bu^t

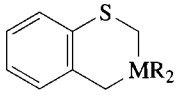
(**45**)



R^1 = H, R^2 = H or Ph
R^1 = Me, R^2 = Ph

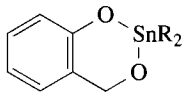
(**46**)

Salt elimination reactions also provide a route to bicyclic ring systems. For example, reaction of the dilithiated derivative of 1-methyl-2-(methylthio)benzene, 1,2-$C_6H_4SCH_2Li(CH_2Li)$, with Me_2SiCl_2, $MePhSiCl_2$ or Ph_2SiCl_2 and Ph_2SnCl_2 or Me_2SnCl_2 gives (**47**; M = Si or Sn respectively) with the elimination of LiCl ⟨89JOM(366)1⟩. In a similar fashion, 1,2-$C_6H_4OCH_2Na(CH_2ONa)$ reacts with a variety of R_2SnCl_2 reagents (R = Cl, Me, Bu, octyl, or Bn) in benzene to form 4*H*-1,3,2-benzodioxastannins (**48**) ⟨82IJC(A)726⟩.



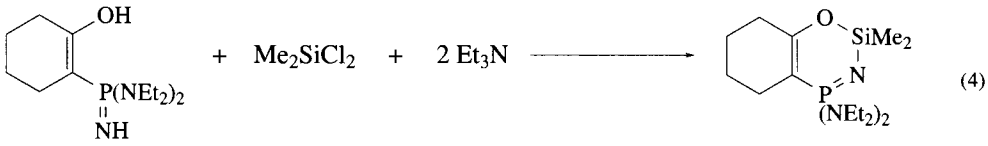
M = Si or Sn

(**47**)



(**48**)

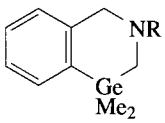
Dichlorodiethylgermane reacts with salicyclic acid or thiosalicylic acid in the presence of triethylamine to form 1,3,2-benzodioxagermin-4-ones or 3,1,2-benzoxathiagermins respectively ⟨91PS(63)341⟩. Other base-promoted cyclizations occur when the iminophosphonate (**49**) reacts with dichlorodimethylsilane in the presence of triethylamine to form (**50**) (Equation (4)) ⟨92HAC163, 92JGU1255⟩, and in the synthesis of a 1,4,2,3-benzodioxadisilin from 1,2-dichlorotetramethyldisilane and catechol in the presence of pyridine ⟨86JGU773⟩.



(4)

(**49**) (**50**)

Heating (2-bromomethylphenyl)chloromethyldimethylgermane with the primary amines methylamine, 3-(dimethylamino)propylamine, or aniline affords the corresponding 3-substituted heterocyclic 3,1-benzazagermines (**51**) in high yields ⟨88JOM(339)259⟩.



R = Me, Ph, or $CH_2CH_2CH_2NMe_2$

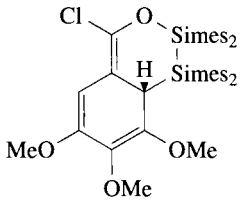
(**51**)

Many ring systems have been conveniently synthesized by the trapping of reactive, unsaturated species. For example, silenes $R_2Si{=}C(TMS)_2$ (R = Ph or Me) combine with various reagents such as $Ph_2C{=}N\text{-}TMS$ ⟨81CB3518, 86JOM(315)9, 87ZN(B)1055, 87ZN(B)1062, 89CB409⟩ and $Ph_2C{=}O$ ⟨88ZN(B)1468⟩

with [2 + 4] cycloaddition to yield various benzo-fused adducts such as 2,3-benzazasilines, 1,2,3-benzodiazasilines, and 1*H*-2,3-benzoxasilins. In a similar manner, a 2,3-benzoxagermanin results when the germaethene $Me_2Ge{=}C(TMS)_2$ reacts with $Ph_2C{=}O$ ⟨86CB2980⟩.

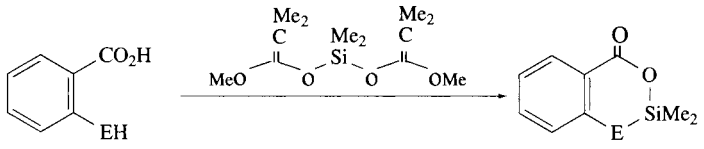
2,3-Benzazasilines and 2,3-benzoxasilins can also be formed when the silene $(TMS)_2Si{=}C(O\text{-}TMS)R$ (R = admantyl or Bu^t) reacts with the imines $Ph_2C{=}NR$ (R = Ph or TMS) ⟨93OM3666⟩ and simple acylsilanes such as $Ph_3SiCOC_6H_4X$-*p* (X = H, F, Cl, Br, or OMe) ⟨93OM4085⟩ respectively in a [2 + 4] cycloaddition. 2,3-Benzoxasilins also result from the reaction between silene $(TMS)_2Si{=}C(O\text{-}TMS)Ph$ and ketones such as benzophenone or fluorenone ⟨87OM1246⟩, and they are also transient intermediates during one-electron oxidation of 2,2-dimethyl-2-silaindane by $K_5Co^{III}W_{12}O_{40}$ ⟨93CC1691⟩.

Tetramesityldisilene and 3,4,5-trimethoxybenzoyl chloride react together to form an air-stable yellow 2*H*-3,1,2-benzoxadisilin derivative (**52**) in 25% yield which has been analyzed by gel permeation chromatography, mass spectrometry, and ^1H and ^{29}Si NMR spectroscopy ⟨93OM2177⟩. Reactive Ge=N containing species can be treated with 3,5-di-tert-butyl-*ortho*-quinone to give 1,4,2,3-benzodioxazagermine derivatives ⟨88JOM(358)77, 92JOM(431)17⟩.



(**52**)

Many bicyclic ring compounds are prepared in high yields by the condensation reaction of proton-acidic compounds with the divinyloxysilane $Me_2Si(OC(=CMe_2)OMe)_2$ ⟨83TL1273⟩. These are summarized in Equation (5).



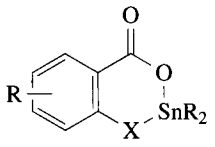
(5)

E = O, 98%; E = NH, 95%; E = S, 94%

Alkylsilyl cyanides such as $Et_2Si(CN)_2$ can be used to silylate dihydroxy compounds such as salicyl alcohol or salicylic acid to obtain 4*H*-1,3,2-benzodioxasilins (e.g. E = O in Equation (5) ⟨86JOC3545⟩). They can also be prepared regio- and stereoselectively in intramolecular Diels–Alder reactions of $R^1{}_2Si(OR^2)(OR^3)$ species (R^1 = Ph or Bu^t, R^2 = butadienyl, R^3 = substituted vinyl) ⟨91TL1145⟩.

A large number of tin-containing heterocycles are prepared using diorganotin oxides and salicylic acid and substituted derivatives of salicylic acid as starting reagents. For example, 4*H*-1,3,2-benzodioxastannins (**53**) result from the cyclocondensation of di-*n*-butyltin oxide or di-benzyltin oxide and salicylic acid, methylsalicylic acids, methoxysalicylic acids, aminosalicylic acids, or 3,5-diiodosalicyclic acids ⟨87JOM(328)61, 88BSB873, 88ICA21, 90MI 627-01⟩. Di-*n*-butyltin oxide reacts with 2-acetamidobenzoic acid, 2-benzenesulfonamidobenzoic acid, or 2-(4-toluenesulfonamido)-benzoic acid to afford the corresponding 2*H*-3,1,2-benzoxazastannine compounds ⟨88ICA21⟩. Thiosalicylic acid reacts with the diorganotin oxides $(R^1R^2SnO)_n$ where $R^1 = R^2$ = Me ⟨84OM750⟩, $R^1 = R^2$ = Bu, $R^1 = R^2$ = Ph, or R^1 = Et, R^2 = Ph ⟨91HAC447⟩, resulting in 4*H*-3,1,2-benzoxathiastannins. These compounds are characterized by ^1H, ^{13}C, ^{119}Sn NMR, ^{119}Sn Mössbauer, and IR spectroscopy and mass spectrometry.

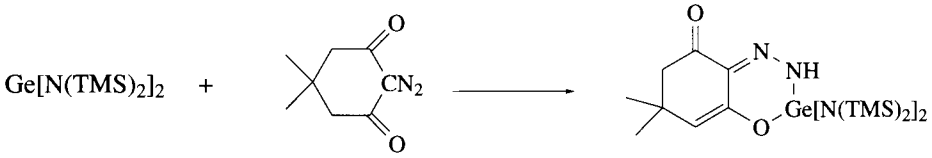
Platinum catalyzed reactions of nitriles with *o*-bis(dimethylsilyl)benzene give 2,1,4-benzazadisilines in high yields ⟨92CL45⟩. Also, platinum catalyzed dehydrogenative double silylation of several carbonyl compounds (aldehydes and ketenes) with *o*-bis(dimethylsilyl)benzene results in 1*H*-2,1,4-benzoxadisilins ⟨91JAP03258792, 92OM2639⟩. The latter compounds may also be prepared by the platinum ⟨93OM4987⟩ or nickel ⟨92JOM(439)19, 93OM87⟩ catalyzed reactions of (**44**) with carbonyl compounds.



X = O, N or S

(53)

The 1 : 1 addition of the cyclic diazo-compound (**54**) to the germylene $Ge(N(TMS)_2)_2$ affords the 2*H*-1,3,4,2-benzoxadiazagermine (**55**) (Equation (6)) which has been characterized by ^1H, ^{13}C, and ^{15}N NMR experiments and by mass spectrometry ⟨87JCS(D)501⟩.



(6)

(54) (55)

1,2,3,4-Tetrasilanaphthalenes are prepared by the Diels–Alder reaction of 2,3-dimethylbuta-1,3-diene with a strained monocyclic 1,2,3,4-tetrasilacyclohex-5-yne ⟨92JA4920, 92OM1009, 93OM803⟩.

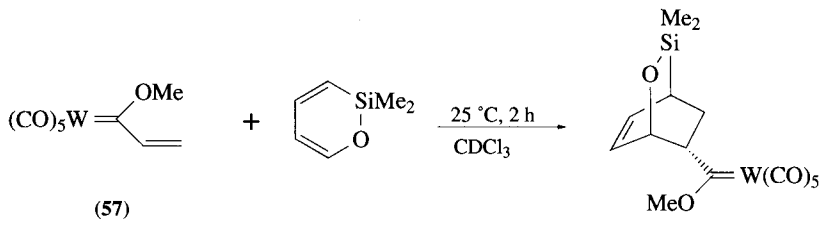
6.27.3.2.2 Bicyclo[a.b.c]anes and bicyclo[a.b.c]enes

As the names suggest, these compounds contain two rings that share two carbon 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.

(i) Synthesis of rings

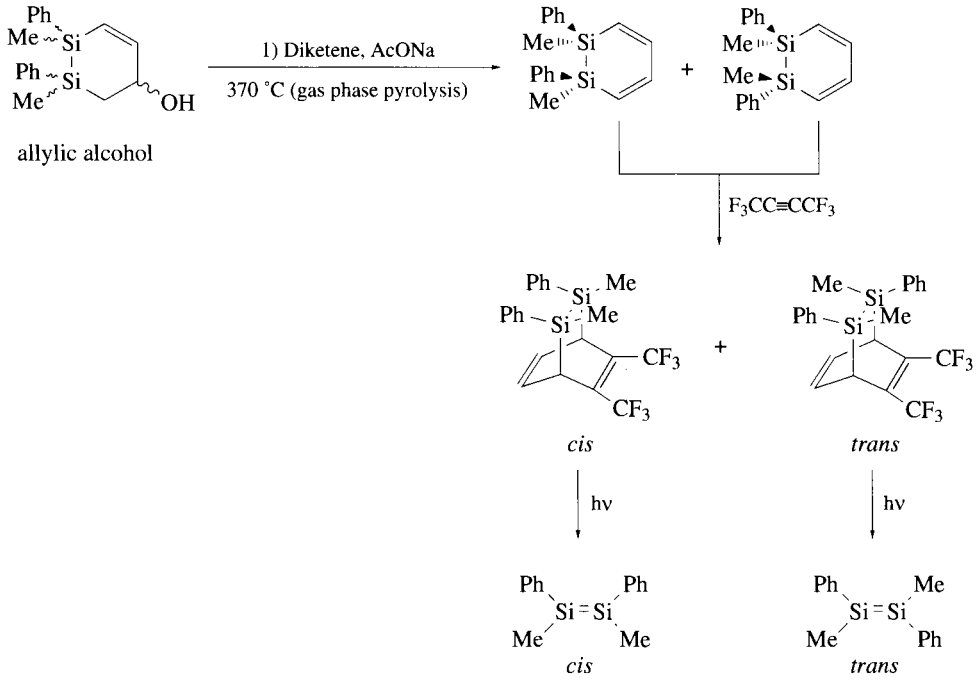
The 2,3-disilabicyclo[2.2.2]octa-5-ene ring can be prepared by the co-condensation reaction between difluorosilylene and cyclohexa-1,3-diene (via initial formation of $\cdot F_2SiSiF_2\cdot$, which adds to the ring) ⟨82JOM(226)21⟩ and 2,3-disilabicyclo[2.2.2]octa-5,7-dienes can be made from the Diels–Alder reaction of hexafluorobut-2-yne and stereoisomeric mixtures of 1,2-methyl-1,2-phenyl-1,2-disilacyclohexa-2,4-dienes, the products from which may both be used as disilene precursors (Scheme 6) ⟨93JA11460⟩.

A 2-oxa-3-silabicyclo[2.2.2]oct-5-ene derivative (**56**) has been made by a Diels–Alder reaction of the Fischer carbene complex (**57**) with a 1-oxa-2-silacyclohexa-3,5-diene heterocycle (Equation (7)) ⟨83JA6726, 90JA3642⟩.



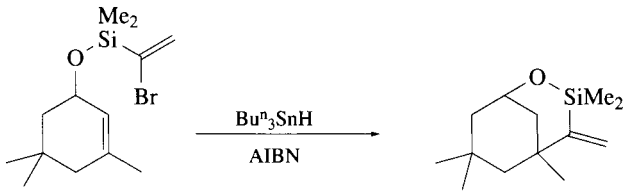
(7)

(57) (56)



Scheme 6

Silicon-mediated regio- and stereoselective hydroacylation and hydrovinylation of allylic alcohols results in 2-oxa-3-silabicyclo[3.3.1]nonanes (see, for example, Equation (8)) ⟨89JA4984⟩.



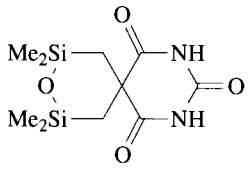
(8)

6.27.3.2.3 Spiro[5.5]undecanes

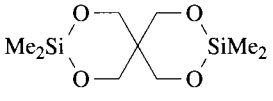
As the name implies, these ring systems are spirocyclic, i.e. the six-membered rings share a common carbon atom (see Table 5).

(i) Experimental structural methods

Both rings in these types of compounds have distorted chair conformations as determined by x-ray crystallographic studies of the 3-oxa-8,10-diaza-2,4-disila- and 2,4,8,10-tetraoxa-3,9-disila-spiro[5.5]undecanes (**58**) and (**59**) respectively ⟨81MI 627-04, 86MI 627-04⟩.



(**58**)



(**59**)

(ii) Synthesis of rings

The reaction of a silicon substituted malonic ester with urea in the presence of sodium ethoxide affords the 3-oxa-8,10-diaza-2,4-disilaspiro[5.5]undecan-9-one (**58**) ⟨81MI 627-04⟩.

1,1,3,3,5,5,7,7,9,9,11,11-Dodecamethyl-1,3,5,7,9,11-hexasilaspiro[5.5]-undecane is prepared by lithiation of 1,1,3,3,5,5-hexamethyl-6,6-dibromo-1,3,5-trisilacyclohexane followed by the addition of $(BrMe_2SiCH_2)_2SiMe_2$ ⟨81ZAAC(481)60⟩.

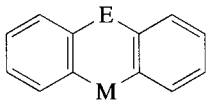
6.27.3.3 Tricyclic Systems

6.27.3.3.1 Dibenzo-fused systems

These compounds consist of two benzene rings flanking the heterocycle; therefore, the heterocycle contains only two heteroatoms. Most of the work on these compounds has centered on theoretical studies of the electronic structures and aromatic properties of these heterocycles; references are given in Table 6.

(i) Theoretical methods

As already mentioned, much of the research on the compounds (**60**) has revolved around *ab initio* theoretical methods. The influence of atomic orbitals and lone pairs of electrons of heteroatoms on the luminescence–spectroscopic properties of a series of dibenzyl compounds has been investigated experimentally and within the framework of CNDO/S-CI calculations ⟨81MI 627-03, 82MI 627-02, 84MI 627-03, 85MI 627-04, 86MI 627-03, 87MI 627-02, 91MI 627-02⟩. The conjugation effects and hence the electronic structures of these compounds have also been studied by photoelectron spectroscopy, ionization potentials, and other quantum chemistry calculations ⟨81JGU1099, 82JGU2015, 83MI 627-02, 88MI 627-03, 89MI 627-06, 90JGU2240⟩. MNDO calculations indicate these systems are inherently planar, but that ring-puckering is a very low energy process that can arise from intramolecular effects, for example, *peri*- or transannular interactions, and/or intermolecular interactions such as crystal packing forces ⟨86H(24)2457⟩.



(**60**)

E = NEt, M = $SiMe_2$ or SiHMe
E = O, M = SiMeH
E = O, M = $GePh_2$
E = O, M = $SnPh_2$
E = S, M = $SiMe_2$, $GeMe_2$ or $SnPh_2$
etc.

(ii) Experimental structural methods

The structures of many of the known compounds of the type (**60**) have been determined (for details see Table 7). All the molecules are nonplanar and have an open book conformation and the angle of folding along the M···E vector, α, describes the deviation from planarity (the lower the value, the greater the deviation). The central heterocycle has a boat conformation.

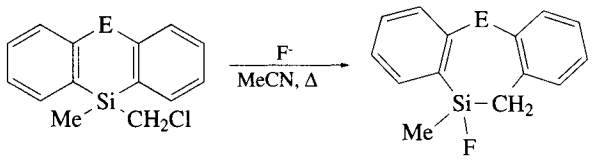
Some conclusions can be drawn from Table 7: (i) the phenoxa derivatives are the most planar and it may be argued, therefore, that aromaticity is the greatest in them; (ii) the phenazastannine compounds show a marked loss of planarity which is greater than that found for the azasilines and azagermines; and (iii) in general, the introduction of electron acceptor substituents into the molecule, regardless of position, increases the nonplanarity of the molecule and hence weakens its aromatic properties ⟨84IZV1795⟩.

Compounds in which E = Si, Ge, or Sn and M = Si are similar in structure in that the heterocyclic ring has a boat conformation and the molecules on the whole are nonplanar ⟨84OM255, 84OM1755⟩. In fact, the silanthrene (E = M = Si in Table 7) retains this structure when it forms a cationic chromium(I) complex in 9,9,10,10-tetramethyl-9,10-disiladihydroanthracene(benzene)chromium(I) tetraphenylborate ⟨88MI 627-02⟩. The chromium atom is coordinated in a sandwich fashion between

one of the aromatic silanthrene rings and a benzene ring; these are almost parallel to each other and the $Cr(C_6H_6)$ moiety is in an *endo* position. The angle of folding along the Si···Si vector is 142°. A similar arrangement is found in the $Cr(CO)_3$ derivative, and *cis* and *trans* isomers may be formed in the bis $Cr(CO)_3$ derivative ⟨84OM1755⟩.

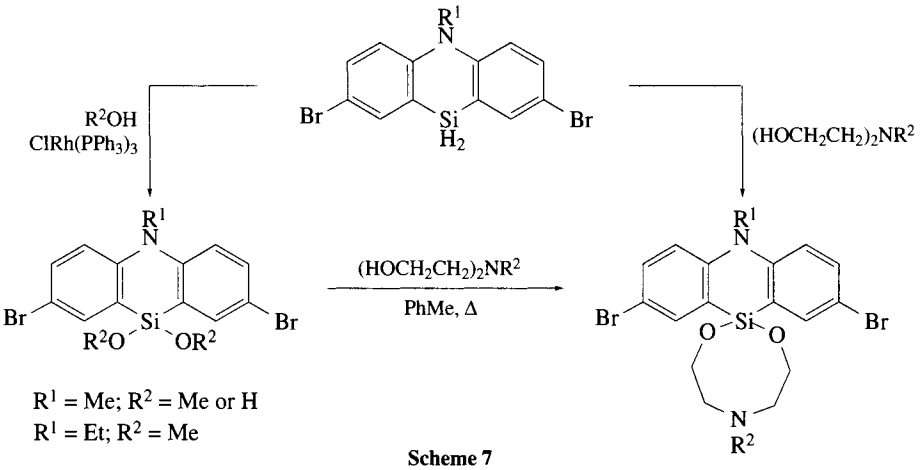
(iii) Reactivity of rings

Fluoride ions induce Ph group migration in dibenzo-fused tricyclic silicon-containing systems to produce ring-expanded products (Equation (9)) ⟨84OM1051⟩. Spirocyclic pseudosilatranes are prepared from the condensation of $(HOCH_2CH_2)_2NMe$ with dihydrophenazasilines or by alcohol exchange with dialkoxyphenazasilines (Scheme 7) ⟨90JOM(399)221⟩.



(9)

E = NMe or O



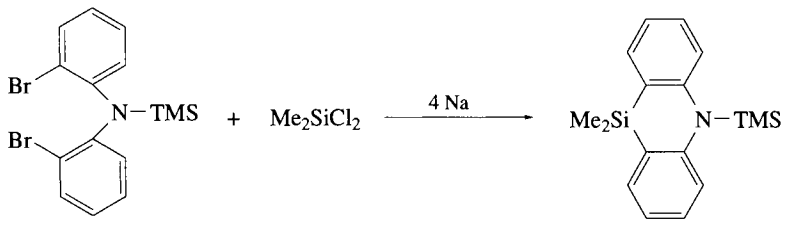
R^1 = Me; R^2 = Me or H
R^1 = Et; R^2 = Me

Scheme 7

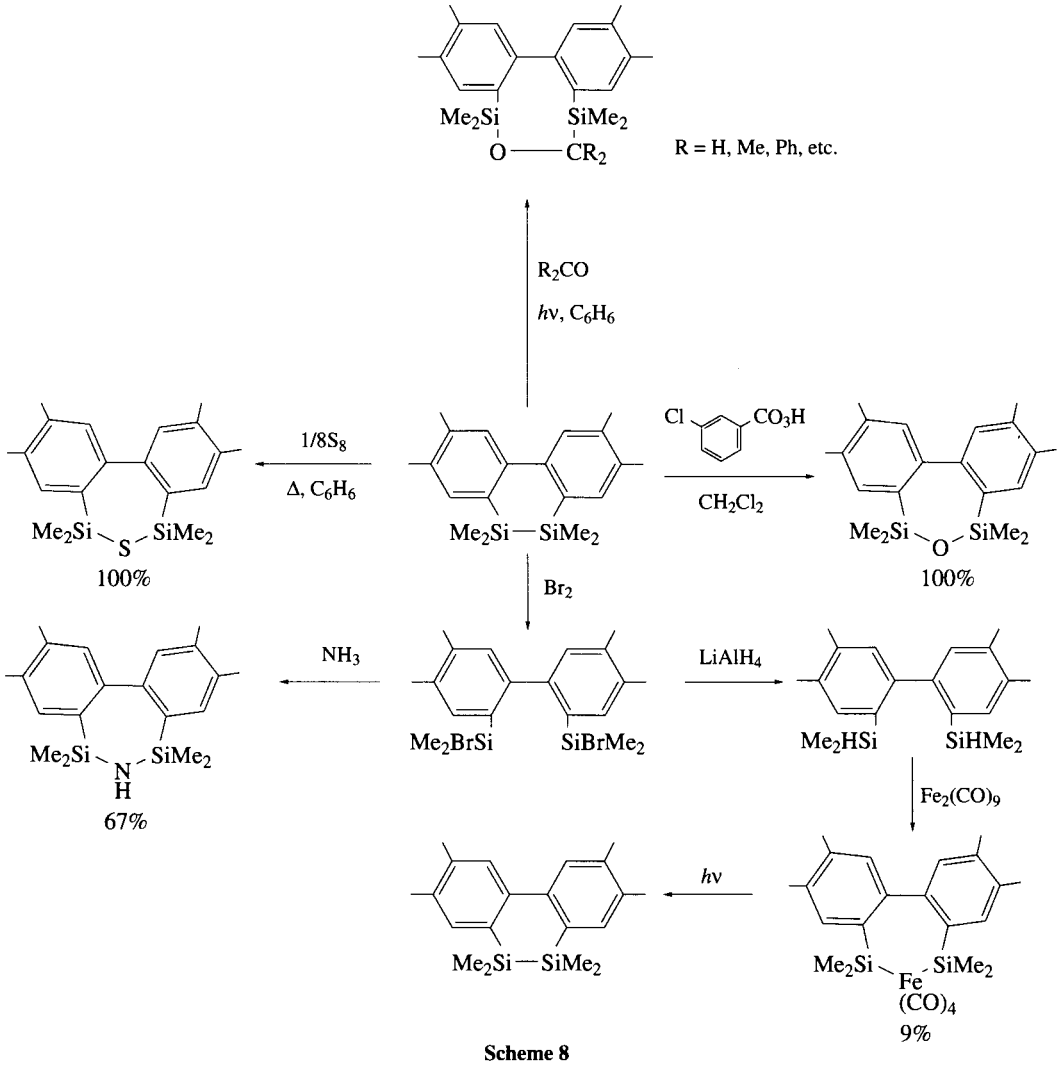
Photolysis reactions of 9,10-disilaphenanthrene in the presence of ketones or formaldehyde have been studied in detail (Scheme 8); the product distribution obtained depends on the type of carbonyl compound used ⟨87CL983⟩. Insertion reactions of this phenanthrene are also shown (Scheme 8) ⟨87CL1075⟩.

(iv) Synthesis of rings

Phenazasilines are synthesized by ring-closure reactions of *N*-trimethylsilylbis(2-halogenophenyl) amines with dichlorodimethylsilane (Equation (10)) followed by acid cleavage of *N*-silyl groups ⟨88ZN(B)104⟩. Other phenazasiline derivatives have been prepared similarly by condensation of $(o\text{-}MC_6H_4)_2NMe$ (M = Li, MgCl) with trichlorosilane followed by reduction with $LiAlH_4$ ⟨86JOM(304)93⟩.



(10)



Scheme 8

Lithiation of diphenyl ether followed by the addition of dichlorodimethylsilane affords a phenoxasilin ⟨87JGU632⟩ and a phenothiasilin is formed in the reaction of diphenylsulfone with dichlorodimethylsilane and lithium 2,2,6,6-tetramethylpiperidide at 0 °C in THF ⟨83JA6155⟩.

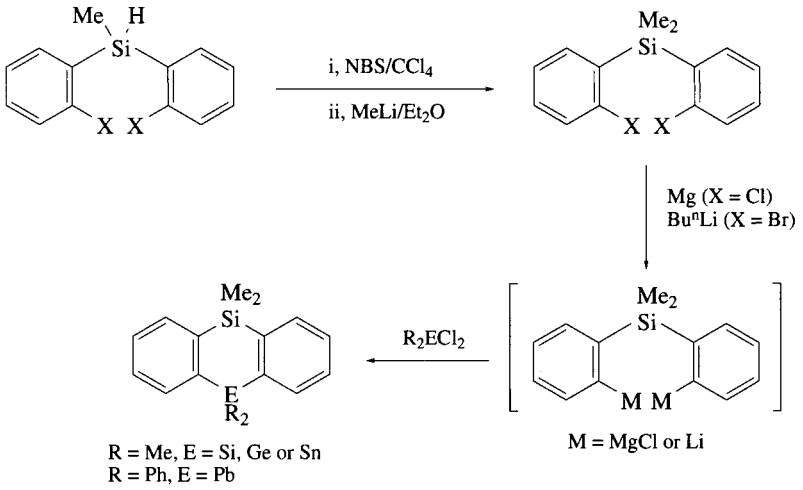
The synthesis and reactions of many derivatives of silanthrene and its germanium analogue have been reviewed extensively ⟨85JGU1283⟩. One of the successful ways of preparing a range of silanthrenes, or 5,5,10,10-tetramethylphenosila-germanin, -stannin, and -plumbin, is from methylbis(2-halogenophenyl)silane precursors as outlined in Scheme 9 ⟨84JOM(271)319, 84OM255⟩.

6.27.3.3.2 Naphtho-fused systems

The naphthalene part of the molecule in these compounds can be fused in the three different ways indicated in Table 6.

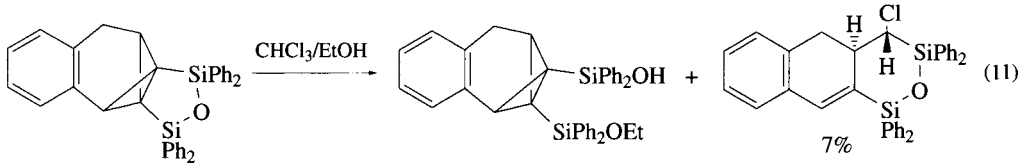
(i) Synthesis of rings

The reaction of dichloroneopentylsilene with α-naphthaldehyde results in a 1*H*-naphth[2,1-*d*][1,2]oxasilin ⟨90ZN(B)909⟩. The oxadisilin (**61**) may be prepared according to Equation (11) but in very small yield ⟨92T89⟩. When the oxygen atom in the starting reagent in Equation (11) is replaced by a silicon atom, a trace of acid from, for example, silica gel, leads to formation of a 1,2,3-



Scheme 9

trisilaanthracene ⟨90TL4185, 92T89⟩. A wide range of naphtho[1,8-*de*]-1,3,2-dioxasilins are prepared in 60–90% yields by the reaction of chlorosilanes with 1,8-dihydroxynaphthalene ⟨81TL4999, 86MI 627-02⟩.



(11)

(61)

6.27.3.3.3 Miscellaneous tricyclic systems

Detailed references to the rings described in this section may be found in Table 6.

(i) Synthesis of rings

The addition of lithium naphthalenide to $Bu^t_2SiCl_2$ in DME results in a 1,4-etheno-2,3-disilanaphthalene ⟨83OM1464⟩ whilst a germanium analogue is prepared from benzyne and 3,6-diphenyl-1,1,2,2-tetramethyl-1,2-digermacyclohexa-3,5-diene ⟨84TL2467⟩.

1,2,4,5-Tetrakis(dimethylsilyl)benzene reacts with diphenylalkyne in the presence of a platinum catalyst resulting in the highly symmetrical 1,4,5,8-tetrasilaanthracene, as shown in Table 6 ⟨93CC744⟩.

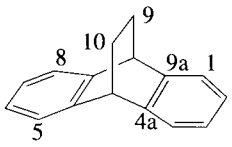
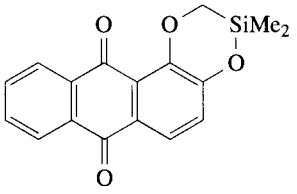
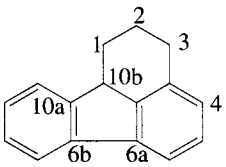
6.27.3.4 Higher Cyclic Rings

There are examples of tetracyclic and higher cyclic compounds, some of which will be briefly mentioned here. Further details can be found in Table 8.

6.27.3.4.1 Experimental structural methods

The structure of the only known anthra[1,2-*e*][1,4,2]dioxasilin-7,12-dione has been investigated (see Table 8). It exists in two polymorphs which have slight conformational differences due to

Table 8 Higher polycyclic compounds.

Ring system	*Heteroatoms*[a]	*Ref.*
		
9,10-Disilanoanthracene	M = Si, M = Si	Prep. ⟨82JA6156, 86JOM(308)177, 86OM1911⟩; prep. & reaction ⟨84CC724⟩
9,10-Digermoanthracene	M = Ge, M = Ge	Prep. ⟨84TL2467⟩
Anthracene-fused rings		
		
Anthra[1,2-*e*][1,4,2]dioxasilin	E = O, E = O, M = Si	Prep. & x-ray ⟨86MI 627-05⟩; use as sorbent ⟨90MI 627-05⟩
Miscellaneous rings		
		
Fluoreno[1,9-*de*]-1,2-azasiline	E = N, M = Si	Prep. & rearrangement ⟨93OM3666⟩
2*H*-Fluoreno[1,9-*de*]-1,2-oxasilin	E = O, M = Si	Prep., photochem. & thermolysis ⟨87OM1246⟩; prep. & x-ray ⟨86JA4241⟩

[a]The location of the heteroatoms is as indicated in the ring system name.

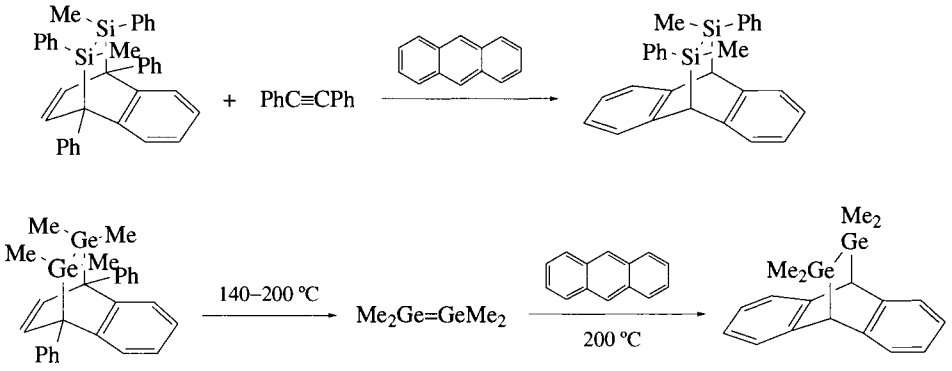
features of the intermolecular interactions in the crystal structure ⟨86MI 627-05⟩. It forms two sets of monoclinic crystals, a yellow form which has the space group $P2_{1/c}$, and a dark red form of space group $P2_{1/n}$.

6.27.3.4.2 Synthesis of rings

Various synthetic methods provide 9,10-disilanoanthracenes. The trapping of disilenes with anthracene is one example ⟨82JA6156⟩, and the reaction of lithium anthracenide with 1,2-dihalogenotetraalkyldisilanes, $R^1R^2XSi—SiXR^1R^2$, is another ($R^1 = R^2 = Pr^i$, X = Cl, ⟨84CC724⟩; $R^1 = R^2$ = cyclohexyl, X = Cl, I; R^1 = cyclohexyl, $R^2 = Bu^t$, X = Cl, Br, I, ⟨86JOM(308)177⟩). Pyrolysis of a substituted *trans*-1,4-etheno-2,3-disilanaphthalene in the presence of diphenylalkyne and anthracene results in the *trans* isomer of the corresponding 9,10-disilanoanthracene with over 90% stereospecificity ⟨85CL643⟩. Thermolysis of a 1,4-etheno-2,3-benzodigermanin in the presence of anthracene similarly results in a 9,10-digermanoanthracene ⟨84TL2467⟩. These last two reactions are summarized in Scheme 10.

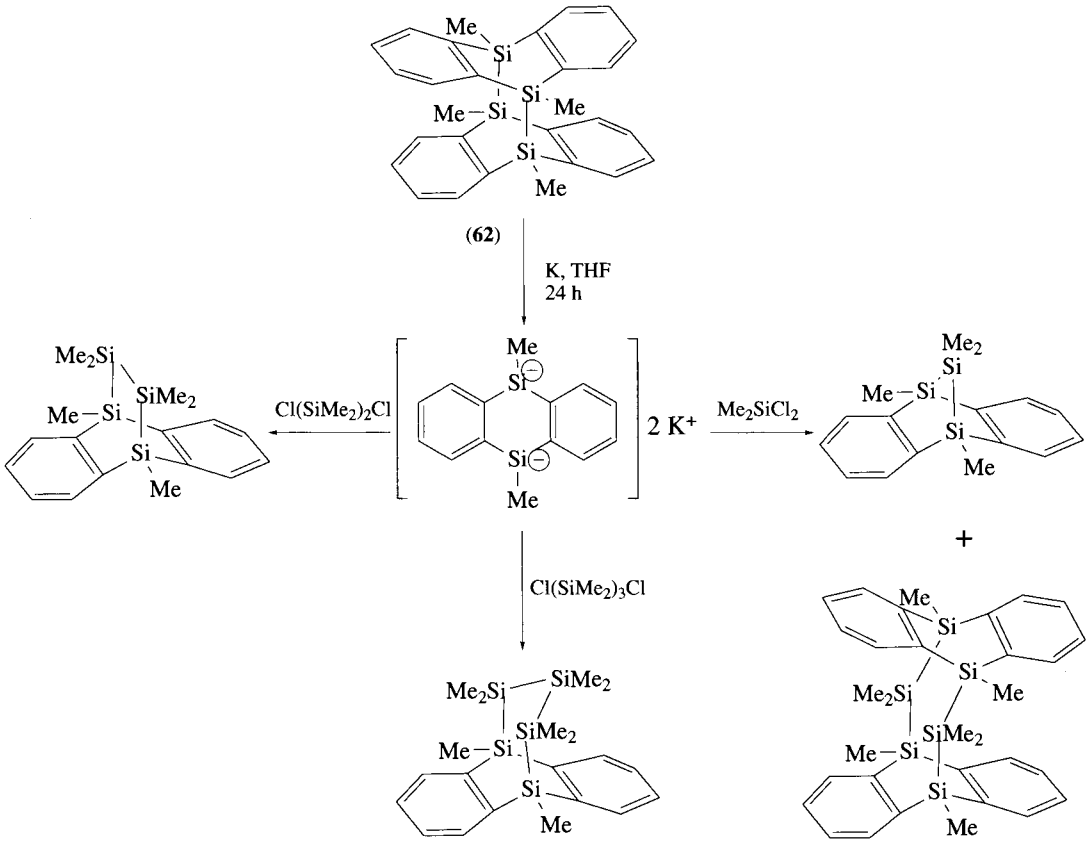
A derivative of anthra[1,2-*e*][1,4,2]dioxasilin-7,12-dione can be produced by the interaction of chloromethyldimethylchlorosilane with alizarin in the presence of triethylamine ⟨86MI 627-05⟩. On crystallization from chloroform it gives a mixture of red crystals and yellow crystals which are the two polymorphic forms described in Section 6.27.3.4.1 above.

The dimeric 9,10-disilaanthracene (**62**) may be prepared by direct reduction of 9,10-dihydro-9,10-dimethyl-9,10-disilaantharacene by two equivalents of Li. Use of excess Li or K leads to Si—Si



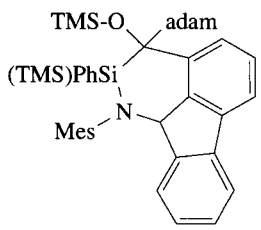
Scheme 10

bond cleavage to give a dianionic 9,10-dilithio derivative which reacts with various dichlorosilanes to give further polycyclic species (Scheme 11) ⟨95OM3625⟩.

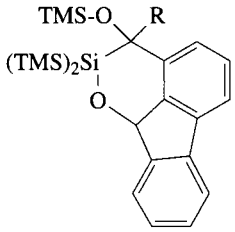


Scheme 11

Another class of compounds that can be included here are fluorene derivatives. For example, fluoreno[1,9-*de*]-1,2-azasilines such as (**63**) are synthesized from the reaction of imines with silenes ⟨93OM3666⟩ whilst oxasilin analogues such as (**64**) are formed from the reaction of silenes with fluorenone ⟨87OM1246⟩.



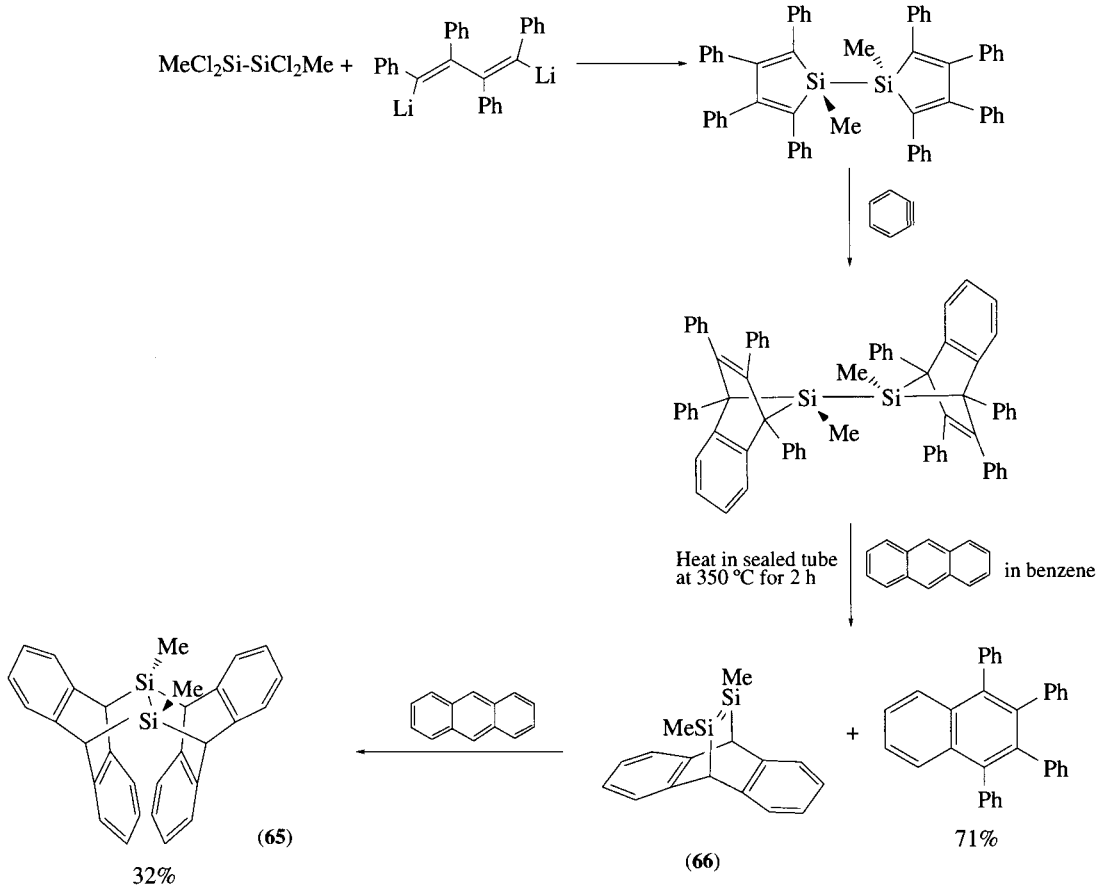
(63)



R = Bu^t or adam

(64)

A silicon bridgehead heterocycle (**65**), in effect a formal adduct of dimethyldisilyne, is formed as shown in Scheme 12 ⟨86JA4241⟩. Its structure was confirmed by x-ray crystallography. Formation of the adduct is thought to proceed via the interesting, but undetected, disila-dibenzobarrelene (**66**), containing an Si=Si double bond.



(65)

32%

(66)

71%

Scheme 12

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6.28
Six-membered Rings with Two or More Heteroatoms with at least One Boron

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University of Puerto Rico, Río Piedras, PR, USA

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6.28.1 INTRODUCTION

As noted in the title, the scope of this chapter is limited to boron-containing heterocycles which also have at least one other heteroatom within the six-membered ring nucleus. Benzo-fused derivatives are also included while other polycyclic systems are not. Borazines and boroxines as well as other boron-containing ring systems which do not contain carbon atoms are also omitted from this survey. The literature covered emphasizes the period of 1983–1995 with previous material included for historical background, perspective and clarity. The present coverage is designed to be comprehensive, rather than exhaustive. The material has been selected to highlight the major aspects of research involving these ring systems. Toward this end, heteroatom-containing borinanes and their applications to synthesis are covered as well as the heteroaromatic boron-containing rings which were extensively covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and related works ⟨84CHEC-I(1)629, 82COMC-I(1)311⟩. The significant structural features as well as spectroscopic and theoretical calculations on new systems are integrated into the text which describes their synthesis and reactions.

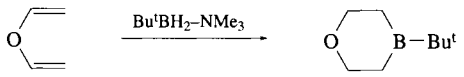
The methods employed for the construction of boracycles obviously depend most upon the atoms to which the boron atom is bonded in the ring system under consideration. With this in mind, representative examples of the various ring types are selected from the earlier literature and these are used to illustrate the various methods employed for the construction of the ring. Examples are chosen which produce the ring systems covered in the present chapter. However, these processes often have been used to prepare other medium-sized ring systems. The reader is recommended to consult other chapters of this work which consider other boron-containing ring systems for these applications. For clarity, divisions have been made for C—B—C, C—B—X, and X—B—X categories where X represents any element other than carbon. Examples of both unsaturated and saturated ring systems are included within each heading as are benzo-fused systems.

6.28.2 BORACYCLES WITH THE C—B—C LINKAGE

The most common methods of ring construction employ cyclic hydroboration, radical additions of H_2Y to unsaturated organoboranes and transmetallation procedures. Specific examples of these processes are presented in the following sections.

6.28.2.1 Representative Synthetic Methods

The cyclic hydroboration of α,ω-dienes with monoalkylboranes leads to boracycles, often producing these ring systems in high isomeric purities. An early example of this process is represented by the cyclic hydroboration of divinyl ether (**1**) with *t*-butylborane-trimethylamine complex (Equation (1)) ⟨61JA2541⟩.



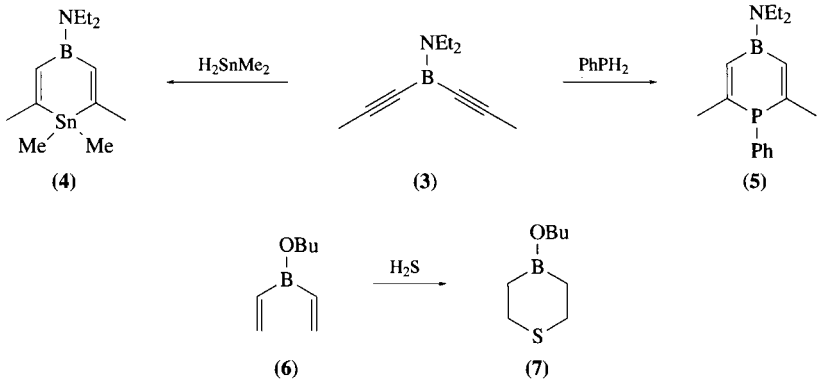
(1)

(1) (2)

The success of this process in producing the borinane ring (e.g., (**2**)) exclusively can be attributed to the powerful β-directive effect of the heteroatom as a π-donor. With less effective donors (e.g., CH_2, $SiMe_2$) the related process leads to borolanes (five-membered rings) rather than to borinanes as the major cyclic products ⟨77T2331, 84JOC2565⟩.

The radical addition of H_2SnMe_2, H_2PPh, and H_2S to unsaturated organoboranes provides an alternative method for the introduction of a heteroatom to a position remote from the boron in the construction of heteroatom-substituted borinanes. Representative examples of these processes are illustrated for the syntheses of the 1-stanna-4-boracyclohexa-2,5-diene (**4**), 1,4-phosphaborine (**5**), and 1,4-thiaborinane (**7**) systems (Scheme 1) ⟨78ZN(B)641, 82COMC-I(1)311⟩.

Transmetallation provides a convenient entry to boracyclohexadienes. The common stanna-

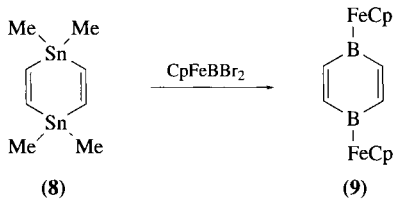


(4) (3) (5)

(6) (7)

Scheme 1

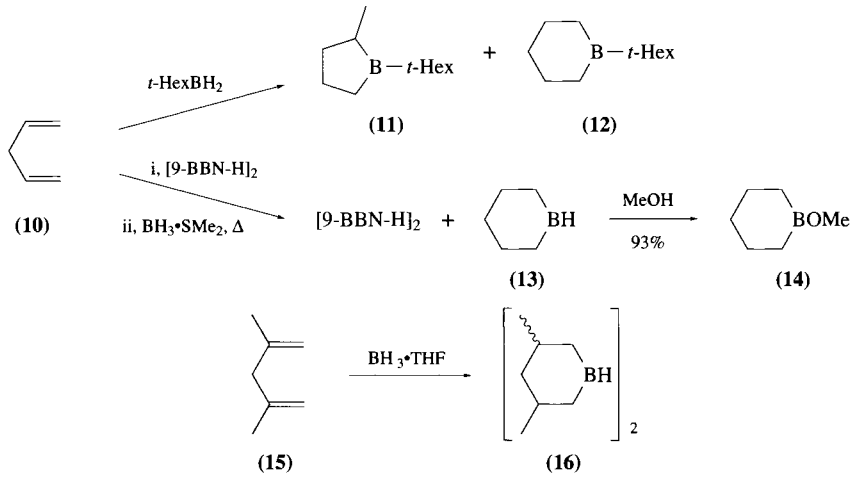
cycle/boron halide route is illustrated for the preparation of a 1,4-diboracyclohexa-2,5-diene (**9**) in Equation (2) ⟨78JOM(161)C36⟩.



(8) (9) (2)

6.28.2.2 4-Borinanes Containing 1-Heteroatom Substitution

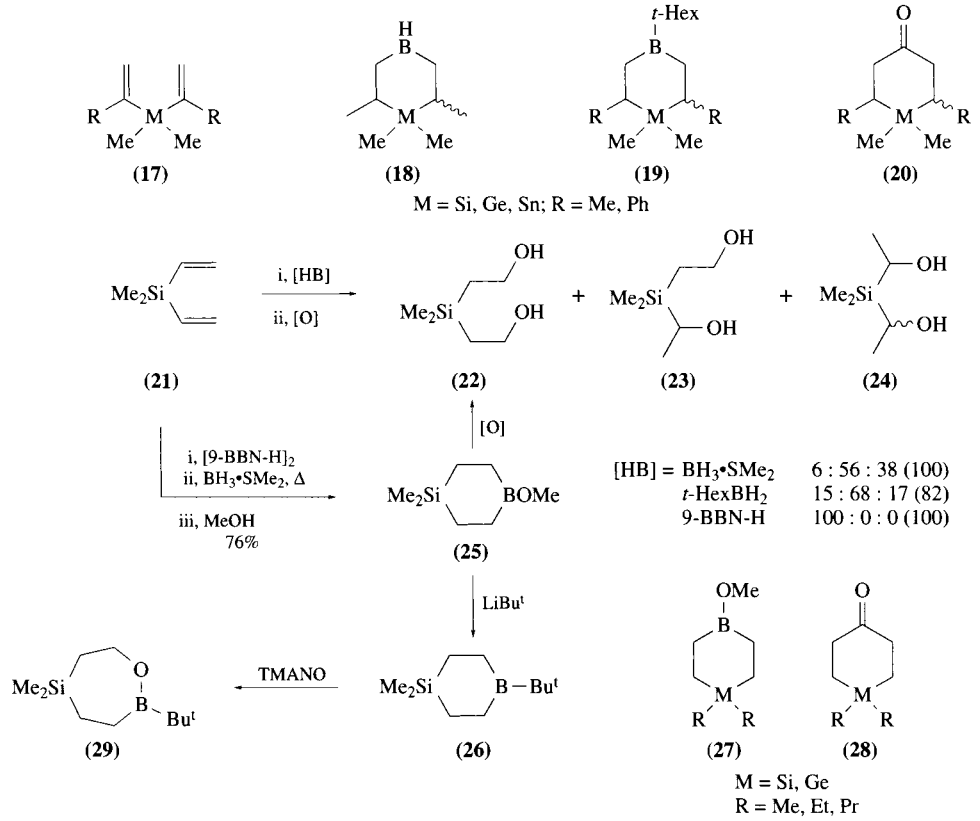
The cyclic hydroboration of divinyl compounds can provide a convenient entry to borinanes (e.g. (**2**)). However, this process is not general. For example, 1,4-pentadiene (**10**) gives a 72:28 mixture of the 2-methylborolane (**11**) and its borinane counterpart (**12**) with *t*-hexylborane (2,3-dimethyl-2-butylborane) (Scheme 2) ⟨77T2331⟩. Employing BH_3-THF, the hydroboration is further complicated by the formation of 3:2 diene/borane adducts. To overcome these problems, these adducts are thermally isomerized and subsequently exchanged with BH_3-THF to obtain bisborinane (**13**) in pure form ⟨71JOM(26)C67⟩. A more convenient approach to this heterocycle utilizes the remarkable regioselectivity of 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer to establish the essential 1,5-diboryl regiochemistry. Subsequent exchange of these intermediates with BH_3-SMe_2 regenerates 9-BBN-H dimer and gives the dimers (**13**). These are methanolyzed to their *B*-methoxy derivatives, from which pure (**14**) is easily isolated by distillation ⟨82H(18)77, 83JOM(250)13, 86JOC1330⟩. The regioisomeric problems described for 1,4-pentadiene can also be circumvented by the additional 2,4-dimethyl substitution in the substrate (i.e. (**15**)) from which the 2,5-dimethylborinane (**16**) is obtained directly from hydroboration with BH_3-THF ⟨73JA6757⟩.



Scheme 2

These findings have been utilized to prepare the more elusive 1-metalla-4-borinane derivatives of silicon, germanium, and tin where the metals lack the powerful *β*-directive effect observed in the hydroboration of simple alkenes ⟨83JOC1801⟩. Thus, in contrast to the hydroboration behavior of (**15**) with BH_3-THF, (**17**) does not lead to (**18**) exclusively, but rather to a 70:30 mixture of this heterocycle together with its borolane counterpart (Scheme 3). However, using *t*-hexylborane, (**19**) is produced quantitatively and these metallaborinanes were converted to metallacyclohexan-4-ones (**20**) through the cyanoborate process (i. KCN, ii. TFAA, iii. [O]). The regiochemical problem was even more severe in the parent system (**21**), but this was eventually overcome using the 9-BBN-H/BH_3 exchange process, which gave (**25**) in isomerically pure form ⟨84JOC2565⟩. Reaction of (**25**) with $LiBu^t$ gave (**26**) in isomerically pure form for the first time. Other silicon and germanium, but not tin, borinane derivatives (**27**) are available through this methodology and these were converted

into metallacyclohexan-4-ones (**28**) through the DCME reaction (i. $CHCl_2OMe/LiOCR_3$, ii. [O]) ⟨89JOC2462⟩. Monooxidation of (**26**) with anhydrous trimethylamine *N*-oxide (TMANO) affords the 1,5,2-oxasilaborepane (**29**) ⟨86JOC1330⟩.

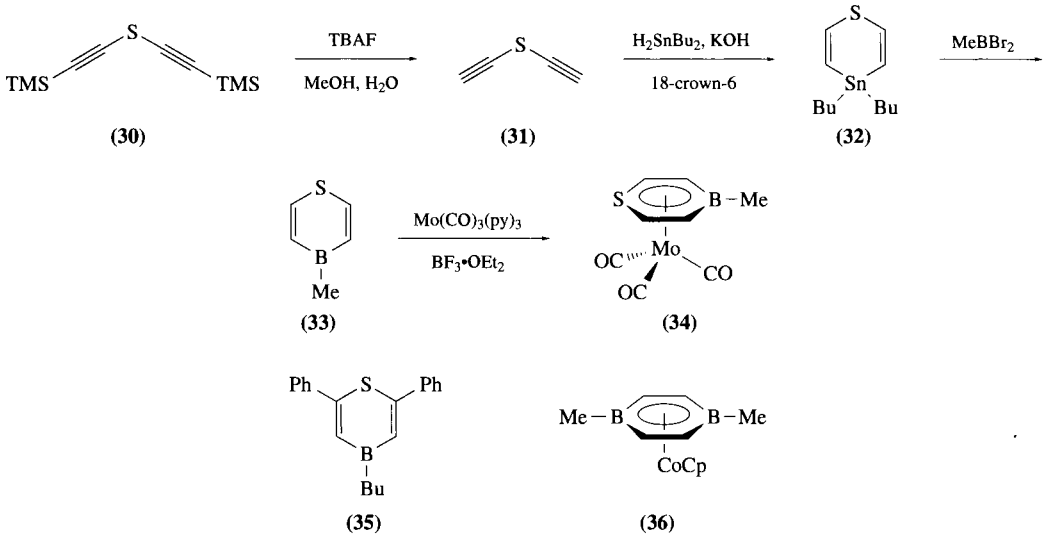


Scheme 3

6.28.2.3 4-Borins Containing 1-Heteroatom Substitution

Illustrating the preparation of heterocyclic boranes through a transmetallation sequence from an organotin precursor, the synthesis of 4-methyl-1,4-thiaborin (**33**) from the reaction of dibromomethylborane and a 1-thia-4-stannacyclohexa-2,5-diene (**32**) was recently accomplished in 57% yield ⟨95OM3141⟩ (Scheme 4). The aromatic nature of this ring system was established through NMR studies where both downfield ^1H signals (δ 7.99 (H-2), 7.40 (H-3)) and an upfield ^{11}B signal (δ 50.1) are found. These values are consistent with analogous signals in other boraaromatic systems (e.g. 1-methylborepin: ^1H NMR (δ 7.66 (H-2), 7.73 (H-3)); ^{11}B NMR (δ 54.8)). Interestingly, the previously known 1-butyl-2,6-diphenyl-1,4-thiaborin (**35**) has a much more downfield ^{11}B NMR resonance (δ 66.8) suggesting that this additional substitution may result in a ring system with less aromatic character ⟨82ZN(B)43⟩. A tricarbonyl(η^6-1,4-thiaborin)molybdenum complex (**34**) was prepared and its single crystal x-ray structure revealed bond lengths (i.e., C—C (1.37, 1.38 Å); C—S (1.75 Å); B—C(3)(1.52 Å)) essentially identical to similar bonds in related metal complexes of the aromatic borepin and thiophene systems. Related metal complexes are also known for symmetrical 1,4-diboracyclohexadienes (**36**) ⟨80JOM(192)421⟩.

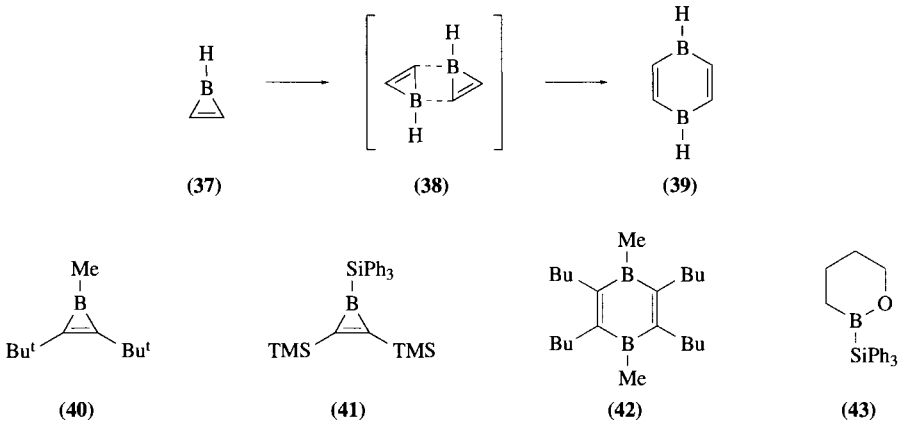
The dimerization of borirene (**37**) to produce 1,4-diboracyclohexa-2,5-diene (**39**) has been calculated to have a very low activation energy (11 kcal mol^{-1}) through a C_2 transition state (**38**) (Scheme 5). The barrier can be raised by either π-donors on boron or bulky substituents ⟨86JA3960⟩. This is consistent with earlier experimental results which report borirene (**40**) (plus a 1,3-diboretene) from di-(*t*-butyl)acetylene and $MeBBr_2/C_8K$ ⟨84POL271⟩. However, with the less bulky di-(*n*-butyl)-acetylene the dimeric (**42**) is formed. The low temperature photolysis of tristriphenylsilylborane in bistrimethylsilylacetylene produces $BSiPh_3$ which adds to gives a borirene (**41**) ⟨84AG(E)454⟩. The



(30) (31) (32) (33) (34) (35) (36)

Scheme 4

silylborylene intermediate can also undergo insertion reactions which, in the case of THF, gives the 1,2-oxaborinane (**43**). For (**39**), calculations also support the six-membered ring structure shown as the most stable isomer of the unknown $B_2C_4H_6$ ⟨88JA125⟩ and its known *B*-difluoro counterpart ⟨95JA1403⟩. For $B_4C_2H_8$, calculations do not provide a clear distinction between the relative stabilities of a cyclic and a *nido*-2,3-$B_4C_2H_8$ structure ⟨89JPC1265⟩. Calculations for $B_4C_2H_6$ suggest a 1,6-*nido* (D_{4h}) structure ⟨92CRV177⟩ but its *B*-tetrachloro counterpart is predicted to have the classical cyclic structure ⟨95JA1403⟩.



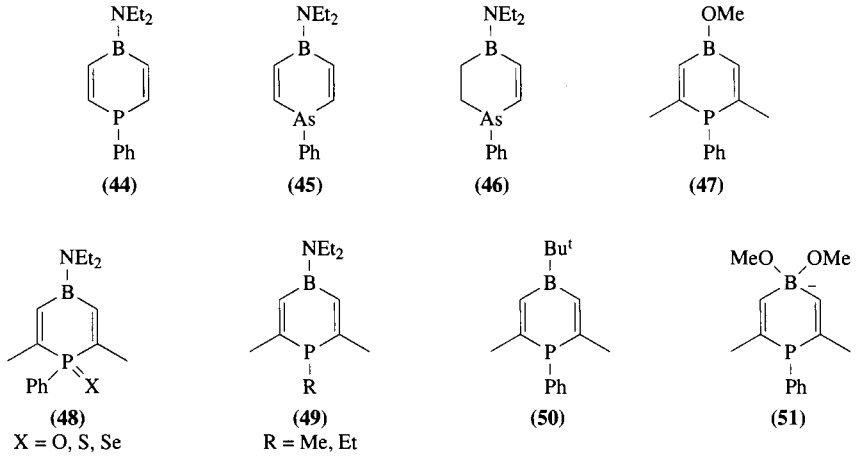
(37) (38) (39) (40) (41) (42) (43)

Scheme 5

The chemistry of 1-phospha-4-boracyclohexa-2,5-dienes has been further developed to include preparations of the less substituted derivative (**44**) and its 1-arsa analogue (**45**) which is formed as a 2:1 mixture with its dihydro counterpart (**46**) (Scheme 6). The chemistry of (**5**) includes its methanolysis to (**47**), its oxidation with chalcogens to phosphorus(V) compounds (**48**), and its conversion to *P*-methyl and ethyl derivatives (**49**) with potassium in DME followed by alkylation with alkyl halides. The *B*-*t*-butyl derivative (**50**) is also available from the addition of the alkylithium, but attempts to prepare the corresponding *B*-Me derivative were thwarted by the failure of the intermediate 'ate' complex (**51**) to undergo demethoxylation ⟨83JOM(250)33⟩.

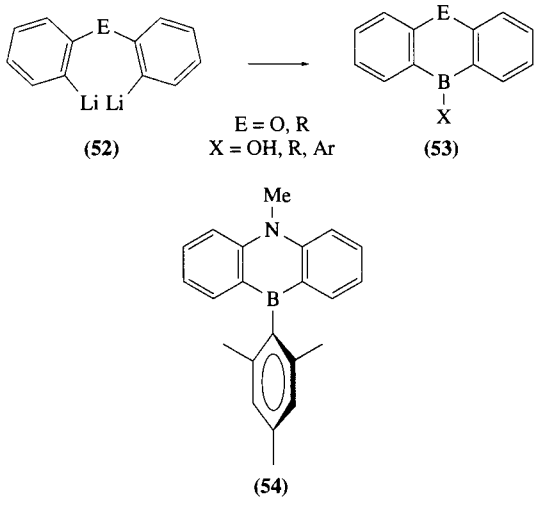
6.28.2.4 10-Boraanthracenes Containing 9-Heteroatom Substitution

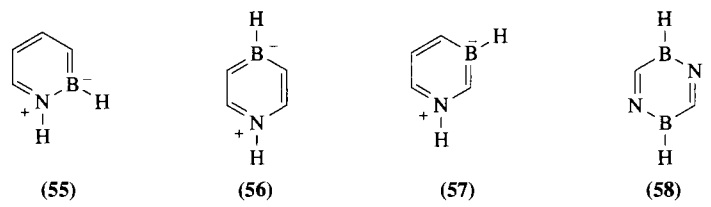
The synthesis and properties of 9-hetera-10-boraanthracenes have been studied in detail over the ten years since 1985. The 9-oxa and 9-aza derivatives (**53**) were prepared from the reaction of their



Scheme 6

2,2′-dilithiated precursors (**52**) with tributylboroxine and boron trifluoride, respectively (Scheme 7) ⟨87ZOB716, 92CC1247⟩. In the latter instance, further reaction with mesityllithium gave the triaryl derivative (**54**) whose x-ray structure suggested to the authors that the conjugation of the π system is interrupted by the boron atom (i.e., ring C—C (1.42 Å); ring C—N (1.38 Å); ring B—C (1.54 Å). The ^{11}B NMR shift (δ 54.0) of (**54**) is positioned between that of (**33**) (δ 50.1) and 9-phenyl-9,10-dihydro-9-boraanthracene (δ 58.0). The ability of (**53**) to exhibit both donor and acceptor properties was established experimentally through their charge transfer complexes ⟨88ZOB1296, 89KGS1676⟩. Like its sila analogue, bora substitution affects triplet-triplet transitions and its unoccupied orbital contributes significantly to the LUMO of the system ⟨89JPU348, 90MI 628-01, 91JGU2240⟩. Calculations at the MP2/6-31G* level on the unknown dihydro-1,2-, 1,4-, and 1,3-azaborines (**55**)–(**57**) suggest that the stabilities diminish in this order, a consequence of changes in both the σ and π frameworks ⟨92JOC5492⟩. In the calculated isomers of $C_2H_4B_2N_2$, the dihydro-1,4,2,5-diazadiborine structure (**58**) in the boat form is predicted to be the most stable isomer ⟨92JA10955, 94JPC8653⟩.





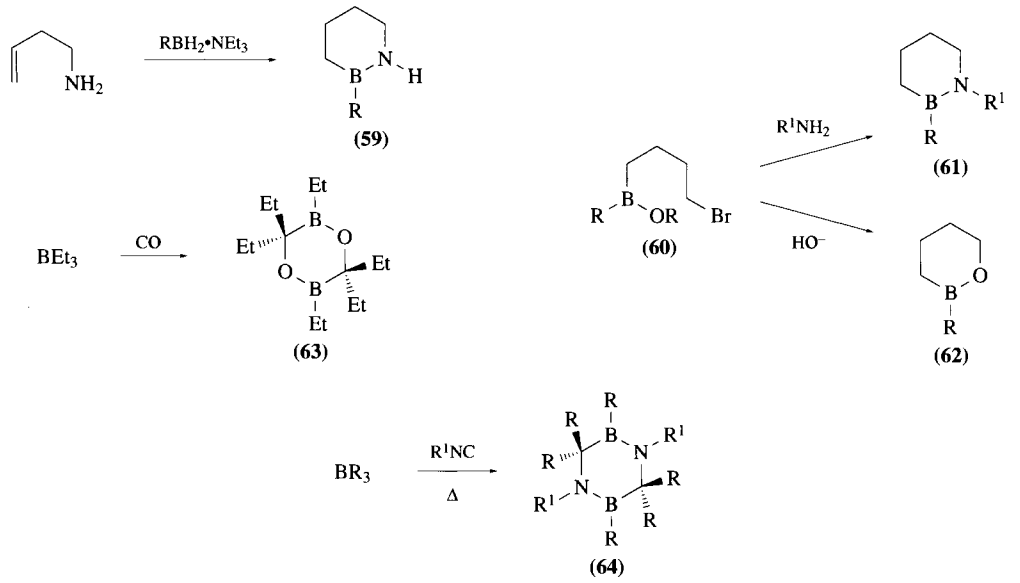
Scheme 7

6.28.3 BORACYCLES WITH THE C—B—X LINKAGE

The most common methods of C—B—X ring construction employ hydroboration/amination, aminolysis of 4-bromoalkylborinate esters, electrophilic additions of boron halides to *o*-amino-styrenes and -biphenyls, insertion of hydrazines into 1,2,5-thiadiborolenes, and aldol-type condensations. Specific examples of these processes are presented in the following sections 6.28.3.1 and 6.28.3.2.

6.28.3.1 Representative Synthetic Methods

The hydroboration/amination protocol has been used successfully for the preparation of 1-aza-2-borinanes (**59**) (Scheme 8) ⟨63JA3634⟩. Alternatively, the aminolysis of 4-bromoalkylborinate esters (**60**) with primary amines also provides related heterocycles (**61**) while their hydrolysis gives the corresponding 1-oxa-2-borinanes (**62**) ⟨70IZV198⟩. The carbonylation of trialkylboranes leads to 1,4-dioxa-2,5-diboracyclohexanes (**63**) which can also undergo further conversion to boroxines ⟨62JA4715, 63JA982, 63JA1626, B-88MI 628-01⟩. Analogous to the carbonylation process, isocyanides have been found to undergo related complexation followed by successive 1,2-alkyl B → C migrations give 1,4-diaza-2,5-diboracyclohexanes (**64**) ⟨82COMC-I(1)311⟩.



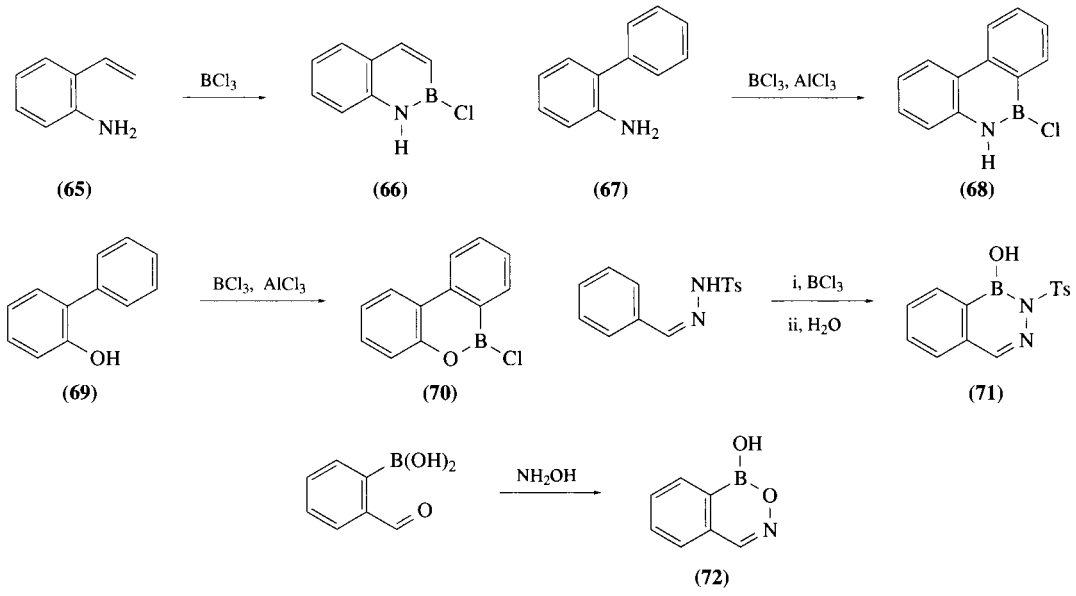
Scheme 8

Electrophilic additions of boron halides to *o*-amino-styrenes and -biphenyls provides an important entry to the 1,2-azaborine systems ((**66**), (**68**)) (Scheme 9) ⟨58JCS3073, 82COMC-I(1)311⟩. A related process is observed for 2-hydroxybiphenyl, which affords the 9-oxa-10-boraphenanthrene (**70**) ⟨77CHE381⟩. Considerable generality has been found in this approach and numerous related polycyclics have been prepared through appropriate substrate modifications, some finding applications as lubricants and antioxidants ⟨82USP4353807, 86ZAAC(536)24, 88USP4759873⟩. The addition of boron tribromide to the tosylhydrazone of benzaldehyde gives, after the hydrolysis of the bromoborane intermediate, the 3,4-azaboraisoquinoline ring system (**71**) ⟨78HCA325⟩. *o*-Formylbenzeneboronic acid condenses with hydroxylamine to produce the related 3-oxa analogue (**72**) ⟨82COMC-I(1)311⟩.

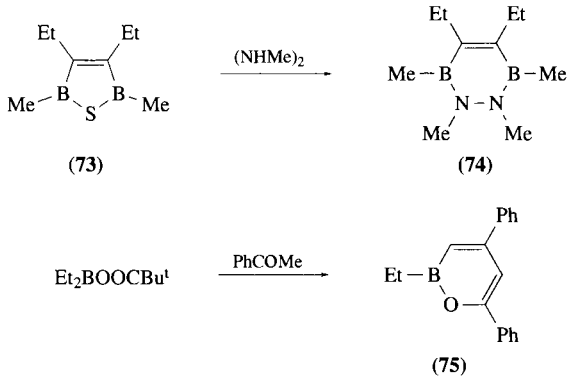
The insertion of hydrazines into 1,2,5-thiadiborolenes (**73**) provides a 3,6-diborapyrazine (**74**), a process which has been employed for the preparation of several related systems ⟨76AG(E)45⟩ (Scheme 10). The unusual pyrolytic behavior of dialkylboryl esters with acetophenone leading to the 1,2-oxaborine (**75**) suggests an aldol condensation through the intermediacy of an enolborane ⟨73S674⟩.

6.28.3.2 1,2-Azaborines

With an interest in the design, synthesis, and properties of boracycles related to naturally occurring purines, the preparation of a series of benzodiazaborines has been described ⟨94JA7597⟩. Reduction



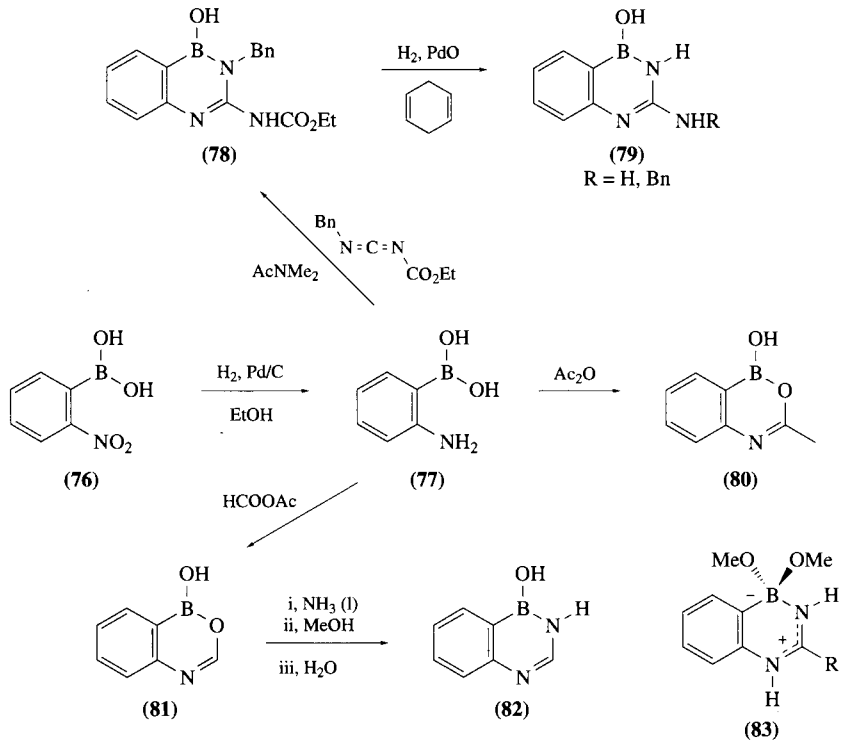
Scheme 9



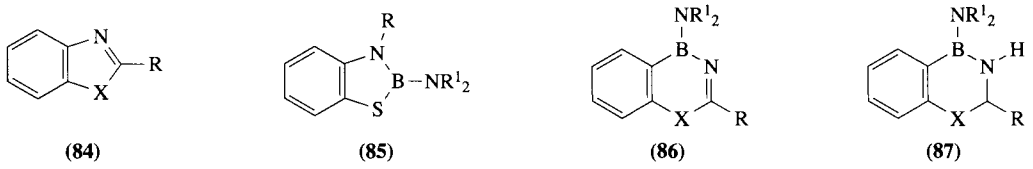
Scheme 10

of the nitro precursor (**76**) produces *o*-aminobenzeneboronic acid (**77**), which is acetylated or formylated ultimately giving the 1,2-dihydro-1*H*-2,4,1-benzoxazaborines (**80**) and (**81**), respectively (Scheme 11). The diazaborine (**82**) was prepared via an amination sequence through the isolated methanol adduct (**83**), followed by methanol removal, hydrolysis, and freeze-drying. For the guanine analog (**79**), the addition of carbodiimide to (**77**) produces (**78**) which gives a ca. 1 : 3 mixture of (**79**; R = H) and its *N*-benzyl derivative (**79**; R = Bn). These were isolated as their bismethanol adducts and each was converted to the corresponding 3-aminodiazaborines (**79**). The x-ray structure of (**83**) supports its zwitterionic nature. The endocyclic B—C and B—N bond lengths in (**83**) are 1.60 Å and 1.58 Å, respectively. The upfield shift observed in the ^{11}B NMR spectra upon changing to more coordinating solvents for both (**81**) (c.f. δ 8.8 (MeCN) vs δ −13.1 (MeOH)) and (**82**) (δ 11.9 (MeCN) vs δ −17.3 (MeOH)) is consistent with the formation of borates such as (**83**).

Other benzoxazaborines and their thia analogues (**86**, **87**; X = O, S) have been observed as minor products in the Na/K alloy reductions of benzoxazoles and benzothiazoles (**84**), respectively, in the presence of aminoboron dihalides. The thiazole gives 2,3-dihydro-1,3,2-benzothiazaborole (**85**) and $(R'_2N)_2BCN$ as the major products while the oxazole gives a dioxazadiborepin, $(R'_2N)_2BCN$, and $R'_2NB(OPh)_2$ ⟨90ZAAC(590)151⟩.



Scheme 11



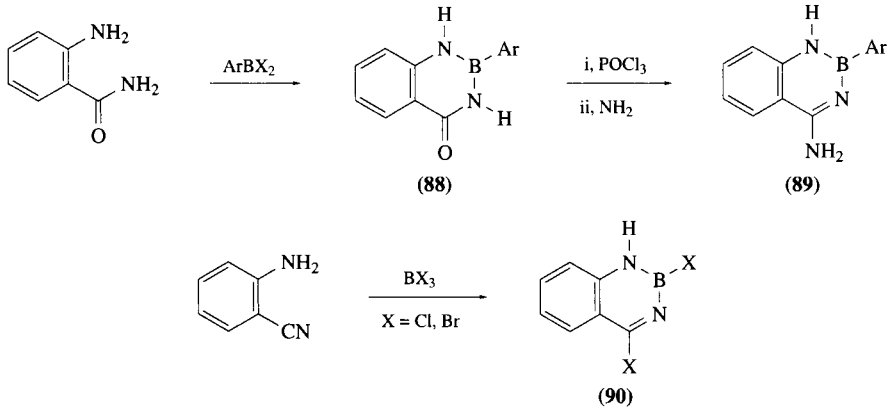
6.28.4 BORACYCLES WITH THE X—B—X LINKAGE

The most common methods of X—B—X ring construction employ condensation reactions of boronic acid derivatives with γ-diamines, diols, and amino alcohols. Specific examples of these processes are presented in the following sections 6.28.4.1–6.28.4.6.

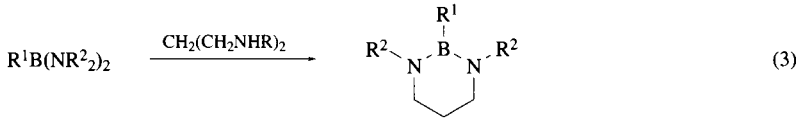
6.28.4.1 Representative Synthetic Methods

Boronic acid derivatives undergo condensation reactions with *o*-aminobenzamide to produce 2,3-dihydro-1,3,2-benzodiazaborin-4(1*H*)-ones (**88**) which are converted into (**89**) through a dehydration/aminolysis procedure (Scheme 12) ⟨61JA2708, 62JA688, 62JA689⟩. A related process used *o*-aminobenzonitrile and boron trihalides to give this ring system (i.e., (**90**)) ⟨84CHEC-I(1)629⟩.

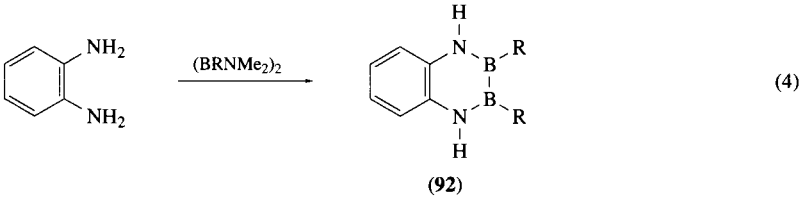
The transamination of diaminoboranes with α,ω-diamines has provided numerous 1,3,2-diazaboracycles (**91**) (Equation (3)) ⟨64IC1077⟩. Related systems are available from aminoboranes and haloboranes using these diamines ⟨71IC2343, 77IS164⟩. Moreover, 1,2-diaminodiboranes undergo a similar process to produce (**92**) (Equation (4)) ⟨61AG762, 63ZAAC(324)129⟩.



Scheme 12

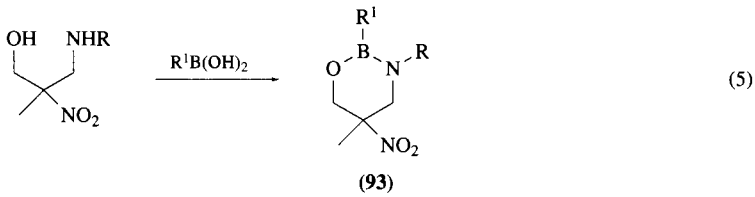


(3)

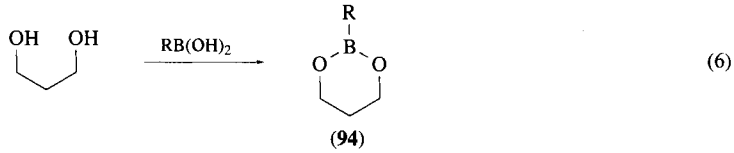


(4)

Boronic acids undergo condensation reactions with amino alcohols to give 1,3,2-oxazaborinanes (e.g., (**93**)) ⟨64MI 628-01, 77RZC1997⟩. The corresponding reactions with 1,3-propanediols or o-hydroxybenzyl alcohols are particularly efficient routes to 1,3,2-dioxaborinanes (e.g., (**94**)) ⟨78BCJ524⟩. Amino chelates (**95**) are formed when β-amino acids are heated with trialkylboranes ⟨74LA112⟩. Carbonyl groups also form six-membered ring chelates (e.g. (**96**)) with β-ketoaminoboranes ⟨73ZOB1115⟩ (Equations (5)–(8)).



(5)



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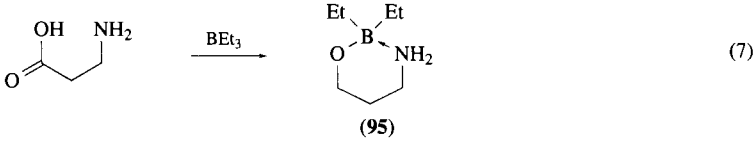

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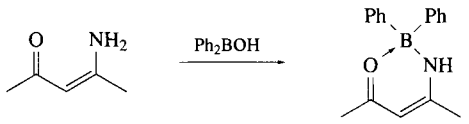


(8)

(96)

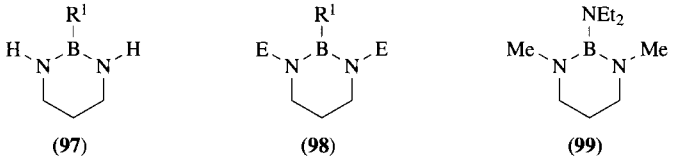
6.28.4.2 Theoretical and Spectroscopic Studies

Theoretical calculations support the role of ring-opening in the epimerization of chiral boron centers in imine complexes of borinic esters ⟨82CC542⟩. NMR experiments confirmed the plausibility of this process by observing the equilibration of such heterocyclic species through the coalescence of the benzylic methylene protons in the cyclic borinate complexes derived from the bis-benzylimine of 2,6-diformyl-*p*-cresol ⟨82CC1008⟩. The mechanism of the Rh-catalyzed hydroboration of alkenes has been studied theoretically employing 1,3,2-dioxaborinanes as model systems ⟨94JA10693, 95PAC257⟩.

Two-dimensional inverse $^{1}H[^{15}N]$ experiments have been successfully employed for the detection of broad ^{15}N NMR resonances in B—N—H 1,3,2-diazaborinane systems ⟨92MR393⟩. The ^{1}H NMR features of *B*-isopropyl-1,3,2-dioxaborinanes have been examined ⟨91KGS1262, 92KGS1262⟩. NMR-based conformational studies on several 1,3-dioxa, oxaza, oxathia, and dithia-2-borinanes have been reported which suggest that, in addition to rapidly equilibrating chair forms, a more planar C—X—B—X—C array (sofa) may best describe the most stable conformation for several of these systems ⟨85ACS(B)671, 86ZOB613, 87ZOB2016, 90KGS1424, 90ZOB119, 92ZSK31⟩. Through a systematic comparison of ^{17}O NMR chemical shifts of boronate esters and other cyclic organoboranes, the important role of BO(pp)π-bonds was demonstrated ⟨90CB1013⟩. The complexation of nitrogen bases with cyclic boronates has been studied by NMR with the conclusion that, although comparable, the 1,3,2-dioxaborolanes are slightly more stable than the corresponding 1,3,2-dioxaborinanes ⟨87JCS(P2)745⟩. Infrared and Raman spectra have been interpreted and vibrations assigned for the 1,3,2-dithiaborinane system ⟨86SA(A)913⟩. The boratropylium ion ($C_6H_6B^+$, m/z 89) has been proposed as the major ion fragment formed from the decomposition of *B*-phenyl-1,3,2-diazaborinanes upon electron impact ⟨84JOM(263)261⟩. Loss of the neural OBR fragment in 1,3,2-oxathiaborinanes has been proposed as the major decomposition pathway for these heterocycles upon electron impact ⟨92ZOB129⟩.

6.28.4.3 1,3,2-Diazaborinanes

A series of alkyl- and phenyldiaminoboranes react with 1,3-diaminopropane to give 1,3,2-diazaborinanes (**97**) which can be metallated with butyllithium and subsequently, these intermediates displace halides from phosphorus(III), phosphorus(V), silicon, and boron to provide *N*-substituted derivatives (**98**). Mixed derivatives are also available from the replacement of *N*-silyl groups by other electrophiles (e.g., $PhBCl_2$) ⟨88IC976, 89PS(41)141, 90PS(51/2)161, 94IC3239⟩. In contrast to the reaction of 1,2-diaminoethanes with tris(dialkylamino)boranes which gives borazines, the corresponding reaction of 1,3-diaminopropanes leads to isolable *B*-dialkylamino boracycles (**99**) ⟨86JOM(303)329⟩.



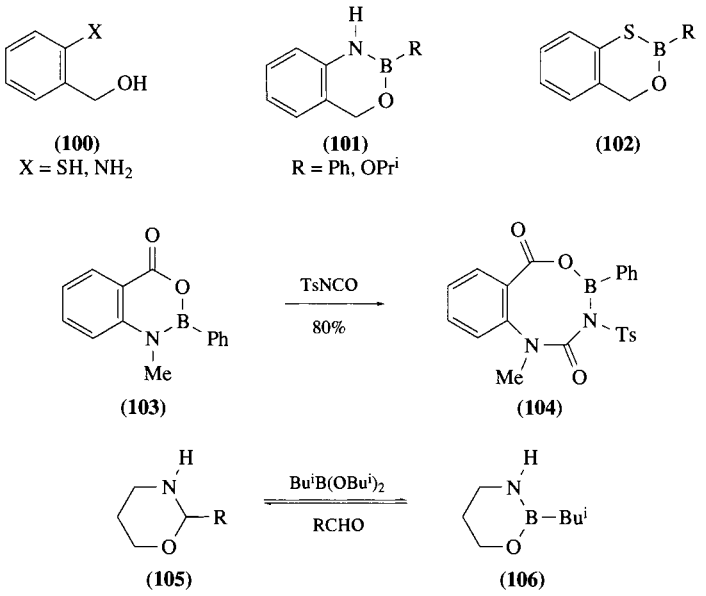
(97) (98) (99)

E = PXR, PMe_2(=N-TMS), SiR_3, BXR

6.28.4.4 1,3,2-Oxazaborinanes

The condensation of trialkyl borates and boronic acids with 2-thio- and 2-aminobenzyl alcohols (**100**) was demonstrated to give good yields of the thermally stable, but hydrolytically unstable,

1,3,2-benzazoxaborines (**101**) and oxathiaborines (**102**) ⟨82JHC297⟩. The insertion of tosyl isocyanate into the B—N bond of 3,1,2benzoxazaborinones (**103**) yields 5,1,3,4-benzoxadiazaborocanes (**104**). The condensation of phenylboronic acid with *N*-methylanthranilic acid provides the starting heterocycle ⟨85JOM(294)1⟩. Other derivatives are available from *o*-aminobenzyl alcohols ⟨94MI 628-01⟩. Tetrahydro-1,3-oxazines (**105**) also produce related 1,3,2-oxazaborinanes (**106**) ⟨87KGS712, 89ZOR2202⟩.



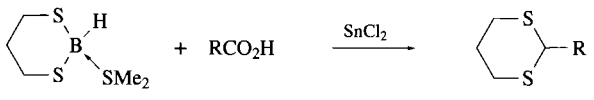
(**100**) X = SH, NH_2 (**101**) R = Ph, OPr^i (**102**) (**103**) (**104**) (**105**) (**106**)

Scheme 13

6.28.4.5 1,3,2-Dioxa- and Dithiaborinanes

The $ZnCl_2$-catalyzed conversion of aldehydes to 1,3-dioxanes (**108**) with 1,3,2-dioxaborinanes (**107**) equilibrates to favor dioxane formation when R = Me (95%), but is less favorable for larger groups (i.e., 28% for R = Pr^i) (Equation (9)) ⟨83ZOB1432⟩. Variations on these interconversions include: (1) 1,3-dioxanes to 1,3,2-dioxaborinanes with dichloro(ethyl)borane ⟨85ZOB1651⟩, (2) 1,3,2-dioxasila- and germa- cyclohexanes to 1,3,2-dioxaborinanes with boronate esters ⟨91UKZ868, 92ZOB712⟩, (3) 1,3,2-oxazaborinanes to tetrahydro-1,3-oxazines with aldehydes and ketones ⟨89ZOB1438, 89ZOR2202⟩, and (4) 1,3,2-thioxa- and dithiaborinanes to 1,3-oxathianes and 1,3-dithianes, respectively, with 1,3-dioxanes ⟨86ZOR2621⟩. However, the reductive conversion of carboxylic acids to 1,3-dithianes with 1,3,2-dithiaborinane (**109**) through a tin(II)-mediated process is very efficient (Equation (10)) ⟨87JOC2114⟩.

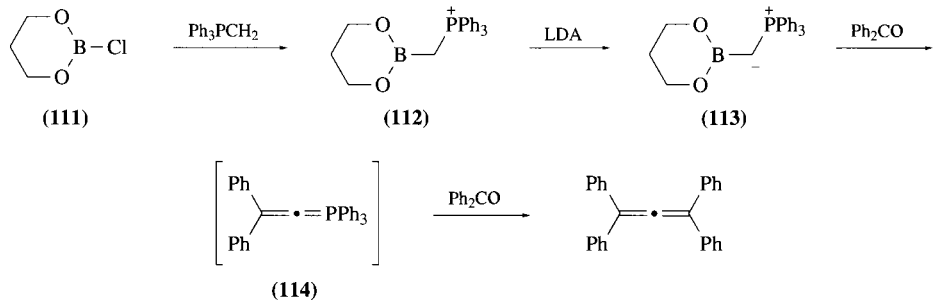
(**107**) (**108**) (9)



(**109**) (**110**) (10)

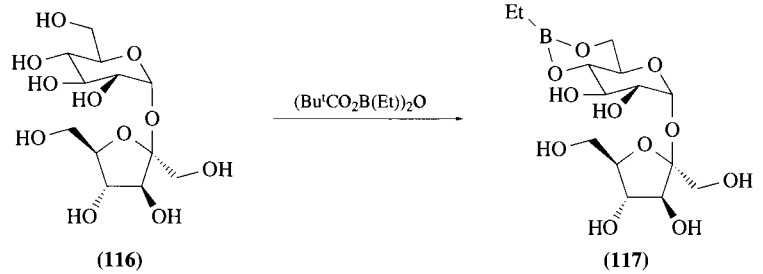
Unfortunately, 1,3,2-dioxaborinanes proved to be ineffective in the Hg(II)-catalyzed conversion of arylboronic acid derivatives to aryllead triacetates, in contrast to other arylboronate species

〈90JCS(P1)715〉. However, these dioxaborinanes have been demonstrated to be the boron ligands of choice for the generation of α-boryl carbanions and transmetallation reactions including B/Hg exchange. Their application in the synthesis of boron-substituted ylides (**113**) has led to a novel synthesis of arylated allenes (**115**) (Scheme 14) 〈73JOM(57)231, 75JOM(93)21, 76CC401, 76JOM(110)25, 78JOM(152)1, 82OM20, 83OM1529〉. Additionally, the selective formation of the 4,6-*O*-ethylboranediylsucrose (**117**), achieved with a 1,3-bispivaloyldiboxane derivative, provides an entry to hexaacylated sugars (Equation (11)) 〈83LA1422, 87LA463, 90ZOB443〉.



(111) (112) (113) (114)

Scheme 14

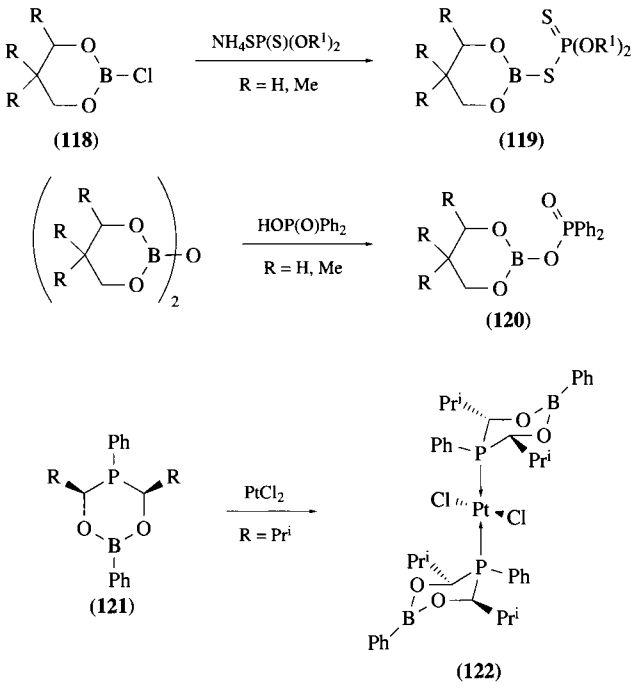


(116) (117) (11)

Novel phosphorus-containing 1,3,2-dioxaborinanes (**119**), (**120**) have been reported through *B*-substitution on the appropriate boracycles (**118**), (**120**) (Scheme 15) 〈91PS(60)147, 94M607〉. The 1,3,2,5-dioxaboraphosphinines behave as monodentate ligands in their complexation with a variety of metals (B, Pt, Pd, Cu, Ag, Mo) and the 4,6-diisopropyl system was found to produce a *trans*-dichloroplatinum complex (**122**) whose x-ray structure was obtained 〈93ZOB2775〉.

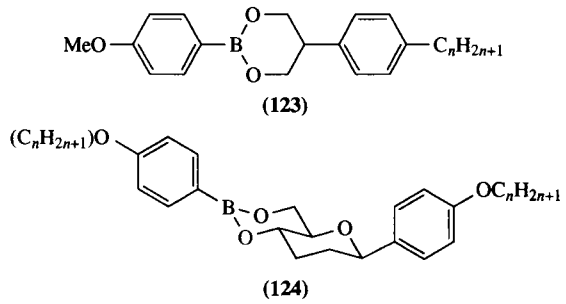
Dioxaborinane-based liquid crystals including chiral derivatives have been reported which form stable nematic and/or smectic mesophases (**123**), (**124**) (Scheme 16) 〈89BCJ3896, 93CC857, 95CC1047, 95LA1055〉. The 2-(α-aminoalkyl)-1,3,2-dioxaborinanes (**125**) are promising aminopeptidase inhibitors 〈86B1286〉. Several formamidomethyl boronate esters (**126**) have been prepared. The dioxaborolane derivative was converted into a borylmethyl isocyanide 〈95TL2109〉. While 2-(β-aminocycloalkyl)-1,3,2-dioxaborinanes (e.g., (**127**)) are available by the hydroboration of enamine derivatives of acyclic and larger ring (i.e., >6 members) ketones, the enamines from smaller ring cycloalkanones give product mixtures. More interesting is the fact that β,β-disubstituted aldehyde-derived enamines (**128**) give intermediate alkylaminoboranes (**130**) through a novel rearrangement process 〈87JOC4014, 93JA440〉.

Novel tetrahedral boronate complexes have been prepared as potential ligands for affinity chromatography either from the amination ($LiN(TMS)_2$) of α-haloalkylboronates followed by *N*-acetylation (i.e., (**132**)) or, alternatively, from the α-iodo derivatives and acetamidine (i.e., (**133**)) (Scheme 17). The 1,3,2-dioxaborinanes proved to be less stable than the pinanediol derivatives to silica gel. ^{11}B NMR as well as other data confirmed their chelated nature (e.g., (**132**); δ 6.8) 〈92JOM(431)255〉. Spiroborates (e.g. (**134**)) have also been prepared from boric acid, diols, and enolizable 1,3-dicarbonyl compounds 〈86JPR755〉. Vinylzirconocenes (**135**) are converted to vinylboronates (**136**) with chloroboranes 〈91OM3777〉. The hydrozirconation of *B*-vinylboronates (**137**) produces the mixed 1,1-dimetallaalkanes (**138**) which are readily converted to α-haloalkylboronates (**139**) 〈94JOM(474)49, 94JCC127〉.

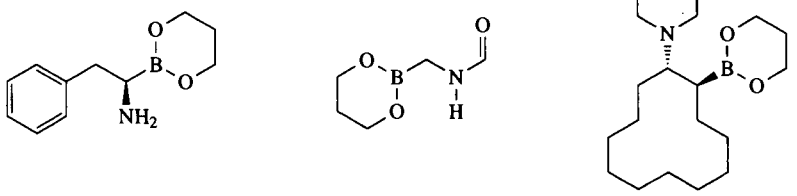


(118) (119) (120) (121) (122)

Scheme 15



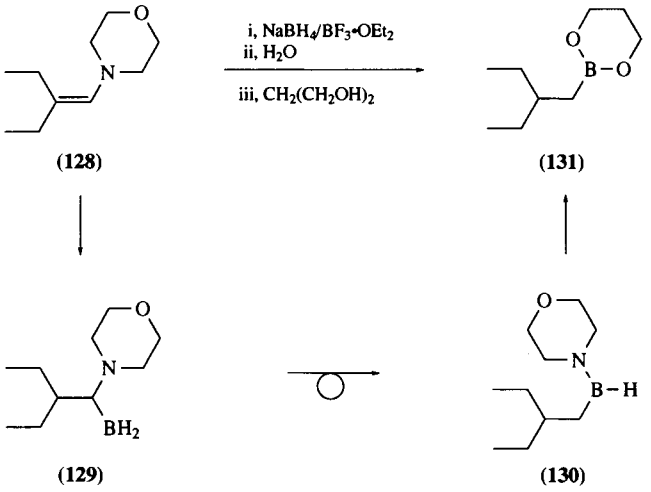
(123) (124)



(125) (126) (127)

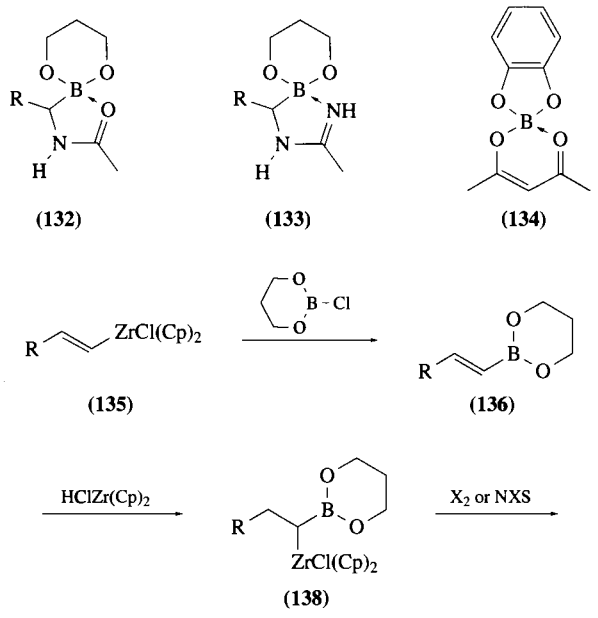
6.28.4.6 Synthetic Applications

Considerable interest in the 1,3,2-dioxaborinane ring system has been directed toward their applications in both organic synthesis and in chemical analysis. The relative ease of formation and stability of *B*-phenyl-1,3,2-dioxaborinanes has popularized the conversion of 1,3-diols to these heterocycles with phenylboronic acid as an integral part of many synthetic and isolation procedures. For example, these intermediates provide a useful method for preparing derivatives of 1,3-diols for NMR or spectroscopic analysis and, in some systems, gas and liquid chromatographic separations ⟨82JA7319, 83JOC3252, 83MI 628-01, 91ABC2785, 91JC(550)155, 94CL953, 95T1893⟩. The selective protection of 1,3-diols can be accomplished through this methodology which can permit, for example, the PCC-mediated oxidation or other conversions of unprotected alcohol functionality within the compound ⟨88T4591, 94HCA2341⟩.



(128) (131) (129) (130)

Scheme 16

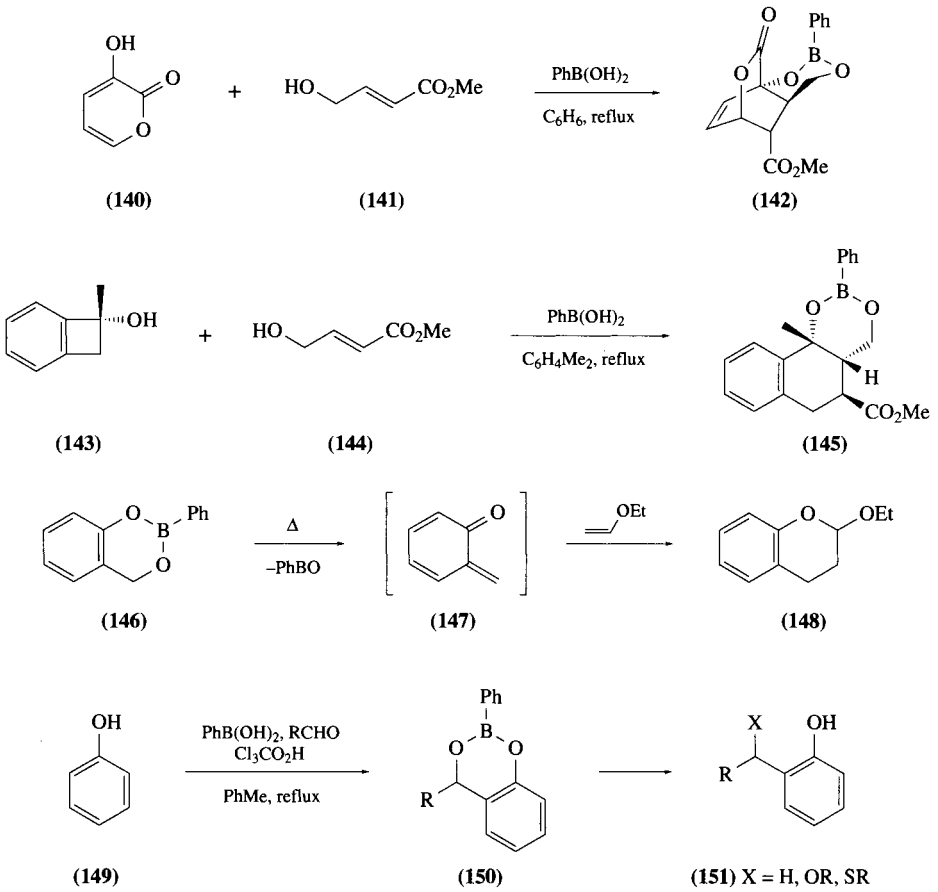


(132) (133) (134) (135) (136) (137) (138) (139)

Scheme 17

The thermal stability of these systems permits the use of phenylboronic acid to facilitate Diels–Alder reactions (e.g., (**142**)) through the formation of mixed boronate esters thereby converting the addition to an intra rather than intermolecular process (Scheme 18) ⟨91S1171⟩. The reaction is also useful for orchestrating Diels–Alder cycloadditions (e.g., (**143**)) which involve particularly unstable dienes (e.g., *o*-quinodimethanes) ⟨93BCJ1254⟩. The dioxaborinanes can provide precursors to related species (e.g., *o*-methylenequinone (**147**)) ⟨91BSF378, 92CJC1717⟩. The *ortho*-alkylation of phenols with aldehydes and phenylboronic acid leads to 1,3,2-dioxaborinane intermediates (**150**) which are either reduced with *t*-$BuNH_2$-BH_3 or converted to ether or thioether 2-alkylphenols under acidic conditions with alcohols and thiols, respectively (cf. (**151**)) ⟨79S365, 89CJC1384⟩.

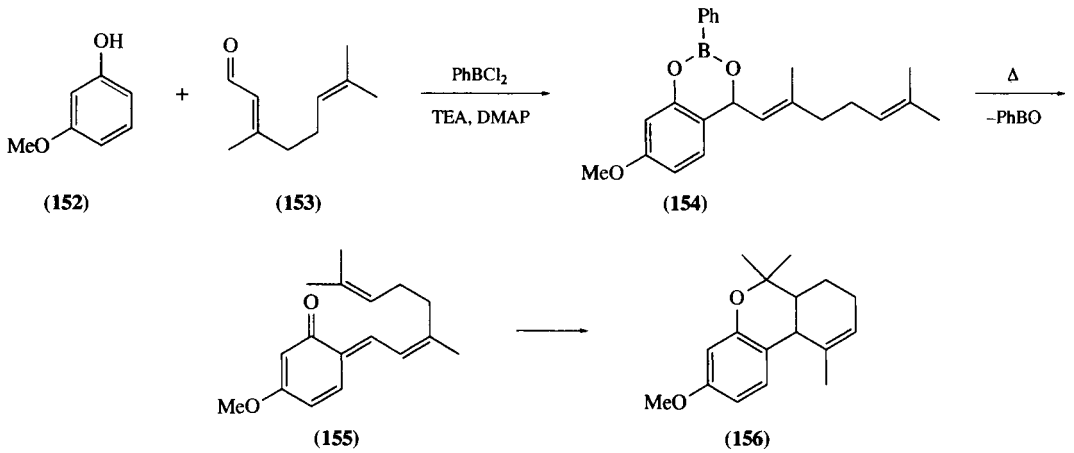
The use of $PhBCl_2$ gives improved yields of the dioxaborinanes (**154**) in some cases and this has been employed in the synthesis of some THC analogues (**156**) through the *in situ* generation of *o*-methylenequinones (**155**) which undergo the intramolecular Diels–Alder process (Scheme 19) ⟨93TL5527⟩. Polycyclic chromans (**160**) have also been prepared through the reaction of allylsilanes with these boracycles (**158**) ⟨94TL3691⟩. The arylation of a cyclic boronate intermediate (**162**) has provided the key step in the synthesis of thielocin B (**164**) (Scheme 20) ⟨94TL7747⟩.



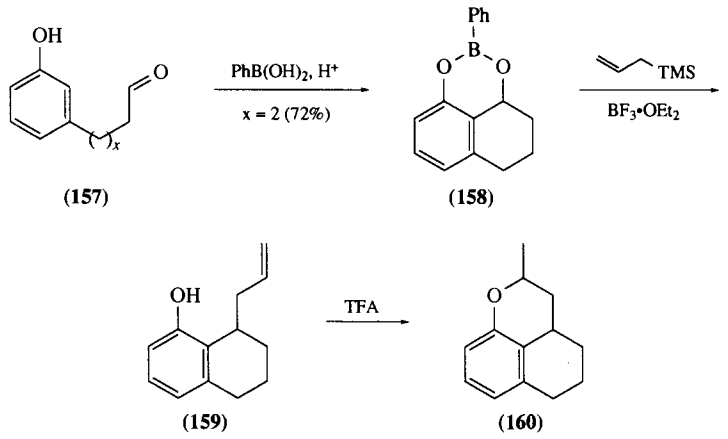
(140) (141) (142) (143) (144) (145) (146) (147) (148) (149) (150) (151) X = H, OR, SR

Scheme 18

The Suzuki–Miyaura coupling of boronic acid derivatives, including 1,3,2-dioxaborinanes, to aryl and vinylic halides provides a very useful method for the construction of C—C bonds. This process has been applied to the synthesis of versatile intermediates as well as to natural products. The coupling with *B*-vinyl or aryl boronates is normally quite effective and various palladium catalysts and bases can be employed. Alkylboronates are less effective in this coupling. However, employing special reaction conditions such as thallium(I) bases with dichloro-[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) in benzene/water mixtures, good results have been obtained for the crosscoupling of these derivatives ⟨89CL1405, 89JA314⟩. Developments include the application of

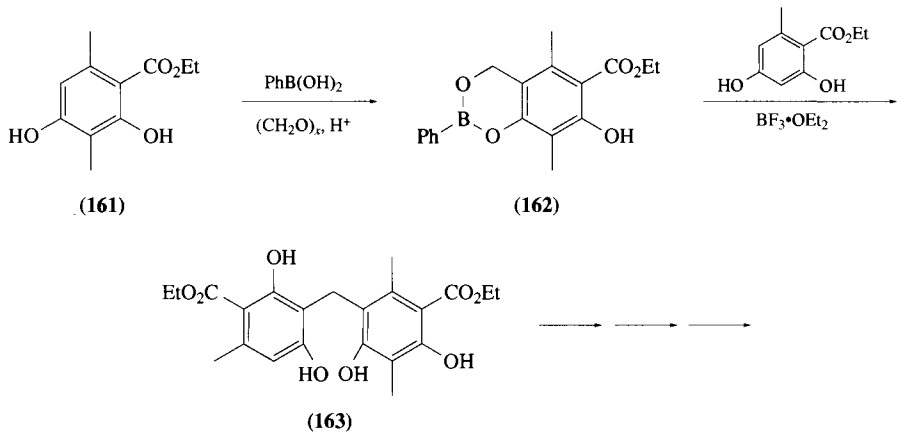


(152) (153) (154) (155) (156)



(157) (158) (159) (160)

Scheme 19

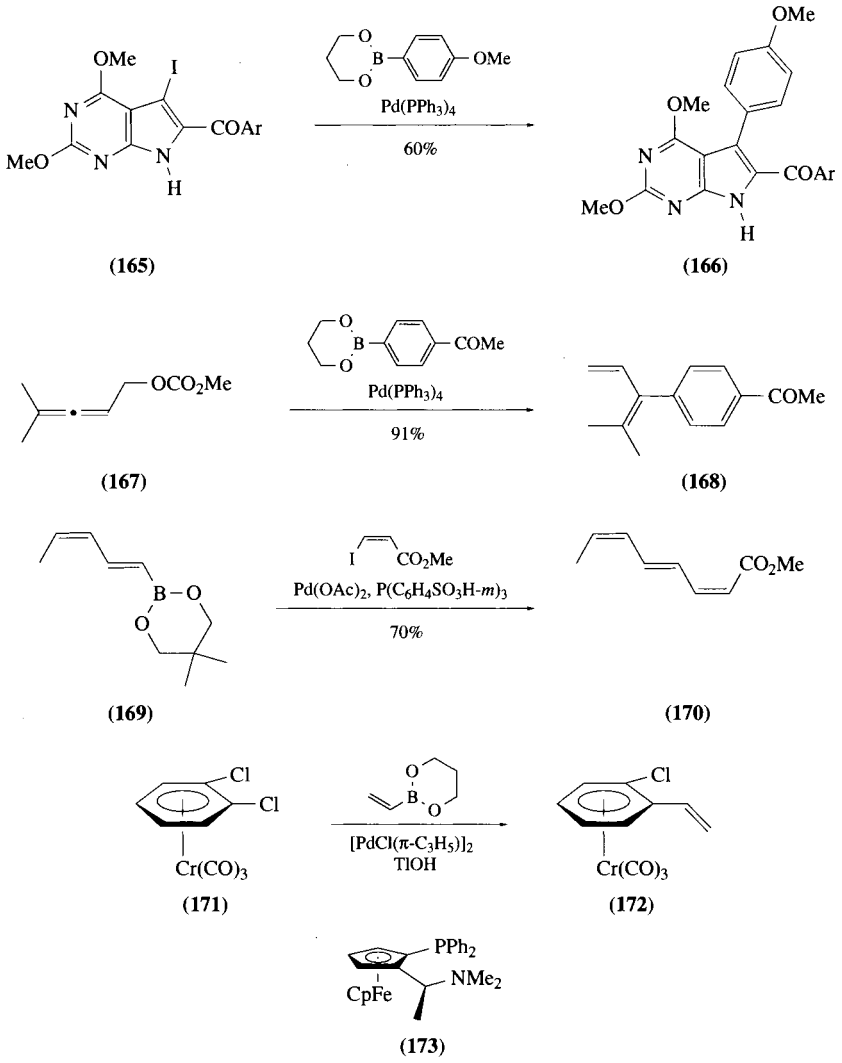


(161) (162) (163) (164)

Scheme 20

this coupling for the preparation of the key intermediate in the synthesis of the marine alkaloid, rigidin (**166**), the facile conversion of 2,3-dienyl carbonates to 2-substituted-1,3-butadienes (**168**), coupling processes (i.e. (**169**) → (**170**)) with water-soluble catalysts, asymmetric induction (39% *ee*) in the vinylated product (**172**) of *o*-dichlorobenzenechromium tricarbonyls (**171**) employing chiral ligands (e.g., (**173**)), and a remarkable new synthesis of a *β*-linked porphyrin dimer (**176**) (Schemes 21 and 22) ⟨93TL107, 94CC2493, 94TL2919, 94T7961, 95TL1443⟩. However, the most spectacular application of this process remains Kishi's construction of the C(75)-C(76) bond in his palytoxin synthesis, which employs a *B*-vinyl-1,3,2-dioxaborinane generated through the Matteson protocol ⟨89JA7525⟩.

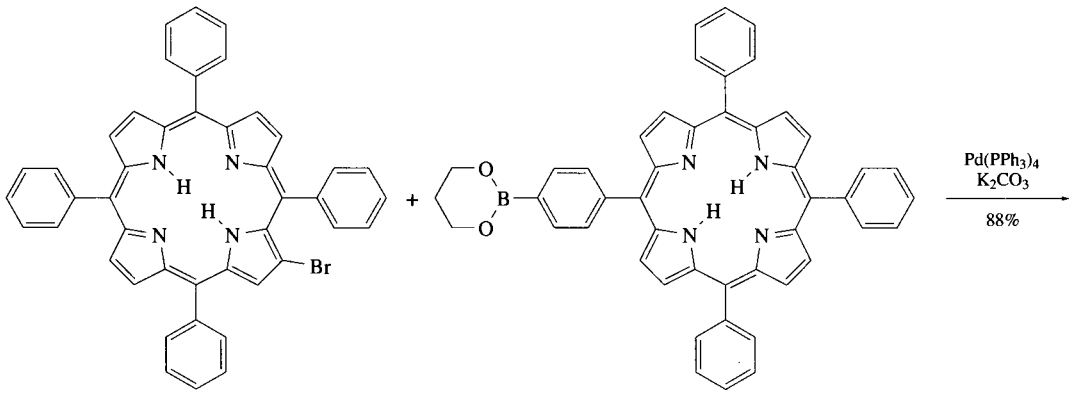
Other important applications of these 1,3,2-dioxaborinanes take advantage of the thermal stability of this bidentate ligation and its ability to survive substitution of the third ligand through the formation of tetrahedral borate intermediates ⟨85OM816, 86JOC337, 89JOC6085, 93OM1058⟩. One such example is represented by the Matteson homogation of *B*-alkyl boronate esters with lithium dichloromethide (Scheme 23) ⟨83OM1529⟩. Addition occurs at low temperatures (−100 °C) and R group



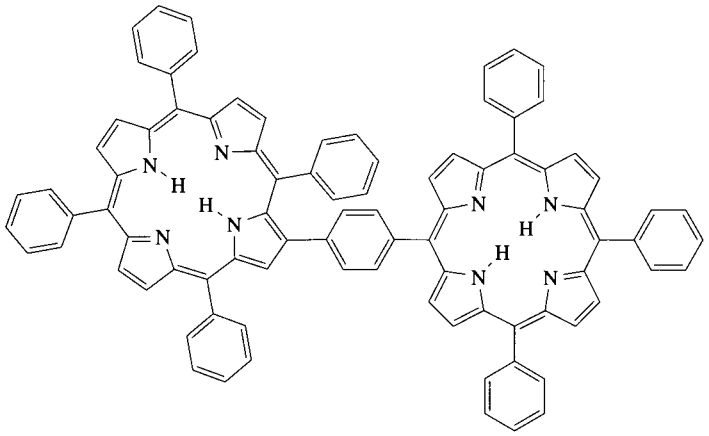
Scheme 21

migration from (**179**) follows as the mixture is warmed to room temperature. Although 1,3,2-dioxaborolanes have been popular substrates for this process, the borinane has also been employed successfully, even for enantiomerically pure derivatives ⟨85JOC4032, 85JOC5586⟩. The homogation (i.e. (**177**) → (**178**)) can be accomplished through the reduction of the intermediate α-chloroalkylboronate (**180**) with potassium triisopropoxyborohydride. The species (**180**) can also be conveniently generated at 0 °C (LDA/CH_2Cl_2) or, alternatively, the reduction can be avoided with the direct preparation of $LiCH_2Cl$ ($LiBu^t/BrCH_2Cl/-78\,°C$), both by *in situ* procedures (Scheme 23) ⟨85JOC4032, 85OM1925, 86JOC3150, 86OM994, 94TL8957⟩. Vinyl boronates can also be homologated to provide allylboranes stereospecifically ⟨93TL7845⟩. The alkynyl- to propargylboronate conversion is best accomplished with $LiCH_2I$ ⟨94TL8961⟩. Several one-carbon extensions of alkyl boronates and their sulfur analogues are also known through related methodology (cf. Scheme 25) ⟨83JA6285, 84JOC892, 86OM994⟩. Three-carbon homologations can also be achieved by the *in situ* deprotonation of allyl chloride with LDA in the presence of the borinate at −78 °C followed by the addition of organometallic reagents and isomerization and catalytic reduction (i.e., (**181**) → (**184**)) (Scheme 24) ⟨90TL7113, 90TL7115, 92OM1948⟩.

Hydroboration of alkenes (**185**) with dibromoborane gives alkyldibromoboranes (**186**) which are easily converted into dioxaborinanes (**187**) (Scheme 25). These heterocycles also provide a convenient entry to aldehydes (**189**) through the addition of lithiated α-methoxy thioethers ⟨83JA6285⟩. Unsymmetrical borinate esters (**191**) can be prepared from these boronates through the addition of organolithium compounds (cf. (**190**)) followed by treatment with acetyl chloride ⟨85OM1788,

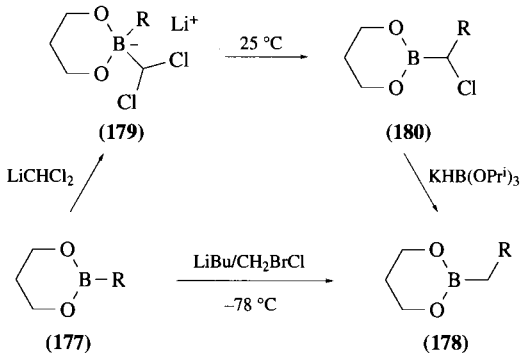


(174) (175)



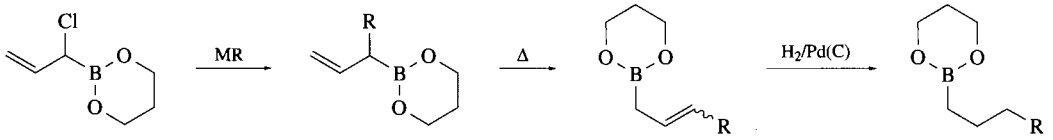
(176)

Scheme 22



(179) (180) (177) (178)

Scheme 23

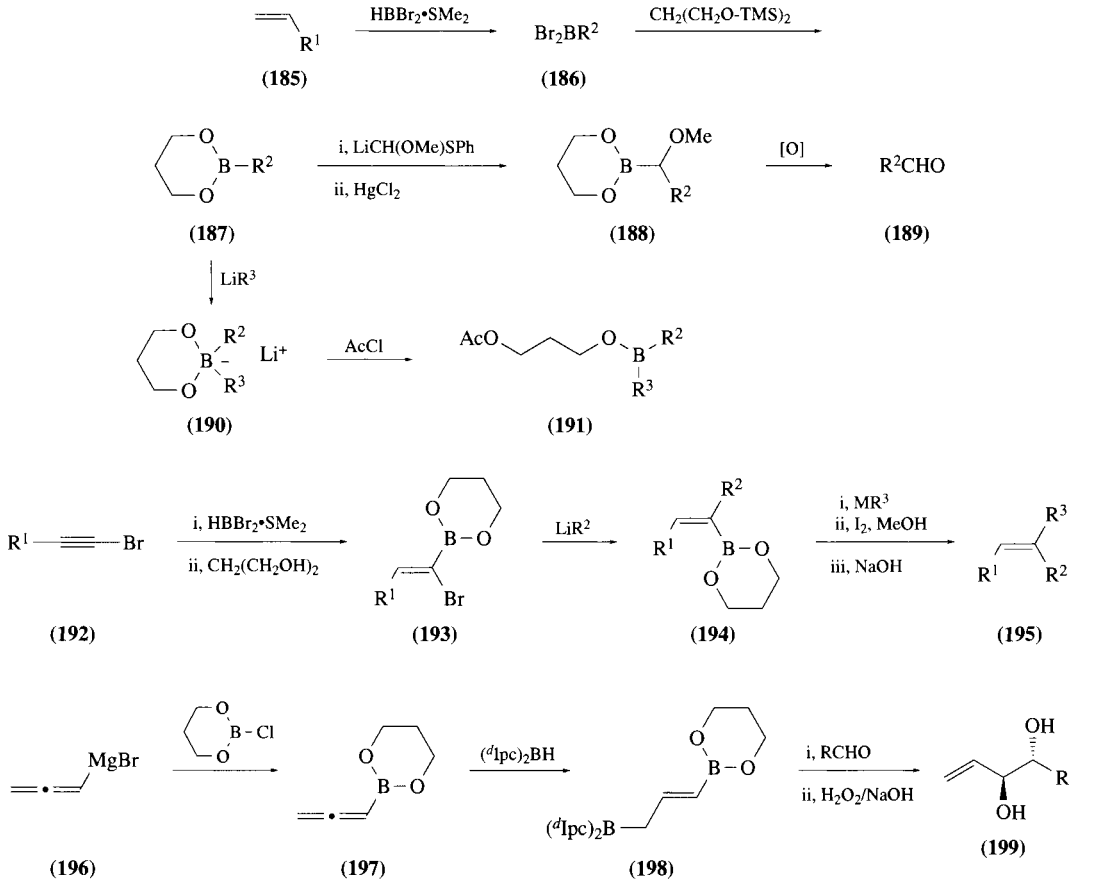


(181) (182) (183) (184)

M = Li, MgX; R = alkyl, aryl

Scheme 24

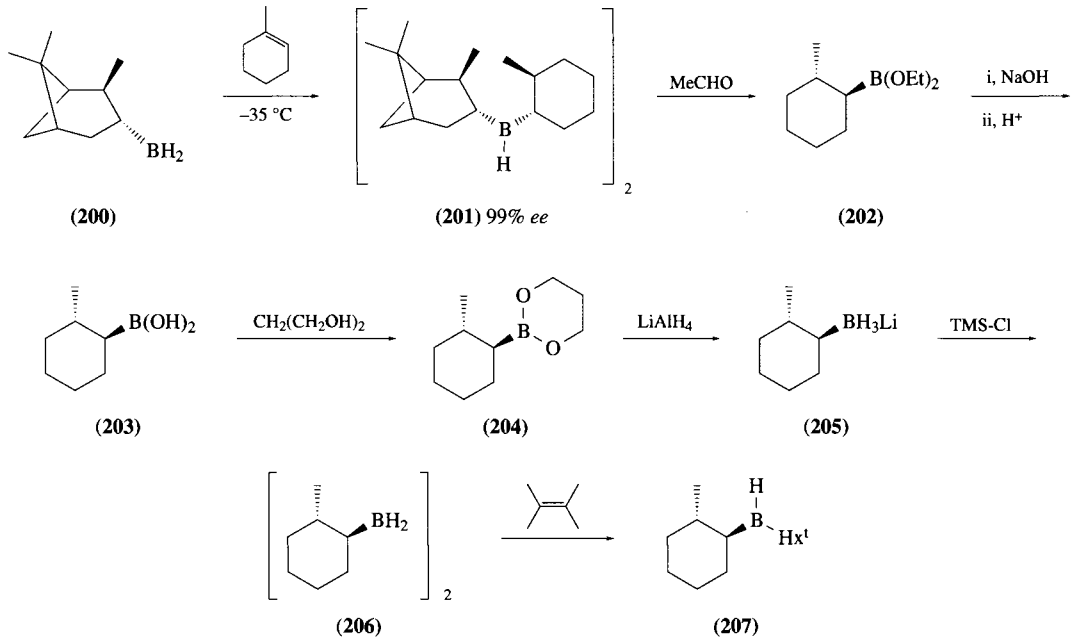
87JA5420〉. The hydroboration of 1-alkynes and 1-halo-1-alkynes (**192**) with dibromoborane and related derivatives affords vinylboranes (e.g., (**193**)) which can be converted to stereodefined (*E*)- or (*Z*)-trisubstituted alkenes (**194**) as well as their 1,2-disubstituted counterparts 〈83OM1311, 86JOC5277, 88JOC239, 88JOC6009〉. Boronates can also be alkylated to give mixed borinate derivatives or semi-hydrogenated to provide *cis*-vinylboronates 〈87OM629, 88TL2631〉. The stabilities of the 1,3,2-dioxaborinane system makes these systems well-suited to these and related conversions of vinylic organoboranes 〈94TL6963〉. New procedures for their preparations from diisopinocampheyl derivatives have been described 〈93SC2851〉. A most impressive example of the effect of the lowered Lewis acidity of these boronate esters compared to dialkylboryl substituents is illustrated in the recent conversion of the allenyl boronate (**197**) via the asymmetric hydroboration product (**198**) into optically active 3-butene-1,2-diols (**199**) 〈95JOC4686〉.



Scheme 25

Another important application of 1,3,2-dioxaborinanes is found in the asymmetric synthesis of chiral monoalkylboranes and their subsequent conversions to optically active organic compounds (Scheme 26) 〈88ACR287〉. In this protocol, optically pure monoisopropinocampheylborane (**200**; $IpcBH_2$) is used to hydroborate a prochiral alkene such as 1-methylcyclohexene, forming a diastereomerically-enriched mixed dialkylborane (**201**). The selective crystallization of this dimeric material provides the basis for its separation in enantiomerically pure form 〈85JA4980〉. The sequential reduction of acetaldehyde first by the remaining B—H moiety followed by the 3-pinanyl group produces the boronate ester (**202**) and α-pinene. Alkaline hydrolysis gives the boronic acid (**203**) which is smoothly converted to the corresponding 1,3,2-dioxaborinane (**204**) with 1,3-propanediol in pentane. These provide highly useful intermediates for use in many organoborane conversions (e.g. amination, alkylation of α-halo esters, ketones and nitriles, homologations, vinylation, and allylboration studies) 〈86JA6761, 89JA1754, 90JOC1868, 91JOC1170, 91JOC3286, 92JOC504〉. Reduction with LAH provides stable solutions of the monoalkylborohydride (**205**) species which is easily converted into an alkyl(*t*-hexyl)borane (**207**) by treatment with chlorotrimethylsilane (TMS-Cl) followed by

2,3-dimethyl-2-butene. These derivatives are very selective hydroborating reagents whose derived organoboranes undergo many conversions where the *t*-hexyl moiety functions as a stationary ligand, not competing with the other groups in both C—C bond-forming reactions, nor with the functional group conversions which are common to organoboranes ⟨88JA1529⟩.



(200) (201) 99% *ee* (202)

(203) (204) (205)

(206) (207)

Scheme 26

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References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "The Tautomerism of Heterocycles," in "Advances in Heterocyclic Chemistry," Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code "MI" for miscellaneous with the whole code for books prefixed by the letter "B-".
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe–Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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