

8.01

Pyridazines and their Benzo Derivatives

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8.01.1 Introduction

Two comprehensive reviews on the synthetic aspects of pyridazines and their benzo derivatives appeared since 1995 <2000AHC(75)167, 2000HC(57)1>. The most recent comprehensive work published on pyridazines <2004SOS(16)125>, phthalazines <2004SOS(16)315>, and cinnolines <2004SOS(16)251> was written by Haider and Holzer for the *Science of Synthesis* series. The majority of the review material that appeared deals with specific synthetic topics in the field and are often accounts of the authors own scientific work <2001T4059, 2001T4489, B-2002MI369, 2004COR1463, 2004SL1123, 2006COR277, 2006COR377, B-2006MI541, 2006SL3185>. Some reviews only deal partly with 1,2-diazines <2004CRV2433, 2006S2625>. It is not our intention to cite all available reviews of the last decade, but merely to give the reader an idea of the types of published related review material as well as a first insight into this literature.

Around the subject area of this chapter also biannual international conferences are organized which started in Strasbourg (1988) and were held in Sopron (1996), Clearwater Beach (1998), Santiago de Compostela (2000), Ferrara

(2002), Antwerp (2004), and Strasbourg (2006) in the covered period of this chapter. Certainly there has been a lot of activity in the pyridazine and benzo derivative field in the 1996–2006 period. A search on the ‘Web of Science’ revealed 1756 articles for the topic ‘pyridazin*’, 574 for ‘phthalazin*’ and 168 for ‘cinnolin*’. The same search on the ‘Scifinder’ database revealed 5203, 1943 and 462 hits for the concepts ‘pyridazin’, ‘phthalazin’, and ‘cinnolin’, respectively. Patents have only been taken into account in Section 8.01.12. In this chapter emphasis has been put on new and adapted older methods, as well as new interesting examples of well established methods. Selections necessarily had to be made due to the large amount of material published within the considered timeframe. Fully conjugated pyridazines, phthalazines and cinnolines as well as (partly) reduced and oxo forms (both only in the 1,2-diazine ring) are covered in this work.

IUPAC nomenclature has been used in the majority of the names. Only when the readability of the manuscript was hampered, we decided to use alternative names. Trivial names have only been included when they are really well established.

8.01.2 Theoretical Methods

A survey of nine computational methods was undertaken to calculate C–H bond-dissociation energies of monocyclic aromatic molecules including pyridazine. Comparison of the calculated bond-dissociation energies with the available experimental values for these molecules revealed that the B3LYP method provides the best agreement (3 kcal mol^{−1}) of calculated with experimental values <1999JA491>. The relative stability and energy barriers toward tautomerism of the conventional radical-cation and its α -distonic tautomer of pyridazine and other heterocycles have been determined by computational methods. Both radical cations are stable species which exist in discrete energy wells, with a significant barrier towards their interconversion. The conventional radical cation is the more stable one <2004IJM1>.

Ab initio calculations have been used to interpret the observed basicities of monocyclic and bicyclic azines. In two separate series, A (pyridine and the monocyclic diazines) and B (the benzodiazines), a good linear relationship exists between the experimental p*K*_a values and the highest occupied molecular orbital (HOMO) energy. Therefore, basicities of azines may directly be interpreted in terms of HOMO energies <1995JMT(339)255>. Similarly in series A a good linear relationship is observed between experimental p*K*_a values and the contractions of the polarizability by the effect of single protonation <2004CPL(396)117>.

Hydrogen-bonding interaction received considerable interest because of its important role in chemical and biological processes. Absorption and fluorescence solvatochromic shifts of dilute pyridazine in water as a result of solvent–solute interactions are calculated. Support is provided to the hypothesis that two linear hydrogen bonds to the pyridazine N-atoms are formed in dilute aqueous solutions <1996JPC9561>. A survey of the Cambridge Structural Database and intermolecular perturbation theory calculations on N···HOCH₃ interactions suggests that the hydrogen bonds are formed primarily in the direction traditionally assigned to the nitrogen lone pair <1997JCC2060>. Inertia moments derived from millimeter spectra of the 1:1 complex between pyridazine and water suggest a planar structure in which one hydrogen of the water molecule is bound to the nitrogen of the aromatic ring, and the ‘free’ water hydrogen is *entgegen* to the ring (Figure 1) <1998JPC8097>.

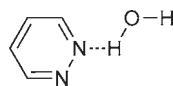


Figure 1 Pyridazine–water complex.

This bent hydrogen bond is confirmed by *ab initio* calculations using the B3LYP density functional method and a 6-31+G(d,p) basis set, performed in a more general study on pyridazine–(water)_n clusters <2002CPH(276)277>. Thermodynamic parameters for the hydrogen-bonding interaction of azabenzenes with thioacetamide in carbon tetrachloride solution were determined using near-IR absorption spectroscopy (IR – infrared), and the association energy of these complexes has been calculated at the B3LYP/6-311G** and B3LYP/6-31+G** levels, showing excellent agreement with the relative hydrogen-bonding strength. Also the association energy of 1:1 complexes with acetamide and water was calculated at the B3LYP/6-31+G** level. Bifurcated hydrogen bonding of the two adjacent nitrogen atoms of pyridazine may enhance the stability of the complexes <2004JPC921>.

Infrared spectra for 2-substituted 4,5-dimethoxypyridazin-3(2*H*)-ones were measured in hexane-CHCl₃ and CH₃CN-D₂O mixtures. Free, linearly, and angularly hydrogen-bonded pyridazinones were distinguished by a correlation study of $\tilde{\nu}$ (C=O) values with mole fractions of the less polar components of the binary solvent mixtures <2002CCCC1790>. Geometrical optimizations of nine tautomers and rotamers of 4-methyl-1,2-dihydropyridazine-3,6-dione were carried out at the B3LYP/6-31G(d), B3LYP/6-31+G(d,p), and MP2/6-31G(d) levels. Energies, thermodynamic quantities, rate constants, and equilibrium constants of ten tautomeric and rotational transformations between the nine forms in the gas phase and aqueous phase were obtained <2005CPL(415)176>.

A theoretical study of the structure and tautomerism of the four possible hydroxypyridazine *N*-oxides, as well as pyridazine 1,2-dioxide is presented. Gas-phase properties are modeled with high-level *ab initio* calculations employing large basis sets (6-311++ G(3df,3pd)) and quadratic configuration interaction treatment of electron correlation (QCISD(T)). Since these acidic heterocycles are of interest as carboxylate bio-isosteres, their anionic conjugate bases are also examined. Aqueous solution-phase properties are investigated using the isodensity polarized continuum model (IPCM), and the semi-empirical AM1-SM2 and PM3-SM3 models, and relative acidities compared. The calculated properties are generally in good agreement with existing experimental data, indicating that the oxo-1-hydroxy tautomer predominates both in the gas phase and in solution in the case of the 6-substituted system, and that the hydroxy-1-oxide tautomers predominate in the 3- and 5-substituted systems. The behavior of the 4-substituted isomer is less clear, with nonplanar 1-hydroxy and planar 4-hydroxy tautomers being similar in stability <1997JMT(419)97>.

The lipophilicity of 4- and 5-aminopyridazin-3(2*H*)-ones has been calculated by KOWWIN-EVA and 3DNET computational methods. The calculated log *P* values are in good agreement with the experimental values. Generally, the 4-amino derivatives have been found to possess higher log *P* values. It seems that hydrogen-bonding capacity and/or aromaticity are the most relevant parameters determining the log *P* values of this class of compounds <2003JFA5262>.

Semi-empirical AM1 and PM3 calculations, and density functional theory (DFT) calculations have been executed to support proposed reaction mechanisms of the 1,3-dipolar cycloaddition reaction of 5-substituted pyridazinones with nitrile imines <2000JMT(528)13>, the ring-closure reaction of 5-morpholino-4-vinylpyridazin-3(2*H*)-ones by *tert*-amino effect <2003JMT(666/7)667> and the reaction of chloropyridazin-3(2*H*)-ones with 57% HI or sodium iodide in dimethylformamide (DMF) <2005JMT(713)235>. The selectivity of free-radical brominations of methyl-3-methoxypyridazine derivatives with *N*-bromosuccinimide (NBS) is confirmed to be related to the stability of the free radicals formed in the rate-limiting step. Semi-empirical calculations using the PM3 Hamiltonian generally give relative energies which qualitatively reproduce the selectivities observed experimentally <1996JMT(368)235>. A topological analysis of the electron localization function has been applied to explore the nature of bonding in the thermal cyclization of (2-ethynylphenyl)triazene to cinnoline. The analysis shows that this cyclization is a pseudo-pericyclic process in contrast to the cyclization of 2-ethynylstyrene to naphthalene which is a more pericyclic process <2005JPC4352>.

The structural properties of pyridazine and phthalazine derived from microwave spectroscopy, electron and X-ray diffraction have been compared with theoretical data obtained from transitional *ab initio* calculations, including both restricted Hartree-Fock and second-order Moller-Plesset perturbation theory, and DFT calculations <1996JPC6973, 1998JMT(423)225, 2005JMT(717)171>. In addition, theoretical data were obtained from infrared and/or Raman spectroscopy in the vapor, the liquid, or the crystalline phases, which were used to interpret the vibrational spectra of pyridazine <1995JMT(349)409, 1996JPC6973, 1998JMT(423)225, 2001JPC9354>, chlorinated pyridazines <2000PCA2599, 2001JPC9354>, and phthalazine <2005JMT(717)171>. These studies not only include results obtained by using standard (scaled) harmonic force field calculations, but also incorporate results derived by using newer methodologies employed for the prediction of anharmonic force fields <2004JPC3085, 2004JPC4146> and by using corrections for anharmonic resonances <2005PJP425>. Finally, different methodologies used for the prediction of electronic spectra <2000CPH(257)1, 1998JRS547> and resonance-enhanced multiphoton ionization (REMPI) spectra <1998JPC8084> have been evaluated.

8.01.3 Experimental Structural Methods

8.01.3.1 X-Ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

In CHEC(1984) <1984CHEC(2)1> electron diffraction, microwave spectroscopy, and X-ray analysis of pyridazine and simple derivatives were included. All data are consistent with a planar structure and significant N-N single bond character. CHEC-II(1996) <1996CHEC-II(6)1> contained some additional structural parameters derived from X-ray

analysis of 1,2-diazines such as pyridazine-3,6-dicarboxylic acid. Phthalazine derivatives were also discussed. New work includes X-ray data on the 1:1 salt of pyridazine and 4-chloro-3-nitrobenzoic acid <2002AXE1081>, 3,4,6-tris(pyrazol-1-yl)pyridazine <2002AXE1408>, and 2-bromobenzo[*c*]cinnoline 6-oxide <2001AXE645>. The tricyclic skeleton of the last mentioned compound consists of almost planar rings. The N–O bond seems to be shorter than in the corresponding bond in pyridine *N*-oxide which is probably a result of the electron resonance between the oxygen atom and the aromatic nucleus. Also several pyridazin-3(2*H*)-one derivatives have been analyzed via X-ray <1996JST(374)251, 2004T12177, 2005T4785, 2006AXE446>. Interesting to mention is the further study of the polymorphism of maleic hydrazide <2001AXB697>. There seems to be a third polymorph which is monoclinic. X-Ray data up to mid-1998 have been summarized by Tišler <2000AHC(75)167>.

8.01.3.2 NMR Spectroscopy

8.01.3.2.1 ¹H NMR

In CHEC(1984) <1984CHEC(2)1>, ¹H NMR spectra of simple pyridazines, pyridazin-3(2*H*)-ones, and pyridazine *N*-oxides were tabulated. Cinnoline derivatives were also covered in this way. A reference to the ¹H NMR spectrum of phthalazine was given. Besides the shift values also coupling constants were nicely summarized for all these 1,2-diazines. In CHEC-II(1996) <1996CHEC-II(6)1>, phthalazin-1(2*H*)-ones were mentioned. Moreover, useful general shift and coupling constant trends for ¹H NMR spectra of 1,2-diazines were provided. ¹H NMR is now a routine technique and a majority of the full paper articles contain interpreted data. Taking into account the importance of pyridazin-3(2*H*)-ones (Figure 2) and the limited number provided in the CHEC(1984) table, we included here a new table (Table 1). Additionally, we have tabulated data for some bicyclic derivatives: [1,2,4]triazolo[4,3-*b*]pyridazines and tetrazolo[1,5-*b*]pyridazines (Table 2 and Figure 3).

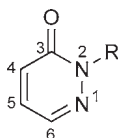


Figure 2 Structure and numbering of pyridazin-3(2*H*)-ones.

8.01.3.2.2 ¹³C NMR

Since the publication of CHEC(1984) <1984CHEC(2)1>, the use of ¹³C NMR seriously expanded. The majority of the full papers now published contain ¹³C NMR spectroscopic data. Unfortunately, this is usually only for characterization of the synthesized compounds and no interpretation of the data is provided. In CHEC-II(1996) <1996CHEC-II(6)1>, a representative and very useful table with assigned ¹³C shifts of simple pyridazines and pyridazin-3(2*H*)-ones was published. Phthalazin-1(2*H*)-ones were also briefly mentioned. As an extension we here summarize some assigned ¹³C NMR data of bicyclic derivatives: [1,2,4]triazolo[4,3-*b*]pyridazines and tetrazolo[1,5-*b*]pyridazines (Table 2 and Figure 3), and isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (Table 3 and Figure 4).

8.01.3.2.3 ¹⁵N NMR

In CHEC-II(1996) <1996CHEC-II(6)1> ¹⁵N shifts of pyridazine, phthalazine, cinnoline, as well as some derivatives were mentioned. ¹⁵N NMR data of some simple [1,2,4]triazolo[4,3-*b*] and tetrazolo[1,5-*b*]pyridazines are summarized in Table 2. The ¹⁵N NMR is especially useful for structure analysis of such compounds as they consist of a large number of nitrogen atoms consequently leading to limited information resulting from classical ¹H and ¹³C NMR spectra. After all, the ¹⁵N shift gives an immediate correlation with the electronic environment of the chemically different nitrogen atoms present in the molecule. For the [1,2,4]triazolo[4,3-*b*]pyridazines ¹⁵N NMR in dimethyl sulfoxide (DMSO) supported a triazolo rather than an open azido form <1999MRC493>. More derivatives were studied in a later paper <2002MRC507>. Holzer and Dal Piazz provided ¹⁵N shifts of the synthetically (see Section 8.01.10.5) and biologically important isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (Table 3).

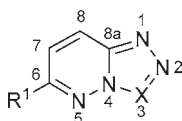
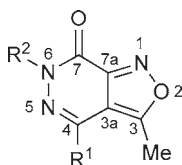
Table 1 $^1\text{H-NMR}$ δ -values of substituted pyridazin-3(2*H*)-ones

<i>Substituents</i>	$\delta\text{-NH}$ (bs)	$\delta\text{-(H-4)}$	$\delta\text{-(H-5)}$	$\delta\text{-(H-6)}$	$\delta\text{-Substituents}$
4-Cl,5-MeO ^{b,c}	13.26			8.10	4.06 s 3H
4-Br,5-MeO ^{b,c}	13.24			8.10	4.07 s 3H
4-Cl,5-N ₃ ^{b,c}	13.26			8.08	
4-Br,5-N ₃ ^{b,c}	13.32			8.04	
4-Cl,5-NHEt ^{a,c}	12.42			7.63	1.32 t 3H, 3.41 q 2H, 5.19 bs 1H
4-Br,5-NHEt ^{a,c}	12.42			7.42	1.12 t 3H, 3.21 q 2H, 4.98 bs 1H
4-Cl,5-OPh ^{a,c}				7.54	7.26-7.48 m 5H
4-Br,5-OPh ^{b,c}	13.43			7.53	7.23-7.51 m 5H
6-Ph ^{b,d}	13.18	6.98 d <i>J</i> = 9.9 Hz	8.00 d <i>J</i> = 9.9 Hz		7.84 m 2H, 7.46 m 3H
5-Cl,6-Ph ^{b,d}	13.85	7.44			7.58-7.50 m 5H
5-Br,6-Ph ^{b,d}	13.78	7.45			7.51 m 5H
5-N ₃ ,6-Ph ^{b,d}	13.16	6.80			7.58 m 2H, 7.45 m 3H
5-OMe,6-Ph ^{b,d}	12.86	6.31			7.59 m 2H, 7.14 m 3H; 3.80 s 3H
5-SMe,6-Ph ^{b,d}	12.93	6.59			7.48 m 5H; 2.39 s 3H
5-CN,6-Ph ^{b,c}	14.03	7.93			7.63 m 2H, 7.50 m 3H
5-CH ₂ OH,6-Ph ^{b,c}	13.07	6.93			7.46-7.44 m 5H; 5.62 s 1H, 4.26 s 2H
5-CHO,6-Ph ^{a,f}	13.82	7.46			7.70-7.60 m 5H; 9.87 s 1H
5-COMe,6-Ph ^{a,f}	12.64	7.43			7.44 m 5H; 2.14 s 3H
<i>Substituents</i>	$\delta\text{-NMe}$ (s)	$\delta\text{-(H-4)}$	$\delta\text{-(H-5)}$	$\delta\text{-(H-6)}$	$\delta\text{-Substituents}$
5-OMe ^{b,g}	3.72	6.15 d <i>J</i> = 2.9 Hz		7.54 d <i>J</i> = 2.9 Hz	3.80 s 3H
5-OPh ^{a,g}	3.74	5.98 d <i>J</i> = 2.8		7.75 d <i>J</i> = 2.8	7.09 d 2H, 7.29 t 1H, 7.44 t 2H
5-NHEt ^{a,g}	3.67	5.68 d <i>J</i> = 2.6		7.31 d <i>J</i> = 2.6	1.27 t 3H, 3.12 m 2H, 4.54 bs 1H
5-I ^{a,h}	3.72	7.46 d <i>J</i> = 2.05		7.90 d <i>J</i> = 2.05 Hz	
4-Cl,5-OMe ^{b,i}	3.69			8.21	4.07 s 3H
4-OMe,5-Cl ^{b,j}	3.64			7.99	4.14 s 3H
4-Cl,5-OPh ^{a,h}	3.82			7.45	7.44 m 2H, 7.27 tt 1H, 7.09 dd 2H
4-OPh,5-Cl ^{a,h}				7.80	7.32 dd 2H, 7.12 tt 1H, 6.96 dd 2H
<i>Substituents</i>	$\delta\text{-NPh}$	$\delta\text{-(H-4)}$	$\delta\text{-(H-5)}$	$\delta\text{-(H-6)}$	$\delta\text{-Substituents}$
4,5-diCl ^{a,k}	7.59-7.42			7.91	
4-Cl,5-OMe ^{a,k}	7.58-7.39			7.95	
4-Cl,5-N ₃ ^{a,k}	7.58-7.41			7.76	
4-OMe,5-Cl ^{b,j}	7.50-7.53			8.16	4.17 s 3H
<i>Substituents</i>	$\delta\text{-NCl}$	$\delta\text{-(H-4)}$	$\delta\text{-(H-5)}$	$\delta\text{-(H-6)}$	$\delta\text{-Substituents}$
4,5-diCl ^{a,l}				7.76	
4-Cl,5-OMe ^{a,l}				8.21	4.07 s 3H

^aCDCl₃.^bDMSO-*d*₆.^c1999JHC277.^d2002BMC2873.^e1999JHC985.^f2003CPB427.^g1998JHC819.^h2004T2283.ⁱspectrum recorded in the lab of the authors.^j2001T1323.^k2004TL8781.^l2005S1136.

Table 2 ^1H , ^{13}C and ^{15}N NMR values of 6-substituted [1,2,4]triazolo[4,3-*b*]pyridazines and tetrazolo[1,5-*b*]pyridazines

R^1	$X = \text{CH}$		$X = \text{N}$					
	Cl^{d}	$\text{N}((\text{CH}_2)_2)_2\text{O}^{\text{d}}$	$\text{H}^{\text{a,d}}$	$\text{Cl}^{\text{a,d}}$	$\text{OMe}^{\text{a,d}}$	$\text{N}((\text{CH}_2)_2)_2\text{O}^{\text{a,d}}$	$\text{N}_3^{\text{b,c}}$	$\text{NPPH}_3^{\text{c,e}}$
$\delta\text{-(H-3)}$	9.63	9.20						
$\delta\text{-(H-7)}$	7.48	7.36		8.05	7.50	7.71	7.43	7.26
$\delta\text{-(H-8)}$	8.45	8.09		8.95	8.63	8.40	8.62	7.83
$\delta\text{-(H-2')}$		3.50				3.65		
$\delta\text{-(H-3')}$		3.74				3.76		
$\delta\text{-(H-OMe)}$					4.12			
J_{7-8} (Hz)		10.15		9.46	9.46	10.00	9.5	9.5
$\delta\text{-(C-3)}$	138.8	138.3						
$\delta\text{-(C-6)}$	149.1	155.1	148.4	151.4	162.3	156.2	155.8	160.5
$\delta\text{-(C-7)}$	123.0	114.8	125.9	127.3	120.9	117.9	121.8	128.4
$\delta\text{-(C-8)}$	126.6	124.1	125.6	128.2	126.1	123.7	127.7	121.6
$\delta\text{-(C-8a)}$	142.2	141.7	143.2	142.6	141.4	139.7	143.1	140.0
$\delta\text{-(C-2')}$		45.6				45.3		
$\delta\text{-(C-3')}$		65.5				65.4		
$\delta\text{-(C-OMe)}$					55.8			
$\text{J}_{\text{CH-3}}$ (Hz)	221.0	216.7						
$\text{J}_{\text{CH-7}}$ (Hz)	180.1	171.0		182.4	176.7	172.6		
$\text{J}_{\text{CH-8}}$ (Hz)	178.3	174.7		181.3	180.4	178.8		
$\delta\text{-(N-1)}$	-74.7	-77.1	-64.2	-63.1	-64.1	-64.0	-63.5	-68.6
$\delta\text{-(N-2)}$	-48.8	-54.8	+14.5		+10.6	+8.6	+12.3	+3.8
$\delta\text{-(N-3)}$			-25.6		-26.1	-26.4	-27.0	-28.6
$\delta\text{-(N-4)}$	-153.5	-161.2	-99.9	-101.6	-109.3	-105.4	-106.2	-103.9
$\delta\text{-(N-5)}$	-84.8	-133.9	-68.9	-82.5	-124.4	-131.5	-108.8	-121.4
$\delta\text{-(N-1')}$		-302.6				-297.7	-276.8	-284.0
$\delta\text{-(N-2')}$							-146.0	
$\delta\text{-(N-3')}$							-140.3	

^aDMSO- d_6 .^bacetone- d_6 .^c CDCl_3 .^d1999MRC493.^e2002MRC507.**Figure 3** Structure and numbering of 6-substituted [1,2,4]triazolo[4,3-*b*]pyridazines and tetrazolo[1,5-*b*]pyridazines.**Figure 4** Structure and numbering of 4,6-disubstituted 3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones.

8.01.3.3 Mass Spectrometry

The electron ionization (EI) mass spectral behavior of pyridazine, pyridazin-3(2*H*)-one, and phthalazine was discussed in CHEC(1984) <1984CHEC(2)1>. In CHEC-II(1996) <1996CHEC-II(6)1> the comparison of the high-resolution EI mass spectra of pyridazin-3(2*H*)-one, phthalazin-1(2*H*)-one and cinnolin-3(2*H*)-one was mentioned.

Table 3 ^{13}C and ^{15}N NMR δ -values (DMSO- d_6) of 4,6-disubstituted 3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones <2005MRC240>

R^1 R^2	2-Thienyl <i>H</i>	3-Thienyl <i>H</i>	<i>Ph</i> <i>H</i>	<i>Me</i> <i>H</i>	<i>Me</i> <i>Me</i>	<i>Me</i> <i>Ph</i>	<i>Phe</i> <i>Me</i>	4-Pyridyl <i>Me</i>
^{13}C								
C-3	171.0	171.1	171.0	171.3	171.7	171.9	171.3	171.3
C-3a	110.4	111.0	110.9	112.0	112.0	111.9	111.0	110.5
C-4	136.8	138.3	142.5	140.4	140.1	140.9	141.9	139.6
C-7	153.3	153.5	153.5	153.7	152.4	152.4	152.3	152.4
C-7a	151.9	151.9	152.0	151.6	151.3	152.1	151.7	151.7
3-Me	14.3	13.8	13.7	12.8	12.8	12.9	13.7	13.9
R^1	135.7(2), 129.0(3), 128.5(5), 127.7(4)	134.7(3), 127.6(4), 127.0(5), 126.7(2)	133.8(1), 129.6(4), 128.5(3,5), 128.4(2,6),	18.7	18.7	18.9	133.4(1), 129.8(4), 128.5(3,5), 128.4(2,6)	150.1(2,6), 140.8(4), 122.8(3,5)
R^2					37.5	140.9(1), 128.6(3,5), 127.6(4), 126.2(2,6)	38.0	38.1
^{15}N								
N-1	-1.2	-0.9	-0.7	-0.1	-0.2	1.4	-0.8	-0.7
N-5	-71.5	-70.3	-69.0	-74.6	-65.6	-66.4	-60.5	-57.7
N-6	-190.5	-190.8	-190.2	-192.0	-195.2	-180.7	-193.5	-192.4

EI mass spectral behavior of 1,10-diethylbenzo[*c*]cinnoline was also discussed. There are not so many scientific papers that specifically study fragmentation of 1,2-diazines. In most cases the reported work deals with synthetic aspects of 1,2-diazines and low- or high-resolution mass spectra are just used as a characterization tool to confirm the molecular mass of the molecule. In the last decade one can clearly see that more and more mass spectrometry (MS) data reported do not use classical EI but electrospray ionization (ESI) to ionize the 1,2-diazine molecule. ESI (based on protonation or deprotonation) (no unpaired electrons) is a softer method than EI (unpaired electrons), inherently leading to less easy fragmentation of the generated ion. New fundamental mass spectrometry studies that appeared include the EI ionization and fragmentation of 2-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)phthalazin-1(2*H*)-one **1** <2000SAA1045> (Scheme 1), 6-phenyl-4-phenylsulfonylpyridazin-3(2*H*)-one **2** <2001H(54)237> (Scheme 2), and 6-phenyl-2-phenylsulfonylpyridazin-3(2*H*)-one **3** <2001H(54)237> (Scheme 2).

8.01.3.4 UV, IR, and Raman

The IR spectrum of pyridazine was obtained as the pure liquid and in solution, in the gas phase, and as a polycrystalline film. A Raman spectrum of the liquid was also reported <1998JRS547>. Vibrational spectra of simple derivatives such as 3,6-dichloropyridazine and 3,4,5-trichloropyridazine as solids and in solution were reported as well <2000PCA2599>. Sotelo and co-workers studied the $\tilde{\nu}$ C=O absorption band in IR spectra of several 5-substituted (H, CHO, CN, SO₂Me, NH₂, OEt) 6-phenylpyridazin-3(2*H*)-ones as solids confirming that the lactam form is the major tautomer <2002T2389>. The ^{13}C NMR shifts of the carbon atom of the CO's were in agreement with these IR data. An IR study on pyridazin-3(2*H*)-one and 4,5-dichloropyridazin-3(2*H*)-one revealed their existence in a lactam–lactim tautomeric equilibrium in dioxane. Upon dilution the equilibrium shifts to the enol form. The compounds probably appear as intermolecular cyclic dimers similar to the well-known carboxylic acid dimers <1997JST(408)467>. Konečný studied IR spectra of 5-disubstituted-amino 4-acetylamino-2-phenylpyridazin-3(2*H*)-ones. The spectra displayed two NH bands in the 3240–3400 cm⁻¹ region assigned to the intramolecular bonded NH groups. The $\tilde{\nu}$ /C=O bands of the carbonyl groups overlapped with the $\tilde{\nu}$ /C=N and $\tilde{\nu}$ /C=C owing to the very high absorption coefficients of the bands at 1610 cm⁻¹. For 5-disubstituted-amino 4-amino-2-phenylpyridazin-3(2*H*)-ones, the symmetric and asymmetric $\tilde{\nu}$ /NH₂ are observed in the 3370–3500 cm⁻¹ region. The $\tilde{\nu}$ /C=O are shifted to higher wave numbers in comparison with 5-disubstituted-amino 4-acetylamino-2-phenylpyridazin-3(2*H*)-ones <1997CCC800>. The $\tilde{\nu}$ /SH in 2-substituted 4-alkoxy-5-mercaptopyridazin-3(2*H*)-ones and $\tilde{\nu}$ /OH in 2-substituted 5-alkylthio-4-hydroxypyridazin-3(2*H*)-ones was also investigated <1996CCC437>. Ultraviolet (UV) spectroscopy has been used to study the self-association of pyridazine in aqueous solution at neutral, acidic, and basic



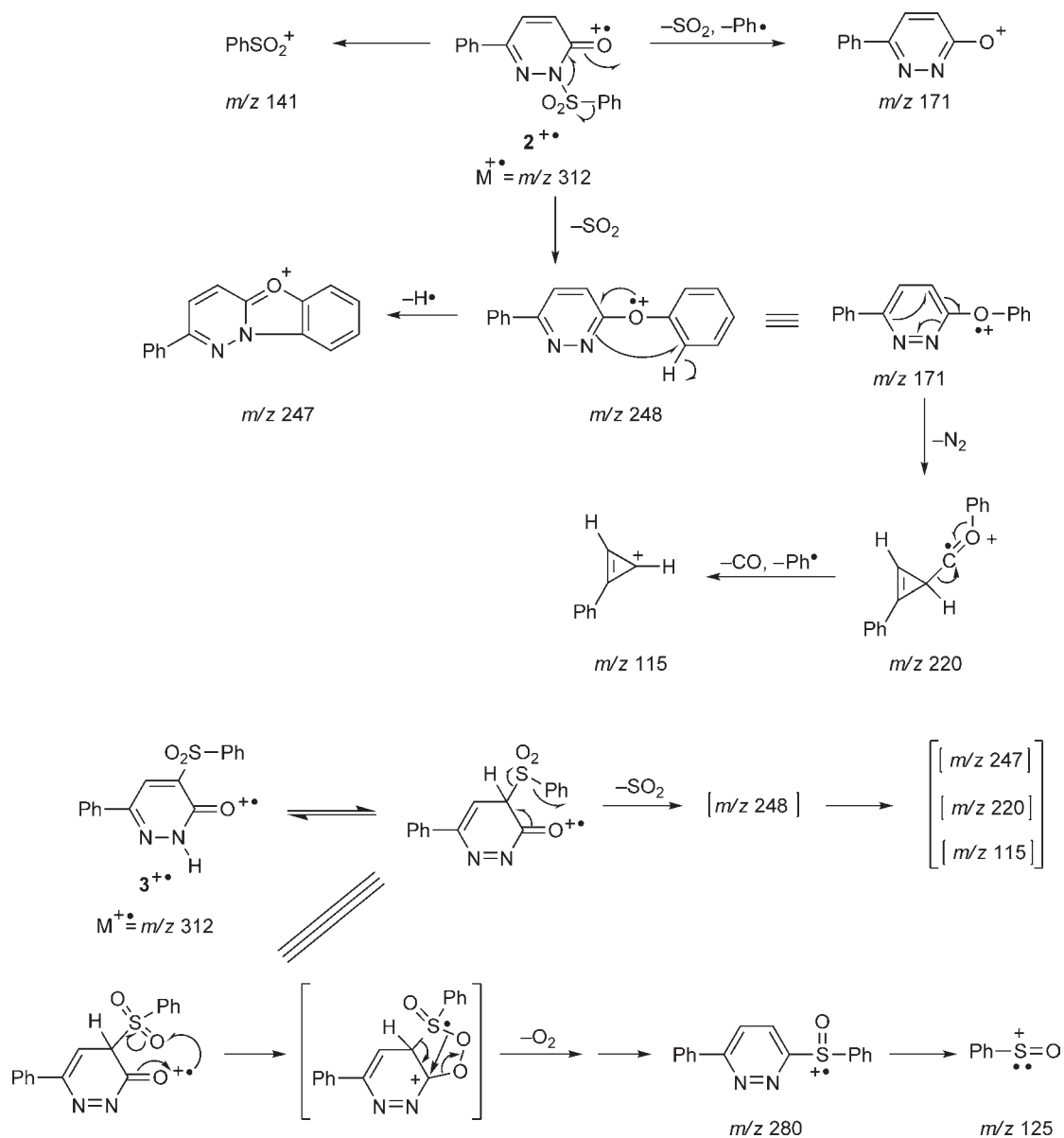
Scheme 1

pH <2003SAA1223>. Electronic spectra and solvatochromic behavior of azo cinnolines **4** in different solvents were also studied (Figure 5) <2004SAA103>. For the above-mentioned 5-disubstituted-amino 4-acetylamino-2-phenylpyridazin-3(2*H*)-ones, 5-disubstituted amino 4-amino-2-phenylpyridazin-3(2*H*)-ones, 2-substituted 4-alkoxy-5-mercaptopyridazin-3(2*H*)-ones, and 2-substituted 5-alkylthio-4-hydroxypyridazin-3(2*H*)-ones UV data were also provided <1996CCCC437, 1997CCCC800>.

8.01.4 Thermodynamic Aspects

8.01.4.1 General Physical Properties

In CHEC-II(1996) <1996CHEC-II(6)1>, some standard physical properties of pyridazine, phthalazine and cinnoline were summarized. When one compares the melting (pyridazine -8°C , phthalazine $89-92^{\circ}\text{C}$, cinnoline $40-41^{\circ}\text{C}$) and boiling points (pyridazine 208°C , phthalazine $315-317^{\circ}\text{C}$, cinnoline $114^{\circ}\text{C}/0.35\text{ mm}$) with the corresponding dideaza analogs the effect of the introduction of two electronegative nitrogen atoms becomes visible. The nitrogen atoms are hydrogen bond acceptors which for pyridazine, for instance, results in a complete miscibility with water and alcohols. Melting points of pyridazin-3(2*H*)-one ($104-105^{\circ}\text{C}$), pyridazin-4(1*H*)-one ($245-246^{\circ}\text{C}$), phthalazin-1(2*H*)-one ($183-184^{\circ}\text{C}$), and cinnolin-3(2*H*)-one ($201-203^{\circ}\text{C}$) were also incorporated in CHEC-II(1996) <1996CHEC-II(6)1>. Some melting points of simple substituted pyridazin-3(2*H*)-ones are summarized in Table 4. A general trend is that N-unsubstituted pyridazin-3(2*H*)-ones have higher melting points than the corresponding substituted derivatives. Similarly, hydroxypyridazin-3(2*H*)-ones melt at a higher temperature than the corresponding ethers <2000HC(57)1, 2002T5645>. Log *P* values of substituted pyridazin-3(2*H*)-ones, which are important indications for their potential to be ‘drugable’, received attention. Mátyus studied the lipophilicity of a set of 4- and



Scheme 2

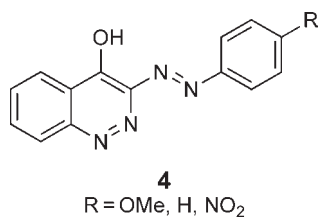


Figure 5

5-aminopyridazin-3(2*H*)-one regioisomers. The log *P* values of the 4-isomers were found to be significantly higher than those of the 5-isomers indicating a higher lipophilicity for the former class. This trend could be confirmed by calculations <2002JMT(578)89, 2003JFA5262>.

Table 4 Melting points of substituted pyridazin-3(2*H*)-ones

<i>Subst. (N-2)</i>	<i>Subst. (C-4)</i>	<i>Subst. (C-5)</i>	<i>mp</i> (°C)
H	Cl	Cl	199–200
Me	Cl	Cl	92
Bn	Cl	Cl	85
Ph	Cl	Cl	163–164
H	Cl	OMe	235
Me	Cl	OMe	153–155
Bn	Cl	OMe	94
Ph	Cl	OMe	149–150
Me	Cl	OH	261
Bn	Cl	OH	237–242
Ph	Cl	OH	273–274

8.01.4.2 Ionization

The pK_a values of pyridazine (2.3), phthalazine (3.5), and cinnoline (2.3) were mentioned in CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>. When one compares the pK_a of pyridazine (2.3) with that of pyrimidine (1.3) and pyrazine (0.7) and similarly the pK_a of phthalazine (3.5), cinnoline (2.3) with that of quinazoline (1.9) and quinoxaline (0.65), one can clearly see that the 1,2-diazines are more basic than their corresponding diazine isomers. This is attributed to the lone pair repulsion in 1,2-diazines. A good linear relationship was found between the experimental pK_a value and the HOMO energy for the diazine and benzodiazine series. The list included pyridazine, phthalazine, and cinnoline. The basicity of the azines can therefore be directly interpreted in terms of the HOMO energies <1995JMT(339)255>. pK_a values of a set of 1,2-diazine derivatives including pyridazines, pyridazin-3(2*H*)-ones, and 1,2-dihydropyridazine-3,6-diones have been predicted using theoretical calculations <2004JMT(683)221>. Acidities of a set of twelve 6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones were also calculated. A satisfactory correlation between experimental and computed acid dissociation constants was found <2003JMT(666/7)609>. In CHEC(1984) <1984CHEC(2)1>, pK_a values of several substituted pyridazinones as well as pyridazines were tabulated. Pyridazin-3(2*H*)-one (10.5) has an acidity similar to phenol for proton loss from the neutral molecule, while pyridazin-4(1*H*)-one is even more acidic (8.7).

8.01.4.3 Aromaticity

The resonance energy of pyridazine (calc. 43.9 kJ mol⁻¹, exp. 33.5 kJ mol⁻¹), phthalazine (calc. 87.4 kJ mol⁻¹, exp. 80.1 kJ mol⁻¹), and cinnoline (calc. 83.4 kJ mol⁻¹, calc. 69.8 kJ mol⁻¹) has been calculated from molecular dimensions, including nitrogen–nitrogen bond contributions <1997T13111>. When one subtracts the calculated resonance energy value for benzene (46.4 kJ mol⁻¹) from the value for phthalazine and cinnoline, a value for the pyridazine unit in these bicycles can be obtained. In this way one can clearly deduce that the aromaticity of the pyridazine unit in phthalazine (41 kJ mol⁻¹) and cinnoline (37 kJ mol⁻¹) is less than in pyridazine itself. The resonance energy of the pyridazine ring in *N*-(2-chloropyridin-3-yl)pyridazin-3-amine (34.3 kJ mol⁻¹) and *N*-(3-bromopyridin-2-yl)pyridazin-3-amine (32.6 kJ mol⁻¹) has been calculated applying the same model <2007T3818>.

8.01.4.4 Conformation of Nonconjugated Compounds

Some conformational studies of piperazic acids (hexahydropyridazine-3-carboxylic acids) have been reported <1998CSR437>. Piperazic acids are important compounds as they appear as subunit in many natural products (see Sections 8.01.6 and 8.01.12.2). They can be considered as rigid proline equivalents <1998JA80>. The conformation of derivatives of 3,4-dihydrophtalazine-2(1*H*)-carboxylic acid, a new conformationally restricted analog of phenylalanine, was also studied <1998T165>.

8.01.4.5 Tautomerism

In CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>, examples of keto–enol, thione–thiol, amino–imino, methyl–methylene tautomerism were given. New examples of most of these subclasses appeared since 1995.

8.01.4.5.1 Keto–enol tautomerism

In general, hydroxyl substituents on the heterocyclic ring of pyridazines, phthalazines, and cinnolines exist in the keto form. When two hydroxyl groups are present, only one will be in the keto form and the other one in the enol form <1984CHEC(2)1, 1996CHEC-II(6)1>. In agreement with this, Sotelo and co-workers concluded on the basis of IR and ^{13}C NMR experiments that 5-substituted 6-phenylpyridazin-3(2*H*)-ones exist in the lactam form. Calculations revealed that the difference in energy between the lactam and lactim form is in the order of 42 kJ mol^{-1} . Comparison of these energy data showed that the presence of electron-releasing substituents in C-5 stabilizes the keto form to a greater extent. For some of the reported compounds, X-ray data are available which are in agreement with the other experimental data <2002T2389>. IR showed that pyridazin-3(2*H*)-one and 4,5-dichloropyridazin-3(2*H*)-one occur in lactam–lactim tautomeric equilibrium in dioxane solution <1997JST(408)467>.

8.01.4.5.2 Amino–imino tautomerism

Generally, pyridazinamines, phthalazinamines, and cinnolinamines exist in the amino form <1984CHEC(2)1, 1996CHEC-II(6)1>. The dimethyl-substituted compounds **6** mostly exist in the amino tautomer (**B**), while for the corresponding unsubstituted derivatives **5** the equilibrium is shifted toward the imino tautomer (**A**) (Figure 6) <2002BMC3197>. The hydrazone of phthalazine-1-hydrazine (hydralazine) and methyl 2-oxopropanoate **7** exists in the imino form. This was confirmed by NMR in solution as well as with X-ray diffraction (Figure 6) <2000J(P2)2259>.

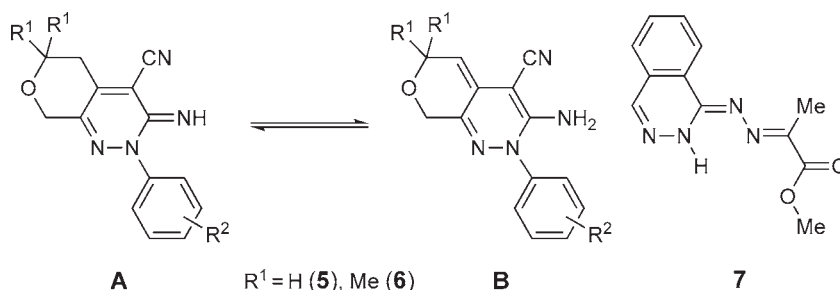


Figure 6 Tautomerism in **5–7**.

8.01.4.5.3 Double bond tautomers in nonconjugated systems

Dihydrocinnoline **8** appears in tautomeric form **A** in solution. Addition of D_2O caused the disappearance of two NH signals at 6.83 and 11.00 ppm and a simultaneous decrease of integration of the C-4 olefinic proton at 6.83 ppm to 0.5H (C-4 H and one of the two NH signals appear at the same position) in the ^1H NMR spectrum. This observation shows that **8A** tautomerizes with **8B** (Figure 7) <1999CPB791>.

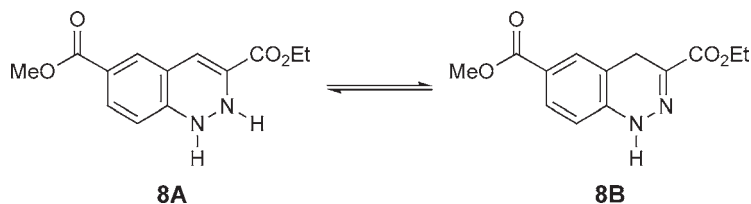


Figure 7 Tautomerism in **8**.

8.01.4.5.4 Methyl–methylene tautomerism

On the basis of ^1H NMR, nuclear Overhauser effect (NOE) experiments, and X-ray diffraction Guard and Steel showed that earlier reported benzylidene-4,5-dihydropyridazines should be represented as aromatic pyridazine

tautomers <1995AJC1601>. Although in **9** the aromaticity is broken going from methyl tautomer **A** to methylene tautomer **B**, its presence was clearly confirmed via NMR (Figure 8) <2001MOL959>.

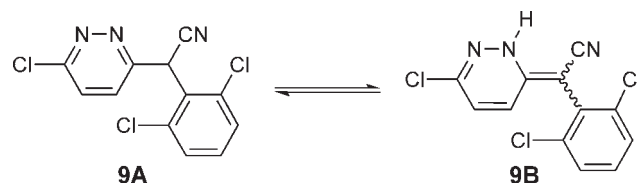


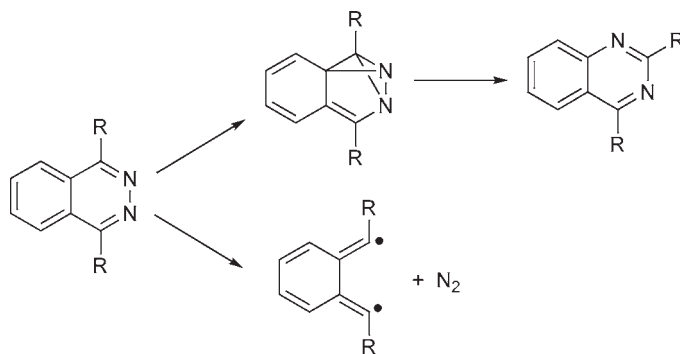
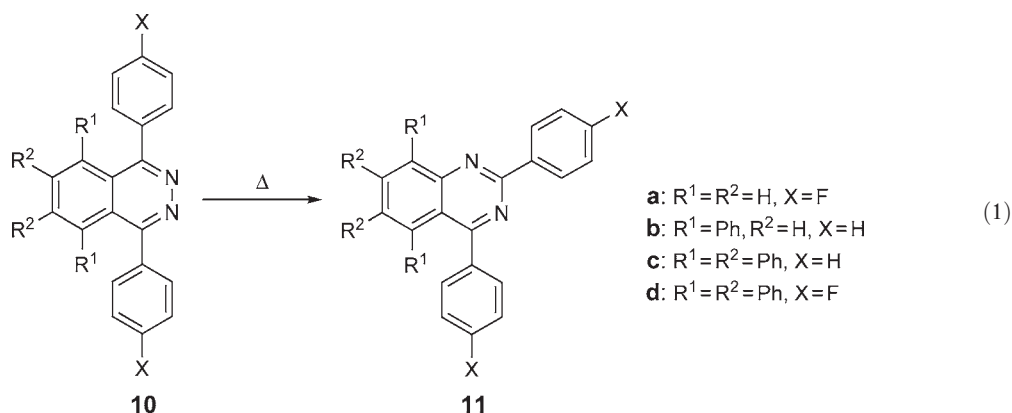
Figure 8 Tautomerism in **9**.

8.01.5 Reactivity of Fully Conjugated Rings

8.01.5.1 Intramolecular Thermal and Photochemical Reactions

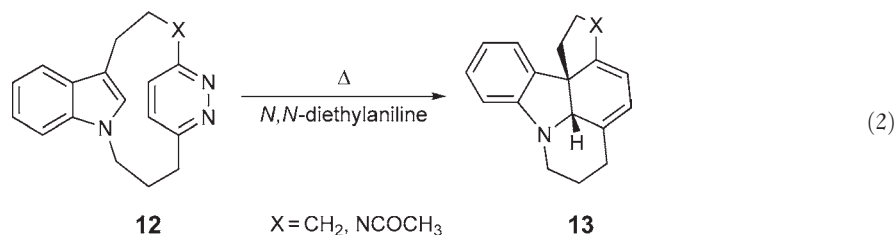
8.01.5.1.1 Intramolecular thermal reactions

In 1995 Hay reported the first observation of a thermal rearrangement reaction of phthalazines to their quinazoline isomers. Heating polyphenylated phthalazines **10b–d** at 360 °C for 30 min gave the corresponding quinazolines **11b–d** in high yield. However, in the case of the less sterically crowded 1,4-bis(4-fluorophenyl)phthalazine **10a** a higher temperature and a longer reaction time were needed, and only a low yield of quinazoline **11a** was obtained along with the formation principally of a black insoluble material (Equation 1) <1995JOC3131>. After heating a 1:1 mixture of **10c** and **10d**, only **11c** and **11d** were found. No cross-over products were detected, suggesting that the reaction is unimolecular. A probable mechanism for this rearrangement is a unimolecular pathway through a benzvalene-type intermediate (Scheme 3). The formation of the black insoluble material in the thermolysis of **10a** and of minor side products in the other cases is thought to be the result of coupling reactions of a diradical intermediate formed by nitrogen elimination <1996PSA1923>.

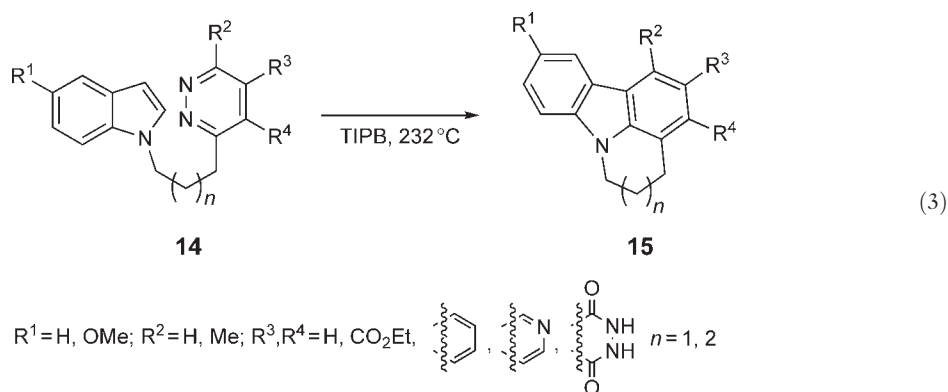


Scheme 3

Since the publication of CHEC-II(1996) <1996CHEC-II(6)1>, in which thermally induced [4+2] cycloadditions have been reviewed, significant progress has been realized in this strategy, especially for the synthesis of polycyclic heterocycles. Cyclophanes **12** containing pyridazine and indole units were used for the synthesis of pentacyclic compounds **13** via a thermally induced transannular inverse-electron-demand Diels–Alder reaction (Equation 2) <2002OL127, 2002AGE3261>.



Similarly, mono- and bicyclic 1,2-diazines tethered to indole dienophiles by only one alkylene chain **14** afford tetra- and pentacyclic condensed carbazoles **15**. Unactivated pyridazines undergo these thermally induced [4+2] cycloaddition reactions only very sluggishly. However, the examples with the more activated electron-deficient pyridazines, especially pyridazine diesters and pyridazino[4,5-*d*]pyridazindiones, demonstrate the synthetic usefulness of this strategy for the construction of polycyclic carbazoles (Equation 3) <2004T6495>.

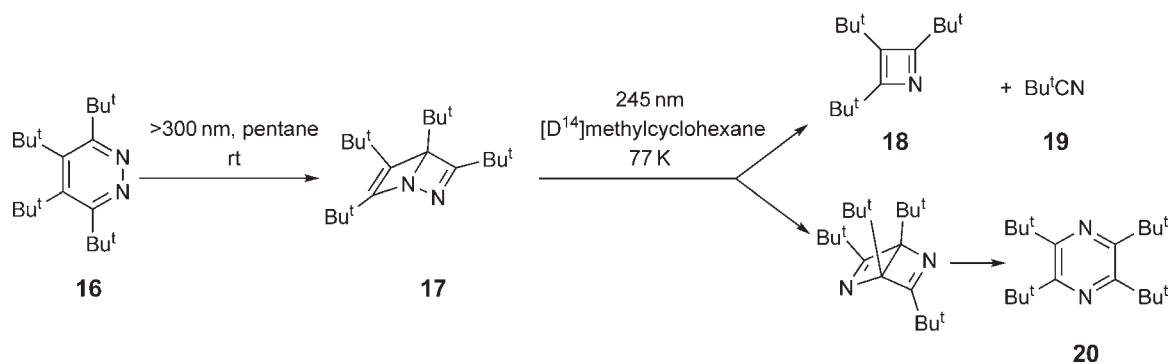


Flash vacuum pyrolysis of 3-benzoylcinnolines has been presented as an interesting route toward polynuclear aromatic compounds <2001T7377>.

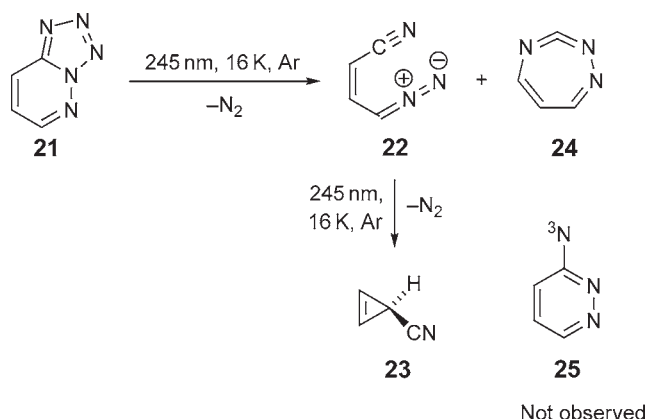
8.01.5.1.2 Intramolecular photochemical reactions

Pyridazines which are highly crowded with bulky substituents can be converted photochemically into the corresponding 1,2-Dewar pyridazines. Their stability compared to the pyridazines is due to the lowered steric strain and to the rearrangement being thermally forbidden according to the Woodward–Hoffmann rules. Thus, tetra-*t*-butylpyridazine **16** is converted quantitatively into its 1,2-Dewar isomer **17** when irradiated in pentane at room temperature with UV light of wavelength >300 nm. After irradiation of this 1,2-Dewar pyridazine with UV light of 245 nm, a mixture of 82% tri-*t*-butylazete **18** and pivalonitrile **19** and 18% of tetra-*t*-butylpyrazine **20** is obtained (Scheme 4) <1995LA169>. Similarly, irradiation of 3,4,5-tri-*t*-butyl-6-isopropylpyridazine and 3,4,6-tri-*t*-butyl-5-isopropylpyridazine with UV light of wavelength >300 nm gives quantitatively the corresponding 1,2-Dewar pyridazines. However, irradiation of these 1,2-Dewar pyridazines with UV of 245 nm gives only 2,3-di-*t*-butyl-4-isopropylazete and 2,4-di-*t*-butyl-3-isopropylazete, respectively, and pivalonitrile; no pyrazine is formed <1995LA173>.

Photolysis (245 nm) of tetrazolo[1,5-*b*]pyridazine **21** in an argon matrix at 16 K leads to nitrogen extrusion and ring opening to form (2*Z*)-4-diazobut-2-enenitrile **22**. Further photolysis produces predominantly cycloprop-2-ene-1-carbonitrile **23** and small amounts of 1,3,7-triazacyclohepta-1,2,4,6-tetraene **24**. No formation of triplet pyridazine-3-nitrene **25** is observed (Scheme 5) <2003PCP1051>.



Scheme 4



Scheme 5

Nucleophilic addition of 1,2-diazines such as pyridazine **26** and phthalazine **27** to the diketone **28** afforded the 4a,5-dihydropyrrolo[1,2-*b*]pyridazines **30**, which undergo ring opening to the betaines **29** after irradiation with UV light. The photochromic properties of these compounds were studied and half-lives of the betaines in the order of 2–100 s were measured. Treating the compounds **30** with hydrazine afforded the 4a,5-dihydropyrrolo[1,2-*b*:4,5-*d'*]dipyridazines **31**. These compounds showed no photochromism at room temperature or after cooling with liquid nitrogen. However, laser fast spectroscopy was successfully used for the determination of the half-lives of the betaines **32** (3.9–5.1 ns). The system **31** ⇌ **32** is the fastest bleaching system in the indolizidine series for which photochromism was clearly established. The reason for this is the fixed *cis*-conformation of the bridge in the betaines **32**, which does not allow rotation to a more relaxed *trans*-conformation (Scheme 6) <2001EJO4077>.

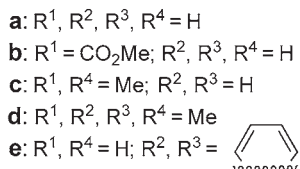
8.01.5.2 Electrophilic Attack at Nitrogen

8.01.5.2.1 Introduction

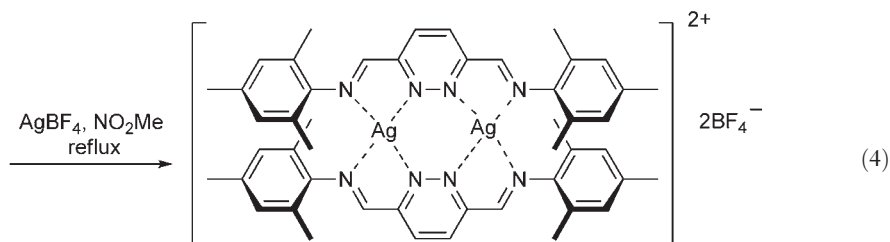
Pyridazine and its benzo derivatives are electron-deficient ring systems. Nevertheless, many examples of successful reactions of electrophiles on one of the nitrogen atoms of these skeletons have been described.

8.01.5.2.2 Metals

While this topic has only received moderate attention in CHEC-II(1996) <1996CHEC-II(6)1>, the synthesis of complexes containing 1,2-diazine ligands has been a field of intensive research in the last decade and has been reviewed <2002EJI2535>. Several metal salts have been used for this purpose. The synthesized complexes involve multidentate ligands in which the two nitrogen atoms of the 1,2-diazine unit are involved <2004JCD1153>. Also other parts of the 1,2-diazine ligand can be additionally involved such as the nitrogen of an imine functionality (Equation 4) <2006JCD1491>.



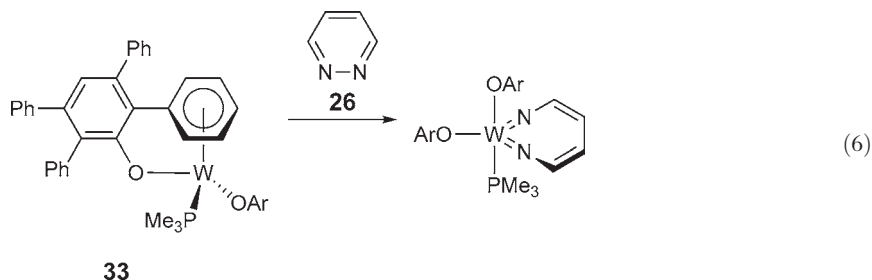
The chemical structure of 4,4'-bis(2,6-dimethylphenyl)-2,2'-bipyridine (DMBP) is shown. It consists of two 2,6-dimethylphenyl rings connected to a central bipyridine core at the 2 and 2' positions. The bipyridine core is a fused system of two pyridine rings. The 2,6-dimethylphenyl rings are attached to the 2 and 2' positions of the bipyridine core. The methyl groups are located at the 2 and 6 positions of each phenyl ring.



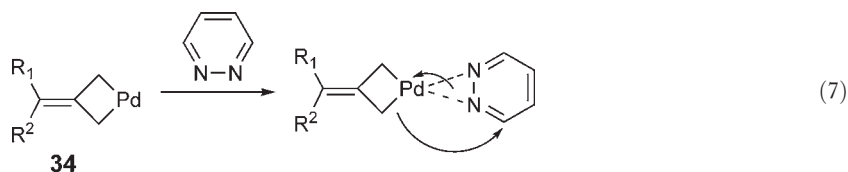
Chemical reaction scheme showing the synthesis of a macrocyclic catalyst. The starting material is a 1,4-bis(4-OR-phenyl)-1,3,5-hexatriene derivative. It reacts with $\text{Pd}(\text{OAc})_2$ to form a macrocyclic catalyst. The catalyst is a Pd complex with a macrocyclic ligand containing two OR groups and two AcO groups, and a 1,3,5-hexatriene ligand. The catalyst is shown with a 2 in a circle, indicating it is a dimer.

(5)

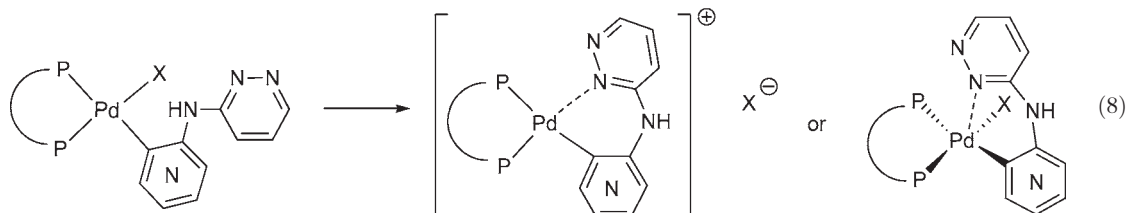
Macrocyclic 1,2-diazines were also investigated as ligands [<2000AGE1968>](#). Especially interesting is the reaction of 1,2-diazines (pyridazine **26**, phthalazine, and benzo[*c*]cinnoline) with tungsten(II)aryloxide complexes **33** as the N–N bond is cleaved (Equation 6) [<2002CC2482>](#).



Electrophilic attack of a metal complex on one of the nitrogen atoms of 1,2-diazines has been reported to occur in the mechanism of new metal mediated methods to prepare C–N bonds. Pyrrolo-fused pyridazines and phthalazines for instance were synthesized via attack of the 1,2-diazine on a palladacyclobutane intermediate **34** formed via oxidative addition of an alkylidenecyclopropane to Pd(PPh₃)₂ (Equation 7) [<2004JOC3202>](#).



In 2006 Maes and co-workers described the intramolecular Pd-catalyzed amination of *N*-(2-chloropyridin-3-yl)pyridazin-3-amine and *N*-(3-bromopyridin-2-yl)pyridazin-3-amine which involves intramolecular coordination of Pd(II) to the N-2 nitrogen of the *N*-arylpyridazin-3-amine entity (Equation 8). *N*-(2-Chloropyridin-3-yl)pyridazin-3-amine and *N*-(3-bromopyridin-2-yl)pyridazin-3-amine are intermediates in the auto tandem amination of 2-chloro-3-iodopyridine and 2,3-dibromopyridine with pyridazin-3-amine, respectively [<2004CC2466, 2006JOC260>](#). In the former case the ring closure proceeds partly via an S_NAr process.



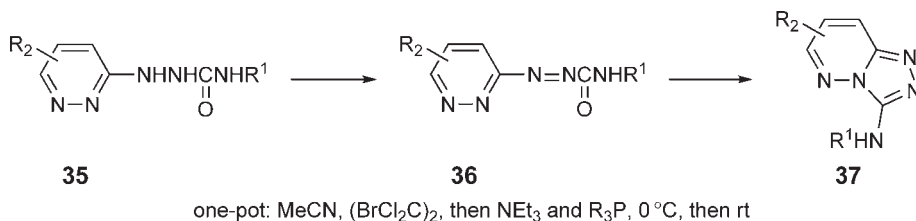
8.01.5.2.3 Alkyl halides

S_N2 reaction of pyridazines with (functionalized) alkyl halides is well documented in CHEC(1984) [<1984CHEC\(2\)1>](#) and CHEC-II(1996) [<1996CHEC-II\(6\)1>](#) and remains a frequently used reaction [<1996PHA76, 1998H\(48\)1609, 2001H\(55\)1105, 2002JME563, 2004S1072>](#). Also intramolecular alkylations are reported [<2001PHAS50>](#). For instance, the treatment of 3-(ω-hydroxyalkoxy)pyridazines with SOCl₂ yields 3-(ω-chloroalkoxy)pyridazines as intermediates. These give intramolecular S_N2 reaction. A subsequent ring opening with chloride affords 2-(ω-chloroalkyl)pyridazin-3(2*H*)-ones. Quaternization of pyridazine and phthalazine with α-bromoacetophenones yields compounds that upon treatment with base give access to methylides that can be used in cycloaddition reactions [<2005H\(65\)1871, 2005RRC353>](#). Methylides have also been prepared directly via the reaction of pyridazines with tetracyanoethylene oxide [<1995CC2067>](#). When an amino group is present in the 3-position of the pyridazine, quaternization with α-bromoacetophenones is followed by intramolecular condensation [<2001S595, 1996AJC451>](#).

8.01.5.2.4 Acyl halides and related compounds

As described in detail in CHEC-II(1996) [<1996CHEC-II\(6\)1>](#) N-acylation of 1,2-diazines is often used to make the nucleus more susceptible for nucleophilic attack (see Section 8.01.5.4.4). Intramolecular reactions on nitrogen

involving the carbonyl of a hydrazide and semicarbazide have also been described. *In situ* formed *N*-acylhydrazides, via acyl transfer with 4-acylhydrazinomethylene-2-phenyloxazol-5(4*H*)-ones to pyridazin-3-hydrazines, were converted with ZrCl_4 to 1,2,4-triazolo[4,3-*b*]pyridazines derivatized in the 3-position with a carbon substituent <2000H(54)1011>. 3-Amino-substituted derivatives **37** on the other hand were synthesized via the oxidation of semicarbazides of pyridazin-3-hydrazines **35** to the corresponding diazenes **36** which can be cyclized upon treatment with R_3P (Scheme 7) <1996SL652>. More examples on 1,2,4-triazolo[4,3-*b*]pyridazine formation can be found in Section 8.01.7.11.2.



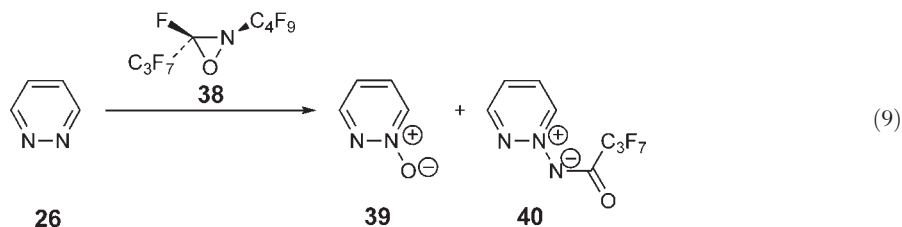
Scheme 7

8.01.5.2.5 Peracids

1,2-Diazine *N*-oxides can be regioselectively formed with H_2O_2 in formic acid as exemplified by the reaction of 2-chlorobenzo[*f*]cinnolines, 2-chloro-5,6-dihydrobenzo[*f*]cinnolines, and 3-chloro-9*H*-indeno[2,1-*c*]pyridazines <2000AP341>. This area was extensively discussed in CHEC(1984) <1984CHEC(2)1>.

8.01.5.2.6 Aminating agents

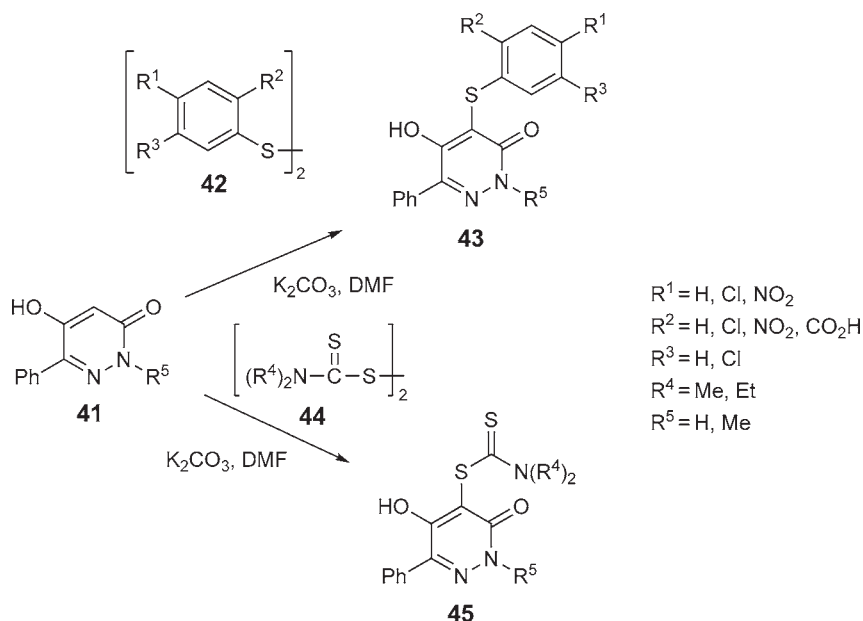
In the reaction of pyridazine **26** with perfluoro-(2-butyl-3-propyloxaziridine) **38** both pyridazin-1-oxide **39** and *N*-(perfluorobutanoyl)pyridazinium-1-aminide **40** were formed (Equation 9) <1996J(P1)2517>. In CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>, the *N*-amination with hydroxylamine-*O*-sulfonic acid and derivatives was covered.



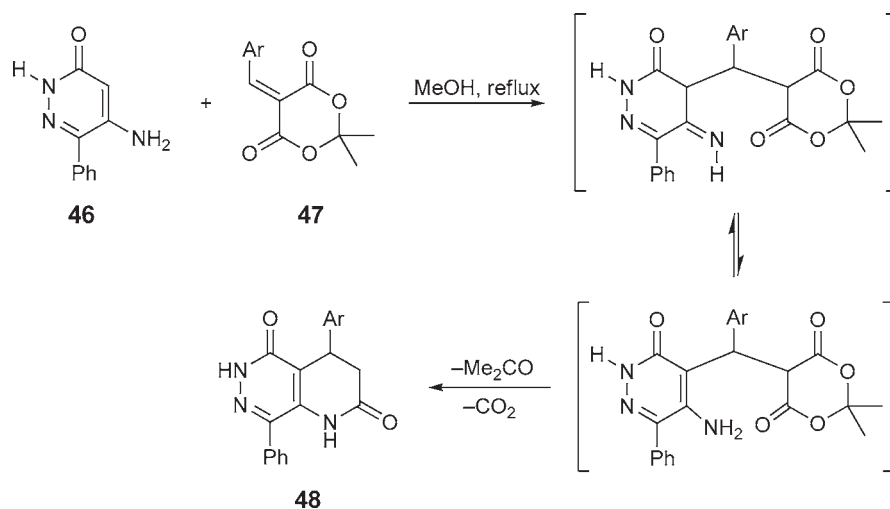
8.01.5.3 Electrophilic Attack at Carbon

Electrophilic attack at carbon was well covered in CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>. Since 1995 several new interesting examples have been published. Enolate anions of the 1,3-dicarbonyl system in 5-hydroxypyridazin-3(2*H*)-ones **41** generated by potassium carbonate in dimethylformamide react with diaryl disulfides **42** to yield 4-arylthiopyridazin-3(2*H*)-ones **43**. The arylthiolate anions formed in this reaction can be oxidized by air to yield the starting disulfides again. Tetraalkylthiuram disulfides **44** react in the same manner to yield 4-dialkyldithiocarbamate derivatives **45** (Scheme 8) <2000JHC911>.

Pyrido[2,3-*d*]pyridazine derivatives **48** have been synthesized by refluxing equimolar amounts of an appropriate 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **47** with 5-amino-6-phenylpyridazin-3(2*H*)-one **46** in methanol or a methanol acetic acid mixture. The electron-poor carbon atom of the polarized carbon-carbon double bond of **47** is the electrophile attacking C-4 of the 5-aminopyridazinone **46**. Imino-enamine tautomerization of the intermediate is followed by ring closure and subsequent loss of acetone and carbon dioxide affording the reaction products **48** as stable crystalline solids in 70–90% yield (Scheme 9) <2000T2473>.



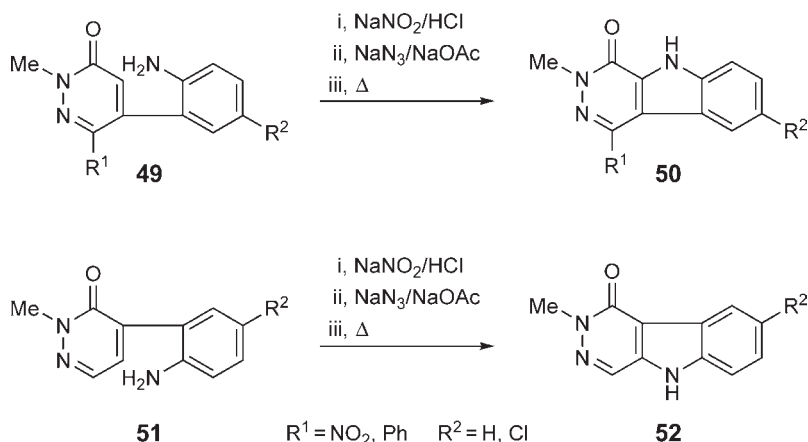
Scheme 8



Scheme 9

Nitration of 4-amino-6-methylpyridazin-3(2*H*)-one at C-5 was performed in two steps. Treatment with concentrated nitric acid affords 6-methyl-4-(nitroamino)pyridazin-3(2*H*)-one whose rearrangement in concentrated sulfuric acid led to the formation of 4-amino-6-methyl-5-nitropyridazin-3(2*H*)-one <2001RJO1026>.

Substituted 3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-ones **50** <2001H(55)1105, 2002T10137> and 2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones **52** <2006T121> have been synthesized from 5-(2-aminophenyl)pyridazin-3(2*H*)-ones **49** and 4-(2-aminophenyl)pyridazin-3(2*H*)-ones **51**, respectively. For this purpose diazotization of the amino groups was followed by a nucleophilic substitution with sodium azide affording aryl azides. Upon heating of these compounds, the ring-closed products were obtained most probably via the formation of an electrophilic nitrene (Scheme 10).



Scheme 10

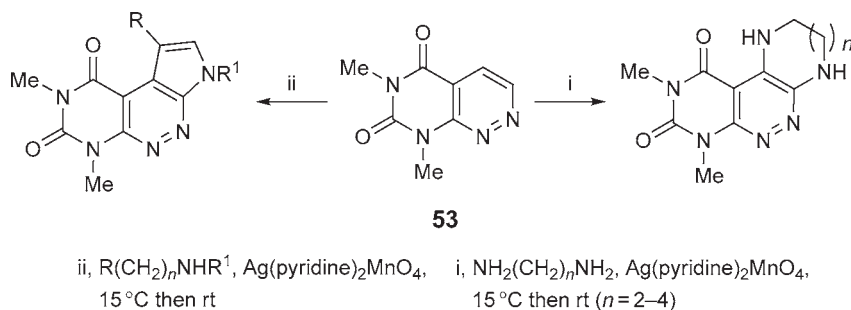
8.01.5.4 Nucleophilic Attack at Carbon

8.01.5.4.1 Introduction

Attack of nucleophiles on pyridazines and benzopyridazines followed by oxidation with air or another oxidant is a very attractive way to functionalize the 1,2-diazine nucleus. For less nucleophilic reagents nucleophilic addition requires activation of the 1,2-diazine via N-quaternization. If the substituent on the nitrogen atom is a suitable leaving group oxidation can occur via simple elimination. Also the nucleophile can contain a leaving group allowing to restore the unsaturation (vicarious nucleophilic substitution). Although less frequent, dihydro-1,2-diazines are the targeted compounds.

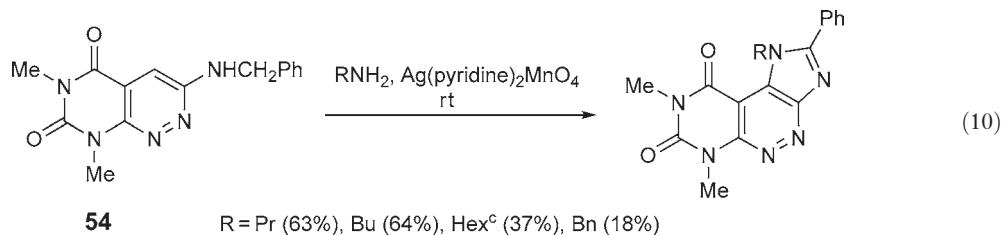
8.01.5.4.2 Amines

The introduction of an amino group on the 1,2-diazine nucleus via KNH_2 in liquid NH_3 or only with NH_3 (nucleophile and solvent), for sufficiently activated nuclei, using KMnO_4 as the oxidant has been thoroughly discussed in CHEC-II(1996) <1996CHEC-II(6)1>. The nucleophilic substitution of hydrogen on 1,2-diazines with ammonia/amide has been extended to alkylamines by Gulevskaya and Pozharskii. The substrate of primary interest of the Rostov team is the purine analog 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **53**, which is sufficiently activated for σ -adduct formation at C-3 (primary as well as ammonia) and C-4 (secondary) with alkylamines <1999RCB1150>. Reactions are performed in alkylamine using $\text{Ag}(\text{pyridine})_2\text{MnO}_4$ as oxidant. $\text{Ag}(\text{pyridine})_2\text{MnO}_4$ has a better solubility in alkylamines than KMnO_4 and is therefore often crucial for the success of the reaction. With alkanediamines even tandem nucleophilic substitution of hydrogen was achieved (Scheme 11) <2000MC150>. Also pyrrole and imidazole ring annulation can be obtained <2001TL5981, 2003T7669>. Pyrrole formation involves initial oxidation of the aliphatic amine to the corresponding imine followed by tautomerization (Scheme 11). The enamine is the actual reagent involved in a tandem C–C (C-4) and C–N (C-3) bond-forming process. Imidazole can be formed via initial oxidation of the alkylamine to the corresponding imine, followed by attack of the amino group of the 3-alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones on this *in situ* formed imine. Subsequent intramolecular



Scheme 11

attack on C-4 and oxidation, results in imidazole annulation. Oxidation of the 3-alkylamino group to the corresponding imine and subsequent addition of alkylamine on the imine, followed by intramolecular nucleophilic attack at C-4 and oxidation, can also proceed yielding another substitution pattern. The exact mechanism depends on the relative ease of oxidation of 3-alkylamino in comparison with alkylamine. Equation (10) gives some representative examples starting from 3-benzylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **54**. Depending on the type of alkylamines used also imidazolines are obtained.



8.01.5.4.3 Hydrazine

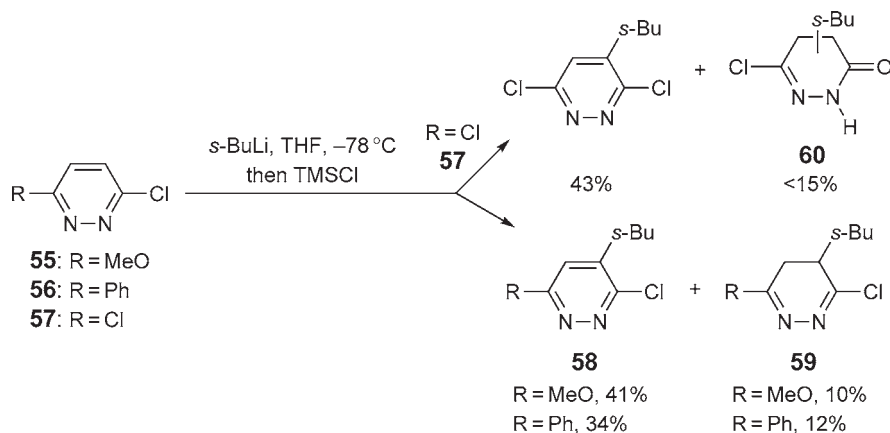
The synthesis of 4-aminopyridazin-3(2*H*)-ones by reaction of the corresponding pyridazin-3(2*H*)-ones with hydrazine was mentioned in CHEC-II(1996) <1996CHEC-II(6)1>. In 1999, Cignarella and co-workers provided examples on cinnolin-3(2*H*)-ones. Heating benzo- and thieno-fused cinnolin-3(2*H*)-ones with hydrazine hydrate gave access to the corresponding 4-aminocinnolin-3(2*H*)-ones <1998JHC1161, 1999JHC485, 1999JHC1253>.

8.01.5.4.4 Carbon nucleophiles

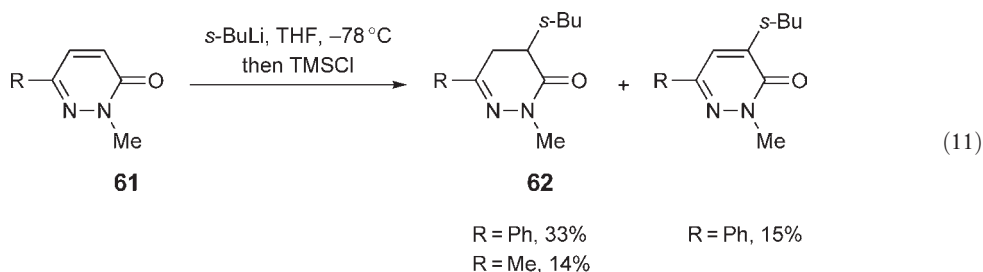
This section has been the subject of many papers and it is covered very well by CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>.

8.01.5.4.4(i) Organometallic compounds

The reaction of 6-substituted 3-chloropyridazines **55–57** with alkyllithium compounds yields mainly the corresponding 4-alkylated pyridazines **58** <1998SL762>. The main product was accompanied by a low amount of the corresponding 4-alkylated-4,5-dihydropyridazines **59** and traces of 5-alkylated regioisomers (Scheme 12). For 3,6-dichloropyridazine **57** as substrate regioisomeric 4(5)-alkylated 4,5-dihydropyridazin-3(2*H*)-ones **60** were formed as side compounds (Scheme 12). Interestingly, a similar reaction with less reactive organolithium compounds such as phenyllithium or vinylolithium did not proceed. A similar alkylation reaction on 6-substituted 2-methylpyridazin-3(2*H*)-ones **61** gave predominantly 4-alkylated 6-substituted 2-methyl-4,5-dihydropyridazin-3(2*H*)-ones **62** (Equation 11) <1998SL762>. In all these alkylation reactions trimethylsilyl chloride (TMSCl) was used to quench the reaction mixture yielding neutral dihydropyridazin[3(2*H*)-on]es allowing rearomatization.



Scheme 12



Treatment of pyridazine *N*-oxide with the dilithium salt of TosMIC followed by benzyl bromide yields a 1-hydroxydiazene <2004H(62)357>. This reaction is in agreement with the well-known fact that pyridazine *N*-oxide is known to yield ring-opened product as the main component in reactions with nucleophiles. Nucleophilic addition of MeMgI on 2-alkylphthalazinium halides in diethyl ether gave 2-alkyl-1-methyl-1,2-dihydrophthalazines in good yield <1995JHC643>. 2-Alkyl-1-methylphthalazinium halides were also successfully used as substrates in a similar reaction yielding 2-alkyl-1,1-dimethyl-1,2-dihydrophthalazines <1995JHC643>.

8.01.5.4.4(ii) Activated methyl and methylene carbanions

Reaction of pyridazine **26** with ethyl chloroformate (in pyridine) yields an activated intermediate that reacts with electron-rich five-membered rings such as the pyrazole unit in pyrazolo[1,5-*a*]pyridine <1999JME779>. Oxidation of the 4-substituted 1-ethoxycarbonyl-1,4-dihydropyridazine was achieved with air and KOBu^t in Bu^tOH. In a reaction with silyl enol ethers **63** on 1-ethoxycarbonylpyridazinium salt both attack in the α **65** and γ **64** position was observed (Equation (12) and Table 5) <1997H(46)83>. The ratio depends on the substitution pattern of the enol nucleophile. The same team also investigated the reaction with allyltrimethylsilane <1998H(49)67>. Interestingly, the addition of an equimolar amount of TBDMSOTf is beneficial. The triflate ion seems to be both a promoter of quaternary salt formation (1-ethoxycarbonylpyridazinium salt) as well as a stabilizer. Also phthalazine was used as substrate but in this case 0.2 equiv of TMSOTf was used. *N*-(5-Oxopentyl)phthalazinium iodide **66** could undergo intramolecular nucleophilic addition in a stereoselective way using chiral pyrrolidines as catalyst <2005AGE6058>. *In situ* enamine (and water) is formed with the chiral pyrrolidine **67** which acts as the nucleophile. The water allows hydrolysis of the iminium iodide after ring closure, releasing the chiral catalyst for the asymmetric annulation reaction (Equation 13). 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-substituted phthalazinium salt can be generated *in situ* from 1-hydroxy-2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazine <2003H(60)571>. Reaction with (hetero)aryl methyl ketones yields 1-[2-(hetero)aryl-2-oxoethyl]-2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazines.

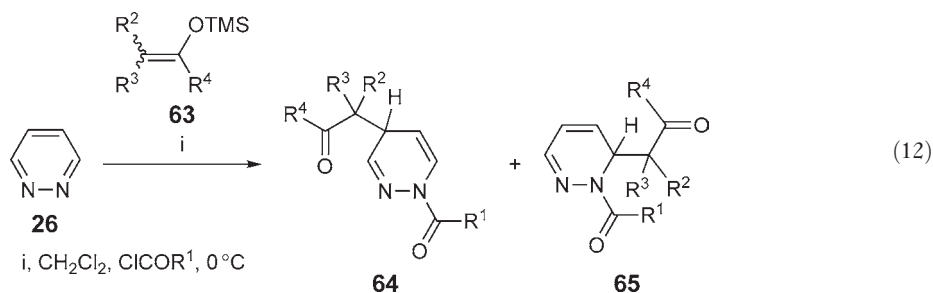
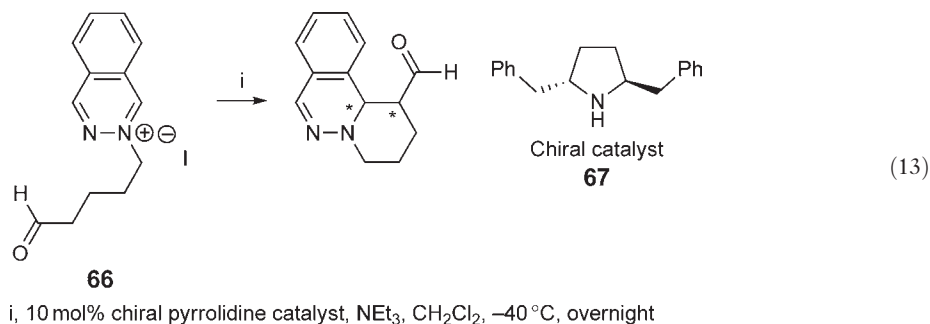


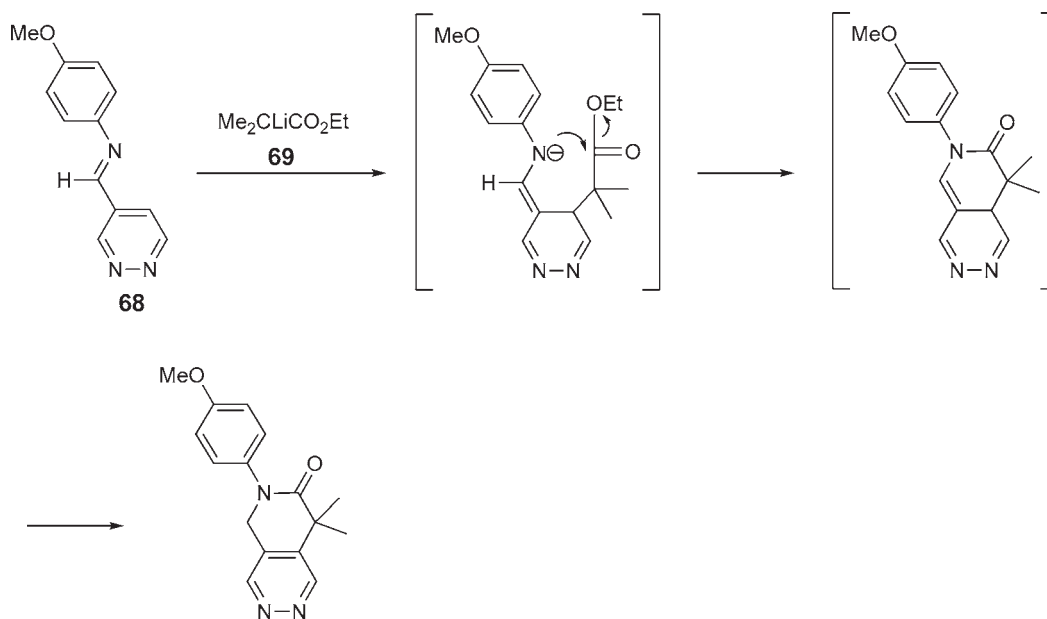
Table 5 Reaction of **63** in the α **65** and γ **64** position of 1-ethoxycarbonylpyridazinium salt

R^1	R^2	R^3	R^4	Yield of 64 (%)	Yield of 65 (%)
OEt	Me	Me	OMe	89	0
OEt	Me	H	OMe	49	48
OEt	TMS	H	OMe	31	40
CH(OAc)Ph	Me	H	OMe	55	22
OEt	H	H	Ph	35	54
OEt	H	H	OPh	6	78



Vicarious nucleophilic substitution was studied on pyridazinium 1-dicyanomethylides with $\text{ClCHXSO}_2\text{Ar}$ ($\text{X} = \text{Cl}$ or H) and KO^tBu as base in THF–DMF (THF – tetrahydrofuran) [<1998J\(P1\)1637>](#). Even with substituents in the 3-position regioselective introduction of CHXSO_2Ar in the 4-position was achieved. Since the dicyanomethylene group can be removed via a radical reaction with $(\text{NH}_4)_2\text{S}_2\text{O}_8$, this procedure gives an easy access to 3,4-disubstituted pyridazines.

4-Imino-substituted pyridazine **68** reacted in the 5-position with the lithium enolate of ethyl 2-methylpropanoate **69** via an interesting cascade of nucleophilic addition, ring closure via addition–elimination and tautomerization ([Scheme 13](#)) [<1996JHC1731>](#).



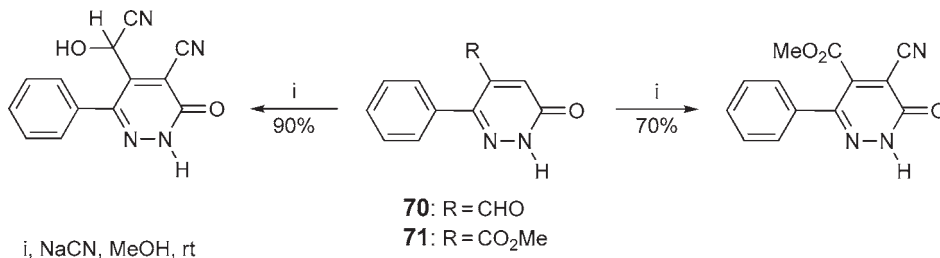
Scheme 13

8.01.5.4.4(iii) Cyanide ions, Including Reissert reactions

More examples of Reissert-type reactions on pyridazine *N*-oxides have been published exemplified by the reaction of 3,4-di(4-methoxyphenyl)pyridazine 1-oxide with KCN and BnCl in H_2O at 0°C which yields 69% of 3-cyano-5,6-di(4-methoxyphenyl)pyridazine [<2001BML2369>](#). A modified Reissert reaction using phosgene, trimethylsilyl cyanide, and a catalytic amount of BF_3 on phthalazine gave the stable carbonyl chloride 1-cyano-2-chlorocarbonyl-1,2-dihydrophthalazine in 52% yield [<1995JHC643>](#). Also diphosgene and triphosgene could be used to replace phosgene. Even the 1-methylated and 1,1-dimethylated 2-alkyl-1,2-dihydrophthalazines gave Reissert compounds [<1995JHC643>](#).

With triphosgene also 2-trichloromethoxycarbonyl derivatives were formed. More examples on nucleophilic substitution of hydrogen by cyano in pyridazin-3(2*H*)-ones have also appeared. Substrates **70** and **71** were used in

a reaction with cyanide in MeOH (**Scheme 14** <2001TL2863>. The reaction can proceed at room temperature due to the activation of the 5-substituent. The mechanism involves Michael addition of the cyanide to the α,β unsaturated carbonyl followed by air oxidation of the dihydropyridazin-3(2*H*)-one.



Scheme 14

8.01.5.4.5 Chemical reduction

The reduction of the 1,2-diazine nucleus has been discussed in detail in CHEC-II(1996) <1996CHEC-II(6)1> as this part was not present in CHEC(1984) <1984CHEC(2)1>. Dubreuil investigated electrochemical reduction of pyridazines substituted with electron-withdrawing groups. Initially, 1,2-dihydro derivatives were obtained which, depending on the nature of the ring substituents, can rearrange into 1,4-dihydropyridazine isomers or further be electrochemically reduced into activated pyrroles <2000TL647, 2004TL1031>. Selective 1,2-dihydrophthalazine formation was achieved via reduction with H₂ using a PtO₂ catalyst <2002BML5>. Reduction of 2-alkylphthalazinium halide with NaBH₄ in water yields 2-alkyl 1,2-dihydrophthalazine <1995JHC643>. For more examples, see Section 8.01.6.

8.01.5.5 Nucleophilic Attack at Hydrogen Attached to Ring Carbon or Nitrogen

8.01.5.5.1 Metallation at carbon

The metallation, especially the lithiation, of pyridazines, mentioned briefly in CHEC-II(1996) <1996CHEC-II(6)1>, has been developed extensively since 1995 by Quéguiner and co-workers for the derivatization of pyridazines and benzopyridazines. The bases of choice are usually lithium 2,2,6,6-tetramethylpiperidide (LTMP) and lithium diisopropylamide (LDA). Special efforts have been made to achieve regioselective lithiations.

Pyridazines with an *ortho*-directing group at C-4 are lithiated regioselectively at C-5 <1995JHC841>. 3-Bromo-6-phenylpyridazine gives C-4 metallation. LDA has been shown to be a better base than LTMP <2005JHC509>. 3-Chloro-6-methoxypyridazine can be lithiated selectively at C-5 only with the use of very hindered lithium dialkylamides <1996T10417>. 3-Methoxy-6-(phenylthio)pyridazine is lithiated regioselectively *ortho* to the methoxy group. On the contrary, 3-methoxy-6-(phenylsulfinyl)pyridazine is lithiated *ortho* to the phenylsulfinyl group. In the case of 3-methoxy-6-(phenylsulfonyl)pyridazine C-4 and C-5 lithiation is observed, the latter being the major pathway <1997JHC621>. Pyridazine-3-carboxamides are lithiated *ortho* to the carboxamide group. However, the use of iodine as electrophile afforded the *meta*-iodo derivative as the result of a 'halogen-dance'. Also an unexpected regioselectivity at the *meta*-position of the pyridazin-3-thiocarboxamide was observed and a mechanistic explanation for this has been proposed <2002T2743>. In the lithiation of 3-phenyl-6-pyridin-2-ylpyridazine the pyridine group, via its N-atom, has shown to be a good *ortho*-directing group <2005T9637>.

Lithiated 3,6-dimethoxypyridazine, obtained by reaction with BuⁿLi, has been transmetallated to the corresponding organozinc compound with zinc chloride <1998H(49)205>.

Attempts to lithiate the benzene moiety of 1,4-dimethoxyphthalazine and of 1-methoxy-4-phenylphthalazine were unsuccessful. However, treatment of 6-chloro-1,4-dimethoxyphthalazine with BuⁿLi results in the regioselective lithiation at C-7 <1999T5389>.

4-Chloro- and 4-methoxycinnoline were lithiated selectively at C-3 and 3-chloro-, 3-methoxy-, and 3-sulfinylcinnolines at C-4 <1995T13045, 2005T8924>. A further lithiation at C-8 of the 3,4-disubstituted cinnolines is observed <1995T13045>. Using this interesting observation 4-arylcinnolines have been lithiated at C-3, treated with chloro(trimethyl)silane, and once again lithiated at C-8 <2000T5499>.

Reactions of the metallated compounds with electrophiles are discussed in Section 8.01.7.16.

8.01.5.5.2 Alkylation of anions formed by deprotonation of azinones

In CHEC-II(1996) only one example of N-alkylation of a cinnolin-4(1*H*)-one is given <1996CHEC-II(6)1>. Nowadays, N-alkylation of pyridazinones is a quite general reaction. In most cases alkylations are achieved by a nucleophilic substitution reaction of the deprotonated azinone on alkyl halides and exceptionally also on aryl halides. Reagents other than halides are also used.

8.01.5.5.2(ii) Alkylation and arylation with alkyl and aryl halides

Yoon alkylated 4,5-dichloro- and 4,5-dibromopyridazin-3(2*H*)-one at N-2 with alkyl chlorides or bromides and K₂CO₃ in DMF at 60–70 °C <1996JHC1579> or refluxing CH₃CN <1996JHC615>. Similarly, a benzyl-protective group has been incorporated with benzyl chloride or bromide and microwave irradiation <1999JHC1095>, or with benzyl bromide and phase-transfer conditions (Bu₄NBr) <2002T5645>. Also the 4-methoxybenzyl group has been used as a protective group <2004BML1551>. Alkylation of pyridazin-3(2*H*)-ones with dibromomethane affords pure 2,2'-methylenebis(pyridazin-3(2*H*)-ones) **72** <1995EJM71, 1997JHC209>. However, alkylation with 1,ω-dibromoalkanes gives a mixture of 2,2'-alkane-1,ω-diylbis(pyridazin-3(2*H*)-ones) **73**, 2-(ω-bromoalkyl)pyridazin-3(2*H*)-ones **74**, and 2-[3-(pyridazin-3-yloxy)alkyl]pyridazin-3(2*H*)-ones **75** (Figure 9) <1997JHC209>. Successful cyclizations of 1,1'-bis[pyridazin-3(2*H*)-one-6-yl]ferrocene with dibromides, resulting in a series of novel ferrocenophanes **76**, were performed under phase-transfer conditions (Bu₄NOH, CH₂Cl₂-MeOH 20:1) (Figure 9) <2005JOM(690)802>.

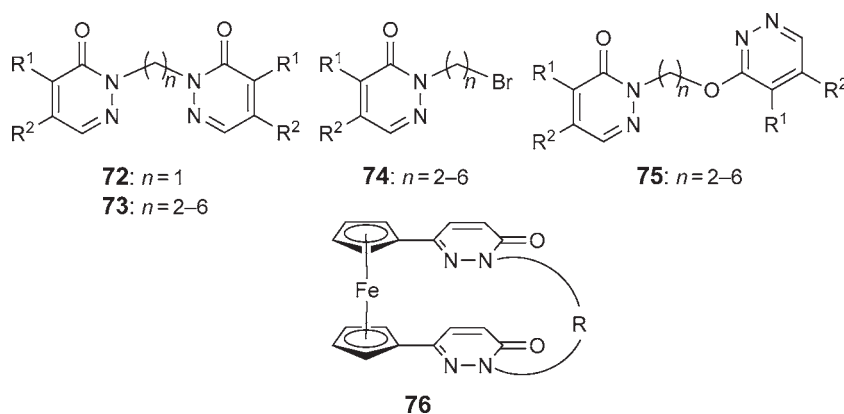


Figure 9 N-2-alkylated pyridazin-3(2*H*)-ones.

Also functionalized side chains have been introduced. 4,5-Dihalopyridazin-3(2*H*)-ones have been oxoalkylated with chloroacetone or with 4-bromo-3-oxobutanoic acid <1997JHC1307>. Benzo[*h*]cinnolin-3(2*H*)-ones were derivatized with ethyl ω-bromoalkanoates and with chloroacetonitrile <2000FA544>. *N*-Glycosides of 6-(4-methoxyphenyl)pyridazin-3(2*H*)-one were prepared under phase-transfer condition (Bu₄NBr) with 1-bromoglycosides <2003SC1155>. A useful protecting group for the lactam function of pyridazin-3(2*H*)-ones is a methoxymethyl (MOM) group which can easily be introduced using methoxymethyl chloride (MOMCl), 4-dimethylaminopyridine (DMAP), and *i*-Pr₂NEt in CH₂Cl₂ <1999S1666>.

Aryl halides bearing strong electron-withdrawing groups and thus allowing nucleophilic aromatic substitution can be used for the arylation of azinone anions. 4-(4-Hydroxy-3-methylphenyl)phthalazin-1(2*H*)-one has been arylated simultaneously at N-2 and at the phenolic OH with 4-chlorobenzonitrile and potassium carbonate in dimethylacetamide (DMA) <2005CHJ200>.

8.01.5.5.2(iii) Alkylation with other reagents

In a synthesis of nucleoside analogs, the sodium salts of phthalazine-1,4-dione, phthalazin-1(2*H*)-one, and two pyridazin-3(2*H*)-ones, prepared with sodium hydride in DMF, were alkylated with (±)-2,3-*O*-isopropylidene-1-*O*-(4-toluenesulfonyl)glycerol by a nucleophilic substitution of the tosyloxy group <1999AP327>.

Cyclic amino alcohols have been used in a Mitsunobu alkylation of 4-substituted phthalazin-1(2*H*)-ones <1996LA1477>. Mitsunobu alkylation has also been used to graft 6-chloropyridazin-3(2*H*)-one on a Wang resin. In this case competitive N- and O-alkylation is observed <2005JCO414>.

4-Aryl-2-(dialkylaminomethyl)-6-methoxyphthalazin-1(2*H*)-ones have been prepared from the 4-aryl-6-methoxyphthalazin-1(2*H*)-ones by a Mannich reaction (formaldehyde, dialkylamine, methanol, and reflux) <2005SC179>.

8.01.5.5.3 Acylation of anions formed by deprotonation of azinones

Acylation of anions formed by deprotonation of azinones are not described in previous editions <1984CHEC(2)1, 1996CHEC-II(6)1>. 4,5-Dichloropyridazin-3(2*H*)-one is smoothly acylated at N-2 with acyl chlorides in the presence of triethylamine in dichloromethane at room temperature, -10 or -22°C <2002S733>. The resulting compounds have been used as mild acylating reagents for amines (see Section 8.01.8.4).

8.01.5.5.4 Sulfonylation of anions formed by deprotonation of azinones

Sulfonylation of anions formed by deprotonation of azinones are not described in previous editions <1984CHEC(2)1, 1996CHEC-II(6)1>. 4,5-Dichloropyridazin-3(2*H*)-one is sulfonylated at N-2 with several benzenesulfonyl chlorides in the presence of a base <2002JHC203>. Reactions of the resulting compounds with amines yield sulfonamides (see Section 8.01.8.5).

8.01.5.5.5 Other reactions

In this section several azinone derivatizing reactions are collected which do not occur at an anion formed by initial deprotonation of the azinone, because they occur in neutral medium, acidic medium, or via metal-mediated processes.

An interesting N-methylation procedure for pyridazin-3(2*H*)-ones is based on a simple heating of the substrates with dimethylformamide dimethylacetal (DMFDMA) in DMF <2002SC1675>.

In 1994 Yoon mentioned briefly the N-2 hydroxymethylation of 4,5-dichloropyridazin-3(2*H*)-one and 4,5-dichloro-6-nitropyridazin-3(2*H*)-one by simply refluxing these azinones in a 35% formalin solution <1994JHC1199>. Later following the same procedure, other representatives such as 4,5-dibromo-2-hydroxymethylpyridazin-3(2*H*)-one and 5-bromo-2-hydroxymethyl-6-phenylpyridazin-3(2*H*)-one were prepared <1999JHC277, 2002SL2062>. These building blocks were used for nucleophilic substitution of a halogen and/or Pd-catalyzed derivatization. In all cases N-2 deprotection immediately followed <1999JHC277, 2003TL4459, 2002SL2062>. A solid-phase variant in which the 2-hydroxymethylpyridazin-3(2*H*)-ones are reacted with Ellman's resin was also described <2003SL1113>. This is further discussed in Section 8.01.8.1.

South described the protection of 4,5-dichloropyridazin-3(2*H*)-one as a 2-tetrahydropyranyl derivative. The pyridazinone is treated with 3,4-dihydro-2*H*-pyran in the presence of *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate in refluxing tetrahydrofuran <1995JHC1473>. The deprotection is discussed in Section 8.01.8.1.

2-Nitro derivatives of several halogenated pyridazin-3(2*H*)-ones have been prepared by treating the pyridazinones with a mixture of a nitrate salt and acetic anhydride or trifluoroacetic anhydride <2003JOC9113>. These compounds have been used for the synthesis of nitramines (see Section 8.01.8.3).

2-Chloro derivatives of 4,5-dichloropyridazin-3(2*H*)-one and 4-chloro-5-methoxypyridazin-3(2*H*)-one have been synthesized by treating the pyridazinones with NaOCl in acetic acid <2005S1136>. These pyridazinones can be used as reagents for the chlorination of active methylene compounds (see Section 8.01.8.2).

Pyridazinone derivatives can be N-arylated via several metal-mediated and -catalyzed cross-coupling reactions. 2-Phenylphthalazin-1(2*H*)-one has been prepared from phthalazin-1(2*H*)-one and iodobenzene by a Cu-catalyzed reaction <1997CPB719>. Some 2-(4-methylphenyl)pyridazin-3(2*H*)-ones were synthesized from the corresponding pyridazinones and (4-methylphenyl)boronic acid by a Cu-mediated Chan Lam reaction <1999T12757>. A variety of chlorinated pyridazin-3(2*H*)-ones have been directly N-arylated in good yield using lead tetraacetate/zinc chloride in benzene or in substituted benzenes, including chloro- and bromobenzene <2004TL8781>. N-Arylation of pyridazin-3(2*H*)-one and 6-methylpyridazin-3(2*H*)-one with (hetero)aryl bromides or iodides has been achieved in 70–94% isolated yield using catalytic amounts of a stable copper(II)hydroxyquinolate complex under standard Ullmann–Goldberg reaction conditions <2006TL149>.

8.01.5.6 Reactions with Radicals

The reaction of nucleophilic radicals with 1,2-diazines has been documented very well in CHEC-II(1996) <1996CHEC-II(6)1>. Due to the electron-deficient character of protonated 1,2-diazines, that are the actual substrates, this reaction type allows smooth alkylation, acylation, benzoylation, and alkoxyacylation of the nucleus. Recent examples are the 4,5-diethoxycarbonylation of 3-iodo- and 3-iodo-6-methylpyridazine with the oxyhydroperoxide of ethyl pyruvate as radical source in a two-phase system (toluene/aq H_2SO_4) <2000H(53)2527>. In the former case regioisomeric diethyl 4,6-dicarboxylate as well as 4- and 6-mono ethoxycarbonylated 3-iodopyridazine were formed as side compounds. 3-Iodo-6-phenylpyridazine did not react under the same conditions as only a trace of reaction product (monosubstitution) was observed. Phenylloxymethylation of ethyl 4-pyridazinecarboxylate was also reported <1995H(41)1464>. Radicals were generated from phenoxylacetic acid by silver ion-mediated

decarboxylation. Dimer formation of the desired reaction product was the major reaction product with phenyloxy-methyl radical. It could be suppressed in favor of the desired compound by working in a two-phase system (toluene/aq H_2SO_4) allowing protection of the desired reaction product from dimerization by extraction into the organic phase. When thiophenoxyacetic acid was used, phenylthiomethylation could be performed.

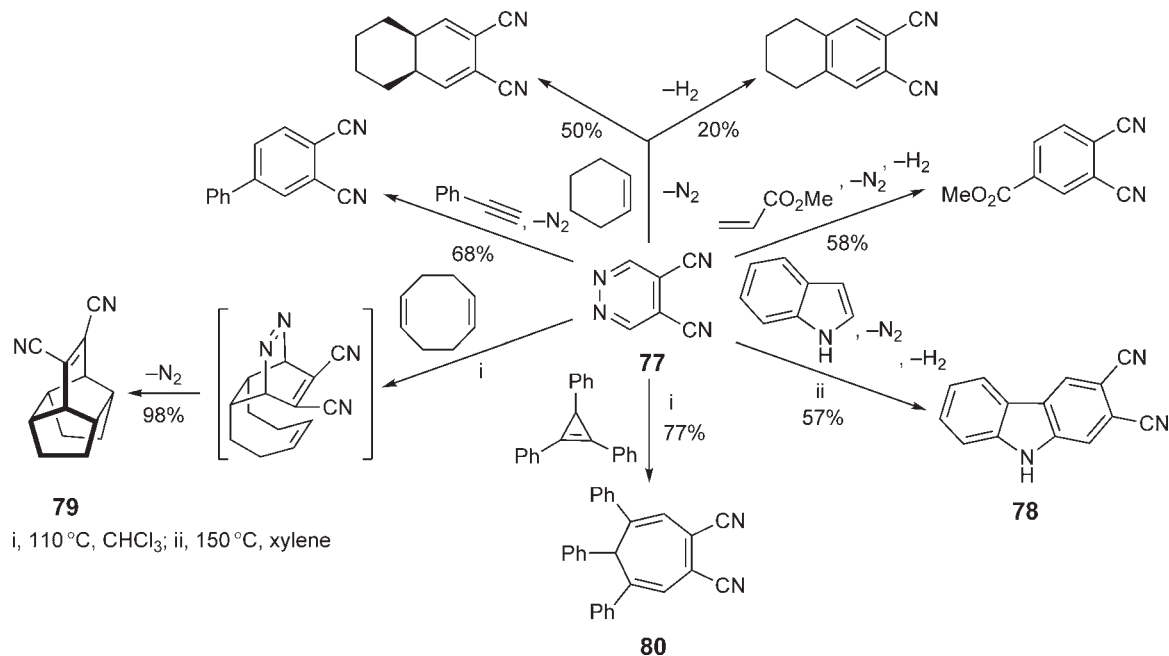
8.01.5.7 Cycloaddition Reactions

8.01.5.7.1 [2+4] Cycloaddition reactions

Electron-deficient heteroaromatic systems such as 1,2,4-triazines and 1,2,4,5-tetrazines easily undergo inverse electron demand Diels–Alder (IEDDA) reactions. 1,2-Diazines are less reactive, but pyridazines and phthalazines with strong electron-withdrawing substituents are sufficiently reactive to react as electron-deficient diazadienes with electron-rich dienophiles. Several examples have been discussed in CHEC-II(1996) <1996CHEC-II(6)1>. This IEDDA reaction followed by a retro-Diels–Alder loss of N_2 remains a very powerful tool for the synthesis of (poly)cyclic compounds.

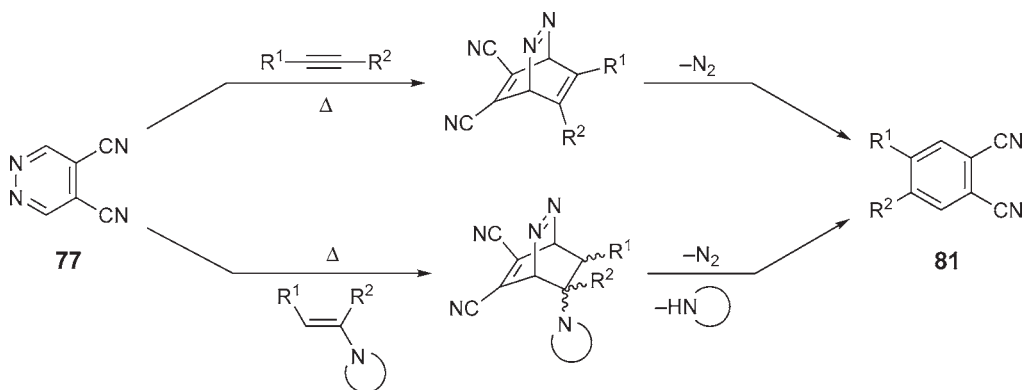
As an extension of intermolecular reactions described earlier, some intramolecular IEDDA reactions of electron-deficient pyridazines with alkyne dienophiles have been presented <1998MOL10, 2001TL7929>.

In 1994 Giomi introduced pyridazine-4,5-dicarbonitrile **77** as a strongly electron-deficient diazadiene reagent <1994T9189>. This reagent shows IEDDA addition, followed by N_2 elimination, with alkynes, for example, ethynylbenzene, but also with unactivated alkenes, for example, cyclohexene, and even with electron-poor alkenes such as methyl acrylate <1995CC2201>. Yields of reactions with 1-methylpyrrole are low, but with indoles carba-zoledinitriles such as **78** are obtained in reasonable yields <2002T8067>. An interesting alternative for the reaction with 1-methylpyrrole has been found in the cycloaddition with 1-methyl-5-(methylthio)-2,3-dihydro-1*H*-pyrrole followed by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) <2003JOC3340>. With dienes, for example, cycloocta-1,5-diene, **77** shows intermolecular IEDDA reaction of the diazadiene with one double bond of the diene, followed by the loss of N_2 and further intramolecular Diels–Alder reaction of the resulting cyclohexadiene intermediate with the other double bond of the diene <1996JOC6028>. In this way several carbo-(such as **79**) and heteropolycyclic cage compounds have been synthesized <2000JOC360>. Compound **77** reacts easily with 1,2,3-triphenylcyclopropene to give 4,5,6-triphenylcyclohepta-1,3,6-triene-1,2-dicarbonitrile **80** through a [4+2] cycloaddition and a ring enlargement (Scheme 15) <1997T11711>.



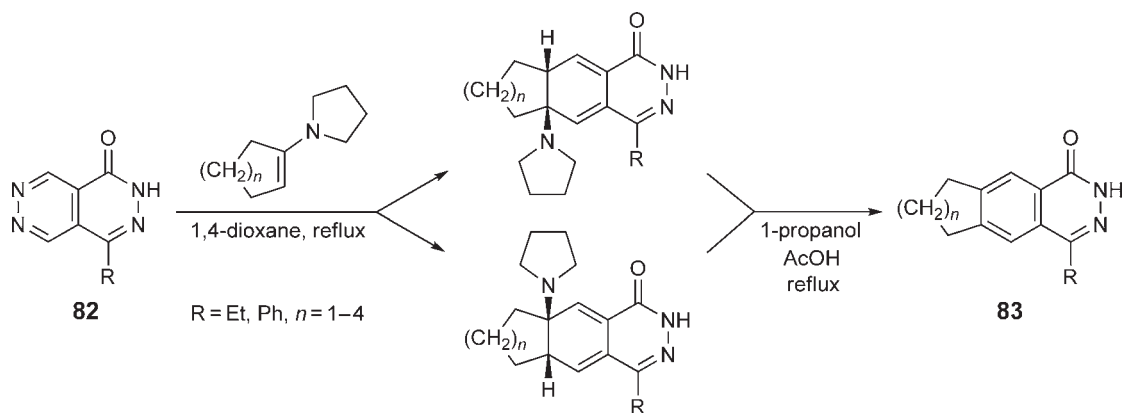
Scheme 15

The reaction of **77** with alkynes has further been elaborated for the synthesis of substituted phthalonitriles **81**. An alternative for the synthesis of these compounds is the cycloaddition reaction of **77** with enamines followed by a retro-Diels–Alder loss of N₂ and elimination of the amine (**Scheme 16**). Generally, more forcing reaction conditions are required and lower yields are obtained in reactions with alkynes than in reactions with enamines, for example, 4-ethyl-5-methylphthalonitrile is obtained in 51% yield from 2-pentyne (xylene, 150 °C, 18 days) and in 73% yield from 4-(1-ethylprop-1-en-1-yl)morpholine (CHCl₃, 70 °C, 7 days) <1998T1809>. The mechanism of the reaction with enamines has been studied in detail. This revealed a [1,5] sigmatropic rearrangement in the cyclohexa-2,4-dien-1-amine intermediates formed after the loss of N₂ <1998T10851>.



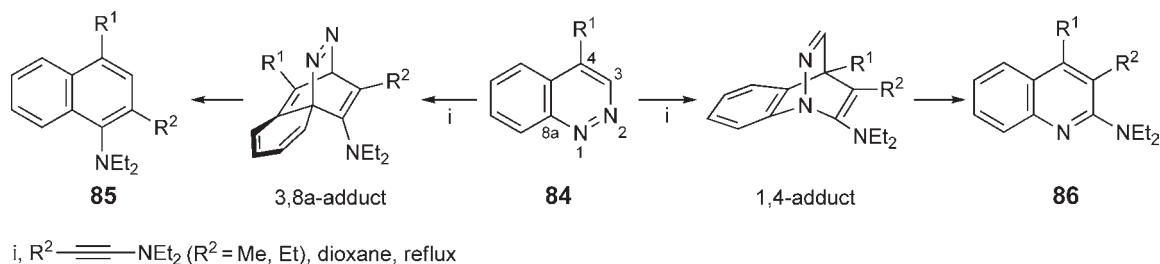
Scheme 16

Pyridazino[4,5-*d*]pyridazin-1(2*H*)-one **82** shows a similar behavior as pyridazin-4,5-dicarbonitrile **77** since it is a pyridazine derivative with electron-withdrawing groups at C-4 and C-5 too. Haider used this fused pyridazine for the synthesis of cycloalkene annelated phthalazin-1(2*H*)-ones **83** in good yields (54–87%) (**Scheme 17**) <1995H(41)2519>.



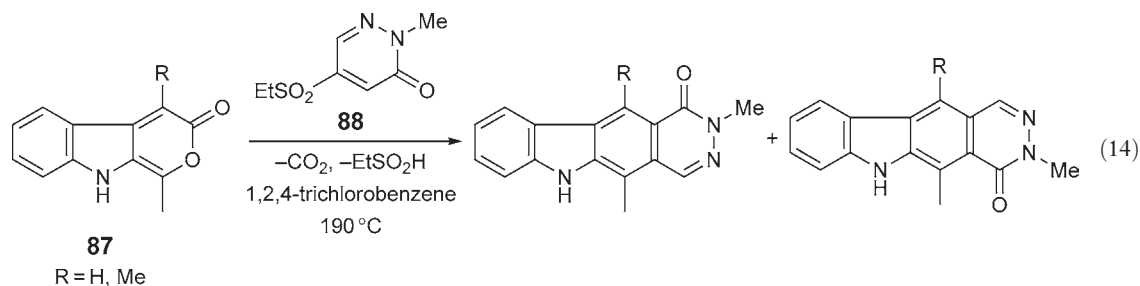
Scheme 17

IEDDA reactions of phthalazines bearing strong electron-withdrawing substituents at C-1 and optionally at C-4 with ynamines result in substituted naphthalenes. These reactions have been discussed in CHEC-II(1996) <1996CHEC-II(6)1>. Similar reactions of cinnolines **84** with electron-withdrawing substituents at C-4 give naphthalene **85** and/or quinoline **86** derivatives through two types of [4+2] adducts (**Scheme 18**). Overlap between the first lowest unoccupied molecular orbital (LUMO) of cinnoline and the HOMO of the ynamines gives quinoline derivatives via 1,4-adducts at cinnoline, and overlap between the second LUMO of cinnoline and the HOMO of the ynamines gives naphthalenes *via* 3,8a-adducts. In the case of steric hindrance at the 4-position, the second path is followed preferentially <1995H(43)2409>.



Scheme 18

Analogous to reactions with phthalazines described earlier [<1996CHEC-II\(6\)1>](#), the phthalazine aza-analog 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine has been used in reactions with indole-type dienophiles for the synthesis of pyridocarbazoles, structurally related to the alkaloids ellipticine and isoellipticine [<1995H\(41\)1445>](#). According to a method developed by Mátyus [<1993H\(36\)1975>](#) some ellipticine analogs have been synthesized from pyrano[3,4-*b*]indol-3(9*H*)-ones **87** with 5-(ethylsulfonyl)-2-methylpyridazin-3(2*H*)-one **88** in which the 4,5 double bond reacts in a normal Diels–Alder reaction as electron-deficient dienophile (Equation 14) [<1999H\(51\)2703>](#).



1,4-Bis(trifluoromethyl)-4a,8a-methanophthalazine **89** is an interesting propellane possessing both an electron-rich cyclohexadiene and an electron-deficient diazadiene system in one and the same molecule. The electron-rich dienophiles ethoxyacetylene and *N,N*-diethylprop-1-yn-1-amine and the strained cyclooctyne react selectively with the electron-deficient diazadiene side to yield interestingly substituted 1,6-methano[10]anulenes **90**. Benzyne, however, reacts selectively with the cyclohexadiene side to yield a pentacyclic pyridazine derivative **91** (Scheme 19) [<1996LA773>](#).

8.01.5.7.2 1,3-Dipolar cycloaddition reactions

In CHEC-II(1996) [<1996CHEC-II\(6\)1>](#) several examples of cycloaddition reactions of 1,3-dipoles to the 1,3-dipolarophilic 4,5-double bond of pyridazin-3(2*H*)-ones have been discussed. Only two examples of 1,3-dipolar pyridazine derivatives reacting with 1,3-dipolarophiles are given.

8.01.5.7.2(i) 1,3-Dipolarophilic pyridazine derivatives

Pyridazine shows a high dipolarophilic activity to benzonitrile oxide. Generation of this nitrile oxide *in situ* in diethyl ether at 0 °C in the presence of 3 equiv of pyridazine affords a stable mono-cycloadduct **92** in 70% yield. In solution, upon standing in contact with the air, the cycloadduct is slowly oxidized to pyridazin-3(2*H*)-one. The mono-cycloadduct is still reactive toward benzonitrile oxide and its exposure to 2 equiv of the nitrile oxide affords mainly the bis-cycloadduct **93** (Figure 10) [<1996T6421>](#).

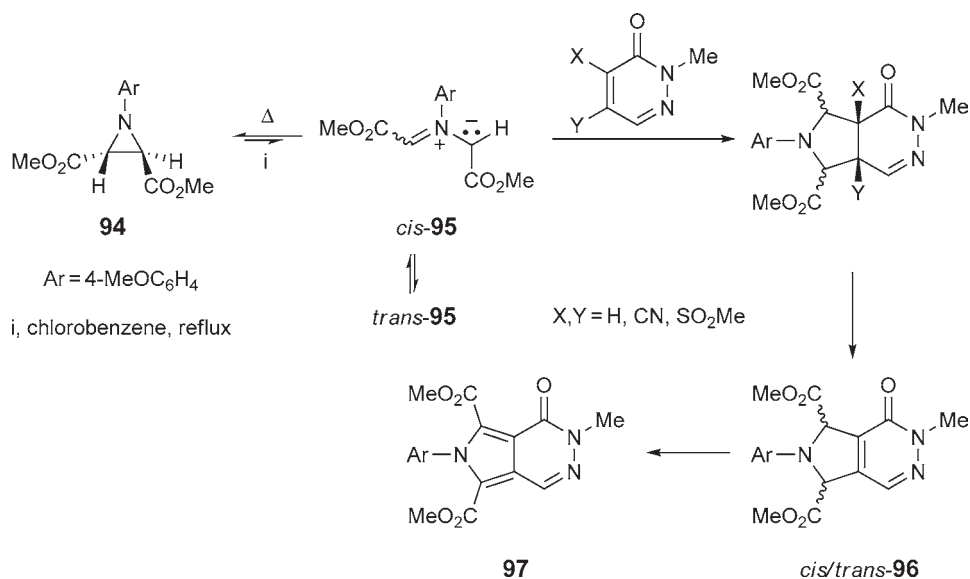
In the examples presented in CHEC-II(1996) in which a pyridazin-3(2*H*)-one is the 1,3-dipolarophile, two types of 1,3-dipoles are used: nitrile oxides and diazoalkanes. Two other 1,3-dipoles have to be mentioned now. The 1,3-dipolar cycloaddition of the azomethine ylide **95** generated *in situ* by thermal ring opening of dimethyl *trans*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate **94** to some 4- or 5-substituted 2-methylpyridazin-3(2*H*)-ones has been



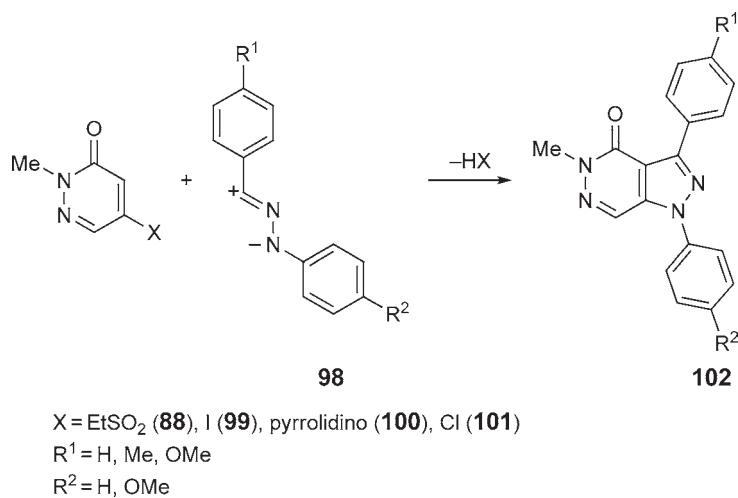
The 1,3-dipolar cycloaddition of diarylnitrile imines **98**, generated *in situ* from arylhydrazones with chloramine T or from α -chlorobenzylidenephénylhydrazine with triethylamine, to some 5-substituted 2-methylpyridazin-3(2*H*)-ones **88**, **99–101** has been shown to afford 1,3-diaryl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyridazin-4-ones **102** regioselectively (Scheme 21) <2000JMT(528)13>.

Since 1995 cycloadditions with 1,3-dipolar pyridazine derivatives have been studied intensively.

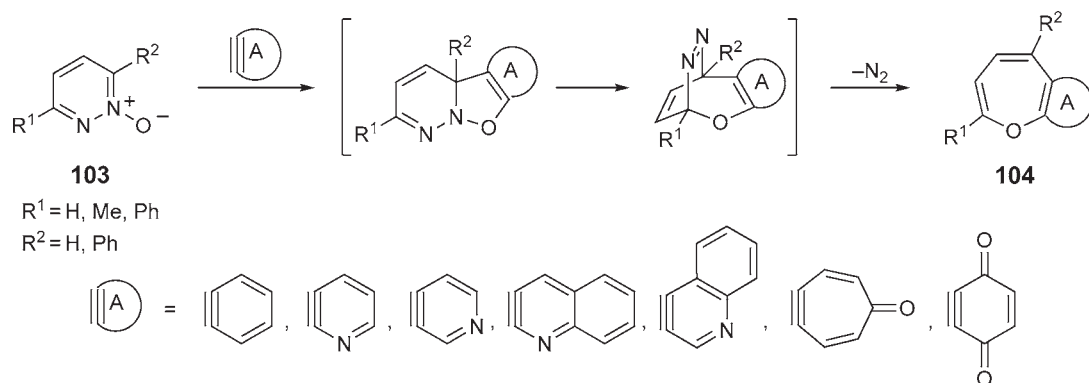
The reaction of pyridazine *N*-oxide **103** with benzyne, briefly mentioned in CHEC(1984) <1984CHEC(2)1>, has been extended in the 1990s to reactions with several heteroarynes <1990H(31)1937>, 4,5-didehydrotropone <1994H(38)957>, and finally to a reaction with 2,3-didehydro-*p*-benzoquinone <1996H(43)1601>. The reaction starts with a 1,3-dipolar cycloaddition of the aryne to the pyridazine *N*-oxide, followed by a rearrangement of the cycloaddition product and the expulsion of N₂ resulting in the formation of ring fused oxepines **104** (Scheme 22). 1-Aminopyridazinium salts have also been used in 1,3-dipolar cycloaddition reactions as discussed in Section 8.01.8.6.



Scheme 20

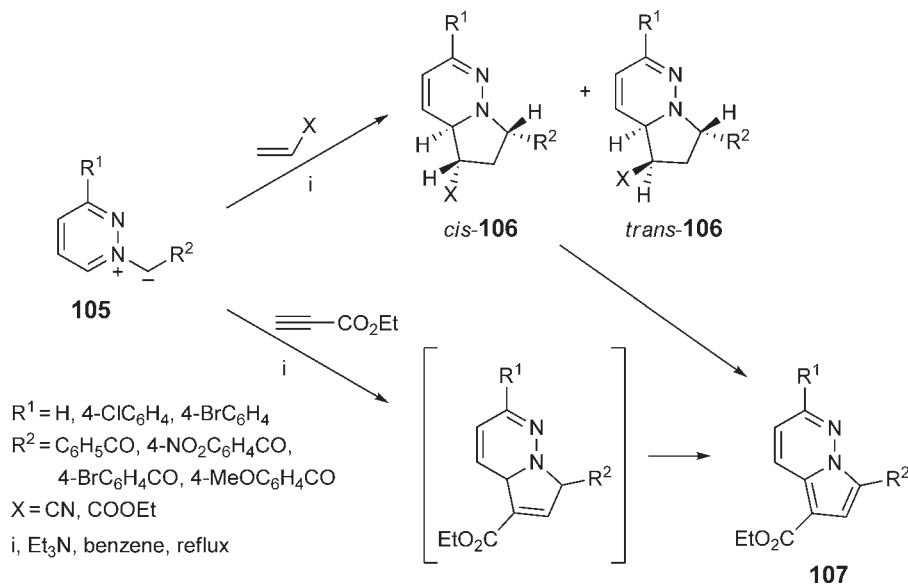


Scheme 21



Scheme 22

Mangalagiu studied the regioselectivity of the 1,3-dipolar cycloaddition of several pyridazinium methylides **105** to ethyl acrylate, ethyl propiolate, and acrylonitrile. The reaction is HOMO controlled from ylides and only one regioisomer **106** (major isomer *cis* and minor isomer *trans*) or **107** is formed, namely the one in which the ylide carbanion makes a new bond with the most electrophilic carbon of the 1,3-dipolarophile. In some cases oxidation of **106** to **107** is observed in the reaction mixture in contact with the air (Scheme 23), which can be avoided by working in N₂ atmosphere <1996T8853, 1997ACS927, 1999EJO3501>.



Scheme 23

More recently, this group published the synthesis of one analog of *cis*-**106** with an epimeric 4a,5,6,7-tetrahydropyrrolo[1,2-*b*]pyridazine core **108** (Figure 11). Cycloaddition of **105** to the symmetrical 1,3-dipolarophile *N*-phenylmaleimide occurs in a highly stereospecific way, giving the compound **109** (Figure 11) <2005H(65)1871>. Highly fluorescent pyrrolo[1,2-*b*]pyridazines **110** have been synthesized efficiently by executing the cycloaddition reactions under microwave irradiation <2006SL804>. Cycloaddition reactions, in liquid and in solid phase, of phthalazinium methylides to the 1,3-dipolarophiles used in Scheme 23 were executed with classical heating and under microwave irradiation. In the liquid phase microwave irradiation shows a remarkable acceleration of the rate of formation of the reaction products which are also formed with classical heating. In the solid phase on a solid KF-Al₂O₃ support, no matter if classical or microwave heating is used, no [3+2] cycloaddition to the 1,3-dipolarophiles is observed, but a [3+3]

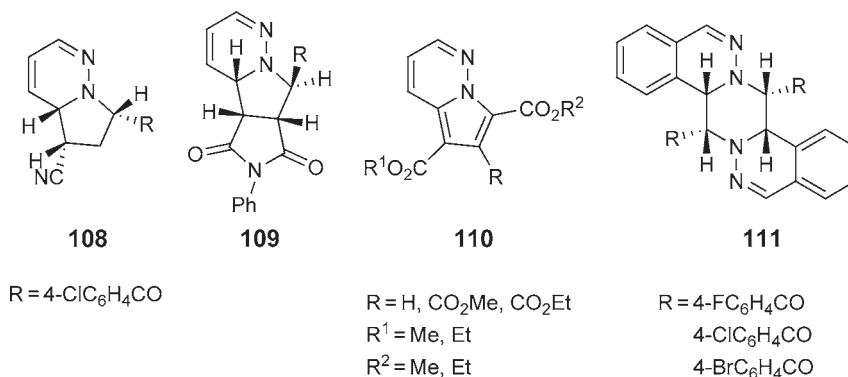
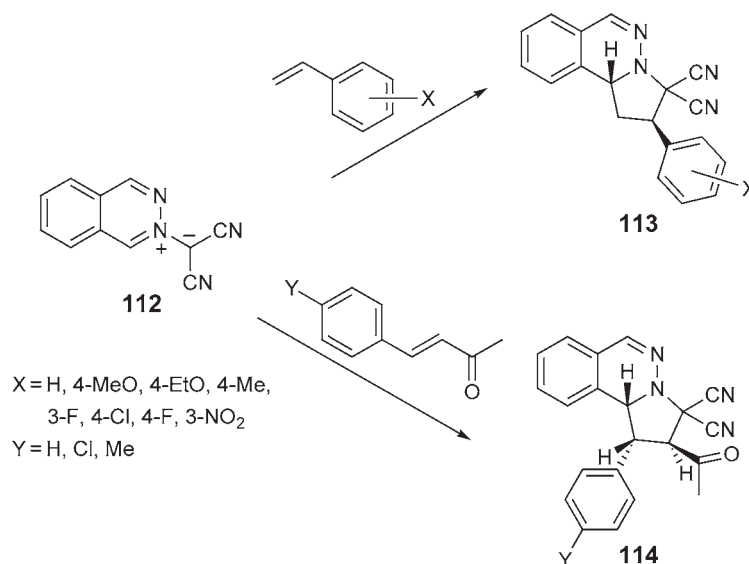


Figure 11 Some cycloadducts.

cycloaddition reaction of a methyldide molecule to another one takes place giving **111** (Figure 11) <2005RRC353>. Cycloadditions of phthalazinium methylides to 1,3-dipolarophiles in the presence of the oxidant tetrakis-pyridine cobalt(II)dichromate gives immediately the fully aromatized pyrrolo[2,1-*a*]phthalazines <2000JHC1165>.

Butler studied the regio- and *endo/exo*-selectivity in the cycloaddition of phthalazinium dicyanomethylide with symmetrical and unsymmetrical 1,3-dipolarophiles. The selectivities are controlled by orbital interactions and dipole alignments in the transition state, but show a gradual reversal caused by steric effects <1996JCM418, 1998J(P1)869, 2001J(P1)1391>. Kinetic studies on the cycloaddition reactions of phthalazinium and pyridazinium dicyanomethylide with twenty-six dipolarophiles ranging from electron poor to electron rich revealed that these reactions may be dipole-HOMO or -LUMO controlled depending on the nature of the dipolarophile <2001J(P2)1781>. These kinetic studies revealed also a surprising rate increasing effect of water. The dipolarophiles were classified into two groups: water-normal and water-super. The former displayed rate enhancements of <20 times and the latter of >45 times, but more often some 100 times, on changing the solvent from acetonitrile to water <2002J(P2)1807>. The results suggest that a dominant hydrogen-bonding effect operates in water-induced rate enhancements of 1,3-dipolar cycladdition reactions with water-super dipolarophiles as well as hydrophobic effects <2004JA11923>. The major products from cycloaddition reactions of phthalazinium dicyanomethylide **112** with substituted styrenes and 4-phenylbutenones were *exo*-2-aryl- **113** and 1-*endo*,2-*exo*-2-acetyl-1-aryl-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine-3,3-dicarbonitriles **114**, respectively (Scheme 24) <2005HCA1611>.



Scheme 24

8.01.6 Reactivity of Nonconjugated Rings

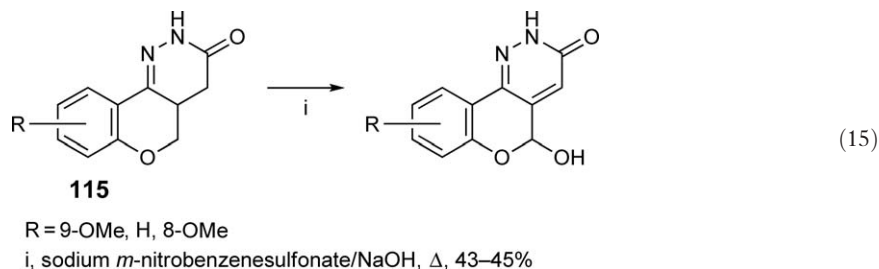
8.01.6.1 Introduction

The reactivity of pyridazine derivatives containing a nonconjugated ring was well covered in CHEC(1984) <1984CHEC(2)1> under the heading of 'Saturated and partially saturated rings' and in CHEC-II(1996) <1996CHEC-II(6)1> under the heading 'Reactivity of nonconjugated rings'. Here we use the same subdivisions as in CHEC-II(1996).

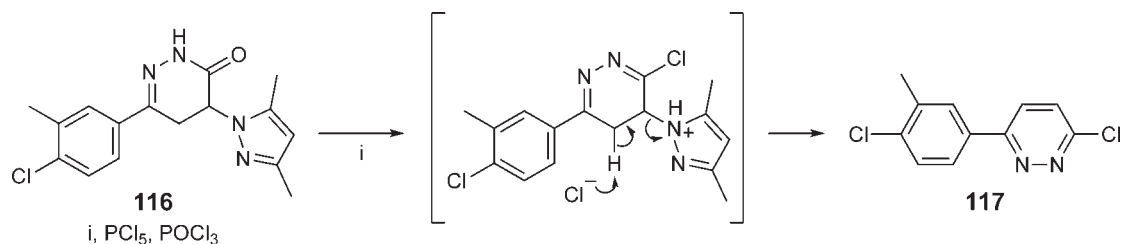
8.01.6.2 Dihydro Derivatives Containing a Carbonyl Group in the Ring

As stated in CHEC-II(1996) the dihydropyridazin-3-(2*H*)-ones are more stable than the corresponding dihydropyridazines and constitute the majority of the dihydro compounds reported. Methods to oxidize 4,5-dihydropyridazin-3(2*H*)-ones to pyridazin-3(2*H*)-ones mentioned in CHEC-II(1996), such as addition of Br₂ in acetic followed by a spontaneous elimination of HBr, and oxidation with sodium *m*-nitrobenzenesulfonate, with SeO₂ or with MnO₂ have

proved to be very useful and can be found in several new applications <1996JME4396, 1997CPB1151, 2002BMC2873, 2002H(57)39, 2002T2743>. Also dehydrogenation of 4,5-dihydropyridazin-3(2*H*)-ones with DDQ has been presented <2002BML689, 2005SL2743>. In 1995 Bernáth presented a new mild procedure for the synthesis of pyridazin-3(2*H*)-ones from 4,5-dihydropyridazin-3(2*H*)-ones with CuCl₂ in MeCN. The proposed mechanism is a halogenation followed by a spontaneous HCl elimination <1995S1240>. This method is quite successful and several applications have been published <1997H(45)323, 1999OL1253, 2002BMC2873, 2006S103>. In the dehydrogenation of 4a,5-dihydro-2*H*-chromeno[4,3-*c*]pyridazin-3(4*H*)-one, derivatives **115** with sodium *m*-nitrobenzenesulfonate Barlocco observed an unexpected concomitant hydroxylation of C-5 (Equation 15) <1995JHC79>.

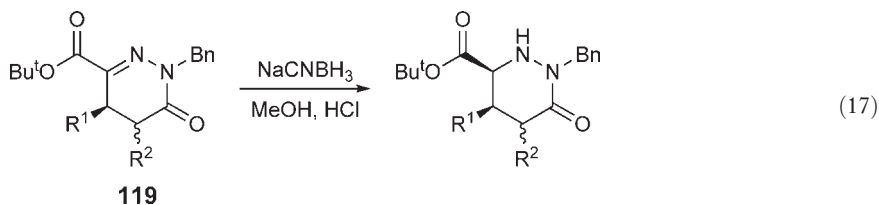
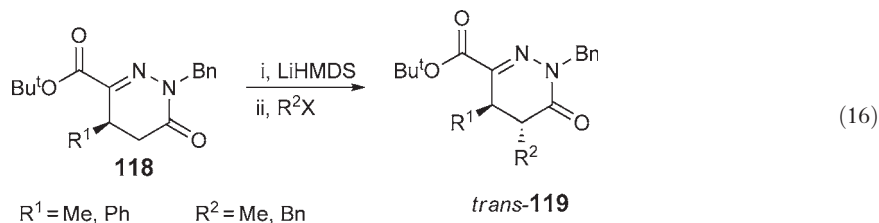


Chlorination of 6-(4-chloro-3-methylphenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4,5-dihydropyridazin-3(2*H*)-one **116** with a mixture of phosphorus pentachloride and phosphorus oxychloride is followed by an elimination of 3,5-dimethyl-1*H*-pyrazole giving the aromatized 3-chloro-6-(4-chloro-3-methylphenyl)pyridazine **117** (Scheme 25) <2005CJC251>.



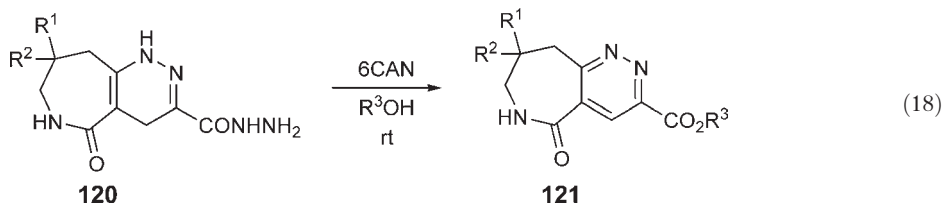
Scheme 25

Alvarez-Ibarra presented the highly diastereoselective alkylation (de > 98%) of compounds **118** giving the *trans*-4,5-disubstituted compounds *trans*-**119** (Equation 16). The synthesis of the corresponding *cis*-isomers *cis*-**119** is also reported (see Section 8.01.9.2.2) <2002JOC2789>. NaCNBH₃ reduction of compounds **119** takes place with high diastereoselectivity in favor of the 3,4-*cis* isomers (Equation 17) <2002JOC2789>. The chemoselectivity of the addition of methylmagnesium bromide to the C=N bond or the ester group of **119** has been studied and optimized <2002EJO4190>.

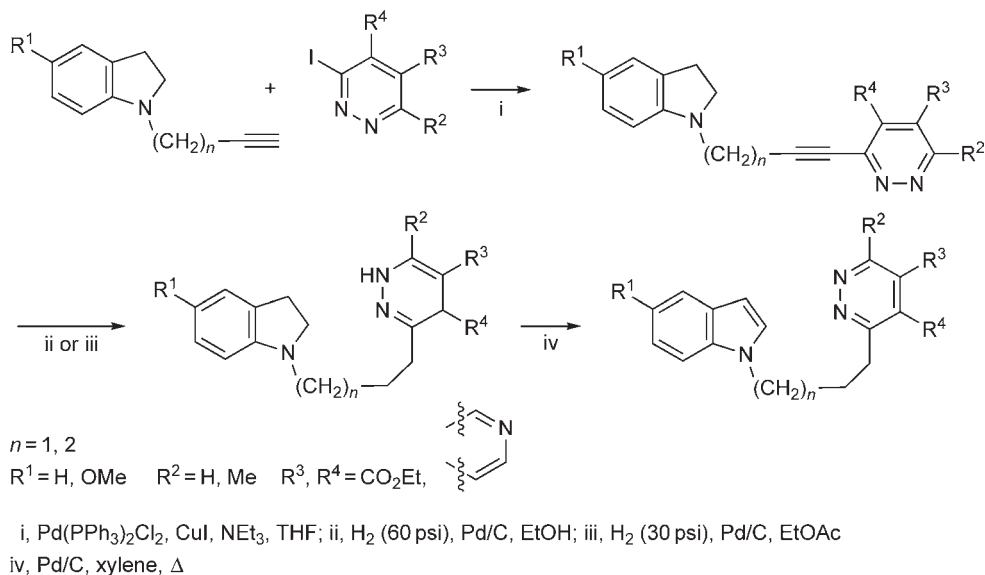


8.01.6.3 Dihydro Derivatives without a Carbonyl Group in the Ring

In the synthesis of some potential atypical antipsychotics, Raviña published the aromatization of substituted 1,4-dihydropyridazines with MnO_2 <2006CBI106>. Kočevar presented a simple method for a similar aromatization proceeding with a concomitant oxidative degradation of a hydrazide group to the corresponding esters. In particular, 5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carbohydrazides **120** are rapidly oxidized using 6 equiv of ammonium cerium(IV) nitrate to the corresponding fused pyridazine esters **121** (Equation 18) <2003S2349>.



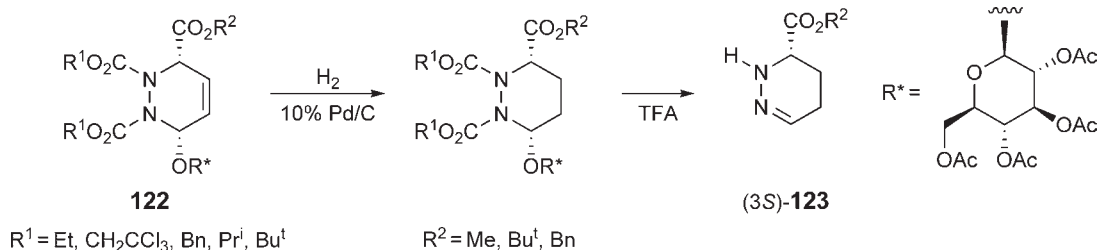
Napoletano synthesized PDE4 (PDE = phosphodiesterase) inhibitors with a 1,2-dihydrophthalazine skeleton by a partial hydrogenation (4 atm H_2 , PtO_2 , THF, rt, 75%) of the corresponding phthalazine compound, followed by alkylation of the newly formed NH group (RCl , Et_3N , CH_2Cl_2 , rt, 60–80%) <2002BML5>. Haider synthesized mono- and bicyclic 1,2-diazines tethered to indoles for further intramolecular Diels–Alder reactions. In this synthesis an alkyne group in the chain tethering together the two heterocycles had to be hydrogenated. However, simultaneously the diazine rings were partially reduced to dihydro derivatives, which could be rearomatized by refluxing them with Pd/C in xylene (Scheme 26) <2004T6495>.



Scheme 26

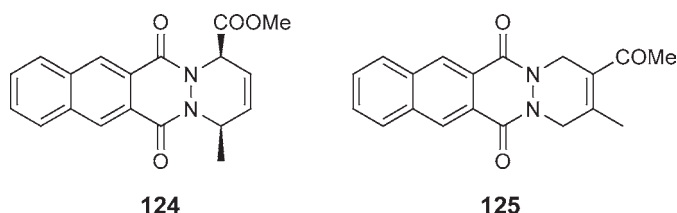
8.01.6.4 Tetrahydro Derivatives

In CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>, several reactions on tetrahydropyridazines are presented: thermal decompositions, reduction to hexahydropyridazines, dehydrogenation to dihydropyridazines, and several kinds of oxidations. 2,3,4,5-Tetrahydropyridazine-3-carboxylic acid **123** has been found in some natural products, such as the cyclic hexapeptide L-365,209, an oxytocin antagonist, and the linear heptapeptide antrimycin Av with anti-tubercular activity. The (*S*)-enantiomer (3*S*)-**123** has been synthesized by Stoodley. After assembling the intermediate tetrahydropyridazine **122** (see Section 8.01.9.2.2), the tetrahydropyridazine ring is reduced to the corresponding hexahydropyridazine ring. After deprotecting the N-atoms and eliminating the tetraacetyl β -D-glucopyranosyl moiety (3*S*)-**123** is obtained (Scheme 27) <1999J(P1)2591>. (3*S*)-**123** has also been synthesized by Vidal from L-*N*-benzyl- δ -hydroxyvaline <2004JOC2367>.



Scheme 27

Gómez-Contreras synthesized the 1,2,3,6-tetrahydropyridazine containing 1,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-diones **124** and **125** (Figure 12), diaza-analogs of anthracyclines, an important class of antitumor agents. Hydroxy-bromo and -dibromo derivatives of the tetrahydropyridazine ring were obtained via reaction with NBS or epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) followed by ring opening of the epoxide <2004H(63)1299>. For redox reactions between tetrahydro- and hexahydropyridazines, see Section 8.01.6.5.

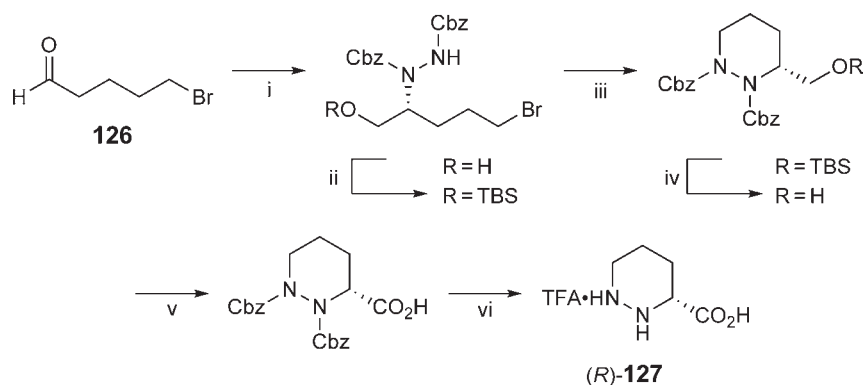
Figure 12 1,2,3,6-Tetrahydropyridazine containing 1,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-diones.

8.01.6.5 Hexahydro derivatives

In CHEC(1984) <1984CHEC(2)1> information is presented about the conformations of 1,2-disubstituted hexahydropyridazines, and in CHEC-II(1996) <1996CHEC-II(6)1> one example of a reaction with hexahydropyridazine is given. In the 1990s the interest in hexahydropyridazines strongly increased since several natural products with remarkable biological activities were isolated (see Section 8.01.12.2) containing piperazic acid (hexahydropyridazine-3-carboxylic acid) **127**, (3*R*,5*R*)-5-hydroxypiperazic acid (3*R*,5*R*)-**128** and 5-chloropiperazic acid. To synthesize these natural products and to evaluate their biological activity, the need was felt to have access to sufficient amounts of both enantiomers of piperazic acid. In 1998 Ciufolini published a review presenting methods to synthesize piperazic acid <1998CSR437>. A more recent method developed by Hamada is mentioned here because of its simplicity, cost-effectiveness, and the possibility to execute it on a multigram scale <2004TA3477>. The synthesis of (*R*)-piperazic acid (*R*)-**127** is shown in Scheme 28. The key step is the (*S*)-proline-catalyzed α -hydrazination of the readily available 5-bromopentanal **126**. The overall yield is 80% and the enantiomeric excess >99%. The enantiomer (*S*)-**127** is obtained by the use of (*R*)-proline in a similar efficiency and through the same reaction sequence.

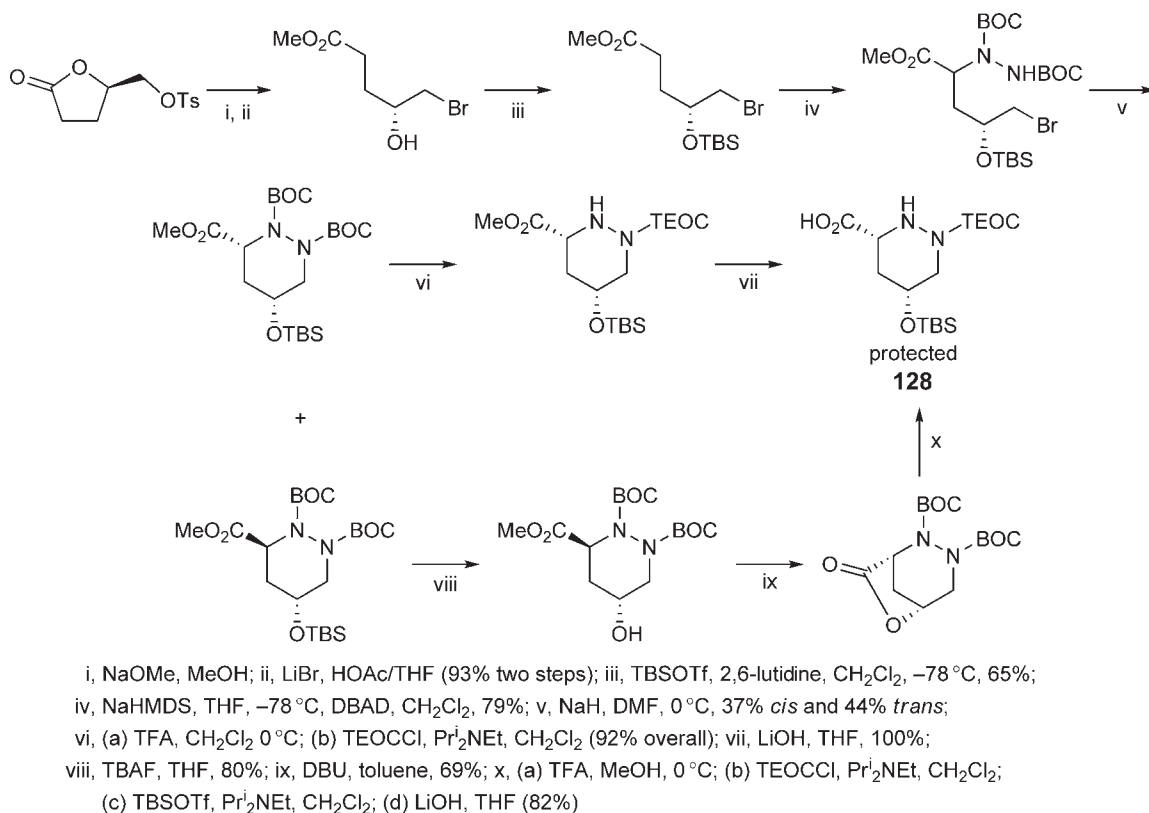
A few other methods for the synthesis of piperazic acid have been published <1996T1047, 2003JOC6899, 2004JOC2367, 2005TL555>. Herbert presented a synthesis of [^{15}N]-(*S*)-piperazic acid <1998JLR859>. (3*S*,5*S*)-5-Hydroxypiperazic acid (3*S*,5*S*)-**128** has been prepared from D-mannitol in a multistep synthesis <1998TL7163>. Protected versions of (3*R*,5*R*)-5-hydroxypiperazic acid (3*R*,5*R*)-**128** have been synthesized enantioselectively in two novel ways by Depew. The first derives its chirality from D-glutamic acid (Scheme 29), whereas the second uses an Evans amination and a diastereoselective bromolactonization to establish the two chiral centers (Scheme 30) <2000TL289>.

In 1997 Bols synthesized (3,4-*trans*-4,5-*trans*)-3-(hydroxymethyl)hexahydropyridazine-4,5-diol (1-azafagomine) **132** (Scheme 31), a potent inhibitor of glycosyl cleaving enzymes. Diels–Alder reaction between (2*E*)-penta-2,4-dien-1-ol and 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione gives the tetrahydropyridazine derivative **129**. Epoxidation of **129** with 3-methyl-3-(trifluoromethyl)dioxirane gives the *trans*-epoxide **130**, which is hydrolyzed with perchloric acid giving the glycol **131** with the desired all-*trans*-configuration. After hydrazinolysis of **131** 1-azafagomine **132** is obtained in an overall yield of 32% <1997CEJ940>. In 1999 a slightly modified procedure was presented starting from (2- ^{13}C)(2*E*)-penta-2,4-dienoic acid for the synthesis of (3- ^{13}C)-**132** <1999J(P1)3323>. Also a chemoenzymatic



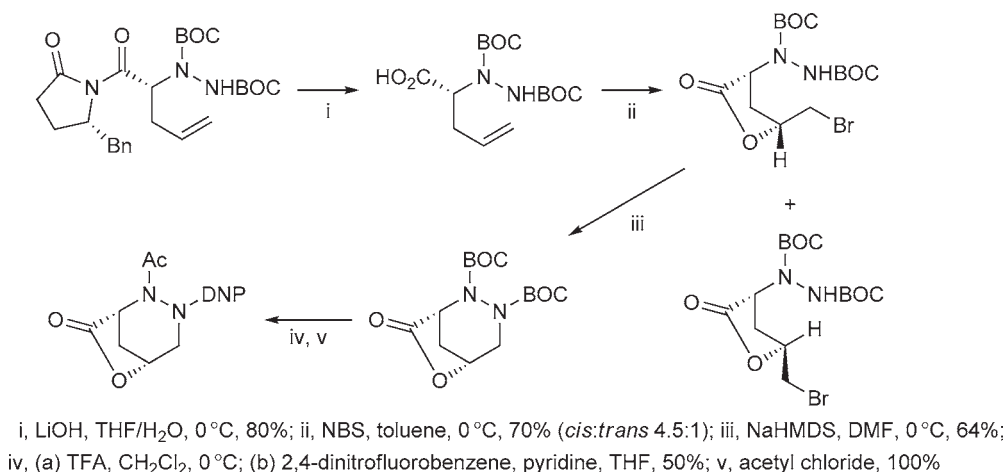
- i, (a) dibenzyl azodicarboxylate, (*S*)-proline (10 mol%), MeCN, 0 °C;
 (b) NaBH₄, ethanol, 0 °C, 91% (overall yield); ii, TBSCl, imidazole, DMF, rt, 100%;
 iii, NaH, DMF, 0 °C, 97%; iv, TBAF, THF, 0 °C, 100%; v, TEMPO, NaClO–NaClO₂, MeCN,
 phosphate buffer (pH 6.8), rt, 90%; vi, H₂, 5% Pd/C, TFA, CH₂Cl₂, rt, 100%

Scheme 28

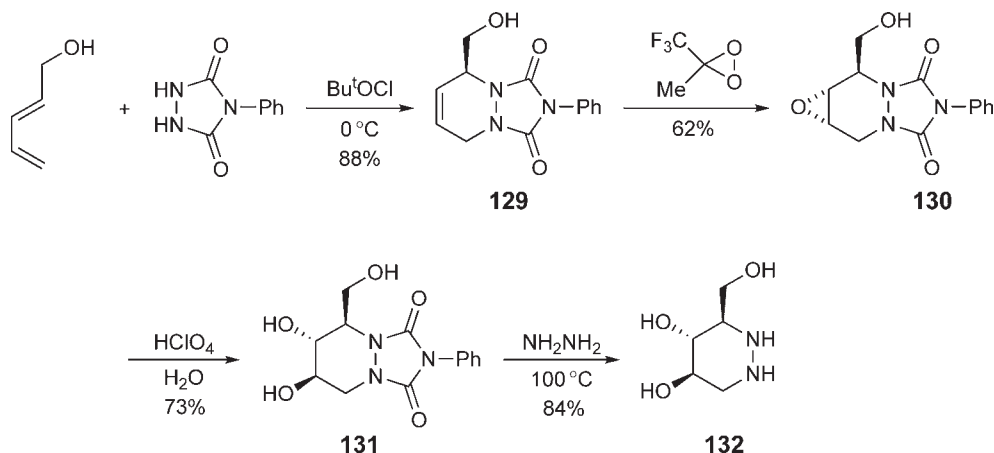


Scheme 29

synthesis of both enantiomers of **132** is reported. The synthesis starts from the achiral materials (*2E*)-penta-2,4-dien-1-ol and 4-methyl-3*H*-1,2,4-triazol-3,5(*4H*)-dione. The Diels–Alder product of these compounds is submitted to a lipase R/Novozym 435-catalyzed enantioselective esterification <1999JOC8485>. A 5-fluoro analog of **132** has been synthesized by opening the epoxide **130** with HF-pyridine <1997T9357> and a 5-amino analog by opening with TMSN₃·BF₃·Et₂O <2000J(P1)659>.



Scheme 30



Scheme 31

1-(2-Fluoro-4-nitrophenyl)hexahydropyridazine has been prepared by a nucleophilic aromatic substitution of hexahydropyridazine on 1,2-difluoro-4-nitrobenzene in the synthesis of a Linezolid analog [<2005BML2834>](#).

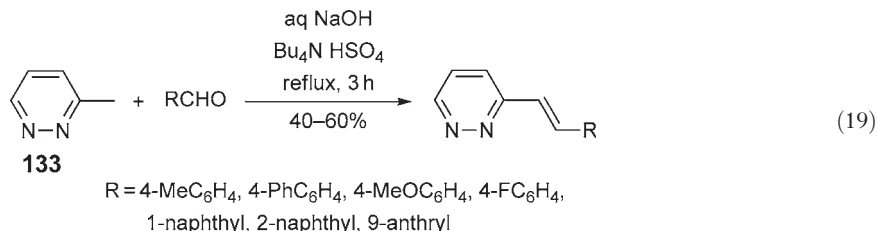
N-2-Protected derivatives of hexahydropyridazine-3-carboxylic esters are readily obtained from the corresponding 1,4,5,6-tetrahydro esters by reduction with NaBH₃CN, and are readily oxidized to the 1,4,5,6-tetrahydro derivatives with *t*-butyl hypochlorite [<1998CSR437>](#). Recently, 1-benzyloxycarbonyl-1,4,5,6-tetrahydropyridazine has been prepared by oxidation of 1-benzyloxycarbonylhexahydropyridazine in an O₂-atmosphere in the presence of copper salts [<2004H\(63\)2379>](#). On prolonged standing at the air 1-azafagomine **132** is oxidized to the corresponding 2,3- and 5,6-dehydrogenated forms. A similar oxidation is smoothly obtained by MnO₂ as the oxidant [<2000J\(P2\)665>](#).

8.01.7 Reactivity of Substituents Attached to Ring Carbons

8.01.7.1 Alkyl Groups

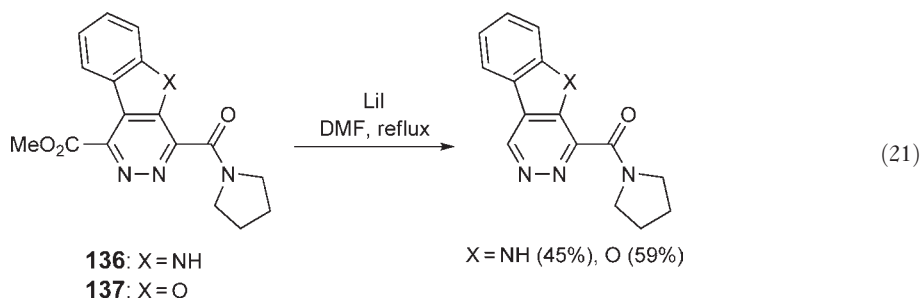
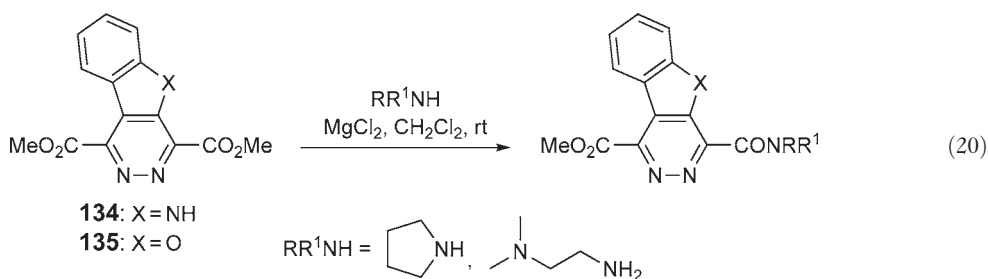
Since 1995 new interesting examples appeared although no fundamentally new synthetic methods, in comparison with what has been described in CHEC-II(1996) [<1996CHEC-II\(6\)1>](#), have been used. For instance, the methyl group of a 2-aryl-4-cyano-5-methylpyridazin-3(2*H*)-one, substituted in the 6-position with an ethoxycarbonyl or cyano group, is sufficiently acidic to react directly with DMFDMA allowing its enamination [<1995JCM488>](#). Less acidic

methyl groups such as in 2-aryl-6-arylthio-4-methylpyridazin-3(2*H*)-ones can be deprotonated with LHMDS followed by alkylation (LHMDS=lithium bis(trimethylsilyl)amide). As electrophiles enantiomerically pure 2-methyloxirane (R and S) as well as allyl bromide were used <2003BML4431>. An interesting case is the condensation of benzaldehyde with 3,6-dimethylpyridazine as activation by ZnCl₂ seems to be sufficient to allow the formation of 3,6-bis(2-phenylvinyl)pyridazine <1996JCD2117>. In fact, this is a procedure already earlier described by Wiley <1987MI1183>. A more recent example is the condensation of 3-methylpyridazine **133** with substituted benzaldehydes and benzo analogs in basic medium (Equation 19) <2005T10227>.



8.01.7.2 Carboxylic Acids and Esters

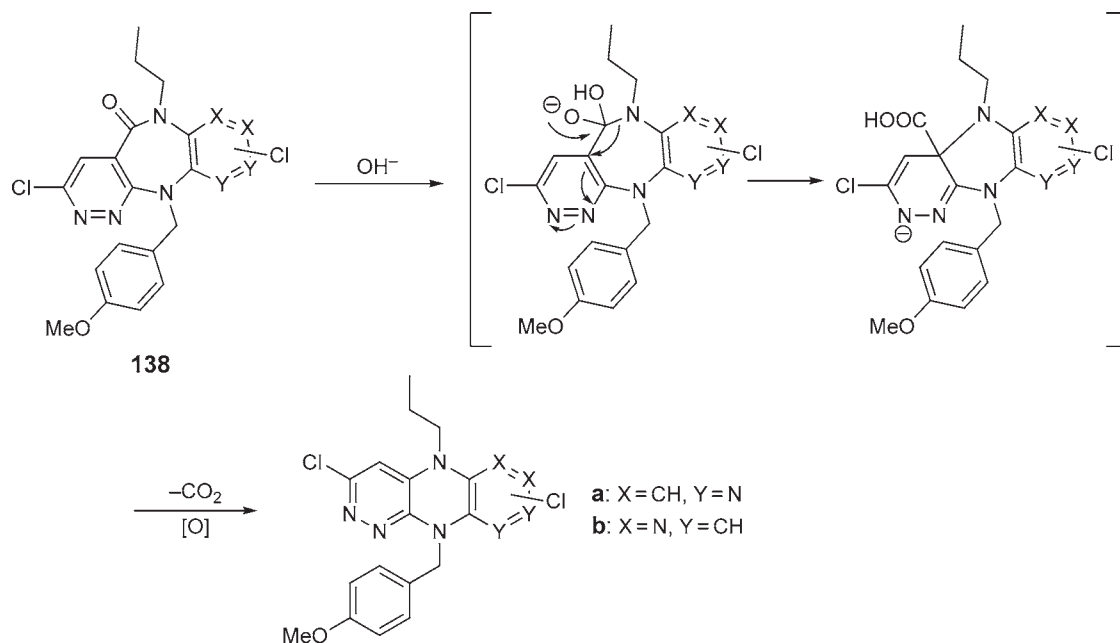
While in CHEC(1984) <1984CHEC(2)1> there is an emphasis on decarboxylation reactions of pyridazinecarboxylic acids and the choice of esterification methods, in CHEC-II(1996) <1996CHEC-II(6)1> more examples of reactions with pyridazinecarboxylic esters appeared. More recently, the aminolysis of 1,2-diazinecarboxylic esters such as 1,4-bis(methoxycarbonyl)pyridazino[4,5-*b*]indole, 1,4-bis(methoxycarbonyl)pyridazino[4,5-*b*]benzo[*b*]furan, 8-methyl-1,4-bis(methoxycarbonyl)pyridazino[4,5-*j*]angelicin, and 6,10-dimethyl-1,4-bis(methoxycarbonyl)pyridazino[4,5-*b*]psoralen has been studied <2002SL2095, 2003T8171>. These reactions were performed in CH₂Cl₂ at room temperature using MgCl₂ as a Lewis acid. Interestingly, regioselectivity could be observed in several cases. For instance, on 1,4-bis(methoxycarbonyl)pyridazino[4,5-*b*]indole **134** and 1,4-bis(methoxycarbonyl)pyridazino[4,5-*b*]benzo[*b*]furan **135**, reaction at the C-4 methoxycarbonyl is preferred (Equation 20). Nevertheless, depending on the number of equivalents of amine and the type of amine used generally also a diamide is formed as a minor compound. When a primary amine is used and an appropriate group, such as a dimethylaminoethenyl entity, is present in the *ortho*-position, a ring-closure reaction can immediately follow <1995JCM488>. Interestingly, direct decarboxylation of methyl pyridazinecarboxylic esters **136** and **137** using LiI in refluxing DMF was also described. This is a mild method which avoids tedious classical procedures involving hydrolysis followed by thermal decarboxylation (Equation 21) <2002SL2095>.



Additional examples of Friedel–Crafts-type reactions also appeared. Transformation of pyridazine-3,6-dicarboxylic acid in SOCl_2 (with the addition of DMF) into the corresponding dicarbonyl chloride, followed by reaction with benzene (solvent and reagent) using AlCl_3 as Lewis acid, yields 3,6-dibenzoylpyridazine in 60% [<1996JHC2059>](#). Pyridazinecarbonyl halides also react with classical nucleophiles exemplified by the reaction of 3,6-dichloropyridazine-4-carbonyl chloride with 3,6-dichloro-*N*-propylpyridazin-4-amine [<1999H\(51\)1035>](#). This is certainly an interesting case as no competitive nucleophilic substitution of one of the chlorine atoms on the pyridazine nucleus was observed.

8.01.7.3 Carboxylic Amides

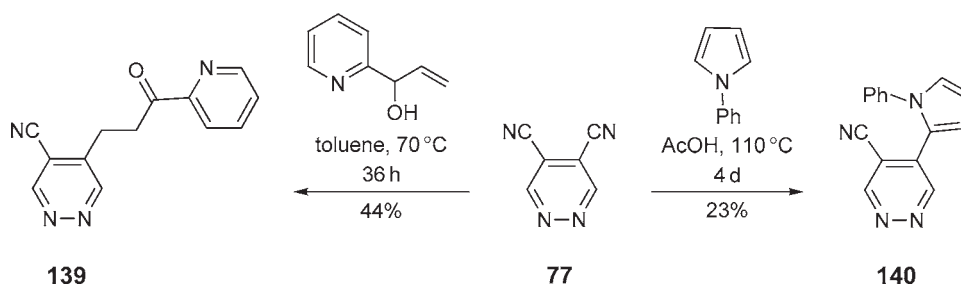
Dehydration, hydrolysis, Hofmann degradation, and Curtius rearrangement of 1,2-diazinecarboxamides were described in CHEC(1984) and CHEC-II(1996) [<1984CHEC\(2\)1, 1996CHEC-II\(6\)1>](#). A recent example of Curtius rearrangement on a pyridazin-3(2*H*)-one, namely 5-carboxy-6-phenylpyridazin-3(2*H*)-one, was reported by Raviña and co-workers [<1999JHC985>](#). In 1999 an interesting ring contraction was published which mechanistically is initiated by attack of hydroxide on the pyridazine-4-carboxamides **138** (Scheme 32) [<1999H\(51\)1625>](#).



Scheme 32

8.01.7.4 Nitriles

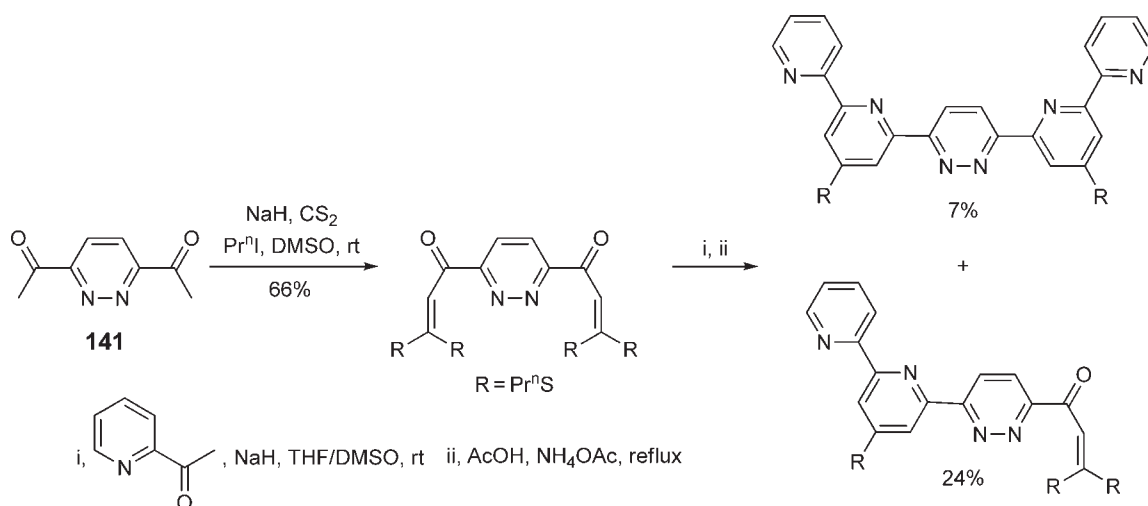
Transformations of pyridazinenitriles to the corresponding amidines, amides, and ketones have been discussed in CHEC(1984) and CHEC-II(1996) [<1984CHEC\(2\)1, 1996CHEC-II\(6\)1>](#). New examples on ketone synthesis were described by Hampl and co-workers [<1999CCC1159>](#). As nucleophiles Grignard reagents were used. A recent example of hydrolysis of a nitrile to a carboxamide on a pyridazin-3(2*H*)-one, namely 5-cyano-6-phenylpyridazin-3(2*H*)-one, was reported by Raviña and co-workers [<1999JHC985>](#). Although it is still a rarely investigated/observed process, a cyano group can behave as a leaving group if the 1,2-diazine is sufficiently electron deficient. Reaction of pyridazine-4,5-carbonitrile **77** with 1-pyridin-2-ylprop-2-en-1-ol yields 5-(3-oxo-3-pyridin-2-ylpropyl)pyridazine-4-carbonitrile **139** (Scheme 33) [<2004TL2113>](#). In this reaction, the 1-pyridin-2-ylprop-2-en-1-ol acts as a ‘vinylogous picoline’ carbon nucleophile. Reaction of pyridazine-4,5-dicarbonitrile **77** with pyrroles and indoles gives the corresponding 5-pyrrol-2-yl- **140** and 5-indol-3-ylpyridazine-4-carbonitriles (Scheme 33) [<2006T12281>](#). The reactions are executed in acetic acid and involve a classical addition–elimination mechanism. The acid is crucial since it makes the addition step of the $\text{S}_{\text{N}}\text{Ar}$ easier. In the absence of (Lewis) acid, inverse electron-demand Diels–Alder reactions between the same substrates are observed (see Section 8.01.5.7.2).



Scheme 33

8.01.7.5 Aldehydes and Ketones

The reactivity of carbonyl derivatives in condensation-type reactions has been carefully addressed in CHEC-II(1996) <1996CHEC-II(6)1>. New examples on this topic have appeared since 1995. For instance, Lehn described the reaction of 3,6-diacetylpyridazine **141** with CS₂ using NaH as base. PrⁿI was subsequently used as thiolate alkylating agent. The bis-Michael acceptor was then allowed to react with the enolate of 2-acetylpyridine which yielded a mixture of mono-coupled and bis-coupled product. Subsequent treatment of the mixture with AcOH/NH₄OAc resulted in pyridine ring formation <2002CEJ3448> (Scheme 34). Condensation of 5-acetylpyridazin-3(2H)-ones with the dimethyl acetal of benzaldehyde in the presence of the Lewis acid AlCl₃ smoothly gave access to the corresponding 5-(3-phenylprop-2-enyl) derivative <2006BML1080>. Reaction of 5-acetyl-6-phenylpyridazin-3(2H)-one with DMFDMA gives vinylogous amide formation. When a large excess of DMFDMA was used, N-methylation also occurred (see also Section 8.01.5.5.5) <2003CPB427>. 4-Formylpyridazin-3(2H)-ones with a *t*-amino group in the 5-position have frequently been used by Mátyus and co-workers. Condensation with an active methylene group yields *ortho*-vinyl-*t*-amines which can undergo cyclization via the type 2 *t*-amino effect <2006S2625> (see also Section 8.01.7.10.3). Applications of the Wittig reaction have also appeared. The reaction of 2-PMB protected 6-formylpyridazin-3(2H)-one with (2-carboxyethyl)triphenylphosphonium bromide using NaH as base is a representative example <2004BML1551>. Cyanohydrin formation on 5-formyl-6-phenylpyridazin-3(2H)-one with additional cyanation in the 4-position via nucleophilic substitution of hydrogen was already mentioned in Section 8.01.5.4.4 <2000TL2863>.



Scheme 34

Also other reaction types have been dealt with in CHEC(1984) and CHEC-II(1996) like reduction to alcohols (e.g., sodium borohydride), Wolff Kishner reduction, nucleophilic addition via reaction with Grignard reagents or organolithium compounds, and formation of imine type functional groups (e.g., hydrazones). New examples are the reaction of

pyridazine-4-carbaldehyde with benzylamine and *p*-anisidine. Reactions were performed in CH_2Cl_2 using Na_2SO_4 to trap the formed water <1996H(43)1057>. Another more challenging example is the reaction of pyridazine-3,6-dicarbaldehyde with propane-1,3-diamine which yields Schiff-base macrocycles <1996JCD2117>. In this case $\text{Pb}(\text{ClO}_4)_2$ is used as a template-forming agent. The size of the macrocycle depends on the ratio of reagents used. Raviña described the synthesis of the oxime of 5-formyl-6-phenylpyridazin-3(2*H*)-one via reaction with hydroxylamine hydrochloride in pyridine. The oxime functional group is interesting as it can be transformed into a cyano group via reaction with Ac_2O . This transformation to 5-cyano-6-phenylpyridazin-3(2*H*)-one can also be performed in one step using hydroxylamine hydrochloride in formic acid <1999JHC985>. The synthesis of pyridazine-3,6-dicarbaldehyde dioxime and 3,6-dibenzoylpyridazine dioxime from the corresponding carbonyl derivatives was also reported <1996JHC2059>. Recent reductions with hydrides are exemplified by the reaction of 5-acetyl-4-methoxy-2-methyl-6-phenylpyridazin-3(2*H*)-one and 3-formyl-6-methylpyridazine both with NaBH_4 in methanol <1996EJM65, 2005JME1367>. Reductions performed with organometallic compounds are exemplified by the reaction of 5-formyl-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-one with MeLi at -78°C in THF allowing smooth secondary alcohol formation <2003CPB427>. Oxidation of a formyl substituent, such as in 5-formyl-6-phenylpyridazin-3(2*H*)-one, to the corresponding carboxylic acid using Ag_2O also appeared <1997CPB1151>.

8.01.7.6 Other Substituted Alkyl Groups

Not so many different reaction types in this section have been studied and therefore mentioned in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>. Most of the reports deal with reactions of hydroxyalkyl groups. Recent examples in this section include the halohydroxylation of 5-(hydroxymethyl)-6-phenylpyridazin-3(2*H*)-one with $\text{CBr}_4/\text{PPh}_3$ to the corresponding bromomethyl derivative useful for further transformation via reaction with nucleophiles <1999JHC985>. Also tosylate esters prepared from the corresponding alcohols have been used in nucleophilic substitution reactions <2002TL11>. Oxidation of 1-hydroxyalkyl-substituted pyridazines and pyridazin-3(2*H*)-ones (or benzo-fused derivatives) to the corresponding ketones and aldehydes is often described and usually performed with MnO_2 <1995T13045, 1995JHC1057, 1996JCD2117, 1997CPB1151, 2002BMC2873, 2003CPB427>. When a 4,5-dihydropyridazin-3(2*H*)-one is used, oxidation to the pyridazin-3(2*H*)-one occurs in a tandem fashion <2004BML1551>. Although very useful, the formation of an alkenyl group via elimination of water, exemplified by the reaction of 5-(1-hydroxyethyl)-4-methoxy-2-methyl-6-phenylpyridazin-3(2*H*)-one in concentrated H_2SO_4 <1996EJM65>, did not appear in CHEC(1984) and CHEC-II(1996). The reaction of benzyl cyanide (or substituted and heteroaromatic analogs) with 3-chloropyridazines via $\text{S}_{\text{N}}\text{Ar}$ followed by oxidative decyanation to the corresponding ketone already appeared in CHEC-II(1996). More examples appeared since then <2004JOC1364>. In the new examples $\text{Na}_2\text{O}_2/\text{NH}_4\text{OAc}$ was used as an oxidant for the oxidative decyanation while previous examples made use of O_2 in base.

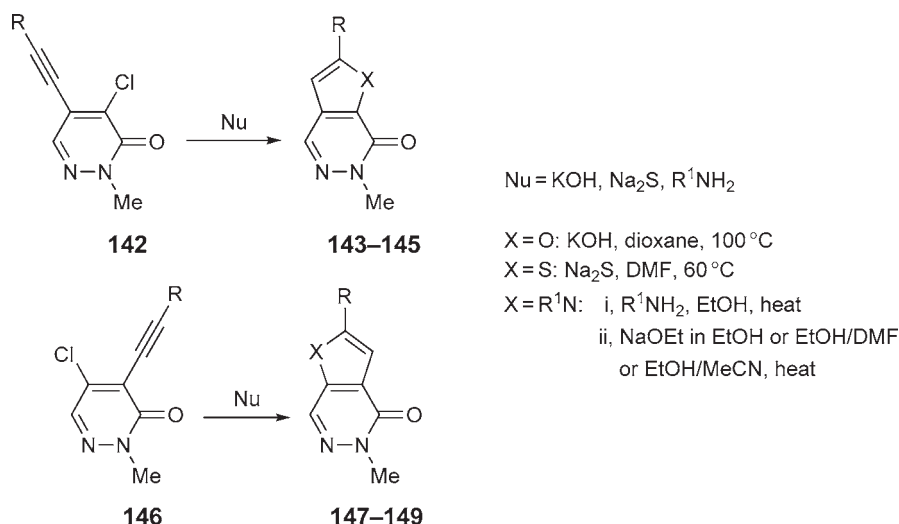
8.01.7.7 Alkenyl Groups

This section did not appear in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>. 1-Ethoxyvinyl-substituted 1,2-diazines can easily be obtained from the corresponding halo derivatives via a Stille reaction with $\text{CH}_2=\text{C}(\text{OEt})\text{SnBu}_3$ (see Section 8.01.7.15.2(iii)). Treatment with an acid like HCl yields an acetyl substituent <2002CEJ3448, 2003CPB427, 2006BML1080>. Ozonolysis of vinyl or substituted vinyl substituents has also been investigated which smoothly gives access to a formyl group <1996JCD2117, 2002BML1575, 2003CPB427>. A good example is the ozonolysis of 3,6-distyrylpyridazine which gives 3,6-diformylpyridazine in 64% yield <1996JCD2117>.

8.01.7.8 Alkynyl Groups

Reactions on the alkynyl group of alkynyl-substituted 1,2-diazines have been incorporated starting from CHEC-II(1996) <1996CHEC-II(6)1>. Double nucleophilic additions (of the Michael type) with NaOMe and hydration in acid with the aid of the Lewis acid HgSO_4 were mentioned in the previous edition. A recent interesting example published by Sotelo and co-workers involves the addition of HCl to 5-alkynyl-6-phenylpyridazin-3(2*H*)-ones. The smooth anti-Markovnikov addition was discovered when trying to deprotect 2-MOM-protected pyridazin-3(2*H*)-ones in 6M HCl . The nature of the alkynyl group determines if deprotection and addition or only deprotection occurs <2005T4785>. Selective MOM deprotection can always be obtained if AlCl_3 is used. Maes and co-workers

investigated the reaction of 5-alkynyl-4-chloro-2-methylpyridazin-3(2*H*)-ones **142** and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones **146** with hydroxide, sulfide, and primary amines (and ammonia) which gave access to the corresponding furano-, thieno-, and pyrrolo-annulated pyridazin-3(2*H*)-ones **143–145** and **147–149** in good yields (**Scheme 35**) <2002H(57)2115, 2003H(60)2471>. The mechanism involves nucleophilic addition on the alkyne and substitution of the chlorine via addition–elimination on the pyridazinone core or the reverse. One has to be careful when performing reactions of rather basic nucleophiles with alkynylpyridazin-3(2*H*)-ones which contain propargylic hydrogens since these seem to be rather acidic due to the conjugation with the pyridazin-3(2*H*)-one nucleus.



Scheme 35

8.01.7.9 Aryl Groups

This section did not appear in CHEC-I(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>. Examples are the intramolecular Heck-type reaction of 2-benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one and 5-(2-bromophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one which yields 2-benzylidibenzo[*f,h*]phthalazin-1(2*H*)-one and 2-methyldibenzo[*f,h*]cinnolin-3(2*H*)-one, respectively <2003T5919>. The same compounds were also obtained from the corresponding 2-aminophenyl (instead of 2-bromophenyl) derivatives via diazotization and subsequent Pschorr reaction.

8.01.7.10 Amino and Imino Groups

The reaction of 1,2-diazinamines with electrophiles is well studied while the substitution of amines–imines by nucleophiles is a highly nonstandard process. Nevertheless, even in the latter class new examples appeared since CHEC-II(1996) <1996CHEC-II(6)1>. A new section dealing with the so-called *t*-amino effect was added since many examples on 1,2-diazines have appeared since the mid-1990s.

8.01.7.10.1 Reaction of electrophiles at the amino group

8.01.7.10.1(i) Acyl halides or acid anhydrides as electrophiles

Reaction of cinnolin-4-amine with pivaloyl chloride yielded the expected corresponding amide as well as a disubstituted compound resulting from the reaction of 4-pivaloylaminocinnoline with a second molecule pivaloyl chloride at N-1 <1995T13045>. Similarly, other amides have been made from 5-aminopyridazin-3(2*H*)-ones <1997BML2857>. Also acid anhydrides have been used as electrophiles for amide formation on 5-aminopyridazin-3(2*H*)-ones <1998JHC1421>.

8.01.7.10.1(ii) Isocyanate and isothiocyanate as electrophiles

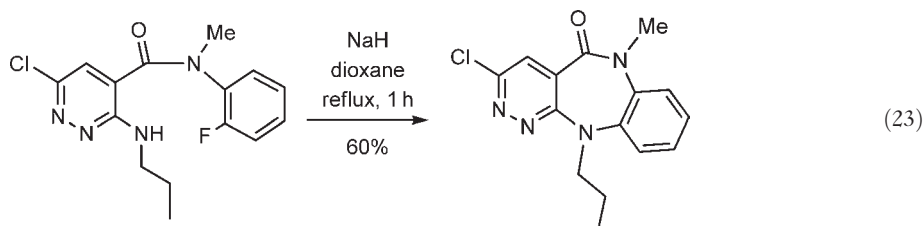
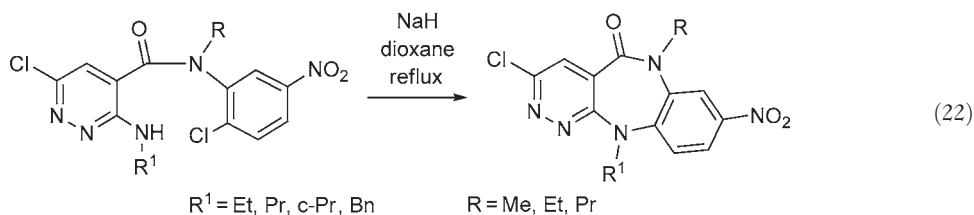
Reaction of pyridazinamines with substituted phenyl isocyanates or phenyl isothiocyanates yields respectively the corresponding substituted *N*-phenyl-*N'*-pyridazinylureas and *N*-phenyl-*N'*-pyridazinylthiureas <1997AP207, 2001JHC945>. Interestingly, depending on the substitution pattern of the phenyl ring a further reaction to a biuret can be observed. If additional attack occurred, it always preferred the nitrogen atom bonded to the phenyl ring as it is more nucleophilic than the one connected to the diazine unit. Electron-withdrawing groups on the phenyl ring prevent biuret formation due to the reduced nucleophilicity <2001JHC945>. Macrocycles have been prepared using *N*-substituted pyridazine-3,6-diamines and 2,6-toluene diisocyanate or 1,3-benzene diisocyanate <2005CC5751>.

8.01.7.10.1(iii) Ketones and aldehydes as electrophiles

Reductive alkylation is a well-known reaction in heterocyclic chemistry and has also successfully been executed on 1,2-diazinamines. The reaction of 6-aryl-5-aminopyridazin-3(2*H*)-ones with formalin and NaBH₃CN as reductant for instance yields 6-aryl-5-dimethylaminopyridazin-3(2*H*)-ones <1998JHC1421>.

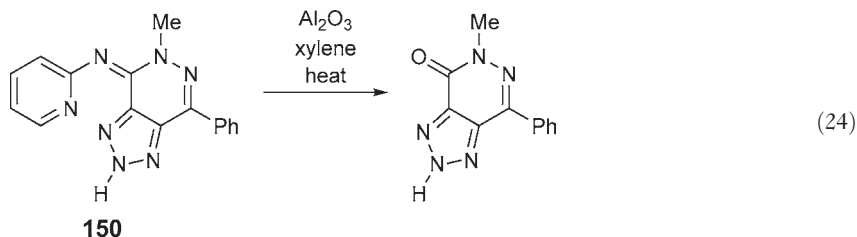
8.01.7.10.1(iv) Aryl halides as electrophiles

Although 1,2-diazinamines are not very nucleophilic by themselves the nucleophilicity can be increased via initial deprotonation with strong base. This strategy has been followed by Heinisch and co-workers when studying intramolecular S_NAr reactions (Equations 22 and 23) <1997H(45)673, 1997AP29>.



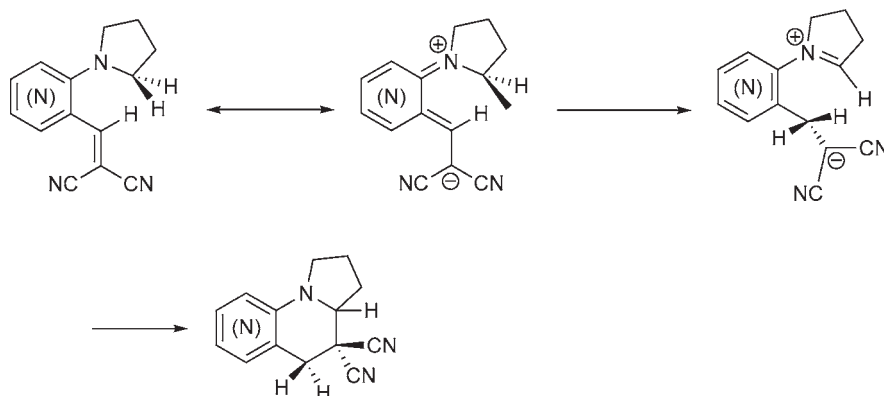
8.01.7.10.2 Reaction of amino and imino groups with nucleophiles

Although a very rarely studied reaction type, the recently reported hydrolysis of 2-substituted pyridazin-3(2*H*)-imines such as **150** to the respective pyridazin-3(2*H*)-ones falls into this reaction class (Equation 24) <2000CC1785>. Al₂O₃ in boiling xylene was used to execute this transformation.

8.01.7.10.3 *t*-Amino effect

Ring-closure reactions that involve a *t*-amino group on a 1,2-diazine skeleton and a vinyl moiety in its *ortho*-position occur via the so-called *t*-amino effect. Although this reaction does not involve reaction at the nitrogen atom itself, it is a very specific reaction that can only occur on *t*-amines and is therefore incorporated in this section. The reaction

mechanism occurs via a hydrogen migration on a dipolar structure in the first step followed by internal rotation and bond formation between the two oppositely charged carbon atoms. The hydrogen migration can occur via a [1,5] sigmatropic or hydride shift. A general mechanism is presented in [Scheme 36](#). The process is proved to be very useful for the synthesis of many tetrahydropyridine fused pyridazines. Stereo- and regiochemical issues have also been studied in detail [<2006S2625>](#). Since the ring-closure reactions usually occur rather slowly under classical heating, requiring prolonged heating in high boiling solvents, the effect of microwave irradiation on these reactions was also investigated [<2004GC125>](#). Even solvent-free reactions were studied under microwave heating [<2005T9052>](#).



Scheme 36

8.01.7.11 Other N-Linked Substituents

8.01.7.11.1 Nitro groups

As already mentioned in CHEC-II(1996) the nitro group is an excellent leaving group on a 1,2-diazine core [<1996CHEC-II\(6\)1>](#). More examples have appeared in the last decade. Alkoxides, alkylthiolates, and amines have been used to substitute the nitro group in an inter- or intramolecular fashion on a pyridazin-3(2*H*)-one nucleus [<1997FA173, 2001JST\(545\)75, 2001JME2403>](#). Especially interesting to mention are 2-methyl- or 2-phenyl-5-acetyl-4-nitro-6-phenylpyridazin-3(2*H*)-ones as upon reaction with sodium ethyl thioglycolate thieno-annulated systems were obtained. Similarly, starting from this substrate pyrazolo-, pyrrolo-, and pyridopyridazinone skeletons were generated which involve substitution of the nitro group by an appropriate nitrogen nucleophile [<1997JME1417>](#). Also active methylene groups have been used to substitute a nitro group with the reaction of malononitrile with 4,5-dichloro-2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-6-nitropyridazin-3(2*H*)-one as a representative example. A mixture of compounds resulting from C-4 (5%), C-5 (49%), and C-6 (19%) attack was obtained [<2001JHC1179>](#). Even halides have been used as nucleophiles via reaction with HX. For instance, 5-acetyl-2-methyl-4-nitro-6-phenylpyridazin-3(2*H*)-ones can be transformed into the corresponding 5-acetyl-4-halo-2-methyl-6-phenylpyridazin-3(2*H*)-ones via reaction with HBr or HCl in acetone [<1997FA173>](#). Similarly, 3-benzylamino-4-nitro-6-phenylpyridazin-3(2*H*)-one was converted into 3-benzylamino-4-bromo-6-phenylpyridazin-3(2*H*)-one with HBr in AcOH. When a 2,4-dimethoxybenzylamino group was present in the starting compound, deprotection occurred in the same step [<2003SL1482>](#). Reductions of nitro-substituted pyridazin-3(2*H*)-ones were also executed [<2000JHC1603, 2001H\(55\)1927, 2001JHC1179, 2001RJO1026, 2001JST\(545\)75>](#). Several reaction conditions are available for such a transformation.

8.01.7.11.2 Hydrazino groups

Hydrazone formation of pyridazine-3-hydrazines with aldoses, dialdofuranoses, and dialdopyranoses was studied by Stanovnik and co-workers. The respective hydrazones could be cyclized with Br₂ in MeOH or Pb(OAc)₄ to *s*-triazolo[4,3-*b*]pyridazin-3-yl substituted polyols [<1997JHC1115, 1998JHC513>](#). Similarly, 4-[(dimethylamino)-methylene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one was reacted with pyridazine-3-hydrazines and the resulting mixtures were subsequently treated with Pb(OAc)₄. Besides *s*-triazolo[4,3-*b*]pyridazine formation also diazenes were obtained. This can be rationalized by the enehydrazine–hydrazone mixtures observed in the first reaction. For phthalazin-1-hydrazines only diazenes were obtained after oxidation [<2005TA2927>](#). Also cyclizations of

phenylhydrazones of 6-chloropyridazine-3-hydrazine and phthalazine-1-hydrazine with CuCl_2 were reported <2005T5942>. More examples on 1,2,4-triazolo[4,3-*b*]pyridazine formation containing C-3 substitution, including reactions with a hydrazino entity as functional group of the 1,2-diazine, were already described in Section 8.01.5.2.4. 1,2,4-Triazolo fusion, without substitution at C-3, can be achieved in one step via reaction of a pyridazine-3-hydrazine in formic acid <1997JHC65, 2002JHC889>. Simple hydrazone formation with pyridazine-3-hydrazines without further synthetic applications also appeared <2003HAC334>.

8.01.7.11.3 Carbodiimido groups

This section is new and only one article appeared in this area. The reaction of *N*-*t*-butyl-*N'*-pyridazin-3-ylcarbodiimide with amines, thiols, and alcohols was studied by Rakowitz and co-workers and yielded respectively novel guanidines, isothiouras, and isoureas <2002JHC695>.

8.01.7.11.4 Azido groups

This was previously not covered as a separate section and was only briefly mentioned in the hydrazino group part as a route to obtain tetrazolo[1,5-*b*]pyridazines <1996CHEC-II(6)1>. 5-Azido-4-chloro- and 5-azido-4-bromo-2-methylpyridazin-3(2*H*)-one, obtained via nucleophilic substitution with sodium azide in methanol on the corresponding 4,5-dihalopyridazin-3(2*H*)-one, could be reduced to 5-amino-2-methylpyridazin-3(2*H*)-one at room temperature using Pd/C in ethanol and a balloon of hydrogen gas. In a similar way 5-azido-2-(1,1-dibromo-2-oxopropyl)-4-chloropyridazin-3(2*H*)-one could be prepared from 2-(1,1-dibromo-2-oxopropyl)-4,5-dichloropyridazin-3(2*H*)-one. For the reduction of the azide group and the dehalogenation of this substrate again Pd/C and H_2 were used. In this case a mixture of aq NaOH and methanol was used as solvent. Aq NaOH was added to allow additional deprotection of the 2-position. Besides deprotection no desired reaction occurred since substitution of the azide for a methoxy group was observed <1998JHC819>. Another type of reaction typical for azides is the transformation to nitrenes. Thermolysis of tetrazolo[1,5-*b*]pyridazines 10–20 °C above their melting point yields nitrenes, via the corresponding 3-azidopyridazines, that undergo ring contraction to pyrazole-1-carbonitrile <2000TL2699>.

8.01.7.12 Hydroxy and Oxo Groups

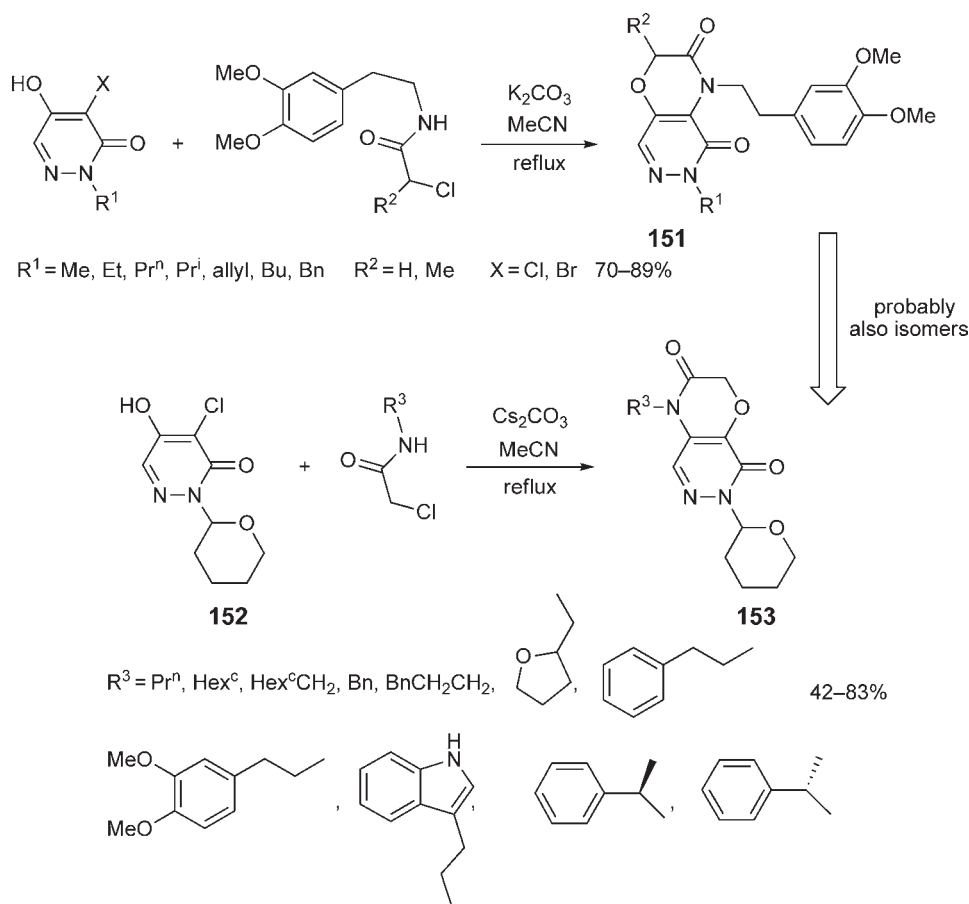
8.01.7.12.1 Reactions with electrophiles

O-Alkylation of hydroxypyridazin-3(2*H*)-ones appeared in CHEC-II(1996) <1996CHEC-II(6)1>. Although no substituent is present in the 6-position of 2-substituted 4-halo-5-hydroxypyridazin-3(2*H*)-ones, selective alkylation with a *N*-substituted 2-chlorocarboxamide occurred at oxygen. Interestingly, it is claimed that O-alkylation is immediately followed by ring closure at C-4 (Scheme 37) <1998JHC601>. It is doubtful that the authors really made 4,6-dihydro-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,5-diones **151** since in 2003 they published a paper dealing with the synthesis of 2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-diones **153** via reaction of 2-(tetrahydro-2*H*-pyran-2-yl)-4-chloro-5-hydroxypyridazin-3(2*H*)-one **152** with *N*-substituted 2-chloroacetamides (Scheme 37) <2003TL8995>. While the same solvent at the same reaction temperature (also in the presence of a carbonate base) was used as for the synthesis of **151** they report in this case Smiles rearrangement to occur. The latter process is confirmed by X-ray of one of the prepared derivatives.

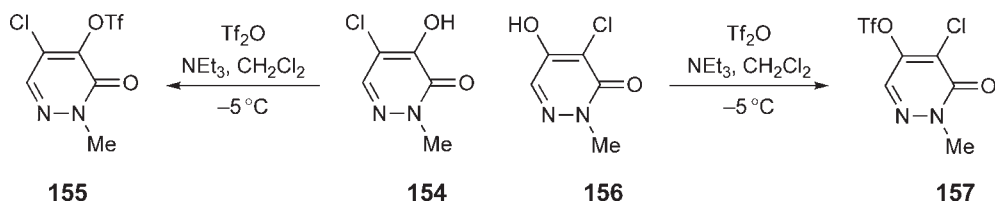
While 1,2-diazinones usually give *N*-alkylation, O-alkylation can be achieved by first transforming them into the trimethylsilyloxy-1,2-diazines or silver salts <1996CHEC-II(6)1>. This approach has been used by El Ashry to attach sugar moieties to the oxygen atom of phthalazin-1(2*H*)-one <2003CAR2291>.

More examples appeared on the synthesis of trifluoromethanesulfonate esters as these are very useful as pseudohalides in Pd-catalyzed reactions <2001SL150, 2001T10009>. While the transformation of pyridazin-3(2*H*)-ones into pyridazin-3-yl triflates was already described in CHEC-II(1996) <1996CHEC-II(6)1>, the transformation of hydroxypyridazin-3(2*H*)-ones into trifluoromethanesulfonyloxypyridazin-3(2*H*)-ones is new <2001T10009>. This is exemplified by the transformation of **154** and **156** into **155** and **157** (Scheme 38). Also phthalazin-1(2*H*)-ones have been subjected to similar reaction conditions <2005JHC1245>. 4-Methylbenzenesulfonate and 2,4,6-triisopropylbenzenesulfonate esters of 1,2-dihydropyridazin-3,6-diones have recently been prepared and were, similarly to the triflates, used as pseudohalides in Pd-catalyzed reactions <2006TL6125>.

Esterifications were also studied. Reaction of pivaloyl chloride with 5-hydroxy-2-methyl-4-(2-methylphenyl)pyridazin-3(2*H*)-one using NEt_3 as base gave 58% of the corresponding ester <2005JHC427>. Maes and co-workers published the synthesis of isomeric isochromeno[3,4-*d*]pyridazinediones via lactonization of 2-benzyl-5-(2-carboxyphenyl)-4-hydroxypyridazin-3(2*H*)-one and 2-benzyl-4-(2-carboxyphenyl)-5-hydroxypyridazin-3(2*H*)-one with H_2SO_4 <2002T9713>.



Scheme 37

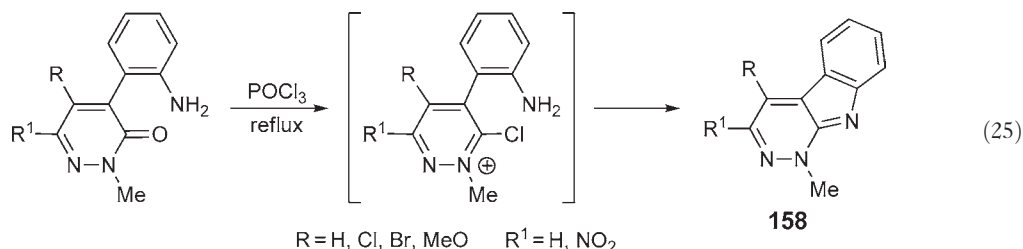


Scheme 38

8.01.7.12.2 Reactions with nucleophiles

Deoxy-halogenation of pyridazinones and benzo-fused analogs with phosphorus halide reagents (PX_3 , POX_3 , PX_5) is a very important and well-known reaction type as most of the chloro- and bromo-1,2-diazines are prepared in this way. The nucleophile is generated after reaction of the phosphorus containing electrophile with oxygen. New examples include the synthesis of 5-bromo-3-chloro-6-phenylpyridazine from 5-bromo-6-phenylpyridazin-3(2*H*)-one via reaction with POCl_3 in dioxane [<2002SL223>](#). 5-Bromo-3-chloro-6-phenylpyridazine is an interesting compound since it allows selective functionalization (see [Section 8.01.7.15.2](#)). Worth mentioning in the benzo-fused derivatives is the improved synthesis of 3-chloro- and 4-chlorocinnoline from 3-hydroxy- and 4-hydroxycinnoline, respectively [<1995T13045>](#). New in this section is the reaction of POCl_3 with a 2-alkylpyridazin-3(2*H*)-one which yields a 2-alkyl-3-chloropyridazinium salt. When an amino group is positioned properly within the same molecule, ring

closure can be achieved via trapping of the unstable 2-alkyl-3-chloropyridazinium salt. Via this methodology 1-methyl-1*H*-pyridazino[3,4-*b*]indoles **158** could be prepared (Equation 25) <2006T121>. These are analogs of the natural product neocryptolepine. Similarly, intermolecular reactions with oxygen, sulfur, and nitrogen nucleophiles have also been studied. In this case the 2-alkyl-3-chloropyridazinium salt was prepared via alkylation of the corresponding 3-chloropyridazine <1998T9519>.



Transformation of 1,2-diazinones into 1,2-diazinethiones is a standard reaction that can be easily performed using P_2S_5 or Lawesson's reagent <1996CHEC-II(6)1>.

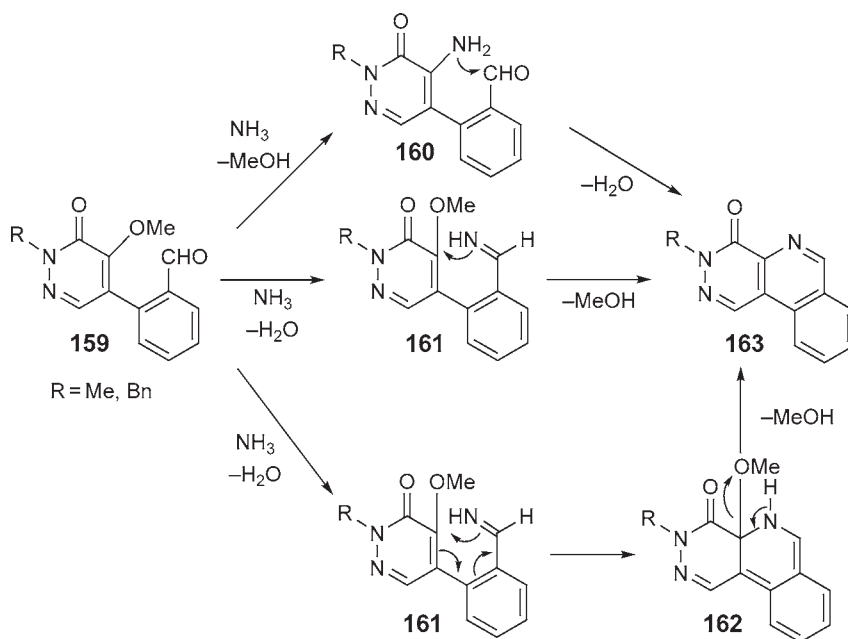
8.01.7.13 Other O-Linked Substituents

8.01.7.13.1 Alkoxy and aryloxy groups

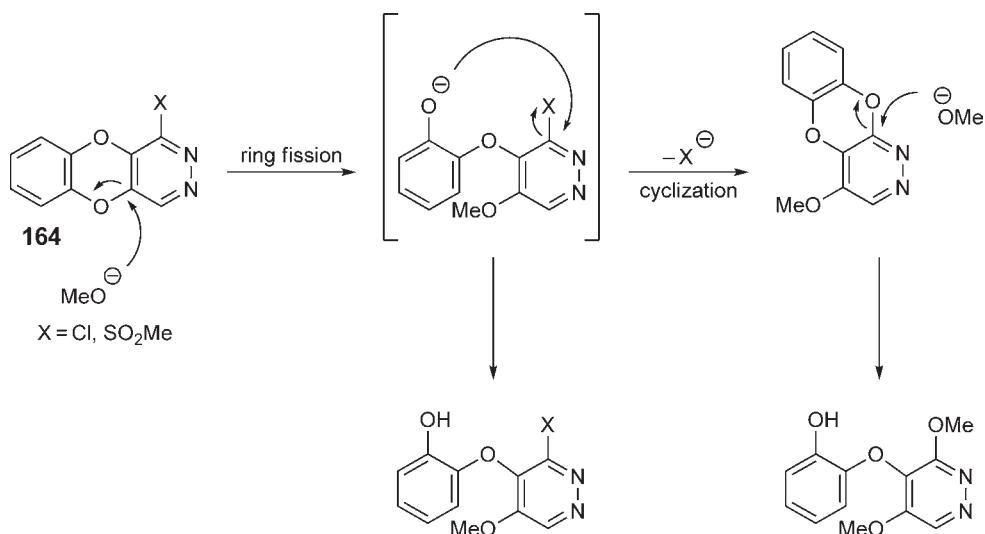
Hydrolysis of alkoxy-1,2-diazines was already covered in CHEC(1984) <1984CHEC(2)1>. In CHEC-II(1996) <1996CHEC-II(6)1> another approach for this transformation appeared, namely via a demethylation reaction with amines. In the last decade additional examples on the hydrolysis of alkoxy-1,2-diazines appeared, exemplified by the reaction of 2-substituted 4-aryl-5-methoxypyridazin-3(2*H*)-ones and 2-substituted 5-aryl-4-methoxypyridazin-3(2*H*)-ones with KOH in water at reflux <2002T9713>. Although the solubility of these substrates in aq KOH is not very good, working under dilute reaction conditions and relying on complete solubility while the reaction proceeds worked perfectly. Of course it cannot be excluded that also these presumed classical hydrolysis reactions partly occur via demethylation. Hydrolysis of alkoxy groups under acidic conditions are also well known. Quéguiner described that 4-acetyl-5,6-diaryl-3-methoxypyridazines can be transformed into 4-acetyl-5,6-diarylpyridazin-3(2*H*)-ones via reaction with HI in MeOH at 80 °C <1995JHC1057>. Interestingly, BBr_3 in CH_2Cl_2 or HI in water gave poor results due to degradation.

When synthesizing isomeric pyridazino[4,5-*c*]isoquinolinone cores, Hajós and co-workers studied the substitution of the methoxy group in the 4- and 5-position of an *ortho*-2-formylphenyl-substituted pyridazin-3(2*H*)-one <2002T5645>. As an example the rationalization of the mechanism for the reaction of 2-substituted 4-methoxy-5-(2-formylphenyl)pyridazin-3(2*H*)-one **159** with ammonia is presented in Scheme 39. An obvious interpretation would be that the first step is the nucleophilic displacement of the methoxy group with an amino moiety, (i.e., formation of **160**) followed by a condensation of the amino and formyl groups. However, attempts to transform related 4- and 5-methoxy derivatives (4-methoxy-2-methyl-5-phenylpyridazin-3(2*H*)-one and its isomer 5-methoxy-2-methyl-4-phenylpyridazin-3(2*H*)-one) into the corresponding amino derivatives under the same reaction conditions as used for the ring-closure procedure were unsuccessful, which is fully in accordance with the poor leaving group properties of an alkoxy group. Therefore, most probably the cyclization consists of imine **161** formation followed by nucleophilic displacement of the methoxy group (**161** → **163**) rather than the reverse sequence. Since an imine is a rather weak nucleophile, the good leaving group properties of the methoxy group must be ascribed to the formation of the new aromatic ring as the driving force for the irreversible cyclization. Another possibility for the ring closure of the proposed imine intermediate **161** is that an electrocyclic reaction takes place (**161** → **162**) followed by elimination of methanol (**162** → **163**).

Aryloxy groups have also been used as leaving groups. Reaction of 1-chloro- and 1-methanesulfonyl[1,4]benzodioxino[2,3-*d*]pyridazine **164** and 4-chloro[1,4]benzodioxino[2,3-*c*]pyridazine with NaOMe afforded ring-opened and cyclized pyridazines (Scheme 40). Their reaction with amines afforded 1-substituted [1,4]benzodioxino[2,3-*d*]pyridazines **165**, 4-substituted [1,4]benzodioxino[2,3-*c*]pyridazines **166**, and/or 2-hydroxyphenoxy-pyridazines **167** (Scheme 41) <2004H(63)591>.



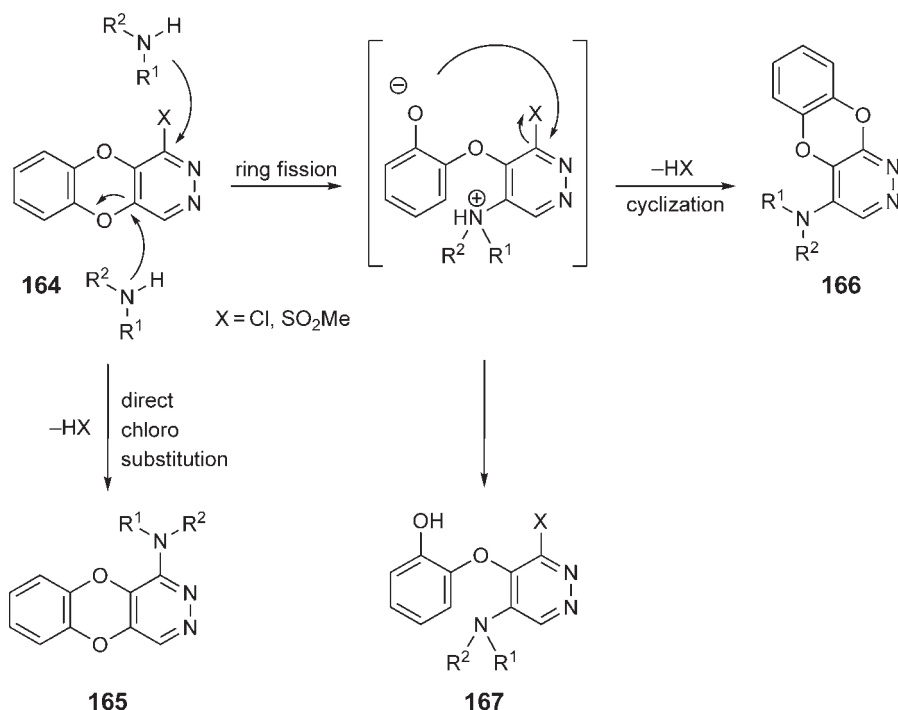
Scheme 39



Scheme 40

8.01.7.13.2 Triflate and tosylate esters

Triflate esters are very popular in Pd-catalyzed cross-coupling reactions. They can easily be prepared from pyridazin-3(2*H*)-ones or hydroxypyridazin-3(2*H*)-ones as shown in [Section 8.01.7.12.1](#). Their preparation is more practical than that of the corresponding bromo and chloro derivatives as these require the use of phosphorus halide reagents (PX₃, POX₃, PX₅) (often as reagent and solvent). While at the time of publication of CHEC-II(1996) <1996CHEC-II(6)1> only examples on Sonogashira reactions had appeared; in the meantime, Suzuki reactions <2001SL150, 2002T9713, 2003T5919>, Stille reactions <2001SL150>, and Pd-catalyzed alkoxy carbonylations <1996H(43)1459, 2003SL2225> have been published involving triflate esters of pyridazines and pyridazinones. Triflate esters also allowed chemoselective Pd-catalyzed reactions versus a chlorine atom. Sonogashira reaction on



Scheme 41

4-chloro-2-methyl-5-trifluoromethanesulfonyloxy pyridazin-3(2H)-one **157** and 5-chloro-2-methyl-4-trifluoromethanesulfonyloxy pyridazin-3(2H)-one **155** yielded respectively smooth C-5 and C-4 selective alkylation <2001T10009>. The synthesis of the substrates was already covered in Section 8.01.7.12.1. Triflate esters in the benzene ring of a phthalazin-1(2H)-one have also been used in Sonogashira reactions. Interestingly, there seems to be no need for N-H protection in this case <2000BML2235>. Recently, tosylate esters and 2,4,6-triisopropylbenzene-sulfonate esters were also used as leaving groups in Pd-catalyzed cross-coupling reactions <2006TL6125>.

8.01.7.14 S-Linked Substituents

8.01.7.14.1 Thiol and thione groups

Diazinethiones standardly react at sulfur in alkylation, Michael addition, and acylation reactions <1984CHEC(2)1>. For alkylation reaction at nitrogen was also reported. While reaction of 6-substituted 4-arylmethylpyridazine-3(2H)-thiones with Me_2SO_4 in ethanol/NaOH at room temperature gave S-alkylation, reactions with the same electrophile in refluxing acetone using K_2CO_3 as base gave N-methylation <2003HAC334>. Mannich reaction with formalin and piperidine on the same substrate also gave N-functionalization <2003HAC334>. Direct substitution of a thione group is also possible. Thiourea and hydrazine have been used as nucleophiles yielding the corresponding 1-pyridazin-3-ylthioureas and pyridazine-3-hydrazines respectively <2003HAC334>. On the contrary for the latter also reduction to a pyridazine via reaction with hydrazine has been observed <2004MOL849>. Oxidation reactions of pyridazinethiones are not frequently described. A new interesting example is the oxidation of 6-methoxypyridazine-3(2H)-thione to 6-methoxypyridazine-3-sulfonyl fluoride with $\text{KHF}_2/\text{Cl}_2(\text{g})$ in $\text{MeOH}/\text{H}_2\text{O}$ <2003JME2283>. Esterification of 5-mercapto-4-methoxy-2-phenylpyridazin-3(2H)-one with acyl halides, acid anhydrides, and chloroformate was also studied <1996CCC437>. Interestingly, 2-substituted 4-alkoxy-5-mercaptopyridazin-3(2H)-ones can rearrange to 5-alkylthio-4-hydroxypyridazin-3(2H)-ones by heating in solvents that can act as a good hydrogen bond acceptor (e.g., DMF, DMSO, pyridine, and triethylamine). The electrophilic rearrangement can be explained in terms of the higher nucleophilicity of the sulfur atom in comparison with the oxygen atom. Alkaline salts of the substrates, which are anyway more nucleophilic, can rearrange with virtually no solvent dependence (e.g., also in xylene or alcohols) <1996CCC437>.

8.01.7.14.2 Alkylthio, alkylsulfinyl, and alkylsulfonyl groups

Oxidation of alkylthio- (or arylthio-)1,2-diazines to the corresponding sulfinyl and sulfonyl derivatives has been described in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>.

Oxidation to a sulfonyl group has been achieved with KMnO_4 <2004H(63)591, 2004T7983>, MCPBA <2005JME6326, 2002BMC2873>, or AcOOH/AcOH <2000JHC911>. Selective oxidation to a sulfinyl group has been executed with NaIO_4 <1999H(51)617>, $\text{SO}_2\text{Cl}_2/\text{AgNO}_3$ <1997FA173>, MCPBA <2004T7983> or $\text{H}_2\text{O}_2/\text{NaOH}$ <2000JHC911>. Oxidation of a sulfoxide to a sulfone also appeared <1997FA173>. $\text{H}_2\text{O}_2/\text{AcOH}$ was used for this transformation.

An alkylsulfonyl group on a 1,2-diazine core can be substituted for a nucleophile via an addition–elimination process. For instance, 5-methylsulfonyl-6-phenylpyridazin-3(2*H*)-one smoothly reacts with methanol, aniline, and NaOPh . <2002BMC2873>. There is also a report on substitution of an alkylsulfinyl group. Reaction of 4-*t*-butylsulfinylcinnoline with PhSLi at -78°C in THF gives complete substitution in 1 h yielding 91% of 4-phenylthiocinnoline <2005T8924>. Also 4-*t*-butylsulfinyl-3-phenylthiocinnoline is still susceptible to nucleophilic attack by PhSLi as was observed in metallation experiments with LDA on 4-*t*-butylsulfinylcinnoline using PhSSPh as electrophile <2005T8924>.

8.01.7.15 Halogen Atoms

The section ‘Replacement of halogen by metal or by coupling’ in CHEC-II(1996) <1996CHEC-II(6)1>, mentioning only a few examples of metal-catalyzed reactions, is divided in this edition in Sections 8.01.7.15.1 and 8.01.7.15.2.

8.01.7.15.1 Replacement of a halogen by a metal

Since 1995 major advances have been made in the field of the replacement of a halogen by a metal. Pioneering work on diazines has been provided by the Quéguiner team in France. They found that metal–halogen exchange in THF with RMgX ($\text{R} = \text{Bu}^n$ or Pr^i) on 4-iodo-3,6-dimethoxypyridazine at room temperature smoothly yielded (3,6-dimethoxypyridazin-4-yl)magnesium halide. Half an equivalent of Bu_2Mg could also be used to achieve an exchange reaction. 4,5-Diiodo-3,6-dimethoxy- and 4,5-dibromo-3,6-dimethoxypyridazine were also used as substrate providing halogen–magnesium exchange of one of the halogen atoms <2000T265>. In 2006 Bu_3MgLi was tested as halogen–metal exchange reagent. It proved beneficial as there is no restriction to electron-rich halopyridazines, as is the case with Grignard derivatives. Moreover, in comparison to Bu^nLi no low temperature is required <2006SL1586>. Barbier-type reaction (electrophile is present from the start allowing immediate reaction of the immediately formed lithio compounds) with lithium metal at room temperature in THF under sonication was also investigated by the same research team. 3-Iodo-6-methoxypyridazine, 4-iodo-3,6-dimethoxypyridazine, and 4-iodo-3-methoxycinnoline were successfully used as substrates <2000T3709>. Stevenson reported the bromine or iodine–lithium exchange with Bu^nLi at -70°C in THF on 4-halopyridazin-3(2*H*)-ones. In the same paper the substitution of the bromine atom of 4-bromo-5-methoxy-2-methylpyridazin-3(2*H*)-one for a trimethylstannyl group using a Pd-catalyzed cross-coupling reaction with $(\text{Me}_3\text{Sn})_2$ as the organometallic partner was shown <2005JHC427>. Lithium–bromine exchange on 3-bromopyridazine using Bu^nLi followed by transmetalation with ZnCl_2 was reported by Wonnacott <2002JME3235>. Reactions of metallated 1,2-diazines with electrophiles are treated in Section 8.01.7.16.

8.01.7.15.2 Replacement of a halogen by transition metal mediated coupling

This is a very important topic since the 1,2-diazine entity is electron deficient and therefore generally not easily C-functionalizable via classical electrophilic substitution reactions. Before 1995, only a few Sonogashira and Suzuki reactions on halopyridazines were reported. Examples of the former have been included in CHEC-II(1996) <1996CHEC-II(6)1>. Since 1995, driven by the need for new carbon functionalization methods, a wide variety of palladium-mediated coupling reactions on halopyridazines and their benzo derivatives has been reported. This is definitely the area in the field of pyridazines and benzo analogs in which most advances have been made in the period 1995–2006. Due to the fact that all positions of a 1,2-diazine subunit are activated for nucleophilic attack, chlorinated derivatives normally react with palladium catalysts based on triarylphosphine ligands; a feature specific for the α - and γ -position of azines which is uncommon when using halogenated carbocyclic arenes. Initially, when halopyridazin-3(2*H*)-ones were used the acidic NH was always blocked with a substituent. As NH protecting group a MOM group has been most frequently used <1999S1666, 2001TL8633>. More recently, a hydroxymethyl group has been introduced <2003TL4459>. This seems to be the preferred protecting group since it can easily be introduced via

reaction of the pyridazin-3(2*H*)-one substrate with formaldehyde. After the Pd-catalyzed reaction, it is *in situ* removed via a base induced or thermal retro-ene reaction <2004COR1463> which avoids an additional deprotection step. Very recently, a few successful Pd-catalyzed reactions on halopyridazin-3(2*H*)-ones with a free NH have been reported <2005JME6004, 2006COR277, 2006JME2600>. The use of triflate esters as leaving groups is covered in Section 8.01.7.13.2 and the application of metallated pyridazines as transmetallating agents in Section 8.01.7.16. Especially the Suzuki, Stille, and Sonogashira reactions are now reasonably well explored while data on Kumada, Negishi, Heck, and carbonylation reactions are far more limited. In cases where classical nucleophilic substitution via S_{AE} completely failed or gave only poor yields, palladium-mediated carbon heteroatom bond formation has been studied. There is an extensive review <2006COR377>, an account <2006SL3185> and a book chapter <B-2006MI541> available on the subject of this section.

8.01.7.15.2(i) Kumada reaction

Cross-coupling of arylmagnesium halides with fluorodiazines has been studied by Quéguiner. Nickel catalysts were used for this Kumada-type process. The reactions work at room temperature in THF. Only one example on a 1,2-diazine core was studied, namely the coupling of 3-fluoro-6-phenylpyridazine with 4-methoxyphenylmagnesium bromide <2002JOC8991>.

8.01.7.15.2(ii) Negishi reaction

C-3 Selective Negishi reaction of 3,6-dichloropyridazine with 1.05 equiv of aryl and alkyl organozinc compounds yielded, respectively, 3-aryl- and 3-alkyl-6-chloropyridazines with a selectivity higher than 98% over the 3,6-diaryl- and 3,6-dialkylpyridazines (Equation 26 and Table 6) <2005TL1303>. Yields were often low due to an incomplete conversion of substrate. Unfortunately, either increasing the loading of catalyst or prolonging the reaction time did not give complete conversions. Interestingly, the use of a larger excess of organozinc compound proved to be beneficial and in most cases did not dramatically influence the mono/di selectivity. A second Negishi cross-coupling reaction on the remaining C-6-Cl of the 3-aryl- and 3-alkyl-6-chloropyridazines at a higher reaction temperature smoothly gave unsymmetrically 3,6-substituted pyridazines.

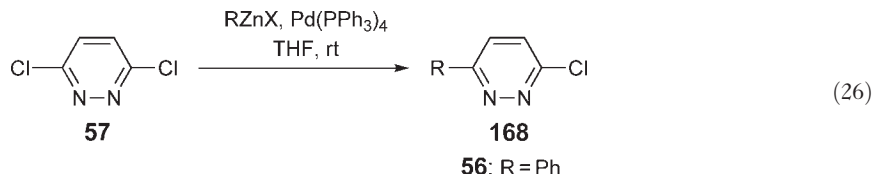
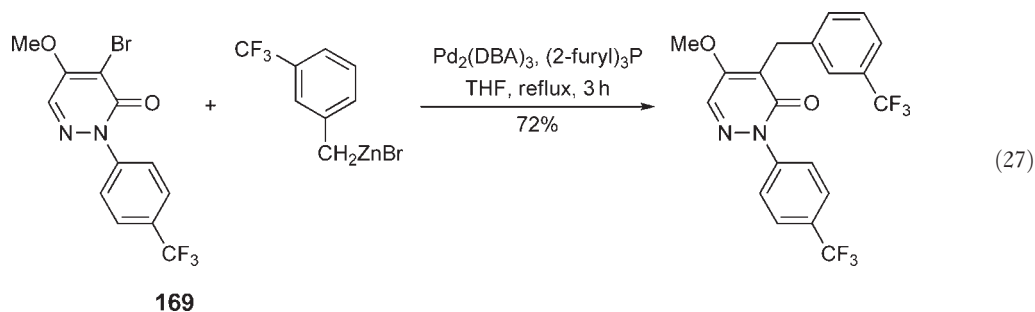


Table 6 Negishi reactions on **57**

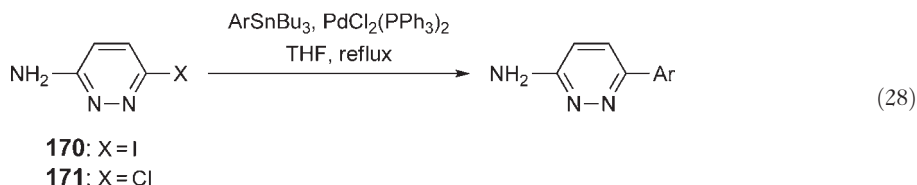
<i>RZnX</i>	<i>Equiv RZnX</i>	<i>Mono+di (%)</i>	<i>Mono:di</i>
BnZnBr	1.05	65	>98:2
BnZnBr	1.6	86	88:12
3-ClC ₆ H ₄ CH ₂ ZnCl	1.6	64	>98:2
PhZnBr	1.05	37	>98:2
PhZnBr	1.6	72	92:8
4-MeOC ₆ H ₄ ZnCl	1.6	92	96:4
4-ClC ₆ H ₄ ZnCl	1.6	86	92:8
4-EtO ₂ CC ₆ H ₄ ZnI	1.05	61	>98:2
<i>n</i> -BuZnBr	1.6	87	>98:2
PhCH ₂ CH ₂ ZnBr	1.6	63	>98:2
CyZnBr	2	27	>98:2

Also a pyridazin-3(2*H*)-one, namely 4-bromo-5-methoxy-2-(4-trifluoromethylphenyl)pyridazin-3(2*H*)-one **169**, has been successfully tackled (Equation 27) <2005JHC427>. In this case, the use of a tri(2-furyl)phosphine rather than a triphenylphosphine-based palladium catalyst was essential to achieve high yields.



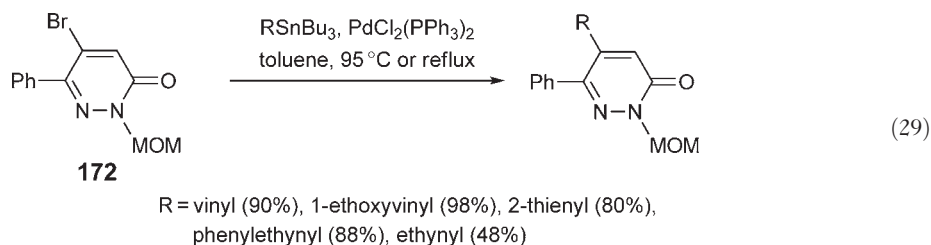
8.01.7.15.2(iii) Stille reaction

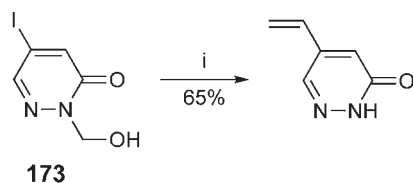
3-Substituted 6-iodopyridazines were the first representatives studied [<1995JOC748>](#). Interestingly, a free amino group is well tolerated and a comparison of Stille reactions on 6-iodo- **170** and 6-chloropyridazin-3-amine **171** with aryl(tributyl)stannanes remarkably revealed that the latter react substantially faster (Equation 28 and [Table 7](#) [<2000T1777>](#)).

**Table 7** Stille reactions on **170** and **171**

X	ArSnBu ₃	Time (h)	Yield (%)
Cl		20	89
Cl		30	96
I		39	99
I		107	87

N-2-Protected 5-halopyridazin-3(2*H*)-ones such as **172** and **173** and 4,5-dihalopyridazin-3(2*H*)-ones were also viable coupling partners (Equations 29 and 30) [<1999S1666, 2001TL8633, 2002SL2062, 2003CPB427, 2003TL4459, 2004T12177>](#). A MOM or a hydroxymethyl group has been used to protect the lactam nitrogen atom.



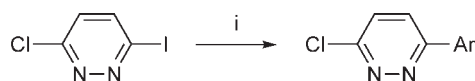


(30)

i, $\text{CH}_2=\text{CHSnBu}_3$, $\text{PdCl}_2(\text{PPh}_3)_2$, Et_3N , DMF, 75°C , 12 h

8.01.7.15.2(iv) Suzuki reaction

Suzuki reaction of a chloropyridazine was first investigated by Quéguiner in the context of a new strategy for the synthesis of the antidepressant Minaprine <1993BSF488>. Attempts to perform C-3 selective Suzuki phenylation on 3,6-dichloropyridazine, under classical Suzuki conditions, gave a 7:3 mixture of mono- and diphenylated pyridazine. More recently, Stanforth showed that complete selectivity can be obtained using 3-chloro-6-iodopyridazine **174** as substrate under Gronowitz-type reaction conditions (Equation 31) <1999T15067>. For 1,4-dichlorophthalazine, however, selective C-1 arylation via Suzuki reaction with isoquinoline-5-boronic acid has been claimed <2006BML1579>. Several 6-substituted 3-halopyridazines, which can be easily obtained via $\text{S}_{\text{N}}\text{Ar}$ starting from the corresponding 3,6-dihalopyridazine, have also been used as substrates for Suzuki reactions <1993BSF488, 1995JOC748, 1999S1163, 2000T1777, 2005JCO414>. The substituents introduced include alkoxy, amino, alkyl-amino, and dialkylamino groups (Equation 32 and Table 8). An interesting example dealing with the synthesis of 6-arylpyridazin-3(2*H*)-ones was published by Turck and co-workers <2005JCO414>. $\text{S}_{\text{N}}\text{Ar}$ on 3,6-dichloropyridazine with the alcoholate of Wang resin, followed by Suzuki reaction and cleavage of the resin with acid, smoothly gave access to a wide range of 6-arylpyridazin-3(2*H*)-ones. The $\text{S}_{\text{N}}\text{Ar}$ –Suzuki concept on 3,6-dichloropyridazine has also been extended to benzo-fused systems <2001S699, 2005BML4696, 2006BML1579>.



(31)

174: Ar = Ph (85%), 2-thienyl (66%)

i, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{ArB}(\text{OH})_2$, Na_2CO_3 , DME/ H_2O , reflux, 12 h



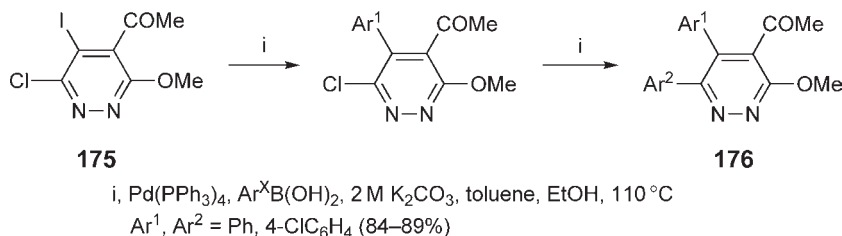
(32)

i, $\text{Pd}(\text{PPh}_3)_4$, $\text{ArB}(\text{OH})_2$, 2 M Na_2CO_3 , toluene, reflux

Table 8 Suzuki reactions on 3-(alkyl)amino-6-halopyridazines

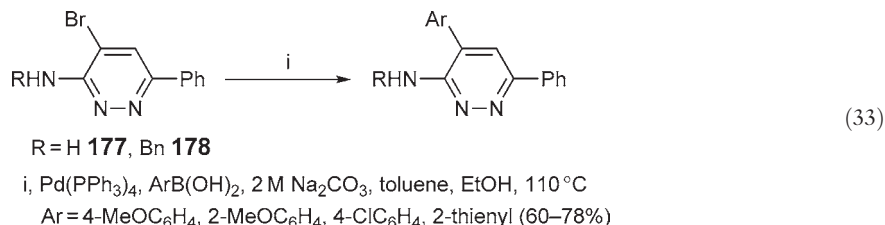
R^1	R^2	X	Ar	Yield (%)	Reference
H	H	Cl	Ph	69	2000T1777
H	H	Cl	4- FC_6H_4	84	2000T1777
H	H	Cl	4-MeOC $_6\text{H}_4$	78	2000T1777
H	H	Cl	3-Thienyl	74	2000T1777
H		Cl	Ph	40	1999S1163
H		Cl	2-MeOC $_6\text{H}_4$	45	1999S1163
H		Cl	3,5-(CF_3) $_2\text{C}_6\text{H}_3$	50	1999S1163
Me	Me	I	Ph	58	1995JOC748

Besides 3-chloro-6-iodopyridazine, selective Suzuki reaction was also studied on 4-acetyl-6-iodo-3-methoxy-pyridazine **175** (Scheme 42) <1995JHC1057>. C-5 Selective arylation could be achieved using a slight excess of arylboronic acid while a large excess of organometallic compound easily gave access to 4-acetyl-5,6-diaryl-3-methoxy-pyridazine **176** if desired.

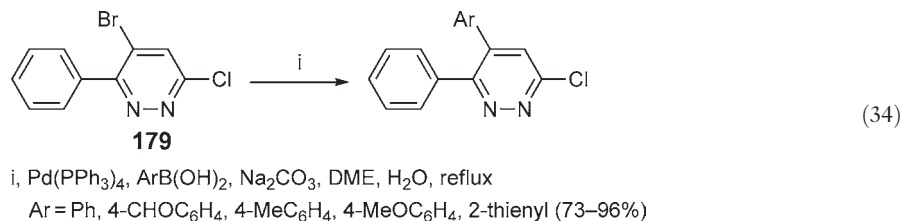


Scheme 42

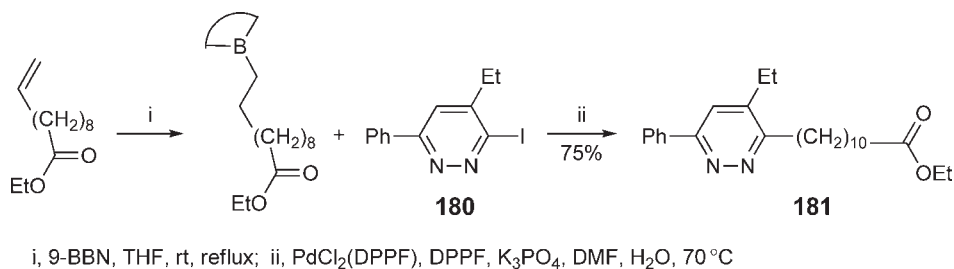
There are also other examples where a halogen atom in the 4- or 5-position of the nucleus is involved in a Suzuki reaction <2002SL223, 2003SL1482>. The *ortho*-brominated pyridazinamines 4-bromo-6-phenylpyridazin-3-amine **177** and *N*-benzyl-4-bromo-6-phenylpyridazin-3-amine **178** are especially interesting since, as observed for 6-halo-pyridazin-3-amines, no protection of the primary or secondary amino group is required (Equation 33) <2003SL1482>.



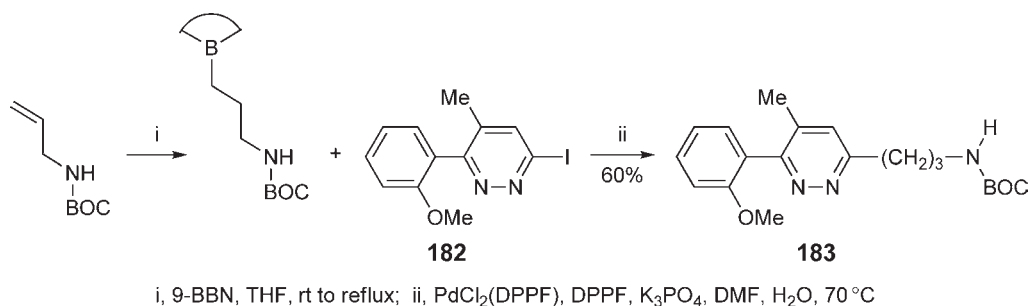
Suzuki reaction on 4-bromo-6-chloro-3-phenylpyridazine **179** shows that selectivity can also be achieved between a bromine and a chlorine atom and there is no requirement to have an iodine and chlorine atom on the skeleton (Equation 34) <2002SL223>.



While the introduction of aryl groups has been well documented, the use of alkylboronic acids to decorate the pyridazine core is hitherto not well explored. Wermuth and co-workers nicely showed that hydroboration of alkenes with 9-BBN followed by Suzuki coupling with 3-iodopyridazines **180** and **182** yielded the corresponding 3-alkylpyridazines **181** and **183** in good yield (Schemes 43 and 44) <2002SL1123>.

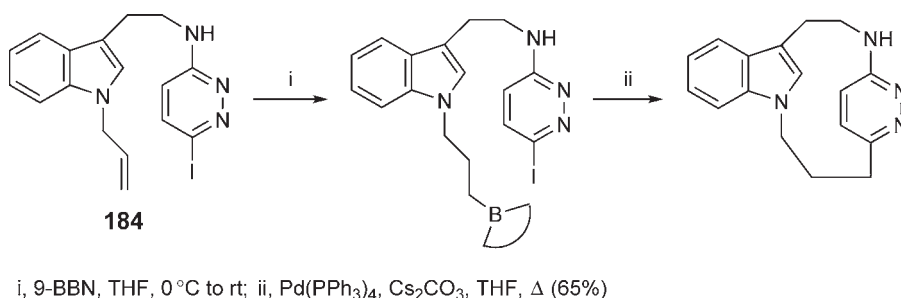


Scheme 43



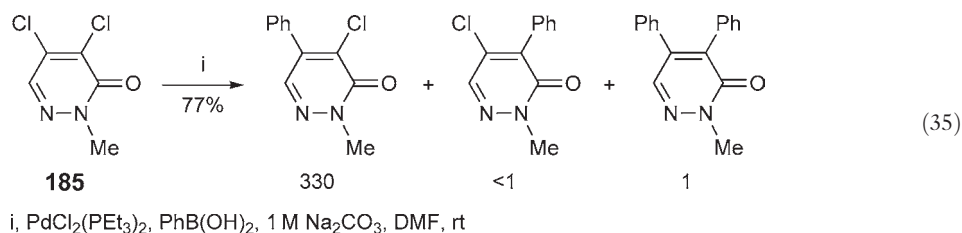
Scheme 44

Similarly, while exploring a route toward the synthesis of strychnine, Bodwell and Li reported hydroboration of *N*-[2-(1-allyl-1*H*-indol-3-yl)ethyl]-6-iodopyridazin-3-amine **184** followed by intramolecular Suzuki reaction (Scheme 45) <2002AGE3261>.

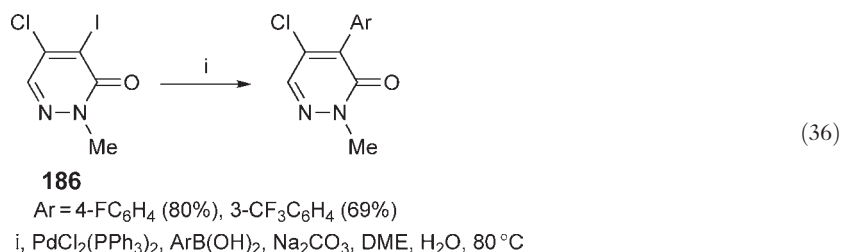


Scheme 45

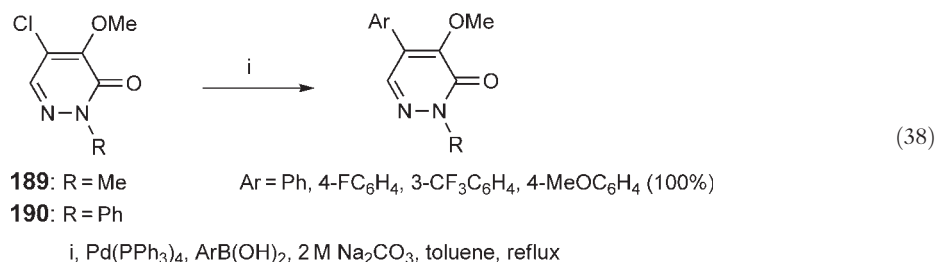
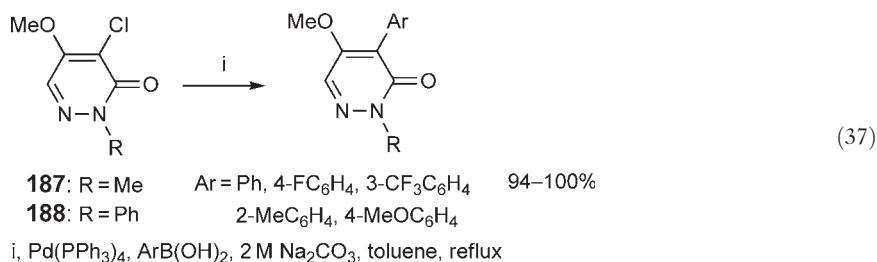
Easily accessible *N*-2-substituted 4,5-dichloro- <2001T1323> and 4,5-dibromopyridazin-3(2*H*)-ones <2005JHC427> were also used as substrates. Unfortunately, selective monoarylation proved to be impossible under standard Suzuki or Gronowitz conditions. Interestingly, a detailed study by Gong and He revealed that selective C-5 coupling of 4,5-dichloro-2-methylpyridazin-3(2*H*)-one **185** with phenylboronic acid could be achieved if Pd(PET₃)₂Cl₂ in DMF and 1 M Na₂CO₃ as base at room temperature were used as reaction conditions (Equation 35) <2004H(62)851>. An important feature to achieve high mono (versus di) selectivity is the use of a twofold excess of pyridazin-3(2*H*)-one versus boronic acid. Unfortunately, the generality of these carefully optimized reaction conditions for the introduction of other aryl groups was not studied.



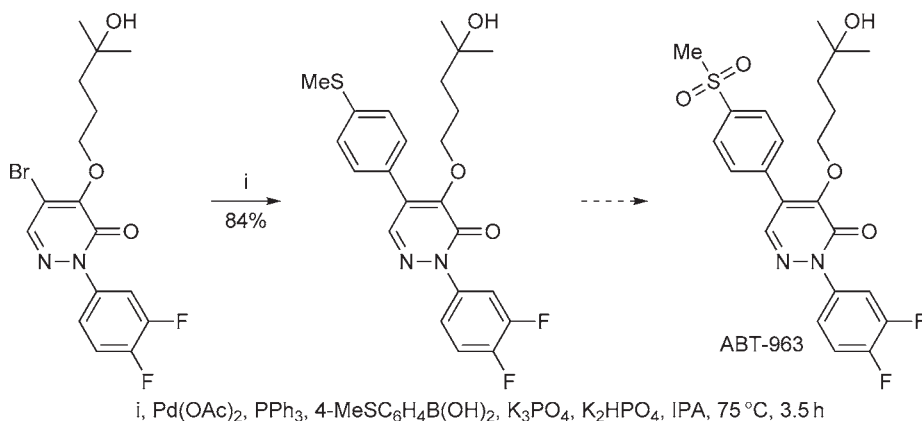
4-Arylated 5-chloro-2-methylpyridazin-3(2*H*)-ones could be accessed regioselectively by exploiting the difference in reactivity of the C–Cl and the C–I bond of **186** in an oxidative addition reaction (Equation 36) <2005JHC427>.



The selectivity problem on 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones has also been solved in another way. Mátyus, Maes, and Riedl introduced the concept of ‘provisionally masked functionalities’ (PMFs) [<2004SL1123>](#). A PMF is a functional group that can be easily introduced in the 4- or 5-position of the pyridazin-3(2*H*)-one in a completely regioselective way and is not reactive in Pd catalysis. After the Pd-catalyzed reaction, involving the remaining C–X, the PMF should be easily substituted directly or after transformation into a better leaving group. The methoxy group proved to fulfil these requirements and **187–190** are ideal substrates ([Equations 37 and 38](#)). The principle easily allows the preparation of several pyridazino-fused ring systems (see [Section 8.01.11.2](#)).

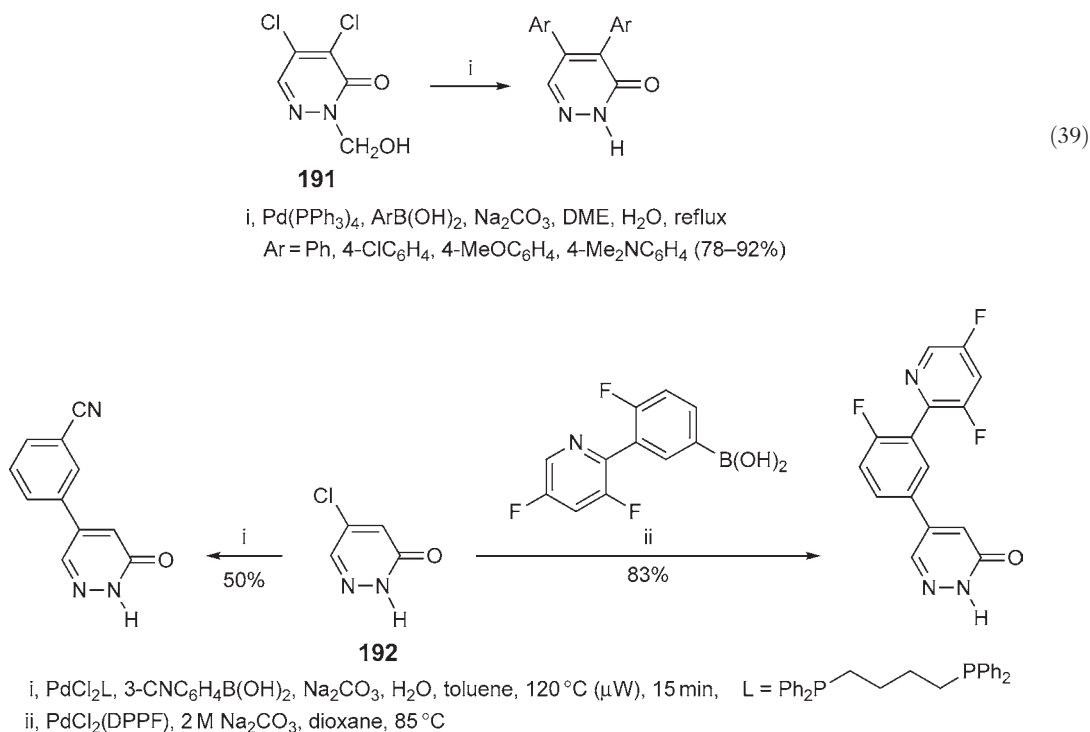


Of course, in some cases a desired substituent can immediately be introduced via a selective substitution on the 4,5-dihalopyridazin-3(2*H*)-one, followed by Suzuki reaction as exemplified by the multikilogram synthesis of the selective COX-2 inhibitor ABT-963 ([Scheme 46](#)) [<2006OPD512>](#).



Scheme 46

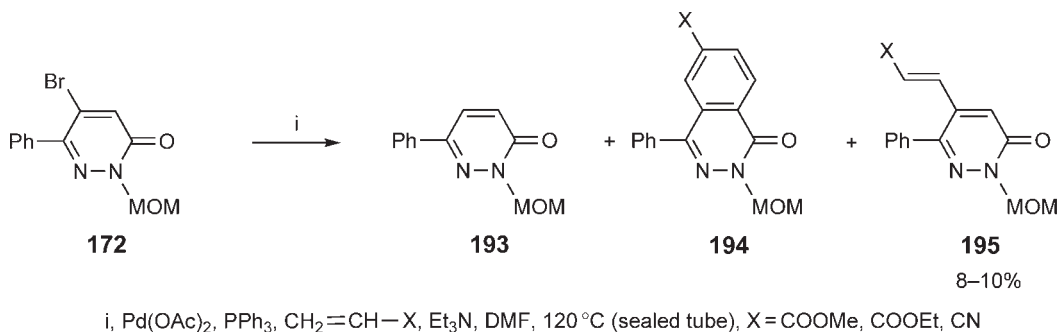
While a hydroxymethyl group has been successfully used to temporarily block the lactam nitrogen of halopyridazin-3(2*H*)-ones such as **191** for Suzuki reactions <2003TL4459>, and the resulting aryl-2-hydroxymethylpyridazin-3(2*H*)-ones have been immediately deprotected *in situ* via a base-induced or thermal retro-ene reaction (Equation 39), two recent reports show that Suzuki reaction on unprotected substrates like 5-chloropyridazin-3(2*H*)-one **192** is feasible (Scheme 47) <2005JME6004, 2006JME2600>.



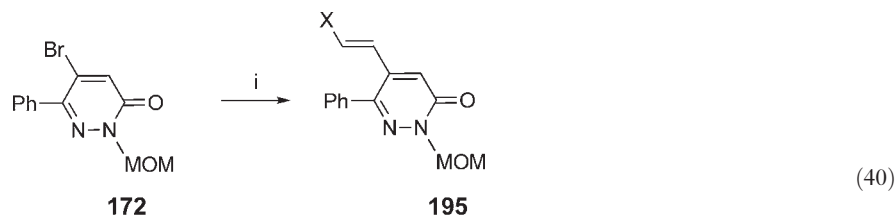
Scheme 47

8.01.7.15.2(v) Heck reaction

Only a very limited number of examples of Heck reactions on halopyridazin-3(2*H*)-ones have been reported and no examples on the corresponding halopyridazines. Heck reaction of 5-bromo-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-one **172** with alkyl acrylates and acrylonitrile gave a mixture of desired reaction product **195**, dehalogenated substrate **193**, and a phthalazin-1(2*H*)-one **194** (Scheme 48) <2004TL3459>. The formation of the substituted phthalazin-1(2*H*)-one **194** can be rationalized via a tandem Pd-catalyzed process. When PPh₃ was substituted for P(*o*-tolyl)₃ as the ligand of the catalyst, the formation of the desired 5-alkenyl-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-ones **195** was favored (Equation 40). Besides a MOM group the hydroxymethyl group was also used as protecting group <2004BML321>.



Scheme 48



i, $\text{PdCl}_2[\text{P}(\text{o-tolyl})_3]_2$, $\text{CH}_2=\text{CH}-\text{X}$, Et_3N , DMF
 120 °C (sealed tube)
 X = COOMe (70%), COOMe (73%), CN (40%), Ph (50%)

8.01.7.15.2(vi) Sonogashira reaction

In 1995, Bailey showed that several 6-substituted 3-iodopyridazines **196** could be coupled with alkynes at room temperature (Equation 41 and Table 9) <1995JOC748>. When strong electron-releasing C-6 substituents are present, and the presence of an iodine atom allows very mild reaction conditions in comparison with reactions on the corresponding chlorinated substrates. Selective C-6 Sonogashira reaction is reported on 3-chloro-6-iodopyridazine **174**, but unfortunately only low yields of 6-alkynyl-3-chloropyridazine **197** were obtained (Equation 42) <1999T15067>. Dialkynylation of 3,6-diiodopyridazine has also been studied <2002HCA2195>.

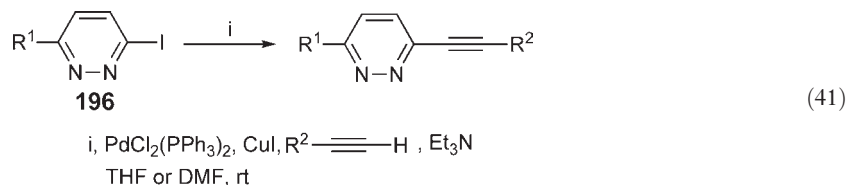
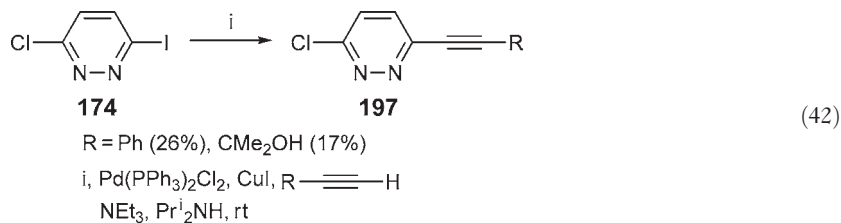
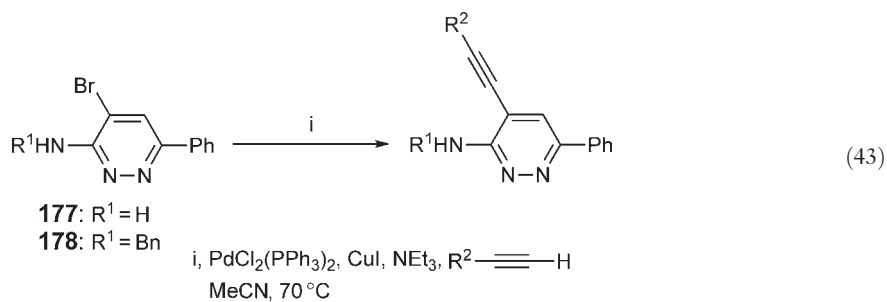


Table 9 Sonogashira reactions on 6-substituted 3-iodopyridazines

R^1	R^2	Yield (%)
MeO	CH_2OH	93
MeO	Ph	67
NMe_2	CH_2OH	85
NMe_2	Ph	85
F	CH_2OH	64

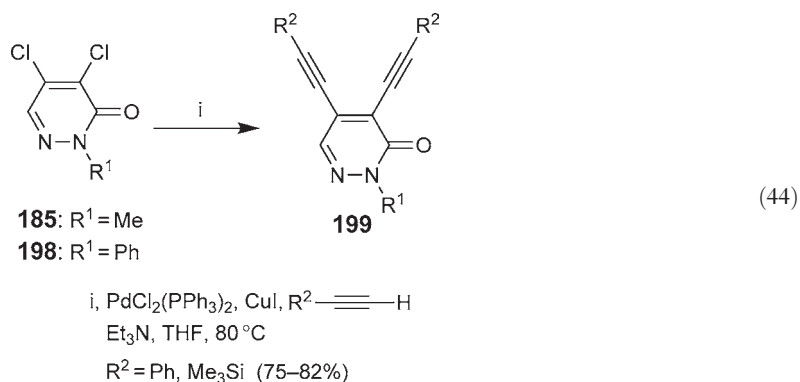


4-Bromo-6-phenylpyridazin-3-amine **177** and *N*-benzyl-4-bromo-6-phenylpyridazin-3-amine **178** which have been used successfully in Suzuki reactions could also be alkynylated via Sonogashira reactions (Equation 43 and Table 10) <2003SL1482>.

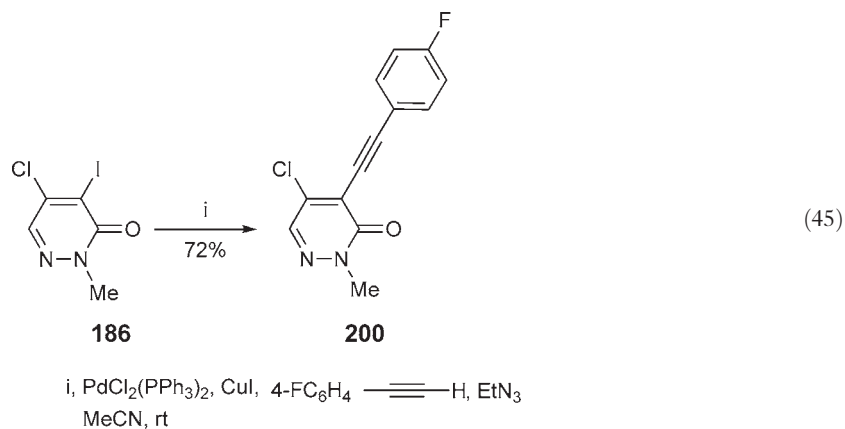
**Table 10** Sonogashira reactions on **177** and **178**

R^1	R^2	Yield (%)
H	Me_3Si	88
H	Ph	65
Bn	Ph	79
Bn	$(\text{CH}_2)_3\text{OBn}$	40

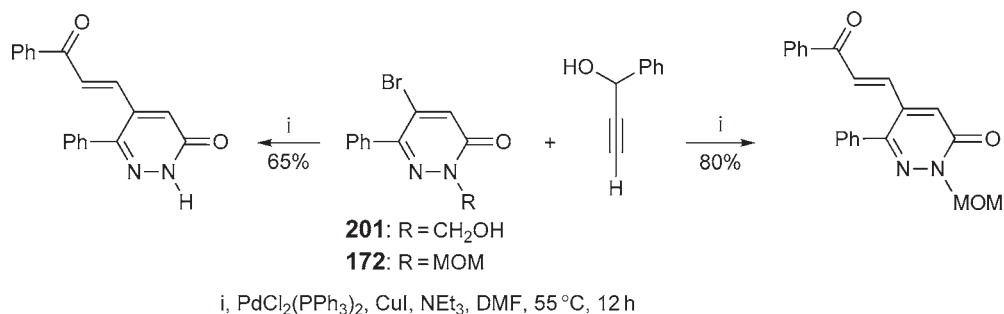
Sonogashira reactions on 2-substituted 4,5-dihalo-1H-pyridazin-3(2H)-ones **185** and **198** were not reported before 2001 <2001T10009>. Selective substitution proved impossible but 2-substituted 4,5-dialkynylpyridazin-3(2H)-ones **199** were easily obtained (Equation 44).



5-Chloro-4-[(4-fluorophenyl)ethynyl]-2-methylpyridazin-3(2H)-one **200** could be accessed regioselectively if 5-chloro-2-methyl-4-iodopyridazin-3(2H)-one **186** was used as coupling partner (Equation 45) <2005JHC427>.



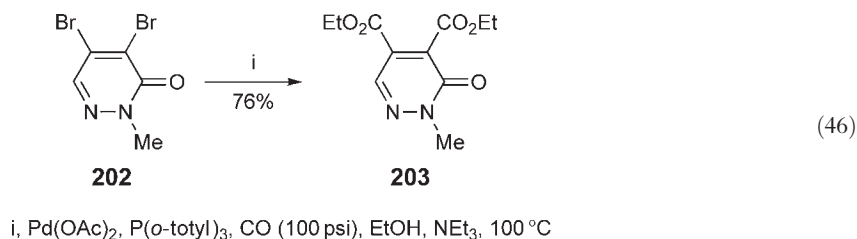
A methoxymethyl (as in **172**) and hydroxymethyl (as in **201**) group has been used to protect the lactam nitrogen for Sonogashira reactions (Scheme 49) <2002SL2062, 2004BML321>. While there are two reports dealing with successful Suzuki reactions on halopyridazin-3(2*H*)-ones without the presence of a protection group <2005JME6004, 2006JME2600>, no such cases have been reported yet for Sonogashira reactions. Interestingly, when 1-phenylprop-2-yn-1-ol was used as alkyne, a tautomeric (1*E*)-3-oxo-3-phenylprop-1-en-1-yl substituent could be introduced on the nucleus <2003T2477, 2004BML321>. This isomerization to the (*E*)-chalcone occurs via an *in situ* base-catalyzed mechanism.



Scheme 49

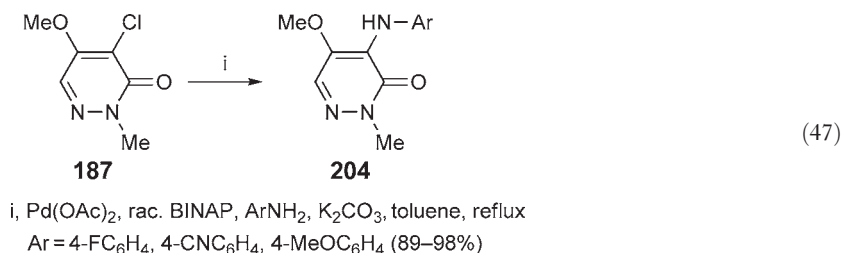
8.01.7.15.2(vii) Carbonylations

Ethoxycarbonylation of 4,5-dibromo-2-methylpyridazin-3(2*H*)-one **202** under a high CO pressure in EtOH yielded diethyl 1-methyl-6-oxo-1,6-dihydropyridazine-4,5-dicarboxylate **203** (Equation 46) <2005JHC427>. Surprisingly, aldehyde and ketone formation making use of Pd-catalyzed reactions involving CO insertion has not been studied yet.



8.01.7.15.2(viii) Buchwald–Hartwig amination

Maes and Košmrlj investigated the usefulness of Pd-catalyzed aminations on 2-methyl 4-chloro-5-methoxypyridazin-3(2*H*)-one **187** and 2-substituted 5-chloro-4-methoxypyridazin-3(2*H*)-ones **189–190** with anilines since a direct nucleophilic substitution was not possible on these substrate types. Interestingly, this yielded the corresponding arylamino derivatives **204–205** in excellent yields if a large excess of carbonate base was used (Equations 47, 48, and Table 11) <2000SL1581>. Later, applying the same protocol other pyridazin-3(2*H*)-one substrates were also tackled <2004T2283>.





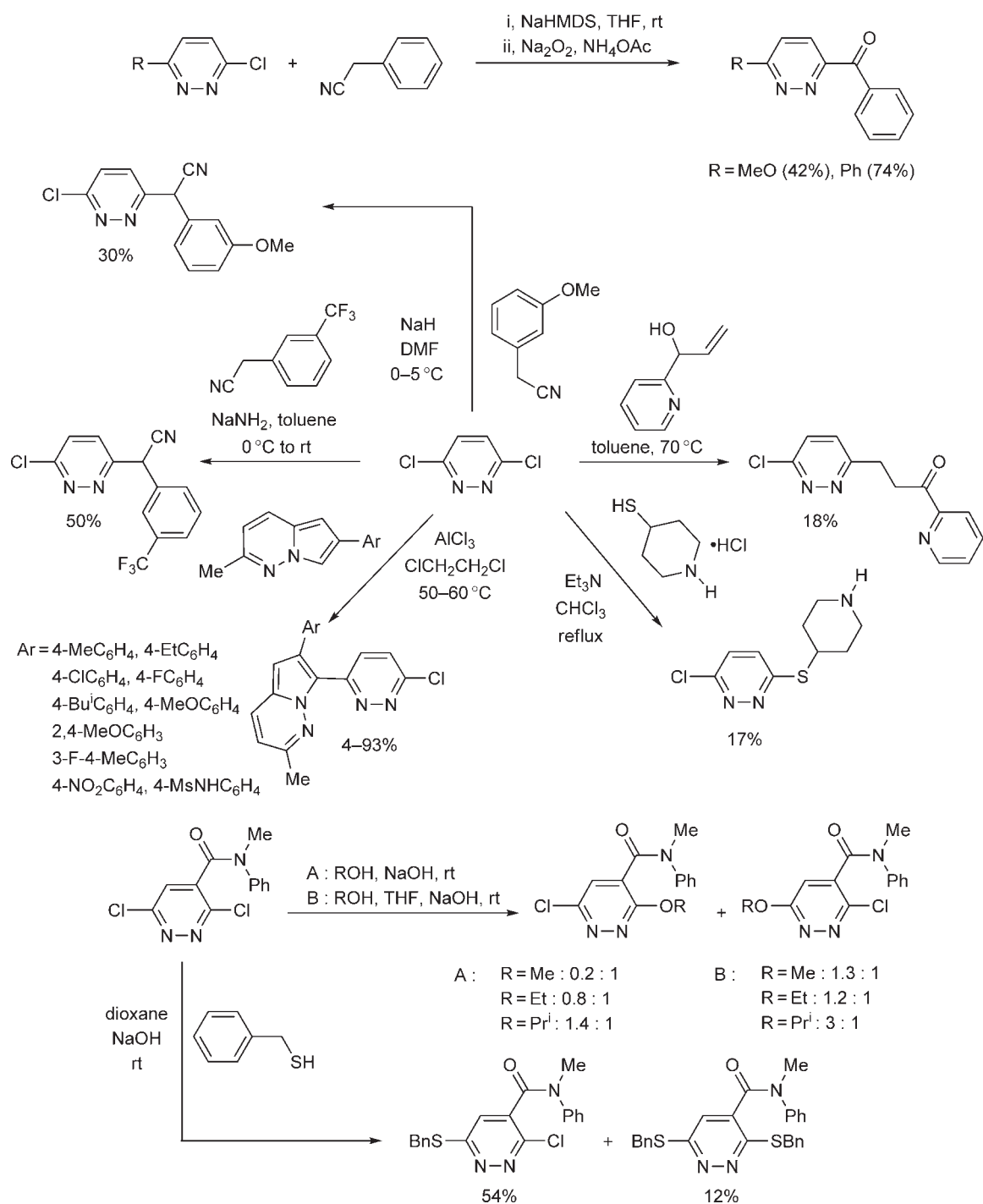
<i>R</i>	<i>Ar</i>	<i>Yield (%)</i>
Me	4-FC ₆ H ₄	99
Me	4-CN C ₆ H ₄	99
Ph	4-FC ₆ H ₄	98

i, Pd(DPPF)Cl₂, DPPF, RNH₂, NaOt-Bu, 1,4-dioxane
 80 °C, 6 h

R = , Bn ,

75% 80% 70%

Nucleophilic aromatic substitution on halo-1,2-diazines (mainly chlorine) with O, N, S, and even C nucleophiles is a very well explored field and also covered in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>. The many examples available in the literature (including the last decade) are obvious when one takes into account the fact that many dihalo-1,2-diazines are readily available through synthesis or even commercially (e.g., 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones, 3,6-dichloropyridazine, 1,4-dichlorophthalazine, and 3-chloro- and 4-chlorocinnoline). Aspects of selectivity in S_NAr reactions on dihalo-1,2-diazines were also incorporated in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)1, 1996CHEC-II(6)1>. **Scheme 50** <2004JOC1364, 2004TL2113, 1996H(43)151, 1997H(45)2385, 2002EJM339, 1999CCC363, 2002T9933, 1999H(51)617, **Scheme 51** <2001JHC1179, 2001JME2118, 1999JHC905, 2006OPD512, 2004T2283, 2002H(57)2115, 2006BML1080> and **Scheme 52** <2003JOC6806, 2005BML4696, 2001S699, 2004T7983, 1999JME5369, 2004BMC795, 2000BML2235, 2000JME2523> summarize some new selected examples of S_NAr on halopyridazines, halopyridazin-3(2*H*)-ones, and halocinnolines/halophthalazines, respectively. Especially interesting to mention is a fundamental study of Gillies and Rees. They found that substitution of the chlorine atom in 6-chloropyridazin-3-amine and 4-chlorophthalazin-1-amine for alkoxide, which are slow and low yielding reactions, can be smoothly performed when the amino group is transformed into an acetamide. The acetamido anion seems to act as an activator (**Scheme 53**) <1996TL4065>.



Scheme 50

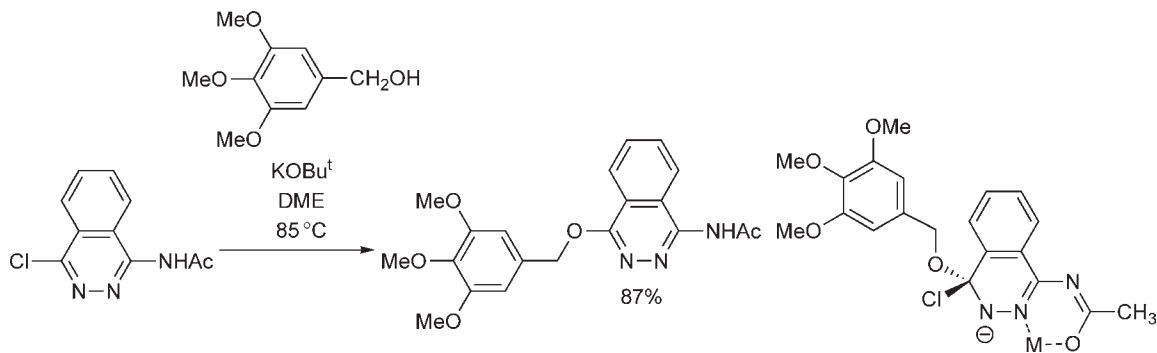
There are also examples where intended substitution of a halogen does not lead to the desired reaction product. For instance, Haider reported that reaction of 1-chloro-4-methyl-5H-pyridazino[4,5-b]indole with hydrazine (solvent and nucleophile) gave 4-methyl-5H-pyridazino[4,5-b]indole in 50%. Mechanistically, the initially formed hydrazine is oxidized by air oxygen under the $\text{S}_\text{N}\text{Ar}$ reaction conditions (oxidative dehydrazination) yielding reduced compound. Interestingly, by exclusion of oxygen the desired hydrazino-substituted compound could be obtained in 99% yield



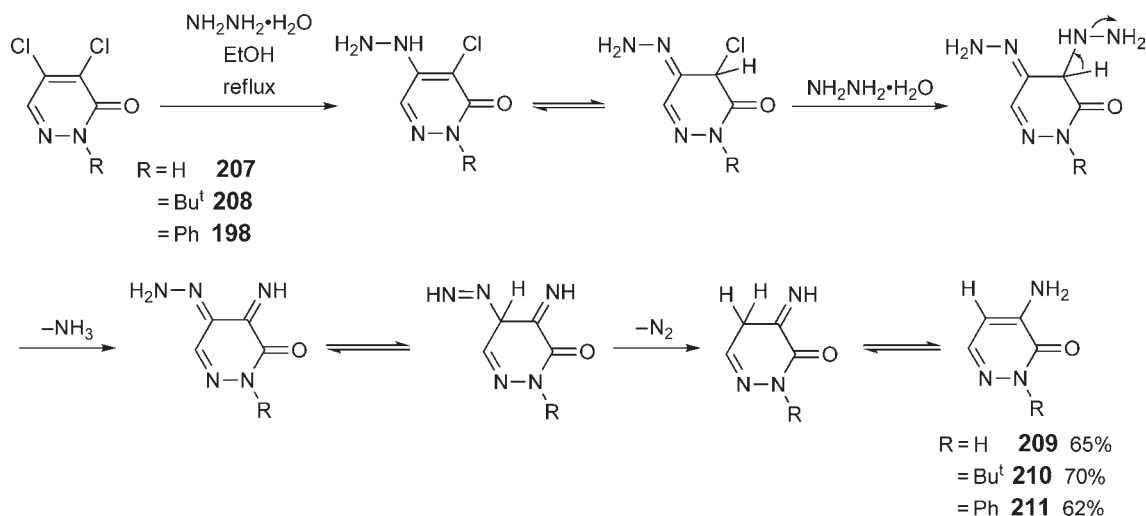


Scheme 52

<2004MOL849>. Also reaction of 4,5-dichloropyridazin-3(2*H*)-ones (**198**, **207**, and **208**) with hydrazine in refluxing ethanol gave unexpected results. While initially the expected 4-chloro-5-hydrazinopyridazin-3(2*H*)-ones were formed, prolonged heating gave 4-aminopyridazin-3(2*H*)-ones **209–211** (Scheme 54) <2001CL54>.



Scheme 53



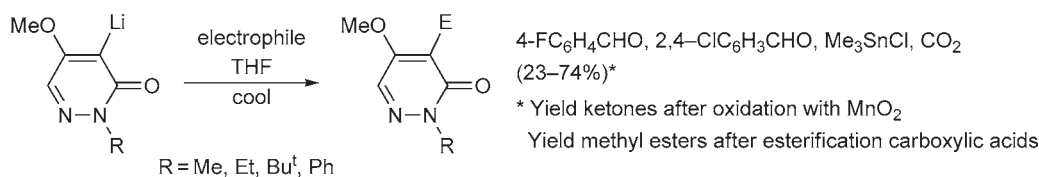
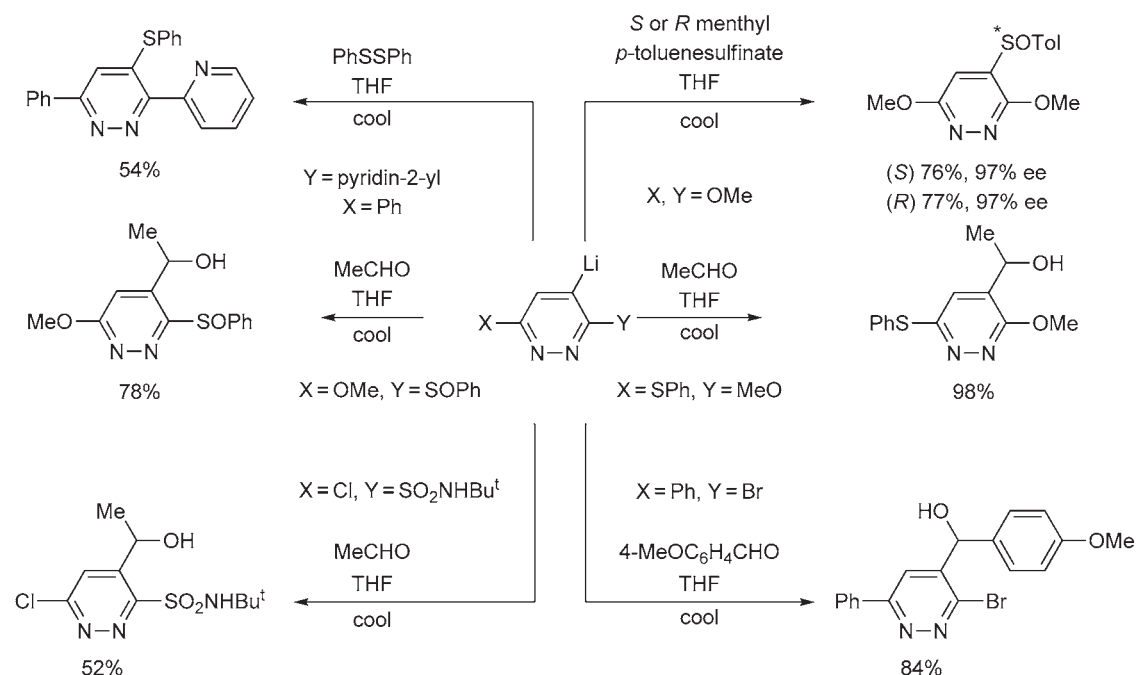
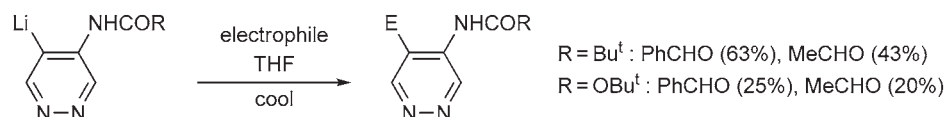
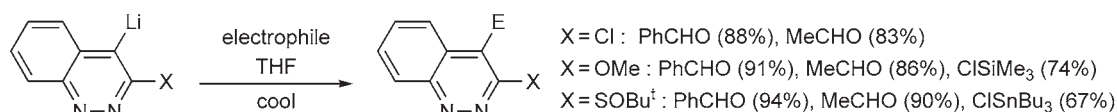
Scheme 54

Although transhalogenation on chloro-1,2-diazines received already some attention before 1995 the interest certainly increased since then. Mainly, chlorine–iodine exchange has been studied. The importance of the iodo-1,2-diazine class can be mainly attributed to their well-known higher reactivity in the oxidative addition reaction of Pd-catalyzed cross-couplings. Reaction of 3,6-dichloropyridazine with aq HI (55%)/ICl yielded 75% 3,6-diiodopyridazine <1999JHC1135>. Selective transformation into 3-chloro-6-iodopyridazine has also been achieved (see Section 8.01.11.1). Heating 4,5-dichloropyridazin-3(2*H*)-ones in aq HI (57%) gave the corresponding 5-iodopyridazin-3(2*H*)-ones (note the reduction) (see Section 8.01.11.1). There are also reports of transhalogenation without the use of mineral acid. Reaction of 4,5-dichloro-2-methyl-6-nitropyridazin-3(2*H*)-one with NaI in DMF at reflux gave 4-iodo-2-methyl-6-nitropyridazin-3(2*H*)-one in 25% yield. Note that in this case reductive deiodination occurs in C-5 and not in C-4. Theoretical calculations supported that the more electron-deficient iodo atom of the initially formed 4,5-diiodopyridazinones undergoes reductive deiodination since in this way the more stable anionic intermediate is obtained. Substituents on the pyridazinone core as well as protonation, when one works in acid, are governing factors in this reduction process <2005JMT(713)235>. ¹²³I labeling can also be the area of interest as exemplified by the transhalogenation reaction performed on 3-benzamidomethyl-6-bromo-2-(4-*t*-butylphenyl)imidazo[1,2-*b*]pyridazine with Na¹²³I. In this case Cu(I) was added to assist the bromine–iodine exchange. The reaction was performed at 200 °C using Na₂S₂O₅ as reducing agent <2004MI305>. Finally, Pommelet and Lequeux investigated fluorination

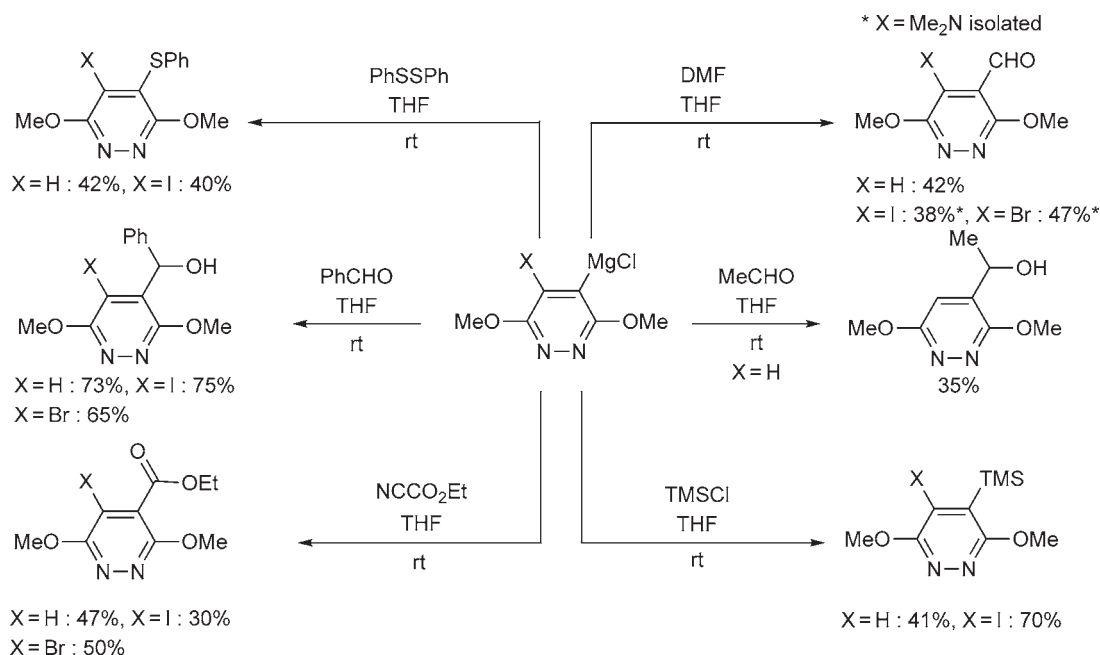
8.01.7.16 Metals and Metalloid Derivatives



X = Cl : MeCHO (89%), MeI (86%), I₂ (70%), CO₂ (57%)
 X = OMe : MeCHO (81%), MeI (34%), I₂ (77%), HCO₂Et (57%)
 X = 4-CF₃C₆H₄ : ClSiMe₃ (96%)



Scheme 55



Scheme 56

1997JHC621, 1998JHC429, 1999JOC4512, 2000T265, 2000T5499, 2005JHC509, 2005T8924, 2005T9637, 2005JHC427>. Besides classical lithium–trimethylsilyl or tributylstannyl, other metal–metal exchanges proved also useful. Tin–lithium exchange, a common procedure for vinyltin, has been investigated on 4-tributylstannylpyridazine. For the exchange BuLi in a mixture of Et₂O/THF at –80 °C was used. Quenching of the 4-lithiated pyridazine with Me₃SiCl, Ph₂PdCl, and PhSeBr as electrophiles gave the corresponding substituted pyridazines in 30–40% yield <1997TL5791>. Trimethylsilyl–tributylstannyl exchange is also possible using (Bu₃Sn)₂O and tetrabutylammonium fluoride (TBAF) in THF <2000TL781>. As already mentioned in Sections 8.01.5.5.1 and 8.01.7.15.1, lithium–zinc exchange has been investigated in the pyridazine series.

Although not many representatives are known, pyridazinylzinc halides as well as trialkylstannylpyridazines and pyridazinylboronic esters have been used as organometallic partners in Pd-catalyzed cross-coupling reactions <1997TL5791, 1998H(49)205, 1998T4297, 2000TL781, 2001BMC2683, 2005AGE3889, 2005JHC427>.

Electrophilic substitution of silylated pyridazines has been reported. Reaction of 6-chloro-3-methoxy-4-trimethylsilylpyridazine with benzaldehyde, acetaldehyde, and propanal in THF at room temperature yielded the corresponding secondary alcohols in good yields. TBAF was used as desilylating agent in these reactions <1995JHC1057>. A similar procedure was used on 6-chloro-2-phenyl-7-trimethylsilyl-1,2,4-triazolo[4,3-*b*]pyridazine. In this case [BuN₄][Ph₃SnF₂] was selected as catalytic fluoride source. In a reaction with (BrF₂C)₂, using the same fluoride source, bromine was smoothly introduced. A tributylstannyl group on a 1,2-diazine nucleus can be replaced by a halogen via reaction with elemental halogens <1998T4297>. The masked anion properties of a trimethylsilyl group were also used to introduce a methoxycarbonyl entity on 6-chloro-2-phenyl-7-trimethylsilyl-1,2,4-triazolo[4,3-*b*]pyridazine. Here a stoichiometric amount of [(Me₂N)₃S][Me₃SiF₂] as fluoride source was required and methyl cyanofornate was used as electrophile <2000TL781>.

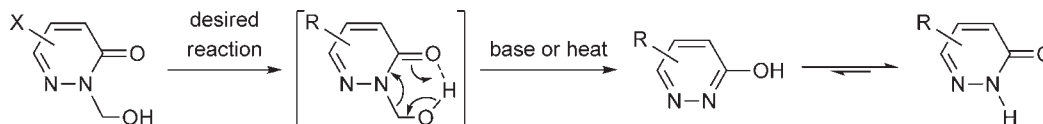
8.01.8 Reactivity of Substituents Attached to Ring Nitrogens

While this part was only briefly addressed in CHEC(1984) <1984CHEC(2)1>, it substantially expanded in CHEC-II(1996) <1996CHEC-II(6)1>. Since 1995 interesting advances have been made in this area and therefore new sections have been included in this edition.

8.01.8.1 N-Alkyl Groups

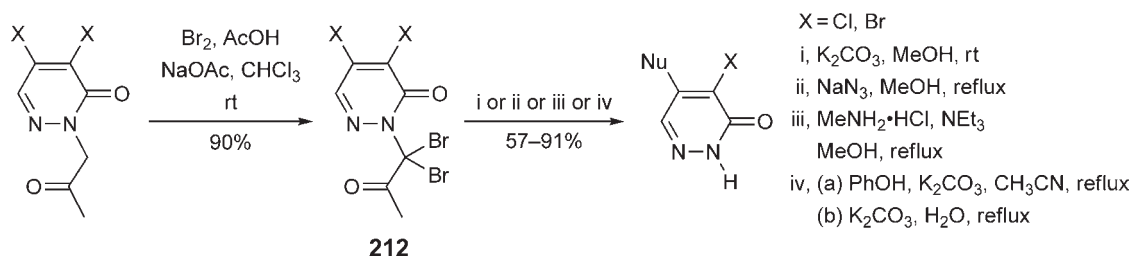
Important advances have been made in the identification of suitable N-2 protection groups for pyridazin-3(2*H*)-ones since CHEC-II(1996) appeared <1996CHEC-II(6)1>.

The most attractive protecting group to block the N-2 of a pyridazin-3(2*H*)-one currently available surely is a hydroxymethyl group as it can easily be introduced and no separate deprotection step is required. After the desired reaction, deprotection immediately occurs via base or a thermally induced retro-ene reaction in a tandem fashion (Scheme 57). The foundations for this were laid by Mátyus and appeared already in 1993 <1993H(36)519>. The concept was matured to a synthetically useful method by Yoon (see also Section 8.01.5.5.5). Examples of the use of the hydroxymethyl protecting group include substitution reactions of nitrogen, oxygen, and sulfur nucleophiles on 4,5-dihalo-2-hydroxymethylpyridazin-3(2*H*)-ones <1999JHC277>. Sotelo used this approach for the temporary N-2 protection of several halogenated pyridazin-3(2*H*)-ones in Pd-catalyzed reactions. Several examples of the latter can be found in Section 8.01.7.15.2. A drawback of the 2-hydroxymethylpyridazin-3(2*H*)-ones is that they have to be carefully stored as they are not very stable. Therefore as an alternative an 1-acetyloxymethyl group has been used <1999JHC413>.



Scheme 57

A 2-oxopropyl group is another reported protective group. Dibromination affords 2-(1,1-dibromo-2-oxopropyl)pyridazin-3(2*H*)-ones. Reaction of 2-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-3(2*H*)-ones **212** with nitrogen and oxygen nucleophiles gave tandem substitution and deprotection <1998JHC595> (Scheme 58). For the introduction of a phenoxy group (or *para*-substituted derivatives), a separate deprotection step was required.

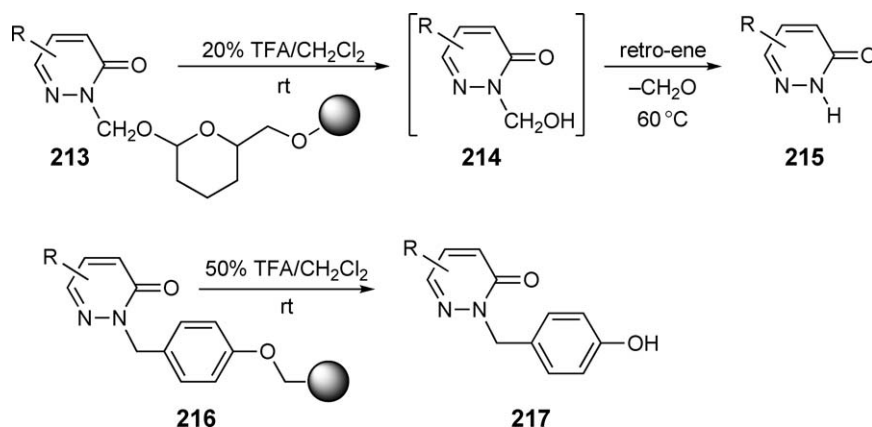


Scheme 58

Already for a long time the benzyl and tetrahydropyranyl groups are known as reliable protecting groups (see also Section 8.01.5.5). New examples appeared <1995JHC1473, 2002T5645, 2003T5919, 2004H(63)75> even performed on a very large scale. For the removal of the latter, Brønsted (aq HCl) as well as Lewis acids (BF₃) were used. Heating with AlCl₃ in toluene is a reliable method to remove a benzyl group.

Solid-phase linkage of pyridazin-3(2*H*)-ones via the N-2 atom also appeared (see also Section 8.01.5.5.2). In the reported examples, the linker has a double role as it is also used as a protecting group, providing a smooth way to access many substituted pyridazin-3(2*H*)-ones. Deprotection of **213** (based on Ellman's resin) with trifluoroacetic acid (TFA) in CH₂Cl₂ for instance yields 2-hydroxymethylpyridazin-3(2*H*)-ones **214** which undergo retro-ene reaction yielding the desired pyridazin-3(2*H*)-ones **215** <2003SL1113> (Scheme 59). Pyridazin-3(2*H*)-ones **216** linked with a Wang resin via N-2 are unfortunately not very useful as upon treatment with TFA in CH₂Cl₂ 2-(4-hydroxybenzyl)pyridazin-3(2*H*)-ones **217** are obtained. In contrast, when linkage with the C-3 oxygen of pyridazin-3(2*H*)-ones was tested, smooth cleavage occurred <2005JCO414>.

Besides removal of alkyl-based groups located at the N-2 of a pyridazin-3(2*H*)-one also 'real' reactions in the side chain appeared. Pyridazinium ylides, obtained via deprotonation of *N*-alkylpyridazinium salts, have been reacted with phenyl isocyanates and benzenediazonium salts <2002MI287, 1997T4411>. As discussed in Section 8.01.5.7.2 1,3-dipolar cycloaddition with ethyl acrylate and ethyl propiolate were also studied.



Scheme 59

8.01.8.2 *N*-Chloro

The synthesis of 2-chloropyridazin-3(2*H*)-ones has been discussed in [Section 8.01.5.5.5](#). They can be used as mild electrophilic chlorinating agents for active methylene compounds in the presence of acids in water or Lewis acids in CH_2Cl_2 [<2005S1136>](#).

8.01.8.3 *N*-Nitro

The synthesis of 2-nitropyridazin-3(2*H*)-ones has been discussed in [Section 8.01.5.5.5](#). These compounds showed excellent nitro group transfer properties allowing the *N*-nitration of secondary amines under mild neutral conditions [<2003JOC9113>](#).

8.01.8.4 *N*-Acyl

The synthesis of 2-acylpyridazin-3(2*H*)-ones has been discussed in [Section 8.01.5.5.3](#). These compounds have been used as mild acylating reagents for amines [<2002S733>](#). Symmetrical and unsymmetrical 1,3,4-oxadiazoles were also synthesized starting from these 2-acyl(or aroyl)pyridazin-3(2*H*)-ones [<2003S560>](#).

8.01.8.5 *N*-Sulfonyl

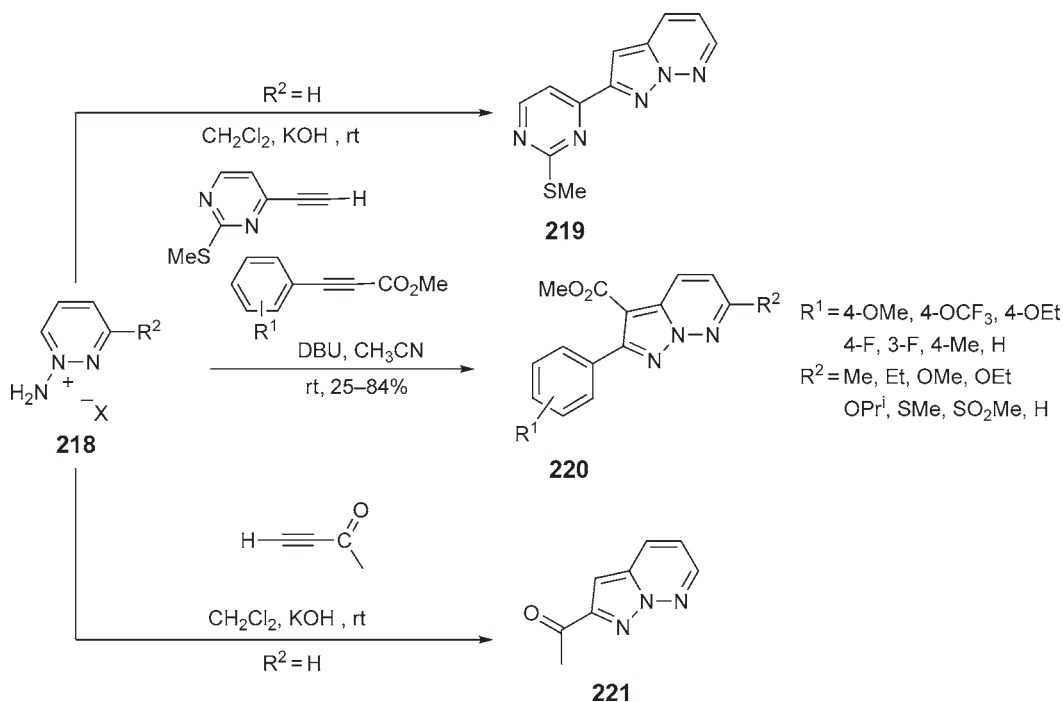
The synthesis of 2-benzenesulfonylpyridazin-3(2*H*)-ones has been discussed in [Section 8.01.5.5.4](#). They can be used to prepare *N*-alkylbenzenesulfonamides via reaction with aliphatic amines [<2002JHC203>](#). 4,5-Dichloro-2-[(4-nitrophenyl)sulfonyl]pyridazin-3(2*H*)-one proved to be useful for the preparation of carboxylic anhydrides from the corresponding acids in the presence of base in THF or CH_2Cl_2 [<2003S1517>](#).

8.01.8.6 *N*-Amino

1-Aminopyridazinium salts **218** proved to be useful as reagents for the construction of pyrazolo[1,5-*b*]pyridazines **219-221** via 1,3-dipolar cycloaddition with acetylenes ([Scheme 60](#)) [<2004BML5445, 2004JME4716>](#). For other 1,3-dipolar cycloaddition reactions, see [Section 8.01.5.7.2](#).

8.01.8.7 *N*-Oxide

Microbial deoxygenation of benzo[*c*]cinnolin-5-ium oxide with Bakers' yeast–NaOH in EtOH/water at reflux yielded 90% of benzo[*c*]cinnoline [<1997TL845>](#). The same deoxygenation has been achieved in a similar yield via heating in EtOH with NaOEt at 160°C in a sealed tube [<2004JOC7720>](#).



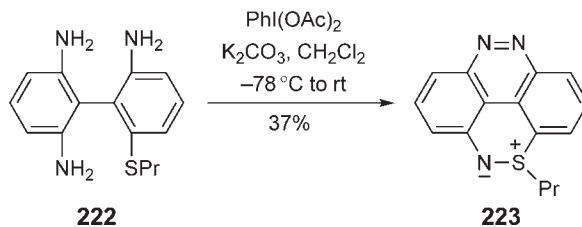
Scheme 60

8.01.9 Ring Synthesis

8.01.9.1 Formation of One Bond

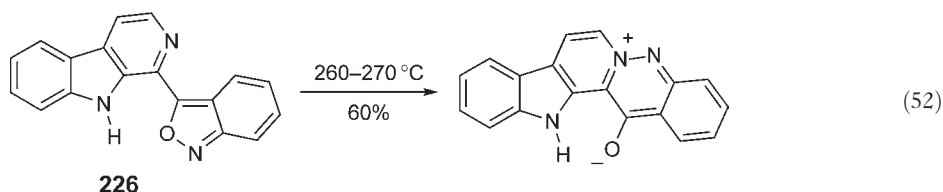
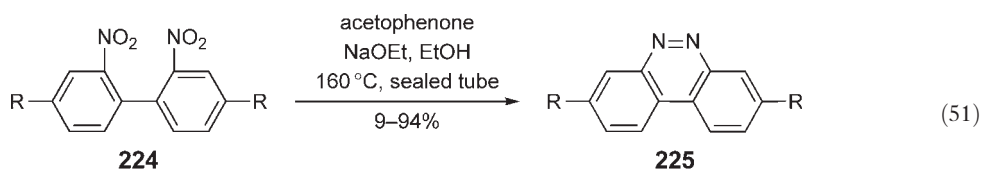
8.01.9.1.1 Between two heteroatoms

In CHEC(1984) <1984CHEC(2)1> the synthesis of pyridazine-1,2-dioxides via oxidative cyclization of unsaturated 1,4-dioximes was covered. The synthesis of tetrahydropyridazines via oxidation of the corresponding 1,4-diamines was also included. CHEC-II(1996) <1996CHEC-II(6)1> summarized the synthesis of benzo[*c*]cinnolines and their *N*-oxides and *N,N'*-dioxides from 2,2'-dinitrobiphenyls via reductive procedures. A recent addition in this field is the synthesis of 1,10-disubstituted benzo[*c*]cinnolines from 6,6'-disubstituted 2,2'-dinitrobiphenyls. The N–N bond formation via cyclization can be achieved by reaction with basic Raney nickel or with Zn/CaCl_2 –air both yielding the *N*-oxide as the primary reaction product. While there is evidence in the former case that 2-hydroxylamino-2'-nitrosobiphenyls are the intermediates allowing cyclization, Zn/CaCl_2 yields full reduction to the 2,2'-diaminobiphenyl compounds in the absence of air. This indicates that 2-hydroxylamino-2'-nitrosobiphenyls are either not formed during the reduction or are too short-lived under the reaction conditions to form the N–N bond. Upon contact of the 2,2'-diaminobiphenyls with air reoxidation occurs, finally yielding the corresponding benzo[*c*]cinnolines <2000JOC6388>. Oxidation of 2,2',6-triamino-6'-propylthiobiphenyl **222** with iodobenzene diacetate yielded a new tetracyclic ring system **223** (Equation 50) <2000JOC6388>. The cyclization of symmetrically 5,5'-disubstituted 2,2'-diaminobiphenyls to the corresponding benzo[*c*]cinnolines using iodobenzene diacetate as the oxidant was already disclosed in 1996 <1996J(P1)83>. Dibenzo[*c,h*]cinnolines have been obtained from 2-(2-nitrophenyl)-1-nitronaphthalenes via reduction with LiAlH_4 in THF <2003BMC1475>.



(50)

In 2004 Bjørsvik described the synthesis of symmetrically 3,8-disubstituted benzo[*c*]cinnolines **225** from the corresponding 4,4'-disubstituted 2,2'-dinitrobiphenyls **224**. For the cyclization acetophenone is used as reductant in a basic solution. Electron-releasing as well as -withdrawing substituents were tolerated. Only groups that can participate in the radical processes are not allowed (e.g., NH₂, COMe, CHO, and CH₂OH). Also in this case 2-nitroso-2'-hydroxylaminobiphenyls are assumed to be intermediates (Equation 51) <2004JOC7720>. Initially, the *N*-oxides are formed which are deoxygenated under the reaction conditions. NaOEt in EtOH is responsible for this deoxygenation reaction (see also Section 8.01.8.7). Reduction of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone with zinc dust and ammonium chloride in aqueous ethanol from 0°C to room temperature gave pyrrolo[1,2-*b*]cinnolin-10(5*H*)-one as the major compound <2000T9675>. The mechanism most probably proceeds via the nitroso compound. A new approach is based on thermolysis. Ring opening of the isoxazole ring of **226** yields a nitrene allowing a subsequent intramolecular reaction with the imine function of the pyridine moiety (Equation 52) <1996H(43)1887>.



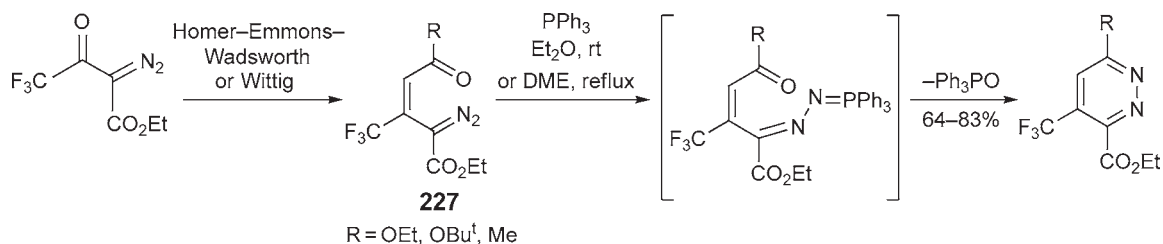
8.01.9.1.2 Adjacent to a heteroatom

CHEC(1984) <1984CHEC(2)1> particularly reviewed pyridazine ring construction by formation of a bond between the terminal nitrogen of hydrazones and an appropriately positioned cyano group or Michael acceptor. CHEC-II(1996) <1996CHEC-II(6)1> contained more examples of such a strategy. Additional examples mentioned include base-induced cyclization of a hydrazone of a 1-aryl-4-chlorobutan-1-one and attack of the terminal nitrogen of a hydrazone of a 2,3-dioxopentanedioate on the carbonyl of the ester function. Examples of the construction of the pyridazine unit of phthalazines and cinnolines were also covered in CHEC-II(1996) <1996CHEC-II(6)1>. Heating of the half amide hydrazide of 5-nitrophthalic acid in diethylene glycol gave 1-hydroxy-6-nitrobenzo[*g*]phthalazin-4(3*H*)-one. Cyclization of 2-hydrazone or 2-hydrazonophosphorane derivatives of 3-(2-fluoro- or 2-chlorophenyl)-3-oxopropanoates yielded cinnolin-4(1*H*)-ones. The hydrazones undergo cyclization via nucleophilic aromatic substitution. The hydrazonophosphoranes react more readily and do not require base.

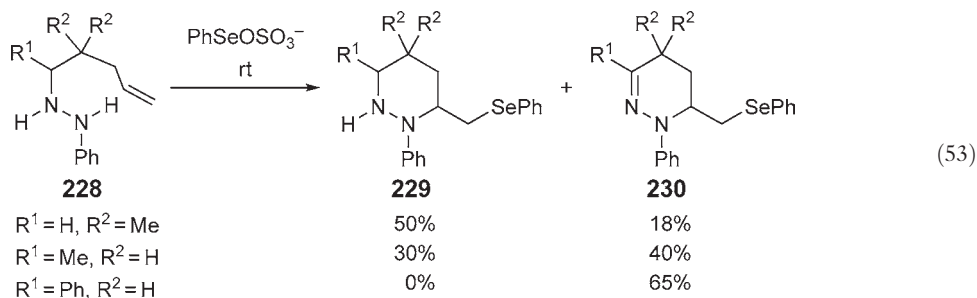
Many additional examples of pyridazine ring construction via the reaction of the terminal nitrogen of hydrazones and a properly positioned cyano or ester group appeared since 1995 and some selected references are mentioned here <1996T5819, 2001T1813, 2001T6787, 2006H(67)815>.

A new method reported by Guillaume starts from vinyl diazomethanes **227** prepared from ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate via Wittig or Horner–Emmons–Wadsworth reaction. Treatment of **227** with triphenylphosphine gave intermediate phosphazine that immediately cyclizes via “diaza-Wittig” reaction. Alternatively, an inverse approach also starting from 2-diazo-4,4,4-trifluoro-3-oxobutanoate, involving reaction with triphenylphosphine followed by Wittig or Horner–Emmons–Wadsworth, can be used as well (Scheme 61) <1995S920>.

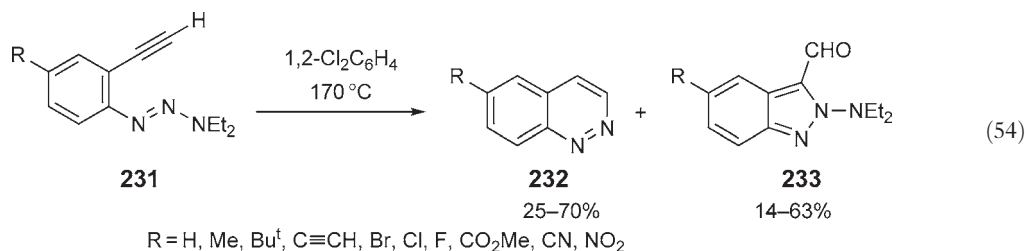
Pent-4-en-1-ylhydrazines **228** were reacted with phenylselenenyl sulfate which gave phenylseleno-substituted hexahydropyridazine derivatives **229** and **230** (Equation 53). Upon column chromatography the hexahydropyridazines **229** were partly or completely oxidized to tetrahydropyridazines **230** <1997T10591>. More examples on hexahydropyridazine ring synthesis, involving bond formation adjacent to the nitrogen atom, were already covered in Section 8.01.6.5.



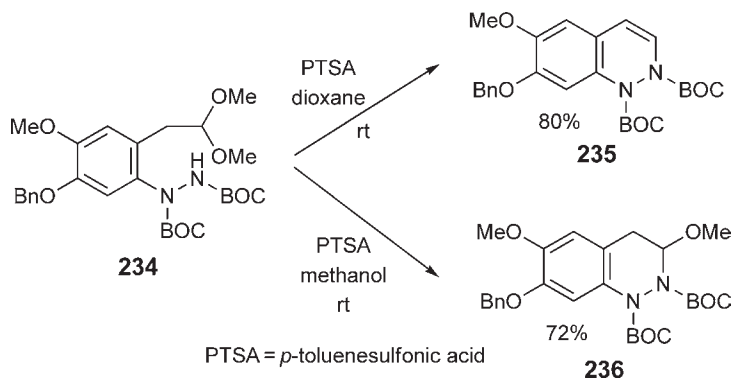
Scheme 61



Cinnolines **232** have been constructed via the thermal cyclization of 3,3-diethyl-1-(2-ethynylphenyl)triaz-1-enes **231**. The mechanism probably occurs via a pericyclic pathway and involves a zwitterionic dehydrocinnolinium intermediate. Formation of 3-formylisoindazole **233** is a competitive pathway at 170 °C (Equation 54) <2000OL3825, 2002JOC6395, 2002JA13463>. Interestingly, the reaction is temperature sensitive since at higher temperature (200 °C) the cinnoline/isoindazole ratio was altered which yielded cinnolines in high yield (90%). Cinnoline synthesis from N-3 solid phase-bound substituted 3-benzyl-1-(2-ethynylphenyl)triaz-1-enes has also been reported. In this case acid is used to regenerate diazonium salt which can cyclize in a Richter-type fashion <1999TL6201>.

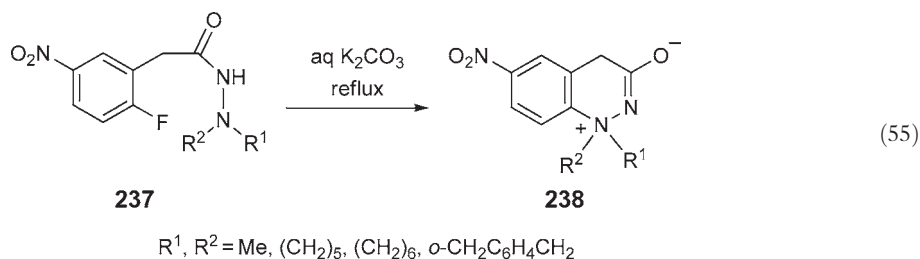


1,2-Dihydrocinnoline derivative **235** could be synthesized from the [2-(2,2-dimethoxyethyl)phenyl]hydrazine **234** via acid-catalyzed cyclization in dioxane. When methanol was used as solvent, a 3-methoxy-1,2,3,4-tetrahydrocinnoline **236** was formed (Scheme 62) <1995LA1303>.

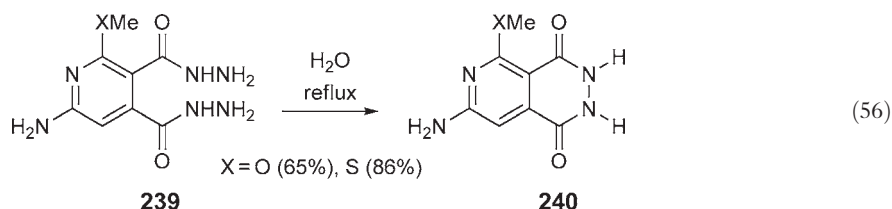


Scheme 62

Intramolecular cyclization of *N,N*-disubstituted 2-(2-fluorophenyl)acetohydrazides **237** gave 1,1-disubstituted 1,4-dihydrocinnolin-1-ium-3-olates **238** (Equation 55) <1997J(P1)2229>.



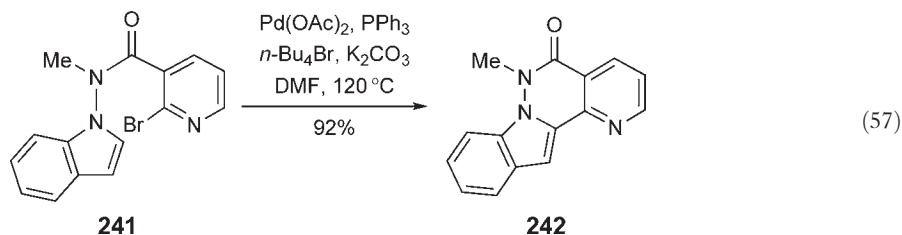
An aza analog of phthalazine **240** (pyrido[3,4-*d*]pyridazine skeleton) was obtained via intramolecular addition–elimination reaction in azaphthalohydrazide **239** with the loss of hydrazine (Equation 56) <1997T8225>. In a similar approach also the 5,6-dihydro[1,2,3]triazolo[4,5-*d*]pyridazin-4,7-dione skeleton was constructed <2002JHC889>.



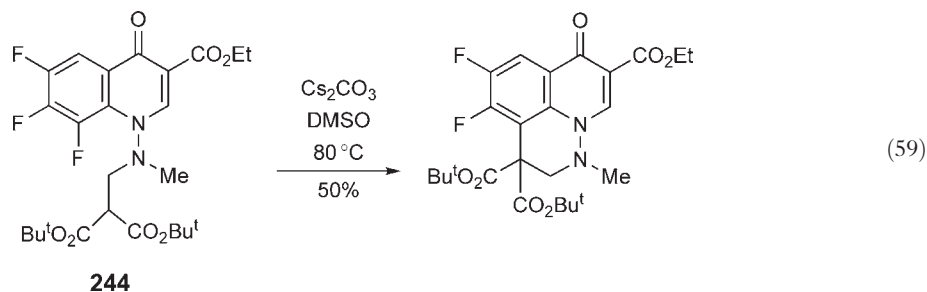
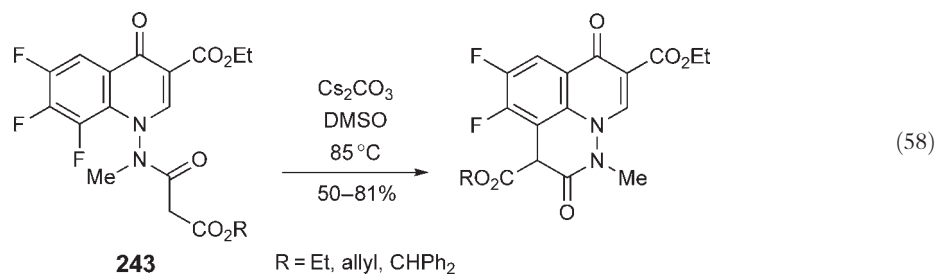
8.01.9.1.3 γ to a heteroatom

In CHEC(1984) <1984CHEC(2)1> mainly methods to prepare cinnolines were reviewed although examples for the preparation of pyridazines were also mentioned. This is not surprising as generally the method is more suitable for cinnoline construction. CHEC-II(1996) <1996CHEC-II(6)1> covered more examples on pyridazine synthesis. The reactions mentioned to achieve cyclization are: ketazine deprotonation with LDA followed by rearrangement, intramolecular Wittig reaction of phosphoranes obtained from the reaction of the coupling product of 1,3-dicarbonyl compounds and benzenediazonium chloride with phosphacumulenyldes, intramolecular condensation of a phenylsulfonyl-activated methylene with a ketone and heating of trichloroacetyl derivatives of *N*-methyl-*N*-*t*-butylhydrazones of aldehydes with hydroquinone, for pyridazine ring construction. Intramolecular Friedel–Crafts acylation of mesoxalyl chloride phenylhydrazones, thermal cyclization of iminium hydrazones, DABCO-catalyzed cyclization (DABCO – 1,4-diazabicyclo[2.2.2]octane) of 2-acetylphenylhydrazone of nitroformaldehyde, and intramolecular Wittig reaction of certain arylazomethylenetriphenylphosphoranes were used for cinnoline construction.

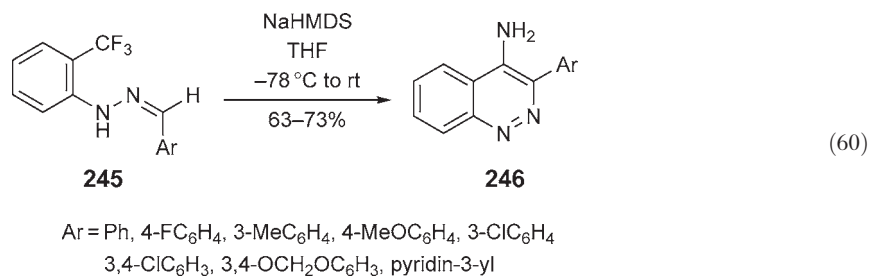
Intramolecular Heck-type reaction of 2-bromo-*N*-(1*H*-indol-1-yl)-*N*-methylnicotinamide **241** yielded tetracyclic 6-methylpyrido[3',2':4,5]-pyridazino[1,6-*a*]indol-5(6*H*)-one **242** in 92% yield (Equation 57) <1995T1941>.



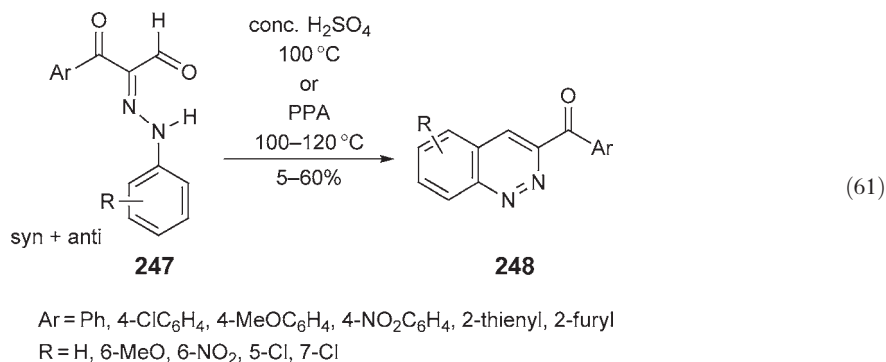
Intramolecular nucleophilic aromatic substitution on **243** allowed 1,4-dihydropyridazin-3(2*H*)-one ring construction (Equation 58) <1995T11125>. Similarly, a tetrahydropyridazine unit could be constructed starting from **244** (Equation 59) <1995JOC3928>.



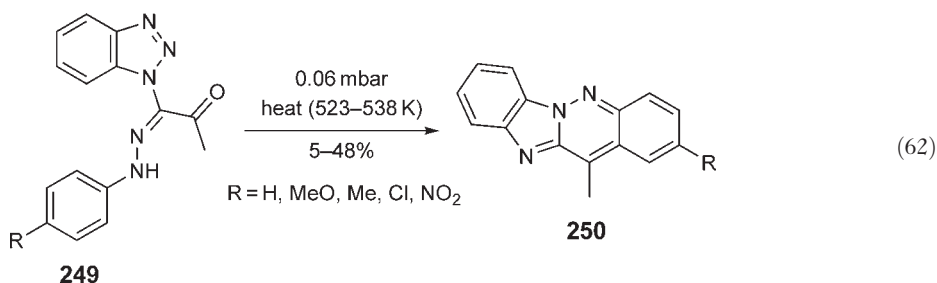
3-Arylcinnolin-4-amines **246** could be obtained from *o*-trifluoromethylphenyl hydrazones **245** via treatment with NaHMDS in THF at -78°C (Equation 60). The mechanism consists of quinine methide formation followed by electrocyclization and elimination of HF yielding 3-aryl-4-fluorocinnolines. Nucleophilic aromatic substitution of the fluorine atom with NaHMDS gave, after basic hydrolysis, 3-arylcinnolin-4-amines **246** <1999TL5111>.



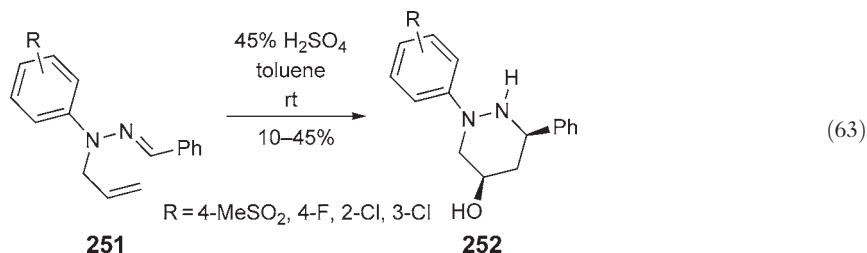
3-Benzoylcinnolines **248** could be synthesized via acid-catalyzed cyclization of 3-oxo-3-aryl-2-arylhydrazonopropanals **247** (Equation 61) <2001T1609>. A related process for the synthesis of 3-(1*H*-benzotriazol-1-yl)-4-methylcinnoline was published by the same team <2002HAC141>.



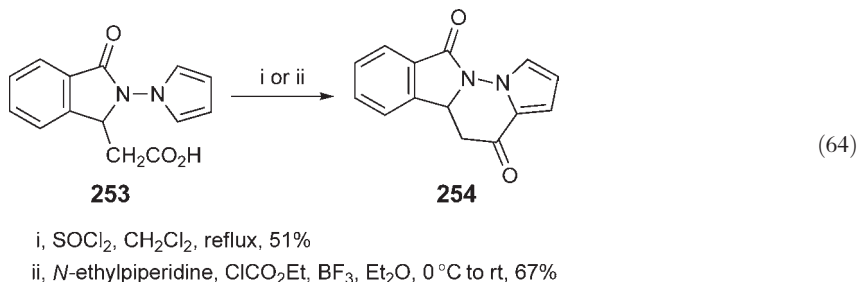
Benzimidazo[1,2-*b*]cinnolines **250** were prepared via pyrolysis of benzotriazoles **249** (Equation 62) <2003T9455>.



Treatment of benzaldehyde 1-allyl-[4-(methylsulfonyl)phenyl]hydrazone **251** with 45% sulfuric acid gave **252** rather than the expected 1-allyl-1-[4-(methylsulfonyl)phenyl]hydrazine (Equation 63). Halogen-substituted hydrazones gave similar results. Unsubstituted benzaldehyde phenylhydrazone gave normal hydrolysis <1996JHC213>.



Activation of the carboxylic acid function of 2-(1*H*-pyrrol-1-yl)isoindolin-1-one **253** yielded 5,5a-dihydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindole-4,10-dione **254** (Equation 64) <1995H(41)689>.



8.01.9.1.4 Formation of benzo rings

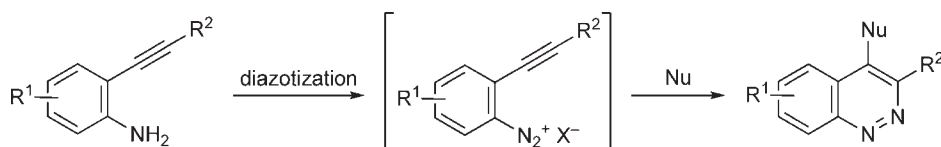
The annelation of benzo rings on pyridazines was covered in CHEC-II(1996) <1996CHEC-II(6)1>. Maes and Mátyus reported new examples in their synthesis of the dibenzo[*f,h*]phthalazin-1(2*H*)-one and dibenzo[*f,h*]cinnolin-3(2*H*)-one skeleton. Palladium-catalyzed intramolecular arylation of 2-benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one yielded 2-benzyl-dibenzo[*f,h*]phthalazin-1(2*H*)-one. The synthesis of this new tetracyclic pyridazinone from 2-benzyl-5-(2-aminophenyl)-4-phenylpyridazin-3(2*H*)-one via a Pschorr-type reaction was also investigated. Similarly, the construction of 2-methyldibenzo[*f,h*]cinnolin-3(2*H*)-one from 2-methyl-5-(2-bromophenyl)-6-phenylpyridazin-3(2*H*)-one and 2-methyl-5-(2-aminophenyl)-6-phenylpyridazin-3(2*H*)-one was performed <2003T5919>.

8.01.9.2 Formation of Two Bonds

8.01.9.2.1 From [5+1] fragments

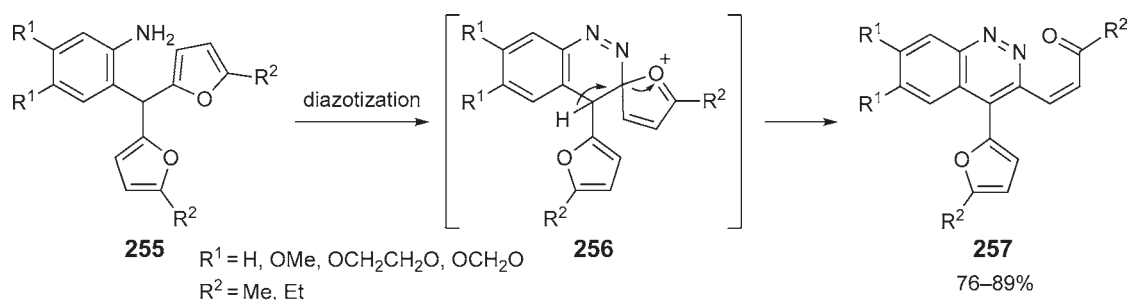
This approach is important for the synthesis of cinnolines. CHEC(1984) <1984CHEC(2)1> already covered several examples. The methodology used starts with an aniline *ortho* substituted with an alkene (Widman–Stoermer type), alkyne (Richter type), or enolisable ketone (Borsche type) which is diazotized, delivering the sixth atom, allowing cyclization. CHEC-II(1996) <1996CHEC-II(6)1> gave more examples.

Since 1995 many examples of the Richter type appeared. In this reaction a nucleophile attacks the C-1 of the alkyne moiety, allowing substitution in the C-4 position of the cinnoline, and a π -bond of the alkyne attacks the diazonium functional group (Scheme 63). Classically, water was used and claimed to be the attacking species in the Richter reaction but more recently chloride and bromide nucleophiles have been successfully used. In fact, Vasilevsky gained proof that in the classical Richter reaction 4-halocinnolines are the actual intermediates which are subsequently hydrolyzed. Therefore, the reaction conditions determine the actual outcome. Richter reaction on 2-(phenylethynyl)aniline yielded 3-phenylcinnolin-4-ol as the main product as well as 5% of 4-chloro-3-phenylcinnoline. When the reaction was performed at room temperature, 41% of 4-chloro-3-phenylcinnoline could be isolated. When hydrobromic acid was used 4-bromo-3-phenylcinnoline was obtained in 86% <1995LA775>. Examples with other 2-arylethynyl- and 2-alk-1-yn-1-ylanilines have been reported <1995LA775, 2004T7983>. The effect of substitution in the *para*-position of the phenyl ring of 2-(phenylethynyl)aniline on the outcome of the reaction has also been investigated. Interestingly, electron donors at the *para*-position seem to favor pyrazole rather than pyridazine ring formation <2003TL5453>. Also for *vic*-alkynylantra- and *vic*-alkynynaphthoquinone diazonium salts pyrazole and pyridazine ring formation has been observed but the mechanism proposed is different from the generally assumed simultaneous mechanism for cyclization of 2-alk-1-yn-1-ylbenzenediazonium salts <2001T1331, 2004T2137>. The Richter method has also been applied to prepare substituted 4-chloro- and 4-bromo-1*H*-pyrazolo[3,4-*c*]pyridazines from 4-alk-1-yn-1-yl-1*H*-pyrazol-5-amine <1995LA775, 1999J(P1)3721>. Isomeric alkynyl-1*H*-pyrazolamines have also been studied as starting materials <1999J(P1)3721>.



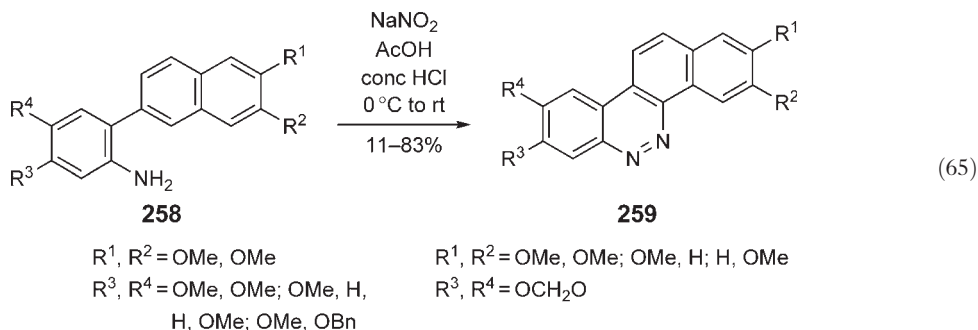
Scheme 63

Diazotization of 2-(di-2-furylmethyl)anilines **255** gave the corresponding diazonium salts. Intramolecular attack of the diazonium functionality on the π -system of one of the electron-rich furan rings yielded **256**. Subsequent elimination results in ring opening which yielded cinnolines **257** (Scheme 64) <1997MOL62, 2000T8933>.

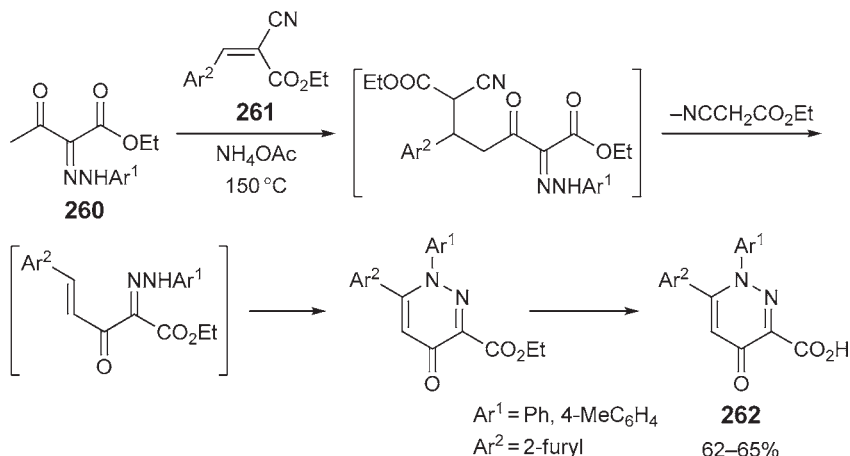


Scheme 64

Dibenzo[*c,h*]cinnolines **259** have been obtained from 2-naphthylanilines **258** via diazotization followed by intramolecular electrophilic aromatic substitution (Equation 65) <2003BMC1475>.

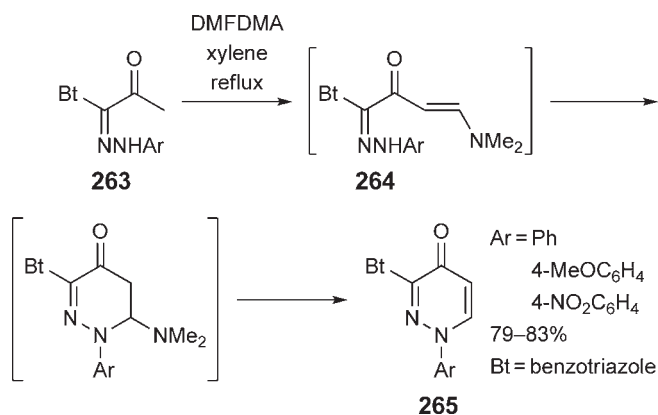


Although the [5+1] strategy is generally considered to be only useful for the synthesis of cinnolines, some examples appeared for the synthesis of pyridazine derivatives. Michael addition of 2-arylhydrazono-3-oxobutanoates **260** on acrylonitrile **261** yielded pyridazin-4(1*H*)-ones **262** (Scheme 65) <2001SC2569>.



Scheme 65

Another example is the reaction of 1-(1*H*-benzotriazol-1-yl)-1-(arylhydrazono)acetones **263** with DMFDMA. The intermediate **264** undergoes Michael addition followed by elimination of dimethylamine yielding pyridazin-4(1*H*)-ones **265** (Scheme 66) <2000JHC167>.



Scheme 66

8.01.9.2.2 From [4+2] fragments

The [4+2] fragments approach is surely the most explored and hitherto used procedure to construct pyridazine, phthalazine, and cinnoline rings. CHEC(1984) <1984CHEC(2)1> as well as CHEC-II(1996) <1996CHEC-II(6)1> covered many examples. We decided to follow the same subdivision as CHEC-II(1996) to cover this area.

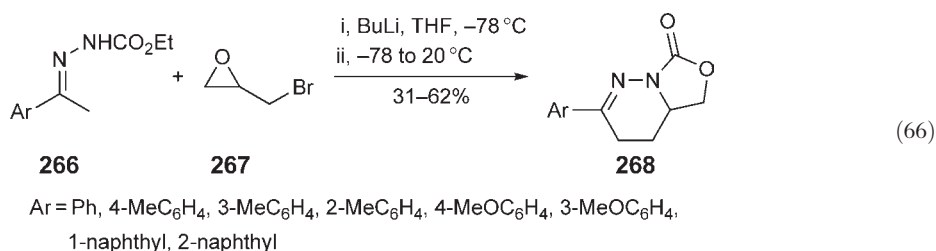
8.01.9.2.2(i) Cyclization with hydrazines

The most straightforward method used to prepare pyridazines and phthalazine derivatives is the reaction of a 1,4-dicarbonyl compound with hydrazines. Many examples were reported in CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>. We refer here to some selected new examples. Combination of aldehyde, ketone, carboxylic acid, ester, thiolester, and even amide functionalities has been used for this purpose <1995JHC1299, 1997J(P)13485, 1998JME3812, 2000T7561, 2002BML689, 2002H(57)723, 2003S436,

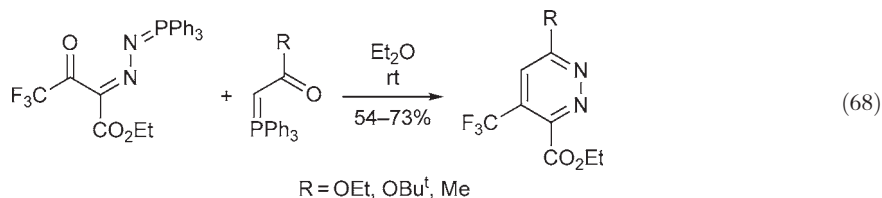
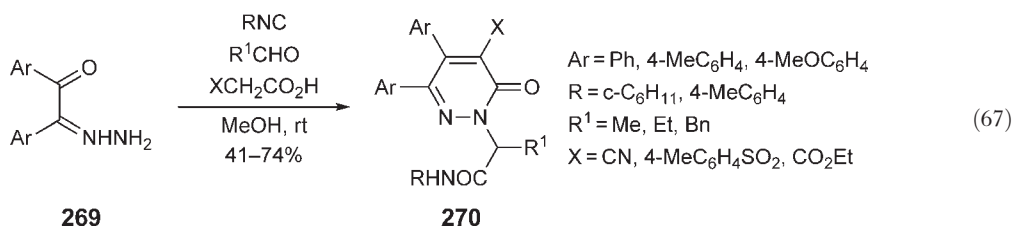
2004BML1295, 2004S1554, 2004SC765, 2004SC1301, 2005SL1907, 2005SL2743, 2005JHC1245>. Procedures on solid support have also been developed <2001MI981, 2003SL711>. An interesting example to mention specifically is the synthesis of 3,5-disubstituted pyridazines from β -hydroxy- γ -keto-aldehydes and hydrazine. β -Hydroxy- γ -keto-aldehydes have been efficiently obtained via the reaction of aldehyde enolates with glyoxals. The aldehyde enolates are generated through Rh-catalyzed enal hydrogenation. The β -hydroxy- γ -keto-aldehyde reaction products are not isolated but immediately reacted further by the addition of hydrazine <2004JOC1380>. One of the carbonyls of 1,4-dicarbonyl compounds can also be a nitrile group. When an unsubstituted nitrogen atom of a hydrazine attacks the carbon atom of the nitrile subsequent tautomerization immediately occurs which gives access to amino-substituted derivatives <1998HCA231, 2002M79>. This method has also been used to synthesize cinnolin-3-amines from halogenated (3-hydroxy-6-oxocyclohexa-2,4-dien-1-ylidene)malononitrile and hydrazine <2003TL3493>. When the nitrogen atom is substituted, imino derivatives are obtained. Depending on the reaction conditions these can immediately be hydrolyzed into pyridazin-3(2*H*)-ones or phthalazin-1(2*H*)-ones.

There are also many other methods published based on hydrazines. Emphasis in this section is put on new synthetic methods and new examples/adaptations of known methodologies with a broad scope. Methods to prepare very specific bicyclic or polycyclic 1,2-diazines have therefore not been incorporated.

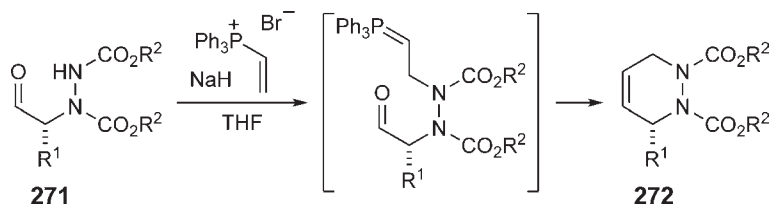
Dilithiated hydrazones of methyl ketones **266** can be transformed into 1,2,3,4-tetrahydropyridazines **268** upon reaction with epibromohydrin **267** (Equation 66) <2006JOC2293>.



A popular route is to start from a β -oxohydrazone. Ugi four-component condensation of diarylethane-1,2-dione monohydrazones **269** with isocyanides, aldehydes, and methylene active acids, for instance, yielded immediately the corresponding substituted pyridazin-3(2*H*)-ones **270** (Equation 67). The intermediate Ugi condensation products were never observed because of their tendency to cyclize <2003S691>. Other methods starting from β -oxohydrazones are based on a classical condensation with an active methylene group or a Wittig reaction on the carbonyl and subsequent intramolecular attack on an ester or cyano group <1996T11915, 1997SC2419, 1997JCM236, 1999JCM648, 2000JHC167, 2000JHC1617, 2001T1813, 2003JHC249, 2004JCM808>. Also the combination of a Wittig and aza-Wittig reaction is reported (Equation 68) <1995S920>.

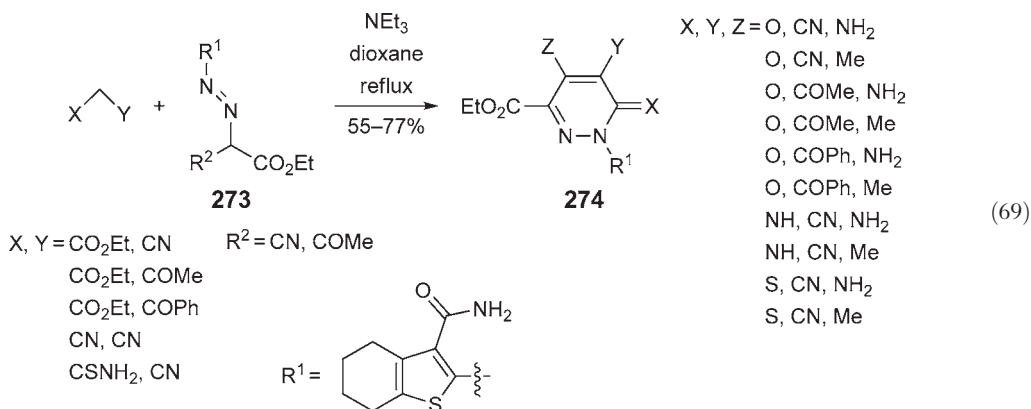


Ley developed an efficient tandem organocatalytic synthesis of chiral dialkyl 3-alkyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylates **272** from β -oxohydrazones **271**. Compound **271** was obtained from commercially available achiral aldehydes and dialkyl azodicarboxylates using (*S*)-pyrrolidinyl tetrazole as the chiral catalyst. This synthesis proceeds with good to excellent yields (58–89%) and enantioselectivities (69–99% ee). The highest ee values are obtained for the most bulky di-*t*-butyl azodicarboxylate and the shortest branched aldehydes (Scheme 67) <2006SL2548>.

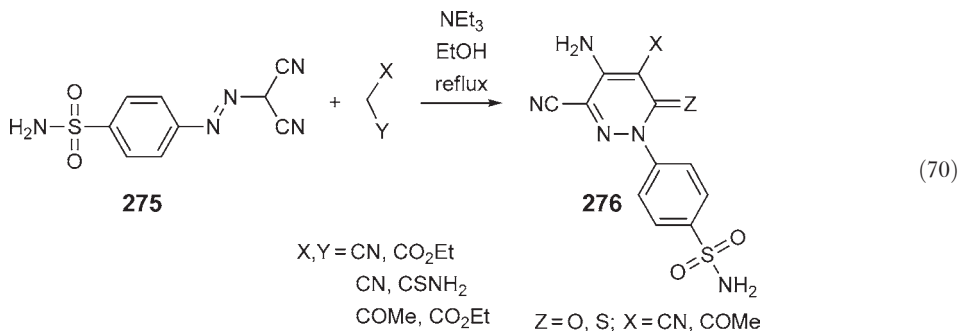


Scheme 67

Closely related are the routes that start from β -oxodiazenes. Pyridazin-4(1*H*)-ones and thio and imino analogs **274** for instance have been synthesized from diazenylacetates **273** and active methylene compounds (Equation 69). In the same paper reactions of **273** with α -substituted cinnamonnitriles were studied which gave access to substituted pyridazin-4(1*H*)-ones <2004HAC300>.

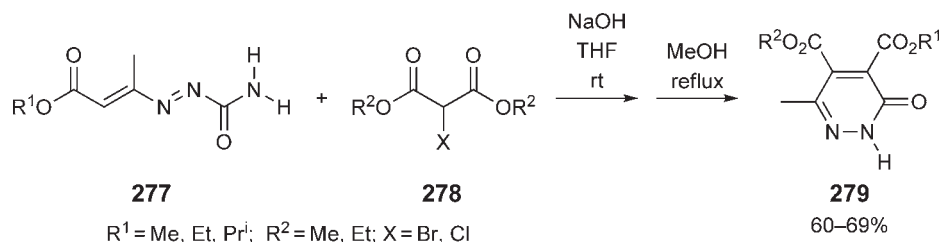


Reaction of the malononitrile-derived diazene **275** with active methylene compounds proceeds via addition to a cyano group followed by intramolecular hydrazide or thiohydrazide formation, pyridazin-3(2*H*)-ones and thio analogs **276** are respectively produced (Equation 70) <1999JCM8>.

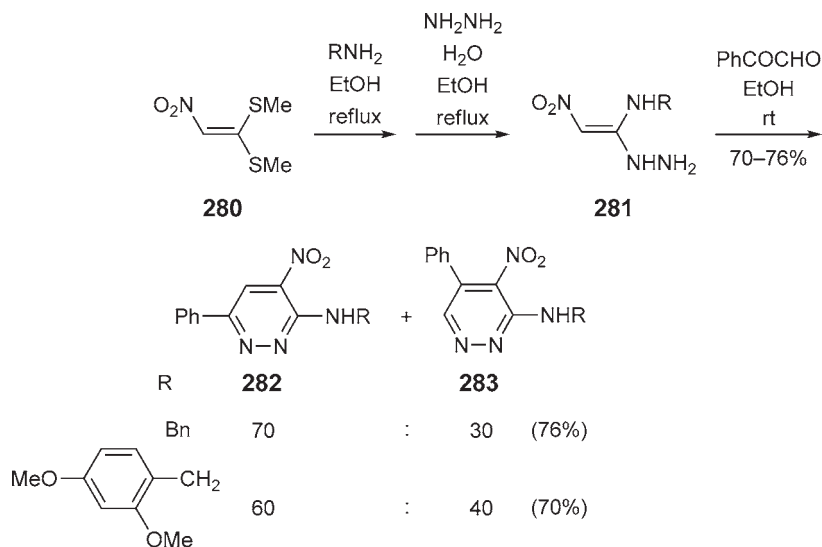


Diazadienes have been utilized in processes other than [4+2] cycloadditions. Addition of a halomalonate **278** to 1-aminocarbonyl-1,2-diaza-1,3-butadienes **277** gave hydrazones. Without isolation, these could be cyclized into pyridazin-3(2*H*)-ones **279** by simple addition of MeOH and heating at reflux (Scheme 68) <1999JOC9653>. The same team also developed similar processes based on the addition of the active methylene group of a 2-substituted 1,3-diketo compound to 1-aminocarbonyl-1,2-diaza-1,3-butadienes <1998JOC9880, 2004JOC2686>. The hydrazone of ethyl 5-bromo-2-oxopent-3-enoate and tosyl hydrazine *in situ* eliminates HBr upon formation. This gives the corresponding diazahexatriene which undergoes a six π -electron electrocyclic yielding ethyl 1-(4-toluenesulfonyl)-1,6-dihydropyridazine-3-carboxylate in 74% yield <1996T14975>.

1,1-Bis(methylthio)-2-nitroethene **280** is an attractive reagent to prepare pyridazin-3-amines **282** and **283**. Reaction with the aliphatic amine desired as substituent for the pyridazine followed by hydrazine yields 1-hydrazino-2-nitroethenamines **281**. These can be transformed into the desired pyridazine-3-amines **282** and **283** via condensation with 1,2-dicarbonyl compounds such as phenylglyoxal (Scheme 69) <2003SL1482, 1999JME730>.

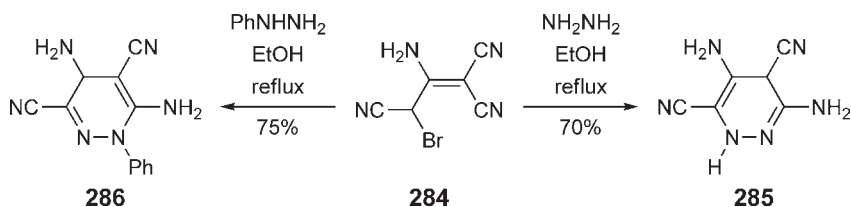


Scheme 68



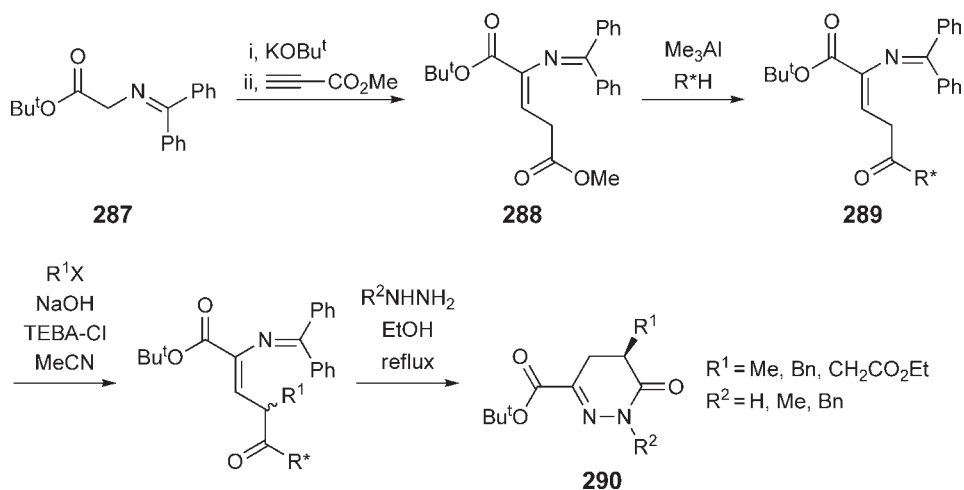
Scheme 69

Reaction of 2-amino-3-bromoprop-1-ene-1,1,3-tricarbonitrile **284**, easily accessible from the bromination of the dimer of malononitrile, with hydrazine or phenyl hydrazine yielded 1,4-dihydropyridazines **285** and **286**, respectively (Scheme 70) <2003HAC612>.



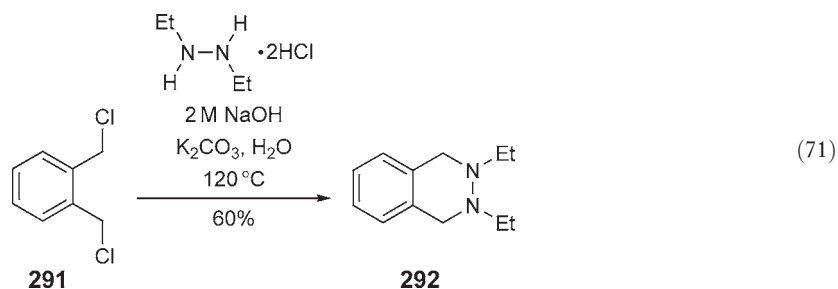
Scheme 70

Asymmetric syntheses of 4-substituted 4,5-dihydropyridazin-3(2H)-ones **290** were also published. Enolization of the *t*-butyl glycinate **287** with KOBu^t followed by reaction with methyl propiolate afforded α,β -didehydroglutamic acid derivative **288** via Michael addition/1,3-prototropic shift. Selective Me_3Al -mediated acylation of the terminal methyl ester with Oppolzer's (2*R*)-(–)-bornane-10,2-sultam gave α,β -didehydroglutamyl sultam **289**. This compound could be regio- and stereoselectively alkylated. Reaction with hydrazine afforded the target compounds **290**. Interestingly, besides the chiral auxiliary a benzophenone imine moiety is lost as leaving group in this reaction (Scheme 71) <2001TL2129>. A similar reaction sequence with higher alk-2-ynoates, but without chiral induction, was used for the stereoselective synthesis of *cis*-4,5-disubstituted analogs of **290** <2002JOC2789>.



Scheme 71

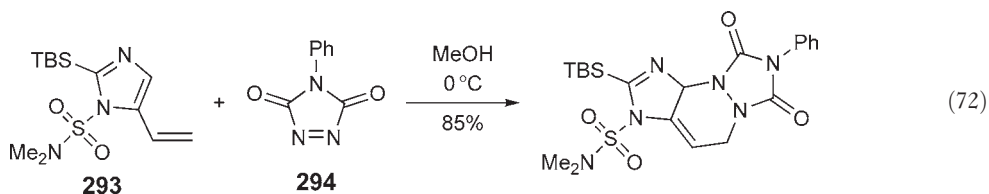
Reaction of 1,2-disubstituted hydrazines with 1,2-bis(halomethyl)benzenes **291** under microwave irradiation has shown to yield 2,3-disubstituted 1,2,3,4-tetrahydropyridazines **292** via double nucleophilic substitution. When a mono-substituted hydrazine is used 2-substituted 1,2-dihydropyridazine was obtained (Equation 71) <2005TL6011, 2006JOC135>.



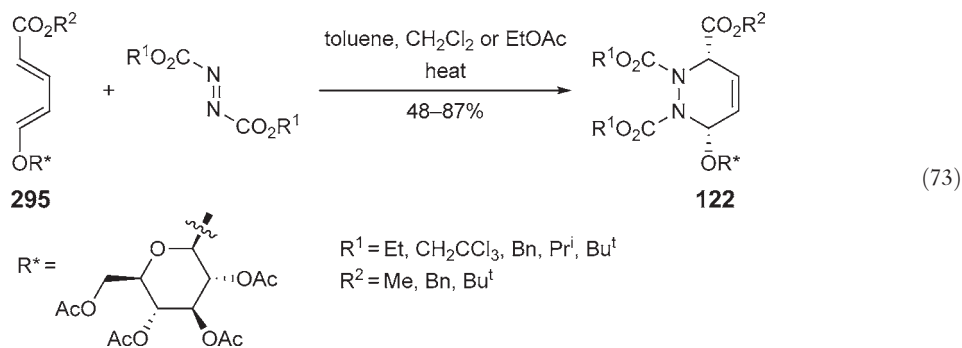
8.01.9.2.2(ii) [4+2] Cycloaddition reaction of C-4, N-2

Many examples of the cycloaddition of substituted butadienes with 1,2-disubstituted diazenes such as diethyl azodicarboxylate, yielding substituted 1,2,3,6-tetrahydropyridazines, were mentioned in CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>. The method has also been used to synthesize 1,2,3,4-tetrahydrocinnolines when styrenes were used as substrates.

New examples involve the reaction of 5-vinyl-1*H*-imidazole **293** with 4-phenyl-1,2,4-triazoline-3,5-dione **294**. In this way, the imidazo[4,5-*c*]pyridazine skeleton was smoothly constructed (Equation 72) <1998TL4561>. Another example using *in situ* formed **294** can be found in Section 8.01.6.5.



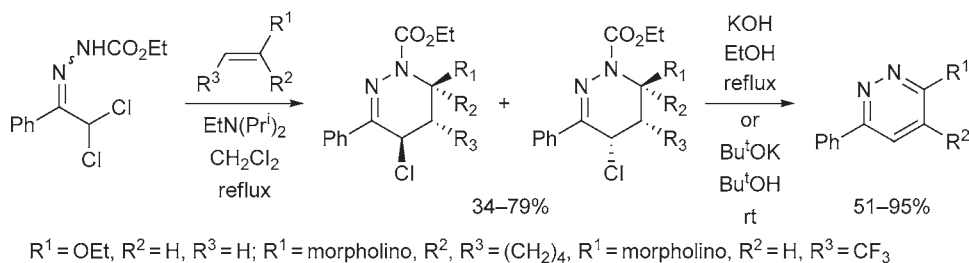
Stoodley developed an asymmetric synthesis of (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (see Section 8.01.6.4). The ring construction was achieved via cycloaddition of dienes **295** bearing a tetraacetyl β -D-glucopyranosyl moiety for chiral induction with azodicarboxylates (Equation 73) <1999J(P1)2591>.



8.01.9.2.2(iii) [4+2] Cycloaddition reaction of C-2-N-2, C-2, or C-1-N-2-C-1, C-2

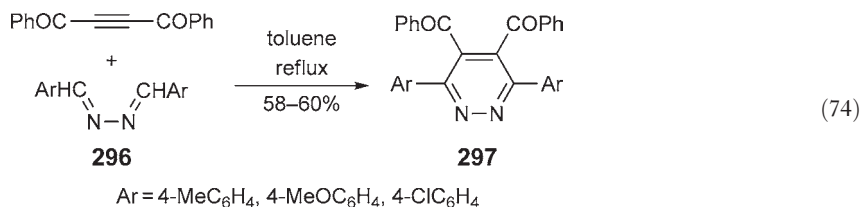
CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1> covered examples of the cycloaddition reaction of diazoalkenes with alkenes yielding 2,3,4,5-tetrahydropyridazines. The diazadiene is normally generated *in situ* from an α -halogenated hydrazone with the assistance of base.

More examples with α -halohydrazones and acyclic (e.g., styrene) as well as cyclic alkenes (e.g., cyclopentadiene, dihydrofuran, and norbornadiene) appeared <2005EJO1142>. The observed stereochemistry can be explained in terms of *endo*- and *exo*-transition states. At the end of the 1990s South and co-workers have been very active in this field using an α,α -dichloro, α,α -dibromo, or α,α,α -trichloro rather than an α -halohydrazone and 1-vinyl-substituted cyclic secondary amines or 1-alkoxyethenes as alkenes. Oxidation of the initially obtained (di)halo-substituted tetrahydropyridazines with the assistance of base yields substituted pyridazines. In fact, the extra halogen(s) on the diazoalkene as well as the alkoxy or amino substituent on the alkene provide this smooth aromatization possibility. The combination of a hetero-Diels-Alder reaction followed by aromatization is a new general synthesis for substituted pyridazines <1995TL5703, 1996JOC8921, 1996TL1351, 1999JHC301>. Representative examples have been incorporated in Scheme 72 <1995TL5703>.



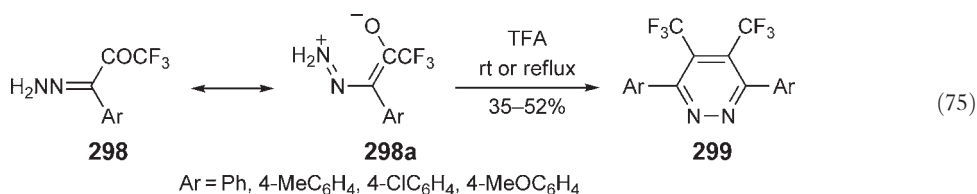
Scheme 72

A procedure based on benzyldiene azines also appeared. Reactions of dibenzoylacetylene with 296 yielded tetrasubstituted pyridazines 297 via cycloaddition and subsequent spontaneous oxidation of the tetrahydropyridazines (Equation 74) <2005CJC57>.



Kamitori investigated the synthesis of 4,5-bistrifluoromethylpyridazines 299 from 1-aryl-3,3,3-trifluoropropane-1,2-dione 1-hydrazones 298 (Equation 75). Mechanistically, the reaction is considered to occur via a [4+2]-type

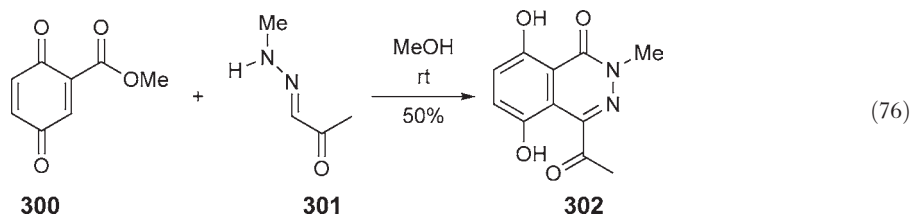
cycloaddition between two molecules of **298**. For this the ionic form of **298**, **298a**, is required which has a diazoalkene structure <1998H(48)2221, 2000H(53)1065>. Acid enhances the dienic character by protonation of the carbonyl oxygen. The team also showed that cycloaddition of **298** with DMAD, acetylacetone, and ethyl acetoacetate also occurs. For these reactions no addition of acid is required. The reactions with acetylacetone and ethyl acetoacetate occur via the enol form <1998H(48)2221, 2004H(63)707>.



8.01.9.2.3 From [3+3] fragments

This part was covered in CHEC(1984) <1984CHEC(2)1>. We feel that the examples covered in CHEC(1984) are examples of ring transformations rather than ring construction from [3+3] fragments. No new examples of the [3+3] type were mentioned in CHEC-II(1996) <1996CHEC-II(6)1>. Although this synthetic approach is not frequently used, some examples appeared.

The reaction of 2-methoxycarbonyl-1,4-benzoquinone **300** with 2-oxopropanal methylhydrazone **301**, for instance, yielded phthalazin-1(2*H*)-one **302** (Equation 76) <2000T5137>.



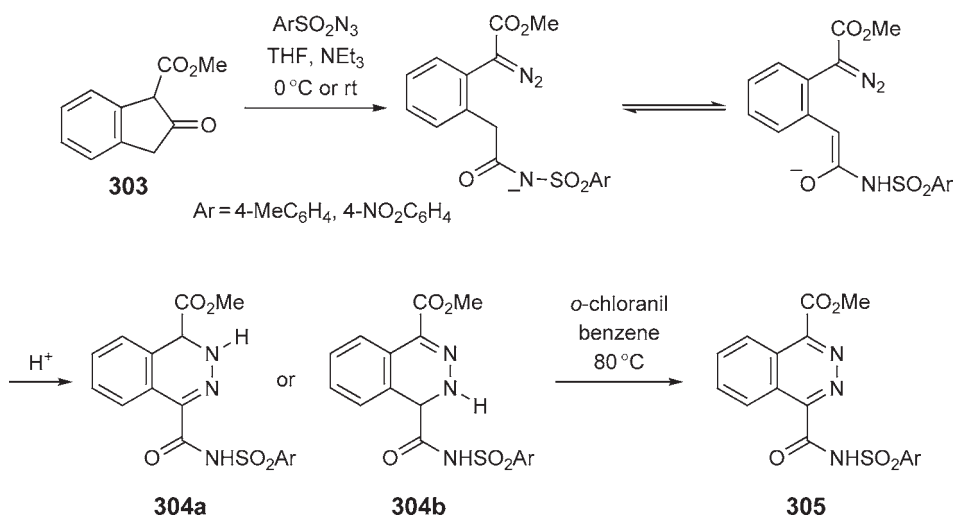
8.01.10 Ring Synthesis by Transformation of Another Ring

8.01.10.1 By Ring Expansion

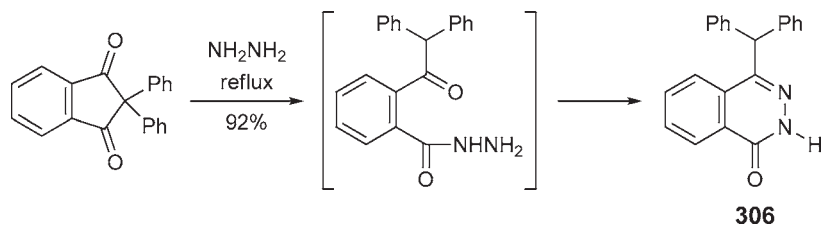
CHEC(1984) <1984CHEC(2)1> showed examples of the rearrangement of 2-aminoisindolin-1-ones and *N*-aminophthalimides into pyridazin-4(1*H*)-ones and 4-hydroxyphthalazine-1(2*H*)-ones, respectively. Oxidative ring expansion of pyrrolidin-1-amines and 1-amino-1,3-dihydro-2*H*-indol-2-ones to tetrahydropyridazines and cinnolin-3(2*H*)-ones, respectively, were also included. CHEC-II(1996) <1996CHEC-II(6)1> covered more work on the oxidative rearrangement of 1-amino-1,3-dihydro-2*H*-indol-2-ones into cinnolin-3(2*H*)-ones. Other rearrangements such as the transformation of 4-alkylidene-2,4-dihydro-3*H*-pyrazol-3-ones into pyridazin-3(2*H*)-ones were also discussed. Several new interesting examples of ring expansion appeared since 1995.

Reaction of methyl 2-oxo-1-indanecarboxylate **303** with tosyl or 4-nitrobenzenesulfonyl azide yielded a dihydrophthalazine **304a** or **304b** which upon oxidation with chloranil gave phthalazine **305** (Scheme 73) <1998JOC4679>. The phthalazine skeleton could also be constructed via reaction of 2-aryl- or 2,2-diaryl-1*H*-indene-1,3(2*H*)-diones with hydrazine exemplified in Scheme 74 for the reaction of the 2,2-diphenyl derivative **306** <2000JME2310, 2002SL823, 2005BML2235, 2006BML1040>.

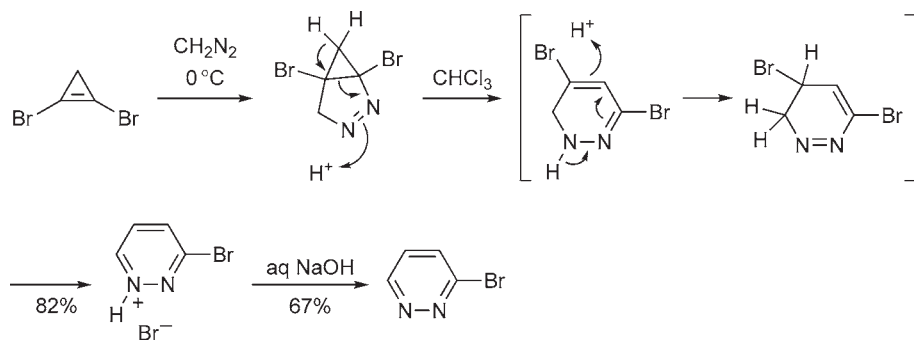
Cycloaddition of diazoalkanes to cyclopropenes yields bicyclic compounds that can ring-open into dihydropyridazines <1998T12897, 2004RJO1027, 2004RJO1033>. If the substitution pattern of the dihydropyridazine is suitable, immediate aromatization can occur. Scheme 75 shows a representative example. Thermolysis of peralkylated diazoalkylcyclopropenes exemplified by **307** also yields pyridazines via a similar bicyclic intermediate (Scheme 76). Peralkylated cyclobutadiene and acetylene are also formed <1995LA169, 1995LA173>. 3,5-Disubstituted pyridazines can be prepared via ring opening and subsequent dimerization of 3-aryl-2*H*-azirines. The reaction is promoted by FeCl₂ which breaks up the three-membered ring into a zwitterionic or radical structure. The radical structure is probably responsible for the pyridazine formation. During this reaction other heterocycles are



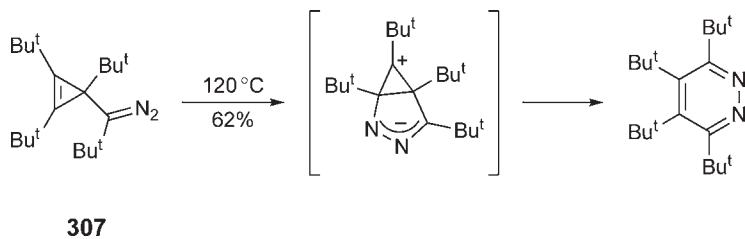
Scheme 73



Scheme 74

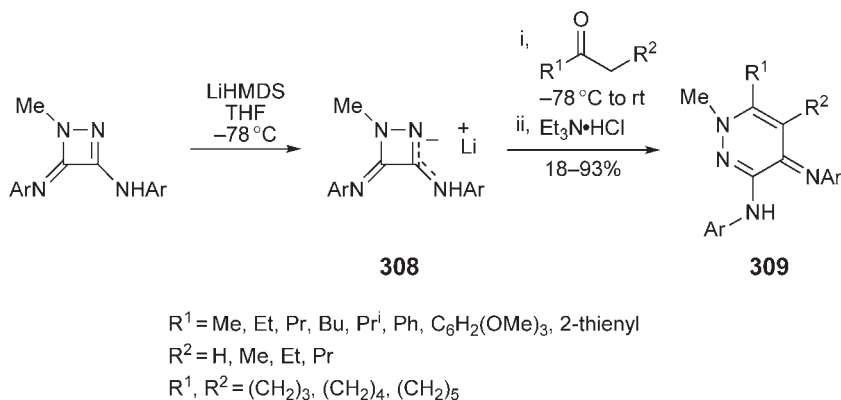


Scheme 75

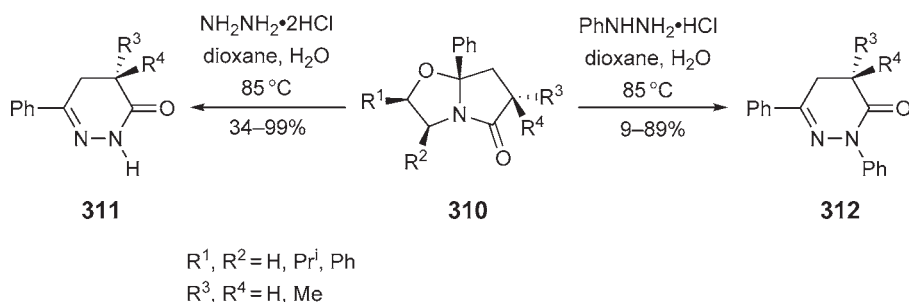


Scheme 76

also formed (diaryl-2*H*-imidazole and diarylpyrazine) together with aryl ketones and traces of α -chloro ketones <2001EJO1183>. Another interesting approach is the reaction of deprotonated 1,2-diazetines **308** with ketones containing an acidic methylene group. This gave access to 1-methyl-*N*-(4-methylphenyl)-4-[(4-methylphenyl)imino]-1,4-dihydropyridazin-3-amines **309** via a sequence of ring opening and recyclization (Scheme 77) <2006S2885>. Chiral 4-methyl, 4,4-dimethyl, and unsubstituted 4,5-dihydropyridazin-3(2*H*)-ones **311** have been obtained from γ -bicyclic lactams **310** via reaction with hydrazine (Scheme 78). 2-Phenyl analogs **312** could be obtained using phenylhydrazine (Scheme 78) <2003TL7799>.



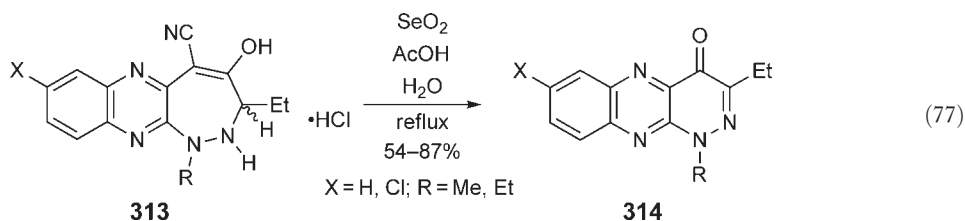
Scheme 77



Scheme 78

8.01.10.2 By Ring Contraction

This route is not frequently reported for the preparation of pyridazines. CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1> summarized examples starting from 5,6-dihydro-4*H*-1,2-diazepines, 5,6-dihydro-4*H*-1,2,5-triazepines, and 2,7-dihydro-1,4,5-thiadiazepines. A new example is the tandem reaction of hydrazine with 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones) which afforded 3,6-diarylpyridazines and 3,5-diaryl-1*H*-pyrazoles. 3,6-Diarylpyridazine formation is believed to proceed via a 3,6-diaryl-2,7-dihydro-1,4,5-thiadiazepine-1,1-dioxide intermediate <2002T2227>. Another new addition is the reaction of 3-(1-alkyl-2-propylidenehydrazino)quinoxaline-1-oxides with 2-chloroacrylonitrile which gave diazepino-fused quinoxalines **313**. Upon treatment of **313** with SeO_2 oxidative ring transformation to 1-alkyl-3-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines **314** occurred (Equation 77) <2001H(54)359>.



8.01.10.3 By Cycloaddition

In CHEC-II(1996) <1996CHEC-II(6)1> the formation of diazines from other heterocycles by cycloaddition reactions was covered, for example, reaction of 3,4-disubstituted thiophene 1,1-dioxides with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, Diels–Alder addition of phthalazine-1,4-dione to bay region polycyclic aromatic hydrocarbons and inverse electron demand Diels–Alder cycloadditions of 1,2,4,5-tetrazines with a wide range of alkynes and alkenes. The latter reaction type has been discussed extensively: reactions with alkynes give immediately diazines as the reaction products; reactions with alkenes give dihydrodiazines from which the diazines are formed after an oxidation or an elimination step. Since 1995 the vast majority of diazines obtained by cycloaddition reactions were synthesized from 1,2,4,5-tetrazines. A selection is presented here: 1,4-bis(trifluoromethyl)-4a,8a-methanophthalazine **89** (see Section 8.01.5.7.1) <1996ZNB348>, 4-(2-deoxyribofuranosyl)pyridazines **315** <2001ARK(ii)95>, *exo*-2-(pyridazin-4-yl)-7-azabicyclo[2.2.1]heptanes **316** as epibatidine analogs <2001JME47>, 1*H*-imidazo[4,5-*c*]pyridazin-2-amine **317** as a zarsissine isomer <2001T5497>, 4-(piperidin-2-yl)pyridazines **318** as anabasine analogs <2002T1343>, ‘proton sponges’ with a 8,9-diazafluoranthene structure **319** <2003RCB218>, metal-complexing 3,6-dipyridin-2-ylpyridazine ligands fused to rigid molecular racks, for example, **320** <1996TL2825, 2003AJC811>, 2,2′-pyridazine-3,6-diylbis(1,10-phenanthroline) <2002OL1253>, and 4-substituted and 4,5-disubstituted 3,6-dipyridin-2-ylpyridazine ligands <2003EJO4887> (Figure 13).

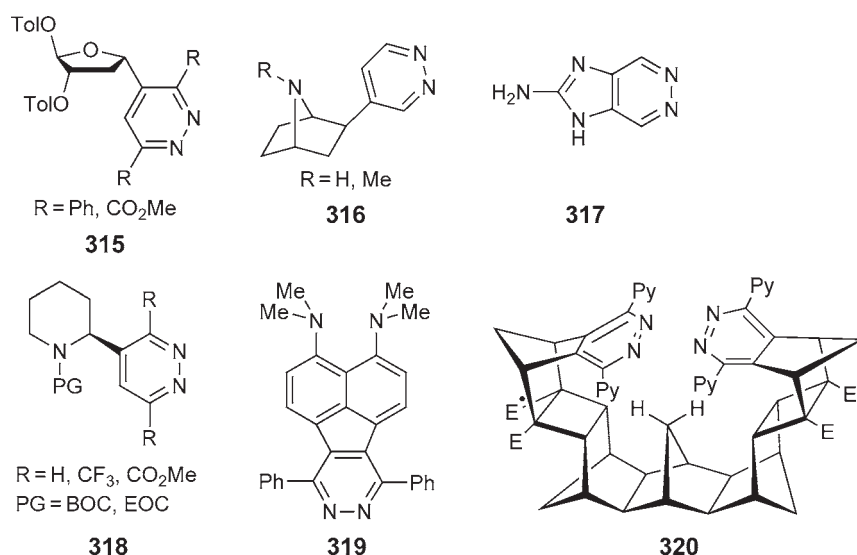
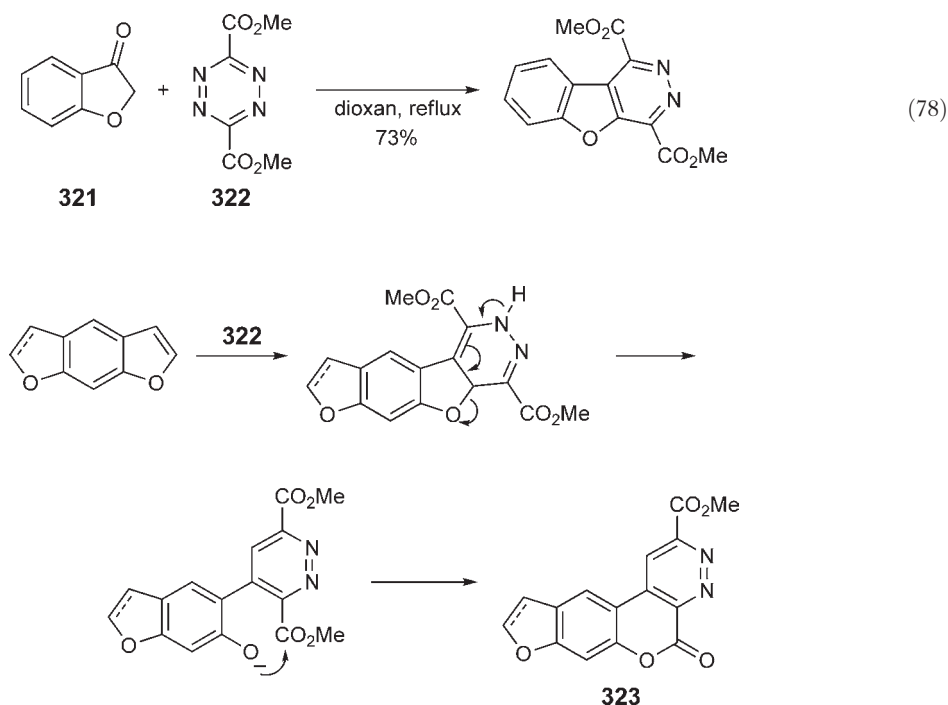


Figure 13 1,2-Diazines obtained by cycloaddition reactions starting from 1,2,4,5-tetrazines.

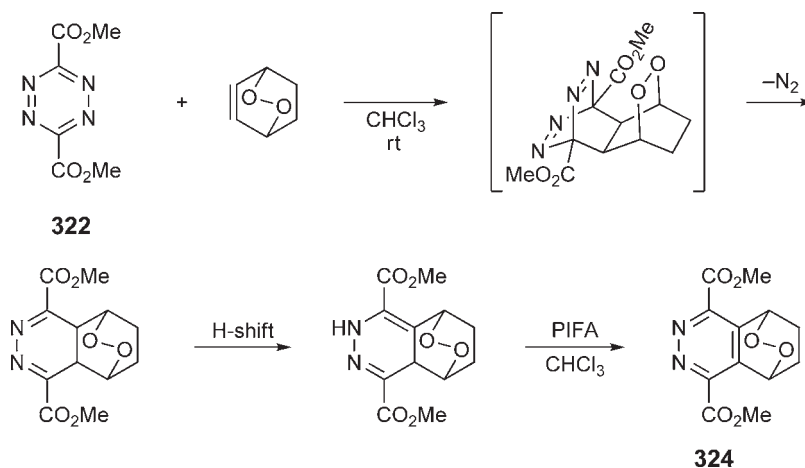
Sauer published a study on the reaction of unsubstituted 1,2,4,5-tetrazine with a large number of open-chain and cyclic dienophiles. The rate constants obtained by extensive kinetic measurements led to quantitative rules for the influence of steric and electronic substituent effects in the dienophile <1998EJO2885>. More recently, he studied the use of 3,6-di-2*H*-tetrazol-5-yl-1,2,4,5-tetrazine and derivatives of this reagent for the synthesis of 3,6-diheteroaryl-substituted pyridazines <2001EJO697>. Boger studied reactions with 6-(*t*-butoxycarbonylamino)-3-methylthio-1,2,4,5-tetrazine, 6-acetylamino-3-methylthio-1,2,4,5-tetrazine, and 6-(benzyloxycarbonylamino)-3-methylthio-1,2,4,5-tetrazine. All three underwent regioselective [4+2] cycloaddition with electron-rich dienophiles to form the corresponding functionalized 1,2-diazines in excellent yields <1998JOC6329>. He also synthesized 3,6-bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine <2003JOC3593>, 3-methylsulfinyl-6-methylthio-1,2,4,5-tetrazine and 3-(benzyloxycarbonylamino)-6-methylsulfinyl-1,2,4,5-tetrazine <2006JOC185>, and studied the scope of their reactivity in cycloaddition reactions.

González-Gómez and Uriarte developed the synthesis of pyridazine analogs of benzofurocoumarins <2002S43, 2003T8171> based on the reaction of 1-benzofuran-3(2*H*)-one **321** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **322** (Equation 78) <2002SL2095>. Pyridazinopsoralen derivatives **323** were synthesized (Scheme 79) <2005T4805> by a furan ring-expansion approach developed earlier <2000JHC907>. Snyder studied the inter- and intramolecular inverse electron demand Diels–Alder reaction of 3-substituted indoles as electron-rich dienophiles with 1,2,4,5-tetrazines in the synthesis of alkaloids <1996TL5061, 1997TL8611, 2001TL7929>.



Scheme 79

Balci published the synthesis of unusual bicyclic endoperoxides containing a pyridazine ring. Unsaturated bicyclic endoperoxides were reacted with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **322**. The primarily formed addition products gave the corresponding 1,4-dihydropyridazine derivatives upon extrusion of nitrogen. Oxidation of the 1,4-dihydropyridazine derivatives with phenyliodo-bis(trifluoroacetate) (PIFA) gave the corresponding pyridazine endoperoxides which can be further converted into highly substituted and functionalized pyridazine derivatives [<1996TL921, 2003JOC7009, 2003JHC529>](#). As an example [Scheme 80](#) shows the synthesis of product **324** from 2,3-dioxabicyclo[2.2.2]oct-5-ene (overall yield 83%).



Scheme 80

3-Aryl-5-tributylstannylpyridazines and 3,6-dichloro-5-tributylstannylpyridazine, very useful reagents for Stille reactions, have been synthesized from 3-aryl-1,2,4,5-tetrazines and from 3,6-dichloro-1,2,4,5-tetrazine respectively with ethynyltributylstannane <1998T4297, 1998TL5873>. More recently, highly substituted pyridazin-4-ylboronic esters, as reagents for C–C cross-coupling and C–O bond-forming reactions, have been made from substituted 1,2,4,5-tetrazines and alk-1-yn-1-yl boronic esters <2005AGE3889>.

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

This strategy, related to the syntheses starting from acyclic 1,4-dicarbonyl compounds and discussed in Section 8.01.9.2.2, is one of the major approaches to synthesize pyridazines and phthalazines. CHEC(1984) <1984CHEC(2)1> as well as CHEC-II(1996) <1996CHEC-II(6)1> showed many examples. Synthetic procedures included start from maleic anhydrides, phthalic anhydrides, 5-hydroxyfuran-2(5*H*)-one, 5-hydroxy/5-alkoxydihydrofuran-2(3*H*)-ones, 3-hydroxy-2-benzofuran-1(3*H*)-ones, 3-alkylidene-2-benzofuran-1(3*H*)-ones, furans, and 2,5-di-alkoxy-2,5-dihydrofurans. More examples starting from these substrate types appeared since CHEC-II(1996) <1996CHEC-II(6)1, 1996TL4145, 1998T6553, 2000BML2235, 2000MOL895, 2001BML33, 2001S2085, 2001T4389, 2003BML597, 2003JHC1065, 2003S2679, 2004EJO2797, 2004OBC1782, 2005BML2235, 2005BMC4425, 2005JHC427, 2005JOC6503, 2005S3654, 2006BML1040, 2006HAC8>. **Scheme 81** covers some representative new examples. For the synthesis of polycyclic 1,2-dihydropyridazine-3,6-diones reaction of the corresponding 3,4-ring fused 1-methyl-1*H*-pyrrole-2,5-diones with hydrazine has been reported in the last decade <1996H(43)1597, 1998FA468, 1999H(50)43, 2002JHC571>.

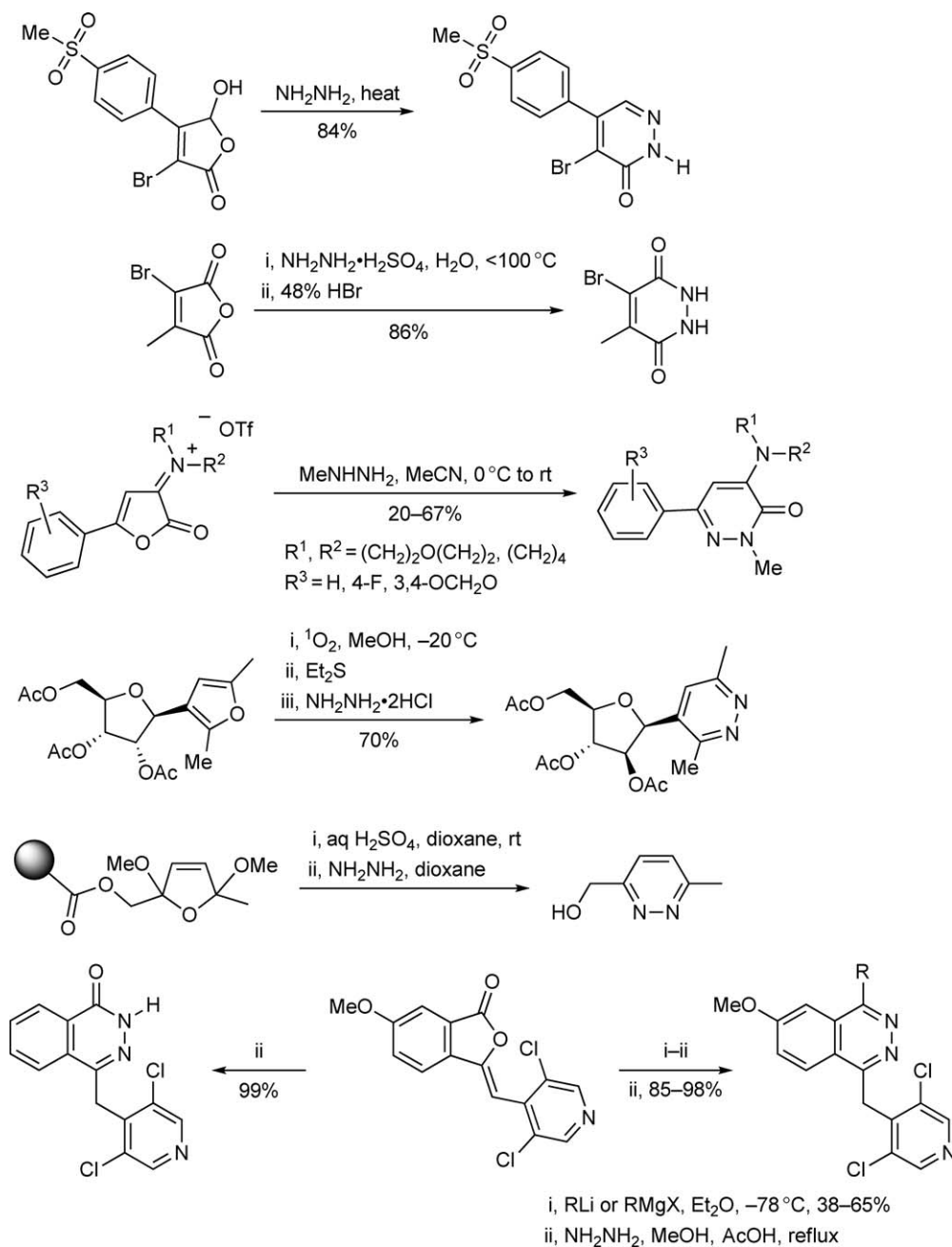
8.01.10.5 By Cleavage of a Second fused Ring

This section was not included in CHEC(1984) <1984CHEC(2)1>. CHEC-II(1996) <1996CHEC-II(6)1> showed examples such as starting from isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones, furo[3,4-*d*]pyridazines, and oxadiazolo[3,4-*d*]pyridazines. More examples on the cleavage of the isoxazolo ring in isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones appeared, yielding substituted pyridazin-3(2*H*)-ones <1997FA173, 1998BMC925>. A new addition is the irradiation of 3,3,4,7-tetramethylpyrazolo[3,4-*d*]pyridazine **325** in pentane–CH₂Cl₂ with a high-pressure mercury lamp through a 365 nm filter. This gave a mixture of 3,6-dimethyl-4-isopropenylpyridazine **326** and 1,4,7,7-tetramethylcyclopropa[*d*]pyridazine **327** (Equation 79). The ratio is a function of the irradiation time and **327** was found to be unstable at the temperature of irradiation and isomerized to alkene **326** <1995CC315>.

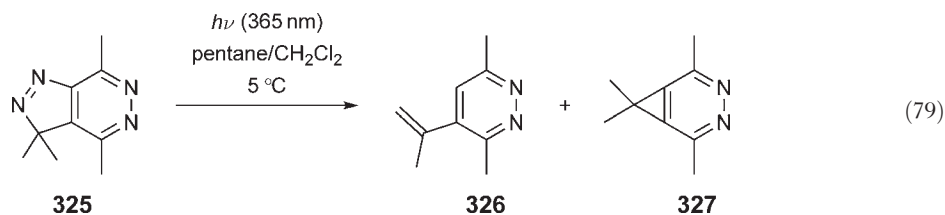
8.01.10.6 Other Methods

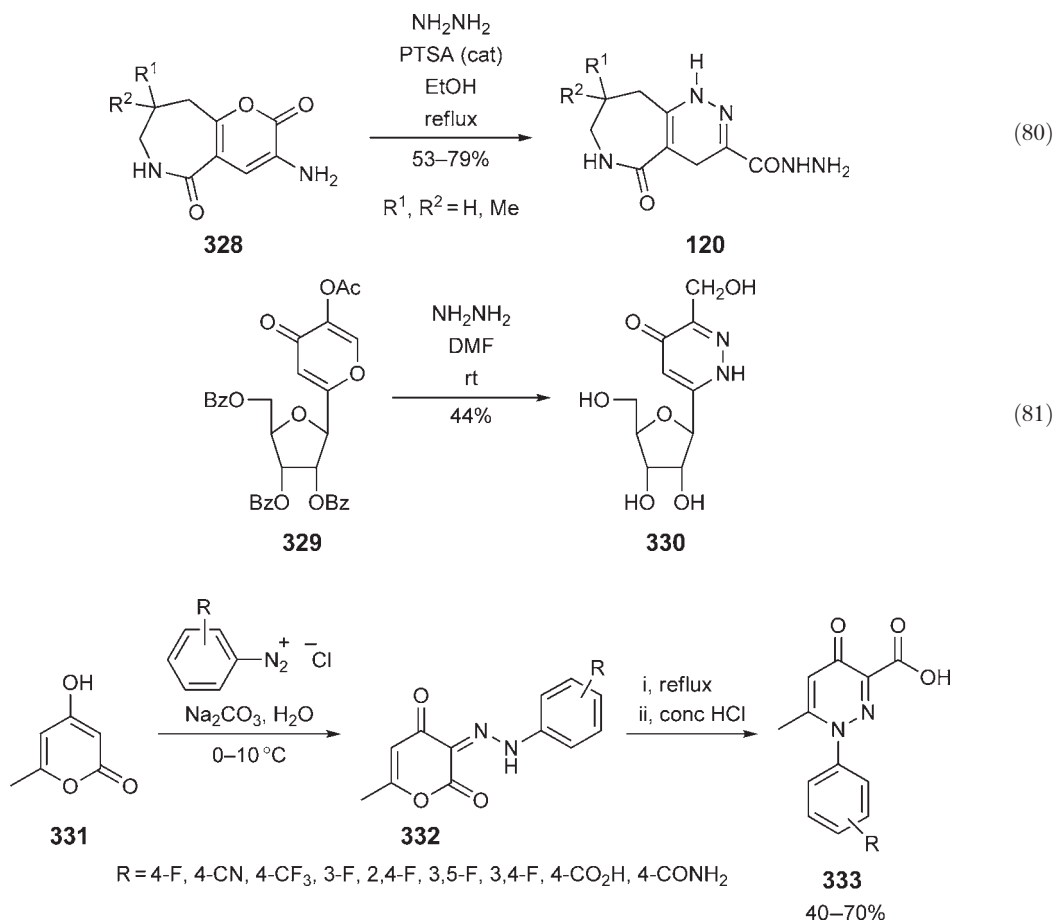
Besides examples in which a 1,2-diazine is formed via ring expansion or contraction involving hydrazine as reagent, there are also procedures where the ring size is not altered. Kočevr reported that reaction of pyrano[3,2-*c*]azepines **328** with hydrazine afforded pyridazino[4,3-*c*]azepine-based compounds **120** (Equation 80) <2000SL254>. Reaction of the 4-oxo-4*H*-pyran-3-yl acetate **329** with hydrazine gave the corresponding 3-(hydroxymethyl)pyridazin-4(1*H*)-one **330** (Equation 81) <1999CAR180>.

Ring transformation involving the intramolecular reaction of a hydrazone or *in situ* formed hydrazone also appeared. The transformation of 6-methyl-2*H*-pyran-2,3,4-trione 3-arylhydrazones **332** into 1-aryl-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acids **333** is an example of the former (**Scheme 82**). Compound **332** are formed via reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one **331** with substituted benzenediazonium chlorides. These are normally not isolated and immediately used further <2005EJM1325>. An example where a hydrazone is formed *in situ* is the reaction of 2-amino-5-aryldiazenyl-4-oxo-6-phenyl-4*H*-pyran-3-carbonitriles **334** with H₂SO₄ in glacial acetic acid, yielding 2-aryl-6-benzoyl-3-hydroxy-5-oxo-2,5-dihydropyridazine-4-carbonitriles **335** (**Scheme 83**) <2001T6787>.

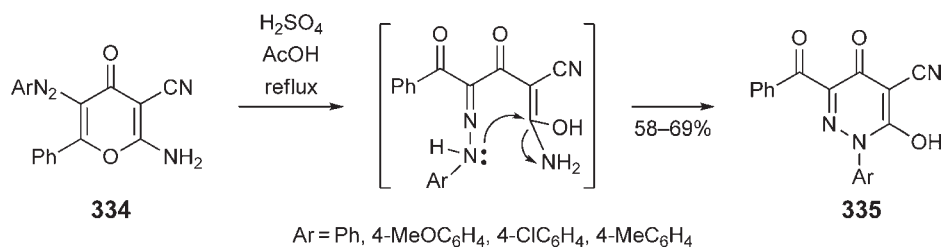


Scheme 81





Scheme 82



Scheme 83

8.01.11 Synthesis of Particular Classes of Compounds

8.01.11.1 Parent Compounds and Synthetically Important Derivatives

In CHEC(1984) and CHEC-II(1996) the most important ways to prepare the commercially available parent compounds pyridazine, phthalazine, and cinnoline were described <1984CHEC(2)1, 1996CHEC-II(6)1>. Also functionalized derivatives that are useful in synthetic programs were nicely covered. The most important type of substrates for this purpose are the easily accessible, halogenated (commonly chlorinated) derivatives exemplified by 3,6-dichloropyridazine, 3,4,5- and 3,4,6-trichloropyridazine, 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones, 1,4-dichlorophthalazine, and

4-chlorocinnoline. Their importance lies in the electron-deficient character of the 1,2-diazine nucleus which makes nucleophilic substitution an easily performable reaction. Chlorine and bromine substituents are mainly introduced via deoxyhalogenation of the corresponding (hydroxy)-1,2-diazinones (e.g., 3,6-dichloropyridazine and 1,4-dichlorophthalazine) <B-2006MI541>. Another classical route, to access a very important class of pyridazine derivatives, involves ring synthesis of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones or 4,5-dibromopyridazin-3(2*H*)-ones via the reaction of hydrazines with mucochloric and mucobromic acid, respectively <B-2006MI541>. A new contribution to this area is the synthesis of 5-chloro-4-iodo-2-methylpyridazin-3(2*H*)-one **186** starting from an appropriate mixed mucohalic acid which can be easily prepared from mucochloric acid via transhalogenation with MeMgI <2005JHC427>. Also other new, easily accessible, halogenated derivatives that will be very useful in synthetic programs have been reported since 1995. Heating (2-substituted) 4,5-dichloropyridazin-3(2*H*)-one(s) in 57% HI yields (2-substituted) 5-iodopyridazin-3(2*H*)-one(s) which represent a very smooth access to a (2-substituted) 5-halopyridazin-3(2*H*)-one otherwise not so easily accessible <2004JST(713)235>. The mechanism involves transhalogenation to the 4,5-diiodo derivative followed by C-4 hydrodeiodination on the *O*-protonated pyridazin-3(2*H*)-one. Desymmetrization of 3,6-dichloropyridazine via mono transhalogenation by heating with NaI in 57% HI at 40 °C gave 3-chloro-6-iodopyridazine **174** <1999T15067>. Reaction temperature and time are crucial factors to obtain a high selectivity in this transhalogenation reaction. Pseudohalides such as triflate esters are a relatively new type of leaving groups prepared via esterification of 1,2-diazinones or hydroxy-1,2-diazinones <1994H(38)1273, 2001SL150, 2001T10009>. The recently increased interest in triflate esters is a consequence of the combination of their ease of formation and applicability as a leaving group in transition metal catalyzed reactions (see Section 8.01.7.13.2). The presence of two different halides or a halide and a triflate ester on a pyridazine or pyridazinone unit allows selective Pd-catalyzed reactions (see Section 8.01.7.15.2).

8.01.11.2 Synthesis of Pyridazino Fused Ring Systems

Recently, a new strategy for the synthesis of 4,5-pyridazino-fused ring systems has been developed. Several representatives (including new skeletons) have been obtained following this new approach. The topic has been reviewed recently <2004SL1123>. The method is based on the combination of a Pd-catalyzed C–C bond-forming process and a C–X (X = N, O) or another C–C bond-forming reaction (C–X: nucleophilic substitution, condensation, lactonization, nitrene C–H insertion, Buchwald–Hartwig amination) (C–C: Suzuki reaction, Pschorr reaction, Heck-type reaction), by which a heterocyclic or carbocyclic moiety is fused to the pyridazine skeleton. The classical route to 4,5-pyridazino-fused systems follows a completely different approach in which the pyridazine ring was built up via the cyclocondensation of an *ortho*-dicarbonyl moiety of a hetero- or carbocycle with a hydrazine. The new procedure starts from easily accessible 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones as substrates (see Section 8.01.11.1). Generally, a nonselective behavior of the two carbon–chlorine bonds of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones in Pd-catalyzed reactions is observed, which obviously limits the direct use of these compounds for such reactions. Only after careful optimization for a specific organometallic compound can selectivity be achieved <2004H(62)851>. Interestingly, several simple nucleophiles can be easily introduced in a regioselective way just by changing the solvent of the reaction. Therefore, by first blocking the 4- or 5-position via reaction with a nucleophile, regioselectivity problems can be simply avoided in a subsequent Pd-catalyzed C–C coupling reaction without laborious optimization. The group introduced by the nucleophilic substitution could then be utilized for another intra- or intermolecular C–C or C–X bond formation as it is or by its simple conversion into a better leaving group. The authors classified these ‘protecting groups’ as PMFs. A methoxy group has shown to be a very useful PMF. In a second approach, 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones were transformed into 2-alkyl-5-iodopyridazin-3(2*H*)-ones. In this case the unfunctionalized C-4 acts as a PMF since after C-5 functionalization it can be used immediately for a cyclization reaction (Heck-type reaction or a nitrene C–H insertion). Interestingly, a similar approach has been used by LaVoie and co-workers to synthesize cinnoline-fused isoquinolinones starting from 4-chlorocinnolines <2004BMC795>.

8.01.12 Important Compounds and Applications

8.01.12.1 Introduction

The interest for applications of pyridazines, phthalazines, and cinnolines as pharmaceuticals, agrochemicals, and materials certainly increased in the period 1996–2006. The database Scifinder revealed that 669 patents containing the topic ‘pyridazine’ were published in this time frame. Similarly, for the benzo analogs ‘phthalazine’ and ‘cinnoline’

respectively 277 and 65 patents appeared. This is of course only a rough picture of the actual number as the Scifinder search result is word dependent. For instance, the topic 'pyridazinone' gave 251 patent answers while 'pyridazin-3(2*H*)-one' resulted in only 23 patent hits. Of course also scientific publications frequently refer to or show very specific applications. Here we see a clear shift. While between 1982 and 1995, the applications were mainly focused on medicinal aspects of 1,2-diazines, more recently there is a clear increased interest from material sciences. The increased scientific activity in 1,2-diazine applications certainly stems from its historical less developed state in comparison with the other diazines. While historically the 1,2-diazine nucleus was treated in a rather stepmotherly way when compared with the 1,3- and 1,4-diazines, it now booms as there is more freedom for IP generation. This section focuses on trends and gives examples in the three application areas mentioned but is certainly not a comprehensive overview of what has been published in the period 1996–2006 as this is out of the scope of this section.

8.01.12.2 Compounds that Occur in Nature

The first natural product containing an aromatic 1,2-diazine ring (Pyridazomycin, **336**) was not described before 1988 <1988JAN595> (Figure 14)! In 1997 Pyridazocidin **337** which is closely related in structure to Pyridazomycin was isolated <1997WSC654> (Figure 14). Fenical at the Scripps Institution of Oceanography reported Azamerone **338**, produced by a marine-derived bacterium related to the genus *Streptomyces*, to be a new representative <2006OL2471> (Figure 14). Although it has been stated (on the basis of NMR data) that the structure of Samoquasine A, isolated from the seeds of the custard apple, can be a benzo[*l*]phthalazin-4(3*H*)-one, Maes and Mátyus recently showed that this assumption is not correct <2007T3870>. Reduced pyridazines have been found earlier in nature. In 1971 the first examples of naturally occurring hexahydropyridazines **339–341** were reported by Hassall and co-workers <1971JC514> (Figure 14). In CHEC-II(1996) <1996CHEC-II(6)1>, several examples of naturally occurring hexahydro- and tetrahydropyridazines were reported. Later Tišler reviewed this topic up to mid-1998 <2000AHC(75)167>. New examples published since then include Sanglifehrin A–D **342** <1999JAN474> (Figure 15), Polyoxypeptins A and B **343** <1999JOC3034> (Figure 16), Chloptosin **344** <2000JOC459> (Figure 17), Pipalamycin **345** <2002JAN1> (Figure 18), Sch 382583 **346** <2004JOC1734> (Figure 19), and Kutznerides 1–9 **347** <2006JNP1776> (Figure 20). The biosynthesis of the N–N bond of the natural products remains an intriguing puzzle with several proposals. It is likely that in the majority of cases this results from the coupling of nitrogen atoms of amino acids. Generally, the late discovery of naturally occurring (reduced) 1,2-diazines is considered to be the main reason for the slower development of the 1,2-diazine chemistry in comparison with the other diazine isomers. After all, one of the major factors stimulating the development of heterocyclic chemistry was and still is the occurrence of heterocyclic skeletons in natural products.

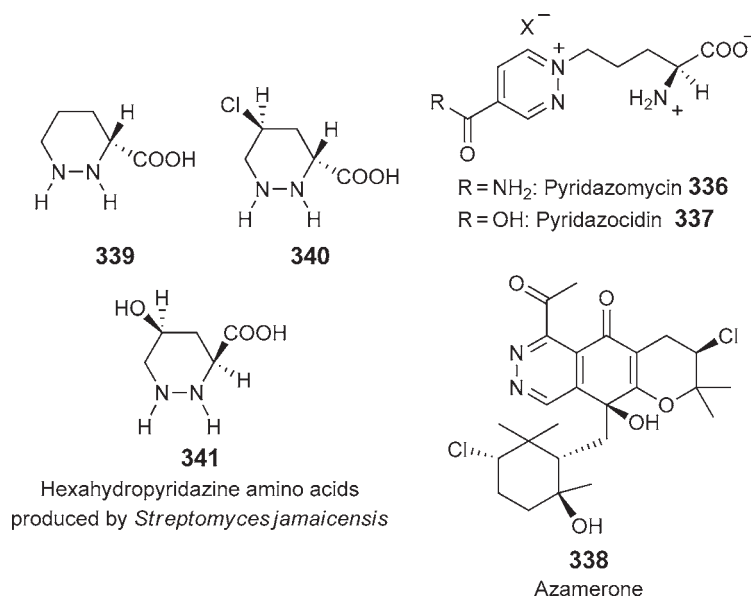
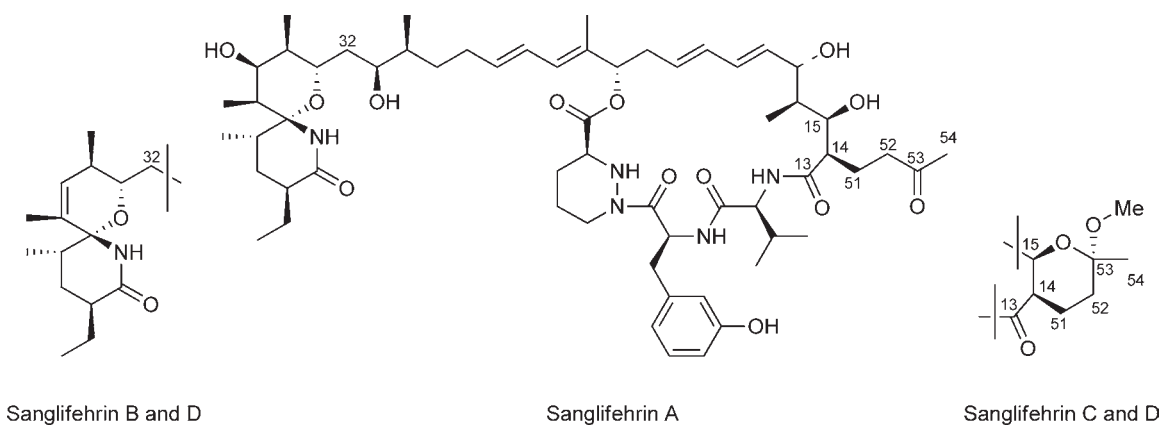
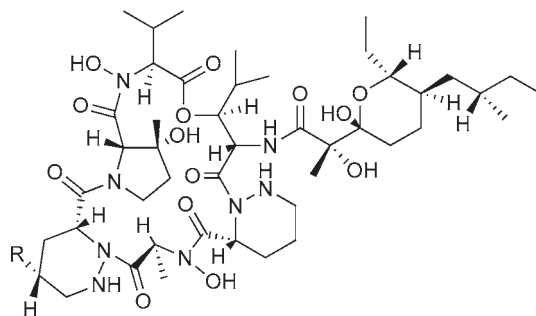


Figure 14 Some naturally occurring 1,2-diazine derivatives.



342

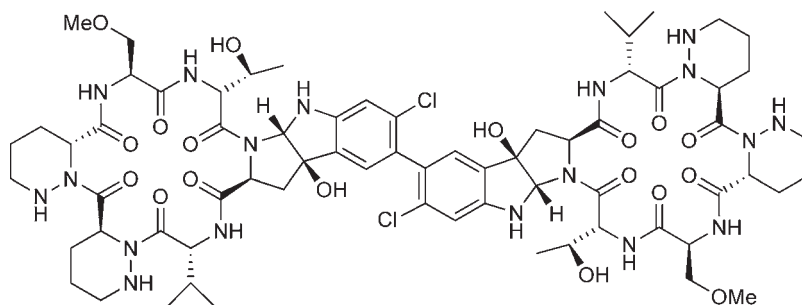
Figure 15 Sanglifehrins A–D.



343

Polyoxypeptin A, R = OH
Polyoxypeptin B, R = H

Figure 16 Polyoxypeptins A–B.



344

Figure 17 Chloptosin.

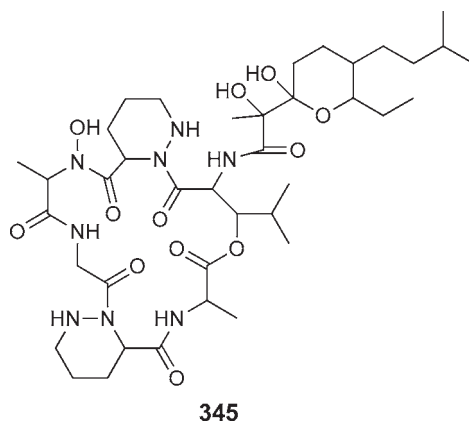


Figure 18 Pipalamycin.

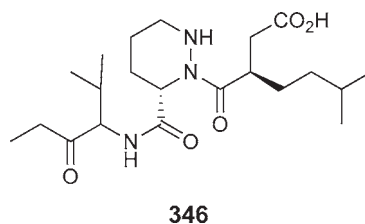


Figure 19 Sch 382583.

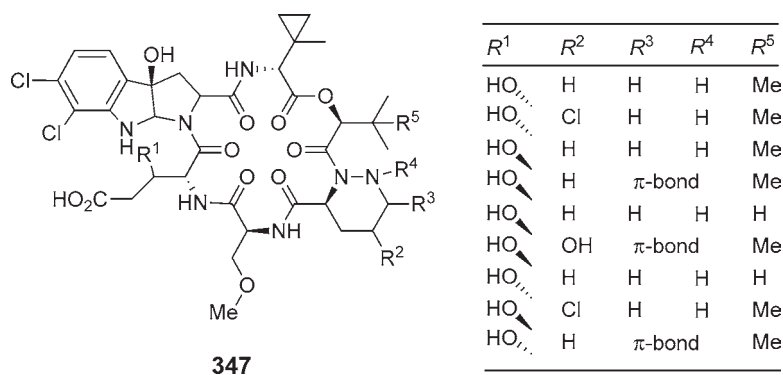


Figure 20 Kutznerides 1–9.

8.01.12.3 Pharmaceuticals

Since the discovery of hexahydropyridazine containing natural products a large number of patents and papers have been published dealing with the synthesis of pharmaceutically useful 1,2-diazine derivatives. Compounds which have been launched as pharmaceutical products include Amezinium metilsulfate **348** (selective noradrenergic antihypotensive), Azelastine **349** (antiasthmatic, antiallergic, antihistaminic), Cadralazine **351** (antihypertensive, vasodilator), Cefozopran **352** (antibacterial), Cinoxacin **353** (antibacterial), Emorfazone **354** (anti-inflammatory, analgesic), Hydralazine **355** (antihypertensive), Minaprine **356** (antidepressant), Nifurpazine **361** (antibacterial), Pildralazine **350** (hypotensive, vasodilator), Pimobendan **362** (cardiotonic, PDE III inhibitor, vasodilator), Sulfamethoxypyridazine **357** (antibacterial), and Sulfachlorpyridazine **358** (antibacterial) (Figure 21). There are also interesting compounds in clinical trials. Vatalanib **359** for instance, a phthalazine-based compound, is an example of a very promising 1,2-diazine that is currently in phase III for the treatment of cancer (Figure 21). Telatinib **360**, a furopyridazine, is in early clinical trials for the same purpose (Figure 21).

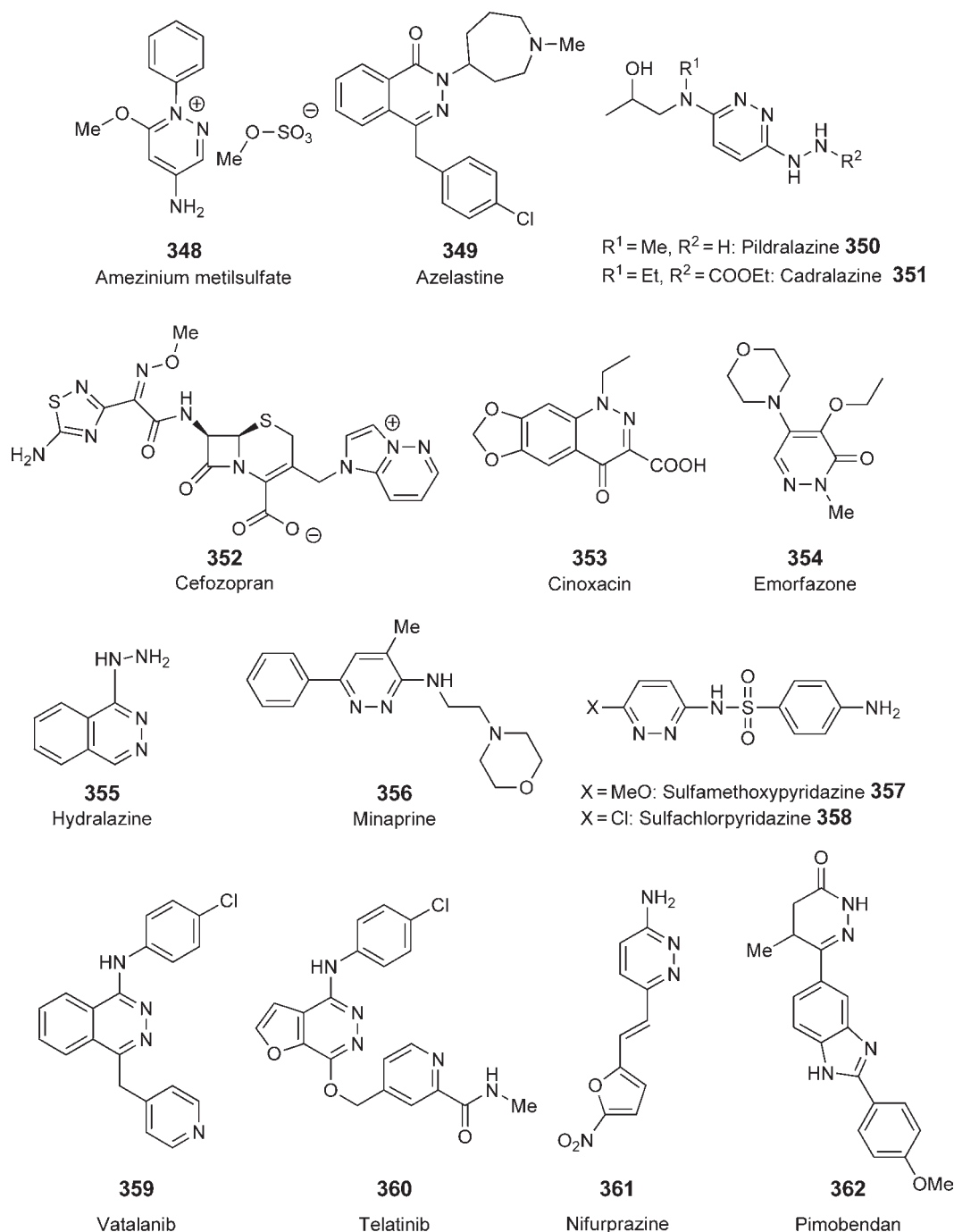


Figure 21 Launched 1,2-diazine derivatives with pharmaceutical applications and some products in clinical trials.

The number of patents that appeared in the last decade, both from industry and from academia, describing 1,2-diazines with a pharmaceutical useful profile is enormous. Therefore, only some recent selected examples are mentioned here (**Figure 22**). Eli Lilly patented imidazo[1,2-*b*]pyridazines as corticotrophin-releasing factor 1 receptor antagonists for threatening psychiatric and neurological diseases. Compound **363** showed a $K_i = 9.98 \text{ nM}$ in a CRF1 filter binding assay <2006WO102194>. Piperazinyimidazo[1,2-*b*]pyridazine-2-carboxamides are claimed to be useful for the treatment of stearyl-CoA desaturase (SCD)-mediated disease (e.g., type II diabetes) by Xenon

pharmaceuticals <2006WO034312>. The same company showed that piperidinylpyridazinecarboxamide derivatives can be used for the same purpose <2006WO034338>. Several substituted pyridazines were patented as modulators of cellular pathways. Compound **364** for instance caused 91% inhibition of human ether-a-go-go related gene (hERG) potassium ion channel binding <2006WO050389>. Medicinal chemistry refinement on **364** yielded Minozac which recently entered in the phase I clinical trials and is a promising candidate for the treatment of Alzheimer. Pyrrolopyridazines exemplified by **365** are PDE-IV inhibitors ($IC_{50} < 1 \mu M$) and inhibit production of tumor necrosis factor alpha (TNF- α) ($IC_{50} = 64 \text{ nM}$) <2006WO004191>. Also pyridazin-3(2*H*)-ones such as **366** ($IC_{50} = 0.07 \text{ nM}$) and **367** ($IC_{50} = 1 \text{ nM}$) are PDE-IV inhibitors <2005WO123693, 2005USP203095>. Merck and Co. described pyrazinopyrrolopyridazines, exemplified by **368** and **369**, as HIV integrase inhibitors <2005WO110415, 2005WO110414>. Pyridazin-3(2*H*)-ones with CDK2 (CDK = cyclin-dependent kinase) inhibitor properties were patented by Aventis Pharma. Compound **370** shows an IC_{50} of $0.033 \mu M$ in CDK2/Cyclin E flashplate assay <2005EUP1598348>. Other kinase inhibitors are, for instance, **371** which is a IKK (I κ B kinase) inhibitor. It exhibits an IC_{50} of $0.88 \mu M$ <2005WO105808>. Merck and Co. reported that triazolopyridazines such as **372** are of interest to treat neuropathic pain <2005WO041971>. Besides phthalazine-based compounds, there are also a substantial number of compounds reported based on a cinnoline nucleus. For instance, **373** is a PDE10 inhibitor that has potential to be used to treat psychiatric or neurological syndromes <2006WO028957>.

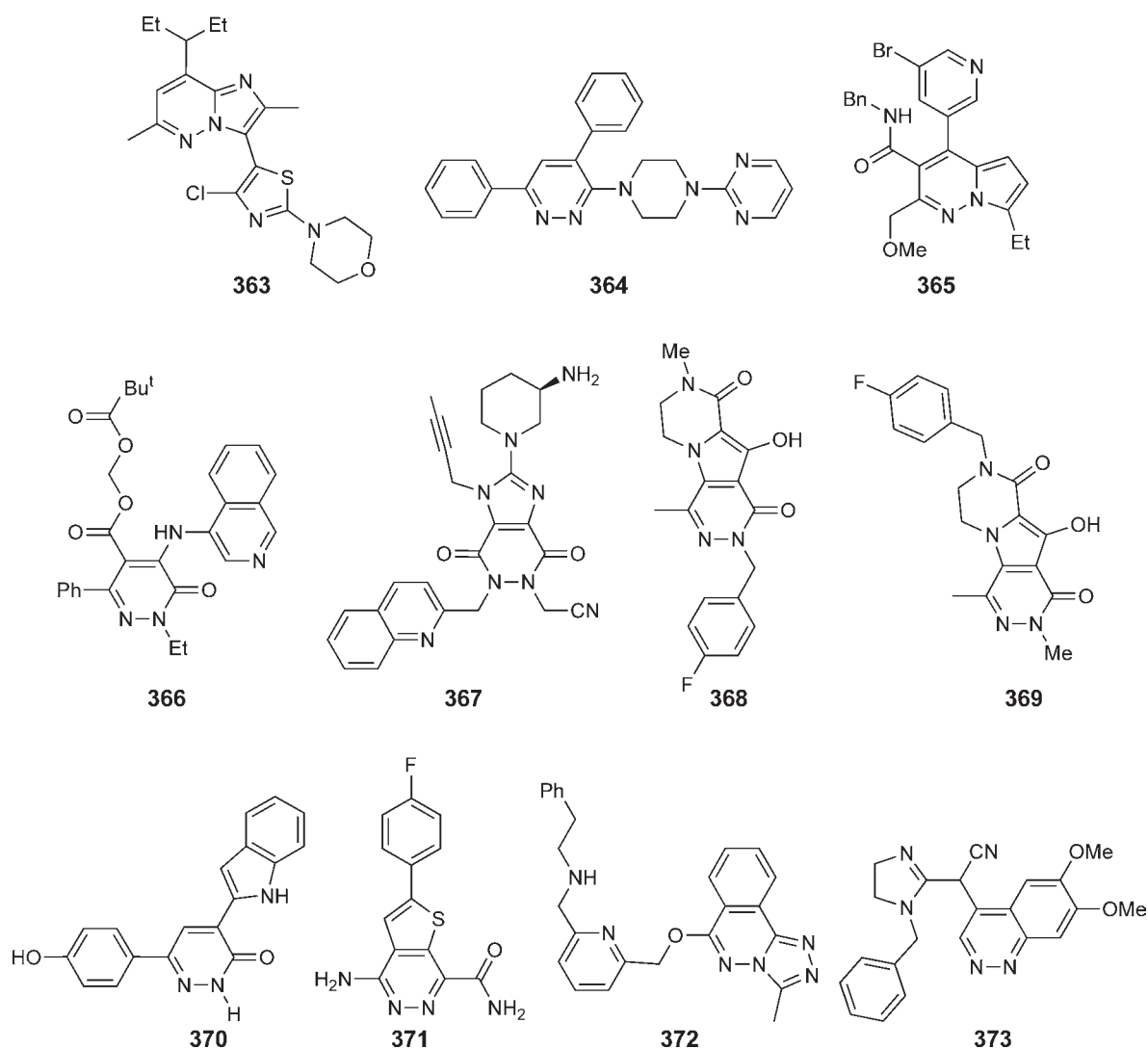


Figure 22 Patented 1,2-diazine derivatives with pharmaceutical applications.

There are several research teams in academia that have focused (an important part of) their research on the specific development of pharmaceutically active compounds based on a 1,2-diazine core. For each lab mentioned a recent reference is provided for each topic allowing the interested reader to find easily the literature published by the team in that specific area. We mention here some leading medicinal chemistry teams and their main line(s) of investigation in the 1996–2006 period. The team of Dal Piaz from Firenze developed antinociceptive compounds <2006JME7826> and potent PDE inhibitors <2006JME5363>. Barlocco's lab in Milan searched for acyl CoA: cholesterol acyl transferase (ACAT) inhibitors <2005JME7708>, $\alpha(1)$ adrenoceptor antagonists <2001JME2403>, nicotinic agents <2002JME4011>, and aldose reductase inhibitors <1999JME1894>. Part of her work has been carried out in collaboration with Cignarella and Dal Piaz. Bourguignon in Strasbourg has been active in several areas including neuroinflammatory compounds <2002JME563>. Together with Watterson from the USA he initiated the development of Minoxac. Wermuth also located in Strasbourg developed potent pyridazin-3-amines with acetylcholinesterase inhibitor and muscarinic M1 agonist activity <1999JME730>. His 'selective optimization of side activities' (SOSAs) approach exemplified by starting from Minaprine has led to 1,2-diazines with a wide variety of biological activities <1998JHC1091, 2004JME1303>. The group of Sotelo and Raviña from Santiago de Compostela mainly focused on the development of platelet aggregation inhibitors <2004BML321>. Haider in Vienna searched for 1,2-diazine analogs of antitumor pyridocarbazole alkaloids (e.g., ellipticine and olivacine) with an improved pharmacological profile <2006COR363>. Heinisch, another prominent scientist from Austria, reported 1,2-diazines as non-nucleoside human immunodeficiency virus type 1 reverse transcriptase inhibitors <1997MI443>. Mátyus worked on several topics including 5-HT_{1A} receptor ligands and adrenoceptor agonists <1997BML2857, 1997MI427, 1997MI513, 1999MI1072>.

8.01.12.4 Agrochemicals

In contrast to the medicinal applications, the interest for the use of 1,2-diazines as agrochemicals has existed for a much longer time. In 1964 BASF already launched the herbicide Chloridazon **374** (Figure 23). Even today Chloridazon is still used for the cultivation of sugar beet and red table beet. Brompyrazon **375**, Norflurazon **376**, Metflurazon **377**, Oxapyrazon **378**, Flufenpyr **379**, and Dimidazon **380** are structurally closely related herbicides (Figure 23). Norflurazon for instance is a crop-protection agent, used for the cultivation of cotton, tree fruit, and vines. Several other pyridazine herbicides found the way to the market, such as Maleic hydrazide **381**, Pydanon **382**, Pyridate **383**, Pyridafol **384**, and Credazine **385** (Figure 23). Diclomezine **386** was launched in 1987 by Sankyo and is a fungicidal pyridazine (Figure 23). There are also examples of commercialized insecticidal 1,2-diazines: the cholinesterase inhibitor Pyridaphenthion **387** (1974, Mitsui Toatsu Chemicals) and the energy metabolism disruption agent Pyridaben **388** (1991, Nissan Chemicals) (Figure 23).

In the last decade there appeared several new patents dealing with new 1,2-diazine representatives with an interesting and promising agrochemical profile. Sankyo Agro Co. for instance patented 6-chloro-3-(3-chloro-1*H*-pyrazol-1-yl)pyridazin-4-ol as a new herbicidal 1,2-diazine <2004JPP284970>. Soil treatment with this pyridazinol revealed a strong growth inhibition of for instance *Echinochloa crus-galli* and *Amaranthus retroflexus* without damage to corn. Sumitomo Chemical Co. reported that the combination of 1-(2-chloro-6-propylimidazo[1,2-*b*]pyridazin-3-ylsulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl)urea and cafenstrole gave a better herbicidal effect against *Echinochloa oryzicola* than when cafenstrole was used alone <2005JPP126415>. They also reported synergistic herbicidal effects (weeds of wheat fields) for combinations of ethyl 2-chloro-4-fluoro-5-(4-methyl-5-trifluoromethyl-3-pyridazinon-2-yl)phenoxyacetate with for instance bromoxynil <2000JPP136104> and proved that several representatives of the 3,6-disubstituted 4,5-diarylpyridazine family **389** are useful to control *Pyricularia oryzae* as a fungicidal activity of $\geq 90\%$ was observed <2006WO001175>. Also the 2-benzyl-6-(4-chlorophenyl)pyridazin-3(2*H*)-one **390**, reported by Rohm and Haas Co., proved to be very promising as fungicide as 85% control of *Phytophthora infestans* infected tomato plants at 300 g ha⁻¹ was achieved (Figure 24) <1996EUP711759>. Several new 1,2-diazines with insecticidal properties were also discovered. *N*-Arylureas of 3-aryl-1,4,5,6-tetrahydropyridazines **391** for instance have shown to be very active (Figure 25). Conformationally restricted analogs such as **392** showed excellent activity against a broad spectrum of lepidopteran pests (Figure 25). Field trials on vegetables and cotton against fall armyworm, cabbage looper, diamondback moth, and tobacco budworm had activities as low as 10–20 g ha⁻¹. The slow degradation of the compound combined with the difficulties to prepare it on large scale led to the decision not to pursue commercialization. The compound **392** however served as a key template for further research and finally led to the oxadiazine insecticide Indoxacarb **393** which has been launched by Dupont Crop Protection in 2000 (Figure 25). The (+)-(*S*)-enantiomer was found to be twice as active as the racemic mixture. In agreement with this observation the (–)-(*R*)-

enantiomer proved to be completely inactive. Indoxacarb is sold as a 3:1 mixture of the (active) (*S*)-isomer and (inactive) (*R*)-isomer. It works via blocking of the sodium channel in neurons, a mode-of-action first identified in pyrazolines <B-2002MI1>. Researchers of Bayer Cropscience patented pyridazin-4-ylcarboxamide **394** since in *Spodoptera frugiperda* corn sheet disk assays at 500 g ha⁻¹ 100% protection was found after 7 days (Figure 25) <2006WO000333>. Rohm and Haas Co. found the 6-arylpyridazin-3(2*H*)-one **395** to be interesting as it gave a good control when tested against Mexican bean beetle and two-spotted spider mite at 300 g ha⁻¹ (Figure 25) <1996EUP738716>. Compound **396**, another representative of this class, gave 95% control of *Plasmopara viticola* on grape plants (Figure 25) <1998EUP835865>. It is intriguing that there is not much activity in academia in the agrochemical application area. A representative example is the group of Qian in Dalian working on the development of new pyridazin-3(2*H*)-one containing insecticides <2003JFA152>.

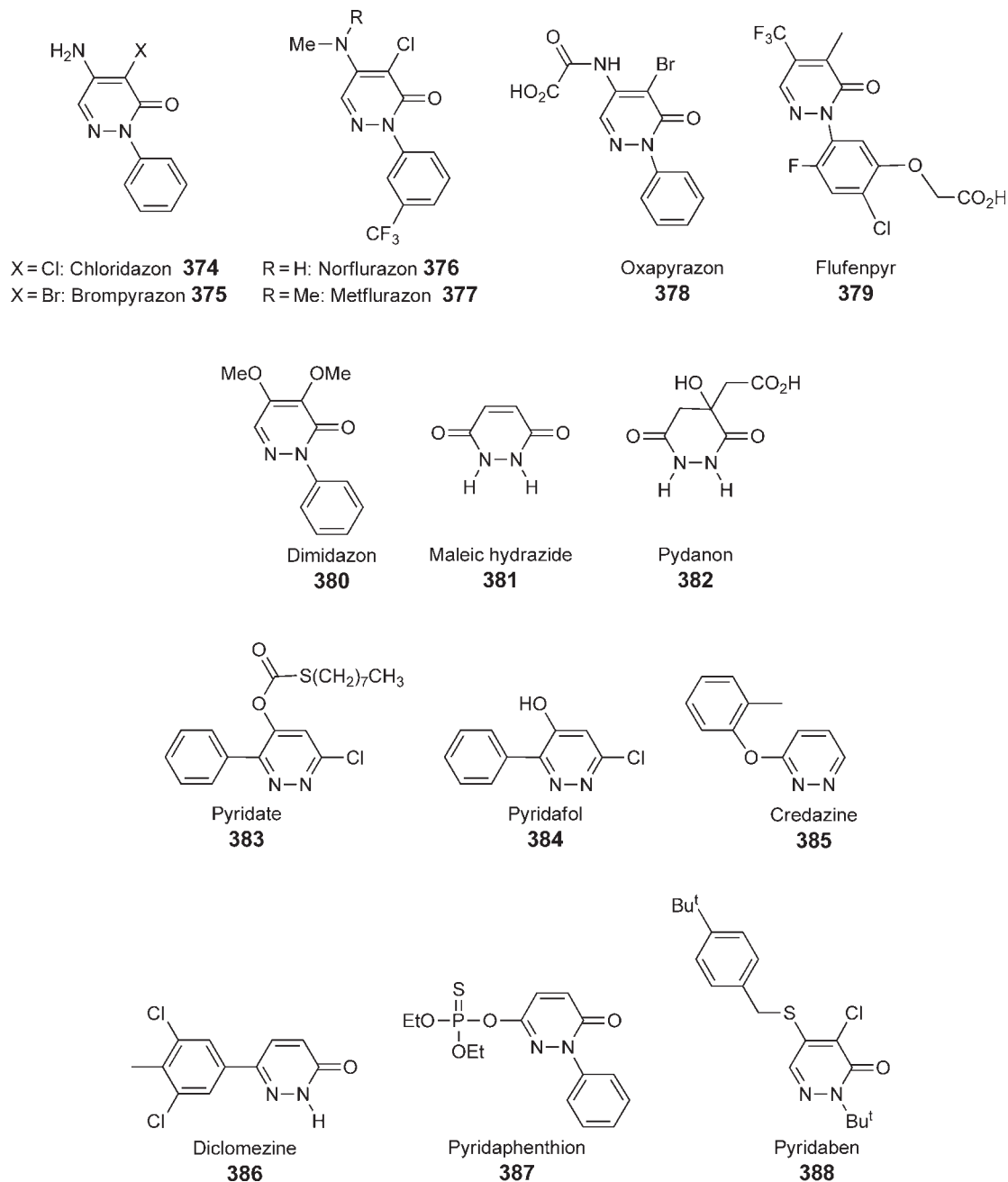


Figure 23 Launched 1,2-diazine derivatives with agrochemical applications.

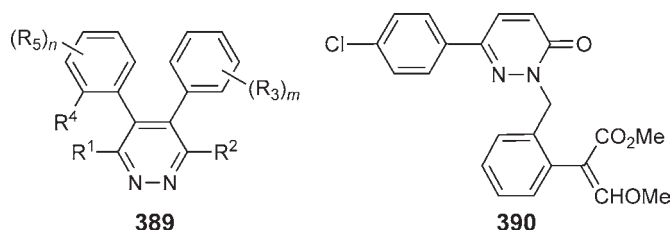


Figure 24 Patented 1,2-diazine derivatives with agrochemical applications.

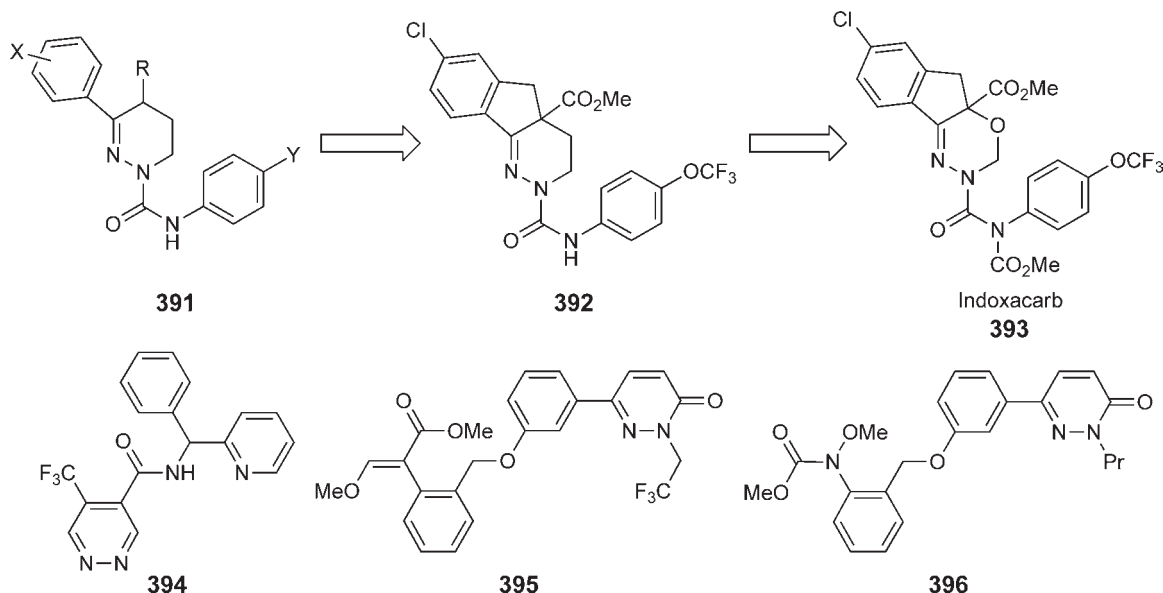


Figure 25 Patented 1,2-diazine derivatives with agrochemical applications.

8.01.12.5 Material Sciences

As already mentioned in Section 8.01.5.2.2, 1,2-diazine-containing molecules have frequently been used to prepare metal complexes. The ability to form complexes with metals has been exploited to get self-assembling systems. An example is the use of 1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (Figure 26) <2004JCD695>. Hydrogen bonding has also been shown to be a useful interaction to induce self-assembly of 1,2-diazines. An example is the phthalazine-1,4-dione entity that can give trimer compounds like **397** via lactim–lactam tautomerism (Figure 27) <1998JA9526>. A self-assembled helical stack based on an oligoheterocyclic pyridine–pyridazine **398** (Figure 28) also appeared <2000AGE233>. The desired transoid conformation around the interheterocyclic bonds of **398** most probably results from (1) a weak, favorable interaction between the lone pair of electrons on nitrogen and the adjacent hydrogen atom on the neighbouring heterocycle in the transoid conformation; (2) favorable antiparallel orientation of the nitrogen dipoles in the transoid conformation; and (3) unfavorable steric interactions between CH sites in the cisoid conformer. Fiber formation via self-aggregation of two coiled-coil self-assembled stacks was also observed. Luminol linked calixarene **399** has been shown to give a specific response to Ag^+ , making it useful as a chromogenic reagent for detection of Ag^+ <1998ANA(362)121>. Compound **400** is a combination of luminol and firefly luciferin that can trigger both horseradish peroxidase and firefly luciferase in solution <1999MI159> (Figure 29). Hydralazine **355** proved useful for the fluorimetric determination of formaldehyde <2001AN104>. Pyridazine-derived ionic liquids, based on a pentafluoro-sulfonyl group, were also reported <2005EJI2573>. Also prevention of corrosion seems to be an attractive material application <2002MI373, 2004MI4205>. Many polymers containing a 1,2-diazine unit have been reported in the period 1996–2006. Applications mentioned include proton exchange membranes for fuel cells <2005MM3564>, high-temperature gas separation <1999JAP2385> and for ultrafiltration and nanofiltration <2000JAP1685> as well as polymers and oligomers with interesting optical and electrochemical properties <2005CM6060, 2002HCA2195>. A photochromic molecular switching device based on a 4a,5-dihydropyrrolo[1,2-*b*]pyridazine skeleton appeared which can be potentially useful for the nondestructive readout optical memory <1998AMI348>.

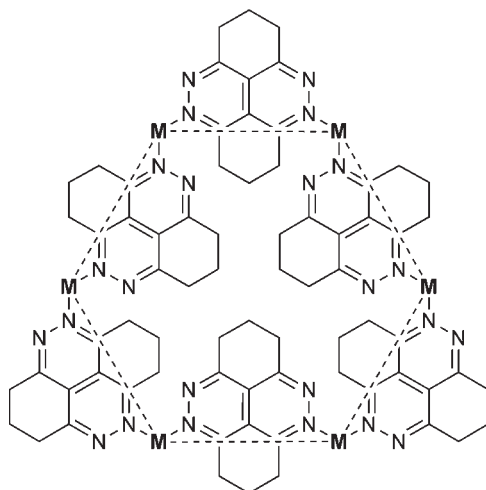
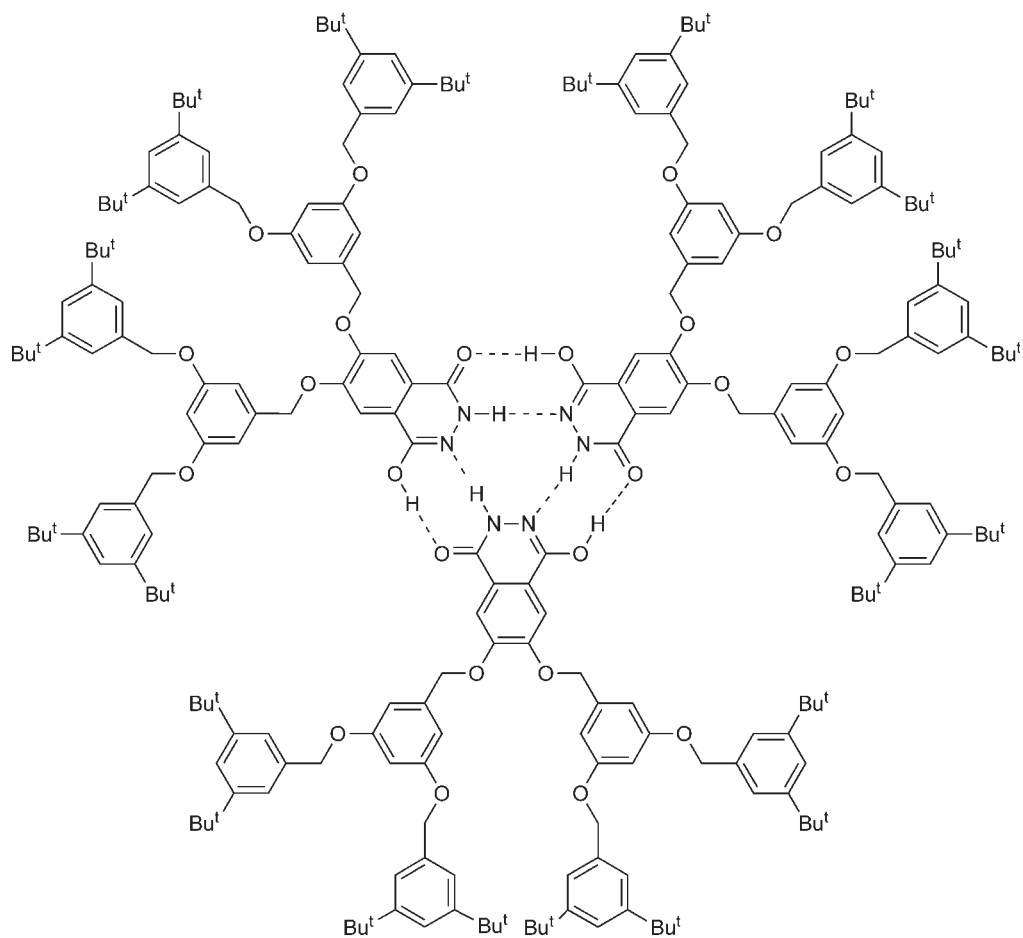


Figure 26 1,2,3,6,7,8-Hexahydrocinnolino[5,4,3-*cde*]cinnoline-based metal complexes.



397

Figure 27 Phthalazine-1,4-dione-based trimer **397**.

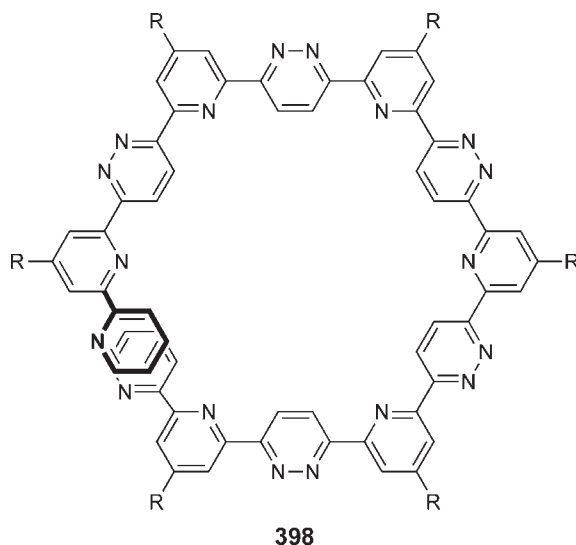


Figure 28 A self-assembled helical stack **398**.

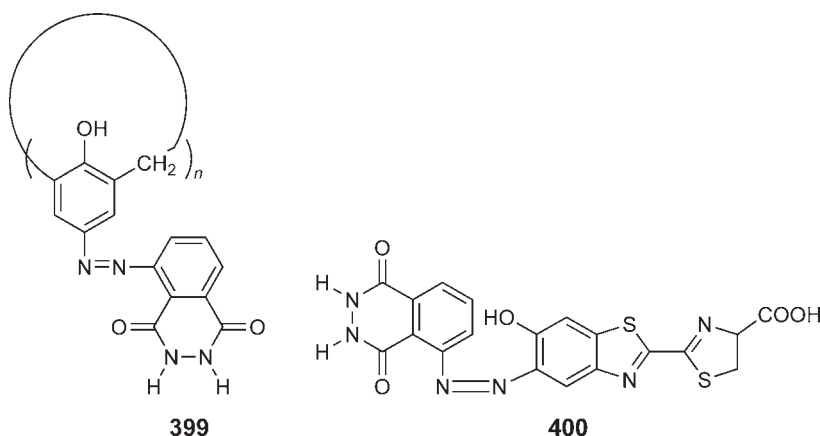


Figure 29 Luminol-linked compounds **399** and **400**.

8.01.13 Further Developments

Partial catalytic hydrogenation in the pyridazine unit of (1*R*,3*R*,4*R*)-3-(6-substituted[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones could be achieved with Pd/C catalyst using 50 bar of H₂ <2006TA79>. Good to excellent de's were obtained.

Additional examples of the Cu-catalyzed *N*-arylation of 4,5-ring fused pyridazin-3(2*H*)-ones appeared <2006JME3753>.

4-Aryl-5-azidopyridazin-3(2*H*)-ones have been used to smoothly prepare azacabolines via a thermolysis reaction involving the formation of nitrenes <2006H(68)2549>.

Polyphosphoric acid (PPA) has recently been used for the intramolecular reaction of a properly positioned amino group with the carbonyl group of the lactam function of a pyridazin-3(2*H*)-one unit as exemplified by the ring closure of 2-(2-aminophenyl)phthalazin-1(2*H*)-one <2006T10018>.

Additional examples on Suzuki <2006H(68)2549, 2006JME3402, 2006MI429>, Stille <2006OL4699, 2006T7339> and Sonogashira reactions <2006JME3753> of halopyridazines and pyridazin-3(2*H*)-ones appeared. The first examples dealing with the arylation of 1-substituted halopyridazin-1(4*H*)-ones were also published <2006OBC4278>. A new

development following the cross-coupling reactions on unprotected halopyridazin-3(2*H*)-ones is the use of 4-halo-1,2-dihydropyridazin-3,6-diones as substrates <2006MI429>.

A novel ring-closure starting from 2-aryl-1-(1*H*-1,2,4-triazol-1-yl)alk-3-yn-2-ols has been reported <2006T8966>. Treatment of these alkynols with Br₂ at room temperature yielded 5-alkyl-7-aryl-6-bromo-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ium bromides which upon hydrolysis give 3-alkyl-5-arylpyridazines.

Although many examples of the reaction of hydrazines with 1,4-dicarbonyl compounds have been published the reaction of 1-benzyl 6-methyl (2*S*)-2-[[[(benzyloxy)carbonyl]amino]-4-oxohexanedioate with hydrazines is worth mentioning as benzyl *N*-[[[(benzyloxy)carbonyl]-3-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-L-alaninates or methyl [(5*S*)-5-[[[(benzyloxy)carbonyl]amino]-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl]acetates can be formed. The product formation seems to depend on the nucleophilicity and steric bulk of the N-substituent of the hydrazine <2006S2376>. One of the carbonyl compounds can also be a nitrile <2006TL8965, 2006H(68)949>. This gives direct access to an amino group. A recent example is the use of methyl 2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate as substrate. Reaction of this compound with hydrazine yielded a mixture of benzyl (6-amino-3-oxo-2,3-dihydropyridazin-4-yl)carbamate and benzyl (1-amino-5-imino-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)carbamate <2006H(68)949>.

Schubert and co-workers investigated the effect of (superheated) microwave conditions on the inverse electron demand Diels–Alder reaction of 3,6-di(pyridine-2-yl)-1,2,4,5-tetrazine with acetylenes. Interestingly, enol tautomers of various ketones and aldehydes could also be used as dienophiles allowing a smooth access to the corresponding 4-substituted pyridazines <2006JOC4903>. Another interesting example is the use of an enamine that is part of an acenaphthylene in an inverse electron demand Diels–Alder reaction with 3,6-bis(2-bromophenyl)-1,2,4,5-tetrazine <2006OL5195>. More examples of the reaction of alk-1-yn-1-yl boronic esters with 1,2,4,5-tetrazines, namely 3,6-dichloro-1,2,4,5-tetrazine, appeared <2006OBC4278>.

2-Aryl-4,5-dichloro- and 2-aryl-4,5-dibromopyridazin-3(2*H*)-ones have been synthesized from commercially available anilines in a well-known procedure involving diazotization, reduction, and reaction with mucohalic acid <2006TL8733>. Initially, a halogen exchange reaction has been observed during the one pot process. This could be easily prevented via the selection of the mineral acid (HX) that contains the same halide as the mucohalic acid used. The optimized procedure allowed a multikilogram scale synthesis of 2-aryl-4,5-dihalopyridazin-3(2*H*)-ones.

Ring synthesis via the transformation of 3-amino-2*H*-pyran-2-ones (including fused derivatives) have been further investigated <2006H(70)235, 2006T9718>. 3-Amino-2*H*-pyran-2-ones could be transformed into the corresponding pyridazine-3-carboxylates via reaction with hydrazine followed by oxidation of the carbohydrazide moiety and 1,4-dihydropyridazine nucleus with CAN.

Acknowledgments

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Biographical Sketch



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8.02

Pyrimidines and their Benzo Derivatives

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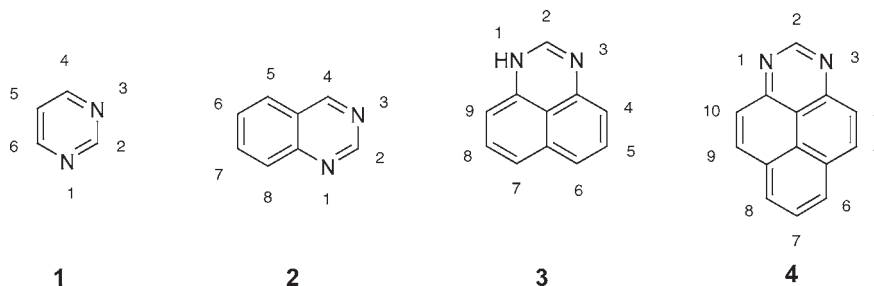
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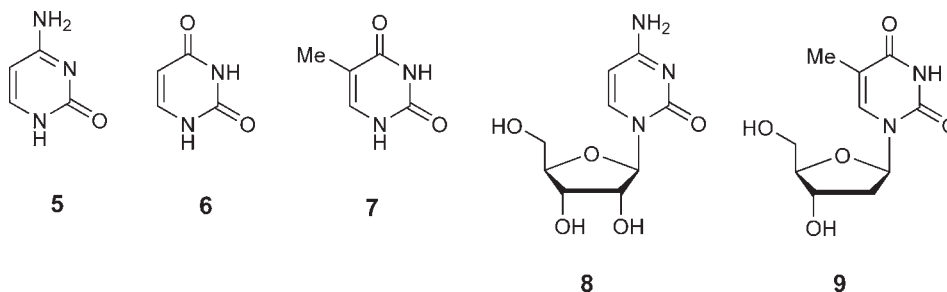
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8.02.1 Introduction

Pyrimidine **1** is the IUPAC accepted name for 1,3-diazabenzene, while quinazoline **2** is the accepted name for benzo[*d*]pyrimidine or 1,3-diazanaphthalene. Perimidine **3** is the IUPAC accepted name for 1*H*-benzo[*de*]quinazoline or 1*H*-naphtho[1,8-*de*]pyrimidine, while benzo[*gh*]perimidine **4** is also known as 1,3-diazapyrene.



Several of the oxo forms of the pyrimidines are particularly important in biological systems, and are normally referred to by their nonsystematic names such as cytosine [4-aminopyrimidin-2(1*H*)-one] **5**, uracil [2,4(1*H*,3*H*)-pyrimidinedione] **6**, and thymine (5-methyluracil) **7**. Their nucleoside derivatives are also normally referred to by their nonsystematic names such as cytidine (1-β-D-ribofuranosylcytosine) **8** and thymidine [1-(2-deoxy-β-D-ribofuranosyl)-5-methyluracil] **9**.



Pyrimidine chemistry was covered in CHEC(1984) and CHEC-II(1996) <1984CHEC(3)57, 1996CHEC-II(6)93>, and is also comprehensively reviewed in the book by D. J. Brown and others, entitled *The Pyrimidines* <1994HC(52)1>. Two additional major reviews have appeared since the publication of CHEC-II(1996) <1998HOU(E9b1)1, 2004SOS(16)379>, and pyrimidine chemistry in crop protection has also been extensively reviewed <2006H(68)561>.

Quinazoline chemistry was reviewed in CHEC-II(1996) <1996CHEC-II(6)93>, and is covered in two comprehensive volumes on quinazoline chemistry with W. L. F. Armarego and D. J. Brown as the respective authors <1967HC(24)1, 1996HC(55)1>. A number of additional reviews of various aspects of quinazoline and quinazoline alkaloid chemistry have also appeared since the publication of CHEC-II(1996) <1998HOU(E9b2)1, 2000SSR(4)71, 2003COR659, 2003H(60)183, 2004SOS(16)573, 2005T10153, 2006THC113, 2006T9787>. In addition, extensive summaries of both pyrimidine and quinazoline chemistry are included in the 'Diazines and benzo derivatives' section of the annual editions of *Progress in Heterocyclic Chemistry* <1997PHC249, 1998PHC251, 1999PHC256, 2000PHC263, 2001PHC261, 2002PHC279, 2003PHC306, 2004PHC347, 2005PHC304, 2007PHC353, 2007PHC383>.

Coverage of perimidine chemistry can be found in two review articles <1981RCR816, 1995AQ151>, while benzo[*gh*]perimidine chemistry is discussed in a review of diazapyrenes <2003CHE1417>.

As described in CHEC-II(1996), pyrimidine has one axis of symmetry, about the 2,5-axis, and has three different pairs of bond lengths and four different bond angles <1996CHEC-II(6)93>. Symmetry is lost on unequal substitution at the 4- and/or 6-position, and accordingly quinazoline lacks the symmetry of pyrimidine. Perimidine is symmetrical about the 2-position because of proton isomerization (prototropy), but this symmetry is lost on substitution other than at the 2-position.

Pyrimidine is a π-deficient heterocycle because of the two electronegative nitrogen atoms. Electron densities at the 2-, 4-, and 6-positions are depleted, making these positions strongly electrophilic. However, electron density at the 5-position is only slightly depleted, and this position retains benzenoid properties. In quinazoline, the pyrimidine ring retains the properties of the parent heterocycle while the carbocyclic ring has benzene-like properties. Perimidine is a 14π electron system with the lone pair of the pyrrole-like nitrogen participating in the π-system of the molecule. A 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 <1996CHEC-II(6)93>.

Hydroxy, thiol, and amino groups in pyrimidine exist in tautomeric equilibria with their oxo, thioxo, and imino forms. An amino group in an electrophilic position exists predominantly as such, and 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. 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 <1996CHEC-II(6)93>.

8.02.2 Theoretical Methods

The calculated electron distribution diagrams for pyrimidine **10**, quinazoline **11**, and perimidine **12** were described in CHEC-II(1996), but are reproduced here to show the gain or loss of π -electrons at each atom (Figure 1). Similar data for benzo[*gh*]perimidine is not yet available. The values for pyrimidine show that there is a considerable depletion of electron density at the 2-, 4-, and 6-positions, and a slight depletion at the 5-position. There is a greatly enhanced density at the N atoms. For quinazoline the electron density values for the 2- and 4-positions are comparable to those for the corresponding positions in pyrimidine, while the benzo-carbons are roughly comparable to C-5 in pyrimidine. With perimidine, C-2 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*-, *m*-, and *p*-positions, respectively, in the naphthalenediamine system <1996CHEC-II(6)93>. Calculations of resonance energy and inductive effects, as well as protonation effects were also covered in CHEC-II(1996).

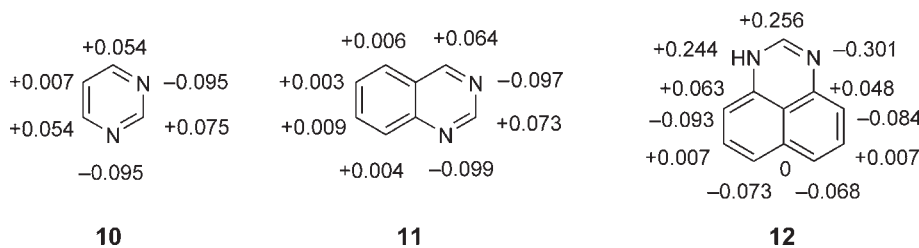


Figure 1 Electron distribution diagrams for pyrimidine **10**, quinazoline **11**, and perimidine **12**.

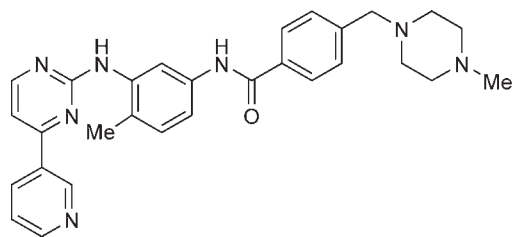
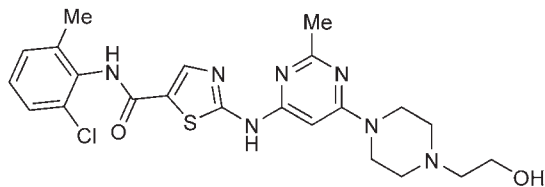
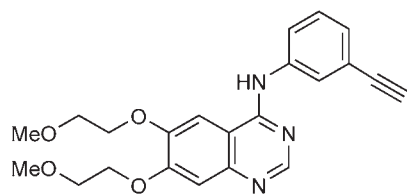
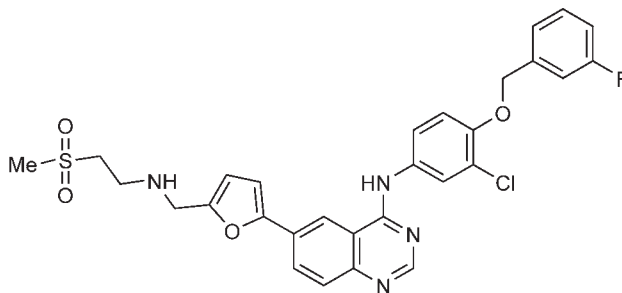
8.02.3 Experimental Structural Methods

8.02.3.1 Molecular Dimensions by X-Ray Structure Analysis

X-Ray derived data describing the bond lengths and bond angles for pyrimidine, quinazoline, and perimidine was summarized in CHEC-II(1996), and showed bond shortening, compared to benzene, for all bonds in pyrimidine that are adjacent to nitrogen atoms. Bond angles are also strongly affected by the nitrogen atoms, with N-1 and N-2 showing an angle of 115°, and C-2 an angle of 129.7°, compared to 120° for benzene. Quinazoline shows similar bond angles and bond shortening in the nitrogen containing ring, while perimidine shows less pronounced bond angle variations despite showing even more pronounced bond length variations.

Numerous pyrimidine and quinazoline derivatives have now been analyzed by X-ray methods, in what has become a very routine procedure. Many of these compounds are listed in the 'Diazines and benzo derivatives' section of the annual editions of *Progress in Heterocyclic Chemistry* and will not be discussed further here. However, one area where X-ray structure analysis has proved to be very useful is in determining the binding modes of biologically important pyrimidine and quinazoline derivatives to their protein receptors. For example, the crystal structures of uracil and 5-fluorouracil bound to uracil phosphoribosyltransferase (UPRTase) have been determined <1998MI3219>. These structures reveal that UPRTase recognizes uracil through polypeptide backbone hydrogen bonds to the uracil exocyclic O-2 and endocyclic N-3 atoms and a backbone–water–exocyclic O-4 oxygen hydrogen bond. This stereochemical arrangement and the architecture of the uracil-binding pocket reveal why cytosine and pyrimidines with exocyclic substituents at ring position 5 larger than fluorine, including thymine, cannot bind to the enzyme.

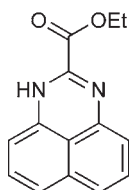
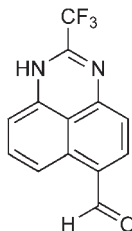
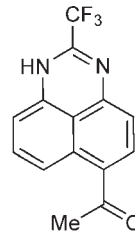
Several antitumor signal transduction inhibitors have also been analyzed by X-ray crystallography, bound in the ATP binding site of the kinase domain of their protein receptors, including imatinib (Gleevec) **13** <2000SCI1938>, dasatinib **14** <2004JME6658>, erlotinib **15** <2002JBC46265>, and lapatinib **16** <2004CNR6652>.

**13****14****15****16**

8.02.3.2 NMR Spectroscopy

Proton nuclear magnetic resonance (NMR) data for pyrimidines was reviewed in CHEC(1984) together with ^{13}C and ^{15}N NMR data, and ^{13}C NMR data for quinazoline and perimidines was discussed in CHEC-II(1996). A tabulation of ^1H , ^{13}C , ^{14}N , and ^{15}N NMR data for simple pyrimidines is available in the book by Brown <1994HC(52)1>. ^{15}N NMR data for quinazoline is now available and shows the chemical shift for N-3 (294.7 ppm) to be very similar to that for the nitrogens of pyrimidine (295.2 ppm), but that N-1 is significantly different (283.3 ppm) due to the fused benzene ring <2002SAA2737>. ^{19}F NMR spectroscopy has proved to be a highly specific tool for identifying fluoropyrimidine drugs and their metabolites in biological media <2000MI271>.

Standard ^1H and ^{13}C NMR data for perimidines was covered in CHEC-II(1996), and recent work has concentrated on looking at prototropic tautomerism. Thus, the ^1H NMR spectrum of ethyl 1*H*-perimidine-2-carboxylate **17** at room temperature was found to exhibit a fairly broad resonance arising from the protons attached to C-4 and C-9, but by increasing the temperature to 50 °C, a fairly sharp doublet ($^3J_{\text{HH}} = 6.9 \text{ Hz}$) was observed <2002T6901>. With 6(7)-formyl- **18** and 6(7)-acetyl-2-trifluoromethylperimidines **19**, both NH tautomers were observed by ^1H NMR in solutions of CDCl_3 and C_6D_6 , even on heating to 60–70 °C <2001CHE733>. The slow tautomerism was interpreted as being due to the cooperative effect of the 2- CF_3 group and the carbonyl substituents decreasing the basicity of the pyridine-like hetero atom to such an extent that transfer of a proton between molecules in the nonpolar medium became very strongly restricted.

**17****18****19**

8.02.3.3 Mass Spectroscopy

The electron impact mass spectra of pyrimidines and quinazolines are characterized by the loss of HCN from C-4 and N-3 as the primary fragmentation route. Subsequent loss of HCN from C-2 and N-1 gives an ionized alkyne or benzyne as a major peak in the spectrum. Uracil and thymine lose HNCO, while barbituric acid loses two HNCO units as a major fragmentation route <1994HC(52)1, 1996CHEC-II(6)93>. The electron impact mass spectra of perimidine, 2-perimidinone, and 2-thioperimidinone are characterized by a strong molecular ion, a doubly charged molecular ion, and relatively weak fragmentation <1981RCR816>.

8.02.3.4 UV and Fluorescence Spectra

The ultraviolet (UV) absorption of pyrimidine, quinazoline, and perimidine, as well as 4(3*H*)-quinazolinone were described in CHEC-II(1996) <1996CHEC-II(6)93>.

8.02.3.5 IR and Raman Spectra

The basic vibrational spectra of pyrimidine derivatives were discussed in CHEC-II(1996) <1996CHEC-II(6)93>.

8.02.3.6 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. Further details were discussed in CHEC-II(1996) <1996CHEC-II(6)93>.

8.02.3.7 Ionization

Pyrimidine has a basic pK_a of 1.3 which is much lower than that for pyridine (5.2) due to the presence of the second electronegative nitrogen. Electron-releasing substituents increase the basicity; while electron-withdrawing groups have the opposite effect. Pyrimidinones have both an acidic and basic pK_a value, while uracil and barbarturic acid each have two acid values. A table of pK_a values for a large number of substituted pyrimidines is available <1994HC(52)1>.

The protonation of quinazolines is accompanied by the formation of covalent 3,4-hydrates which make them stronger bases than pyrimidines. This effect is reduced for quinazolines substituted at the 4-position. For example, the basic pK_a value for quinazoline is 3.51, while that of 4-methylquinazoline is 2.52. Thus, when covalent hydration is allowed, quinazoline derivatives are significantly stronger bases than corresponding pyrimidines, but when the hydration is excluded, the pK_a values are comparable with those for pyrimidine analogs <1967HC(24)1, 1996HC(55)1>. Perimidines are stronger bases than pyrimidines and quinazolines <1981RCR816>.

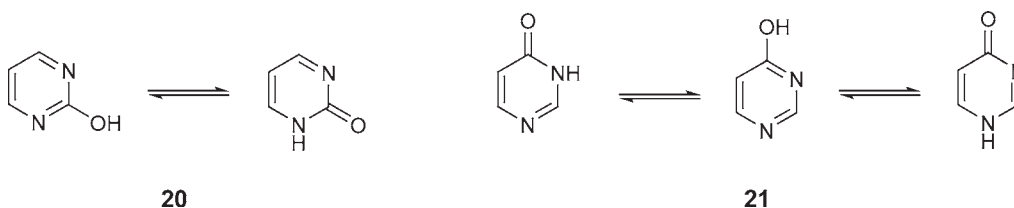
8.02.4 Thermodynamic Aspects

8.02.4.1 Prototropic Tautomerism

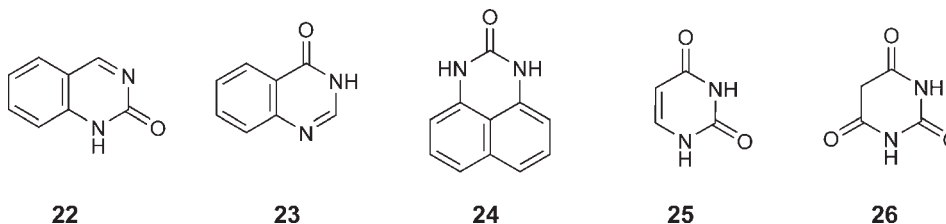
The substituent tautomerism of six-membered ring heterocycles, including pyrimidines, quinazolines, and perimidines, has recently been reviewed in detail <2006AHC(91)1>.

8.02.4.1.1 Hydroxy-oxo-tautomerism

Both 2- and 4-hydroxypyrimidine can exist in both hydroxyl and keto tautomeric forms, and the proportion of each is highly dependent on the state of the molecule. In the gas phase 2-hydroxypyrimidine **20** exists primarily in the hydroxy form, whereas the 4-isomer **21** exists predominantly in the oxo form <2006AHC(91)1>. Solvation tends to shift the equilibrium toward the oxo form for both isomers <2006AHC(91)1>.



Both 2- and 4-hydroxyquinazolines **22** and **23** and 2-hydroxyperimidine **24** exist predominantly in the oxo forms in solution, and the same applies to uracil **25** which exists primarily as the dioxo form [<2006AHC\(91\)1>](#). With barbituric acid [2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione] **26**, the trione form is similarly predominant [<2006IJQ\(106\)1338>](#).



8.02.4.1.2 Thiol-thioxo tautomerism

The stability of the thiol tautomers of mercaptopyrimidines compared to the thione forms is considerably higher than for hydroxypyrimidines, although the thione form is still dominant in solution [<2006AHC\(91\)1, 2006PCA7904>](#).

8.02.4.1.3 Amino-imino tautomerism

2- and 4-Aminopyrimidines exist predominantly in the amino form rather than the imino form, although with 4-aminoquinazolines and 2-aminoperimidines significant proportions of the imino form can also exist, depending upon the nature of attached substituents [<1981RCR816, 2000M895, 2006AHC\(91\)1>](#).

8.02.4.1.4 Perimidine

The NH proton in perimidine migrates rapidly between the two nitrogen atoms (degenerate tautomerism), although uneven substitution in the carbocyclic rings can lead to two energetically different NH -tautomers [<1981RCR816, 1995AQ151>](#).

8.02.5 Reactivity of Fully Conjugated Rings

8.02.5.1 Unimolecular Thermal and Photochemical Reactions

Thermally promoted Claisen rearrangement of simple allyloxypyrimidines is difficult to effect, but is more common with quinazolines where it has been used to prepare allyl derivatives substituted in the carbocyclic ring [<1996HC\(55\)1>](#). An attempted amino-Claisen rearrangement of a 4-allylaminopyrimidine was unsuccessful [<2005AJC368>](#).

Palladium-catalyzed rearrangement of 2-allyloxypyrimidines gives *N*-allyl-2(1*H*)-pyrimidinones [<1996CHEC-II\(6\)93>](#), but otherwise this approach has been little utilized.

8.02.5.2 Electrophilic Attack at Nitrogen

8.02.5.2.1 Acylation

Acylation of a ring nitrogen in the fully conjugated pyrimidine derivative leads to pyrimidinium salts which are powerful acylating agents. In the acylation of tautomeric pyrimidinones, an acyloxypyrimidine, an *N*-acylpyrimidinone, or a mixture of both is formed [<1994HC\(52\)1, 1996CHEC-II\(6\)93>](#). Reactions involving the *N*-acylation of perimidinone have been described [<1981RCR816, 1995AQ151>](#).

Pyrimidinedithiones 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.

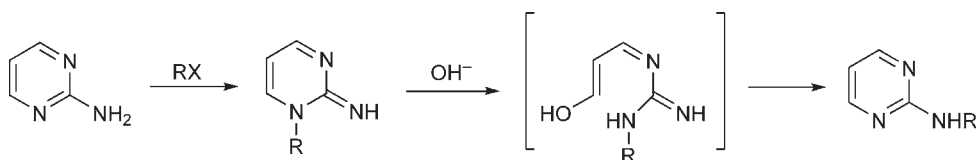
8.02.5.2.2 Alkylation

Reactions of electrophiles with annular nitrogens have been reviewed <1988AHC(43)127>. Simple alkylations of pyrimidines with nontautomerizable substituents are largely controlled by steric factors; quinazoline is preferentially N-3-alkylated. Perimidine has an acidic NH proton and therefore behaves differently from pyrimidine and quinazoline. The product is a neutral molecule. N-Substitution reactions are sensitive to steric interference from 2- and 4(9)-substituents. 4(9)-Substituted perimidines are preferentially alkylated at the remote nitrogen. Alkylation of 2-hydroxy and 4-hydroxy pyrimidines is largely governed by the nature of the alkylating agent, and by steric and electronic effects from adjacent substituents; N-alkylation is sterically more demanding than O-alkylation. The rate of reaction at nitrogen decreases relative to that of oxygen as the bulk of the alkylating reagent increases.

Uracil and its N-unsubstituted derivatives generally form 1,3-dialkyl products under a variety of conditions. Large alkyl groups display a preference for the less hindered N-1 nitrogen. For 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. Cytosine is alkylated largely on N-1 or N-3 depending on the reagent. Barbituric acid derivatives resemble uracils in their preference for N-alkylation with most reagents. Large alkyl groups may favor O-alkylation. Selective N-1-alkylation of 3,4-dihydro-2(1*H*)-pyrimidinones has been achieved using Mitsunobu-type conditions <2002SL1901>.

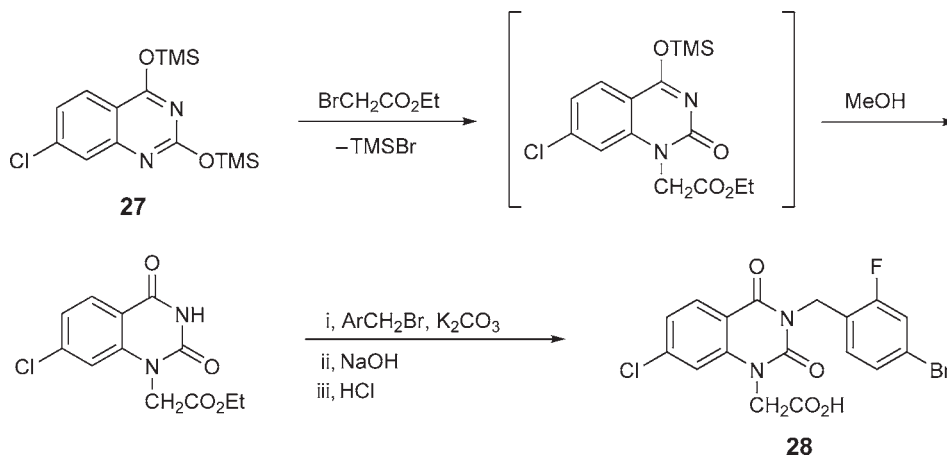
N-Alkylation is promoted by prior conversion of the pyrimidinones into their respective silyl ethers. Besides selectivity in the alkylation reactions, silylation confers solubility on molecules which otherwise may be difficult to dissolve in nonhydroxylic organic solvents. Selective N-3-alkylation of uracils requires initial protection of N-1. 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.

Alkylation of a primary or secondary 2- or 4-, or 6-aminopyrimidine usually takes place on a ring nitrogen to afford a 1-alkyl or 3-alkyl iminopyrimidine, which subsequently may undergo a Dimroth rearrangement to its alkylamino isomer (Scheme 1) <1994HC(52)1, 1999AHC(75)79>.



Scheme 1

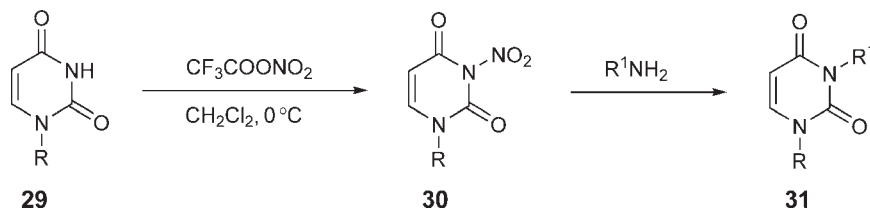
An improved procedure for the selective alkylation of 2,4-quinazolinodiones at the 1-position via the 2,4-bis(trimethylsilyloxy) derivatives has been developed <2003OPD700>. This procedure enabled a large-scale synthesis of the aldose reductase inhibitor FK366 **28** from the bistrimethylsilyloxy quinazoline **27** (Scheme 2).



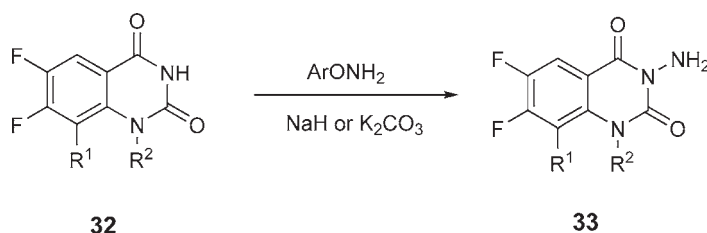
Scheme 2

8.02.5.2.3 N-Amination and N-nitration

The synthesis of 3-nitro-1-substituted uracil derivatives **30** can readily be performed with trifluoroacetic nitric anhydride, and this procedure is used in nucleoside chemistry to convert the uracil 3-nitrogen to a good leaving group <1995JA3665, 1997JOC1547, 2002OL1827>.



Although 3-aminoquinazoline derivatives are normally prepared *de novo* from hydrazine starting materials, they can also be prepared by N-amination reactions. Thus, treatment of 1-substituted-2,4(1*H*,3*H*)-quinazolin-2(1*H*)-ones **32** with *O*-aryl hydroxylamines under basic conditions gives 3-amino-1-substituted-2,4(1*H*,3*H*)-quinazolin-2(1*H*)-ones **33** which are intermediates in the synthesis of 3-amino-2,4(1*H*,3*H*)-quinazolin-2(1*H*)-one antibacterial agents <2002OPD230, 2005JHC669, 2006JME6435>.



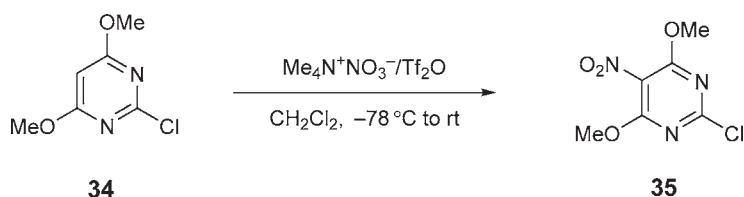
8.02.5.2.4 N-Oxidation

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. Pyrimidine 1,3-dioxides require high activation for direct formation. 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. Steric hindrance by a phenyl substituent is marked although the steric effect of simple alkyl groups is smaller. Nitro groups deactivate and may prevent N-oxidation, and halo substituents also deactivate. Methoxy groups activate, but steric effects may dominate. 2,4-Diaminopyrimidines are oxidized at N-3.

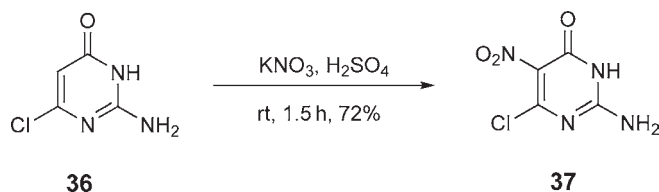
8.02.5.3 Electrophilic Attack at Carbon

8.02.5.3.1 Nitration

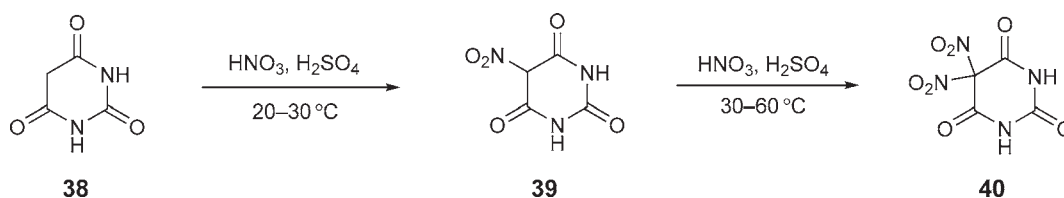
Pyrimidine and its cation are highly π -deficient and resist nitration, although nitration proceeds readily when more than one electron-releasing group is present. Thus, treatment of 2-chloro-4,6-dimethoxypyrimidine **34** with a mixture of tetramethylammonium nitrate and trifluoromethanesulfonic anhydride in dichloromethane at -78°C , followed by warming to room temperature, gave the 5-nitro derivative **35** in yields up to 98% on a millimolar to molar scale <2003JOC267, 2006JME3362>.



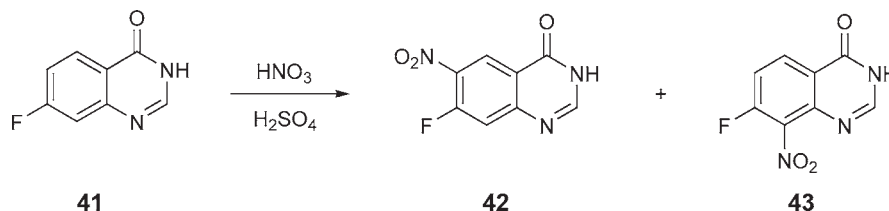
Electron-donating substituents also activate pyrimidinones toward nitration, and 2-amino-6-chloro-4(3*H*)-pyrimidinone **36** is readily nitrated with potassium nitrate in concentrated sulfuric acid at room temperature <2001TL1793>. However, care must be taken to avoid prolonged reaction which leads to hydrolysis of the chlorine atom, which is then followed by a second nitration and a subsequent ring-opening step <2001TL1793>.



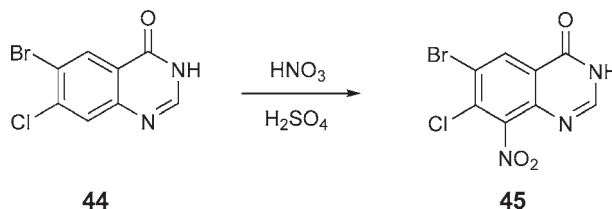
Barbarturic acid **38** can be mono-nitrated at the 5-position with nitric acid and sulfuric acid at room temperature, but with longer reaction times or higher temperature, 5,5-dinitro products **40** are obtained <2002JOC7833>.



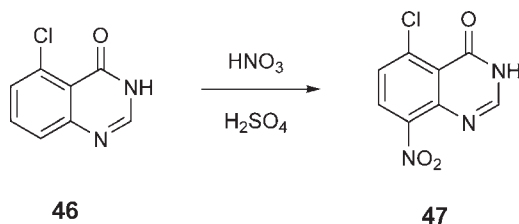
Nitration of quinazolines is normally in the 6-position in the benzene ring, but when that position is blocked, as in 6-methoxyquinazoline, nitration can occur in the 5-position <1983JME1715, 1996HC(55)1>. 4(3*H*)-Quinazolinones also nitrate in the 6-position, but when an *ortho*-directing substituent is at the 7-position, some 8-substituted product is also obtained. Thus 7-fluoro-4(3*H*)-quinazolinone **41** gives a mixture of the 6- and 8-nitro products **42** and **43**, although with the former predominating. Isomerically pure 6-nitro-7-fluoro-4(3*H*)-quinazolinone **42** is obtained in 56% yield following recrystallization from acetic acid <1996JME918>.



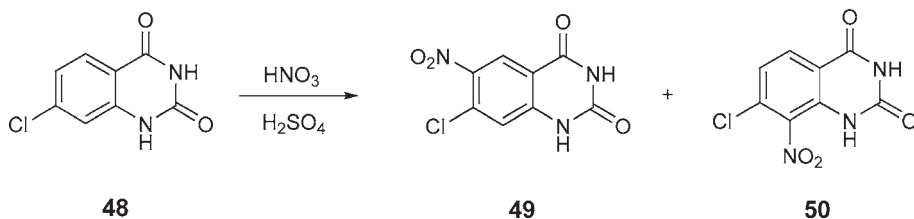
When the 6-position of the 4(3*H*)-quinazolinone is blocked, nitration occurs at the 5-position <1975JOC363>, but when the 7-position is also substituted, as with 6-bromo-7-chloro-4(3*H*)-quinazolinone **44**, the 8-substituted product **45** is obtained as the sole product <1996JME918>.



A 52% recrystallized yield of the 8-nitro product **47** was reported from the nitration of 5-chloro-4(3*H*)-quinazolinone **46** <2005BMC5613>, although it is probable that some the 6-nitro isomer was also produced, as nitration of the analogous 5-fluoro-4(3*H*)-quinazolinone gives a 4:1 mixture of the 6- and 8-nitro derivatives <1991JHC1459>.

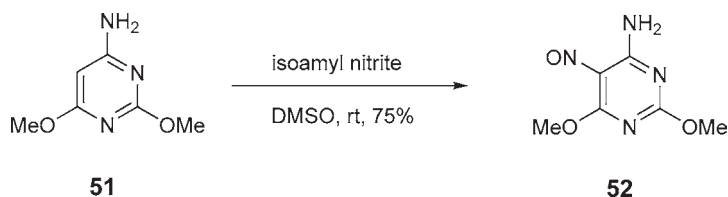


2,4-Quinazolinediones nitrate similarly to the quinazolinones, and thus 7-chloro-2,4-(1*H*,3*H*)-quinazolinedione **48** gave a 20:1 mixture of the 6- and 8-nitro derivatives **49** and **50** when treated with 60% HNO_3 and conc. H_2SO_4 at room temperature, but only a 10:1 mixture when fuming HNO_3 was used [<2001OPD426>](#).



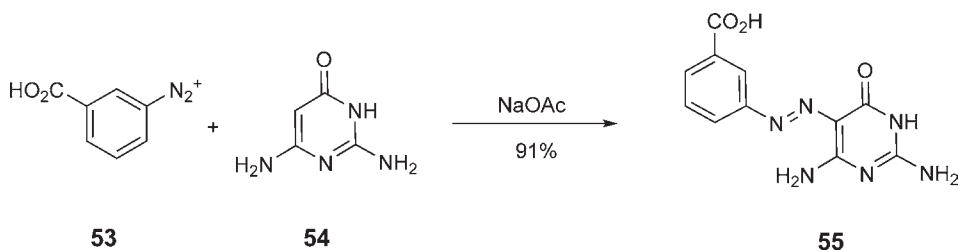
8.02.5.3.2 Nitrosation

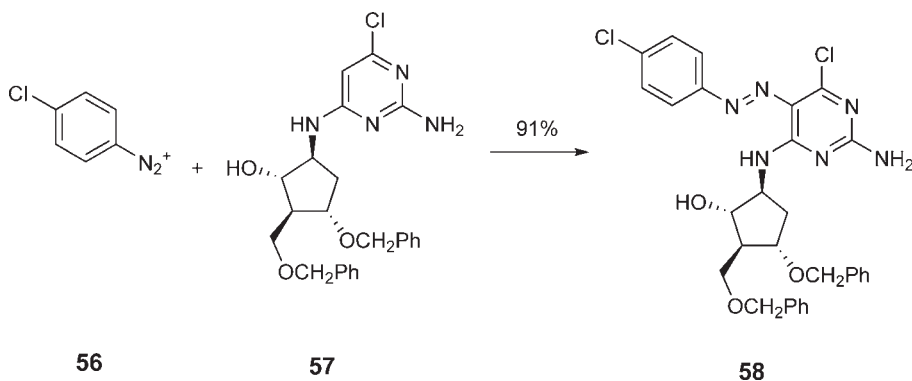
Nitrosation takes place in the benzenoid 5-position in pyrimidines with three strongly electron-donating groups. Nitrosation is brought about by nitrous acid or by nitrite esters, and a simple method, based on treatment with isoamyl nitrite in DMSO, without any added acid, has been developed [<2002SL255>](#). The method proved suitable for a multigram scale and was applicable to a larger range of amino pyrimidine derivatives, including aminodialkoxypyrimidines, than earlier procedures. For example, treatment of 4-amino-2,6-dimethoxypyrimidine **51** with isoamyl nitrite in DMSO at room temperature gave the 5-nitroso derivative **52** in 75% yield [<2002SL255>](#).



8.02.5.3.3 Diazo coupling

The diazonium electrophile is weak, and requires highly nucleophilic counterparts for reaction. At least two strongly electron-releasing substituents at C-2 and C-4 (or C-6) are needed for pyrimidines to couple at C-5 [<1983AJC1659>](#). The reaction takes place under mild conditions that may not affect even quite labile substituents, and high yields can often be achieved. For example, the coupling of 3-carboxybenzenediazonium tetrafluoroborate **53** with 2,6-diaminopyrimidin-4(3*H*)-one **54** occurred in 91% yield [<2004JME1709>](#), and the same 91% yield was achieved for the synthesis of **58**, an intermediate in the synthesis of [^{14}C]-radiolabeled entecavir [<2005JLR645>](#).





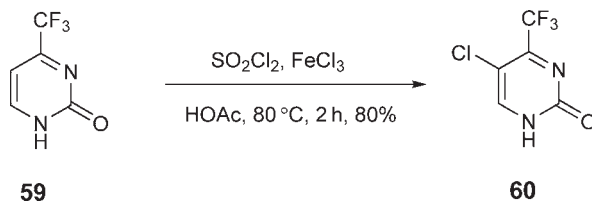
Diazo coupling in quinazolines occurs in the benzene ring, with the normal benzene or naphthalene requirement for the presence of strongly electron-donating substituents. Perimidines couple readily in the 6(7)-position with diazonium salts to form blue azo derivatives. The reaction has been described for perimidine, 2-substituted derivatives, 6(7)-chloroperimidine, and 2-aminoperimidine [\[1981RCR816\]](#).

8.02.5.3.4 Halogenation

Pyrimidines are halogenated directly by electrophilic reagents in the benzenoid 5-position, especially if the substrate bears one or more electron-donating substituents. Halogenations in the electrophilic positions are by nucleophilic exchange reactions. Direct fluorination has been used for the preparation of some 5-fluoropyrimidines, but other routes are more often employed, in contrast to the situation with the other halogens, where direct halogenation is often the method of choice [\[1994HC\(52\)1, 1996CHEC-II\(6\)93\]](#).

8.02.5.3.4(i) Chlorination

For the formation of 5-chloropyrimidines, *N*-chlorosuccinimide is normally the reagent of choice, but several other electrophilic chlorine sources including chlorine gas or sulfuryl chloride can be used [\[1994HC\(52\)1\]](#). For example, the chlorination of 4-(trifluoromethyl)-2(1*H*)-pyrimidinone **59** with ferric chloride and sulfuryl chloride in acetic acid gave the 5-chloro derivative **60** in 80% yield [\[2004EJO3714\]](#).

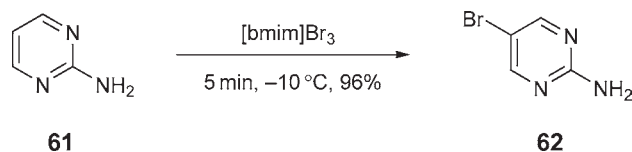


8.02.5.3.4(ii) Bromination

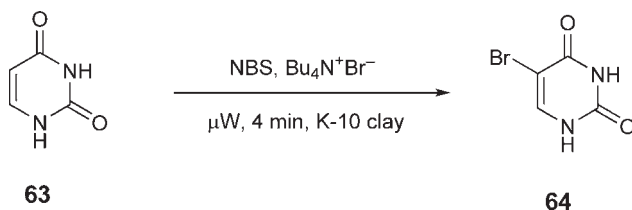
5-Bromopyrimidine is formed by direct bromination of pyrimidine at higher temperatures, but the presence of amino, hydroxy, or oxo groups in the pyrimidine ring greatly assists bromination at lower temperatures [\[1994HC\(52\)1, 1996CHEC-II\(6\)93\]](#).

An amino or hydroxy group facilitates 5-bromination even in aqueous solution. *N*-bromosuccinimide (NBS) and molecular bromine are the commonest reagents used. 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. In the bromination of uracils, addition products, including covalent hydrates, form rapidly, and the acid-catalyzed dehydration step to 5-bromouracils is much slower. Cytosine and related compounds behave similarly [\[1994HC\(52\)1, 1996CHEC-II\(6\)93\]](#).

In order to overcome the difficulties associated with the covalent hydrates, anhydrous reagent systems have been investigated, including ionic liquids [\[2004S2809\]](#) and NBS in tetrabutylammonium bromide [\[2005S1103\]](#). For example, the bromination of 2-aminopyrimidine **61** with the ionic liquid 1-butyl-3-methylimidazolium tribromide $[(bmim)Br_3]$ gave 2-amino-5-bromopyrimidine **62** in 96% yield after 5 min at $-10^\circ C$ [\[2004S2809\]](#).



Bromination of uracil **63** with NBS in tetrabutylammonium bromide gave 5-bromouracil **64** in 78% yield after 2 h, but with microwave assistance in the presence of acidic montmorillonite K-10 clay the reaction time was cut to just 4 min and the yield was increased to 96% <2005S1103>. Cytosine reacted similarly <2005S1103>.



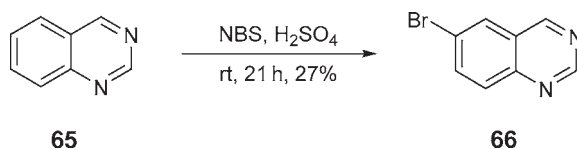
Procedures that involve the bromination of *N*-stannyl or *N*-boronyl derivatives in tetrahydrofuran (THF) have also been investigated <2002OL2321, 2003TL9371>.

8.02.5.3.4(iii) Iodination

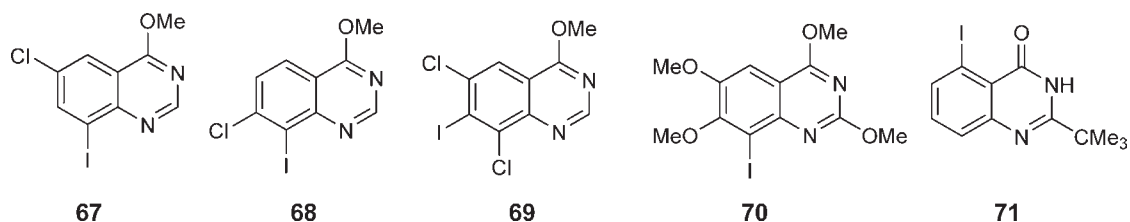
The iodination of pyrimidines requires the presence of an activating substituent, and is normally performed with reagents such as *N*-iodosuccinimide (NIS) or iodine monochloride (ICl). A microwave-assisted procedure for the rapid and high-yielding C-5 iodination of substituted pyrimidinones and pyrimidine nucleosides with NIS in dimethylformamide (DMF) has been developed, and thus the iodination of uracil occurred in 98% yield with just 3 min reaction time <2003S1039>.

8.02.5.3.4(iv) Quinazolines

Electrophilic substitution in quinazolines takes place in the benzene ring, although mixtures of products are often obtained <1996CHEC-II(6)93, 1996HC(55)1>. For example, the bromination of quinazoline **65** with NBS in sulfuric acid at room temperature gave only a 27% yield of 6-bromoquinazoline **66**, in addition to a mixture of other products which included tri- and tetrabrominated compounds <2002S83>.



Regiospecific halogenation of quinazolines can be achieved via metallated intermediates, although the yields are sometimes only moderate. Thus, lithiation of 6- or 7-chloro-4-methoxyquinazoline with lithium tetramethylpiperide followed by quenching with iodine gave the 8-iodo derivatives **67** and **68** in 25% and 32 % yield, respectively, whereas with 6,8-dichloro-4-methoxyquinazoline the 7-iodo analog **69** was obtained in 90 % yield under the same conditions <1997T2871>. 4-Aryl-6,7-dimethoxy-8-iodoquinazolines have similarly been prepared in 66–84% yield <2000T5499>. Blocking of the quinazoline 2-position with a methoxy group allowed butyllithium to be used as the metallating species, enabling 8-iodo-2,4,6,7-tetramethoxyquinazoline **70** to be prepared in 89% yield <1997T2871>. 2-Substituted 4-quinazolinones have also been iodinated, and thus the lithiation of 2-*tert*-butyl-4(3*H*)-quinazolinone with *sec*-butyllithium, followed by quenching with iodine, gave the 5-iodo derivative **71** in 37% yield <2004T5373>.

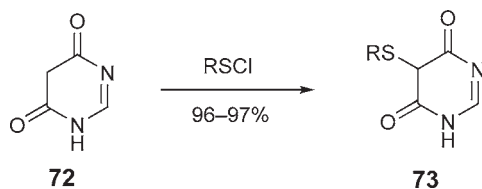


8.02.5.3.4(v) Perimidines

Halogenation of perimidines, perimidinones, and dihydroperimidines occurs at an *ortho*- or *para*-position in the naphthalene system, that is, the 4-, 6-, 7-, 9-positions in the perimidine system, where the donor effects from the nitrogens operate <1981RCR816, 1995AQ151>.

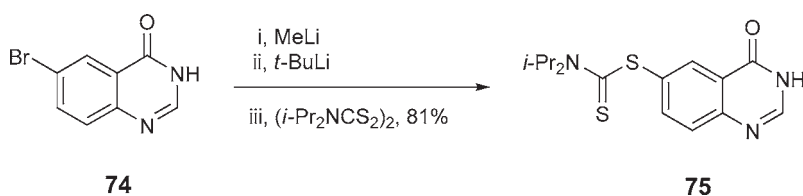
8.02.5.3.5 Sulfonation and thioalkylation

Sulfonic acids are conveniently made by oxidation of the corresponding thiones or disulfides. Direct sulfonation is best effected with chlorosulfonic acid. Direct thiation can be achieved with sulfonyl chlorides to give 5-thiopyrimidines in excellent yields. For example, the reaction of 6-hydroxy-4(1*H*)-pyrimidinone [4,6(1*H*,5*H*)-pyrimidinedione] **72** with benzylsulfonyl chloride or 2-methoxyphenylsulfonyl chloride gave the respective 5-thio derivatives **73** in 96% and 97% yields <1993SC2363, 2001JME3355>.

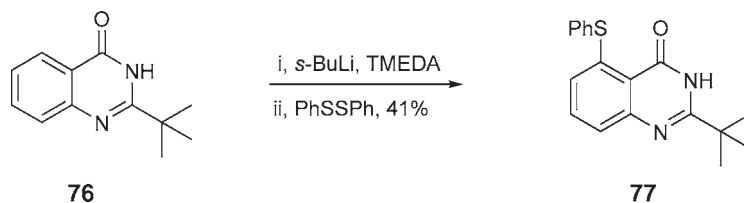


8.02.5.3.5(i) Quinazolines

Thioquinazolines can also be prepared by the reaction of lithiated quinazoline derivatives with disulfides. For example, reaction of the lithio species derived from 6-bromo-4(3*H*)-quinazolinone **74** with tetra-*iso*-propylthiuram disulfide gave the 6-dithiocarbamate **75** in 81% yield <2004M323>.

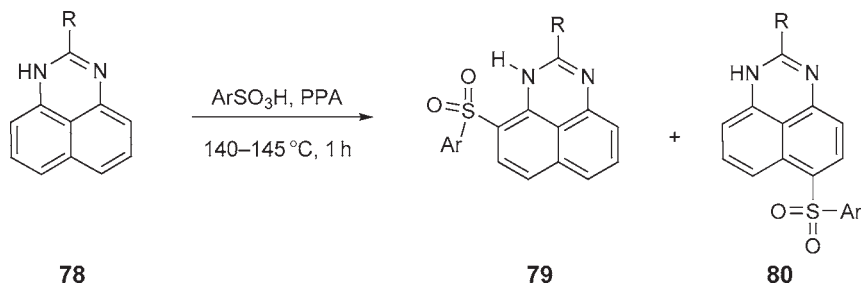


Direct lithiation of 2-*tert*-butyl-4(3*H*)-quinazolinone **76** with *sec*-butyllithium and bis(dimethylamino)ethane (TMEDA) followed by quenching with diphenyldisulfide gave the 5-phenylthio derivative **77** in moderate yield, although a mixture of 5- and 8-substituted products was obtained on quenching with di-*tert*-butyldisulfide <2004T7983>.



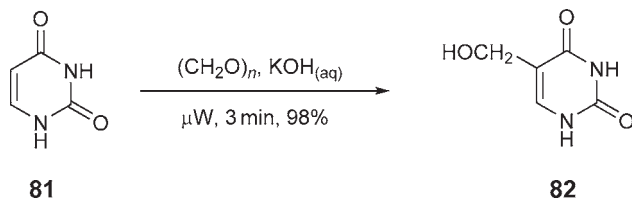
8.02.5.3.5(ii) Perimidines

Arylsulfonation of perimidines **78** ($R = H$ or CF_3) has been carried out in polyphosphoric acid and found to occur at the 6(7)- and 4(9)-positions. Separation of the product sulfones **79** and **80** was easily achieved due to their different chromatographic mobilities. The 4(9)-isomers **79** are more mobile due to the intramolecular hydrogen bond and, in low-polarity solvents, exist virtually completely as the 9-tautomer [<2002CHE1084>](#).

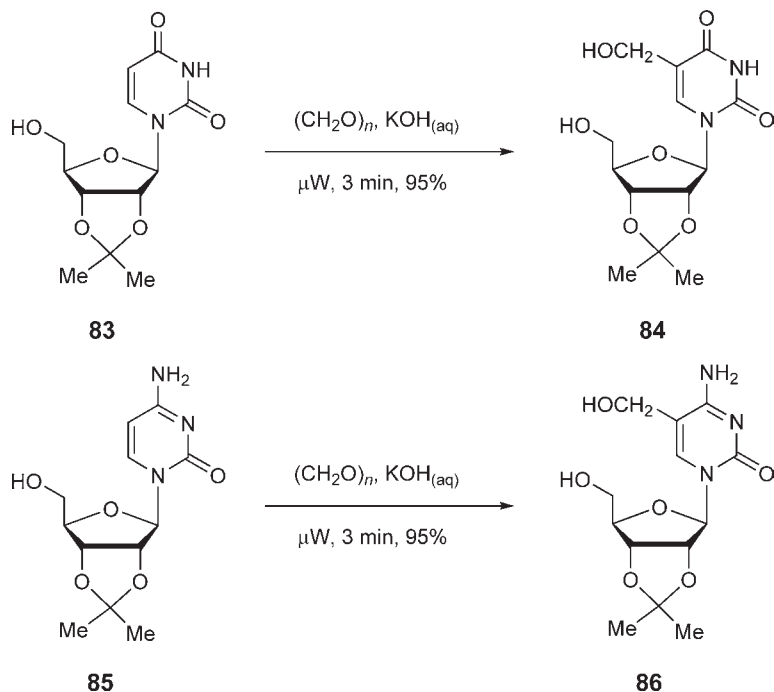


8.02.5.3.6 Alkylation

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. For example, uracil can be 5-hydroxymethylated by formaldehyde under alkaline conditions, and a microwave-assisted procedure has now been developed which allows formation of 5-hydroxymethyluracil in 98% yield, with just 3 min of reaction time [<2002SL2043>](#).

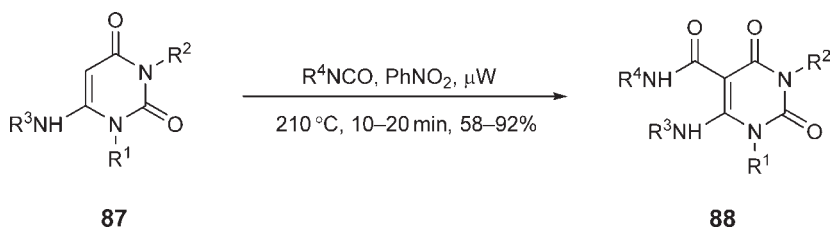


Cytosine reacts similarly, as do both uracil and cytosine nucleoside derivatives such as **83** and **85** which gave their respective 5-hydroxymethyl derivatives **84** and **86** in 95% yield [<2002SL2043>](#).

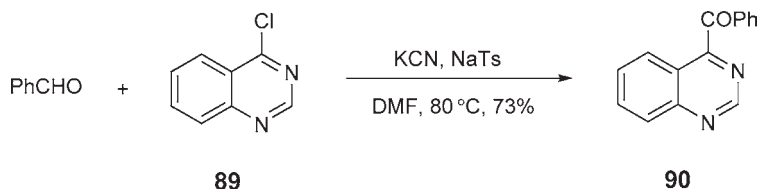


8.02.5.3.7 Acylation

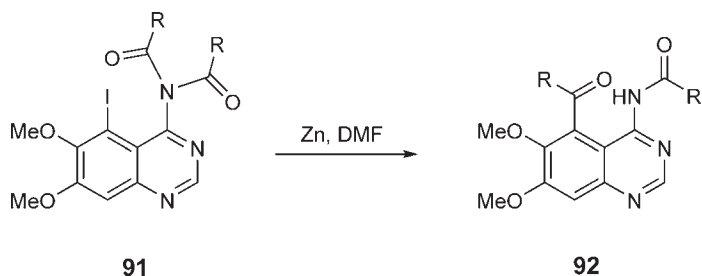
Both the Reimer–Tiemann and the Vilsmeier reactions lead to formylation in the 5-position in pyrimidines with at least two strongly releasing substituents <1994HC(52)1>. The reaction of metallated intermediates with acyl electrophiles can be used to give acyl derivatives <2001T4489>, and direct carbamoylation of 6-aminouracil derivatives **87** has been achieved under microwave-assisted conditions to give **88** <2005S2713>.



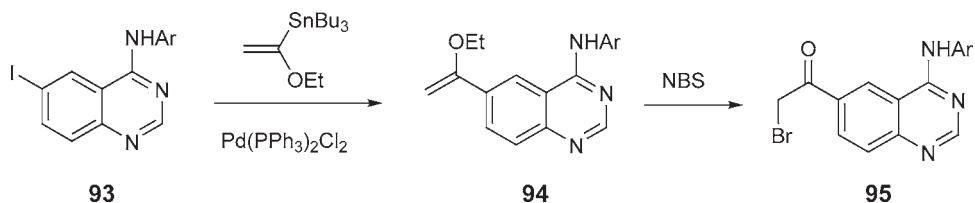
In the presence of catalytic amounts of both sodium *p*-toluenesulfonate and potassium cyanide, the reaction of benzaldehyde with 4-chloroquinazoline **89** gave 4-benzoylquinazoline **90** in good yield <1998H(47)407>. The reaction involves activation of the benzaldehyde by cyanide addition, and activation of the quinazoline as the 4-toluenesulfonyl derivative.



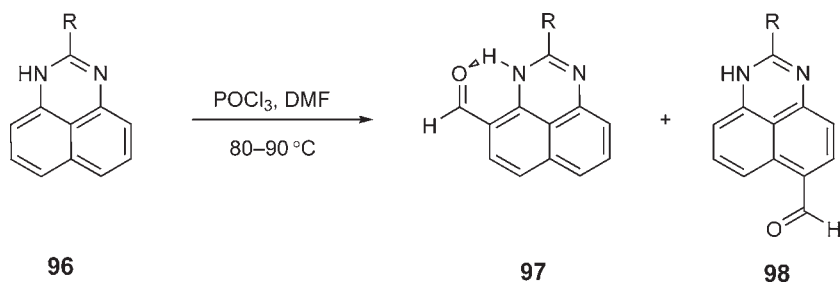
Acylation in the 5-position of a quinazoline by acyl migration from a 4-diacylamino species was observed when the 5-iodo derivative **91** was treated with activated zinc in DMF <2005TL983>.



Acylation in the 6-position of 4-arylaminquinazolines **93** has been performed via the intermediacy of vinyl ethers **94** which were introduced by a Stille reaction using vinylstannanes <2003BML637>.

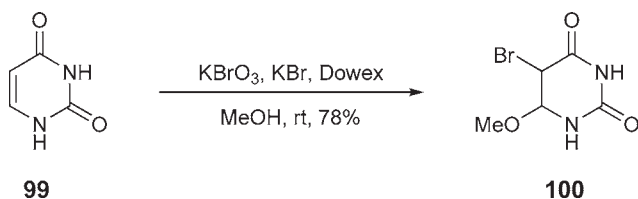


Perimidines are readily acylated under Friedel–Crafts conditions in the carbocyclic ring. Treatment of 2-alkylperimidines **96** ($R = H$ or Me) with the $POCl_3$ and DMF under Vilsmeier reaction conditions gave a mixture of the 4(9)- and 6(7)-carbaldehydes **97** and **98**, although only moderate yields of each were obtained <2006CHE92>.



8.02.5.3.8 Oxidation

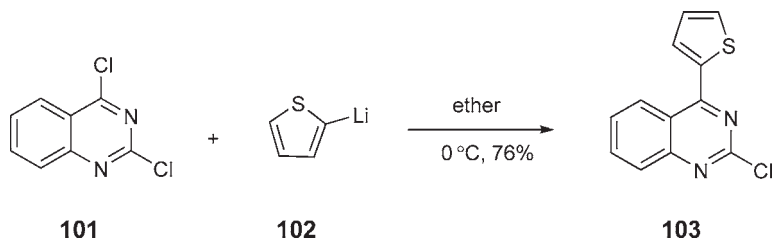
Uracils and related pyrimidines undergo oxidative addition to the 5,6-double bond, and the reaction with a number of oxidants to form 5,6-epoxides and 5,6-diols was discussed in CHEC-II(1996) <1996CHEC-II(6)93>. Oxidative halogenation can also occur <1996SC3583, 1998NN1125>, as shown by the formation of 5-bromo-5,6-dihydro-6-methoxyuracil **100** from uracil **99** by treatment with a mixture of potassium bromate and potassium bromide in the presence of Dowex ion-exchange resin in methanol <1996SC3583>.



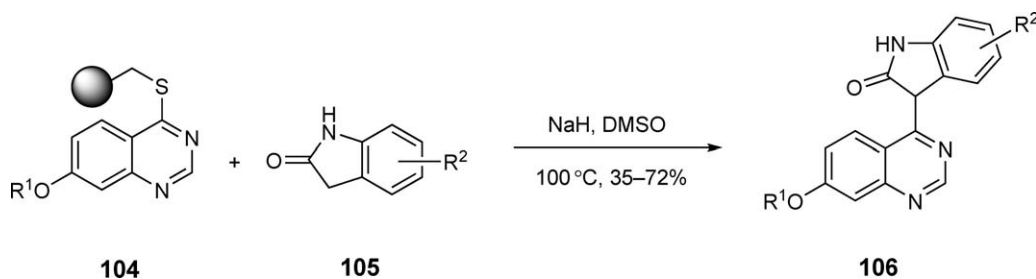
8.02.5.4 Nucleophilic Attack at Carbon

8.02.5.4.1 Alkylation and arylation

Normally organolithium reagents undergo nucleophilic addition to the azomethine moiety of pyrimidines and quinazolines, to give dihydro species, which can subsequently be oxidized to give substituted pyrimidines or quinazolines. However, if all azomethine groups are substituted, nucleophilic addition can occur to activated positions bearing a chlorine. Addition is then followed by the elimination of the chlorine to give the substituted pyrimidines or quinazolines directly, as demonstrated by the reaction of 2,4-dichloroquinazoline **101** with 2-thienyllithium **102** to give the 4-thienyl derivative **103** in 76% yield <1988JOC4137>.



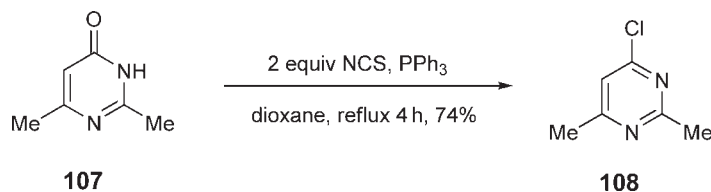
Enolates can also add to activated pyrimidines and quinazolines as shown by the synthesis of 4-(3-oxindolyl)quinazolines **106** from resin-attached 4-alkylthioquinazolines **104** <1999TL3881>.



8.02.5.4.2 Halogenation

8.02.5.4.2(i) Chlorination

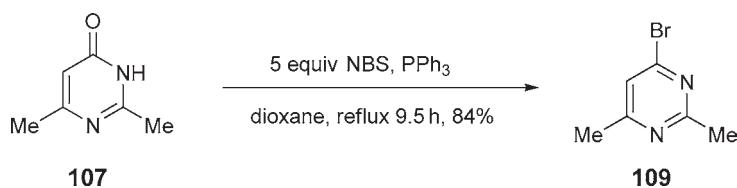
Synthesis of 2-, 4-, or 6-chloro derivatives is usually by a nucleophilic process from hydroxyl compounds using a phosphorus chloride reagent. Amino, alkoxy, and alkylthio substituents are not affected, although oximes and primary carbamoyl functions are frequently converted into nitriles under the reaction conditions <1994HC(52)1, 1996CHEC-II(6)93>. Traditionally, the reactions were frequently carried out in the presence of a tertiary amine base such as *N,N*-diethylaniline, but more recently the addition of quaternary ammonium salts such as tetraethylammonium or benzyltriethylammonium chloride has become more common. The purpose of these added reagents is to accelerate the reaction rate, by providing a higher concentration of chloride ion for the rate-determining step, which involves nucleophilic displacement of dichlorophosphate by chloride. The phosphonium salt generated by the combination of *N*-chlorosuccinimide and triphenylphosphine has been investigated as an alternative halide source for the chlorination of pyrimidines and quinazolines <2001HCA1112>. Thus 2,6-dimethylpyrimidin-4(3*H*)-one **107** gave a 74% yield of the chloro compound **108** on treatment with 2 equiv of the phosphonium reagent in refluxing dioxane <2001HCA1112>.



Attempts to perform the same procedure under microwave irradiation were less successful, and although reaction times were lowered, so were the product yields <2006H(68)1973>.

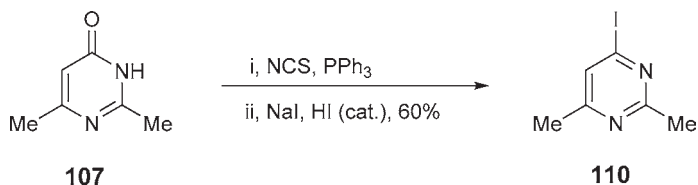
8.02.5.4.2(ii) Bromination

Diazotization of pyrimidinamines provides the corresponding bromides in only low to moderate yields, so transhalogenation from chlorides is a more important route <1994HC(52)1>. POBr₃ can be used to convert pyrimidinones to bromides, although the phosphonium salt generated by the combination of *N*-bromosuccinimide and triphenylphosphine offers advantages <2001HCA1112>. For example, 4-bromo-2,6-dimethylpyrimidine **109** was formed in 84% yield using the NBS phosphonium complex <2001HCA1112>.



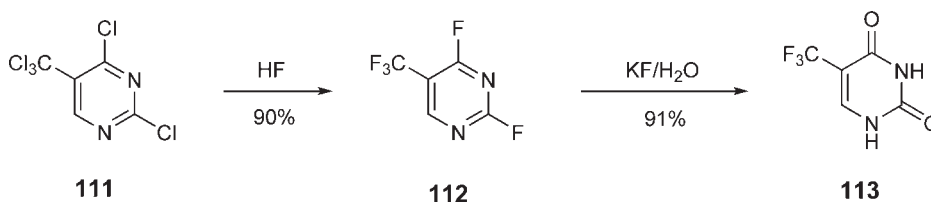
8.02.5.4.2(iii) Iodination

Iodopyrimidines are normally made by transhalogenation of the corresponding chloro- or bromopyrimidines. Cold hydriodic acid is often used, as on warming, hydrolysis or reductive dehalogenation may be competitive processes <1994HC(52)1>. 2-Iodopyrimidines have been prepared by the reaction of 2-chloropyrimidines with HI <2002JOC6550, 2006TA486>, although the procedure is more commonly used to prepare 4- (or 6-) iodopyrimidines <2001TL311, 2004JME4716, 2005BMC2397>. Only a catalytic amount of hydriodic acid is actually required, and a combination of HI and NaI is just as effective <2001HCA1112, 2002JME3639>. Using this combination, a one-pot, two-step procedure for the conversion of pyrimidinones to iodopyrimidines has been developed via the chloro compounds which do not need to be isolated <2001HCA1112>. Thus, the conversion of 2,6-dimethylpyrimidin-4(3*H*)-one **107** to 4-iodo-2,6-dimethylpyrimidine **110** was achieved in one pot in 60% overall yield.



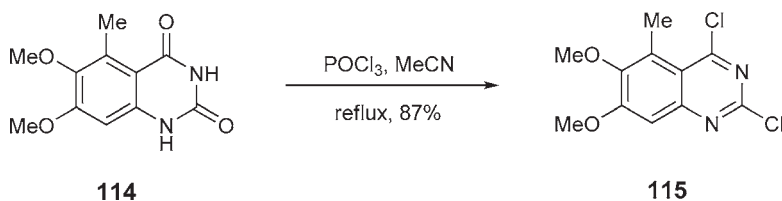
8.02.5.4.2(iv) Fluorination

Fluorination in the electrophilic 2-, 4-, and 6-positions is effected by substitutions of other halides, and this is normally performed by nucleophilic displacement with fluoride ion <1994HC(52)1>. Hydrofluoric acid can also be used, and in the case of 2,4-dichloro-5-trichloromethylpyrimidine **111**, replacement of all five chlorine atoms occurred, to give 2,4-difluoro-5-trifluoromethylpyrimidine **112**, which was subsequently hydrolyzed to give 5-trifluoromethyluracil **113** <1996JFC(77)93>.

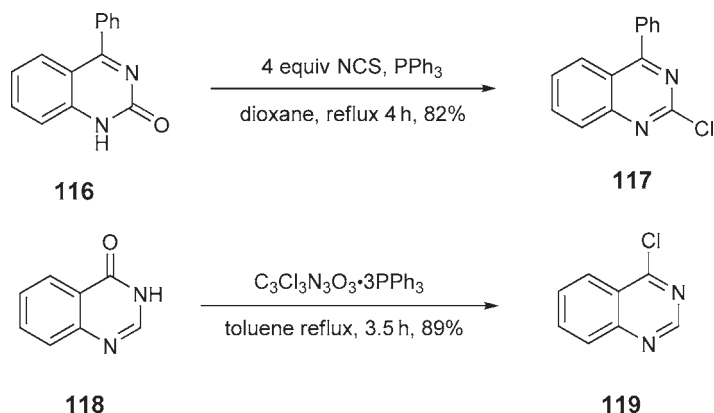


8.02.5.4.2(v) Quinazolines

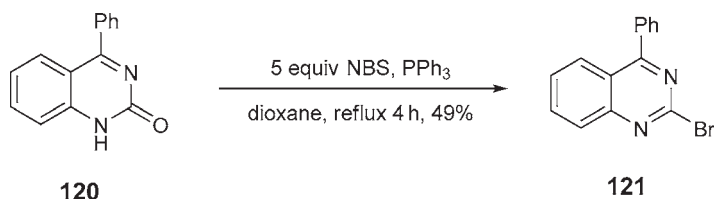
Hydroxy groups in the electrophilic 2- and/or 4-position are substituted by a chlorine on heating with phosphoryl chloride <1967HC(24)1, 1996HC(55)1, 1998HOU(E9b2)1, 2004SOS(16)573, 2005T10153>. In the past, a molar equivalent of phosphorus pentachloride was often added to provide an extra chloride source for the nucleophilic displacement step, but the same effect can be achieved by the addition of a tertiary amine which traps the HCl initially produced. Amines that have been used include tripropylamine <2004OPD330>, *N*-ethyl-diisopropylamine <2005BML5446>, *N,N*-diethyl- or *N,N*-dimethylaniline <2002JOC8284, 2002TL2971, 2005T9375>, and pyridine <2004T7983>. In many cases no additive is required, and POCl₃ alone is sufficient to give 4-chloro derivatives <1996JME267>. On a larger scale, the combination of phosphoryl chloride and acetonitrile as solvent has been found to be useful for the synthesis of 2,4-dichloroquinazolines such as the 5-methyl-6,7-dimethoxy analog **115** from the dione **114** <2006OPD391>.



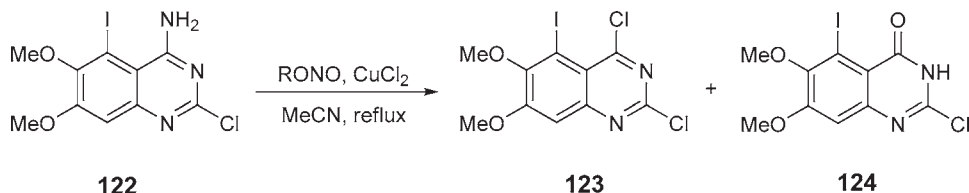
The microwave-assisted chlorination of 4(3*H*)-quinazolinones with phosphoryl chloride has been investigated, and although there were no advantages in terms of product yields, reaction times were considerably shorter, being of the order of 10 min, rather than several hours <2003T1413>. As an alternative to phosphoryl chloride, thionyl chloride can also be used as the chloride source, provided a catalytic amount of DMF is also present <1996JME267, 1996JME918, 2003BMC383>. Oxalyl chloride and catalytic DMF may also be used <1996JME267, 2005JME7445, 2005OPD440>. Other reagent systems that have been used include combinations of triphenylphosphine with *N*-chlorosuccinimide <2001HCA1112>, trichloroisocyanuric acid <2005H(65)181>, and tetrachloromethane <2005BML5446>. Thus, treatment of 4-phenyl-2(1*H*)-quinazolinone **116** with triphenylphosphine and *N*-chlorosuccinimide gave the analogous chloroquinazoline **117** in 82 % yield <2001HCA1112>, while reaction of 4-(3*H*)-quinazolinone **118** with triphenylphosphine and trichloroisocyanuric acid gave 4-chloroquinazoline **119** in 89% yield <2005H(65)181>.



Attempts to convert 4(3*H*)-quinazolinone **118** to 4-bromoquinazoline with triphenylphosphine and *N*-bromosuccinimide were not very successful, although 2-bromo-4-phenylquinazoline **121** was formed from the 2-quinazolinone **120** in 49% yield under the same conditions <2001HCA1112>.



Formation of chloroquinazolines by amine diazotization can also be performed, but in the case of 4-amino-2-chloro-5-iodo-6,7-dimethoxyquinazoline **122**, chlorination with isobutyl nitrite and cupric chloride to give **123** was accompanied by hydrolysis to the analogous quinazolinone **124** <2005TL983>.



4-Fluoro-2-phenylquinazoline has been prepared by fluoride displacement of chlorine from 4-chloro-2-phenylquinazoline <2002JOC8991>.

8.02.5.4.2(vi) Perimidines

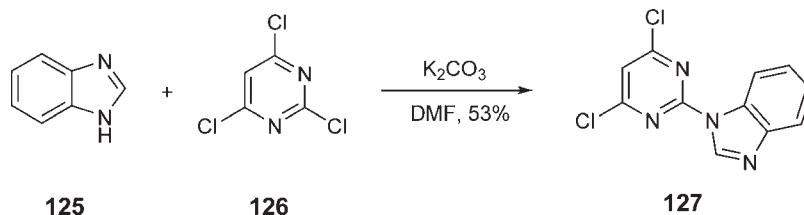
The oxygen atom in perimidin-2-one is replaced using phosphoryl chloride, with formation of 2-chloroperimidine <1981RCR816, 1995AQ151>.

8.02.5.4.3 Amination

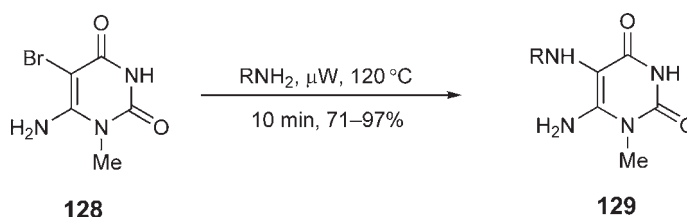
Aminolysis of active halogenopyrimidines is the normal route into 2-, 4-, and 6-aminopyrimidines. Regioselective substitutions in di- and tri-halo derivatives can be achieved in many cases. Chloro, bromo, and iodo substituents undergo aminolysis at approximately the same rates, whereas a fluoro substituent 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, and NMe₂) decrease the rate of aminolysis, whereas electron-withdrawing substituents (Cl, CF₃, NO₂) have the opposite effect <1994HC(52)1>. Elevated temperatures are generally 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 <1994HC(52)1, 1996CHEC-II(6)93>.

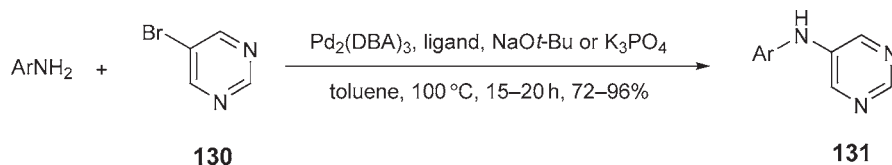
2,4,6-Trihalopyrimidines initially give mixtures of 2- and 4-monoaminated products, although in the case of benzimidazole **125** and 2,4,6-trichloropyrimidine **126**, a simple recrystallization gave clean 2-substituted product **127** in 53% yield <2000CPB1778>.



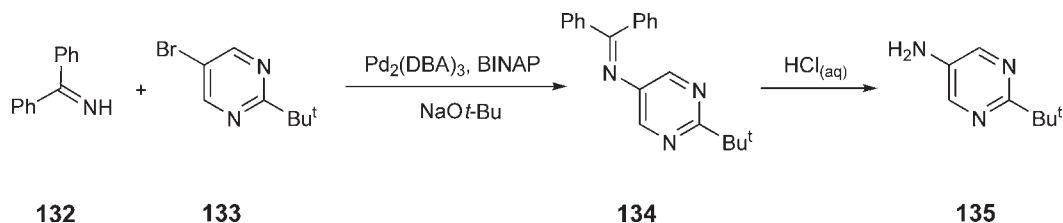
The use of microwave irradiation has enabled pyrimidine amination reactions to be performed more efficiently, especially with less reactive 2-chloropyrimidines <2002T887, 2002TL5739, 2004TL757>, and it has also proved useful for the amination of 5-halouracil derivatives, especially when there is a deactivating 6-substituent present <2005T3107, 2006TL775>. For example, the reaction of 6-amino-5-bromo-1-methyluracil **128** with a variety of alkyl amines gave the 5-amino products **129** in excellent yield, although no reaction was achieved with aromatic amines <2006TL775>.



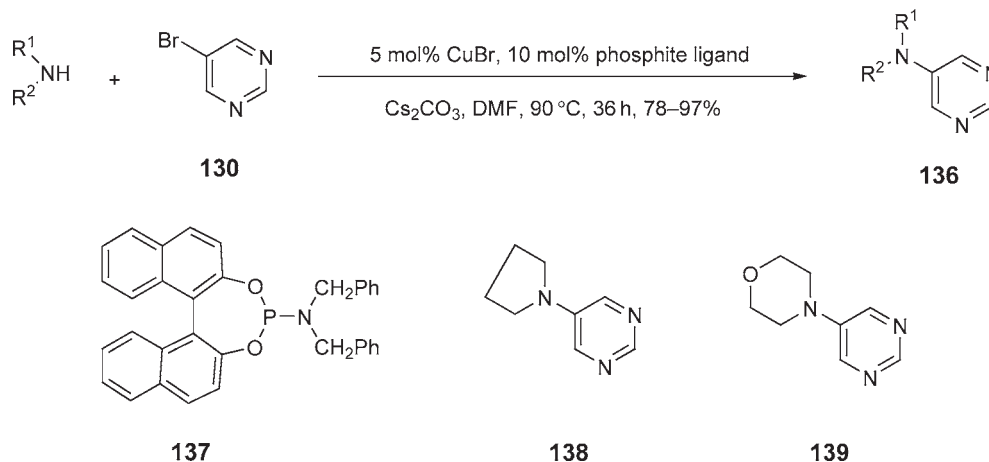
While the direct amination of 5-halouracils occurs readily, even in the absence of microwave irradiation <2005S2227, 2006TL4437>, due to activation by the adjacent carbonyl groups, no such activation occurs with most 5-halogenated pyrimidine derivatives. However, a major change since the publication of CHEC-II(1996) has been in the area of copper- and palladium-catalyzed amination and amidation chemistry <1998ACR805, 1998AGE2046, 2003SL2428, B-2004MI699, 2006CRV2651, 2006SL1283>, which has enabled 5-halopyrimidines to become ready substrates for conversion to 5-aminopyrimidine derivatives <2001CPB1314, 2001JA7727, 2002JA7421, 2003OL793, 2005JME6482, 2005OL3965, 2005TL2405, 2006AGE6523, 2006JOM(691)975, 2006OPD70, 2006T4435, 2006TL2549>. Palladium-catalyzed reactions are particularly suitable for aromatic amines as demonstrated by the efficient amination of 5-bromopyrimidine **130** to 5-anilino derivatives **131** <2005OL3965>.



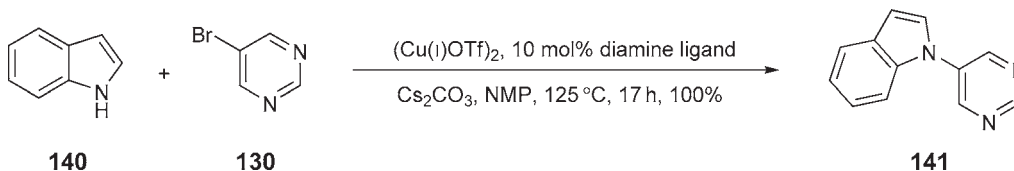
Unsubstituted 5-aminopyrimidine derivatives can also be prepared by the use of benzophenone imine **132** as the amine source, as demonstrated by the synthesis of 2-*tert*-butyl-5-pyrimidinamine **135** from the bromide **133** via the imine **134** <2006OPD70>.



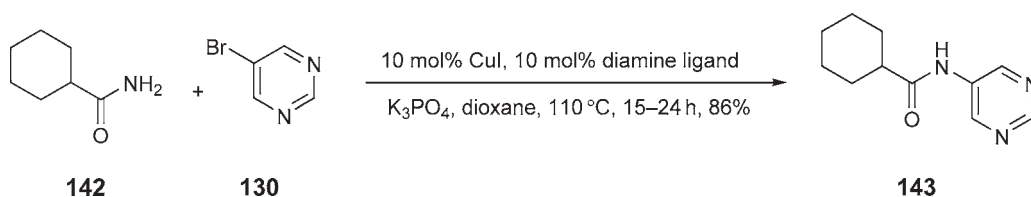
For most aliphatic amines, copper catalysis is normally superior to palladium catalysis <2003OL793, 2005TL2405, 2006T4435>. For example, the reaction of a variety of aliphatic primary and secondary amines with 5-bromopyrimidine **130** using copper bromide and the phosphite ligand **137** gave 5-aminopyrimidines **136** in excellent yields <2006T4435>, and when pyrrolidine and morpholine were used as the amine components the 5-substituted pyrimidines **138** and **139** were obtained in superior yields (83% and 86%, respectively) to those obtained with the analogous palladium-catalyzed reactions (58% and 73%, respectively) <2005OL3965>.



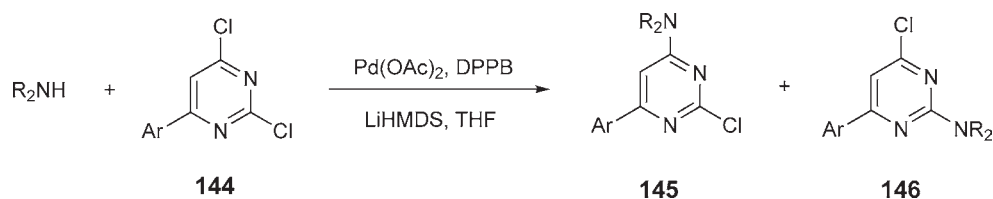
Heterocyclic amines have also been used in conjunction with copper catalysis, as shown by the copper triflate-catalyzed reaction of indole **140** with 5-bromopyrimidine **130**, which gave the product **141** in quantitative yield <2005TL2405>.



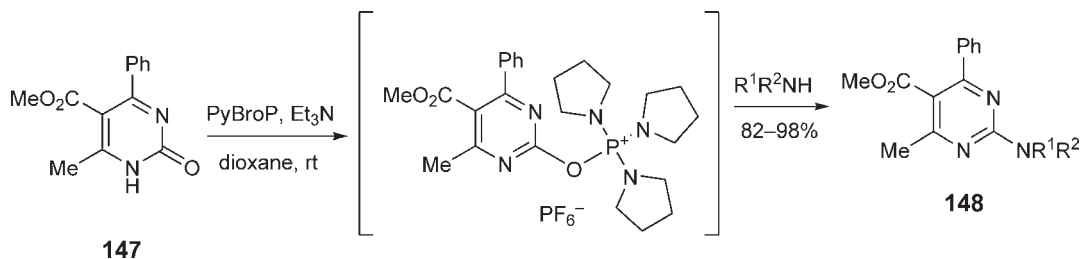
Copper-catalyzed amidation has also been achieved, and an example is the amidation of 5-bromopyrimidine **130** with cyclohexanecarboxamide **142** which went in 86% yield in the presence of catalytic copper iodide and a diamine ligand <2001JA7727, 2002JA7421>.



Palladium catalysis has also been investigated in conjunction with the amination of other halopyrimidine isomers <2002OL3481, 2005OL3965, 2006OL395>, and a highly regioselective amination of 6-aryl-2,4-dichloropyrimidines **144** with aliphatic secondary amines has been developed which strongly favors the formation of the 4-substituted product **145**. The reactions are carried out using LiHMDS as the base and give the 4-substituted isomers in ratios of 95:5 to 99:1 compared to the 2-substituted product **146** <2006OL395>. Aromatic amines did not require the presence of a palladium catalyst and gave the 4-substituted isomers in ratios of 95:5 to 97:3 compared to the 2-substituted product for *N*-methylaniline, and 91:9 for aniline, the only primary amine studied <2006OL395>.

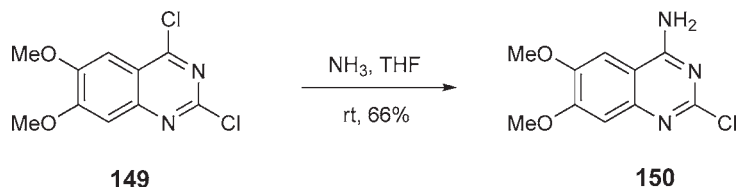


The direct amination of pyrimidinones has also been achieved using bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) as the coupling reagent [<2005JOC1957>](#). Reaction of the 2-pyrimidinone **147** with alkyl- and dialkylamines occurred in high yield to give 2-amino products **148** and reaction with sulfonamides and heterocyclic amines was also achieved in good yield with the addition of sodium *tert*-butoxide [<2005JOC1957>](#).

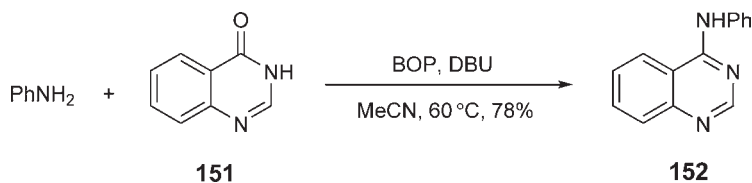


8.02.5.4.3(i) Quinazolines

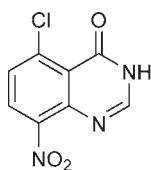
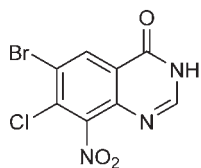
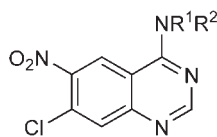
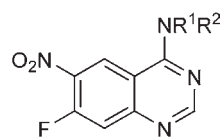
Chlorines in the electrophilic 2- and 4-positions of quinazoline are readily aminolyzed, with a 4-chlorine reacting much faster than a 2-chlorine [<1996HC\(55\)1, 1996CHEC-II\(6\)93>](#). This large difference in reactivity allows easy and stepwise amination in 2,4-dichloroquinazolines, as demonstrated by the reaction of ammonia with 2,4-dichloro-6,7-dimethoxyquinazoline **149** to give the 4-amino product **150** [<2002JOC8284, 2005BMC3681>](#). Subsequent displacement of the 2-chlorine by amines under palladium-catalyzed conditions has been investigated, but appears to offer little advantage over direct amination [<2002JOC8284>](#).



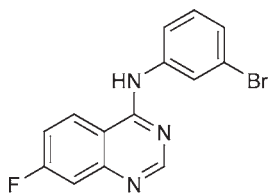
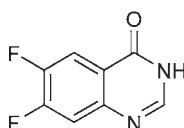
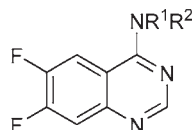
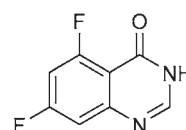
The development of 4-anilinoquinazolines as signal transduction inhibitors has made the synthesis of this class of compound a very important procedure. Normally, this is achieved by reaction of an aniline derivative with a 4-chloroquinazoline under neutral or acid-catalyzed conditions [<2000COR679, 2005T10153, 2006MOL272>](#), although condensation under basic conditions using bases such as NaHMDS has also been performed [<2004JME871>](#). 4-Anilinoquinazolines have also been prepared by reaction of 4-methylthioquinazolines with anilines under acid-catalyzed conditions [<1996JME918, 1997JME1519>](#), and direct reaction between 4(3*H*)-quinazolinone **151** and aniline has also been achieved using a mixture of (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (BOP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [<2006OL2425>](#).



Amination in the benzo ring of quinazolines can readily be achieved when an activating group such as a nitro group is present <1996HC(55)1>, and thus 5-chloro-8-nitro-4(3*H*)-quinazolinone **153** <2005BMC5613>, 6-bromo-7-chloro-8-nitro-4(3*H*)-quinazolinone **154** <1996JME918>, 4-amino-7-chloro-6-nitro-quinazolines **155** <1996JME267, 2002CPB1073, 2003CPB1109>, and 4-amino-7-fluoro-6-nitro-quinazolines **156** <1996JME918, 2005JME5337> have all undergone amination reaction with aliphatic amines.

**153****154****155****156**

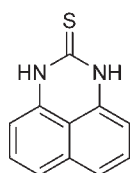
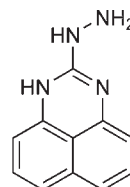
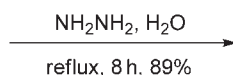
Amination of 5- and 7-fluoroquinazolines can be achieved even without the presence of a nitro group, and thus 4-(3-bromophenyl)amino-7-fluoroquinazoline **157** <1996JME918>, 6,7-difluoro-4(3*H*)-quinazolinone **158** <2003BMC609>, and 4-amino-6,7-difluoro-quinazolines **159** <2003BMC609> all produced 7-amino derivatives, while 5,7-difluoro-4(3*H*)-quinazolinone **160** underwent selective amination at the 5-position with morpholine <2006JME6465>.

**157****158****159****160**

Palladium-catalyzed amination has also been used to prepare aminoquinazolines substituted in the benzo ring <2002JA1594, 2003TL7533>. The reactions were performed on solid support and involved amination of all four chloro isomers with 4-methoxyaniline <2002JA1594>, or the amination of 6-bromo or 6- or 7-chloroquinazoline derivatives with a variety of aliphatic amines <2003TL7533>.

8.02.5.4.3(ii) 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-amines <1981RCR816, 1995AQ151>. For example, reaction of 2-perimidinethione **161** with hydrazine gave 2-hydrazinoperimidine **162** in 89% yield <2006H(68)821>.

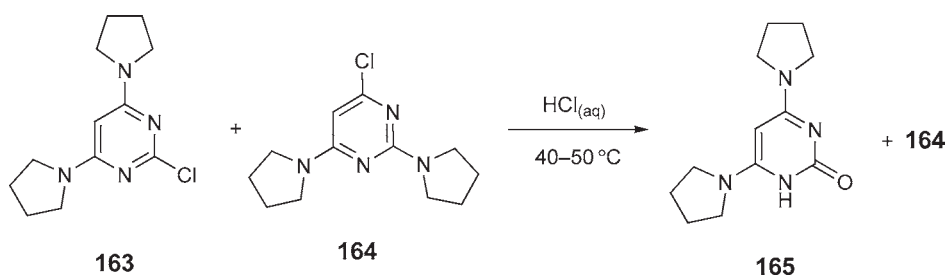
**161****162**

8.02.5.4.3(iii) Amination by addition reactions

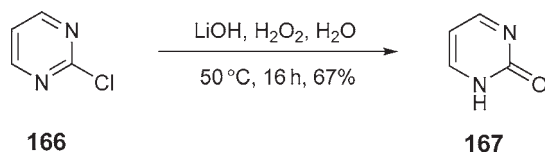
The Chichibabin reaction is not used synthetically as a major route to pyrimidines, quinazolines, or perimidines, and earlier examples have been discussed elsewhere <1994HC(52)1, 1996HC(55)1, 1996CHEC-II(6)93, B-2001MI1>.

8.02.5.4.4 Hydroxylation

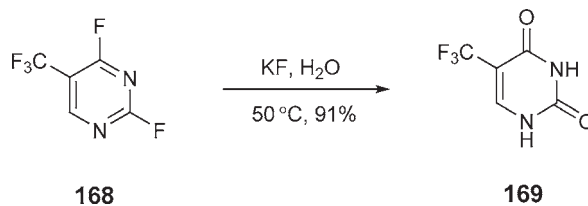
Hydroxyl groups can be introduced by hydrolytic reactions in the electrophilic 2-, 4- and 6-positions, and direct hydrolysis of halopyrimidines can be effected under both acidic and alkaline conditions <1994HC(52)1>. Normally 4-halopyrimidines hydrolyze faster than 2-halo derivatives, but in the case of 2-chloro-4,6-di(pyrrolidinyl)pyrimidine **163** and 4-chloro-2,6-di(pyrrolidinyl)pyrimidine **164**, the 2-chloro isomer **163** was found to hydrolyze 350 times faster (to **165**) than the 6-chloro isomer **164** in 6 N HCl, and 1750 times faster in 12 N HCl <2006OPD921>. This result was interpreted as being due to the transition state for hydrolysis of the 4-chloro isomer involving two more molecules of water (each acting as a base) than the transition state for hydrolysis of the 2-chloro isomer. As the concentration of HCl increases from 6 N to 12 N, there are fewer unprotonated water molecules and thus, hydrolysis of the 4-isomer is less favored. This difference in reactivity was able to be exploited to perform a selective hydrolysis on a production scale <2006OPD921>.



Addition of aqueous hydrogen peroxide significantly accelerates the substitution reactions with hydroxide. For example, treatment of 2-chloropyrimidine **166** with lithium hydroxide and hydrogen peroxide in water at 50 °C afforded 2-pyrimidinone **167** in 67% yield <2006TL4249>.



Fluorinated pyrimidines hydrolyze more readily than the other halogen derivatives and thus 5-trifluoromethyluracil **169** was able to be obtained from 2,6-difluoro-5-trifluoromethylpyrimidine **168** simply by heating with potassium fluoride in water at 50 °C <1996JFC(77)93>.



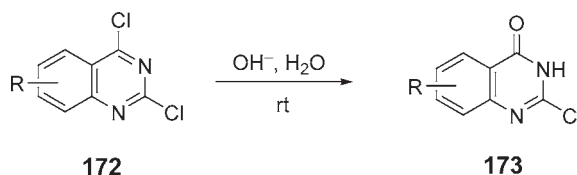
Hydrolysis of pyrimidinamines generally requires more vigorous conditions, although selective hydrolysis can often be achieved. Thus, the acid-catalyzed hydrolysis of 2,4,6-triaminopyrimidine **170** occurred in the 2-position to give 4,6-diamino-2(1*H*)-pyrimidinone **171** <2001JOC192>. Examples of selective diazotization of diamines are also known <2005JOC1612>.



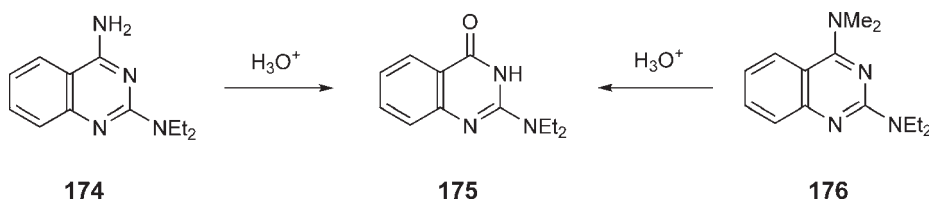
Alkoxides are usually more difficult to hydrolyze than halides, although hydrolysis can be rapid in activated systems. Pyrimidinethiones can sometimes be hydrolyzed directly to pyrimidinones, but it is often better to convert the thiones into alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl derivatives before hydrolysis <1994HC(52)1, 1996CHEC-II(6)93>. The formation of 5-hydroxypyrimidines is not normally performed using hydrolytic procedures, although it can be achieved by the oxidation of boronate species in aqueous solution <1996CC2719, 2006TL7363>.

8.02.5.4.4(i) Quinazolines

The high electrophilic character of the 2- and 4-positions in quinazoline makes hydrolysis to oxo derivatives relatively easy, and both 2- and 4-chloro substituents can be hydrolyzed in either alkaline or acid solution. The significantly higher reactivity in the 4-position simplifies stepwise substitutions, and the synthesis of 2-chloro-4(3*H*)-quinazolinones **173** is readily performed from the dichloro compounds **172** with sodium or potassium hydroxide at room temperature <2003BMC2439, 2005OPD80, 2006H(67)489, 2006OPD391>.



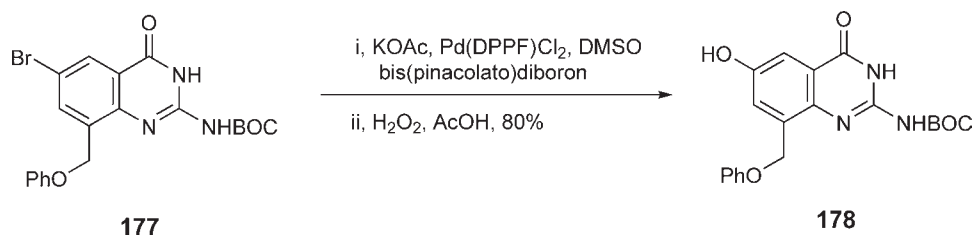
Selective hydrolysis of 2,4-diaminoquinazolines to 2-amino-4(3*H*)-quinazolinones **175** can be achieved under acidic conditions <2000JHC1097, 2002JHC1289>, and it has been found that 4-amino derivatives **174** hydrolyze 10 times faster than 4-dimethylamino compounds **176** <2002JHC1289>.



Quinazolines substituted by hydroxyl groups in the benzene ring are normally prepared by hydrolysis of the corresponding alkoxyquinazoline derivatives <1996HC(55)1>. This can normally be achieved by the use of reagents such as boron tribromide <2004JME4453>, pyridine hydrochloride <1995JME3482, 1996JME267, 2004T5373>, or thiolate <2005BML3881>, but an area that has received some considerable attention is in the selective hydrolysis of alkoxy groups in the presence of other alkoxy groups or hydrolyzable functional groups. A number of selective hydrolyses have been achieved, and these include: the hydrolysis of 5-methoxy and 5-benzyloxy substituents in the presence of the same substituents at the 7-position, with magnesium bromide in pyridine <2006BML1633>; 6-methoxy in the presence of 7-methoxy, with methionine and methanesulfonic acid <2005TL7715>; 7-methoxy in the presence of a (morpholine-containing) 6-alkoxy group, with lithium chloride in DMF <2006BML4102>; hydrolysis of a 7-benzyloxy substituent in the presence of a 4-methylthio group, with refluxing trifluoroacetic acid <2004JME871>; and the hydrolysis of an 8-methoxy group in the presence of 4-dimethylamino, with sodium borohydride in methanol <2004JHC247>.

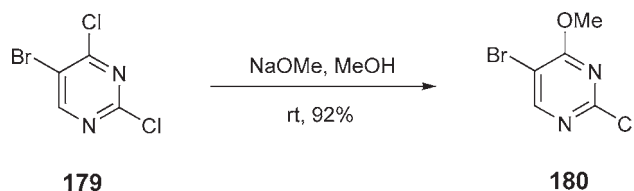
Acetoxy groups can be carried through a quinazoline ring synthesis, and then hydrolyzed in the presence of an alkoxy group, and the hydrolysis of an acetoxy group in the presence of 2- and 4-chloro substituents has also been achieved with methoxymagnesium chloride <2005T9375>. However, the most common route to quinazolines containing both alkoxy and hydroxy substituents is to incorporate a benzyloxy substituent at an early stage in the synthesis and then remove it at a later stage by hydrogenation or treatment with trifluoroacetic acid <2002JME1300, 2002JME3772, 2003JME4910, 2004OL3715, 2005BML5446>. Trityl groups have also been used <2004JHC247>.

Conversion of the 6-bromoquinazolinone **177** to the 6-hydroxy derivative **178** has been achieved through the oxidation of a boron intermediate <2004HCA1333>.

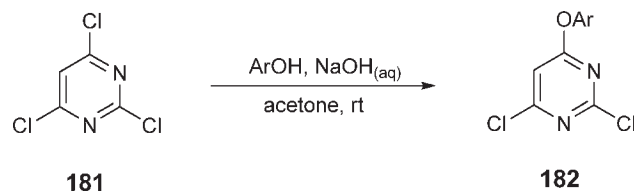


8.02.5.4.5 Alkoxylation and aryloxylation

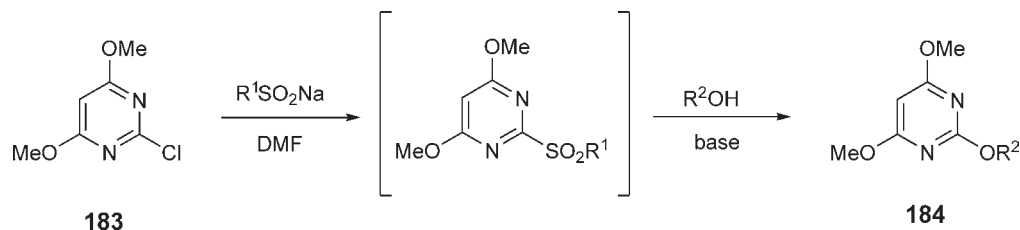
Nucleophilic displacement of 2-, 4-, and 6-halo substituents by alkoxy or aryloxy ions occurs readily except in the presence of strongly electron-releasing substituents in the ring <1994HC(52)1>. Stepwise reaction can be achieved with di- and trihalo-pyrimidines, with the more reactive 4-position being the first site of reaction. For example, even with the presence of a bulky ortho substituent such as a 5-bromine atom, selective methanolysis at the 4-position was still observed with 5-bromo-2,4-dichloropyrimidine **179** <2006TL4415>.



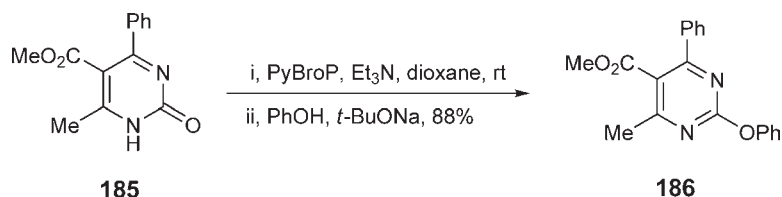
Similarly, reaction of 2,4,6-trichloropyrimidine **181** with 1 equiv of phenoxides gave mainly the 4-substituted products **182** <1998JHC269>.



Sulfonyl substituents are also replaceable on prolonged heating with alkoxides, or mixtures of alcohols and a base. The reactivity is much increased when the sulfide is oxidized to a sulfoxide or a sulfone prior to substitution, and the regioselectivity for nucleophilic substitution can be changed by having a sulfonyl substituent in the 2-position <1994HC(52)1, 1996CHEC-II(6)93>. The sulfonyl substituent can also be introduced by nucleophilic displacement with sulfinates, and this has been used in a catalytic process to greatly enhance the rate of substitution in the reaction of 2-chloro-4,6-dimethoxypyrimidine **183** with alkoxy and aryloxy nucleophiles <2000T4739>.



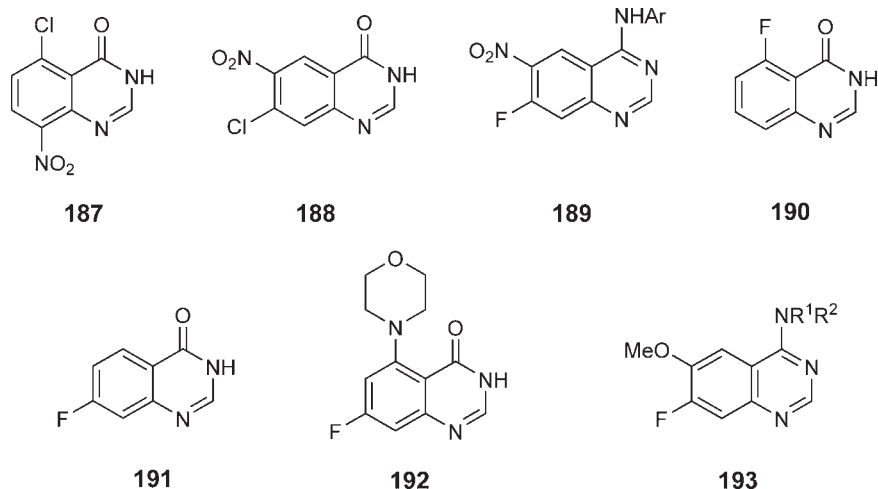
The direct reaction of sodium phenoxide with the 2-pyrimidinone **185** has also been achieved using pyBroP as the coupling reagent <2005JOC1957>.



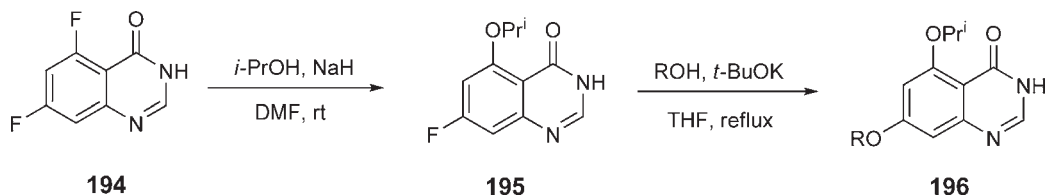
8.02.5.4.5(i) Quinazolines

2- and 4-alkoxyquinazolines are readily prepared by nucleophilic substitution reactions, and 2,4-dialkoxyquinazolines can simply be prepared by boiling 2,4-dichloroquinazolines with 2 equiv of an alkoxide in the appropriate alcohol solvent <1996HC(55)1>. The first substitution is in the more reactive 4-position, so it is possible to isolate both 4-alkoxy and 4-phenoxy monosubstitution products <1977EJM325, 2005BMC3681>, and this selectivity has been used to attach both 2,4,6- and 2,4,7-trichloroquinazoline to a solid support, via the 4-position, for subsequent solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones <2003TL7533>.

Alkoxylation in the benzene ring of quinazolines and quinazolinones is readily achieved in the presence of an *ortho*-nitro group, and even in the absence of a nitro group, displacement of fluorine is still quite facile. Examples of haloquinazolines to have been alkoxyated include 5-chloro-8-nitro-4(3*H*)-quinazolinone **187** <2005BMC5613>, 7-chloro-6-nitro-4(3*H*)-quinazolinone **188** <1996JME267>, 4-arylamino-7-fluoro-6-nitroquinazolines **189** <2000JME1380>, 5-fluoro-4(3*H*)-quinazolinone **190** <2005BML4226>, 7-fluoro-4(3*H*)-quinazolinone **191** <2002JME3772, 2004JME871>, 7-fluoro-5-morpholino-4(3*H*)-quinazolinone **192** <2006JME6465>, and 4-(*N*-alkyl-*N*-arylamino)-7-fluoro-6-methoxyquinazolines **193** <2005JME7560>.



In the case of 5,7-difluoro-4(3*H*)-quinazolinone **194**, selective displacement of the 5-fluorine was achieved at room temperature, and this was followed by displacement of the 7-fluorine by a different alcohol at reflux in THF <2005BML5446>.



Palladium-catalyzed displacement of chlorine from all four benzene ring isomers has been achieved by reaction of 4-methoxyphenol with resin bound 4-dialkylaminoquinazolines <2002JA1594>.

8.02.5.4.6 Thiation

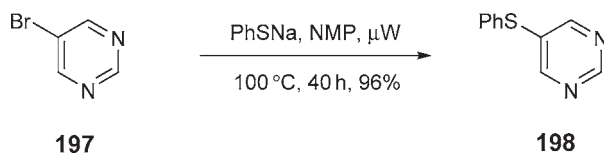
Thiopyrimidines can be prepared by thiolysis of halopyrimidines or by thiation of pyrimidinones with phosphorus pentasulfide or Lawesson's reagent (2,4-bis-*p*-methoxyphenyl-1,3,2,4-dithiadiphosphetane-2,4-disulfide) <2003JOC9971>. The dithiation of uracil and thiamine has also been performed with the assistance of microwave irradiation using phosphorus pentasulfide absorbed on silica gel <2001SC2231>.

8.02.5.4.6(i) Quinazolines

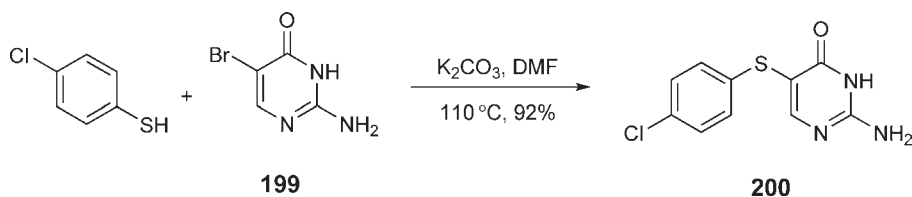
The thiation of quinazolinones is normally achieved by heating with phosphorus pentasulfide <1967HC(24)1, 1996HC(55)1>, although Lawesson's reagent has also been used <2004BMC3529, 2006JME2440>. The combination of Lawesson's reagent and microwave heating has also been investigated, and although yields were not significantly improved, reaction times were considerably shorter <2003T1413>.

8.02.5.4.7 Alkylthioxylation and arylthioxylation

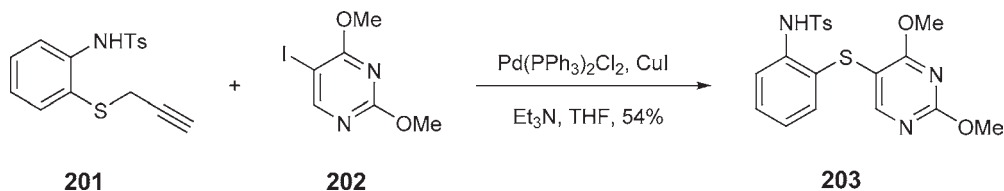
Alkylthio derivatives are normally prepared by alkylation of thiones, but they can also be prepared by alkanethiolysis reactions, and selective reaction can be achieved. Aromatic sulfides are commonly prepared by arenethiolysis reactions with halopyrimidines <1994HC(52)1>. In addition to halide displacement at the electrophilic 2-, 4-, and 6-positions, displacement can also occur at the unactivated 5-position when microwave irradiation is used. Thus, 5-bromopyrimidine **197** gave 5-phenylthiopyrimidine **198** in 96% yield after 40 h of microwave irradiation, whereas the thermal reaction only gave a 7% yield in the same time period <2002T887>.



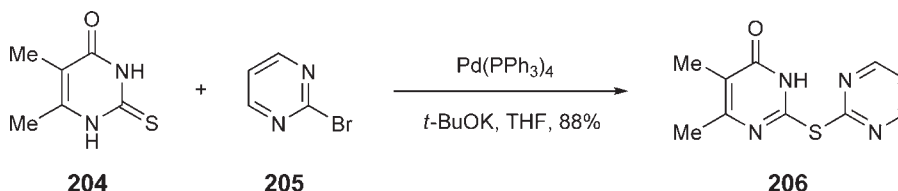
Microwave assistance has also been investigated in conjunction with thioxylation of 5-halouracils <2005T3107>, although successful displacement was achieved with 2-amino-5-bromo-4(3*H*)-pyrimidinone (5-bromoisocytosine) **199** solely under thermal conditions <2000JHC183>.



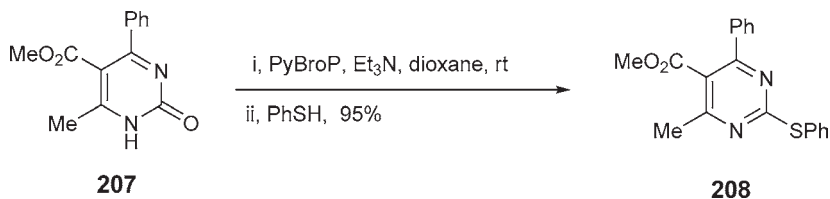
Thioxylation has also been achieved using palladium catalysis, and reaction of 5-iodo-2,4-dimethoxypyrimidine **202** with the arylthiopropyne **201** occurred with loss of the propyne unit and replacement of the iodine by the arylthio group <2000TL7259, 2001T5885>.



Palladium-catalyzed synthesis of the bipyrimidinethiol **206** was achieved by cross-coupling of the 2-pyrimidinethione **204** with 2-bromopyrimidine **205** <1999SL1579>.

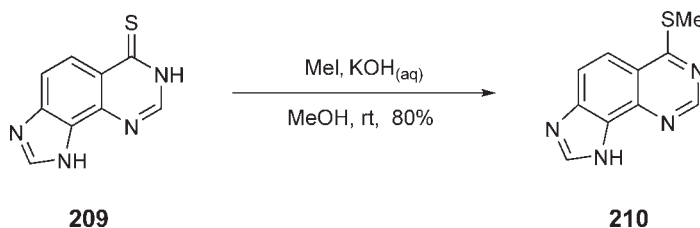


The direct reaction of thiophenol with the 2-pyrimidinone **207** has also been achieved using pyBroP as the coupling reagent [<2005JOC1957>](#).



8.02.5.4.7(i) Quinazolines

Quinazoline alkylthio derivatives are frequently made by S-alkylation of the corresponding quinazolinethiones. The conditions required are very mild, and S-alkylation can be performed in the presence of other groups capable of undergoing alkylation. For example, 1*H*-imidazo[4,5-*b*]quinazoline-6(7*H*)-thione **209** was converted to the 4-methylthio derivative **210** at room temperature, without any alkylation of the nitrogen atoms of the imidazole ring [<1996JME918>](#).



Arylthio, as well as alkylthio derivatives, can also be prepared by nucleophilic substitution of haloquinazolines by the corresponding thiols [<1967HC\(24\)1, 1996HC\(55\)1>](#). Quinazoline derivatives substituted in the benzene ring by alkyl - or arylthio groups have also been prepared by direct halogen displacement [<1996HC\(55\)1, 2000JME1380, 2004BKC1898>](#).

8.02.5.4.7(ii) Perimidines

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

8.02.5.5 Alkylation, Arylation, and Acylation at Carbon

8.02.5.5.1 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 8.02.5.3.6](#).

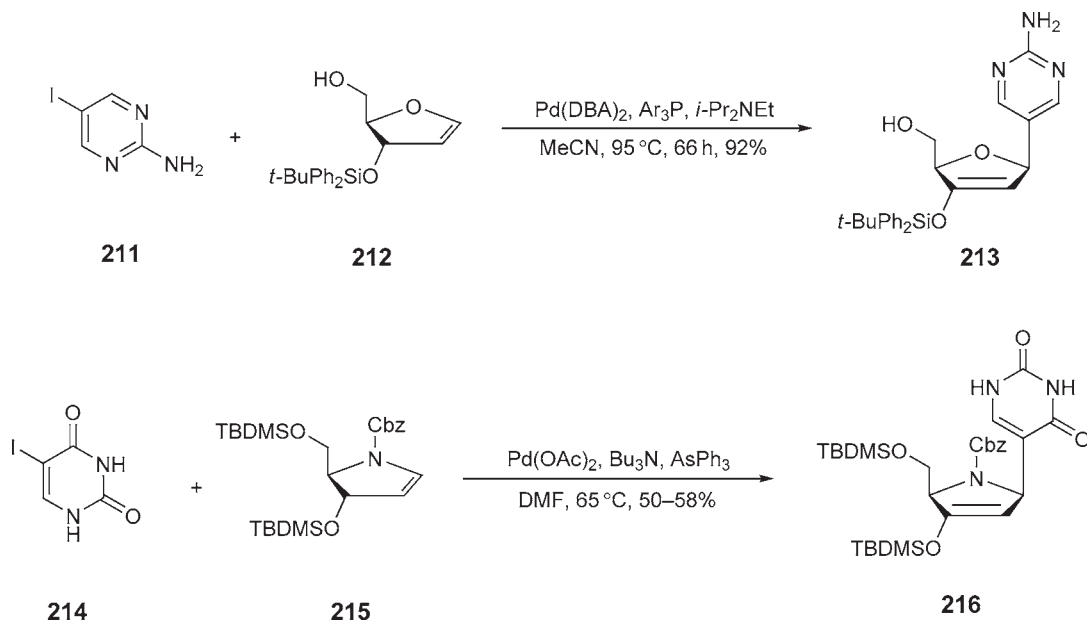
8.02.5.5.2 Transition-metal-mediated alkylation, arylation, and acylation

Palladium-catalyzed reactions represent the vast majority of transition-metal-catalyzed reactions involving pyrimidines and quinazolines [<1990H\(30\)1155, 1995AHC\(62\)305, B-2000MI375, B-2002MI409, 2003CRV1875, 2005T2245, 2006CRV2651, 2006THC155, 2007CRV133, 2007CRV874>](#), although nickel-catalyzed reactions are also well established [<1990H\(30\)1155, 1992S413, 1995AHC\(62\)305>](#), and the importance of co-catalytic copper in

the Sonagashira reaction cannot be underestimated <B-2000MI375, B-2002MI409, 2007CRV874>. More recently, iron-catalyzed cross-coupling reactions have also shown great promise <2002AGE609, 2002JA13856, 2004JOC3943>. Due to the electronegativity of the two nitrogen atoms, palladium chemistry takes place more readily with halopyrimidines than with halopyridines, with the order of oxidative addition correlating to that for nucleophilic substitution <B-2000MI375>. Not only are 2-, 4-, and 6-chloropyrimidines viable substrates for palladium-catalyzed reactions, but good selectivity can also be achieved, with 4- and 6-chloropyrimidines reacting more readily than their 2-chloro isomers.

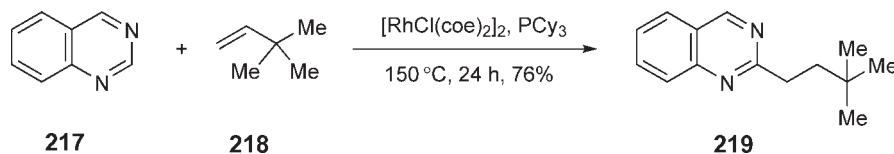
8.02.5.5.2(i) Transition-metal-mediated alkylation

Transition-metal-mediated alkylation of pyrimidine derivatives can occur by a number of different methods, including palladium-catalyzed reactions with organoaluminium, organoboron, organostannane, and organozinc species, and iron- and nickel-catalyzed reactions with organomagnesium (Grignard) reagents. Direct reaction using dimethylcuprate has also been achieved <1997TL4343>, although this is not a commonly used procedure with pyrimidines. However, one procedure that has been well exploited is the use of the Heck coupling reaction to prepare pyrimidinyl or quinazolinyl *C*-glycosides (*C*-nucleosides) <2006NN1309>. Thus, both 2-amino-5-iodopyrimidine **211** and 5-iodouracil **214** gave the unsaturated *C*-glycosides **213** and **216**, which were subsequently converted to the fully saturated analogs by removal of the silyl protecting group with tetrabutylammonium fluoride, and reduction of the resulting ketone with sodium triacetoxyborohydride <2000JOC7468, 2001OL489>. 2-Benzoylamino-5-iodo-4-pyrimidinone reacted similarly <2005OBC1653>.



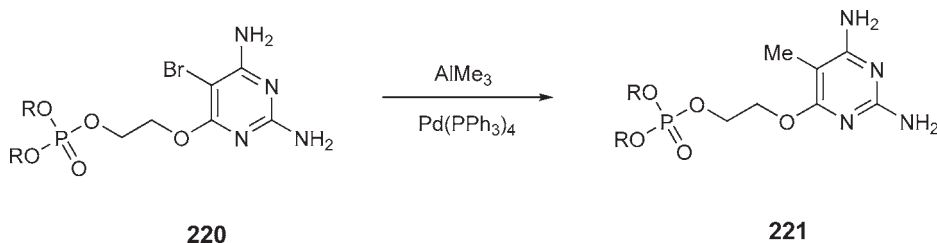
Quinazolines halogenated in the benzene ring react similarly, and 5-bromo-, 6-iodo-, and 8-iodoquinazoline derivatives have been converted to their *C*-glycoside analogs <2003JA2084, 2004JA1102, 2005JOC132>. An amide-protected 2-amino-6-iodo-4(3*H*)-quinazolinone derivative was also successfully converted to a *C*-glycoside <2005JOC132>.

Direct reaction of quinazoline **217** with excess 3,3-dimethylbutene **218** in the presence of a Rh(I) catalyst derived from $[\text{RhCl}(\text{cis-cyclooctene})_2]_2$ and tri(cyclohexyl)phosphine gave the 2-alkylquinazoline **219** in 76% yield, although higher yields were obtained when starting with 3,4-dihydroquinazoline <2006JOC1969>.



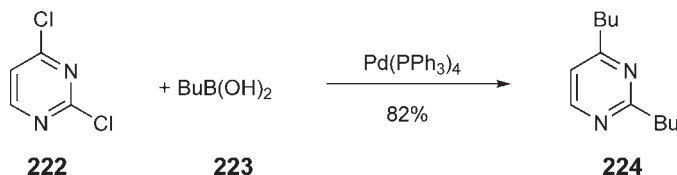
8.02.5.5.2(i)(a) Organoalanes

Palladium-catalyzed cross-coupling of organoaluminium derivatives with pyrimidines has only received modest attention, although alanes are effective donors of an alkyl group to palladium after palladium insertion into a carbon–halogen or carbon–oxygen (triflate) bond <1996CHEC-II(6)93, B-2002MI409>. Alkylation of 2,4-dichloropyrimidine can be effected in a stepwise manner, with initial alkylation occurring in the 4-position, and in 5-bromo-2-chloropyrimidine the bromine substituent in the benzenoid position is replaced by the methyl group to give the product <1997ACS302>. Quinazolines are similarly alkylated <1996TL1309, 2005T10153>. Selectivity for mono-substitution in 6-bromo-2,4-quinazoline was not fully achieved, with the main product being derived from replacement of the 4-chloro substituent, and the minor product from substitution of the 6-bromo group <1997ACS302>. Synthetic applications have included the synthesis of 2-chloro-4,5-dimethylpyrimidine from its 4,5-dichloro precursor <2002MI85>, and the synthesis of 5-methyl-2,4-diamino-6-[2-(phosphonomethoxy)ethoxy]pyrimidines **221** as acyclic nucleoside phosphonate analogs with antiviral activity <2003JME5064>.

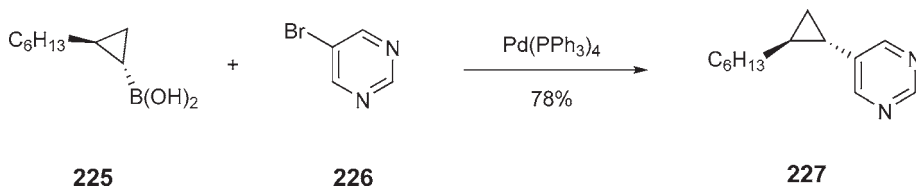


8.02.5.5.2(i)(b) Organoboranes

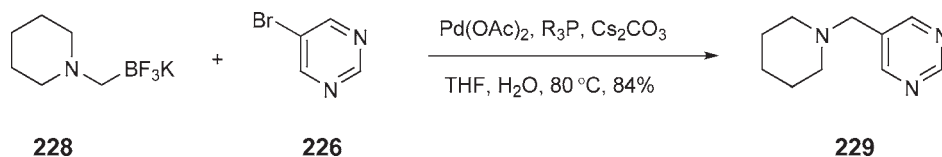
Although widely used in other areas of organic chemistry <2001AGE4544>, alkylboranes have been used less often in Suzuki cross-coupling reactions involving pyrimidine derivatives. However, successful examples involving both 2- and 5-halopyrimidines are known <1997SL1406, 2001T3125, 2004CEJ544>, and 2,4-dichloropyrimidine **222** has been converted to 2,4-dibutylpyrimidine **224** with butylboronic acid **223** in very good yield <2003JFC(120)21>.



In the reaction of *trans*-2-hexylcyclopropaneboronic acid **225** with 5-bromopyrimidine **226**, the *trans*-stereochemistry was retained in the product **227** <1999SC2477>.

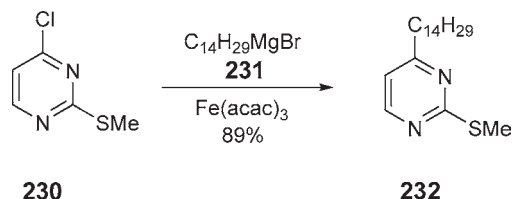


Direct aminomethylation at the 5-position of 5-bromopyrimidine **226** to afford **229** has recently been achieved using potassium *N*-(trifluoroboratomethyl)piperidine **228** as the boron species <2007OL1597>.



8.02.5.5.2(i)(c) Organomagnesium Compounds

The nickel-catalyzed (Kumada) reaction of alkyl Grignard reagents with halo pyrimidines has only received moderate attention, and a study of the reaction of butylmagnesium chloride with 2,4-dichloropyrimidine showed that the reaction proceeded in lower yield than the analogous palladium-catalyzed reaction involving butylboronic acid <2003JFC(120)21>. Better results have been achieved with iron-catalyzed alkylation reactions, where both 2- and 4-chloropyrimidines have been successfully alkylated in high yield with alkylmagnesium reagents using iron(III) acetylacetonate as catalyst <2002AGE609, 2002JA13856>, as demonstrated by the reaction of 4-chloro-2-methylthio-pyrimidine **230** with the Grignard reagent **231** to afford **232**.



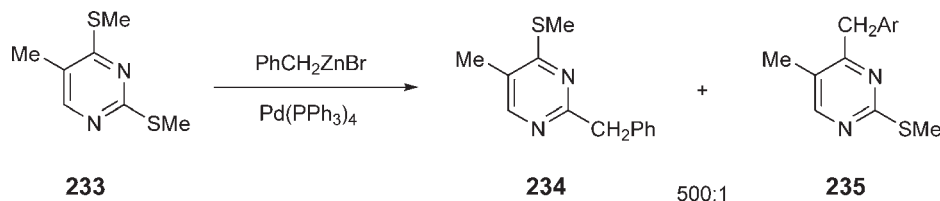
This method is distinguished by a number of advantages over other methods, including the replacement of expensive palladium catalysts with a cheap, toxicologically benign iron salt. The reaction is performed at room temperature under ligand-free conditions, and reaction times are usually very short. Selective reaction at the 4-position of 2,4-dichloropyrimidine can also be achieved <2004JOC3943>. The method also works well with 6-chlorouracil and 4-chloroquinazoline derivatives <2002JA13856>.

8.02.5.5.2(i)(d) Organostannanes

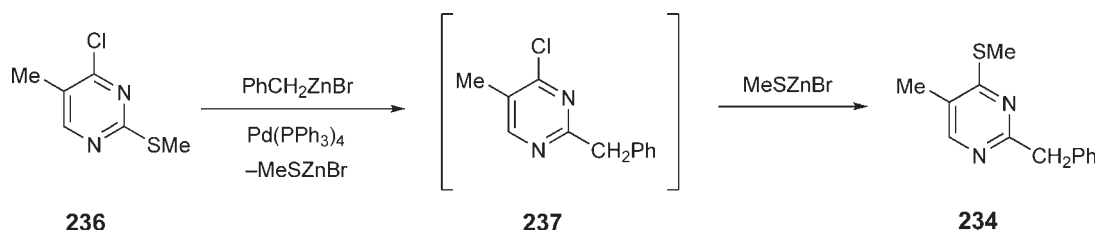
Tetramethyl- or tetrabutylstannane can be used for the preparation of methyl and butyl derivatives, but these reactions often require vigorous conditions <1996CHEC-II(6)93, 1997OR1, B-2002MI409>. The reactivity is enhanced when the sp^3 -hybridized carbon carries an electronegative group or unsaturation, and in the reactions between allyl- or benzyltributylstannane and an iodopyrimidine, it is the allyl or benzyl group which is transferred to the pyrimidine <1996CHEC-II(6)93, 1997OR1, B-2002MI409>. However, for other alkylations of pyrimidine derivatives, it is suggested that alternative alkylation reactions are employed <B-2002MI409>.

8.02.5.5.2(i)(e) Organozinc compounds

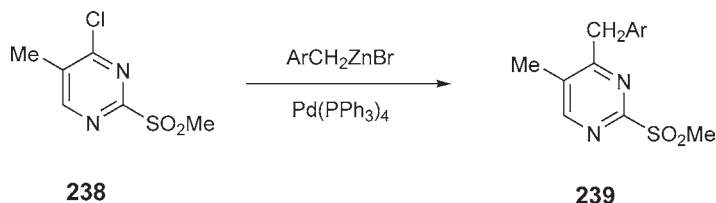
Cross-coupling with organozinc reagents using transition metal catalysis (Negishi reaction) proceeds with high chemo-, regio-, and stereoselectivity, and organozinc reagents are much better than their organotin analogs for the transfer of alkyl groups. Even the Reformatsky reaction can be effected in moderate yields <1996CHEC-II(6)93, B-2002MI409>. The pyrimidinyl triflates show comparable reactivity to the chloropyrimidines in the Pd-catalyzed reactions, although variable yields were seen in reactions involving butylzinc bromide because of competitive alkene formation <1994H(37)501, 1996CHEC-II(6)93>. Alkylation reactions involving benzylic zinc reagents show the expected selectivity with dihalopyrimidines, with benzylation of 2,4-dichloro-5-methylpyrimidine occurring at the 4-position in good yield <2000SL905, 2002MI85>, although the order of reactivity was completely reversed for 2,4-bis-(methylthio)-5-methylpyrimidine **233** where the 2-substituted product **234** was obtained in a 500:1 ratio compared to the 4-isomer **235** <2000SL905>.



The same product was obtained when 4-chloro-5-methyl-2-(methylthio)pyrimidine **236** was reacted with benzylzinc bromide, due to selective palladium-catalyzed displacement of the 2-methylthio group, followed by nucleophilic displacement of the 4-chloro substituent of the intermediate **237** by the liberated zinc thiomethoxide <2000SL905>.



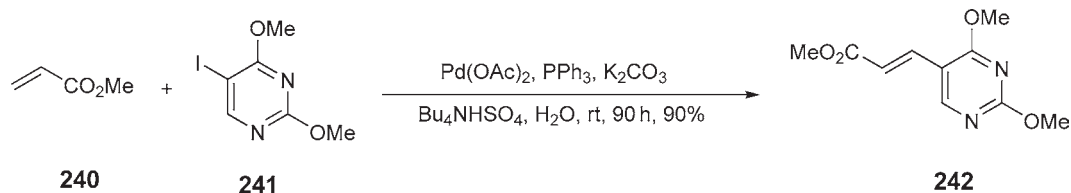
The extraordinary regioselectivity shown with the 2-methylthio group was not displayed by the analogous sulfone **238**, which underwent exclusive reaction at the 4-position <2000SL905>.



Negishi reactions have also been used to insert methyl and ethyl groups at the 2-position of quinazolines <1998BML2891>.

8.02.5.5.2(ii) Transition-metal-catalyzed alkenylation

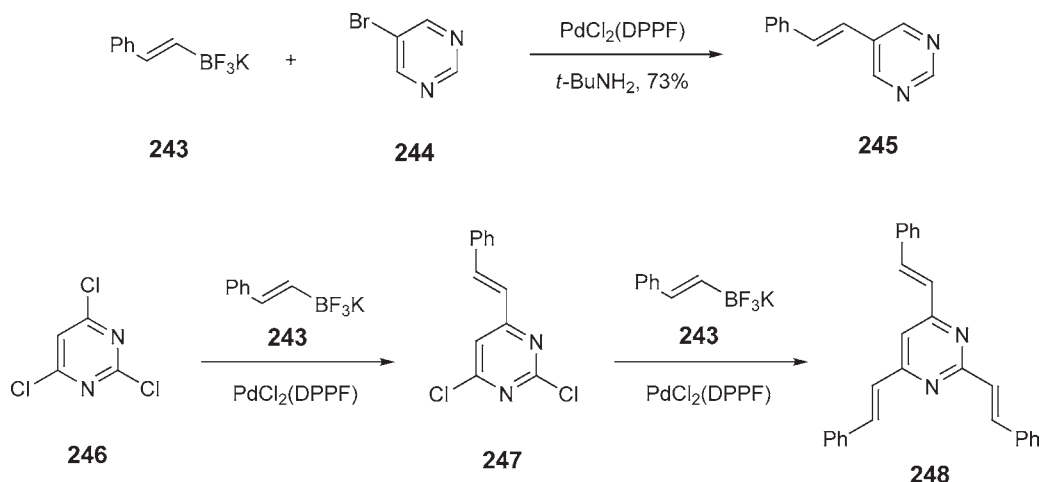
A number of different procedures are available for the alkenylation of pyrimidines or quinazolines, including use of the Heck reaction <2000JME4288, B-2000MI375, 2002JME3246, B-2002MI409, 2004JPO1046, 2005OPD694, 2006BML2173>, as demonstrated by the room temperature coupling of methyl acrylate **240** with 2,4-dimethoxy-5-iodopyrimidine **241** to give the 5-alkenyl product **242** in 90% yield <1997TL4869>.



8.02.5.5.2(ii)(a) Organoboron compounds

The Suzuki–Miyaura cross-coupling of chloropyrimidines with stereodefined alkenylboronic acids gives the corresponding alkenyl-substituted pyrimidines both stereospecifically and regioselectively in good yield <2004SC3773>. Displacement of the 2-chloro substituent occurs readily with 2-chloropyrimidine, whereas with 2,4-dichloro-5-methoxypyrimidine, reaction occurs selectively in the 4-position. With 2,4,6-trichloropyrimidine the order of reactivity was as expected, with reaction occurring first at the 4-position, and then at the 6-position <2004SC3773>.

Potassium alkenyltrifluoroborates can also be used instead of boronic acids, and the process is again stereospecific with regard to the alkenyltrifluoroborate starting material <2002JOC8424>. Thus, 5-bromopyrimidine **244** gave the *trans*-5-substituted product **245** after reaction with potassium *trans*-styryl trifluoroborate **243**, while 2,4,6-trichloropyrimidine **246** gave the 4-monosubstituted product **247** after reaction with 1 equiv of the trifluoroborate **243**, and the trisubstituted product **248** after reaction with 3.5 equiv of the boron reagent <2002JOC8424>. Reaction with 5-bromouracil failed to occur, although 5-substituted uracil derivatives have been obtained with vinyl boronic acids <2005T537>.



8.02.5.5.2(ii)(b) Organostannanes

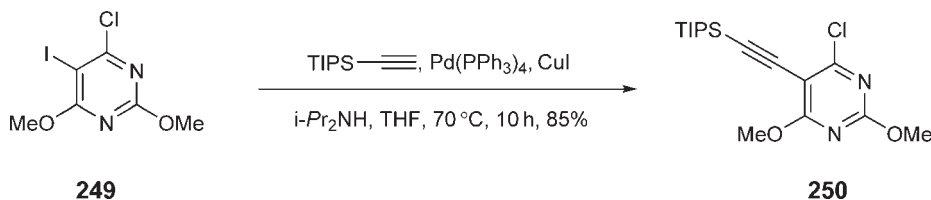
Coupling reactions between halopyrimidines and substituted alkenyltributylstannanes (Stille reaction) are regio-specific and stereospecific in the alkene reagent, with retention of the stereochemistry. The reaction between 2,5-dichloropyrimidine and styryltributylstannane occurs at the activated 2-position, while 5-bromo-2-chloropyrimidine couples selectively at the 5-position. The 2-chlorine can be substituted subsequently. In the reactions of 2,4-dichloropyrimidine and 5-bromo-2,4-dichloropyrimidine with styryltributylstannane, the first carbon substituent goes selectively into the 4-position <1990H(30)1155, 1993ACS102, 1995AHC(62)305, 1996CHEC-II(6)93, 1997OR1, B-2000MI375, B-2002MI409>.

8.02.5.5.2(ii)(c) Organozirconium compounds

Palladium-catalyzed alkenylation reactions involving pyrimidines can be achieved with hydrozirconated terminal alkynes, although the reaction is carried out in the presence of zinc chloride, so transmetalation to the zinc species is presumed to occur prior to the palladium-mediated coupling <1996ACS914, B-2002MI409>. Selective reaction at the 4-position of both 2,4-dichloropyrimidine and 2,4-dichloroquinazoline can be achieved.

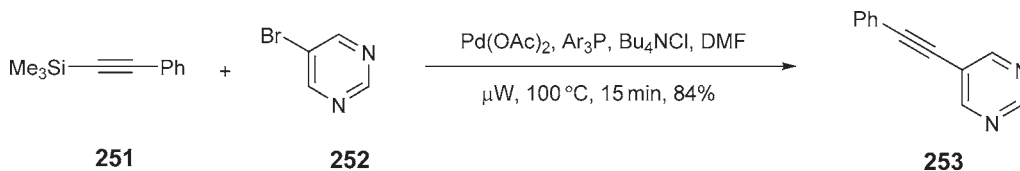
8.02.5.5.2(iii) Palladium-catalyzed alkynylation

Most alkynylations of pyrimidines involve the Sonogashira reaction, which has been described as a “booming methodology in synthetic organic chemistry” <2007CRV874>. The order of reactivity is the same as that seen with other palladium-catalyzed and nucleophilic processes, with a 4-halogen being replaced in preference to a 2-halogen <2003BML1665, 2004JOC5638, 2006OL269>, and a 2-halogen being replaced in preference to a halogen in the 5-position <B-2000MI375, B-2002MI409, 2007CRV874>. Replacement of a 5-bromine or 5-iodine can also be achieved, as demonstrated by the sequential one-pot Sonogashira alkynylation of 2-iodo-5-bromopyrimidine, where first the 2-iodine was replaced at 30 °C, and then the 5-bromine was replaced at reflux in THF <2001OL173>. The greater reactivity of an iodine atom compared to the other halogens is shown by the selective displacement of the 5-iodine in 4-chloro-5-iodo-2,4-dimethoxypyrimidine 249 <2000OL3761>, whereas similar reactions involving 4-chloro-5-bromopyrimidines result in selective replacement of the 4-chlorine <2006TL3923>.

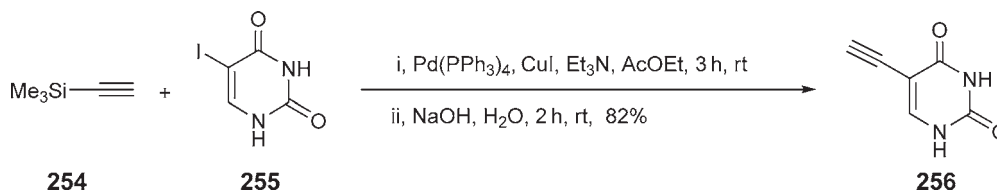


Although the Sonogashira reaction is normally performed with a copper cocatalyst, a copper-free, one-pot procedure for direct coupling with 1-aryl-2-trimethylsilylacetylenes has been developed <2005T2697>. The procedure uses a mixture of palladium acetate and tri(*o*-tolyl)phosphine as catalyst in the presence of tetra-*n*-butylammonium chloride

in DMF at 100 °C, in combination with microwave heating to give a reaction time of just 15 min. However, while an 84% yield of the product **253** was obtained in the reaction of 1-phenyl-2-trimethylsilylacetylene **251** with 5-bromopyrimidine **252**, the procedure was not quite as successful with 2-bromopyrimidine, where a product yield of only 44% was obtained <2005T2697>.



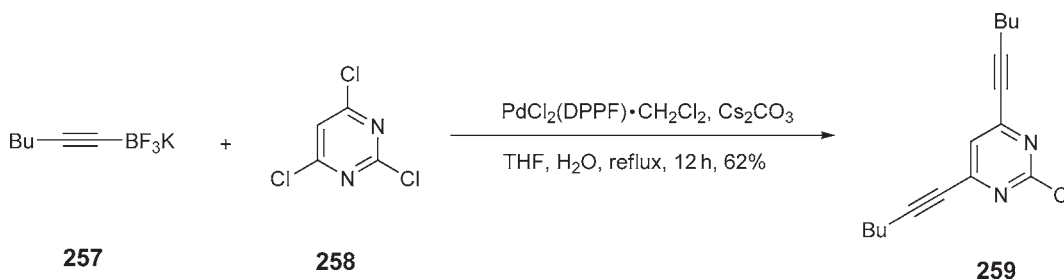
5-Iodouracil derivatives are particularly reactive under normal Sonogashira conditions, as demonstrated by the room temperature synthesis of 5-ethynyluracil (eniluracil) **256** from trimethylsilylacetylene **254** and 5-iodouracil **255** <2006CJC580>.



Similarly, many examples of the successful synthesis of nucleoside derivatives are known, often without the need for protecting groups <2007CRV874>.

Quinazoline derivatives behave similarly to pyrimidines, and a 4-chlorine can be replaced in the presence of a 2-chlorine <1996ACS914>. Reaction in the benzene ring has been successfully performed at all four isomeric positions and the method is now well established as a route to quinazoline and 4(3*H*)-quinazolinone derivatives with a variety of interesting biological properties <1995JME745, 2002CBC250, 2003OPD533, 2004HCA1333, 2005BMC2637, 2005OPD440>.

Non-Sonogashira alkynylation procedures have also been employed with pyrimidines, and selective replacement of the 4- and 6-chlorine atoms of 2,4,6-trichloropyrimidine **258** was able to be achieved using potassium (1-hexyn-1-yl)-trifluoroborate **257** <2002JOC8416>.

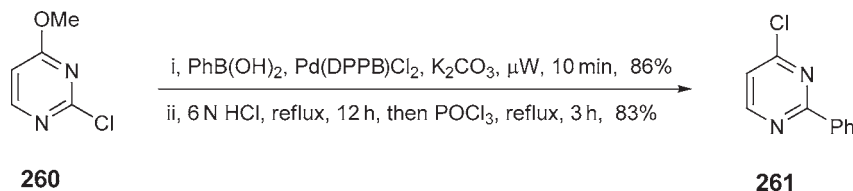


Alkynylation using organostannanes (Stille reaction) has also been performed <1992J(P1)1883, 1997OR1, 2004NN183, 2005BMC197, 2006JCO388>, and sodium tetraalkynylaluminates, prepared from NaAlH₄ and terminal alkynes, have also been used <2002JOC6287>.

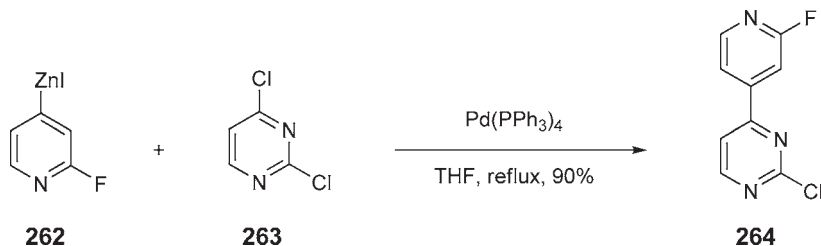
8.02.5.5.3 Palladium-catalyzed arylation or heteroarylation

A variety of different methods are available for the palladium-catalyzed arylation and heteroarylation of pyrimidines and quinazolines <1995AHC(62)305, 1997OR1, B-2000MI375, B-2002MI409, 2005T2245>, including organoboron (Suzuki), organotin (Stille), and organozinc (Negishi) reaction procedures. Often the procedures are complimentary, with availability of starting materials being a determining factor, although increasingly Suzuki reactions are becoming more preferred because of ease of reaction and low toxicity of the boron reagents. A comparison of the palladium-catalyzed organoboron (Suzuki) and nickel-catalyzed organomagnesium (Kumada) diarylation of 4,6-dichloropyrimidine found that in every case, higher yields were obtained with the boronate procedure <2003JFC(120)21>.

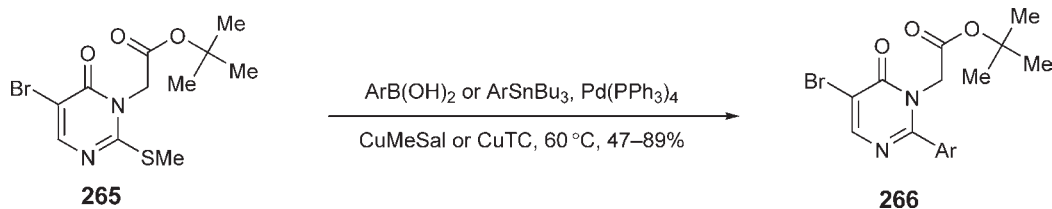
With polyhalopyrimidines the order of reactivity follows that seen with other palladium-catalyzed procedures, with 4-halogens being replaced in preference to 2-halogens, and 2-halogens being displaced in preference to 5-halogens <1999BMCL1057, 2001JOC7125, 2006JHC127, 2006TL4415>. For example, with 2,4,6-trichloropyrimidine the order of reactivity is 4, then 6 and then 2 <2001JOC7125, 2006JHC127>, while with 2,4,5-trichloropyrimidine the order is 4 then 2 then 5 <2006TL4415>. Methoxy groups can be used as masked chlorine atoms in order to reverse the order of reactivity. Thus, palladium-catalyzed cross-coupling of 2-chloro-4-methoxypyrimidine **260** with phenylboronic acid under microwave-assisted conditions gave the 2-phenyl derivative, which was then converted to 4-chloro-2-phenylpyrimidine **261** by sequential hydrolysis and chlorination with POCl₃ <2006TL4415>. A similar procedure was used to prepare 4-chloro-2,5-diphenylpyrimidine <2006TL4415>, and 4-chloro-6-methoxypyrimidine was used as a masked version of 4,6-dichloropyrimidine to ensure clean mono-arylation <2005TL3977>.



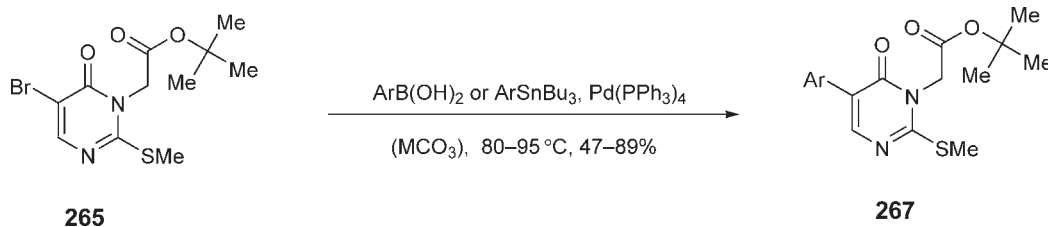
A variety of different substituted arylpyrimidines have now been prepared under Suzuki conditions <1996CC2719, 2002JA1594, 2001T2787, 2002TL5739, 2005TL3573, 2006BML4796, 2006T10055>, including reactions with both aryl- and heteroaryltrifluoroborates <2003JOC4302, 2007T3623>, and advances in palladium catalyst technology mean that excellent reaction yields are now able to be achieved with a variety of chloropyrimidine substrates <2006OL1787, 2007JA3358>, including 5-chloropyrimidines <2006AGE3484>. Phosphine-free procedures have also been developed, and excellent yields have been achieved in reactions with 5-bromopyrimidine <2004JOC4330, 2005JOC2191, 2006T10888>. Good yields have also been achieved in palladium-catalyzed cross-couplings with organomagnesium <2002T4429> and organozinc reagents <2002J(P1)1847, 2003SL1862, 2004JA13028, 2006T2380, 2006T7521>, and organozinc (Negishi) cross-coupling reactions are the preferred procedure in those cases where Suzuki reactions cannot be used, or perform poorly, due to the nonavailability or instability of heteroaryl boronates <2005JOC5215, 2007OPD237>. Thus, for example, the cross-coupling of (2-fluoropyridin-4-yl)zinc iodide **262** with 2,4-dichloropyrimidine **263** gave a 90% yield of the 4-substituted pyrimidine product **264** <2005JOC5215>, whereas much lower yields have been reported for cross-coupling reactions involving the analogous boronic acid <2005OL4753>.



In addition to halogens, triflate groups can also be replaced under Stille conditions, and methylthio and phenylthio groups have also been shown to be replaceable under modified Stille or Suzuki conditions, provided a copper source such as copper(I) 3-methylsalicylate (CuMeSal) or copper(I) bromide-dimethyl sulfide was present in at least stoichiometric amounts <2002OL979, 2003OL801, 2003OL803>. In the case of the 5-bromo-2-methylthiopyrimidinone **265**, selective palladium-catalyzed replacement of the methylthio group occurred in good yield with either arylboronic acids or arylstannanes in the presence of CuMeSal or copper(I) thiophene-2-carboxylate (CuTC) <2003OL4349>.



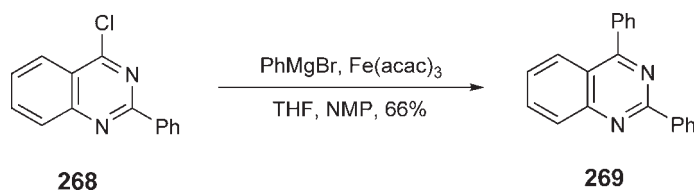
However, in the absence of the copper cofactor, standard Suzuki or Stille coupling reactions prevailed, with selective replacement of the bromine rather than the methylthio group occurring to give 5-aryl derivatives [267](#) [<2003OL4349>](#).



Haloquinazolines behave similarly to pyrimidines in palladium-catalyzed cross-coupling reactions, and selective replacement of the 4-chlorine in 2,4-dichloroquinazolines by aryl groups has been achieved under Stille reaction conditions [<1998BML2891>](#). Successful reaction at both the 2- and 4-positions of monohalogenated quinazolines has also been achieved under Stille conditions [<1998BML2891, 2000T5499, 2004T5373, 2005T2897>](#), and the use of the Suzuki reaction to convert 2- and 4-chloroquinazolines to their respective aryl derivatives is also well established [<2000POL541, 2000T5499, 2000TL2475, 2001JHC1265, 2002JA1594, 2004JCO426, 2004JOC6572, 2004T5373, 2005T2897, 2005T9808, 2005TL3573>](#). In addition, both Stille and Suzuki reactions have been used to successfully prepare quinazoline derivatives substituted with aryl and heteroaryl substituents at all four possible positions of the benzene ring [<2000T5499, 2001BML1157, 2002JA1594, 2004T5373, 2006JOC3959>](#), including 6-haloquinazoline intermediates associated with the synthesis of the antitumor agent lapatinib [<2002T1657, 2006MI435>](#).

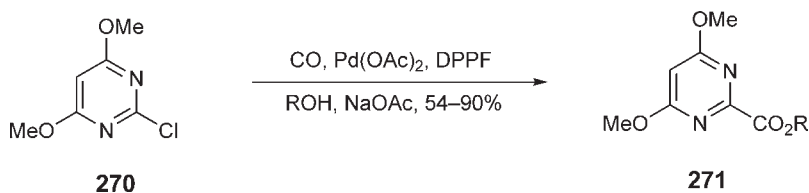
8.02.5.5.4 Iron- and nickel-catalyzed arylation

Although a lot less common than palladium-catalyzed reactions, nickel-catalyzed organomagnesium (Grignard) and organozinc (Negishi) cross-coupling reactions can also be performed with halogenated pyrimidines and quinazolines in quite reasonable yields [<2002JOC8991, 2002SL1008, 2003JFC\(120\)21, 2005OL4871, 2006T7521>](#). However, better results have been achieved with iron-catalyzed organomagnesium coupling reactions which have been performed with both pyrimidines and quinazolines [<2002JA13856, 2005JHC1423>](#), as demonstrated by the formation of 2,4-diphenylquinazoline [269](#) from the 4-chloro precursor [268](#) in 66% yield [<2002JA13856>](#). Cobalt-catalyzed organomagnesium coupling reactions with 2-chloropyrimidine have also been reported, albeit with low yields [<2006S3547>](#).

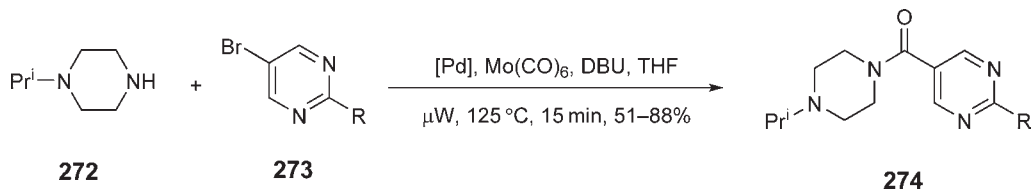


8.02.5.5.5 Palladium-catalyzed carbonylation

The synthesis of pyrimidine carboxylic esters can be achieved by palladium-catalyzed carbonylation of halopyrimidines with carbon monoxide and an alcohol [<1999T405, 2001S1098>](#), as shown by the formation of a variety of esters [271](#) from 2-chloro-4,6-dimethoxypyrimidine [270](#) [<1999T405>](#).



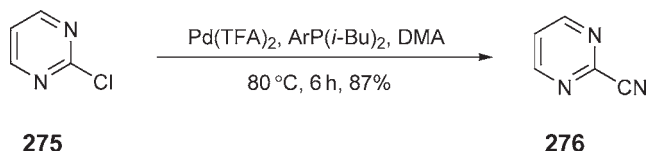
Palladium-catalyzed aminocarbonylations, using solid Mo(CO)_6 as the carbon monoxide source, have been performed under microwave-assisted conditions, with both 5-bromopyrimidine and 2-substituted-5-bromopyrimidines **273** <2007TL2339>.



The same procedure failed to work with 2-bromopyrimidine due to direct nucleophilic displacement of the bromine by the amine component <2007TL2339>.

8.02.5.5.6 Palladium-catalyzed cyanation

Although the cyanation of halopyrimidines and quinazolines is normally carried out by heating with CuCN in a solvent such as DMF <2001BML2235, 2002BML1203, 2004HCA1333>, a palladium-catalyzed procedure has now been developed using zinc cyanide that allows for cyanation to be performed under milder conditions. Thus, 2-chloropyrimidine **275** gave 2-pyrimidinecarbonitrile **276** in 87% yield after 6 h at 80°C <2007OL1597>.

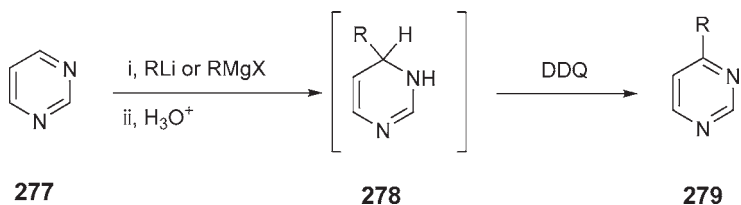


8.02.5.5.7 Tin, zinc, and boron metallopyrimidines in alkylation and arylation reactions

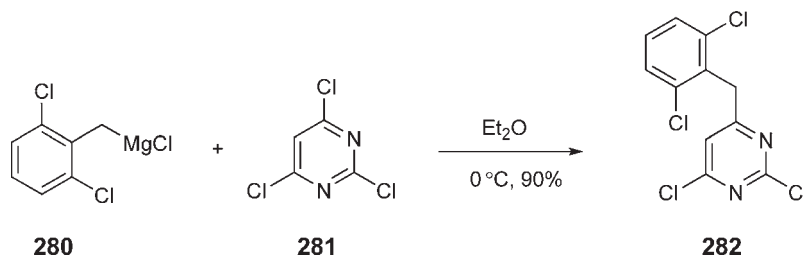
The use of pyrimidinyl boronates and stannanes in cross-coupling reactions is now well established as a route to functionalized pyrimidine derivatives <1995AHC(62)305, 1997OR1, B-2000MI375, B-2002MI409, 2003S469, 2004CRV2667, 2004OBC852, 2005JOC3741, 2005T2897, 2006AGE1282>, and although less common, cross-couplings involving organozinc species formed *in situ* have also been achieved <1998H(49)205, B-2000MI375>.

8.02.5.5.8 Alkylation and arylation by organometallic adduct formation

Organometallics add across the 3,4-double bond of pyrimidines **277** to give 3,4-dihydropyrimidines **278** which can be readily oxidized to 4-substituted pyrimidines **279** with reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) <1988JOC4137, 1990JHC1393, 1998J(P1)3515, 2001OPD28, 2002MI85, 2004JA11778, 2005OL4113, 2006BML2724, 2006JCR785>. Sequential addition and oxidation reactions can be used to prepare 4,6-disubstituted derivatives <2004JA15396>, and when both the 4- and 6-positions are blocked, addition can occur at the 2-position <1988JOC4137, 2002BML81>.



When all three electrophilic positions of pyrimidine are occupied, addition can still occur by displacement of a chlorine atom <1988JOC4137, 1999SC1503>, as demonstrated by the addition of 2,6-dichlorobenzylmagnesium chloride **280** to 2,4,6-trichloropyrimidine **281** to give the 4-substituted product **282** <2001BML2235>.

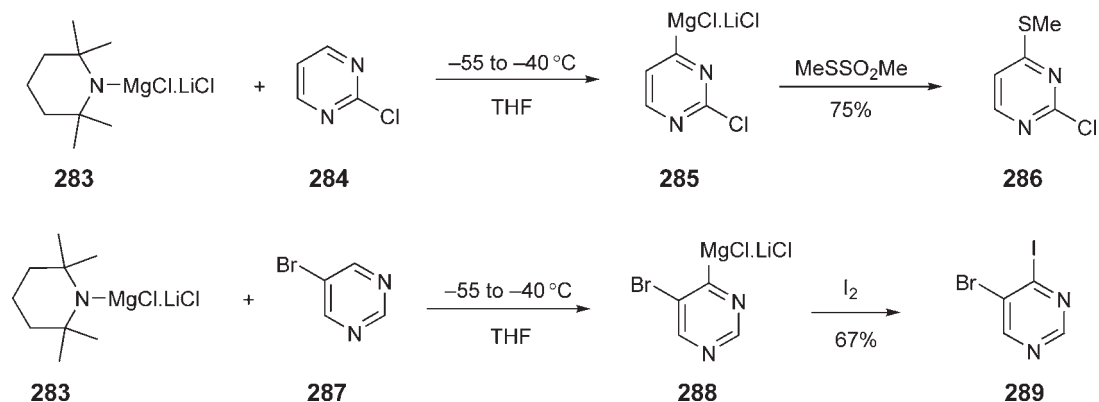


2,4-Dichloro- and 2-substituted 4-chloroquinazolines undergo a similar addition at the 4-position, while 2-unsubstituted 4-chloroquinazolines undergo an addition at the 2-position which is followed by a ring-opening reaction <1988JOC4137>.

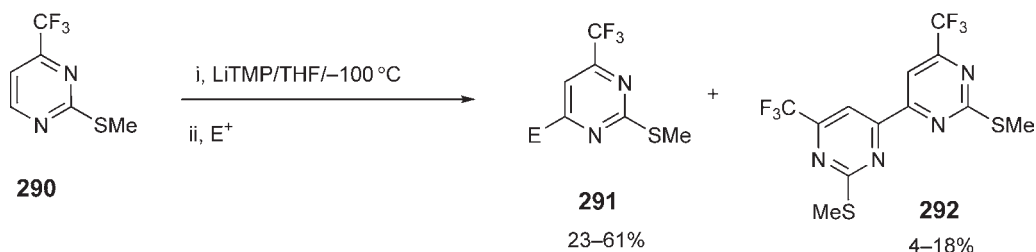
8.02.5.6 Nucleophilic Attack at Hydrogen Attached to Carbon

8.02.5.6.1 Metallation in neutral rings by hydrogen substitution

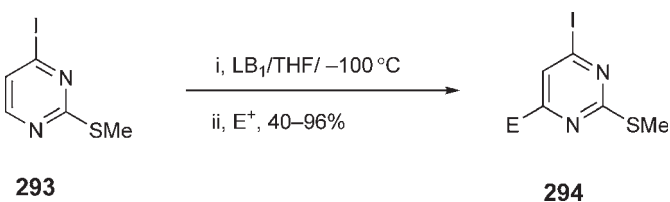
The generation of a carbanionic center adjacent to a neutral azine nitrogen is unfavored due to charge repulsion by the nitrogen lone pair <1993AHC(56)155>. In pyrimidines, C-5 is the only position not subject to this adjacent lone-pair effect. Also, the lithiation of azines is subject to addition of the base to the azomethine (C=N) bond, although the use of low temperatures and sterically hindered amide bases such as lithium tetramethylpiperidide (LiTMP) can often prevent this type of addition from occurring <2000JHC615, 2001T4489, 2004CRV2667>. Recently, less nucleophilic mixed magnesium–lithium amide bases such as TMPMgCl·LiCl **283** have been introduced to this field <2006AGE2958>. TMPMgCl·LiCl is stable in THF solution at room temperature, and allows for the direct regioselective functionalization of pyrimidines at the 4-position. Addition of either 2-chloro- or 5-bromopyrimidine **284** or **287** to a THF solution of the base **283** at $-55\text{ }^{\circ}\text{C}$ provided completely regioselectively the corresponding 4-magnesiated derivatives **285** and **288**, which reacted with a range of electrophiles to give the corresponding 4-functionalized pyrimidines **286** and **289** <2006AGE2958>.



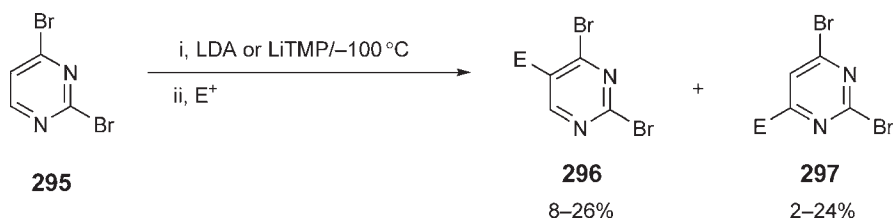
The good yields seen with TMPMgCl·LiCl and these two pyrimidines are in marked contrast to the situation seen with the lithium diisopropylamide (LDA) or LiTMP and the same heterocycles, where dimeric products were obtained unless the reaction was performed in the presence of an electrophile <1979JOC2081, 1995JOC3781>. These results demonstrate the much greater stability of magnesiopyrimidines compared to their lithio analogs where dimer formation is often a complicating factor <2001T4489>. For example, even at $-100\text{ }^{\circ}\text{C}$, treatment of 2-methylthio-4-trifluoromethylpyrimidine **290** with LiTMP gave mixtures of 6-substituted products **291** and small amounts of dimer **292** <1997JHC551>. Only when the lithiation could be performed in the presence of the electrophile was clean reaction seen.



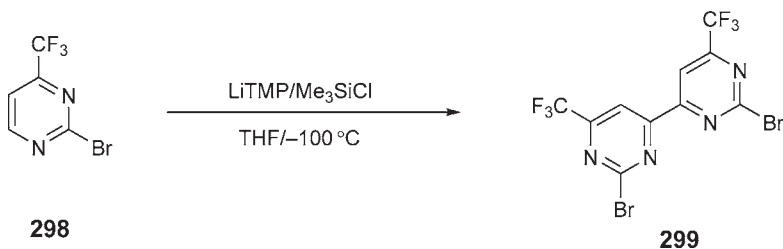
The lithiation of 4-iodo-2-methylsulfonylpyrimidine **293** also occurred regioselectively at the 6-position, although in this case, best results were achieved with the very hindered base lithium *N*-*t*-butyl-*N*-(1-*i*-propylpentyl)amide (LB_1) [<1998T9701>](#).



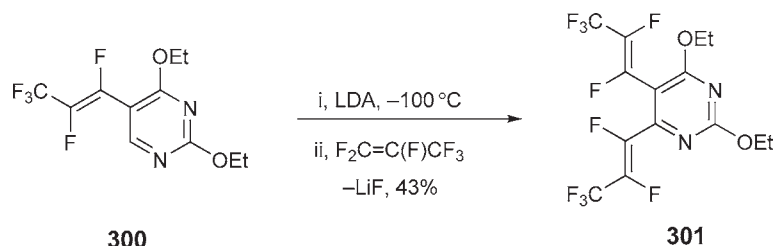
The lithiation of 4-chloro-2-methylthio- and 2,4-dichloropyrimidines was earlier shown to give mixtures of 5- and 6-substituted products [<1990JHC1377, 1993TL1605, 1998H\(49\)205>](#), and the same was found for 2,4-dibromopyrimidine **295** [<2005JHC509>](#). The 5-substituted derivative **296** was the main product isolated when LDA was used as the lithiating species, while LiTMP gave the 6-isomer **297** in the greatest quantity, but in both cases product yields were only moderate.



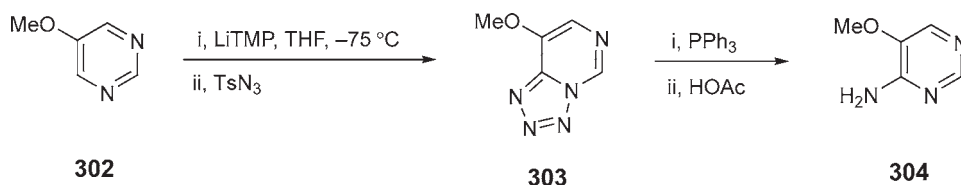
Lithiation of 2-bromo-4-trifluoromethylpyrimidine **298** with LiTMP also occurred predominantly at the 6-position, but in this case only the dimeric product **299** was obtained, even when the reaction was performed in the presence of trimethylsilyl chloride [<2006EJO1593>](#).



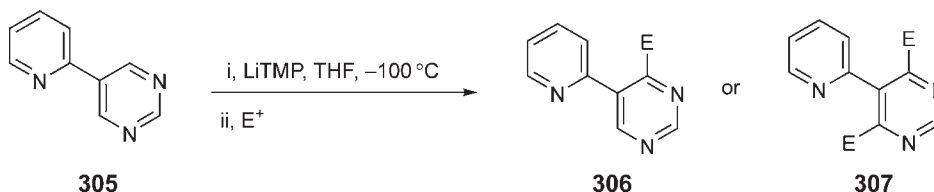
Clean lithiation at the 6-position can be achieved when all other positions are blocked, as demonstrated by the synthesis of the bis(pentafluoropropenyl) derivative **301** in 43% yield [<2006JOC8842>](#).



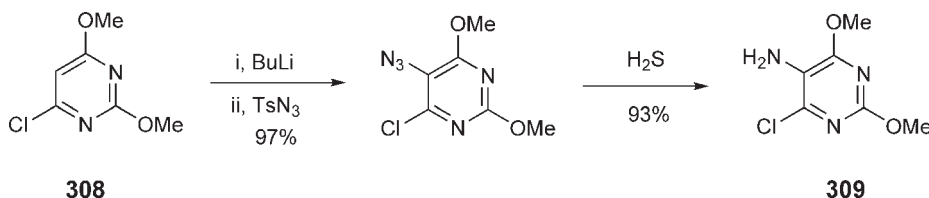
The presence of a 5-substituent containing a heteroatom capable of coordinating to a 4-lithio atom results in a stabilization of the system [<1993AHC\(56\)155>](#), making stabilized 4-lithiopyrimidines synthetically useful intermediates. For example, 5-methoxypyrimidine **302** is readily lithiated at the 4-position with LiTMP [<1990JOC3410>](#), and the resulting lithiated species has been used as a source of 4-amino-5-methoxypyrimidine **304** which was used in the synthesis of an aza analog of Nevirapine [<1996S838>](#).



Metallation of 5-(2'-pyridyl)pyrimidine **305** with 4 equiv of LiTMP, followed by reaction with *p*-methoxybenzaldehyde, gave the analogous 4-substituted derivative **306** in 43% yield, but when diphenylsulfide or tributyltin chloride were used as the electrophile, 4,6-disubstituted products **307** were obtained in 46% and 65% yield, respectively, showing that the pyridine nitrogen was functioning as a *ortho*-metallation directing group [<2005T9637>](#).

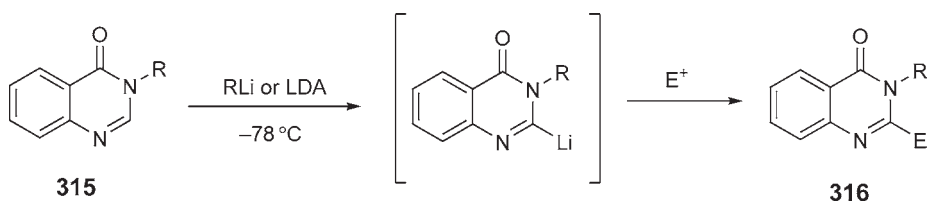


Lithiation of pyrimidines occurs at the 5-position when directed metallation groups (DMGs) are present at the 4- or 6-positions [<1991AHC\(52\)187, 1993AHC\(56\)155, 2001T4489>](#), and often high yields can be achieved. LiTMP is generally used for this transformation, although butyllithiums can also be used when electron-donating substituents such as methoxy are present at the 2-position. For example, metallation of 4-chloro-2,6-dimethoxypyrimidine **308** was performed with butyllithium during a synthesis of the 5-amino analog **309** [<1996S838>](#).

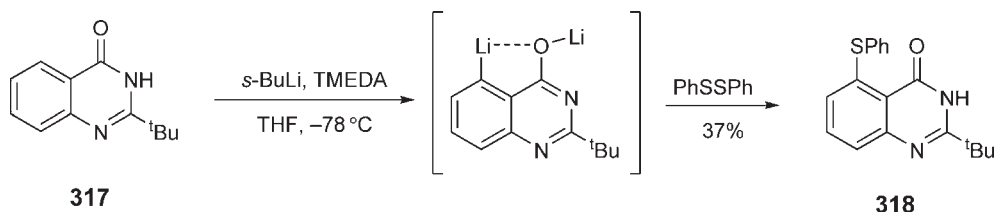


The lithiation of 4-chloro-2,6-dimethoxypyrimidine has also been used in a synthesis of inhibitors of lumazine synthase [<1999BML39, 1999JOC3838>](#), and other pyrimidine derivatives to be successfully lithiated and derivatized at the 5-position include 2,4- and 4,6-dimethoxypyrimidines [<1996BKC868>](#), 2,4-dibenzyloxypyrimidine [<1999TL4825>](#), 4,6-dichloropyrimidine [<2004BML4165>](#), 4,6-dichloro-2-(methylthio)pyrimidine [<2005BML1485>](#), and 2-chloro-4-iodo-6-methoxypyrimidine [<2005OL835>](#).

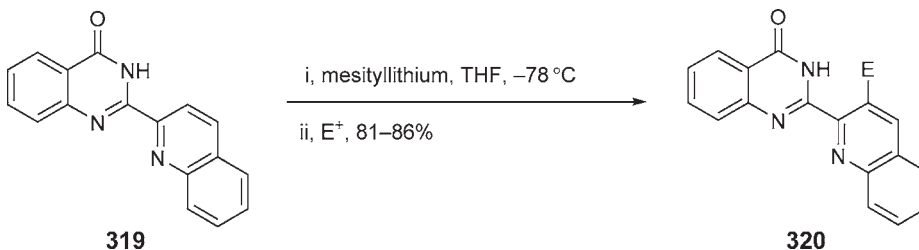
In addition to N-deprotonation, pyrimidinones can also be C-metallated. Lithiation at the 6-position of uracils and related uridines and thymidines can be achieved with butyllithium or LDA provided that the hydroxyl groups of the sugar are protected in the case of the nucleoside derivatives [<1993AHC\(56\)155, 2006JOC8842>](#). When the 6-position in uridine nucleosides is blocked, lithiation can occur at the 5-position. With LDA, lithiation in the



3-Unsubstituted quinazolinones can be lithiated in the benzene ring since ionization of the NH group prevents further reaction in the pyrimidine ring. Thus, 2-*tert*-butyl-4(3*H*)-quinazolinone **317** gave the 5-phenylthio derivative **318** after lithiation and quenching with phenyl disulfide, although quenching with the more hindered *tert*-butyl disulfide gave a mixture of 5- and 8-substituted products <2004T7983>.

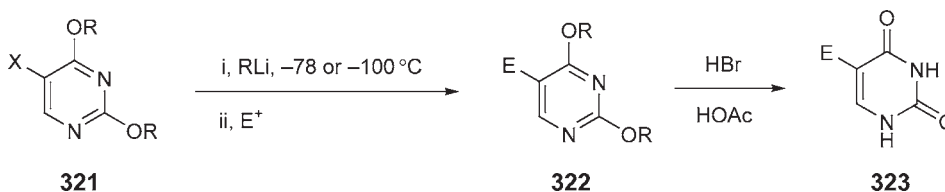


Clean lithiation at the 8-position has been achieved with 4-quinazolinones containing a directing group at the 7-position <1999T5389>, while reaction at the 7-position occurred when the 8-position was blocked by a lithiation directing *tert*-butylsulfinyl substituent <2005T8924>. Exocyclic lithiation has also been observed, and thus the 2-(2-quinolinyl) derivative **319** underwent derivatization in the quinoline ring <2004JOC4563>.



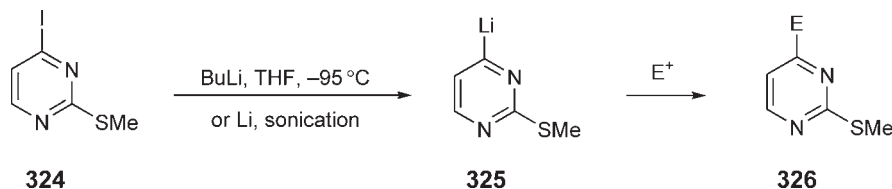
8.02.5.6.2 Lithiations by halogen substitution

Halogen–metal exchange reactions can be performed at temperatures as low as -100°C with reaction occurring specifically at the halogenated carbon, without the side reactions often seen in direct lithiation reactions at higher temperature. Several 5-lithiated pyrimidines have been synthesized via halogen–metal exchange reactions with the analogous bromides and although this type of transformation has also been used to give 4-lithio derivatives, attempts at extending this reaction to the 2-isomeric system have been generally unsuccessful <1993AHC(56)155>. The reaction is often used with 5-bromo- or 5-iodo-2,4-dialkoxy pyrimidines **321** which are subsequently converted to 5-substituted uracil derivatives **323**.

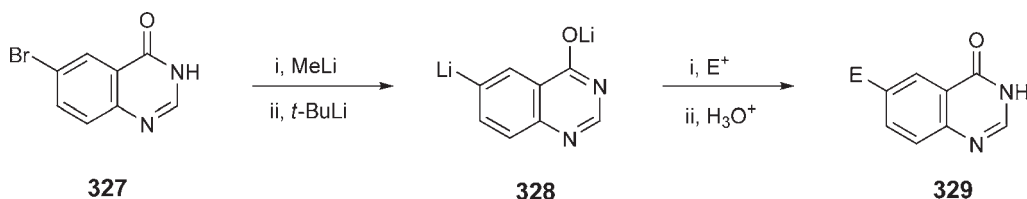


Examples of alkoxy groups that have been used in this transformation include methoxy <2003OL4277, 2005JOC1963, 2006T5201>, ethoxy <2006JOC8842>, isopropyl <2006JOC8842>, *tert*-butyl <2003TL8321, 2006JOC8842>, benzyl <2006JOC8842>, and *p*-methoxybenzyl (PMB) <2003OBC3160>. 6-Substituted uracil derivatives have also been prepared from 4-chloro-2,6-dimethoxypyrimidine in combination with naphthalene-catalyzed lithiation <2000T4043>.

An example of a 4-lithio species that has been prepared is the 2-methylthio derivative **325** that has been prepared from the iodo compound **324** by both conventional halogen–metal exchange reaction with butyllithium <2001TL311, 2001TL8697, 2005JOC6204> and under Barbier conditions with sonication <2000T3709>.

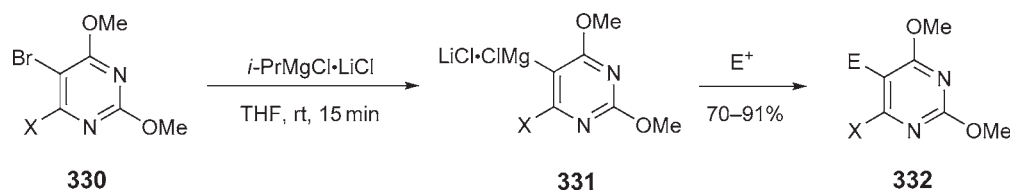


Halogen–lithium exchange has also successfully been performed with 6-bromo-4(3*H*)-quinazolinone **327**, by first using methyl lithium to deprotonate the NH group, and then *tert*-butyllithium to give the dilithio species **328** <2004M323>.

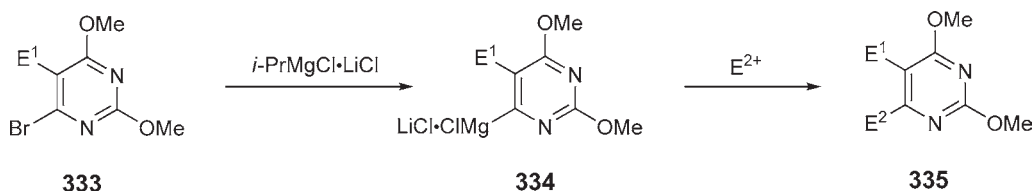


8.02.5.6.3 Magnesiations by halogen substitution

Pyrimidinyl Grignard reagents are much more stable than the analogous lithium compounds <1956JA2136>, although they are difficult to prepare from the corresponding halides and magnesium metal due to competing addition reactions. However halogen–magnesium exchange reactions can successfully be achieved at lower temperatures, with *i*-PrMgCl or *i*-PrMgBr usually being the preferred reagent <2003AGE4302>, although EtMgCl, EtMgBr, and BuMgBr have also been used <1998JOC7207, 1999J(P1)1193, 1999S495>. Lithium tributylmagnesi-ate (Bu₃MgLi) has also been investigated in one case <2006SL1586>. The addition of 1 equiv of LiCl considerably accelerates bromine–magnesium exchange reactions <2004AGE3333>, and *i*-PrMgCl·LiCl is able to produce pyrimidinyl magnesium species within 15 min at room temperature <2006OL3737>. Good selectivity can be achieved using this reagent combination, with both 5,6-dibromo-2,4-dimethoxypyrimidine **330** (X = Br) and 5-bromo-4-chloro-2,6-dimethoxypyrimidine **330** (X = Cl) giving exclusively the 5-magnesium derivative **331**, as evidenced by the isolation of 5-substituted derivatives **332** after reaction with a range of electrophiles <2006OL3737>.

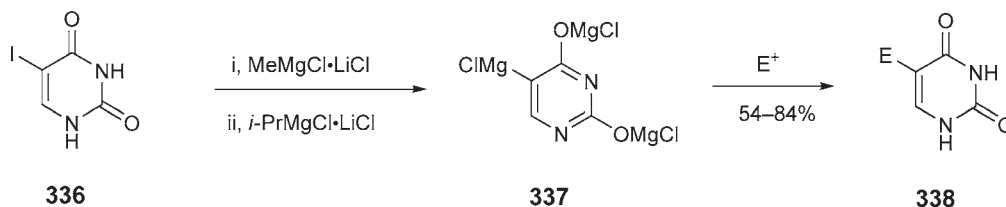


In those cases where the initially added electrophile is chemically nonreactive toward the magnesium reagent, further reaction can be achieved to give a 6-magnesium species **334**, and this can be performed either separately, or in a one-pot procedure <2006OL3737>.

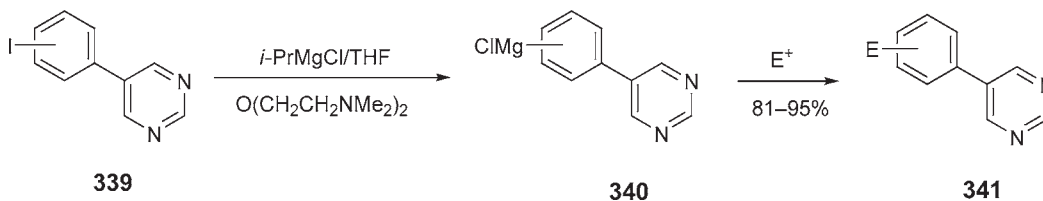


Further examples of halogen–magnesium exchange reactions being used to prepare pyrimidine Grignard reagents include reactions with 5-bromo-2,4-di(*tert*-butoxy)pyrimidine [<1998JOC7207, 1999S495>](#), 5-bromo-2,4-dimethoxy-pyrimidine [<1999J\(P1\)1193>](#), 2-iodo-4-methoxypyrimidine [<2000T265>](#), 4-iodo-2-(methylthio)pyrimidine [<2000T265, 2006SL1586>](#), and 5-bromopyrimidine [<2003SC795>](#). Selective reaction at the 2-position of 2-iodo-5-bromopyrimidine [<2000JOC4618>](#), and at the 5-position of 4,5-dibromo-6-(trifluoromethyl)pyrimidine and 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine has also been achieved [<2006EJO1593>](#). The method has also been extended to 1,3-disubstituted-5-iodouracil derivatives [<1999SL1577, 2000JOC4618>](#).

With unsubstituted 5-iodouracil **336**, a trimagnesiated species **337** can be formed by sequential treatment with methylmagnesium chloride and isopropylmagnesium chloride, and reaction with various electrophiles then selectively gives 5-functionalized uracil derivatives **338** [<2007OL1639>](#). The same procedure was also successfully applied to the functionalization of 6-iodouracils, including the synthesis of Emivirine and 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) precursors [<2007OL1639>](#).



The successful formation of aryl Grignard derivatives from 5-(iodoaryl)pyrimidines **339** was achieved with $i\text{-PrMgCl}$ when bis[2-(*N,N*-dimethylamino)ethyl]ether was present [<2006OL3141>](#). The presence of the complexing ligand prevented both reduction of the pyrimidine ring and addition of $i\text{-PrMgCl}$. Reaction with a variety of electrophiles then gave the products **341** in 81–95% yield [<2006OL3141>](#).

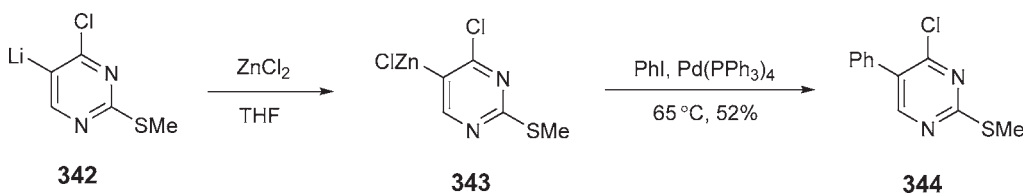


8.02.5.6.4 Stannylation by transmetallation and halogen–metal exchange reactions

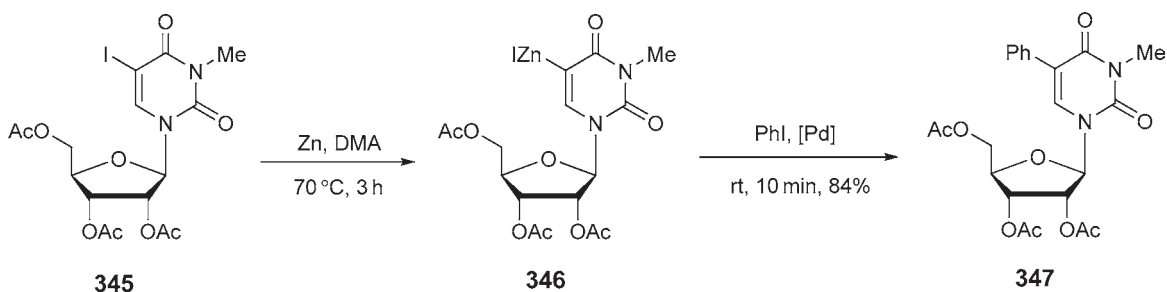
Stannylpyrimidines are stable compounds that are normally prepared by reaction between an organostannyl chloride and lithiated pyrimidines [<1995AHC\(62\)305, B-2000MI375, B-2002MI409>](#), although they can also be formed by addition of a stannyl anion to a halopyrimidine [<1994T275, 2005JA10456, 2005T2897>](#), or by palladium-catalyzed coupling of a halopyrimidine with hexamethyldistannane [<1998HCA1909, 2003TL6191, 2003JOC10020, 2004JME2453>](#). A number of stannylpyrimidine derivatives are now commercially available including the 2-(tributylstannyl), 4-methoxy-6-(tributylstannyl), 2-(methylthio)-4-(tributylstannyl), and 2-chloro-5-(tributylstannyl) derivatives. 4-Stannylquinazolines have also been prepared [<2005T2897>](#).

8.02.5.6.5 Zincation by transmetallation and halogen–metal exchange reactions

Normally zinc reagents are prepared by a transmetallation reaction between aryllithium or arylmagnesium halides and zinc halides at low temperature (-78°C), and are then used *in situ* in cross-coupling reactions [<1985JOC2456, 1995AHC\(62\)305, 1998H\(49\)205, B-2000MI375, 2002JME3235, B-2002MI409>](#). For example, the one-pot, three-step lithiation, transmetallation, and cross-coupling of 4-chloro-2-methylthiopyrimidine **342** with iodobenzene proceeded in 52% overall yield [<1998H\(49\)205>](#).

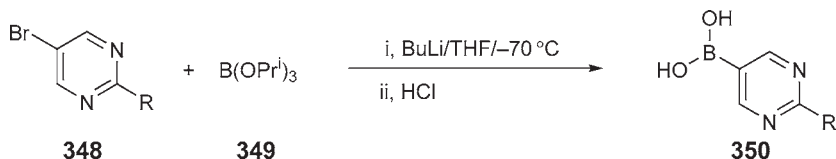


Zincated uracil derivatives form readily with activated zinc dust [<1996TL8375, 1997T7237, 1997T16711>](#), and then also readily undergo palladium-catalyzed cross-coupling reactions as demonstrated by the protected 5-iodo nucleoside **345** which gave the 5-phenyl derivative **347** in 84% yield with bis(dibenzylideneacetone) palladium(0) [Pd(DBA)₂] and tri(2-furyl)phosphine [<1996TL8375, 1997T7237>](#). Similar results were seen with 6-iodo uracil derivatives [<1997T16711>](#).



8.02.5.6.6 Boronation by transmetalation

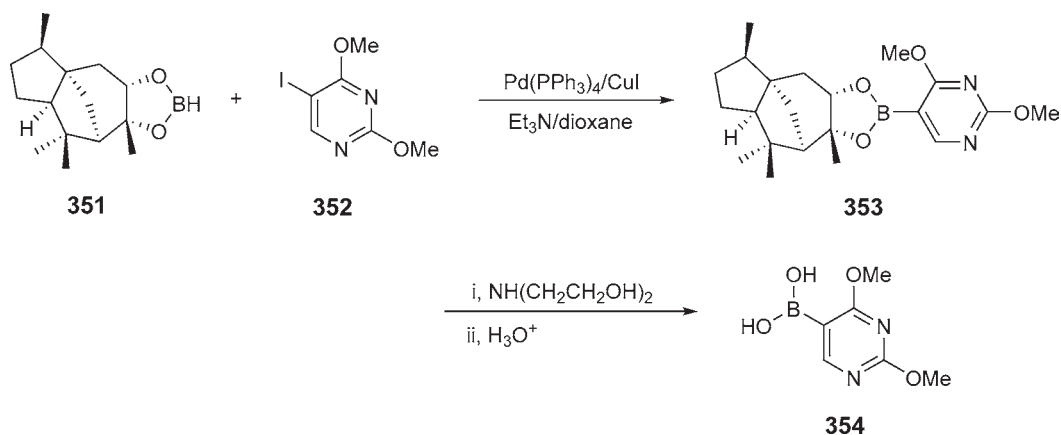
Pyrimidines lithiated in the 5-position can be boronated, although initially the halogen–metal exchange between halopyrimidines and butyllithium had to be carried out at very low temperatures (−100 °C) to avoid 1:1-adduct formation with the lithiated species [<1986CS305>](#). However, an improved procedure has now been developed which allows for the *in situ* synthesis of pyrimidine-5-boronic acids at −70 °C [<2002JOC5394; 2004OBC852>](#). Addition of butyllithium to a mixture of 5-bromopyrimidine **348** (R = H) and triisopropyl borate **349** at −70 °C, followed by acid quench, gave pyrimidine-5-boronic acid **350** (R = H) in 76% yield [<2002JOC5394>](#). The same method has also been used to prepare 2-methoxypyrimidine-5-boronic acid **350** (R = OMe) in 61% yield [<2004OBC852>](#), 2-chloropyrimidine-5-boronic acid **350** (R = Cl) in 72% yield [<2007OPD237>](#), and 2,4-dibenzyloxypyrimidine-5-boronic acid in 95% yield [<2005JOC1612>](#).



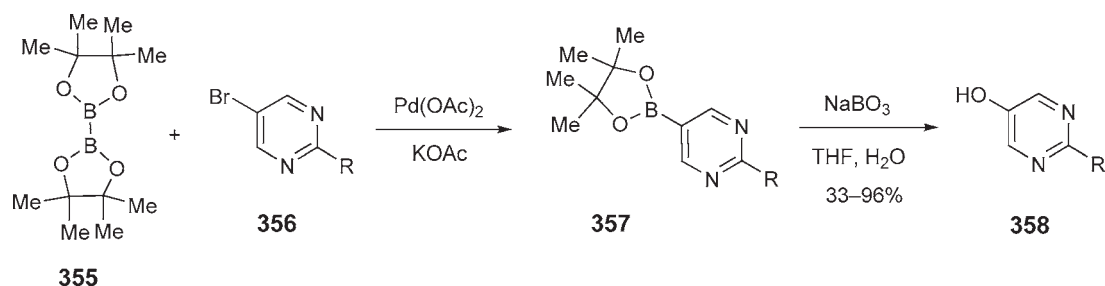
An alternative procedure using *i*-Pr₂MgCl and *tris*-trimethylsilyborate was able to be performed at 0 °C, and gave pyrimidine-5-boronic acid in 72% yield [<2003SC795>](#).

An alternative synthesis of pyrimidine boronic acids, which avoids lithiation chemistry altogether, has been developed [<2001SL266>](#). Thus, reaction of 2,4-dimethoxy-5-iodopyrimidine **352** with cedrane-8,9-diolborane **351** using catalytic amounts of Pd(PPh₃)₄ and CuI gave the intermediate boronate **353** which could be converted to the free boronic acid **354** in 83% yield by transesterification with diethanolamine, followed by treatment with acid (**Scheme 3**) [<2001SL266>](#).

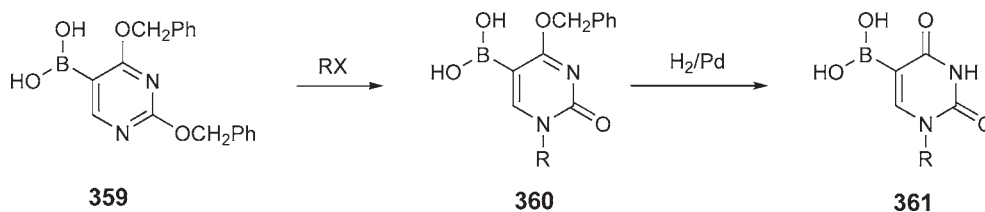
Bis(pinacolato)diboron **355** has also been used as a source of the analogous pyrimidine-5-boronate **357** with subsequent oxidation with sodium perborate giving 5-hydroxypyrimidines **358** in 33–96% overall yield [<2006TL7363>](#).



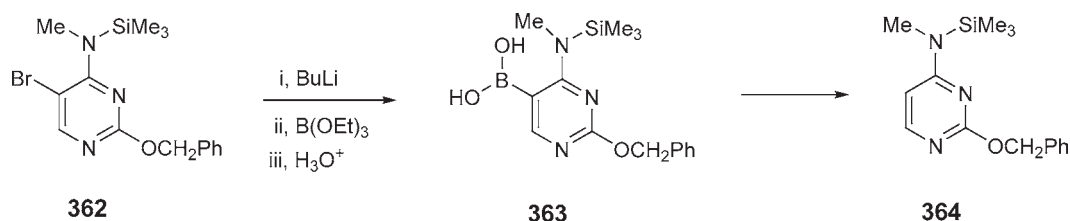
Scheme 3



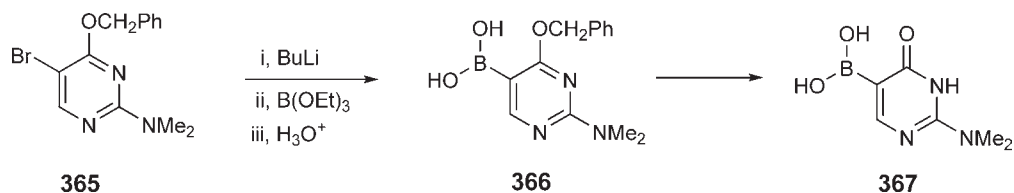
2,4-Dialkoxypyrimidine-5-boronic acids represent masked uracil derivatives and can either be used directly in Suzuki cross-coupling reactions [<1995JHC1159, 1996JHC409, 2005JOC1612>](#) and then hydrolyzed to the dione form, or be hydrolyzed directly to the analogous uracil boronic acids [<1998OPP433>](#). Alkylation of 2,4-dibenzyloxy-pyrimidine-5-boronic acid **359** at N-1 has also been achieved, to give 1-substituted uracil-5-boronic acids **361** via the 2-pyrimidinones **360** [<1998OPP433>](#).



Attempts at preparing substituted cytosine 5-boronic acid derivatives **363** were unsuccessful, as it was found that these compounds underwent a very fast deboronation to produce **364** [<1998J\(P2\)841>](#).



Similar problems were not observed with isocytosine derivatives **366**, and isocytosine 5-boronic acids **367** were successfully obtained [<1998J\(P2\)841>](#).

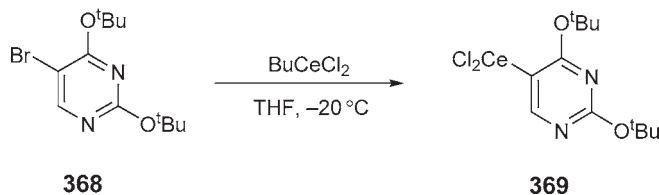


Although less common than the 5-isomers, pyrimidine-4-boronic acids have also been prepared and utilized [<1978TL4981, 1985JOC841, 2003JME5663, 2005JME6632, 2005JOC3741>](#), and there is one report in the patent literature of pyrimidine-2-boronic acid being used in the synthesis of potentiators of glutamate receptors [<2005WO040110>](#).

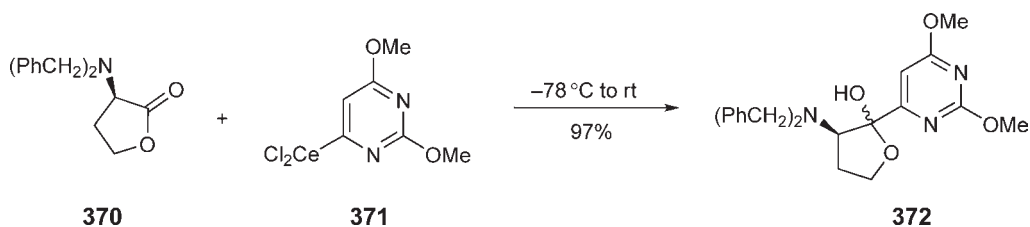
Several pyrimidine boronic acid derivatives are now commercially available, and numerous other examples can be found in the literature, as their use in Suzuki and related cross-coupling chemistry is now well established [<B-2000MI375, 2004S429, 2006AGE1282>](#).

8.02.5.6.7 Cerium derivatives by transmetallation reactions

Organocerium derivatives possess low basicity, and are normally available by low-temperature metal–metal exchange using cerium trichloride and lithiated pyrimidines. They are superior to the lithio analogs in reactions with aldehydes and ketones, especially in reactions with enolizable aldehydes and ketones, and in the 1,2-addition to α,β -unsaturated carbonyl derivatives [<1989ACS816; 1996CHEC-II\(6\)93>](#). Reaction with cerium trichloride could not be achieved in the case of the sterically hindered 2,4-di(*tert*-butoxy) 5-lithiopyrimidine, although the desired cerium reagent **369** could be obtained by direct reaction of the bromide **368** with butylcerium chloride [<1999S495>](#).



Addition of 2,6-dimethoxy-4-cerium chloride **371** to the chiral lactone **370** occurred without racemization of the chiral center, and the product **372** was subsequently used in a successful total synthesis of (–)-7-epicyclindrospermopsin [<2002JA4950, 2005JOC1963>](#). The cerium reagent was prepared *in situ* from 4-bromo-2,6-dimethoxy-5-lithiopyrimidine by sequential addition of butyllithium and cerium trichloride. Addition of the same dimethoxy-4-cerium derivative to a chiral lactam has also been reported [<1999J\(P1\)1193>](#).

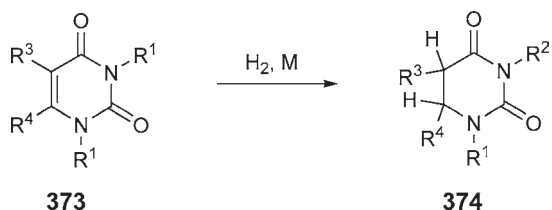


8.02.5.7 Reduced Pyrimidines

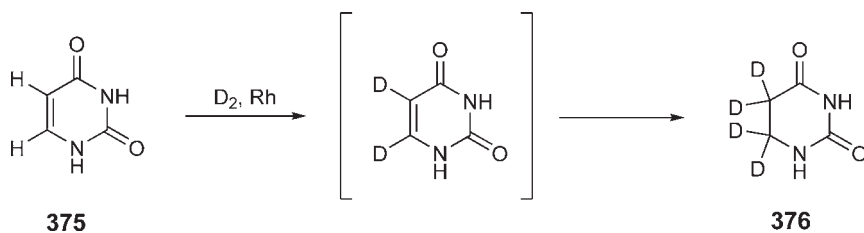
Besides ring cyclization reactions, reductive methods can also provide access to reduced forms of pyrimidines, quinoxalines, and perimidines. Both hydrogenation and metal hydride addition can be used [<1994HC\(52\)1, 1996HC\(55\)1>](#).

8.02.5.7.1 Dihydropyrimidines

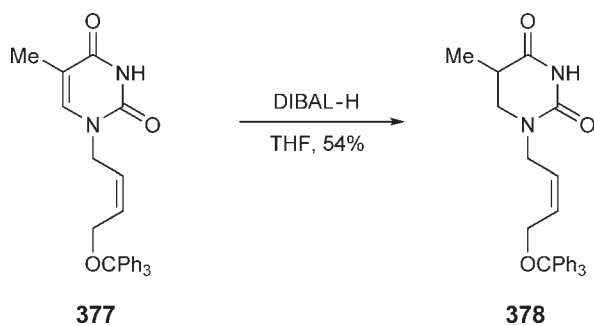
Many examples of dihydropyrimidine synthesis involve the catalytic hydrogenation of the 5,6-bond of uracil derivatives **373**, with both palladium on carbon [<2001BML529, 2004OL4643>](#) and rhodium on alumina [<1997JA1828, 2005OBC1685, 2006CC445>](#) being among the commonly used metal catalysts.



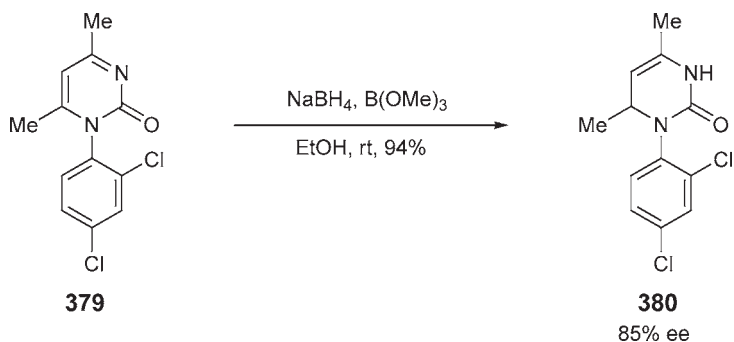
Exchange of the existing 5- and 6-protons is faster than the reduction step, so the deuteration of uracil actually produces the tetradeutero derivative **376** <2001JLR7>. Thymine behaves similarly, producing a trideutero derivative <2001JLR7>. Analogous results were seen with the tritiation of uracil, where the tetratritio derivative was obtained <2002MI295>.



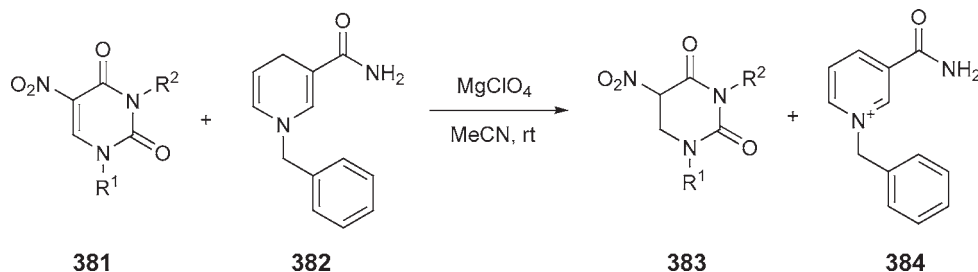
Diisobutylaluminium hydride (DIBAL-H) can also be used to reduce uracil derivatives, as demonstrated by the reduction of the uracil **377** where hydrogenation could not be used due to the presence of a double bond in the N¹ substituent <2002JME4254>.



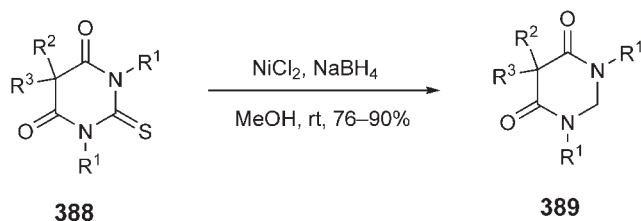
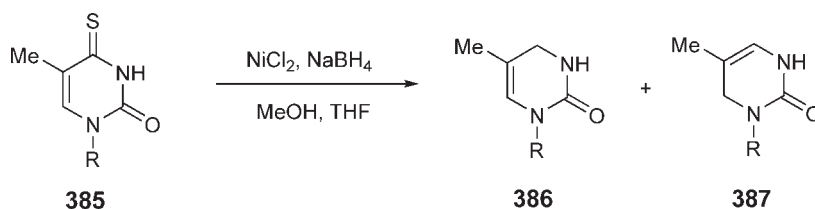
Sodium borohydride can be used to reduce pyrimidinones to their dihydro derivatives, and the reduction of the axially chiral pyrimidinone **379** occurred stereoselectively to give the dihydropyrimidinone **380** in 94% yield and 85% enantiomeric excess <2003AGE4360>.



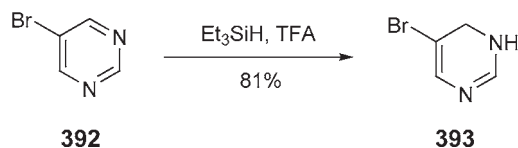
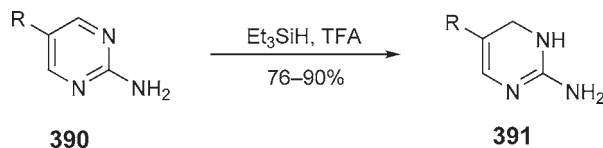
The reduction of 5-nitouracil derivatives **381** has been performed using 1-benzyl-1,4-dihydronicotinamide **382** as a reduced nicotinamide adenine dinucleotide (NADH) model <1998H(49)475>, although the same products can also be obtained with sodium borohydride <1976JME1072>.



Nickel boride, formed *in situ* from sodium borohydride and nickel chloride, has been used to prepare dihydro derivatives from thiothymine **385** <2001JME1853> and thiobarbituric acid derivatives **388** <2002J(P1)2520>. With 4-thiothymine derivatives, an isomeric mixture of 3,4- and 3,6-dihydro derivatives **386** and **387** was obtained <2001JME1853>, but with 2-thiobarbiturates, clean reduction at the 2-position was able to be achieved <2002J(P1)2520>.

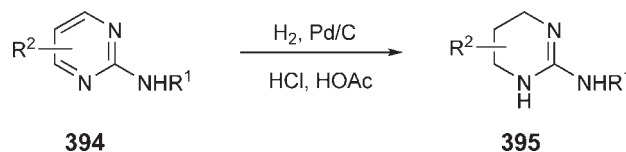


While all of the above examples have involved pyrimidinone derivatives, pyrimidines themselves can also be reduced to dihydro derivatives using triethylsilane and trifluoroacetic acid <2004TL2107>. Thus, a variety of 2-aminopyrimidines **390** were reduced to their 1,6-dihydro derivatives **391** in good yield by treatment with trifluoroacetic acid (TFA) and triethylsilane at room temperature, while 5-bromopyrimidine **392** similarly gave the dihydro derivative **393** in 81% yield under the same conditions <2004TL2107>.

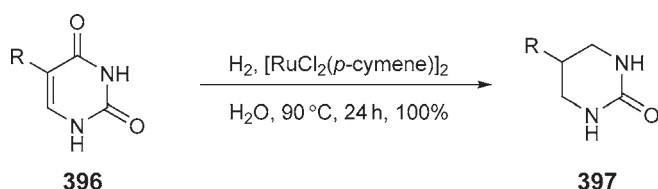


8.02.5.7.2 Tetrahydropyrimidines

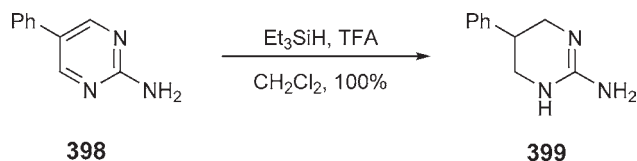
The hydrogenation of pyrimidines under acidic conditions stops at the 1,4,5,6-tetrahydro stage due to protonation of the amidine produced. 2-Aminopyrimidines **394** readily form guanidines **395** under the same conditions, and are therefore often used synthetically as a source of cyclic guanidines <2000BML1715, 2000JME3736, 2001JA4451, 2004SC795, 2006BMC4158>.



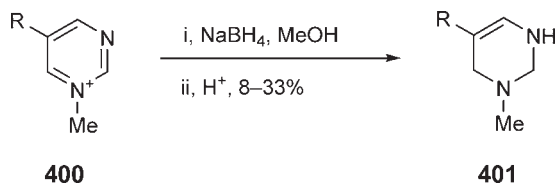
Uracil derivatives can also be reduced by hydrogenation, using the water-soluble ruthenium precatalyst $[\text{RuCl}_2(p\text{-cymene})]_2$, to give tetrahydro-2-pyrimidinones <2005AGE2021>. Thus, both uracil **396** ($\text{R} = \text{H}$) and 5-aminouracil **396** ($\text{R} = \text{NH}_2$) gave the analogous tetrahydro-2-pyrimidinones **397** in quantitative yield using these conditions <2005AGE2021>.



In addition to the dihydro compounds discussed above, the triethylsilane/trifluoroacetic acid reduction system can also be used to prepare tetrahydro pyrimidine derivatives, especially when dichloromethane is used as the solvent <2004TL2107>. Thus, treatment of 2-amino-5-phenylpyrimidine **398** with 2.5 equiv of triethylsilane and 5 equiv of TFA in dichloromethane at room temperature gave a quantitative yield of the tetrahydro derivative **399**, whereas only a dihydro derivative was obtained with 10 equiv of the silane in the absence of dichloromethane <2004TL2107>.

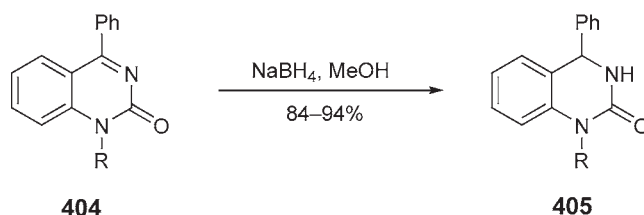
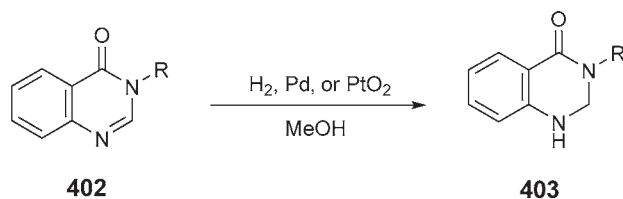


Although sodium borohydride is not a strong enough reducing agent to reduce unactivated pyrimidines, it has been used to reduce quaternized pyrimidines **400** to their 1,2,3,4-tetrahydro derivatives **401**, although only moderate product yields were achieved <2000JHC969, 2001AP79>.

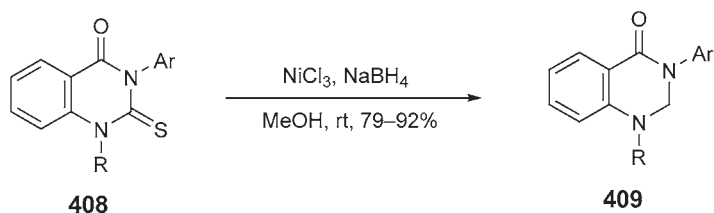
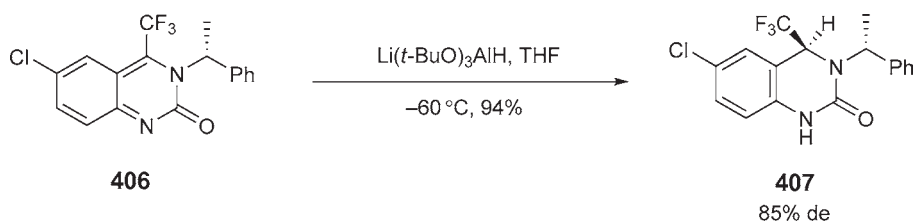


8.02.5.7.3 Reduced quinazolines

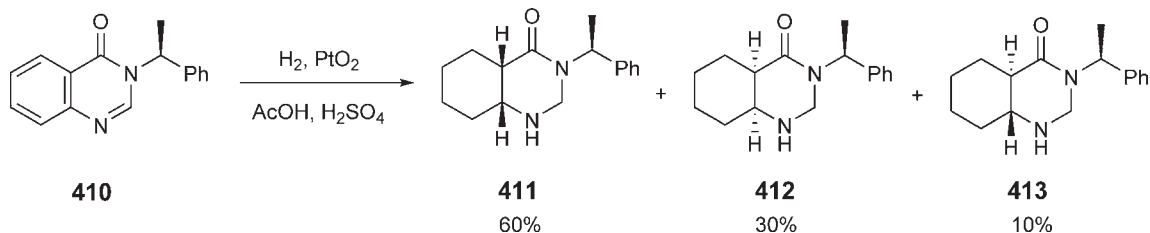
The hydrogenation of 3-substituted 4(3*H*)-quinazolinones **402** has been performed with both palladium and platinum oxide to give the 1,2-dihydro derivatives **403** <2001JME1971, 2004H(63)2019>, while the reduction of 2(1*H*)-quinazolinones **404** is readily performed with sodium borohydride in methanol <1990H(30)493>.



The chiral, reactive 2(3*H*)-quinazolinone **406** underwent diastereoselective reduction with lithium tri(*tert*-butoxy)-aluminium hydride at -60°C to generate the 1,4-dihydro derivative **407** <2003JOC754>, while nickel boride reduction of the 2-thioxoquinazoline **408** gave the 2,3-dihydro-4(1*H*)-quinazolinone **409** <2003JHC677>.

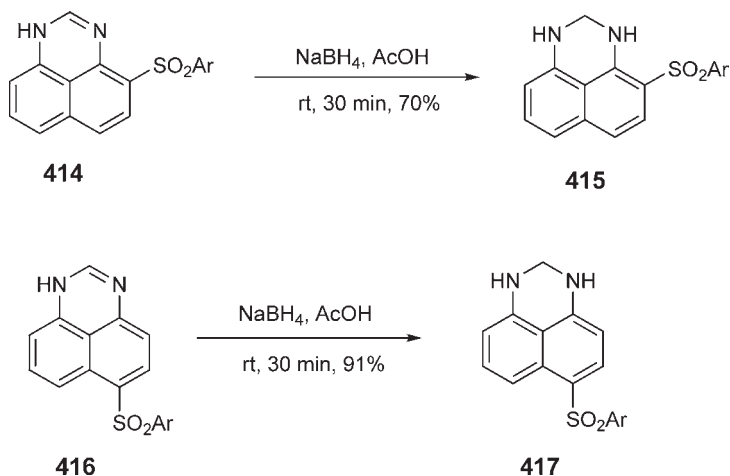


Reduction of the benzene ring of quinazolines can also occur, as demonstrated by the platinum oxide hydrogenation of the chiral 4(3*H*)-quinazolinone **410**, which gave a mixture of the three diastereomeric octahydro-4(1*H*)-quinazolinones **411–413** <2004TA3545>.



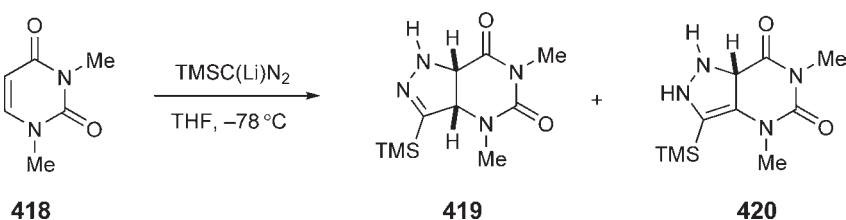
8.02.5.7.4 Dihydropyrimidines

The reduction of pyrimidines **414** and **415** containing electron-withdrawing sulfonyl substituents at the 4- or 6-positions gave the analogous 2,3-dihydropyrimidines **415** and **416** with sodium borohydride and acetic acid <2002CHE1084>.

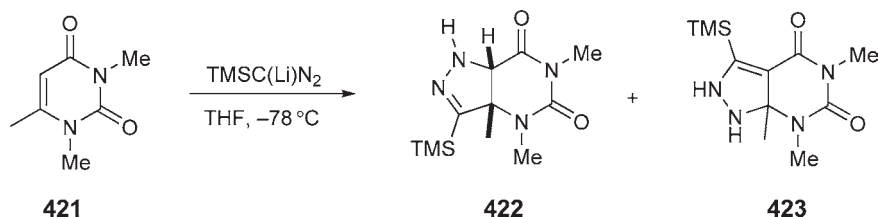


8.02.5.7.5 Reduced pyrimidines by adduct formation with organometallics

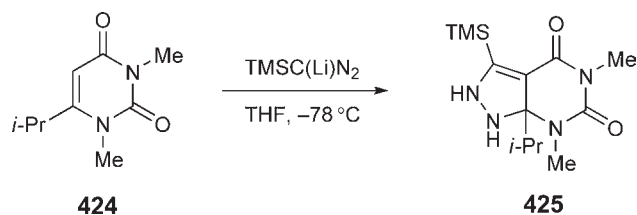
The addition of organometallics to unactivated pyrimidines normally produces unstable dihydro derivatives which readily oxidize back to the pyrimidine oxidation level, although successful conjugate addition to pyrimidinone derivatives can occur. Thus, the addition of lithium trimethylsilyldiazomethane $[\text{TMSC}(\text{Li})\text{N}_2]$ to 1,3-dimethyluracil **418** occurred at the 6-position to produce a mixture of the two pyrazolo[4,3-*d*]pyrimidine-5,7-diones **419** and **420**, where the initial addition had been accompanied by cyclization [<1997T7045>](#).



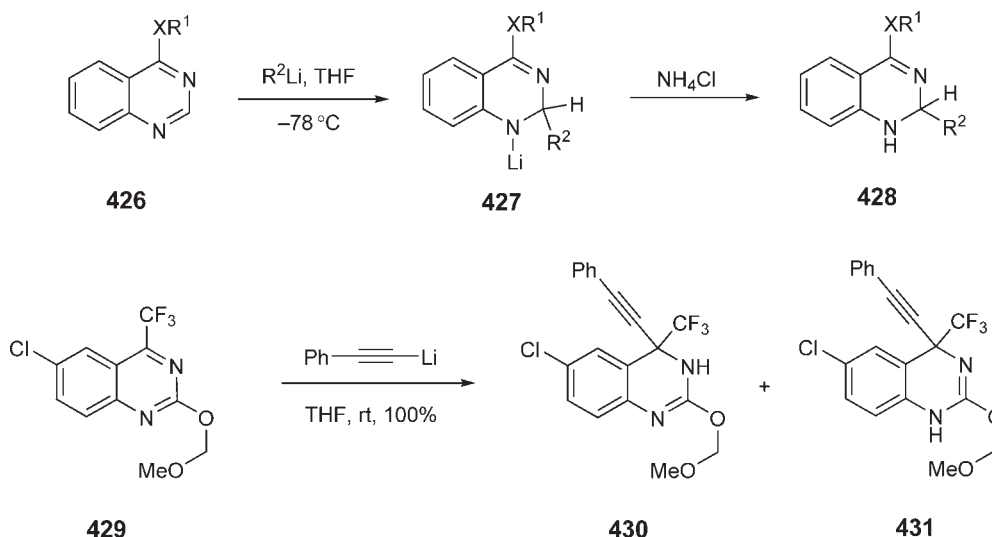
In the case of 1,3,6-trimethyluracil **421**, addition was also seen at the less hindered 5-position, giving rise to a mixture of products **422** and **423** arising from addition and cyclization at both the 5- and 6-positions [<1999EJO2751>](#).



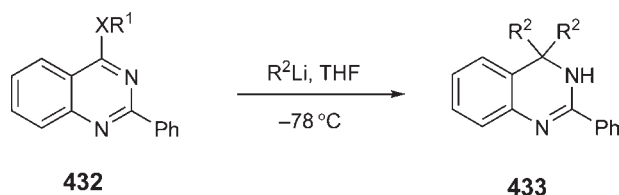
With the more hindered 1,3-dimethyl-6-isopropyluracil **424**, only addition at the 5-position was seen. [<1999EJO2751>](#).



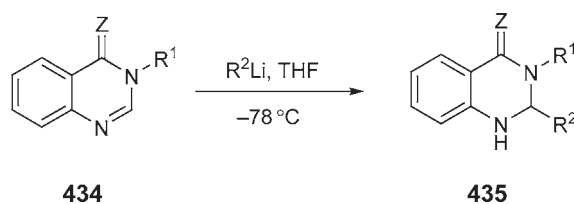
With 2-unsubstituted quinazolines **426** ($X=O$ or S), organometallic addition occurs at the 2-position to give 2-alkyl-1,2-dihydroquinazolines **428** <2005JSF121, 2005S2951>, while with 2-alkoxyquinazolines addition of organometallics occurs at the 4-position, as demonstrated by the addition of lithium phenylacetylide to the 2-methoxy-methyl quinazolinone **429** which gave a quantitative yield of a tautomeric mixture of the 3,4- and 1,4-dihydro derivatives **430** and **431** <2004JA5427>.



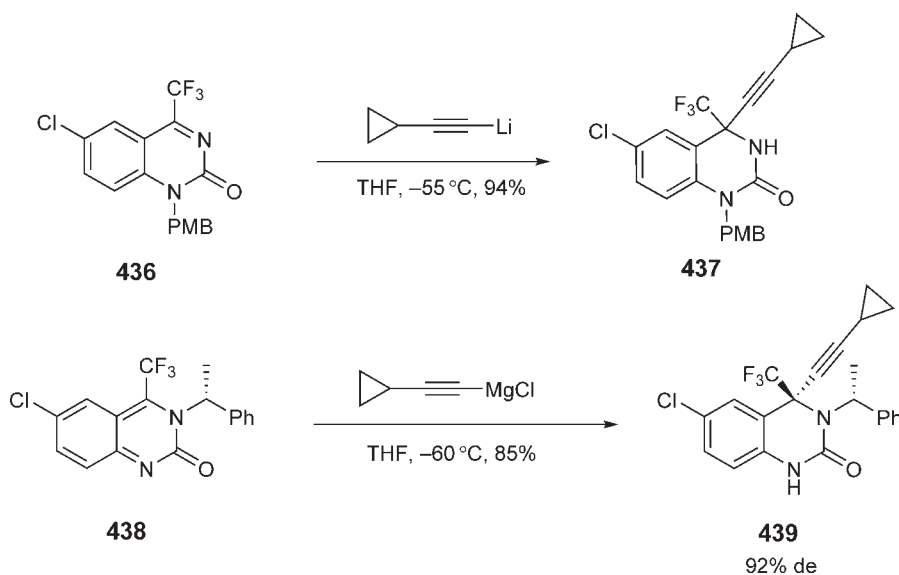
With 4-alkoxy- or 4-thioalkoxy 2-phenylquinazolines **432** ($X=O$ or S), alkyllithium addition at the 4-position is accompanied by loss of the 4-substituent, which enables a second addition step to occur <1997T2871, 2005JSF121>. Good yields of 4,4-dialkyl-2-phenylquinazolines **433** are normally obtained, with the exception being with the bulky *tert*-butyllithium which only gave a 49% product yield <2005JSF121>.



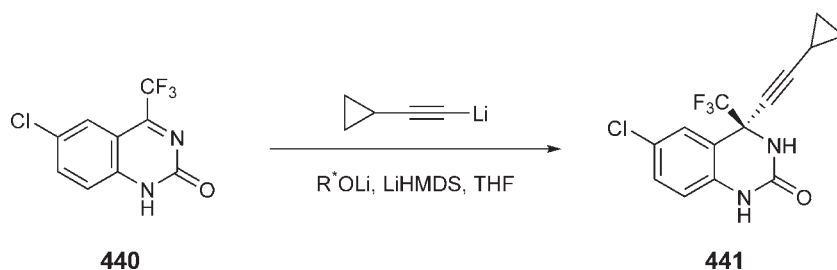
The pattern of organometallic addition to quinazolinones follows that for the quinazolines, with both 4(3*H*)-quinazolinones **434** ($X=O$) and 4(3*H*)-quinazolinethiones **434** ($X=S$) undergoing addition at the 2-position. Both 3-unsubstituted ($R^1=H$) and 3-acylamino ($R^1=MeCONH$ or $t-BuCONH$) derivatives **435** have been prepared <1996JOC656, 2004M323, 2005JSF121>.



The PMB-substituted 2(1*H*)-quinazolinone **436** underwent addition at the 4-position with lithium cyclopropylacetylide <2003JOC754>, while the more reactive 3-substituted 2(3*H*)-quinazolinone **438** underwent a diastereoselective addition with cyclopropylacetylenemagnesium chloride to give the 1,4-addition product **439** <2000TL3015, 2003JOC754>.

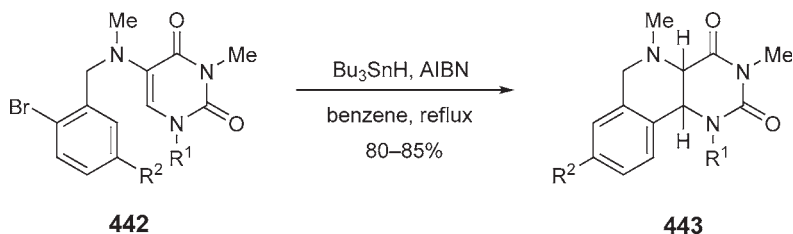


The above two quinazolinones were prepared as intermediates in the synthesis of the chiral nonnucleoside reverse transcriptase inhibitor DPC 961 **441**, although compounds of this type can also be formed directly by the addition of lithium cyclopropylacetylide to the N-unsubstituted 2(*1H*)-quinazolinone **440**, in the presence of a chiral alkoxide moderator <2000OL3119, 2004JA5427>.

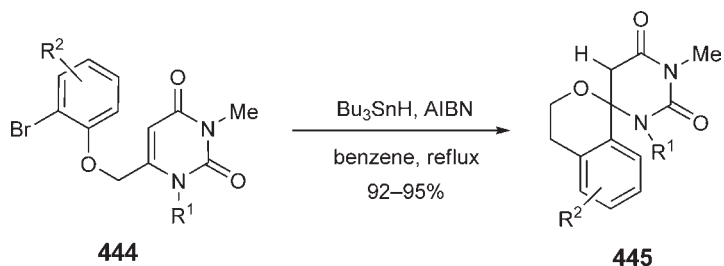


8.02.5.7.6 Reduced pyrimidines by radical ring-closure reactions

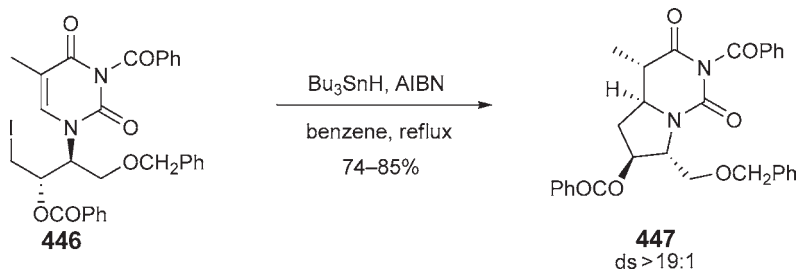
The formation of bicyclic dihydropyrimidine derivatives by radical ring-closure reactions is a well-established route with N¹-substituted uracil and thymine derivatives <1999TL7591, 2001TL6637, 2003S920, 2003T3009, 2004S1864, 2006CC844>. For example, reaction of bromobenzylamino uracil **442** with tributyltin hydride generated a radical at the brominated position, which then underwent ring closure at the uracil 6-position to give pyrimidino[3,2-*c*]tetrahydroisoquinolin-2,4-dione derivatives **443** <2003S920>.



Ring closure at the uracil 6-position also occurred with brominated aromatic derivatives **444** linked to the 6-position, to give benzopyrano[4,3-*d*]pyrimidine-2,4-dione spiro derivatives **445** <2004S1864>.



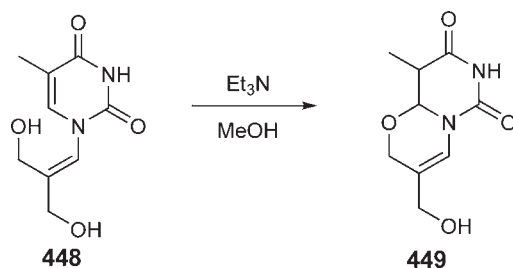
Alkyl halides can also be used to generate the radical center, and N¹-substituted uracil and thymine derivatives have been used to prepare octahydropyrrolo[1,2-*c*]pyrimidinedione derivatives [<2001TL6637, 2006CC844>](#) as demonstrated by diastereoselective synthesis of the azabicycle **447** [<2006CC844>](#).



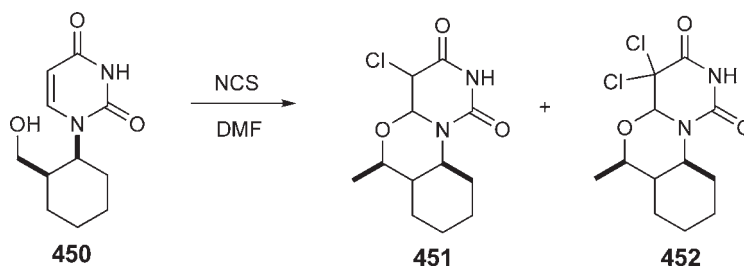
Several examples of the synthesis of cyclonucleoside derivatives by radical ring-closure reactions are also available [<1996T9496, 1999J\(P1\)1257, 2000T8689, 2002CBC534, 2005EJO4640>](#).

8.02.5.7.7 Reduced pyrimidines by adduct formation with O-nucleophiles

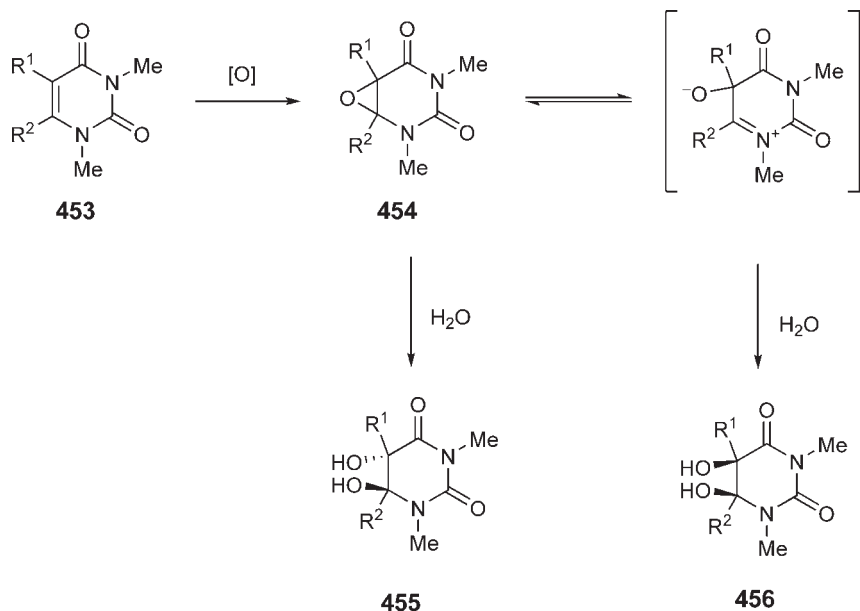
Adduct formation with oxygen nucleophiles is reversible, and the products can normally be isolated only if there is a strongly electron-withdrawing substituent such as a pyrimidinone carbonyl group in the ring. Cyclic derivatives also appear to be more stable [<2000T9885>](#), as demonstrated by the thymine alcohol **448** which underwent ring closure to the bicyclic derivative **449** on treatment with triethylamine at room temperature in methanol [<2004OBC1245, 2005OBC1964>](#).



When the N¹-2-(hydroxymethyl)cyclohexyluracil **450** was treated with *N*-chlorosuccinimide in DMF at room temperature, ring closure again occurred to give a mixture of monochloro- (5%) and dichloro- (92%) hexahydropyrrolo[1,6-*a*][3,1]benzoxazin-1,3-diones **451** and **452** [<2006T9949>](#).



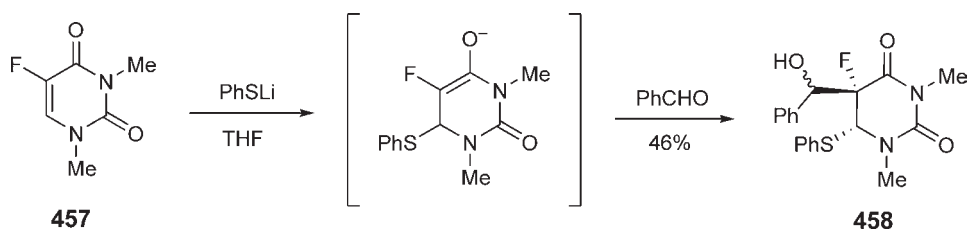
Several acyclic examples of alcohol or water addition accompanying halogenation are also known <1996SC3583, 1998J(P1)3145, 1998NN1125, 2000IC117, 2001BMC2341, 2006JA13287>, although these products are generally not as stable as the cyclic example shown above. 5,6-Dihydro-5,6-dihydroxyuracil derivatives **455** and **456** are also known, being formed by the addition of water to epoxide intermediates **454** <1996TL2647, 2000T10031> (Scheme 4).



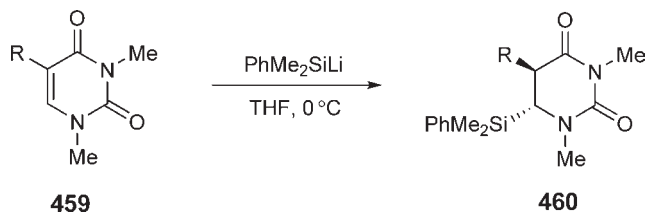
Scheme 4

8.02.5.7.8 Reduced pyrimidines by adduct formation with other nucleophiles

Thiol anions normally add reversibly to uracil derivatives <1991T4361>, although stable adducts can be isolated when the intermediate enolate is trapped with an added electrophile <2006JHC1095>. Thus, the addition of lithium phenylthiolate to 5-fluoro-1,3-dimethyluracil **457** in the presence of benzaldehyde gave a 46% yield of the adduct **458** as a mixture of only two diastereomers <2006JHC1095>.



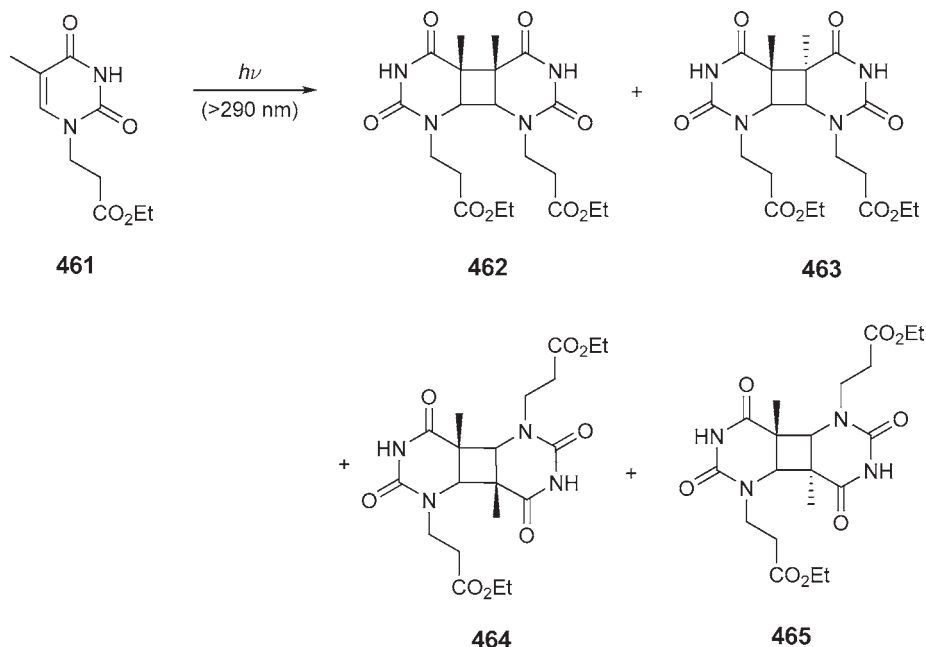
Silicon nucleophiles have also been investigated with uracil derivatives, and thus the addition of dimethylphenylsilyllithium to 5-substituted 1,3-dimethyluracils **459** was found to give stable products of addition at the 6-position **460**, although products arising from addition at the 5-position were also observed with some 6-substituted derivatives <1998H(48)2601>.



8.02.5.8 Cycloaddition Reactions

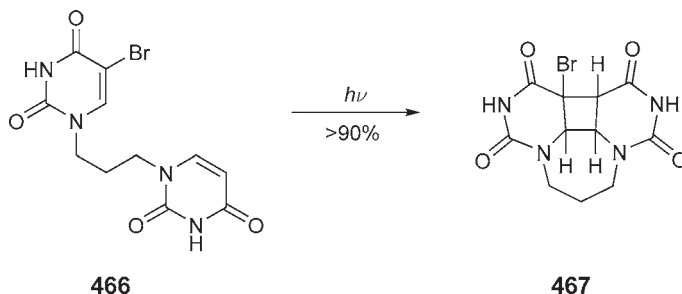
8.02.5.8.1 Photodimerization

Uracil and thymine, and many of their substituted derivatives, including nucleosides and nucleotides, are dimerized in solution when irradiated by UV in the range 200–300 nm to yield cyclobutane dimers <1994HC(52)1>. In the dimerization, two regioisomers are formed in which the pyrimidine rings can be regarded as parallel (*syn*) or antiparallel (*anti*), and 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. For example, the photolysis of the thymine derivative **461** gave a mixture of all four possible isomers from which the *cis-syn* dimer **462** was able to be isolated in 36% yield <2005EJO1097> (Scheme 5).



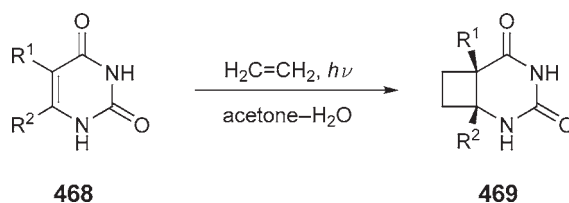
Scheme 5

When the two uracil units are joined by a short N¹-linker group, *anti*-addition is prevented, and thus the 5-bromouracil derivative **466** gave the *cis-syn* cyclobutane photoadduct **467** as the major product in greater than 90% yield <2002TL5127>.

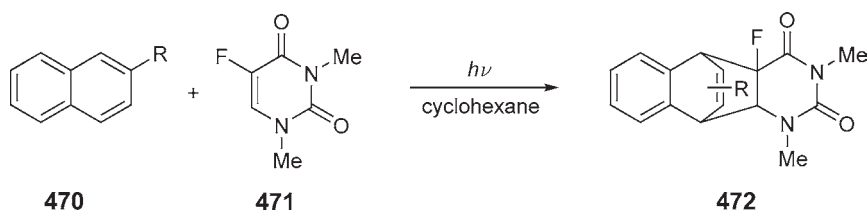


8.02.5.8.2 Photocycloadditions across the 5,6-positions

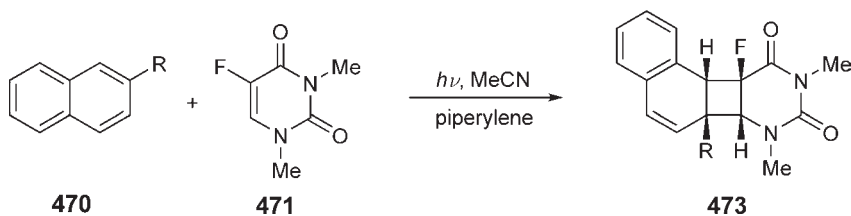
The 5,6-double bond in uracil derivatives can also participate in [2+2] photocycloaddition reactions other than dimerization discussed above. For example, reaction with ethylene gives *cis*-cyclobutane adducts **469** <2002TL6177, 2004TL7095, 2006SL1394>. Similar photocycloaddition reactions have been performed with both electron-donating and electron-withdrawing alkenes <2002H(57)665, 2004TA283>, and intramolecular reactions have also been performed <2004TL5767>.



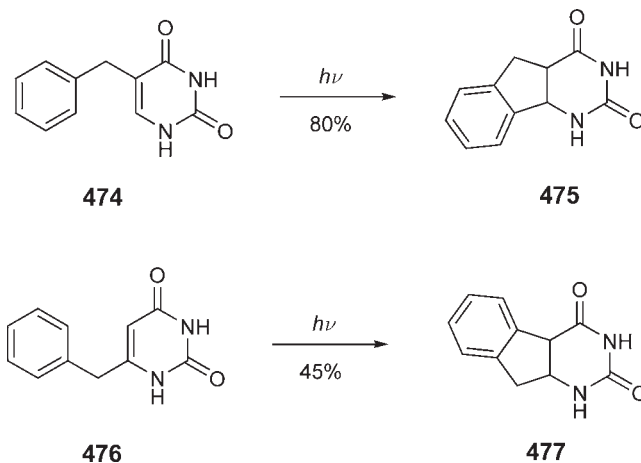
Aromatic compounds can participate in both [2+2] and [4+2] photocycloaddition reactions with uracil derivatives to give either benzocyclobutane or ethenoquinazoline (barrelene) derivatives, which can then undergo a number of subsequent photochemical reactions. The products obtained are dependent upon the reaction conditions, and thus the photocycloaddition reaction between naphthalenes **470** and 1,3-dimethyl-5-fluorouracil **471** in cyclohexane gave 4a-fluoro-5,10-ethenobenzo[*f*]quinazolines **472** as products as a result of a [4+2] photocycloaddition (photo-Diels–Alder) reaction <2002TL3113, 2003H(61)377>.



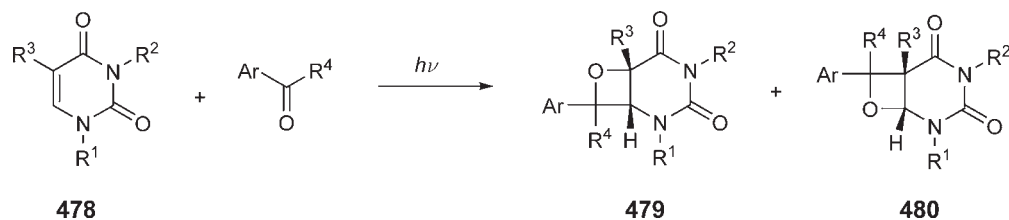
However, when the same reaction was performed in the presence of piperylene, 1,2-cycloaddition was observed to give naphthalene ring fused cyclobutapyrimidines **473** with high regio- and stereoselectivity <2005CPB258>.



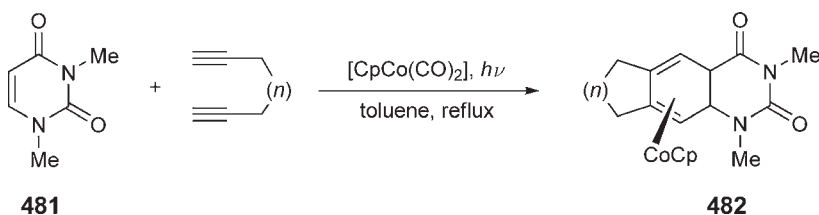
Several other examples of photocycloaddition reactions involving aromatic substrates are available <1997H(46)141, 2000H(53)1247, 2001CPB384, 2005CPB258, 2005H(65)2583, 2005H(66)143>, including intramolecular examples <1997CC817, 2006OL681>. For example, irradiation of 5-benzyluracil **474** at 254 nm gave the 1*H*-indenopyrimidinones **475** by a proposed radical mechanism <2006OL681>. 6-Benzyluracil **476** behaved similarly to give **477** <2006OL681>.



The photochemical [2+2] cycloaddition of carbonyl compounds with alkenes (Paterno–Büchi reaction) can also be applied to uracils, to give two series of regioisomeric oxetanes, the head-to-head (hh) oxetanes **479** and the head-to-tail (ht) oxetanes **480**, with the hh isomer normally predominating. Several successful examples of this reaction are available <2002AGE767, 2003BOC357, 2005JOC2522, 2006CEJ553, 2006EJO1790, 2006OBC291, 2006OBC3652>, although it is less successful with thiobenzophenone, where low thietane yields were obtained <2005OBC1937>.

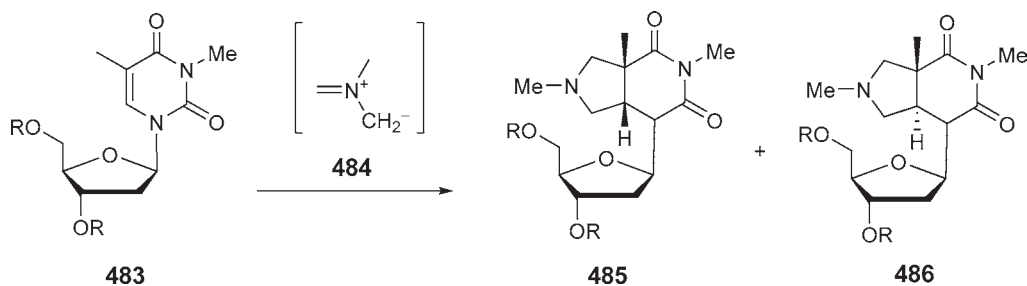


Uracil derivatives can also participate in cobalt-mediated [2+2+2] cycloaddition reactions with dialkynes under photochemical conditions, to give cobalt complexed dihydrobenzo[*g*]quinazoline derivatives **482** <1999CEJ3549>.

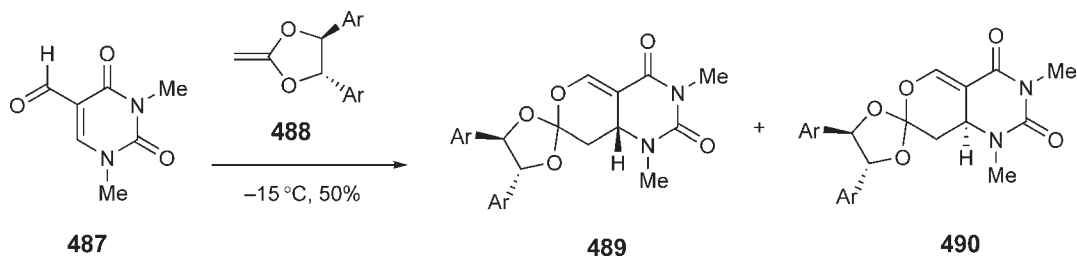


8.02.5.8.3 Thermal cyclizations

The 5,6-double bond in activated pyrimidines can participate in thermal [4+2] cyclization reactions as demonstrated by the 1,3-dipolar cycloaddition reactions of O-protected thymidine derivatives **483** with the nonstabilized azomethine ylide **484**, which is generated from trimethylamine *N*-oxide by reaction with LDA <2002SC1977>.



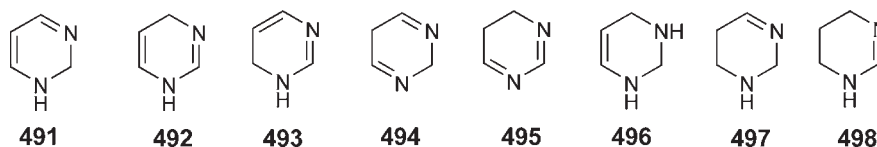
Substituent groups can also participate in cyclization reactions, as shown by the [4π+2π] cycloaddition between 1,3-dimethyluracil-5-carboxaldehyde **487** and the ketene acetal **488** (Ar = *p*-tolyl) <2003T341>.



8.02.6 Reactivity of Nonconjugated Rings

8.02.6.1 Dihydro-, Tetrahydro-, and Hexahydropyrimidines

There are five possible dihydropyrimidine forms, although most of the known dihydropyrimidines have either the 1,2- **491** or the tautomeric 1,4- **492** or 1,6-dihydro structures **493** <1986H(24)1433>. Of the three possible tetrahydropyrimidine forms, the most commonly found is the 1,4,5,6-tetrahydro- or cyclic amidine structure **498**.

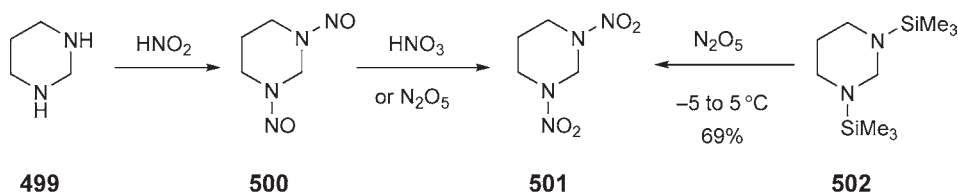


8.02.6.1.1 N-Alkylation and acylation

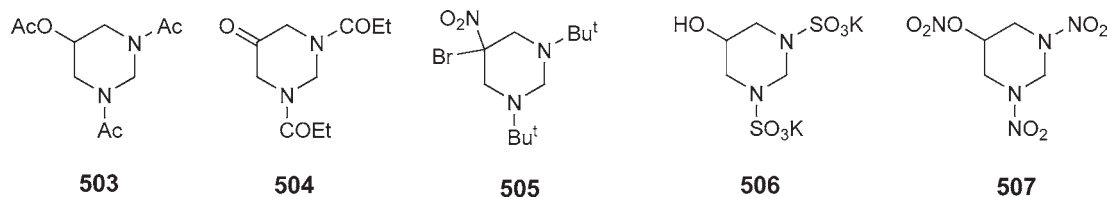
N-Alkylation and acylation reactions show the normal behavior for cyclic amines.

8.02.6.1.2 N-Nitrosation and nitration

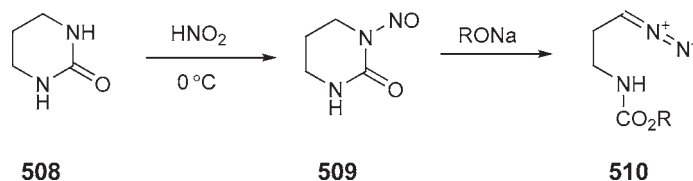
Direct nitrosation of hexahydropyrimidine **499** gives the 1,3-dinitroso compound **500** which can be converted to the dinitro compound **501** by treatment with nitric acid or solutions of N_2O_5 in nitric acid <1984JOC5147>, although better yields can now be achieved using nitrodesilylations of the bis(trimethylsilyl) derivative **502** with N_2O_5 <1997T4371>.



Other pyrimidine substrates to be converted to N^1 , N^3 -dinitro derivatives by loss of N-substituents include the diacyl compounds **503** and **504**, and the di-(*tert*-butyl) compound **505** <2000JOC1200>. In the case of the disulfamic acid derivative **506**, O-nitration also occurred, to give the trinitro derivative **507** <2000RCB1082>.



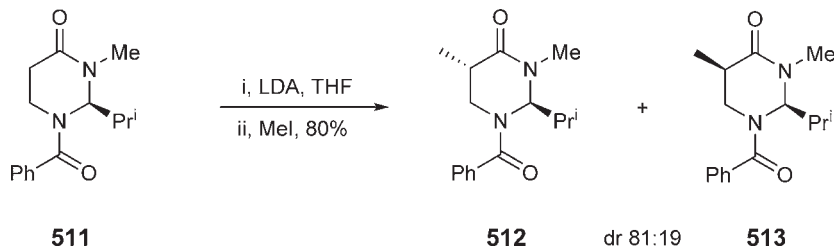
While all of the above reactions give rise to di- N -nitroso or nitro derivatives, mono reaction can be achieved with 2-pyrimidinones. Thus, treatment of tetrahydro-2(1*H*)-pyrimidinone **508** with nitrous acid at 0 °C gave the unstable N -nitroso derivative **509**, which was not isolated but converted to diazocarbamates **510** by treatment with alkoxides <1997SC1569, 2006BML427>.



8.02.6.1.3 C-Alkylation

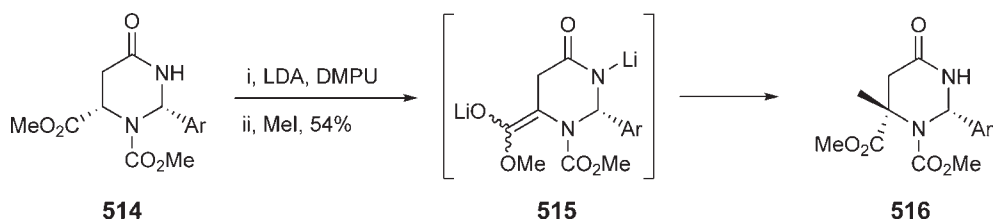
The C-5 protons in reduced 4-pyrimidinones are acidic and can be removed by strong bases. The resulting enolate can then be alkylated by a variety of different electrophiles. This alkylation can occur diastereoselectively

<1991JOC2553>, and in the case of chiral substrates high enantioselectivity is often observed <1996TA2233, 1998TA3881, 1999TA3493, 2003T4223, 2004HCA1016>. For example, in the alkylation of (*R*)-1-benzoyl-2-isopropyl-3-methyltetrahydropyrimidin-4(1*H*)-one **511** with LDA and methyl iodide, an 81:19 diastereoisomer ratio of the (2*R*,5*S*):(2*R*,5*R*) products **512** and **513** was obtained <2004HCA1016>.



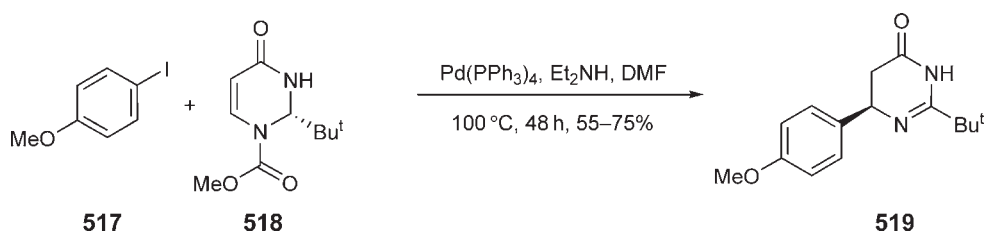
In addition to alkylation with alkyl halides, electrophilic amination has been achieved with di-(*tert*-butyl) azodicarboxylate <2004HCA1016>, and reactions with aldehydes have generated alcohol derivatives <1999JOC8668, 2003TL671>. Dialkylation at the 5-position has also been achieved <1998TA3881>.

Alkylation at the 6-position can also be achieved with N^3 -unsubstituted 4-pyrimidinones, via a dianion, when there is an electron-withdrawing group also present at the 6-position. Thus, alkylation of the chiral pyrimidinone **514** (Ar = *p*-chlorophenyl) gave a 54% yield of the enantiomerically pure methyl derivative **516** via the dianion **515** <1999JOC7885>.

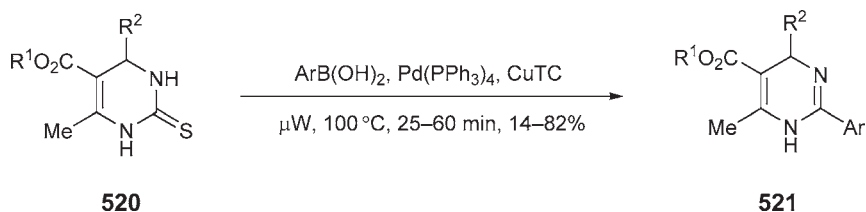


8.02.6.1.4 C-Arylation

Although much less common than with fully conjugated pyrimidines, cross-coupling reactions can still be performed with dihydropyrimidines, and thus the Heck reaction of the dihydropyrimidinone **518** with 4-iodoanisole **517** gave the product **519** where the double bond had migrated to the more stable 1,2-position <1996OS201>.

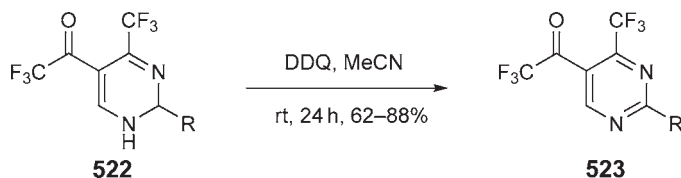


A Pd(0)-catalyzed/Cu(I)-mediated carbon–carbon cross-coupling of 3,4-dihydropyrimidine-2-thiones **520** and boronic acids occurs under microwave-assisted conditions to give 2-aryl-1,4-dihydropyrimidines **521** in moderate to high yield <2004OL771>. In contrast, Cu(II)-mediated reaction of the same substrates leads to carbon–sulfur cross-coupling.

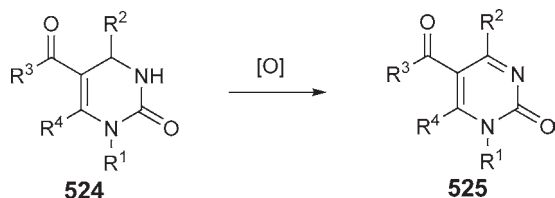


8.02.6.1.5 Oxidations (dehalogenation)

Dihydropyrimidines are normally readily oxidized to the corresponding pyrimidines by dehydrogenation, hydrogen transfer, or disproportionation reactions <1994HC(52)1, 1996CHEC-II(6)93>. For example, the oxidation of a series of trifluoromethyl ketones **522** with DDQ occurred readily at room temperature <1997H(44)349>. Facile room temperature oxidation with ceric ammonium nitrate (CAN) has also been achieved <2003ARK(xv)22>.

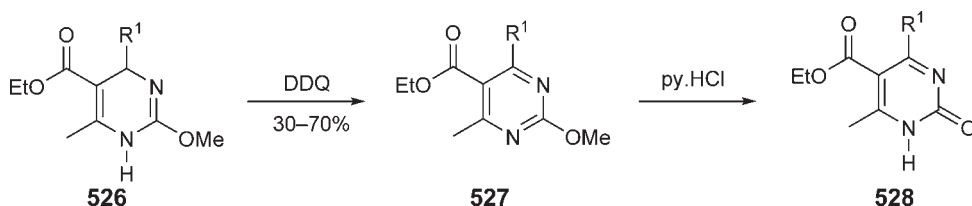


However, dihydropyrimidinones **524** derived from the Biginelli reaction are less readily oxidized <1997H(45)1967>, and there have been several investigations of oxidation systems that can convert compounds of this class to the fully conjugated pyrimidine derivatives **525**.

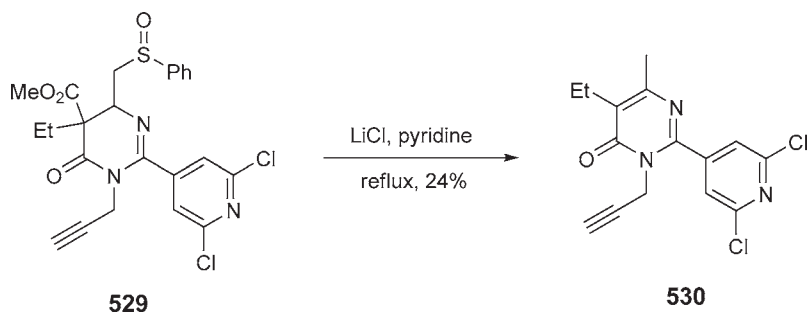


Oxidants that have been identified as being capable of performing this transformation include nitric acid at low temperatures <2001JHC1345, 2005JOC1957>, *tert*-butyl hydroperoxide in combination with a copper salt <2005OL4673>, and CAN in the presence of NaHCO₃ <2006T9726>. Aromatization was accompanied by dealkylation with Jones reagent <2003JOC6172>, while with CAN in acetic acid, both dealkylation and oxidation to a 2,4-pyrimidinedione were observed <2006T9726>.

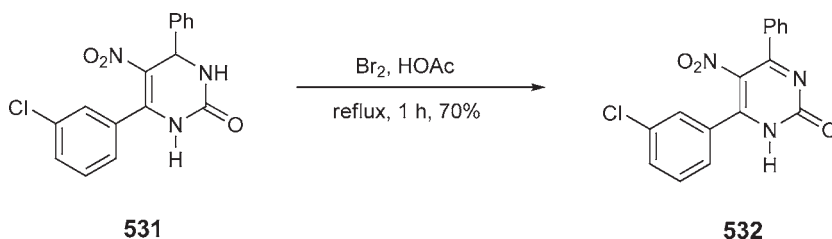
As an alternative procedure, 2-methoxy-1,4-dihydropyrimidines **526**, derived from the 'Hideg-modification' of the Biginelli reaction can be readily oxidized to the fully conjugated 2-methoxypyrimidines **527**, and these can then be hydrolyzed to the pyrimidinone form **528** with pyridine hydrochloride <1997H(45)1967>. Several different oxidants can be used, although dealkylation was observed in some cases with MnO₂, KMnO₄, or CAN. No dealkylation was seen with chloranil or DDQ <1997H(45)1967>.



An alternative approach was used in the synthesis of the herbicide **530**, where the sulfoxide **529** was converted to **530** in a single step by heating with lithium chloride in refluxing pyridine <1997TL4339>. The one-pot transformation involves sigmatropic sulfoxide elimination, lithium chloride-induced demethylation of the carbomethoxy group, decarboxylation, and a final isomerization/aromatization step <1997TL4339>.

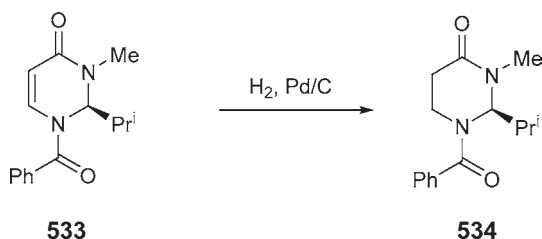


The oxidation of dihydropyrimidinones to pyrimidinones can also be achieved via a bromination, dehydrobromination sequence [<2000CPB1504, 2005RJO417, 2005TL8749>](#), often in one-pot, as demonstrated by the conversion of the 5-nitro-dihydropyrimidinone **531** to the pyrimidinone **532** with bromine in refluxing acetic acid [<2005RJO417>](#). *N*-Bromosuccinimide has also been used to oxidize hexahydropyrimidines to amidine salts [<2000H\(53\)2437, 2004H\(63\)2557>](#).

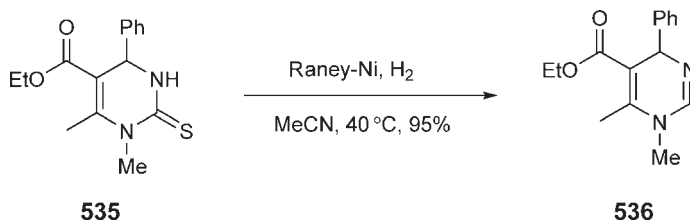


8.02.6.1.6 Reductions

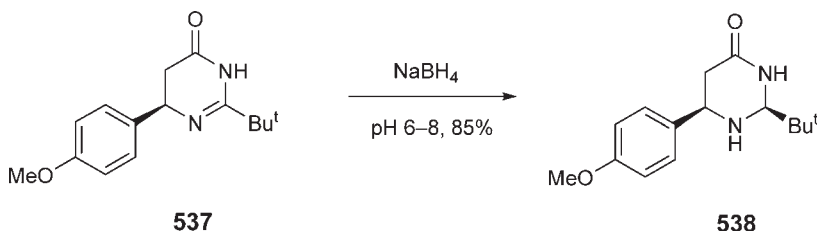
Dihydropyrimidinones can be reduced by hydrogenation over palladium on charcoal, as demonstrated by the synthesis of the tetrahydropyrimidinone **534** from the chiral precursor **533** [<1996TA2233, 1999JOC8668, 2004HCA1016>](#).



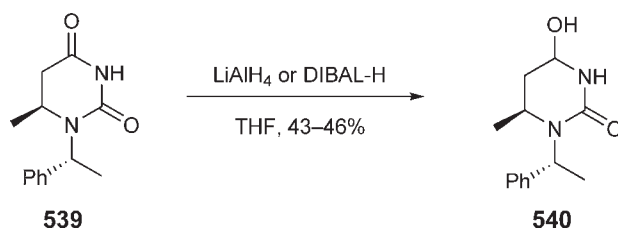
Hydrogenation over Raney nickel can be used to reduce dihydropyrimidinethiones to dihydropyrimidines and thus the thione **535** was converted to the dihydropyrimidine **536** in 95% yield using a continuous flow hydrogenation method [<2005JCO641>](#).



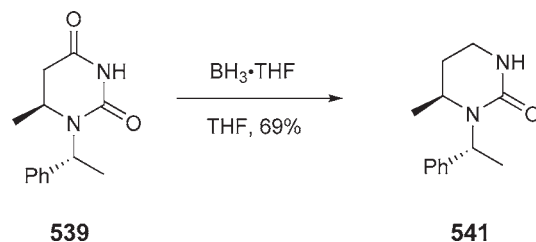
Although sodium borohydride cannot reduce unactivated pyrimidines, it can reduce the polarized C=N bonds in dihydropyrimidines to their tetrahydro derivatives. For example, the reduction of the dihydropyrimidinone **537** can be performed enantioselectively with sodium borohydride to give the tetrahydropyrimidinone **538** in 85% yield [<1996OS201>](#).



Stronger hydrides can reduce carbonyl groups of dihydropyrimidinediones, and thus both LiAlH_4 and diisobutylaluminium hydride regioselectively gave the 4-hydroxy derivative **540** on reduction of the 5,6-dihydro-2,4-pyrimidinedione **539** [<2001TL8629>](#).

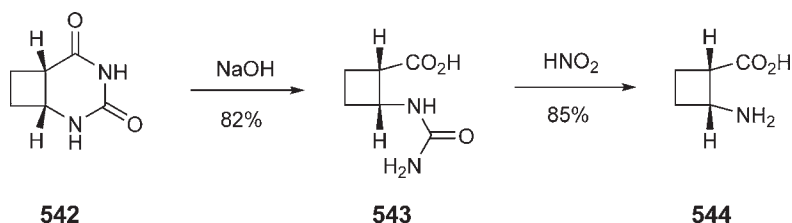


Reduction of the same substrate with $\text{BH}_3 \cdot \text{THF}$ also took place regioselectively, this time giving the tetrahydropyrimidinone **541** <2001TL8629>. $\text{BH}_3 \cdot \text{THF}$ has also been used to reduce tetrahydropyrimidines to hexahydropyrimidines, but the products were not isolated, being hydrolyzed without isolation <1999JHC105>.

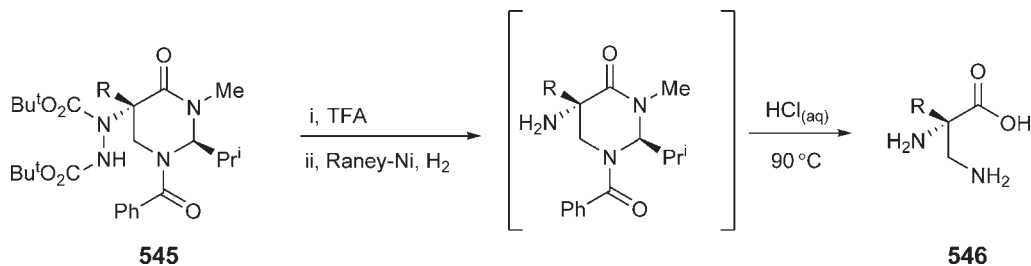


8.02.6.1.7 Hydrolysis

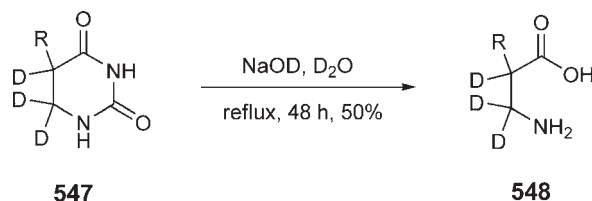
Reduced pyrimidines are much less stable toward hydrolysis than the fully conjugated analogs, and this is often used synthetically to produce amino acids and diamines. The BH_3 reduction of cyclic amidines (1,4,5,6-tetrahydropyrimidines) to hexahydropyrimidines, and their subsequent hydrolysis was mentioned above <1999JHC105>, but there are many more examples. For instance, *cis*-cyclobutane β -amino acids **544** can be prepared from the cyclobutane derivatives **542** formed by the [2+2] photocycloaddition reaction between uracil and ethylene <2002TL6177, 2004TL7095, 2006SL1394>.



Many examples involve the hydrolysis of chiral substrates <1996JA8727, 1996OS201, 1996TA2233, 1998TA3881, 1999JOC7885, 1999SL727, 1999TA3493, 2001T195, 2003T4223, 2004HCA1016, 2004TL7095>, as demonstrated by the synthesis of α -substituted α,β -diaminopropanoic acids **546** <2004HCA1016>.

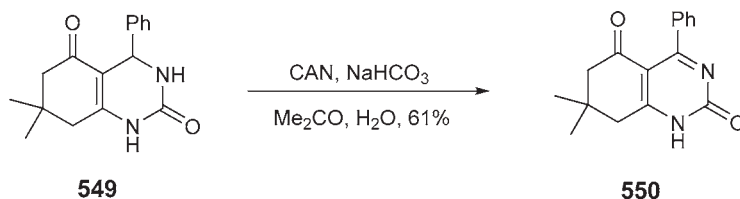


Labeled compounds have also been produced by the hydrolysis of reduced pyrimidine derivatives, and thus the basic hydrolysis of 5,5,6,6-tetradeuterouracil **547** ($\text{R} = \text{D}$) gave 2,2,3,3-tetradeutero- β -alanine **548** ($\text{R} = \text{D}$) in 50% yield <2001JLR7>. 5,6,6-Trideuterothymine **547** ($\text{R} = \text{Me}$) behaved similarly to give 2,3,3-trideutero-3-amino-2-methylpropanoic acid **548** ($\text{R} = \text{Me}$), also in 50% yield <2001JLR7>. Similar procedures have been performed with tritiated uracil derivatives <2002MI295>.

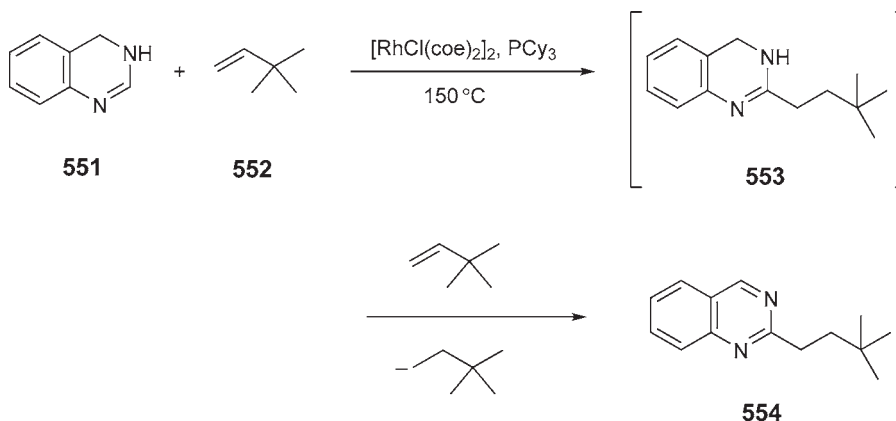


8.02.6.2 Dihydro- and Other Reduced Quinazolines

Dihydroquinazolines can be aromatized by the same procedures used for the dihydropyrimidines [<2000T9343, 2002JFC\(118\)73, 2006JOC1969, 2006T9726>](#), and thus the tetrahydroquinazolinone **549** gave the dihydro analogue **550** in 61% yield with CAN and NaHCO₃ [<2006T9726>](#).

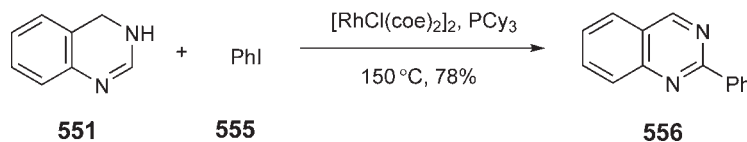


Aromatization was also observed during a coupling reaction between 3,4-dihydroquinazoline **551** and excess 3,3-dimethylbutene **552** which gave the 2-alkylquinazoline **554** in the presence of a Rh(I) catalyst derived from [RhCl(*cis*-cyclooctene)₂]₂ and tri(cyclohexyl)phosphine [<2006JOC1969>](#). Even though the same product could be obtained by reaction with quinazoline, it was shown unequivocally that the dehydrogenation step occurred on the intermediate 2-alkyl-3,4-dihydroquinazoline **553**, rather than on the starting material **551** [<2006JOC1969>](#) (Scheme 6).

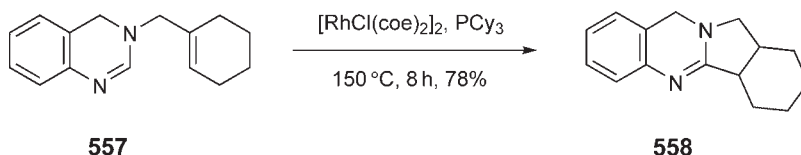


Scheme 6

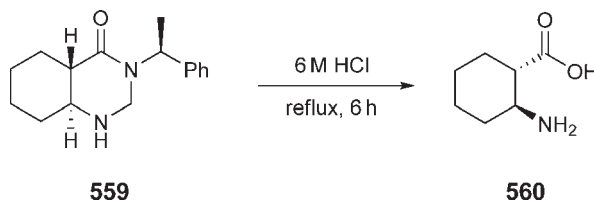
With careful control of the reaction conditions dihydroquinazoline products such as **553** could be isolated in good yield [<2006JOC1969>](#). Aromatization was also observed when arylation of dihydroquinazoline **551** was performed with iodobenzene **555** [<2004OL35>](#) and a similar result was reported with bromobenzene [<2006AGE1589>](#), although the product yield was lower (50% vs. 78%).



Intramolecular coupling reactions could also be performed, as demonstrated by the synthesis of the tetracyclic derivative **558** <2006JOC1969>.



Hydrolysis of reduced quinazoline derivatives has also been performed, as demonstrated by the synthesis of enantiopure 2-aminocyclohexanecarboxylic acid **560** from octahydroquinazoline **559** <2004TA3545>.

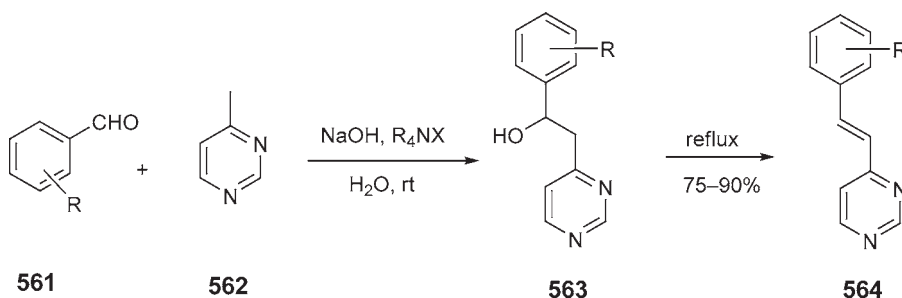


8.02.7 Reactivity of Substituents Attached to Ring Carbon Atoms

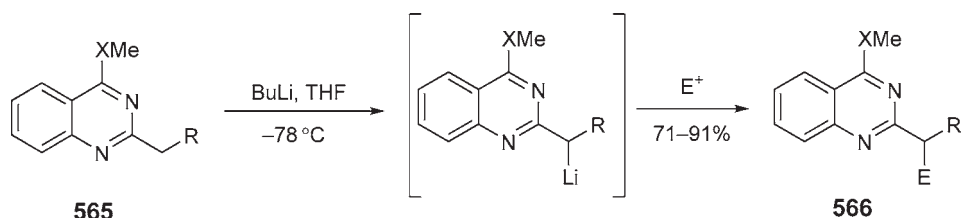
8.02.7.1 Reactivity of Alkyl Groups

8.02.7.1.1 Alkylation, elimination, addition, and condensation reactions

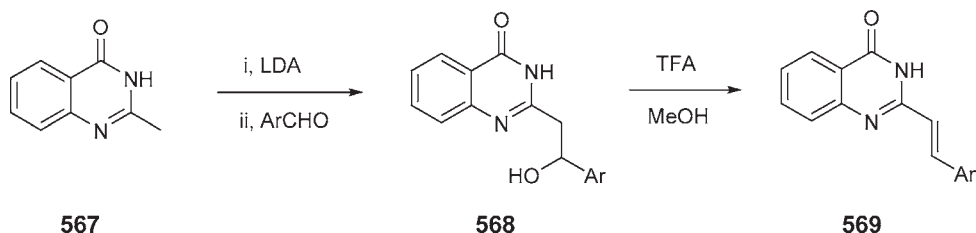
The α -carbon of an alkyl group in the electrophilic 2-, 4-, or 6-positions is activated toward deprotonation because the negative charge can be dissociated over the ring nitrogen atoms. An alkyl group in the benzenoid 5-position is less activated than in the other positions, but still more strongly than in an alkylbenzene. Earlier work focused on the use of strong bases to generate a carbanion which then reacted with an electrophilic carbon in an alkyl halide or sulfonate ester to elongate the side-chain alkyl group, or with a carbonyl carbon in an aldol or Claisen-type reaction <1994HC(52)1, 1996CHEC-II(6)93>. However, it has now been shown that successful reactions can be performed with sodium hydroxide in water, provided that a catalytic amount (10 mol%) of a quaternary ammonium salt such as methyltriocetylammmonium chloride (Aliquat 336) or tetrabutylammmonium hydrogen sulfate is also present <2001SC3167, 2002JCP6442, 2004LOCI112>. Thus, the reaction of 4-methylpyrimidine **562** with aromatic aldehydes **561** at room temperature gave alcohol adducts **563**, which readily lost water on heating to give the alkene products **564** <2001SC3167>.



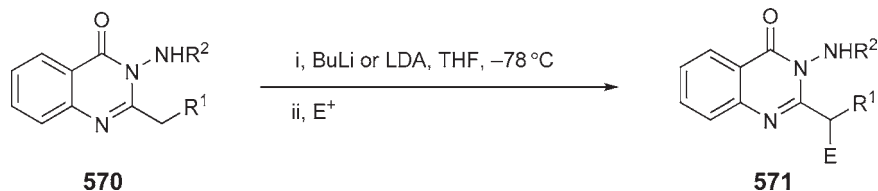
With 4-substituted 2-alkylquinazolines **565** (R = H, Me or Et; X = O or S), deprotonation of the 2-alkyl group can be performed with butyllithium at $-78\text{ }^{\circ}\text{C}$ <2005S2951>. Subsequent reaction with a variety of electrophiles occurred in good yield to give a range of alkyl-substituted derivatives **566** <2005S2951>.



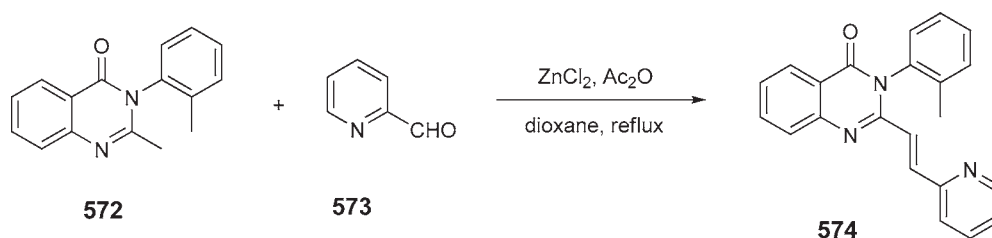
Functionalization of 3-aryl-2-methyl-4(3*H*)-quinazolinones has also been achieved using LDA as the base [\[1980JOC2169\]](#), although in the case of *N*-unsubstituted pyrimidinones and quinazolinones, deprotonation of the amide group occurs first, thereby deactivating the system. However with strong bases such as butyllithium, a second deprotonation can occur on an alkyl group adjacent to nitrogen [\[1974JOC595\]](#), and in the case of 2-methyl-4(3*H*)-quinazolinone **567** this double deprotonation can be performed using either butyllithium or LDA [\[1974JOC595, 1980JOC2169, 1999CCC515, 2000H\(53\)1839, 2006JHC1057\]](#). Condensation of the dianion with a range of electrophiles can be achieved, and in the case of aromatic aldehydes, the product alcohols **568** have been dehydrated to the alkenyl products **569** with either aqueous sulfuric acid [\[1974JOC595\]](#) or TFA in methanol at reflux [\[2006JHC1057\]](#).



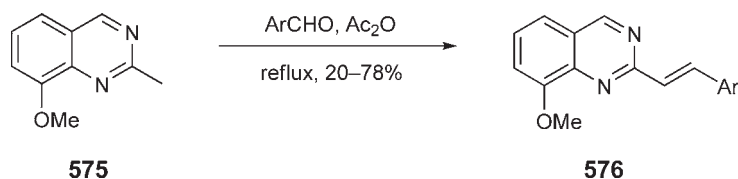
The double lithiation and subsequent substitution of 2-alkyl-4(3*H*)-quinazolinethiones has also been performed [\[2004S363\]](#), and a number of 3-amino- and 3-acylamino-2-alkyl-4(3*H*)-quinazolinones **570** have also been derivatized via their dianions [\[1995J\(P1\)1029, 1996JOC647, 1996JOC656, 2000H\(53\)1839, 2004S2121\]](#).



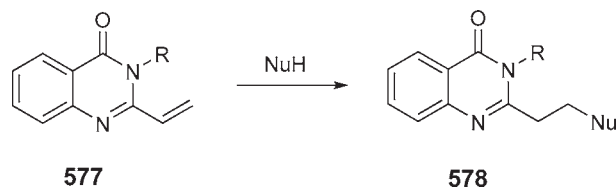
Alkenyl quinazolinone derivatives can also be prepared under Lewis acid conditions, as demonstrated by the synthesis of analogs of the anticonvulsant piriqualone **574**, where aldehyde condensation and elimination of water was conveniently effected with zinc chloride and acetic anhydride [\[2001BML177\]](#).



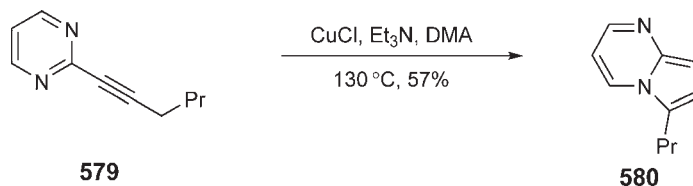
In the case of 8-methoxy-2-methylquinazoline **575**, alkenyl products **576** could be obtained merely by heating in acetic anhydride, although often yields were only moderate [\[2002AP277, 2004AP20\]](#).



Due to the electron-withdrawing nature of the pyrimidine ring, alkenylpyrimidines can undergo addition reactions at the β -carbon, and while this is a well-established route to substituted pyrimidine derivatives <1994HC(52)1, 1996CHEC-II(6)93>, it has also been used to prepare quinazolinone derivatives **578** from 2-alkenyl-4(3*H*)-quinazolinones **577** <2000T7245>.

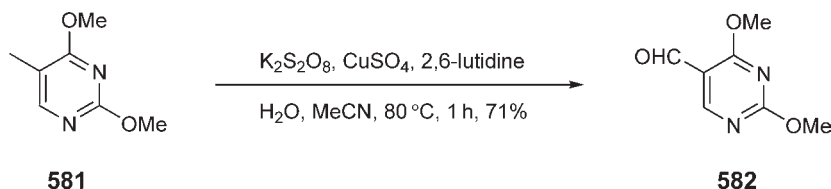


Alkenylpyrimidines can undergo a copper(I)-catalyzed isomerization and cyclization on to an adjacent ring nitrogen as demonstrated by the synthesis of 6-propylpyrrolo[1,2-*a*]pyrimidine **580** from the 2-alkynyl precursor **579** <2001JA2074>. A similar procedure with 2,4-dipropynylpyrimidine resulted in the formation of a bispyrrolopyrimidine <2002OL4697>.

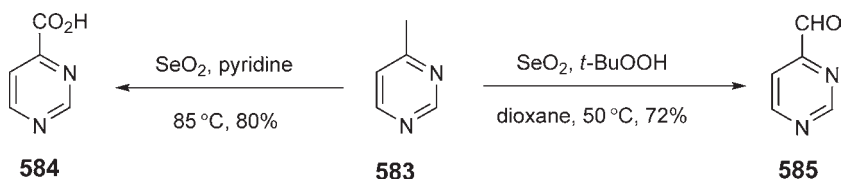


8.02.7.1.2 Oxidation

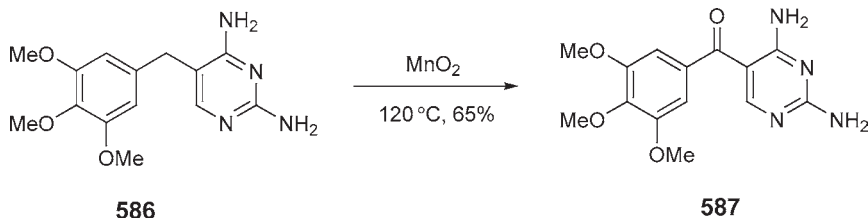
Methyl groups in the pyrimidine 2-, 4-, or 6-positions can readily be oxidized to carboxylic acid groups by oxidizing agents such as potassium permanganate, while milder oxidizing agents can be used to produce aldehydes. For example, 2,4-dimethoxypyrimidine-5-carbaldehyde **582** was prepared in 71% yield by treatment of 2,4-dimethoxy-5-methylpyrimidine **581** with a mixture of $\text{K}_2\text{S}_2\text{O}_8$ and CuSO_4 in 2,6-lutidine <2005JHC1135>.



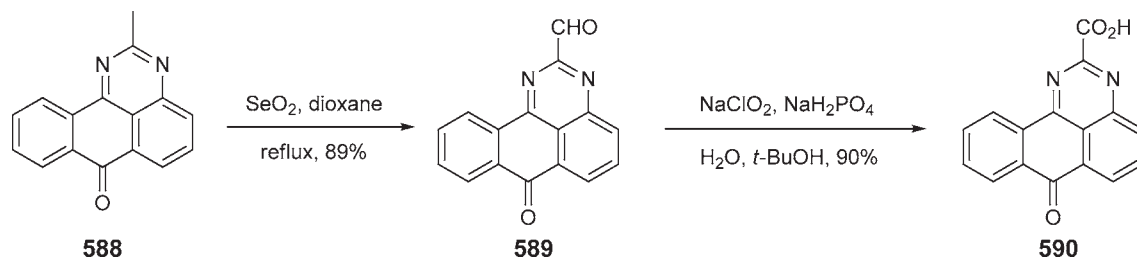
Selenium dioxide can be used to prepare either aldehydes or carboxylic acids, depending on the reaction conditions. For example, treatment of 4-methylpyrimidine **583** with 1.5 equiv of selenium dioxide in pyridine at 85 °C gave the carboxylic acid **584** in 80% yield <2006ICA(359)1255>, while reaction at 50 °C in dioxane with 1 equiv of *tert*-butyl hydroperoxide gave the corresponding aldehyde **585** in 72% yield <2003H(60)953>. Increasing the amount of *tert*-butyl hydroperoxide to 10 equiv, while maintaining all other factors the same gave a 72% yield of the carboxylic acid **584** <2003H(60)953>.



Manganese dioxide can also be used for oxidations of activated alkyl groups, as demonstrated by the oxidation of the clinical dihydrofolate reductase (DHFR) inhibitor trimethoprim **586**, to give the aryl ketone **587**, without any need for protection of the two amino groups [<2006BML4366>](#).

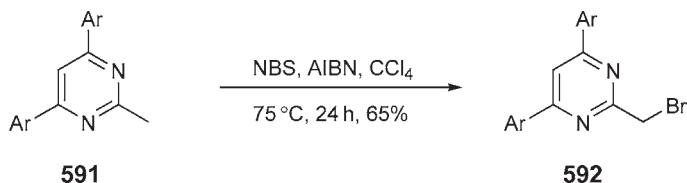


Benzo[*e*]perimidinone carbaldehyde and carboxylic acid derivatives have also been prepared by alkyl oxidation. Thus, treatment of the 2-methyl derivative **588** with selenium dioxide at reflux in dioxane gave the aldehyde **589**, which then gave carboxylic acid **590** on reaction with sodium chlorite [<2001JME2004>](#).



8.02.7.1.3 Halogenation

Simple alkylpyrimidines can be α -halogenated, although strongly electron-releasing groups may direct the halogenation into the pyrimidine 5-position. Care must also be taken to avoid dihalogenation, as often mixtures of mono- and dihaloalkyl derivatives are obtained. The best procedure appears to involve bromination with NBS under radical conditions, as demonstrated by the bromination of 4,6-diaryl-2-methylpyrimidines **591** with NBS and 2,2'-azobis(isobutyronitrile) (AIBN) which gave a variety of 2-bromomethyl derivatives **592** [<2006BML2969>](#).



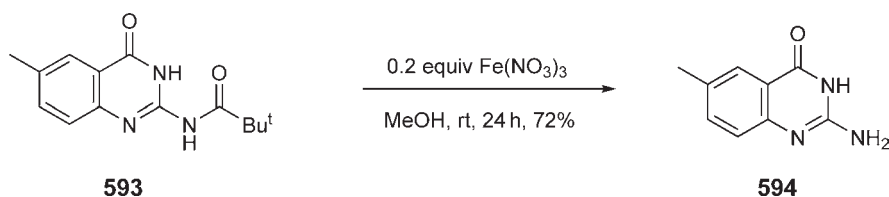
Haloalkyl pyrimidines can also be prepared from hydroxyalkyl derivatives by use of the standard reagents for the alcohol-to-halide conversion [<1994HC\(52\)1, 1996CHEC-II\(6\)93>](#).

8.02.7.2 Carbonyl Derivatives

In general, pyrimidine aldehydes, ketones, carboxylic acids, esters, and carboxamides show the normal reactivities for such groups.

8.02.7.3 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. Treatment of 2-, 4-, or 6-aminopyrimidines with alkylating agents takes place initially on a ring nitrogen atom, and this may be followed by a Dimroth rearrangement where the alkylated ring nitrogen has become part of an alkylamino substituent (Section 8.02.5.2.2). Nitro, nitroso, and arylazo groups at the 5-position can all be reduced to primary amines, usually by hydrogenation using Pd or Raney-Ni, or by the use of inorganic reducing agents such as sodium dithionite or zinc metal. Azides can also be reduced to primary amines, but unlike the other groups their use is not restricted to the 5-position, as they can also be introduced at the 2-, 4-, and 6-positions by halogen displacement reactions with sodium azide <2001JME3355, 2002JA9476, 2004BML3161, 2004BML5085>. An improved procedure for the hydrolysis of the pivalamido group of 2-pivalamido-4(3*H*)-pyrimidinones and 4(3*H*)-quinazolinones **593** has been discovered using $\text{Fe}(\text{NO}_3)_3$ in methanol at room temperature <2004TL5643>.



8.02.7.4 Reactivity of Hydroxy Groups

8.02.7.4.1 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. Generally soft electrophiles favor N-alkylation and harder electrophiles O-alkylation <1992ACS1219>, although the choice of solvent can also have an effect <2006T6848>.

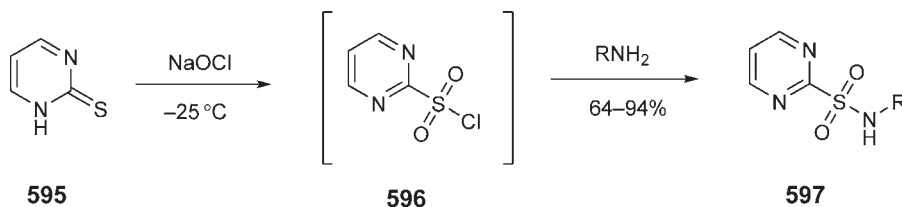
8.02.7.4.2 O-Silylation

Silylation is an important reaction for hydroxyl protection during synthetic transformations. The trimethylsilyl group is most frequently used as it is both easily added and easily removed.

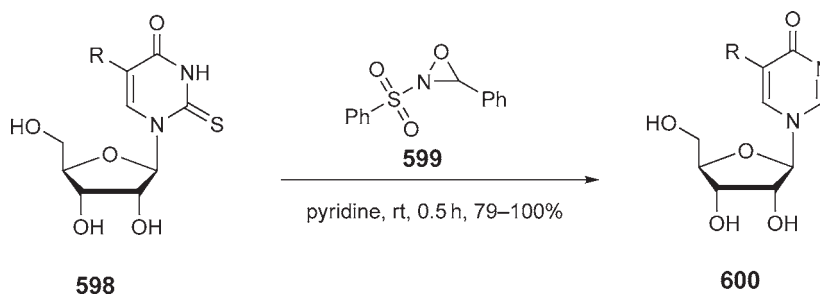
8.02.7.5 Reactivity of Thiols and Sulfides

8.02.7.5.1 Oxidation of the thiol group

Oxidation of 2-thiopyrimidines **595** with sodium hypochlorite at -25°C has been used to prepare pyrimidine-2-sulfonyl chlorides **596** which were then reacted with amines *in situ* to prepare sulfonamides **597** <2006JOC1080>. Alternatively, reaction of the chlorides with KHF_2 and a quaternary ammonium can be used to prepare sulfonyl fluorides, which are stable enough to isolate <2006JOC1080>.



Oxidative desulfurization can also be used to prepare pyrimidine derivatives as demonstrated by the reaction of thymidine derivatives **598** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine (PSO) **599** at room temperature, where the dethiated derivatives **600** were obtained in very good yield <2004TL6729>.



8.02.7.5.2 S-Alkylations

Thiopyrimidines are readily alkylated on the sulfur atom by alkyl halides, sulfonates, or sulfates under mild conditions in the presence of a base <1994HC(52)1>.

8.02.7.5.3 Oxidation of sulfides

Sulfides in the electrophilic positions are often oxidized to sulfones to facilitate nucleophilic displacement reactions. The sulfoxide is initially formed, and can sometimes be isolated, but normally the oxidation is allowed to proceed fully to give the sulfone. Peroxyacids are commonly used as the oxidant, although other reagents such as oxone (potassium peroxymonosulfate) can also be employed <2003OL1011, 2006ARK(vii)452>.

8.02.8 Reactivity of Substituents Attached to Ring Heteroatoms

8.02.8.1 Alkyl, Alkenyl, and Acyl Groups

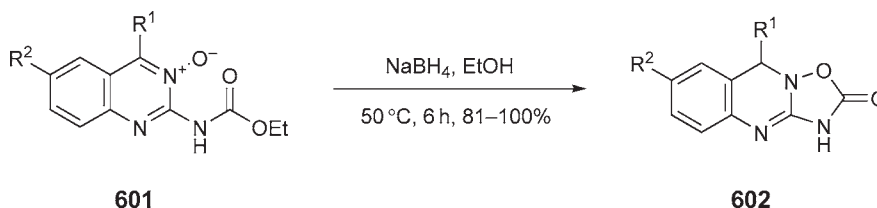
N-Benzyl groups on pyrimidinones and quinazolinones are removable by hydrogenolysis, although it is now more common to use a PMB substituent that can be removed with either TFA or CAN. Other *N*-protecting groups to be commonly used include benzyloxymethyl (BOM), removable by hydrogenation, *tert*-butoxycarbonyl (BOC), removable by anhydrous acid, and pivaloyloxymethyl (POM), which is removable by methanolic ammonia at room temperature. *N*-Alkenyl pyrimidinones have been employed in 1,3-dipolar cycloaddition reactions to prepare heterocyclic nucleotides.

8.02.8.2 Amino Derivatives

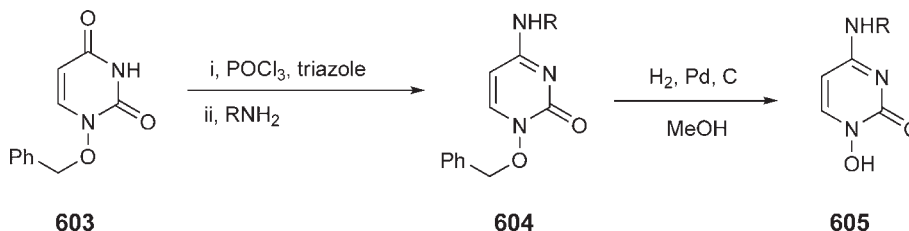
N-Aminopyrimidinones and quinazolinones can be acylated and sulfonylated to give amide and sulfonamide derivatives, and also reacted with isocyanates to give ureas, and with aldehydes and ketones to give imines. They can also participate in cyclization reactions to form fused pyrimidine heterocycles.

8.02.8.3 *N*-Oxides and *N*-Hydroxy Derivatives

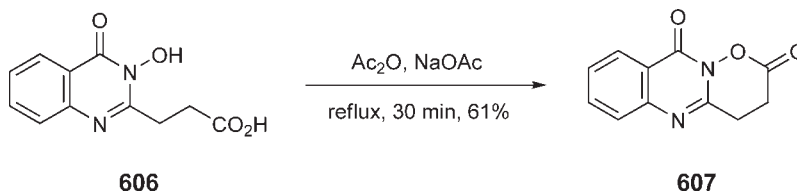
Pyrimidine and quinazoline *N*-oxides are less readily prepared than the corresponding pyridine and quinoline *N*-oxides, due to the lower nucleophilicity of the nitrogen atoms, and normally are prepared by ring closure and in rearrangement reactions <1990H(31)923, 1994HC(52)1, 1996HC(55)1>. The oxygen can be removed by the normal reductive methods including catalytic reduction, low-valent phosphorus (PCl₃), and low-valent titanium (TiCl₃) <1990H(31)923, 1999H(51)2653>. The oxygen atom can also participate in ring-closure reactions to give fused heterocyclic derivatives as demonstrated by the reductive ring closure of 3-oxidoquinazoline-2-carbamates **601** to give 3,9-dihydro-2*H*-[1,2,4]oxadiazolo[3,2-*b*]quinazolin-2-one derivatives **602** <2000S2009>. 1,3-Dipolar cycloaddition reactions can also be performed <2003RCB1195, 2005OBC4351, 2006OBC2408>.



N-Hydroxypyrimidinones and quinazolinones are much more stable toward reductive deoxygenation than the above *N*-oxides, and can be readily prepared by hydrogenolysis of the analogous benzyloxymethyl derivatives. This has been used as last step in a route to *N*-substituted-1-hydroxycytosine derivatives **605** from uracil precursors **603** <1997JOC3618, 2000CC2311, 2002H(58)371>.



N-Hydroxy derivatives can be alkylated and acylated on the oxygen atom, and this can also be performed intramolecularly to give ring-closure products such as the oxazino[3,2-*b*]quinazolinone **607** <2006RJO382>.



8.02.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

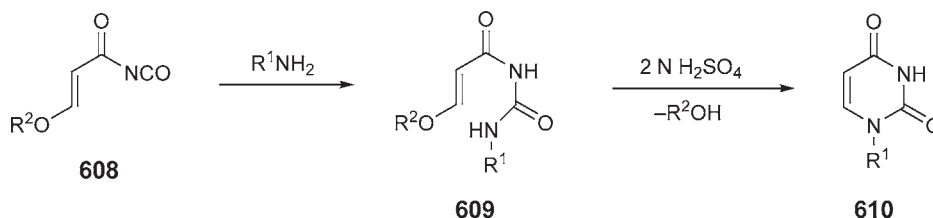
8.02.9.1 Pyrimidines

Various aspects of these ring syntheses have been reviewed elsewhere <1984CHEC(3)57, 1994HC(52)1, 1996CHEC-II(6)93, 1998HOU(E9b1)1, 2004SOS(16)379>, so the present discussion will concentrate on the more synthetically useful procedures.

8.02.9.1.1 Six ring atoms

In most of these reactions, it is nitrogen of a urea, thiourea, isothiurea, or an amidine which is the nucleophile for the addition to an appropriately situated electrophilic carbon. Conditions which enhance the electrophilic character of the carbon, or the nucleophilicity of the nitrogen, promote cyclization. Most commonly, this cyclization is affected by nitrogen addition to the electrophilic β -carbon of a Michael acceptor, and can be performed under acid or basic conditions.

Synthetically, this approach is commonly used for the synthesis of carbocyclic nucleosides and other *N*-1-substituted uracils **610**, where the newly created bond is between the uracil *N*-1 and C-6 positions <1958JCS157, 1999JHC293, 2001S239, 2004OL3941, 2004S2517, 2005HCA3210, 2006S73>. Synthesis of the starting *N*-acylureas **609** is achieved by the reaction of an amine with 3-methoxy- or 3-ethoxy-2-propenyl isocyanate **608** <1958JCS157>, and an improved synthesis of the latter reagent means that the overall synthesis from amine to uracil derivative can be achieved quite efficiently <2001S239>. Ring closure is normally performed using acid catalysis.

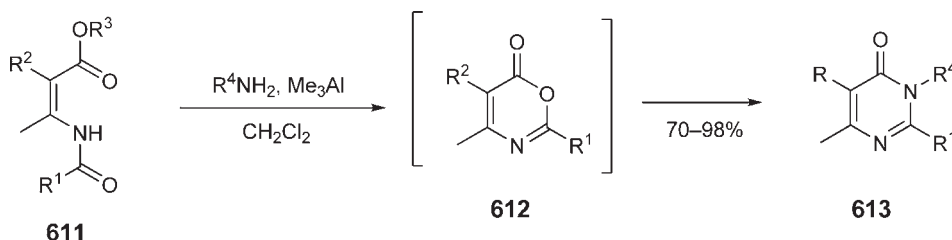


8.02.9.1.2 From two components of one and five ring atoms

In most reactions the one atom component is N-1, N-3, or C-2.

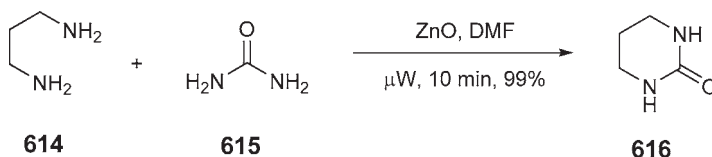
8.02.9.1.2(i) N-1 or N-3 in ring formation

In this synthetic strategy ring formation is normally effected by reaction of a precursor with ammonia or a primary amine <1994HC(52)1, 1996CHEC-II(6)93>. A new route to 3-substituted 3*H*-pyrimidin-4-ones **613** involves the cyclization of enamide esters **611**, derived from β -keto esters, with trimethylaluminium and primary amines <2004OL1013>. The reaction proceeds through an oxazinone intermediate **612** which undergoes ring opening and subsequent ring closure by reaction with the primary amine. Both aliphatic and aromatic primary amines can be used <2004OL1013>.

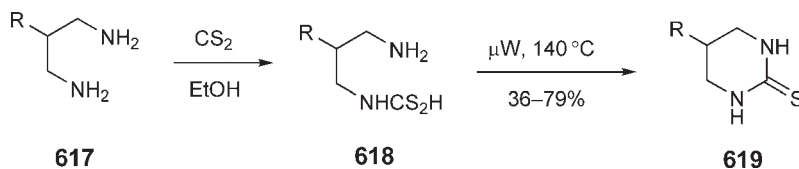


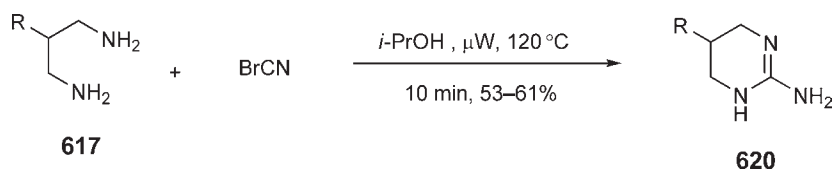
8.02.9.1.2(ii) C-2 in ring formation

This approach is commonly used for the synthesis of reduced pyrimidines from 1,3-propanediamines and earlier examples of this approach have been reviewed <1994HC(52)1, 1996CHEC-II(6)93>. Cyclic guanidines, and cyclic ureas and cyclic thioureas represent frequent targets <2000H(53)1317, 2004OPD571, 2005BML3896, 2005HCA1664>, and microwave-assisted procedures have now been developed for the synthesis of both cyclic ureas and cyclic thioureas <2004JOC1571, 2004TL7205>. For example, reaction of 1,3-propanediamine **614** with urea **615** under microwave irradiation using zinc oxide as catalyst gave a 99% yield of tetrahydro-2(1*H*)-pyrimidinone **616** <2004TL7205>.



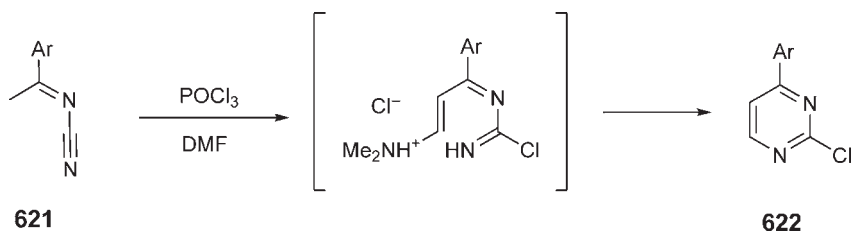
Reaction of 2-substituted 1,3-propanediamines **617** with carbon disulfide, followed by ring closure under microwave conditions gave 2-pyrimidinethiones **619**, while reaction of the same diamines with cyanogen bromide in a one-pot microwave procedure gave cyclic guanidines **620** <2004JOC1571>.





8.02.9.1.2(iii) C-4 or C-6 in ring formation

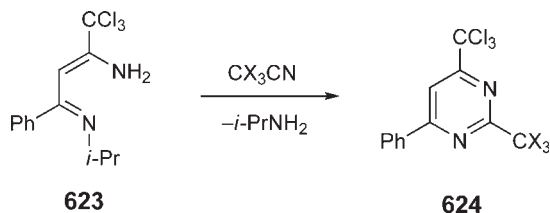
The addition of C-4 or C-6 is not a common route to pyrimidines, although in an example of this approach, 4-aryl-2-chloropyrimidines **622** were prepared from acetophenone cyanoimines **621**, where the C-6 carbon came from DMF via the Vilsmeier reagent <2002SC3011>. The starting acetophenone cyanoimines were readily prepared from the analogous acetophenones by successive treatment with titanium tetrachloride and bis(trimethylsilyl)carbodiimide <2002SC3011>.



8.02.9.1.3 From two components of two and four ring atoms

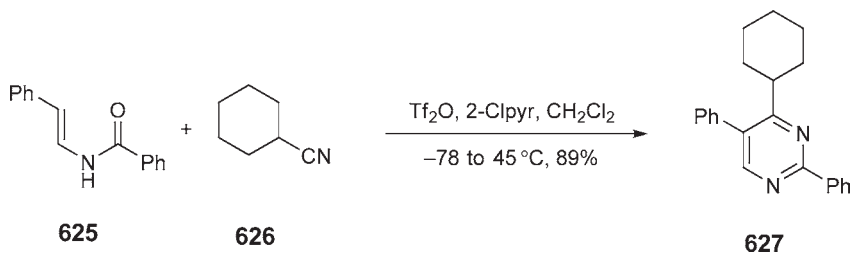
8.02.9.1.3(i) The two-atom component consists of N-C(2)

In this approach the four-atom unit is an unsaturated β -amino ester, β -amino nitrile, β -amino amide, or an equivalent structure, and the two-atom unit can be a variety of different species <1994HC(52)1>. A recent example involves the formation of 2-trichloromethyl- and 2-trifluoromethylpyrimidines **624** by thermal reaction of the respective nitriles with aminoazabutadiene **623** <2002T1375>.



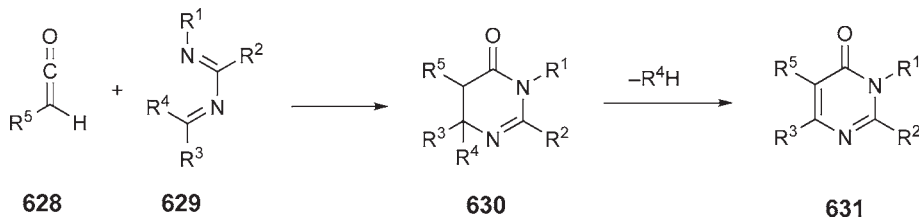
8.02.9.1.3(ii) The two-atom component consists of N(3)-C(4)

A new route to 4-substituted pyrimidines involves the condensation of nitriles with *N*-vinyl amides which are activated by trifluoromethanesulfonic anhydride and 2-chloropyridine <2006JA14254>. The method is illustrated by the synthesis of 4-cyclohexyl-2,5-diphenylpyrimidine **627** from *N*-styrylbenzamide **625** and cyclohexanecarbonitrile **626** in 89% yield <2006JA14254>.

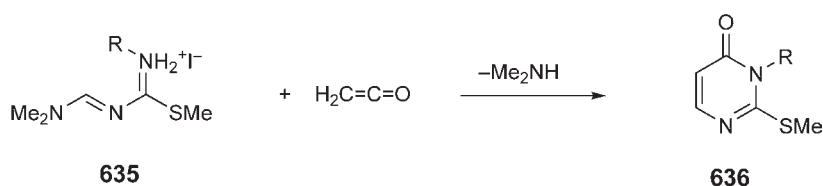
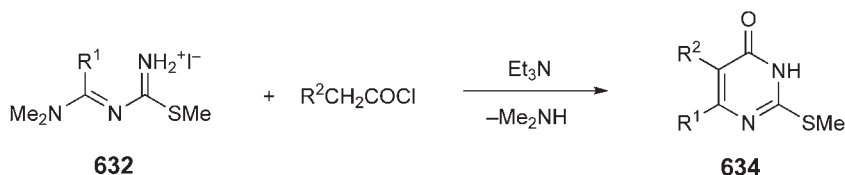
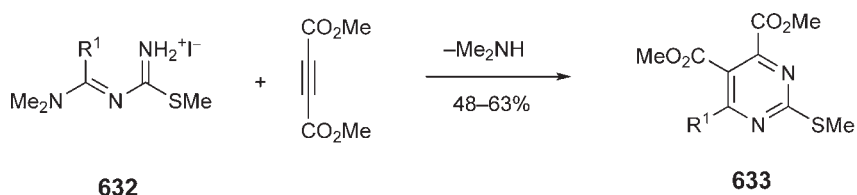


8.02.9.1.3(iii) The two-atom component consists of C(4)–C(5)

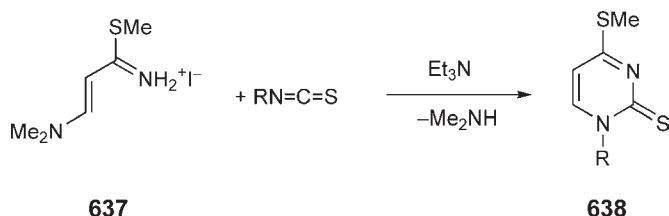
The [4+2] cycloaddition of ketenes **628** with 1,3-diazabutadienes **629** is now a well-established route to 5,6-dihydro-4-pyrimidinones **630** and, when a leaving group is present, 4-pyrimidinones **631** <1997T13841, 1998H(47)933, 2001H(55)2283, 2002ARK(vii)106, 2002J(P1)774>.

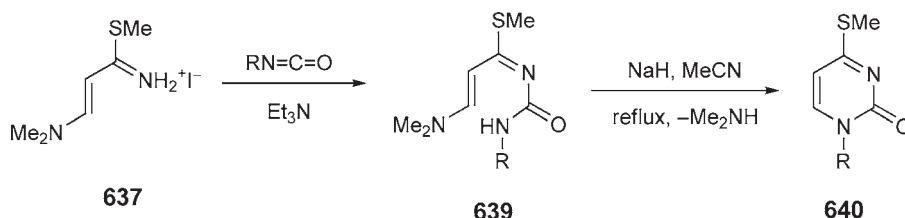


S-Methyl aza- and diazadienium iodides, readily prepared by reaction of thioamides with methyl iodide, have been introduced as stable and versatile reactants for the preparation of a variety of pyrimidine derivatives <2000H(53)2667, 2000S695, 2001JHC93, 2006EJO634>. For example, reaction of diazadienes **632** with dimethyl acetylenedicarboxylate gave pyrimidine-4,5-dicarboxylates **633** <2001JHC93>, while reaction of the same diazadienes with acid chlorides gave 2-methylthio-4-pyrimidinones **634** <2001JHC93>. Reaction of the isomeric diazadienes **635** with ketenes gave 3-substituted 2-methylthio-4-pyrimidinones **636** <2000H(53)2667>.



The monoazadiene salt **637** reacts with isothiocyanates to give 1-substituted 4-methylthio-2-pyrimidinethiones **638** <2003JOC8583, 2006EJO634>, and when glycosyl isothiocyanates are used, pyrimidine nucleoside analogs are produced <2003JOC8583, 2006EJO634>. Reaction with aryl isocyanates occurred similarly to give 1-aryl-4-methylthio-2-pyrimidinones, but a two-step procedure was necessary with alkyl isocyanates in order to obtain the analogous 1-alkyl-2-pyrimidinones **640** <2006EJO634>.





8.02.9.1.4 From two components with three ring atoms

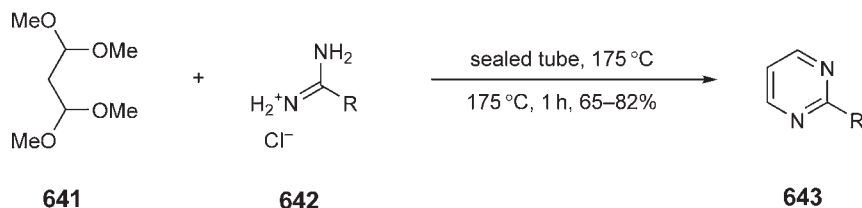
This constitutes by far the most important route for the preparation of pyrimidines. The routes can be divided into two main classes: the combination of an N(1)–C(2)–N(3) with a C(4)–C(5)–C(6) component, and the combination of a C(2)–N(3)–C(4) with a C(5)–C(6)–N(1) component.

8.02.9.1.4(i) Synthesis by combination of an N(1)–C(2)–N(3) and a C(4)–C(5)–C(6) component

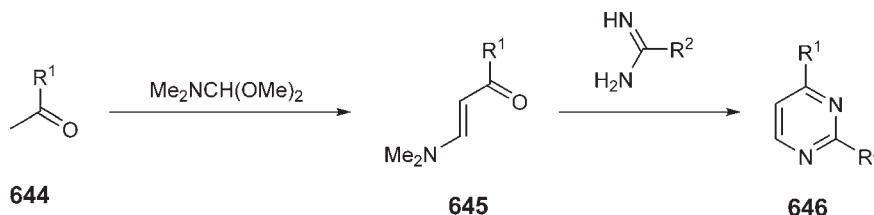
Traditionally, the ring atoms in the 3-carbon component are from a 1,3-dicarbonyl derivative, but more recently the use of alkynyl ketones has become more common. For the 1,3-dicarbonyl derivative, the oxo group may be that of an aldehyde, ketone, ester, or equivalents such as an amide or a nitrile in any combination. The N(1)–C(2)–N(3) component is most frequently an amidine, a guanidine, a urea, or a thiourea or their equivalents. Many examples involving the synthesis of pyrimidines by this approach are known, and are covered in detail in three major reviews of pyrimidine chemistry <1994HC(52)1, 1998HOU(E9b1)1, 2004SOS(16)379>.

8.02.9.1.4(i)(a) β -Dialdehydes, aldehyde ketones, and β -diketones

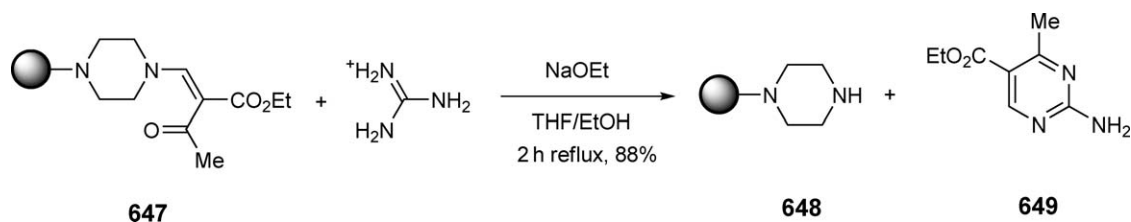
Malonaldehyde is unstable and is therefore used as its diacetal, 1,1,3,3-tetramethoxypropane **641**, in reactions with amidine hydrochlorides **642**. Reaction occurs best in a sealed tube at 175 °C <1997SC2521>.



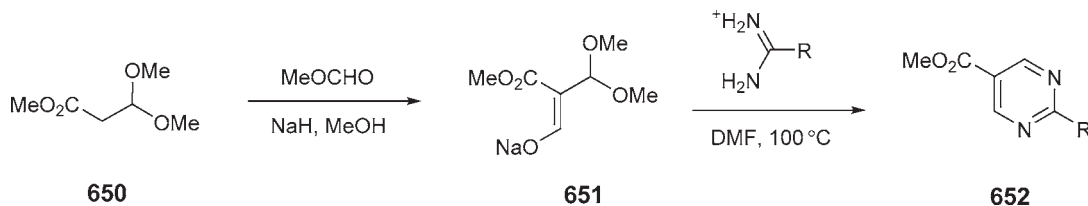
Substituted malondialdehydes form pyrimidines substituted in the 5-position with an alkyl, aryl, halo, or hetero substituent. The pyrimidine is unsubstituted in the 4- and 6-positions. β -Dialdehyde equivalents are frequently used in these reactions, for example, 3-alkoxy- or 3-aminoacroleins. With aldehyde ketones, the pyrimidine carries a substituent in the 4- or 6-position. The formyl group in the ketone is normally masked as an alkoxymethylene ketone or as an aminomethylene ketone. A commonly used procedure involves the preparation of a dimethylaminomethylene ketone **645** by reaction of a methyl ketone **644** with DMF dimethylacetal and subsequent reaction with an amidine or guanidine to form the target pyrimidine **646** <2003MI237, 2004JHC461>.



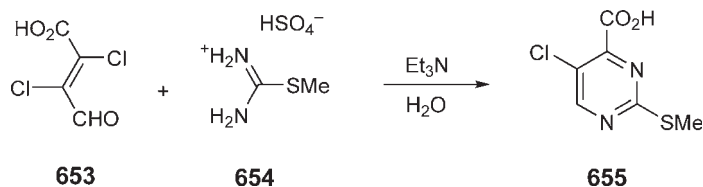
This approach has been used synthetically for the preparation of a large number of biologically important pyrimidine derivatives including the antitumor agent Gleevec (imatinib) and its analogs <1996AP371, 1996BML1221, 1997BML187, 2004BML5793>. A solvent-free modification of the dimethylaminomethylene ketone procedure has been developed, using DBU as the base <2005SL2531>, and the aminomethylene method has also been used on solid phase. Especially notable is the enamino ketone **647** where attachment to the solid support is via the amino component <2004JCO105>. Displacement of the product **649** from the support occurred during the final amine elimination step, in a ‘catch and release’ strategy that enabled the bound amine **648** to be recycled.



Enolates can also function as masked aldehydes or ketones and a new synthesis of 2-substituted pyrimidine-5-carboxylic esters **652** used a doubly masked dialdehyde **651**, where one aldehyde was protected as an acetal and the other was used in the form of its sodium enolate [<2002S720>](#).

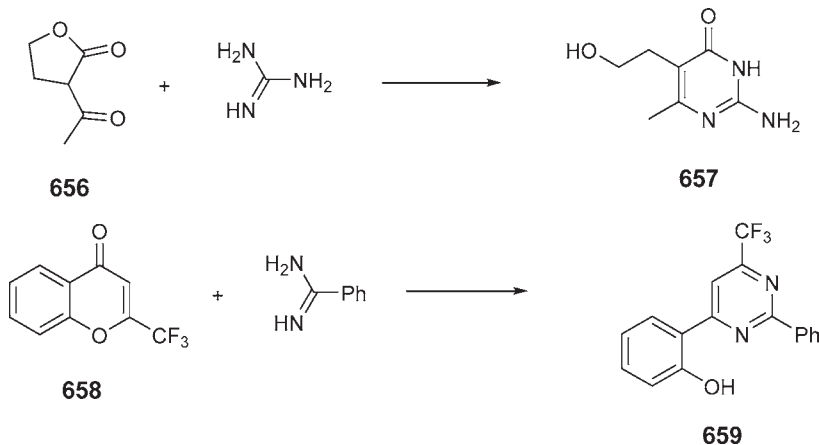


Thioureas react readily with β -diketones, and reactions with thioureas in many cases give higher yields than ureas in pyrimidine cyclizations. *S*-Alkylisothioureas are frequently used instead of thioureas, as demonstrated by the reaction of *S*-methylthiuronium sulfate **654** with mucochloric acid (2,3-dichloromalealdehydic acid) **653** which represents an example of reaction with a masked ketoaldehyde where the ketone is protected as a vinyl chloride [<2002SC153>](#).

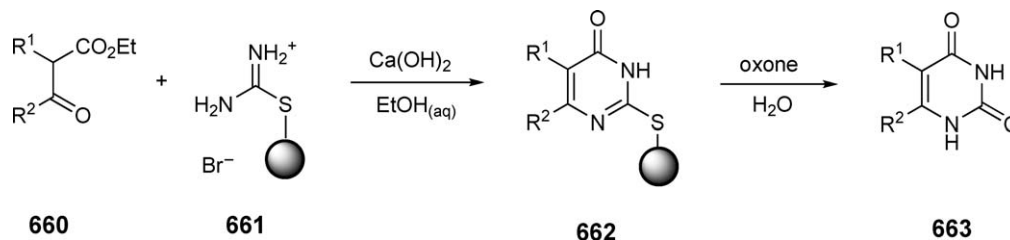


8.02.9.1.4(i)(b) β -Aldehyde esters, β -keto esters, and β -diesters

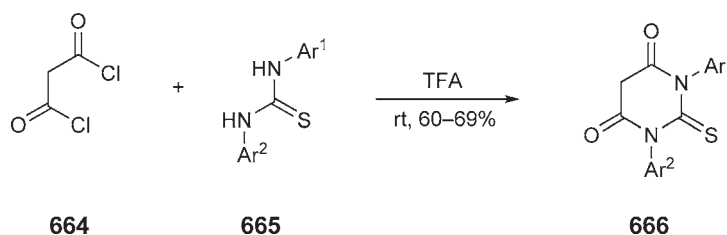
There are few cases in which free β -aldehyde esters have been condensed successfully with ureas. Commonly, alkoxymethylene esters are used. The initial reaction leads to an acyclic intermediate that may require a separate treatment to induce ring closure. The reaction of a β -keto ester with urea may 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. When the ester component is a lactone or chromone, the product contains a hydroxyalkyl [<2000JME3837>](#) or 2-hydroxyphenyl substituent [<2004S942>](#), as shown by the synthesis of the 5-(2-hydroxyethyl)-4-pyrimidinone **657** and the 6-(2-hydroxyphenyl)-pyrimidine **659**.



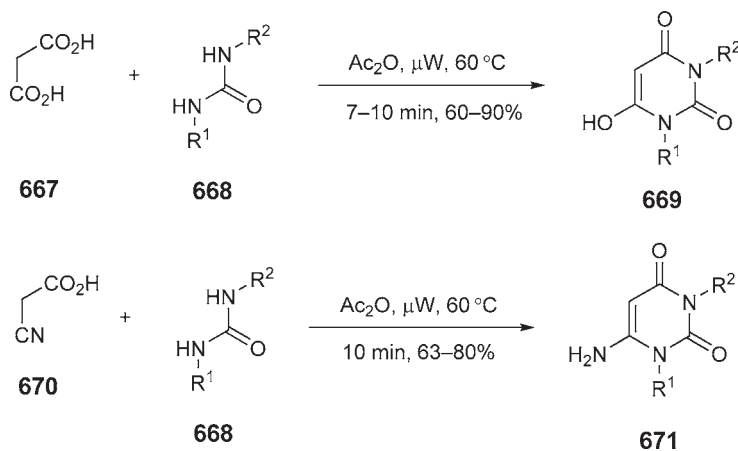
The reaction with β -keto esters **660** has also been performed where the amidine component **661** was attached to a solid support, as shown by the synthesis of 2,4-pyrimidinediones **663** where oxidation of the thio linker of **662** was followed by hydrolytic cleavage from the solid support <2004ARK(v)349>.



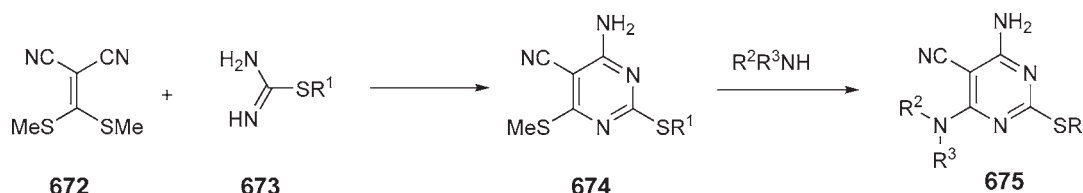
β -Diesters are malonates, and are often used for the synthesis of barbiturates. Malonyl dichlorides can be used in place of a malonyl diesters, in which case the reaction can be performed at room temperature, as demonstrated by the synthesis of *N*-phenyl and *N*-pyridyl 2-thiobarbituric acids **666** from malonyl dichloride **664** and *N*¹,*N*³-diarylureas **665** <2002AJC287>.



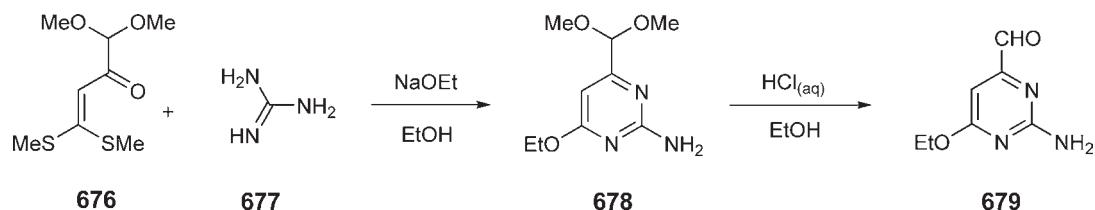
Microwave-assisted procedures have also been developed for the condensation of substituted amidines and ureas with malonic acid derivatives <2005TL5727, 2007AJC120>. For example, reaction of substituted ureas **668** with malonic acid **667** in the presence of acetic anhydride gave 1,3-disubstituted barbituric acids **669**, while similar condensation with cyanoacetic acid **670** gave 6-aminouracil derivatives **671** <2005TL5727>.



Ketene dithioacetals represent masked thioesters, and these can be used to place a thioalkyl group at the 4- or 6-position of a pyrimidine for later displacement by amines or other nucleophiles. For example, reaction of 3,3-bis(methylthio)-2-cyanoacrylonitrile **672** with 2-alkylthioamidines **673** gives 4-amino-2,6-dialkylthiopyrimidine-5-nitriles **674** <1998HCA646, 2003SC3989>, from which the 6-methylthio group can be selectively displaced by amines <1998HCA646>.



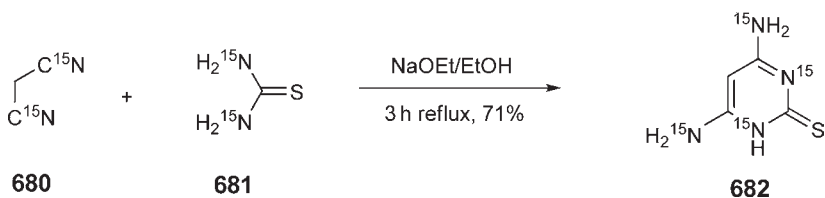
Displacement of the methylthio group can also be performed with alkoxides, in a one-pot procedure without isolation of the methylthio intermediate, as demonstrated by the synthesis of 2-amino-6-ethoxypyrimidine-4-carbaldehyde **679** from the protected aldehydes **676** and **678** <2003T2631>.



The ketene dithioacetal method group has proved useful for the synthesis of a number of biologically interesting molecules <2000BML703, 2004EJM969>, including 5-cyanopyrimidine derivatives which are orally active inhibitors of p38 α MAP kinase <2005JME6261>.

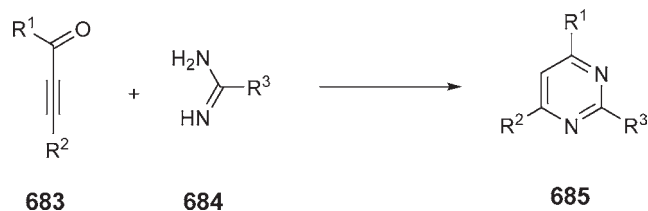
8.02.9.1.4(i)(c) β -Aldehydo nitriles, β -keto nitriles, β -ester nitriles and β -dinitriles

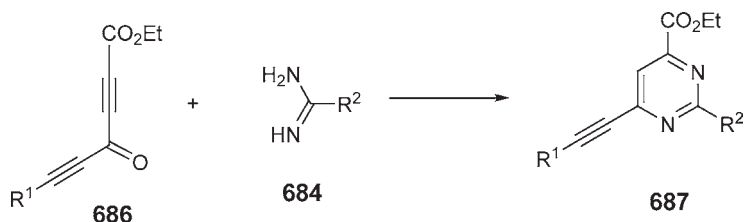
β -Aldehydo nitriles are readily available and can be used to prepare 4-amino-6-unsubstituted pyrimidines carrying one or more substituents in any of the other positions. Equivalents of the formyl group are also often used, for example, a 3-ethoxy-, 3-amino-, or 3-haloacrylonitrile. Most syntheses with β -keto nitriles are carried out with equivalents thereof. Such equivalents are β -substituted β -alkoxy-, β -amino-, or β -haloacrylonitriles. β -Ester nitrile reactions are also well established. Malononitriles and substituted malononitriles react readily with thiourea and N-substituted thioureas in refluxing ethanolic sodium ethoxide to form pyrimidine-4,6-diamines. An example is the reaction of $^{15}\text{N}_2$ -malononitrile **680** with $^{15}\text{N}_2$ -thiourea **681** to give $^{15}\text{N}_4$ -4,6-diamino-2-(1*H*)-pyrimidinethione **682** which was then used in the synthesis of $^{15}\text{N}_5$ -labeled adenine derivatives <2001JOC5463>.



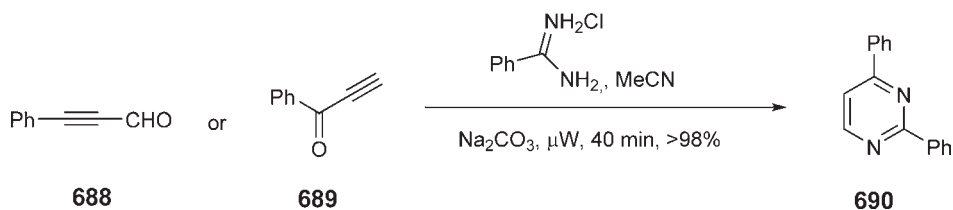
8.02.9.1.4(i)(d) 2-Propynyl aldehydes, 2-propynyl ketones, and 2-propynyl esters

Alkyne groups can be formally considered as highly masked aldehyde or ketone equivalents, and in practice 2-propynyl ketones **683** react readily with amidine derivatives **684** to give 2,4-disubstituted pyrimidines **685** in good yields <1997HCA65, 1999J(P1)855, 2004SOS(16)379, 2003T9001>. With diacetylenic ketones **686**, reaction occurs on the more electron deficient triple bond to give 4- or 6-alkynylpyrimidines **687** <2001J(P1)2906, 2003T2197>.

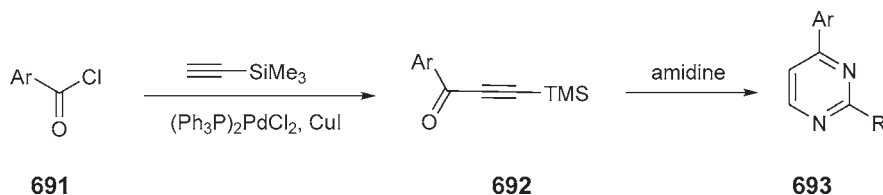




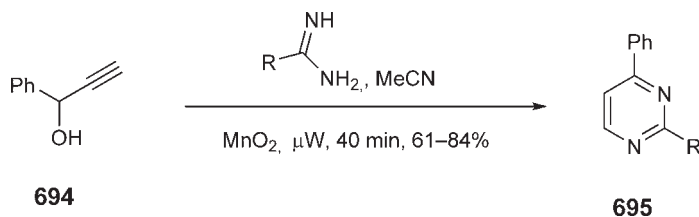
2-Propynyl aldehydes have also been shown to undergo the reaction [<2003SL259, 2004QSA859>](#), and although less commonly utilized, 2-propynyl esters have also been used to give 4*H*-pyrimidinones [<1990JME1230>](#). The method is amenable to microwave assistance and the application of this technology has enabled alkynyl ketones to become a high-yielding source of pyrimidine derivatives. For example, 2,4-diphenylpyrimidine **688** was prepared in greater than 98% yield after 40 min of microwave irradiation, regardless of whether the phenylalkynyl aldehyde **688** or the alkynylphenyl ketone **689** was used as the starting material [<2003SL259, 2004QSA859>](#).



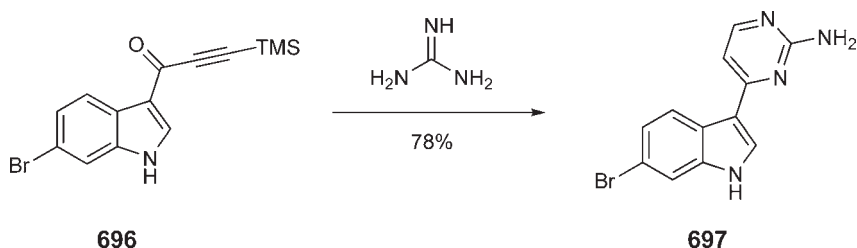
The ready availability of propynyl ketones from acid chlorides, by a modified Sonogashira route [<2003OL3451, 2003S2815, 2004S2015>](#), has helped to make this method a very valuable route to pyrimidines. Procedures have been developed that enable both the Sonogashira coupling and amidine reaction steps to be performed in one pot, as demonstrated by the conversion of aryl acid chlorides **691** to 4-arylpyrimidines **693** via the trimethylsilylalkynes **692** [<2003OL3451, 2003S2815>](#).



An alternative source of the alkynyl ketone is via alkyne addition to an aldehyde, followed by oxidation of the alkynyl alcohol. Several different oxidants have been utilized, although manganese dioxide is the most commonly used [<2001J\(P1\)2906, 2003SL1443, 2003T9001, 2005AJC104, 2005BMC2397, 2005BMC5346>](#). A one-pot procedure for performing both the oxidation and ring-closure steps under microwave irradiation has been developed, as demonstrated by the synthesis of 4-phenylpyrimidines **695** from the alkynyl alcohol **694** [<2003SL1443>](#).

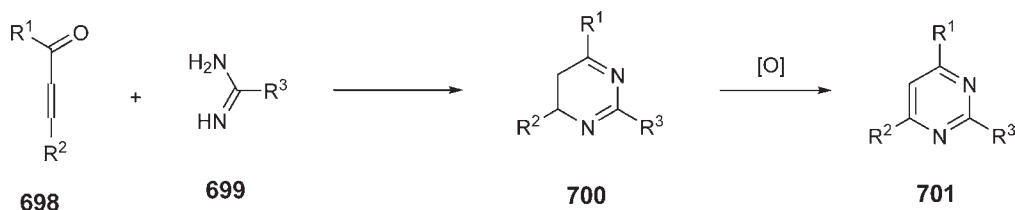


The alkynyl ketone route to pyrimidines is now well established synthetically, and an example of its use in natural products chemistry is the synthesis of several meridianin analogs, including meridianin D **697** from the indole precursor **696** [<2005AGE6951>](#).



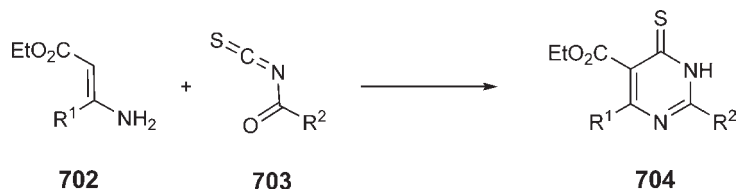
8.02.9.1.4(i)(e) Alkenyl ketones

Although alkenyl ketones **698** or chalcones are at a lower oxidation level than alkynyl ketones, and lack the leaving group of enamino ketones, they can still be used as a source of fully conjugated pyrimidine derivatives, provided oxidation of the intermediate 4,5-dihydropyrimidine **700** can occur. In many cases no added oxidant is needed, and oxygen in the air is sufficient to ensure isolation of pyrimidines **701** in good yield [<1998JOC723, 2000OL1967, 2003OPD533>](#). When an added oxidant is required, hydrogen peroxide has been found to be useful [<2003T655>](#), and palladium on charcoal has also been used [<2003T9001>](#).

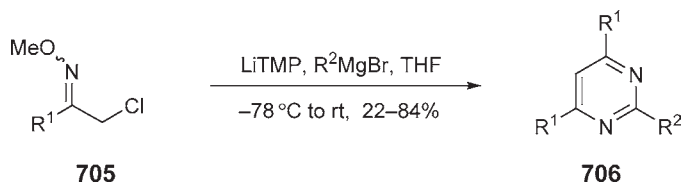


8.02.9.1.4(ii) Synthesis by combination of a C(2)–N(3)–C(4) and a C(5)–C(6)–N(1) component

Traditionally, the C(5)–C(6)–N(1) component has been an enamine which reacts with an acyl isothiocyanate to form 4(3*H*)-pyrimidinethiones **704**, and this is demonstrated by the condensation of enaminoesters **702** with acyl isothiocyanates **703** [<1999JPR147, 2002PS\(177\)2745>](#).



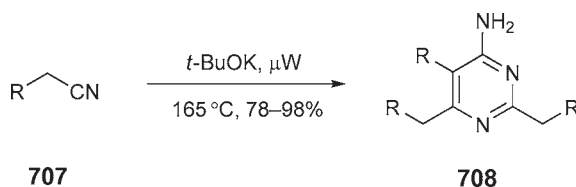
A new approach to this synthesis category involves the dimerization of halogenated oxime ethers **705** by reaction with Grignard reagents, where the C-2 atom of the product **706** arises from a rearrangement that is proposed to proceed via azirene intermediates [<2002JA9032, 2004CL122>](#).



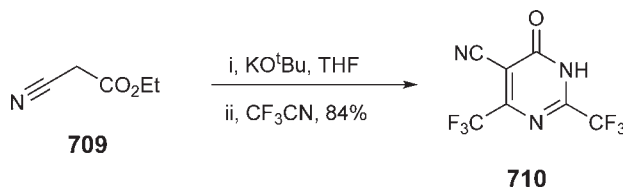
8.02.9.1.4(iii) From three components of ring atoms

8.02.9.1.4(iii)(a) Synthesis by combination of C(2)–N(3), C(4)–C(5), and C(6)–N(1) components

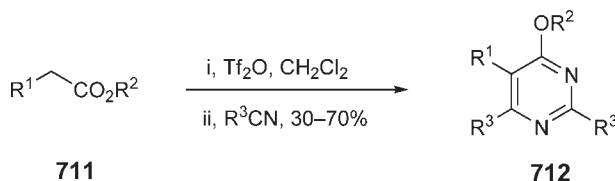
In this approach the C(2)–N(3) and C(6)–N(1) components are usually the same. Formamide or nitriles are common C–N components. A classical example is the trimerization of acetonitrile to give 2,6-dimethyl-4-pyrimidinamine [<1994HC\(52\)1>](#), while a modern example involves a similar trimerization of a variety of alkyl and benzylic nitriles **707** under microwave conditions [<2005JCO483>](#).



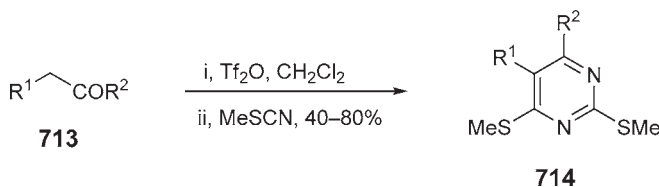
Another recent example is the condensation of ethyl cyanoacetate **709** with 2 equiv of trifluoroacetonitrile in the presence of potassium *tert*-butoxide to give 5-cyano-2,6-bis(trifluoromethyl)-4(3*H*)-pyrimidinone **710** in 84% yield <2004SC903>.



Triflic anhydride can also be used to activate esters **711** for condensation with nitriles, in which case 4-alkoxy-pyrimidines **712** are obtained <1999T4825>.

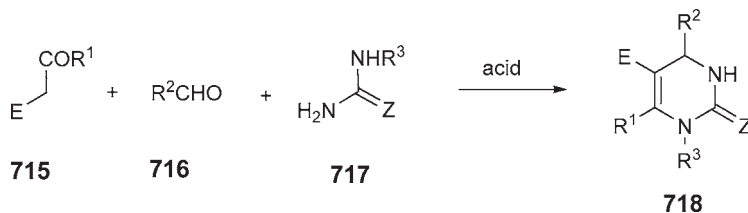


When ketones **713** are used in the same reaction in place of the ester, tri- or tetraalkylalkylpyrimidines are obtained, and when methyl thiocyanate is used in place of the nitrile, 2,4- or 2,6-bis(methylthio)pyrimidines **714** are obtained <1994SL559, 1996T7973>.



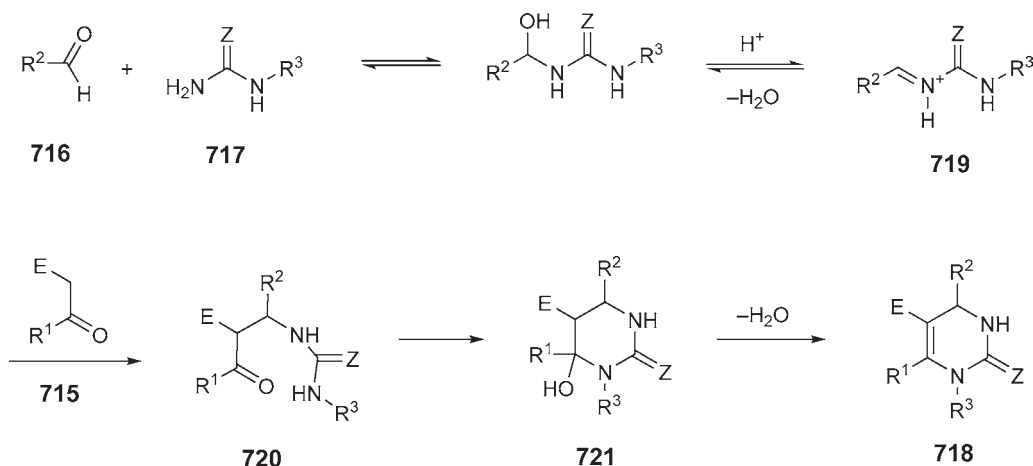
8.02.9.1.4(iii)(b) Synthesis by combination of N(1)-C(2)-N(3), C(4)-C(5), and C-6 components

The most important synthesis within this subgroup is the Biginelli reaction, which involves reaction between a methylene ketone **715**, an aldehyde **716**, and either a urea **717** (Z = O) or thiourea **717** (Z = S) to give a dihydro-2-pyrimidinone **718** (Z = O) or dihydro-2-pyrimidinethione **718** (Z = S) <1993T6937, 2000ACR879, 2004OR1>.



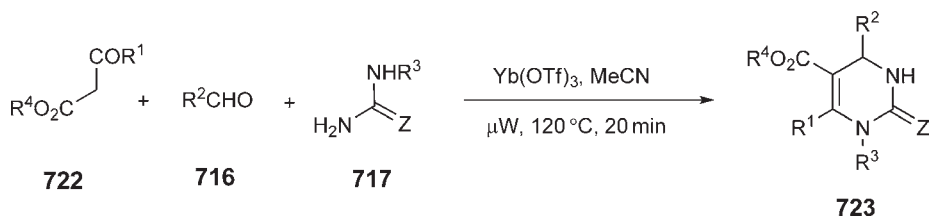
In the currently accepted mechanistic pathway outlined in Scheme 7, the key step in the Biginelli sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **719** from the aldehyde and urea precursors <1997JOC7201, 2000ACR879, 2004OR1>. Interception of the iminium ion **719** by the CH-acidic carbonyl component **715**, presumably through its enol tautomer, produces an open-chain ureide **720**, which subsequently cyclizes to hexahydropyrimidine **721**. Acid-catalyzed elimination of water from **721** ultimately leads to the

final dihydropyrimidinone product **718**. The reaction mechanism can therefore be classified as an α -amidoalkylation, or, more specifically, as an α -ureidoalkylation. Consistent with this mechanistic formulation, monosubstituted ureas and thioureas furnish exclusively the N-1 alkylated dihydropyrimidinones. *N,N'*-Disubstituted ureas do not react under the reaction conditions <2000ACR879, 2004OR1>.

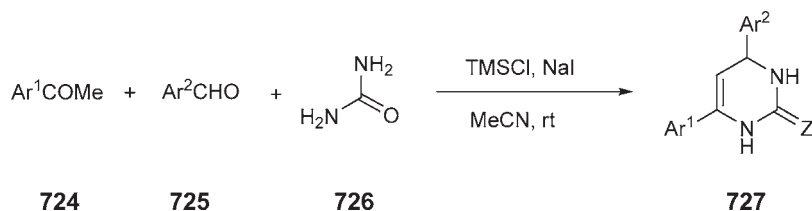


Scheme 7

The Biginelli procedure is amenable to microwave technology, and several microwave-assisted procedures have now been published <2002SC147, 2004SL235>. An example is the microwave-assisted solution-phase synthesis of dihydropyrimidine C-5 amides and esters **723** using ytterbium triflate as the Lewis acid catalyst <2006T4651>.

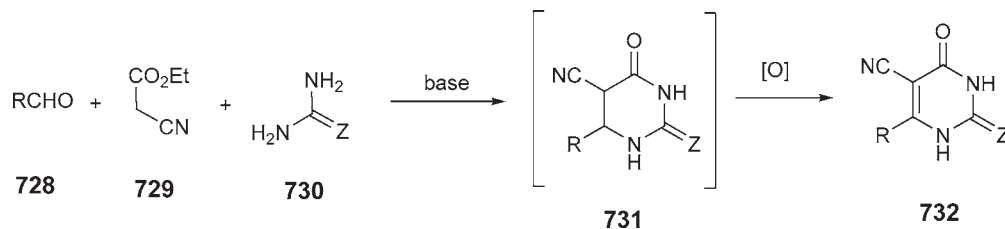


In a related three-component reaction procedure, aryl methyl ketones **724** have been combined with aryl aldehydes **725** and urea **726** at room temperature, using trimethylsilyl iodide as catalyst, to give 4,6-diaryl-3,4-dihydro-2(1*H*)-pyrimidinones **727** <2005HCA2996>. A procedure using zinc iodide and microwave irradiation gave similar products <2007T1981>.



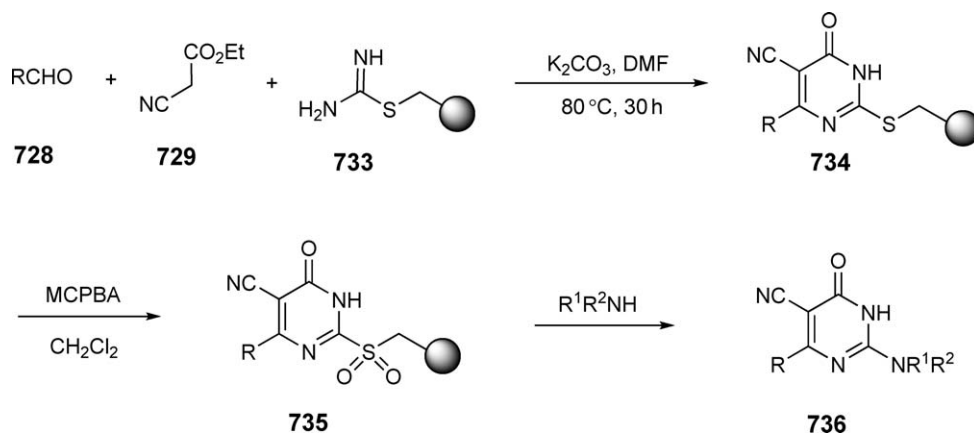
When the methylene ketone component of the three-component reaction is replaced by ethyl cyanoacetate **729**, 5-cyanouracils <1979S287, 2003JHC213> or their 2-thioxo analogs <1979S287, 2000T8631, 2006JHC821> are obtained under basic conditions. The reaction proceeds via initial condensation of the aldehyde and ester

components to give α,β -unsaturated ester derivatives which then combine with the urea or thiourea to give dihydro intermediates **731**, which can be isolated in certain cases, but are normally oxidized *in situ* to give the uracil **732** ($Z=O$) or thiouracil **732** ($Z=S$) products.



Potassium carbonate is often used as the base, although piperidine has been shown to give superior results in the case of reactions involving thiourea, since the product precipitates directly from the reaction mixture as a crystalline piperidinium salt <2000T8631, 2006JHC821>. Acidification of the salt then gives the 2-thiouracil in greater yield than for the potassium carbonate procedure. The piperidine procedure has also been performed under microwave irradiation, and although yields were not improved, reaction times were considerably shorter <2006JHC821>.

S-Methylisothiurea has also been used in place of thiourea to give 2-methylthio-5-cyanopyrimidinone derivatives <2006JME3988>, and polymer-bound thiuronium salts **733** have also been used to prepare derivatives **734** which can be displaced from the solid phase by oxidation of the sulfur atom to give sulfone **735**, and subsequent displacement with amines <2002BML667> (Scheme 8).



Scheme 8

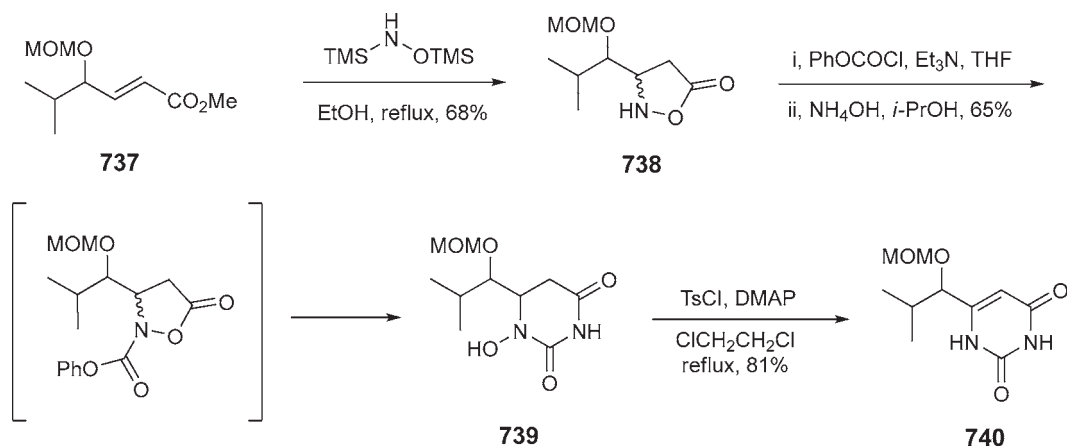
8.02.9.1.4(iii)(c) Synthesis by combination of N-1, C(2)–N(3), C(4)–C(5)–C(6) components

The three-carbon component in this subgroup is either a β -dicarbonyl compound or a β -keto nitrile. The N and C–N components in the reactions with β -dicarbonyl compounds come from formamide, a nitrile, a thiocyanate, or a cyanamide <1994HC(52)1>.

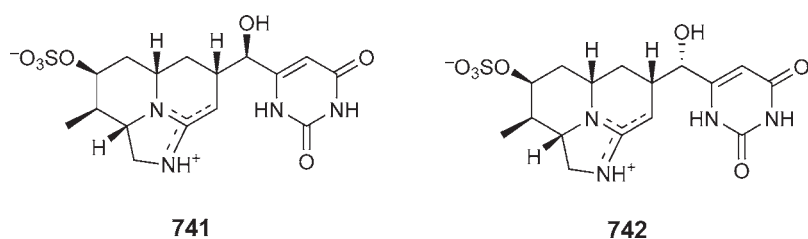
8.02.9.1.4(iv) Synthesis by combination of four components

Pyrimidines can be formed in reactions involving multiple bond formations, and the reactions of this subgroup have a long history <1994HC(52)1>. A recent example is the synthesis of a 6-substituted uracil derivative **740** (Scheme 9), where an α,β -unsaturated ester **737**, *N,O*-bis(trimethylsilyl)hydroxylamine, phenyl chloroformate, and ammonia supplied the four components of C(4)–C(5)–C(6), N-1, C-2, and N-3, respectively <2000TL4307>:

This procedure was successfully used as part of the total synthesis of the freshwater cyanobacterial hepatotoxins cylindrospermopsin **741** and 7-epicylindrospermopsin **742** <2001JA8851, 2002JA3939>.



Scheme 9



8.02.9.2 Quinazolines

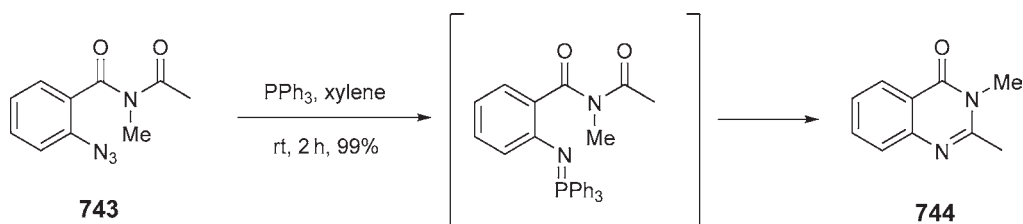
Quinazoline derivatives have attracted a lot of interest in recent years because of their important biological properties, and partly as a consequence of this, several review articles on various aspects of quinazoline and quinazoline alkaloid chemistry have appeared since the publication of CHEC-II(1996) <1996HC(55)1, 1998HOU(E9b2)1, 2000SSR(4)71, 2003COR659, 2003H(60)183, 2004SOS(16)573, 2004QSA440, 2005T10153, 2006THC113, 2006RMC625, 2006T9787>. In addition, certain aspects of quinazoline chemistry have been discussed in reviews covering topics such as the chemistry of 4*H*-3,1-benzoxazin-4-ones <1999JHC563, 2000JHC1369>, 4-(phenylamino)pyrimidine derivatives as protein kinase inhibitors <2000COR679>, the synthesis of heterocyclic compounds based on isatoic anhydrides <2001CHE385>, approaches to fused pyrimidine derivatives <2001PJC1661>, the solid-phase synthesis of medicinally relevant benzoannulated nitrogen heterocycles <2002BMC2415>, the combinatorial synthesis of bicyclic privileged structures <2003CRV893, 2006RMC71>, the chemistry of anthranilic acid <2006CSY379>, and the aza-Wittig reaction <2007T523>.

8.02.9.2.1 Benzenes as substrates

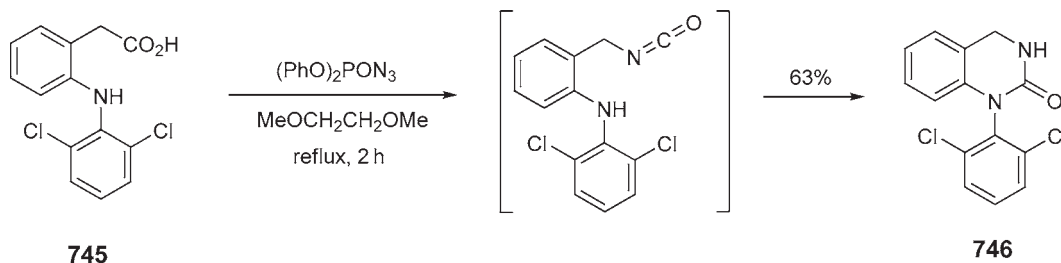
The synthesis of quinazolines from benzene substrates can be accomplished in two ways, either by cyclization of substrates already bearing appropriate substituents, or by treatment of functionalized benzene derivatives with synthons able to provide one or more of the ring atoms needed to complete the pyrimidine ring <1996HC(55)1>.

8.02.9.2.1(i) Synthesis by cyclization across N(1)–C(2)

This construction can be accomplished using an intramolecular aza-Wittig approach, as demonstrated by the synthesis of 2,3-dimethyl-4(3*H*)-quinazolinone **744** <1989T6375>, although the method has not been exploited greatly.

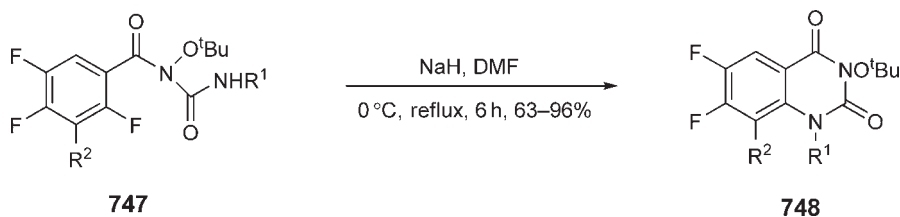


3,4-Dihydro-2-quinazolinones are available from diphenylamine-2-acetic acids via isocyanate intermediates, and thus the nonsteroidal anti-inflammatory agent diclofenac **745** gave the dihydro derivative **746** in 63% yield on treatment with diphenylphosphoryl azide [<2004BML357>](#).

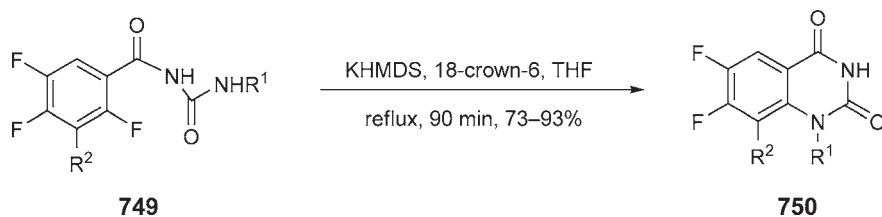


8.02.9.2.1(ii) Synthesis by cyclization across N(1)–C(8a)

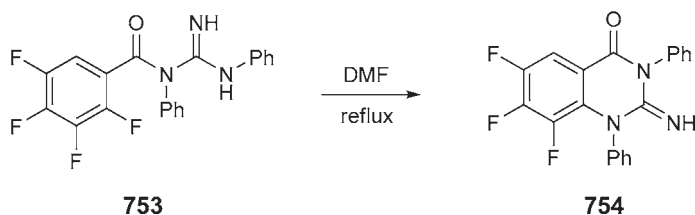
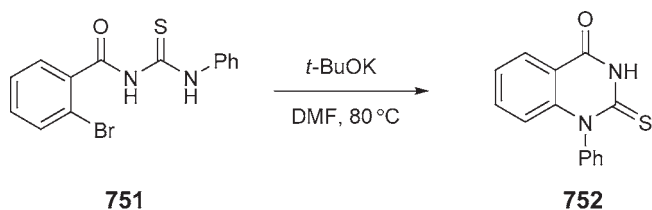
The formation of 4(3*H*)-quinazolinones by a ring closure involving the nucleophilic displacement of an *ortho*-halogen of a benzamide by an attached nitrogen species has been known for some time [<1981BCJ3447>](#), but has recently attracted greater synthetic attention. For example, deprotonation of the urea **747** with sodium hydride enabled ring closure to occur by displacement of fluoride, giving rise to 3-*tert*-butoxy-2,4(1*H*,3*H*)-quinazolidinedione derivatives **748** [<2004BML4405>](#).



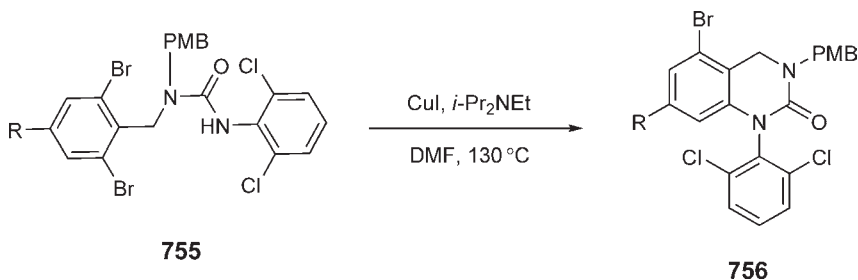
In the case of the less substituted urea **749**, it was necessary to perform a double deprotonation with potassium bis(trimethylsilyl)amide (KHMDs), but ring closure to the quinazolidinedione **750** could still be achieved in good yield [<2005JHC669>](#).



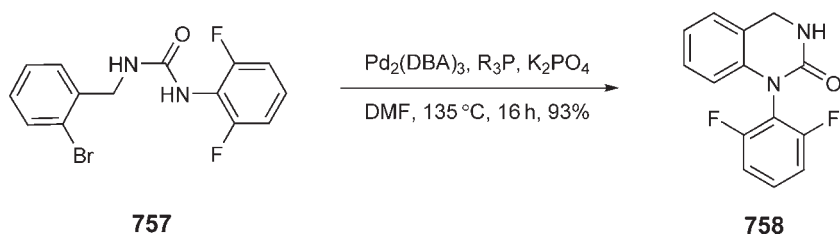
Other examples this type of quinazoline synthesis include the formation of the thione analog **752**, by displacement of bromine from thiourea **751** [<2003ARK\(x\)434>](#), and the imino compound **754**, which could be formed by heating the guanidine derivative **753** in DMF, without the need for any added base [<2005RJO1071>](#).



3,4-Dihydro-2-quinazolinones can also be prepared by a related procedure, using either copper or palladium catalysis [<2003BML277, 2003BML467, 2004BML357>](#). Thus cyclization of PMB-protected ureas **755** using copper catalysis gave 5-bromo-3,4-dihydroquinazolinone derivatives **756** [<2003BML277, 2003BML467>](#).

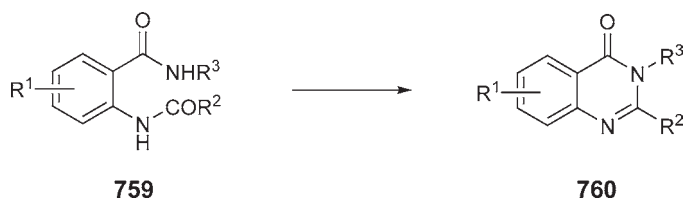


Protection of the urea nitrogen was not necessary when palladium catalysis was used for the ring-closure step, and the *N*-difluorophenyl derivative **758** was obtained in 93% yield by ring closure of the bromourea **757** [<2004BML357>](#).

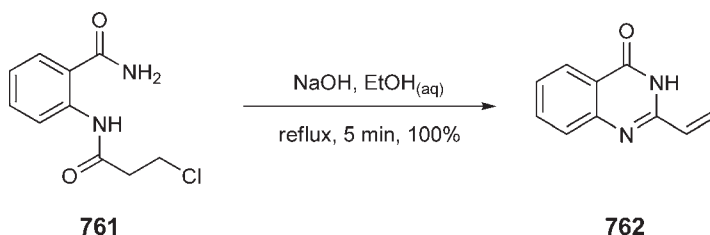


8.02.9.2.1(iii) Synthesis by cyclization across C(2)–N(3)

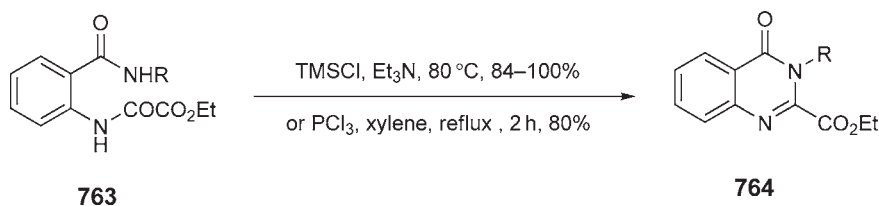
Cyclization of *o*-acylaminobenzamides **759** leads to 2-substituted 4(3*H*)-quinazolinones **760**. The benzamide may be generated *in situ* from an ester and an amine, and the ring closure can be performed under either acidic or basic conditions [<1996HC\(55\)1, 1997IJH101, 2002JHC351, 2004SOS\(16\)573, 2006JOC382, 2007TL3243>](#).



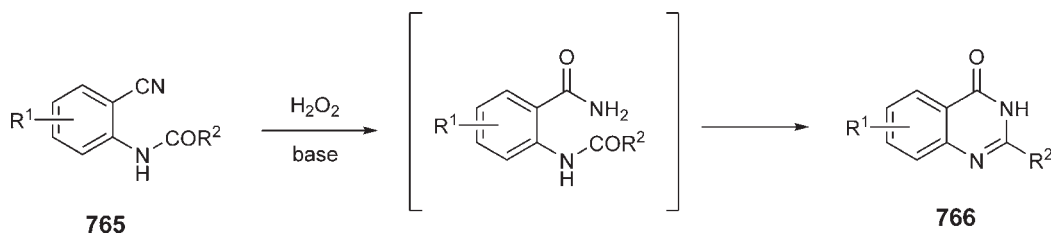
In the case of the 3-chloropropanamide **761**, ring closure was accompanied by elimination of HCl to give a 2-vinylquinazolinone **762** <2000T7245>.



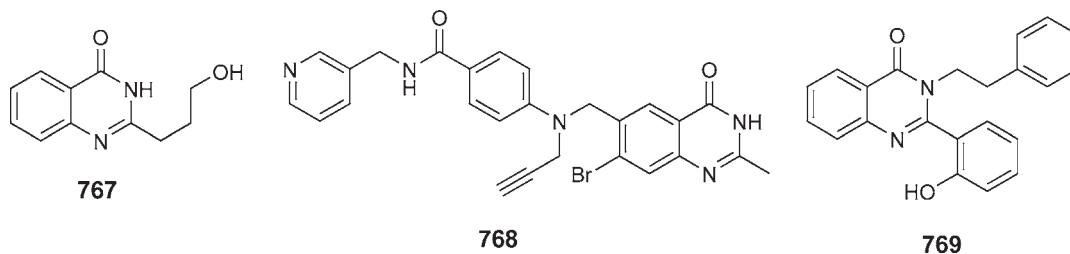
4(3*H*)-Quinazolinones containing a 2-ester group **764** were obtained by ring closure of the carbamate precursors **763** using a mixture of chlorotrimethylsilane (TMSCl) and triethylamine <2005T4297>, or by the use of dehydrating agents such as phosphorus trichloride <2004TL997>.



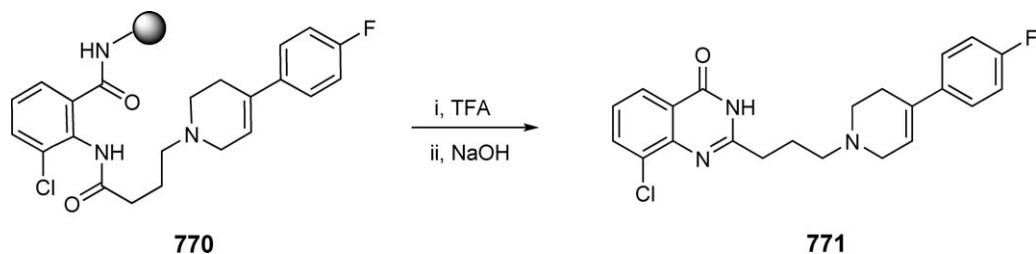
3-Unsubstituted 4(3*H*)-quinazolinones **766** can also be prepared from *o*-amidobenzonitriles **765** following *in situ* conversion of the cyano group to a primary amide using urea–hydrogen peroxide or aqueous hydrogen peroxide <1997SC2065, 1998SC4547, 1999J(P1)1495, 2001BML1193, 2003OBC1943, 2007T1537>.



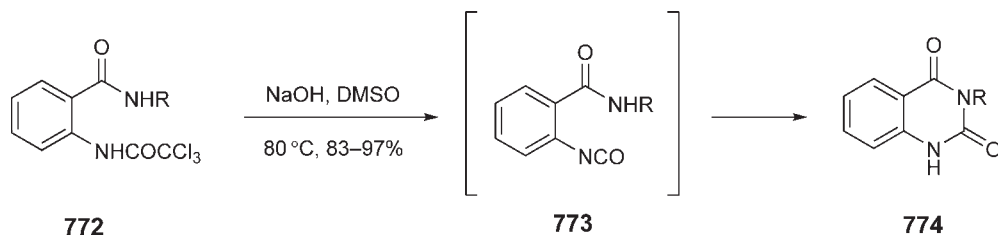
Synthetic applications of the 1-acylaminobenzamide ring-closure method have included the synthesis of the natural product pergamine **767** <2001JOC9038>, water-soluble analogs of the antitumor agent CB30865 **768** <2002JME3692>, and potent calcium receptor antagonists such as **769** <2005BML1557>. In addition, there are numerous examples of natural product synthesis which use the amide ring-closure method for the preparation of intermediates along the pathway to the end product <2004JOC4563, 2006T9787, 2007TL3243>.



The amide ring-closure method has also been used in a solid-phase combinatorial synthesis of inhibitors of poly(ADP-ribose)polymerase (PARP-1). The penultimate intermediates **770** were cleaved from the resin with trifluoroacetic acid, and this was followed by ring closure with sodium hydroxide, at room temperature, to give the quinazolinone products **771** <2004JME4151>.

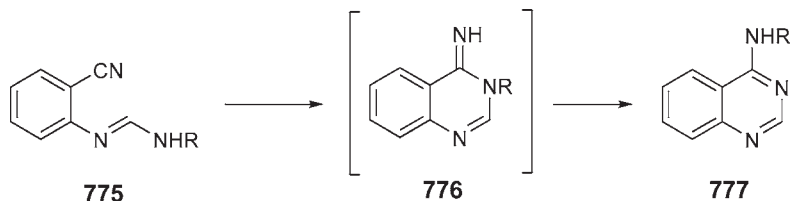


3-Substituted (1*H*,3*H*)-quinazoline-2,4-diones **774**, as well as the 3-unsubstituted parent compound **774** (R = H), are available by treatment of 2-[(trichloroacetyl)amino]benzamides **772** with sodium hydroxide in DMSO. The reaction proceeds via intermediate isocyanato compounds **773** which undergo ring closure to the final products [<2005OPP560>](#).

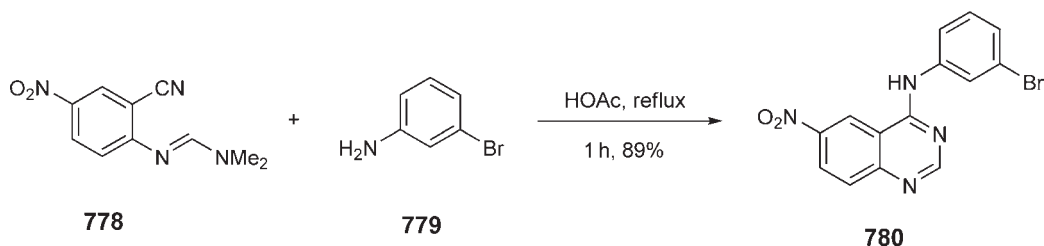


8.02.9.2.1(iv) Synthesis by cyclization across N(3)–C(4)

The ring closure of amidines onto *ortho*-nitrile groups represents a significant new route to 4-aminoquinazolines [<1997J\(P1\)3021, 2001JME2719>](#), and related heterocycles [<1997JME3601>](#), that has been successfully used for the synthesis of a number of biologically important molecules [<2001JME2719, 2004EJM1001, 2005JME7560, 2006JME955, 2006JME3544>](#). The reaction proceeds via a 4-iminoquinazoline intermediate **776**, which can be isolated in certain cases [<2006JME955>](#), but normally this readily undergoes a Dimroth rearrangement to give the product 4-aminoquinazoline **777**.

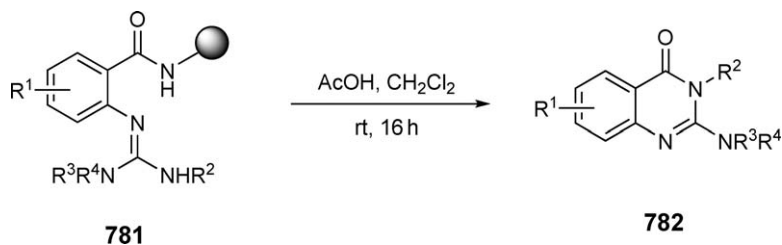


The starting amidines are normally generated *in situ*, by the reaction of amines with *N,N*-dimethylformamidines (formed using dimethylformamide dimethyl acetal), with the ring-closure and rearrangement steps then following to give the product quinazoline, in a one-pot procedure, as demonstrated by the synthesis of 4-(3-bromophenylamino)-6-nitroquinazoline **780** in 89% yield [<2001JME2719>](#).

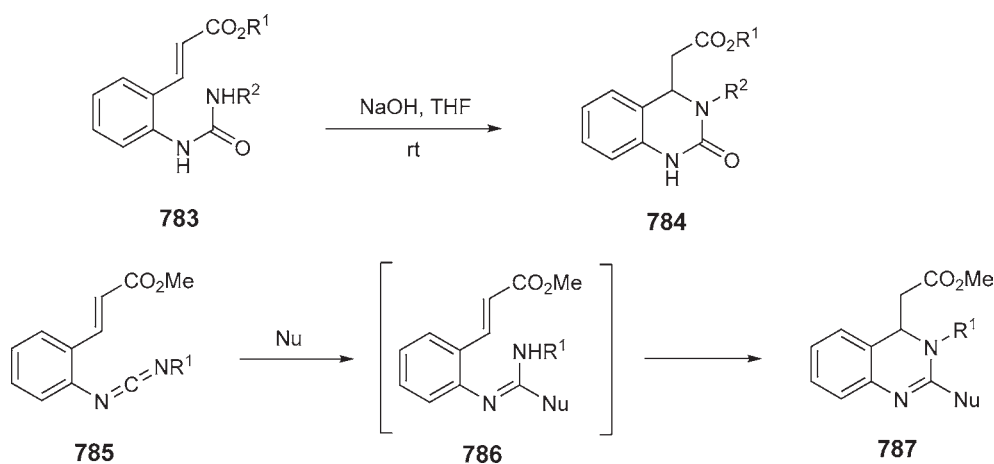


The procedure has also been performed under microwave irradiation, and the optimum reaction conditions were found to be at a temperature of 160 °C for 10 min in an acetic acid, acetonitrile solvent mix [<2004OL4775>](#). Product yields were of the order of 88–97% [<2004OL4775>](#).

4(3*H*)-Quinazolinones can also be generated by a ring-closure reaction involving an amidine group, and this has been used in a solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones **782**, where the ring-closure step also resulted in cleavage from the solid phase <2002TL5579>.



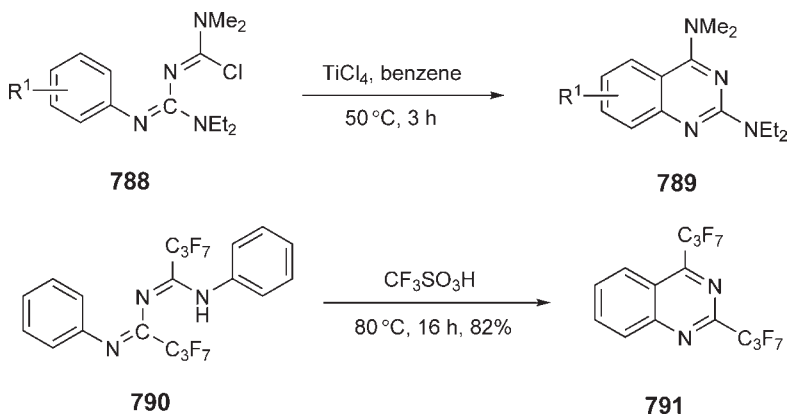
3,4-Dihydroquinazoline 4-acetic acid derivatives have been generated by ring-closure reactions involving Michael addition to α,β -unsaturated esters. For example, ring closure of urea derivatives **783** with sodium hydroxide occurs readily at room temperature to give dihydroquinazolinones **784** <2000TL1147>, while with carbodiimides such as **785**, addition of nucleophiles generates an intermediate amidine **786** which spontaneously undergoes ring closure to the product **787** by amine addition to the α,β -unsaturated ester.



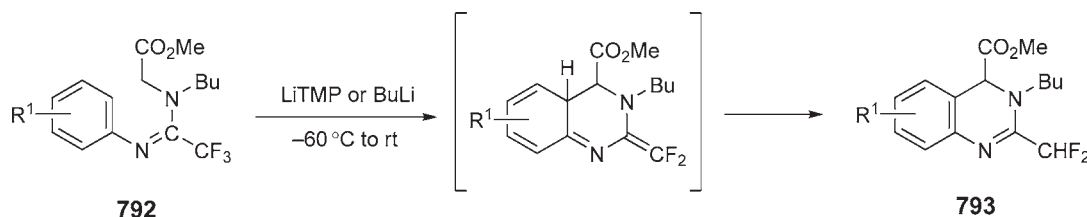
Nucleophiles that have been used include amines <2004BML3379, 2005BML283, 2006BMC3502>, Grignard reagents <2004BML3379, 2004H(63)95>, and alkyl enolates <2004H(63)95>.

8.02.9.2.1(v) Synthesis by cyclization across C(4)-C(4a)

Most examples of this type of cyclization involve thermal reactions <1996HC(55)1, 2005S3059>, although there are some examples of acid- or Lewis acid-initiated cyclization. For example, treatment of the chloro amidine **788** with titanium tetrachloride gave 2,4-diaminoquinazolines **789** <1998H(48)319>, and heating the triazapentadiene **790** in trifluorosulfonic acid gave 2,4-bis(heptafluoropropyl)quinazoline **791** <2003IC2596>.

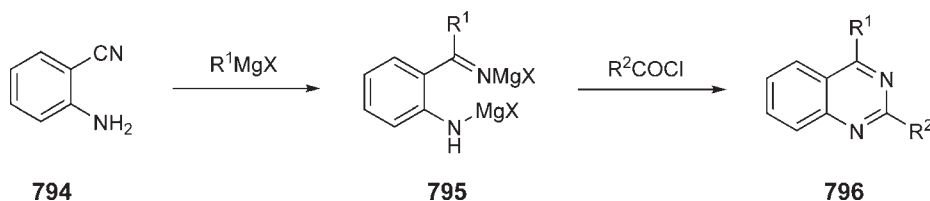


Base-initiated cyclization has also been achieved with trifluoromethyl amidines **792** where ring closure to 3,4-dihydroquinazoline-4-carboxylates **793** was accompanied by loss of fluorine <2000CC1883>.

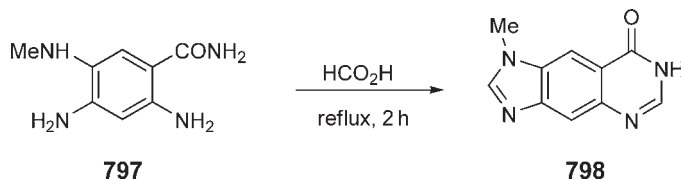


8.02.9.2.1(vi) Synthesis involving C-2 Insertion and cyclization

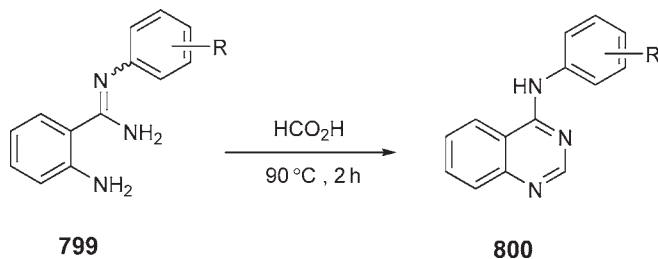
A great variety of synthons can be used to supply C-2, with or without an attached substituent, and to induce the subsequent cyclization to quinazoline derivatives <1996HC(55)1>. For example, 2,4-dialkylquinazolines **796** can be prepared following Grignard addition to the nitrile group of 2-aminobenzonitriles **794** and quenching of the resulting dianion **795** with acid chlorides <1986T3697, 2003OBC367>.



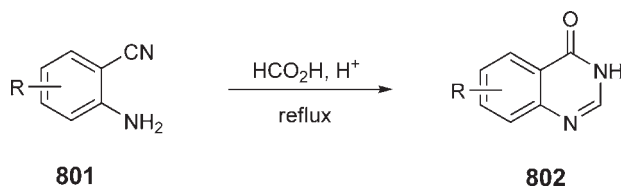
However, perhaps the simplest route to quinazoline derivatives involves the heating of 2-aminobenzamides with formic acid to give 4(3*H*)-quinazolinones, where the formic acid provides the solvent, the C-2 synthon, and the acid catalysis of the ring-closure step. For example, in the synthesis of the imidazoquinazolinone **798**, both the imidazo and pyrimidine rings were formed simply by heating the triamino amide **797** in formic acid for 2 h <1996JME918>.



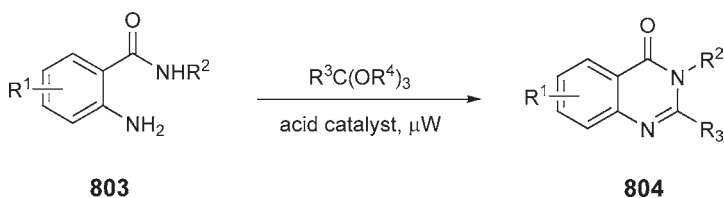
2-Aminobenzamidines **799** can also be readily ring-closed with formic acid as demonstrated by the synthesis of 4-anilinoquinazolines **800** <1998TL1785, 2000T9343>.



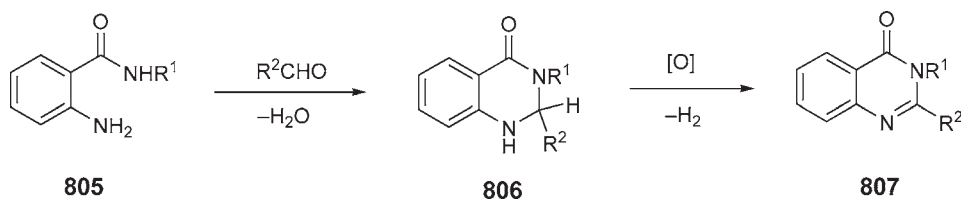
2-Aminobenzonitriles **801** can also be converted to 4-quinazolinones **802** in good yield with formic acid, provided that a strong acid such as sulfuric, hydrochloric, or methanesulfonic acid is also present <1996JHC2051, 2003JME4313, 2005BML1135, 2006JME3544, 2007H(71)39>.



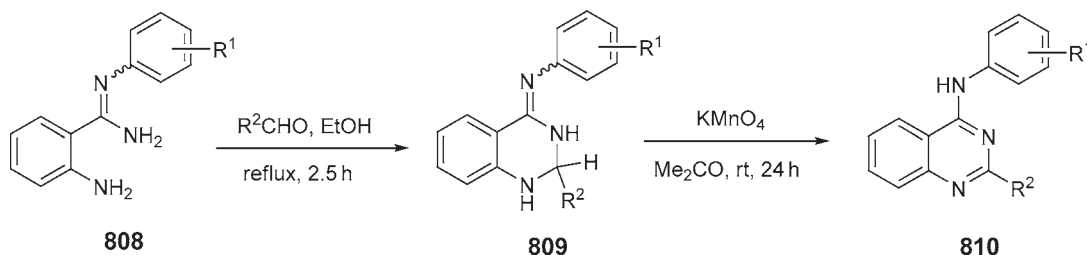
Higher carboxylic acids do not provide quinazoline derivatives quite as readily as formic acid, so when 2-substituted derivatives are required, orthoesters are often used, usually in combination with an acid catalyst <2000SL1670, 2003BMC383, 2003BMC609, 2006JME2440>. A number of microwave-assisted procedures have now been developed for the conversion of 2-aminobenzamides **803** to 4-quinazolinones **804** using orthoesters and a variety of acid catalysts. Catalysts to have been successfully employed under microwave conditions include *p*-toluenesulfonic acid <2003T4757>, sulfuric acid adsorbed on silica gel <2004PS(179)2533>, montmorillonite clay <2004JCM570>, and a mixture of AlCl_3 and ZnCl_2 supported on silica gel <2005SC279>.



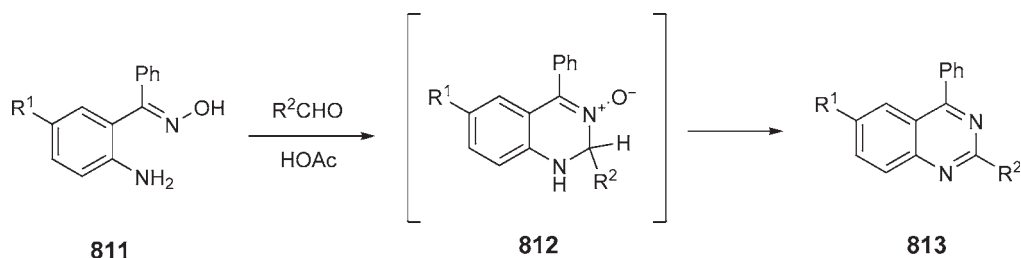
Aldehydes can also be used as C-2 synthons with 2-aminobenzamides, to give 1,2-dihydro-4-quinazolinones **806** which can then undergo dehydrogenation to the fully conjugated system **807**, either spontaneously or under the influence of an added oxidant. Both one-pot and two-step oxidation procedures can be used. Oxidants that have been used in one-pot procedures include cupric chloride <2004TL3475>, and iodine <2004SC2169>, while potassium permanganate <1997TL8445, 2004T9931> and manganese dioxide <2002JFC(118)73> are examples of oxidants that have been added in the second step of two-step procedures. A one-step microwave-assisted procedure using DDQ as the oxidant has also been reported <2000IJB220>.



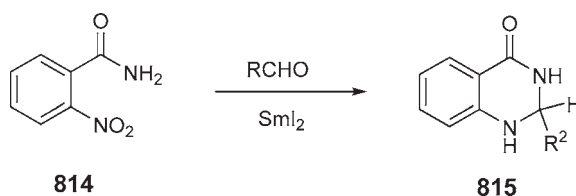
2-Aminobenzamidine **808** can also be combined with aldehydes to give dihydro intermediates **809**, which provide 2-substituted-4-anilinoquinazolines **810**, after oxidation with potassium permanganate in a separate step <2000T9343>.



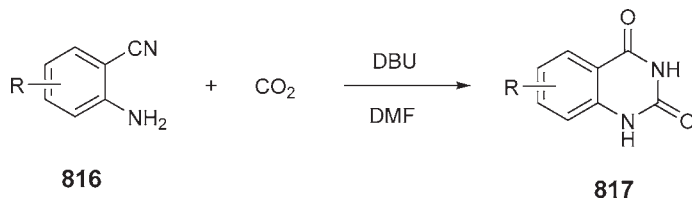
Aldehydes have also been condensed with 2-aminobenzophenone oximes **811**, but in this case an added oxidant is not needed, as loss of water from the *N*-oxide intermediate **812** provides 2-substituted-4-phenylquinazolines **813** directly <2004AP239>.



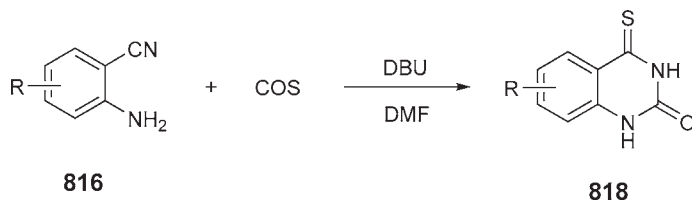
When 1,2-dihydroquinazolines are actually desired as the reaction product, they can often be contaminated with their conjugated analogs due to spontaneous dehydrogenation [<2000JME4479>](#), but this can be avoided under reductive conditions, as demonstrated by the preparation of 2-substituted-1,2-dihydroquinazolines **815** by the reductive condensation of 2-nitrobenzamides **814** with aldehydes in the presence of samarium iodide [<2002JHC1271>](#).



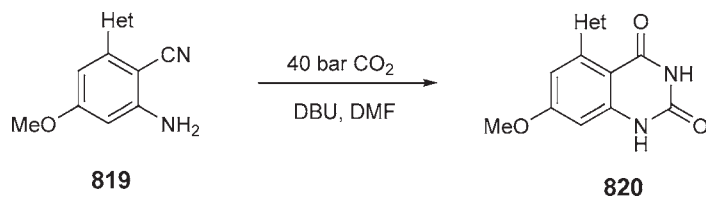
Carbon dioxide can also be used as a C-2 synthon in the synthesis of 2,4-quinazolinediones **817** from 2-amino-benzonitriles **816**. The reaction can be performed under mild conditions using 1 atm of CO_2 with DBU as catalyst in DMF [<2000TL1051, 2000HAC428, 2002T3155>](#). More recently, a modified procedure, using supercritical CO_2 as both solvent and reagent, has also been developed [<2004TL7073>](#).



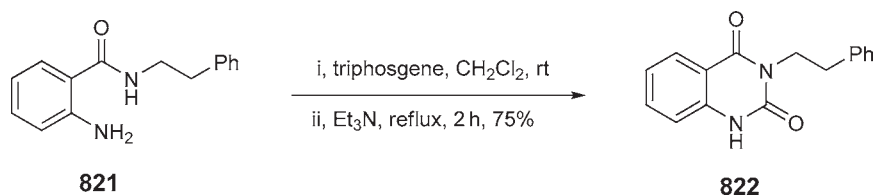
When the carbon dioxide is replaced with carbonyl sulfide, generated *in situ* from carbon monoxide and sulfur, 4-thioxo-2-quinazolinones **818** are produced [<2000HAC428>](#).



The carbon dioxide/DBU procedure has been used synthetically for the synthesis of 5-heterocyclic substituted 2,4-quinazolinediones **820**, although in this case it was necessary to operate at a much higher pressures than for the standard method [<2006H\(67\)489>](#).

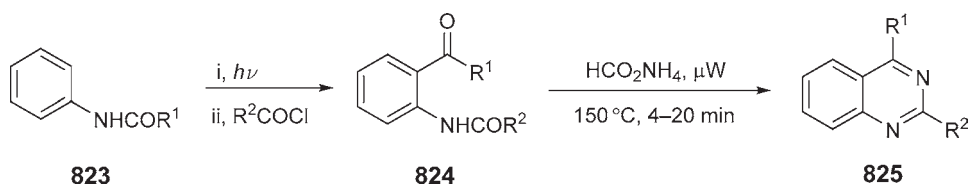


N-Substituted 2,4-quinazolinediones are often prepared by the reaction of substituted 2-aminobenzamides with triphosgene, as demonstrated by the synthesis of the alkaloid precursor **822** <2004MOL609>.

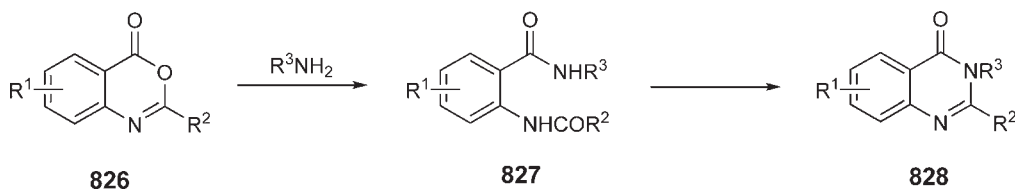


8.02.9.2.1(vii) Synthesis involving N-3 Insertion and cyclization

2,4-Dialkylquinazolines **825** are available by microwave-assisted amination and ring closure of 2-acylamino phenylketones **824** with ammonium formate <2007OL69>. The 2-aminophenyl ketone precursors of the amides **824** are available by a photochemically induced Fries rearrangement of anilides **823**, which enables a variety of different alkyl substituents to be incorporated at the 4-position of the quinazoline <2007OL69>.

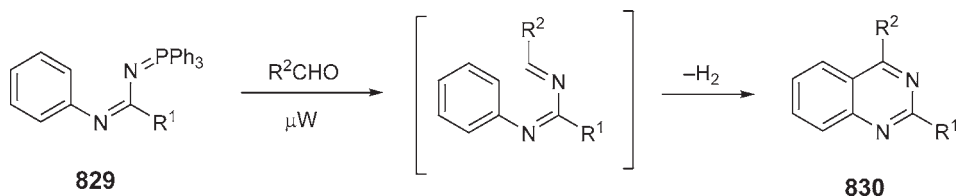


A useful method for the preparation of 2,3-disubstituted-4-quinazolinones **828** involves the reaction between a primary amine and 3,1-benzoxazin-4-ones **826**. Although amidinium salt intermediates are sometimes involved, the reaction normally proceeds through 2-(acylamino)benzamide intermediates **827** which undergo ring closure on heating. The benzoxazine starting materials are normally prepared separately by acylation and cyclodehydration of anthranilic acids <1999JHC563, 2000JHC1369>, although microwave-assisted procedures have now been developed which allow the whole procedure to be performed in a pot process <2004JFC(125)1835, 2005TL1241>.

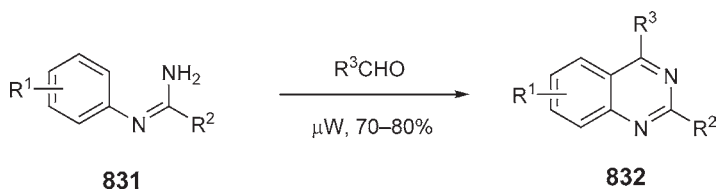


8.02.9.2.1(viii) Synthesis involving C-4 insertion and cyclization

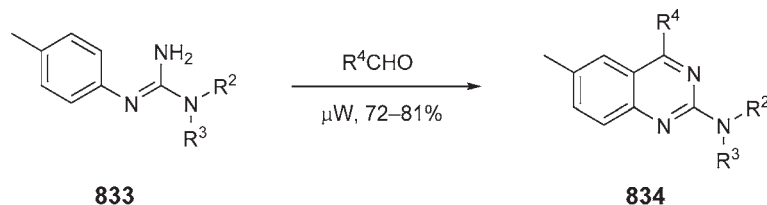
The reaction of aldehydes with *N*-imidoyliminophosphoranes **829** under thermal conditions leads to a mixture of 4-substituted quinazolines and their 3,4-dihydro analogs <1990TL903, 1991T5819>, but when the same reaction is performed under microwave irradiation only the fully aromatic products **830** are obtained <2004SC49, 2004BML5211, 2005T3533>. 4-Substituted quinazolines can also be produced when ketenes are used in place of the aldehydes <2001TL2235>.



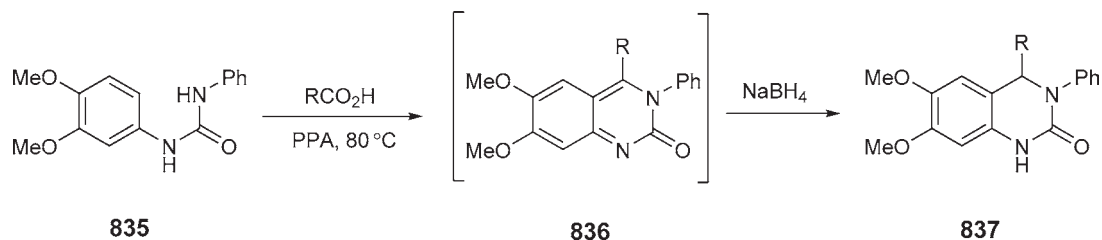
A phosphine-free procedure has now been developed that avoids the need to prepare the iminophosphoranes altogether. Thus, treatment of benzamidines **831** with aldehydes under microwave conditions results in direct formation of 4-substituted quinazolines **832** and benzoquinazolines <2005T3533>.



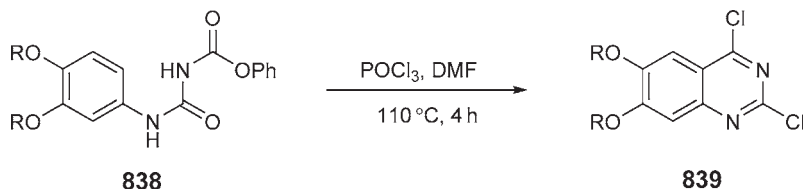
The same microwave procedure has also been used with guanidine derivatives **833** to give 2-amino-4-substituted quinazolines **834** <2005BML2145, 2005T3533>.



Carboxylic acids can also be used as a source of the C-4 atom, and the reaction of a diphenylurea derivative **835** with carboxylic acids in polyphosphoric acid (PPA), followed by treatment of the intermediates **836** with sodium borohydride has been used as a source of 3,4-dihydro-2-quinazolinones **837** <2006H(68)1443>.

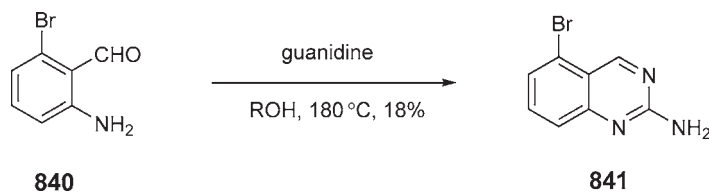


Other sources of C-4 include the Vilsmeier reagent formed from POCl₃ and DMF, which gives 2,4-dichloroquinazolines **839** with *N*¹-aryl-*N*²-(phenoxy carbonyl)urea derivatives **838** <1998BML2891>.

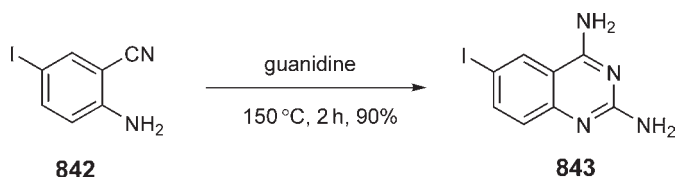


8.02.9.2.1(ix) Synthesis involving C(2)-N(3) and cyclization

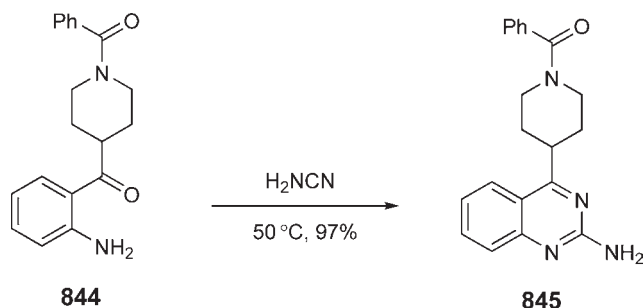
2-Aminoquinazolines can be prepared by the reaction of guanidine with 2-aminobenzaldehydes, although yields are only moderate, as shown by the synthesis of 2-amino-5-bromoquinazoline **841** which occurred in only an 18% yield <2003JA2084>.



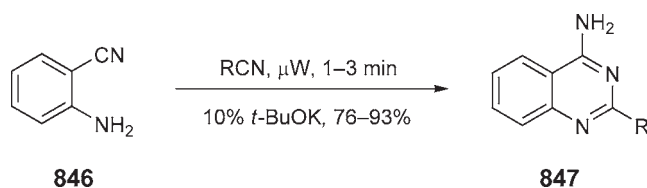
Better results are achieved with guanidine and 2-aminobenzonitriles which give 2,4-diaminoquinazolines in very good yield. For example, 2,4-diamino-6-iodoquinazoline **843** was formed in 90% yield on heating 2-amino-5-iodobenzonitrile **842** with guanidine <2005BMC2637>.



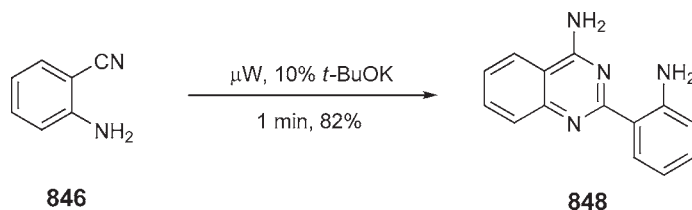
Cyanamide can also be used as a source of the C(2)–N(3) unit, to give 2-aminoquinazolines, and good results can be achieved in condensations with 2-aminoketones [<2000BML1317, 2005JOC8764>](#), as shown by the 97% yield achieved in the synthesis of the 2-amino-4-piperidinyl derivative **845** from the aminoketone **844** [<2000BML1317>](#).



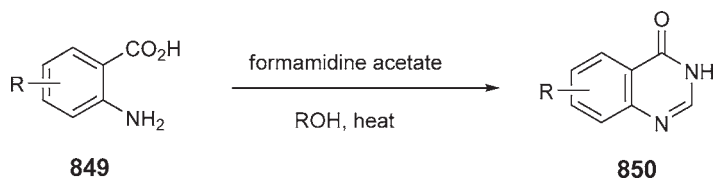
2-Substituted 4-aminoquinazolines **847** can be prepared by combining 2-aminobenzonitriles **846** with nitriles under basic conditions [<2000JME2227, 2005SC2481>](#), and a microwave-assisted procedure is now available that enables these compounds to be produced very efficiently [<2000TL2215>](#).



In the absence of an added nitrile, the 2-aminobenzonitrile undergoes a self-condensation to give 4-amino-2-(2-aminophenyl)quinazoline **848** [<2000TL2215>](#).

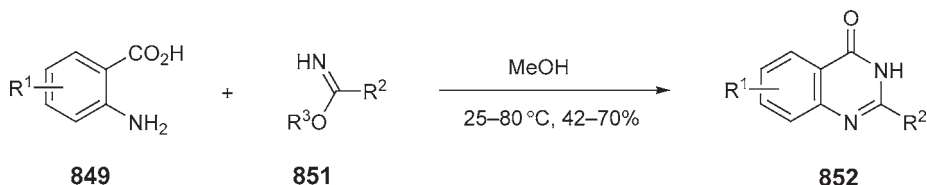


The importance of 2-unsubstituted 4-(arylamino)quinazolines as tyrosine kinase inhibitors [<1999CME825, 2000COR679, 2001CRV2541>](#) has meant that many different syntheses of the 2-unsubstituted 4(3*H*)-quinazolinone precursors have been performed in the period since the publication of CHEC-II(1996). The original Niementowski route to 2-unsubstituted 4(3*H*)-quinazolinones **850** involved heating anthranilic acids **849** with formamide [<1895JPR564>](#), but this procedure is not without its problems [<2004CME2549, 2004S429>](#), and formamidine acetate, usually with an added alcohol solvent, has proved to be synthetically a much better source of the C(2)–N(3) unit [<1986JOC616, 1996JME918, 2004S429, 2005JME744, 2005OPD440, 2006BML1633>](#).

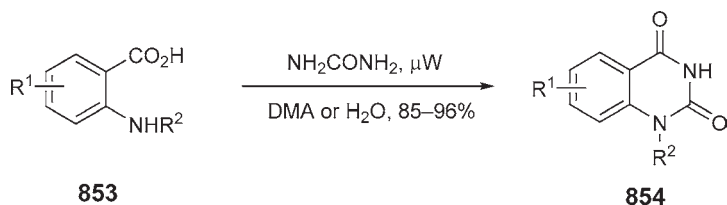


The Niementowski route to 4(3*H*)-quinazolinones has been reinvestigated under microwave-assisted conditions, and significant improvements compared to the thermal method have been achieved <2001HCO337, 2002TL3911, 2003TL4455>. However, perhaps the best microwave-assisted route to 2-unsubstituted 4(3*H*)-quinazolinones is one that uses 3 equiv of formamidine acetate in 1 equiv of formamide as solvent <2004CME2549>. Using this procedure reaction times were significantly shorter than for the thermal method, although in many cases product yields were no greater than for thermal reaction with formamidine acetate in an alcohol solvent <1986JOC616, 2005OPD440>.

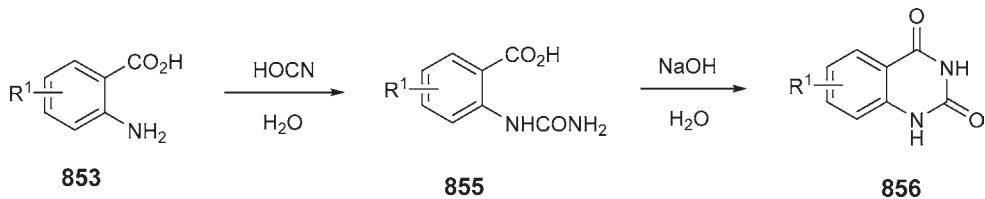
When 2-substituted 4(3*H*)-quinazolinones **852** are desired, the reaction of anthranilic acids with imidates **851** provides a good route to this class of compound <1996JME695, 2001SL1707, 2004JOC6572, 2005T9808>.



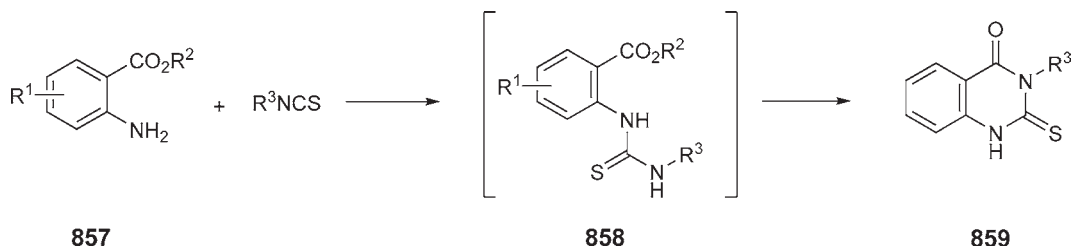
A common method for the preparation of 2(1*H*),4(3*H*)-quinazolin-2(1*H*)-ones consists of the fusion of anthranilic acid derivatives **853** with urea, and a microwave-assisted procedure has now been developed that produces the quinazolin-2(1*H*),4(3*H*)-ones **854** in excellent yields <2005CL1438>.



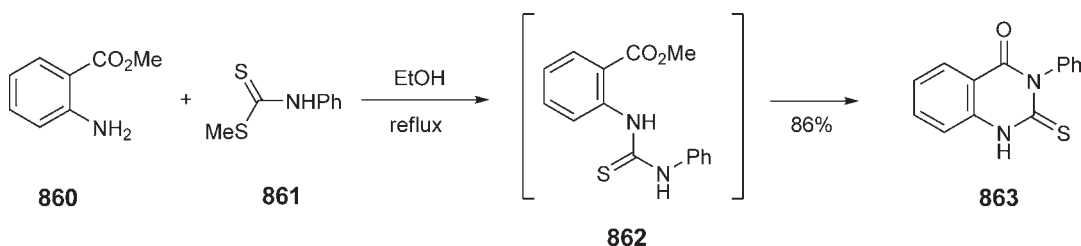
The same microwave procedure can also be performed with potassium cyanate, although not as efficiently as with urea <2005CL1438>. However, nonmicrowave procedures, using sodium or potassium cyanate with acetic acid in water, have produced N-unsubstituted 2,4-quinazolin-2(1*H*),4(3*H*)-ones **856** in excellent yield, after ring closure of the intermediate urea **855** with sodium hydroxide <2002JOC8284, 2003OPD700, 2005GC586, 2005T9375>.



N-3-Substituted 2-thioxo-4-quinazolinones **859** are formed when alkyl or aryl isothiocyanates are reacted with anthranilic acids or esters **857**, <2001JME1710, 2002AP556, 2004JCO584, 2006JME2440>. The intermediate di-substituted thiourea **858** is normally not isolated, but is directly ring-closed *in situ* to the thioxoquinazolinone product **859**. When 3-unsubstituted products are required, benzoyl isocyanate can be used <2000S714>.

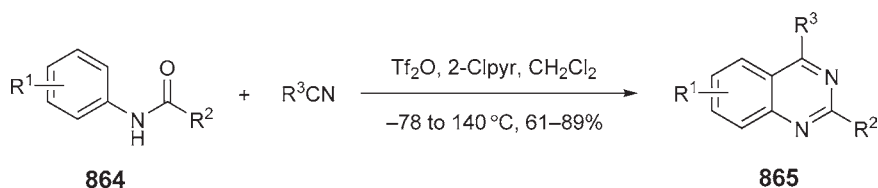


Similar results can be achieved by using cyanothioformamides <2002HAC291, 2002HAC611> or dithiocarbamates **861** <2005BML1877> instead of isothiocyanates, as shown by the synthesis of 2-phenyl-2-thioxo-4-quinazolinone **863** <2005BML1877>. Once again the intermediate thiourea **862** is not isolated.

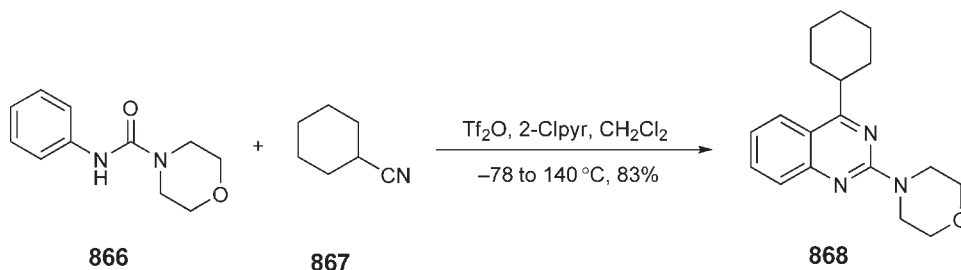


8.02.9.2.1(x) Synthesis involving N(3)–C(4) insertion and cyclization

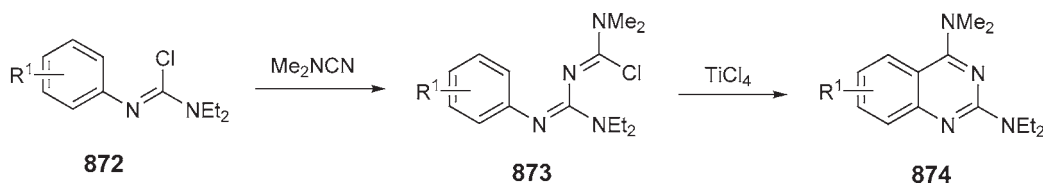
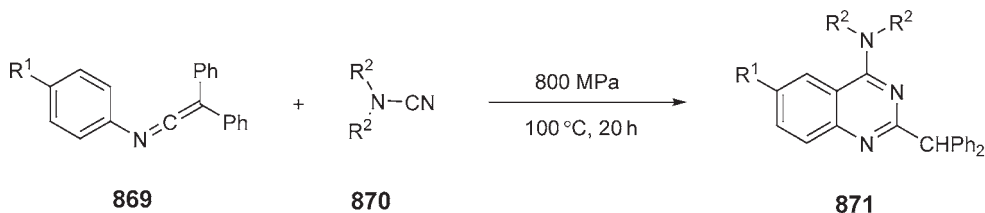
The synthesis of quinazoline derivatives by the addition of N(3)–C(4) fragment units has not previously been a major synthetic route, but 2,4-dialkyl, alkyl/aryl, and diaryl quinazolines **865** are now readily available by a new procedure that involves activation of *N*-arylamides **864** with trifluoromethanesulfonic anhydride and 2-chloropyridine, and subsequent addition of nitriles [<2006JA14254>](#). Either normal or microwave heating can be used to perform the final ring-closure step.



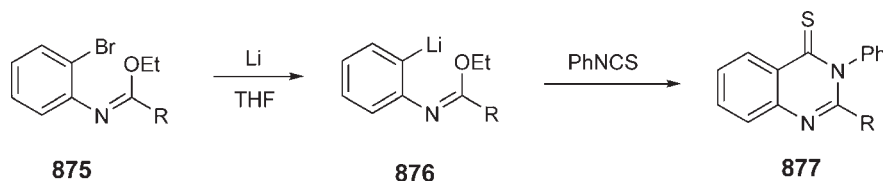
The procedure has also been extended to the synthesis of 2-dialkylamino-4-substituted quinazolines, as shown by the synthesis of 4-cyclohexyl-2-morpholinoquinazoline **868** [<2006JA14254>](#).



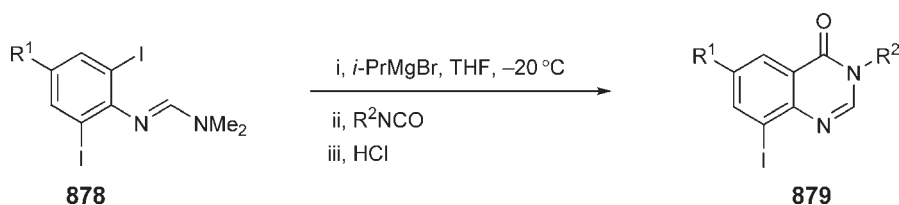
4-Dialkylamino-2-substituted quinazolines **871** are available by reaction of *N*-arylketenimines **869** with *N,N*-disubstituted cyanamides **870** under high pressure [<2002CPB426>](#), while the same compounds, as well as 2,4-(dialkylamino)quinazolines **874**, have been produced by treatment of chloroamidines **872** with *N,N*-dimethylcyanamide, followed by titanium tetrachloride-catalyzed cyclization of the intermediate **873** [<1996H\(43\)1201, 1998H\(48\)319, 2004JHC247>](#). 4-Amino-2-(dialkylamino)quinazolines are similarly produced when cyanamide itself is used [<2000M895, 2002JHC1289>](#).



Isocyanates can be used as the source of the N(3)–C(4) unit by reaction with organometallic intermediates. For example, the reaction of ethyl 2-(bromophenyl)imidates **875** with lithium metal, followed by quenching of the lithiated intermediate **876** with phenyl isothiocyanate gave 3-phenyl-2-substituted 4(3*H*)-quinazolinethiones **877** <1996SC3167>.

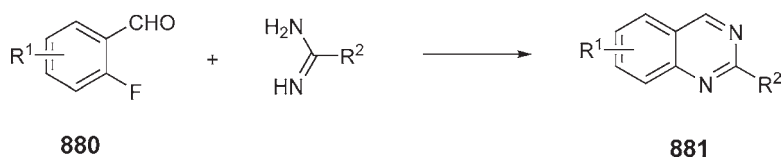


In a related organometallic approach, treatment of the diiodoarylformamidines **878** with isopropylmagnesium bromide gave an organomagnesium intermediate which reacted with a variety of alkyl, allyl, and aryl isocyanates to give 3-substituted-8-iodo-4(3*H*)-quinazolinones **879** <2002OL1819>.

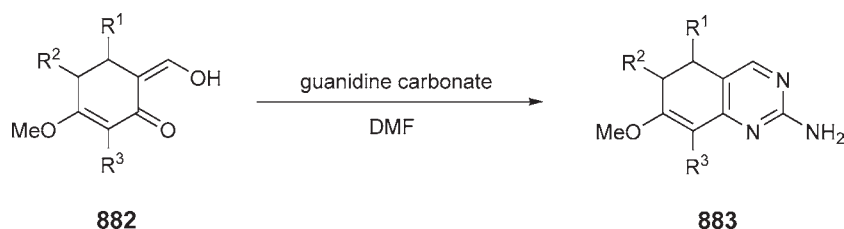


8.02.9.2.1(xi) Synthesis involving N(1)–C(2)–N(3) insertion and cyclization

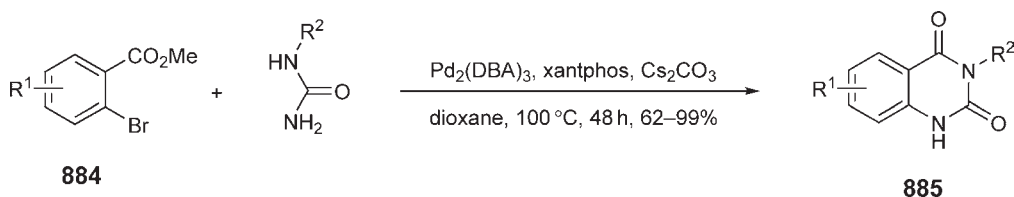
The condensation of amidines and guanidines with 2-halobenzaldehydes **880** provides a short direct route to 2-substituted quinazolines **881**, although sometimes yields are only moderate <1997JHC385, 1999SL1993, 2002CHE1014, 2004CHE888, 2006JME5671, 2006JOC3959>. The reaction has also been performed with ketones <1995JHC1185>, and is a continuation of earlier work with 2-halobenzonitriles which gave 2,4-diaminoquinazolines on reaction with guanidine carbonate <1988JHC1173, 1991JHC1357, 1992JHC915>.



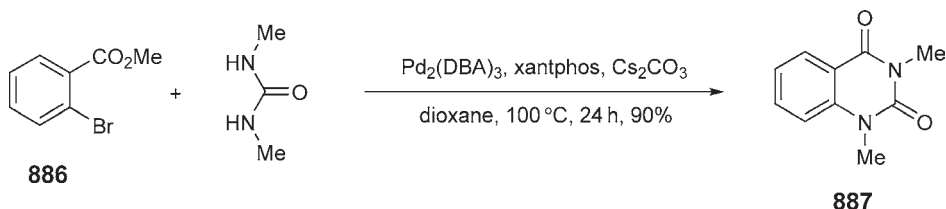
Guanidine carbonate has also been combined with unsaturated 2-hydroxymethyl ketones **882** to give 2-amino-5,6-dihydroquinazolines **883**, which were subsequently dehydrogenated to the fully conjugated 2-aminoquinazolines <2002TL3295>.



ortho-Halobenzoates **884** can be combined with ureas in a tandem palladium-catalyzed arylation–ester amidation sequence to deliver 2,4-quinazolinone products **885** <2006OL5089>. With mono-substituted ureas the reactions are regioselective for formation of the 3-*N*-alkyl (or aryl) isomers.

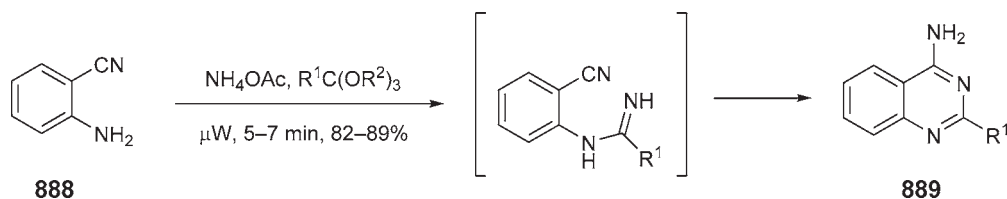


Significant variation of both coupling partners is possible, allowing the synthesis of a diverse array of substituted products. 2-Chlorobenzoates can be used as the ester component, although the bromo analogs are preferred. With *N,N*-dimethylurea a faster reaction was observed, and the 1,3-dimethyl-2,4-quinazolidinedione product **887** was obtained in 90% yield after 24 h [<2006OL5089>](#).

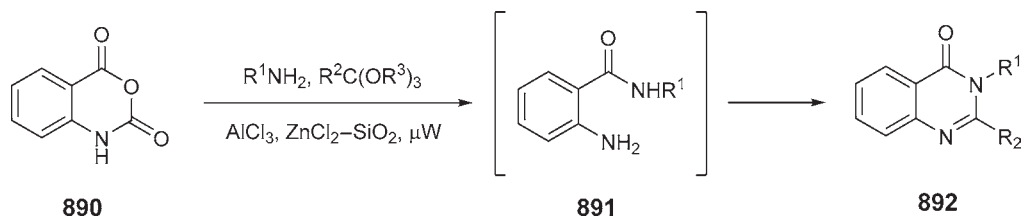


8.02.9.2.1(xii) Synthesis involving separate C-2 and N-3 insertion and cyclization

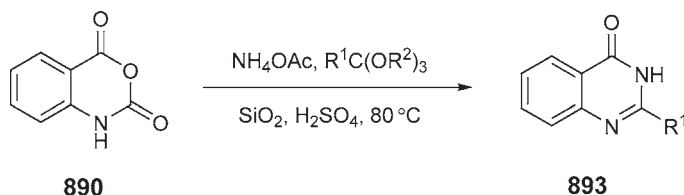
A one-pot procedure for the synthesis of 4-aminoquinazolines **771** from 2-aminobenzonitrile **770**, ammonium acetate, and trialkyl orthoesters under solvent-free microwave conditions has been developed [<2006JHC913>](#). Product yields are comparable to those obtained under thermal conditions, although reaction times are significantly shorter. An attempt to extend the method to include aromatic orthoesters was unsuccessful.



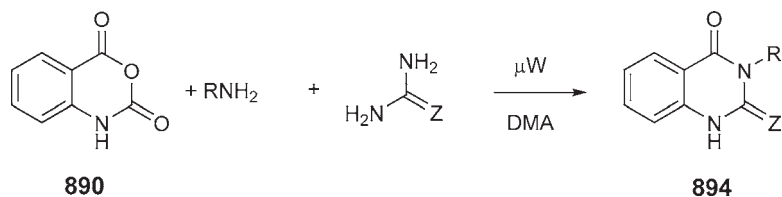
2-Aminobenzamides **891** are often prepared by reaction of amines with isatoic anhydrides [<2001CHE385>](#), and a one-pot procedure for the synthesis of 2,3-disubstituted 4(3*H*)-quinazolinones **892** from isatoic anhydride **890**, primary amines and orthoesters has been developed using AlCl_3 and ZnCl_2 supported on silica gel as the catalyst [<2005SC279>](#). Good yields were obtained under standard thermal conditions, although slightly higher yields were achieved with microwave irradiation [<2005SC279>](#).



An alternative procedure, using sulfuric acid on silica as the catalyst, under solvent-free conditions, gave similar products, and 3-unsubstituted 4(3*H*)-quinazolinones **893** could also be prepared using ammonium acetate as the amine source [<2005TL7051>](#).

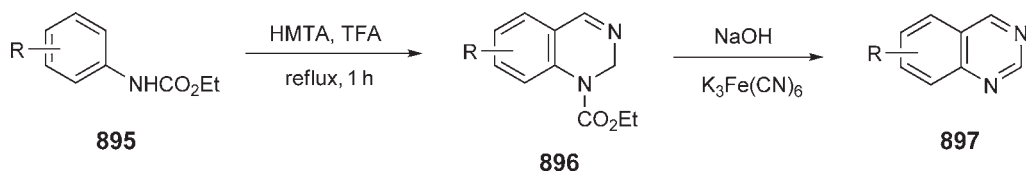


2,4(1*H*,3*H*)-Quinazolinediones **894** ($Z = \text{O}$) and 2-thioxo-4-quinazolinones **894** ($Z = \text{S}$) can be prepared in a one-pot procedure from the condensation of isatoic anhydride, primary amines, and urea or thiourea under microwave irradiation <2003SC415>. No additional catalytic reagents are required, and both alkyl and aryl amines can be used <2003SC415>.

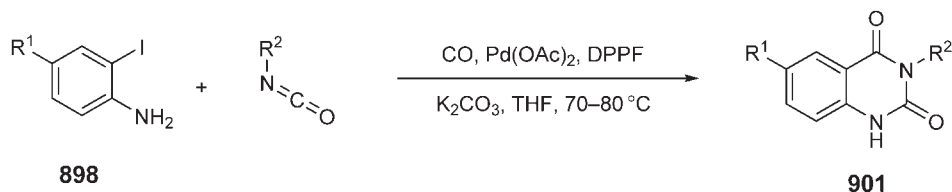
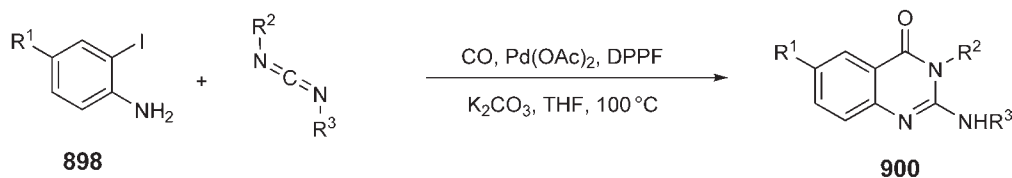
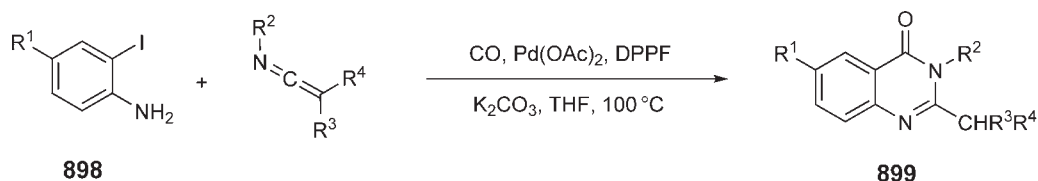


8.02.9.2.1(xiii) Synthesis involving C-2, N-3, and C-4 insertion and cyclization

A new synthetic route to quinazolines from *N*-protected anilines **895** is available using hexamethylenetetramine (HMTA) in trifluoroacetic acid and potassium ferricyanide in aqueous ethanolic KOH. The method affords substituted quinazolines **897** with good selectivity <2006T12351>, and although only moderate yields were initially achieved, good yields have now been obtained under microwave-assisted conditions <2007TL3229>. The method has also been used to prepare benzoquinazolines <2006OL255>.

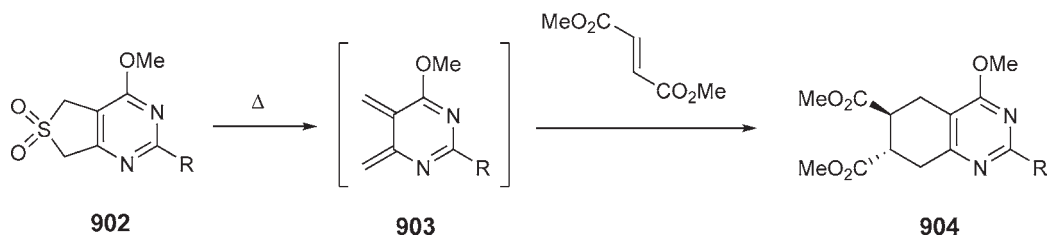


Palladium-catalyzed carbonylation of 2-iodoanilines **898** gives a 2-acylpalladium species that can be reacted with ketenimines to give 2,3-disubstituted-4(3*H*)-quinazolinones **899** <2000JOC2773>. When carbodiimides are used in place of the ketenimines under the same conditions, 2-amino-4(3*H*)-quinazolinones **900** are produced, and when isocyanates are employed, 2,4(1*H*,3*H*)-quinazolinediones **901** are obtained <2000JOC2773>.

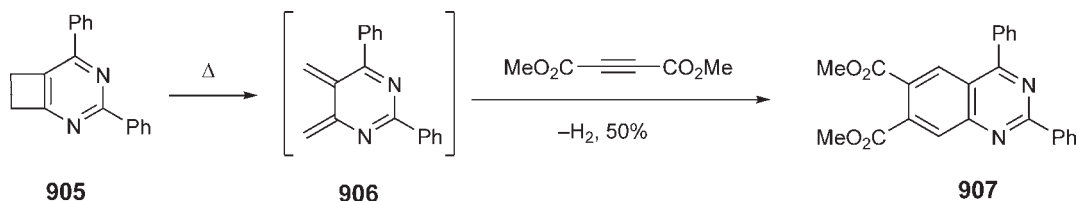


8.02.9.2.2 Pyrimidines as substrates

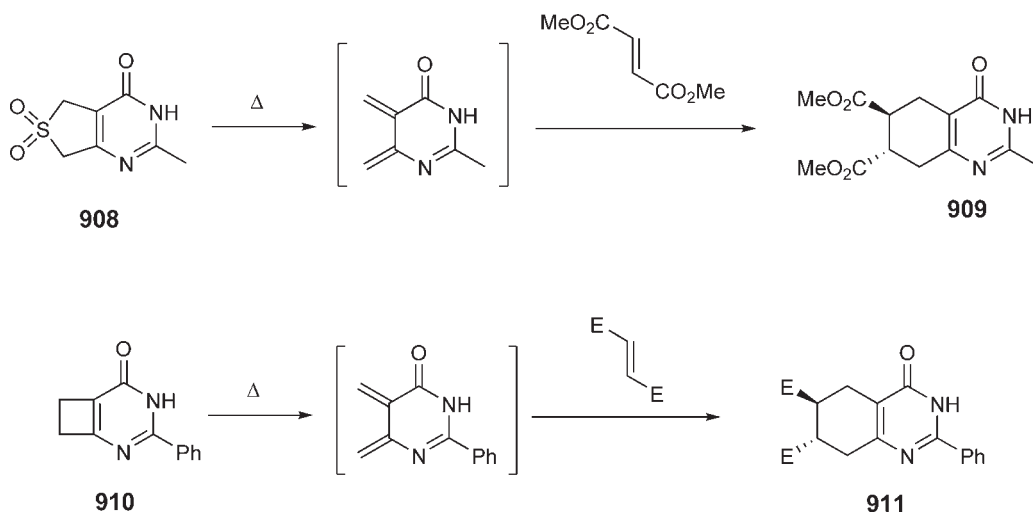
5,6,7,8-Tetrahydroquinazoline derivatives can be prepared by Diels–Alder cycloaddition reactions involving pyrimidine *ortho*-quinonedimethanes <1996T1735, 1997TL4873, 2002MOL507, 2006LOC703>. For example, thermal extrusion of sulfur dioxide from the pyrimidine sulfone **902** occurred when heated in 1,2,4-trichlorobenzene at reflux (*c.* 214 °C), and the resulting quinonedimethane **903** could be trapped with dienophiles such as dimethyl fumarate to give the 5,6,7,8-tetrahydroquinazoline-6,7-diester **904** <1996T1723>.



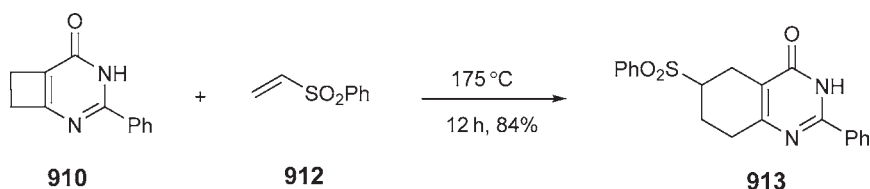
Pyrimidine *ortho*-quinodimethanes can also be produced from 5,6-dihydrocyclobuta[*d*]pyrimidine precursors <1997TL4873, 2002MOL507, 2006LOC703>, and in the case of the 2,4-diphenyl example **905**, trapping of the intermediate **906** with dimethyl acetylenedicarboxylate was accompanied by aromatization to give dimethyl 2,4-diphenylquinazoline-6,7-dicarboxylate **907** in 50% yield <2002MOL507>.



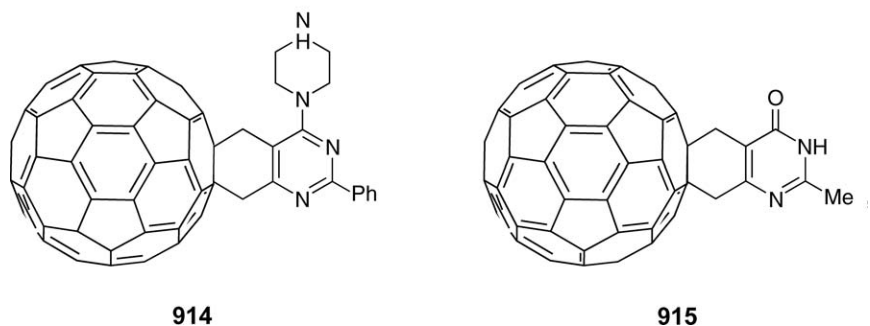
5,6,7,8-Tetrahydro-4(3*H*)-quinazolinones have also been produced from pyrimidinone *ortho*-quinodimethanes, and again both sulfone and cyclobutene precursors have been used <1993SL347, 1996T1723, 2002OL839, 2006EJO2753>. For example, the pyrimidinone sulfone **908** gave the tetrahydrodiester **909** <1993SL347, 1996T1723>, while the cyclobuta[*d*]pyrimidinone **910** gave similar 2-phenyl substituted products **911** <2002OL839>.



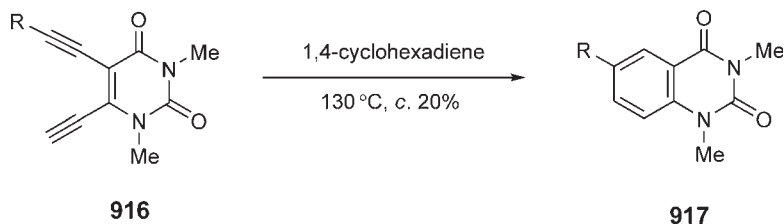
Normally, isomeric mixtures are obtained with monosubstituted dienophiles, but in the case of phenyl vinyl sulfone **912**, 2-phenyl-6-(phenylsulfonyl)-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone **913** was isolated in 84% yield as a single regioisomer <2006EJO2753>.



[60] Fullerene-substituted tetrahydroquinazoline derivatives have also been prepared by reaction of pyrimidine and pyrimidinone *ortho*-quinodimethanes with C₆₀ <1997TL2557, 1997TL4873, 1998JOC6807, 1998T11141, 2005T1423>. Examples of products obtained include the piperazinyl tetrahydroquinazoline **914** and the tetrahydroquinazolinone **915**.

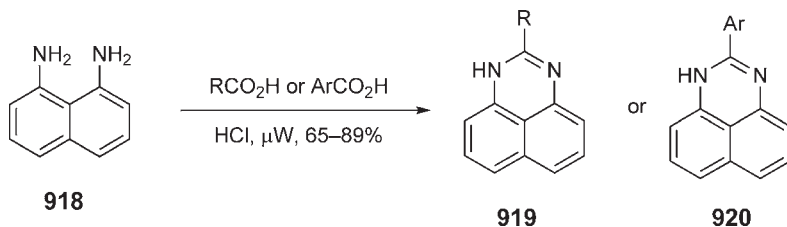


Lastly, 2,4-quinazolinedione derivatives **917** have been prepared by thermal Bergman cycloaromatization of diethynylluracils **916** in 1,4-cyclohexadiene at 130 °C, although the yields were quite low <2000TL8741>.

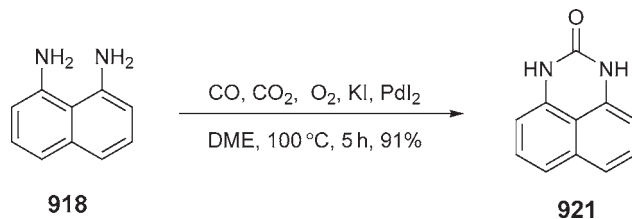


8.02.9.3 Perimidines and Benzo Derivatives

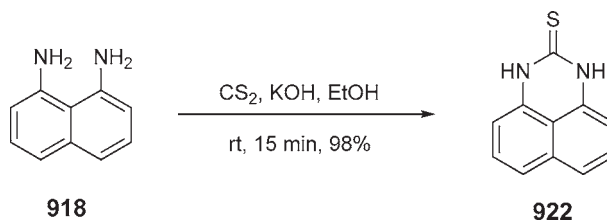
Perimidines are derivatives of 1,8-naphthalenediamine and can be formed from the diamine by ring-closure reactions that involve insertion of a one-carbon unit between the two nitrogen atoms. Carboxylic acids and their derivatives such as acid chlorides, anhydrides, esters and iminoesters, as well as amidines and a variety of other more specialized cyclization agents can be used <1981RCR816, 1995AQ151, 1996CHEC-II(6)93>. While 2-alkylperimidines can be readily obtained by heating aliphatic carboxylic acids with 1,8-naphthalenediamines, more vigorous conditions are normally needed with aromatic carboxylic acids. However, a microwave-assisted procedure has now been developed which works equally well for both aliphatic and aromatic carboxylic acids, and enables both 2-alkyl and 2-arylperimidines **919** and **920** to be prepared in good yield <2005ASJ2411>.



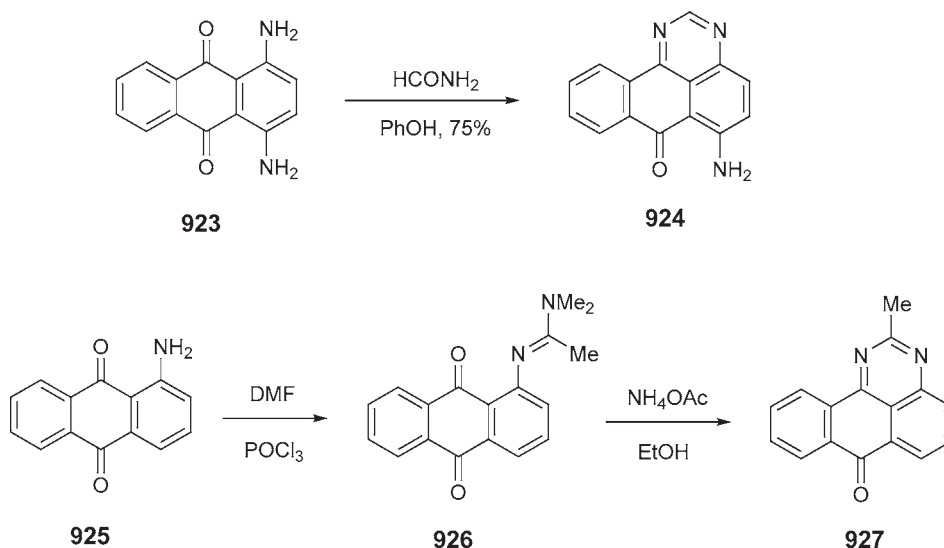
2,3-Dihydro derivatives are readily formed in reactions with aldehydes and ketones, and aldehyde addition products can be dehydrogenated to the fully conjugated heterocycles [<1981RCR816, 1995AQ151>](#). In a new procedure, palladium iodide-catalyzed carbonylation of 1,8-naphthalenediamine **918** gave 2(1*H*)-perimidinone **921** in 91% yield [<2004JOC4741>](#).



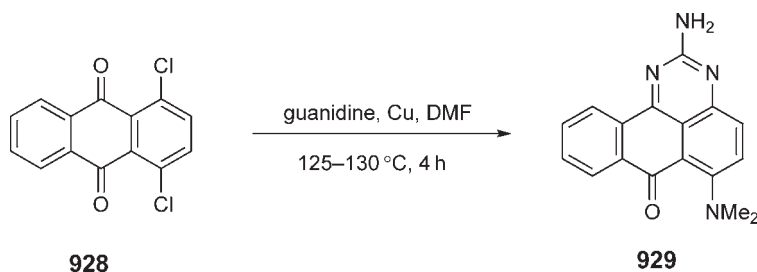
2(1*H*)-Perimidinethiones are readily available by cyclization reactions involving 1,8-naphthalenediamines and carbon disulfide, as shown by the synthesis of the parent compound **922** in 98% yield in just 15 min at room temperature [<2006H\(68\)821>](#).



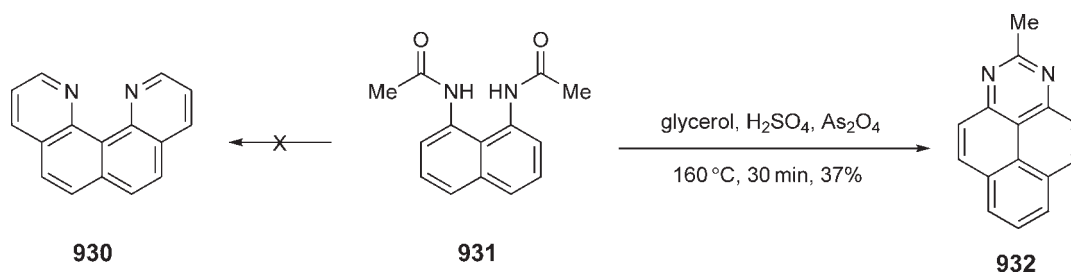
7*H*-Benzo[*e*]perimidin-7-one derivatives have shown promise as antitumor agents, so there has been renewed interest in the synthesis of these heterocycles which are normally produced from anthracenedione precursors. For example, heating 1,4-diamino-9,10-anthracenedione **923** with formamide at reflux in phenol gave 6-amino-7*H*-benzo[*e*]perimidin-7-one **924** in 75% yield [<1993JME38>](#), while synthesis of the 2-methyl derivative **927** was achieved by reaction of 1-amino-9,10-anthracenedione **925** with the Vilsmeier reagent formed with POCl₃ and DMF, followed by a ring-closure step that involved heating the intermediate amidine **926** with ammonium acetate [<2001JME2004, 2005BMC3657>](#).



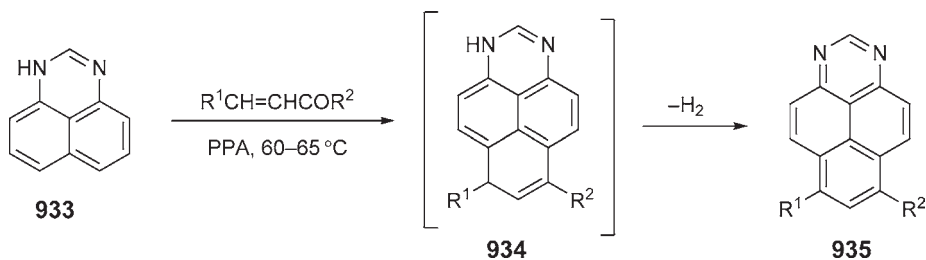
Copper-catalyzed reaction of guanidine with 1,4-dichloro-9,10-anthracenedione **928** in DMF not only resulted in formation of the targeted 7*H*-benzo[*e*]perimidin-7-one ring system, but also resulted in substitution of the second chlorine atom by a dimethylamino group from the DMF solvent to give **929** [<2002BMC1025>](#).



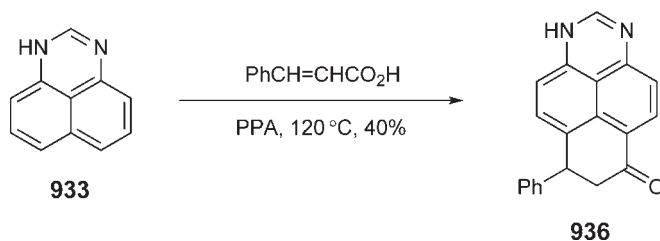
Benzo[*ghi*]perimidines (1,3-diazapyrenes) have also received recent attention and are discussed in a review article on diazapyrenes <2003CHE1417>. The first synthesis of this ring system came during attempted formation of quino[7,8-*h*]quinoline **930** by a Skraup reaction on the naphthalene-1,8-diacetamide **931** <1967JC1415>, and only later was it realized that the product was actually 2-methylbenzo[*ghi*]perimidine **932** and not the expected quinoquinoline **930** <1985TL727>. The reaction is presumed to proceed via initial formation of 2-methylperimidine which then reacts at the 6- and 7-positions with acrolein generated *in situ* from the glycerol.

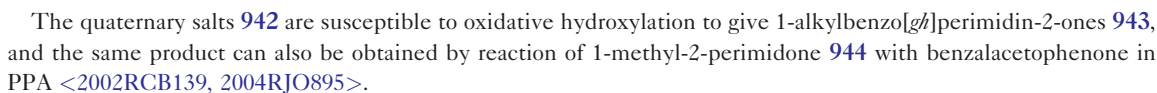
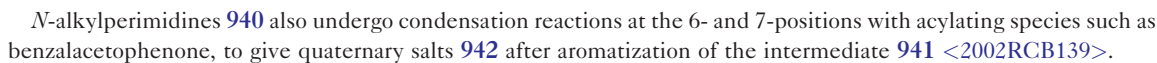
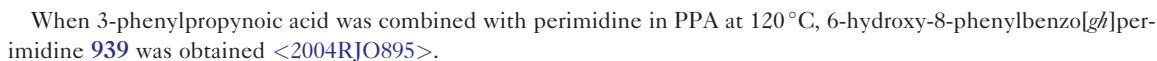


The proposed route is supported by the fact that perimidine **933** does undergo reaction with glycerol in PPA at 180–190 °C to give the parent benzo[*ghi*]perimidine **935** ($R^1 = R^2 = \text{H}$), and with other α,β -unsaturated ketones in PPA at 60–65 °C to give substituted benzo[*ghi*]perimidine derivatives **935** <1997CHE1367, 2002CHE968, 2003CHE1417>.



The reaction between perimidines and α,β -unsaturated ketones can also be achieved under basic conditions, although much harsher conditions, such as sodium glycolate in ethylene glycol, at 180–185 °C are required <2002CHE257>. Cinammic acids can also be condensed with perimidine **933** in PPA to give 7,8-dihydro-6-perimidinones **936** <2002RCB860>, but when the analogous acid chlorides are used with AlBr_3 under Friedel–Crafts reaction conditions, dearylation of the intermediate **937** occurs to give 6-hydroxybenzo[*ghi*]perimidine **938** <2001CHE1046, 2002RCB860>.



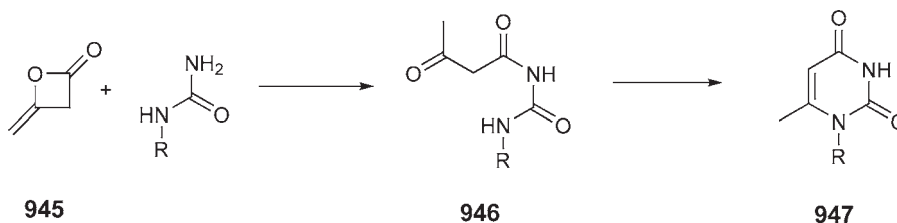


8.02.10.1 Pyrimidines

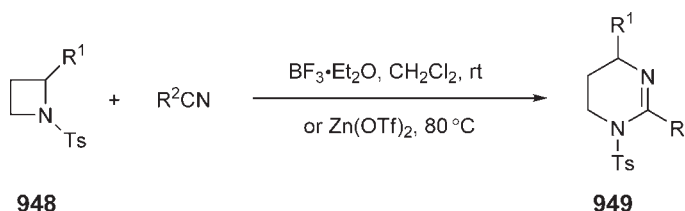
Pyrimidines have been obtained after transformation of other monoheterocycles, or from fused pyrimidine heterocycles in reactions in which the pyrimidine ring is set free in ring-opening or elimination reactions.

8.02.10.1.1 Ring synthesis by transformation of a four-membered ring

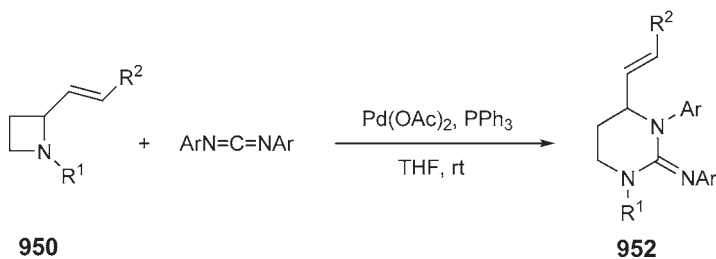
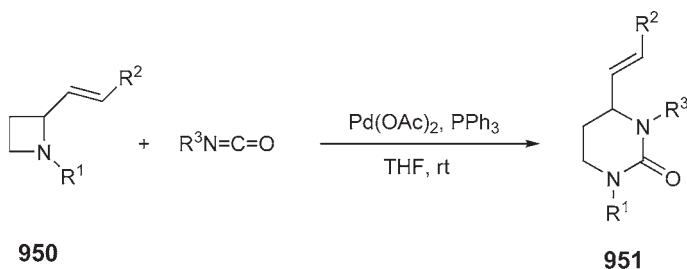
6-Methyluracils **947** are readily prepared by reaction of ureas with diketene **945** in acetic acid, and although mixtures of products are obtained with substituted ureas, this procedure has been used synthetically to prepare a variety of 1-substituted and 1,3-disubstituted 6-methyluracils, using both solution- and solid-phase procedures <2000TL1487, 2003CPB1025, 2004JME1259>.



Tetrahydropyrimidines **949** are produced by the formal [4+2] cycloaddition of *N*-tosylazetidines **948** with nitriles under the influence of boron trifluoride or zinc triflate catalysis <2004OL4829, 2005JA16366, 2006TL5393>.



Tetrahydro-2-pyrimidinone **951** derivatives are produced by the palladium-catalyzed reaction between 2-vinylazetidines **950** and isocyanates, while tetrahydro-2-pyrimidinimines **952** can be prepared under similar conditions using diarylcarbodiimides <2001SL914>.



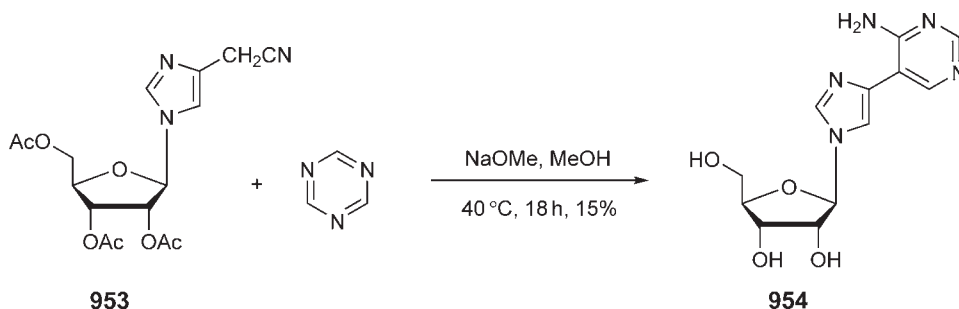
8.02.10.1.2 Ring synthesis by transformation of a five-membered ring

The synthesis of pyrimidines by transformation of a five-membered ring is not a general route and only limited examples are known <1994HC(52)1, 1996CHEC-II(6)93>.

8.02.10.1.3 Ring synthesis by transformation of a six-membered ring

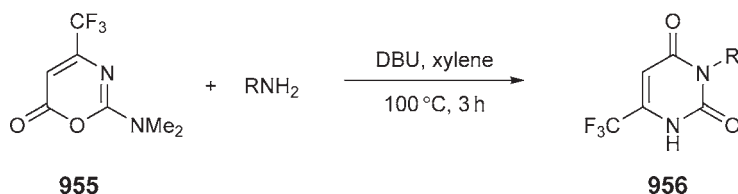
8.02.10.1.3(i) Triazines

1,3,5-Triazine reacts with compounds having an activated methylene group to give 4,5-disubstituted pyrimidines <1994HC(52)1>. Nitriles give 4-amino-5-substituted pyrimidines <1977LA537, 1994AP533>, although this procedure has not received a lot of synthetic attention, probably due to low product yields. For example, a recent synthesis only reported a 15% yield for the conversion of the nitrile **953** to the imidazole nucleoside derivative **954** <2005OL63>.

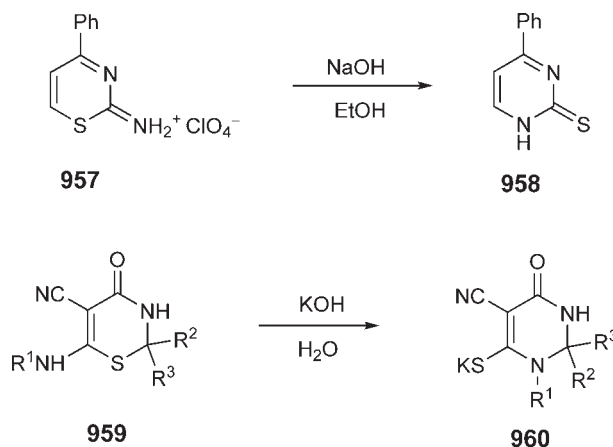


8.02.10.1.3(ii) Oxazines and thiazines

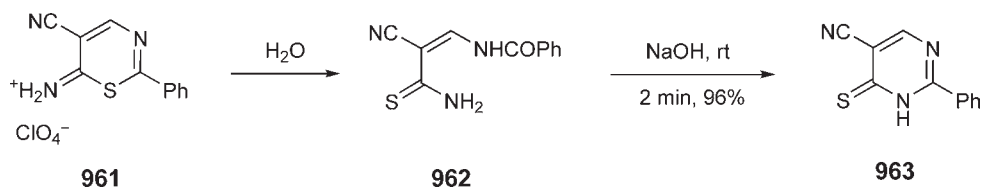
1,3-Oxazines and 1,3-thiazines have been used quite extensively as substrates in pyrimidine syntheses <1994HC(52)1>, and an improved procedure for the synthesis of 6-trifluoromethyluracil derivatives **956** from 2-dimethylamino-4-trifluoromethyl-1,3-oxazine-6-one **955** has been developed using DBU in xylene <2000USP6140270, 2002USP6355796>.



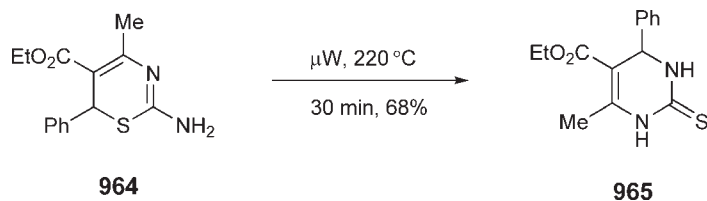
Rearrangement reactions involving 1,3-thiazines are often very facile. For example, reaction of 2-imino-4-phenyl-2*H*-1,3-thiazinium perchlorate **957** with NaOH at room temperature gave 4-phenylpyrimidine-2(1*H*)-thione **958** <2004CHE1595>, while treatment of 6-amino-2,3-dihydro-1,3-thiazin-4(1*H*)-ones **959** with KOH readily gave the potassium salt of the dihydropyrimidinone **960** <2005HAC426>.



In the case of the 6-iminium salt **961**, it was possible to isolate the ring-opened intermediate **962** on treatment with water, but this rapidly ring-closed to the pyrimidethione **963** on treatment with NaOH at room temperature <2003H(60)2273>.

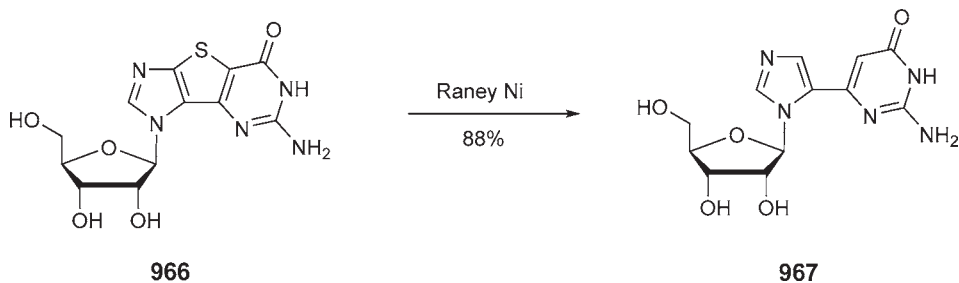


Microwave technology has also been used for the Dimroth rearrangement of the aminothiazine **964** to the pyrimidinethione **965**. The optimized conditions involved heating a solution of the thiazine **964** in toluene together with a silicon carbide heating element at 220 °C for 30 min to provide a 68% product yield after recrystallization <2006JOC4651>.



8.02.10.1.4 Ring synthesis from a fused pyrimidine with a five- or six-membered ring

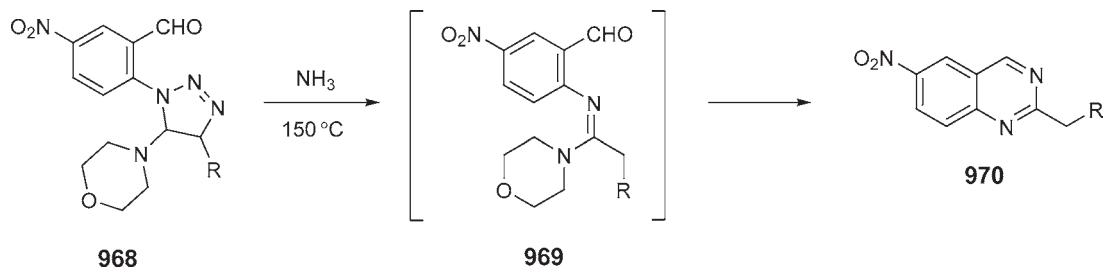
A number of pyrimidines fused to five- or six-membered rings have been degraded to substituted pyrimidines and many of these reactions have been summarized elsewhere <1994HC(52)1>. A recent example used Raney nickel to remove a sulfur atom from the imidazo[4',5':4,5]thieno[3,2-*d*]pyrimidinone **966** <2001OL3209, 2002JOC3365>.



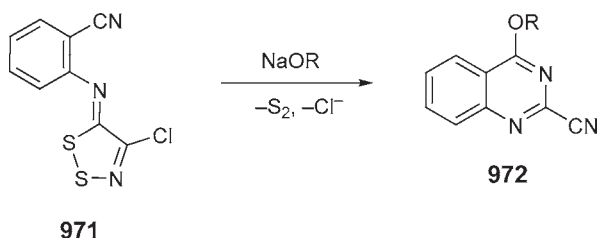
8.02.10.2 Quinazolines

8.02.10.2.1 Ring synthesis by transformation of a five-membered ring

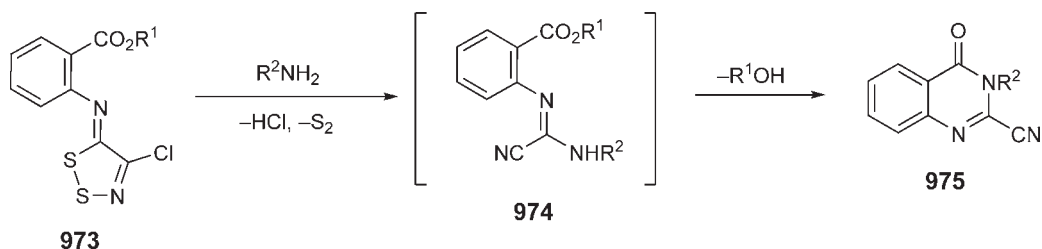
2-Substituted quinazolines **970** have been prepared by treatment of dihydrotriazolines **968** with ammonia, in a process which involves initial thermal ring opening to an amidine **969**, and cyclocondensation of the ammonia with the amidine and carbonyl groups <1999J(P1)421>.



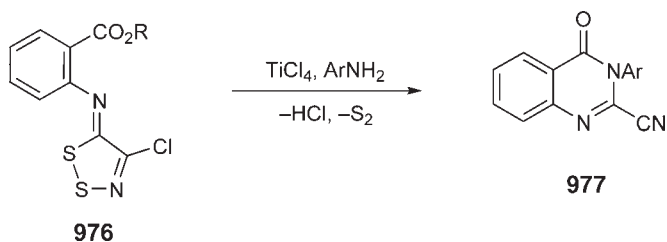
A novel route to 4-alkoxy-3-cyanoquinazolines **972** is available by treatment of *o*-cyano-*N*-arylimino-4-chloro-5*H*-1,2,3-dithiazole **971** with alkoxide <1996J(P1)2857, 1998T6475>. The reaction proceeds via initial attack of alkoxide on the nitrile group. The starting imino compounds are prepared by reaction of anthranilonitriles with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt).



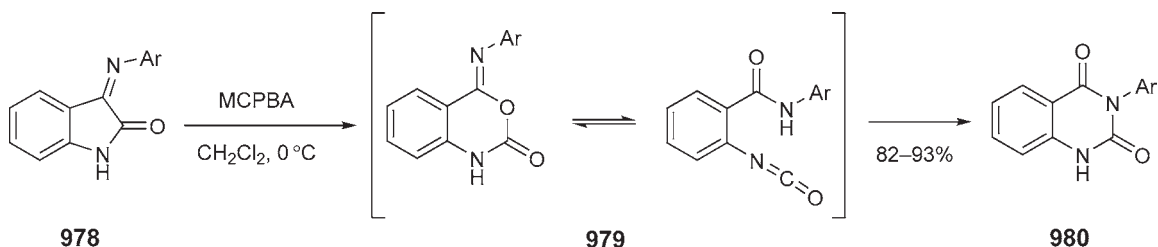
2-Cyano-4-quinazolinones (4-oxo-3,4-dihydro-2-quinazolinecarbonitriles) **975** are available from 2-[*N*-(chlorodithiazole)imino]benzoate esters **973** by reaction with primary aliphatic amines at room temperature <1998JHC659, 2002H(57)1471, 2002TL3993, 2005TL7477>.



Arylamines do not react with the chlorodithiazole intermediates under the standard conditions, but successfully give nitriles **977** when activated by a Lewis acid such as titanium tetrachloride <2002SL1423>.



3-Aryl-2,4-quinazolinones **980** can be prepared from 3-arylimino-2-indolinones **978** by oxidation with *m*-chloroperbenzoic at 0 °C <2000TL5265>. The reaction proceeds through benzoxazinone and isocyanate intermediates **979**.

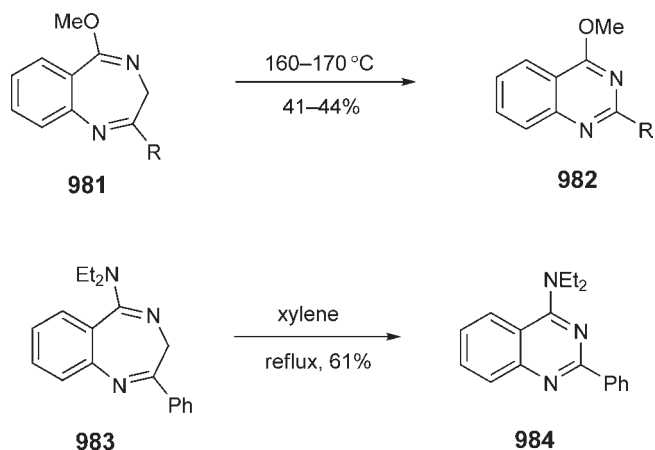


8.02.10.2.2 Ring synthesis by transformation of a six-membered ring

The synthesis of quinazoline derivatives by ring-opening and ring-closure reactions involving isatoic anhydrides and 3,1-benzoxazin-4-ones is covered in [Section 8.02.9.2](#).

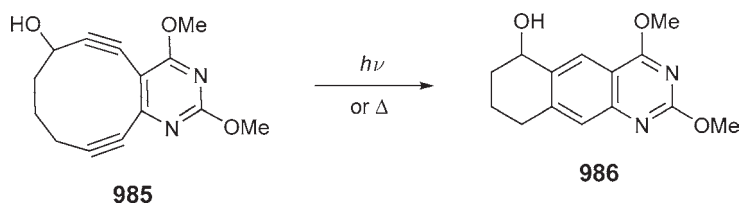
8.02.10.2.3 Ring synthesis by transformation of a seven-membered ring

4-Substituted quinazoline derivatives can be prepared by thermal ring contraction of 3*H*-1,4-benzodiazepines <1999H(51)2407>. Both 5-methoxy **981** and 5-diethylamino-3*H*-1,4-benzodiazepines **983** have been converted to the analogous 4-substituted quinazolines **982** and **984**.



8.02.10.2.4 Ring synthesis by transformation of a 10-membered ring

Bergman cyclization of the enediyne alcohol **985** gave the tetrahydrobenzoquinazoline **986**, both thermally and photochemically in isopropanol, while the analogous ketone only showed efficient thermal cyclization [<2000OL3761>](#).



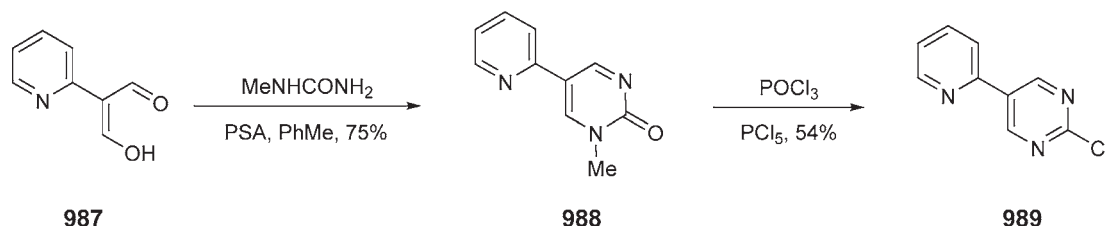
8.02.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

A wide variety of synthetic routes to pyrimidine, quinazoline, and perimidine derivatives have been described in various sections of this chapter. While ring synthesis has traditionally been, and still is, the major synthetic route, large advances in metal-catalyzed amination and cross-coupling chemistry mean that the modification of existing substrates has become a much more feasible approach. Therefore, the best choice of synthetic route to any particular compound or class of compound is not straightforward and depends upon a number of different factors that are continually changing. The cost of raw materials and reagents, the number of synthetic steps, the stability, toxicity, and ease of manipulation of intermediates are all factors that must be considered. For example, while Stille cross-coupling reactions often proceed in good yield with pyrimidine substrates, toxicity issues mean that other cross-coupling procedures are often much more favored.

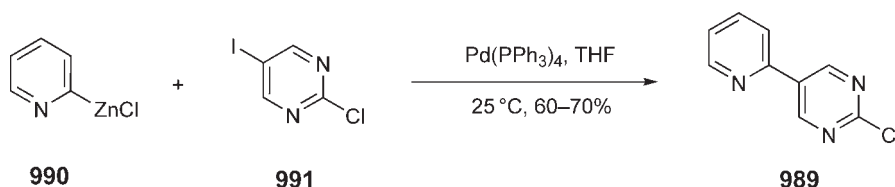
The purpose of the synthesis also has a bearing on the type of procedure chosen. Thus, in medicinal chemistry, synthetic procedures that allow for the greatest compound diversity as late as possible in the synthesis are desirable, but these may not be the optimum procedures once the final drug candidate is identified. Additionally, procedures that require chromatography for product purification may be perfectly acceptable on a laboratory scale, but are often undesirable on an industrial scale. Legal issues can also influence the choice of synthetic procedure if the preferred route is covered by a competitors' patent. Therefore, it is not possible to say categorically that one synthetic route is superior to another until all of the various factors have been fully assessed, and even then the result is only valid for that point in time, as a new or improved procedure may appear at any time.

8.02.11.1 Synthesis of Pyrimidines

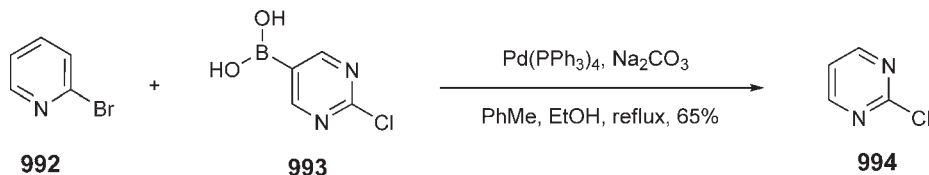
Factors influencing the choice of synthetic routes to pyrimidines depend very much upon the substitution pattern of the desired product. For pyrimidines unsubstituted at the 4- and 6-positions, a two-component ring synthesis reaction involving a 1,3-dialdehyde and a urea or amidine derivative is the most straightforward route, but only if the dialdehyde is readily available. For example, synthesis of 2-chloro-5-(2-pyridyl)pyrimidine **989**, an intermediate in the synthesis of a selective PDE-V inhibitor, was achieved in two steps in 40% overall yield by condensation of 2-(2-pyridyl)malondialdehyde **987** with methylurea, followed by demethylation/chlorination of the pyrimidinone **988** with a mixture of POCl_3 and PCl_5 <2007OPD237>.



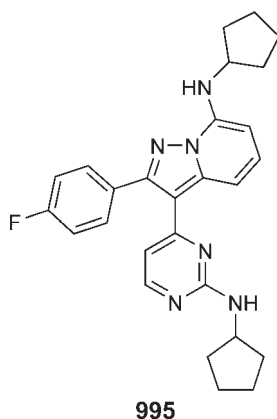
However, while this procedure was acceptable on a laboratory scale, it was unsuitable for scale-up due to difficulties with the preparation of the dialdehyde **987** in bulk quantities. Therefore, an alternative procedure was developed that involved a Negishi cross-coupling approach. Thus, coupling of 2-pyridylzinc chloride **990** and 2-chloro-5-iodopyrimidine **991** in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ was able to be achieved in 60–70% yield with a product purity for **989** of greater than 95% <2007OPD237>.



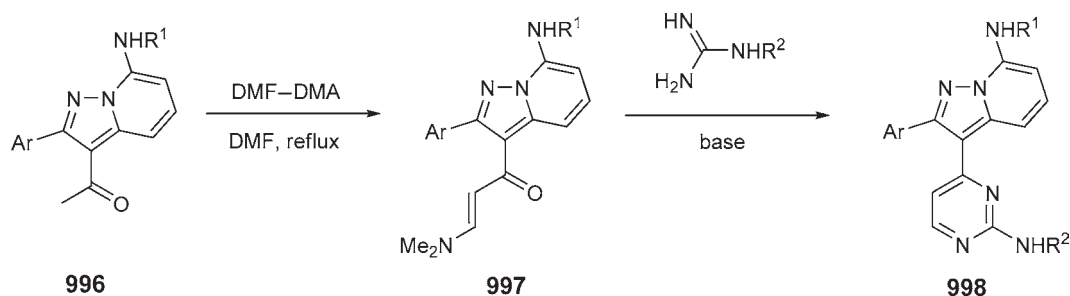
An alternative Stille approach was not considered due to concerns about the toxicity of tin, and an attempted Kumada coupling between 2-pyridylmagnesium bromide and 5-iodo-2-chloropyrimidine **991** in the presence of $\text{Ni}(\text{Cl}_2)\text{DPPF}$ failed to give the desired product. An attempted Suzuki coupling with 2-bromopyridine **992** also failed, due to the deboronation of 2-chloropyrimidine-5-boronic acid **993**, which gave 2-chloropyrimidine **994** as the major product <2007OPD237>.



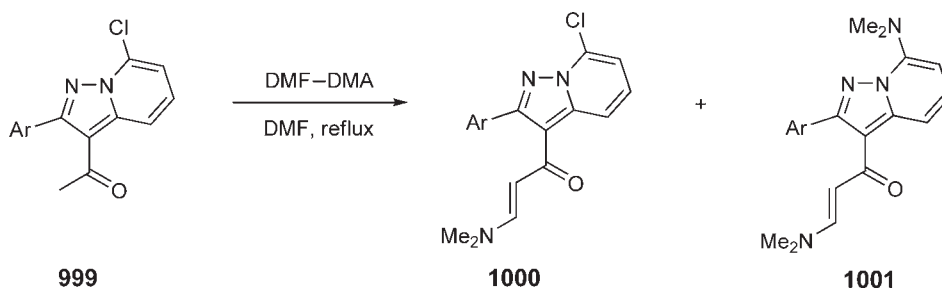
Pyrimidines substituted at the 4-position can be prepared by a number of different routes, as described in Section 8.02.9.1, so deciding upon the best synthetic method is often determined by a number of other factors, including both the nature and placement of other substituents. For example in the synthesis of novel analogs of the antihypertensive agent GW3733 **995**, three different synthetic procedures were successfully utilized for attachment of the 2-amino-pyrimidine group to the pyrazolo[1,5-*a*]pyridine core <2003T9001, 2005BMC5346>.



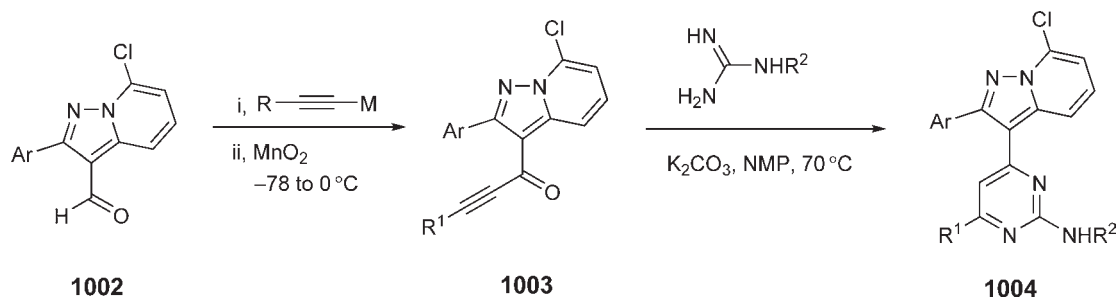
The first procedure involved starting with the methyl ketone **996**, formation of the enamino ketone **997**, and condensation with substituted guanidine derivatives to give the desired products **998**, with substituent variation on the pyrimidine amino group.



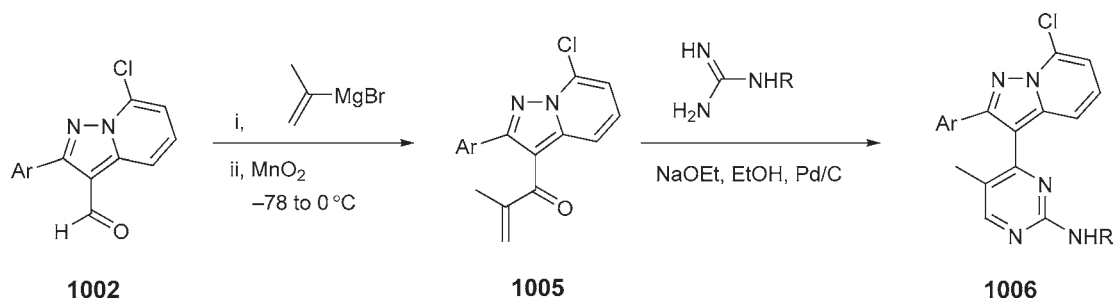
In order to introduce substituent variation on the amino group at the pyrazolo[1,5-*a*]pyridine 7-position, a modified procedure was investigated where a 7-chloro substituent was carried through the synthesis. However, this procedure was compromised by the fact that dimethylamine displacement of the chlorine also occurred during formation of the enamino ketone **1000**, giving the dimethylamino compound **1001** as a major by-product <2003T9001, 2005BMC5346>.



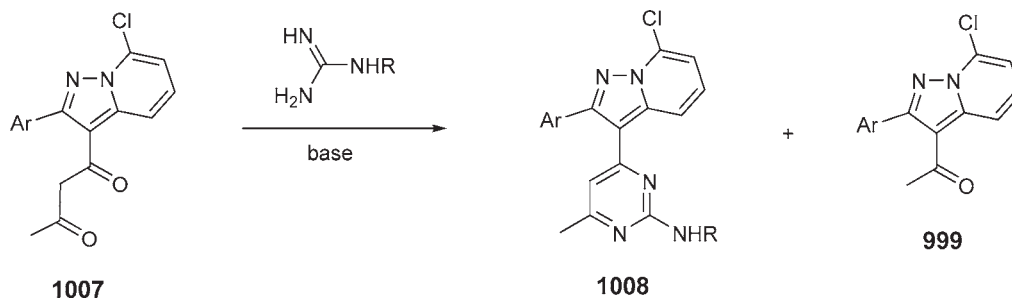
The pyrimidine synthesis was therefore changed to the alkynyl ketone route as the appropriate precursors could be formed under much milder conditions. Thus, treatment of the chloro aldehyde **1002** with ethynyl Grignards or lithium species at low temperature, followed by mild oxidation with manganese dioxide, gave the desired chloro alkynyl ketones **1003**, which could be successfully converted to the pyrimidine products **1004**, by condensation with substituted guanidines, without displacement of the chlorine atom <2003T9001, 2005BMC5346>.



While the alkynyl ketone route occurs under mild conditions, and can provide 4-substituted pyrimidines both substituted and unsubstituted at the 6-position, it cannot provide products substituted at the 5-position. However, this can be achieved by use of an oxidative enone cyclization, as demonstrated by the synthesis of the 3-(5-methylpyrimidinyl)pyrazolo[1,5-*a*]pyridine **1006** from **1002**, where air oxidation of the initial adduct was catalyzed by the addition of palladium on carbon <2003T9001>.



The diketone **1007** was also investigated but only low yields of the product **1008** were obtained. Instead, fragmentation back to ketone **999** was found to be a major route.

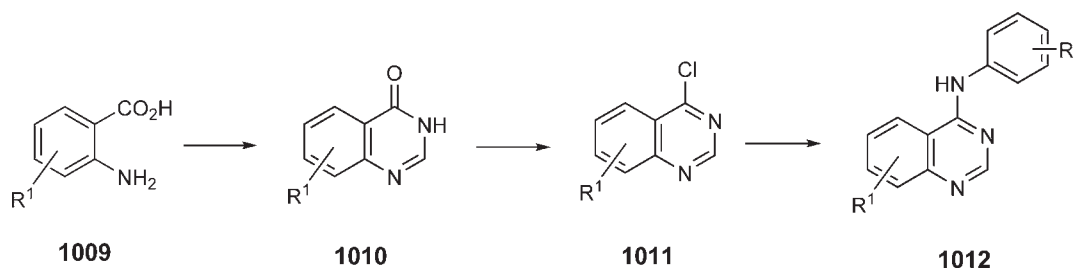


Thus of the five different synthetic procedures investigated above, three were found to be successful, and since each of them was the optimum procedure for the appropriate product substitution pattern, it is not possible to say that any one procedure is superior to the other.

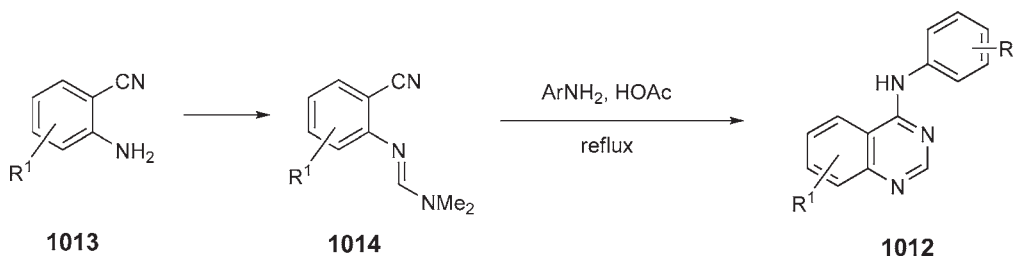
For the synthesis of most pyrimidines the choice of synthetic route is not between different methods of ring synthesis, as above, but between ring synthesis and the modification of existing substituents. Since a large number of pyrimidine derivatives are commercially available, the latter route is particularly attractive in many cases. For example, halogenated pyrimidines such as 2,4-dichloro-, 4,6-dichloro-, 2,4,6-trichloro-, and 5-bromo-2,4-dichloropyrimidine are all readily available, and a lot of recent effort has gone in to investigations of their selective functionalization under a number of amination, alkoxylation, and metal-catalyzed cross-coupling procedures, using both conventional and microwave-assisted conditions <2005T2245, 2005TL3977, 2006JHC127, 2006T10055>. Alkenyl and alkynyl derivatives are readily prepared by cross-coupling procedures <B-2000MI375, B-2002MI409, 2007CRV874>, although alkylpyrimidines are probably still best prepared by ring synthesis procedures. Both types of procedure can readily be used for the synthesis of aryl and heteroaryl derivatives, so the choice of best route is determined by a combination of a number of factors such as the availability of starting materials and substitution pattern of the desired product.

8.02.11.2 Synthesis of Quinazolines

The synthesis of quinazoline derivatives is best achieved by ring-closure routes from benzene precursors, with subsequent modification of substituents giving rise to the desired product <1996HC(55)1, 2004SOS(16)573, 2005T10153>. Therefore, the choice of which procedure to use comes down to selecting the most appropriate benzene precursor. For example, in the synthesis of 4-anilinoquinazoline antitumor agents, two quite different procedures have been used, but both start with benzene derivatives. The most commonly used route involves the ring closure of an anthranilic acid derivative **1009** to give a 4-quinazolinone **1010**, which is then converted to a 4-chloroquinazoline **1011** and aminated with an aniline derivative to give the 4-anilinoquinazoline products **1012** <2000COR679, 2005T10153, 2006MI435>.



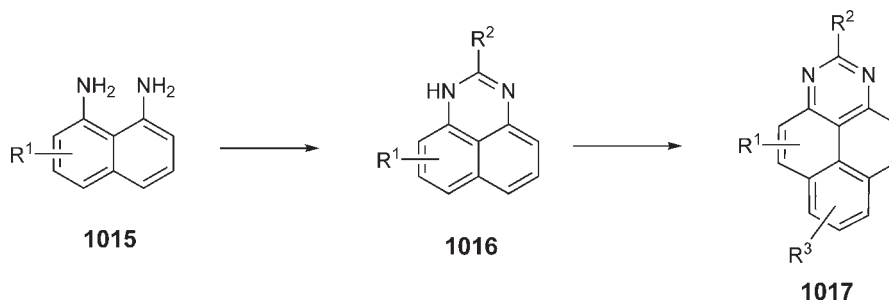
The alternative route that has also been used involves starting with an anthranilonitrile derivative **1013** which is converted to an amidine derivative **1014** with dimethyl formamide dimethyl acetal. Subsequent steps are all combined, with the aniline addition and ring-closure steps occurring in one pot, to directly give the same 4-anilinoquinazoline products **1012** via an iminoquinazolinone intermediate which then undergoes a Dimroth rearrangement <2000COR679, 2005T10153>.



However, regardless of the route to the 4-anilinoquinazoline, subsequent standard manipulation of substituents can be used to produce the desired products.

8.02.11.3 Synthesis of Perimidines

Perimidine derivatives **1016** are best prepared from 1,8-naphthalenediamines **1015** by ring-closure methods <1981RCR816, 1995AQ151>, while benzo[*gh*]perimidines **1017** are available in moderate yields from perimidines using Friedel–Crafts reaction conditions <2003CHE1417>.



8.02.12 Important Compounds and Applications

8.02.12.1 Pyrimidines

The most important pyrimidine derivatives are those upon which biological organisms depend. Cytosine **1018** and uracil **1019** are found in ribonucleic acid (RNA) in the form of their ribonucleotides, cytidine **1020** and uridine **1021**, while in deoxyribonucleic acid (DNA), cytosine and thymine **1022** are found in the form of their 2'-deoxyribonucleotides, 2'-deoxycytidine **1023** and thymidine **1024**. 5-Methylcytosine **1025** is also found to a small extent (*c.* 5%) in human DNA in the form of its 2'-deoxyriboside **1026**, and 5-(hydroxymethyl)cytosine-2'-deoxyriboside **1027** has also been detected in smaller amounts [\[2005CBI1\]](#). Many variants of cytosine and uracil can be found in RNA including orotic acid **1028** in the form of its ribonucleotide orotidine **1029**. Other pyrimidine derivatives to have been isolated from various biological sources include 2'-deoxyuridine **1030**, alloxan **1031**, and toxopyrimidine (pyramine) **1032** ([Figure 2](#)).

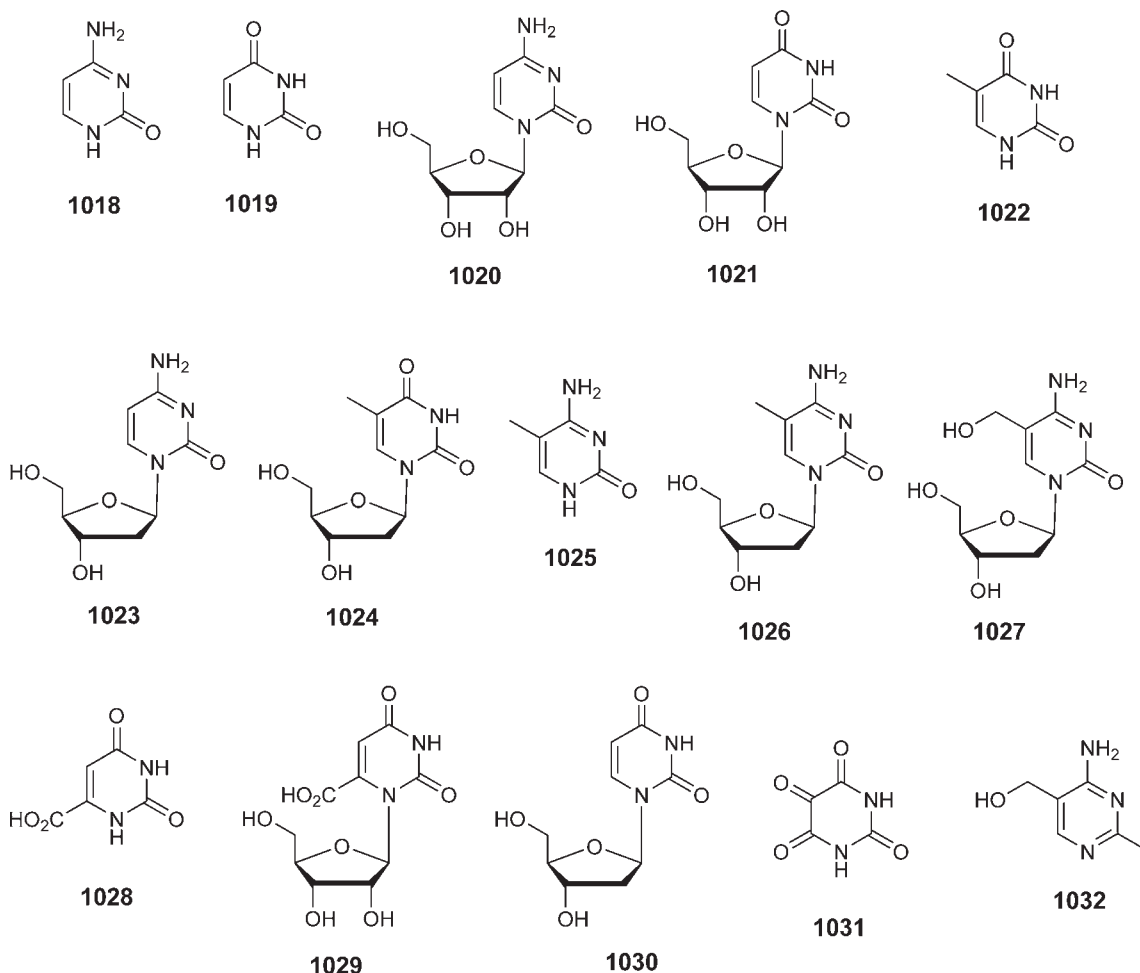
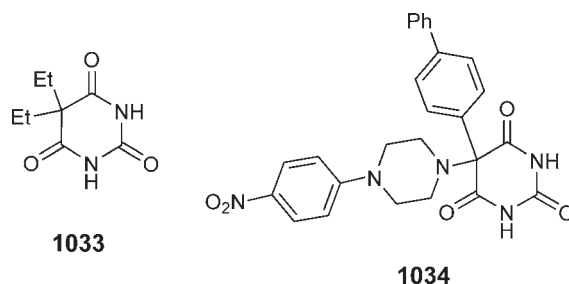


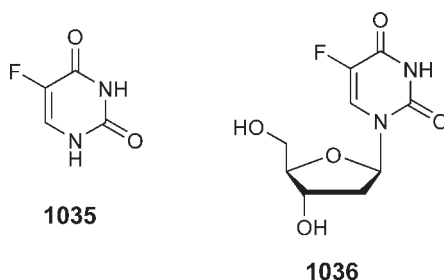
Figure 2 Biologically important pyrimidine derivatives.

Many synthetic pyrimidine derivatives have important pharmaceutical or agrochemical properties [\[2003CME269, 2005H\(65\)667, 2006JFC\(127\)303, 2006JFC\(127\)992, 2006H\(68\)561, 2006MI793\]](#), and one of the earliest series of pyrimidine pharmaceuticals is represented by the hypnotic barbiturates such as barbitol (barbitone) **1033** which is the 5,5-diethyl derivative of barbituric acid. However, the activity of barbiturates is not restricted to their sedative properties, and recently the 5-piperazinyl derivative Ro-28-2653 **1034** was shown to have potent antitumor and antiangiogenic properties due to selective inhibition of matrix metalloproteinases (MMPs), which are a family of zinc endopeptidases [\[2001MI1277, 2004CLC4038, 2004OPD411\]](#).



8.02.12.1.1 Pyrimidine antitumor agents

Apart from Ro-28-2653, mentioned above, another important class of pyrimidine antitumor agents is represented by 5-fluorouracil (5-FU) **1035**, which shows activity against a variety of different solid tumor types by functioning as an inhibitor of thymidylate synthase (TS) [\[2005CME2241\]](#). 5-Fluoro-2'-deoxyuridine (FdUrd, floxuridine) **1036** is also widely used [\[2006JFC\(127\)303\]](#).



Several orally bioavailable pro-drug forms of 5-FU and FdUrd have now been introduced [\[2002CME267\]](#), including carmofur **1037**, tegafur **1038**, doxifluridine **1039**, and capecitabine **1040** [\[2000BMC1697\]](#). Other pyrimidine-based antitumor agents to have been used include the antimetabolites cytarabine (cytosine arabinoside, Ara-C) **1041** and gemcitabine **1042**, and the alkylating agents uramustine **1043** and nimustine **1044**. In addition, the ribonucleotide reductase inhibitor tezacitabine **1045** has been shown to enhance the antitumor effects of fluoropyrimidines [\[2007BP44\]](#) (Figure 3).

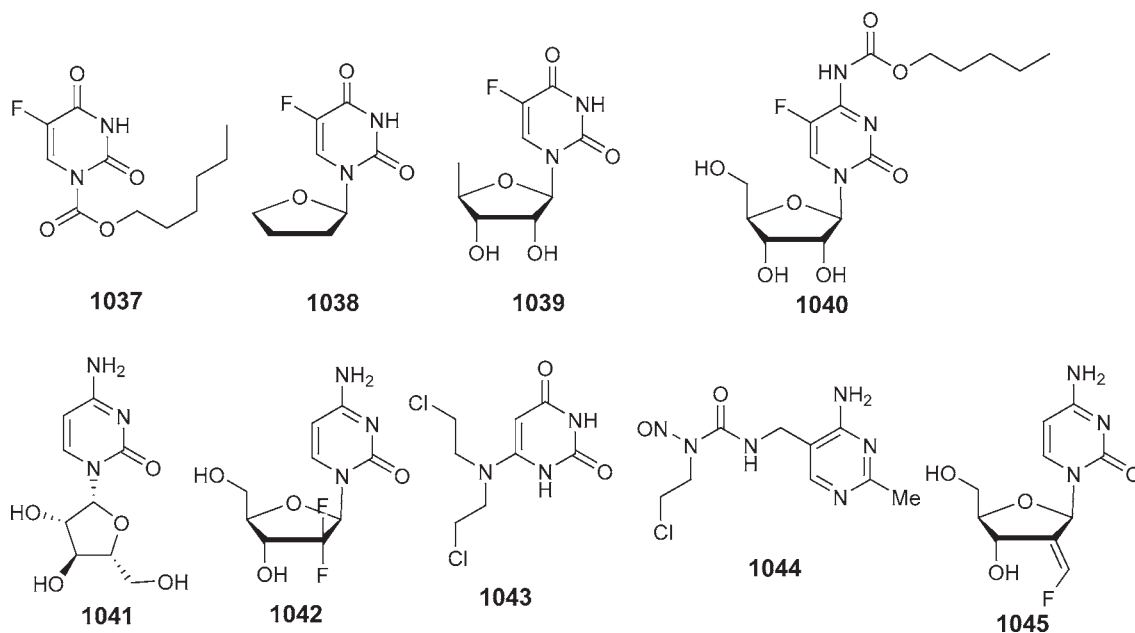


Figure 3 Pyrimidine antitumor agents.

However, the anticancer area that has expanded the most in recent years has involved the emergence of a new class of antitumor agents known as signal transduction inhibitors, with the first and best-known member of this class being the 2-(phenylamino)pyrimidine (PAP) derivative imatinib (Gleevec, Glivec, STI-571, CGP 57148) **1046** <1995PNA2558, 1997BML187, 2000SCI1938, 2001MI499, 2005JME249, 2007CMC-II(7)183>. Imatinib is an ATP-competitive inhibitor of the tyrosine kinase activity of the Bcr-Abl protein, which is implicated in the development of chronic myelogenous leukemia (CML). Further development of this class of ATP competitive tyrosine kinase inhibitor has led to the second-generation compound dasatinib (BMS-354825) **1047**, a dual inhibitor of both the Src and Abl kinases, which shows activity against mutant kinase forms that are resistant to imatinib treatment <2004JME6658, 2006JME6819>. X-Ray crystallographic studies showed that dasatinib binds to the active conformation form of the Abl kinase <2004JME6658>, whereas imatinib binds to the inactive conformation <2000SCI1938>. Two further members of the imatinib class of antitumor agents to have recently entered human clinical evaluation are nilotinib (AMN107) **1048** <2005BBA(1754)3, 2006MI1765> and NS-187 (INNO-406) **1049** <2005MI3948, 2006MI371>.

Other important examples of signal transduction inhibitors in clinical evaluation are the aurora kinase inhibitor VX-680 **1050** <2004MI262, 2006CNR1007>, which blocks the activity of various imatinib- and dasatinib-resistant mutant forms of Abl, by binding to the active conformation of the kinase <2006CNR1007>, the vascular endothelial growth factor (VEGF) receptor inhibitor pazopanib (GW786034B) **1051**, which targets both tumor and endothelial cells in multiple myeloma <2006PNA19478>, and R547 **1052**, a potent and selective cyclin-dependent kinase (CDK) inhibitor (Figure 4) <2006JME6549>.

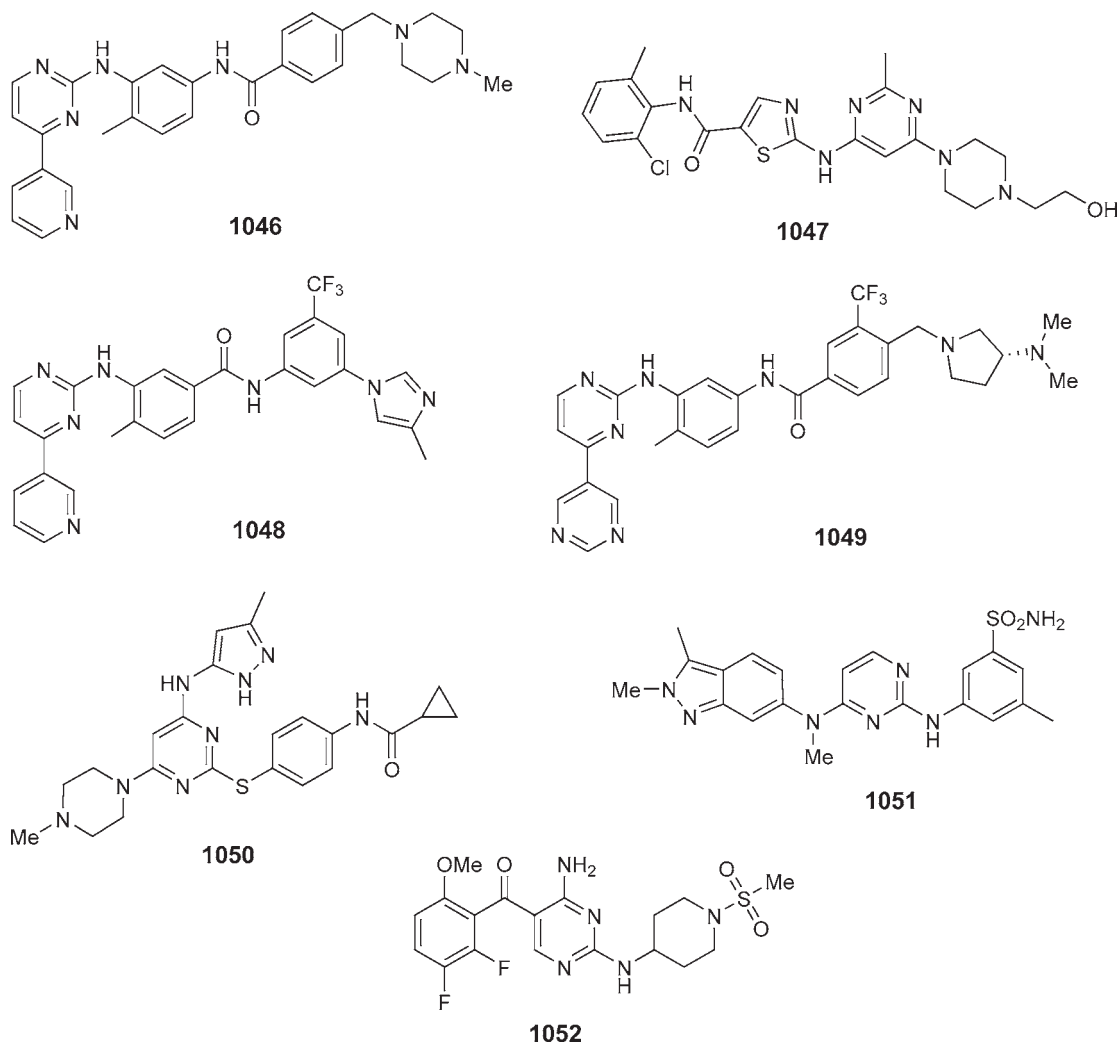


Figure 4 Pyrimidine signal transduction inhibitors.

Many other examples of pyrimidine-based kinase inhibitors have been investigated as potential antitumor agents, including 2-phenylamino derivatives <2003BML1673, 2003BML3021, 2004BML2245, 2004MPH635>, 4-phenylamino derivatives <2006BML1146, 2006BML2419>, 2,4-bis(phenylamino) derivatives <2003BML2961>, 4,6-bis(phenylamino) derivatives <2003BML2955, 2006JA2182>, and 4-aryl-substituted derivatives <2007JME627>. In addition, the 4-(phenylamino)pyrimidine pharmacophore is found in several fused-ring examples of ATP-competitive protein kinase inhibitors, such as purines, quinazolines, and pyrido-, pyrimido-, pyrazolo-, and pyrrolo-pyrimidines <2000COR679; 2001CRV2541, 2001MI499>.

8.02.12.1.2 Pyrimidine antiviral agents

Most pyrimidine antiviral agents are nucleoside or nucleotide analogs <2006MI793, 2006MI851, 2007CMC-II(7)295>, such as 2',3'-dideoxycytidine (ddC, zalcitabine) **1053**, 5-iodo-2'-deoxyuridine (IDU) **1054**, fialatidine (FIAC) **1055**, brivudin (BVDU) **1056** <2005MI1>, trifluridine **1057** <2002OPD847>, zidovudine (retrovir, AZT) **1058** <2000CME995>, lamivudine **1059** (R=H) <2002SC2355, 2005TL8535>, emtricitabine **1059** (R=F) <2005OPD23>, stavudine (d4T) **1060** <1996NN47, 1998TL729, 2002TL3503, 2003T941, 2003TL1003>, elvicitabine **1061** <1996JME1757, 1997JOC3449>, or the acyclic phosphate cidovir **1062** <1994TL3243> (Figure 5).

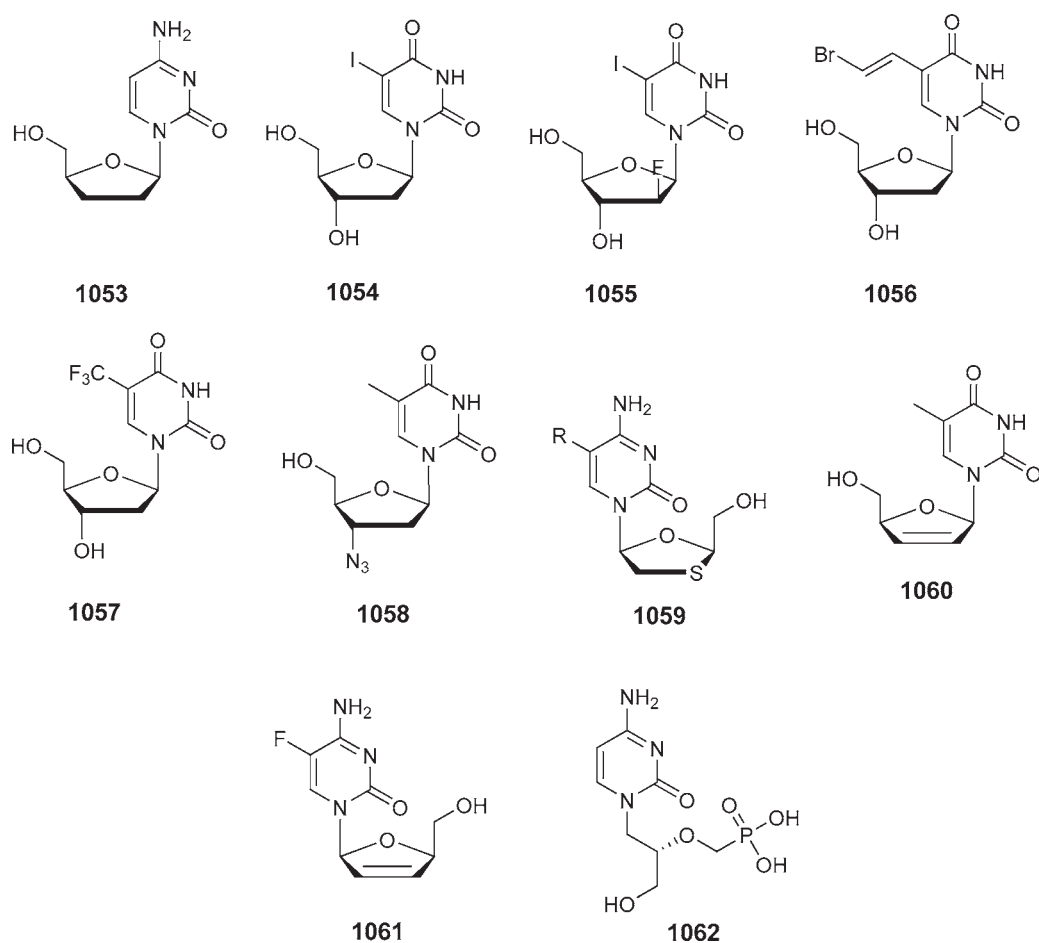


Figure 5 Pyrimidine antiviral agents.

Important examples of non-nucleoside reverse transcriptase inhibitor (NNRTI) antivirals are emivirine (MKC-442) **1063** <1995JME2860, 2006OL3737>, dapivirine (TMC120) **1064** <2001BML2235>, etravirine (TMC125) **1065** <2004JME2550>, rilipivirine (TMC 278) **1066** <2005JME1901, 2005JME2072>, and lopinavir (ABT-378) **1067**,

which contains a tetrahydro-2-pyrimidinone (cyclic urea) group <1999OPD145, 2000OPD264, 2003BMC2803>. There has also been considerable interest in TSAO-T {[1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-b-D-ribofuranosyl]thymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide)} **1068** derivatives as HIV-1 reverse transcriptase (RT) inhibitors because of a specific interaction of the amino group of the 3'-spiro moiety with a glutamic acid residue at position 138 of the p51 subunit of HIV-1 RT <2001JME1853, 2002JME3934, 2004JME3418, 2005JME6653, 2006MI1895>. Another non-nucleoside pyrimidine antiviral compound to have undergone clinical evaluation is PNU 142721 **1069** <1998JME1357, 2004T3311> (Figure 6).

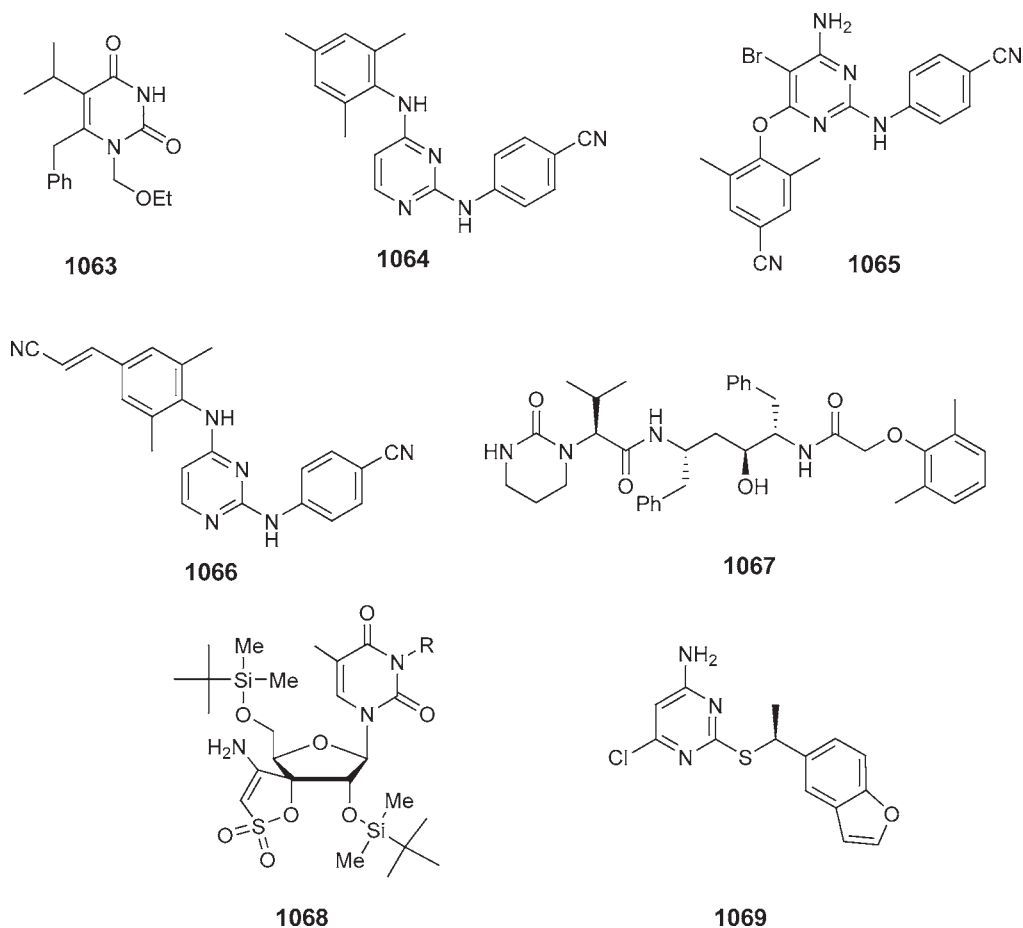


Figure 6 Pyrimidine non-nucleoside reverse transcriptase inhibitor (NNRT) antiviral agents.

8.02.12.1.3 Pyrimidine antibacterial agents

The diaminopyrimidine derivative trimethoprim (TMP) **1070** (R = OMe) is a selective inhibitor of bacterial dihydrofolate reductase (DHFR), which is widely conserved and essential in bacterial pathogens <2006BP941>. Related analogs include brodimoprim **1070** (R = Br) and tetroxoprim **1070** (R = O(CH₂)₂OMe) and the more recent addition to the field iclaprim (AR-100) **1071**, which is used clinically as a racemic mixture of two enantiomers <2006BP941>. Pyrimidine 2-sulfonamides such as sulfadiazine **1072** (R¹ = R² = R³ = H), sulfamerazine **1072** (R¹ = Me, R² = R³ = H), sulfadimidine **1072** (R¹ = R³ = Me, R² = H), sulfaperin **1072** (R¹ = R³ = H, R² = Me), and sulfameter **1072** (R¹ = R³ = H, R² = OMe) have all been used in bacterial therapy, as have related sulfonamides such as sulfisomidine **1073** (R¹ = R² = Me), sulfadimethoxine **1073** (R¹ = R² = OMe), sulfamethomidine **1073** (R¹ = Me, R² = OMe), sulfamethoxine **1074**, and sulfacytine **1075** <2006MI793> (Figure 7).

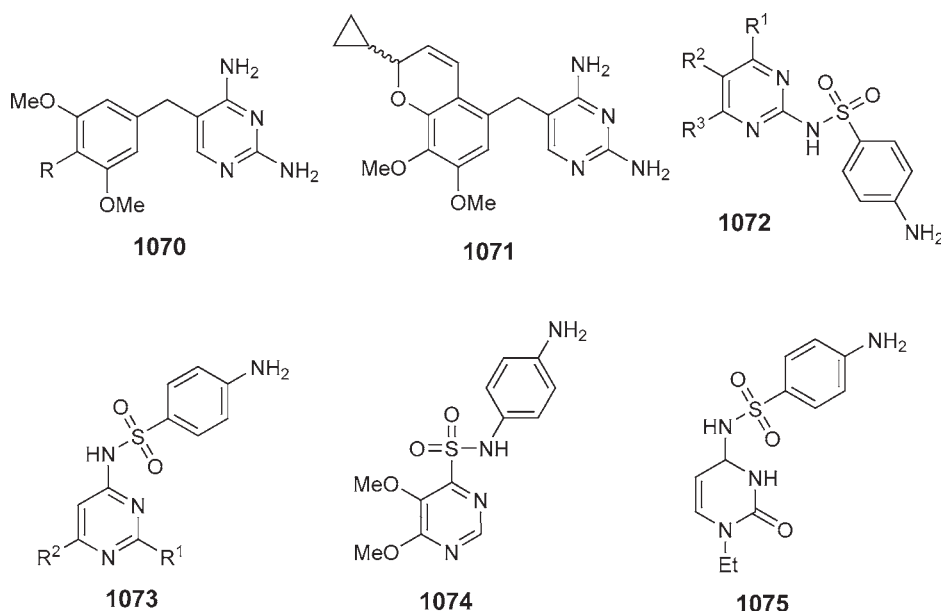


Figure 7 Pyrimidine antibacterial agents.

8.02.12.1.4 Pyrimidine antifungal agents

2-Phenylaminopyrimidines (anilinopyrimidines) are effective against a variety of phytopathogens, possibly by inhibition of methionine biosynthesis <2006H(68)561>. Commercial examples include pyrimethanil **1076**, andoprime **1077**, cyprodinil **1078**, and mepanipyrim **1079**. Other 2-aminopyrimidine derivatives to have fungicidal activity include ferimzone **1080**, ethirimol **1081**, bupirimate **1082**, and dimethirimol **1083**. A 4-phenylaminopyrimidine derivative is represented by diflometorim **1084** which is a mitochondrial respiration inhibitor <2006H(68)561>. The strobilurin fungicides were developed from the natural product strobilurin A **1085**, an inhibitor of mitochondrial respiration <2006H(68)561>. Two commercial examples are axoxystrobin **1086** and fluoxastrobin **1087**. Another class of pyrimidine fungicides is represented by the diphenyl pyrimidin-5-ylmethanol derivatives fenamidol **1088**, nuarimol **1089**, and triarimol **1090**, which are inhibitors of sterol biosynthesis <2006H(68)561>, while the newer triazole derivative voriconazole **1091** similarly blocks essential biosynthesis by inhibition of P-450-dependent 14 α -demethylase <1996BML2031, 2001OPD28, 2006JFC(127)1013>. 5-Fluorocytosine (flucytosine) **1092** is marketed as an antifungal agent, while the peptidyl-nucleoside antibiotic, Blasticidin S **1093**, a metabolite of *Streptomyces griseochromogenes*, has been used commercially on a large scale for the control of *Pyricularia oryzae* (rice blast). It blocks protein biosynthesis in eukaryotic and prokaryotic cells by interference of peptidyl transfer reactions <2005H(65)667>. A total synthesis has recently been performed <2004CEJ3241>.

The polyoxins represent another important class of peptidyl nucleosides, which were isolated as metabolites of *Streptomyces cacaoi* var. *asoensis*. They interfere with fungal cell wall synthesis by specifically blocking *chitin synthetase* <2005H(65)667>. A total synthesis of polyoxin B **1094** (R = CH₂OH) and polyoxin D **1094** (R = CO₂H) has been performed <2000H(53)2253>, although both compounds are produced commercially by fermentation (Figure 8).

8.02.12.1.5 Pyrimidine herbicides

There are several commercially available sulfonylurea herbicides that contain a 2-pyrimidine group <2006H(68)561>. These compounds, which function by inhibition of acetolactate synthase (ALS), an enzyme involved in the early stage of branched-chain amino acid synthesis, include sulfometuron-methyl **1095**, primisulfuron-methyl **1096**, chlorimuron-ethyl **1097**, bensulfuron-methyl **1098**, ethoxysulfuron **1099**, nicosulfuron **1100**, and pyrazosulfuron-ethyl **1101**. Related nonsulfonylureas include the sulfide pyriftalid **1102** and the ether pyriminobac-methyl **1103**.

Uracil derivatives can also function as herbicides by inhibition of the enzyme protoporphyrinogen-IX-oxidase (PPO), which is involved in the biosynthesis of chlorophyll <2006H(68)561>. Commercial examples of such PPO inhibitors include isocil **1104**, bromacil **1105**, terbacil **1106**, flupropacil **1107**, lenacil **1108**, butafenacil **1109**, and benzfendazole **1110** (Figure 9).

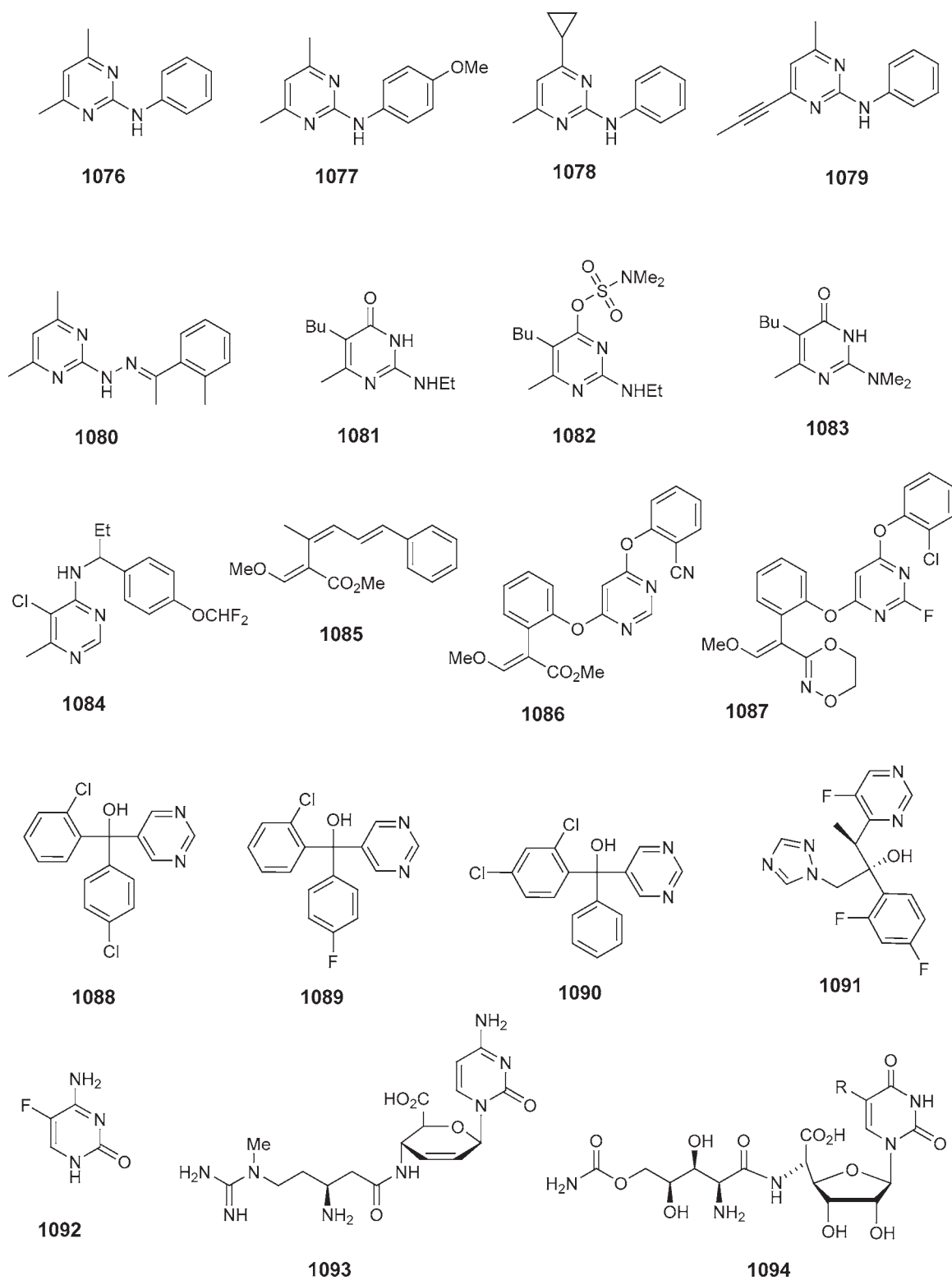


Figure 8 Pyrimidine antifungal agents.

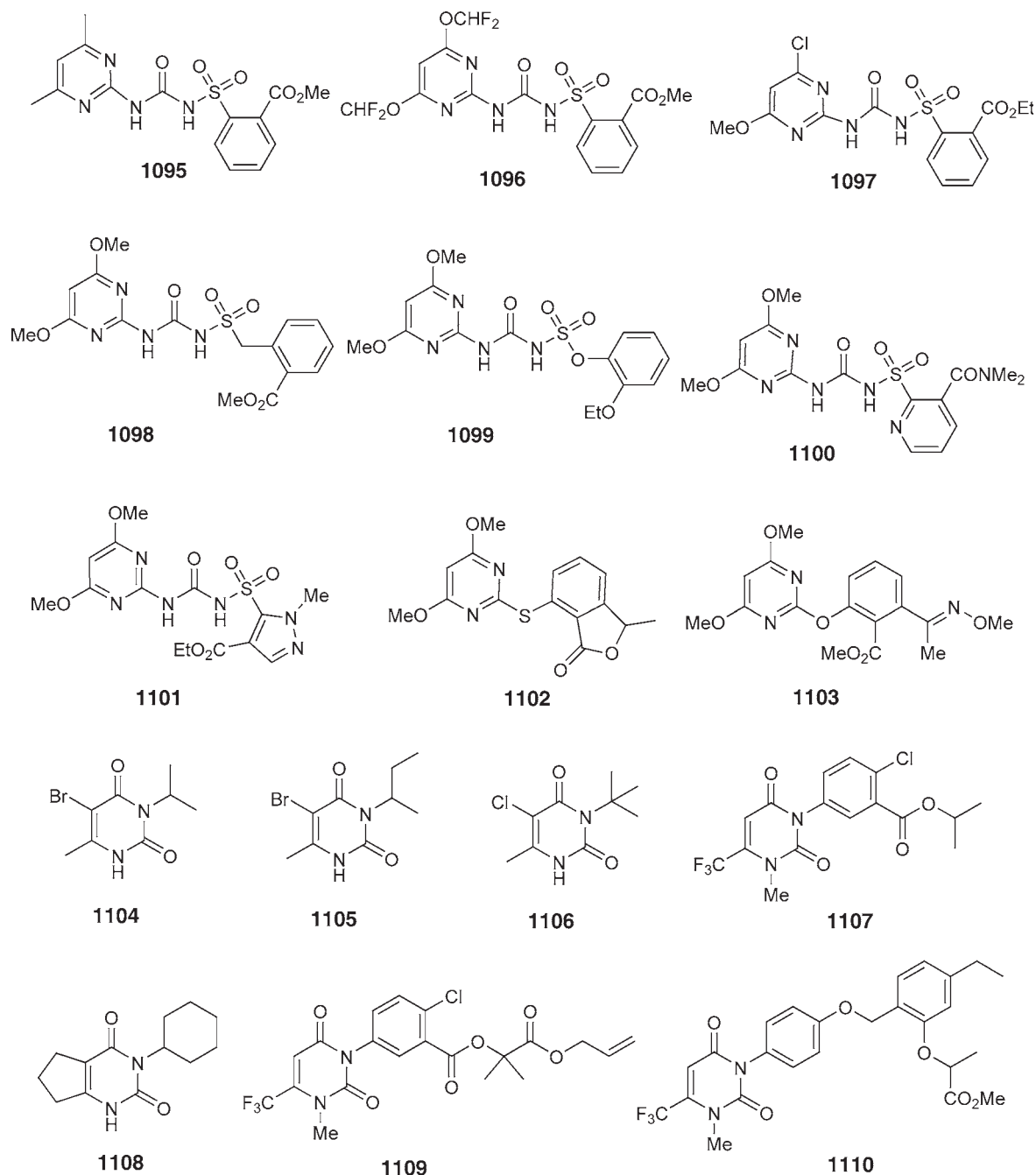


Figure 9 Pyrimidine herbicidal agents.

8.02.12.1.6 Pyrimidine insecticides

Older examples of pyrimidine insecticides are represented by the phosphorothionates and carbamates, diazinon **1111**, pirimiphos-methyl **1112**, tebufipirimifos **1113**, and pirimicarb **1114**, which function by inhibition of acetylcholinesterase. Three newer examples are pyrimidifen **1115** and flufenimer **1116**, which function by interrupting mitochondrial electron transport, and flucyprym **1117** which is related to the strobilurin fungicides (**Figure 10** <2006H(68)561>).

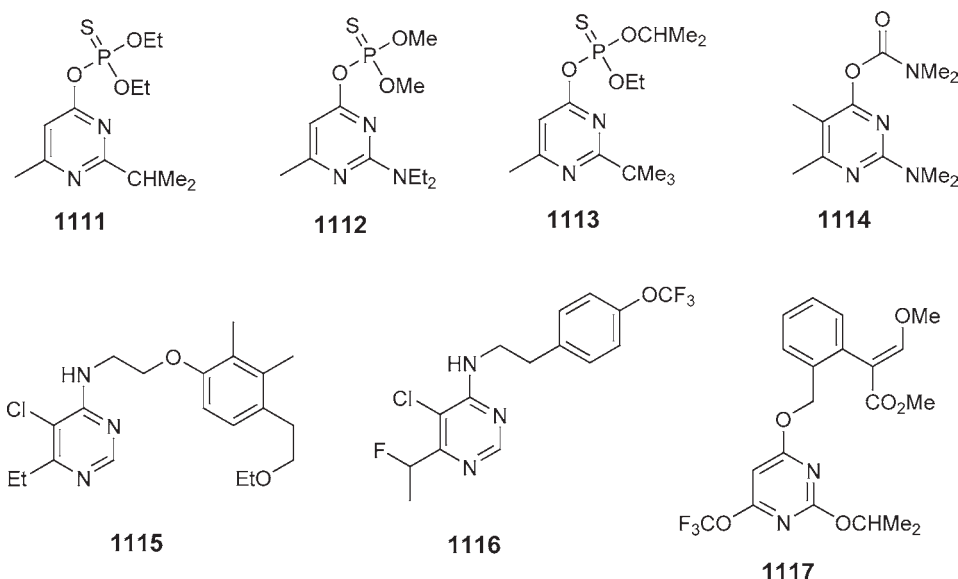
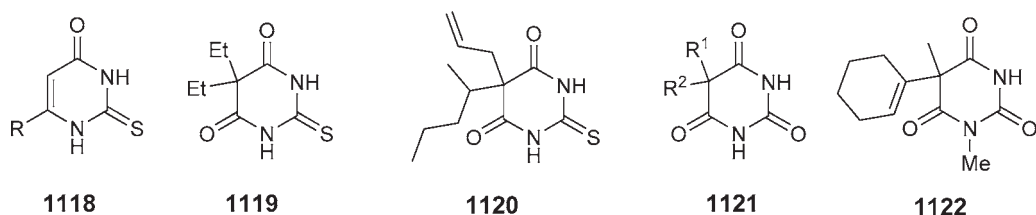


Figure 10 Pyrimidine insecticides.

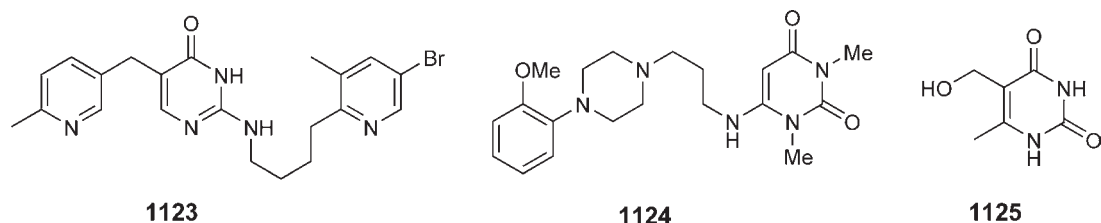
8.02.12.1.7 Other activities

There are a variety of natural antibiotics which contain a pyrimidine or reduced pyrimidine ring [<2005CB11>](#), and several of these are used therapeutically for a number of different applications. Blasticidin S and the polytoxins were mentioned in the section on antifungals, but other examples include amicetin, capreomycin, gougerotin, and viomycin, as well as the bleomycins and phleomycins.

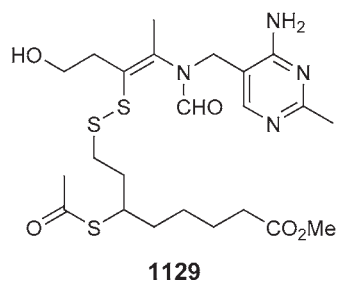
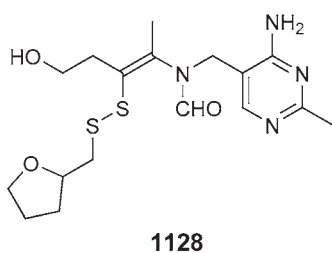
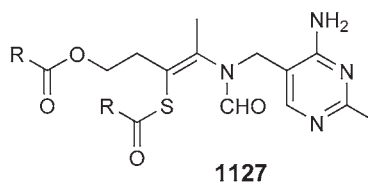
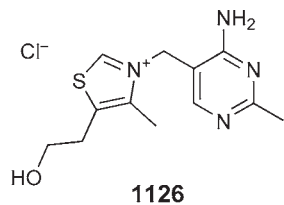
Cyclic thioureas such as 2-thiouracil **1118** ($R = H$), its 6-methyl **1118** ($R = Me$) and 6-propyl derivatives **1118** ($R = Pr$), as well as thiobarbital **1119** are effective agents against hyperthyroidism, while thiamylal **1120** is used as an anesthetic. A large number of barbituric acid derivatives have hypnotic or sedative effects, and allobarbital **1121** ($R^1 = R^2 = allyl$), aprobarbital **1121** ($R^1 = allyl$, $R^2 = i\text{-}Pr$), cyclobarbital **1121** ($R^1 = Et$, $R^2 = 1\text{-cyclohexenyl}$), pentobarbital **1121** ($R^1 = Et$, $R^2 = 2\text{-pentyl}$), phenobarbital **1121** ($R^1 = Et$, $R^2 = Ph$), propallyonal **1121** ($R^1 = isopropyl$, $R^2 = 2\text{-bromoallyl}$), and secobarbital **1121** ($R^1 = allyl$, $R^2 = 2\text{-pentyl}$) are all examples of N-unsubstituted barbiturates, while hexobarbital **1122** represents an N-methylated derivative.



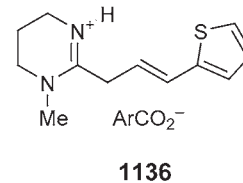
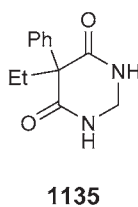
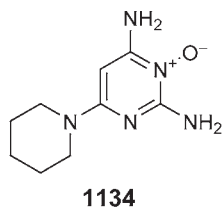
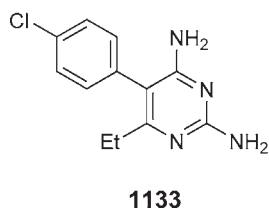
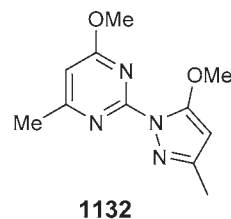
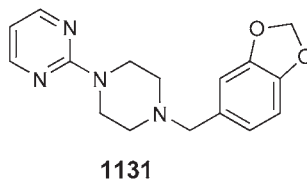
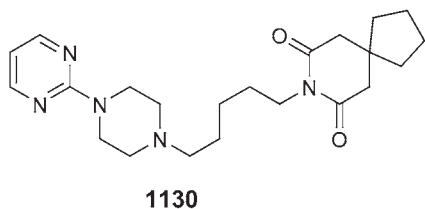
Other important pyrimidinone derivatives include temelastine **1123**, an antihistaminic agent, urapidil **1124**, an antihypertensive, and 5-hydroxymethyl-6-methyluracil (pentoxyl) **1125** which is used as a leukopoietic stimulant in wound healing.



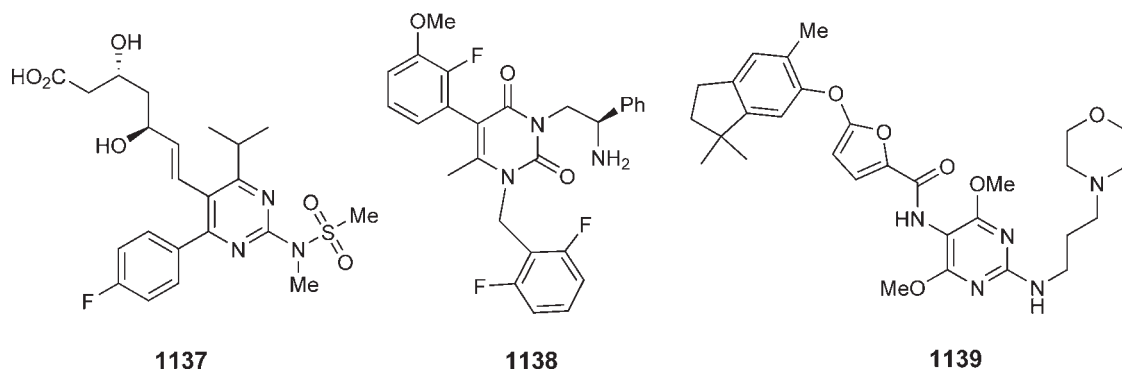
Lipid soluble analogs of thiamine (vitamin B₁) **1126** have a number of therapeutic uses, and examples are acetiamine **1127** (R = Me), bentiamine **1127** (R = Ph), fursultiamine **1128**, and octotiamine **1129** which has anti-inflammatory activity.



Other examples of pyrimidine-based pharmaceuticals include busipirone **1130**, used to treat anxiety disorders, piribedil **1131** used for Parkinson's disease, eprizole **1132**, a nonsteroidal antinflammatory (NSAID), pyrimethamine **1133**, an antimalarial, minoxidil **1134**, which is used for treating alopecia (male baldness), primidone **1135**, which is used as an antiepileptic agent, and pyrantel pamoate **1136**, which is used as an antiparasitic.



Newer additions to the pharmaceutical field include the hypolipidemic drug rosuvastatin **1137** <2005MI233>, which was designed to reduce low density lipoprotein cholesterol (LDL-C), and NBI 42902 **1138** <2005JME1169>, which underwent clinical evaluation as an orally available, high-affinity nonpeptide antagonist of the human gonadotropin-releasing hormone (GnRH) receptor, although development has now been discontinued. Another compound designed to target the GnRH receptor is the pyrimidine **1139** <2006JME3362>.

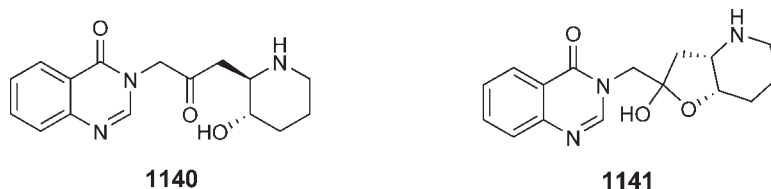


8.02.12.2 Quinazolines

8.02.12.2.1 Quinazoline alkaloids

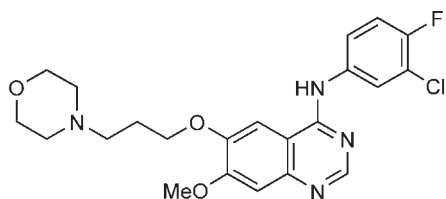
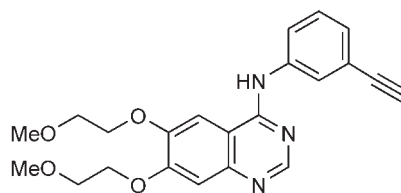
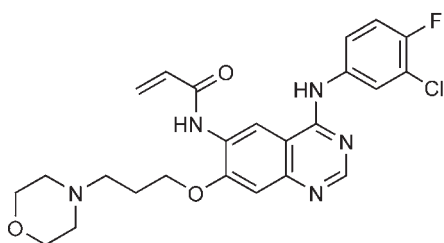
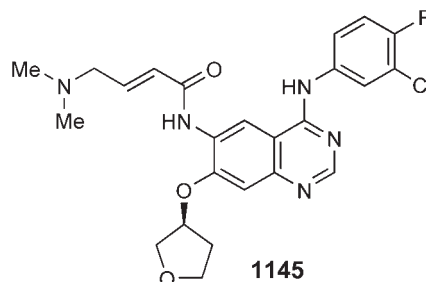
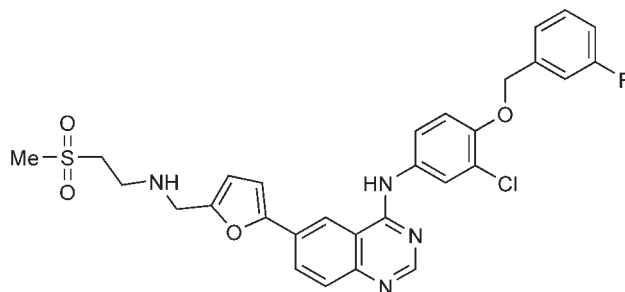
A large number of quinazoline and quinazolinone alkaloids are known and the subject has been extensively reviewed <1997MI221, 2000RCC203, 2003COR149, 2003COR659, 2005CBI1, 2006THC113, 2006T9787>. Further detailed coverage is included in yearly natural products reports on quinoline, quinazoline, and acridone alkaloids <1997NPR11, 1997NPR605, 1998NPR595, 1999NPR697, 2000NPR603, 2001NPR543, 2002NPR742, 2003NPR476, 2004NPR650, 2005NPR627, 2007NPR223>.

Two important examples of quinazolinone alkaloids include febrifugine **1140** and isofebrifugine **1141**, which have antimalarial properties, and for which several syntheses have been published <1999JOC6833, 1999TL2175, 2000CC1643, 2000OL3193, 2001JA12510, 2001JOC809, 2001MI65, 2001OL953, 2001SL1225, 2001T1213, 2003SL1663, 2004TL6221, 2005SL346, 2006H(67)189>. Unfortunately however, both compounds are too toxic for human use, and efforts are underway to find less toxic analogs <2002JME2563, 2006JME4698>.

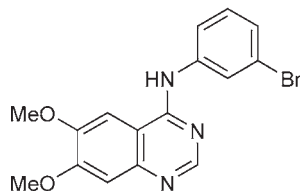
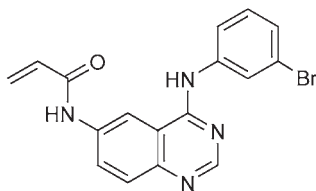
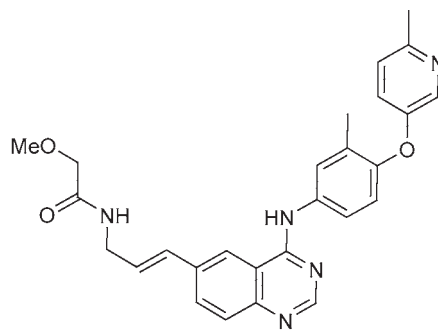


8.02.12.2.2 Quinazoline antitumor agents

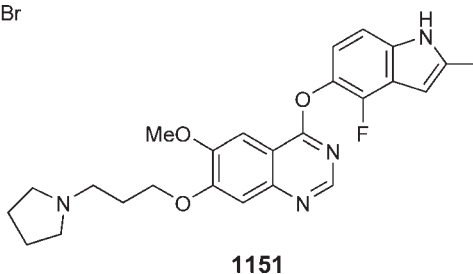
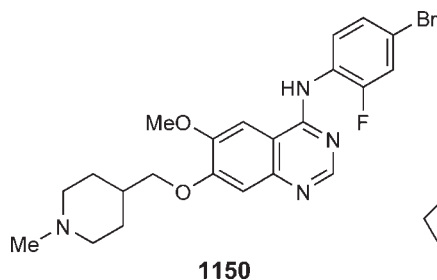
Although the first signal transduction kinase inhibitor to proceed to clinical deployment was the pyrimidine derivative imatinib **1044**, many of the subsequent investigations have employed quinazoline derivatives, with 4-anilino derivatives being particularly dominant in this regard <2000COR679, 2001CRV2541, 2004RMC273, 2005MI199, 2006MI569, 2006RMC1101, 2006CLC4441, 2007CMC-II(7)183>. Examples of this class of compounds to have advanced to human clinical trial include gefitinib (Iressa, ZD1839) **1142** <2001BML1911>, erlotinib (Tarceva, OSI 774) **1143** <1997CNR4838, 2002JBC46265>, canertinib (CI 1033; PD183085) **1144** <2000JME1380>, BIBW2990 **1145** <2002WO050043>, and lapatinib (Tykerb, GW572016) **1146** <2004CNR6652, 2005MI1225, 2006BML4686>. All of these ATP-competitive binding compounds were designed to target the tyrosine kinase domain of the epidermal growth factor receptor (EGFR), also known as erbB1 or HER1, or related receptors. Gefitinib and erlotinib are reversible inhibitors of EGFR autophosphorylation, while canertinib and BIBW2990 are irreversible inhibitors, having been designed to bind to a specific cysteine residue by Michael addition. Since this cysteine is also found in other members of the erbB family, canertinib and BIBW2990 are classed as pan-erbB inhibitors. Despite only being a reversible inhibitor, lapatinib is actually a dual inhibitor of both the EGFR and erbB2 tyrosine kinases, which it achieves by virtue of a very slow off-rate <2004CNR6652>. X-Ray crystallographic studies have shown that lapatinib binds to an inactive-like conformation of EGFR <2004CNR6652>, that is very different from the active-like structure bound to by the reversible inhibitor erlotinib <2002JBC46265>.

**1142****1143****1144****1145****1146**

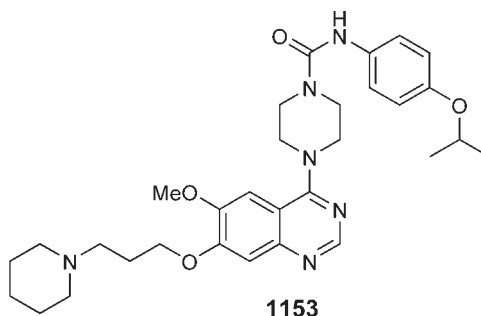
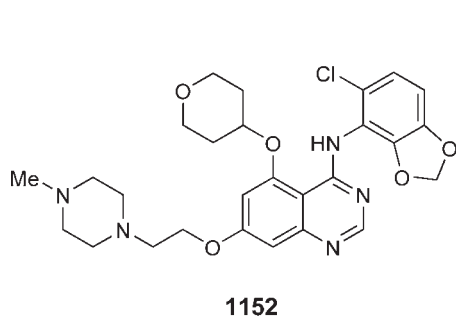
Other 4-anilinoquinazolines to have received investigation as EGFR tyrosine kinase inhibitors include PD 153035 **1147** <1994SCI1093, 1995JME3482, 1996JME267> and PD168393 **1148** <1998PNA12022, 1999JME1803, 2001JME2719>, while CP-724714 **1149** is a selective erbB2 inhibitor <2005OPD440>.

**1147****1148****1149**

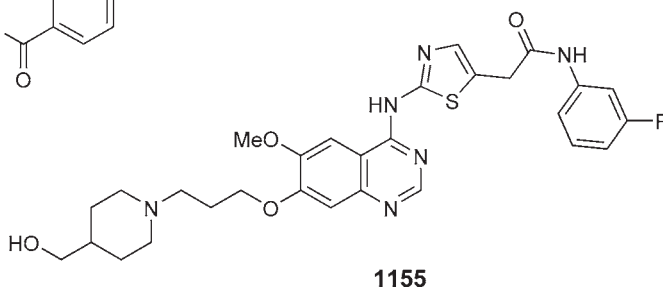
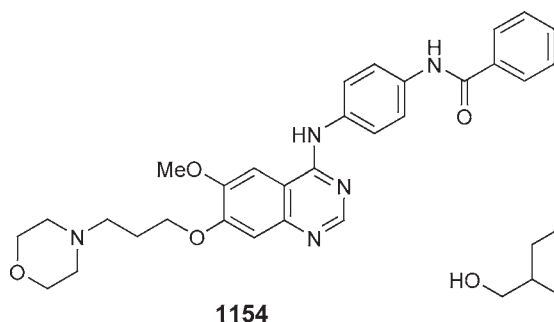
Another important tyrosine kinase target is the VEGF receptor, which is involved in tumor angiogenesis. Two examples of quinazoline derivatives being investigated clinically as VEGF inhibitors are vandetanib (Zactima, ZD6474) **1150** <2002JME1300> and cediranib (AZD 2171) **1151** <2005CNR4389>.



Examples of quinazoline-based tyrosine kinase inhibitors undergoing clinical evaluation against multiple kinase targets include AZD0530 **1152**, which shows dual specificity for the tyrosine kinase domain of the c-Src and Abl enzymes <2006JME6465>, and tandutinib (MLN-518) **1153** <2002JME3772, 2006MI3674> an inhibitor of FMS-like tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGFR), and KIT.

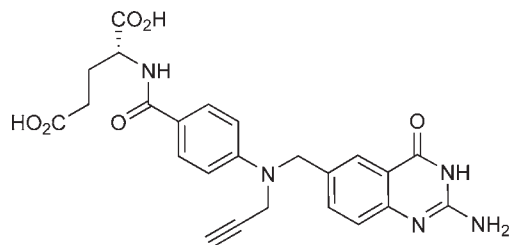
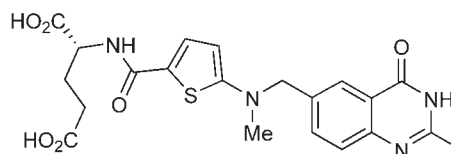
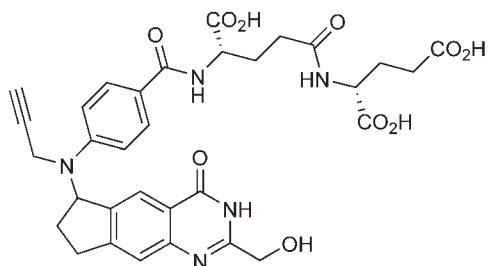
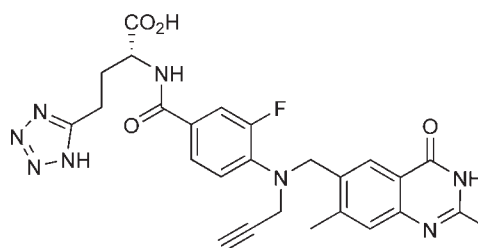
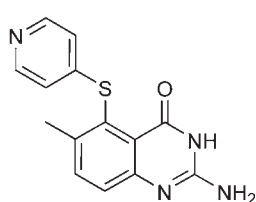
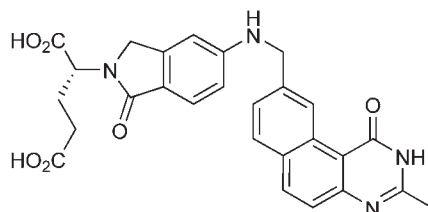
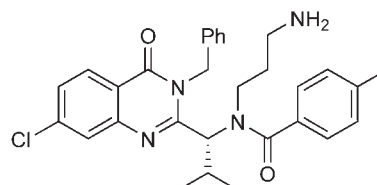


Further anticancer kinase targets currently being investigated include the Aurora family of serine/threonine protein kinases which are critical for the proper regulation of mitosis. Examples of quinazoline inhibitors undergoing evaluation against the Aurora kinases include the 4-anilinoquinazoline ZM447439 **1154** <2006BML1320> and the 4-(2-thiazolyl)amino derivative **1155** <2006JME955>.



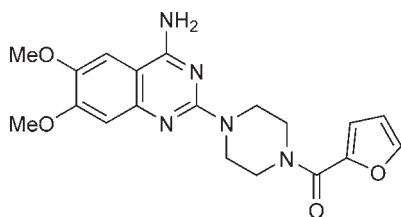
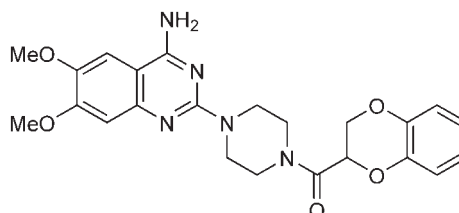
A totally different anticancer target is thymidylate synthase (TS) which is a critical enzyme for DNA replication and cell growth because it is the only *de novo* source of thymine nucleotide precursors for DNA synthesis. Several TS inhibitors, structurally analogous to 5, 10-methylenetetrahydrofolate, the second substrate of TS, have now been designed and tested clinically <2003MI80>. The first example investigated was CB3717 **1156** <1988JME449>, but this was found to cause renal toxicity due to precipitation in the kidney. The more water-soluble analog raltitrexed (Tomudex; ZD 1694) **1157** <1991JME1594, 2003SC3519> is used as a treatment for colorectal cancer. Other related TS inhibitors being investigated include BGC 945 **1158** <2006BMC5020>, plevitrexed (BGC 9331, ZD9331) **1159** <1999JME3809>, nolatrexed (Thymitaq, AG337) **1160** <1996MI509>, and OSI7904 (BW 1843U89, GW 1843) **1161** <1994JME838>.

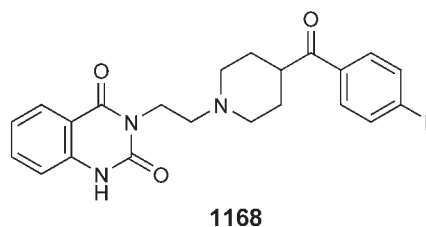
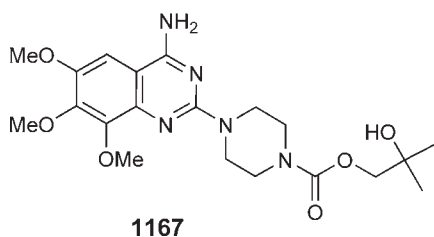
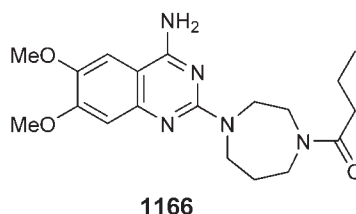
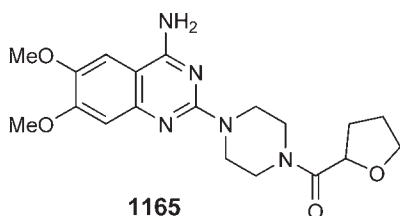
Another class of quinazoline antitumor agent under development is represented by ispinesib (SB 715992) **1162**, a KSP kinesin inhibitor, which is being evaluated against head and neck cancer <2006MI627>.

**1156****1157****1158****1159****1160****1161****1162**

8.02.12.2.3 Quinazoline antihypertensive agents

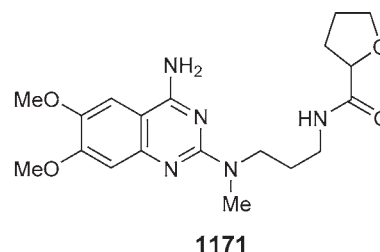
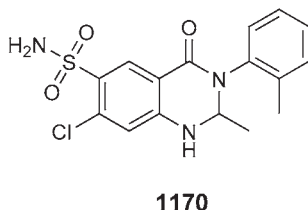
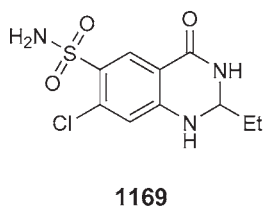
Several quinazoline derivatives have antihypertensive activity. Examples include prazosin **1163**, doxazosin **1164**, terazosin **1165**, bunazosin **1166**, and trimazosin **1167**, which bind to α_1 -adrenoreceptors, and ketanserin **1168**, a serotonin 5-HT₂ receptor antagonist.

**1163****1164**

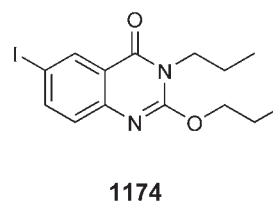
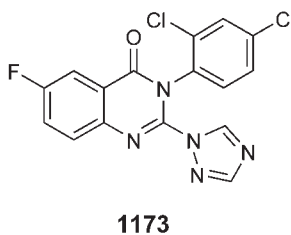
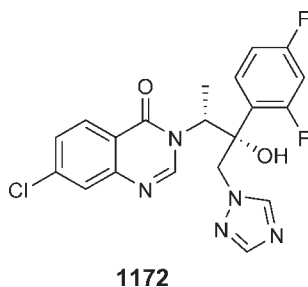


8.02.12.2.4 Other activities

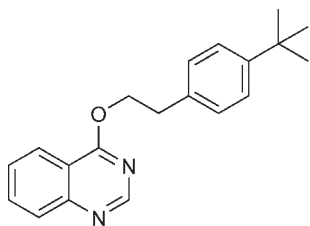
Quinethazone **1169** and metolazone **1170** are used medically as diuretics, and alfazosin **1171**, an α_1 -adreno-receptor antagonist related to prazosin is used to improve urinary flow rate in the treatment of benign prostatic hyperplasia.



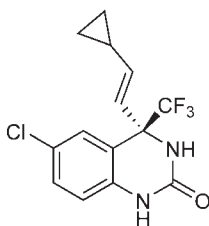
Albaconazole (UR 9825) **1172** <1998JME1869> and fluquinconazole **1173** are used as antifungals, while proquinazid **1174** has high activity against powdery mildew diseases of cereals, grape and apple <2006H(68)561>.



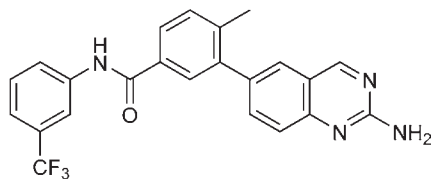
The ascaricide fenazaquin **1175** is active against several spider mite species, while DPC-083 (BMS 561390) **1176** is an anti-HIV reverse transcriptase inhibitor <2000JME2019>. The quinazoline **1177** has recently been identified as a lead compound for the development of selective inhibitors of lymphocyte-specific kinase (Lck) which is involved in T-cell-mediated autoimmune and inflammatory disease <2006JME5671>.



1175



1176

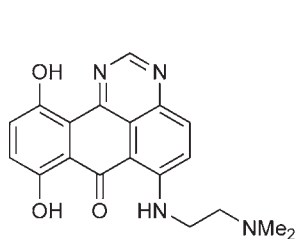


1177

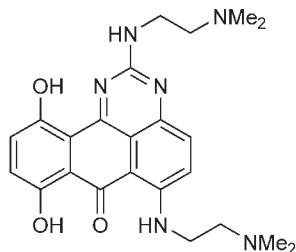
Lastly, tetrodotoxin, the Japanese puffer fish toxin, is a polyhydroxylated reduced 2-aminoquinazoline derivative that has attracted a lot of interest, and a number of asymmetric total syntheses have recently been published [<2003JA8798, 2003JA11510, 2004AGE4782, 2005CRV4537>](#).

8.02.12.3 Perimidines

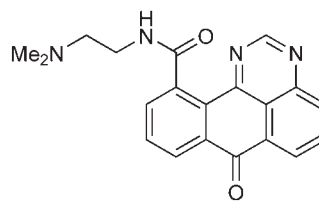
Perimidine derivatives such as the benzoperimidinones **1178**, **1179**, and **1180** have been investigated as antitumor agents [<1993JME38, 1999JME3494, 2001JME2004, 2002BMC1025, 2005BMC3657>](#), although none were sufficiently active for further development.



1178



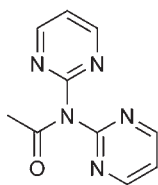
1179



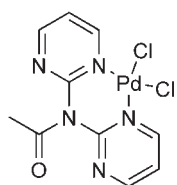
1180

8.02.12.4 Other Applications

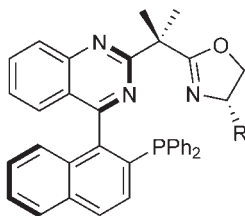
Both pyrimidine and quinazoline derivatives have been investigated as ligands for palladium-mediated reactions. Examples of ligands prepared include the phosphine-free bipyrimidine **1181**, which gave the isolable palladium dichloride catalyst **1182** [<2001JOM\(634\)39>](#), and the chiral oxazolinyl-quinazoline BINAP analogs **1183** and **1184** [<2006OL5109>](#).



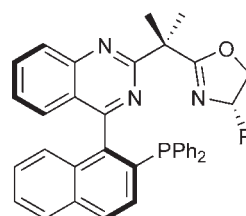
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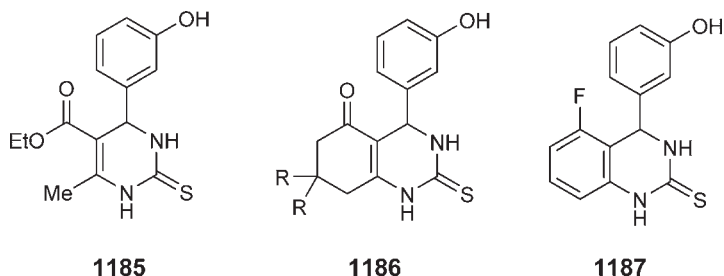
1183



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8.02.13 Further Developments

Dihydro and hexahydroquinazolinethione analogs of the dihydropyrimidinethione mitotic kinesin spindle protein (KSP; Eg5) inhibitor monastrol **1185**, such as enastron **1186** (R = H), dimethylenastron **1186** (R = Me), and vanastrol (VS-83) **1187** have received recent attention [<2005CBC1173, 2005CBC2005, 2006MI293, 2007MI157>](#).



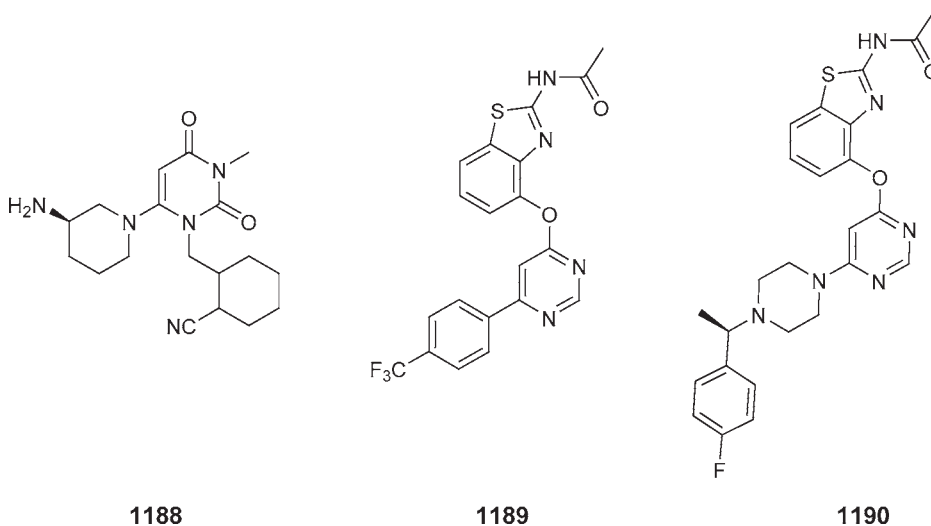
Since the original identification of monastrol as a KSP inhibitor <1999SCI971> there have been several published syntheses of both the parent compound and analogs using Biginelli reaction chemistry <2000T1859, 2002TL5913, 2004SL279, 2005ARK(iii)228, 2006BOC173>, and this has continued with a number of recent examples <2007BMC6474, 2007LOC357, 2007MI317>. Dihydropyrimidinethiones have been used as source of 2-amino-4-arylpyrimidine-5-carboxylic acid derivatives <2007JCO275>. The synthetic procedure involves initial S-alkylation of the dihydropyrimidinethione with methyl iodide, aromatization with manganese dioxide and then oxidation of the thiomethyl group with Oxone to provide 2-methylsulfonylpyrimidines which are then reacted with amines and other nucleophiles <2007JCO275>. The synthesis of related dihydropyrimidinones has also received recent attention <2007JCO415, 2007JHC211, 2007JHC979, 2007T11822, 2007TL7343, 2007TL7392>, and the 1,2- or 1,4-addition of nucleophiles to 2(1*H*)-pyrimidinones has given access to compounds not readily available by the Biginelli reaction route <2007T12215, 2007TL1349>. In addition to the normal oxidation with nitric acid <2007TL1349>, the 2(1*H*)-pyrimidinones have also been prepared by an oxidation–dealkylation of 4-alkyl-3,4-dihydro-2(1*H*)-pyrimidinones with $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{K}_2\text{S}_2\text{O}_8$ in aqueous acetonitrile <2007T666>.

Palladium catalysed cross-coupling chemistry continues to be developed, and 5-aryldihydropyrimidinones have been prepared via Liebeskind–Srogl boronic acid cross-couplings with the corresponding pyrimidine thiol esters <2007JCO415, 2007SL43>. The cross-coupling of boronic acids with 2-pyrimidinethiones, as well as dihydro- and tetrahydro- derivatives, has also been achieved under similar conditions, whereas under oxidative palladium-free conditions carbon-sulfur coupling was observed <2007JOC4440>. New catalysts for Suzuki–Miyaura coupling reactions of heteroaryl chlorides, including chloropyrimidines, have been developed <2007JOC5104>, and an improved procedure for the palladium-catalyzed amidation of heteroaryl bromides, including 5-bromopyrimidine, has been described <2007JA7734>. New methods for the palladium-catalyzed cyanation of aryl and heteroaryl chlorides including 2-chloropyrimidine have also been developed <2007OL1711>.

Starting from a single, chiral, bicyclic derivative of uracil, all four stereoisomers of 2-aminocyclobutanecarboxylic acid have been prepared in enantiomerically pure form, using a synthetic sequence which includes a photochemical [2+2] cycloaddition reaction <2007S2222>. A number of new routes to 2,4-(1*H*,3*H*)-quinazolinone derivatives have been published <2007BML1312, 2007CL858, 2007OPD441, 2007S2524, 2007T9764>, and the syntheses of biologically active quinazolinone natural products using microwave technology has been reviewed <2007CSY223>. Formylation of perimidine with 1,3,5-triazine in 80% polyphosphoric acid (PPA) gave the 6(7)-carbaldehyde in 91% yield compared to only 10% yield with the Vilsmeier reagent <2007CHE527>. Using substituted triazines, the analogous 6(7)-methyl and phenyl ketones were obtained in 78 and 64% yields respectively <2007CHE527>.

In the signal transduction inhibitor area a new microwave-assisted solid phase synthesis of imatinib has emerged <2007TL3455>, while the development of second generation BCR-ABL inhibitors for the treatment of imatinib resistant chronic myeloid leukaemia (CML) continues <2007MI345, 2007MI407, 2007MI834>. Several other types of pyrimidine based kinase inhibitors have also been identified <2007BML668, 2007BML688, 2007BML2179, 2007BML3266, 2007BML3463, 2007BML4861, 2007JME627, 2007MI63, 2007OBC1577>. In the quinazoline area new syntheses of erlotinib and gefitinib have been published <2007H(71)39, 2007SC3409, 2007OPD813, 2007ARK(i)40, 2007MOL673>, and several other examples of quinazoline based kinase inhibitors have been described <2006BML4686, 2007BMC3635, 2007BML3081, 2007BML5863, 2007BML6326, 2007BML6373, 2007CCR3682, 2007JME2213, 2007JME2605, 2007MI431, 2007MI577>.

In other therapeutic areasalogliptin **1188**, a potent inhibitor of dipeptidyl peptidase IV is in clinical trials in patients with type 2 diabetes <2007JME2297>, and the vanilloid receptor-1 antagonists AMG517 **1189** and AMG628 **1190** have been selected for clinical evaluation <2007JME3497, 2007JME3515, 2007JME3528>. Analogs of the $\alpha 1$ -adrenoceptor antagonist (+)-cyclazosin have also been prepared <2007BMC2334>.



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Biographical Sketch



Gordon Rewcastle obtained his PhD in Organic Chemistry from the University of Auckland in 1978, and after post-doctoral study in the U.S., he joined the Auckland Cancer Society's Research Laboratory as a medicinal chemist in 1980. Since then has participated in a number of antibacterial and anticancer drug development projects, and is the author or co-author of over 100 scientific papers and patents in the anticancer area. In all, he has made significant contributions to the development of six of the eight anticancer drugs to have gone to clinical trial from the Auckland Cancer Centre.

After starting with the synthesis of analogues of the antileukemia agent Amsacrine, he moved to the development of new chemical routes to the (2-dimethylaminoethyl)acridine-4-carboxamide (DACA) series of antitumor drugs. Next he performed much of the early work on the phenazine-1-carboxamide series of antitumor agents, which subsequently led to the development of two derivatives (XR11576 and MLN944) which went to clinical trial. His next project involved an investigation of analogues of flavoneacetic acid, during which he helped to develop the anti-vascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA), now in clinical trial as AS1404 with Antisoma/Novartis. For his contributions to the acridine, phenazine and xanthenone work, he was awarded the Royal Society of Chemistry/New Zealand Institute of Chemistry Easterfield Medal in 1989.

The 1990's saw a change in direction, with the design and synthesis of tyrosine kinase inhibitors being the main area of activity. This work was performed in close collaboration with the Parke-Davis Division of the Warner-Lambert Company, and culminated in the development of the Epidermal Growth Factor Receptor (EGFR) irreversible inhibitor canertinib (CI-1033) which entered Phase I clinical trial with Pfizer in 1999. Gordon made several important contributions to the design of this drug, including performing the first chemical synthesis of it in 1997. In 1998 the Auckland Cancer Society Research Laboratory became part of the University of Auckland, and from 1999 to 2004 Gordon was the Group Leader of a number of Pfizer funded projects in both the anticancer and antibacterial drug development areas. In 2005 he joined the Maurice Wilkins Centre for Molecular Biodiscovery at the University of Auckland, where his current research involves an investigation of isoform-selective phosphoinositide 3-kinase (PI3K) inhibitors as potential anticancer agents.

8.03

Pyrazines and their Benzo Derivatives

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8.03.1 Introduction

The first synthesis of a pyrazine was described in 1844 by Laurent, whose product was later shown to be 2,3,5,6-tetraphenylpyrazine. The concept that pyrazines contain a six-membered ring system analogous to pyridine was first proposed in 1882. The parent pyrazine was prepared in 1888 in trace amounts by heating aminoacetaldehyde diethyl acetal. The name 'pyrazine' was first suggested in 1887, and finally adopted by the Widman systematic nomenclature. Extensive reviews on pyrazines by McCullough <1995SRC(4I/4J)93, 2000SSR(4I/4J)99>, Brown <B-2002MI1> and Sato <2004SOS(16)751>, on quinoxalines by Brown <B-2004MI1> and Gobec and Urleb <2004SOS(16)845>, and on phenazines by Bolton <2000SSR(4I/4J)173> and Gobec and Urleb <2004SOS(16)913>, have been issued since the publication of CHEC-II(1996).

Although there is an overlap of a few years with CHEC-II(1996) <1996CHEC-II(6)233>, this chapter covers 1993 through 2005 together with some selected references for 2006.

Owing to the amount of material available, it is not possible to include all relevant references. As in CHEC(1984) and CHEC-II(1996), references to patents generally have been omitted on account of the frequent difficulty of abstracting meaningful information from them. 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 unnecessary. All possible reduced derivatives of pyrazine **1**, and several of those of its benzo analogues quinoxaline **2** and phenazine **3**, are known. 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 chapter. 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 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 (Figure 1).

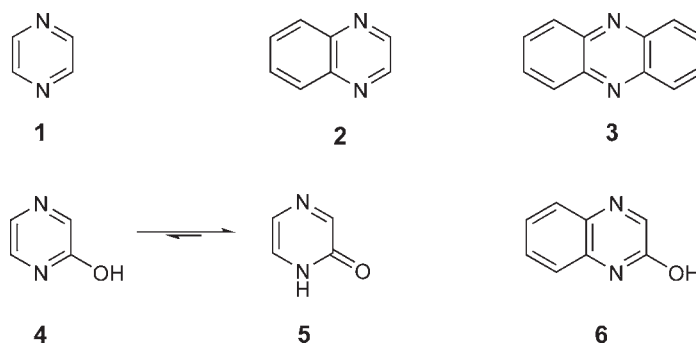


Figure 1

8.03.2 Theoretical Methods

Theoretical calculations have been a successful approach for the description of structures and thermochemistry for a wide variety of chemical substances; in fact, the theoretical methods have greatly increased in importance for investigating various properties of pyrazines, quinoxalines, and phenazines <1996CHEC-II(6)233>. In most cases, the calculated results have been discussed in comparison with spectroscopic properties; accordingly, in this chapter, such examples are shown in each section on spectroscopy.

Ab initio full geometry optimization at the 3-21G and 6-31G* levels were performed for 2,3-dimethylpyrazine, trimethylpyrazine, and tetramethylpyrazine, and MP2/RHF/3-21G/3-21G, and density functional theory (DFT) energies were also calculated for all the methylpyrazine isomers <1996STC329>. Their isodesmic resonance energies were estimated by comparison of the resulting calculated values with experimental ones from standard molar enthalpies of combustion. Thermochemical and theoretical study of pyrazine 1,4-dioxide, 5-methylpyrazine-2-carboxylic acid, quinoxaline 1,4-dioxide, 2-methylquinoxaline 1,4-dioxide, 2-acetyl-3-methylquinoxaline 1,4-dioxide, and 2-carbomethoxy-3-methylquinoxaline 1,4-dioxide was performed <1997JOC3722>, in which unconstrained geometry optimizations by *ab initio* calculations using STO minimal basis sets showed the effect of steric hindrance on changes in extended delocalizations and were in accord with the trends in the mean bond dissociation enthalpies. Semi-empirical (AM1 and PM3) and *ab initio* (MP2/6-31 + G*//HF/6-31 + G*) calculations revealed a preference for the dioxo tautomer of 2,3-dihydroxypyrazine in solution and in the gas phase <1998JCM222>. Similarly, DFT at B3LYP level and *ab initio* calculations were carried out to investigate the stability of different tautomers of 2-hydroxy and 2,3-dihydroxypyrazines <1999JMT(459)229>. The effects of the N-atom protonation on the static dipole polarizability of representative monocyclic azines containing pyrazine were studied using *ab initio* and DFT methods <2004CPL(396)117>. The protonation induces significant negative variations in the dipole polarizability of monocyclic azines. The geometries of polynitropyrazines and their *N*-oxides were fully optimized employing the density functional B3LYP method and the 6-31++G** basis set <2004MI231>. Calculated results show that the aromaticity of the pyrazine ring of polynitropyrazine is lower than that of its *N*-oxides. Theoretical studies using the B3LYP and MP2 levels of calculation, with the 6-31++G** basis set, were used to characterize hydrogen-bonded complexes between pyrazine and HX linear acids with X = F, NC, CN and C≡CH <2005JST(744/7)217>.

Additional examples of theoretical calculations for pyrazines, quinoxalines, and phenazines are arranged in Sections 8.03.3 and 8.03.4.

8.03.3 Experimental Structural Methods

8.03.3.1 X-Ray and Electron Diffraction Analysis

The X-ray crystal structures of several substituted pyrazines have been determined, for example, methyl 3-(triphenylphosphoranylidene)aminopyrazine-2-carboxylate <1996J(P1)247>, 2-chloro-3-methyl-5-phenylpyrazine 1-oxide <1997J(P1)3167>, 2,6-diarylpyrazines <1998HAC341>, 2,5-diamino-3,6-dichloropyrazine <1998AXC1018>, tetraphenylpyrazine <1999AXC1034>, pyrazine 1,4-dioxide <2002AXEo1253>, and aminopyrazine derivatives <2005JST(741)67>. A new pyrazine-based marine natural product, clavulazine, was also determined by X-ray analysis <1998H(49)269>. Crystal structures of methyl-substituted pyrazines were determined by X-ray diffraction analysis to

examine the effect of C–H group acidity on the nature of C–H $\cdots$ N interactions, suggesting weak hydrogen bonds <2000NJC463>. A very short O_{acid}–H $\cdots$ O_{water} hydrogen bond in the crystal structure of pyrazinetetracarboxylic acid was characterized by variable-temperature neutron diffraction analysis <2004PCA9406>. Adducts of pyrazine-2,3-dicarboxylic acid with 2-aminobenzoic acid (1:2) and 3-aminobenzoic acid (1:1 dihydrate) <1995AXC2629>, and crystalline polymorphs produced from mixtures of 2,3,5,6-tetramethylpyrazine 1,4-dioxide and tetracyanoethene (TCNE) were studied by X-ray crystallography <1997AGE1864>. In addition, X-ray studies were executed on a variety of metal complexes with pyrazine <1997AXC1186, 1998AXC302, 1999CL367, 1999BCJ2681, 2000BCJ1205, 2002CL1208, 2005BCJ445, 2005POL3074>, methylpyrazines <2005POL3074>, alkenylpyrazine <2005JST(754)37>, pyridylpyrazines <1998ACS770, 1998AXC1277, 1999JCD331, 1999IC6164, 2000BCJ1843, 2004EJI4836>, bipyrazine <2004EJI4836>, pyrazinecarboxylic acids <1998PJC2014, 2001JIC444, 2002JOC556, 2004JCD1832, 2005JCR1429, 2006JOM(691)1235>, pyrazine-2,3-dicarboxylic acids <1996CJC433, 1997PJC493, 1997SM(85)1661, 1998PJC627, 1999AGE140, 1999POL1507, 1999CL773, 2002BCJ1521>, the isomeric pyrazinedicarboxylic acids <2002JIC458, 2004JCR167, 2005EJI2586>, pyrazinetetracarboxylic acid <2005EJI4880>, and pyrazinecarboxamide <1999JCD1535, 2001B14166>.

The X-ray crystal structure determinations of 2(1*H*)-quinoxalinone, 3,4-dihydro-2(1*H*)-quinoxalinone <1993PHA523>, 2,3(1*H*,4*H*)-quinoxalinediones <1996AXB487>, 2,3-disubstituted quinoxaline <1998JHC977>, and 3-substituted-2-chloroquinoxaline <1998JHC113> have been conducted. A large number of metal complexes with 2-pyridylquinoxalines were explored by X-ray analysis <1994ICA(227)129, 1994POL3209, 1995POL1461, 1995ICA(240)673, 1996POL1035, 1998JCD185, 1998AXC485, 1998ICA(274)1, 1999POL601, 1999JCD331, 2004EJI4836>.

Structures of two new phenazine antibiotic metabolites isolated from a *Streptomyces* have been determined by X-ray analysis <1995JAN1081>. The pair-stacked structure of 10-(4-nitrophenyl)-5(10*H*)-phenaziny radicals <1995AXC1420> and structure of the β -polymorph of phenazine <2002AXCo181> were also established. A few highly fluorinated phenazines were characterized by single crystal X-ray analysis and ^1H , ^{19}F nuclear magnetic resonance (NMR) spectroscopy <2006JFC(127)200>. Weak hydrogen bonds in the crystal structure of phenazine, 5,6-dihydrophenazine, and their molecular complexes were concluded by X-ray analyses <2000NJC143>. A number of metal complexes of phenazines were investigated by X-ray analysis <1993IC826, 1993JCD3463, 1994JCD2771, 1995JCD2201, 2001CEJ5222>.

8.03.3.2 NMR Spectroscopy

The ^1H , ^{13}C , and ^{15}N NMR spectra of mono-, di-, and trisubstituted pyrazines with acetyl, alkyl, alkoxy, and methylthio substituents were reported <2000MRC907>. The assignment of chemical shifts to the ring carbons and nitrogens were verified by ^1H , ^{13}C and ^1H , ^{15}N correlation spectra, respectively. In the proton spectra of monosubstituted pyrazines, the $^nJ_{(\text{H},\text{H})}$ coupling constants are $^3J_{(\text{H}-5, \text{H}-6)} = 2.49\text{--}2.83\text{ Hz}$, $^4J_{(\text{H}-3, \text{H}-5)} = 0.27\text{--}0.36\text{ Hz}$, and $^5J_{(\text{H}-3, \text{H}-6)} = 1.44\text{--}1.62\text{ Hz}$. The same range of values has been found for the three isomers of disubstituted pyrazines in numerous studies, but the exceptions are pyrazinethiol with $^3J_{(\text{H}-5, \text{H}-6)}$ at 4.0–4.1 Hz <1993J(P1)15> and azidopyrazines with $^3J_{(\text{H}-5, \text{H}-6)}$ at 4.6 Hz <1994S931>. The substitution pattern of di- and trisubstituted pyrazines can be elucidated by a combination of NMR methods, especially in mixtures by gradient selected ^1H , ^{15}N heteronuclear multiple bond correlation (HMBC) experiments at the natural abundance level <2000MRC907>. In the case of disubstituted pyrazines, it is easy to distinguish between 2,3-/2,5- and 2,6-disubstituted isomers. This also allows the determination of ^{15}N NMR chemical shifts including the assignments even at relatively low concentrations. The ^{15}N NMR spectra of pyrazine, methylpyrazines, and their *N*-oxides were also reported <1996MRC567>, in which the chemical shifts of two ring nitrogen atoms were assigned on the basis of π -electron densities calculated by the modified neglect of diatomic overlap (MNDO) method. The ring nitrogens of methyl-substituted pyrazines and the *N*-oxides were unambiguously assigned by ^{15}N NMR spectra of ^{15}N -labeled pyrazines which were prepared from ^{15}N -alanine <1995JLR85>. The ^{19}F NMR spectrum of fluoropyrazine was measured for comparison with statistical substituent chemical shift (SSCS) values proposed previously for fluoroarenes <1994JFC(68)181>.

A ^{17}O and ^{14}N NMR study of 2,3-(1*H*, 4*H*)-quinoxalinediones and 1,4-substituted oxamides <1996JHC643, 1996TL3191> and a ^{13}C NMR study of quinoxaline spirans and carboxyureides <1996H(43)1873> were conducted, and a multinuclear NMR investigation of sterically congested 2,3-disubstituted quinoxalines was reinforced by PM3 and *ab initio* calculations <1998JST(444)199>. The ^1H , ^{13}C , and ^{15}N NMR chemical shifts for a variety of quinoxalines were determined by two-dimensional (2-D) correlation measurement methods <2005MRC816>. The experimental chemical shifts have good correlation with estimates calculated using the gauge-independent atomic

orbital (GIAO) DFT approach. In nonpolar solvents, quinoxalines exist as dimers owing to strong hydrogen bond. Calculations for dimers improve the correlation between experimental and theoretical values.

8.03.3.3 Mass Spectrometry

Mass spectrometry (MS) is a powerful analytical method for the detection and characterization of the infinitesimal quantities of naturally occurring pyrazines in red wine <1995JFA769>, yogurt flavor <1997JFA850>, trail pheromones of ants <2003RCM2071>, and cigarette smoke <2004MI23, 2004MI175>. These analyses were usually performed by gas chromatography/mass spectrometry (GC/MS) with capillary column separation and electron impact ionization (EI), in which much more sensitive technique for quantitative analysis, for example, selected ion monitoring (SIM), was employed recently <2004MI175>. A sample of tobacco essential oil <2005ANA224> and cigarette smoke condensate <2004MI101>, especially the latter being composed of a complex chemical matrix, was analyzed by comprehensive 2-D gas chromatography coupled to a time-of-flight mass spectrometry (GC×GC/TOFMS). On the other hand, resonance-enhanced multiphoton ionization (REMPI) combined with time-of-flight mass spectrometry (TOFMS) proved to be an analytical method capable of online monitoring of trace compounds in complex matrixes containing pyrazines <2006MI72, 2006MI454>.

Quantitative determination of diacetyl and 2,3-pentanedione during beer fermentation was achieved by GC/MS method as 2,3-dimethylquinoxaline and 2-ethyl-3-methylquinoxaline, respectively, after reacting with 1,2-diaminobenzene <2006MI52>.

8.03.3.4 IR and Raman Spectroscopies

Infrared (IR) and Raman vibrational spectra of 3-aminopyrazine-2-carboxylic acid <1993SAA283>, pyrazine-2,3-dicarboxylic acid as well as its dipotassium salt <1993SPL57>, pyrazine-2,5-dicarboxylic acid in addition to its dipotassium salt <1993JMT(101)91>, and pyrazinecarbaldehyde <1993JCF43> were recorded and assigned, and in the latter two studies the vibrational frequencies and/or the minimal energy geometry were calculated by *ab initio* methods. The high-resolution IR spectrum of pyrazine was measured in a molecular beam in the vicinity of the C–H stretching transition <1993MI1>. The rotational structure in the spectrum of pyrazine from 3065 to 3073 cm^{−1} reveals that the C–H stretch is coupled to one other vibrational mode in the molecules. Vibrational transitions of pyrazine in the lowest triplet state were observed as transient charges in the intensity of the phosphorescence induced by the free electron laser FELIX (free electron laser infrared experiments) <1997JCP2984>. All seven fundamental IR-active modes between 250 and 1600 cm^{−1} were detected, and all vibrational frequencies are considerably lower than the corresponding ones in the ground state. A comparative study on the IR and Raman vibrational spectroscopies of pyridazine, pyrimidine, and pyrazine was carried out <1998JMT(423)225>, where the vibrational fundamental frequencies were calculated applying *ab initio* quantum-chemical methods. The quartic force field of pyrazine was calculated using the B3LYP/6-31G(d) hybrid density functional method, and the IR (3800–250 cm^{−1}) and Raman (3200–400 cm^{−1}) spectra of pyrazine were interpreted on the basis of the resulting calculation <2005MI9>. Experimental and DFT study of pyrazinecarboxamide <2005CPH(316)153> showed that the intermolecular hydrogen bonds were confirmed by comparison of Fourier transform infrared (FTIR)/attenuated total reflectance (ATR), Raman, and NMR spectra with theoretical calculations at B3LYP and BLYP/6-31G(d) and cc-pVDZ levels.

Spectroscopic (MS, NMR, IR) studies of quinoxalines were conducted <1995JCM10>. The structure and vibrational spectra of 2,3-bis(2-pyridyl)quinoxaline (bpq) and 2(*N*-methylpyridyl)-3-pyridylquinoxaline (meppq) useful for building blocks for dendrimers were measured by crystal X-ray diffraction and IR spectral experiments, respectively <2002JMT(589/90)301>. Those results were compared with ones calculated from the *ab initio* Hartree–Fock and the hybrid density functional methods.

8.03.3.5 UV and Related Spectroscopies

Vibronic coupling in the triplet absorption spectrum of pyrazine was analyzed <1993CJC1537>, and characterization of the *S*₁–*S*₂ conical intersection in pyrazine was realized using *ab initio* multiconfiguration self-consistent field and multireference configuration interaction methods <1994JCP1400>. Hydrogen bond and the delocalized nature of *S*₁ ¹(*n*,*π*^{*}) excited state of pyrazine were discussed on the basis of interpretation of the absorption and fluorescence solvent shift <1995JA8618>. The effect of molecular structure on the photophysical behavior of substituted styryl pyrazine derivatives was investigated through the measurement of fluorescence quantum yields <1997MI237>. The

vibronic fine structure in electronic spectra of benzene and pyrazine at different temperatures was calculated <1998PCA7157>, and the equilibrium geometries and frequencies determined at complete active space self-consistent field (CASSCF) level as well as the calculated spectra are in good agreement with experimental data. The self-association of pyrazine was studied in aqueous solution at acidic, neutral, and basic pH values, by ultraviolet (UV) spectroscopy <2003SAA1223>.

Derivative spectrometric methods for the detection of diazines were reported <1998C251>, where pyrazine and 2,2'-bipyrazyl can be detected in their mixture best of all using the first derivative spectra, and quinoxaline and 2-methylquinoxaline using the second derivative spectra. Chromophore-labeled quinoxaline derivatives were investigated for their influence on photophysical and thermal properties for use in electroluminescent materials <2005CM1860>. Absorption, fluorescence excitation, and fluorescence spectroscopy, combined with time-dependent spectroscopy and semi-empirical (AM1) and DFT using Gaussian 98 program calculations, were used to study the effects of solvent and acid or base concentration on the spectral characteristics of methyl 3(4*H*)-quinoxalinone-4-carboxylate <2005MI114>.

Electronic absorption and fluorescence excitation and emission spectra of phenazines were determined in several solvents of various polarities <1995SAA603>, and the effect of the solvent upon the spectral characteristics was studied.

8.03.3.6 ESR and Related Spectroscopies

Electron spin polarization transfer between pyrazine as a donor and nitroxyl radicals as acceptors was examined by time-resolved electron spin resonance (ESR) spectroscopy <1993CPL(216)231>. The excited molecule-free radical interactions were shown to rely on the solvent used for the measurement. The radical cation of *N,N'*-dimethylated pyrazine, which formed by mixing the pyrazine, dimethyl sulfate, and a reducing agent such as tetrabutylammonium borohydride or zinc powder in a sample tube containing benzene as a solvent, was detected by ESR spectroscopy <1994G455>. Spin polarization in the triplet state of pyrazine after flash photolysis was verified through chemically induced dynamic electron polarization (CIDEP) observation in benzene or 2-octanol <1997MI297>. Electrochemically generated radical cation of pyrazine 1,4-dioxide was studied by ESR electrolysis <2004MI1035>.

An electrochemical and ESR study of 2,7-disubstituted phenazines has appeared <1996CPB1448>. The electrochemically generated radical cation of phenazine *N,N'*-dioxide was investigated by ESR electrolysis and cyclic voltammetry <2002MI4245>. Time-resolved and steady-state ESR spectra were observed for the lowest excited triplet (T_1) states of phenazine and its monoprotonated cation (phenazinium) in sulfuric acid-ethanol mixture at 77 K <2005SAA1147>.

8.03.4 Thermodynamic Aspects

8.03.4.1 Boiling Points, Melting Points, Solubility, and Stability

An extensive table by Brown <B-2002MI1> of boiling points and melting points of simple pyrazines described up to the end of 2000, together with reported spectra or other physical properties, is available.

Most pyrazines are thermally stable, but pyrazinecarboxylic acids undergo decarboxylation at high temperature above 200 °C. This reaction is practically utilized for the synthesis of alkyl- or arylpyrazines, pyrazinones, and pyrazinamines from the corresponding pyrazinecarboxylic acids (Section 8.03.7.1).

The pyrazine ring is stable toward permanganate oxidation, and this explains a variety of pyrazinecarboxylic acids that have been prepared from quinoxalines or benzo-fused quinoxalines. In contrast, alkyl side chains on pyrazines are effectively oxidized by permanganate, selenious acid, selenium dioxide, or dichromate to afford the corresponding carboxylic acids (Section 8.03.7.1). Oxidation of pyrazines with hydrogen peroxide or percarboxylic acids gives pyrazine *N*-oxides and/or *N,N'*-dioxides (Section 8.03.5.2).

Thermal stability and thermal degradation of pyrazine 1,4-dioxide were examined in comparison to those of several heteroaromatic compounds <1995KGS1573>, and a correlation between thermal stability and electronic charge on the oxide oxygen was demonstrated. The stability of 2,6-dihydroxypyrazines was found to depend on the substituents; thus, 3-methyl-5-phenyl-2,6-dihydroxypyrazine was successfully isolated by demethylation of the corresponding dimethoxypyrazine although the 3,5-dimethyl derivative was extensively decomposed by the same procedure <1997J(P1)3167>. Analogous to 2,6-dihydroxypyrazines, the isomeric 2,5-dihydroxy derivatives carrying mono- or no substituent are extremely unstable and have not been isolated so far. However, hydrolysis of

2-hydroxy-5-methoxypyrazine with hydrochloric acid was reported to yield the parent 2,5-dihydroxypyrazine <2000H(53)69>. Reinvestigation of the hydrolysis, in which 2-hydroxy-5-methoxypyrazine was obtained by an independent synthetic pathway, resulted in no formation of any aromatic compounds <2005JCM747>.

A solubility study coupled with IR and titrametric measurements and *ab initio* molecular orbital calculations was performed on 2,3-pyrazinedicarboxylic acid <2000JST(526)191>, demonstrating that the dicarboxylic acid exists in the solid as such and not in a zwitterionic form. In addition, one internal and one external $\text{O}\cdots\text{O}=\text{C}$ hydrogen bond per molecule were proposed.

The stability of dihydropyrazines is discussed in Section 8.03.6.

8.03.4.2 Chromatographic Behavior

Quantitative analysis of methylpyrazine and 2,5-dimethylpyrazine was studied by GC using pyrimidine as an internal standard <1997MI409>, and the retention factor of monosubstituted pyrazines was determined by reversed-phase high-performance liquid chromatography (HPLC) <1999QSA26, 2000CPB1973>. The retention behavior of some pyrazine derivatives was also investigated by thin-layer chromatography (TLC) on silica gel and cellulose utilizing different eluents <2001MI125>. The chromatographic behavior depends on their molecular structure, the nature and polarity of eluent, and the nature of stationary phase.

The use of headspace solid-phase microextraction (HS-SPME) combined with GC was effective for isolation and determination of alkylpyrazines in cocoa liquor <2004JBS267, 2004MI291>, and similarly methoxypyrazine in wine was analyzed by HS-SPME/2-D GC <2005MI1075>.

A mixture of pyrazinecarboxamide (pyrazinamide, PZA), rifampicin (PIF), and isoniazid (INH) has been used together with either ethambutol (EMB) or streptomycin (SM) for initial chemotherapy of tuberculosis; therefore, a large number of chromatographic methods have been reported for the simultaneous analysis by HPLC <1994JCH(B)(658)391, 1997JLC459, 2000MI345, 2001JCH(B)(754)477, 2002JCH(B)(766)181, 2002JCH(B)(766)357, 2003MI607, 2004ANA231, 2004MI702>, micellar electrokinetic capillary chromatography (MEKC) <2002MI432>, and TLC <1999MI217, 2001JLC1479>.

Rapid and sensitive HPLC methods were developed for the detection of an antimicrobial growth promoter and its main metabolites containing quinoxaline-2-carboxylic acid <2005MI1495>. The major phenazine pigments of *Pseudomonas aeruginosa* such as 1-hydroxyphenazine and phenazine-1-carboxylic acid <1997JCH(A)(771)99>, and 2-aminophenazine as an impurity in a bactericide <1999MI632>, were also analyzed by HPLC methods.

8.03.4.3 Aromaticity

Since the first proposal in 1989, Katritzky and co-workers developed the concepts of classical (geometric and energetic) and magnetic aromaticities, which are orthogonal to each other, on the basis of principal components analysis <1993QSA146>. Some groups claimed that linear relationships exist among the energetic, geometric, and magnetic criteria of aromaticity, or that good linear relationships exist between experimental diamagnetic susceptibility enhancements and the corresponding resonance energies and/or aromaticity indexes. In response to these doubts, Katritzky's group reaffirmed aromaticity as a multidimensional characteristic <1998JOC5228>.

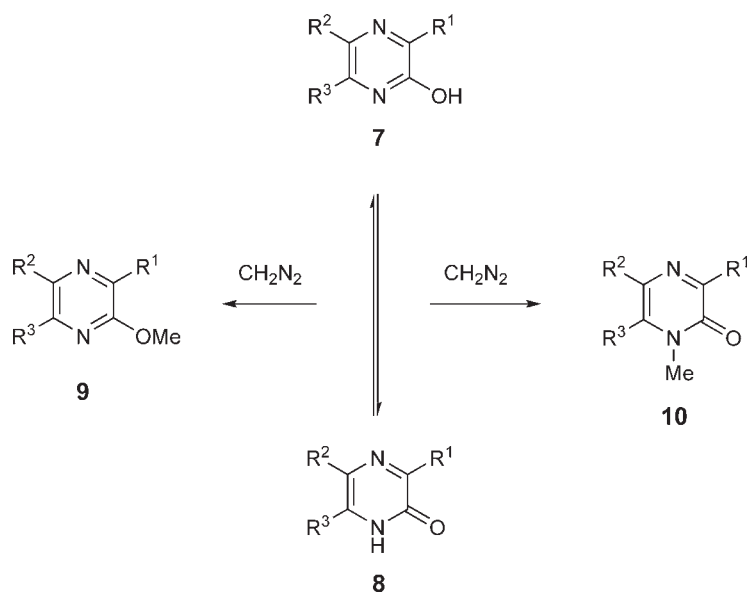
For several years, claims that the phenomenon of aromaticity can be described by a single index have appeared. For example, a multicenter bond index involving the $\sigma + \pi$ electron population was proposed as a measure of aromaticity <2000PCP3381>. It is related both to the energetic and to the magnetic criteria. A localized fragment molecular orbital basis set was constructed to perceive the aromaticity and conjugation <2000PCA1736>. *Ab initio* (HF and MF2) and hybrid DFT (B3LYP) calculations were performed on a series of monocyclic aromatics including diazines <2003JMT145>. The aromaticity in this class of compounds is evaluated based on the nucleus-independent chemical shift (NICS) value. On the other hand, a number of the aromaticity indexes, especially magnetic ones containing NICS, for six-membered heteroaromatics were calculated <2004JPO303>. Correlation coefficients between the indexes revealed that mutual relationships between them depend on their composition and that some magnetic characteristics themselves may be orthogonal to others.

A thermochemical study of quinoxaline was carried out by combustion calorimetry <1998MI93>, and using these experimental values the resonance energy was determined.

8.03.4.4 Tautomerism

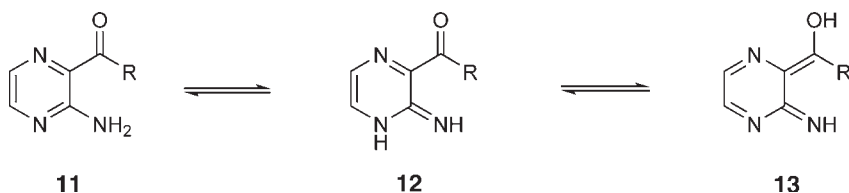
A typical example of tautomerism is represented by the equilibrium between hydroxypyrazine **4** or **7** and 2(1*H*)-pyrazinone **5** or **8**, in which the latter keto form predominates over the hydroxyl or enol form. A similar situation exists in hydroxylquinoxaline **6**. The tautomeric equilibrium, however, is susceptible to the additional substituents. For example, 6-amino-2(1*H*)-pyrazinone **8** ($R^1 = \text{Me}$, $R^2 = \text{Bn}$, $R^3 = \text{NH}_2$) has been shown to predominate over the hydroxyl form **7** <1993JOC7542>. On the contrary, 6-methoxy-2-hydroxypyrazines **7** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = \text{OMe}$) exist in the hydroxyl form rather than as the tautomeric amide <1997J(P1)3167>, and these examples have a predominance of the hydroxyl form parallel the isomeric 5-methoxy-2-hydroxypyrazines as well as the chloro-hydroxypyrazine field <1996CHEC-II(6)233>.

The elucidation of the hydroxypyrazine–pyrazinone tautomerism has been made using spectral methods. An IR spectral analysis focuses on the carbonyl absorption of the amide group in the keto tautomer. A more useful method is UV spectroscopy, that is, the objective structure in solution is easily estimated by comparison with the UV spectra of bond-fixed compounds related to the two tautomers, namely O-methylated and N-methylated derivatives **9** and **10**, which are prepared by methylation of the hydroxypyrazines or pyrazinones with diazomethane (Scheme 1). The above two investigations were achieved by this methodology.



Scheme 1

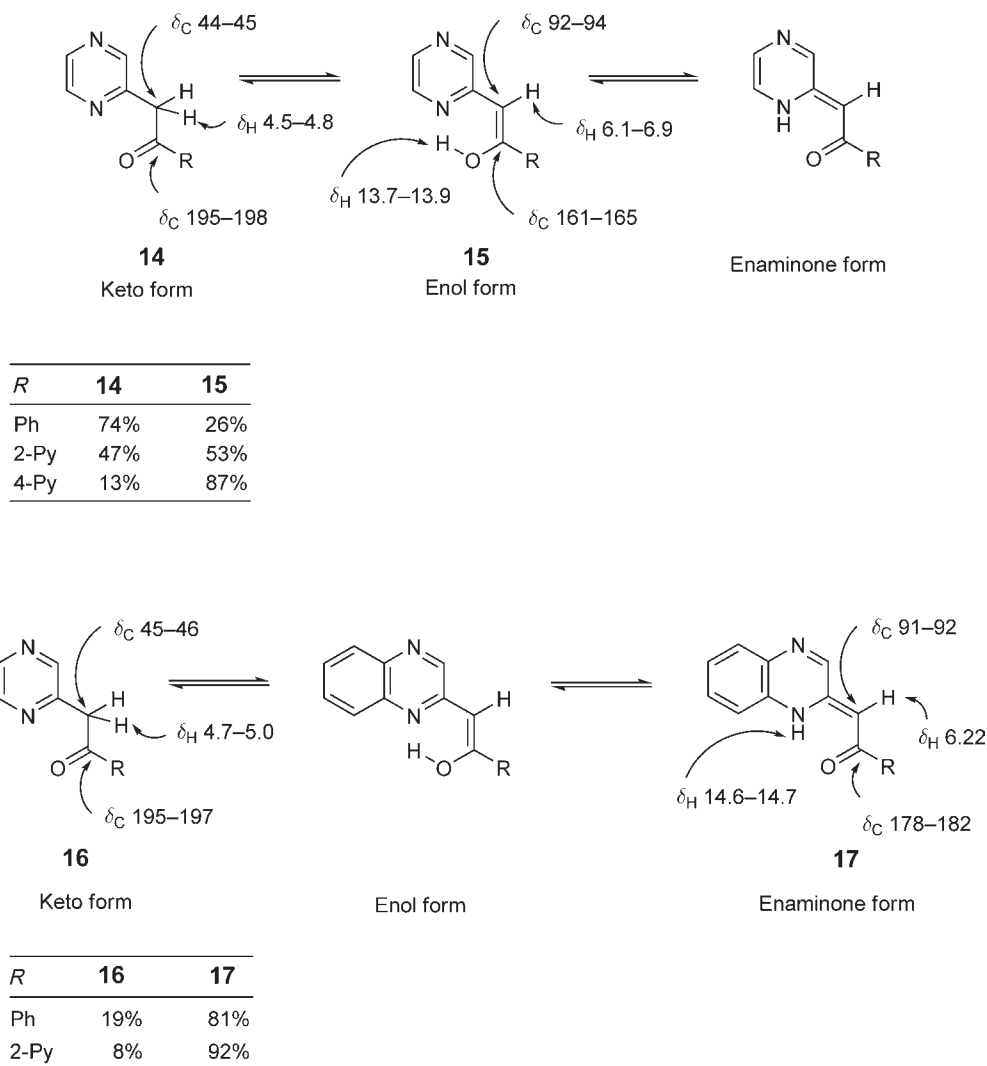
Amine–imine tautomerism in 3-acyl-substituted aminopyrazines has been examined by ^1H , ^{13}C , and ^{15}N spectral analysis as well as X-ray crystallography <2005JST67>. In the same way as the parent aminopyrazine, those aminopyrazines have been shown to exist in the amino form **11** ($R = \text{H}$, Me , Ph) (Scheme 2) in contrast to an expectation that the electron-withdrawing acyl groups adjacent to the amino substituent would stabilize the imino tautomers **12** and **13**. Thus, all NMR spectra showed only existence of the amino tautomer **11**, and additionally the



Scheme 2

theoretical calculations at the hybrid Becke 3LYP/6-31G* level reveals that the tautomers **12** and **13** have much higher energy values of about 86 kJ mol⁻¹ and 170 kJ mol⁻¹, respectively.

¹H and ¹³C NMR spectra in CDCl₃ have been efficiently utilized for distinguishing enol and enaminone tautomers of acylmethyl-substituted pyrazines **14** and quinoxalines **16** <1994J(P2)2461>. As shown in Scheme 3, signals characteristic of each structure are clearly observed, indicating that the tautomeric equilibrium between keto **14** and enol forms **15** in the pyrazine series dominates whereas that between keto **16** and enaminone forms **17** dominates in quinoxalines. Kinetic and equilibrium measurements for ionization and enolization of phenacetylpyrazine in aqueous solution at 25 °C yield a tautomeric constant pK_E = 2.05 (where K_E = [enol]/[ketone]) and pK_a's for loss of a methylene proton and for protonation at nitrogen of 11.90 and 0.40 <1994J(P2)2471>.

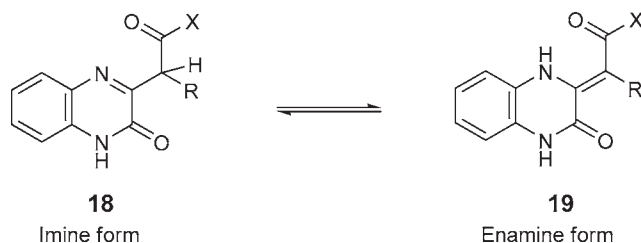


Scheme 3

The X-ray diffraction analysis of the crystal structure of pyrazinecarbohydroxamic acid revealed that the molecule is present in the keto tautomeric form and possesses the (Z)-configuration <2001RJ0866>.

Tautomeric equilibrium between imine **18** and enamine **19** forms of 2(1*H*)-quinoxalinonyl acetic acid derivatives (Scheme 4) has been recognized already but found to be affected by the substituent R on the side chain. When R is hydrogen and X is alkoxy or arylamino group, both tautomers **18** and **19** exist in DMSO-*d*₆ or CDCl₃ <1994ZOR1681,

[1995JHC671](#)> in a similar fashion to the precedent (DMSO = dimethyl sulfoxide). However, the quinoxalinone **18** (R = Me, X = C₆H₅O) exists only in the imine form due to the steric hindrance of the methyl group [1997JHC773](#)>.



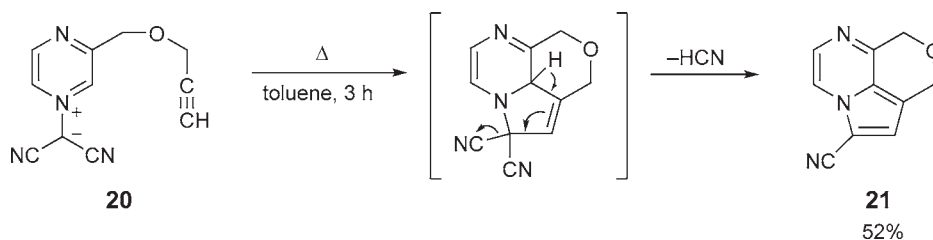
Scheme 4

8.03.5 Reactivity of Fully Conjugated Rings

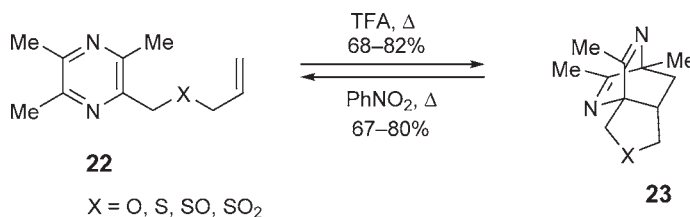
Reactivity dealt with in the following sections is limited only to that of the heteroaromatic ring of pyrazines, quinoxalines, and phenazines, but exceptionally the reactivity on the benzo moiety of quinoxaline and phenazine is described in the [Section 8.03.5.3](#). In general, any type of substitution 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.

8.03.5.1 Thermal and Photochemical Reactions

Thermally induced intramolecular [3+2] cycloaddition reactions of the pyrazinium dicyanomethylides **20**, carrying a variety of side chains with terminal alkynes as dipolarophiles, lead to the novel fused 7-azaindolizines **21** in high yields ([Scheme 5](#)) [1995H\(40\)69](#)>. On the other hand, pyrazines **22** bearing alkenyl side chains can undergo intramolecular Diels–Alder reaction in refluxing trifluoroacetic acid to give bridged tricyclic adducts **23** ([Scheme 6](#)) [1996TL8205](#)>. A retro-Diels–Alder regeneration of the starting material occurs in hot PhNO₂. The azadiene system in 2-(1*H*)-pyrazinones has been often used in [4+2] cycloaddition reactions. Hoornaert and his group showed

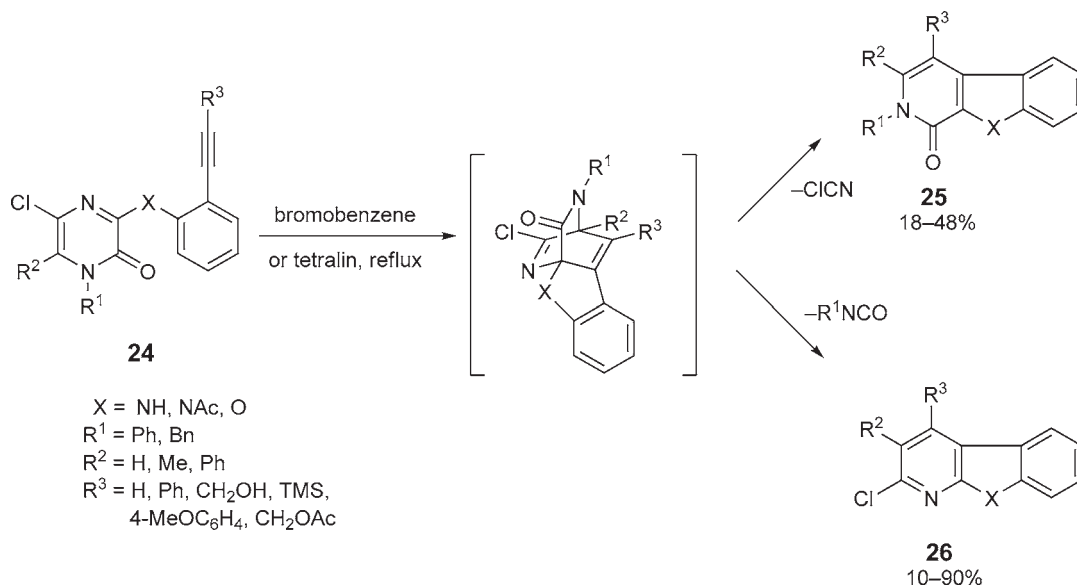


Scheme 5



Scheme 6

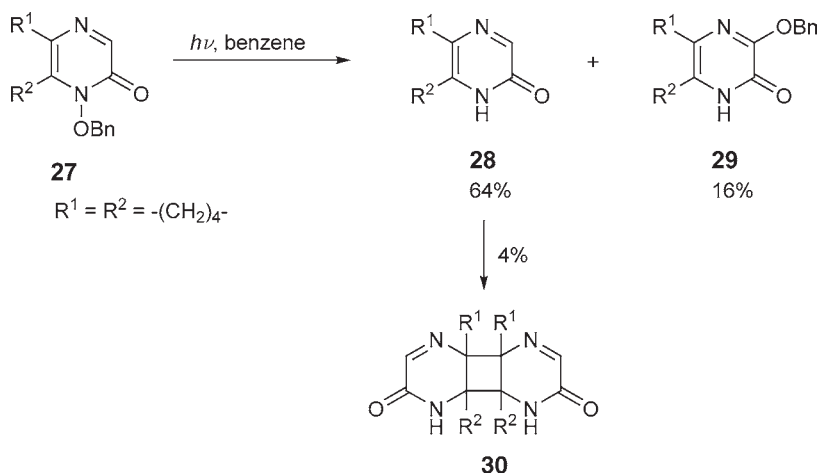
that 2(1*H*)-pyrazinones **24** having an appropriate alkynyl substituent undergo intramolecular cycloaddition–elimination on thermolysis yielding planar tricyclic compounds **25** and in some cases **26** (Scheme 7) <1998T13211, 1999T14675>. In the case of (2-propynylthio)methyl-2(1*H*)-pyrazinones, dihydrothieno-fused pyridines was formed by refluxing in toluene <2003T5481>. In the same fashion, 2(1*H*)-pyrazinones possessing alkenyl side chain provide bridged tricyclic ring systems <2002TL447, 2003T4721>.



Scheme 7

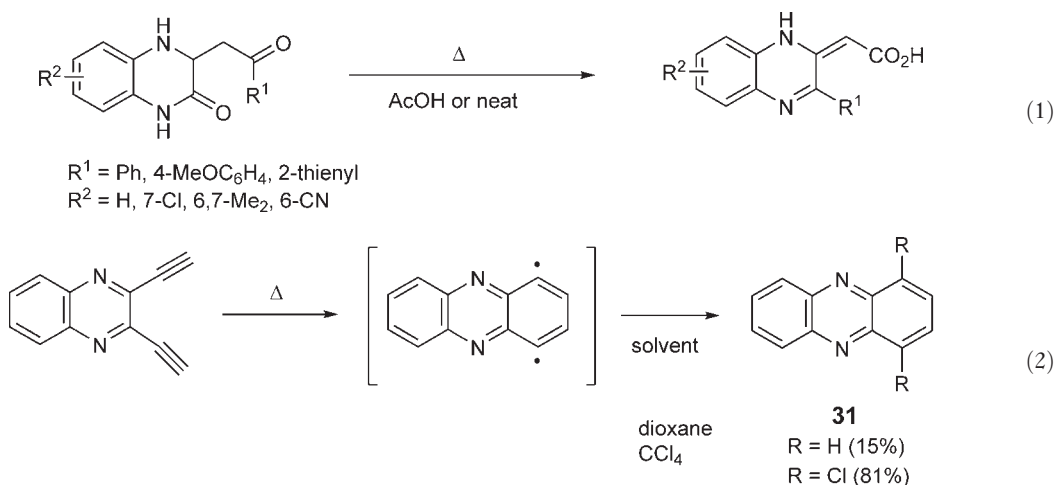
The intramolecular hetero-Diels–Alder reactions in functionalized 2(1*H*)-pyrazinones to give bicyclo adducts were found to undergo a significant rate enhancement using controlled microwave irradiation in ionic liquid doped solvents <2002JOC7904>.

Irradiation of 1-benzyloxy-2(1*H*)-pyrazinones **27** causes N–O bond cleavage resulting in the formation of 2(1*H*)-pyrazinones **28** (Scheme 8) <1996H(43)883>. Additionally, the leaving benzyloxy group rearranges to the ring carbon adjacent to the carbonyl moiety to yield 3-benzyloxy-pyrazinone **29**, and a portion of 2(1*H*)-pyrazinone **28** which undergoes [2+2] cycloaddition forming planar tricyclic compound **30**.

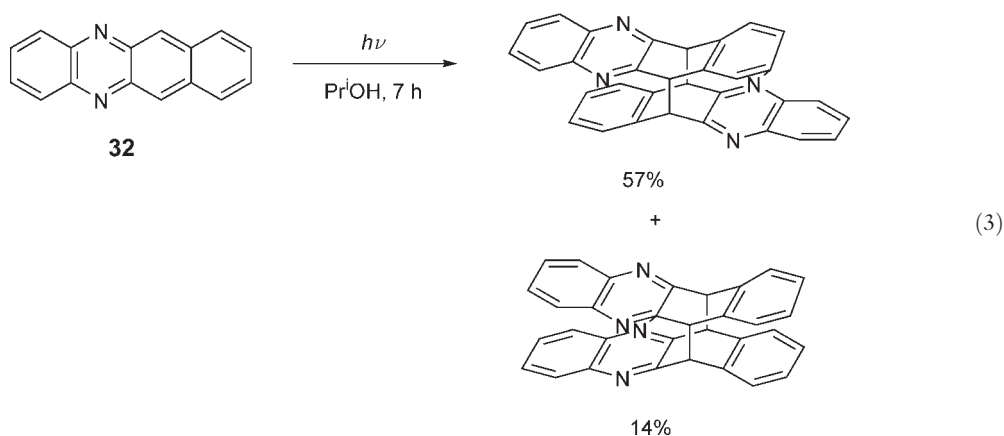


Scheme 8

Thermal rearrangement of 3-phenacyl-2(1*H*)-quinoxalinones to 2-carboxymethylidene-3-aryl-1,2-dihydroquinoxalines was undertaken (Equation 1) <2003MI31>, and photochemical transformation of 5-nitroquinoxalines was studied <1998RJC451>. Thermocyclization of 2,3-diethynylquinoxaline to the 1,4-disubstituted phenazines **31** was studied kinetically (Equation 2) <1999TL3835>, and the cyclization rates observed depended upon the solvent used.



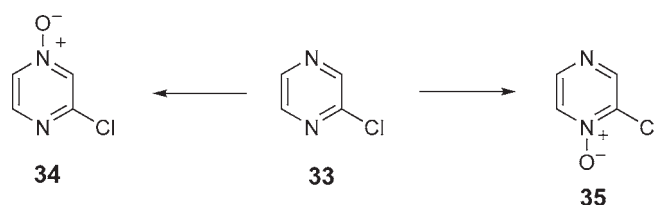
Photoinduced reactions of benzo[*b*]phenazine **32** are governed by the presence of low-lying $\pi\pi^*$ states, and include both [4+4] dimerization and self- or exogenously sensitized photooxygenation (Equation 3) <1995H(40)577>.



8.03.5.2 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. The N-1 nitrogen in 2(1*H*)-pyrazinone **5** is methylated using chloro(chloromethyl)dimethylsilane followed by desilylation with cesium fluoride to yield 1-methyl-2(1*H*)-pyrazinone <2000TL4933>.

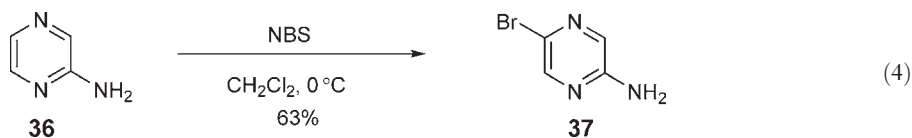
N-oxidation of chlorinated pyrazine **33** with *m*-chloroperbenzoic acid produces 3-chloropyrazine 1-oxide **34** (Scheme 9) <1996JHC1047>. The oxidation to *N*-oxides **34** has been also accomplished by treatment with peracetic, peroxymaleic, or peroxytrifluoroacetic acids. A new oxidizing reagent for chloropyrazines is dimethyldioxirane (DMDO), in which the reaction is completely regioselective and the products are easily isolated in good yields <2003HCO221>. Meanwhile, *N*-oxidation of chloropyrazine **33** with peroxysulfuric acid, which is generated *in situ* from potassium persulfate in concentrated sulfuric acid, yields 2-chloropyrazine 1-oxide **35** <1997J(P1)3167>. The structure of this product, whose direction of the *N*-oxidation is opposite to that in the former, was definitely confirmed by X-ray crystallographic analysis.



Scheme 9

8.03.5.3 Electrophilic Attack at Carbon

Owing to 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 occur, but these are limited in number. Such an example is bromination of aminopyrazines. Direct conversion of aminopyrazine **36** to 2-amino-5-bromopyrazine **37** was first achieved by treatment with bromine in chloroform in the presence of pyridine (Equation 4). The yields of bromination have been improved by using tetrabutylammonium perbromide with pyridine <1995SL1227>, or *N*-bromosuccinimide (NBS) in dichloromethane <2005JCM747>. Treatment of 2,6-diaminopyrazine with NBS in aqueous DMSO gives the 3,5-dibromo derivative <2001S768>. Bromination of 2-amino-3-benzoylpyrazine is easily effected by classical procedure using bromine in acetic acid to afford an 88% yield of the 5-bromopyrazine <1996SL509>, and similar treatment of 2-methylamino-3-cyanopyrazine affords an 86% yield of the 5-bromo compound <2000J(P1)89>.



Hydroxypyrazines or 2(1*H*)-pyrazinones are also subject to electrophilic halogenation. A new result is that 1-benzyl- or 1-phenyl-substituted 2(1*H*)-pyrazinones undergo bromination with NBS or *N*-iodosuccinimide (NIS) to give the 5-bromo or iodo-2(1*H*)-pyrazinones in 66–82% yields <2004TL1885, 2005T3953>.

Nitration of 6,7-disubstituted 3,4-dihydro-2(1*H*)-quinoxalinones with fuming nitric acid in trifluoroacetic acid produces the 5-nitro-2,3(1*H*, 4*H*)-quinoxalinediones in good yields <1995JOC5838>. Methyl 6-methyl-2,3(1*H*,4*H*)-quinoxalinedione-5-carboxylate is regioselectively nitrated with a mixture of potassium nitrate in concentrated sulfuric acid to give the corresponding 7-nitro derivative <1999JHC1271>.

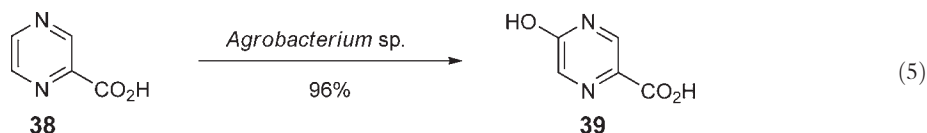
8.03.5.4 Nucleophilic Attack at Carbon

8.03.5.4.1 Displacement of ring protons

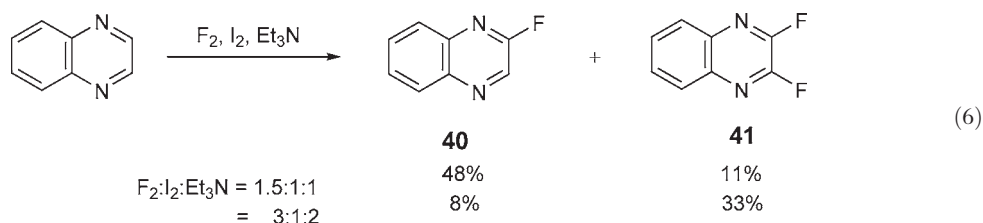
Unlike benzene compounds, which undergo ready electrophilic substitution, the highly deficient pyrazine and quinoxaline nuclei are susceptible toward nucleophilic attack by a number of reagents. The direct nucleophilic substitution with organolithium or Grignard reagents to form alkyl or aryl heteroaromatics, however, is rather ineffective, and the dihydro and/or tetrahydro compounds are formed preferentially. A typical reaction involving replacement of ring hydrogen is the Tschitschibabin reaction, in which pyrazine **1** is successfully converted into aminopyrazine **36** by treatment with KNH_2/NH_3 followed by potassium permanganate oxidation. Unfortunately, there are few new findings for this category of transformation since 1993. Such an exceptional example is the reaction of 2-acylamino- or aminopyrazine with alkylolithiums in tetrahydrofuran (THF) resulting in regioselective alkylation at C-3 in moderate yields <1996SL1015>.

An interesting report is the hydroxylation of pyrazinecarboxylic acid **38** with biocatalysts <1994SL814>, where all isomers of hydroxypyrazinecarboxylic acids can be prepared by the use of three individual wild-type microorganisms in whole-cell biotransformations. The enzymatic hydroxylation is most practical for the synthesis of

5-hydroxypyrazine-2-carboxylic acid **39** (Equation 5). Conversely, the 6-hydroxy isomer is less stable and the biotransformation leading to the 3-hydroxy isomer is less productive.



Reaction of quinoxaline with the fluorine–iodine–triethylamine system gives 2-fluoroquinoxaline **40** and 2,3-difluoroquinoxaline **41**, whose yields depend on the fluorine usage (Equation 6) <1999J(P1)803>. Using 6-chloroquinoxaline or 6,7-dichloroquinoxaline as the substrate, the monofluoro product is predominantly formed regardless of the amount of fluorine used. It is suggested that the reaction proceeds via attack of the fluoride ion on the α -carbon of an intermediate *N*-iodo quinoxalinium species followed by elimination of hydrogen iodide with triethylamine.



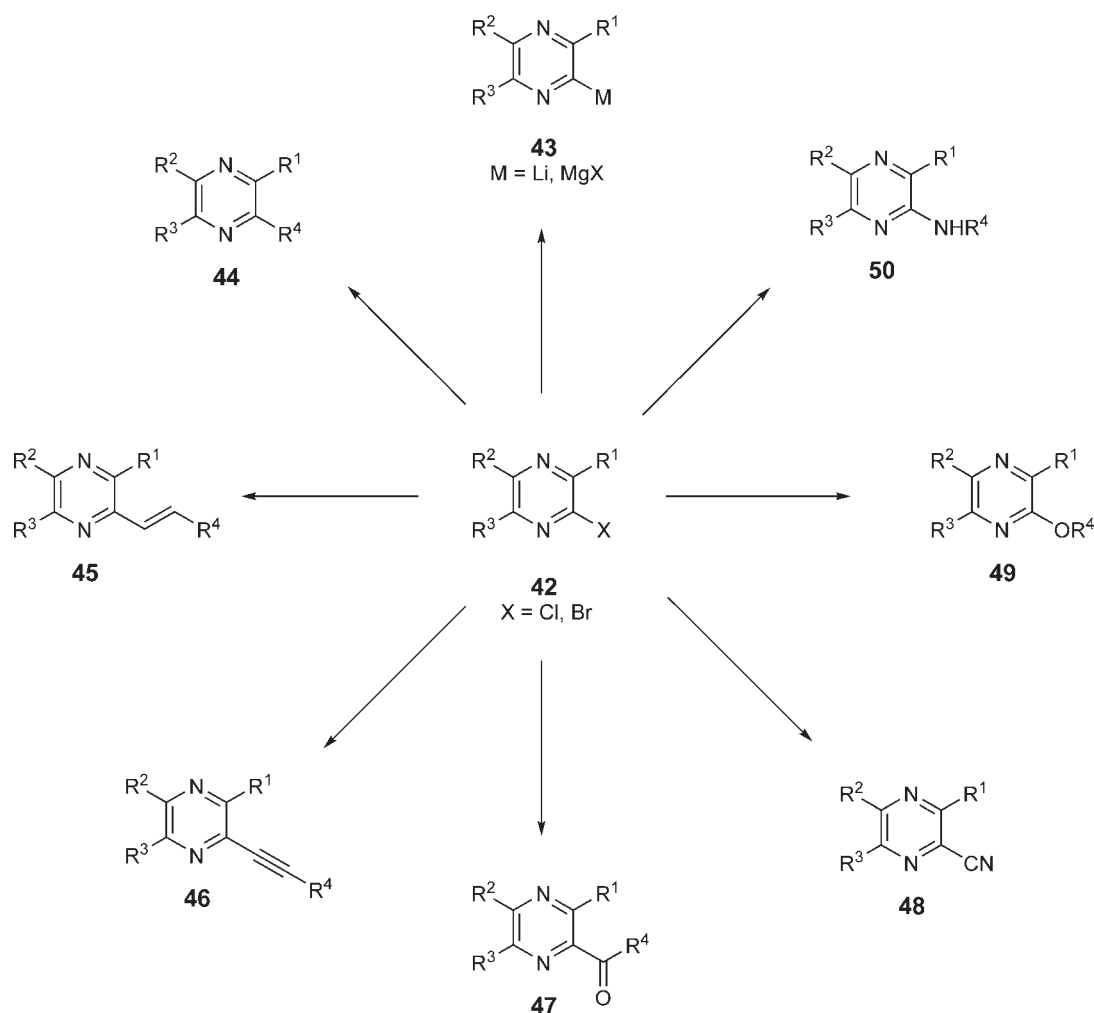
8.03.5.4.2 Nucleophilic displacement of substituents

Nucleophilic displacement of halogen in pyrazines and quinoxalines is the most common method for the synthesis of otherwise inaccessible heterocycles (Scheme 10). Halogen–metal exchange is an efficient method for the formation of pyrazinyl lithium, in addition to lithiation promoted by directing metalation group (DMG; see Section 8.03.5.5). Naphthalene-catalyzed reductive lithiation results in chlorine–lithium interconversion; thus, chloropyrazines **42** (X = Cl) are transformed into pyrazinyl lithium **43** (M = Li) without involving *ortho*-lithiation <2000T4043>. Iodopyrazines undergo halogen–magnesium exchange, yielding the corresponding Grignard derivatives, in which *n*-butyl or isopropylmagnesium chloride is effectively used <2000T265>. These organometallic substances **43** (M = MgX) can be converted into a variety of alcohols or ketones (see Section 8.03.11.2).

Although in the benzene series only the iodo derivatives undergo metal-catalyzed substitution reactions, chloropyrazines **42** and the bromo analogues can be cross-coupled with organometallic reagents. Palladium-mediated Stille coupling of bromopyrazines with aryltributylstannanes produces good yields of arylpyrazine **44** <1995SL1227, 2003T6375, 2005T9637>. A Suzuki coupling approach using arylboronic acids is also effective for arylation of pyrazines <1996SL509, 1998TL5541, 2001S768, 2002T283, 2002JOC9392, 2003S513, 2003H(60)1891, 2003T6375, 2004TL1885, 2004T835, 2004OL4627, 2005JOC388, 2005JOC2616, 2005T3953>. The details of the arylation are discussed in Section 8.03.11.1. A novel example is synthesis of 2,2'-bipyrazines <2005SL777>, where 1-alkyl- or aryl-substituted 3,5-dichloro-2(1*H*)-pyrazinones are homo-coupled by means of a Suzuki-type reaction of an *in situ*-generated boronate. A classical method for alkylation involves the cross-coupling reaction between a halogenopyrazine and a Grignard reagent but the yields are usually low. This type reaction is promoted by nickel catalyst, for example, catalytic [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (NiCl₂(dppp)) is employed in the reaction of dialkylzinc with chloropyrazines <1996J(P1)2345>. This method gives satisfactory results in terms of yields but the nickel catalyst is not effective for the cross-coupling of chloropyrazine *N*-oxides with organozincs <1996JHC1047>.

The palladium-catalyzed cross-coupling of chloropyrazines with alkenes generally gives low to moderate yields of alkenyl products **45**, but the Heck reaction using 3,5-dichloro-2(1*H*)-pyrazinones provides high yields of 3-alkenyl 5-chloro-2(1*H*)-pyrazinones, in the same way 5-bromo-2(1*H*)-pyrazinone affords 5-alkenyl products <2004TL1885, 2005T3953>. Alkynylation of bromo- or iodopyrazines to alkynylpyrazines **46** is achieved by Sonogashira coupling using alkynes in the presence of palladium catalyst and CuI <1994JHC1449, 2000J(P1)89, 2003T6375, 2004NJC912, 2005H(65)843>.

Acylpyrazines **47** are obtained by Stille reaction of bromopyrazines with 1-ethoxyvinylstannanes, where the coupling is cocatalyzed by copper <2000J(P1)89>. The copper additive increases the yields of products **47** from



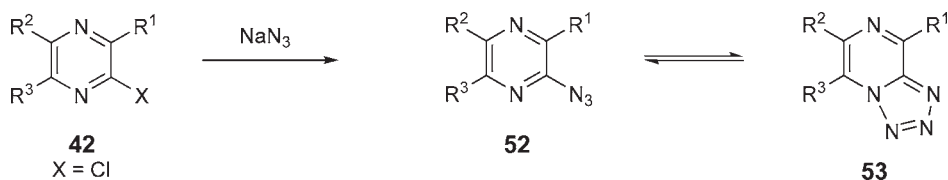
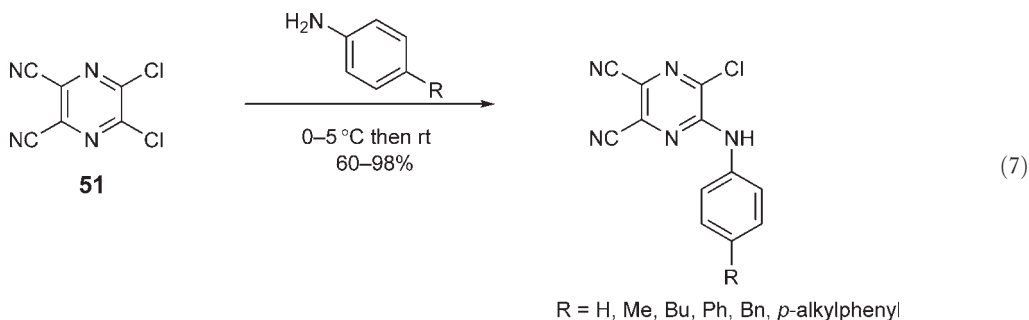
Scheme 10

31% to 93% <2001S1551>. Palladium-catalyzed cross-coupling of pyrazinyltributylstannane with benzoic chloride also gives acylpyrazines <2005JOC2616>.

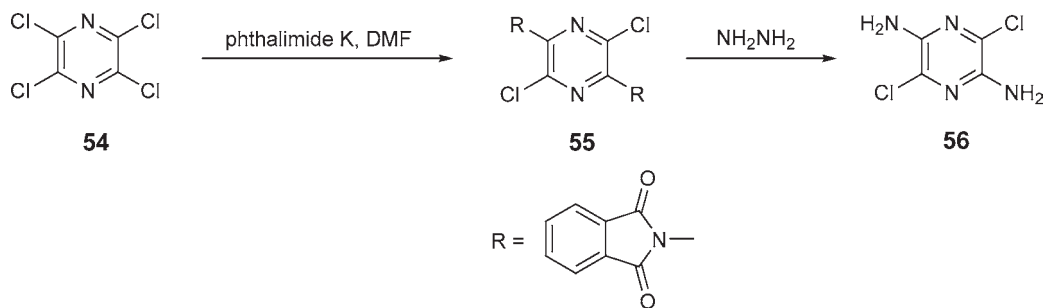
Although there have been few new developments in the period since 1993, halogenopyrazines **42** have been convenient precursors for a variety of pyrazine derivatives. For example, the halogenopyrazines **42** are cyanated by palladium-catalyzed cross-coupling with alkali cyanide or by treatment with copper cyanide in refluxing picoline, to yield cyanopyrazines **48**. Alkoxypyrazines **49** are produced by treatment with alkoxide-alcohol, and aminopyrazines **50** are prepared by amination with ammonia or appropriate amines. The nucleophilic substitution of chloropyrazine with sodium alkoxide, phenoxide, alkyl- or arylthiolate is efficiently effected under focused microwave irradiation <2002T887>.

Several other selected cases are described. Fluoropyrazine is obtained by treatment of chloropyrazine with anhydrous potassium fluoride in *N*-methyl-2-pyrrolidone (NMP) at elevated temperatures <1998T4899>. Conversion of chloropyrazines into iodopyrazines is accomplished by heating with TsOH, NaI, and 15-crown-5 in sulfolane at 150 °C (Ts = tosyl group) <1994JHC1449> or with acetic acid, sulfuric acid, and NaI in acetonitrile <1998T9701>. It should be noted that 5,6-dichloro-2,3-dicyanopyrazine **51** undergoes monoamination with anilines at 0–5 °C, then room temperature, in 61–98% yields (Equation 7) <1997JHC653>. Reaction of chloropyrazines **42** with sodium azide gives azidopyrazines **52** <1996J(P1)247, 2001S768>, rather than the bicyclic tautomers, tetrazolo[1,5-*a*]pyrazines **53** (Scheme 11). Tetrachloropyrazine **54** reacts with potassium phthalimide to produce 2,5-dichloro-3,6-diphthalimidopyrazine **55**,

which is hydrolyzed with hydrazine forming 2,5-diamino-3,6-dichloropyrazine **56** (Scheme 12), although the yield was not given <1998AXC1018>. The structure is confirmed by X-ray analysis (Section 8.03.3.1).

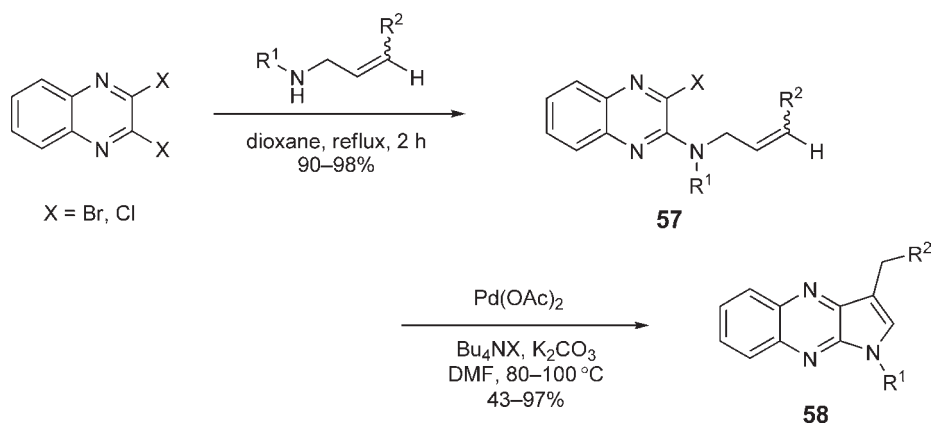


Scheme 11

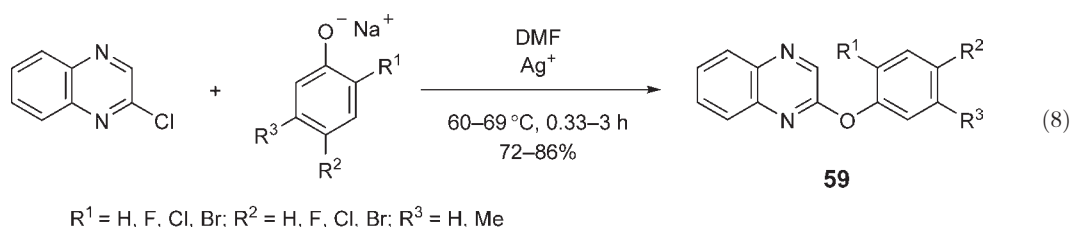


Scheme 12

Analogous to the pyrazine series, halogenoquinoxalines undergo Suzuki and Stille cross-coupling reactions <1999TL4507>. The Suzuki coupling, however, suffers from the drawback of using strong base for completing the reaction which results in degradation of the heterocyclic boronic acids. Conversely, the Stille reactions proceeds without incident, that is, 2-amino-3-bromoquinoxalines smoothly react with heteroarylstannanes in the presence of palladium catalyst to afford 72–98% yields of the substituted quinoxalines. Sonogashira cross-coupling of halogenoquinoxalines likewise affords alkynyl-substituted products <2001J(P1)978>. A curious outcome is observed in the intramolecular Heck reaction of 2-allylamino-3-bromoquinoxalines **57**, giving pyrrolo[2,3-*b*]quinoxalines **58** in moderate to excellent yields (Scheme 13) <1999JOC8425>. Formation of phenolic ethers **59** from 2-chloroquinoxaline is significantly promoted by adding silver ion, which considerably reduces the reaction time and lowers the temperatures required for the displacement compared to those in the absence of silver ion (Equation 8) <1999SC1393, 2002SC813>. The addition of silver ion also suppresses the formation of a byproduct, benzofuro[2,3-*b*]quinoxaline, which is produced in the reaction without the silver ion. Cesium carbonate is also effective for the formation of the phenolic ether of quinoxalines <1993JME2335>.



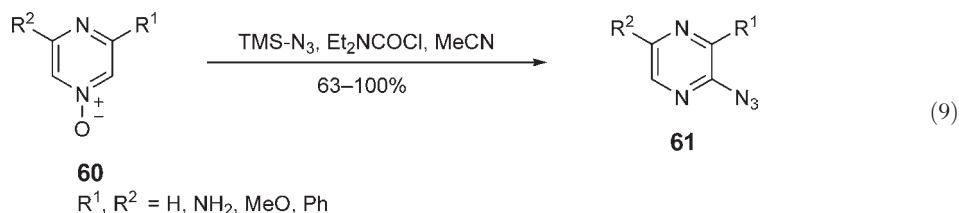
Scheme 13



A solid-phase synthetic approach using 2,3-dichloro-6-aminoquinoxaline whose 6-substituent links on AMEBA resin facilitates the displacement of chlorine with amines, alkoxides, or other nucleophiles <2005TL4979>.

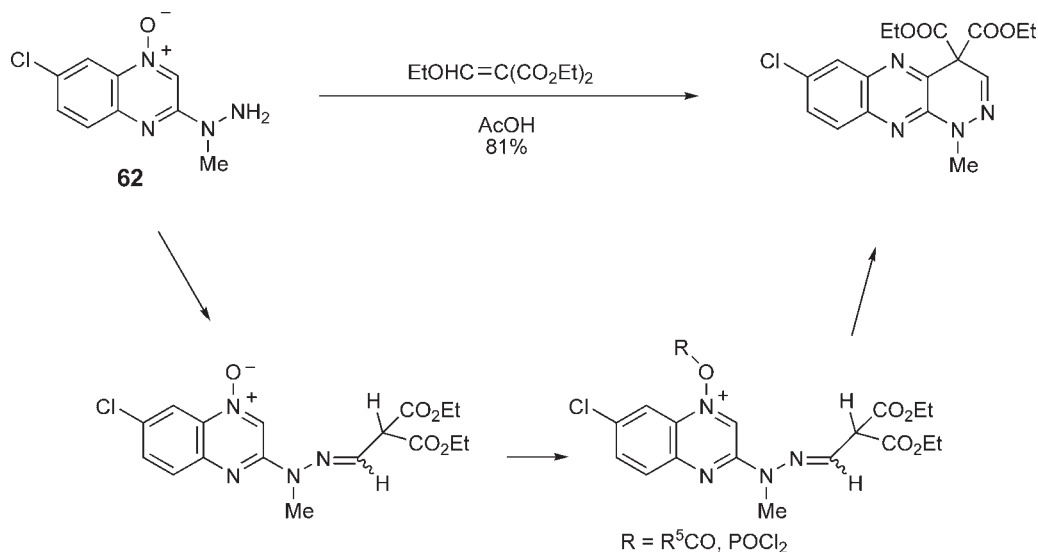
8.03.5.4.3 Deoxidative nucleophilic substitution of *N*-oxides

Deoxidative substitution of pyrazine or quinoxaline *N*-oxides with nucleophiles is a very important method for introducing an α -substituent into the heteroaromatic rings. In particular, reaction with phosphoryl chloride or other acid chlorides yields chloroheterocycles although the regioselectivity of chlorination depends upon the substituents on the pyrazine *N*-oxides. Addition of zinc bromide and/or triethylamine or other organic bases improves regioselectivity and yields of the deoxidative chlorination and acetoxylation <1994JHC1177, 1994JHC1229>. A new example of deoxidative nucleophilic substitution for pyrazine *N*-oxides is synthesis of azidopyrazines <1994J(P1)885>. The azidopyrazines bearing amino, methoxy, and/or phenyl groups were synthesized by reaction of pyrazine *N*-oxides with trimethylsilyl azide in the presence of diethylcarbamoyl chloride in refluxing acetonitrile. In most cases, the azidation occurs only at the carbon α to the *N*-oxide function; thus 3-substituted pyrazine 1-oxides **60** gave 2-azido-3-substituted pyrazines **61** (Equation 9). Conversely, methyl, chloro, and methoxycarbonylpyrazine *N*-oxides did not undergo azidation.



Intramolecular deoxidative nucleophilic substitution of 2-(1-methylhydrazino)quinoxaline 4-oxides **62** to tricyclic heteroaromatics has been extensively researched by Kurasawa *et al.* <1995JHC1085, 2000JHC1257, 2002H(56)291, 2002H(58)359, 2003JHC837>. The cyclization consists of initial formation of hydrazone followed by nucleophilic

attack of the side chain on the α -carbon of the *N*-oxide function (Scheme 14). In general, the latter step is efficiently promoted by adding phosphoryl chloride or acid anhydride, whereas lack of these additives resulted in low-yield formation of tricyclic compounds <1995KGS1245>.

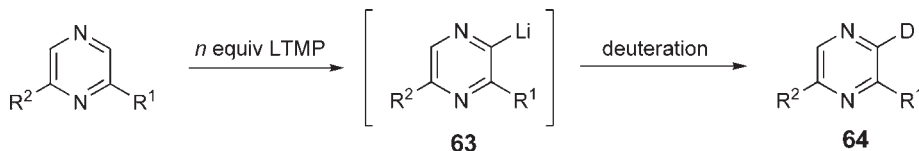


Scheme 14

8.03.5.5 Nucleophilic Attack at Hydrogen Attached to Carbon

Nucleophilic attack at hydrogen attached to aromatic carbon, in other words, the formation of a carbanion, can be realized by treatment of the aromatic compound with a strong base such as an organolithium. Quéguiner and his group have developed extensively this field of heteroaromatics. A variety of DMGs are used for the metalation of electron-deficient heteroaromatic systems on the *ortho*-carbon to the substituent <1994H(37)2149, 2001T4489>. Thus, lithiation of the ring hydrogens on pyrazines with organolithium, usually using lithium diisopropylamide (LDA) or LTMP, is directed by adjacent iodo <1998T9701>, bromo <2005JHC509>, chloro <1994JHC1449, 1996SL509, 1996TL5325, 1998JME1236, 1999H(51)2349, 2001JOC4783>, fluoro <2002T283>, methoxy <1994JHC1449, 1996S838, 1996TL5325, 1999H(51)2349>, methylsulfinyl, phenylthio, phenylsulfinyl, phenylsulfonyl <1997JHC621>, *t*-butylsulfonyl <1998JHC429>, or thiocarbonyl substituents <1999H(51)2349>. The last substituent results in the metalation on the *para*-position unlike the other *ortho*-directing groups. In methylsulfonylpyrazines, the lithiation occurs at the methyl carbon of the substituent, not at the ring carbon of pyrazine <1997JHC621>. In the case of 2-halogeno-6-methoxypyrazine, the lithiation takes place predominantly or exclusively on the carbon adjacent to the methoxy substituent <1994JHC1449, 1996TL5325>. Meanwhile, fluoropyrazine is lithiated stepwise on the *ortho*-, then *meta*-, and finally *para*-carbons; therefore, the metalation using 4 equiv of LTMP followed by iodine leads to the formation of triiodosubstituted fluoropyrazine <2002T283>. The pyridyl group is also an effective DMG <2005T9637>.

The lithio derivatives **63** are converted into deuteriopyrazines **64**, and their yields can be equivalent to those of the hydrogen/lithium exchange (Scheme 15). As a result, the lithiation of chloropyrazines and pyrazinethiocarboxamide is optimized at -70 to -75°C , whereas that of methoxy- or acylamino-pyrazines at 0°C . Conversely,



Scheme 15

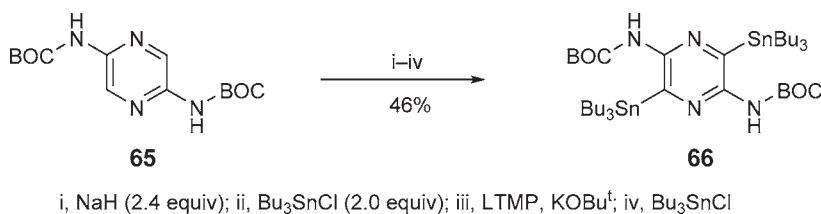
t-butylpyrazinecarboxamide undergoes *ortho*-lithiation at 0 °C, but the competitive formation of *para*-lithiated species is recognized at lower reaction temperatures. The *ortho*-lithiation is considerably affected by the organolithium used, its equivalents, reaction temperatures, and times (Table 1).

Table 1 Lithiation of substituted pyrazines and subsequent quenching with deuterated solvents

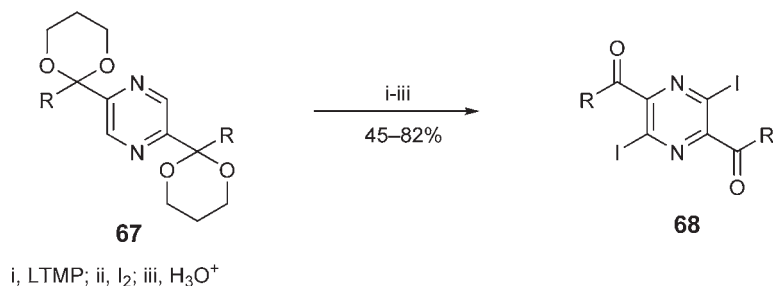
R^1	R^2	n	Temp. (°C)	Deuteration reagents	Yield (%)	Reference
Cl	H	1.2	−70	MeOD	75–85	1988S881
H	CSNH <i>t</i> -Bu	4.1	−75	EtOD, DCl	100	1999H(51)2349
OMe	OMe	2.2	0	EtOD	100	1991JOM(412)301
NHCOBu ^t	H	4	0	EtOD, DCl	25	1992JHC699
CONHBu ^t	H	4	0	EtOD, DCl	75	1992JHC699
Cl	Benzoyl acetal	1	−78	EtOD	98	2005JOC2616

As can be seen also with pyridazines and pyrimidines, the protons of pyrazines are relatively acidic <2001T4489>, and the simple pyrazine is lithiated with 4 equiv of LTMP at −75 °C <1995JOC3781>. Since the lithio intermediate, however, is highly unstable, the subsequent substitution with electrophiles should be carried out within a very short reaction period.

A notable example of the lithiation/trapping sequence is the synthesis of 2,5-bis(tributylstannyl)pyrazine **66** and 2,5-diiodopyrazine **68** (Schemes 16 and 17), which are ultimately coupled together to form pyrazine polymers <1999JA8783>. *t*-Butoxycarbonyl (BOC)-protected diaminopyrazine **65** resists being lithiated although the *N*-BOC group has been shown to have an effect on the directed metalation in pyridines and five-membered heteroaromatics series. When the carbamate hydrogen of **65** is protected with tributylstannyl group, the metalation can be achieved using a mixture of LTMP and KO^tBu, the combination of which provides a marked increase in the basicity of the organolithium. The subsequent quenching with Bu₃SnCl gives stannylpyrazine **66**. The other substrate of diiodopyrazines **68** is prepared by the reaction of **67** with LTMP followed by trapping with iodine. This lithiation can be rationalized to proceed smoothly because of stabilization of the lithiated species by the acetal oxygens.



Scheme 16



Scheme 17

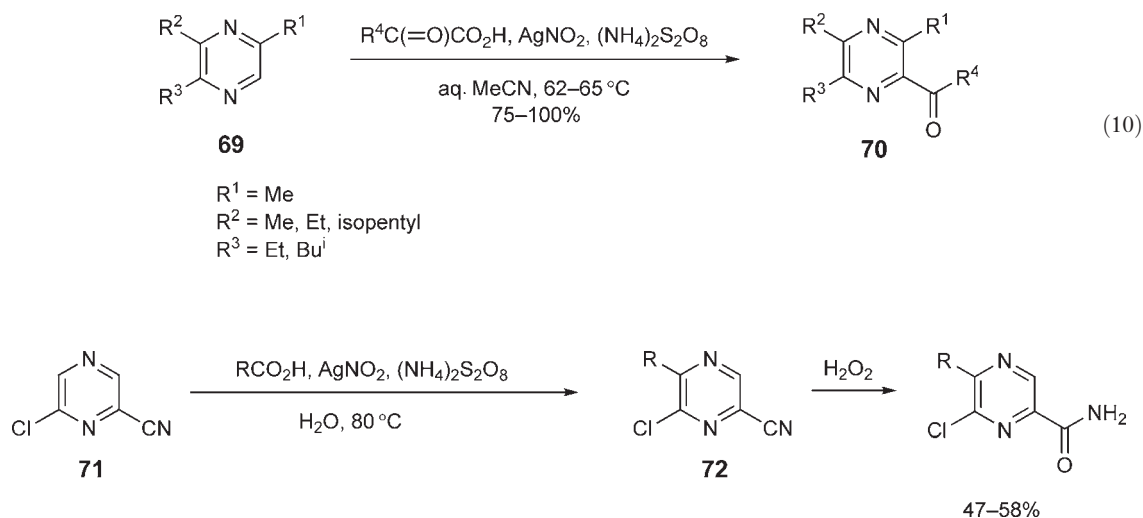
Directed *ortho*-metalations are also applied to quinoxalines possessing 2-chloro, 2-methoxy, and pivaloylamino substituents <1993JHC1491>, but successful syntheses via the lithio intermediates are far fewer compared to pyrazines. In fact, no example of metalation on aromatic carbons can be found in the literature since 1994. However, lithiation on benzene carbons of 6-chloro-2,3-dimethoxyquinoxaline was reported <1999T5389>.

Efforts in the 1990s toward the lithiation/trapping sequence for pyrazines and quinoxalines have been reviewed <2001T4489, B-2002MI2>.

8.03.5.6 Reactions with Radicals and Reductions

8.03.5.6.1 Radical reactions

Minisci-type substitution is one of the most useful reactions for the synthesis of alkyl- and acyl-substituted heteroaromatics. The acyl radicals are formed by the redox decomposition from aldehyde and *t*-butyl hydroperoxide or by silver-catalyzed decarboxylation of a α -keto acid with persulfate. Synthesis of acylpyrazines **70** as ant pheromones are achieved by this methodology using trialkyl-substituted pyrazines **69** with the acyl radicals generated from aldehydes or α -keto acids (Equation 10) <1996J(P1)2345>. The latter radicals are highly effective for the acylation. Homolytic alkylation of 6-chloro-2-cyanopyrazine **71** is performed by silver-catalyzed decarboxylation of alkanolic acids to provide 5-alkyl-substituted pyrazines **72** (Scheme 18) <1996CCC1109>.



Scheme 18

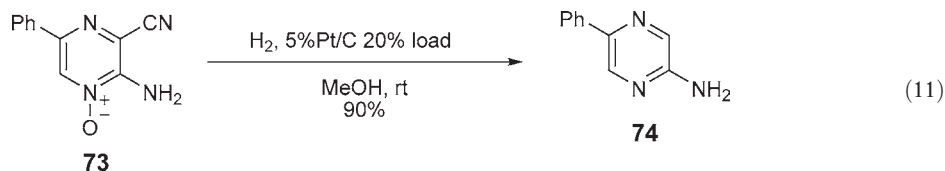
A new process for the homolytic acylation of protonated heteroaromatic bases was developed by Minisci *et al.* <2003JHC325>. A phthalimide *N*-oxyl radical (PINO) generated from *N*-hydroxyphthalimide by air oxygen and Co(II) removes a hydrogen atom from an aldehyde. The resulting nucleophilic acyl radical attacks to a heteroaromatic base, which is then rearomatized in a chain process. In this methodology, pyrazine and quinoxaline are acylated in more than 80% yields with high regioselectivity.

8.03.5.6.2 Reductions

The reduction potentials of some pyrazines and their benzo-fused analogs have been summarized as part of an ESR study of the electron-transfer interaction between nitrogen heterocycles and *n*-Bu₄N⁺BH₄⁻ <1995JOM(494)123>.

The reductive decyanation of cyanopyrazine using H₂ and Pt/C under acidic conditions has been reported <2002TL6747>, that is, 2-amino-3-cyano-5-phenylpyrazine 1-oxide **73** is hydrogenated to 2-amino-5-phenylpyrazine **74** in 90% yield (Equation 11). The double reduction has also been shown to be realized with sodium dithionite,

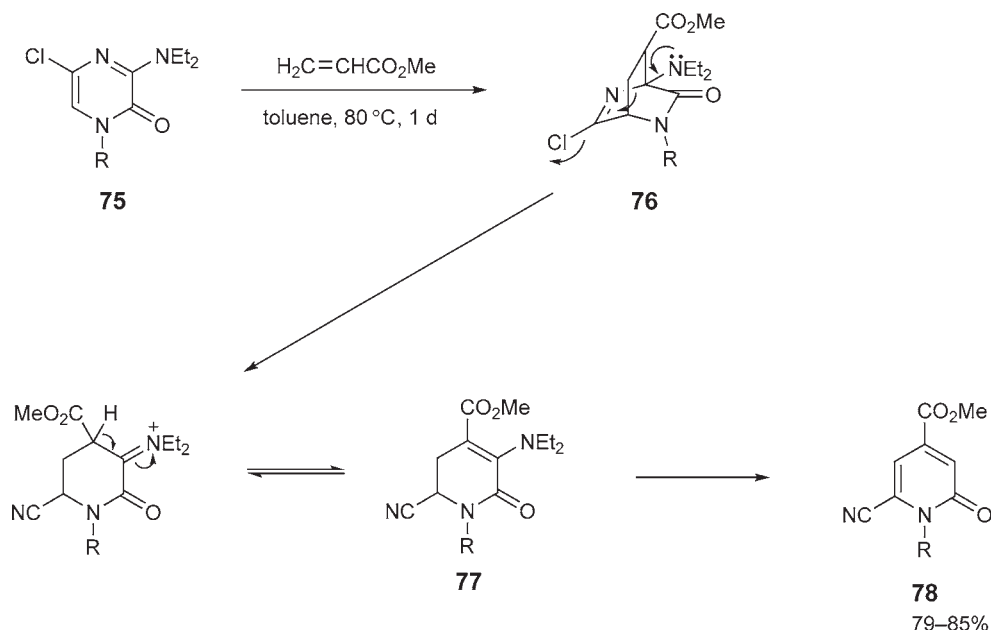
titanium chloride, or samarium diiodide, but those yields are somewhat lower than that of the hydrogenation. Additionally, the reductive decyanation is specific to pyrazines, and cyanopyrimidine and cyanopyridine are inert.



Quinoxalines can be reduced by treatment with indium metal and ammonium chloride in refluxing ethanol to provide high yields of 1,2,3,4-tetrahydroquinoxalines <1998SL1029, 2001J(P1)955>. *N*-Methylphenazinium methyl sulfate, prepared by treatment of phenazine with dimethyl sulfate, was reduced with sodium dithionite to afford 5-methyl-5,10-dihydrophenazine <1999JHC1057>. Reduction of phenazine was achieved by refluxing in acetic anhydride with zinc giving 5,10-diacetyl-5,10-dihydrophenazine <2005T4495>.

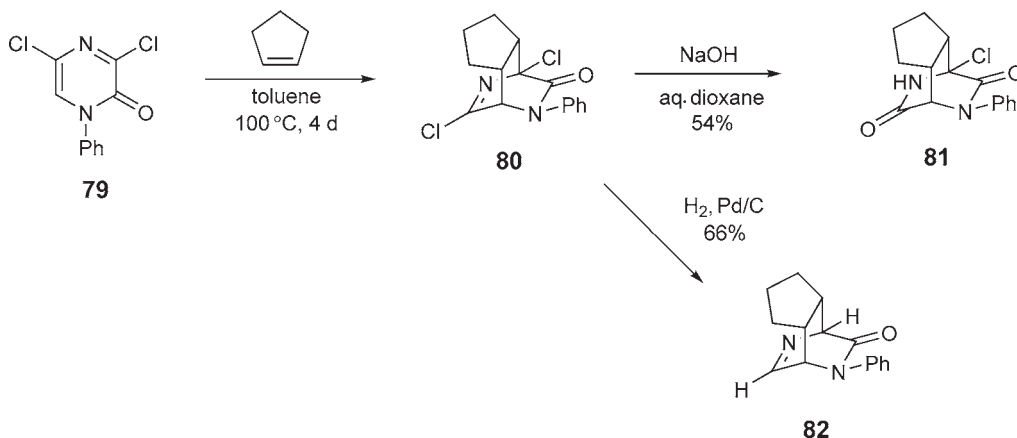
8.03.5.7 Cyclic Transition State Reactions with a Second Molecule

The azadiene structure of 1-substituted 2(1*H*)-pyrazinones can undergo Diels–Alder reactions with alkenes and alkynes as indicated in Section 8.03.5.1, where intramolecular [4+2] cycloadditions of the pyrazinones having alkenyl or alkynyl side chain are described. Hoornaert and co-workers also developed intermolecular hetero-Diels–Alder reactions using 1-substituted 2(1*H*)-pyrazinones. Heating of 3-amino-5-chloro-2(1*H*)-pyrazinone **75** (R = Me, Ph) with methyl acrylate in toluene at 80 °C gives 2(1*H*)-pyridone **78** (Scheme 19), whereas using pyridine instead of toluene provides the precursor tetrahydro-2-pyridone **77** in 72–78% yield <1996JOC304>. The reaction proceeds via bicyclic adduct **76** although it was not isolated, and the following process, especially the loss or retention of amine substituent, is suggested in the light of the normal behavior in cycloadditions of 2(1*H*)-pyrazinone derivatives. The cycloaddition of 3,5-dichloro-2(1*H*)-pyrazinones **79** with cyclic alkenes affords stable bicyclic adducts **80** (Scheme 20), which are hydrolyzed or hydrogenated to produce bicyclic piperazine compounds **81** or **82** <2001T3209>. The use of monosubstituted alkenes, methyl acrylate or vinyl ethers, as the dienophile results in poor regioselectivity in cycloaddition. A variety of analogues of *cis*-5-amino-6-oxo-2-piperidinemethanol and *cis*-5-amino-2-piperidinemethanol as potential substance P antagonists have been prepared via Diels–Alder reaction of 1-benzyl-5-chloro-2(1*H*)-pyrazinones with ethene followed by acid methanolysis of the bridged lactam adducts. Further



Scheme 19

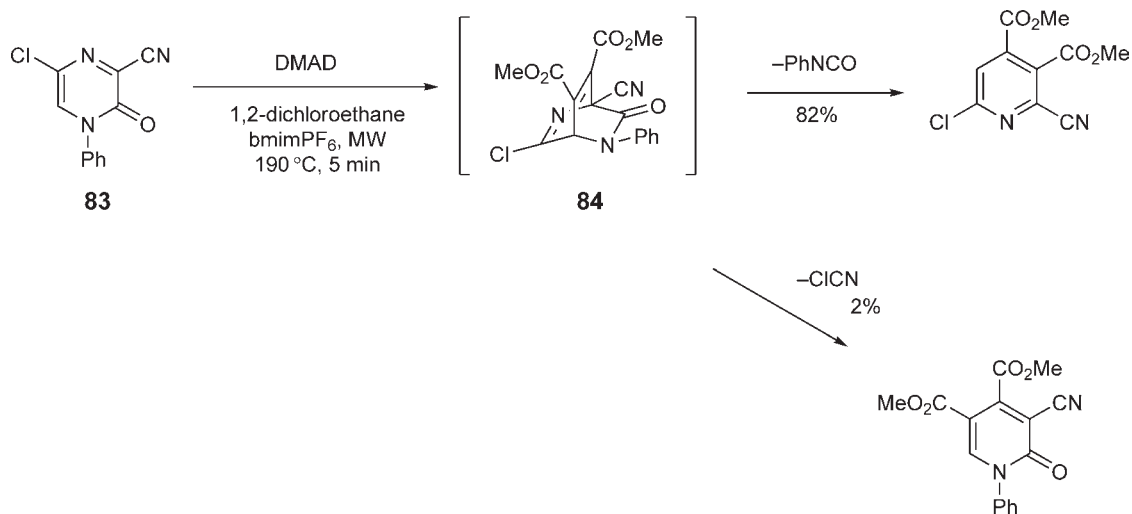
reduction of the resulting methyl 2-piperidinecarboxylate ester compounds leads to the corresponding 2-piperidine-methanol products <2003T5047>.



Scheme 20

Numerous alkyl- and/or aryl-substituted 2(1*H*)-pyrazinones react with 4*H*-1,2,4-triazoline-3,5-dione to give high yields of [4+2] adducts <1998JHC655>.

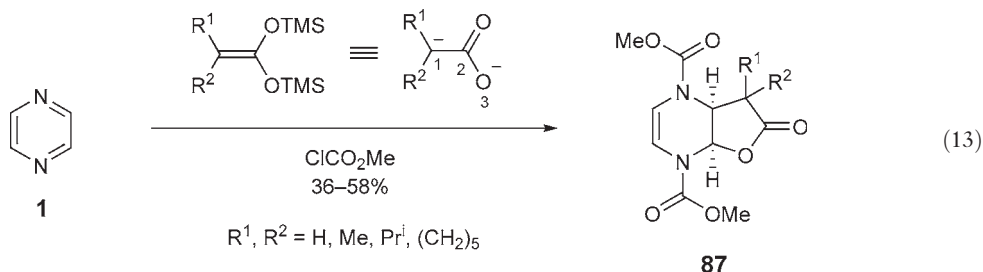
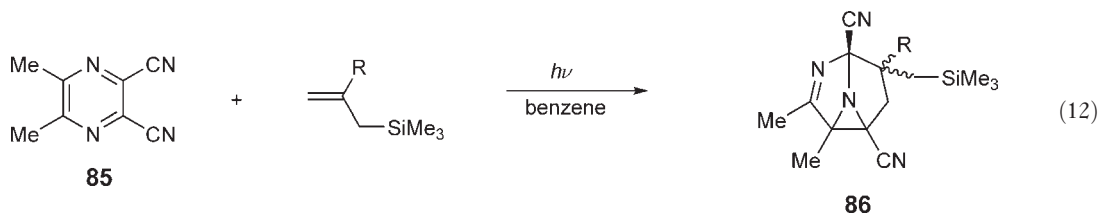
As can be seen in the intramolecular cycloaddition (Section 8.03.5.1), the intermolecular Diels–Alder reactions between functionalized 2(1*H*)-pyrazinones **83** and dimethyl acetylenedicarboxylate (DMAD) forming bicyclo adducts **84** has been shown to be significantly rate enhanced and increased in yields by using controlled microwave irradiation compared to the conventional thermal protocols (Scheme 21) <2002JOC7904>. The microwave-assisted Diels–Alder reactions of substituted 2(1*H*)-pyrazinones with ethene are significantly more effective utilizing pre-pressurized (up to 10 bar) reaction vessels <2004OBC154>.



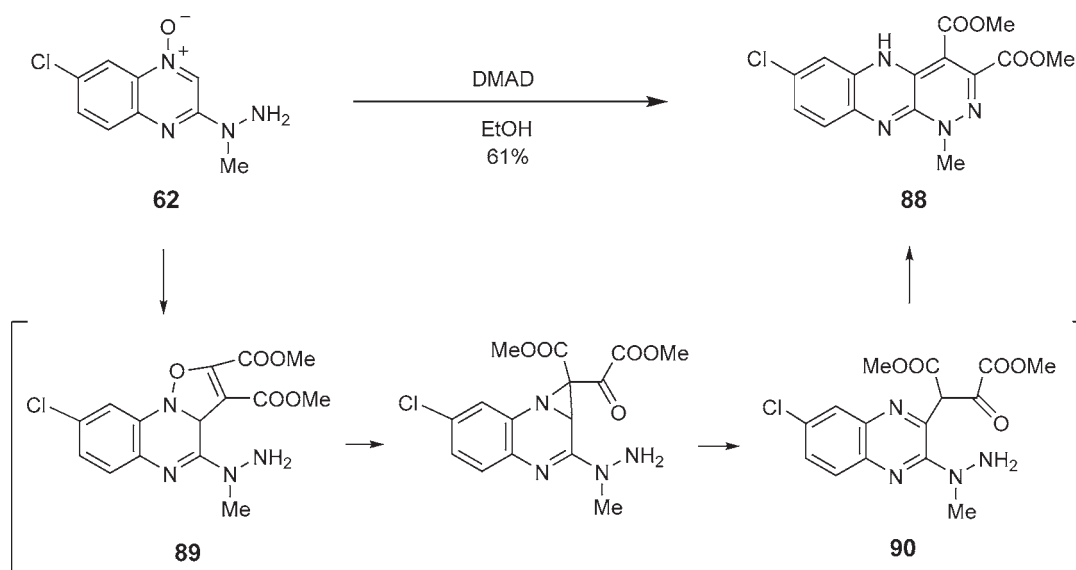
Scheme 21

Irradiation of a mixture of 2,3-dicyano-5,6-dimethylpyrazine **85** and allylic silanes leads to the formation of 2,8-diazatricyclo[3.2.1]oct-2-enes **86** via [2+2] photocyclization followed by rearrangement (Equation 12)

<1997TL5313>. Pyrazine **1** reacts with bis(TMS)ketene acetals behaving as 1,3(C, O) dinucleophiles to produce bicyclic γ -lactones **87** <2005TL3449>, in which methyl chloroformate activates the cycloaddition (Equation 13).

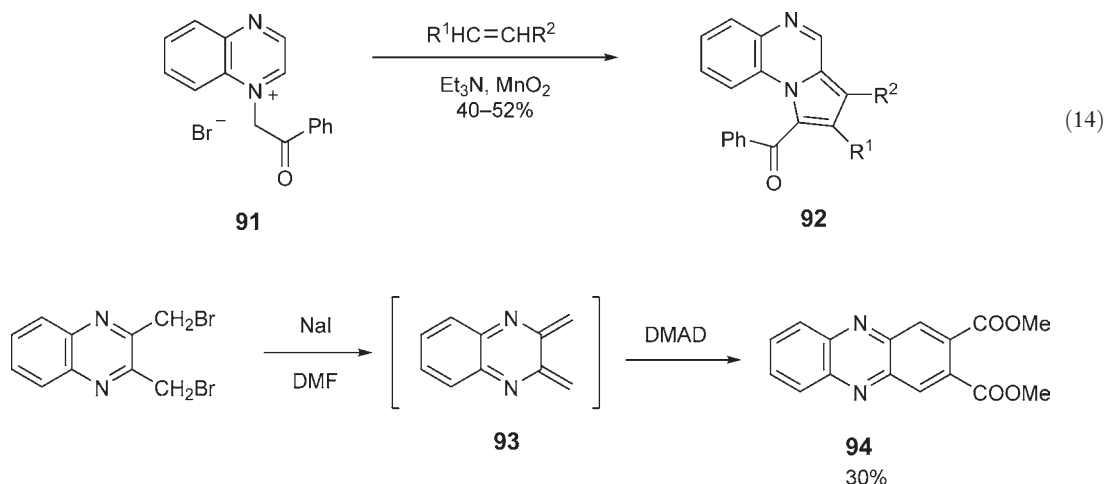


Quinoxaline *N*-oxides and the *N,N'*-dioxides undergo 1,3-dipolar cycloaddition with dipolarophilic alkenes or alkynes to yield isoxazolo-fused quinoxalines such as compounds **89**. Cycloaddition between quinoxaline *N*-oxide **62** and DMAD, however, affords pyridazine-condensed quinoxalines **88** <2000JHC791>. This can be rationalized by the initial formation of normal adduct **89**, which then rearranges to 2,3-difunctionalized quinoxaline **90** and finally cyclizes to form the pyridazine ring (Scheme 22). In a similar fashion, quinoxaline *N*-oxides react with diethyl azodicarboxylate (DEAD) <1996JHC757> or 2-chloroacrylonitrile <2005JHC249>. The 1,3-dipolar cycloaddition of the ylide derived from **91** with various alkenes produces tricyclic compounds **92** after aromatization (Equation 14), and the reaction proceeds significantly more selectively in the presence of manganese dioxide <1999JCM552>.



Scheme 22

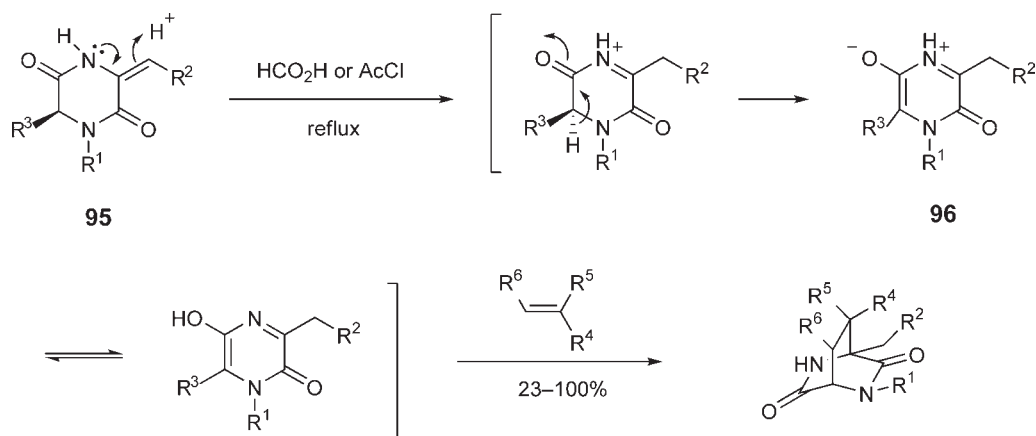
The unstable species quinoxalino-2,3-quinodimethane **93**, which can be formed by treatment of 2,3-bis(bromo-methyl)quinoxaline with sodium iodide, is trapped with dienophiles such as DMAD or DEAD to give phenazine-2,3-dicarboxylate **94** (Scheme 23) <1995TL6777>.



Scheme 23

8.03.6 Reactivity of Nonconjugated Rings of Pyrazines and Quinoxalines

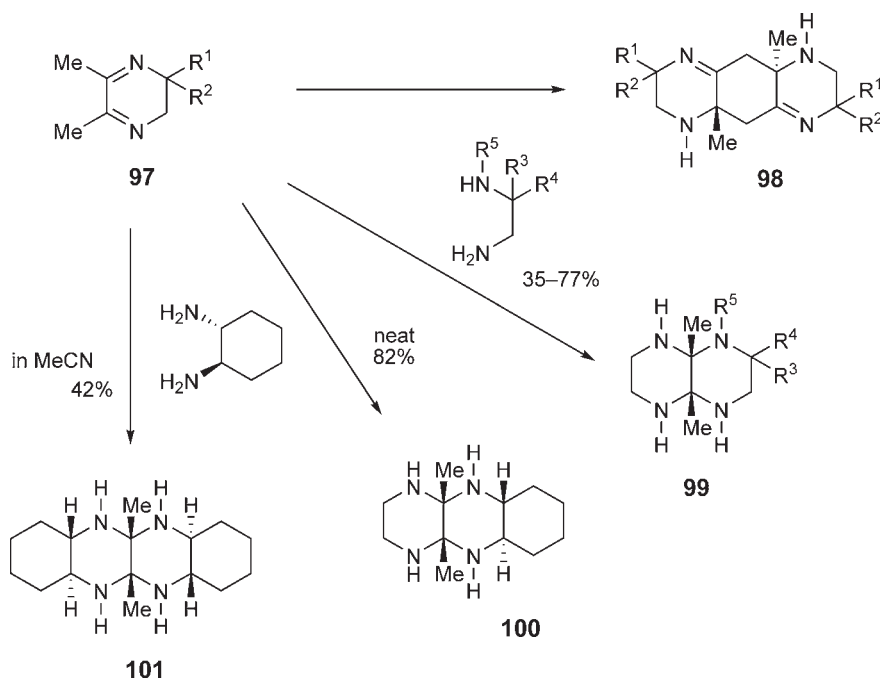
A series of aromatic compounds dealt with in this section should be firstly 2(1*H*)-pyrazinones and their 1-substituted derivatives, which have been already noted as a useful azadiene system in Diels–Alder cycloaddition (Sections 8.03.5.1 and 8.03.5.7). In the same fashion, 3-alkylidenepiperazine-2,5-diones **95** can undergo intra- and intermolecular Diels–Alder reactions under acidic conditions or in the presence of acetyl chloride (Scheme 24) <2001JOC3984>. The intermediate azadiene system **96** is discussed on the basis of theoretical calculation at B3LYP/6-31G**/B3LYP/6-13G* levels. This procedure is a convenient path to the bridged diazabicyclo[2.2.2]octane ring system, which is found in biologically active mold secondary metabolites. Another example in this class of compounds is 6-alkylidene-3,6-dihydro-2(1*H*)-pyrazinones, whose reactivity toward various nucleophiles was investigated <1996J(P1)231>.



Scheme 24

Permanganate oxidation of 2,3-(1*H*,4*H*)-quinoxalinediones in aqueous basic solution failed to produce 5,6-(1*H*,4*H*)-pyrazinedione-2,3-dicarboxylic acids but led to dimerization of the quinoxalinedione via a novel radical process <1994HCA1549>.

Among the four isomers of dihydropyrazines, the 2,3-dihydro isomers are most explored because these reduced pyrazines have been easily prepared by condensation of 1,2-diamines and 1,2-dicarbonyl compounds. This class of compounds is unexpectedly unstable resulting in dimerization at room temperature. Thus, 2,3-dihydropyrazine **97** ($R^1 = R^2 = \text{Me}$) gradually dimerizes to form tricyclic system **98**, fused with two tetrahydropyrazine units (**Scheme 25**), and the structure of the product has been confirmed by X-ray analysis <1999T675>. Dihydropyrazine **97** ($R^1 = R^2 = \text{H}$) reacts with 1,2-diamines to produce *cis*-tetraazadecalins **99**, which are extremely unstable crystalline substances but are laboriously able to be recrystallized <1999H(51)2305>. Hence, the structure is also verified by X-ray analysis. In solution, the bicyclic compounds **99** exist as such at -20 to -60°C , but at room temperature decomposition is induced to regenerate the dihydropyrazines **97**. When dihydropyrazine **97** ($R^1 = R^2 = \text{H}$) is reacted with 1,2-diaminocyclohexane, the anticipated product **100** is formed by mixing in neat but a novel tetracyclic compound **101** is formed by reaction in acetonitrile <2000H(53)1677>. This formation can be explained by recognizing that the mixture of the dihydropyrazines and 1,2-diaminocyclohexane in solvent is in equilibrium by transfer of an ethylenediamine unit in dihydropyrazines **97**, and the preferential equilibrium species, hexahydroquinoxaline, undergoes dimerization to yield the compound **101**. Solvent effect on the sensitized photo-oxygenation of 5,6-dimethyl and 5-methyl-6-phenyl-2,3-dihydropyrazines has been investigated <2003JOC3009>.

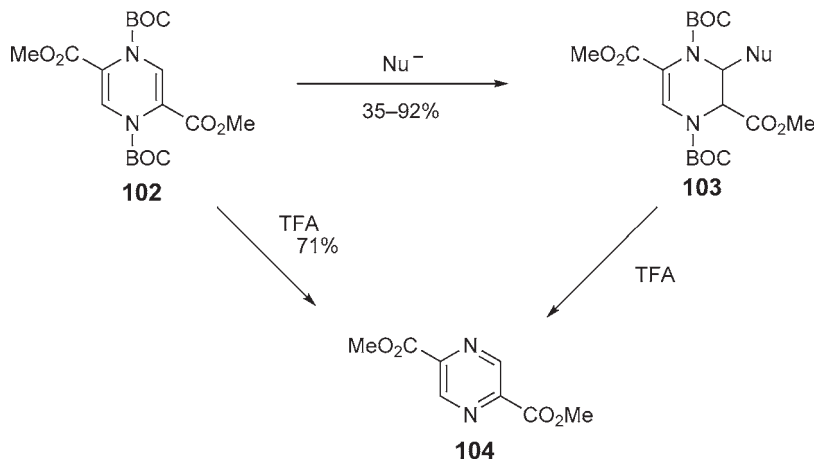


Scheme 25

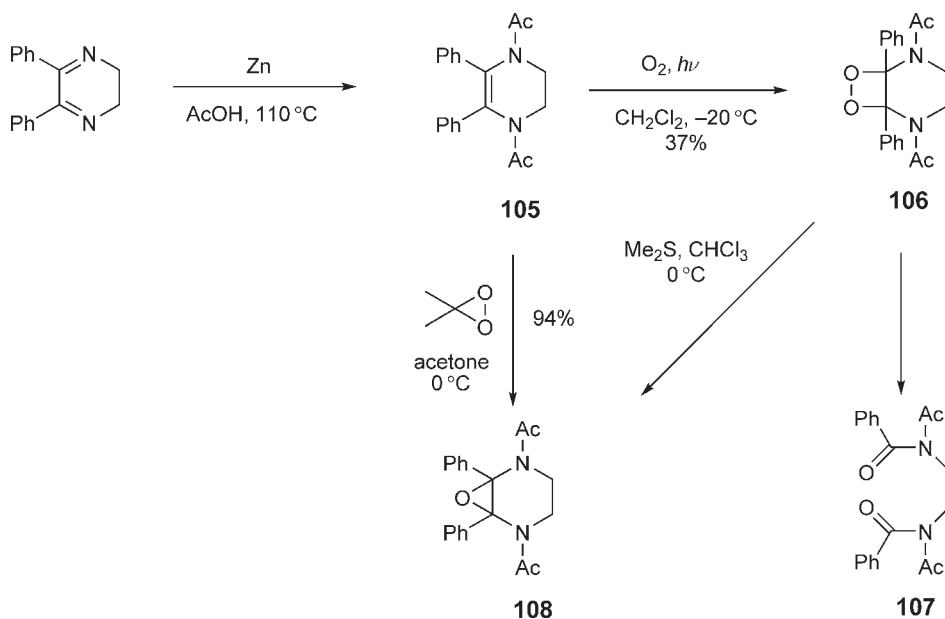
Since 1,4-dihydropyrazine itself is unknown, various substitutions of the ring system are required to produce stable isolable molecules. Carbonyl-stabilized 1,4-dihydropyrazines are synthesized by self-condensation of 3-chloromethyl-5,6-dihydro-1,5,5-trimethyl-2(1*H*)-pyrazinone <1998J(P1)289>. Another carbonyl-stabilized example is provided by *N,N'*-BOC-protected 1,4-dihydropyrazine **102**, which can undergo Michael addition with nucleophiles such as 1,2,4-triazole, 3-formylindole, 4-bromothiophenol, benzylamine, or sodium methoxide to yield tetrahydropyrazines **103** (**Scheme 26**) <2004T8489>. Treatment of the di- and tetrahydropyrazines with trifluoroacetic acid leads to cleavage of BOC groups and/or elimination of the nucleophile to both afford dimethyl 2,5-pyrazinedicarboxylate **104**.

N,N'-Acetyl-protected 1,2,3,4-tetrahydropyrazines **105**, which are prepared by treatment of 2,3-dihydropyrazine with acetic anhydride and zinc (**Scheme 27**), undergo photooxidation to produce new dioxetanes **106** <1995JA9690>. Upon thermolysis, the dioxetanes **106** decompose quantitatively to tetraacyl ethylenediamines **107**. Dimethyldioxirane oxidation of tetrahydropyrazine **105** affords novel epoxide **108**, which is also generated by deoxygenation of dioxetane **106** with dimethyl sulfide. In 2,3,4,5-tetrahydropyrazine 1-oxide **109**, which is prepared

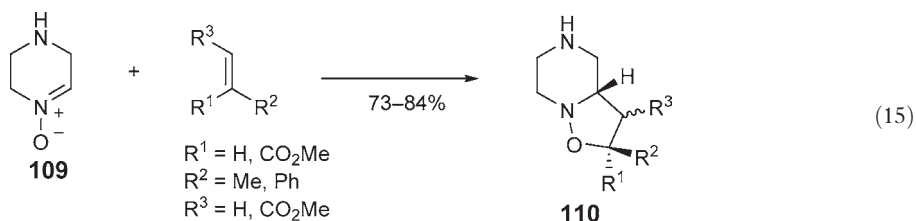
by oxidation of piperazine with hydrogen peroxide followed by mercury(II) oxide oxidation of the resulting 1-hydroxypiperazine, the nitron functionality behaves as a 1,3-dipole and undergoes regio- and stereoselective cycloaddition with several alkenes to yield bicyclic isoxazolines **110** (Equation 15) <2000T7229>.



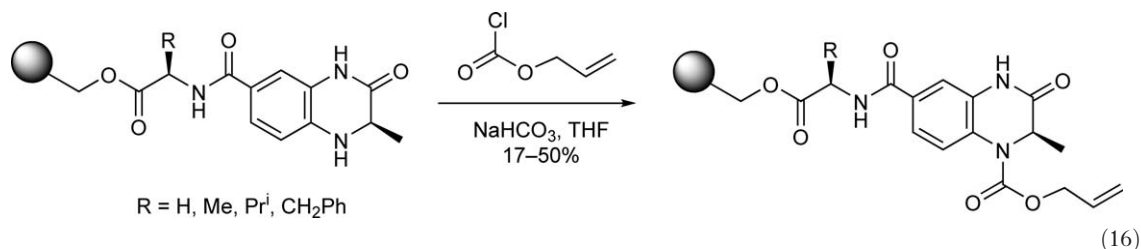
Scheme 26



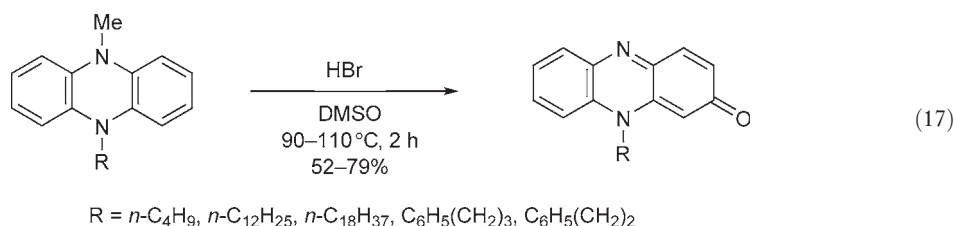
Scheme 27



N-Acylation of 1,2,3,4-tetrahydro-2-quinoxalinones anchored to Wang resin was achieved by the usual procedure to give 4-acyl derivatives (Equation 16) <1998JOC1172>.



Oxidation of 5,10-dialkyl-5,10-dihydrophenazines with hydrobromic acid in DMSO gives 10-alkyl-2(10*H*)-phenazinone in 52–79% yields (Equation 17) <1999JHC1057>. Depending on the alkyl substituents on C-5 and C-10 carbons, the parent phenazine is generated as the by-product.

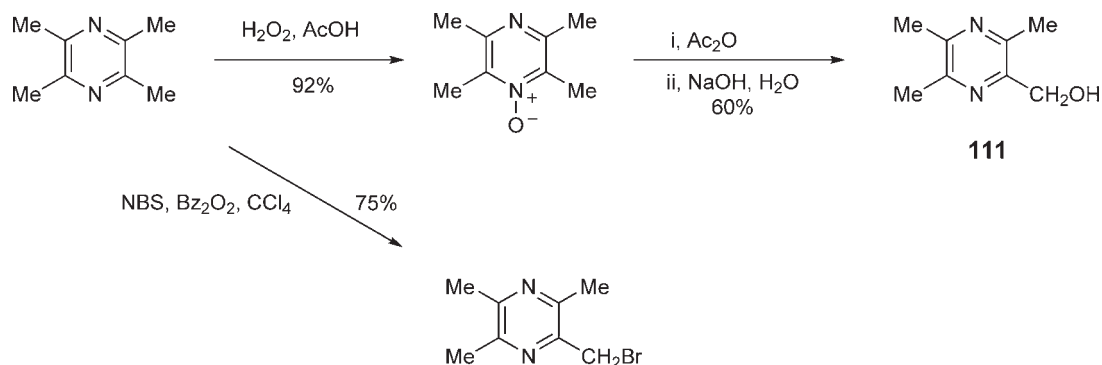


8.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

8.03.7.1 Carbon Substituents

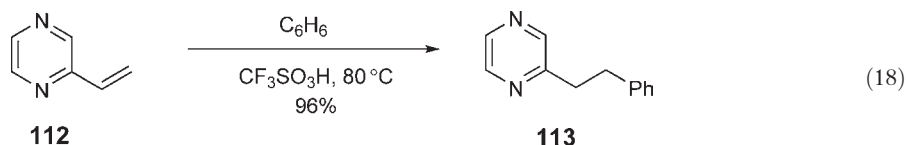
A great number of methods for the modification of carbon substituents on pyrazines have been developed, and the functionalization of the methyl group is discussed first.

In comparison of benzene compounds, the methyl groups on pyrazine rings are very susceptible to metalation, Mannich reaction, or condensation with aldehydes. For example, 5-methylpyrazine-2,3-dicarbonitriles can be converted into 5-styryl derivatives by treatment with 4-dialkylaminobenzaldehydes in refluxing acetic anhydride, or benzene or ethanol containing catalytic amount of base <1996DP(31)141, 1998DP(40)11>. A methyl group adjacent to an *N*-oxide function reacts with acetic anhydride resulting in deoxidative acetoxylation to give hydroxymethylpyrazine **111** after hydrolysis <1996TL8205>. Bromination of an alkyl side chain is completed using NBS by addition of peroxide, and the resultant bromomethyl group reacts easily with nucleophiles (Scheme 28) <1996TL8205>.

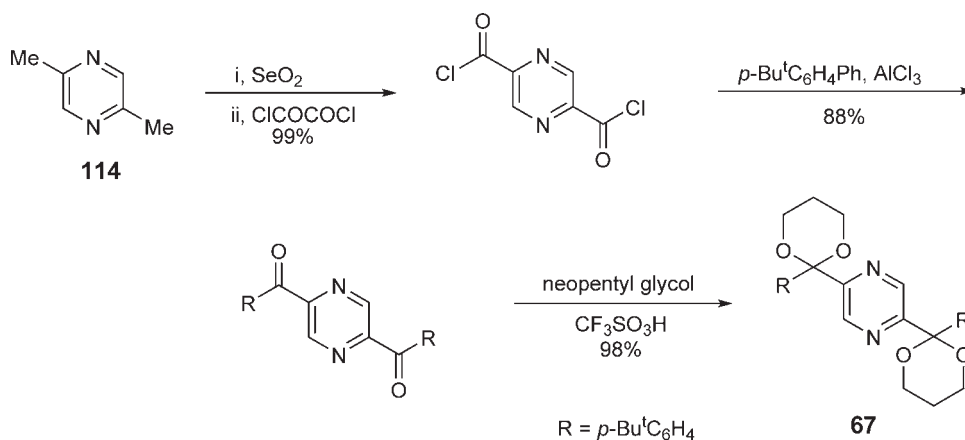


Scheme 28

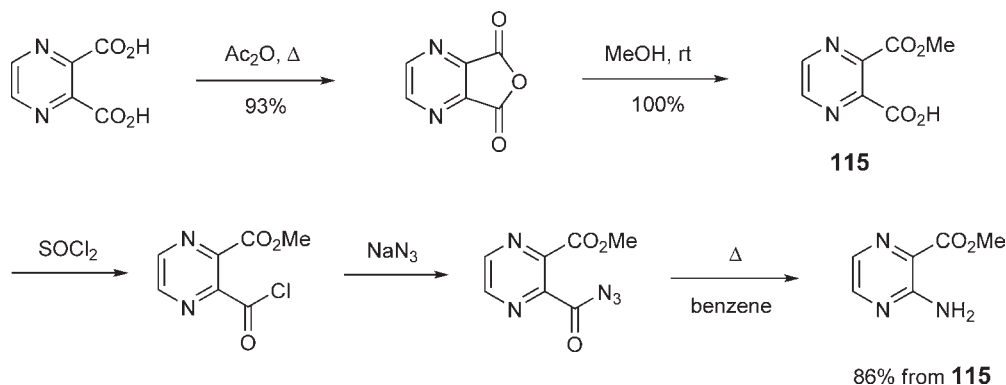
Alkenylpyrazines **112** react with benzene in trifluoromethanesulfonic acid giving anti-Markovnikov-type products **113** (Equation 18) <2005OL2505>.



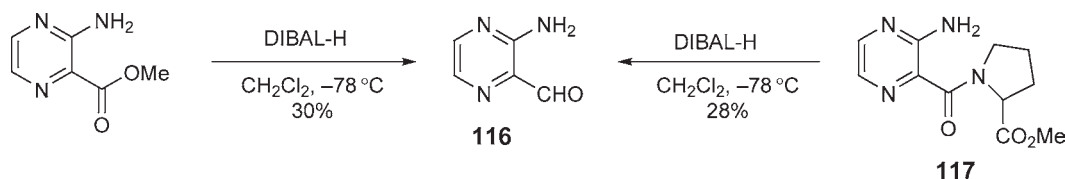
Oxidation of 2,5-dimethylpyrazine **114** with selenium dioxide produces pyrazine-2,5-dicarboxylic acid <1999JA8783>, derivatization from which is illustrated in Scheme 29. A sequence of conversions from pyrazine-2,3-dicarboxylic acid <1996SC617> is also shown in Scheme 30. Pyrazinylmethanols are readily oxidized with manganese dioxide to form ketone compounds <1996SL509, 2005JOC2616>, and conversely the carbonyl group tethered to a pyrazine ring is reduced with sodium borohydride <1996J(P1)2345>. 3-Carbomethoxypyrazine 1-oxide is reduced with lithium tri-*t*-butoxyaluminum hydride in THF to give a 51% yield of the corresponding alcohol without removal of *N*-oxide oxygen <1994H(38)1581>. Controlled reduction of 3-aminopyrazine-2-carboxylic methyl ester with diisobutylaluminum hydride (DIBAL-H) at -78°C gives 3-aminopyrazinealdehyde **116** <2005JST(741)67>, albeit in 30% yield. This compound **116** is also obtained by reduction of pyrazinecarboxamide **117** under similar reaction conditions (Scheme 31) <1998T5853>. Pyrazinecarboxamides undergo thionation with Lawesson's reagent to afford the thiocarboxamides <1996CCC1109, 1999H(51)2349>.



Scheme 29



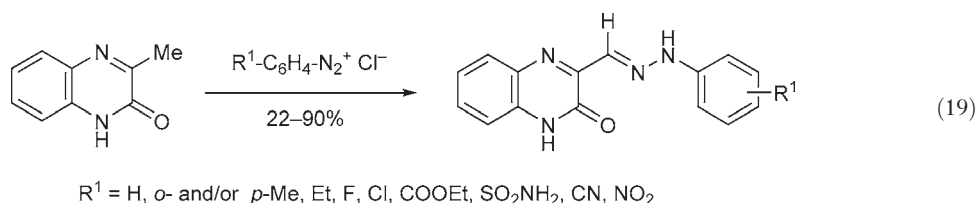
Scheme 30



Scheme 31

A useful reaction involving substitution of carbon functionalities is decarboxylation of pyrazinecarboxylic acids. This conversion is readily achieved by heating directly or in high-boiling solvent, or distillation over copper compounds. Fusion under reduced pressure has been occasionally effective for the transformation <2002JOC556>.

Methyl groups of 3-methyl-substituted 2(1*H*)-quinoxalinone <2003S2345> and 2(1*H*)-quinoxalinethione <2003S2799> are easily lithiated with *n*-butyllithium at -78°C , and quinoxalinones and thiones having various side chains are obtained after trapping with electrophiles. Moreover, the methyl group at C-3 carbon of 2(1*H*)-quinoxalinone reacts with various diazonium salts to afford the 3-arylhydrazonomethyl-2(1*H*)-quinoxalinones (Equation 19) <1995JHC531, 1996JHC421, 1997JHC305>.



8.03.7.2 Nitrogen Substituents

The direct alkylation of aminopyrazines is usually unsatisfactory as a synthetic method because it mainly takes place at the most basic ring nitrogen. However, 3,6-diamino-2,5-dicyanopyrazines are successfully alkylated by treatment with alkyl iodide or bromide in protic solvent in the presence of alkali such as NaOH in dimethylacetamide (DMA) to form bis(dialkylamino)pyrazines <1998DP(39)49>. Reaction of 2,6-diamino-3,5-diarylpyrazine with methylglyoxal in aqueous HCl-ethanol led to *N,N'*-alkylation but no formation of the expected bicyclic imidazolo[1,2-*a*]pyrazine <2001S768>.

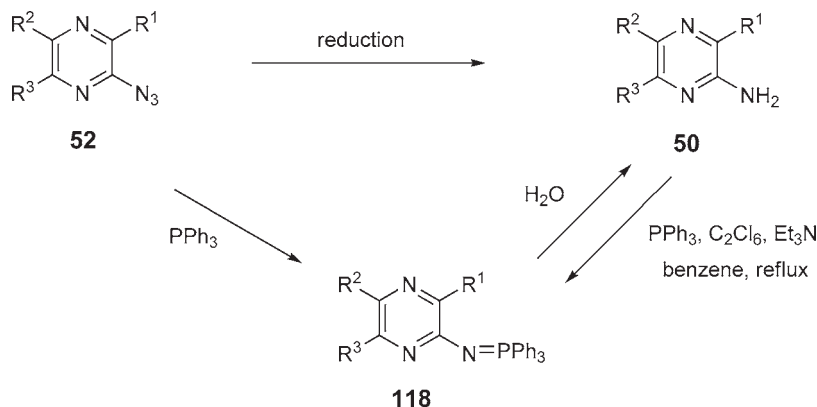
Reaction of aminopyrazines with acetic anhydride or benzoyl chloride yields both mono- and diacylated products <1998DP(39)49>, and the reverse transformation, namely hydrolysis of diacylamino to amino substituents, is realized by treatment with aqueous hydrazine <1993JOC7542>. Diazotization of 3-aminopyrazinecarboxylic ester in concentrated hydrochloric acid followed by warming affords a mixture of 3-chloro- and 3(4*H*)-pyrazinonecarboxylic esters in 49% and 40% yields, respectively <1996J(P1)247>. Similarly, aminopyrazine *N*-oxides are converted to the chloropyrazine *N*-oxides <1994H(38)1581>. The use of 40% hydrobromic acid in place of hydrochloric acid can realize the transformation of 2-amino-5-bromo-3-methoxypyrazine into the 2,5-dibromopyrazine in 54% yield <2002JOC9392>.

Azidopyrazines **52**, which are easily prepared by reaction of halogenopyrazines with sodium azide (Section 8.03.5.4.2) or pyrazine *N*-oxides with trimethylsilyl azide (Section 8.03.5.4.3), are converted into aminopyrazines by hydrogenolysis in the presence of ammonium hydroxide and palladium-on-carbon or by reduction with tin(II) chloride in methanolic hydrochloric acid <1994S931, 2001S768>. In addition, azidopyrazines **52** react with triphenylphosphine to form iminophosphoranes **118** <1996J(P1)247, 1996S838>, which are hydrolyzed to yield aminopyrazines <1996S838>. Conversely, aminopyrazines **50** are converted into iminophosphoranes **118** (Scheme 32) <1996J(P1)247, 1998J(P1)2277, 1998T5853>, which can undergo aza-Wittig reaction with isocyanates.

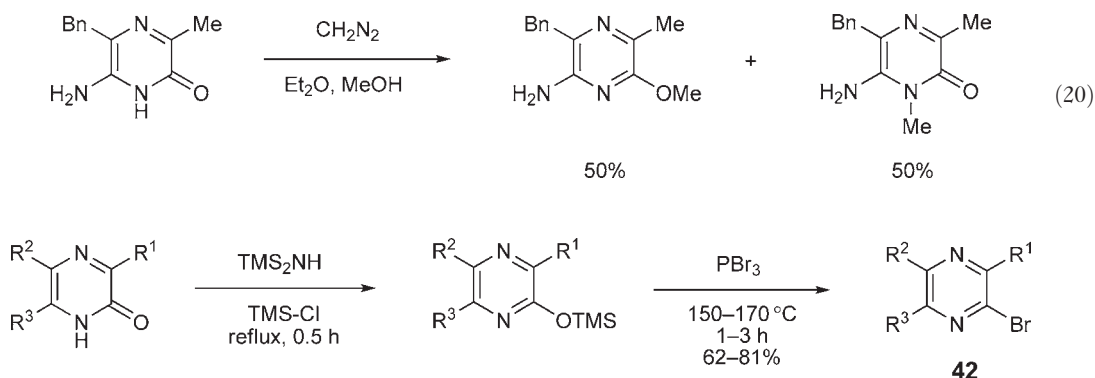
8.03.7.3 Oxygen Substituents

Although methylation of 2(1*H*)-pyrazinones with diazomethane gives a mixture of *O*- and *N*-methylated pyrazines as the fixed tautomers (Equation 20) <1993JOC7542>, the trimethylsilylation leads to the exclusive formation of *O*-silyl compounds, which are effectively converted to bromopyrazines **42** (Scheme 33) <1999JHC783>. In the same

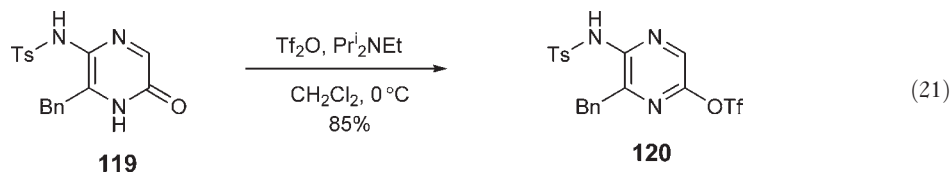
manner, reaction of 2-(1*H*)-pyrazinone **119** with trifluoromethanesulfonic anhydride affords an 85% yield of triflate **120** (Equation 21), which was subjected to Suzuki–Miyaura coupling <2004T835, 2005H(65)843>. The *O*-triflate of 3-methyl-5-phenyl-2-(1*H*)-pyrazinone is also formed under similar reaction conditions, and the substituent can be converted into an amino function by treatment with alkylamines <2004SL2031>.



Scheme 32

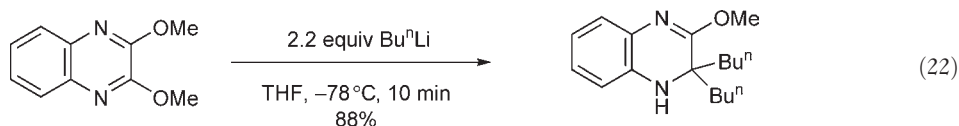


Scheme 33



Pyrazinyl ketones can be protected as the acetal by treatment with alkanediol in the presence of trifluoromethanesulfonic acid <1999JA8783> or 8-amino-1,3,6-pyrenetrisulfonic acid (APTS) <2005JOC2616>.

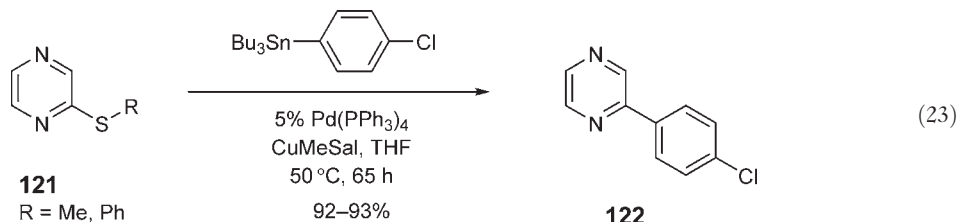
Ether cleavage of 2,3-dimethoxyquinoxaline to give 2,3(1*H*,4*H*)-quinoxalinedione was performed by treatment with iodotrimethylsilane generated *in situ* from chlorotrimethylsilane and sodium iodide, albeit in 15–40% yields <1999JHC1271>. 2,3-Dimethoxyquinoxaline reacts with 2 equiv of butyllithium to furnish 2,2-dibutyl-3-methoxy-1,2-dihydroquinoxaline (Equation 22) <1999T5389>.



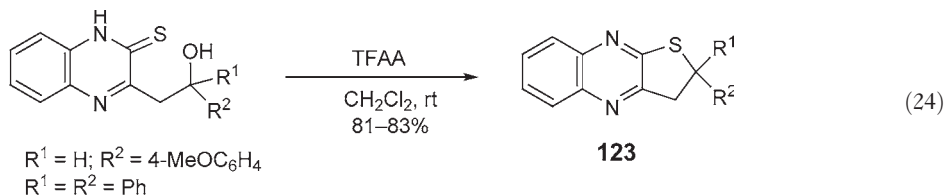
8.03.7.4 Sulfur Substituents

t-Butylthiopyrazine, which is prepared by reaction of chloropyrazine with lithium *t*-butanethiolate, is oxidized with MCPBA to *t*-butylsulfinylpyrazine or *t*-butylsulfonylpyrazine depending on the amounts of oxidizing reagent used <1998JHC429>. The oxidation of phenylthio substituent is also achieved with sodium perborate in acetic acid at room temperature <2001SC725>. Pyrazinethione is converted into *N,N*-diethyl pyrazinesulfonamide by a one-pot procedure using chlorine in the presence of potassium hydrogen fluoride and diethylamine, probably through sulfonyl fluoride <1998JHC429>.

Methylthio- and phenylthiopyrazines **121** undergo cross-coupling with arylstannanes in the presence of palladium catalyst and copper(I) 3-aminosalicylate to afford 92–93% yields of arylpyrazines **122** (Equation 23) <2003OL801>.



Quinoxalinethione carrying 2-hydroxyethyl substituent at C-3 carbon cyclizes by trifluoroacetic anhydride to produce 2,3-dihydrothieno[2,3-*b*]quinoxalines **123** (Equation 24) <2003S2799>.



8.03.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms

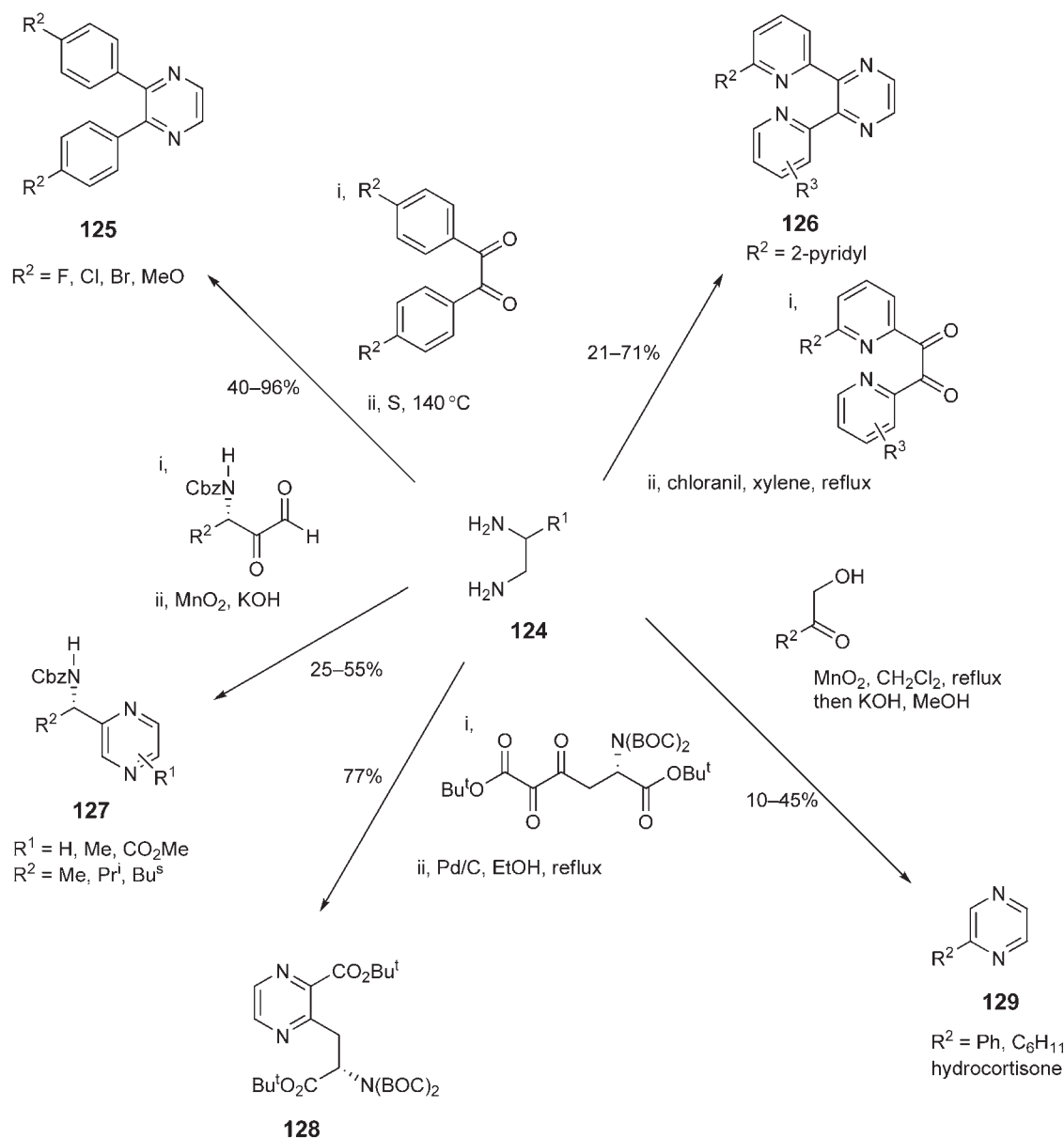
The major reactions in this section are those involving an *N*-oxide oxygen. Deoxygenation along with decyanation from 2-amino-3-cyano-5-phenylpyrazine 1-oxide is noted in Section 8.03.5.6.2. Numerous pyrazine *N*-oxides are deoxygenated to the parent pyrazines under mild conditions using zinc and aqueous ammonium chloride in THF <1997S891>, and the yields are more than 90% in most cases. However, deoxygenation of 1-hydroxy-2(1*H*)-pyrazinone does not proceed at all. Reduction with zinc in refluxing acetic acid <2002CPB301> or hydrogen in the presence of 10% Pd on carbon at 50 °C <2002TL9287> is effective for the removal of oxygen from 2-aminopyrazine 1-oxides.

Deoxygenation of quinoxaline *N*-oxides or *N,N'*-dioxides has been realized with sodium dithionite <1996S1477, 2005AF754>.

8.03.9 Ring Syntheses Classified by the Number of Ring Atoms in Each Component

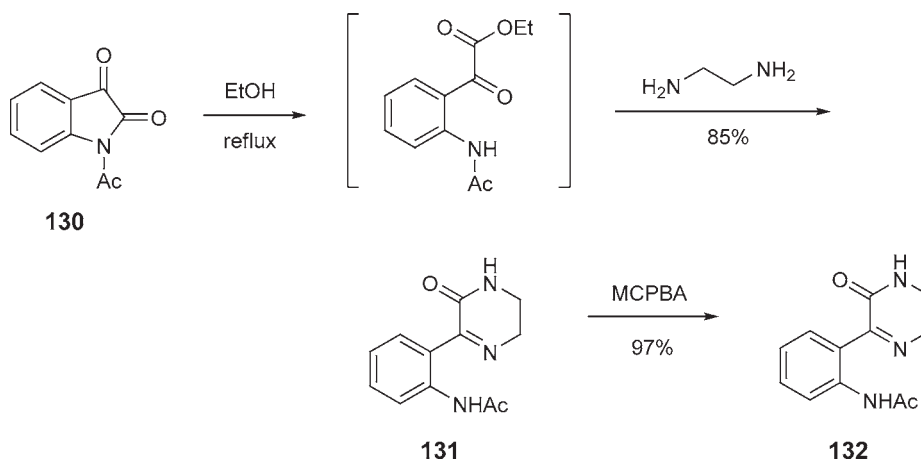
8.03.9.1 From 1,2-Diamino Compounds and their Synthetic Equivalents ('4+2 Components')

The oldest and most general synthetic method for pyrazines, particularly quinoxalines, involves the condensation of 1,2-alkanediamines **124** with 1,2-dicarbonyl compounds followed by oxidation of the resulting 2,3-dihydropyrazines. The 1,2-ethanediamine or 1,2-propanediamine undergoes condensation with a variety of 1,2-diketones leading to substituted pyrazines **125** <1997MI1076>, **126** <1999SL1203>, **127** <2000J(P1)381>, **128** <2001J(P1)668>, or their 2-methyl derivatives after oxidative dehydrogenation (Scheme 34). Although the aromatization is sometimes completed during the workup, it is usually prompted using mild oxidizing reagents. Dehydrogenation of the dihydropyrazines is also accomplished by heating with carbonyl compounds such as acetone, benzaldehyde



Scheme 34

derivatives, or naphthalene carbaldehyde in the presence of KOH [\[1997MI1076\]](#). By manganese dioxide-based tandem oxidation process, α -hydroxy ketones are converted to 1,2-carbonyl compounds followed by trapping with 1,2-diamines and finally oxidation of the resulting dihydropyrazines to produce pyrazines **129** [\[2003CC2286\]](#). When using 1,2-diaminocyclohexane in place of diamine **124**, the yields are higher than those of pyrazines **129**. In addition, the one-pot procedure using manganese dioxide/sodium borohydride in methanol gives 52–87% yields of piperazines. On the other hand, phenylglyoxylate ester, which is prepared *in situ* by refluxing *N*-acetylrisatin **130** in ethanol, condenses with ethylenediamine, and the resultant dihydropyrazinone **131** is dehydrated with *m*-chloroperbenzoic acid yielding 2(1*H*)-pyrazinone **132** (Scheme 35) [\[1997ACS742\]](#). Reaction of 1,2-dihydroxylamines with 1,2-dicarbonyl compounds provides 2,3-dihydropyrazine 1,4-dioxides [\[1993KGS514\]](#). Synthesis of pyrazines using 1,2-diamines with oxirane compounds is also reported [\[1995IJB573, 1998JFC\(87\)49\]](#).



Scheme 35

Diaminomaleonitrile (DAMN) **133**, a tetramer of hydrogen cyanide, is an important precursor for the synthesis of pyrazine-2,3-dicarbonitriles **134** (Scheme 36; Table 2). The condensation with α -diketones proceeds at room temperature or by warming for a short time.



Scheme 36

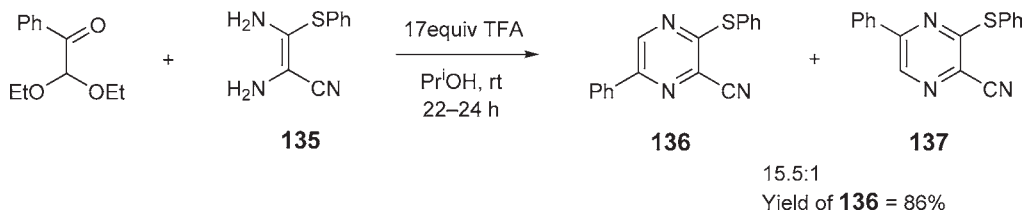
Table 2 Synthesis of pyrazine-2,3-dicarbonitriles from DAMN

R^1	R^2	Conditions	Yield (%)	Reference
$\text{C}\equiv\text{CSiPr}_3$	$\text{C}\equiv\text{CSiPr}_3$	AcOH, rt, 5 min	81	1997T14655
CH_2Br	CH_2Br	MeCN, 70 °C, 1 h	96	1997JPR473
Me	COMe	Dioxane, reflux, 2 h	22	1998DP(40)11
CF_3	CF_3	CHCl_3 , rt, 20 h	42	2000TL9267
CF_3	H	Dil. H_2SO_4 , 0 °C, 1 h	94	2001JHC773

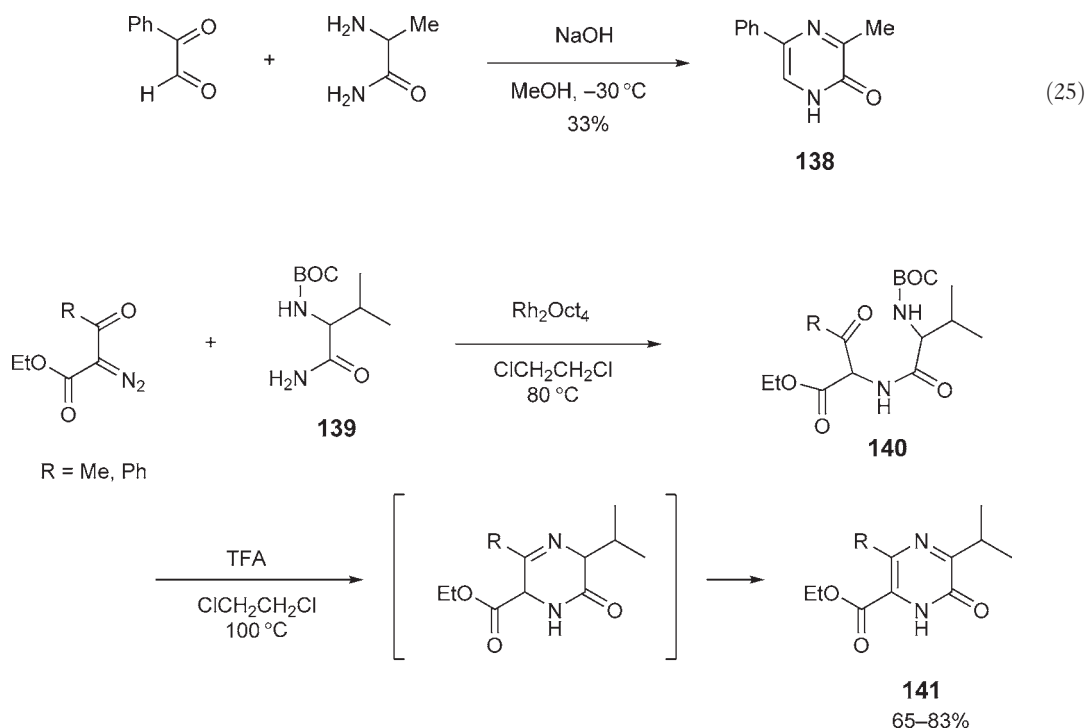
Another efficient 1,2-diamine for synthesis of cyanopyrazines is 2,3-diamino-3-phenylthioacrylonitrile **135**, an adduct of thiophenol to aminomalononitrile tosylate (Scheme 37). The condensation with phenylglyoxal diethyl acetal affords a mixture of two possible isomers **136** and **137**, whose regioselectivity is improved by addition of trifluoroacetic acid; finally, the isomer **136** is isolated in 86% yield <2001SC725>.

Condensation of α -amino carboxamides with 1,2-dicarbonyl compounds is the most practical approach to 2(1*H*)-pyrazinones. Sato *et al.* provided regioselective synthesis of 3-methyl-5-phenyl-2(1*H*)-pyrazinone **138** by Jones' condensation of alaninamide and phenylglyoxal (Equation 25) <1997J(P1)3167>. The use of α -aminohydroxamic acids as the 1,2-diamine leads to the formation of 1-hydroxy-2(1*H*)-pyrazinones <1995JOC1583, 1996H(43)883>. BOC-valine amide **139** is reacted with α -diazo- β -keto esters in the presence of rhodium catalyst (Scheme 38). The resulting N–H insertion products **140** are treated with acid, giving the 1,4-diazine intermediates, which are oxidized

by air to form the corresponding 2(1*H*)-pyrazinones **141** <2004OL4627>. This synthesis is also successfully performed using a solid-phase approach.



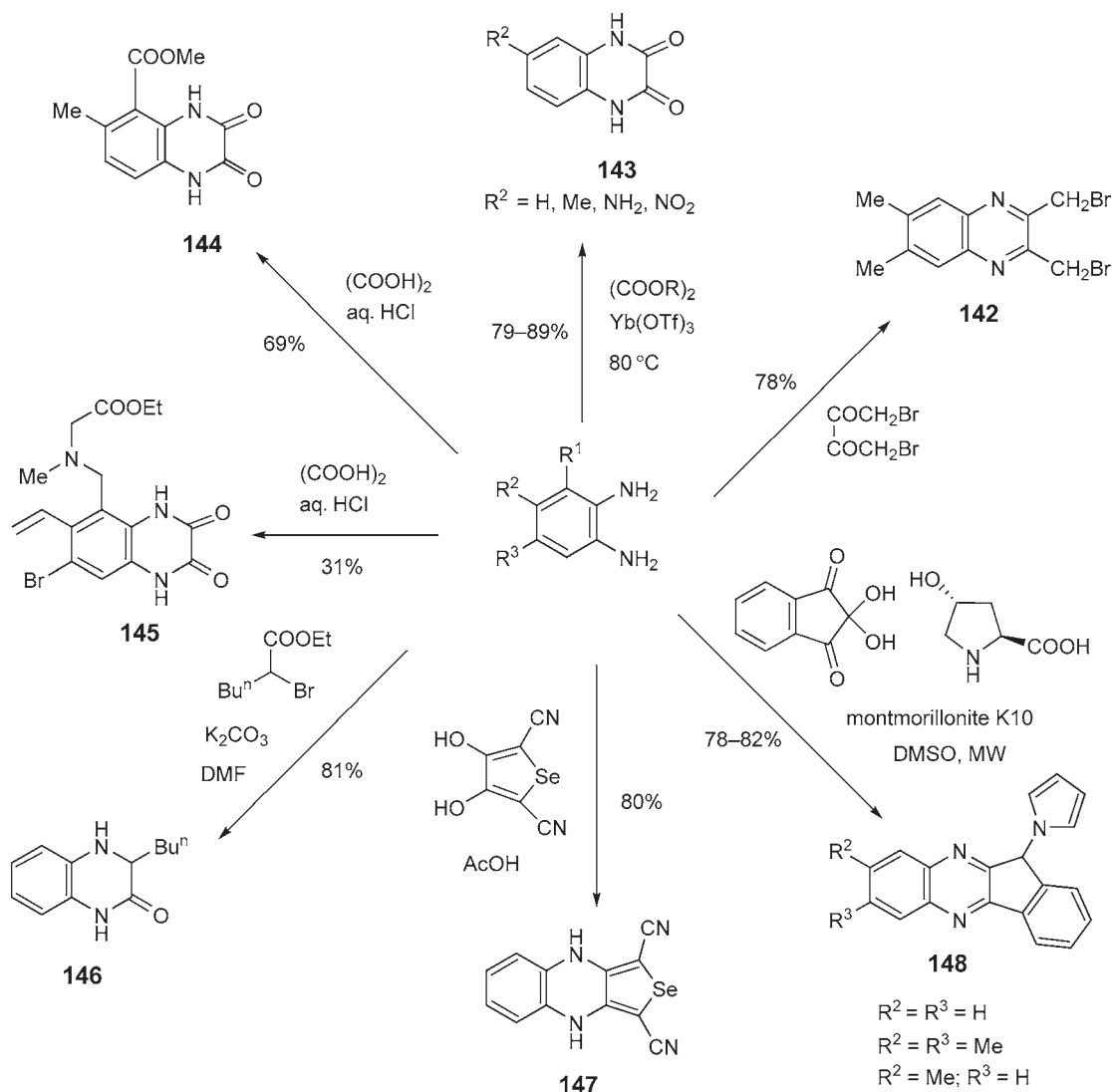
Scheme 37



Scheme 38

Condensation of 1,2-diaminobenzenes with 1,2-dicarbonyl compounds furnishes a variety of substituted quinoxalines **142** <1995JOC8283>, **143** <2004SC1349>, **144** <1999JHC1271>, **145** <1999JME2266>, **146** <1993JME2335>, **147** <2003OL4089>, and **148** <2005TL6155> (**Scheme 39**).

Ytterbium trifluoromethanesulfonate catalyzes the Philipe-type heterocyclization of 1,2-diaminobenzenes with alkyl oxalates under mild solvent-free conditions to provide 2,3(1*H*,4*H*)-quinoxalinediones **143** in high yields. Condensation to quinoxalinedione **144** was completed by refluxing in hydrochloric acid. An attempted use of dimethyl oxalate in refluxing methanol instead of the above procedure was unsuccessful. The compound **145** was synthesized for the purpose of screening as an α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and Gly_N receptor antagonist. The synthesis of compounds **148** was realized through a complicated reaction pathway.



Scheme 39

Various reaction conditions have been developed for the above condensation, in which addition of iodine in catalytic amount (10 mol%) was shown to significantly promote the condensation <2005TL6345, 2005TL7183>.

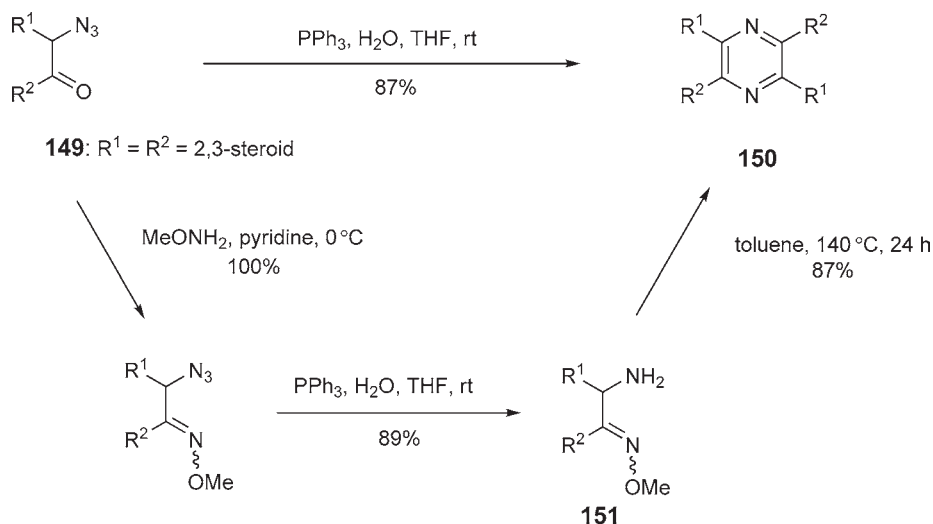
In addition to 1,2-dicarbonyl compounds, 1,2-diaminobenzenes condense with α -oximino ketones <2000JHC355>, epoxides <1999SC3459>, ethyl pyruvate <2000H(52)911>, and ethyl carboethoxyformimidate <1997S301, 1999J(P1)1789> to produce quinoxaline derivatives.

Reaction of 1,2-diaminobenzene with 1,1,1-trifluoro-2,3-alkanediones gives trifluoromethylquinoxalines in high yields <2001JHC773>, and that with perfluoro-2,3-butanedione mono(dimethylhydrazone) gives 2,3-trifluoromethylquinoxaline <2000TL9267>.

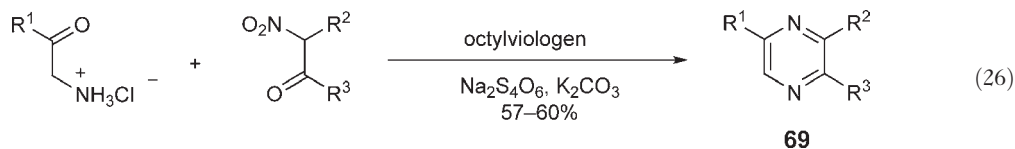
8.03.9.2 From α -Amino Ketones and their Synthetic Equivalents ('3+3 Components')

One of the classical methods for the synthesis of pyrazines involves dimerization of an α -amino carbonyl compound and subsequent aromatization. Cyclic dimerization of the α -amino ketone, which is formed by reduction of α -azido ketone **149** with triphenylphosphine, leads to the formation of a pyrazine derivative **150** (Scheme 40) <1994JOC6828>. Reduced Te also dimerized α -keto azide **149** to give pyrazine **150** <2006JOC2797>.

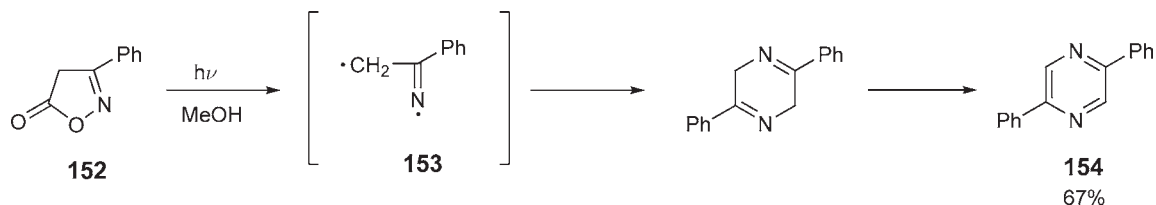
O-Methylated α -amino oxime **151** also undergoes self-condensation by heating in toluene to give the pyrazine **150**. Total synthesis of unsymmetrical pyrazine marine alkaloid, dihydrocephalostatin, has been achieved by stepwise construction starting from imine formation between α -amino methoxime and α -acetoxy ketone <1994JOC6828, 1996JA10672>. The trialkyl-substituted pyrazines have been shown to be prepared via reaction of α -amino ketones with α -nitro ketones using octylviologen as reducing agent to convert the nitro into an amino group (Equation 26) <2005OL5529>.



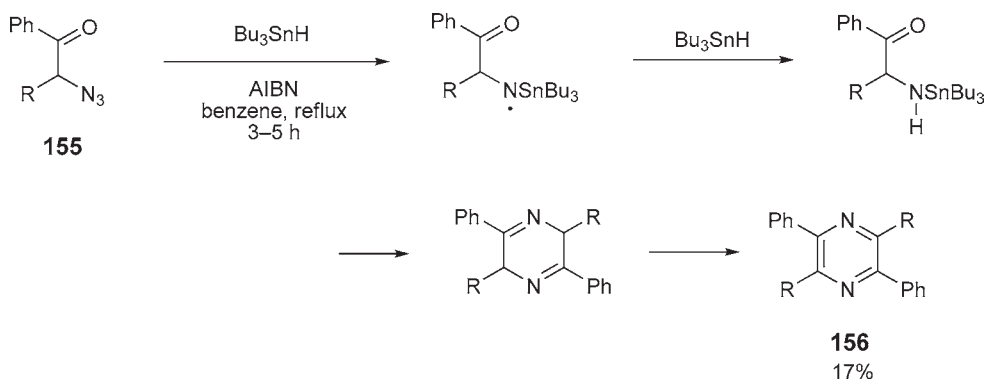
Scheme 40



Photolysis of 3-phenyl-5(4*H*)-isoxazolone **152** gives 2,5-diphenylpyrazine **154** in 67% yield (Scheme 41) <1997JIC648>, probably through diradical intermediate **153**. Radical chain reactions of α -azido ketones **155** with tributyltin hydride lead to symmetrical alkylpyrazines **156**, albeit in low to moderate yields (Scheme 42) <2002T3485>.

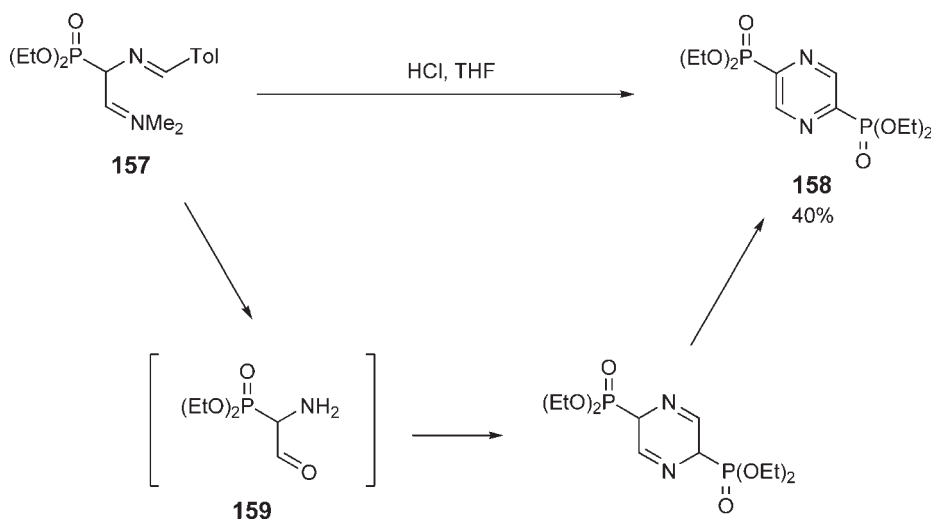


Scheme 41



Scheme 42

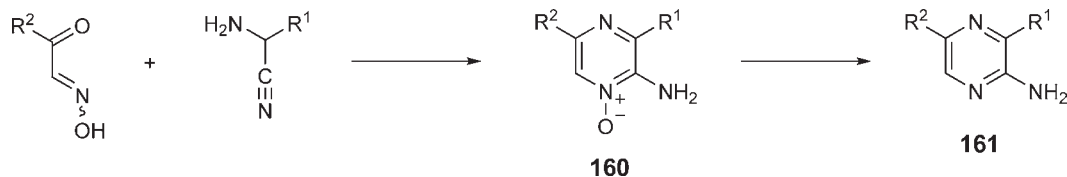
Azadiene **157**, which is prepared by aza-Wittig reaction of diethyl azidomethylphosphonate followed by reaction with dimethylformamide (DMF) diethyl acetal, is hydrolyzed with hydrochloric acid to produce α -amino ketone **159**, affording the unusual pyrazine phosphonate **158** (Scheme 43) <2003T2617>.



Scheme 43

8.03.9.3 From α -Amino Nitriles ('3+3 Components')

The synthetic strategy of preparing pyrazines by condensation of 2-keto aldoximes with α -amino nitriles is well represented by Taylor's pteridine synthesis, in which a variety of 2-amino-3-cyanopyrazine 1-oxides have been prepared by using aminomalononitrile <2002TL6747> as the amino nitriles. In the same fashion, some other α -amino nitriles, which are often the Strecker synthesis products, are converted into 2-aminopyrazine 1-oxides **160** (Scheme 44). The condensations are realized by treatment with *N*-methylmorpholine <1993JOC7542>, and



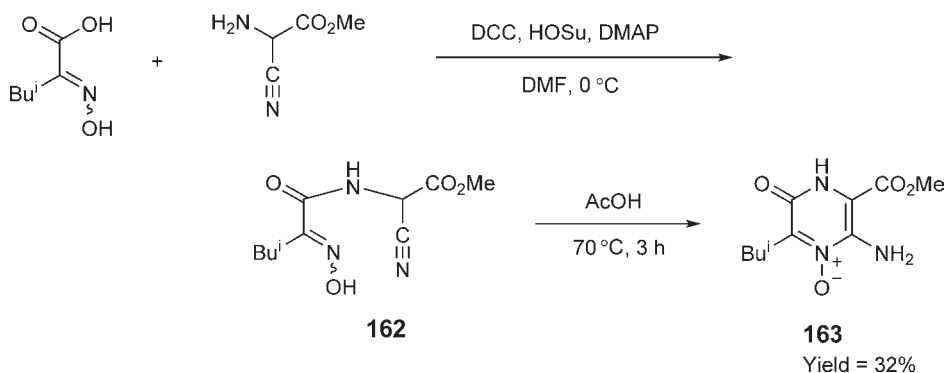
Scheme 44

especially addition of Lewis acids has proved to be effective (Table 3) <1997J(P2)1711, 2002CPB301, 2002TL9287>. The ferric chloride-induced condensation of 2-oximino ketones with excess aminoacetonitrile results in the further deoxygenation by prolonged heating to afford high yields of 2-aminopyrazines **161** <2002TL9287>.

Table 3 Synthesis of 2-aminopyrazine 1-oxides by condensation of α -amino nitriles with 2-oximino ketones

R^1	R^2	Conditions	Yield (%)	Reference
Bn	Me	<i>N</i> -methylmorpholine, CHCl ₃ , reflux, 4 h	63	1993JOC7542
Bn	Ph	TiCl ₄ , pyridine, 0 $\rightarrow$ 82–83 °C, 3 h	38	1997J(P2)1711
Bn	4-HOC ₆ H ₄	TiCl ₄ , pyridine, –5 $\rightarrow$ 20 °C, 0.5 h	94	2002CPB301
H	Ph	FeCl ₃ , aq. MeOH, 20 °C $\rightarrow$ reflux, 4 h	85	2002TL9287

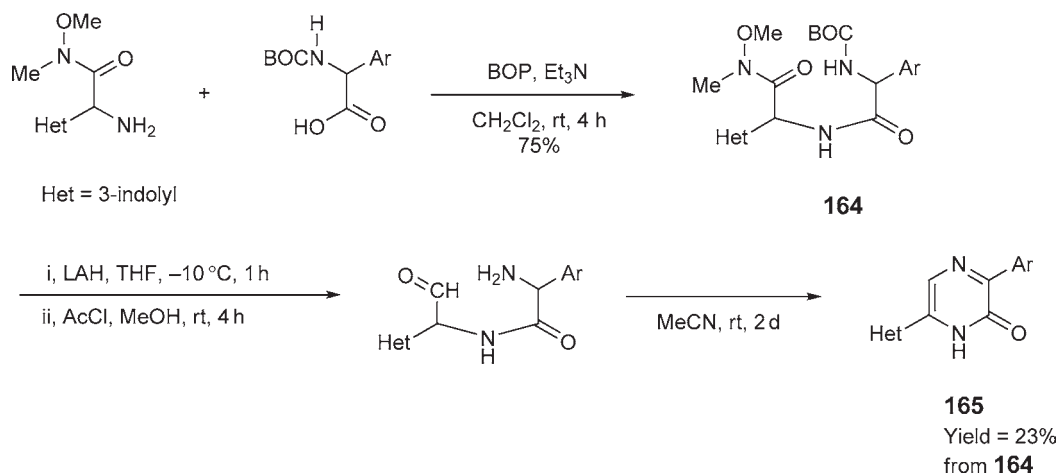
Construction of pyrazine rings from α -amino nitriles has been sometimes completed through multistep reactions. For example, 2-aminopyrazine 1-oxide **163** is synthesized via amide intermediate **162** formed by reaction of methyl α -aminocyanoacetate with α -oximino carboxylic acid (Scheme 45) <1994H(38)1581>.



Scheme 45

8.03.9.4 From α -Amino Acids ('3+3 Components')

One of useful building blocks for the synthesis of 2-(1*H*)-pyrazinones is *N*-BOC amino acids, whose carboxylic acid moiety reacts with the amino group of another component having cyano or carbonyl functionality at the α -position, such as α -amino nitriles <2004T835>, α -amino amide (Scheme 46) <2000H(53)1559>, α -amino ketones

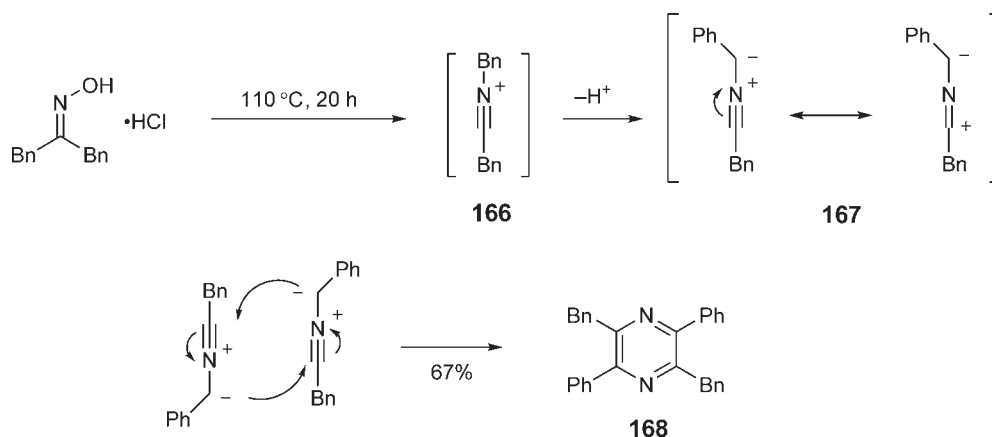


Scheme 46

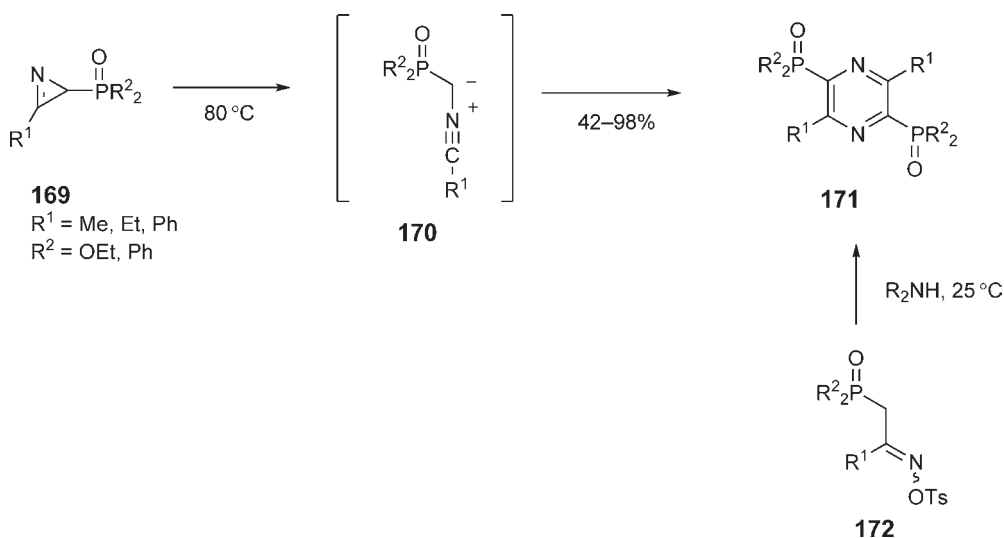
<2004SL2031>, or α -amino α' -chloro acetones <1994TL1231, 1995T7361, 1997JCM10, 1997JRM171>. The dipeptidyl products **164** are, after deprotection of BOC group, cyclized usually by heating to yield 2(1*H*)-pyrazinones **165**. Schöllkopf's bis-lactim ether auxiliary (3*S*)-3,6-dihydro-2,5-dimethoxy-3-isopropylpyrazine was prepared by four-step sequence of reactions starting from L-valine <1998TA321>. Thus, the amino acid is protected with phosgene, and the resultant *N*-carboxy-Leuchs' anhydride is reacted with glycine methyl ester. The dipeptide is cyclized by heating in toluene to produce 2,5-piperazinedione, which is finally methylated with Meerwein reagent to give dihydrodimethoxypyrazine.

8.03.9.5 From Nitrile Ylides and their Synthetic Equivalents ('3+3 Components')

A new approach for primary synthesis of pyrazines is cyclic dimerization of the unstable nitrile ylide dipole. It was found in researching the Beckmann rearrangement of keto oximes without solvent. Heating neat dibenzyl ketoxime hydrochloride causes the Beckmann rearrangement to form nitrilium species **166**, which loses a proton to generate nitrile ylide **167** (Scheme 47). Dimerization of the unstable dipole yields 2,5-dibenzyl-3,6-diphenylpyrazine **168** <2001TL8123>. Analogously, azirines **169** undergo ring opening by heating at 80 °C without solvent to form nitrile ylide **170**, which dimerizes to symmetrically phosphorus-substituted pyrazine **171** (Scheme 48) <2002OL2405>.



Scheme 47

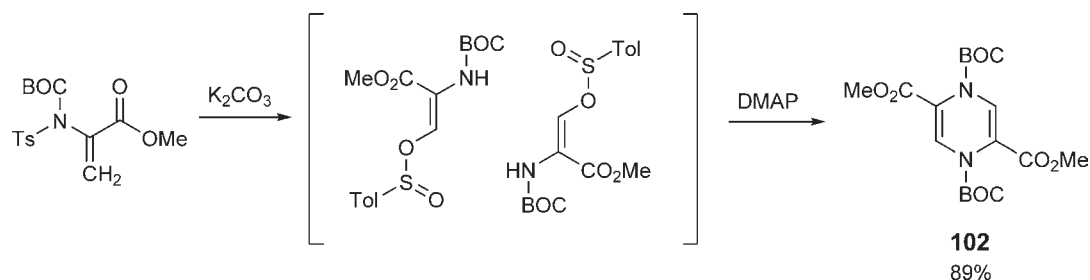


Scheme 48

The product **171** is also prepared by reaction of oxime *O*-tosylate **172** with primary or secondary amines. Higher reaction temperatures than 110 °C cause reductive elimination of one phosphorus substituent.

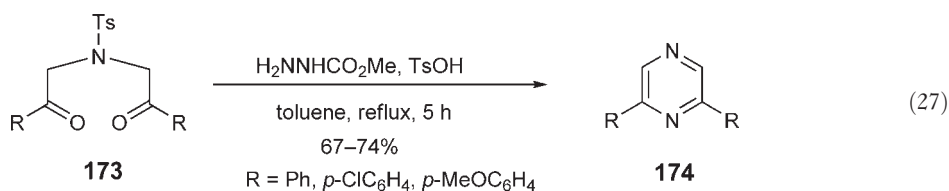
8.03.9.6 Other Syntheses

N,N'-BOC-protected 1,4-dihydropyrazine was prepared by dimerization of *N*-BOC-*N*-tosylated enamine (**Scheme 49**) <2004T8489>.

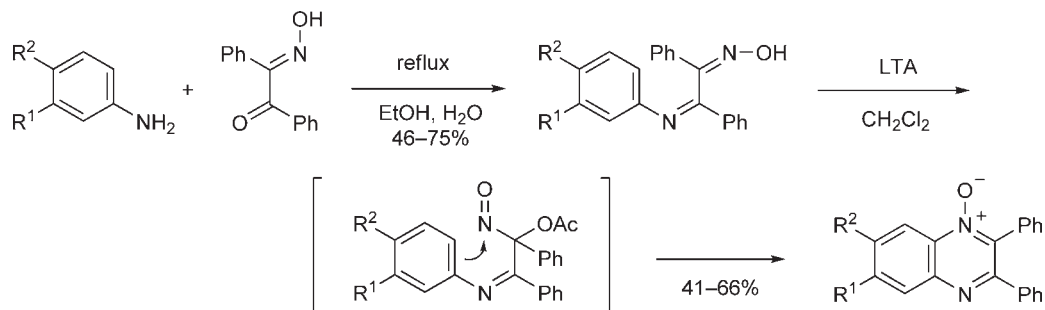


Scheme 49

N,N-Bis(phenacyl)-*p*-toluenesulfonamides **173** are readily synthesized by reactions of *p*-toluenesulfonamide with phenacyl bromides or *p*-toluenesulfonyl chloride with phenacyl amines, and converted into 2,6-diarylpyrazines **174** in high yields by treatment with methyl hydrazinocarboxylate (**Equation 27**) <1998HAC341>. Another construction involving cyclization at the final stage by treatment with ammonia was conducted for the synthesis of the framework of a marine alkaloid <2000H(53)1559>.

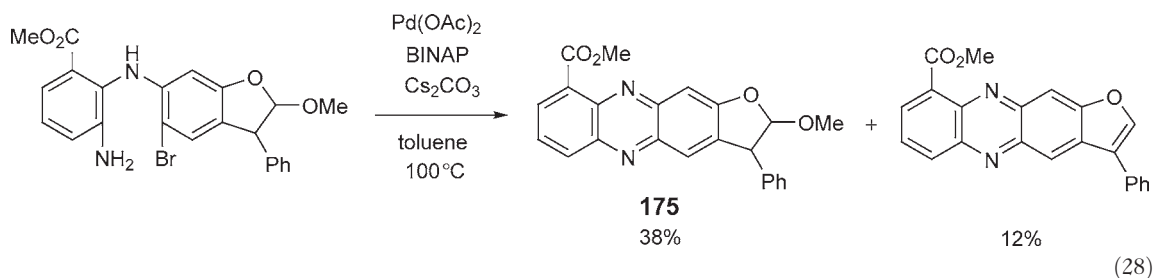


A particular class of quinoxaline *N*-oxides can be synthesized by a reaction sequence starting from condensation of anilines with α -oximino ketones (**Scheme 50**) <1998S1769>. The key step is oxidation of the oxime to an α -acetoxy nitroso group, which behaves as an electrophile leading to the formation of the quinoxaline ring.



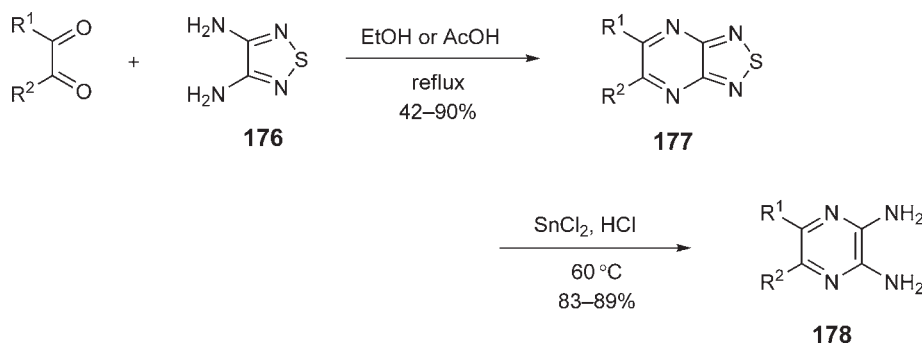
Scheme 50

Phenazine **175** was prepared by palladium-catalyzed intramolecular reaction (Equation 28) <2000TL355>. The ring-closure step was accomplished according to the procedure of Buchwald.



8.03.10 Ring Synthesis by Transformation of Another Ring

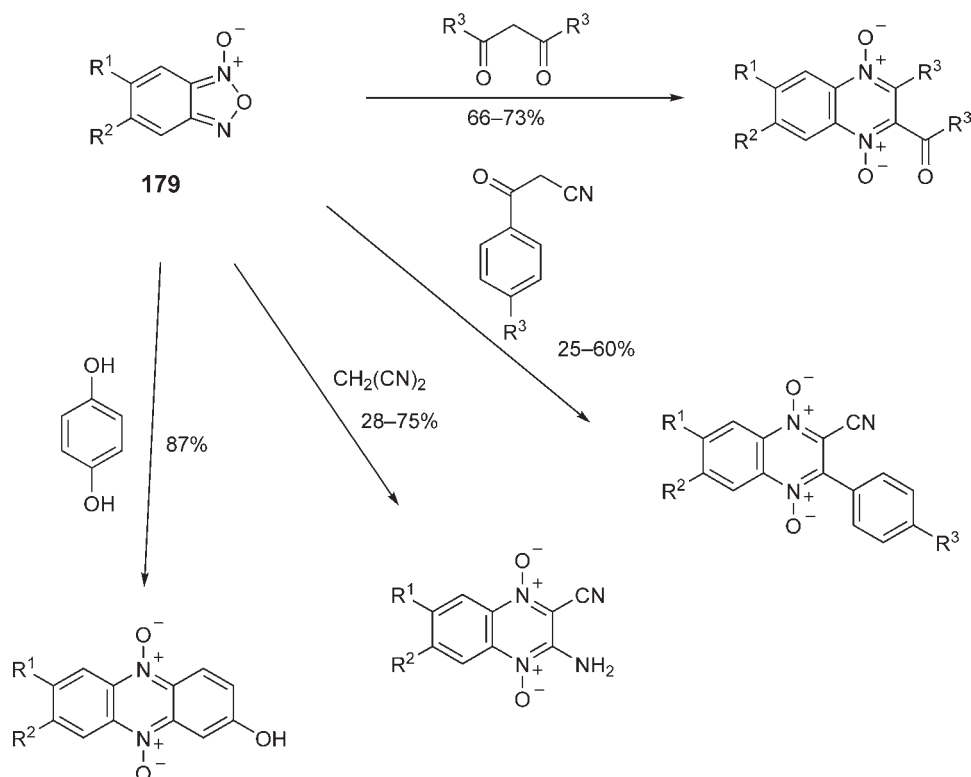
2*H*-Azirines are dimerized under various conditions to dihydropyrazines or their dehydrogenated products, namely pyrazines (Section 8.03.9.5). Quinoxalines are oxidized with potassium permanganate to afford 2,3-pyrazinedicarboxylic acids, and pteridines are hydrolyzed to give 3-amino-2-pyrazinecarboxylic acid derivatives. Condensation of 3,4-diamino-1,2,5-thiadiazole **176** with α -diketones produces 1,2,5-thiadiazolo[3,4-*b*]pyrazines **177**, which are reduced to provide 2,3-diaminopyrazines **178** (Scheme 51) <1997JCM250>.



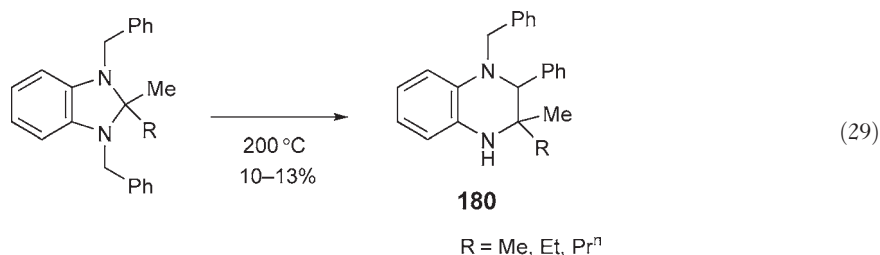
Scheme 51

A simple, efficient, one-step synthesis of quinoxaline 1,4-dioxides from the reaction of benzofurazan oxide **179** with activated alkenes such as enamines was named the Beirut reaction in honor of the city of its discovery. Developments up to 1993 were surveyed by Haddadin and Issidorides <1993H(35)1503>, who first demonstrated this reaction. The benzofurazan oxide **179** (Scheme 52) also condenses with 1,3-diketones <1995M1217, 1996JHC1057, 1999CHE459, 2003EJM791, 2005H(65)1589>, β -keto acid derivatives <1995H(41)2203, 1999CHE459>, β -cyano ketones <2005AF754>, malononitrile <1995JME1786>, and 1,4-dihydroxybenzene <1995M1217, 2000H(53)2151> in basic medium, usually using triethylamine, or molecular sieves, the latter of which is particularly effective in completing the reaction and improvement of yields <1996JHC1057, 2000H(53)2151>. Silica gel also proved to be effective additive for condensation to quinoxaline dioxides <2005H(65)1589>.

Pyrolysis of 2-substituted 1,3-dibenzyl-2-methylbenzimidazoles at 200°C results in ring expansion to afford the tetrahydroquinoxalines **180** (Equation 29) <1996TL3355>. The reaction was suggested to proceed by an ionic mechanism rather than a radical one.



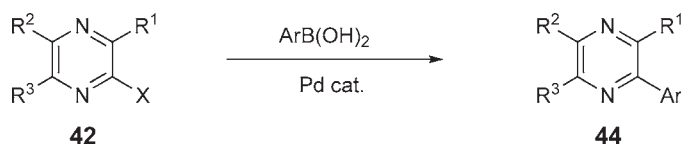
Scheme 52



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

8.03.11.1 Alkyl- and Arylpyrazines, and Quinoxalines

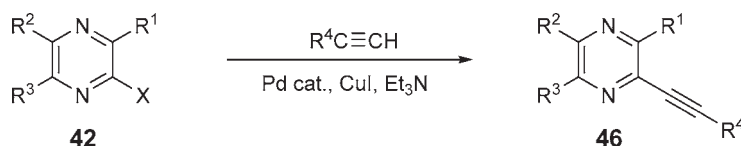
Alkyl- and arylpyrazines have been often produced by primary synthesis from aliphatic components (Section 8.03.9). One of the additional approaches for these synthesis involves transition metal-catalyzed cross-coupling of halogenopyrazines (Section 8.03.5.4.2). In particular, Suzuki and Suzuki–Miyaura coupling reactions using arylboronic acids have been extensively utilized for the arylation (Scheme 53; Table 4). Stille coupling of stannylpyrazines with aryl halides yields arylpyrazines <2003T6375, 2005T2897>. A practical synthetic method for alkynylpyrazines from bromo- or iodopyrazines is Sonogashira coupling using alkynes in the presence of palladium catalyst (Scheme 54; Table 5). Alkylation of chloropyrazines is conveniently realized by the nickel-catalyzed cross-coupling reaction between halogenopyrazines and organozincs <1996J(P1)2345>. Lithiopyrazines react with methyl iodide affording methylpyrazines <1998T9701, 1999H(51)2349>. In addition, alkylation of pyrazines with alkyl radicals has been reported (Section 8.03.5.6.1).



Scheme 53

Table 4 Suzuki and Suzuki-Miyaura coupling reactions of halogenopyrazines

R^1	R^2	R^3	X	Ar	Yield (%)	Reference
H	NH ₂	COPh	Br	Ph, etc	70–96	1996SL509
H	NH ₂	Bn	Br	4-BnO-3-FC ₆ H ₃ , etc.	92–93	1998TL5541
NH ₂	NH ₂	Br ^a	Br	Ph, 4-MeOC ₆ H ₄ , etc.	68–82	2001S768
F	H	H	I	Ph, etc	70–73	2002T283
OMe	Br ^a	H	Br	Ph	94	2002JOC9392
H	H	Cl ^a	Cl	Ph, etc	71–94	2003H(60)1891
H	NH ₂	H	Br	4-TBDMS-OC ₆ H ₄	72	2003S513
F	Ar	H	I	Ph, etc	71–86%	2003T6375
H	NHTs	Bn	OTf	Ph, 4-MeOC ₆ H ₄	85–89	2004T835
Pr ⁱ	Ph	CO ₂ Et	Br	biphenyl	100	2004OL4627
H	NH ₂	Bn	OTf	Ph	82	2005H(65)843
H	NH ₂	H	Br	MeO-pyridyl, etc	51–70	2005JOC388
H	H	Cl	Cl	4-MeOC ₆ H ₄	70 ^b	2005JOC2616

^aThis bromo substituent reacts also with arylboronic acid, hence the yield given in table is that of diarylpyrazine.^bMonoaryl product.

Scheme 54

Table 5 Sonogashira coupling reactions of halogenopyrazines

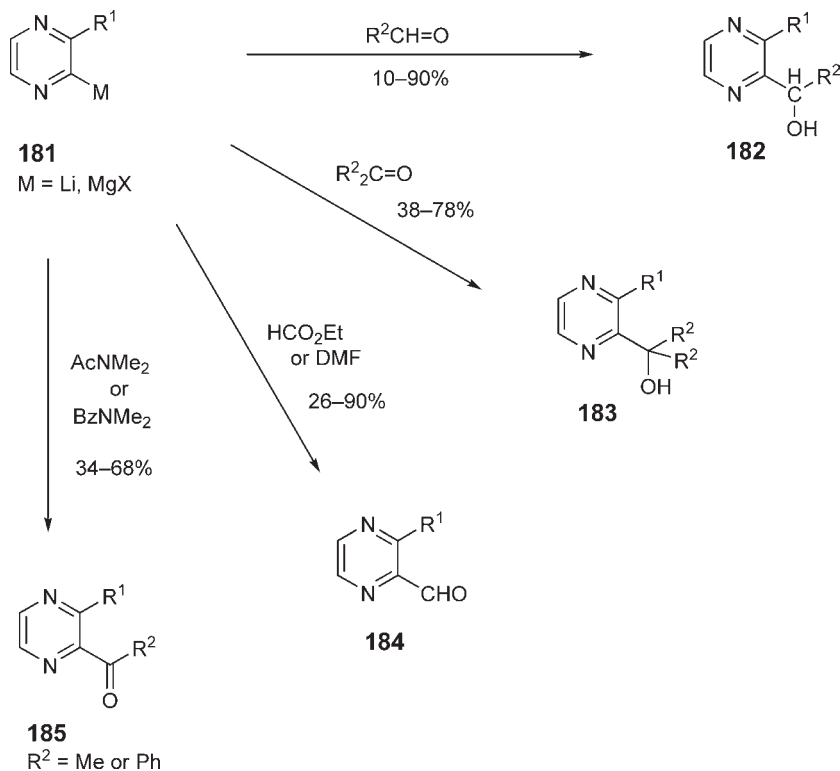
R^1	R^2	R^3	X	R^4	Yield (%)	Reference
H	H	OMe	I	CH ₂ OH	82	1994JHC1449
H	NHMe	CN	Br	Me	72	2000J(P1)89
F	Ar	H	I	<i>n</i> -Hexyl	60–78	2003T6375
Me	Br ^a	Me	Br	Me ₂ CHOH	95	2004NJC912
H	NH ₂	Bn	OTf	Ph	97	2005H(65)843

^aThis bromo substituent reacts also with acetylene, hence the yield given in table is that of dialkynylpyrazine.

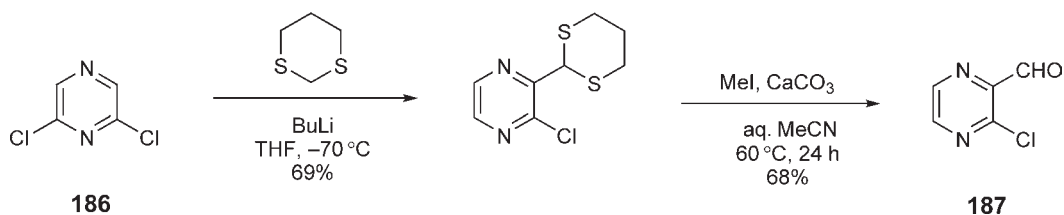
8.03.11.2 Acyl and Related Pyrazines and Quinoxalines

Pyrazinyl methanols **182** and **183** have been directly prepared by trapping of the highly reactive metalated pyrazines **181** (Sections 8.03.5.4.2 and 8.03.5.5) with aldehydes or ketones (Scheme 55) <1994JHC1449, 1995JOC3781, 1996SL509, 1997JHC621, 1998T4899, 1998T9701, 1999H(51)2349, 2000T265, 2000T4043, 2002T283, 2005T9637>. Reactions with ethyl formate or DMF give pyrazinecarbaldehydes **184** <1998T4899, 1998T9701>.

and those with *N,N*-dimethylcarboxamides furnish acylpyrazines **185** <1998T4899>. Lithiopyrazines react with carbon dioxide, ethyl cyanofornate, and phenyl isothiocyanate to form pyrazinecarboxylic acids <1998T9701>, the esters <1998JME1236>, and thiocarboxamides <1999H(51)2349>, respectively. Reaction of 2,6-dichloropyrazine **186** with dithiane anion yield 2-formyl-3-chloropyrazine **187** after deprotection (Scheme 56) <2006TL31>, whereas that of 2,3-dichloropyrazine provides 2-formyl-6-chloropyrazine. A tele-substitution mechanism accounts for these observations and is supported by deuterium labeling studies. Homolytic acylation is a useful method for preparation of acylpyrazines **185** (Section 8.03.5.6.2). The acylpyrazines have been also prepared by Stille reaction of bromopyrazines with 1-ethoxyvinylstannanes (Section 8.03.5.4.2). On the other hand, tributylstannylpyrazine reacts with benzoic chloride in the presence of a palladium catalyst yielding benzoylpyrazine <2005JOC2616>.



Scheme 55

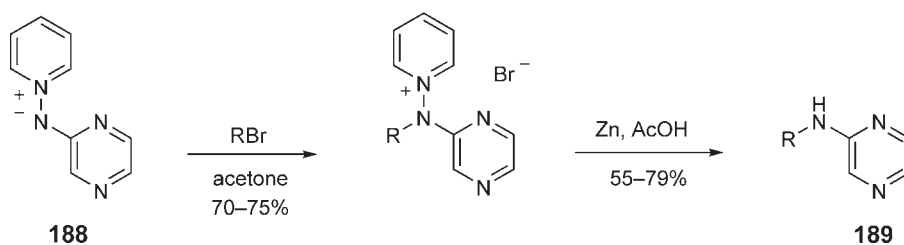


Scheme 56

2-Acetyl or 2-benzoyl-3-aminopyrazines have been prepared by treatment with 3-aminopyrazinecarboxylic acid with acetic anhydride or benzyl chloride followed by addition of methyllithium or phenylmagnesium bromide, albeit in low yields <2005JST(741)67>.

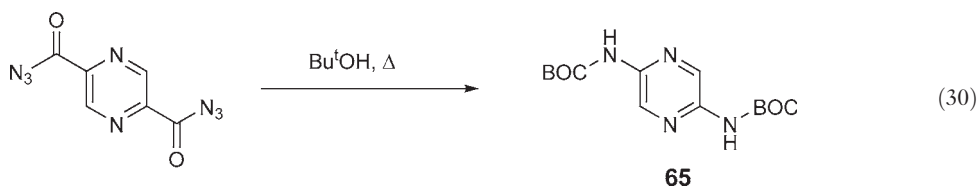
8.03.11.3 Amino Derivatives

Traditional syntheses of aminopyrazines include amination of halogenopyrazines but this is usually unsatisfactory as a preparative method (Section 8.03.7.2). However, the amination has been shown to be promoted by a carbonyl substituent at *ortho*- or especially *para*-positions <1994SL814, 1996SL509>. Recently, reduction of azidopyrazines has been often employed for the preparation of aminopyrazines (Section 8.03.7.2), probably because of the facile formation of azidopyrazines under mild reaction conditions as well as easy reduction. A phthalimido substituent may be used to generate an amino group, that is, 2,5-diamino-3,6-dichloropyrazine is prepared from tetrachloropyrazine via 2,5-diphthalimidopyrazine (Scheme 12). Alkylation of the amino group has been attempted by several procedures <2003S513>. Regioselective synthesis of 2-alkylaminopyrazines **188** away from alkylation of the ring nitrogen is achieved by reaction of pyridinium *N*-(2'-pyrazinyl)amide **189** with alkyl bromide followed by reduction (Scheme 57) <2000T2481>.



Scheme 57

Amino or *N*-BOC-amino pyrazines have been produced by Curtius degradation of pyrazinecarbonyl azides in *t*-butanol (Equation 30) <1999JA8783>.



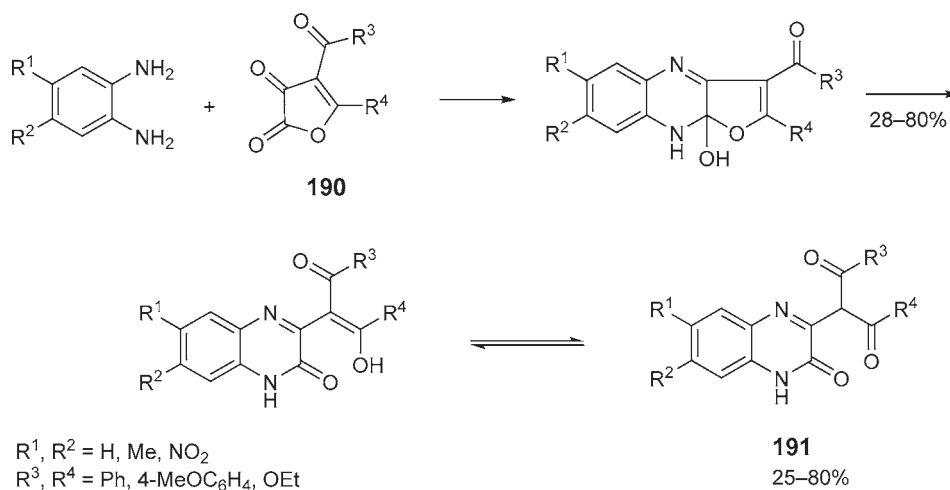
8.03.11.4 Pyrazinones and Quinoxalinones

An old but practical synthetic method for 2(1*H*)-pyrazinones is Jones' procedure which involves condensation of α -amino amides with 1,2-dicarbonyl compounds (Section 8.03.9.1). A number of stepwise approaches using α -amino acids to 2(1*H*)-pyrazinones have been discussed in Section 8.03.9.4.

Numerous 2(1*H*)-quinoxalinones and their 1-methyl derivatives were prepared by multistep manipulation starting from anilines <2005H(65)2741>. A considerable interest attaches to reaction of 2,3-furandiones **190** with 1,2-diaminobenzenes to produce 2(1*H*)-quinoxalinones **191**, which can be converted into 3-phenacyl quinoxalinones by alkaline hydrolysis (Scheme 58) <2005H(65)2161>.

8.03.11.5 Halogeno Compounds

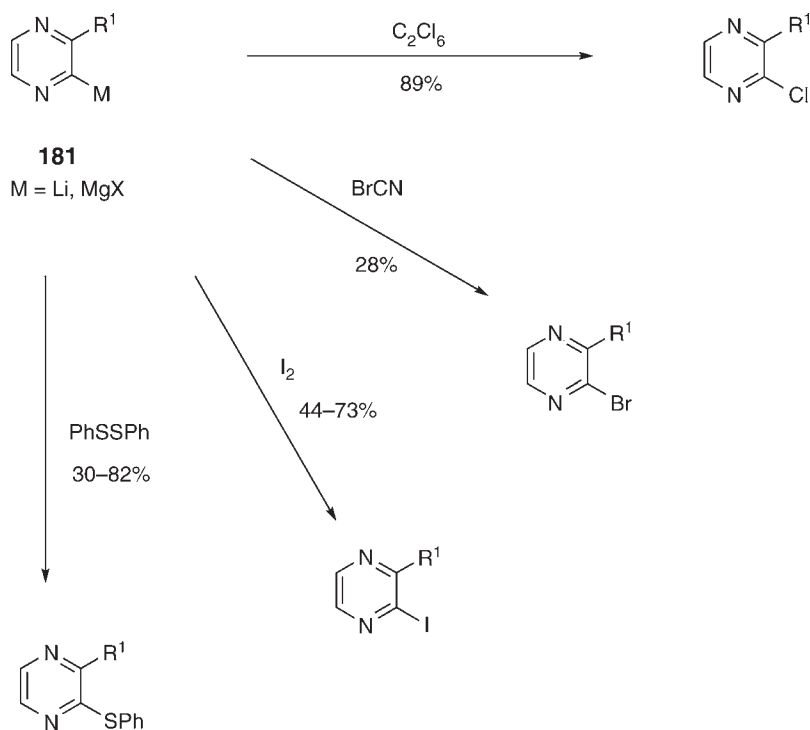
The most convenient synthesis of halogenopyrazines and -quinoxalines is by halogenation of pyrazinones and quinoxalinones with phosphoryl or other acid halides; for example, 5-hydroxy-2-pyrazinecarboxylic acid, rather than 5(4*H*)-pyrazinone-2-carboxylic acid, is chlorinated with phosphorus pentachloride/phosphoryl chloride to afford a 63% yield of 5-chloro-2-pyrazinecarbonyl chloride <1994SL814>. Sato and Narita provided an improved synthesis of various halogenopyrazines in which 2(1*H*)-pyrazinones were activated with chlorotrimethylsilane to give silyl ethers (Section 8.03.7.3). This procedure is most effective for synthesis of bromopyrazines whose overall yields are 62–81% <1999JHC783>. Bromopyrazine is directly prepared by treatment of 2-(1*H*)-pyrazinone with phosphoryl



Scheme 58

bromide at 100 °C in 46% yield [<2005JHC509>](#) or with the same reagent in 1,2-dichloroethane at 100 °C in 73–99% yields [<2004OL4627>](#).

Lithiopyrazines **181** react with iodine [<1995JOC3781, 1998T4899, 1998T9701, 1999H\(51\)2349, 2002T283, 2005JHC509>](#), cyanogen bromide [<1998T4899>](#), or hexachloroethane [<1999H\(51\)2349>](#) forming iodo-, bromo-, or chloropyrazines, respectively ([Scheme 59](#)). The conversion of amino to halogeno substituent by diazotization has been discussed ([Section 8.03.7.2](#)).



Scheme 59

Deoxidative chlorination of alkyl- or aryl-substituted pyrazine *N*-oxides with refluxing phosphoryl chloride for 1 h provides 76–78% yields of the chloropyrazines [<1997MI1076>](#).

Chlorination of methyl 2,3(1*H*,4*H*)-quinoxalinedion-5-ylcarboxylate was efficiently achieved by reaction with phosphene in DMF at room temperature in 90% yield <1999JHC1271>. Other procedures using phosphoryl chloride alone or with phosphorus pentachloride or *N,N*-dimethylaniline decrease remarkably the yields of dichloroquinoxaline.

8.03.11.6 Pyrazinethiones and Quinoxalinethiones

Pyrazine- and quinoxalinethiones have been synthesized by treatment of halogeno compounds with sodium or potassium hydrogen sulfide, sodium polysulfide, phosphorus pentasulfide, or thiourea. For example, pyrazinethione is prepared by treatment of chloropyrazine with sodium hydrogen sulfide in 91% yield <1998JHC429>. *t*-Butylthiopyrazines have been also synthesized by reaction of chloropyrazine with lithium *t*-butylthiolate <1998JHC429>. In contrast, several phenyl pyrazinyl sulfides have been obtained by trapping of lithiopyrazines with diphenyl disulfide (Scheme 59) <1998T4899, 1998T9701, 1999H(51)2349, 2005JHC509>.

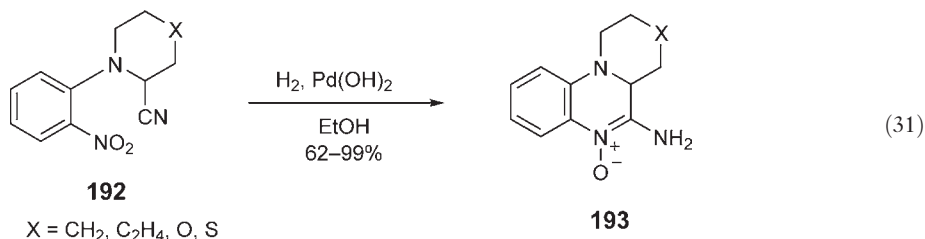
Quinoxalinethione is conveniently prepared by treatment of quinoxalinone with Lawesson's reagent <1997H(44)357>.

8.03.11.7 Pyrazine and Quinoxaline *N*-Oxides

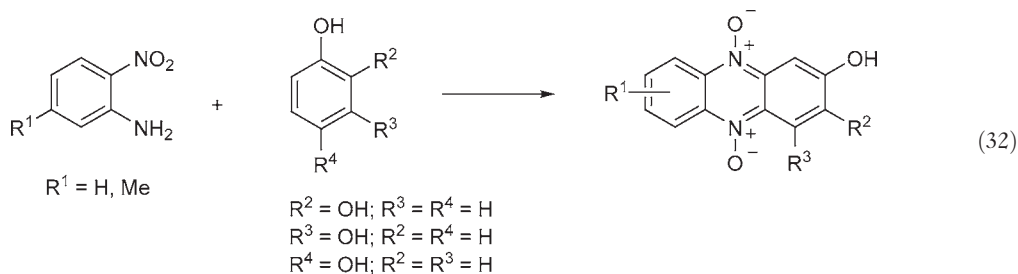
Pyrazine *N*-oxides have been conveniently synthesized by oxidation of pyrazines (Section 8.03.5.2), and by condensation of α -amino nitriles with α -oximino ketones (Section 8.03.9.3).

Like chloropyrazines (Section 8.03.5.2), *N*-oxidation of 2-chloroquinoxalines with *m*-chloroperbenzoic acid yields the 4-oxides, while that with peroxysulfuric acid affords the 1-oxides <1993JME2335, 1996JHC757>.

Catalytic hydrogenation of *N*-(*o*-nitrophenyl)aminoacetonitriles **192** with palladium(II) oxide hydrate gives high yields of quinoxaline *N*-oxides **193** through condensing the reduced hydroxylamine intermediate with nitrile (Equation 31) <2001EJO987>.



Many quinoxaline 1,4-dioxides have been prepared by the Beirut reaction (Section 8.03.10). Phenazine 5,10-dioxides are prepared by the Beirut reaction using hydroquinone (Section 8.03.10), and they can be also synthesized by treatment of *o*-nitroanilines with dihydroxybenzenes (Equation 32) <1995M1217>.



8.03.11.8 Metalated and Related Compounds

Tributylstannylpyrazines have been conveniently synthesized by treatment of lithiopyrazines with tributyltin chloride <1998T4899, 1999JA8783, 1999H(51)2349, 2002T283, 2003T6375, 2005JOC2621> and by that of chloropyrazines with tributyltin lithium <2005T2897>. Trimethylsilylpyrazines have been also prepared from reaction of lithiopyrazines with chlorotrimethylsilane in high yields <1998T9701, 1999H(51)2349, 2002T283, 2005JOC2616>.

8.03.12 Important Compounds and Applications

8.03.12.1 Naturally Occurring Products

A number of new pyrazine alkaloids have been isolated from marine invertebrates, for example, clavulazine **194** from the Okinawa soft coral *Clavularia viridis* <1998H(49)269> and botryllazine A and B **195** from red ascidian *Botryllus leachi* <1999T13225>. Barrenazine A **196** (R = CH₂CH₃) and B **196** (R = CH=CH₂) have been also isolated from an unidentified tunicate collected at Barren Islands, Madagascar <2003OL2433>. The new compounds are of an unprecedented heterocyclic framework. In the terrestrial area, six new polyhydroxy-*p*-terphenyl pyrazinediol dioxides conjugates related to sarcodonin have been isolated from the fruiting bodies of the basidiomycete *Sarcodon leucopus* <2004EJO592>.

As a naturally occurring phenazine, though relatively rare, diphenazithionin **197** (R¹ = R² = H) was isolated from *Streptomyces griseus* ISP5236 <1996TL9227>, and it works as an inhibitor of lipid peroxidation. This substance is composed of two different phenazinecarboxylic acid units which attach to a sulfur atom (Figure 2).

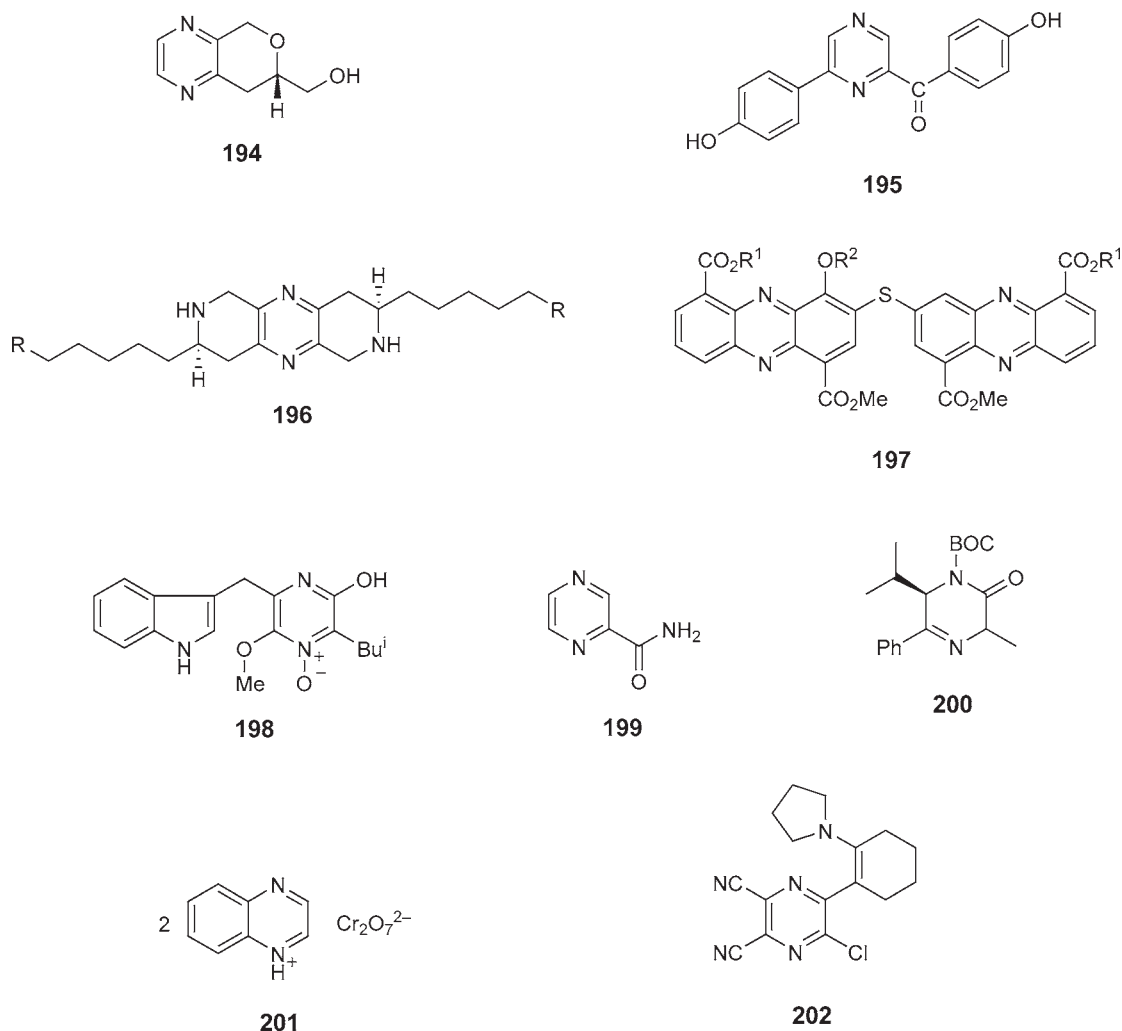


Figure 2

The total synthesis of several naturally occurring pyrazines has been accomplished, for example, tri- and tetra-substituted pyrazines as ant pheromones <1996J(P1)2345>, cephalostatins as complex steroidal pyrazine isolated from marine worm *Cephalodiscus gilchristi* <1994JOC6828, 1996AGE1572, 1996JA10672, 2004SL1414>, POC-15161 **198** as inhibitor of superoxide anion generation <1994J(P1)875>, and botryllazine A and B <2005JOC2616>. A total

synthesis of the pyrazine alkaloid botryllazine B **195** from the red ascidian *B. leachi* has been accomplished, and a previously proposed structure is shown to be confirmed (Figure 2) <2004M333>.

Numerous fragrant pyrazines generated from sugars and proteins or amino acids by the Maillard reaction which occurs during roasting, cooking, and baking of foods have been reviewed <2003MI30>.

8.03.12.2 Pharmaceutical Agents

Pyrazinamide (pyrazinecarboxamide) **199** is a well-known synthetic antimycobacterial agent and is still used for the therapy of tuberculosis (Figure 2). Numerous derivatives of pyrazinecarboxamide <1995AAC2088, 1995CCC1236, 1996CCC1102, 1996CCC1109, 2003FA1105, 2006BML2113> and those of pyrazinecarboxylic acid <1998JME2436, 2001JME1560, 2002JME5604, 2003FA1105> have been prepared and tested for antitubercular activity. In particular, 5-chloropyrazinecarboxamide proved to be more active than pyrazinamide against tuberculous and nontuberculous mycobacteria <1998AAC462>. A quantitative structure–activity relationship (QSAR) study for the *in vitro* antimycobacterial activity of 5-chloropyrazinecarboxylic acid esters was executed <1996JME3394>.

Several β -pyrazinecarbonylstyrenes were bioassayed for *in vitro* antifungal, antimycobacterial and photosynthesis-inhibiting activity <2002FA135, 2006CCC44>. A series of pyrazinyl ethers have been shown significant antibacterial and antimycobacterial activity against the microbial strains *in vitro* <2004BMC2151>. A nonpeptide $\alpha_v\beta_3$ antagonist containing a 2(1*H*)-pyrazinone central scaffold was synthesized <2003BML1809>.

A number of 1-substituted 2(1*H*)-pyrazinone derivatives show antithrombotic activity as selective inhibitors of the tissue Factor VIIa complex <2003BML2319> and were examined as mast cell tryptase inhibitors <2004BML4819>. As a curious effect, dihydropyrazines proved to show DNA strand-breakage activity <2005CPB1359>.

A considerable number of quinoxaline derivatives have been synthesized for the purpose of pharmaceutical agents. The substances assayed for antimycobacterials are quinoxaline-2-carboxylic acid derivatives <2001PHA205, 2002JME5604>, their 1,4-dioxides <2001PHA205, 2003BMC2149>, and 2,3-dianilido derivatives <1997PHA797>. Moreover, the compounds developed as antimicrobials are quinoxalinecarboxamides <2002IJB1480> and 3-substituted 2(1*H*)-quinoxalinones having trifluoromethyl and chloro substituents on the benzo-moiety <2003FA1251>. The following materials were tested in expectation of multiple medicinal effects such as antimycobacterial, antifungal, anticandida, anticancer, and anti-HIV activity: 2,3-disubstituted quinoxalines <1997FA157, 1997FA531>, 6,7-difluoro-2(1*H*)-quinoxalinones <1999FA169>, quinoxaline 1,4-dioxides <2002EJM355>, and 6,7-difluoroquinoxaline 1,4-dioxides <2004EJM195>. Several derivatives of 2,3-(1*H*, 4*H*)-quinoxalinediones have been studied for glutamate receptor (AMPA, *N*-methyl-D-aspartate (NMDA), and NMDA/glycine) antagonists <1996JME3971, 1997BML2441, 1998BML65, 1998BMC271, 1998BML71, 1998BML493>. In addition, 6-imidazolyl-7-nitro-2,3-(1*H*,4*H*)-quinoxalinedione hydrochloride (YM90K) and related compounds were proposed as novel antiepileptic agents <1994JME467>.

A great number of quinoxalines fused with other heteroaromatics have been reported, especially of interest for their potential use in fighting various pathophysiological conditions like epilepsy, Parkinson's, and Alzheimer's diseases. These compounds as well as fused pyrazines are important for pharmaceutical agents, but they are excluded here since they are beyond the scope of this chapter.

Phenazines and their derivatives are known to be biologically significant molecules, particularly in the field of photodynamic therapy. A recent example of the preparation of red-shifted azine dyes potentially useful for photodynamic therapy was reported <1999JHC25>.

8.03.12.3 Technical Applications

A poly(phenylquinoxaline) was prepared for electroluminescence applications <1996SM(76)105>. Crystallization of solution donor–acceptor complexes of 2,3-dimethylquinoxaline 1,4-dioxide or phenazine 5,10-dioxide with TCNE afforded two-component solids containing weakly bound 1-D donor–acceptor arrays <1997TL7665>. A pyrazine ladder polymer was constructed from two different pyrazine units, as an optical device <1999JA8783>. The new electron-deficient macrocycle tetrakis-2,3-[5,6-di(2-pyridyl)pyrazino]porphyrizine was prepared from 1,2-di(2-pyridyl)ethanedione and 2,3-diaminomaleonitrile for a study of its electrochemical properties <2004IC8626>.

8.03.12.4 Reagents for Synthetic Use

Poly- η -(pyrazine)-Zn(BH₄)₂ has been developed as a shelf-stable reducing agent for aldehydes, ketones, acid chlorides, and azides <1995SC3089>. Functionalities such as nitrite, epoxide, oxime, ester, amide, and nitro are unaffected by this reagent. A pyrazine-based polymeric complex of oxodiperoxochromium(VI) was shown to be a new stable, mild, efficient, and versatile oxidant for organic synthesis. Among the reactions promoted by this reagent are 1,2-diol cleavage, α -hydroxy carboxylic acid decarboxylation, and alcohol, benzylamine, thiol, hydroxyphenol, *t*-amine, phosphine, sulfide, anthracene, and phenanthrene oxidations <1997T7889>. Efficient air oxygenation of methane and other lower alkanes in acetonitrile was achieved with a catalytic system employing a (Bu₄N)VO₃-pyrazinecarboxylic acid complex <1997T3603>. Chiral 1,2,3,6-tetrahydro-2-pyrazinone template **200** was employed for the asymmetric synthesis of α -methyl α -amino acids <1998TA2211>. Quinoxalinium dichromate (QxDC, **201**) was shown to be a new and efficient reagent for the oxidation of primary and secondary alcohols and oximes, as well as of anthracene (Figure 2) <2002M1417>.

8.03.12.5 Miscellaneous

Dicyanopyrazine derivatives **202** (Figure 2) were prepared as potential pesticides <1993JHC1571> and 2,6-diamino-3,5-dinitropyrazine 1-oxide as an insensitive high-explosive compound <2004MI81>. A sensitive fluorescence prelabeling reagent for the chromatographic or electrophoretic determination of saccharides is 2-amino-3-phenylpyrazine, and the labeled monosaccharides show strong fluorescence under various pH conditions <2003JCH(A)(1004)99>. Some 2(1*H*)-quinoxalinone-3-propionic hydrazides were found to be useful for direct determination of free phenylacetic acid in human plasma and urine <1994MI283> and of platelet-produced thromboxane B₂ in human serum <2000MI45>, by column-switching HPLC with fluorescence detection. A quinoxalinone fluorescent tag was evaluated as a carboxylic acid-derivatizing reagent for detection by peroxyoxalate chemiluminescence <1994JCH(B)(653)123>.

8.03.13 Further Developments

This section describes further developments to May, 2007. A new topic relevant to thermodynamic aspects (Section 8.03.4.1) is solubility of pyrazine and its derivatives in supercritical carbon dioxide <2006CED2056>. A notable example of nucleophilic displacement of substituents (Section 8.03.5.4.2) is represented by highly selective mono-substitution of chloro substituent in 2,3-dichloropyrazine, which is converted by treatment with α -lithio ketones into α -(3-chloropyrazin-2-yl) ketones <2006T9919>. Similarly α -(chloropyrazinyl) acetic ester or acetonitrile derivatives are synthesized by using α -lithio acetic esters or acetonitriles, respectively.

Several efforts for ring construction from aliphatic components (Section 8.03.9) have been reported recently. Electron-deficient alkenes undergo 1,4-addition to 1,2-diamines leading to pyrazines, their hydro derivatives and quinoxalines <2006JOC5897>, and the products obtained under solution, solvent-free or solid-phase conditions are examined. Microwave-assisted condensation of 1,2-diamines and 1,2-dicarbonyl compounds to quinoxalines is a convenient protocol reducing drastically reaction time (usually ~5 min) <2004TL4873, 2007JBS297>. Recent developments in synthesis of quinoxalines by microwave-assisted procedures have been reviewed <2006H(70)665>. Cyclization of dipeptides to pyrazine rings (Section 8.03.9.4) is also considerably promoted by microwave-assisted heating in water <2006TL5199>. Tri- and tetrasubstituted pyrazines are prepared from epoxides and α -amino alcohols in three reaction steps <2007JOC1492>. Three-component tandem reactions which involve epoxide-opening process with 1,2-diaminobenzene lead to the formation of quinoxalines <2007TL2155>.

Bioactivity and pharmaceutical use for naturally occurring as well as synthetic pyrazines (Section 8.03.12) have been reviewed <2006CLY959>.

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Biographical Sketch



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8.04

1,2-Oxazines and their Benzo Derivatives

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8.04.1 Introduction

The chemistry of 1,2-oxazines and their benzo derivatives has been reviewed earlier [<1984CHEC\(2\)995, 1996CHEC-II\(6\)279, 2002H\(57\)915>](#). This chapter covers all significant developments concerning 1,2-oxazines which appeared in the literature during the period 1996–2006. Since 1996, there have been several new developments in the synthesis and reactivities of dihydrooxazines, particularly by reductive cleavage. Several research groups have investigated ring synthesis of dihydro 1,2-oxazine via intra- and intermolecular [4+2], tandem[4+2][3+2], domino[4+2][4+2][3+2], homo [3+2] and [3+3] cycloaddition reactions. Several oxazine containing ring systems have been encountered in natural products, pharmaceuticals, and agrochemicals. In this chapter, most of the information refers to the mono- and bicyclic oxazines and benzo-fused bi- and tricyclic cyclic ring systems. The 1,2-oxazine containing fused heterocyclic and bi- or tricyclic bridgehead ring systems with nitrogen at the bridgehead are covered in Volumes 10 and 11 instead of this chapter.

The nomenclature of ring systems containing the partially or fully hydrogenated monocyclic, bicyclic, and tricyclic fused 1,2-oxazine ring skeleton are shown in [Figure 1](#).

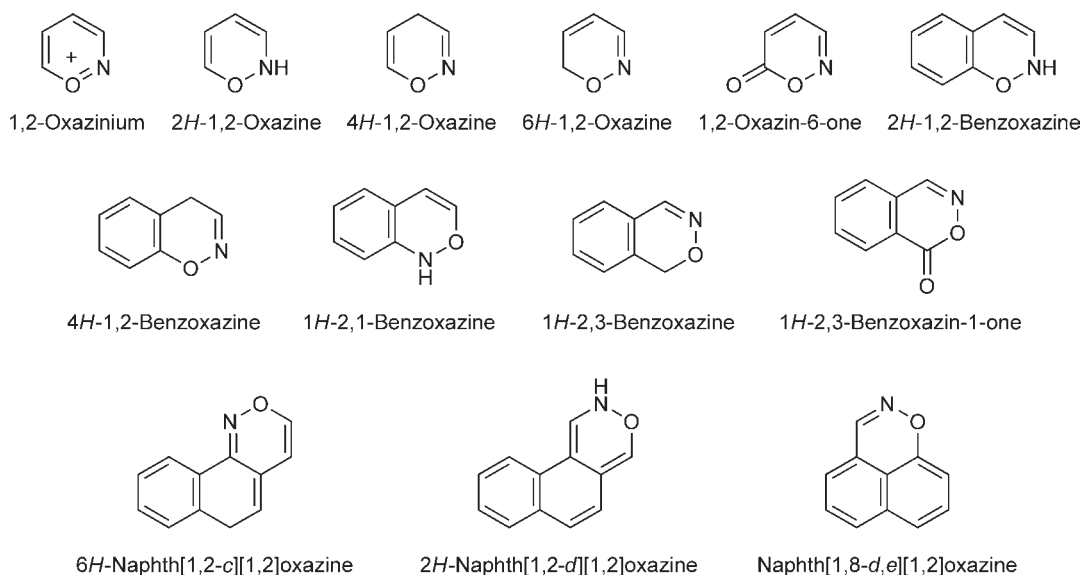
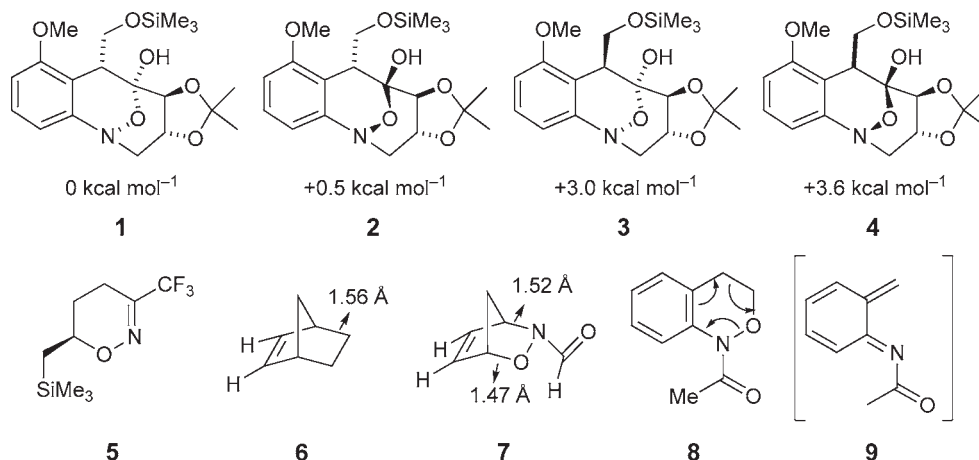


Figure 1

8.04.2 Theoretical Methods

Bond distances and charges at the atoms in the 1,2-oxazinium cation have been calculated earlier by the MINDO/3 method (MINDO = modified intermediate neglect of differential overlap) [<1996CHEC-II\(6\)279>](#). The thermal stability of the major isomer **1** is supported by preliminary semi-empirical calculations comparing the relative stability of four diastereomeric hemiacetals **1–4** [<2004JOC2831>](#). The 7 α -isomers **1** and **2** are lower in energy relative to the corresponding 7 β -isomers **3** and **4**. Modified neglect of diatomic overlap (MNDO) calculation indicates that the deprotonation of the 3-CF₃-substituted 1,2-oxazine **5** is energetically more favored by approximately 11.95 kcal mol^{−1} than the deprotonation of the corresponding 3-phenyl-substituted 1,2-oxazine [<1996JFC\(80\)21>](#). Geometric features of the STO-3G-optimized structures of norbornene **6** and *N*-formyl-2-oxa-3-azanorbornene **7** were studied [<2000EJO2613>](#). The replacement of the CH₂–CH₂ bridge in compound **6** with N–O resulted in shortening of the

C–O, N–O, and N–C bonds, and this induces additional strain in the oxazine system **7** <2000EJO2613>. Extrusion of formaldehyde from *N*-acetyl-2,1-benzoxazine **8** to give imine **9** involves a concerted breaking of both the C–C and N–O bonds <1996J(P2)1367>. The experimental barriers are lower than the theoretical one predicted by AM1 for the decomposition of **8** in the gas phase.

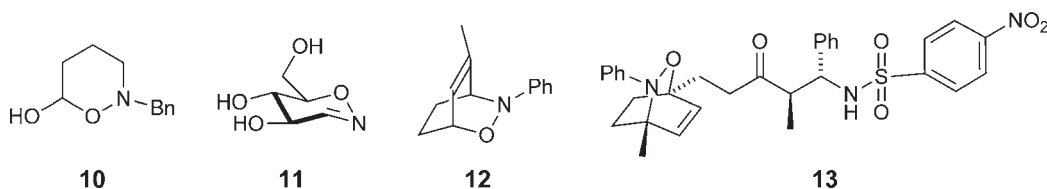


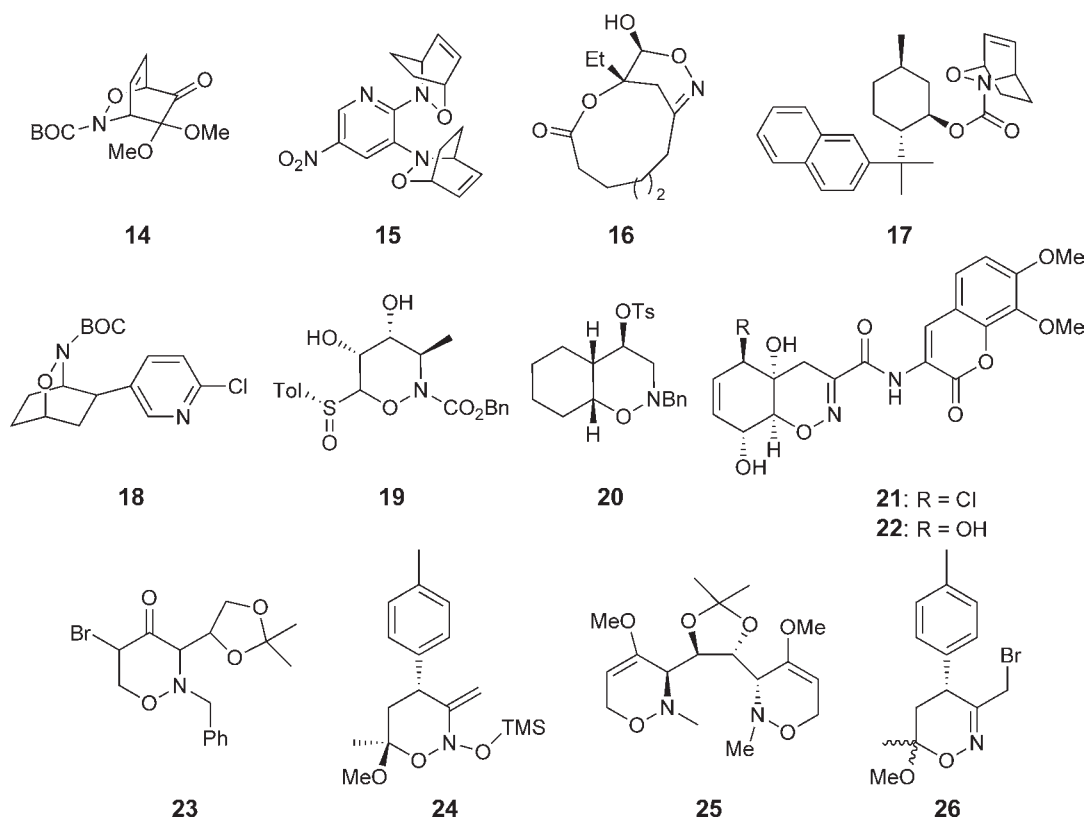
8.04.3 Experimental Structural Methods

A previous review has covered the crystal structure data and ^{13}C nuclear magnetic resonance (NMR) of 1,2-oxazinium cation and of 5,6-dihydro-4*H*-1,2-oxazines <1996CHEC-II(6)279>. Studies related to infrared (IR) absorption frequencies for C=N and C=C bonds in conjugated oxazinones have been reviewed earlier <1996CHEC-II(6)279>.

8.04.3.1 X-Ray Crystal Structures

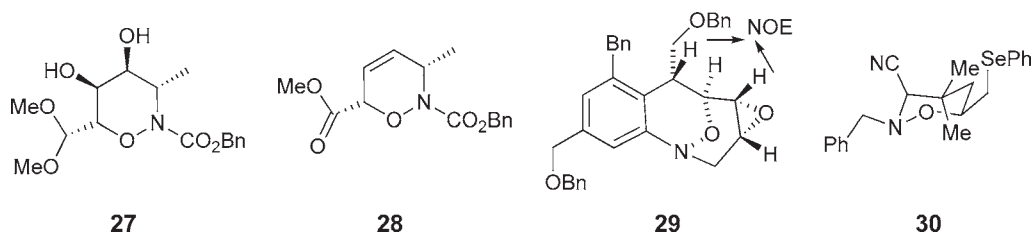
Structures of the following compounds were established via X-ray crystallography studies: *N*-benzyl-6-hydroxytetrahydrooxazine **10** <1998CC1487>, 6-hydroxymethyl-4,5-dihydroxy-oxazine **11** <2002CJC857>, *N*-phenylbicyclooxazines **12** and **13** <2000POL569, 2003CL582>, dimethoxy *N*-BOC-bicyclooxazinone **14** <2001CC1624>, 5-nitropyridine-2,3-bisoxazine derivative **15** <1999CC1009>, lactone **16** (*cis*-arrangement of hydroxy and ethyl group) <2005OL2197>, *N*-acyl-1,2-oxazine **17** <1998JOC8397>, epibatidine analog **18** (*meta*-aza regioisomer favored over the *para*-aza) <1998TL4513>, and 6-tolylsulfinyl-1,2-oxazine **19** <2000OL3165>. Bicyclic tetrahydro-1,2-oxazine **20** in the solid state is conformationally mobile with the tosyl group in an axial position and the benzyl group in an equatorial position of the bicyclic system <1998JCX133>. Trichodermamides A and B **21** and **22**, two modified dipeptides, have been isolated from cultures of the marine derived *Trichoderma virens*. Both trichodermamides possess a rare cyclic *O*-alkyloxime functionality incorporated into a six-membered ring <2003JNP423>. The structure of **22** was established by X-ray diffraction analysis while the structure assignment of **21**, and determination of the absolute stereochemistry, was accomplished by spectral and chemical methods <2003JNP423>. The 5-bromotetrahydrooxazin-4-one **23** ring adopts a chair conformation with all substituents in equatorial positions <2000NCS73>. X-Ray analysis of 2-silyloxytetrahydrooxazine **24** revealed that in the solid state it adopts a chair conformation with a pyramidal nitrogen atom <2003JOC9477>. The structure of *syn/syn* bis(1,2-oxazine) **25** was unequivocally confirmed by X-ray and ^1H NMR analysis <2005EJO1003>. X-ray crystal structure analysis revealed that the 3-bromomethyl-4-phenyldihydrooxazine **26** preferred the half-chair conformation <2004SI159>.

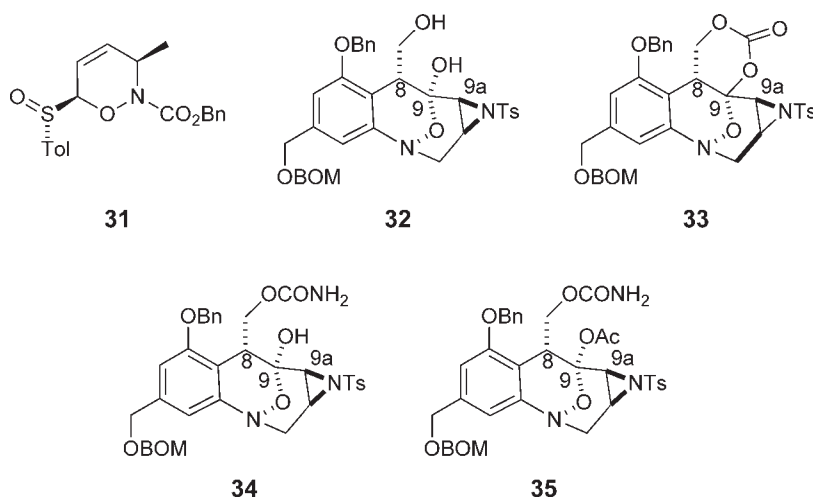




8.04.3.2 NMR Spectra

The structure of the oxazine 4,5-diol **27** was confirmed through configuration and conformation analysis by ^1H NMR data [\[1997T13783\]](#). N-substituted oxazine **28** is known to exhibit hindered rotation around the O–N–C=O bond whose energy barrier is lower than that of the corresponding amides; the coalescence temperature of the signals of the groups near the carbamate moiety is close to 300 K [\[1998HCA1417\]](#). The relative configuration of the tricyclic oxazine **29** is assigned based on observed nuclear Overhauser effect (NOE) interaction between the indicated protons (2D-NOESY) (NOESY = nuclear Overhauser enhancement spectroscopy) [\[2002AGE4688\]](#). Differential NOE and NOESY experiments of 2-benzyl-3-cyano-6-(phenylselenomethyl)-2*H*-tetrahydro-1,2-oxazine **30** showed that the PhCH_2 group occupies an equatorial position and that the CN group is axial [\[1996T6811\]](#). Vicinal coupling constants for 6-tolylsulfynyldihydro-1,2-oxazine **31** were determined to be $J_{3,4}$ (4.4 Hz) and $J_{5,6}$ (1.3 Hz), values which are consistent with the relative pseudoequatorial and pseudoaxial arrangements for H-3 and H-6 associated with the Me group in an axial orientation and the *p*-tolylsulfinyl group in an equatorial arrangement [\[2000OL3165\]](#). The stereochemistries at the C-9 position of the diastereomeric bridged tetracyclic compounds **32–35** were confirmed by NOE experiments in their 400 MHz- ^1H NMR spectra. NOEs between the signals of C-8H and C-9aH have been found to be 3.1%, 3.2%, 3.5%, and 2.9%, respectively. Based on these studies, the stereostructures of **32–35** were assigned as depicted [\[1997T10253\]](#).

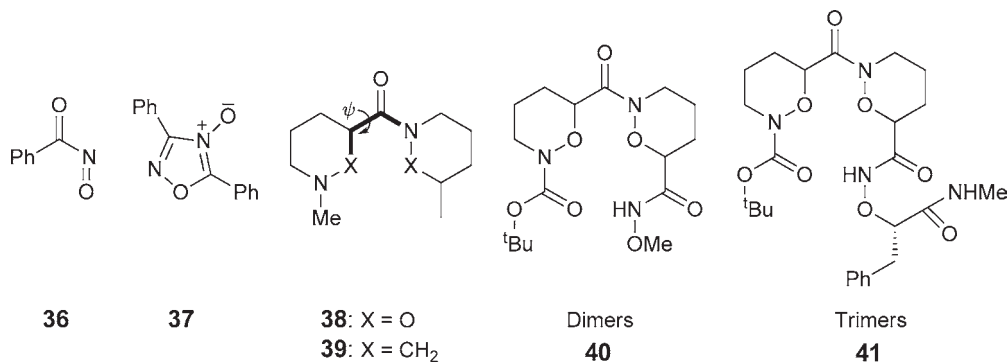




8.04.3.3 IR Spectra

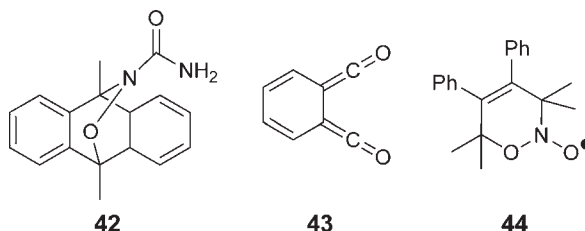
Intermediate α -nitrosobenzaldehyde **36** was generated in solution by laser photolysis of 3,5-diphenyl-1,2,4-oxadiazole-4-oxide **37** and its time-resolved infrared (TRIR) spectroscopy has been recorded [\[2003JA1444\]](#). The second-order rate constants for reaction with diethylamine and 1,3-cyclohexadiene were determined to be $(1.3 \pm 0.5) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ and $(6.0 \pm 0.5) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, respectively [\[2003JA1444\]](#).

Ab initio, quantum calculations showed that both **38** and **39** adopted unusual folded structures with consecutive β - and γ -turn-like conformations [\[2003OL971\]](#). The conformation analysis of oxanipectic acid dimers **40** and α -aminoxyl tripeptide analog **41** has been studied using Fourier transform infrared (FTIR), and NMR data. Oxanipectic acid dimers **40** with preferred β -turnlike conformations can be used as a novel turn motif. α -Aminoxyl tripeptides **41** composed of dimeric oxanipectic acid and α -aminoxyl acid in CHCl_3 adopted two different turn conformations, consecutive β - and γ -turns. IR spectra of **40** indicated that the ratio of hydrogen-bonded and non-hydrogen-bonded stretching NH bands reflects the position of the conformational equilibrium. Both dimers displayed exclusively one peak at $3230\text{--}3260 \text{ cm}^{-1}$ that corresponds to a hydrogen-bonded NH stretching bond. The ^1H NMR chemical shift of oxyamide NH for dimers in CDCl_3 exhibited remarkably downfield shifts to 10.9 and 10.7 ppm, respectively. For trimers **41**, four possible NH stretching bands (hydrogen-bonded amide/oxyamide NH bands and non-hydrogen-bonded amide/oxyamide NH bands) were displayed in their IR spectra. The hydrogen-bonded amide oxyamide NH band appears at $3320\text{--}3350 \text{ cm}^{-1}$ and only three absorption bands were displayed in the NH stretching region in the IR spectra. The oxyamide NH resonance for three trimers in CDCl_3 appeared significantly downfield (10.5–11.3 ppm) relative to oxyamide NH (7.8 ppm). This demonstrates that the oxyamide NH group is exclusively involved in an internal hydrogen bond [\[2003OL971\]](#).



8.04.3.4 EPR

Electron paramagnetic resonance (EPR) and NMR spectroscopy provided evidence for $\text{HN}=\text{O}$ release from *N*-hydroxyurea during the process of cycloaddition of acylnitroso to 9,10-dimethylantracene (9,10-DMA) cycloadduct **42** via retro-Diels–Alder reaction <2004BML5565>. EPR studies with hydroxyurea detected the formation of nitroxide radical <2002JA3473, 2004JME3495>. In the presence of nitric oxide, the bisketene **43** was generated via photolysis from benzocyclobutenedione in addition to *N*-hydroxyphthalimide and phthalic anhydride; cheletropic trapping of NO with 3,4-diphenyl-2,5-dimethyl-2,4-hexadiene gave strong persistent electron spin resonance (ESR) signals for **44**, and the nature of the signal is dependent on the purity of the NO <1996TL2113>.



8.04.4 Thermodynamic Aspects

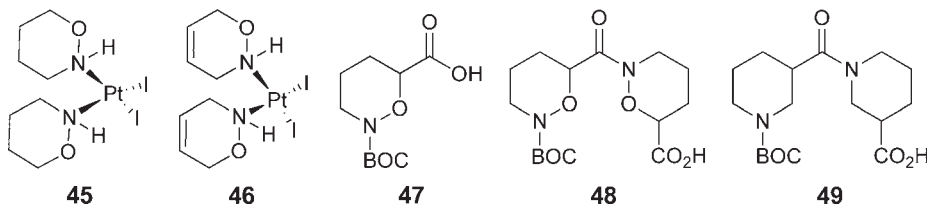
8.04.4.1 Aromaticity of Conjugated Rings

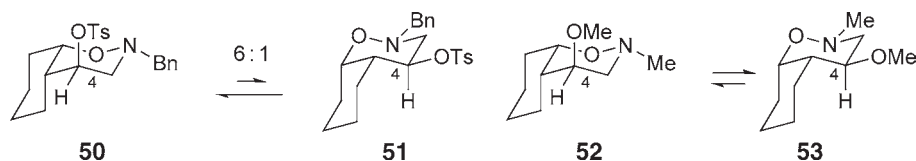
Theoretical and experimental studies concluded that the 1,2-oxazinium cation is a planar, aromatic cation, although the X-ray structure reveals that the bond distances tend to alternate (e.g., the $\text{C}=\text{N}$ bond distance is not significantly greater than that in oximes and imines). The ring 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 <1996CHEC-II(6)279>.

8.04.4.2 Conformations of Nonconjugated Rings

In the solid state, 2-silyloxy-1,2-oxazine **24** adopts a chair conformation with the pyramidal nitrogen atom, whereas in solution it exists as an equilibrating mixture of two conformers (ΔG 13–14 kcal mol^{−1}) <2003JOC9477>. Both oxazine ligands **45** and **46** possess a chair conformation with bond distances and angles similar to those in reported saturated oxazine derivatives. Ligands **45** and **46** have opposite absolute configurations at nitrogen atoms <2000AXC335>.

Ab initio calculation and circular dichroism experiments reveal that oxa oligomers adopted pronounced non-hydrogen-bonded helical structures. Introduction of an asymmetric chemical environment into oxanipeptotic acid **47** to constrain all the torsional angles produced pseudopeptides with more pronounced helicity than the corresponding Nip oligomers. In addition, α -aminoxyl peptides adopting seven-membered hydrogen-bonded helical conformations are able to adopt non-hydrogen-bonded helical structures in the case of oligomeric cyclic α -aminoxyl acids <2003CC968>. Baek *et al.* demonstrated that oxa dimers **48** adopted more stable turn conformations than the corresponding Nip dimers **49** <2003TL3447>. In conformer **51**, there are two 1,6-H/H interactions. In conformer **50**, only one such interaction exists; the other is replaced by a 1,3-diaxial OTs/H interaction, which should cause less steric strain. Thus, conformer **50** should be slightly more stable than **51**. Molecular modeling studies were performed with the structures **52** and **53**, which are truncated analogs of **50** and **51**. The calculated vicinal NMR coupling constants for H-4 in **52** and **53** matched exceptionally well with those observed for **50** and **51** <1998JOC4485>.





8.04.5 Reactivity of Fully Conjugated Rings

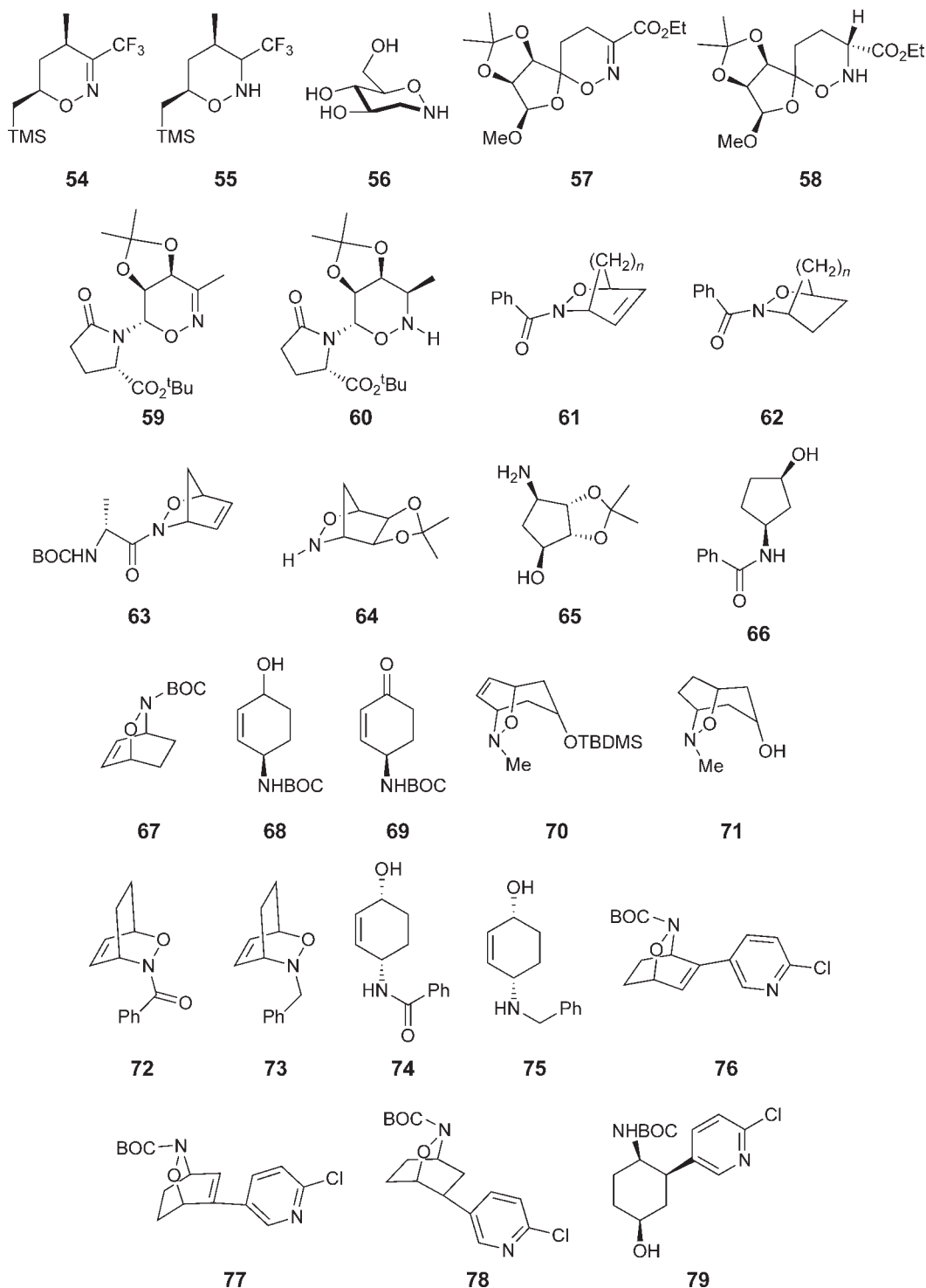
A previous review covered few examples in this category <1996CHEC-II(6)279>. Because of the highly electrophilic nature of the 1,2-oxazinium cation, no general chemistry has been developed comparable to that of the pyrylium salts. Triaryl-1,2-oxazinium cations on hydration are converted into 6-hydroxy-6*H*-oxazinium cations which react with nucleophiles <1996CHEC-II(6)279>.

8.04.6 Reactivity of Nonconjugated Rings

In an earlier review, the reactivity of nonconjugated oxazine rings was organized based on the types of compounds, for example, benzoxazine, 3,6-dihydro-2*H*-1,2-oxazines, 5,6-dihydro-2*H*-1,2-oxazines <1996CHEC-II(6)279>. Further, within each series, electrophilic and nucleophilic substitution reactions and reductive C–N cleavage reactions have been discussed <1996CHEC-II(6)279>. In this review, the reactivity of oxazine ring systems is organized mainly based on the type of reactions and including the following subsections: ozonolysis, epoxidation, ring transformation, and retro-Diels–Alder reactions.

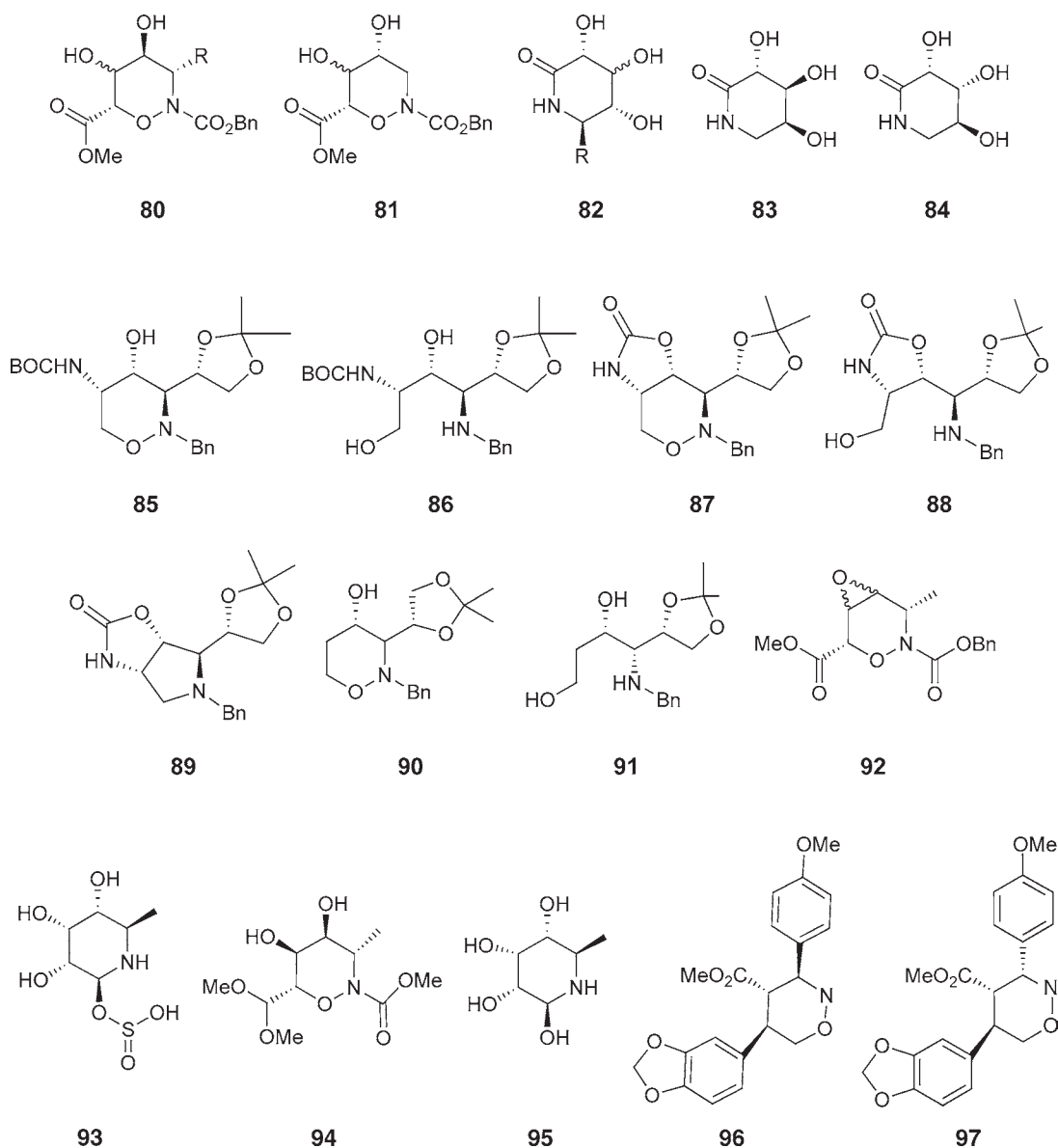
8.04.6.1 Hydrogenation/Reduction/Reductive Ring Cleavage of the N–O Bond

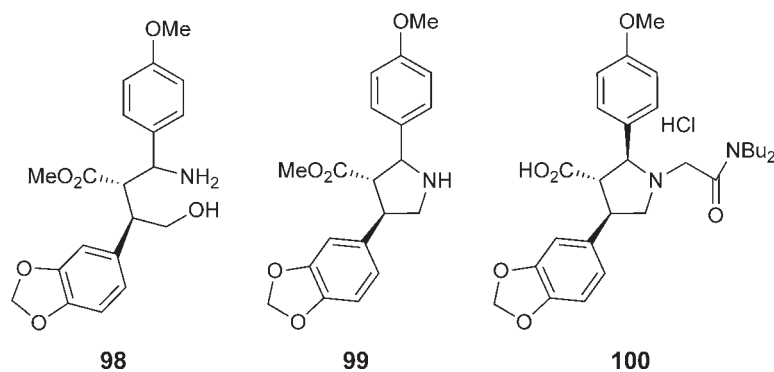
Very useful synthetic methods for the preparation of nitrogen containing compounds have been developed via intermediates possessing N–O bonds. The most common procedures for such reductive cleavage reactions employ H₂/Pd/C, Mg(Hg)/TiCl₄, Al/Hg, Li/Hg, Na/Hg, and SmI₂. Reductive cleavage of the N–O bond was usually promoted by SmI₂ <1995TL7419>. The N–O bond of the oxazine was selectively cleaved in good yield using Na/Hg and the method has been used with chiral oxazines <1999TL3081, 2003OL2203>. For dihydrooxazines in which the N–O bond is not activated, the bond can be cleaved using zinc and acetic acid. Direct quenching of the reaction mixture with acylating agents provided high yields of protected amines in a one-pot process from oxazine derivatives <1999T11755>. LiAlH₄ selectively reduced the C=N bond of substituted 3,4-dihydro-6*H*-oxazine **54** to give tetrahydrooxazine **55** <1996JFC(80)21>. Sodium cyanoborohydride in acetic acid selectively reduced C=N bond in dihydrooxazine without cleaving the ring N–O bond. Reduction of C=N bond of dihydrooxazine **11**, **57**, and **59** with NaCNBH₃ led to the corresponding tetrahydrooxazines **56**, **58**, and **60** <2000TL4819, 2000SL1366>. Reduction of the C=N bond of **59** produced the more hindered product **60** in which the Me group adopts the *syn*- orientation relative to the acetonide <2000SL1366>. Both aluminium amalgam and catalytic hydrogenation methods are effective for the reduction of 3-ethoxycarbonyl oxazines **57**, but the mechanisms may differ because the stereoselectivity of the reduction depends on the choice of reagent. Hydrogenation of the C=C bond of bicyclic oxazines **61** with Pd/C and LAH afforded tetrahydrooxazines **62** <2000JOC7667>. Reduction of the C=C bond of the dihydrooxazine **63** with sodium cyanoborohydride in acetic acid produced the tetrahydrooxazine <2002CJC857>. Reductive cleavage of **64** with Pd/C in MeOH under an atmosphere of H₂ provided the desired protected 4,5-diol of 1-aminocyclopentan-3-ol **65** in quantitative yield <2000TL9537>. The N–O bond in **62** (*n* = 1) was reductively cleaved with Al/Hg in tetrahydrofuran (THF)–H₂O to the corresponding *cis*-1,3-aminocyclopentanol derivative **66** in excellent yield <1998TL1309>. Reductive cleavage of **67** afforded substituted aminocyclohexenol **68** and aminocyclohexenone **69**, while Mo(CO)₆ reductively cleaved the N–O bond of **67** directly to **69** in wet acetonitrile <1998TL2059>. Chemoselective reduction of C=C bond followed by deprotection was achieved with H₂/Pd in the transformation of **70** to **71** <1998T3631>. The SmI₂-promoted reductive cleavage of the N–O bond in **72** and **73** provided cyclohexenol derivatives **74** and **75**, respectively <1999T11755>. The mixture **76** and **77** underwent catalytic hydrogenation over PtO₂ to furnish the regioisomeric tetrahydrooxazines **18** and **78** <1998JOC8397>. Reductive cleavage of the N–O bond of **18** with Mo(CO)₆ resulted in formation of the *N*-BOC amino alcohol **79** <1998JOC8397>.



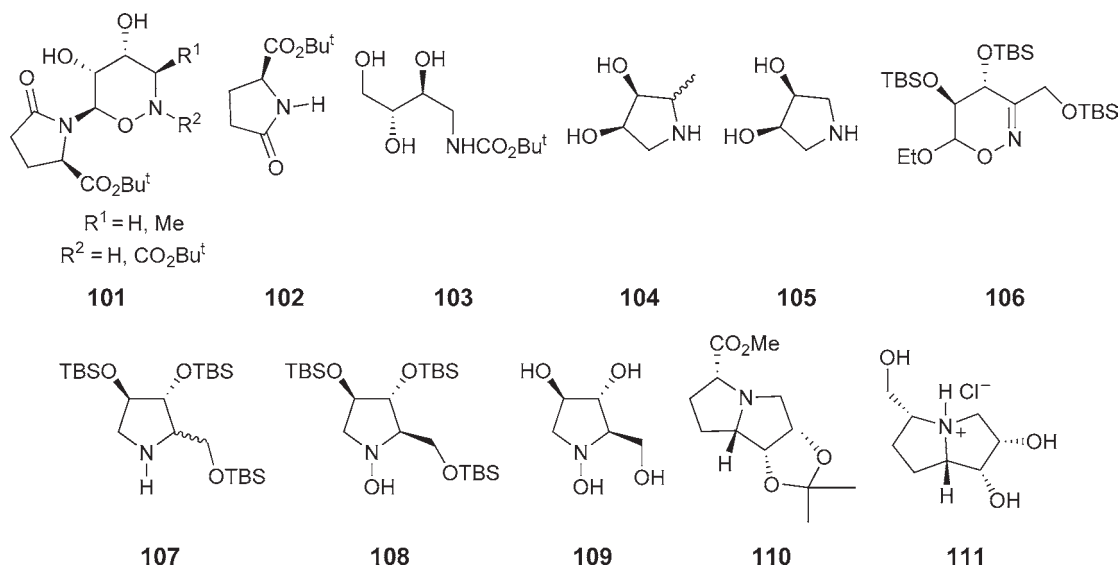
Sodium borohydride, lithium aluminium hydride (LAH), and diisobutylaluminium hydride (DIBAL-H) have also been used for the reductive cleavage of several tetrahydrooxazines. The chiral 4,5-dihydroxyoxazines **80** (R=H, Me) and **81** were base sensitive and underwent hydrogenolysis in a neutral medium (MeOH/Pd/C, H₂). In this reduction process, both the *N*-carbamate group and the N–O bond cleaved to produce linear amino esters which were cyclized at once in good yield to give δ -lactams **82** (R=H, Me), **83**, and **84** <1998HCA1417>. The N–O bond of **85** was readily cleaved with SmI₂ to provide N-protected 1,3-amino alcohol **86** <2005JOC6991>.

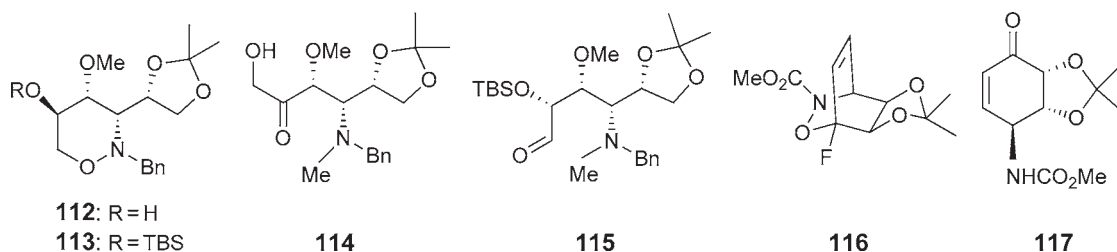
Catalytic hydrogenolysis of **85** with Pd/C in the presence of $(\text{BOC})_2\text{O}$ also provided amino alcohol **86** <2003SL405>. Reduction of oxazine **87** with SmI_2 promoted the N–O bond cleavage and led to formation of hydroxymethyloxazolidinone **88** and pyrrolidine derivative **89** <2003SL405>. The SmI_2 -promoted N–O bond cleavage of **90** led to formation of 1,4-amino alcohol **91** <2003SL405>. Epoxide **92**, cleaved by NaNO_2/DMF at 100°C , gave directly the mixture of 4,5-diol **80** ($\text{R}=\text{Me}$; DMF = dimethylformamide) <1998HCA1417>. Hydrogenolysis of 4,5-diol **94** with Pd/C, followed by hydrolysis in the presence of SO_2 , afforded trihydroxypiperidine derivative **93**. Saponification of **93** with $\text{Ba}(\text{OH})_2$ gave tetrahydroxypiperidine **95** <1995SL1187>. The N–O bond of the major 1,2-oxazine diastereomers **96** and **97** was cleaved in quantitative yield by either dissolving metal reduction (Zn/AcOH) or hydrogenolysis (Pd/C , H_2 , EtOH) to produce diastereomerically pure 2,3,4-trisubstituted-4-aminobutanol **98**, which was further cyclized to the substituted pyrrolidine **99**; it is an intermediate in the synthesis of the endothelin antagonist ABT-627 **100** <1999TL7175>.



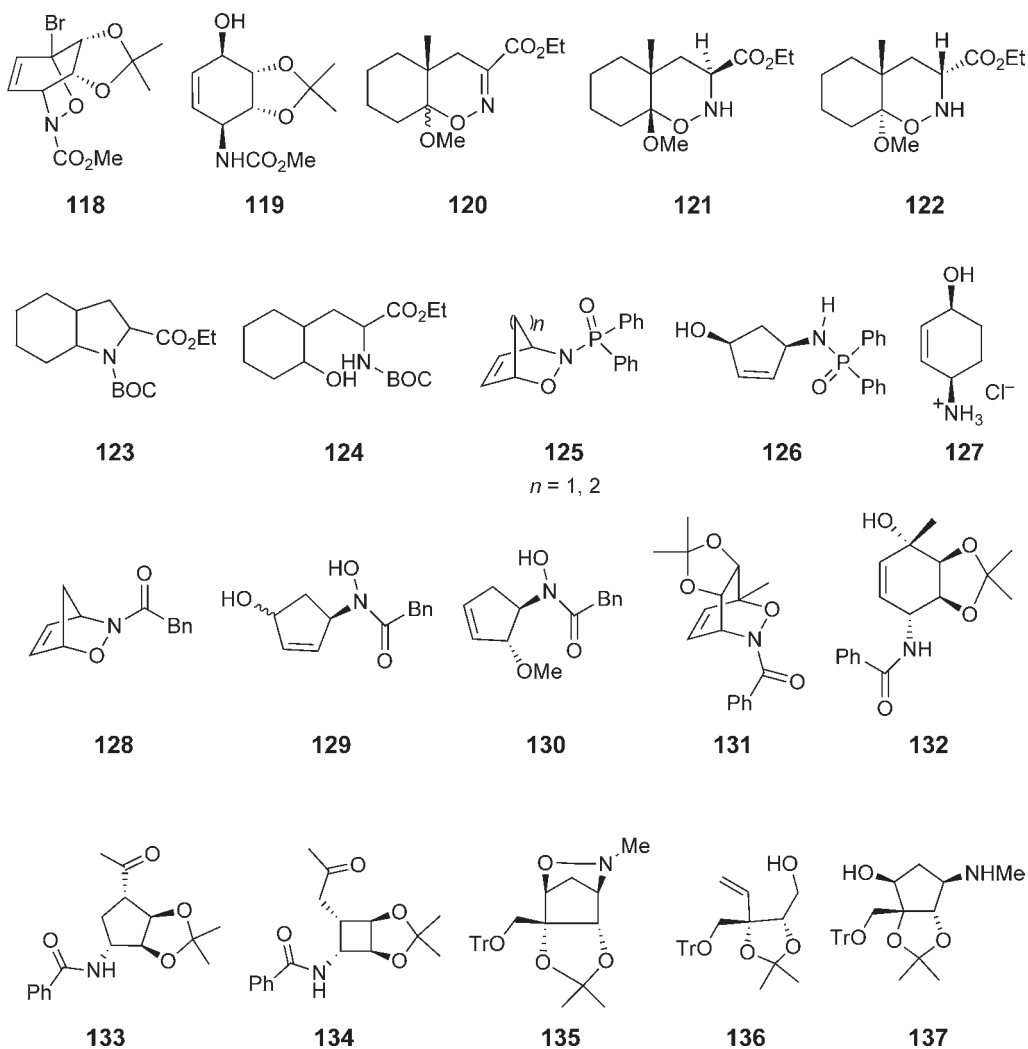


Samarium diiodide-induced N–O bond cleavage of **101** ($R^2 = \text{CO}_2\text{Bu}^t$) generated pyrrolidone **102** and 1,4-amino alcohol **103**. Further **103** recycled to polyhydroxylated pyrrolidines **104** and **105**, which are potential glycosidase inhibitors <2002OL2353>. Reductive cleavage of the N–O bond in O,N-disubstituted oxazines is difficult when not strained and such reduction has been accomplished with SmI_2 or Na/Hg . Raney–Ni reduction of **101** ($R = \text{CO}_2\text{Bu}^t$) led to pyrrolidone **102** and acyclic 1-acylamino-1-deoxy-D-erythritol **103**. Hydrogenolysis of 4,5-diol **101** ($R = \text{CO}_2\text{Bu}^t$) under mild conditions (room temperature (rt)), Pd/C) gave only N-deprotected tetrahydrooxazine **101** ($R = \text{H}$) <2003T543>. However, hydrogenolysis was more efficiently performed over Raney nickel, which directly led to 3,4-dihydroxy-3-methylpyrrolidine **104** ($R^1 = \text{Me}$) <2003T543>. At 50 °C, reductive cleavage of the N–O bond occurred to produce *cis*-3,4-dihydroxypyrrolidine **105** ($R^1 = \text{H}$) <2003T543>. Highly substituted dihydro-1,2-oxazines **106** are reductively cleaved by $\text{H}_2/\text{Pd-C}$ or NaCNBH_3 , and subsequent rearrangement followed by cyclization produced pyrrolidines **107** and **108**, respectively, the latter of which was deprotected by HF to afford **109** <2000TL4481>. Hydrogenation of **106** with Raney nickel in the presence of H_3BO_3 gave pyrrolizidine **110** <2000TL4819>. Reductive N–O bond cleavage of **106** via hydrogenation triggered a sequence of tandem condensation–hydrogenation reactions, which led to pyrrolizidine ester **110**. Reduction of the ester **110** with $\text{LiBH}_4/\text{THF/HCl}$ yielded the desired hydroxymethylpyrrolizidine HCl **111**. Tetrahydrooxazine **112** cleaved under mild conditions with MeOTf/MeCN at rt to keto alcohol **114** via an enediol intermediate <2005SL1152>. However, when the hydroxy group is protected as in **113** with the *t*-butyldimethylsilyl group, then the cleavage led to aldehyde **115** <2005SL1152>. The N–O bond cleavage of bicyclic oxazine **116** with either Na/Hg or $\text{Mo}(\text{CO})_6$ gave protected amino ketone **117** <1999TL3081>.

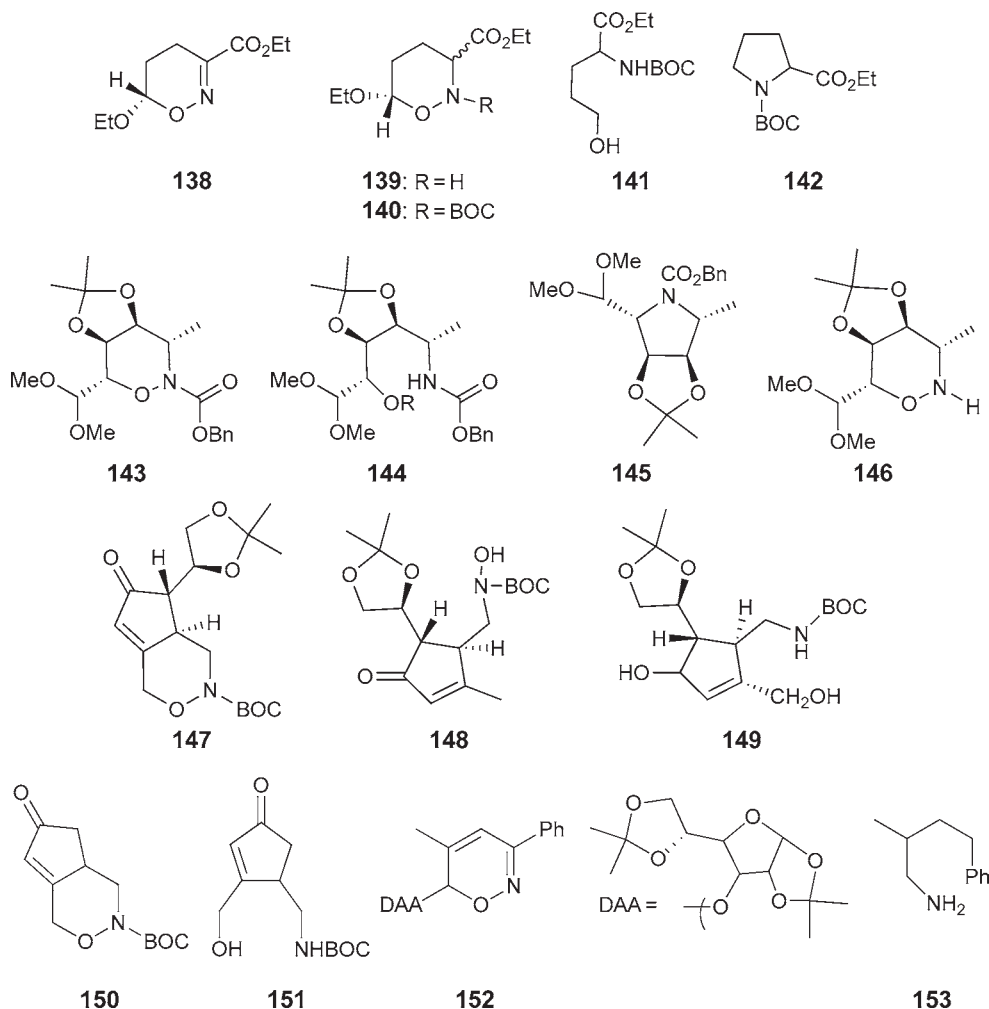


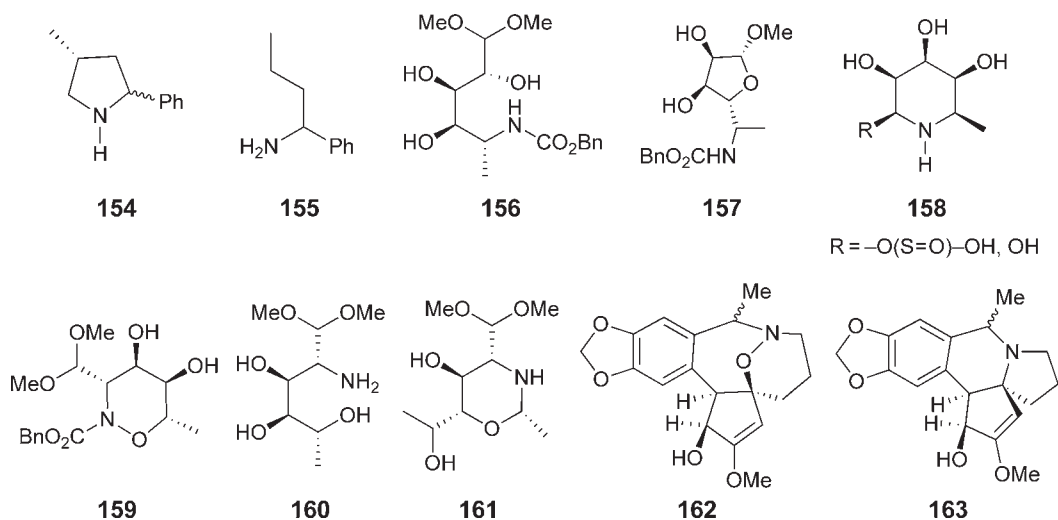


Reductive cleavage of oxazine **118** to aminocyclohexenol **119** was achieved using Al/Hg [\[2002JOC8726\]](#). NaCNBH₃ reduction of C=N bond of bicyclic acetal **120** led to the formation of four diastereoisomers **121** and **122**. Raney Nickel catalytic hydrogenation of the *cis/trans*-mix **121** and **122** afforded the proline derivative **123** and reductive N–O bond cleaved product **124**. Oxazinyolphosphinamides **125** ($n = 1, 2$) underwent N–O bond cleavage with Mo(CO)₆ to provide substituted aminocyclopentenol **126** and aminocyclohexenol **127** [\[1999JA6769\]](#). Lewis acid and CuSO₄ catalyzed the ring cleavage of the N-benzylated oxazine **128** followed by cyclization, providing substituted cyclopentenones **129** and **130** [\[2001JOC2466\]](#). The SmI₂ reduction of **131** at –78 °C led to exclusive formation of the amido alcohol **132**, while reduction in refluxing THF (67 °C) gave the bicyclic **133**. However, at low temperature (25 °C), **131** produced a mixture of **133** and **134** [\[2000OL1457\]](#). The *N*-methyltetrahydrooxazine **135** in turn prepared from **136** underwent N–O bond cleavage with H₂ over Pd(OH)₂ to produce 1-aminocyclopentan-3-ol **137** [\[2001TL5769\]](#).



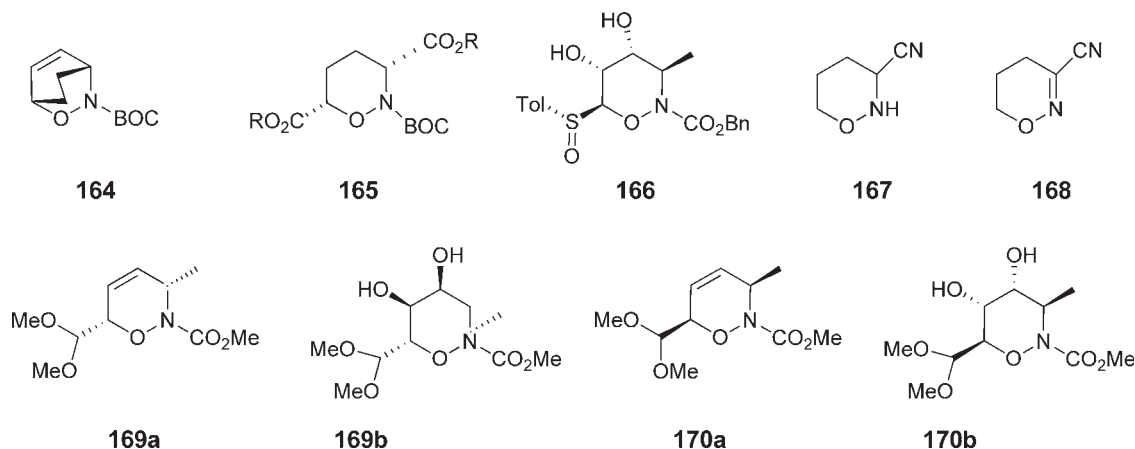
The NaCNBH_3 reduction of the $\text{C}=\text{N}$ bond in oxazine **138** produced **139** <2005T565>. Hydrogenolysis of the oxazine **139** with Raney nickel in the presence of $(\text{BOC})_2\text{O}$ afforded directly *N*-BOC-pyrrolidine, **142**, in 55% yield. Reductive $\text{N}-\text{O}$ bond cleavage of *N*-protected *cis*-oxazine **140** with Raney nickel led to amino acid ester **141** <2005T565>. Protected 4,5-diol **143** was subjected to hydrogenolysis over Pd/C and afforded the ring-opened product **144**, which is further cyclized with NaOH/MeOH to provide 2,5-*trans*-pyrrolidine derivative **145** <2000T971>. Hydrogenation of **146** with $\text{H}_2/\text{Pd}/\text{C}$ gave tetrahydropiperidine **95** <1995SL1187>. Reductive cleavage of **147** with SmI_2 provided the desired cyclopentene derivatives **148** and **149** <2003OL2203>. Treatment of oxazine **147** with Na/Hg resulted in the formation of cyclopentenol **149** in 77% yield <2003OL2203>. The SmI_2 -facilitated smooth cleavage of **150** gave 3,4-disubstituted cyclopentenone **151** in 76% yield <2000TL9393>. No reductive cleavage products were produced from **150** with Zn/AcOH or H_2/Pd . 3-Phenyl-6*H*-1,2-oxazine **152** was hydrogenolyzed with Pd/C in MeOH at rt and furnished the expected 2-methyl-4-phenyl-1-butylamine **153** in 68% yield. Hydrogenation of **152** in the presence of 2 *N* HCl produced disubstituted pyrrolidine derivative **154** (63:37 mixture of *cis-trans*-isomers) in addition to the unexpected amine **155** <2002S1553>. Amino sugars obtained from **27** were hydrogenolyzed as a mixture of **156** and the corresponding highly substituted THF **157** <1997T13769>. Hydrolysis of **156** with $\text{SO}_2/\text{H}_2\text{O}$ led to trihydroxypiperidinesulfonic acid **158**, which on further hydrolysis with $\text{Ba}(\text{OH})_2$ produced a mixture of tetrahydropiperidine **158** ($\text{R}=\text{H}$, α - and β -anomers) <1997T13769>. Hydrogenolysis of **159** with H_2 Pd/C in EtOH gave deprotected amino alcohol **160** and substituted 1,3-oxazine **161** <1997T13769>. Reduction of **162** with Zn/HOAc gave the ring contracted homoharringtonine analog **163** in high yield <1997JOC8251>.

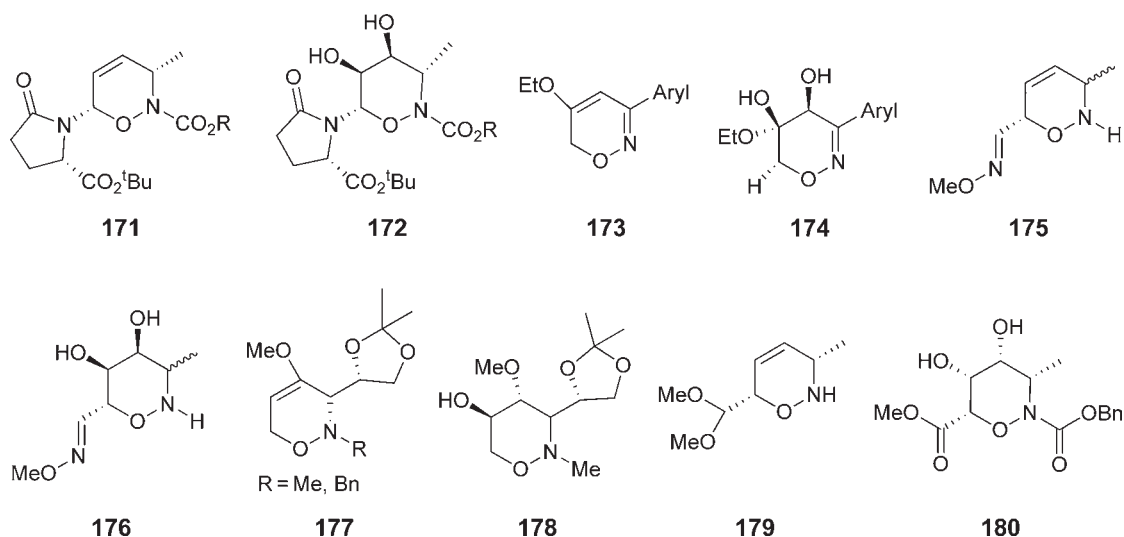




8.04.6.2 Hydroxylation of the Ring Carbon–Carbon Double Bond/Oxidation

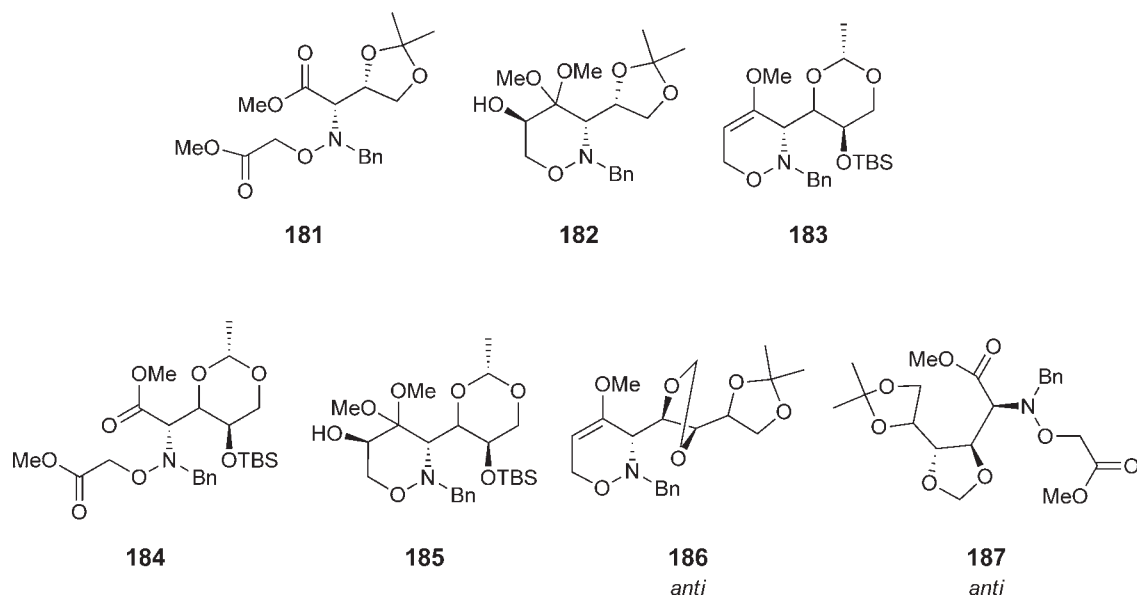
Racemic cycloadduct **164** was converted to the 3,6-dicarboxylic acid by oxidative C=C bond cleavage under phase transfer conditions (Bu_4NHSO_4 , KMnO_4 , PhH) followed by esterification to produce the desired diester **165** in satisfactory yield [\[2002CC1066\]](#). 3-Cyanotetrahydro-1,2-oxazine **167** was oxidized with $\text{Pb}(\text{OAc})_4$ to provide 3-cyano-4,5-dihydrooxazine **168** [\[1997JOC2098\]](#). Oxidation of cycloadducts **31**, **169a**, **170a**, **171**, and **175** with OsO_4 produced corresponding 4,5-diols **166**, **169b**, **170b**, **172**, and **176** [\[2000OL3165, 1995SL1187, 2006BML1172, 2000SL1366, 1996HCA560\]](#). The *cis*-dihydroxylation of 5-ethoxy-6*H*-1,2-oxazine **173** proceeded efficiently with KMnO_4 at low temperature or with $\text{RuCl}_3/\text{NaIO}_4$ at 5 °C to give the 4,5-dihydroxy-1,2-oxazine **174** [\[1999S1223\]](#). The 4,5-diol, **174**, was obtained as a diastereomerically pure compound with two newly introduced OH groups positioned *trans* to the 5-alkoxy group [\[1999S1223\]](#). Hydroboration of **177** (R = Me) with $\text{BH}_3\cdot\text{THF}$ and subsequent oxidation with H_2O_2 led to 5-hydroxytetrahydro-1,2-oxazine **178** [\[2002OL2353\]](#). Oxidation of **179** with $\text{OsO}_4/\text{acetone}/\text{H}_2\text{O}$ produced protected *cis*-diol **146** [\[1995SL1187\]](#). Oxidation of oxazine **28** with catalytic amounts of OsO_4 in acetone/ H_2O with *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant afforded *cis*-dihydroxy diester **180**.





8.04.6.3 Ozonolysis

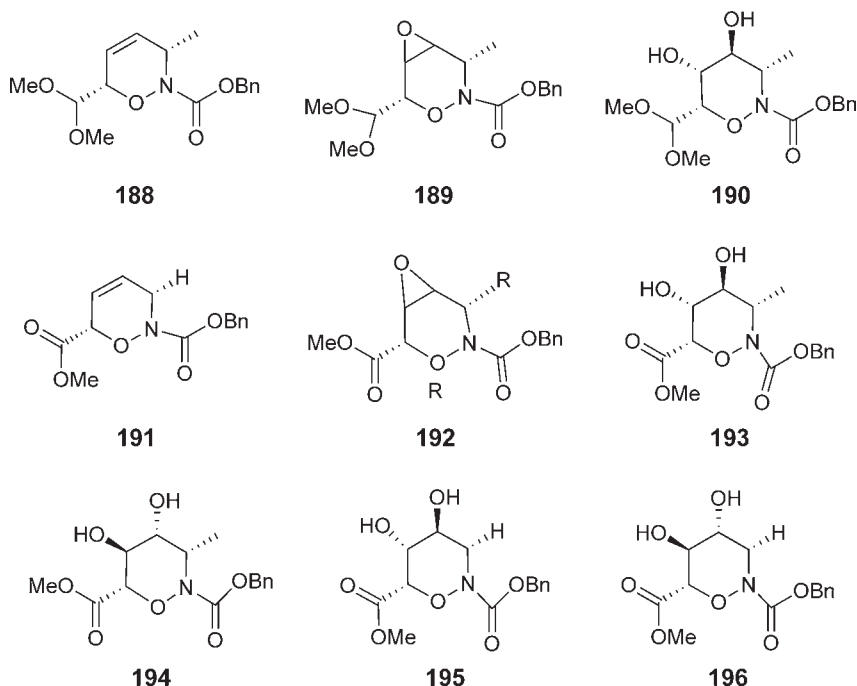
By ozonolysis and subsequent *in situ* acylation in the presence of base, the enantiopure 1,2-oxazine **177** (R = Bn) was converted to the highly functionalized α -amino- β -hydroxy ester **181** along with a minor product 5-hydroxylated oxazine **182** <2005EJO998>. Similarly, D-erythrose-derived *syn*- and *anti*-compounds **183** afforded the expected diastereomeric *syn*- and *anti*-oxazine esters **184** and 5-hydroxylated oxazine **185** <2005EJO998>. The arbinose-derived anti-configured 1,2-oxazine **186** was subjected to an ozonolysis/elimination sequence which provided the desired functionalized α -amino ester **187** in 75% yield.



8.04.6.4 Epoxidation

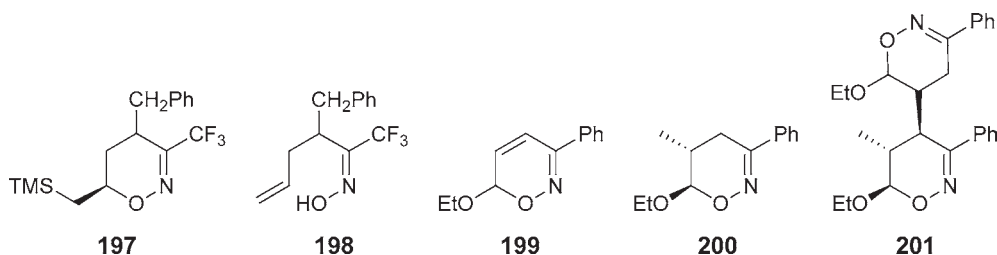
Epoxidation of the racemic adduct **188** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 proceeded slowly to give the epoxide **189** which further oxidized, usually in acid medium, to ($\pm$)-*trans*-4,5-diol **190** as a diastereoisomeric mixture (70:30) <1997T13783>. Epoxidation of substituted oxazines **28** and **191** with MCPBA led to epoxide esters

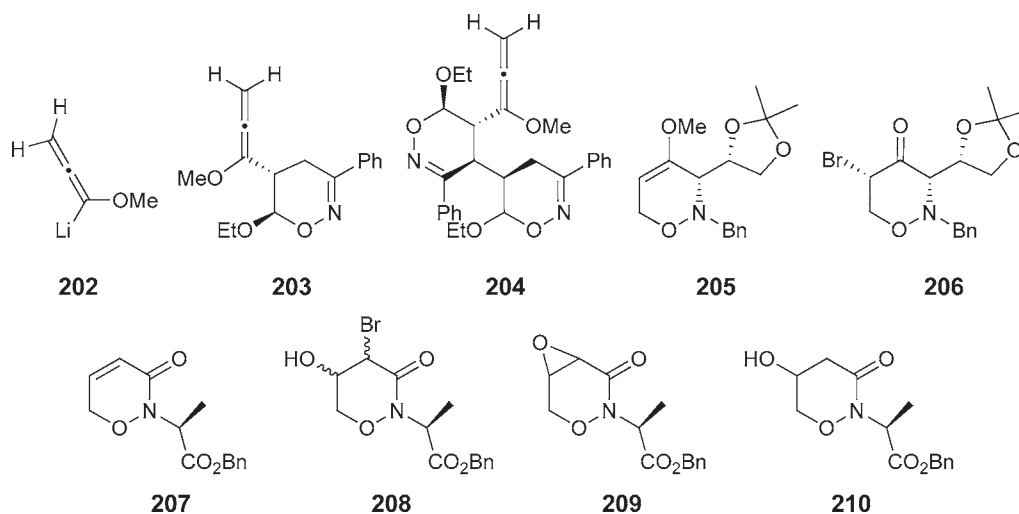
192 (R=H, Me, respectively), which were further cleaved with formic acid to afford a mixture of diols **193–196** <1998HCA1417>.



8.04.6.5 Reaction with Electrophiles

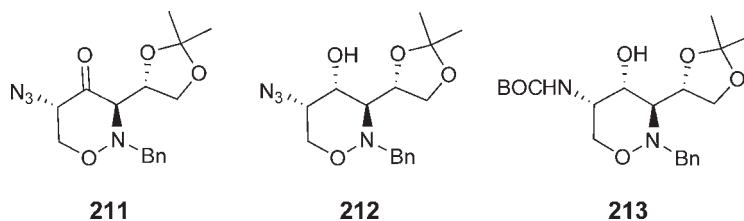
Reaction of 3-trifluoromethyl-substituted 1,2-oxazine **5** with lithium diisopropylamide (LDA) resulted in smooth deprotonation at C-4 and allowed subsequent alkylation with various electrophiles. Reaction of **5** with MeI furnished the 4-methyl-1,2-oxazine **54** in good yield and with excellent *cis*-diastereoselectivity, whereas carbonyl compounds could not be employed successfully as electrophiles <1996JFC(80)21>. Treatment of 3,4,6-trisubstituted 1,2-oxazine **197**, obtained from **5** in this way, with HClO₄ provided the ring-opened oxime **198** in good yield <1996JFC(80)21>. 1,4-Addition of alkyl- and aryllithium compounds to 1,2-oxazines **199** proceeded without detectable interference of competing 1,2-addition to the C=N bond <1999H(50)393>. Conjugate addition of reactive organolithium compounds such as MeLi and allenyllithium **202** to 6*H*-1,2-oxazines **199** gave 1,4-addition products **200** and **203** in addition to highly substituted bis(1,2-oxazines) **201** and **204** <2002S1412>. Diastereoselective electrophilic bromination of *syn*- and *anti*-**205** led to 5-bromo-1,2-oxazin-4-one **206** <2003SL405>. With *N*-bromosuccinimide in aqueous DMF, a 6*H*-2,3-dihydro-1,2-oxazin-3-one **207** afforded a separable 1:1 mixture of bromohydrins **208**, which could be cyclized to epoxides **209** or hydrogenolyzed to 5-hydroxytetrahydro-1,2-oxazin-3-ones **210** <2005CJC93>.





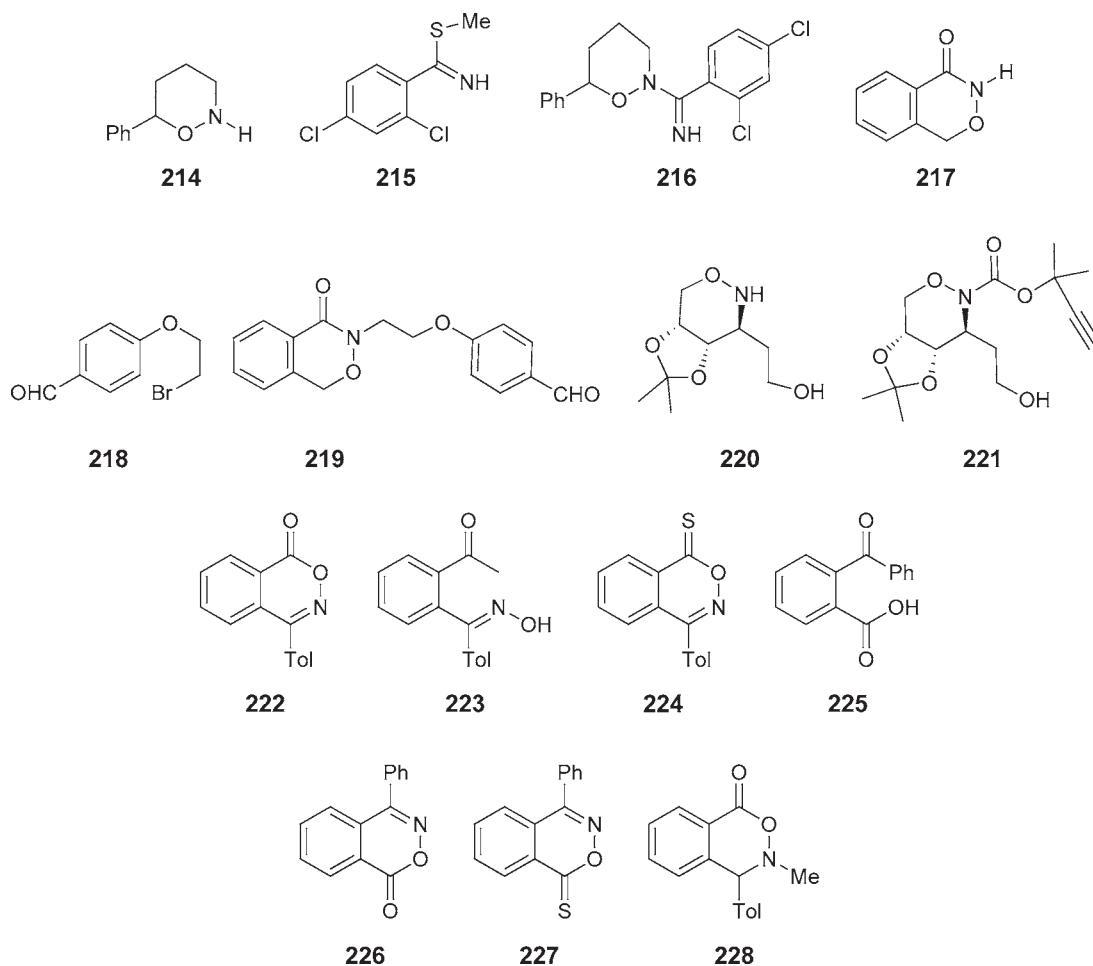
8.04.6.6 Reaction with Nucleophiles

The C-3 in 5,6-dihydro-4*H*-1,2-oxazines is electrophilic; when additional activation is present, a variety of nucleophiles can attack at this position. A halogen substituent at C-5 of tetrahydrooxazine **206** can undergo S_N2 displacement by nucleophiles such as amines and azide, fluoride, and malonate anions. Nucleophilic substitution of the bromo functionality by NaN_3 gave 5-azidooxazine **211**. Reduction of carbonyl function in **211** resulted in alcohol **212**. Reduction of azide **212** with $\text{PPh}_3/\text{H}_2\text{O}$ in the presence of $(\text{BOC})_2\text{O}/\text{NEt}_3$ gave protected 5-aminooxazine **213** <2003SL405>.



8.04.6.7 N-Alkylations/N-Acylations

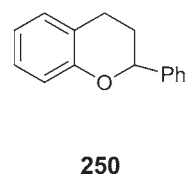
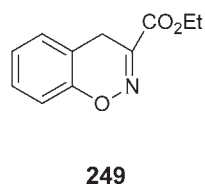
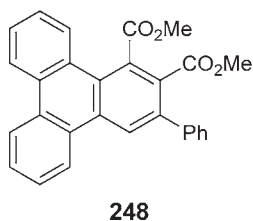
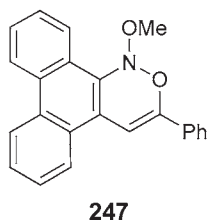
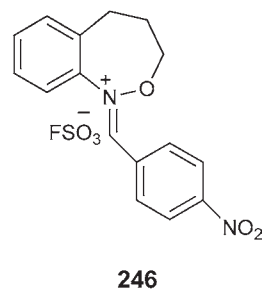
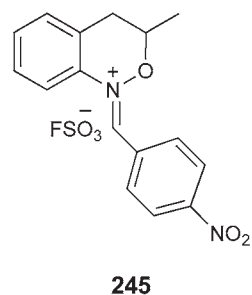
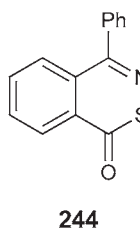
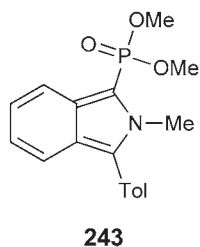
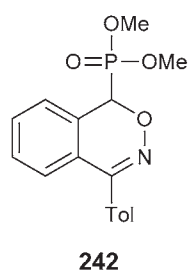
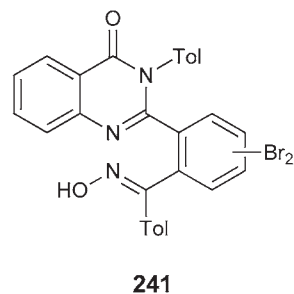
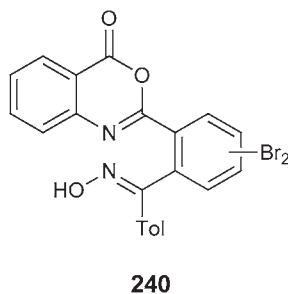
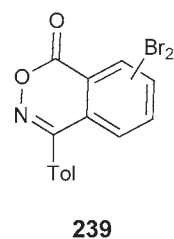
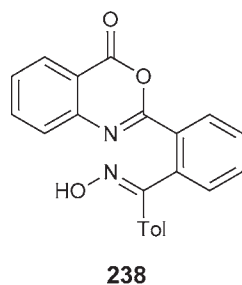
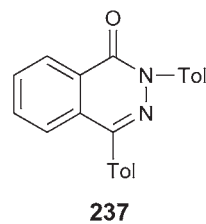
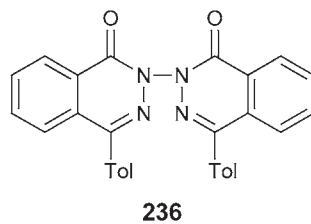
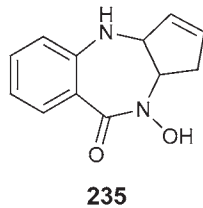
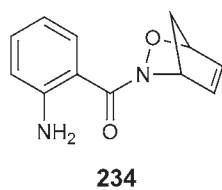
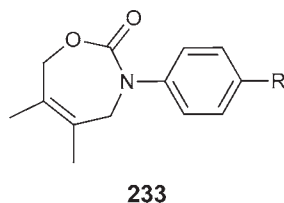
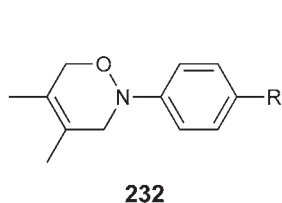
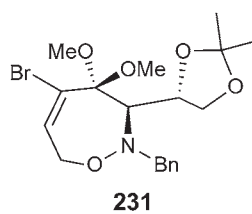
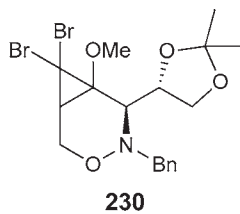
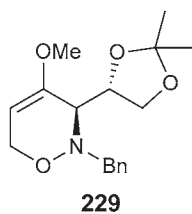
Substituted amidine **216** was prepared by treating the thioimide **215** with the 6-phenyltetrahydro-oxazine **214** <2000BMC601>. N-Alkylation of 2,3-benzoxazin-4-one **217** with 4-(2-bromo-ethoxy)benzaldehyde **218** using $\text{DMF}/\text{K}_2\text{CO}_3$ produced **219** <2001EJM627>. N-Acylation of oxazine **220** with the appropriate chloroformate under basic conditions afforded N-acylated oxazine **221** <2002TL8519>. Grignard reactions of **222** with MeMgBr afforded the oxime **223**. Thiation of **222** with P_2S_5 in boiling xylene gave the thione **224** <1999EJC301>. Benzoxazinone **226** was prepared via cyclization of the keto oxime of **225** with N_2H_4 <2000PS257>. 4-Phenyl-2,3-1*H*-benzoxazine-1-thione **227** was prepared by the treatment of the corresponding benzoxazine-1-one **226** with P_2S_5 . Benzoxazinone **222** with dimethyl diphosphonate produced only 3-methyl-4*H*-2,3-benzoxazinon-1-one **228** <2004HAC77>.



8.04.6.8 Ring Transformations

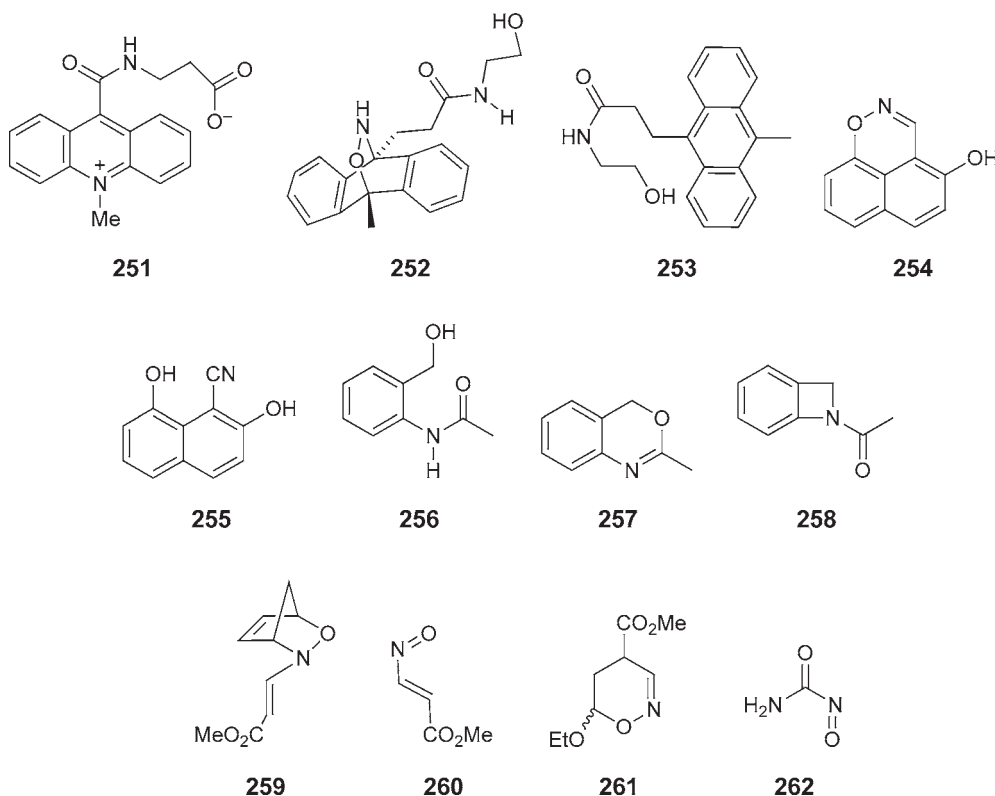
Ring contraction of oxazine **97** to pyrrolidine **99** was effected via N–O bond cleavage followed by cyclization of **98** using triphenylphosphine and CBr_4 <1999TL7175>. Phase-transfer-catalyzed cyclopropanation of **229** produced geminal dibromocyclopropane **230** which underwent ring expansion to 1,2-oxazepine **231** <2005SL2376>. The carbonylative ring expansion of 3,6-dihydro-2*H*-1,2-oxazine **232** proceeded in the presence of $\text{Co}_2(\text{CO})_8$ with insertion of CO into the N–O bond to give the cyclic carbamate, 4,7-dihydro-1,3-oxazepin-2(3*H*)-one **233** ($\text{R} = \text{Me}$) <1996TL2713>. Ring opening of acylnitroso-derived hetero-Diels–Alder adduct **234** by $\text{Pd}(\text{PPh}_3)_4$, followed by ring expansion with $\text{Yb}(\text{OTf})_3$, gave benzodiazepine **235** <2002OL139>. Reaction of hydrazine hydrate with 3,2-benzoxazin-4-one **222** in boiling ethanol gave bisphthalazinone **236**. The 3,2-benzoxazin-4-one **222** reacted with *p*-toluidine and anthranilic acid to give phthalazinone **237** and 3,1-benzoxazin-4-one **238**, respectively <2000EJC421, 1999EJC301>. The 3,2-benzoxazin-4-one **239** was treated with anthranilic acid in boiling butanol to give 3,1-benzoxazin-4-one **240** via heteroring opening and recyclization <2000EJC421, 1997EJC231>. 3,1-Benzoxazin-4-one **240** further reacted with arylamine *via* heteroring opening and recyclization to give quinazoline derivative **241** <1997EJC231>. Reaction of 3,2-benzoxazin-4-one **222** with trimethyl phosphite provided access to the new phosphono-substituted 2,3-benzoxazine **242** and isoindoline **243** <2004HAC77>. The thermal rearrangement of **227**, catalyzed by metallic Cu, yielded benzothiazine-1-one **244** <2000PS(161)257>.

3,4-Dihydro-2,1-benzoxazin-4-one **245** is thermodynamically less stable and it is isomerized with time to the 2,1-benzoxazepin-4-one **246** <2003CHE205>. Phenanthrene-fused *N*-methoxy-1,2-oxazine **247** has been used as a Diels–Alder diene which reacted with dimethyl acetylenedicarboxylate (DMAD) to provide polycyclic aromatic diester **248** by elimination of methyl nitrite <1996TL1097>. Gentle heating of bicyclic 1,2-oxazine **249** with styrene in toluene resulted in oxazine ring opening/recyclization with formation of chroman **250**, whereas basic hydrolysis gave the ring opening/decarboxylation product, *o*-cyanomethyl phenol <2003JA5282>.



8.04.6.9 Retro-Diels–Alder Reaction

Several types of 1,2-oxazines undergo thermal pericyclic reactions in which the N–O bond is cleaved by a retro-Diels–Alder process under very mild conditions. An antibody raised against acridinium hapten **251** catalyzed the retro-Diels–Alder reaction of the anthracene–HNO cycloadduct **252** to release substituted anthracene **253** and H–N=O <1996JA3550>. Peri-annulated 1,2-oxazine **254** was readily cleaved by thermal treatment to the 1-cyano-2-hydroxynaphthalene **255** <2000TL1845, 2001T3445>. Extrusion of formaldehyde from *N*-acetylbenzoxazine **8** afforded *N*-acetylaza-*o*-xylylene **9** via retro-Diels–Alder thermal decomposition which involves a concerted breaking of both the C–C and N–O bonds <1996J(P2)1367>. The resultant intermediate *N*-acylazaxylylene undergoes a 6 π -electrocyclization to give 2-substituted 4*H*-3,1-benzoxazine **257** rather than a 4 π -electrocyclization to give the *N*-acetyl-1,2-dihydrobenzazete **258**. Flash vacuum pyrolysis of **256** also directly produced 3,1-benzoxazine **257**. Cycloadduct **259** underwent facile retro [4+2] Diels–Alder reaction in solution to give cyclopentadiene and nitroso intermediate **260** which is further trapped by vinyl ether to produce 4,5-dihydrooxazine **261** <2000OL1323>. Retro-Diels–Alder reaction of **42** produced 9,10-DMA, acylnitroso **262**, and nitrous oxide, which indicates the intermediacy of nitroxyl <2000TL4265>.



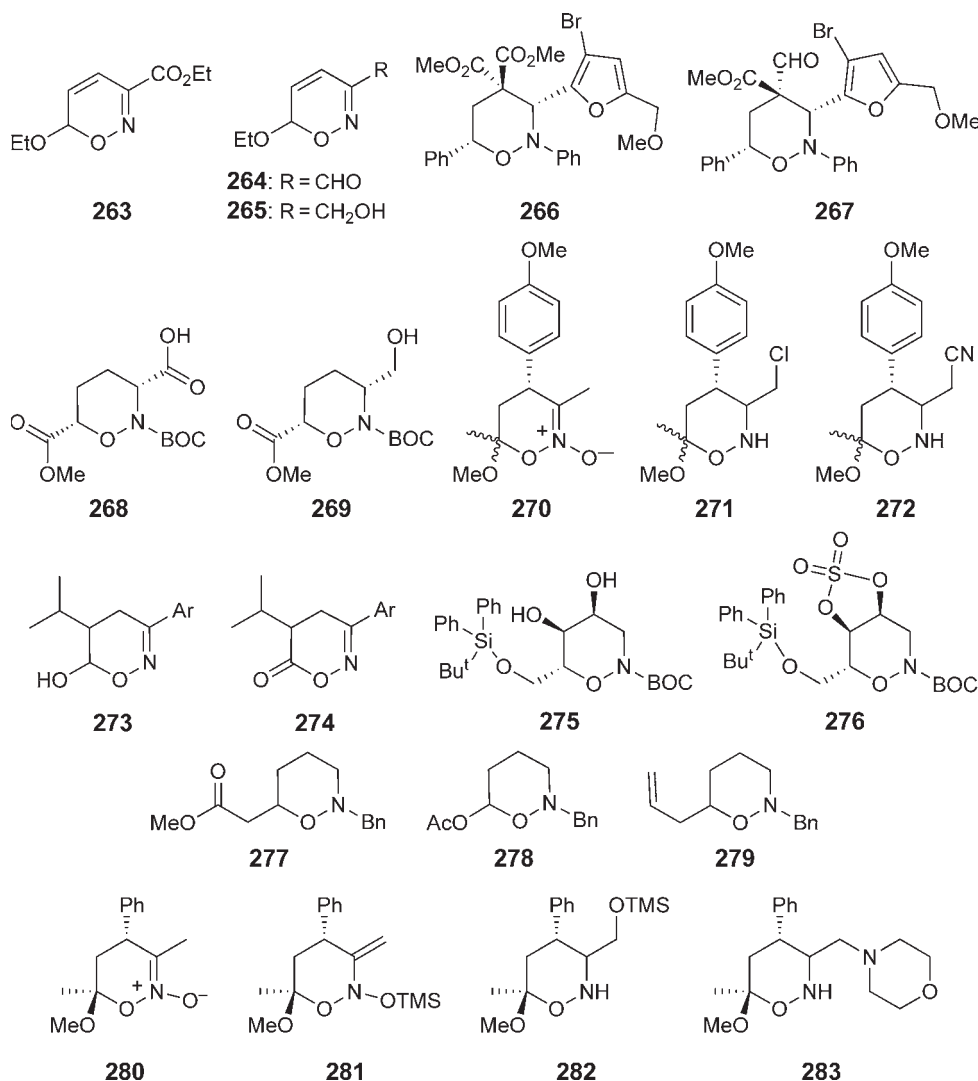
8.04.7 Reactivity of Substituents Attached to the Ring Carbon Atoms

This section covers the reactivity of certain functional groups attached to carbons of the oxazine ring: bromide displacement (C-5) with NaN₃, hydrolysis of azido group to amino, reduction of esters to alcohols, reduction of aldehyde to alcohol, hydrolysis of ester to acids, etc. Reduction of the ester function in 5,6-dihydrooxazine **263** with DIBAL-H produced alcohol **265** via aldehyde **264** <2002S1412>. In the case of *gem*-diester **266**, DIBAL-H selectively reduced one of the ester functions to aldehyde **267** <2005OL953>. Selective hydrolysis of 3,6-diester **165** using LiOH/H₂O₂ produced monoester **268**. Reduction of diester **165** with NaBH₄ supported on alumina selectively gave the alcohol **269**. Reduction of acid **268** with BH₃·SMe₃ also afforded 3-hydroxymethyl-1,2-oxazine **269** in high yield <2004OBC828>. A general and convenient method for the synthesis of the scarcely known 3-chloromethyl-5,6-dihydro-4*H*-1,2-oxazine **271** was achieved via silylation/rearrangement sequence of the

corresponding six-membered cyclic nitronate **270** <2004S1159>. Functional group elaboration of chloromethyloxazine **271** was extended with NaCN to give cyanomethyloxazine **272**. Oxidation of hemiacetal **273** (Ar = C₆H₄-MeO-*p*) with pyridinium chlorochromate (PCC) led to substituted oxazine-5-one **274** (Ar = C₆H₄-MeO-*p*) <2004OBC828>. The 4,5-Dihydroxyoxazine **275** was converted into the cyclic sulfate **276** using SOCl₂ followed by oxidation. When **276** was further reacted with sodium benzoate in DMF followed by acid/base hydrolysis, it gave **56** <1999TL3461>. Wittig reaction of 6-hydroxytetrahydrooxazine **10** with Ph₃Ph=CHCO₂Me gave the ester **277** via initial alkene formation from the aldehyde tautomer followed by an intramolecular Michael addition <1998CC1487>. The acetate **278** reacted with allyltrimethylsilane in the presence of BF₃·Et₂O to yield the allyloxazine **279** <1998CC1487>.

8.04.8 Reactivity of Substituents Attached to the Ring Nitrogen Atom

Amidation of *N*-BOC-tetrahydro-1,2-oxazine-6-carboxylic acid **47** with free oxanipectic acid afforded amide **48** <2003TL3447>. The 3-methyl-substituted 1,2-oxazine *N*-oxide **280** can be selectively transformed into 2-silyloxy-1,2-oxazines **281**, upon treatment with silylating reagents (ClSiMe₃). Now, the synthetic utility of 2-silyloxy-1,2-oxazine **281** is extended and it can be rearranged into 3-silyloxymethyl-1,2-oxazine **282** and can further react with morpholine to produce 3-morpholinomethyl-1,2-oxazine **283** which exists in a tautomeric equilibrium with the corresponding open-chain oxime <2003JOC9477>.

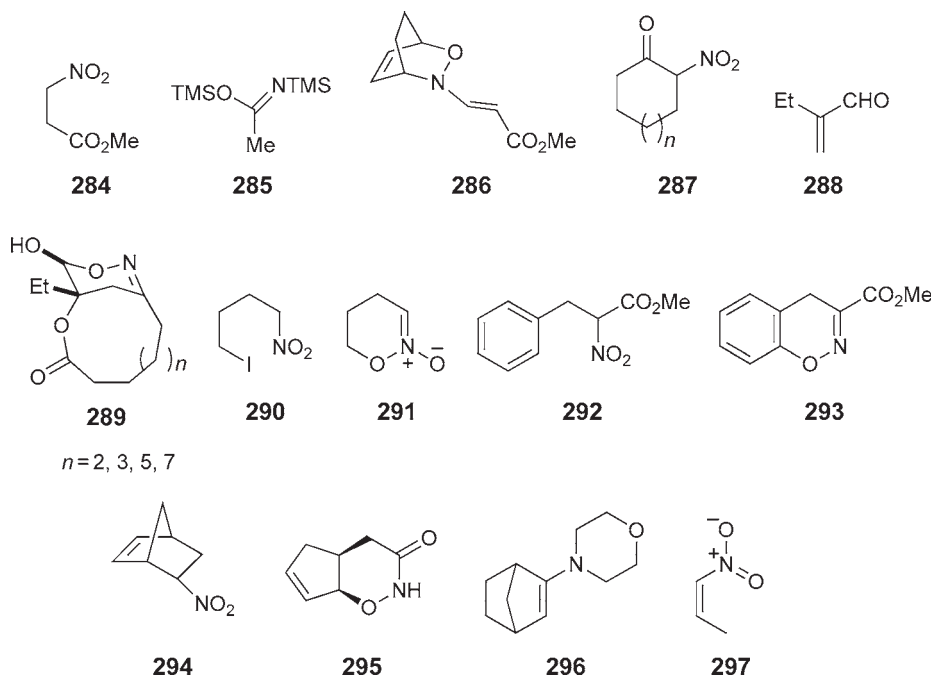


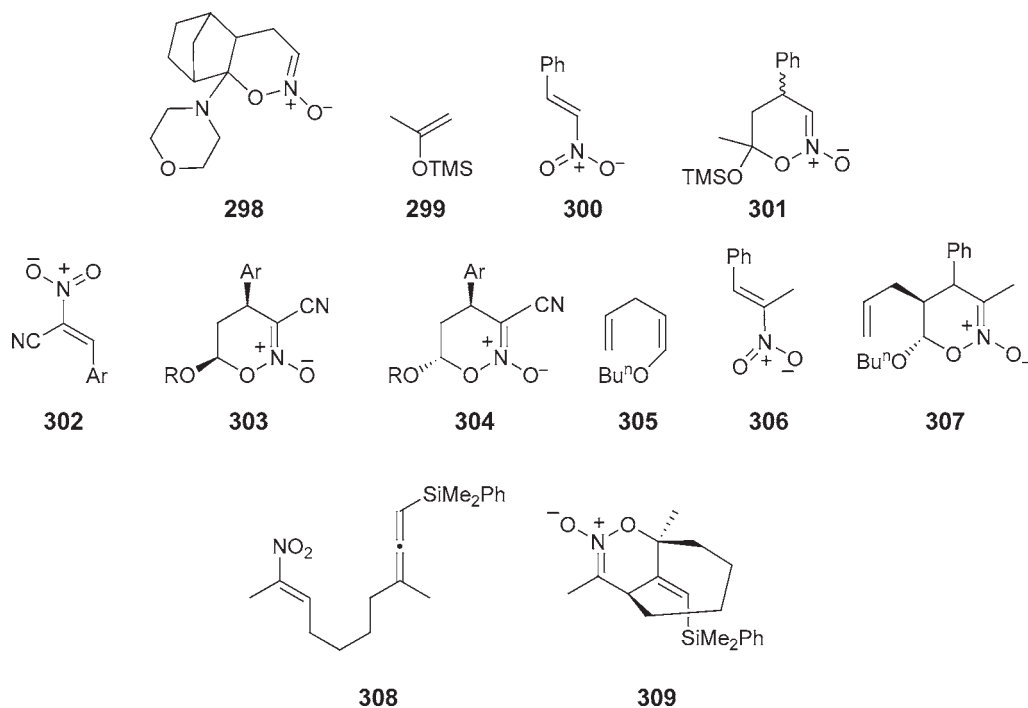
8.04.9 Ring Syntheses

A previous review has highlighted the following methods of ring synthesis: intramolecular cyclization of oximes, nitro alkenes, and nitrones, and [4+2] cycloaddition reactions <1996CHEC-II(6)279>. In addition to that, this review includes the intramolecular cyclization of hydroxylamines, hydroxamates, hetero-Diels–Alder [4+2], 1,3-dipolar cycloaddition of nitrile oxides to alkenes, and [3+3] cycloaddition reactions. This review does not cover cycloaddition reactions of the [4+2][3+2] and [4+2][3+2][3+2] types which primarily led to heterocycle-fused oxazine ring systems.

8.04.9.1 Cycloaddition of Nitroalkanes/Nitroalkenes to Unsaturated Compounds

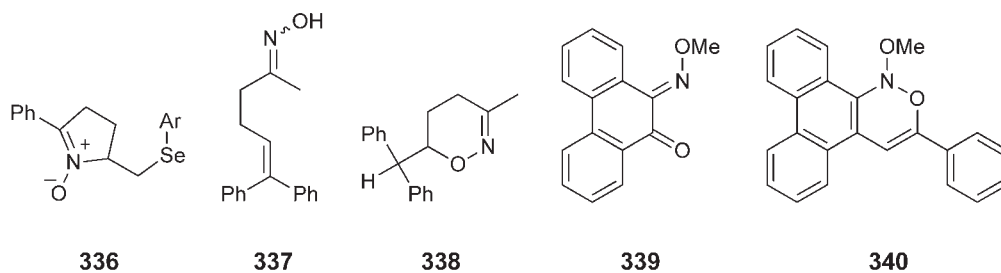
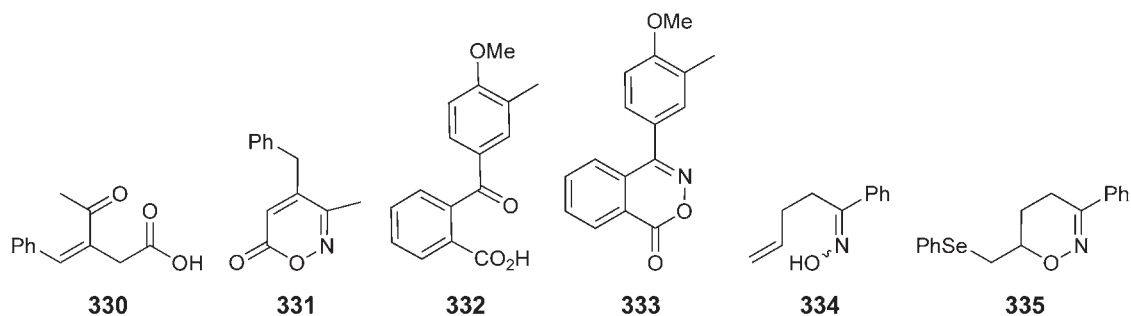
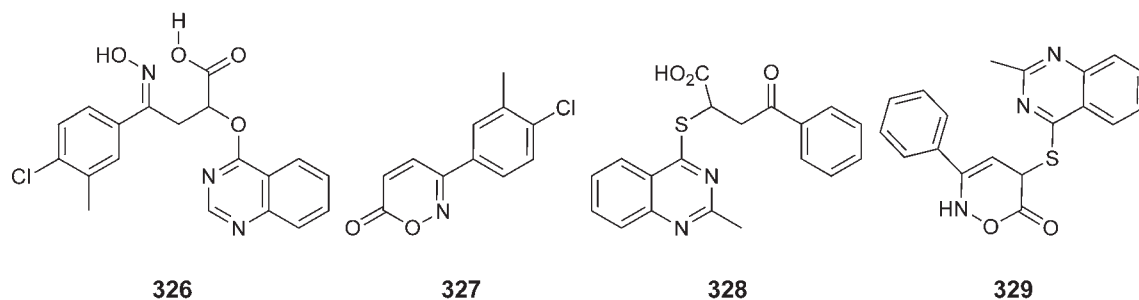
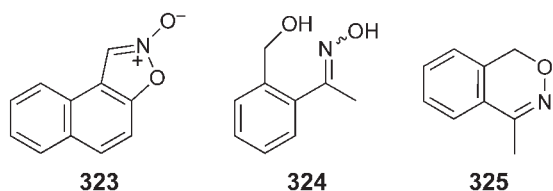
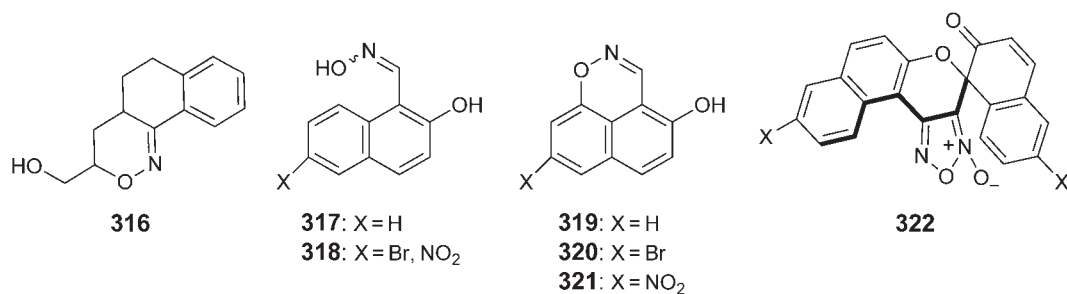
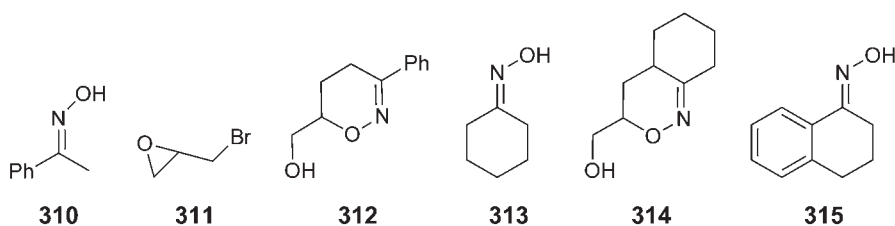
Cycloaddition reactions of nitroalkenes to enamines, enolate anions, and silyl enol ethers are well established. Chiral enol ethers have been used as partners in the cycloaddition process. Nitroso alkene **260** was generated from **284** using *N,O*-bis(trimethyl)acetamide **285** and was trapped by cyclohexadiene to give the Diels–Alder adduct **286** <2000OL1323>. In a novel one-pot synthesis, functionalized, bridged, bicyclic lactones containing 10-, 11-, 13-, and 15-membered rings **289** were prepared by Michael addition-initiated domino reaction from α -nitrocycloalkanones **287** and α -alkyl- α,β -unsaturated aldehyde **288** <2005OL2197>. Reaction of 4-iodo-1-nitrobutane **290** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave nitronate **291** in 80% yield <1998TL8869>. Acid-catalyzed ($\text{CF}_3\text{SO}_3\text{H}$) cyclization reaction of 1-nitro-2-arylethane derivative **292** is described as a general method to obtain the corresponding 4*H*-1,2-benzoxazine **293** <2003JA5282>. The sodium salt of nitrobicyclohept-5-ene **294** undergoes an abnormal Nef reaction with AlCl_3 , TiCl_4 , $\text{BF}_3\cdot\text{OEt}_2$, or SnCl_4 to give the cyclic hydroxamic ester **295** <2000T1631>. The reaction of the enamine **296** toward a conjugated nitroalkene **297** resulted in the formation of the corresponding 1,2-oxazine *N*-oxides **298** through an *exo*-approach of the electrophiles <2001ARK(v)140>. Treatment with $\text{Me}_3\text{SiOTf}/\text{Et}_3\text{N}$ has promoted hetero [4+2] cycloaddition of 2-(trimethylsilyloxy)propene **299** to (*E*)-2-nitro-1-phenylethene **300**, to give nitronate **301** <2000EJO3229>. The [4+2] cycloaddition of (*E*)-2-aryl-1-cyano-1-nitroethene **302** ($\text{Ar} = \text{C}_6\text{H}_4\text{MeO-}p$) with enantiopure vinyl ethers in a one-pot procedure provided oxazines **303** ($\text{R} = \text{Me}$) and **304** ($\text{Ar} = \text{C}_6\text{H}_4\text{MeO-}p$) <2001JOC4661, 2002JOC7238>. The [4+2] cycloaddition of (*E*)-2-methyl-2-nitrostyrene **305** with 1-butoxy-1,4-pentadiene **306** gave cyclic nitron **307** in 94% yield <1998JOC6178>. Intramolecular [4+2] cycloaddition of the nitroalkene–vinylsilane derivative **308** in the presence of SnCl_4 produced the bicyclic nitron **309** <2002H(58)129>.



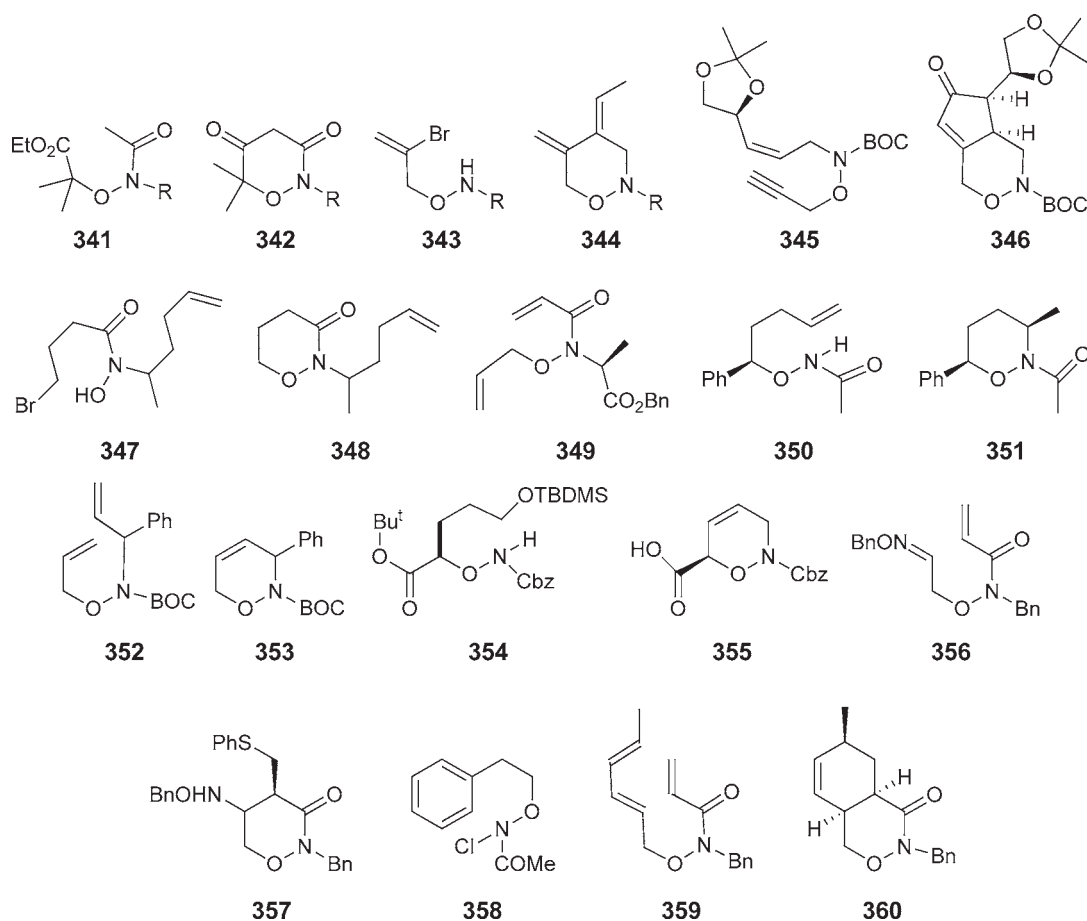


8.04.9.2 Inter- and Intramolecular Cyclization of Oximes

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 center. 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. 1,2-Oxazines can also be synthesized by intramolecular addition of oximes to C=C bonds. These reactions are not general: nitrones and other products can be formed in competition with oxazines. 6-Hydroxymethyl-oxazine **312** and its benzo- **314** and naphtho- **316** derivatives were prepared regioselectively by one-pot cyclization of the corresponding ketoximes **310**, **313**, and **315** with the dilithiated derivative of epibromohydrin **311** <2005TL1017>. The oxidation of 2-hydroxynaphthaldehyde oxime **317** with lead tetraacetate (LTA) gave a mixture of naphtho[1,8-*de*][1,2]oxazine **319** and a spiro dimer **322**. In contrast, LTA oxidation of 6-bromo (or 6-nitro)-2-hydroxynaphthaldehyde oximes **318** provided only spiro dimers **322** (25% of each) but not the corresponding oxazines **320** and **321** <2001T3445>. In another report, 2-hydroxy-1-naphthaldehyde oxime **317** underwent a one-pot *o*- and *peri*-oxidative cyclization with LTA to afford the isomeric products naphth[1,2-*d*]isoxazole-2-oxide **323** and naphth[1,8-*de*]-1,2-oxazine **319** <2000TL1845>. A common *o*-nitrosoquinonemethide intermediate is involved in the formation of **319** and **323**. A convenient and efficient method was described for the preparation of benzoxazines **325** via acid-catalyzed intramolecular Mitsunobu reaction of **324** <2001TL6895>. Intramolecular cyclization of oxime **326** gave 1,2-oxazine-6-one **327** <2004AFF304>. Condensation of the mercaptoquinazoline derivative **328** with hydroxylamine hydrochloride in boiling pyridine yielded 5,6-dihydrooxazin-6-one **329** <2005JHC125>. The addition of hydroxylamine to keto-acid **330** afforded 4-benzyl-3-methyl-1,2-oxazin-6-one **331** <1997CPB659>. Treatment of 2-(4-methoxy-3-methyl-benzoyl)benzoic acid **332** with hydroxylamine hydrochloride gave 2,3-benzoxazin-1-one **333** <2000EJC421>. Oximes possessing γ -, δ -, or ω -C=C bonds were cyclized by PhSeBr or by PhSeCl and an appropriate silver salt to cyclic nitrones <2003AGE3023>. Intramolecular cyclization of γ -alkenyl oxime **334** gave either the 1,2-oxazine **335** or the cyclic five-membered nitrone **336**; in both cases, the reactions proceeded with excellent yields (82–83%), complete regioselectivity, and good diastereoselectivity (75:25) <2001TA3297>. 9,10-Dicyanoanthracene-sensitized irradiation of 6,6-diphenylhex-5-en-2-one oxime **337** causes a novel photochemical cyclization, yielding 5,6-dihydro-4*H*-1,2-oxazine **338** <1996CC2715, 1996T11601>. Wittig alkenation of 10-(methoxyimino)phenanthren-9-one **339** with benzoylmethylene(triphenyl)-phosphorane gave 1-methoxy-3-phenyl-1*H*-phenanthro[9,10-*c*]-1,2-oxazine **340** <1996TL1097>.

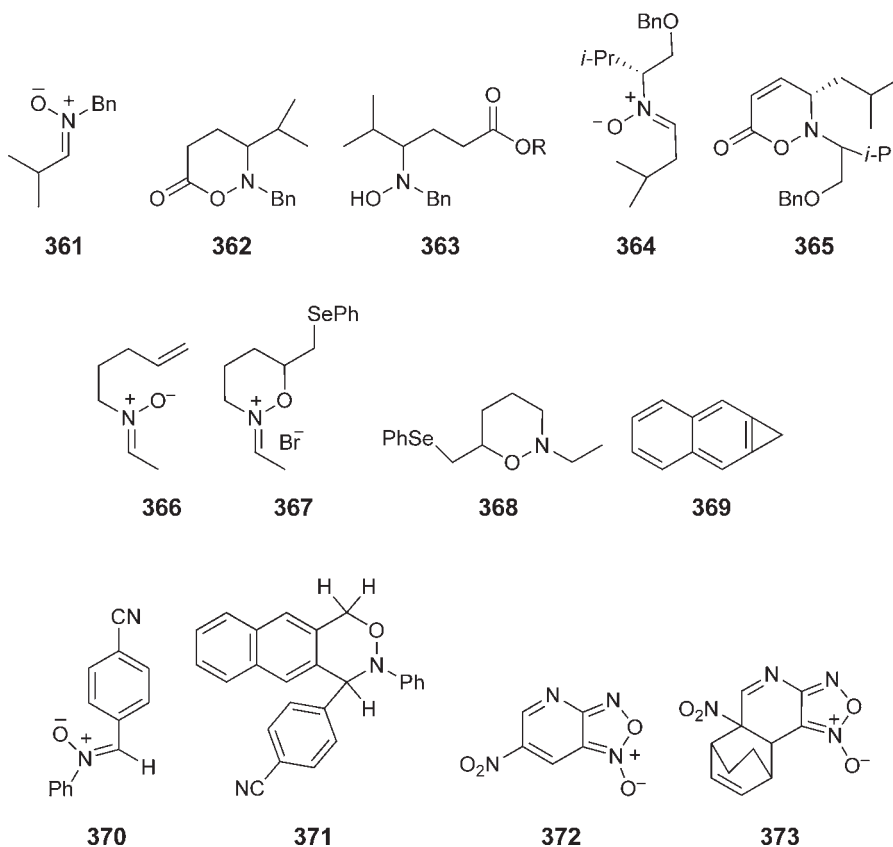


The *O*-alkylated hydroxylamine derivative **341** was prepared from *N*-alkyl-*N*-hydroxyacetamide and ethyl 2-bromo-isobutyrate. In the presence of LiHMDS in THF at -78°C , **341** cyclized to give 1,2-oxazinane-3,5-dione **342** in excellent yield [<1999BKC965>](#). The oxazine **344** containing an exocyclic diene was prepared from hydroxylamine derivative **343** via tandem reaction initiated by a palladium-mediated allylic amination followed by a Heck reaction [<1999CC433>](#). Oxime ether **345** was treated with TMSOTf in the presence of *n*-Bu₃N to give diastereomeric 1,2-oxazines **147** and **346** (9:1) in 88% yield [<1999TL7175, 2005JOC6995>](#). Cyclization of **347** was carried out on alumina impregnated with KF in the absence of solvent and gave *N*-alkylated oxazine-6-one **348** in 90% yield [<1997JOC2098>](#). Treatment of oxime ether **345** with Co(CO)₈ in CH₂Cl₂ enabled *in situ* formation of the dicobalt-alkyne complex, and further addition of trimethylamine *N*-oxide provided cyclopentenones **346** and **147** as the major cyclization products [<2003OL2203>](#). Cyclization of *N*-acryloyl-*N*-alkoxyamino ester **349** in the presence of the ring-closing metathesis (RCM) catalyst bis(tricyclohexylphosphine)benzylideneruthenium dichloride provided oxazin-3-one **207** [<2005CJC93>](#). Alkoxyamide radical was generated from the corresponding acylated alkoxyamines **350** using *o*-iodoxybenzoic acid (IBX) and successfully underwent cyclization to give *cis*-3-methyl-5-phenyloxazine **351** [<2005JOC6991>](#). The *O*-allylhydroxylamine **352**, having *N*-electron withdrawing substituents, proceeded smoothly to afford oxazine **353** using either IrCl(cod)₂ or Pd(PPh₃)₄ [<2003SL567>](#). Desilylation of oxamate **354** with BF₃·EtO followed by intramolecular Mitsunobu reaction of the deprotected alcohol in the presence of Ph₃P and diisopropyl azodicarboxylate afforded oxazine **355** [<2000JOC7667>](#). The radical addition–cyclization of α,β -unsaturated hydroxamates, containing an oxime ether **356** in the presence of PhSH and AIBN, provided a novel method for the stereoselective synthesis of 5-amino-1,2-oxazin-3-one **357** [<2004OBC1274>](#). *N*-Chloro-*N*-(2-phenylethoxy)amide **358** was cyclized with AgBF₄/Et₂O to benzoxazine **8** [<1998T7229>](#). Intramolecular Diels–Alder (IMDA) reaction of hydroxamate-tethered triene **359** provided bicyclic oxazine **360** with predictable stereoselectivity and in high yield [<2001JA4607>](#).



8.04.9.4 Cycloaddition of Nitrones to Unsaturated Compounds

Conjugate addition of the alkyl nitron **361** to an α,β -unsaturated ester at high temperature led to the corresponding oxazin-6-one **362** as the main product <2003AGE2265>, and **362** was also prepared via predominant cyclization of the *N*-hydroxylamine derivative **363** <2003OL229>. A diastereoselective addition of *t*-butyl lithiopropiolate to a chiral nitron **364** was followed by selective hydrogenation of the resulting alkyne derivative using Pd/BaSO₄ to the alkene which was finally deprotected and cyclized to give 2,3-dihydro[1,2]oxazin-6-one **365** <2003OL4081>. Cyclization of **366** was induced by PhSeBr to produce oxazinium bromide **367** <1996T6811>, which is further reduced with NaBH₄ to produce tetrahydrooxazine **368**. Lewis acid-catalyzed reaction of naphtho[*b*]cyclopropene **369** with *C,N*-diarylnitron **370** afforded the dihydronaphthoxazine derivative **371** with very high selectivity <2005JA5764>. The reaction is considered to proceed through a $[4\pi+2\sigma]$ -type cycloaddition process *via* a zwitterionic intermediate generated by a rupture of the C–C σ -bond of the three-membered ring caused by a nucleophilic attack of the nitron **370** <1998H(48)1769>. Oxadiazolopyridine *N*-oxide **372** with 1,3-cyclohexadiene afforded 2:1 mixture of adduct **373** and bisadduct **15** via *o*-nitroso intermediate <2002CC2110>.

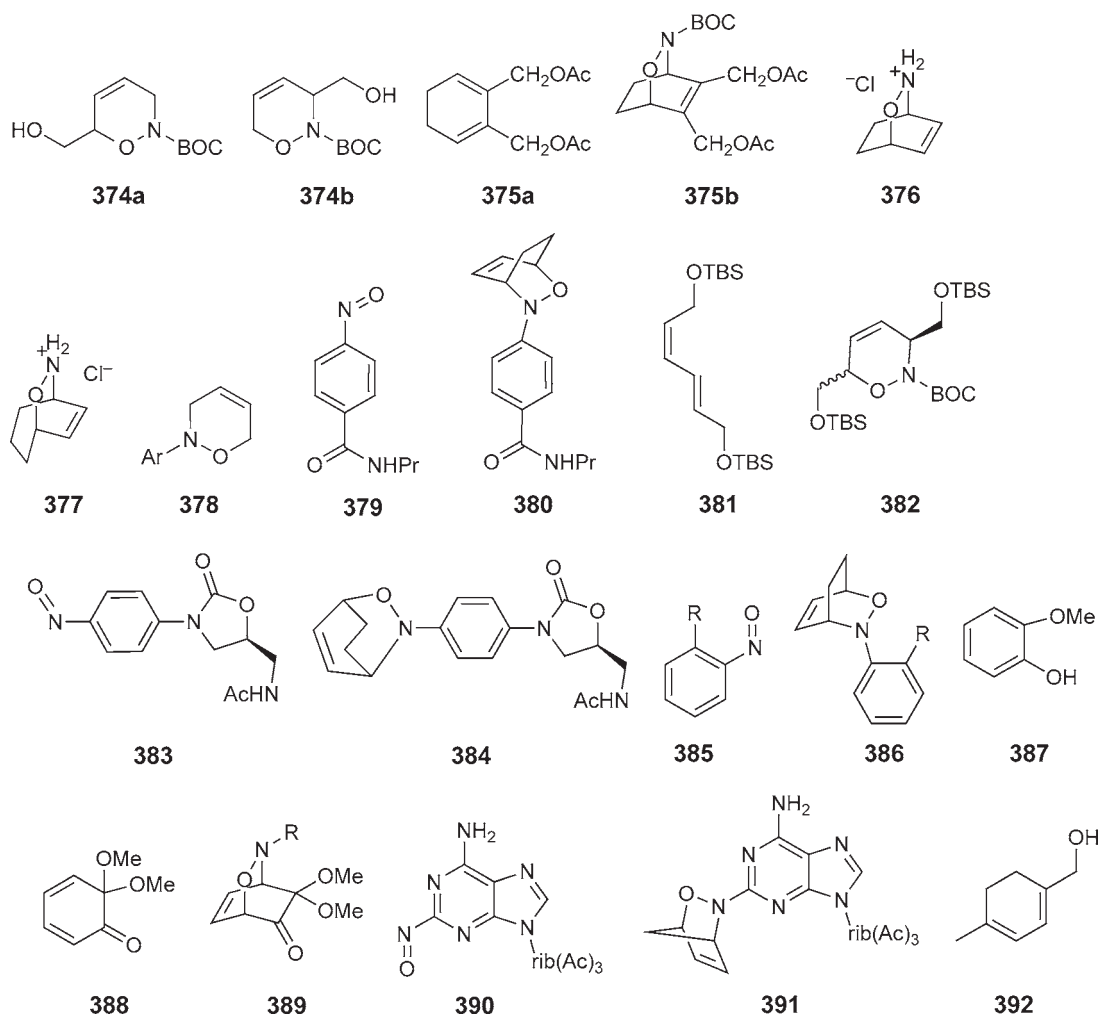


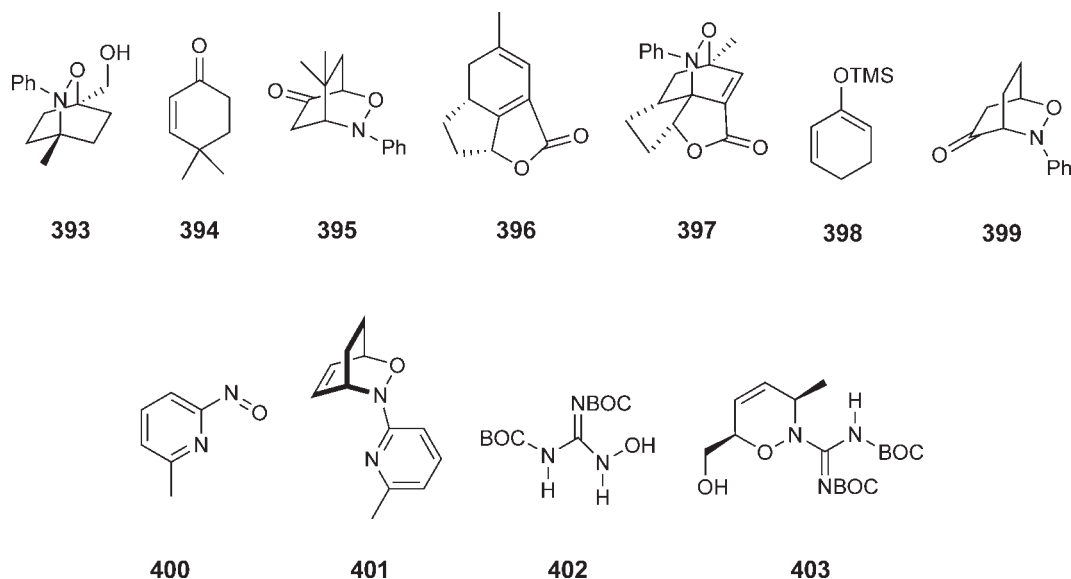
8.04.9.5 Hetero-Diels–Alder [4+2]-Reactions

8.04.9.5.1 Cycloaddition of nitroso to unsaturated compounds

N-Protected hydroxylamine was oxidized to BOC–N=O, then reacted *in situ* with pentadienol to give 3,6-dihydro-6-hydroxymethyloxazines **374a** and **374b** in 2:1 ratio in a combined yield of 78% <1999TL3461>. The 2,3-disubstituted 1,3-cyclohexadiene **375a** underwent cycloaddition under oxidative conditions (Bu₄NIO₄) with BOC–N=O to yield the cycloadduct **375b** in 75% yield without any aromatization of the cyclohexadiene <2006OL2539>. Nitroso intermediate, H–N=O, generated *in situ* from hydroxamic acid, was added to cyclic dienes (cyclohexa-1,3-diene and 1,3-cycloheptadiene) to produce bicyclic oxazines isolated as their hydrochlorides **376** and **377**, respectively <2000J(P1)329, 2002TA691>. A new molybdenum-catalyzed procedure has been developed for the formation of oxazines **378** via hetero-Diels–Alder reaction of the product from aniline and hydrogen peroxide, with conjugated

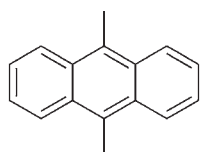
dienes <1996JOC5770>. The catalytic molybdenum–peroxo complex is chemoselective and catalyzes oxidation of the primary aromatic amine to the corresponding nitroso compound leaving conjugated dienes and other substituents untouched. The Diels–Alder cycloaddition of cyclohexadiene with *N*-alkyl 4-nitrosobenzamide **379** afforded bicyclic oxazine adduct **380** <1996BMC1051>. Nitroso Diels–Alder cycloaddition of (*E*),(*Z*)-diene **381** with BOC-NHOH and NaIO₄ provided *cis*- and *trans*-oxazine **382** <2004OL1805>. Linezolid analog **384** utilizing dihydro-1,2-oxazine as morpholine mimic was prepared from nitrosoamine **383** and cyclohexadiene <2005BML2834>. Arylnitroso dienophiles, for example, (*o*-XC₆H₄N=O) **385** (R = H, OMe), exist in equilibrium with their dimeric counterparts, which in turn form stable bidentate complexes with Sc(OTf)₃, and react with cyclohexadiene to give the corresponding Diels–Alder adducts **386** (R = H, OMe) <2002CC2072>. Hetero-Diels–Alder reaction of masked *o*-benzoquinone **388** generated from *o*-methoxyphenol **387** with BOC-N=O afforded the oxazine derivative **389** <2001CC1624>. Nitrosoadenosine **390** with cyclopentadiene gave the oxazine derivative **391** <2001J(P1)1908>. A nitroso Diels–Alder-type reaction between nitrosobenzene and α,β -unsaturated cyclic ketones yielded corresponding bicyclic adducts up to 99% ee <2005TL3385>. Hetero-Diels–Alder reaction between nitrosobenzene intermediate and hydroxymethylcyclohexadiene **392**, cyclohexenone **394**, tricyclic lactone **396**, and cyclohexadienyl silyl ether **398** afforded the corresponding cycloadducts **393**, **395**, **397**, and **399** <2003CL582, 2004JA5962, 2004EJO2783, 2000J(P1)329>. Similarly, Diels–Alder reaction between 2-nitrosopyridine **400** and cyclohexadiene produced **401** <2004JA4128>. The complex RuCl₂(PPh₃)₄ was found to be highly effective catalyst for the oxidation of *N*-BOC hydroxylamine to an *N*-nitroso dienophile <2001CC1812>. The resultant nitrosoadducts were versatile intermediates for the formation of functionalized guanidines. The transient nitrosoamidine, obtained by oxidation of protected *N*-hydroxyguanidine **402**, was trapped *in situ* by pentadienol to give [4+2] cycloadduct **403**, in good yields with high regioselectivity <2004OL699>.



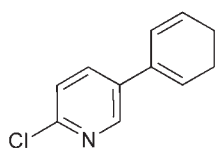


8.04.9.5.2 Cycloaddition of *N*-acylnitroso compounds to dienes

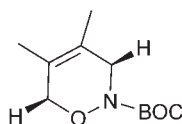
The more bulky acylnitroso compounds react with simple dienes to give adducts in high yield and excellent diastereoselectivity. The alternative approach, which is the addition of an achiral acylnitroso compound to a chiral diene, has been explored. Several IMDA reactions of acylnitroso compounds have been investigated, particularly as steps in target synthesis. Acylnitroso dienophiles are not isolable but 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, can also be used <2001JOC2466, 1997JOC3806>. Oxidation of hydroxyurea with H_2O_2 in the presence of 9,10-dimethylantracene **404** produced a cycloadduct **42** in 28% yield <1998JOC6452>. The identification of this cycloadduct provided clear evidence for the involvement of the C-nitrosoformamide, **262**. Cycloaddition of 2-chloro-5-(1,5-cyclohexadienyl)pyridine **405** with *tert*-butyl *N*-hydroxycarbamate (*t*-BuOCONHOH) was performed via Swern oxidation to give an inseparable mixture of cycloadducts **76** and **77** in 79% yield <1998JOC8397, 1998TL4513>. The *N*-BOC-nitroso intermediate derived from *N*-BOC-hydroxylamine was trapped by 2,3-dimethylbutadiene to produce cycloadduct **406**. Diels–Alder cycloaddition of cyclopentadiene or cyclohexadiene with acylnitroso compounds derived from Swern oxidation of hydroxamic acid produced the cycloadducts **407** ($n = 1, 2$; $\text{R} = \text{NH}_2$, OBu^t , OBn), whereas with substituted cyclohexa-1,3-dienes **408** and **409** they afforded the corresponding bicyclic adducts **410** and **411** ($\text{R} = \text{NH}_2$, OBu^t , OBn), respectively <2001JOC6046, 2002J(P1)2058>. Cycloaddition of benzyl nitrosoformate to the TBDMS derivative of cyclohepta-3,5-dienol **412** led to the oxazine adduct **413** <1998T3631, 2001JOC2466>. Cycloaddition of α -nitrosobenzaldehyde [$\text{Ph}-(\text{C}=\text{O})-\text{N}=\text{O}$] to cyclopentadiene afforded *N*-benzoyloxazine **414** ($\text{R} = \text{H}$) <2002EJO1175, 2002EJO2058>. *N*-benzoyloxazanorbornene **414** ($\text{R} = \text{CO}_2\text{Me}$) was obtained by the cycloaddition of **416** and cyclopentadiene <2000EJO2613>. Intermediate **416** in turn was generated from the mild oxidation of substituted benzamide **415** with aryl nitrile *N*-oxide and NMO <2000EJO2613>. Sodium periodate oxidized a hydroxamic acid, readily accessible from (*S*)-alanine, to the acylnitroso species, which was trapped *in situ* with cyclopentadiene to produce cycloadducts **407** <2003TL4571>. Pyrrolidinone diene **417** with hydroxamic ester gave oxazine **418** <2000SL1366>. The reaction of 3-methylene-4-penten-1-ol **419** with the nitroso dienophile generated from acetohydroxamic acid and $\text{Et}_4\text{N IO}_4$ led to a 1:1 mixture of inseparable cycloadducts **420** and **421** <2004JOC3025>. Acylnitroso Diels–Alder cycloaddition of hexa-2,4-dienal dimethyl acetal **422** to achiral acylnitroso dienophile, $\text{BnO}_2\text{C}-\text{N}=\text{O}$ **423**, gave the racemic cycloadducts **188** and **424** <1997T13769>. The oxidation of hydroxamic acids <1998JOC885>, *N*-hydroxyureas <2004JME3495>, and *N*-hydroxycarbamates with Dess–Martin periodinane generated acyl nitroso intermediates that readily reacted with conjugated cyclic and acyclic dienes to produce the corresponding cycloadducts **425–427** <2000SC947>.



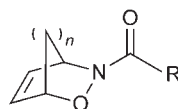
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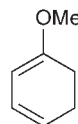
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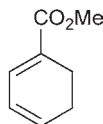
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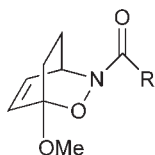
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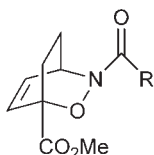
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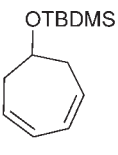
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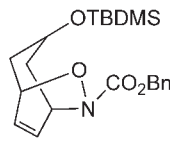
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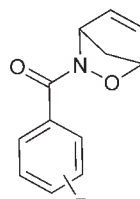
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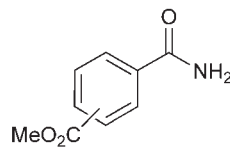
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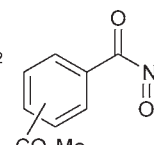
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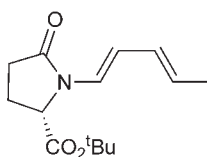
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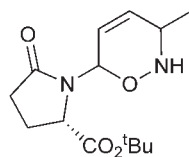
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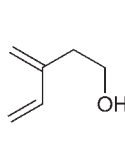
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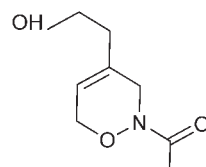
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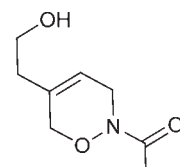
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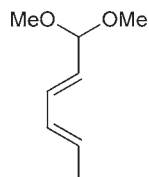
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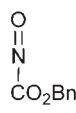
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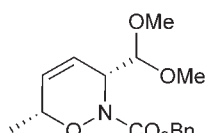
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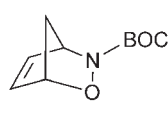
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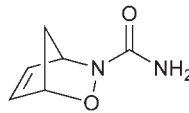
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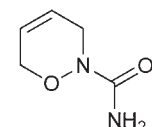
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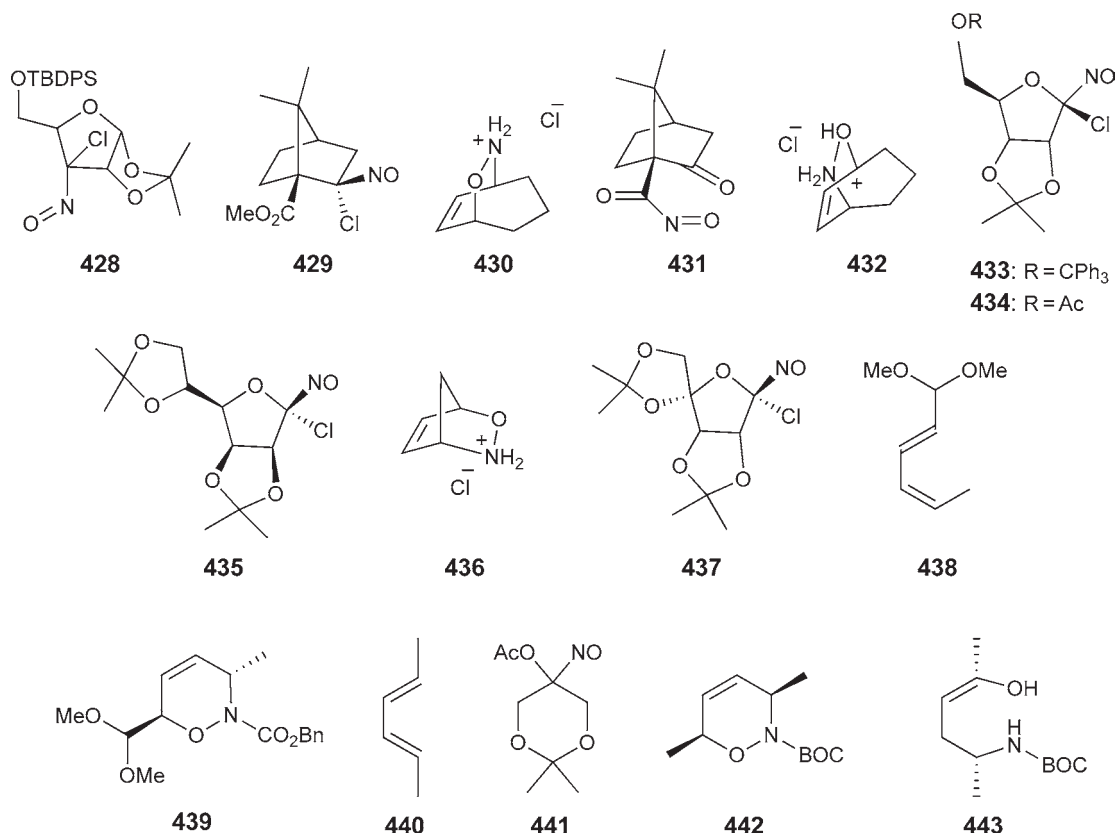
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427

8.04.9.5.3 Cycloaddition of α -chloronitroso compounds to dienes

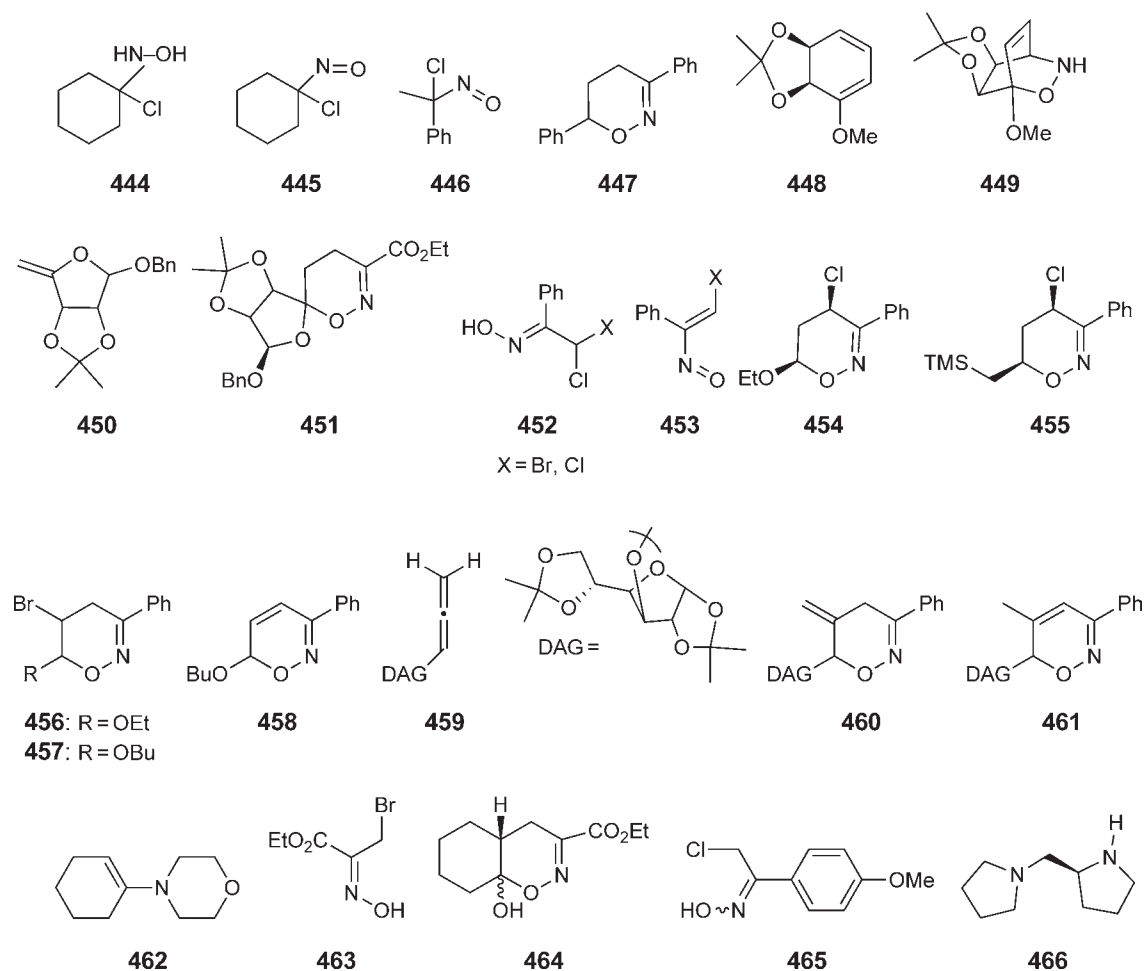
The α -chloronitroso compound **428** derived from D-xylose underwent cycloaddition with 1,3-cyclohexadiene to give bicyclic oxazine **376** <1998CC2251>. A unique reversal in the absolute stereochemistry of the oxazine hydrochlorides was observed for the products **430** and **432** from the cycloaddition of camphor-based acylnitroso **431** as compared to the oxazine obtained through reactions of the corresponding camphor-based chloronitroso compound **429** <2002TA691>. The chloronitroso dienophiles **428** and **433** or **434** reacted with cyclohexadiene and cycloheptadiene to give the corresponding oxazines **376** and **432**, respectively <2000S1719, 2000J(P1)329, 1998CC2251>. A highly diastereoselective Diels–Alder reaction of D-mannose-derived chloronitroso derivative **435** with cyclopentadiene generated hetero [2.2.1] bicyclic oxazine salt **436** in an enantiomeric purity of 96% <1998JOC885>. Asymmetric Diels–Alder reaction of the chiral chloronitroso derivative **437** of mannose with hexadienal dimethyl acetal **438** gave the chiral adduct **439** with excellent diastereomeric excess <1995SL1187, 1997TA363>. Cycloaddition of the α -acetoxynitroso derivative **441** with 2,4-hexadiene **440** allowed to selectively obtain 3,6-dihydro-1,2-oxazine **442** in an aqueous medium or the corresponding N–O bond-cleaved product **443** in anhydrous medium <2005OBC4395, 2004OL2449>. These very reactive dienophiles gave good yields of cycloadducts under very mild conditions <1998T10537>.



8.04.9.5.4 Cycloaddition of nitrosoalkenes to alkenes

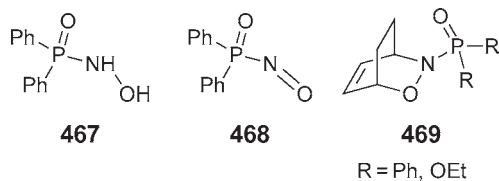
Conjugated nitrosoalkenes are 4π components unlike other nitroso compounds in that they act as dienes, rather than as dienophiles, in the Diels–Alder reaction. This reaction is the best general method for the preparation of 5,6-dihydro-4*H*-1,2-oxazines. The nitrosoalkenes, which are used in these reactions, 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. The reaction of freshly cracked cyclopentadiene with chloronitrosocyclohexane **445**, derived from **444** in dry diethyl ether-ethanol, afforded **436** in 94% yield [1997T3347, 2002TA691]. Reaction of ketoximes containing an α -methylene group with chloramine-T followed by treatment with Et₃N leads to the formation of α -nitroso alkene via α -nitroso chloride **446**, which can react *in situ* intramolecularly with styrene to produce 5,6-dihydro-4*H*-1,2-oxazine **447** in good yield [2005JHC877]. Bicyclic oxazine **449** was prepared from asymmetric hetero-Diels–Alder reaction of **445** with the dihydrocatechol derivative **448** [1997TL2883]. Hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to pent-4-enofuranosides **450** gave 5,6-dihydrooxazine **451** [2000TL4819, 2000SL1366, 2002T9351]. α -Aryl- β -chloro- (or bromo-) α -nitrosoethylene **453**, prepared *in situ* from α -monochloro (or bromo) ketoximes **452**, reacted with ethyl vinyl ether and allyltrimethylsilane, to afford exclusively *trans*-(4*S*,6*S*)-**454** and *trans*-(4*R*,6*R*)-**455**, respectively, albeit in low yields [2001JOC7334]. The stereochemistries were assigned based on the ¹H NMR coupling constants, which were unambiguously determined by the decoupling experiments. All reactions proceeded with very high regioselectivity [2001JOC7334]. 6-Butoxy-3-phenyl-1,2-oxazine **458** has been prepared by hetero-Diels–Alder reaction of α -nitroso alkene, CH₂=C(Ph)N=O, with appropriate vinyl ethers and subsequent elimination of HBr from **456** and **457** by DBU (e.g., **457** led to **458**) [1998JPR649, 1996IJB475]. The hetero-dienes CH₂=C(Ph)NO were generated *in situ* from α -halo ketoximes. Hetero-Diels–Alder reaction of CH₂=C(Ph)N=O with alkoxyallene **459** gave oxazine **460** with a diastereomeric ratio of 90:10. Isomerization of **460** provided the thermodynamically more stable 6*H*-1,2-oxazine **461** [2002S1553, 2003SL2017]. Hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate, which in turn was derived from **463**, to electron-rich enamine **462** gave bicyclic oxazine **464** after hydrolysis [2003TL3905]. Nitroso alkenes, generated *in situ* from α -halooxime **465**, underwent [4+2] cycloaddition with

isovaleraldehyde and enamines as dienophiles (in turn produced from aldehydes and chiral amine, **466**) to afford 6-hydroxyoxazine **273** <2004OBC828>.



8.04.9.5.5 Cycloadditions of *P*-nitrosophosphine oxide to cyclic dienes

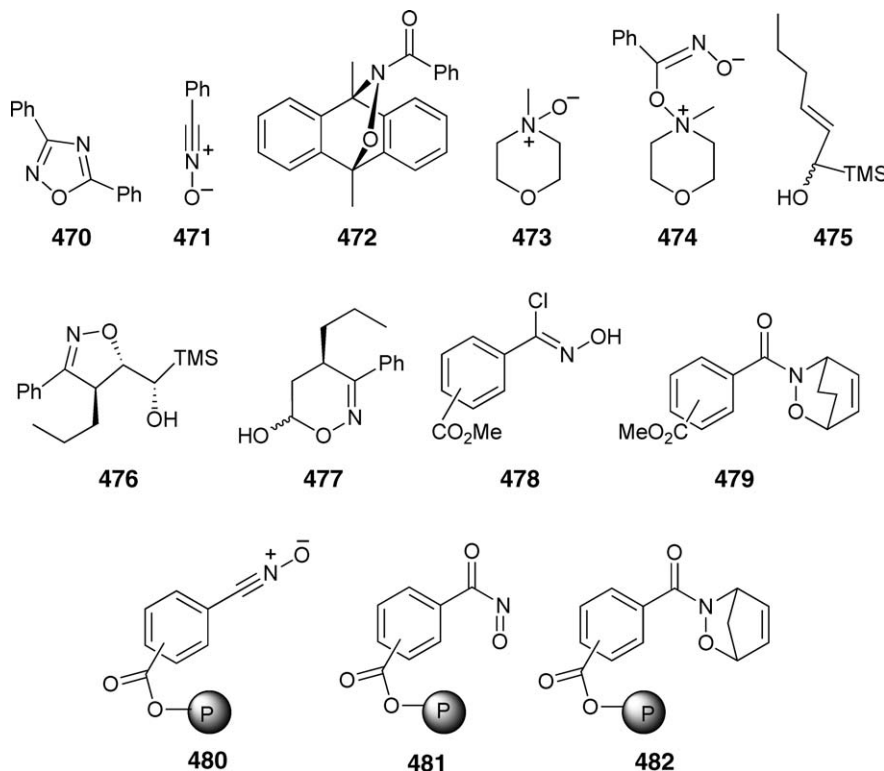
p-Nitrosophosphine oxide **468**, which in turn was obtained from *N*-hydroxyphosphinamide **467**, reacted with cyclohexa-1,3-diene to produce the cycloadduct **469** <2002JOC6174, 2000JOC8725>.



8.04.9.6 1,3-Dipolar Cycloaddition of Nitrile Oxides with Cyclic Dienes

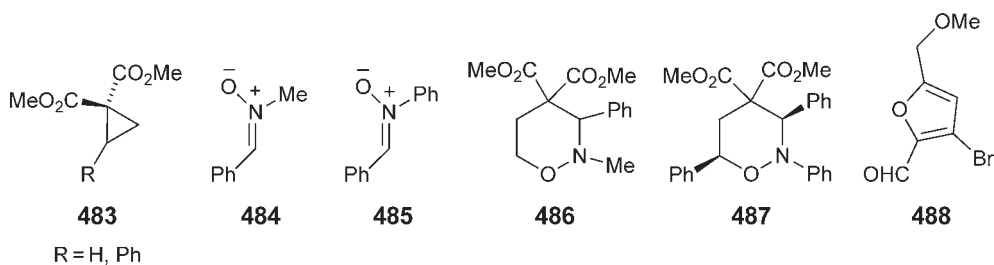
Oxygen transfer from oxadiazole *N*-oxide **37** to benzonitrile yielded 3,5-diphenyl-1,2,4-oxadiazole **470**, benzonitrile *N*-oxide **471**, and the resulting nitroso carbonyl intermediate **36** was trapped by 9,10-DMA to give the adduct **472** <1997T1787>. NMO **473** was added to the electrophilic carbon of the benzonitrile *N*-oxide affording the zwitterionic adduct **474**. Intermediate **474** fragmented to the *N*-methylmorpholine and ArCONO **36**, which was trapped by 9,10-DMA to provide cycloadduct **472** <1999T10497, 1996TL1909>. Regio- and stereoselective 1,3-dipolar

cycloaddition of nitrile oxide to optically active α -silyl allyl alcohol **475** provided 3,4,5-trisubstituted 4,5-dihydroisoxazole **476**, which is readily converted into chiral 4-substituted 6-hydroxy-5,6-dihydro-4*H*-[1,2]-oxazine **477** in 73–100% yields on treatment with tetrabutylammonium fluoride (TBAF) <1999TL4349, 2002T9613>. Ring enlargement occurred only under anhydrous conditions. The elaboration of the C-5 side chain in dihydroisoxazole **476** has been accomplished in a highly selective manner to **477** without loss of optical purity <1999TL4349>. Sunlight exposure of **478** in methanol in the presence of 1,3-cyclohexadiene afforded benzonitrile and cycloadduct **479** in almost quantitative yield <1999TL797>. Wang resin- (*p*-benzyloxybenzyl alcohol polystyrene resin) supported benzonitrile *N*-oxide **480** showed increased stability because of being on the solid phase, and it underwent clean transformation into nitroso carbonyl intermediate **481**, which was trapped by cyclopentadiene to afford oxazine **482** in moderate yield <2002EJO1175>.



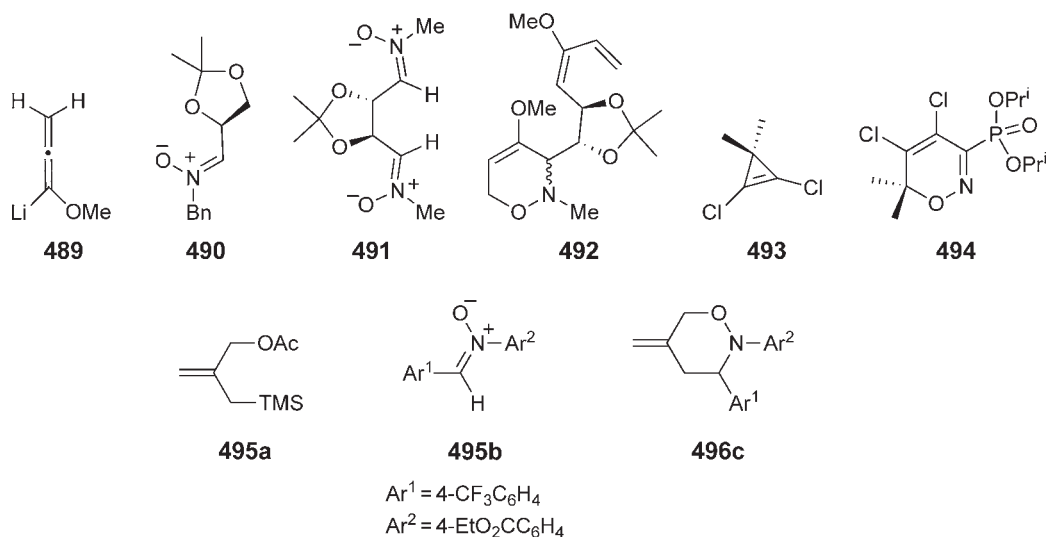
8.04.9.7 Homo [3+2] 1,3-Dipolar Cycloaddition

A new mode of reactivity of cyclopropanediester **483** with nitrones **484** and **485** was described leading to **486** and **487** <2003AGE3023, 2004OL139>. This reaction represents the first example of 1,3-dipolar homo [3+2] cycloaddition. The utility of the stereoselective reaction was demonstrated in a two-step preparation of the tricyclic skeleton of FR900482 <2005JA5764>. Three-component coupling of the cyclopropane diester **483** (R = Ph), PhNHOH, and substituted furfural **488** produced Diels–Alder cycloadduct **266**, which is used further in the synthesis of the tetracyclic core ring of the alkaloid nakadomarin A <2005OL953>.



8.04.9.8 [3+3] Cycloaddition

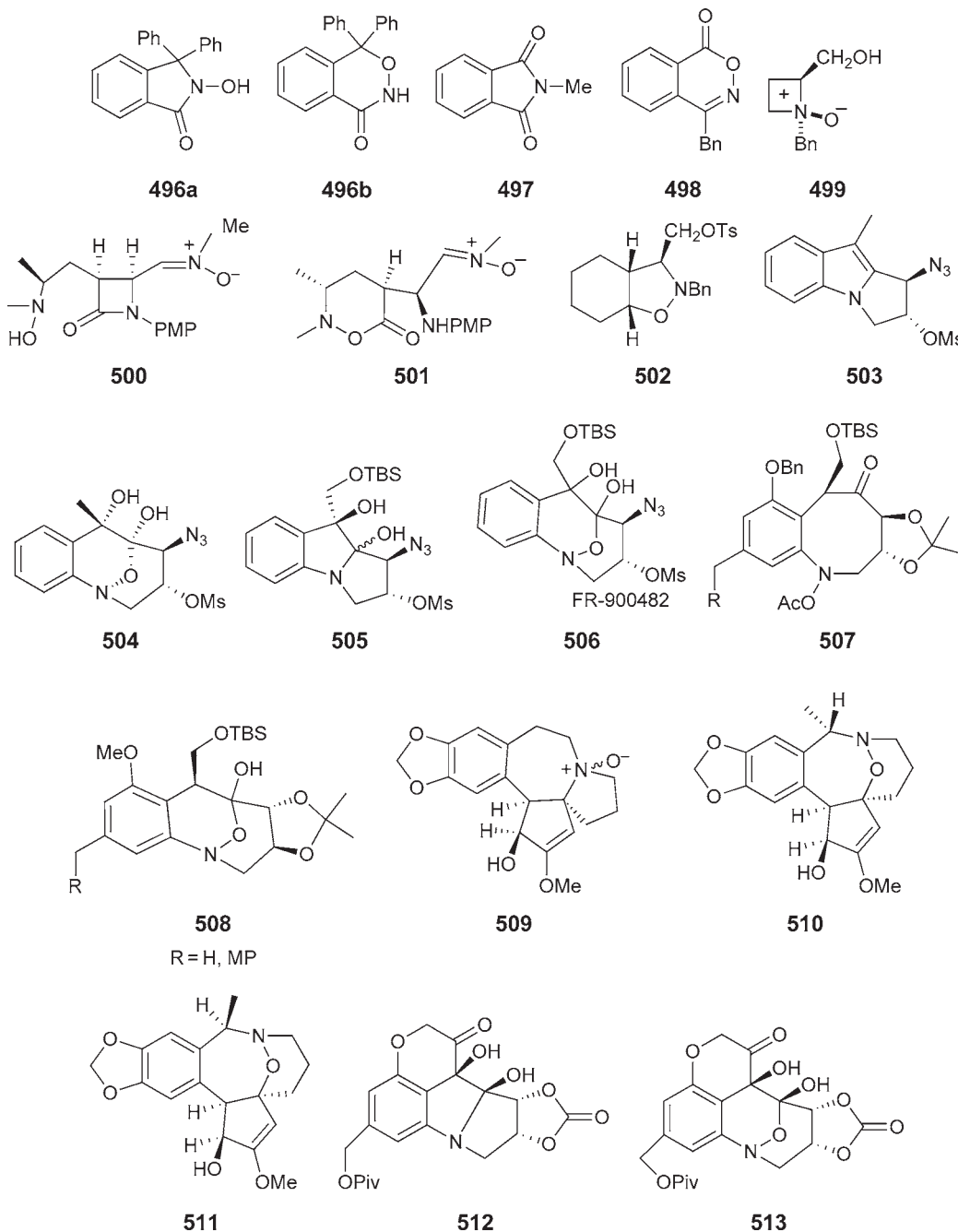
Enantiopure 3,6-dihydro-2*H*-1,2-oxazines **177** and **229** were formed by addition of lithiated methoxyallene **489** to (*R*)-glyceraldehyde-derived nitron **490** with excellent *syn*-selectivity in moderate yields via a novel [3+3] cyclization process <2002OL2353>. Cycloaddition of lithiated methoxyallene **489** to bisnitron **491** furnished a mixture of six compounds among which the major component was *syn/syn*-bis(1,2-oxazine), **25**. The diastereoselectivities of reactions between allenes and nitrones are based on Dondoni's model <2005EJO1003>. Addition of an excess of lithiated methoxyallene to bisnitron **491** under standard conditions not unexpectedly furnished a relatively complex mixture consisting of at least six different compounds: dieny-substituted 1,2-oxazine **492** (*syn* and *anti*) and bis(1,2-oxazine) **25** (*syn/syn*, *anti/anti*, and *syn/anti*) <2005EJO1003>. [3+3] Cycloaddition between dimethyldichlorocyclopropene **493** and diisopropoxyphosphoryl nitrile oxide led to 1,2-oxazine **494** <1996T8877>. Cyclopropene **493** undergoes a cyclopropene-vinylcarbene rearrangement at ambient temperature, and the vinylcarbene can be trapped in a range of intermolecular reactions with alkenes, alkynes, and a phospho-alkyne <1996T8877>. [3+3] Cycloaddition reaction of (2-(acetoxymethyl)-2-propenyl)trimethylsilane **495a** with nitron **495b** provides the corresponding cycloadduct **496c** in 90% yield <2006JA6330>.



8.04.10 Ring Synthesis by Transformation of Another Ring

The reaction of the *N*-hydroxyphthalimide with AlCl₃ in benzene produced 2,3-dihydroisindol-1-one **495** and the isomeric 1,1-diphenyl-1*H*-benzo-2,3-oxazin-4-one **496** <1996H(43)633>. *N*-Methyl phthalimide **497** reacted with benzylmagnesium bromide to give 4-benzyl-2,3-benzoxazin-1-one **498** via a one-pot addition-decyclization-cyclocondensation process <2004SC1301>. Azetidine *N*-oxide **499** was found to undergo a quantitative ring expansion to yield **10**, a potentially useful intermediate for further synthetic transformations <1998CCC1487>. The β-lactam **500** underwent ring expansion to give 1,2-oxazine **501** <2005EJO1680>. Bicyclic isoxazolidine **502** underwent thermally induced ring expansion to give oxazine **20** <1998JOC4485, 1998JCX133>. The pyrroloindole derivative **503** substituted with Me group at C-9 undergoes an oxidative ring expansion in the presence of dimethyldioxirane (DMDO) to give the model compound **504** for a possible intermediate for the synthesis of an FR900482 analog <2003OL785>. Treatment of **505** with OsO₄, hydrogen sulfide, magnesium monoperoxyphthalic acid (MPP), and triphenylphosphine resulted in the formation of oxazine **506** as a mixture of three diastereomers in a 44–50% yield <2000SC351>. Treatment of the eight-membered ring ketone **507** with excess N₂H₄ resulted in a transannular reaction to give the desired hydroxylamine hemiacetal **508** as a mixture of the diastereoisomers (79:21) in 78% yield <2004JOC2831, 2001OL2575, 1996TL3479, 2003JOC130>. Removal of the acetyl group in **507** with K₂CO₃/MeOH caused spontaneous internal hemiacetalization to give oxazine **508** as the sole product <1997T10253, 1996T10239, 2004OL1745, 1997TL4033, 1996TL3475, 1997JOC1083>. One-step deprotection/oxidative cyclization of the eight-membered ring aminoketone **507** to the unique hydroxylamine hemiketal ring system **508** was also

achieved with DMDO. This reaction provided a distinctive structural motif of FR900482 <2004JOC2825, 2002AG(E)4683>. Ring expansion of pentacyclic pyrrolidine *N*-oxide **509** afforded oxazines **510** and **511** <1997JOC8251>. Oxidative ring expansion of diol **512** to **513** was achieved with DMDO <1996TL5243>.



8.04.11 Synthesis of Key Compounds and Comparison of Available Methods

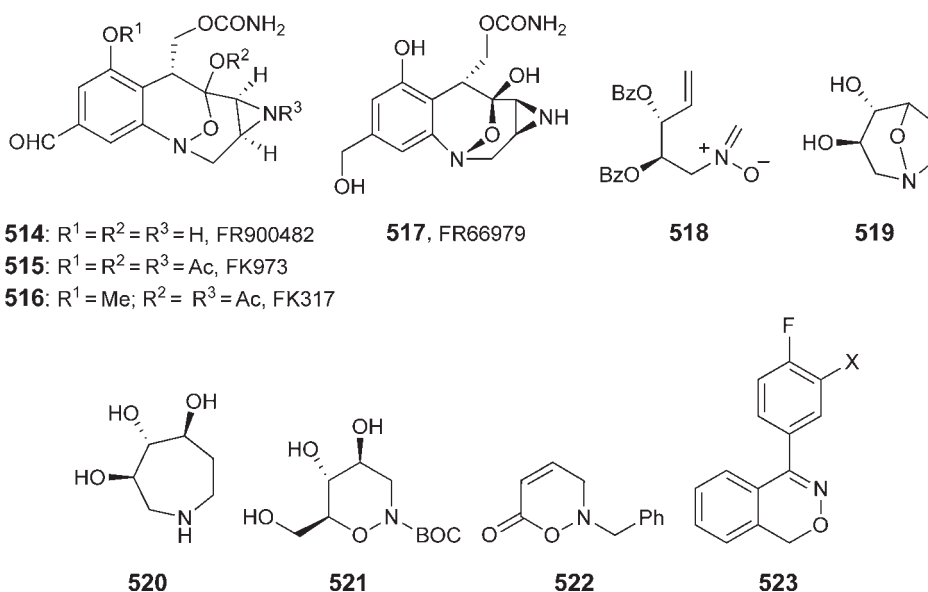
The diverse range of different structures prepared over the period in question together with the small number of publications on any given system preclude any meaningful comparison of the various methods available.

8.04.12 Applications

The main application of 1,2-oxazine derivatives has been as intermediates in synthesis since the weak N–O bond allows oxazines having a defined substitution pattern to be constructed and then cleaved.

The compound FR900482 **514** was isolated from the culture broth of *Streptomyces sandaensis* at Fujisawa Pharmaceutical Co. Ltd., Japan, and exhibits exceptionally potent antitumor activity against various types of mammalian solid tumors. A formal, enantioselective synthesis of the antitumor antibiotic (+)-FR900482 has been completed using an approach that featured the RCM of a diene to give the key intermediate benzazocine **507** <2000JA10781, 2002AGE4688, 1997JA5999>. A second synthetic strategy for the natural product (+)-FR900482 was developed by featuring a convergent and enantioselective sequence, which commences with 5-hydroxyisophthalic acid and L-diethyl tartrate <1996TL3471>. FK973 **515**, a stable semisynthetic triacetyl derivative, displays approximately 3 times more potent activity than mitomycin, with significantly lower toxicity. Both FK973 and FK317, **516**, are semisynthetic derivatives of FR900482 and showed highly promising antitumor activity in human clinical trials <2002AGE4683>. FR66979, **517**, exhibits antitumor activity and its total synthesis has been explored <2002AGE4686>. FR66979 and FR900482 are believed to undergo bioreductive activation *in vivo*, enabling them to alkylate DNA <2000BMC173, 1998JA2192>. Iron(II) was critical for the reduction of (+)-FR66979 in the absence of DNA <1997TL343>.

The synthesis of a trihydroxyazepane **520** was accomplished from **519** formed via an intramolecular alkene–nitronc cycloaddition of **518**. Reductive N–O bond cleavage of **519** to **520** was affected with H₂/Pd/C. Compounds **519** and **520** were evaluated as glycosidase inhibitors <2005TA487>. 4,5-Dihydroxy-6-hydroxy-methyloxazine **521** found to inhibit almond β -glucosidase, while very low inhibition of yeast α -glucosidase and galactosidase was observed <1999TL3461>. The 6-hydroxymethyl-4,5-dihydroxyoxazine **56** was an effective inhibitor of two β -glucosidases (K_i = 27 and 35 μ M) <2002CJC857>. Linezolid analog **384** utilizing dihydro-1,2-oxazine as a morpholine mimic was prepared via a nitrosoamine/diene [4+2] cycloaddition strategy. It has potency similar to linezolid against a panel of Gram-positive bacteria <2005BML2834>. Plasma glucose and plasma *in vivo* pharmacological studies have been done for N-alkylated benzoxazinone **219** and it has a greater activity than thiazolidinedione <2001EJM627>. Diastereoselective syntheses of ABT-627 **100** (atrasentan) gave a racemic mixture and it showed extremely potent and selective endothelin receptor antagonist activity <1999TL7175, 2003EJO3524>. In pharmacological evaluation of N-benzyloxazin-6-one **522** in mice, it performed as a nonclassical antinociceptive agent <1999TL7175, 1997CPB659>. 4-Benzyl-3-methyl-1,2-oxazin-6-one **331** was evaluated for analgesic activity <2000AF353>. A series of 1H-2,3-benzoxazine derivatives **523** were synthesized, and their herbicidal activity against upland weeds and selectivity against crops were assessed. Studies of the structure–activity relationship revealed that the strongest herbicidal activity was achieved when position 4 in the benzoxazine ring was substituted with a 3-chloro-4-fluorophenyl or a 3-bromo-4-fluorophenyl group. The treated weeds showed strong bleaching symptoms <2002JPES53>.



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Biographical Sketch



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8.05

1,3-Oxazines and their Benzo Derivatives

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8.05.1 Introduction

As in CHEC-II(1996) <1996CHEC-II(6)301>, the chemistry of 1,3-oxazines is treated here in a separate chapter, which allows a more detailed discussion of their reactions and synthetic methods published in the period 1995–2007.

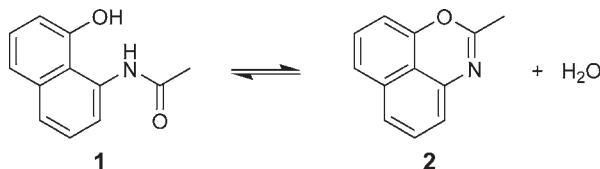
The chemistry of various 1,3-oxazine derivatives has been reviewed since 1995. The topic list of these surveys includes the synthesis and reactions of 4*H*-1,3-oxazines <1998CHE629>, the chemistry of 4*H*-3,1-benzoxazin-4-ones <1999JHC563>, the synthesis and reactions of 4*H*-3,1-benzoxazin-4-ones bearing a substituent attached to position 2 via a heteroatom <2000JHC1369>, the synthesis of heterocyclic compounds from isatoic anhydrides (2*H*-3,1-benzoxazine-2,4-diones) <2001CHE385>, and the chemistry of 4*H*-3,1-benzoxazines and their dihydro derivatives <2003CHE137>. A review of the synthesis, stereochemistry, and transformations of cycloalkane-fused 1,3-heterocycles furnishes many details on the corresponding 1,3-oxazine derivatives <1998AHC(69)349>. A number of reviews covering various aspects of the ring–chain tautomerism of various 1,3-oxazine derivatives have also been published since 1995 <1996AHC(66)1, 2002RCB205, 2003EJO3025, 2004CSY155>.

With the increasing demand for chiral nonracemic compounds, stereoselective methods for the synthesis of 1,3-oxazine derivatives and applications of enantiopure 1,3-oxazines in asymmetric transformations have gained in importance in the past decade, as reflected by the increasing trend in the number of publications on this topic, and accordingly by the share of this topic in the present compilation. The limited size of this survey and the scope of this chapter do not allow a discussion here of the applications of 1,3-oxazines in polymer chemistry and the synthesis and properties of 1,3-benzoxazine-containing hetero-calixarenes.

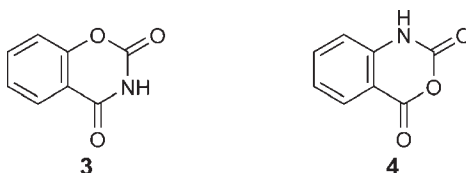
As in CHEC-II(1996), the reactions of 1,3-oxazines will be presented before the methods applied for their synthesis. In each of the sections and subsections, the compounds will be discussed in the sequence of decreasing number of double bonds in the ring.

8.05.2 Theoretical Methods

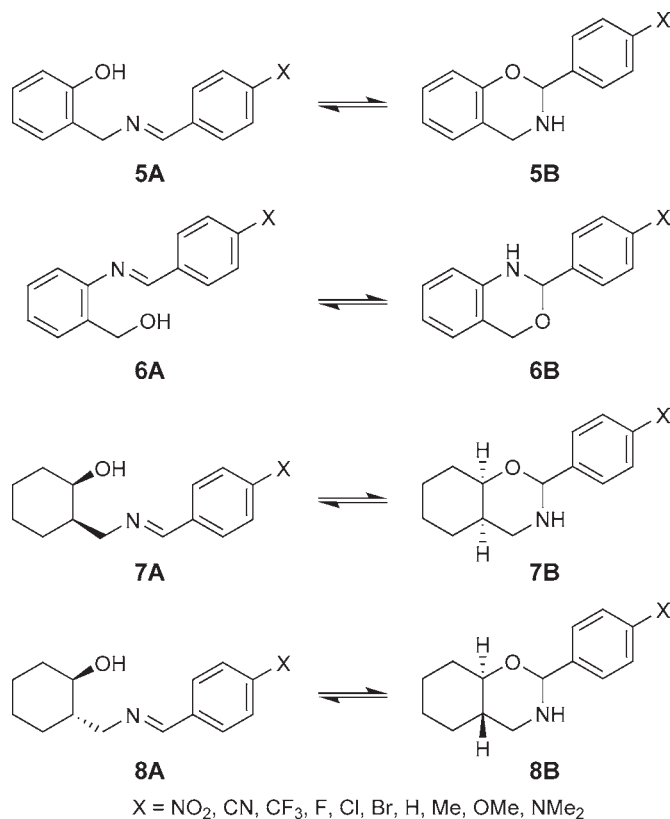
Theoretical calculations of minimum-energy structures and thermodynamic terms using self-consistent field theory with thermodynamic and solvation corrections concluded that the cyclization of 1-hydroxy-8-(acetylamino)naphthalene **1** to give 2-methylnaphth[1,8-*d,e*][1,3]oxazine **2** with the liberation of water was much less favorable ($\Delta G = -2.0 \text{ kJ mol}^{-1}$, $\Delta H = +31.0 \text{ kJ mol}^{-1}$, and $T\Delta S = +33.1 \text{ kJ mol}^{-1}$ at 298.2 K) in the gas phase than the corresponding ring closure of 1-amino-8-(acetylamino)naphthalene, which was in qualitative agreement with experimental observations for the reactions in solution <1998J(P2)635>.



Density functional calculations (B3LYP/6-31G* and B3LYP/6-311G*) relating to 2*H*-1,3-benzoxazine-2,4(3*H*)-dione **3** and isatoic anhydride **4** confirmed the experimental evidence of the nearly identical thermochemical stability of these isomers. Through a combination of theoretical calculations and associated isodesmic reactions directed to investigation of the aromatic or antiaromatic character of isatoic anhydride, it was deduced that it enjoys some degree of aromatic stabilization <2003OBC2566, 2004OBC1647>.

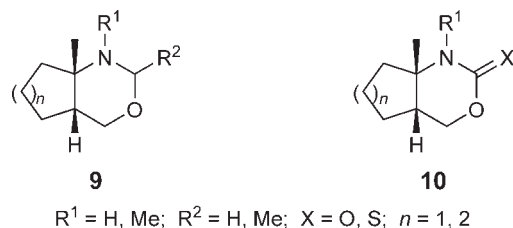


Substituent effects on the stabilities of the ring (**B**) and chain (**A**) forms in the tautomeric equilibria (see [Section 8.05.4.1.2](#)) of 2-aryl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines **5**, 1,4-dihydro-2*H*-3,1-benzoxazines **6**, and the related *cis*- and *trans*-perhydro-1,3-benzoxazines **7** and **8** ([Scheme 1](#)) were studied by means of PM3 charge density and energy calculations. The reaction energies of the isodesmic reactions revealed that electron-donating substituents stabilized both the chain and ring tautomers, but the effect on the stability of the chain form was stronger than that on the stability of the ring form. It was concluded that the substituent dependence of the relative stability of the ring and chain tautomers in equilibrium was governed by a number of different electronic effects. Intramolecular hydrogen bonding between the imine nitrogen and the hydroxy group and the polarization of the C=N bond were found to contribute in the chain form. The increases caused in the stability of the ring form by electron-donating substituents were explained by stereoelectronic and electrostatic effects [\[2001JOC4132\]](#).



Scheme 1

The energies of the preferred conformations of saturated, *cis*-fused, bicyclic tetrahydro-1,3-oxazines **9** and 1,3-oxazin-2-ones and -2-thiones **10** bearing a methyl substituent at the annelation were investigated by density functional theory methods. Following geometry optimization at the B3LYP/6-31G(d,p) level, both the proton chemical shifts and the vicinal coupling constants between the hydrogen at the annelation (H-4a) and the hydrogens attached to the carbons adjacent to the annelation (H-4 and H-5) were calculated at the B3LYP/cc-pVTZ level. The agreement between the calculated and the experimental chemical shifts and vicinal coupling constants was found to be good, indicating that this methodology is comparable in many respects to experimental approaches for determination of the conformational equilibria of such systems [\[2003JA4609\]](#).



8.05.3 Experimental Structural Methods

8.05.3.1 X-Ray Methods

X-Ray crystallographic investigations of 1,3-oxazine derivatives have been made in numerous cases either to prove unambiguously the correct structure of the isolated crystalline product or, especially if the product contains newly formed chiral carbon(s), to determine the configuration of the centers of asymmetry <1996CC1629, 1997TL3573, 1997TL4917, 1998CC43, 1998TL6561, 1999J(P1)1933, 1999H(51)2893, 1999JOC4152, 2000JOC6540, 2000T8173, 2003T8163, 2004TA155, 2005JHC669, 2005OL3797, 2005S2426, 2006EJO3309, 2006JOC2332, 2006OBC2753>.

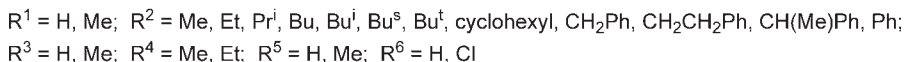
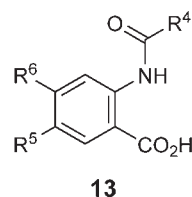
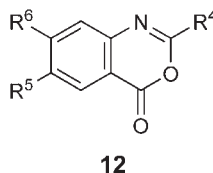
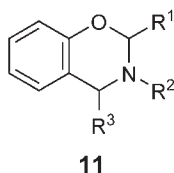
For some 1,3-oxazine derivatives, more detailed X-ray studies on the solid-state conformation and/or crystal packing have been performed. The list of such compounds includes 2-amino-4,6-diphenyl-1,3-oxazin-2-ium trifluoroacetate <2005AXEo3149>, 5-(4-methoxybenzyl)-6-(4-methoxyphenyl)-3-phenyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione <2005AXEo3910>, a spiro-condensed tetrahydro-1,3-oxazin-2-one <2000JST(524)233>, a perhydro-1,3-benzoxazine derivative <1999AXC1587>, 2,2-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazine <2006AXEo908>, three 2-(2-arylethenyl)-substituted 4*H*-3,1-benzoxazin-4-ones <2000AXCe408>, several 2*H*-1,3-benzoxazin-4(3*H*)-ones <2005AXEo814, 2005AXEo990, 2005AXEo3196, 2005AXEo3252, 2006AXEo3011>, 6-bromo-2*H*-3,1-benzoxazine-2,4(1*H*)-dione <1996AXC3108>, *trans*-3,7-dibenzyl-1,5-dioxo-3,7-diazadecalin and *trans*-1,5-dibenzyl-3,7-dioxo-1,5-diazadecalin <1999EJO2033>, 3-acetoxy- and 3-hydroxy-4,4-dimethyl-6-phenyltetrahydro-1,3-oxazine <1999J(P2)877>, and two steroidal 1,3-oxazine derivatives <1998AXC372, 2000AXCe363>.

8.05.3.2 NMR Spectroscopy

The most useful methods for elucidation of the structures of 1,3-oxazine derivatives are ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, which have been applied extensively for the determination of their conformations and configurations. Geminal and vicinal H,H-coupling constants and ^{13}C chemical shifts (together with dynamic NMR measurements) have proved to be the most informative structural parameters. For numerous compounds, the configurations of 1,3-amino alcohols were determined via NMR analysis of their conformationally restricted 1,3-oxazine derivatives <1995JOC6515, 1997CC565, 1999EJO805, 2001JOC4759, 2006ASC2080, 2006TA1308>.

In some cases, well-definable correlations could be demonstrated between the NMR data and the structural parameters of the 1,3-oxazine molecule. The magnitude of the γ -effects on the ^{13}C chemical shifts of 3,4-dihydro-2*H*-1,3-benzoxazines **11** turned out to be influenced significantly by the substituents R^2 attached to the nitrogen atom. A correlation between the δ_{C} values and the steric substituent constants (E_{s}') of the N-substituents proved useful in characterizing the variation of the γ -effects together with the conformational factors <1995STC77>.

^1H and ^{13}C NMR studies on 4*H*-3,1-benzoxazin-4-one derivatives **12** and their acylanthranilic acid precursors **13** led to the conclusion that differentiation between these two series of compounds was best achieved through the characteristic J_{CH} coupling interactions in the high-frequency carbonyl region <2000SAA1079>.

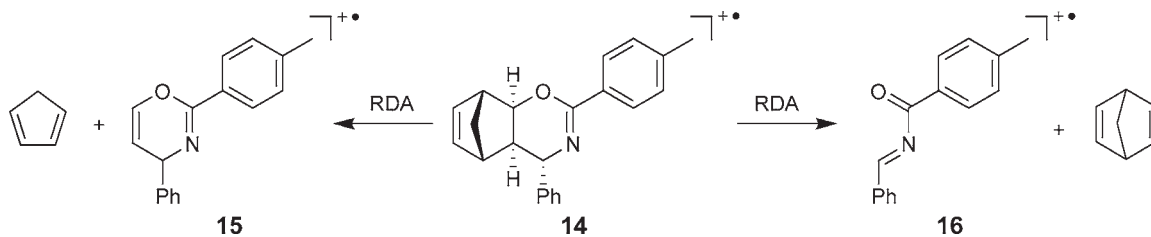


The ^{13}C NMR chemical shifts of the $\text{C}=\text{N}$ carbon in the open tautomeric forms of 2-aryl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines **5** and 1,4-dihydro-2*H*-3,1-benzoxazines **6** exhibited a reverse dependence on the benzyldenic substituents X. Electron-withdrawing substituents caused shielding (the shift was reduced), while electron-donating ones caused deshielding <2003JOC2151>.

8.05.3.3 Mass Spectrometry

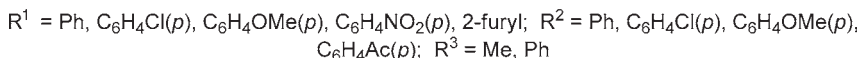
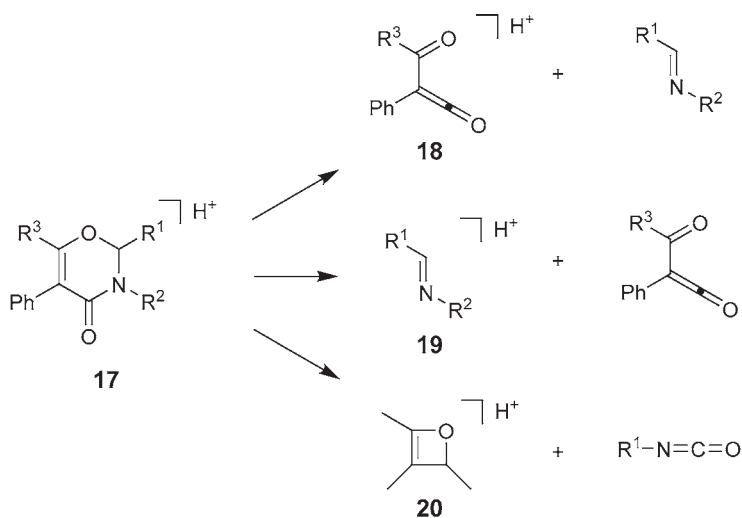
Their electron impact mass spectra indicated that the molecular ions of *diexo* norbornane-fused 1,3-oxazines underwent retro-Diels–Alder (RDA) fragmentations, leading to cleavage of the heterocyclic ring with the loss of norbornene, whereas

in the norbornene-fused analog **14**, two concurrent RDA fragmentations occurred with the loss of either cyclopentadiene or norbornadiene (Scheme 2). The RDA fragmentation processes of norbornane or norbornene-fused 1,3-oxazines have also been examined by energy-resolved electrospray mass spectrometry <1997RCM249, 1999MI253>.



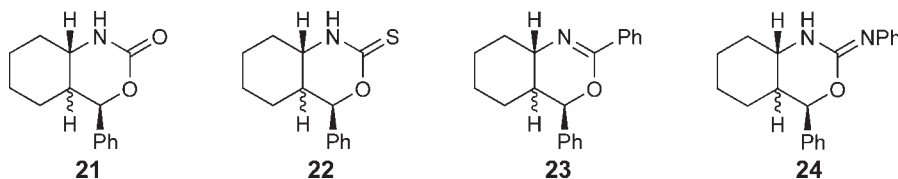
Scheme 2

The mass spectral behavior of 2,3-dihydro-4*H*-1,3-oxazin-4-ones under electrospray ionization could be characterized by a predominant RDA fragmentation pathway, producing a pair of complementary ions **18** and **19**. However, the decomposition of **17** also followed another pathway, resulting in ring contraction to form oxete ions **20** by the loss of isocyanate (Scheme 3) <2004RCM1116>.



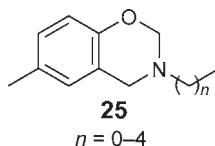
Scheme 3

The effects of stereochemistry, substitution, and (for 2-phenylimino derivatives) an intramolecular cyclization of the ions $[M-H]^+$ have been observed in the electron ionization mass spectra of *cis*- and *trans*-fused 4-phenyloctahydro-2*H*-3,1-benzoxazin-2-ones **21** and -2-thiones **22**, 2,4-diphenylhexahydro-3,1-benzoxazines **23**, and 2-phenylimino-4-phenylhexahydro-3,1-benzoxazines **24**. The mass spectral behavior was similar for the isomeric compounds, although they could usually be differentiated from each other on the basis of the relative abundances of their characteristic fragment ions <2005ARK(iv)39>.



8.05.3.4 UV/fluorescence, IR/Raman, and Photoelectron Spectroscopy

The fundamental vibrations of a series of 3-alkyl-6-methyl-3,4-dihydro-2*H*-1,3-benzoxazines **25** were assigned by analysis of the fingerprint region of their infrared (IR) and Raman spectra. The alkyl chain attached to the nitrogen atom was varied from methyl ($n=0$) to pentyl ($n=4$), which altered the position of the peaks resulting from the oxazine ring, but had little influence on the benzene ring vibrations <1995SAA1061>.

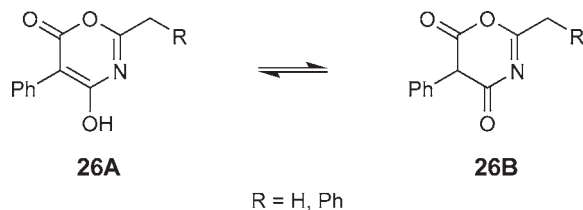


8.05.4 Thermodynamic Aspects

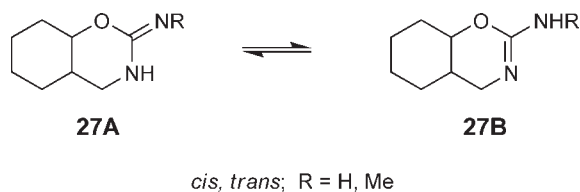
8.05.4.1 Tautomerism

8.05.4.1.1 Prototropic tautomerism

Similarly to their 2-aryl-substituted analogs <1996CHEC-II(6)301>, 2-methyl- and 2-benzyl-5-phenyl-1,3-oxazine-4,6(5*H*)-diones **26B** proved to be less favored tautomers than the corresponding 4-hydroxy-1,3-oxazin-6-ones **26A** in (CD₃)₂SO. ¹H NMR measurements showed the ratio of the tautomers **26A** and **26B** to be 55:45 for the 2-methyl- and 60:40 for the 2-benzyl-substituted derivative <2005ARK(xv)88>.

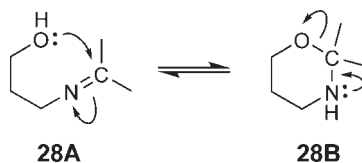


The NMR spectra of the *cis*- and *trans*-cyclohexane-condensed 1,3-oxazine derivatives **27** exhibited no sign of tautomeric equilibria between the imino and amino forms, but all four compounds appeared to attain (at least almost) exclusively the 2-imino-1,3-oxazine form **27A** <2003MRC435>.



8.05.4.1.2 Ring-chain tautomerism

The structures and reactivities of N-unsubstituted saturated 1,3-oxazines can be characterized by their ring-chain tautomerism, that is, the reversible intramolecular addition of an OH group to a C=N bond to form a cyclic structure. According to the Baldwin rules, the ring closure of **28A** to **28B** is a favored process (6-*endo-trig*). The ring-chain tautomeric equilibria of various 1,3-oxazine derivatives have been investigated intensively in recent years and several reviews covering certain parts of this topic have been published since 1995 <1996AHC(66)1, 1998AHC(69)349, 2002RCB205, 2003EJO3025, 2004CSY155>.



For the tautomeric equilibria of perhydro-1,3-oxazines and their benzo derivatives bearing an X-substituted phenyl group at position 2, the proportion of the ring-closed forms has been found to be strongly dependent on the electronic character of the substituent X on the phenyl ring. For these compounds, a linear correlation (Equation 1) has been found between the $\log K_X$ values of the equilibria ($K_X = [\text{ring}]/[\text{chain}]$) and the Hammett–Brown parameters σ^+ of the substituents X on the 2-aryl group:

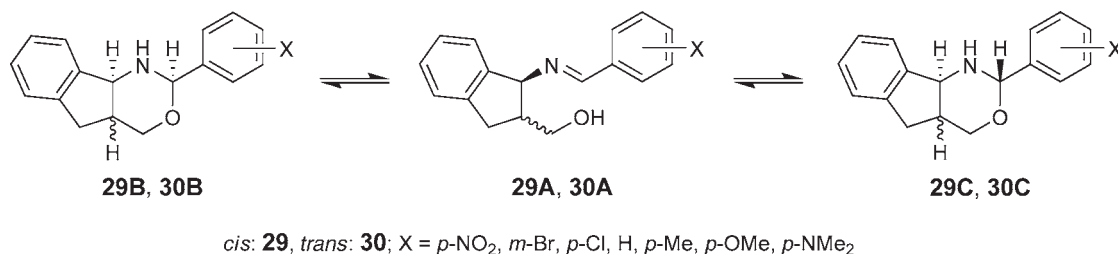
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

The values of ρ have been accurately determined for numerous perhydro-1,3-oxazines and their benzo analogs, and the electronic character of a substituent at position 2 can therefore be calculated via Equation (1) by measuring the ring–chain ratios. This principle has been applied to determine the σ^+ values for numerous substituents X (X = *para*-situated 1-imidazolyl, 1-benzimidazolyl, 1-benzotriazolyl, 2-benzotriazolyl, and 1,2,4-triazolo[2,3-*a*]pyridin-2-yl) via their 2-(X-phenyl)perhydro-1,3-oxazine derivatives <1997JHC289, 1998MI653>.

To characterize the electronic and steric effects of the substituents at positions 4–6 on the stability of the 2-aryl-1,3-oxazine ring forms exhibiting ring–chain tautomerism, a relative ring stability parameter (c) has been introduced. The value of c is calculated as the difference between the value of $\log K_{X=H}$ for a 2-aryl-1,3-oxazine derivative bearing substituents at positions 4–6 and the intercept value ($\log K_0 = -0.15$) for the parent unsubstituted 2-arylperhydro-1,3-oxazine ($c = \log K_{X=H} - \log K_0$).

The scope and limitations of Equation (1) have been thoroughly studied from the aspects of the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in that equation, and the applicability of Equation (1) in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms.

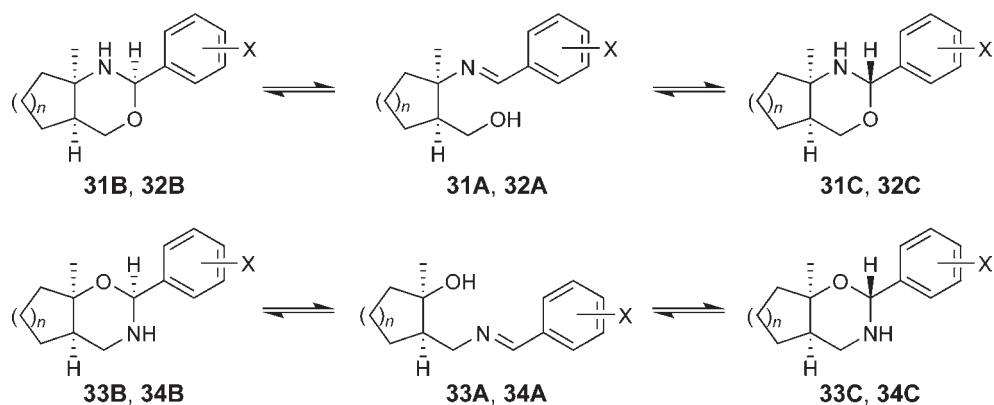
The stereochemistry of the connection of the saturated rings has a dramatic influence on the ring–chain tautomerism of indane-condensed 2-arylperhydro-1,3-oxazines **29** and **30** (Scheme 4). For the *cis*-fused isomers **29**, three-component tautomeric equilibria with an open (**29A**) and C-2-epimeric ring forms (minor: **29B**, major: **29C**) (CDCl₃, 300 K) have been observed that can be characterized by Equation (1). For the *trans*-isomers **30**, the tautomeric equilibria are shifted virtually quantitatively toward the open tautomer **30A**, even in the case of a compound bearing a strong electron-withdrawing substituent X (**30**: X = *p*-NO₂). The difference in the tautomeric behavior of the isomers of **29** and **30** has been explained in terms of the distance of the OH group from the N=CH bond, which is too large in the *trans*-isomer **30**, with a resultant substantial increase in the energy barrier of intramolecular proton transfer <2004JHC69>.



Scheme 4

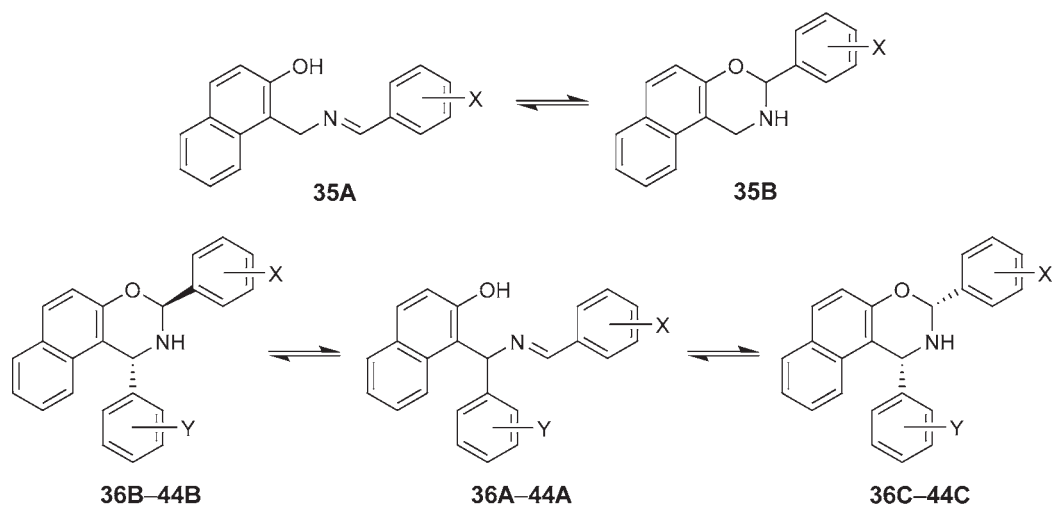
On annelation, a methyl group causes opposite effects on the stabilities of the ring forms in the three-component tautomeric equilibria of regioisomeric 2-aryltetrahydro-1,3-oxazines *cis*-connected to a cyclopentane or cyclohexane ring at positions 4,5 **31** and **32** or 5,6 **33** and **34** (Scheme 5). In the equilibria of **31** and **32**, the ring-closed tautomers (major: **B**, minor: **C**) are present in higher proportions than in the corresponding oxazines not containing this methyl group, but the opposite has been found for **33** and **34**. It is presumed that this reverse stabilization effect of the bridgehead methyl group arises from relative destabilization of the open tautomers of **31** and **32**, and of the cyclic forms of **33** and **34** <1998T1013>.

Aryl substituents on the 1,3-oxazine ring give rise to a characteristic effect on the two- or three-component ring–chain tautomeric equilibria of 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **35–44** and the regioisomeric 3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines **45–51** (Scheme 6). The major ring forms of the equilibria **36–51** contain the 1,3- or



$n = 1$: **31, 33**; $n = 2$: **32, 34**; $X = p\text{-NO}_2, m\text{-NO}_2, p\text{-Br}, p\text{-Cl}, m\text{-OMe}, \text{H}, p\text{-Me}, p\text{-OMe}, p\text{-NMe}_2$

Scheme 5



$Y = p\text{-NO}_2$: **36**, $m\text{-NO}_2$: **37**, $m\text{-Br}$: **38**, $p\text{-Br}$: **39**, $p\text{-Cl}$: **40**, H : **41**, $p\text{-F}$: **42**, $p\text{-Me}$: **43**, $p\text{-OMe}$: **44**

$Y = m\text{-NO}_2$: **45**, $m\text{-Br}$: **46**, $p\text{-Br}$: **47**, $p\text{-Cl}$: **48**, H : **49**, $p\text{-Me}$: **50**, $p\text{-OMe}$: **51**
 $X = p\text{-NO}_2, m\text{-Br}, p\text{-Br}, p\text{-Cl}, m\text{-OMe}, \text{H}, p\text{-Me}, p\text{-OMe}, p\text{-NMe}_2$

Scheme 6

2,4-diaryl substituents in the *trans*-position (**B**). In consequence of the annelated naphthalene ring, increased ring stability as compared with the parent unsubstituted compound is observed for **35B** and all 1,3-diarylnaphth[1,2-*e*] [1,3]oxazines bearing *trans* diaryl substituents **36B–44B** (Table 1) <2003T2877, 2004EJO2231>. The double substituent effects of the aryl groups on the tautomeric ratios for the equilibria involving the *trans* cyclic and the open forms (**B** $\rightleftharpoons$ **A**) can be characterized by a Hansch-type equation (Equation 2) for both regioisomeric naphthoxazines bearing *p*-Y substituents **36**, **39–44**, and **47–51**. The inductive effect (σ_F) of substituent Y has

Table 1 Substituent effects on the ring-chain equilibria of 2-aryl-substituted perhydro-1,3-oxazines in CDCl₃. Linear regression analysis data according to Equation (1)

<i>Equilibrium</i>	<i>No. of points</i>	<i>Slope (ρ)</i>	<i>Intercept ($\log K_{X=H}$)</i>	<i>Correlation coefficient</i>	<i>c</i>	<i>Reference</i>
29A $\rightleftharpoons$ 29B	7	0.78	0.32	0.981	0.47	2004JHC69
30A $\rightleftharpoons$ 30C	7	0.81	0.42	0.979	0.57	2004JHC69
31A $\rightleftharpoons$ 31B + 31C	9	0.69	1.21	0.994	1.36	1998T1013
32A $\rightleftharpoons$ 32B + 32C	8	0.81	1.39	0.986	1.54	1998T1013
33A $\rightleftharpoons$ 33B + 33C	9	0.76	−0.07	0.988	0.08	1998T1013
34A $\rightleftharpoons$ 34B + 34C	7	0.76	−0.73	0.971	−0.58	1998T1013
35A $\rightleftharpoons$ 35B	7	0.81	0.52	0.994	0.67	2003T2877
37A $\rightleftharpoons$ 37B	7	0.93	0.70	0.995	0.85	2003T2877
37A $\rightleftharpoons$ 37C	6	1.04	−0.33	0.999	−0.18	2003T2877
38A $\rightleftharpoons$ 38B	7	1.00	0.64	0.985	0.79	2003T2877
38A $\rightleftharpoons$ 38C	6	1.01	−0.33	0.985	−0.18	2003T2877
40A $\rightleftharpoons$ 40B	7	0.96	0.62	0.993	0.77	2003T2877
40A $\rightleftharpoons$ 40C	6	0.81	−0.42	0.979	−0.27	2003T2877
41A $\rightleftharpoons$ 41B	7	0.92	0.53	0.988	0.68	2003T2877
41A $\rightleftharpoons$ 41C	6	0.98	−0.34	0.983	−0.19	2003T2877
43A $\rightleftharpoons$ 43B	7	0.95	0.49	0.989	0.64	2003T2877
43A $\rightleftharpoons$ 43C	6	0.95	−0.42	0.993	−0.27	2003T2877
44A $\rightleftharpoons$ 44B	7	0.95	0.52	0.991	0.67	2003T2877
44A $\rightleftharpoons$ 44C	6	0.94	−0.40	0.986	−0.25	2003T2877
45A $\rightleftharpoons$ 45B	7	0.95	−0.12	0.992	0.03	2004EJO2231
45A $\rightleftharpoons$ 45C	7	0.97	−0.45	0.994	−0.30	2004EJO2231
46A $\rightleftharpoons$ 46B	7	1.07	−0.22	0.997	−0.07	2004EJO2231
46A $\rightleftharpoons$ 46C	7	1.09	−0.45	0.998	−0.30	2004EJO2231
47A $\rightleftharpoons$ 47B	7	0.93	−0.18	0.977	−0.03	2004EJO2231
47A $\rightleftharpoons$ 47C	7	0.91	−0.41	0.988	−0.26	2004EJO2231
48A $\rightleftharpoons$ 48B	7	0.93	−0.20	0.981	−0.05	2004EJO2231
48A $\rightleftharpoons$ 48C	7	0.91	−0.39	0.991	−0.24	2004EJO2231
49A $\rightleftharpoons$ 49B	7	0.92	−0.27	0.9814	−0.12	2004EJO2231
49A $\rightleftharpoons$ 49C	7	0.90	−0.40	0.994	−0.25	2004EJO2231
50A $\rightleftharpoons$ 50B	7	0.97	−0.33	0.984	−0.18	2004EJO2231
50A $\rightleftharpoons$ 50C	7	0.97	−0.42	0.994	−0.27	2004EJO2231
51A $\rightleftharpoons$ 51B	7	0.92	−0.26	0.991	−0.11	2004EJO2231
51A $\rightleftharpoons$ 51C	7	0.86	−0.36	0.994	−0.21	2004EJO2231
64A $\rightleftharpoons$ 64B + 64C	9	0.67	−0.48	0.991	−0.33	1997T1081
65A $\rightleftharpoons$ 65B	7	0.72	−1.32	0.983	−1.17	2003JOC2175
65A $\rightleftharpoons$ 65C	7	0.74	−0.22	0.986	−0.07	2003JOC2175
66A $\rightleftharpoons$ 66B	7	0.75	−0.05	0.968	0.10	2003JOC2175
66A $\rightleftharpoons$ 66C	7	0.75	−0.68	0.976	−0.53	2003JOC2175
71A $\rightleftharpoons$ 71B	6	0.68	0.36	0.995	0.51	1999JOC1166
71B $\rightleftharpoons$ 71C	6	0.69	0.35	0.992	0.50	1999JOC1166
72A $\rightleftharpoons$ 72B ^a			0.09		0.24	1999JOC1166
72B $\rightleftharpoons$ 72C ^a			−0.78		−0.68	1999JOC1166
73A $\rightleftharpoons$ 73B	6	0.65	0.80	0.999	0.95	1999JOC1166
73B $\rightleftharpoons$ 73C	6	0.52	1.19	0.993	1.34	1999JOC1166
74A $\rightleftharpoons$ 74B ^a			1.15		1.30	1999JOC1166
74B $\rightleftharpoons$ 74C ^a			−1.32		−1.17	1999JOC1166

^aFor the equilibrium in (CD₃)₂SO.

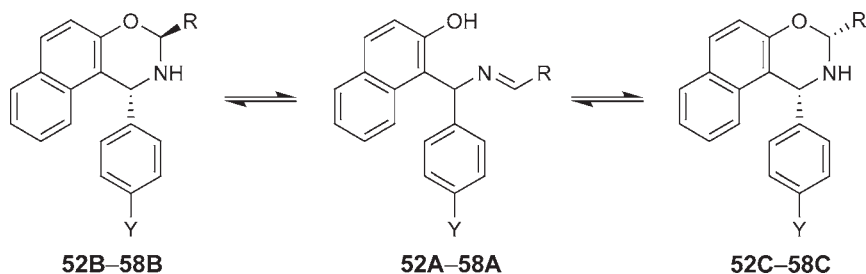
been found to cause a significant effect on the equilibria ($\rho_F^{(Y)}$: 0.33 for **36**, **39–44**, and 0.28 for **47–51**), but the resonance effect (σ_R) of Y is insignificant ($\rho_R^{(Y)}$: ~ 0) for both sets of compounds <2004EJO2231, 2004JOC3645, 2005MI18>.

$$\log K_X = \rho^{(X)} \sigma^{+(X)} + \rho_F^{(Y)} \sigma_F^{(Y)} + \rho_R^{(Y)} \sigma_R^{(Y)} + k \quad (2)$$

The effects of both alkyl and aryl substituents can be observed in the two-component tautomeric equilibria of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines containing C-3-epimeric naphthoxazines **52B–58B** and **52C–58C** (Scheme 7). The influence of the Meyer parameters (V^a) of the alkyl substituents on the epimerization constants (K_R) ($K_R = [B]/[C]$) can be characterized by Equation (3). Multiple linear regression analysis of $\log K_R$ according to Equation (4) leads to the conclusion that these equilibria are also influenced significantly by the inductive effect of substituent Y ($\rho_F^{(Y)}$: 0.48) <2004JOC3645>.

$$\log K_R = 0.55 + 7.88 V^a \quad (3)$$

$$\log K_R = \rho^{(R)} V^a + \rho_F^{(Y)} \sigma_F^{(Y)} + \rho_R^{(Y)} \sigma_R^{(Y)} + k \quad (4)$$

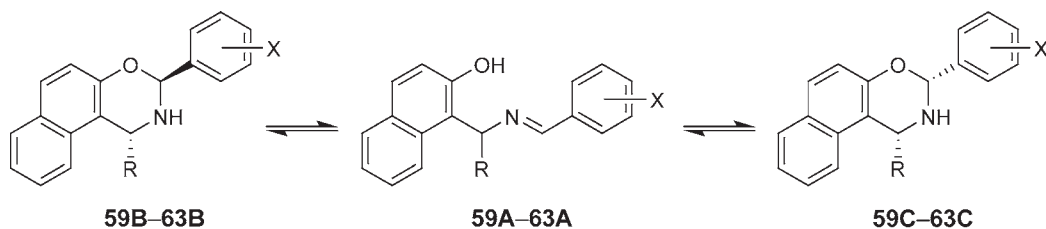


Y = NO₂: **52**, Br: **53**, Cl: **54**, H: **55**, F: **56**, Me: **57**, OMe: **58**; R = Me, Et, Pr, Prⁱ, Bu^t

Scheme 7

In the ring–chain tautomeric equilibria of 1-alkyl-3-arylnaphth[1,2-*e*]oxazines **59–63** in CDCl₃, in contrast with their regioisomers **52–58**, three tautomeric forms $B \rightleftharpoons A \rightleftharpoons C$ could be detected (Scheme 8), with the exception of the *tert*-butyl-substituted derivatives **63**, for which the equilibria were shifted totally toward the open form A. To characterize the substituent effects on the three-component system, a Hansch-type equation (Equation 5) proved to describe with a good correlation both the effects of the electronic character (σ^+) of the aromatic substituents and the Meyer parameters (V^a) of the alkyl substituents on the equilibria. The differences in the parameters of Equation (5) for the equilibria $[B]/[A]$ and $[C]/[A]$ were explained by the different anomeric effects of the substituents in the C-2-epimeric ring forms <2006EJO4664, 2006EJO4670>.

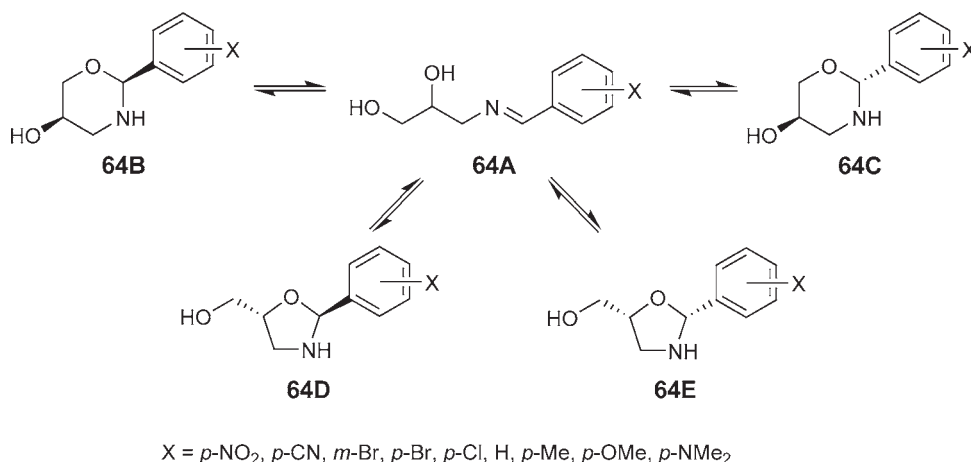
$$\log K = k + \rho^{(R)} V^a + \rho^{(X)} \sigma^+ \quad (5)$$



R = Me: **59**, Et: **60**, Pr: **61**, Prⁱ: **62**, Bu^t: **63**
X = *p*-NO₂, *m*-Cl, *p*-Br, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe₂

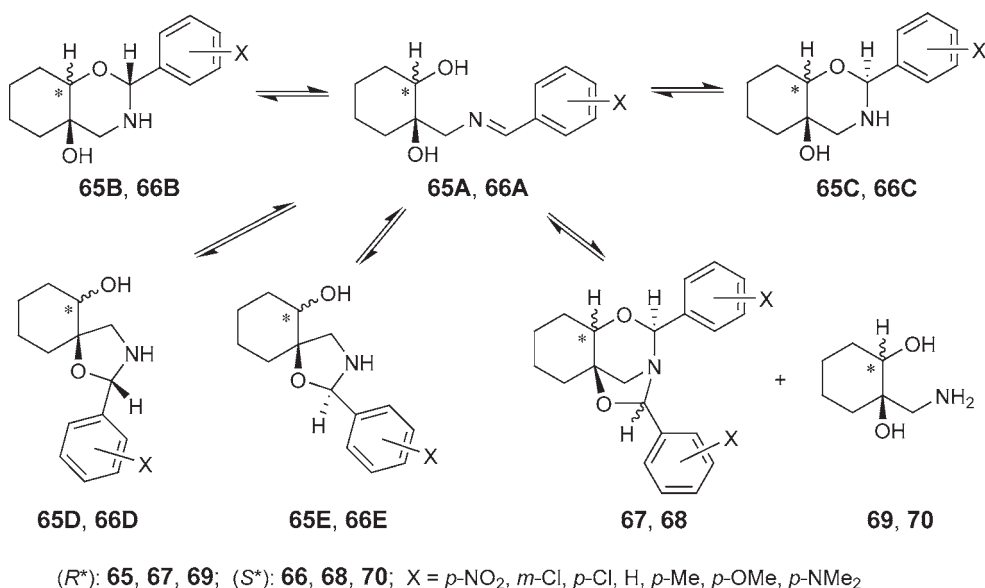
Scheme 8

The ring-chain tautomerism of the Schiff bases **64A** containing 1,2- and 1,3-amino alcohol moieties results in five-component tautomeric mixtures containing C-2-epimeric 2-aryltetrahydro-1,3-oxazines **64B** and **64C** and 2-aryloxazolidines **64D** and **64E** (Scheme 9). The ratios of the two types of ring-closed forms in the equilibria of **64** can be described by Equation (1) (Table 1). The equilibria of **64A–E** prove that, when two types of ring closure are possible in a ring-chain tautomeric process, the favored *6-endo-trig*-route does not exclude ring closure via the unfavored *5-endo-trig*-route <1997T1081>. The ring-chain tautomerism of **64** could also be detected in the gas phase by mass spectrometry <1995RCM916>.



Scheme 9

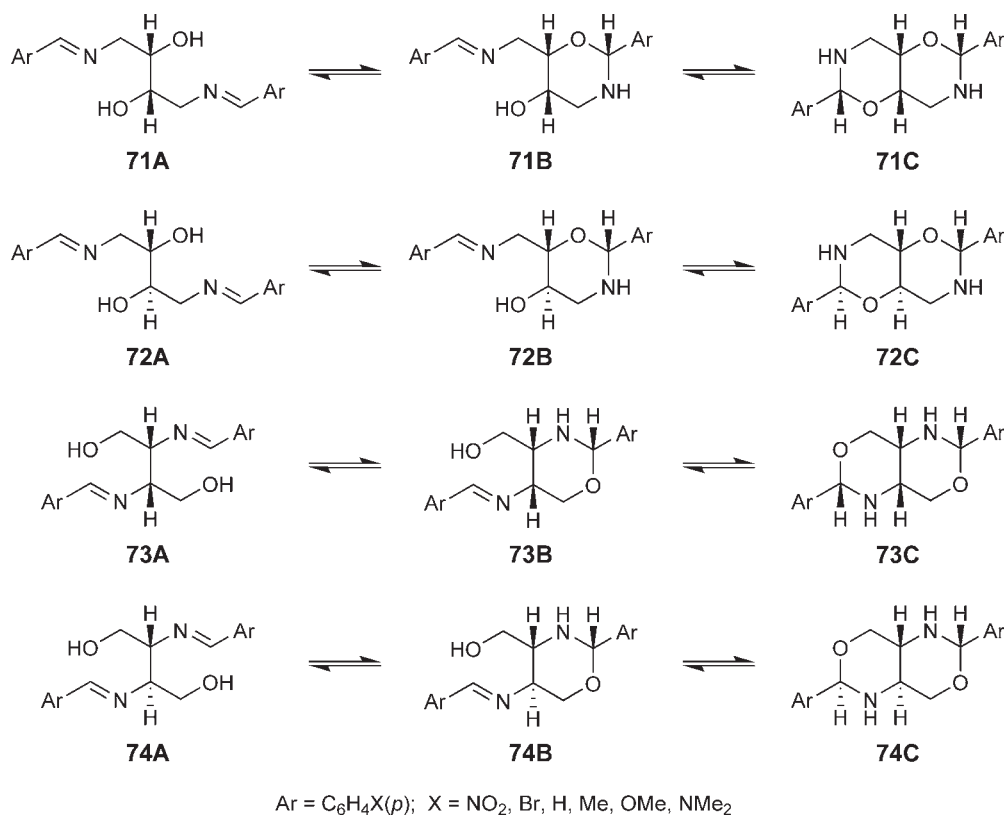
Both single and double cyclizations of the Schiff bases **65A** and **66A** occur in the multicomponent tautomeric mixtures derived from *cis*- and *trans*-cyclohexane aminodiols **69** and **70**, to give monocyclized ring forms of C-2-epimeric perhydro-1,3-benzoxazines (B and C) and oxazolidines (D and E), besides 7,11-dioxo-9-azatricyclo[7.2.1.0^{1,6}]-dodecane diastereomers **67** and **68** (Scheme 10). The tautomeric ratios are found to satisfy by Equation (1) (Table 1) and are influenced by the *cis*- or *trans*-geometry of the cyclohexane substituents in the Schiff base (A). For the equilibria



Scheme 10

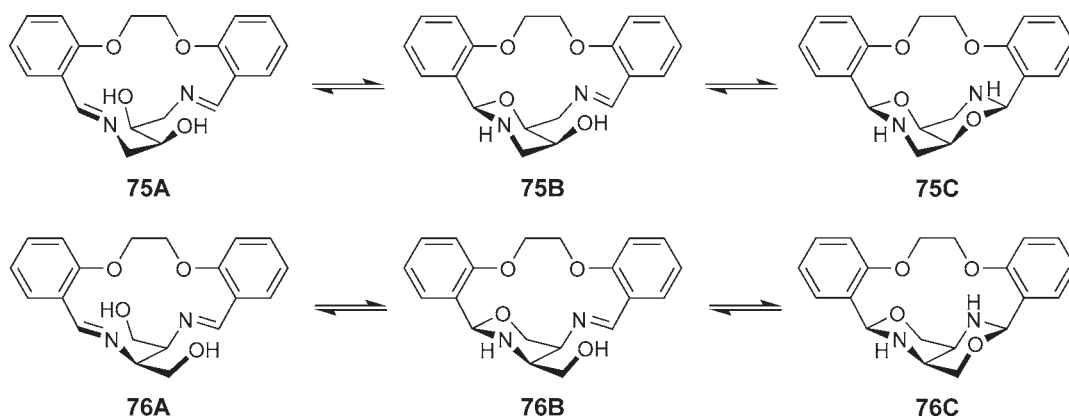
derived from the *cis*- open form **65A**, **65C** is the major monocyclized tautomer, while for the *trans*-counterparts **66B** proves to be the corresponding major monocyclized component. The unusual formation of the tricycles **67** and **68** has been rationalized in terms of aldehyde-transfer reactions between the open forms **65A** or **66A** and the major monocyclic tautomeric forms **65C** or **66D** <2003JOC2175>.

The condensation products **71–74** of *erythro*- and *threo*-1,4-diamino-2,3-butanediol and 2,3-diamino-1,4-butanediol with 2 equiv of aromatic aldehydes participate in two-step ring–chain tautomeric equilibria involving perhydro-1,3-oxazine (**B**) and dioxadiazadecalin (**C**) tautomeric forms besides the Schiff bases (**A**) (Scheme 11). Both of the consecutive ring closures to give 1,3-oxazines are stereoselective, yielding the mono- and bicyclic forms **B** and **C** as the main diastereomers, with the configurations depicted in Scheme 11. Each equilibrium of type $A \rightleftharpoons B$ and of type $B \rightleftharpoons C$ for **71** and **73** can be characterized by Equation (1), but the values of $\log K_{X=H}$ can also be determined for the equilibria of **72** and **74** (Table 1). In contrast with the cyclohexane-condensed 2-arylperhydro-1,3-oxazines, where the *trans*-fused rings increase the stability of the ring-closed tautomers to a higher extent than the *cis* ring junction, the values of c indicate more stability for the *cis*-fused dioxadiazadecalins **71C** and **73C** than for their *trans*-fused counterparts **72C** and **74C** <1997TL3573, 1999JOC1166, 2001EJO729>.



Scheme 11

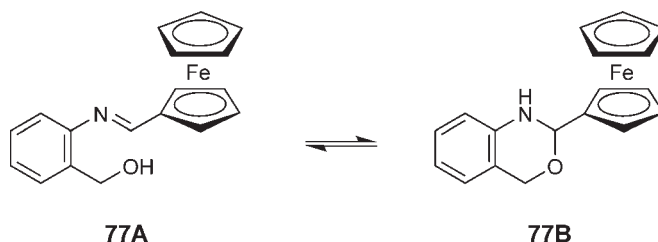
As a consequence of the ring–chain tautomeric process, macrocycles containing a perhydro-1,3-oxazine unit(s) (e.g., **75** and **76**) can be regarded as dynamic combinatorial virtual libraries. The equilibria of **75** and **76** are shifted toward the double ring-closed tautomers (**C**) both in CDCl₃ and in (CD₃)₂SO solution at 298 K. Heating of the solutions does not cause any change in the tautomeric ratios for **75** in CDCl₃ or for **76** in either solvent, but elevated temperatures lead to increases in the proportions of the open and the monocyclic tautomers (**A** and **B**) in the equilibria of **75** in (CD₃)₂SO (Scheme 12). The ring–chain tautomerism exerts a strong influence on the cavity size and therefore on the metal ion complexation processes of **75**. Ni²⁺, Cd²⁺, and Pb²⁺ are complexed by **75** in different tautomeric modes, depending on the size of the cation. The metal ion complexation properties of **76** are not influenced by the ring–chain tautomerism <2000AGE2685, 2001JOM(630)67>.



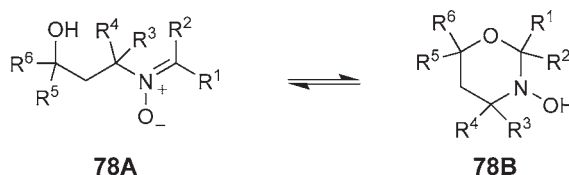
Scheme 12

As a further interesting extension of the ring-chain tautomeric concept, 2-aryl-1,4-dihydro-2*H*-3,1-benzoxazines encapsulated in a cage macromolecule exhibited different tautomeric ratios inside the cavity than those measured in deuterated mesitylene solution <2006JA9308>.

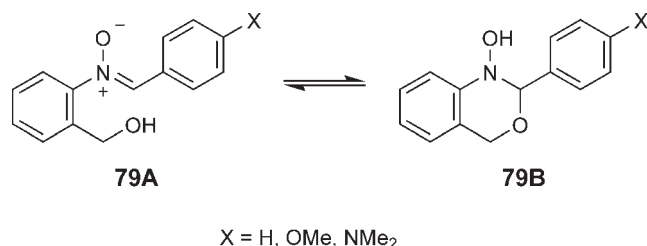
The condensation product **77** of ferrocenecarbaldehyde and 2-aminobenzyl alcohol exhibits solvent-dependent ring-chain tautomerism, in which the proportion of the ring form **77B** decreases as the dielectric constant of the solvent increases ([**77B**]/[**77A**]: 13.7 [C_6D_6], 2.50 [$(CD_3)_2CO$], 1.1 [$(CD_3)_2SO$], and 0.5 [CD_3OD]). As a consequence of the stronger electron-donor ability of the ferrocenyl group than that of the phenyl substituent, the tautomeric equilibrium of **77** involves a higher concentration of the open tautomeric form (**B**) than that in the corresponding equilibrium of 2-phenyl-1,4-dihydro-2*H*-3,1-benzoxazine <2005JOC4857, 2006OM596>.



3-Hydroxyperhydropyrido-1,3-oxazines have been found to participate in the ring-chain tautomeric equilibria of the open nitron (**78A**) and the corresponding cyclic hydroxylamine (**78B**) forms in $CDCl_3$. The tautomeric ratios for **78** depend strongly on the substituents: the cyclic forms **78B** are the predominant tautomers for 6-monosubstituted derivatives ($R^5 = H$; $R^6 = Ph, CH_2OH$), while for the 6,6-disubstituted ester **78** ($R^5 = Me$; $R^6 = CO_2Me$) the equilibrium undergoes a slow but quantitative shift toward the nitron form **78A** <1998T12959, 1999J(P2)877>.

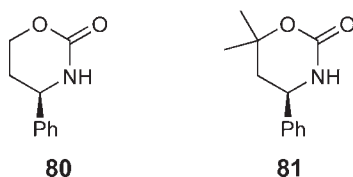


The electronic effect of the substituent X on the 2-phenyl ring proved to influence the ring-chain tautomeric equilibria of 2-aryl-1-hydroxy-1,4-dihydro-2*H*-3,1-benzoxazines **79**. While the proportion of the cyclic tautomer **B** in $CDCl_3$ was 90% for the unsubstituted ($X = H$) and 70% for the *p*-methoxy derivative ($X = OMe$), no cyclic form could be detected in the case of the *p*-dimethylamino compound ($X = NMe_2$). Independently of the substituent X, the tautomeric equilibria of the regioisomeric 2-aryl-3-hydroxy-3,4-dihydro-2*H*-1,3-benzoxazines likewise contained no detectable amounts of the cyclic forms <1997CJC1830, 1998CJC389>.

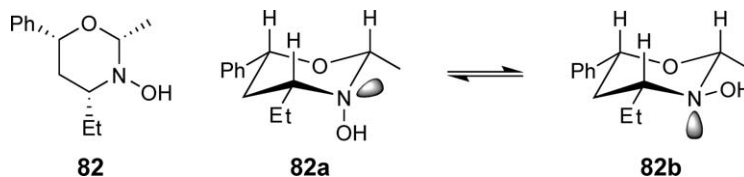


8.05.4.2 Conformational Aspects

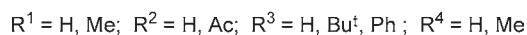
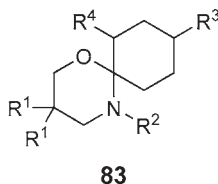
Methyl substituents at position 6 caused a change in the solid-state conformations of 4-phenyltetrahydro-1,3-oxazin-2-ones **80** and **81**. In the 6-unsubstituted heterocycle **80**, the 4-phenyl group was situated in an axial position, whereas 1,3-interactions arising from the presence of geminal methyl groups at position 6 of **81** led to an equatorial orientation for the 4-phenyl substituent [<2006OBC2753>](#).



The conformational equilibria of 3-hydroxytetrahydro-1,3-oxazines and their 3-acetyloxy derivatives were found to be shifted toward conformers in which the lone pair on the nitrogen displayed an equatorial orientation. The preferred conformation was stabilized by a strong anomeric effect. The ^1H NMR spectrum of **82** indicated the presence of the major and minor conformers **82a** and **82b** in a ratio of ca. 4:1 in CDCl_3 at 243 K [<1999SAA1445, 1999J\(P2\)877>](#).

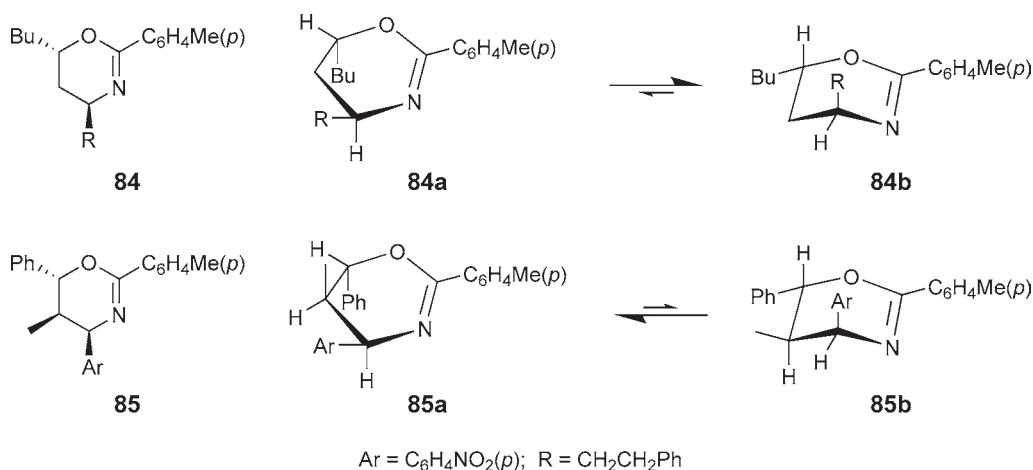


The flexible, semi-flexible, or anancomeric behavior of tetrahydro-1,3-oxazines **83** spiro-connected to cyclohexane was studied by NMR spectroscopy. The possible stereoisomers were deduced by taking into account the special chirality of the heterocycle and the spiro skeleton [<2000M975>](#).

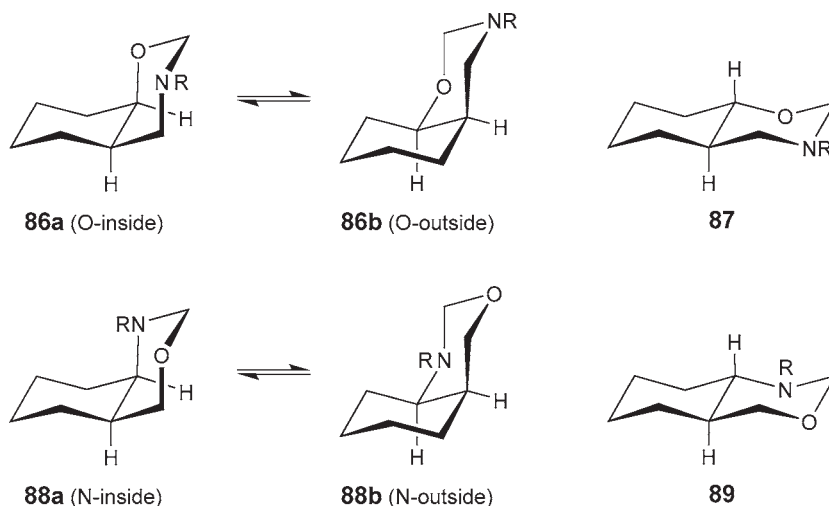


Both steric repulsion and anomeric effects proved to influence the conformational equilibria of 5,6-dihydro-4*H*-1,3-oxazines involving half-boat structures. For the *trans*-4,6-dialkyl-substituted compound **84**, the conformational equilibrium was driven by steric repulsion; it appeared that a 6-alkyl group in the axial position **84a** is more hindered than an axial 4-alkyl **84b**. However, for the *trans*-4,6-diaryl-substituted derivative **85**, the major conformation in the

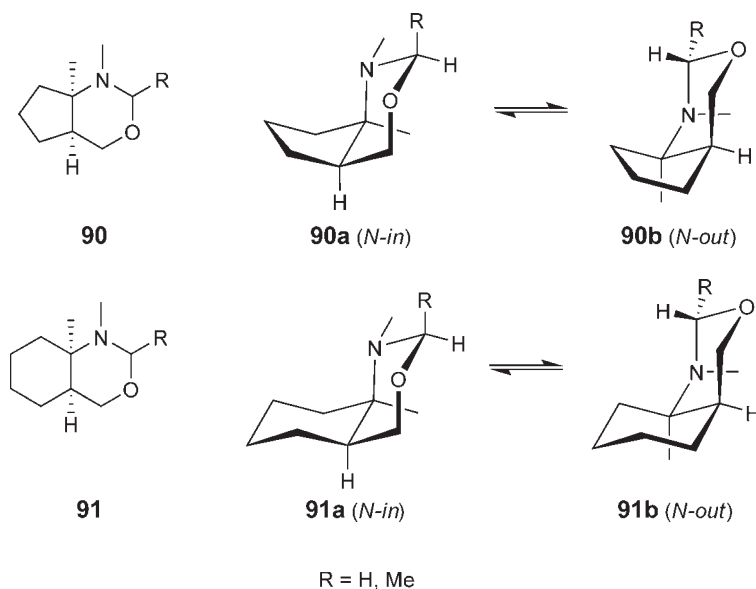
equilibrium was the one with an axial 6-aryl group **85a**. This difference was explained by an anomeric interaction between the oxygen of the 1,3-oxazine ring and the sp^2 carbon attached to position 6 <2001J(P2)530>.



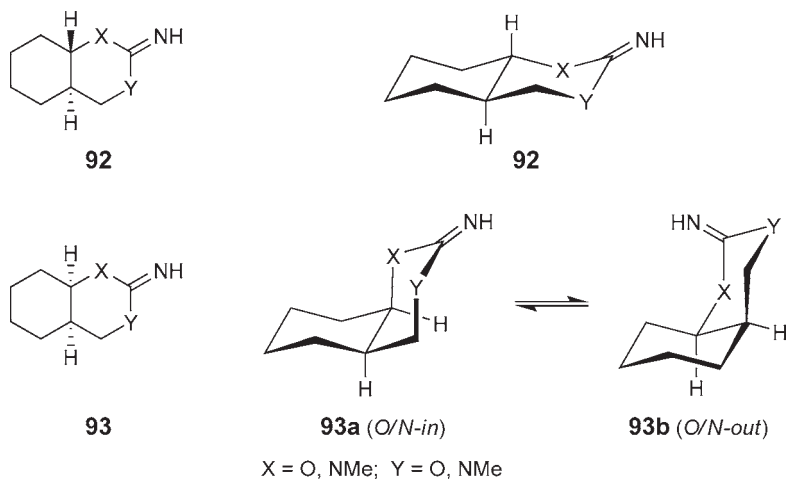
Studies on the stereostructures of *cis*- and *trans*-perhydro-1,3- and 3,1-benzoxazines **86–89** revealed that *trans*-fused derivatives **87** and **89** attain a biased chair-chair conformation, while their *cis*-counterparts **86** and **88** can be characterized by conformational equilibria of the O-in/N-in (**a**) and O-out/N-out (**b**) isomers, which, for 3,1-benzoxazines **88**, are strongly influenced by the bulkiness of the substituent R attached to the nitrogen <1996CHEC-II(6)301, 1998AHC(69)349>.



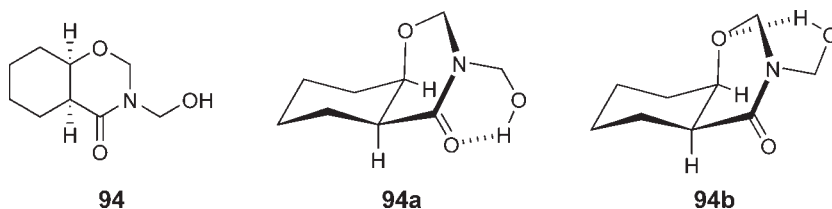
The conformational equilibria of tetrahydro-1,3-oxazines *cis*-fused to cyclopentane or cyclohexane, and bearing a methyl substituent at the annelation (**90** and **91**), have been studied by NMR spectroscopic methods. The 2-unsubstituted derivatives **90** and **91** (R = H) were present in CDCl₃ as rapidly interconverting equilibria of the N-in and N-out conformers. As a consequence of their ring-chain tautomeric character, the 2-methyl derivatives **90** and **91** (R = Me) were each found to be mixtures of interconvertible C-2 epimers, with the N-in conformer predominating for one epimer **90a** and **91a** and the N-out conformer predominating for the other **90b** and **91b**, both predominant conformers having the 2-methyl group oriented equatorially. The methyl substituent on the nitrogen was found to be mainly equatorial for the N-in conformers (**a**), while for the epimeric 2-methyl derivatives with N-out conformations (**b**) the *N*-methyl substituent was oriented axially due to both steric hindrance and the generalized anomeric effect <2002CH187>. Similarly, in CDCl₃ at ambient temperature, *cis*-1,2-dimethylperhydro-3,1-benzoxazine, lacking the methyl group at the annelation, was found to be a ca. 3:2 mixture of two C-2 epimers with the N-in and N-out conformations <1996MRC998>.



From a structural analysis of *cis*- and *trans*-2-imino-1,3- and -3,1-perhydrobenzoxazines **92** and **93**, it was concluded that all these *trans*-fused compounds exist in biased chair-chair conformations **92**, as expected, whereas the *cis*-fused 1,3-benzoxazines **93** (X = O, Y = NMe) attain exclusively the O-in conformations **93a**. For the *cis*-fused 3,1-benzoxazines **93** (X = NMe, Y = O), predominance of the *N-out* form **93b** was found, owing to the favorable axial orientation of the *N*-methyl substituent <2003MRC435>.



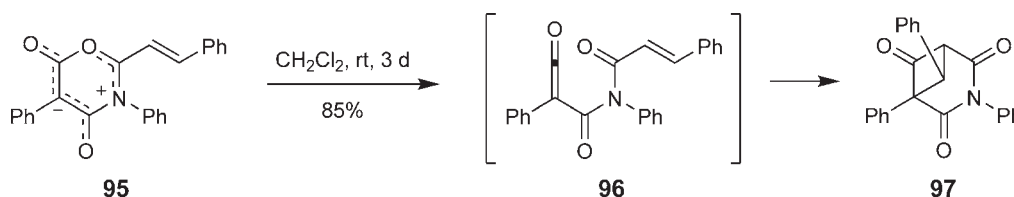
^1H and ^{13}C NMR conformational studies indicated that *cis*-3-(hydroxymethyl)perhydro-1,3-benzoxazin-4-one **94** could be characterized by an O-in predominant conformation consisting of two intramolecularly hydrogen-bonded forms (between the hydroxy proton and the carbonyl oxygen **94a** or the oxygen of the 1,3-oxazine ring **94b**) and a non-hydrogen-bonded form <2001MRC141>.



8.05.5 Reactivity of Fully Conjugated Rings

8.05.5.1 Unimolecular Thermal and Photochemical Reactions

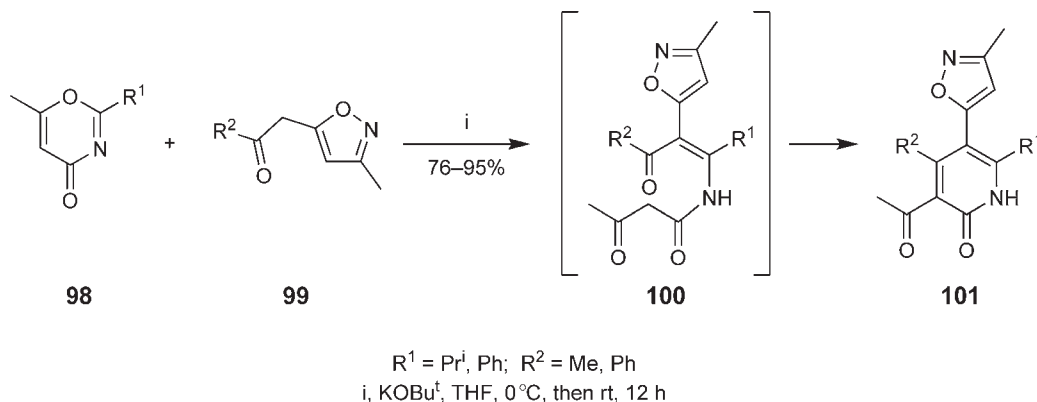
Mesoionic 1,3-oxazinium olate **95** underwent pseudo-pericyclic ring opening to the transient amidylketene **96**, which was recycled to 3-azabicyclo[3.1.1]heptanetrione **97** by criss-cross [2+2] cycloaddition of the vinyl substituent to the ketene C=C bond (Scheme 13). The energy surface connecting oxazinium olate **95**, several possible conformers of ketene **96**, and the cyclization product **97** were evaluated computationally at the B3LYP/6-31G* level <2005JOC5859, 2005JOC5862>.



Scheme 13

8.05.5.2 Nucleophilic Attack on Carbon

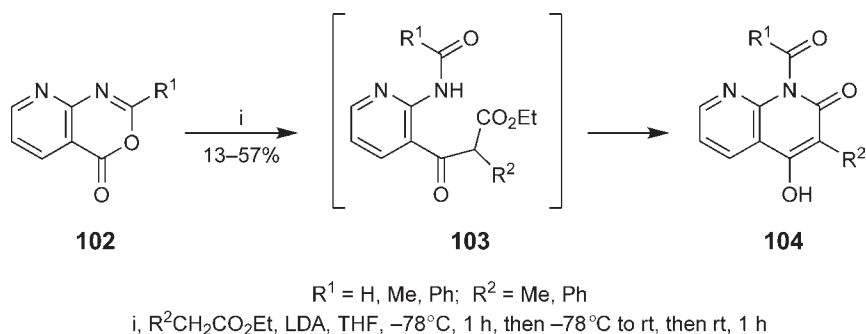
The reactions of 2-substituted 6-methyl-4*H*-1,3-oxazin-4-ones **98** with isoxazole ketones **99** in the presence of potassium *tert*-butoxide furnished 3-acetyl-5-(3-methylisoxazol-5-yl)-2-pyridones **101** in good to excellent yields (Scheme 14). The formation of 2-pyridones **101** presumably proceeds via nucleophilic addition of the methylene carbon of **99** to the carbon atom at position 2 of the 1,3-oxazin-4-ones **98**, followed by ring opening to give the acetoacetyl intermediates **100**, which are transformed into **101** by intramolecular aldol condensation <2005H(66)299>.



Scheme 14

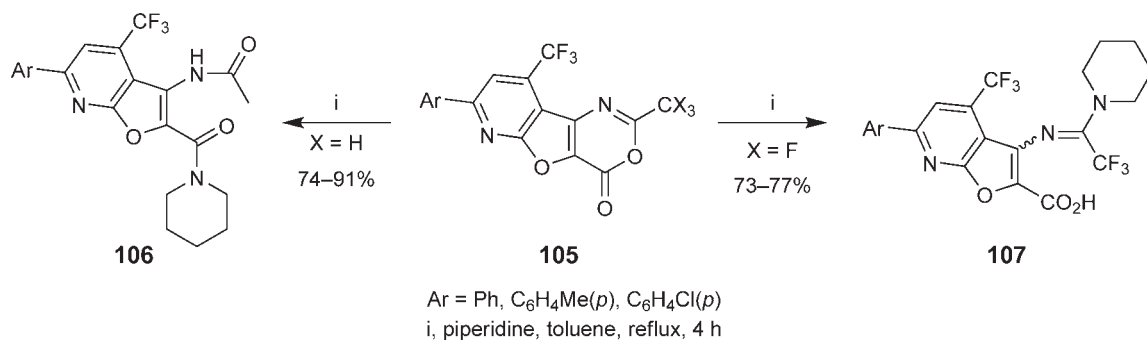
Nucleophilic ring opening of 4*H*-pyrido[2,3-*d*][1,3]oxazin-4-ones **102** by ester enolates led to the ketoester intermediates **103**, which underwent spontaneous cyclization under the conditions employed to give 1-acyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones **104** in low to moderate yields (Scheme 15) <2003JOC4567>.

The flash vacuum thermolysis of 4-hydroxy-2,5-diphenyl-1,3-oxazin-6-one resulted in carboxy(phenyl)ketene and benzonitrile as the major and benzoyl isocyanate as the minor product. This was interpreted in terms of the influence of the tautomeric forms on the thermal fragmentation pathways <2007JOC1399>.



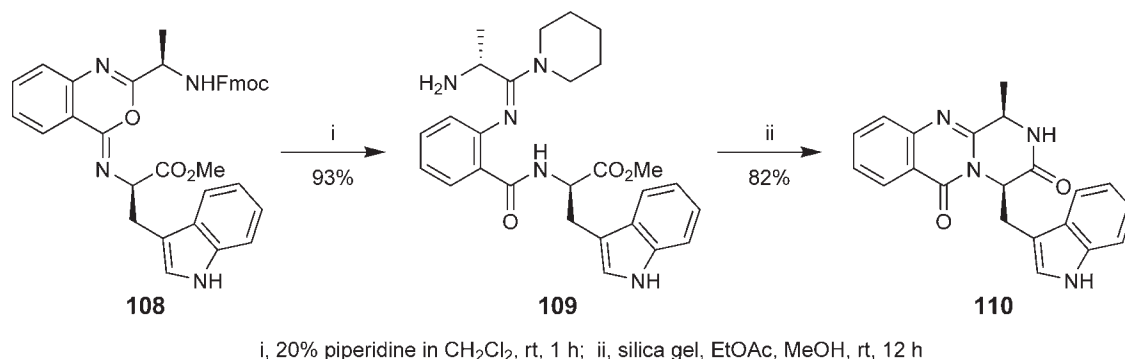
Scheme 15

The fluoro substituents proved to induce changes in the reactivities of the methyl- ($X = \text{H}$) and trifluoromethyl-substituted ($X = \text{F}$) pyrido[3',2':4,5]furo[3,2-*d*][1,3]oxazin-4(*H*)-ones **105** with nucleophiles. When methyl-substituted compounds **105** ($X = \text{H}$) were reacted with piperidine in toluene, *N*-acetylamino carboxamides **106** were formed by nucleophilic attack at the carbonyl group of the 1,3-oxazin-4-one ring (Scheme 16). However, the similar reactions of the trifluoromethyl-substituted analogs **105** ($X = \text{F}$) resulted in formation of amidino carboxylic acids **107** by attack at electron-poor position 2 <1995JFC(74)1>.



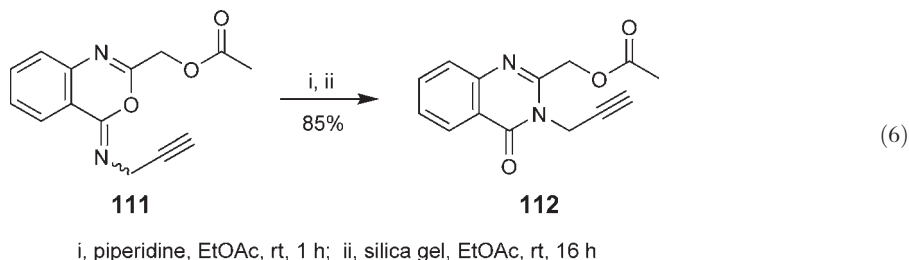
Scheme 16

When 4-imino-4*H*-3,1-benzoxazine **108** was treated with piperidine, not only cleavage of the *N*-protecting 9-fluorenylmethoxycarbonyl (Fmoc) group took place, but the iminobenzoxazine ring opened to form amidine **109**, which, on treatment with silica gel, gave the pyrazino[2,1-*b*]quinazoline alkaloid fumiquinazoline G **110** by double cyclization (Scheme 17) <1999JOC1397, 2000JOC1022>.

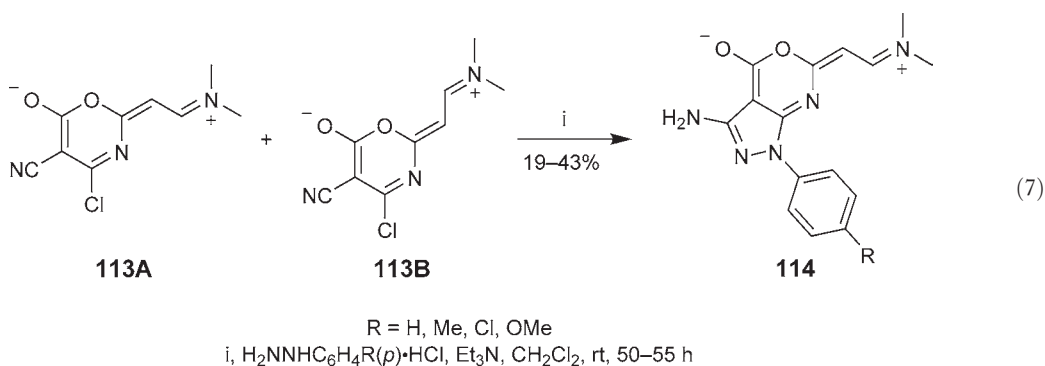


Scheme 17

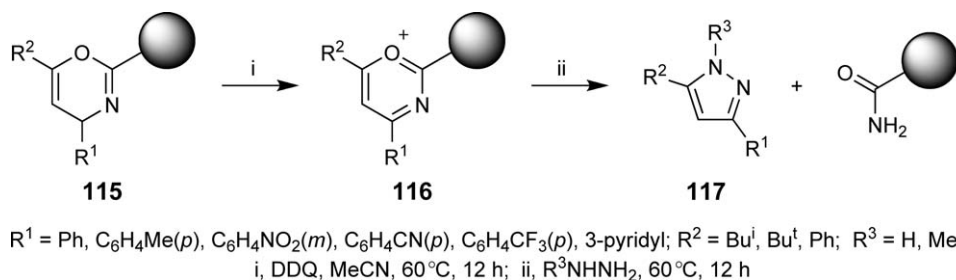
The base-induced, two-step, one-pot isomerizations of various 4-imino-4*H*-3,1-benzoxazines were applied in the synthesis of the corresponding quinazolin-4-ones <2000JCO186, 2000OL4103, 2002OL1087, 2003H(61)173, 2004SL2497>. Rearrangement of 4-propargylimino-4*H*-3,1-benzoxazine **111** by using piperidine and silica gel resulted in formation of quinazolinone derivative **112** (Equation 6) <2004OL4913>.



When the zwitterionic 1,3-oxazine iminium salt **113**, which is a 1:1 mixture of (*E*)- and (*Z*)-isomers **A** and **B**, was treated with phenylhydrazine, pyrazolo[3,4-*d*][1,3]oxazine derivatives **114** were formed in moderate yields (Equation 7). Surprisingly, the products of the cyclizations **114** existed only as the (*E*)-isomers. Products with an (*E*)-double-bond were also formed exclusively on nucleophilic replacement of the 4-chloro substituents of **113A** and **113B** by various amines or α -amino esters <1999H(51)2893>.



The resin-bound 1,3-oxazinium salt **116**, obtained by oxidation of 4*H*-1,3-oxazines **115** with 2,3-dicyano-5,6-dichloro-*p*-benzoquinone (DDQ), behaved as β -diketone equivalents and formed pyrazoles **117** through a functionalizing release process on treatment with hydrazines (Scheme 18). When the hydrazines were substituted ($\text{R}^3 = \text{Me}$, Ph), the oxazinium salts reacted selectively to afford one regioisomer **117** <2004JCO846>.



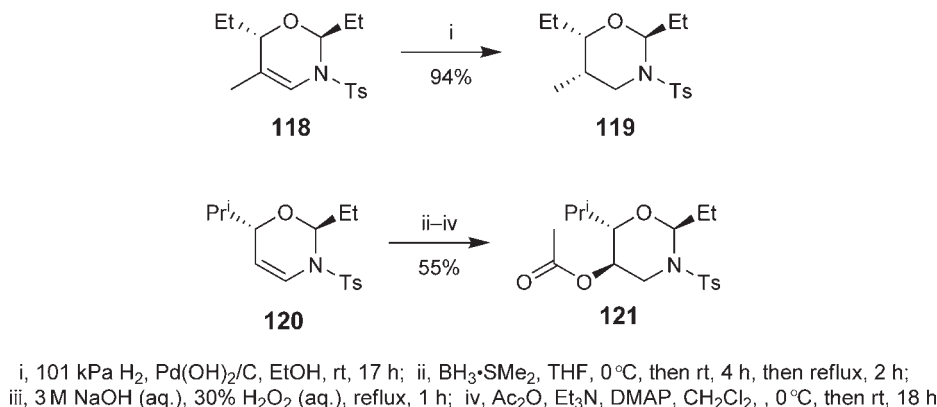
Scheme 18

8.05.6 Reactivity of Nonconjugated Rings

8.05.6.1 3,6-Dihydro-2*H*-1,3-oxazines

The catalytic hydrogenation of dihydro-1,3-oxazine **118** afforded the tetrahydro-1,3-oxazine derivative **119** as a single diastereomer, in excellent yield. Hydroboration of the double bond in dihydro-1,3-oxazine **120** yielded the acetate **121** as a single regio- and stereoisomer. The configurations of the products indicated that both the hydrogenation of

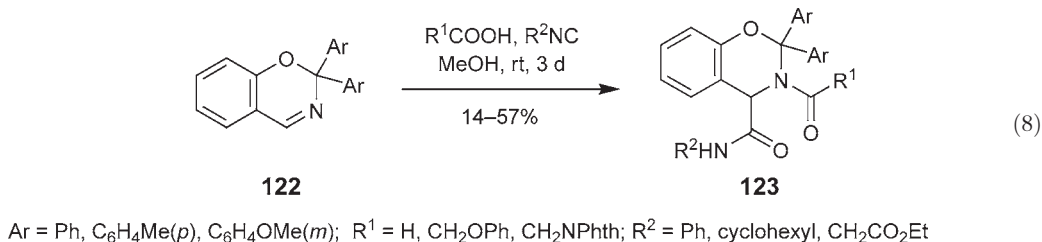
118 and the hydroboration of **120** took place from the face of the molecule opposite the large pseudoaxial arylsulfonamide moiety (Scheme 19) <1996T3135>.



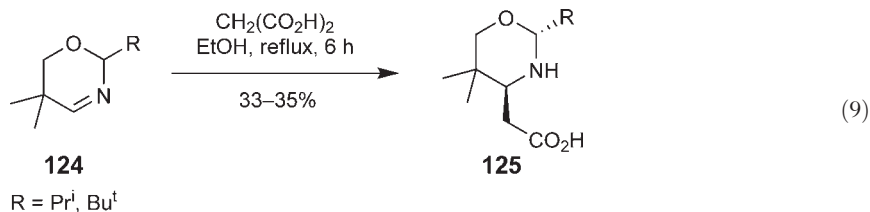
Scheme 19

8.05.6.2 5,6-Dihydro-2*H*-1,3-oxazines and -2*H*-1,3-benzoxazines

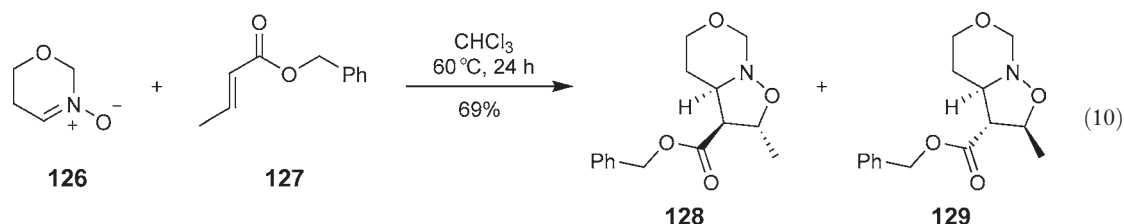
2,2-Diaryl-2*H*-1,3-benzoxazines could be successfully applied as preformed cyclic imines to replace the usual amine and aldehyde starting materials in Ugi multicomponent condensations. Treatment of **122** with isocyanides in the presence of carboxylic acids resulted in formation of 3-acyl-3,4-dihydro-2*H*-1,3-benzoxazine-4-carboxamide derivatives **123** in moderate yields (Equation 8) <1995T7173>. Similar reactions of 5,6-dihydro-2*H*-1,3-oxazines with diethyl isocyanomethylphosphate and N-protected α -amino acids gave phosphono oligopeptides containing a tetrahydro-1,3-oxazine moiety <1995SC1677>.



The substituent R at position 2 proved to determine the type of the product formed in the malonic acid additions of 5,6-dihydro-2*H*-1,3-oxazines **124**. For compounds bearing bulky substituents R (Prⁱ, Bu^t), *trans*-substituted 1,3-oxazine β -amino acids **125** were formed in diastereoselective additions (Equation 9), while the analogs with less bulky substituents (R = Me, Et) gave *C*₃-symmetrical, nitrogen-bridged, tricyclic 1,3-oxazine derivatives, instead of the corresponding β -amino acids, under the same conditions <1995T139>.

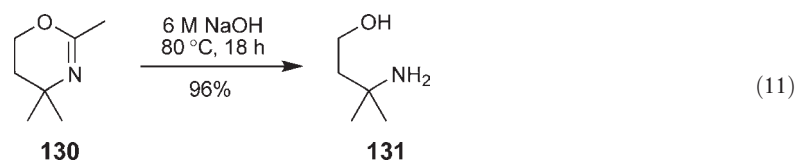


5,6-Dihydro-2*H*-1,3-oxazine 3-oxide **126** underwent cycloaddition with benzyl crotonate **127** in a fully regioselective and highly stereoselective way to afford an 85:15 mixture of diastereomeric perhydroisoxazolo[2,3-*c*][1,3]oxazine derivatives **128** and **129** (Equation 10). The 5,6-dihydro-1,3-oxazine nitrene **126** was characterized as a slightly less reactive compound in cycloadditions than the corresponding C-analog tetrahydropyridine nitrene, but more reactive than the homologous 4,5-dihydrooxazole nitrene <1998J(P2)2699>.



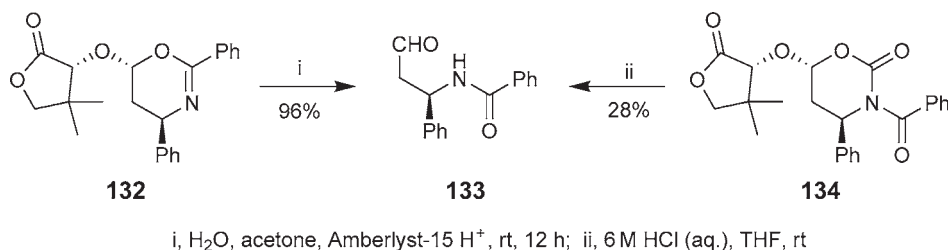
8.05.6.3 5,6-Dihydro-4*H*-1,3-oxazines

Alkaline hydrolysis of 5,6-dihydro-4*H*-1,3-oxazines is a convenient method via which to obtain the corresponding 1,3-amino alcohols or their *N*-acyl derivatives [<1996CC1629>](#). The yields are usually excellent, as in the transformation of 2,4,4-trimethyl-5,6-dihydro-4*H*-1,3-oxazine **130** to 3-amino-3-methylbutan-1-ol **131** (Equation 11) [<2001JLR265>](#).



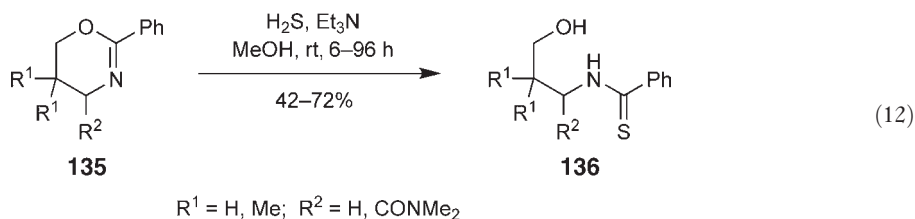
Acidic hydrolysis of 2-trichloromethyl-5,6-dihydro-4*H*-oxazine derivatives gave the corresponding amino alcohols in high yields [<1996CC355, 1997TL607, 1998CC761>](#).

No loss of optical purity was observed in the mild acidic hydrolysis of the enantiomerically pure 6-alkoxy-4-phenyl-5,6-dihydro-4*H*-1,3-oxazine **132**, which resulted in formation of (*R*)-3-benzoylamino-3-phenylpropanal **133** in excellent yield (Scheme 20). Hydrolysis of the analogous tetrahydro-1,3-oxazin-2-one **134** to **133** required a stronger acidic medium and took place only in poor yield, but without any decrease in the optical purity [<2000OL585, 2003JOC4338, 2004TL9589>](#).

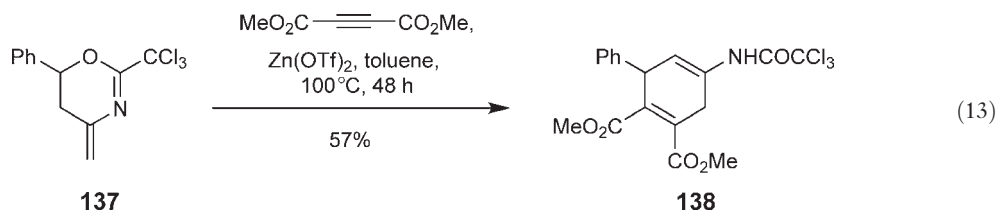


Scheme 20

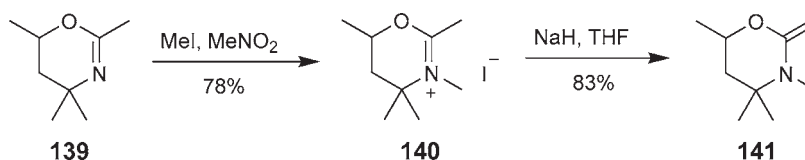
Thiolysis of oxazines **135** with a solution of H_2S in methanol-triethylamine (1:1) provided thioamides **136** in moderate to good yields (Equation 12). The duration of the reaction was dependent on the level of ring substitution; thiolysis of the least substituted oxazine ($\text{R}^1 = \text{R}^2 = \text{H}$) was complete in 6 h, while the more substituted oxazine ($\text{R}^1 = \text{Me}$) required 4 days for a reasonable yield of the corresponding thioamide [<1998T6987>](#).



4-Methylene-6-phenyl-2-trichloromethyl-5,6-dihydro-4*H*-1,3-oxazine **137** proved applicable as a precursor for a 2-acylamino-1,3-diene as a Diels–Alder cycloaddition partner. Treatment of **137** with DMAD in the presence of $\text{Zn}(\text{OTf})_2$ (0.2 equiv) in toluene at 100 °C provided cycloadduct **138** in 57% yield after 2 days (Equation 13) <2006OL3537>.

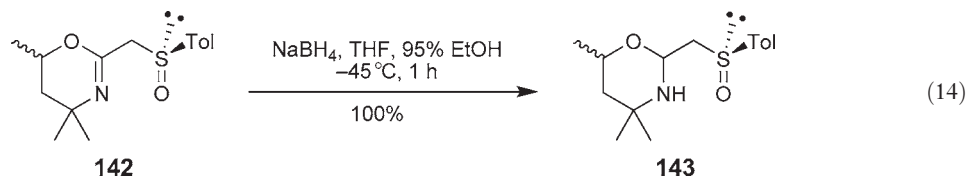


N-Methylation of **139** with iodomethane in nitromethane afforded 2,3,4,4,6-pentamethyl-5,6-dihydro-4*H*-oxazinium iodide **140**. Deprotonation of **140** with sodium hydride resulted in formation of the cyclic ketene-*N,O*-acetal derivative tetrahydro-1,3-oxazine **141** (Scheme 21) <2006JC0262>.

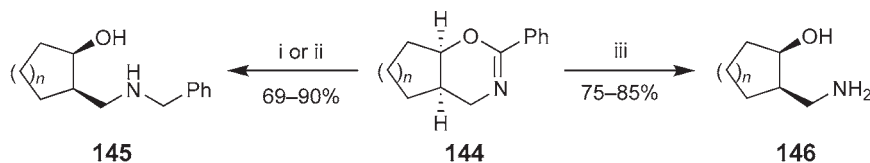


Scheme 21

4,4,6-Trimethyl-2-(*p*-tolylsulfinylmethyl)-5,6-dihydro-4*H*-1,3-oxazine **142** was reduced with NaBH_4 to the corresponding tetrahydro-1,3-oxazine **143** in quantitative yield (Equation 14) <2001H(55)1937, 2004T9171>.



Reduction of cycloalkane-condensed 2-phenyl-5,6-dihydro-4*H*-1,3-benzoxazines **144** with lithium aluminium hydride (LAH) afforded *N*-benzyl-substituted 2-(aminomethyl)cycloalkanols **145** in a reductive ring opening via the ring–chain tautomeric tetrahydro-1,3-oxazine intermediates. Catalytic reduction of 1,3-oxazines **144** under mild conditions in the presence of palladium-on-carbon catalyst similarly resulted in formation of the *N*-benzyl-1,3-amino alcohols **145**. When the catalytic reduction was performed at elevated temperature at hydrogen pressure of 7.1 MPa, the *N*-unsubstituted 2-(aminomethyl)cycloalkanols **146** were formed in good yields (Scheme 22) <1998SC2303>.



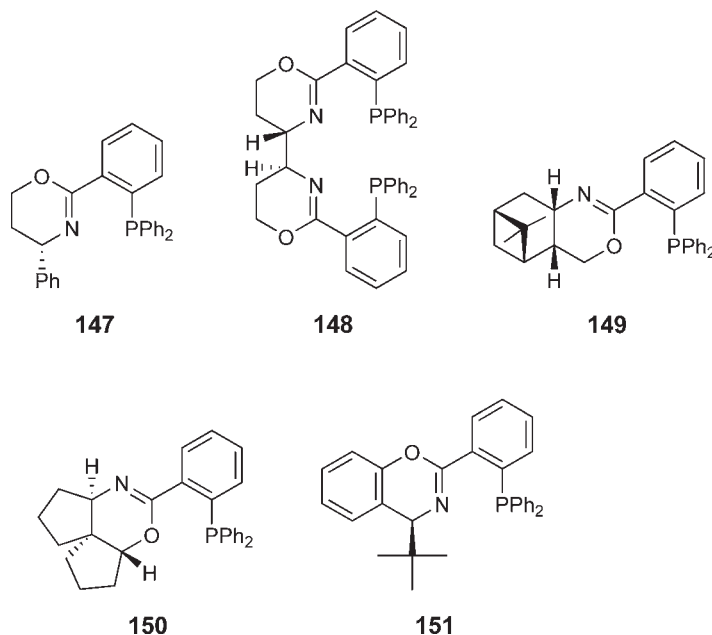
$n = 1-4$

i, LAH, THF, reflux, 3 h; ii, 2.0 MPa H_2 , 10% Pd/C, EtOH, rt, 1 h; iii, 7.1 MPa H_2 , 10% Pd/C, EtOH, 80 °C, 5–7 h

Scheme 22

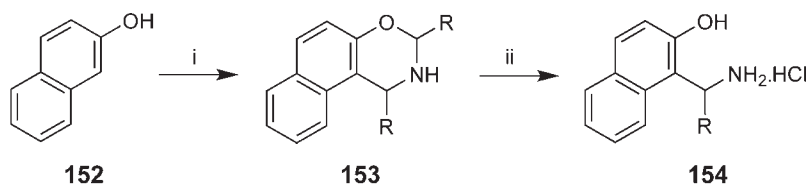
Chiral nonracemic bidentate 2-[*o*-(diphenylphosphino)phenyl]-5,6-dihydro-4*H*-1,3-oxazine derivatives proved to be effective P,N-ligands in Pd-catalyzed asymmetric transformations. When used in the Pd-catalyzed allylic alkylations of 1,3-diphenylallyl acetate with dimethyl malonate, phosphino-oxazines **147** and **148** and the

alicyclic-condensed analogs **149** and **150** gave ee values of up to 99%, 95%, 95%, and 91%, respectively <1996TL9143, 1999TA1795, 2000HCA1256, 2004TA155>. On use of the Pd complex of **149**, high ee values (90–98%) could be obtained in the allylic alkylations of (*E*)- and (*Z*)-vinyllogous sulfonates of β -phenylcinnamyl alcohol derivatives with dimethyl malonate <1999OL1563>. Phosphino-1,3-benzoxazine **151** was applied in Pd-catalyzed Heck reaction between phenyl triflate and 2,3-dihydrofuran, giving a product with 91% ee <1999HCA1360>.



8.05.6.4 Tetrahydro-1,3-oxazines, Dihydro-1,3-benzoxazines, and Dihydro-3,1-benzoxazines

The acidic or alkaline hydrolysis of perhydro-1,3-oxazines derivatives is a convenient route to 1,3-amino alcohols <2001SC3707, 2005CHE921, 2006JOC8481, 2006TL7923>. On acidic hydrolysis of naphthalene-condensed 1,3-oxazines **153**, formed in the Betti reaction, that is, the condensation of 2-naphthol **152** and an aldehyde in a ratio of 1:2 in the presence of ammonia, the corresponding 1,3-aminonaphthols **154** were obtained (Scheme 23). This procedure was extended to the preparation of various 1-(α -aminoalkyl)-2-naphthol derivatives <2003T2877, 2004JOC3645, 2006EJO4664>.

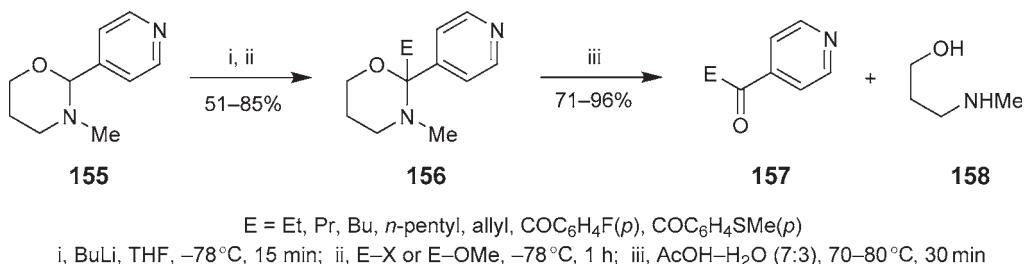


R = Me, Et, Pr, Prⁱ, Bu^t
 i, RCHO, 25 NH₃ (MeOH), MeOH, 60 °C, 4–72 h; ii, 10% HCl (aq.), 60 °C, 3 h; yield: 27–95% (i + ii)

Scheme 23

Hydrolytic reactions can also be applied in the synthesis of aldehydes or ketones via the corresponding 1,3-oxazine derivatives. The anion formed from 3-methyl-2-(4-pyridyl)tetrahydro-1,3-oxazine **155** on treatment with BuLi proved to react with various electrophiles (alkyl halides, carboxylic esters, acid chlorides, or aldehydes) exclusively at position 2 of the 1,3-oxazine ring and not at the pyridine nitrogen atom. The readily formed 2,2-disubstituted-1,3-oxazine

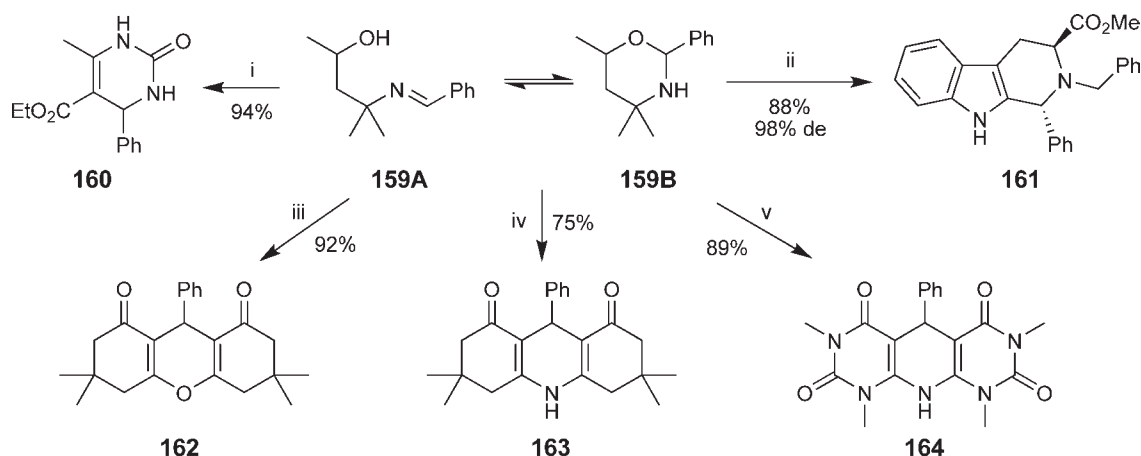
derivatives **156** were hydrolyzed under acidic conditions to give pyridyl ketones **157** only in the cases depicted in **Scheme 24**. The destabilizing effect of the pyridine ring caused decomposition of the remaining compounds under the acidic conditions of hydrolysis <2003SC2263>.



Scheme 24

Because of their ring-chain tautomeric character, tetrahydro-1,3-oxazines can be used as aldehyde sources in acid-catalyzed condensation reactions involving the carbon transfer via the open forms. This approach is especially advantageous in those cases where the aldehydes required for the condensations are unstable or difficult to access <2003EJO3025>.

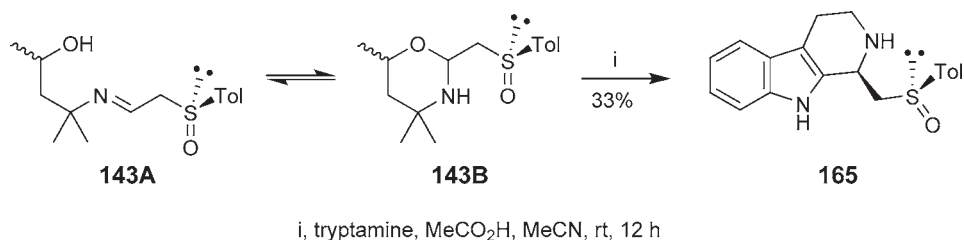
Applications of 4,4,6-trimethyl-2-phenyltetrahydro-1,3-oxazine **159** as a benzaldehyde equivalent in a modified Biginelli dihydropyrimidine synthesis, Pictet-Spengler ring closure, and condensations with 5,5-dimethylcyclohexane-1,3-dione, 3-amino-5,5-dimethylcyclohex-2-en-1-one, and 6-amino-1,3-dimethyluracil were chosen as examples to illustrate the synthetic applicability of the carbon-transfer reaction (**Scheme 25**). These transformations take place in the presence of acetic acid or trifluoroacetic acid (TFA) to provide various heterocyclic products **160-164** in high yield, and for tetrahydro- β -carbolines **161** with excellent diastereoselectivity <1996T14273, 1998T935, 1999H(51)1509, 1999T12873, 2000TL4977, 2001T7939>. Tetrahydro-1,3-oxazines were reported to participate as aldehyde equivalents in condensations with pyrroles and indoles, affording 5-substituted dipyrromethanes, 5,10-disubstituted tripyranes, and bis(heterocycl)methanes <2005T6614, 2005SC929>.



i, ethyl acetoacetate, urea, TFA, MeCN, reflux, 6 h; ii, *N*-benzyl-(*S*)-tryptophan methyl ester, TFA, MeCN, reflux, 9 h; iii, 2 equiv 5,5-dimethylcyclohexane-1,3-dione, AcOH, reflux, 4 h; iv, 2 equiv 3-amino-5,5-dimethylcyclohex-2-en-1-one, TFA, MeCN, reflux, 20 h; v, 2 equiv 6-amino-1,3-dimethyluracil, TFA, MeCN, reflux, 4 h

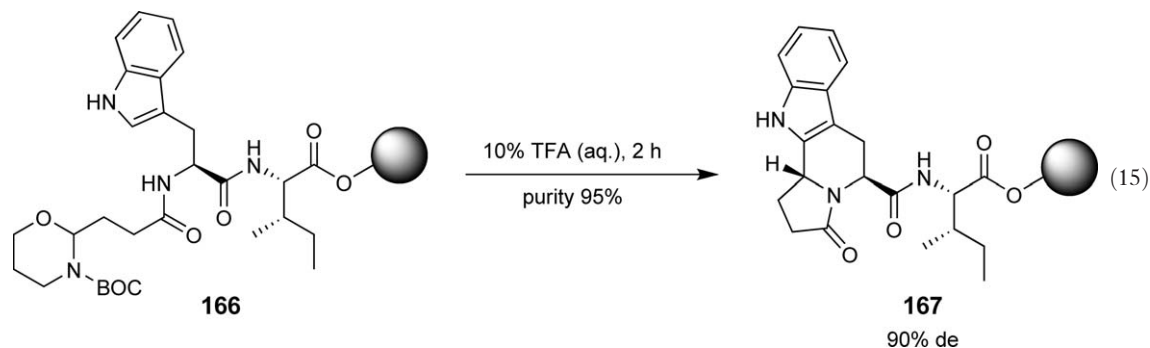
Scheme 25

An asymmetric carbon-transfer reaction was also performed by using 2-(*p*-tolyl)sulfinylmethyltetrahydro-1,3-oxazine **143** as the chiral aldehyde equivalent in the Pictet-Spengler ring closure with tryptamine, but only moderate diastereoselectivity ($\sim 40\%$ de) was observed in favor of the (1*R*)-tetrahydro- β -carboline **165**, and the enantiopure main product could be isolated only in low yield (**Scheme 26**) <2001H(55)1937, 2004T9171>.



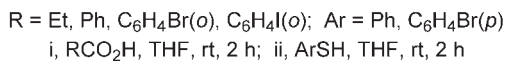
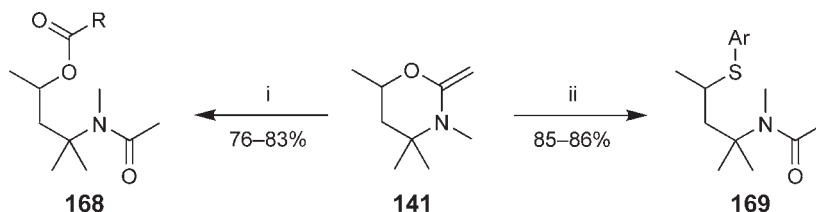
Scheme 26

Intramolecular carbon-transfer reactions in which the aldehyde function was protected as an *N*-BOC-tetrahydro-1,3-oxazine moiety and liberated *in situ* under acidic conditions were successfully applied in solid-phase Pictet–Spengler reactions or other cyclizations to form nitrogen-bridged 1,3-heterobicycles (BOC = *t*-butoxycarbonyl) <2001JCO34, 2005JCO599, 2005OL3601, 2006CEJ8056>. On treatment of the *N*-acetyltryptophan derivative **166**, containing a masked aldehyde building block, with Brønsted acids, hexahydroindolizino[8,7-*b*]indole derivative **167** was formed via the cyclization of the corresponding acyliminium intermediate, in a highly stereoselective reaction favoring the (5*S*,11*bR*)-*trans*-diastereomer (Equation 15) <2004JOC3765>.



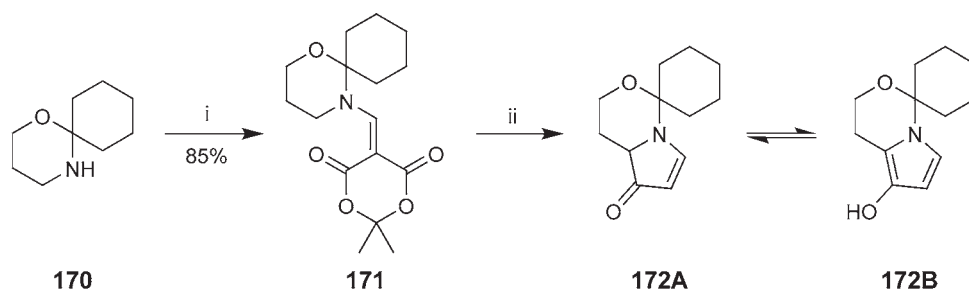
By the addition of 2-sulfanylacetic acid to the open tautomeric form of tetrahydro-1,3-oxazines, 3-(3-hydroxypropyl)thiazolidin-4-ones were obtained in moderate to good yields. The process proved to be slower than the analogous reactions of oxazolidines <2006RJO1101>.

2-Methylene-substituted tetrahydro-1,3-oxazine **141** underwent ring opening in response to nucleophilic attack by carboxylic acids or thiophenols to afford the *N*-acetyl derivatives of the corresponding *O*-acyl-1,3-amino alcohols **168** or aminoalkyl sulfides **169** in high yields (Scheme 27) <2006JCO262>.



Scheme 27

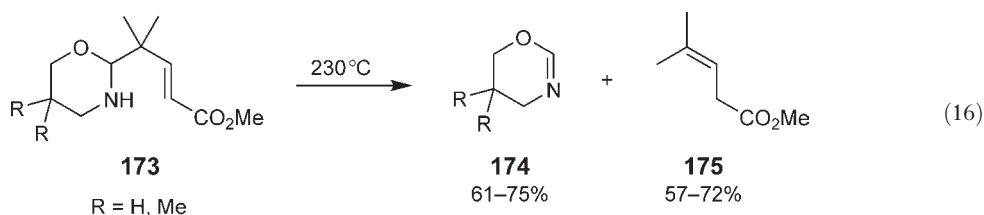
Flash vacuum pyrolysis (FVP) of the tetrahydro-1,3-oxazine derivative **171**, derived from the condensation of spiro-oxazine **170** and methoxymethylene-substituted Meldrum acid, resulted in formation of pyrrolo[1,2-*c*][1,3]oxazine **172**, which in (CD₃)₂CO at –20 °C proved to be a 47:53 mixture of the keto (A) and enol (B) tautomers (Scheme 28) <2002J(P1)548>.



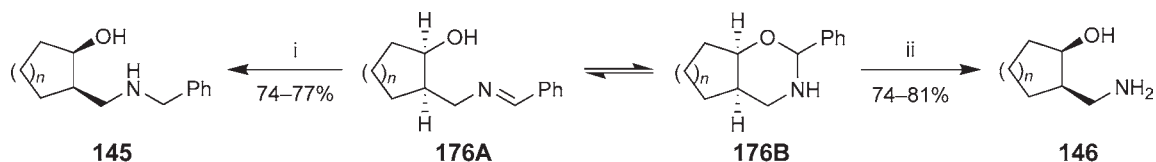
i, 2,2-dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione, MeCN, rt, 3 h; ii, FVP (600°C, 1.3 Pa, 15 min)

Scheme 28

When heated at 230 °C, tetrahydro-1,3-oxazines **173**, bearing an α,β -unsaturated ester substituent at position 2, underwent a retro-ene reaction and yielded 5,6-dihydro-4*H*-1,3-oxazines **174** together with methyl 4-methyl-3-pentenoate **175** (Equation 16). For the methyl-substituted oxazine **173** (R = Me), the yields of both products were somewhat higher than those in the reaction of the unsubstituted analog **173** (R = H) <1997JHC501>.



In the catalytic reduction of cycloalkane-condensed 2-phenyltetrahydro-1,3-benzoxazines **176** under mild conditions, *N*-benzyl-1,3-amino alcohols **145** were formed via reduction of the C=N bond of the open tautomeric form (**A**) of **176**. Higher temperature and higher hydrogen pressure, however, led to the formation of the *N*-unsubstituted amino alcohols **146** by debenzilation (Scheme 29) <1998SC2303>. Reductions of tetrahydro-1,3-oxazines with LAH or NaBH₄ resulted in formation of *N*-substituted 1,3-amino alcohols via hydride attack on the open tautomeric forms <1998TA3667, 1999T14685, 2000SL104, 2000TA3361, 2001J(P1)2962, 2001T6089>.

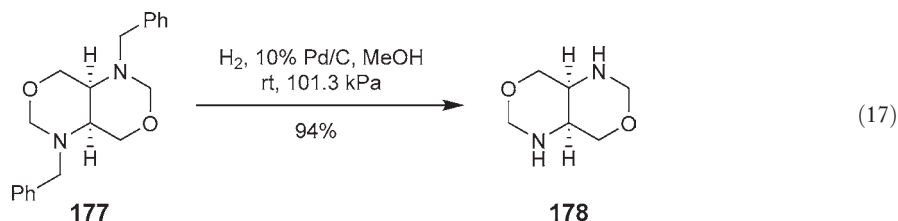


$n = 1, 2$

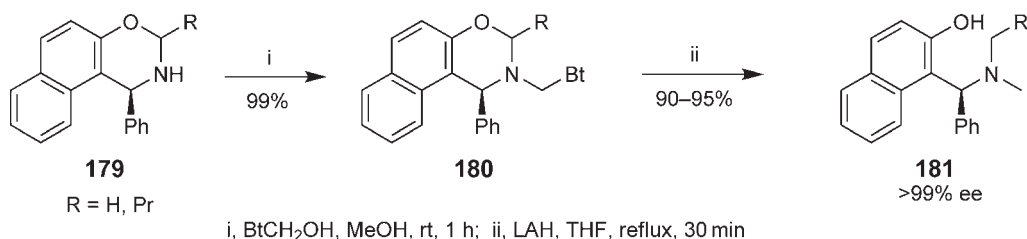
i, 2.0 MPa H₂, 10% Pd/C, EtOH, rt, 1 h; ii, 7.1 MPa H₂, 10% Pd/C, EtOH, 80 °C, 5–7 h

Scheme 29

No reductive ring opening was detected in the catalytic hydrogenation of *cis*-1,5-dibenzyl-3,7-dioxo-1,5-diazadecalinalin **177** at room temperature under atmospheric pressure, in which the unsubstituted derivative **178** was formed by debenzilation (Equation 17) <2006S1093>.

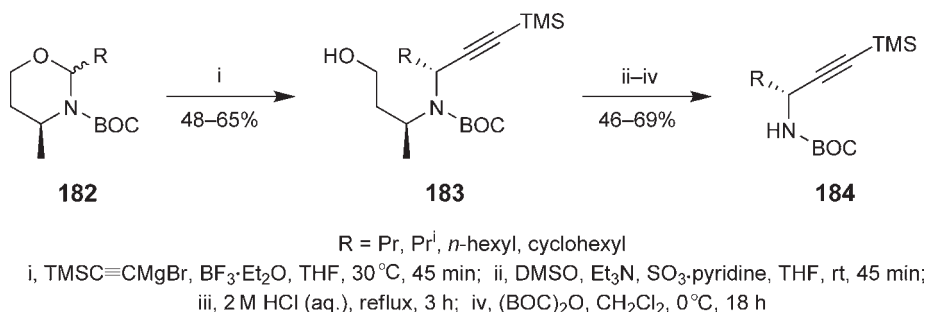


The partial racemization observed in the reductive alkylation/ring opening of (1*S*)-1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*]oxazines **179** on successive treatment with formaldehyde and NaBH₄ could be overcome by applying another procedure, based on the application of 1-hydroxymethylbenzotriazole (BtCH₂OH) as a convenient N-methylating agent (Scheme 30). Reduction of the benzotriazol-1-ylmethyl derivative **180** with LAH gave the dialkyl-substituted Betti base **181** in high yield and without loss of enantiopurity <2004TA1667>.



Scheme 30

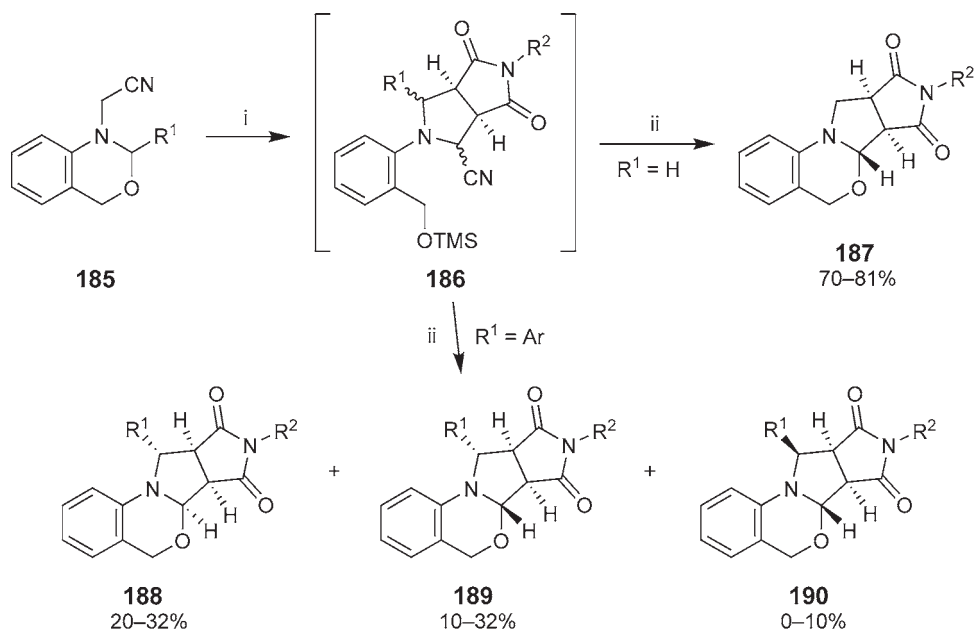
The ring openings of 2-substituted 3-(BOC)-4-methyltetrahydro-1,3-oxazines **182** with the Grignard reagent of (trimethylsilyl)acetylene under Lewis acidic conditions gave the amino alcohol derivatives **183**, which were converted to the propargylamines **184** by oxidation and a subsequent retro-Michael β -elimination (Scheme 31). With ee values of 40–86% for **184**, the configuration of the major enantiomer of which was determined to be (*R*), the Grignard reactions of **182** took place with moderate to good diastereoselectivities <1998TL6561, 1999J(P1)1943>. 3,4-Disubstituted 3,4-dihydro-2*H*-1,3-benzoxazines and (–)-8-(benzylamino)menthol-derived perhydro-1,3-benzoxazines readily underwent the nucleophilic addition of Grignard reagents with the formation of tertiary amine derivatives via a similar ring opening <1996JOC4130, 2001T6089>.



Scheme 31

Azomethine ylides derived from 1-cyanomethyl-1,4-dihydro-2*H*-3,1-oxazines **185** were successfully applied in cycloaddition reactions with maleimides to yield highly substituted, tetracyclic pyrrolopyrrolidine derivatives. Through the use of one-pot, sequential methodology (ylide generation and cycloaddition followed by treatment with AgBF₄) starting from the 2-unsubstituted oxazine **185** (R¹ = H), compound **187** was obtained as a single diastereomer, while the similar reactions of the 2-heteroaryl-substituted derivatives **185** (R¹ = 3- or 4-pyridyl, 2-furyl) gave mixtures of diastereomers **188–190** (Scheme 32) <2002H(57)1599>.

Despite the high proportion of the open forms, stabilized by intramolecular hydrogen bonds, in the ring–chain tautomeric equilibria of N-unsubstituted 2-(*o*-hydroxyphenyl)tetrahydro-1,3-oxazine derivatives, these compounds gave nitrogen-bridged polycyclic systems on treatment with aldehydes or phosgene. These reactions occurred with considerable diastereoselectivity and were explained by the quantitative shift of the tautomeric equilibrium toward a cyclic form as a consequence of the crystallization of the polycyclic product <2006CHE1068, 2006T11081>.

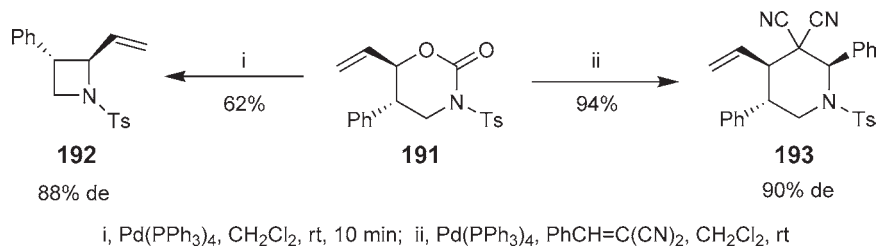


$R^1 = H, 3\text{-pyridyl}, 4\text{-pyridyl}, 2\text{-furyl}; R^2 = CH_2Ph, Ph$
 i, *N*-benzyl- or *N*-phenylmaleimide, Pr_2NEt , TMSOTf, CH_2Cl_2 , $-78^\circ C$ to rt, 12 h; ii, $AgBF_4$, THF, rt, 5 h

Scheme 32

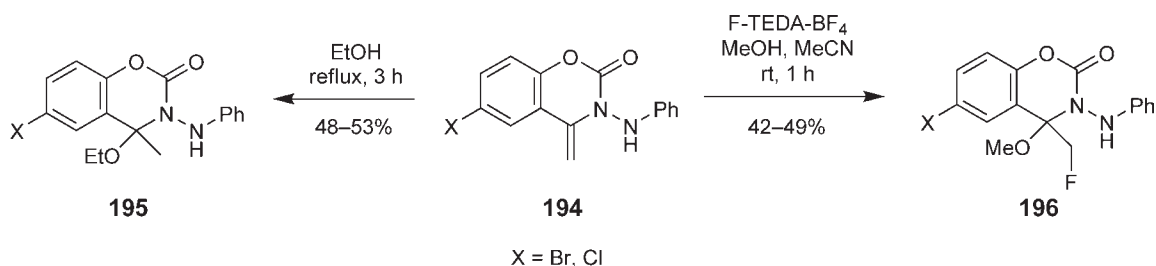
8.05.6.5 1,3-Oxazin-2-ones, 1,3-Benzoxazin-2-ones, and 3,1-Benzoxazin-2-ones

As a cyclic allylic carbamate derivative, 5-phenyl-3-tosyl-6-vinyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazin-2-one **191** underwent decarboxylative ring contraction in the presence of a palladium(0) catalyst to form vinyl azetidine **192**. Ring contraction proceeded with a high degree of retention of the stereochemistry, which was explained by the backside attack of the nitrogen anion on a π -allyl-palladium complex intermediate. When the reaction was performed in the presence of a Michael acceptor such as benzylidenemalononitrile, highly substituted piperidines, for example **193**, were formed with good diastereoselectivity by decarboxylative alkene insertion (Scheme 33) <2006OL3211>.



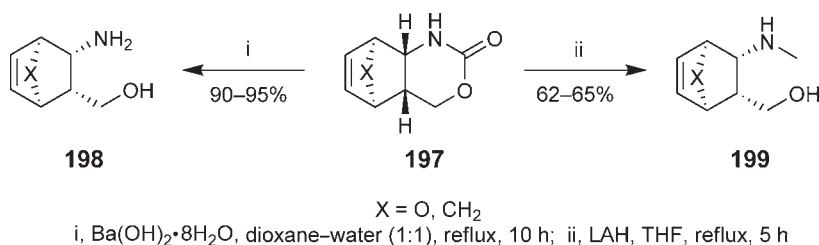
Scheme 33

4-Methylene-1,3-benzoxazin-2-ones **194** were found to be susceptible to addition to the exocyclic double bond. On heating under reflux in ethanol, oxazinones **194** were transformed to the 4-ethoxy derivatives **195**. Treatment of **194** with 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA- BF_4), an electrophilic fluorinating reagent, in the presence of methanol, led to the 4-fluoromethyl-4-methoxy-substituted compounds **196** (Scheme 34) <2003T8163>.



Scheme 34

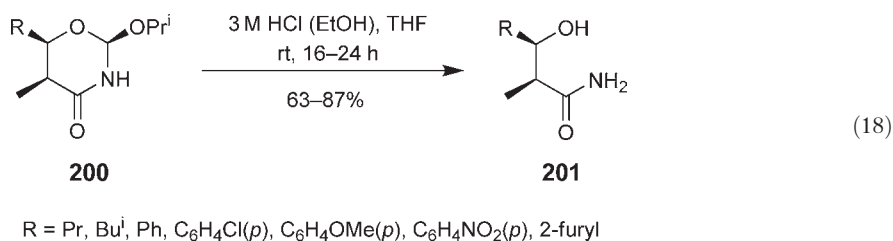
Tetrahydro-1,3-oxazin-2-ones can be conveniently transformed to the corresponding 1,3-amino alcohol derivatives. Hydrolysis of the oxygen- or methylene-bridged perhydro-3,1-benzoxazin-2-ones **197** resulted in formation of the N-unsubstituted amino alcohols **198** in high yields, while LAH reduction of **197** led to the *N*-methyl-substituted amino alcohols **199** (Scheme 35) <2003OPP429>. *cis*-2-Amino-2-undecylcyclobutanemethanol was also prepared by LAH reduction of the corresponding cyclobutane-fused 1,3-oxazin-2-one <2006TL5981>.



Scheme 35

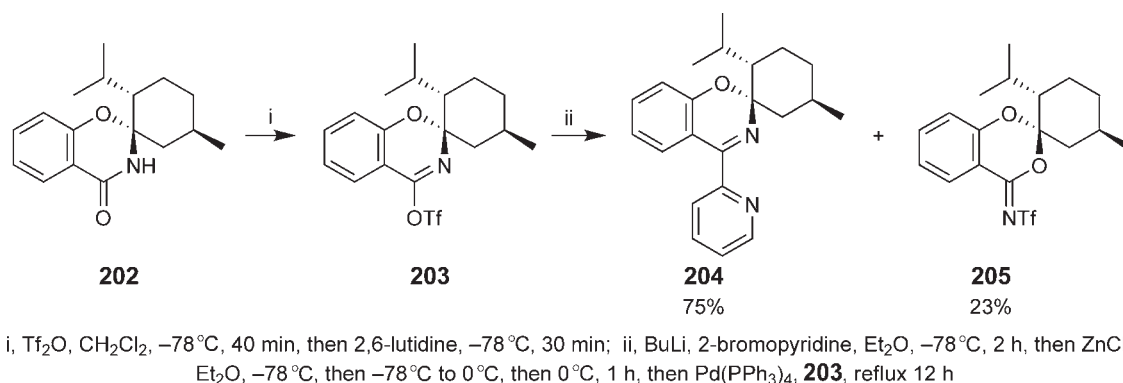
8.05.6.6 1,3-Oxazin-4-ones and 1,3-Benzoxoxazin-4(3*H*)-ones

By acidic ethanolysis of 2-isopropoxy-5,6-dihydro-2*H*-1,3-oxazin-4(3*H*)-ones **200**, the corresponding β -hydroxy amides **201** were obtained (Equation 18) <1999TL7079, 2002S2043>.



Treatment of the (–)-menthone-derived 2*H*-1,3-benzoxazin-4(3*H*)-one **202** with triflic anhydride gave the triflate **203** in quantitative yield. Palladium-catalyzed cross-coupling of **203** with 2-pyridylzinc halide resulted in formation of an approximately 3:1 mixture of the 4-(2-pyridyl)-2*H*-1,3-benzoxazine **204** and a 4-imino-1,3-benzodioxane derivative **205** (Scheme 36). Compound **205** was formed by the isomerization of **203**, which occurred with complete retention of stereochemistry. The 4-(2-pyridyl)-1,3-benzoxazine derivative **204** was applied in enantioselective allylic alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate as a chiral ligand inducing a 62% ee in the product <2005JOM(690)2027>.

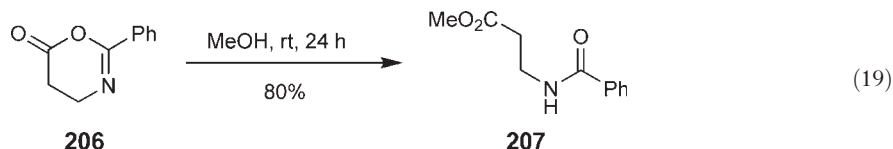
The nonracemic 2*H*-1,3-benzoxazin-4(3*H*)-one **202** was successfully applied as a chiral auxiliary in asymmetric transformations: the titanium enolate-mediated aldol reactions of its *N*-acyl derivatives provided the products in high yields and with excellent diastereoselectivity <1996SL455, 1996TL5565>.



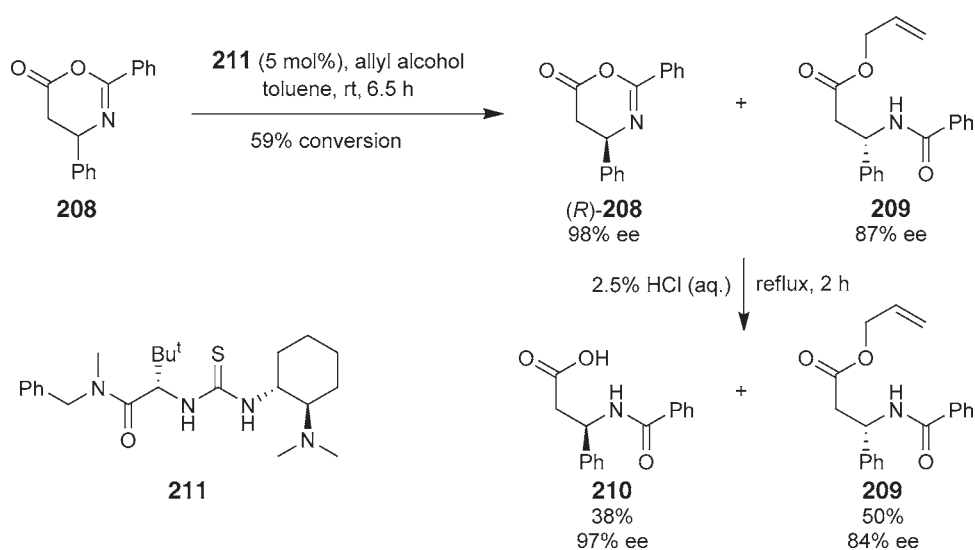
Scheme 36

8.05.6.7 1,3-Oxazin-6-ones

The ring-opening reactions of 1,3-oxazin-6-ones with nucleophiles or electrophiles both result in β -amino acid derivatives. Methanolysis of 2-phenyl-4,5-dihydro-1,3-oxazin-6-one **206** under very mild conditions gave methyl 3-(benzoylamino)propionate **207** (Equation 19) <2003OL1575>.

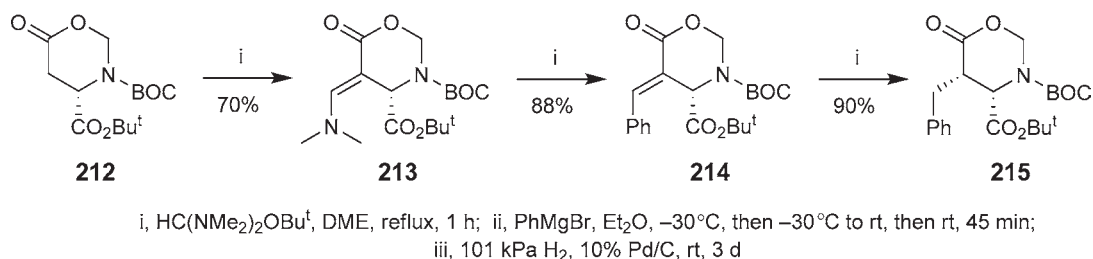


The asymmetric alcoholic ring opening of 4-substituted-2-phenyl-4,5-dihydro-1,3-oxazin-6-ones proved to be a efficient method for the preparation of enantiomerically pure β -amino acid derivatives <2005AGE7466>. Treatment of 2,4-diphenyl-4,5-dihydro-1,3-oxazin-6-one **208** in the presence of the bifunctional chiral thiourea catalyst **211** resulted in formation of an enantiomerically enriched mixture of the unchanged oxazinone (*R*)-**208** and allyl (*S*)-3-benzoylamino-3-phenylpropanoate **209**. The resolved material (*R*)-**208** and the product **209** could easily be separated by a selective hydrolytic procedure that converted oxazinone (*R*)-**208** quantitatively into the insoluble *N*-benzoyl β -amino acid **210** (Scheme 37).



Scheme 37

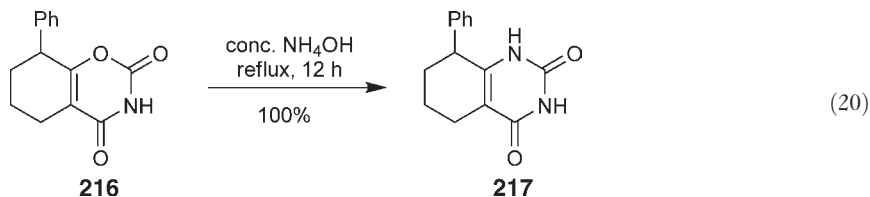
When the tetrahydro-1,3-oxazin-6-one **212** was reacted with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), the enamine **213** was obtained as a single (*E*)-isomer (Scheme 38). The reaction of **213** with phenylmagnesium bromide gave 5-benzylidene-substituted oxazinone **214**, again as a single (*E*)-isomer. The hydrogenation of **214** took place with complete diastereoselectivity, resulting in *cis*-4,5-disubstituted-1,3-oxazin-6-one **215**, a key intermediate in the synthesis of β -benzyl-substituted aspartic acid derivatives <1999TL4275, 2000J(P1)3451>.



Scheme 38

8.05.6.8 1,3-Oxazine-2,4(3*H*)-diones

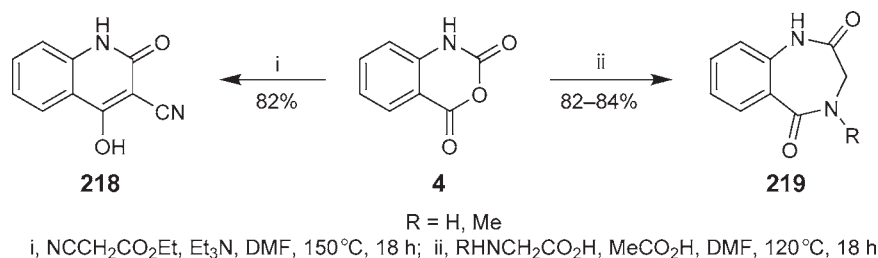
1,3-Oxazine-2,4(3*H*)-diones are known to react with ammonia at C-2 to form uracil derivatives <1996CHEC-II(6)301>. Through this procedure, 8-phenyl-5,6,7,8-tetrahydro-1,3-benzoxazine-2,4(3*H*)-dione **216** was converted to the corresponding tetrahydroquinazoline-2,4-dione **217** (Equation 20) <2000J(P1)3035>.



8.05.6.9 2*H*-3,1-Benzoxazine-2,4-diones

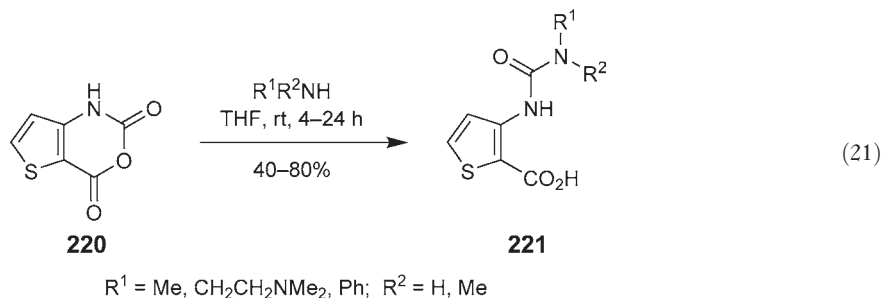
The wide range of chemical transformations to which 2*H*-3,1-benzoxazine-2,4-dione (isatoic anhydride) **4** has been subjected is beyond the scope of this chapter. A review published a few years ago on the transformations of isatoic anhydrides to heterocyclic compounds contains valuable information on other aspects of the chemical behavior of these compounds <2001CHE385>.

Among the numerous recent examples of the ring-opening reactions of isatoic anhydrides with nucleophiles, aminolysis leading to anthranilic amides <1998CPB928, 1998SC2077, 2000CHE287, 2000JME883, 2000T7245, 2001JHC419, 2002BML1881, 2002H(57)1501, 2002HAC63, 2003BML1873, 2004TL997, 2005TL6123, 2006JHC731, 2006TL693>, condensation with ethyl cyanoacetate to form 3-cyano-4-hydroxy-2(1*H*)-quinolone **218** <2004JME5923>, and ring-enlargement reactions with α -amino acids or esters to furnish 1,4-benzodiazepine derivatives, for example **219** <2003JHC29, 2003JME5567, 2004BML2603, 2004SL1841, 2004MI259, 2005TL8207> (Scheme 39), may be mentioned. The one-pot three-component acid-catalyzed condensation of isatoic anhydride with primary amines or ammonium carbonate and aromatic aldehydes afforded 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones in high yields <2005SL1155>. In the reaction of isatoic anhydride with 2,3-dihydro-4-pyridone, an unstable tricyclic piperidone derivative, 5a,6,8,9-tetrahydro-5*H*-pyrido[2,1-*b*]quinazoline-7,11-dione, was formed <2004TL6725>. An unusual O-acylation and subsequent decarboxylation was observed in the reactions of isatoic anhydride with acetyl- or benzoylmethylenetriphenylphosphoranes, resulting in 2-substituted-2-(triphenylphosphoranylidene-methyl)-1,2-dihydro-4*H*-3,1-benzoxazin-4-ones in good yields <2006CHE1107>.

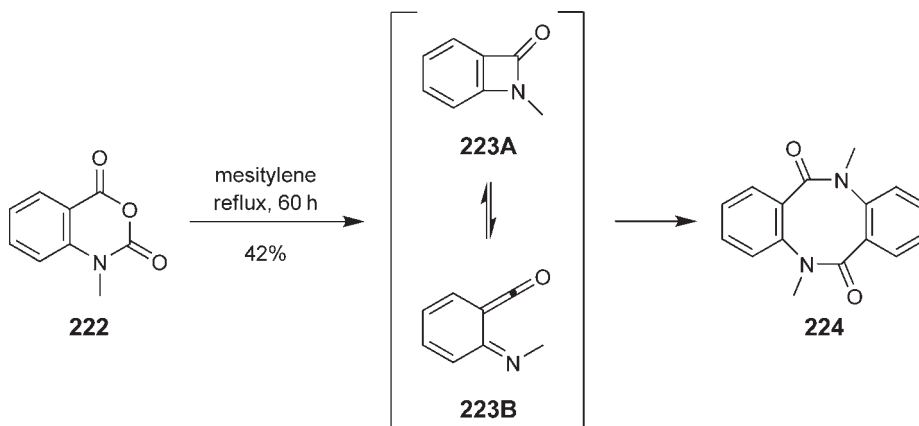


Scheme 39

The thieno analogs of isatoic anhydrides, 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione **220**, and its regioisomer, 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, and their derivatives with aryl substituents on the thiophene ring reacted with amines to give exclusively carbamoylaminothiophenecarboxylic acids, for example **221**, instead of the corresponding thiophenecarboxamides, by attack of the nucleophile on position 2 of the 1,3-oxazine ring (Equation 21) <1998T10789, 2003T10051, 2005JCO253>.



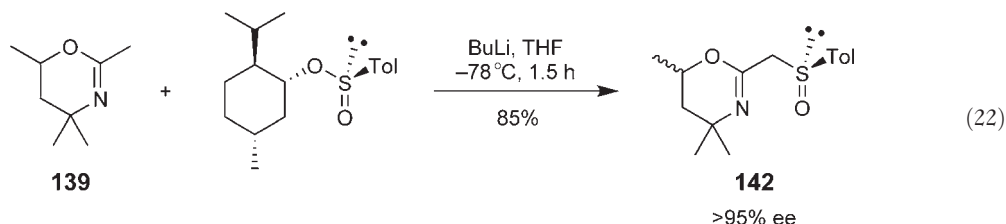
Solution pyrolysis of *N*-methylisatoic anhydride **222** gave the formal [4+4] dimer **224** (Scheme 40). The formation of **224** was explained by the lack of a stabilizing hydrogen bond in the *N*-substituted imidoalkene intermediate **223**, leading to an addition product to the $\text{C}=\text{C}$ bond instead of the $\text{C}=\text{O}$ bond of **223B**, this behavior being opposite to that usual for *N*-unsubstituted imidoalkenes <2004JOC86>.



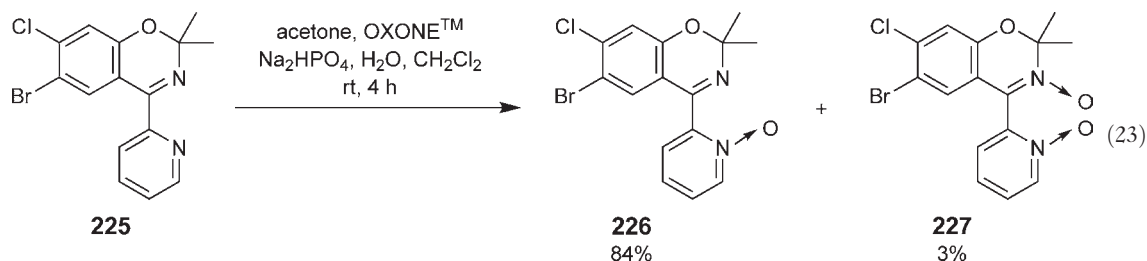
Scheme 40

8.05.7 Reactivity of Substituents Attached to Ring Carbon Atoms

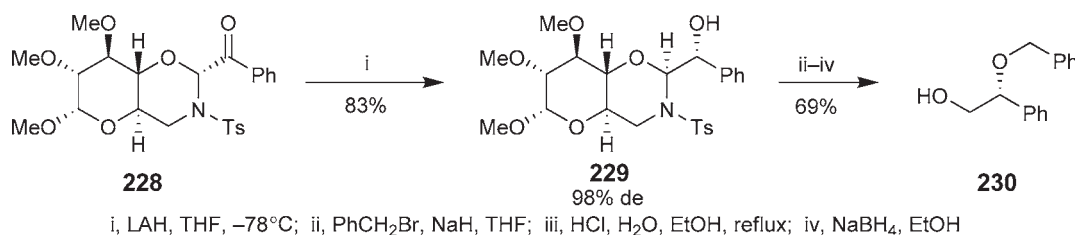
The reaction of 2,4,4,6-tetramethyl-5,6-dihydro-4*H*-1,3-oxazine **139**, lithiated at the 2-methyl group, with (–)-(*S*)-menthyl *p*-toluenesulfonate afforded 2-arylsulfinylmethyl-1,3-oxazine **142** as a mixture of its diastereomers (Equation 22) <2001H(55)1937, 2004T9171>.



In the preparation of TCV-295 **226**, a 2*H*-1,3-benzoxazine derivative with potassium channel-activating activity, N-oxidation of the 4-(2-pyridyl) substituent of **225** was achieved with good regioselectivity by using dimethyldioxirane generated *in situ* in an Na_2HPO_4 buffer system (Equation 23). Oxidation of **225** with *m*-chloroperbenzoic acid (MCPBA) provided **226** with only moderate regioselectivity <2001T7501>.



Excellent diastereoselectivities were observed in the reductions of the D-glucose-derived 2-benzoyl-tetrahydro-1,3-oxazine derivative **228** with chelating agents such as LAH and L-selectride, affording **229** as the main product. The configuration of the newly formed carbinol center was proved via the (*R*)-2-benzyloxy-2-phenylethanol **230** obtained by subsequent benzylation, hydrolysis, and reduction of **229** (Scheme 41). Formation of **229** with the (*R*)-configuration as the major product suggested that the reduction of **228** proceeded through a chelation mode involving the ring oxygen atom <1997TL407>.

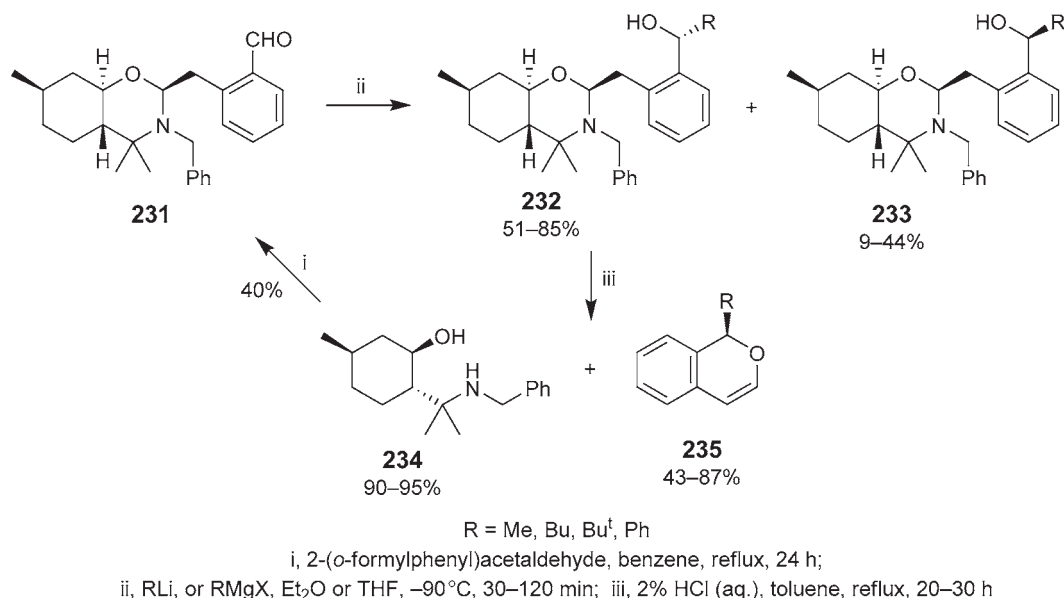


Scheme 41

The synthetic utility of enantiopure perhydro-1,3-benzoxazines derived from (–)-8-aminomenthol in asymmetric transformations was already emphasized in CHEC-II(1996) <1996CHEC-II(6)301>. The application of these compounds in the synthesis of chiral nonracemic nitrogen-containing heterocycles was reviewed recently <B-2005MI65>. In the past decade, numerous examples emerged that demonstrated that (–)-8-aminomenthol-derived 2,3-disubstituted perhydro-1,3-benzoxazines are very effective chiral templates in various asymmetric reactions, including additions or cycloadditions to the $\text{C}=\text{O}$, $\text{C}=\text{N}$, or $\text{C}=\text{C}$ bonds of the substituents attached to position 2 of the benzoxazine ring <1998TL9117, 1998TL9121, 1999CC31, 1999JOC4273, 1999JOC5230, 2000JOC831, 2000TA2809, 2001T4005, 2002JOC782, 2002OL2513, 2003JOC4923, 2003S1457, 2003TA2985, 2005EJO2449, 2005JOC1408, 2005JOC4332, 2005JOC7273, 2006EJO3259, 2006JOC2177, 2006JOC8854>. The limited size of this chapter allows only two recent publications on this topic to be discussed.

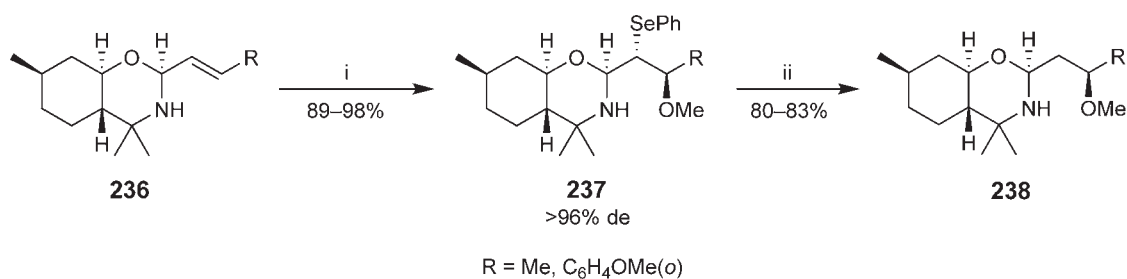
The addition of different organometallics to the aldehyde function of **231**, obtained by the regio- and diastereoselective ring closure of (–)-8-(benzylamino)menthol **234** and 2-(*o*-formylphenyl)acetaldehyde, resulted in formation of a mixture of diastereomeric secondary alcohols **232** and **233**. The formation of the major diastereomers **232** was

explained by the coordination of the organometallics to the oxygen of the template, which directs the addition to the less-hindered, oxygen face of the heterocycle. On hydrolytic cleavage of **232**, the enantiopure 2-substituted isochromenes **235** were obtained besides the recovered chiral amino alcohol **234** (Scheme 42) <2006EJO5110>. Similar transformations on the homolog of **231**, obtained from (–)-8-(benzylamino)menthol **234** and *o*-phthalaldehyde, resulted in enantiopure 3-substituted isobenzofuran-1-ones <2006T10400>.



Scheme 42

In the reactions of the perhydro-1,3-benzoxazine derivatives **236** with benzeneselenenyl chloride in dichloromethane–methanol, methoxyselenenylation of the double bond in the C-2 side chain occurred in a highly regio- and diastereoselective way (Scheme 43). Reductive deselenenylation of **237** with triphenyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) resulted in formation of the methoxy derivatives **238** <2006JOC2424>.

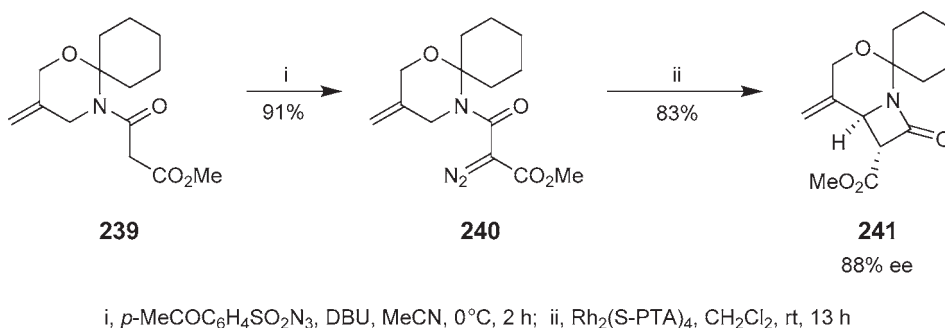


i, PhSeCl, MeOH, CH₂Cl₂, 22°C, 72 h (R = Me) or –15°C, 23 h (R = C₆H₄OMe(*o*)); ii, Ph₃SnH, AIBN, toluene, reflux, 5 h

Scheme 43

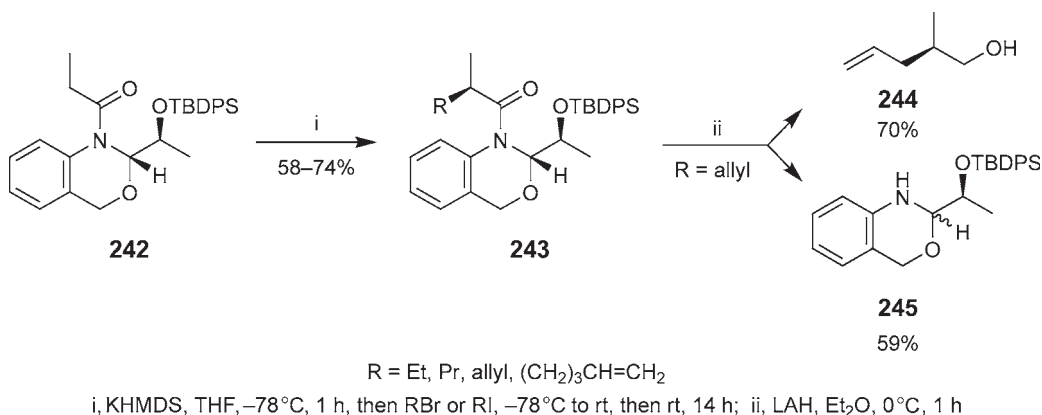
8.05.8 Reactivity of Substituents Attached to Ring Heteroatoms

The methylmalonyl substituent at the nitrogen atom could be utilized to form a β -lactam ring attached to 1,3-oxazine. In a diazo-transfer reaction, *N*-methylmalonyl-1,3-oxazine **239** was converted to the corresponding α -diazoamide **240**. Treatment of **240** with dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate] (Rh₂(*S*-PTA)₄) resulted in formation of azeto[1,2-*c*][1,3]oxazine **241** in good yield and ee (Scheme 44) <1998CC1517>.



Scheme 44

Almost complete retention of chirality was achieved in the alkylations of 1-propionyl-1,4-dihydro-2*H*-3,1-benzoxazines **242** bearing a stereogenic center in the substituent at position 2 (TBDPS = *tert*-butyldiphenylsilyl, KHMDs = potassium hexamethyldisilazide). The alkylations took place with high de's (70–92%) in favor of isomers **243**, isolated after chromatographic separation. The allyl-substituted compound **243** (R = allyl) was reduced with LAH to yield the enantiopure (*R*)-3-methylpent-4-en-1-ol **244** and the N-unsubstituted 3,1-benzoxazine **245** as a 5:1 diastereomeric mixture (Scheme 45) <2000JOC6540>.

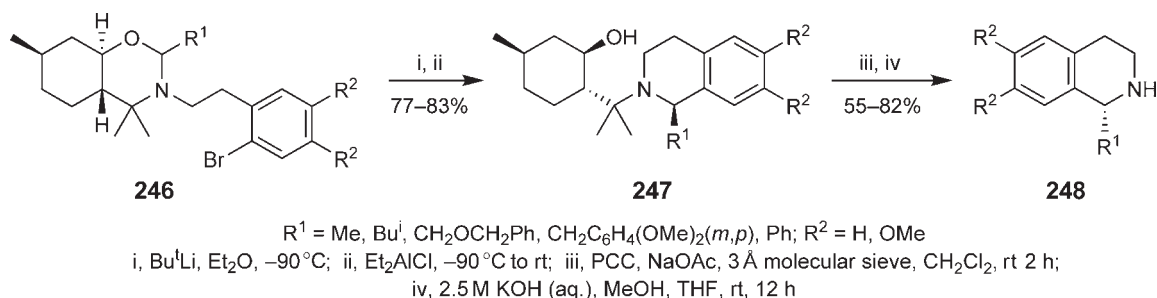


Scheme 45

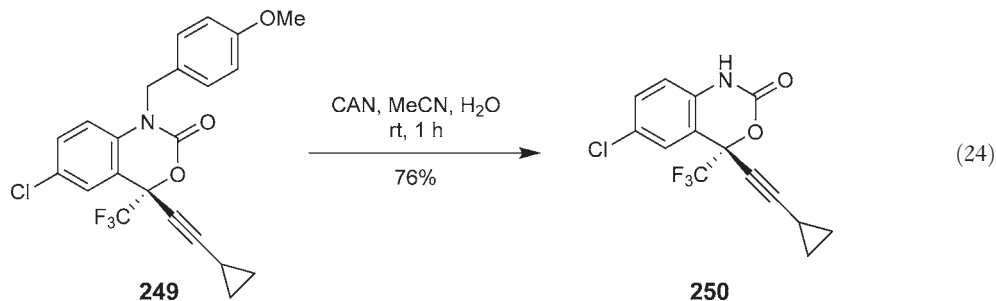
Transformations involving the participation of the C=O or C=C bonds of the substituents attached to the nitrogen atom of (–)-8-aminomenthol-derived perhydro-1,3-benzoxazines (see Section 8.05.7) have been applied in numerous asymmetric reactions, for example, additions or cycloadditions <1996TL9085, 1997TL1463, 1999JOC4282, 1999TL2421, 2000JOC831, 2006JOC5388>, aryl radical cyclizations <1997SL1391>, carbolithiations <2001JA1817>, and Heck cyclizations <2002SL259>.

The perhydro-1,3-benzoxazine moiety furnished the necessary chiral environment and was the source of the nitrogen atom in the final heterocycle when the chiral, nonracemic perhydro-1,3-benzoxazine **246**, bearing a 2-(*o*-bromophenyl)ethyl substituent on the nitrogen, was transformed to enantiopure 1-substituted 1,2,3,4-tetrahydroisoquinolines **248** (Scheme 46). On treatment of **246** with Bu^tLi and Et₂AlCl, the resulting arylmetal derivatives underwent intramolecular ring opening, affording tetrahydroisoquinolines **247** as single diastereomers, the N-substituent of which was removed in a two-step oxidation–elimination reaction <2001JOC243>.

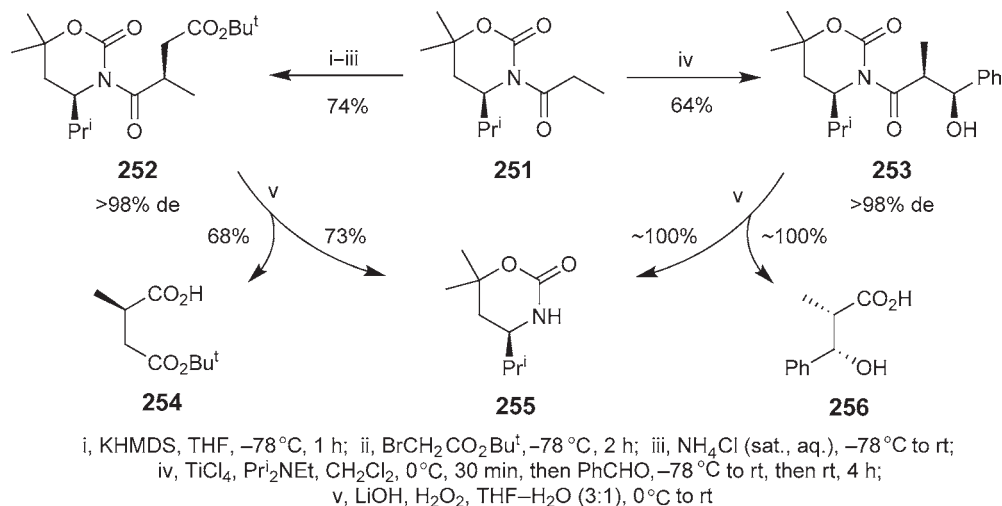
Treatment of the 3,1-benzoxazin-2-one derivative **249** with cerium ammonium nitrate (CAN) resulted in removal of the *p*-methoxybenzyl substituent, by oxidation of its α-position, which led to the human immunodeficiency virus-1 (HIV-1) reverse transcriptase inhibitor efavirenz **250** and anisaldehyde (Equation 24) <1998JOC8536>.



Scheme 46

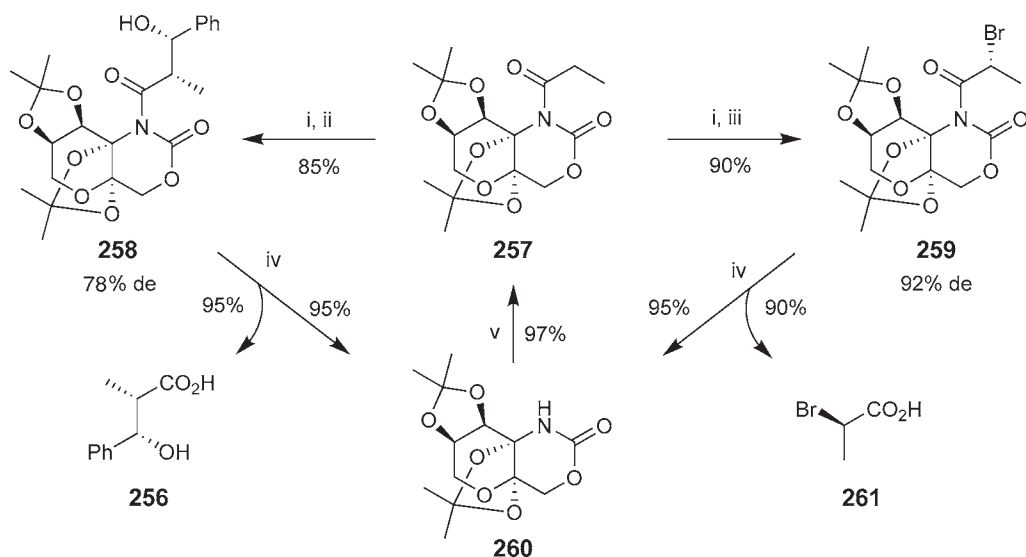


The *N*-acyl derivatives of 4-substituted-3,4,5,6-tetrahydro-2*H*-1,3-oxazin-2-ones proved to behave as effective chiral auxiliaries in asymmetric enolate alkylations and aldol reactions, the stereoselectivities of which were found to be higher for 4-isopropyl than for 4-phenyl derivatives [<2006OBC2753>](#). The transformations of 4-isopropyl-6,6-dimethyl-3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazin-2-one **251** to **252** or **253** proceeded with excellent diastereoselectivities ([Scheme 47](#)). 6,6-Dimethyl substitution within the oxazine ring facilitated exclusive exocyclic cleavage upon hydrolysis of the C-alkylated and the aldol products **252** and **253**, to furnish α -substituted carboxylic acids **254** or α -methyl- β -hydroxycarboxylic acids **256**.



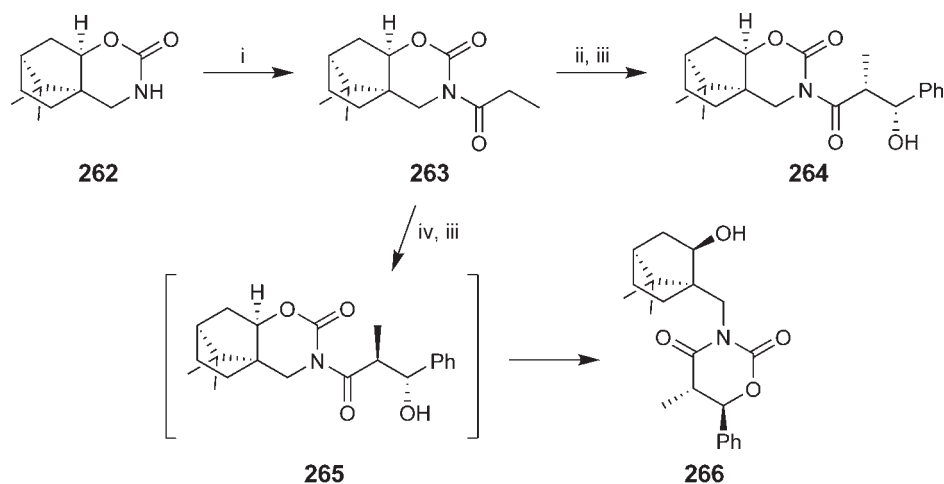
Scheme 47

The D-fructose-derived, chiral, nonracemic 1,3-oxazin-2-one derivative **260** exerted smooth stereocontrol, resulting in high levels of asymmetric induction and good chemical yields in various synthetic transformations. The chiral fragments **256** and **261** formed in the aldol or α -bromination reactions of the *N*-propionyl derivative **257** could easily be removed from the parent auxiliary by mild hydrolysis ([Scheme 48](#)). The Diels–Alder cycloadditions of the *N*-acryloyl and *N*-cinnamoyl derivatives of **260** were also characterized by excellent diastereofacial selectivity [<1998T9765>](#).



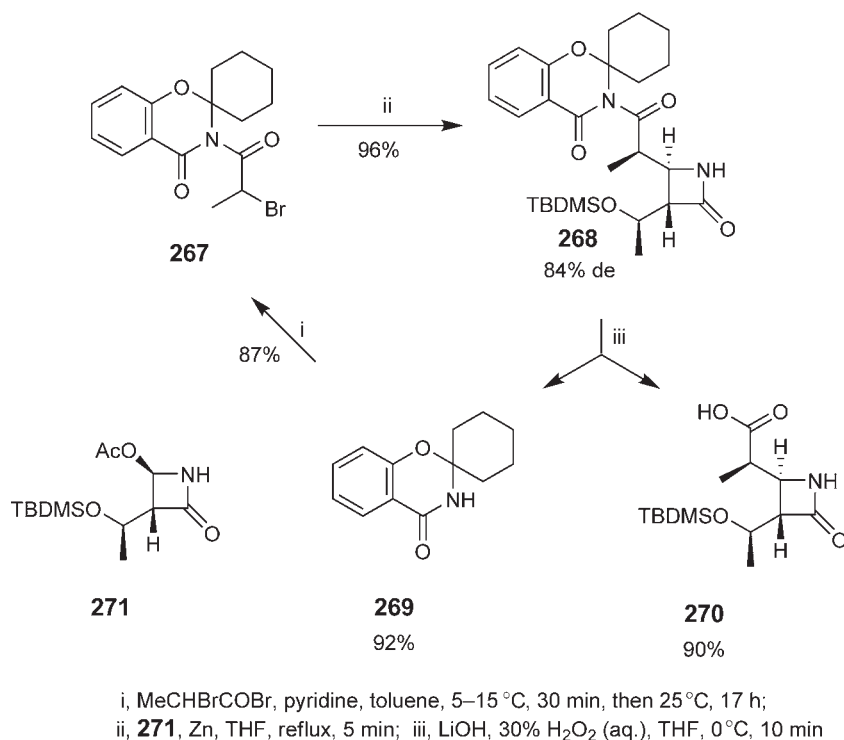
Scheme 48

The *syn*- or *anti*-selectivity of the process and the further rearrangement of the product were found to depend strongly on the amount of Bu_2BOTf applied in the boron-mediated aldol additions of the chiral, nonracemic, terpenoid-derived 3-propionyl-1,3-oxazin-2-one **263** and benzaldehyde. On use of a stoichiometric amount of Bu_2BOTf , the *syn*-aldol product **264** was formed with nearly complete diastereoselectivity. In the presence of an excess of Bu_2BOTf , the addition resulted in formation of the *anti*-aldol product **265**, which underwent an unexpected ring cleavage and recyclization to give the tetrahydro-1,3-oxazine-2,4-dione **266** in virtually quantitative yield (Scheme 49). The opposite asymmetric inductions in the formation of **264** and **266** were explained by the different boron-chelated intermediates in the transition states of the reactions <1997TL4917>.



Scheme 49

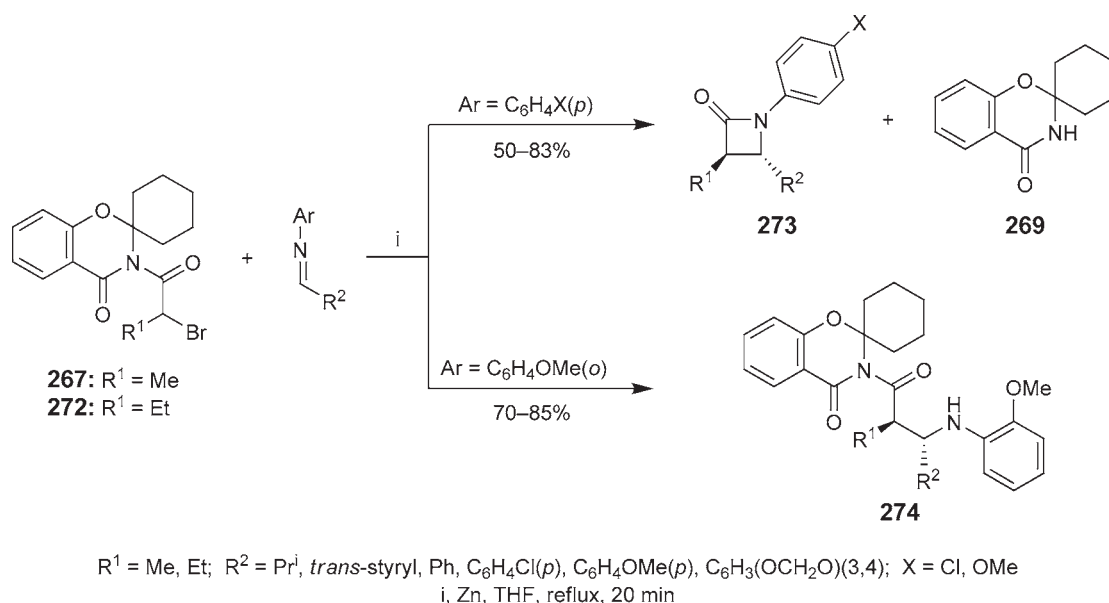
The salicylamide-derived 1,3-benzoxazin-4-one **269** proved to be an efficient auxiliary in the stereocontrolled synthesis of the 1- β -methylcarbapenem key intermediate **270**. The Reformatsky reaction of *N*-(2-bromopropionyl)-1,3-benzoxazin-4-one **267** with the acetoxyazetidinone **271** gave 2-substituted azetidinone derivative **268** with high diastereoselectivity and in high chemical yield (Scheme 50) <1995JOC1096, 1996J(P1)2851, 1997JOC2877, 2001OPD186>. Azetidinone **268** could be obtained with similarly high diastereoselectivity, but in lower yields, by the reaction of the sodium enolate generated from *N*-propionyl-2,2-disubstituted-1,3-benzoxazin-4-ones with **271** <1996TL4967>. The diastereomerically pure **268**, obtained by recrystallization of the crude product, was hydrolyzed to **270** at low temperature by using lithium hydroxide and hydrogen peroxide.



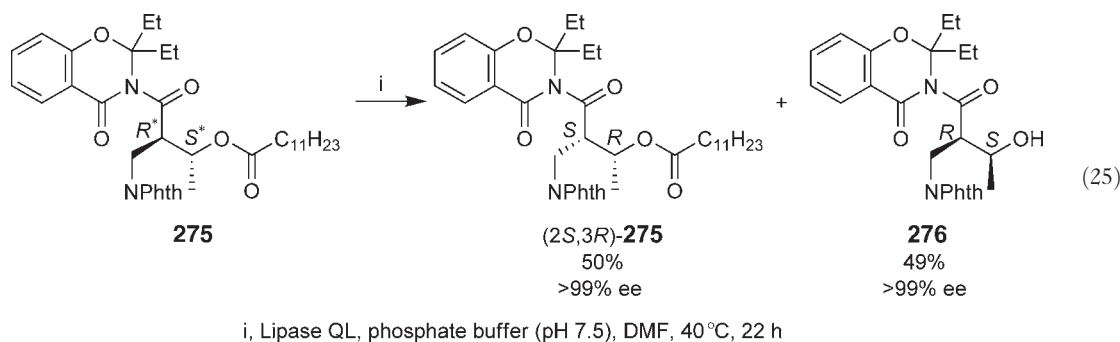
Scheme 50

Reformatsky reactions of *N*-(2-bromoalkanoyl)-1,3-benzoxazin-4-ones **267** and **272** and imines derived from aniline or *p*-substituted anilines gave *trans*- β -lactams **273** with complete diastereoselectivity, and the 1,3-benzoxazin-4-one auxiliary **269** could also be recycled. However, in the similar transformations of imines containing an *o*-methoxyphenyl substituent on the nitrogen, no cyclization to azetidinone occurred and *anti*- β -aminocarboxamide derivatives **274** were the only products formed (Scheme 51) <2005S725>.

Kinetic resolutions by means of the selective formation or hydrolysis of an ester group in enzyme-catalyzed reactions proved to be a successful strategy in the enantioseparation of 1,3-oxazine derivatives. Hydrolysis of the racemic laurate ester **275** in the presence of lipase QL resulted in formation of the enantiomerically pure alcohol derivative **276** besides the (2*S*,3*R*)-enantiomer of the unreacted ester **275** (Equation 25) <1996TA1241>. The porcine pancreatic lipase-catalyzed acylation of 3-(ω -hydroxyalkyl)-4-substituted-3,4-dihydro-2*H*-1,3-oxazines with vinyl acetate in tetrahydrofuran (THF) took place in an enantioselective fashion, despite the considerable distance of the acylated hydroxy group and the asymmetric center of the molecule <2001PAC167, 2003IJB1958>.



Scheme 51

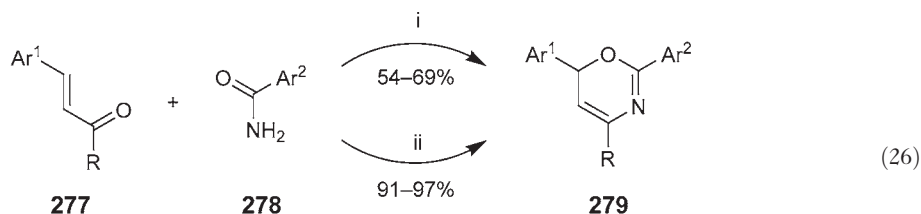


8.05.9 Ring Syntheses from Acyclic Compounds, Classified by Number of Ring Atoms Contributed by Each Component

As in CHEC-II(1996), the syntheses of 1,3-oxazine derivatives and their carbo- or heterocycle-fused analogs are discussed according to the numbers and elemental compositions of the assembling units. Within a given type of assembling units, the sequence of discussion follows the decreasing number of double bonds in the 1,3-oxazine ring.

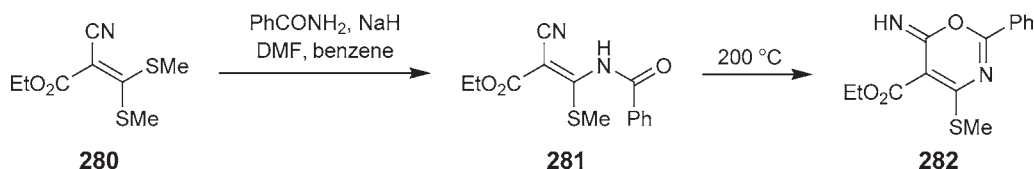
8.05.9.1 [3+3] Types

The Lewis acid-catalyzed condensation of α,β -unsaturated ketones **277** with amides **278** furnished 2,4,6-trisubstituted-6*H*-1,3-oxazines **279**. An environmentally benign solvent-free version of this process, based on the application of montmorillonite K-10 clay and a brief microwave irradiation, provided oxazines **278** in higher yields than in the conventional solution-phase method (Equation 26) <2004BCJ2265>.



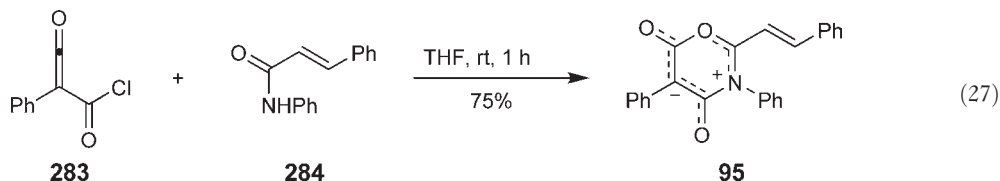
Ar¹ = Ph, 2-furyl, 3-indolyl, C₆H₄OMe(*p*); Ar² = Ph, 2-furyl; R = Me, Ph, C₆H₄Br(*p*)
 i, Et₂O·BF₃, CHCl₃, reflux, 4–6 h; ii, K-10 montmorillonite clay, microwave irradiation, 2–4 min

In a base-catalyzed substitution reaction with benzamide, ethyl 2-cyano-3,3-bis(methylsulfanyl)acrylate **280** gave the 3-aminoacrylate derivative **281**, which on thermal cyclization yielded the functionalized 6-imino-1,3-oxazine **282** (Scheme 52) <1995BML695>.



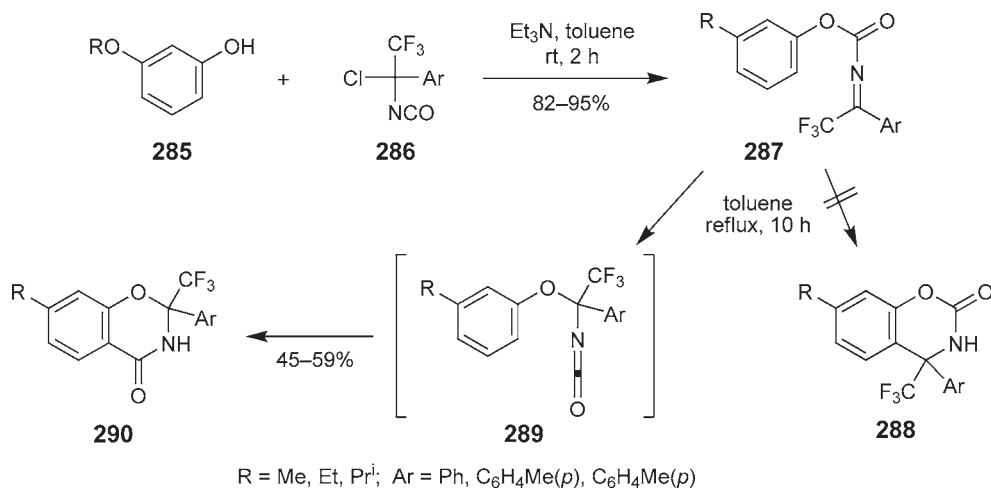
Scheme 52

In the reaction of chlorocarbonylphenylketene **283** and *N*-phenylcinnamoyl amide **284**, the mesoionic 1,3-oxazinium derivative **95** was obtained as a metastable, but isolable, red solid (Equation 27) <2005JOC5859>.

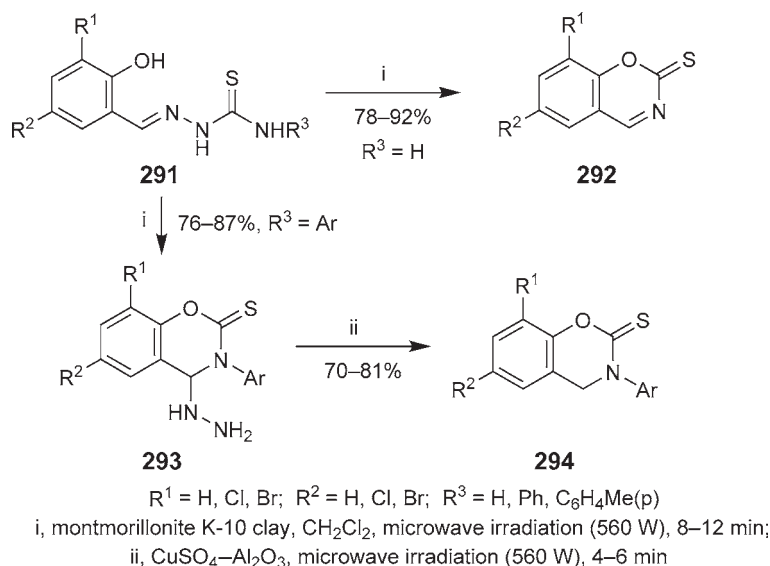


In the thermal cyclization of 3-alkoxyphenyl *N*-(1-aryl-2,2,2-trifluoroethylidene)carbamates **287**, obtained from 3-alkoxyphenols **285** and 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates **286**, 2-aryl-2-trifluoromethyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-ones **290** were formed instead of the regioisomeric 1,3-benzoxazin-2-ones **288** (Scheme 53). The formation of **290** was explained by a thermal isomerization of **287** involving a skeletal 1,3-rearrangement of the electron-rich aryloxy group to the azomethine carbon, which is electron deficient due to the electron-withdrawing CF₃ group <2002JFC(116)97>.

The montmorillonite K-10 clay-catalyzed cycloisomerization of salicylaldehyde thiosemicarbazones **291** under microwave irradiation resulted in formation of 1,3-benzoxazine-2-thione derivatives. Depending on the substituent R³ on the thiosemicarbazone nitrogen atom, products of either 2*H*-1,3-benzoxazine-2-thione **292** or 4-hydrazino-3,4-dihydro-2*H*-1,3-benzoxazine-2-thione **293** type were formed in high yields. On reductive dehydrazination on alumina-supported copper(II) sulfate under solvent-free microwave irradiation, compounds **293** furnished 3,4-dihydro-2*H*-1,3-benzoxazine-2-thiones **294** (Scheme 54) <1998JCM307, 2004T131>. Similar transformations starting from semicarbazones of *o*-hydroxyacetophenone or salicylaldehyde and its substituted derivatives gave the corresponding 3,4-dihydro-2*H*-1,3-benzoxazin-2-ones <2004JOC8118>.



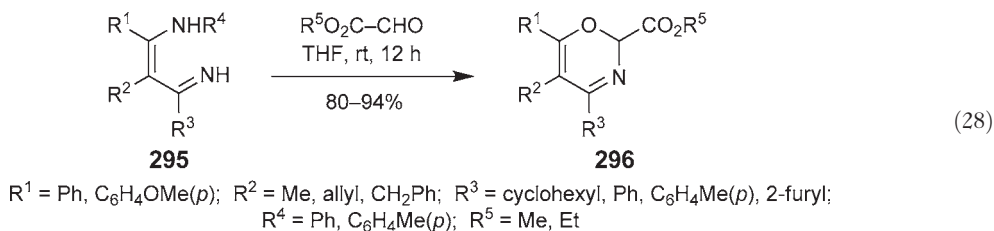
Scheme 53



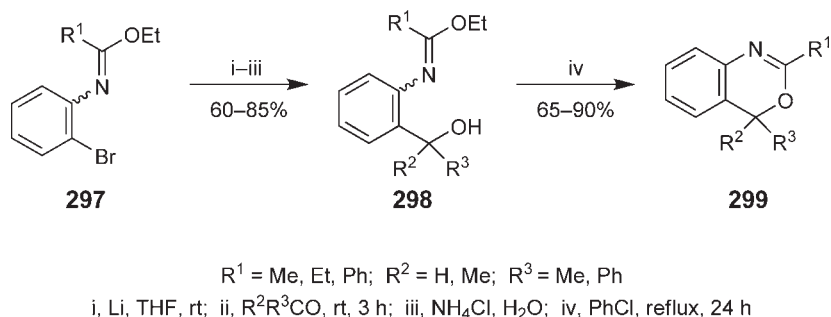
Scheme 54

8.05.9.2 [4+2] Types

In the reactions of 4-amino-1-azadienes **295** with esters of glyoxylic acid, chemoselective cyclization occurred with displacement of the amino group NHR⁴, and 2*H*-1,3-oxazine-2-carboxylic acid derivatives **296** were formed in high yields instead of the corresponding 1,2-dihydropyrimidines usually obtained in the reactions of **295** with aliphatic or aromatic aldehydes (Equation 28) <1996T3095>.

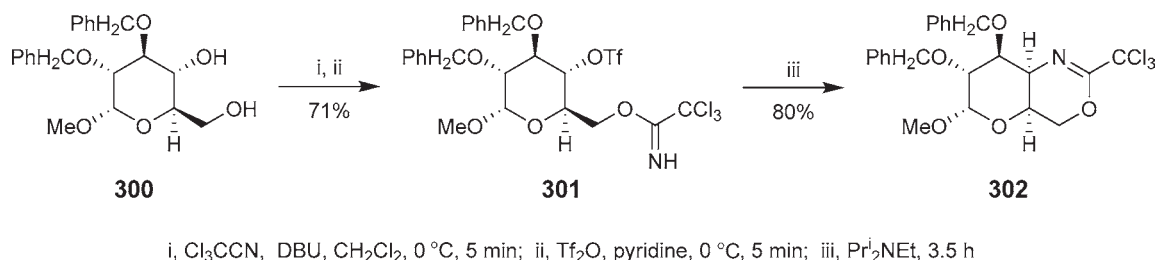


In the reactions of aldehydes and ketones with ethyl *N*-(2-bromophenyl) imidates **297** in the presence of lithium, hydroxyimides **298** were formed, the thermal cyclization of which in refluxing chlorobenzene resulted in formation of 4*H*-3,1-benzoxazines **299** in good yields (Scheme 55) <1996SC3167>.



Scheme 55

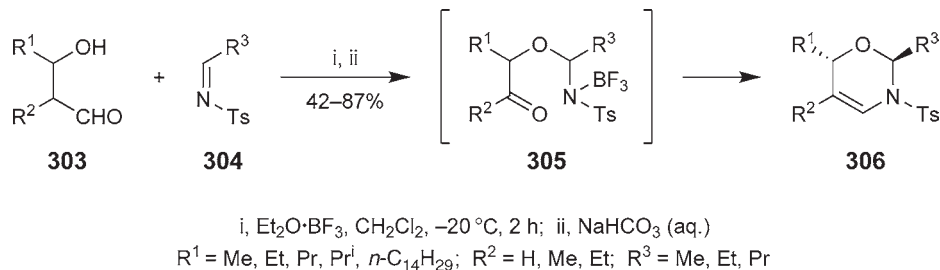
The stereoselective introduction of an axially oriented amino function on methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside **300** was achieved via the 1,3-oxazine intermediate **302**. Treatment of **300** with trichloroacetonitrile in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the selective formation of the 6-*O*-acetimidate. Introduction of the 4-*O*-triflate followed by base-mediated cyclization of the resulting **301** gave 2-trichloromethyl-1,3-oxazine **302** (Scheme 56). This three-step, one-pot procedure was successfully applied for the preparation of the corresponding 1,3-oxazine derivatives, starting from analogous thioglycosides <2003OBC4160>.



Scheme 56

Chiral nonracemic 1-aryl-2-aminopropane-1,3-diols were converted to 2-trichloromethyl-5,6-dihydro-4*H*-1,3-oxazine derivatives with complete diastereoselectivity via the corresponding bistrichloroacetimidate intermediates. In this transformation, one trichloroacetimidate participated as a leaving group, and the other as a nucleophile <2007OL247>.

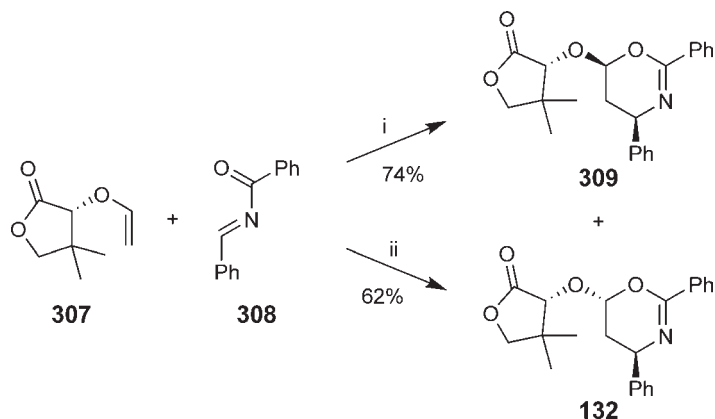
In the condensation of β -hydroxy aldehydes **303** with *N*-sulfonyl aliphatic aldimines **304** (which could also be prepared *in situ* from the aliphatic aldehyde and *N*-sulfinyl *p*-toluenesulfonamide), 2,5,6-trisubstituted 3,6-dihydro-2*H*-1,3-oxazines **306** were formed as single *trans*-stereoisomers (Scheme 57). No oxazine formation was observed in the



Scheme 57

analogous reactions of β -hydroxy ketones or *N*-sulfonyl aromatic aldimines. The surprisingly high stereoselectivity of the reaction was explained by the amido acetal equilibration process in the transformation of the intermediates **305** to the thermodynamically more stable *trans*-dihydro-2*H*-1,3-oxazines **306** <1995SL527, 1996T3135>.

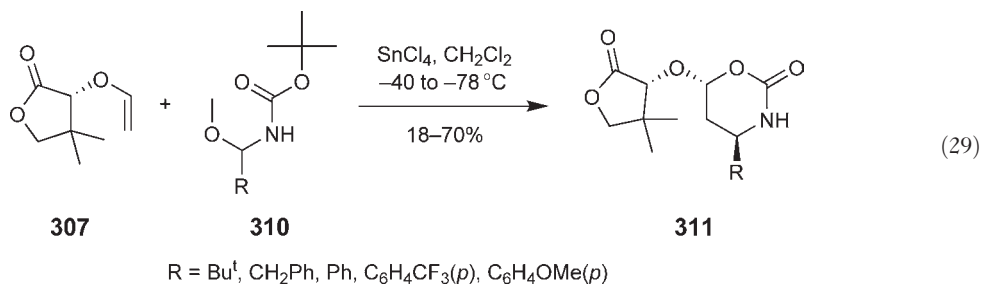
The heterocycloaddition between (*R*)-*O*-vinylpantolactone **307** and *N*-benzoylbenzaldimine **308** gave high and divergent diastereoselectivities when carried out in the presence of a catalytic amount of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium [Yb(FOD)₃] or a stoichiometric amount of tin(IV) chloride, resulting in C-4-epimeric 6-alkoxy-2,4-diphenyl-5,6-dihydro-4*H*-1,3-oxazines **309** and **132** as the main products (Scheme 58), both of which are precursors of (*R*)-3-benzoylamino-3-phenylpropanal **133** (see Section 8.05.6.3) <2000OL585>. It was later found that replacement of the *N*-benzoyl aldimines by *N*-acyl-*O*-methyl-*N,O*-acetals extended the possibilities of the reaction, and various 3-substituted-3-benzamidopropanals were prepared in this highly enantioselective way via the corresponding 4-substituted-5,6-dihydro-4*H*-1,3-oxazines <2003JOC4338>.



i, Yb(FOD)₃, cyclohexane, 80 °C, 3 d; ii, SnCl₄, CH₂Cl₂, -78 °C, 30 min

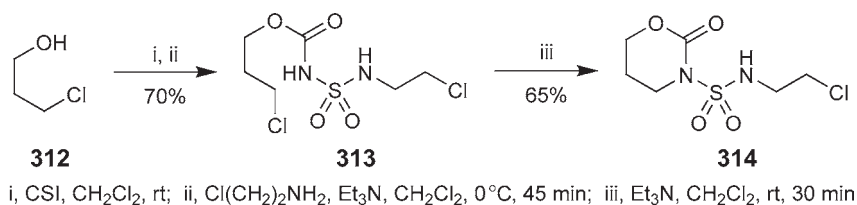
Scheme 58

In the reactions of (*R*)-*O*-vinylpantolactone **307** and *N*-BOC-*O*-methyl-*N,O*-acetals **310**, the corresponding tetrahydro-1,3-oxazin-2-ones were formed as a result of loss of the *tert*-butyl group. The heterocycloadditions took place with high facial selectivity, leading to isomers **311** as the main products (Equation 29). Compounds **311** could also be utilized in the synthesis of β -aminoaldehyde derivatives (see Section 8.05.6.3) <2004TL9589, 2006EJO3309>.



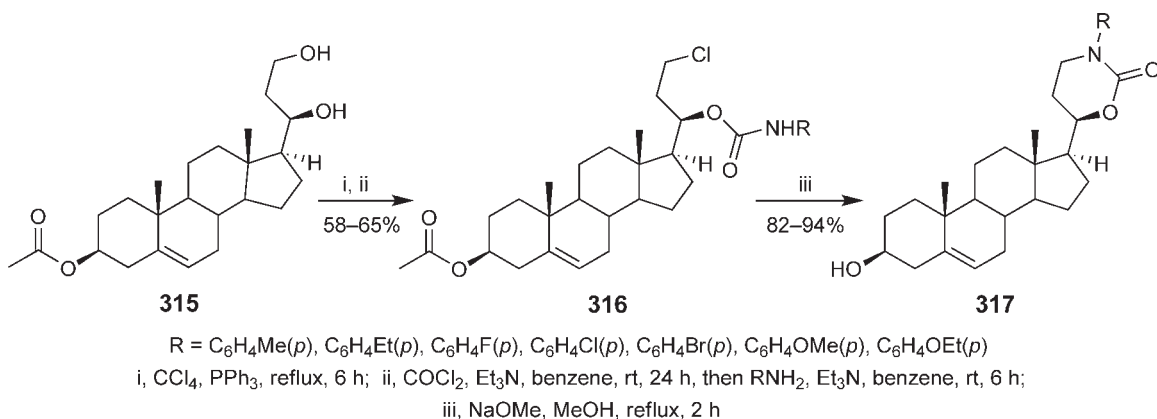
3-Bromopropylamine was reported to form tetrahydro-1,3-oxazin-2-one in moderate yield when treated with the carboxylating reagent (O₂^{•-}/CO₂) formed by the electrochemical reduction of oxygen in acetonitrile in the presence of carbon dioxide <1997JOC6754>.

On the reaction of 3-chloropropanol **312** with chlorosulfonyl isocyanate (CSI) and then with 2-chloroethylamine, an acyclic *N*-sulfamoyl urethane **313** was formed, treatment of which with triethylamine resulted in formation of the 1,3-oxazin-2-one derivative **314** (Scheme 59) <1996T14217>.



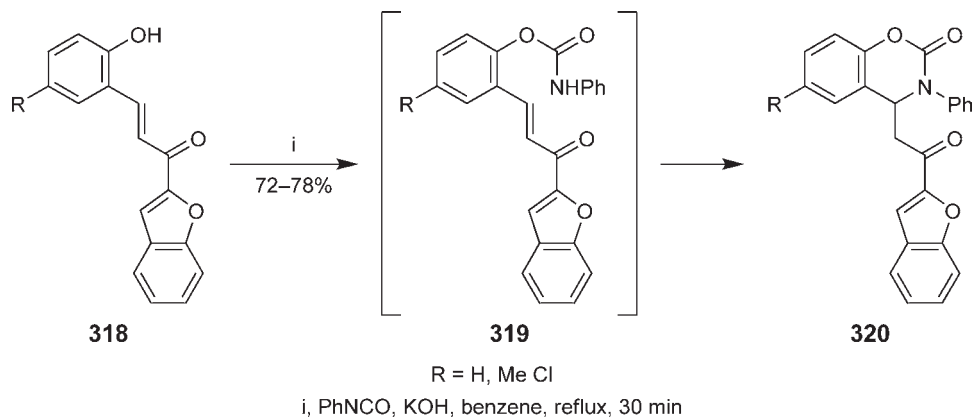
Scheme 59

During the alkaline methanolysis of 3 β -acetoxy-21-(chloromethyl)pregn-5-ene-20 β -*N*-aryl carbamates **316**, cyclization of the chloroalkyl carbamate moiety occurred besides the splitting off of the *O*-acetyl group, and steroidal tetrahydro-1,3-oxazin-2-ones **317** were formed (Scheme 60). Compounds **316** were prepared in two steps starting from 3 β -acetoxy-21-(hydroxymethyl)pregn-5-en-20 β -ol **315**; exchange of the primary hydroxy substituent in the Appel reaction was followed by formation of the carbamate group through the use of phosgene and substituted anilines <2004STE451>.



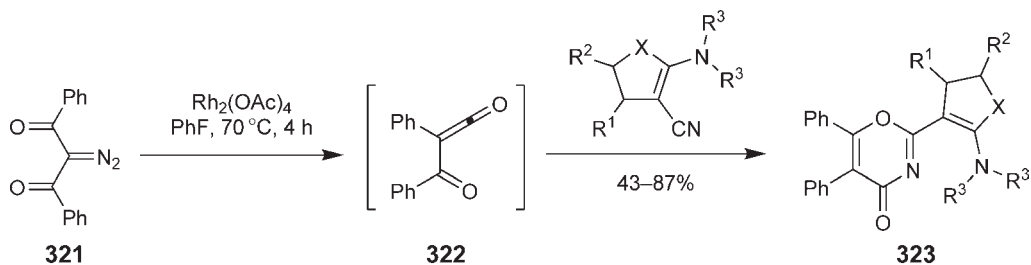
Scheme 60

The carbamates formed from 2-hydroxychalcones and alkyl or aryl isocyanates readily cyclize to 3,4-dihydro-1,3-benzoxazin-2-one derivatives <1996CHEC-II(6)301>. When hydroxychalcones **318** with a benzofuran moiety were heated under reflux with phenyl isocyanate in benzene in the presence of a catalytic amount of potassium hydroxide, 1,3-benzoxazin-2-one derivatives **320** were formed through the intermediate open-chain carbamates **319** (Scheme 61) <2006JHC437>.



Scheme 61

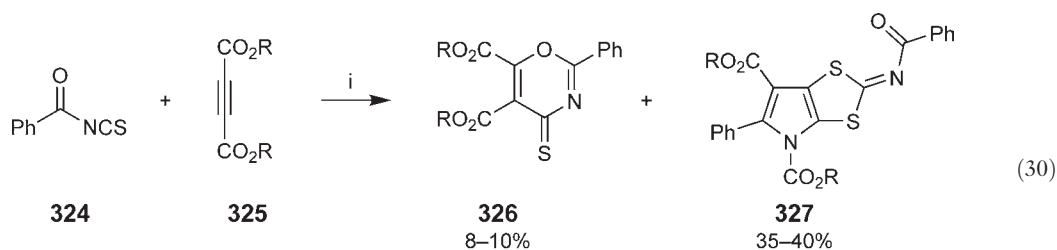
The rhodium(II) acetate-catalyzed reaction of dibenzoyldiazomethane **321** with 2-amino-4,5-dihydro-3-furan- or -3-thiophenecarbonitriles gave 4*H*-1,3-oxazin-4-one derivatives **323** through the [4+2] cycloaddition of the cyano group to the benzoylphenylketene **322** generated by the thermal Wolff rearrangement of dibenzoyldiazomethane (Scheme 62). With furan carbonitriles, when 3 equiv of dibenzoyldiazomethane was used for the reactions, furo[2,3-*b*]pyran derivatives were formed instead of **323** <1995LA187, 1998JPR51>.



X = O, S; R¹ = H, Ph; R² = H, Me, Ph; N(R³)₂ = 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl

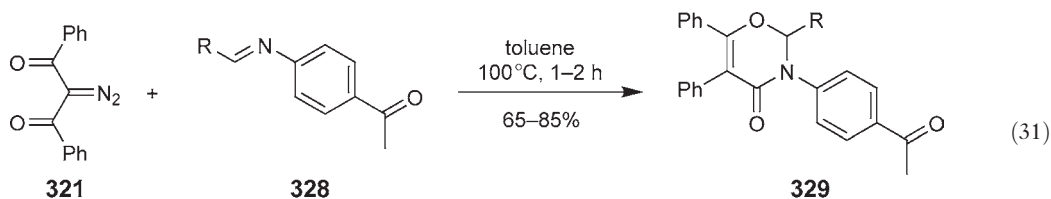
Scheme 62

In the reactions of benzoyl isothiocyanate **324** and dialkyl acetylenedicarboxylates **325** in the presence of triphenylphosphine, 2-phenyl-4-thioxo-4*H*-1,3-oxazine-5,6-dicarboxylates **326** and dialkyl 2-(benzoylimino)-5-phenyl-4*H*-[1,3]dithiolo[4,5-*b*]pyrrole-4,6-dicarboxylates **327** were formed in a ratio of 1:3 (Equation 30) <2006TL2953>.



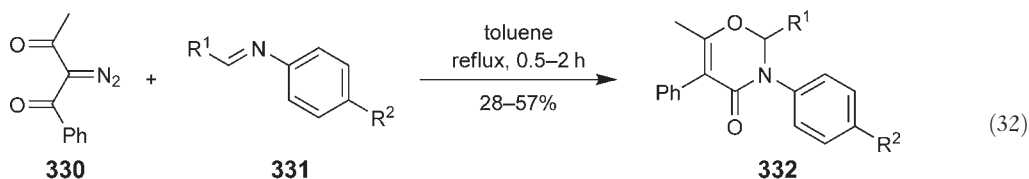
R = Me, Et, Bu^t
i, PPh₃, CH₂Cl₂, -10 °C to rt, then rt, 24 h

The benzoylphenylketene generated from **321** displayed a pronounced tendency to form chemospecific [2+4] Diels–Alder adducts with the C=N group of keto-imines. When compounds **328**, derived from *p*-aminoacetophenone and aromatic aldehydes, were reacted with α -diao- β -diketone **321**, 2,3-dihydro-4*H*-1,3-oxazin-4-ones **329** were obtained via the addition of benzoylphenylketene to the C=N bond, and no formation of the corresponding C=O adducts, 4*H*-1,3-dioxin-4-ones, was observed (Equation 31) <2001J(P1)2266>.

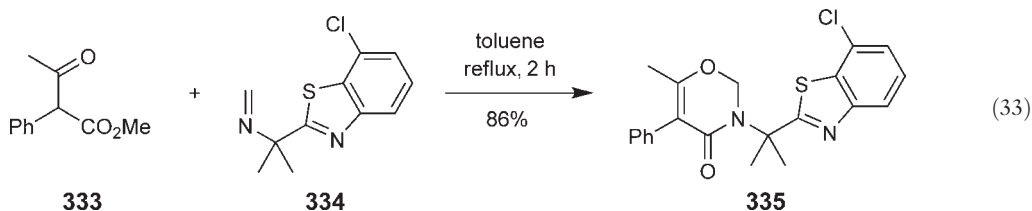


R = Ph, C₆H₄OMe(*p*), C₆H₄Cl(*p*), C₆H₄NO₂(*p*)

The cycloaddition reactions of the unsymmetrical α -diao- β -diketone, 2-diao-1-phenyl-1,3-butanedione **330**, with diaryl imines **331** took place with high regioselectivity, affording exclusively the 6-methyl-5-phenyl-substituted 4*H*-1,3-oxazin-4-ones **332** via the acetylphenylketene, generated by the thermal Wolff rearrangement of **330** (Equation 32) <2002HAC165>.

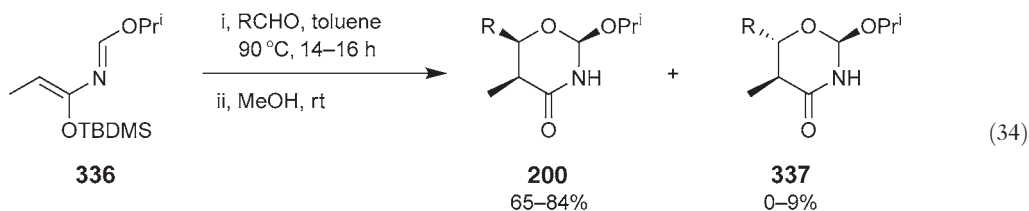


The cyclocondensation of methyl 2-phenyl-3-oxobutanoate **333** with the Schiff base **334** derived from the corresponding arylisopropylamine and paraformaldehyde resulted in formation of 2*H*-1,3-oxazin-4(3*H*)-one **335** in good yield (Equation 33) <2004MI981>.

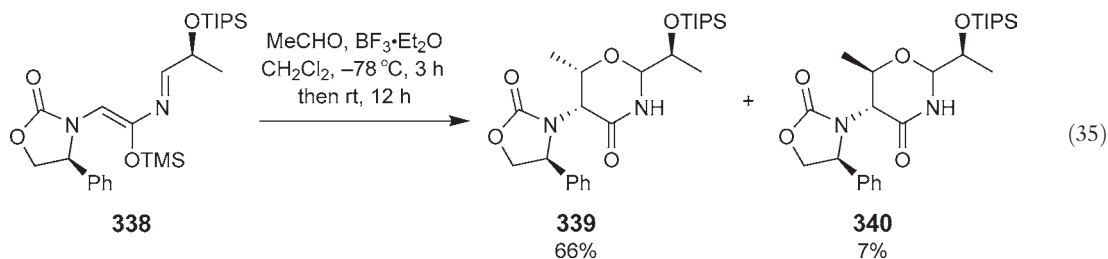


The Lewis acid-mediated reactions of 2-aza-1,3-dienes and aldehydes, resulting in tetrahydro-1,3-oxazin-4-one derivatives, were explained in terms of the competitive existence of two reaction pathways: a [4+2] hetero-Diels–Alder cycloaddition reaction and a Mukaiyama aldol reaction <2001TA439>.

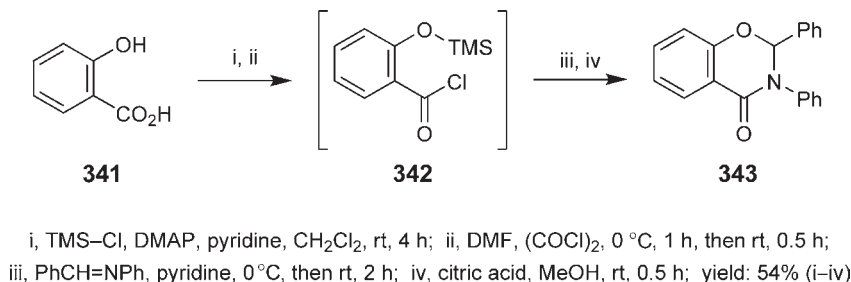
When 2-aza-3-silyloxy-1,3-diene **336** was heated with aliphatic or aromatic aldehydes in toluene, stereoisomeric tetrahydro-1,3-oxazin-4-one derivatives **200** and **337** were obtained without Lewis acid catalysis (Equation 34). The cycloaddition proved to be highly diastereoselective in favor of the *endo*-adducts, leading to the *cis*-isomers **200** as the main products <1999TL7079, 2002S2043>.



When the azadiene cycloaddition reaction was applied for the synthesis of nonracemic chiral 1,3-oxazin-4-one derivatives, the best diastereofacial selectivities were achieved with azadienes carrying two chiral auxiliaries. Tetrahydro-1,3-oxazin-4-one **339**, the key intermediate for the synthesis of D-threonine, was prepared by a highly stereoselective cycloaddition of **338**, derived from Evans chiral (4*S*)-oxazolidinone and (*S*)-lactic aldehyde, with acetaldehyde in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Equation 35) <1997JOC8911, 1999SL1735, 2001TA439>. A similar hetero-Diels–Alder reaction was applied for the preparation of optically active 5-phenylthiotetrahydro-1,3-oxazin-4-ones, the key intermediates for the synthesis of both enantiomers of fluoxetine and duloxetine <2006T12270>.

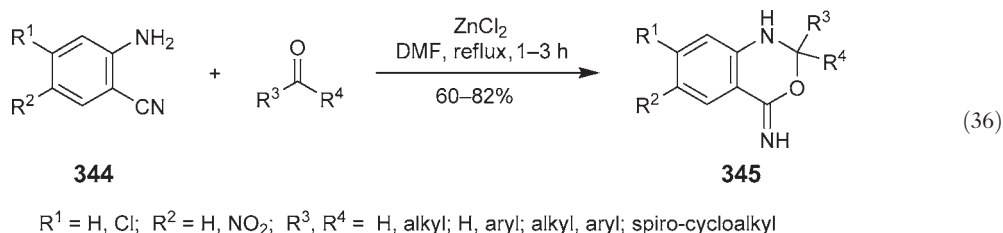


O-(Trimethylsilyl)salicyl chloride **342**, prepared *in situ* starting from salicylic acid **341** by using a two-step procedure, proved to react conveniently with diphenylimine under very mild conditions to form 2,3-diphenyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one **343** (Scheme 63) <1997JHC681>.

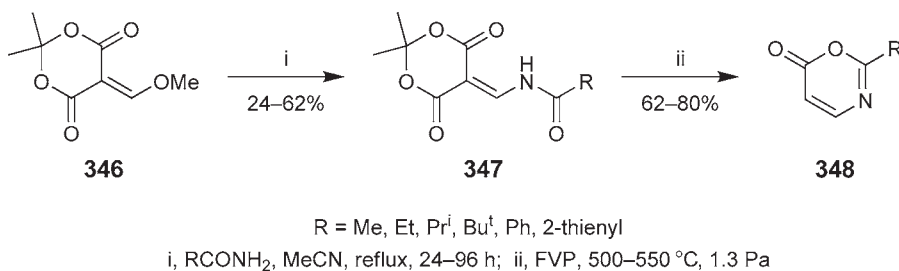


Scheme 63

A short and facile synthesis of 4-imino-1,4-dihydro-2*H*-3,1-benzoxazine derivatives **345** was accomplished in moderate to good yields through the cyclocondensation of *o*-aminobenzonitriles **344** with aldehydes or ketones in the presence of zinc chloride (Equation 36). For chloro- or nitro-substituted *o*-aminobenzonitriles, higher yields were observed than for the unsubstituted analogs <2005CCL1424, 2006JHC745, 2006MI928, 2006T7999>. The reactions of 5-nitrobenzonitrile **344** (R¹ = H, R² = NO₂) and aromatic aldehydes were also performed successfully under microwave conditions <2006SC1537>.

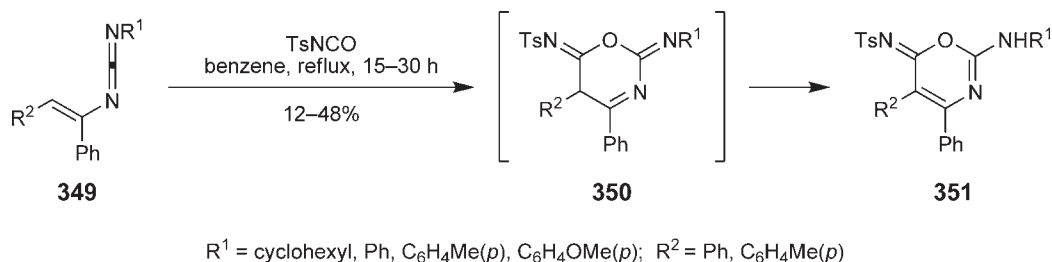


FVP of the Meldrum acid derivatives **347** gave the 2-substituted 1,3-oxazin-6-ones **348** (Scheme 64). This method proved to be an effective procedure for the preparation of both 2-aryl- and 2-alkyl-substituted derivatives. The yields were not significantly influenced by the increasing bulkiness of the alkyl groups R <1996T3163>.



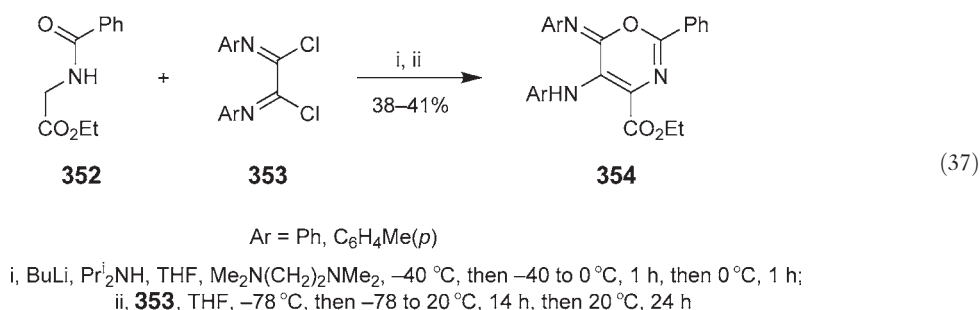
Scheme 64

Under thermal conditions, α,β -diarylvinylcarbodiimides **349** reacted as 2-azadienes (4 π -component) with *p*-tosyl isocyanate at the C=O bond (2 π -component) to form the intermediate cycloadducts **350** which, through H-migration, gave 2-amino-1,3-oxazin-6-imines **351** in moderate yields (Scheme 65) <1998J(P1)3065>.

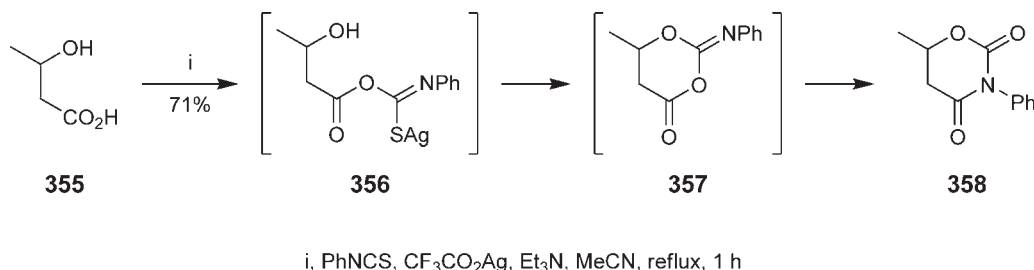


Scheme 65

The reactions of ethyl hippurate **352** with 1,2-diimidoyl-1,2-dichloroethanes **353** afforded 6-imino-6*H*-1,3-oxazines **354** by regioselective cyclization via the carbon and oxygen atoms of the dianion formed by the dilithiation of **352** (Equation 37) <2006JOC2332>.



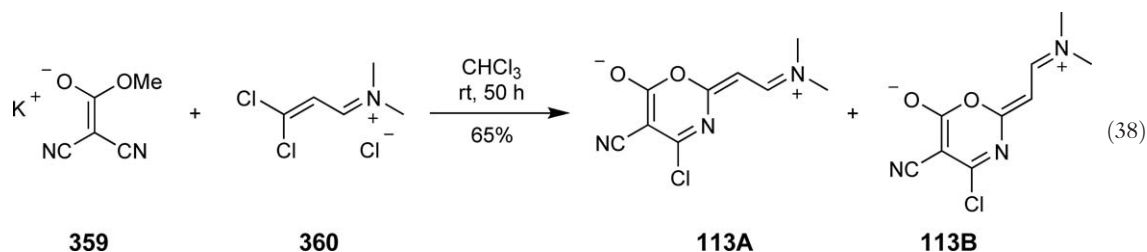
Isothiocyanates were found to form 1,3-oxazine-2,4-dione derivatives with β -hydroxy acids via a silver ion-mediated desulfuration–cyclization reaction (Scheme 66). In the presence of excess Et₃N and a silver salt, the anion of the hydroxy acid **355** formed an adduct **356** with isothiocyanate. Through desulfuration with silver ion, **356** afforded a dioxane intermediate **357** which was converted immediately to **358** by an intramolecular O- to *N*-acyl migration <1999H(51)2667>. Isocyanates proved to form 3-substituted 1,3-benzoxazine-2,4-diones with salicylate esters in the presence of Et₃N and 4-dimethylaminopyridine (DMAP) under mild conditions <1998TL2629>. The reaction of *N*-(*o*-hydroxybenzoyl)benzotriazole with *p*-tolyl isocyanate in the presence of Et₃N gave 3-(*p*-tolyl)-1,3-benzoxazine-2,4-dione in 40% yield <2007ARK(vi)6>.



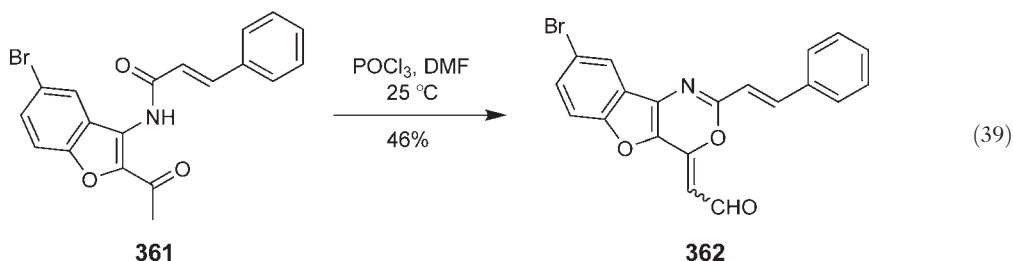
Scheme 66

8.05.9.3 [5+1] Types

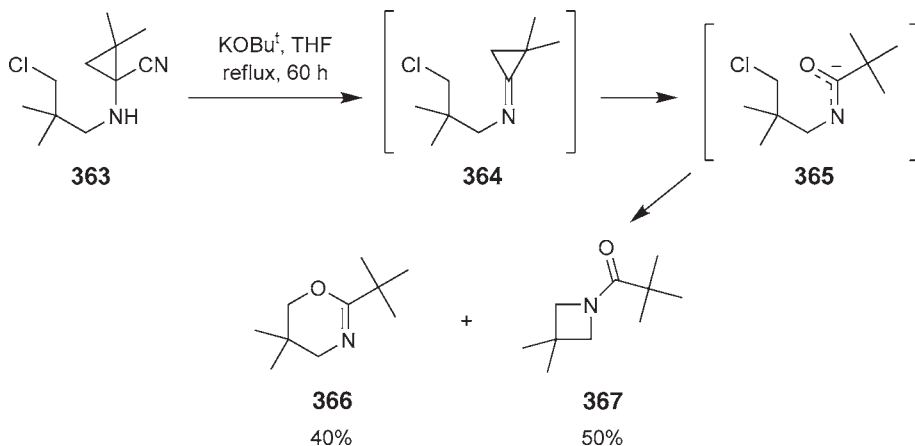
Potassium methyl dicyanoacetate **359** reacted smoothly with (3,3-dichloro-2-propenylidene)dimethylammonium chloride **360** in chloroform at room temperature to yield a 1:1 mixture of the (*E*)- and (*Z*)-isomers of the zwitterionic 1,3-oxazine iminium salts **113A** and **113B** (Equation 38) <1999H(51)2893>.



Treatment of 2-acetyl-(*E*)-3-styrylcarbonylaminobenzo[*b*]furan **361** with the Vilsmeier–Haack–Arnold reagent afforded ((*E*)-2-styrylbenzo[*b*]furo[3,2-*d*][1,3]oxazin-4-ylidene)acetaldehyde **362** (Equation 39). The cyclization was found to be markedly dependent on the chemical properties of both the 3-carbonylamino and the 2-acyl substituents of the benzo[*b*]furan ring: 3-styrylcarbonylmino and 2-acetyl groups favored oxazine ring formation <2006BML5849>.



Treatment of γ -chloroamine **363** with potassium *tert*-butoxide in refluxing THF gave rise to a mixture of (2-*tert*-butyl)-5,5-dimethyl-5,6-dihydro-4*H*-1,3-oxazine **366** and 1-pivaloylazetidene **367** (Scheme 67). The heterocycles **366** and **367** were formed through generation of the Favorskii intermediate **364** by dehydrocyanation, which was followed by opening of the cyclopropylideneimine by *tert*-butoxide with the subsequent loss of isobutene and a subsequent intramolecular N-alkylation or O-alkylation of the amide anion **365** <1999EJO239>.



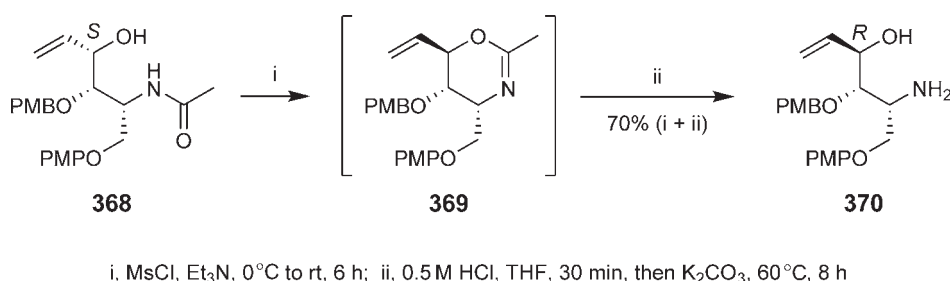
Scheme 67

The cyclocondensation of 1,3-amino alcohols with carboxylic acid derivatives is a method often applied for the synthesis of 5,6-dihydro-4*H*-1,3-oxazines <1996CHEC-II(6)301>. Ebsorb-4, a weakly acidic zeolite-type adsorbent with 4 Å pore size, proved an efficient catalyst of the cyclization of benzoic acid and 3-aminopropanol <2002TL3985>. In the presence of zinc chloride as a catalyst, the expulsion of ammonia drove the reactions of 3-aminopropanol with nitriles to completion, affording 2-substituted 5,6-dihydro-4*H*-1,3-oxazines in good yields

<1996BKC115>. Amides derived from aromatic carboxylic acids and benzotriazole were reported to form 2-aryl-5,6-dihydro-4*H*-1,3-oxazines with 3-aminopropanol in excellent yields when subjected to microwave irradiation in the presence of SOCl₂ <2004JOC811>. Imidates have often been applied to cyclize 1,3-amino alcohols directly to 5,6-dihydro-1,3-oxazine derivatives <1996ACS922, 2004JHC69, 2004JHC367>.

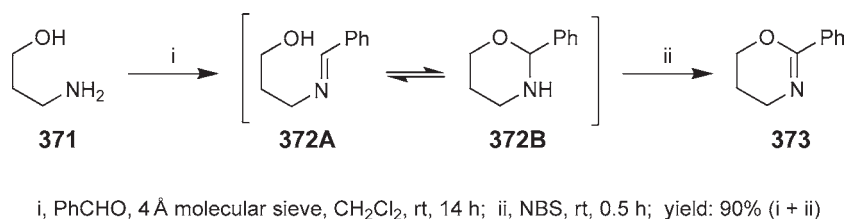
The cyclodehydration of *N*-acylated 1,3-amino alcohols with polyethylene-linked Burgess reagent (a carboxysulfamoyl triethylammonium inner salt) <1998T6987> or methanesulfonic acid <2001CRC497> resulted in formation of the corresponding 5,6-dihydro-4*H*-1,3-oxazine derivative. Treatment of *o*-(acylamino)benzyl alcohols with diethylaminosulfur trifluoride (DAST) resulted in parallel cyclodehydration and hydroxy-fluoro replacement, leading to mixtures of 2-substituted-4*H*-3,1-benzoxazines and *o*-(acylamino)benzyl fluorides, the ratio of which was dependent on the substituents at the α -position and the acyl groups <2006H(67)247>.

The ring closures of *N*-acylamino alcohols with thionyl chloride or mesyl chloride that take place via inversion of the hydroxy group at low temperature could be utilized for the epimerization of amino alcohols containing the hydroxy group attached to a chiral carbon atom. Through this principle, the (*S*)-configuration of the hydroxy-substituted carbon atom in the di-*O*-protected (PMP = *p*-methoxyphenyl, PMB = *p*-methoxybenzyl) *N*-acetylamino-triol **368** was inverted to (*R*)-**370** through dihydrooxazine **369** by treatment of **368** with MsCl/Et₃N and subsequent hydrolysis of the cyclic intermediate (Scheme 68) <2004TL7239>.



Scheme 68

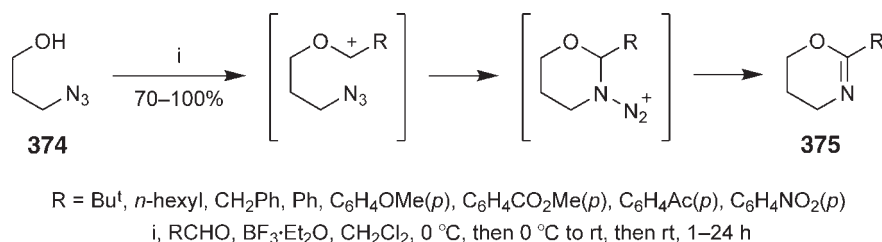
A convenient, one-pot procedure devised for the preparation of 2-phenyl-5,6-dihydro-4*H*-1,3-oxazine **373** was based on the *N*-bromosuccinimide oxidation of tetrahydro-1,3-oxazine **372**, formed *in situ* from 3-aminopropanol **371** and benzaldehyde (Scheme 69) <2006S2996>.



Scheme 69

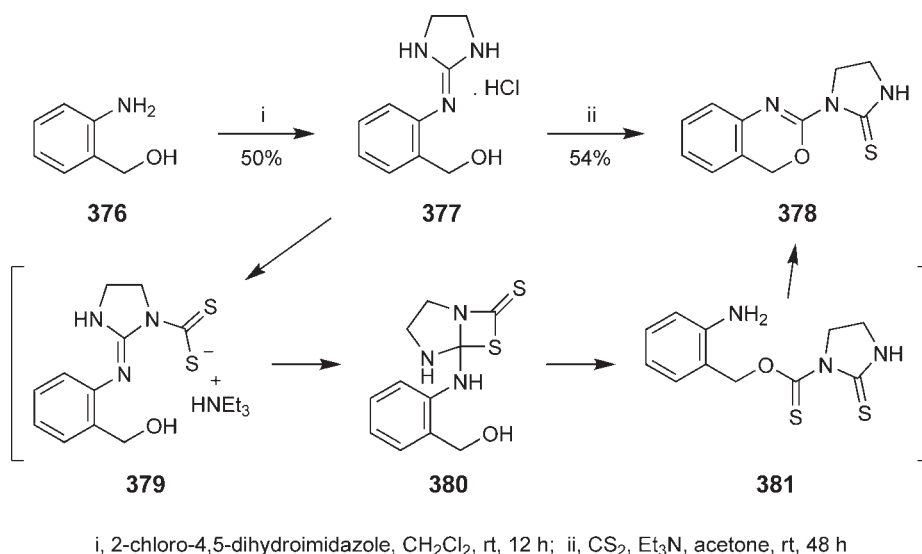
A modified Schmidt reaction of 3-azidopropanol **374** was reported to form 2-substituted 5,6-dihydro-4*H*-1,3-oxazines **375** in the presence of sulfuric acid <1984CHEC(3)995>, but good yields could be achieved only by using electron-poor aldehydes. Replacement of sulfuric acid by Lewis acids allowed the reaction to proceed under milder conditions and provided oxazines **375** in good to excellent yields even for aliphatic or electron-rich aromatic aldehydes (Scheme 70) <1996JOC2484>. The procedure was successfully extended to the synthesis of steroidal 5,6-dihydro-4*H*-1,3-oxazine derivatives <2002SL1077, 2004MI40, 2006STE809>.

The amidoalkylation of alkenes is a versatile process that is often applied for the synthesis of 5,6-dihydro-4*H*-1,3-oxazines <1996CHEC-II(6)301, 1998T1013>. In a recent version of this reaction, *N*-acyliminium ions were generated from *N*-(benzotriazol-1-ylmethyl)amides in the presence of zinc bromide <2001J(P2)530>.



Scheme 70

The reaction of 2-aminobenzyl alcohol **376** with 2-chloro-4,5-dihydroimidazole afforded [2-(4,5-dihydro-1*H*-imidazol-2-ylideneamino)phenyl]methanol hydrochloride **377**, which upon treatment with carbon disulfide gave 1-(4*H*-3,1-benzoxazin-2-yl)imidazolidine-2-thione **378** (Scheme 71). The assumed reaction mechanism involved the initial formation of the dithiocarbamate **379**, which underwent intramolecular nucleophilic addition to furnish the unstable thiazetidine **380**. By nucleophilic attack of the hydroxy group on the carbon atom of the thiazetidine ring, thiocarbamate derivative **381** was formed, which gave the final 3,1-benzoxazine **378** by an intramolecular cyclocondensation with the evolution of H₂S <2006H(68)687>.

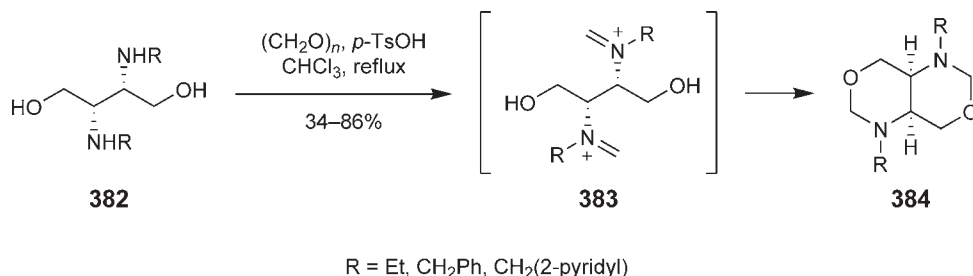


Scheme 71

In the reactions of 1,3-amino alcohols with aldehydes and ketones (or their acetal or ketal equivalents), perhydro-1,3-oxazines, as cyclic hemiaminals, are formed, the N-unsubstituted derivatives of which often exhibit a ring-chain tautomeric character (see Section 8.05.4.1.2). This cyclization is frequently carried out for the purpose of acquiring a conformationally restricted cyclic derivative which provides a better possibility to determine the relative configuration of the starting 1,3-amino alcohol <1995JOC6515, 1997CC565, 1999EJO805, 2004JBS971, 2006TA1308>. The ring closures of amino alcohols containing a primary amino group with aldehydes, or the cyclizations of secondary amino alcohols with formaldehyde or acetaldehyde, usually proceeded under mild conditions <1996MRC998, 1999EJO805, 2000OPD513, 2001JOC4759, 2001T6809, 2002BML787, 2002CH187, 2004JBS971, 2004TA1667, 2006JOC9891, 2007JOC1867>, though the analogous reactions of secondary amino alcohols or cyclizations by using ketones required higher temperature or the removal of water from the reaction mixture <1995JOC6515, 2000M975, 2001TL4837, 2005RJO1043>. The cyclization of 2-aminobenzyl alcohol with aromatic aldehydes also proceeded in molten trifluoromethanesulfonate salts of azaheterocycles (ionic liquids) <2000GC133>.

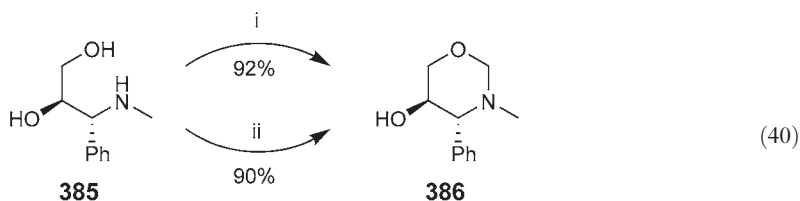
The ring closures of 1,4-diaminobutane-2,3-diols or 2,3-diaminobutane-1,4-diols with aldehydes resulted in formation of fused bis(tetrahydro-1,3-oxazine) heterocycles, diastereomeric 1,5-dioxo-3,7-diazadecalins and 1,5-diaza-3,7-dioxadecalins, as main products <1997TL3573, 1999EJO2033, 1999JOC1166, 2001EJO729>. As in the case of the N-substituted

diaminodiols **382** with formaldehyde (Scheme 72), these cyclizations proved to follow the Baldwin rules, since the ring closures of the iminium ion intermediates (e.g., **383**) to bis(1,3-oxazines) (e.g., **384**) are favored 6-*endo-trig*-processes, in contrast with the unfavored 5-*endo-trig*-ring closures to the corresponding bisoxazolidine derivatives <2006S1093>.



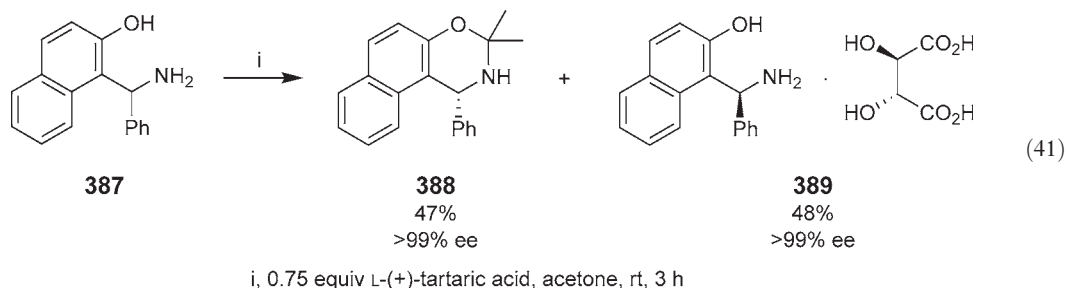
Scheme 72

A highly regioselective differentiation of the hydroxy groups was observed in the reaction of (2*R*,3*R*)-3-phenyl-3-methylamino-1,2-propanediol **385** with either formaldehyde or dichloromethane, both of which afforded the corresponding (2*R*,3*R*)-3-methyl-4-phenyltetrahydro-1,3-oxazin-5-ol **386** (Equation 40) <2004T10353>.



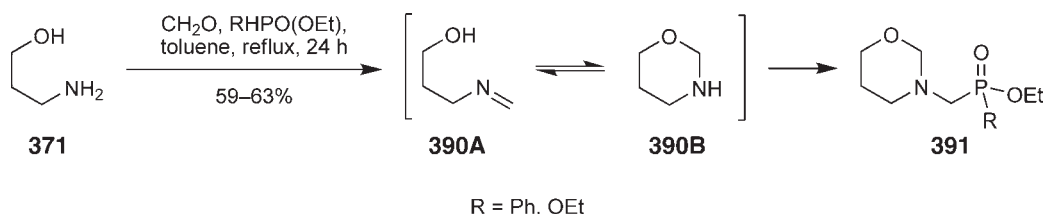
i, (CH₂O)_n, benzene, rt, 20 h; ii, CH₂Cl₂, NaHCO₃, H₂O, 100 °C (in a pressure reactor), 24 h

An efficient and simple kinetic resolution of the racemic Betti base **387** was achieved via its reaction with acetone in the presence of L-(+)-tartaric acid. When a suspension of racemic **387** in acetone was treated with L-(+)-tartaric acid, the (*S*)-enantiomer formed a crystalline L-tartrate salt **389**; this was filtered off, and the (*R*)-enantiomer could be isolated as a naphth[1,2-*e*]oxazine derivative **388** from the filtrate (Equation 41). Both enantiomers were obtained in excellent yields and ee's. The enantioseparation is presumed to take place via a kinetically controlled N,O-deketalization of the (*S*)-naphth[1,2-*e*]oxazine derivative <2005JOC8617>. An improved method for the enantioseparation of **387** was developed by the reaction of the ring-chain tautomeric 1,3-diphenyl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazine (**41**: X, Y = H) and L-(+)-tartaric acid, yielding the crystalline **389** in 85% yield <2007SL488>.



The carbamate derivatives of amino alcohols also proved applicable for the synthesis of cyclic hemiaminal derivatives. Through the ring closures of *N*-BOC-substituted 1,3-amino alcohols with aldehydes or acetals, 3-BOC-1,3-oxazine derivatives were obtained <1998TL6561, 1999J(P1)1933, 2006JOC8481, 2006T8687, 2006TL7923>.

The condensation of 3-aminopropanol **371** with formaldehyde and ethyl phenylphosphinate or diethyl phosphite afforded the corresponding (tetrahydro-1,3-oxazin-3-ylmethyl)phosphinate **391** (R = Ph) or phosphonate **391** (R = OEt) derivative (Scheme 73). These condensations probably take place via addition of the phosphite/phosphinate to the C=N bond of the open form of the ring-chain tautomeric tetrahydro-1,3-oxazine intermediate **390** <2006HAC75, 2006HAC81>.

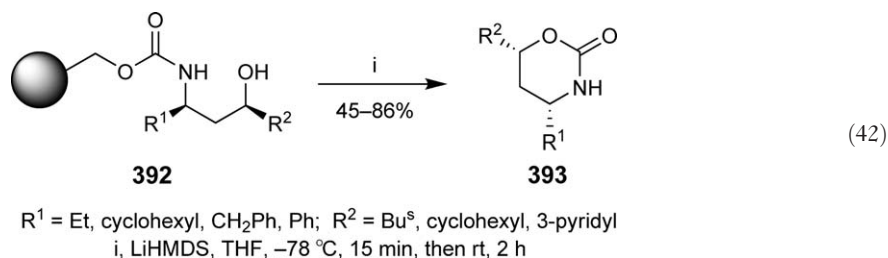


Scheme 73

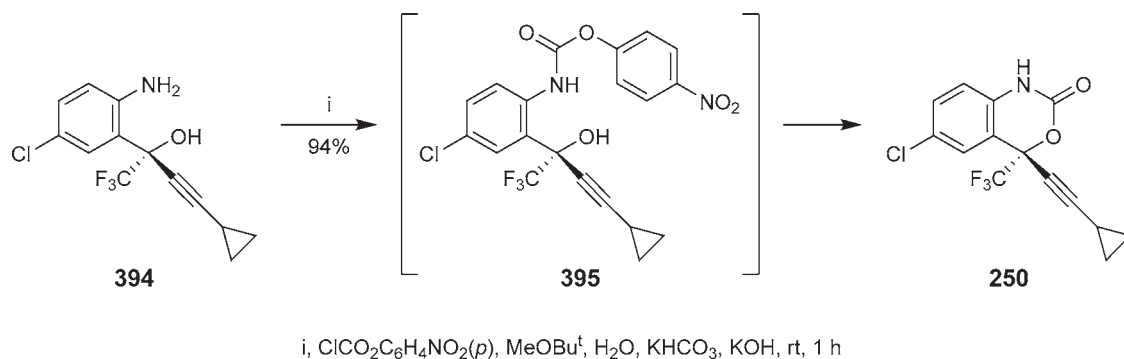
Both one-step and two-step procedures are applied for the preparation of tetrahydro-1,3-oxazin-2-ones and -2-thiones from the corresponding 1,3-amino alcohols <1996CHEC-II(6)301>. Ring closures of the amino alcohols with phosgene <1997JOC9331, 1998JOC8536, 2001T3175, 2006RJO1417>, triphosgene <1995JME4634, 1998JME2146, 2005JME2080, 2005JBS1255, 2006BMC3174>, or carbonyldiimidazole <1995M75, 2001EJO141, 2004BML2483, 2005JOC463, 2006TA1308, 2007BML189> result directly in the cyclic carbamate products. The analogous reactions with thiophosgene yield the corresponding 1,3-oxazine-2-thiones <2002CH187, 2003SL341>.

Treatment of the acyclic carbamate derivatives of 1,3-amino alcohols with bases (e.g., NaOMe, NaH, KOBu^t) is a two-step method often applied for the synthesis of 1,3-oxazin-2-ones <1998J(P1)457, 1998TL6555, 2001T3175, 2002CH187, 2006ASC2080, 2006MI477, 2006OBC2753>. The two-step preparation of 1,3-oxazine-2-thiones involves cyclization of the corresponding dithiocarbamate derivatives of amino alcohols with ethyl chloroformate/triethylamine <2001T3175>, lead(II) nitrate <2002CH187>, or hydrogen peroxide <1997H(45)2471, 2006EJO4916>.

An elegant cyclization–cleavage strategy has been devised for the removal of resin-bound 1,3-amino alcohol derivatives **392** as 1,3-oxazin-2-ones **393** upon treatment with lithium hexamethyldisilazide (LiHMDS) (Equation 42) <2001OL3177>.

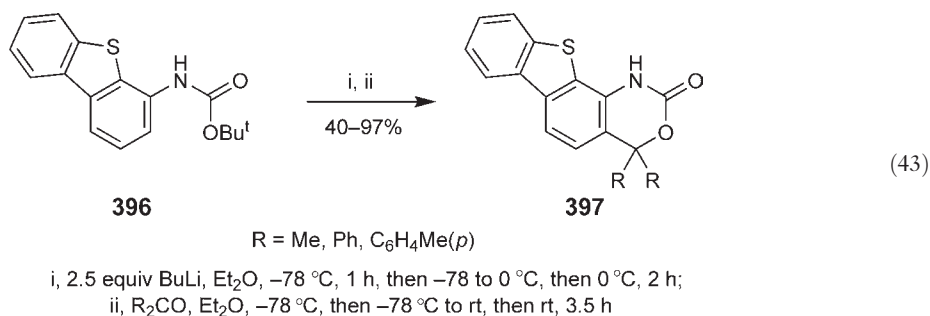


Formation and subsequent cyclization of a hydroxyalkyl carbamate bearing an activating O-substituent can also be achieved in a one-pot procedure. When 2-(hydroxymethyl)aniline **394** was treated with *p*-nitrophenyl chloroformate, the formation of the *p*-nitrophenylcarbamate intermediate **395** was followed by *in situ* ring closure to give the 3,1-benzoxazin-2-one derivative efavirenz **250** in high yield and with high purity, free from the intermediate **395** (Scheme 74) <1998JOC8536>.

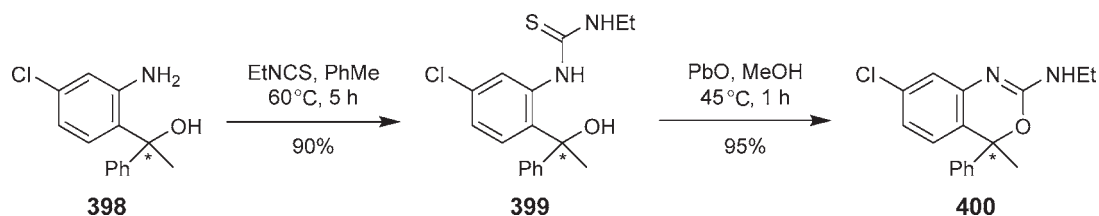


Scheme 74

Dibenzothiophene carbamate **396** was converted to the corresponding 1,3-oxazin-2-one derivatives **397** in a two-step, one-pot procedure. Lithiation of **396** gave a bis-anion intermediate, treatment of which with ketones led to cyclization to tetracyclic 1,3-oxazin-2-ones **397** (Equation 43). In the similar reaction of the analogous dibenzofuran carbamate, a hydroxymethyl-substituted acyclic compound was formed <1998J(P1)457>.



N-Hydroxyalkyl-substituted thioureas derived from 1,3-amino alcohols and isothiocyanates readily cyclize to 2-amino-1,3-oxazine derivatives on consecutive treatment with methyl iodide and base <1984CHEC(3)995>. This procedure was successfully applied for the preparation of cycloalkane-fused 2-(phenylimino)- and 2-(ethylimino)-perhydro-1,3-oxazines <2000TA4571, 2001T3175, 2003TA3965, 2004JHC69, 2004JHC367>. In the synthesis of the isotope-labeled anxiolytic compound etifoxine, containing ¹⁴C at position 4 **400**, the thiourea derivative **399** was cyclized in excellent yield on treatment with lead(II) oxide (Scheme 75) <1997JLR907>.



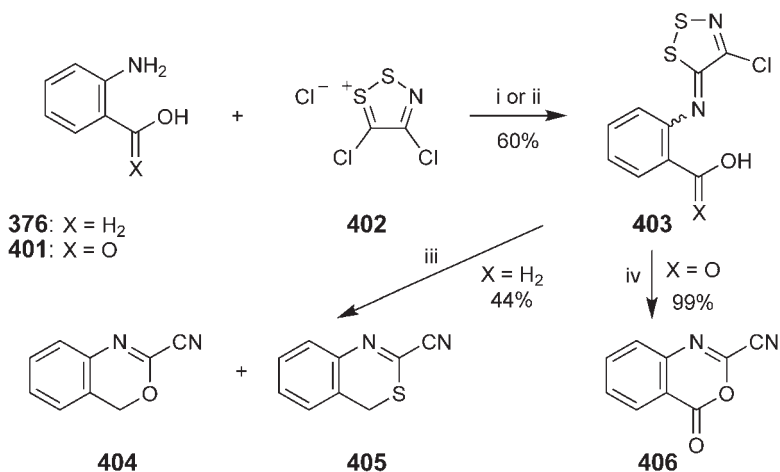
Scheme 75

In the condensations of *o*-aminobenzyl alcohol **376** or anthranilic acid **401** with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) **402**, imino-1,2,3-dithiazoles **403** were formed. Heating of the imino alcohol **403** (X = H₂) in THF in the presence of NaH afforded an 11:1 mixture of 3,1-benzoxazine **404** and 3,1-benzothiazine **405** in moderate yield. Thermal cyclization of imino acid **403** (X = O) resulted nearly quantitatively in formation of 3,1-benzoxazin-4-one **406** (Scheme 76) <1995CC1419, 1995J(P1)2097, 1997SL704>.

Cyclization of anthranilic acid or its substituted derivatives with an appropriate anhydride at elevated temperature or with an acid chloride in the presence of a base are well-known, versatile routes to 3,1-benzoxazin-4-ones <1999JHC563>. This method has been utilized in the preparation of various 3,1-benzoxazin-4-one derivatives <2000BMC2095, 2002RJO87> and a large number of structurally diverse hetero-analogs <2000BMC2803, 2003M1395, 2005JCCS975, 2006AP401>, for example, the two-step cyclization of the benzothiophene β -amino ester **407** to the corresponding benzothieno[2,3-*d*][1,3]oxazin-4-one **409** (Scheme 77) <2002CPB1215>.

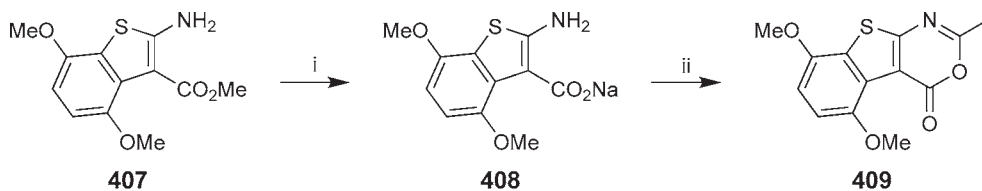
The acetic anhydride-induced cyclodehydration of the symmetrical diamide **411**, derived from the tetrahydro-benzothiophene β -amino ester **410** and diethyl malonate, afforded the thieno[2,3-*d*][1,3]oxazine derivative **413** rather than the expected bis-oxazine **412** (Scheme 78). The reaction probably takes place through sequential cyclizations, in which the pyridine ring of **413** is produced by condensation of the exocyclic double bond of the enamine tautomeric form of the 1,3-oxazine moiety and the mixed anhydride formed by the carboxylic group and acetic anhydride <2003PS245>.

The gallium(III) triflate-mediated condensation of anthranilic acid with fluorinated ketones gave the corresponding 2,2-disubstituted 1,2-dihydro-4*H*-3,1-benzoxazin-4-ones in high yields <2007OL179>.



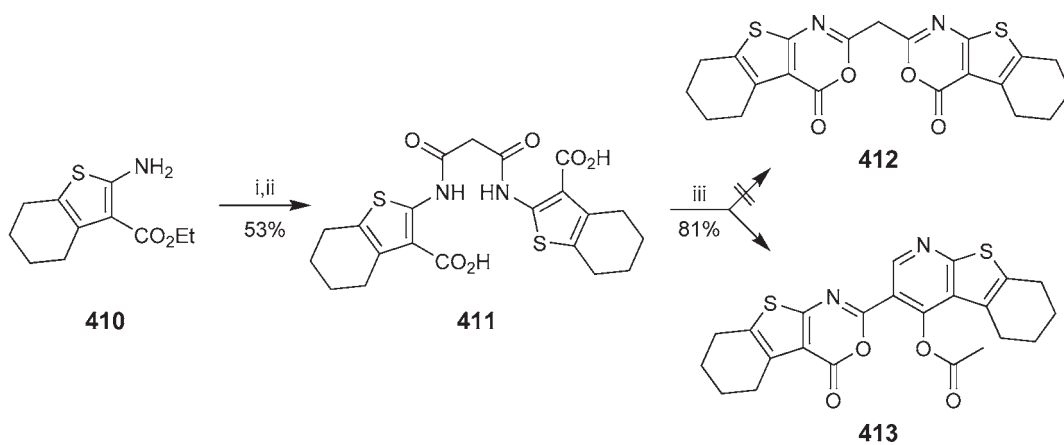
i, CH_2Cl_2 , pyridine, rt, 2 h ($X = H_2$); ii, CH_2Cl_2 , rt, 2 h ($X = O$); iii, NaH, THF, reflux, 1 h, **404:405** = 11:1; iv, toluene, reflux, 2 h

Scheme 76



i, NaOH, EtOH, reflux, 2 h; ii, Ac_2O , reflux, 3 h; yield: 55% (i + ii)

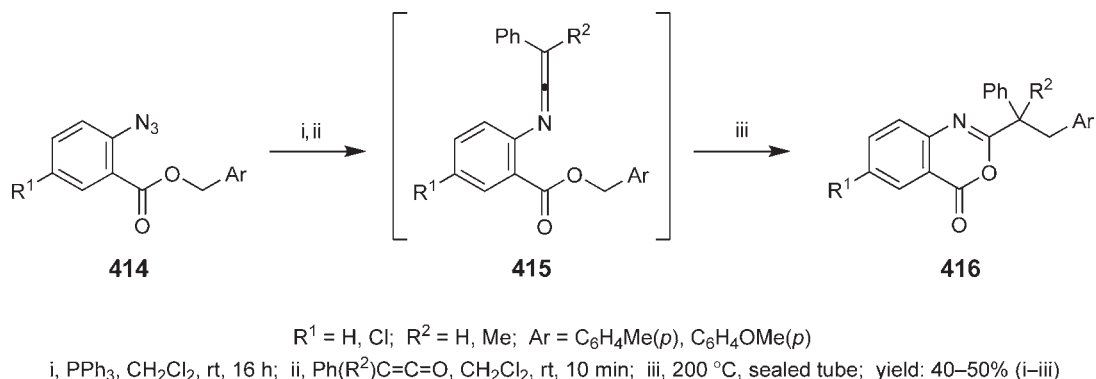
Scheme 77



i, $CH_2(CO_2Et)_2$, xylene, reflux, 5 h; ii, 10% NaOH (aq.), EtOH, reflux, 2 h, then HCl; iii, $Ac_2O-AcOH$ (3:1), reflux, 3 h

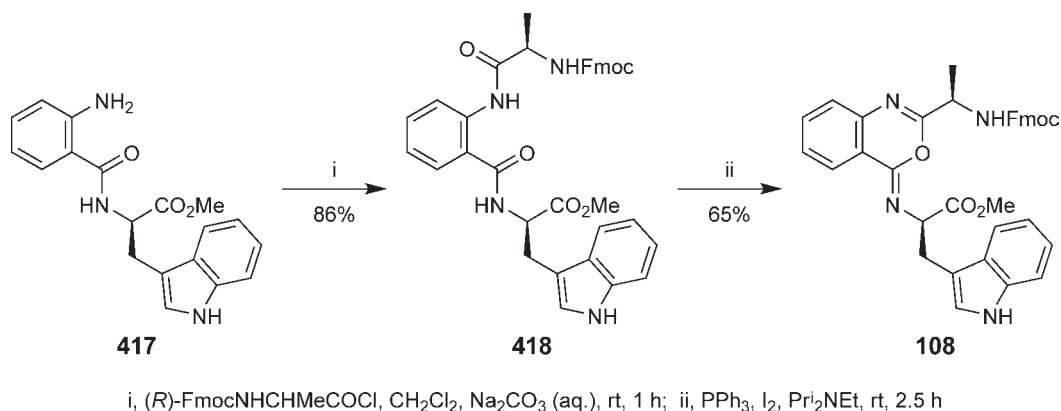
Scheme 78

The thermally induced cyclization of *N*-(benzyloxycarbonyl)phenyl ketenimines **415**, obtained in a two-step, one-pot procedure from benzyl 2-azidobenzoates **414**, led to 2-substituted-4*H*-3,1-benzoxazin-4-ones **416** (Scheme 79). The reaction involves the formation of a new carbon–oxygen bond and migration of the benzyl group from the oxygen atom to the terminal carbon atom of the ketenimine fragment <2005S2426>.



Scheme 79

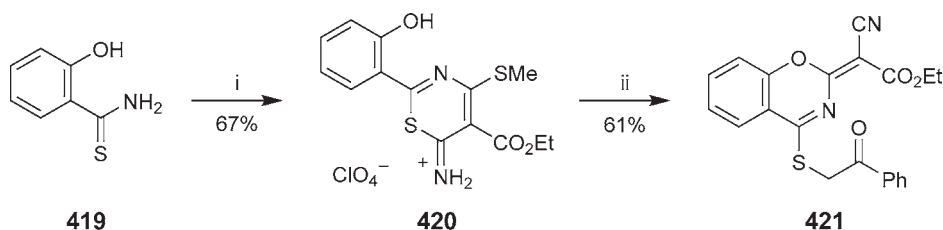
Dehydrative cyclization of *N*-acylanthranilamide derivative **418** with a large excess of a PPh_3/I_2 /tertiary amine combination gave the 4-imino-4*H*-3,1-benzoxazine **108** in good yield (Scheme 80) <1999JOC1397, 2000JOC1022>.



Scheme 80

In the reaction of salicylic acid thioamide **419** with 2-cyano-3,3-bis(methylsulfanyl)acrylate under acidic conditions, a 2-(*o*-hydroxyphenyl)-6-imino-1,3-thiazine derivative was obtained as a perchlorate salt **420**; on treatment with phenacyl bromide, this underwent a ring transformation to yield 4-benzoylmethylthio-2*H*-1,3-benzoxazin-2-ylidene-substituted ethyl cyanoacetate **421** (Scheme 81) <2003H(60)2273, 2004H(63)2319>.

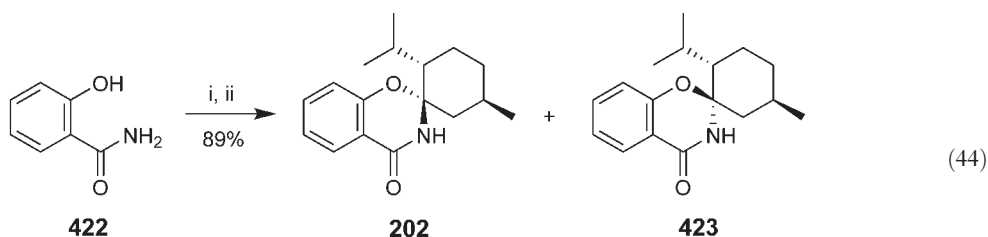
The cyclizations of β -hydroxycarboxamides with aldehydes, ketones, or their equivalents results in 1,3-oxazin-4-one derivatives <1996CPB734, 2006BMC584, 2006BMC1978>. In the acid-catalyzed condensation of salicylamide **422** with (–)-menthone, a 2:1 mixture of *C*-2-epimeric 2*H*-1,3-benzoxazin-4(3*H*)-ones **202** and **423** was formed, the equilibrium of which could be shifted toward the (2*S*)-enantiomer **202** by base-catalyzed isomerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*-methyl-2-pyrrolidone (NMP) to yield a 14:1 mixture of **202** and **423** (Equation 44) <1996TL3129>.



i, (MeS)₂C=C(CN)CO₂Et, 2.3 M HClO₄ in AcOH, 60 °C, 30 min;

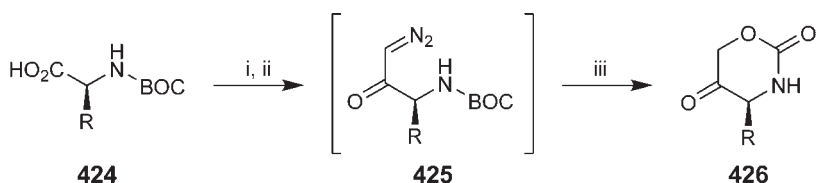
ii, PhCOCH₂Br, Et₃N, MeOH, 10–15 °C, then rt, 30 min

Scheme 81



i, (-)-menthone, *p*-TsOH, toluene, reflux, 24 h; ii, DBU, NMP, 25 °C, 24 h, then -20 °C, 24 h,
202:423 = 14:1

The reactions of *N*-BOC-protected α -amino acids **424** and diazomethane in the presence of *N*-methylmorpholine-polystyrene and isobutyl chloroformate resulted in formation of diazoketones **425**, which, on treatment with indium(III) triflate, were cyclized to 4-substituted-tetrahydro-1,3-oxazine-2,5-diones **426** in high overall yields (Scheme 82) <2006TL7969>.



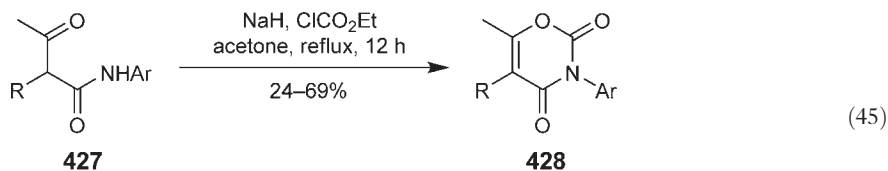
R = H, Me, Et, Bu, cyclopropyl, cyclohexyl, CH₂Ph, CH₂CH₂Ph, Ph

i, *N*-methylmorpholine-polystyrene, ClCO₂Buⁱ, THF, -20 °C, 2 h; ii, CH₂N₂, -20 °C, 1 h, then -20 °C to rt;

iii, In(OTf)₃, CH₂Cl₂, 0 °C to rt, 30 min; yield: 93–98% (i–iii)

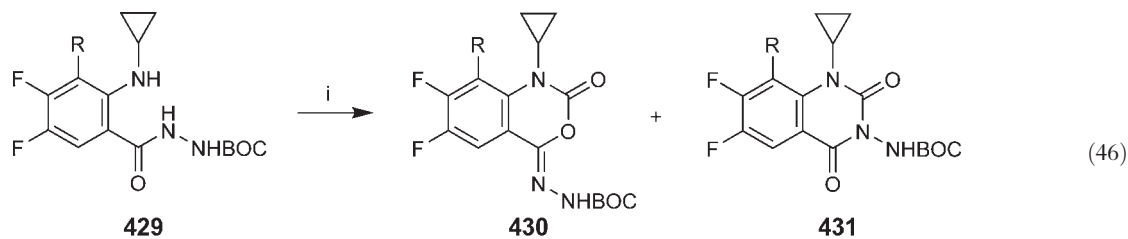
Scheme 82

Alkylated acetoacetanilides **427** were cyclized to 1,3-oxazine-2,4-diones **428** on treatment with ethyl chloroformate in the presence of NaH (Equation 45). The yields of this stepwise O-acylation/cyclization reaction were strongly dependent on the electronic properties of the aromatic substituents: the yield was substantially higher for the *p*-methoxyphenyl-substituted derivative than for the *p*-chlorophenyl analog <2006H(68)465>.



R = Me, Bu, CH₂Ph; Ar = C₆H₄Cl(*p*), C₆H₄OMe(*p*)

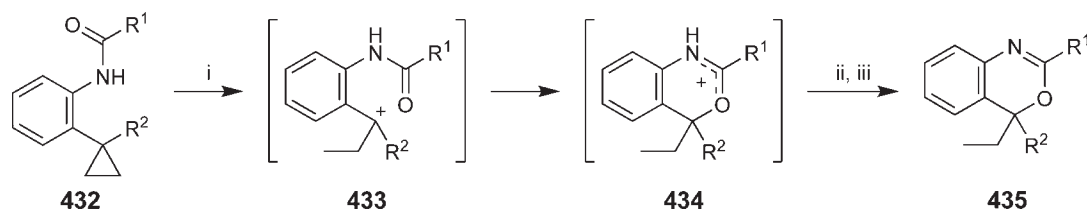
The products obtained in the reaction of *N*-cyclopropyl-4,5-difluoroanthranilic acid hydrazides **429** with triphosgene were dependent on the steric hindrance imposed by substituent R at position 3, and not the electronic effect of this group. While the unsubstituted compound **429** (R = H) gave exclusively the 4-hydrazono-3,1-benzoxazin-2-one-type product **430**, the similar reactions of the chloro-, methyl-, and methoxy-substituted analogs **429** (R = Cl, Me, OMe) resulted in formation of the corresponding quinazoline-2,4-diones **431** as the sole products. For the fluoro-substituted compound **429** (R = F), a 20:80 mixture of the products **430** and **431** was obtained (Equation 46) <2005JHC669>.



i, $(\text{Cl}_3\text{CO})_2\text{CO}$, K_2CO_3 , THF, reflux; R (**430/431**) = H (100/0), F (20/80), Cl (0/100), Me (0/100), OMe (0/100)

8.05.9.4 [6+0] Types

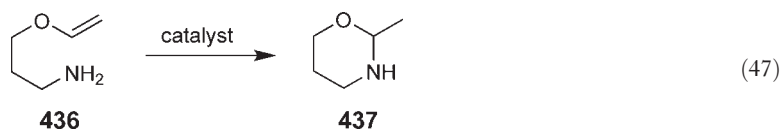
The intramolecular rearrangement of *N*-acyl-2-cyclopropylanilines **432** on treatment with sulfuric acid gave substituted 4*H*-3,1-benzoxazines **435** in high yields (Scheme 83). The reaction was initiated by the proton-catalyzed opening of the cyclopropane ring and generation of the benzylic carbenium ion **433**, which cyclized to the corresponding 3,1-benzoxazinium ion **434**. *N*-Acylamino-2-alkenylbenzenes, in which the double bond of the alkyl chain was conjugated with the benzene ring, proved to be capable of undergoing a similar rearrangement <2003CHE794>.



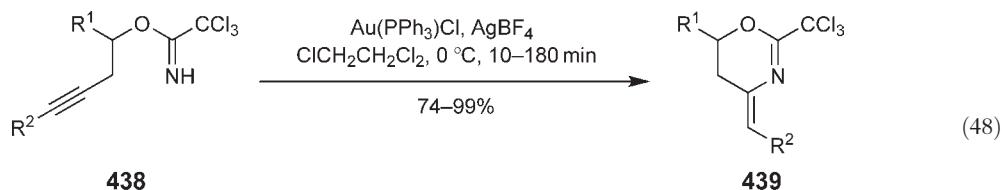
$\text{R}^1 = \text{H, Me}; \text{R}^2 = \text{Me, Ph, C}_6\text{H}_4\text{Me}(p), \text{C}_6\text{H}_4\text{Me}(m), \text{C}_6\text{H}_4\text{Cl}(p), \text{C}_6\text{H}_4\text{Cl}(o), \text{C}_6\text{H}_4\text{Br}(p), \text{C}_6\text{H}_4\text{Br}(o), \text{C}_6\text{H}_4\text{NO}_2(p)$
 i, H_2SO_4 , -10°C , then 20°C , 30 min; ii, H_2O ; iii, Na_2CO_3 ; yield: 71–97% (i–iii)

Scheme 83

The direct addition of an amine functionality to a carbon–carbon multiple bond, that is, hydroamination, is a convenient, atom-efficient procedure via which various nitrogen-containing compounds, including 1,3-oxazine derivatives, can be synthesized. Hydroamination can take place either through catalytic activation of an N–H bond or through catalytic activation of a C–C multiple bond, followed by attack by a N-nucleophile. The cyclization of 3-aminopropyl vinyl ether **436** to 2-methyltetrahydro-1,3-oxazine **437** is a model system often chosen to test the activities of catalysts applied in hydroamination reactions (Equation 47) <2000CC51, 2000CJC568, 2001TMC261, 2001T6027, 2002CC906, 2004CC2562, 2004JCT(221)302>.

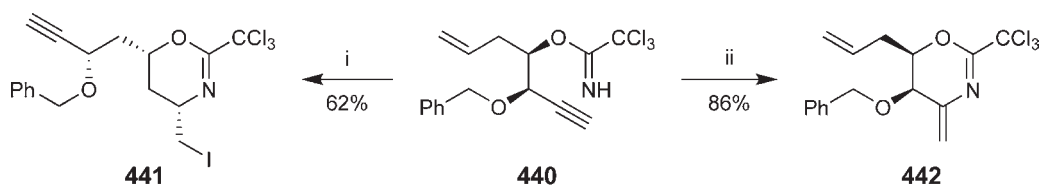


The excellent ability of late transition metal complexes to activate alkynes to nucleophilic attack has made them effective catalysts in hydroamination reactions. The gold(I)-catalyzed cyclizations of trichloroacetimidates **438**, derived from homopropargyl alcohols, furnished 2-(trichloromethyl)-5,6-dihydro-4*H*-1,3-oxazines **439** under exceptionally mild conditions (Equation 48). This method was successfully applied to compounds possessing aliphatic and aromatic groups R^1 . With $R^2 = \text{Ph}$, cyclization resulted in formation of **439** with complete (*Z*)-stereoselectivity <2006OL3537>.



$R^1 = \text{H, Pr, Bu}^t, \text{cyclohexyl, Ph, C}_6\text{H}_4\text{OMe}(p), \text{C}_6\text{H}_4\text{CN}(p), \text{C}_6\text{H}_4\text{Cl}(p)$; $R^2 = \text{H, Ph}$

The orthogonal reactivities exhibited by IBr (2.5 equiv at -78°C) and $\text{Au(PPh}_3\text{)BF}_4$ (5 mol% at 0°C) in the activation of the alkene and alkyne groups of trichloroacetimidate **440** could be utilized in regioselective cyclizations toward 5,6-dihydro-4*H*-1,3-oxazine derivatives **441** or **442**, respectively (Scheme 84) <2006OL3537>.

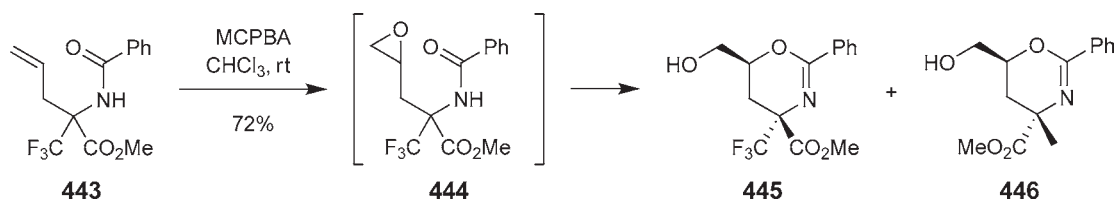


i, IBBr, K_2CO_3 , EtCN, -78°C , 30 min; ii, $\text{Au(PPh}_3\text{)Cl}$, AgBF_4 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, 4°C to rt, then rt, 24 h

Scheme 84

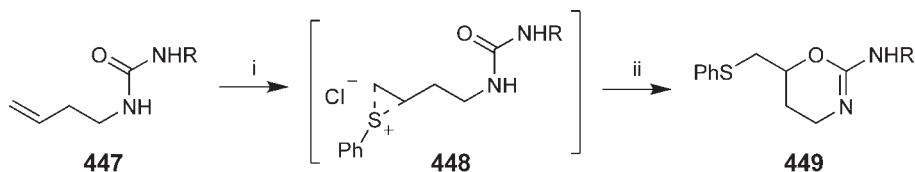
Trichloroacetimidates derived from tetrahydrofuran homopropargyl alcohols were cyclized by mercury(II) trifluoroacetate-induced hydroamination to the corresponding 5,6-dihydro-4*H*-1,3-oxazine derivatives with excellent stereoselectivity <1998CC761>.

When the unsaturated *N*-benzoyl α -amino ester **443** was treated with MCPBA, the oxirane **444** formed first immediately underwent an intramolecular rearrangement with cleavage of the oxirane ring by attack of the amide oxygen to give a 3:1 mixture of two *cis*- and *trans*-isomers of 5,6-dihydro-4*H*-1,3-oxazine derivatives **445** and **446**, the configurations of which were determined via their *O*-3,5-dinitrobenzoyl derivatives (Scheme 85) <2003M69>.



Scheme 85

An intramolecular regioselective sulfenocyclization of unsaturated ureas **447** resulted in formation of 5,6-dihydro-4*H*-1,3-oxazine derivatives **449** (Scheme 86). The procedure employed phenylsulfenyl chloride and ethyldiisopropylamine to generate an episulfonium ion intermediate **448**, from which the cyclic products **449** were formed by internal nucleophilic displacement <1995M609>.

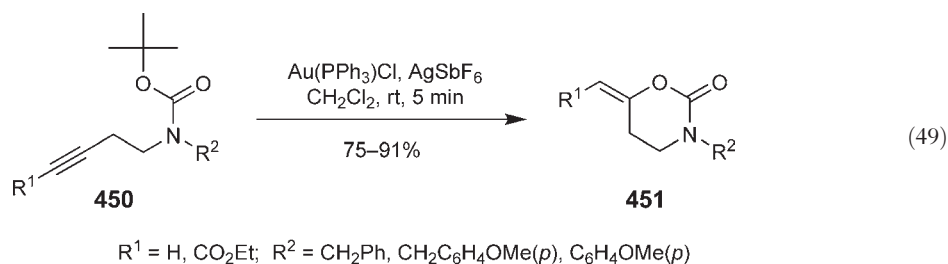


R = H, Ph

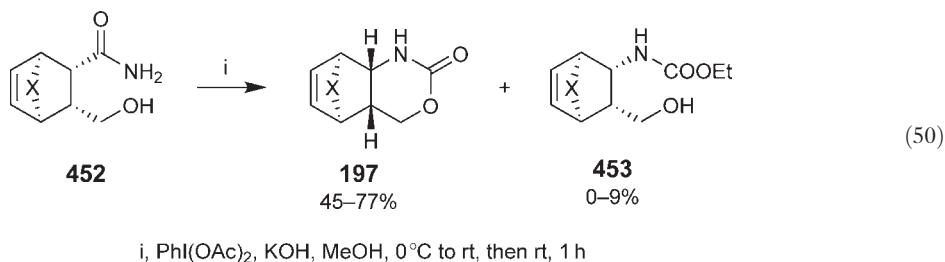
i, PhSCl, MeCN, rt, 30 min; ii, Pr_2NEt , MeCN, rt, 30 min; yield: 78–79% (i + ii)

Scheme 86

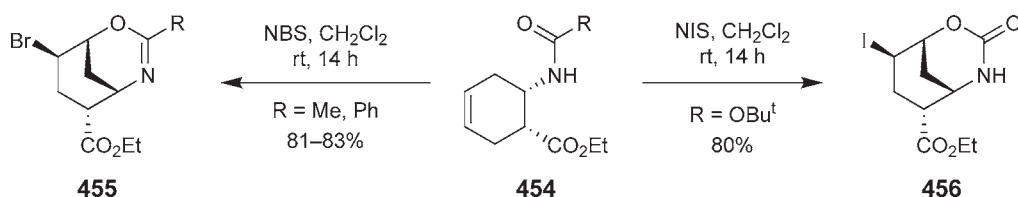
Late transition metal-catalyzed processes also proved to be very useful tools for formation of the C–O bond of the 1,3-oxazine ring from the corresponding alkynes. In the presence of 1–5 mol% of a cationic gold(i) complex, *N*-BOC-protected alkynylamines **450** were converted to 6-alkylidene-1,3-oxazin-2-ones **451** under very mild conditions (Equation 49) <2006JOC5023>.



Whereas the Hofmann rearrangement of the amidoalcohols **452** with the usual NaOCl did not occur, reaction of the oxygen-bridged **452** (X = O) with bis(acetoxy)iodobenzene under mild conditions led to a 9:1 mixture of the corresponding cyclic and acyclic carbamate derivatives **197** and **453** (X = O) (Equation 50). In the similar reaction of the methylene-bridged analog **452** (X = CH_2), the product of perhydro-3,1-benzoxazin-2-one type **197** (X = CH_2) was obtained exclusively <2003OPP429>.



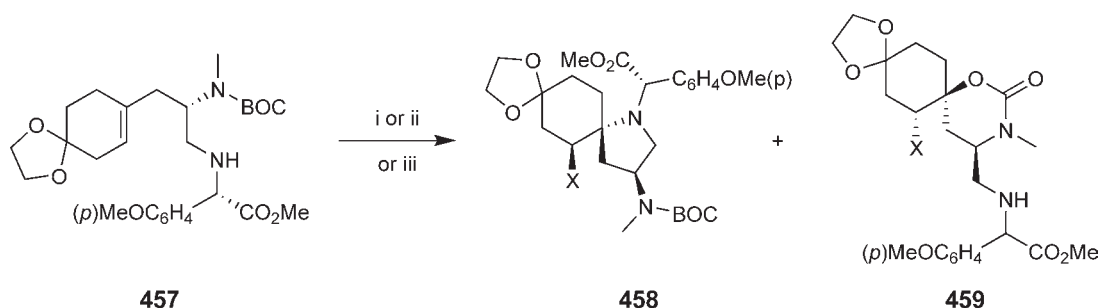
Haloaminocyclization of *N*-acyl-substituted homoallylamines resulted in formation of 1,3-oxazine derivatives. Depending on the nature of the *N*-acyl substituents in **454**, products of either 5,6-dihydro-4*H*-1,3-oxazine **455** or tetrahydro-1,3-oxazin-2-one **456** type (NIS = *N*-iodosuccinimide) could be prepared (Scheme 87). Because of the highly stereocontrolled formation of the 1,3-oxazine ring, haloaminocyclizations were utilized in the stereoselective hydroxylation of aminocycloalkene derivatives to form amino alcohols <2004HCA2764> or hydroxy-substituted α - or β -amino acids <1995SL891, 1997S165, 2005EJO3214, 2005EJO4017, 2005M2051>.



Scheme 87

The iodocyclizations of 2-alkoxycarbonylamino-3-alken-1-ols proved to be highly stereoselective processes resulting in either 1,3-oxazin-2-one or THF derivatives, depending on the substituents at the double bond and the nitrogen protecting group <2000TA3769>.

Competition between the *N*-BOC and the neighboring amino group in the haloaminocyclizations of 1-(2,3-diaminopropyl)cyclohexene derivatives **457** resulted in formation of spiro-condensed pyrrolidine **458** and 1,3-oxazin-2-one **459** derivatives (Scheme 88). The best regioselectivity toward the product of 1,3-oxazin-2-one type **459** was observed in the two-step transformation of **457** with the use of *N*-chlorosuccinimide (NCS) and $\text{TiCl}_3\text{-BF}_3\cdot\text{Et}_2\text{O}$. Each reaction could be characterized by a high degree of diastereoselectivity except for the formation of the pyrrolidine derivative **458** ($\text{X} = \text{Br}$), which was obtained as a mixture of α - and β -bromo-substituted diastereomers (TBCO = 2,4,4,6-tetrabromo-2,5-cyclohexadienone) <2003T2657>.



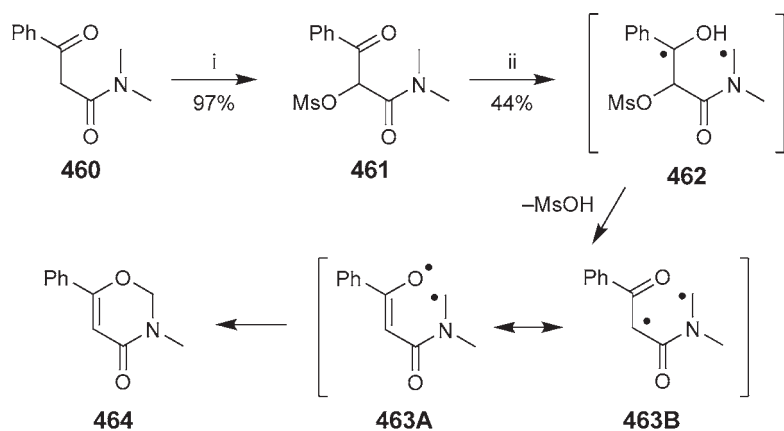
	Reaction conditions	X	Yield of 458 (%)	Yield of 459 (%)
i	I_2 , NaHCO_3 , $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$, rt, 16 h	I	19	31
ii	TBCO, CH_2Cl_2 , rt, 1 h	Br	52 ^a	13
iii	i, NCS, CH_2Cl_2 , rt, 24 h; ii, TiCl_3 , $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , -78°C , 3 h	Cl	~0	70

^aThe sum of α -Br- (22%) and β -Br-substituted (30%) diastereomers.

Scheme 88

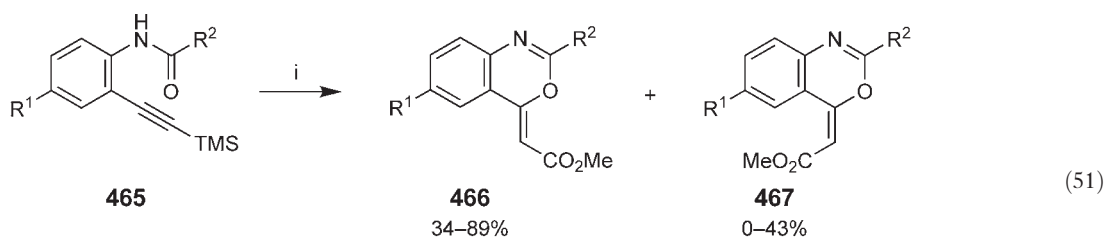
The synthesis of 1,3-oxazin-4-ones of type **464** is the first example of the formation of a C–O bond in the course of the Norrish–Yang reaction. Upon treatment with 1-hydroxy-1-phenyl- λ^3 -iodanyl mesylate, β -keto amide **460** was converted to the corresponding α -mesyloxy- β -keto amide **461** in excellent yield. On ultraviolet (UV) irradiation ($\lambda > 300\text{ nm}$) of **461**, δ -hydrogen transfer to the excited carbonyl group occurred and the diradical **462** thus formed underwent MsOH elimination to enolate diradical **463**, cyclization of which resulted in formation of 3-methyl-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-4-one **464** (Scheme 89) <2001SI258>.

Through the *in situ* deprotection of *N*-acyl-2-(trimethylsilyl)ethynylanilines **465** followed by palladium-catalyzed cyclization–methoxycarbonylation, stereoisomeric 4-methoxycarbonylmethylene-3,1-benzoxazine derivatives **466** and **467** were obtained (Equation 51). The (*Z*)-isomers **466** were consistently found to be the main product, with the exception of the *p*-(methoxycarbonyl)phenyl-substituted compounds ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_4\text{CO}_2\text{Me}(p)$), for which a higher amount of the (*E*)-isomer **467** was formed <2004JOC2469>.



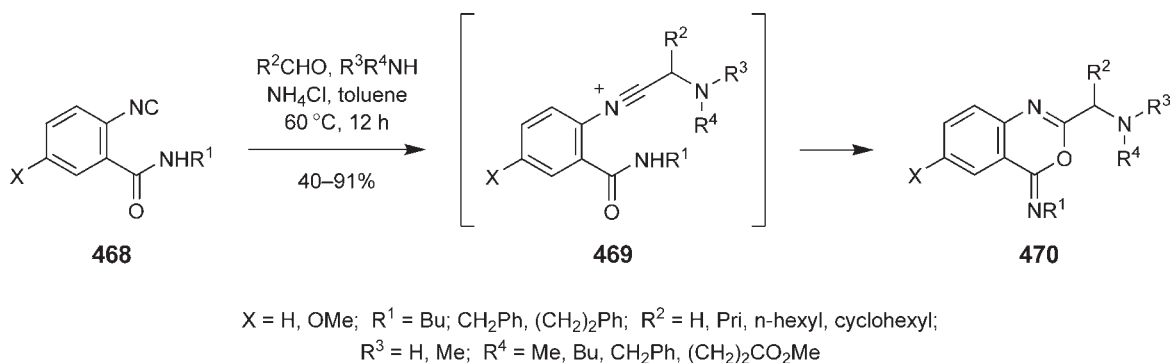
i, $\text{PhI}(\text{OH})(\text{OMs})$, CH_2Cl_2 , 40°C , 1 h; ii, $h\nu$ ($\lambda > 300 \text{ nm}$), N-methylimidazole, CH_2Cl_2

Scheme 89



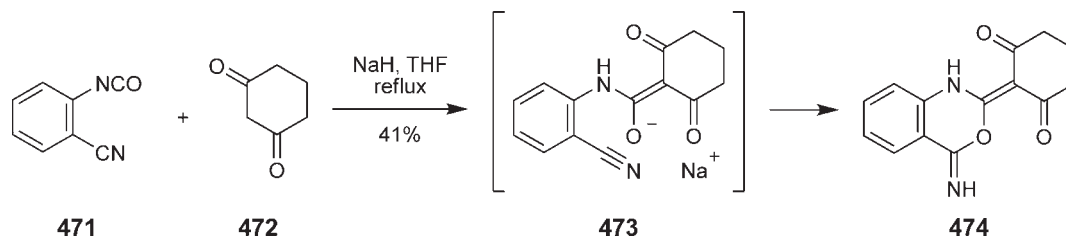
$\text{R}^1 = \text{H}, \text{Me}, \text{Cl}, \text{CO}_2\text{Me}, \text{CN}$; $\text{R}^2 = \text{vinyl}, \text{allyl}, 1\text{-propenyl}, 2\text{-phenylvinyl}, \text{Ph}, \text{C}_6\text{H}_4\text{Me}(p), \text{C}_6\text{H}_4\text{Cl}(p), \text{C}_6\text{H}_4\text{OMe}(p), \text{C}_6\text{H}_4\text{CO}_2\text{Me}(p), \text{C}_6\text{H}_4\text{CN}(p), \text{C}_6\text{H}_4\text{NO}_2(p)$
 i, 10% Pd/C, Bu_4NI , KF, MeCN/MeOH (7:1), CO/air (2.4 MPa at rt), 65°C , 24 h

In the reactions of 2-isocyanobenzamides 468 with aldehydes and primary or secondary amines, 2-aminomethyl-4-imino-4*H*-3,1-benzoxazines 470 were obtained in moderate to excellent yields. The benzoxazine derivatives were formed by cyclization of the amide oxygen with a nitrilium intermediate 469, produced by the reaction of the isonitrile group and the iminium derived from the aldehyde and amine (Scheme 90). The best yields were achieved when the three components were heated in toluene in the presence of a stoichiometric amount of NH_4Cl or $\text{Et}_3\text{N}\cdot\text{HCl}$ (formed *in situ* from amine hydrochloride and Et_3N). Primary amines usually gave lower yields <2005OL5285>.



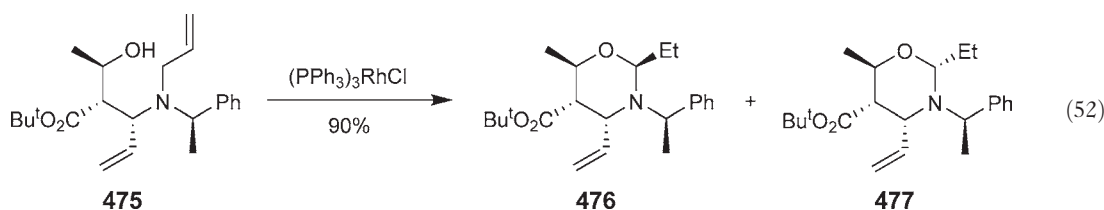
Scheme 90

The base-mediated, one-pot cyclization of 2-isocyanatobenzonitrile **471** with cyclohexane-1,3-dione **472** afforded 4-imino-3,1-benzoxazine **474** without Dimroth rearrangement (Scheme 91). The reaction was explained by the attack of the carbanion derived from **472** on the central carbon atom of the isocyanate moiety to give the intermediate **473**, which cyclized by attack of the oxygen atom on the nitrile group <2003SL1503>. The similar reactions of 3-chloropropyl isocyanate or 2-(chloromethyl)phenyl isocyanate with active methylene compounds in the presence of Et₃N gave substituted 2-methylenetetrahydro-1,3-oxazines or the corresponding dihydro-3,1-benzoxazines, respectively <2006JOC9743>.



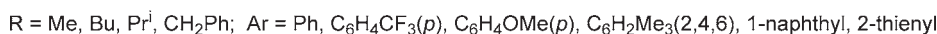
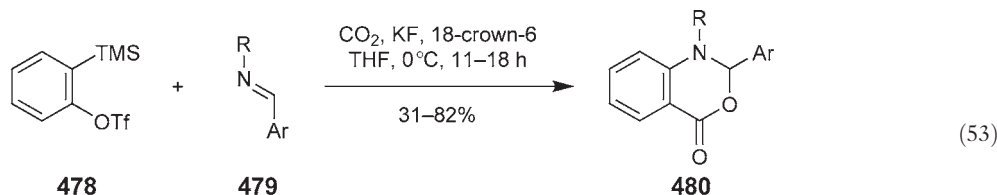
Scheme 91

For determination of its configuration via a conformationally restricted cyclic derivative, *N*-allylamino alcohol derivative **475** was treated with tris(triphenylphosphine)rhodium(i) chloride to afford a 19:1 mixture of the C-2-epimeric tetrahydro-1,3-oxazines **476** and **477** by intramolecular trapping of the intermediate iminium species, in equilibrium with the enamine generated in the isomerization of the allyl double bond (Equation 52) <1997CC565>.

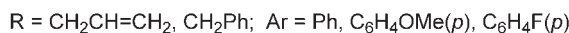
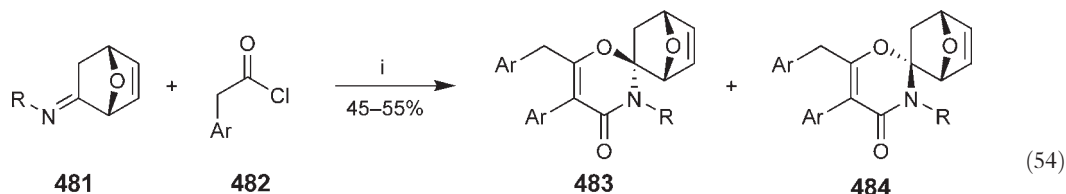


8.05.9.5 [2+2+2] Types

The reactive zwitterions arising from the nucleophilic attack of imines **479** on the benzyne generated *in situ* from 2-(trimethylsilyl)phenyl triflate **478** proved to be an appropriate molecular scaffold for the capture of CO₂ with sufficient electrophilicity to yield 2-aryl-3,1-benzoxazin-4-ones **480** (Equation 53). Both substituents of the C=N bond affected the course of the reaction considerably: the best yields were achieved by using imines with electron-rich or neutral aryl groups on the carbon, and benzyl or nonbranched chain alkyl substituents on the nitrogen atom. With substituted derivatives of **478**, the unsymmetrically substituted arynes led to regioisomeric products <2006JA9308>.

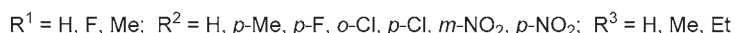
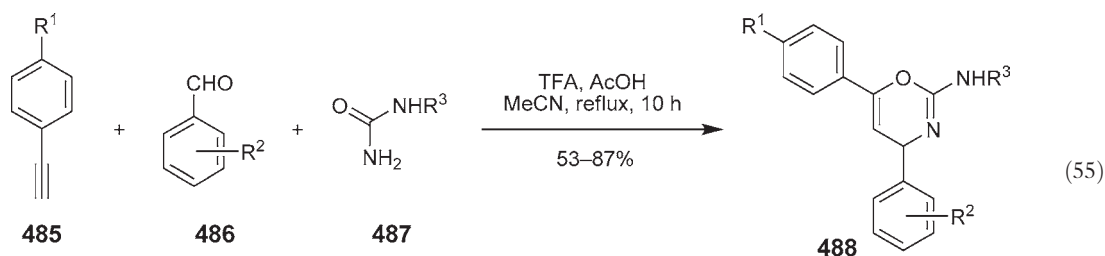


The Staudinger reaction of imines **481** derived from 7-oxanorbornenone with arylacetic acid chlorides **482** furnished a 0–40:60–100 mixture of C-2-epimeric, spiro-condensed 1,3-oxazin-4-one derivatives **483** and **484**, the ratio of which proved to depend on the substituents on the aromatic rings and on the nitrogen atom (Equation 54) <2002TL6405>.

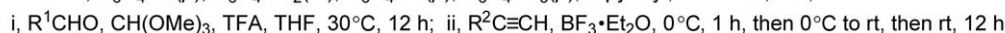
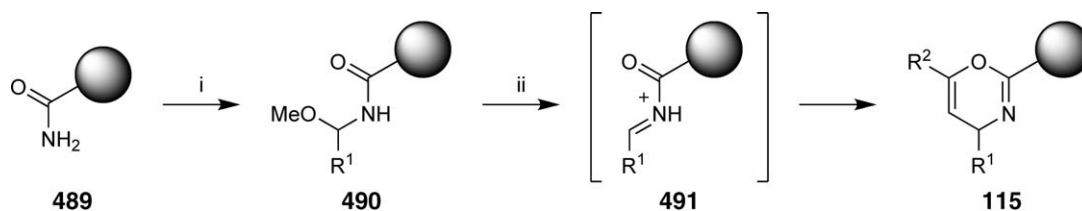


8.05.9.6 [3+2+1] Types

A three-component, one-pot condensation of arylalkynes **485**, aromatic aldehydes **486**, and urea or its N-substituted derivatives **487** in a mixture of TFA and acetic acid resulted in formation of 2-amino-4,6-diaryl-4*H*-1,3-oxazines **488** via a presumed hetero-Diels–Alder cycloaddition of the alkyne and the heterodiene intermediate formed from the aldehyde and urea (Equation 55). The presence of an electron-withdrawing or electron-releasing group R^2 on the aromatic aldehydes did not exert a significant effect on the yield, though for arylalkyne **485** containing an electron-withdrawing fluoro substituent ($\text{R}^1 = \text{F}$), decreased yields were observed <2005OL3797>. In a similar, three-component reaction of *p*-fluorostyrene, benzaldehyde, and urea, the *cis*-isomer of 2-amino-6-(*p*-fluorophenyl)-4-phenyl-5,6-dihydro-4*H*-1,3-oxazin-3-ium chloride was formed with complete diastereoselectivity <2006OL2599>.

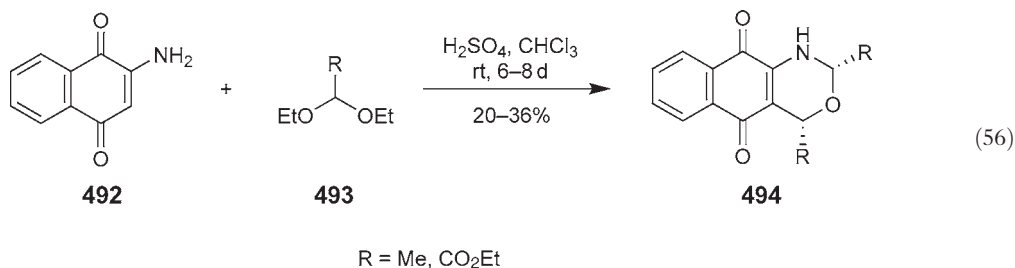


Resin-bound 4*H*-1,3-oxazines **115** were synthesized by the stepwise condensation of an amide resin **489**, an aldehyde, and an alkyne. Formation of the oxazine ring took place in the presence of the catalyst $\text{BF}_3 \cdot \text{Et}_2\text{O}$ via a hetero-Diels–Alder cycloaddition of the alkyne and the acyliminium **491** arising from the condensation of the amide and the aldehyde (Scheme 92). The quantitative efficacy of the process was determined by elemental analysis of a model system bearing a bromine atom on the aldehyde moiety ($\text{R}^1 = \text{C}_6\text{H}_4\text{Br}(p)$), which indicated a 78% conversion for the heterocyclization <2001CEJ2318, 2004JCO846>.

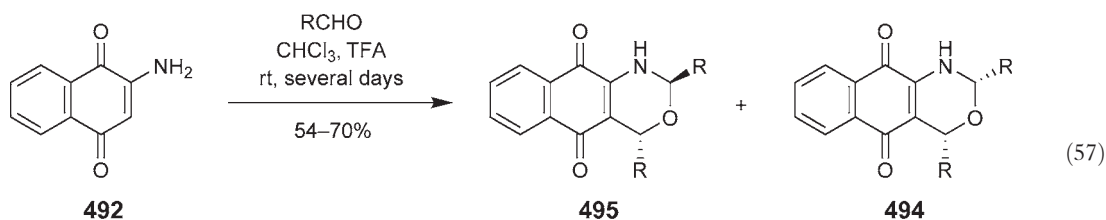


Scheme 92

2-Amino-1,4-naphthoquinone **492** was reacted as a bidentate nucleophile in condensations with acetals **493** to form *cis*-2,4-disubstituted-1,4-dihydro-2*H*-naphth[2,3-*d*][1,3]oxazine-5,10-diones **494** stereoselectively by 6-*endo-trig*-ring closure of the N,C-dialkylated intermediates (Equation 56) <1995T6565>.



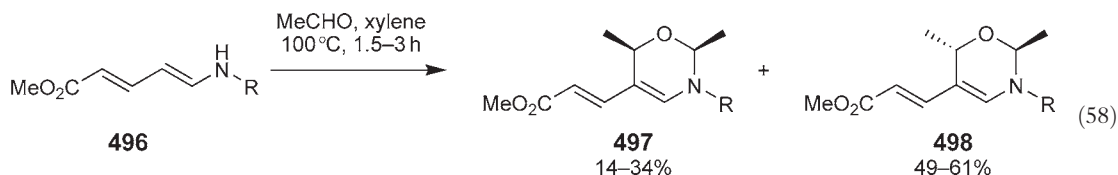
When 2-amino-1,4-naphthoquinone **492** was reacted with aliphatic aldehydes in the presence of a catalytic amount of TFA, the opposite diastereoselectivity of the reaction was reported. Except for the unsubstituted compound (R = H), the product proved to be a mixture of the diastereomers of 1,4-dihydro-2*H*-naphth[2,3-*d*][1,3]oxazine-5,10-diones in which the *trans*-isomer **495** was the predominant component (Equation 57). A slight tendency could be observed for increasing bulkiness of the substituent R to favor a higher proportion of the *cis*-isomer **494** in the diastereomeric mixture <2003MI51>.



R (**495/494**) = H, Me (90/10), Et (96/4), Pr (94/6), Prⁱ (74/26), Bu^t (89/11)

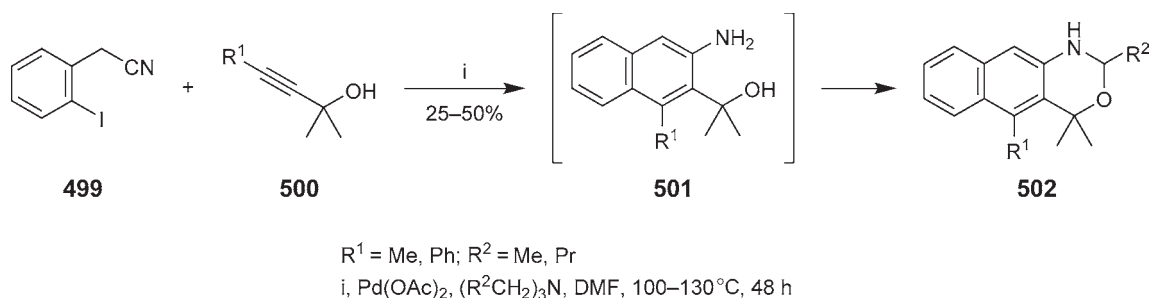
3-Aminoacridine derivatives reacted with formaldehyde in acidic medium to form (depending on the stoichiometry) various condensation products, among them 3,4-dihydro-1*H*-1,3-oxazino[4,5-*c*]acridines <1997T2891, 1998H(48)755, 2001J(P1)2962, 2006BML4641>.

When methyl 5-amino-2,4-pentadienoates **496** were heated with an excess of acetaldehyde in a sealed tube, diastereomeric mixtures of 2,3-dihydro-6*H*-1,3-oxazine derivatives **497** and **498** were obtained instead of the expected [4+2] cycloaddition products (Equation 58). Each condensation took place in a stereoselective way to give the *trans*-isomer **498** as the major product <1997CPB27>.



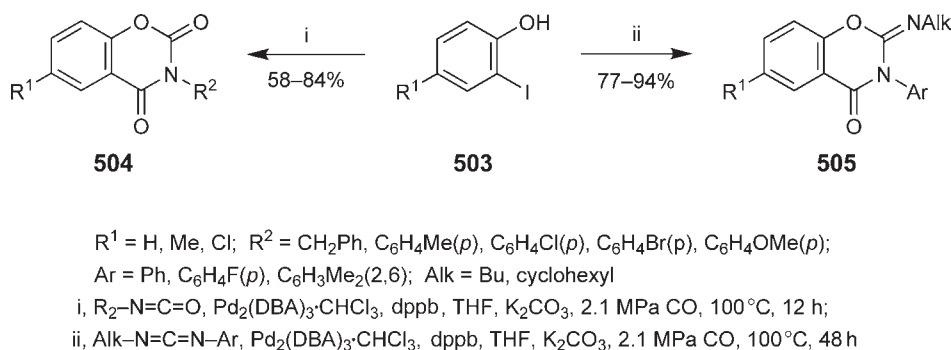
R = CH₂Ph, CH₂CH₂Ph, (2-pyridyl)methyl, (3-pyridyl)methyl, (4-pyridyl)methyl, 2-(4-pyridyl)ethyl, 2-(3-indolyl)ethyl.

(2-Iodophenyl)acetonitrile **499** was found to react with hindered propargyl alcohols **500** in the presence of palladium acetate and trialkylamine bases to yield naphth[2,3-*d*][1,3]oxazine derivatives **502** by intramolecular carbopalladiation of the cyano group (Scheme 93). C-2 of the oxazine ring proved to originate from the trialkylamine bases, indicating that naphthoxazines **502** were formed by condensation of the 2-amino-3-(1-hydroxyalkyl)naphthalene intermediates **501** with the iminium ion species derived from the trialkylamine bases used in the reaction <2003JOC339>.



Scheme 93

Cyclocarbonylation of *o*-iodophenols **503** with isocyanates or carbodiimides and carbon monoxide in the presence of a catalytic amount of a palladium catalyst (tris(dibenzylideneacetone)dipalladium(0): $\text{Pd}_2(\text{DBA})_3$) and 1,4-bis(diphenylphosphino)butane (dppb) resulted in formation of 1,3-benzoxazine-2,4-diones **504** or 2-imino-1,3-benzoxazine-4-ones **505** (Scheme 94). The product yields were dependent on the nature of the substrate, the catalyst, the solvent, the base, and the phosphine ligand. The reactions of *o*-iodophenols with unsymmetrical carbodiimides bearing an alkyl and an aryl substituent afforded 2-alkylimino-3-aryl-1,3-benzoxazin-4-ones **505** in a completely regioselective manner <1999JOC9194>. On the palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with acyl chlorides and carbon monoxide, 2-substituted-4H-3,1-benzoxazin-4-ones were obtained <1999OL1619>.

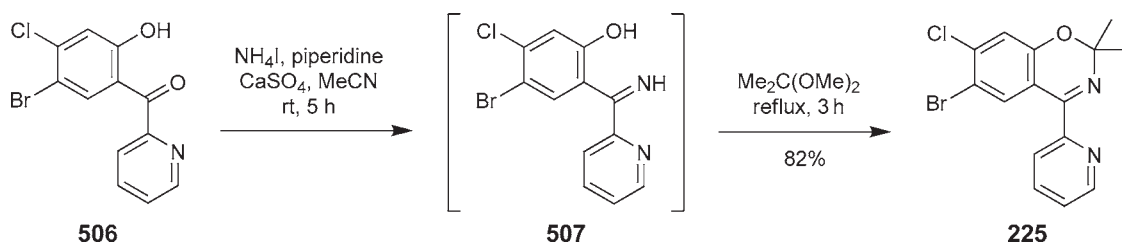


Scheme 94

The dimeric ring-closed products formed in the palladium-catalyzed carbonylation of 4-substituted-2-iodoanilines were strongly dependent on the substituent at position 4. Starting from 4-unsubstituted- or 4-methyl-2-iodoaniline, 2-aryl-4H-3,1-benzoxazin-4-ones were formed in good yields, while the analogous reactions of 4-chloro-, bromo-, cyano-, or nitro-2-iodoanilines gave the corresponding 2,8-disubstituted-dibenzo[*b,f*][1,5]diazocine-6,12-dione derivatives <2006T12051>.

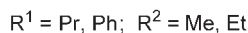
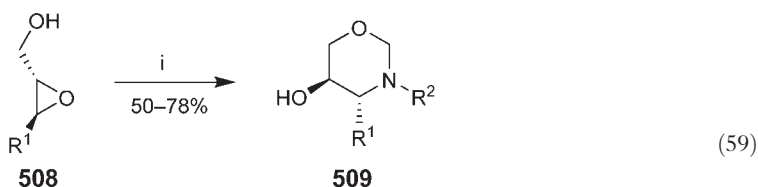
8.05.9.7 [4+1+1] Types

The condensation of 2-(5-bromo-4-chloro-2-hydroxybenzoyl)pyridine **506** in a sealed tube with ammonia and acetone proved a convenient route to 2H-1,3-benzoxazine derivative **225** via the imine intermediate **507** <1996CPB734>. The yield was improved considerably and a closed vessel was not required for the reaction when the ammonia was prepared *in situ* from NH_4I and piperidine, and 2,2-dimethoxypropane was used instead of acetone (Scheme 95). The improved method was extended to the preparation of other 2,2-disubstituted-2H-1,3-benzoxazine derivatives <2001T7501>.

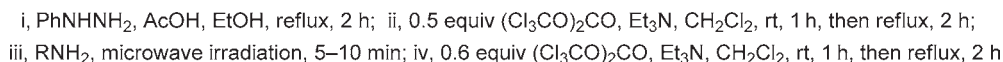
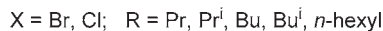
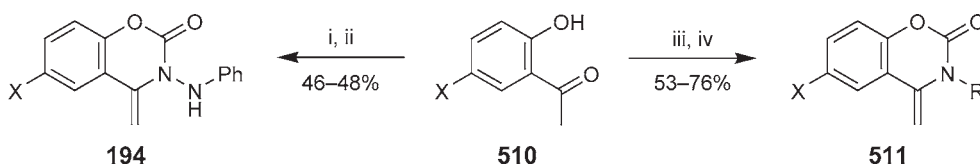


Scheme 95

When dichloromethane was applied as solvent for the reactions of epoxyalcohols **508** with methyl- or ethylamine in the presence of titanium(IV) tetraisopropoxide, cyclization of the aminodiols intermediates with the solvent to form 3,4-disubstituted-tetrahydro-1,3-oxazin-5-ols **509** was observed (Equation 59). Compounds **509** were obtained in the best yields when the reaction was carried out at 60 °C in a pressure reactor. In the analogous reaction with propylamine, no cyclized product was detected <2000T8173>.

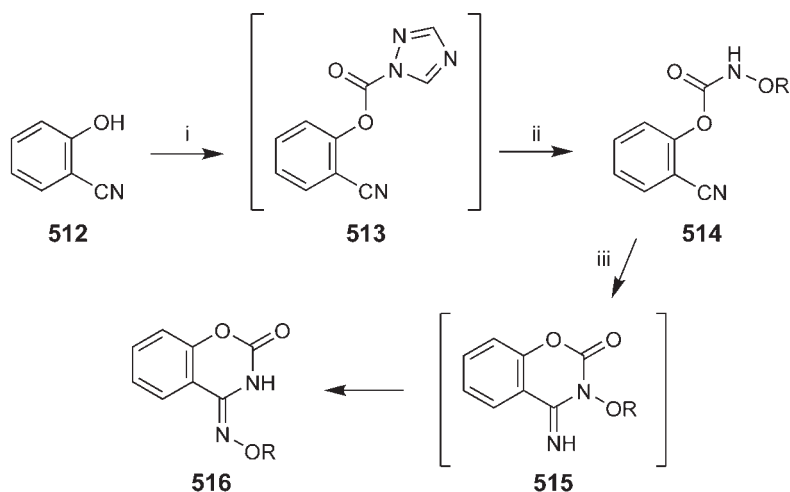


Both phenylhydrazones and imines derived from 5-halogeno-2-hydroxyacetophenones **510** were cyclized to the corresponding 4-methylene-substituted 1,3-benzoxazin-2-ones **194** and **511** on treatment with 0.5 or 0.6 equiv of triphosgene under mild conditions (Scheme 96) <2003T8163, 2004SC71>. In the similar reactions of arylhydrazones of 2-hydroxyacetophenones with 1 equiv of triphosgene, spiro-1,3-benzoxazine dimers were formed <2002JCM473>.



Scheme 96

In a one-pot, three-component method starting from 2-hydroxybenzonitrile **512**, 4-arylalkoxy/methoxy-1,3-benzoxazin-2-ones **516** were prepared. Treatment of **512** with 1,1'-carbonyldi(1,2,4-triazole) (CDT) furnished a triazolidine intermediate **513**, which was reacted with O-substituted hydroxylamines to give hydroxycarbamates **514**. Ring closure of **514** in refluxing Et_3N led to benzoxazines **515**, which underwent a base-catalyzed Dimroth rearrangement to afford **516** (Scheme 97) <2004S1987>. Similar transformations of 3-hydroxypyridine-2-carbonitrile were applied for the synthesis of pyrido[2,3-*e*][1,3]oxazine derivatives, that is, 5-aza-analogs of **516** <2005T3091>.



R = Me, CH₂Ph, (CH₂)₂Ph, (CH₂)₃Ph, CH₂C₆H₄Me(*p*), CH₂C₆H₄F(*p*), CH₂C₆H₄Br(*p*)

i, CDT, THF, rt, 10 min;

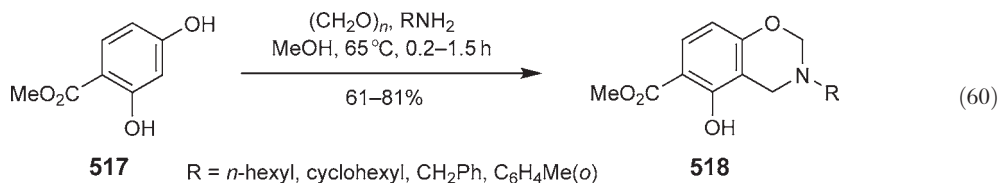
ii, H₂N-OR, THF, rt, 30 min, then evaporation;

iii, Et₃N, reflux, 45–60 min; yield: 53–64% (i–iii)

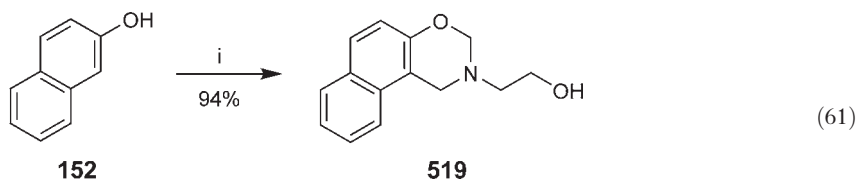
Scheme 97

8.05.9.8 [3+1+1+1] Types

Regioselective aminomethylation and subsequent cyclization of methyl 2,4-dihydroxybenzoate **517** was accomplished through a Mannich reaction with formaldehyde and primary amines in methanol to yield 3-substituted-3,4-dihydro-2*H*-1,3-benzoxazine derivatives **518** (Equation 60). Simultaneous mixing of the reactants resulted in poor yields, but good yields were achieved by the pretreatment of paraformaldehyde with a primary amine to form a Schiff base, followed by the addition of compound **517** <2001TL7273>.

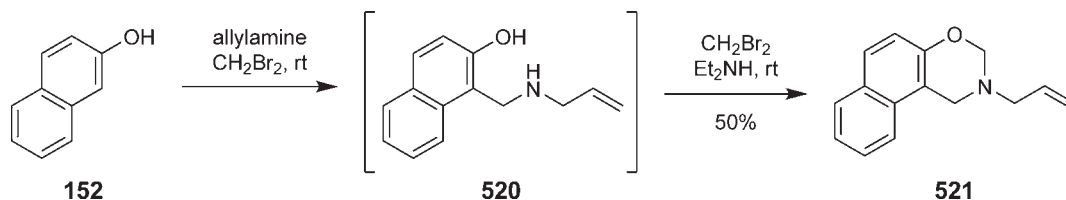


In the condensation of 2-naphthol with an aldehyde in the presence of ammonia (Betti reaction), a naphth[1,2-*e*] [1,3]-oxazine is formed <1998TA3667, 2004CSY155>. Various modifications of the Betti reaction have resulted in formation of a great number of naphthalene-condensed 1,3-oxazine derivatives, which could also be utilized in the synthesis of 1-(α -aminoalkyl)-2-naphthols (see Section 8.05.6.4). The modifications of the Betti procedure involve the application of various aromatic or aliphatic aldehydes <2003T2877, 2004JOC3645, 2006EJO4664>, 1-naphthol <2004EJO2231>, hetero-analogs of 2-naphthol <1996CPB605>, or iminium salts formed from aldehydes and primary amines <1996S883>. In the condensation of 2-naphthol **152**, formaldehyde, and 2-aminoethanol, the corresponding N-substituted 1,3-oxazine derivative **519** was obtained (Equation 61) <1999JOM(592)180>.



i, HOCH₂CH₂NH₂, 37% CH₂O (aq.), MeOH, reflux, 12 h

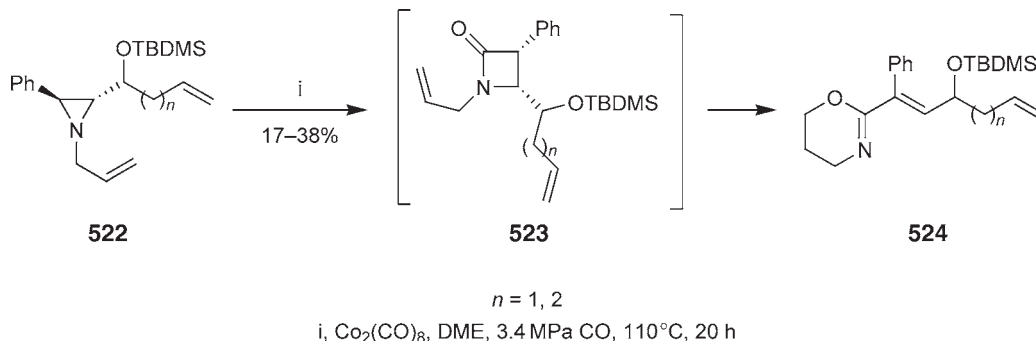
Consecutive condensations of 2-naphthol, allylamine, and dibromomethane comprised another route to naphthalene-condensed 1,3-oxazines. A preheated mixture of allylamine and dibromomethane was reacted with 2-naphthol **152** to yield the aminophenol intermediate **520**, which was cyclized with the salt formed in the reaction of dibromomethane and diethylamine to give 3-allyl-3,4-dihydro-2*H*-naphth[1,2-*e*][1,3]oxazine **521** on further reaction (Scheme 98) <2004SC2253>.



Scheme 98

8.05.10 Ring Syntheses by Transformations of Another Ring

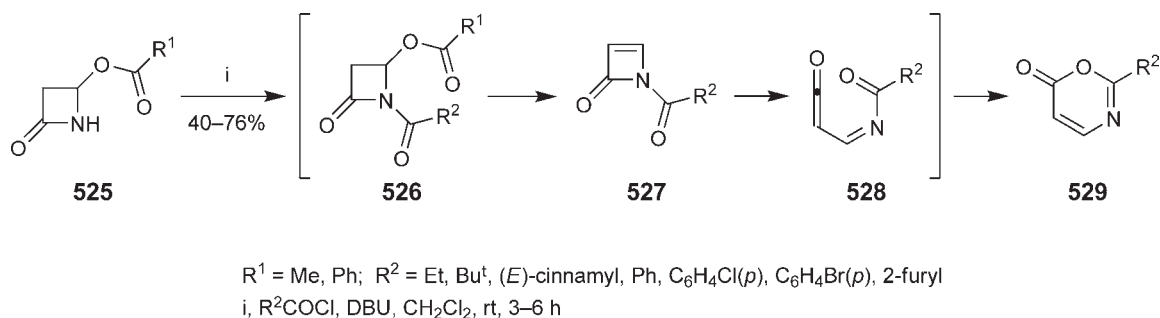
1,2-Dialkenylaziridines proved to undergo carbonylative ring expansion in the presence of $\text{Co}_2(\text{CO})_8$ as catalyst. The reaction was influenced substantially by the steric arrangement of the substituents on the aziridine ring. While *cis*-aziridines gave stable *trans*- β -lactam derivatives, for *trans*-aziridines **522**, the carbonyl insertion resulted in formation of the *cis*- β -lactam intermediates **523**, which rearranged unexpectedly to yield 5,6-dihydro-4*H*-1,3-oxazine derivatives **524** as mixtures of (*Z*)- and (*E*)-stereoisomers (Scheme 99). The formation of compounds **524** was explained by the abstraction of H-3, followed by cleavage of the N–C(4) bond and attack by the carbonyl oxygen on the allylic double bond <2004H(63)2495>.



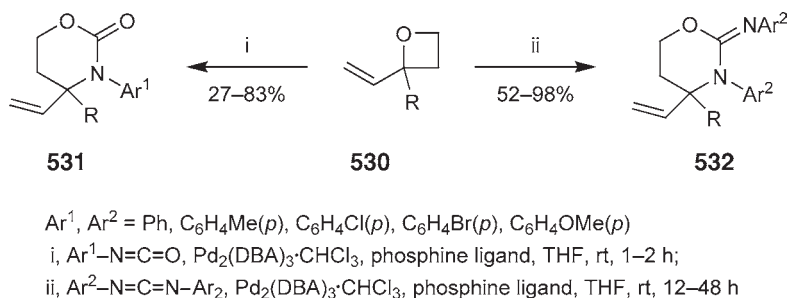
Scheme 99

4-Acyloxy- β -lactams **525** were converted to 1,3-oxazin-6-ones **529** under basic conditions in a one-pot procedure. The reaction took place via the N-acylation of **525** and base-promoted elimination of $\text{R}^1\text{CO}_2\text{H}$ from the C(3)–C(4) bond of the β -lactam ring of **526**, giving rise to the highly strained *N*-acylazetinone intermediates **527**. Compounds **527** rearranged to the final products **529** in a sequence of two electrocyclic processes (Scheme 100) <2000OL965>. The mechanism of the conversion was investigated by using *ab initio* and density functional theories <2001JOC8470>.

The palladium–phosphine-catalyzed cycloaddition reactions of vinyloxetanes **530** with aryl isocyanates or diarylcarbodiimides led to 4-vinyl-1,3-oxazin-2-ones **531** or 1,3-oxazin-2-imines **532**, respectively (Scheme 101). In the absence of phosphine ligands (PPh_3 , bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (dppp), no conversion of heterocumulenes was observed. Starting from fused-bicyclic vinyloxetanes, both types of cycloadditions proceeded in a highly stereoselective fashion, affording only the *cis*-isomers of alicycle-condensed 1,3-oxazine derivatives <1999JOC4152>.

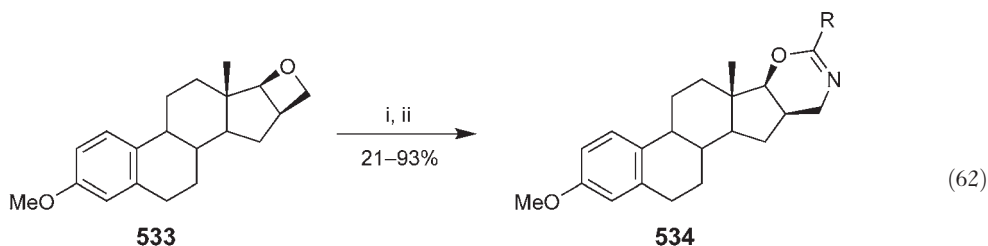


Scheme 100



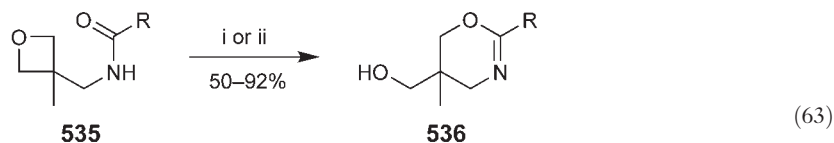
Scheme 101

The ring expansion of nonfused oxetanes under the conditions of the Ritter reaction to yield the corresponding 5,6-dihydro-4*H*-1,3-oxazines is a well-known procedure [<1996CHEC-II\(6\)301>](#). Further stereochemical details of these reactions were revealed by the ring expansions of oxetano[3',2':16,17]estrane derivatives with alkyl and aryl nitriles in the presence of the tetrafluoroboric acid–diethyl ether complex. While the 16 β ,17 β -connected oxetane **533** gave the corresponding 1,3-oxazine-fused steroids **534** in low to excellent yields ([Equation 62](#)), the analogous reaction of its 16 α ,17 α -counterpart led to cleavage of the oxetane ring followed by stabilization of the resulting carbocation by a Wagner–Meerwein rearrangement [<1998CCCC1613>](#).



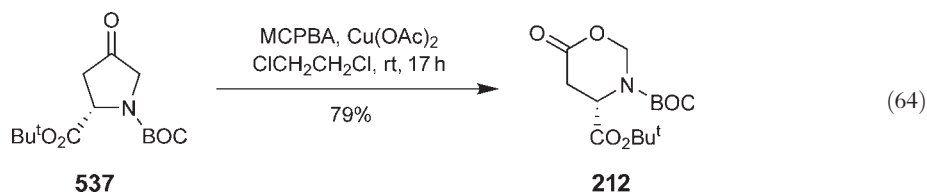
$R = \text{Me, cyclohexyl, Ph, C}_6\text{H}_4\text{Me}(p), \text{C}_6\text{H}_4\text{Cl}(p), \text{C}_6\text{H}_4\text{Br}(p), \text{C}_6\text{H}_4\text{OMe}(p), \text{C}_6\text{H}_4\text{NO}_2(p)$
 i, $\text{RCN, HBF}_4\cdot\text{Et}_2\text{O, CH}_2\text{Cl}_2$, 0 °C, then rt, 6 h, then Et_2O ; ii, NaHCO_3

The chemoselective isomerization of secondary amide-substituted oxetanes **535** in the presence of Lewis acids gave 5-hydroxymethyl-5,6-dihydro-4*H*-1,3-oxazines **536** in moderate to fairly good yields ([Equation 63](#)). The isomerization was dependent on the substituent on the amide nitrogen atom, since tertiary amide analogs of **535** afforded dioxazabicyclo[2.2.2]octane derivatives under similar conditions [<1998CC43, 2002T7049>](#).

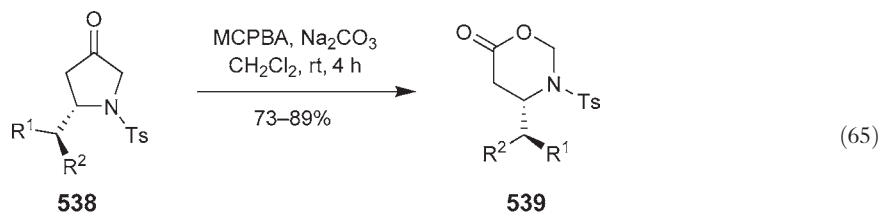


R = H, Me, Pr, CH₂Ph, Ph
 i, AlMe₃, PhCl, 120 °C, 24 h; ii, BF₃·Et₂O, CH₂Cl₂, 35 °C, 96 h

The Baeyer–Villiger lactonization of pyrrolidine ketones resulted in formation of 1,3-oxazin-6-one derivatives. When the chiral nonracemic pyrrolidinone **537** was treated with MCPBA in the presence of a catalytic amount of copper(II) acetate, tetrahydro-1,3-oxazin-6-one **211** was obtained in good yield and without racemization at the α-center during the reaction (Equation 64). The regioselectivity of the reaction was explained by the effect of the nitrogen lone pair directing the formation of the intermediates <1999TL4275, 2000J(P1)3451>.

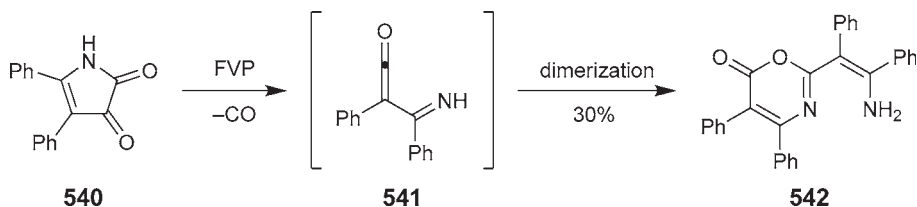


Studies on the Baeyer–Villiger lactonization of *N*-tosylpyrrolidinones **538** revealed that the corresponding 1,3-oxazin-6-ones **539** could be obtained in better yields if copper(II) acetate was replaced by sodium carbonate in the reaction (Equation 65) <2006TL4865, 2006T10843>. This procedure has also been applied successfully for the ring enlargement of 1-tosyl-2-vinylpyrrolidin-4-one <2006H(68)2031>.



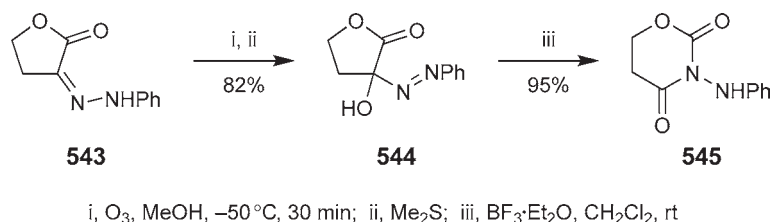
R¹ = H, Pr, allyl, Ph, C₆H₄OMe(*o*); R² = H, Ph, OCH₂Ph

FVP of 4,5-diphenylpyrrole-2,3-dione **540** resulted in the loss of CO and formation of the imidoalkene **541**, which underwent dimerization to the 1,3-oxazin-6-one derivative **542** (Scheme 102) <2004OBC3518>.



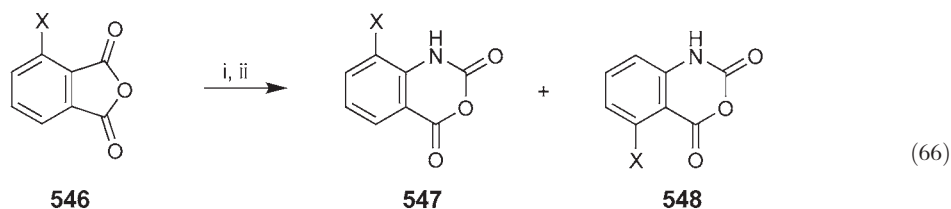
Scheme 102

2-Hydroxy-2-phenylazo-γ-butyrolactone **544**, obtained by the ozonolysis of 2-phenylhydrazo-γ-butyrolactone **543**, was found to undergo a facile rearrangement to 3-phenylaminotetrahydro-1,3-oxazine-2,4-dione **545** when treated with BF₃·Et₂O at room temperature (Scheme 103). The ring expansion of **544** took place by a 1,2-migration of an oxycarbonyl group from carbon to the azo nitrogen <1997CC571>. Oxidation of **543** with nickel peroxide provided 1,3-oxazine-2,4-dione **545** in a yield of only 10%, together with some other products <1998MI4>.



Scheme 103

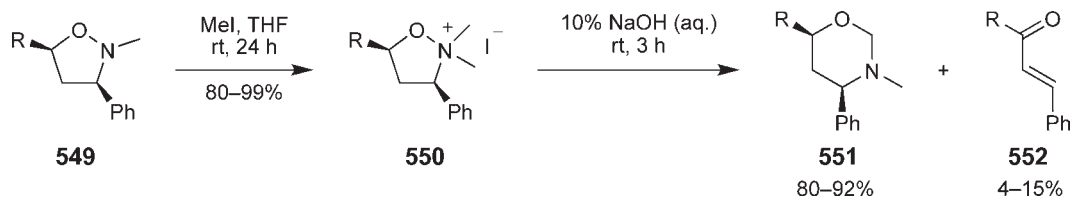
The reaction of maleic anhydride with trimethylsilyl azide was reported to provide 1,3-oxazine-2,6-dione in good yield. Control of the temperature proved essential in order to avoid a violent, exothermic reaction; this could readily be accomplished by running the reaction in methylene chloride at 0 °C <1995OPP651>. Similar transformations of 3-substituted phthalic anhydrides **546** resulted in formation of 8- **547** or 5-substituted **548** isatoic anhydrides (Equation 66). The ratio of the regioisomeric products was strongly influenced by the substituent X: while nitro and acetylamino derivatives **546** (X = NO₂, NHAc) gave exclusively the 8-substituted isomers, only the 5-substituted product was formed from 3-aminophthalic anhydride **546** (X = NH₂) <1998JOC6797>.



X (yield of **547/548**) = H (76), NO₂ (75/0), OAc (12/41), NH₂ (0/85), NHAc (74/0), OMe (55/6), OCH₂Ph (68/9)
 i, TMSN₃, benzene or THF, reflux, 3 h; ii, EtOH

In boiling toluene solution, in the presence of *p*-toluenesulfonic acid, steroidal *N*-methylisoxazolidines were reported to undergo an intramolecular rearrangement involving their *N*-methyl group, to give perhydro-1,3-oxazine derivatives in a yield of 42–54% <1999T6681>.

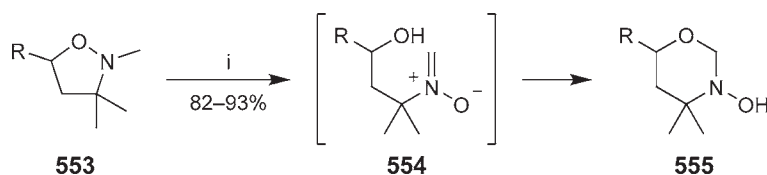
A substantial difference was observed in the reactivities of the *cis*- and *trans*-isomers of 3,5-disubstituted quaternary isoxazolinium iodides on alkaline treatment. The attack by the base at the *N*-methyl hydrogens probably led to a hydroxyiminium intermediate, which, for the *cis*-isomers, gave tetrahydro-1,3-oxazine derivatives **551** as the main products by recyclization, besides small amounts of the α,β -enones **552**, formed by a Hofmann-like elimination (Scheme 104). For the *trans*-counterparts, the α,β -enones **552** were obtained as the exclusive products <1995T2979>.



R = *n*-pentyl, *n*-hexyl, Ph, C₆H₄Me(*p*), C₆H₄Cl(*p*), C₆H₄OMe(*p*)

Scheme 104

Oxidation of 5-substituted 2,3,3-trimethylisoxazolidines **553** with MCPBA afforded 6-substituted-3-hydroxytetrahydro-1,3-oxazines **555** in high yields via the nitron **554** intermediates formed by abstraction of hydrogen from the *N*-methyl group (Scheme 105) <1998T12959>.

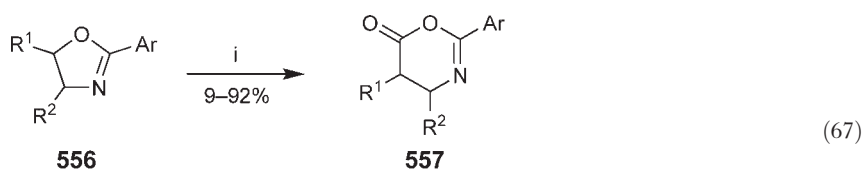


R = CH₂OH, CH₂OAc, CH₂CH₂OH, Ph

i, MCPBA, CH₂Cl₂, –15°C, 0.5 h, then 0°C, 0.5 h, then 20°C, 0.5 h

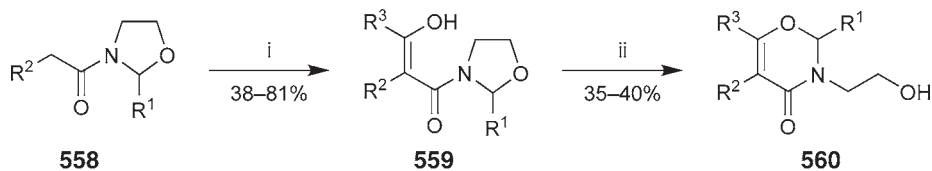
Scheme 105

2-Aryl-4,5-dihydrooxazoles **556** underwent cobalt-catalyzed carbonylation to give 4,5-dihydro-1,3-oxazin-6-ones **557**, usually in good yields, but an exception was the ring enlargement of **556** containing a 5-methyl (R¹ = Me) or a sterically bulky 2-(*o*-tolyl) substituent (Equation 67) <2003OL1575>.



Ar = Ph, C₆H₄Me(*o*), C₆H₄Me(*p*), C₆H₄F(*m*), 2-thienyl, 2-furanyl; R¹ = H, Me, Ph; R² = H, Me
i, PhCH₂Co(CO)₄, PhCH₂CoCo(CO)₄, 1.4–6.9 MPa CO, THF, 60°C, 48 h

The oxazolidine system proved a good protecting group with which to mask the ethanolamine moiety in the α -formylation and α -benzoylation of **558**, and it could also be used as an aldehyde donor in the rearrangement, based on the ring-chain tautomeric character of **559**, under acidic conditions to yield 3-(2-hydroxyethyl)-substituted 1,3-oxazin-4-ones **560** (Scheme 106) <1996JOC3358>.



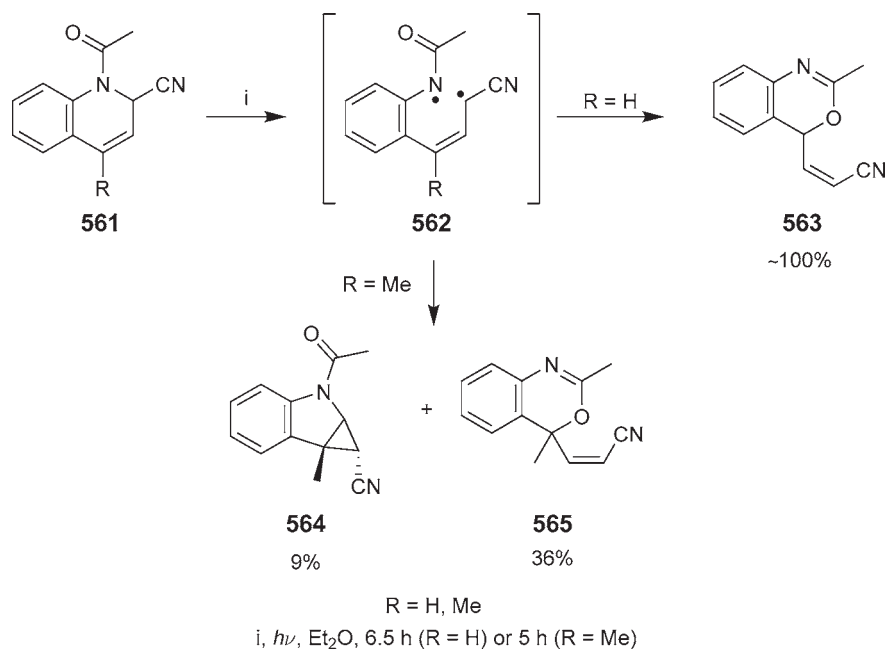
R¹ = H, Me; R² = H, Ph; R³ = H, Ph

i, NaH, THF, R³CO₂Et, reflux, 5 h; ii, 2 N HCl (in Et₂O), EtOAc, rt, 8–24 h

Scheme 106

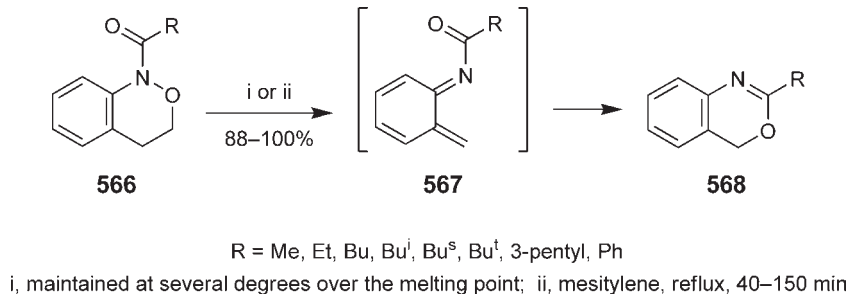
The zinc alkoxides of *syn*- or *anti*-3-(β -hydroxyacyl)oxazolidin-2-ones underwent stereoselective rearrangement under mild conditions to afford *syn*- or *anti*-3-(2-hydroxyethyl)tetrahydro-1,3-oxazine-2,4-diones in good yields. The procedure was utilized in the synthesis of (*E*)-trisubstituted α,β -unsaturated amides and acids <2005OBC2976, 2005SL1090>.

A reinvestigation of the experiments on the UV irradiation of 1-acetyl-1,2-dihydroquinoline-2-carbonitriles (Reissert compounds) **561** unequivocally demonstrated that the rearrangement via the diradical intermediate **562** gave 4*H*-3,1-benzoxazines **563** and **565** rather than the benzazete derivatives described earlier. The yields and the type of products were strongly influenced by the substituent R at position 4: while irradiation of the unsubstituted quinoline **561** (R=H) gave 3,1-benzoxazine **563** in nearly quantitative yield, the amount of the corresponding methyl-substituted analog **565** that could be isolated was considerable lower, due to its irreversible isomerization via **562** to the stable cycloprop[*b*]indole derivative **564** (Scheme 107) <1998H(49)121>.



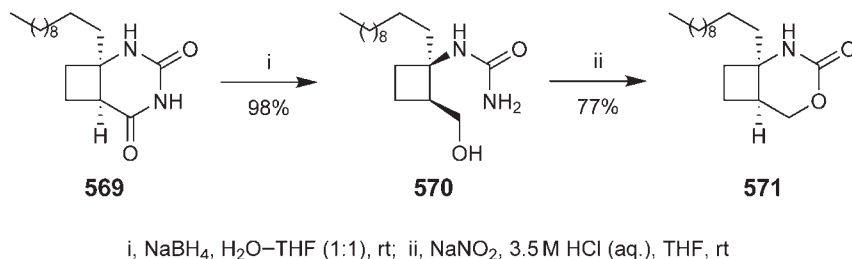
Scheme 107

In the thermal decomposition of 1-acyl-3,4-dihydro-1*H*-2,1-benzoxazines **566**, an RDA reaction involving the loss of formaldehyde occurred, and 5-acylimino-6-methylidenecyclohexa-1,3-dienes **567** were formed, which underwent electrocyclicization to 2-substituted-4*H*-3,1-benzoxazines **568** (Scheme 108) <1996J(P2)1367>.



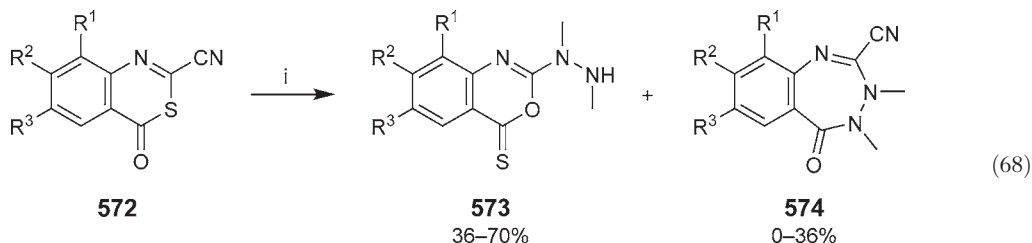
Scheme 108

Cyclobutane-fused hexahydropyrimidine-2,4-dione **569** was converted to the corresponding 1,3-oxazin-2-one derivative **571** in a two-step procedure (Scheme 109). Compound **569** was reduced with NaBH_4 to give ureidoalcohol **570** in excellent yield, the diazotization of which provided the cyclic carbamate derivative **571** <2006TL5981>.



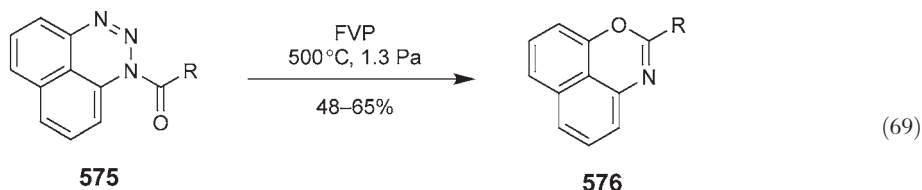
Scheme 109

The condensation of 4-oxo-4*H*-3,1-benzothiazine-2-carbonitriles **572** with 1,2-dimethylhydrazine under microwave irradiation resulted in formation of 2-hydrazino-4*H*-3,1-benzoxazine-4-thiones **573** and 5-oxo-4,5-dihydro-3*H*-1,3,4-benzotriazepine-2-carbonitriles **574** (Equation 68). The ratio of **573** and **574** was strongly influenced by the substituents R^1 – R^3 ; methoxy substituents facilitated the formation of **574**, while in their absence 1,3-benzoxazine-4-thiones **573** were formed as the exclusive products <2005T8288>.



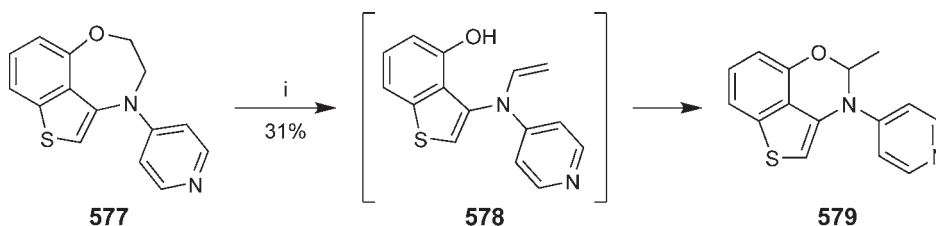
$R^1 = \text{H, OMe}; R^2 = \text{H, OMe}, R^3 = \text{H, Me, OMe}$
i, MeNHNHMe·2HCl, Et₃N, pyridine, microwave irradiation (80 W), 10 min

FVP of 1-acylnaphtho[1,8-*de*][1,2,3]triazines **575** gave exclusively the corresponding 2-substituted-naphth[1,8-*de*][1,3]oxazines **576** (Equation 69). The reaction was presumed to start with the elimination of N₂ to give 1-(acylamino)naphthalene diradicals, which then underwent intramolecular cyclization to give the oxazines **576** <2005T10507>.



$R = \text{Me, Ph, C}_6\text{H}_4\text{Me}(p), \text{C}_6\text{H}_4\text{Cl}(p), \text{C}_6\text{H}_4\text{OMe}(p), \text{C}_6\text{H}_4(\text{OCH}_2\text{CH}=\text{CH}_2)(o)$

In the presence of a strong base (NaH) and heat, 4,5-dihydro-3-(4-pyridyl)thieno[4,3,2-*ef*][1,4]benzoxazepine **577** rearranged to the isomeric 3,4-dihydro-4-methyl-3-(4-pyridyl)thieno[4,3,2-*de*][1,3]benzoxazine **579** (Scheme 110). The ring contraction was explained by base-induced proton abstraction from the methylene group α to the nitrogen, which was followed by β -elimination and subsequent protonation, resulting in the enamine intermediate **578** which cyclized in response to attack by the phenolic hydroxy group <1997JHC1769>.



i, 1 equiv NaH, NMP, 100 °C, 1 h, then 4 equiv NaH, 100 °C, 0.5 h

Scheme 110

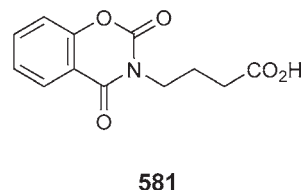
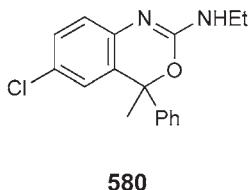
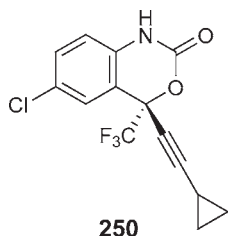
8.05.11 Synthesis of Particular Classes of Compounds

The diverse range of different structures prepared over the period in question together with the small number of publications on any given system preclude any meaningful comparison of the various methods available.

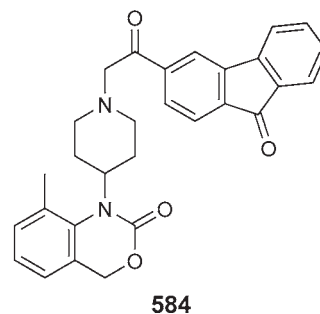
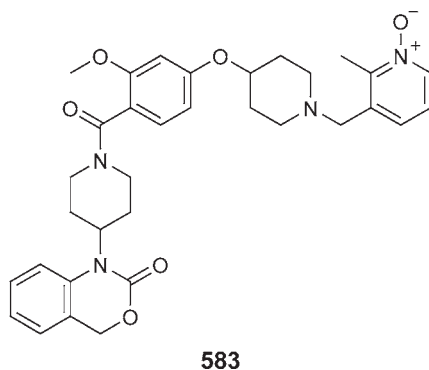
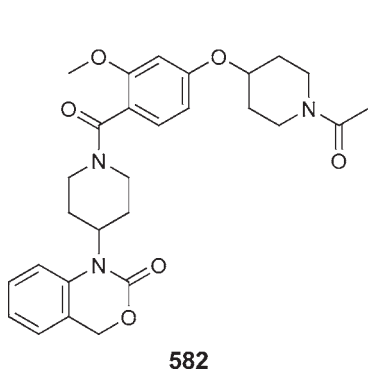
8.05.12 Important Compounds and Applications

Various 1,3-oxazine derivatives and their carbo- or heterocycle-fused analogs exhibit valuable biological activities. Two such compounds, both with a 3,1-benzoxazine skeleton, have become drugs approved for human application. Efavirenz (Stocrin[®], Sustiva[®]) **250** is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used in combination with other antiretrovirals for the therapy of HIV infection <1995AAC2602, 2004MI115>. Etifoxine (Stresam[®]) **580** is an anxiolytic which potentiates the GABA_A (γ -aminobutyric acid) receptor function. It is applied for the short-term treatment of anxiety <2000MI1523, 2003MI293>.

4-(3,4-Dihydro-2,4-dioxo-2*H*-1,3-benzoxazin-3-yl)butyric acid **581** possesses good anticonvulsant activity and its ability to block bicuculline-induced convulsions suggested that it could be a GABA mimetic drug <1997PHA272, 1997MI57>.



Numerous 1-(4-piperidyl)-substituted 3,1-benzoxazin-2-ones have been reported to possess considerable pharmacological activity. The *N*-benzoylpiperidine derivatives L-371,257 **582** and L-372,662 **583** proved to be selective nonpeptide antagonists for the oxytocin receptor, with potential application for the treatment of preterm labor. Modification of the acetylpiperidine terminal of **582** to pyridine *N*-oxide led to **583**, with improved pharmacokinetics and excellent oral bioavailability <1995JME4634, 1998JME2146, 2005MI349>. The fluorenyl derivative **584** exhibited selective neuro-peptide Y5 antagonist properties, with potential application for the treatment of obesity <2005JME2080>.

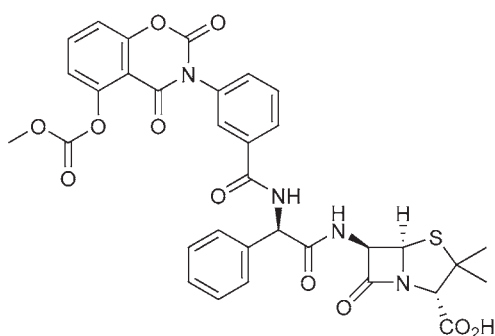


2-Amino-3,1-benzoxazin-4-ones and thieno[2,3-*d*][1,3]oxazin-4-ones have been found to inhibit human leukocyte elastase and chymase <1998JME1729, 1999JME5437, 2001BMC947>. 2-Aryl-4*H*-3,1-benzoxazine-4-ones and their hetero-analogs proved to be inhibitors of tissue factor/factor VIIa-induced coagulation <2000BMC2095, 2000BMC2803>. 6-Aryl-3,1-benzoxazine derivatives have been reported to be progesterone receptor modulators (2002BML787, 2002JME4379, 2004BML2185, 2005JME5092).

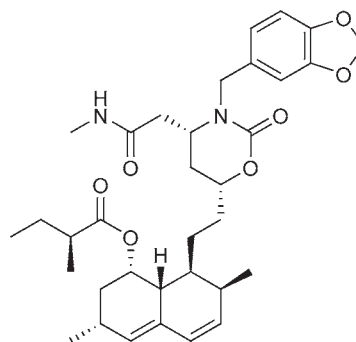
Various 3-aryl- or 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones possess *in vitro* activity against *Mycobacterium tuberculosis*, *Mycobacterium kansasii*, and *Mycobacterium avium*. For the 3-aryl-substituted derivatives, the antimycobacterial effect was found to be enhanced as the hydrophobicity and electron-withdrawing properties of the substituents on the phenyl ring increased. Replacement of the oxo groups by sulfur also resulted in an elevation of the antimycobacterial activity <1996MI701, 1998AP3, 1999CCC1902, 1999MI123, 2000EJM733, 2001FES803, 2001CPA323, 2003FES1137, 2003PHA83>.

In twin compounds of 8-acyloxy-1,3-benzoxazine-2,4-diones and β -lactam antibiotics (e.g., ampicillin derivative **585**), the catechol analog 1,3-benzoxazine moiety proved to behave as an effective siderophore component, utilizing the iron transport system of the bacterium to invade the cell. This resulted in significantly increased antibacterial activities of the conjugates against Gram-negative bacteria as compared with the parent antibiotics <2000AF752>. The statin analog tetrahydro-1,3-oxazin-2-one **586** displayed a considerable anti-inflammatory

activity *in vivo*, based on inhibition of the binding of the lymphocyte function-associated antigen (LFA)-1 and the intercellular adhesion molecule (ICAM)-1 <2004BML2483>.



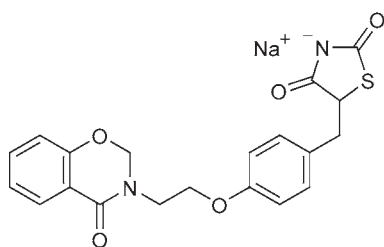
585



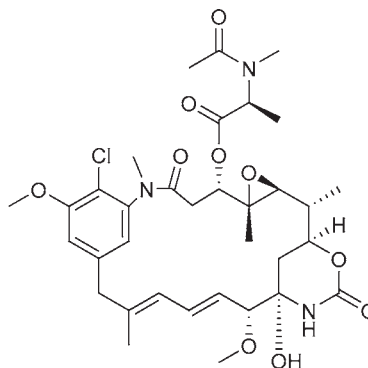
586

The 3,4-dihydro-2*H*-1,3-benzoxazin-4-one derivative DRF-2519 **587**, bearing a 2,4-thiazolidinedione moiety in the side chain attached to the nitrogen atom, proved to be an activator of the α - and γ -types of the peroxisome proliferator-activated receptors (PPAR- α and - γ), which endowed it with antidiabetic and hypolipidemic potential. Compound **587** demonstrated significant plasma glucose-, insulin-, and lipid-lowering activity in mice and improvement in lipid parameters in fat-fed rats <2006BMC584>.

Maytansine **588** is a macrocyclic tetrahydro-1,3-oxazin-2-one derivative isolated from higher plants, mosses, and an actinomycete, *Actinosynnema pretiosum*. Despite the extraordinary antitumor activity found for many maytansine derivatives, the Phase II clinical trials with maytansine turned out to be disappointing. The chemistry and biology of maytansinoids have recently been reviewed <2004CPB1>.

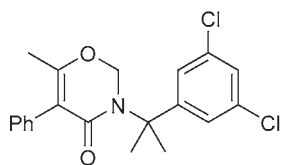


587

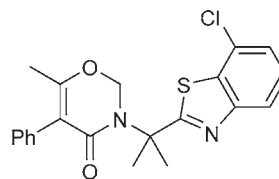


588

Some 2,3-dihydro-4*H*-1,3-oxazin-4-one derivatives exhibit potent herbicide activity. Oxaziclomefone **589** proved effective in controlling cockspur (*Echinochloa crus-galli*) and other grasses and annual sedges that can substantially reduce the yield of rice in paddy fields. It was reported to inhibit cell expansion in maize cell cultures, without affecting the turgor pressure or wall acidification <2003JPE221, 2005MI1097, 2005MI323>. The benzothiazole-substituted analog MI-3069 **590** was likewise found to be an effective herbicide for use against *Echinochloa oryzicola* in transplanted rice paddy fields. Its herbicide activity exhibited a long duration of action in consequence of its long-lasting residual effect <2004MI981>.



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8.05.13 Further Developments

While this chapter was being edited and revised, new data appeared on the chemistry of 1,3-oxazine derivatives. In a recent review on the applications of 1,3-amino alcohols in asymmetric organic syntheses, the use of numerous 1,3-oxazine derivatives for this purpose was discussed <2007CRV767>. A compilation on the progesterone receptor ligands provides a brief summary of the progesterone receptor modulatory effects of 6-aryl-1,4-dihydro-3,1-benzoxazin-2-ones <2007MI374>.

The ring-chain tautomeric character of tetrahydro-1,3-oxazine derivatives was made use of in the preparation of *N*-substituted 1,3-amino alcohols through reductive alkylation procedures <2007JHC403, 2007STE446>. Tetrahydro-1,3-oxazine was found to react with ketone oximes and paraformaldehyde to form ketone *O*-(tetrahydro-1,3-oxazin-3-ylmethyl)oximes as aminomethylation products <2007RJO943>. Excellent *trans* selectivity was observed for double bond formation in the reactions of 3-methyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazines with Grignard reagents to give *N*-acetylhomallylamine derivatives <2007TL2345>. The protecting groups at the amino acid functions proved to direct the highly stereo- and chemoselective iodocyclization of (*S*)-allylalanine derivatives, resulting in a product of tetrahydro-1,3-oxazin-2-one type in the case of the *N*-BOC benzyl ester <2007OL2365>. Montmorillonite K-10-catalyzed cycloisomerization of salicylaldehyde semicarbazones under solvent-free microwave irradiation furnished 3-aryl-4-hydrazino-2*H*-1,3-benzoxazin-2-ones, which underwent dehydrazinative β -glycosylation directly with unprotected D-ribose <2007SL1227>. Cyclizations of the dipeptide intermediates formed from 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione and natural α -amino acids led to 3,4-dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione and 3-(thien-3-yl)imidazolidine-2,4-dione derivatives <2007JOC2662, 2007T7538>. Enolate reactions of 4-substituted tetrahydro-1,3-oxazin-6-ones gave the corresponding 5-hydroxy- or 5-alkyl-substituted products with excellent *trans* diastereoselectivity, and these products were converted to various derivatives of the corresponding α,β -disubstituted β -amino acids <2007JOC3340>.

Some further examples have emerged for the preparation of 1,3-oxazine derivatives by cyclization of the corresponding 1,3-amino alcohol or phenol with triphosgene <2007T5579>, thiophosgene <2007JST(830)116> and aldehydes in the presence of (diacetoxyiodo)benzene <2007SL1921>. Lewis acid-catalyzed ring closure of substituted 3-azidopropanols with aldehydes was applied in the synthesis of 5,6-dihydro-4*H*-1,3-oxazine libraries <2007JCO473>. Palladium(0)-catalyzed cyclizations of *N*-homallylbenzamides through the corresponding π -allylpalladium(II) complexes were reported to give 5,6-dihydro-4*H*-1,3-oxazine derivatives with moderate to excellent diastereoselectivity <2007EJO1586>. The preparation of numerous naphth[1,2-*e*][1,3]oxazine derivatives was achieved in modified Betti reactions, in which urea <2007SL821>, aliphatic <2007CH374> or heterocyclic aldehydes <2007MOL345>, and 1,3,5-triaryl-2,4-diazapenta-1,4-dienes <2007MC239> were applied in the condensations. Various substituted *o*-quinone methides, generated by thermal decomposition of the corresponding 4*H*-1,2-benzoxazines, were reported to undergo Diels–Alder reactions with *N*-methylidenbenzylamine to yield 3-benzyl-3,4-dihydro-2*H*-1,3-benzoxazines <2007ASC669>.

Two naturally occurring 1,3-oxazine derivatives with a unique, 2-chlorinated tetrahydro-1,3-oxazine structure were reported as metabolites isolated from extracts of the endophytic fungus *Geotrichum* sp. AL4 <2007MI1520>. Halogenated 3-(4-alkylphenyl)-1,3-benzoxazine-2,4(3*H*)-diones were found to exhibit antimycobacterial activity <2007AP264>.

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Biographical Sketch



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8.06

1,4-Oxazines and their Benzo Derivatives

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8.06.1 Introduction

In the *Comprehensive Heterocyclic Chemistry* series, 1,4-oxazines were last included in CHEC(1984) <1984CHEC(3)995>, where they were considered along with all isomeric oxazines and thiazines and their benzo derivatives, thus meaning that this relatively rare ring system did not get adequate coverage. In CHEC-II(1996), 1,4-oxazines were omitted entirely. Therefore, this chapter is a comprehensive review of the literature on 1,4-oxazines for the period 1982–2006, with many references prior to 1982 that were not included in the first edition. A detailed review of the known synthetic methods for 1,4-oxazines has recently appeared <2004SOS(17)55>.

As shown in Figure 1, the fully conjugated ring systems that appear in this chapter include the aromatic oxazinium ion **1**, which has six ring π -electrons, but of which there is no experimental knowledge. The fully conjugated noncharged

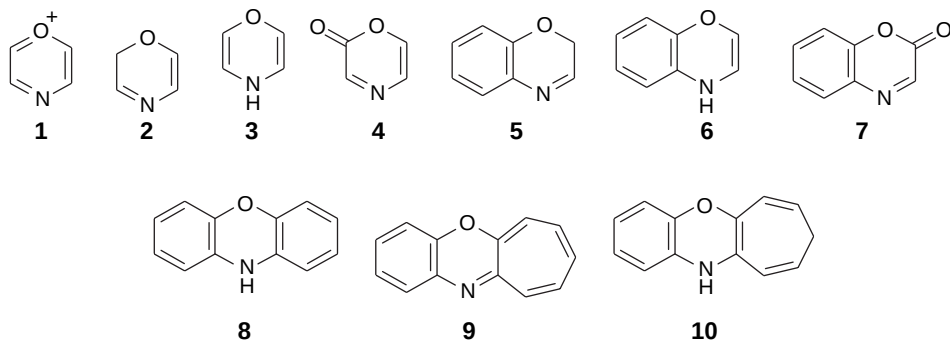


Figure 1 The fully conjugated oxazine ring systems covered in this chapter.

structures covered are 2*H*-1,4-oxazine **2**, 4*H*-1,4-oxazine **3**, 2*H*-1,4-oxazin-2-one **4**, the corresponding benzo derivatives **5–7**, dibenzoxazine (phenoxazine) **8**, and the benzo[*b*]cyclohept[*e*]-1,4-oxazine **9** and its dihydro derivative **10**.

The nonconjugated 1,4-oxazines covered in this chapter are shown in **Figure 2**. The dihydrooxazines included are compounds of the types **11–21**. They include the 2*H*-5,6-dihydrooxazine **11** and its *N*-oxide **13** and 2*H*-3,4-dihydrooxazine **12**. Also included are the isomeric dihydrooxazinones **14–16**, 2*H*-5,6-dihydrooxazin-2-one *N*-oxide **17**, 2*H*-3,4-dihydrooxazine-2,3-dione **18**, benzodihydrooxazine **19**, and the isomeric benzodihydrooxazinones **20** and **21**.

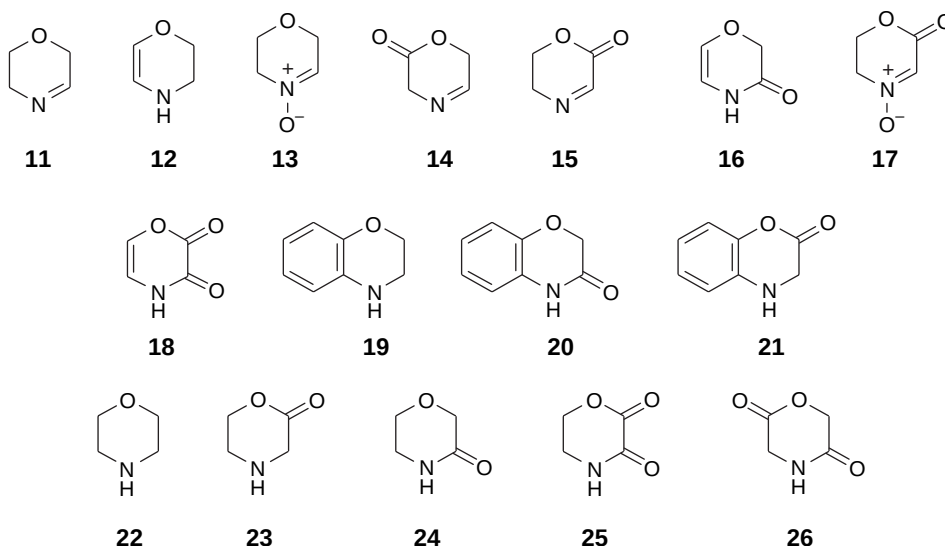


Figure 2 The nonconjugated oxazine ring systems covered in this chapter.

The fully saturated tetrahydrooxazines discussed have the general structures **22–26**. In addition to the basic tetrahydrooxazine (morpholine) **22**, the isomeric tetrahydrooxazinones **23** and **24** and tetrahydrooxazinones **25** and **26** have been studied.

8.06.2 Theoretical Methods

Theoretical calculations have provided the only data available for the basic structures of fully conjugated 1,4-oxazines, as these compounds have never been synthesized. The aromatic dehydro-1,4-oxazinium cation **1** has been computed by the semi-empirical MINDO/3 program to have a heat of formation of 644.4 kJ mol^{−1}, ionization energy of 14.41 eV, and the charge distribution shown in **Figure 3** <1987JOU646>. The 4*H*-1,4-oxazine structure **3** has been calculated to have the π -electron density and bond lengths shown in **Figure 3**, and an aromatic stabilization energy of −2.1 kJ mol^{−1} <1971JST(8)236>. *Ab initio* calculations using a 6-31G basis set suggest its equilibrium conformation to have the torsion angles shown in **Figure 3** <1998JST(446)11>.

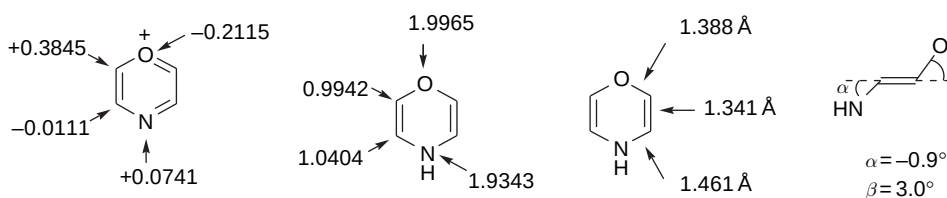


Figure 3 Theoretically derived data for 1,4-oxazinium salt **1** and 1,4-oxazine **3**.

All the isomers **27–31** of benzoxazinotropone are subject to keto–enol tautomerism (**Figure 4**), which was proven by their O-acetylation. However, the keto forms were predicted to be favored energetically by calculations using the

MINDO/3 method and Aihara's graph theory of aromaticity <1991BCJ2131>. The enol forms, with their double bond at the oxazine 3,4-position, are calculated to have higher ring currents around the three-ring system and lower ring currents around the individual carbocyclic rings and MINDO/3 calculations indicate a planar lowest energy conformation for all of the molecules. Some calculated data for these compounds are shown in Table 1 <1991BCJ2131>.

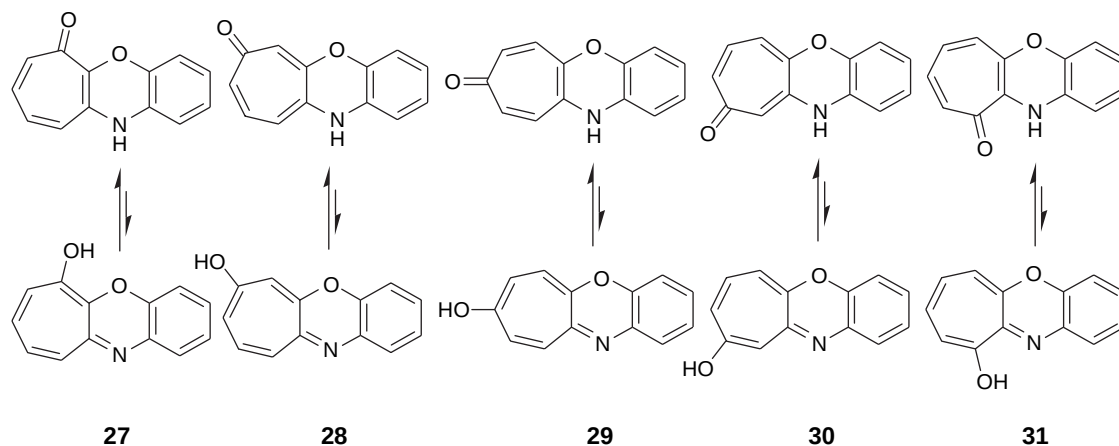


Figure 4 Keto-enol tautomerism of benzoxazinotropones.

Table 1 Resonance energies and heats of formation for compounds 27–31

Compound	Keto form		Enol form	
	RE (β)	ΔH_f (kJ mol^{-1})	RE (β)	ΔH_f (kJ mol^{-1})
27	0.401	–105.0	0.312	–92.8
28	0.404	–148.0	0.319	–133.0
29	0.402	–121.7	0.314	–118.8
30	0.403	–146.4	0.318	–128.4
31	0.402	–125.5	0.315	–113.8

8.06.3 Experimental Structural Methods

8.06.3.1 X-Ray Diffraction

X-Ray crystallography has frequently been used to determine the stereochemistry of chiral 1,4-oxazines, to prove the regiochemistry of a new compound or the general structure of an unexpected product. The 1,4-oxazine-containing crystal structures located include 1,4-oxazines 31–33, the 4*H*-dihydro-1,4-oxazines 34–39, the 2*H*-dihydro-1,4-oxazines 40–51 and the tetrahydro-1,4-oxazines 52–59. Table 2 lists the bond lengths and Table 3 the bond angles around the oxazine ring for these compounds where they are available. The benzoxazinotropone 31 was found to exist in the crystal as a hydrogen-bonded dimer, thus explaining its anomalous reactivity compared to the isomers 27–30 <1991BCJ2131>. In the case of 35, the gross structure could be confirmed, but crystallographic disorder prevented any meaningful data on the oxazine ring being obtained <2003OM987>. It should be noted that the data for this compound in the Cambridge Crystallographic Database (Refcode MUZRUI) is erroneous. X-Ray diffraction was used to show that compounds 38 and 39 had the (*Z*)-configuration shown, although no further details were provided <2005H(65)579>. The structure of 51 shows intramolecular hydrogen bonding between the O–H and ester carbonyl group <2002JOC66>. For compound 55, the absolute configuration was determined to be *R,R* by anomalous single crystal X-ray analysis <1992JME480>.

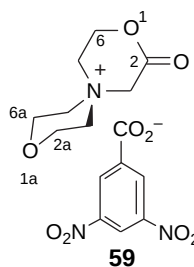
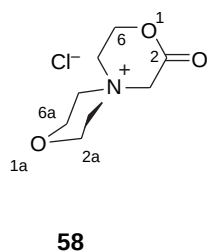
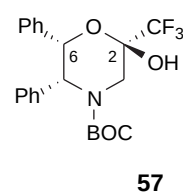
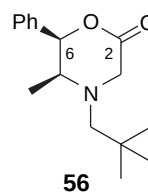
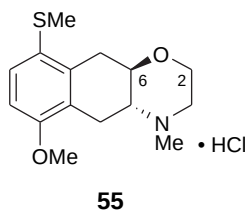
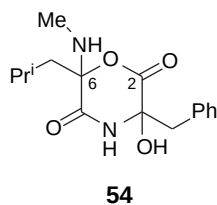
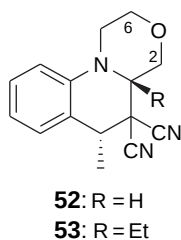
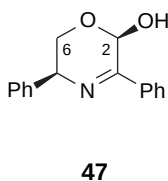
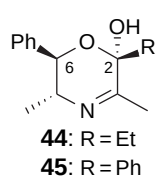
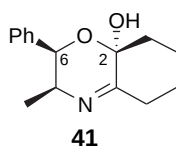
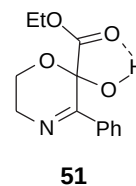
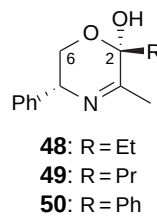
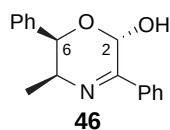
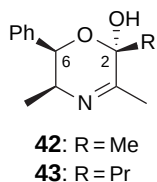
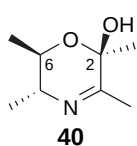
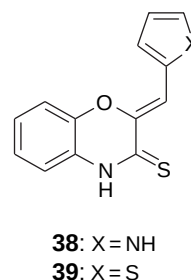
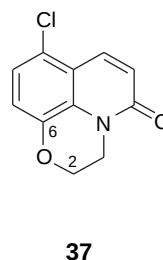
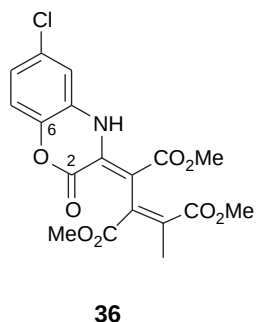
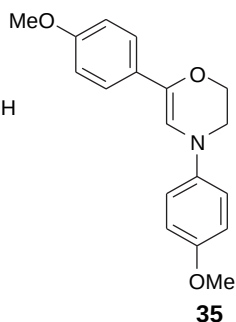
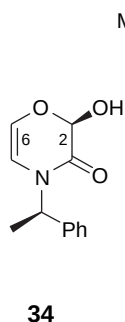
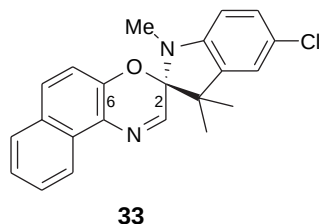
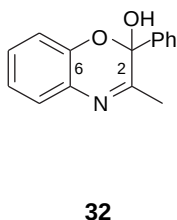
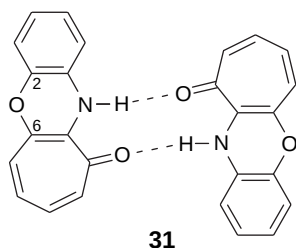


Table 2 Bond lengths in 1,4-oxazines (Å)

<i>Compound</i>	<i>O1–C2</i>	<i>C2–C3</i>	<i>C3–N4</i>	<i>N4–C5</i>	<i>C5–C6</i>	<i>C6–O1</i>	<i>Reference</i>
31	1.345	1.450	1.383	1.395	1.400	1.345	1991BCJ2131
32	1.428	1.538	1.274	1.408	1.386	1.375	1999M1481
33	1.464	1.506	1.278	1.417	1.371	1.367	2004BMC1037
34	1.420	1.522	1.344	1.415	1.323	1.365	1997NCS419
36	1.38	1.48	1.38	1.41	1.38	1.39	1984CPB1163
37	1.437	1.494	1.462	1.391	1.379	1.365	2004TL9361
40	1.410	1.527	1.273	1.468	1.516	1.435	1992JOC2446
41	1.416	1.519	1.268	1.472	1.523	1.436	1995TA2715
42	1.408	1.543	1.271	1.467	1.531	1.435	1995TA2715
43	1.423	1.527	1.274	1.478	1.523	1.437	1995TA2715
44	1.426	1.550	1.265	1.475	1.528	1.433	1995TA2715
45	1.418	1.549	1.249	1.458	1.550	1.443	1995TA2715
46	1.417	1.523	1.268	1.474	1.516	1.431	1996JHC1271
47	1.398	1.539	1.278	1.472	1.534	1.422	1996JHC1271
48	1.410	1.540	1.261	1.474	1.519	1.431	2000SC2721
49	1.410	1.529	1.270	1.467	1.519	1.424	2000SC2721
50	1.412	1.541	1.273	1.473	1.507	1.427	2000SC2721
52	1.408	1.518	1.446	1.470	1.498	1.419	1989JOC209
53	1.387	1.533	1.455	1.466	1.494	1.429	1989JOC209
54	1.350	1.543	1.444	1.310	1.524	1.479	1992JAN1553
56	1.323	1.486	1.427	1.458	1.514	1.450	1999SC1277
57	1.417	1.535	1.450	1.478	1.531	1.437	2000JCM310
58	1.310	1.450	1.505	1.603	1.248	1.402	2004JST(704)129
58^a	1.409	1.214	1.568	1.469	1.387	1.433	2004JST(704)129
59	1.372	1.475	1.525	1.504	1.507	1.393	2004JST(704)129
59^a	1.390	1.519	1.500	1.504	1.513	1.402	2004JST(704)129

^aNon-carbonyl-containing ring.**Table 3** Internal bond angles (at atom indicated) in 1,4-oxazines (deg)

<i>Compound</i>	<i>O(1)</i>	<i>C(2)</i>	<i>C(3)</i>	<i>N(4)</i>	<i>C(5)</i>	<i>C(6)</i>	<i>Reference</i>
32	115.83	110.56	121.81	118.44	120.97	119.51	1999M1481
33	118.93	110.10	127.15	116.76	121.04	121.95	2004BMC1037
34	112.56	111.99	115.28	119.80	119.43	121.90	1997NCS419
36	122.1	117.4	118.3	122.0	118.6	121.1	1984CPB1163
37	111.62	112.13	109.18	118.12	120.02	123.14	2004TL9361
40	113.02	111.43	124.29	119.84	110.36	107.39	1992JOC2446
41	112.03	113.03	124.33	118.79	109.82	106.58	1995TA2715
42	112.81	112.07	124.10	119.18	109.56	106.64	1995TA2715
43	112.03	111.30	124.86	119.31	110.99	107.51	1995TA2715
44	113.74	110.12	124.36	120.99	112.73	109.42	1995TA2715
45	114.43	110.46	126.11	119.45	112.94	107.46	1995TA2715
46	112.47	112.65	124.28	119.00	111.91	107.34	1996JHC1271
47	111.36	111.82	123.27	120.13	113.08	110.73	1996JHC1271
48	113.2		124.9	119.9		108.7	2000SC2721
49	112.5		124.8	119.3		108.9	2000SC2721
50	111.5		124.4	119.9		119.3	2000SC2721
52	110.10	110.91	109.08	110.19	110.50	110.82	1989JOC209
53	107.71	113.81	108.65	116.71	111.21	111.60	1989JOC209
54	127.19	118.99	112.36	128.23	121.12	111.37	1992JAN1553
56	121.54	119.37	116.08	110.93	106.81	110.94	1999SC1277
57	113.04	112.51	108.51	115.57	106.34	111.17	2000JCM310
58	117.4	120.9	118.5	105.3	111.0	118.7	2004JST(704)129
58^a	108.6	118.6	123.9	107.1	111.8	121.5	2004JST(704)129
59	113.0	115.4	109.1	108.3	111.4	113.5	2004JST(704)129
59^a	110.3	110.1	111.3	108.5	111.0	112.8	2004JST(704)129

^aNon-carbonyl-containing ring.

8.06.3.2 NMR Spectroscopy

8.06.3.2.1 ^1H NMR

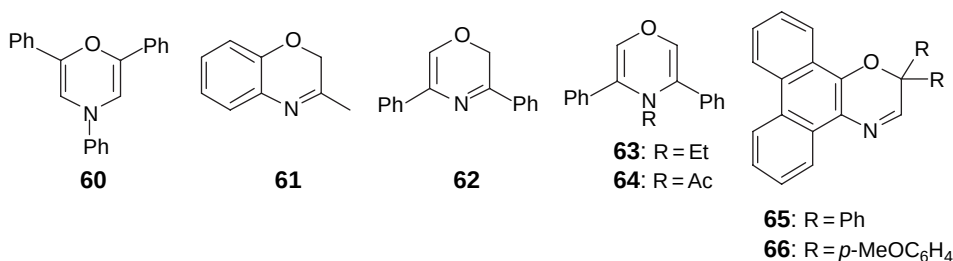
A fair amount of ^1H nuclear magnetic resonance (NMR) data for various 1,4-oxazines exist, but the observed chemical shifts depend heavily on the substitution pattern as well as the number of ring double bonds. Representative data for most of the known types of 1,4-oxazines and dihydro-1,4-oxazines are given in [Table 4](#).

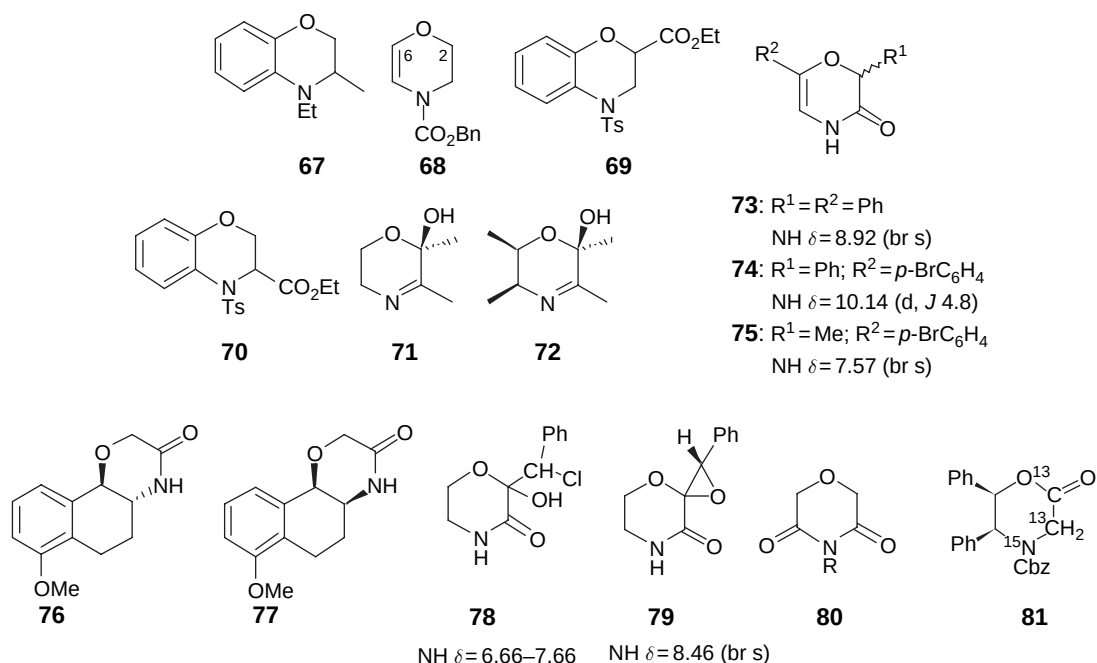
Table 4 ^1H NMR chemical shifts (ppm) for oxazine protons

Compound	2- <i>H</i>	3- <i>H</i>	5- <i>H</i>	6- <i>H</i>	Reference
60		6.44	6.44		1973JOC3433
61	3.78				1979M257
62	4.78			6.93	1982AP684
63	6.14			6.14	1982AP684
64	6.54			6.54	1982AP684
65		8.12			2003WO42195
66		8.03			2003WO42195
67	3.95 (m)	3.45 (m)			1979M257
68	3.54–4.35 (4 H, m)		5.87 (2 H, m)		1981JHC825
69	4.48 (dd, <i>J</i> 3, 2)	3.47, 3.99 (2 dd, <i>J</i> 12, 3 and 12, 2)			1987M273
70	3.52, 4.57 (2 dd, <i>J</i> 3, 12 and 2, 12)	5.11 (dd, <i>J</i> 3.5, 2)			1987M273
71			3.46, 3.48	3.65, 3.85	1992JOC2446
40			3.00	3.44	1992JOC2446
72			3.41	4.00	1992JOC2446
48			4.48	ax. 3.59, eq. 3.82	2000SC2721
49			4.47	ax. 3.58, eq. 3.79	2000SC2721
50			4.79	ax. 3.66, eq. 3.95	2000SC2721
33		7.72			2004BMC1037
73	5.68		6.31		2002TL8523
74	5.64		6.69		2004RCB1092
75	4.62		6.31		2004RCB1092
76	4.44		3.50–3.66 (m)	4.46 (d, <i>J</i> 9)	1987AQ322
77	4.22		3.74 (m)	4.74 (d, <i>J</i> 3.8)	1987AQ322
78			3.10–3.37 (m)	3.75–4.02 (m)	1993CHE250
79			3.23–3.50 (m)	3.86–4.13 (m)	1993CHE250
80	4.20–4.55			4.20–4.55	2001CHE1526
81		4.64, 4.57	5.31 (br s)	6.21 (br s)	2001JOC8010

Tetrahydro-1,4-oxazines are better known, and spectra for morpholine and its *N*-methyl derivative were published as early as 1964 [\[1964JCS4269\]](#), so only a few examples of data for fused ring and oxo derivatives are collected here. The chemical shifts for the NH protons are shown for compounds [73–75](#), [78](#), and [79](#).

The isotopically labeled compound **81** has given valuable information on the magnitude of coupling constants with the protons at C-3 showing $^1J_{\text{C-H}}$ 143, $^2J_{\text{C-C-H}}$ 17.7, and $^2J_{\text{N-C-H}}$ 6.5 Hz [\[2001JOC8010\]](#). A dynamic NMR study of *N*-substituted morpholines has allowed determination of the energetics of ring inversion [\[1991T7465\]](#).





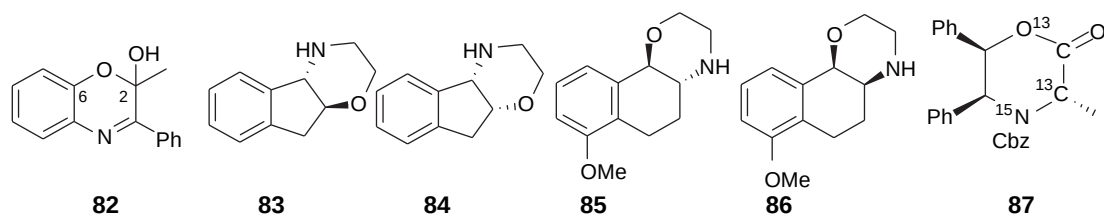
8.06.3.2.2 ^{13}C NMR

Selected data for representative 1,4-oxazine systems are given in Table 5. For the diastereomeric pairs **83/84** and **85/86**, the carbon chemical shifts differ so that *trans*-compounds have higher shifts than their *cis*-isomers. Smaller variations can be seen for the compound groups **32/82**, **48/49/50**, and **73/74/75**, which only differ in the substituents around the oxazine ring.

Table 5 ^{13}C chemical shifts (ppm) for oxazine carbons

Compound	C-2	C-3	C-5	C-6	Reference
32	141.0	162.3	94.0	145.0	1999M1481
82	136.2	161.6	92.9	145.1	1999M1481
48	94.0	167.8	60.3	64.3	2000SC2721
49	93.6	168.2	60.2	64.2	2000SC2721
50	93.4	167.6	59.5	64.0	2000SC2721
73	78.0	165.1	102.0	138.2	2002TL8523
74	78.2	164.8	105.6	136.0	2004RCB1092
75	73.3	166.9	106.2	136.3	2004RCB1092
22	68.1	47.1	47.1	68.1	
80	66.6–68.1	168.2–171.5	168.2–171.5	66.6–68.1	2001CHE1526
83	68.5	45.9	65.5	84.4	1984CHE724
84	66.5	40.7	60.8	77.9	1984CHE724
85	68.4	46.6	56.9	80.1	1987AQ322
86	64.7	43.1	51.6	73.8	1987AQ322

The multiply-labeled compounds **81** and **87** have allowed determination of coupling constants as well as chemical shifts in the tetrahydrooxazin-2-one system <2001JOC8010>. In both cases, the presence of carbamate rotamers at the *N*-Cbz group leads to doubling of most signals. For **81**, C-2 gives signals at 166.8 and 167.2 ppm, both with a 56 Hz coupling to C-3. The signal for C-3 comes at 45.3 with a 56 Hz coupling to C-2 and 11 Hz coupling to ^{15}N . In the methylated compound **87**, similar values are observed with C-2 signals at 170.0 (J 55) and 170.1 (J 56) while C-3 gives signals at 52.8 ($J_{\text{C-C}}$ 55, $J_{\text{C-N}}$ 11) and 52.9 ($J_{\text{C-C}}$ 55, $J_{\text{C-N}}$ 9).



8.06.3.2.3 ^{14}N , ^{15}N , and ^{17}O NMR

Nitrogen NMR data have been obtained using both the low-abundance, spin = 1/2 ^{15}N and the predominant spin = 1 ^{14}N nuclei. Several different references have been used for nitrogen NMR including aqueous ammonia, ammonium salts, acetonitrile, nitric acid, and nitrates. Current opinion favors neat nitromethane, and the compilation of the known data for 1,4-oxazines (**Table 6**) is expressed with respect to this reference and arranged in order of the observed chemical shift. For the ^{13}C -labeled compound **87**, carbamate rotamers lead to two separate signals and the value of $^1J_{\text{C-N}}$ can be determined: $\delta_{\text{N}} -283.98$ (d, J 9) and -284.46 (d, J 11) <2001JOC8010>.

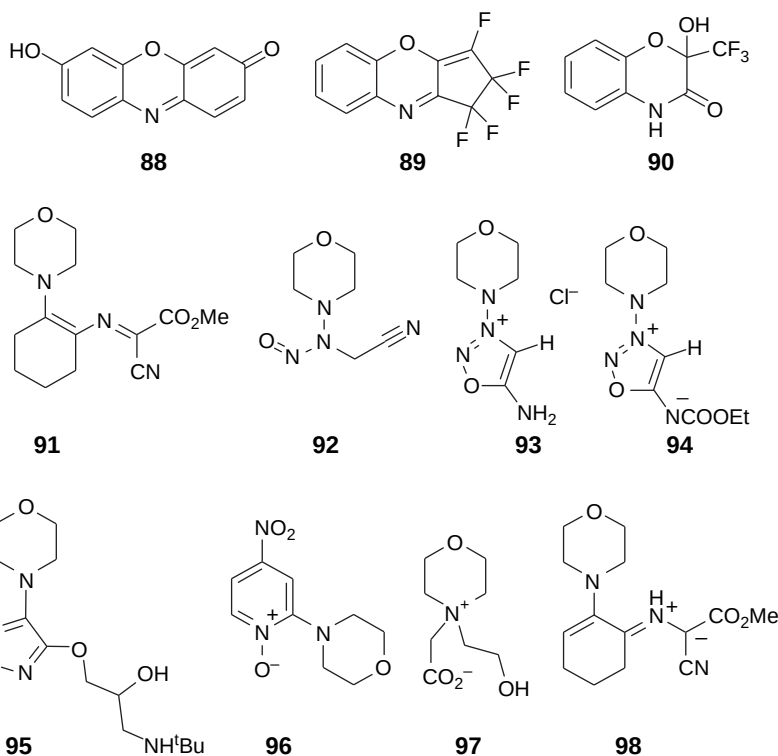


Table 6 ^{14}N and ^{15}N NMR data for 1,4-oxazines

Compound	Chemical shifts relative to MeNO_2 or $\text{Me}^{15}\text{NO}_2$	
	δ ^{15}N (δ ^{14}N)	Reference
88	-61.3	1996MI2764
89	-80.5	1987J(P1)763
<i>N</i> -Nitrosomorpholine	-146	1990CC1598
90	-240	1988BAU1056
91	-247.8	1984BSB559
92	-253.8	1996CHE1358
93	-258.6	1996CHE1358

(Continued)

Table 6 (Continued)

<i>Compound</i>	<i>Chemical shifts relative to MeNO₂ or Me¹⁵NO₂</i>	
	$\delta^{15}\text{N}$ ($\delta^{14}\text{N}$)	<i>Reference</i>
94	−260.3	1996CHE1358
<i>N</i> -(<i>p</i> -Toluoyl)morpholine	−268.4	1991JA7563
94 ·CF ₃ COOH	−277.2	1996CHE1358
87	−284	2001JOC8010
<i>N</i> -(<i>p</i> -Bromophenyliminomethyl)morpholine	−284.5	1995J(P2)1127
<i>N</i> -(<i>p</i> -Chlorophenyliminomethyl)morpholine	−286.6	1995J(P2)1127
<i>N</i> -(1-(3-Oxo)cyclohex-1-enyl)morpholine	−287.5	1977JOC2249
<i>N</i> -(Phenyliminomethyl)morpholine	−287.7	1995J(P2)1127
<i>N</i> -(<i>p</i> -Toluylinomethyl)morpholine	−288.9	1995J(P2)1127
<i>N</i> -(1,2,4-Triazin-3-yl)morpholine·CF ₃ CO ₂ H	(−289.3)	1988CHE434
<i>N</i> -(<i>p</i> -Methoxyphenyliminomethyl)morpholine	−289.6	1995J(P2)1127
<i>N</i> -(1,2,4-Triazin-3-yl)morpholine	(−290.3)	1988CHE434
<i>N</i> -(2,4-Dinitrophenyl)morpholine	−304.7	2000JST(524)217
<i>N</i> -(Trifluoromethylsulfonyl)morpholine	−304.7	2000JST(524)217
<i>N</i> -(1-Cyclohept-1-enyl)morpholine	−306.6	1977JOC2249
Timolol 95	−307.2	1984ACS(B)67
<i>N</i> -(1-Cyclohex-1-enyl)morpholine	−309.8	1977JOC2249
<i>N</i> -(1-Cyclohex-1-enyl)morpholine	−311.9	1984BSB559
Tri(<i>N</i> -morpholinyl)borane	(−312.7)	1972CB2883
96	−313.0	2003MRC721
<i>N</i> -(1-Cyclopent-1-enyl)morpholine	−313.2	1977JOC2249
<i>N</i> -Cyclohexylmorpholine	(−321.6)	1989J(P2)1249
8	−322.3	1996MI2764
<i>N</i> -Cyclopentylmorpholine	−322.9	1977JOC2249
<i>N</i> -(2,4-Dinitrophenyl)morpholine·H ₂ SO ₄	−323.7	2000JST(524)217
58	−323.83	2004JST(704)129
<i>N</i> -Cycloheptylmorpholine	−326.9	1977JOC2249
97	−327.13	2004JST(704)129
<i>N</i> -Cyclohexylmorpholine	−328.3	1977JOC2249
<i>N</i> -(2-Hydroxyethyl)morpholine·HBr	−333.17	2004JST(704)129
<i>N</i> -(<i>p</i> -Nitrophenylselenenyl)morpholine	−335.22	1987MRC955
98	−337.1	1984BSB559
<i>N</i> -(<i>o</i> -Nitrophenylselenenyl)morpholine	−337.64	1987MRC955
<i>N</i> -(2-Hydroxyethyl)morpholine	−338.54	2004JST(704)129
Morpholine·CF ₃ SO ₃ H	−341.93	2000JST(524)217
<i>N</i> -Methylmorpholine	−347.7	1991JA7563
<i>N</i> -(2-Vinyloxyethyl)morpholine	(−351.3)	1987BAU697
22	(−359.7)	1972CB2883
22	−366.2	2003MRC307

Oxygen-17 NMR has seldom been used for compounds of this type and all the existing ¹⁷O NMR data for 1,4-oxazines are collected in [Table 7](#).

Table 7 ¹⁷O NMR data for phenoxazine **8**, morpholine **22**, and substituted morpholines

<i>Compound</i>	δ_{O} relative to H ₂ ¹⁷ O	<i>Reference</i>
8	93.0	1987JHC365
22	2.6	1979TL3649
<i>N</i> -(<i>o</i> -Nitrophenylselenenyl)morpholine	−2	1987MRC955
<i>N</i> -(<i>p</i> -Nitrophenylselenenyl)morpholine	1.1	1987MRC955
<i>N</i> -(2-Vinyloxyethyl)morpholine	2	1987BAU697
<i>N</i> -(2-Acetylvinyl)morpholine	2.6	1996MRC595
<i>N</i> -(2-Benzoylvinylyl)morpholine	2.4	1996MRC595
<i>N</i> -(2,2-Diacetylvinyl)morpholine	1.2	1997MRC432

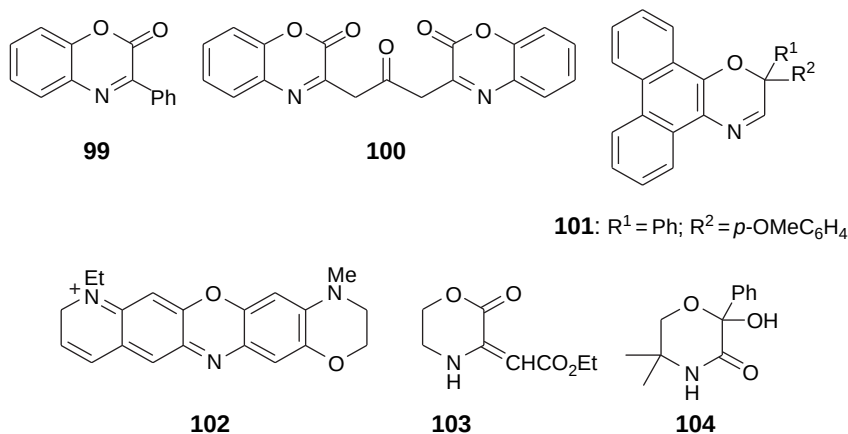
8.06.3.3 UV-Vis and Infrared Spectroscopy

There have been relatively little ultraviolet-visible (UV-Vis) spectroscopic data for 1,4-oxazines, but selected data are presented in **Table 8**. UV spectroscopy is important for photochromic compounds, such as spirooxazines. The UV spectra of 33 spirooxazines in five different solvents are collected in a review <2002RCR893>, and the more recently reported examples of photochromic oxazines **65**, **66**, **101**, and **102** are shown here. It can be seen from **Table 8** that both adding methoxy substituents to the oxazine and changing to a more polar solvent give a UV maximum at a higher wavelength. This solvent effect can also be seen in the case of **102**, which also has important fluorescence properties, discussed in **Section 8.06.12.2**.

Table 8 UV and IR spectra of 1,4-oxazines

Compound	$\lambda_{\max}$ nm ($\log \epsilon$)	$\nu_{\max}$ (cm^{-1})	Reference
99	330(4.20)		1961CB1676
100	490(4.51), 504(4.51)	1779 (lactone C=O)	1961CB1851
60	238(4.3), 348(4.3), 440(3.5)	1640, 1250, 1040	1973JOC3433
65	451 (hexane), 456 (toluene), 444 (MeCN)		2003WO42195
101	473 (hexane), 478 (toluene), 466 (MeCN)		2003WO42195
66	487 (hexane), 493 (toluene), 483 (MeCN)		2003WO42195
102	649 in MeOH, 657 in H ₂ O		2005WO16934
46		3490 (O–H), 1640 (C=N)	1996JHC1271
47		3475 (O–H), 1640 (C=N)	1996JHC1271
103		3311 (N–H) in D ₂ O 2475 (N–D)	1961CB2778
104	258	1663 (C=O) 1075–1030 (hemiacetal)	1961CB2785

The typical infrared (IR) peaks are also shown for some important structural features in oxazines: 1779 cm^{-1} for the lactone C=O in **100**, 1663 cm^{-1} for the lactam C=O in **104**, and 1640 cm^{-1} for the C=N of 2*H*-oxazines **46** and **47**. In **103**, the observation of the NH absorption at 3311 cm^{-1} was used to establish the presence of this tautomeric form (see **Section 8.06.4.2**), and adding deuterium oxide changed the absorption to the lower frequency of 2475 cm^{-1} characteristic of an N–D bond.



8.06.4 Thermodynamic Aspects

8.06.4.1 Melting points

Although many of the known oxazines are solids, there has been no systematic study of their melting points. **Figure 5** shows the melting points for representative simple oxazines **60** <1973JOC3433>, **62** and **64** <1982AP684>, **104** <1961CB2785>, **105** <1979M257>, **106–108** <1962CB1460>, and the isomeric tetrahydrooxazines **109** and **110** <1978CB1164>.

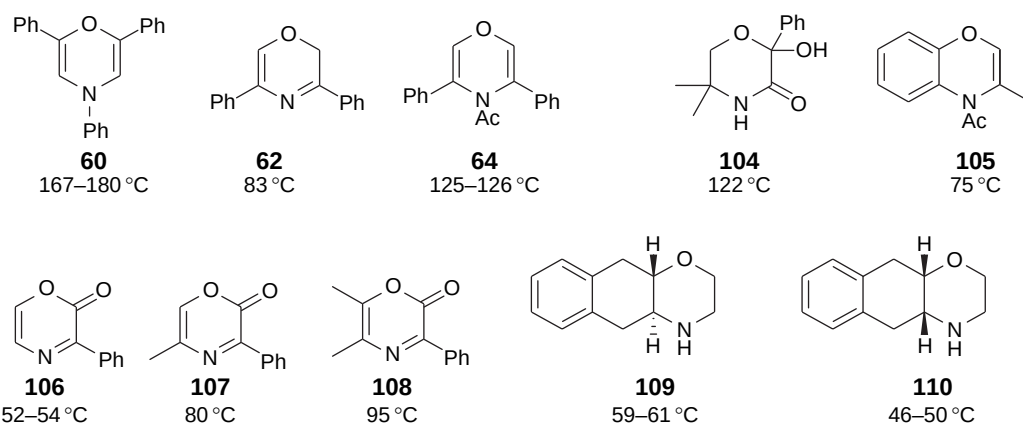


Figure 5 Melting points of some simple oxazines.

8.06.4.2 Other Physical and Thermodynamic Properties

Like the compounds **27–31** which were the subject of a theoretical study, oxazines with an electron-withdrawing substituent joined by CH₂ to the 3-position are subject to tautomerism (**Figure 6**), and this has been investigated for **100** <1961CB1851> and **103** <1961CB2778>.

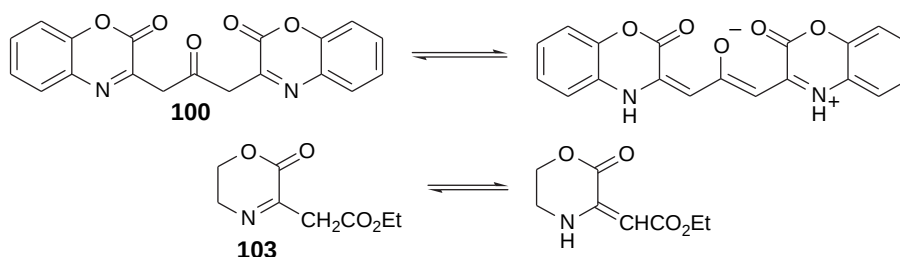
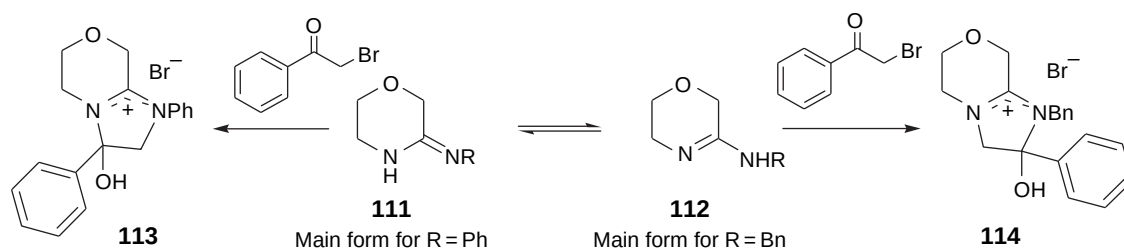


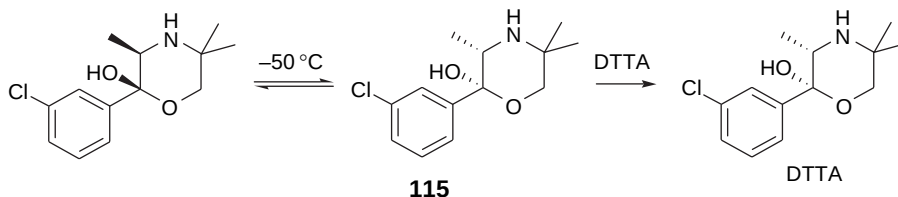
Figure 6

Furthermore, tautomerism is favored if it increases conjugation in the molecule. The 3-aminodihydrooxazines exhibit tautomerism between the forms **111** and **112**. For R=Ph the form **111** with the double bond conjugated to the phenyl ring is favored, while for R=Bn form **112** predominates (**Scheme 1**). This causes a difference in the regioselectivity of reaction with phenacyl bromide <2001CHE1054>. In each case, the sp³ nitrogen reacts with the carbonyl group and the sp² nitrogen with the CH₂Br to form the hemiaminal **113** from **111** and **114** from **112**.



Scheme 1

Oxazine **115** with a 2-hemiacetal racemizes in ethyl acetate solution at above 50 °C but the racemic mixture can be resolved by chiral stationary phase chromatography <2005WO40140>, or crystallization using (–)-(R,R)-di-*p*-toluoyl-tartaric acid (DTTA) <2005WO40141> as shown in **Scheme 2**.

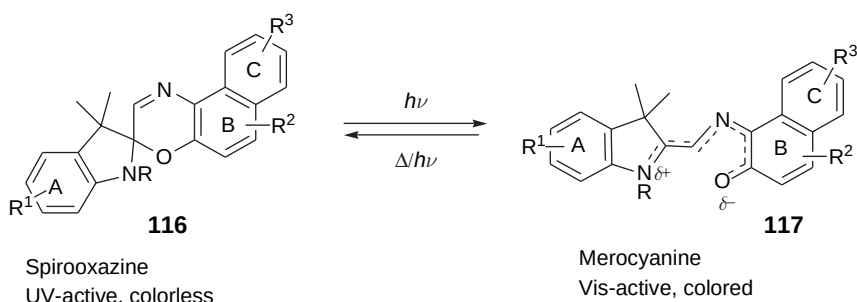


Scheme 2

8.06.5 Reactivity of 1,4-Oxazines

8.06.5.1 Unimolecular Reactions

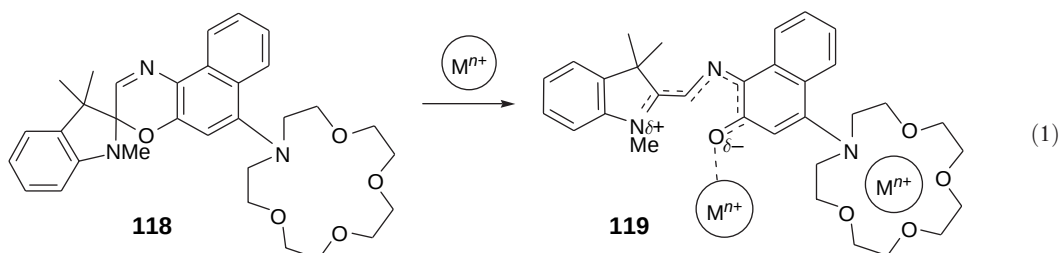
Spirooxazines exhibit photochromism and this has led to several detailed studies and patent applications. The practical importance of photochromism is discussed in [Section 8.06.12.2](#). The principle of photochromism in spirooxazines is shown in **Scheme 3**. Usually, irradiation of the spirooxazine **116** with UV light converts it to the merocyanine form **117**, which absorbs visible light <1981TL3945, 1994J(P2)1387>. The two aromatic moieties A and B + C of spirooxazines are often as shown in **Scheme 3**, but may also contain additional fused rings <1981TL3945>. Analogous heteroaromatic systems have also been synthesized <1994MCL(246)9, 1994MCL(246)17, 1995DP(29)241>.



Scheme 3 Reaction of spirooxazines with UV light.

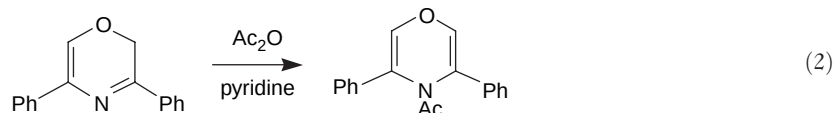
Solvatochromism and thermochromism are also characteristic of spirooxazines (**Scheme 3**) <1994RCB780>. The two forms **116** and **117** are in equilibrium in solution and more polar solvents shift the equilibrium more to the colored, acyclic form **117**. Higher temperatures have the same effect for both solid spirooxazines and their solutions. A comprehensive review of spirooxazines <2002RCR893> has a collection of the absorption maxima for a large number of spirooxazines and their colored forms, which have their absorption maxima in the visible range at 480–670 nm.

The formation of the merocyanine form **119** can be induced by addition of heavy metal cations (Pb²⁺, La³⁺, Eu³⁺, Tb³⁺) to a solution of a spirooxazine **118** containing a crown ether group in the B-ring (**Equation 1**). The chelation occurs first to the crown ether and then to the negatively charged oxygen. In contrast, **118** does not react upon addition of alkaline earth metal cations (Mg²⁺, Ca²⁺, Ba²⁺) <2005JPO504>.

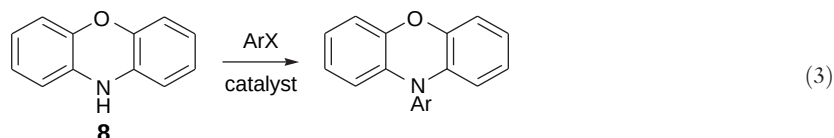


8.06.5.2 Electrophilic Attack at Nitrogen

Compound **62** was reacted with acetic anhydride in pyridine to give **64** in 61% yield (Equation 2). Substitution of the nitrogen required isomerization from the 2*H*-1,4-oxazine to the 4*H*-1,4-oxazine <1982AP684>.



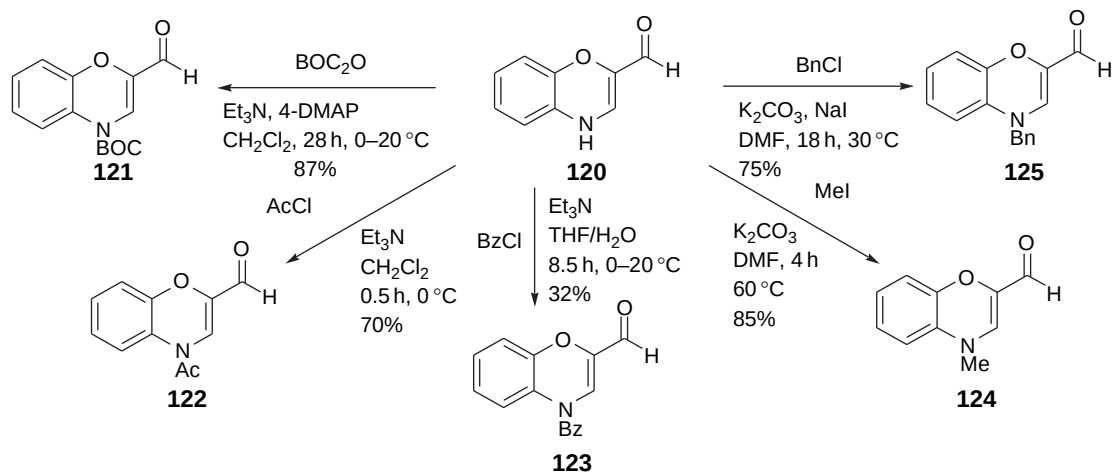
Due to their synthetic accessibility, phenoxazines of the type **8** are the best-known 1,4-oxazines whose 4-nitrogen has been reacted with electrophiles. The nucleophilicity of this nitrogen can be compared to that of diphenylamine, and numerous examples of alkylation and acylation have been reviewed already in early literature <1962HC(17)377>. This section therefore includes only examples of N-arylation of phenoxazines (Equation 3) that were not included in CHEC(1984) <1984CHEC(3)995>.



Compound **8** can be reacted with substituted iodoarenes using copper metal and potassium carbonate <1980CB358> or potassium hydroxide <1994MCL(242)127> as a base. The reaction proceeds at 170–180 °C and gives good yields. Addition of crown ether 18-Cr-6 allows a lower temperature to be used <2000JCD2105>.

The use of soluble metal catalysts makes it possible to react **8** and its substituted derivatives with aryl bromides and triflates at 100 °C. The catalyst systems that have been used are Pd₂(dba)₃ and (±)BINAP with calcium carbonate as base (dba = dibenz[*a,h*]anthracene, BINAP = 2,2-bis(diphenyl-phosphanyl)-1,1'-binaphthyl) <2000JA2178>, and 2-(di-*t*-butylphosphino)biphenyltris(dibenzylideneacetone)palladium with sodium *tert*-butoxide as base <2003T3109>.

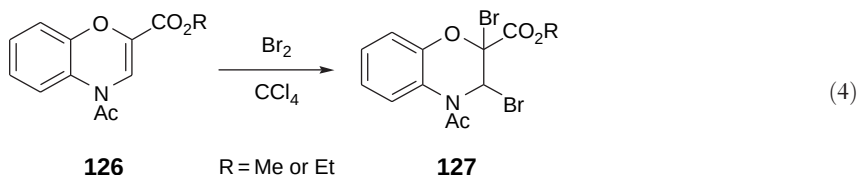
The reactions of another 1,4-oxazine **120** with various electrophiles has been the subject of a detailed study <1996JHC191>, and the conditions for each reaction are presented (Scheme 4).



Scheme 4 Reactions of **120** with electrophiles.

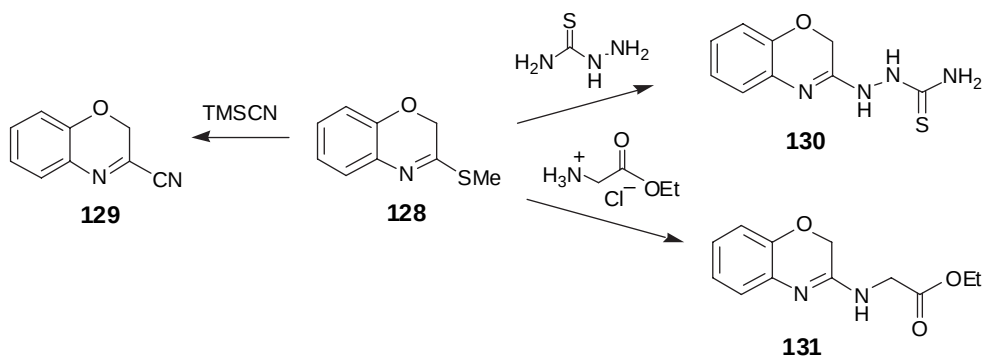
8.06.5.3 Electrophilic Attack at Carbon

The 2,3-double bond of 4-acetylbenz-4*H*-1,4-oxazine **126** can be brominated (Equation 4) using bromine in carbon tetrachloride <1984H(22)2789>. There is also one example of an electrophilic substitution as a competing reaction (Equation 20, Section 8.06.8).

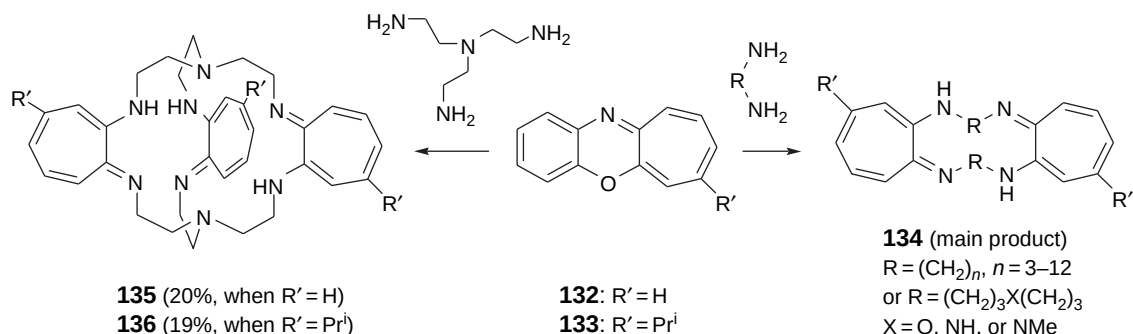


8.06.5.4 Nucleophilic Attack at Carbon

The only carbon susceptible to a nucleophilic attack is the imine-type 3-carbon in 2*H*-1,4-oxazines. This compound type only exists in the 3-substituted form as it would otherwise be too reactive. There are three interesting examples of nucleophilic substitution at the 3-carbon and they are shown in [Schemes 5 and 6](#). The methylthio compound **128** can be converted by nucleophiles to **129** <1988M1439>, **130**, and **131** <1989JHC205>. In a more deep-seated transformation, **132** and **133** can be reacted with diamines to give compounds of the type **134** and with a triamine to give **135** and **136** ([Scheme 6](#)) <2003MI47>.



Scheme 5

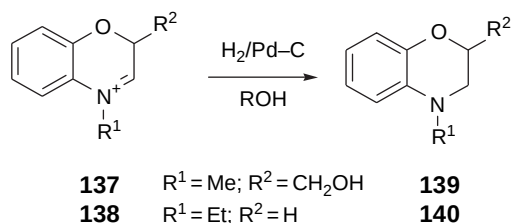


Scheme 6

8.06.5.5 Reduction and Reactions with Radicals

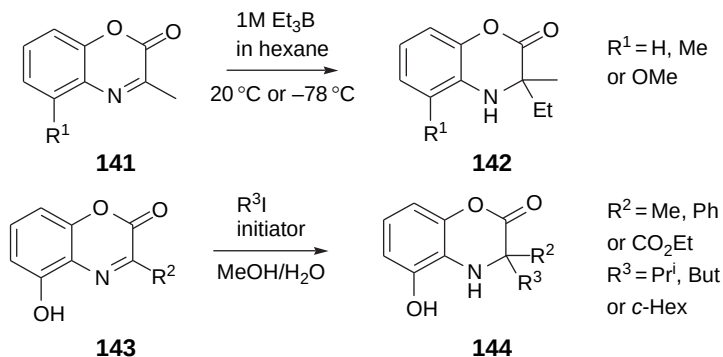
2*H*-1,4-Oxazine **62** can be hydrogenated to the fully saturated form, whereas the 4*H*-1,4-oxazines **63** and **64** do not react <1982AP684>. Catalytic hydrogenation reduces the 3,4-double bond of 2*H*-1,4-benzoxazines such as **99** <1961CB1676> and **61** <1979M257>, and the 2,3-double bond of 4*H*-1,4-benzoxazines <1982AP545, 1982AP561, 1982JHC1189>, while the aromatic ring and other substituents are unaffected. The hydrogenations were carried out

in methanol, ethanol, or ethyl acetate. It is to be noted that an aldehyde substituent does not survive in hydrogenation but is reduced to the corresponding alcohol <1982JHC1189>. Raney nickel has also been used successfully as a catalyst <1961CB1676>. The oxazinium salts **137** and **138** were also hydrogenated to give products **139** and **140**, respectively (Scheme 7) <1982JHC1189, 1982AP561>.



Scheme 7

Benzoxazinones **141** and **143** have been reacted in a reductive radical alkylation using triethylborane as the alkyl radical source <2004SL2597>. Triethylborane could also be used in catalytic amount with isopropyl, *tert*-butyl, or cyclohexyl iodide as the alkylating agent. Zinc with copper iodide could also be used as initiator (Scheme 8).



Scheme 8

The merocyanine form of spirooxazines can react with free radicals, which is important as it causes degradation of the photochromic materials <1995JOC5446>.

8.06.6 Reactivity of Dihydro-1,4-oxazines and Tetrahydro-1,4-oxazines

8.06.6.1 Introduction

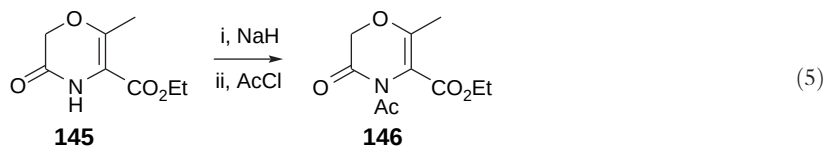
In this section, emphasis is placed on reactions which are characteristic of the ring systems present and do not depend on the presence of particular substituents. In addition, the well-known and widely applied behavior of morpholine as a basic and nucleophilic secondary amine is not covered and neither is the aniline-like nucleophilic and basic behavior of dihydrobenzoxazines save for a few special examples.

8.06.6.2 Electrophilic Attack at Nitrogen of Dihydrooxazines

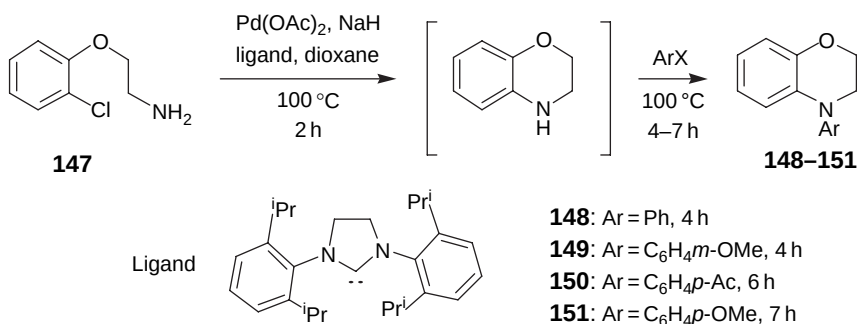
The reaction of tautomeric 3-amino-2*H*-5,6-dihydrooxazines **111** and **112** with an α -bromoketone was discussed in a previous article <2001CHE1054>. Generally, the sp^3 -hybridized nitrogen of 4*H*-5,6-dihydrooxazines is a better nucleophile and all the examples here are of 4*H*-5,6-dihydrooxazines or their benzo derivatives.

Dihydrobenzoxazines have been N-ethylated using diethyl sulfate <1979M257>, and N-benzylated with a substituted benzyl bromide using sodium iodide as nucleophilic catalyst and potassium carbonate as base <1990JME2621>. N-Acetylation has been carried out with acetic anhydride and pyridine <1982AP538>, and a toluenesulfonyl group has been introduced using toluenesulfonyl chloride and pyridine <1983JHC45>.

Dihydrooxazine **145** is a lactam and its acetylation (Equation 5) requires a strong enough base for deprotonation <1982AP761>.



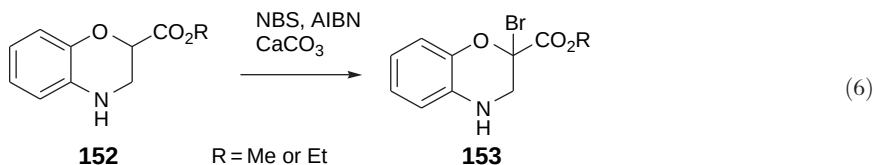
Similarly, 3-oxo-6-nitrobenzoxazine, which is also a lactam, has been N-arylated using sodium hydride and 4-nitrochlorobenzene in dimethylformamide (DMF) <1985IJB1263>. The reaction is a nucleophilic aromatic substitution assisted by the 4-nitro group and is therefore not general to all aryl halides. However, there is a route to N-arylated benzoxazines **148–151** through a catalyzed tandem cyclization–arylation reaction of **147**, shown in Scheme 9 <2004S2527>.



Scheme 9

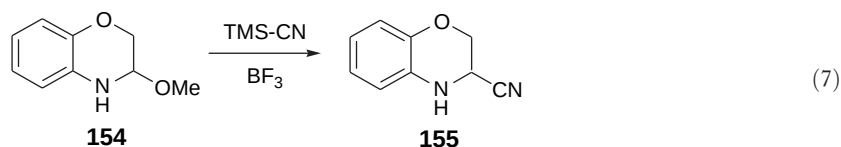
8.06.6.3 Electrophilic Attack at Carbon of Dihydrooxazines

The 2,3-double bond of compound **145** can be dibrominated with bromine <1982AP761>. The reaction is an analog of the dibromination of **126** described in Section 8.06.5.3. The 2-bromination of **152** to give **153** (Equation 6) was claimed to be a radical reaction, but is more likely to be an electrophilic attack, as a base catalyst was used and the reaction needed the presence of a 2-alkoxycarbonyl group to proceed <1984H(22)2789>. In a similar way, the α -carbons of dihydrooxazin-2-ones and dihydrooxazin-3-ones can also be deprotonated and then reacted with electrophiles; these reactions are described in Section 8.06.6.5.

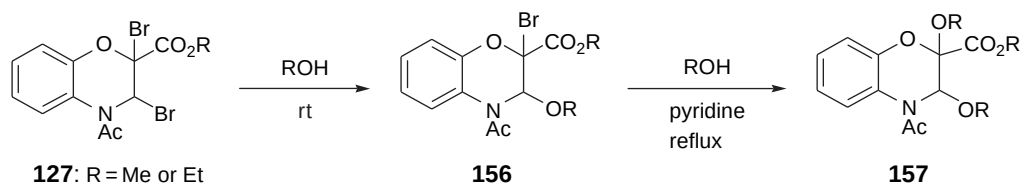


8.06.6.4 Nucleophilic Attack at Carbon of Dihydrooxazines

Nucleophilic substitution can occur at an sp^3 -hybridized carbon in dihydrooxazines. 3-Methoxydihydrobenzoxazine **154** was treated with trimethylsilyl cyanide with boron trifluoride catalysis (Equation 7) to give the 3-cyanobenzoxazine **155** <1986H(24)3483>, and the N-acetylated derivative of **154** reacted similarly <1983JHC45>.

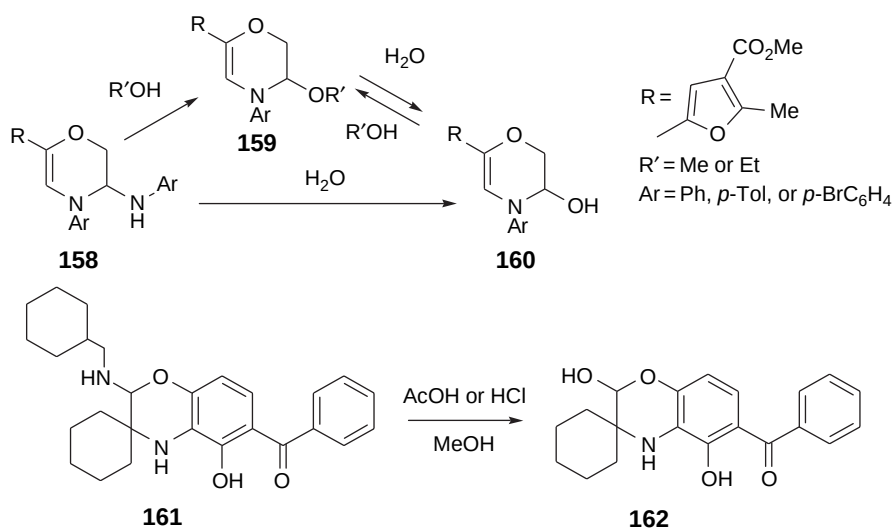


The two bromine atoms of benzoxazine **127** were exchanged to alkoxy substituents in two steps, as shown in [Scheme 10](#) <1984H(22)2789>.



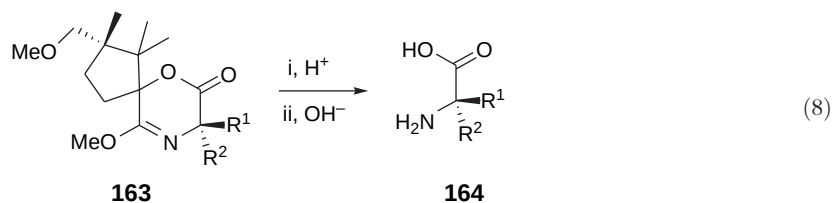
Scheme 10

The reactivity of aminooxazines **158** and **161** toward oxygen nucleophiles is shown ([Scheme 11](#)). 3-Aminooxazine **158** is subject to alcoholysis to give **159** and hydrolysis to give **160** <1986AQ224>, which can also be interconverted as shown. The 2-aminooxazine **161** can also be hydrolyzed to give **162** under acidic conditions <2004JOC882>.



Scheme 11 Hydrolysis and alcoholysis of aminooxazines.

Nucleophilic attack may also occur at unsaturated carbons and 2-oxo-5-methoxydihydrooxazines such as **163** can be hydrolyzed to give amino acids **164** (Equation 8) <1999EJO1967>.



20: R = H
 165: R = Me

Lawesson's reagent
 or P_2S_5

166: R = H
 167: R = Me

(9)

165

 $\xrightarrow[\text{NaH, xylene}]{\text{R-CHO}}$ **168**

 $\xrightarrow[\text{R-CH=CH-C(OMe)R}]{\text{NaH, xylene}}$ **169**

 R = H or OH

170

 $\xrightarrow[\text{R}^1\text{X}]{s\text{-BuLi}}$ **171**

 $\xrightarrow[\text{R}^2\text{X}]{s\text{-BuLi}}$ **163**

167

 $\xrightarrow[\text{piperidine, benzene, reflux}]{\text{X-CHO}}$ **172**

 X = S or NH

Scheme 13

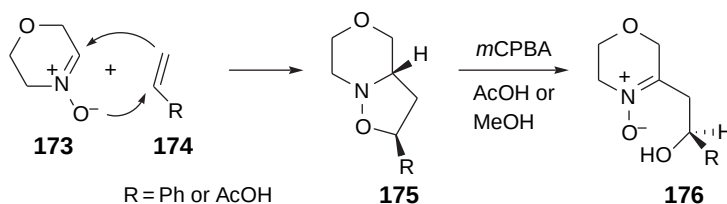
8.06.6.6 Reduction and Reactions of Dihydrooxazines with Radicals

Just as in the case of oxazines, catalytic hydrogenation reduces the double bond both in *2H*-dihydrooxazines <1962CB1451> and *4H*-dihydrooxazines <1982AP761>.

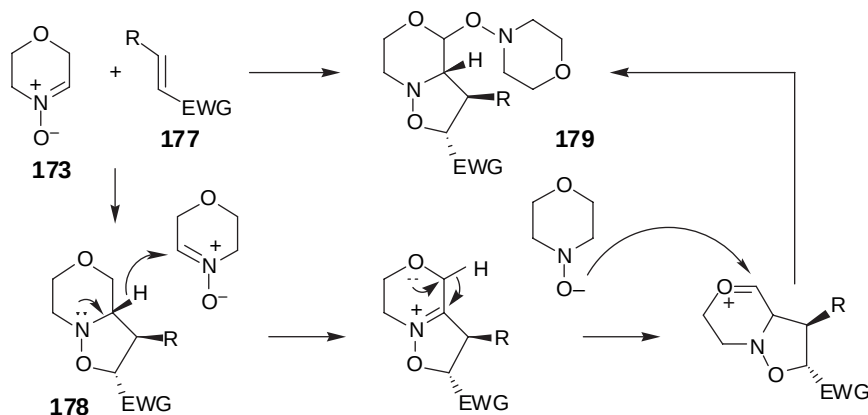
The reductive radical alkylation of oxazines using triethylborane as reagent or catalyst (Scheme 8) is also applicable to dihydrooxazines, and can be performed stereoselectively <2003CC426, 2005JOC3324>. This gives the reaction importance in the synthesis of enantiomerically pure amino acids, and it is discussed further in Section 8.06.11.3.

8.06.6.7 [2+3] Dipolar Cycloadditions of Dihydrooxazines

2H-5,6-Dihydrooxazine *N*-oxide (3,4-dehydromorpholine *N*-oxide) **173** reacts as a 1,3-dipole with alkenes **174** and can be alkylated at the 3-position by a dipolar cycloaddition to give **175** followed by oxidative cleavage to **176**, as shown in Scheme 14 <1993T7373>. In unsymmetrical (*E*)-alkenes **177**, the more electron-withdrawing substituent prefers to react at the O-end of the dipole and the larger substituent is oriented away from the oxazine ring in the cycloaddition reaction (Scheme 15). An excess of the *2H*-5,6-dihydrooxazine *N*-oxide can oxidize and add to the initial cycloaddition product **178**, giving **179** as the main product <2005TL2619>.

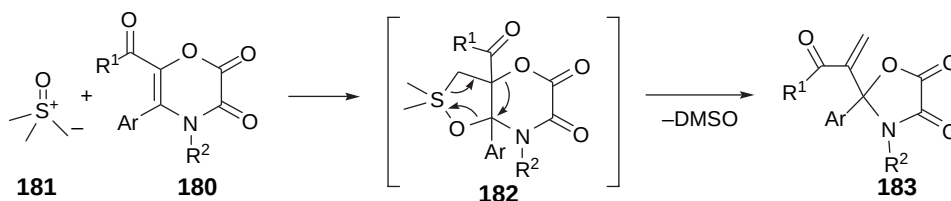


Scheme 14



Scheme 15

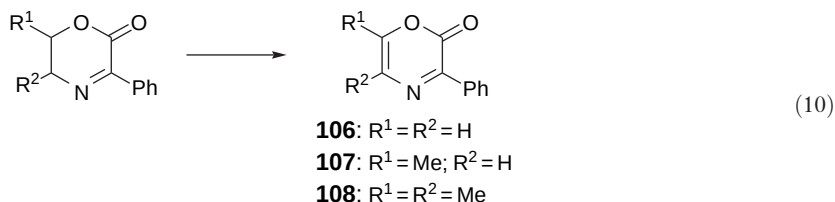
An unusual type of dipolar cycloaddition is known to occur to *2H*-dihydrooxazine **180** when it is treated with dimethylsulfoxonium methylide **181** (Scheme 16) <1994CPB739>. Ring contraction of the intermediate **182** results in formation of the oxazolidine-4,5-dione **183**.



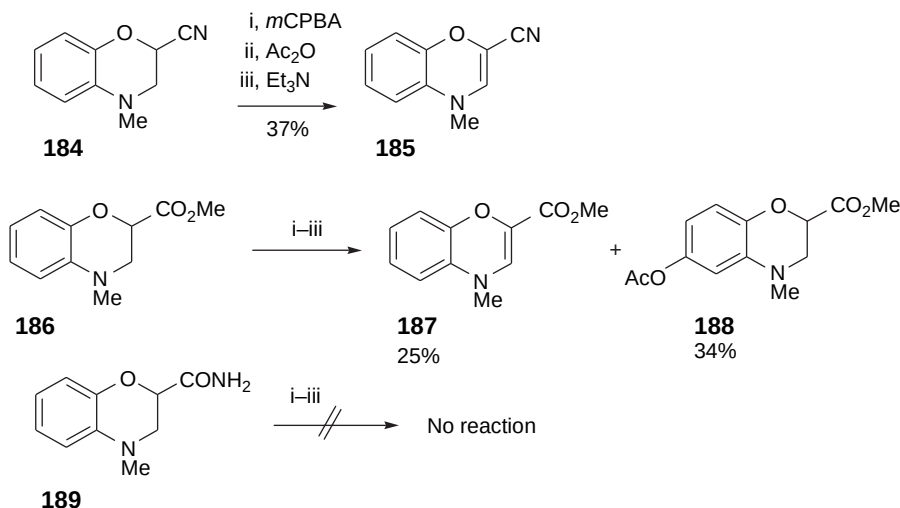
Scheme 16

8.06.6.8 Oxidation (Dehydrogenation) of Dihydrooxazines

In early work, *p*-chloranil was used to prepare the oxazines **106–108** from the corresponding 5,6-dihydro derivatives (Equation 10) <1962CB1460>. The reaction proceeded in a very low yield for **106** and yields of 55% for **107** and 15% for **108**. Mercurous oxide, chromium trioxide, and selenium dioxide were also tried unsuccessfully as oxidants for this process.



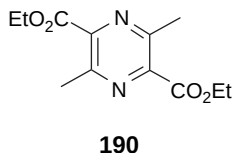
Another way to prepare oxazines from dihydrooxazines is the Polonovski reaction involving formation of an *N*-oxide, its O-acetylation, and subsequent elimination <1982JHC1189, 1988LA491>. An electron-withdrawing substituent at the 2-position is essential for the reaction, as can be seen from Scheme 17 <1982JHC1189>. Thus while **184** and **186** react to give **185** and **187**, respectively, the amide **189** does not react. Unfortunately, the oxidant is not completely selective but oxidizes also the aromatic 6-carbon to give products such as **188**. Substituting this position with a methyl group increases its reactivity toward oxidation <1988LA491>.



Scheme 17

In the synthesis of compounds of the same kind as **161** but with only one substituent at the 3-position, the reaction conditions caused the electrochemical oxidation of the dihydrooxazines to give a 2*H*-oxazine <2004JOC882>. The reaction will be discussed with the syntheses of conjugated 1,4-oxazines in Section 8.06.9.3 (Scheme 34).

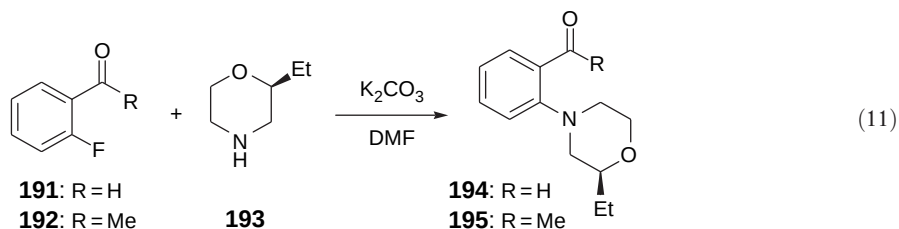
Hydrogen peroxide and *N*-bromosuccinimide cause oxidative degradation–dimerization of dihydrooxazine **145** and its *N*-acetylated derivative **146** to give **190** <1982AP761>.



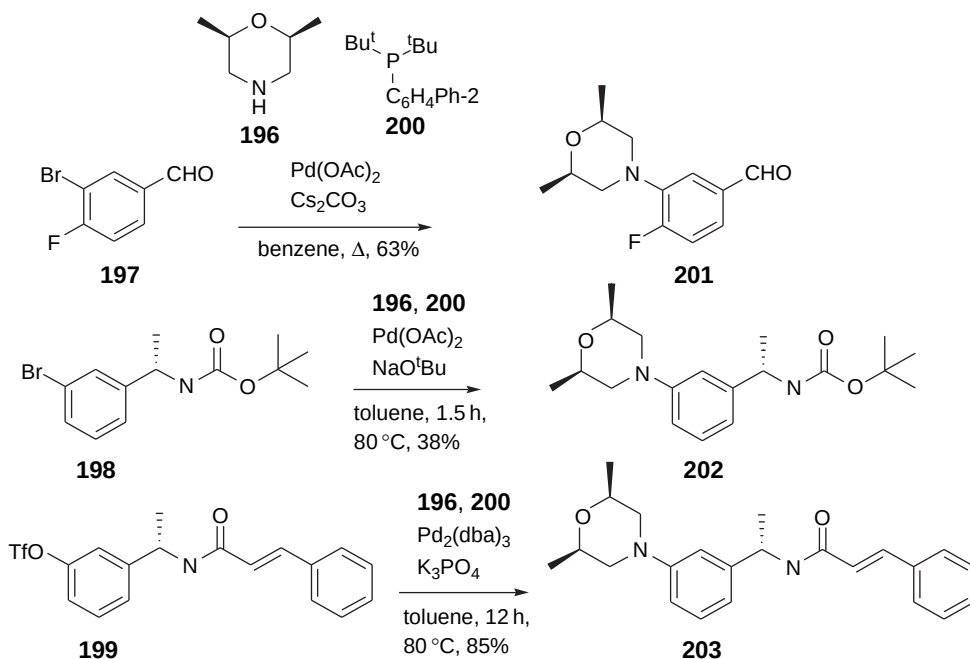
8.06.6.9 Electrophilic Attack at Nitrogen of Tetrahydrooxazines

Morpholine shows nucleophilic character typical of secondary amines, and substituted tetrahydro-1,4-oxazines can also be reacted with various carbon electrophiles. For example, the pharmaceutically important, cycloalkane-fused tetrahydrooxazines have been N-alkylated using propyl iodide <1985EJM247>, ethyl bromide <1978CB1164>, as well as alkyl chlorides <1986FES229>. N-Alkylation has also been achieved using various acyl chlorides followed by lithium aluminium hydride (LAH) reduction of the resulting amide <1986FES229>. Similar to this is N-methylation by reaction with formaldehyde followed by catalytic hydrogenation of the imine <1992JME480>. Other aldehydes have also been used successfully in this process <1985DEP3520104>.

New developments in this area include the N-arylation of substituted morpholines, where an aromatic halogen atom is replaced by the morpholine. The first example is of a nucleophilic aromatic substitution. 2-Fluorobenzaldehyde **191** and 2-fluoroacetophenone **192** were reacted with (3*R*)-3-ethylmorpholine **193** to give the 2-(3*R*)-3-ethylmorpholinyl derivatives **194** and **195** in 25% and 23% yields, respectively (Equation 11). The reaction required heating under reflux for several days <1989JOC209>.



Organometallic catalysts give better yields, and (2*R*,6*S*)-2,6-dimethylmorpholine **196** has been reacted with aromatic bromides **197** <2002TL9291> and **198** and triflate **199** <2004JME2887> using a palladium catalyst with ligand **200**, under three different sets of conditions to give the morpholino derivatives **201–203** (Scheme 18).

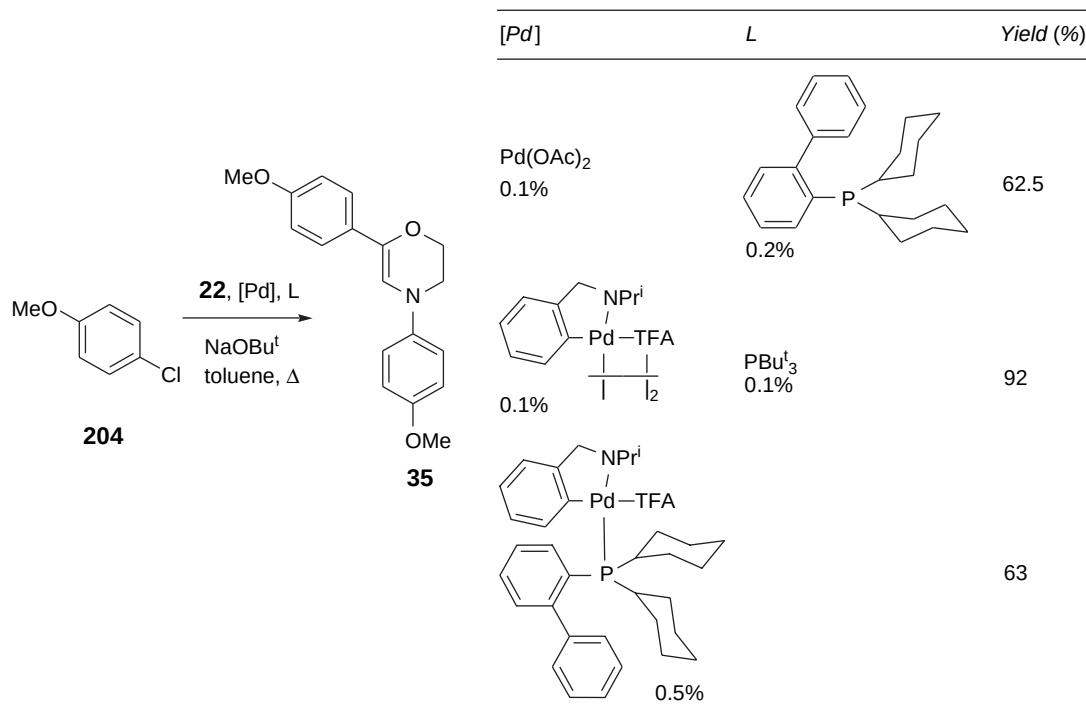


Scheme 18

Aryl chloride **204** was reacted with morpholine using similar conditions, but gave an unexpected product **35**, resulting from an electrophilic attack at the morpholine carbon <2003OM987>, and the reaction is therefore discussed in the next section.

8.06.6.10 Electrophilic Attack at Carbon of Tetrahydrooxazines

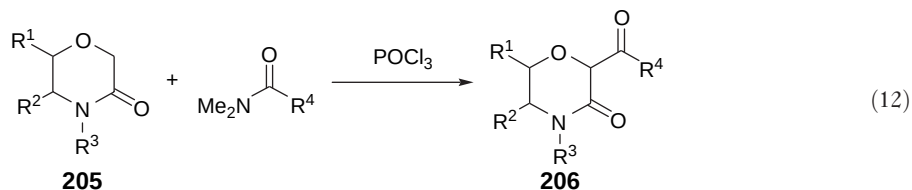
When morpholine and **204** were reacted using various catalytic mixtures of palladium and ligands, **35** was obtained as the main product, in good yields, and with quite low catalyst loading (**Scheme 19**) <2003OM987>.



Scheme 19

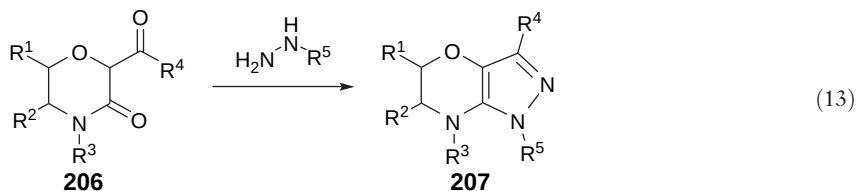
Following the same pattern as with the dihydrooxazines, the reactions of deprotonated tetrahydrooxazines with electrophiles (electrophilic attack at carbon) are discussed in [Section 8.06.6.12](#).

As shown in [Equation \(12\)](#), the Vilsmeier reaction of a 1,4-oxazin-3-one **205** gives products **206** <1984EPP111809>.

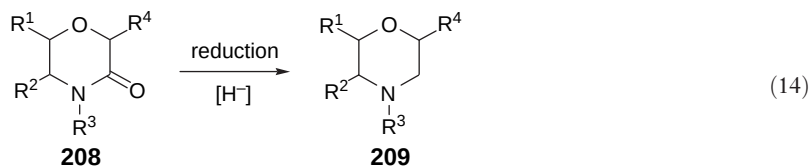


8.06.6.11 Nucleophilic Attack at Carbon of Tetrahydrooxazines

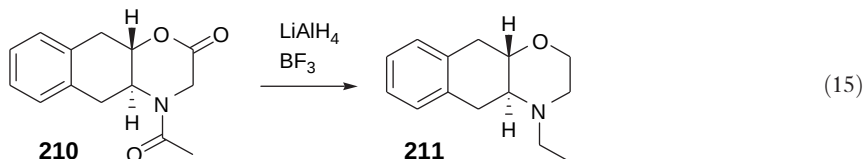
There are no reports of nucleophilic attack at an unsubstituted carbon of tetrahydrooxazines, but the oxo derivatives are reactive toward nucleophiles. Nucleophilic substitutions are also known. The reactions of tetrahydrooxazin-3-ones are discussed first, followed by the less commonly used tetrahydrooxazin-2-ones. Both carbonyl groups of **206** react with hydrazines to form **207** ([Equation 13](#)) <1984EPP111809>.



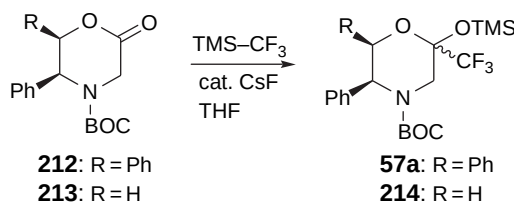
The tetrahydro-1,4-oxazin-3-ones **208** are lactams that can be reduced with LAH in tetrahydrofuran, tetrahydropyran, dimethyl or diethyl ether to the corresponding tetrahydro-1,4-oxazines **209** (Equation 14). The reaction, which involves nucleophilic attack by H^- has been used in numerous studies, including several patents, especially in the syntheses of drugs for the central nervous system <1975JME573, 1982USP4349548, 1983EPP80115, 1984FES255, 1984JME1607, 1985EJMC247, 1985DEP3520104, 1986FES229, 1987AP625, 1987AQ322, 1992JME480>. Other reducing agents used include borane <1983EPP80117, 1982USP4349548> and Red-Al <2005OL937>.



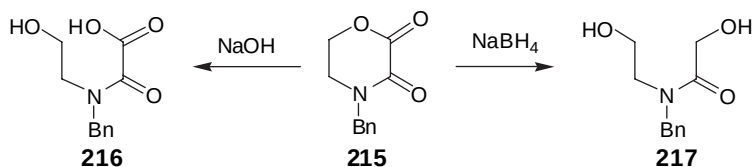
The tetrahydro-1,4-oxazin-2-ones are lactones and have been reduced to the corresponding hemiacetals (tetrahydro-1,4-oxazin-2-ols) using diisobutylaluminium hydride <1998T10419> and lithium triisobutylborohydride <2004TL8917>. Rather remarkably, treatment of the tricyclic tetrahydro-1,4-oxazin-2-one **210** with LAH and boron trifluoride results in complete reduction of both carbonyl groups to afford the tetrahydro-1,4-oxazine **211** (Equation 15) <1978CB1164>.



Another example of a nucleophilic attack at the lactone carbonyl is the reaction of **212** and **213** with (trimethylsilyl)trifluoromethane to give **57a** and **214**, respectively (Scheme 20) <2000JCM310>. The reaction tolerates small substituents in the 3-position. However, to avoid ring cleavage, the reaction conditions must be chosen carefully: the reactivity of the lactone 2-position can be seen from the ring cleavage reactions of tetrahydro-1,4-oxazine-2,3-dione **215** to give **216** and **217** (Scheme 21) <2004TL8917>.



Scheme 20

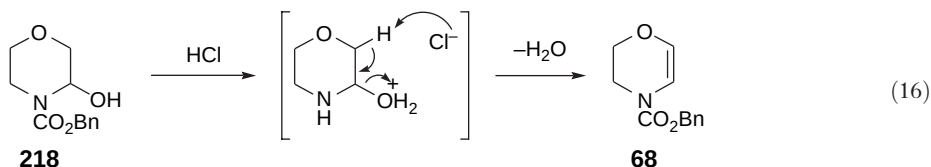


Scheme 21

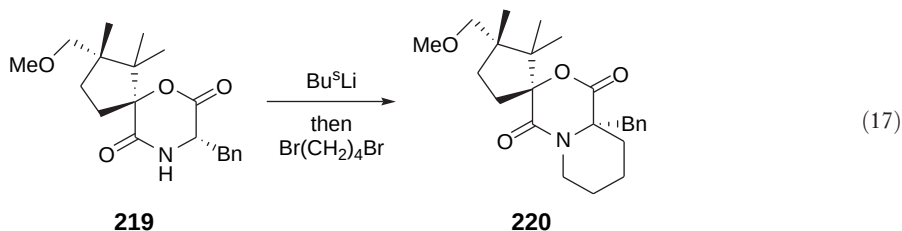
There are a number of examples of nucleophilic substitutions in tetrahydrooxazines. Bromine substituents at 2- and 3-positions have been exchanged to alkoxy groups in a reaction much like that of **127**, shown in [Scheme 10](#) [<1982AP761>](#). 2-Acetyloxy-1,4-oxazines have been reacted with trimethylsilyl cyanide and boron trifluoride to give the corresponding 2-cyanooxazines [<2001JA3472>](#) and with allyltrimethylsilane and boron trifluoride or titanium tetrachloride to give the 2-allyloxazines [<1998T10419>](#). A 3-methoxy group has also been replaced with a cyano group by reaction with trimethylsilyl cyanide [<1987M273>](#).

8.06.6.12 Nucleophilic Attack at Hydrogen Attached to Carbon of Tetrahydrooxazines

Water was eliminated from 3-hydroxytetrahydrooxazine **218** to give **68** in 96% yield using a catalytic amount of hydrochloric acid in acetone at room temperature ([Equation 16](#)) [<1981JHC825>](#). Dehydration of 3-hydroxytetrahydrooxazines was also studied but required a higher temperature and gave lower yields [<1981JHC825>](#).



Tetrahydro-1,4-oxazin-2-ones can be deprotonated and then reacted with electrophiles. Thus, for example, the nonlabeled analog of compound **81** was deprotonated at the 3-position with sodium hexamethyldisilazide and ethylated using ethyl iodide. The reaction was performed in a 1:10 mixture of hexamethylphosphoramide (HMPA) and tetrahydrofuran [<1998T10419>](#). If a dihalide is used and the oxazine has a free 4-nitrogen, cycloalkylation can be achieved as shown in the reaction of **219** to give **220** ([Equation 17](#)) [<1993LA477>](#).



8.06.6.13 Reduction of Tetrahydrooxazines

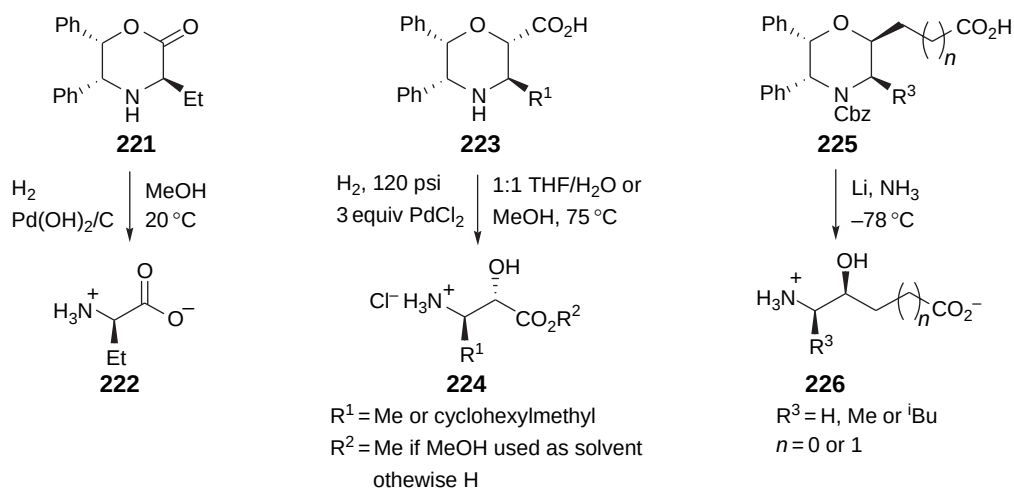
The 5,6-diphenyltetrahydroxazines contain a benzylic PhC–O bond and a benzylic PhC–N bond that can both be cleaved by hydrogenation or dissolving metal reduction. This gives some biologically interesting molecules, and variations are discussed further in [Section 8.06.11.3](#). Three examples of the ring cleavage are given in [Scheme 22](#): 5,6-diphenyltetrahydroxazin-2-one **221** was converted into α -amino acid **222** [<2003CC426>](#), 2-carboxy-5,6-diphenyltetrahydroxazine **223** into α -hydroxy- β -amino acid **224** [<2001JA3472>](#), and **225** into peptide mimic **226** [<1998T10419>](#).

8.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

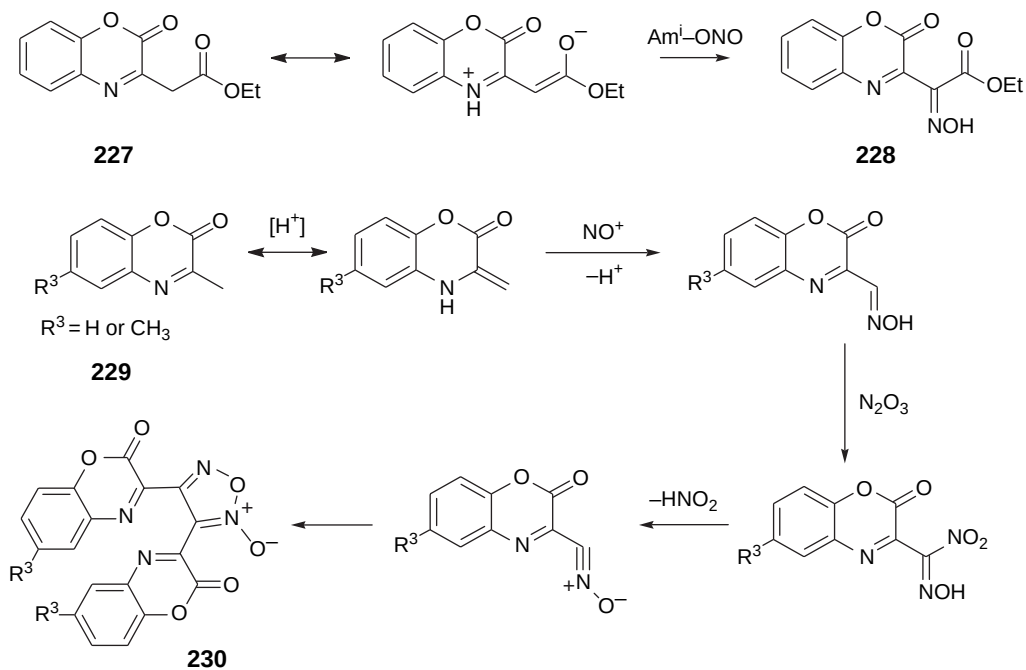
8.06.7.1 1,4-Oxazines

Tautomerism in 2*H*-benzoxazin-2-ones allows carbon substituents at the 3-position to be reactive toward the NO⁺ electrophile. Compounds **227** [<1963LA83>](#) and **229** [<1963LA93>](#) reacted with the nitrosyl cation to give the derivatives **228** and **230** as shown in [Scheme 23](#).

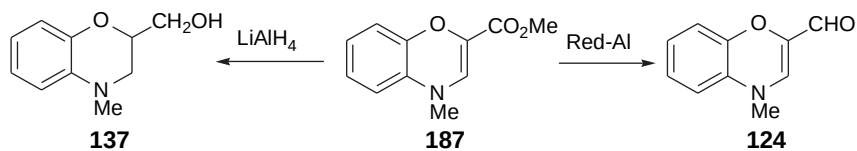
There are several examples of reactions of a carboxylic acid derivative at the 2-position of a 1,4-benzoxazine. The methyl ester in **187** can be reduced selectively to the aldehyde **124** using Red-Al, whereas LAH reduces the ester to the alcohol and also the 2,3-double bond of the oxazine to give **137** ([Scheme 24](#)) [<1982JHC1189>](#).



Scheme 22

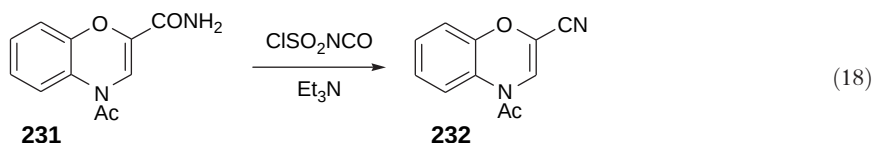


Scheme 23



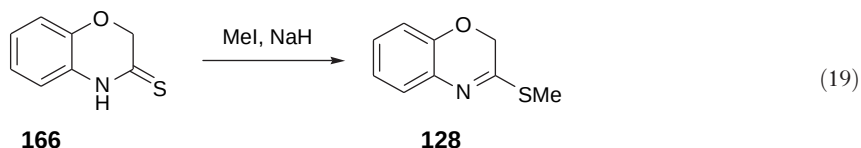
Scheme 24

An amide at the 2-position as in **231** was dehydrated to the nitrile **232** using chlorosulfonyl isocyanate and triethylamine (Equation 18) <1982AP545>.

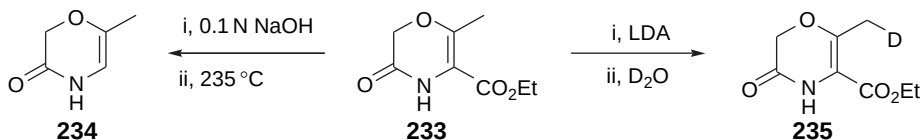


8.06.7.2 Dihydro-1,4-oxazines

There is one example where tautomerism has allowed the reaction of a 3-substituent of a dihydro-1,4-benzoxazine with an electrophile. The compound **166** was reacted with methyl iodide and sodium hydride to give the S-methylated compound **128** (Equation 19) <1988M1439>.

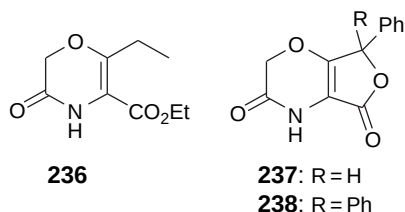


An unusual decarboxylation of **233** was carried out by thermolysis of the corresponding carboxylic acid to give **234** (Scheme 25) <1950JCS909>. The methyl group at the 2-position of **233** is acidic because of its relationship to the α,β -unsaturated ester and can be deprotonated and reacted with deuterium oxide to give **235** <1989AP291>.



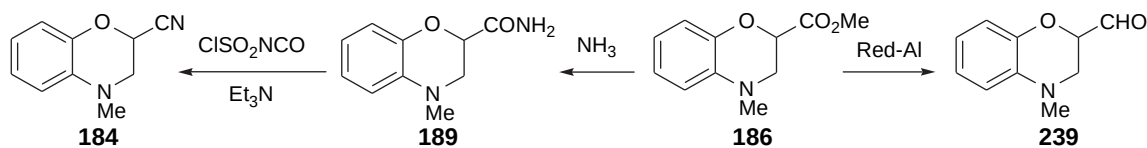
Scheme 25

If methyl iodide was used instead of deuterium oxide, compound **236** was obtained, along with the product of N-methylation. Using benzaldehyde or benzophenone as the electrophile gave the cyclized products **237** and **238**, respectively <1989AP291>.

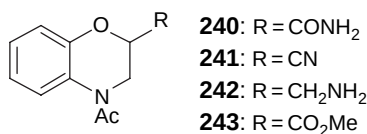


The ester group of **233** was reduced to the alcohol using LAH in 22% yield <1982AP761>. 2,3-Dihydrobenzoxazines generally allow a greater number of selective reactions of 2- and 3-substituents, as their basic structure **19** is relatively inert and tolerates various reductive and hydrolytic reaction conditions. The 2-alkoxycarbonyl substituent of **186** has been reduced with Red-Al to give aldehyde **239** and converted to amide **189** with ammonia (Scheme 26) <1982JHC1189>.

The amide **189** was converted to the nitrile **184** using chlorosulfonyl isocyanate and triethylamine (Scheme 26) <1982JHC1189>, and the same conversion has been performed on the N-acetylated derivative **240** to give **241** <1982AP545>.

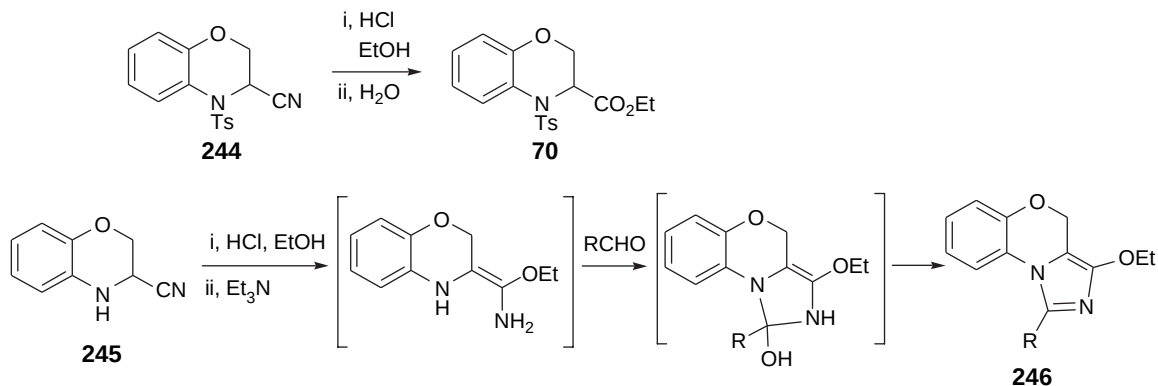


Scheme 26



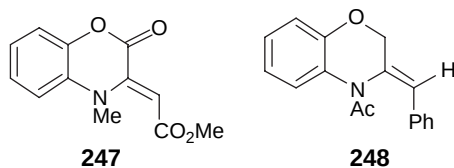
Nitrile **241** was reduced to the amine **242** with Red-Al in morpholine at -40°C . However aluminium hydrides are mostly unsuitable if there is an *N*-acetyl group that is required to be conserved and this is discussed further in [Section 8.06.8](#). Also, **240** could be prepared from the ester **243** by reaction with ammonia [<1982AP538>](#).

Hydrolytic conditions are tolerated by dihydrobenzoxazines, and this allows the selective hydrolysis of the ester group of **243** into the free acid with 10% sodium hydroxide [<1983JHC45>](#). The nitrile of **244** was converted into the iminium salt followed by hydrolysis to give the ester **70** [<1987M273>](#). Conversion of **245** into an iminium salt followed by base treatment to give the α -ethoxy enamine then allows cyclization with an aldehyde to give product **246** as shown in [Scheme 27](#) [<1986H\(24\)3483>](#).



Scheme 27

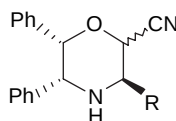
The exocyclic C=C double bond has been hydrogenated in **247** with a palladium catalyst [<1983JHC45>](#), and enantioselectively in **248**, using rhodium with (*R,R*)-Me-DuPhos ligand as catalyst [<2005JOC1679>](#).



8.06.7.3 Tetrahydro-1,4-oxazines

Tautomerism caused the different reactivity of 3-iminotetrahydrooxazines **111** and **112** shown in [Scheme 1](#), [Section 8.06.4.2](#) [<2001CHE1054>](#). Otherwise there are no examples of a tetrahydrooxazine ring having a significant effect on

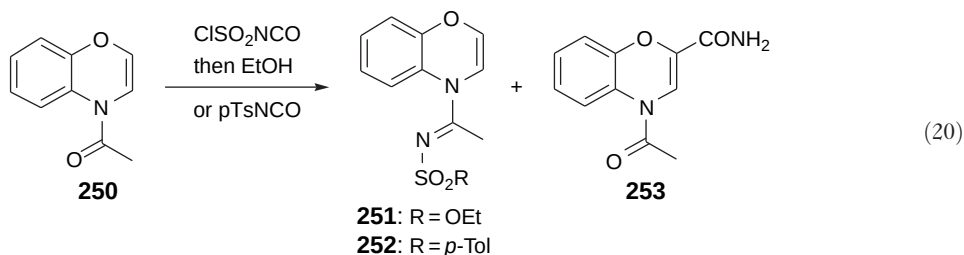
the reactivity of its substituents. The 2-cyano group of **249** was hydrolyzed using potassium hydroxide in glycol at 150–170 °C, giving the carboxylic acid **223** as product <2001JA3472>.



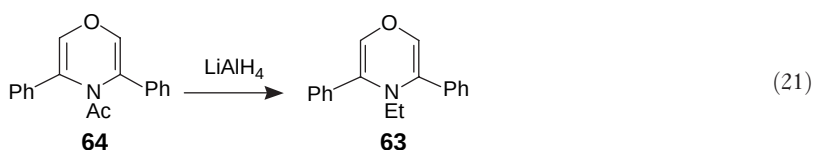
249: R = Me or cyclohexylmethyl

8.06.8 Reactivity of Substituents Attached to Ring Heteroatoms

The compound **250** was reacted with chlorosulfonyl isocyanate followed by ethanol or *p*-toluenesulfonyl isocyanate to give, respectively, **251** in 33% yield and **252** in 59% yield (Equation 20) <1982AP545>. In the case of chlorosulfonyl isocyanate, the reaction competed with an electrophilic substitution at the 2-position, forming **253** in 31% yield.



LAH was used to reduce **64** to **63** (Equation 21) <1982AP684>. LiAlH₄ also reduces *N*-acetylbenzoxazine **250** to give **138**, which was not isolated but was hydrogenated directly to **140** as shown in Scheme 7 <1982AP561>. The reactivity of dihydrobenzoxazines **240**, **241**, and **243** toward aluminium hydrides was also examined. LiAlH₄, Red-Al, and sodium borohydride all reduced both the *N*-acetyl group and the functional group in the 2-position of each compound, giving mixtures of products <1982AP538>.

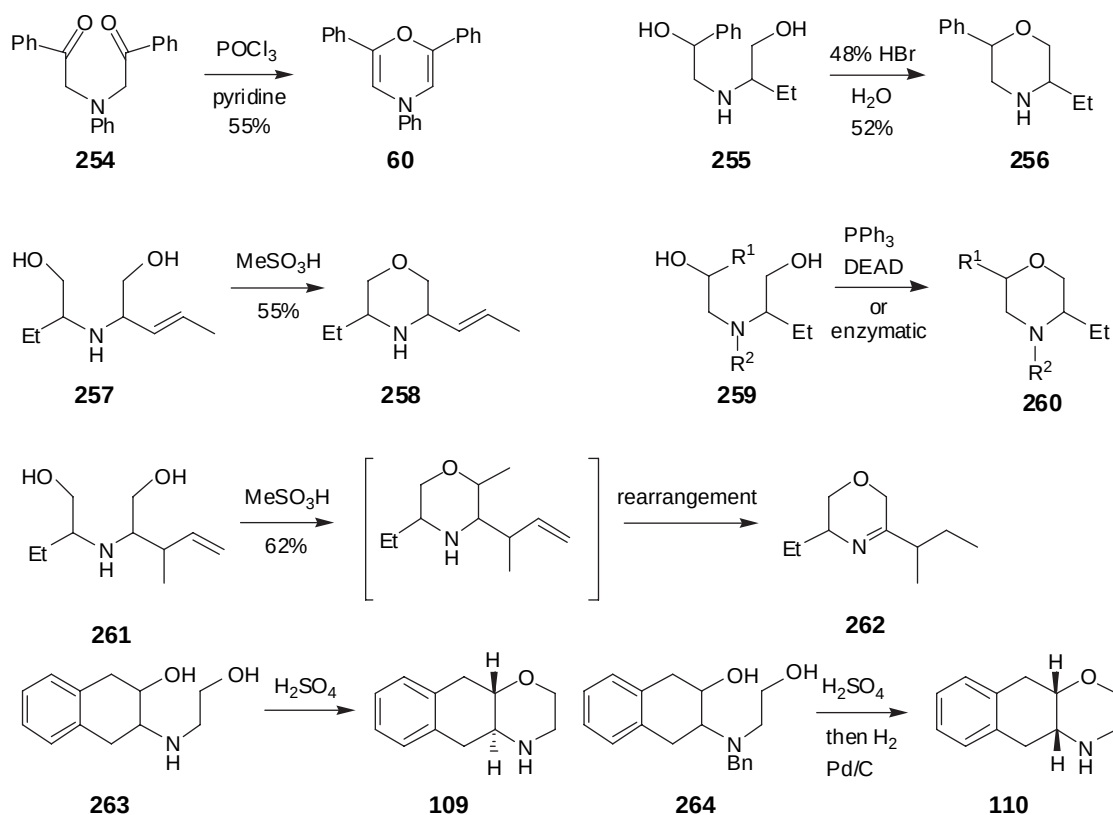


8.06.9 Ring Synthesis

8.06.9.1 One-Bond Formation Adjacent to a Heteroatom

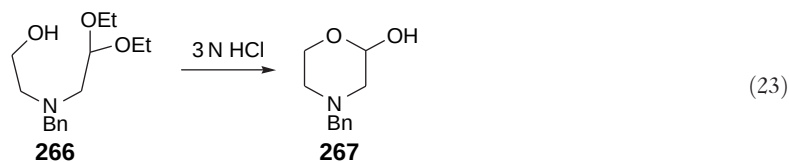
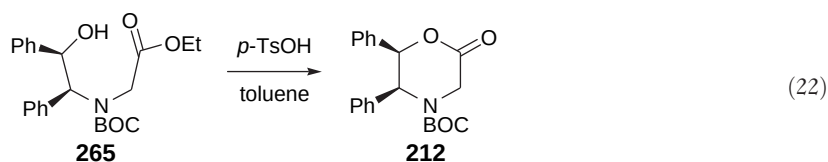
8.06.9.1.1 Adjacent to oxygen

Dehydrations have been used successfully in cyclization reactions to form 1,4-oxazines (Scheme 28). The fully unsaturated oxazine **60** was synthesised by dehydration of diketone **254** in 55% yield using phosphorus oxychloride in pyridine <1973JOC3433>. Dehydration of 3-azapentanediois is a convenient synthetic method for tetrahydrooxazines and has been used to form **256** from **255** with aqueous hydrogen bromide <1962CB1451> and **258** from **257** with methanesulfonic acid <1996JOM(517)37>. Diols of the type **259** can be cyclized to give oxazines **260** under Mitsunobu reaction conditions, or enantioselectively by an enzymatic dehydration <2003WO99798>. Spontaneous rearrangement in the cyclization of **261** gives dihydrooxazine **262** as product <1996JOM(517)37>. Finally, sulfuric acid was used to prepare the fused oxazine isomers **109** and **110** from **263** and the *N*-benzyl derivative **264** <1978CB1164>.

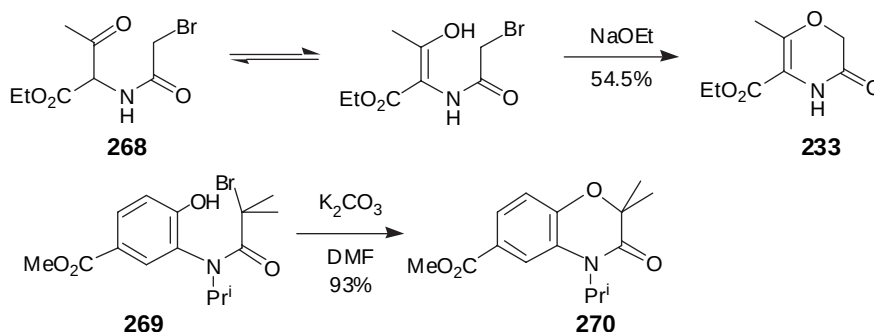


Scheme 28 Dehydrative cyclizations to give 1,4-oxazines.

Oxazine ring in **212** was formed by spontaneous lactonization in the hydrolysis of 3-aza-5-hydroxy ester **265** (Equation 22) <2005SL693>. The same method was used in the synthesis of **219** <1993LA477>. Oxazine **267** was formed in the hydrolysis of a 3-aza-5-hydroxyaldehyde diethyl acetal **266** <1981JHC825> (Equation 23).



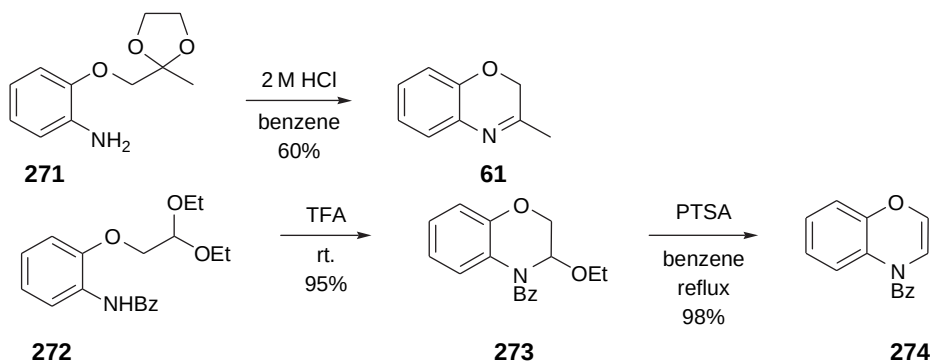
The Williamson etherification of 3-aza-5-bromoalcohols, using a strong base such as sodium hydride to deprotonate the alcohol, has been used in the cyclization approach to medicinally important fused tetrahydrooxazines <1983EPP80115, 1983JOC2675>. Another option is a Lewis acid-catalyzed cyclization of a 3-aza-5-diazo alcohol <1983EPP80117, 1984USP4431167>. These strategies are discussed in more detail in Section 8.06.11.1. Ether formation from the enol form of **268** <1950JCS909> and phenol **269** <1998JAP10017535> give dihydrooxazines **233** and **270**, respectively, as shown in Scheme 29.



Scheme 29 Etherification used in the synthesis of dihydrooxazines.

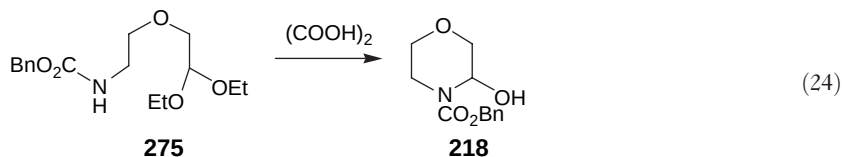
8.06.9.1.2 Adjacent to nitrogen

A good way to introduce a new double bond at the cyclization stage is by imine or enamine formation from a δ -aminocarbonyl compound. The carbonyl group is typically protected as an acetal, and the acidic conditions needed to hydrolyze the acetal also catalyze the dehydrative imine formation. The benzoxazine **61** was prepared from **258** in this way [\[1979M257\]](#). In **259**, the 4-*N* is substituted with an electron-withdrawing group and more forcing conditions are required to complete the benzoxazine formation [\[1984H\(22\)2789\]](#). The syntheses are shown in [Scheme 30](#).

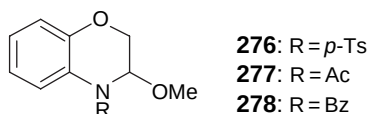


Scheme 30

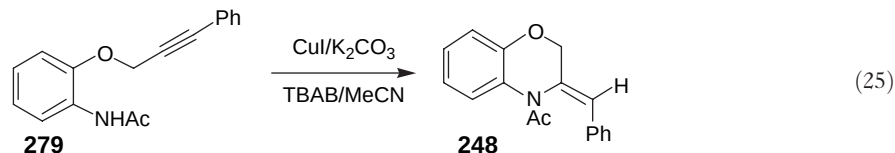
In a similar way to the formation of **273** from **272**, the 3-hydroxytetrahydrooxazine **218** was prepared from the 3-oxa-5-aminoaldehyde diethyl acetal **275** in 60% yield using oxalic acid to bring about the cyclization ([Equation 24](#)) [\[1981JHC825\]](#).



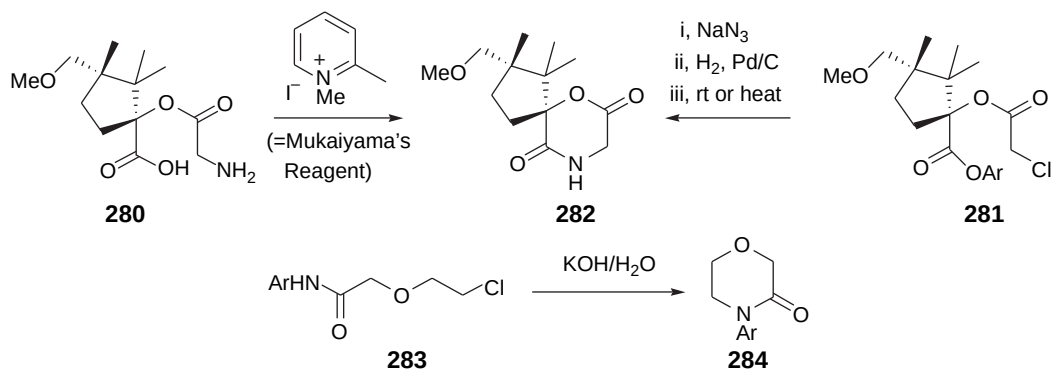
For 3-methoxydihydrobenzoxazine **276**, trifluoroacetic acid (TFA) in dichloromethane at 0 °C was used [\[1987M273\]](#). *p*-Toluenesulfonic acid (PTSA) is suitable also for the cyclization stage, but the reaction must be followed carefully to avoid the alcohol elimination. The 3-methoxydihydrobenzoxazines **277** and **278** were prepared using PTSA in toluene at 75 °C [\[1986H\(24\)3483\]](#).



Scheme 9 showed a convenient way to directly prepare N-arylated dihydrobenzoxazines **148–151** from 2-(2-aminoethoxy)chlorobenzene **147** using a soluble palladium catalyst [2004S2527](#). A copper catalyst was used in the cyclization of **279** to give **248** (Equation 25). The reaction was also performed on derivatives with different substituents on the nitrogen and the two aryl rings and the yields range from 30% to 60% [2005JOC1679](#).



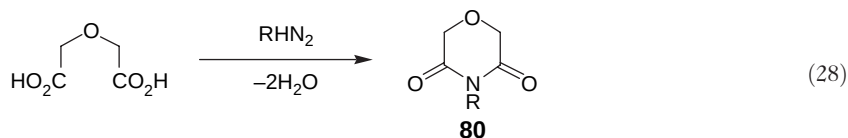
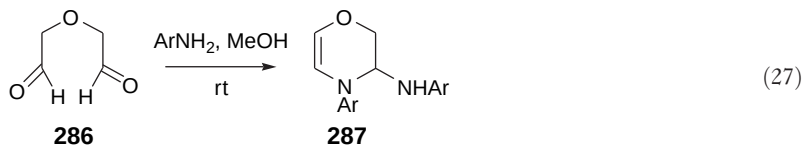
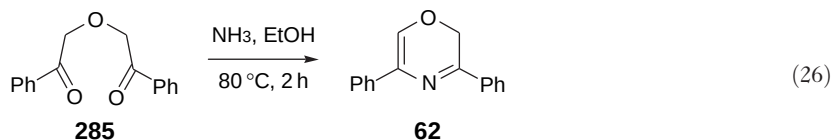
When the desired product is a tetrahydrooxazin-3-one, it is sometimes favorable for the amide bond formation to be the final step. **Scheme 31** shows two ways to form the amide linkage in **282** starting from **280** or **281** [1999EJO1967](#) and formation of **284** [2005WO16899](#) by intramolecular N-alkylation of the amine function in **283**.



Scheme 31 Methods to form lactam-type oxazines.

8.06.9.2 Two-Bond Formation from [5+1] Atom Fragments

Ammonia can be reacted with diketone **285** to give oxazine **62** (Equation 26). At 20 °C, ammonia only reacts with one of the two carbonyl groups to form an imine, but this can be further converted into **62** by heating [1982AP684](#). Dialdehyde **286** does not give an oxazine upon reaction with *p*-bromoaniline, but rather the 3-aminodihydrooxazine **287** (Equation 27). The 6-substituted derivative **158** was also prepared in this manner [1986AQ227](#). The reported NMR spectrum of **287** unfortunately could not be assigned unambiguously and there must remain some doubt as to the authenticity of this compound. Distillation of a mixture of diglycolic acid and ammonia or an amine results in dehydration to give the tetrahydro-1,4-oxazine-3,5-diones **80** (Equation 28) [2001CHE1526](#).

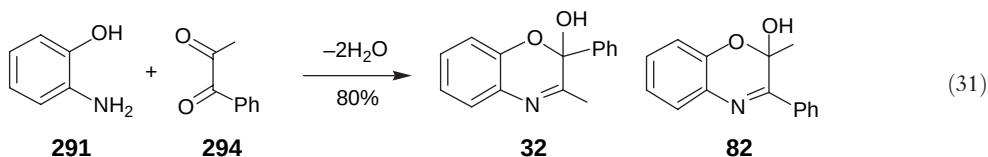
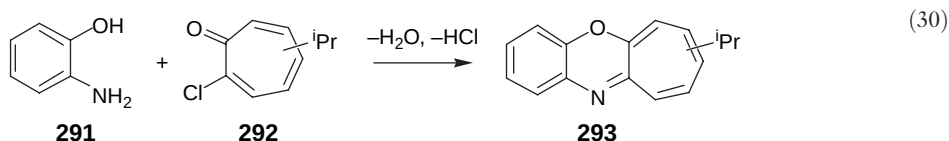
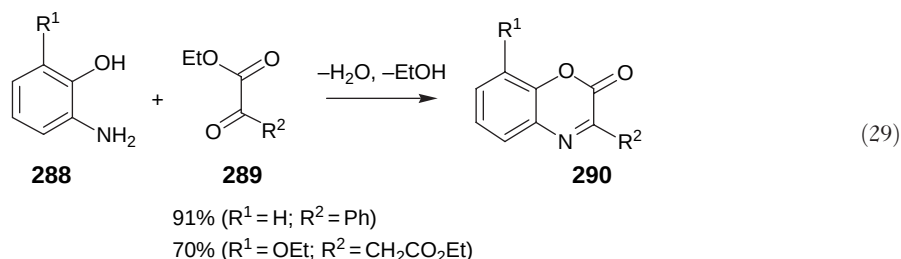


8.06.9.3 Two-Bond Formation from [4+2] Atom Fragments

This is the biggest group of ring syntheses and has been divided in 1,4-oxazine, dihydrooxazine, and tetrahydrooxazine syntheses.

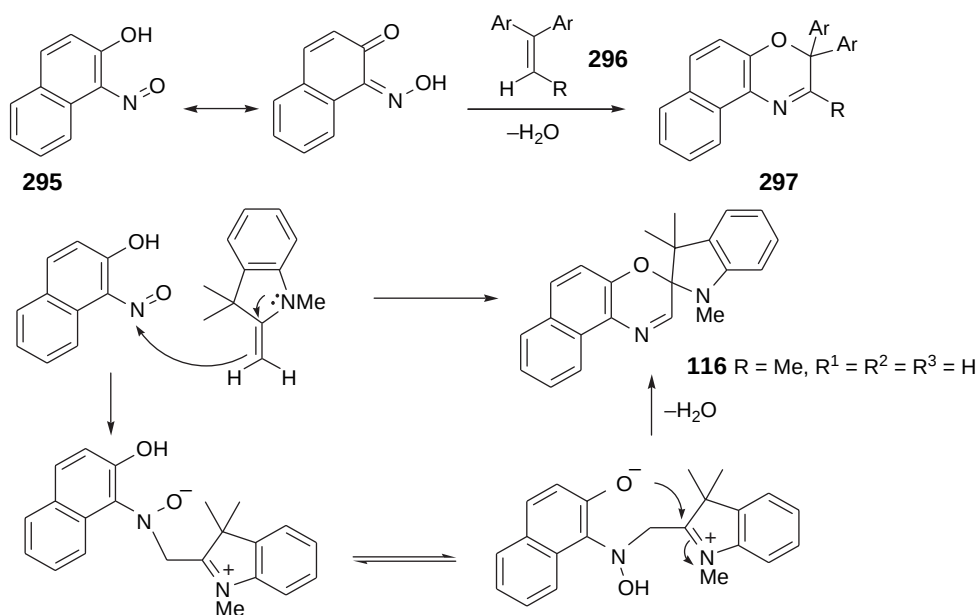
8.06.9.3.1 1,4-Oxazines

Benzoxazines have been prepared from 2-aminophenols, which react with 1,2-dielectrophiles. Using aminophenol **288** with α -ketoester **289** gives **290** (Equation 29) <1961CB1664>, which is probably the result of initial rapid imine formation followed by lactonization. When 2-aminophenol **291** and α -chloroketones **292** are heated in acetic acid, the products **293** (Equation 30) are formed in 89–90% yield <1978BCJ3316>, and thus it seems the amine prefers to react with the halide and the phenol with the carbonyl group. Conjugate addition of the amine instead of reaction with halide gives rise to different products and can be promoted by altering the reaction conditions <1991BCJ2131>. The reaction of **291** and 1-phenyl-1,2-propanedione **294** gave a mixture of the isomeric compounds **32** and **82** in a 3:2 ratio (Equation 31) <1999M1481>.

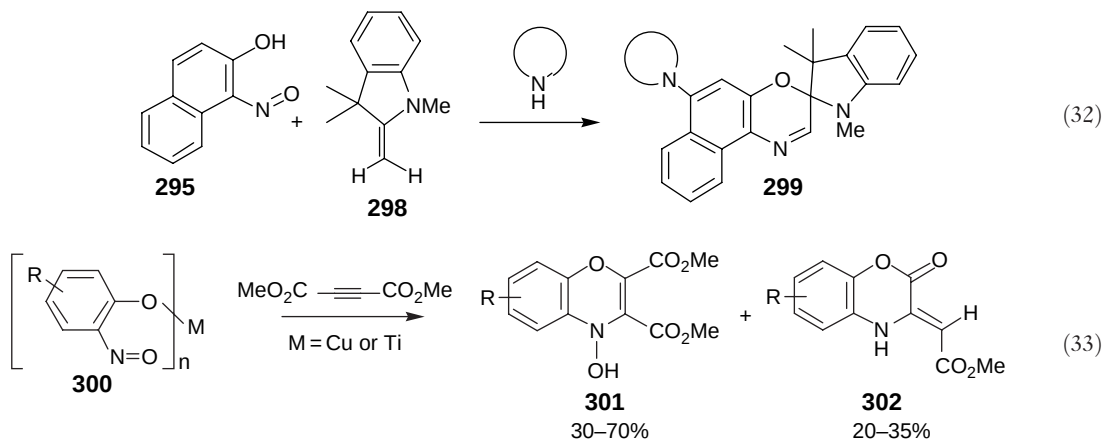


[4+2]-Cycloadditions have also been used to form benzoxazines, especially in the syntheses of photochromic materials. The reactants are typically an alkene such as **296** and a phenanthrenequinone monoxime or a 1-nitroso-2-naphthol **295**. Scheme 32 shows the synthesis of two photochromic materials **297** and **116** <1981TL3945>. The latter is a spirooxazine, for which a two-step mechanism, also shown in Scheme 32, was later suggested <2004BMC1037>.

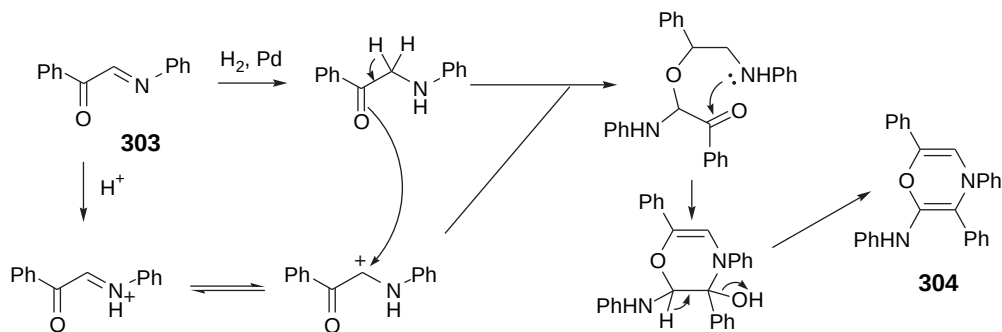
Microwave heating was found to improve yields of this process <2004SC315>. A one-pot reaction was also reported where the cyclization was accompanied by introduction of a new cyclic amino substituent on the aromatic ring (Equation 32) <2005S1876>. A similar but metal-catalyzed cycloaddition of a 1,2-benzoquinone monoxime **300** with dimethyl acetylenedicarboxylate (DMAD) gives both **301** and **302** (Equation 33) <1995JCM454, 1995JRM2701>.



Scheme 32 Formation of benzoxazines by cycloaddition reactions.



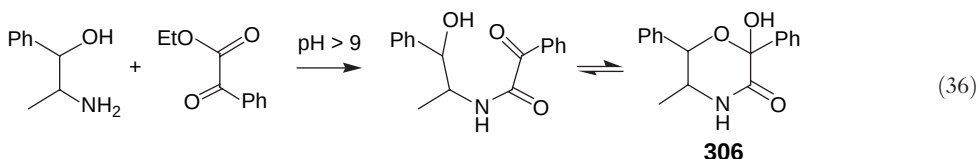
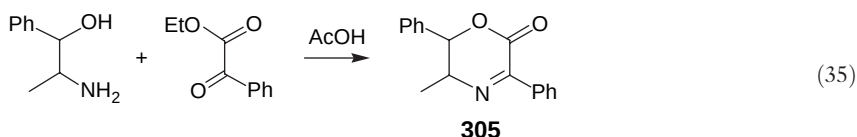
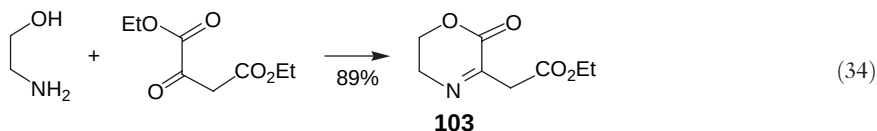
An electrochemical cyclization leading to both benzoxazines and dihydrobenzoxazines is shown later in this section (**Scheme 34**). Finally, oxazine **304** was formed in a reductive, dehydrative dimerization of **303** (**Scheme 33**) <1961CIL254>.



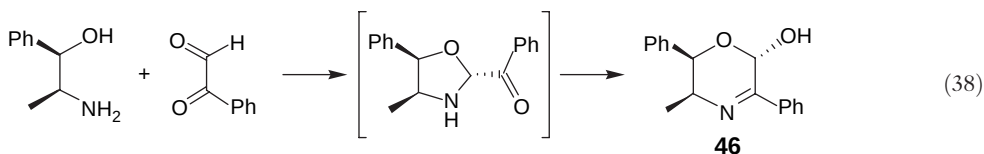
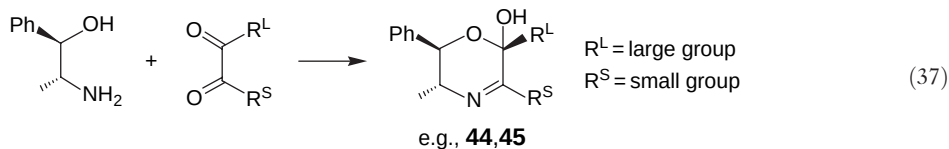
Scheme 33

8.06.9.3.2 Dihydro-1,4-oxazines

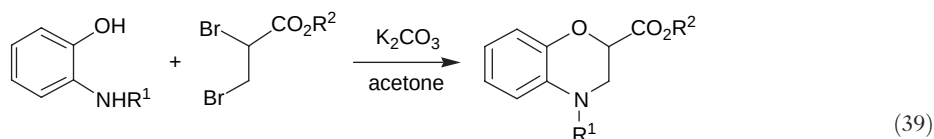
5,6-Dihydro-2*H*-1,4-oxazines can be synthesized conveniently from a 2-amino alcohol and a 1,2-dielectrophile that has one aldehyde or ketone to form an imine bond and another group to react with the alcohol. If this second group is an ester, the product is the 2*H*-5,6-dihydro-1,4-oxazin-2-one, such as **103** (Equation 34) <1961CB2778> and **305** (Equation 35) <1961CB2785>. In conditions where an ester is not stable, the reaction takes place with opposite regioselectivity to give **306** from the same components (Equation 36) <1961CB2785>.



If the second group is also an aldehyde or ketone, a 5,6-dihydro-2*H*-1,4-oxazin-2-ol is formed <1992JOC2446, 1995TA2715, 1996JHC1271, 2000SC2721>. Two examples illustrating the observed regioselectivity are shown in Equations (37) <1995TA2715> and (38) <1996JHC1271>. The amine prefers to react with the less sterically hindered end but in the case one of the carbonyl groups is an aldehyde, the reaction proceeds by a different mechanism and the imine is formed with the ketone carbonyl.



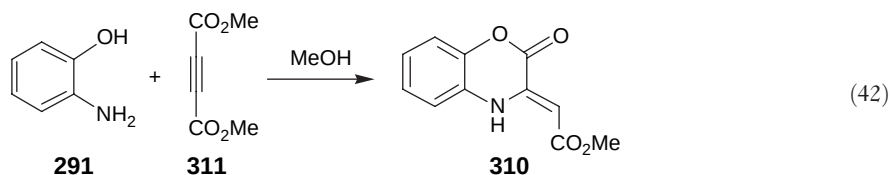
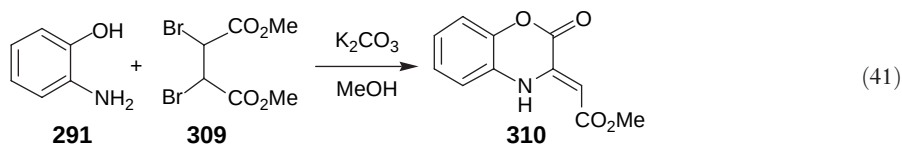
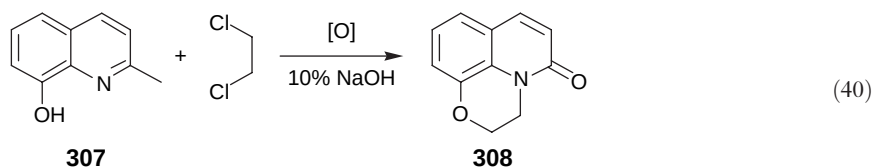
2-Aminophenol **291** and its *N*-substituted derivatives react with 1,2-dihalides to give dihydrobenzoxazines. Ethyl and methyl 2,3-dibromopropionates were reacted with **291** <1982AP538, 1983JHC45> and its *N*-methylated <1982JHC1189, 1983JHC45> and *N*-tosylated derivative <1987M273> in acetone using potassium carbonate as base (Equation 39) to give the compounds **152**, **186**, and **69** in good yields. Dichloroethane was used as a dielectrophile to prepare **308** from **307** in a similar addition, which was performed under oxidative conditions with loss of the methyl group as formaldehyde (Equation 40) <2004TL9361>. In contrast, **291** reacted preferentially with diethyl 2,3-dibromosuccinate **309** at the 1,2-positions rather than the 2,3-positions to give **310** (Equation 41) <1983JHC45>. The same product **310** is formed in a reaction of **291** with DMAD **311**, resulting from a conjugate addition of the amine followed by lactonization (Equation 42) <1983JHC45, 1984CPB1163>.



152: R¹ = H; R² = Me or Et

186: R¹ = R² = Me

69: R¹ = *p*-Ts; R² = Et

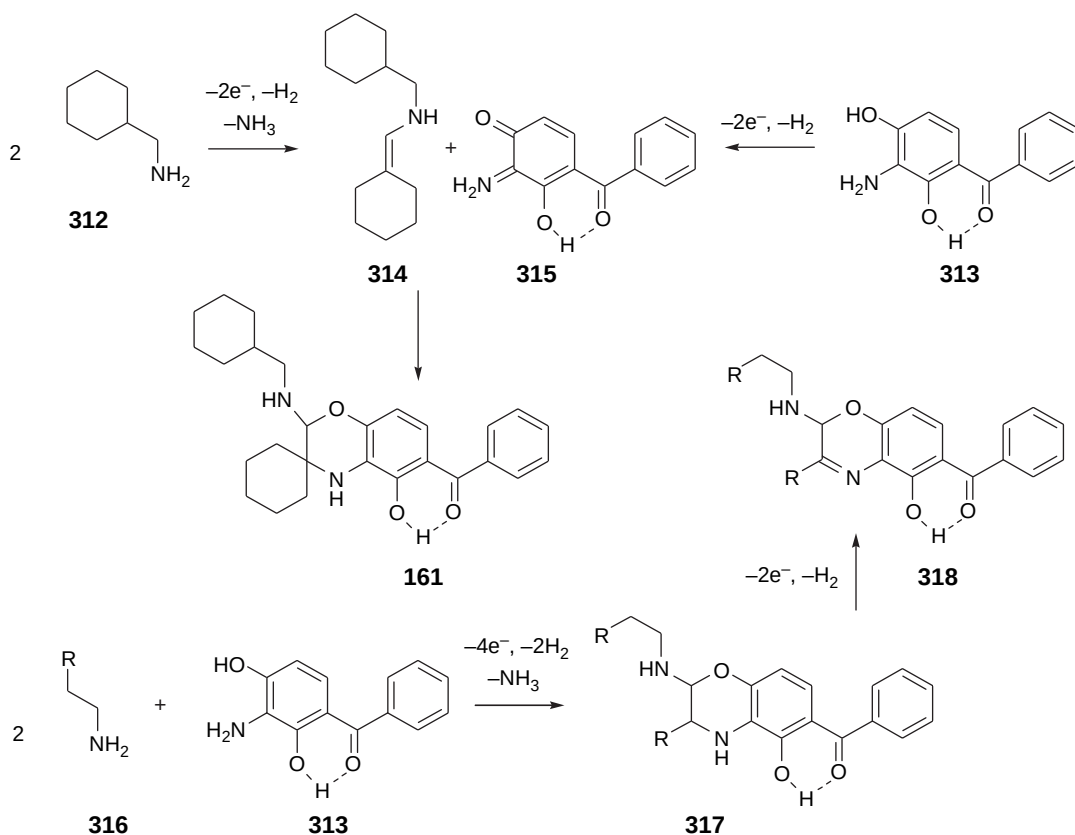


Photochromic materials such as **161**, first mentioned in [Section 8.06.6.4](#), were formed by an electrochemical reaction shown in [Scheme 34](#). The starting materials, amine **312** and aminophenol **313**, are oxidized into an enamine **314** and a 1,2-benzoquinone imine **315**, which then undergo a [4+2] cycloaddition reaction to give the benzoxazine **161** [<2002AGE824, 2004JOC882, 2005JME1282>](#). If the starting amine is unbranched like **316**, the forming dihydrobenzoxazine **317** is further oxidized electrochemically to the fully unsaturated 2*H*-benzoxazine **318** [<2004JOC882>](#).

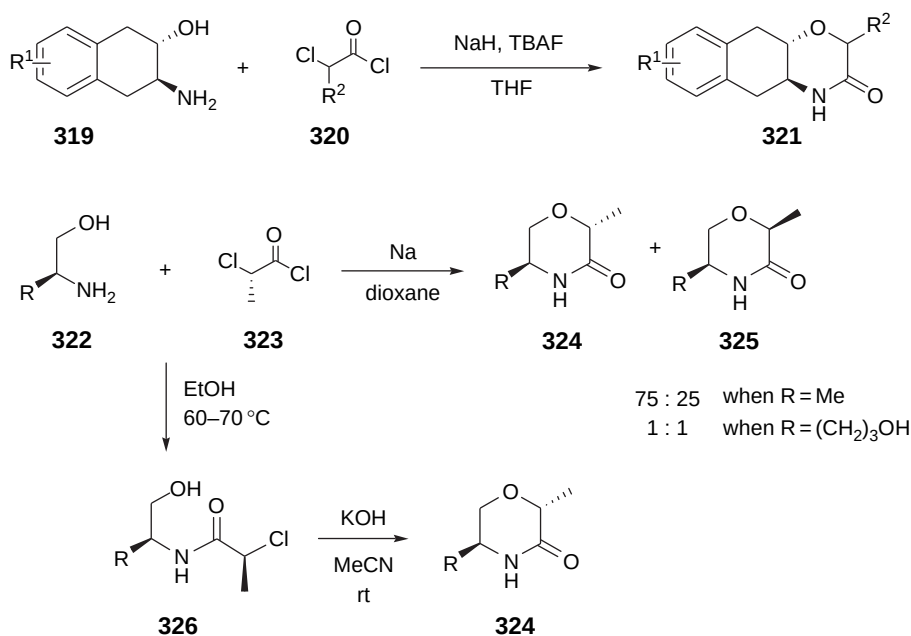
8.06.9.3.3 Tetrahydro-1,4-oxazines

Tetrahydrooxazines have been synthesized by very similar methods to unsaturated oxazines. The most commonly used reagents are a 2-amino alcohol and a 2-chloroacyl chloride [<1975JME573, 1983JOC2675, 1983USP4420480, 1984FES255, 1984JME1607, 1985EJM247, 1985DEP3520104, 1987AP625, 1987AQ322, 1988LA851, 1992JME480, 2005OL937>](#). The acid halide reacts with the amine first. The alcohol is then deprotonated with a strong base and reacts with the 2-chloro carbon to form an ether. The reaction can be performed in one pot or by isolating the amide intermediate. The product is a tetrahydrooxazin-3-one that can be conveniently reduced to a tetrahydrooxazine, as was described in [Section 8.06.6.11](#). Two typical examples are shown ([Scheme 35](#)). The first is from a synthesis of a cycloalkane-fused tetrahydrooxazine **321**, a structure that has been the basis of numerous drugs for the central nervous system from *trans*-amino alcohol **319** and 2-chloroacyl chloride **320** [<1985GEP3520104>](#) (see also [Sections 8.06.11.1](#) and [8.06.12.1](#)). The second is an asymmetric synthesis using enantiomerically pure starting materials **322** and **323** [<1988LA851>](#). When sodium is used as a base, the product is a mixture of diastereomers **324** and **325**. To avoid racemization of the 2-carbon, a two-step synthesis through **326** with milder conditions was developed, giving pure **324** as product.

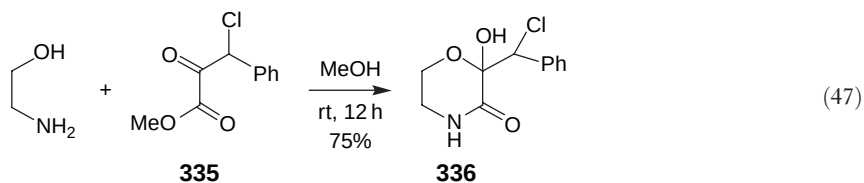
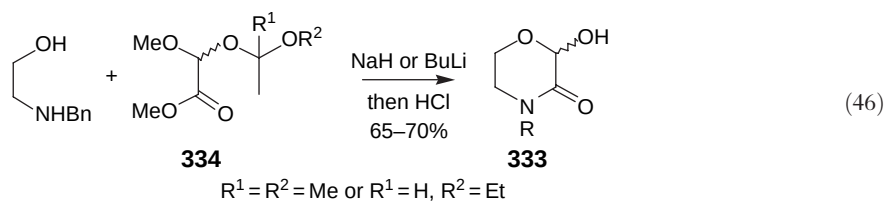
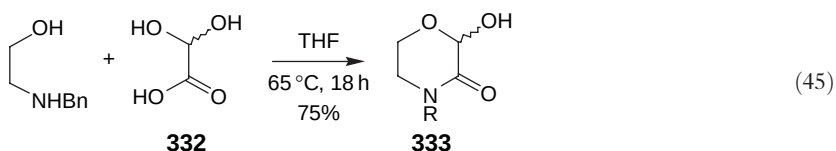
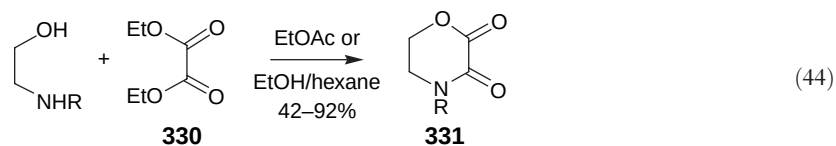
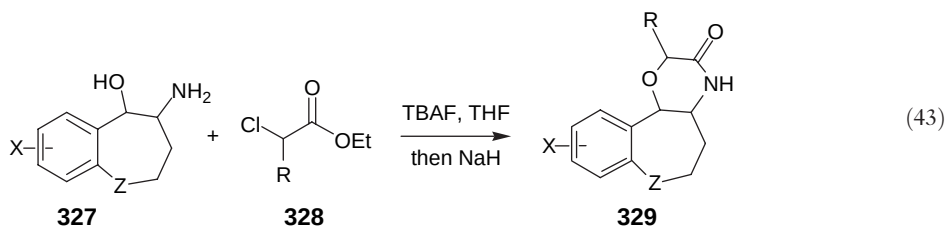
A 2-haloester **328** has been used instead of an acid chloride in the synthesis of cycloalkane-fused tetrahydrooxazines **329** [<1986FES229>](#) from **327** ([Equation 43](#)). Diethyl oxalate **330** gives tetrahydrooxazine-2,3-diones **331** ([Equation 44](#)), and a glyoxylic acid hydrate **332** or its ester and acetal-protected equivalent **334** afford the same 2-hydroxytetrahydrooxazin-3-one **333** ([Equations 45 and 46](#)) [<2004TL8917>](#). An example of regioselectivity is provided by the synthesis of 2-hydroxytetrahydrooxazin-3-one **336** from the 3-chloro-2-ketoester **335** and 2-aminoethanol ([Equation 47](#)) [<1993CHE250>](#). The two carbonyl groups are more reactive than the chloride toward nucleophilic attack and the lactam-hemiacetal product **336** is more stable than the alternative lactone-imine product.



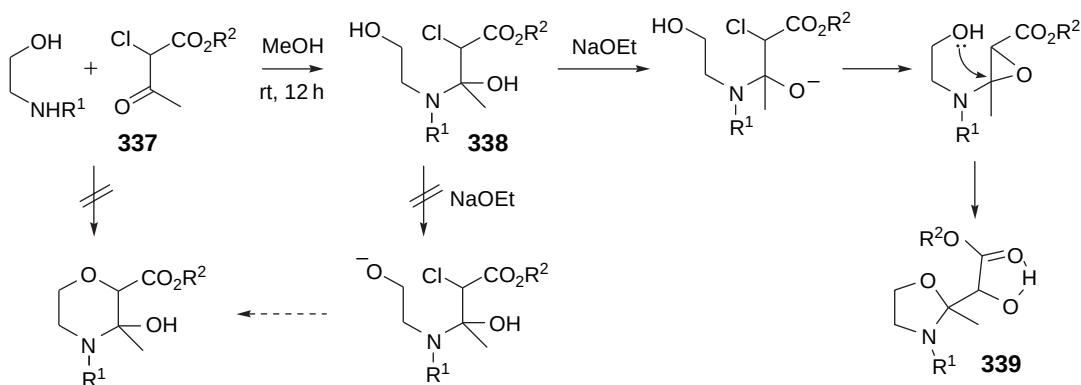
Scheme 34



Scheme 35

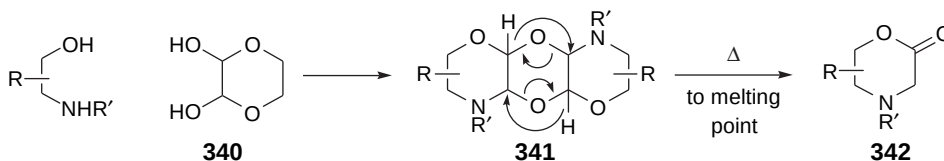


There is a significant report of a failed oxazine synthesis starting from 2-chloro-3-ketoester **337** <1998JCM30>. The amine attacks the ketone in **337** forming the hemiaminal **338**, but addition of base results in the deprotonation of the wrong hydroxyl group in **338**, leading to the oxazolidine product **339**, as shown in **Scheme 36**. Tetrahydrooxazin-2-ones of the type **342** have been synthesized from a 2-amino alcohol and the glyoxal equivalent

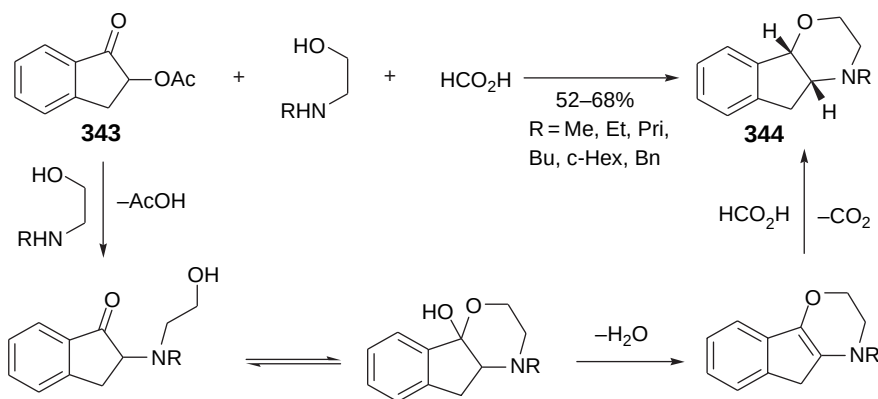


Scheme 36

340 through a thermal rearrangement of the initial product **341** (Scheme 37) <1986EPP191345>. A mechanistically interesting synthesis of a cycloalkane-fused tetrahydrooxazine **344** starting from **343** is shown in Scheme 38 <1990AP43>.



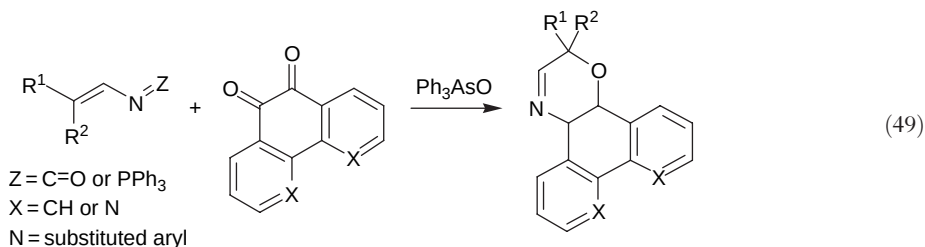
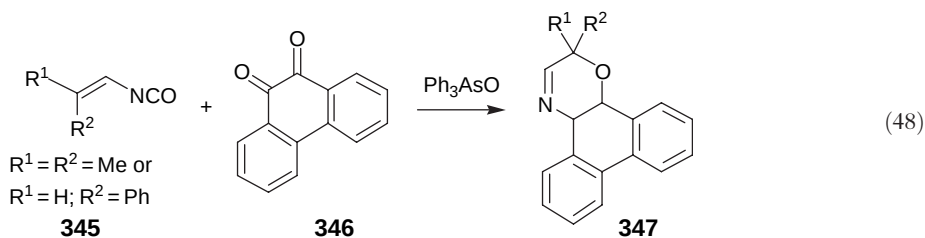
Scheme 37

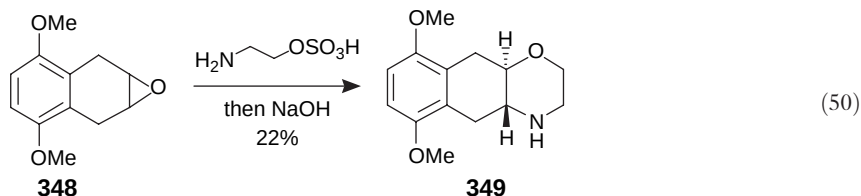


Scheme 38

8.06.9.4 Two-Bond Formation from [3+3] Atom Fragments

Isocyanates **345** react with phenanthrenequinone **346** and triphenylarsine oxide to give photochromic oxazines **347** (Equation 48) <1993PS(81)37>. The isocyanate can be replaced by a phosphinimine and the phenanthrene structure can also be replaced by the corresponding phenanthroline (Equation 49) <2003WO42195>. The *trans*-fused tetrahydrooxazine **349** was prepared from epoxide **348** and 2-aminoethyl sulfate (ethanolamine *O*-sulfonic acid) (Equation 50) <1987AP625>.

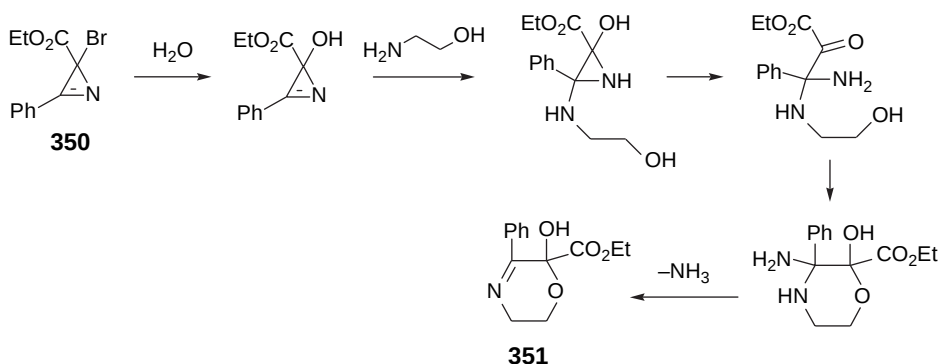




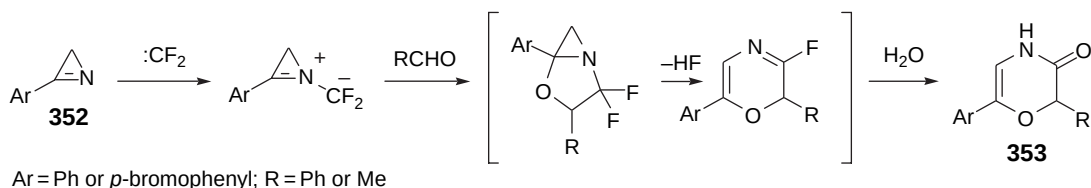
8.06.10 Ring Synthesis by Transformation of Other Heterocyclic Rings

8.06.10.1 Three-Membered Rings

The synthesis of tetrahydrooxazine **349** from an epoxide was shown in Equation 49. Azirines **350** and **352** have been used in the synthesis of dihydrooxazines. Scheme 39 shows the formation of 2*H*-dihydrooxazine **351** <2002JOC66> from **350** and Scheme 40 the formation of 4*H*-dihydrooxazin-3-one **353** from **352** <2004RCB1092>.



Scheme 39



Scheme 40

8.06.10.2 Five-Membered Rings

Dihydrooxazin-2,3-diones can be prepared by Baeyer–Villiger oxidation of dihydropyrrole-2,3-diones (Equation 51, Table 9).

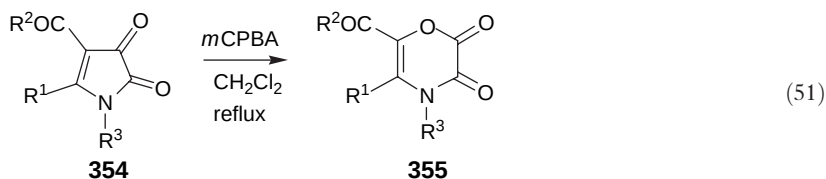


Table 9 Yields for Baeyer–Villiger oxidation of **354** to **355**

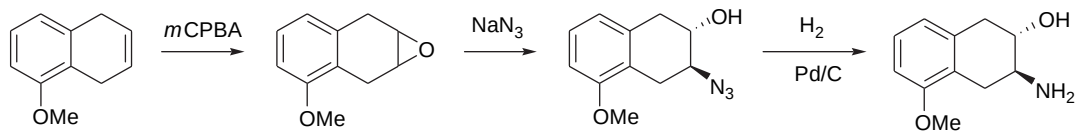
R^1	R^2	R^3	Yield (%)	Reference
Ph	Ph	Ph	51	1994H(37)523
Ph	OE _t	H	39	1994H(37)523
Ph	OE _t	Me	58	1994H(37)523
Ph	OE _t	Ph	66	1994H(37)523
Ph	OE _t	Allyl	82	1994H(37)523
Ph	OE _t	Bu	73	1994H(37)523
Piperonyl	OE _t	Me	36	1994CPB739

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

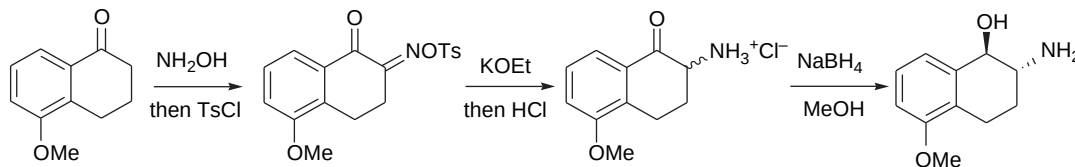
8.06.11.1 Fused Tetrahydrooxazines

This is the largest group of 1,4-oxazines and also the one with the largest number of published papers. The most commonly used synthetic strategy is the coupling of a cyclic amino alcohol with a dielectrophile. The syntheses involve three stages: synthesis of the amino alcohol, reaction of the amino alcohol with the dielectrophile, and completion of synthesis, that is, N-functionalization and/or reduction if necessary. The amino alcohol can be made by three routes shown in **Scheme 41**, that have all been used successfully. The starting material is either an alkene that is epoxidized (route A) <1992JME480> or a carbonyl compound that is reacted with a nitrosating agent (routes B and C) <1987AQ322>. Route C allows the formation of a cyclic *cis*-amino alcohol. In route A, the azide addition is not regiospecific, which lowers the yield of the step to 40% <1992JME480>. None of the routes are enantiospecific but rely on resolution of racemates if enantiomerically pure compounds are needed.

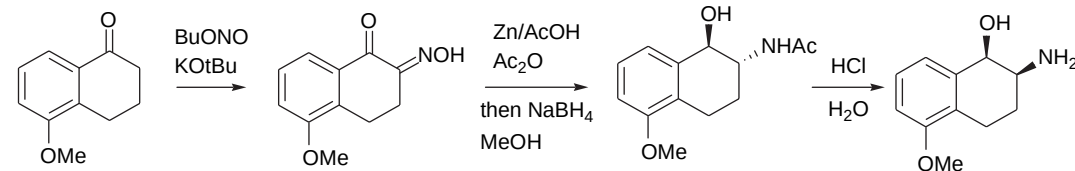
Route A



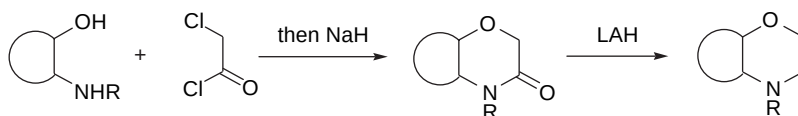
Route B



Route C

**Scheme 41**

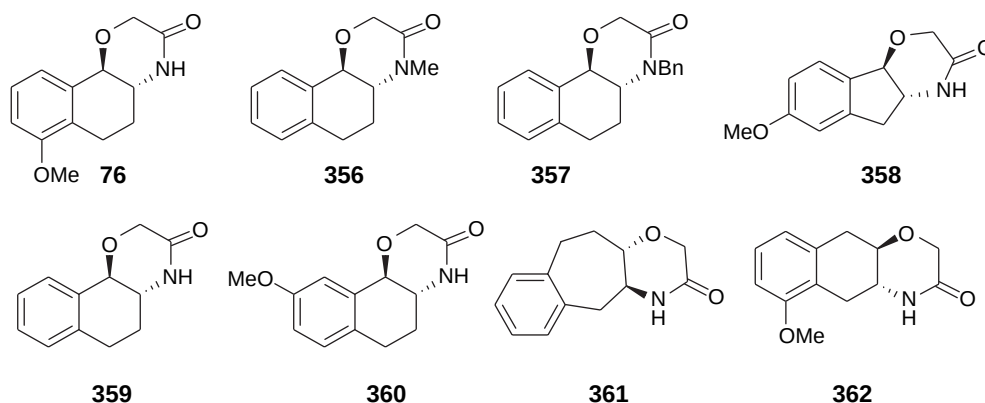
The formation of the oxazine ring from amino alcohols can be achieved by several alternative methods. The most important of these is the reaction of a cyclic amino alcohol with chloroacetyl chloride followed by sodium hydride to give a tetrahydrooxazin-3-one which is then reduced as shown in [Scheme 42](#). The reduction of the 3-oxo group has been described earlier in this chapter ([Equation 14](#)). It is notable that in all but two reports LAH has been used. It typically gives good yields as shown in [Table 10](#). The use of borane instead of LAH was mentioned in two patents <1982USP4349548, 1983EPP80117>. The range of compounds prepared by this route is illustrated by the selection displayed in [Figure 7](#) and the yields are given in [Table 10](#).



Scheme 42

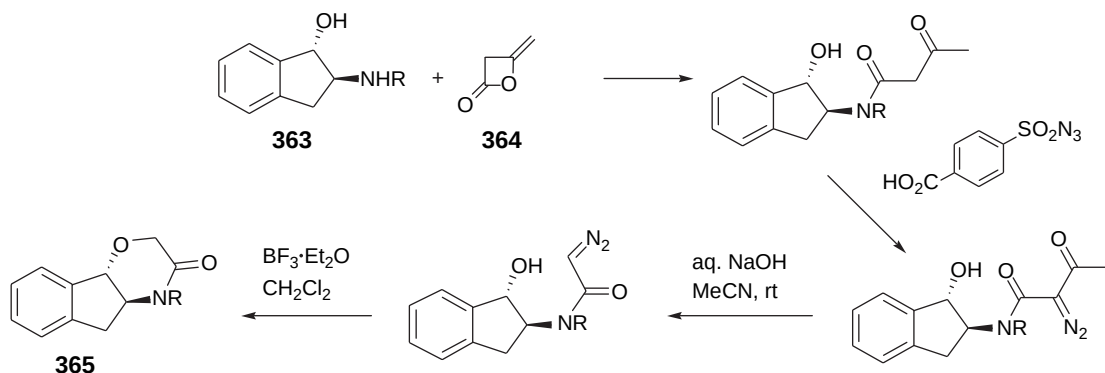
Table 10 Formation and reduction of oxazin-3-ones as in [Scheme 42](#)

Compound	Cyclization yield (%)	Reduction yield (%)	Reference
76	60	72	1987AQ322
356	(Overall yield 81%)		1982USP4349548
357	78	64	1983EPP80115
358	38	38	1984FES255
359	71	95	1984JME1607
360	78.5	90	1985EJM247
361	89	60	1986FES229
362	73	76	1992JME480

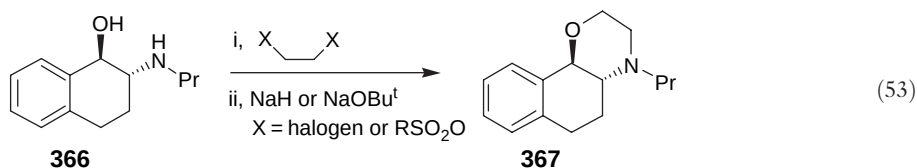
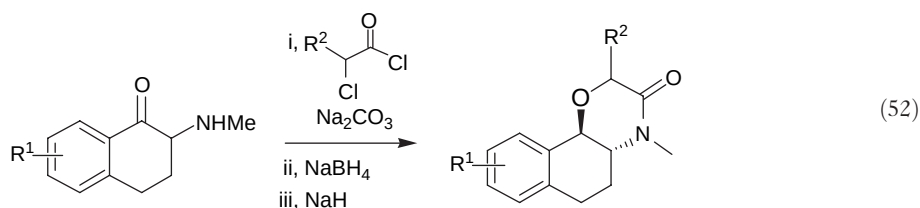
**Figure 7** Cycloalkane-fused tetrahydro-1,4-oxazin-3-ones.

The second method of forming the oxazin-3-one ring is illustrated by reaction of [363](#) with diketene [364](#) followed by diazo exchange, base hydrolysis, and Lewis acid-catalyzed cyclization to give [365](#) as shown in [Scheme 43](#). This method has been used in fewer reports <1983JOC2675, 1983EPP80117, 1984USP4431167>.

As mentioned in [Section 8.06.9.3](#), a 2-chloro ester can be used instead of an acid chloride <1986FES229>. [Equation \(52\)](#) <1983EPP80115, 1983USP4420480> shows a different order to perform the general steps discussed above. Using a dihalide or equivalent gives the oxazine product [367](#) from [366](#) without the need for LAH reduction ([Equation 53](#)) <1983EPP80115>.



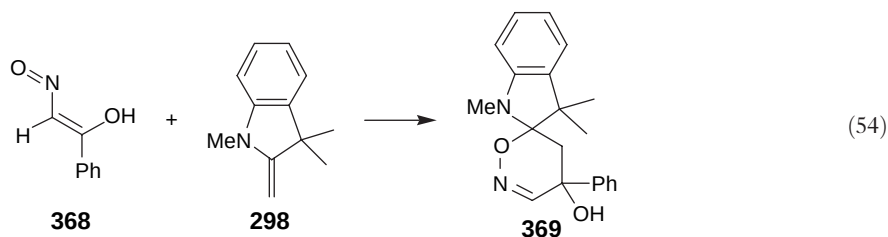
Scheme 43



The second altogether different strategy does not involve a cyclic amino alcohol but an acyclic one, and its reaction with a cyclic epoxide or dielectrophile. The reactions have been shown in [Scheme 28](#) for both *cis*- or *trans*-fused tetrahydrooxazines ([263](#) to [109](#) and [264](#) to [110](#)) [\[1978CB1164\]](#), in [Scheme 38](#) for *cis*-fused tetrahydrooxazines of the type [344](#) [\[1990AP43\]](#), and in [Equation \(50\)](#) for a *trans*-fused tetrahydrooxazine [349](#) [\[1987AP625\]](#).

8.06.11.2 Spirooxazines

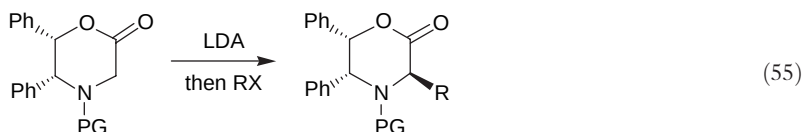
The methods to prepare spirooxazines have been reviewed extensively [\[2002RCR893\]](#). The method shown in [Scheme 32](#) and [Equation \(32\)](#), [Section 8.06.9.3.1](#) [\[1981TL3945, 2004SC315, 2005S1876\]](#), has been used most commonly in the synthesis of spirooxazines. This method is not suitable for spiro-1,4-oxazines that are not fused to an aromatic system; when the acyclic nitrosoenol [368](#) is reacted with [298](#), a 1,2-oxazine [369](#) is formed instead of the desired 1,4-oxazine ([Equation 54](#)) [\[1996DP\(31\)155\]](#).



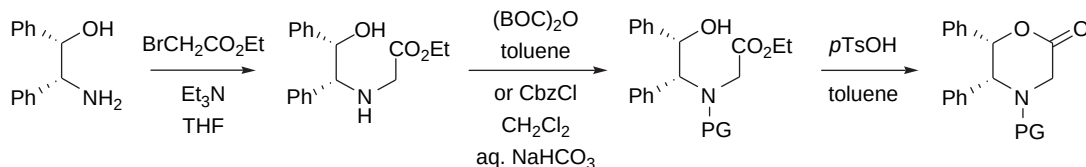
8.06.11.3 Tetrahydrooxazin-2-ones in the Asymmetric Synthesis of α -Amino Acids

Suitably protected chiral tetrahydro-1,4-oxazin-2-ones can be deprotonated at the 3-position and the resulting enolates alkylated to give, after oxazine hydrolysis, α -amino acids. The advantage of the method shown in [Scheme 13](#) using compound [170](#) to give [163](#) is that it can be used in the synthesis of α -quaternary amino acids [<1999EJO1967>](#).

The approach of the alkylation of 5,6-diphenyltetrahydro-1,4-oxazin-2-one enolates ([Equation 55](#)) has the additional benefit that it could be extended to the synthesis of β -amino acids [<2001JA3472>](#) and γ - or δ -amino acids [<1998T10419>](#), as was shown in [Scheme 22](#).

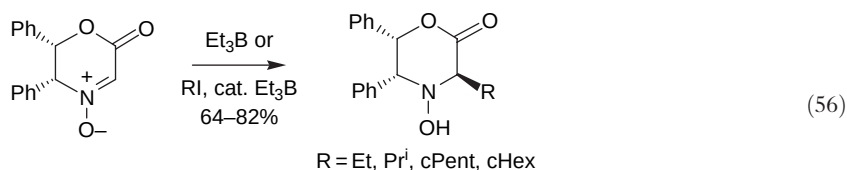


An improved route to the enantiomerically pure 5,6-diphenyltetrahydro-1,4-oxazin-2-ones is shown in [Scheme 44](#) [<2005SL693>](#). The starting amino alcohols are commercially available but can also be obtained by resolution of the (–)-mandelic acid salts of the two enantiomers. The reaction time was significantly shorter than with older methods and the yields over the three steps were 75% for the *N*-*t*-butoxycarbonyl oxazinone and 86% for the *N*-benzyloxycarbonyl oxazinone.



Scheme 44

The asymmetric radical alkylation was briefly mentioned in [Section 8.06.6.6](#). It is shown in [Equation \(56\)](#) and gives the products in over 98% diastereomeric excess [<2003CC426>](#).

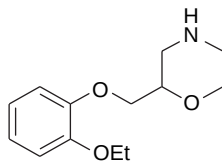


8.06.12 Applications

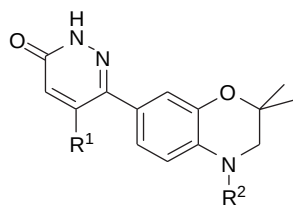
8.06.12.1 Pharmaceutical and Medicinal Applications

The first oxazine compound to be patented as an antidepressant was [370](#) [<1975JME573>](#). The main use of compounds like those shown in [Figure 7](#) is as pharmaceuticals for the central nervous system [<1987AP625>](#). This includes treatment of Parkinson's disease [<1983EPP80115, 1983USP4420480, 1984JME1607, 1984USP4431167>](#), depression [<1982USP4349548, 1983EPP80117, 1983USP4420480, 1985DEP3520104, 2005WO40140>](#), hypertension [<1982USP4349548, 1983EPP80115, 1983EPP80117, 1983USP4420480>](#), and, less commonly, also anxiety, aggressiveness, and schizophrenia [<1999EPP899267>](#), and general pain or migraine [<1995EPP641787>](#). The compounds' mode of action is as dopamine agonists [<1984JME1607, 1985EJM247>](#), α -agonists, or β -blockers [<1987AQ322, 1992JME480>](#). The *trans*-fused tetrahydrooxazines are

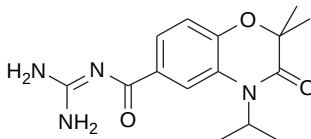
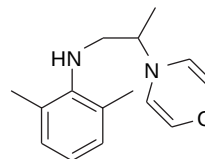
the active diastereoisomers <1987AQ322>, and most patents and articles involve them instead of *cis*-fused compounds. Cycloheptane-fused oxazines **329** were also tested for gastric ulcer medication, but were found to have side effects <1986FES229>.

**370**

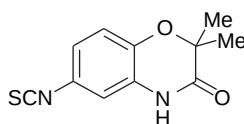
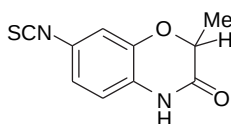
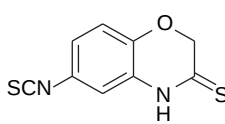
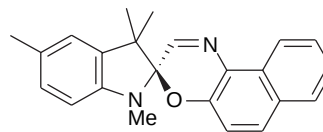
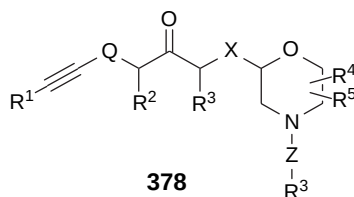
To a lesser extent, dihydrobenzoxazines have also been reported to be α_2 -agonists <1989JME1627> and LTD₄ receptor antagonists <1990JME2621>. Benzoxazine **161** is a potential neuroprotective agent <2005JME1282>. Benzoxazines have also found applications in the treatment of heart conditions: **371** is an inotrope (increases the force of contraction of the heart muscle) <2004OPP292> and **372** is used in the treatment of ischaemic heart diseases and ischemia or reperfusion injury <1998JAP10017535>. The oxazine **373** is claimed as an antiarrhythmic drug <1982DEP3207813>, but this is most likely an error in the patent, which should in fact refer to the corresponding tetrahydrooxazine.

**371**

R¹ = H or Me; R² = H or Me

**372****373**

Dihydrobenzoxazinone **374** was found to be active against hookworm, and **375** and **376** against tapeworm <1985IJB1263>. Spirooxazine **377** has modest antiviral activity <2004BMC1037>. The compound **54** is an immunomodulator <1992JAN1553>. The different variations of structure **378** were patented as anti-inflammatory agents <2003WO99798>. A number of fused tetrahydrooxazines have also shown anti-inflammatory activity <2005MI481>.

**374****375****376****377****378**

X = CHR or CR₂

Z = CO or SO₂

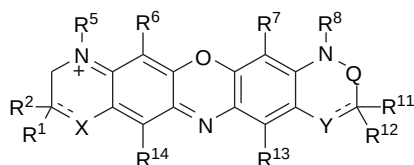
Q = alkyl, also branched

R = aryl or heteroaryl

R¹⁻⁵ = alkyl

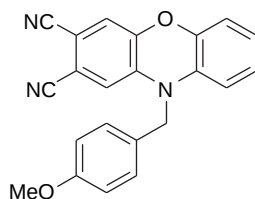
R⁴, R⁵ can form ring

A medicinal application for a photochromic dye is the use of compounds of the type **379** as near-infrared imaging agents <2005WO16934>. The compounds are used to label amyloid plaques in the brain and aid in the detection of Alzheimer's disease.

**379**

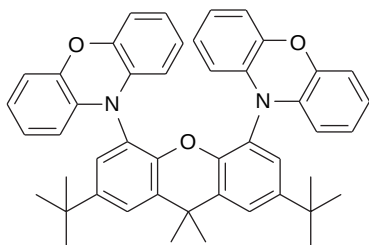
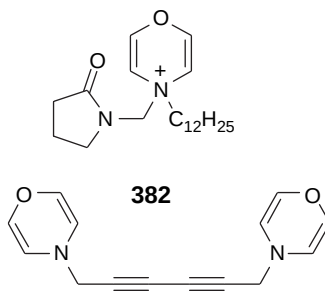
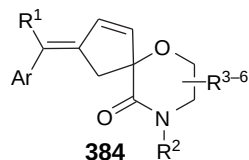
8.06.12.2 Photochromic Dyes and Optical Applications

The medicinal use of the photochromic oxazine **379** was discussed in the previous section. The principle of photochromism was shown in [Scheme 3, Section 8.06.5.1](#). Photochromic spirooxazines **101**, **116**, and **297** that have appeared in this chapter and their various substituted derivatives have been patented as photochromic materials [<2003WO42195>](#) and used as photochromic dyes in a microsphere-based sensor [<2005USP19954>](#). The compound **299** is also used as photochromic material [<2005S1876>](#). More detailed information about the applications of spirooxazines can be found in a review [<2002RCR893>](#). The phenoxazine **380** has also been patented for use in optics [<2005SUA2246491>](#).

**380**

8.06.12.3 Other Applications

The phenoxazine derivative **381** has been developed for use as a 'wide-bite-angle' ligand [<2000JCD2105>](#). Two 1,4-oxazine-derived compounds have been patented but in the absence of analytical data, it is not possible to say whether there really is an oxazine ring present or if this is an error and should actually be the more common morpholine ring: the compound **382** was claimed to have been prepared by alkylation of *N*-dodecyloxazine and was used as a component in conditioning shampoo [<1988WO02985, 1989USP4883655>](#), and **383** was claimed to be useful as a yellow dye in photography that could be activated by irradiation with 254 nm light [<1974USP3822134>](#). In view of the elusive nature of simple monosubstituted 1,4-oxazines as described earlier in this chapter, it seems likely that the structures of both **382** and **383** are erroneous. Finally, 2-spiropentenyltetrahydrooxazin-3-ones of the type **384** have been patented as antifeedant-type insecticides [<2003MIP1431210>](#).

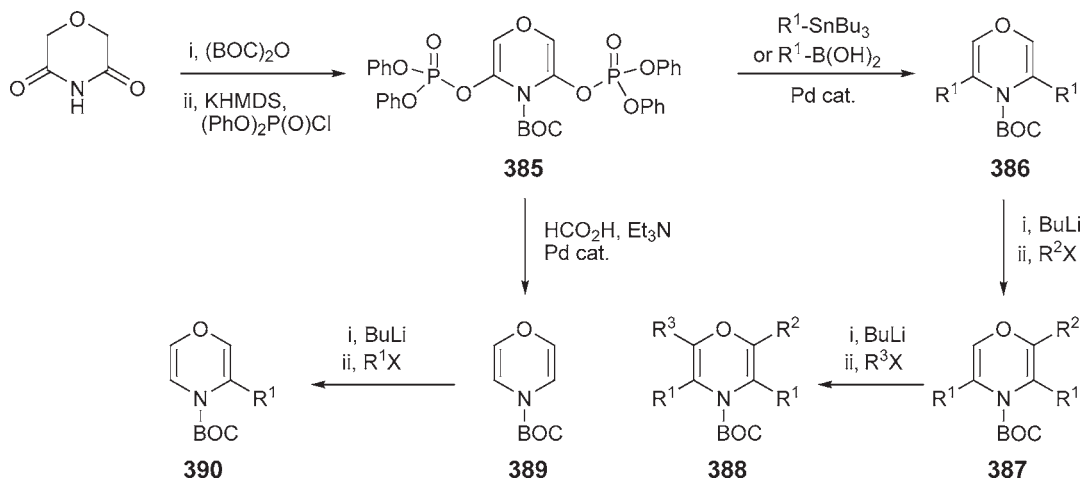
**381****383****384**

R¹⁻⁶ = H, alkyl, alkenyl
 R², R³ can form a ring
 Ar = pyrazolyl or hydrocarbyl

8.06.13 Further Developments

A review of asymmetric 1,3-dipolar cycloaddition of cyclic ylides derived from chiral 1,2-amino alcohols includes examples of tetrahydrooxazinone-based azomethine ylides and nitrones <2006SL2349>. Addition of dichlorocarbene to the 3,4-double bond of 3-phenyl(2*H*)-1,4-benzoxazine gives a dichlorocyclopropane which can subsequently be ring opened in various ways <2007S2225>. Catalytic asymmetric reduction of the 3,4-double bond of 3-aryl(2*H*)-1,4-benzoxazines using a dihydropyridine hydrogen donor and a binaphthol phosphate catalyst occurs in up to 96% ee <2006AGE6751>. Copper(II) salt catalyzed reaction of *N*-benzoyloxymorpholine with diarylzincs provides a convenient new synthesis of *N*-arylmorpholines in 70–95% yield <2006OS31>. A palladium(II) catalyzed domino Wacker–Heck reaction of an *ortho*-methallylaminophenol with MVK leading to a dihydro-1,4-benzoxazine has been described <2006H(70)309>. *O*-Benzoylquinidine-catalyzed cycloaddition between an *ortho*-quinone imine and an acid chloride in the presence of base provides an asymmetric synthesis of 3-chiral 1,4-benzoxazin-2-ones in up to 99% ee <2006AGE7398>.

In a landmark paper, convenient access to simple *N*-*tert*-butoxycarbonyl-1,4-oxazines bearing one, two, three or four *C*-substituents has been described <2007JOC4832>. *N*-Protection of the cyclic imide of diglycolic acid followed by deprotonation and reaction with diphenyl chlorophosphate affords the key intermediate **385**. This undergoes ready Stille or Suzuki coupling to give **386** which may then be further alkylated with a variety of electrophiles to give **387** and **388**. Alternatively, reductive cleavage of **385** gave **389** which could be alkylated to give **390**. In some cases further transformations were also described such as Wittig reaction of **387** ($R^1 = \text{Ph}$, $R^2 = \text{CHO}$) and Sonogashira coupling of **387** ($R^1 = \text{Ph}$, $R^2 = \text{I}$). Full ^1H and ^{13}C NMR data are reported for all these products, expanding greatly the knowledge in this area. It should also be noted that a similar approach was previously applied by the same authors to synthesis and functionalization of *N*-*tert*-butoxycarbonyl-1,4-benzoxazines <2000T605>.



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Biographical Sketch



Alan Aitken was born in the Dumfries and Galloway area of SW Scotland. He studied at the University of Edinburgh where he obtained a B.Sc. in 1979 and his Ph.D. in 1982 under the direction of Dr I. Gosney and Professor J. I. G. Cadogan. After spending two years as a Fulbright scholar in the laboratories of Professor A. I. Meyers at Colorado State University, he was awarded a Royal Society Warren Research Fellowship and moved in 1984 to the University of St. Andrews where he has been a senior lecturer since 1997. His research interests are in the area of synthetic and mechanistic organic chemistry including asymmetric synthesis, synthetic use of flash vacuum pyrolysis, heterocyclic chemistry, and organophosphorus and organosulfur chemistry.



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8.07

1,2-Thiazines and their Benzo Derivatives

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8.07.1 Introduction

1,2-Thiazines **1** are six-membered heterocyclic rings composed of four contiguous carbon atoms along with adjacent sulfur and nitrogen atoms (Figure 1). The nomenclature of the 1,2-thiazines is complicated by varying degrees of saturation of the ring atoms, double-bond regioisomers, multiple oxidation states of sulfur, and the interconversion of

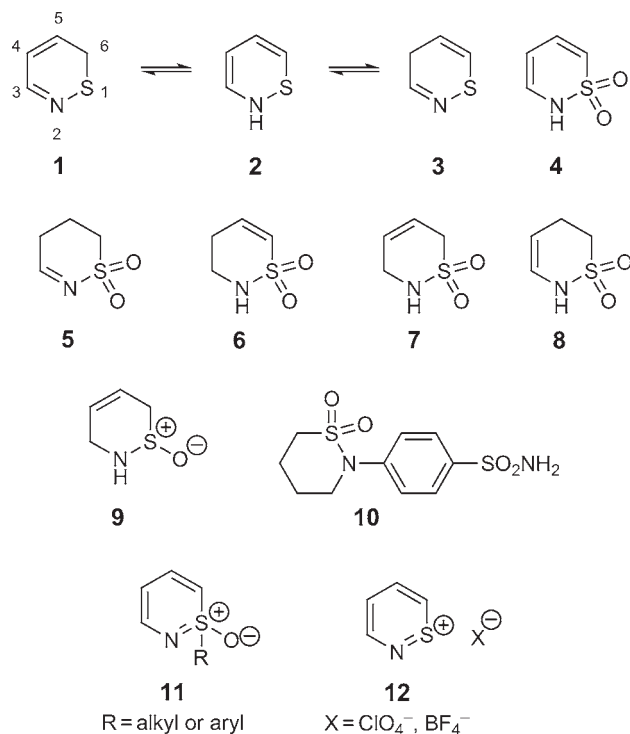


Figure 1

isomers through tautomerization. The parent 1,2-thiazine theoretically should exist as three tautomers known as the 6*H*-1,2-thiazine **1**, 2*H*-1,2-thiazine **2**, and 4*H*-1,2-thiazine **3**, although none of these simple unsubstituted compounds has ever been observed. However, substituted 1,2-thiazines have been prepared and prefer to exist as the 6*H*-tautomer **1**.

A majority of the compounds encountered in this class of heterocycles exist as *S,S*-dioxides. The nomenclature for such compounds is somewhat ambiguous as the terms sultam, sulfonamide, and 1,2-thiazine 1,1-dioxide have all been used to describe these molecules. The reactivity of 1,2-thiazine 1,1-dioxides **4** (as the 2*H*-tautomer) has been thoroughly investigated and much of this work has been described in Chapter 6.06 of CHEC-II(1996) <1996CHEC-II(6)349>. This S(vi)-oxidized compound **4** undergoes both nucleophilic and electrophilic attack, which are often non-regioselective.

Four regioisomeric dihydrothiazine 1,1-dioxides are possible depending upon the position of the double bond. The most common examples of this subclass include 5,6-dihydro-4*H*-1,2-thiazine 1,1-dioxides **5**, 3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxides **6**, and 3,6-dihydro-2*H*-1,2-thiazine 1,1-dioxides **7**. Scant interest has been paid to 5,6-dihydro-2*H*-1,2-thiazine 1,1-dioxides **8** or their substituted derivatives. Related 3,6-dihydro-2*H*-1,2-thiazine 1-oxides **9** are also an important subclass of compounds due to their ease of preparation via [4+2] cycloaddition reactions.

The biology and chemistry of 3,4,5,6-tetrahydro-1,2-thiazine 1,1-dioxides, such as **10** (or 1,2-thiazinane 1,1-dioxides), has garnered significant attention in the past 10 years. For instance, interest in the tetrahydro-1,2-thiazine 1,1-dioxide drug sulthiame **10** has been renewed by recent work on its efficacy in treatment of both childhood benign and focal epilepsies. From the synthetic perspective, new methods have been developed to prepare 1,2-thiazinane 1,1-dioxides via a transition metal-mediated C–H-insertion reaction.

Fully conjugated 1,2-thiazines have been prepared with both S(II) and S(vi) oxidation states. While the zwitterionic compound **11** has been known for some time <1984CHECI(3)995, 1996CHEC-II(6)349>, thiazinylium salts **12** have only recently been prepared. Both fully unsaturated 1,2-thiazine derivatives are considered to be nonaromatic due to poor p–d π -bonding. Furthermore, the six-membered ring of 1-alkyl-1,2-thiazine 1-oxide **11** is not planar, but instead exists in a puckered, half-boat conformation thereby precluding aromaticity <1978CC197>.

The fused benzo derivatives of 1,2-thiazines are of great commercial importance due to their potent biological activity (Figure 2). The three regioisomers of the benzothiazine *S,S*-dioxide structure are known: 2,1-benzothiazine

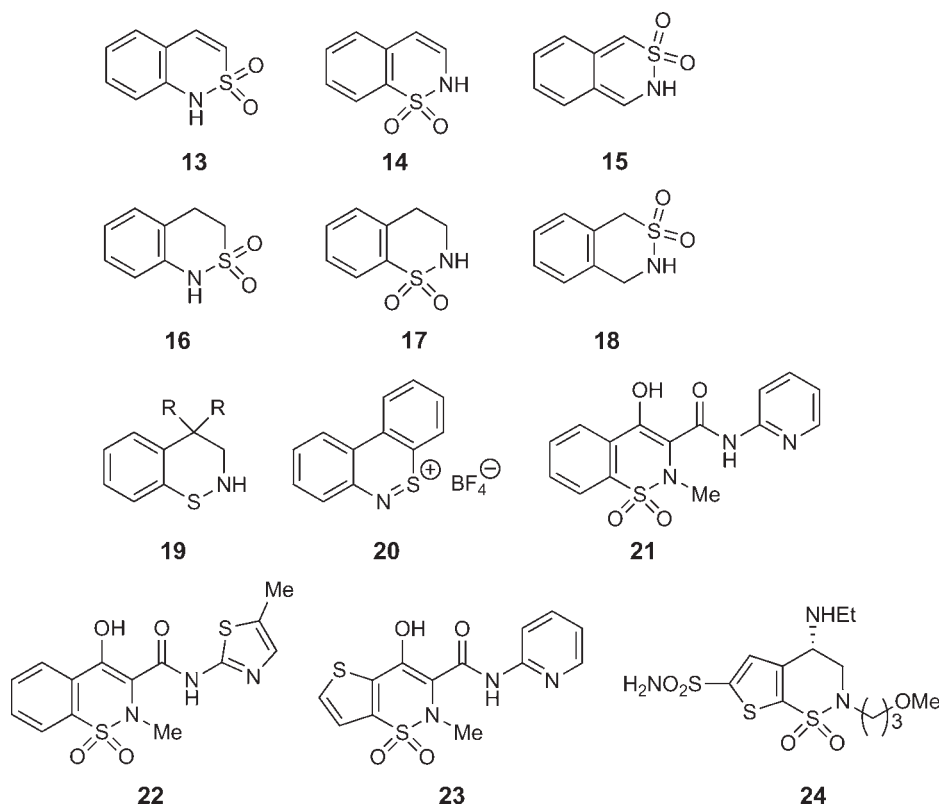


Figure 2

13, 1,2-benzothiazine **14**, and 2,3-benzothiazine **15**, along with the related dihydro compounds **16–18**. The majority of these compounds exist in the dioxo sulfur oxidation state, although 2,1-benzothiazine **19** and the fully conjugated 1,2-benzothiazinium salt **20** have been prepared. 2,3-Benzothiazine dioxides **15** have rarely been described in the literature and none have been reported since CHEC-II(1996).

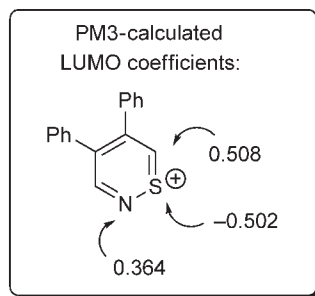
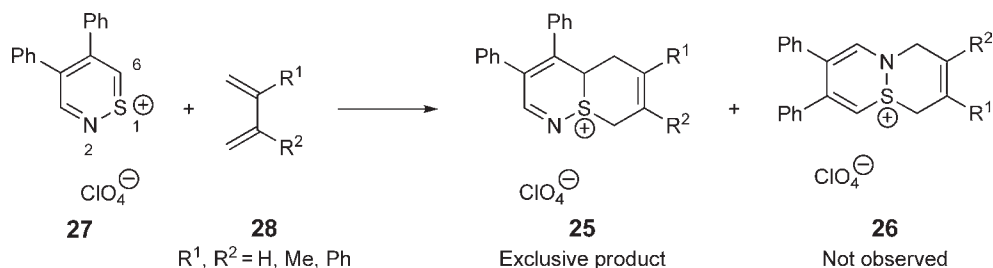
The most biologically active members of the benzothiazines, known as the oxicams, include piroxicam (Feldene®) **21**, meloxicam (Mobic®) **22**, and tenoxicam **23** which have a 1,2-benzothiazine 1,1,4-trioxide structure. Recently, the 1,2-thiazine-containing drug brinzolamide **24** (Azopt®) was approved as an ophthalmic suspension for the treatment of glaucoma.

The chapter on 1,2-thiazines in CHEC(1984) provided an introduction to both thiazines and oxazines <1984CHEC(3)995>. Chapter 6.06 in CHEC-II(1996) covered the synthesis and reactivity besides the chemical and physical properties of 1,2-thiazines reported in the literature prior to 1996 <1996CHEC-II(6)349>. The highlights of this chapter included advances in hetero-Diels–Alder reactions for the synthesis of 3,6-dihydrothiazine-1-imines and 1-oxides. Another important focus was on pericyclic rearrangements of the Diels–Alder adducts and the usefulness of the synthons generated through this methodology for the stereoselective construction of a variety of natural products. CHEC-II(1996) also detailed the wealth of information on the preparation and reactions of benzothiazines. In continuation of CHEC-II(1996), an update of the literature from 1996 to 2006 on physical and structural properties, preparation, and applications of 1,2-thiazines and their benzo derivatives is presented in the pages that follow.

8.07.2 Theoretical Methods

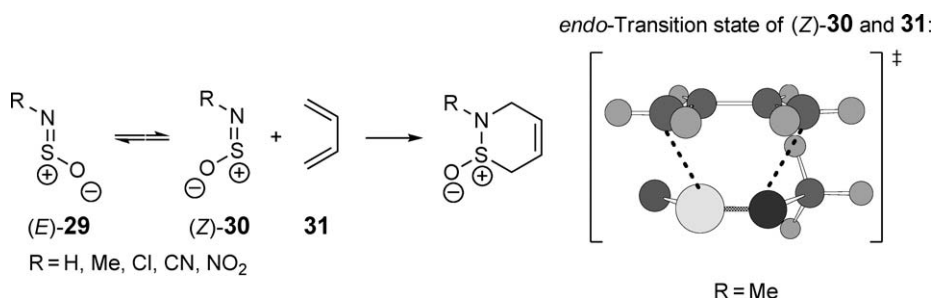
8.07.2.1 Overview of Semi-Empirical and *Ab Initio* Molecular Orbital Methods

Theoretical calculations have been an important means of rationalizing the electronic course of hetero-Diels–Alder and related pericyclic reactions for the formation of 1,2-thiazines **25** and **26**. MOPAC 93 PM3 calculations have been used to deduce the regioselectivity of [4+2] cycloaddition reactions involving thiazinylium perchlorate **27** (Scheme 1) <1999TL1505>. Due to the higher lowest unoccupied molecular orbital (LUMO) coefficient at C-6 compared to N-2, the C-6 and S-1 behave preferentially as the dienophile double bond in cycloaddition reactions of this substrate with butadienes **28**.



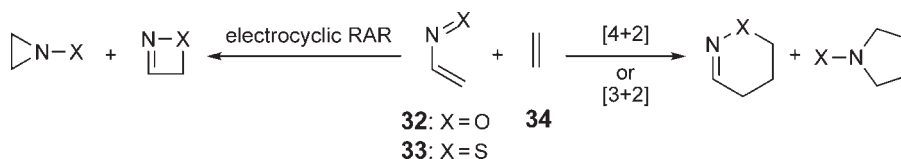
Scheme 1

Theoretical work on the gas-phase hetero-Diels–Alder reaction of *N*-sulfinyl dienophiles was used to study both *endo*- and *exo*-modes of cycloaddition for both (*E*)-**29** and (*Z*)-**30** dienophiles at the B3LYP/6-31G* level (Scheme 2) <2000JOC3997>. In summary, these calculations have predicted that (1) the *N*-sulfinyl dienophiles prefer the (*Z*)-**30** orientation over (*E*)-**29** stereochemistry by 5–7 kcal mol^{−1}, (2) the transition state is concerted but nonsynchronous, and (3) an *endo*-transition state with diene **31** is favored over the *exo*-approach both kinetically and thermodynamically.



Scheme 2

An *ab initio* study at the post-Hartree–Fock level of theory was conducted for the pericyclic reactions of both nitrosoethylene **32** and thionitrosoethylene **33** (Scheme 3) <1996LA1615>. Thionitrosoethylene **33** was calculated to have a 15–20 kcal mol^{−1} lower activation energy than nitrosoethylene **32** in all ring closures studied. The results of this study indicate that [4+2] and [3+2] cycloaddition reactions of both substrates **32** and **33** with ethylene **34** are highly exothermic, while electrocyclic ring-closing rearrangements (RARs) are predicted to be endergonic.



Scheme 3

Zerner's intermediate neglect of differential overlap (ZINDO)/PM3 calculations of thiazinylium compound **35** were compared to its ultraviolet/visible (UV/Vis) absorption spectrum (Figure 3) <2000JOC6388>. The authors attribute the observed 453 and 403 nm bands (calculated to be at 456 and 412 nm) to highest occupied molecular orbital (HOMO)–LUMO and HOMO–LUMO + 1 transitions of the 1,2-thiazine sulfonium imide.

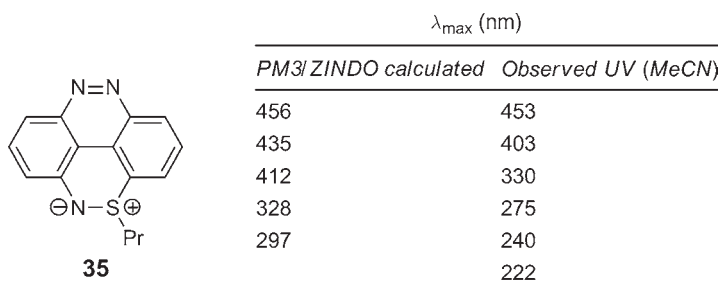


Figure 3

8.07.2.2 Applications of Molecular Mechanics

The X-ray crystal structure of the protein MSNAT (the arylamine *N*-acetyltransferase of the bacterium *Mycobacterium smegmatis*) has led to work on the simulated annealing of a 1,2-benzosulfonamide **36** (Figure 4) <2003BML2527>. From the AutoDock analysis, the major interactions of the 1,2-benzosulfonamide **36** with MSNAT involve the sulfonamide bound to the active site cysteine, π -stacking of the benzothiazine benzene ring with a neighboring histidine, and a combination of nonbonding, hydrophobic–hydrophobic and π -stacking interactions between the biphenyl and MSNAT protein.

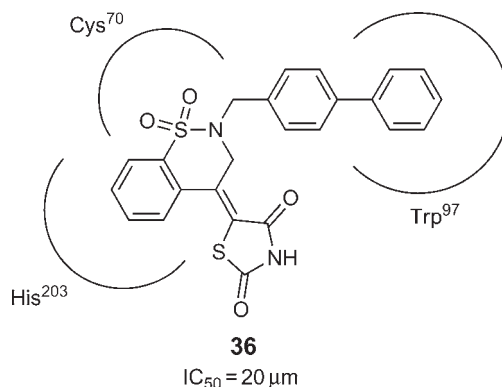


Figure 4

8.07.3 Experimental Structural Methods

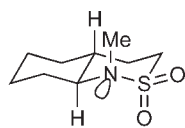
8.07.3.1 X-Ray Diffraction

The nature of the anomeric effect in the bicyclic *trans*-fused octahydro-1-methyl-1*H*-2,1-benzothiazine 2,2-dioxide **37** has been examined by single crystal X-ray structure analysis (Figure 5) <1998CJC164>. The crystal structure of **37** shows that the *N*-Me group assumes an axial position in the solid state. The authors suggest that this conformation is also the most stable in solution and propose that this hyperconjugation effect is >2.0 kcal mol⁻¹.

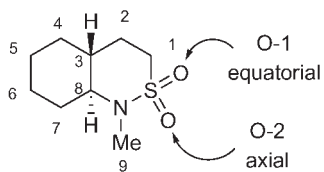
The X-ray crystal structure of the sultam hydroxamate ligand **38** with the zinc metalloproteinase MMP-13 was recently disclosed by scientists at Bristol-Myers Squibb (Figure 6) <2004JME2981>. This sulfonamide **38** was found to bind via the hydroxamate functionality to the zinc moiety of the enzyme in a bidentate manner and through the sulfonamide to a neighboring leucine in the protein backbone. These two binding events allow access to the S1' binding pocket by the pyridine functionality of ligand **38**. In related examples, several crystal structures have been solved for thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide inhibitors co-crystallized with carbonic anhydrase (CA) II. This information, coupled with computationally predicted structures of inhibitors bound to CA IV, has led to insights into the selective binding of these molecules to CA II <2002JME888>.

The structure of *N*-sulfinyl compound **39** was solved using a single crystal grown by the slow evaporation of a solution of dichloromethane (DCM) and hexane (Figure 7) <2003T4651>. The *N*-sulfinyl compound crystallizes with two molecules in a unit cell. This work provides additional evidence for the (*Z*)-preference of this dienophile used in [4+2] cycloaddition reactions to prepare 1,2-thiazines.

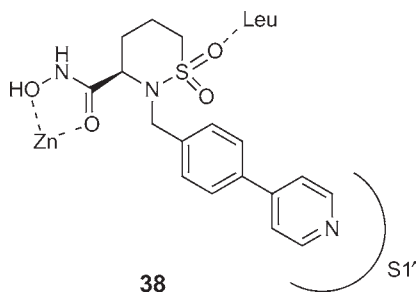
Also of note, the X-ray crystal structures of several fully conjugated, planar 1,2-thiazines have been determined <1996JOC9178, 2005JOC9314>. The solid-state structures of several bicyclic sulfonamides <2000T873, 2001OL369, 2002TA2407, 2002HCA1973, 2003T7047>, an oxaziridine derivative <1997JOC3625>, and fluorinated sulfonamides <2005T6982, 2003T9669> have been determined by X-ray crystallography. The structures of metal complexes containing meloxicam and tenoxicam have been further investigated through crystallography <2003POL1355, 2004POL1909>.

**37**

Atom numbering:



<i>Bond</i>	<i>Bond length (Å)</i>	<i>Bond</i>	<i>Bond/torsional angle</i>
S–O(1)	1.430	O(1)–S–O(2)	118.42
S–O(2)	1.439	O(1)–S–N	108.48
S–N	1.638	O(2)–S–N	106.89
S–C(1)	1.764	O(1)–S–C(1)	110.60
N–C(8)	1.490	O(2)–S–C(1)	108.03
N–C(9)	1.474	N–S–C(1)	103.30
C(1)–C(2)	1.519	C(8)–N–S	112.05
C(2)–C(3)	1.536	C(9)–N–C(8)	116.5
C(3)–C(4)	1.528	C(9)–N–S	115.05
C(3)–C(8)	1.534	C(2)–C(1)–S	109.8
C(4)–C(5)	1.520	C(3)–C(2)–C(1)	113.9
C(5)–C(6)	1.513	C(2)–C(3)–C(4)	110.8
C(6)–C(7)	1.519	C(2)–C(3)–C(8)	112.3
C(7)–C(8)	1.518	C(4)–C(3)–C(8)	110.0
		C(5)–C(4)–C(3)	112.8
		C(4)–C(5)–C(6)	111.1
		C(5)–C(6)–C(7)	110.7
		C(8)–C(7)–C(6)	110.9
		N–C(8)–C(7)	111.0
		N–C(8)–C(3)	113.2
		C(7)–C(8)–C(3)	111.4

Figure 5**38****Figure 6**

39

Selected bond lengths (Å) and angles (deg.)
for the two molecules (I and II) of the unit cell:

For I	For II
C(1)–N(1) = 1.401	C(17)–N(2) = 1.395
N(1)–S(1) = 1.499	N(2)–S(2) = 1.495
S(1)–O(1) = 1.453	S(2)–O(6) = 1.448
C(1)–N(1)–S(1) = 129.5	C(17)–N(2)–S(2) = 132.8
N(1)–S(1)–O(1) = 119.6	N(2)–S(2)–O(6) = 120.0

Figure 7

8.07.3.2 NMR Spectroscopy: ^1H and ^{13}C

^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy has been applied extensively to the structural elucidation of these heterocyclic compounds. A summary of NMR data of several representative members of the 1,2-thiazine class is given. Fully unsaturated derivatives **40**, **41**, and **27** are characterized by protons with chemical shifts in a range of 8.62–11.04 ppm (Figure 8) <1999TL1505, 2001TL4183>. The C-6 protons have been assigned as the furthest downfield signals: 11.04, 10.77, and 10.97 ppm for **40**, **41**, and **27**, respectively. The ^{13}C NMR spectrum for diphenyl-substituted compound **27** has also been reported. The carbon shifts for C-4 and C-5 are 149 and 152 ppm, while the signals at 164 and 174 ppm are attributed to C-3 and C-6, respectively. Upon solvolysis of fully conjugated thiazine **40** in ethanol, the ^1H NMR spectrum of the product **42** displays an upfield shift of H-3 from 10.12 to 8.07 ppm and H-4 from 8.62 to 6.23 ppm (Figure 9).

40

^1H	C-5Me	C-3	C-4	C-6
δ	2.85	10.12	8.62	11.04
No. of H's	3H	1H	1H	1H
Multi, J (Hz)	s	d, 5	d, 5	s

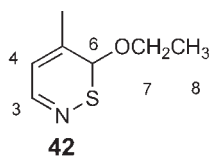
41

^1H	C-4Me & C-5Me	C-3	C-6
δ	2.74 & 2.82	10.03	10.77
	3H, s & 3H, s	1H, s	1H, s

27

	C-3	C-4 & C-5	C-6	Ph
^1H	10.25 (d, J = 1.5 Hz)		10.97 (d, J = 1.5 Hz)	7.34–7.59 (m, 10H)
^{13}C	164.4 (s)	149.2 (s) & 151.5 (s)	174.3 (s)	128.4 (d), 128.5 (d), 129.7 (d), 130.0 (d), 131.1 (d), 133.3 (s), 133.5 (s)

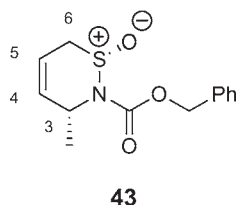
Figure 8



^1H	C-3	C-4	C-5Me	C-6	C-7	C-8
δ	8.07	6.23	2.13	5.08	3.28–3.70	0.88
No. of H's	1H	1H	3H	1H	1H	3H
Multi, J (Hz)	d, 4	d, 4	s	s	m	t, 7

Figure 9

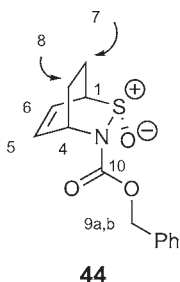
The ^1H NMR spectra of two diastereomeric hetero-Diels–Alder adducts **43** has been obtained (Figure 10) <2004JOC7198>. The diastereotopic α -protons of the sulfonamide (C-6) fall in the range of 3.4–3.5 ppm, while the C-3 protons occur around 4.6 ppm. Both C-4 and C-5 vinylic hydrogens occur in the characteristic region for double-bond protons.



^1H	C-3Me	C-3	C-4	C-5	C-6
δ	1.48	4.62–4.55	6.02	5.73	3.43–3.40
No. of H's	3H	1H	1H	1H	2H
Multi, J (Hz)	d, 7	m	dd, 11.0, 2.7	ddd, 11.0, 6.0, 2.9	m

Figure 10

The ^1H NMR spectrum of a related hetero-Diels–Alder-derived bridged bicyclic compound **44** exhibits proton shifts at a much lower frequency than monocyclic 1,2-thiazine **43**, perhaps reflecting the ring strain and shielding effects in compound **44** (Figure 11) <2002TA2407>. Similar to the previous case, the C-4 hydrogens of **44** resonate at a higher frequency than the C-1 hydrogen and the vinylic C-5 proton is downfield relative to the C-6 proton. Curiously, the C-5 hydrogen is observed at 6.9 ppm, perhaps due to shielding interactions by the *N*-Cbz (carbobenzyloxy) group.

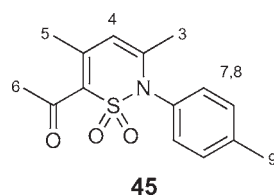


^1H	C-1	C-4	C-5	C-6	C-7	C-7 & C-8	C-8
δ	4.23	5.17	6.90	6.32	1.63–1.55	1.83–1.70	1.29–1.19
No. of H's	1H	1H,	1H	1H	1H	2H	1H
Multi, J (Hz)	t, 5.2	br s	t, 7.5	t, 7.3	m	m	m

^{13}C	C-1	C-4	C-5	C-6	C-7	C-8
δ	55.7	48.7	136.6	125.9	15.3	24.0

Figure 11

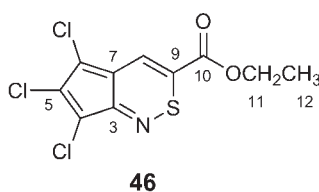
The C-4 hydrogen of the sulfonamide **45** occurs at 6.02 ppm in the proton NMR, while the C-3 and C-5 methyl substituents are found at 1.90 and 2.28 ppm (Figure 12) <1999JPR37>.



^1H	C-3Me & C-5Me	C-4	C-6	Ar-7	Ar-8	C-9
δ	1.90 & 2.28	6.02	2.42	7.32	7.23	2.36
No. of H's	3 H & 3 H	1 H	3 H	2 H	2 H	3 H
Multi, J (Hz)	s & s	s	s	d, 7.7	d, 7.2	s

Figure 12

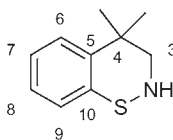
Fully conjugated thiazine **46** has only one hydrogen (C-8) in the 1,2-thiazine ring which is observed at 8.59 ppm, while the resonance of the attached carbon atom occurs at 141.4 ppm in the ^{13}C NMR spectrum (Figure 13) <2005JOC9314>.



	C-3	C-4 to C-7 & C-9	C-8	C-10	C-11	C-12
^1H			8.59		4.48	1.45
^{13}C	151.7	112.0, 112.1, 118.6, 124.7, 132.1	141.4	161.8	62.7	14.2

Figure 13

The ^1H and ^{13}C NMR spectra of 1,2-dihydrobenzothiazine **47** were obtained and the only 1,2-thiazine ring hydrogen resonance was observed at 3.17 ppm (Figure 14) <2000JOC8152>.



	C-3	C-4	C-4Me	C-5 to C-10
^1H	3.17 (br s, 2 H)		1.28 (s, 6 H)	6.86 (m, 1 H), 7.04 (m, 2 H), 7.36 (m, 1 H)
^{13}C	59.9	31.5	29.1	121.8, 125.2, 126.6, 127.8, 134.7, 140.5

Figure 14

The ^1H NMR spectrum of simple *N*-methyl-substituted oxicam **48** has been determined (Figure 15) <1997JME980>. The *N*-methyl group occurs at 2.95 ppm, while the methyl ester protons are observed at 3.96 ppm. The aromatic protons (C-3 to C-6) occur as an unresolved multiplet in the range of 7.71–8.05 ppm.

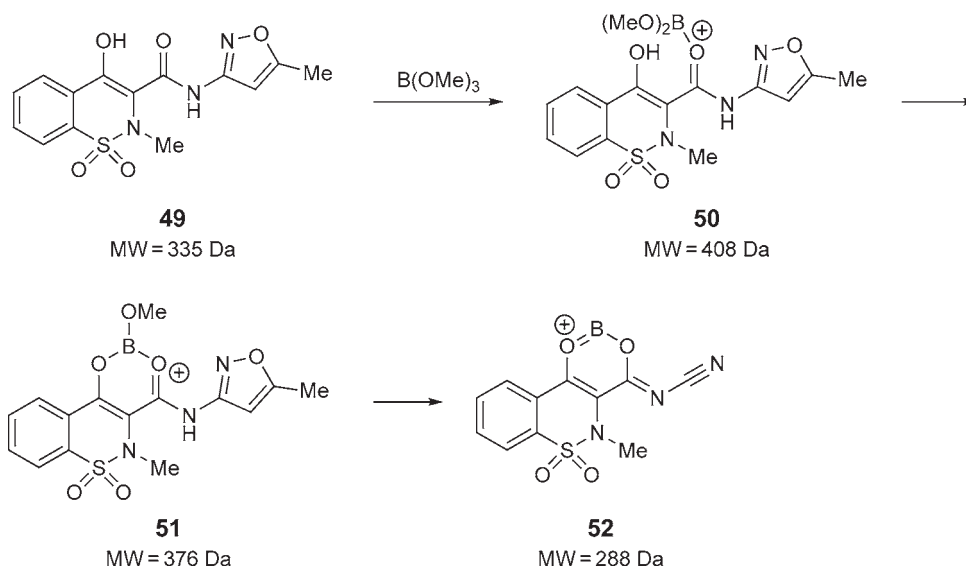
48

^1H	C-1	C-2	C-3 to C-6	C-7OH
δ	2.95	3.96	7.71–8.05	12.05
No. of H's	1	1	4	1
Multi, J	s	s	m	s

Figure 15

8.07.3.3 Mass Spectrometry

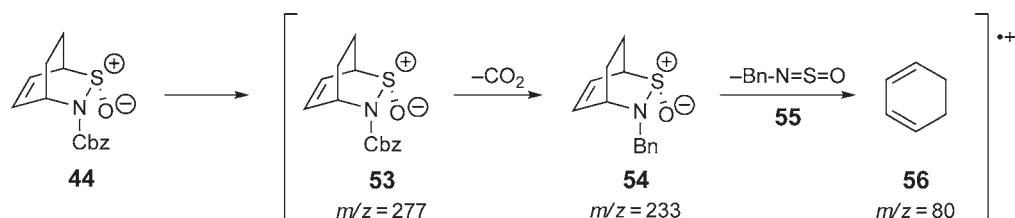
The efficacy of trimethyl borate for the chemical ionization of Lewis-basic pharmaceutically relevant molecules has been demonstrated (**Scheme 4**) <1997JMP846>. In general, upon treatment of the donor analyte with trimethyl borate, a molecular ion of either $[\text{M}+73]^+$ or $[\text{M}+41]^+$ is most often observed, corresponding to $\text{M}+\text{B}(\text{OMe})_2^+$ and $\text{M}+\text{B}(\text{OMe})^+$, respectively. In the case of isoxicam **49** (MW = 335), the major ion **50** is at 408 Da due to $\text{M}+\text{B}(\text{OMe})_2^+$. Tandem mass spectrometry was utilized to examine the fragment fingerprint of this boronate ion. The major fragments **51** and **52** are proposed to arise from loss of methanol and fragmentation of the isoxazole ring.



Scheme 4

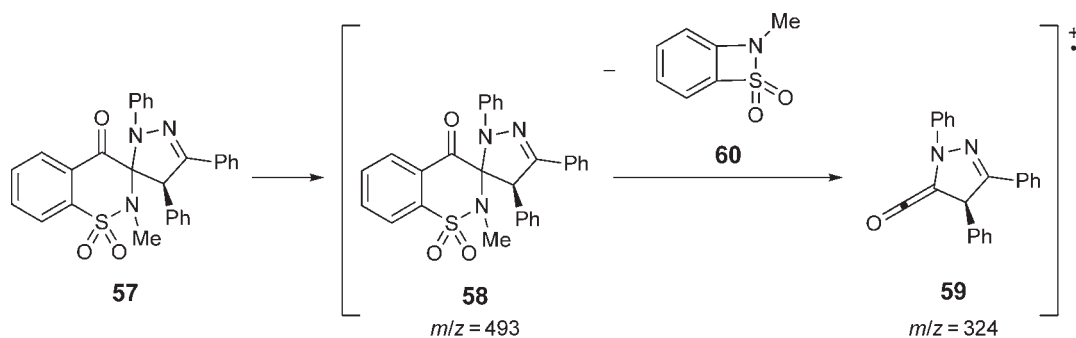
Application of electron impact ionization mass spectrometry (EI-MS) techniques for the analysis of 1,2-thiazines has waned since the publication of CHEC-II(1996). In one recent example of this technique, bicycle **44** was ionized at 70 eV and 180 °C to afford radical cation **53**, **54** via loss of CO_2 , and *N*-sulfinyl compound **55** and 1,3-cyclohexadiene radical cation **56** via a retro-[4+2] reaction in the gas phase (**Scheme 5**) <2002TA2407>.

Another application of EI-MS involves the spirocycle **57** (**Scheme 6**) <1994CJC1424>. Fragmentation of **58** at 70 eV afforded a rather complex spectrum, although the peaks at $m/z = 493$ (M^+) and 324 have been assigned the structures **58** and **59**, respectively, via loss of **60**.



<i>m/z</i>	% Relative intensity
277	0.2
233	2
107	3
91	100
80	35

Scheme 5



<i>m/z</i> (70 eV)	Relative intensity
493	7.9
388	2
324	36
296	3
221	3
195	7.9
178	14
104	15.8
69	100

Scheme 6

Both electrospray and chemical ionization techniques have found broad application in the structural elucidation of highly sensitive 1,2-thiazines (Figure 16). High-resolution mass spectrometry applied to sulfonamide **61** <2004OL2201> and isoxazole-fused 2,1-benzothiazine **62** <2004SL101> showed the molecular ions plus Na^+ . The peak corresponding to $[\text{M-H}]^-$ is observed upon electrospray ionization of benzothiazine 1,1-dioxide **36** in the negative mode of the mass spectrometer <2003BML2527>.

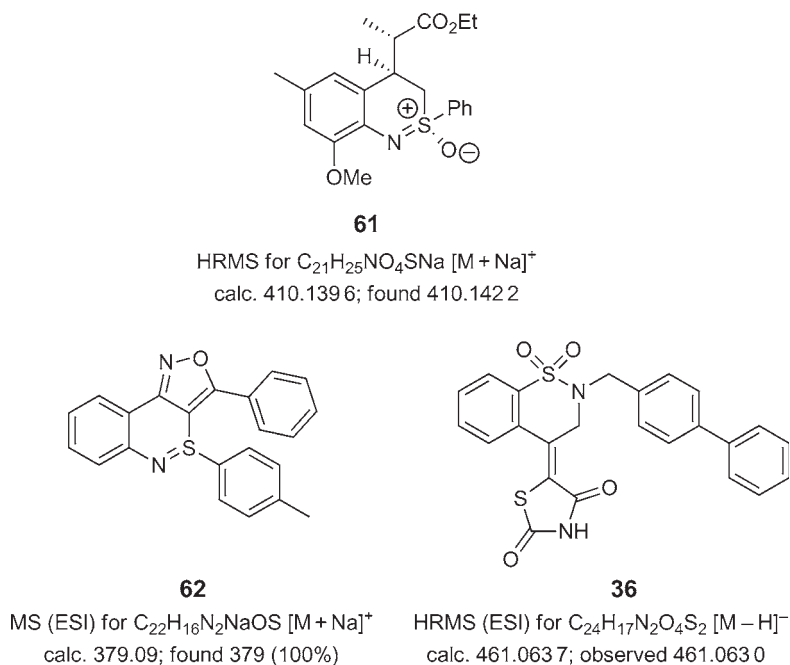
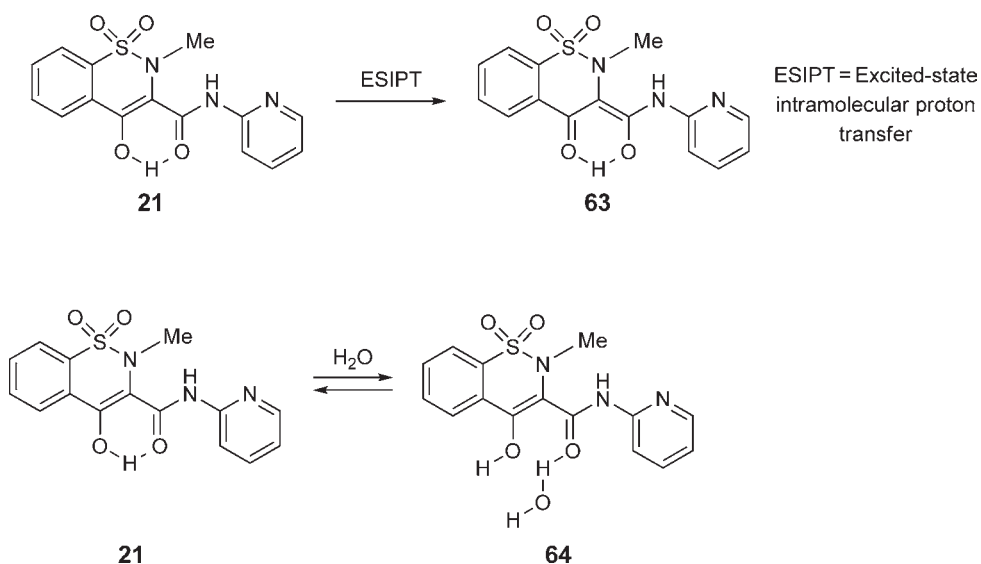


Figure 16

8.07.3.4 UV/Fluorescence

The fluorescence spectrum of the nonsteroidal anti-inflammatory agent piroxicam **21** has been determined in a variety of solvents (Scheme 7) <1999PCP4213>. The key observations are that the molecule exists with a strong H-bond between the phenolic OH and the adjacent amide. A very high Stokes shift in the excited state was observed and attributed to the proton-transfer event (tautomerization) between the phenolic and amide oxygens (cf. **21** → **63**). In the case of protic solvents, such as water, the open conformation **64** was observed.



Scheme 7

8.07.3.5 IR Spectroscopy

Infrared (IR) spectroscopy has rarely been utilized for the structural elucidation of 1,2-thiazines, mainly due to a lack of a characteristic N–S absorption. Sulfur oxides do exhibit characteristic symmetrical and asymmetrical stretching vibrations, which in 1,2-benzothiazine **36** occur at 1340 cm^{-1} and 1167 cm^{-1} , respectively (Figure 17) <2003BML2527>.

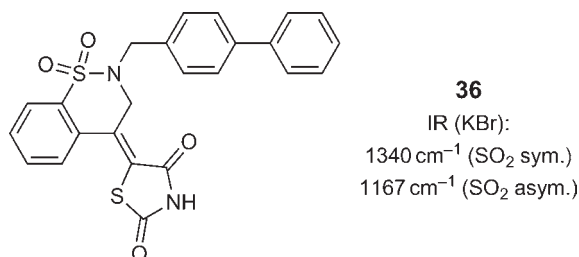


Figure 17

IR spectroscopy of dihydro-1,2-thiazines (cf. **65**) is useful for the elucidation of the tautomeric form present, where the C=N stretch is observed at 1450 cm^{-1} (Figure 18) <1999TL1505>.

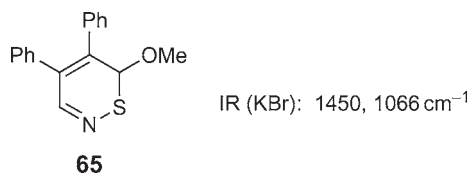


Figure 18

The S(VI)-oxidized compound **61** exhibits a complex IR spectrum due to the various functionalities (Figure 19) <2004OL2201>. Aromatic C–H stretches are observed at 2978 and 2937 cm^{-1} . The C=O stretching peak occurs at 1724 cm^{-1} , S=N at 1462 cm^{-1} , S–O at 1258 cm^{-1} , and C–O 1155 cm^{-1} .

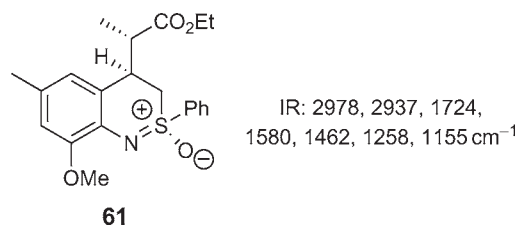


Figure 19

Bicyclic Diels–Alder adduct **53** has a carbonyl stretching absorption at 1717 cm^{-1} , S–O at 1297 cm^{-1} , and 1117 cm^{-1} , and BnO at 1094 cm^{-1} (Figure 20) <2002TA2407>.

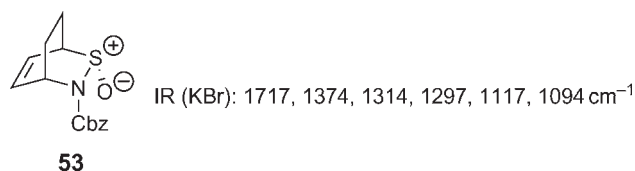
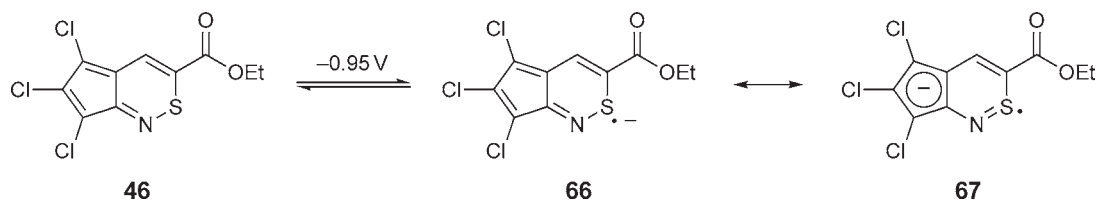


Figure 20

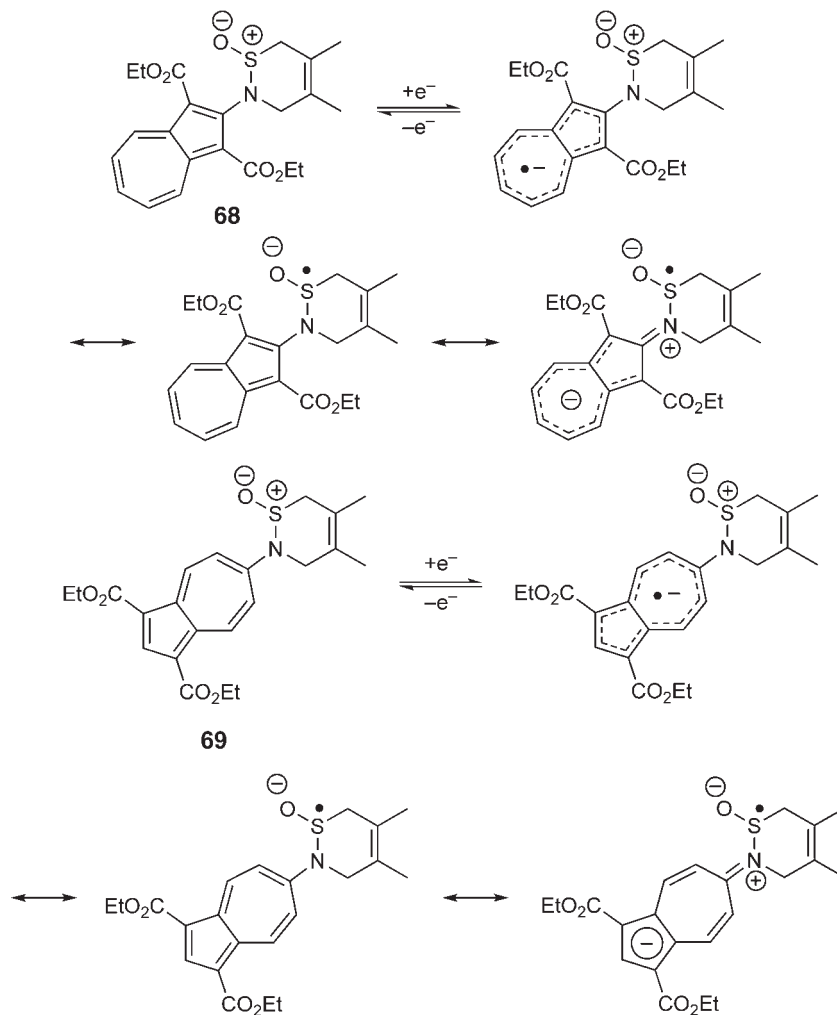
8.07.3.6 Redox Potentials

The peak potentials from the cyclic voltammetry of 2,1-cyclopentathiazine **46** were registered at 100 mV s^{-1} in a $5 \times 10^{-4} \text{ M}$ solution in DCM <2005JOC9314>. This material displayed a reversible reduction wave at -0.95 V , which is attributed to the stability of the delocalized cyclopentadienyl radical anion, as depicted in resonance structures **66** and **67** (Scheme 8).



Scheme 8

The azulenes **68** and **69** displayed a reversible reduction wave at -1.48 V for **68** and -1.42 V for **69**, which have been attributed to the delocalization of the radical anion between the azulene and 1,2-thiazine ring systems (Scheme 9) <2003T4651>.



Scheme 9

8.07.4 Thermodynamic Aspects

8.07.4.1 Melting Points

Several 1,2-thiazines show potential for application in liquid crystal displays. In one such example, liquid crystalline transition temperatures were recorded for compound **70** (Figure 21) <1996JOC9178>. At a temperature below 200 °C, 1,2-thiazine **70** exists as a crystalline solid. Upon heating **70** from 215 °C to the melting point of 240 °C the material exists as a liquid crystalline mesophase, which displays birefringence observed using a hot-stage polarizing microscope.

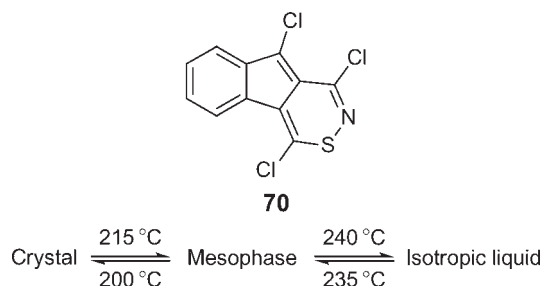


Figure 21

The majority of 1,2-thiazines are solids at room temperature and therefore have been characterized by their melting points. A few representative examples are listed in Figure 22. The 1,2-thiazines **47** <2000JOC8152> and

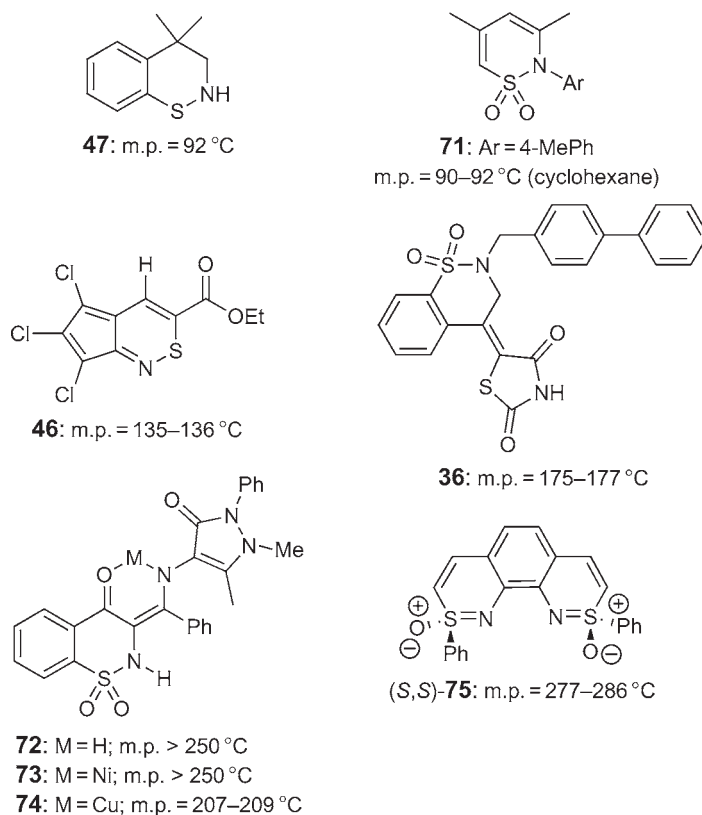
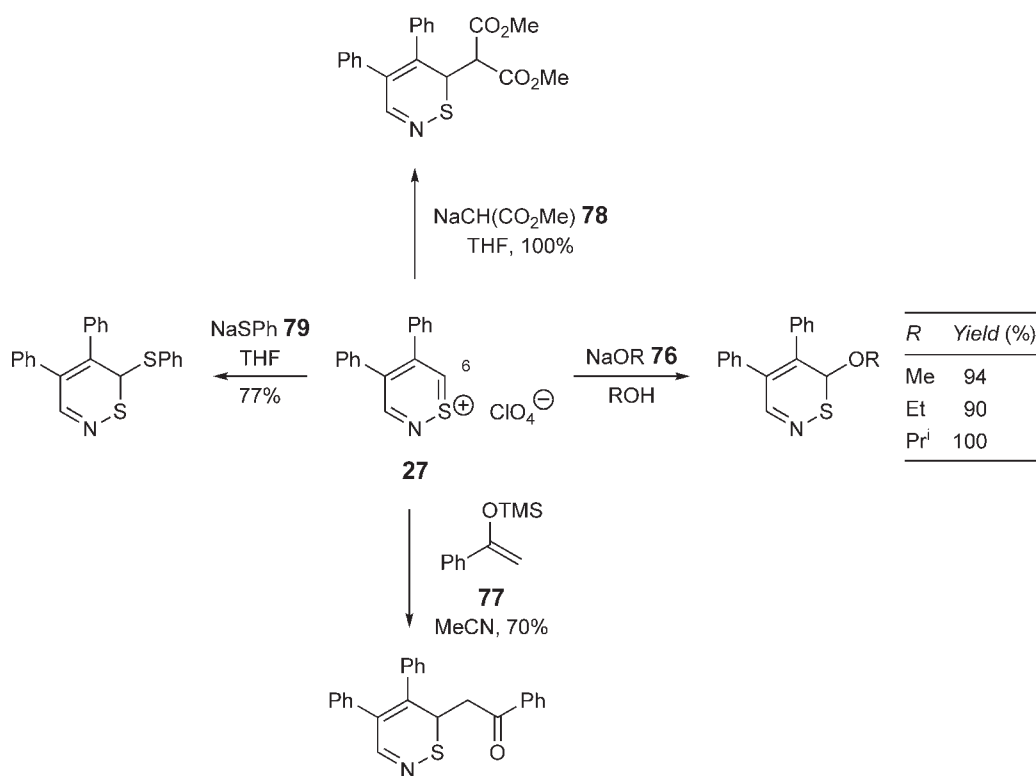


Figure 22

71 <1999JPR37> display much lower melting points than the corresponding 1,2-thiazines **46** <2005JOC9314> and **36** <2003BML2527>. The melting points of coordination compounds of oxicam, **73** and **74**, have been measured and compared to the parent oxicam **72** <2004POL1909>. While both the parent molecule **72** and its nickel salt **73** have similar melting points, the copper complex **74** exhibits significant melting point depression. The S(vi)-oxidized fully conjugated compound **75** displays the highest melting point of the group at 277–286 °C <2001OL3321>.

8.07.5 Reactivity of Fully Conjugated Rings

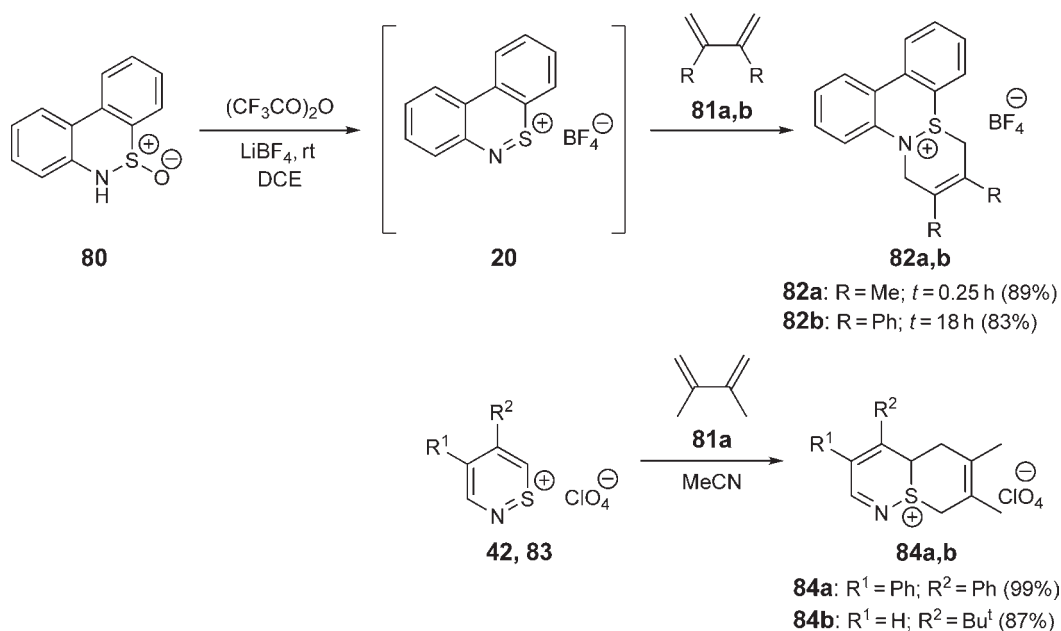
Fully conjugated species are somewhat rare in the 1,2-thiazine class of heterocycles. These molecules are comprised of two separate subclasses, the first of which includes the highly reactive 1,2-thiazinylium salts. Although these salts, such as **27**, have in some cases been isolated, they readily react regioselectively at C-6 with a variety of nucleophiles including sodium alkoxides **76**, silyl enol ethers **77**, sodium malonates **78**, and sodium thiophenoxide **79** (Scheme 10) <2001T8965>.



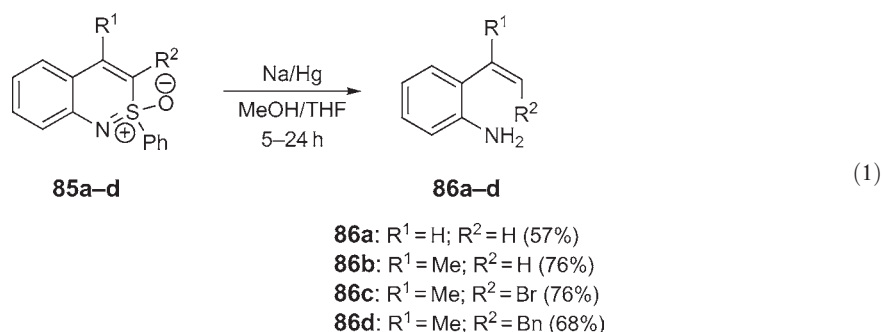
Scheme 10

The polar cycloaddition of the *in situ*-prepared 1,2-thiazinylium salt **20** from *N*-oxide **80** (*vide infra*) with 2,3-disubstituted butadienes **81a** and **81b** affords adducts **82a** and **82b** (Scheme 11) <1999TL95>. Mono- and disubstituted salts **42** and **83** are more stable than the diphenyl-1,2-thiazinylium salt **20** and can in fact be isolated. These dienophiles undergo [4+2] cycloaddition reactions with butadiene **81a** affording products **84a** and **84b** with a different regioselectivity than dibenzo-1,2-thiazinylium salts **82a** and **82b** <1999TL1505, 2001TL4183>.

The second class of fully conjugated ring systems include the S(vi) oxidation state compounds, such as **85a–d**, which react only under forcing conditions. For instance, the 2-alkenylanilines **86a–d** have been prepared via the reduction of sulfoximines **85a–d** with sodium amalgam (Equation 1) <1995S713>. In the case of disubstituted sulfoximines **85c** and **85d**, the major products **86c** and **86d** of this reaction contain a (*Z*)-double bond. The corresponding (*E*)-by-products are usually isolated in <10% yield.



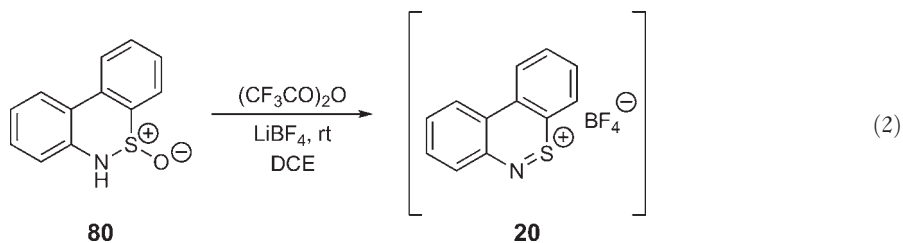
Scheme 11

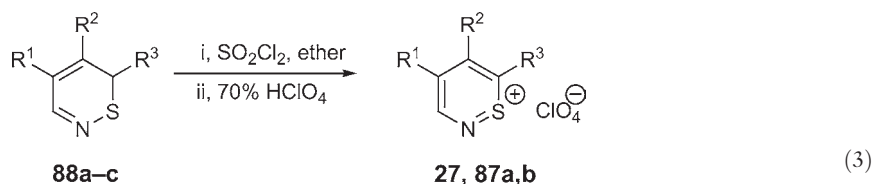


8.07.6 Reactivity of Nonconjugated Rings

8.07.6.1 Elimination

A variety of fully conjugated 1,2-thiazines have been synthesized via elimination reactions of compounds containing an appropriate leaving group. A thiazinylium tetrafluoroborate **20** was formed *in situ* by the reaction of dibenzothiazine *S*-oxide **80** with TFAA and LiBF₄ (Equation 2) <1999TL95>. Thiazinylium perchlorates **27**, **87a** and **87b** were synthesized via chlorination of thiazine **88a–c** with SO₂Cl₂ and perchloric acid, followed by subsequent elimination of HCl (Equation 3) <2001T8965, 2001TL4183>. Similarly, thiazinylium triflate **89** was obtained by the treatment of 6*H*-1,2-thiazine **90** with SO₂Cl₂ and triflic acid (Equation 4) <2001TL4183>.

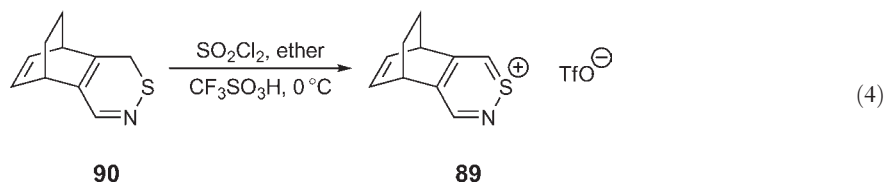




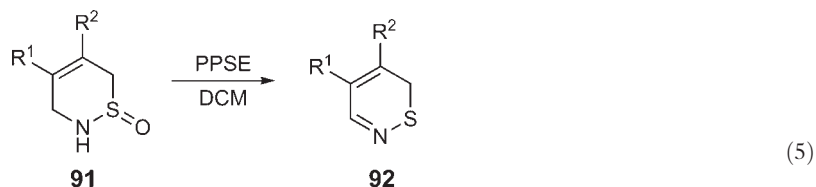
27: $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$ (85%)

87a: $R^1 = R^2 = \text{Ph}$; $R^3 = 3,4-(\text{MeO})_2\text{C}_6\text{H}_3$ (100%)

87b: $R^1 = R^3 = \text{H}$; $R^2 = \text{Bu}^t$ (87%)



Conversion of 3,6-dihydro-2*H*-1,2-thiazine 1-oxides **91** to 6*H*-1,2-thiazines **92** takes place in the presence of the dehydrating agent polyphosphoric acid trimethylsilyl ester (PPSE) (Equation 5) <2001TL4183>.

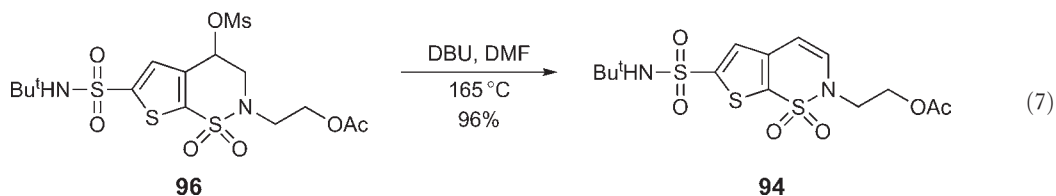
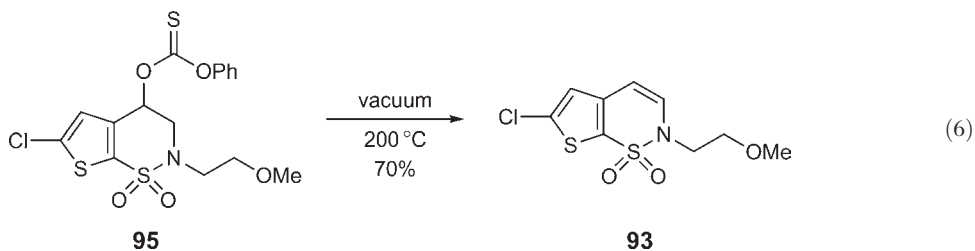


$R^1 = \text{H}$; $R^2 = \text{Me}$ (100%)

$R^1 = R^2 = \text{Me}$ (91%)

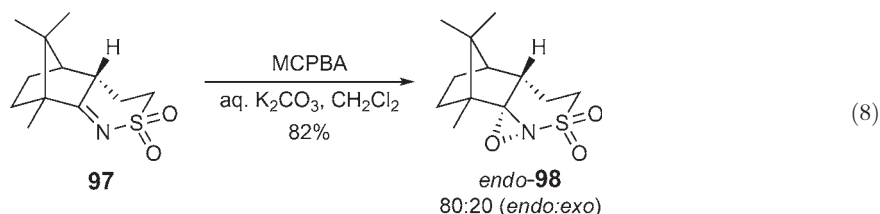
$R^1 = \text{H}$; $R^2 = \text{Bu}^t$ (89%)

Related thieno[3,2-*e*][1,2]thiazines **93** and **94** have been prepared by the pyrolysis of **95** (Equation 6) <2005BMC2052> and the base-promoted methanesulfonate elimination of **96** (Equation 7) <2000BMC957>.

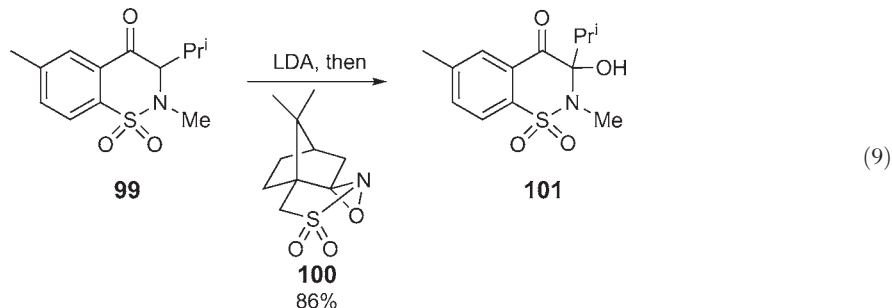


8.07.6.2 Oxidation

Oxaziridination of bridged bicyclic *N*-sulfonylimine **97** with *m*-chloroperbenzoic acid (MCPBA), in the presence of K_2CO_3 , affords *endo*-compound **98** in high yields and 60% de (Equation 8) <1997JOC3625>.

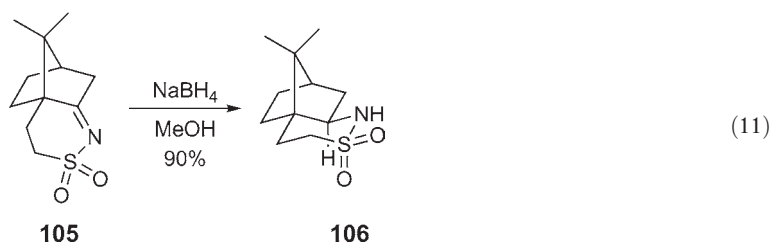
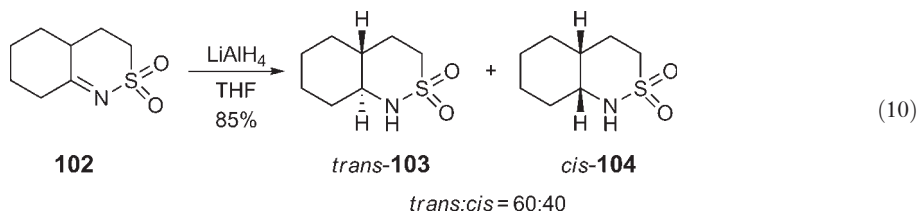


Hydroxylation of 4-oxo-substituted 1,2-thiazine **99** via the racemic Davis oxaziridine reagent **100** afforded alcohol **101** in good yields. Efforts to produce **101** as a single enantiomer with chiral oxaziridine reagents afforded products with only a modest 46% ee (Equation 9) <2002EJP221>.

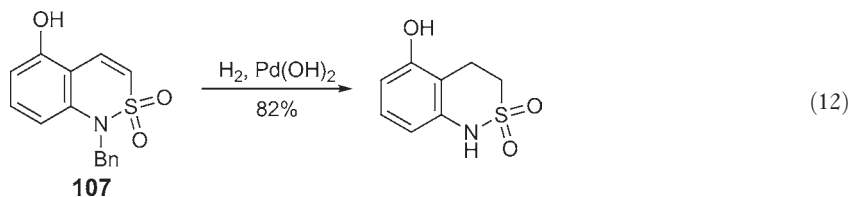


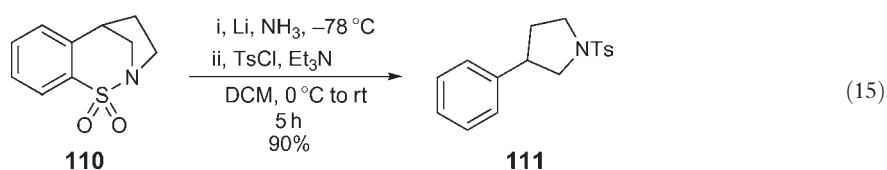
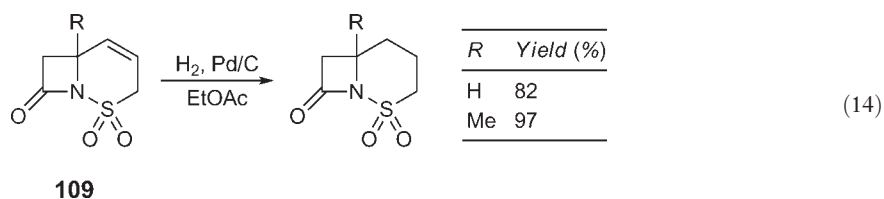
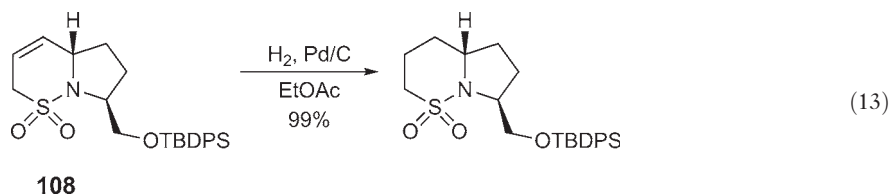
8.07.6.3 Reduction

Reduction of *N*-sulfonimine **102** with LAH affords a 60:40 mixture of *trans*:*cis* reduced bicyclic perhydro-1,2-thiazines **103** and **104** in 85% combined yield (Equation 10) <1998CJC164>. In contrast, the NaBH₄ reduction of bridged bicycle **105** affords compound **106** as a single diastereomer (Equation 11) <2002HCA1973>.



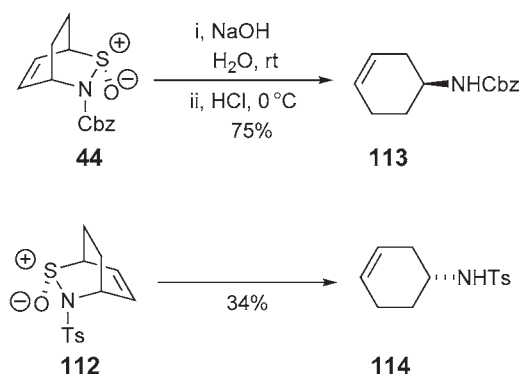
Hydrogenation of the double bond of 2,1-benzothiazine 1,1-dioxide **107** occurs with concomitant removal of the *N*-benzyl group (Equation 12) <1994TL2911>. Hydrogenation is commonly employed with alkenes **108** and **109**, which are the products of ring-closing metathesis (Equations 13 and 14) <2003T7047, 2004S1696>. Dissolving metal reduction of bicyclic aryl sulfonamides such as **110** has been used to synthesize 3-aryl-substituted pyrrolidines **111** (Equation 15) <2005OL43>.





8.07.6.4 Addition of Nucleophiles

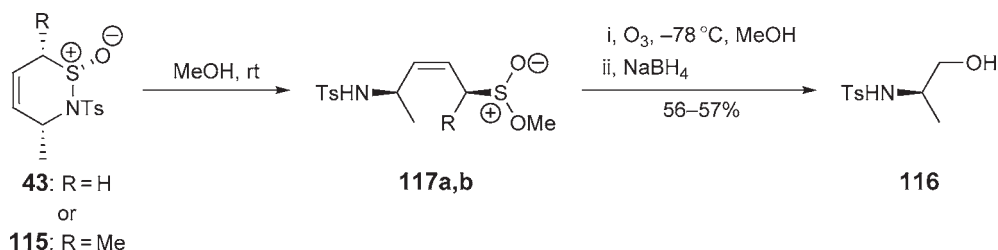
Solvolysis of Diels–Alder adducts provides a useful means of preparing a variety of nitrogen-containing compounds. For instance, the hydrolysis of *N*-Cbz or *N*-Ts bicyclic sulfonamides **44** and **112** with NaOH affords the homoallylic carbamate **113** and sulfonamide **114**, respectively (Scheme 12) <2000TL3743, 2002TA2407>. Related hydrolysis reactions have also been reported with monocyclic 1,2-dihydrothiazine oxides <2004JOC7198>.



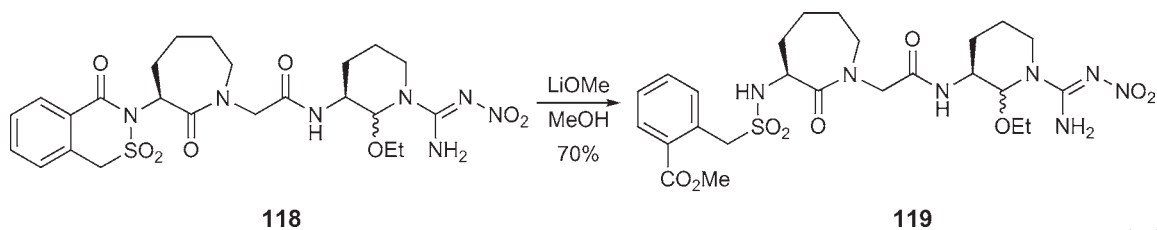
Scheme 12

Methanolysis of *N*-Cbz bicyclic sulfonamides **43** or **115** was used to furnish tosyl-protected amino alcohol **116** after ozonolysis and reductive workup of the intermediate sulfoxides **117a** and **117b** (Scheme 13) <2004JOC7198>.

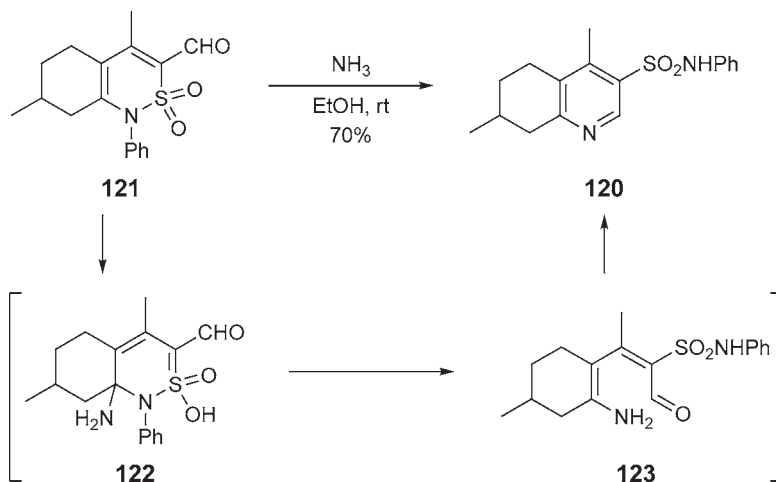
Ring opening of a 1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide **118** with lithium methoxide has been accomplished in good yield to afford sulfonamide ester **119** (Equation 16) <1998BML3683>.



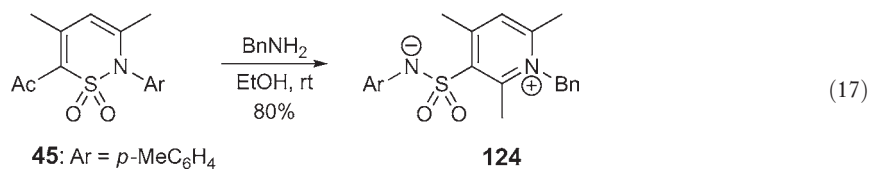
Scheme 13



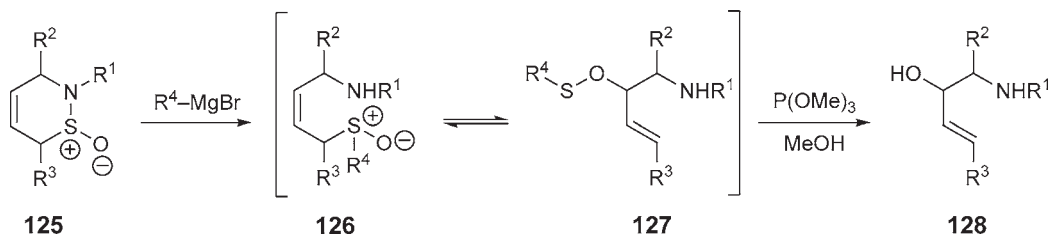
A facile transformation to pyridine-3-sulfonanilides **120** is observed upon treatment of 1,2-dioxo-1,2-thiazine-6-carbaldehydes **121** with ammonia in EtOH (**Scheme 14**) <1996S1375>. The reaction is believed to take place by the addition of ammonia to the 3-position of the 1,2-thiazine 1,1-dioxide ring to form intermediate **122**, followed by ring cleavage and cyclization via attack of nitrogen onto the aldehyde substituent of compound **123**. Analogous reactions are observed with NH₂OH or RNH₂ as nucleophiles, which afford either pyridine *N*-oxides or pyridinium salts, respectively. For example, the reaction of 1,2-thiazine 1,1-dioxide **45** with benzylamine furnishes zwitterion **124** in 80% yield (**Equation 17**) <1999JPR37>.



Scheme 14

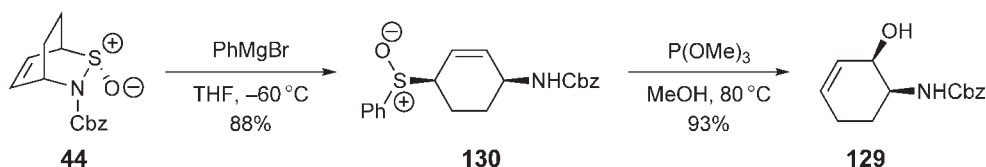


The Grignard addition/rearrangement sequence of 3,6-dihydro-1,2-thiazine 1-oxides and 1-imines to allylic amino alcohols and allylic diamines continues to find important synthetic applications (**Scheme 15**). The mechanism of this transformation generally involves addition of the organometallic reagent to the sulfur of the 1,2-thiazine derivative **125** and concurrent ring cleavage. Following the aqueous workup of the Grignard adduct, the sulfoxide **126** is converted to a sulfenate ester **127** via a [2,3]-sigmatropic rearrangement. *In situ* desulfurization with trimethyl phosphite of sulfenate ester **127** affords the corresponding allylic alcohol **128** (see CHEC-II(1996) <1996CHEC-II(6)349> for a full discussion of the mechanism and scope of this reaction). This methodology has found application in the synthesis of benzodiazepines and benzothiadiazepines (see **Section 8.07.12.5**).



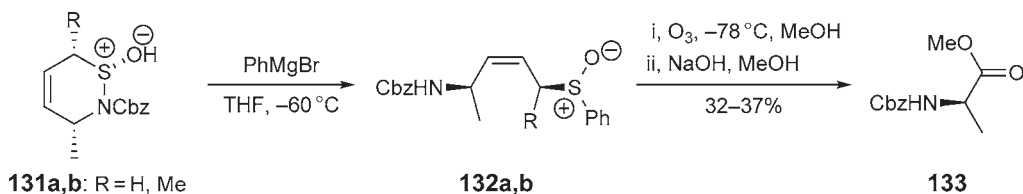
Scheme 15

One notable advance in this chemistry since the publication of CHEC-II(1996) is the use of enantiomerically enriched 3,6-dihydro-1,2-thiazine 1-oxides in the rearrangement sequence. For instance, *N*-Cbz-protected bicyclic 1,2-dihydrothiazine **44** undergoes ring opening upon treatment with phenylmagnesium bromide (**Scheme 16**). The synthesis of allylic amino alcohol **129** is completed in excellent yield upon exposure of the intermediate sulfoxide **130** to trimethyl phosphite and methanol at 80 °C <2002TA2407, 2000TL3743>.



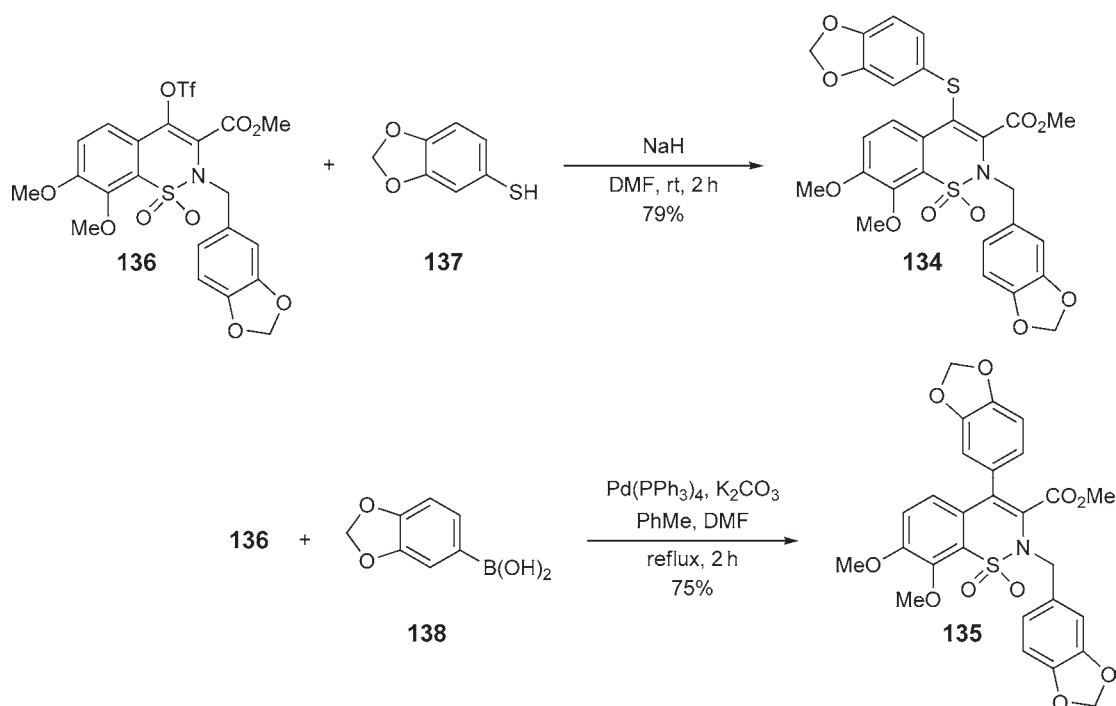
Scheme 16

It is also possible to intercept the chiral sulfoxide intermediate and convert this species to an α -amino ester. Thus, the Grignard addition to dihydro-1,2-thiazine 1-oxides **131a** and **131b** followed by NH_4Cl workup and subsequent ozonolysis of **132a** and **132b** affords amino ester **133** with excellent retention of the absolute stereochemistry (**Scheme 17**) <2004JOC7198>.



Scheme 17

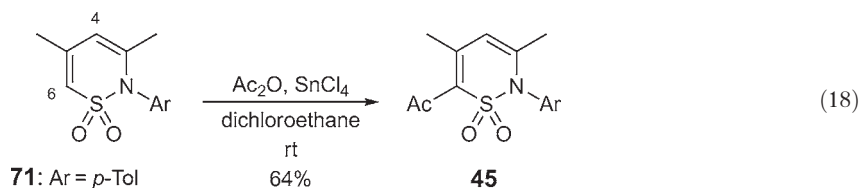
Endothelin receptor antagonists **134** and **135** were prepared from the triflated oxicam derivative **136** (**Scheme 18**) <1998BMC1447>. Addition of aryl thiol **137** to the C-4 position gave product **134**. Palladium-catalyzed Suzuki coupling of aryl boronic acid **138** and aryl triflate **136** affords the sulfonamide product **135**.



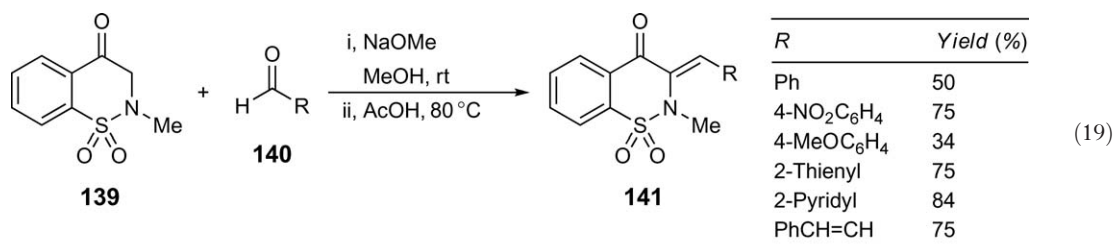
Scheme 18

8.07.6.5 Addition of Electrophiles to Ring Carbon

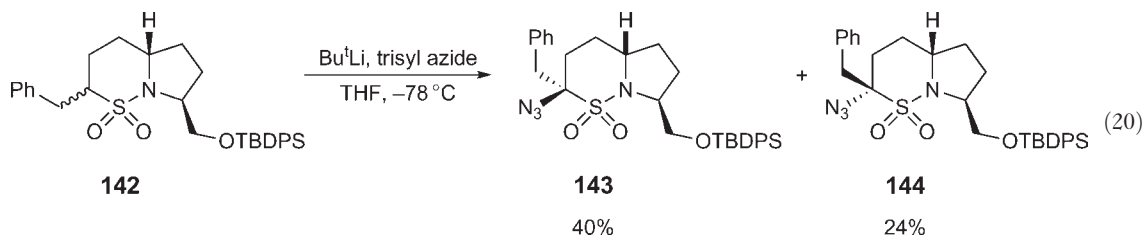
The reactions of 1,2-thiazine 1,1-dioxides with electrophiles can often lead to a mixture of products due to competing addition at C-4 and C-6. A selective Friedel–Crafts-type acylation of the C-6 position of the 1,2-thiazine 1,1-dioxo ring was observed in reaction of 3,5-dimethyl-1,2-thiazine 1,1-dioxide **71** with anhydrides, such as acetic anhydride, furnishing compound **45** (Equation 18) <1999JPR37>.



4-Oxo-1,2-benzothiazine 1,1-dioxide **139** undergoes aldol condensation reactions upon deprotonation with NaOMe and treatment with an aldehyde **140** (Equation 19) <1992SC2621>. The intermediate aldol adducts are then dehydrated with acetic acid to afford condensation products **141** <2000JME2040>.



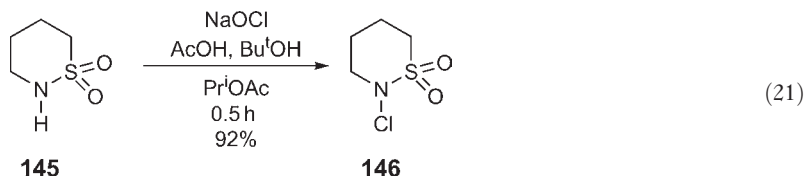
Sulfonamide anions react with a variety of electrophiles, as was showcased in CHEC-II(1996). One example from the recent literature involves the reaction of bicyclic sulfonamide **142** with trisyl azide to afford approximately a 2:1 mixture of diastereomers **143** and **144** (Equation 20) <2003T7047>.



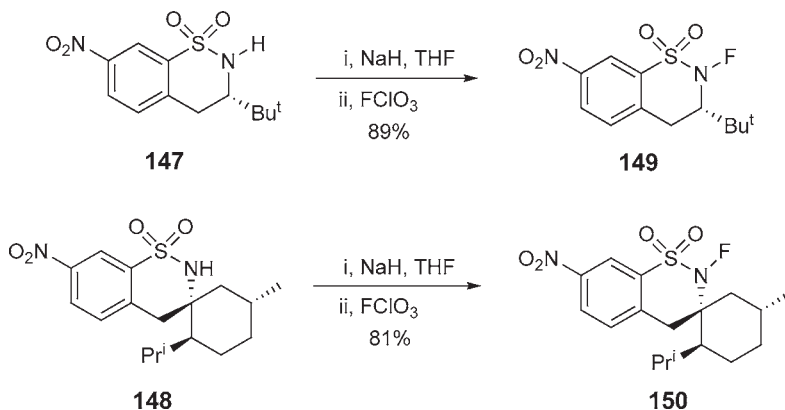
8.07.6.6 Addition of Electrophiles to Ring Nitrogen

8.07.6.6.1 N-Halogenation

Reaction of sulfonamide **145** with *t*-BuOCl in *i*-propyl acetate affords *N*-chlorinated sulfonamide **146** in 92% yield (Equation 21) <2005TL1099>. These conditions provide an attractive industrial-scale process for Bu^tOCl formation, as this oxidant is created *in situ* upon the slow addition of NaOCl to a solution of *t*-BuOH and AcOH, thereby reducing heat generation.



Fluorination of sulfonamides **147** and **148** takes place upon deprotonation with NaH and reaction with perchloryl fluoride, FClO₃, to give products **149** and **150** (Scheme 19) <2000JOC7583, 2000CPB1954>. The resulting *N*-fluorosultams **149** and **150** have been used for the asymmetric fluorination of aryl ketone enolates (*vide infra*).



Scheme 19

8.07.6.6.2 N-Arylation

Two methods have been described for the catalytic *N*-arylation of tetrahydro-1,2-thiazine 1,1-dioxides (Equation 22; Table 1) <2004TL3305>. The first involves the copper-catalyzed *N*-arylation of sulfonamide **151** in the presence of 2,2'-bipyridine and K₃PO₄ in *N*-methyl-2-pyrrolidone (NMP) at 120 °C. A variety of aryl bromides/iodides and

2-chloro- and 2-bromopyridines react to form compounds **152** in 35–93% yields. *ortho*-Substituents on the aryl ring slow the rate of the reaction. The second method, the Pd-catalyzed reaction with Xantphos and CsCO₃ in toluene at 90 or 100 °C, generally gave results superior to the copper procedure.

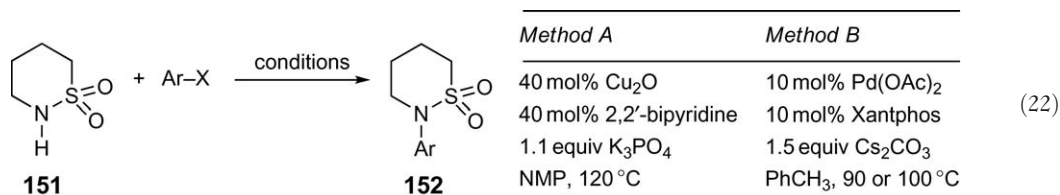
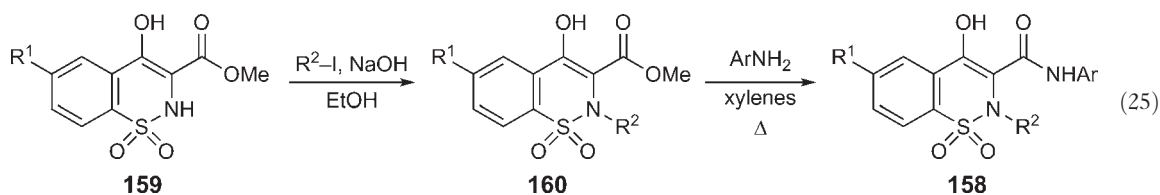
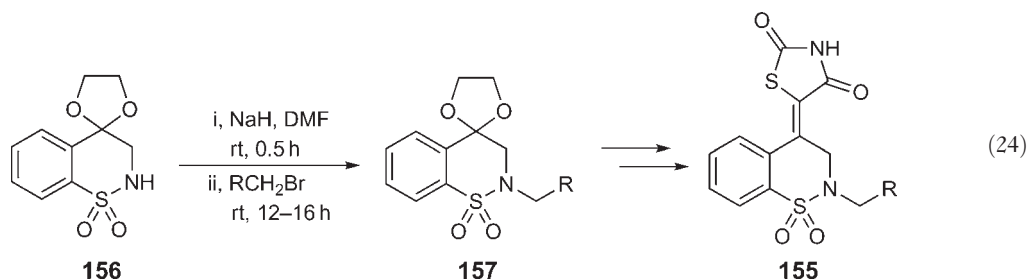
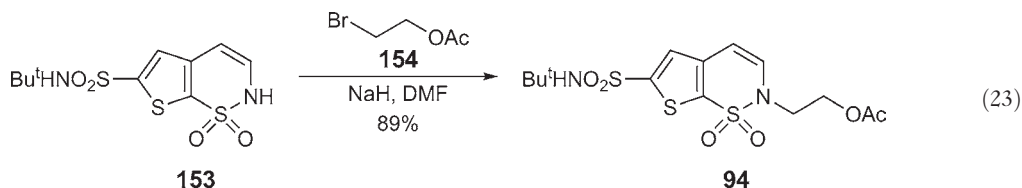


Table 1 Metal catalyzed *N*-arylation reactions

Entry	Ar-X	Method	Temperature (°C)	Time (h)	Yield (%)
1		A	120	6	93
2		B	100	6	62
3		A	120	18	44
4		B	90	3	70
5		A	120	36	35
6		B	100	17	80
7		B	100	28	80
8		B	100	3	89
9		B	100	19	79

8.07.6.6.3 N-Alkylation

N-Alkylation of 1,2-thiazines is an important means of generating small libraries of 1,2-benzothiazine 1,1-dioxides for pharmacological evaluation. For example, the reaction of sulfonamide **153** with an alkyl bromide like **154**, NaH, and DMF was used to prepare carbonic anhydrase inhibitors related to **94** (Equation 23) <2005BMC2052, 2000BMC957>. A library of 5-(1,1-dioxo-1,2-benzothiazin-4-ylidene)thiazolidine-2,4-dione derivatives **155** has been prepared via N-alkylation of 1,2-benzothiazine 1,1-dioxides **156**, followed by subsequent chemistry of alkylated product **157** (Equation 24) <2003BML2527>. Lazer *et al.* have also used this methodology for derivatization at N-1 in combination with an amidation reaction of the C-5 carboxylate group for the synthesis of a library of 4-oxo-1,2-benzothiazine-3-carboxamides **158** from **159** via alkylated product **160** (Equation 25) <1997JME980>.

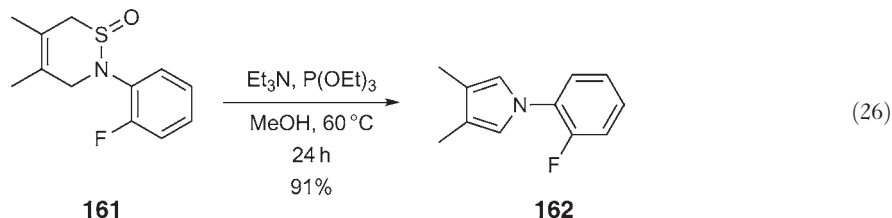


8.07.6.6.4 N-Deprotection

An N-debenzylation reaction with concomitant hydrogenation of a double bond in the thiazine ring was observed with 1,2-thiazine nitrogen **107** (see Equation 12) <1994TL2911>.

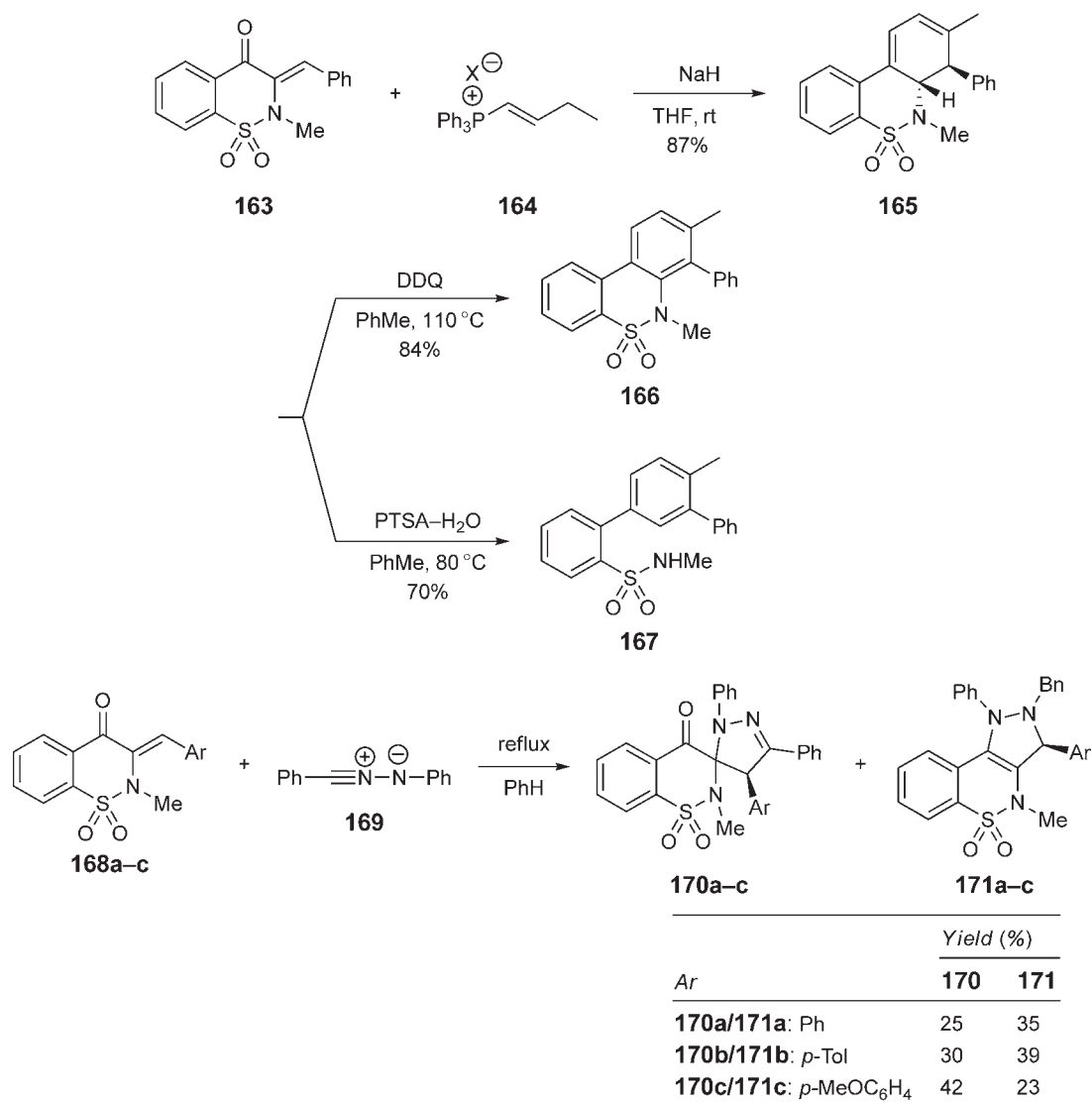
8.07.6.7 Rearrangement: Formation of Pyrroles

The rearrangements of Diels–Alder-derived sulfinamides have been examined for the formation of pyrroles <1996CHEC-II(6)349>. Recently the [4+2] cycloadduct **161** was shown to undergo this rearrangement under mild conditions affording the pyrrole **162** in excellent yield (Equation 26) <2003T9669>, see also <2004TL7553> and <1994SC175>.



8.07.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Since the publication of CHEC-II(1996), there have been very few examples related to the reactivity of substituents attached to ring carbon atoms. One case involves the reaction of 3-benzylidene-2,3-dihydro-2-methyl-1,2-benzothiazin-4-one 1,1-dioxide **163** with the alkylidenephosphorane derived from salt **164** forming the tricyclic-fused ring compound **165** (Scheme 20) <1996J(P1)2541>. This material **165** was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affording the biphenyl **166**. Ring-opened product **167** was produced from **165** upon exposure to *p*-toluene-sulfonic acid and heat.



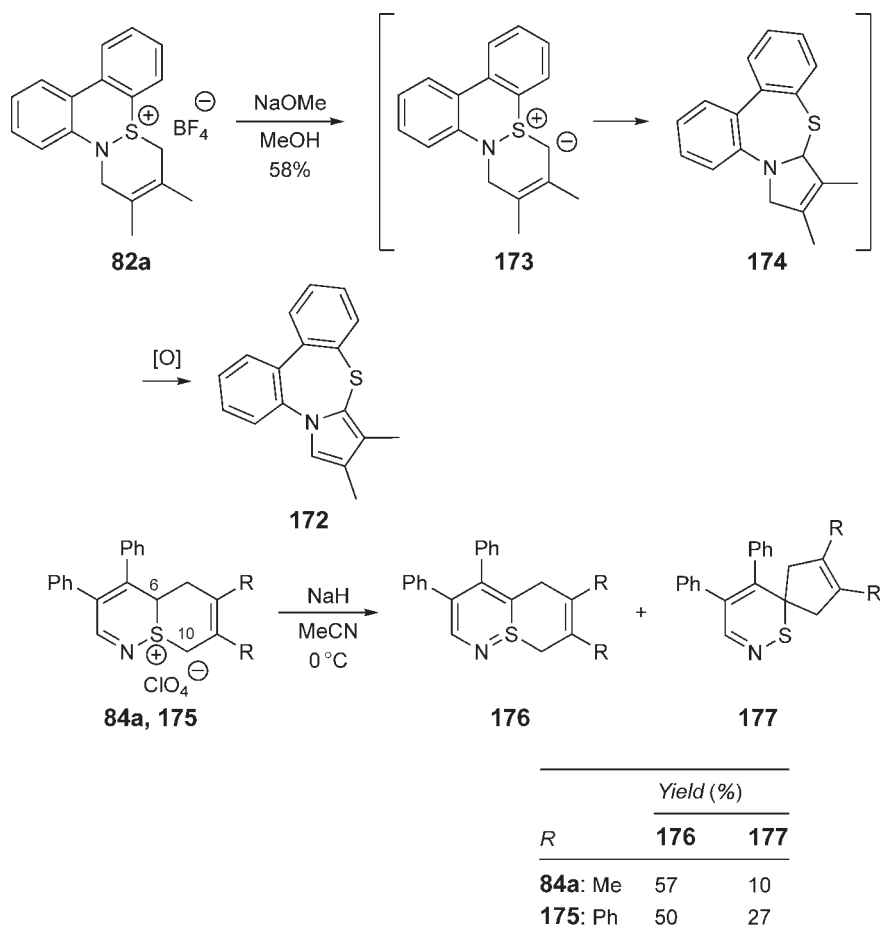
Scheme 20

A reaction occurs with compounds **168a-c** in the presence of diphenylnitrile imine **169** leading to a mixture of products **170a-c** and **171a-c**, whose structures have been determined by X-ray crystallography <1994AXC791, 1994CJC1424>. The authors propose that spirocyclic compounds **170a-c** arise from a [3+2] dipolar cycloaddition reaction, and that fused compounds **171a-c** are formed via the rearrangement of the cycloadduct.

8.07.8 Reactivity of Substituents Attached to Ring Heteroatoms

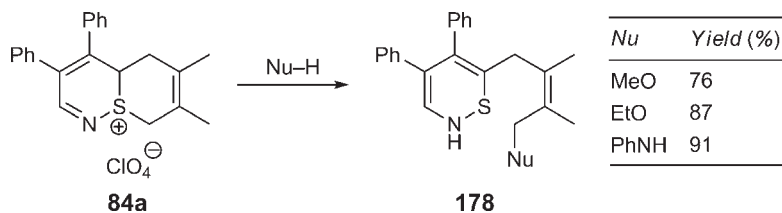
8.07.8.1 Sulfur

A number of transformations are observed involving carbon atoms directly attached to the sulfur atom of 1,2-thiazinylium ions. For example, thiazinylium tetrafluoroborate **82a** reacts with NaOMe in MeOH to afford pyrrole **172** in 58% yield (Scheme 21) <1999TL95>. The proposed mechanism for this transformation involves initial deprotonation of **82a** by base to give **173** and migration of the ylide carbon to the neighboring amino group, followed by oxidative aromatization of intermediate **174**. In the absence of a nucleophile, 1,2-thiazinylium ions such as **84a** and **175** undergo deprotonation at both C-6 and C-10 to afford fully conjugated 1,2-thiazinylium salts **176** along with spirocyclized, rearrangement products **177** <1999TL1505>.



Scheme 21

The reaction of 1,2-thiazinylium salt **84a** with nucleophiles yields ring-opened products **178** by cleavage of the S–C bond (Equation 27) <1999TL1505>.

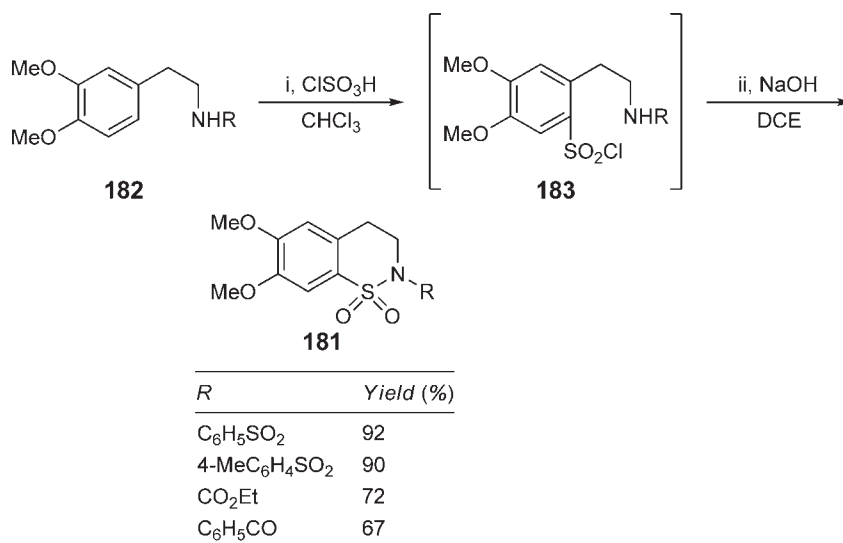


(27)

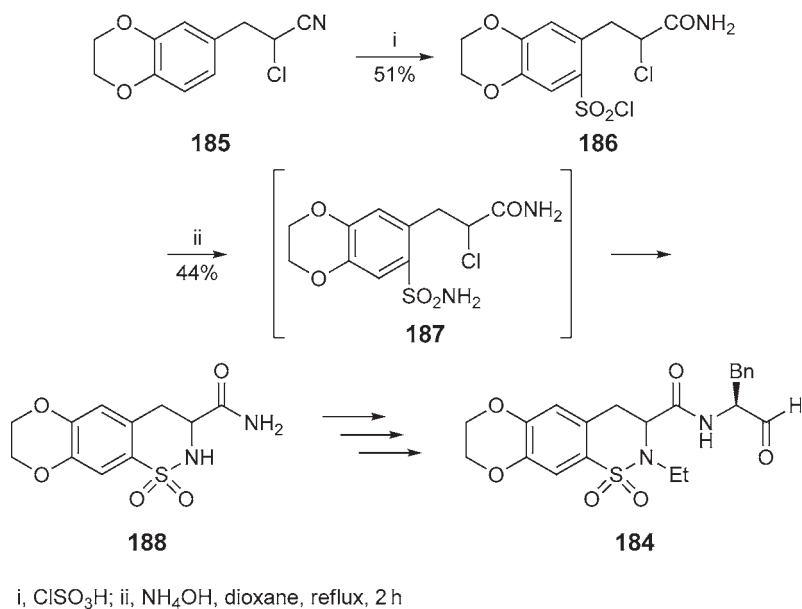
8.07.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

8.07.9.1 Introduction

The following section provides an update to the synthesis of the title ring systems covering material published from 1996 to 2006. Similar to CHEC-II(1996), this information is organized by the type of disconnection, beginning with the one-bond disconnections A–F, followed by [4+2] and [3+3] two-bond disconnections (Figure 23). There have been several notable advancements in the synthesis of 1,2-thiazines since the publication of CHEC-II(1996). For one,

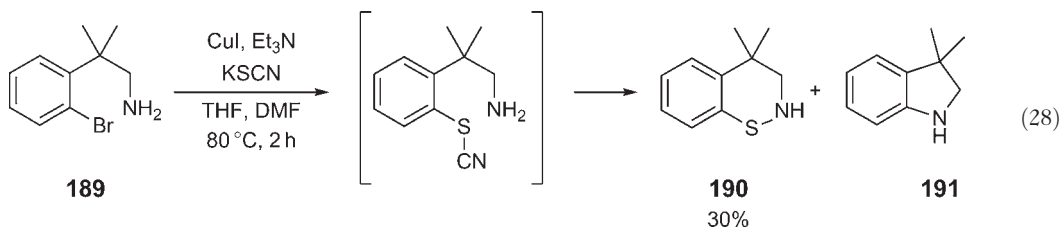


Scheme 23

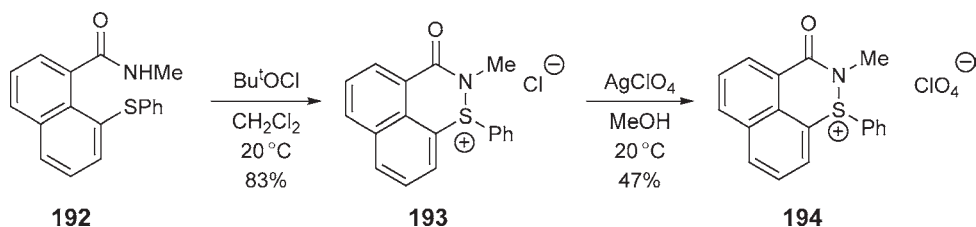


Scheme 24

A variety of methods exist for the formation of 1,2-thiazines via the construction of an S–N bond by nucleophilic attack of nitrogen onto a sulfur-bearing leaving group. For example, the reaction of aryl bromide **189** with potassium thiocyanate in the presence of copper(I) iodide and triethylamine affords benzothiazine **190**, although in low yield and as a mixture with indoline by-product **191** (Equation 28) <2000JOC8152>.

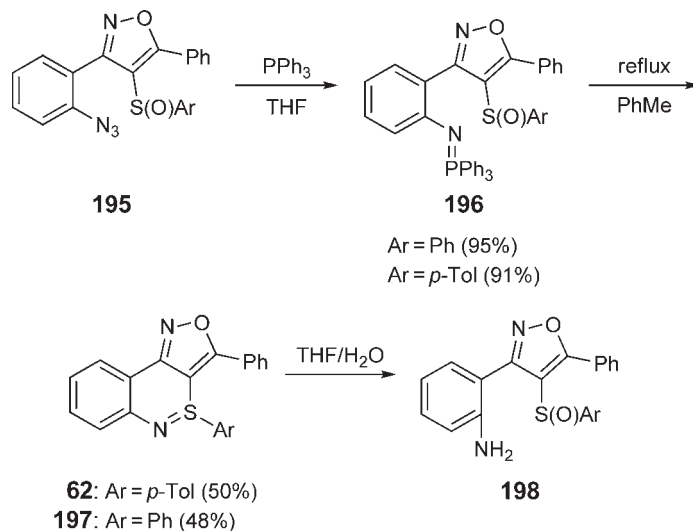


Activation of diaryl sulfides with proximal amide functionality, such as **192**, with *t*-BuOCl generates hypervalent sulfuranes **193** (Scheme 25) <1999JST(476)157>; see also <2003JOC9574>. Anion exchange of the chloride complex **193** to the perchlorate salt **194** was accomplished by treatment with silver perchlorate.



Scheme 25

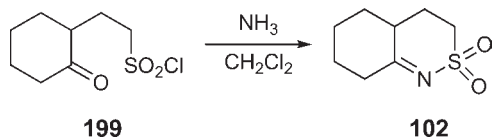
An alternative approach to N–S bond formation involves the aza-Wittig-type reaction of sulfoxides (Scheme 26) <2004SL101>. Initial Staudinger ligation of aryl azide **195** with triphenylphosphine afforded iminophosphorane **196**, which was purified by column chromatography and then heated in anhydrous toluene, producing benzothiazines **62** and **197**. The N–S bond was found to be rather sensitive to hydrolysis and cleavage to **198** was observed upon treatment of benzothiazines **62** or **197** with wet THF.



Scheme 26

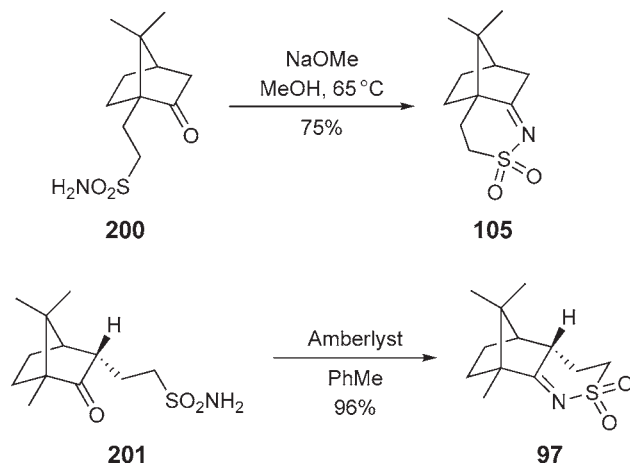
8.07.9.2.2 Disconnection B (Between nitrogen and C-3)

Fused *N*-sulfonylketenimine **102** has been synthesized upon treatment of sulfonyl chloride **199** with ammonia (Equation 29) <1998CJC164>.



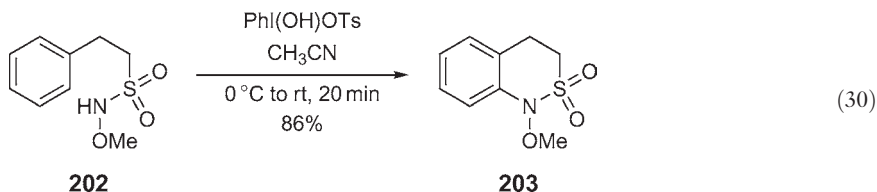
(29)

Intramolecular imine formation has also been successfully applied to the synthesis of bicyclic *N*-sulfonylketenimines **105** and **97** (Scheme 27) <2002HCA1973, 1997JOC3625>. In these cases, cyclization occurs under either basic or acidic conditions from the primary *N*-sulfonamides **200** and **201** in high yield.

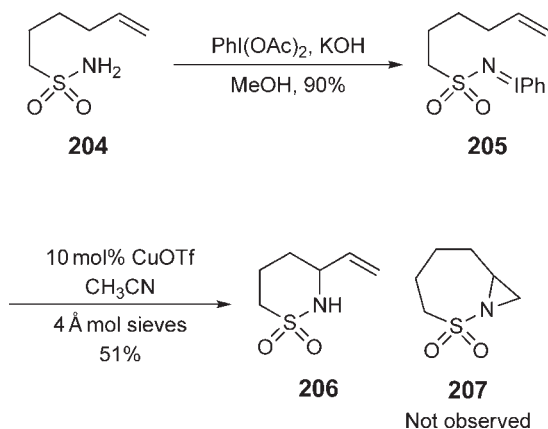


Scheme 27

Oxidative C–H amination has been an area of intensive research since the publication of CHEC-II(1996). This methodology has been applied to the synthesis of a variety of 1,2-thiazine 1,1-dioxides. In the simple cases, substrates containing an aromatic C–H can be cyclized in the presence of hypervalent iodine. For instance, the reaction of *N*-methoxy(2-arylethane)sulfonamide **202** with [hydroxyl(tosyloxy)iodo]benzene rapidly affords benzenesulfonamide **203** in excellent yield (Equation 30) <2003OBC1342>; see also <2000JOC926> and <2000JOC8391>.



The C–H insertion of alkyl sulfonamides using hypervalent iodine reagents in the presence of a transition metal catalyst was initially disclosed by Dauban and Dodd <2000OL2327>. In this report, sulfonamide **204** was treated with PhI(OAc)₂ and base to form an intermediate iminoiodinane **205** (Scheme 28). The material **205** was first



Scheme 28

isolated from the reaction mixture by extraction and evaporation of the solvent, and characterized by ^1H NMR. The resulting amorphous solid **205** was immediately treated with a copper catalyst, creating sulfonamide **206** in 51% yield via nitrogen insertion into the allylic position of iminoiodane **205**. The corresponding seven-membered aziridination product **207** is not observed under these conditions.

This methodology has since been improved to allow the *in situ* formation and subsequent insertion of the iminoiodane intermediates. Copper <2001JA7707>, rhodium <2004JOC6377, 2004HCA1607>, and ruthenium <2004JOC3610> catalysts have been utilized for the insertion step. Rhodium catalysts generally afford the highest yields of C–H insertion products and, in some cases, the copper-based reactions afford higher proportions of aziridination by-products. The oxidants include $\text{PhI}=\text{O}$ and $\text{PhI}(\text{OAc})_2$, and either MgO or Al_2O_3 can be employed as the base.

The scope of this amidation was explored by Fruit and Muller, and separately by Che and co-workers with both allylic and aliphatic substrates (Equation 31; Table 2) <2004HCA1607, 2002OL4507>. Butanesulfonamide **208a** (entry 1) did not afford any C–H insertion product. The synthesis of substituted cyclic sulfonamides **209b**, **c** and **206** however, was accomplished in 51–77% yields (entries 2–4). In these cases, the six-membered sultam rings **209b**, **c** and **206** were produced selectively over five-membered ring compounds **210**. The use of Al_2O_3 as the base in this reaction significantly improves the yield of the vinyl-substituted product **206** (entry 5). Attempts at the asymmetric synthesis of methyl-substituted sulfonamide **209b** with a chiral rhodium catalyst afforded the product with ee's only up to 66% <2004HCA1607>. See also <2003TL5917> for related examples.

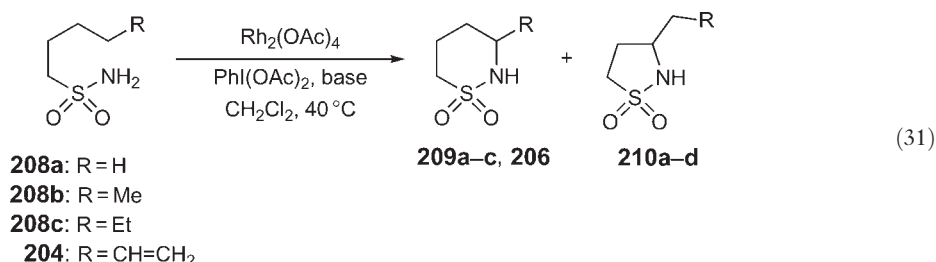


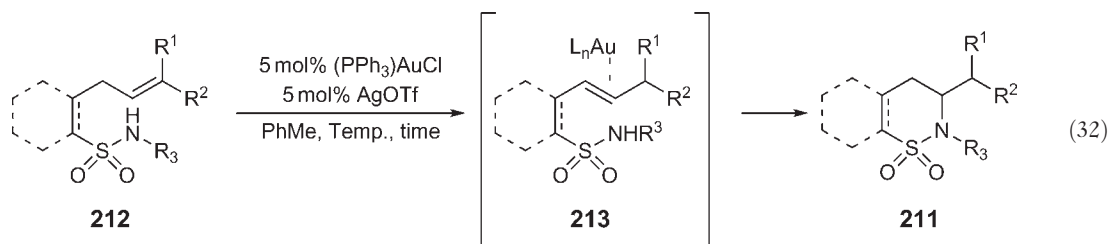
Table 2 Rhodium-catalyzed C–H insertion of sulfonamides

Entry	R	Base	Rh_2OAc_4 (mol%)	Time (h)	Yield (%)	209a–c or 206:210a–d ^a	Reference
1	H	MgO	2.0	4.5	0		2004HCA1607
2	Me	MgO	5.0	4	70	93:7	2004HCA1607
3	Et	MgO	5.0	2	77	77:23	2004HCA1607
4	CH=CH ₂	MgO	2.0	3	51	99:1	2004HCA1607
5	CH=CH ₂	Al_2O_3	2.0	3	90	NR ^b	2002OL4507

^aDetermined by GLC.

^bNR = not reported.

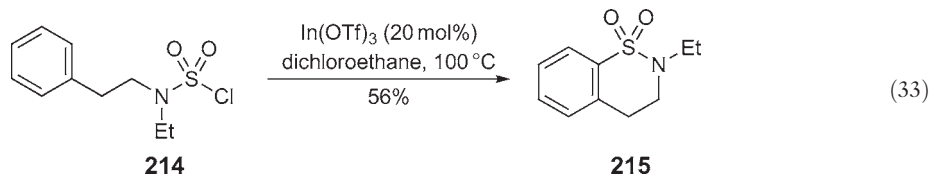
Until recently, the hydroamination of alkenes was a reaction of limited scope, low yield, and only modest selectivity. Che and co-workers have discovered an *in situ*-prepared phosphine–gold(I) hydroamination catalyst system which affords 1,2-thiazines **211** in excellent yields (Equation 32; Table 3) <2006OL2707>. Initial screening of several catalysts for this reaction (e.g., AgOTf , $(\text{Ph}_3\text{P})\text{AuCl}$, or $\text{AuCl}_3/\text{AgOTf}$) failed to afford any cyclized products. However, the combination of a catalytic amount of AgOTf and $(\text{Ph}_3\text{P})\text{AuCl}$ produced a nearly quantitative transformation of sulfonamides **212** to 1,2-thiazine 1,1-dioxides **211**. The proposed mechanism for the reaction is believed to involve an *in situ* isomerization of alkene **212** and a hydroamination reaction of intermediate **213**. In the case of *N*-*tert*-butyl-substituted starting materials, the reaction temperature was critical for cyclization, as an *in situ* deprotection of the *tert*-butyl group occurs at a much lower temperature (entries 2 and 3). Both electron-rich and electron-deficient aromatic primary sulfonamides **212** cyclized in excellent yield (entries 4 and 5). Hex-5-ene-1-sulfonic acid amide (entry 7) afforded the six-membered product **211** exclusively.

**Table 3** Phosphine–gold(III)-catalyzed isomerization and hydroamination reaction of sulfonamides

Entry	212	211	Temp. (°C)	Time (h)	Yield of 211 (%)
1			100	24	99
2			60	12	95
3			100	48	99
4			100	48	99
5			100	12	99
6			100	72	95
7			100	48	88

8.07.9.2.3 Disconnection C (Between sulfur and C-6)

As mentioned in the introduction, recent synthetic developments now allow access to the 1,2-thiazine structure via disconnection type C (Figure 23). This process can be accomplished by a Friedel–Crafts-type cyclization of sulfamoyl chlorides. The initial report of this reaction utilized a stoichiometric amount of aluminium chloride promoter <1992OPP463>. Recently, however, *N*-ethyl phenethylsulfamoyl chloride **214** was shown to undergo Friedel–Crafts cyclization to form sultam **215** with just a catalytic amount of $\text{In}(\text{OTf})_3$ (Equation 33) <2002SL1928>.



8.07.9.2.4 Disconnection D (Between C-5 and C-6)

Very few methods exist for the stereoselective synthesis of fused bicyclic sulfonamides. One example, developed by Tozer and co-workers, involves an inverse electron demand Diels–Alder reaction (Equation 34; Table 4) <2001OL369>. Electron-deficient sulfonamide trienes **216**, which are prepared in a few steps from *N*-BOC-protected methanesulfonamide, react slowly at high temperature in a sealed tube to produce *cis*-**217** as the major isomeric cycloadduct (BOC = *t*-butoxycarbonyl).

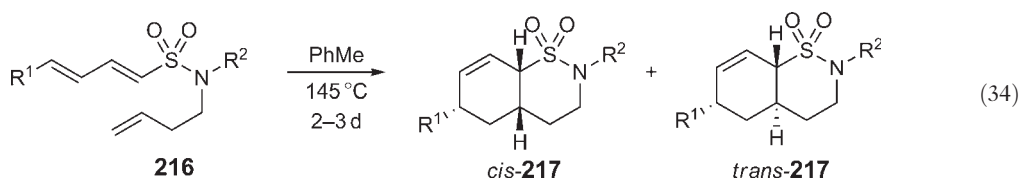
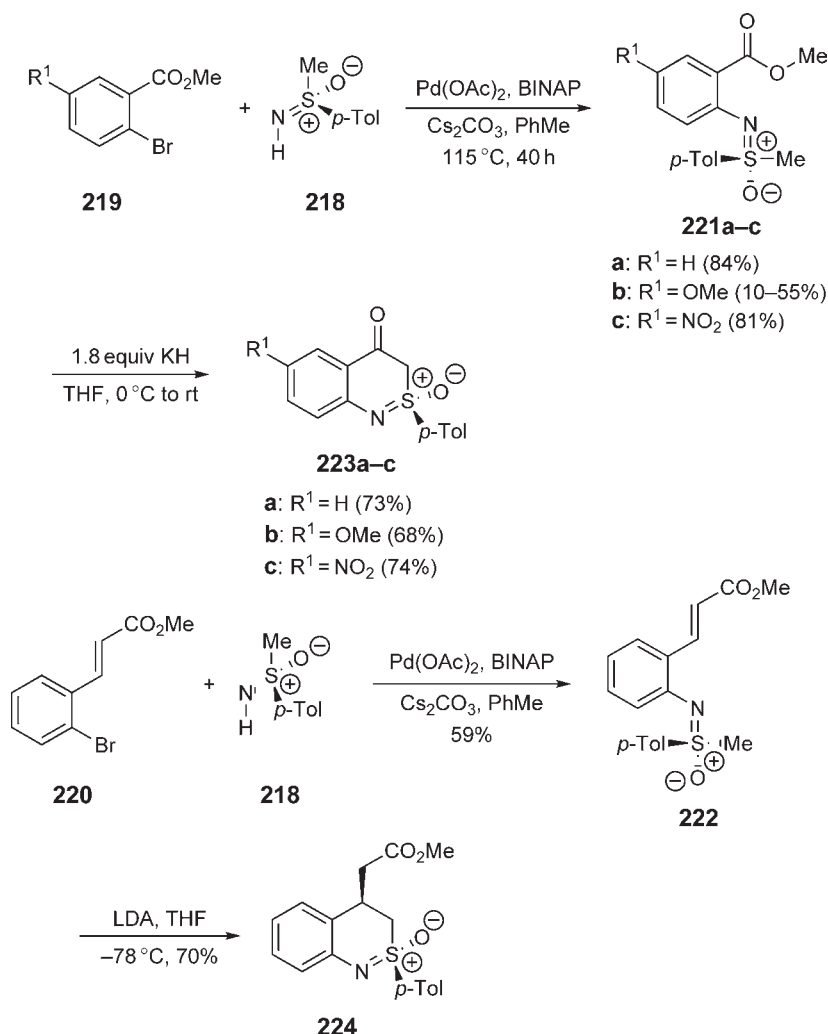


Table 4 Intramolecular inverse electron demand Diels–Alder reaction of vinyl sulfonamides

Entry	R^1	R^2	Combined yield (%)	<i>cis</i> - 238 : <i>trans</i> - 238
1	H	4- $\text{ClC}_6\text{H}_4\text{CH}_2$	66	5:1
2	Me	4- $\text{ClC}_6\text{H}_4\text{CH}_2$	74	6:1
3	Ph	4- $\text{ClC}_6\text{H}_4\text{CH}_2$	92	4:1
4	Ph	Bu ⁿ	80	4:1

A two-step coupling of chiral sulfoximine **218** with aryl bromides containing an ester in the *ortho*-position **219** or an *ortho*-substituted α,β -unsaturated ester **220** affords enantiomerically pure 2,1-benzothiazines **221** and **222**, respectively (Scheme 29) <1999AGE2419>. The key to this chemistry is a new methodology developed by Bolm and Hildebrand which enables the Pd-catalyzed coupling of enantiomerically pure sulfoximines and aryl halides <1998TL5731>. In most cases, the yields for this N–C bond formation are quite high, with the exception of *p*-methoxyaryl bromides **221b** (10% yield with 5% of Pd catalyst and 55% yield with 10% of Pd catalyst). Deprotonation of the α -methyl group of the aryl sulfoximines **221a–c** with a strong base, such as KH or lithium diisopropylamide (LDA), affords the condensation products **223** in good yields. In the latter case, Michael addition of a coupled product **222** affords the 2,1-benzothiazine product **224** as a single diastereomer, whose relative stereochemistry has been elucidated by X-ray crystallography.



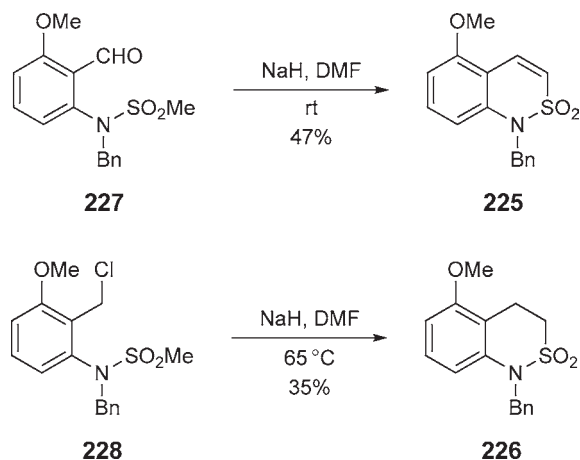
Scheme 29

Intramolecular methanesulfonamide anion alkylation and aldol condensation reactions have been employed for the synthesis of 2,1-benzothiazine 2,2-dioxides. For instance, Blondet and Pascal have utilized such a process for the formation of compounds **225** and **226** from *ortho*-substituted aldehyde **227** and alkyl chloride **228**, respectively (Scheme 30) <1994TL2911>.

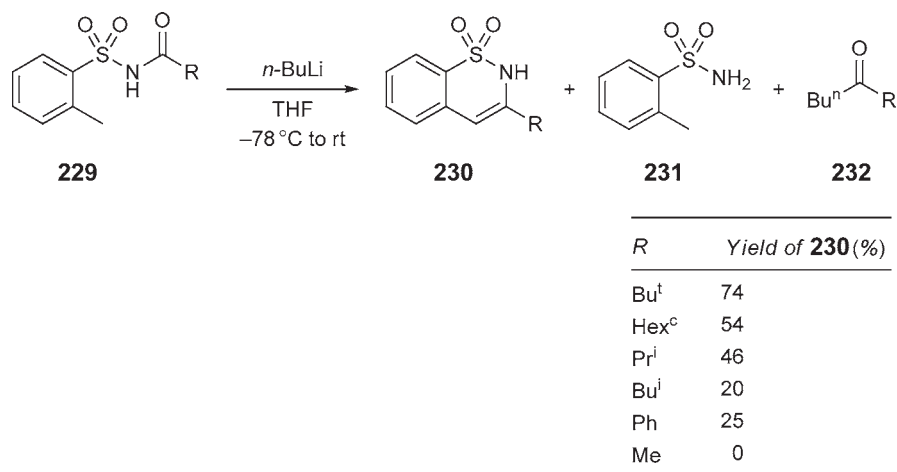
8.07.9.2.5 Disconnection E (Between C-3 and C-4)

In CHEC-II(1996), the preparative-scale formation of 2,3-benzothiazine 2,2-dioxides via the Pictet–Spengler reaction of benzylsulfonamides and aldehydes under strongly acidic conditions (TFA, MeSO_3H , etc.) was described <1996CHEC-II(6)349>. Recent improvements for this reaction utilizing Amberlyst resins as catalysts greatly simplify the workup and, in general, significantly increase the product yield <2002SC3675>.

Directed *ortho*-methyl lithiation/cyclization of *N*-acyl-*o*-toluenesulfonamides **229** provides a second approach to the synthesis of 1,2-benzothiazine 1,1-dioxides **230** via creation of the bond between C-3 and C-4 (Scheme 31) <1999CPB1730>. The best yields of cyclization products are achieved when the R group on the amide **229** is bulky. In the case of substrates with small R groups (Me, Ph, etc.), products **231** and **232** are formed from attack of the Bu^nLi on the carbonyl carbon.



Scheme 30



Scheme 31

8.07.9.2.6 Disconnection F (Between C-4 and C-5)

An anionic equivalent of the Friedel–Crafts cyclization reaction has been developed for the formation of the C-4/C-5 bond of the 1,2-benzothiazine structure (Equation 35; Table 5) <1997SL1079>. In this reaction, directed metalation of sulfonamide-substituted aromatic systems **233** with an excess of LDA affords aryl lithium species **234** in a regiocontrolled fashion. This intermediate then reacts *in situ* with a proximal amide to form 1,2-benzothiazine-4-one 1,1-dioxides **235**. The yields of this transformation appear to be highly dependent upon the substitution pattern in **233**. The authors attribute the low yield when R² = methyl and R³ = H to α -deprotonation of the amide moiety.

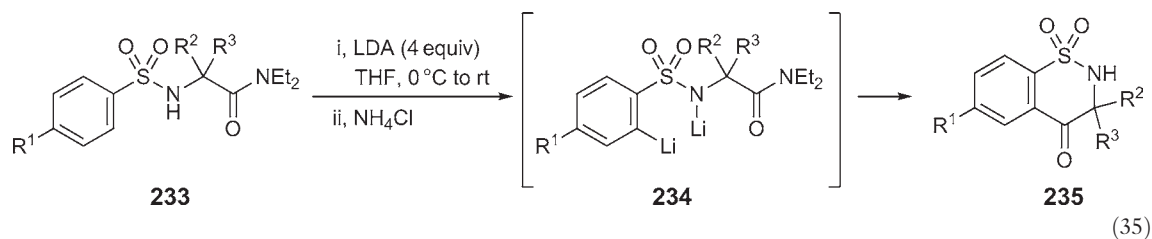
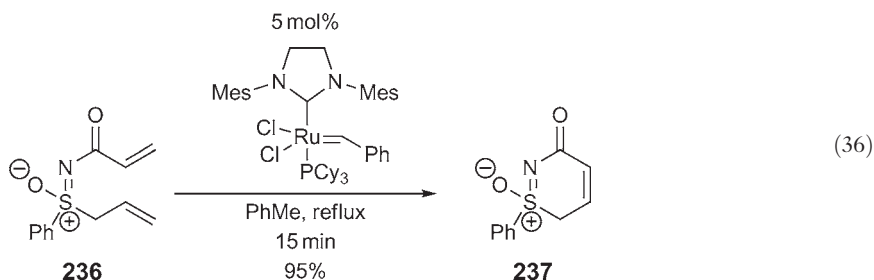


Table 5 Directed metalation and *in situ* acylation of arylsulfonamides

Entry	R^1	R^2	R^3	Yield (%)
1	H	Me	H	20
2	H	Me	Me	85
3	H	Bu ⁱ	H	57
4	Me	Bu ⁱ	H	29

Ring-closing metathesis is another efficient process for the construction of 1,2-thiazines via the disconnection at C-4 and C-5. The reaction of sulfoximine **236** with 5 mol% of Grubbs' second-generation ring-closing metathesis catalyst affords the corresponding cyclized product **237** in excellent yield (Equation 36) <2005SI1421>.

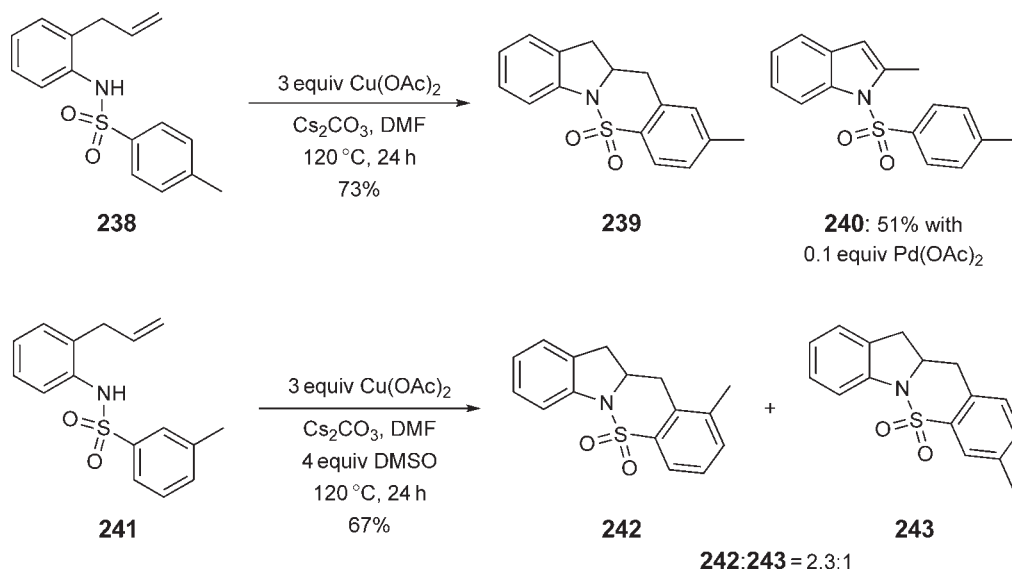


8.07.9.3 Intermolecular Reactions

8.07.9.3.1 [4+2] Components

8.07.9.3.1(i) Intramolecular Cu-catalyzed cyclizations

N-*p*-Tosylaniline **238** reacts with an excess of $\text{Cu}(\text{OAc})_2$ (3 equiv) and Cs_2CO_3 at 120°C to afford tetracycle **239** via oxidative cyclization (Scheme 32) <2004OL1573>. Interestingly, when a catalytic amount of $\text{Pd}(\text{OAc})_2$ is

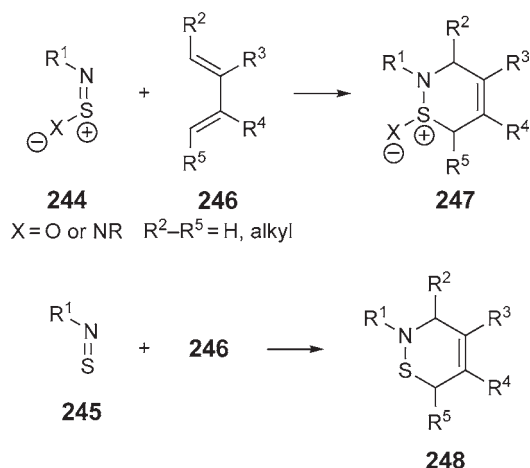


Scheme 32

added to the reaction mixture, indole **240** is isolated as the sole product. The corresponding *m*-sulfonyl-substituted starting material **241** affords a mixture of regioisomeric products **242** and **243**. The authors have proposed a mechanism for this reaction sequence which involves radical intermediates, although they have not ruled out an ion pair mechanism.

8.07.9.3.1(ii) Hetero-Diels–Alder reactions

The hetero-Diels–Alder reaction of *N*-sulfinyl **244** or thionitrosoarene **245** dienophiles with dienes **246** is a thoroughly studied method for the formation of 3,6-dihydro-2*H*-1,2-thiazine 1-oxides **247** or 3,6-dihydro-2*H*-1,2-thiazines **248** (Scheme 33). This reaction was first reported by Wichterle and Rocek in 1954 using *N*-sulfinylaniline <1954CCCC282>. CHEC-II(1996) focused on the wealth of information in this area and included mechanistic and stereochemical aspects of the reaction, which are not covered in detail here. To summarize a few of the key points: thionitrosoarenes are transient in nature, rather difficult to prepare, and thus have a limited role in the synthesis of 1,2-thiazines. On the other hand, *N*-sulfinyl compounds and related sulfur diimines are more stable and are isolable species. The common means of preparation of the *N*-sulfinyl compounds involves the treatment of an amine or amide with SOCl₂ and base. *N*-Sulfinyl dienophiles containing an electron-withdrawing group undergo [4+2] cycloaddition reactions with a variety of 1,3-dienes at room temperature, while unactivated alkyl-substituted dienophiles often require a Lewis acid or high pressure to react (see also Section 8.07.2.1).

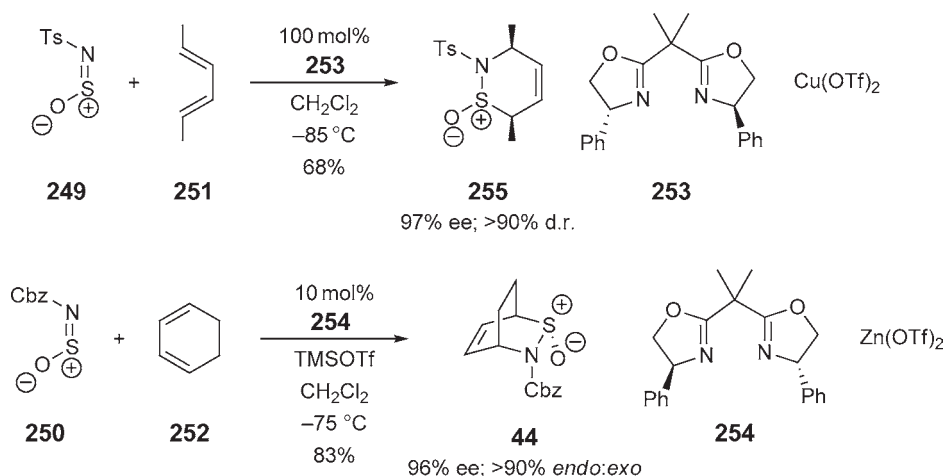


Scheme 33

Some recent advances in this field include the work by Hemming toward the synthesis of benzodiazepines and benzothiazepines (see Section 8.07.12.5) <2000TL10107, 2004T3349, 2004TL7553>. This hetero-Diels–Alder reaction has found important applications in the preparation of organic thin-film transistors (OTFTs, see Section 8.07.12.4). Diels–Alder cycloaddition reaction of azulene-substituted *N*-sulfinylamines with 2,3-dimethyl-1,3-butadiene at high pressure was studied by Ito *et al.*, who reported compounds with interesting redox properties (see Section 8.07.3.6) <2003T4651>. Also, Liu and co-workers have recently studied the reactions of polyfluorinated *N*-sulfinyl dienophiles <2005T6982, 2003T9669>.

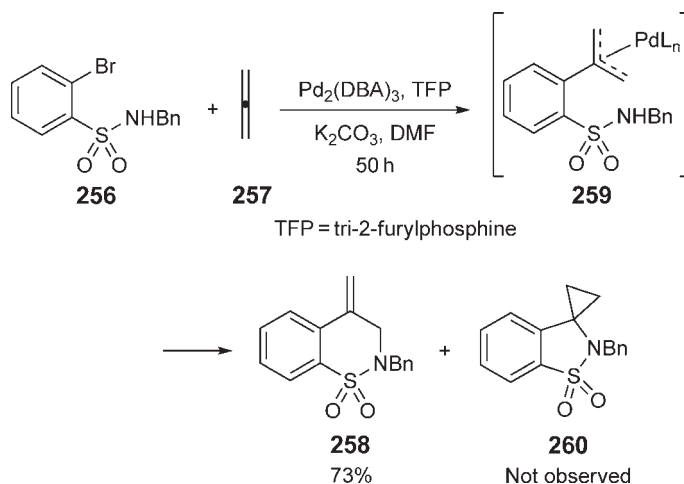
8.07.9.3.1(iii) Asymmetric hetero-Diels–Alder reactions

The initial work on the asymmetric [4+2] cycloaddition reactions of *N*-sulfinyl compounds and dienes was performed with chiral titanium catalysts, but low ee's were observed <2002TA2407, 2001TA2937, 2000TL3743>. A great improvement in the enantioselectivity for the reaction of *N*-sulfinyl dienophiles **249** or **250** and acyclic diene **251** or 1,3-cyclohexadiene **252** was observed in the processes involving catalysis with Cu(II) and Zn(II) complexes of Evans' bis(oxazolidinone) (BOX) ligands **253** and **254** <2004JOC7198> (Scheme 34). While the preparation of enantio-merically enriched hetero-Diels–Alder adduct **255** requires a stoichiometric amount of chiral Lewis acid complex, a catalytic asymmetric synthesis of **44** is achieved upon the addition of TMSOTf.



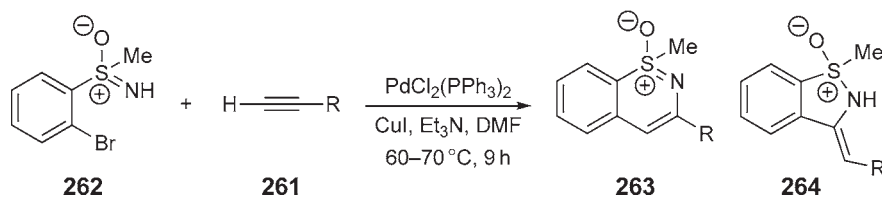
Scheme 34

The reaction of *o*-halobenzenesulfonamide **256** with allene **257**, in the presence of Pd(0), affords the exocyclic alkene **258** via nitrogen attack on the π -allyl Pd-intermediate **259** (Scheme 35) <2001EJO707>. The related cyclopropane product **260**, formed in high yields in the analogous reactions of carboxamides, is not observed for the sulfonamide substrate **256**.



Scheme 35

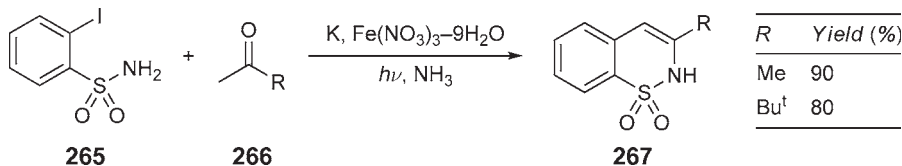
Harmata *et al.* have developed a tandem Sonogashira/nitrogen-addition reaction of acetylenes **261** to sulfonamide **262** to prepare S(VI)-oxidized compounds **263** and **264** (Scheme 36) <2005OL143>. When R = alkyl (e.g., Prⁿ), the 1,2-thiazine **263** is the major product (70%) formed via an endocyclization process, along with a minor amount (20%) of exocyclized product **264**, while the five-membered ring product **264** (81%) is preferred when R = Ph.



Scheme 36

8.07.9.3.1(iv) Photochemical reactions

Reaction of *o*-iodobenzenesulfonamide **265** with the potassium enolate of ketones **266** in liquid ammonia under photochemical conditions affords 1,2-benzothiazine 1,1-dioxides **267** in excellent yield (Scheme 37) <2005JOC9147>. While a variety of other ketone substrates have been investigated for this reaction, those containing β -hydrogens afford significant amounts of benzenesulfonamide by dehalogenation of the starting material **265**.



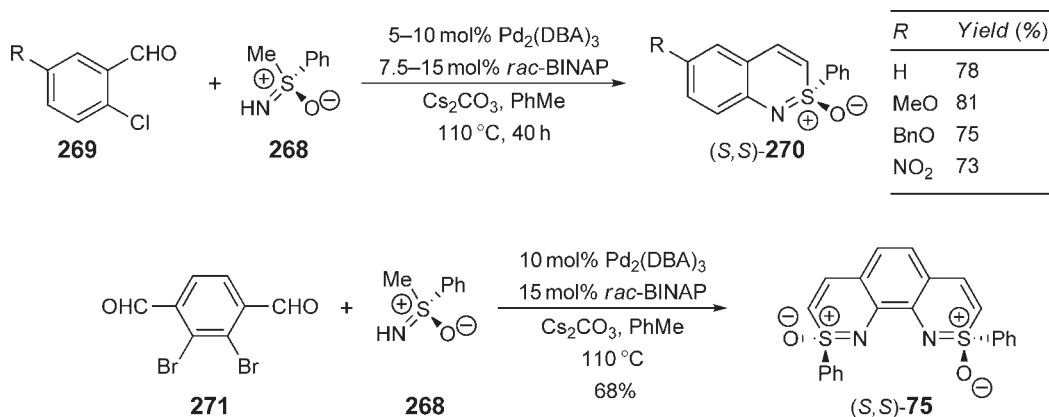
Scheme 37

8.07.9.3.2 [3+3] Components

8.07.9.3.2(i) Pd-catalyzed coupling

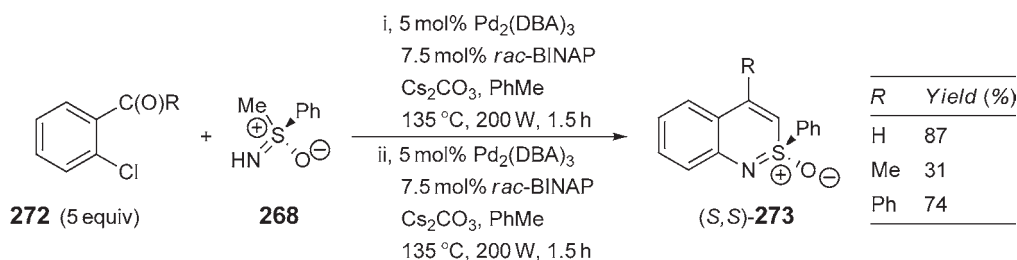
A reaction of sulfoximine **268** with *ortho*-substituted halobenzaldehydes **269** takes place in the presence of a catalytic amount of Pd(II), 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP), and caesium carbonate at 110 °C to afford fully conjugated 2-phenyl-2,1-benzothiazine 2-oxides **270** with a S(VI) oxidation state (Scheme 38) <1999AGE2419>. Bis-benzothiazine **75** has been prepared from dibromo-dialdehyde **271** in a similar manner and investigated as a ligand for Pd-catalyzed allylic alkylation reactions (see Section 8.07.12.3) <2001OL3321>.

The reaction of *ortho*-substituted chlorophenyl ketones in the [3+3] coupling reaction generally requires long reactions times and results in poor yields of the 1,2-thiazine products. A microwave-assisted reaction of chloroaryl ketones **272** with sulfoximine **268** has been developed which provides the cyclized products **273** in improved yields after two cycles of treatment with the Pd-catalyst (Scheme 39) <2004TL5233>.

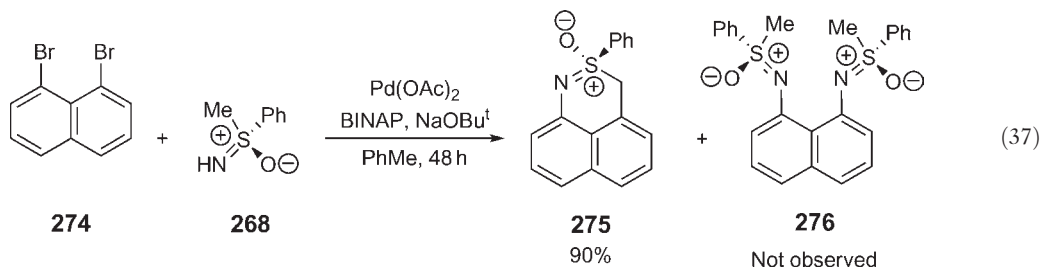


Scheme 38

Dibromonaphthalene **274** undergoes a Pd(0)–BINAP [3+3] coupling reaction, believed to involve an initial N-arylation reaction and subsequent C–C bond formation of product **275** (Equation 37) <2004OL3293>. Bis(sulfonamide) **276** (formed in 56% yield in the presence of CuI and CsOAc in dimethyl sulfoxide (DMSO)) is not observed under the palladium-catalyzed conditions.

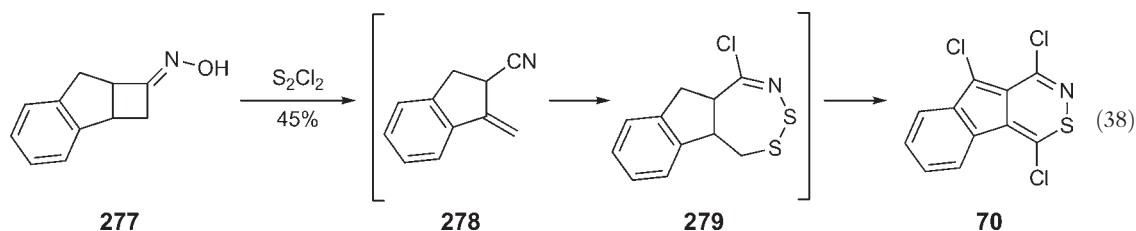


Scheme 39

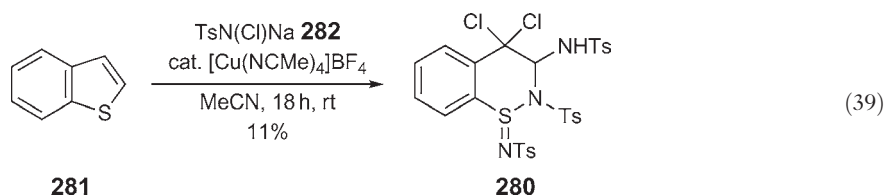


8.07.10 Ring Synthesis by Transformations of Another Ring

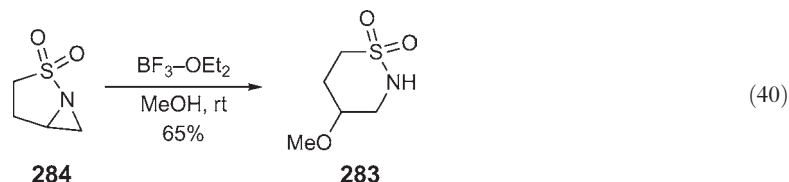
The reaction of cyclobutanone oxime **277** with S_2Cl_2 affords the conjugated 1,2-thiazine **70** in 45% yield (Equation 38) <1996JOC9178>. The proposed mechanism for this transformation involves the intermediate nitrile **278**, which reacts to form imino-disulfide **279**. Following ring contraction of **279** and further chlorination, product **70**, whose structure was confirmed by X-ray analysis, is obtained.



1,2-Thiazine **280** can be prepared in low yield by the sulfimidation of benzo[*b*]thiophene **281** with chloramine-T **282** in the presence of a Cu-catalyst (Equation 39) <2003CC1736>.



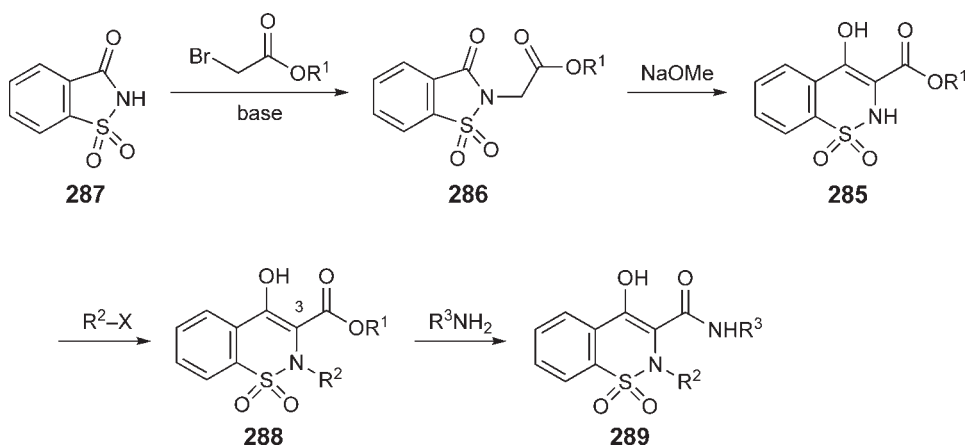
1,2-Thiazine **283** has been prepared through the nucleophilic ring opening of fused bicyclic aziridine isothiazolidine 1,1-dioxide **284** with MeOH in the presence of $BF_3 \cdot OEt_2$ (Equation 40) <2000OL2327, 2004JOC6377>.



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

8.07.11.1 Oxicams

The standard means for preparing oxicams **285**, initially developed by Lombardino, is through the base-promoted rearrangement reaction of isothiazole dioxides **286**, which in turn are prepared from saccharin derivatives such as **287** (Scheme 40) <1981AHC(28)73>. The oxcam core can be further derivatized by N-alkylation of oxcam **285** and amidation of the C-3 ester functionality of **288** to form the common drug scaffold **289**.



Scheme 40

8.07.12 Important Compounds and Applications

8.07.12.1 Biological/pharmaceutical

Significant research has centered on the preparation and investigation of oxcam derivatives as pharmaceutical agents. This interest was fueled by the successes of the nonsteroidal anti-inflammatory drugs (NSAIDs) piroxicam (Feldene®) **21**, meloxicam (Mobic®) **22**, and tenoxicam **23** (Figure 24).

Much of the recent work has concentrated on the anti-inflammatory, analgesic, and antipyretic activities of oxcam derivatives in animal models. Several groups have synthesized and performed structure–activity relationship (SAR) studies on a small library of meloxicam analogues for selective cyclooxygenase-2 (COX-2) inhibition <1997JME980>. Of the small molecule inhibitors screened, meloxicam displayed the highest selectivity for COX-2 over COX-1 ($IC_{50} = 9.4 \mu\text{m}$ for COX-2; $IC_{50} = 50 \mu\text{m}$ for COX-1). Similarly, *N*-methyl-3-isopropyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxides and related analogues have been studied as nonsteroidal anti-inflammatory agents with reduced ulcerogenic effects in rats <2002EJP221>. Racemic bicycle **290** displayed the highest activity with an ED_{50} of 4.5 mg kg^{-1} .

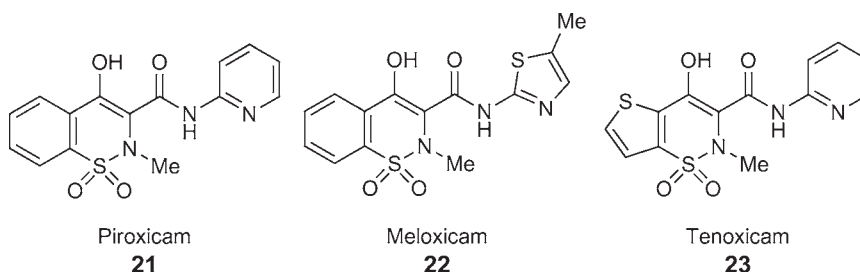
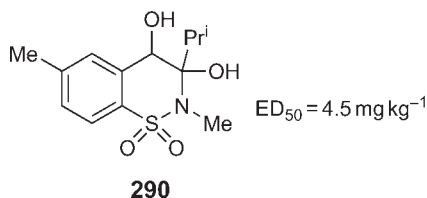
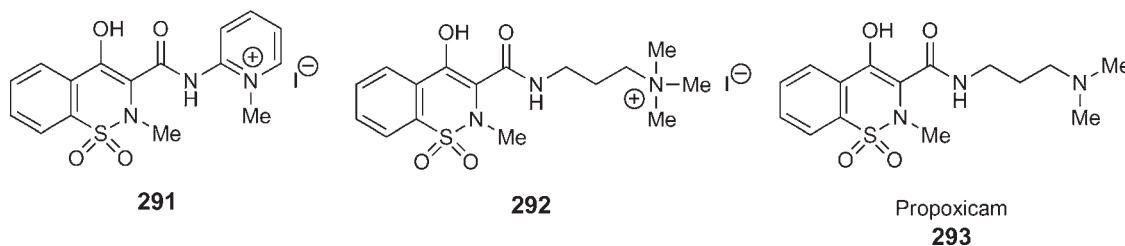


Figure 24



The calculation of membrane affinity can often be a tedious task to perform experimentally, especially for charged active pharmaceutical ingredients (APIs) which afford substantial errors when measuring the partition coefficient between octanol and water. A new method for determining membrane affinity was developed using solid-supported lipid membranes (TRANSIL[®]) and applied to the oxicam-containing drug piroxicam **21** <2001JPS599>.

Due to the strong affinity of ammonium salts and oximes to proteoglycans in cartilage, quaternary ammonium oxicam derivatives **291** and **292** have been prepared to target cartilage <1999JME5235>. Pharmacokinetic work on the labeled drug substances demonstrated the proof of concept: a large accumulation of the ammonium salts **291** and **292** is observed in the cartilage, while the neutral oxicams **21** and **293** are equally distributed between cartilage and blood. Quite surprisingly, introduction of the quaternary ammonium functionality in **21** and **293** does not impact the anti-inflammatory activity. The authors believe these compounds could potentially lower the administered dose of the NSAID, thereby reducing adverse digestive issues of COX-1/COX-2 nonselective inhibitors.



Along with anti-inflammatory biological activity, the oxicams have been targeted as anticancer agents, and as possible treatments for neurodegeneration resulting from cerebral ischemia, traumatic brain injury, or even spinal cord trauma. Researchers at Cephalon have prepared a small library of peptide mimetic aldehyde inhibitors of calpain I consisting of substituted 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxides (Figure 25) <2001JME3488>. Of these molecules, aldehyde **184** displayed the best activity for calpain I which is associated with neurodegenerative processes. The compound **184** was evaluated *in vivo* in the MOLT-4 (human T-cell leukemia cell line) whole cell assay and showed good potency for calpain I, along with good cell permeability and aqueous solubility. Given the sensitivity of aldehydes to decomposition, ketoamide analogues of **184** were further screened and sulfonamide **294** was identified with a slightly diminished activity compared to **184** <2004BML1035>.

Parke-Davis workers have performed SAR studies on endothelin receptor antagonists derived from a dimethoxy-substituted oxicam in the search of treatments for hypertension, congestive heart failure, renal failure, pulmonary hypertension, ischemia, and cerebral vasospasm <1998BMC1447>. Compound **295** displayed a 40-fold selectivity for endothelin receptor antagonist A (ET_A) over endothelin receptor antagonist B (ET_B) (Figure 26).

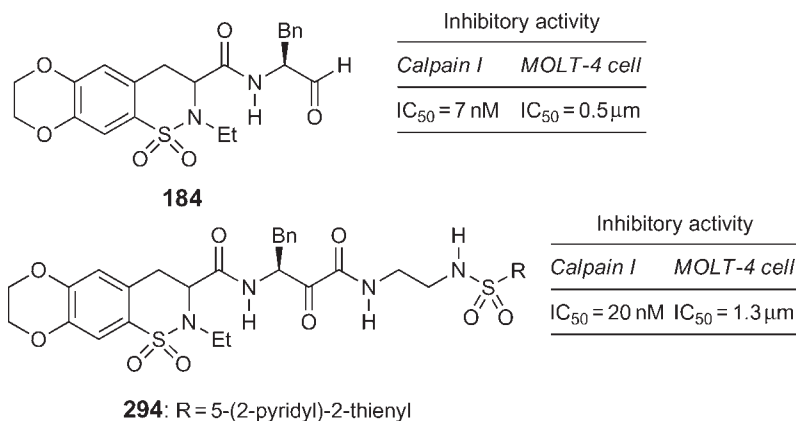


Figure 25

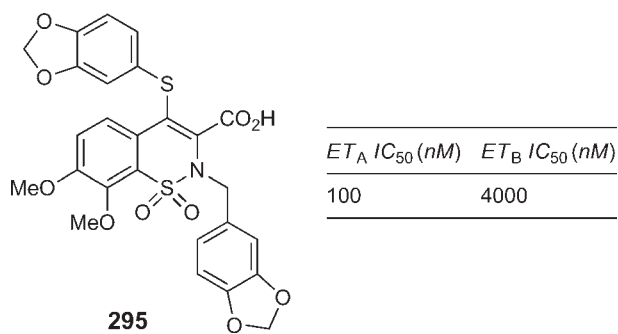
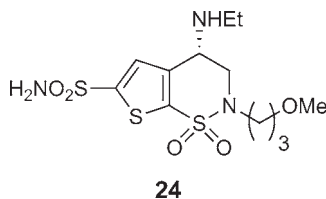
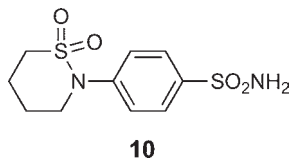


Figure 26

A variety of thiophene-fused 1,2-thiazines have been prepared as carbonic anhydrase inhibitors for the treatment of glaucoma [\[2002JME888, 2000BMC957\]](#). The drug brinzolamide (under the trade name Azopt®) **24** has recently been approved by the FDA.



Several examples of non-oxicam-type 1,2-thiazine-containing small molecule enzyme inhibitors have been disclosed. The landmark work in this area involves the antiepileptic drug sulthiame **10**, first discovered and approved for use over 30 years ago. Interest in this carbonic anhydrase inhibitor has been renewed by recent work on its efficacy in treatment of both childhood benign and focal epilepsies [\[2002MI469\]](#).



Among the many other non-oxcam-type substances discovered are a sultam pro-drug for potential P₃-lactam thrombin inhibitors <1998BML3683>. Furthermore, an anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) pharmacophore based on the 1,2-thiazine structure has also been recently disclosed <1999BML673>. Workers at Bristol-Meyers Squibb have synthesized and evaluated sultam hydroxamates as MMP-2 inhibitors <2004JME2981>. Hydroxamate **38** displayed the best selectivity for MMP-2 over the other proteins in this superfamily of peptidases (Figure 27). As noted in Section 8.07.3.1, an X-ray crystal structure of **38** bound to the protein MMP-13 protein has been solved.

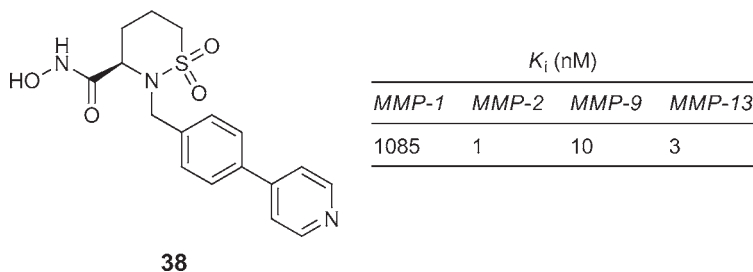
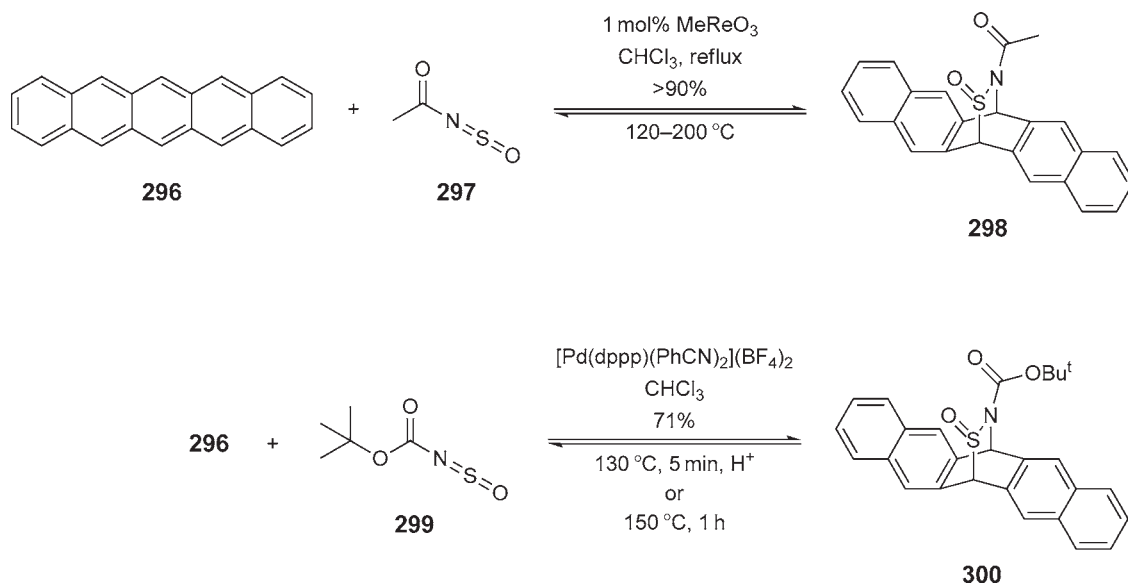


Figure 27

8.07.12.2 Materials

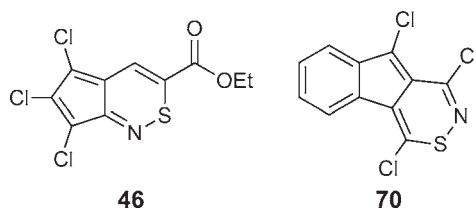
Pentacene **296** has found applications in the area of organic thin film transistors (OTFTs) for use in electronics, including light-emitting diodes (LEDs) and photovoltaic cells (Scheme 41) <2002JA8812>. The low solubility of pentacene in organic solvents has hampered efforts for processing pentacene semiconductors for use in plastic devices. Current efforts have focused on the reversible derivatization of pentacene to develop more soluble precursors to the OTFTs. Pentacene is known to undergo a Diels–Alder reaction with



Scheme 41

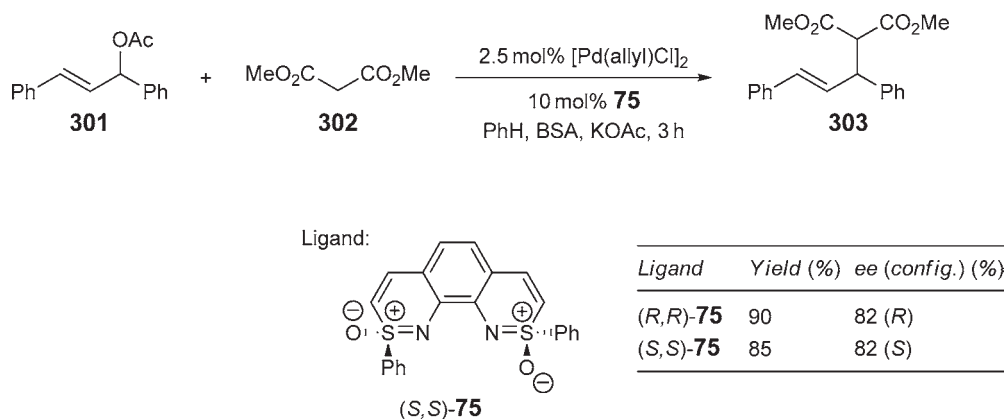
N-sulfinylacetamide **297** in greater than 90% yield when a catalytic amount of methyltrioxorhenium is employed. Furthermore, the hetero-Diels–Alder adduct is highly soluble in both chlorinated and ethereal solvents. A detailed investigation of the retro-Diels–Alder reaction of **298** by thermogravimetric analysis revealed an onset temperature of 120 °C and complete conversion of bicycle **298** to pentacene **296** at 160 °C, which are temperatures compatible with the polymer supports typically used in electronics applications. The electronic properties of these newly prepared OTFTs are similar to those prepared by traditional methods. Later improvements to this chemistry included the use of *N*-sulfinyl-*tert*-butylcarbamate **299** as the dienophile <2004JA12740>. The retro-Diels–Alder reaction of substrate **300** proceeds at much lower temperatures (130 °C, 5 min with H⁺-catalyst; 150 °C, 1 h with no catalyst).

1,2-Thiazines have found applications in materials, such as liquid crystal displays. New synthetic methods for the synthesis of highly chlorinated 1,2-thiazines allow access to promising new substrates **46** <1996JOC9178> and **70** <2005JOC9314>.



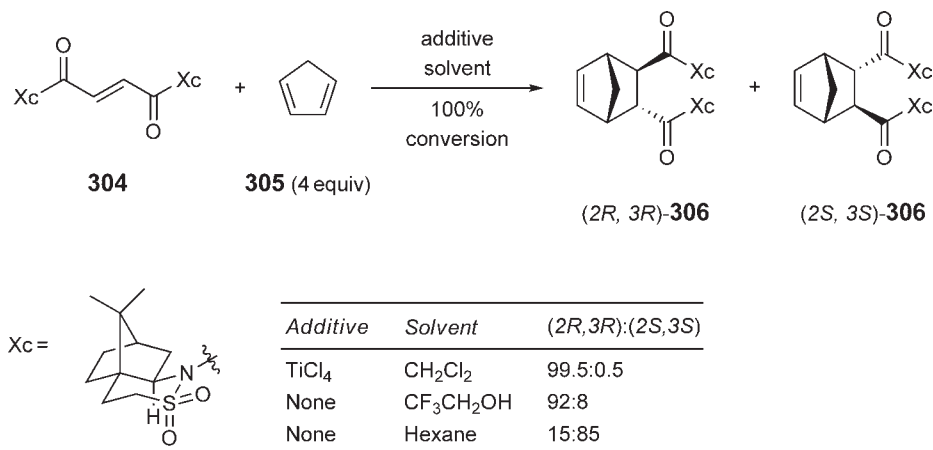
8.07.12.3 Ligands and Auxiliaries

The chiral nonracemic bis-benzothiazine ligand **75** has been screened for activity in asymmetric Pd-catalyzed allylic alkylation reactions (Scheme 42) <2001OL3321>. The test system chosen for this ligand was the reaction of 1,3-diphenylallyl acetate **301** with dimethyl malonate **302**. A stoichiometric amount of bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc were added to the reaction mixture. A catalytic amount of chiral ligand **75** along with a variety of Pd-sources afforded up to 90% yield and 82% ee's of diester **303**. Since both enantiomers of the chiral ligand are available, both *R*- and *S*-configurations of the alkylation product **303** can be obtained. The best results in terms of yield and stereoselectivity were obtained in nonpolar solvents, such as benzene. The allylic alkylation of racemic cyclohexenyl acetate with dimethyl malonate was performed but with lower yields (up to 53%) and only modest enantioselectivity (60% ee).



Scheme 42

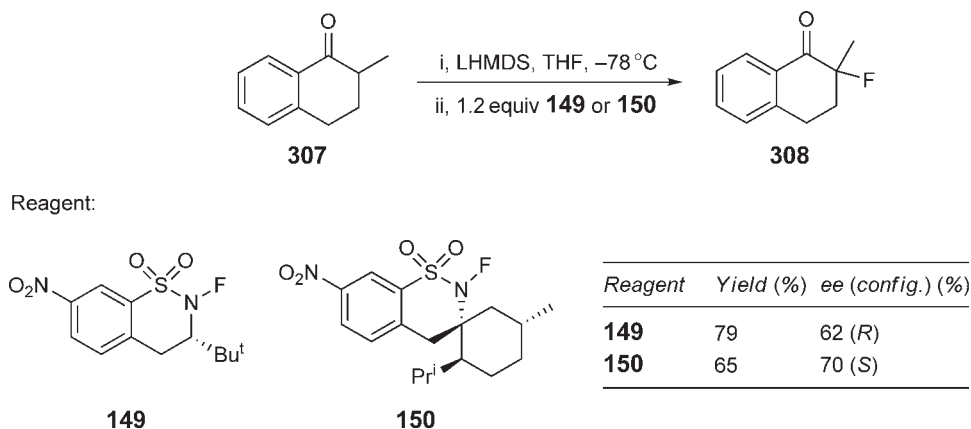
Oppolzer sultam-like chiral auxiliary (e.g., Xc in **304**) has been studied in Diels–Alder cycloaddition reactions (**Scheme 43**) <2003JPO700>. The TiCl_4 -promoted reaction of dienophile **304** and 1,3-cyclopentadiene **305** in DCM is complete within 18 h and excellent diastereoselectivity of product **306** is observed. The same reaction in the absence of Lewis acid provides product **306** in very low yield. However, switching to trifluoroethanol as the solvent, the cycloaddition reaction proceeds to completion, albeit with slightly diminished levels of diastereoselectivity for Diels–Alder adduct **306**. Surprisingly, the use of hexane as the solvent affords the opposite (*2S,3S*)-diastereomer of **306** as the major product.



Scheme 43

8.07.12.4 Reagents

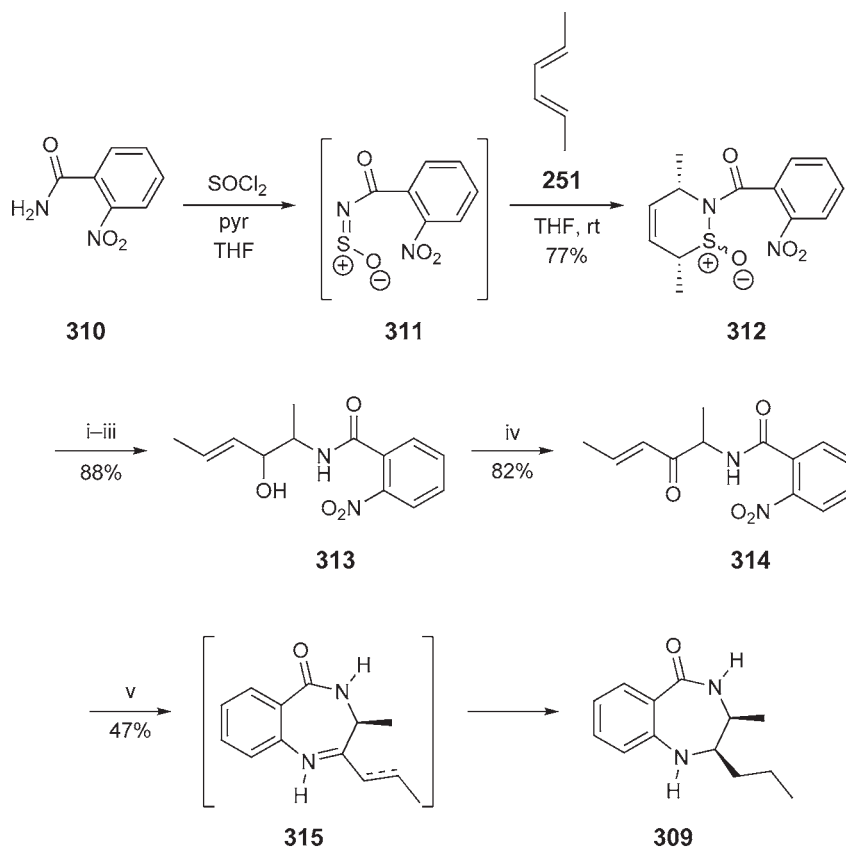
Asymmetric fluorination of the lithium enolate derived from tetralone **307** has been achieved with several new chiral *N*-fluoro-1,2-benzothiazine reagents (**Scheme 44**) <2000JOC7583, 2000CPB1954, see also 1999JFC(97)65>. For instance, sulfonamides **149** and **150** afford the opposite enantiomers of fluoroketone **308** in up to 79% yield and 62–70% ee.



Scheme 44

8.07.12.5 Complex Alkaloid Total Synthesis

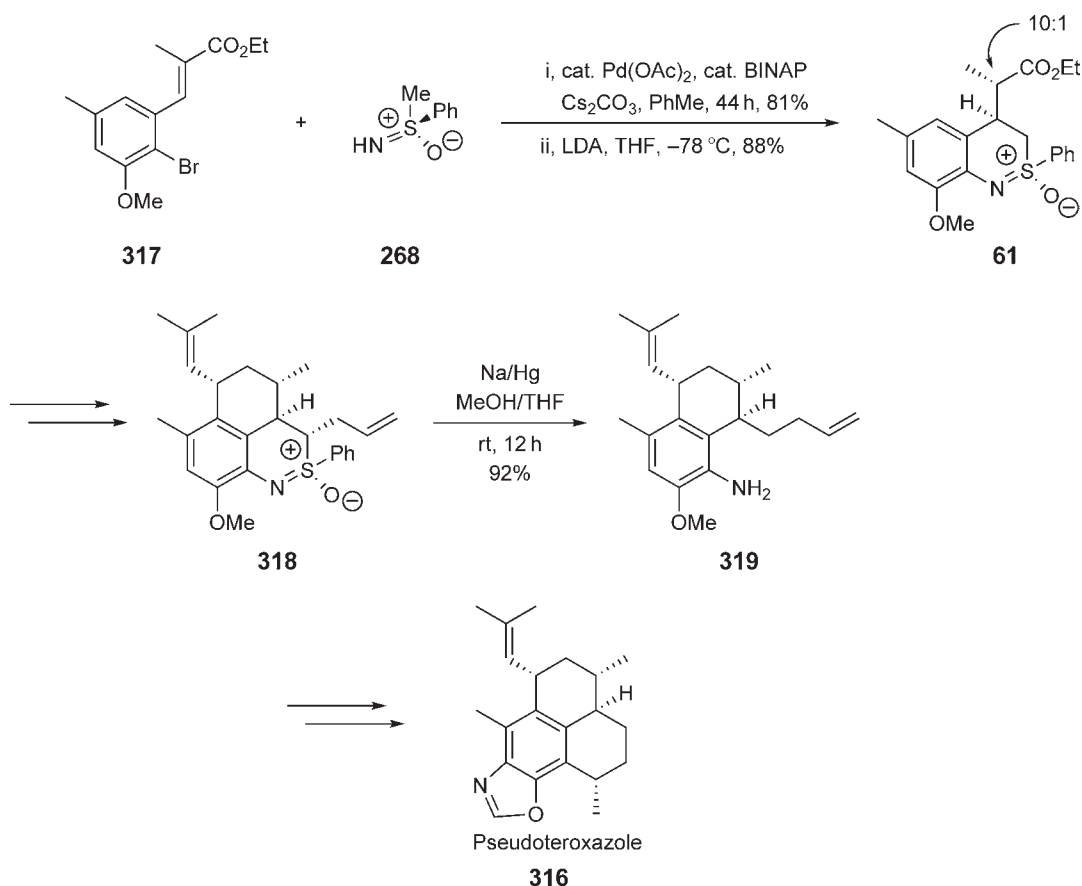
Application of the Diels–Alder reaction of *N*-sulfinylamides with dienes and subsequent ring-opening/[2,3]-sigmatropic rearrangement (see Section 8.07.6.3) has been utilized in the preparation of 1,4-benzodiazepines **309** and 1,2,5-benzothiadiazepines (Scheme 45) <2000TL10107, 2004T3349>. Starting from 2-nitrobenzamide **310**, the sulfinyl amide **311** is prepared *in situ* by treatment with thionyl chloride and undergoes [4+2] cycloaddition with *E,E*-1,4-dimethylbutadiene **251**. The allylic alcohol **313** is then synthesized in good yield by the ring opening and rearrangement of dihydro-1,2-thiazine adduct **312**. Dess–Martin oxidation and Pd/C-reduction of the nitro group of **314** furnishes the benzodiazepine core **315** upon cyclization. The imine **315** is further hydrogenated to arrive at the fully saturated benzodiazepine **309**.



i, PhMgBr, THF, 240 °C, 3 h; ii, NH₄Cl (aq.); iii, MeOH, P(OMe)₃, 60 °C, 10–15 h;
 iv, Dess–Martin periodinane, CH₂Cl₂, rt, 1 h; v, H₂, Pd/C, MeOH, rt, 16–20 h

Scheme 45

The antitubercular agent, pseudopteroxazole **316** has been prepared by Harmata via chemistry which utilizes a 2,1-benzothiazine as a key synthetic intermediate (Scheme 46) <2004OL2201, 2005OL3581>. The 2,1-benzothiazine ring of the bicyclic intermediate **61** was synthesized via a two-step procedure involving Pd-catalyzed coupling of the sulfoxime **268** with aryl bromide **317**. Ring closure to **61** then occurs upon treatment with LDA in THF at low temperature. This material was then relayed to intermediate **318**, where the 2,1-benzothiazine moiety was reductively removed with Na/Hg. Further transformation of **319** afforded the natural product pseudoteroxazole **316** in nine steps from **317** in 18% overall yield.



Scheme 46

8.07.13 Further Developments

Several new papers have appeared on the use of 1,2-thiazines in organic synthesis including work by Harmata and co-workers [\[2007OL2701\]](#) and recent progress in the chemistry of 2,1-benzothiazines has been reviewed [\[2007PHC1\]](#). Enders and co-workers have developed a new asymmetric synthesis of 1,2-thiazine 1,1-dioxides utilizing their previously developed SAMP technology [\[2006EJO1271\]](#). A new simple and much improved method for the synthesis of oxicams has been recently published by Vidal and colleagues [\[2006S591\]](#). Scientists at Merck have recently described the synthesis of a potent gamma-secretase inhibitor based on a 1,2-thiazine 1,1-dioxide that was synthesized via a novel, stereocontrolled intramolecular nitrile oxide–alkene cycloaddition reaction [\[2006JOC3086\]](#).

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Biographical Sketch



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Robert K. Orr (born 1976) received his bachelor's degree from the Richard Stockton College of New Jersey in 1998, where he conducted research under the guidance of Kenneth Overly. He entered the Virginia Polytechnic Institute and State University for graduate studies in chemistry under the supervision of Michael Calter, and moved to the University of Rochester with the Calter research group in the summer of 1999. Following the completion of his Ph.D. work in 2003, Dr. Orr performed postdoctoral work with Steven M. Weinreb at the Pennsylvania State University. Currently, he is a senior scientist engaged in the process research and development efforts at the Schering–Plough Research Institute.

8.08

1,3-Thiazines and their Benzo Derivatives

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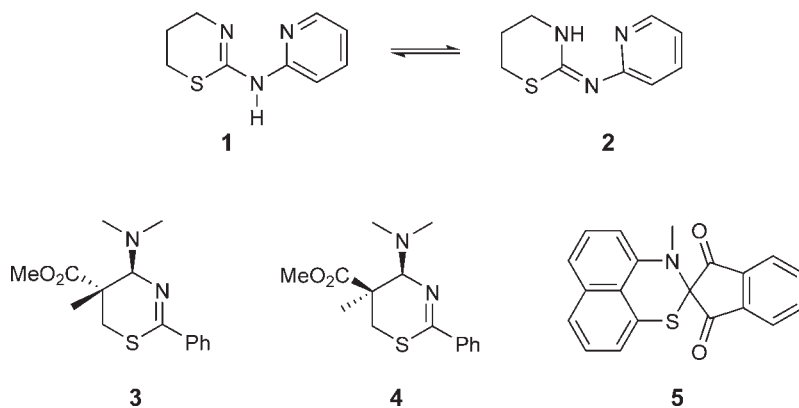
8.08.1 Introduction

Oxazines and thiazines were considered together in CHEC(1984) and this meant that the review was restricted. In CHEC-II(1996) <1996CHEC-II(6)383>, the individual heterocycles and their derivatives were reviewed separately, which allowed for a thorough coverage. This trend is continued in this edition where the 1,3-thiazines and their derivatives are discussed, and this includes a review of the chemistry, syntheses, and applications. It does not include the vast literature dealing with cepheids and related systems and other fused systems are not included unless their chemistry illustrates some significant property of the 1,3-thiazine heterocycle itself.

There have been no recent reviews of the area and research in this field has increased. As in the earlier editions, the reactions of 1,3-thiazines will be considered before the synthetic approaches to them, and 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-thiazines and benzothiazines will take precedence over their reduced forms and thiazinones, thiazinediones, and their derivatives will normally be dealt with last.

8.08.2 Theoretical Methods

The use of theoretical methods to investigate the structure of 1,3-thiazine derivatives has not been a very active area of research. The structure of a Cu(II) complex of *N*-(pyridin-2-yl)-5,6-dihydro-4*H*-1,3-thiazine-2-amine **1** was solved by both molecular modeling and powder X-ray analysis. The modeling process employed direct space methods with a 'Monte Carlo/parallel tempering' search algorithm, where the starting configuration was obtained by means of molecular mechanics calculations <2004MI993>. The structure of the ligand was shown to be the amino form **1** and not the imino form **2**, which is the normally preferred form of the heterocycle in the solid state.

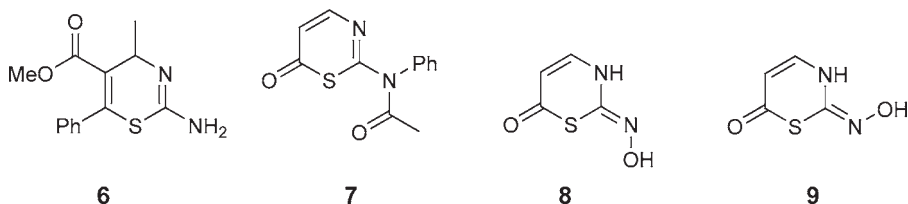


Calculations by PM3 methods have been carried out on molecules such as the diastereomers of methyl 4-(dimethylamino)-5-methyl-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate, and the *trans*-diastereomer **3** was shown to be significantly more stable than the corresponding *cis*-diastereomer **4** <2002TL6067>. The structure of the spiro compound **5**, which acts as a charge-transfer dye, was calculated by PM3 methods <1996JA1471>.

8.08.3 Experimental Structural Methods

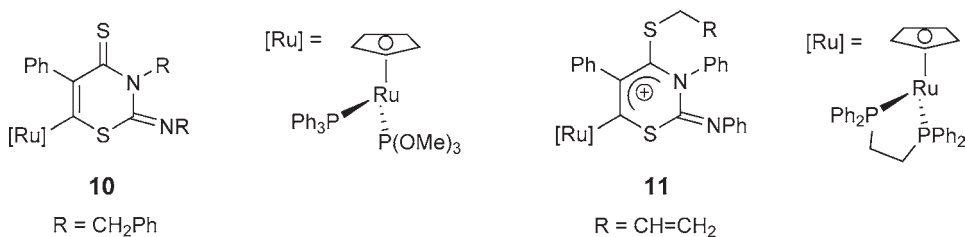
8.08.3.1 X-Ray Studies

The number of analyses of 1,3-thiazine derivatives by single crystal X-ray crystallography has increased significantly. Hydrogen bonding is observed throughout the structure of methyl 2-amino-4-methyl-6-phenyl-4*H*-1,3-thiazine-5-carboxylate **6** <2005AXEo2207>. The structure of 2-(*N*-phenylacetamido)-6*H*-1,3-thiazin-6-one **7** demonstrates that the thiazine ring and the amide group are nearly coplanar and the phenyl ring is roughly perpendicular to the acetamidothiazin-6-one moiety <2002AXEo288>. The structure of 2-(hydroxyimino)-2,3-dihydro-1,3-thiazine-6-one shows that the exocyclic carbon–nitrogen double bond is nearly standard and that the molecule exists in the (*Z*)-form **8** and not the (*E*)-form **9** <1996JCX215>.

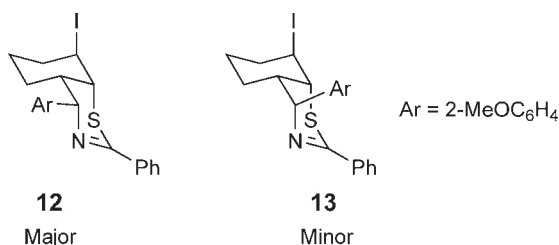


Single crystal X-ray analysis has proved to be valuable for the determination of the stereochemistry of chiral 1,3-thiazine derivatives and provided support for the mechanisms in stereoselective reactions [<2001EJO3553, 2001EJO3025, 2002TL6067, 2004T1827>](#).

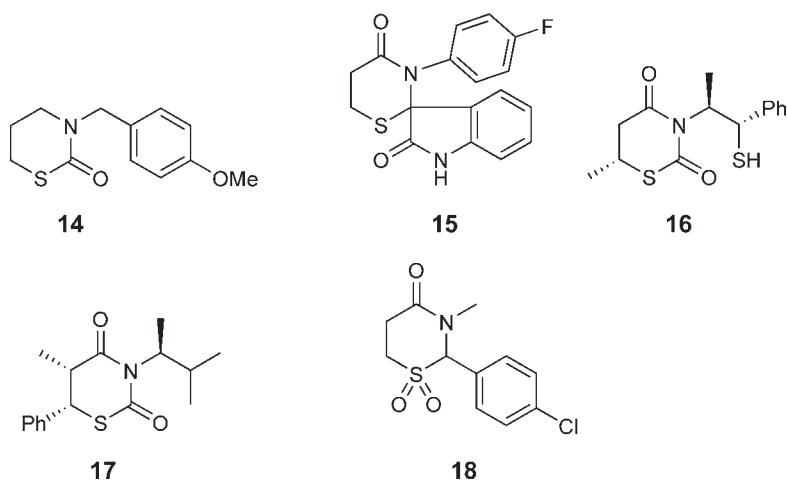
Analysis of *N*-(pyridin-2-yl)-5,6-dihydro-4*H*-1,3-thiazine-2-amine by crystallography has established that the predominant tautomer is the imino **2** and not the amino form **1** and, while both (*Z*)- and (*E*)-isomers are possible, only the (*E*)-isomer was observed [<2004JIB\(98\)15>](#). The conformation of the thiazine ring in the solid state is near to a half-boat with C-5 deviating above the plane. Interestingly, in the structures of the Cu(II) [<2004JIB\(98\)15, 2004MI993>](#), Co(III), and Ni(II) complexes [<2004POL1453>](#) of *N*-(pyridin-2-yl)-5,6-dihydro-4*H*-1,3-thiazine-2-amine, the amino form is preferred, presumably because of the intermolecular hydrogen bonding possible in the crystal structures. Structures of the ruthenium complexes of 1,3-thiazines **10** and **11** have also been reported [<1998OM2534, 2002JOM\(660\)127>](#).



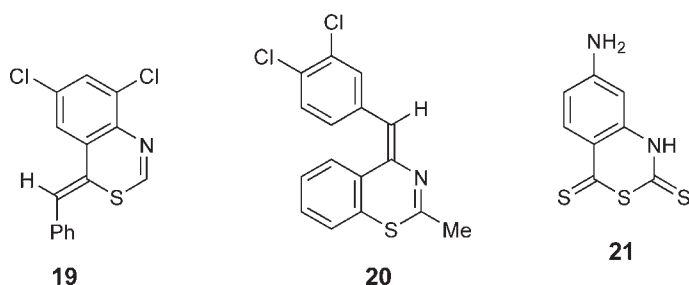
The stereochemistry of two diastereomers of 2,4-diaryl-5,6-dihydro-4*H*-1,3-thiazines **12** and **13**, which are isolated as a diastereomeric mixture, was identified, and the major diastereomer **12** contains the aryl group in the equatorial position [<2004CL508>](#).



In the simple 3-(4-methoxybenzyl)tetrahydro-1,3-thiazin-2-one **14**, tautomerism is not possible [<2004OL3489>](#), while enol-keto tautomeric forms are possible for some tetrahydro-1,3-thiazine-2,4-diones. The structure of compound **15** has the spiro carbon atom almost tetrahedral, and both the carbonyl groups are in the keto form [<2003SUL201>](#). The structure of two examples of *N*-substituted tetrahydrothiazines confirmed that ring atoms of the chiral diones, 3-(1-mercapto-1-phenylprop-2-yl)-6-methyltetrahydro-1,3-thiazine-2,4-dione **16** [<2003TL5053>](#) and 5-methyl-3-(3-methylbut-2-yl)-6-phenyltetrahydro-1,3-thiazine-2,4-dione **17** [<2006TL1153>](#), are nearly planar and the carbonyl at position 4 is in the keto form. The structure of racemic 2-(4-chlorophenyl)-3-methyltetrahydro-1,3-thiazin-4-one 1,1-dioxide (chlormezazone) **18** contains two crystallographically independent molecules [<2005ANSx57>](#). The tetrahydrothiazine and phenyl rings occupy orientations that are significantly different in each molecule. The tetrahydrothiazine rings in both molecules adopt distorted half-chair conformations, with the ring in one molecule being considerably flatter than the other.



The solid-state structures of the benzo derivatives (*Z*)-4-benzylidene-6,8-dichloro-4*H*-benzo[*d*][1,3]thiazine **19** <2003SL2231>, (*E*)-4-(3,4-dichlorobenzylidene)-2-methyl-4*H*-benzo[*e*][1,3]thiazine **20** <2004JOC4545>, and 7-amino-1*H*-benzo[*d*][1,3]thiazine-2,4-dithione **21** <2005AXE0387> have been determined. As expected, they possess planar structures, and the thiazine-2,4-dithione **21** molecules pack in the solid state through amino–thione hydrogen bonds <2005AXE0387>.



8.08.3.2 NMR Spectroscopy

8.08.3.2.1 Proton NMR

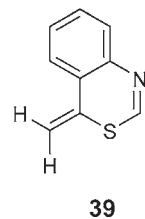
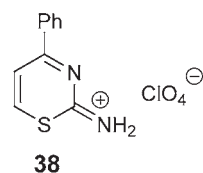
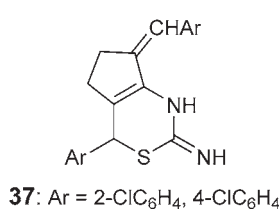
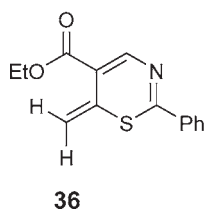
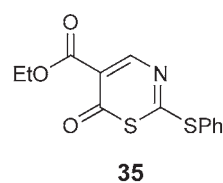
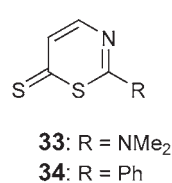
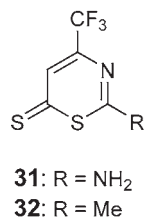
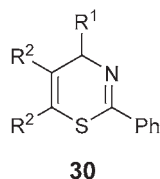
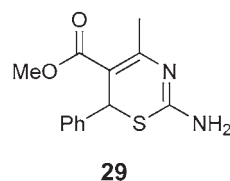
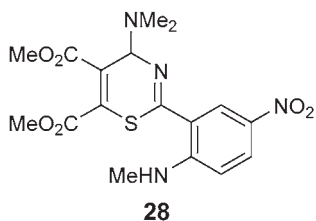
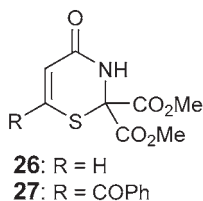
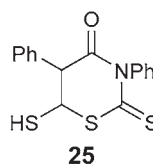
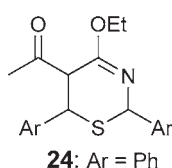
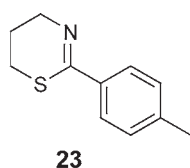
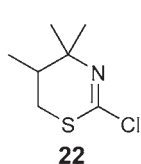
There is sufficient ^1H nuclear magnetic resonance (NMR) data available on the various structural types of 1,3-thiazines to be able to predict the chemical shift of the ring protons <1996CHEC-II(6)383>. A compilation of the data for some new derivatives is displayed in **Table 1**.

In the 4*H*-1,3-thiazine **28**, proton H-4 appears at 5.61 ppm as expected <2004TL5913>. The 5-H signal of **32** resonates at 7.23 ppm, which is a higher value compared to **31** and other 4-aryl/alkyl-2-amino-1,3-thiazines-6-thiones <2001RJO644>. This can be explained by the increase in electron density arising from the amino nitrogen in the thiazine ring of 2-amino-thiazinethiones which is transmitted through the conjugated bonds. The chemical shift of H-4 in 6*H*-1,3-thiazine-6-thiones **33** and **34** is not affected when the 2-phenyl substituent is replaced by a disubstituted amino group; however, the 5-H moves to a lower chemical shift <1997S573>.

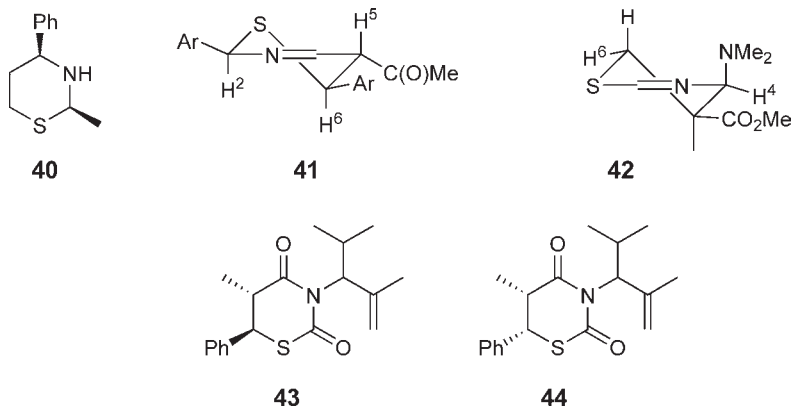
The pattern of chemical shifts in 6*H*-1,3-thiazines is known: the signal for H-4, which is next to the nitrogen, is generally at 6.3–6.55 ppm. The presence of an ester, which is an electron-withdrawing group, at C-5 reduces electron density at C-4 and the signal moves to a higher chemical shift value (usually 7.7–7.95 ppm). The additional electron depletion induced by the enone system causes the resonance of 4-H in ethyl 6-oxo-2-(phenylthio)-6*H*-1,3-thiazine-5-carboxylate **35** to appear at 8.66 ppm <1998J(P1)3245>. The spectrum of 4-phenyl-2*H*-1,3-thiazin-2-iminium perchlorate **38** contains signals for the H-5 and H-6 protons at typically high chemical shift values <2004CHE1595>.

Table 1 Proton NMR data for some 1,3-thiazine derivatives

Compound	δ_H (ppm)				Reference
	2-H	4-H	5-H	6-H	
22			1.75	2.92	2002CHE1150
23		3.90	1.84–1.93	3.90	2005HCA187
24	6.11		4.64	4.00	2000CHE862
25			6.74	6.60	2005T10013
26			6.15	7.10	2003SC4339
27			6.60		2003SC4339
28		5.61			2004TL5913
29				5.35	2005QSA364
30		5.94–6.35			2005CHE86
31			6.85		2001RJO644
32			7.23		2001RJO644
33		7.64	6.65		1997S573
34		7.58	7.02		1997S573
35		8.66			1998J(P1)3245
36		7.75			2004S775
37				5.80	2006PS1655
38			8.92	8.21	2004CHE1595
39	8.19				2003SL2231
40	4.34	3.77	1.67, 2.03	2.93, 3.19	2004TL1503
43			3.24	4.23	2006TL1153
44			3.30	4.60	2006TL1153



The H-5 and H-6 methylene protons of 2-methyl-4-phenyltetrahydro-1,3-thiazine **40** appear as separate signals with the protons in the equatorial positions at 2.03 and 2.93 and the axial protons at 1.67 and 3.19 ppm <2004TL1503>. Conformational preferences can be established using H–H and ^{13}C –H coupling constants through one, two, or three bonds <1996JOC1256, 2003CHE802, 2000CHE862, 2003TL5637>. For example, in 1-(2,6-diaryl-5,6-dihydro-2*H*-1,3-thiazin-5-yl)ethanone **41**, $J_{\text{H-5,H-6}} = 10.8\text{ Hz}$ corresponds to a *trans*-diaxial orientation of these hydrogens; therefore, the 5-acetyl and 6-phenyl groups occupy the pseudoequatorial positions. The coupling $J_{\text{H-2,H-5}} = 1.8\text{ Hz}$ confirms that the 2-aryl is also equatorial <2000CHE862>. The diequatorial protons, H-4 and H-6, in methyl 4-(dimethylamino)-5-methyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate **42** exhibit long-range coupling of 2 Hz <2002TL6067>. The relative configuration in the *syn*- and *anti*-diastereomers of a tetrahydro-1,3-thiazine-2,4-dione are identified using $J_{\text{H-5,H-6}}$ values, where $J_{\text{H-5,H-6}} = 10.2\text{ Hz}$ corresponds to the *anti*-diastereomer **43**, and $J_{\text{H-5,H-6}} = 4.2\text{ Hz}$ is observed for the *syn*-diastereomer **44** <2006TL1153>.



8.08.3.2.2 Carbon NMR

There are sufficient ^{13}C NMR data available in the literature on the various structural types of 1,3-thiazines to be able to predict the chemical shift of the ring carbon atoms <1996CHEC-II(6)383>. A compilation of the data for some new derivatives is displayed in Table 2. ^{13}C NMR is useful for demonstrating the existence of isomers since the chemical shifts are affected by the stereochemistry.

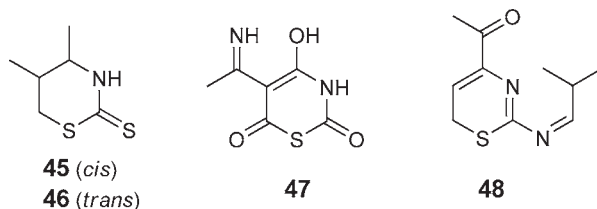


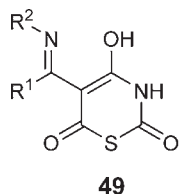
Table 2 Carbon NMR data for some 1,3-thiazine derivatives

Compound	δ_{C} (ppm)				Reference
	2-C	4-C	5-C	6-C	
23	158.3	48.0	26.5	19.1	2005HCA187
24	63.5	159.9	57.5	47.3	2000CHE862
25	192.1	165.4	25.8	42.4	2005T10013
33	168.8	150.3	117.6	198.2	1997S573
34	174.9	143.0	125.5	204.9	1997S573
36	176.5	157.6	112.0	189.7	1998J(P1)3245
38	172.9	171.3	115.5	149.7	2004CHE1595
45	194.6	49.0	29.4	42.8	2003CHE802
46	195.0	49.8	32.6	44.8	2003CHE802
47	174.8	167.2	96.3	163.1	2005RJC134
48	169.4	150.1	114.1	22.9	2003EJO421

8.08.3.3 Mass Spectrometry

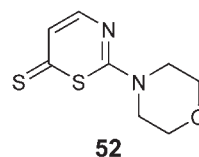
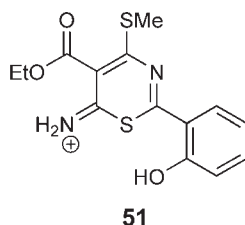
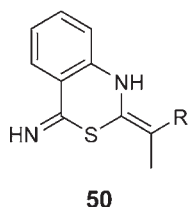
The mass spectra of diverse types of 1,3-thiazines are reported in the literature and in most examples the molecular ion contains the intact 1,3-thiazine. Subsequent ring fragmentation follows a similar pattern within a given series of compounds.

The series of 4-hydroxy-5-(imino)-3*H*-1,3-thiazine-2,6-diones **49** displays a characteristic fragmentation pattern <2005RJC134>.



M^{+} , $[M-CO]^{+}$, $[M-COS(COSH)]^{+}$, $[M-COHNCO]^{+}$, $[M-R^2]^{+}$, $[M-CO-COS(COSH)]^{+}$, $[M-2COHNCO]^{+}$, $[M-CO-COS(COSH)-R^1]^{+}$, $[M-R^2N=CR^1]^{+}$, $[R^2N=CR^1]^{+}$, $[M-CO-HNCO-COS(COSH)]^{+}$, and $[M-COS(COSH)-R^1NCO]^{+}$

The spectrum of **50** contains the molecular ion (100%) followed by the loss of the following fragments: CN, NHCS, and NHCSCN <2003SL1503>. The fragmentation pattern of **37** (Ar = 1-naphthyl) shows the molecular ion peak at m/z 418 as the base peak <2006PS1655>. The other fragments of interest are m/z 420 ($M+2$, 10%), 419 ($M+1$, 29%), 386 ($M-S$, 4%), 359 ($M-HNCS$, 5%).



The 6*H*-1,3-thiazine-6-iminium ring **51** fragments to give the following ions: $[M]^{+}$, $[M-HSMe]^{+}$, $[HOC_6H_4CS]^{+}$ as the base peak, $[OC_6H_4CS]^{+}$, $[HOC_4H_4CO]^{+}$, $[OC_6H_4CO]^{+}$, and $[HOC_6H_4CNH]^{+}$ <2003H(60)2273>. The spectrum of 2-morpholino-1,3-thiazine-6-thione **52** shows a strong signal for the molecular ion followed by loss of CS and $N(CH_2CH_2)_2O$ <1997S573>.

The mass spectra of *cis*- and *trans*-*N*-(4-phenylhexahydro-1*H*-benzo[*d*][1,3]thiazin-2(4*H*)-ylidene)benzenamine **53** display intense molecular ion peaks under electron ionization (EI) conditions and these are the base peaks <2005ARK(iv)39>. The loss of hydrogen, which occurs readily, can be explained by possible intramolecular cyclization between the *ortho*-carbon of the iminophenyl group and the ring nitrogen <1995RCM615>. Some of the interesting fragments observed are presented in Figure 1. In comparison with the mass spectra of the analogous oxazines, the pattern of fragmentation shows some differences; for example, there is no equivalent loss of OH[•] from the molecular ion.

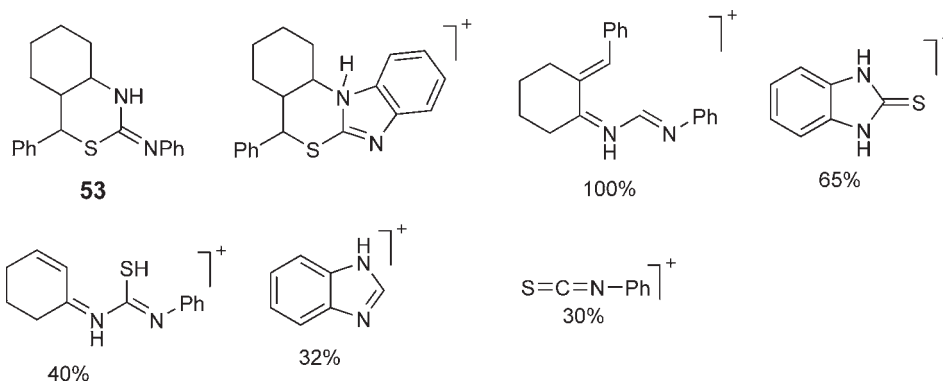


Figure 1

8.08.3.4 UV Spectroscopy

Characteristic absorption bands of the various structural forms of the 1,3-thiazines are known <1996CHEC-II(6)383>. An interesting photochromic behavior of 4-heteroaryl-5,6-di(2,5-dimethyl-3-thienyl)-2-phenyl-4*H*-1,3-thiazines **54** was observed on irradiation of the colorless compounds (Figure 2). The resulting tetracyclic compounds **55** are colored <2005CHE86>.

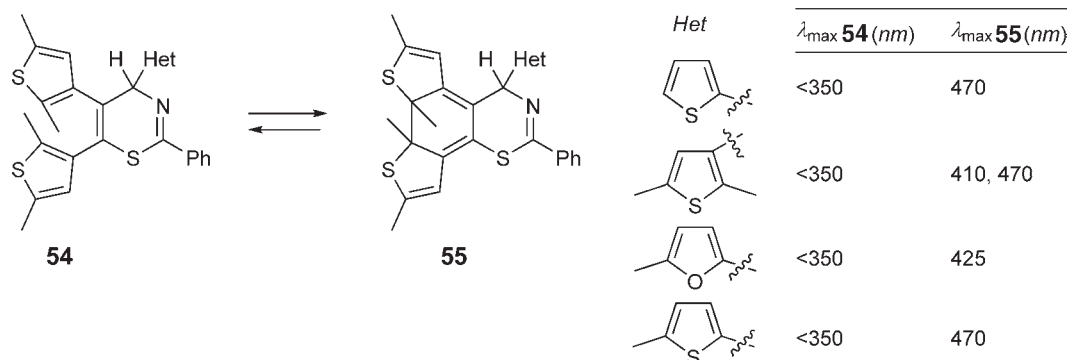
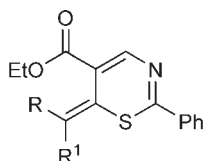


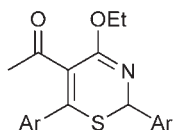
Figure 2

The spectrum of the intramolecular charge-transfer dye **5** contains an absorption band at $\lambda_{\max}$ = 390 nm <1996JA1471>. Three bands are observed in the spectra of 6-alkylidene-2-phenyl-6*H*-1,3-thiazine-5-carboxylates **56** and **57**, with the second band dependent on the substituents attached to the 6-alkylidene moiety <2004S775>. 1-(4-Ethoxy-2,6-diaryl-2*H*-1,3-thiazin-5-yl)ethanones **58** and **59** give rise to ultraviolet (UV) bands at $\lambda_{\max}$ = 205, 276, and 325 nm, and the 5,6-dihydro analogues **24** exhibit two UV bands at $\lambda_{\max}$ = 205 and 237 nm <2000CHE862>. Ethyl 5-methyl-2-(phenylimino)-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate **60** has two UV signals at $\lambda_{\max}$ = 267 and 302 nm <1999J(P1)3565>.



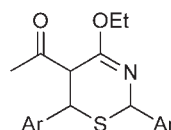
56: R = H; R¹ = Me; $\lambda_{\max}$ = 246, 284, 304 nm

57: R = Me; R¹ = Et; $\lambda_{\max}$ = 246, 235, 310 nm



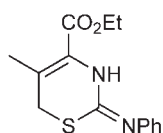
58: Ar = Ph; $\lambda_{\max}$ = 205, 276, 325 nm

59: Ar = 4-MeOC₆H₄; $\lambda_{\max}$ = 208, 238, 333 nm

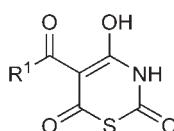


24: Ar = Ph, 4-MeOC₆H₄, 4-MeC₆H₄, 4-BrC₆H₄;

$\lambda_{\max}$ = 205, 222–237 nm



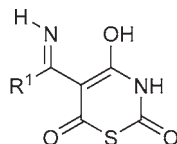
60: $\lambda_{\max}$ = 267, 302 nm



61: R¹ = Me, Et, Pr; $\lambda_{\max}$ = 199, 216–218, 276–279 nm

Three absorption bands are found in the UV spectra of 6*H*-1,3-thiazine-6-thiones **33** and **34**. The spectrum of the 2-phenyl derivative contains bands at $\lambda_{\max} = 253, 314$, and 425 nm. A blue shift is seen when the 2-phenyl substituent is replaced by the dimethylamino group and the bands are observed at $\lambda_{\max} = 240.5, 288$, and 428 nm <1997S573>.

The UV spectra of 4-hydroxy-5-iminoalkyl-3*H*-1,3-thiazine-2,6-diones **49** display three strong absorption bands at $\lambda_{\max} = 199\text{--}209, 227\text{--}292$, and 298–315 nm. The 5-acyl-4-hydroxy-3*H*-1,3-thiazine-2,6-diones **61** also display three absorption bands and these appear at $\lambda_{\max} = 199, 216\text{--}218$, and 276–279 nm <2005RJC134>. The UV bands in **62–66** undergo a red shift when the methyl ($R^1 = \text{Me}$) is replaced by an allyl, benzyl, or aryl group <2005RJC134>.



62: $R^1 = \text{Me}$; $\lambda_{\max} = 203, 227, 287$

63: $R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $\lambda_{\max} = 233, 284, 298 \text{ nm}$

64: $R^1 = \text{CH}_2\text{Ph}$; $\lambda_{\max} = 205, 261, 300 \text{ nm}$

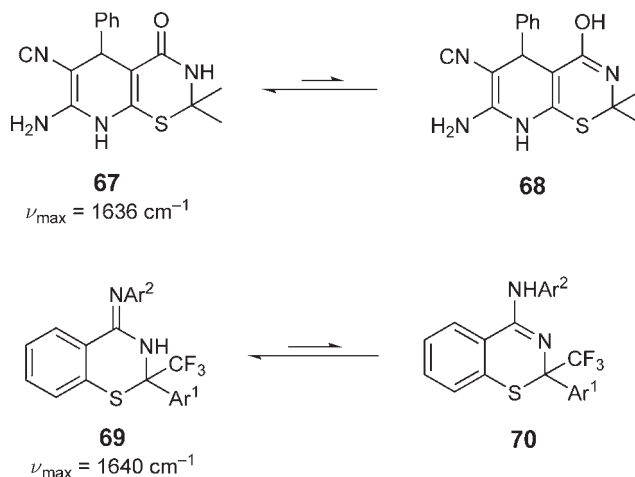
65: $R^1 = 1\text{-naphthyl}$; $\lambda_{\max} = 220, 262, 306 \text{ nm}$

66: $R^1 = 4\text{-MeC}_6\text{H}_4$; $\lambda_{\max} = 201, 262, 307 \text{ nm}$

8.08.3.5 IR Spectroscopy

Infrared (IR) spectra of the different 1,3-thiazine structural types have been well documented <1996CHEC-II(6)383>. IR spectroscopy provides valuable information on structure and tautomerism in the solid state and in solution.

The C=N vibration in 2-chloro-4,4,5-trimethyl-5,6-dihydro-4*H*-1,3-thiazine **22** is found at $\nu_{\max} = 1566 \text{ cm}^{-1}$ <2002CHE1150>. The distinctive peaks in the spectrum of 1-(4-ethoxy-2,6-diaryl-5,6-dihydro-2*H*-1,3-thiazin-5-yl)ethanone **24** are at $\nu_{\max} = 1640$ and 1720 cm^{-1} , which correspond to the N=C and C=O groups <2000CHE862>. Characteristically, the peaks shift to $\nu_{\max} = 1600, 1620$, and 1660 cm^{-1} in 1-(4-ethoxy-2,6-diphenyl-2*H*-1,3-thiazin-5-yl)ethanone **58**. The spectra of 4-hydroxy-5-iminoalkyl-3*H*-1,3-thiazine-2,6-diones **49** and **62–66** contain signals corresponding to C=N and C=O at $\nu_{\max} = 1660$ and 1580 cm^{-1} <2005RJC134>. The absorption bands in **35** are consistent with known 1,3-thiazine-6-ones <2004S775>. 2-Amino-5-(trifluoromethyl)-6*H*-1,3-thiazine-6-thione **31** gives rise to vibrations at $\nu_{\max} = 1635, 1570, 1500$, and 1300 cm^{-1} , which correspond to C=N, C=C, and C=S vibrations <2001RJO644>.



IR evidence shows the dominance of the keto form **67** as opposed to the enol isomer **68** <2001CHE378> and imino form **69** as opposed to the enamine **70** <2001CHE522>. The spectra of the 4-oxo-3,4-dihydro-1,3-thiazine-2,2-dicarboxylates contain three bands in the case of **26** when $R = \text{H}$ ($\nu_{\max} = 3425, 1751, 1677 \text{ cm}^{-1}$) with the bands at 1751 and 1677 cm^{-1} corresponding to $\nu(\text{C}=\text{O})$ and $\nu(\text{C}=\text{C})$. In compound **27**, when $R = \text{COPh}$, six bands ($\nu_{\max} = 3164, 1760, 1746, 1669, 1650, 1594 \text{ cm}^{-1}$) are observed <2003SC4339>.

8.08.4 Thermodynamic Aspects

The melting points, enthalpies, and associated entropies for a series of *N*-aryl-4*H*-benzo[*d*][1,3]thiazin-2-amines **71** are presented in [Table 3](#) <2004MI6291>. The melting points of the compounds determined by differential scanning calorimetry (DSC) agreed with the results obtained by hot-stage microscope.

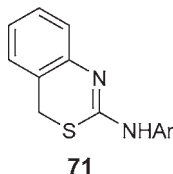


Table 3 Enthalpies, entropies, and melting points of *N*-aryl-4*H*-benzo[*d*][1,3]thiazin-2-amines **71**

<i>Ar</i>	$\Delta H_f (J g^{-1})$	$\Delta H_f (J mol^{-1})$	$T_m (^\circ C)$
4-MeC ₆ H ₄	118.4 ± 5.9	39.5 ± 2.0	113, 127
4-MeOC ₆ H ₄	92.9 ± 4.6	32.5 ± 1.6	132
4-MeCOC ₆ H ₄	56.2 ± 4.6	20.3 ± 1.6	137
4-ClC ₆ H ₄	29.0 ± 3.4	10.3 ± 1.2	129
4-BrC ₆ H ₄	211.3 ± 8.8	84.1 ± 3.5	137, 139
2-Me-4-ClC ₆ H ₃	314.8 ± 8.7	115.8 ± 3.2	136, 142

The ¹H NMR spectra of 2-(4,4-dimethyl-5,6-dihydro-4*H*-1,3-thiazin-2-yl)-*N*-arylacetamides **72** and **73** in chloroform or methanol contain signals at 3.3 ppm and 4.5 ppm corresponding to the imine–enamine tautomers ([Figure 3](#)) <1997AJC755>. The enamine form of 2-(2-methylphenyl) derivative **74** was not observed. ¹H NMR spectra of 1,3-thiazines **75** in dimethyl sulfoxide (DMSO) shows that the compounds exist entirely in the bicyclic tautomeric form **76** ([Figure 4](#)) <2001RJC1759>. A distinctive one-proton singlet, characteristic for an OH group, is observed at 8.14–8.23 ppm, which disappears on addition of D₂O. The $\nu(OH)$ at 3060–3080 cm^{−1} (KBr) and the absence of the carbonyl vibration bands confirm that the bicyclic tautomer is also preferred in the solid state <2001RJC1759>. The ¹H NMR spectra of 6,7-dihydrocyclopenta[*d*][1,3]thiazin-2(1*H*,4*H*,5*H*)-imines **37** in DMSO exhibit two NH signals, confirming that the structures in solution are not the amino forms **77** ([Figure 5](#)) <2006PS1655>.

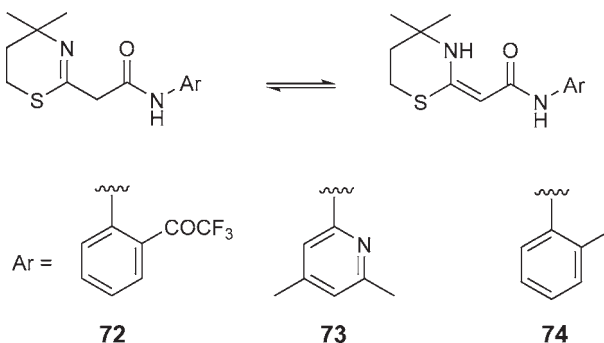


Figure 3

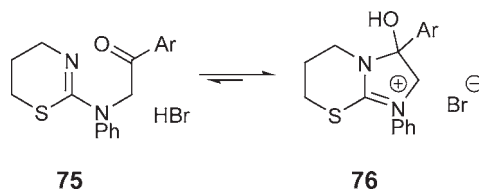


Figure 4

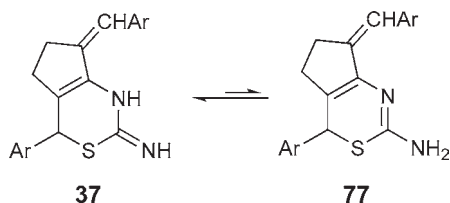


Figure 5

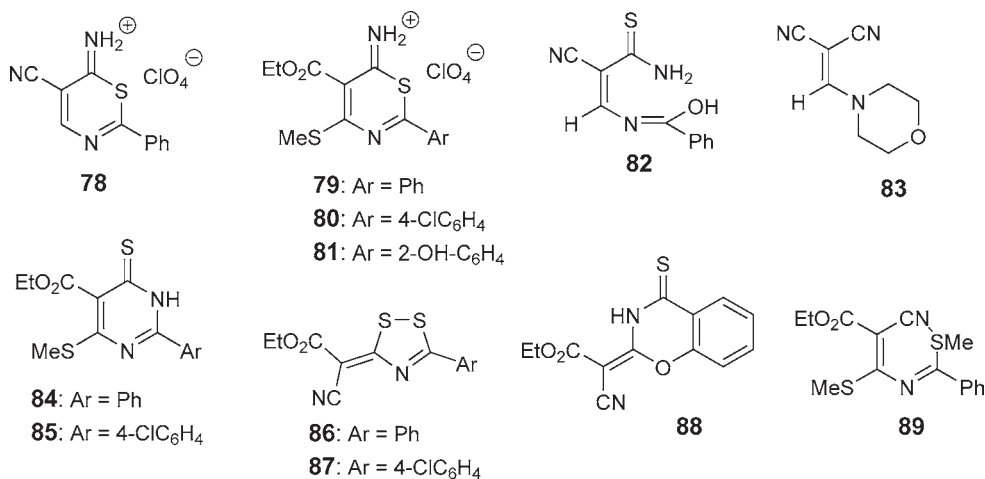
8.08.5 Reactivity of Fully Conjugated Rings

8.08.5.1 Introduction

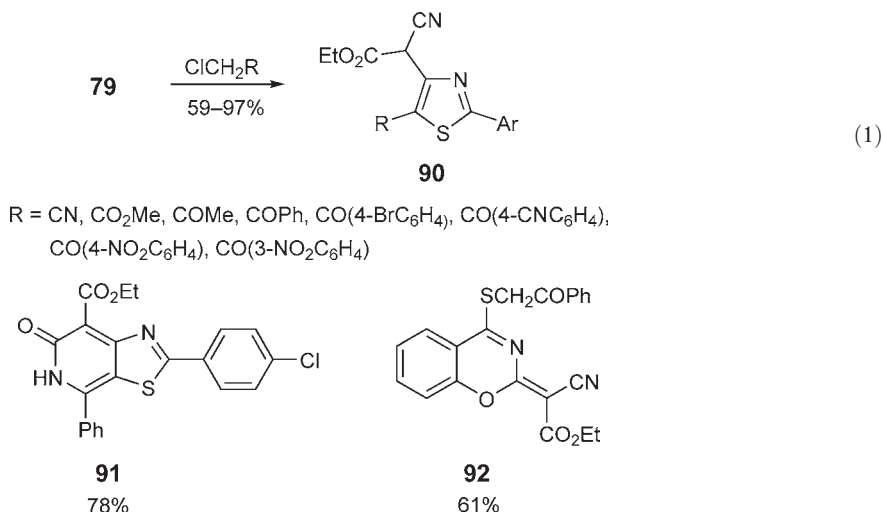
In this context, conjugated ring systems refers to 1,3-thiazine rings which do not contain an sp^3 -hybridized carbon or nitrogen. There has been little activity in this area and developments are limited to the reaction of 6*H*-1,3-thiazin-6-iminium salts.

8.08.5.2 Reactions with Bases and Nucleophiles

The 6*H*-1,3-thiazin-6-iminium hydrop perchlorate salts **78–81** give interesting products when treated with nucleophiles <2003H(60)2273>. Hydrolysis of 6-imino-6*H*-1,3-thiazine hydrop perchlorate **78** affords (2*Z*,4*Z*)-2-cyano-5-hydroxy-5-phenyl-4-azapenta-2,4-dienethioamide **82** in excellent yield, while treatment with morpholine gives 2-(morpholinomethylene)malononitrile **83** and thiobenzamide. The 5-(ethoxycarbonyl)-4-(methylthio)-2-aryl-6*H*-1,3-thiazin-6-iminium salts **79** and **80** react with hydroxide or morpholine to afford ethyl 4-(methylthio)-2-aryl-6-thioxo-1,6-dihydropyrimidine-5-carboxylates **84** and **85**. In the case of the 4-chloro analogue **80**, the (*Z*)-ethyl 2-(5-(4-chlorophenyl)-3*H*-1,2,4-dithiazol-3-ylidene)-2-cyanoacetate **87** is also formed for the reaction with sodium hydroxide. The 1,2,4-dithiazoles **86** and **87** can be obtained as the sole product when **79** and **80** are treated with sodium acetate in DMSO. Benzoxazine **88** is isolated when the iminium salt **81** is treated with morpholine or triethylamine. Nitrile **89** is formed as a (*E/Z*)-mixture when 6-imino-6*H*-1,3-thiazine hydrop perchlorate **79** is reacted with triethylamine and iodomethane in methanol <2003H(60)2273>.



Reactions of the salts **79–81** with chloroacetonitrile, methyl chloroacetate, chloroacetone, or substituted phenacyl bromide yield different products: the thiazoles **90** are formed in excellent yield from the reaction with **79** (Equation 1) and when salts **80** and **81** are treated with phenacyl bromide, thiazolopyridine **91** and benzoxazine derivative **92** are formed, respectively <2004H(63)2319>.



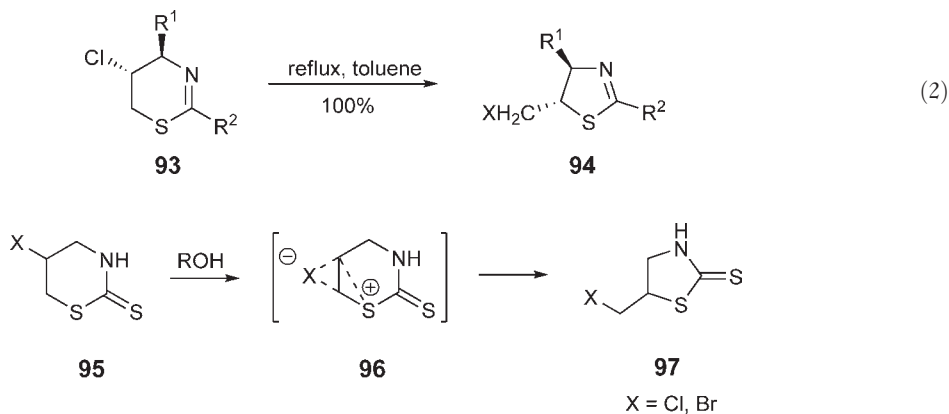
8.08.6 Reactivity of Nonconjugated Rings

8.08.6.1 Introduction

There has been considerable progress in this area and new developments include the thermal rearrangement of *trans*-4*H*-5,6-dihydro-1,3-thiazines and thiazine-2,6-diones and photochemical reactions of some 2,3-dihydro-6*H*-1,3-thiazines. The reactions at the ring nitrogen and ring carbon atoms have been exploited for the synthesis of fused heterocycles, including lactams. Ring contractions have produced five-membered rings.

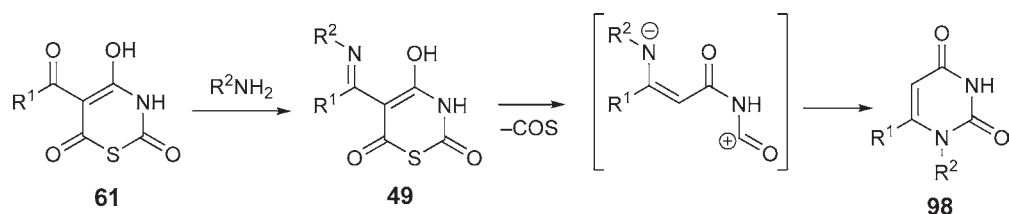
8.08.6.2 Unimolecular Thermal and Photochemical Reactions

Intramolecular thermal rearrangement of *trans*-4*H*-5,6-dihydro-1,3-thiazines **93** affords *trans*-4,5-dihydro-1,3-thiazoles **94** (Equation 2) <1997JPP09136881>. 5-Halotetrahydro-1,3-thiazine-2-thiones **95** undergo facile rearrangement when heated with methanol, ethanol, or isopropanol, probably via intermediate **96**, to give 5-(halomethyl)thiazolidine-2-thiones **97** (Scheme 1). No solvolysis products are observed <2002CHE1533>.

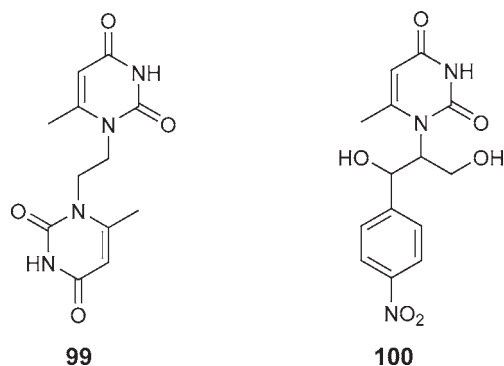


Scheme 1

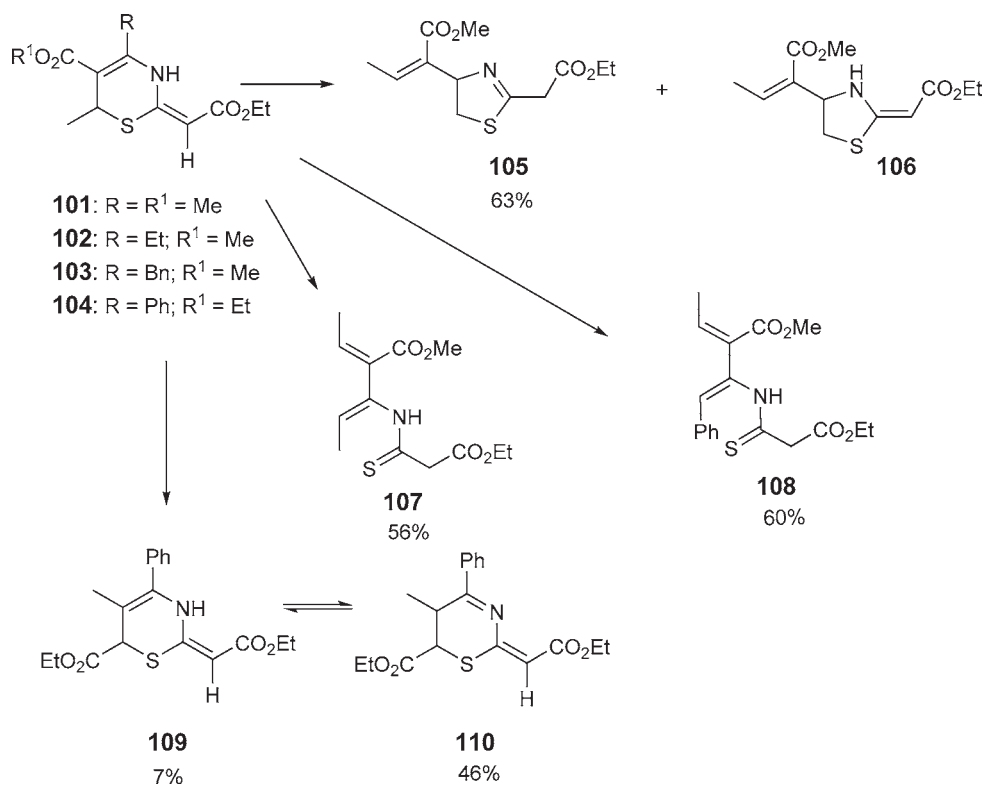
The thiazine-2,6-diones **49** lose one molecule of COS in boiling dimethylformamide (DMF) to afford 1-substituted-6-alkyl uracils **98** (Scheme 2) <2005RJC134, 2003TL5279>. The same products are obtained when 5-acyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-diones **61** are heated together with the corresponding primary amine in boiling DMF. The dimeric compound **99** and the nitrophenyl hydroxylated example **100** are produced by the same route <2005RJC134>.



Scheme 2

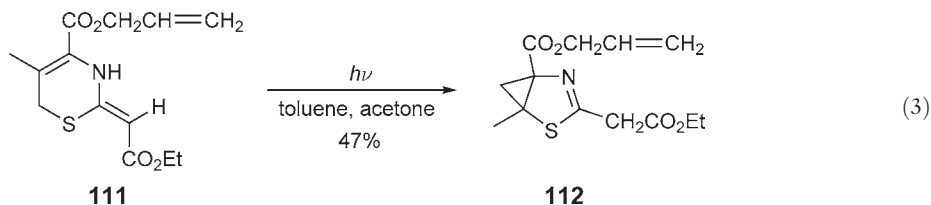


Photolysis of the four examples of 2,3-dihydro-6*H*-1,3-thiazines **101**–**104** resulted in the formation of different products which is dependent on R and R¹ (Scheme 3). When both groups are methyl (**101**), isomeric thiazolines **105** and **106** are isolated, the thiazoline **106** being the major isomer. The ethyl analogue **102** reacts differently and the thioamide **107** is formed. All four thioamide isomers are formed when the benzyl analogue **103** is photolyzed and the



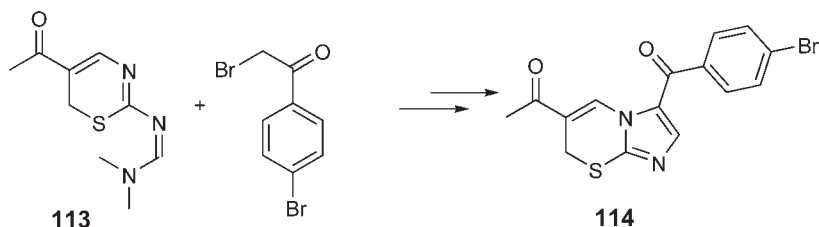
Scheme 3

major product, the *Z,Z*-isomer **108**, was isolated in 60% yield. Thiazines **109** and **110** are suggested as photolysis products of the phenyl analogue **104** <1998J(P1)569>. When the 2,3-dihydro-6*H*-1,3-thiazine **111** is subjected to photolysis, it undergoes rearrangement to give the bicyclic product **112** (Equation 3) <1999J(P1)2449>.



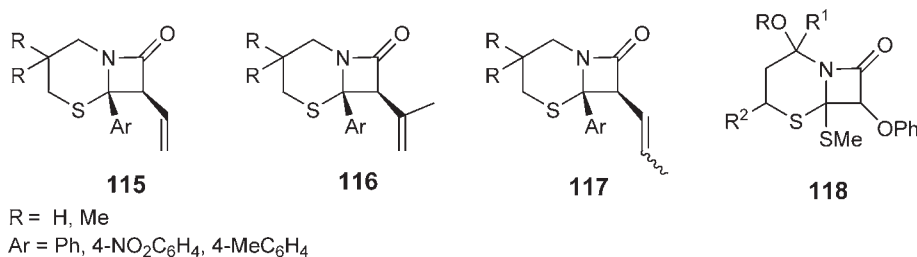
8.08.6.3 Electrophilic Attack at Nitrogen

Alkylation of *N'*-(5-acetyl-6*H*-1,3-thiazin-2-yl)-*N,N*-dimethylformamidine **113** with 2-bromo-1-(4-bromophenyl)ethanone resulted in attack at the nitrogen in the ring and formation of the *N*-alkylated salt (Scheme 4). The latter was not isolated but treated directly with 2 equiv of base to give, after loss of dimethylamine, the imidazo[2,1-*b*][1,3]thiazine **114** <2003EJO421>.

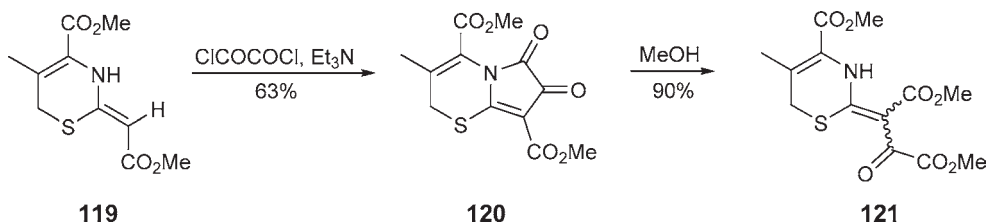


Scheme 4

Conversion of 2-phenyl-5,6-dihydro-4*H*-1,3-thiazines into bicyclic β -lactams **115** was effected by the use of triallyl phosphate, CO pressure, diisopropylethylamine, and triphenylphosphine/transition metal catalyst <1996JOC1256>. The catalysts used were $\text{Pd}(\text{Ph}_3)_2\text{Cl}_2$, $[\text{Pd}(2\text{-methylallyl})\text{Cl}]_2$, $\text{Pd}(\text{PhCN})_2\text{Cl}_2$, $[\text{Rh}(\text{COD})\text{Cl}]_2$, and $(\eta^6\text{-PhBPh}_3)^-\text{Rh}^+(\text{COD})$ (COD = cyclooctadiene). The yields depended on the substituent on the aryl group: phenyl and 4-nitrophenyl gave higher yields (61% and 78%, respectively), while a moderate yield (47%) was obtained for the 4-methoxyphenyl. Substitution of triallyl phosphate with diethyl 2-methylprop-2-enyl phosphate gave the corresponding products **116** in significantly lower yields, whereas treatment with diethyl but-2-enyl phosphate (*E/Z* = 9:1) yielded a (*E/Z*)-isomeric mixture **117** <1996JOC1256>. Reaction of 4-alkoxy-2-(methylthio)-5,6-dihydro-4*H*-1,3-thiazines with phenoxyacetyl chloride produces the cephams **118** <1996KGS557>.

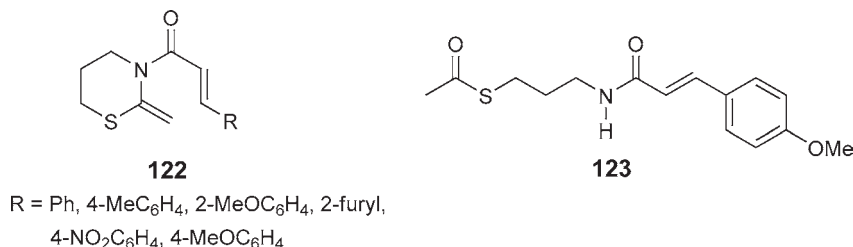


The γ -lactam **120**, which is very reactive, is obtained from the reaction of methyl 2-(2-methoxycarbonylmethyl)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate **119** with oxalyl chloride and in the presence of triethylamine (Scheme 5). Subsequent treatment with methanol affords 3,6-dihydro-2*H*-1,3-thiazine **121** as a mixture of isomers. Similar treatment of the 4-allyl carboxylate analogue with oxalyl chloride/triethylamine yielded the corresponding γ -lactam <1999J(P1)2449>.



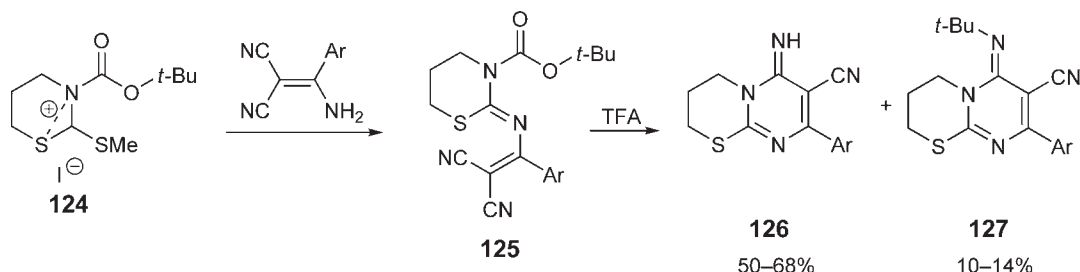
Scheme 5

N-Acylation of 2-methyl-5,6-dihydro-4*H*-1,3-thiazine with cinnamoyl chloride in the presence of triethylamine furnishes (*E*)-1-(2-methylenetetrahydro-1,3-thiazin-3-yl)-3-arylprop-2-en-1-ones **122**. These products undergo hydrolysis readily due to the *S,N*-ketene acetal-type bonds present in the molecules and are therefore not stable. Thus (*E*)-3-(3-(4-methoxyphenyl)acrylamido)propyl ethanethioate **123** is isolated in 92% yield from the corresponding thiazine after column chromatography on SiO₂ or Al₂O₃ <2001S135>.

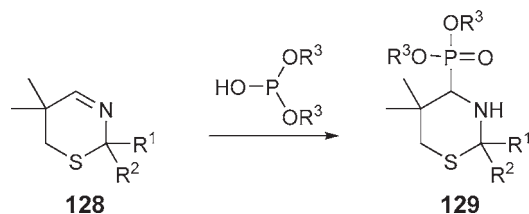


8.08.6.4 Nucleophilic Attack at C

1,3-Thiazinium salts are useful precursors for the synthesis of a wide range of compounds <1996JHC1791, 1996JHC1785, 1996JHC1903>. Treatment of 2-methylthiotetrahydro-1,3-thiazinium iodide **124** with 3-amino-2-cyano-3-arylacrylonitriles gave the N-protected (tetrahydro-1,3-thiazin-2-ylideneamino)(aryl)methylenemalononitrile derivatives **125** in low to moderate yields (Scheme 6). Deprotection of the latter with trifluoroacetic acid (TFA) results in the formation 6-imino-8-aryl-2,3,4,6-tetrahydropyrimido[2,1-*b*][1,3]thiazine-7-carbonitriles **126**. The *N*-*tert*-butyl derivatives **127** are formed by the reaction of **126** with the isobutylene evolved during the deprotection step <1996JHC1903>. The 2*H*-thiazines **128** react at C-4 with dialkyl phosphites to produce aminophosphonic esters **129** (Equation 4) <1996PS(116)123>.



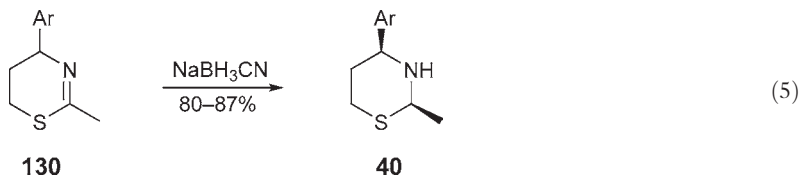
Scheme 6



(4)

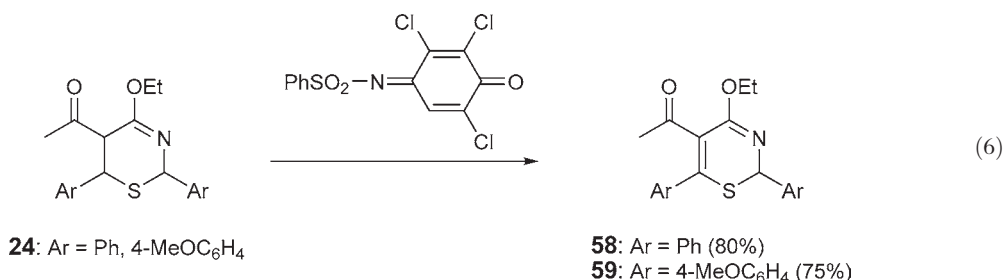
8.08.6.5 Reduction

A facile synthesis of 2,4-disubstituted-tetrahydro-1,3-thiazines **40** involves reduction of the 5,6-dihydro-4*H*-1,3-thiazine **130** with NaBH_3CN to give the *syn*-isomers (Equation 5) <2004TL1503>.



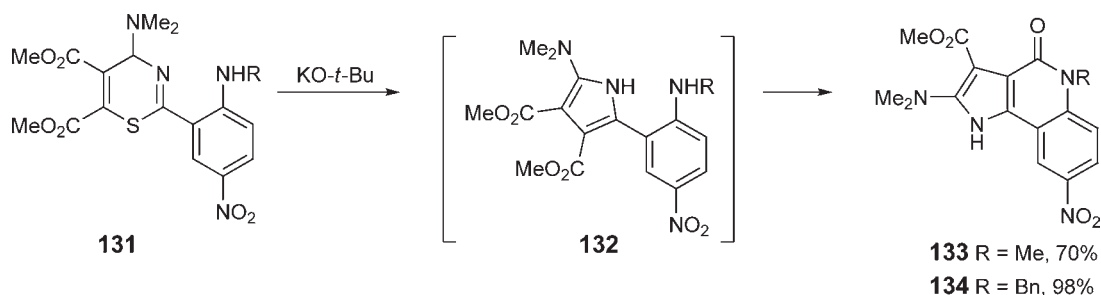
8.08.6.6 Oxidation

N-(2,3,5-Trichloro-4-oxocyclohexa-2,5-dienylidene)benzenesulfonamide oxidations of 5,6-dihydro-1,3-thiazines **24** afford excellent yields of 1-(4-ethoxy-2,6-diaryl-2*H*-1,3-thiazin-5-yl)ethanone **58** and **59** (Equation 6) <2000CHE862>.



8.08.6.7 Reactions with Bases and Nucleophiles

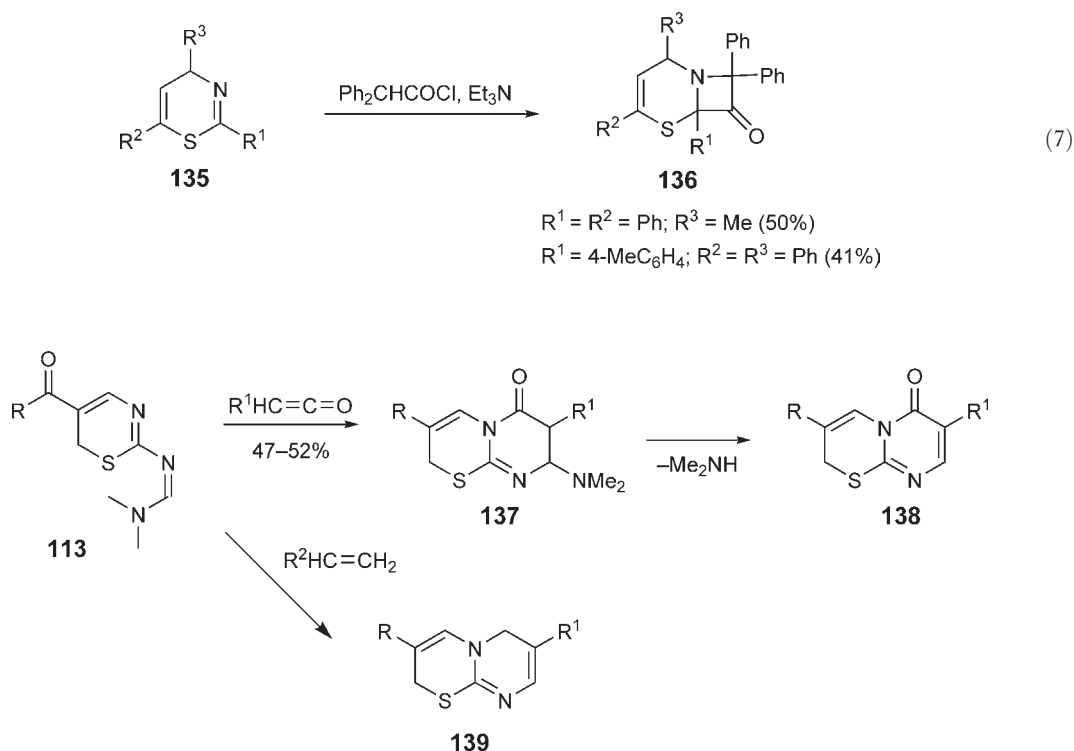
Ring contraction with desulfurization occurs when the 4*H*-1,3-thiazines **131** are reacted with potassium *t*-butoxide (Scheme 7) <2004TL5913>. The bis(methoxycarbonyl)pyrroles **132** are not isolated but instead give the 4-oxo-4,5-dihydro-2*H*-pyrrolo[3,4-*c*]quinolines **133** and **134**.



Scheme 7

8.08.6.8 Cycloaddition

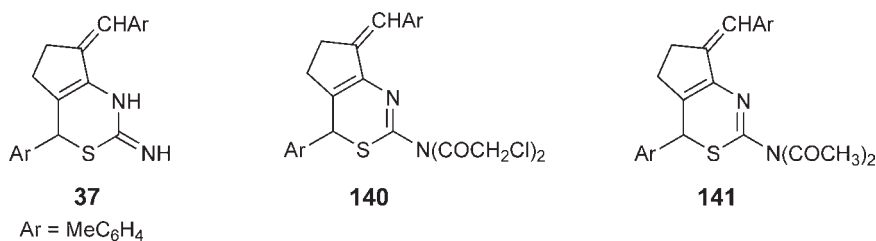
Cephems are formed by treating 6*H*-1,3-thiazines with ketenes <1997PS(131)147>. Trisubstituted 4*H*-1,3-thiazines **135** undergo [2+2] cycloaddition with diphenylketene to afford the β -lactams **136** (Equation 7) <2001HCA2347, 2000H(52)111>. *N'*-(5-Acetyl-6*H*-1,3-thiazin-2-yl)-*N,N*-dimethylformamidine **113** undergoes [4+2] cycloaddition with a series of ketenes to give pyrimido[2,1-*b*][1,3]thiazine-6-ones **138** with loss of dimethylamine (Scheme 8). Similarly, cycloaddition with alkene dienophiles formed pyrimido[2,1-*b*][1,3]thiazines **139** <2003EJO421>. All these adducts are isolated in modest yields.



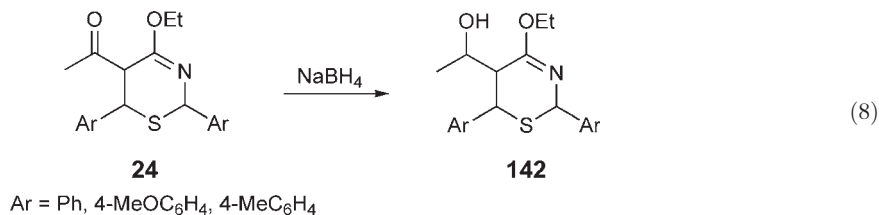
Scheme 8

8.08.7 Reactions of Substituents Attached to Ring Carbon

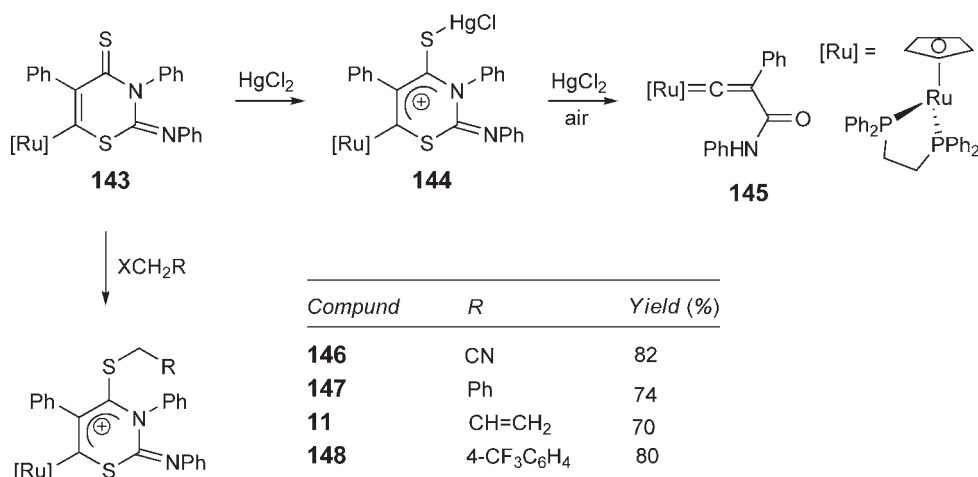
Reaction occurs at the nitrogen attached to C-2 when the 7-arylmethylene-4-aryl-6,7-dihydrocyclopenta[*d*][1,3]-thiazin-2(1*H*,4*H*,5*H*)-imines **37** are treated separately with chloroacetyl chloride and acetic anhydride to give the *N,N*-di(chloroacetyl) and the *N,N*-diacetyl derivatives **140** and **141** <2006PS1655>.



When 5,6-dihydro-1,3-thiazines **24** are treated with sodium borohydride, the carbonyl group is reduced to the alcohol **142** and the azomethine bond remains intact (Equation 8) <2000CHE862>. This is in contrast to 4*H*-1,3-thiazines where the azomethine bond does react <1964JHC300>.

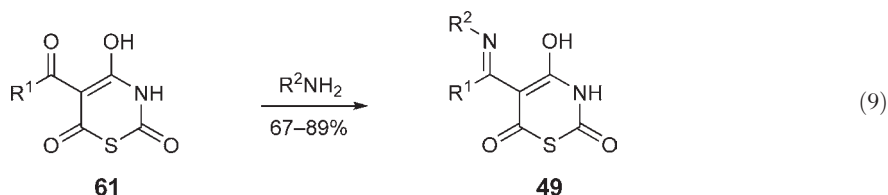


The ruthenium complex **143** reacts with mercury(II) chloride to give complex **144**, which, when treated with excess mercury(II) chloride in air, undergoes ring opening to give the ring-opened complex **145** [\[2002JOM\(660\)127\]](#). Reaction of complex **143** with electrophiles, XCH_2R , gives high yields of compounds **11** and **146–148** (Scheme 9).



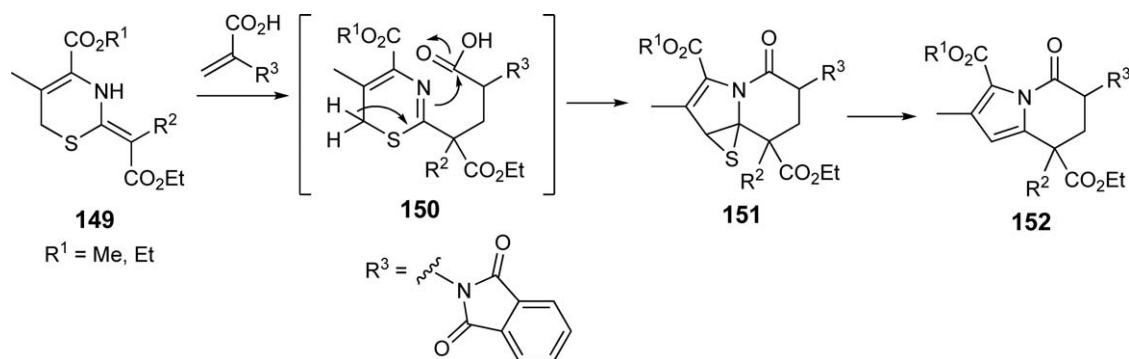
Scheme 9

5-Acetyl-4-hydroxy-2H-1,3-thiazine-2,6-diones **61** react with primary amines to give Schiff bases **49**. These products are stable under conditions of excess base and prolonged heating in boiling propan-2-ol (Equation 9) [\[2005RJC134, 2003TL5279\]](#).



4-Substituted phenacyl bromides react at the exocyclic nitrogen of *N*-(tetrahydro-1,3-thiazin-2-ylidene)benzenamine to give product **75**, which exists entirely in the bicyclic form **76** [\[2001RJC1759\]](#). Similarly the condensation of the corresponding *N*-benzyliminotetrahydro-1,3-thiazine with phenacyl bromides gives the corresponding salts **76**.

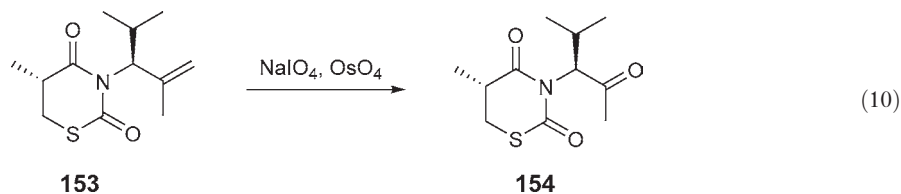
The Michael attack of the enamine moiety in the 3,6-dihydro-2H-1,3-thiazine **149** on α -phthalimido acrylic acid affords the cyclic product **152**, most probably through the intermediate **150**. Support for the mechanisms comes from the isolation of the 5,6,7,8-tetrahydro-1a*H*-thiireno[2,3-*i*]indolizine **151** in 10% yield (Scheme 10) [\[1999J\(P1\)3565\]](#).



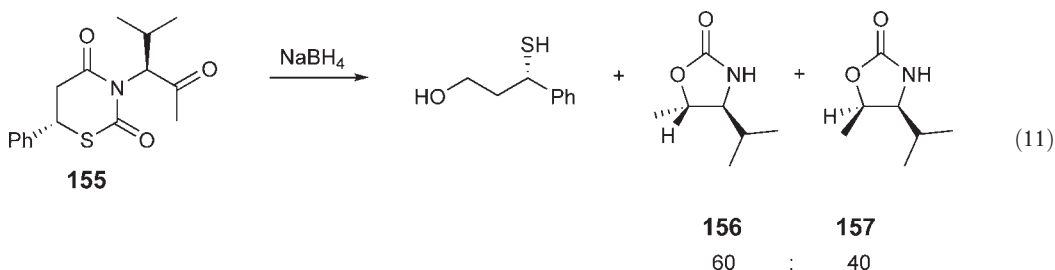
Scheme 10

8.08.8 Reactions of Substituents Attached to Ring Heteroatoms

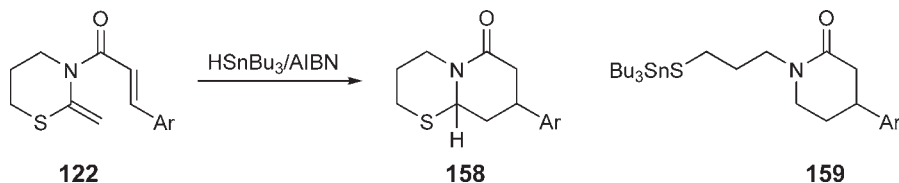
Treatment of the 1,3-thiazine **153** with 3 equiv of NaIO_4 and catalytic OsO_4 results in oxidation at the C–C double bond to give the (2-methyl-4-oxopentan-3-yl)tetrahydro-1,3-thiazine-2,4-dione **154** in moderate yield (Equation 10) <2006TL1153>.



When the 5-phenyltetrahydro-1,3-thiazine-2,4-dione **155** is treated with NaBH_4 , the thiazine ring fragments to produce (*S*)-3-mercapto-3-phenylpropan-1-ol in 45% yield and the oxazolidin-2-ones **156** and **157** as a mixture of diastereomers (Equation 11) <2006TL1153>.



The reaction of (*E*)-1-(2-methylenetetrahydro-1,3-thiazin-3-yl)-3-arylprop-2-en-1-ones **122** in the presence of tributyltin hydride and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) gives different products depending on the Ar group at position 3. Thus 8-aryl-hexahydropyrido[2,1-*b*][1,3]thiazin-6(2*H*)-one **158** is isolated as a diastereomeric mixture from thiazine **122** when Ar = Ph and 4-MeC₆H₄. The 1-(3-(tributylstannylthio)propyl)piperidin-2-one **159** is formed as a stable compound when Ar = 4-MeOC₆H₄, and the 4-NO₂C₆H₄ analogue is unreactive <2001S135>.



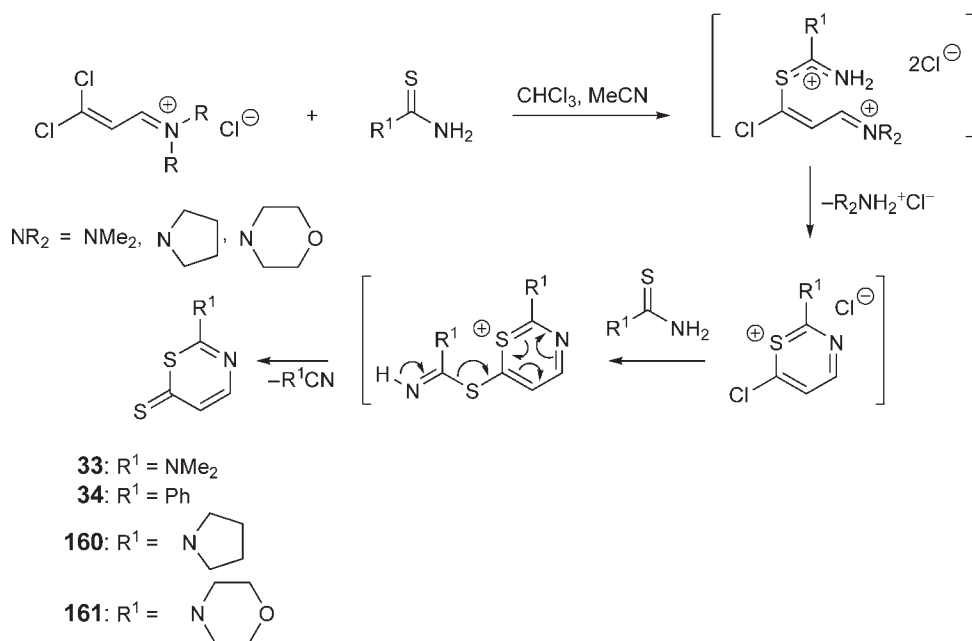
8.08.9 Ring Synthesis

The classification used in CHEC-II(1996) <1996CHEC-II(6)383> is followed. Therefore the syntheses of 1,3-thiazines and their derivatives are classified according to the composition of the assembled fragments.

The discussion will follow the trend: thiazines, thiazinones and thiones, dihydrothiazines, dihydrothiazinones and thiones, perhydrothiazines and perhydrothiazinones, and thiones. Discussion on 1,3-benzothiazines and 3,1-benzothiazines is incorporated within the appropriate section, depending on the oxidation state of the heterocyclic ring.

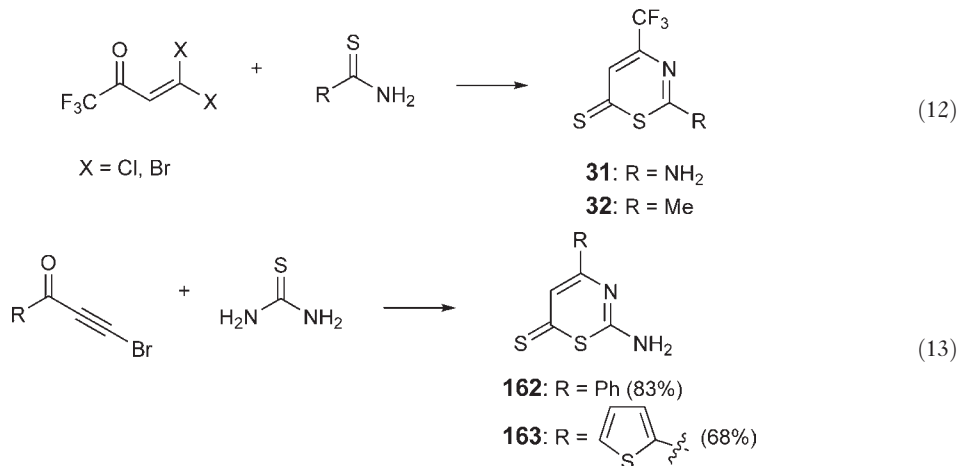
8.08.9.1 Syntheses from [3+3] Fragments

The 2-substituted 1,3-thiazin-6-thiones **33** and **34** and **160** and **161** are accessible by reacting 3,3-dichloroprop-2-ene iminium salts (vinylogous Viehe salts) with thiobenzamide or *N,N*-disubstituted thioureas (Scheme 11) <1997S573>. The ring closure occurs with loss of amine as the hydrochloride salt and the thiones are generated after a reaction with another thioamide molecule.

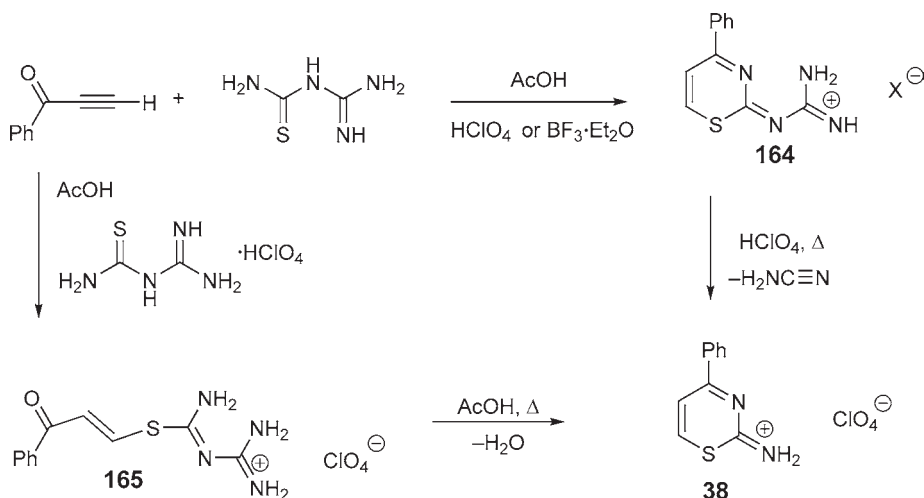


Scheme 11

Condensation of thiourea and thioamides with α,β -unsaturated carbonyl compounds is a common route to substituted 1,3-thiazines. Trifluoromethyl analogues have been prepared using the trifluoromethyl derivatives, 2,2-dichloro- or 2,2-dibromovinyl trifluoromethyl ketones, with thiourea and thioacetamide. Both halogen atoms are lost on cyclization, which generates 2-amino-4-trifluoromethyl-1,3-thiazine-6-thione **31** and 2-methyl-4-fluoromethyl-1,3-thiazine-6-thione **32** (Equation 12) <2001RJO644, 2003RJO807>. 2-Amino-4-phenyl-1,3-thiazine-6-thione **162** and 2-amino-4-(2-thienyl)-1,3-thiazine-6-thione **163** are formed as the hydrobromide salts when the corresponding 1-acyl-2-bromoalkynes are treated with 2 equiv thiourea in acetic acid and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Equation 13) <2000RCB1917>. The free bases are isolated by recrystallization from ethanol/water mixture.

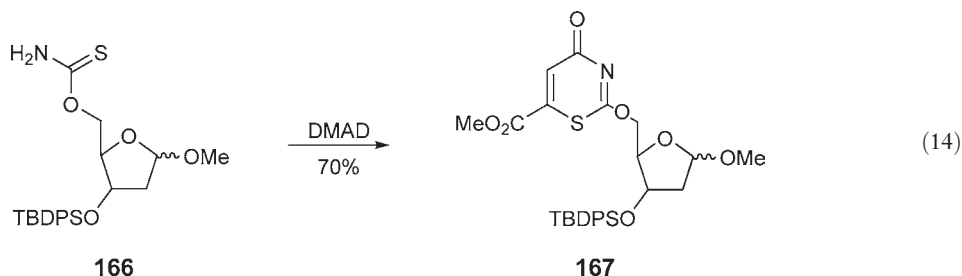


Condensation of thioamides and thiourea with α,β -unsaturated ketones is a general method for the construction of the 1,3-thiazine skeleton. In a variation of the reaction, 1-phenylprop-2-yn-1-one was reacted with *N*-amidinothiourea in glacial acetic acid and in the presence of HClO_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give [4-phenyl-2*H*-1,3-thiazin]-2-ylideneguanidium perchlorate salts **164** (Scheme 12). Heating the latter compound in perchloric acid causes elimination of cyanamide and formation of 2-imino-4-phenyl-2*H*-1,3-thiazinium perchlorate **38** <2004CHE1595>. The reaction presumably occurs via the benzoyl-vinylisothiuronium salts. This seems likely since the reaction of *N*-amidinothiourea perchlorate salt with 1-phenylprop-2-yn-1-one gives salt **165** which can be isolated and cyclized in the presence of acetic acid to give **38** directly.



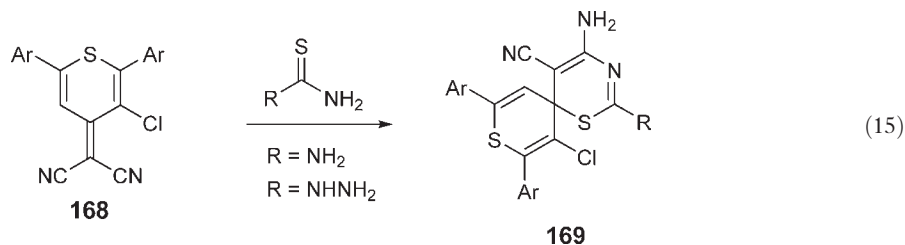
Scheme 12

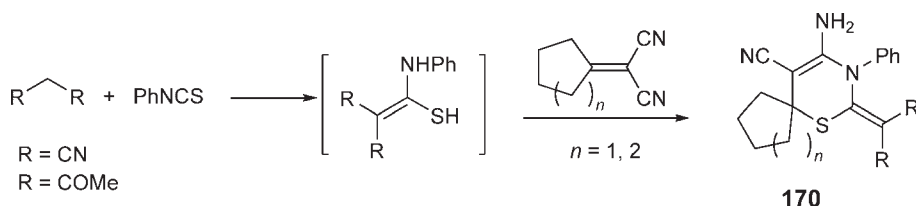
The cycloaddition of the deoxyribose-derived thionocarbamate **166** with dimethyl acetylenedicarboxylate (DMAD) gives the corresponding 1,3-thiazinone **167** (Equation 14) <2001PAC1189>. 5-Acyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-diones **61** were prepared by the reaction of potassium thiocyanate with malonic acid and acid anhydride in the presence of the corresponding acid at room temperature <2003TL5279, 2004RJC312>. The yields are low and range from 20% to 46%. The 5-acetyl derivative had been previously obtained by heating a mixture of dithiocarbamide, malonic acid, and PCl_3 ; however, the melting point reported for this compound is considerably lower <1964M495>.



It is well known that 1,3-thiazine-4,6-diones can exist in three tautomeric forms <1960CB671, 1976KGS1042>. Cycloaddition of chlorocarbonyl ketenes with thioamides has been reported to produce only the 4-hydroxy-1,3-thiazin-6-ones, whereas the same reaction with amides gives either 4-hydroxy-1,3-oxazin-6-ones or a mixture of tautomers depending on the substituents on the starting materials <2005ARK(xv)88>.

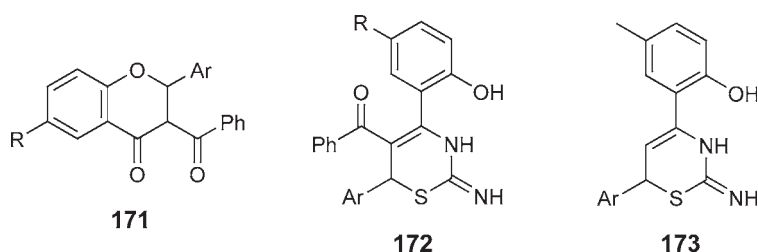
Cycloaddition reactions of 3-chloro-4-thiopyridinemalononitriles **168** with thiourea or thiosemicarbazide in the presence of piperidine results in the formation of the spiro derivatives **169** (Equation 15) <2004PS1075>. The stereochemistry and reactivity of cyclopentane-, cyclohexane-, cycloheptane-, and cyclooctane-fused 1,3-thiazines have been reviewed <1998AHC(69)349>. Dicyanoketene *N,S*-acetal and diacetylketene *N,S*-acetal, prepared from the reaction of phenyl isothiocyanate with malononitrile and pentan-2,4-dione, respectively, react with cycloalkylenemalononitriles to give the spiro[1,3]thiazine derivatives **170** (Scheme 13). Use of heterocyclic derivatives of malononitriles produces the corresponding spiro-1,3-thiazines <2004PS1237>.



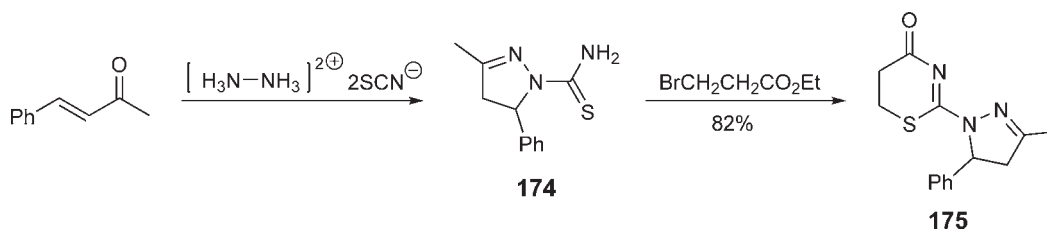


Scheme 13

2-Imino-3,6-dihydro-1,3-thiazines **172** were prepared by reacting 3-benzoylflavanones or 2-furyl-3-benzoylchromanones **171** with thiourea under basic conditions <2001ASJ990, 2002OJC331>. The base-catalyzed synthesis of a series of 2-(2-imino-6-aryltetrahydro-1,3-thiazin-4-yl)-4-methylphenol derivatives **173** was studied under various conditions by reacting chalcones with thiourea <2001ASJ1560>.



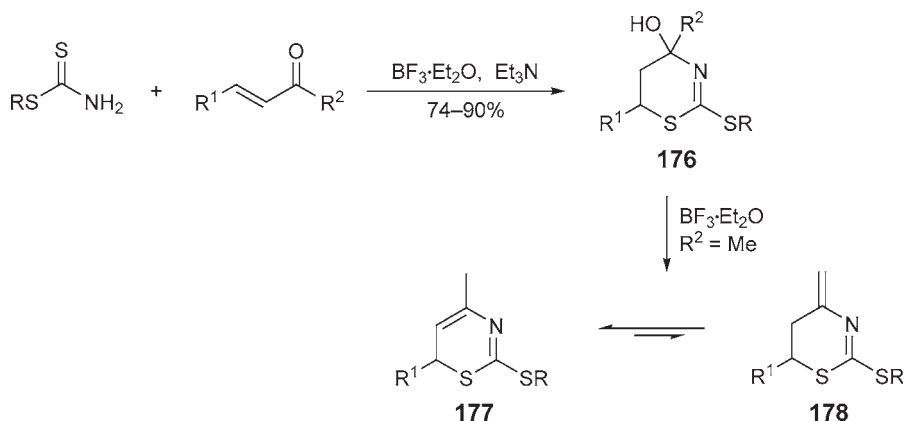
1-Thiocarbamoyl-2-pyrazoline **174**, readily prepared from α,β -unsaturated ketones and hydrazinedium dithiocyanate, reacts with ethyl 3-bromopropionate in boiling chlorobenzene as the solvent to give the pyrazolyl-1,3-thiazin-4-one **175** (Scheme 14) <2003M1623>.



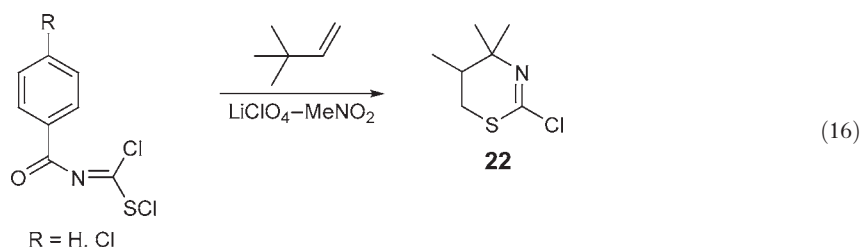
Scheme 14

A convenient route to 2-alkylthio-4-alkyl-4-hydroxy-5,6-dihydro-4*H*-1,3-thiazine derivatives **176** is the reaction of *S*-alkyldithiocarbamates with α,β -unsaturated ketones in the presence of boron trifluoride etherate at 0°C (Scheme 15) <2002HAC377>. The predominant diastereomer displayed a *cis*-relationship between the hydroxyl group and the C-4 substituent. Subsequent dehydration led to two isomeric products **177** and **178** with an equilibrium mixture resulting in a ratio of 94:6 in the case of 2-benzylthio-4-hydroxy-4-methyl-5,6-dihydro-4*H*-1,3-thiazine. 2-Phenyl-4-alkyl-4-hydroxy-5,6-dihydro-4*H*-1,3-thiazine derivatives are similarly prepared by reacting thio-benzamide with α,β -unsaturated ketones at room temperature <2002EJP307>.

The cycloaddition of *N*-benzoyliminochloromethanesulfonyl chloride and 3,3-dimethyl-2-butene in nitromethane and in the presence of lithium perchlorate involves addition of the electrophile at the double bond and 1,2-methyl shift. Unusually, the ring closure is accompanied by elimination of the benzoyl group (Equation 16) <2002CHE1150>.

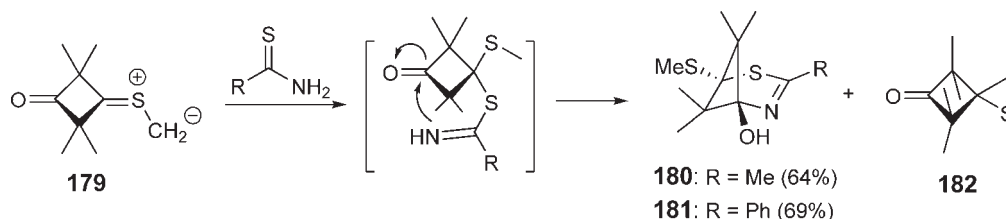


Scheme 15



(16)

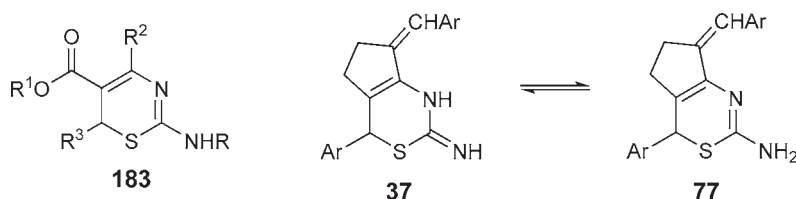
Trapping of the thiocarbonyl ylide **179** with thioacetamide and thiobenzamide does not give the expected products, the 2-thia-4-azabicyclo[3.1.1]hept-3-ene derivatives **180** and **181** are generated together with **182** (Scheme 16) <1999HCA290>.



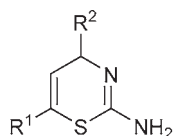
Scheme 16

8.08.9.2 Syntheses from [3+2+1] Fragments

1,3-Thiazine-5-carboxylates **183** are conveniently prepared by initial Knoevenagel condensation of β -ketoesters with aldehydes, R^3CHO , followed by reaction with thiourea. A modification of this method was developed in which polymer-supported reagents are used <2004AGE621, 2004CEJ2919, 2005QSA364>. In the most advantageous method, the catalyst, piperazine, is immobilized on a solid support, and is used first for the Knoevenagel condensation. Subsequent reactions with thioureas produce the 1,3-thiazines. The key step involves treatment of the crude reaction mixtures with a polymer-bound sulfonic acid which traps only the thiazine products, and the by-products are easily removed. The products are released from the polymer under basic conditions. A diverse range of 6*H*-1,3-thiazine-5-carboxylates **183** can be expediently prepared in this way.



A series of 4-heteroaryl-5,6-di(2,5-dimethyl-3-thienyl)-2-phenyl-4H-1,6-thiazines **54** with photochromic properties was prepared by reacting 3-(2-(2,5-dimethylthiophen-3-yl)ethynyl)-2,5-dimethylthiophene with thiobenzamide and aldehydes <2005CHE86, 2005PS1503>. The acid-catalyzed cyclocondensation of cyclopentanone, aromatic aldehydes, ArCHO, and thiourea affords the cyclopenta[4,1,3]-thiazines **37** <2006PS1655>. Two equivalents of the aldehyde are required. The same products are isolated when 2,5-dibenzylidenecyclopentanones are treated with thiourea under the same conditions. 2-Amino-4H-1,3-thiazines **184** are easily synthesized in one pot by the reaction of aromatic alkynes, $R^1C\equiv CH$, aromatic aldehydes, R^2CHO , and thiourea in the presence of TFA/acetic acid <2005OL3797>.

**184**

50–75%

 $R^1 = \text{Ph}, 4\text{-FC}_6\text{H}_4$ $R^2 = \text{Ph}, 4\text{-FC}_6\text{H}_4, 4\text{MeC}_6\text{H}_4, 4\text{MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4$

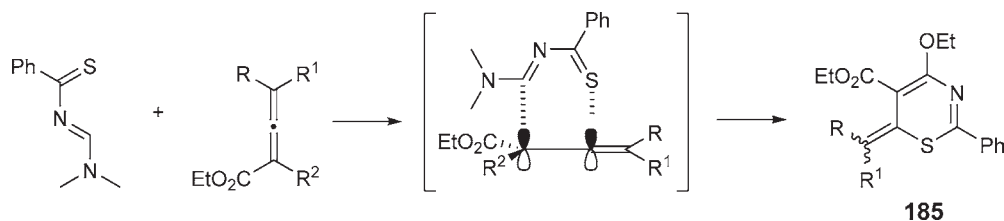
A solution of *m*-phenylenediamine dihydrochloride and carbon disulfide in ethanol and at pH 7–8 was heated at 100 °C in an autoclave to give the benzothiazine-2,6-dithione **21** <2005AXEo387>.

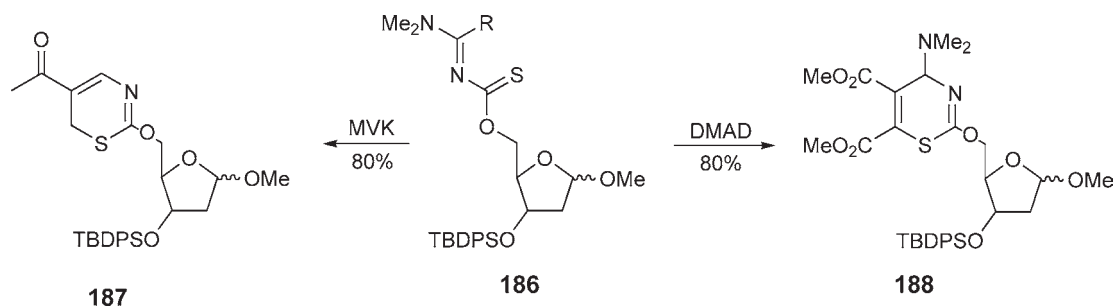
8.08.9.3 Syntheses from [4+1+1] Fragments

1-(4-Ethoxy-2,6-aryl-5,6-dihydro-2H-1,3-thiazin-5-yl)ethanones **24** are accessible by the reaction of ethyl acetothionoacetate under conditions of the Hantzsch synthesis <2000CHE862>. Benzo[*e*][1,3]thiazine-2,4-diones are available from benzamides by directed *ortho*-lithiation and followed by treatment with S and phosgene. Substitution of phosgene with thiophosgene gives access to 2-thioxo-2,3-dihydrobenzo[*e*][1,3]thiazin-4-one derivatives <2001JHC723>.

8.08.9.4 Syntheses from [4+2] Fragments

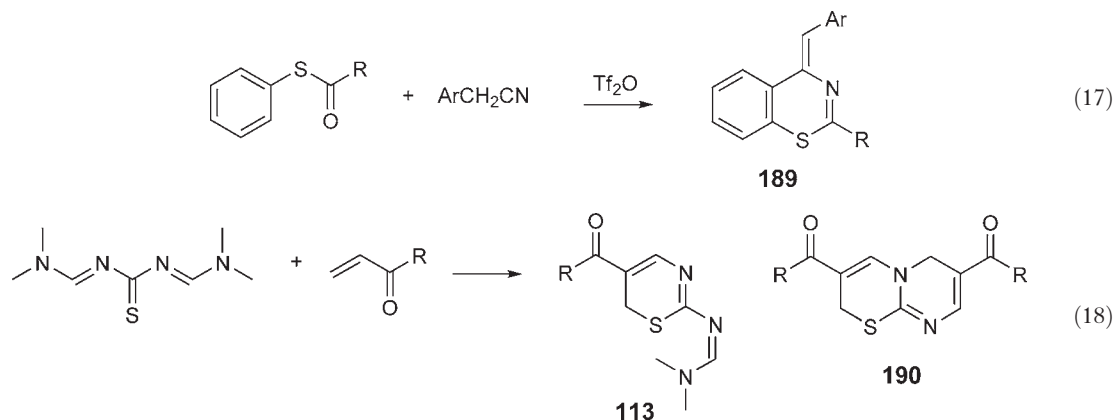
The stereoselective [4+2] cycloaddition of 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene with allenic esters produces a mixture of (*E/Z*)-6-alkylidene-6H-2-phenyl-5-ethoxycarbonyl-1,3-thiazines **185** after elimination of dimethylamine (Scheme 17) <2004S775>. The reaction involves the electron-deficient C(2)–C(3) π -bond of the allenic esters. The reaction of a 2,4-diamino-1-thia-3-azabutadiene and ketene gives 2-(*N*-phenylacetamido)-6H-1,3-thiazin-6-one **7** <2000H(53)2667, 2002AXEo228> and cycloaddition with acrylic dienophiles produces 6H-1,3-thiazines <2000PS(156)135>. Similarly, cycloaddition of the sugar-derived thiaazaheterodienes **186** with DMAD and methyl vinyl ketone forms thiazines **187** and **188** (Scheme 18) <2001PAC1189>.

**Scheme 17**



Scheme 18

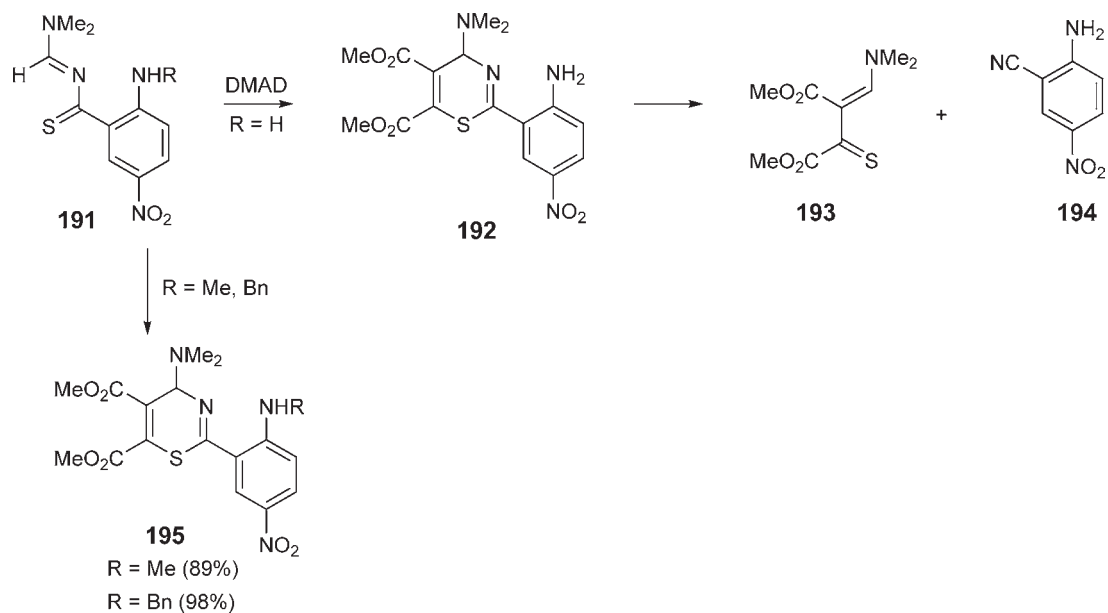
S-Phenyl alkylthioates undergo stereoselective reaction with substituted benzyl nitriles in the presence of triflic anhydride to give substituted (4*Z*)-4-benzylidene-2-alkyl-4*H*-1,3-benzothiazines **189** (Equation 17) <2004JOC4545>. The [4+2] cycloaddition of *N,N*-bis[(dimethylamino)methylene]thiourea, prepared by the condensation of dimethylformamide dimethyl acetal and thiourea in boiling dichloromethane, with methyl vinyl ketone or acrolein gives access to 1,3-thiazines **113** after elimination of dimethylamine (Equation 18) <2003JOC4912, 2003EJO421>. The yields were modest due to competing side reactions which gave the bicyclic compound **190** due to a second [4+2] cycloaddition with methyl vinyl ketone. The reaction with acrolein, however, results in the formation of 5-formyl-2-formylamino-6*H*-1,3-thiazine during the workup.



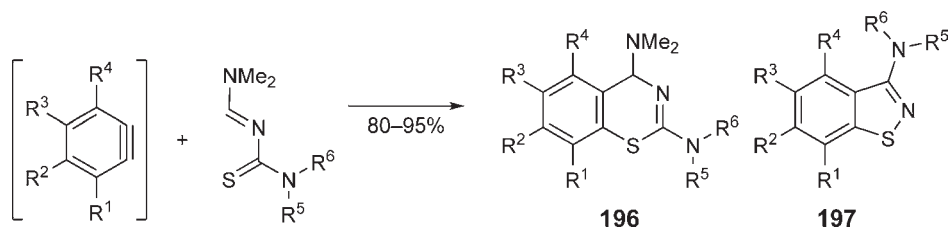
Treatment of 2-amino-5-nitrothiobenzamide with *N,N*-dimethylformamide dimethyl acetal gives 2-amino-*N*-((dimethylamino)methylene)-5-nitrobenzothioamide **191** in excellent yield <2004TL5913>. Cycloaddition reaction of **191** with DMAD results in formation of dimethyl 2-(2-amino-5-nitrophenyl)-4-(dimethylamino)-4*H*-1,3-thiazine-5,6-dicarboxylate **192** in low yield when R = H. This is caused by cycloreversion of thiazine **192** to give dimethyl 2-((dimethylamino)methylene)-3-thioxosuccinate **193** and 2-amino-5-nitrobenzonitrile **194** (Scheme 19). When *N*-((dimethylamino)methylene)-2-(alkylamino)-5-nitrothiobenzamides **191** (R = Me, Bn) are reacted with DMAD, the expected 4*H*-1,3-thiazine-5,6-dicarboxylates **195** are produced as stable compounds.

Cycloaddition of benzyne intermediates with aminothiazadienes provide access to substituted 2,4-diamino-4*H*-1,3-benzothiazines **196** in high yields. The benzyne intermediates are prepared by the treatment of (phenyl)[*o*-(trimethylsilyl)aryl]-iodonium triflates with 1.5 equiv of tetrabutylammonium fluoride (Scheme 20). Interestingly, 3-substituted-1,2-benzisothiazoles **197** are obtained when 4 equiv of tetrabutylammonium fluoride is used <2005H(65)1615>.

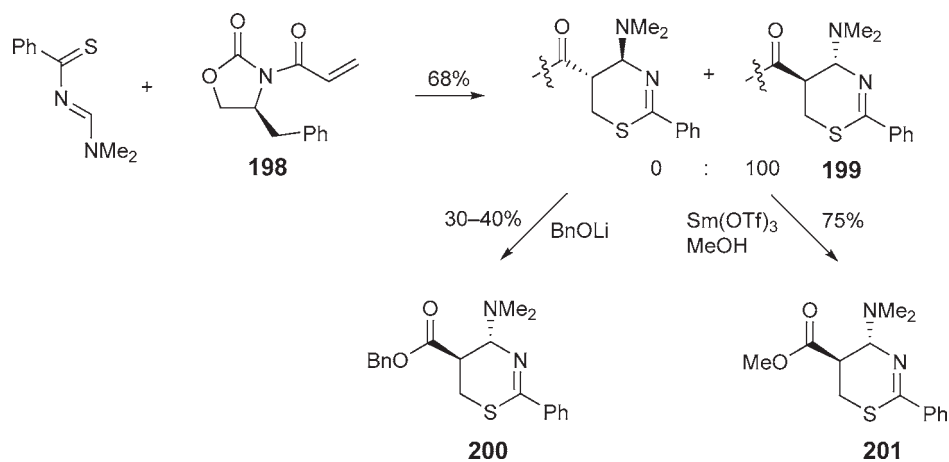
The diastereoselective cycloaddition of 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene with a choice of dienophiles and in the presence of a Lewis acid provides a convenient route to 5,6-dihydro-4*H*-1,3-thiazines <2002TL6067, 2004T1827>. The more stable *trans*-adducts are produced exclusively. The approach using (4*S*)-3-acryloyl-4-benzoyloxazolidin-2-one **198** provides access to the chiral 5,6-dihydro-4*H*-1,3-thiazine **199** <2004T1827>. The exceptional level of selectivity is only achieved when magnesium bromide is used. The chiral auxiliary was removed by reaction with lithium benzoate to give the benzyl ester **200**, and reaction with catalytic amount of samarium triflate and methanol provides the methyl ester **201** (Scheme 21). 2-Substituted-5,6-dihydro-1,3-thiazines are conveniently synthesized from nitriles or thiocyanates and 4-mercapto-2-methylbutan-2-ol to produce



Scheme 19

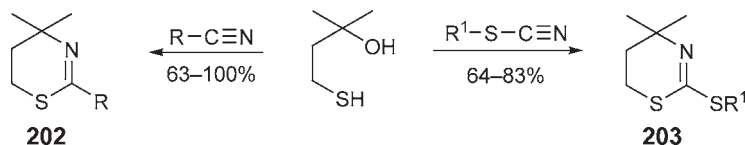


Scheme 20



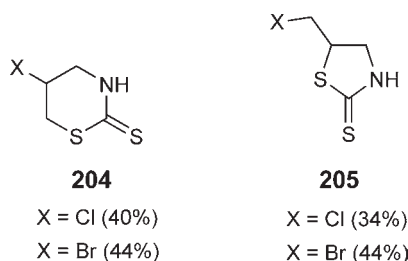
Scheme 21

4,4-dimethyl-2-alkyl/aryl-5,6-dihydro-4*H*-1,3-thiazines **202** and 4,4-dimethyl-2-(alkylthio)-5,6-dihydro-4*H*-1,3-thiazines **203**, respectively <1997AJC755>. This is a modification of an existing method <1960JOC1147> in which concentrated sulfuric acid is replaced by methanesulfonic acid as the solvent (Scheme 22).



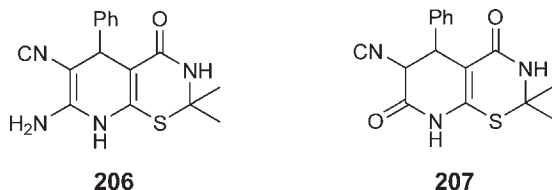
Scheme 22

The spiro compound **15** is obtained in excellent yield by the cycloaddition of 3-(4-fluorophenylimino)indolin-2-one with mercaptopropionic acid under microwave irradiation <2003SUL201>. Treatment under basic conditions of 2,3-dihalopropylamines with carbon disulfide results in the formation of two isomeric products: 5-halotetrahydro-1,3-thiazine-2-thione **204** and 5-(halomethyl)thiazolidine-2-thione **205** <2002CHE1533>.



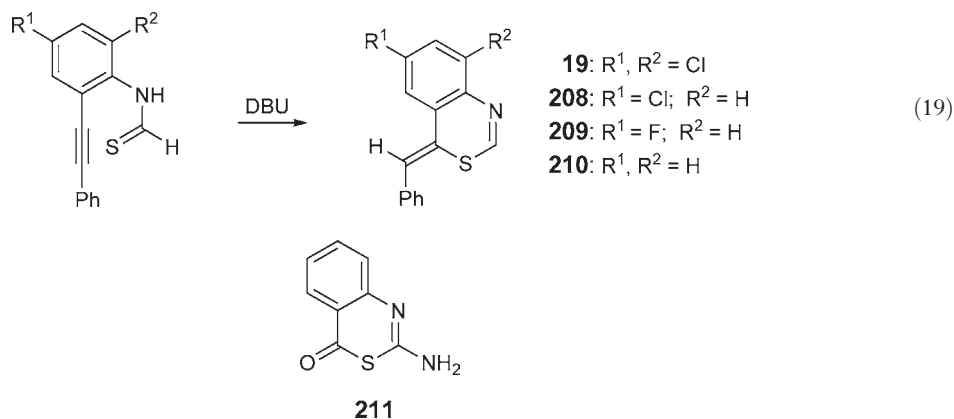
8.08.9.5 Syntheses from [5+1] Fragments

The highly colored spiro compound **5**, which can be used as a charge-transfer dye, is accessible by the acid-catalyzed condensation of ninhydrin with 8-(methylamino)-1-naphthalenethiol <1996JA1471>. Treatment of 6-amino-5-isocyano-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide with 2 equiv of HCl in acetone followed by neutralization gives a low yield of 7-amino-6-isocyano-2,2-dimethyl-5-phenyl-5,8-dihydro-2*H*-pyrido[3,2-*e*][1,3]-thiazin-4(3*H*)-one **206** <2001CHE378>. Further reaction of the latter with HCl in acetone gives the 7-keto derivative **207**, which can also be prepared directly from 6-amino-5-isocyano-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide using a 10-fold excess of HCl in acetone.

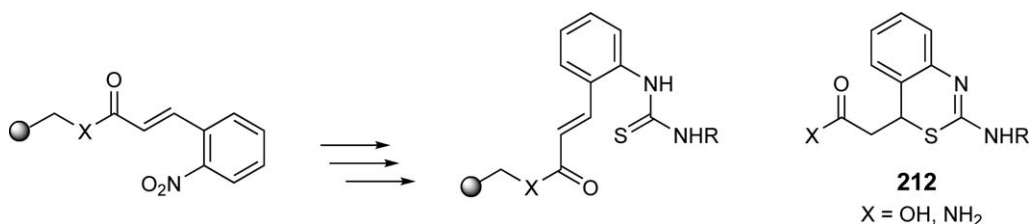


8.08.9.6 Syntheses from [6+0] Fragments

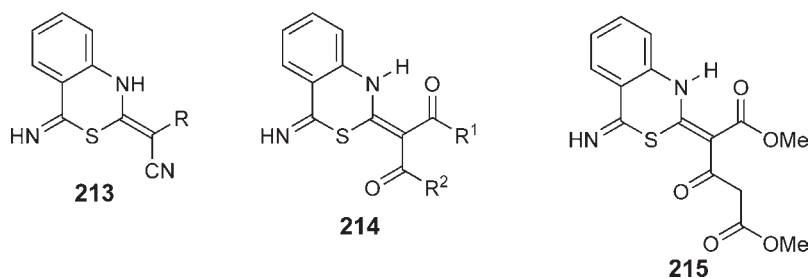
N-(2-Phenylethynylaryl)methanethioamides undergo 6-*exo-dig*-cyclization to yield (*Z*)-4-benzylidene-4*H*-3,1-benzothiazines **19** and **208–210** along with small quantities of 2-phenyl indoles (Equation 19) <2003SL2231>. The cyclocondensation of *o*-(*N'*-benzoylthioureido)benzoic acid derivatives, catalyzed by zeolites, HY-zeolite, HEMT, and H-zeolite beta, affords 2-amino-3,1-benzothiazin-4-one **211** <1997TL3179>. None of the 2-benzoylamino derivatives, accessible by the sulfuric acid-catalyzed route, was observed <1996JHC355>.



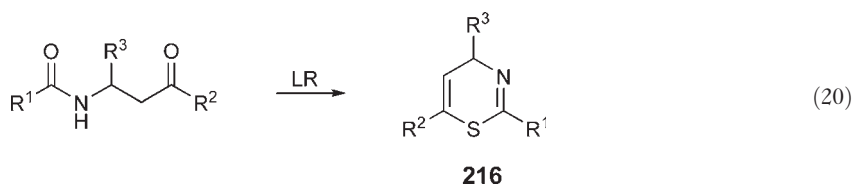
Perfluoro(3-isothiocyanato-2-methyl-2-pentene) reacts with N-nucleophiles to produce a series of fluoroalkyl-substituted 6*H*-1,3-thiazines [<1997RJO720>](#). The acid-catalyzed cyclization of thioureas immobilized on Wang ($X = \text{O}$) or Rink resin ($X = \text{NH}$) provides a convenient route to a wide range of 2-amino-4*H*-benzothiazine derivatives **212** ([Scheme 23](#)) [<2000OL3667>](#). The thioureas are obtained in four steps from 2-nitrocinnamic acids. A general synthesis of 2-alkylidene-4-imino-1,4-dihydrobenzo-1,3-thiazines **213–215** involves treatment of 2-isothiocyanatobenzonitrile with acidic methylene compounds under basic conditions [<2003SL1503>](#). The (*E*)-isomers are the predominant isomers formed.



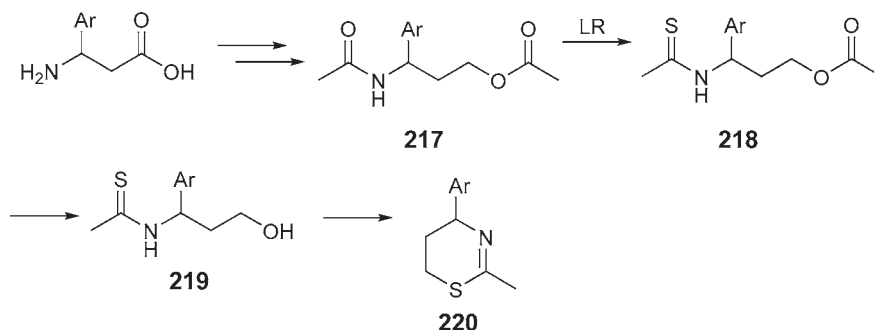
Scheme 23



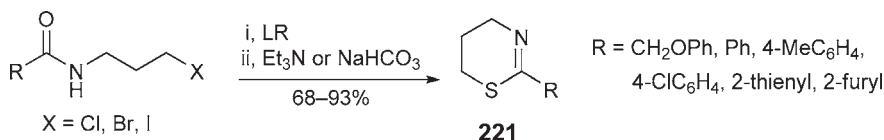
Thionation of 3-*N*-acylamino ketones with Lawesson's reagent (LR) gives the 3-*N*-thioacylamino thiones which cyclize to the 1,3-thiazines **216** with loss of H_2S ([Equation 20](#)) [<2000H\(52\)111, 2001HCA2347>](#).



A facile synthesis of 2-methyldihydro-1,3-thiazines **220** from β -aryl- β -amino acids involves initial reduction and reaction with acetic anhydride to give the 3-acetamido-3-arylpropyl acetates **217** <2004TL1503>. The amide intermediates are then treated with LR to give the thioamides **218**. Cyclization of **219** is accomplished in two ways: by the Mitsunobu reaction using $\text{Ph}_3\text{P}/\text{DEAD}$ or by conversion of the hydroxyl group to the mesylate in the presence of triethylamine which produced higher yields (Scheme 24). Treatment of *N*-(3-halogenopropyl)amides with LR affords the corresponding thioamides which undergo cyclization in the presence of base to generate 2-substituted-1,3-thiazines **221** (Scheme 25) <2005HCA187>.

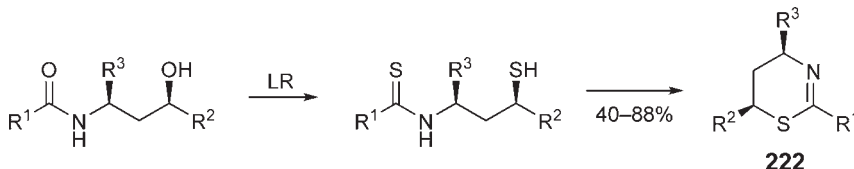


Scheme 24



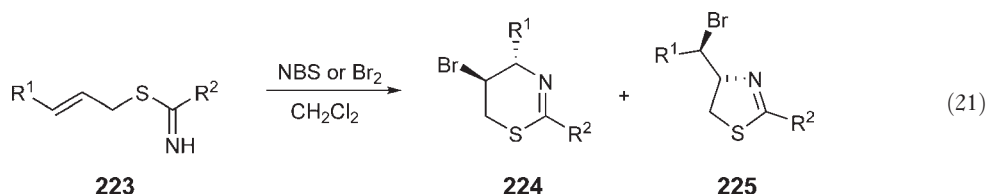
Scheme 25

Reactions of *syn*-3-*N*-acylamino alcohols with 1 equiv of LR give the corresponding *syn*-5,6-dihydro-1,3-thiazine derivatives **222** in 40–88% yield (Scheme 26) <2001EJO3553>. Similarly, the *anti*-3-*N*-acylamino alcohols give access to the *anti*-5,6-dihydro-1,3-thiazine derivatives.

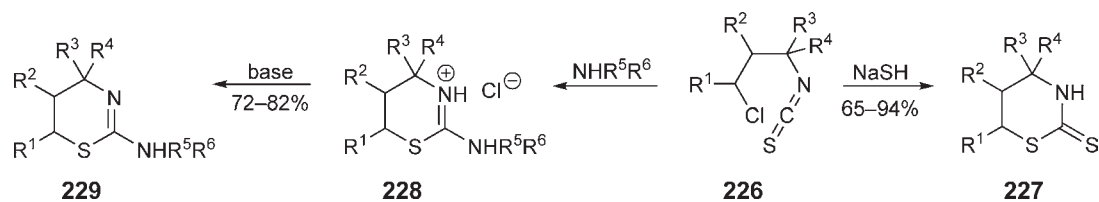


Scheme 26

(*E*)-Allyl amidothiolates **223** undergo stereoselective intramolecular cyclization when treated with *N*-bromosuccinimide (NBS) or bromine in aprotic solvents. The 5-bromo-4*H*-5,6-dihydro-1,3-thiazines **224** are obtained as the *anti*-diastereomers in low yields together with the 4,5-dihydrothiazole **225** (Equation 21) <1996NKK546, 1997RHA119>. (*E*)-Allyl imidothiolates afford *anti*-4*H*-5,6-dihydro-1,3-thiazines in addition to *anti*-4,5-dihydrothiazoles when reacted with NBS or bromine. Similarly, the (*Z*)-allyl imidothiolates generate the *syn*-analogues. In contrast, under the same conditions, 5,6-dihydro-1,3-thiazines are exclusively formed on cyclization of the (*E*)-allyl imidothiocarbonates and (*E*)-allylisothioureas to give the corresponding *anti*-isomers. *syn*-4,5-Dihydrothiazoles are produced from the (*Z*)-allyl imidothiocarbonates and (*Z*)-allylisothioureas.

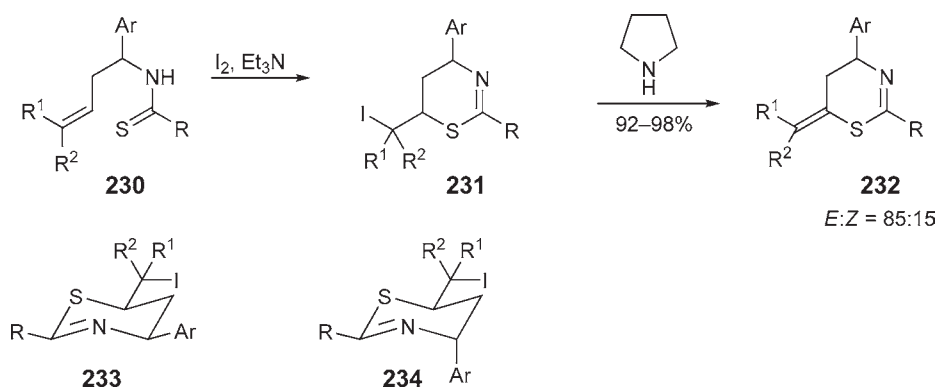


1,3-Chloroisoithiocyanatoalkanes **226** react with NaSH to give the tetrahydro-1,3-thiazine-2-thiones **227** while reaction with ammonia and amines affords salts **228**. Subsequent treatment with base produces the tetrahydro-2-amino-1,3-thiazines **229** (Scheme 27) <2003CHE802>. The 1,3-chloroisoithiocyanatoalkanes are available from 3-isothiocyanato ketones. The acid-mediated cyclization of *N*-allylthiourea and ³⁵S-labeled *N*-allylthiourea gives, along with other products, 2-amino-5,6-dihydro-4*H*-1,3-thiazine <1998MI151>.



Scheme 27

5,6-Dihydro-4*H*-1,3-thiazines **231** are conveniently prepared by the iodocyclization of *N*-homoallyl thioamides **230** in the presence of triethylamine (Scheme 28) <2004CL508>. The selectivity of the reaction was dependent on the groups attached to the thioamide, and high diastereoselectivities are achieved with the 1-naphthyl or the 2-methoxyphenyl groups giving the major product **233** with the aryl group in the equatorial position rather than **234**. Treatment of thiazines **231** with pyrrolidine resulted in the formation of 6-alkylidene-5,6-dihydro-4*H*-1,3-thiazines **232**.

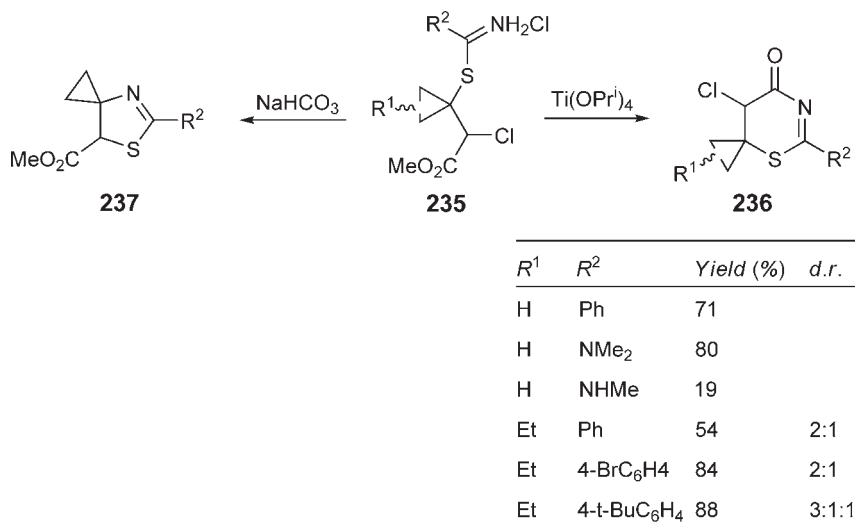


Scheme 28

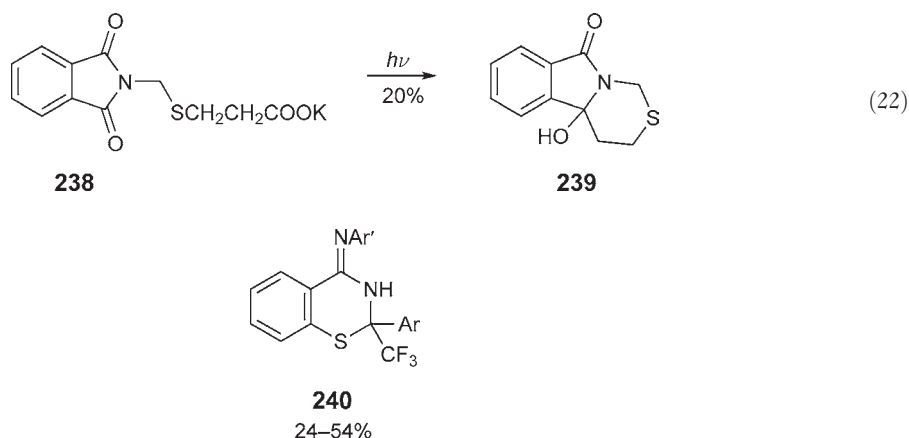
Thiazin-4-ones **236** are obtained when 2-chloro-2-(1-(1-iminomethylthio)cyclopropyl)acetates **235** are reacted with titanium tetrakisopropoxide in dichloromethane <2001EJO3025>. The yield is dependent on the group attached to C-2 and observed diastereoselectivities are poor. Representative examples are shown in (Scheme 29). Interestingly, thiazolines **237** are formed under basic conditions.

The potassium salt of the 3-mercaptopropionic acid derivative **238** undergoes photoinduced decarboxylative cyclization to give the tricyclic product **239** in a low yield after prolonged irradiation (Equation 22)

<2001EJO1831>. The reaction was more successful with mercaptoacetic and 2-mercaptopropionic acid derivatives producing the corresponding heterocycles in moderate to high yields. Intramolecular cyclization of *N*-(1-arylthio-1-trifluoromethylbenzyl)-*N'*-arylcarbodiimides, available from the reaction of 1-chloroalkylcarbodiimides with thiophenols, at 100 °C gives the 4-arylimino-2-trifluoromethyl-3,4-dihydro-2*H*-benzo-1,3-thiazines **240** in low to moderate yields <2001CHE522>.

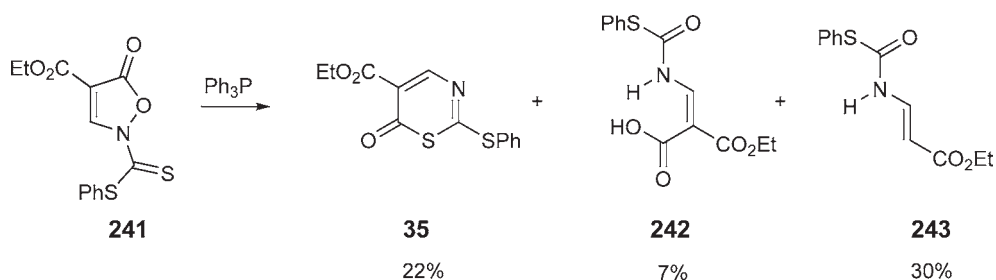


Scheme 29

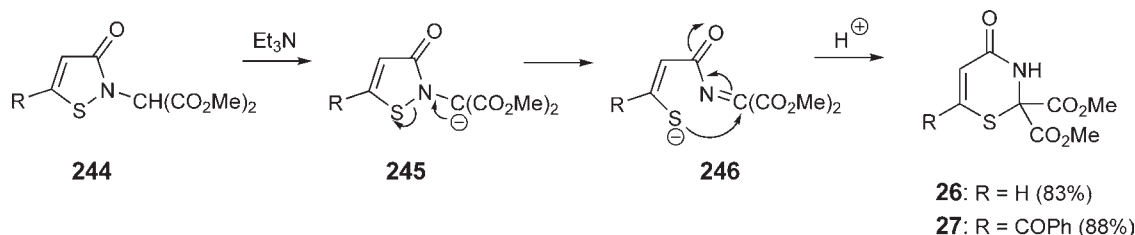


8.08.10 Synthesis by Transformation of Another Ring

All examples in this section involve formation from a five-membered ring. Ethyl 6-oxo-2-(phenylthio)-6*H*-1,3-thiazine-5-carboxylate **35** was obtained serendipitously in low yield on reaction of the isoxazolinone **241** with triphenylphosphine (Scheme 30) <1998J(P1)3245>. Two other products, 2-(ethoxycarbonyl)-3-(phenylthiocarbonylamino)acrylic acid **242** and ethyl 3-(phenylthiocarbonylamino)acrylate **243**, were also isolated. Substituted isothiazolinones **244** undergo rearrangement under basic conditions to generate the corresponding 1,3-thiazin-4-ones **26** and **27** via an elimination–addition mechanism (Scheme 31) <2003SC4339>. The initial step involves proton abstraction to give the anion **245**, which undergoes S–N bond cleavage to give the acylimine intermediate **246**; it then cyclizes to give 1,3-thiazines.

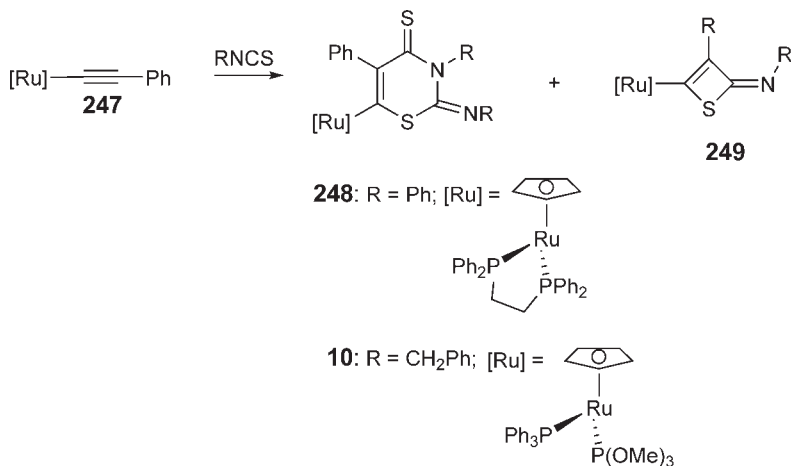


Scheme 30



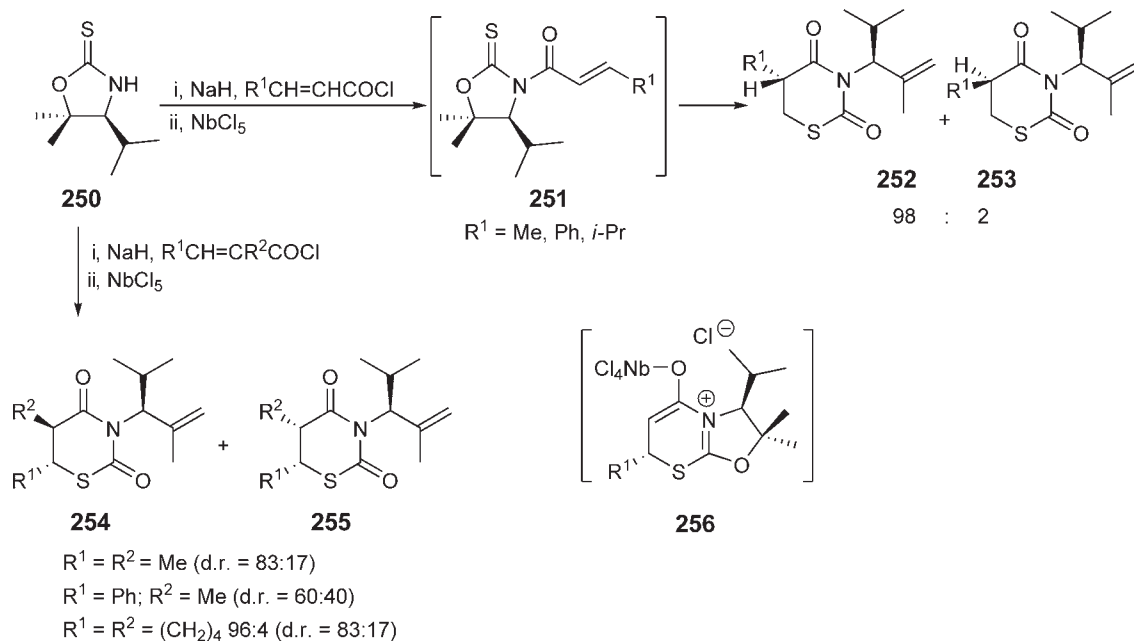
Scheme 31

When the ruthenium complex **247** is reacted with an excess of isothiocyanates, the 2-imino-1,3-thiazine-4-thione ruthenium complexes **248** and **10** are formed by a [2+2+2] cycloaddition together with the [2+2] adduct **249**, formed from cycloaddition of $\text{C}\equiv\text{C}$ with the $\text{C}=\text{S}$ (Scheme 32) <1998OM2534, 2002JOM(660)127>. Treatment of **247** with an excess of isothiocyanate gives the six-membered ring directly and in improved yields.



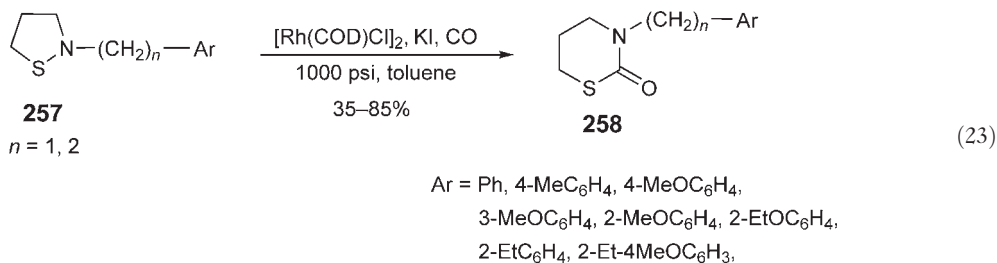
Scheme 32

Treatment of the chiral oxazolidinethione **250** with sodium hydride and *trans*-crotonyl chloride resulted in the unexpected formation of chiral 5-alkyl/aryltetrahydro-1,3-thiazine-2,4-diones (Scheme 33) <2003TL5053>. This rearrangement is efficiently achieved in the presence of NbCl_5 to obtain N-substituted 1,3-thiazine-2,4-diones **252** and **253** containing two stereogenic centers and 5,6-disubstituted-1,3-thiazine-2,4-diones **254** and **255** possessing three stereogenic centers <2006TL1153>. The mechanism of the reaction could be explained by the initial intramolecular attack of sulfur at the β -C of oxazolidinone **251** resulting in the formation of an immonium ion intermediate **256**.



Scheme 33

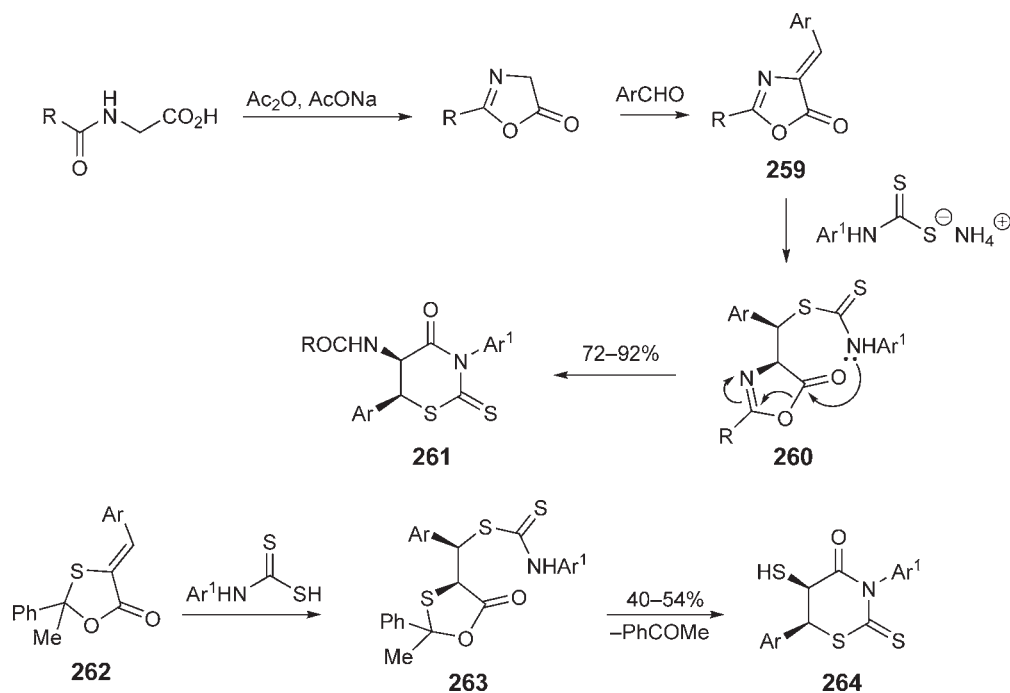
The $[\text{Rh}(\text{COD})\text{Cl}]_2$ - and KI-mediated carbonylation of substituted *N*-alkylisothiazolidines **257** occurs regioselectively at the S–N bond (Equation 23) <2004OL3489>. The most favorable solvent for this ring expansion of the *N*-alkylisothiazolidines to give tetrahydro-2*H*-1,3-thiazin-2-ones **258** is toluene. The yields were dependent on the nature of the aryl group. A range of alternative metal catalysts were also screened, however carbonylation was observed with $\text{Co}(\text{CO})_8$, and $\text{Pd}(\text{OAc})_2$ only.



Microwave irradiation of a mixture of *N*-acylglycine, acetic anhydride, anhydrous sodium acetate, an aromatic aldehyde, and ammonium *N*-aryldithiocarbamate produces 5-acylamino-3,6-diaryl-2-thioxo-1,3-thiazin-4-ones **261** via the intermediate oxazolin-5-one **259** (Scheme 34) <2003TL5637>. Similarly, microwave irradiation of 4-benzylidene-1,3-oxathiolan-5-one **262**, prepared *in situ* from 2-methyl-2-phenyl-1,3-oxathiolan-5-one and aromatic aldehydes, results in a Michael-type addition of *N*-aryldithiocarbamic acid to give the intermediate adducts **263**, which undergo ring expansion to give 5-mercapto-3,6-diaryl-2-thioxotetrahydro-1,3-thiazin-4-ones **264**. The diastereoselectivity of the reaction is >96%, affording the *cis*-isomers in 43–54% yield. The Michael adducts can be isolated and cyclized to the corresponding tetrahydro-1,3-thiazin-4-ones <2005T10013>.

8.08.11 Best Methods of Synthesis

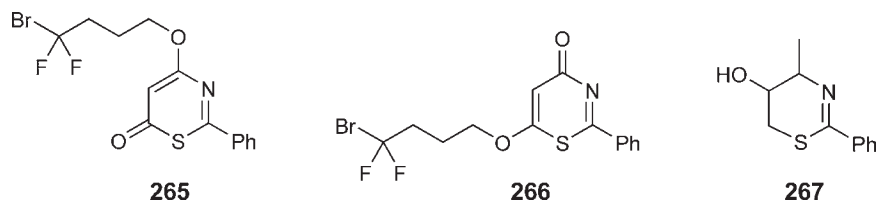
The diverse range of different structures prepared over the period in question together with the small number of publications on any given system preclude any meaningful comparison of the various methods available.

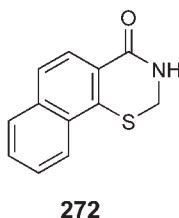
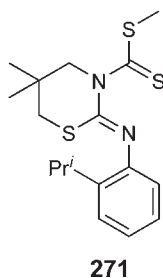
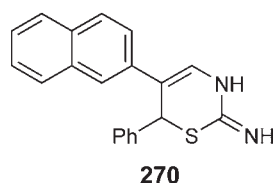
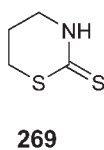
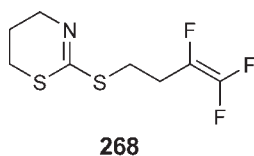


Scheme 34

8.08.12 Applications

1,3-Thiazine derivatives display a broad spectrum of biological activities. They possess antibacterial <2002WO028868, 2006PS1655>, antimycobacterial <2002EJP307>, antiviral <2002WO014295>, and biocidal properties <2002WO006256, 1999JPP11140063>. The 1,3-thiazines **265** and **266** have been patented for their properties as pesticides, miticides, and nematocides <2000JPP309580>. The 5,6-dihydro-4*H*-1,3-thiazine **267** and similar derivatives are valuable as insecticides, agrochemicals, and medicinal microbicides <2000JPP119263>. The 2-substituted-5,6-dihydro-4*H*-1,3-thiazine **268** and tetrahydro-1,3-thiazine-2-thione **269** are insecticides <1999JPP11140063>. The 5-(naphthalen-2-yl)-6-phenyl-3,6-dihydro-2*H*-1,3-thiazin-2-imine **270** has weak antibacterial activity <1997OJC69>. The antibacterial activity of 5,6-dihydro-4*H*-thiazines has been tested and these compounds have weak activity as antitubercular agents <2002EJP307>. 2,5-Disubstituted-4*H*-1,3-thiazines, which act as pesticides, have been shown to block the gamma-aminobutyric acid (GABA)-gated chloride channel in house fly and mouse brain membranes and they are also toxic to topically treated flies <1999MI237>. Substituted 2-amino-1,3-thiazines act as nitric oxide synthase inhibitors and may be exploited for the treatment of diseases characterized by elevated nitric oxide levels <1996EUP717040, 1996EUP713704, 1996JBC28212>. The 2-iminotetrahydro-1,3-thiazine **271** and derivatives <2001WO019807, 2002WO072562, 2005WO026138> have been patented for their activity as cannabinoid receptor agonists. The naphtho[2,1-*e*][1,3]thiazin-4-one **272** possesses anti-human immunodeficiency virus (HIV) activity <2003WO024941>.





The chemistry of 1,3-thiazines as ligands for the synthesis of metal complexes is relatively underexploited. There are reports on ruthenium [\[1998OM2534, 2002JOM\(660\)127\]](#), copper [\[2004JIB\(98\)15, 2004MI993\]](#), cobalt [\[2004POL1453, 2001ASJ1127, 2005POL129\]](#), nickel [\[2004POL1453, 2001ASJ1127\]](#), and iron complexes [\[1997ASJ327\]](#).

8.08.13 Further Developments

Recent studies on the phototautomerization mechanism of the nitroenamine functionality in 2-(nitromethylene)-tetrahydro-1,3-thiazine were performed using complete active space self-consistent field reaction path computations [\[2007JA3703\]](#).

The solid state structures of seven substituted 1,3-thiazines have been determined. The analysis of the *syn* diastereomers of 2-amino-6-phenyl-4-*p*-tolyl-5,6-dihydro-4*H*-1,3-thiazin-3-ium chloride by single crystal X-ray crystallography shows the ring in a twisted half-chair conformation and the H atoms at both nitrogens participate in weak intermolecular hydrogen bonds [\[2006AX\(E\)o3667\]](#). The structures of six substituted 5,6-dihydro-4*H*-1,3-thiazines, 4-hydroxy-4-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-thiazine [\[2006AX\(E\)o1218\]](#), *trans*-2,2'-[(2-butene-1,4-diyl)-dithio]bis(4,5-dihydro-1,3-thiazine) [\[2006AX\(E\)o4621\]](#), 2,2'-(*p*-phenylenedimethylenedithio)bis(4,5-dihydro-1,3-thiazine) [\[2006AX\(E\)o3949\]](#), 4-ethyl-4-hydroxy-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine [\[2006AX\(E\)o1666\]](#), 2-[3,5-bis(5,6-dihydro-4*H*-1,3-thiazin-2-yl)sulfanylmethyl]-2,4,6-trimethylbenzylsulfanyl]-5,6-dihydro-4*H*-1,3-thiazine [\[2007AXEo3370\]](#), 2-(3,4-dichlorophenyl)imino-*N*-(4*H*-5,6-dihydro-1,3-thiazin-2-yl)tetrahydro-1,3-thiazine and its Zn(II) complex [\[2006JIB\(100\)1861\]](#) were solved by X-ray crystallography.

New synthetic methods for the construction of the 1,3-thiazine ring include the [3+3] cyclocondensation of α -chlorobenzyl isocyanates and 1-aryl-2,2,2-trifluoro-1-chloroethyl isocyanates with *N,N*-disubstituted cyanothioacetamides to give 3,4-dihydro-2*H*-1,3-thiazine-4-ones in 31–52% yield [\[2007RJO553\]](#). A 2-thioxo-1,3-thiazine-4,6-dione derivative and a 6-imino-2-thioxo-1,3-thiazine-4-one derivative were synthesized by the reaction of a carbamodithioic acid derivative with diethyl malonate and ethyl cyanoacetate respectively [\[2007PS1717\]](#). Rearrangement of the *N*-(1,2-dithiole-3-ylidene)thioamides to 2,3-dihydro-4*H*-1,3-thiazine-4-thiones occurs in the presence of NaBH₄ in ethanol. Moderate yields (55–62%) are reported [\[2007T1937\]](#).

Catalytic SeO₂ oxidation of 2-ethyl-5,6-dihydro-4*H*-1,3-thiazine gave 2-acetyl-5,6-dihydro-4*H*-1,3-thiazine in low yield (35%). Olfactory evaluation and odor threshold of the compound was also studied [\[2007T4762\]](#). The Schiff base formed from the condensation of 5-acetyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione with an equimolar amount of *o*-phenylenediamine was reacted with a series of aldehydes and ketones to give substituted 1,5-benzodiazepines [\[2006RJC801\]](#). Ring contraction to give 5-(bromomethyl)thiazolidine-2-thione is observed when 5-bromo-tetrahydro-1,3-thiazine-2-thione is heated in acetic anhydride [\[2006CHE419\]](#).

2-Aminodihydrothiazine derivatives have been patented as β -secretease inhibitors [\[2007WO049532\]](#). A series of 2-naphthylimino-5,5-disubstituted-1,3-thiazine derivatives [\[2006WO129609\]](#) and 2-azolylimino-1,3-thiazine derivatives have been patented for their activity as cannabinoid receptor agonists [\[2006WO080287\]](#).

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8.09

1,4-Thiazines and their Benzo Derivatives

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8.09.1 Introduction

1,4-Thiazines were last included CHEC(1984) <1984CHEC-I(3)995> and did not appear in CHEC-II(1996). This chapter is thus a comprehensive review of the literature on 1,4-thiazines for the period 1982–2006 with references prior to year 1982 that were not included in the first volume. A review of the synthetic methods leading to 1,4-thiazines is also available <2004SOS(17)117>.

Fully conjugated 1,4-thiazines can have either two or three double bonds, depending on the oxidation state of the sulfur. Of the thiazines discussed in this chapter (Figure 1), only the structures **1** and **2** contain three double bonds. Two-double-bond-containing 1,4-thiazines prefer the *2H*-structure **3** as was established with the unsubstituted 1,4-thiazine which could not be N-sulfonylated <1948JA684>. Electron-withdrawing substituents in the 2- and 6-positions promote the isomeric *4H*-form **4** and 1,4-thiazine 1,1-dioxides exist in the *4H*-form **5** <1967JME501, 1969JOC250>. Other structures include **6** and the salts **7** and **8**, benzothiazine systems **9–15**, phenothiazines **16–18**, and the other fully conjugated structures **19–22**.

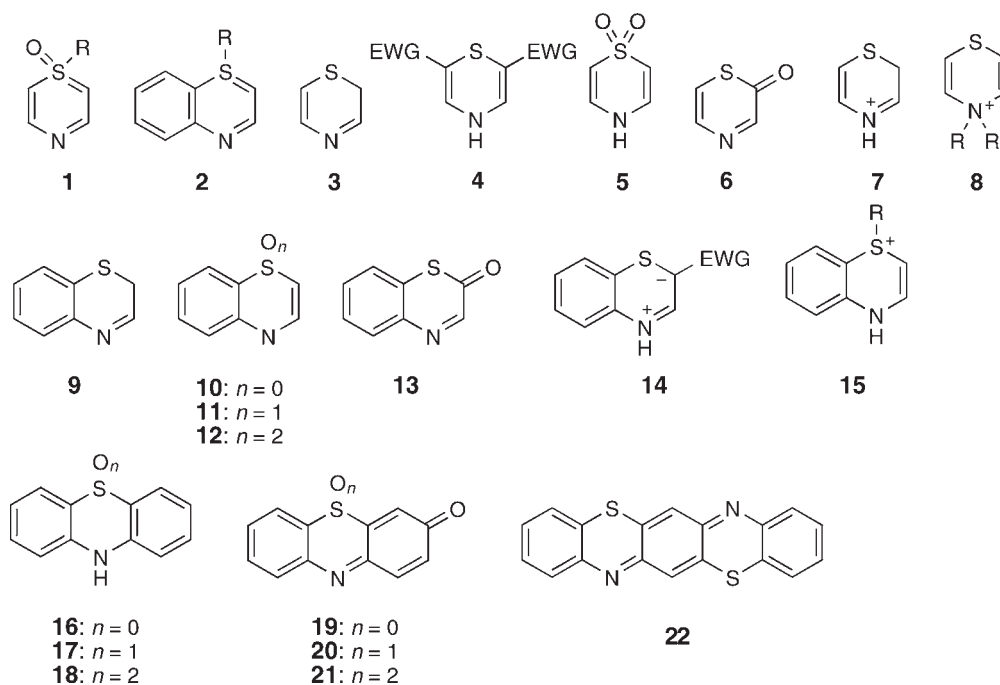


Figure 1 The fully conjugated thiazine ring systems covered in this chapter.

Dihydro-1,4-thiazines that appear in this chapter include structures **23–31** and the benzo derivatives **32–37**. Some tetrahydro-1,4-thiazines having general structures **38–43** are also discussed (**Figure 2**).

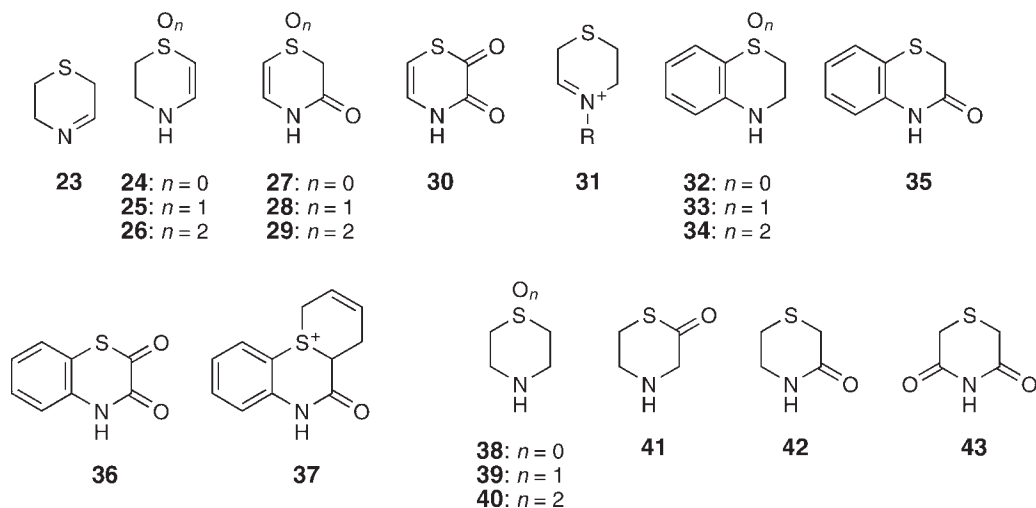


Figure 2 The nonconjugated thiazine ring systems that appear in this chapter.

Naturally occurring thiazines (**Figure 3**) include the pigment trichochrome C **44** in mammalian red hair <1969G323>, which appeared already in CHEC(1984). Its biosynthesis from 5-(*S*)-cysteinyl-DOPA **45** under oxidative conditions has been studied <1996JOC598, 1999JOC3009, 2001JOC6958>. Additionally, dihydrothiazine **46** has been isolated from the marine sponge *Anchinoe tenacior* <1994TL2421> and thiazinotrienomycin E **47** from *Streptomyces* MJ672-m3 <2000JOC3738>.

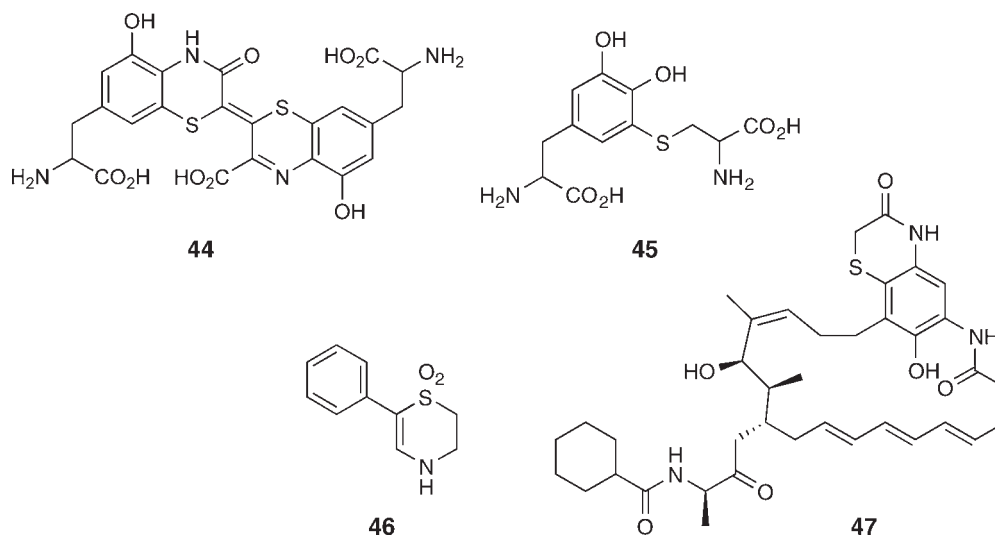
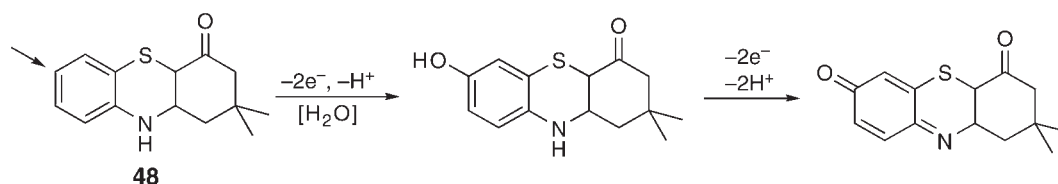


Figure 3 Trichochrome C and its precursor and other naturally occurring 1,4-thiazines.

8.09.2 Theoretical Methods

Theoretical methods have been used to understand and predict charge densities and oxidation potentials, nuclear magnetic resonance (NMR) shifts and cycloconjugation in 1,4-thiazines, and the lowest-energy conformation in a dihydro-1,4-thiazine.

The TREPE (topological resonance energy per π -electron) values, calculated for a group of benzothiazines, were in good correlation with their first oxidation potentials. Calculation of the charge density distribution in compound **48** allowed prediction of the site for nucleophilic attack (Scheme 1) <1987JOC4053>. The site with the lowest electron density is marked with an arrow. In another study, the Hammett σ_p -coefficients computed for phenothiazine derivatives were in good correlation with their first oxidation potentials, fluorescence, and ultraviolet/visible (UV/vis) absorption maxima <2003EJO3534>.



Scheme 1 Electrochemical oxidation of benzothiazine **48** in water.

The ^{13}C and ^{15}N NMR shifts of thiazine **49** and thiazepine **53**, resulting from competing 6-*exo*- and 7-*endo*-cyclizations, were calculated by the gauge-independent atomic orbital (GIAO)/ density functional theory (DFT) method based on the absolute shielding of each atom. The calculated values were compared to the experimental values for **50–52** <2005T6642>. The aim was to distinguish a thiazine from a thiazepine by NMR: this was possible even though the calculated values were not exactly the same as the experimental ones.

The energies were calculated for the resonance forms **54** and **55** of 4-formyl-1,4-thiazine 1,1-dioxide (Figure 4). Cycloconjugation from the sulfur–oxygen bond in **55** gives the molecule aromatic character in the first reported example of overlapping of p and d orbitals. This discourages the movement of the free electron pair of the nitrogen toward the formyl carbonyl to form a planar amide bond. When **55** is more stabilized, the rotation of the amide bond becomes easier (calculated $\Delta H^\ddagger = 11.3 \text{ kcal mol}^{-1}$, NMR line-shape analysis gives $11.7 \text{ kcal mol}^{-1}$) <1986JA5339>. Saturated centers in the corresponding dihydro and tetrahydro derivatives interrupt cycloconjugation and rotation of the amide becomes more difficult ($\Delta H^\ddagger$ for amide rotation $\approx 17 \text{ kcal mol}^{-1}$ in both) <1992JA4307>.

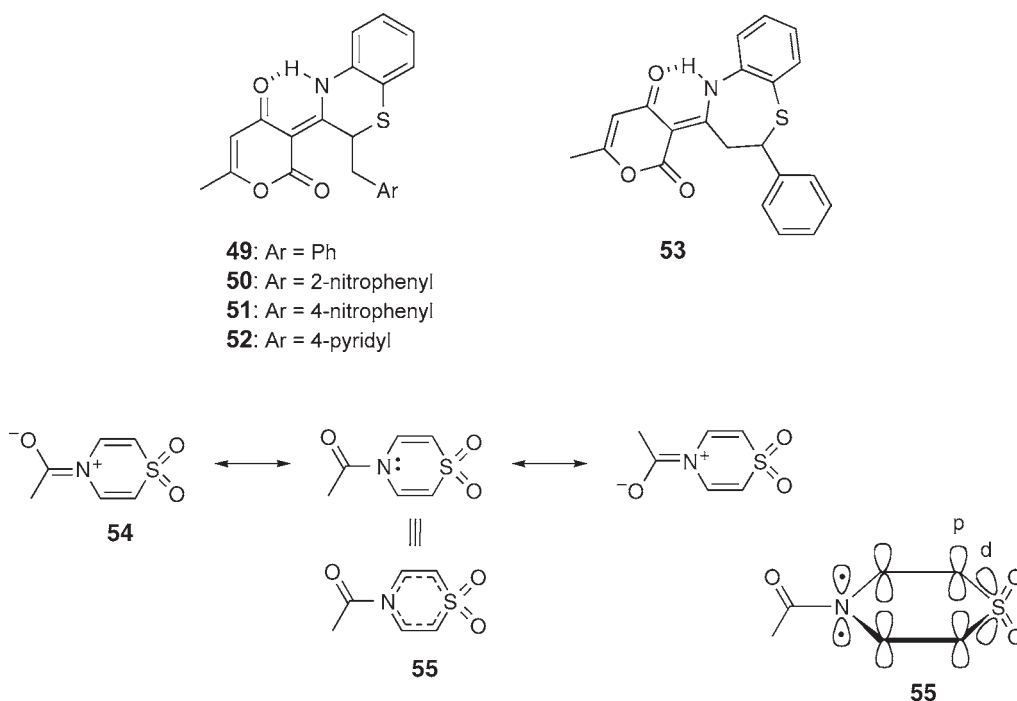
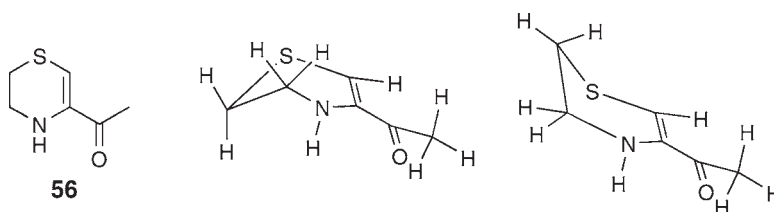


Figure 4

The lowest energy conformations of dihydro-1,4-thiazine **56** (Figure 5) were calculated by computer using a molecular dynamics simulation and the information was used to calculate the geminal coupling constants <1995JFA2195>.

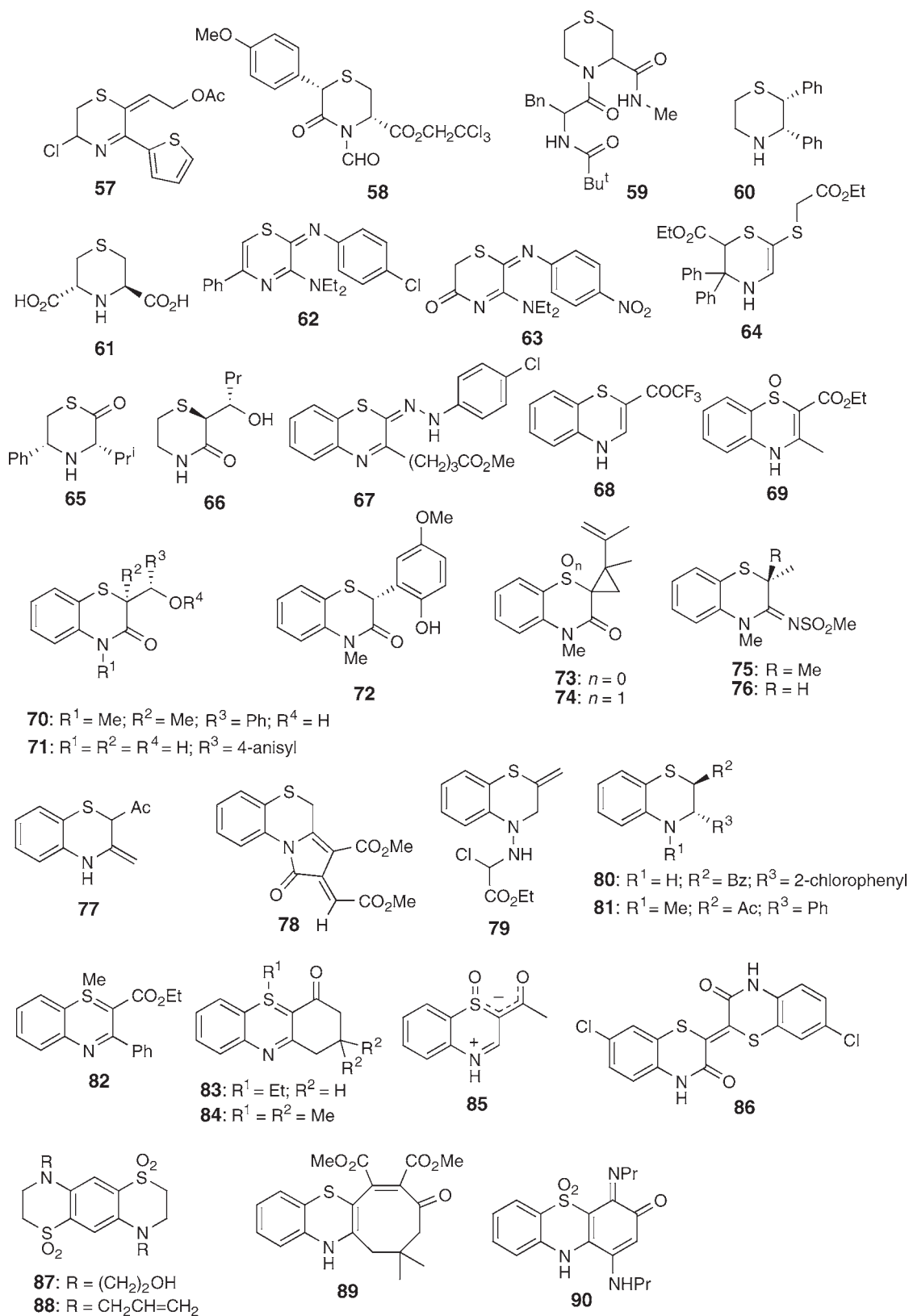
Figure 5 Lowest-energy conformations of dihydro-1,4-thiazine **56**.

Circular dichroism (CD) has also been used as a tool in determining the absolute stereochemistry of a side chain of a benzothiazine. The CD spectrum was compared against a computer-generated model <1999J(P1)149>.

8.09.3 Experimental Structural Methods

8.09.3.1 X-Ray Diffraction

Table 1 gives the bond lengths for 1,4-thiazines for which the X-ray structures have been reported. **Table 2** gives the angles around the thiazine ring. For compounds **68** <2001JFC(108)51> and **72** <1990JME1898>, structures have been determined and presented but accurate bond lengths and angles are not available.



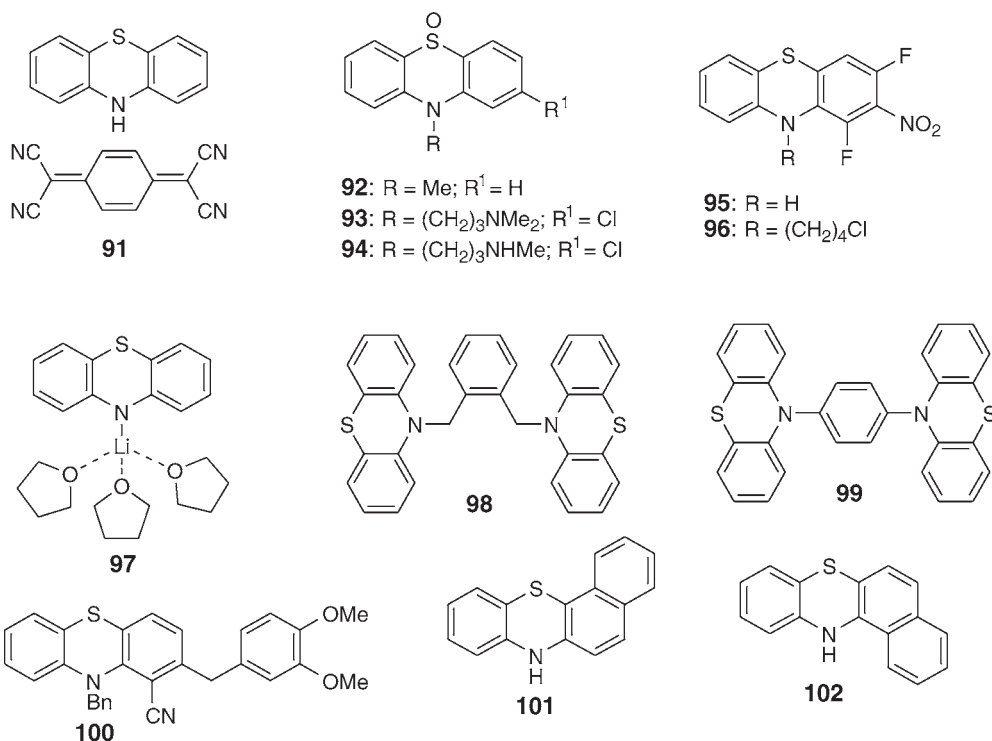


Table 1 Bond lengths in the 1,4-thiazines **22**, **54**, **57–67**, **69–71**, and **73–102** (Å) (numbered clockwise as shown starting from S)

Compound	S(1)–C(2)	C(2)–C(3)	C(3)–N(4)	N(4)–C(5)	C(5)–C(6)	C(6)–S(1)	Reference
22	1.744	1.411	1.403	1.302	1.465	1.745	1985AXC1062
54	1.707	1.330	1.388	1.374	1.327	1.717	1986JA5339
57	1.762	1.501	1.292	1.403	1.407	1.763	1980TL1705
58	1.821	1.540	1.462	1.397	1.508	1.824	1986J(P1)2187
59	1.788	1.520	1.472	1.463	1.523	1.789	1988BSB343
60	1.841	1.552	1.479	1.470	1.500	1.821	1992JOC4215
61	1.807	1.518	1.501	1.500	1.522	1.813	1993AXC976
62	1.757	1.505	1.300	1.381	1.343	1.716	1998T2459
63	1.747	1.503	1.302	1.366	1.496	1.809	1998T2459
64	1.755	1.332	1.344	1.448	1.548	1.817	2006EJO1555
65	1.755	1.512	1.462	1.473	1.523	1.820	2006SL3259
66	1.811	1.518	1.327	1.453	1.429	1.817	1999J(P1)149
67	1.753	1.468	1.283	1.402	1.395	1.744	1997H(45)1183
69	1.750	1.379	1.348	1.384	1.381	1.760	2005AXEo2716
70	1.836	1.532	1.360	1.421	1.393	1.762	1985T569
71	1.804	1.514	1.336	1.402	1.391	1.758	1997AXC313
73	1.776	1.504	1.366	1.425	1.397	1.756	1997J(P1)309
74	1.776	1.496	1.402	1.368	1.393	1.771	1998J(P1)1569
75	1.832	1.525	1.372	1.429	1.382	1.740	1992LA1259
76	1.802	1.511	1.355	1.425	1.396	1.750	1996LA1541
77	1.799	1.377	1.855	1.410	1.393	1.765	2006AXEo1636
78	1.722	1.339	1.425	1.415	1.407	1.769	1987J(P1)1027
79	1.749	1.492	1.482	1.411	1.406	1.750	1986AXC1425
80	1.824	1.547	1.465	1.383	1.406	1.755	1985TL1457

(Continued)

Table 1 (Continued)

<i>Compound</i>	<i>S(1)–C(2)</i>	<i>C(2)–C(3)</i>	<i>C(3)–N(4)</i>	<i>N(4)–C(5)</i>	<i>C(5)–C(6)</i>	<i>C(6)–S(1)</i>	<i>Reference</i>
81	1.818	1.523	1.459	1.384	1.412	1.750	1994T5037
82	1.726	1.419	1.315	1.383	1.399	1.757	1984TL2635
83	1.731	1.417	1.316	1.388	1.405	1.762	1985HCA2216
84	1.735	1.419	1.297	1.384	1.411	1.760	1985HCA2216
85	1.765	1.382	1.342	1.402	1.385	1.768	1994AXC1756
86	1.779	1.480	1.348	1.392	1.386	1.766	2003NCS129
87	1.765	1.520	1.455	1.400	1.414	1.781	1996CHE1023
88	1.760	1.523	1.464	1.406	1.412	1.783	1996RCB414
89	1.777	1.334	1.381	1.413	1.379	1.758	1989JPR141
90	1.736	1.473	1.271	1.378	1.422	1.725	1987JOC4000
91	1.752	1.391	1.376	1.378	1.399	1.750	1995AXC249
92	1.757	1.404	1.399	1.395	1.394	1.760	1985AXC1111
93	1.750	1.412	1.393	1.395	1.402	1.756	1985AXC383
94	1.758	1.400	1.397	1.393	1.391	1.765	1985AXC386
95	1.746	1.398	1.370	1.400	1.386	1.775	1996AXB713
96	1.746	1.400	1.398	1.409	1.387	1.769	1996AXB713
97	1.761	1.420	1.366	1.385	1.411	1.772	1995AGE921
98	1.764	1.400	1.413	1.414	1.407	1.761	2004JA1388
99	1.754	1.402	1.416	1.409	1.406	1.754	2004JA1388
100	1.760	1.397	1.402	1.418	1.393	1.761	1991AXC2465
101	1.772	1.377	1.418	1.417	1.397	1.767	1993AXC333
102	1.767	1.383	1.405	1.404	1.405	1.778	1993AXC333

Table 2 Internal bond angles (at atom indicated) in the 1,4-thiazines **22**, **54**, **57–67**, **69–71**, and **73–102** (°) (numbered clockwise as shown starting from S)

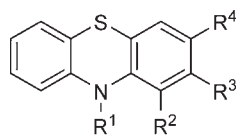
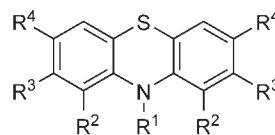
<i>Compound</i>	<i>S-1</i>	<i>C-2</i>	<i>C-3</i>	<i>N-4</i>	<i>C-5</i>	<i>C-6</i>	<i>Reference</i>
22	103.1	122.0	125.1	122.5	126.8	120.3	1985AXC1062
54	100.8	124.6	124.9	119.8	126.00	123.8	1986JA5339
57	99.93	114.41	124.60	122.13	124.04	120.97	1980TL1705
58	100.2	107.1	111.9	124.1	121.8	117.0	1986J(P1)2187
59	94.7	113.6	112.1	116.8	111.6	111.7	1988BSB343
60	99.0	110.1	113.0	114.4	111.0	111.6	1992JOC4215
61	95.6	111.9	109.9	116.4	110.0	111.6	1993AXC976
62	103.3	115.6	123.7	125.2	123.4	124.2	1998T2459
63	100.6	116.4	119.9	121.7	116.8	111.4	1998T2459
64	98.5			122.8	108.8	111.5	2006EJO1555
65	105.9	121.7	112.3	112.9	107.7	112.6	2006SL3259
66	98.2	114.4	120.9	130.2	114.6	113.9	1999J(P1)149
67	102.1	121.0	126.2	122.7	125.6	122.4	1997H(45)1183
69	98.0	123.3	121.8	125.2	121.4	123.7	2005AXEo2716
70	97.1	106.1	118.9	124.3	120.9	121.0	1985T569
71	97.7	110.2	117.1	127.7	120.7	119.7	1997AXC313
73	96.5	112.5	116.0	124.7	120.5	119.7	1997J(P1)309
74	94.7	114.8	115.3	124.0	123.0	120.8	1998J(P1)1569
75	98.9	108.4	117.3	125.2	120.6	119.1	1992LA1259
76	96.8	110.0	117.8	123.9	120.9	119.9	1996LA1541
77	102.2	122.2	123.1	127.2	121.7	122.7	2006AXEo1636
78	102.0	124.6	124.6	123.4	120.8	124.3	1987J(P1)1027
79	97.0	111.2	112.8	123.5	121.6	119.4	1986AXC1425
80	98.9	112.0	114.4	126.4	123.0	120.1	1985TL1457

(Continued)

Table 2 (Continued)

Compound	S-1	C-2	C-3	N-4	C-5	C-6	Reference
81	95.85	110.8	114.1	124.5	122.4	119.9	1994T5037
82	100.3	118.4	126.8	119.4	126.3	119.1	1984TL2635
83	100.5	120.7	126.8	120.0	126.3	120.0	1985HCA2216
84	100.3	122.0	128.2	119.8	126.7	121.4	1985HCA2216
85	99.0	121.5	123.7	124.9	121.3	122.6	1994AXC1756
86	103.7	119.8	122.1	129.1	121.2	124.0	2003NCS129
87	101.5	108.9	112.9	116.4	124.3	122.1	1996CHE1023
88	102.0	109.0	113.1	115.5	125.0	121.6	1996RCB414
89	99.7	120.6	121.6	122.9	121.5	118.6	1989JPR141
90	104.2	116.1	128.4	125.0	121.6	122.3	1987JOC4000
91	102.8	122.9	122.2	127.3	121.5	123.3	1995AXC249
92	96.0	121.9	121.7	120.4	121.3	122.5	1985AXC1111
93	96.8	124.0	122.1	121.5	121.6	124.6	1985AXC383
94	96.1	122.0	121.8	121.4	121.8	122.4	1985AXC386
95	101.3	123.9	123.2	125.4	122.3	123.9	1996AXB713
96	98.3	119.3	119.7	117.8	119.4	119.3	1996AXB713
97	100.6	120.2	126.5	119.5	126.2	120.4	1995AGE921
98	99.4	120.4	120.8	121.0	120.7	120.3	2004JA1388
99	100.3	121.4	120.5	121.5	120.4	121.3	2004JA1388
100	98.9	120.0	118.9	119.2	120.0	119.1	1991AXC2465
101	98.6	119.1	120.5	118.3	119.3	119.6	1993AXC333
102	100.9	121.4	120.5	122.3	121.7	119.2	1993AXC333

Phenothiazines, being of pharmaceutical importance, have been examined by X-ray crystallography more than any other type of thiazines. As the compounds are very similar in structure, the properties were given only for selected phenothiazines. **Table 3** lists the other phenothiazines for which X-ray structures have been reported.

**103****104**

8.09.3.2 NMR Spectroscopy

8.09.3.2.1 ¹H NMR

A good variety of compounds have been prepared and characterized allowing us to obtain reliable information on the chemical shifts of saturated and unsaturated ring protons. A selection of different structures are shown in **Table 4**. The thiazine derivatives have been organized in groups for comparison. The effects of saturation (**54**, **105**, **106**), substituents of variable electronegativity (**107**, **108**), increasing oxidation state of sulfur (**121**, **122**, **27–29**), and deprotonation (**109–111**) can be observed.

In general, a saturated center adjacent to sulfur has a proton shift of 2–3 ppm and a saturated center adjacent to nitrogen 3–4 ppm, whereas double-bond protons are 5.7–7 ppm adjacent to sulfur and about 1 ppm higher adjacent to nitrogen. Unfortunately, no information is available of CH=N proton shifts as the parent compound **3** <1948JA684> has not been analyzed by NMR, as is the case with the only other reported 2*H*-thiazine with an unsubstituted 3-carbon <1954CCCC754>.

Table 3 X-Ray structures determined for phenothiazines of structure **103** and **104**

R^1	R^2	R^3	R^4	Reference
<i>Type 103</i>				
Me	<i>i</i> -Pr	H	H	1984AXC1281
(CH ₂) ₃ NMe ₂ ·HBr	Cl	H	H	1984AXC2113
(CH ₂) ₃ NMe ₂ ·HBr	H	Cl	H	1984AXC2113
Ph	H	H	H	1985AXC1202
TMS	TMS	H	H	1985AXC1804
(CH ₂) ₂ NMe ₂ ·HCl·H ₂ O	H	H	H	1985BCJ437
(CH ₂) ₂ NHMe ₂] ²⁺ ·CuCl ₄ ²⁻	H	H	H	1985BCJ437
Ph	H	Cl	H	1986AXC750
(CH ₂) ₃ NMe ₂	H	OMe	H	1986AXC889
(CH ₂) ₃ NMe ₂ ·HCl·1/2 H ₂ O	H	Cl	H	1986AXC1083
(CH ₂) ₂ NEtPr ¹	H	H	H	1987AXC1737
H	CONH(CH ₂) ₂ NMe ₂ ·HCl	H	H	1992AXC2004
(CH ₂) ₄ Cl	H	H	NO ₂	1996AXB713
Et	H	H	H	1998AXC1151
(CH ₂) ₃ NMe ₂ ·HCl	H	H	H	1998CC931
Me	H	H	Ph	2001TL8619
CH=CHPh	H	H	H	2002OL623
<i>Type 104</i>				
Et	H	H	Br	1986AXC1794
CSNHMe	H	NMe ₂	H	1996BCJ1423
CSNHbN	H	NMe ₂	H	1996BCJ1423
H	<i>z</i> -Bu	H	<i>z</i> -Bu	2000JST(526)279
H	H	H	C≡CH	2000OL3723
<i>n</i> -Hex	H	H	C≡CH	2003EJO3534

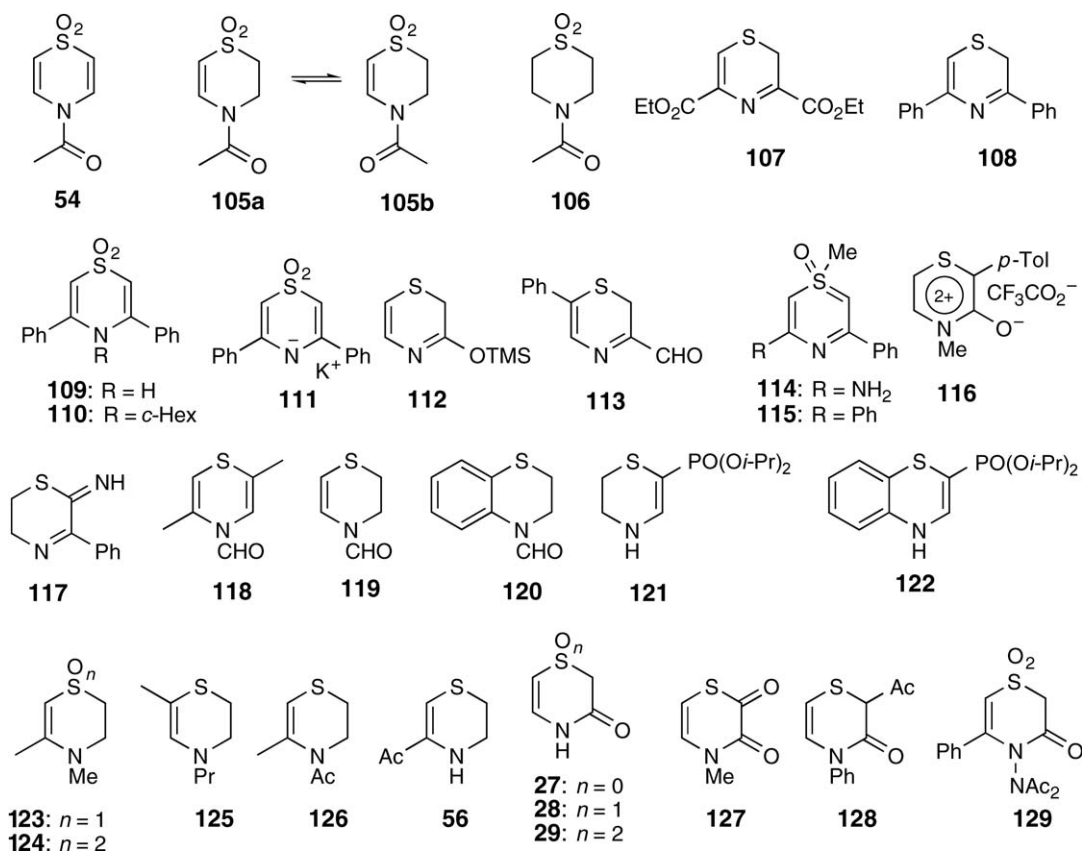
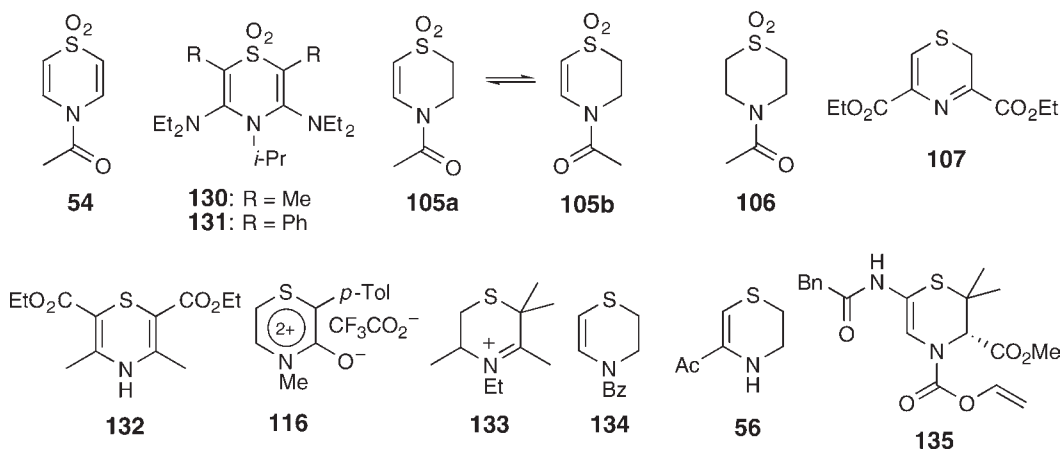


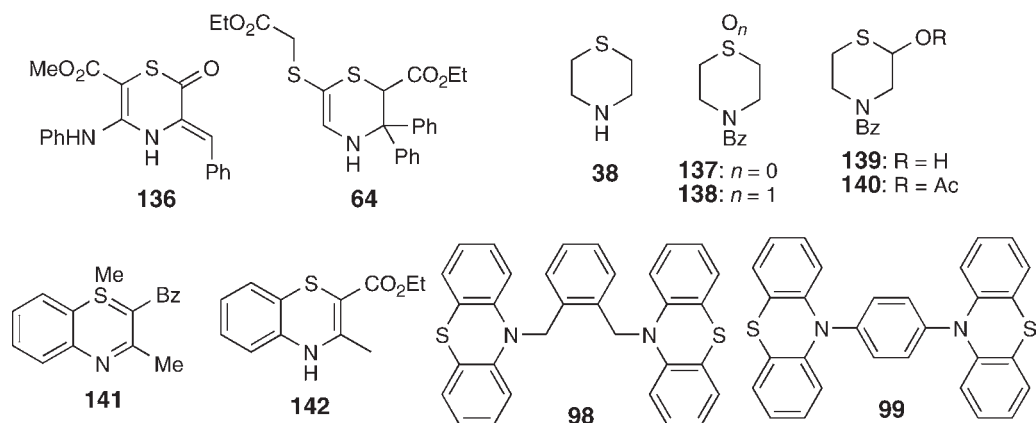
Table 4 ^1H NMR chemical shifts (ppm) for thiazine protons

Compound	2-H	3-H	5-H	6-H	Reference
54 /182 K	6.51	8.04	7.92	6.41	1992JA4307
105a /261 K	3.28	4.33	7.87	5.84	1992JA4307
105b /261 K	3.28	4.33	7.54	5.71	1992JA4307
106	2.99	3.98	3.98	2.99	1992JA4307
107	3.40			7.54	1985JOC413
108	3.36			6.44	1968G17
109	6.36			6.36	1969JOC250
110	6.68			6.68	1974CB1334
111	5.91			5.91	1969JOC250
112	N/A		6.3	5.9	1988JME1575
113	3.42		7.98		1991S543
114	6.05			4.9	1986LA1648
115	6.30			6.30	1965CB3724
116			8.57	7.78	1988JOC2209
117			3.77	2.97	1993EJM29
118		7.29		5.23	1992T4545
119	3.03	3.95	7.14	5.48	1995JOC2597
120	3.13	4.06			1995JOC2597
121		7.10	3.45	2.85	2005RJO508
122		7.10			2005RJO508
123	2.3–3.0	3.1–3.9		5.02	1979S47
124	3.0–3.3	3.7–3.9		5.02	1979S47
125		2.6–3.3		5.85	1980BSF361
126	3.00	3.81		5.63	1973RTC879
56	3.01	3.51		6.19	1995JFA2195
27	3.21		6.26	5.56	1982JHC131
28	3.87		7.05	6.23	1982JHC131
29	4.33		7.17	6.30	1982JHC131
127			6.76	5.97	1982S424
128	4.14		6.44	5.56	1996JOC3894
129	4.49			6.38	1972T2307

8.09.3.2.2 ^{13}C NMR

Although ^{13}C NMR spectroscopy has been used on 1,4-oxazines only from the late 1970s, there are sufficient data for almost all types of thiazine carbons. A selection is presented in **Table 5**. Generally the carbons adjacent to nitrogen have higher shifts than the carbons adjacent to sulfur, but substituents and the oxidation state of sulfur have large effects.



**Table 5** ^{13}C chemical shifts (ppm) for thiazine carbons

Compound	C-2	C-3	C-5	C-6	Reference
54	109.8	131.2	127.72	102.52	1992JA4307
130	109.27	151.76	151.76	109.27	1995LA1795
131	117.17	152.02	152.02	117.17	1995LA1795
105a	39.43	43.64	132.5	107.7	1992JA4307
105b	39.43	39.64	136.03	105.9	1992JA4307
106	52.99	45.84	41.02	52.67	1992JA4307
107	20.17	136.92	137.52	127.22	1985JOC413
132	95.85	150.3	150.3	95.85	1999TL6439
116	171.0	155.5	149.3	111.4	1988JOC2209
133	N/A	191.3	N/A	N/A	1982CJC2644
134 (243 K)	25.9	40.0/47.5 ^a	124.5/121.5 ^a	101.2/104.5 ^a	1977CJC937
56	26.6	40.9	137.6	106.5	1995JFA2195
135	41.47	52.3	116.1	150.6	1983TL201
136	161.9	N/A	N/A	N/A	1987ZC368
64	45.5	62.9	136.6	88.8	2006EJO1555
38	28.3	47.9	47.9	28.3	1977CJC937
137	27.9 ^b	50.0	44.2	27.3	1977CJC937
138	38.4 ^b	45.2	44.4	32.8	1977CJC937
139	69.4	53.3	46.7	23.6	1977CJC937
140	101.4	123.2	41.3	23.6	1977CJC937
141	77.05	162.37	141.06	106.49	1985HCA2216
142	86.00	152.9	139.2	119.58	2006ARK(xv)68
98	133.6	144.1	144.1	133.6	2004JA1388
99	130.3	143.0	143.0	130.3	2004JA1388

^aThe two values represent two rotamers that are present in a ratio of 2.2–2.8 to 1.^bCompound is not symmetrical due to restricted rotation around the amide bond.8.09.3.2.3 ^{14}N , ^{15}N , and ^{33}S NMR

The compounds for which nitrogen NMR has been reported are shown in Table 6. The chemical shifts have been converted to the nitromethane scale. Sulfur NMR has not so far been investigated for 1,4-thiazines.

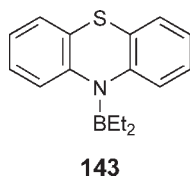


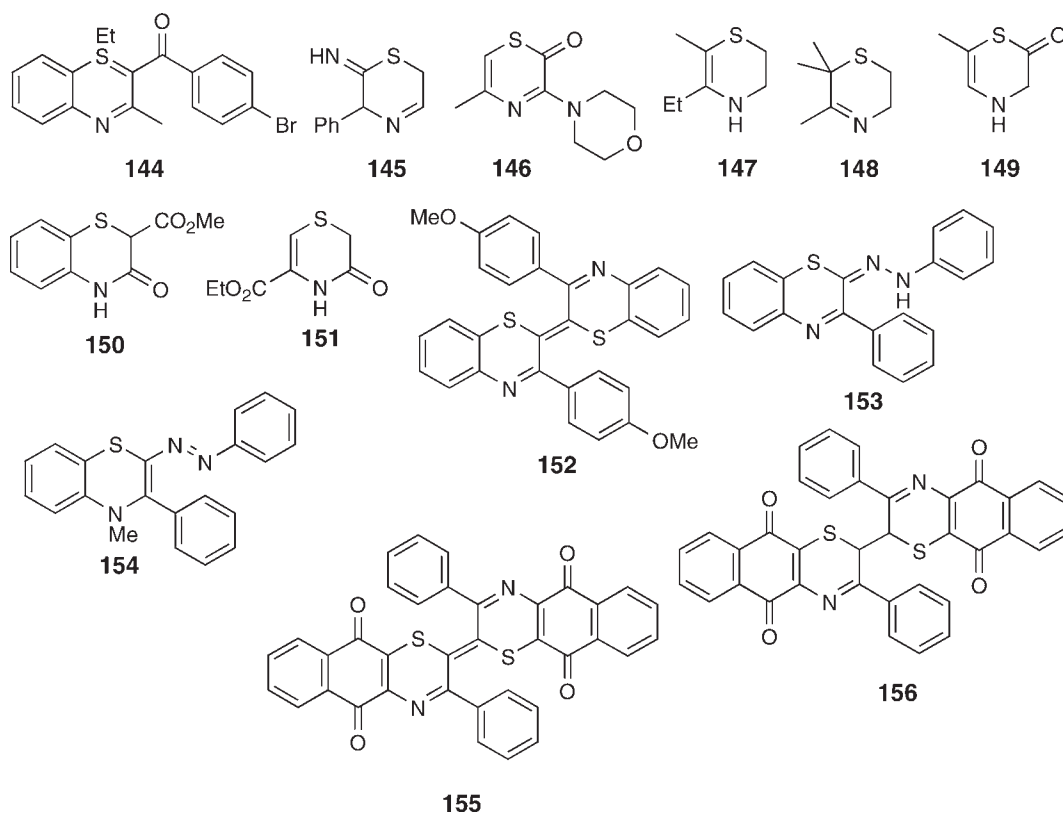
Table 6 ^{14}N and ^{15}N NMR data for 1,4-thiazines

Compound	Chemical shifts relative to MeNO_2 or $\text{Me}^{15}\text{NO}_2$, $\delta^{15}\text{N}$ ($\delta^{14}\text{N}$)	Reference
38 (thiomorpholine)	−358	2002SAA2737
38	−362.6	2003MRC307
16 (phenothiazine)	(−313.7)	1973CB1145
143	(−220.7)	1973CB1145
50	−225.9	2005T6642
51	−226.4	2005T6642
52	−226.4	2005T6642

8.09.3.3 UV-Vis and Infrared Spectroscopy

Infrared (IR) spectroscopy has been of analytical importance when investigating whether a 1,4-thiazine exists in the *2H*- or *4H*-form, and the presence of an NH signal at $3200\text{--}3300\text{ cm}^{-1}$ confirms the *4H*-form. Selected UV-Vis and IR spectra are given in [Table 7](#).

The dyes **152–156**, with structures inspired by the trichochrome pigments, are discussed further in [Sections 8.09.4.3 and 8.09.12.2](#). A false 1,4-thiazine structure was reported for the dye coumarin 540, along with its UV/Vis spectrum, when in fact the compound is a benzothiazole [<2004SAA435>](#).



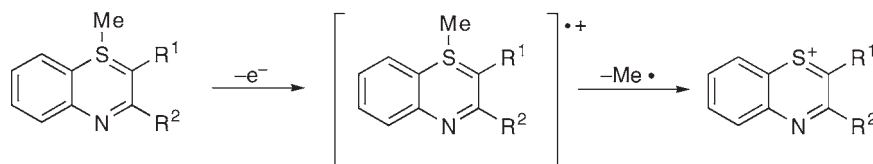
8.09.3.4 Mass Spectrometry

Some information has been obtained on the fragmentation patterns of 1,4-thiazine derivatives. A group of 2- and 3-substituted *S*-methylated benzothiazines with the general structure **2** ($\text{R} = \text{Me}$) lost a methyl radical in electron impact mass spectrometry at 70 eV ([Scheme 2](#)) [<1982J\(P1\)831>](#).

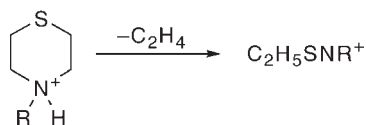
Table 7 UV and IR spectra of 1,4-thiazines

Compound	$\nu_{\max}$ (cm^{-1})	$\lambda_{\max}$ (nm) ($\log \epsilon$)	Reference
109	3380 (N-H), 1100 (S=O)		1967JME501
110	1640 (C=C), 1250, 1120 (S=O)	208 (3.97), 220 (3.95), 315 (3.83)	1974CB1334
130	1630 (C=C), 1318 (S=O)		1972T2307
82	1675, 1640		1984TL2635
144	1590, 1180, 1010, 970, 820, 750	280 (3.89), 328 (3.76)	1989JPR82
145	1615 (C=N), 785 (C-S)		1993EJM29
146	1600, 1550		1992CPB1025
147	1655 (C=N)		1962LA(652)50
148	3340 (N-H), 1655 (C=C)		1962LA(652)50
149	3399 (N-H), 1683 (C=O), 1656 (C=C)	295 (3.39)	1958JA5198
142	3329 (N-H), 1641, 1592		2006ARK(xv)68
150	3205 (N-H), 1741, 1691		2006ARK(xv)68
151	3300 (N-H), 1715, 1665, 1610	224.5 (3.89), 238.5 (3.82), 320 (3.83)	1965AJC1071
27		299	1982JHC131
28		266	1982JHC131
152		217 (4.27), 266 (4.23), 310 (3.89), 368 (3.82), 464 (3.39)	1980J(P1)2923
152^a		217 (4.24), 266 (4.15), 335 (3.81), 424 (3.79), 584 (3.27)	1980J(P1)2923
153		426 (4.09)	1980J(P1)2923
154		505 (4.17)	1980J(P1)2923
155		275 (4.53), 353 (4.10), 562 (3.59)	1980J(P1)2923
156		292 (4.55), 372 (4.53), 570 (3.04)	1980J(P1)2923

^aProtonated form, HCl was added to the solution.

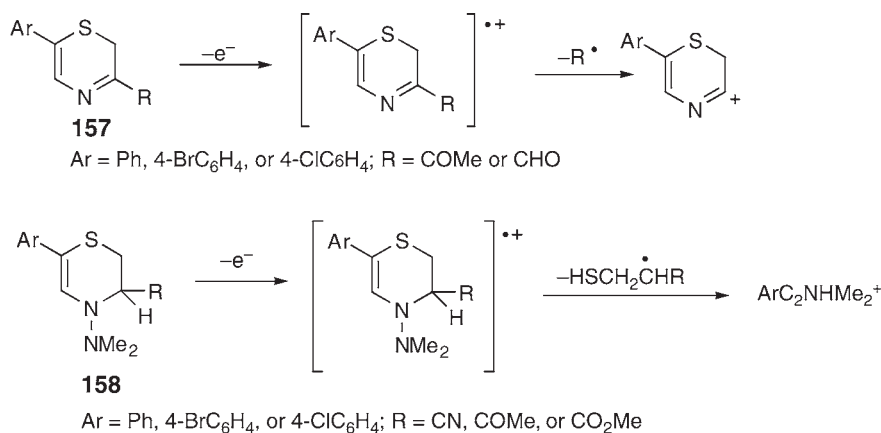
**Scheme 2** Fragmentation of benzothiazine ylides.

Protonated thiomorpholine loses ethylene in chemical ionization giving the cation $\text{C}_2\text{H}_6\text{NS}$ as main peak (m/z 76). Methylated and ethylated derivatives lose ethylene in a similar manner (**Scheme 3**) <1984OMS539>.

**Scheme 3** Fragmentation of thiomorpholinium ions.

Patterns were also observed for the fragmentation of substituted thiazines; the main peaks observed were M^+ and $(\text{M}-\text{R})^+$ for thiazines **157**, whereas *N*-dimethylaminodihydrothiazines **158** gave the peaks M^+ and $(\text{M}-\text{HSCH}_2\text{CHR})^+$ (**Scheme 4**) <1991S543>.

When fast atom bombardment mass spectrometry (FABMS) and tandem mass spectrometry (MS/MS) were applied using β -cyclodextrin as host and thioglycerol as matrix for compound **56**, the main peaks were the molecular peak $[\text{56} + \text{host} + \text{matrix} + \text{H}]^+$ (100%) and $[\text{56} + \text{host} + \text{matrix} - \text{H}_2\text{O} + \text{H}]^+$ (6%) <1997JMP807>.

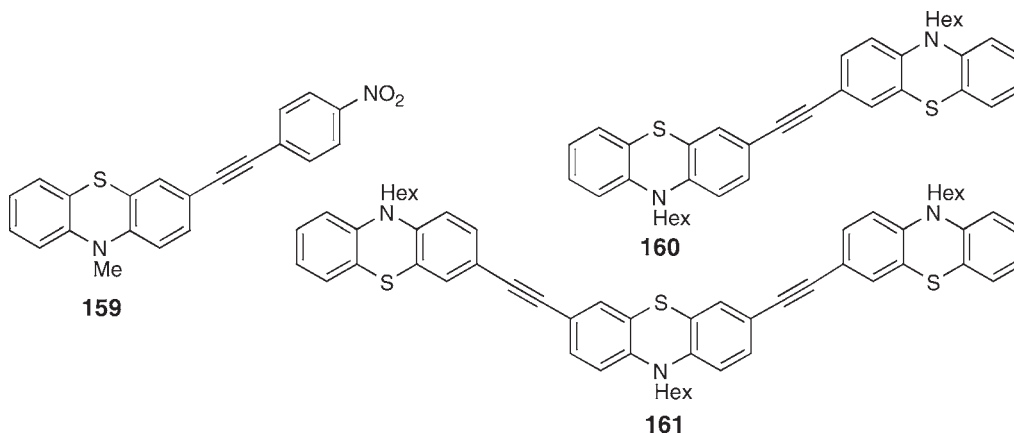


Scheme 4

8.09.3.5 ESR and Cyclic Voltammetry

Compound **141** has been analyzed by electron spin resonance (ESR) spectroscopy during 1 h irradiation at 254 nm at room temperature at a frequency of 9.64 GHz and a magnetic field of 3445 G. The signal observed was a quartet, splitting 5.667 G, due to loss of SMe and interaction of the resulting thiazinyl radical with the methyl hydrogens at C-3 <1989JPR82>.

Phenothiazine derivatives and compounds with two or three thiazine rings conjugated to each other, such as **98** and **99** <2004JA1388>, **159**, **160**, and **161** <2003EJO3534>, have interesting electronic properties (see also Section 12.2) and their cyclic voltammetry has been studied. These compounds are oxidized stepwise until each phenothiazine moiety has lost an electron.



8.09.4 Thermodynamic Aspects

8.09.4.1 Melting Points

The parent compound **3** is a liquid boiling at 76.5–77 °C <1948JA684>, but most reported 1,4-thiazines are either solids or liquids that can be distilled at reduced pressure. Figure 6 shows melting or boiling points for the simple thiazinone **27** and the 1,1-dioxide **29** <1982JHC131>, **149** <1948JA3517> and its 4-methyl derivative **162** <1979S272>, **108** <1968G17> and the corresponding 1,1-dioxides **109** <1967JME501> and **110** <1974CB1334>, dihydrothiazine **105** <1973RTC879>, dihydrothiazin-3-one **163** and dihydrothiazin-2,3-dione **127** <1982S424>, ylide **82** <1984TL2635>, and diastereoisomeric compounds **164** and **60** <1992JOC4215>.

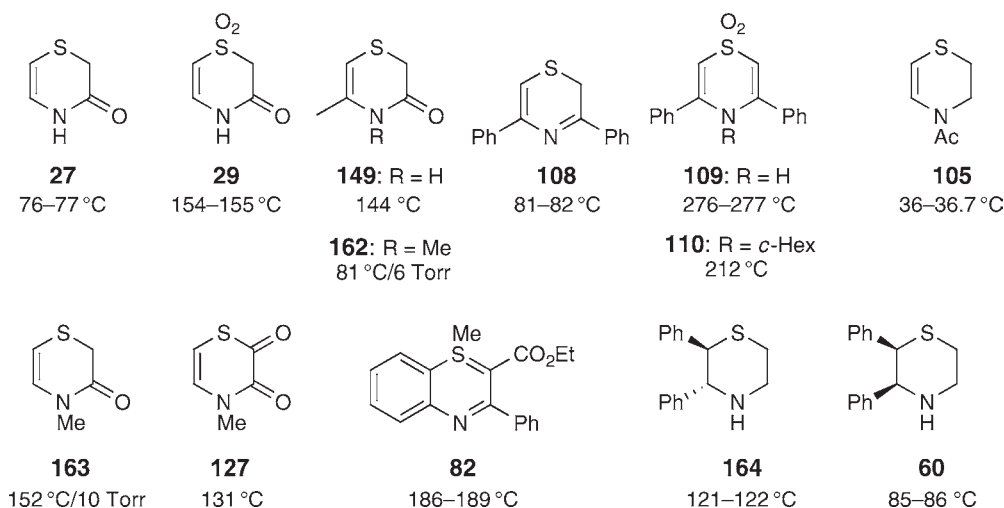


Figure 6 Melting points and boiling points for 1,4-thiazines.

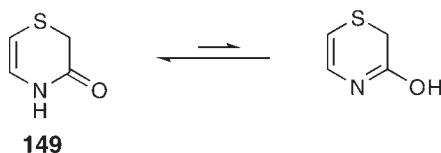
8.09.4.2 Aromaticity and Stability

As shown in Section 8.09.1, thiazines can contain three double bonds when sulfur is at a higher oxidation state. The X-ray structures of compounds **82–84** show that the molecules are not planar. The cation **116** is aromatic as was established by spectroscopic methods <1988JOC2209>.

The carbon–sulfur bond of thiazines can be reductively cleaved (Sections 7.06.5.7 and 7.06.6.7) and 2*H*-thiazines, being imines, can be hydrolyzed (Section 7.06.5.5). Saturated thiazines (thiomorpholines) are stable toward alkaline hydrolysis <1981CPB1554> and Lewis-acidic boron trifluoride <1980JHC449>.

8.09.4.3 Tautomerism

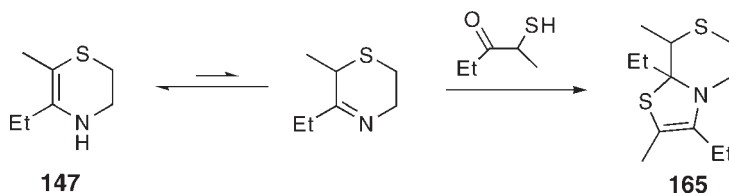
As mentioned at the beginning of this chapter, unsubstituted 1,4-thiazine **3** prefers the 2*H*-form <1948JA684> but oxidation of sulfur as well as electron-withdrawing substituents make the compound adopt the 4*H*-form. This can be seen in IR spectroscopy by the appearance of an N–H band and in the ease of N-alkylation. IR spectroscopy helped also to prove the structure **149** to be the lactam <1958JA5198> as opposed to the aza-enol first reported (Scheme 5) <1948JA3517>.



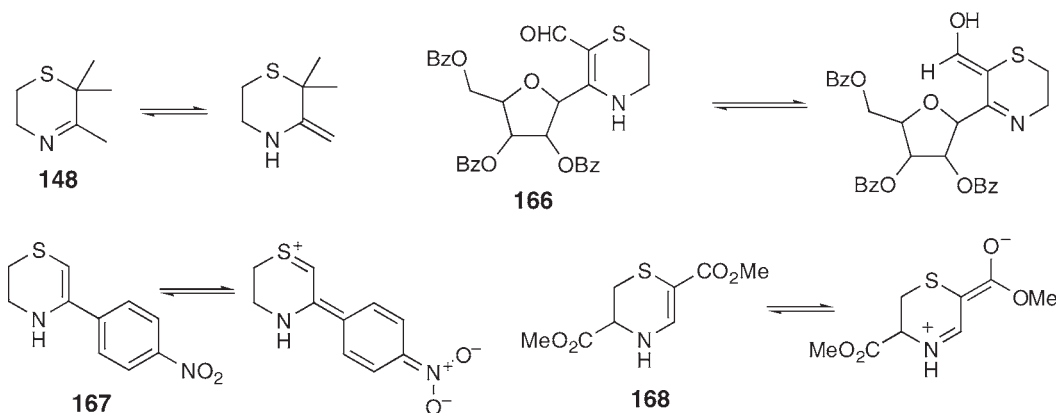
Scheme 5

IR spectroscopy showed the compound **147** to exist almost completely in the 4*H*-form; however, the minor tautomer can undergo a nucleophilic attack by an α -mercaptoketone to the 3-carbon followed by enamine formation to give **165** (Scheme 6) <1962LA(652)50>.

The 2*H*-dihydrothiazine **148** has a tautomer with a saturated oxazine ring and an exocyclic methylene group <1964M1335>. The 4*H*-structure of thiazines with electron-withdrawing substituents is stabilized by this kind of tautomerism. Carbonyl groups conjugated to a 2,3-double bond of thiazines as in **166** give an enol-type tautomer <1992H(34)2131> and can even withdraw electrons from sulfur atom as in **167** <1962G1367> or nitrogen as in **168** <1968T2985> to give zwitterions (Scheme 7).

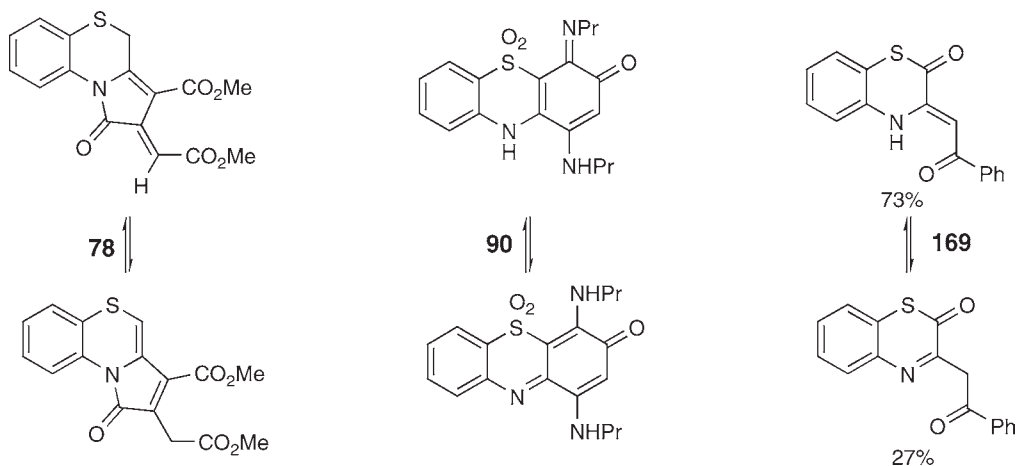


Scheme 6



Scheme 7

When there is a carbonyl group in the thiazine side chain, the compounds have tautomers where all double bonds are conjugated to the carbonyl carbon (**Scheme 8**). Compound **78** has two competing carbonyl groups <1987J(P1)1027>, **90** has both *para*- and *ortho*-quinone imine tautomers <1987JOC4000>, and in **169** the two forms are in equilibrium when they are formed in hot acetic acid but can be isolated at room temperature <2002CHE365>. Compounds **50–52** are also subject to similar tautomerism and the correct structures were proven to be the those presented in Section 8.09.2 <2005T6642>.



Scheme 8

Scheme 9 shows the tautomerism of 2-arylazosubstituted benzothiazines. Both **67** <1997H(45)1183> and **153** prefer the **A** form; **153** can only be forced to adopt the **B** form by N-alkylation to give **154** <1980J(P1)2923>.



Scheme 9

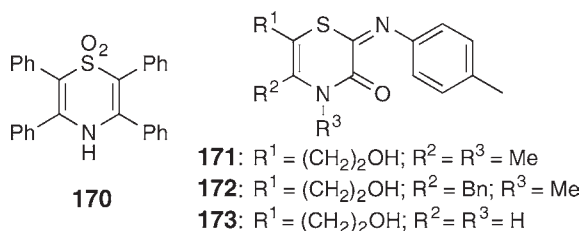
8.09.4.4 Restricted Rotation and Conformations

An acyl substituent in the 4-position causes restricted rotation around the amide bond which prefers to be planar (see [Figure 4](#), [Section 8.09.2](#)). This often leads to separate NMR signals for each thiazine proton and carbon. Restricted rotation has been encountered for *N*-formyl- [<1992T4545>](#), *N*-acetyl- [<1969TL3063, 1984OMR676, 1986JA5339, 1992JA4307>](#), and *N*-benzoylthiazines [<1977CJC949, 1984OMR676>](#). In the case of 4-acyldihydrothiazines, the amide oxygen prefers slightly to be *syn* to the 2,3-double bond [<1969TL3063, 1992JA4307>](#). The energy barrier for rotation was reported for *N*-benzoyl derivatives to be 60.9 kJ mol^{-1} ($14.56 \text{ kcal mol}^{-1}$) in saturated rings. In dihydrothiazines, the barrier is 60.1 kJ mol^{-1} ($14.37 \text{ kcal mol}^{-1}$) toward the preferred form and 61.8 kJ mol^{-1} ($14.79 \text{ kcal mol}^{-1}$) toward the other form [<1977CJC949, 1984OMR676>](#). The effect of sulfur oxidation to the rotation was studied on a theoretical basis and is discussed in [Section 8.09.2](#).

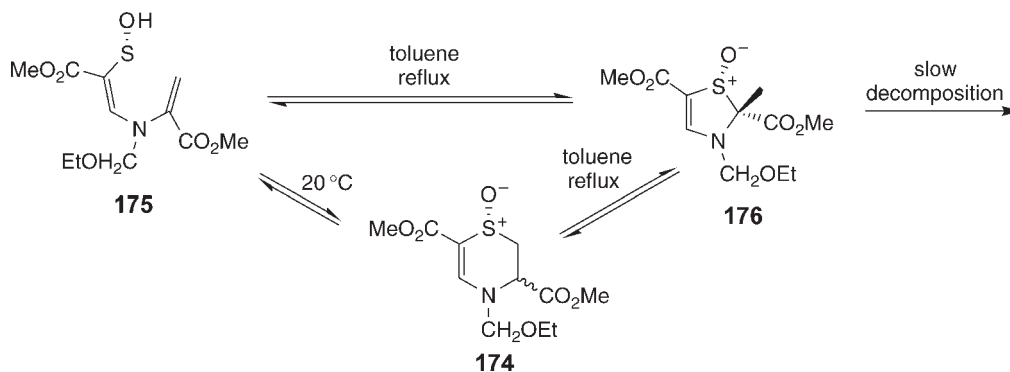
Preferred conformations for 2*H*-dihydrothiazines were discussed in CHEC(1984). The conformations for three 4*H*-dihydrothiazines with 2-methoxycarbonyl substituents have also been reported [<1969TL2979, 1969TL3367, 1973JA3439>](#).

8.09.4.5 Other Physical and Thermodynamic Properties

Chromatographic purification has been applied to 1,4-thiazines from an early stage. Compound **170** was purified using 2:3 EtOAc/benzene as eluent and obtained in good yield [<1972S311>](#). Of the three dihydrothiazine derivatives shown, **171** and **172** were recrystallized and **173** was purified by column chromatography. In these cases, the yields were much better when recrystallization was possible (see [Section 8.09.10.2](#) for synthesis) [<1974CPB311>](#). Recrystallization is still the first and often easiest choice for purification of 1,4-thiazines, although chromatography is also used.



There is an example of a thiazine **174** which at room temperature is in equilibrium with the open-chain starting material **175** it was made from, and at 110°C additionally with thiazoline **176**, which slowly decomposes at this temperature ([Scheme 10](#)) [<1976CC366>](#). After 4 h reflux and cooling, the solvent was removed and the mixture



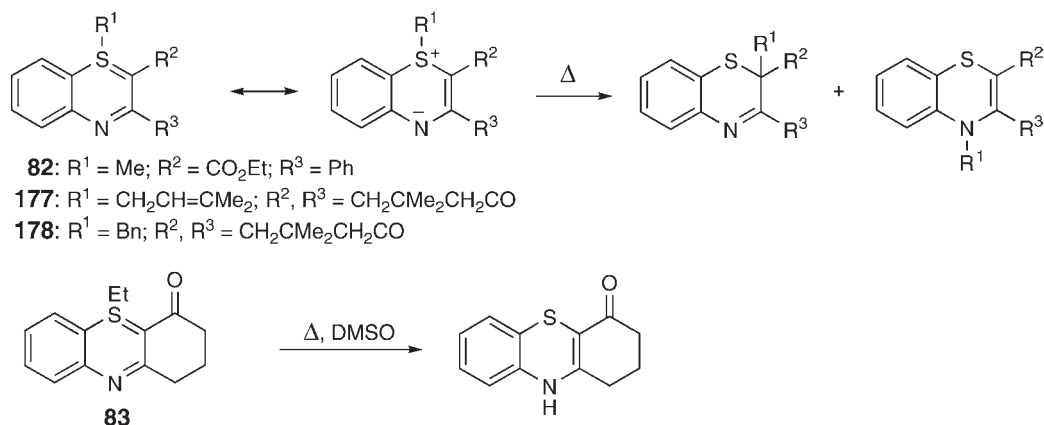
Scheme 10

found by ^1H NMR to contain the six-membered and five-membered rings in 55:45 ratio. Different N-substituents were found to change the equilibrium composition <1976J(P1)2540>.

8.09.5 Reactivity of 1,4-Thiazines

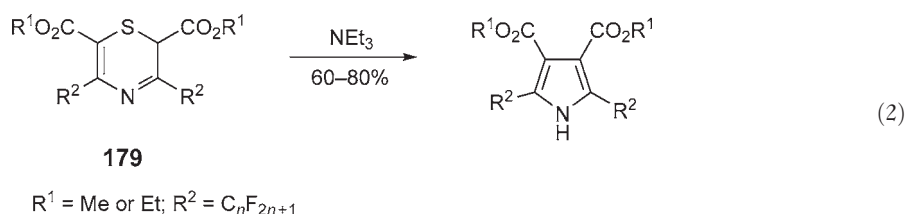
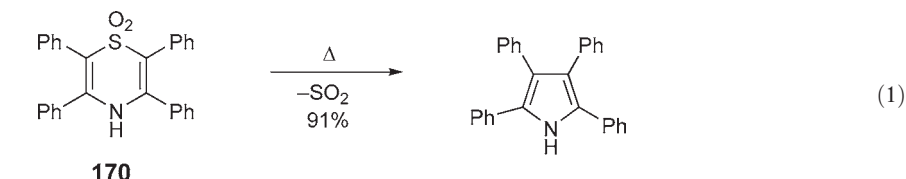
8.09.5.1 Unimolecular Reactions

It was already mentioned in Section 8.09.4.2 that compounds with the general structure **2** are not aromatic. In fact, they can be described as ylides or vinylogous sulfonium imides because nitrogen is more electronegative than sulfur. Although these compounds are stable at room temperature, they can be thermolyzed. In this process, either the 4-nitrogen or the 2-carbon acts as a nucleophile to remove the *S*-alkyl group. This reactivity was reported for **82** <1984TL2635>, **177**, and **178** <1991J(P1)2249>. When thermolysis of **83** is performed in a polar solvent, the nitrogen atom is protonated and the sulfur atom is dealkylated (Scheme 11) <1985HCA2216>.

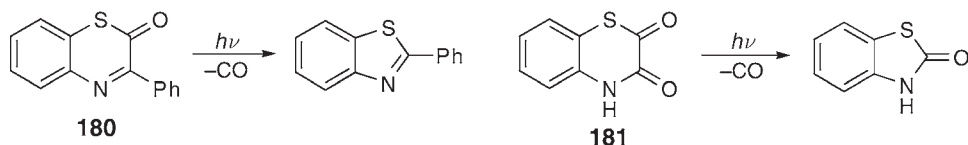


Scheme 11

A variety of unimolecular processes involving loss of small molecules are shown below. Thiazine 1,1-dioxide **170** loses sulfur dioxide when heated (Equation 1) <1972S311>, whereas thiazines with the general structure **179** undergo desulfurization to give pyrroles when treated with triethylamine (Equation 2) <1984JOC4780, 1985JHC1621>.

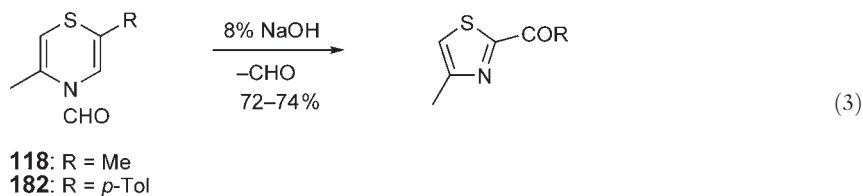


Benzothiazinones **180** and **181** lose carbon monoxide under irradiation to give benzothiazoles as shown (Scheme 12) <1986CB215>.



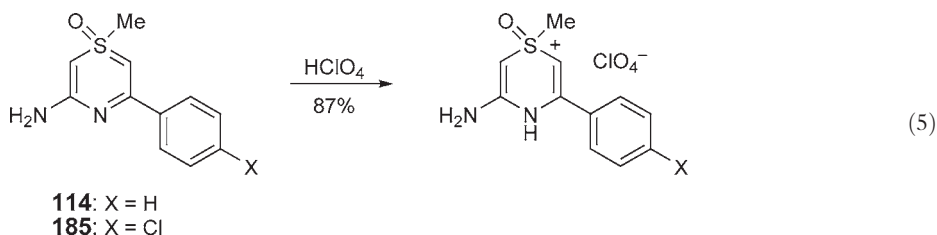
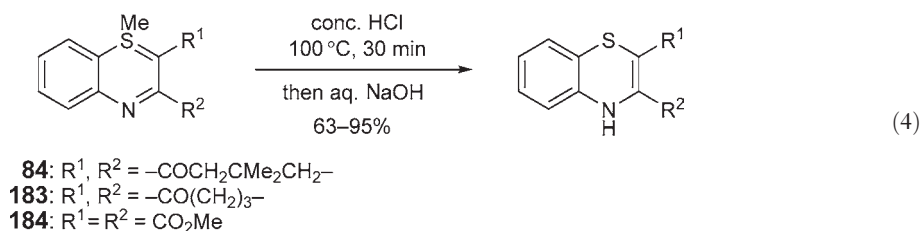
Scheme 12 Loss of carbon monoxide.

The *N*-formylthiazine **118** and the *p*-tolyl derivative **182** undergo deformylation and rearrangement to thiazoles when treated with alkali (Equation 3) <1992T4545>.

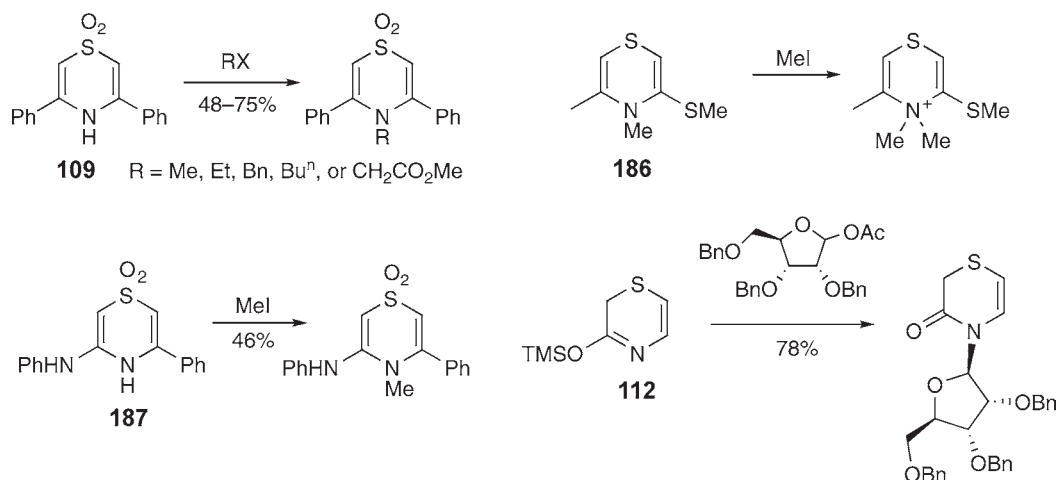


8.09.5.2 Electrophilic Attack at Nitrogen

As was already shown in Scheme 11, benzothiazine ylides have a nucleophilic nitrogen that was protonated with loss of the *S*-alkyl group even when heated in dimethyl sulfoxide (DMSO). Reacting the ylides **84**, **183**, and **184** with acid results in the same transformation (Equation 4) <1982J(P1)831>. Compound **114** and the 4-chlorophenyl derivative **185** could also be protonated with perchloric acid but in this case *S*-dealkylation did not occur and a salt was obtained (Equation 5) <1986LA1648>.

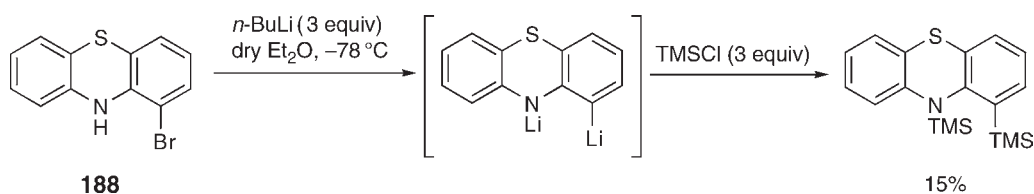


Regardless of the oxidation state of sulfur, the nitrogen of 4*H*-1,4-thiazines is almost as easy to alkylate as an amine, as can be seen from the reactions of **109** <1967JME501>, **186** <1969JHC247>, and **187** <1976JPR865>, whereas the only 2*H*-1,4-thiazine that could be *N*-alkylated is the silyl iminol ether **112** <1988JME1575> (Scheme 13).



Scheme 13

The nitrogen of phenothiazine **16** can be deprotonated and alkylated, for example, with a palladium catalyst <1985AXC1804>. When an excess of butyllithium was used for **188**, an additional halogen–metal exchange occurred and the compound could be doubly silylated (Scheme 14) <2002OL623>.

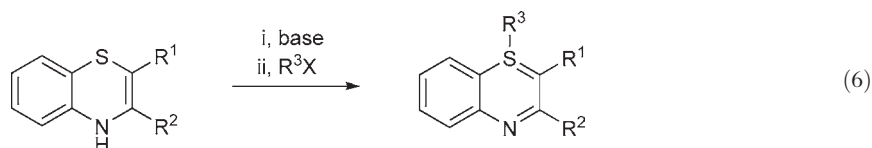


Scheme 14

8.09.5.3 Electrophilic Attack at Sulfur

Oxidation of thiazine sulfur to give *S,S*-dioxides has been performed successfully on substituted 1,4-thiazines <1999TL6439> and 3-acetyloxyphenothiazine <1987JOC4000> using *m*-chloroperoxybenzoic acid (MCPBA). Another oxidant is hydrogen peroxide, which was used to carry out the same transformation on a 4*H*-benzothiazine <2003JFC(122)207>.

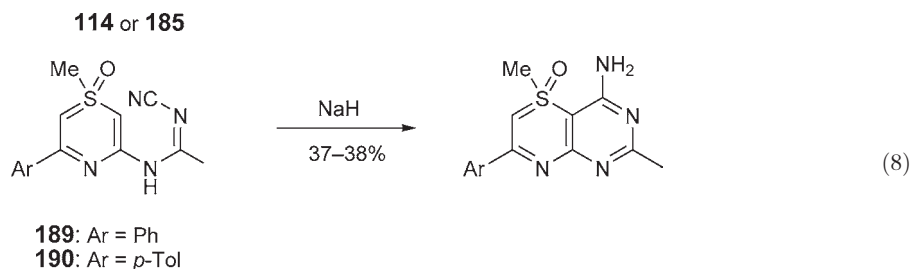
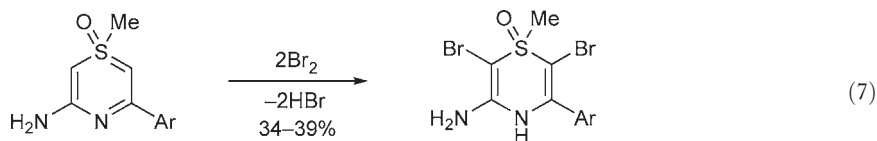
All benzothiazine ylides **82** <1984TL2635>, **83**, **84**, and **141** along with a variety of other derivatives <1985HCA2216>, **177** and **178** <1991J(P1)2249>, and **183** and **184** <1982J(P1)831> were prepared by alkylation of benzothiazines, typically by deprotonation with sodium hydride followed by treatment with alkyl halide (Equation 6). In the case of **82**, the transformation was conducted in two stages: alkylation of sulfur with methyl triflate followed by deprotonation of the resulting salt with sodium bicarbonate <1984TL2635>. The reaction is very versatile: almost any alkyl halide can be reacted with a variety of alkyl- or acyl-substituted benzothiazines.



One failed synthesis using this method was also reported; instead of the thiazine ylide its thermolysis products (see [Scheme 11](#)) were obtained, even if the reaction was performed at -78°C . The synthesis was also extended from benzothiazines to 2*H*-1,4-thiazines, but these products were unstable [<1991J\(P1\)2249>](#).

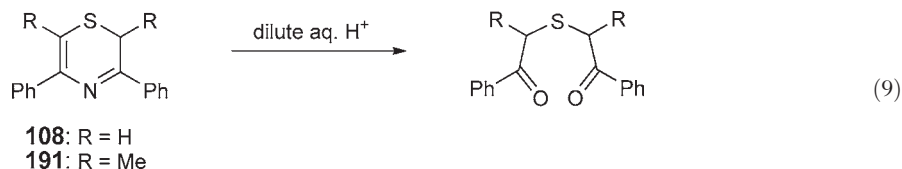
8.09.5.4 Electrophilic Attack at Carbon

Reactions similar to electrophilic aromatic substitution of 1,4-thiazine carbon atoms with electrophiles are shown below. Compounds **114** and **185** were ring-brominated ([Equation 7](#)) [<1986LA1648>](#) and **189** and **190** reacted with the electrophilic side chain to give bicyclic products ([Equation 8](#)) [<1987LA551>](#).

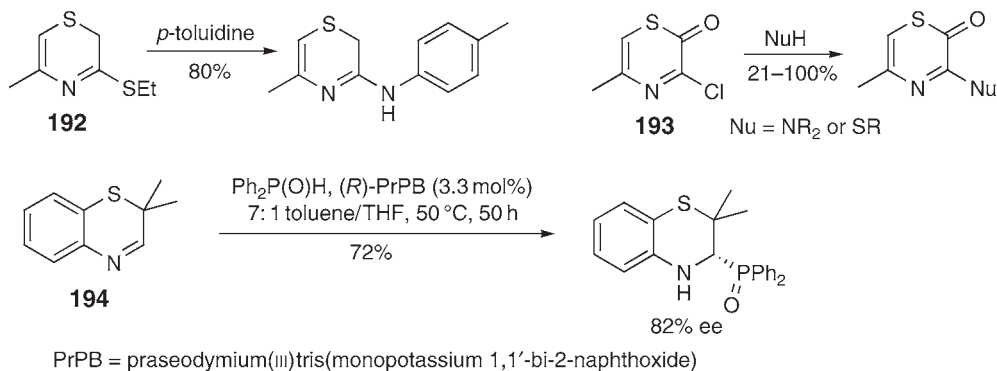


8.09.5.5 Nucleophilic Attack at Carbon

Nucleophilic attack occurs most readily at the 3-carbon of 2*H*-1,4-thiazines, and makes them susceptible toward hydrolysis. 3,5-Diphenyl-1,4-thiazine **108** and its 2,6-dimethyl derivative **191** were both hydrolyzed with dilute acid ([Equation 9](#)) [<1968G17>](#).

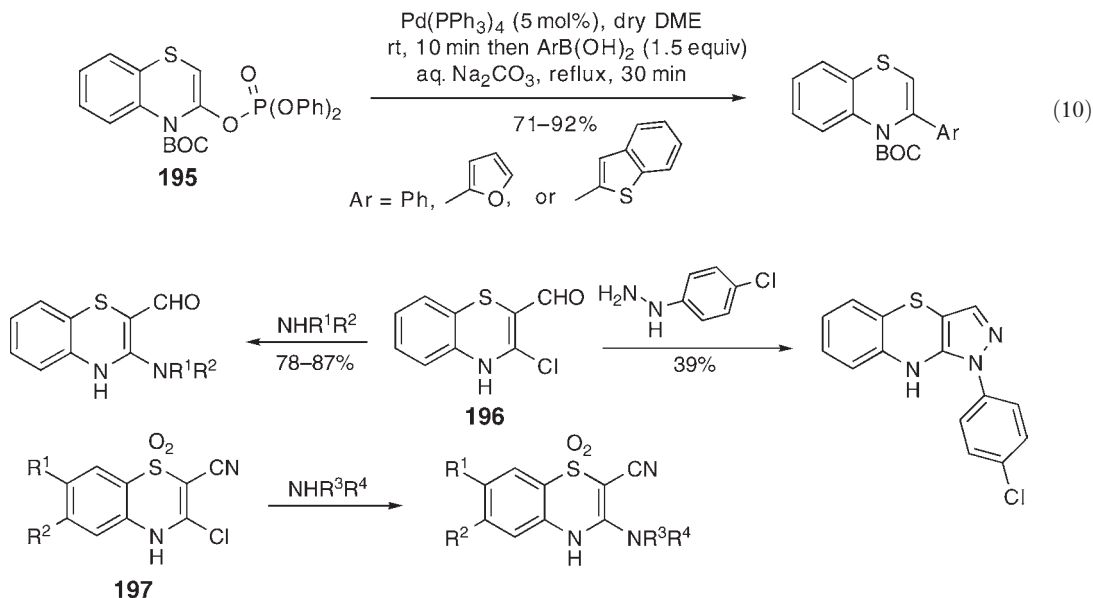


Nucleophilic substitution at the 3-carbon of 2*H*-1,4-thiazines **192** [<1969JHC247>](#) and **193** [<1992CPB1025>](#) and nucleophilic addition to the 3-carbon of 2*H*-1,4-benzothiazine **194** [<1999TL2565>](#) have been reported ([Scheme 15](#)). The catalyst used in the reaction of **194** is prepared from praseodymium(III) isopropoxide and (*R*)-binaphthol.



Scheme 15

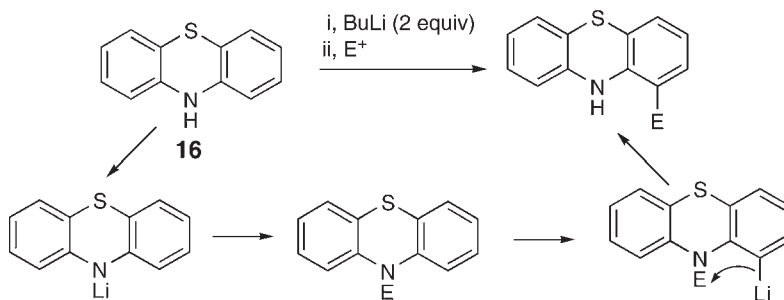
Nucleophilic substitution at the 3-carbon of 4*H*-1,4-benzothiazine **195** was achieved using a palladium catalyst (Equation 10) <1999TL6373>, whereas in compounds **196** <1972CPB1325> and **197** <2005BMC141> nucleophilic attack occurred because the 2,3-double bonds were conjugated to electron-withdrawing groups at the 2-position (Scheme 16).



Scheme 16

8.09.5.6 Nucleophilic Attack at Hydrogen

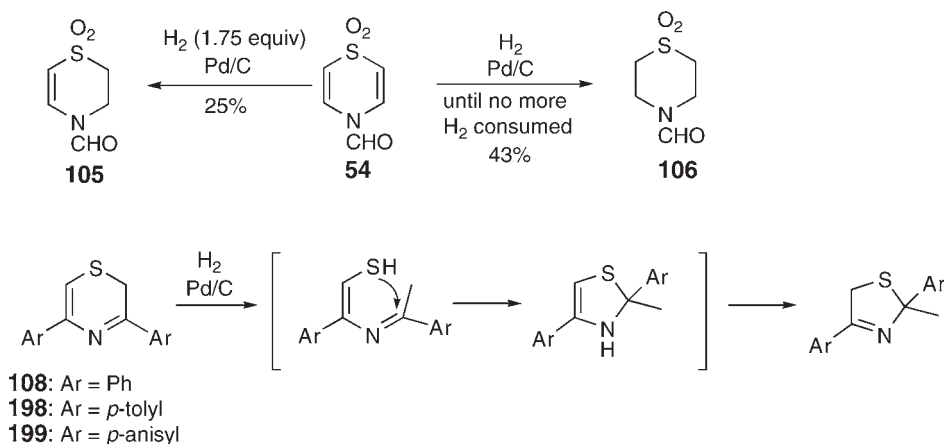
As shown in Scheme 14, deprotonation of phenothiazine may be accompanied by a halogen–metal exchange when an excess of butyllithium was used. The same position in the benzene ring seems to be lithiated even in non-brominated phenothiazine **16**. Reaction of the organolithium species with an electrophile E then results in alkylation of the aromatic ring only instead of the nitrogen atom <1988S215, 1995AGE921>. It was proved that the reaction does not proceed through a dilithiated species but instead through initial N-alkylation followed by lithiation of the adjacent aromatic carbon to which the N-substituent is then transferred (Scheme 17) <2007ARK(vi)47>.



Scheme 17

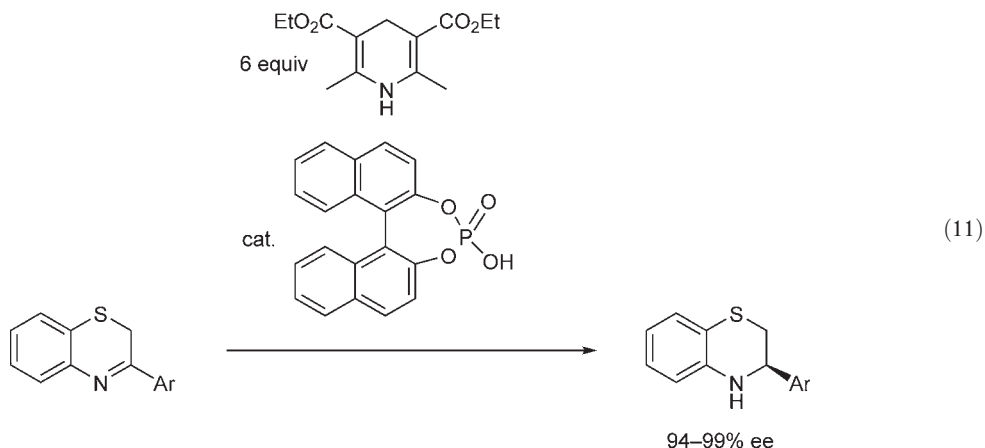
8.09.5.7 Reduction and Reactions with Radicals

Catalytic hydrogenation of 1,4-thiazines is shown in Scheme 18. Both partial and complete hydrogenation of **54** has been performed successfully <1992JA4307>, but 2*H*-1,4-thiazines **108**, **198**, and **199** underwent reductive cleavage of the C–S bond followed by cyclization to form a five-membered ring under similar conditions <1968G488>.



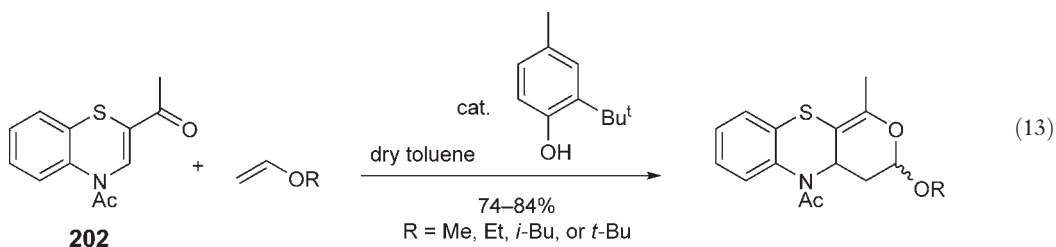
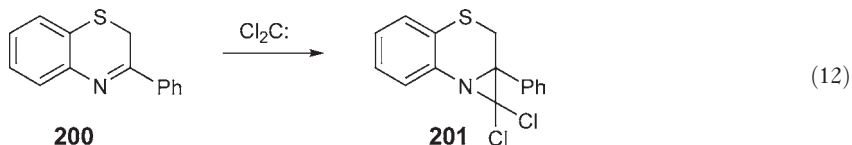
Scheme 18

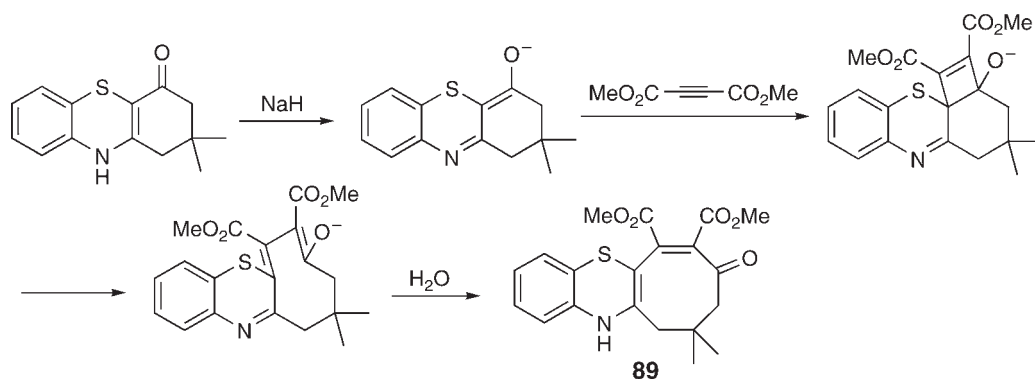
Enantioselective reduction of 3-aryl-2*H*-1,4-benzothiazines using a dihydropyridine as the reducing agent has been reported (Equation 11) <2006AGE6751>.



8.09.5.8 Cycloadditions

The 2*H*-1,4-benzothiazine **200** reacts with dichlorocarbene to form aziridine **201** (Equation 12) <2007S225>, and benzothiazine **202** underwent a [2+4] cycloaddition with a range of vinyl ethers (Equation 13) <1992CB1507>. A [2+2] cycloaddition was the initial step in the formation of **89** (Scheme 19) <1989JPR141>.



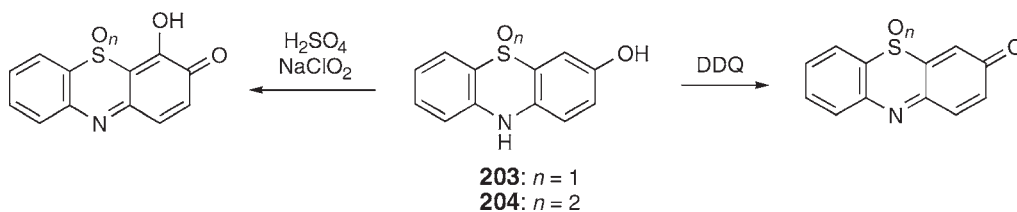


Scheme 19

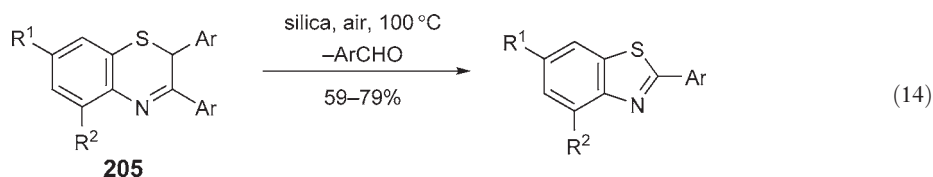
8.09.5.9 Oxidation/Dehydrogenation

The oxidative dimerization of thiazines and benzothiazines to form structures such as **44**, **152**, **155**, and **156** was already described in CHEC(1984), and can be achieved using various oxidants <1970JHC1143, 1980J(P1)2923>.

Phenothiazines **203** and **204** were oxidized to give quinones by two different oxidants (Scheme 20) <1987JOC4000>. Oxidation of benzothiazines with the general structure **205** gave benzothiazoles with loss of ArCHO, and a mechanism was suggested for this reaction (Equation 14) <2001T4195>.



Scheme 20

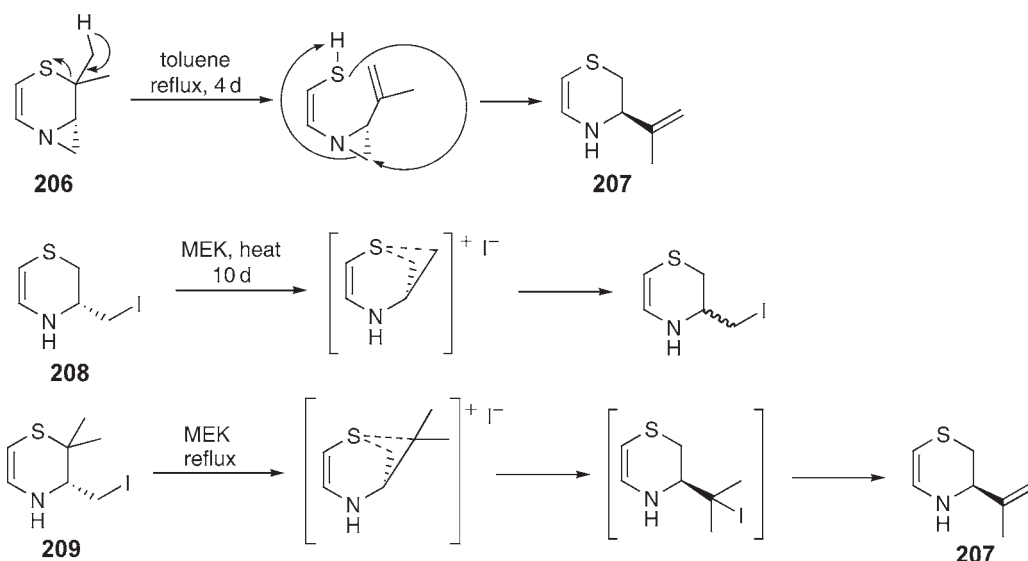


8.09.6 Reactivity of Dihydro-1,4-thiazines and Tetrahydro-1,4-thiazines

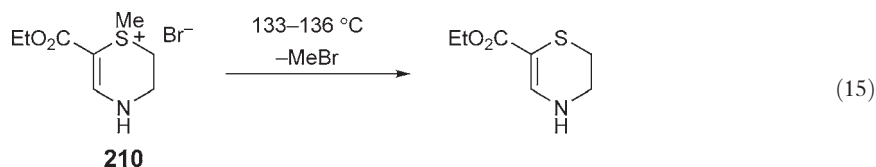
8.09.6.1 Unimolecular Reactions

Dihydro- and tetrahydrothiazines undergo many interesting rearrangements that can be catalyzed by heat or Lewis acid, base, and nucleophilic catalysts. The racemization of **208** <1969CC1169> and the reactions of **206** <1969CC1368> and **209** <1972J(P1)2509> to give **207** (Scheme 21) are caused by the weakness of the S–C bond and the nucleophilicity of the sulfur atom.

Similarly to the benzothiazine ylides, the salt **210** undergoes S-dealkylation upon heating (Equation 15) <1985S688>.



Scheme 21 Thermal rearrangements of dihydro-1,4-thiazines.



Pummerer rearrangement (**Scheme 22**) can be very useful for the dehydrogenation of dihydro- and tetrahydrothiazines or formation of 2-hydroxy derivatives, depending on the reaction conditions. Because S-oxidation is the first step of Pummerer rearrangement, it is included in these examples; more oxidations are discussed in [Sections 8.09.6.3 and 8.09.6.11](#). The rearrangement of **138** gave a 1:1 mixture of 2-acetylated and dehydrogenated products [<1977CJC937>](#), whereas **211** reacted to give only the dehydrogenated product **212** along with a small amount of bicyclic product **213**, for which a detailed mechanism of formation was suggested [<2002JKC489, 2002H\(57\)1697>](#). Dehydration of **28** [<1982JHC131>](#) and **215** [<1978CPB722>](#) is not possible and the the Pummerer products are therefore 2-hydroxythiazine **214** and 2-acetylthiazine **216**, respectively.

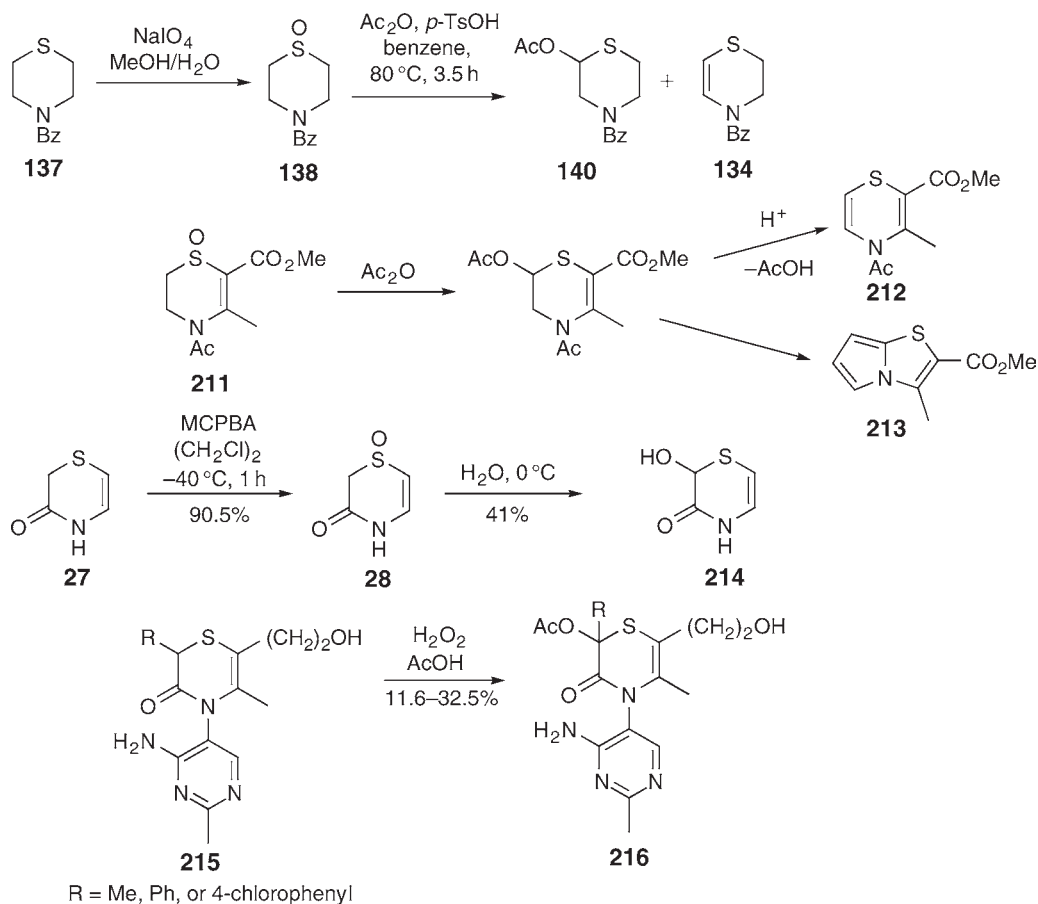
Compounds **217** and **218**, which are the hydrated forms of **118** and **182**, give the same products when treated with 8% NaOH ([Equation 16](#); see [Equation 3](#) for comparison) [<1992T4545>](#). The ring expansion of **201** ([Equation 17](#)) [<2007S225>](#) and photochemical ring contractions of benzothiazines (**Scheme 23**) [<1994TL3365>](#) have also been reported.

8.09.6.2 Electrophilic Attack at Nitrogen of Dihydrothiazines

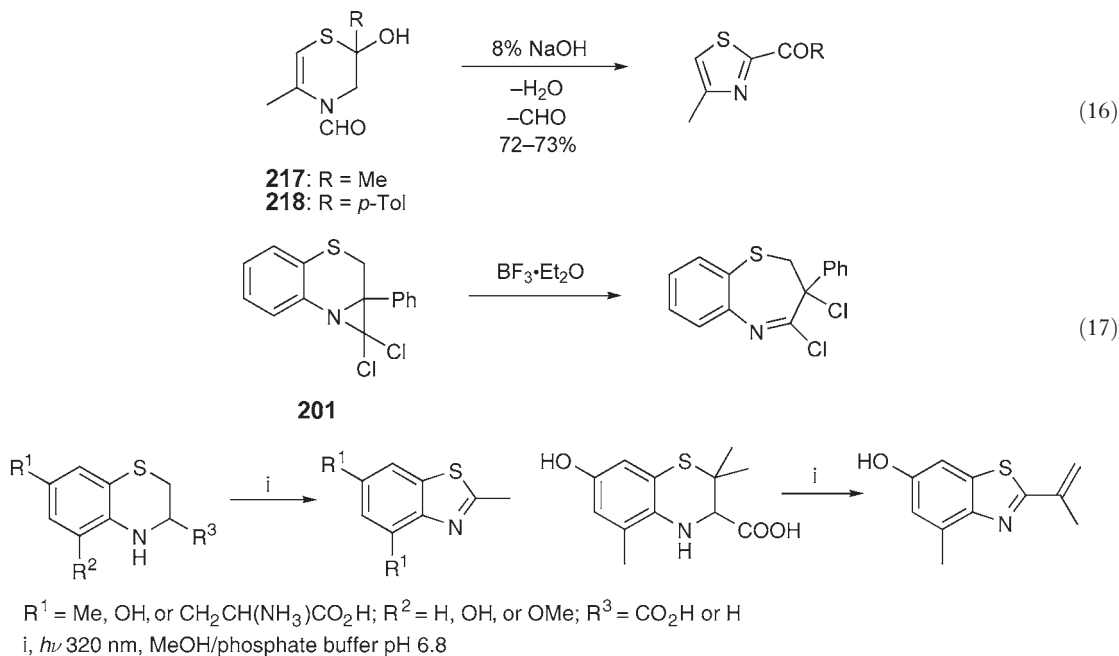
The nitrogen of 2*H*-dihydrothiazines reacts readily with alkyl or acyl halides in the presence of a base. [Table 8](#) contains a selection of N-alkylations and N-acylations performed on dihydro-1,4-thiazine derivatives.

Some unusual electrophiles are shown. Benzothiazines **219–221** were reacted with HNO₂ to give the versatile *N*-nitroso derivatives **222–224** or with cyclopentenone/*N*-bromosuccinimide (NBS) to give **225–227** (**Scheme 24**) [<2003JME3670>](#). Dihydrothiazinedicarboxylic acid **228** was reacted with 2,2-dimethoxypropane to form bicyclic product **229** ([Equation 18](#)) [<1968T2985>](#).

If a carboxylic acid ester side chain is introduced at the 3-position of a thiazine with a free NH group, lactam formation may occur [<1987J\(P1\)1027>](#). Compound **78** is a result of lactam formation, and the synthesis of similar compounds is shown in **Scheme 44** ([Section 8.09.7](#)). Reactions where the nitrogen reacts with a side chain introduced by a nucleophilic attack at the 3-carbon of 2*H*-dihydrothiazines are shown in **Schemes 6 and 27**.



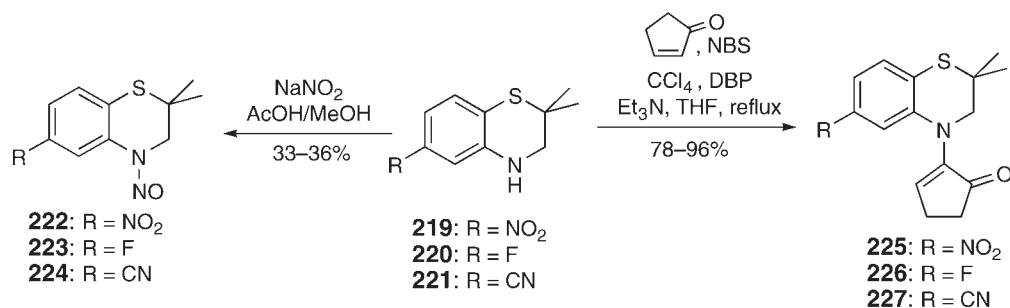
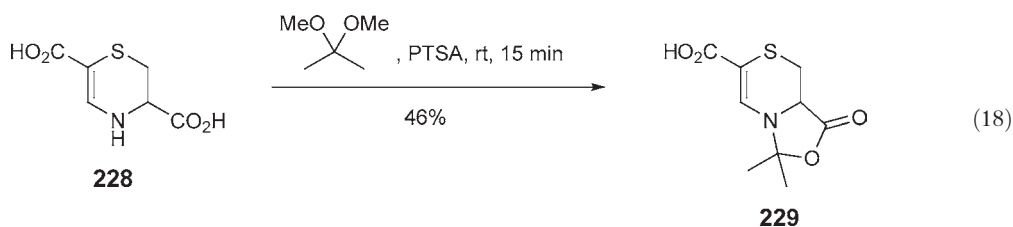
Scheme 22 Pummerer rearrangements.



Scheme 23

Table 8 N-alkylations and N-acylations of dihydro-1,4-thiazines

Compound type	Electrophile, conditions, yield	Reference
Dihydrobenzothiazine	RCOCl^a , Et_3N , CH_2Cl_2 , 29–74%	2003JME3670
3-Alkoxycarbonyldihydrothiazine	Ac_2O , rt, 24 h, 86%	1993CHE219
2-Alkoxycarbonyldihydrothiazine	BnBr , NaH , THF, rt, 3 h, 94%	1995CPB1137
Dihydrobenzothiazin-3-one	BnBr , NaH , DMF, 100 °C, 1 h, 73%	1972CPB892
Dihydrobenzothiazin-3-one	MeI , KOH , EtOH , reflux, 5 h, 37%	1972CPB892
Dihydrobenzothiazin-3-one	$n\text{-BuBr}$, KOH , DMSO/EtOH , 50 °C, 15 h, 68%	2001FA689
Dihydrobenzothiazin-3-one	$n\text{-C}_8\text{H}_{17}\text{Br}$, KOH , DMSO/EtOH	2003EJM769
Dihydrobenzothiazin-3-one ^b	Several RX , NaH , DMF, 20–75%	2001TL1167
Dihydrobenzothiazin-3-one 1,1-dioxide	AcCH_2Cl , K_2CO_3 , DMF, 40 °C, 1 h, 65%	2000BMC393

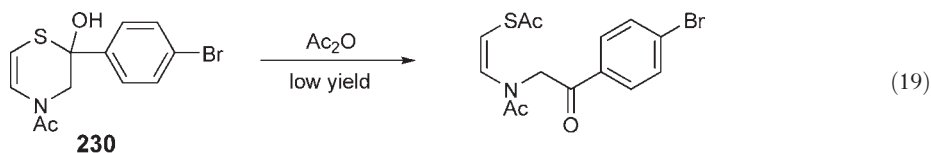
^a $\text{R} = \text{Me}$, 3-fluorophenyl, or CH_2Cl .^bSolid-bound benzothiazines.**Scheme 24**

8.09.6.3 Electrophilic Attack at Sulfur of Dihydrothiazines

The most important reaction of this type is S-oxidation. Some examples were discussed already with the Pummerer reaction (Scheme 22) <1978CPB722, 1982JHC131>. The oxidation to S-oxide is typically carried out with 1 equiv of MCPBA in dichloromethane at between -78 and 0°C <1973T3023, 1985JOC413, 1998J(P1)1569> but hydrogen peroxide <1998J(P1)1569>, bromine <1994ACS517>, and sodium periodate <1973JA3439> have also been used successfully. The reactions usually proceed smoothly and in good yields, but in one case MCPBA gave thiazin-2-one as the main product and the S-oxide only as a minor product <1988JME1575>.

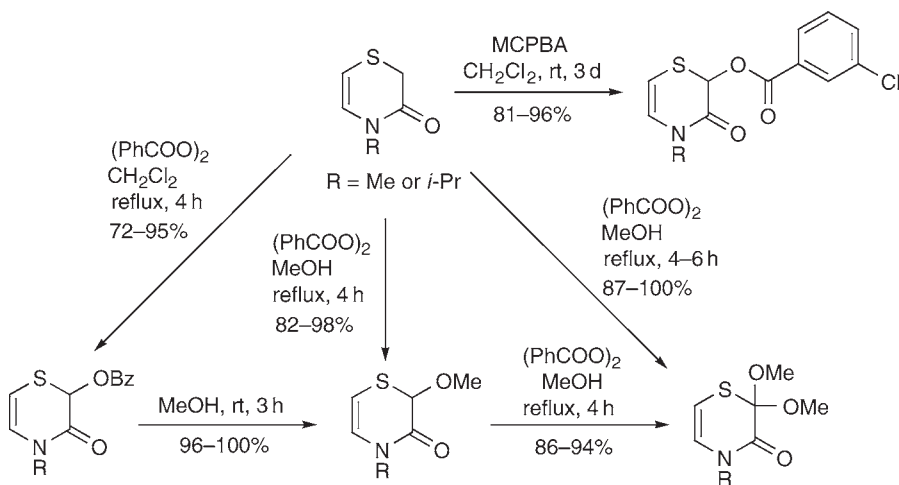
To obtain S,S-dioxides, an excess of MCPBA can simply be used <2000BMC393>. Other reagents include hydrogen peroxide followed by manganese dioxide <1959JA3756> and potassium hydrogen persulfate <1994ACS517>.

Acetic anhydride was reported to react as an electrophile at the sulfur atom of **230** promoting ring opening (Equation 19) <1969TL3063>.



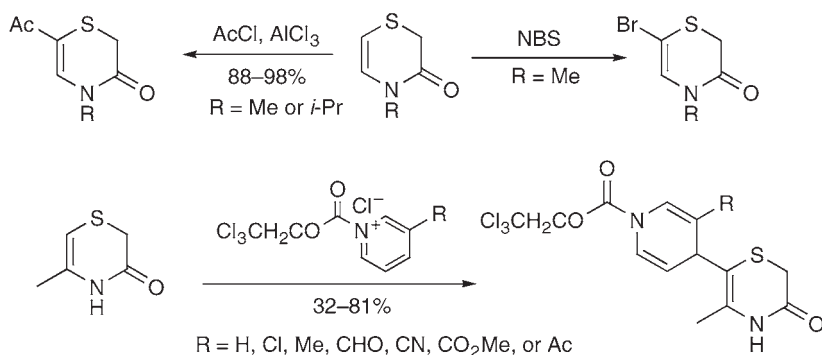
8.09.6.4 Electrophilic Attack at Carbon of Dihydrothiazines

In acidic solution, dihydrothiazin-3-ones are in equilibrium with their enol form and susceptible to electrophilic attack at the 2-carbon. They can be oxidized at this site with peracids or diacyl peroxides (Scheme 25) <1982S312, 1982S424>.



Scheme 25 Oxidation at the 2-carbon.

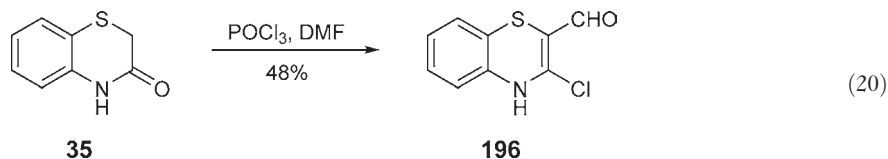
Other electrophiles react at the enamine-type 6-carbon (Scheme 26) <1982S312, 1987CPB2243>.



Scheme 26 Electrophilic attack at the 6-carbon.

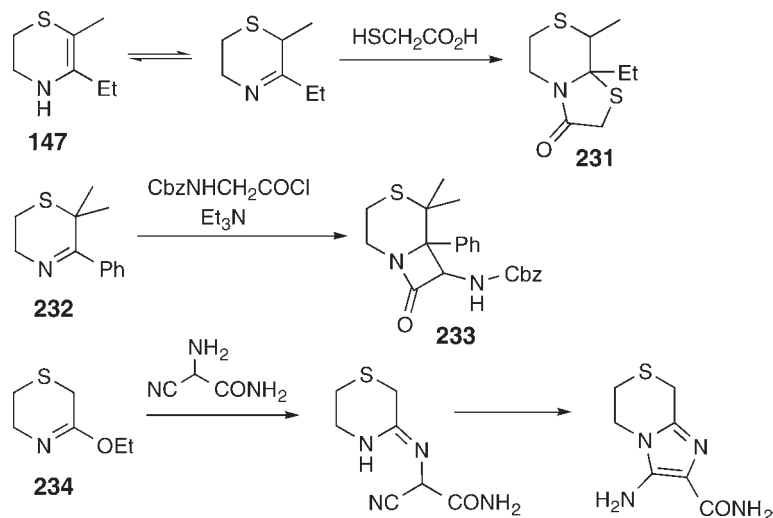
Dihydrobenzothiazin-3-ones have been fluorinated at the 2-position using $\text{HF} \cdot \text{Et}_3\text{N}$ in acetonitrile with electrochemical oxidation <1992TL7017>. Chlorination at this carbon has been achieved using thionyl chloride <1990JME1898, 2004BML1477> and *N*-chlorosuccinimide <1998J(P1)1569> as Cl^+ -sources.

Wadsworth–Emmons reaction of the phosphonate anion of a benzothiazine (compound **239**, synthesis shown in Equation (23)) has been reported <2004BML1477>. Compound **35** was formylated in a Vilsmeier reaction (Equation 20) <1972CPB1325>.



8.09.6.5 Nucleophilic Attack at Carbon of Dihydrothiazines

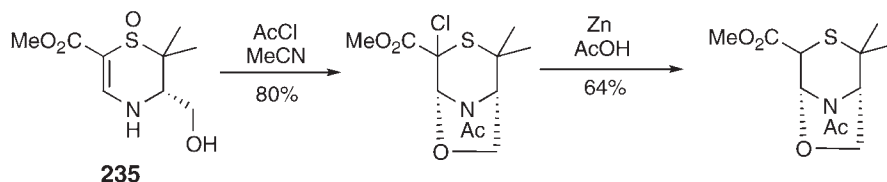
Analogously to 2*H*-thiazines, the dihydro derivatives have an imide bond and a carbon reactive toward nucleophiles. The reaction of **147** to give **165** was shown in [Scheme 6](#) ([Section 8.09.4.3](#)). Similar reactions where nucleophilic addition to 3-carbon is followed by electrophilic attack of the side chain to the nitrogen atom have been reported for other α -mercaptoketones [<1964M1335>](#), mercaptoacetic acid (which was reacted with **147** to give **231** [<1964M1391>](#)), and 2-benzoyloxycarbonylamidoacetyl chloride (which forms a β -lactone structure **233** with thiazine **232**) [<1975J\(P1\)1880>](#) ([Scheme 27](#)). A nucleophilic ‘substitution’ followed by electrophilic attack at nitrogen is involved in the reaction of **234** [<1968CHE322>](#), which is also shown in [Scheme 27](#).



Scheme 27

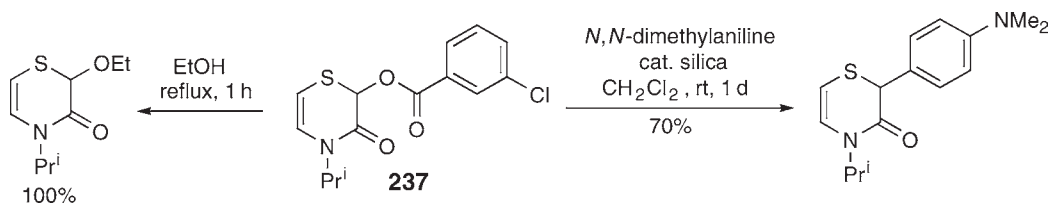
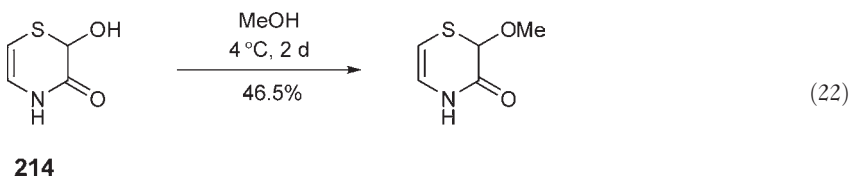
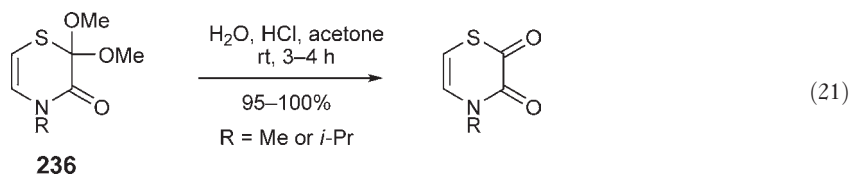
The nucleophilic attack of an existing N-substituent at carbon of a dihydrothiazine is shown in [Scheme 50](#) ([Section 8.09.8](#)).

The 3,4-double bond thus has been the only electrophilic site of dihydrothiazines, and all other reactions are either nucleophilic substitutions, carbonyl additions, or conjugate additions caused by good leaving groups or electron-withdrawing substituents in the ring. In contrast, dihydrothiazine 1-oxide **235** undergoes Pummerer rearrangement assisted by the hydroxy-containing side chain [<1972CC959>](#). The product is then dehalogenated using dissolving metal reduction ([Scheme 28](#)).

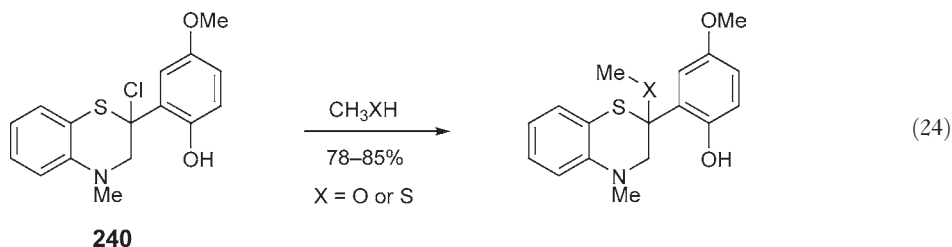
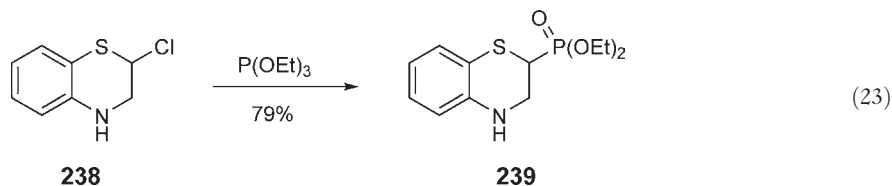


Scheme 28

Examples of nucleophilic attack at the saturated 2-carbon of dihydro-1,4-thiazines, which may be assisted by the neighboring sulfur atom, are shown below. The nucleophiles include water, which was used in the acid-catalyzed hydrolysis of the ketal in **236** ([Equation 21](#)) [<1982S424>](#), methanol in the conversion of **214** into a monothioacetal ([Equation 22](#)) [<1982JHC131>](#), ethanol and dimethylaniline, which both reacted with **237** ([Scheme 29](#)) [<1982TL4963>](#), and triethyl phosphite that was used to convert **238** into the phosphonate **239** required for Wadsworth–Emmons reaction ([Equation 23](#)) [<2004BML1477>](#). Compound **240** reacted with both methanol and methanethiol ([Equation 24](#)) [<1990JME1898>](#).

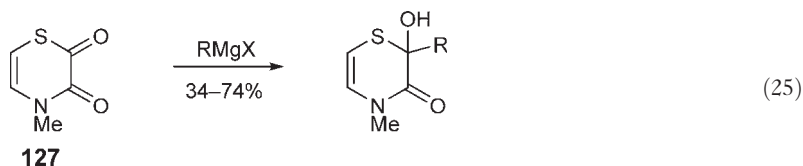


Scheme 29

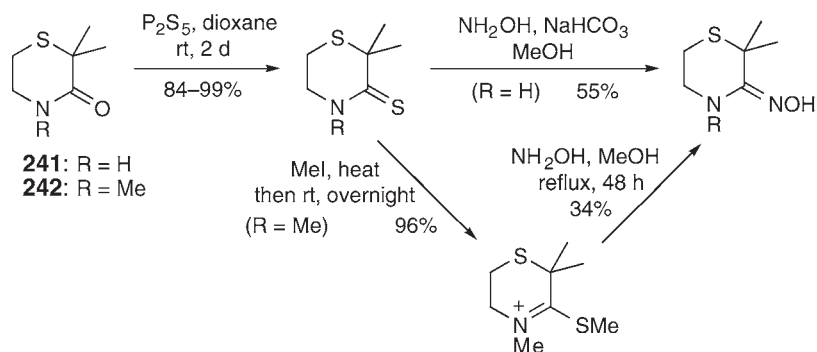


Dihydrothiazinones undergo carbonyl additions or conjugate additions when treated with nucleophiles. It is possible to reduce dihydrobenzothiazin-3-ones of the general structure **35** into the corresponding dihydrobenzothiazines of the structure **32** with boron hydrides: calcium borohydride [<1990JME1898>](#) and borane in tetrahydrofuran (THF) [<2000BMC393, 2003JME3670>](#) have been used.

Some examples of nucleophilic attack at carbonyl groups present in dihydrothiazines are shown here. Grignard reagents prefer the 2-carbonyl to the 3-carbonyl of **127** (Equation 25) [<1988JOC2209>](#).

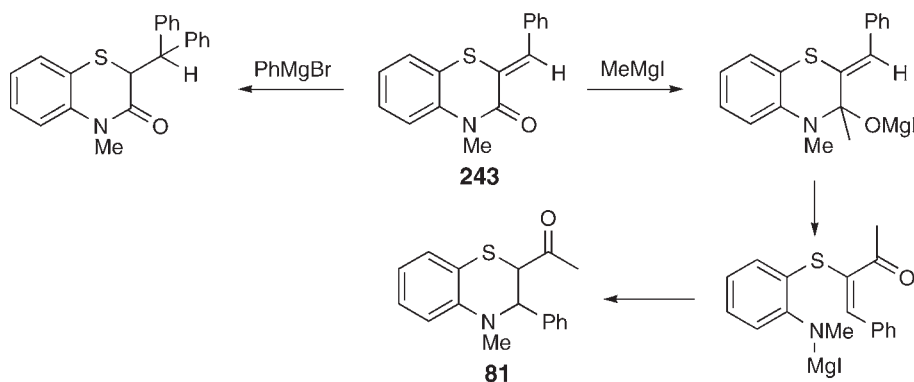


The carbonyl group in **241** and **242** can be converted into thiocarbonyl which in turn is attacked by hydroxylamine to form an imine (Scheme 30) [<1980JOC4198>](#). The reverse reaction, that is, conversion of thiocarbonyl to carbonyl, is possible with trifluoroacetic anhydride in dichloromethane [<1991TL1195>](#).



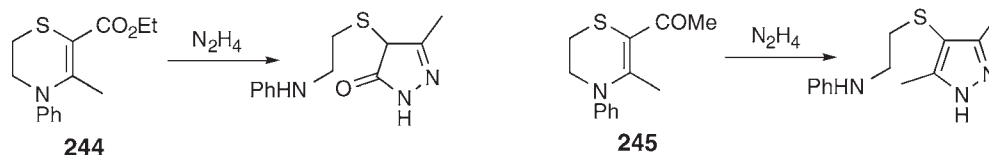
Scheme 30

Methylmagnesium iodide reacts with the 3-carbonyl group of **243** and gives rearranged product **81**. When phenylmagnesium bromide is used instead, conjugate addition occurs (Scheme 31) <1994T5037>.

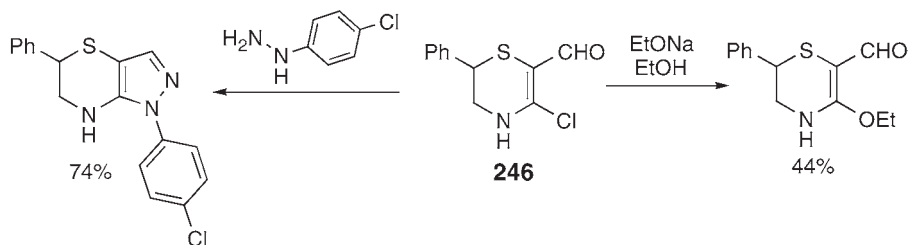


Scheme 31

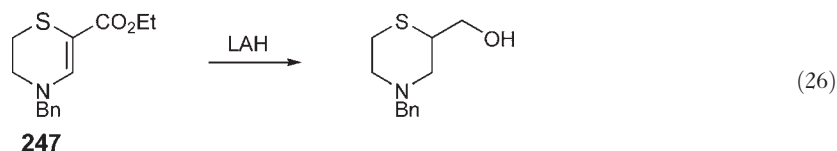
Other conjugate additions have also been reported when **244** and **245** were reacted with hydrazine (Scheme 32) <1962G1367>, **246** with sodium ethoxide or arylhydrazine (Scheme 33) <1972CPB1325>, and **247** with lithium aluminium hydride (LAH) (Equation 26) <1995CPB1137>.



Scheme 32

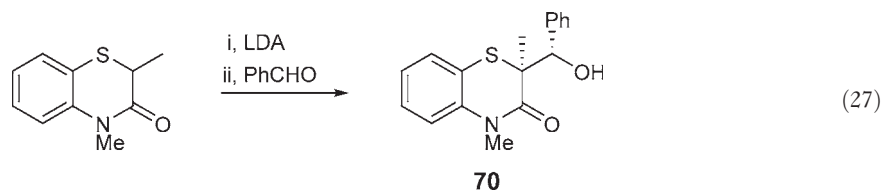


Scheme 33

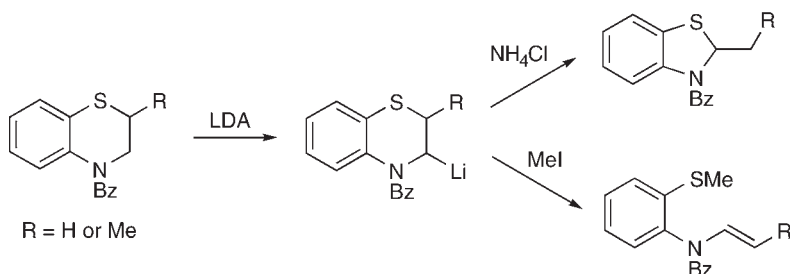


8.09.6.6 Nucleophilic Attack at Hydrogen Attached to Carbon of Dihydrothiazines

Deprotonation of a dihydrothiazine ring, followed by a reaction with an electrophile, is most straightforward in benzothiazin-3-ones (general structure [35](#)), which are deprotonated at the 2-position by lithium diisopropyl amide (LDA). The enolate can then react with a variety of electrophiles including deuterium oxide, methyl iodide, and aldehydes [\[1982T3059\]](#). Compound **70** was prepared in this manner from 2,4-dimethyldihydro-1,4-benzothiazin-3-one (Equation 27) [\[1985T569\]](#).

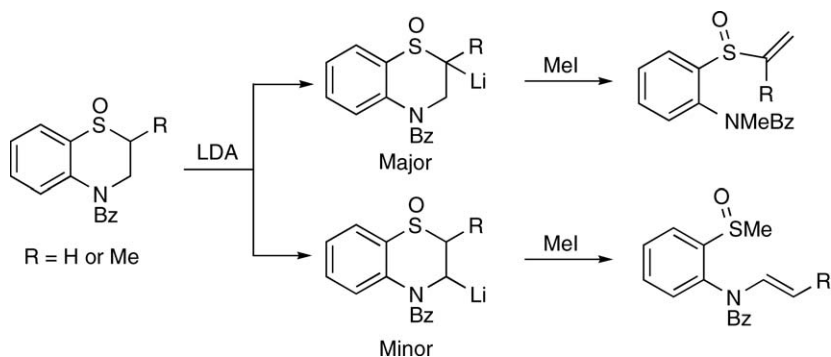


There are, however, examples of deprotonation of dihydrobenzothiazines that do not have carbonyl carbons in the ring. A group of *N*-benzoyldihydrobenzothiazines [\[1983JOC4082\]](#) was deprotonated in the 3-position with LDA and reacted with methyl iodide to give ring-opened products (Scheme 34). Treating the intermediate anion with ammonium chloride gave a benzothiazoline product.



Scheme 34

When *S*-oxide analogues were reacted similarly with LDA, 2-deprotonation competed with 3-deprotonation (Scheme 35) and two products were obtained upon reaction with MeI [\[1984J\(P1\)1949\]](#).

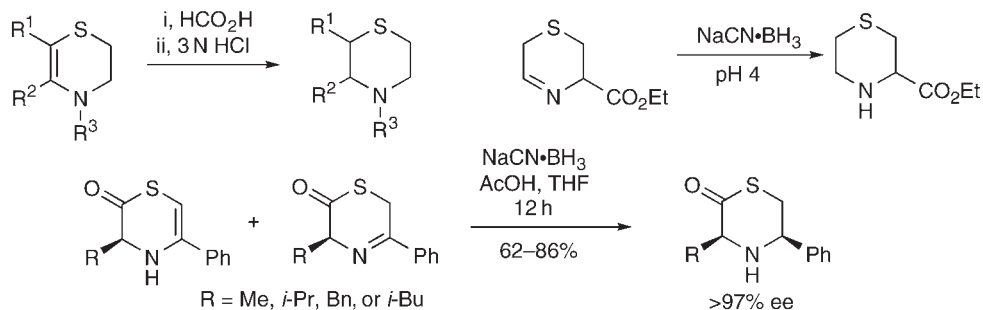


Scheme 35

8.09.6.7 Reduction and Reactions of Dihydrothiazines with Radicals

Reducing agents can cleave the C–S bond in dihydrothiazines when double-bond reduction is attempted. This was observed for sodium and potassium in ammonia <1973RTC879, 1980CC429> and when using sodium cyanoborohydride in methanol <2006SL3259>. The carbon–sulfur bond was cleaved in a 1,4-thiazine-based sulfonium salt using samarium iodide <1997J(P1)309>.

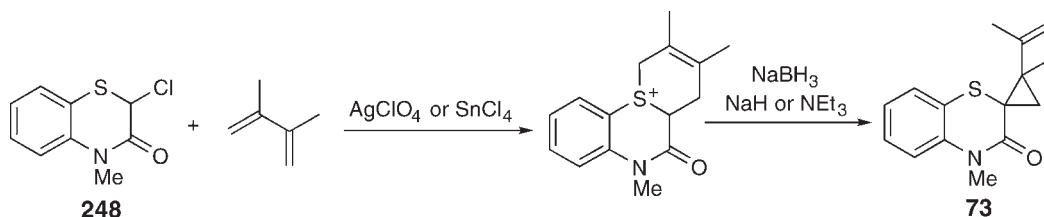
Successful double-bond reductions are shown in **Scheme 36**. Formic acid can be used <1970LA(739)32>, although N-formylation may occur <1970M1295>. With the right conditions, sodium cyanoborohydride is also a suitable reagent for dihydrothiazines <1994ACS517> and dihydrothiazin-2-ones <2006SL3259>.



Scheme 36

8.09.6.8 Cycloadditions of Dihydrothiazines

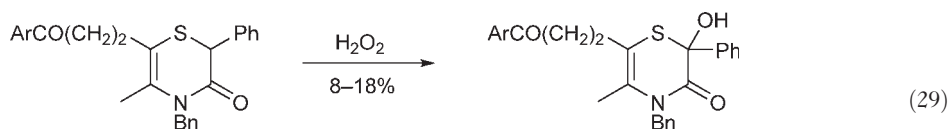
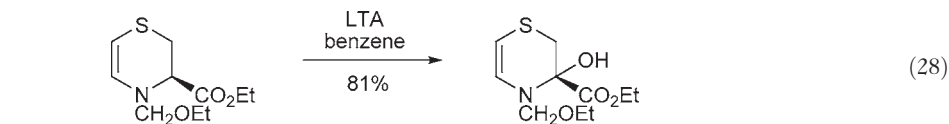
The [4+2] cycloadditions of the sulfonium salt, derived by loss of Cl[−] from 2-chlorodihydrobenzothiazine **248** with a diene, followed by a rearrangement give product **73** (**Scheme 37**) <1997J(P1)309, 1998J(P1)1569>.



Scheme 37

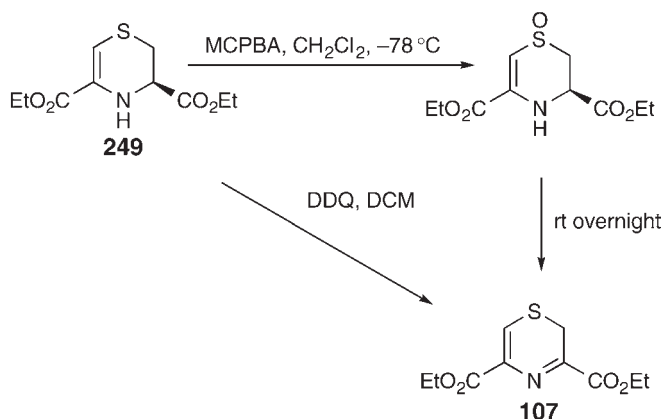
8.09.6.9 Oxidation (Dehydrogenation) of Dihydrothiazines

Introduction of a hydroxy group into a dihydrothiazine has been achieved using lead tetraacetate (**Equation 28**) <1972CPB892> and hydrogen peroxide (**Equation 29**) <1976CC366>. The latter example may proceed as a Pummerer reaction, and one starting material underwent ring contraction under the reaction conditions.



Ar = Ph, *p*-chlorophenyl, or *m*-chlorophenyl

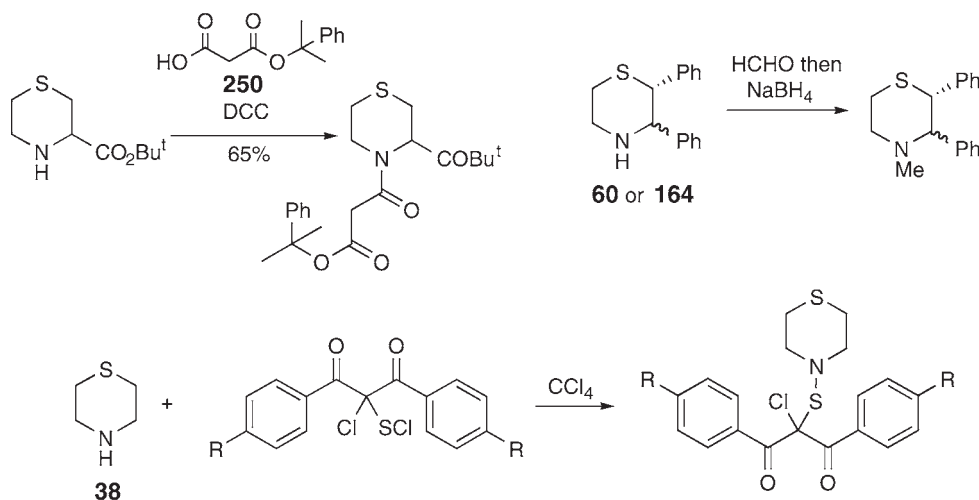
Dehydration of dihydrothiazines is possible using either Pummerer reaction or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and compound **107** was prepared by both routes from **249** (Scheme 38) <1985JOC413>.



Scheme 38

8.09.6.10 Electrophilic Attack at Nitrogen of Tetrahydrothiazines

Thiomorpholines are comparable to other secondary amines in nucleophilicity and ease of N-alkylation or acylation with alkyl or acyl halides. Alkylation of lactams with the general structure **42** is also straightforward, although the reaction needs a strong base such as sodium hydride <1989JPS937>. Other examples include amide formation using dicyclohexylcarbodiimide (DCC) and free acid **250** <1973J(P1)1321>, methylation of **164** and **60** using formaldehyde followed by LAH reduction <1992JOC4215>, and formation of sulfenamides using **38** in excess as both a nucleophile and a base <1996M895> (Scheme 39).



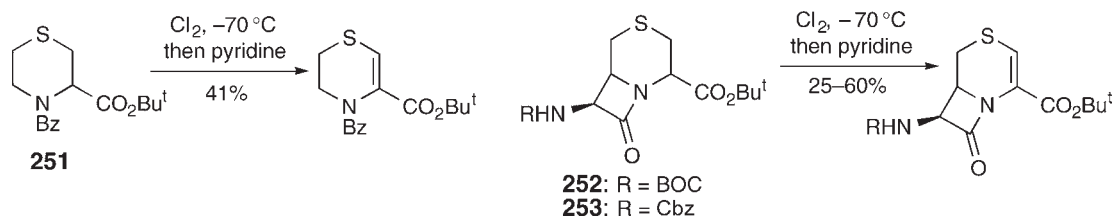
Scheme 39 Electrophilic attack at nitrogen of thiomorpholines.

8.09.6.11 Electrophilic Attack at Sulfur of Tetrahydrothiazines

One example of S-oxidation was shown already when discussing Pummerer reaction (Scheme 22, 137→138) <1977CJC937>. Sodium periodate has been the reagent of choice in forming S-oxides <1980JHC449, 1981CPB1554>, and a tetrahydrothiazine S,S-dioxide was obtained from the corresponding S-oxide using MCPBA <1980JHC449>.

8.09.6.12 Electrophilic Attack at Carbon of Tetrahydrothiazines

Compound **246** was prepared by a Vilsmeier reaction analogous to that shown in [Scheme 16](#) for the synthesis of **196** [<1972CPB1325>](#). The halogenation and subsequent elimination of HCl from **251–253** is made possible by the ester substituent at the 3-position ([Scheme 40](#)) [<1973J\(P1\)1321>](#).



Scheme 40 Halogenation–elimination.

8.09.6.13 Nucleophilic Attack at Carbon of Tetrahydrothiazines

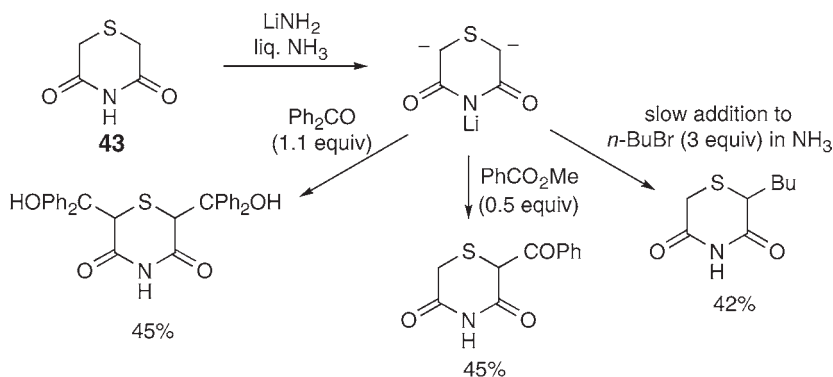
Tetrahydrothiazin-3-ones are lactams that have been reduced to tetrahydrothiazines with borane [<1980JHC449>](#), sodium borohydride [<1992JOC4215>](#), or LAH [<1987H\(26\)1503>](#), without cleavage of carbon–sulfur bond. In one case, incomplete reduction occurred with LAH: the intermediate lactol was dehydrated to give a dihydrothiazine as main product [<1989JPS937>](#).

A nucleophilic substitution of a 2-hydroxy group with 6-chloropurine via a Mitsunobu reaction has also been reported [<1977CJC937>](#).

8.09.6.14 Nucleophilic Attack at Hydrogen Attached to Carbon of Tetrahydrothiazines

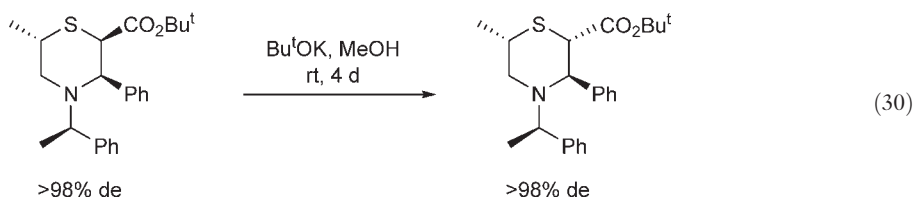
Elimination of HCl from a chlorinated tetrahydrothiazine was shown in [Scheme 40](#) [<1973J\(P1\)1321>](#).

Deprotonation of **43** with lithium amide gives a dianion that can be reacted with electrophiles ([Scheme 41](#)) [<1970JOC3600>](#).



Scheme 41

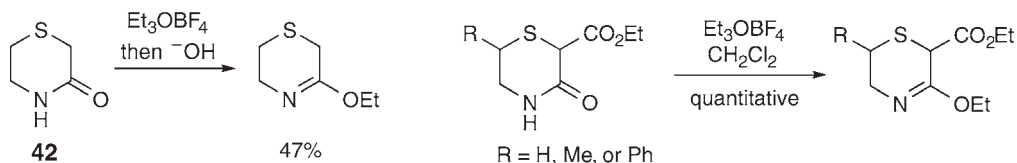
Tetrahydrothiazines containing ester side chains are susceptible to racemization under basic conditions or, as shown in [Equation \(30\)](#), equilibration to the most stable diastereomer [<2006TA1135>](#).



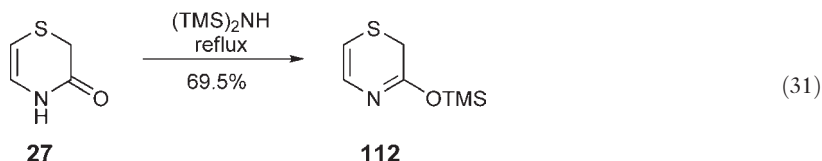
8.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

8.09.7.1 Reactions Involving Carbonyl, Thiocarbonyl, or Methylene at the 3-Position

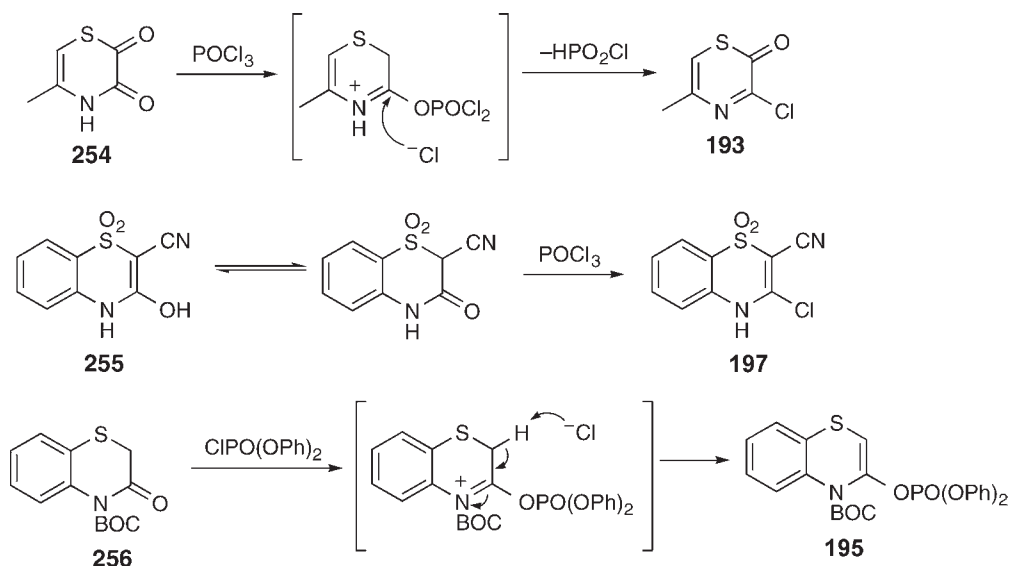
Conjugation to the free electron pair of the thiazine nitrogen makes these 3-substituents nucleophilic. The first example is reaction of **42** <1968CHE322> and its 2-ethoxycarbonyl derivatives <1983JME559> with triethyl-oxonium tetrafluoroborate (Scheme 42). Another is the reaction of **27** with hexamethyldisiloxane to give **112** (Equation 31) <1988JME1575>.



Scheme 42

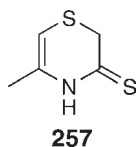


The reaction with phosphoric acid derivatives proceeds through the same mechanism, as can be seen in Scheme 43 for the examples of **254** which reacts with POCl_3 to give **193** <1992CPB1025>, **255** which gives **197** with the same reagent <2005BMC141>, and **256** which gives **195** <1999TL6373>.

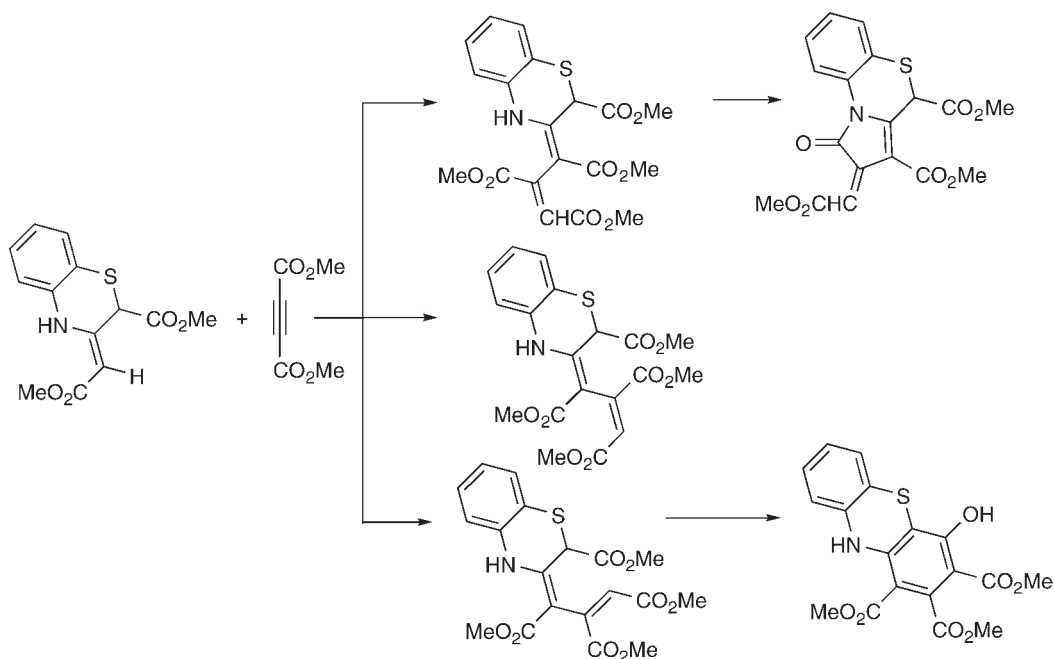


Scheme 43

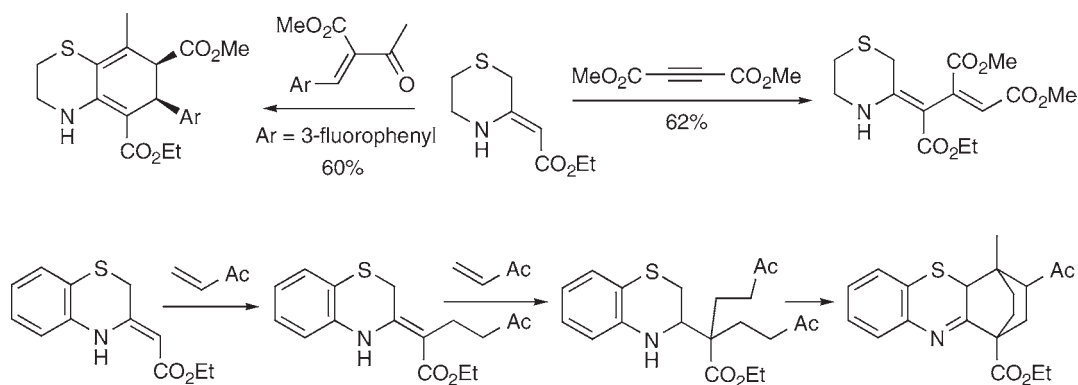
Sulfur at this position behaves similarly to oxygen; alkylation of dihydrothiazine-3-thione **257** <1969JHC247> was reviewed already in CHEC(1984) and another example of S-methylation was shown earlier in **Scheme 30** <1980JOC4198>.



Two examples of exocyclic alkenes at the 3-position acting as carbon nucleophiles have also been published. The reactions are shown in **Schemes 44** <1987J(P1)1027> and **45** <1999T7915>.



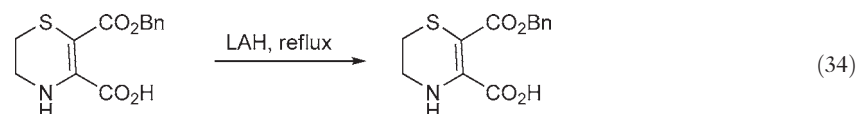
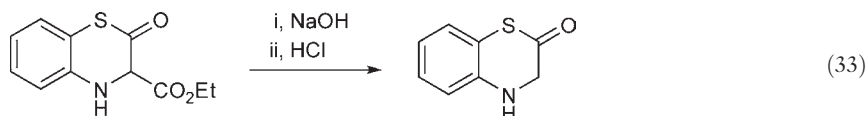
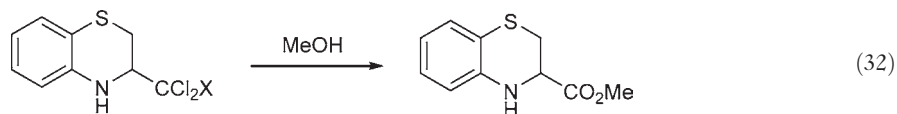
Scheme 44



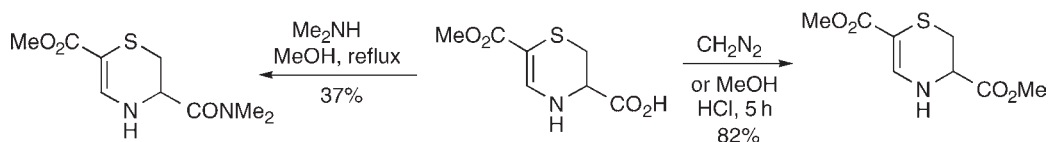
Scheme 45

8.09.7.2 Reactions Involving Carboxylic Acid Substituents

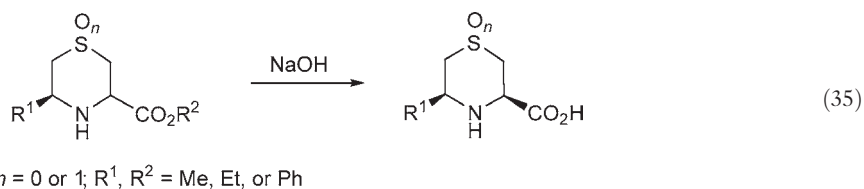
A methyl ester was formed by methanolysis of a trihalide (Equation 32) <2007S225>. Decarboxylation of the β -ketoacid resulting from hydrolysis has also been reported (Equation 33) <1980LA1917>. A carboxylic acid substituent was reduced to aldehyde with LAH (Equation 34) <1974J(P1)2092>. Thiazine nitrogen probably participates in this reaction.



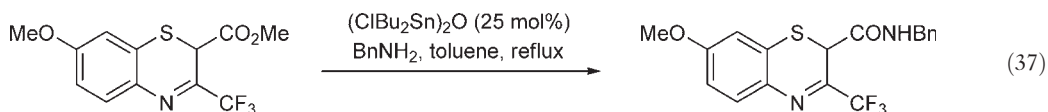
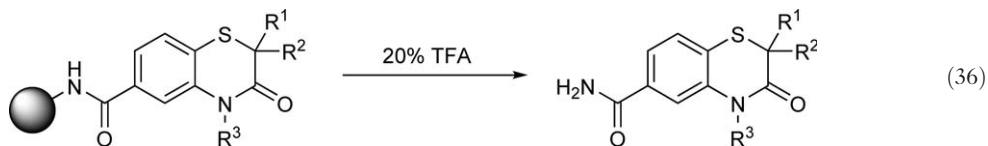
Esterification and amide formation were performed using standard methods (Scheme 46) <1968T2985>. Ester substituents can be hydrolyzed with aqueous sodium hydroxide in tetrahydrothiazines that are stable toward hydrolysis (Equation 35) <1981CPB1554>.

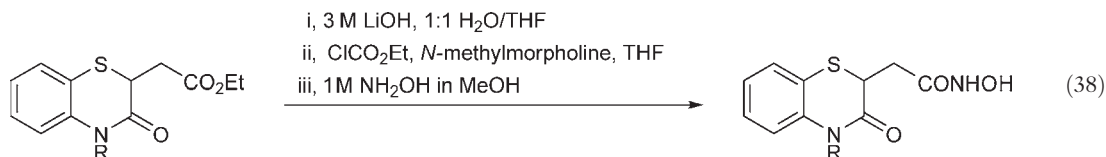


Scheme 46

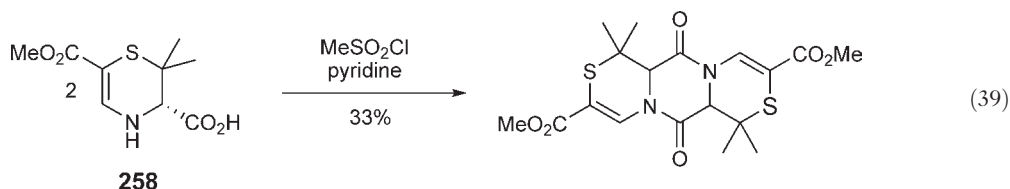


An amide linkage to a solid resin was also hydrolyzed with 20% trifluoroacetic acid (TFA) (Equation 36) <2001TL1167>, and 95% TFA has also been used <2005TL7443>. Two esters were converted to amides using two very different methods, one of which proceeded through direct reaction of benzylamine with the ester (Equation 37) <2001JOC1026> and the other through hydrolysis of the ester and converting the acid into a mixed anhydride that is easily attacked by hydroxylamine (Equation 38) <2004BML1477>.



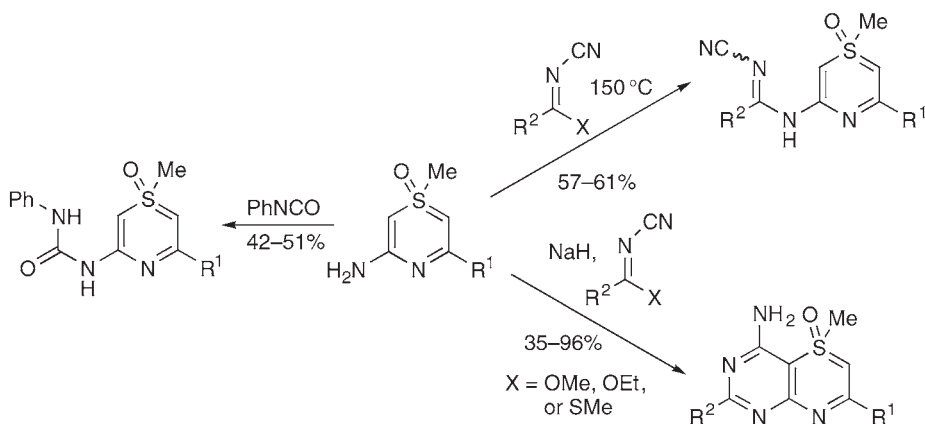


Methanesulfonyl chloride catalyzes the dimerization of 3-carboxythiazine **258** (Equation 39) <1979CHE983>.



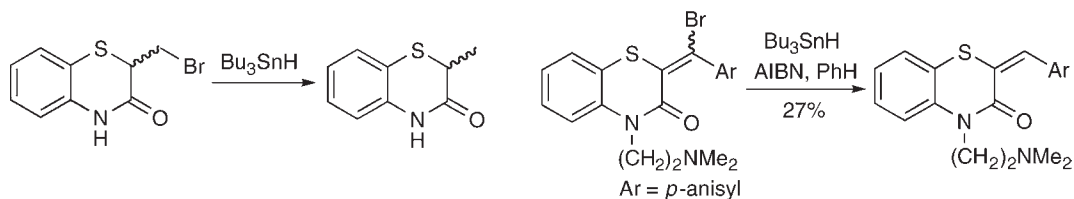
8.09.7.3 Other Reactions

The amino substituents in compounds **114**, **185**, and several other derivatives react with electrophilic phenyl isocyanate <1986LA1648> and cyanoimides <1987LA551>. If a base is used with the latter electrophile, bicyclic compounds are obtained (Scheme 47).

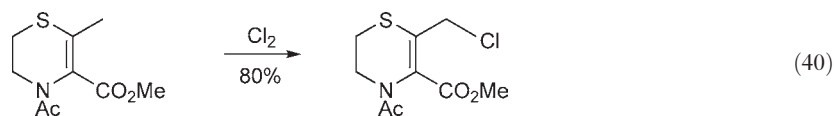


Scheme 47

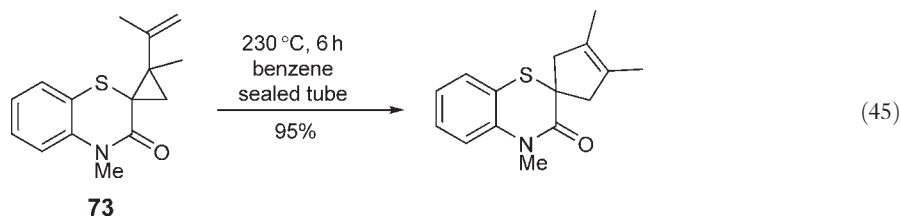
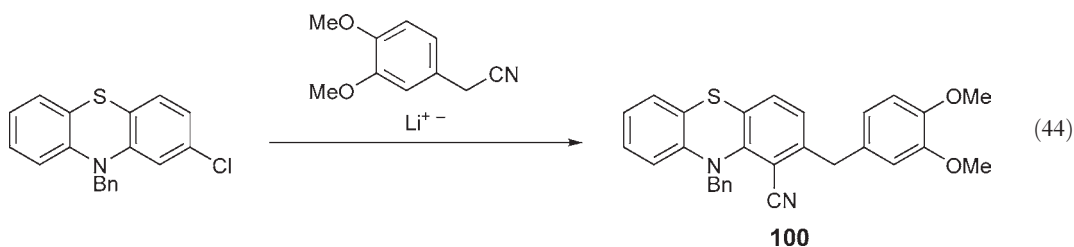
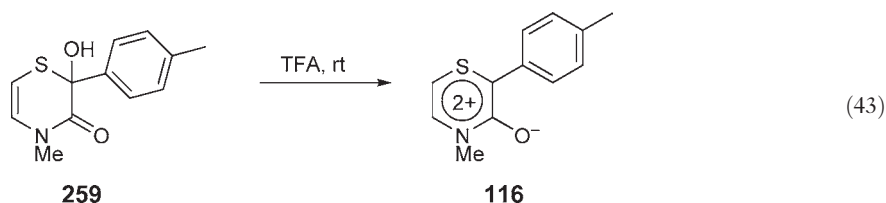
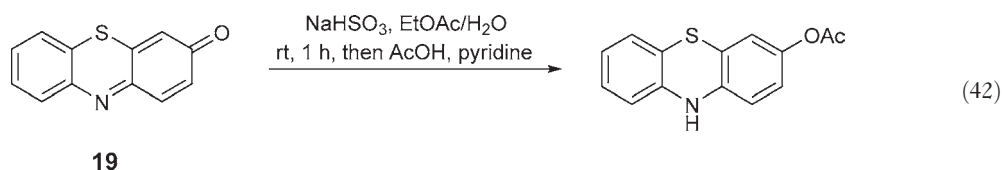
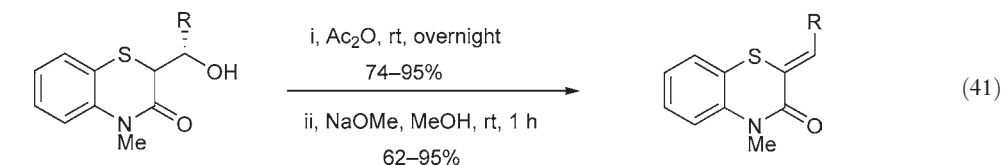
Halogenation (Scheme 48) <1993JHC1105> and dehalogenation (Equation 40) <1992LA403> of alkyl and alkenyl side chains have also been reported.



Scheme 48



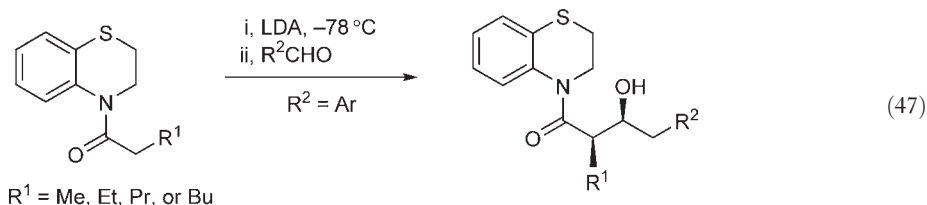
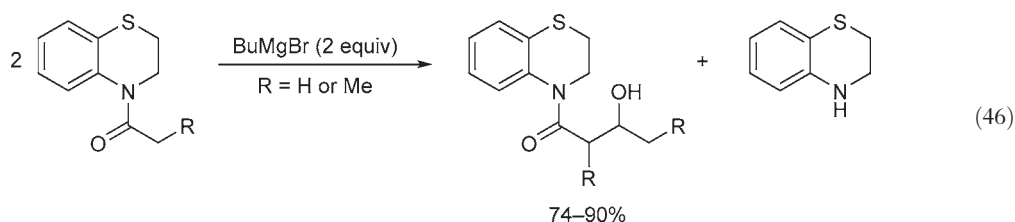
A variety of other reactions have been collected below. The side chain of aldols from the reaction of dihydrobenzothiazin-3-one enolate with aldehydes can be dehydrated (Equation 41) <1982T3059>. Quinone **19** was reduced with sodium hydrogen sulfite (Equation 42) <1987JOC4000>. Strong acid makes **259** lose OH^- to give cation **116** (Equation 43) <1988JOC2209>. Compound **100** was an unexpected product from a nucleophilic attack at a chlorophenothiazine (Equation 44) <1991AXC2465>. The side chain in **73** rearranges thermally into the more stable five-membered ring (Equation 45) <1997J(P1)309>.



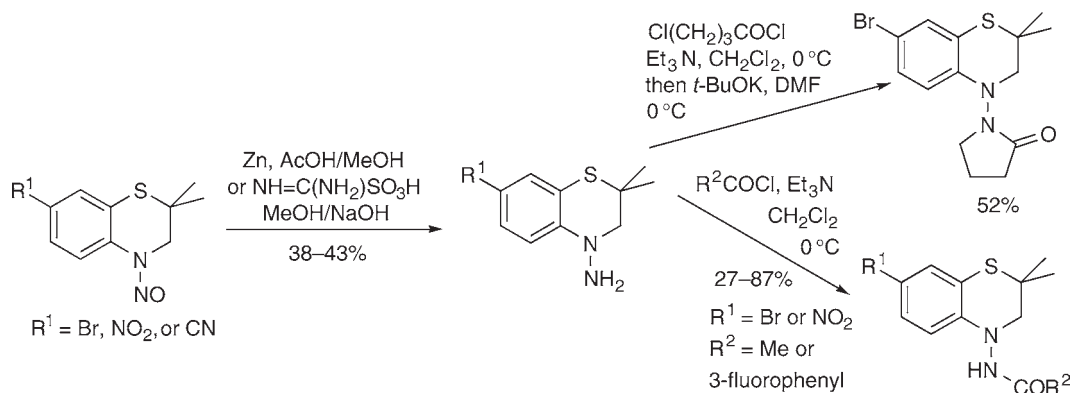
8.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

The thermal S-dealkylation of benzothiazine ylides was shown in Scheme 11 and the dealkylation of a sulfonium salt in Scheme 37. All other reported reactions involve N-substituents.

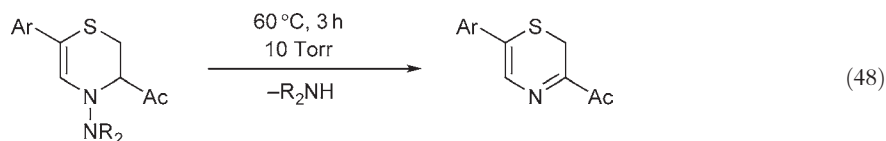
Deprotonation of the N-acyl substituent of benzothiazines gives a nucleophile that reacts by deacylation with a second molecule of starting material (Equation 46) <1980TL3001>. Such anions also react with ketones in an *erythro*-selective aldol condensation (Equation 47) <1983TL3883>. The selectivity is due to the formation of a *Z*-enolate and the reaction was also extended to N-acylphenothiazines.



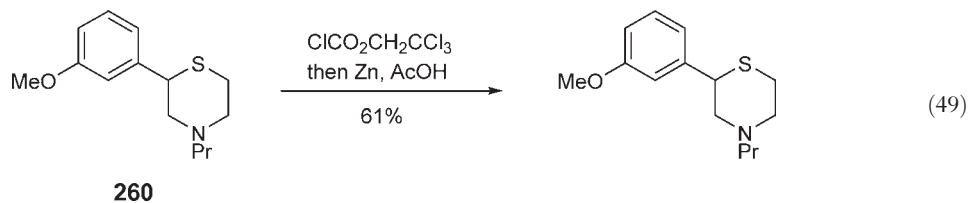
Modification of an *N*-nitroso substituent is shown in [Scheme 49](#) <2003JME3670> and removal of an *N*-amino group in [Equation \(48\)](#) <1991S543>.

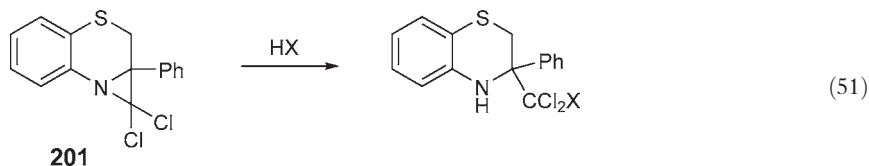
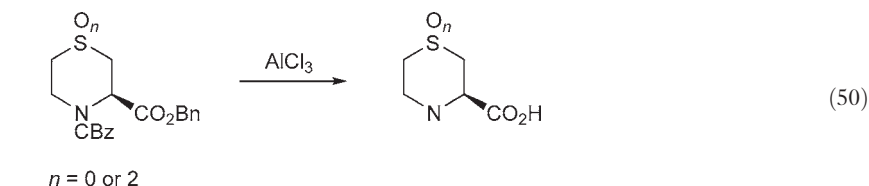


Scheme 49

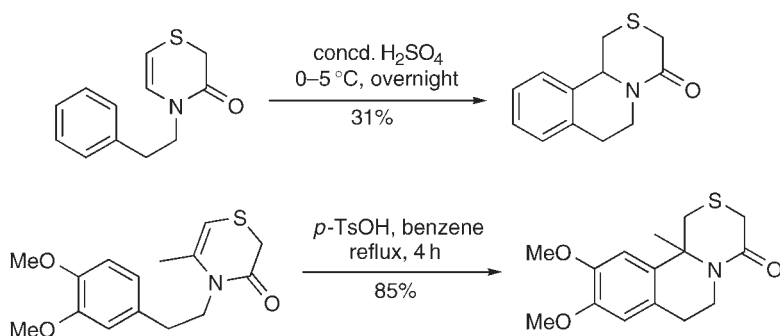


Three N–C bond-cleavage processes are shown here. Dealkylation of **260** was carried out in two steps ([Equation 49](#)) <1987H(26)1503>, and the benzoxycarbonyl protective group was removed with a Lewis acid ([Equation 50](#)) <1994ACS517>. The aziridine ring of **201** was cleaved with acid ([Equation 51](#)) <2007S225>.





A nucleophilic attack of an N-tethered phenethyl substituent is shown in [Scheme 50](#). The protonated thiazine ring brings about an intramolecular electrophilic aromatic substitution on the aryl substituent, whether this is a phenyl [<1992CHE832>](#) or a veratryl ring [<1980JHC449>](#).



Scheme 50

8.09.9 Ring Synthesis

8.09.9.1 One-Bond Formation

8.09.9.1.1 Adjacent to sulfur

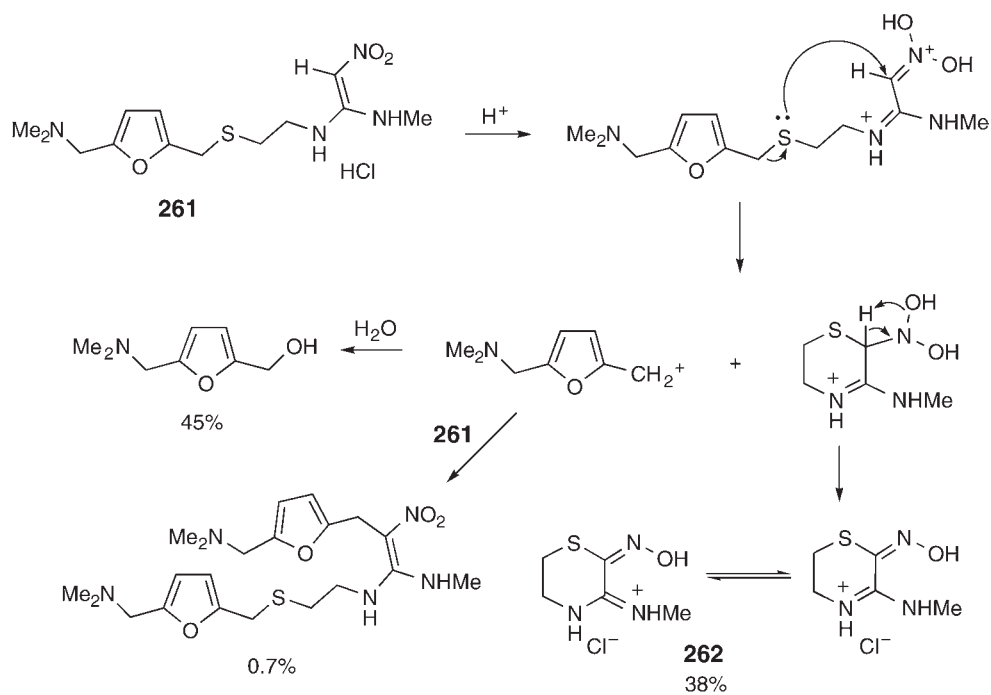
Sulfur atom can act as a nucleophile or an electrophile in ring closure. Nucleophilic behavior can be seen in the hydrolysis of the H-2 receptor antagonist ranitidine **261**, which gives thiazine **262** as the main product ([Scheme 51](#)) [<1987J\(P1\)951>](#).

Ring syntheses may involve nucleophilic attack of sulfur at a carbonyl group ([Equation 52](#)) [<1978CPB722>](#) or at a carbene followed by migration of the allyl group from positively charged sulfur to the adjacent carbon ([Scheme 52](#)) [<1998T9689>](#).

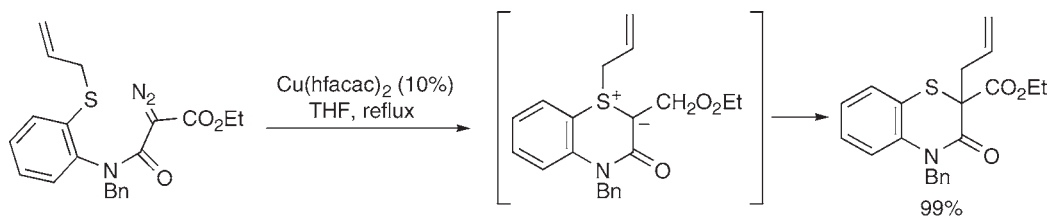
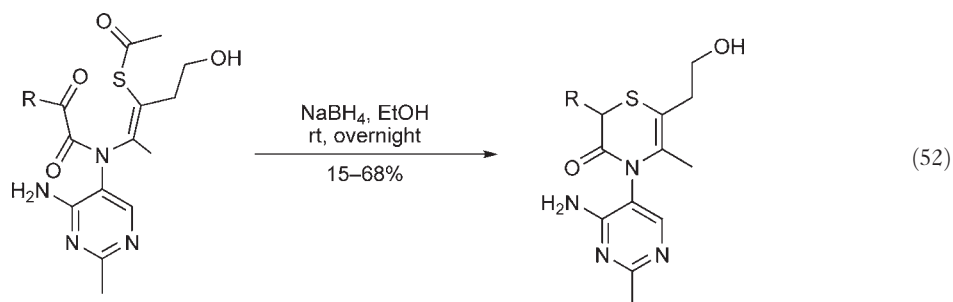
Intramolecular addition of SH across a triple bond has been achieved by irradiation ([Scheme 53](#)) [<1980BSF361>](#), or by heating a suitable precursor in the presence of a base ([Equation 53](#)) [<2001JOC4563>](#).

The disulfide sulfur of **263** acts as an electrophile with the enolate anion resulting in ring closure ([Equation 54](#)) [<1980LA1917>](#). DMSO oxidizes the sulfur of **264** which then reacts with the enamine double bond ([Equation 55](#)) [<2001JFC\(108\)51>](#).

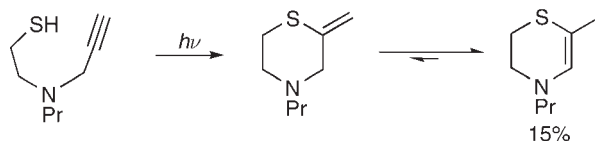
Benzothiazine ylides can be prepared by reaction of a sulfoxide with trifluoroacetic anhydride followed by an intramolecular nucleophilic attack of enamine and elimination of OAc from the sulfur ([Equation 56](#)) [<1982J\(P1\)831, 1991J\(P1\)2249>](#). An interesting variation is the replacement of the enamine with an aniline ([Equation 57](#)) [<1997JCM416>](#).



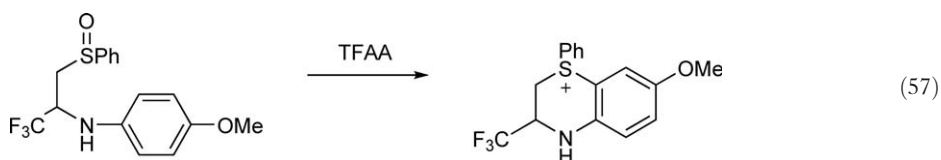
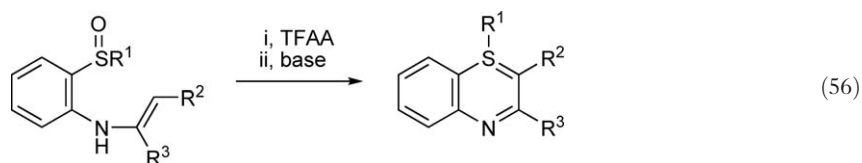
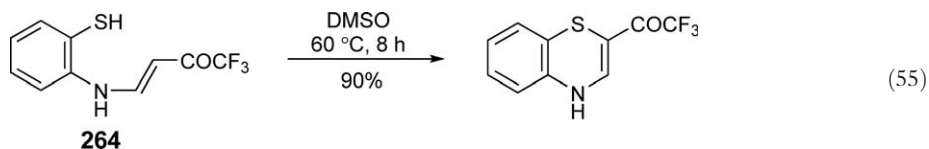
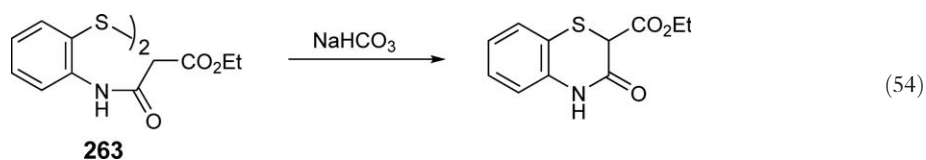
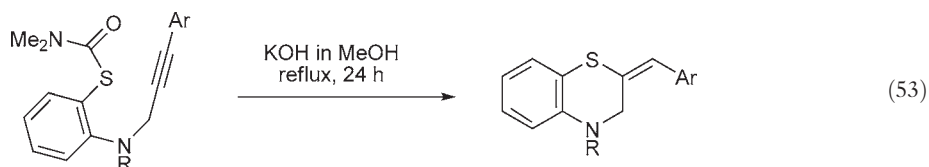
Scheme 51 Hydrolysis of ranitidine.



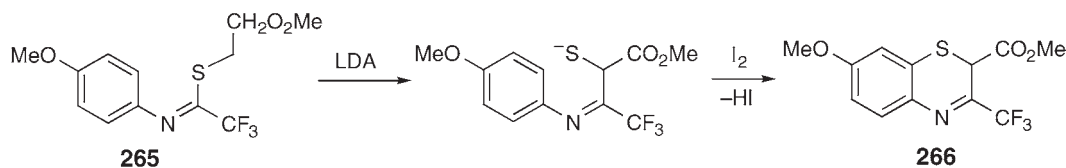
Scheme 52



Scheme 53



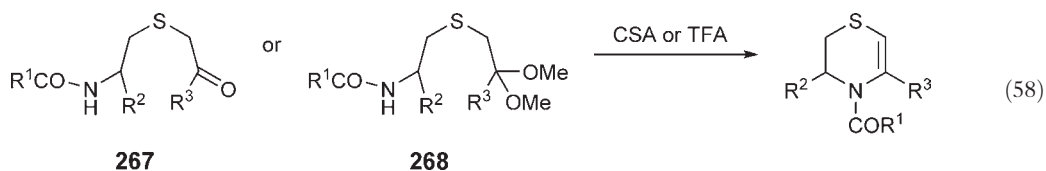
Cyclization of **265** to give **266** involves an initial rearrangement followed by S-iodination and electrophilic aromatic substitution ([Scheme 54](#) <2001JOC1026>).



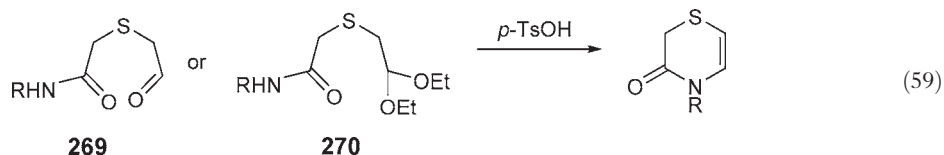
Scheme 54

8.09.9.1.2 Adjacent to nitrogen

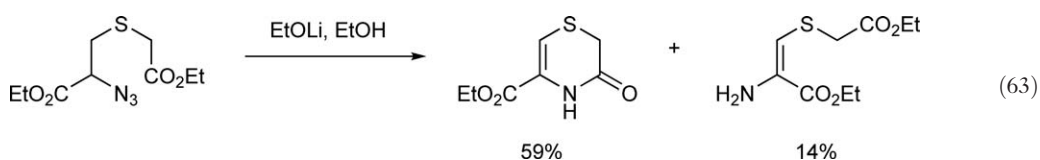
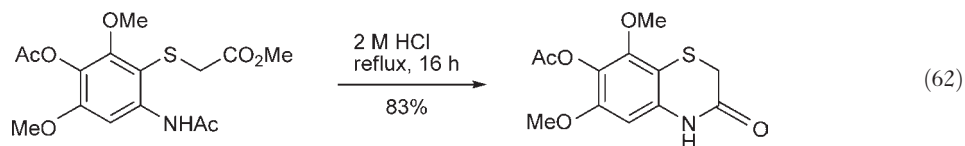
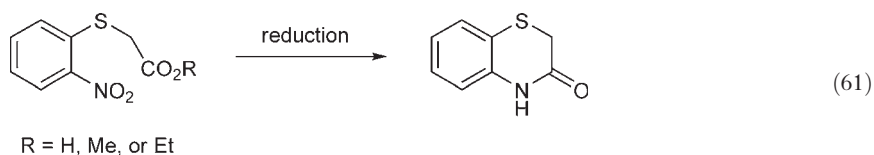
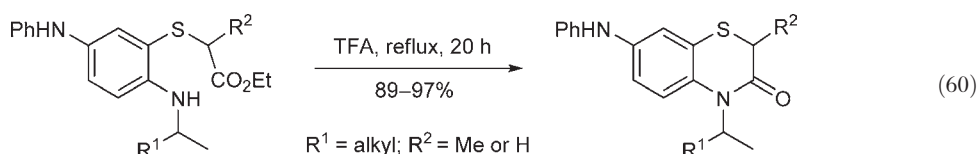
Most ring formations reported have been based on the nucleophilic nitrogen atom. A very common method of cyclization has been enamine formation from compounds with a general structure **267** <1992CB1507, 1998JFA2278, 2006SL3259> or **268** <2002SC1579> using an acid catalyst to give *N*-acyldihydrothiazines ([Equation 58](#)).



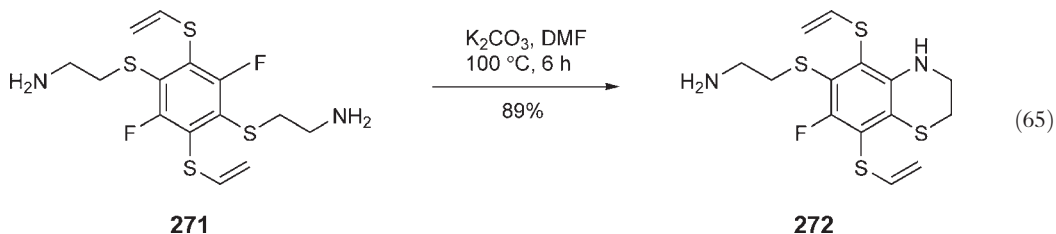
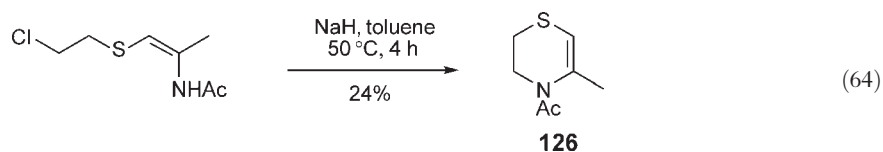
In the same manner, compounds with the general structure **269** <1980JHC449> or **270** <1980CC429, 1982JHC131, 1988JME1575, 1992CHE832> can be cyclized to give dihydrothiazin-3-ones (Equation 59). Reaction of a sulfone can also be carried out this way to give a dihydrothiazin-3-one 1,1-dioxide <1982JHC131>.



Dihydrothiazin-3-ones and especially the benzo derivatives have been formed by cyclization of amino acids (Equation 60) <2001JOC6792>. In several cases, the cyclization to benzothiazines was induced by reducing a nitro acid by electrochemical reaction <1981JPR924>, iron(II) sulfate <2003JME3670> or sodium dithionite <2007H(71)411>, or a nitro ester with iron in hydrochloric acid <2000BMC393> or stannous chloride in hydrochloric acid <1993JOC5855, 2000JOC3738, 2001TL1167> (Equation 61). Alternatively, the nucleophilic amino group can be formed by hydrolysis of an acetamide (Equation 62) <1993JOC5855> or an azide (Equation 63) <1982CL527> and will form the lactam spontaneously.



Cyclization using the amino group as nucleophile is versatile; the reaction proceeds by an S_N2 mechanism in the synthesis of **126** (Equation 64) <1973RTC879>, nucleophilic aromatic substitution of **271** gives **272** (Equation 65) <1998CHE625>, and Mitsunobu reaction converts 5-amino-3-thiaalcohols into tetrahydrothiazines (Equation 66) <1994ACS517>.

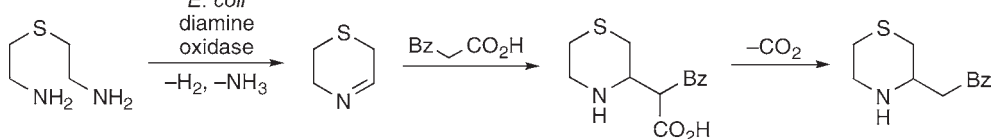




The synthesis of **273** proceeds through a benzyne intermediate (**Scheme 55**) <2005TL7443>. An enzymatic cyclization has also been reported (**Scheme 56**) <1990TL6907>.



Scheme 55

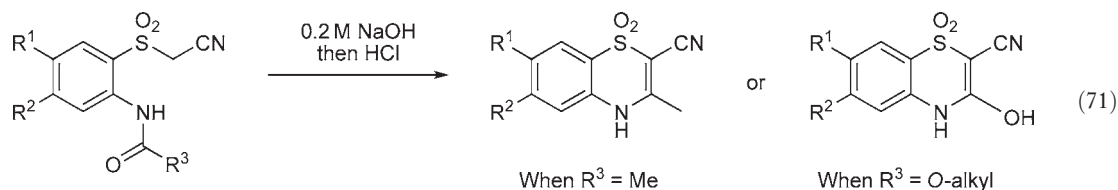


Scheme 56

8.09.9.1.3 Between two carbons

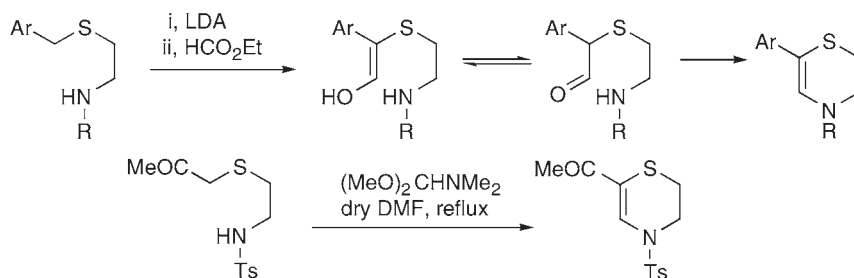
All syntheses in this group follow the same principle: a carbanion is formed adjacent to a sulfur atom and then reacts with an electrophilic carbonyl derivative. Examples are shown in Equations (67) <1984J(P1)1899>, (68) <1985TL1457>, (69) <1986LA1648>, (70) <1987H(26)1503>, and (71) <2005BMC141>.





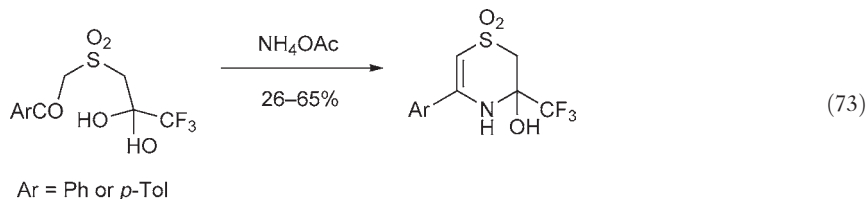
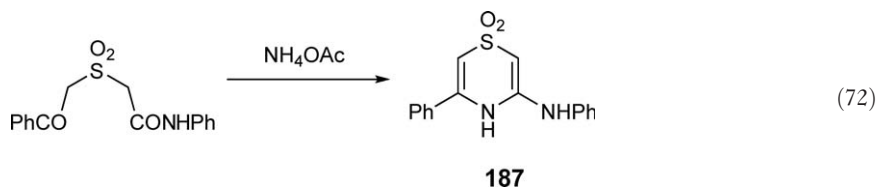
8.09.9.2 Two-Bond Formation from [5+1] Atom Fragments

The last atom to be added to make a thiazine has been carbon in only two cases, in the form of ethyl formate <1989JPS937> and dimethylformamide (DMF) dimethyl acetal <1992CB1507> (Scheme 57).

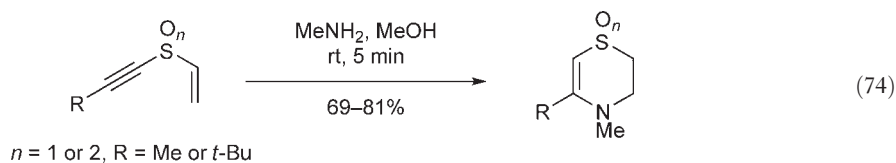


Scheme 57

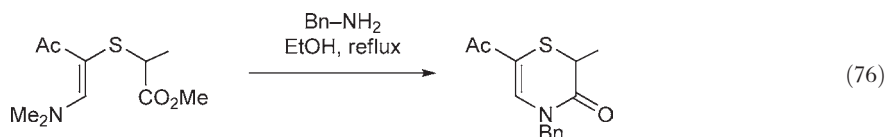
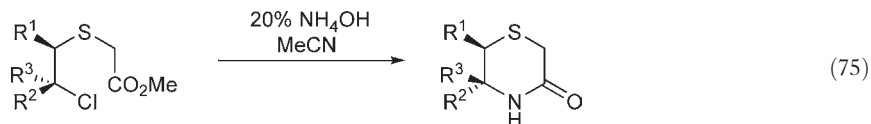
Nucleophilic nitrogen reagents have been used most commonly as the one-atom unit. The reaction of 3-thia-1,5-diketones with amines to form fully conjugated 1,4-thiazines, as well as 1,4-thiazine *S,S*-dioxides, was already reviewed in CHEC(1984). By changing one keto group to an amide, 3-aminothiazines such as **187** are obtained (Equation 72) <1976JPR865>. In one case, a similar reaction resulted in incomplete dehydration to give a dihydrothiazine (Equation 73) <1995JHC207>.



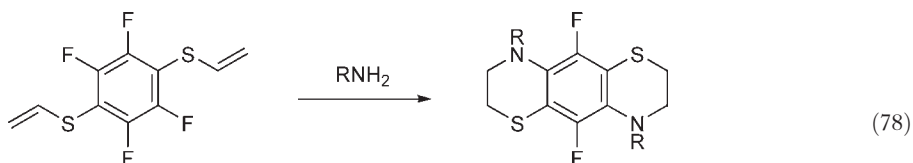
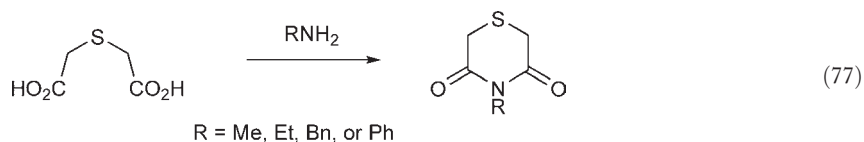
Conjugate addition of methylamine to vinyl alkynyl sulfoxides and sulfones also led to formation of 1,4-thiazine 1-oxides and 1,1-dioxides (Equation 74) <1979S47>.



Insertion of a nitrogen fragment between an ester and a halide (Equation 75) <1992JOC4215> or an enamine (Equation 76) <1992CB1507> has also been reported.

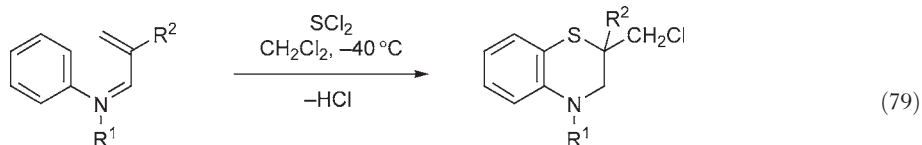


The syntheses of *N*-alkyl derivatives of **43** (Equation 77) <2001KGS1678>, as well as compounds **274** <1996CHE1023> and **275** <1996RCB414> (Equation 78), using suitable amines have been reported.

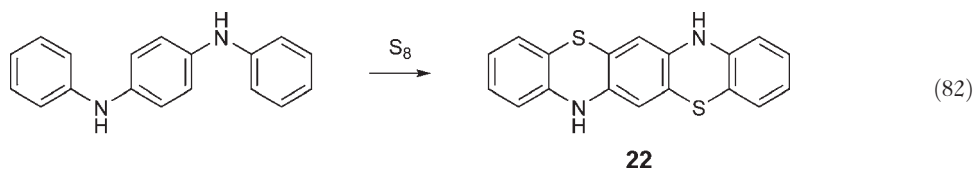
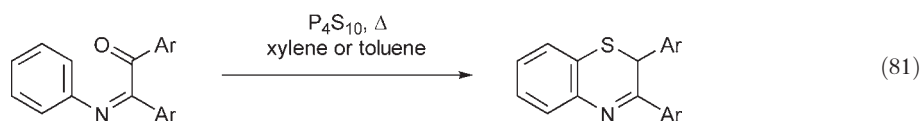
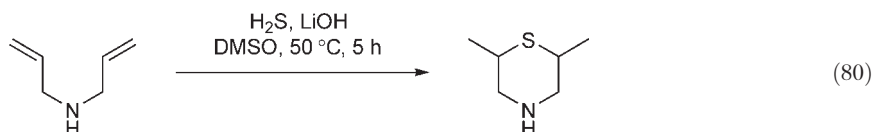


274: R = (CH₂)₂OH
275: R = allyl

There are also methods where sulfur is used as the one-atom unit. Reagents include sulfur dichloride (Equation 79) <1983TL3203>, hydrogen sulfide (Equation 80) <1995RJC300>, and phosphorus pentasulfide (Equation 81) <2001T4195>. Elemental sulfur was used in the synthesis of **22** (Equation 82) <1985AXC1062>.



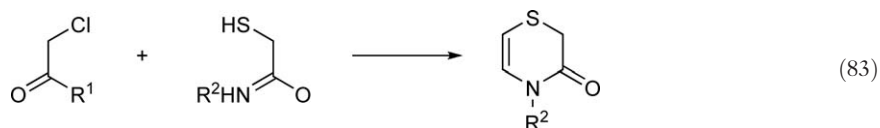
R¹ = *p*-Ts or CO₂Et; R² = H or Me



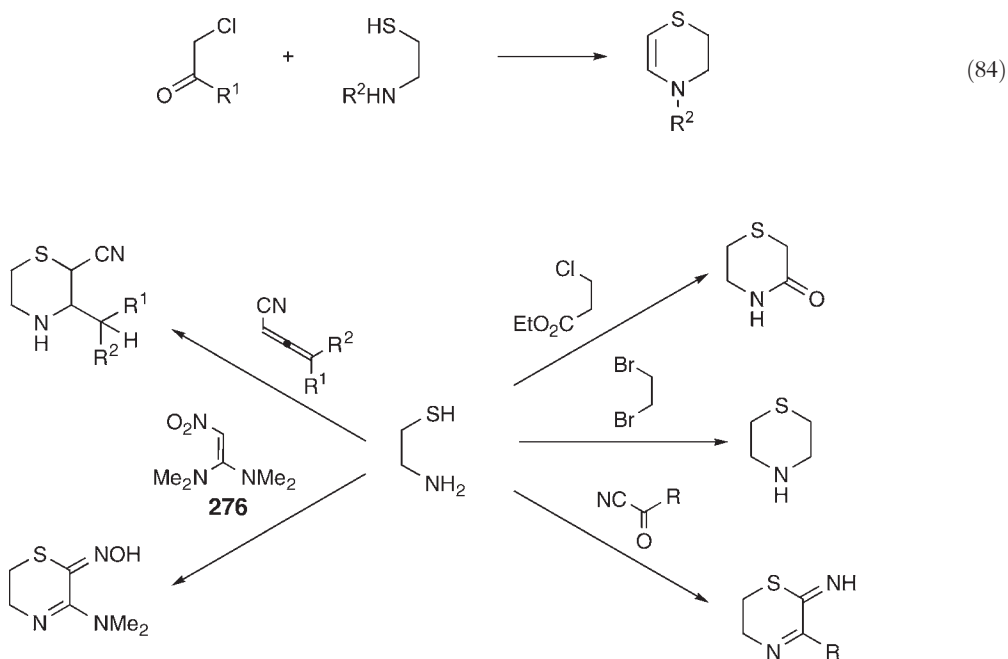
8.09.9.3 Two-Bond Formation from [4+2] Atom Fragments

This approach allows the two nucleophilic heteroatoms to react with a dielectrophile and has therefore been the most popular one, although some other [4+2] combinations are discussed at the end of the section. Due to the large number of examples with only minor substituent variations, the reactions are shown here using basic unsubstituted structures.

Some of the earliest examples used 2-mercaptoamides, which were reacted with α -chloroketones to give dihydrothiazin-3-ones (Equation 83) <1948JA3517, 1958JA5198, 1959JA3756, 1969JHC247, 1972S136>.

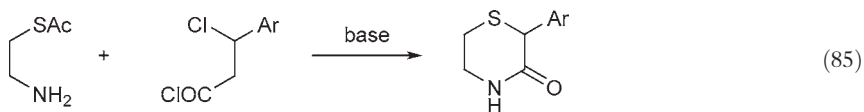


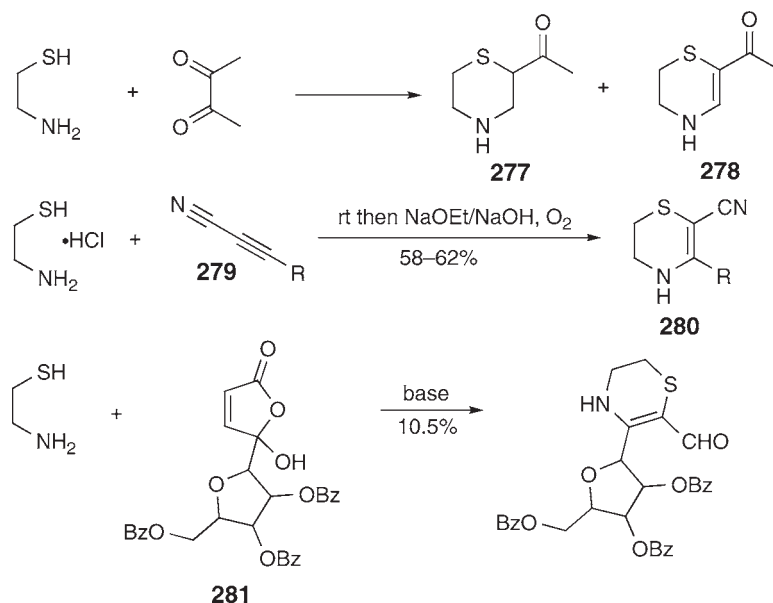
More nucleophilic and thus more versatile are 2-aminothiols: they can be reacted not only with α -chloroketones to give dihydrothiazines under basic or neutral conditions (Equation 84) <1962G1367, 1962LA(652)50, 1970M1295, 1981CPB1554, 1984H(22)387, 1989JHC1447, 1993CHE219, 1993JHC1105, 1994ACS517, 1998JFA664, 2002JFA5394>, but also with 2-chloroesters <1983JME559>, 1,2-dibromoalkanes <1973J(P1)1321>, 2-ketocyanides <1993EJM29>, compound **276** <1987J(P1)951>, and cyanoallenes <1988J(P1)1759> (Scheme 58).



Scheme 58

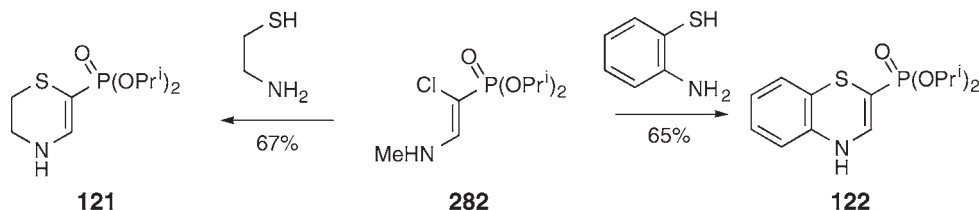
An S-acetylated 2-aminothiol was reacted with 2-chloroacyl chlorides (Equation 85) <1989JPS937>. The reactions of 2-aminoethanethiol with 2,3-butanedione <1998JFA2278>, alkynyl cyanide **279** <1993TL5681>, and cyclic hemiacetal **281** <1992H(34)2131> are shown in Scheme 59. Mechanisms for the formation of products **277**, **278**, and **280** were suggested, but not however for the unexpected product from **281**.





Scheme 59

Both 2-aminoethanethiol and 2-aminothiophenol can be reacted with the same chloroenamine **282** to give **121** and **122** (Scheme 60) <2005RJO508>.



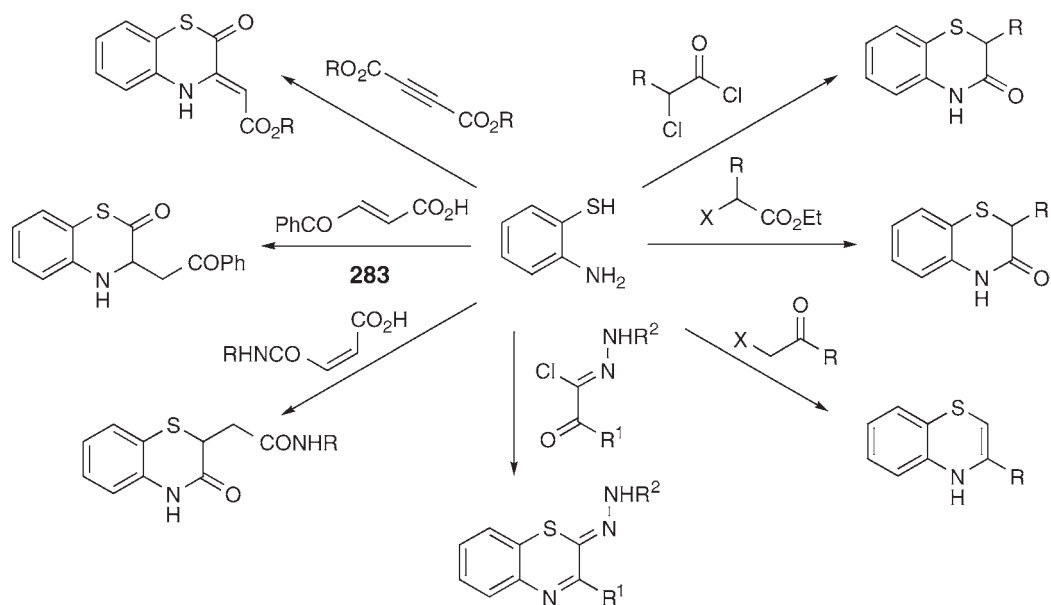
Scheme 60

Other dielectrophiles such as 2-chloroacyl chlorides <1972CPB892, 1990EJM403>, 2-haloesters <2003JME3670, 1992EJM419>, α -halogenoketones <1980J(P1)2923, 1999T7915>, iminochloroketones <1980J(P1)2923, 1997H(45)1183>, maleic acid amides <1986T2731>, compound **283** <2001CHE1289>, and acetylenedicarboxylates <2003T4785> react with 2-aminothiophenol to give a variety of benzothiazine derivatives (Scheme 61). Further examples were already mentioned in CHEC(1984).

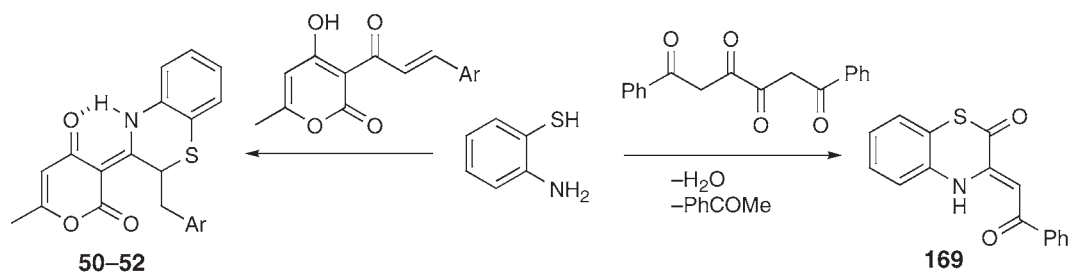
Additionally, compounds **50–52** <2005T6642> and **169** <2002CHE365> were prepared from 2-aminothiophenol (Scheme 62).

The disulfide dimers of 2-aminothiophenols have also been used in the syntheses of benzothiazines. In this case, nitrogen acts as a nucleophile and sulfur as an electrophile. Reagents that have nucleophilic carbons adjacent to an electrophilic carbon can be reacted with these disulfides. Examples include α,β -unsaturated esters that undergo conjugate addition followed by enolate addition to sulfur (Equation 86) <1983J(P1)567>, and 1,3-dicarbonyl compounds such as ethyl acetoacetate <2005AXEo2716> and dimethyl malonate <2006ARK(xv)68> (Scheme 63).

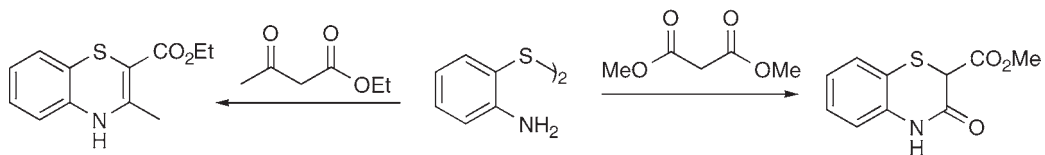
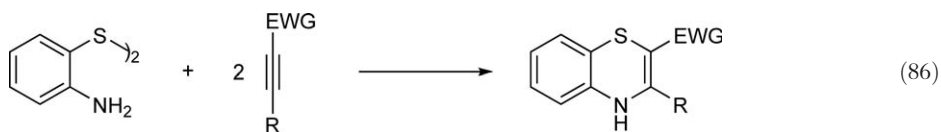
DMSO can oxidize 2-aminothiophenols into the disulfide dimers, which then undergo a reaction with 1,3-diketones to give benzothiazines (Scheme 64) <1985JFC(28)381, 1986JFC(31)19, 1987JOC4053, 1989JFC(44)1, 1999JFC(94)169, 2003JFC(122)207>. An enol ether derivative of a ketoaldehyde reacts in the same way (Equation 87) <2001JFC(108)51>.



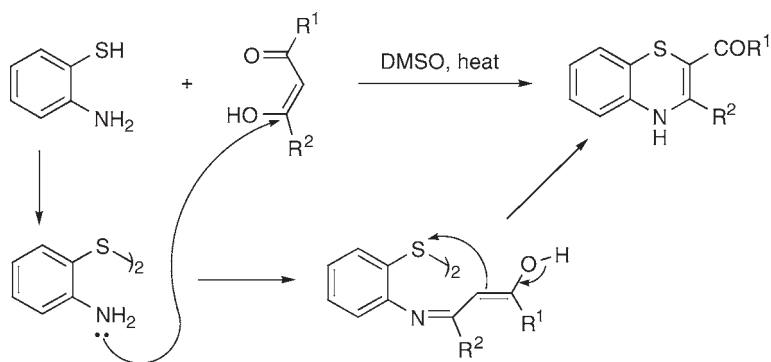
Scheme 61



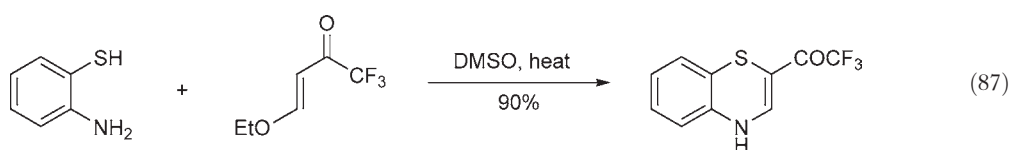
Scheme 62



Scheme 63



Scheme 64

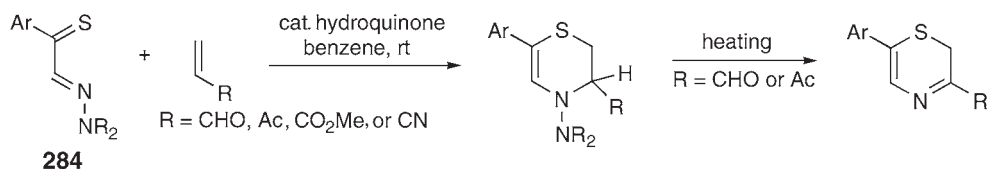


Samarium iodide-induced radical reaction of di(2-nitrophenyl)disulfides with α -bromoketones has also been reported (Scheme 65) <2001HAC156, 2001TL3125>.

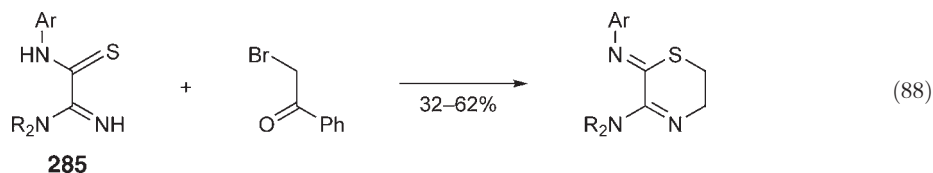


Scheme 65

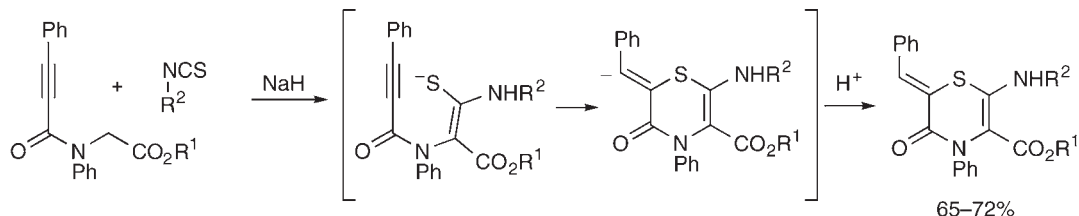
Compounds of the general structure 284 undergo a cycloaddition with dienophiles (Scheme 66) <1991S543> and those with general structure 285 react with dielectrophiles to give dihydrothiazines (Equation 88) <1998T2459>.



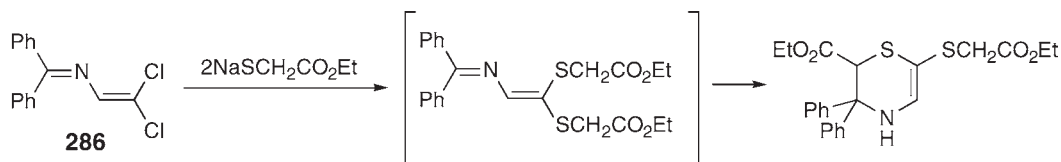
Scheme 66



Only two syntheses use different approaches from the reaction of N–C–C–S and C–C fragments. In the first one, an isothiocyanate was used to supply a C–S fragment (**Scheme 67**) <1988ZC58>. In the second synthesis, compound **286** reacted three times as an electrophile (**Scheme 68**) <2006EJO1555>.



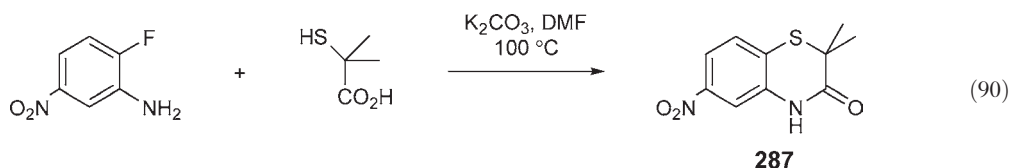
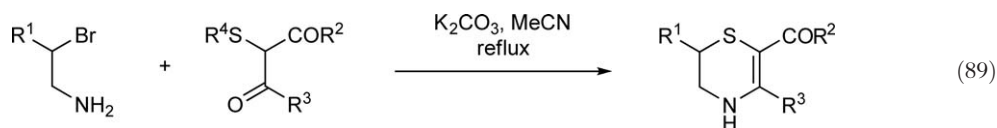
Scheme 67



Scheme 68

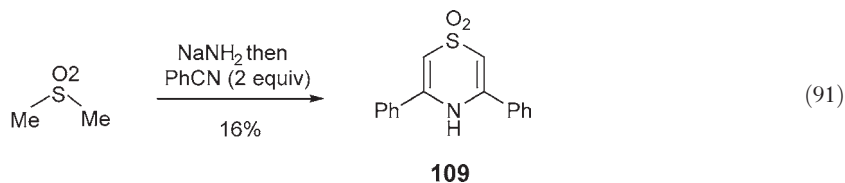
8.09.9.4 Two-Bond Formation from [3+3] Atom Fragments

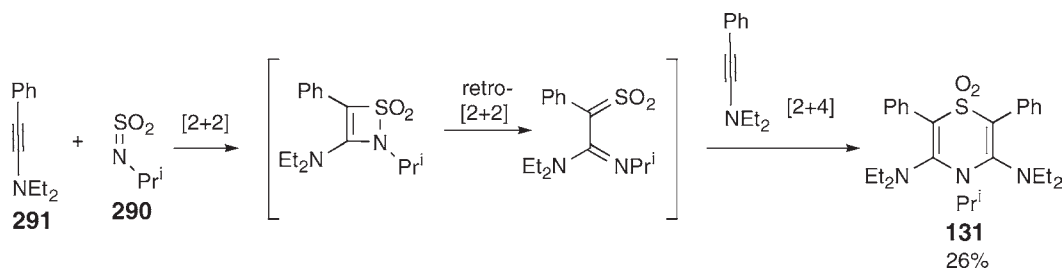
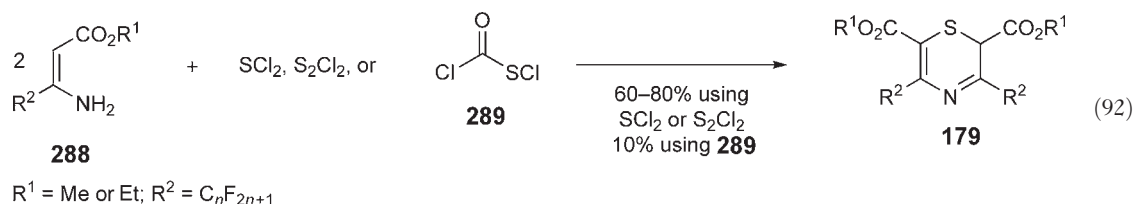
One method was already included in CHEC(1984) <1976H(4)1875>. The other approach is to react 2-mercapto-carbonyl compounds with 2-chloroamines or 2-amino alcohols (**Equation 89**) <1985S688>. A 2-fluoroaniline was reacted similarly to give a benzo derivative **287** <2003JME3670> (**Equation 90**).



8.09.9.5 Three- or Four-Bond Formation

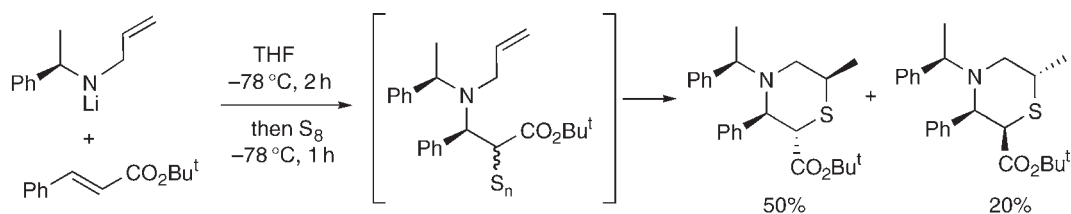
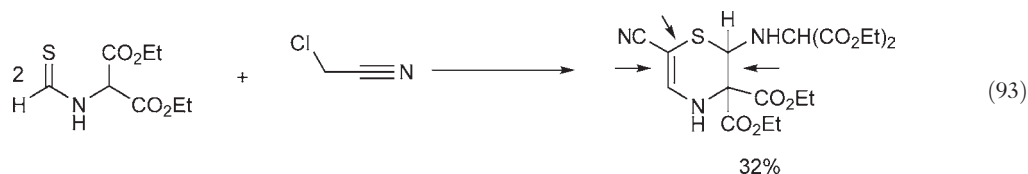
When deprotonated dimethyl sulfone is reacted with 2 equiv of benzonitrile, compound **109** is obtained in low yield (**Equation 91**) <1973JOM(59)53>. Compounds of the general structure **179** can be prepared from two molecules of enamino esters **288** and sulfur dichloride or disulfur dichloride <1984JOC4780> or in low yield using chlorocarbonylsulfenyl chloride **289** as the source of sulfur <1985JHC1621> (**Equation 92**). A series of cycloadditions lead to the formation of **131** from **290** and two molecules of the ynamine **291** (**Scheme 69**) <1995LA1795>.





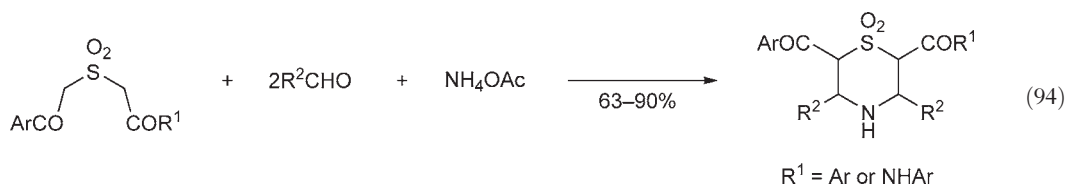
Scheme 69

The two nonsymmetrical approaches reported are shown in Equation (93) (newly formed bonds marked with arrows) <1978H(11)203> and Scheme 70 <2006TA1135>.



Scheme 70

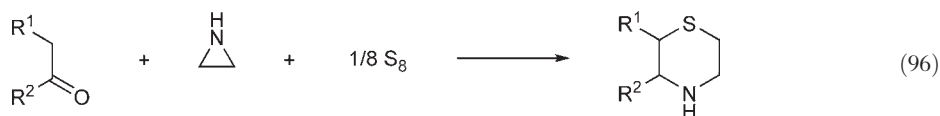
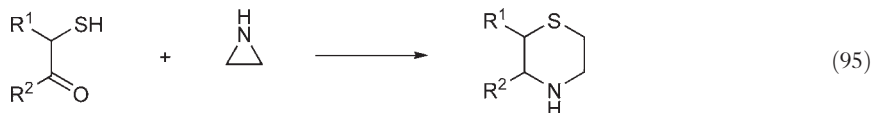
In one approach, tetrahydrothiazines were constructed from four molecules (Equation 94) <1961JOC969, 1976JPR865>. Using primary amines instead of ammonium acetate gives N-substituted derivatives.



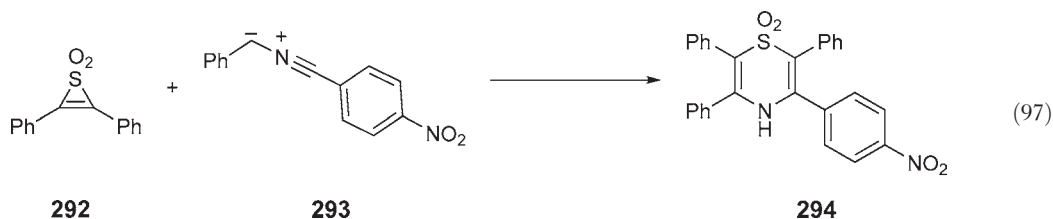
8.09.10 Ring Synthesis by Transformation of other Heterocyclic Rings

8.09.10.1 Three-Membered Rings

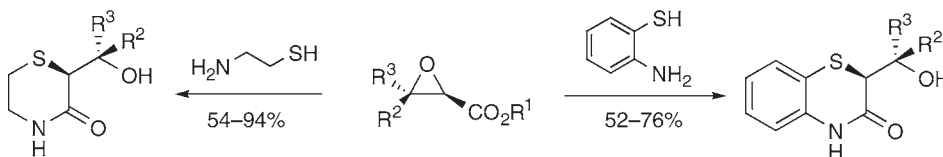
The reaction of aziridines with α -mercaptoketones gives dihydrothiazines as products (Equation 95) <1962LA(652)50, 1962G1367, 1964M1335>. Alternatively, a ketone can be reacted with an aziridine and elemental sulfur (Equation 96) <1970M1281, 1970M1295, 1971M321>, and this reaction also works when selenium is used instead of sulfur <1968M2084>.



The use of thiirene dioxide **292** as a dipolarophile in the synthesis of thiazine 1,1-dioxides was already mentioned in CHEC(1984) <1975CL1153>. The same compound also reacts with nitrile ylide **293** to afford **294** <1984JOC1300> (Equation 97).



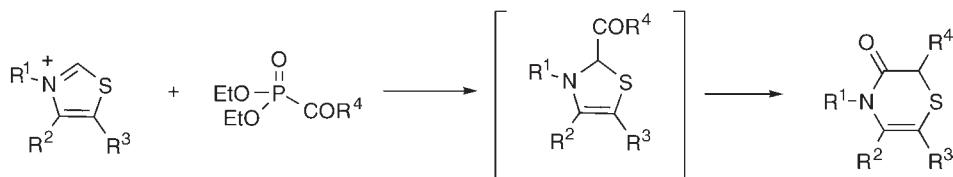
Both 2-aminoethanethiol and 2-aminothiophenol were reacted with epoxysters to give thiazin-3-ones (Scheme 71) <1999J(P1)149>.



Scheme 71

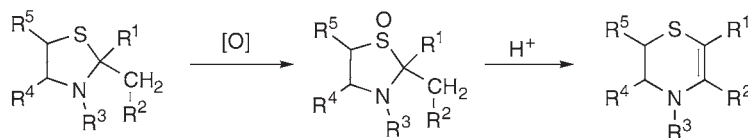
8.09.10.2 Five-Membered Rings

The Takamizawa reaction gives tetrasubstituted dihydrothiazin-3-ones (Scheme 72) and has been used to prepare a large number of derivatives <1966CPB407, 1966CPB742, 1967CPB1178, 1968CPB1773, 1968JOC4038, 1969CPB1356, 1972CPB892, 1974CPB293, 1974CPB311, 1974CPB2818>.



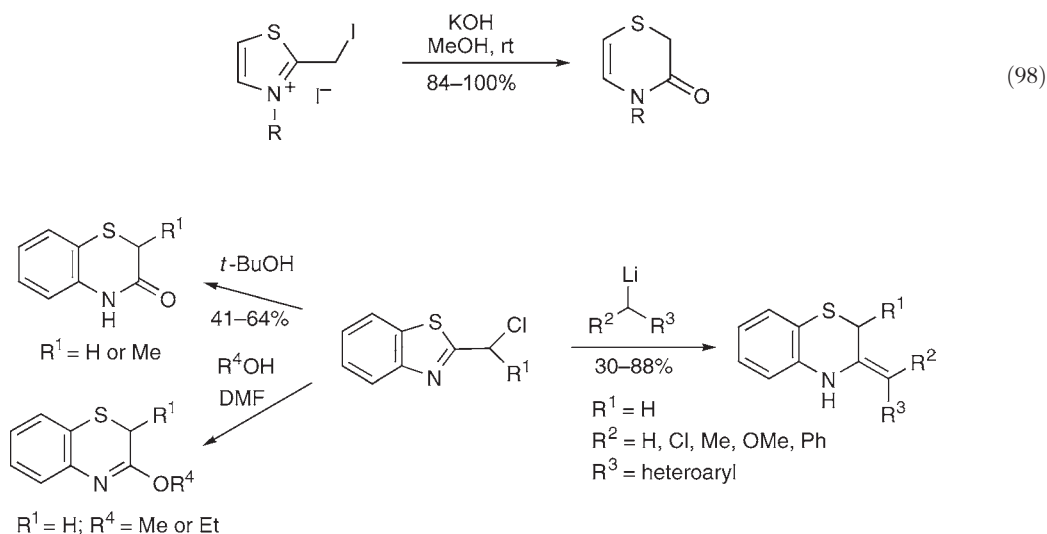
Scheme 72 Takamizawa reaction.

The ring expansion of thiazolidine *S*-oxides has also been widely used to prepare substituted dihydrothiazines (**Scheme 73**) <1978CJC326, 1979CJC2388, 1982H(19)465, 1989JHC1447, 1993JHC1105, 1999JHC271> and benzo derivatives <1978S744>, which were included in CHEC(1984). The reaction can also be brought about by treatment with sulfur instead of oxidation <1970LA(739)32>.

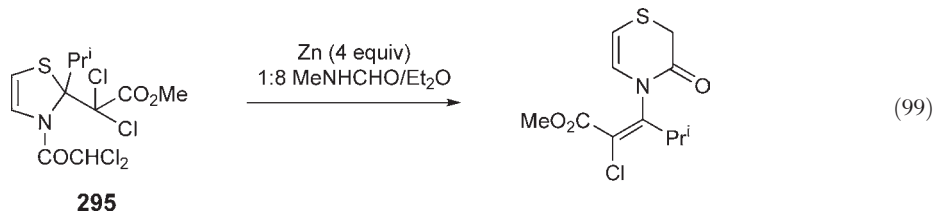


Scheme 73

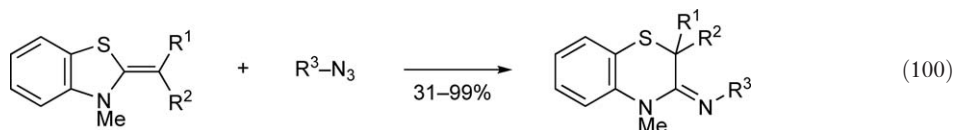
Following the hydroxide-induced ring expansion reported for *N*-alkylthiazolium iodides (**Equation 98**) <1979S272>, the neutral benzo derivatives were found to undergo similar processes with organolithium reagents <1995TL1913> and alcohols <1997T5839> (**Scheme 74**). The chlorinated thiazoline **295** underwent a different rearrangement (**Equation 99**) <1984H(22)2341>.



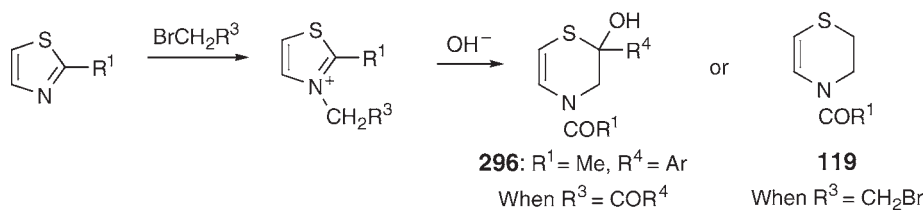
Scheme 74



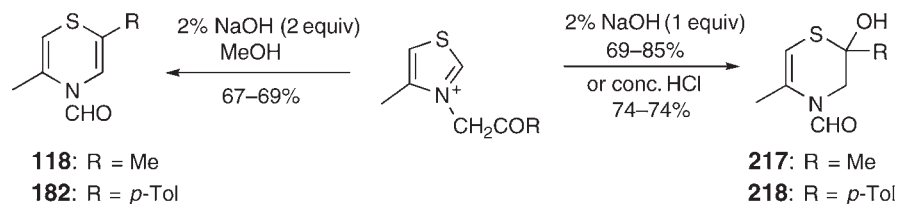
Azides react with 2-alkylidenbenzothiazolines to give benzothiazines (**Equation 100**) <1992LA1259, 1996LA1541>. The yields are lowest when both R^1 and R^2 are hydrogen.



Thiazoles have been converted into thiazines by N-alkylation followed by treatment with base (**Scheme 75**), as shown for synthesis of **296** <1969TL3063> and **119** <1995JOC2597>. Compound **120**, the benzo derivative of **119**, was prepared using the same method <1995JOC2597>. A similar reaction afforded both **217** and **218** and the dehydrated compounds **118** and **182** from the 4-methyl starting materials (**Scheme 76**) <1992T4545>.

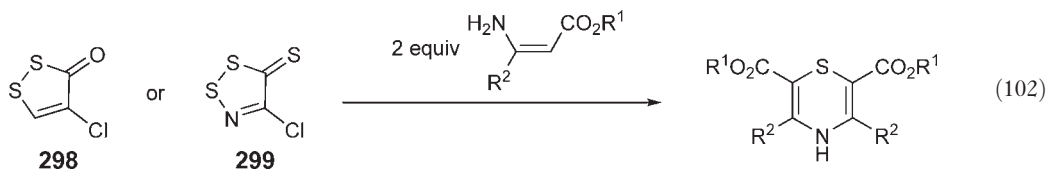
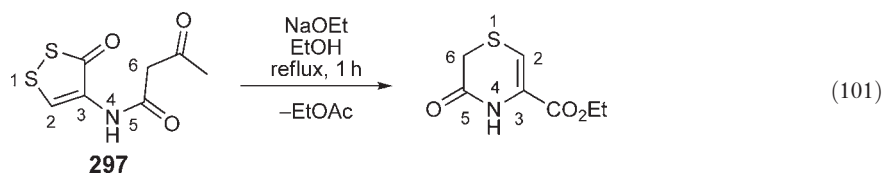


Scheme 75

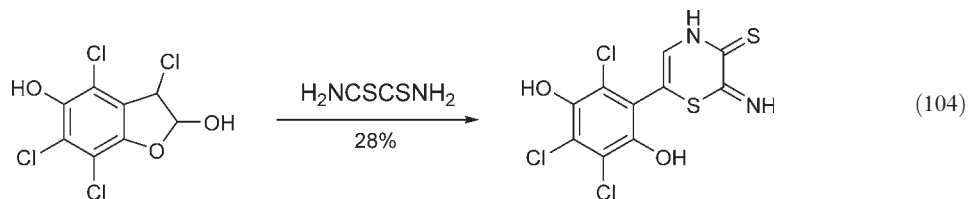
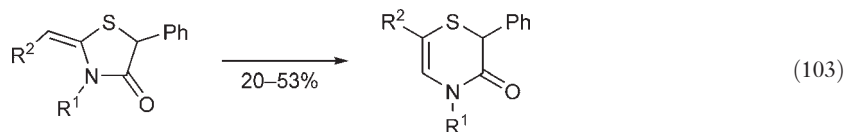


Scheme 76

The reaction of **297** with ethanol <1965AJC1071> gives a dihydrothiazine with the origin of the product ring atoms as shown (**Equation 101**). The related compounds **298** <1999TL6439> and **299** <2002JHC29> donate only a sulfur atom to the thiazines formed (**Equation 102**).

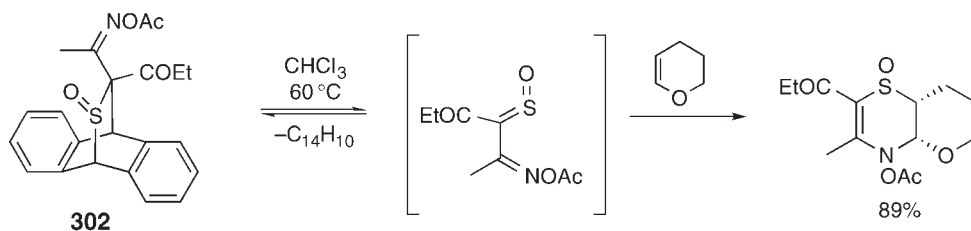
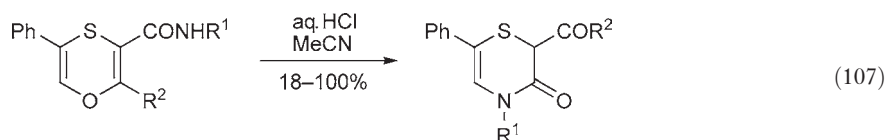
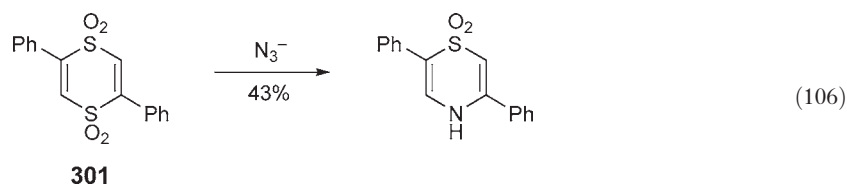
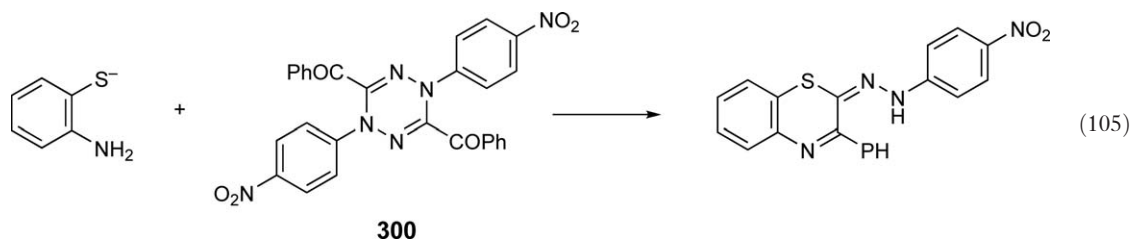


Two other syntheses starting from five-membered rings are shown in **Equations (103)** <1978LA473> and (104) <1999CHE866>.



8.09.10.3 Six-Membered Rings

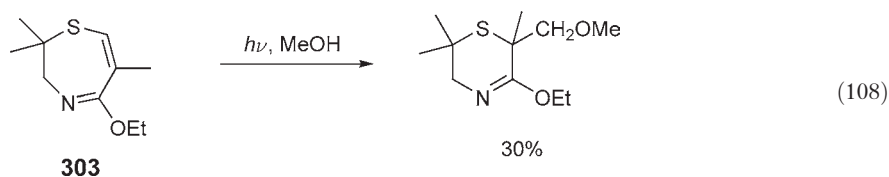
Thiazines have been synthesized from the nitrile imine dimer **300** (Equation 105) <1980J(P1)2923>, 1,4-dithiin 1,1,4,4-tetraoxide **301** (Equation 106) <1982TL299>, 1,4-oxathiins (Equation 107) <1996JOC3894>, and the anthracene adduct **302** (Scheme 77) <1998S915>.

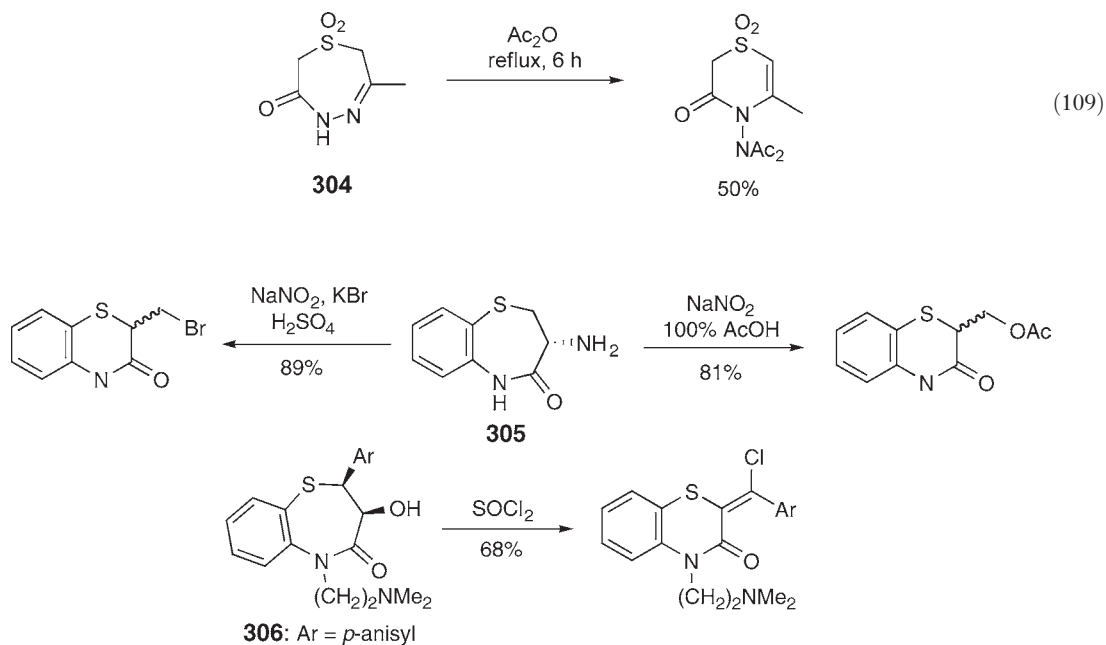


Scheme 77

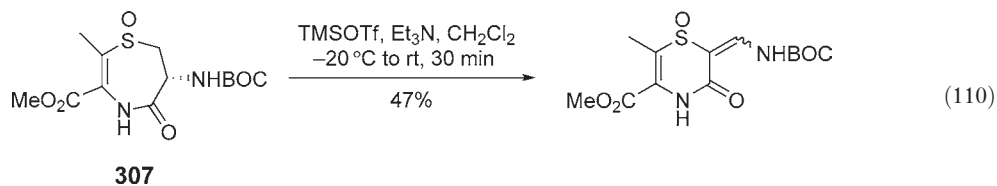
8.09.10.4 Seven-Membered Rings

The formation of thiazine systems by ring contractions of 2,3-dihydro-1,4-thiazepine **303** (Equation 108) <1971CC698>, 2,3,4,7-tetrahydro-1,4,5-thiadiazepin-3-one S,S -dioxide **304** (Equation 109) <1972T2307>, 2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-ones **305** and **306** (Scheme 78) <1992LA403>, and 6,7-dihydro-1,4-thiazepin-5(4*H*)-one S -oxide **307** (Equation 110) <1999H(51)1639> has been published.



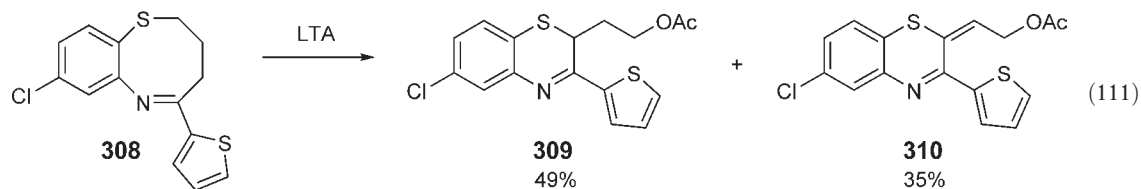


Scheme 78



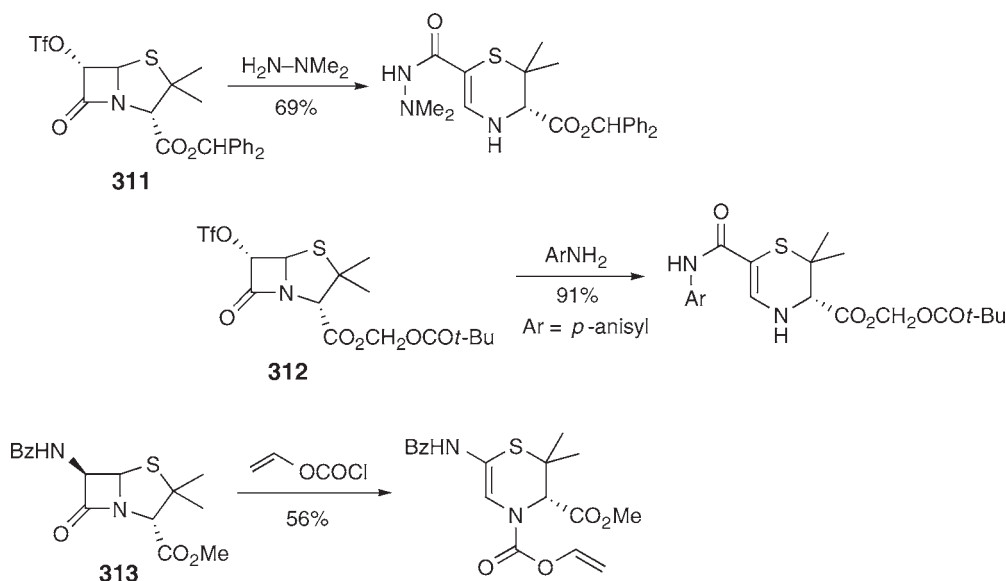
8.09.10.5 Eight-Membered Rings

Lead tetraacetate was used to convert 3,4-dihydrobenzo[*b*][1,4]thiazocine **308** into a benzothiazine **309** and its dehydrogenated form **310** (Equation 111) <1980TL1705>.

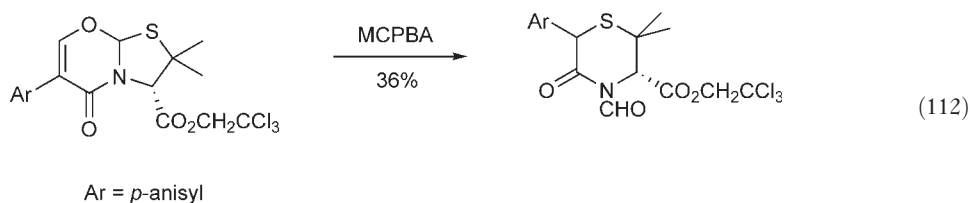


8.09.10.6 Bicyclics

The penicillin derivatives **311**, **312** <1982SC85>, and **313** <1983TL201> were converted to 1,4-thiazines in good yields (Scheme 79). Another synthesis of a 1,4-thiazine from a bicyclic compound has also been reported (Equation 112) <1986J(P1)2187>.



Scheme 79



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

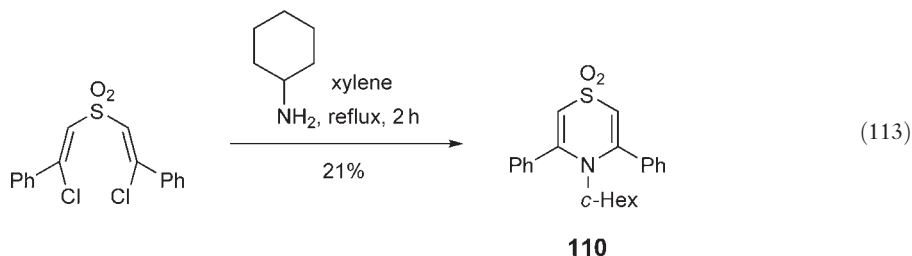
8.09.11.1 Fully Conjugated 1,4-Thiazines

The fully conjugated 1,4-thiazines include 2*H*-1,4-thiazines, 4*H*-1,4-thiazine *S,S*-dioxides, and *S*-methyl-1,4-thiazine *S*-oxides which have three double bonds. Most of the synthetic methods leading to these compounds were published prior to 1984 and are included in CHEC(1984).

Synthesis of unsubstituted 2*H*-1,4-thiazine **3** was first achieved by pyrolysis of **43** in 13% yield <1948JA684>, and a variety of 3,5-diaryl derivatives as well as 2,6-dimethyl-3,5-diaryl derivatives were prepared in excellent yields by allowing the appropriate 3-thia-1,5-diketones react with ammonium acetate <1968G17>. The newer approaches, on the other hand, have given routes to 2,6-dialkoxycarbonyl derivatives (see Scheme 38) <1985JOC413> and 3,5-dialkoxycarbonyl derivatives (Equation 92) <1984JOC4780, 1985JHC1621>.

In Equation (102) is shown the only synthetic method leading to 4*H*-1,4-thiazines of the general structure **4**. The symmetry of these compounds was proven by NMR spectroscopy <1999TL6439> (See Table 5, compound **132**; NH was also seen in ¹H NMR).

As 4*H*-1,4-thiazine *S,S*-dioxides are the sulfone analogues of 4*H*-1,4-thiazines, they can also be prepared from 3-thia-1,5-diketone 3,3-dioxides and various ammonia equivalents <1961JOC970, 1967JME501, 1972S311, 1976JPR865> in very good yields. The *N*-substituted analogues can be prepared by alkylation of these products or as in the synthesis of **110** (Equation 113), which however was not high-yielding <1974CB1334>. Some newer approaches have been shown in Equations (91), (97), and (106) and Schemes 69 and 76. These syntheses generally gave low to moderate yields and their generality was not investigated further.



Two syntheses of fully conjugated *S*-methyl-1,4-thiazine *S*-oxides were included in CHEC(1984) <1965CB3724, 1976H(4)1875>. The new approach (Equation 69) made possible the synthesis of 3-amino-5-aryl derivatives <1986LA1648>.

8.09.11.2 Benzothiazine Ylides

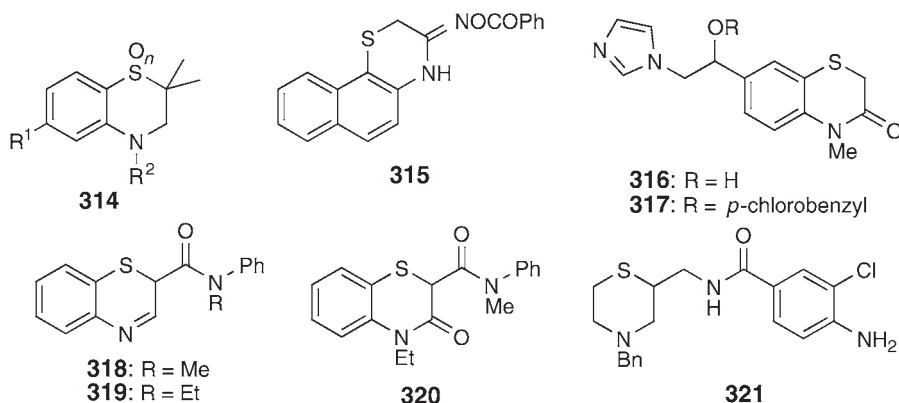
Benzothiazine ylides can be prepared by *S*-alkylation (Equation 6) or cyclization (Equation 56). The cyclization has been performed for *S*-methyl, benzyl, or isoprenyl substituents <1982J(P1)831, 1991J(P1)2249>, whereas almost any alkyl halide could be reacted with benzothiazines to induce *S*-alkylation <1984TL2635, 1985HCA2216>. The yields are good to excellent using either method and the deciding factor thus becomes the availability of the starting materials.

8.09.12 Applications

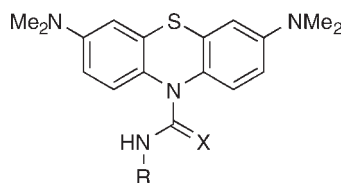
8.09.12.1 Pharmaceutical and Medicinal Applications

As mentioned in CHEC(1984), phenothiazine derivatives are best known as pharmaceuticals for the central nervous system, and are used not only for treatment of various mental illnesses <1986AXC1083> but also as neuroleptics, sedatives, analgesics, anti-emetics, and antihistamines <1987AXC1737>. A review has appeared on use of phenothiazines in the treatment of Creutzfeldt-Jacob disease <2001JAA411>.

A number of thiazine derivatives have been found to exhibit anti-hypertensive and/or vasorelaxant activity <1987CPB2243, 1989EJM479, 2000BMC393, 2005BMC141, 2004BML1477>, most promisingly compounds with a general structure **314** <2003JME3670>. Potential anticancer compounds have also been reported <1985JFC(28)381, 1992AXC2004, 2000JOC3738, 2003BMC3245>, as well as antibacterial agents <1994CJC1051, 1994CJC1066, 2000BML465>. Active antifungal compounds are **315** <1990EJM403>, **316**, and **317** <1998BMC103>. Compounds **318–320** are very good immunomodulators <1992EJM419> and **321** is a gastroprokinetic compound comparable to commercial products <1995CPB1137>.



Compound **322** is a functional dye that decomposes to methylene blue in biological systems, and it is used in diagnostics. The thiourea analogues **323** and **324** were synthesized in the hope they would be more stable than **322** and cause less background noise, but this was unfortunately not the case <1996BCJ1423>.



322: X = O; R = Me

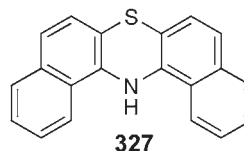
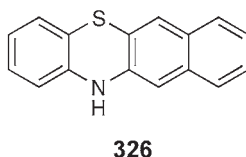
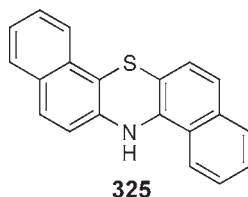
323: X = S; R = Me

324: X = S; R = Bn

8.09.12.2 Other Applications

A number of benzothiazine-based dyes including compounds **152–156** were prepared and exhibited a rich variety of colors, which in some cases could be altered by protonation of the compound <1980J(P1)2923>.

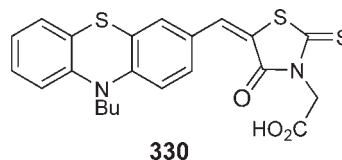
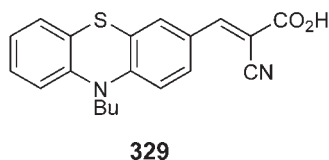
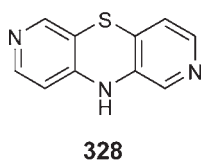
Compounds **159–161** could be used as models for redox-active molecular wires <2003EJO3534>. Photovoltaic cell measurements showed **325–327** to be p-type semiconductors and **22** to be an n-type semiconductor <1994BCJ2017>.



Compound **56** is a roast-smelling odorant that has been described to have a strong, popcorn-like aroma and thus has applications in food flavoring <1995JFA2195, 1995JFA2187, 1997JMP807, 2002JFA5394>.

8.09.13 Further Developments

Synthesis of a new dipyrido-1,4-thiazine **328** has been described involving a Smiles rearrangement, and *N*-alkylation, arylation and heteroarylation of **328** have been reported as well as its promising anti-tumor activity <2007H(71)1347>. Phenothiazine derivatives such as **329** and **330** have been developed for use in dye-sensitized solar cells <2007CC3741>.



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1966CPB407
1966CPB742
1967CPB1178
1967JME501
1968CHE322
1968CPB1773
1968G17
1968G488
1968JOC4038
1968M2084
1968T2985
1969CC1169
1969CC1368
1969CPB1356
1969G2325
1969JHC247
1969JOC250
1969TL2979
1969TL3063
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1970JOC3600
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Biographical Sketch



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8.10

1,2-Dioxins, Oxathiins, Dithiins, and their Benzo Derivatives

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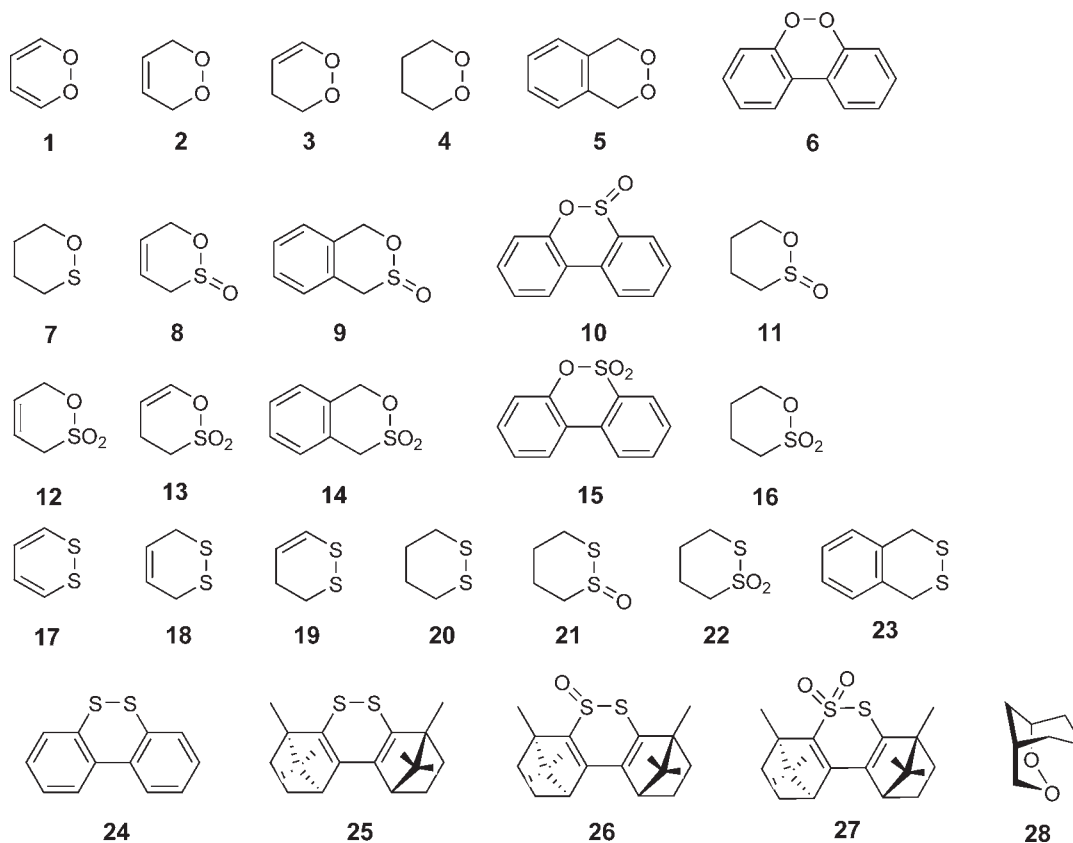
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8.10.1 Introduction

In this chapter, the structures and chemistries of 1,2-dioxins, 1,2-oxathiins, and 1,2-dithiins, including both their partly and fully saturated forms as well as their benzo analogs, are described (cf. [Scheme 1](#)). Though the material of this chapter is presented according to the usual format, there are, however, some exceptions resulting from (1) the fact that there are no substituents attached to the ring heteroatoms (except sulfoxides and sulfones) and therefore no attendant reactivity, and (2) the appropriateness of discussing syntheses according to the ring system involved rather than by the type of ring closure or transformation. Since the present subject matter was not included in



Scheme 1

CHEC-II(1996), this chapter therefore covers the relevant literature back to 1984. Parallel to CHEC-II(1996), the material was reviewed by Saito and Nittala <B-1983MI356>.

After beginning with the theoretical, structural, spectroscopic, and thermodynamic studies, the main body of the chapter deals with the reactivities and syntheses of the different heterocyclic systems categorized by their degree of unsaturation and the heteroatoms present. Heterocyclic ring systems have been particularly well investigated theoretically and because the theoretical techniques are now so well developed, they replicate experimental results extremely closely and thus at the state-of-the-art level, both the electron distributions and geometries of the structures are fully understood.

1,2-Dioxin **1**, the 3,6- and 3,4-dihydro analogs **2** and **3**, and 1,2-dioxane **4**, as well as the corresponding benzoderivatives **5** and **6**, are all well known and have been studied in detail. The photooxidation of conjugated dienes generating endoperoxides (3,6-dihydro-1,2-dioxins) is nowadays an important part of singlet oxygen chemistry and is of increasing value in organic synthesis because there are several naturally occurring endoperoxides with biological activity and, furthermore, these endoperoxides can be readily used as synthetic intermediates for the introduction of oxygen functionalities into conjugated dienes. Moreover, it is the very existence of a 'six-membered ring with a peroxide bond' in a number of natural products, for example, in marine sponges, that has proved to be responsible for their antimicrobial, antimalarial, or/and antimycotic pharmacological actions <1998H(47)643>. Thus, marine sponges continue to attract attention as a rich source of structurally novel cytotoxic secondary metabolites that are potential lead compounds for the development of new anticancer drugs. Interestingly, the biological activities of the 1,2-dioxanes and 3,6-dihydro-1,2-dioxins in natural products could possibly be due to decomposition products, for example, the OH radical as shown to be present by electron spin resonance (ESR) spectroscopy, rather than the peroxides themselves. Alternatively, their biological activities may be diminished by their instabilities; thus their stabilities under certain conditions have been of continuing interest. Finally, the stereoselectivity of the [4+2] Diels–Alder cycloaddition of singlet oxygen to *s-cis*-butadienes has been closely scrutinized both experimentally and theoretically.

For the second group of compounds incorporating one sulfur atom, only very few new results concerning 1,2-oxathiins, their dihydro analogs, and 1,2-oxathiane have been published, and furthermore, only two actually concern 1,2-oxathianes **7** (cf. Section 8.10.3). 1,2-Oxathiins as well as their corresponding benzo analogs are unknown and have not even been detected spectroscopically, though they have been studied from the theoretical point of view. By contrast, the corresponding sulfoxides (sultines **8–11**) and sulfones (sultones **12–16**) are known and both their structures and chemistries have been studied both experimentally and theoretically with respect to both electron distribution and the conformation of the six-membered ring system and S=O groups. Also, a number of 3,6-dihydro-1,2-oxathiin 2-oxides **8**, unstable above -50°C , were able to be isolated and structurally characterized by NMR spectroscopy; while ^1H or ^{13}C nuclear magnetic resonance (NMR) spectra were not sufficiently indicative, ^{17}O chemical shifts of the S=O moieties were theoretically calculated and employed to assign the reaction products. On the other hand, 1,4-dihydro-2,3-benzoxathiin 3-oxide **9** proved to be an ideal reagent for the *in situ* synthesis of *o*-quinodimethane (*o*-xylylene) that has been used widely as a latent diene component in Diels–Alder addition reactions; the total synthesis of nonactic acid with excellent stereocontrol via sultone intermediates has been published and 3,4-dihydro-1,2-oxathiin 2,2-dioxides **13** have been synthesized by ring-closing metathesis (RCM) of sulfonates (cf. Section 8.10.9.3.4).

As in the case of the 1,2-dioxins, the 1,2-dithiins exist in various states of saturation, oxidation, and benzoannellation (cf. Scheme 1, 17–27) and they have been studied in detail both theoretically and experimentally. Not only were the conformations of the ring and attached substituents investigated, but the valence isomerism of 1,2-dithiin by both NMR and high-level *ab initio* molecular orbital (MO) calculations and the dithiol/disulfide equilibrium by MP2 calculations were also examined. The latter equilibrium has been applied successfully as a luminescent molecular switch (cf. Section 8.10.2.1). Finally, as a very interesting 1,2-dithiin derivative, the synthesis, structure, and reactivity of the (+)-camphor-derived analog **25** and its sulfoxide **26** and sulfone **27** have been reported. Both the synthesis and the antimalarial activity of the 2,3-dioxabicyclo[3.3.1]nonane pharmacophore **28**, which contains the 1,2-dioxane moiety, have been reviewed recently <2006BML2991>.

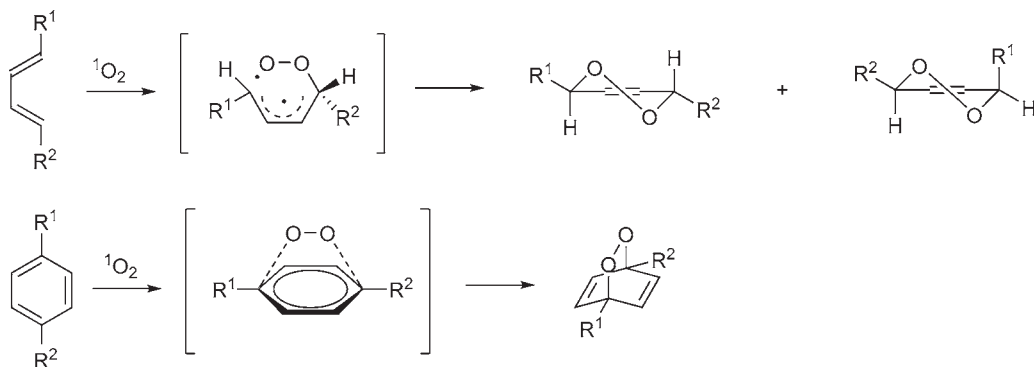
Recently, synthetic methods for preparing 1,2-dioxins and their benzo- and dibenzofused derivatives <2004SOS(16)13> and 1,2-dithiins <2004SOS(16)39> have been reviewed.

8.10.2 Theoretical Calculations

The geometries of both 3,4-dihydro- and 3,6-dihydro-1,2-dioxin have been calculated at the Hartree–Fock (HF) and MP2 *ab initio* levels of theory. In each case, half-chair conformers were found to be the most stable structures followed by boat conformers which represent the transition states for ring interconversion <2000JST(503)145, 1997JCC1392,

1993JCC1376, 1991JST(235)25>. For comparison, the 1,3- and 1,4-isomers of the dihydro-1,2-dioxins were also calculated and found to be much more stable <1988JST(163)111>. Interestingly, 1,2-dioxin and its 3,6-di-*p*-tolyl derivative were found to be ca. 66 kcal mol⁻¹ less stable than their valence tautomer (Z)-1,4-di-*p*-tolylbut-2-ene-1,4-dione by a combined theoretical and experimental study <2003JOC4108>. In the adopted half-chair conformation, the C–O–O–C torsion angle was 60.6° and the toluene ring was tilted by 20.5° with respect to the butadiene plane.

The 1,4-cycloaddition reaction of singlet oxygen (¹Δ_g) with *s-cis*-1,3-butadiene and also with benzene has been studied in detail by means of *ab initio* MO calculations <2000JA8112>. However, the reaction occurs through different mechanisms in the different systems: a stepwise mechanism involving a linear biradical as intermediate (as in the case of oxygen addition to isolated C=C bonds) was proposed for the *s-cis*-1,3-butadienes but a single-step mechanism with a symmetric transition state and significant charge transfer (CT) from the organic donor to oxygen was proposed for the aromatic compounds (Scheme 2), both in accordance with the solvent effect and the nonstereospecificity of the oxygen addition.



Scheme 2

In the case of 1-phenyl-4-methyl-1,3-butadiene in benzene using tetraphenylporphyrin (TPP) as a sensitizer at ambient temperature under a 100 W tungsten lamp, the *cis*-isomer (phenyl group pseudoequatorial in both *cis*- and *trans*-isomers) was found to be preferred as evidenced by the observed nuclear Overhauser effect (NOE) between the methyl and *o*-phenyl hydrogen atoms. However, only a slight energy difference between the two isomers was calculated using *ab initio* methods <1999JOC493>.

A theoretical density functional theory (DFT) study of *trans*-3,6-dimethoxy-1,2-dioxane found that the diaxial conformer with the 1,2-dioxane ring in a chair conformation was the preferred structure by more than 2 kcal mol⁻¹ <2003ARK(xv)1>. It was concluded that the main reason for this is the anomeric effect. Furthermore, the di- and tetrahalogenated derivatives of 1,2-dioxane were analyzed structurally by semi-empirical AM1 and PM3 methods <2003JIC14, 2003MI173>; as observed for the previous compound, *trans*-3,6-dichloro- and 3,6-difluoro-1,2-dioxanes prefer diaxial positions for the halogen substituents with the 1,2-dioxane ring in a chair conformer. Finally, both 1,2-dioxane itself and further halogen-substituted derivatives prefer chair conformations in line with results of *ab initio* calculations.

One theoretical paper has been published <2002STC149> wherein HF, MP2, and DFT calculations were employed to study both the geometries and relative energies of chair, half-chair, sofa, twist, and boat conformers of 1,2-oxathiane. The chair conformer of 1,2-oxathiane was found to be aligned closely to that of cyclohexane, though quite naturally bond-angle and bond-length variations arise from the characteristic differences between CH₂ and oxygen and sulfur. The chair conformation was determined to be the most stable conformation of the set, in agreement with experiment, followed by the twist conformer (4–5 kcal mol⁻¹ less stable). In both of these two conformers, hyperconjugative stereoelectronic interactions were deduced to be active.

Dithiins are the only biomolecules found in nature that are formally nonaromatic; living organisms tend to avoid synthesizing antiaromatic compounds because of their thermodynamic and kinetic instability. *Ab initio* calculations of 1,2-dithiin at the HF/6-31G* level of theory revealed that the compound was essentially nonaromatic (antiaromaticity is markedly reduced by assuming a nonplanar structure) with Dewar resonance energies close to zero <1999JST(461/2)553>. By careful study of its magnetic susceptibility and nuclear shielding constants <2003CPL(375)583>, 1,2-dithiin was

revealed to behave nonaromatically in response to an external magnetic field with the geometrical distortions from planarity sufficient to consider antiaromaticity not to be in effect according to magnetic criteria. However, 1,2-dithiin (and similarly 1,2-dioxin and 1,2-oxathiin) exhibit small antiaromatic features (cf. their ring current effects <2001J(P2)1893> with those of benzene and cyclobutadiene in **Figure 1**) and, accordingly, nucleus-independent chemical shift (NICS) values are slightly negative (NICS = -0.3 ppm) <2000JMM177>.

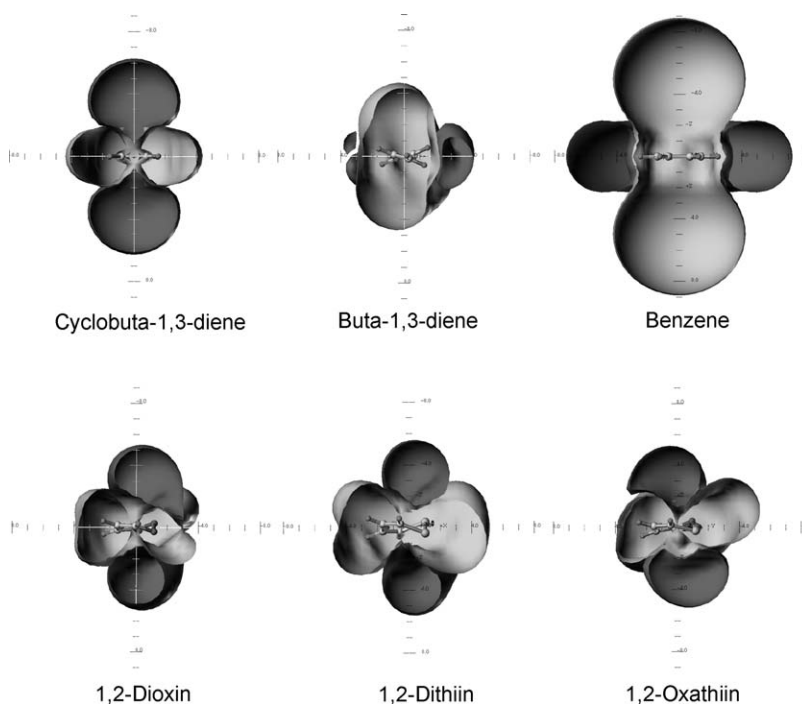
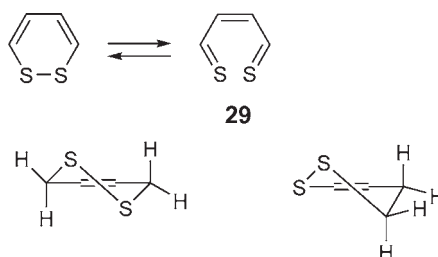


Figure 1 Calculated ring current effects of 1,2-dioxin, 1,2-oxathiin, and 1,2-dithiin (in comparison with the ring current effects of cyclobuta-1,3-diene, benzene and the anisotropic effect of buta-1,3-diene); shielding isochemical shielding surface (ICSS) of -0.1 ppm, gray, and deshielding ICSS of 0.1 ppm, dark gray.

The nonplanar global minimum structure of 1,2-dithiin possesses C_2 symmetry <1998CPL(289)391, 1991JST(230)287, 1982JA582>, and, in addition, dithiin (with small biradical character) was determined to be thermodynamically less stable by $1.2 \text{ kcal mol}^{-1}$ than the open-chain 2-butenedithial isomer **29** (having significant biradical character) (**Scheme 3**) <1998CPL(289)391>. The most stable structure is a half-chair conformer, interconverting via the planar structure to the alternative half-chair conformer <2000JMM177>. The barrier to interconversion is relatively low, calculated as $8.7 \text{ kcal mol}^{-1}$ at the MP2/6-31G(2df,g) level of theory, which is in good agreement with the only available experimental value of ca. 8 kcal mol^{-1} (for 3,6-bis(acetoxymethyl)-1,2-dithiin <2000JMM177>).



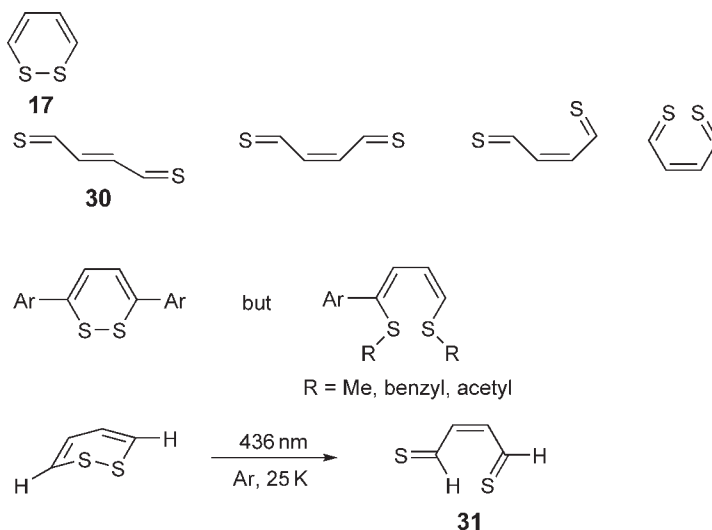
Scheme 3

3,4- and 3,6-Dihydro-1,2-dithiins adopt half-chair conformers (**Scheme 3**) and are more stable by 2.4 kcal mol⁻¹ and 7.2 kcal mol⁻¹, respectively, than their boat conformers (as calculated at the MP2/6-31G* level of theory) <1998JCC1064, 1993JCC1376>. Hyperconjugative orbital interactions, for example, the anomeric effect, have been examined with respect to the relative stability of the conformers <1998JCC1064>. The dimerization of 3,6-dihydro-1,2-dithiin has been studied at the DFT level <2005JST(723)37> and, in agreement with experiment (*vide infra*), was not found to dimerize at ambient temperature. It does so, however, in the presence of light.

The conformations of the 1,2-dithiane sulfoxides and sulfones were studied very recently at the MP2/6-31G*/HF/6-31G* and B3LYP/6-311G(2df,p)//HF/6-31G* levels of theory <2006PS1681, 2006PS1693>: 1-oxo-1,2-dithiane prefers the axial conformation of the sulfoxide oxygen (4.8 kcal mol⁻¹ more stable than the equatorial analog) and the 1,2-dioxo-1,2-dithiane favors the corresponding diaxial conformation. In 1,1,2-trioxo-1,2-dithiane, the axial conformer proved to be 5.1 kcal mol⁻¹ more stable than the corresponding equatorial S → O analog.

8.10.2.1 Valence Isomerism of 1,2-Dithiin

The valence isomerism of 1,2-dithiin was studied in detail by semi-empirical (modified neglect of diatomic overlap, MNDO) <1988CCC2096> and by *ab initio* MO calculations (MP2) <1995JST(331)51>: the 1,2-dithiin structure (C–S–S–C dihedral angle ca. 55°) was found to be more stable than the open-chain 2-butenedithial valence isomer **29** by more than 20 kcal mol⁻¹. However, the barrier to valence isomerization is low enough to allow transformations to occur at room temperature. Therefore, the solution structures of 1,2-dithiins were studied using ¹H and ¹³C NMR (in CDCl₃) in order to determine if dithione structures are participating by comparison with the corresponding spectra of their starting materials, the 1,4-(bis-organylthio)-buta-1,3-dienes (see **Scheme 4**) <1988ZNB605>. The chemical shifts and scalar couplings were assigned using the full arsenal of one-dimensional (1-D) and 2-D NMR experiments available at the time. The ¹³C chemical shifts proved the ring structure of **17** (by the absence of thiocarbonyl resonances) and the vicinal H,H-coupling constants proved the Z/Z-configuration and *s-cis*-conformation of the 1,2-dithiins, and the *s-trans*-conformation of the open-chain form **30**.

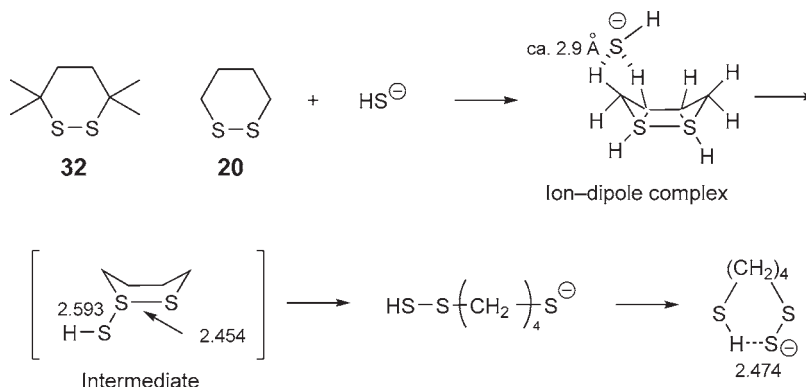


Scheme 4

By irradiation with visible light (436 nm, 2 h) in an argon matrix at 25 K, 1,2-dithiin was transformed into *s-trans-Z-s-cis*-2-butenethial **31**, which is twisted by ca. 40° away from planarity (**Scheme 4**) <1996JA4719>.

An *ab initio* MO study of 1,2-dithiane **20** and its 3,3,6,6-tetramethyl analog **32** (cf. **Scheme 5**) has been published <2004PS2015>. Both compounds prefer a chair conformation as the most stable geometry followed by twist conformers which are less stable by 5.2 and 2.0 kcal mol⁻¹, respectively. The smaller energy difference between the chair and twist conformers in **32** can be attributed to the unfavorable repulsion between axial methyl groups and *gauche* sulfur atoms, thereby decreasing the stability of the chair conformer relative to the one in **20**; the repulsion

being ineffective in the corresponding twist conformer. The calculated barriers to ring interconversion ($13.5 \text{ kcal mol}^{-1}$ in **20** and $14.6 \text{ kcal mol}^{-1}$ in **32**) are in good agreement with the experimental values determined by dynamic NMR spectroscopy ($11.6 \text{ kcal mol}^{-1}$ in **20** and $13.6 \text{ kcal mol}^{-1}$ in **32**) <2004PS2015>.

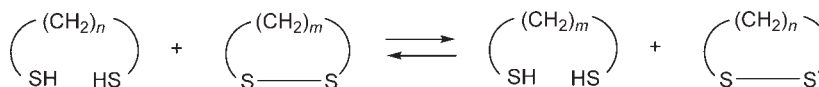


Scheme 5

The nucleophilic attack by HS^- at sulfur in 1,2-dithiane **20**, which proceeds by an addition–elimination pathway, was studied experimentally <1988PS(37)27> and theoretically in detail at the DFT and MP2 levels of theory (**Scheme 5**) <2002JOC8983>. Initially, in the gas state, thiolate and 1,2-dithiane form an ion–dipole complex (proven theoretically and experimentally <1995JOC4488, 1995JOC6731>); the reaction then proceeds by thiolate swinging toward the disulfide bond (thereby lengthening the $\text{S}^- \cdots \text{H}$ hydrogen bond) and consequent progress of the first transition state to an intermediate (the two S–S bonds at this stage are of similar length, ca. $2.5 \text{ \AA}$). The reaction then continues via the second transition state (here the S–S_{nucl} is fully formed and S–S_{ring} is ca. $4 \text{ \AA}$), leading directly to the products which stabilize, via proton transfer, to the more stable disulfide anion possessing an intramolecular hydrogen bond <2002JOC8983>.

Molecular mechanics calculations (MM2(85)) were employed to rationalize the relationship between structure and the equilibrium constants of the thiol–disulfide interconversion (**Scheme 6**) <1990JA6296>. An excellent correlation ($r=0.93$) between experimental ΔG values and calculated differences in strain energy ΔSE was obtained, $\Delta G = 0.41 \text{ kJ mol}^{-1}$ and $\Delta SE = 0.5 \text{ kJ mol}^{-1}$, thereby supporting the facile formation and stability of 1,2-dithianes.

Of note, the dithiol/disulfide equilibrium (**Scheme 6**) has been successfully employed as a luminescent molecular switch <2006CEJ689>.

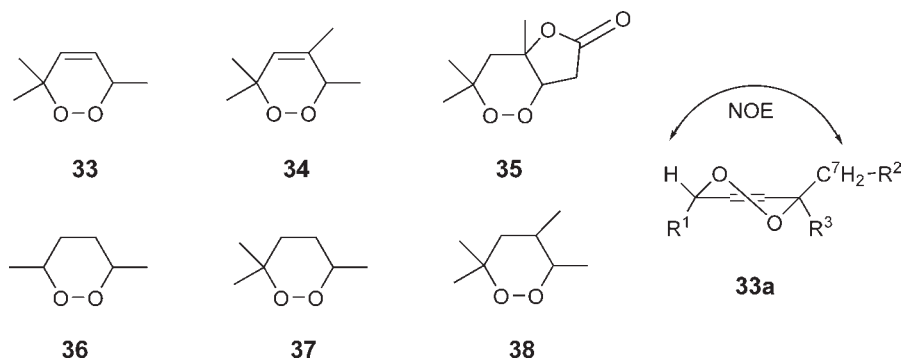


Scheme 6

8.10.3 Experimental Structural Methods

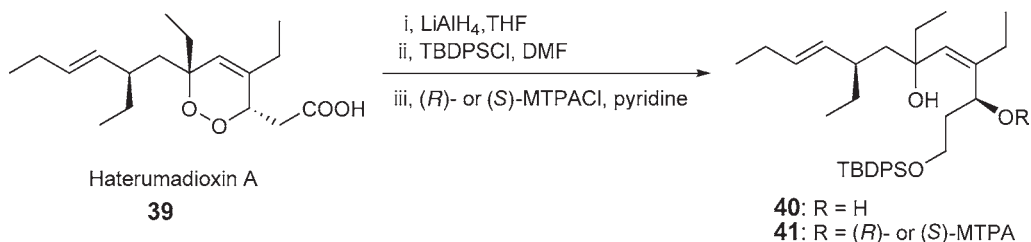
The microwave spectrum of 3,6-dihydro-1,2-dioxin **2** was measured in the frequency range of 10–26 GHz at dry ice temperature <1994JST(323)79>; the structures on the basis of the rotational constants are half-chair conformers which readily interconvert at ambient temperature by ring puckering. This interconversion process could be frozen out spectroscopically and its free energy of activation determined ($\Delta G^\ddagger = 9.82 \text{ kcal mol}^{-1}$) by low-temperature NMR.

There are three classes of cyclic peroxides (**33** and **34**; **35**; and **36–38**) that are commonly associated with marine sponges (cf. **Scheme 7**): steroidal norsesterterpenoid and norditerpenoid peroxides <1999NPR55>. Numerous examples have been described, but during the 1980s and the early 1990s, in many cases, the relative and absolute stereochemistries were not defined. Later, considerable progress was made in addressing this deficiency by employing a full complement of NMR experiments. With respect to the substituents on the six-membered ring, 3,3,6-tri- and 3,4,6,6-tetrasubstituted 3,6-dihydro-1,2-dioxins and 3,6-di-, 3,3,6-tri-, and 3,3,5,6-tetrasubstituted 1,2-dioxanes (**Scheme 7**) were studied stereochemically and for this NMR parameters proved to be unequivocally indicative (*vide infra*).



Scheme 7

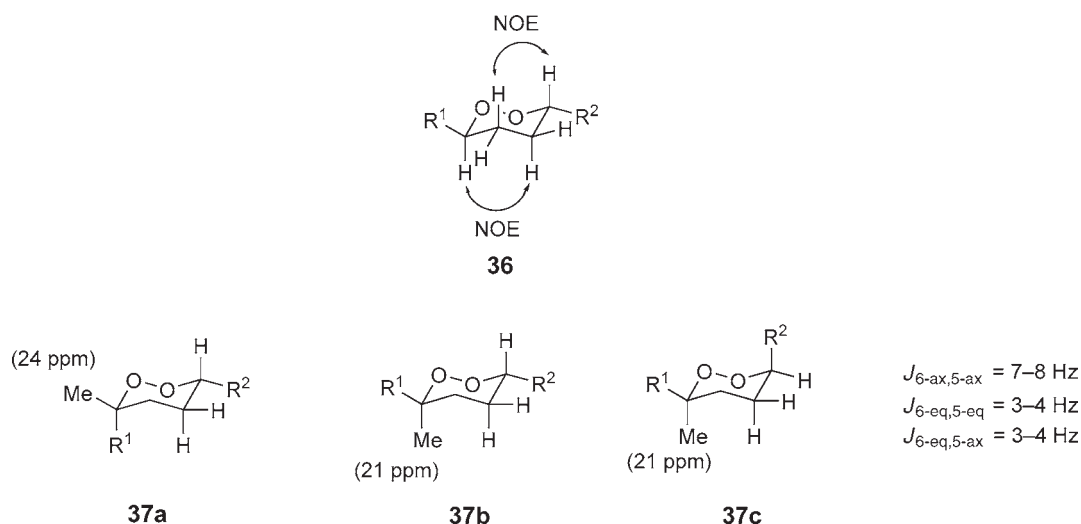
The 3,6-dihydro-1,2-dioxins **33** and **34** adopt half-chair conformers and display almost identical vicinal H,H-coupling constants which can be analyzed according to the Karplus relationship to estimate the H,H-dihedral angles <1986JOC4260>. However, it was an NOE (1%) between H-3 and H-7 that confirmed unequivocally the *cis*-configuration in **33a** (see Scheme 7) <2005JNP759, 2001JNP356, 1993JNP2178>. Previously, the loss of O₂-characteristic for cyclic peroxides – was identified by the presence of the [M – 32]⁺ peak in high-resolution mass spectrometry (MS) <1991JNP1451>. The absolute stereochemistry of C-3 was determined using Mosher's method <1991JA4092>: reduction of **39** by LiAlH₄ followed by *t*-butyldiphenylsilyl (TBDPS) chloride/imidazole protection yielded the ether **40** and treatment of **40** with (*R*)- or (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) chloride provided the two (*S*)- and (*R*)-MTPA esters **41a** and **41b**, the signals of which were assigned by 2-D NMR spectroscopy. Evaluation of $\Delta\delta$ (ppm) ($\delta_S - \delta_R$) established that the absolute stereochemistry of C-3 is 3*S* (Scheme 8). In the same manner, the absolute stereochemistry of the first sponge-derived polyketide peroxide **35** (Scheme 7) was also determined <1995JNP27>.



Scheme 8

1,2-Dioxanes **36–38** prefer chair conformers; the equatorial orientation of the 3,6-substituents in **36** was determined unequivocally by the NOEs between H-3_{ax} and H-5_{ax} and between H-4_{ax} and H-6_{ax} <2000T6031, 2000TL429, 2006TL2175> (Scheme 9). If the 1,2-dioxane ring is 3,3,6-trisubstituted (e.g., **37**) and one of the 3-substituents is methyl, careful examination of ¹H and ¹³C NMR spectra indicated a number of features correlating with specific stereochemical configurations **37a–c**: <1985T3391> (1) 3-Me_{ax} is shielded compared with 3-Me_{eq} and (2) ³J_{H-6ax,H-5ax} is 7–8 Hz, larger than either ³J_{H-6eq,H-5eq} or ³J_{H-6eq,H-5ax}, both of which are smaller than 4 Hz (Scheme 9). X-Ray structures in the solid state were in agreement with the solution-obtained assignment <2004JNP1611, 2001JNP1332, 2001JNP522, 1999JNP214, 1998AJC573, 1997TL6285, 1993JOC2999, 1987JOC339, 1987T263, 1984TL931>. Using this approach, a number of sponge-based sesterterpenes have been stereochemically assigned <2004JNP112, 1993AJC1363, 1991JNP190, 1991JOC2112, 1988T1637, 1988CC523, 1987JNP225>. When 3-methyl is present instead of 3-methoxy, in addition to the stereospecific vicinal coupling constants, NOEs between axial protons and the Me groups can also be employed <2001JNP131, 1998JNP491>. The absolute stereochemistry at C-3 was again established experimentally by application of Mosher's method <1999T7045, 1998JNP525, 1998JNP1033, 1998HCA1285>.

The same NMR spectroscopic analysis (³J_{ax,ax} values and NOEs between 1,3-diaxial protons and/or protons on the substituent) was employed to assign the 3,3,5,6-tetrasubstituted analogs **38** <2004JNP221, 2003JNP655, 2002JNP1509, 2001T9379, 2001JNP281, 2000T7959, 2001JNP281, 1998JNP1427, 1998JNP1038, 1996JNP219, 1994JNP123, 1993JNP1827>.

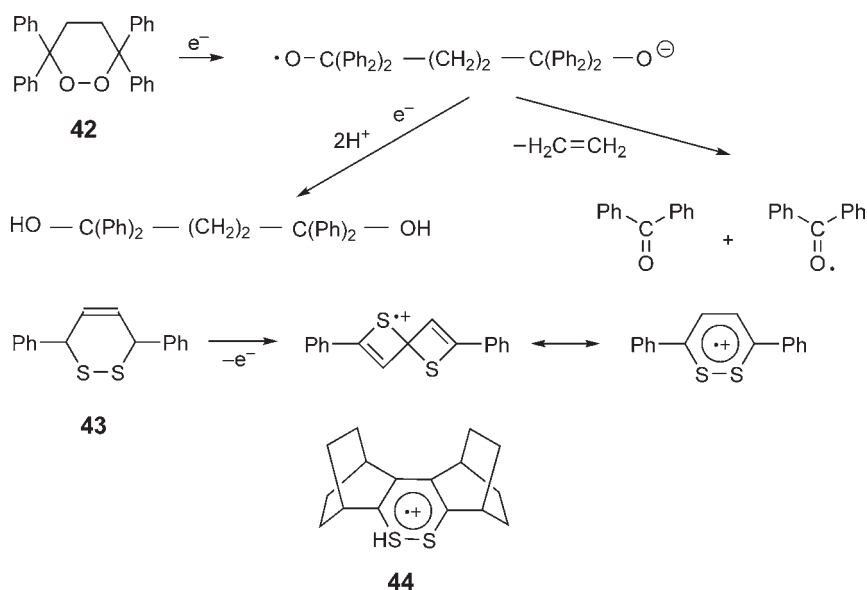


Scheme 9

The structure of a natural product hexacyclinol, a polycyclic endoperoxide, was reassigned on the basis of calculated ^{13}C chemical shifts (HF-gauge-independent atomic orbital (GIAO) level of theory) [<2006OL2895>](#).

Cyclic peroxides possess a variety of biological activities, and although most of the mechanisms of these activities are still unclear, it has been suggested that they could be mediated by capture of OH radicals generated immediately or further along during decomposition. Radical generation was confirmed by ESR studies using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a spin-trapping reagent; neither DMPO nor the peroxides alone gave rise to any signals but when DMPO was mixed with peroxides at room temperature, small ESR signals consisting of a 1:2:2:1 quartet were observed [<1991CPB545, 1985MI25>](#). The equal nitrogen and hydrogen hyperfine coupling constants (14.86 G) in these spectra are characteristic of the OH radical spin adduct of DMPO. Direct involvement of water in the decomposition of the peroxides in aqueous solution was confirmed by an ^{18}O -isotopic tracer experiment [<1991CPB545>](#).

Furthermore, electron transfer (ET) to the O–O bond is believed to be critical to the bioactivities of the cyclic peroxides [<2003CC1246>](#) and the ET reaction chemistry of 3,3,6,6-tetraphenyl-1,2-dioxane **42** has been studied by cyclic voltammetry. Reaction products, besides the expected diol and benzophenone, were identified based on the standard reduction potentials and product analysis ([Scheme 10](#)).



Scheme 10

The one-electron oxidation of 3,6-diphenyl-3,6-dihydro-1,2-dithiin **43** by cyclic voltametry yielded the corresponding 1,2-dithiin radical cation, absorbing at 330 and 520 nm, respectively (several additional absorptions at 600–1100 nm are also characteristic for it); the presence of several isosbestic points confirmed the stability of the radical cation (Scheme 10) <2006PCA2039>. The radical nature was confirmed by ESR spectroscopy which showed a well-resolved triplet at $g=2.0095$ with hyperfine splitting $a_H=0.70$ mT. This can be attributed to the coupling to the two magnetically equivalent protons, and a symmetrical satellite splitting to ^{33}S in the 1,2-dithiin ring ($I=3/2$, 0.75% natural abundance). Parallel DFT calculations reveal a moderately twisted structure of the radical cation. Previously <2002JA15038>, the 1,2-dithiin radical cation **44** (Scheme 10), absorbing at 428 nm, was produced and identified by the same methods; however, the 1,2-dithiin ring moiety proved to be planar and a nine-line ESR signal was obtained and interpreted from spin density calculations: the spin densities on α and β carbons are transmitted to the corresponding *anti*-protons ($\text{H}_\alpha^{\text{anti}}$, $\text{H}_\beta^{\text{anti}}$) of the ethano bridges via a W-coupling path. Because of similar values on $\text{H}_\alpha^{\text{anti}}$ and $\text{H}_\beta^{\text{anti}}$ (0.0015 and 0.0016, respectively), the ESR signal is split by the two sets of four equivalent *anti*-protons into the nine-line resonance <2002JA15038>.

The ^{17}O chemical shifts of 17 bicyclic 1,2-dioxanes and 3,6-dihydrodioxins (relative to 1,4-dioxane, $\delta(^{17}\text{O})=254$ ppm in benzene, referenced externally to water) have been published <1985JOC4484> and show a fair linear correlation to the ^{13}C chemical shifts of the corresponding carbons in the hydrocarbon analogs. The O–O stretching vibration of some alkyl-substituted 1,2-dioxanes has also been studied in detail <1984CJC277> wherein the O–O stretching frequencies are all near 730 cm^{-1} .

The absolute configuration of an endoperoxide, acetylmajapolene A **45a**, isolated from *Laurencia* was determined by vibrational circular dichroism (VCD) <2001T1483>: the diastereomeric mixture of **45a** was separated by high-performance liquid chromatography (HPLC) (cf. Figure 2); ^1H NMR spectra of the diastereomers **45b** and **45c** were similar, impossible to assign the stereochemistries <2006TL4389>. But the IR spectra of both **45b** and **45c** showed a characteristic band at 1048 cm^{-1} , which was attributed to the endocyclic peroxide moiety and employed for the VCD studies. Next, the preferred conformers of **45b** and **45c** were calculated theoretically at the DFT level and the VCD spectra were simulated. Experimental and population-weighted theoretical VCD spectra for both **45b** and **45c** were found in excellent agreement, with the peroxide band at 1048 cm^{-1} showing an opposite sign; unambiguously, the absolute configurations of **45b** as 1*R*,4*R*,7*S*,10*S* and of **45c** as 1*S*,4*S*,7*S*,10*S* could be assigned <2006TL4389>.

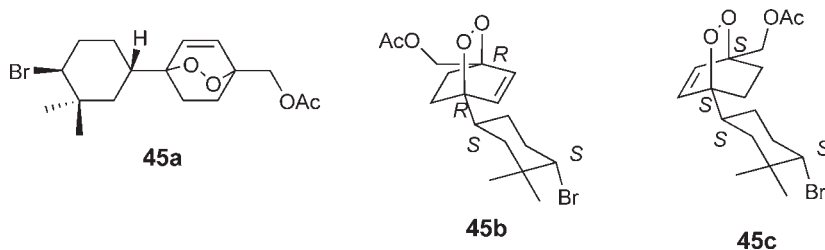
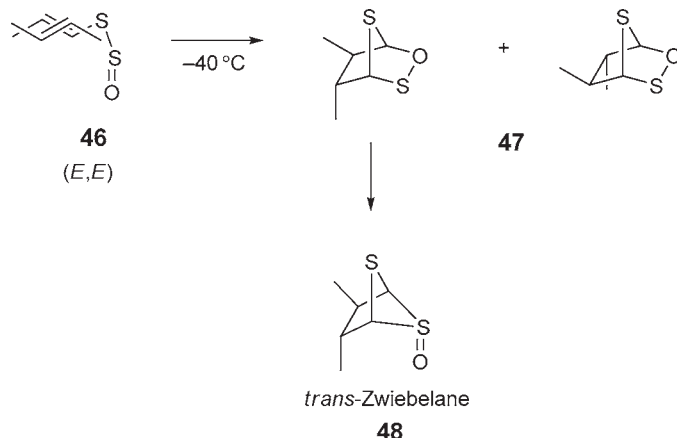


Figure 2 Diastereomers 1*R*, 4*R*, 7*S*, 10*S* **45b** and 1*S*, 4*S*, 7*S*, 10*S* **45c** of the natural product acetylmajapolene A **45a** isolated from the red algal genus *Laurencia*.

Only two reports concerning 1,2-oxathiane derivatives have been published since 1984 <1998TL1251, 1992AGE1135>, where, for example, the treatment of a series of 4-sulfanyl-1,3-diols with $\text{Et}_3\text{N}/\text{TsCl}$ in CH_2Cl_2 provided a number of substituted 1,2-oxathianes in high yield by cyclization. The stereochemistries of the stereogenic centers were confirmed by NMR spectroscopy where the anticipated chair conformations of the 1,2-oxathianes were consistent with the observed NOE enhancements and characteristic ax/ax versus ax/eq and eq/eq vicinal H,H-coupling constants <1998TL1251>.

During the rearrangement of the isomeric thiosulfonates **46** (cf. Scheme 11) at -40°C , all four 5,6-*exo/endo*-isomers of 5,6-dimethyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane **47** were obtainable in various yields depending on the stereochemistry of the starting material <1992AGE1135>. The isomers react easily with thiophenol by ring contraction to

the corresponding thiolanes. It is plausible that the 5,6-*endo,endo*- and the 5-*endo*-6-*exo*-isomers isomerize to *cis*- and *trans*-zwiebelanes **48**, respectively, during the cutting of anions (cf. [Scheme 11](#)). Of note, the latter compounds are novel antithrombotic agents [<1992AGE1135>](#).

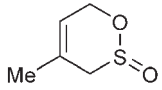
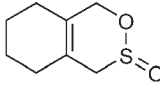
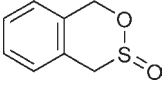
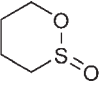
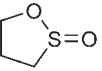
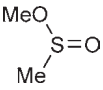
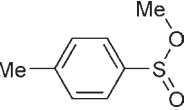


Scheme 11

On the other hand, both structures and chemistries of the stable sulfoxides (sultines) and sulfones (sultones) of 1,2-oxathianes and their derivatives have been well documented (*vide infra*).

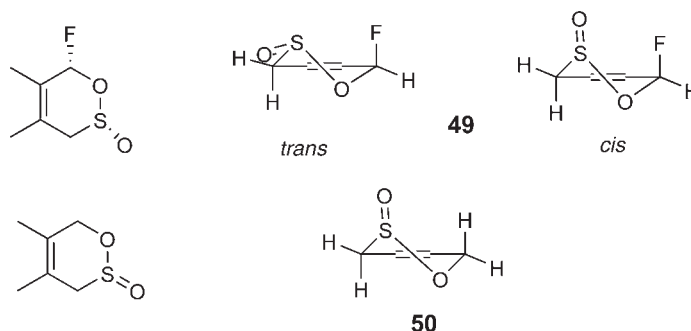
At low temperature and in the presence of catalyst, simple conjugated dienes add SO_2 reversibly via hetero-Diels-Alder addition and generate 3,6-dihydro-1,2-oxathiine 2-oxides **8** (sultines) [<1992JA9210, 1993TL6269, 1998JA13276>](#). The products are unstable above -50°C and at higher temperatures undergo fast cycloreversion liberating the starting dienes and SO_2 . Therefore, initially, sultines were only characterized in solution by NMR and, because of their instability at higher temperatures, were not consequently isolated and characterized in the solid state (the liberated diene also polymerizes above -30°C in the presence of SO_2 [<2000CEJ1858>](#)). In addition to the sultines, five-membered sulfolene structures were also obtained. As both the ^1H and ^{13}C NMR spectra of the different structures were expected to be very similar, providing a distinction between the two products was problematic. For this reason, ^{17}O NMR data of comparable sultines and sulfolenes were acquired and compared with theoretical ^{17}O NMR chemical shifts obtained from *ab initio* GIAO HF, MP2, and many-body perturbation theory (MBPT) calculations [<2000CEJ1858>](#). The experimental ^{17}O NMR data of sultines gathered thus far are presented in [Table 1](#). Even with varying substituent effects, degree of unsaturation of the sultine ring, and annulation, the two oxygens of the sulfinate

Table 1 ^{17}O chemical shifts (relative to internal 1,4-dioxane) for sultines in CD_2Cl_2 at ambient temperature (or lower) [<2000CEJ1858>](#)

	79 ppm 116 ppm		87 ppm 133 ppm
$\text{CD}_2\text{Cl}_2/\text{SO}_2$ (1:1), at -80°C		$\text{CD}_2\text{Cl}_2/\text{SO}_2$ (1:1), at -40°C	
	109 ppm 135 ppm		98 ppm 115 ppm
		CDCl_3 , at 25°C	
			114 ppm 139 ppm
		CDCl_3 , at 25°C	
	107 ppm 142 ppm		97 ppm 109 ppm

moiety have similar chemical shifts, and quantum-chemical calculations were therefore requisite. By considering electron correlation effects in the calculation of the ^{17}O chemical shifts of the sultine oxygens and, additionally, of the respective oxygens in the six-membered hetero-Diels–Alder adducts and the five-membered cheletotropic addition products, the likely structures could be distinguished readily on the basis of their ^{17}O NMR spectra.

Of late, stable sultine derivatives have been crystallized and their structures determined by X-ray diffraction studies. 6-Fluoro-3,6-dihydro-1,2-oxathiin 2-oxide derivatives **49** prefer a sofa conformation (the ring oxygen lies almost in the plane of the four carbon centers) <2001CC1214, 2002CEJ1336> and its $\text{S}=\text{O}$ bond resides in a pseudoequatorial orientation in the *trans*-isomer (cf. **Scheme 12**) but in a pseudoaxial position in the *cis*-isomer. The fluorine substituent retains its stable pseudoaxial orientation in both instances. High-level quantum-chemical calculations confirm the existence of a stabilizing enthalpic anomeric effect which was interpreted in terms of an $n_{\text{O1}} \rightarrow \sigma^*_{\text{C(6)-F}}$ hyperconjugative interaction <2002CEJ1336>. Detailed NMR studies, however, suggest that these sultines exist as interconverting equilibria of several conformers in solution <2001CC1214, 2002CEJ1336>.



Scheme 12

In the corresponding nonfluorinated 4,5-dialkylsultines, the sultine ring adopts a half-chair conformation with the $\text{S}=\text{O}$ bond in a pseudoaxial orientation **50** (cf. **Scheme 12**) <2003CEJ4911>. Again, hyperconjugative interactions within the sulfinyl moiety (the 'anomeric effect') were found to be responsible for the conformational preference.

Sultines can be versatile synthetic intermediates; for example, they undergo ring-opening reactions, alkylation, reductive desulfurization <B-1990MI240>, and oxidation at sulfur to give sultones.

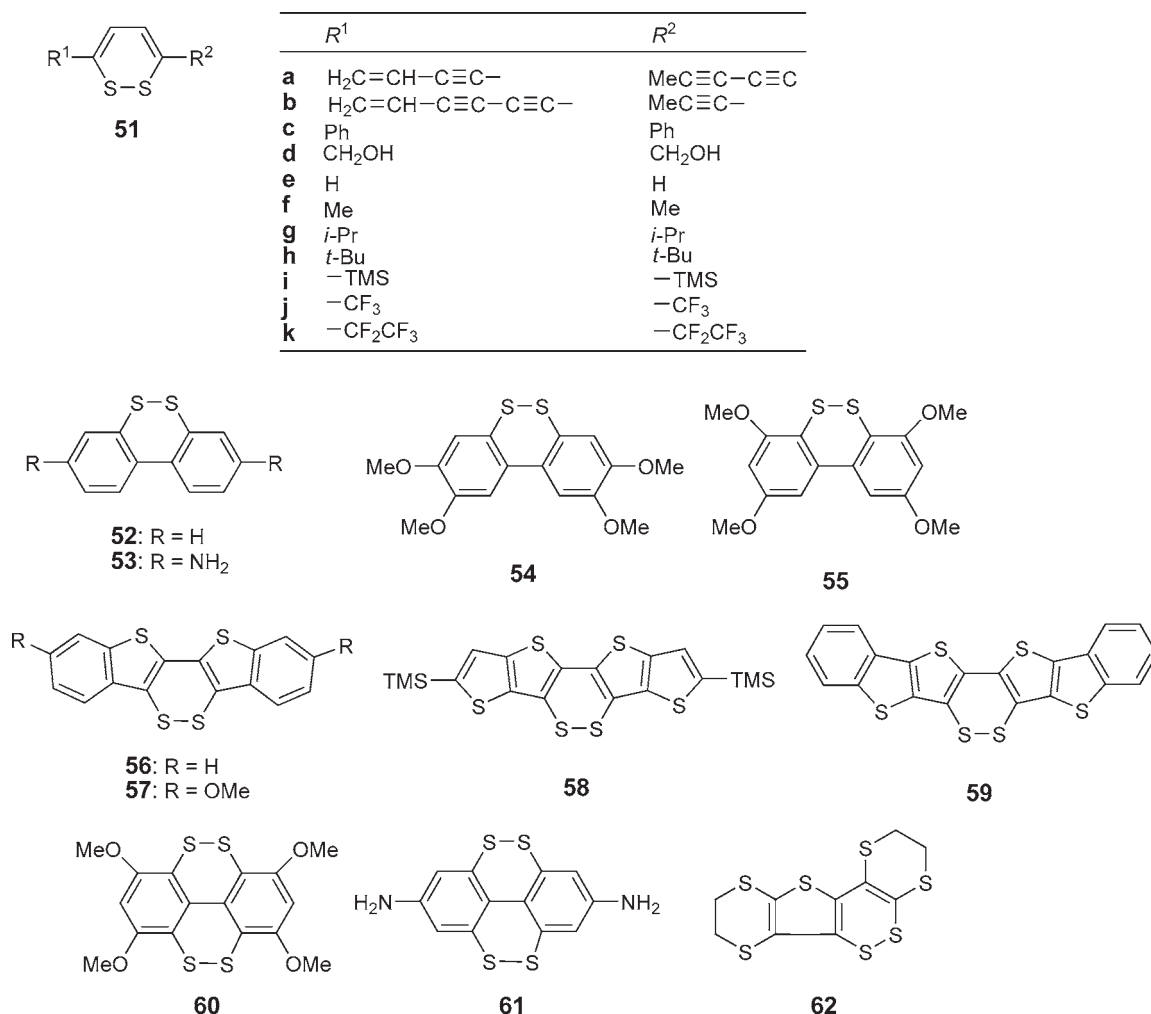
Only structures pertaining to the saturated 1,2-oxathiane 2,2-dioxides have been published. The preferred chair conformer is preserved in both polycyclic <1989AGE202, 1998CEJ1480, 1996CCC431, 1994JOC3687> and spiro derivatives <1998EJO2073> with the sulfone oxygens in pseudoaxial and pseudoequatorial orientations.

The rotational spectrum of 1,2-dithiin was measured using a pulsed-beam microwave spectrometer in the 8–18 GHz range <1996JSP(180)139>; by Stark effect measurements, the electric dipole moment was also determined ($\mu_a = 1.85$ D). The molecule proved to be of C_2 symmetry with a twisted conformation about the S–S bond and a C–S–S–C dihedral angle of 53.9° .

In spite of the absence of a typical chromophore, 1,2-dithiin is a bright reddish-orange color. Absorption maxima were found at 451 (2.75 eV), 279 (4.36 eV), and 248 nm (5.00 eV), and the colored band was assigned to a ^1A excitation <1991JST(230)287>. The main reason for the colored absorption of 1,2-dithiin is the low HOMO–LUMO gap of the KS orbitals which amounts to only 3.6 eV (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital; KS = Kohn–Sham) <2000JMM177>. By comparison, saturated 1,2-dithiane is colorless (290 nm).

The spectroscopic data of a number of 1,2-dithiin derivatives (**Scheme 13**) are summarized in **Table 2**. Comparison of the ^1H NMR spectroscopic data of the dithiins **51** with those of the corresponding thiophenes shows that both the α - and β -protons are significantly shielded in **51**, reflecting the presence of the ring current effect in the thiophenes <2000JA5052>.

The gas-phase photoelectron spectra of 1,2-dithiins **51e–k** and **62** (**Scheme 13**) were studied to evaluate the effect that substituents have upon the electronic structure <2002PCA5924, 2000JA5065>; it was ascertained that electron-withdrawing substituents (e.g., CF_3 or CF_2CF_3) raise the ionization energies of the four highest MOs (**Tables 3** and **4**) <2003JOC8110>. Present in the photoelectron spectra is an ionization from an orbital that is predominantly an S–S weakly bonding σ -bond; this bond is suggested to result from the lowest unoccupied MO of **51** and thus the lowest HOMO–LUMO transition can be described as a $\pi/\text{lone-pair} \rightarrow \sigma^*$ transition, thereby explaining the observed color of the compounds <2000JA5065>.



Scheme 13

Table 2 Selected spectroscopic data for 1,2-dithiins <2000JA5052>

Compound	NMR $\delta_{\text{H}-\alpha}$ ($\delta_{\text{C}-\alpha}$) ppm	NMR $\delta_{\text{H}\beta}$ ($\delta_{\text{C}-\beta}$) ppm	UV-Vis ^a λ (ϵ) nm
51e	6.07 (119.43) ^b	6.26 (129.74) ^b	452 (90)
51f	(128.47)	6.05 (125.93)	422 (47)
51g	(142.06)	6.08 (122.78)	420
51h	(146.52)	6.16 (122.02)	406 (175)
51i	(139.08)	6.43 (135.47)	478 (520)
1,2-Dithiin 1-oxide	7.18, 7.03–7.08 ^c	6.98, 7.03–7.08 ^c	
1,2-Dithiin 1,1-dioxide	7.14, 6.83 ^d	6.76, 6.94 ^d	316
51h (1-oxide)	(145.70, 138.42)	6.69, 6.64 ^c (120.01, 116.21)	314
56			468 (3.41)
57			473 (3.56)
58			4.73 (3.81)
59			480 (3.99)

^aLong-wavelength maxima only.^b $J_{\alpha,\beta} = 9.3$ Hz, $J_{\beta,\beta'} = 1.6$ Hz, $J_{\alpha,\beta'} = -0.1$ Hz.^c $J_{\alpha,\beta} = 9.5$ Hz, $J_{\beta,\beta'} = 1.1$ Hz.^d $J_{\alpha,\beta} = 10$ Hz, $J_{\beta,\beta'} = 6.5$ Hz, $J_{\alpha,\alpha'} = 10$ Hz.^e $J_{\beta,\beta'} = 7.7$ Hz.

Table 3 Ionization energies of dithiin derivatives

<i>Compound</i>	<i>Assignment</i>	<i>Position (eV)</i>	<i>Width (eV)</i>	<i>Reference</i>
51e	A	8.16	0.46	2002PCA5924
	B	9.82	0.40	
	C	10.06	0.50	
	D	11.51	0.53	
	S-S σ	12.17	0.26	
	S-C σ	12.66	0.75	
	S-C σ	13.15	0.75	
	C-C, C-H σ	14.40	0.44	
	C-C, C-H σ	14.97	0.88	
51f	A	7.78	0.46	2000JA5065
	C	9.31	0.42	
	B	9.63	0.36	
	D	10.93	0.52	
51g	A	7.67	0.46	2000JA5065
	C	9.01	0.38	
	B	9.34	0.44	
51h	A	7.65	0.46	2000JA5065
	B	8.93	0.36	
	C	9.21	0.39	
51j	A	9.10	0.47	2003JOC8110
	B	10.57	0.46	
	C	10.87	0.48	
	D	12.44	0.55	
51k	A	9.06	0.46	2003JOC8110
	B	10.44	0.36	
	C	10.67	0.49	
	D	12.10		
62	A	8.90		2000JA5065

Table 4 Oxidation potentials E (V) of **51**, **52**, and **54–62** in CH₃CN

51a–e	0.67–0.74 ^a	1.03–1.40 ^b
	0.81–0.85 ^c	
51k,l	1.25–1.48 ^a	1.40–1.67 ^b
51m	0.18 ^c	0.81 ^c
52	0.75	
54	0.59	
55	0.78	
56	0.72	1.08 (–1.54)
57	0.54	0.80 (–1.51)
58	0.63	0.91 (–1.46)
59	0.62	0.99 (–1.45)
60	1.47	
61	0.932 (1.170)	
62	0.58 ^d	

^aReversible.

^bIrreversible.

^cIn CH₂Cl₂.

^dMore potentials at 0.78 V and 0.93 V.

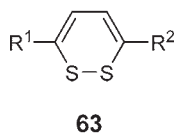
Mass spectra of the dibenzo-1,2-dithiins **52** and **53** display intense parent ions, indicating that loss of an electron gives rise to particularly stable radical cations <2000JA5052>.

The nonplanarity of substituted 1,2-dithiins was also proven by X-ray crystallography <1997LA1677, 1996T12677, 1995BCJ1193, 1994TL1973, 1994CB401, 1994AGE739, 1993ZK145, 1993ZK148>, whereby it was shown that the heterocycle adopts a half-chair conformation and the torsional angles at the S–S bond (52.6–58.9°) are those of a normal cyclic disulfide. Similarly, the X-ray structures of the dibenzo-1,2-dithiins **56** and **57** are also nonplanar <1997PCB10012, 1995PS(101)235, 1985MCL(120)277> and the dihedral angle between the two phenyl rings was measured as lying in the range 25–30° with the dihedral angles C_{Ar}–S–S–C_{Ar} and C_{Ar}–C_{Ar}–S–S being 55.6° and 41.3°, respectively. The same geometry has been reported for compounds **60** and **61** (cf. Scheme 13) <1998EJO2409>.

The electrochemistries of variously substituted 1,2-dithiins **51** and dibenzo-1,2-dithiins **52–61** (cf. Scheme 13) were studied using the technique of cyclic voltammetry in CH₃CN <1997PS(120/1)439, 1992MI725, 1985ZNB39, 1985ZNB774> and the oxidation potentials so obtained are presented in Table 4. It appears that the oxidation potentials of these compounds do not linearly correlate with their ionization potentials because of geometrical changes occurring during the electrochemical measurements that do not occur during the spectroscopic measurements <2003JOC8110> (Table 3). They are anomalously low compared with the ionization potentials of the same dithiins (*vide supra*) primarily due to the conformational difference between, for example, **51** and its cation radical. The ESR spectrum of the radical cation of **51**⁺ indicates the structure to be planar, or nearly so, and the measured *g*_{av} value is in the range of that reported for other disulfide radical cations <2000JA5052>.

Due to solubility reasons, the redox behavior of **61** was investigated <1998EJO2409> in dichloromethane (cf. Scheme 13 and Table 4); the electroreduction results in the formation of the tetrathiolate anion of **61** but the latter was not found to be oxidizable <1998EJO2409>.

A number of reddish 1,2-dithiin polyines, called thiarubrines (e.g. thiarubrine-A, **63a**), have been isolated by reversed-phase HPLC from the root extracts of Asteraceae plants (Scheme 14) <1993P224, 1993P113, 1990P2901, 1989P3523, 1988P3533> and subsequently shown to be bioactive <1986MI51, 1985E419, 1985MI225>. The absorption maxima observed in the region 484–490 nm are characteristic for the highly conjugated moiety that is present. The retention times of the isolates indicated tentatively their polarity and their elemental compositions were determined by accurate mass measurements. Fragmentations in the mass spectra involving the loss of sulfur are common to these types of dithiin natural products. The structures were fully characterized by ¹H NMR spectroscopy and characteristic features are (1) the ABX-coupling patterns of R², (2) the AB coupling of the 1,2-dithiin moiety, and (3) the long-range coupling constant ⁶J_{H,H} of R¹(Me) with the corresponding ring proton.

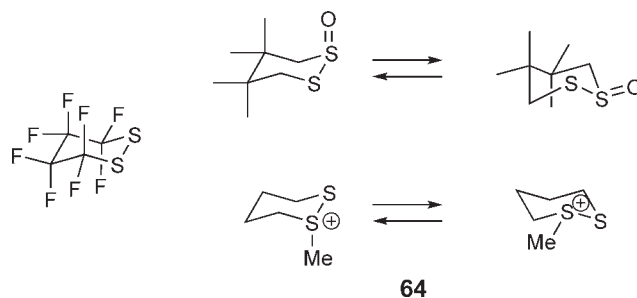
	R ¹	R ²	Compound
	Me–C≡C–	(C≡C) ₂ CH=CH ₂	63a
	Me(C≡C) ₂	–C≡C–CH=CH ₂	63b
	Me–C≡C–	(C≡C) ₂ HC–O–CH ₂	63c
	Me–C≡C–	(C≡C) ₂ CHOH–CH ₂ OH	63d

Scheme 14

The X-ray structures of dibenzo-1,2-dithiin **52** (cf. Scheme 13) and its 1,1-dioxide, 1,1,2-trioxide, and 1,1,2,2-tetraoxide have been reported <2005HAC346>. The dithiin moiety has a typical twisted conformation, as reported for other dithiins <1996JA4719, 1996JSP139, 2002JA15038>, and the S–S bond lengths vary upon oxidation of the sulfur atoms in the order S–S < SO–S < SO₂–S < SO₂–SO < SO₂–SO₂, otherwise the C–S bond lengths and O–S–C bond angles in each of the four structures are within or very close to the normal range.

Both the measured dipole moments and ¹H NMR spectra of 1,2-dithiane, its 4,4,5,5-tetradeutero analog, 3,3,6,6-tetramethyl-1,2-dithiane, and the *cis/trans*-isomers of 3,6-dimethyl-1,2-dithiane provided unequivocal evidence for the chair conformation adopted by the saturated six-membered ring, supported further by X-ray solid-state structures. Other conformers, for example the twist conformer, were not detected <B-1995MI201>.

Perfluoro-1,2-dithiane (**Scheme 15**), previously reported in error, is conformationally stiff at ambient temperature and fully rigid at -64°C , having a barrier to ring interconversion of $\Delta G^{\ddagger}$ in the range of $14.0\text{--}14.5\text{ kcal mol}^{-1}$ <1998JFC(90)97>, a value which is appreciably higher than for other saturated six-membered ring heterocycles <B-1995MI201>. The corresponding barrier to ring interconversion of 1,2-dithiane proved to be enthalpy driven ($\Delta S^{\ddagger} = 2 \pm 2\text{ cal mol}^{-1}\text{ K}^{-1}$); the $\Delta G^{\ddagger}$ value of $11.9\text{ kcal mol}^{-1}$, which was obtained, lies in the normal range expected for this kind of heterocyclic compound <1993JOC3805>.



Scheme 15

The conformational equilibria of 1,2-dithiane 1-oxide and its 2,2,3,3-tetramethyl analog, rare but stereochemically extremely interesting products, were investigated by variable-temperature NMR spectroscopy <1988JOC3334, 1984T1477>. The axial conformers dominate the equilibria ($\Delta G^{\circ} > 1.7\text{ kcal mol}^{-1}$) to such an extent that the equatorial conformers could not be detected (**Scheme 15**). As indicators for an axial S=O bond orientation, the large chemical shift difference of the C-6 protons ($\Delta\delta = 1.45\text{ ppm}$), relevant NOEs between spatially adjacent protons and an ^1H NMR lanthanide-induced shift (LIS) study, as well as the 11–13 ppm shielding of C-5 relative to the corresponding carbon atom in 1,2-dithiane, were all employed. It was suggested that stereoelectronic effects ($n_{\text{S}} \rightarrow \sigma^*_{\text{S=O}}$, the ‘anomeric effect’) strongly contribute to the unusual stability of the axial conformer <1988T5653>.

Both ^1H and ^{13}C NMR and *ab initio* MO calculations of the 1-methyl-1,2-dithianium cation **64** and of a number of methyl-substituted derivatives proved a fixed conformation in which the $\text{S}^+ - \text{Me}$ group is axial (**Scheme 15**) <1985PS(23)169, 1985JA2807>. The decisive parameter for determining this conformation was the long-range coupling constant $^4J_{\text{SMe,H-6ax}}$ ($[0.3]\text{ Hz}$) based on the well-documented results from conformationally rigid steroids and terpenes. Each 1,2-dithianium cation was determined to be conformationally and configurationally rigid. Calculations favored the axial over the equatorial position by ca. 3 kcal mol^{-1} ; the origin of this stabilization is associated with the strong $n_{\text{S-2}} \rightarrow \sigma^*_{\text{S-Me}}$ hyperconjugative interaction together with repulsive lone-pair interactions (minimized in the axial orientation). The stereoelectronic effect stabilizes the 1,2-dithiane ring system because ring strain effects obviously play no role.

Both the cation and anion radical of 1,2-dithiane have been studied theoretically, using the MNDO method, and experimentally by ESR spectroscopy. In the cation radical, the ring adopts a chair conformation possessing C_2 symmetry with a calculated torsional angle for the C–S–S–C moiety of ca. 8° only <1984J(P2)407>. On varying the temperature, the ESR spectrum of the anion radical displayed line width changes, a phenomenon indicative of dynamic ring interconversion <1993JOC3805>. At -70°C , the spectrum shows different α -splittings for the pseudoaxial and pseudoequatorial protons ($a_{\text{H}} = 9.3$ and 3.0 G , respectively) and dihedral angles of 3° and 58° could be thus determined thereby proving the chair conformation of 1,2-dithiane to be affected inappreciably by the presence of the additional unpaired electron. The only variation in the radical is the lengthening of the S–S bond due to the fact that this three-electron bond is weaker than the normal two-electron S–S bond. Computer line shape analysis yielded the free energy of activation for the ring inversion process ($\Delta G^{\ddagger} = 5.8\text{ kcal mol}^{-1}$).

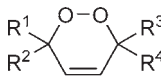
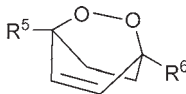
By a pulse radiolysis study, both the mechanism and corresponding rate constants of the formation of the *trans*-4,5-dihydroxy-1,2-dithiane radical anion were quantitatively determined <1997JA5735, 1987ZNC134>; the reaction was monitored by ultraviolet–visible (UV–Vis) spectroscopy.

8.10.4 Thermodynamic Aspects

The thermodynamic ideal gas properties of 3,6-dihydro-1,2-dioxin **2** <1992MI121>, 3,4-dihydro-1,2-dioxin **3**, and 1,2-dioxane **4** <1997CPL(268)175, 1997PCA2471> have been calculated by a difference method (formation enthalpies were suggested to be the same for the 3,4- and 3,6-dihydro-1,2-dioxin isomers) <1992MI121>, the semi-empirical PM3-method (by scaling PM3 calculated ΔH°_{f298} empirical values with experimentally available ΔH°_{f298} data) <1997PCA2471>, and *ab initio* MP2 calculations using isodesmic reactions <1997CPL(268)175>. Considering that experimental data are not available, the rather different IR spectra that were calculated were not evaluated but the enthalpies and entropies of formation can be considered acceptable on the basis of theoretical results for other peroxides in comparison to their known experimental data: $\Delta H^\circ_{f298} = -31.74 \pm 0.96 \text{ kcal mol}^{-1}$ (1,2-dioxane) <1997CPL(268)175>, $-11.45 \text{ kcal mol}^{-1}$ (3,4-dihydro-1,2-dioxin) <1997PCA2471> and $-29.86 \text{ kcal mol}^{-1}$ (3,6-dihydro-1,2-dioxin) <1992MI121>; $S^\circ_{298} = 73.79 \text{ cal mol}^{-1} \text{ K}^{-1}$ (1,2-dioxane), $75.07 \text{ cal mol}^{-1} \text{ K}^{-1}$ (3,4-dihydro-1,2-dioxin) <1997PCA2471>; and $74.48 \text{ cal mol}^{-1} \text{ K}^{-1}$ (3,6-dihydro-1,2-dioxin) <1992MI121>.

Substituted mono- and bicyclic 1,2-dioxins are considered good donors though they only form weak electron donor–acceptor (EDA) complexes with tetracyanoethene (TCNE) <1993J(P2)243>. The formation of EDA complexes is evident by the change of colorless solutions of the peroxides in CH_2Cl_2 to yellow/orange/red-colored solutions upon addition of TCNE. The CT absorption bands of the EDA complexes and their oxidation potentials are given in Table 5, wherein the bicyclic peroxides **66** are seen to be the better donors compared with the corresponding monocyclic analogs **65**. The formation constants of the EDA complexes are small ($2.1\text{--}2.3 \text{ dm}^3 \text{ mol}^{-1}$), indicating that the EDA complexes are weak.

Table 5 Oxidation potentials (E°_{ox}) of the peroxides **65** and **66** together with the CT absorption maxima (λ_{max}) of the TCNE·EDA complexes

							
65				66			
R^1	R^2	R^3	R^4	R^5	R^6	E_{ox}^{a}	$\lambda_{\text{max}}^{\text{b}}$ (nm)
Ph	H	Ph	H			2.35	368
<i>p</i> -MeC ₆ H ₄	H	<i>p</i> -MeC ₆ H ₄	H			2.12	394
<i>p</i> -MeC ₆ H ₄	H	Ph	H			1.75	475
<i>p</i> -MeOC ₆ H ₄	H	<i>p</i> -MeOC ₆ H ₄	H			1.67	492
Ph	H	H	H			~2.4	375
<i>p</i> -ClC ₆ H ₄	H	H	H			~2.4	392
<i>p</i> -MeC ₆ H ₄	H	H	H			2.14	392
<i>p</i> -MeOC ₆ H ₄	H	H	H			1.86	494
				Me	<i>iso</i> -Pr	1.92	448
				Ph	Ph	1.80	362

^aMeasured in acetonitrile; values are all irreversible.

^bMeasured in CH_2Cl_2 .

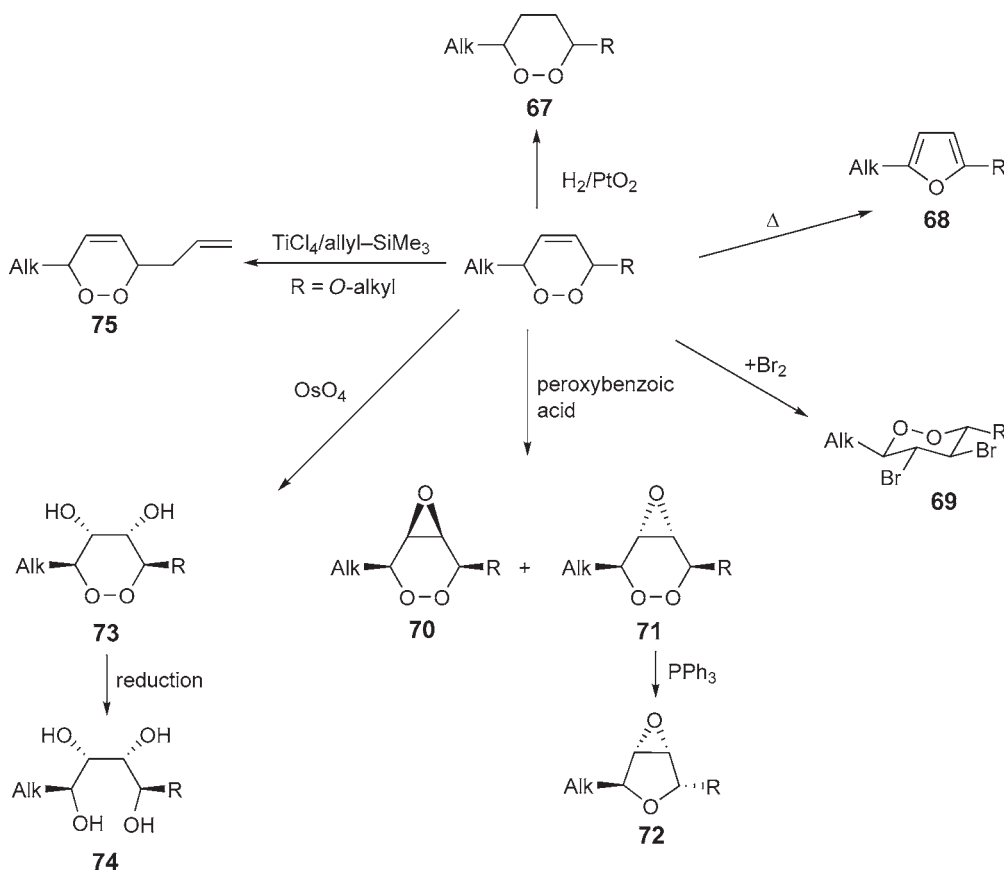
8.10.5 Reactivity of Fully Conjugated Rings

The syntheses and reactivities of fully conjugated rings for these kinds of compounds have not been reported in the available literature. However, the positional isomers of the 1,2-disubstituted benzenes have been theoretically studied using *ab initio* calculations at the HF, MP2, and CCSD(T) levels of theory and also by using the DFT theory <2000JA11173> and are discussed, together with the 1,3- and 1,4-positional isomers, in Chapter 8.11.

8.10.6 Reactivity of Nonconjugated Rings

8.10.6.1 1,2-Dioxins

The stability and reactivity of 3,6-dialkyl-3,6-dihydro-1,2-dioxins have been examined (Scheme 16) <1984J(P1)2199>. Hydrogenation yielded the fully saturated 1,2-dioxane derivative **67** and heating in various solvents at reflux or at 80 °C gave an appreciable amount of the corresponding furan derivative **68** (at 450 °C, decarboxylation was also observed <1989CC1674>); bromination in CD₂Cl₂ was complete within 5 min and with almost quantitative yield (the dibromide **69**, by the H-4 ¹H NMR coupling pattern (14.0 and 8.0 Hz), evidently has all four substituents in equatorial positions); epoxidation (at room temperature with 3-chloroperoxybenzoic acid) yielded quantitatively the epoxide (the configuration was not assigned) but oxidation with singlet oxygen and reduction with either NaBH₄ or diimide in dry methanol were both unsuccessful. The epoxidation was later proven to deliver both isomers **70** and **71** with moderate diastereoselectivity (the major *trans*-isomer was identified by the virtually nonexistent ³J_{H-3,H-4} coupling, which is large in the *cis*-isomer) <2003JOC5205>.



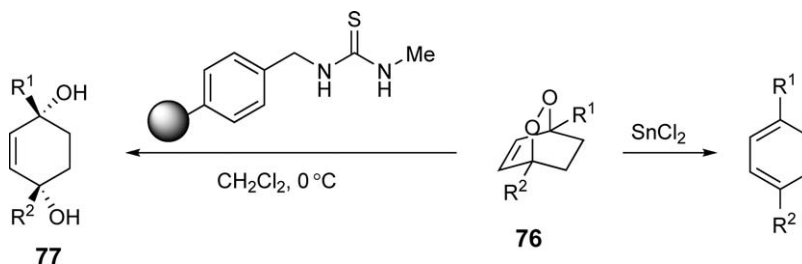
Scheme 16

3,6-Disubstituted-3,6-dihydro-1,2-dioxines can be dihydroxylated readily with OsO₄ to furnish the 4,5-diols **73** in yields of 33–98% and with *de* values not less than 90%. Subsequent reduction of the peroxy bond allowed the stereospecific synthesis of tetraols **74** without the use of protecting groups <2006JOC7236>.

When a mixture of the *trans*-epoxide **71** and triphenylphosphine was heated to reflux in CDCl₃, the ring-contracted product **72** was isolated in 81% yield (Scheme 16) <2004JOC2577>. Hydrogenation of substituted 3,6-dihydro-1,2-dioxins was explored under several sets of conditions <1995SC2613> whereby a high yield was obtainable by catalytic reduction over PtO₂.

Alkylation of 3-alkoxy-3,6-dihydro-1,2-dioxin derivatives in the presence of TiCl₄ or SnCl₄ produced allylated dioxins **75** in moderate yields (Scheme 16) <2000JOC8407, 1993JA6458>; the products were isolated as 3:2 *cis*/*trans*-mixtures, regardless of the stereochemistry of the starting material and identified by the ³J_{H-3,H-4} coupling constant.

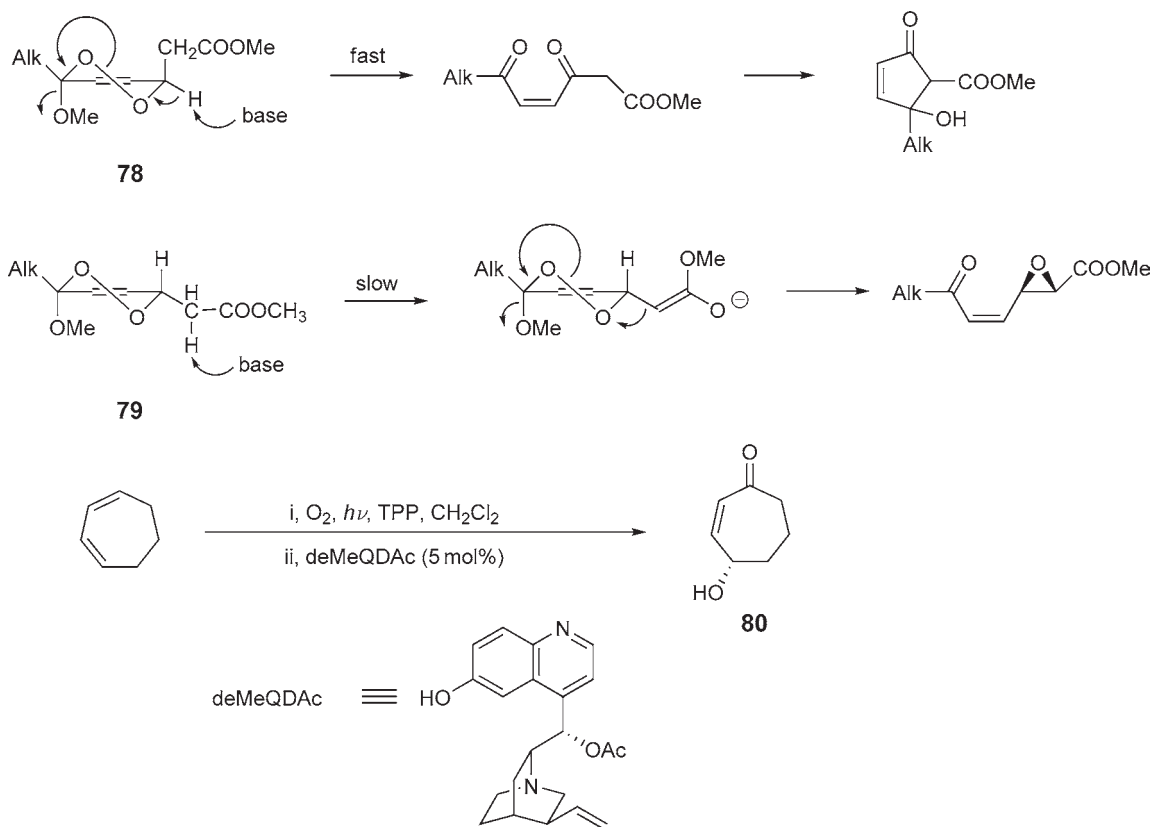
The retro-Diels–Alder reaction of bicyclic 1,3-diene 1,4-endoperoxides **76** with SnCl_2 regenerated the starting dienes in 15–70% yield depending on the structure of the 1,2-dioxane moiety (Scheme 17) <1988CL1477>. When treated with catalytic amounts of $\text{RuCl}_2(\text{PPh}_3)_3$ in CH_2Cl_2 , the O–O bond was cleaved to yield a mixture of products arising from fragmentation, reduction, and disproportionation <1989JOC5292>; if a solid-supported *N*-methylthiourea reagent was used, the O–O bond was hydrogenolyzed providing the *cis*-diol **77** in excellent yield (Scheme 17) <2005CC4426>.



Scheme 17

The photolysis and thermolysis of 3,3,6,6-tetraaryl-1,2-dioxanes have also been studied <1996TL8181>.

The base-catalyzed decomposition of a cyclic peroxy ketal shows a strong stereochemical dependence <1994JOC1726>. In one of the isomers, **78**, the CH_2COOMe substituent at position 6 must be in a pseudoaxial orientation, as in this position the corresponding 6-hydrogen proved *anti*-periplanar to the O–O bond resulting in facile base-catalyzed E2 elimination. The same hydrogen is *gauche* in isomer **79** and E2 elimination cannot occur. However, enolization of the ester group in **79** affords a pseudoequatorial enolate, suitably oriented for $\text{S}_{\text{N}}2$ reaction to provide finally the epoxide (cf. Scheme 18) <1994JOC1726>; the reaction products were unequivocally assigned by the H,H-coupling patterns in their NMR spectra.



Scheme 18

In the case of chiral base catalysis of the E2 elimination, enantioenriched γ -hydroxyenones from the corresponding endoperoxides were obtained [\[2006JA12658\]](#); in fact, a one-pot asymmetric 1,4-dioxygenation of 1,3-cycloheptadiene by sequential reaction with singlet oxygen and 5 mol% chiral catalyst provided the γ -hydroxyenones **80** in 90% yield and 92% ee ([Scheme 18](#)).

Treatment of the endoperoxide **81**, obtained by tetraphenylporphyrin-sensitized photooxygenation of a cycloheptatriene derivative in 73% yield (*vide infra*), with a catalytic amount of triethylamine in CHCl_3 at -30°C provided a new tropolone derivative **82** as the sole product in 97% yield ([Figure 3](#)) [\[2006T4003\]](#). When **81** was heated to 60°C in a sealed tube for 6 h, the epoxyketal **83** was isolated in 53% yield ([Figure 3](#)); structures were accomplished by detailed NMR analysis. A second endoperoxide **84** was synthesized also by the same procedure and the reactivity studied [\[2006T4003\]](#).

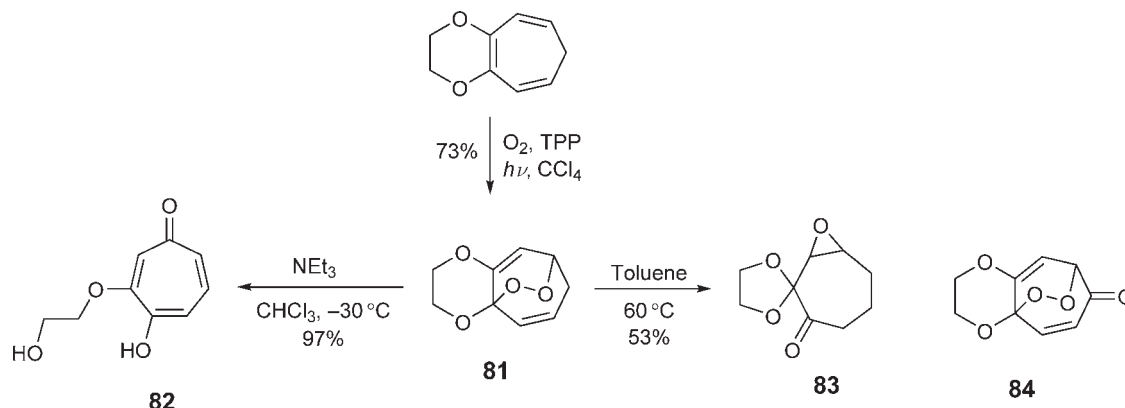
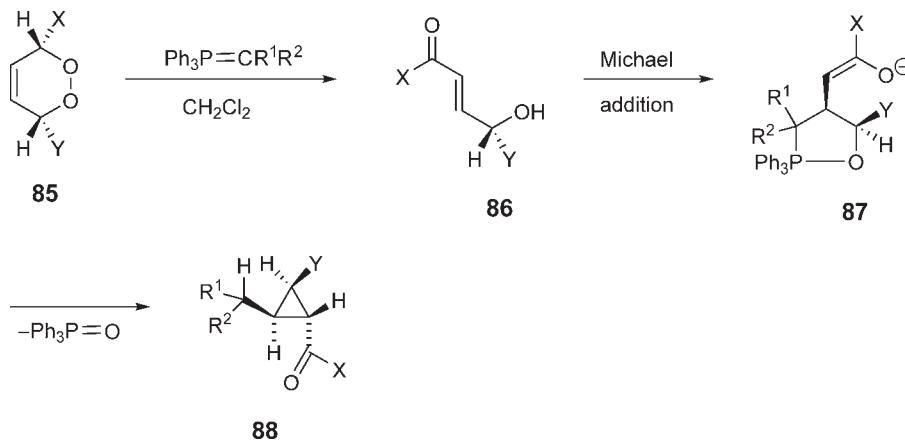


Figure 3 Reactivity of endoperoxide **81** and structure of endoperoxide **84**.

8.10.6.1.1 As reactants for highly diastereoselective cyclopropanation reactions

1,2-Dioxins **85** react under mild conditions (anhydrous CH_2Cl_2 under N_2 at ambient temperature) with stabilized, nonbulky phosphorus ylides to afford novel diastereomerically pure cyclopropanes **88** ([Scheme 19](#)) [\[1998CC333, 2000JOC5531\]](#); $\text{Co}(\text{salen})_2$ ($\text{salen} = 2,2'[\text{ethane-1,2-diylbis}(\text{nitrilomethylidene})]\text{dibenzothiolato}$) in a catalytic manner rapidly induces the rearrangement of the 1,2-dioxins. Key features are the ylides (as mild bases induce ring opening which are then added by Michael addition to the intermediate *cis*- γ -hydroxy enones **86**) and cyclization of the resultant enolates **87** affording the cyclopropanes **88** in excellent *de*'s and yields. Sterically bulky ylides ($\text{R}^1 = t\text{-Bu}$, 1-Ad), however, favor the formation of different diastereomers [\[2000J\(P1\)1319\]](#). The structures and



Scheme 19

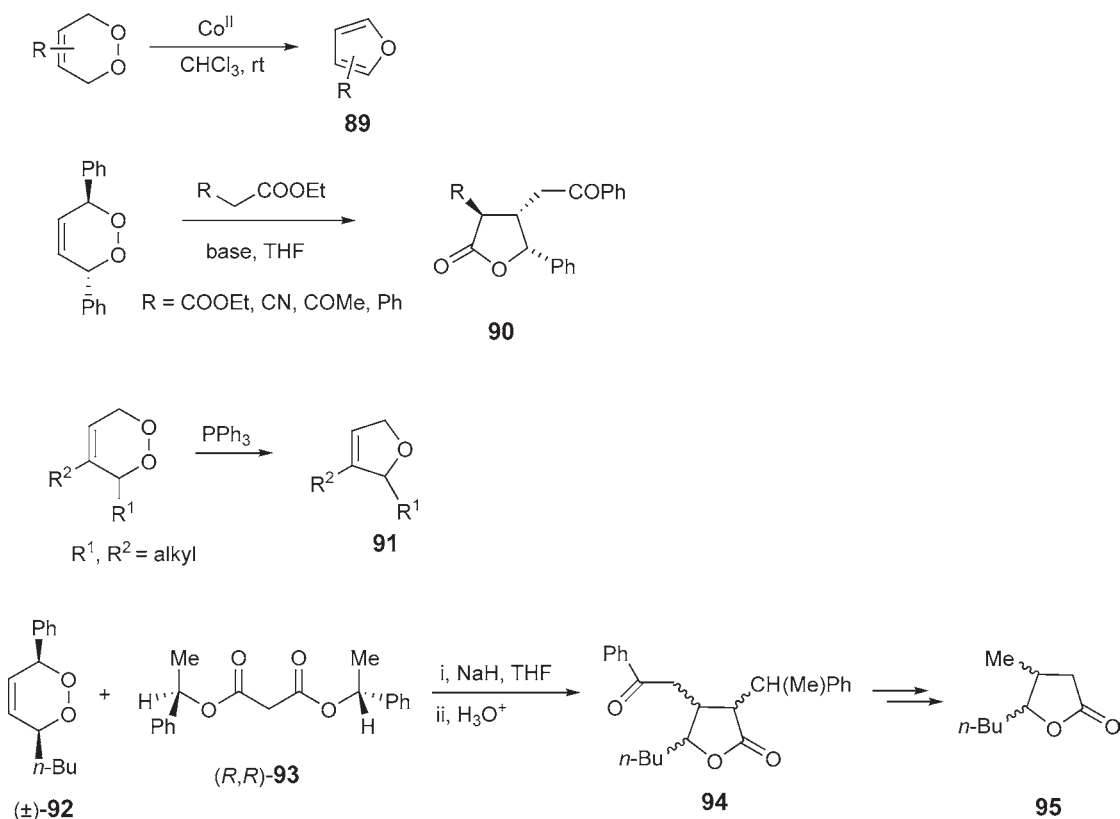
stereochemistries of the new cyclopropanes were unambiguously elucidated by a combination of X-ray crystallography and the full arsenal of 1-D and 2-D NMR experiments. Alternatively, from the *cis*- γ -hydroxy enones **86**, several (2*E*,4*Z*)-6-hydroxy-2,4-dienoates <2005JOC470> or *trans*-4-hydroxy-2,3-epoxyketones <2004JOC2580> were able to be prepared in moderate yield.

If a chiral cobalt complex, instead of Co(salen)₂, is used, enantioselectivity during the ring-opening process is induced (at -20 °C the optimal *ee* was 76%) <2002CC28>. The application of stabilized Horner–Wadsworth–Emmons phosphonates represents a viable alternative to ylides in the cyclopropanation reaction <2002JOC3142>.

Recently, the total synthesis of grenadamide, a naturally occurring chiral cyclopropyl amide isolated from marine cyanobacterium *Lyngbya majuscula* <1998JNP681>, was published employing the aforementioned diastereoselective cyclopropanation protocol as the key step in the synthesis <2006OBC323>.

8.10.6.1.2 Ring contraction forming the corresponding furan derivatives

The weakness of the endocyclic peroxide bond means that a range of reagents may be used to transform 1,2-dioxins into interesting molecules such as furans. For example, treatment of 3,6- and 4,5-disubstituted 3,6-dihydro-1,2-dioxins with CoTPP provided access to the substituted furans **89** <1997T13867, 1989JOC3475>; *trans*-3,6-disubstituted-3,6-dihydro-1,2-dioxins upon reaction with the enolates of disubstituted esters afforded the lactones **90** in excellent yield <2002JOC5307>; and, when treated with 1.5 equiv of triphenylphosphine at 60 °C in CHCl₃, provided the ring-contracted dihydrofurans **91** <2004JOC2577, 2003JOC4239> (Scheme 20).

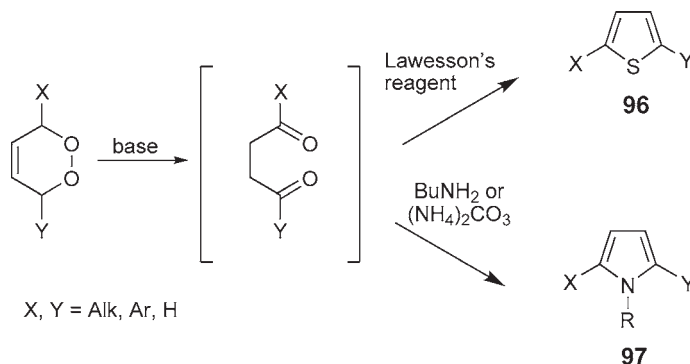


Scheme 20

The natural products *cis*- and *trans*-whisky lactones **95** have been prepared from the furanones **94** (92–93% yield), which were themselves obtained from *cis*-3-phenyl-6-butyl-3,6-dihydro-1,2-dioxin **92** and a chiral malonate ester **93** in 54% yield <2006OL463>; chromatographic separation on silica gel provided the pure (3*R*,4*S*,5*S*)- and (3*S*,4*R*,5*R*)-diastereomers of **94** which were converted into two nature-identical and two non-natural isomers of **95**.

Additionally, the acid-catalyzed decomposition of substituted tetrahydro-1,2-dioxin-3-ols yielded adequately the substituted furan derivatives <1994JHC1219, 1998S1457>.

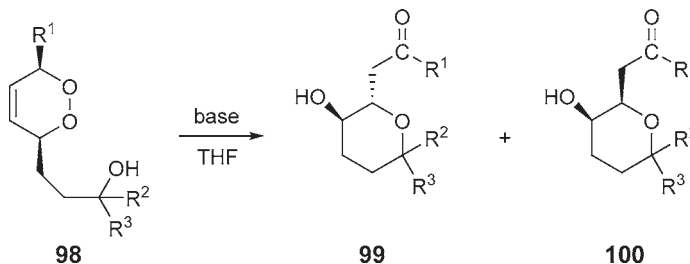
2,5-Disubstituted thiophenes **96** and 1,2,5-tri- and 2,5-disubstituted pyrrole derivatives **97** are available readily from *cis*-3,6-disubstituted-3,6-dihydro-1,2-dioxins in a one-pot synthesis. The reaction proceeds by an initial Kornblum–de la Mare rearrangement of the 3,6-dihydro-1,2-dioxin to its isomeric 1,4-diketone followed by the condensation with Lawesson's reagent, ammonium carbonate, or a primary amine (**Scheme 21**) <2002TL3199>.



Scheme 21

8.10.6.1.3 As convenient precursors for pyran syntheses

cis-3,6-Disubstituted-3,6-dihydro-1,2-dioxins **98** react with equimolar amounts of base in tetrahydrofuran (THF) to form the *cis/trans*-isomeric pyran derivatives **99** and **100** (**Scheme 22**) <2005JOC8344>. The stereochemistries were elucidated unambiguously by a combination of X-ray crystallography and the full arsenal of 1-D and 2-D NMR experiments. If the hydroxy group at C-3 in not protected (via acetylation in excellent yield), the pyran product is furanized. There is a clear preference for the *trans*-isomer when using LiOH as base while 1,4-diazabicyclo[2.2.2]-octane (DABCO) favors *cis*-pyran formation.



Scheme 22

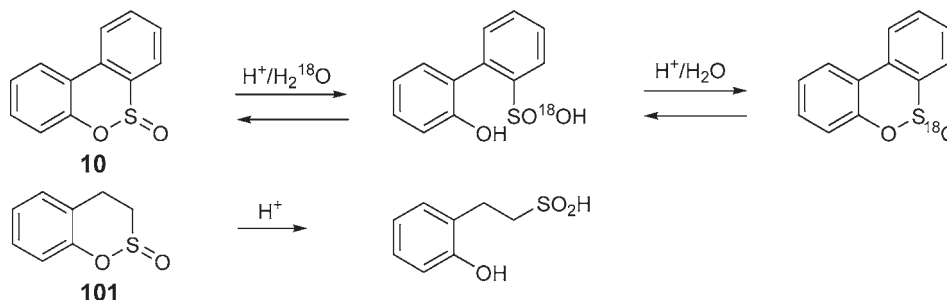
8.10.6.1.4 Reduction of the peroxy bond

The peroxy bond is one of the most fragile covalent bonds found in organic compounds with an average bond energy less than 34 kcal mol⁻¹ <B-1983M11>, therefore, the reductions of compounds containing peroxy bonds are considered risky procedures. The susceptibility of organic peroxides to reducing agents during the reduction of saturated esters showed that LiBH₄ was the most suitable reductant, though LiAlH₄, LiAlH(O-*t*-Bu)₃, and LiBHEt₃ can also be applied <2005JOC4240>.

8.10.6.2 1,2-Oxathiins

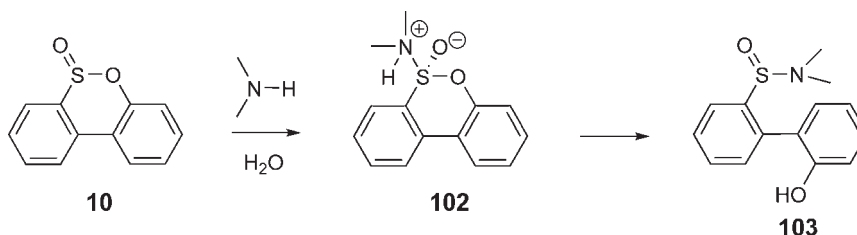
The ring-opening reactions of benzo- and dibenzooxathiin 2-oxides have been studied in acidic and buffered solutions <1996BCJ2639, 1995CL997, 1993HAC223, 1992CL2055>. The dibenzo sultine **10** proved to be stable

in acidic solution though with a microscopically reversible ring-opening/ring-closure process taking place, as evidenced by the following experiment: in an ^{18}O -enriched acidic solution, isotope labeling at the sulfinyl oxygen occurred with 100% incorporation of one ^{18}O label as determined by MS. That the incorporation of the label occurred solely for the sulfinyl oxygen but not the endocyclic oxygen was proven by ^{18}O -isotope shifts in the ^{13}C NMR spectrum <1993HAC223>. 3,4-Dihydro-1,2-benzoxathiin 2-oxide **101**, however, undergoes a pseudo-first-order, ring-opening reaction (Scheme 23).



Scheme 23

The aminolysis of dibenzo[1,2]oxathiin 6-oxide **10** with primary and secondary amines in water was quantitatively followed by the absorption at 270 nm in UV spectroscopy, from which the reaction was found to obey pseudo-first-order kinetics <1999TL8901>. Because of the lack of a distinct difference in the magnitude of k_{obs} between primary and secondary amines, and between acyclic and cyclic amines, the aminolysis reaction must proceed in two steps: the first is a fast formation of intermediate **102** followed by a second slow decomposition step to the reaction product **103** (Scheme 24).



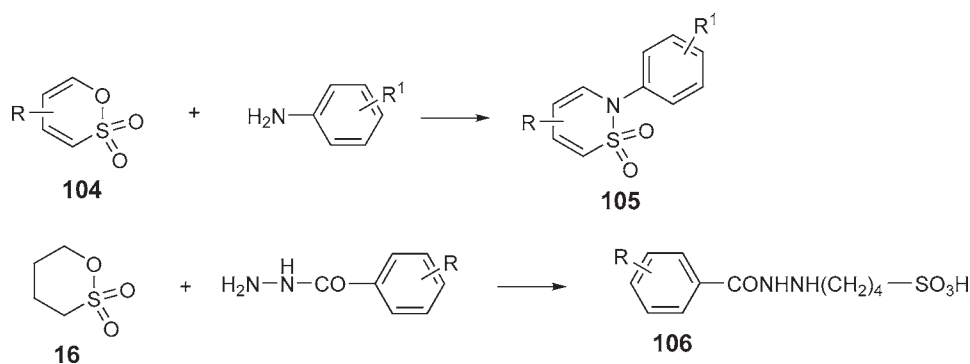
Scheme 24

Using a general procedure for the careful fluorination of sulfur-containing compounds, 1,2-oxathiane 2,2-dioxide **16** can be successfully fluorinated by treating the sultone with a mixture of elemental fluorine and helium gas at -78°C for 8 h, after which the crude reaction product is collected and fractionated in cooled traps <1991IC789>. The perfluoro sultone, that resulted, was isolated and characterized by ^{19}F and ^{13}C NMR spectroscopy, and MS.

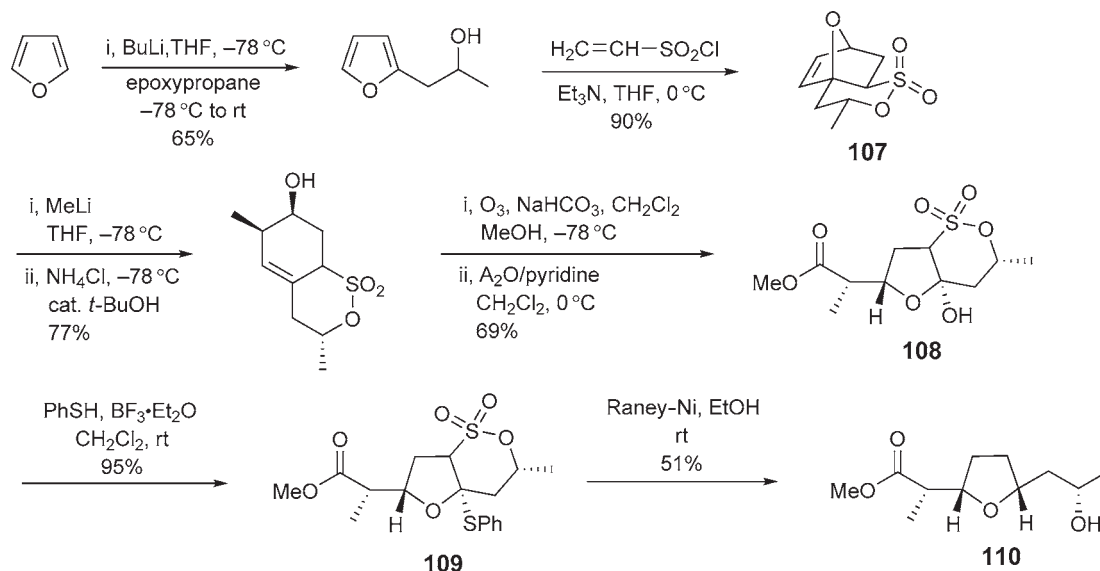
Bromination of the same compound takes place preferentially at C-6 whereby the sultone ring is opened to yield brominated sulfonic acids with either three or four bromine atoms <1989EJC259, 1985EJC365>. The action of iodine monochloride in CHCl_3 leads to the 3-iodo-substituted sultone which further reacts with aniline to the corresponding sultam <1990AFF428>.

Sultones react easily with amines and anilines <1989PHA294, 1989EJC259, 1987LA481>: 1,2-oxathiin 2,2-dioxide derivatives **104** condensed to give the corresponding sultams **105** but 1,2-oxathiane 2,2-oxides **16** were cleaved by aniline or benzoylhydrazine derivatives to provide the corresponding sulfonic acids **106** (Scheme 25) <1993AFF256>.

A six-step synthesis of nonactic acid with excellent stereocontrol via sultone intermediates has been published (Scheme 26) <1998EJO2073>. The tricyclic sultone **107** was synthesized by a tandem esterification/cycloaddition with vinylsulfonyl chloride whereby only the *exo*-adduct with *exo*-Me was obtained <1989AGE202>. Next, the tandem elimination/alkoxide-directed 1,6-addition first led to a mixture of sulfones, but equilibration with catalytic



Scheme 25



Scheme 26

amounts of *KOt*-Bu resulted in the thermodynamically more stable sultone **108**, which was, by ozonolysis and subsequent chemoselective acylation, transformed into the tetrahydrofuranosultone **109**. The hydroxy group was then exchanged for the phenylthio group and finally the two C–S bonds were cleaved by chemoselective reduction in the one reaction resulting in methyl nonactate **110**, which needs only to be saponified to ultimately yield nonactic acid. All sultones produced during the course of the synthesis were characterized by X-ray diffraction analysis <1996CC431, 1989AGE202>.

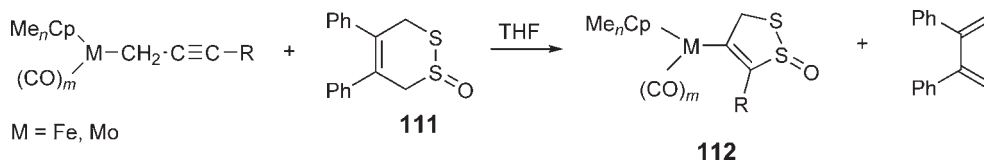
A sultone analog of **107** (4-Me_(eq)) instead of 3-Me_(eq)) is the key intermediate of the first enantioselective total synthesis of the antileukemic 1,10-*seco*-eudesmanolides, (–)-eriolanin and (–)-eriolangin <2001EJO3669, 2006EJO1144>.

8.10.6.3 1,2-Dithiins

8.10.6.3.1 Unsaturated analogs

Reactions of cyclopentadienyl- and (pentmethylcyclopentadienyl)iron dicarbonyl 2-alkynyl complexes as well as cyclopentadienylmolybdenum tricarbonyl 2-alkynyl complexes with 4,5-diphenyl-3,6-dihydro-1,2-dithiin 1-oxide **111** were shown to yield transition metal-substituted five-membered ring thiosulfinate esters **112** in moderate to excellent yields (Scheme 27) <1991OM2936, 1989JA8268>. These reactions are formal [3+2] cycloadditions. When

chiral, but racemic, 2-alkynyl complexes were studied, the reactions did not display high diastereoselectivity. 4,5-Diphenyl-3,6-dihydro-1,2-dithiin 1-oxide **111** has been used as an S_2O source for insertion into metal carbon bonds (it decomposes upon drying *in vacuo* at 80 °C to yield presumably S_2O and 2,3-diphenyl-1,3-butadiene) <1991JOM(407)81, 1990JOM(384)105, 1988OM1013>; 5,6-di-*tert*-butyl-2,3,7-trithiabicyclo[2.2.1]hept-5-ene 2-*endo*-7-*endo*-dioxide has been employed for this purpose as well <2004JA9085>.

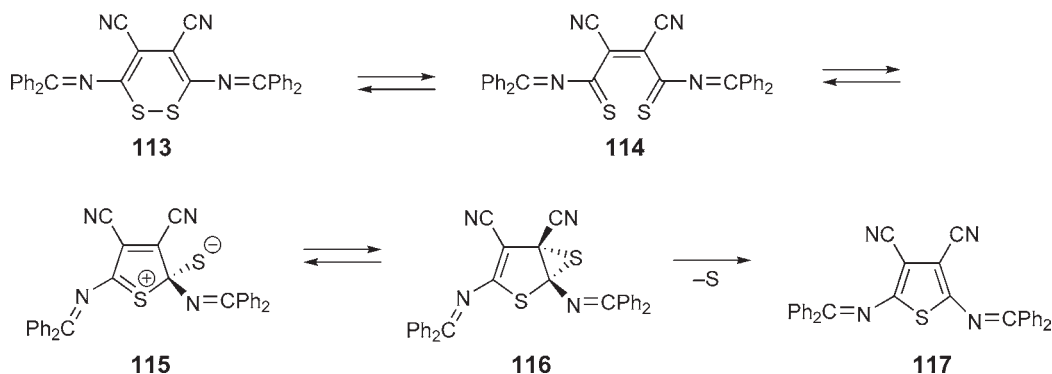


Scheme 27

1,2-Dithiane 1,1-dioxide and its 4,5-benzo analog have been tested as potential sulfur-transfer reagents during the automatic synthesis of oligodeoxyribonucleoside phosphorothiolates via the ‘deoxyribonucleoside phosphoramidite’ approach and were found to be efficient reagents for this purpose. The most efficient reagent, however, proved to be the five-membered thiosulfonate 3*H*-1,2-benzodithiol-3-one 1,1-dioxide <1990JOC4693>.

8.10.6.3.1(i) Conversion of dithiins to thiophenes by thermal or photochemical sulfur loss

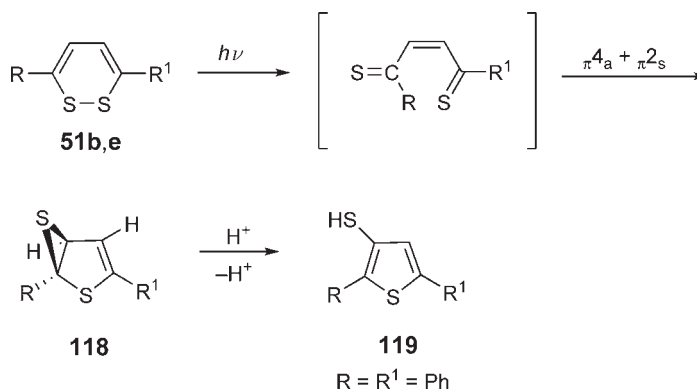
The thermal sulfur elimination **113** → **117** (Scheme 28) was studied in benzonitrile at 100 °C in the dark <1985TL1849, 1994CB401, 1997LA1677>; the dissipation of **113** was measured at 550 nm, at which wavelength the absorption of the yellow thiophene derivative **117** is negligible. The reaction was found to be first order and though untreated it is slow ($k_1 = 7.2 \times 10^{-6} \text{ s}^{-1}$, $\Delta G_{373} = 30.8 \text{ kcal mol}^{-1}$), it is accelerated strongly in the presence of triethyl phosphite or triphenylphosphine. The desulfurization begins with electrocyclic ring opening of the dithiin to the dithione **114**, followed by an intramolecular cycloaddition to the intermediate **115**, which is, due to the weakness of the π bond in $\text{C}=\text{S}$, in equilibrium with the thiirane **116** which finally loses sulfur thermally.



Scheme 28

The copper-mediated desulfurization from **56** (cf. Scheme 13) to the corresponding thiophene derivative at high temperature has been reported <1994CB401>; in a similar manner, **57–59** were converted into the corresponding heteroarenes <2005OL5301>. A dimeric Ni(II) complex was produced via desulfurization of **58** with a stoichiometric amount of $\text{Ni}(\text{COD})_2/2\text{PPh}_3$ (COD = cyclooctadiene) <2006OM2374>; the reaction proceeds via oxidative addition of the disulfide bond to the Ni(0) center and the complex proved by X-ray analysis to be of dimeric structure in which one sulfur, derived from the disulfide bond, bridges two Ni(II) centers. Also, the complex undergoes readily desulfurization at higher temperatures <2006OM2374>. Alternatively, the platinum bisphosphine complexes of the dibenzo[1,2]dithiins or their oxides can be synthesized by oxidative addition to $[\text{Pt}(\text{PPh}_3)_4]$ <2006CEJ895>; the complexes were fully characterized by multinuclear NMR spectroscopy and, in selected cases, by X-ray crystallography. Both simple S/S and bimetallic platinum bisphosphine complexes were obtained.

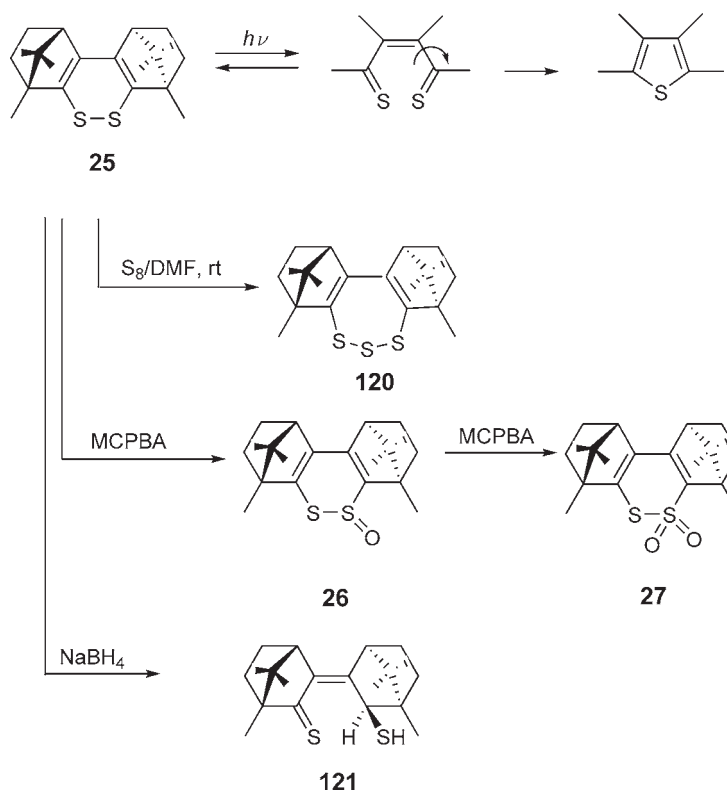
To study the photochemistry of the dithiins **51b** (Scheme 13) in solution, the compounds were irradiated with visible light at -60 to -75 °C to afford the thiiranes **118** in excellent yields which were characterized by ^1H and ^{13}C NMR spectroscopy. Upon warming or further exposure to light, the thiiranes **118** afforded the thiophenes **119** (Scheme 29) <2000MI159, 1996JA4719>.



Scheme 29

A facile [4+1]-type synthetic route to thiophenes from dienol silyl ethers and elemental sulfur has been published; however, the intermediate 1,2-dithiin derivatives were not isolated <2006T537>.

Whilst the 3,6-disubstituted-1,2-dithiins undergo facile sulfur extrusion, the (+)-camphor analog **25** is extremely stable (Scheme 30) <1995T13247, 1994TL1973>; even in 70 eV electron ionization (EI) mass spectra, no peak



Scheme 30

attributable to the loss of sulfur was observed. Obviously, the torsional hindrance about the C(3)–C(4) bond for the conversion of *s-cis,s-cis*-dithione to *s-cis,s-trans*-dithione (Scheme 30; the configuration necessary for the intramolecular cycloaddition) is too high and is thus the limiting factor for sulfur extrusion from **25**.

In total contrast, the unusual dithiin **25** shows a marked tendency for the insertion of sulfur with the formation of the diborneo-1,2,3-trithiepine **120**. The structure of **120** was elucidated by X-ray crystallography and the seven-membered ring interconversion studied by dynamic ^1H NMR ($\Delta G^\ddagger = 13.0 \text{ kcal mol}^{-1}$) <1995T13247>.

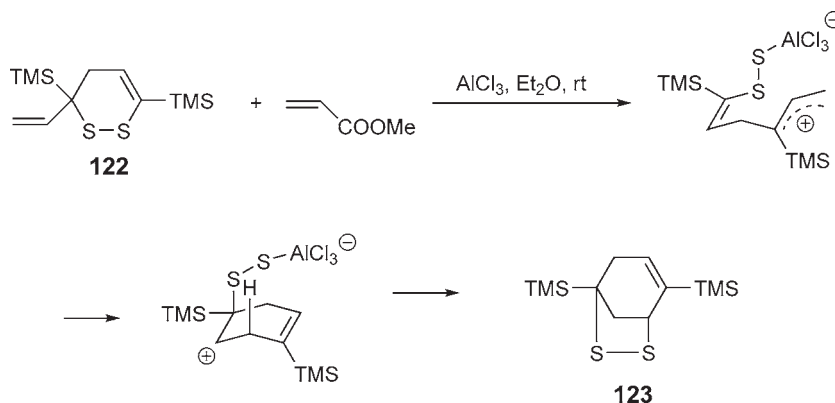
8.10.6.3.1(ii) Oxidation of dithiins

Another effect of the high steric hindrance in dithiin **25** due to the 3,3'-dibornane skeleton is the fact that this dithiin can be oxidized readily (with 1 mol of *m*-chloroperbenzoic acid (MCPBA) at 0°C) to sulfoxide **26** <1995T13247, 1994TL1973> (Scheme 30), a structure which is remarkably stable in contrast with the usual characteristics of sulfoxides in the dithiin series. The six-membered ring interconversion of the sulfoxide **26**, slowed obviously by the steric bulk hindrance, was investigated by dynamic NMR ($\Delta G^\ddagger$ ca. $10\text{--}11 \text{ kcal mol}^{-1}$). With an excess of MCPBA at elevated temperature, the sulfoxide **26** is oxidized to the sulfone **27**; parallel treatment with oxygen, however, failed to yield the same compound.

Reduction of **25** with NaBH_4 results in the formation of the blue-violet mercapto-(*Z*)-enethione **121**. The configuration was determined by ^1H and ^{13}C NMR and stereochemical-determining NOEs in solution, and by X-ray crystallography in the solid state <1995T13247>.

8.10.6.3.1(iii) Unusual chemical behavior of silylated 1,2-dithiins

Due to the presence of silyl functionalities in the 1,2-dithiin skeleton, the reaction of **122** with carbonyl dienophiles provided the bicyclic sulfurated adducts **123** in high yield but without any trace of the expected Diels–Alder products. Other dienophiles reacted in an identical fashion. The structure of **123** was elucidated on the basis of MS, ^1H and ^{13}C NMR, and X-ray crystallography <2005TL4711>. The Lewis acid initially attacks the sulfur atom resulting in ring opening; subsequent rearrangement of the disulfide bridge, with double-bond shift and hydride migration, leads to the formation of the isolated product (Scheme 31).



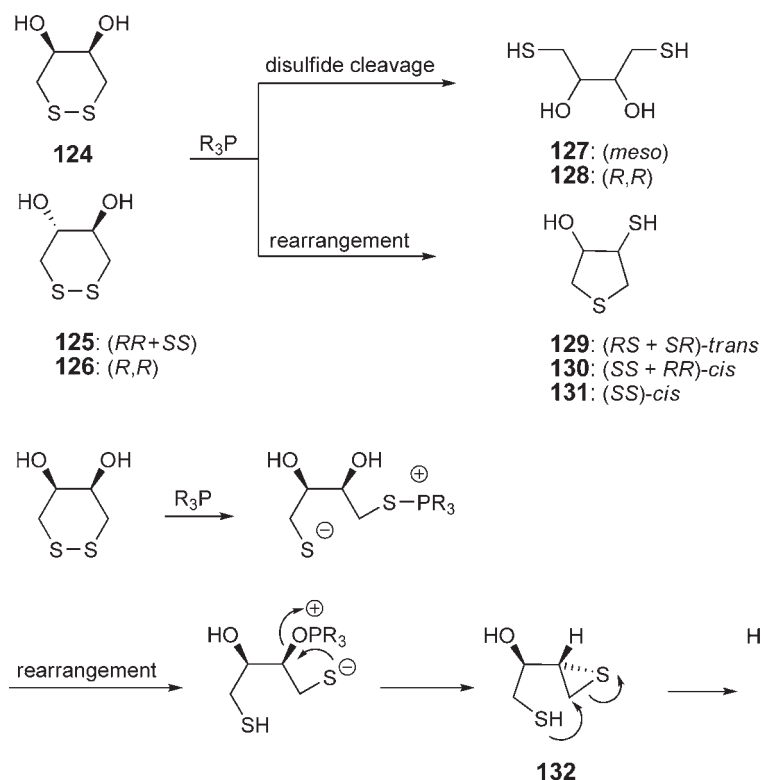
Scheme 31

8.10.6.3.2 Saturated analogs

8.10.6.3.2(i) Desulfurization to yield five-membered thiolanes

The phosphine-mediated desulfurization of substituted 1,2-dithianes to the corresponding tetrahydrothiophenes proceeds stereospecifically; for the corresponding reactions of *cis*- and *trans*-4,5-dihydroxy-1,2-dithianes **124** and **125/126**, three different phosphines R_3P ($\text{R} = \text{Et}$, Ph , $(\text{CH}_2)_2\text{COOH}\cdot\text{HCl}$) were employed <2003H(60)47>. The reaction is pH-dependent: under mildly acidic conditions, the thiols **127** and **128** were obtained; under neutral or moderately basic conditions, however, the 4-hydroxy-3-mercaptotetrahydrothiophenes **129–131** were formed (Scheme 32). From **124** and **125** racemic **129** and **130** were obtained, while for **126** the stereospecific product **131** was isolated; the identity of

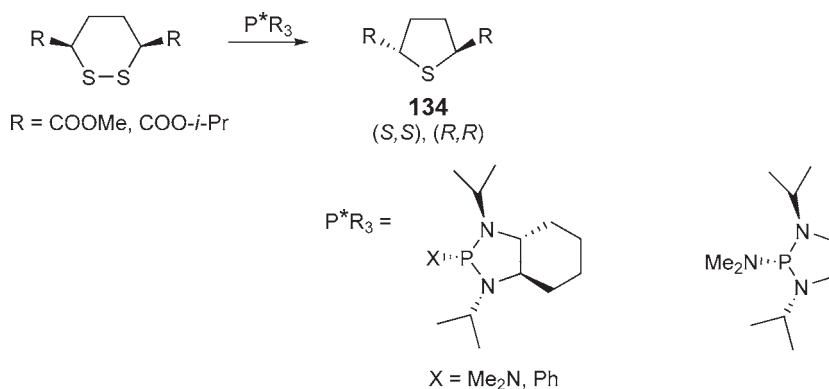
the products **129** and **130/131** was unequivocally determined by ^1H and ^{13}C NMR and 2-D nuclear Overhauser enhancement spectroscopy (NOESY) spectra. The reaction proceeds by initial phosphine-assisted disulfide cleavage, followed by subsequent cyclization of the solvolysis product to the thiirane **132** and release of phosphine oxide. Finally, intramolecular $\text{S}_{\text{N}}2$ reaction at the methylene site in thiirane **132** by the terminal thiol yields the stable tetrahydrothiophenes **133**. The intermediate formation of thiirane was monitored *in situ* by ^1H and ^{13}C NMR.



Scheme 32

The photolysis of *trans*-4,5-dihydroxy-1,2-dithiane in aqueous and CH_2Cl_2 solutions yielded the two isomers (the *trans*-orientation of the hydroxy substituents remains constant) of 3,4-dihydroxy-2-mercaptotetrahydrothiophene which were characterized by ^1H and ^{13}C NMR and electrospray ionization (ESI) MS [\[2004PCA2247\]](#).

In the desulfurization of 3,6-disubstituted-1,2-dithianes with chiral phosphines (**Scheme 33**) [\[2000J\(P1\)1595\]](#), enantiomerically enriched tetrahydrothiophenes **134** with up to 36% *ee* were obtained. Both yield and *ee* proved to be dependent on solvent, temperature, and the phosphine employed.

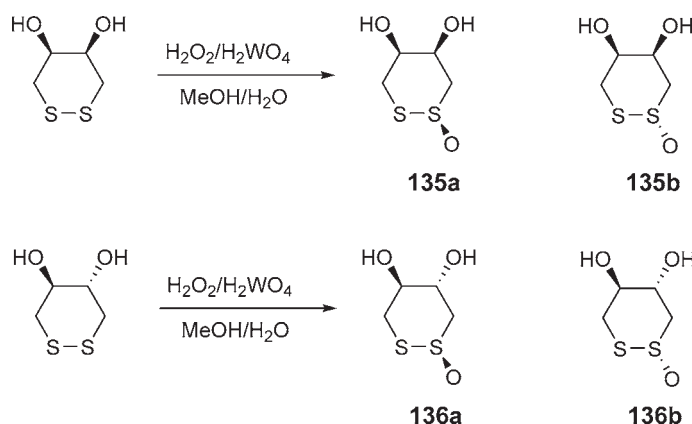


Scheme 33

The kinetics of the reduction of 1,2-dithiane with triphenylphosphine was studied in aqueous ethanol at various temperatures by UV spectroscopy <1991PS(60)215>. First-order kinetics was clearly observed and the reaction rate was found to depend strongly on the solvent polarity.

8.10.6.3.2(ii) Oxidation of 1,2-dithiane derivatives

Dissimilar products were obtained from the oxidation of 1,2-dithiane with 30% H_2O_2 in methanol/water <1984ZOR669, 1988UKZ1206> and by photooxidation ($2\text{--}4 \times 10^{-5}$ M rose bengal, ambient temperature, oxygen-saturated solvent, 650 W tungsten lamp) <1994TL4723>: the sulfone was obtained in the former case but a mixture of the sulfoxide and the sulfone was obtained in the latter case. The four diastereoisomers of 4,5-dihydroxy-1,2-dithiane 1-oxide **135a,b** and **136a,b** were synthesized by oxidizing the corresponding diols with H_2O_2 in methanol/water using tungstic acid as catalyst and MnO_2 to destroy excess H_2O_2 ; the products were subsequently separated by chromatography (Scheme 34) <1988JOC2608>. The four isomers were assigned on the basis that hydrogen bonding of the 5-hydroxy group should result in broader infrared (IR) bands at lower frequency when positioned *cis* to $\text{S}=\text{O}$ than when *trans*; thus the two isomers showing broad bands between $3400\text{--}3150\text{ cm}^{-1}$ were assigned as the *cis*-isomers **135a** and **136b**. By extending the reaction the corresponding stereoisomeric 1,1-dioxides were obtained <1988SUL107>, and by esterifying the hydroxyl groups also the corresponding 1,1-dioxide was obtained <1988MI43>.



Scheme 34

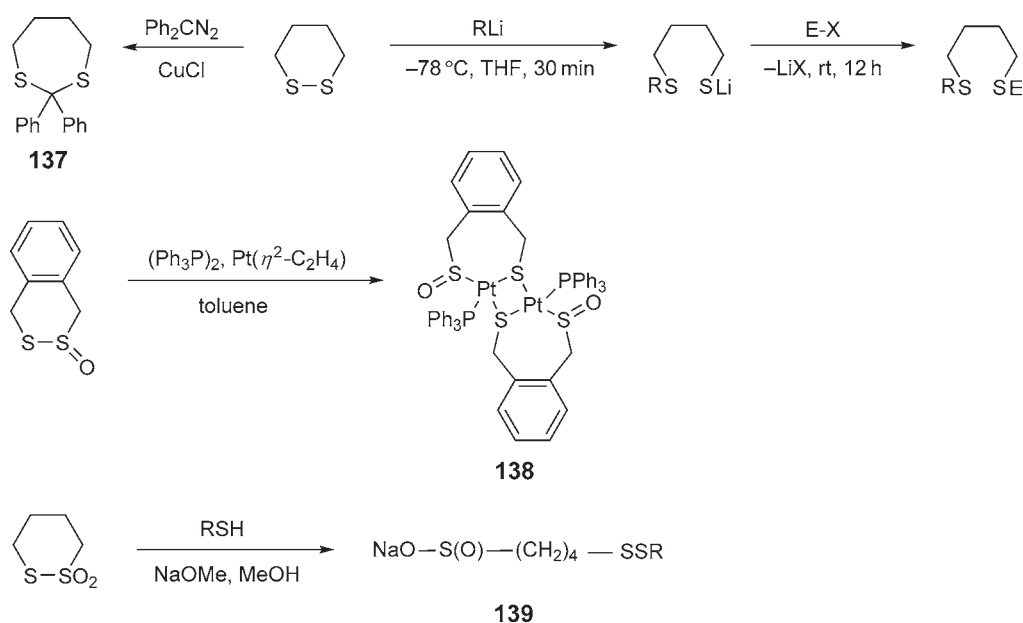
(4*R*,5*S*)-Dihydroxy-1,2-dithiane was synthesized from (2*R*,3*S*)-dihydroxybutane-1,4-dithiol in 40% yield <1989SUL251>.

Oxidation of *trans*-4,5-dihydroxy-1,2-dithiane with ozone gave rise to 100% 1-oxide and singlet oxygen <2001J(P2)1109>.

The enzyme-catalyzed stereoselective oxidations of 1,2-dithiane and 1,4-dihydro-2,3-benzodithiin were also investigated <2002CC1452>. Using naphthalene dioxygenase and chloroperoxidase, enantiomerically enriched sulfoxides (1,2-dithiane 1-oxides) were obtained: 1,4-dihydro-2,3-benzodithiin yielded a product of 32–47% *ee* with an excess of the (*S*)-configuration while 1,2-dithiane yielded almost enantiopure (96% *ee*) (*R*)-configured 1-oxide. Finally, 1,4-dihydro-2,3-benzodithiin 2-oxide was also prepared by perborate oxidation <1988JOC2608>.

8.10.6.3.2(iii) Reactions with other reagents

A number of other reactions of 1,2-dithiane and its 1-oxide and 1,1-dioxide have been reported (Scheme 35). With organolithium reagents, nucleophilic ring opening of 1,2-dithiane was observed, wherein the intermediates were able to be treated with electrophiles <1995J(P1)2381>, and reactions with carbenes, generated by catalytic and photochemical decomposition of the diazo compounds, yielded the corresponding 1,3-dithiepanes **137** <1985TL5187>. The oxidative addition of 1,2-dithiane 1-oxide or 1,4-dihydro-2,3-benzodithiin 2-oxide to $(\text{Ph}_3\text{P})_2\text{Pt}(\eta^2\text{-C}_2\text{H}_4)$ yielded the monomeric seven-membered chelate **138**, characterized by X-ray diffraction (Scheme 35) <1992CB1047>. The corresponding 1,1-dioxides were cleaved by thiolates to yield substituted alkylthiobutanesulfinate salts **139** (Scheme 35) <1986PS(27)247>.



Scheme 35

The stability of substituted 1,2-dithianes toward ring-opening polymerization was tested by heating the disulfides with a catalytic amount of sodium methanethiolate [<1989T91>](#); none of the 1,2-dithianes were stable with respect to polymerization under these conditions. The thermal polymerization of 1,2-dithiane was also studied in detail [<2005POJ512, 2004MM3143>](#).

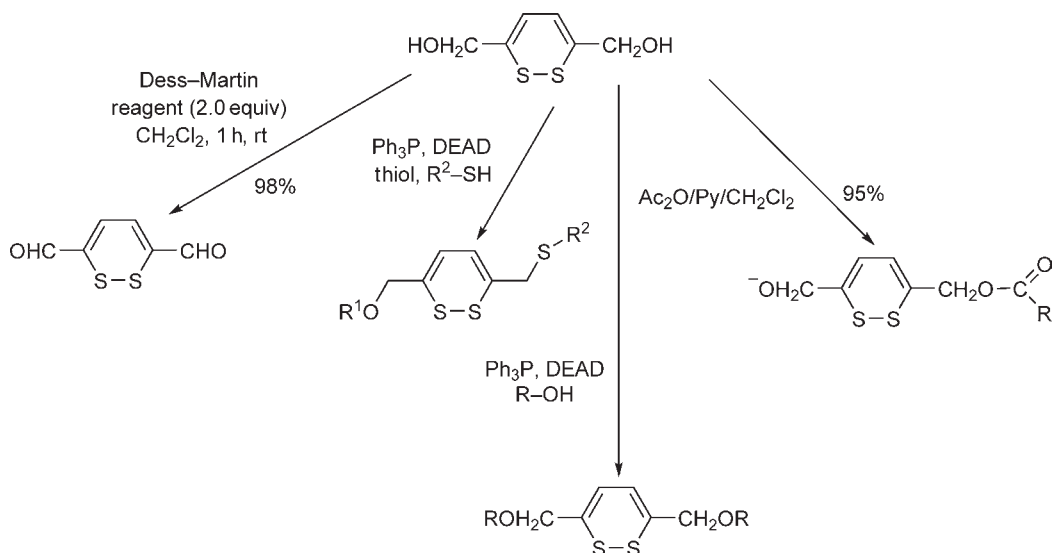
The efficient resolution of *trans*-4,5-dihydroxy-1,2-dithiane into the two enantiomers in large quantities has been reported by the reaction of the racemic mixture with the amino acid *N*-*t*-butoxycarbonyl-(*S*)-phenylalanine [<1997TL7657>](#). By fractional crystallization, the (4*S*,5*S*)- and (4*R*,5*R*)-esters were separated followed by hydrolysis, which provided the desired enantiomeric diols in excellent yield and >99% *ee*. These reactive diols provide isomerically pure analogs with interesting selectivity and therapeutic potential; for example, 4,5-dihydroxy-1,2-dithiane derivatives have been reported to inhibit the replication of HIV-1 and HIV-2 (human immunodeficiency viruses).

8.10.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Simple side-chain reactions of 1,2-dithiin diols have been conducted. Besides the formation of esters, ethers (R = Me, Et, *i*-Pr, cyclopropyl, Ph, pyridyl, cyclopentyl), and thioethers (R¹ = H, TBDMS; R² = 4'-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol), selective oxidation of the primary alcohol groups in the presence of the 1,2-dithiin heterocycle could be readily achieved (**Scheme 36**) [<1995JME2628, 1994SL201>](#). Additionally, amides, ureas, and carbamates of the dithiin diol were synthesized [<1995JME2628>](#).

8.10.8 Reactivity of Substituents Attached to Ring Heteroatoms

There are no examples of reactions of substituents attached to ring oxygen atoms; compounds with substituents on sulfur atoms other than oxygen (sulfoxides and sulfones) have not been reported and computations have not appeared in the accessible literature. The syntheses and reactivities of sulfoxides and sulfones are covered by the sections concerned with 1,2-oxathianes, 1,2-dithianes, and their derivatives.



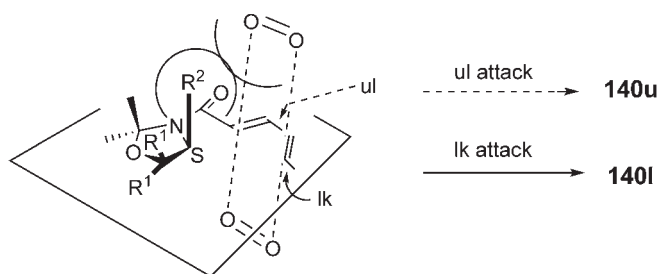
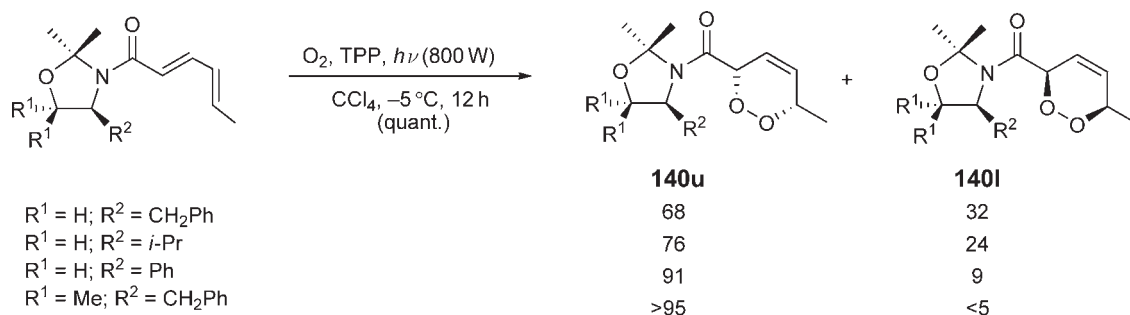
Scheme 36

8.10.9 Ring Syntheses from Acyclic Compounds

8.10.9.1 Dioxins, Dihydro- and Tetrahydrodioxins

8.10.9.1.1 [4+2] Cycloaddition of 1,3-dienes with singlet oxygen

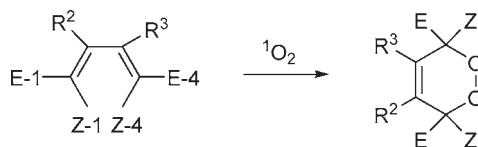
It is well known that 1,3-dienes react with singlet oxygen to give endoperoxides; the reaction is a typical ¹O₂ reaction and can be classified as a Diels–Alder-type [4+2] cycloaddition reaction. The stereoselectivity of this reaction, controlled by chiral auxiliaries, has been studied in detail; for example, the addition of singlet oxygen to sorbate derivatives was tested by the optically active amides containing the 2,2-dimethyloxazolidine chiral auxiliary (Scheme 37) <2002EJO3944, 1998JA4091>. The endoperoxides **140u** and **140l** were the only detectable reaction products. The diastereoselectivity depends on the substitution pattern of the auxiliary and increases in the order



Scheme 37

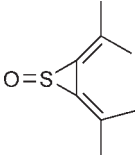
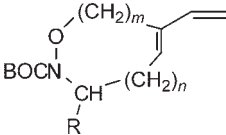
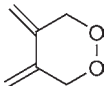
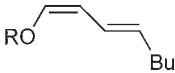
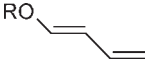
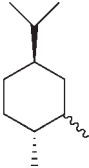
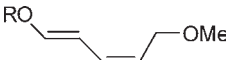
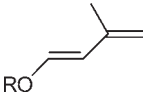
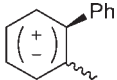
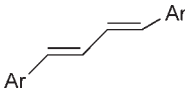
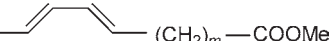
$\text{CH}_2\text{Ph} < i\text{-Pr} < \text{Ph}$ as expected from the increasing steric interactions between R^2 and the incoming singlet oxygen dienophile in the **140u** and **140l** transition states (**Scheme 37**). The absolute configuration was determined after amalgam reduction and subsequent diacetylation of the peroxides by X-ray crystallography. The trends of diastereoselectivity were further studied by diverse auxiliaries including a menthol derivative, several related cyclohexanes, and the Oppolzer sultam [<2002EJO3944>](#). The addition of $^1\text{O}_2$ to chiral dienol ethers with different auxiliaries (menthyl, 2-phenylcyclohexyl, and 1-phenylethyl) led to the same conclusion: diastereoselectivity depends on both the conformational preferences of the dienol ether and the ability of the auxiliary to shield one face of the diene (cf. **Tables 6(a)** and **6(b)** [<1999T11437>](#)).

Table 6(a) [4+2] Cycloaddition of dienes with singlet oxygen as dienophile



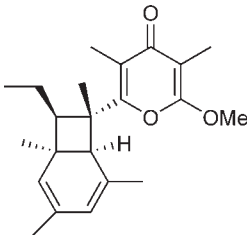
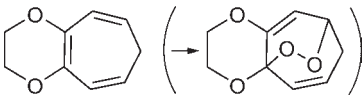
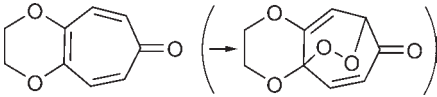
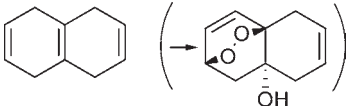
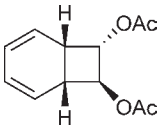
Entry	E-1	Z-1	R ²	R ³	Z-4	E-4	Reaction conditions	Yield (%)	Reference
1	<i>O</i> - <i>t</i> -Bu	H	H	H	H	H	~78 °C, CH_2Cl_2	35	1987JA2475
	<i>O</i> - <i>t</i> -Bu	H	H	H	H	H		70	1987JA2475
	H	Ph	H	H	<i>n</i> -Bu	H	Rose bengal, CH_2Cl_2 , $h\nu$	79	2006OL463
	H	Ph	H	H	C_7H_{15}	H	Rose bengal, CH_2Cl_2 , bis(triethylammonium) salt (cat.), $h\nu$, 5 °C, 6 h	37	2006OBC323
	H	Ph(<i>p</i> -OMe)	H	H	C_7H_{15}	H			
	H	Ph(<i>o</i> -OMe)	H	H	C_7H_{15}	H			
	Cyclohexyl	Cyclohexyl	H	H	H	H	Rose bengal, bis(triethylammonium) salt, $h\nu$, CH_2Cl_2 , 7 h, 5 °C		2006BML920
	Cyclopentyl	Cyclopentyl	H	H	H	H			
	Cyclobutyl	Cyclobutyl	H	H	H	H			
	Cyclohexyl	H	H	H	H	H			
	Cyclopentyl	H	H	H	H	H			
2	H	H	Alk	H	H	H	rt, acetone, hematoporphyrine, 30 W fluorocent lamp	72	1995TL3141
3	H	H	Me	H	H	H	0–5 °C, CFCl_3 , 500 W halogen lamp, rose bengal	50	1985T2147
	Me	H	H	H	H	H		31	
	Me	H	H	H	H	Me		56	
	H	H	Me	H	H	Me		58	
	Ph	H	H	H	H	H		76	
	H	H	Ph	H	H	H		57	
	Ph	H	H	H	H	Me		82	
	Ph	H	H	H	H	Me		92	
	H	H	<i>t</i> -Bu	H	H	H		62	
	Ph	H	H	H	Me	Me		28	
	H	H	Me	H	Me	Me		41	
	H	H	Ph	H	Me	Ph		78	
	H	H	Me	H	Me	Ph		78	
	H	H	CH_2Ph	H	H	H		84	
4	H	H	$(\text{CH}_2)_2\text{OBn}$	H	H	OE <i>t</i>	CH_2Cl_2 , MeOH		2003OL3819
5	$\text{MeOOC}(\text{CH}_2)_2$	H	H	H	H	$(\text{CH}_2)_2\text{COOMe}$	CCl_4/MeOH (9:1), rose bengal, rt	67	1991JCM326

Table 6(b) [4+2] Cycloaddition of dienes with singlet oxygen as dienophile

Entry	Starting material	Reaction conditions	Yield (%)	References
1		rt, benzene, TPP	72	1986JOC2122
2		0 °C, acetonitrile, 400 W tungsten lamp, rose bengal	69–82	2004BKC1307
3		rt, TPP, CHCl ₃	80	1992TL8127
4	 <i>trans:cis</i> 1,6 : 1 (a) 2,9 : 1 (b)	0 °C, CH ₂ Cl ₂ , TPP, 200 W, 10–15 min		1999T11437
	 1,3 : 1 (a) 2,0 : 1 (b)	(a) R = 		
	 1,25 : 1 (a)			
	 1,14 : 1 (a)	(b) R = 		
5		CCl ₄ , TPP, 2 kW xenon lamp, 0.5 h	100	1990JPO509
6		–20 °C, CHCl ₃ , TPP, 200 W, halogen lamp, 20 h		1997MI207
7	CH ₃ (CH ₂) _n —  <i>n</i> = 6; <i>m</i> = 6 <i>n</i> = 5; <i>m</i> = 7	CCl ₄ /MeOH (95:5)	>80	1984J(P1)2199

(Continued)

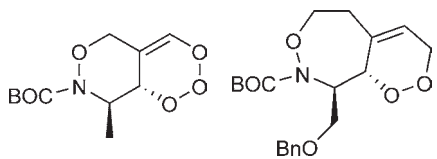
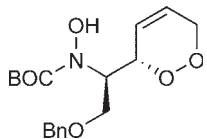
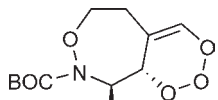
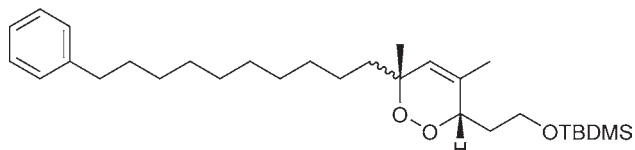
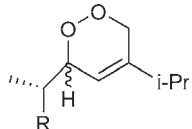
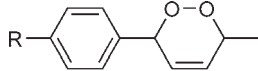
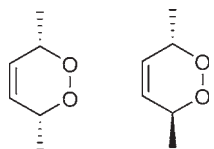
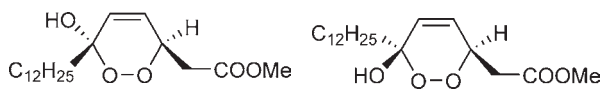
Table 6(b) (Continued)

Entry	Starting material	Reaction conditions	Yield (%)	References
8		Rose bengal, CH ₂ Cl ₂ :MeOH (9:1), 5 °C, 6 h, mercury vapor lamp, 175 W	71	2006SL2119
9		Methylene blue, CHCl ₃ , <i>hν</i>	67	2005TL465, 2006SL2295
10		TPP, <i>hν</i> , CCl ₄	73	2006T4003
11		TPP, <i>hν</i> , CHCl ₃	94	2006T4003
12		TPP, ¹ O ₂ /CH ₂ Cl ₂	80	2006HCA1246, 2006OL1791
13		TPP, <i>hν</i> , CH ₂ Cl ₂ , rt	70	2006TL7031

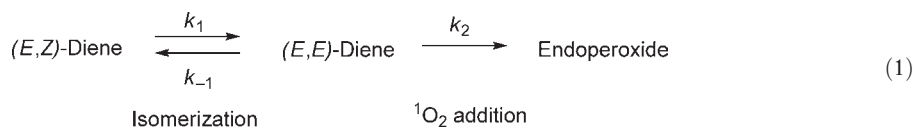
The addition of ¹O₂ to acyclic dienes proved to be strongly dependent on terminal substitution and the substituents at other positions of the conjugated system, and, furthermore, it must be accompanied by photoisomerization of (*E,Z*)-dienes to (*E,E*)-dienes because singlet oxygen adds exclusively to (*E,E*)-dienes to yield endoperoxides (cf. **Tables 6(a)**, **6(b)**, and **7**, and references therein).

Quantitative kinetic studies of the relative rates of isomerization and photocyclization have been conducted (Equation 1) <1999JOC493,1990JPO509>. [2+2] Addition reactions, an 'ene' reaction, a vinylogous 'ene' reaction, and the quenching of singlet oxygen were observed to be in competition with endoperoxide formation; from kinetic analyses, adequate mechanisms have been proposed <1984T3235>. Details including solvent influences <1998EJO2833> and efficiency of the photosensitizer <2002CCI1594, 1999CL469> were also investigated. The photooxidation of the corresponding enone was the key step in the total syntheses of the antitumor compounds (±)-chondrillin, (±)-plakorin, and other related peroxy ketals <1992JA1790, 1998JME2164>.

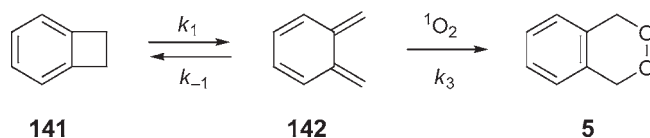
Table 7 Diastereoselectivity of the [4+2] cycloaddition with singlet oxygen as dienophile

Entry	Product	Diastereoselectivity	Yield (%)	Reference
1		<i>trans</i> only ^a	ca. 60	2004BKC1307
		<i>trans:cis</i> 80:20	70	
	 R = Me R = Ph	51:49 ^a 58:42 ^a	78 71	
2		65:35		2002OL2763
3	 3 <i>R</i> 3 <i>S</i>	70 30		1984JOC4297
4	 R = H, Me, OMe	<i>cis</i> only ^a	72–84	1999JOC493
5		From <i>E,E</i> 91:9 <i>E,Z</i> 79:21 <i>Z,Z</i> 82:18	81 58 52	1988JA7167
6		60:40	45	1990JOC5669 ^b

^aThe relative stereochemistries were determined by NOE experiment.^bThis photooxygenation (rose bengal or CuSO₄ as a sensitizer, sun lamp, CH₂Cl₂) was employed as the key step of the total syntheses of a number of natural products <1992JA1790, 2002T2449> and other antimalarial cyclic peroxy ketals <1998JME2164, 2003JME2516, 2006JME4120>.



The formation of 1,4-dihydro-2,3-benzodioxin **5** from the benzocyclobutene **141**/*o*-quinodimethane **142** equilibrium has been utilized as a trapping experiment for the kinetic analysis of diradical reactions (Scheme 38) <2002CC1594, 1988CB1357>.



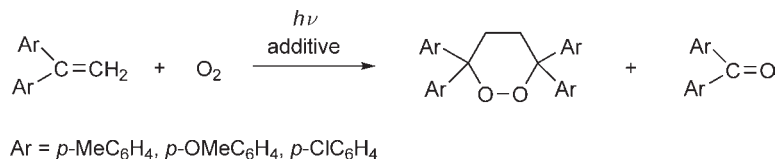
Scheme 38

9,10-Dimethylantracene was used as a singlet oxygen acceptor in competitive photooxidation reactions of arylphosphines <2006T10729>. A new hydrophilic and nonionic anthracene derivative has been synthesized and was tested successfully in biological investigations as a chemical trap for singlet molecular oxygen <2006T10762>. On the other hand, a thermolabile naphthalene endoperoxide derivative was used to generate ^{18}O -labeled singlet oxygen for mechanistic studies of DNA oxidation reactions <2006T10709> and of silylamines with $^1\text{O}_2$ <2006OL1783>. A number of endocyclic dienes were trapped by the addition of singlet oxygen to give the corresponding bicyclic *endo*-peroxy hydroperoxides <2006T10633>. A detailed theoretical study (DFT level) of the Diels–Alder reaction of acenes with singlet and triplet oxygen has been published <2006CC1179>. Further, the saturated endoperoxides derived from fulvenes were employed as a convenient entry into 2-vinyl-2-cyclopentenones <2006T10676>.

The diozonolysis of cyclo-1,3-dienes leads to a mixture of substituted 1,2-dioxanes <1990CJC1369, 1989CB145>; the product composition, but not the stereochemistries of the reaction products, was determined by ^1H and ^{13}C NMR spectroscopy. 3,3-Diphenyl-1,2-dioxan-4-one was isolated and characterized by ^1H NMR spectroscopy as one reaction product of the ozonolysis of (diphenylmethylene)cyclopropane <2001HCA1943>.

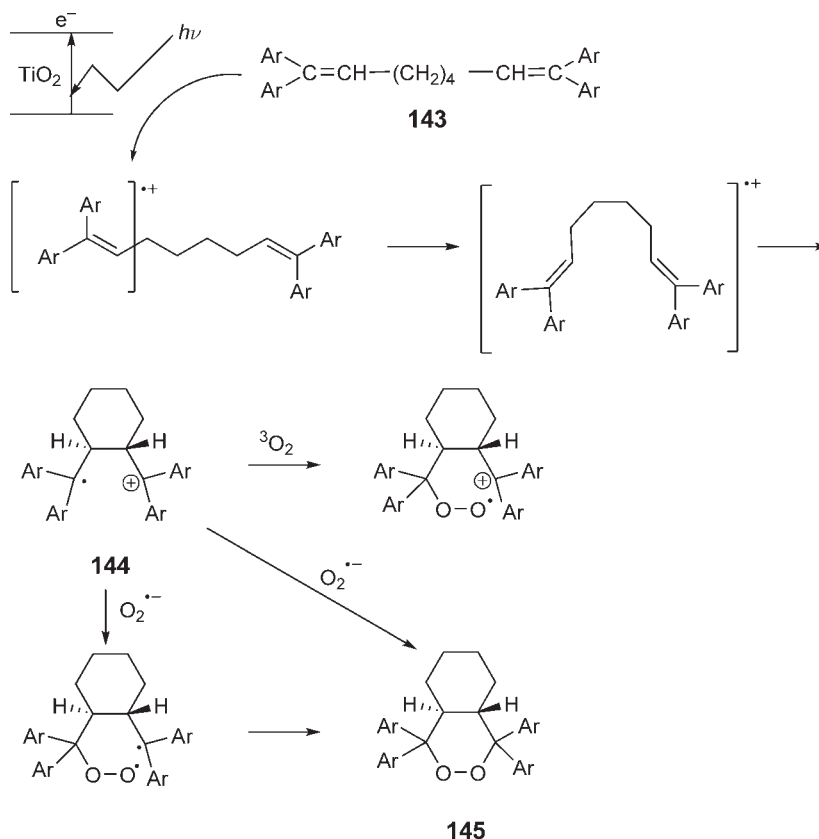
8.10.9.1.2 Synthesis by ET photooxygenation of 1,1-disubstituted alkenes

ET photooxygenation of 1,1-diarylethylenes in the presence of electron acceptors such as cyanoaromatics, Lewis acids, and dyes occurs efficiently to yield 1,2-dioxanes as the main product in addition to diarylketones as side products. The yield of the 1,2-dioxane derivatives proved to be dependent on aryl substitution, solvent polarity, the electron acceptor, and the excitation wavelength (Scheme 39).



Scheme 39

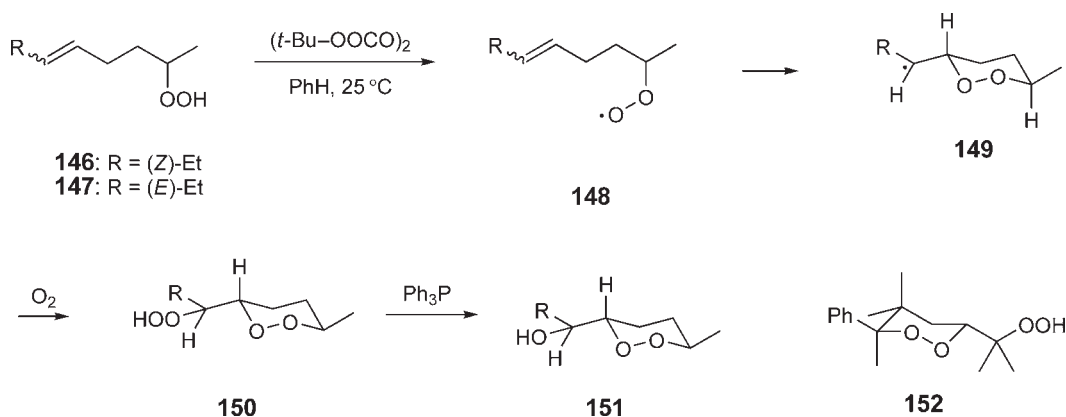
Instead of photocatalysts (e.g., 10-methylacridinium ion <1996BCJ743> or dicyanoanthracene <1991JPH55, 1984TL185, 1984TL2735>), the band of the contact charge-transfer (CCT) pairs of the aromatic alkenes with oxygen <1998BCJ2211, 1993CL979, 1993JOC6049> can be excited selectively. Further, semiconductors such as TiO₂, CdS, and ZnS were employed as redox-type heterogeneous photocatalysts <2004CL462> leading to excellent yields, and inorganic salts such as Mg(ClO₄)₂, KClO₄, NaClO₄, LiClO₄, and LiBF₄ were used to enhance the rate of photoexcitation. The mechanism proposed is exemplified in Scheme 40 using the photoreaction of **143** to afford **145** via the key intermediate **144**. For synthetic use, TiO₂, as a heterogeneous photocatalyst, can be removed simply by filtration and, in addition, is clean, inexpensive, and efficient <2004CL462>.



Scheme 40

8.10.9.1.3 Synthesis via cyclizations of unsaturated hydroperoxides

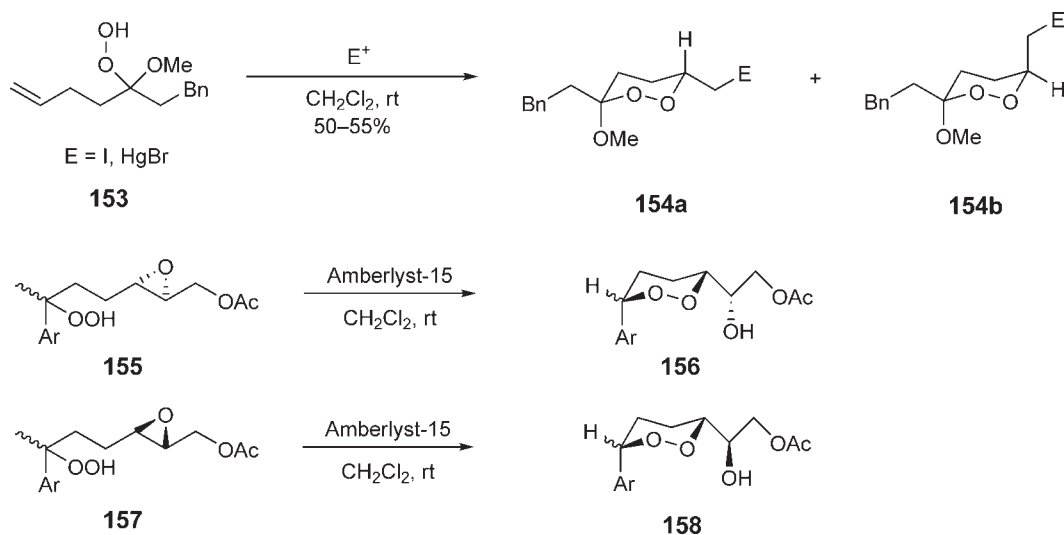
Cyclization of unsaturated hydroperoxides (e.g., **146** and **147**; cf. [Scheme 41](#)) for the synthesis of the corresponding 1,2-dioxanes proceeds generally in good yield by free radical and mercury-catalyzed reactions but the overall strategy, however, is often limited by low yields in the synthesis of the peroxide precursors [\[2002T2449, 1998SL122, 1985CC1472, 1984JOC1345\]](#). The peroxy radical **148** displays a weak triplet in the ESR spectrum [\[1993T2729, 1988J\(P2\)575\]](#) but the expected signal of the cyclized radical **149** could not be observed by ESR even though it could be trapped with oxygen to yield the hydroperoxide **150** which was subsequently reduced to the corresponding alcohol



Scheme 41

151. One hydroperoxide **152** was isolated and the stereochemistry proven by NMR spectroscopy in solution and by X-ray crystallography in the solid state <2005JOC251> (which therefore represents one of the very rare examples of peroxide crystal structures).

The corresponding hydroperoxide acetals or ketals **153** were cyclized by both peroxyiodination and peroxymercuration to give the stereoisomers **154a** and **154b** <2000JOC1069, 2000H(53)1293, 1996TL463, 1995JOC8218, 1995JOC784, 1993JOC5469>; whereas peroxyiodination progressed with a complete lack of diastereoselectivity, peroxymercuration furnished **154a** selectively in good yield (**Scheme 42**). The stereoisomers were assigned by ^1H NMR spectroscopy. During the total synthesis of two antimalarial peroxides <2001TL7281, 1995TL4167>, α -faranese <1996SL349> and a sponge-derived natural product <2005OL2509>, the 1,2-dioxane moiety involved was produced by the same protocol.

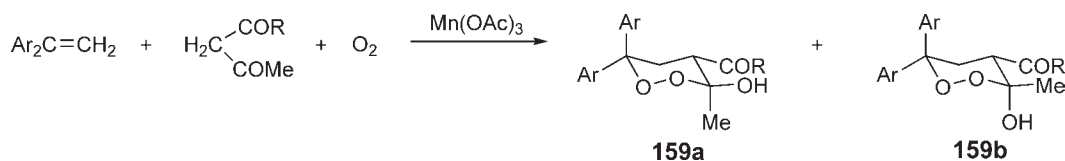


Scheme 42

If the double bond in the γ -position to the peroxy group is epoxidized instead as in **155** and **157**, cyclization can also be obtained by nucleophilic attack of the OOH group. For example, strongly acidic Amberlyst-15 as reagent gave the desired 1,2-dioxanes **156** and **158** in 65% yield (**Scheme 42**) <1995JOC3039, 1994TL9429>.

8.10.9.1.4 Synthesis of 1,2-dioxan-3-ols

Alkenes and 1,3-dicarbonyl compounds together with molecular oxygen can be cyclized in a one-step synthesis to 1,2-dioxan-3-ols **159** by a thermodynamically-controlled Mn(III)-based oxidation (**Scheme 43**).



Scheme 43

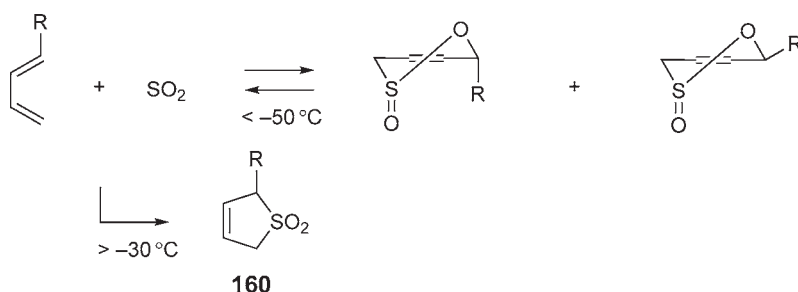
1,3-Diketones <1995JHC1783, 1991BCJ1800, 1990TL6371, 1990TL2425>, β -keto esters <1993J(P1)609, 1992BCJ1371>, and acetoacetamides <1991BCJ3557> were used as 1,3-dicarbonyl entities; alternatively, other active methylene compounds (sulfinyl-2-propanone and sulfonyl-2-propanone derivatives <1993JHC209> and acyl-acetonitriles <1997S899, 1996TL4949>) have been employed as building blocks for the 3-hydroxy-1,2-dioxanes. The mechanism of this radical reaction was studied in detail <1997S899>. The reactions of the 1,3-diketones yielded

single stereoisomers while the reactions of acetoacetamides, however, yielded a mixture of two stereoisomers. Both isomer ratio and stereoisomerism were assigned by ^1H and ^{13}C NMR spectroscopy <1993JHC209, 1991BCJ3557>; X-ray structures have not been published. The preparation of 1,2-dioxin moieties during the total synthesis of two naturally occurring alkoxy-1,2-dioxins <1999JOC1789> follows this protocol whereby identically therapeutic retinoids were obtained <1991MI826>.

8.10.9.2 Sultines

8.10.9.2.1 By hetero-Diels–Alder reaction of conjugated dienes and SO_2

As previously mentioned, the synthesis of 3,6-dihydro-1,2-oxathiin 2-oxides (sultines) by Diels–Alder addition of SO_2 to conjugated dienes is limited to temperatures below -50°C and with the presence of a protic or Lewis acid catalyst <1993HCA2250>. Because of their thermal instability, sultines undergo readily a retro-Diels–Alder reaction to the corresponding dienes and SO_2 at higher temperatures followed by a thermodynamically more favorable addition reaction (cheletropic reaction). This latter reaction produces stable five-membered ring adducts, the corresponding 2,5-dihydrothiophene 1,1-dioxides **160** (sulfolenes) (Scheme 44). The thermodynamic and kinetic data for these reactions, together with theoretical parameters from DFT calculations, indicate the sultines (obtained under conditions of kinetic control) to be ca. 10 kcal mol^{-1} less stable than their isomeric sulfolenes in $\text{CH}_2\text{Cl}_2/\text{SO}_2$ solution. The activation energies of the hetero-Diels–Alder addition were calculated to be ca. 2 kcal mol^{-1} smaller than the activation enthalpies of the corresponding cheletropic additions <2002HCA712>. The two reaction mechanisms have been studied in detail <2002JOC1882, 1996JPO17>.

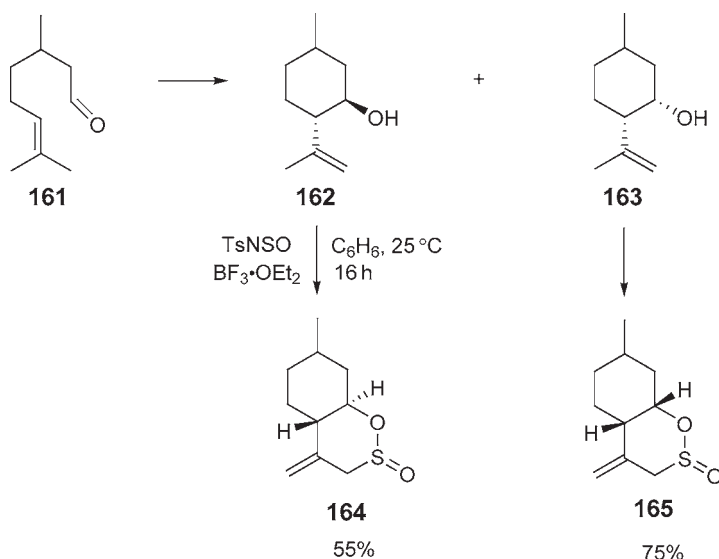


Scheme 44

The result of the competition between two possible addition reactions of SO_2 depends on the nature of the 1,3-diene substituents <2002CEJ1336, 1998JOC9490, 1994TL4743>. The hetero-Diels–Alder additions of SO_2 to 1-substituted (*E*)-butadienes, for example, are highly regioselective yielding exclusively the corresponding 6-substituted sultines <2002HCA761, 2002HCA733>.

8.10.9.2.2 From unsaturated alcohols and TsNSO

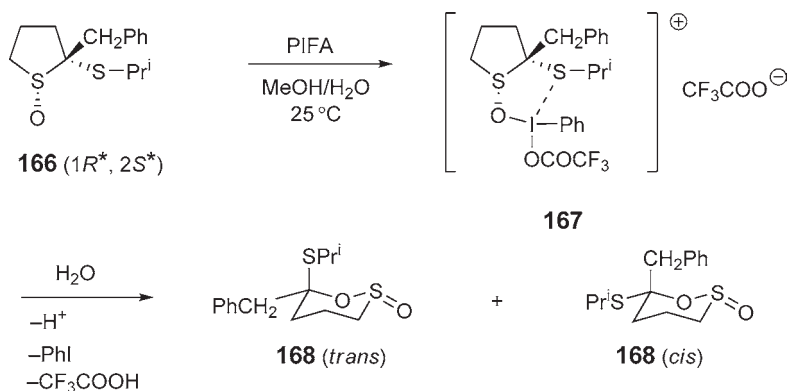
The isopulegol isomers **162** and **163** obtained from (*R*)-citronellal **161** by an initial oxo-ene reaction (cf. Scheme 45) were separated by column chromatography and each unsaturated alcohol was reacted with *N*-sulfinyl-*p*-toluenesulfonamide (TsNSO) in benzene at ambient temperature. Subsequently, $\text{BF}_3 \cdot \text{OEt}_2$ was introduced, and after 16 h the resulting sultines **164** and **165** were isolated by column chromatography <1995JOC8067>. The sultines were obtained in high yields and their structures confirmed by X-ray analysis <1993CC1195>, which showed consistent relative configurations of the sultines and starting alcohols and an axial orientation for the $\text{S}=\text{O}$ oxygen. Thus the synthesis proceeds stereoselectively and the stereochemical integrity of the C- α to the ring oxygen atom in the sultine is preserved. In addition, a number of other cyclic and acyclic unsaturated alcohols have been reacted stereoselectively using TsNSO in benzene/ $\text{BF}_3 \cdot \text{OEt}_2$. By this protocol, highly crystalline and thermally stable sultines could potentially be synthesized stereoselectively at ambient temperatures.



Scheme 45

8.10.9.2.3 By ring enlargement

2-(Alkylthio)-2-benzylthiolane 1-oxides **166** and 2-(alkylthio)-2-(α -hydroxybenzyl)thiolane 1-oxides are able to be oxidized with [bis(trifluoroacetoxy)iodo]benzene (PIFA), and by subsequent ring enlargement the corresponding sultines **168** can be obtained (Scheme 46) <1999EJO943>. Of the two diastereomers of the starting thiolane 1-oxide, only one stereoisomer ($1R^*$, $2S^*$ relative stereochemistry as assigned by NMR) reacts with no product forthcoming from the other one. This surprising selectivity could be explained by a chelate-like intermediate **167** (Scheme 46), which is cleaved by solvolysis and the resulting sultines are thus formed as mixtures of diastereomers. The resulting diastereomeric sultines were separable by column chromatography and for each isolated compound, a chair conformation was found to be present with equatorial orientations of the sulfoxide oxygen in both cases.

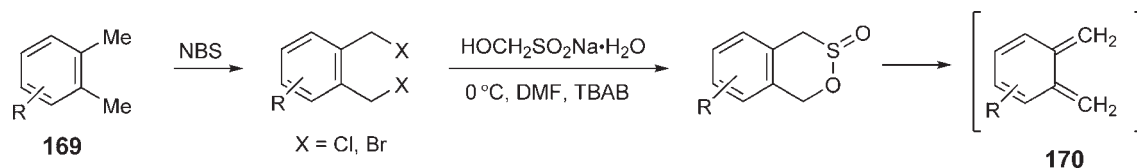


Scheme 46

The oxidation of 3,4-di-*tert*-butylthiophene 1,1-dioxide with peracids (MCPBA or trifluoroperacetic acid) affords the corresponding sultone in only moderate yield <1991JOC4001>, though the sultine intermediate could be isolated and characterized structurally.

8.10.9.2.4 Synthesis of 1,4-dihydro-2,3-benzoxathiin 3-oxide as a useful precursor of *o*-quinodimethane
The sultine 1,4-dihydro-2,3-benzoxathiin 3-oxide **9** and substituted derivatives are ideal reagents for the *in situ* synthesis of *o*-quinodimethanes (*o*-xylylenes) **170** because they decompose smoothly in refluxing benzene at ca. 80 °C and do not

produce any by-products except for SO₂, and, in the absence of a dienophile, any polymeric material <B-1990MI240>. They are therefore used widely as latent diene components in Diels–Alder addition reactions <2004CC1734, 2004S558, 2000BML1755, 2000JOC2379, 1997JOC7585, 1997T2599, 1995TL8307, 1985CJC3526>. Their syntheses start from the corresponding α,α' -dihalo-*o*-xylenes **169** by reaction with sodium hydroxymethanesulfinate in dimethylformamide (DMF) at 0 °C with the absence of water and in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB) (Scheme 47) <1991JOC1947>. This procedure has also been used for the preparation of furan, thiophene, and pyrrole-fused sultines <1995CC2537, 2006IJB227>.



Scheme 47

Alternatives, besides those given in CHEC(1984), for obtaining 1,4-dihydro-2,3-benzoxathiin 3-oxide **9** include the electrolysis of α,α' -dibromo-*o*-xylene in the presence of SO₂ <1973MI291> and the photolysis of *o*-tolualdehyde in the presence of SO₂ followed by NaBH₄ reduction and finally cyclization to the sultine by treatment with acid <1986CJC246, 1985JOC4829, 1984TL5287>. However, the first method requires apparatus not normally available in synthetic laboratories and the second is a three-step synthesis requiring more expensive reagents.

8.10.9.3 Sultones

8.10.9.3.1 Ring closure of hydroxyalkylsulfonyl chlorides

δ -Hydroxy-1-butanefulfonyl chloride can readily be obtained from the corresponding mercaptan by aqueous chlorination. During workup, cyclization to the corresponding sultone, 1,2-oxathiane 2,2-dioxide **16**, already partially occurs and further reaction with triethylamine in CH₂Cl₂ provides the sultone almost quantitatively <1987PS(33)165, 1987PS(31)161>. With dilute solutions, there was no sign of polymer formation but at higher concentrations minor signals arising from polymeric products appeared in the ¹H NMR spectrum.

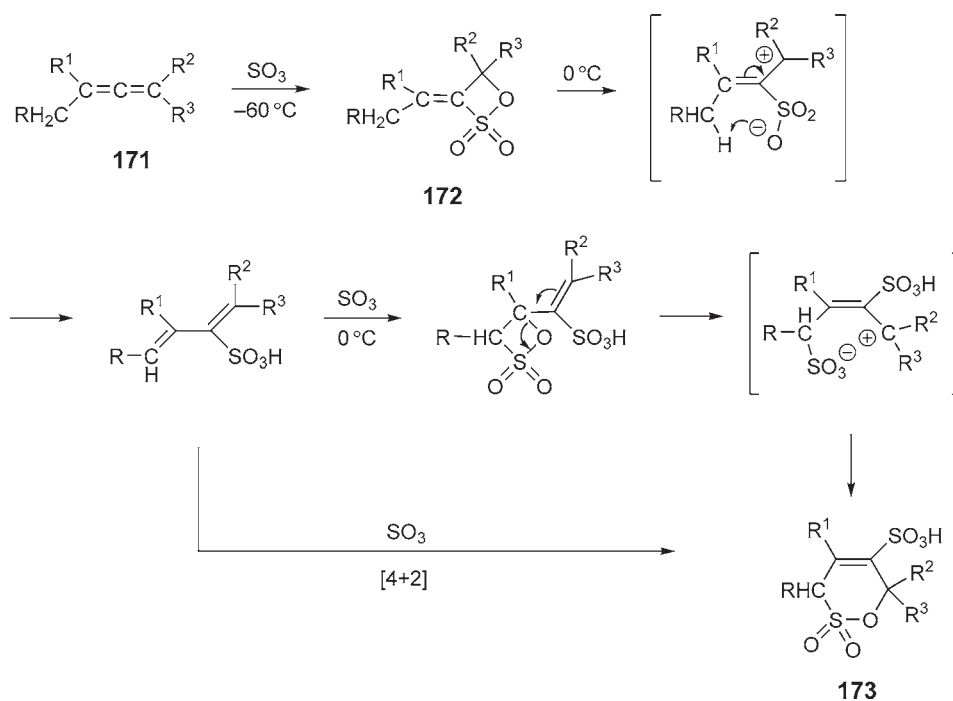
8.10.9.3.2 Reaction of cumulative and conjugated double bonds and SO₃

The reaction of a series of cumulative and conjugated dienes (cf. Table 8 and Scheme 48) with SO₃ was studied over the temperature range from –60 °C to ambient temperature using CH₂Cl₂ as solvent and 1.5 equiv of dioxane as reactivity moderator <1993RTC201>. In the case of the allenes **171**, the β -sultones **172**, that were first obtained

Table 8 Allenes and conjugated dienes reacted with SO₃

R^1	R^2	R^3/CH_2R	R^4	R^5	R^6
$R^1R^3C=C=CR^2R^4$					
Me	Me	Me	Me		
Me	H	Me	H		
H	H	Me	Me		
H	H	Et	H		
H	H	–(CH ₂) ₆ –			
$R^1R^2C=C(R^3)–C(R^4)=CR^5R^6$					
H	H	H	H	Me	Me
H	Me	H	H	H	Me
H	Me	H	H	Me	H
H	H	H	H	H	Me
H	H	H	H	Me	H
H	H	Me	H	H	H

after raising the temperature to 0 °C and applying an excess of SO₃, rapidly converted into unsaturated δ -sultones **173** in yields of ca. 80% (Scheme 48). Reaction of the 1,3-dienes with 1 equiv of SO₃ at –60 °C quantitatively provided the unsaturated sultones. The reactions proceeded nonstereospecifically via a two-step mechanism: The initial [2s+2s] cycloaddition is subsequently followed by a very fast conversion of the resulting β -sultones into δ -sultones. Under the same reaction conditions, from *exo*-methylenecyclopentane, 4-methylene-1,2-oxathiane 2,2-dioxide was isolated as a white solid <1993RTC457>.



Scheme 48

Similarly, using either sulfuric acid, the SO₃/dioxane complex, or a solution of SO₃ in chloroform/dioxane, 4,6-diphenyl-1,2-oxathiin 2,2-dioxide was obtained from phenyl acetylene <1999RJO415>, 3,6-disubstituted-1,2-oxathiane 2,2-dioxides were obtained from allylphenol <2002RJO1210>, and 3,4-dihydro-6-phenyl-1,2-oxathiin-4-one 2,2-oxide was obtained from Ph–CO–CH₂–COMe <1991CIL253>.

8.10.9.3.3 By Michael addition

The Michael addition (K₂CO₃, 18-crown-6, 90 °C) of vinyl sulfonates and sulfonamides with phenylacetic esters **174** was utilized as the key step in the general synthesis of sultones <1991JOC3549>. The desired mono-Michael adduct **175** was isolated in 48% yield (Scheme 49), reduced using diisobutylaluminium hydride (DIBAL-H) to the corresponding alcohol **176** and then treated with sodium hydride to give the sultone **177**. This methodology could also serve well for the syntheses of other target sultone precursors.

8.10.9.3.4 Synthesis by RCM

The sultones **180** can be synthesized by RCM of sulfonates using the second-generation Grubbs' ruthenium catalyst (Scheme 50) in excellent yields, with short reaction times and low catalyst loading. The vinylsulfonates **179** are readily generated by esterification of the corresponding alcohols **178** with vinylsulfonyl chloride <2004S1696, 2002SL2019, 2006T9017>. These α,β -unsaturated sultones **180** add dienes (e.g. cyclohexadiene) by intermolecular Diels–Alder reactions to give products such as **181**.

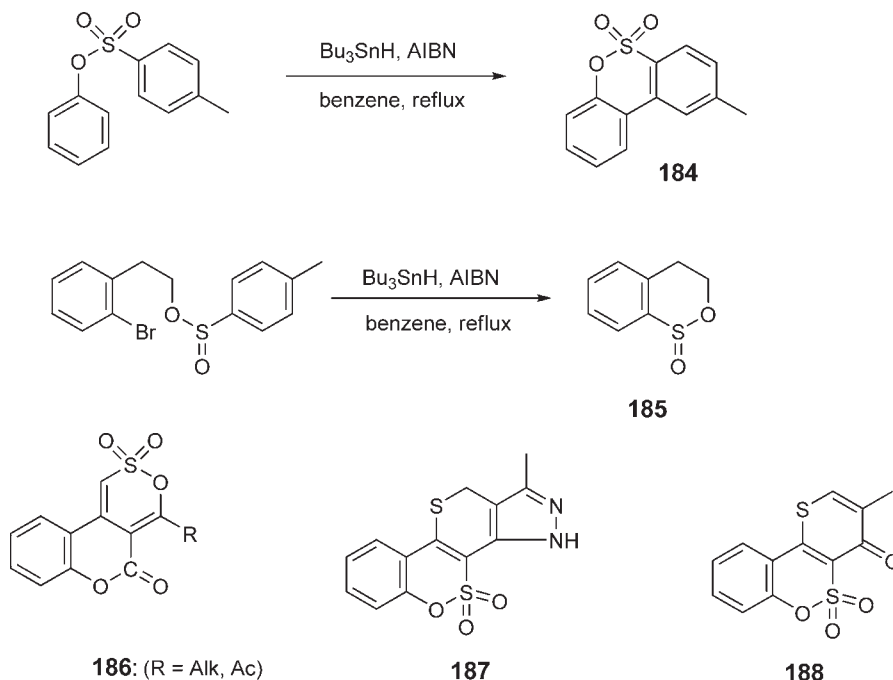


Arenesulfonate esters of homopropargyl alcohol **182** (Scheme 51) can be transformed into 4-aryl-5,6-dihydro-1,2-oxathiin 2,2-dioxides **183** by an *n*-butylstannyl radical-catalyzed rearrangement in reasonable yield <1992CC1067, 1997H(46)523>. Isolation and X-ray structural characterization of the α -tributyltin-substituted sulfone analogs as side products provided evidence that the already ring-closed radical is the intermediate in this cyclization–fragmentation–cyclization reaction sequence <2002SL778>.



4-Chromone-3-sulfonate <1994JHC405, 1986LA1124, 1985LA2012> and the analogous sulfonyl chlorides <1984LA1395> can be converted by ring transformation into the corresponding 1,2-benzoxathiin 2,2-dioxides, obviously via an addition-elimination mechanism <1985LA2012>. If the oxathiin derivatives are treated with hydroxylamine/HCl, re-formation of the ring is possible <1988AP729>.

By consideration of the intramolecular free radical *ipso*-substitution approach <1988TL2987> for the synthesis of biaryls, the direct [1,6]-addition product **184** was obtained in 63% yield from the corresponding *p*-toluenesulfonyl derivative (Scheme 52) <1991CC877>. Under similar reaction conditions, the sultine **185** was available in 89% yield from the readily available substrate <2006AGE633>.



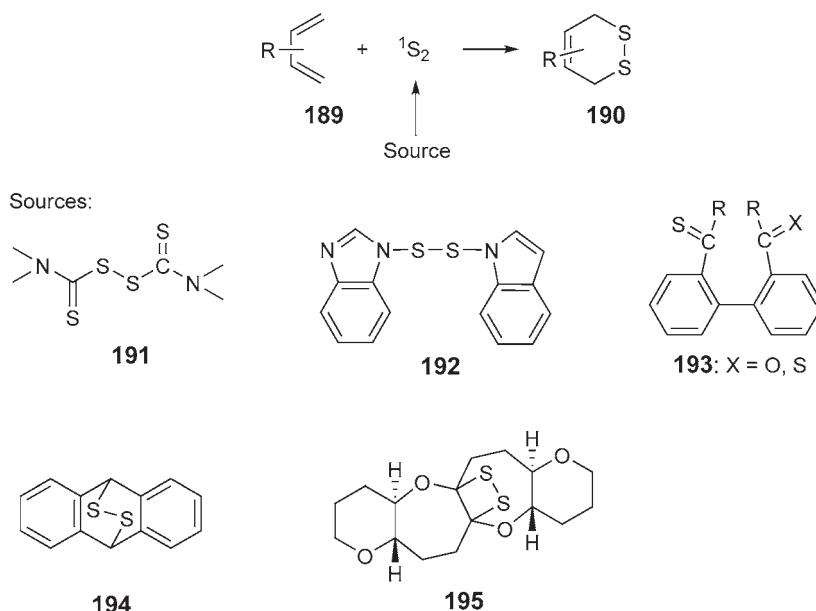
Scheme 52

Reaction sequences for the synthesis of a number of exotic sultones **186–188** have also been proposed and the compounds synthesized subsequently in high yields (Scheme 52) <1990AP987, 1984H(22)2293>.

8.10.9.4 Dithiins and Dihydrodithiins

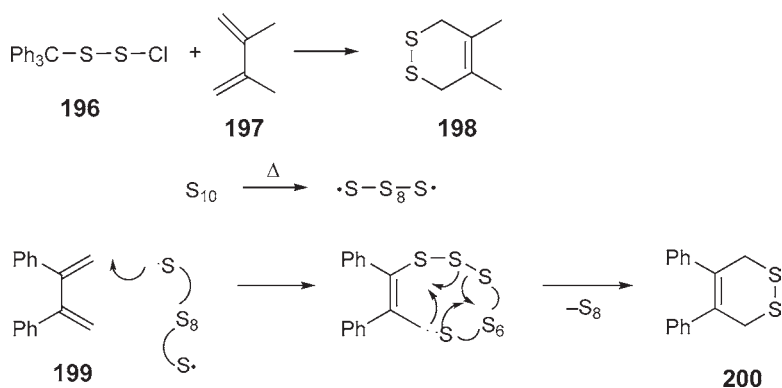
8.10.9.4.1 Dihydro-1,2-dithiins by Diels–Alder reaction with sulfur as dienophile from different sources
Singlet diatomic sulfur $^1\text{S}_2$ from different sources reacts selectively to convert dienes **189** into 3,6-dihydro-1,2-dithiins **190** in a Diels–Alder fashion (Scheme 53) <1984JA799>. A number of synthetically useful procedures to generate and transfer singlet sulfur have been reported: $^1\text{S}_2$ was liberated from aliphatic and aromatic dialkoxy disulfides <2002TL8781, 1995JA9067>, tetramethylthiuram disulfide **191** <1993SUL19>, benzimidazole disulfide **192** <2000SUL163>, cyclopentene/cyclohexene adducts of Ph_3CSSCl and Ph_3CSSSCl <1994TL7167>, cyclic and linear diselenatetrasulfides <2004TL9181>, 2,2'-biphenyl thione derivatives **193** <1987JA926>, 9,10-epidithio-9,10-dihydroanthracene **194** <1990T5093, 1987TL6653>, organometallic precursors (different titanium and zirconium pentasulfides) <1988JOC3812>, silicon and germanium trisulfides <1984JA799>, and dithiatopazine **195** <1988JA4868>. The $^1\text{S}_2$ Diels–Alder-type addition, consistent with Woodward–Hoffmann rules, occurs stereospecifically <1990JA7819>, whereby only the adducts of 100% *syn*-addition were obtained.

Elemental sulfur (S_8) directly reacts with conjugated dienes to yield 3,6-dihydro-1,2-dithiins in the presence of catalytic amounts of organometallic polysulfides (e.g., Cp_2MoS_4 , Cp_2WS_4 , Cp_2TiS_5 , Cp_2ZrS_5 <1998TL9139>) or $\text{Pd}(\text{acac})\text{PPh}_3\text{--AlEt}_3$ (1:3:4) in absolute toluene (acac = acetylacetonate) <1987ZOR1793>. Trapping S_2O , a very reactive sulfur species, instead of sulfur with 2,3-dimethyl-1,3-butadiene yielded the corresponding 4,5-dimethyl-3,6-dihydro-1,2-dithiin 1-oxide <2000JOM(611)127, 2001AGE1924>.



Scheme 53

It was reported that chloro(triphenylmethyl) disulfide **196** reacts with 2,3-dimethyl-1,3-butadiene **197** to give the Diels–Alder product **198** (Scheme 54); the structure of the reaction product was assigned unequivocally by ^1H and ^{13}C NMR and with MS displaying characteristic loss of S_2 <1991TL7651>. From the other sulfur allotropes, S_{10} (readily available from Cp_2TiS_4 and SO_2Cl_2 after extraction from the mixture of allotropes) was reacted with 2,3-diphenylbutadiene **199** and provided 4,5-diphenyl-3,6-dihydro-1,2-dithiin **200** in moderate yield (Scheme 54) <1999TL7961>; the high selectivity of S_{10} was rationalized by the cycloelimination of S_8 . The reaction of SCl_2 with alkoxy and other activated aromatic compounds was found to yield dibenzodithiins **54–61** (Scheme 13) <1989PS(42)111>. Finally, at $130\text{--}140^\circ\text{C}$, 3,6-dihydro-1,2-dithiins are known to polymerize readily <1992JOC1699, 1992CC1460, 1989SR207>.

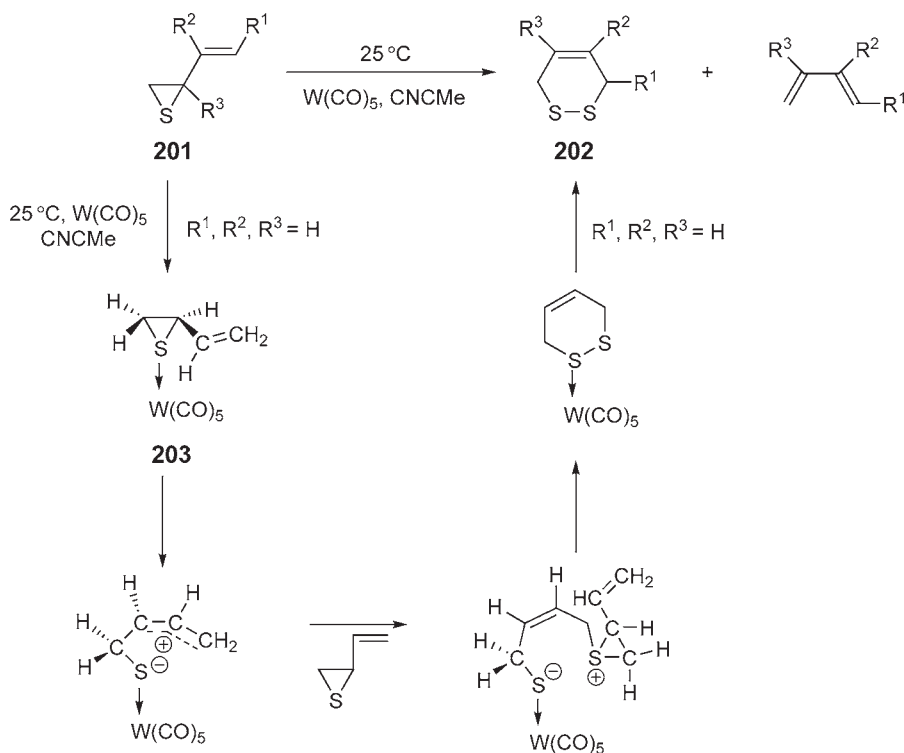


Scheme 54

8.10.9.4.2 3,6-Dihydro-1,2-dithiins by catalytic transformation of vinylthiiranes

$\text{W}(\text{CO})_5(\text{NCMe})$ transformed vinylthiirane and substituted vinylthiiranes **201** into 3,6-dihydro-1,2-dithiins **202** in excellent yields (Scheme 55) <2000POL521, 1999JA3984, 1998JA1922, 1997OM1430, 1996JA10674>. Two equivalents of the vinylthiirane are required and 1 mol of butadiene is produced by transferring its sulfur to the other vinylthiirane molecule. In the absence of the catalyst or in the presence of $\text{W}(\text{CO})_6$, only traces of the 3,6-dihydro-1,2-dithiins

202 were formed; the catalyst is long-lasting and relatively insensitive to air. The mechanism is depicted in **Scheme 55** showing that the catalyst reacts with 1 mol of vinylthiirane to form the intermediate $W(CO)_5$ complex **203**, which then reacts with the second mole of vinylthiirane with ring opening of the coordinated vinylthiirane and addition of the second sulfur to its vinyl group. Elimination, finally, of butadiene from the positively charged sulfur atom and S–S single-bond formation leads to the reaction products.



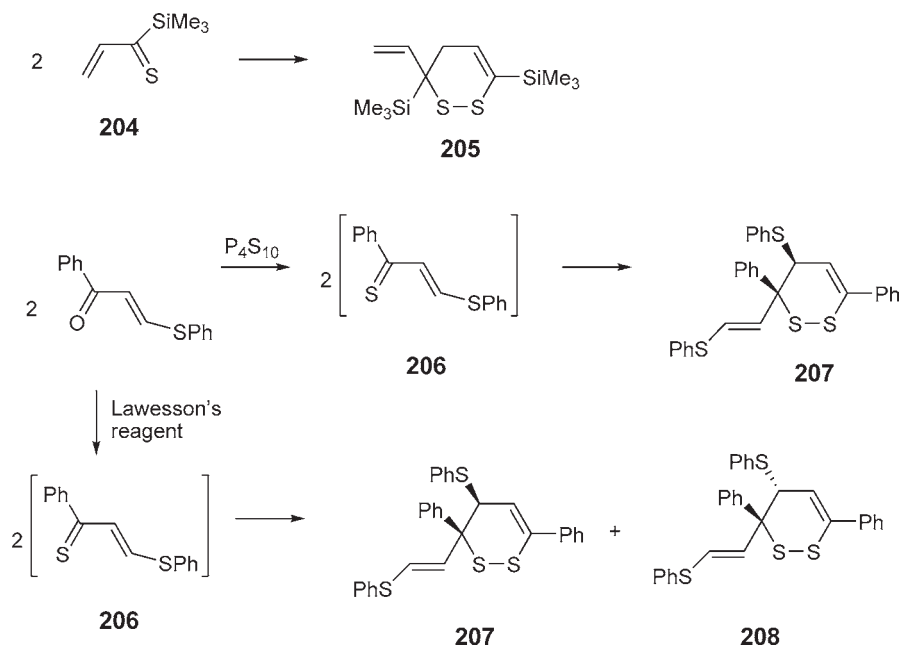
Scheme 55

Rate data were measured by ^1H NMR ($CDCl_3$, $21^\circ C$) whereby thiirane consumption was estimated using hexamethylbenzene as internal standard; acetonitrile cannot be used as solvent since the catalyst binds to it and the reaction is completely inhibited [\[2002T4517\]](#). The rate-determining step is the associative coordination of thiirane moiety to tungsten and an increase in the steric bulk upon substitution of the thiirane ring or the vinyl group was found to decrease the reaction rate [\[2002T4517\]](#).

3-Vinyl-3,6-dihydro-1,2-dithiin 2-oxide has been isolated as one of the main components from garlic (*Allium sativum*) [\[2001MI867\]](#). Its structure was elucidated by NMR and MS.

8.10.9.4.3 Silylated 3,6-dihydro-1,2-dithiins via self-dimerization of α,β -ethylene thioacylsilanes

α,β -Unsaturated thioacylsilanes **204** (readily accessible in high yield from substituted allenes with hexamethyldisilathiane in the presence of $CoCl_2 \cdot 6H_2O$) undergo a self-dimerization, hetero-Diels–Alder reaction to afford polyfunctionalized 3,4-dihydro-1,2-dithiins **205** (**Scheme 56**) [\[2005TL4711, 2003TL2831\]](#). The structure of the expected 3,4-dihydro-1,2-dithiins **205** was proven by analyzing the ABX-coupling pattern of the 4,5-protons (especially the large geminal coupling of the CH_2 group in position 5, $^2J_{gem} = 19.4$ Hz). β -Arylthio α,β -unsaturated thioketones **206** were found to readily dimerize to the 3,4-dihydro-1,2-dithiin derivatives **207** and **208** at ambient temperature [\[1986BCJ335\]](#); the same products (**Scheme 56**) were obtained when treating 1-phenyl-3-phenylthioprop-2-en-1-one with P_4S_{10} or Lawesson's reagent in refluxing CS_2 . Consideration of the ^1H NMR coupling constants, especially $^3J_{4,5}$, facilitated the assignment of the *cis*- and *trans*-isomers. In the case of P_4S_{10} , only the *cis*-isomer **207** was obtained; in the case of Lawesson's reagent, both *cis*- and *trans*-isomers **207** and **208** were isolated.



Scheme 56

8.10.9.4.4 Synthesis of 1,2-dithiins by ring-closure reactions

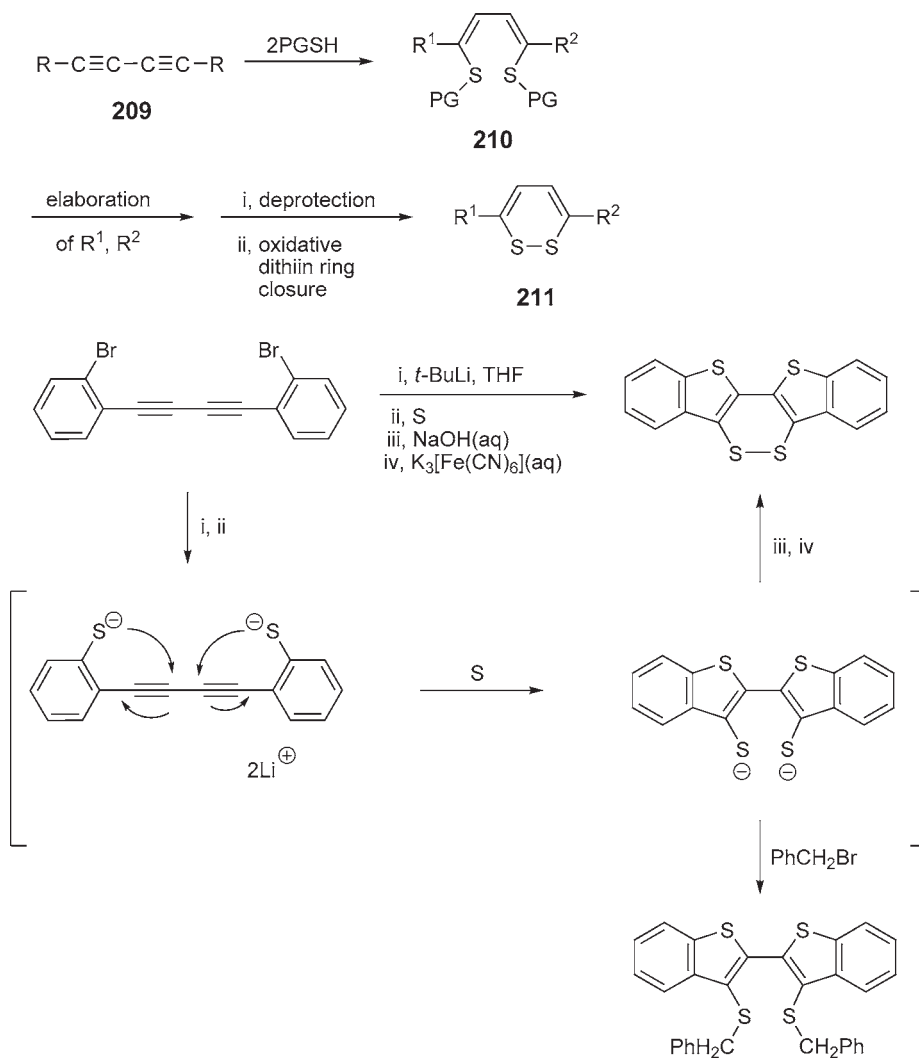
The synthetic methods reported to access the 3,6-disubstituted-1,2-dithiin ring system **211** follow the route portrayed in **Scheme 57**. The initial stereo- and regiocontrolled bis-addition of a thiol to a diyne **209** to give **210** is followed (after manipulation, as required of the substituents R^1 and R^2) by removal of the protecting groups, oxidative ring closure, and S-S bond formation <1997JOC446>. As protected thiols (PGSH), benzyl mercaptan <2003JOC8110, 2000JA5052, 1999AGE1604, 1994SL201, 1994JA9403, 1965AGE884>, 2(trimethylsilyl)ethyl mercaptan <1998JOC8644, 1994JA10793>, 2-mercaptopropionitrile <1995JME2628>, and *t*-butyl mercaptan <1997JOC446> have been employed successfully. This method, together with others published up to 1997 and 1999, has been reviewed extensively <1999PS(153/4)173, 1997HOU(E9)209>. Similarly, dibenzo-1,2-dithiin and substituted derivatives could be synthesized from the corresponding biphenyl precursors <1997HOU(E9)209, 1989SR207>; more recent papers, though, have not been published and only the open-chain 2,2'-dimercapto-6,6'-dimethoxy-1,1'-biphenyl as precursor for the dibenzodithiin was synthesized in enantiomerically pure form <1998TA2819>.

A general and facile synthetic route to fused 1,2-dithiins based on intramolecular triple cyclization of bis(*o*-haloaryl)dialkynes has been reported (**Scheme 57**) <2005OL5301>; the cyclization involves three reaction steps: (1) dilithiation with *t*-BuLi in THF followed by trapping with 4 mol of sulfur, (2) intramolecular dianion attack followed again by trapping with sulfur, and finally (3) exchange of lithium for sodium anions by addition of aqueous NaOH, following the ring closure by the oxidant $K_3[Fe(CN)_6]$. The anionic mechanism was proved by trapping the intermediate with benzyl bromide which afforded the corresponding bis(benzylthio) compound <2005OL5301>.

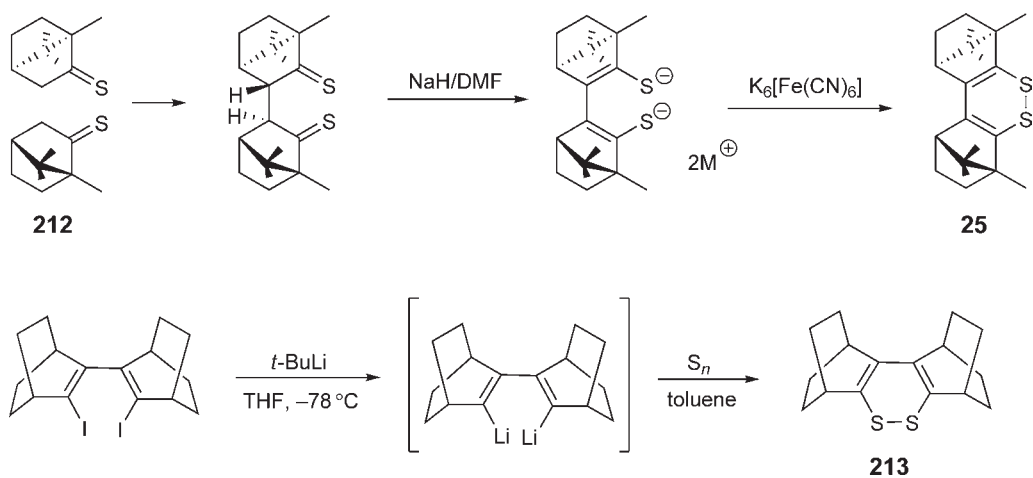
Diborneo-1,2-dithiin **25** was synthesized from (*R*)-thiocamphor **212** via disulfide oxidation (of the enethiol form) and Cope rearrangement to the bis-thiocamphor, which was deprotonated employing NaH/DMF to form the dienolate and then finally oxidized with $K_3[Fe(CN)_6]$ (**Scheme 58**) <1995T13247, 1994TL1973>; only the racemic dithiin derivative **25** was obtained.

The corresponding 1,2-dithiin derivative with bicyclo[2.2.2]oct-7-ene units **213** was synthesized from the diiodide in 59% yield by treatment with 4 equiv of *tert*-butyllithium in THF at -78°C and subsequent treatment with a toluene solution of an excess amount of elemental sulfur (**Scheme 58**) <2002JA15038>. The two 1,2-dithiin derivatives **25** and **213** were so stable that decomposition or sulfur extrusion was not observed in daylight and at room temperature in sharp contrast to the light-sensitive nature of other 1,2-dithiin derivatives.

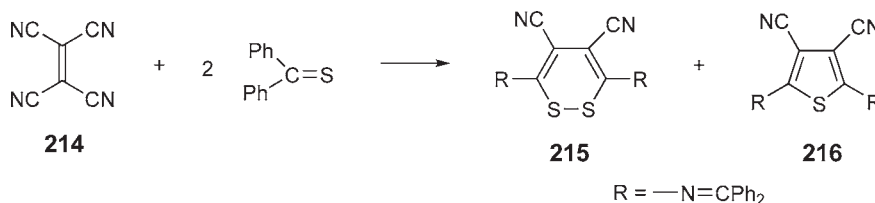
Finally, an unorthodox pathway to the dithiin systems has been reported: Tetracyanoethylene **214** combines with two molecules of thiobenzophenone in refluxing benzene to give the tetrasubstituted 1,2-dithiins **215**. However, these were obtained only in addition to the corresponding thiophenes **216** as the main reaction products (**Scheme 59**) <1985TL1849, 1997LA1677>.



Scheme 57



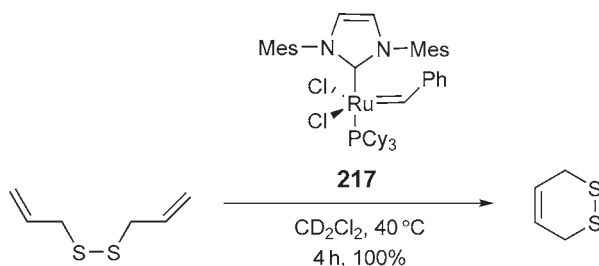
Scheme 58



Scheme 59

8.10.9.4.5 Dihydro-1,2-dithiins by RCM of diallyl sulfides

1,3-Dimesitylimidazol-2-ylidene ruthenium benzylidene catalyst **217** (Scheme 60) was successfully employed in the RCM of diallyl disulfide and which led quantitatively to 3,6-dihydro-1,2-dithiin **18** (Scheme 60) <2002OL1767>; both Grubbs' and Schrock's catalysts gave lower yields (15% and 77%, respectively).



Scheme 60

8.10.9.5 1,2-Dithianes

8.10.9.5.1 By oxidation of butane-1,4-dithiols

Selective oxidation of butane-1,4-dithiol to 1,2-dithiane under mild conditions is not an easy task because thiols are among the functional groups which can be readily overoxidized, for example, to the corresponding sulfoxides, sulfones, or even sulfonic acids. For this reason, extensive research has been conducted on developing methods to control this oxidation. Most of these methods involve the use of metal catalysts or other reagents (like chlorohydrocarbons or halogens) and thus suffer from the disadvantage that toxic metal ions and/or solvents are in use. A number of methods have been published and characteristic data for the reaction are presented in Table 9. Solubility in water and/or organic solvents, price, stability, commercial availability, as well as mild and stable oxidation potential are the major criteria for the reagents developed.

Changing the sulfoxide component of the Re-catalytic system (entry 5 in Table 9) from Me₂S=O to Ph₂S=O resulted in rapid oxidation to 1,2-dithiane 1-oxide in 84% yield <1997JA9309>.

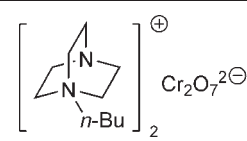
meso-2,5-Dimercapto-*N,N,N',N'*-tetramethyladipamide (*meso*-DTA) has been synthesized as a potential reducing agent for biochemical applications (Scheme 61) <1991JOC7328>; this reagent, compared to others, is strongly reducing, inexpensive to synthesize, and kinetically fast. During the reduction reaction of *meso*-DTA, the corresponding 3,6-disubstituted-1,2-dithiane (*meso*-DTA^{ox}) was obtained.

8.10.9.5.2 By ring closure of butane-1,4-dihalides, diacetates, or ditosylates

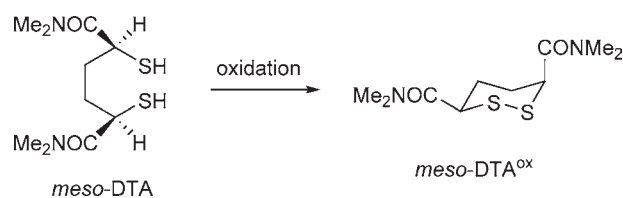
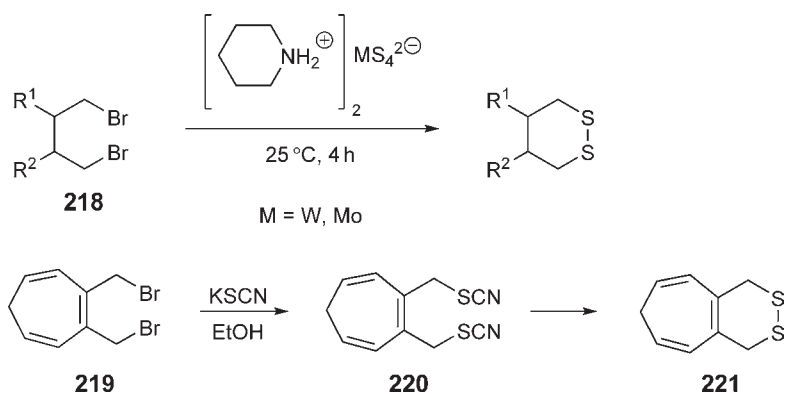
Instead of 1,4-dithiols, the corresponding alkyl dihalides **218** can also be employed and transformed into 1,2-dithiane derivatives by reaction with piperidinium tetrathiotungstate <1992JOC1699> or with piperidinium tetrathiomolybdate <1989JOC2998> in good to excellent isolated yields under very mild reaction conditions (Scheme 62). By this approach, 1,2-dithiane and 1,4-dihydro-2,3-benzodithiin have been synthesized. Using the same reaction conditions, the corresponding 4-methyl-3,6-dihydro-1,2-dithiin was obtained from 2-methyl-1,4-ditosyloxybut-2-ene <1992JOC1699>.

Table 9 Oxidative coupling of dithiols to 1,2-dithianes with different reagents

$$\text{HS}-(\text{CH}_2)_4-\text{SH} \longrightarrow \text{a}$$


Entry	Reagent	Solvent, temperature, time	Yield (%)	Reference
1		CH ₃ CN, reflux, 1.2 h	98	2004JRM286
2	(PhCH ₂ P ⁺ (Ph) ₃) ₂ S ₂ O ₈ ²⁻	CH ₃ CN, reflux, 1.2 h	98	2003PS1277
3	Me ₄ N ⁺ ·chlorochromate (HCl)	CH ₃ CN, reflux, 2.0 h	96	2002JCM547
4	KMnO ₄ /CuSO ₄ ·5H ₂ O	CH ₂ Cl ₂ , rt, 1.2 h	97	1998S1587
5	Re(O)Cl ₃ (PPh ₃) ₂	CH ₂ Cl ₂ , rt, DMSO	94	1997JA9309
6	CCl ₄ /NEt ₃	CH ₃ CN, -78 °C	95	1989SUL251
7	(<i>n</i> -Bu) ₃ SnCl/NEt ₃	i, CCl ₄ , rt, 3 h ii, CH ₂ Cl ₂ , 0 °C, I ₂ or Br ₂ , 5–10 min	95–96	1986TL441
8	BrCH(COOEt) ₂ /NEt ₃	CH ₂ Cl ₂ , -16 °C	82	1986CPB486
9	DMSO/SbCl ₅ (1:1)	DMSO, rt	73	1985NKK29
10	SiO ₂ -Cl ₂ (5 mol%)	CH ₂ Cl ₂ , 0 °C, 10 min	97	2006CL1048

^am.p. 30–32 °C; M⁺ = 130 (56%); ¹H NMR: δ 2.90–2.62 ppm and 2.05–1.71 ppm.

**Scheme 61****Scheme 62**

Sulfur transfer can also occur from sulfurated borohydride exchange resin <2001TL6741>; the reaction proceeds in methanol at ambient temperature rapidly (<5 min) and in high yield (91%). From 1,4-di(acetylthio)butane, 1,2-dithiane can be obtained by a one-pot synthesis in excellent yield (98%) using Bu₂Sn(OMe)₂, FeCl₃, and a catalytic amount of CsF as a promoter in THF solution <1990TL3595>.

3,4-Bis(bromomethyl)-1,3,5-cycloheptatriene **219** reacted with potassium thiocyanate in refluxing ethanol and afforded quantitatively the corresponding bithiocyanate **220**, which could be transformed readily to 3,6,9-trihydro-cyclohepta[*d*][1,2]dithiin **221** in 70% yield with NaBH₄/EtOH/THF (cf. [Scheme 62](#)) <2006H(68)1031>.

8.10.10 Ring Syntheses by Transformation of Another Ring

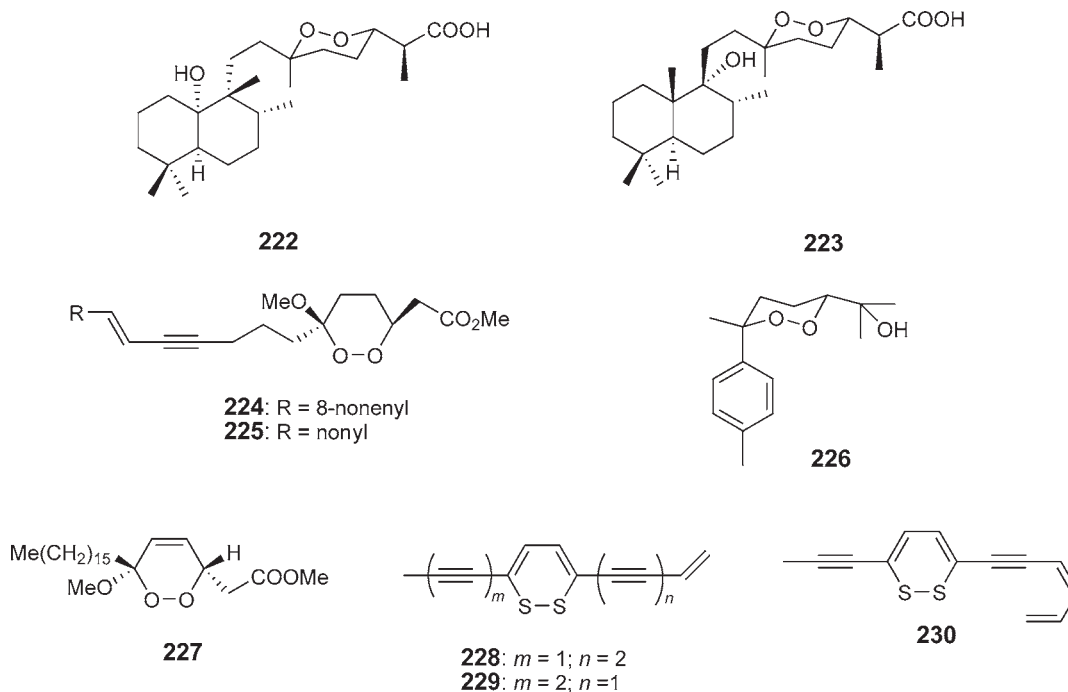
Only a few examples of ring syntheses by transformation of another ring have been published, as exemplified by the preparation of the sultines **168** by ring enlargement of five-membered thiolane 1-oxides **166** (cf. [Section 8.10.9.2.3](#)) and the 3,6-dihydro-1,2-dithiins **202** by catalytic transformation of vinylthiiranes **201** (cf. [Section 8.10.9.4.2](#)). Because possibilities to synthesize six-membered rings with oxygen and/or sulfur as heteroatoms in 1,2-positions are rather limited, these reactions have been covered already in [Section 8.10.9](#) together with alternative syntheses from alicyclic compounds.

8.10.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Reports on the new syntheses of six-membered ring systems with two oxygen and/or sulfur atoms in 1,2-positions are rather limited and are covered already in [Section 8.10.9](#). Often, only one really successful synthetic path has been described or the derivatives obtained were simply by-products. Thus, a comparison of various synthetic strategies for obtaining certain dioxane/oxathiane/dithiane derivatives is not meaningful.

8.10.12 Important Compounds and Applications

There are three classes of cyclic peroxides that were found in marine sponges: steroidal peroxides, norsesterterpene and norditerpene peroxides, and polykide peroxides; many of them were isolated and their relative and absolute stereochemistry was determined. Most of them (even as crude extracts) show exceptional antimicrobial and antifungal properties (cf. [Section 8.10.3](#)). For example, the norsesterterpene 1,2-dioxides mycaperoxides A and B **222** and **223** ([Scheme 63](#)) showed significant cytotoxicity and *in vitro* antiviral activity.



Scheme 63

Thus, research concentrated on the synthesis of these biologically active sponge-derived natural products: among many others, the total synthesis of peroxyacarnates A and D **224** and **225**, which show exceptional activity against fungal and cancer cell lines, has been published <2005OL2509>.

After the discovery of the antimalarial properties of artemisinin, its analogs attracted considerable attention. As another antimalarial principle, yingzhaosu C **226**, isolated from a traditional Chinese herbal medicine, was intensively investigated within the time period covered. The total synthesis of the four stereoisomers of yingzhaosu C <1995TL4167, 1994TL9429> and also a preparative-scale synthesis of this intriguing natural product <2005JOC3618> was reported. Structurally related analogs (containing the 2,3-dioxabicyclo[3.3.1]nonane system) were synthesized <2002T2449, 1998SL122> and their antimalarial activity was tested <1998JME2164>.

Cyclic peroxides were also applied as antifungal agents. Plakorin **227** is an agent with extremely high antitumor activity <1995JME2628>; in the patent literature, applications of the corresponding 1,2-oxathiins (sultines, sultones) as photoresists for high-resolution lithography, as additives to electrolytes of secondary lithium batteries, as herbicides and plant growth regulators, and as antifungals and anti-infectives were reported.

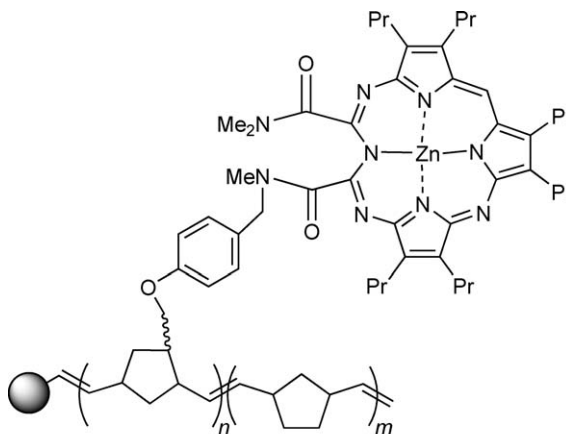
The most important 1,2-dithiine derivatives are, in retrospect, thiarubrine A **228** and thiarubrine B **229** which exhibit a wide spectrum of biological activity including antiviral and antibiotic activities. They were first isolated from the young leaves of *Aspilia mossambicensis* and *Aspilia plurisetta* <1993P113, 1989P3523, 1985E419>. The total synthesis of these two potent antibiotics <1994JA10793, 1994JA9403>, of thiarubicine C **230** <1998JOC8644>, and of other 3,6-disubstituted 1,2-dithiins <1995JME2628, 1994SL201> was not long in coming; their photochemistry was studied in detail <1996JA4719>.

Application of the rod-like 3,6-disubstituted-1,2-dithiins in liquid crystal compositions and also as antifungal agents and anti-infectives was reported in the patent literature.

8.10.13 Further Developments

8.10.13.1 1,2-Dioxin and 1,2-Dioxane Derivatives

Another review concerning the synthesis of cyclic peroxides has been published <B-2006MI189> and a solid-supported catalyst **231** for both cycloaddition reactions and singlet oxygen ene reactions was synthesized and demonstrated to be an efficient, mild, and recyclable alternative to solution-phase photooxygenation catalysts <2006JOC724>.

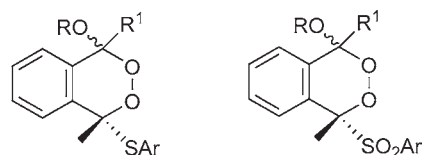


231

Further, the thio-olefin co-oxidation (TOCO) radical chain reaction (cf. Chapter 9.11.9.3.3) using ground state molecular oxygen was employed to synthesize a series of benzo-fused cyclic peroxy ketals **232** in good yield (Scheme 64) <2006T4120>.

A number of endoperoxide derivatives from marine organisms – the nitro derivative of plakoric acid <2006CHJ1190>, a number of 1,2-dioxanes of the plakortin family <2006JME7088>, some 4,5-dihydro-1,2-dioxins of litseaverticillol family <2006T5308> – and from plant extracts, used in traditional Chinese medicine, coronarin E

and chinensines A–E, respectively <2007JOC4826>, were synthesized by different types of the reaction of singlet oxygen; in addition some 4,5-dihydro-1,2-dioxin derivatives could be isolated from a Chinese soft coral <2006STE955, 2006T6802>.

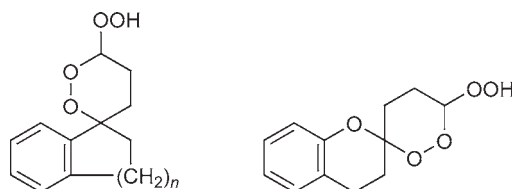


232

R = H, Me, CH₂CF₃
R¹ = Me, *t*-Bu

Scheme 64

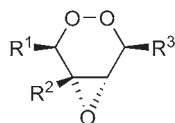
Finally, a series of novel hydroperoxy-1,2-dioxanes **233a, b** (Scheme 65) were synthesized by hydroperoxide rearrangement and ozonolysis <2006EJO2174>; all the products showed weak antimalarial activity. Also the epoxy-endoperoxides **234a, b** were designed which proved to have inhibitory activity against *Candida albicans* (Scheme 65) <2007BMC36>.



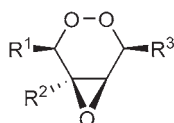
$n = 1, 2$

233a

233b



234a

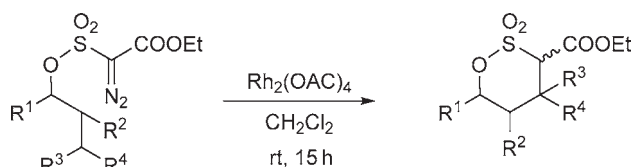


234b

Scheme 65

8.10.13.2 1,2-Oxathiane 2,2-Dioxides (Sultones)

The preferential formation of the sultones **236** by intramolecular carbene C–H insertion was observed <2007OL61>; hereby the diazosulfonates **235** required as substrates were prepared by standard methods. The insertion conditions are: Rh₂(OAc)₄, CH₂Cl₂, slow addition at rt over 5 h, then 10 h at rt; the cyclization products could be isolated in good yield (Scheme 66).



235

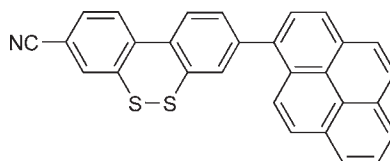
236

Scheme 66

Further, a 1,2-oxathiane 2,2-dioxide derivative was obtained as a by-product (15–25%) in the enantioselective synthesis of Oasomycin A <2007AG545>; all efforts to suppress this side reaction were not successful, and the reaction products of the hexafluorobutadiene sulfotrioxidation (among the main products a 4,5-dihydro-1,2-oxathiin 2,2-dioxide derivative) were identified by ^{19}F NMR spectroscopy <2007RJA424>.

8.10.13.3 1,2-Dithiins, Partially and Fully Saturated Analogs

The synthetic procedure to create the dibenzo[1,2]dithiin derivative **237** (Scheme 67) with a well-defined chromophore and also electroactive under mild conditions has been published <2006TL9135>; the disulfide bridge proved electrochemically switchable.



237

Scheme 67

3-Substituted 4,5-dihydro-1,2-dithiins were obtained as by-products in the copper-catalyzed ring expansion of vinyl thiiranes <2007JA2768>.

Also the preparation of methyltriphenylphosphonium dichromate $((\text{Ph}_3\text{PMe})_2\text{Cr}_2\text{O}_7)$ and the application of this compound as efficient, inexpensive, stable and mild reagent for coupling a variety of aliphatic and aromatic thiols and aliphatic dithiols to their corresponding acyclic and cyclic disulfides has been published <2006JSF441>; 1,2-dithiane was obtained by this procedure in 90% yield.

Finally, both the content and the antioxidant activity of 3,4-dihydro-3-vinyl-1,2-dithiin (among others) in *Allium* species was studied <2006MI135, 2006MI351, 2006MI394>; in addition, 3-methyl-1,2-dithian-4-one was identified among the volatile components of cooked salmon <2007JFA1427> and as a result (among other compounds) of the Maillard reaction of xylose, cysteine, and thiamine <2007JFA1552>.

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Biographical Sketch



Professor Erich Kleinpeter obtained his diploma from the University of Leipzig, Germany, in 1970 and his Dr. rer. nat. in 1974 under the direction of Professor Rolf Borsdorf. He continued teaching and doing research work at the University of Leipzig until 1979, when he spent a year in the laboratories of Professor Rainer Radeglia at the Academy of Sciences, Berlin. Following this, he returned to Leipzig and habilitated in 1981. After spending 1982–85 as associate professor of organic chemistry at the University of Addis Ababa, Ethiopia, he moved to the University of Halle-Wittenberg, Germany, where he was appointed a docent in spectroscopy, followed later by his appointment as professor of analytical chemistry in 1988. In 1993, he took up his present position as full professor of analytical chemistry at the University of Potsdam, Germany. His research interests include all aspects of physical organic chemistry, in particular the application of NMR spectroscopy, quantum-chemical calculations, and mass spectrometry to the examination and investigation of all kinds of interesting structures, and new phenomena in organic, bioorganic, and coordination chemistry.

8.11

1,3-Dioxins, Oxathiins, Dithiins, and their Benzo Derivatives

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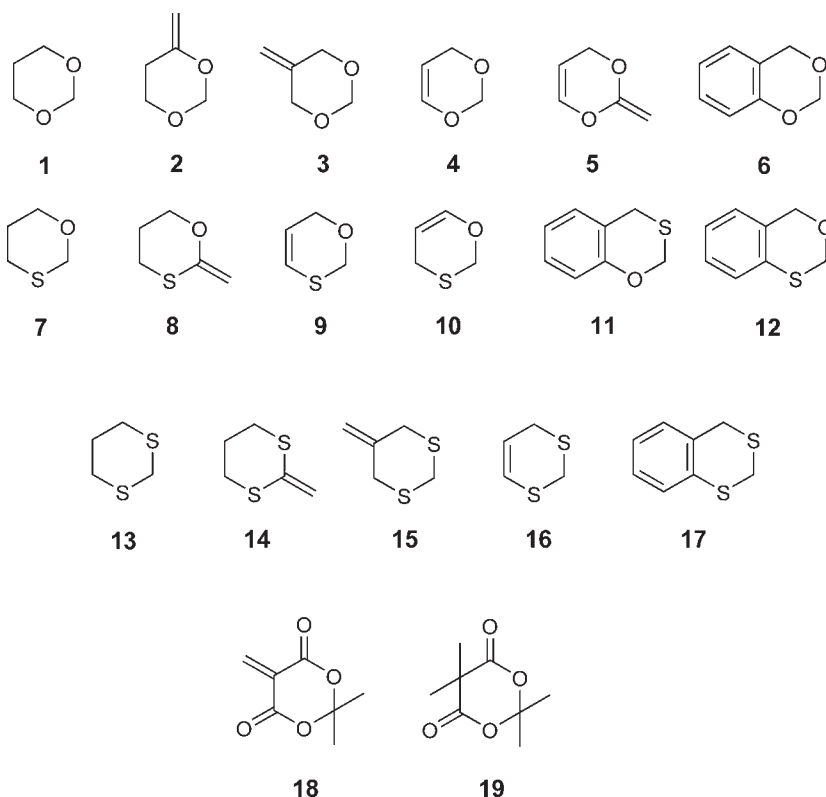
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8.11.1 Introduction

In this chapter, the structures and chemistries of 1,3-dioxins, 1,3-oxathiins, and 1,3-dithiins are described, including both their fully saturated forms (**1**, **7**, and **13**) as well as their benzo analogs (**6**, **11**, **12**, and **17**). The formally fully unsaturated monocyclic structures (**4**, **9**, **10**, and **16**) contain only one endocyclic double bond with further unsaturation being accommodated by exocyclic double bonds (**2**, **3**, **5**, **8**, **14**, and **15**), for example, by the introduction of a carbonyl group. Well known and intensively studied are the Meldrum's acid derivatives **18** and **19**. In addition, 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane moieties can be part of spiro structures as well as bi- and tricyclic analogs. And finally, both the structures and chemistries of the corresponding sulfoxides and sulfones are also reported.



Though the material of this chapter is presented according to the usual format, there are, however, some exceptions resulting from (1) the fact that there are no substituents attached to the ring heteroatoms (except in the case of sulfoxides and sulfones) and therefore no attendant reactivity, and (2) the appropriateness of discussing syntheses according to the ring system involved rather than by the type of ring closure or transformation. Since this chapter was included in CHEC-II(1996) <1996CHEC-II(6)415>, it therefore covers the relevant literature from 1996 onward.

After beginning with theoretical, structural, spectroscopic, and thermodynamic studies, the main body of this chapter deals with the reactivities and syntheses of the different heterocyclic systems categorized by their degree of unsaturation and the heteroatoms present. Heterocyclic ring systems have been particularly well investigated theoretically and because the theoretical techniques are now so well developed, they replicate the experimental results extremely closely, and, thus at the state-of-the-art level, both the electron distributions and geometries of the structures are well understood.

Several reviews on the conformational behavior of 1,3-dithianes <B-1995MI201>, the conformational analysis of six-membered oxygen-containing heterocyclic rings (including 1,3-dioxanes) <1998AHC217>, the stereochemistry of 1,3-heterocycles (including 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes) <1999UKZ73>, and the conformational analysis of saturated six-membered rings (including 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes) <2004AHC41> have been published. The stereochemistries, active stereoelectronic effects, chemical reactivities, and the protonations of 1,3-oxathianes published prior to 1996 have been reviewed in 2000 by Hashper *et al.* <2000MI17>. Structures, syntheses, and reactivities of six-membered ring spiranes including not only carbocycles, but also 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane ring systems, were reviewed <2005COR1287> by a group of Romanian authors.

8.11.2 Theoretical Calculations

8.11.2.1 Combined and Comparative Studies

8.11.2.1.1 NMR parameters

8.11.2.1.1(i) ^1H and ^{13}C chemical shifts

Density functional theory (DFT) calculations employing sum-over-states DF perturbation theory were applied to calculate both the ^1H and ^{13}C chemical shifts of 1,3-dioxane, 1,3-oxathiane, 1,3-dithiane, and the parent cyclohexane <1997JMT(418)231>. Both 'normal' and 'anomalous' trends in the ^1H chemical shifts could be reproduced well and,

indeed, excellent correlations of experimental versus calculated results were obtained for both the ^1H and ^{13}C chemical shifts. However, analysis of the relevant orbital contributions to the nuclear magnetic resonance (NMR) shieldings was not consistent with the stereoelectronic interactions (hyperconjugation) as proposed within the context of the so-called Perlin effect.

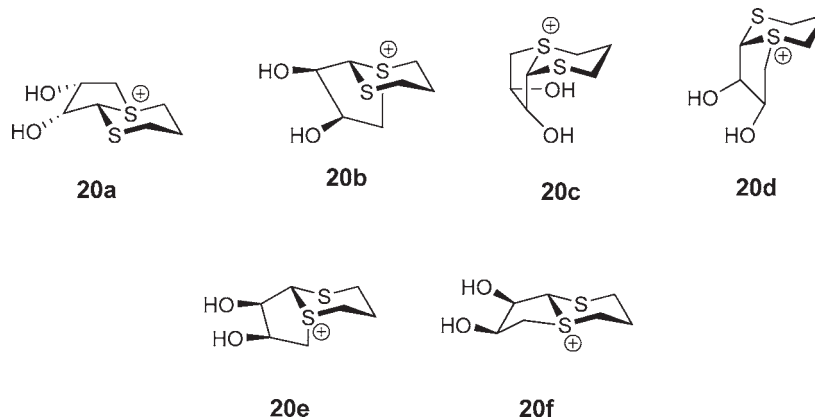
8.11.2.1.1(ii) Coupling constants $^1J_{\text{H,C}}$

Ab initio calculations of the C–H one-bond coupling constants in 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes have been used to prove stereoelectronic effects as the major source of the Perlin effect <1999PCA932, 2002JA13088> and as a reliable tool for conformational analysis <2005T7349>. Working at the DF level of theory, a correlation between $^1J_{\text{H,C}}$ and the corresponding C–H distances was not found, though the Perlin effect was correctly predicted <1999PCA932>. However, changes in C–H bond lengths due to stereoelectronic hyperconjugative effects on $^1J_{\text{H,C}}$ were correctly reproduced. It should be noted that very recent calculations of $^1J_{\text{H,C}}$ coupling constants <2005JA6168, 2005AGE2360> revealed that $^1J_{\text{H,C}}$ coupling is not only dependent on hyperconjugation, but, in fact, is even more dependent on polar interactions.

Ab initio calculations at the MP2 level of theory of a collection of substituted 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes have been employed to study both the position of the conformational equilibria and the validity of the Perlin effect <2005T7349>. The $^1J_{\text{H,C}}$ coupling constant proved to be a valuable tool in conformational analysis: both twist conformers, in addition to the chair and alternative chair forms, could be readily identified simply by comparing experimental $^1J_{\text{H,C}}$ coupling constants to the corresponding calculated values in the particular forms. In addition, the Perlin and reversed-Perlin effects of the $\text{C}_2\text{--H}$ fragments ($^1J_{\text{H}_{\text{ax}},\text{C}} < ^1J_{\text{H}_{\text{eq}},\text{C}}$ in 1,3-dioxanes, $^1J_{\text{H}_{\text{ax}},\text{C}} \sim ^1J_{\text{H}_{\text{eq}},\text{C}}$ in 1,3-oxathianes and $^1J_{\text{H}_{\text{ax}},\text{C}} > ^1J_{\text{H}_{\text{eq}},\text{C}}$ in 1,3-dithianes) were correctly reproduced <2005T7349>.

Theoretical calculations at the highest levels of theory for *ab initio* or DFT in conjunction with natural bond orbital (NBO) methods have been directed to the complex dependence of stereoelectronic (hyperconjugation) effects, anomeric/homoanomeric and Perlin/reversed-Perlin effects, C–H bond lengths, and the corresponding $^1J_{\text{H,C}}$ coupling constants in 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes <2000JOC3910, 2000MI42, 2001JOC2918, 2003JA14014>. The situation, however, remains complicated and is more problematic than was anticipated.

Nevertheless, practical application of the method proves to be really successful, especially if well-established methods of structure elucidation fail; for example, the calculation of the vicinal H,H-coupling constants of all possible isomers of a 1,3-dithiane-based sulfonium salt inhibitor **20a–f** using the DFT (geometry optimization at *ab initio* Hartree–Fock (HF)/6-311G** level) and considering the Fermi contact term only showed remarkable overall agreement with configuration **20d** <2004JA6866>. To complement the quantum-chemical J -data, the nuclear Overhauser effect (NOE) intensities in **20a–f** were calculated; again only structure **20d** gave rise to NOE data consistent with the experiment <2004JA6866>. Thus, theoretical calculations reached the level of providing a reliable method to elucidate structures.



8.11.2.1.1(iii) Barriers to rotation

The *ab initio* calculation of the internal rotational barrier about the exocyclic partial C=C bonds of five- and six-membered heterocyclic derivatives is difficult because the perpendicular transition state structure cannot be obtained using HF wave functions. Recently <2001JMT(541)101, 2001JMT(572)169>, an empirical approach has been developed aimed at deriving a twofold potential, V_2 , based on *ab initio* molecular orbital (MO) total energies for molecular conformations and coupled with HF functions. This approach was applied to five- and six-membered 1,3-heterocycles with a double bond at position 2 (**21** and **22**, Figure 1). The rotational barriers about the exocyclic partial C=C bond refer to the twofold potential energy V_2 and whose values represent homogeneously the rotational barrier from unpolarized ethylene to compounds **21** and **22** having marked push–pull character <2001JMT(544)141>.

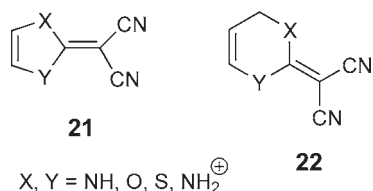
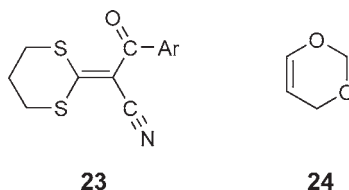


Figure 1 Push-pull alkenes with a heterocyclic moiety.

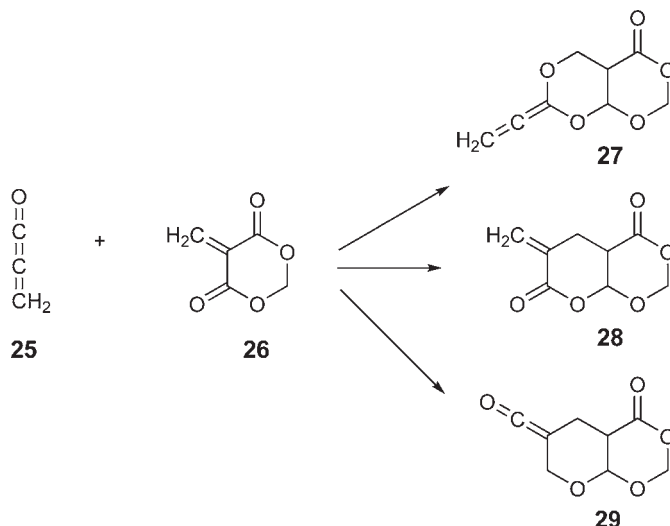
The dynamic behavior of a 1,3-dithiane **23** bearing an *exo*-double bond has been studied theoretically; the geometries of both the ground and the transition states of the restricted rotation about the C=C bond were calculated at the MP2 level of theory and compared with the barriers to rotation determined experimentally by dynamic NMR spectroscopy wherein the agreement between the two was found to be adequate <2004JOC4317>. Furthermore, the length of the C=C bond could be correlated with the barrier to rotation <2004JOC4317>. The length of the C=C bond of these push-pull alkenes, on the other hand, proved to be linearly dependent on the quotient of the occupation numbers of the π -bonding and π^* -antibonding orbitals of the C=C bond, $\pi^*_{C=C}/\pi_{C=C}$, which was thus identified as a useful general parameter to quantify the push-pull effect present in this class of compounds <2005TL5995>.

The interconversion barrier between the two twisted conformers of **24**, among other oxygen-containing cyclohexene analogs, has been determined utilizing a hindered pseudorotational model, molecular mechanics calculations (MM3), and far-IR spectroscopy (IR = infrared) <1996BKC7>. The interconversional barrier, thus obtained, proved to be 9.6 kcal mol⁻¹ and was found to be in excellent agreement with the value determined from the potential energy surfaces for ring-bending and ring-twisting vibrations.



8.11.2.1.1(iv) Chemical Reactions

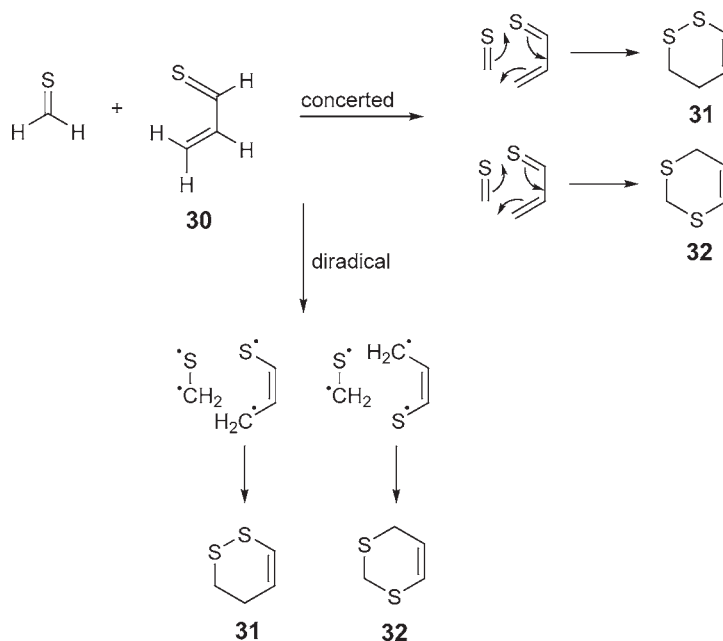
The cycloaddition reaction of methyleneketene **25** and 5-methylene-1,3-dioxan-4,6-dione **26** was studied by DFT at the B3LYP/6-31G* level of theory both in the gas phase and in chloroform solution <1999JMT(488)187>. In the gas phase, the activation barriers for reactions to **27**, **28**, or **29** (Scheme 1) were calculated to be 21.81, 0.25, and 2.96 kcal mol⁻¹, respectively; thus, the reaction leading to the 1,2-adduct **28** was lowest, in agreement with the



Scheme 1

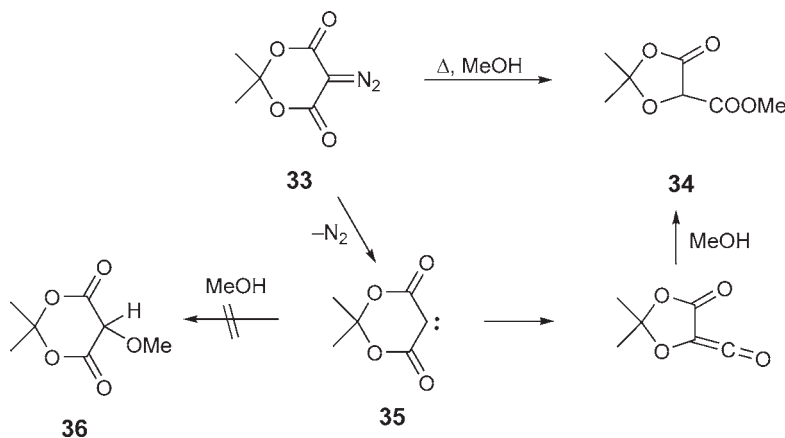
observed regioselectivity. The presence of polar media (using the self-consistent reaction field model) did not significantly influence the activation barriers of the three reactions.

During a general DFT study at the B3LYP/6-31G(d) level of theory of the chalcogeno Diels–Alder reaction, the corresponding reaction of thioformaldehyde with thioacrolein **30** was examined theoretically [\[2001JOC4026\]](#) with both stepwise diradical and concerted pathways being considered (**Scheme 2**). The diradical pathway was predicted to be energetically less favorable; the two reagents with very small HOMO–LUMO gaps form a prereaction complex which precedes the cyclic transition structure and the reaction thus proceeds almost without an activation barrier (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital).



Scheme 2

Also, the Wolff rearrangement of diazo Meldrum's acid **33**, studied by DFT at the B3PW91/6-311+G(3df,2p) level of theory, proved to be a concerted process because the product of the photochemical or thermal decomposition in methanolic solution was the ketoester **34** (**Scheme 3**) while the expected products of the singlet carbene **35**, for example **36**, were not detected [\[2003JA14153, 2005CJC1382\]](#).



Scheme 3

The diastereoselectivities in the nucleophilic addition reactions of 1,3-dioxane-5-ones **37** and 1,3-dithiane-5-ones **38** were studied by employing two newly available theoretical tools, the exterior frontier orbital electron (EFOE) density of the $\pi_{C=O}^*$ -orbitals and the π -plane-divided accessible space (PDAS) as quantitative measures of the π -facial steric effects <1999CRV1243, 1999CC621, 1999CL1161, 2000H(52)1435, 2001HAC358>. The two parameters predict correctly the experimentally observed stereochemical reversal of **37** and **38** (R = Ph; see Table 1); in particular, the PDAS values for both substrates clearly show the opposite steric environment about the carbonyl carbon atom of these heterocyclic ketones and prove sizeable ground-state conformational differences to be responsible for the observed reversed facial stereoselection.

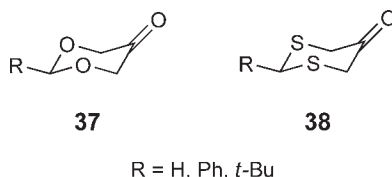


Table 1 Theoretical analysis of the nucleophilic addition reaction of 1,3-diheterocyclohexane-5-ones **37** and **38**^a

Compound	EFOE density (%)		PDAS (au ³)		δ (%) ^b	Reagent	Obs. (ax.eq)
	ax	eq	ax	eq			
37 : R = Ph	1.739	0.243	71.2	26.2	40.4	LiAlH ₄ MeMgI EtMgI <i>i</i> -PrMgI	94:6 98:2 98:2 96:4
38 : R = Ph	0.277	0.834	18.4	54.6	−20.5	LiAlH ₄ MeMgI EtMgI <i>i</i> -PrMgI	15:85 7:93 11:89 9:91

^aAt the HF/6-31G(d) level of theory.

^bOrbital distortion index. A positive sign indicates distortion toward the axial direction.

Ground-state and excited-state reactions of chiral Meldrum's acid derivatives **39** with the enone function have been reviewed with an emphasis on the facial selectivity in the C=C bond (Figure 2) <1996H(42)861>. Top-face preference, even when it is sterically more hindered than bottom-face attack, is supported by hyperconjugation $n_O \rightarrow \pi_{C=C}^*$ **39a**, whereas bottom-face preference is dominated by steric effects in the sofa conformation of the molecule **39**. The trajectory of the attacking reagent plays a balancing role.

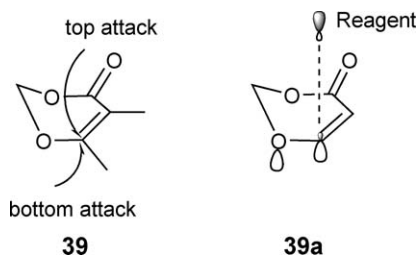
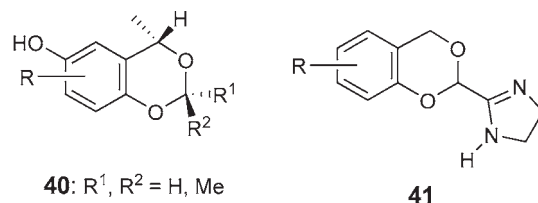


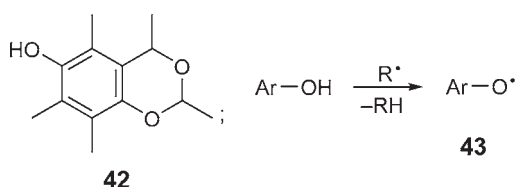
Figure 2 Possible trajectories of nucleophilic attack on 1,3-dioxin-4-ones.

Semi-empirically AM1-obtained, but *ab initio*-validated, quantum-chemical descriptors (HOMO, ΔH_{ox} , and ΔH_{abs}) were employed as predictors of the antioxidant activity of vitamin E and its analogs <1997HCA1613>. A number of 4*H*-1,3-benzodioxin-6-ol derivatives **40** were evaluated in this way and a series of 4*H*-1,3-benzodioxin

derivatives **41** were tested as pharmacophores during a three-dimensional quantitative structure–activity relationship (3-D QSAR) comparative molecular field analysis (CoMFA) study on imidazolinergic I₂ ligands <2000JME1109>. *cis*- and *trans*-Chromanol **42** (Equation 1), as well as other chromanol-type compounds, act as antioxidants in biological systems by reduction of oxygen-centered radicals **43** <2005JOC3472>; their efficiency was determined by both the rate constants for the primary antioxidative reaction and for the reactions of the antioxidant-derived radicals which could be identified by optical and electron spin resonance (ESR) spectroscopy. The resolved hyperfine structure of the ESR signals was identified by quantum-chemical calculations in predicting both the distribution of the unpaired electron and the coupling constants to adjacent protons in **43**.

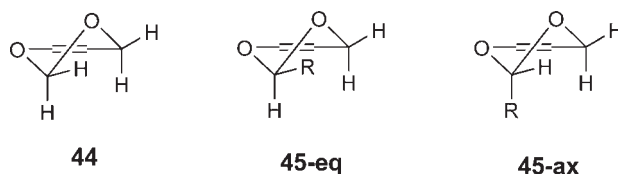


(1)



8.11.2.2 1,3-Dioxins and Dioxanes

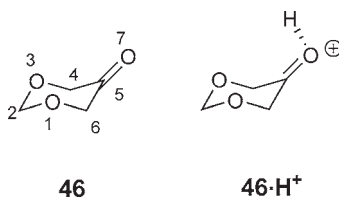
The optimized geometries and total energies of the conformers of 4*H*-1,3-dioxin **44** <1997JCC1392> and the 2-substituted derivatives **45** <2000JMT(503)145> were *ab initio*-calculated at the MP2 level of theory employing various basis sets.



R = Me, Et, *i*-Pr, *neo*-Pen, SiMe₃

4*H*-1,3-Dioxin prefers the half-chair conformer **44**; the corresponding boat and planar conformers proved to be less stable by 10.6 and 12.3 kcal mol⁻¹, respectively. If 4*H*-1,3-dioxin is alkyl-substituted at position 2, the same level of theory indicated the equatorial conformer **45-eq** to be more stable than its axial counterpart, **45-ax** (Me, 2.95 kcal mol⁻¹; Et, 2.89 kcal mol⁻¹; *iso*-Pr, 2.97 kcal mol⁻¹; *neo*-Pen, 2.16 kcal mol⁻¹; and SiMe₃, 4.45 kcal mol⁻¹); since the dipole moments of the two conformers are nearly equivalent, the position of the conformational equilibria of 2-alkyl-substituted 4*H*-1,3-dioxins is influenced by both steric effects (synclinal and H,H-, H,O-nonbonding interactions due to short C–O bonds) and a number of stereoelectronic orbital interactions.

The protonation (to give **46·H⁺**) of 1,3-dioxan-5-one **46** has been studied by *ab initio* MO calculations with complete geometry optimization to consider the geometrical changes in the molecule due to protonation before the attack of a nucleophile <1997TL4483>; the torsional angles O(7)–C(5)–C(4)–O(3) and O(7)–C(5)–C(6)–O(1) enlarge in **46·H⁺** (from 160.15° to 165.42°) and lead to enhanced preference for axial attack. These stereoelectronic arguments are in excellent accord with the experimental results.

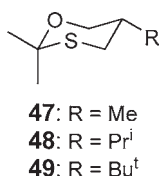


Simple calculations (MM2 and HF/6-31G^{*}), supported by a low-temperature NMR study, reveal that 2-NMe₂-1,3-dioxane and the 5,5-dimethyl derivative exist exclusively in the conformation with the dimethylamino group in *axial* position <2001ARK(xii)58>, and DFT calculations at the B3LYP/6-31G(d,p) level of theory show that the anomeric effect of 2-Cl in 1,3-dioxane is of stereoelectronic origin while 2-F, 2-OMe, and 2-NH₂ substituents on the same molecule are not <2000MI42>.

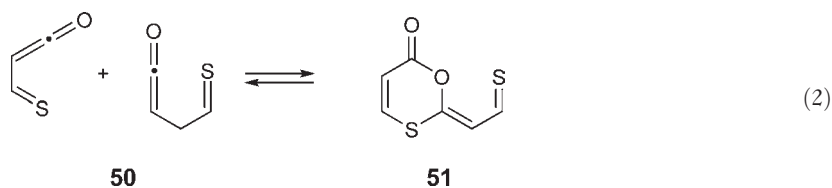
8.11.2.3 1,3-Oxathiins and Oxathianes

Both the structure and relative energies of 1,3-oxathiane and its substituted analogs have been studied by various semi-empirical quantum-chemical methods (modified neglect of diatomic overlap (MNDO), AM1, PM3, and force field) <1998MI14, 2002CHE607>. AM1 geometrical parameters adequately reproduced the experimental structural data while both the global minimum (chair conformer) and local minima (twist conformers) on the potential energy surface were identified similarly by AM1 and PM3 methods.

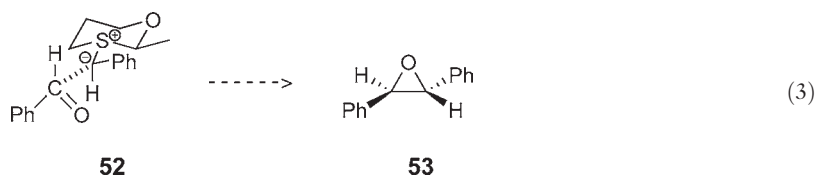
The semi-empirical theoretical study (AM1, PM3, and force field) of 2,2,5-trimethyl-, 2,2-dimethyl-5-*iso*-propyl-, and 5-*tert*-butyl-2,2-dimethyl-1,3-oxathiane **47–49** afforded the correct conformational equilibria as obtained by ¹H NMR spectroscopic conformational analysis <2001RJC1487>. The chair conformation is adopted while the substituent at position 5 is in an equatorial position. Furthermore, there was no indication for the presence of twist conformers.



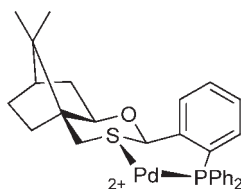
A theoretical study by DFT and MP2 of the dimerization of thioformylketene **50** has been reported <2005OL5817>, wherein both [4+2] and [4+4] pathways were considered. Interestingly, the barriers for [4+2] cycloadditions, for example, in formation of the 1,3-oxathiin-one derivative **51** (Equation 2), are low and the dimerizations are sufficiently exothermic that they are not expected to be in equilibrium with **50** at room temperature.



Also, the reaction pathways of the Corey–Chaykovsky epoxidation reaction have been compared quantum-chemically <1999JOC4596>. As models for one transition state, 1,3-oxathiane compounds such as **52**, suitably substituted to allow comparison with experiment (Equation 3), were calculated and these predicted both the absolute stereochemistry of the main product **53** and the distribution of the other stereoisomers, as supported by experimental results. Thus, this theoretical study was able to identify the transition state which proved to be responsible for the stereoselectivity of the catalytic Corey–Chaykovsky epoxidation reaction.



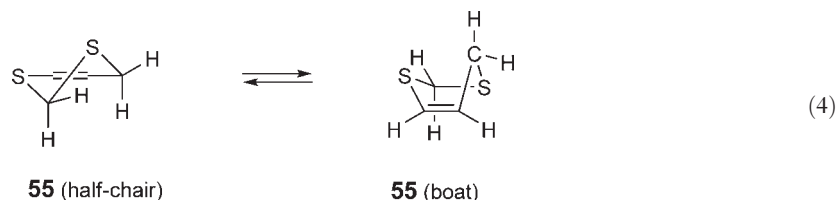
Stereocartography, a new computational tool that allows the mapping of regions of stereinduction around chiral catalysts, has been applied to compound **54**, which contains the 1,3-oxathiane moiety and which was used as a chiral catalyst in Diels–Alder reactions resulting in high *endo*-selectivity but with a low enantioselectivity of 36% ee <2003CH759>. The region of highest enantioinduction was found to be located at the back of the transition metal complex (7.9 Å from the metal), that is, away from where the chemistry actually takes place.

**54**

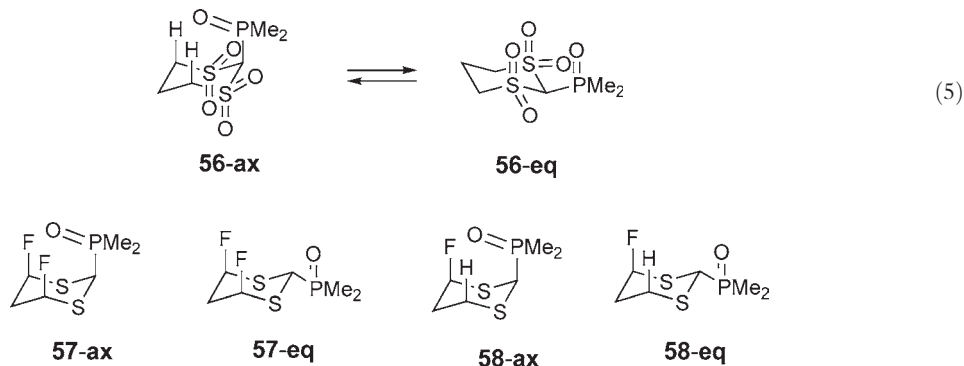
The topological theory of atoms in molecules <2003MI190> has been employed to calculate the conformational preference of monosubstituted 1,3-oxathianes. The preferred conformer results from an energy balance between the ring and the substituent. This method has proven to be general and is a new technique for conformational analysis.

8.11.2.4 1,3-Dithiins and Dithianes

At the MP2 level of theory, the half-chair conformer of 4*H*-1,3-dithiin **55** is 2.0 kcal mol^{−1} more stable than the boat conformer (Equation 4) <1998JCC1064> and has a calculated twist angle of 33.2°; the relative stability of the half-chair conformer was attributed to absent lone-pair–lone-pair repulsions and a decrease of torsional strain owing to an absence of adjacent methylene groups.

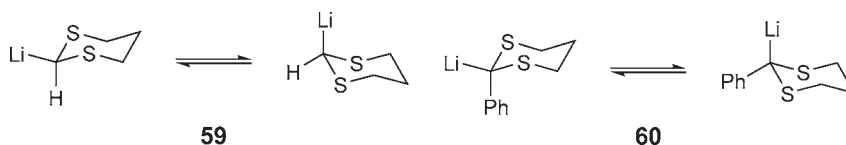


DFT calculations at the B3LYP/6-31G(d,p) level of theory reproduce the experimentally determined axial preference of 2-(dimethylphosphinyl)-1,3-dithiane 1,1,3,3-tetraoxide **56-ax** <2001JOC2925> (Equation 5); hydrogen bonding between the phosphoryl group and axial protons at positions 4 and 6 leads to the stabilization of **56-ax** which is estimated to be ca. 5 kcal mol^{−1} (Equation 5). The fluorinated derivatives **57** and **58**, however, are more stable in their equatorial conformations **57-eq** and **58-eq**, thus reflecting the repulsive electrostatic interaction of the C–F⋯O=P moiety in the corresponding axial counterparts **57-ax** and **58-ax** <2001JOC2925>.



That this preference of 2-P(O)Me₂ in 1,3-dithiane is not of stereoelectronic nature (while the anomeric effect of 2-F, 2-Cl, 2-SMe, 2-PH₃, and 2-COOMe on 1,3-dithiane is) was supported at the B3LYP/6-31G(d,p) and HF/6-31G(d,p)//B3LYP/6-31G(d,p) levels of theory <2000MI42>.

The predominant existence of 2-dimethylamino-1,3-dithiane in the equatorial conformation has been confirmed both in the gas phase and in chloroform solution by *ab initio* calculations on the MP2/6-31G* level of theory <1997J(P2)1835>; the dominant effect proved to be the exo-anomeric effect involving the N-lone pair. DFT-based (B3LYP/6-31G(d,p) level) energetic and structural studies of 2-lithio-1,3-dithiane **59** and 2-lithio-2-phenyl-1,3-dithiane **60** also showed, in agreement with experimental observations, a very high preference for the equatorial C–Li bond (14.2 kcal mol^{−1} in **59** and 4.10 kcal mol^{−1} in **60**, respectively) <1997JA7545>, which is actually of ionic nature. These computed structural data provide support for the stereoelectronic rationalization of the equatorial 1,3-dithiane 2-carbanion and are in line with stabilizing n_C → σ*_{C–S} orbital interaction in the preferred equatorial conformers.



Ab initio calculations at the MP2/aug-cc-pVDZ <2006CPL(426)176> and MP2/6-31G* <2006PS1693> levels of theory of 1,3-dithiane 1-oxide confirmed the preferred equatorial orientation of the sulfoxide group (by 0.71 kcal mol^{−1} <2006PS1693>) dictated by the repulsive interactions between sulfur and oxygen lone pairs in the axial analog. Also 1,3-dithiane *cis*-1,3-dioxide prefers the diequatorial position of the oxygen atoms <2006PS1693>. The 2-substituent in 2-chloro- and 2-bromo-1,3-dithiane *trans*-dioxide, finally, exhibit a pronounced axial preference in CD₂Cl₂ solution <1997J(P1)21>, owing to both the anomeric effect n_S → σ*_{C–Hal} and interactions between S → O and C–Hal dipoles.

8.11.3 Experimental Structural Methods

8.11.3.1 1,3-Dioxanes

8.11.3.1.1 X-Ray diffraction

An enormous number of different 1,3-dioxane structures have been reported since 1996; in Figure 3, mono-, bicyclic and spiro variants are presented, while Figure 4 contains examples of tricyclic structures with the 1,3-dioxane moiety. The conformations, bond lengths, bond and dihedral angles of the 1,3-dioxane rings are determined by the ring fusion, the attached substituents, and the presence of exocyclic double bonds. Thus, published structures are classified as either monocyclic (mono), spiro-substituted (spiro), bicyclic (bi), or tricyclic (tri). The well-known Meldrum's acid derivatives (M) have been most intensively studied.

For each of the five groups, many derivatives were found and a comparison of the experimental bond lengths for the 1,3-dioxane ring system with representatives of the different classes are presented in Tables 2 and 3. The chair proved to be the most stable conformer and was obtained in all kinds of structures, though often some were in fact twisted. In addition to twist and boat conformers, also sometimes twisted when exocyclic double bonds were present, the corresponding half-chair conformers were also obtained.

By X-ray crystallography, the zwitterionic character of a number of Meldrum's acid derivatives **61** could be proven (Equation 6) <2002J(P2)515, 2003ZNB817>. The central C=C bond length varies between 1.41 and 1.48 Å and thus it is intermediate between typical single- and double-bond lengths (1.54 and 1.34 Å, respectively); the twisting angles between the push and pull (Meldrum's acid) parts vary between 3° (**61a** and **61h**) and 83° (**61m**). There is no clear correlation between bond length and twist angle (although larger twist angles increase the bond length), but intramolecular hydrogen bonding clearly favors planarity. In the monosubstituted analogs **61n–q**, both fragments are less twisted <1999CHE1286, 2000JCX189, 2003AXE841> and Meldrum's alkene **62** reveals a centrosymmetric structure with the two six-membered rings folded along their carboxylate carbon axis by 34.9° and linked to a conventional C=C bond (1.35 Å) <2004ZNB525>.

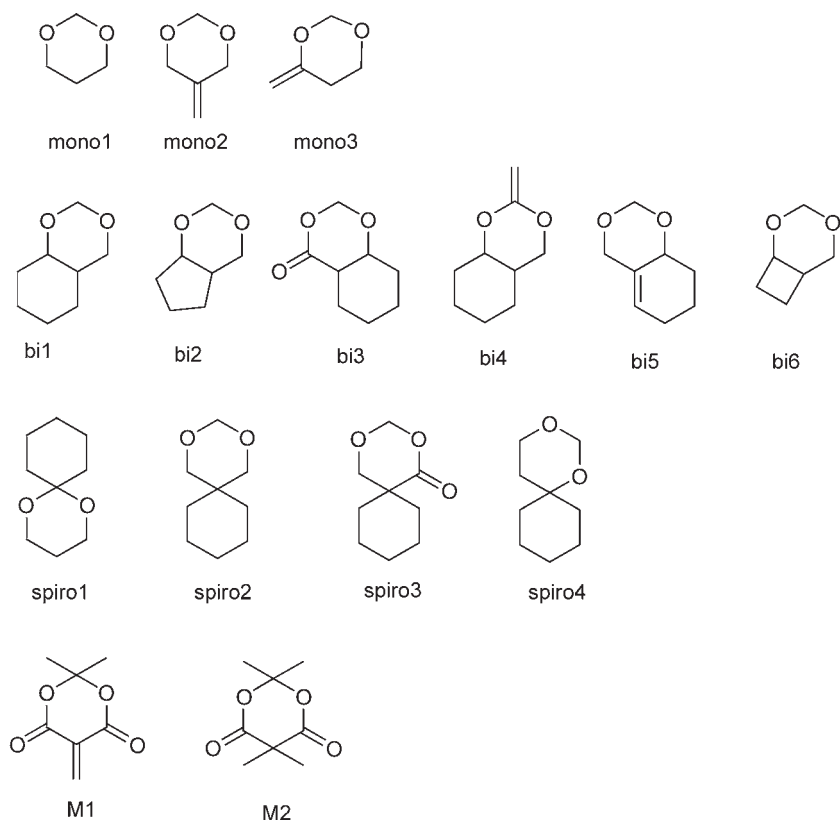


Figure 3 Basic structural motifs present in compounds studies by X-ray diffraction.

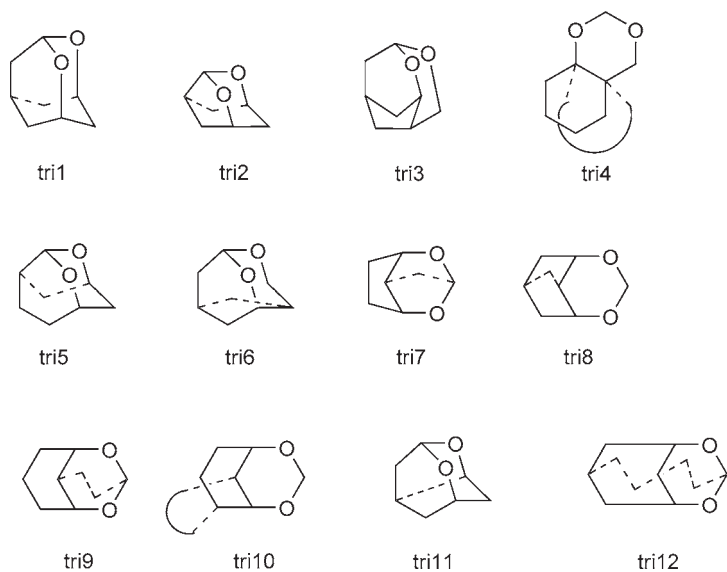


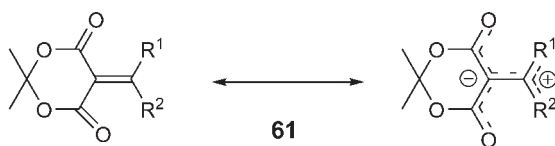
Figure 4 Tricyclic ring systems present in compounds studied by X-ray diffraction.

Table 2 Conformations and bond lengths (Å) of the 1,3-dioxane moiety in different solid-state structures (**Figure 3**)

Class	Conformation	Bond length						Reference
		O(1)–C(2)	C(2)–O(3)	O(3)–C(4)	C(4)–C(5)	C(5)–C(6)	C(6)–O(1)	
mono1	Chair	1.406	1.412	1.432	1.515	1.521	1.430	2003T4039
mono2	Chair	1.413	1.412	1.436	1.478	1.486	1.441	1998TA1657
mono2	Twist	1.430	1.429	1.408	1.519	1.509	1.428	1999JA2651
mono2	Half-chair	1.442	1.411	1.425	1.503	1.421	1.448	2005AGE4079
mono3	Half-chair	1.453	1.396	1.447	1.514	1.502	1.334	2003HCA644
mono3	Twisted chair	1.426	1.409	1.448	1.529	1.493	1.378	2005OL1387
spiro1	Chair	1.410	1.409	1.447	1.534	1.516	1.443	2004OL3569
spiro1	Twist	1.404	1.410	1.438	1.510	1.479	1.292	2004OL3569
spiro1	Half-chair	1.376	1.374	1.456	1.501	1.503	1.461	1998CC1695
spiro2	Chair	1.525	1.419	1.433	1.524	1.528	1.431	2004T4789
spiro2	Twist	1.380	1.380	1.441	1.498	1.498	1.441	2002JA4942
spiro2	Twisted chair	1.425	1.423	1.273	1.542	1.505	1.432	2003JOC240
spiro3	Twist	1.466	1.371	1.433	1.531	1.526	1.330	1998S1645
spiro3	Boat	1.455	1.408	1.445	1.527	1.491	1.339	1999EJO1057
spiro3	Twisted boat	1.467	1.402	1.443	1.530	1.496	1.345	1999EJO1057
spiro4	Chair	1.412	1.408	1.431	1.518	1.526	1.452	2001TA2049
spiro4	Twisted boat	1.398	1.427	1.424	1.517	1.541	1.466	2001TA2049
bi1	Chair	1.421	1.428	1.435	1.517	1.527	1.435	2001EJI2773
bi1	Twisted boat	1.418	1.447	1.428	1.556	1.588	1.419	2003JOC6583
bi1	Twisted chair	1.411	1.407	1.392	1.573	1.543	1.417	2000H(52)1297
bi1	Twist	1.436	1.434	1.433	1.552	1.562	1.435	2000H(52)1297
bi2	Twist	1.436	1.411	1.397	1.528	1.569	1.434	1997TL1697
bi2	Chair	1.416	1.403	1.430	1.502	1.521	1.422	2000TA4995
bi3	Twisted boat	1.464	1.414	1.423	1.503	1.480	1.342	2003OL1491
bi3	Half-chair	1.468	1.408	1.431	1.549	1.503	1.338	2003OL1491
bi4	Twisted boat	1.324	1.330	1.461	1.510	1.536	1.474	2004OL4487
bi4	Half-chair	1.316	1.331	1.451	1.505	1.523	1.481	2004OL4487
bi5	Twist	1.440	1.422	1.432	1.511	1.496	1.433	2003TL3569
bi5	Chair	1.432	1.414	1.434	1.500	1.501	1.434	2003TL3569
bi6	Twisted chair	1.426	1.403	1.442	1.530	1.528	1.411	2000TA4113
M1	Boat	1.439	1.366	1.483	1.486	1.363	1.448	2001J(P2)133
M2	Half-chair	1.434	1.336	1.512	1.500	1.343	1.414	2003OL4983
M2	Flat	1.426	1.321	1.518	1.513	1.327	1.413	2003AGE4233
M2	Boat	1.430	1.345	1.513	1.512	1.344	1.439	1999T6905

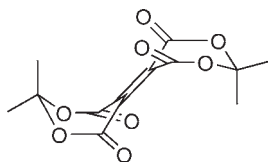
Table 3 Conformations and bond lengths (Å) of the 1,3-dioxane moiety in different tricyclic solid-state structures (Figure 4)

Class	Conformation	Bond length						Reference
		O(1)–C(2)	C(2)–O(3)	O(3)–C(4)	C(4)–C(5)	C(5)–C(6)	C(6)–O(1)	
tri1	Chair	1.433	1.433	1.456	1.519	1.519	1.456	1999CC901
tri2	Chair	1.420	1.423	1.456	1.531	1.516	1.535	2002BMC1189
tri3	Twisted boat	1.414	1.466	1.345	1.491	1.564	1.449	2005OL227
tri4	Chair	1.405	1.410	1.446	1.566	1.547	1.422	1998TL4647
tri5	Twisted chair	1.426	1.414	1.423	1.534	1.551	1.431	2001AXB63
tri6	Twisted boat	1.420	1.424	1.422	1.548	1.570	1.418	2001AXB63
tri7	Boat	1.449	1.419	1.470	1.538	1.518	1.436	1999AXC827
tri8	Half-chair	1.329	1.350	1.425	1.543	1.541	1.441	2005OBC3297
tri9	Boat	1.404	1.441	1.459	1.500	1.557	1.452	1999CEJ1226
tri10	Twisted chair	1.427	1.426	1.432	1.533	1.500	1.426	1997JOC8315
tri10	Twisted boat	1.432	1.400	1.446	1.533	1.496	1.436	1997JOC8315
tri11	Twisted chair	1.437	1.412	1.454	1.543	1.540	1.437	1997JOC8794
tri12	Twisted boat	1.432	1.409	1.467	1.505	1.553	1.443	1998TL1629

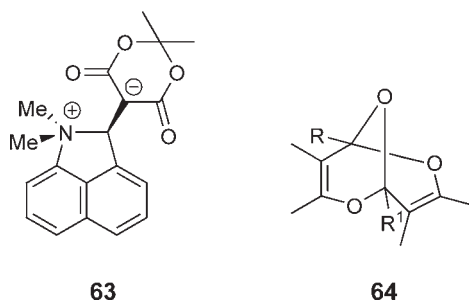


Compound	R ¹	R ²
a		–NHCH ₂ CH ₂ NH–
b		–NMeCH ₂ CH ₂ NMe–
c	NHMe	NHMe
d	NHMe	SMe
e	NHPh	SMe
f	NHC ₆ H ₃ Et ₂ (2,6-)	SMe
g	NHPh	OMe
h	NHPh	NHMe
i	NHC ₆ H ₄ Bu ^t (2-)	NMe ₂
k	NHPh	NMe ₂
l	NHC ₆ H ₂ Me ₃ (2,4,6-)	NMe ₂
m	NHBu ^t	NHBu ^t
n	H	N(Me)OMe
o	H	C ₆ H ₄ NO ₂ (4-)
p	H	C ₆ H ₄ OMe(4-)
q	H	5-NMe ₂ -2-furyl

(6)

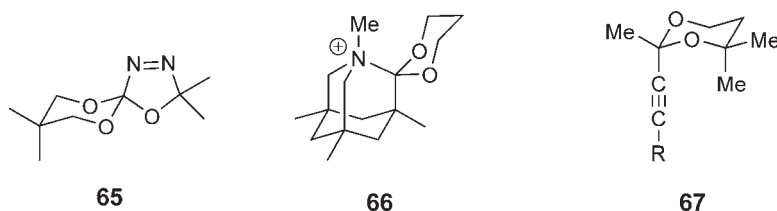
**62**

Also, the structure of **63** is better described as zwitterionic with a C–N bond length of only 1.651 Å <2001J(P2)133>; in the case of methoxy instead of NMe₂, the MeO···C=S separation is longer (2.550 Å) and the two substituents behave as normal *peri*-substituents. Furthermore, the 2,6,9-trioxo-bicyclo[3,3,1]nona-3,7-diene moiety **64** has been structurally characterized as part of Pd(II) complexes <2003JOM(676)93> and as a novel chiral spacer unit in macrocyclic polyethers <2002SMC383, 2004T2857>.



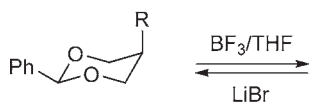
8.11.3.1.2 NMR spectra

The conformations of three 2,2'-disubstituted-1,3-dioxane derivatives **65–67** have been elucidated by NMR spectroscopy <1998CHE141, 1999PAC385, 2001ARK(xii)7>; only the conformers with the more polar substituent in an axial position have been assessed as being in agreement with the anomeric effect.



R = Ph, TMS, C≡C–TMS, SiMe₂C≡C–2,4,4-trimethyl-1,3-dioxane

The salt effect on the conformational equilibria of a number of 5-substituted-2-phenyl-1,3-dioxanes has been studied by equilibration of the diastereomeric 1,3-dioxanes **68–72** (Equation 7) using BF₃ <1997JOC4029>; the corresponding free energy differences are summarized in Tables 4(a) and 4(b). In the absence of salt, both the more polar 5-substituents and the more polar solvent increase the axial preference of the 5-substituent R; dipole–dipole interactions, electrostatic attractions, and intramolecular hydrogen bonding were all used to explain the differences in Δ*G*[°]. The addition of a Li⁺ salt (Table 4(a)) was found to increase the axial preference in **68–72** by increasing the dielectric constant of the solvent, but it increased the equatorial preference in the case of **72** by binding to the carbonyl **72-II** and thereby disrupting the intramolecular hydrogen bond which was stabilizing the axial conformer **72-I**. For **70** and **71**, no significant salt effect on the conformational equilibria was observed (Equation 7). The salt effect on the conformational equilibria of **68a** and **70** was studied by the same authors in more detail (Table 4(b)) <2004JOC9063>. In the case of the 5-carboxy derivative **68a**, in addition to Li⁺, also Ag⁺ and Ca²⁺ were found to increase the axial preference of COOH by interacting with both the endocyclic oxygen atoms and the carbonyl group **68a**; softer and larger cations were too large to fit into the binding site. With regards to the 5-hydroxy derivative **70**, significant salt effects in the presence of Ag⁺, Mg²⁺, and Zn²⁺ were recorded; the observed increased axial preference suggested a similar metal ion coordination.



R	Compound
COOH	68a
COOMe	68b
CONHMe	68c
CH ₂ OH	69
OH	70
OCOMe	71a
OCOCH ₂ OC ₆ H ₄ (o)OMe	71b
NO ₂	71c
NHCOMe	72

(7)

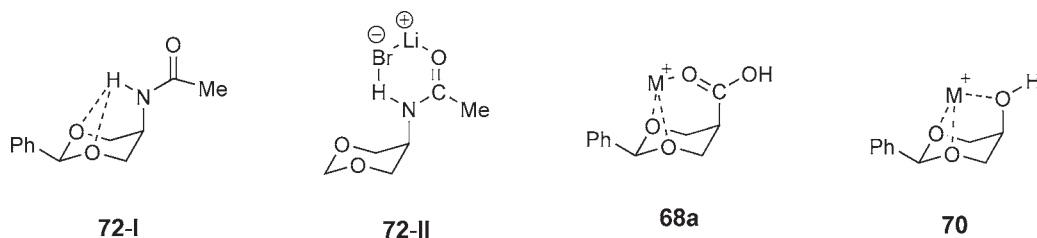


Table 4(a) Conformational equilibria in 5-substituted-2-phenyl-1,3-dioxanes **68–72** in different solvents subject to the presence of salt

Compound	ΔG° (kcal mol ⁻¹)			
	0.0 equiv ^a	1.0 equiv ^b	0.0 equiv ^c	1.0 equiv ^d
68a	-0.77 ± 0.03	-0.41 ± 0.03	-0.80 ± 0.03	-0.25 ± 0.04
68b	-0.50 ± 0.02	-0.15 ± 0.03	-0.75 ± 0.02	-0.11 ± 0.03
68c	-0.76 ± 0.05	-0.67 ± 0.04		
69	-0.20 ± 0.01	-0.04 ± 0.02	+0.18 ± 0.03	+0.25 ± 0.02
70	-0.38 ± 0.04	-0.35 ± 0.03	+0.80 ± 0.02	+0.23 ± 0.03
71a	+0.47 ± 0.01	+0.45 ± 0.02		
71b	+0.56 ± 0.02	+0.89 ± 0.03		
71c	+0.73 ± 0.02	+0.52 ± 0.03		
72	+0.94 ± 0.03	+0.44 ± 0.03	+1.0 ± 0.03	+0.50 ± 0.04

^aAt 25 °C in THF.

^bAt 25 °C in THF and in the presence of LiBr.

^cAt 25 °C in CDCl₃.

^dAt 25 °C in CDCl₃ and in the presence of LiBPh₄.

Table 4(b) Conformational equilibria in 5-substituted-2-phenyl-1,3-dioxanes **68a** and **70** at 25 °C in THF subject to the presence of salt

Salt	ΔG° (kcal mol ⁻¹) ^a	
	68a	70
LiBr	-0.80 ± 0.03	-0.40 ± 0.02
Na(OTf)	-0.41 ± 0.03	-0.38 ± 0.04
Na(OTf)	-0.59 ± 0.08	-0.37 ± 0.04
K(OTf)	-0.72 ± 0.09	-0.44 ± 0.04
Ag(OTf)	-0.42 ± 0.07	-0.22 ± 0.03
Mg(OTf) ₂	-0.51 ± 0.02	+0.74 ± 0.15
Ca(OTf) ₂	-0.62 ± 0.20	-0.24 ± 0.15
Ba(OTf) ₂	-0.68 ± 0.08	-0.36 ± 0.04
Zn(OTf) ₂	-0.59 ± 0.10	-0.31 ± 0.02

^aPositive values indicate a predominance of the *cis*- (axial X) diastereoisomer.

The *erythro*/*threo*-isomers of three 4,5-disubstituted-1,3-dioxanes **73** (cf. **Table 5**), synthesized as chiral building blocks based on the 1,3-dioxane core, were assigned by ¹H NMR spectroscopy (**Table 5**) <1999TA139>; additionally, they are enantiomerically pure.

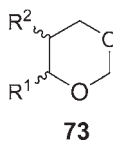
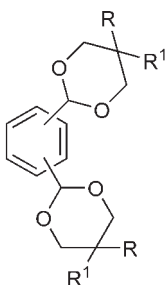


Table 5 NMR assignment of stereochemistry and *erythro*/*threo*-configuration of 4,5-disubstituted-1,3-dioxane derivatives **73**

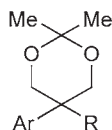
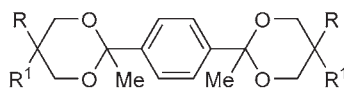
Compound		Coupling constants $J(\text{Hz})$		Conformation		
R^1	R^2	$J_{5,6 \text{ ax}}$	$J_{4,5}$	R^1	R^2	Configuration
73a	—CH=CH—Pent	8.3	9	4-eq	5-eq	<i>erythro</i>
		1.5	0	4-eq	5-ax	<i>threo</i>
73b	—CH ₂ OAc	11	4.5	4-eq	5-eq	<i>erythro</i>
		2.7	0	4-eq	5-ax	<i>threo</i>
73c	—CH ₂ OH	11.1	10.8	4-eq	5-eq	<i>erythro</i>
		8.6	3.4	4-eq	5-ax	<i>threo</i>

The stereochemistry of a large number of 2- and 5-substituted-1,3-dioxane derivatives has been studied by the full arsenal of 2-D NMR spectroscopy and accompanied by X-ray crystallography. *ortho*- and *para*-Substituted benzenes **74** and **75** adequately show *anameric* structures with the aryl substituent preferring an equatorial position, the 5-position substituents Me and Ph preferring equatorial orientations, while the ester substituents favor axial dispositions <1997LA2371, 1998HCO53, 1998ACS366>.



No.	Position	Substituents R, R ¹
74a	<i>ortho</i>	COOEt, COOEt
74b	<i>ortho</i>	COOMe, COOMe
74c	<i>ortho</i>	H, COOH
74d	<i>ortho</i>	H, COOMe
75a	<i>para</i>	H, H
75b	<i>para</i>	COOEt, COOEt
75c	<i>para</i>	Me, Me
75d	<i>para</i>	H, Me
75e	<i>para</i>	H, Ph
75f	<i>para</i>	Me, Et

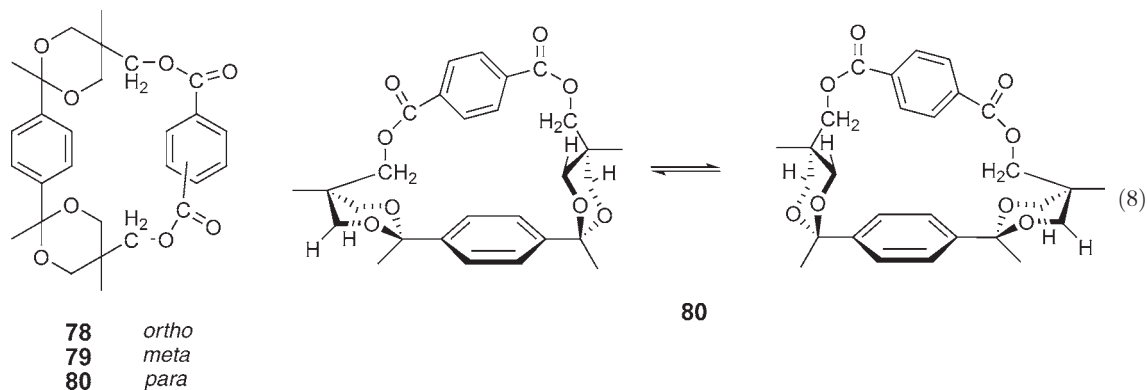
Similarly in the case of 2,2'-disubstitution, compounds **76** and **77** were observed to prefer *anameric* structures; the aryl moiety goes into the axial orientation and 2-Me and 2-CH₂Br into the corresponding equatorial position <1998T2905, 2002M631>. Nothing changes for the 5,5'-substituents: in **77d** and **77e**, Me and Ph are in equatorial orientations. In **77g**, from the two substituents at the 5-position, the CH₂OH group, as the more polar substituent, prefers the axial orientation <2002M631>. The corresponding *meta*-disubstituted benzenes, the 2-pyridine and 2,6-disubstituted pyridine derivatives, reveal the same *anameric* <2002RRC121, 2004HCO139>.

**76**R = Me, CH₂Br

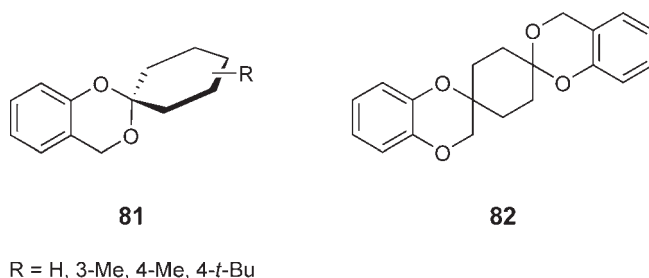
Compound	R, R ¹
77a	H, H
77b	Me, Me
77c	COOEt, COOEt
77d	H, Me
77e	H, Ph
77f	Me, Et
77g	Me, CH ₂ OH

The axial orientation of the aryl substituent in **76** proved to be orthogonal; thus, the aryl rotation is hindered and molecules **76** attain axial chirality; hence, a new class of atropisomers has been realized <1998T2905>.

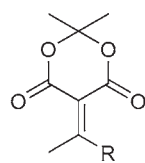
para-, *meta*-, and *ortho*-Aryl-1,3-dioxane moieties have been included into the new cyclophanes **78–80** (Equation (8); in addition, dimers and trimers were also obtained) <2004JOC1337> and the structures determined by NMR spectroscopy and X-ray crystallography. In the case of **80**, a variable-temperature experiment showed dramatic dynamic effects in the NMR spectra; the detailed analysis resulted in a dynamic process described as a ‘molecular rocking chair’ by the authors (Equation 8) <2004JOC1337>. Critical comparison of both the NMR spectra and the X-ray structures of monomers, dimers, and trimers revealed significant intra- and intermolecular π -stacking interaction <2004JOC1337>.



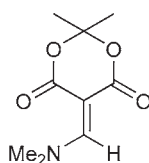
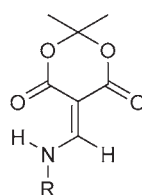
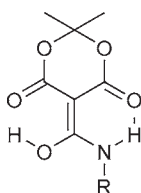
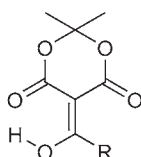
Grosu's group also studied the flexible structures of a number of spiranes **81** and the dibenzo-dispiro derivative **82** <2006HCO313>. The 4[*H*]-1,3-dioxane moieties prefer the ‘flipping’ chiral half-chair conformation with the spiro carbon atom and O-3 out of the plane of the aromatic ring; the substituted cyclohexane ring proves to be anancomeric with the substituents in equatorial orientations. The axially chiral **82** reveals *cis/trans*-isomerism; the *trans*-isomer was isolated and the structure determined by X-ray crystallography. The cyclohexane ring remains in the chair conformation with the O-C₆H₄-moieties in equatorial and the OCH₂-C₆H₄-moieties in axial positions <2006HCO313>.



Further, both the structure and the intramolecular enol tautomerism of a large variety of exo-methylene Meldrum's acid derivatives with alkyl substituents **83** <2005MRC171>, alkylamino substituents, **84** and **85** <1997MOL31, 1997MRC432>, and amino and hydroxyl substituents **86** <2000JA1325, 2003JPO525> have been studied by NMR spectroscopy. Deshielded ¹H-N(¹H-O) signals and the ¹⁷O NMR data clearly showed the existence of strong intramolecular hydrogen bonding and proved a preferred tautomerism. The same tautomerism in the corresponding alkyl derivatives **87** was detected by employing ⁿJ_{C,O-H} coupling constants <1998MRC104> and deuterium-isotope effects on ¹³C shielding, ⁿΔC(OD) <1998MRC315>.

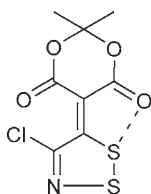
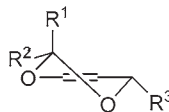
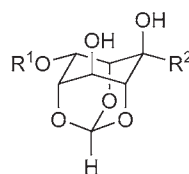
**83**

R = Me, Et

**84****85**R = H, Me, Et, *i*-Pr, *t*-Bu, CH₂Ph**86**R = Ph, *i*-Pr**87**R = H, Me, Et, *i*-Pr, *t*-Bu, CH₂Ph

In the ¹³C NMR spectrum of Appel's salt **88**, two different absorptions for the two carbonyl functions were observed at 166.0 and 166.7 ppm <1997BSB729>; this is reinforced by two C=O vibrations also present in the IR spectrum. The authors therefore concluded that the rotation about the exocyclic partial C=C bond is restricted by a strong attractive S···O interaction.

Finally, structural elucidations of the 1,3-dioxin moiety in 5,6-benzo-1,3-dioxin derivatives in natural <1999MI141, 2003JAN459, 2003JAN1012> and synthetic products <2004CHE986> have been reported wherein half-chair conformations **89** were generally established. The NMR analysis of *myo*-inositol monoorthoformates **90** helped to understand the origins of deuterium-isotope effects <1996JOC9610>; the study revealed isotope effects which proved to be much stronger than in conformationally flexible structures. Obviously, deuterium prefers the bridging position in 1,3-diaxial hydrogen bonds.

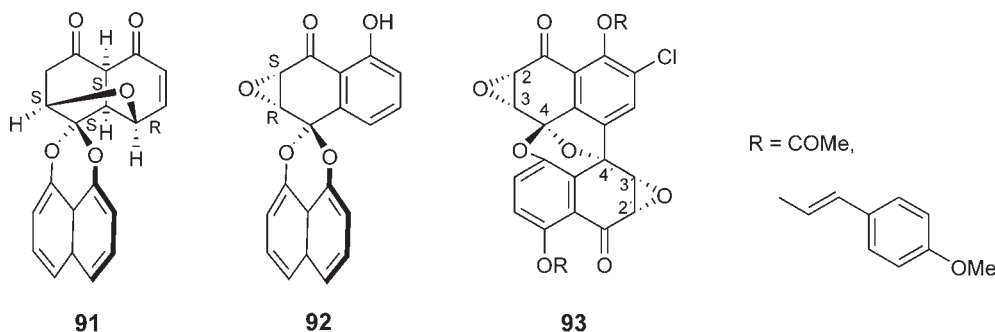
**88****89****90**

R¹ = SiMe₂*t*-Bu
R² = Me, CH₂COOEt

The solution-state structure of the nogalamycin-DNA and respinomycin D-DNA complexes (nogalamycin and respinomycin D both contain a dioxabicyclo[3.3.1]nonane unit incorporating the 1,3-dioxane moiety) was determined using the full arsenal of 2-D NMR spectroscopy and the data refined using restrained molecular dynamics <1998J(P1)3, 1999JMB699, 2000MI98, 2002AGE4754, 2003OBC60>. Details of the interaction and preferred orientation of the antibiotics at the DNA binding site were revealed. The chemical shift of the ¹⁹F nucleus has been employed as a pH indicator for the evaluation of a series of fluorinated vitamin B₆ analogs with respect to the cellular pH and the transmembrane pH gradient in perfused organs and *in vivo* <1998BMC1631, 2005MI255>.

8.11.3.1.3 Absolute configuration of 1,3-dioxane derivatives

Determination of the absolute configuration of natural products containing the 1,3-dioxane moiety is of continuing interest. For the first time, by quantum-chemical calculation of the circular dichroism (CD) spectra of two representatives **91** and **92** of palmarumycins, biologically active compounds from *Coniothyrium* species had their absolute configurations determined without resort to empirical rules or reference material <1997T1655>. The results allow a general procedure for the rapid and unequivocal determination of the absolute configuration within this class of natural products. The 1,3-dioxin moieties in **91** and **92** proved to be in sofa conformations.

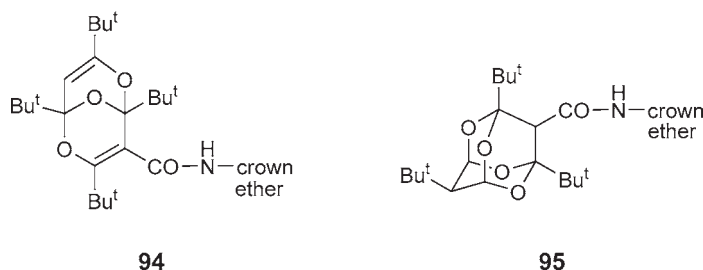


After estimating the relative configurations of certain groups by a full complement of 2-D NMR spectroscopic methods, the exciton-coupled CD method was successfully applied to determine the absolute configuration of a series of spiro-oxins, for example **93**, spiro-ketal-linked bis-epoxydecalinones of fungal origin <1996T435, 2001CJC1786>. The absolute configuration of the six stereogenic centers have been determined as $2S,3R,4S,2'S,3'R,4'S$. Since the initial NMR study proved other members of spiro-oxins to share the same skeletal structure, identical absolute configurations could be assumed. The 1,3-dioxin moiety in **93** proved to adopt a boat conformation.

Using established methods, the absolute configuration could be assigned for kigamicins (obtained from *Amycolatopsis*) by a combination of X-ray and degradation studies <2005JAN56>, emycins by X-ray analysis at low temperature <1999AXB607>, and for a number of polyketides by resolution of the racemic mixture employing a chiral auxiliary and subsequent X-ray crystallographic analysis <2002AGE1198>. These compounds all contain the 1,3-dioxane moiety.

In addition, a new, selective, and sensitive CD difference spectroscopic method based on the oxime formation of the keto group for the determination of the absolute configuration of Δ^4 -3-ketosteroids and 6-keto-morphinans for their pharmaceutical analysis has been published <2003MI185> and a chiral supercritical fluid chromatography (SFC) strategy has been successfully applied to the enantiomeric separation of substituted isopropylidenedioxa-5-hydroxyhepta-2,6-dien-1-ones <1999MI269>. Temperature, pressure, and modifier proved to have only marginal influence.

Several new lariat-crown ethers have been reported bearing either bridged bis-dioxin **94** or tetraoxaadmantane units **95** as chiral substituents; however, they were used only for the transportation of metal ions into organic solvents <2003M509>.



8.11.3.2 1,3-Oxathianes

8.11.3.2.1 X-Ray diffraction

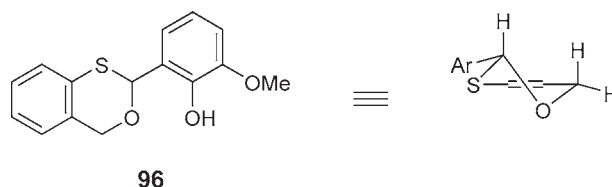
The publication of X-ray structures from 1996 onward has continued and altogether ca. 30 structures have been published. Bond and dihedral angles for the preferred conformation of the 1,3-oxathiane rings are determined by the ring fusion and/or attached substituents; thus, published structures were classified as either monocyclic (mono), spiro-substituted (spiro), bicyclic (bi), or tricyclic (tri). For each of the four groups, derivatives were found and a comparison of the experimental bond lengths for the 1,3-oxathiane ring system with representatives of the different classes are

presented in **Table 6**. They behave normally and deserve no particular comment. The chair proved to be the most stable conformer and was obtained in all structures <1997M201, 1998MC122, 1999ZOR1189, 1999OM4275, 1999JIC617, 2000TA3177, 2000JA10242, 2001TA3095, 2001T8751, 2001JRM405, 2002JOC5011, 2002H(58)457, 2003OM1868, 2003AGE2889, 2003PC1, 2004T3173, 2005ICA(358)303>. Also, crystal structures of the sulfoxide (the oxygen in both axial and equatorial positions) and the sulfone have been published, whereby the 1,3-oxathiane ring system was found to retain its chair conformation in all cases.

Table 6 Conformations and selected bond lengths (Å) for 1,3-oxathianes in the solid state

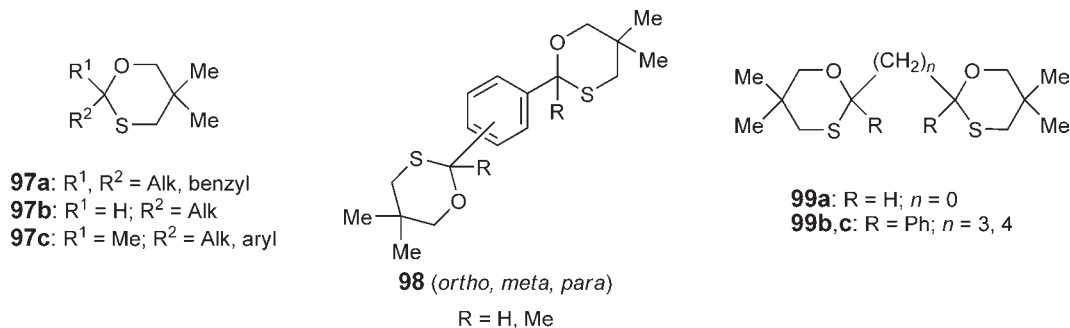
Class	Conformation	Bond lengths						Reference
		C(1)–S(2)	S(2)–C(3)	C(3)–C(4)	C(4)–C(5)	C(5)–O(6)	O(6)–C(1)	
spiro	Chair	1.838	1.812	1.537	1.532	1.432	1.430	2004T3173
mono	Chair	1.823	1.774	1.521	1.507	1.447	1.401	1993STC203
mono	Chair; S=O (eq)	1.853	1.807	1.531	1.495	1.444	1.403	2003PC1
mono	Chair; S=O (ax)	1.777	1.793	1.519	1.471	1.422	1.403	1993STC203
bi	Chair	1.848	1.859	1.530	1.565	1.462	1.432	2000TA3177
tri	Chair	1.843	1.798	1.510	1.509	1.456	1.400	2005ICA(358)303

The solid-state structure of one benzo derivative of 1,3-oxathiane **96** has been studied; the heterocyclic moiety was found to adopt a half-chair conformation with the aryl substituent in an equatorial position <1998JFA4002>.

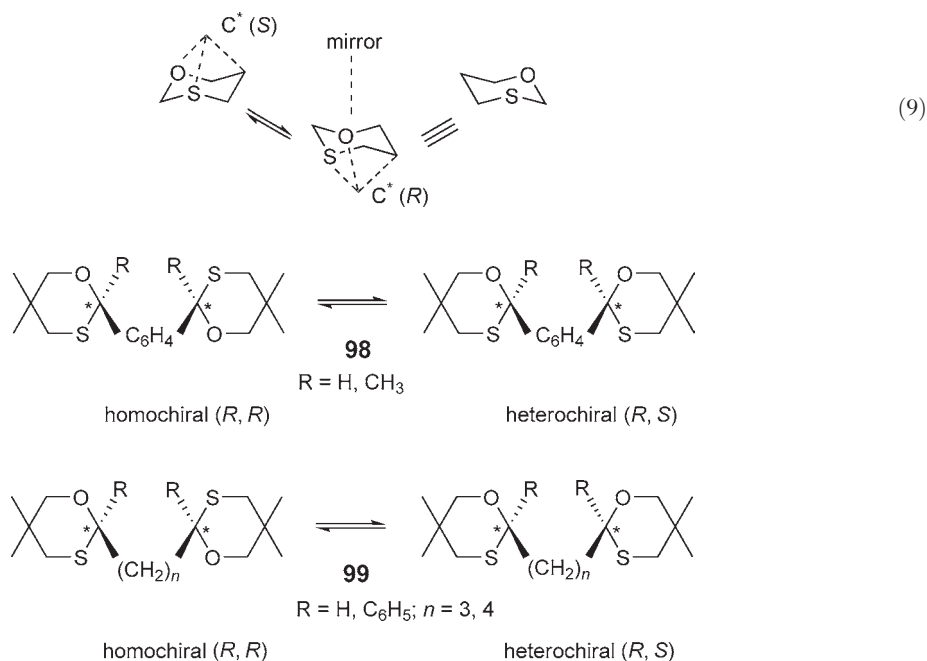


8.11.3.2.2 NMR spectroscopy

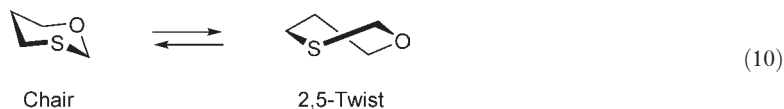
Both the configuration and conformation of a variety of substituted 1,3-oxathianes **97–99** have been studied using the full arsenal of ^1H NMR spectroscopic methods <2005STC369, 2004M89>. Most of the compounds were found to exhibit anancomeric structures; in cases of flexible structures, these were analyzed at low temperature. The preferred orientation of the substituents is equatorial, though in the case of 2-alkyl-2-aryl-1,3-oxathiane derivatives the aryl substituent strongly prefers the axial position. The ring interconversion of the 1,3-oxathiane ring is an enantiomeric inversion <1996CH311>; thus, in **97a**, the prochiral $\alpha\text{-CH}_2$ groups are diastereotopic.



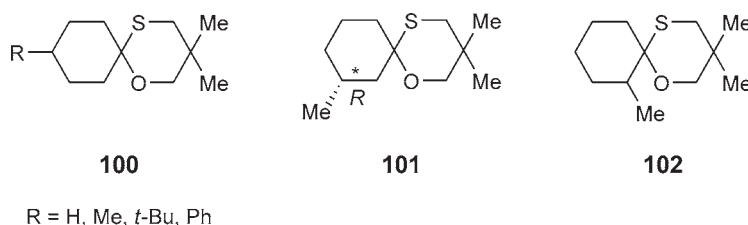
Stereochemically, even more interesting are the bis-1,3-oxathiane derivatives **98** and **99** <2005STC369>. All compounds are chiral and the chiral elements are carbons C-2/C-2' and the 1,3-oxathiane moieties themselves (Equation 9). Due to the bis-structure, compounds **98** and **99** exhibit both homochiral (2*R*,2'*R*; 2*S*,2'*S*) and heterochiral (2*R*,2'*S*) isomers (Scheme 4) and they reveal rapid equilibration in solution via open-chain intermediates, thereby preventing separation and individual analysis of the isomers in solution. In the solid state, the compounds crystallized either as unique heterochiral isomers or as a mixture of the two as a solid solution.

**Scheme 4**

Interestingly, during a low-temperature study of the conformational equilibria, in addition to the generally observed chair conformation of the 1,3-oxathiane ring, a significant contribution of the 2,5-twist conformer (8–9% at 180 K) was also observed (Equation 10) <2005STC369>.



Grosu and co-workers also studied the complex configurational and conformational aspects of the unique stereochemistry of substituted spiro-1,3-oxathiane derivatives **100–102** by NMR spectroscopy <2001T8751>.



Mixtures of *cis*- and *trans*-isomers were observed (Scheme 5 for **101**) and they could only be partly separated by chromatography. The ratio of the isomers was determined by integration of characteristic resonances and proved to be almost constant at 60:40, with the isomer with sulfur in an equatorial position considered as the major species and supported by X-ray crystallography. The compounds exhibit semiflexible structures: the cyclohexane ring is rigid due to anchor groups but the 1,3-oxathiane moiety interconverts on the NMR timescale at room temperature. Low-temperature ^1H NMR studies afforded the stereochemical information.

As an extension, higher members of the polyspiroane series were built up by merging the corresponding monospiranes; their configurations and conformations **103–106** were examined <2004T3173>. The number of stereoisomers, however, increases rapidly with an increasing number of rings, for example, six trispiranes, ten tetraspiranes, etc. For an 'odd' number of monospiro units, all possible stereoisomers are chiral; in the case of an 'even' number, though, achiral isomers (*cis/trans*) are also present. The diastereomers (Figure 5) were separated and studied as single

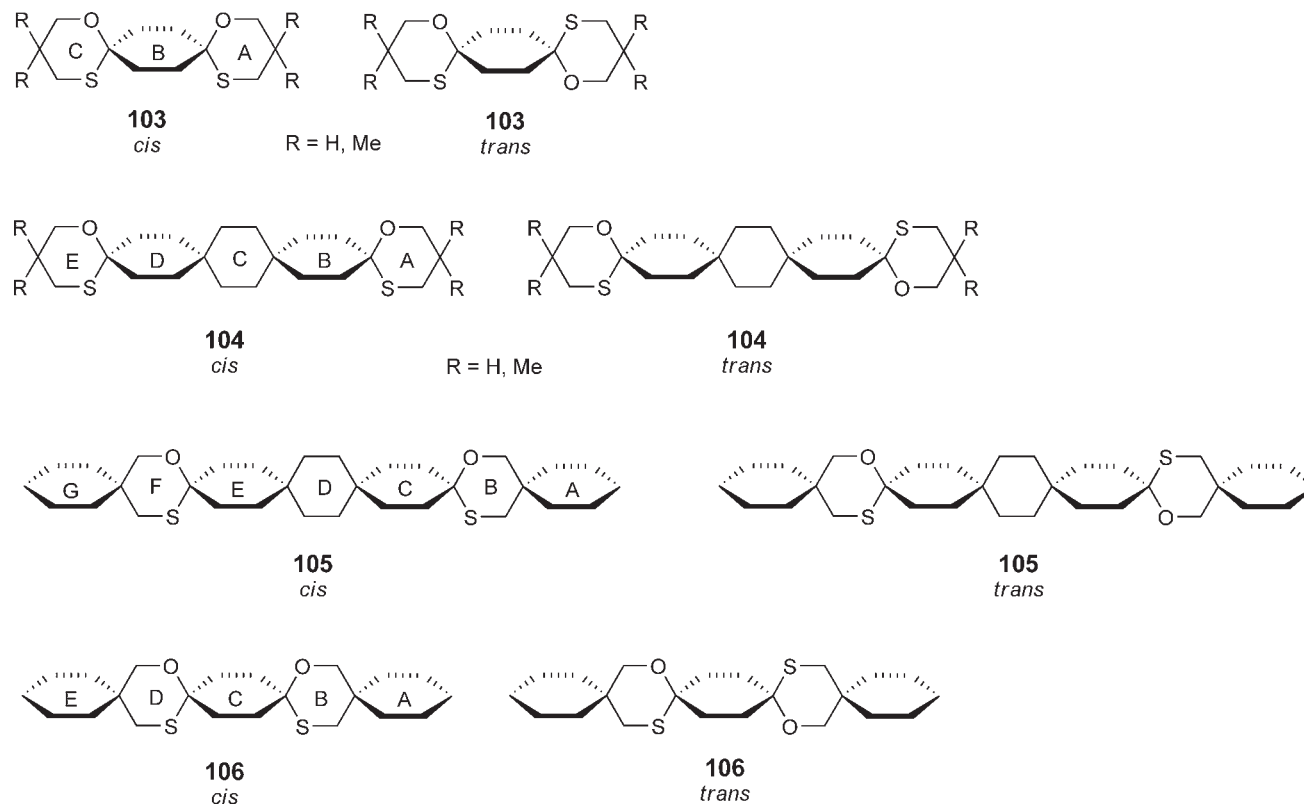
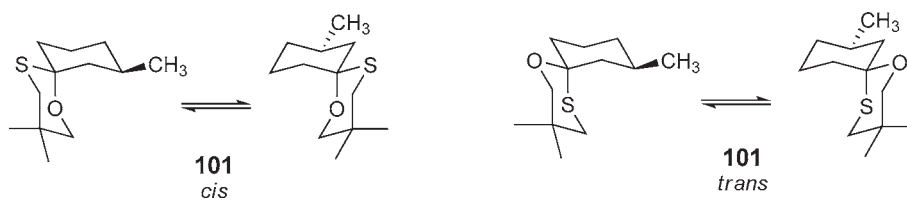


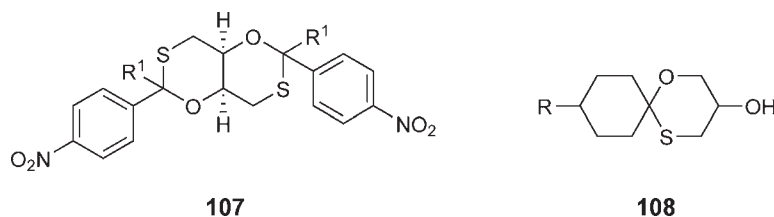
Figure 5 Some *cis*- and *trans*-polyspirans with bis-1,3-oxathiane group.

compounds. All possible conformers of each diastereomer were in equilibrium and again low-temperature NMR spectroscopy was necessary to disentangle the conformational equilibria in effect. Usually, several sets of signals of similar intensity, some overlapped, were obtained.



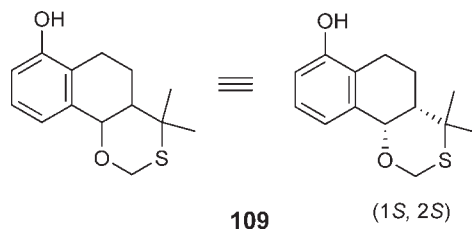
Scheme 5

The complete NMR analysis of the bicyclic decalin-like bis-1,3-oxathiane **107** revealed the *cis*-position of 1,5-dioxo-3,7-dithiadecalin, the equatorial position of the phenyl substituents, and the axial orientation of the R¹ substituent at the same skeletal position <2004C121>. By the same methods, the stereochemistry of the spiro analog **108** was clarified <1998C267>.

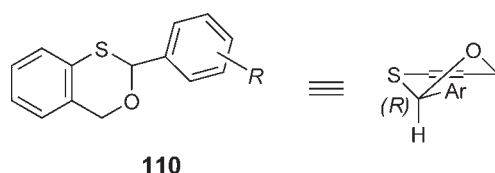


8.11.3.2.3 Absolute configuration of 1,3-oxathiane derivatives

A new chiral 1,3-oxathiane derivative **109** for enantioselective synthesis has been fabricated, fully characterized employing the complete arsenal of 1-D and 2-D NMR experiments and the absolute configuration determined by vibrational circular dichroism (VCD) <2001TA2605>. The latter is a reliable new method for determining absolute configurations and consists of experimentally measuring and *ab initio*-calculating both the VCD and the IR spectrum of a single enantiomer. Comparison between the two then yields the assignment of absolute configuration. (If the calculated principal VCD bands have the same sign as the corresponding experimental VCD bands, then the absolute configuration chosen for the calculation was correct, and conversely otherwise.) In the case of compound **109**, this yielded an absolute stereochemistry of 1*S*,2*S*.



The absolute configurations of three *iso*-vanillic chiral 1,3-oxathianes **110** were established by their CD spectra (supported by X-ray and spatial NMR information) <2000TA3177>. The similarity of the curves and the sign of the Cotton effect allowed the assignment of (*R*)-configuration to the (+)-**110** enantiomer. Only the *R*-(+)-enantiomer is sweet, the others being tasteless. Obviously, steric factors affect structure and thereby the taste of a compound <2000TA3177>, because it is the active configuration which actually interacts with the sweet taste receptor <1998JFA4002>. A QSAR study of sweet *iso*-vanillyl derivatives, considering appropriate physicochemical parameters, has been published <2001QSA3>.



8.11.3.3 Dithianes

8.11.3.3.1 X-Ray diffraction

The publication of X-ray structures since 1996 has continued unabated and a number of different structures (Figure 6) have been published. Conformation, bond lengths, bond and dihedral angles of the 1,3-dithiane rings are determined by the ring fusion, attached substituents, and exocyclic double bonds that are present; thus, published structures were classified as either monocyclic (mono), spiro-substituted (spiro), bicyclic (bi), or tricyclic (tri). For each of the four groups, derivatives were found and a comparison of the experimental bond lengths for the 1,3-dithiane ring system with representatives of the different classes is presented in Table 7. Only one tricyclic structure, which involves the 1,3-dithiane moiety <1996MI761>, was found, but three more spiro1 structures with 1,3-dithiane chair conformations <2000SL92, 1999CC1757, 1999TL2769> were found. The chair proved to be the most stable conformer and was obtained in all kinds of structures. Besides twist conformers, in the case of mono2, the corresponding half-chair conformer was also obtained.

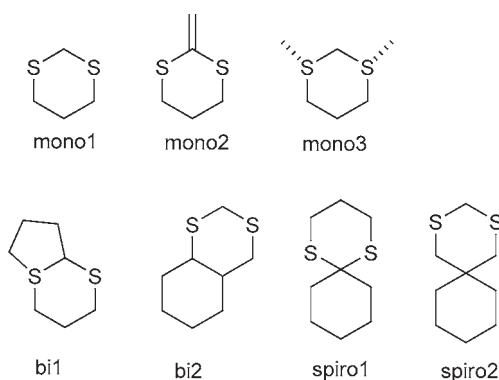
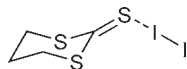


Figure 6 1,3-Dithiane systems characterized by X-ray crystallography.

Table 7 Conformations and selected bond lengths (Å) for the 1,3-dithiane moiety in different solid-state structures

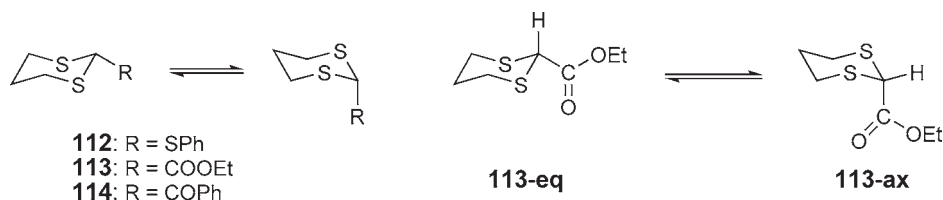
Class	Conformation	Bond length						Reference
		S(1)–C(2)	C(2)–S(3)	S(3)–C(4)	C(4)–C(5)	C(5)–C(6)	C(6)–S(1)	
mono1	Chair	1.802	1.794	1.810	1.511	1.491	1.798	2002CEJ118
mono2	Chair	1.765	1.765	1.768	1.501	1.467	1.799	2003T9677
mono2	Twist	1.755	1.757	1.806	1.508	1.524	1.811	2005TL4399
mono2	Half-chair	1.753	1.766	1.782	1.502	1.363	1.746	2002POL1273
mono3	Chair	1.810	1.795	1.804	1.535	1.480	1.798	2003JCD3534
spiro1	Chair	1.816	1.827	1.807	1.516	1.507	1.809	2003PC2
spiro2	Twist	1.734	1.729	1.806	1.538	1.518	1.815	2001AXC471
bi1	Chair	1.813	1.795	1.807	1.515	1.520	1.815	2003TL2841
bi1	Twist	1.780	1.751	1.768	1.467	1.525	1.814	1996IC4274
bi2	Twist	1.803	1.793	1.816	1.550	1.531	1.809	2005JFC(126)1332
bi2	Chair	1.739	1.798	1.823	1.532	1.525	1.802	2002JOC1910

During studies on the interaction between sulfur donors and suitable acceptors, the solid-state structure of the charge-transfer adduct 1,3-dithiane-2-thione...diiodine **111** was investigated <1999IC4626>; the CS₃ moiety is planar, the I₂ molecule lies in the same plane with the first iodine atom separated by 2.755 Å; and the I–I vector is practically co-linear with the S–I one. The I–I bond length is slightly elongated with respect to a free iodine molecule.

**111**

8.11.3.3.2 NMR spectra

The conformational equilibria of three 2-substituted-1,3-dithianes **112–114** were studied by ¹³C NMR spectroscopy at various temperatures and in different solvents (Scheme 6), and both enthalpy and entropy differences were evaluated (Table 8) <1999T359>. The predominance of the axial conformers proved to be of enthalpic origin, in opposition to the entropic contribution which favors the equatorial conformers. The more polar solvent, on the other hand, stabilizes the more polar equatorial conformation. Parallel DFT calculations in the gas phase and in solution emphasized that both 2-substituents point outside the 1,3-dithiane ring system in the two conformations, for example **113-ax** and **113-eq**, and reproduce the experimentally observed conformational equilibria. Thus, the results of semi-empirical PM3 calculations <1997JMT(418)41> were able to be amended.

**Scheme 6****Table 8** Enthalpy and entropy differences for the 2-substituted-1,3-dithianes **112–114** in different solvents

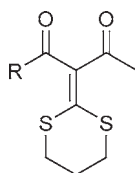
Compound	R	Solvent	ΔH^{oa} (kcal mol ⁻¹)	ΔS^{ob} (kcal mol ⁻¹)
112	SC ₆ H ₅	Toluene- <i>d</i> ₈	1.51 ± 0.4	3.23 ± 0.8
112	SC ₆ H ₅	CD ₂ Cl ₂	1.35 ± 0.5	2.94 ± 0.8
113	CO ₂ Et	Toluene- <i>d</i> ₈	2.13 ± 0.4	3.99 ± 0.8
113	CO ₂ Et	CD ₂ Cl ₂	1.03 ± 0.4	1.32 ± 0.6
113	CO ₂ Et	CD ₃ OD	1.68 ± 0.3	4.25 ± 1.0
114	COC ₆ H ₅	Toluene- <i>d</i> ₈	1.67 ± 0.4	1.92 ± 0.6
114	COC ₆ H ₅	CD ₂ Cl ₂	0.63 ± 0.3	1.01 ± 0.6

^aPositive values indicate that the axial conformer is favored enthalpically.

^bPositive values indicate that the equatorial conformer is favored entropically.

The conformational equilibrium of 1,3-dithiane 1-oxide (the sulfoxide) was studied by low-temperature ¹H and ¹³C NMR spectroscopy <1999RJC5>; at –80 to –90 °C the two chair conformers could be detected (the one with the equatorial S → O bond preferred by ca. 90%). Besides discussing the influence of the sulfoxide conformation on both NMR spectra, the enthalpy and entropy differences ($\Delta H^{\circ} = 0.55 \pm 0.1$ kcal mol⁻¹, $\Delta S^{\circ} = 1.88$ e.u.) between the two conformers were detected in CDCl₃;CS₂ = 1:2.

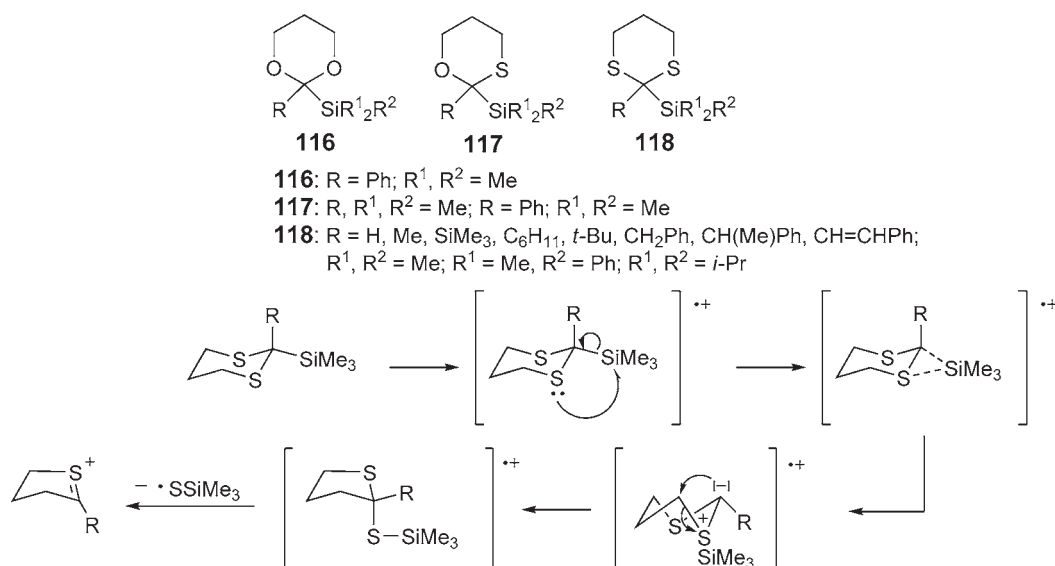
Further, the ¹H/¹³C NMR data and characteristic IR spectra of several dithioacetals of α,α'-dioxoketene **115** have been reported <1996MI487, 2001MI775, 2004MI1069> and the structures fully assigned. However, the isomerism present in **115** was not studied.

**115**

R = Me, Ph

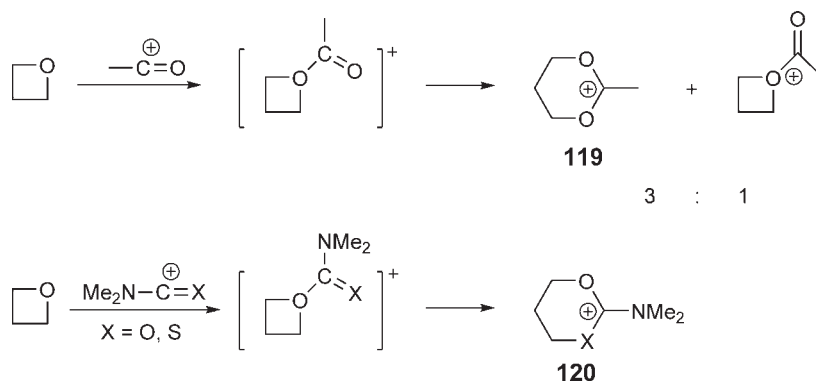
8.11.3.4 Mass Spectrometry, IR Spectroscopy and Other Methods

In order to investigate the factors which influence the unusual fragmentation of 2-trimethylsilyl-1,3-dithianyl derivatives, namely the loss of 105 amu corresponding to SSiMe_3 , the 70 eV electron ionization (EI) mass spectra of SiMe_3 -substituted 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes **116–118** were measured and inspected with respect to the desilylation reaction [<1999JMP226>](#). The molecular ion, though always present, was of low intensity while peaks at m/z 73 (SiMe_3^+) and m/z 149 ($\text{Me}_3\text{SiCS}_2^+$), typical for cyclic silyldithioacetals, were frequently observed. Ions from the loss of 105 amu from the molecular ions were also observed, often as the base peaks of the spectra. As a consequence, the loss of SSiMe_3 can only be achieved by transfer of SiMe_3 to a sulfur atom (**Scheme 7**).

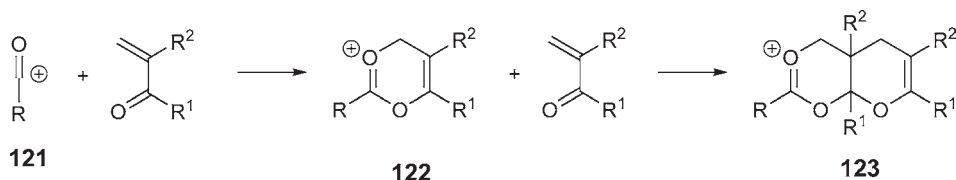
**Scheme 7**

Both steric hindrance and the nature of the geminal substituent R influence the fragmentation and loss of the $\cdot\text{SSiMe}_3$ radical which is accompanied by metastable ion formation and thus evident by *B/E* scanning. Because of the less nucleophilic character of oxygen, the corresponding loss of $\cdot\text{OSiMe}_3$ radicals in the 1,3-dioxane derivatives was not observed. Inspection of the sequential product-ion mass spectra for the reaction of oxetane with $\text{Me}-\text{C}^+=\text{O}$, $\text{Me}_2\text{N}-\text{C}^+=\text{O}$, and $\text{Me}_2\text{N}-\text{C}^+=\text{S}$ revealed that oxetane reacts by four- or six-membered ring expansion to yield the product ions **119** and **120**. The six-membered ring expansion occurs predominantly for $\text{Me}-\text{C}^+=\text{O}$ and exclusively for both $\text{Me}_2\text{N}-\text{C}^+=\text{O}$ and $\text{Me}_2\text{N}-\text{C}^+=\text{S}$ (**Scheme 8**) [<2000CEJ897>](#). When oxetane reacts with thioacylium ions, the reaction promotes O(S) scrambling as indicated by ^{18}O labeling.

Gas-phase reactions of acylium ions with α,β -unsaturated carbonyl compounds have been investigated by pentaquadrupole multiple-stage mass spectrometry (MS) [<2002JMP146>](#). The positively charged acylium ions **121** act as activated O-heterodienophiles in cycloaddition reactions and form resonance-stabilized 1,3-dioxinylium ions **122** which also act as dienophiles and undergo a second cycloaddition reaction across the activated $\text{C}=\text{C}$ ring double bond of **123** (**Scheme 9**). ^{18}O Labeling and characteristic dissociations of **123** indicated both the site and regioselectivity of the cycloaddition reactions corroborated by parallel B3LYP/6-311++G(d,p) calculations.

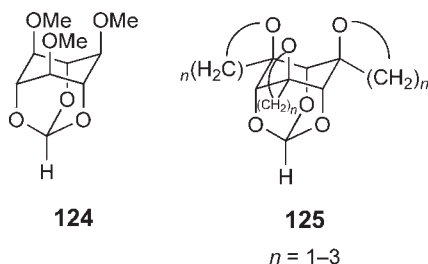


Scheme 8



Scheme 9

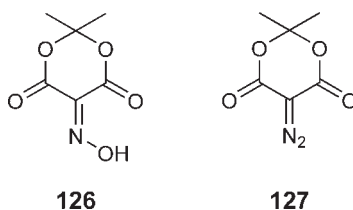
The capacity of inositol orthoformate derivatives **124** and **125** for binding to alkali metal ions was studied by electrospray ionization mass spectrometry (ESI-MS) gas-phase measurements [<2001JOC8629>](#). The [5.5.5]-ionophore **125** ($n = 3$) possessed the highest Li^+/Na^+ selectivity and the best affinity for Li^+ . The results obtained proved to be in agreement with the size-fit concept. Other factors which influence the complexation are the orientation of the oxygen atoms, which are able to bind to metal, the basicity, and the polarizability of the heteroatoms around the perimeter of the binding cavity.



ESI-MS was also successfully employed for the analysis of very weak noncovalent drug/duplex DNA complexes. The DNA complexes of nogalamycin, which contains the 1,3-dioxane moiety, and of several analogs were detected this way [<1998MI342, 1999RCM2489, 2002CC556>](#).

8.11.3.4.1 IR spectroscopy

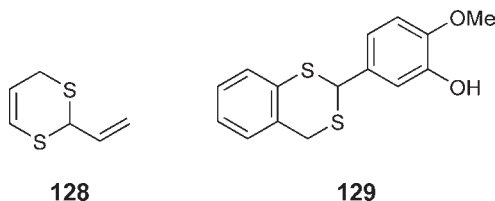
IR spectroscopy has been applied to study the pyrolysis of isonitroso Meldrum's acid **126** [<1997PCA3936>](#) and the photodecomposition of diazo-Meldrum's acid **127** [<1996JA1551, 1997MI43>](#); in the latter case, the application of a new method, ultrafast IR spectroscopy, was necessitated because the reaction was complete within only 20 ps.



8.11.3.4.2 Identification of 1,3-dithiin derivatives in natural products

Gas chromatography (GC), liquid chromatography (LC), GC–MS, LC–MS, and Fourier transform (FT)-Raman spectroscopy were usefully employed methods for the separation and identification, in addition to other unsaturated and acyclic components, of sulfur compounds in garlic oil (*Allium sativum*) <2001CHR356, 2004MI235, 2006MI287>. Of the compounds described in this chapter, 2-vinyl-4*H*-1,3-dithiin **128** was identified together with 2-vinyl-4*H*-1,2-dithiin to be the major organosulfur compounds in fresh garlic. These compounds decompose during isolation and the structure elucidation procedure forming many different sulfur compounds.

An interesting structure–taste study of sweet *iso*-vanillyl derivatives has been published <1998JFA4002, 2001QSA3>. It was found that only one enantiomer of each pair proved to be sweet, the other being tasteless. The *R*-(+)-enantiomer of compound **129** was the sweetest molecule among the variety tested with a relative sweetness, RS, of 20 000 (RS = [sucrose]/[compound]). (The *S*-(-)-enantiomer was also tasteless.) As in these *iso*-vanillyl derivatives, the difference in the taste of two enantiomers seems to be general and helps in defining receptor-active sites.



8.11.4 Thermodynamic Aspects

8.11.4.1 Combined and Comparative Studies

The enthalpies of formation of 1,3-dioxane ($\Delta_f H^\circ_m = -81.4 \pm 1 \text{ kcal mol}^{-1}$), 1,3-dithiane ($\Delta_f H^\circ_m = -0.6 \pm 0.55 \text{ kcal mol}^{-1}$), 1,3-dithiane sulfoxide ($\Delta_f H^\circ_m = -23.4 \pm 0.5 \text{ kcal mol}^{-1}$), and the corresponding sulfone ($\Delta_f H^\circ_m = -77.9 \pm 0.5 \text{ kcal mol}^{-1}$) have been determined <2005CSR347>. 1,3-Dithiane monosulfoxide preferentially adopts a conformation with an equatorial configuration. The enthalpies of formation were compared to those of cyclohexane, oxane, thiane, the 1,4-dioxanes/dithianes, and the 1,3,5-trioxanes/trithianes, accordingly with respect to the relative importance of steric, electronic, electrostatic, and stereoelectronic interactions within these species <2005CSR347>.

The C–H bond-dissociation energies D_{C-H} of the acetals **130** and **131**, monothioacetal **132**, and the dithioacetal **133** (Figure 7) were calculated from experimental reaction kinetic data <2005MI379>. The C–H dissociation energies of the 1,3-dithiane derivative **133** proved to be lowest, followed by the 1,3-oxathiane derivatives **132**,

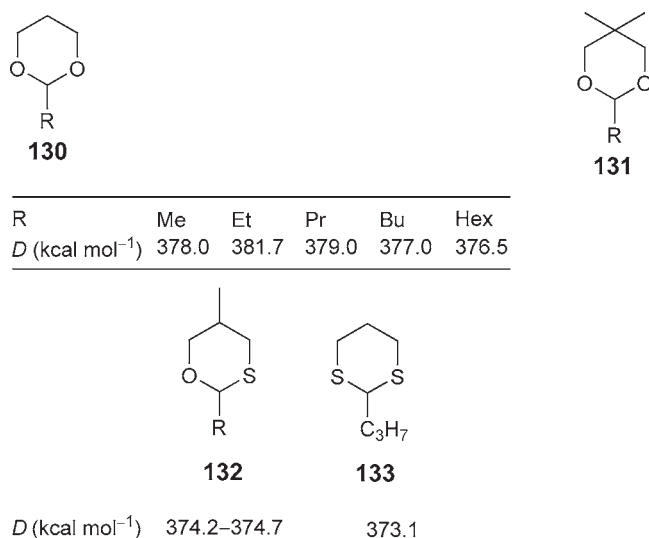


Figure 7 Calculated C–H dissociation energies of 2-substituted-1,3-heterocycles.

and, finally, the 1,3-dioxane derivatives **130** and **131** with lowest C–H acidity. In the case of the latter compounds, the C–H dissociation energies are clearly dependent on the substituent at position 2 (Figure 7).

The acidity constant of Meldrum's acid was determined by means of capillary electrophoresis ($pK_a = 4.89\text{--}5.09$) and was found to be in good agreement with the literature value ($pK_a = 4.83$) <2004ANB664>. Though the anomalously high acidity of Meldrum's acid and of its derivatives is well known, it remains an unresolved issue. For this reason, the localized σ -orbitals of the C–H bonds at C-5 were calculated using reactive hybrid orbital (RHO) theory <2004JOC4309>. The unoccupied RHOs of the C–H moiety of Meldrum's acid displayed a good correlation with the experimental deprotonation energies; thus, the acidity of the C-5 protons of Meldrum's acid can be represented by electron-accepting orbital levels of the unoccupied RHO of the C(5)–H moiety. This aspect proved generally valid for the C–H acidity of the α -protons of carbonyl compounds and suggests that the C–H acidity of Meldrum's acid is consistent with the C–H acidity of other carbonyl compounds. The gas-phase acidities of a series of N-substituted amides of Meldrum's acid were experimentally determined by measuring the equilibrium constants of the reversible proton-transfer reaction between the Meldrum's acid derivative and a reference acid of known acidity and calculated at the B3LYP/6-31+G* level of theory <2004JOC5947>. The correlation between the experimental and calculated acidities proved to be perfectly linear.

8.11.4.2 1,3-Dioxanes

Ideal gas thermodynamic properties (ΔH_f° , S° , and $C_p(T)$, $300 \leq T(K) \leq 1500$) of 34 cyclic oxygenated hydrocarbons (mainly concerning 1,3-dioxane but also including 1,3-dioxin) have been calculated using the PM3 method including 12 species on which data have not been previously reported <1997PCA2471>. Particular correlations of theoretical versus experimental properties were obtained and employed to estimate values for unknown compounds. These values are given in Table 9. The standard deviations of PM3-determined ΔH_f° and S° were evaluated as $2.89 \text{ kcal mol}^{-1}$ and $1.15 \text{ cal mol}^{-1} \text{ K}^{-1}$, respectively, and for heat capacities $C_p(T)$ to be less than $0.92 \text{ cal mol}^{-1} \text{ K}^{-1}$. This semi-empirical method is recommended as a convenient and economic alternative to determine ideal gas thermodynamic properties of oxygenated heterocycles.

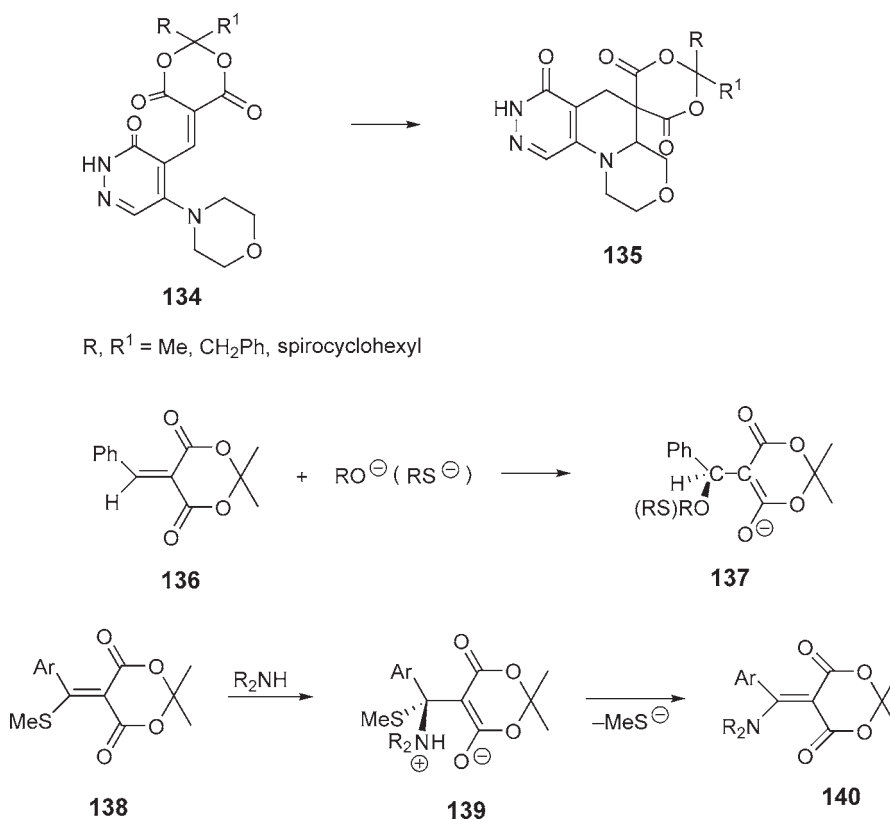
Table 9 Thermodynamic properties

Compound	ΔH_f° (kcal mol ⁻¹)	S° (cal mol ⁻¹ K ⁻¹)	$C_{p,300}$ (cal mol ⁻¹ K ⁻¹)
	-79.06 (-81.81) ^a	73.84 (72.44) ^a	22.66 (21.50) ^a
	-57.44	72.62	21.31

^aExperimental values.

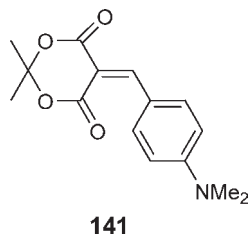
The gas-phase enthalpy of formation for 1,3-dioxane ($-81.4 \pm 1 \text{ kcal mol}^{-1}$) is highly exothermic <2004JOC1670> and the stabilization of 1,3-dioxane has been explained in terms of the 'anomeric' $n_O \rightarrow \sigma_{C-O}^*$ stereoelectronic interaction which stabilizes 1,3-dioxane. The same stabilization was not observed in 1,3-dithiane and this was explained in terms of the lower electronegativity of sulfur relative to oxygen and by the correspondingly high σ_{C-S}^* orbital energy that makes it a poor σ -acceptor (Table 9) <2004JOC1670>.

Both the properties and chemistries of the highly acidic Meldrum's acid and of its derivatives have been of continuing interest; for example, the ring-closure reaction of the Meldrum's acid derivative **134** (Scheme 10) was investigated by differential scanning calorimetry (DSC) <2003JMT(666)667>; the structures of the reaction products **135** were confirmed by spectroscopic methods and both enthalpy values and heats of reactions were obtained from the thermograms and compared with values obtained by PM3 and DFT calculations. Both the thermodynamics and kinetics of the reactions of benzylidene derivatives of Meldrum's acid **136** with thiolate <1998JA7461> and alkoxide <1998JOC6266> ions have been studied in aqueous dimethyl sulfoxide (DMSO) (Scheme 10). Major differences between the alkoxide and thiolate ions with respect to their thermodynamic and kinetic affinities to **136** were detected and the comparison of structure–reactivity data reveal a complex interplay of steric effects, π -donor, π -acceptor,

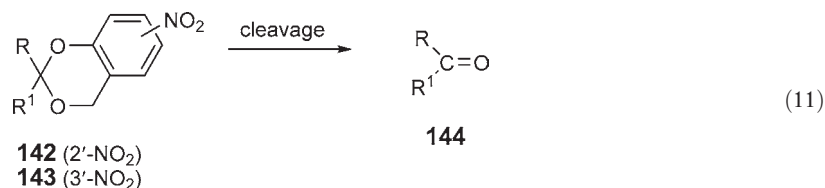


Scheme 10

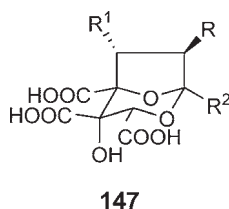
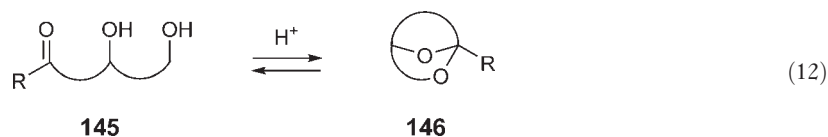
resonance, and anomeric effects [\[1998JA7461, 1998JOC6266\]](#). The same reaction, but using benzylamines, was studied in acetonitrile [\[2003BKC193\]](#). Kinetic isotope effects, when applying deuterated benzylamine nucleophiles, indicated the presence of a hydrogen-bonded transition state. The replacement of the methylthio group in **138** by secondary alicyclic amines (Scheme 10) occurs by a three-step mechanism: first, a zwitterionic intermediate **139** is formed, followed by deprotonation and acid-catalyzed conversion to the reaction products **140**. Both the second and third steps of the reaction, dependent on the amine component, can be rate limiting [\[2004JOC9248\]](#). Also, the condensation reaction of aromatic aldehydes with Meldrum's acid has been studied in great detail [\[2004JCCS139\]](#); the reaction, followed spectrophotometrically, follows overall second-order kinetics. Finally, the solvatochromic behavior of dye **141**, based on Meldrum's acid, was investigated and found to be a case of positive solvatochromism which is sensitive to both dipolarity/polarizability and the acidity of the solvent [\[2004DP\(62\)277\]](#).



Furthermore, the electroreductive cleavage of two substituted benzodioxanes **142** and **143** (Equation 11) was studied in aprotic solution [\[1997MI2089, 2001JEC22\]](#). Application of cyclic voltammetry shows the formation of a radical ion which proved relatively stable on the timescale of cyclic voltammetry. Its cleavage finally occurred with formation of the corresponding ketone **144**.

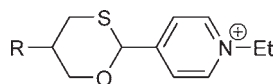


The kinetics and thermodynamics of the ketalization of dihydroxyketones **145** have been examined (Equation 12) <1997T11179>; the major aim of the study was to better understand these kinds of cyclizations for the synthesis of the 2,8-dioxabicyclo[3.2.1]octane core of the zaragozic acids **147**.



8.11.4.3 1,3-Oxathianes

The heat capacity, $C_{p,m}$, a useful parameter in evaluating vaporization, sublimation, and fusion enthalpies with temperature, was determined by DSC measurements for 1,3-oxathiane 3,3-dioxide to be $148.1 \pm 2.6 \text{ J K}^{-1} \text{ mol}^{-1}$ at 298.15 K <2006MI20>. Furthermore, there was a shoulder in the DSC of the sulfone which was not resolved by the calorimeter. Several phase transitions prior to melting were identified as the reason for this effect and were proven to be reproducible even after storing the sample in a desiccator for several months, though the relative intensity of the peaks did change. Also, the enthalpy of formation in the gas phase of 1,3-oxathiane sulfone ($\Delta_f H_m^\circ(\text{g}) = -469.4 \pm 1.9 \text{ kJ mol}^{-1}$) was determined from the experimental values of the standard enthalpy of formation in the crystalline state, $\Delta_f H_m(\text{s})$, and the standard enthalpy of sublimation, $\Delta_{\text{sub}} H_m$, both referred to 298.15 K <2006PC1>. Due to the diequatorial conformation of the 2,5-disubstituted 1,3-oxathiane skeleton, pyridinium-type compounds **148** proved to be useful thermotropic-ionic liquid-crystalline materials <1999BCJ875>.



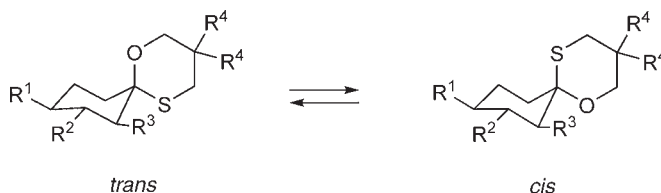
148: R = C₆H₁₃ to C₁₂H₂₅

8.11.4.3.1 Ring-chain tautomerism in spiro-1,3-oxathianes

The isomerization of the *cis*- and *trans*-isomers of the spiro-1,3-oxathianes (Equation 13) was studied in slightly acidic chloroform solution ($[\text{HCl}] = 3.34 \times 10^{-4} \text{ M}$) <2000TL1967, 2001T8751>. This isomerization involves, as the first step, ring opening and formation of an open-chain form, followed by ring closure leading to the two isomers in an equilibrium ratio determined by the different energies of the two structures. The kinetic parameters of the isomerization, determined by NMR spectroscopy, are given in Table 10 and were found to be similar. The reaction was considered to be first order.

Table 10 Kinetic parameters (k_1 , k_{-1}) for the isomerization of compounds **149–152**

Compound	Starting isomer	Initial concentration $\times 10^{-2}$ (mol l $^{-1}$)	K	$k_1 \times 10^{-1}$ (min $^{-1}$)	$k_{-1} \times 10^{-1}$ (min $^{-1}$)
149	<i>trans</i>	9.74		8.71	1.20
150	<i>trans</i>	3.4	1.43	4.24	2.96
151	<i>trans</i>	4.3	0.625	7.37	11.8
152	<i>cis</i>	4.8	0.69	2.63	3.81



(13)

149: R¹ = Ph; R²–R⁴ = H**150:** R¹ = Ph; R², R³ = H; R⁴ = Me**151:** R¹, R³ = H; R², R⁴ = Me**152:** R¹, R² = H; R³, R⁴ = Me

8.11.4.4 1,3-Dithianes

The enthalpies of combustion, sublimation, and formation of 1,3-dithiane and its 1-oxide (sulfoxide) and 1,1-dioxide (sulfone) have been measured (**Table 11**) and *ab initio* MO-calculated at the G2/MP2 level <1999JOC9328, 2004JOC1670, 2004JOC5454>; calculated $\Delta_f H^\circ_m$ (g) values agree well with the experimental values.

Table 11 Standard molar enthalpies of combustion, sublimation, and formation for 1,3-dithiane and its 1-oxide and 1,1-dioxide at 298.15 K

Compound	$\Delta H^\circ_{f,m}(cr)$ (kcal mol $^{-1}$)	$\Delta H^\circ_{sub,m}$ (kcal mol $^{-1}$)	$\Delta H^\circ_{f,m}(g)$ (kcal mol $^{-1}$)
1,3-Dithiane	-65.6 ± 2.2	62.9 ± 0.7	-2.7 ± 2.3
1,3-Dithiane 1-oxide	-46.7 ± 0.4	23.3 ± 0.2	-23.4 ± 0.5
1,3-Dithiane 1,1-dioxide	-102.7 ± 0.4	24.7 ± 0.2	-77.9 ± 0.5

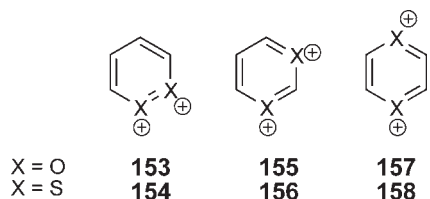
The enthalpies of formation of 1,3-dithiane sulfoxide and sulfone are less exothermic than expected; analysis of the charge distribution in the sulfone suggested that repulsive electrostatic interaction between the positively charged sulfur atoms proved to be responsible for this effect because of a counterbalancing $n_S \rightarrow \sigma^*_{C-SO_2}$ -stabilizing hyperconjugative interaction <2004JOC1670>. The high-level *ab initio* calculations of both the molecular and electronic structure of the sulfoxide revealed the equatorial conformers to be 1.7 kcal mol $^{-1}$ more stable than the axial analog due to $n_S \rightarrow \sigma^*_{C-SO_2}$ -stabilizing hyperconjugative interaction too <2004JOC5454>.

A B3PW91/6-31G** computational procedure for predicting standard gas-phase heats of formation at 298.15 K and heats of vaporization and sublimation has been presented <2005IJQ341>; 1,3-dithiane-2-thione was studied using this procedure and the following heats of formation were predicted: gas phase, 25.7 kcal mol $^{-1}$; liquid phase, 10.3 kcal mol $^{-1}$; and solid phase, 3.1 kcal mol $^{-1}$.

8.11.5 Reactivity of Fully Conjugated Rings

The syntheses and reactivities of fully conjugated rings for these kinds of compounds have not been reported in the available literature. However, the positional isomers of the disubstituted benzenes **153–158** have been theoretically studied using *ab initio* calculations at the HF, MP2, and CCSD(T) levels of theory and also by using DFT <2000JA11173>. Planar structures are characterized as global minima and they show fully delocalized geometrical parameters with no significant indication of bond fixation; the C–C bond lengths are similar to the aromatic bond lengths and the C–O(S) and O–O(S–S) bond lengths are in between the corresponding standard single and double

bond lengths. Hence, according to the criterion of bond-length equalization, **153–158** are expected to be aromatic [<2003IAS49>](#). The 1,3-isomers are more stable than the 1,2-isomers ($>66 \text{ kcal mol}^{-1}$ in the case of $\text{X}=\text{O}$, only slightly more stable in the case of $\text{X}=\text{S}$); in the case of $\text{X}=\text{O}$, the 1,3-isomer is also more stable than the 1,4-analog, whereas in the case of $\text{X}=\text{S}$, the converse applies. A number of factors (e.g., lone pair · · lone pair repulsion, especially for the 1,2-isomers, electrostatic interactions, bond strength, and charge stabilization) could be gainfully employed to explain the computed pattern of relative stabilities.



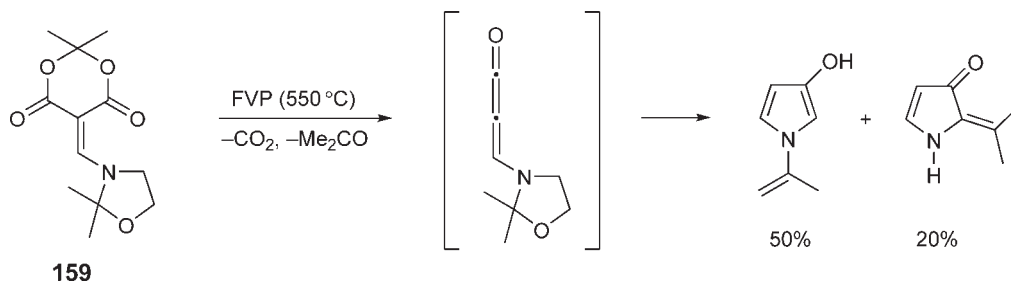
Nucleus-independent chemical shift (NICS) values of **153–158**, calculated at the center of the rings and $1 \text{ \AA}$ above the rings using the gauge-independent atomic orbital (GIAO) procedure at the HF/6-31G* level of theory, are slightly higher than that of benzene indicating slight depletion in aromaticity upon skeletal substitution [<2003JMT\(663\)145>](#).

8.11.6 Reactivity of Nonconjugated Rings

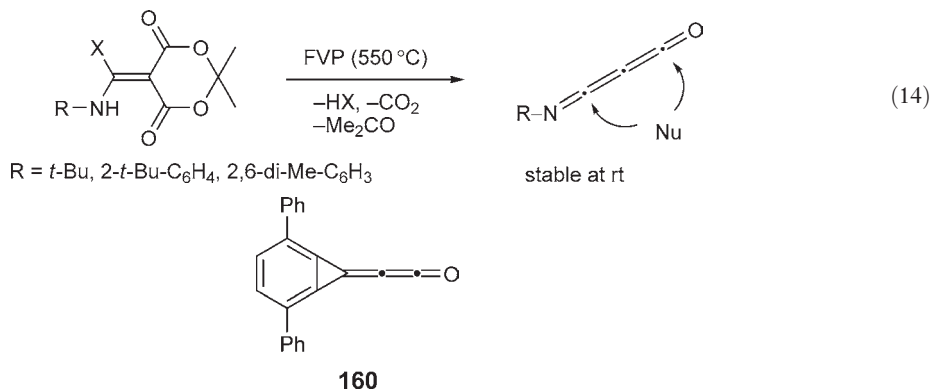
8.11.6.1 Systems with Three or Four Double Bonds

8.11.6.1.1 Unimolecular thermal and photochemical reactions

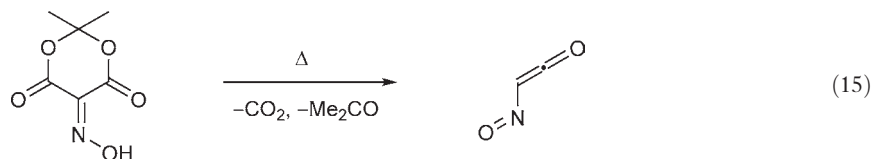
The flash vacuum pyrolysis (FVP) of several 5-alkylidene-1,3-dioxane-4,6-diones has been reviewed [<2004ALD19, 2001S2059>](#). FVP of many 5-aminomethylene-1,3-dioxane-4,6-diones has also been studied. When a cyclic tertiary amine, such as compound **159**, was subjected to FVP, then 3-hydroxypyrroles were isolated in moderate yields (ca. 50%) [<2002J\(P1\)548>](#) (Scheme 11). Interestingly, sterically hindered secondary alkyl- or aryl-substituted derivatives gave rise to iminopropadienones, which are stable at room temperature (Equation 14) [<2002JOC2619, 2002JOC8558>](#). The highly strained cyclopropabenzenyliidenethenone **160** has also been prepared by FVP of a Meldrum's acid precursor [<2005OL949>](#).



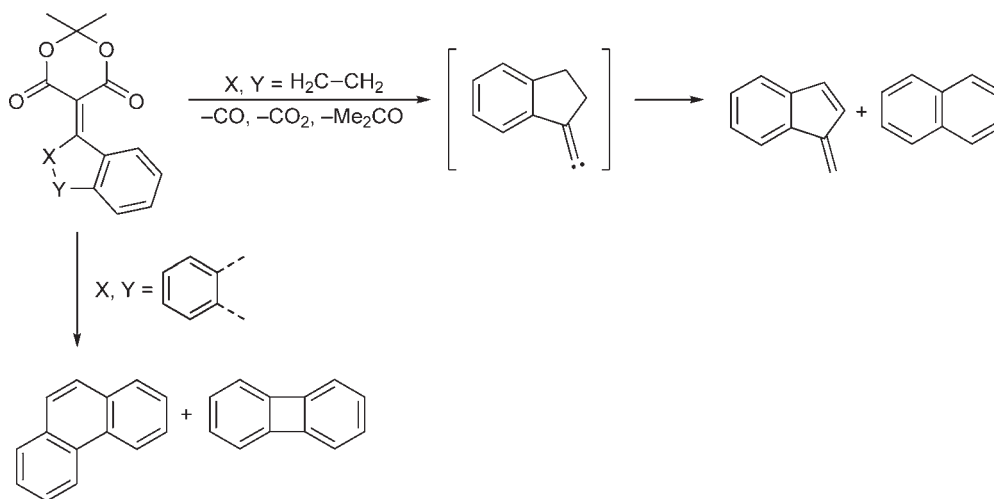
Scheme 11



Meldrum's acid 5-oxime, prepared by reaction of Meldrum's acid and NO followed by tautomerism of the nitroso group, thermolyzes at elevated temperatures analogously to give the highly reactive nitrosoketene [1997H\(46\)503](#), [1998H\(47\)383](#), which has been characterized spectroscopically (Equation 15) [2002JRS443](#).

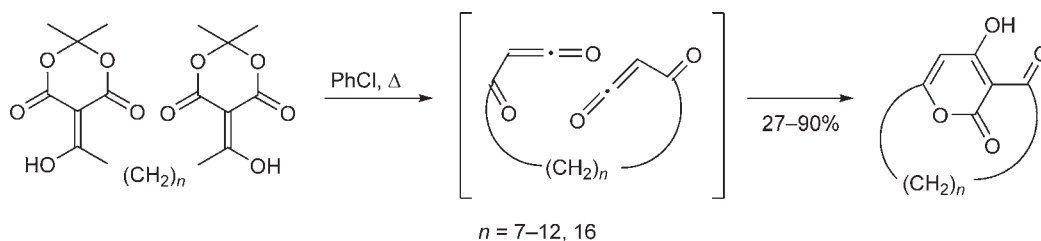


The formation of reactive carbenes from alkylidene Meldrum's acids has also been observed. Thus pyrolysis of 1-indanylidene Meldrum's acid at 640 °C gave the corresponding carbene which further rearranged to benzofulvene and naphthalene (Scheme 12) [1998JA8315](#). Similarly, FVP of 9-fluorenylidene Meldrum's acid at 1100 °C provided a mixture of phenanthrene and biphenylene [1996TL6819](#).



Scheme 12

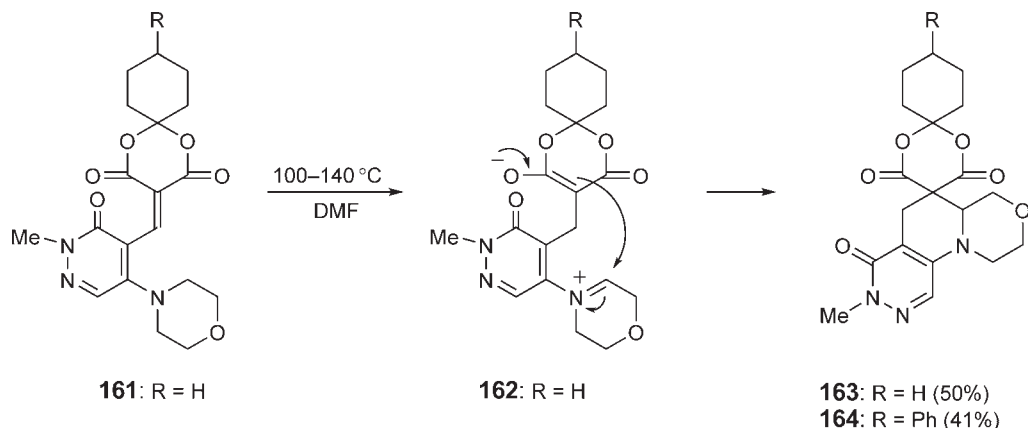
Alkylidene Meldrum's acids have also been thermolyzed in solution at much lower temperature. The synthesis of chiral cyclophanes was achieved by heating bis(4,6-dioxo-1,3-dioxane)s, tethered by alkyl groups, in boiling chlorobenzene at low stationary concentration. After formation of the α -oxoketenes, an intramolecular [4+2] cycloaddition occurred, affording the 2-pyranones in 27–90% yield, depending on the chain length (Scheme 13) [1999JA8270](#). The enantiomeric cyclophanes have been resolved and characterized. A different strategy leading to similar reaction products has been developed using an intermolecular construction of the 2-pyranones having a terminal double bond in the side chain followed by ring-closing metathesis (RCM), though the yields of the ring-closing step are low (~6%) [2005H\(65\)1167](#).



Scheme 13

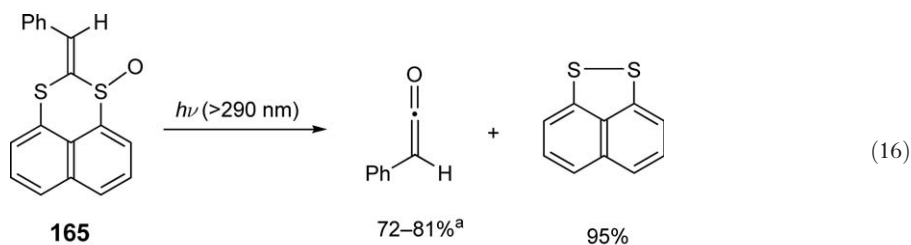
Heating compound [161](#) at 140 °C in DMF gave spirocycle [163](#) in 50% yield [2002CH365](#) and in 73% yield when microwave assisted [2004GC125](#). This unusual unimolecular thermal rearrangement, induced by the 'tert'-amine

effect' <2006MC82>, proceeds via iminium betaine **162** (Scheme 14). Upon introducing a phenyl group at C-4 of the cyclohexane moiety, the product of the thermal rearrangement, compound **164**, has a long-distance chiral axis. The resolution of enantiomers has been demonstrated in this case.

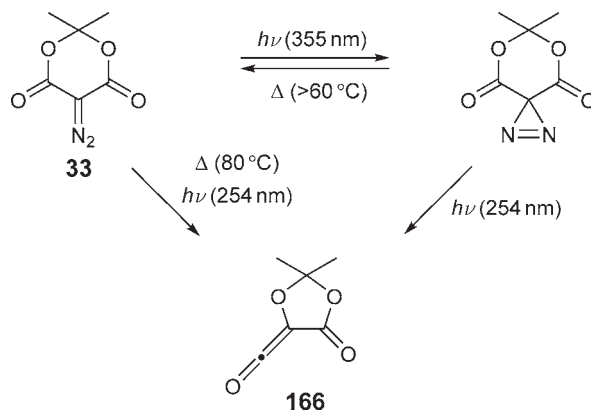


Scheme 14

Naphthodithiin oxide **165** upon irradiation (>290 nm) fragmented to afford phenylketene and naphtho-1,2-dithiole both in high yield. The phenylketene was trapped by several nucleophiles (Equation 16) <1999TL5211>. Unimolecular photochemistry was reported from 5-diazo-1,3-dioxane-4,6-dione, which can be synthesized in 87% yield from Meldrum's acid, mesyl azide, and clay <2004SC951>. As briefly discussed in Section 8.11.2 (Scheme 3), 5-diazo-1,3-dioxane-4,6-dione isomerizes to the corresponding diazirine upon irradiation at 355 nm, which rearranges back to the diazo compound when heated to 60 °C. Irradiation at shorter wavelengths as well as thermolysis of 5-diazo-1,3-dioxane-4,6-dione gave predominantly α -oxoketene **166** (Scheme 15) <1996JA1551, 2003JA14153> which can be trapped by MeOH <2005TL435>.

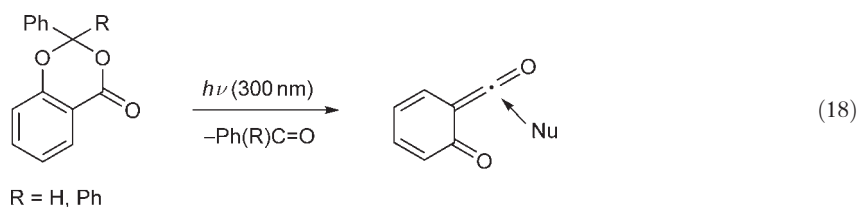
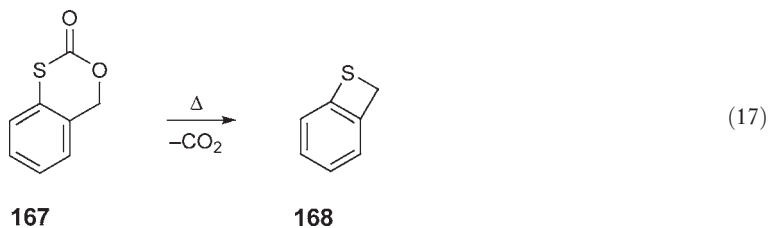


^aYield of trapping products.



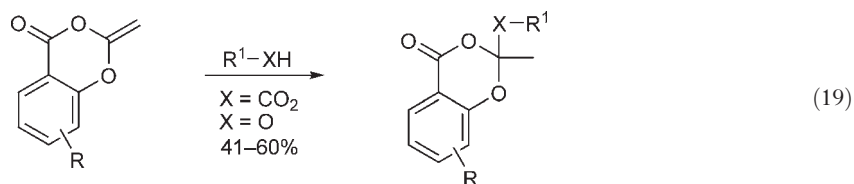
Scheme 15

Thermal extrusion of CO₂ from thiocarbonate **167** gave benzothiete **168** (Equation 17) <1996S327>. Cyclic acetals of salicylic acids with benzaldehyde or benzophenone can photolytically cleave at 300 nm to α -oxoketenes <1998JA6247>. These are strong acylating agents which serve for the esterification of alcohols either inter- <2005AGE1696> or intramolecularly (Equation 18) <2005OL2791>. This reaction has been applied to the synthesis of gustastatin <2005OL685>.

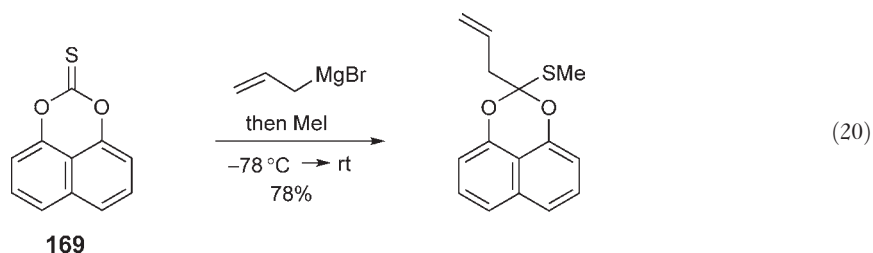


8.11.6.1.2 Reactivity toward nucleophiles

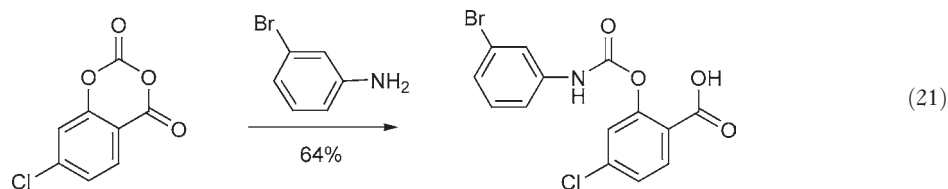
The chemistry of 1,3-dioxins containing four double bonds is poorly developed. A few examples of nucleophilic additions have been demonstrated. The proton-catalyzed addition of alcohol or carboxylic acid nucleophiles to anhydro derivatives of acetylsalicylic acid – new prodrugs of aspirin – was reported to give the C-2 O-substituted 1,3-dioxanes in 41–60% yield (Equation 19) <2001TL5231, 2003CRC265>.



Cyclic thiocarbonates, such as compound **169**, react smoothly with allylmagnesium bromide. Careful control of the reaction conditions allows monoalkylation. Trapping of the intermediate sulfur anion with MeI provided the 1,3-dioxane in 78% yield (Equation 20) <2003H(59)87>.



A 1,3-benzodioxin-2,4-dione containing an anhydride and a carbonate moiety was used for the preparation of biologically active compounds. It was reacted with 3-bromoaniline in such a way that the amino group attacks the anhydride moiety to give the carbamate rather than the expected amide (Equation 21) <2004JME6948>.



The reaction of nucleophiles with 1,3-dioxanes containing three double bonds is mainly confined to the group of 5-alkylidene-1,3-dioxane-4,6-diones. The parent compound, 5-methylene-1,3-dioxane-4,6-dione, is, however, quite unstable. Two reagents **170** and **171** have been developed to prepare 5-methylene-1,3-dioxane-4,6-dione *in situ* (Figure 8) <1996S215, 2002SC2009>.

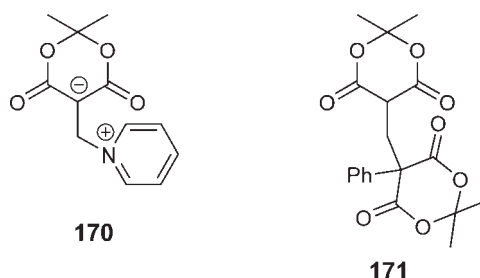
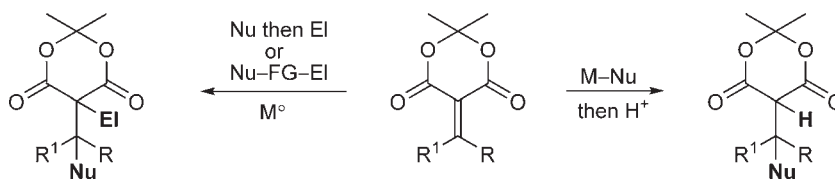


Figure 8 Stable precursors for methylene Meldrum's acid.

Addition of various nucleophiles to the *exo*-double bond of 5-alkylidene-1,3-dioxane-4,6-diones has been reported in the literature. Two different pathways have been examined: (1) the addition of a nucleophile followed by aqueous (protic) workup and (2) the transition metal-catalyzed successive addition of a nucleophile and an electrophile to the double bond (Scheme 16).



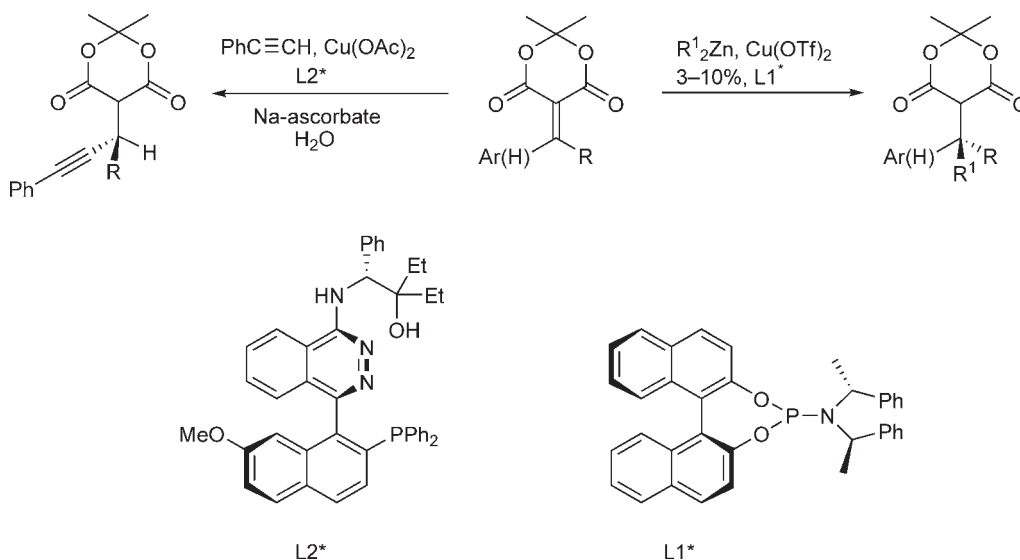
Scheme 16

Sodium borohydride reduced the double bond of 5-alkylidene Meldrum's acids without attacking the carbonyl groups <2006JHC365>. This procedure allows the preparation of 5-monoalkyl Meldrum's acids in high yields, which are otherwise difficult to obtain. Organometallics, such as Grignard reagents <2002OL2001, 2005JOC1316>, aluminium <1999S1792>, zinc (catalytic) <2004OL2281>, tin <2000OL365>, samarium <2000CCL5>, and copper alkyls <2003JA6054> were successfully employed as nucleophiles. The alkynylcopper reagents are particularly

interesting since substoichiometric amounts of copper salts in aqueous media were used for complete alkylation. Complex carbon nucleophiles, such as enolates <2002RJO1380, 2002EJO3481> or deprotonated nitromethane <2004JCM758>, have also been used as well as nonmetallic nucleophiles, such as triphenylphosphine-activated alkynes <2002PS2523> and isonitriles. In the latter case, ring opening by the alcoholic solvent occurs <2001T1375, 2002JCM433, 2004S989>. The same is true, when 5-alkylidene Meldrum's acids react with tetraalkylammonium ylides <2005S2851>. The resulting products are *trans*-4,5-disubstituted γ -butyrolactones, which were isolated in good yield (47–90%) and perfect stereoselectivity.

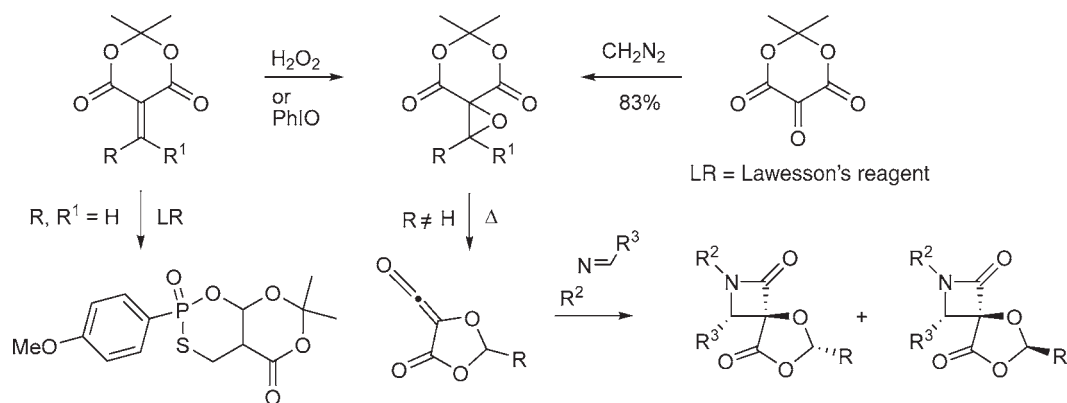
One-pot double functionalization of the double bond of 5-alkylidene-1,3-dioxane-4,6-diones was achieved by a palladium-catalyzed cycloaddition of vinyloxiranes <1998JOC3067> or allylic carbonates <2001JOC7142>. Amines and allenyl stannanes were also suitable nucleophiles in palladium-catalyzed nucleophilic additions to 5-alkylidene-1,3-dioxane-4,6-diones, affording, after trapping of the enolates with allyl halides, the aminoallylation <2002JOC5977> and propargylallylation products <2004JOC4053>, respectively. Allyl esters react with 5-alkylidene-1,3-dioxane-4,6-diones in presence of 10 mol% of a ruthenium catalyst in a tandem Michael addition–allylic alkylation <2005OL2137>. When nucleophile and electrophile are located at one carbon, then cyclopropanation of alkylidene Meldrum's acids occur. Suitable reagents are alkyl- <2005S2718> or alkoxycarbonylalkyltriphenylarsonium salts (cf. **Scheme 16**) <2000SC4523, 2002SC1953>.

The enantioselective nucleophilic addition was achieved with 5-alkylidene-1,3-dioxane-4,6-diones having unsymmetrically substituted *exo*-double bonds. It was shown that the enantioselectivity exceeds 90% when dialkylzinc reagents in the presence of copper salts and a chiral ligand were employed. Tertiary <2003OL4557> and even quaternary <2006JA2774> stereocenters have been obtained in high yields and optical purities. Lithium enolates of ketones (94% yield, 87% ee) <1996TL6343> as well as alkynes in presence of catalytic amounts of aqueous copper salts <2005JA9682> also provided highly optically active addition products (**Scheme 17**).



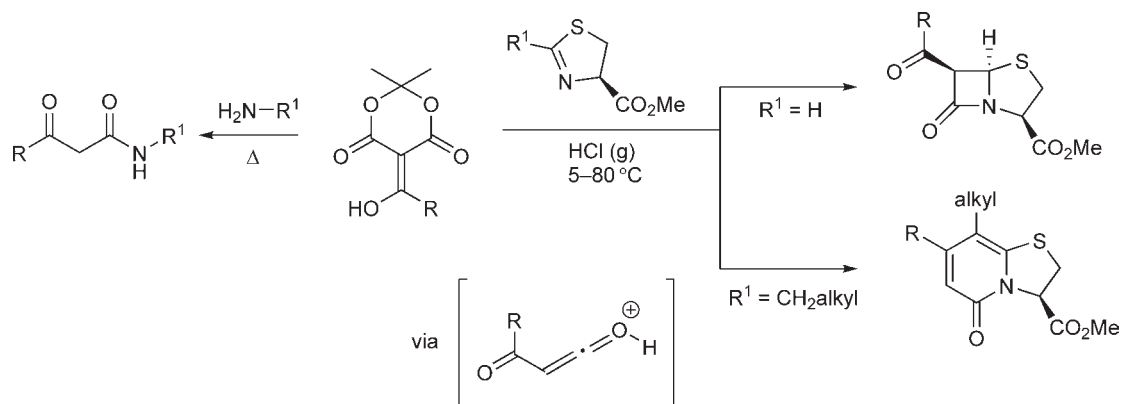
Scheme 17

Meldrum's acid spiro epoxide ($R, R^1 = H$) can be prepared in good yield from either 5-methylene-1,3-dioxane-4,6-dione by nucleophilic epoxidation using hydrogen peroxide <2001MI91> or by reaction of the 1,3-dioxane-4,5,6-trione with diazomethane <2001HCA2071> (**Scheme 18**). In addition, substituted epoxides were obtained from the corresponding 5-alkylidene-1,3-dioxane-4,6-diones with PhIO <2004SL2403> as nucleophilic O-transfer reagent. Substituted epoxides serve as an alternative source for α -oxoketenes <2006JHC21>. These oxoketenes react with imines to afford β -lactams as mixtures of acetal isomers. Interestingly, the reaction of 5-alkylidene Meldrum's acids with Lawesson's reagent (LR) gave heterobicycles in good yields <2004PS2387>.



Scheme 18

Aminolysis of acyl Meldrum's acids proceeds via the corresponding α -oxoketenes <2004JA13002> and produces β -oxoamides in good yields <2002JCO470>. The product formed in the nucleophilic addition of thiazolines to acyl Meldrum's acids depends on the substituent at C-2 of the thiazoline (Scheme 19). C-2-unsubstituted thiazolines gave β -lactams <2000OL2065, 2003OBC1308>, whereas C-2-alkyl-substituted thiazolines produced pyridinones <2001JOC6756, 2006OL935>, probably via protonated α -oxoketenes.

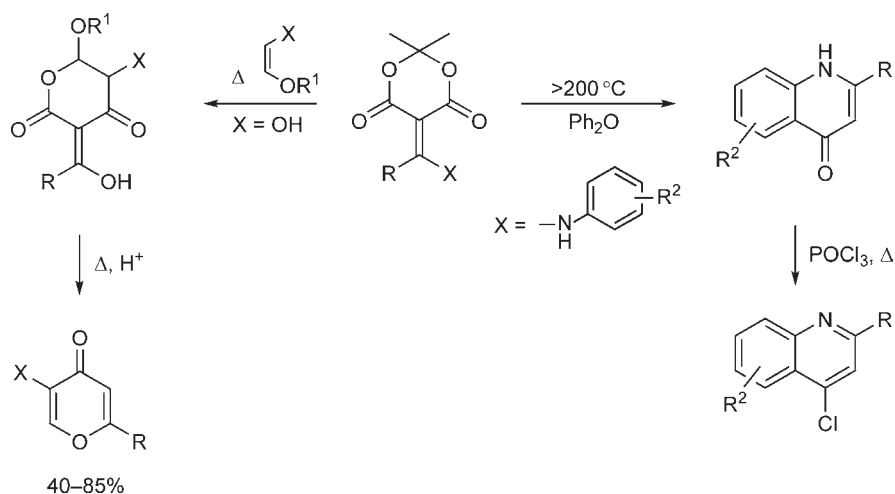


Scheme 19

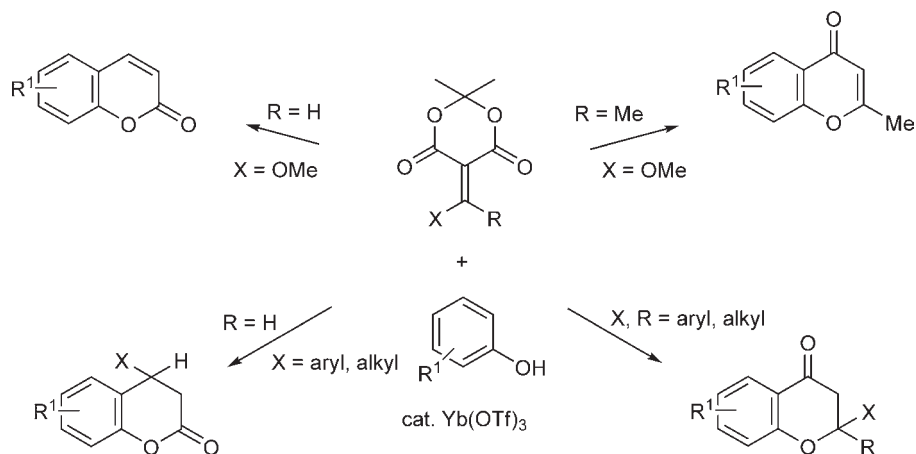
5-Acyl Meldrum's acids have further been used for the synthesis of 4-pyranones (40–85% yield) <1996TL6499>. Intramolecular nucleophilic attack of activated arenes has been observed with 5-arylaminoalkylidene-substituted Meldrum's acids as substrates, which rearranged to 4-chloroquinolines when activated with phosphoryl chloride <2002SC785, 2002T9095> or to 4-quinolones upon thermolysis <2003JCM140>. The latter product group has been prepared from resin-bound Meldrum's acid derivatives (Scheme 20) <2001TL7655>.

Phenols are also suitable nucleophiles for 5-alkylidene-1,3-dioxane-4,6-diones, when activated by $\text{Yb}(\text{OTf})_3$. Depending on the substitution pattern at C-1', several useful coumarins, dihydrocoumarins, 4-chromanones, and chromones were obtained (Scheme 21) <2006JOC409>.

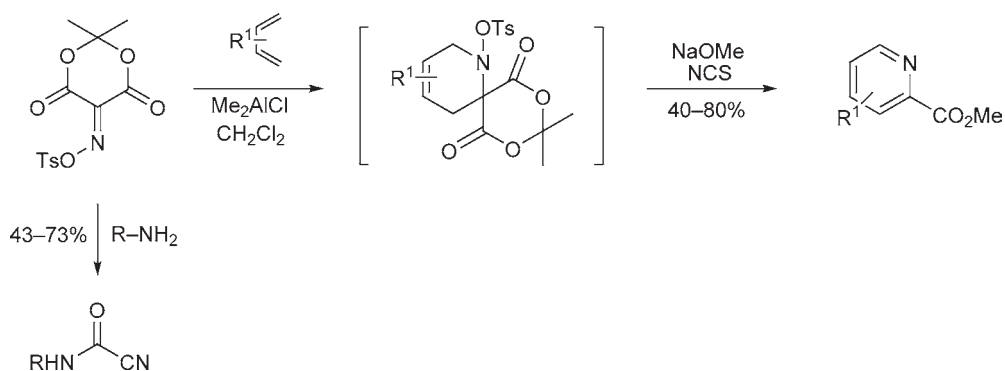
The 5-tosyloximes of 2,2-dimethyl-1,3-dioxane-4,5,6-trione react with various dienes in a hetero-Diels–Alder-type reaction. The products, aza-dioxaspiro[5,5]undecenes, readily decompose with basic *N*-chlorosuccinimide to afford 2-carboxypyridines <1998JOC7840>. The same substrates gave with amines cyanoformamides in 43–73% yield (Scheme 22) <2000H(52)283>.



Scheme 20

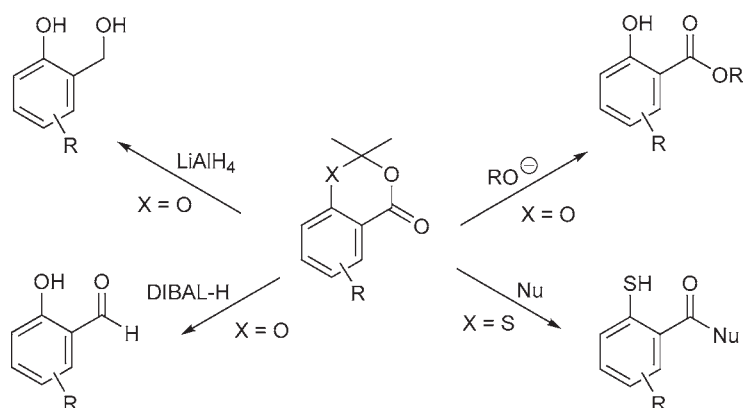


Scheme 21



Scheme 22

Nucleophilic additions to 1,3-dioxanes not deriving from alkylidene Meldrum's acids are mainly attributed to acetals from salicylic acids (**Scheme 23**). Efficient transesterification of these acetals with alkoxides was an important step in the synthesis of (+)-SCH 351448 <2005JOC6321, 2005OL3809>. The carbonyl group of a series of salicylic acid acetals was selectively reduced either to the alcohol by LiAlH_4 or to the aldehyde using diisobutylaluminum hydride (DIBAL-H) <2006JOC3646>. The thio analogs of salicylic acetals are also prone to nucleophilic attack <2000PJC1369>.

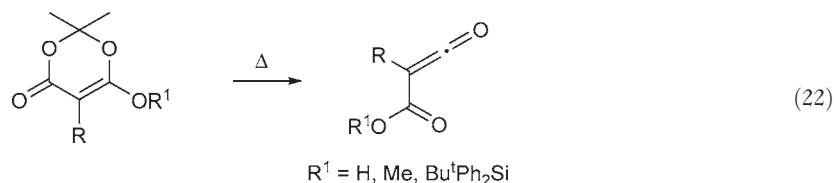


Scheme 23

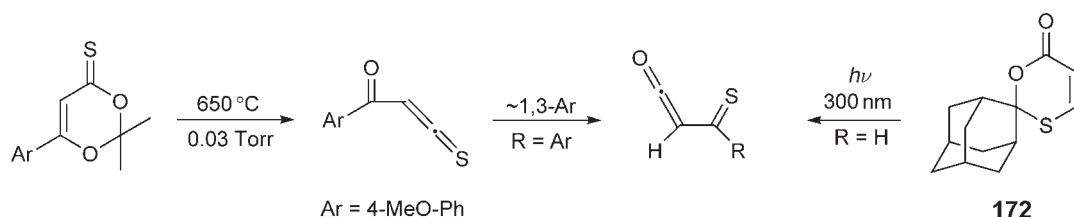
8.11.6.2 Systems with Two Double Bonds

8.11.6.2.1 Unimolecular thermal and photochemical reactions

The synthesis of α -acylketenes from 1,3-dioxin-4-ones is well known and in particular the preparation and chemistry of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones has been reviewed <2001CHE925>. As briefly discussed in the preceding section, Tsuno *et al.* reported an alternative source for α -acylketenes from 2-substituted-1,5,7-trioxaspiro[2.5]octane-4,8-diones <2006JHC21>. Additionally, enolized Meldrum's acids, obtained by reaction of Meldrum's acids with CH_2N_2 , also furnish α -methoxycarbonylketenes (Equation 22) <1997TL6689>.

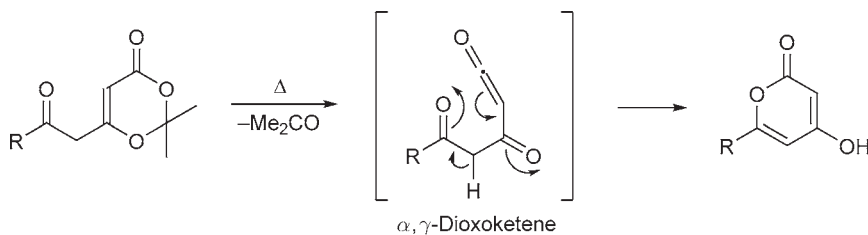


Thiocarbonyl-substituted 1,3-dioxins underwent an analogous fragmentation to the corresponding α -acylthioketenes <1996CC775> upon heating to 140–170 °C. However, 6-aryl-substituted 1,3-dioxin-4-thiones gave under FVP conditions after 1,3-aryl migration the α -thioacylketenes (**Scheme 24**) <2000JOC2706>. Unsubstituted α -thioacylketenes have also been prepared by photolysis of neat 2-adamantylidene-1,3-oxathiin-6-one **172** <2004HCA1906>.



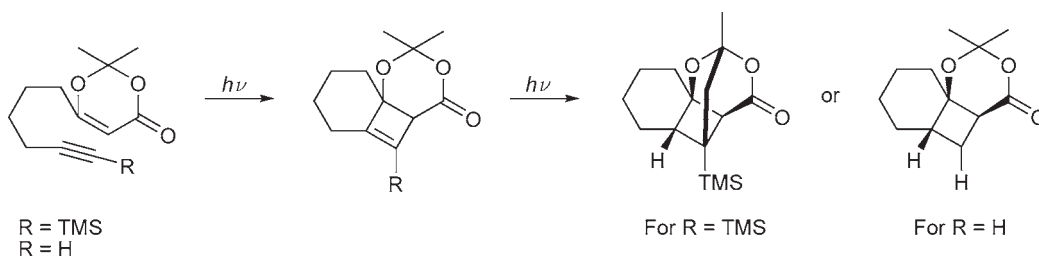
Scheme 24

A unimolecular pyrolysis/rearrangement sequence leading to stable reaction products without the need for nucleophiles was reported by Katritzky *et al.* Thus, 6-(2-oxoalkyl)-1,3-dioxin-4-ones, when heated or irradiated, gave 6-substituted-4-hydroxy-2-pyrones in good yields <2005JOC4854>. α,γ -Dioxoketenes are discussed as intermediates (Scheme 25).



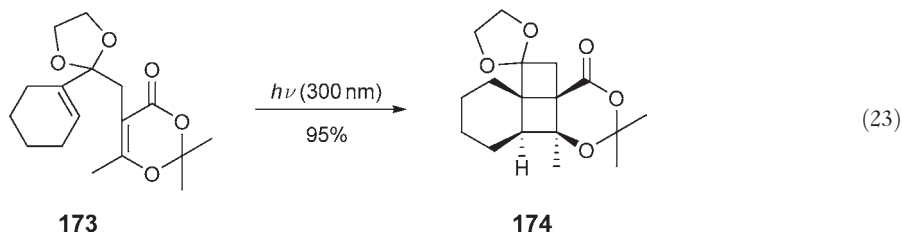
Scheme 25

The intramolecular photochemical [2+2] cycloaddition of 1,3-dioxin-4-ones with double bonds tethered to the heterocycle at C-6 is well established and was used for the construction of polycyclic natural products, such as saudin <1998TL2253, 1999JA7425> or ingenol <2005OL1489> or substituted tetrahydropyranones <1997TL5579>. Winkler and McLaughlin have shown that alkynes are also amenable to the photocycloaddition. The resulting cyclobutenes further react upon prolonged irradiation either to a tricycle (R = trimethylsilyl (TMS), 50%) or to the reduced cyclobutane (R = H, 50%) (Scheme 26) <2005OL227>.

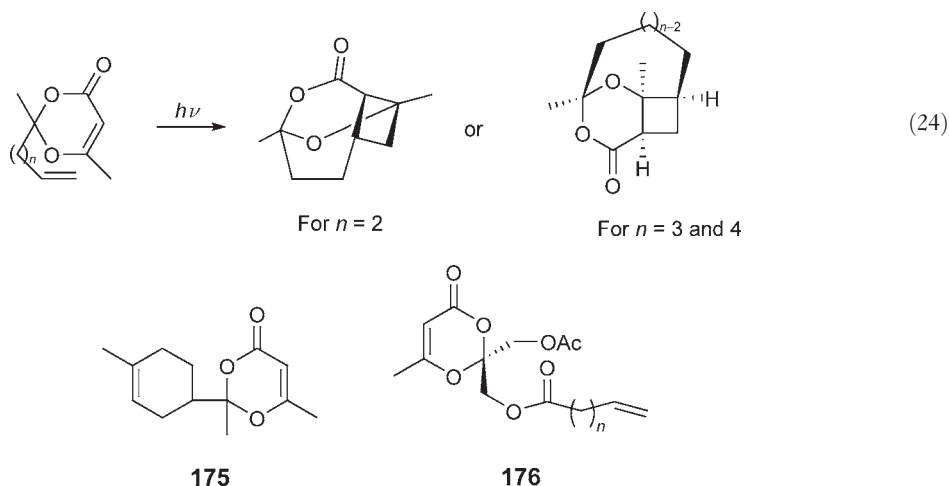


Scheme 26

The intramolecular photocycloaddition is quite general and other cyclic structures have been prepared as well <1997JOC7629, 1996TL3521>. Remarkably good yields of cycloadducts were achieved even when highly strained reaction products result <2001J(P1)2250, 2001JOC233>. For example, irradiation of dioxinone **173** gave product **174** with a bicyclo[2.2.0]hexane core structure as a single diastereoisomer in 95% yield (Equation 23) <2000CC1463>.

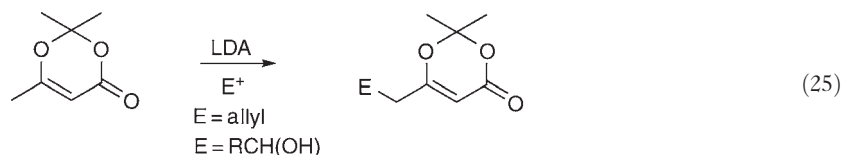


The double bond tethered at the acetal carbon of 1,3-dioxin-4-ones also underwent a photocycloaddition. Depending on the length of the spacer alkyl group, two reaction products have been observed, differing in the connectivity of the two double bonds (Equation 24) <1997TL8663>. Applications of this strategy were the synthesis of eudesmanes by using cyclic *endo*-double bond precursor **175** <2001H(54)765> and the synthesis of optically active cyclobutanols from chiral 1,3-dioxin-4-ones, such as **176**, prepared by enzymatic resolution <2003TA201>.

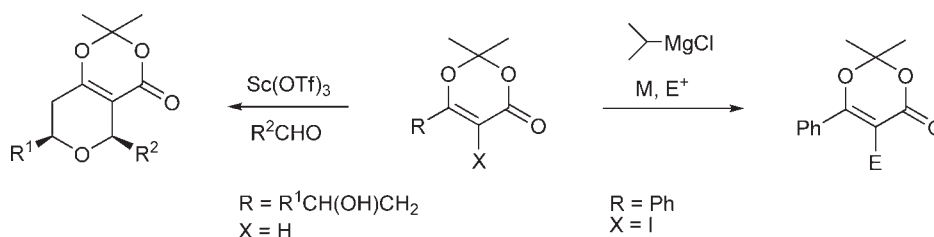


8.11.6.2.2 Reactivity toward electrophiles

For the reaction of 1,3-dioxin-4-ones with electrophiles, activation by deprotonation of the side-chain alkyl group is required. Typically lithium diisopropylamide (LDA) is used as a base. The resulting lithium dienolates react with aldehydes [<2002EJO718>](#) or with allyl bromides in the presence of *N,N'*-dimethylpropyleneurea (DMPU) [<2005AGE820, 2006CEJ2488>](#) exclusively at the side-chain double bond, albeit in modest yields ([Equation 25](#)).

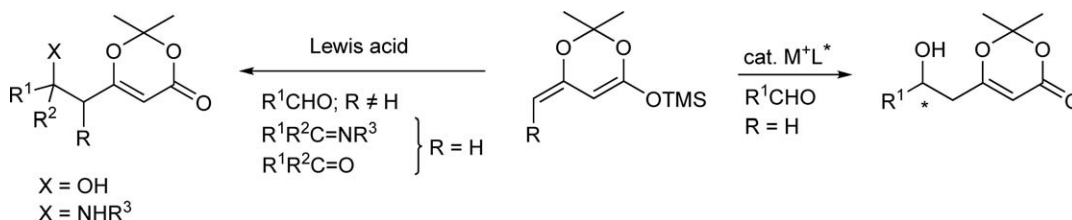


Electrophiles also react at C-5 of 1,3-dioxin-4-ones. Two ways of activation have been reported: (1) magnesiation of 5-iodo-1,3-dioxin-4-ones afforded the Grignard reagents which can be cross-coupled with allyl halides in the presence of copper cyanide [<2001TL6847>](#) or with iodoalkenes under Pd(0) catalysis [<2002T4787>](#) and (2) Sc(OTf)₃-catalyzed reaction of a side-chain-hydroxylated 1,3-dioxin-4-one with aldehydes provided the bicyclic dioxinone in 60–85% yield ([Scheme 27](#)) [<2005OL1113>](#).



Scheme 27

The chemistry of 2,2-dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-dioxin and analogs, especially their reactivity toward electrophiles, was of ongoing interest and has been reviewed in part [<2002SOS\(4\)317>](#). It has been shown that these heterocycles readily react with Michael acceptors either in the absence [<1996JPR349, 2001J\(P1\)3189>](#) or in the presence of Cu(OTf)₂ [<2006T1223>](#). The major application of these silyl dienol ethers was the catalyzed asymmetric vinylogous Mukaiyama aldol reaction with a series of aldehydes ([Scheme 28](#)). It was found that the reaction can be catalyzed by pybox–copper complexes (92% ee) [<1996JA5814, 1999JA669>](#), by Tol–BINAP–CuF₂ (95% ee) [<1998JA837>](#), by Ti–BINOL complexes (95% ee) [<2000TA3187>](#), and by Cr(salen) complexes (99% ee) [<2004SL57>](#), and, even in the absence of a Lewis-acidic metal cation, by a mixture of TADDOL and HCl (up to 90% ee) (pybox = pyridine bis(oxazoline); Tol = toluene; BINAP = 2,2-bis(diphenylphosphonyl)-1,1-binaphthyl;

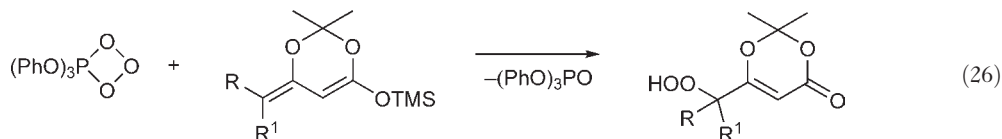


Scheme 28

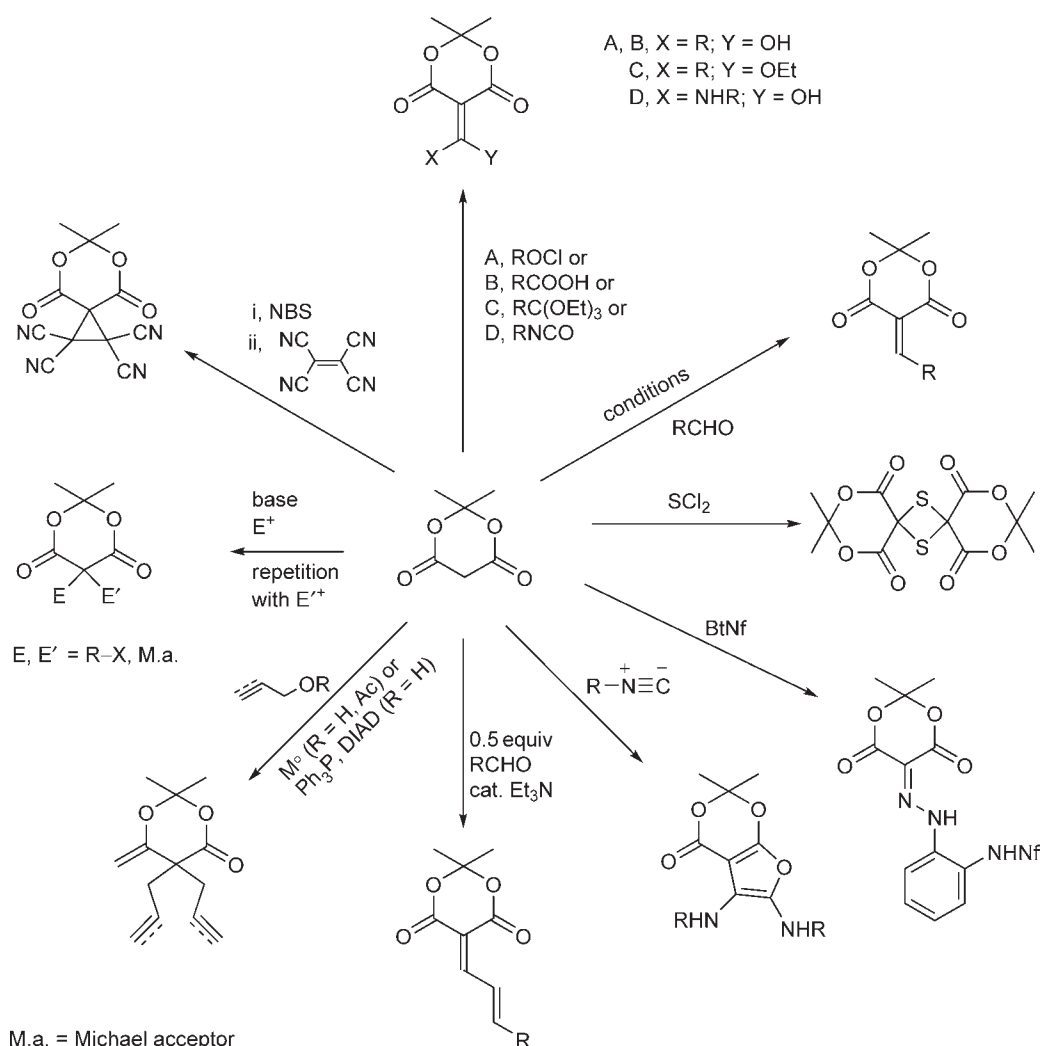
BINOL = 1,1'-bi-2-naphthol; salen = *N,N'*-bis(salicylaldehyde)ethylenediamine; TADDOL = (–)-*trans*-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxolane <2005OL5657>. Some mechanistic details of this reaction have been provided explaining in particular the role of the fluoride ion <1998AGE3124> and the positive nonlinear effect (NLE) in the series of titanium complex-catalyzed reactions <2001TA1529, 2002JA14866, 2003TA2499, 2003TL6087>. The asymmetric vinylogous aldol reaction was also accomplished following the concept of Lewis base activation of Lewis acids <2003JA7800, 2005JA3774>. The variation of the electrophile, for example, α -acylketones (box-Cu(OTf)₂, 74% ee <2003EJO317>, box-CuCl₂, 98% ee <2004OL4097>) or *N*-acyl imines (pybox-Zn(OTf)₂, 88% ee <2003CEJ6145>) was successfully demonstrated as well as the diastereoselective aldol reaction using either chiral aldehydes <2001TL4467, 2006OL1003> or chiral *N*-acyl imines <2001T8385, 2004AGE4349> though the diastereoselectivity was low (box = bisoxazoline). Introduction of an additional stereogenic center by the use of *exo*-alkyl-substituted silyl dienol ethers (R or R¹ not H) either in the Lewis acid- <2005T4091, 2005JA17921> or in the Brønsted acid- <2005TL6141> catalyzed vinylogous aldol reactions did marginally improve the diastereoselectivity. However, the asymmetric Mukaiyama aldol reaction using BINOL–Ti complexes gave preferentially the *syn*-adducts (d.r. = 4–6:1) in high enantioselectivity (89–99% ee) <2004TA3029>. A positive NLE was observed in this case, too.

The asymmetric vinylogous Mukaiyama aldol reaction was applied in several natural product syntheses, such as macquarimicins <2003JA14722, 2004JA11254>, leucascandrolide A <2002AGE4098, 2003JOC9274>, and dactylo- lide <2005AGE3485>.

Hydroperoxylation of silyl dienol ethers was effected by the *in situ*-generated reagent triphenyl phosphite ozonide (Equation 26). The yields are moderate and the products are always accompanied by the hydroxylated equivalents. The mechanism was studied and it was found that the oxygen attached to the carbon came from the central O of the ozonide <2001JOC3548>.



Meldrum's acid and its reactivity toward several (electrophilic) reagents has been briefly reviewed <2004SL1649>. However, the reaction of Meldrum's acid with a variety of electrophiles is of continuing interest. Advances in the well-established Knoevenagel condensation of Meldrum's acid and aldehydes have been made in conjunction with environmentally friendly reaction conditions. Thus, solvent-free reaction conditions <2003T3753, 2006MI107>, ionic liquids as reusable solvents <2005SC739, 2005SC2955, 2006SC3043> or catalysts <2006ARK53>, pure water as solvent <2001TL5203, 2005TL6453>, or ultrasound in the presence of water <2005MI85> and microwave conditions <1998MI235> have been applied to obtain substituted benzylidene Meldrum's acids. Water in the presence of an amine and SiO₂ was suitable to conduct condensation of aliphatic aldehydes <2005MI317>. The three- or four-component reaction of Meldrum's acid and electrophiles is a second major use of this heterocycle <2004CEJ5323, 2005JCO530, 2005TL1659>. A review compiling the multicomponent reactions of Meldrum's acid has been published (Scheme 29) <2006QSA439>. Again, ionic liquids <2006CCL150> and microwave conditions <2004TL2575> have been used to promote the four-component reaction. Analogous Schiff bases, on the other hand, gave rise to ring opening products, such as benzo[*f*]quinolines <2005TL7169>. Meldrum's acids with 1-heterosubstituted alkylidene groups were typically obtained from acyl chlorides <2005H(65)1167> or trialkyl orthoformates <2006JCM37>. Carboxylic acids are also amenable for the condensation with Meldrum's acid, when activated with imidazole <2005HCO149> or used as acylimidazoles <1997CC359>. Alkylidene Meldrum's acids with two heteroatoms at C-1' have been prepared by reaction of Meldrum's acid with isocyanates <1996SL1209>. Heteroatom functionalization at C-5 was achieved with *N*-nonafllylbenzotriazole (BtNf) <2006SL627>, polystyrene-supported

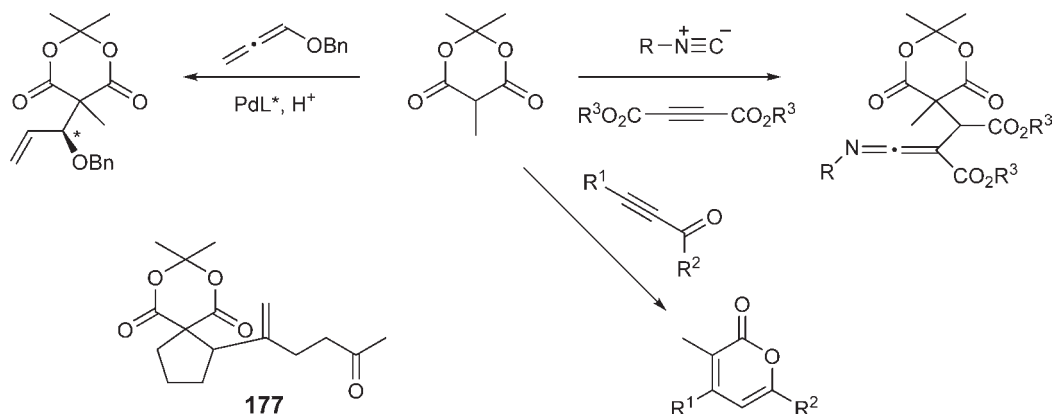


Scheme 29

benzenesulfonyl azide [<2001JOC2509>](#), or clay/mesyl azide [<2004SC951>](#) to give 5-diazo Meldrum's acid (65% or 87%; cf. [Scheme 15](#)), or SCl₂ to a dimer (74%) of 5-thiocarbonyl Meldrum's acid [<2004ZFA1659>](#). The reaction of Meldrum's acid with 2 equiv of an isonitrile gave a furan, presumably via [4+1] cycloaddition of an isonitrile with an intermediate heterodiene [<1996JCM146>](#). Michael acceptors [<2004RJO723, 2005TL7787>](#) can be used as electrophiles for C-5 alkylation of Meldrum's acid in presence of a base. A second alkylation using an alkyl halide is also possible. Double alkylation of Meldrum's acid with alkyl halides was carried out with Cs₂CO₃ as the base [<2005JOC291>](#). Spirocycles can be formed upon alkylation of Meldrum's acid with dihaloalkanes. However, the yields are moderate [<2006OL4157>](#) and C,O-alkylation may be a side reaction or even lead to the major product [<2003JOC7455>](#). Allyl alcohols can also be employed as alkyl-transfer reagents. Activation of allyl alcohols can be accomplished with Ph₃P, diisopropyl azodicarboxylate (DIAD), and a Mitsunobu-like reaction at C-5 of Meldrum's acid occurs [<2006OL471>](#). Active complexes of the transition metals Pd and Ru allow the formation of C-5 mono- and disubstituted 1,3-dioxane-4,6-diones from allyl alcohols (Pd, [<2004JOC2595, 2005H\(65\)1917>](#)) or secondary alkynemethanols (Ru, [<2004JOC3408>](#)) in good yields. Allyl acetates [<2004TL7189>](#), even in water [<2005JOC6441>](#), are transferred when catalyzed by palladium complexes. A spirocyclopropane was synthesized by monobromination at C-5 followed by addition of a Michael acceptor and intramolecular alkylation of the corresponding enolate [<2004RJO1429>](#). The reaction of 2 equiv of Meldrum's acid with an aldehyde and catalytic amounts of triethylamine in refluxing 2-ethoxyethanol gave not the benzylidene Meldrum's acids but the 3-arylallylidene Meldrum's acids in 52–77% yield [<2005HCO55>](#) having an unexpected additional CH=CH moiety

(Scheme 29). Presumably, the two additional carbons come from 1 equiv of Meldrum's acid and the hydrogens derive from the solvent. A similar Meldrum's acid with two conjugated exocyclic double bonds was obtained from the reaction of Meldrum's acid with vinylogous Viehe salt in 93% yield <1997S573>. A polymer-bonded Meldrum's acid for solid-phase synthesis was also reported <2004CHJ212>.

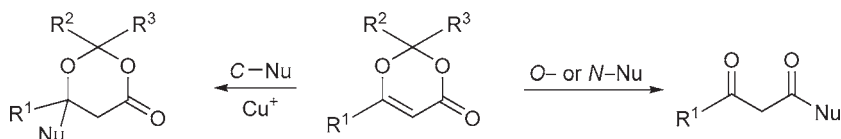
Methyl Meldrum's acid was also subjected to electrophilic alkylation. Alkynones reacted with methyl Meldrum's acid to give pyranones (11–79%) <2004LOC349> and in the presence of isonitriles to give iminoketenes <2006MI247>. The palladium-catalyzed reaction of methyl Meldrum's acid with allenes in presence of a chiral catalyst provided optically active alkylation products in excellent yields and enantioselectivities of 99% ee <2005CEJ7075>. On the other hand, an allenylalkyl Meldrum's acid was used to react with a Michael acceptor to give spirobicycle **177** in 66% yield (Scheme 30) <2006OL3627>.



Scheme 30

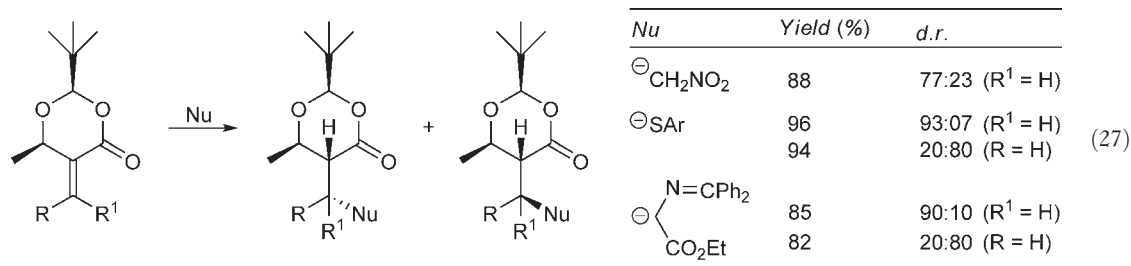
8.11.6.2.3 Reactivity toward nucleophiles

The major purpose of 1,3-dioxin-4-ones is masking β -ketoacids and providing an entry for β -ketoacylation of heteroatom nucleophiles with ring opening. Alcohols <1998T2843, 1999TA487, 1999TA4211, 2000SC455> and deprotonated alcohols <1996JOC2699, 1999OL169, 2002CC2042, 2004JOC122, 2004CC1772> readily react with 1,3-dioxin-4-ones in refluxing toluene or xylene or under microwave-mediated conditions <2000SC1725>, furnishing the β -ketoester in good yields. Amides <1997TL4517, 1997JOC6842, 2005OL47>, amines <1996T1069, 1998JA2493, 1999T4029>, or imines <1996TL7429> gave under similar conditions β -ketoamide intermediates (Scheme 31). This principle has been used for the construction of large macrocycles by intermolecular nucleophilic ring opening of an OH-substituted side chain with different chain lengths <1996TL7683> and for the synthesis of polymer-supported β -ketoesters <2005S2664>. On the other hand, C-nucleophiles in the presence of copper salts gave access to C-6-substituted 1,3-dioxane-4-ones in excellent diastereoselectivities <1996CC1063, 1999CPB293>.

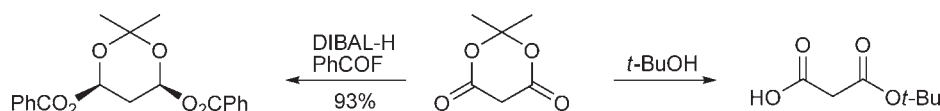


Scheme 31

1,3-Dioxan-4-ones having an exocyclic double bond, such as Seebach's 5-alkylidene-1,3-dioxane-4-ones, gave upon exposure to carbon <1997TA1545, 2000TA4365> or heteroatom nucleophiles <2000J(P1)1897, 2001EJO529> the 1,4-addition products in good yields and stereoselectivities (Equation 27). Apparently, the configuration of the newly formed side-chain stereocenter is dependent on the double-bond geometry. In general, (*E*)-alkenes gave better diastereoselectivities than (*Z*)-alkenes. Analogous compounds, such as *cis*-2,6-dimethyl-5-methylene-1,3-dioxan-4-one, react similarly with nucleophiles <1998TL2043>.

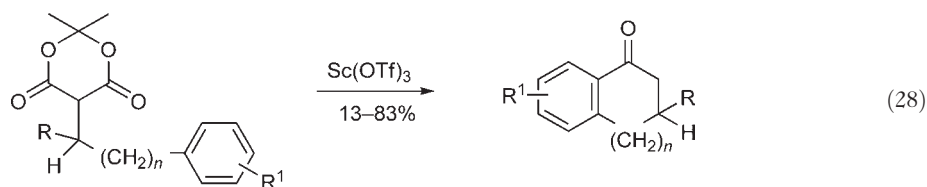


Meldrum's acids react with O-nucleophiles [<2006T4482>](#), for example *t*-BuOH [<2006SC187>](#), with ring opening providing an efficient route to monoesters of malonic acid (**Scheme 32**). In contrast, 5-acyl-substituted Meldrum's acids gave with MeOH, induced by microwave irradiation, the corresponding β -ketoesters in 88–98% yield [<2006IJB823>](#) with ring opening. Hydride nucleophiles in the presence of benzoyl fluoride reduce both C=O bonds of Meldrum's acid to afford the corresponding diacetal diester as a single diastereoisomer (**Scheme 32**) [<2004OL1877>](#).

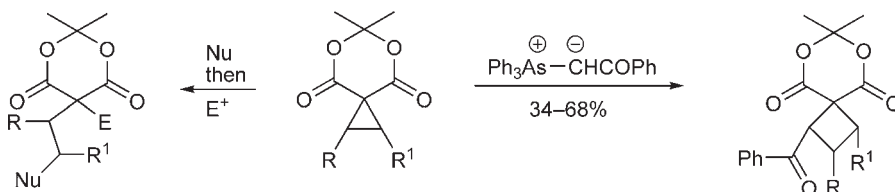


Scheme 32

The scandium-catalyzed intramolecular Friedel–Crafts acylation of 5-arylalkyl-substituted 1,3-dioxane-4,6-diones gave indanones, tetralones, and benzosuberones (**Equation 28**) [<2003OL4653, 2005JOC1316>](#).

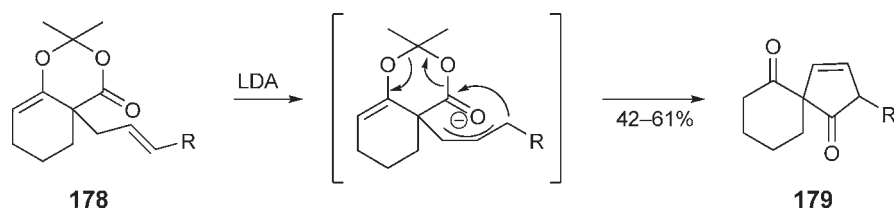


The 1,4-addition of 5-alkylidene-1,3-dioxane-4,6-diones has been discussed in [Section 8.11.6.1.2](#). In addition, it was demonstrated that nucleophiles react with Meldrum's acids containing a three-membered spirocycle. Ylide nucleophiles gave the four-membered spirocycle [<2005CHJ81>](#). Nucleophilic ring opening of the cyclopropane moiety followed by trapping of the enolate with electrophiles gave doubly substituted Meldrum's acids (**Scheme 33**) [<1999H\(51\)833>](#). The same reaction was shown to provide optically active ring opening products (up to 60% ee) by enantioselective desymmetrization of a tricycle mediated by chiral amines [<2005T4373>](#).



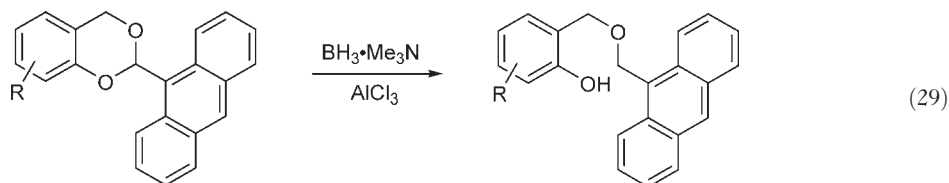
Scheme 33

An intramolecular nucleophilic ring opening of a dioxanone was reported [<1996TL3199>](#). Exposure of compound **178** to LDA affords the allylic anion which attacks the carbonyl group to give spirodiketone **179** in 42–61% yield (**Scheme 34**).



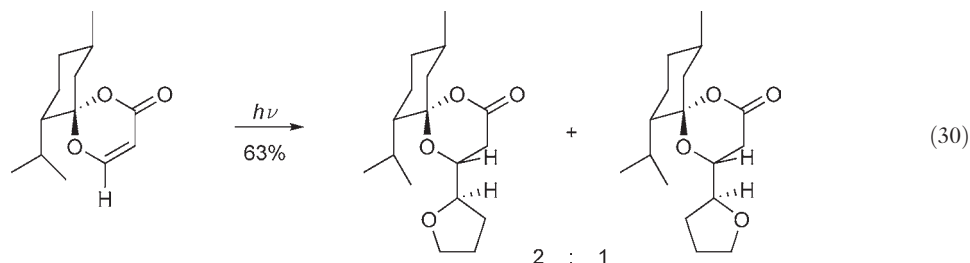
Scheme 34

Nucleophilic ring opening of salicyl alcohol acetals was effected by borane–trimethylamine upon Lewis acid activation with AlCl_3 . This reaction was particularly useful for the construction of fluorescently labeled compounds (Equation 29) <2006JOC3444>.

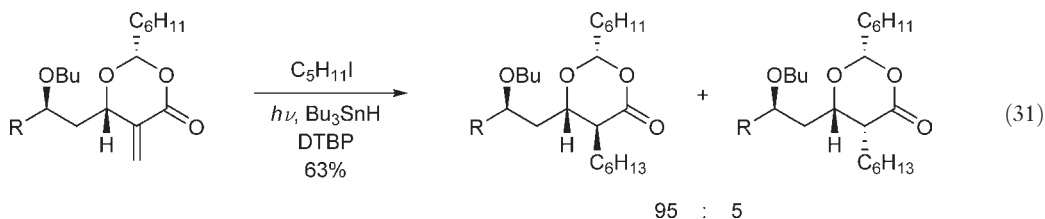


8.11.6.2.4 Reactivity toward radicals

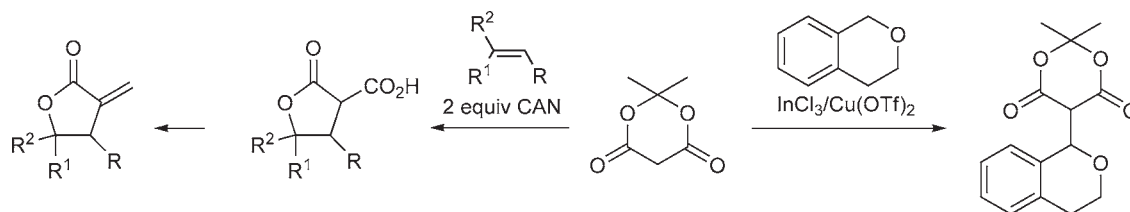
Chiral 1,3-dioxin-4-ones photochemically react intermolecular with (cyclic) ethers, acetals, and secondary alcohols to give the addition products in reasonable yields. The radical addition was completely stereoselective at C-6 of the heterocycle <1999EJO1057>. The exocyclic diastereoselectivity, where relevant, was about 2:1 (Equation 30). In analogy, an intramolecular cascade reaction of a 1,3-dioxin-4-one derived from menthone was used to get a terpenoid or a steroid framework in optically active form <1997JA1129, 1999JA4894>.



Another radical 1,4-addition was reported by Giese and Roth. In the photoaddition of a 5-alkylidene-1,3-dioxan-4-one with pentyl iodide, mediated by Bu_3SnH and di-*tert*-butyl peroxide (DTBP), a 95:5 mixture of diastereoisomeric dioxanones was obtained in 63% yield (Equation 31) <1996JBS243>.

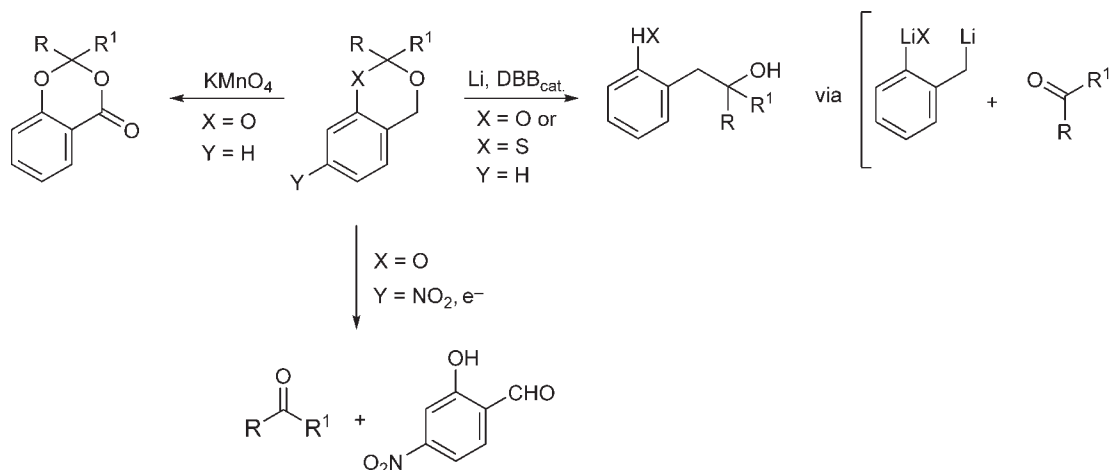


Meldrum's acid, like other 1,3-dicarboxyl compounds, was amenable to radical reactions at C-5. The radical reaction between Meldrum's acid benzyl alkyl ethers mediated by $\text{InCl}_3/\text{Cu}(\text{OTf})_2$ has been reported to proceed regioselectively at the benzylic position of the ether moiety (Scheme 35) <2006AGE1949>. Radical reaction of Meldrum's acid and alkenes was carried out with 2 equiv of ceric ammonium nitrate (CAN) to give the α -carboxylactones which were subsequently subjected to decarboxylative methylenation affording the α -methylene lactones in 35–50% yield (Scheme 35) <2006SL1523>.



Scheme 35

The oxidation of salicyl alcohol acetals to the salicylic acid acetals was effected with KMnO_4 as oxidation reagent in 82% yield [\[1999SC2405\]](#). On the other hand, electrochemical cleavage of 5-nitro-1,3-benzodioxanes liberated effectively the carbonyl moiety, allowing these acetals to be used as electrolabile protecting groups for ketones [\[2001JEC22\]](#). Reductive cleavage of similar 1,3-benzodioxanes and 1,3-benzoxathianes with lithium and a catalytic amount of di-*tert*-butylbiphenyl (DBB) gave homologation of 2-hydroxy or 2-methoxybenzyl alcohols presumably via a benzyllithium derivative ([Scheme 36](#)) [\[1997T17373\]](#).



Scheme 36

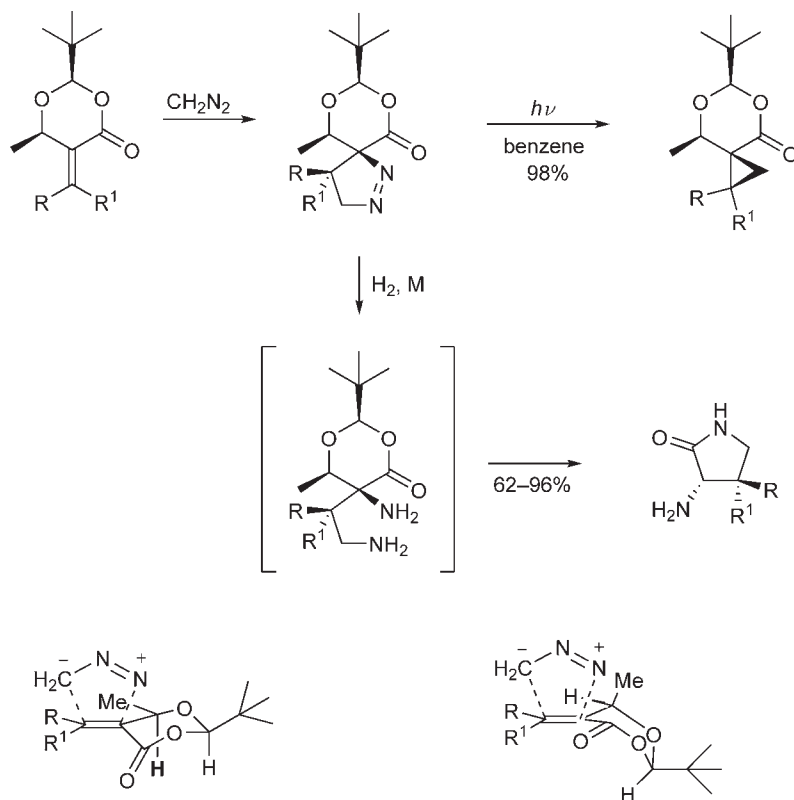
8.11.6.2.5 Cyclic transition state reactions

Cycloaddition reactions have been applied to 5-alkylidene-1,3-dioxan-4-ones. It was found that the [3+2] cycloaddition of diazomethane to either (*E*)- or (*Z*)-alkylidene-1,3-dioxan-4-ones proceed with good yields and diastereoselectivities ([Scheme 37](#)) [\[1998S1645\]](#). Interestingly, the major diastereoisomer derives from a *Si*-face attack of the dipole which is explained by either a half-chair conformation having an axial H blocking the *Re*-face or a half-boat conformation in which the *Re*-face is blocked by a concave acetal moiety. Another reaction pathway from the diazo intermediate is the hydrogenolytic cleavage of the $\text{N}=\text{N}$ bond. The cleavage was effected using standard conditions. The products isolated after workup were substituted pyrrolidinones, which derived from fragmentation of the 1,3-dioxolan-4-one moiety [\[1999SC193\]](#).

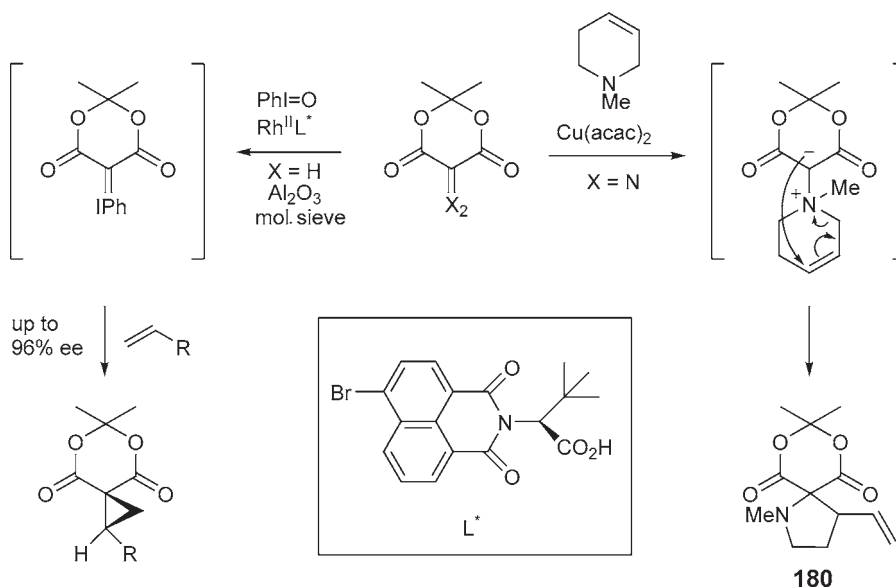
A Wittig-type rearrangement was observed when 5-diazo-Meldrum's acid reacted with *N*-methyltetrahydropyridine. At first, the electrophilic carbene generated by copper acetylacetonate attacked the nitrogen lone pair to give the ylide intermediate. Rearrangement of the ylide gave spirocycle **180** [\[2003OL4775\]](#). A phenyliodonium ylide of Meldrum's acid can be generated *in situ* by the reaction of $\text{PhI}=\text{O}$ with Meldrum's acid in the presence of Al_2O_3 and molecular sieve ([Scheme 38](#)). This ylide further reacts with styrene catalyzed by $\text{Rh}^{\text{III}}\text{L}^*$ salt to afford the cyclopropane in excellent yield and enantioselectivity (96% ee) [\[2004OL4347, 2005HCA216\]](#).

Meldrum's acid was also used for domino Knoevenagel/hetero-Diels-Alder/elimination reactions catalyzed by proline. The initial Knoevenagel condensation has been carried out with several aldehydes bearing a vinyl group at

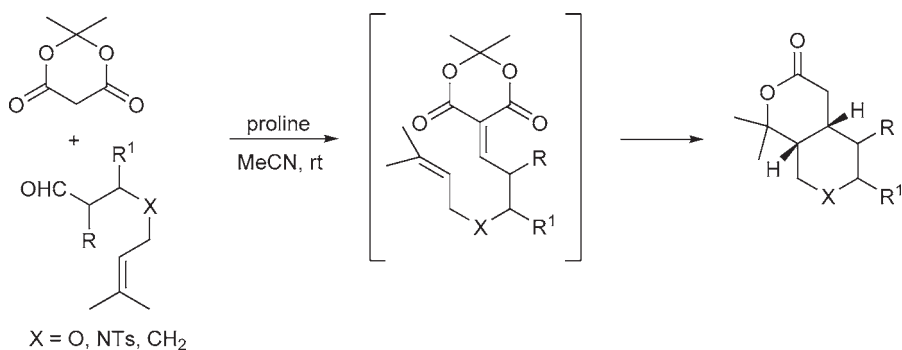
the δ -position. The condensation intermediates readily react in an intramolecular [4+2] hetero-cycloaddition. *In situ* elimination of acetone and CO_2 from the cycloaddition products provided the final bicyclic lactones in 88–96% yield (**Scheme 39**) <2005ASC1353>. In a similar manner, pyrrolo[1,2-*a*]indoles have been prepared from Meldrum's acid and an *N*-allylindole-2-carbaldehyde <2005TL3391>.



Scheme 37

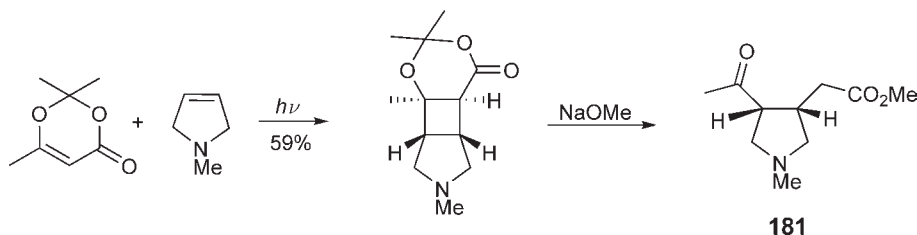


Scheme 38



Scheme 39

An intermolecular [2+2] photocycloaddition of 2,2-dimethyl-1,3-dioxin-4-one and *N*-methylidihydropyrrole was the key step in the synthesis of kainic acid analogs. The cyclobutane intermediate was hydrolyzed with sodium methoxide to give ketoester **181** in good yield (Scheme 40) <2002SL167, 2003T3307>.

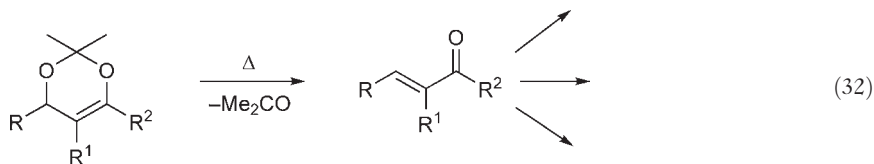


Scheme 40

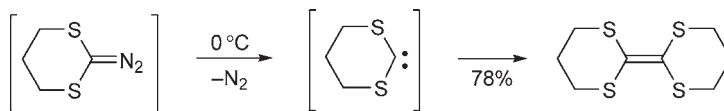
8.11.6.3 Heterocycles with One *exo*- or One *endo*-Double Bond

8.11.6.3.1 Unimolecular thermal or photochemical reaction

Commonly, 1,3-dioxins serve as masked enones. Upon thermolysis, they liberate the enones through retro-[4+2] reaction (Equation 32) <2000T10275>. In general, the enones are stable compounds even when polyenones were obtained after thermal fragmentation <2000S2060>. They readily react with nucleophiles <2001OL3349, 2002JA754> or with alkenes by cycloaddition <1996JOC2598, 2001JA9455, 2001OL3553>. An *in situ* trapping of the enones, for example, by hetero-Diels–Alder reaction, has been conducted in some instances <1999OL1933>. 1,3-Dioxin conversion may be catalyzed by Lewis acids allowing lower temperatures for the enone formation <2001OL3923>.



Thermolysis of 2-diazo-1,3-dithiane, prepared *in situ* from the reaction of 2-lithio-2-trimethylsilyl-1,3-dithiane and tosyl azide, occurs already below 0 °C. The resulting carbene dimerizes efficiently even in the presence of alkenes and alkynes to give bis(1,3-dithianylidene) in 78% yield (Scheme 41) <1997T9269>.



Scheme 41

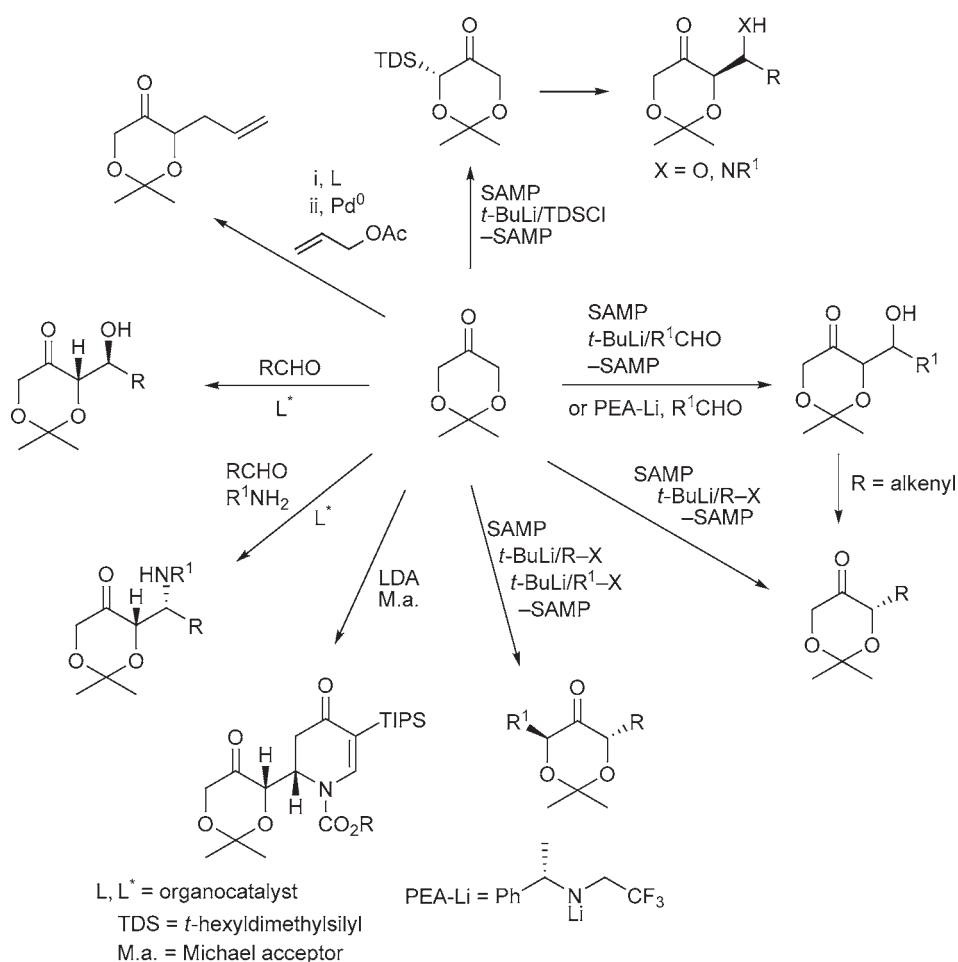
8.11.6.3.2 Reactivity toward electrophiles

The focus in this section is the electrophilic α -functionalization of 2,2-dimethyl-1,3-dioxan-5-one. Various reactions have been carried out, such as alkylations, aldol additions, Mannich reactions, and transition metal-catalyzed reactions. Conditions were described for diastereoselective transformations, or auxiliary controlled diastereoselective transformations, providing enantiomerically pure products, and enantioselectively catalyzed reactions using organo-catalysts.

The stereoselective Michael-type addition of the lithium enolate of 2,2-dimethyl-1,3-dioxan-5-one to a highly electron deficient pyridinium salt was reported to proceed with excellent stereocontrol [\[1999JA2651\]](#). Auxiliary-based alkylations and aldol reactions of 2,2-dimethyl-1,3-dioxan-5-one were intensively explored in Enders' group using (*S*)-(-)-1-amino-2-methoxymethylpyrrolidine (SAMP) or (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine (RAMP) as auxiliary. SAMP or RAMP hydrazones were either directly used to control the stereochemical outcome of the reactions or they were used to introduce an easily removable stereocenter close to the reacting carbon, which subsequently allows diastereoselective (aldol) reactions with high optical purity. Alkylations of the SAMP hydrazone of 2,2-dimethyl-1,3-dioxan-5-one using well-established reaction conditions proceed with good chemical yield (61–87%) and enantioselectivity (90–94% ee after oxidative removal of the auxiliary) to give *S,S*-configured products [\[2000S2099, 2002S1571\]](#). Repetition of the alkylation sequence gave the C_2 -symmetrical *S,S*-products [\[1998EJO2839, 2002SL29\]](#). Further repetition of the alkylation sequence gave upon removal of the auxiliary and reduction 1,2,3-triols with two quarternary stereocenters [\[2005S3517\]](#). A formal enantioselective alkylation of 2,2-dimethyl-1,3-dioxan-5-one was elaborated as well [\[1996S621\]](#). Control of the stereochemistry in aldol additions [\[2002S619\]](#) or Mannich reactions [\[2002S2737\]](#) was achieved using enantiomerically pure α -silylketone. As mentioned, the required starting material was prepared from the SAMP hydrazone of 2,2-dimethyl-1,3-dioxan-5-one (**Scheme 42**) [\[1996S1095\]](#). In a different approach, Majewski and Novak have demonstrated that the chiral lithium amide-mediated aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one with aldehydes yielded the β -hydroxyketones in high optical purity (up to 90% ee) although 1 equiv of the noncovalently bonded chiral source was necessary [\[1999SL1447, 2000JOC5152\]](#). A major advance has been achieved with the discovery that α -amino acids are capable of catalyzing the asymmetric aldol reaction between 2,2-dimethyl-1,3-dioxan-5-one and a variety of aliphatic and aromatic aldehydes. Proline was commonly used in 20–30 mol% to effect the aldol addition in excellent yields and enantioselectivities [\[2005AGE1210, 2005OL1383, 2006JOC3822\]](#). However, substoichiometric amounts of alanine (97–99% ee) [\[2005CC3586\]](#), dipeptides (92–99% ee) [\[2005CC4946, 2006OBC38\]](#), and TBDMS-protected hydroxyproline in water (95% ee) [\[2006AGE958\]](#) catalyze the aldol reaction as well (see **Table 12**). The asymmetric Mannich reaction of *in situ*-generated imines with 2,2-dimethyl-1,3-dioxan-5-one was reported to proceed under similar reaction conditions. With proline [\[2005AGE4077, 2006T357\]](#) or alanine [\[2005CEJ7024\]](#) as organocatalyst, the ee exceeded 94–99%. Since the aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one easily allows access to polyols or aminopolyols, the methodology was used for the synthesis of polyol subunits of sugars [\[2005AGE4079, 2006T329\]](#) or other natural products, such as phytosphingosines [\[2006CC655\]](#). A remarkable combination of organo- and transition metal catalysis was also reported. Thus, pyrrolidine was used for the *in situ* generation of the nucleophile, which subsequently reacts in a palladium-catalyzed allylic alkylation using allyl acetate and $\text{Pd}(\text{Ph}_3\text{P})_4$ as catalyst (**Scheme 42**) [\[2006AGE1952\]](#). 1,3-Dioxan-5-ones differently substituted at C-2 have rarely been used as substrates for electrophilic reactions [\[2000SC2275, 2000TL5909\]](#) and are not discussed further.

Table 12 Asymmetric reactions with 1,3-dioxan-5-ones catalyzed by various α -amino acids

Reaction	L^* (mol%)	Yield (%)	d.r.	Topicity	ee	Configuration	References
Aldol	Proline (20–30)	40–97	86:14–99:1	<i>anti</i>	90–98	<i>S,S</i>	2005AGE1210, 2005OL1383, 2006JOC3822
Aldol	Alanine (30)	56–95	75:25–94:6	<i>anti</i>	75–99	<i>S,S</i>	2005CC3586
Aldol	Val-Phe (30)	51–83	67:33–94:6	<i>anti</i>	99	<i>S,S</i>	2005CC4946, 2006OBC38
Aldol	Ala-Ala (30)	50–88	67:33–93:7	<i>anti</i>	92–99	<i>S,S</i>	2005CC4946, 2006OBC38
Aldol	TBSO-Pro (10)	48	96:4	<i>anti</i>	95	<i>S,S</i>	2006AGE958
Mannich	Proline (30)	47–90	78:22–99:1	<i>syn</i>	81–99	<i>S,R</i>	2005AGE4077, 2006T357
Mannich	Alanine (10)	75	95:5	<i>syn</i>	95	<i>S,S</i>	2005CEJ7024
Aldol	PEA-Li (100)	86	91:9	<i>anti</i>	90	<i>S,S</i>	1999SL1447, 2000JOC5152



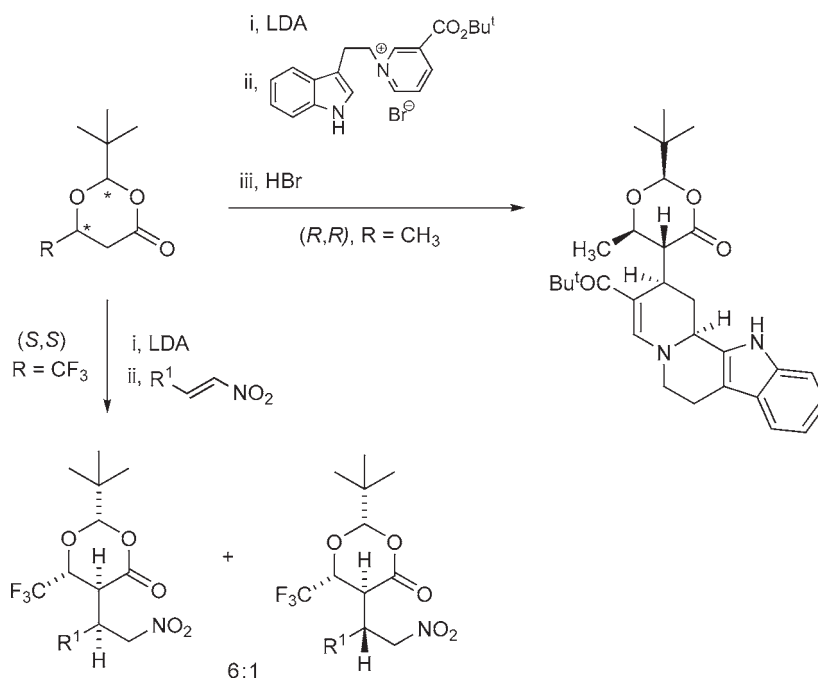
Scheme 42

The diastereoselective α -alkylation of 1,3-dioxan-4-ones with unusual Michael acceptors, such as nitroalkenes or pyridinium salts, has been reported. Whereas the enolate of the 1,3-dioxan-4-one adds to the nitroalkene in excellent yield (97%) and reasonable stereoselectivity at the side-chain stereocenter (d.r. = 6:1) <2003HCA644>, the Michael-type addition of the same enolate to a pyridinium salt afforded a single diastereoisomer albeit in low yield (27% after cyclization) (Scheme 43) <1996LA349>. Diastereoselective α -alkylations of 5-trifluoromethyl-substituted 1,3-dioxan-4-ones have been used to construct optically active fluorine-containing dendrimers <1998HCA1003>. A further application of 1,3-dioxan-4-one alkylation methodology was reported by Crich *et al.* They have developed a new asymmetric synthesis of the taxol C-ring using 1,3-dioxan-4-ones as key intermediates <1997T7127>.

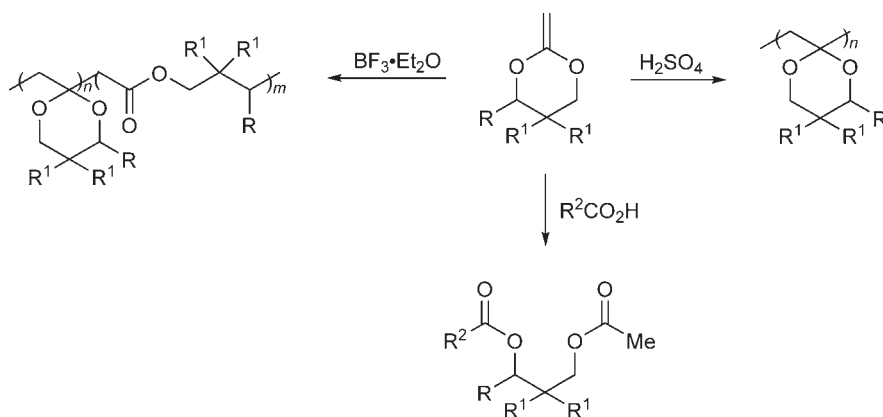
The reaction of 5-alkylidene-1,3-dioxanes with electrophiles has been investigated in two different fields. Most importantly, additions of halogen and other electrophiles have been studied with respect to the stereo- and regiochemical outcome of the reaction and the role of the endocyclic heteroatoms <1998J(P2)1129, 1998J(P2)1139>.

Cyclic ketene acetals have been intensively studied in cationic polymerization reactions, either by homo- <1997PSA3707> or by copolymerization <1998PSA861> using Brønsted or Lewis acids or electron-deficient alkenes <2000PSA2075> as initiators. Clean 1,2-addition polymers were found with H_2SO_4 on carbon, whereas with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ring-opening polymer fragments were observed (Scheme 44) <1999PSA2823>. A proton-induced ring opening using carboxylates as nucleophiles was reported to provide mixed diesters with high levels of regiocontrol when unsymmetrically substituted ketene acetals were employed <1999JOC8386>.

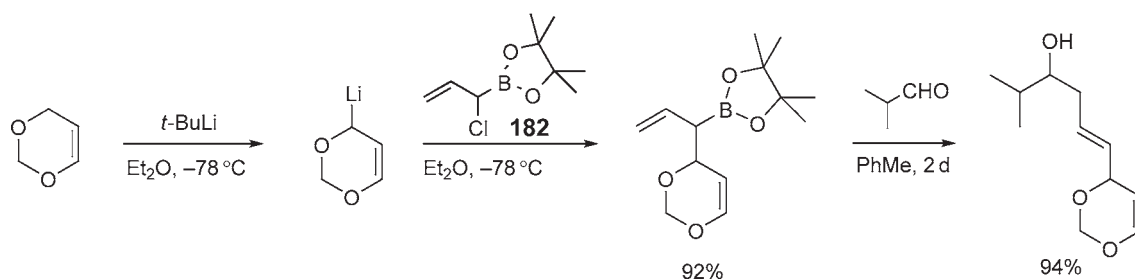
1,3-Dioxin was deprotonated at C-6 using *t*-BuLi as base (-78°C , Et_2O). The metalated dioxin was trapped by the boron-containing allyl chloride **182** in excellent yield (92%) (Scheme 45). The reaction products were used for the allylic alkylation of isobutyraldehyde (94%) <1999OL1713>.



Scheme 43

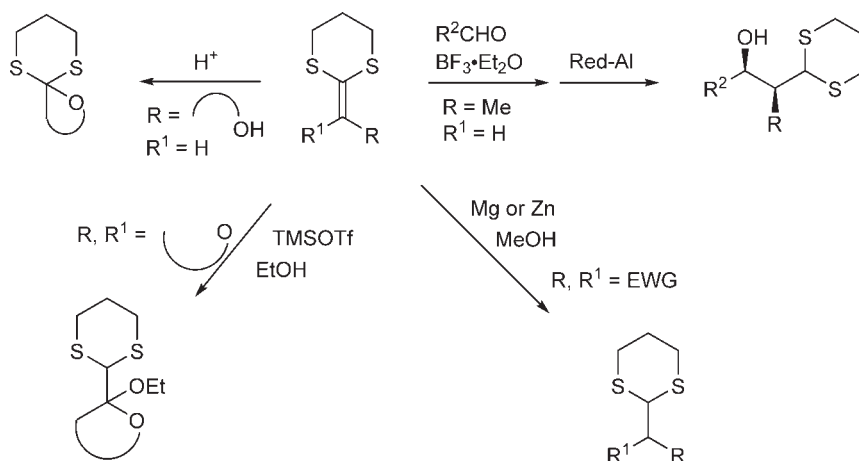


Scheme 44



Scheme 45

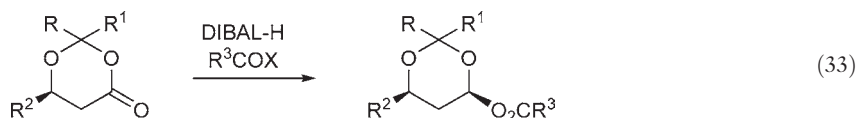
Ketene dithioacetals underwent clean addition to aldehydes upon Lewis acid catalysis. The intermediate sulfur-stabilized carbenium ion can be trapped *in situ* by Red-Al providing neutral aldol products. The *syn/anti*-ratio was dependent on the Lewis acid used. With TMSOTf, the *syn* (81:19) adduct was preferentially obtained, a fact attributed to an open-chain transition state (Scheme 46) <2004CL1032>. In a similar fashion, intramolecular cyclization of ketene dithioacetals at the exocyclic double bond with *in situ*-generated iminium salts was used for the preparation of novel carbapenems <1996TL7811>. The intramolecular proton-catalyzed addition of a hydroxy group to the double bond of a ketene dithioacetal was the key step in an efficient synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO) and 3-deoxy-D-arabino-2-heptulosonic acid (DAH) <2006S1200>. When an oxygen is attached to the exocyclic double bond, regioisomeric addition of alcohols to the double bond occurs. Thus, alcohols added to such substituted ketene dithioacetals mediated by TMSOTf in a highly regioselective manner, giving exclusively the heterocycle with an acetal moiety in the side chain (Scheme 46) <1999PJC973>. 2-Alkylidene-1,3-dithianes were reduced by mixtures of Mg/MeOH or Zn/MeOH to the fully saturated heterocycles in 43–92% yield <1997T17151>. Ring opening of the thioacetal occurs when bis-nucleophiles are employed <1997T17163>.



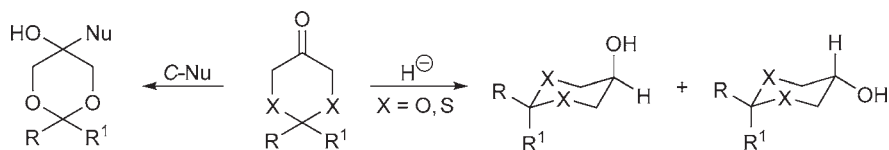
Scheme 46

8.11.6.3.3 Reactivity toward nucleophiles

The carbonyl group of either 1,3-dioxan-4-ones or 1,3-dioxan-5-ones has been reacted with several nucleophiles, especially C-nucleophiles and hydride-transfer reagents. Nucleophilic attack at the carbonyl group of 1,3-dioxan-4-ones results in the formation of a hemiacetal moiety. To conserve the stereochemical outcome of the DIBAL-H-promoted hydride transfer to 1,3-dioxan-4-ones, which is in all cases preferentially the 1,3-*syn*-adduct, it is necessary to protect the hydroxy group *in situ*, typically with the aid of anhydrides (Equation 33) <1996JOC8317, 1999TL41, 2003T8979>. The acetal esters may be further manipulated to produce important intermediates for natural product synthesis <2004OBC1719, 2004JA48>. C-Nucleophiles, such as allylsilanes, reacted with Lewis acid assistance to the corresponding ring-opening products <1996TL1425>.

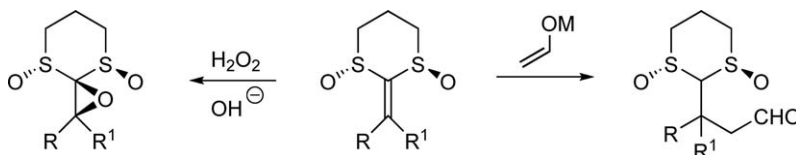


Reduction of the carbonyl group of 1,3-dioxan-5-ones with R ≠ R¹ yields two stereoisomers. The *cis*-compound was obtained when using L-selectride as reducing agent (75% yield), whereas LiAlH₄ gave the *trans*-product in 83% yield <1998S879>. The corresponding dithianones react similarly, although with less stereoselectivity (Scheme 47) <1999JA7130>. Theoretical calculations were conducted to explain the stereochemistry by the exterior frontier orbital extension model <2000H(52)1435, 2001HAC358>. Organometallic reagents have also been successfully employed for the nucleophilic attack at the carbonyl group of 1,3-dioxan-5-ones. Metalated thiazoles <1998HCA889>, alkynes <2000OL2591>, and propenes <2003HCA2458> were used as nucleophiles.



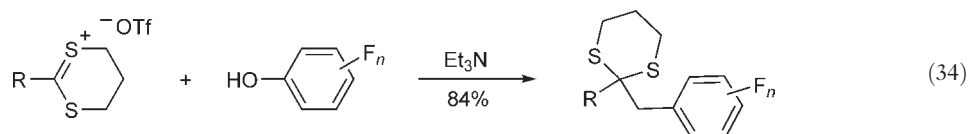
Scheme 47

Optically active 2-alkylidene-1,3-dithiane 1,3-dioxides have been prepared as chiral Michael-type acceptors. It was shown that these compounds react under nucleophilic epoxidation conditions to give diastereoselectively the epoxides. Other heteroatom nucleophiles reacted as well <1998JOC7128, 1999PS(153/4)337>. It was further demonstrated that enolates were also effective nucleophiles for the stereoselective addition to 2-alkylidene-1,3-dithiane 1,3-dioxides (Scheme 48) <2005OL4013>.

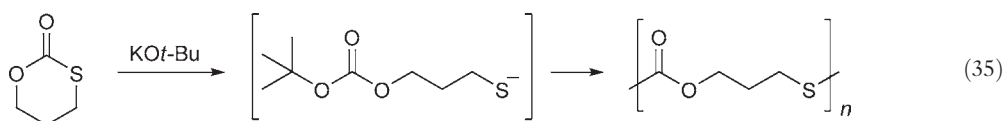


Scheme 48

As expected, 1,3-dithianylum ions readily react with nucleophiles to give the corresponding C-2 addition products. This reaction was used to prepare novel liquid crystals by addition of phenols to 2-substituted-1,3-dithianylum triflates (Equation 34) <2001AGE1480>.



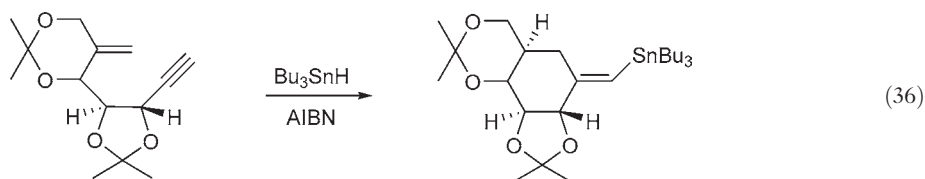
Potassium *tert*-butoxide-induced anionic ring-opening polymerization of 1,3-oxathian-2-one shows a remarkable regioselectivity. It was found that the initiation afforded the thiolate anion by selective C-S cleavage of the thiocarbonate group. The thiolate anion further reacts with the starting material to give a polymer possessing a sulfanyl(carbonyloxy)propyl repeat unit (Equation 35) <1999MM5715>.



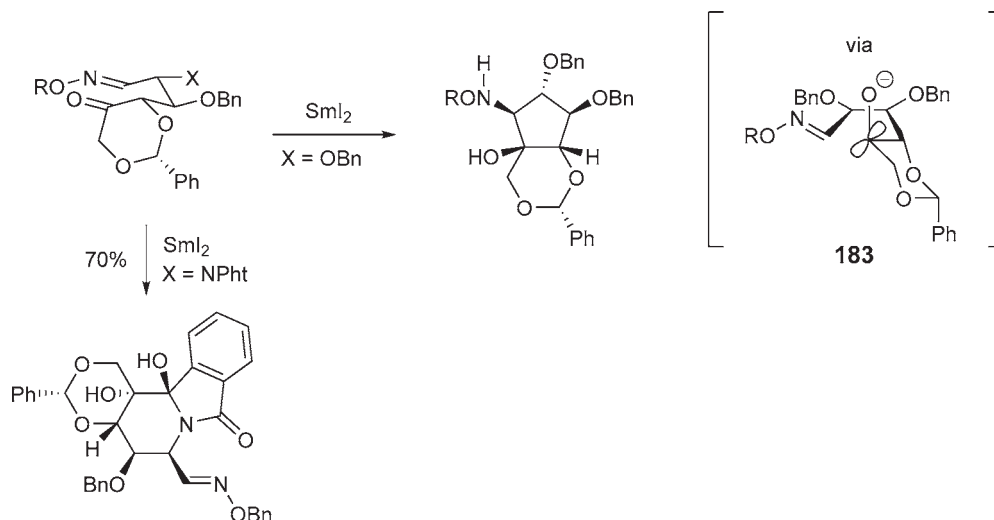
Ring-opening polymerization of several 1,3-dioxan-2-ones using a series of lipases has also been reported and these studies have been reviewed <B-2003MI156>.

8.11.6.3.4 Reactivity toward radicals and carbenes

Only a few radical reactions have been applied to the functionalization of 1,3-dioxanes or 1,3-dithianes bearing one *exo*- or *endo*-double bond. In all cases, ring formation was the goal. The common reagent system, Bu₃SnH/AIBN, was used to achieve a stereoselective ring closing hydrostannylation of an alkenyl alkyne subunit (AIBN = 2,2'-azobisisobutyronitrile; Equation 36) <1998JOC9626>.

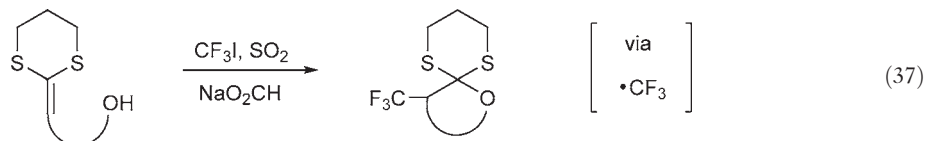


Ring closing was also effected reductively with SmI_2 . In a concise synthesis of trehazoline from glucose, a 1,3-dioxan-5-one-3'-oxime was reacted with SmI_2 to afford the bicyclic reaction product with the desired stereochemistry, probably via intermediate **183** (Scheme 49) <1998JOC5877>. Interestingly, the analogous 2-phthalimide, prepared from glucosamine, failed to give the cyclitol derivative. Instead, by involving the phthalimido group, a six-membered ring was formed in 70% yield <2005JOC4142>.



Scheme 49

An intramolecular cycloaddition occurred, when 2-alkylidene-1,3-dithianes having a hydroxy group at an appropriate distant position (3- or 4-atoms) were treated with trifluoromethyl iodide in the presence of SO_2 . A radical mechanism with 2-alkyl-2-iodo-1,3-dithianes as intermediates is suggested (Equation 37) <1997JOC9107>.



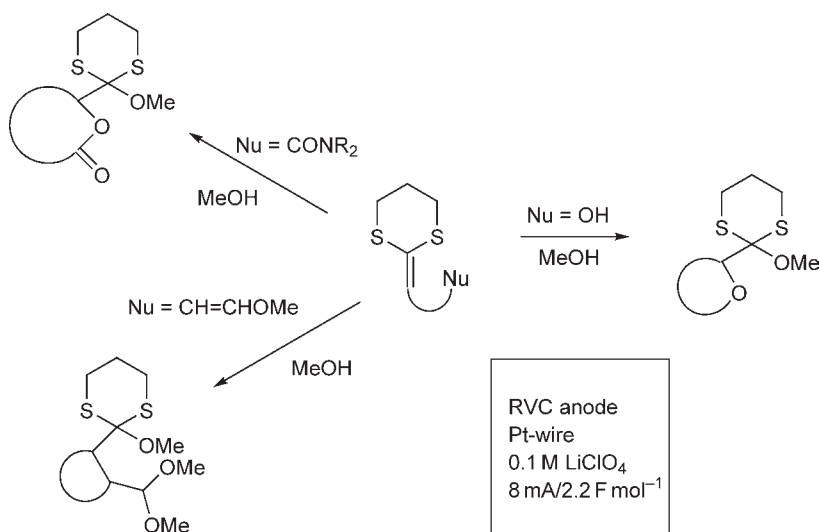
Radical cations of 2-alkylidene-1,3-dithianes can be generated electrochemically by anodic oxidation using a reticulated vitreous carbon (RVC) anode <2002TL7159>. These intermediates readily react with nucleophiles at C-1'. Upon removal of the second electron, the sulfur-stabilized cations were trapped by nucleophilic solvents, such as MeOH, to furnish the final cycloaddition products. Hydroxy groups <2001OL1729> and secondary amides <2005OL3553> were employed as O-nucleophiles and enol ethers as C-nucleophiles (Scheme 50) <2002JA10101>.

2-Alkylidene-1,3-dioxanes were prone to light-induced radical polymerization. The developments in this field have been reviewed <B-1997MI83>.

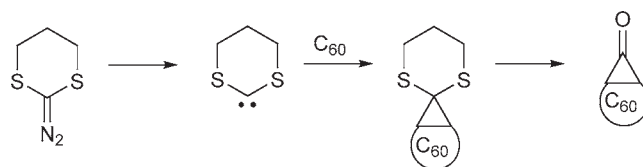
The chemistry of the carbene 1,3-dithian-2-ylidene, generated from 2-diazo-1,3-dithiane, was briefly discussed in Section 8.11.6.3.1. It reacts poorly with alkenes or alkynes if they are not highly electron deficient. However, it was found that C_{60} as source of $\text{C}=\text{C}$ bonds efficiently provides the [2+1] cycloaddition product, which can be hydrolyzed to the C_{60} -cyclopropanone (Scheme 51) <2001HCO223>.

8.11.6.3.5 Cyclic transition state reactions

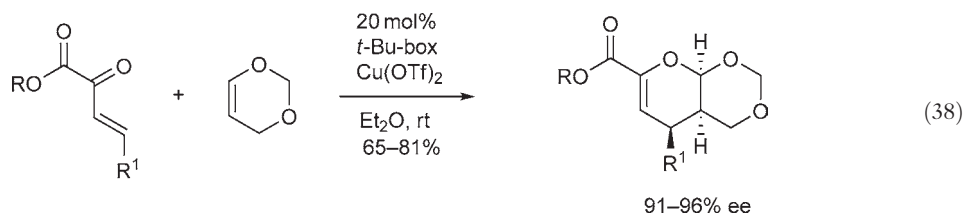
An enantioselective hetero-Diels–Alder reaction between activated enones and 1,3-dioxin was reported. The Evans catalyst (*t*-Bu-box, $\text{Cu}(\text{OTf})_2$) was applied to obtain the bicycles in 65–81% yield and 91–96% ee (Equation 38) <2000JOC4487>.



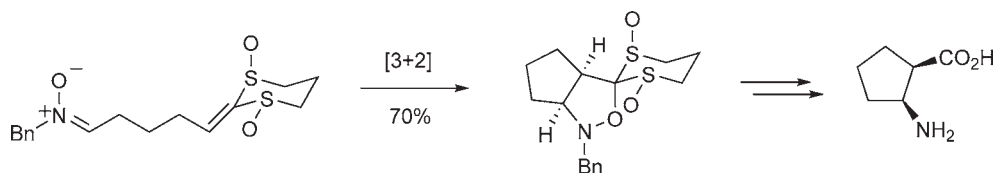
Scheme 50



Scheme 51



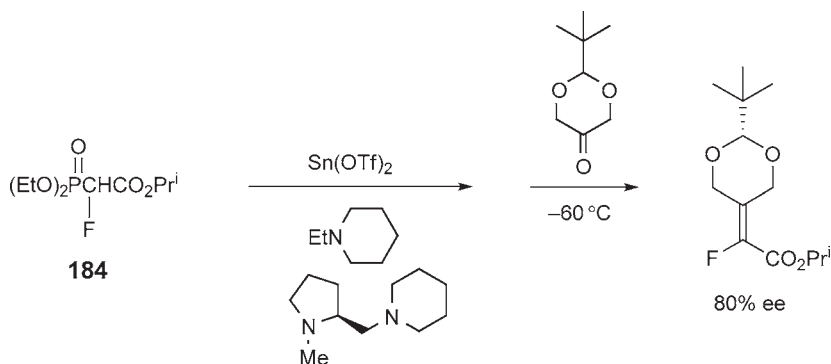
The use of chiral 2-alkylidene-1,3-dithiane 1,3-dioxides in asymmetric cycloaddition reactions has been demonstrated. A highly enantioselective synthesis of (–)-cispentacin by an intramolecular 1,3-dipolar cycloaddition was reported (Scheme 52) <2002OL1227, 2003OBC684>.



Scheme 52

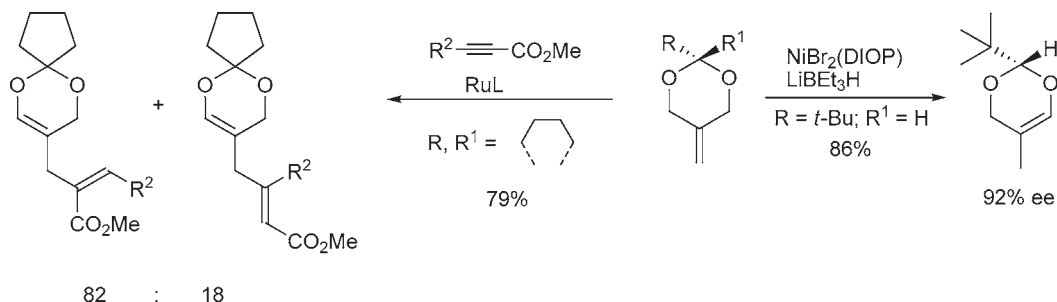
8.11.6.3.6 Miscellaneous reactions

The asymmetric Horner–Wadsworth–Emmons (HWE) reaction of 1,3-dioxan-5-ones with phosphonate **184** and a chiral diamine was reported. With the *tert*-butyl-substituted 1,3-dioxan-5-one, the product possesses a chiral axis. It was obtained in good yield and with 80% ee (Scheme 53) <2002TL281>. The HWE reaction with similar heterocyclic substrates was used to provide conformationally restricted arachidonic acid derivatives <1999TA139>.



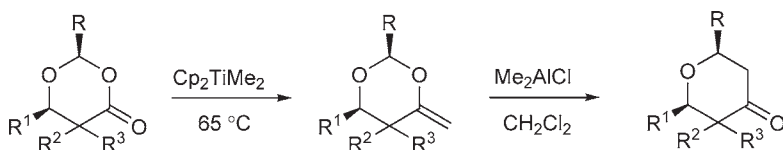
Scheme 53

Some transition metal-catalyzed reactions have been employed for the conversion of the double bond of either 4- or 5-alkylidene-1,3-dioxanes. The $\text{NiBr}_2(\text{DIOP})/\text{LiBEt}_3\text{H}$ -mediated isomerization of 2-*tert*-butyl-5-methylene-1,3-dioxane gave the corresponding 1,3-dioxin in high yield (86%) and ee (92%) (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) <1998TA1103>. The chiral 1,3-dioxins have been submitted to further transformations <2005TA3394>. A ruthenium complex-catalyzed isomerisation/alkyne cross-coupling reaction has been reported <1999TL7739>. The regioisomers (ratio = 82:18) were obtained in good yield (79%, Scheme 54). The intramolecular Heck reaction of a 5-methylene-1,3-dioxane with an alkenyl triflate has been demonstrated as well <1998TL4643, 1998TL4647>.



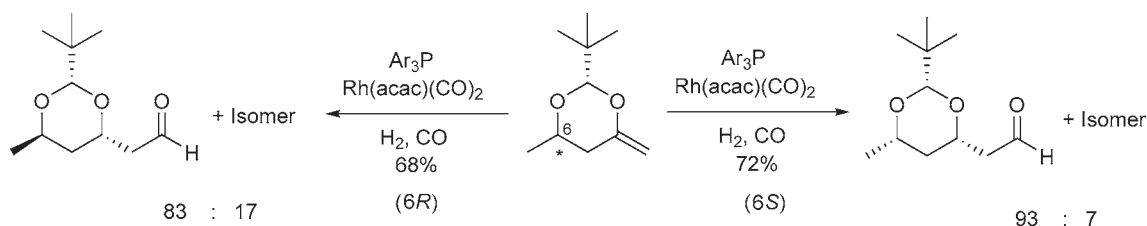
Scheme 54

The reaction of 1,3-dioxan-4-ones with Petasis reagent afforded 4-methylene-1,3-dioxanes. Me_2AlCl -mediated rearrangement of these heterocycles gave rise to the formation of 5-oxotetrahydropyrans <1996TL141>. With *i*- Bu_3Al , the corresponding alcohols were isolated as a mixture of diastereoisomers. The rearrangement protocol shown in Scheme 55 was applied for several natural product syntheses <2001JA12426, 2005JA6948, 2005OL4399>.



Scheme 55

Two 4-methylene-1,3-dioxane diastereoisomers, isomeric at C-6, were subjected to the rhodium-catalyzed hydroformylation. The stereochemistry of the newly formed stereogenic carbon was guided solely by the acetal stereocenter (not by C-6) (Scheme 56) <1997JA11118, 1998TL6423>.



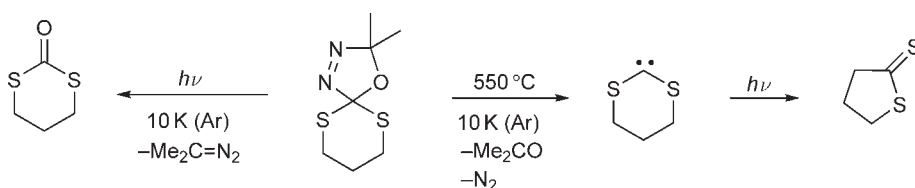
Scheme 56

8.11.6.4 Fully Saturated Heterocycles

The vast majority of studies on fully saturated systems involve 1,3-dioxanes and their application as protecting groups for ketones or 1,3-diols <2006JOC6258>. In this overview, the focus on fully saturated heterocycles is on the nondestructive reactivity of fully saturated 1,3-heterocycles although some ring-opening reactions are also presented.

8.11.6.4.1 Unimolecular thermal or photochemical reactions

In Section 8.11.6.3.1, the chemistry of 2-diazo-1,3-dithiane is described although the existence of the diazo compound or the daughter carbene was just assumed. Schreiner *et al.* have characterized 1,3-dithian-2-ylidene for the first time by FVP of 3,4-diaza-2,2-dimethyl-1-oxa-6,10-dithiaspiro[4.5]dec-3-ene prepared according to Rigby *et al.* (Scheme 57) <2000T10101>. The carbene was trapped in a 10 K argon matrix and its UV and IR spectra recorded. Irradiation of the carbene at 10 K gave the corresponding thiolactone. Interestingly, irradiation of the parent diazaspiron compound at the same temperature provided different products namely 1,3-dithian-2-one and 2-diazopropene <2006AGE3989>.



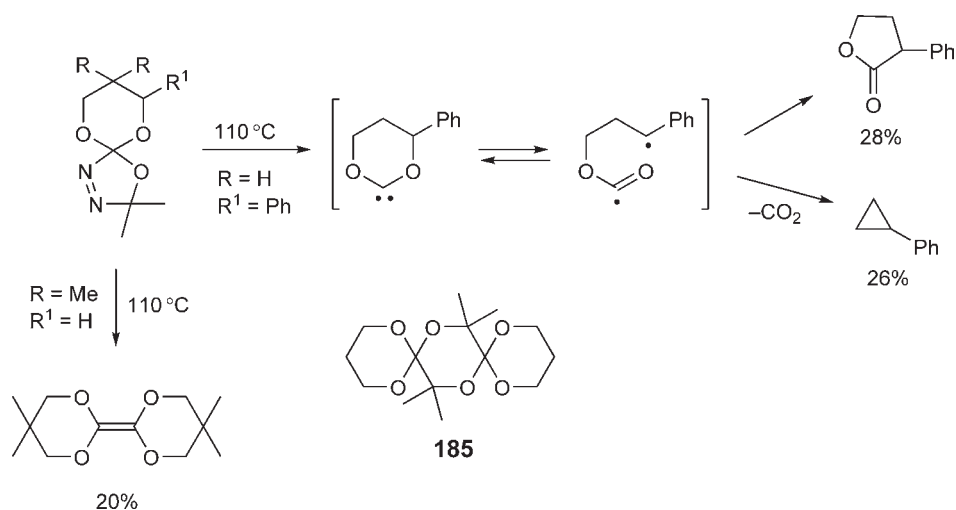
Scheme 57

A similar spiro-fused starting material was prepared to study the thermolysis of a 1,3-dioxane analog. As found for the dithia compound (cf. Section 8.11.6.3.1), a carbene-derived dimer was formed as the major detectable product (20%) <2002TL1927>. Other products, such as tricycle **185**, have been identified in subsequent studies <2004CJC1769>. However, phenyl substitution at C-4 provided completely different thermolysis products, probably via formation of an open-chain bis-radical. Thus, 3-phenyl- γ -butyrolactone and, after CO₂ extrusion, phenylcyclopropane are the major reaction products (Scheme 58) <2002CJC1187>.

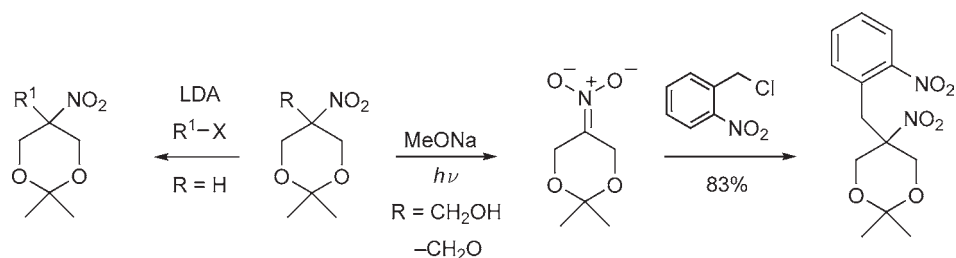
8.11.6.4.2 Reactivity toward electrophiles

For the reaction of fully saturated 1,3-dioxanes with electrophiles, an activation of the heterocycle by metalation either close to an appropriate functional group or by displacement of a functional group is necessary since deprotonation of unfunctionalized 1,3-dioxanes is not a common method. It was reported that 5-nitro-1,3-dioxanes were alkylated at C-5 using standard alkylation conditions (LDA, R-X) <2001TL105, 2006JOC2200> (Scheme 59) or by reaction with Michael acceptors <2002TL8351>. A 5-hydroxymethyl-5-nitro-1,3-dioxane was also amenable to alkylation after a photoinduced retro-aldol reaction had taken place in the presence of sodium methoxide. However, only 2-nitrobenzyl chloride was a suitable electrophile for an efficient alkylation <2004TL1737>.

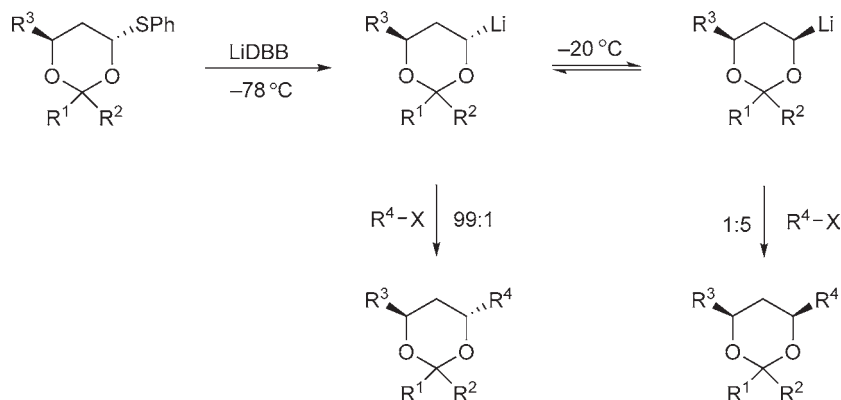
Displacement of a phenylthio group by lithium using LiDBB at -78°C was found to be effective for the preparation of a *trans*-4-lithio-1,3-dioxane configurationally stable at that temperature. Reaction with alkyl halides with retention of the configuration afforded the *trans*-dioxanes with 99:1 selectivity. Equilibration of the *trans*-configured 4-lithio-1,3-dioxane to the thermodynamically more stable *cis*-derivative was achieved upon warming the solution to -20°C . The *trans/cis*-ratio was approximately 1:5. This ratio was also found after alkylation with alkyl halides (Scheme 60) <1999JOC6849>.



Scheme 58

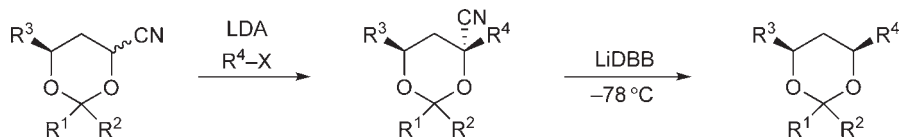


Scheme 59



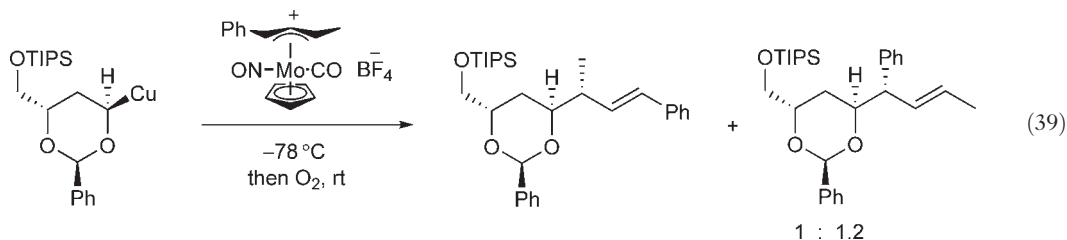
Scheme 60

Alternatively, 4-cyano-1,3-dioxanes can be smoothly metalated and alkylated at C-4. Upon reductive removal of the cyano group, either by using Li/NH_3 or LiDBB , 1,3-dioxanes with a *syn*-substitution pattern were obtained. This reaction sequence has been reviewed ([Scheme 61](#)) <2001TCC(216)51>. The reaction has been applied to several polyol natural product syntheses, such as dermostatin A <2001AGE3224>, apicularen A <2003OL3357>, rimocidin <2004AGE2822>, and nystatin <2004PNA11992>. Progress has been achieved in using the cyano group for further reactions. Thus, it was either transformed to an aldehyde by the well-established DIBAL-H reduction <2004OL4371> or it was used for the construction of spirocycles by reductive removal using LiDBB followed by intramolecular trapping of the lithium species with an adjacent allyl ether moiety <2006JOC1068>.

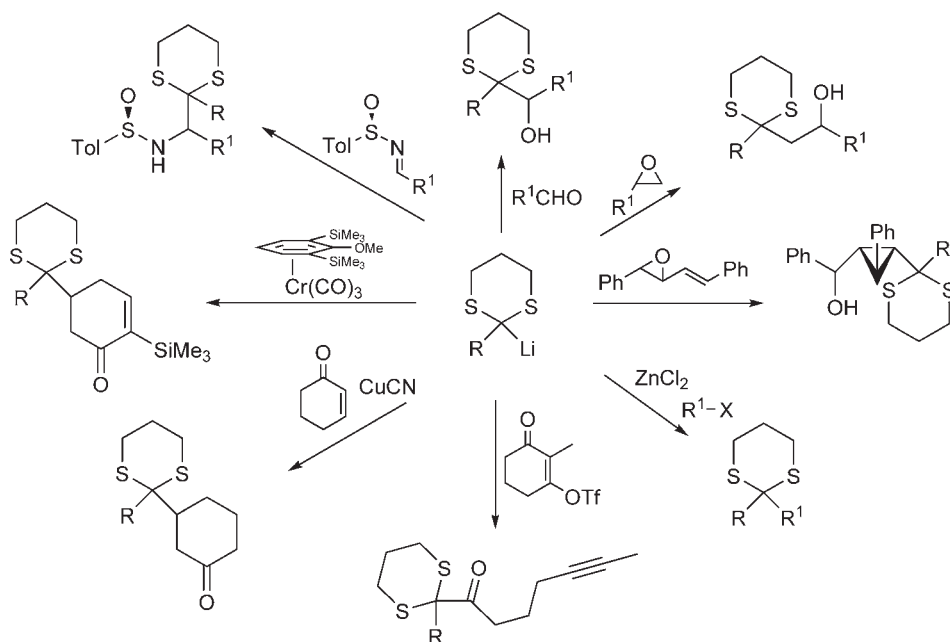


Scheme 61

A metal exchange was used to prepare a 4-cupro-1,3-dioxane from the corresponding lithium derivative. This copper species reacted with an allyl cation complex to give addition products with excellent stereoselectivity but with poor regioselectivity when an unsymmetrically substituted allyl cation was employed (Equation 39) <2000SL463, 2004OBC1719>.

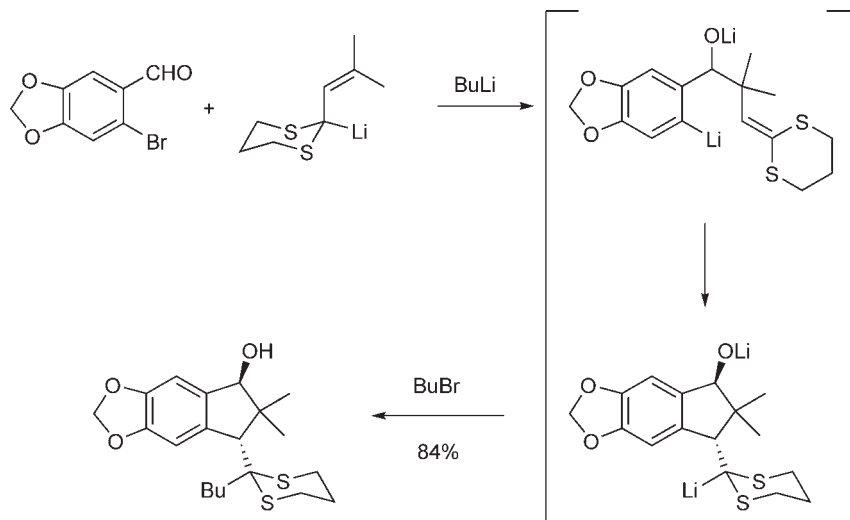


The reaction of lithiated 1,3-dithianes with electrophiles has been often addressed and a plethora of structurally different electrophiles have been used <2006SOS(8a)813>. Two reviews concerning the use of 1,3-dithianes in natural product synthesis have been published <2003T6147, 2004ACR365>. Aldehydes (and ketones) were widely employed as electrophiles. Other effective electrophiles are epoxides <1999BCJ2491, 1999BCJ2501>, chiral imines <2006TL2743>, and Michael acceptors <1997JOC1305, 2001MI10> as well as alkyl halides. In the latter case, it was found that transmetalation of the lithium compound with ZnCl_2 gave much better yields of the alkylation products <1997S1174>. The use of vinyloxiranes gave not the ring-opening products but cyclopropanes as reaction products <2005OL4057, 2006TL205>. Chromium complex-activated arenes were also suitable electrophiles for an efficient alkylation <2006SL2114>. Cyclohex-2-enones bearing a triflate group at C-3 gave open-chain alkylation products with alkylation exclusively at C-1 (Scheme 62) <2006JA6499>. The dependence of the regioselectivity of alkylation products of enones on the reaction conditions has been studied <1999JOC14, 2001JA6527>. Reaction of 2-lithio-1,3-dithiane with dimethylformamide (DMF) provided 2-formyl-1,3-dithiane which was employed for the construction of porphyrins <2004JA13634>. A polymer-bonded 1,3-dithiane, unfunctionalized at C-2 and suitable for combinatorial chemistry, has been reported <2005T9519>.



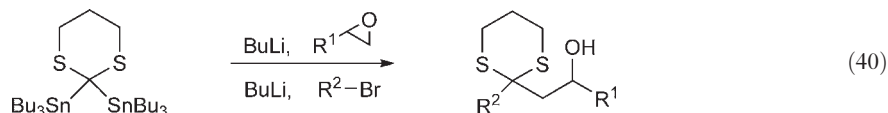
Scheme 62

An interesting sequence of umpolung reaction has been reported by Harrowven and Browne. Starting from 2-alkenyl-2-lithio-1,3-dithiane and 6-bromopiperonal, they managed to achieve cyclization in 84% yield using extra equivalents of BuLi. After initial addition of the terminal vinylic carbon to the carbonyl group, bromine–lithium exchange gave a nucleophilic carbon which added to the ketene dithioacetal in a carbolithiation reaction. The lithium, positioned back at C-2 of the heterocycle, could now be alkylated with alkyl electrophiles (**Scheme 63**) <1996T14951>.

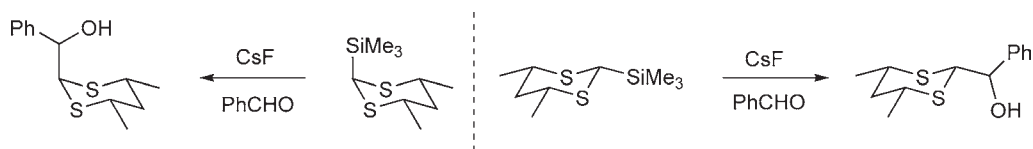


Scheme 63

Stable 2-metallo-1,3-dithianes, such as stannanes or silanes, have also been prepared and reacted with electrophiles. Sequential alkylation of a 2,2-bis-stannyl-1,3-dithiane (i, BuLi, oxirane; ii, BuLi, alkyl bromide) furnished the 2,2-dialkylated products in 40% yield (**Equation 40**) <1997JA2058>.



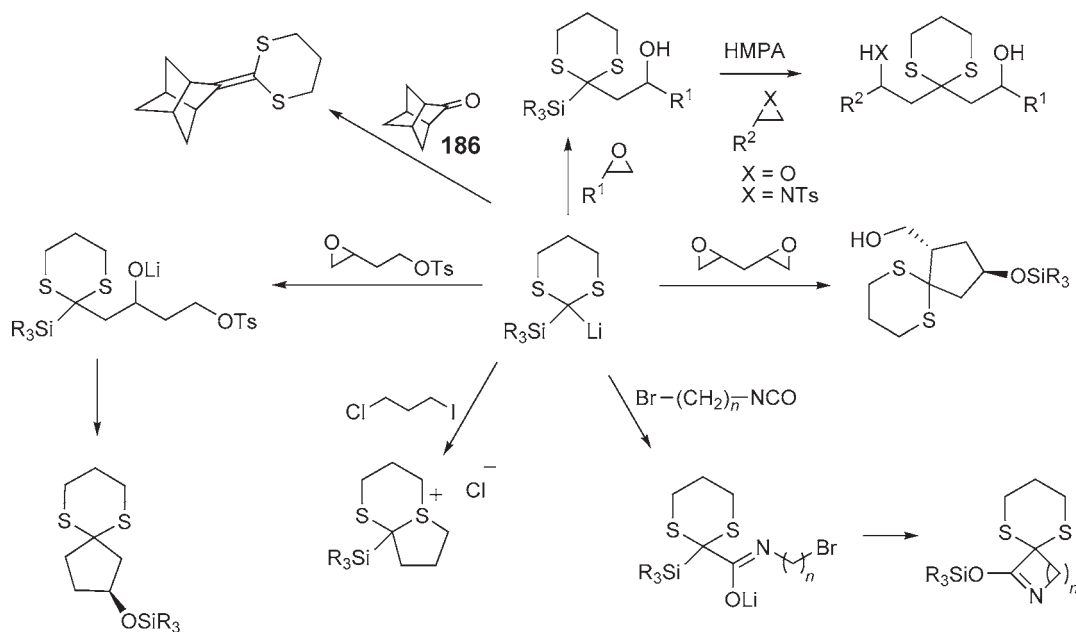
Activation of 2-silyl-1,3-dithianes was effected by tetrabutylammonium triphenyldifluorosilicate <1996JOC6901> or CsF <1999TL2065>. Both, equatorial and even axial silyl groups were reacted with electrophiles with retention of the configuration at C-2 when CsF was used for activation (**Scheme 64**) <2002SL1447>.



Scheme 64

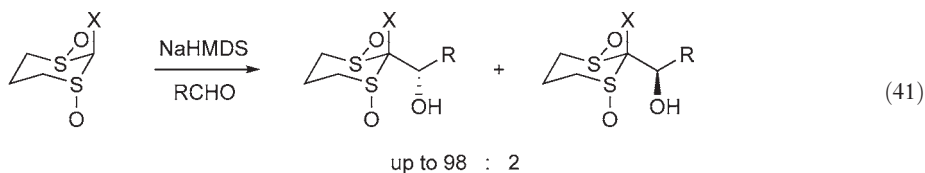
The Brook rearrangement, the silyl transfer from carbon to oxygen at various distances (recent example, <2006JA12368>), was used for the development of a one-pot double functionalization of monolithiated 2-silyl-1,3-dithianes <1997JA6925>. Treatment of these compounds with an oxirane at low temperature gave the alkylation product possessing an oxo anion. Upon addition of hexamethylphosphoramide (HMPA), the Brook rearrangement occurs, affording 2-lithiated-1,3-dithiane which reacts either with a second oxirane <2002JA14516, 2003JA14435> or with an aziridine <2004OL1493> or (in a different reaction mode) with alkyl halides <2006JA66> (**Scheme 65**).

A spiro-fused dithiane can be obtained from ω -tosyloxiranes [<1996LA1811>](#) or methylenedioirane [<2005OL5183>](#). Reaction of 2-lithio-2-silyl-1,3-dithiane with ω -bromo isocyanates yielded heterospirocycles [<2000SL92>](#), and reaction with ketones, such as **186**, gave access to 2-alkylidene-1,3-dithian [<1999EJO73>](#). Interestingly, 2-lithio-2-trimethylsilyl-1,3-dithiane reacted with bifunctional alkyl halide to give bicyclic sulfonium salts in 83% yield instead of dimeric compounds (**Scheme 65**) [<1998T12361>](#).



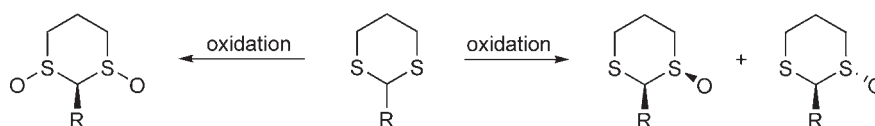
Scheme 65

2-Halo-1,3-dithiane *trans*-1,3-dioxides can be easily accessed by reaction of the parent bis(sulfoxide) with *N*-halo-succinimide in CH_2Cl_2 . Metalation of the 2-halo-1,3-dithianes with LiHMDS followed by addition of aldehydes gave the addition products in acceptable yields and high stereoselectivities (up to 98:2) (**Equation 41**) [<1997J\(P1\)11>](#). Asymmetric variations of this reaction using optically active bis(sulfoxides) were reported as well [<1997T16213, 2002JOC8618>](#). Importantly, sodium hexamethyldisilazide must be used to achieve high stereocontrol.



Oxidation of 1,3-dithianes to 1,3-dithiane 1-oxides has been carried out by various methods using H_2O_2 or *t*-butyl hydroperoxide (TBHP) as oxidant. In the presence of chiral co-oxidants, optically active 1,3-dithiane 1-oxides have been prepared (**Scheme 66**). A compilation of some currently used methods is given in **Table 13**. The oxidation to 1,3-dithiane 1,3-dioxides was conducted similarly. Sharpless conditions were found to be highly effective with 2-alkyl- or alkylidenyl-substituted substrates. The parent 1,3-dithiane 1,3-dioxide was obtained by basic removal of a 2-carboxyl group in 83% yield and 99% ee [<1998JOC7306>](#).

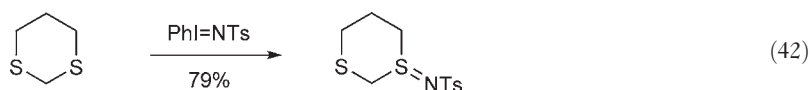
The synthesis of 2-substituted-1,3-dithiane-1-sulfimides using *N*-(*p*-tolylsulfonyl)imino(phenyl)iodinane ($\text{TsN}=\text{IPh}$) and a catalytic amount of $\text{Cu}(\text{OTf})_2\text{-box}$ was reported to proceed with good yields (57–70%) and diastereoselectivity (*trans:cis* 96:4–100:0). However, the ee was low (32–40%) (**Equation 42**) [<1998J\(P1\)2373>](#).



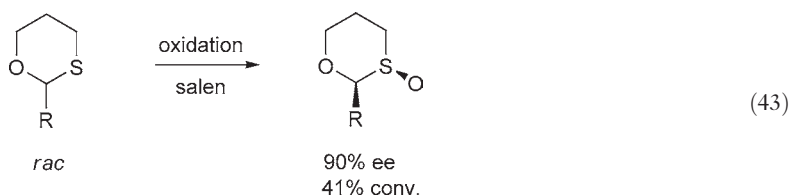
Scheme 66

Table 13 Oxidation of 1,3-dithianes to 1,3-dithiane 1-oxides or 1,3-dithiane 1,3-dioxides under various (asymmetric) reaction conditions

Oxidizing agent	Co-agent	Solvent	Yield (%)	trans:cis	ee (%)	R ^a	References
H ₂ O ₂	Flavine	CH ₃ OH	99			H	2001CEJ297
O ₂	Flavine	CF ₃ CH ₂ OH	97			H	2003JA2868, 1999JOC5620
HNO ₃	(P ₂ O ₅)		80 ^b			H	2005TL5503
H ₂ O ₂	F ₂₀ TPPFe	EtOH	90			H	2004JOC3586
DABCO-Bn ⁺ Cr ₂ O ₇ ²⁻		CH ₃ CN	80 ^b			H	2003PS2441
Cymylhydroperoxide	DET, Ti(OiPr) ₄	CH ₂ Cl ₂	68		10	H	2005TA2271
TBHP	DET, Ti(OiPr) ₄	CH ₂ Cl ₂	55		17	H	1996T2125
Chiral hydroperoxide	Ti(OiPr) ₄	Toluene	95		32	H	2004TA1779, 2004TA413
Acinetobacter		H ₂ O	76 ^c		84–98	H	1997T9695, 1996TL6117, 1999NJC827
H ₂ O ₂	VO(acac) ₂ , imine [*]	CH ₂ Cl ₂	80		95	H	2001JCM263
TBHP	Ti(IV) on polymer		67	99:1		Ph	2006JMO27
TBHP	Cp ₂ TiCl ₂ , MS	CH ₂ Cl ₂	86	98:2		Ph	2002S505
H ₂ O ₂ –urea	Ti(salen)	MeOH	91	trans	99	Ph	2002TL3259
H ₂ O ₂ –urea	Re(v)	CH ₃ CN	85	trans		Ph	1998TL5655
H ₂ O ₂	Cyclohexanonoxime	CH ₃ OH	90	trans		Ph	1997SL1355
H ₂ O ₂	TiBINAP		68	99:1		Ph	2006TL7233, 2006JMO27
H ₂ O ₂	VO(acac) ₂ , imine [*]	CH ₂ Cl ₂	84	99:1	85–88	Ph	1998SL1327, 1999TA3457
H ₂ O ₂	Chiral imine	CH ₂ Cl ₂	100	trans	83	Ph	2000JOC6756
Chiral hydroperoxide	Ti(OiPr) ₄	Toluene	80	trans	50	Ph	2006EJO713
Monooxygenase		H ₂ O	100	>50:1	90	COPh	1996TA565
Yeast		H ₂ O	64	98:2	99	C ₂ H ₄ OCH ₃ , CO ₂ Et	2002ARK(xii)47
TBHP	DET, Ti(Oi-Pr) ₄	CH ₂ Cl ₂	58	98:2	99	C(CH ₃) ₂ OCH ₃	1998J(P1)1087
TBHP	DET, Ti(Oi-Pr) ₄	CH ₂ Cl ₂	95	85:15:3 ^d		Chiral auxiliary	1996J(P1)1879
TBHP	DET, Ti(Oi-Pr) ₄	CH ₂ Cl ₂	66 ^c	trans	97	CO ₂ Et	1998JOC7306
TBHP	DET, Ti(Oi-Pr) ₄	CH ₂ Cl ₂	53 ^c	trans	99	=C ₆ H ₁₂	2003JOC4087

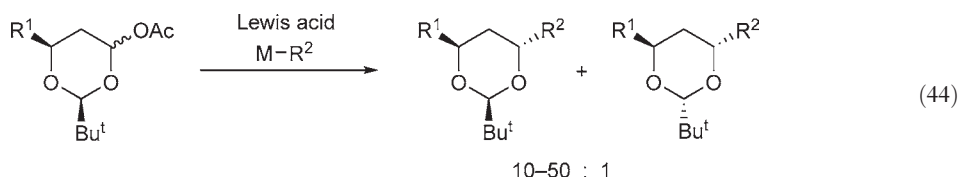
^aFunctional group(s) at C-2.^b10% bis-sulfoxide.^cSome bis-sulfoxide.^dThree of four possible stereoisomers are formed. Ratio of *R-cis*:*S-cis*:*R-trans* is given.^eBis-sulfoxide is the (desired) major product.

Racemic 2-aryl-1,3-oxathianes have been oxidized to chiral, nonracemic sulfoxides using H₂O₂–urea as oxidant and Ti–salen complexes in catalytic amounts. High ee (94% at 41% conversion) was achieved by this method (Equation 43) <2003CH24>.

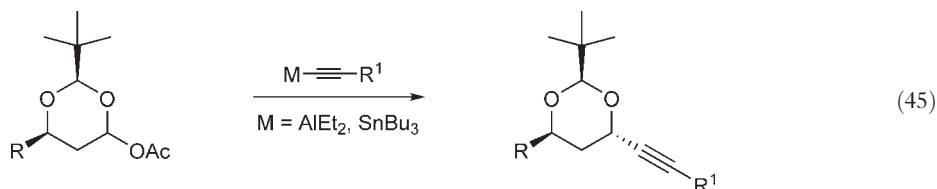


8.11.6.4.3 Reactivity toward nucleophiles

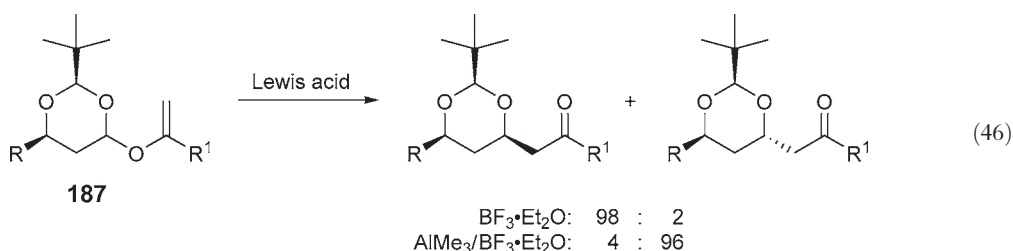
The Lewis acid-catalyzed reaction of 4-acetoxy-1,3-dioxanes with nucleophiles has been reviewed <2001TCC(216)51>. The principles of the reaction are displayed in (Equation 44). The combination of boron trifluoride and organozinc compounds was found to be very efficient <1997JOC6460, 1999JOC2026> but allylsilanes react as well <1996SL536, 1998TL6811>.



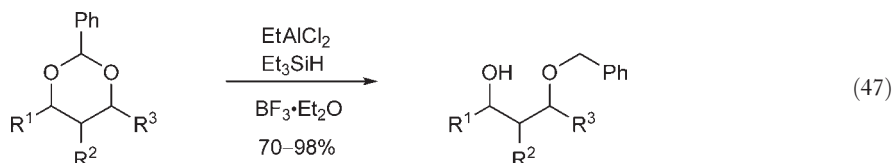
The nucleophilic displacement of the acetoxy group of 4-acetoxy-1,3-dioxanes was also effected by metalated alkynes. Organoaluminium and organotin compounds have been employed <1998TL3103>. The stereochemical outcome is similar to that of the analogous reaction with a high preference for the *anti*-product (Equation 45).

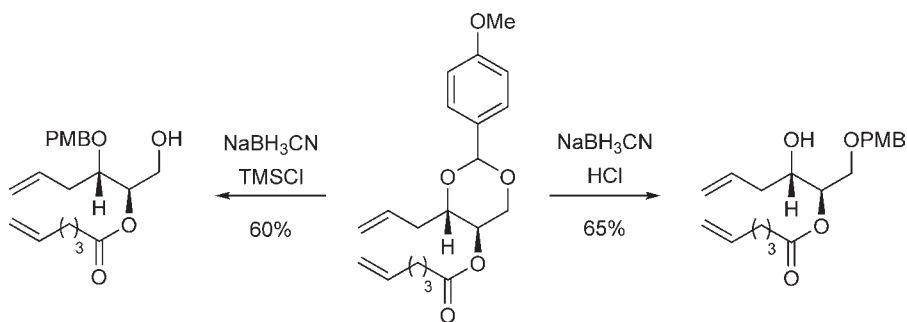


An interesting reversal of the stereochemical outcome has been observed for the nucleophilic acetal displacement using an enol ether as coupling partner. Treatment of **187** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the *syn*-product in 82% yield and 98:2 selectivity, whereas a mixture of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and AlMe_3 gave the *anti*-product in 90% yield and 96:4 selectivity (Equation 46) <2003T8979>.



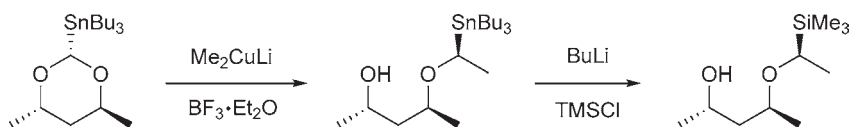
The acetal carbon of 1,3-dioxanes react with nucleophiles in the presence of Lewis acids with ring opening. Hydride transfer to 2-phenyl-1,3-dioxanes was reported to proceed either with boranes <1998T8919> or with a mixture of EtAlCl_2 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and Et_3SiH <2004SL647, 2005TL743> (Equation 47) or with NaBH_3CN . In the latter case, it was observed that regioselective ring opening of unsymmetrically substituted 1,3-dioxanes occurs depending on the acid employed (Scheme 67) <2002ASC657>.





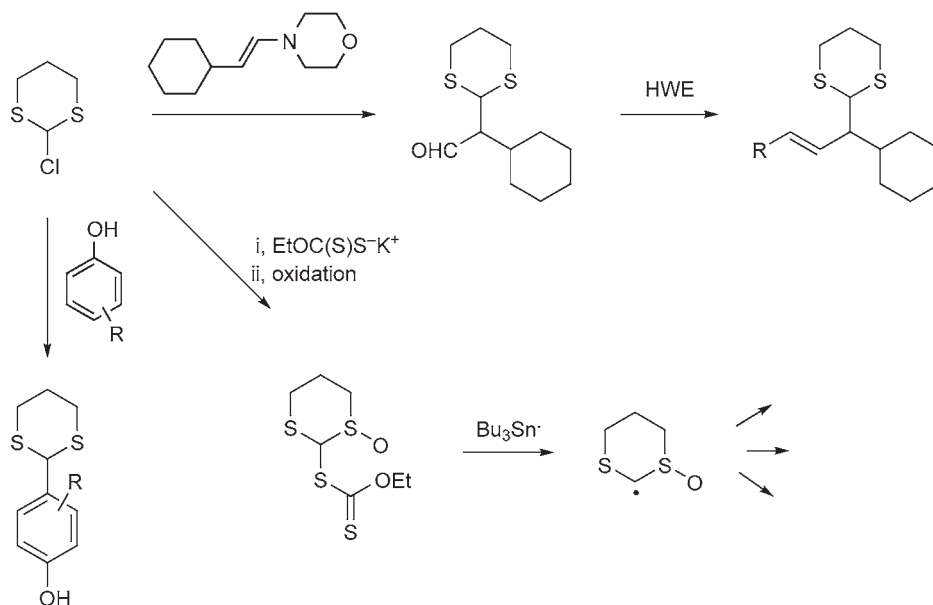
Scheme 67

Cuprates in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ also react with 1,3-dioxanes at the acetal moiety. A transfer of a methyl group to the acetal carbon was obtained, employing Me_2CuLi even in the presence of a tributylstannyl group, which can be subsequently substituted by a trimethylsilyl group (Scheme 68) <1997T7615>.



Scheme 68

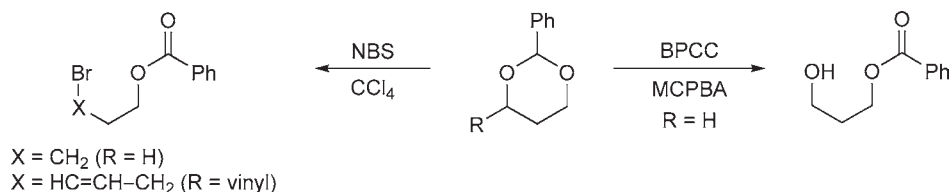
As expected, 2-halo-1,3-dithianes react with nucleophiles under S_N conditions. Suitable nucleophiles are enamines <2002TL9517, 2004T6931> and phenols <1997MOL7>. The reaction with $\text{EtOC}(\text{S})\text{S}^-\text{K}^+$, followed by oxidation, provided a xanthate which generated a 1,3-dithiane 1-oxide radical upon treatment with Bu_3SnH (Scheme 69) <2004T7781>. An efficient one-carbon radical precursor has also been obtained by addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to 2-lithio-1,3-dithiane. The reactivity of this compound has been demonstrated <2005S1389>.



Scheme 69

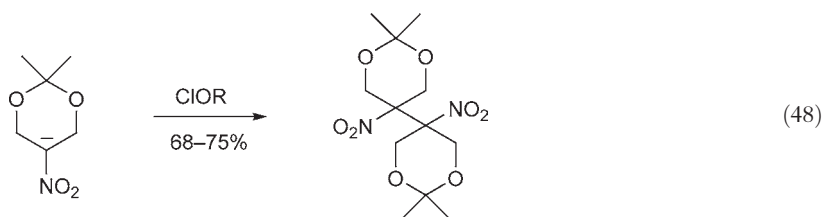
8.11.6.4.4 Reactivity toward radicals and carbenes

2-Phenyl-1,3-dioxanes react with halogen radicals generated from *N*-bromosuccinimide (NBS) to give ring-opening products, such as γ -bromoalkyl benzoates <2005TL2965>. With compounds possessing a vinyl group at C-4, chain elongation results <2004JOC563>. The combination of 2,2'-bipyridinium chlorochromate (BPCC) and *m*-chloroperbenzoic acid (MCPBA) provided γ -hydroxyalkyl benzoates as product (Scheme 70) <1997TL1733>.

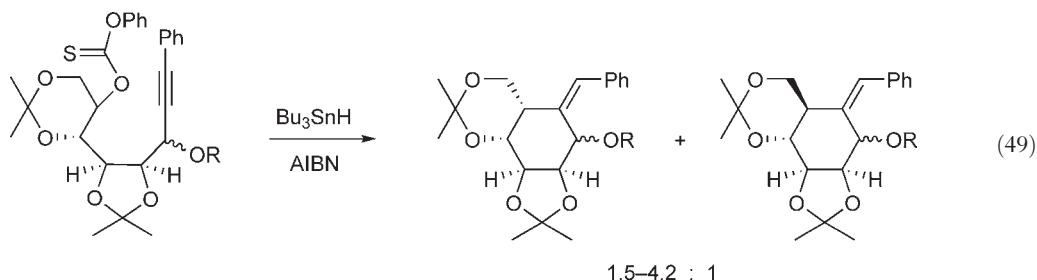


Scheme 70

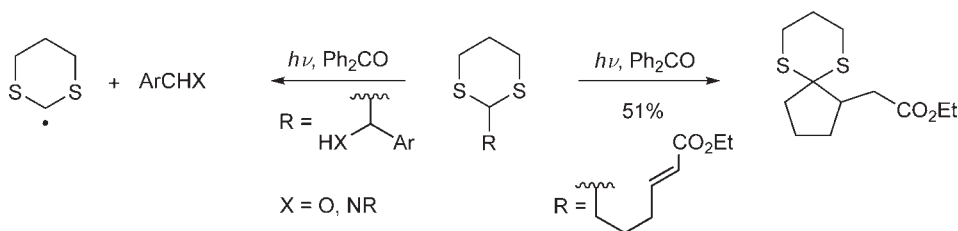
A radical coupling was observed, when the anion of 5-nitro-1,3-dioxane was treated with ClOBu (Equation 48). The dimer was formed in 68–75% yield, depending on the reaction conditions <2000RJO278>.



A radical cyclization has been achieved from a 1,3-dioxolanyl-thiocarbonate containing an alkyne group in an appropriate position (Equation 49) <2003TA2961>. The stereocontrol between *cis*- and *trans*-fused tricycles was 1.5–4.2:1. The products were similar to those depicted in Equation (36).

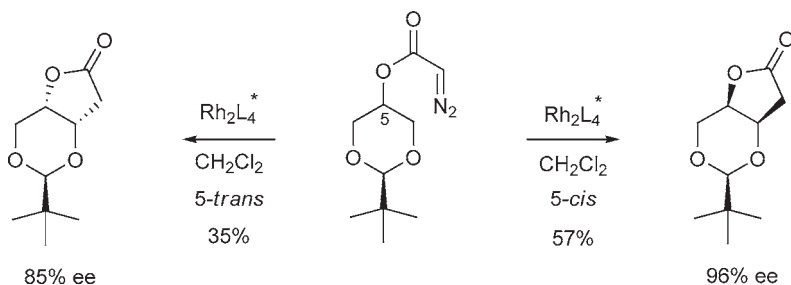


The photoinduced activation of 2-substituted-1,3-dithianes with benzophenone can be used for photocleavage of the C–C bond <2001OL1841, 2004MI20> or for the cyclization if an electron-poor double bond is at an appropriate position (Scheme 71) <1996T9713>.

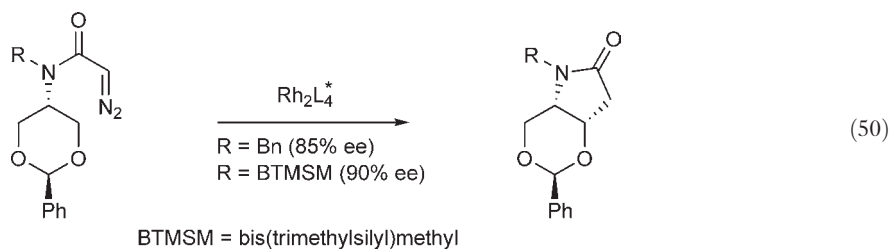


Scheme 71

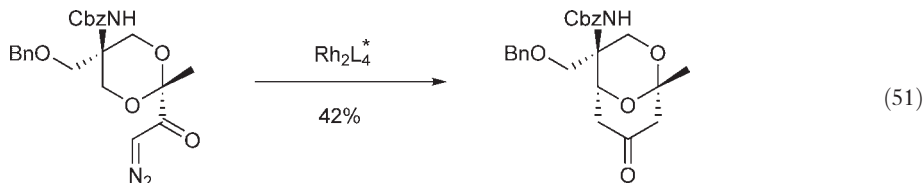
The asymmetric insertion of carbenes into a C–H bond was the key reaction for the construction of bicyclic lactones and amides. Diazoacetic acid esters at C-5 of 1,3-dioxanes have been prepared with *cis*- and *trans*-configuration. In both cases, using Doyle's chiral rhodium catalysts, the carbene insertion gave the lactones in 96% ee and 85% ee, respectively, although the yields are modest (Scheme 72) <1999JOC8907>. The analogous diazoacetamides react similarly, providing the bicyclic amides with up to 90% ee and in 95% yield (Equation 50) <2002ASC91, 2003OL407>.



Scheme 72



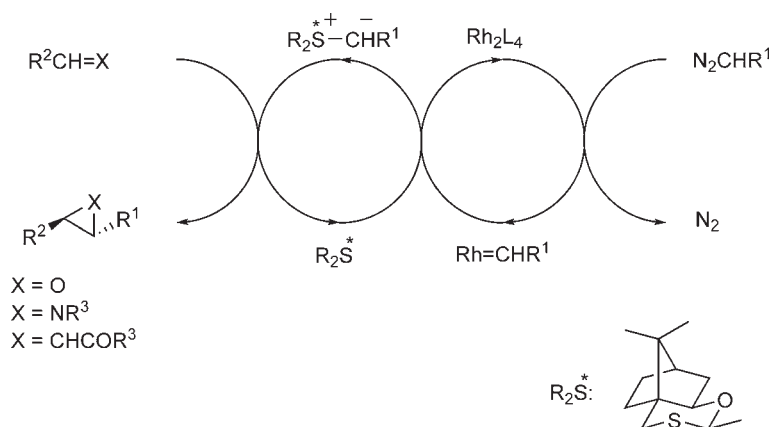
A similar desymmetrization approach was applied to the synthesis of bridged bicyclic systems. Reaction of 2-diazoacetyl-1,3-dioxane in the presence of a chiral rhodium catalyst allow the construction of the bicycle in 27–54% yield, but poor ee (4–12%) (Equation 51) <2003TA929>.



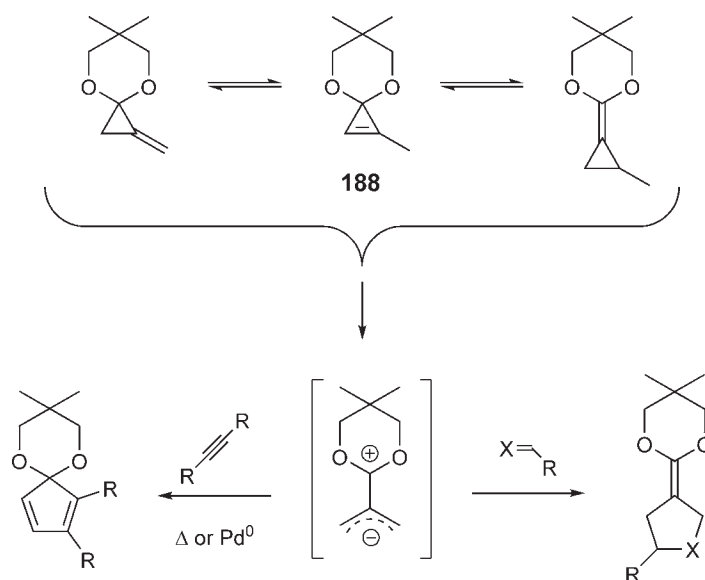
The chemistry of chiral 1,3-oxathianes has been reviewed <2004SOS(27)21>. These compounds have been widely used in catalytic asymmetric cycloaddition reactions such as epoxidation of carbonyl groups <1996JA7004, 2001J(P1)2604>, aziridination of imines <1996JOC8368, 1997PS(120/1)361, 2001J(P1)1635>, and cyclopropanation of alkenes <1997CC1785, 2000J(P1)3267>. The principal chirality transfer is dedicated to the formation of a sulfur ylide, generated by the reaction of the chiral 1,3-oxathiane with a rhodium carbene. This metalcarbene was formed in a second cyclic process from rhodium acetate and a diazo compound (Scheme 73). Some mechanistic details <1998JA8328> and calculations <1999JOC4596> have been reported. Interestingly, generation of the carbene from geminal dihaloalkane gave poor ee <2002EJO319>.

8.11.6.4.5 Cyclic transition state reactions

Examples of cyclic transition state reactions with saturated 1,3-heterocycles are obviously rare. One example is the generation and reaction of dipolar trimethylenemethanes from spirocompound **188**, which has been reviewed <2002ACR867>. The dipolar trimethylenemethanes react with imines <1999CL879>, oximes <1998JOC1694>, electron-deficient <1998EJO257, 2000CL664> and electron-donating alkenes <2001SL1030>, and alkynes <2004OL3569> (Scheme 74). 1,3-Dithiane analogs react similarly <1999OL7>.

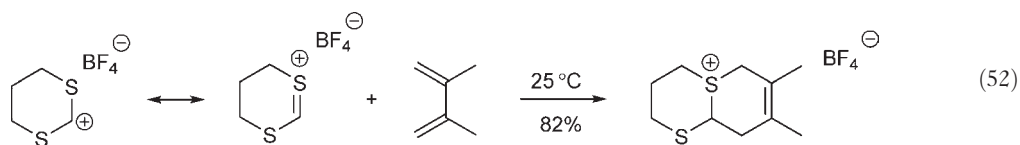


Scheme 73

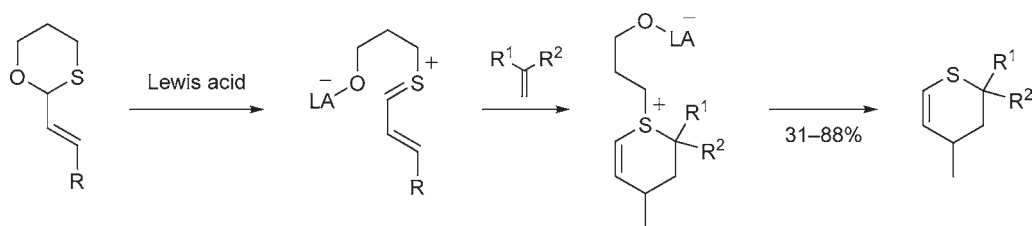


Scheme 74

1,3-Dithianylium ions react with dienes, for example 2,3-dimethylbutadiene, without a catalyst to give the Diels–Alder adduct in 82% yield [<1998EJO1919>](#) (Equation 52).



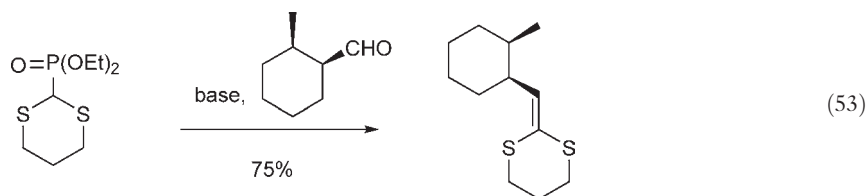
A [4+2] cycloaddition was the key step in the synthesis of substituted dihydrothiopyrans from 2-alkenyl-1,3-oxathianes and an alkene. The reaction was mediated by a Lewis acid. It is assumed that the Lewis acid attacks the oxygen of the heterocycle which upon ring opening gives the highly reactive cationic heterodiene which reacts with alkenes to the thiopyrans in 31–88% yield (Scheme 75) [<2000TL371>](#).



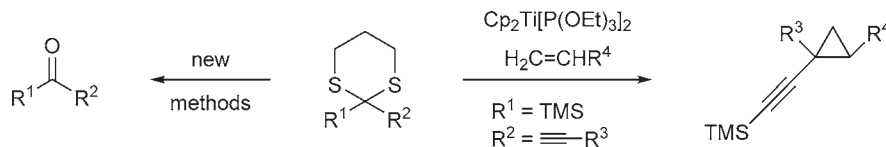
Scheme 75

8.11.6.4.6 Miscellaneous reactions

2-Alkylidene-1,3-dithianes, acting as acyl synthons, can be prepared by the HWE reaction of 2-phosphorylated 1,3-dithianes with aldehydes (Equation 53) <1996SL875, 1997BSF891, 1998TL5425, 2002JOC1746>.

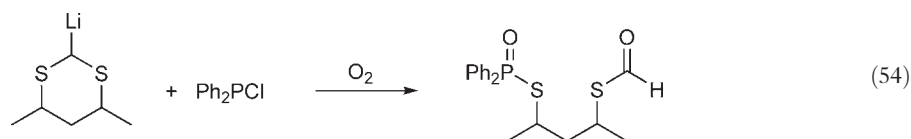


The chemistry of acylsilanes conveniently prepared by cleavage of the corresponding 2-silyl-1,3-dithianes <2000JOM(603)220> has been reviewed <2002SOS(4)513>. Additionally, some new methods for the general cleavage of 1,3-dithianes have been developed, such as HIO₄ <1996TL4331>, Ag⁺/I₂ <1997H(44)393>, and 2-iodoxybenzoic acid (IBX) <2004JA5192>. 1,3-Oxathianes have been cleaved in high yields (82–93%) using *N,N'*-dibromo-*N,N'*-1,2-ethanediybis(*p*-toluenesulfonamide) (BNBTS) <2004PS1787>. Dethiation with Cp₂Ti[P(OEt)₃]₂ gave the titanium carbenes which react with alkenes to cyclopropanes (Scheme 76) <2004OL3207>.

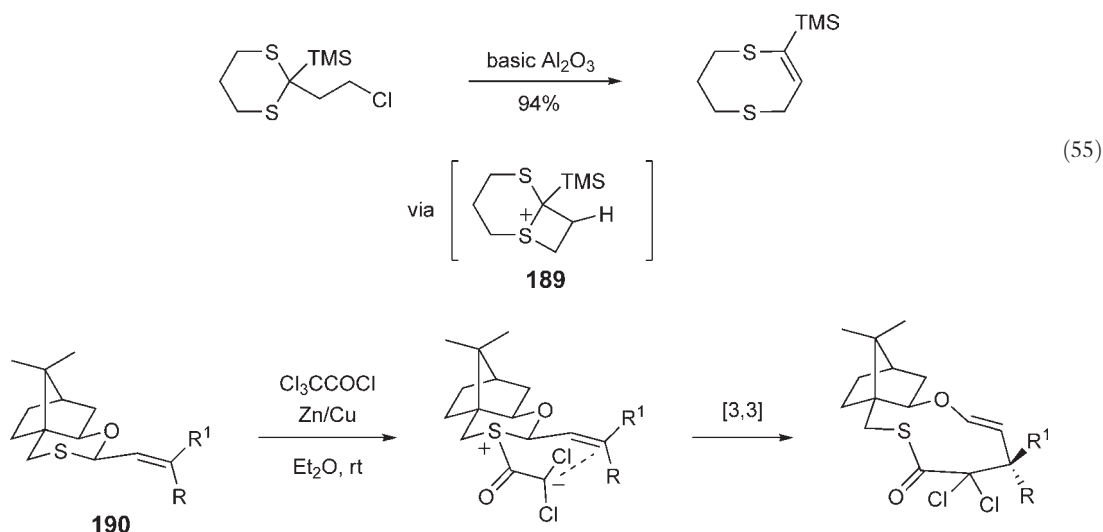


Scheme 76

The reaction of 2-lithio-1,3-dithiane with chlorodiphenylphosphine under oxidative conditions furnished an open-chain reaction product with a formyl thioester and a thiophosphinate moiety (Equation 54) <2003TL5293>.



A ring expansion was observed, when 2-chloroethyl-2-trimethylsilyl-1,3-dithiane was treated with basic Al₂O₃ probably via bicycle **189**. The yield of the eight-membered ring was 94% (Equation 55) <2001TL7779>. In a similar manner, oxathianes, such as **190**, react with dichloroketene (from Cl₃CCOCl and Zn/Cu), affording a 10-membered ring in good yield by [3,3]-rearrangement (Scheme 77) <2002CC2534>.



Scheme 77

Some modified chiral 1,3-oxathianes, based on camphor or pulegone, have been used as ligands for asymmetric Pauson–Khand reactions [<2000JA10242, 2004JOC8053, 2005JA13629>](#), allylic alkylations [<2001JOC620, 2003CC524, 2005TA2551>](#), or Diels–Alder reactions [<2002JOC5011>](#) ([Figure 9](#)). A polymer-bonded 1,3-oxathiane ligand was also developed [<2005TA609>](#) as well as chiral 1,3-oxathianes from terpenes [<2000TL4615>](#) or sugars [<2003TA2361>](#).

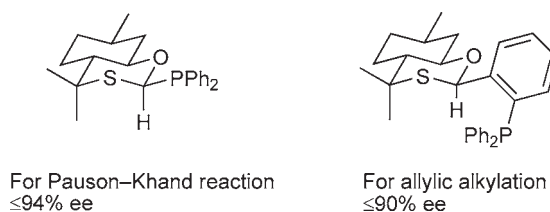
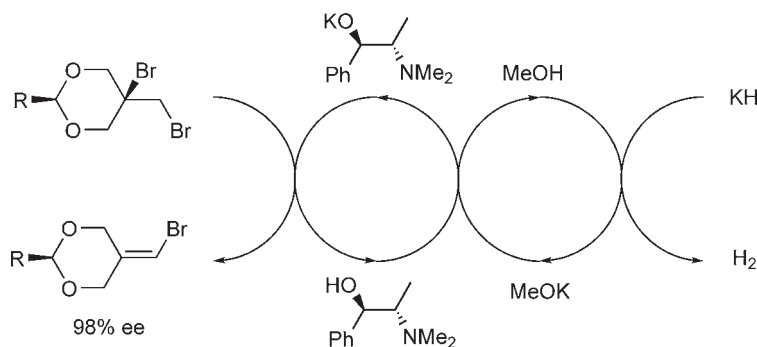


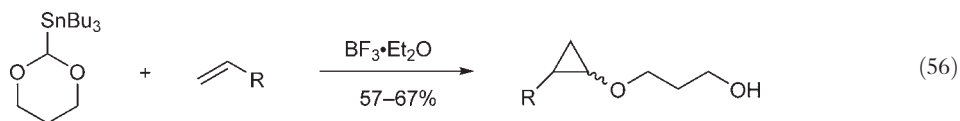
Figure 9 1,3-Oxathiane ligands for asymmetric catalysis.

2-Alkyl-5-alkylidene-1,3-dioxanes, unsymmetrically substituted at the double bond, possess a chiral axis. They have been synthesized in optically active form by asymmetric dehydrohalogenation using catalytic amounts of a chiral base. Regeneration of the chiral base by MeOK occurs in a second catalytic cycle with KH as the stoichiometric component ([Scheme 78](#)). The enantiomeric purity of the axial-chiral 1,3-dioxane was 98% [<1996JA12483, 1998JOC5541, 1999SL960>](#). Chiral ionic liquids have been prepared by this method [<2005TL1137>](#).



Scheme 78

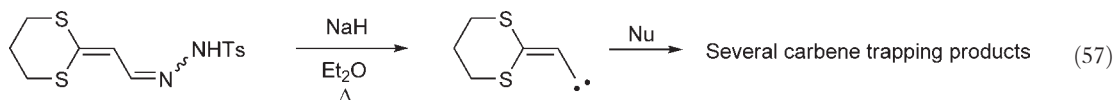
Ring opening of 2-tributylstannyl-1,3-dioxane in the presence of alkenes using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave cyclopropanes in 57–67% yield. The reaction was nonselective, affording *cis/trans*-mixtures of the cyclopropanes (Equation 56) <1998SL1057>.



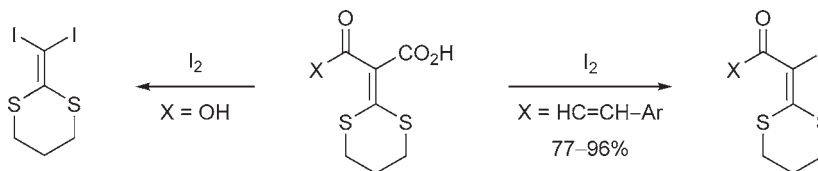
8.11.7 Reactivity of Substituents Attached to Ring Carbon Atoms

The major application of 1,3-heterocycles discussed herein is their function as protecting groups. It is obvious that numerous reactions at the side chain have been carried out in the presence of the heterocycles. The focus in this section is (1) transformations close to the heterocycle, one to two atoms away; (2) interesting (though this is somewhat subjective) reaction at longer distances; and (3) transformations in the side chain influenced by the heterocycle.

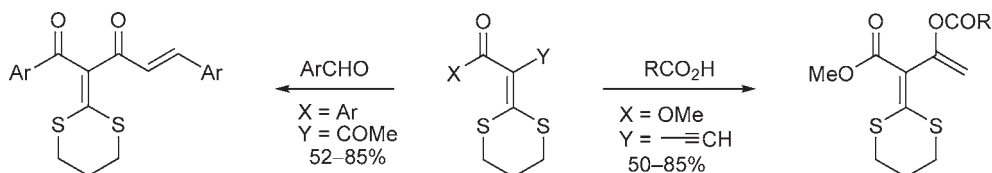
The chemistry of 1,3-dithian-2-ylidene ethyl carbene has been studied. This carbene was prepared by the reaction of the parent hydrazone with NaH (Equation 57). It reacted with nucleophiles *in situ* to give a variety of trapping products <1996J(P1)2773>.



1,3-Dithian-2-ylidene derivatives of β -oxoesters react with iodine with decarboxylation to give mono- or diiodomethylene-1,3-dithianes in excellent yields (77–96%) (Scheme 79) <2002SC3437, 2004SC463>. When an acetyl group was attached to the double bond of such compounds, condensation can be carried out efficiently (52–85% yield) <1999CCL5>. Condensations leading to cyclic products have been reported as well <1996CCL95>. An alkyne in place of the β -oxo group was smoothly transformed to enol esters by various acids (50–85% yield, Scheme 80) <2006SL231>.

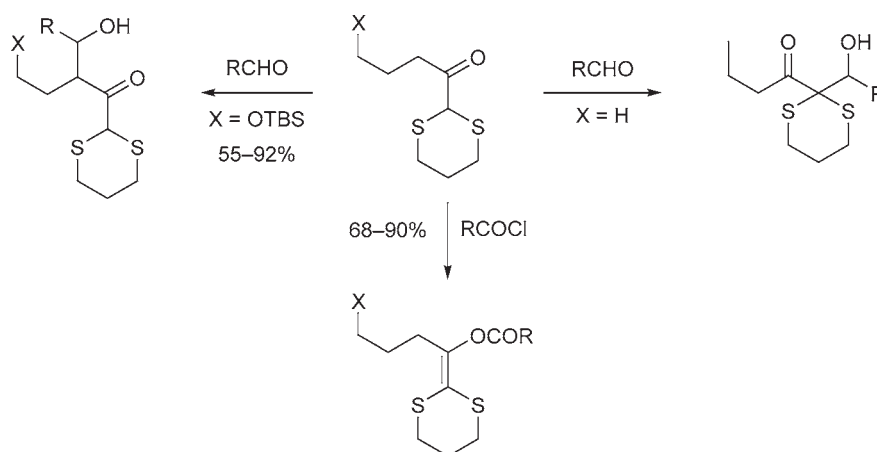


Scheme 79



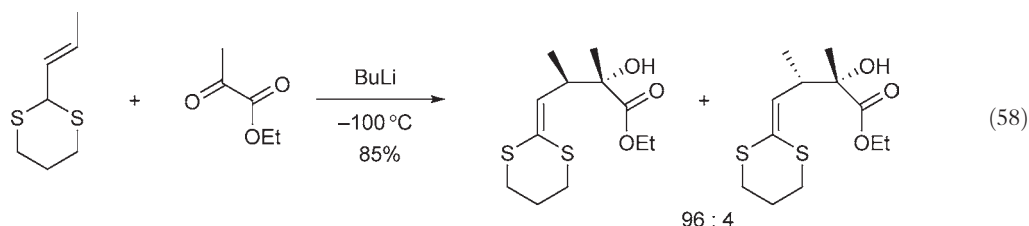
Scheme 80

An unexpected reactivity in the functionalization of 2-acyl-1,3-dithianes has been reported by Mioskowski and co-workers. They found that 2-acyl-1,3-dithianes with no further heteroatom at the acyl side chain react with aldehydes to give 2-acyl-2-hydroxyalkyl-1,3-dithianes, whereas a silyl-protected hydroxy group in the side chain of the 2-acyl-1,3-dithiane led to formation of the aldol product at the opposite site of the carbonyl group. Acyl chlorides always react with 2-acyl-1,3-dithianes to give the enol esters (Scheme 81) <2003TL213>.

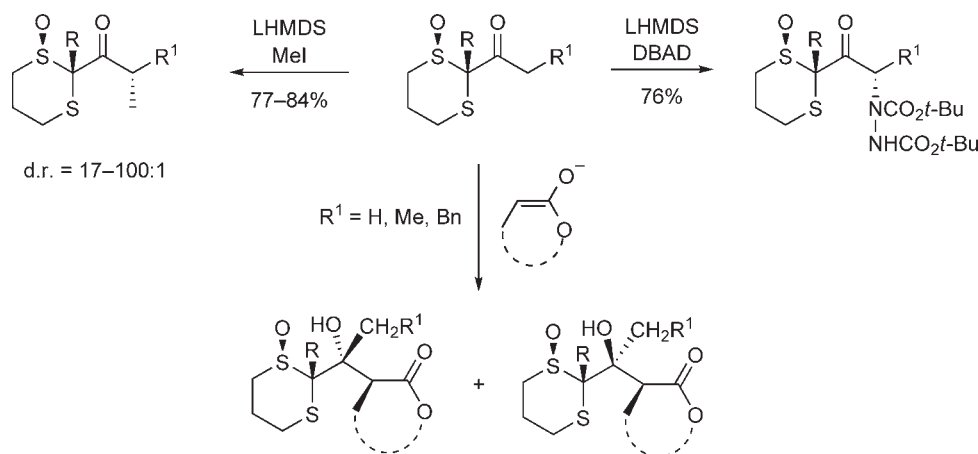


Scheme 81

Lithiation of 2-propenyl-1,3-dithiane generates an allylic anion which reacts with active ketones at the side-chain carbon. The reaction was highly diastereoselective (96:4) and the product was obtained in 85% yield (Equation 58) <1996JOC1473>.

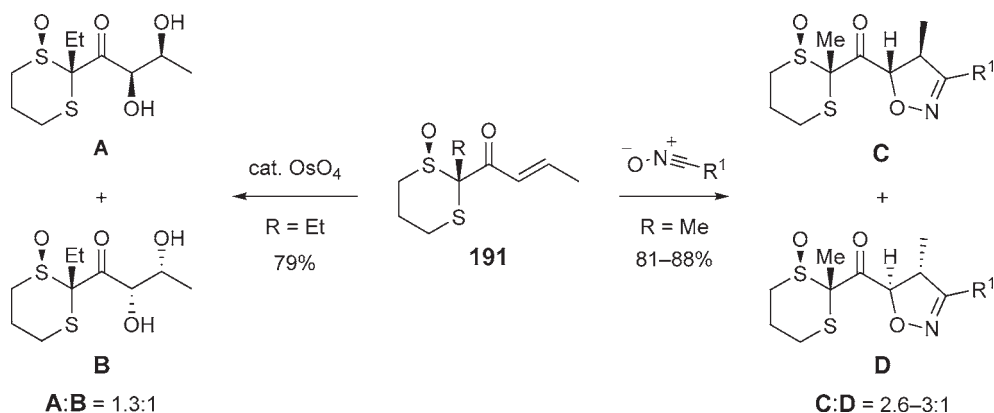


The chemistry of chiral 1,3-dithiane 1-oxides, in particular their use as chiral auxiliaries, has been reviewed <1998OPP145>. Some further developments in this field are the stereoselective α -alkylation with alkyl halides <1997T13149> or α -hydrazination with di-*tert*-butyl azodicarboxylate (DBAD) <2000T9683>. The carbonyl group of 2-acyl-1,3-dithiane 1-oxides was also used as an electrophile (Scheme 82). Interestingly, acyclic enolates react with these substrates to give a 95:5 mixture of *anti*- and *syn*-adduct, whereas cyclic enolates produce a mixture of *anti*- and *syn*-adduct in 8:92 ratio <2000JOC6027>.



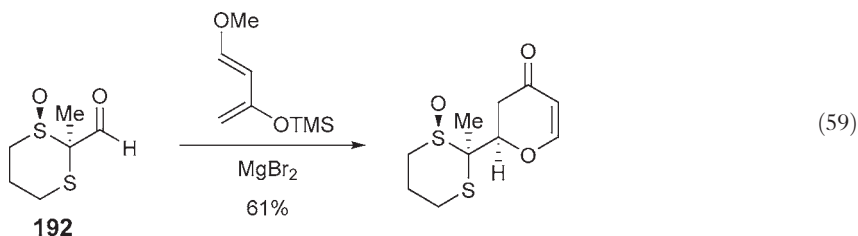
Scheme 82

The double bond of enone **191** was dihydroxylated under well-established reaction conditions but with low diastereoselectivity <1998T14581>. Analogously, enone **191** reacted with nitrile oxides in the presence of ZnCl_2 to give the dipolar cycloaddition products. Again the diastereoselectivity was low (Scheme 83) <1997T1061>. Somewhat higher yields have been achieved upon addition of Lewis acids <1997T7365>.

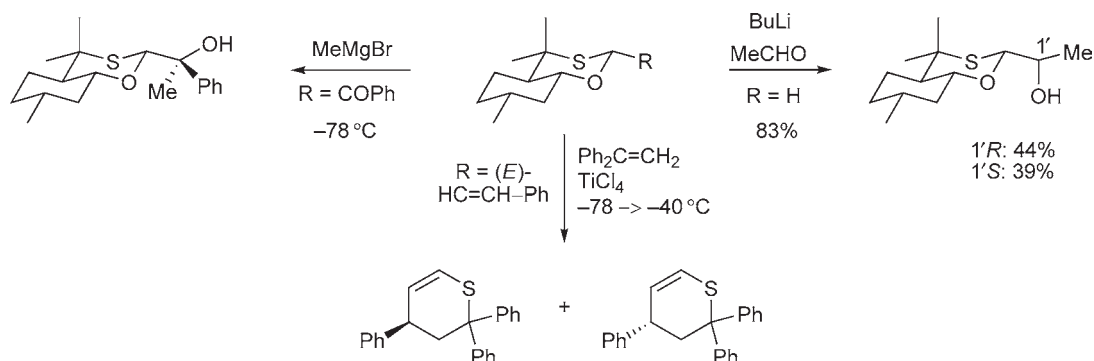


Scheme 83

ZnCl_2 was also used for a hetero-Diels–Alder reaction of **192** with Danishefsky diene. The dihydropyranone was obtained in 61% yield and good diastereoselectivity (Equation 59) <1998T14573>.

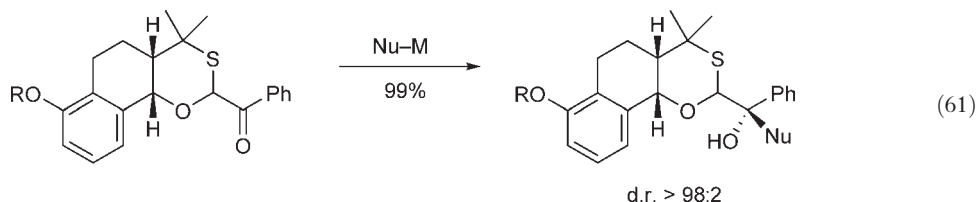
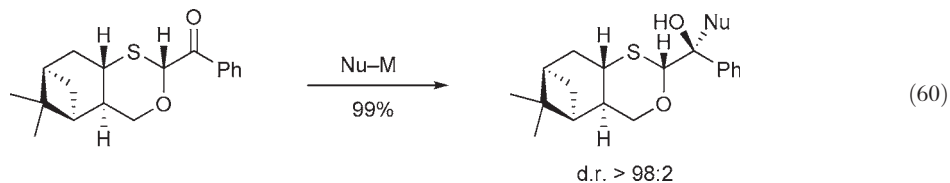


Eliel's oxathiane auxiliary was used for stereoselective transformations and has been reviewed in part <2003H(60)1477>. As expected, reaction of the lithiated auxiliary with acetaldehyde gave the addition product with low stereoselectivity at the side-chain stereocenter <1997M201>. Better stereocontrol was observed, when methyl Grignard reagent was added to 2-acyl-1,3-oxathiane <2000JCCS63>. Reaction of 2-vinyl-1,3-oxathiane with 1,1-diphenylethene, mediated by TiCl_4 , afforded dihydrothiopyrans in 82% yield, albeit with low enantioselectivity (Scheme 84) <2003T1859>.

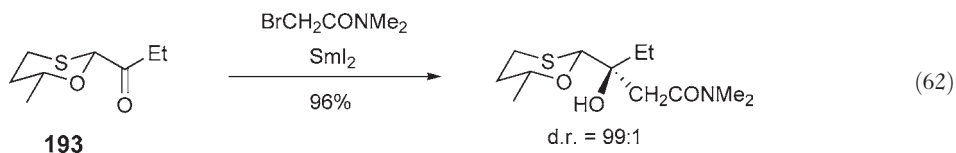


Scheme 84

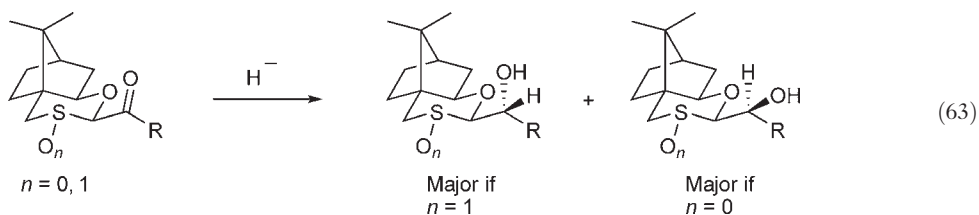
New chiral auxiliaries for nucleophilic reactions have been prepared from 5-hydroxy-1-tetralone <2001TA2605> and myrtenal <2001TA3095> and their use in diastereoselective reactions has been evaluated. It was found that both the tetralone- <2003EJO337, 2003JOC6619> and the myrtenal- <2003TA3225, 2005TA1837> derived 2-acyl-1,3-oxathianes reacted diastereoselectively with nucleophiles (Equations 60 and 61).



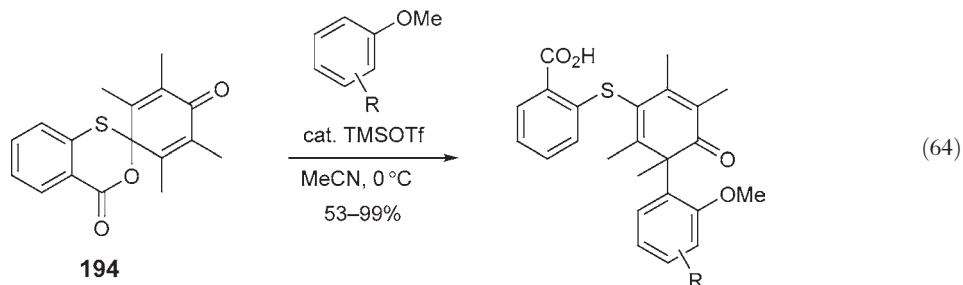
Interestingly, even the simple 2-acyl-1,3-oxathiane **193** containing just a methyl group at C-6 reacts with *N,N*-dimethylbromoacetamide/*SmI*₂ to give the addition product in excellent yield (96%) and diastereoselectivity (99:1) (Equation 62) <2003CH38>.



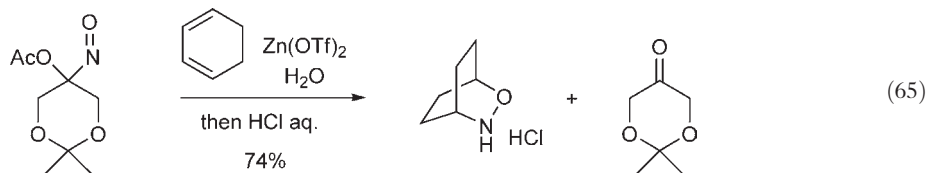
A reversal of the stereochemical outcome of the reduction of 2-acyl-1,3-oxathianes was demonstrated when the 1,3-oxathiane 3-oxide instead of 1,3-oxathiane was treated with chelating reducing agents, such as L-selectride (Equation 63) <1998BKC911>.



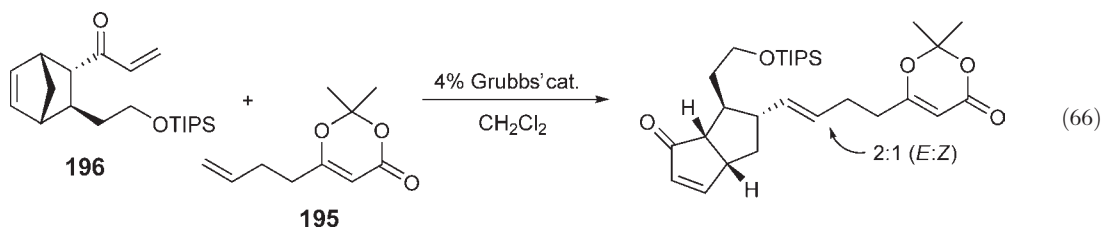
Electron-rich arenes react with quinone monoacetal **194** at the carbon α to the quinone carbonyl group with ring opening of the heterocycle. The reaction was mediated by catalytic amounts of TMSOTf furnishing the aryl addition products in good to excellent yields (53–99%) (Equation 64) <2001CPB1658>.



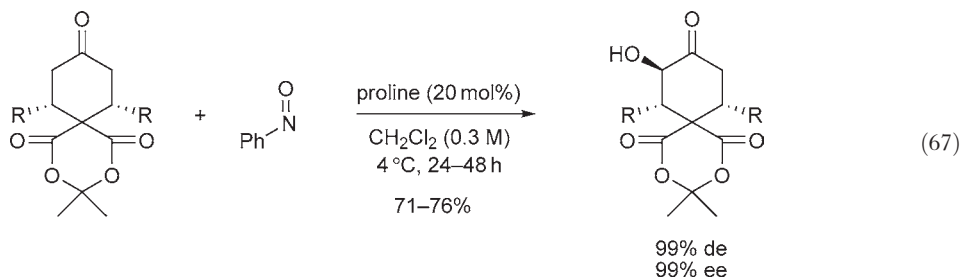
A nitroso Diels–Alder cycloaddition of 5-acetoxy-5-nitroso-1,3-dioxanes was reported to proceed efficiently with $\text{Zn}(\text{OTf})_2$ as Lewis acid. The intermediates were directly hydrolyzed using aqueous HCl. Careful hydrolysis provided 1,2-oxazines and 5-oxo-1,3-dioxane, otherwise dihydroxyacetone was obtained (Equation 65) <2004OL2449, 2005OBC4395>.



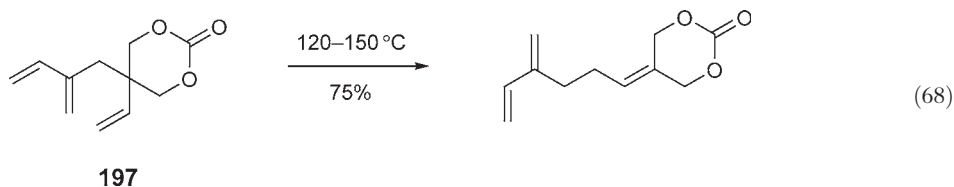
1,3-Dioxinones are typically used as protected β -ketoacids. They have been applied to several natural product syntheses. An interesting reaction involving such a β -ketoacid synthon was the tandem ROM–RCM–CM of dioxinone **195** with bicycle **196** (ROM = ring-opening metathesis; CM = cross metathesis). The product was formed in 59% as a 2:1 mixture of the (*E*)- and the (*Z*)-isomer, separable by chromatography (Equation 66) <2006JA1094>. Interestingly, the double bond of the dioxinone moiety was not involved in any part of the domino metathesis reaction and remained unchanged whereas the terminal enone reacted in the CM.



An organocatalytic asymmetric hydroxylation was developed using spiro-Meldrum's acid derivatives, 20 mol% proline, and nitrosobenzene. In fact, the heterocyclic moiety was necessary for a high-yielding asymmetric induction (Equation 67) <2005OL1577, 2006OBC2685>.



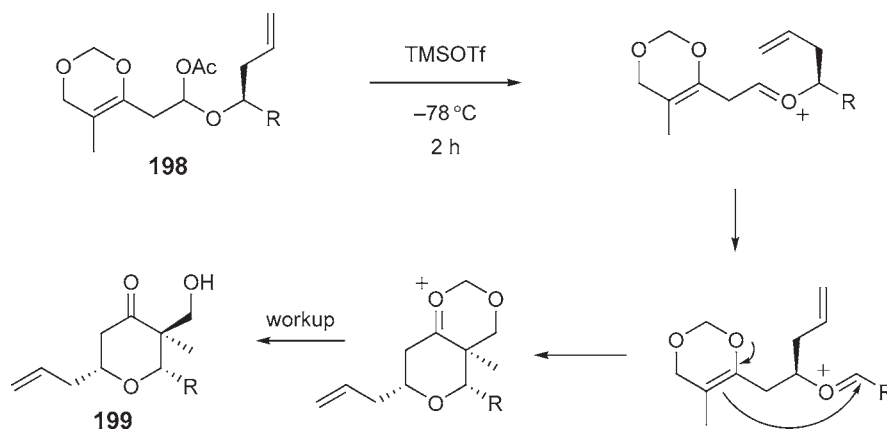
A 5-allyl-5-vinyl-substituted 1,3-dioxan-2-one was used for a Cope rearrangement. Thermal treatment of **197** at 120–150 °C gave 5-alkylidene-1,3-dioxan-2-one in 75% yield (Equation 68) <2001JOC4447>.



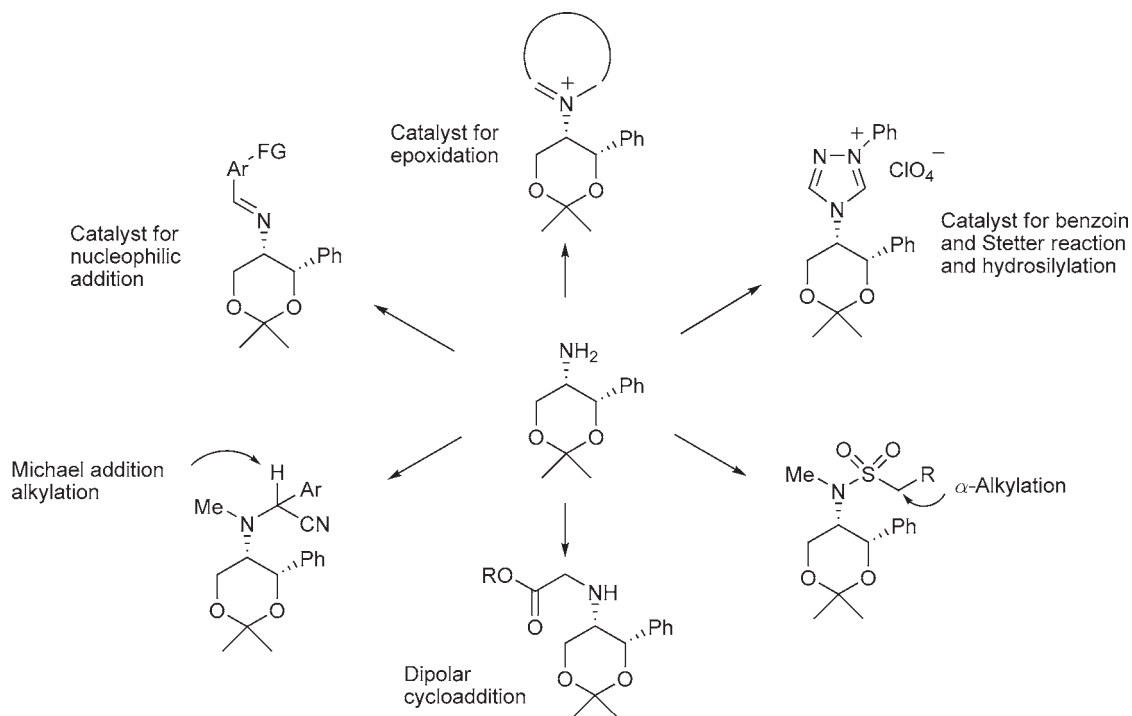
An example of an oxonia-Cope Prins cascade involving a dioxin moiety was reported by Dalgard and Rychnovsky. Treatment of compound **198** with Lewis acids allows the cascade to proceed to give tetrahydropyranone **199** as final product (Scheme 85) <2005OL1589>.

The chiral and commercially available 5-amino-4-phenyl-1,3-dioxane is the key compound for several asymmetric reactions. Manipulation of the amino functional group gave either catalysts or chiral auxiliaries. Catalytic asymmetric reactions based on 5-amino-4-phenyl-1,3-dioxanes are epoxidation <2001JOC6926, 2002SL580>, nucleophilic additions with diethylzinc <1997TA1253, 1998SL965>, benzoin reaction <1996HCA1217, 2003TA3827>, Stetter reaction <1996HCA1899>, hydrosilylation <1997TA3571>, and pinacol coupling of aromatic aldehydes (Scheme 86)

<2000TA3861>. Several 1,3-dioxanes, differently substituted at the 5-iminium moiety, have been prepared from 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane and applied to the catalytic asymmetric epoxidation <2006EJO803>. The epoxidation was conducted either with Oxone <2004OL1543, 2006T6607> or with tetraphenylphosphonium monopersulfate (TPPP) <2004JOC3595, 2005OL375> as oxidant. In addition, it was found that the counterion plays an important role in the asymmetric induction and noncoordinating anions gave higher ee <2002TL8257, 2005JOC5903, 2006TL5297>. The use of 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane as chiral auxiliary was demonstrated in dipolar cycloadditions <1998T10733> and in α -alkylation/Michael reactions of aminonitriles <1997BSF809, 1998EJO63, 1999J(P1)1617> and sulfonamides. In the latter case, the phenyl group was not effective with respect to the diastereoselectivity. Instead, a biphenyl group was used <1998HCA1329, 2002HCA3657>. *N*-Benzyl-substituted or *N*-polymer-bonded 5-amino-4-phenyl-1,3-dioxanes have been further used for the asymmetric deprotonation of (*meso*)ketones. The yields for the subsequent alkylation reactions were in the range of 64–74%. The ee was 51–65% in solution <2002T4567> and 66% for the polymer-bonded derivative <1999TL8755>. Though the majority of ligands or auxiliaries discussed above refer to the commercially available dimethylacetal, other acetals have been prepared and used as ligands as well <1997T1909>.

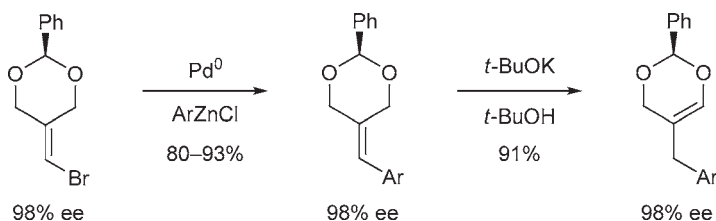


Scheme 85



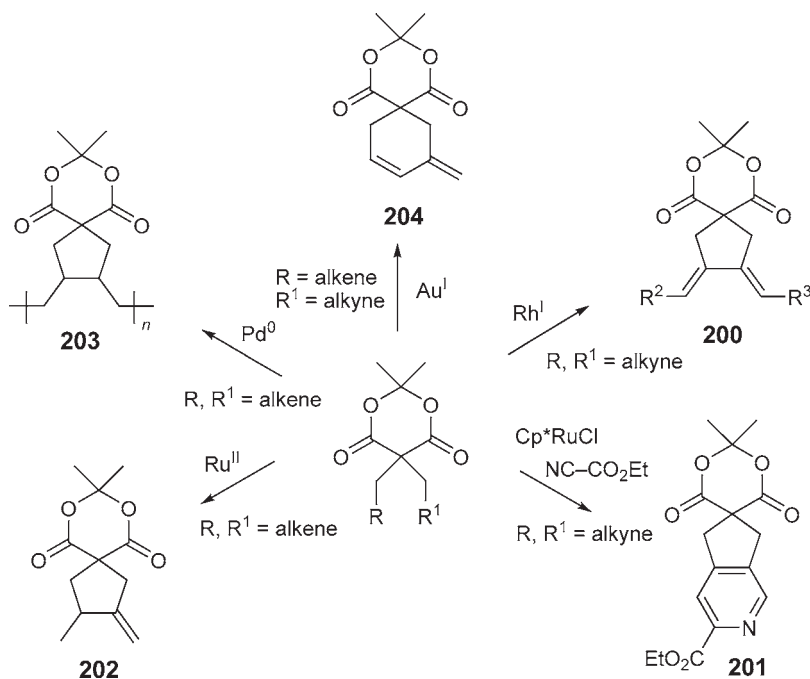
Scheme 86

The optically active, axially chiral 5-alkylidene-2-aryl-1,3-dioxanes, discussed in Section 8.11.6.4.6, were submitted to a Negishi coupling followed by a base-catalyzed isomerization of the double bond. Both reactions proceed with complete retention of the configuration, allowing the preparation of the chiral 1,3-dioxin with no loss of enantiomeric purity (Scheme 87) <1998TA1657>.



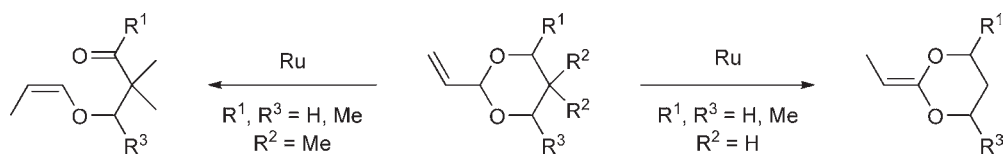
Scheme 87

5,5-disubstituted Meldrum's acids having an allyl or a propargyl group in each of the substituents were subjected to several transition metal-catalyzed cyclizations. Bis-alkynes gave with $\text{Rh}^{\text{I}}/\text{H}_2$ the spirobicyclic **200** <2004JA7875>, whereas Cp^*RuCl afforded with the same substrate pyridine **201** via a [2+2+2] reaction with ethyl cyanoformate <2005JA605>. The $\text{Ru}(\text{II})$ -catalyzed cyclization of bis-allyl Meldrum's acids provide access to cyclopentane **202** <2006CC988>. The same substrates gave polymer **203** when treated with $\text{Pd}(0)$ BARF complexes <2006JA3510>. A mixed double/triple-bond 5,5-disubstituted Meldrum's acid reacted with $\text{Au}(\text{I})$ complexes to give compound **204** having a six-membered ring (Scheme 88) <2006AGE1105>.



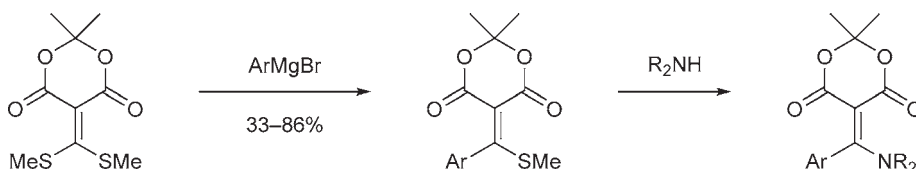
Scheme 88

An interesting case of ruthenium-catalyzed isomerization versus ring opening of differently substituted 2-vinyl-1,3-dioxanes has been reported. It was found that 5,5-dialkyl-substituted dioxanes gave the ring-opened enol ethers and 5,5-unsubstituted dioxanes afforded the (expected) 2-alkylidene-1,3-dioxanes (Scheme 89) <1996PJC1087>.



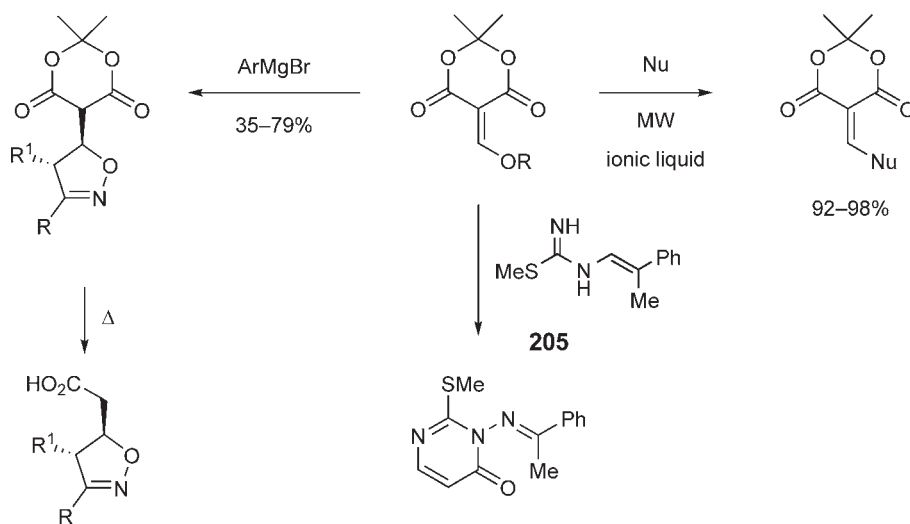
Scheme 89

The nucleophilic vinylic substitution (S_NV) of heteroatom-substituted alkylidene Meldrum's acids has been intensively studied and kinetics of the reaction [<1998JOC6266, 1999CJC584, 2004JOC9248>](#) as well as synthetic applications have been reported [<1997S567, 2002JHC15, 2005EJO4870>](#) (cf. Section 8.11.4.2, [Scheme 10](#)). The preparation of the substrates and a sample application is shown in [Scheme 90](#) [<2001J\(P2\)1534>](#).



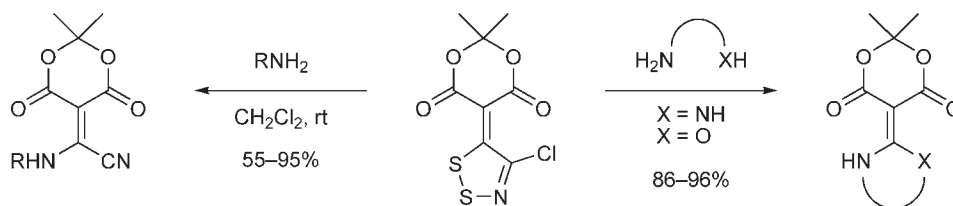
Scheme 90

5-(1'-Alkoxy)alkylidene Meldrum's acids readily react with a variety of nucleophiles using ionic liquids as solvents and microwave irradiation for activation. The S_NV reactions are finished within minutes and the yields were almost quantitative (92–98%) [<2006SC1479>](#). With N-nucleophiles, such as compound [205](#), S_NV reaction and ring opening occur, affording pyrimidones in reasonable yields [<2003SC927>](#). Interestingly, when enolizable oximes were deprotonated with BuLi and subsequently reacted with 5-(1'-methoxy)alkylidene Meldrum's acid, double nucleophilic attack to the exocyclic double bond via S_NV and Michael addition results. The Meldrum's acid moiety of the intermediates was fragmented upon heating in DMF, providing *trans*-isoxazolines in good yield (35–79%) ([Scheme 91](#)) [<1997SC2733>](#).



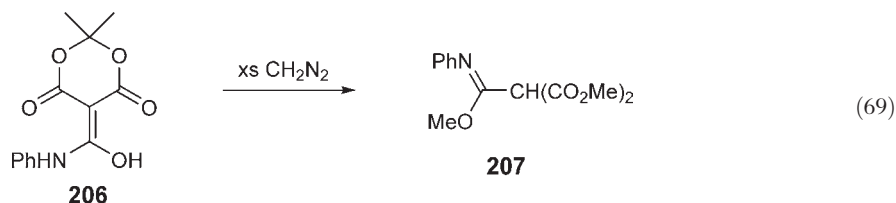
Scheme 91

1,2,3-Dithiazol-5-ylidene Meldrum's acid reacted with N-nucleophiles differently than described in [Scheme 90](#). Monodentate primary amine produced the aminonitrile, and bidentate diamines or amino alcohols gave rise to the formation of cyclic reaction products, as depicted in [Scheme 92](#) [<2000J\(P1\)3107>](#). When RNH_2 is an aromatic amine, the subsequent coupling products rearrange at temperatures above 200 °C to give 4-quinolones in 38–91% yield [<2000TL1943>](#) (cf. Section 8.11.6.1.2).

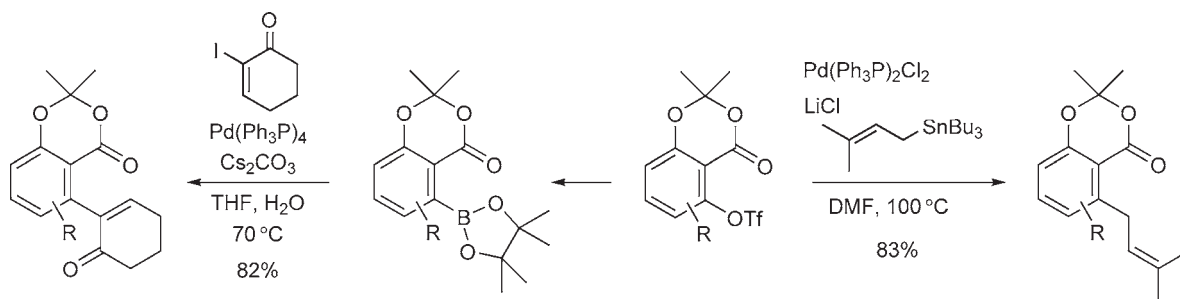


Scheme 92

Unexpected reaction products were obtained when compound **206** was treated with diazomethane. After initial methylation of the enol, ring opening and isomerization of the secondary amine to the imine follows, furnishing compound **207** in good yield (Equation 69) <2002JOC6971>.



Hydroxy acids have been protected as acetals which are 1,3-dioxan-4-ones. Numerous examples of such dioxanones were reported, and they have been widely used in synthetic organic chemistry. In particular, dioxanone triflates prepared from 2,4,6-trihydroxybenzoic acid or analogs were used for several transition metal-catalyzed cross-couplings. A Suzuki coupling <2006EJO1678> and a Stille coupling <2005JOC3686> provide illustrations of this principle (Scheme 93).

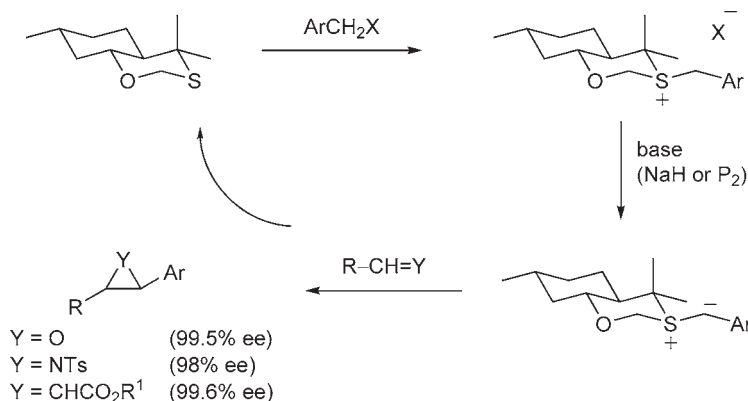


Scheme 93

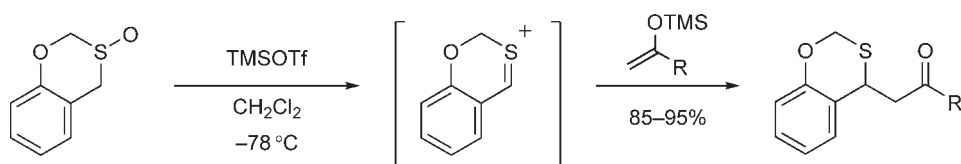
8.11.8 Reactivity of Substituents Attached to Ring Heteroatoms

There are no examples of reactions of substituents attached to ring oxygen atoms. The chemistry of side-chain atoms attached to the ring heteroatom is mainly attributed to the sulfur atom of chiral 1,3-oxathianes. Solladié-Cavallo *et al.* found that these substrates can be easily alkylated with various benzyl halides at the sulfur atom. The resulting sulfonium salts can be deprotonated using NaH <1996TA1783> or a phosphazene base, such as 'P₂' <2000EJO1077>, to afford the ylides similar to those discussed as catalytic intermediates in Section 8.11.6.4.4. Reaction of these ylides with various $\text{C}=\text{X}$ bonds ($\text{X} = \text{O}$ <2000TL7309, 2004CH196>, NTs <2004JOC1409>, CHR <1998AGE1689>) gave the cycloadducts in good yields and exceptionally high ee's (98–99.6%, Scheme 94).

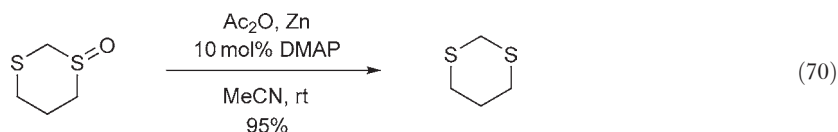
Oxygen at the heterocyclic sulfur atom has been functionalized in two ways: (1) by a TMSOTf-catalyzed Pummerer reaction in the presence of a silyl enol ether (Scheme 95) <1998TL9131> or (2) by reductive removal of the oxygen using $\text{Ac}_2\text{O}/\text{Zn}/\text{cat}$. 4-dimethylaminopyridine (DMAP) <1996SL885>. The formation of 1,3-dithiane from 1,3-dithiane 1-oxide proceeds efficiently in 95% yield (Equation 70).



Scheme 94



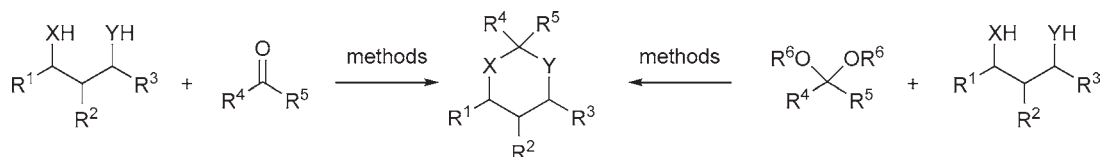
Scheme 95



8.11.9 Ring Syntheses from Acyclic Compounds

8.11.9.1 Condensation of 1,3-Diols and Congeners with Carbonyl Groups

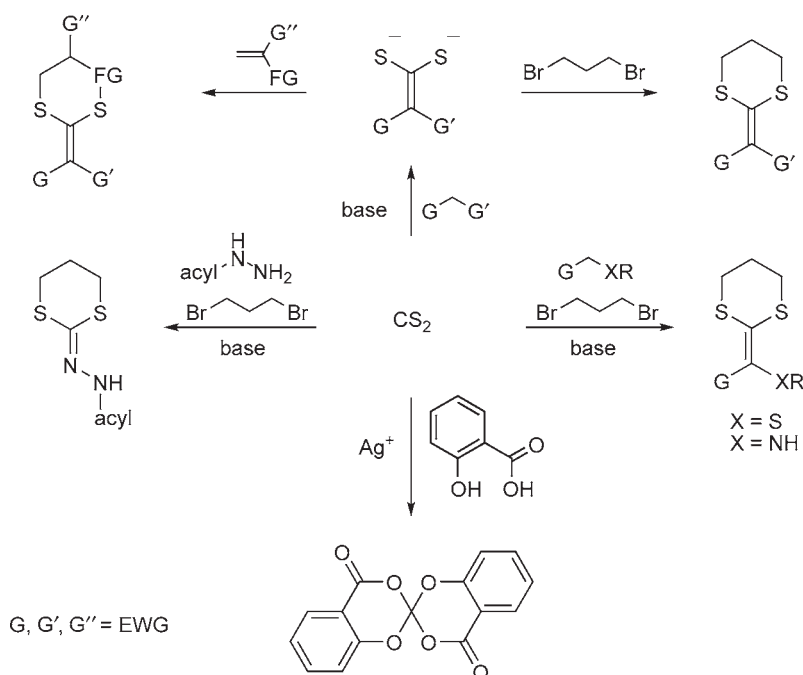
The acid-catalyzed condensation of a 1,3-diol, 1,3-thioalcohol, or 1,3-dithiol with an aldehyde or ketone or a dialkylacetal thereof is by far the most common reaction for the preparation of 1,3-heterocycles containing O and/or S as heteroatoms (Scheme 96). The reaction can be accomplished inter- and also intramolecularly <1996JOC9164, 2000JOC1842> with mineral or Lewis acids. Typically, *p*-TsOH or BF₃·Et₂O were used as catalysts. Some unusual reagents for synthesis of 1,3-heterocycles, such as clay <1998J(P1)965>, phase-transfer catalysis (PTC) <2002PS1291>, Sc(N⁺Tf₂)₃ <1996SL839>, or SiCl₄ <1996JOC6233, 1999T5027> have also been employed as catalysts. 1,3-Oxathianes from aldehydes or unsymmetrically substituted ketones are chiral molecules. An asymmetric synthesis of optically active 1,3-oxathianes was realized by condensation of a planar-chiral chromium–arene complex with a 1,3-thioalcohol and subsequent oxidative removal of the chromium moiety <1996TA1903>. 1,3-Oxathian-4-ones and 1,3-dioxin-4-ones from carboxylic acids <2000PJC1369> or esters <2000JOC8096> have been prepared as



Scheme 96

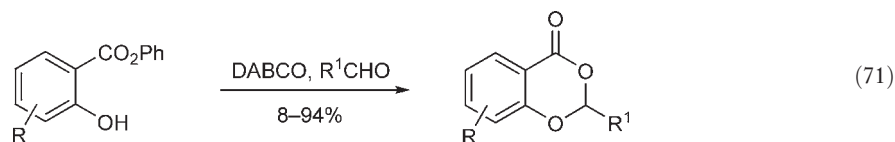
well by this methodology. 1,3-Dioxanes are the key structural motif in preussomerins and palmarumycins, and acetal formation has been applied in some syntheses <1998CC809, 1999J(P1)1073>. A one-step bis-acetalization for the convenient preparation of either unusual spiro-bis(1,3-dioxanes) <2004T3173> or 1,3-oxathiane-containing ionophores has been reported <1997JOC4785>.

Carbon disulfide is, besides the common propane-1,3-dithiol, a practical precursor for the preparation of 1,3-dithianes. It cleanly reacts with a series of nucleophiles to generate the dianions, which in turn upon exposure to electrophiles, such as 1,3-dibromoalkanes <1997JHC1297, 2006H(68)357> or highly activated Michael acceptors <2000PS(160)105, 2000PS(160)159>, provide substituted 1,3-dithianes in good yields (56–85%). 1,3-Dicarbonyl compounds (G, G' = electron-withdrawing groups) <2004PS1>, *N*-acylhydrazines <2000PS(158)107>, alkylthio-alkylnitriles <1996JPR157> or alkylamino analogs <1997PS(120/1)467, 1997PS(122)71> or diketopiperazines <1999SC1553>, and bicyclic ketones <1996PS(116)175> have been examined as suitable nucleophiles for the initial reaction with CS₂ (Scheme 97). Carbon disulfide, when activated with silver ions, also reacts with 2 equiv of salicylic acid as 1,3-diol component <1998H(48)461>. As a result, the corresponding spiro bis-1,3-dioxan-4-one was obtained, albeit in low yield (20%).

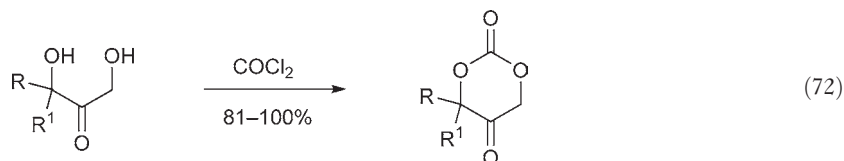


Scheme 97

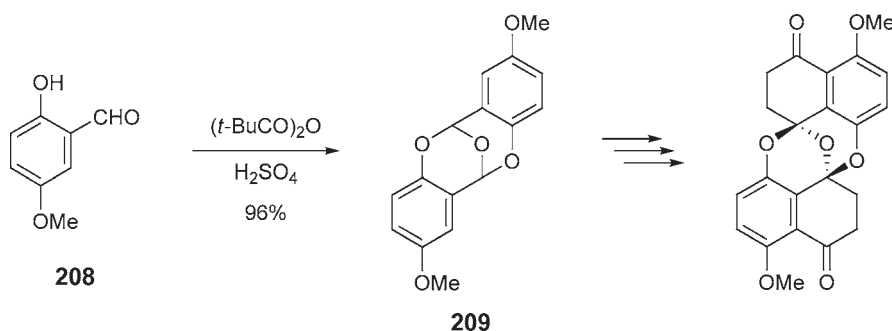
o-Hydroxybenzoic acid phenyl esters smoothly react with several aldehydes to give the corresponding 1,3-dioxan-4-ones under base catalysis using 1,4-diazabicyclo[2.2.2]octane (DABCO) as base (Equation 71). The yields are generally good, with a few exceptions <1996TL3755, 2001ARK(xiii)95>.



The synthesis of cyclic carbonates or 1,3-oxathian-2-ones using phosgene or substitutes has been reviewed <2005SOS(18)379>. α,α' -Dihydroxyketones react with phosgene to the cyclic carbonates in good to excellent yields (Equation 72). This result is not as obvious as it may seem, since many other possible reaction products may be formed <2004OL969>. In some instances, in particular when cyclization cannot occur due to steric reasons, other products, such as 1,3-dioxolan-2-ones, result. Cyclic thiocarbonates were also prepared by reaction of 1,3-thioalcohols with carbonyl diimidazole as phosgene equivalent in 92–99% yield <2006SC1419>.

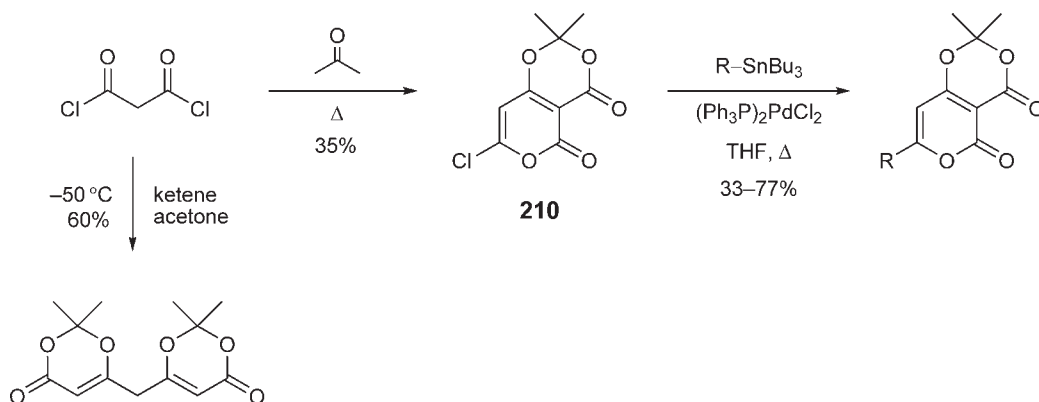


Dimerization of 2-hydroxy-4-methoxybenzaldehyde **208** was carried out using a mixture of pivalic anhydride and sulfuric acid. The product 'double' 1,3-dioxane **209** was obtained in 96% yield (Scheme 98) <2000OL1613>. Other anhydrides were less efficient. The product was used for the construction of the core unit of preussomerins <2004TL4877, 2004OBC2483>.



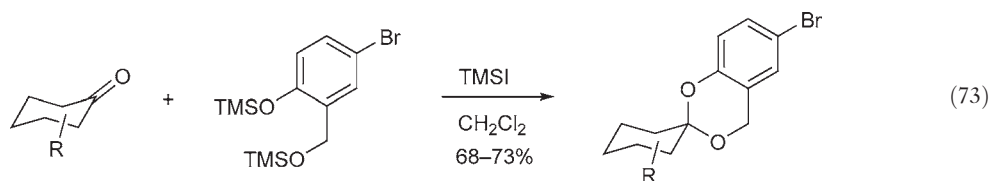
Scheme 98

Malonyl chloride reacted with boiling acetone to give the bicyclic 2:1 adduct **210** comprising a pyranone and a 1,3-dioxan-4-one moiety (Scheme 99). The modest yield was compensated for by the ease of its preparation. Compound **210** bears a chloride which is almost as reactive as an acyl chloride and which can be substituted by various nucleophiles in a Stille coupling in modest yields <1997SL895>. Treatment of malonyl chloride with ketene and acetone at low temperature afforded symmetric bis(1,3-dioxin-4-ones) in 60% yield although a different reaction pathway may be assumed (Scheme 99) <2000TL4959>.



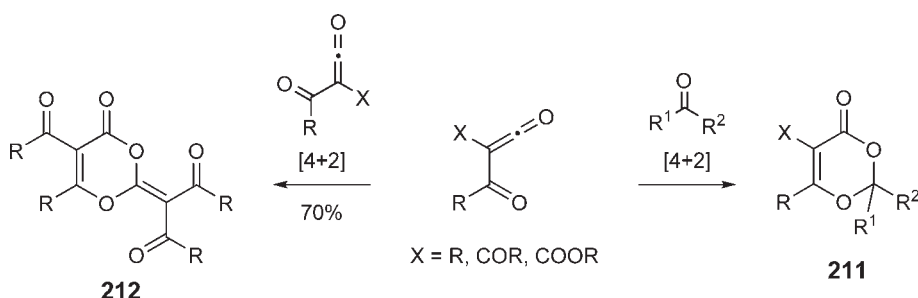
Scheme 99

Acetalization of ketones was also effected using Noyori's kinetic acetalization protocol. Thus, bis-trimethylsilyl-ethers readily react with cyclohexanones to give 1,3-dioxanes in good yield (Equation 73) <1997J(P1)2789>.



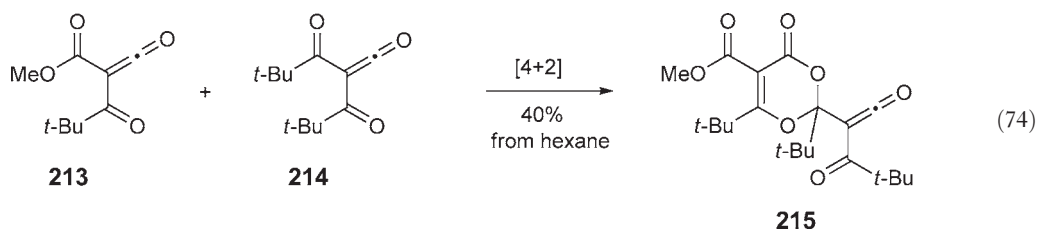
8.11.9.2 [4+2] Cycloaddition

α -Oxoketenes readily react in [4+2] cycloadditions with numerous aldehydes or ketones to afford the 1,3-dioxin-4-ones **211** in good yields <2003JHC697, 2004CHE245>. The mechanism was experimentally and theoretically studied <2000JOC7731>. In the absence of an external carbonyl group, α -oxoketenes may also dimerize to 2-alkylidene-1,3-dioxin-4-ones **212** (Scheme 100). These dimerizations occur at the ketene carbonyl group of one of the α -oxoketenes <1996JA12598, 2001EJO1315>.

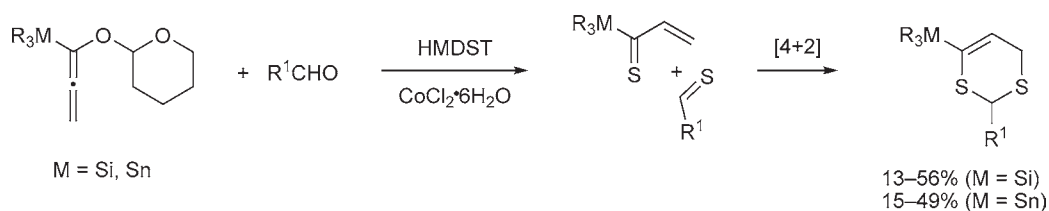


Scheme 100

A different reaction pathway and a remarkably stable ketene-containing 1,3-dioxin-4-one has been prepared by cross dimerization of ketenes **213** and **214**, generated *in situ* by FVP of appropriate precursors. The product, 1,3-dioxin-4-one **215**, was obtained in 40% yield after recrystallization from hexane <2002J(P1)599> (Equation 74).

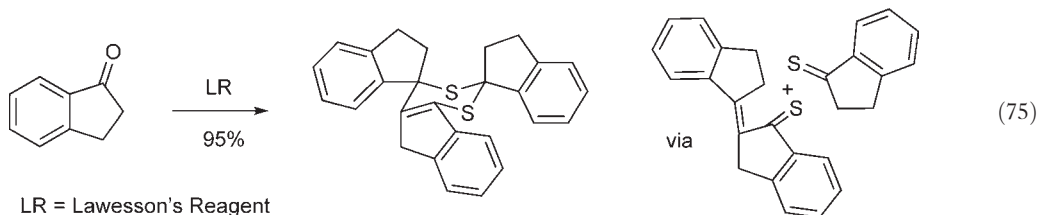


1,3-Dithiins have been prepared by [4+2] cycloaddition of *in situ*-formed thioenones with thiocarbonyl groups (Scheme 101) <2003JOM(686)363, 2004SL2159>. The thio compounds were generated from trialkylsilyl- or trialkylstannyl-tetrahydropyranyloxy allenes using bis(trimethylsilyl)sulfide (HMDST) and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$. The cycloaddition products were isolated in poor to moderate yields.

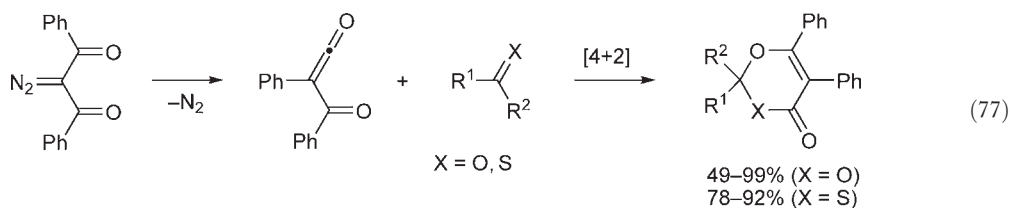
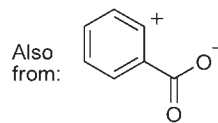
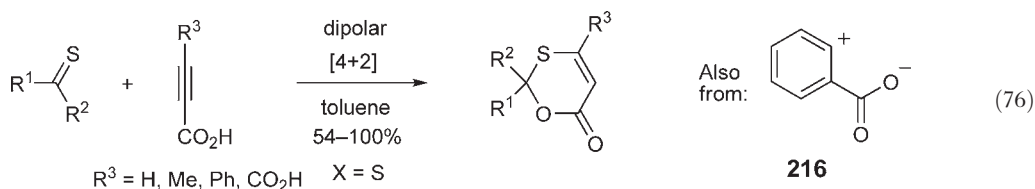


Scheme 101

A 1,3-dithiane was also obtained by the reaction of indanone with LR in 95% yield. Presumably, this product was formed via [4+2] cycloaddition of thioindanone and a thiocarbonyl-containing condensation product, to which the 1,3-dithiane fragmented upon heating (Equation 75) <1999HAC369>. A similar self-condensation of thioacrolein has been reported as well <2000JOC6601>.



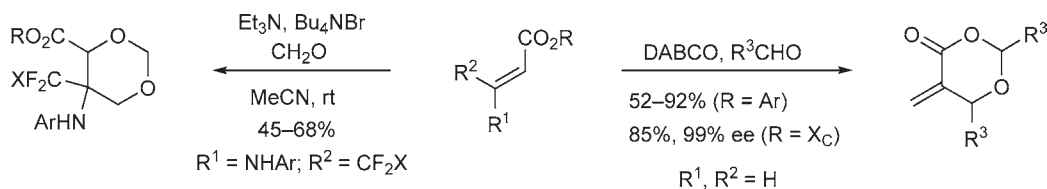
1,3-Oxathiin-6-ones have been conveniently prepared by cycloaddition-type reactions of alkyne carboxylic acids and thiocarbonyl compounds in refluxing toluene (Equation 76) <1997LA2347, 2003EJO3727, 2004BCJ1933>. Betaines, such as **216**, gave with thiocarbonyl compounds similar reaction products <1998CL79, 2000BCJ155> in good yield (82%). α -Diazo- β -diketones, upon loss of N_2 and Wolff rearrangement, gave with ketones <2001J(P1)2266> or thioketones <2001HAC630> the 1,3-dioxinones or oxathiinones in good yields (Equation 77).



8.11.9.3 Other Syntheses

8.11.9.3.1 [2+2+2] reactions

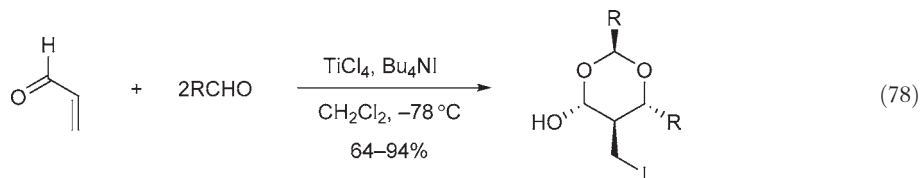
The Baylis–Hillman reaction, the base-catalyzed reaction of enoate esters with aldehydes, is used to yield α -alkylidene- β -hydroxyesters. However, when phenyl esters are applied in the presence of at least 2 equiv of an aldehyde, then cyclic Baylis–Hillman products have been isolated in good yields <1996TL1715>. A remarkable rate acceleration was observed when 1-naphthyl esters have been used as substrates. The 1,3-dioxan-4-ones were obtained in 75–91% yield within 4 h instead of days <2001CC1612>. In general, *cis*-configured 1,3-dioxan-4-ones were isolated. An asymmetric Baylis–Hillman reaction has also been developed using a chiral auxiliary. Thus, enones attached to Oppolzer's sulfonamides reacted with aldehydes to give 1,3-dioxan-4-ones in moderate to good yields (33–98%) and with excellent enantioselectivities (>99% ee) of the cyclic products (Scheme 102) <1997JA4317, 1997T16423>. A positive aspect of these reaction conditions is the loss of the chiral auxiliary during the reaction. Although DABCO is commonly used for



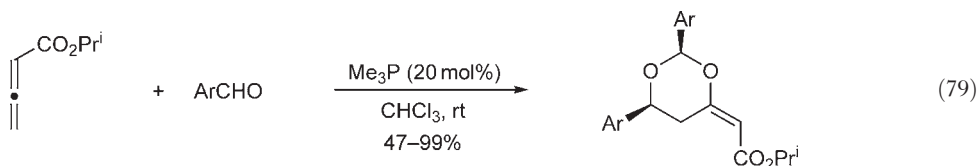
Scheme 102

the Baylis–Hillman reaction in catalytic amounts (20–50%), other bases have been employed as well. β,β -Disubstituted enoate esters readily reacted with formaldehyde to give different cyclic products, namely 1,3-dioxanes in which the complete C=C bond was part of the ring (**Scheme 102**) <2005JOC3801>.

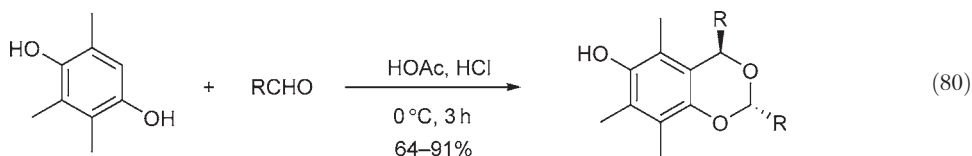
A Lewis acid-mediated reaction of 1 equiv of acrolein (as enone) with 2 equiv of an aldehyde gave access to stereochemically pure 4-hydroxy-1,3-dioxanes when the reaction was carried out in the presence of stoichiometric amounts of Bu_4NI (**Equation 78**). Interestingly, an iodomethyl group rather than the expected exocyclic double bond was formed in the product <1999OL1383>.



Allenecarboxylic acid esters reacted with 2 equiv of an aromatic aldehyde at the terminal double bond. The reaction was mediated by trimethylphosphine <2005OL1387>. 4-Alkylidene-*cis*-2,6-diaryl-1,3-dioxanes have been obtained in good to excellent yields (**Equation 79**).

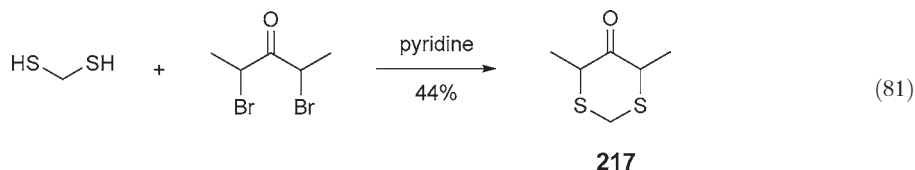


Phenols having at least one unsubstituted *o*-position also react with 2 equiv of aldehydes to 1,3-dioxanes though it is not a simple [2+2+2] reaction since three atoms of the ring came from the phenol and the other three atoms from two aldehyde molecules. The reaction is acid-catalyzed, and gave rise to more complicated products when more than one active site is available. Interestingly, hydroxyformylation and ring closure was the major pathway (48% yield), when morphine was treated with an excess of formaldehyde and conc. HCl <1997PHA744>. Substituted aldehydes were also used for this reaction. For example, acetaldehyde was used for the construction of novel tocopherol analogs containing a 1,3-dioxane moiety from trimethylhydroquinone (**Equation 80**) <2002JOC3607, 2003T2687>. Regioisomeric 1,3-dioxane-containing tocopherol derivatives have been prepared as well using the same methodology <2005T9070>.

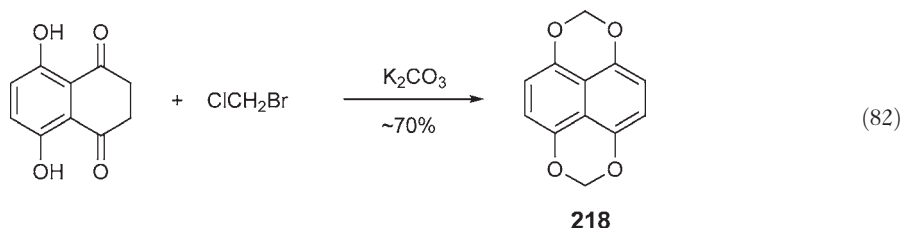


8.11.9.3.2 Preparation from geminal dithiols or dihalides

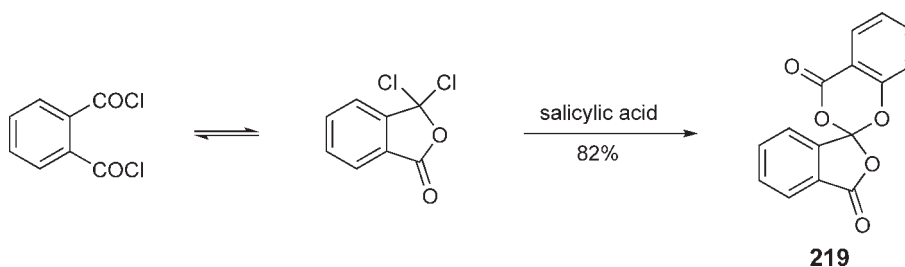
Methylenedithiol was used to construct cyclic meat flavor compounds, such as 1,3-dithian-5-one **217** <1998FFJ177>. The reaction of the geminal dithiol with a 1,3-dibromide proceeds with pyridine as base in 44% yield (**Equation 81**).



Geminal dihalides have also been applied for the construction of 1,3-dioxanes and congeners. For example, bromochloromethane readily reacted with tetrahydroxynaphthalenes to afford the tetracycle **218** in good yield (**Equation 82**). Bisdioxane **218** was subsequently used for the synthesis of alkannin and shikonin <1998AGE839, 2000SC1023>.

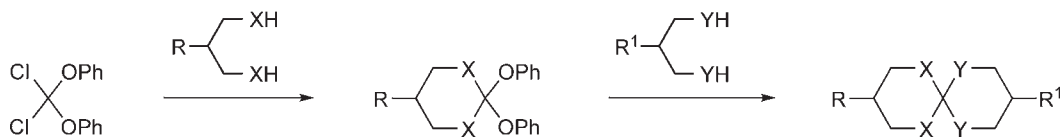


An interesting formation of a 1,3-dioxan-4-one from a geminal dichloride and salicylic acid is displayed in **Scheme 103**. Langer *et al.* have found that phthaloyl chloride cleanly reacted with salicylic acid. The product was not the expected nine-membered ring but spiro-tetracycle **219** in 82% yield. The product formation can be explained by assuming an initial equilibration of phthaloyl chloride and 3,3-dichloro-3*H*-isobenzofuran-1-one <2001EJO1511>.



Scheme 103

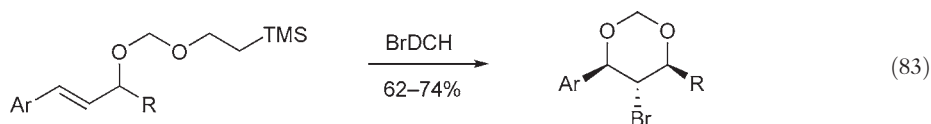
Dichlorodiphenoxymethane was employed for the synthesis of symmetric <1996AJC1261> and unsymmetric spirobis-1,3-dithianes and congeners <1999AJC657>. The smooth formation of unsymmetrical bis-1,3-dithianes is attributed to the large difference in reactivity between the halide and the phenoxy group, also allowing the preparation of monocyclic intermediates (**Scheme 104**).



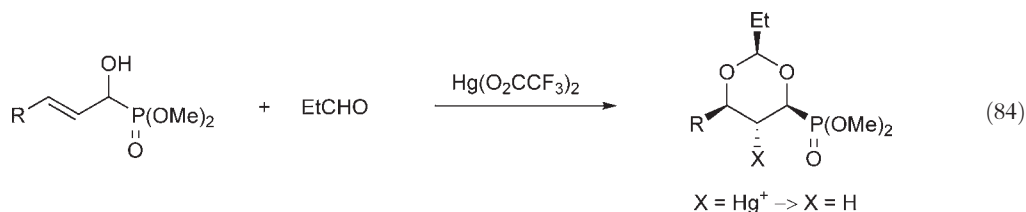
Scheme 104

8.11.9.3.3 Miscellaneous reactions

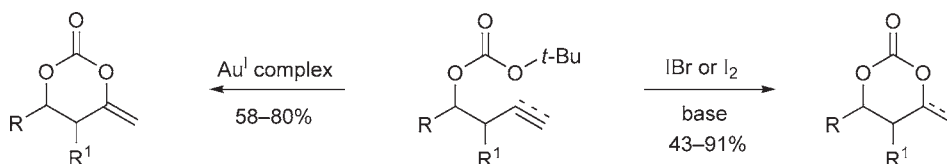
Formation of 1,3-dioxanes was also effected by intramolecular cyclization of suitable precursors possessing a double bond either two or three carbons away from the oxygen functional group. For example, β -trimethylsilylethoxymethyl (SEM)-protected allylic alcohols reacted with bromonium dicollidine hexafluorophosphate (BrDCH) to 5-bromo-1,3-dioxanes in acceptable yields and with a high preference for the 4,6-*cis*-addition product (**Equation 83**) <2000JOC2797>.



In addition, 1,3-dioxanes have been prepared by mercury salt-induced cyclization of 1-hydroxyallylphosphonates with propionaldehyde (**Equation 84**). The Hg was subsequently removed from the heterocycle with cyanoborohydride <2002PS1583>.

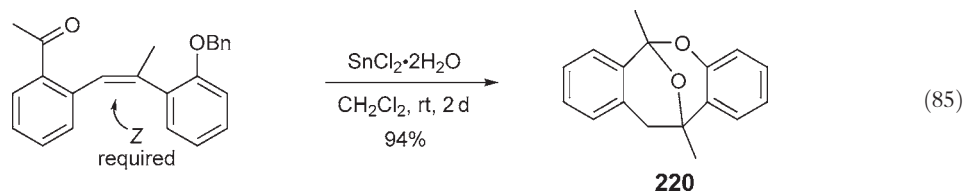


tert-Butoxycarbonyl (BOC)-protected homoallylic alcohols have been cyclized to 1,3-dioxan-2-ones using iodine and NaHCO_3 <2006BCJ489>. BOC-protected homopropargylic alcohols reacted similarly using IBr as halogenating agent (Scheme 105) <1999JOC3798, 2004S1399>. The same homopropargylic substrates can be cyclized to 4-methylene-1,3-dioxan-2-ones in a gold(I) complex-catalyzed reaction. The heterocycles were obtained in 58–80% yield <2006SL717>. However, in some cases, the cyclic products were accompanied by β -hydroxyketones formed by hydrolysis of the 4-methylene-1,3-dioxan-2-ones during the reaction (Scheme 105) <2005BKC1925>.

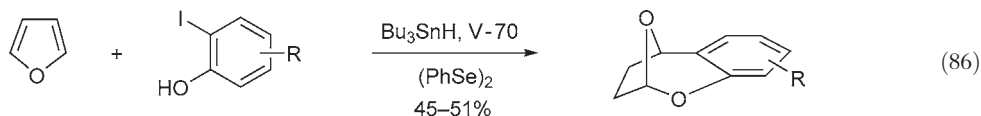


Scheme 105

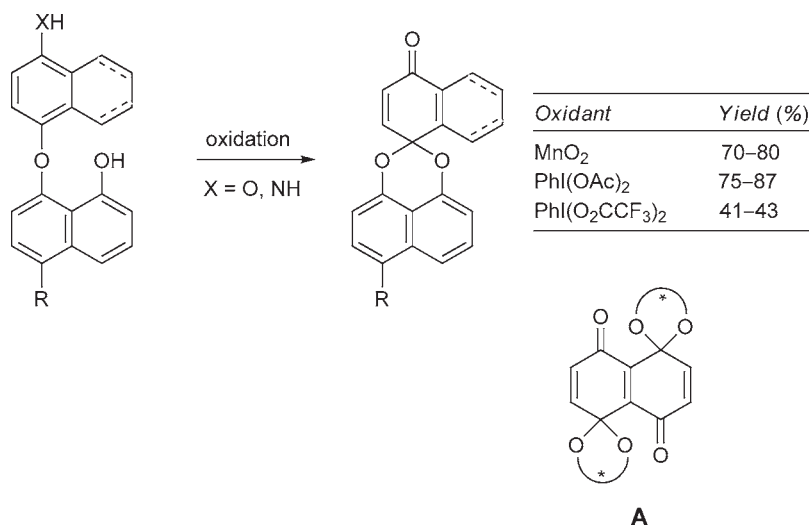
An unusual reductive cycloaddition leading to a bridged bicyclic 1,3-dioxane was reported by Taylor and co-workers <2003OL4441, 2005OBC756>. They found that 2-acyl-2'-benzyloxy-substituted (*Z*)-stilbenes cyclize upon treatment with tin dichloride at room temperature to give the bicyclic product **220** in 94% yield (Equation 85).



A formal [4+3] cycloaddition leading to products with a core structure similar to that of **220** was found when 2-iodophenols and furan are treated with a mixture of Bu_3SnH , 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70), and a catalytic amount of diphenyl diselenide, albeit moderate yields have been achieved (Equation 86) <2005OL3625>.

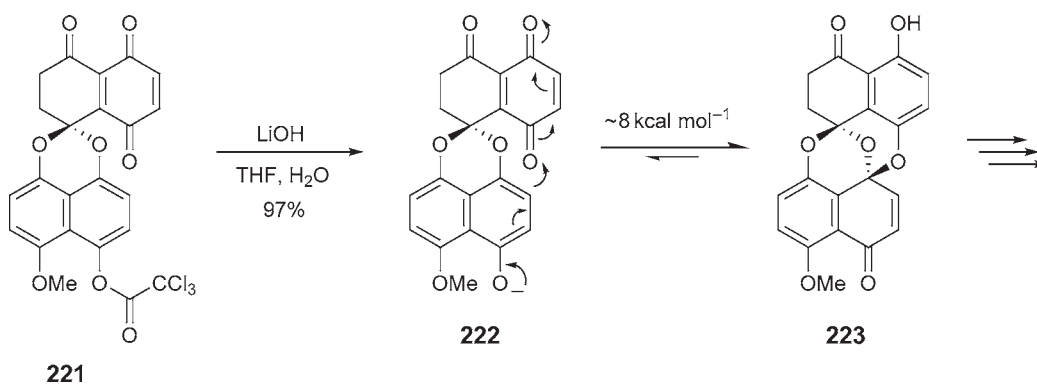


Other examples of the oxidative cyclization of appropriate precursors to 1,3-dioxanes were reported for the construction of spiropolycyclic skeletons for the synthesis of palmarumycins or preussomerins. Some oxidizing agents, such as MnO_2 <2000TL9105> or phenyliodonium acetate <1998JOC3530, 1999JOC1092, 2000JOC6319, 2001T283>, were found to effect the cyclization in reasonable yields (Equation 87). Phenyliodonium trifluoroacetate was less efficient <2004OBC1651>. The oxidative formation of a chiral bis-1,3-dioxane of type **A** for the asymmetric nucleophilic addition to the carbonyl groups of **A** has also been reported to proceed with $\text{PhI}(\text{OAc})_2$ <1997AGE764>.



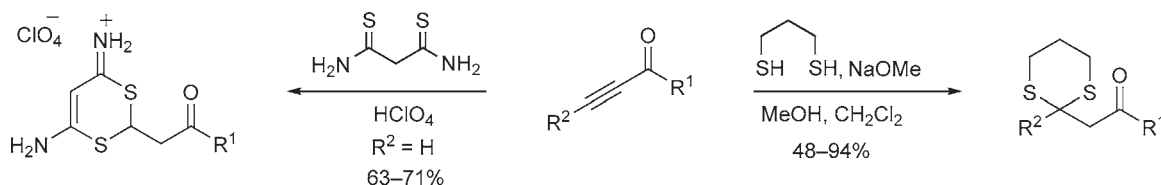
(87)

Another strategy for the preparation of the core structure of palmarumycin or preussomerin commenced with acetate esters, such as trichloroacetate **221**. Hydrolysis of the ester group of compound **221** with LiOH gave the anion **222**, which cyclizes to bridged bis-1,3-dioxane **223** (Scheme 106) <1999OL3>. It was calculated that bis-1,3-dioxane **223** and the protonated form of anion **222** are in thermodynamic equilibrium with a preference for **223** of almost 8 kcal mol⁻¹ <2002JOC2735>.



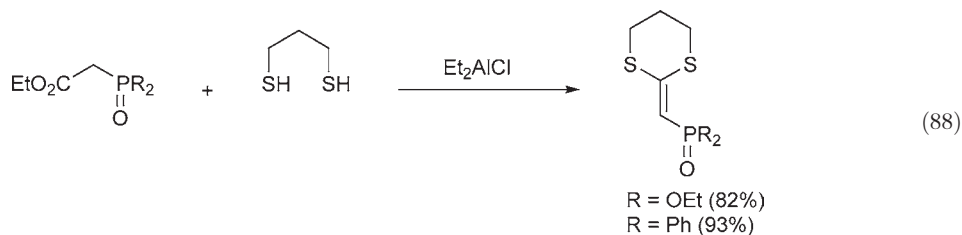
Scheme 106

Alkynones are suitable substrates for the preparation of 2-substituted-1,3-dithianes by Michael addition. Either 1,3-propanedithiol <2003OBC15> or the diamide of thiomalonic acid <2002RJO1205> gave the 1,3-dithianes in reasonable to excellent yields (Scheme 107). The reaction is in the first case base and in the latter case acid-induced.

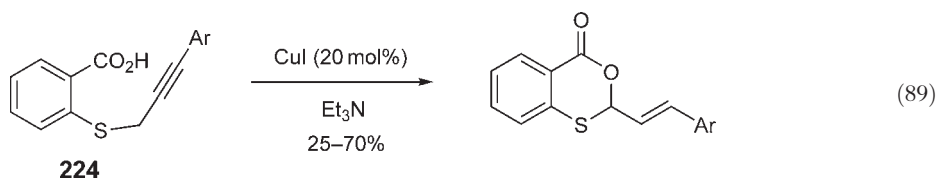


Scheme 107

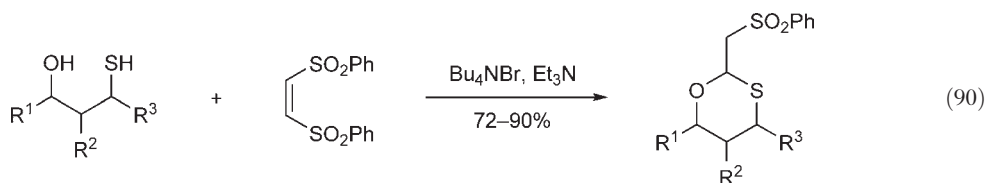
2-Alkylidene-1,3-dithianes have also been synthesized by addition of the ethoxycarbonylmethylphosphonate or the analogous phosphine oxide. The reaction was most efficiently mediated by Et_2AlCl as Lewis acid (Equation 88) <1996JOC8132>.



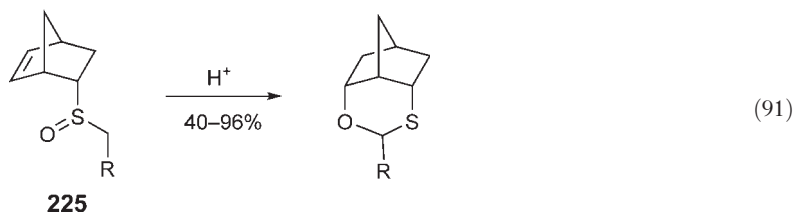
1,3-Oxathiin-6-ones have been conveniently prepared by cyclization of phenylpropargyl thioether **224** mediated by substoichiometric amounts of CuI <2001SL415, 2001J(P1)1649>. Interestingly, not the expected seven-membered ring but the six-membered ring with (*E*)-akenyl group at C-2 was formed as the only cyclic product (Equation 89). To explain this result, an allenic intermediate is discussed.



Various 2-functionalized-1,3-oxathianes have been prepared from 1,3-thioalcohols by a combined $\text{S}_{\text{N}}\text{V}$ /Michael addition sequence using (*Z*)-1,2-bis-phenylsulfonylethylene (BPSE) as Michael acceptor. The yields were in the range of 72–90% for aliphatic 1,3-thioalcohols and somewhat lower for 2-hydroxymethyl-substituted aromatic thiols (33%) (Equation 90) <2003TL5723>.



1,3-oxathianes have also been obtained by Pummerer-type rearrangement of (optically active) sulfoxides. The reaction was proton-catalyzed and gave good yields for bridged bicyclic systems, such as **225** (Equation 91) <1997CPB778>. Benzyl aryl sulfoxides reacted as well <1999H(50)291>. However, Pummerer-type cyclization of optically active sulfoxides mediated by enol esters gave only a poor transfer of chirality with 44% ee at best <1997TA303>.

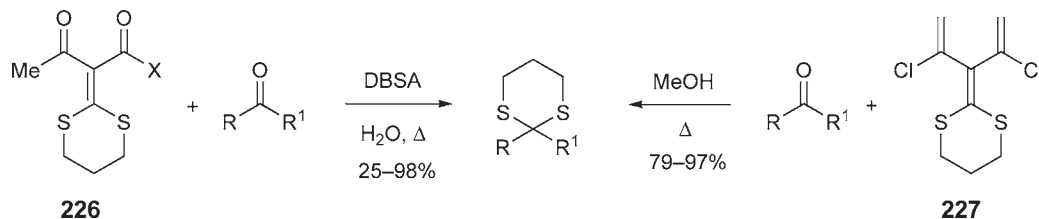


8.11.10 Ring Syntheses by Transformation of Another Ring

8.11.10.1 Preparation by Transacetalization

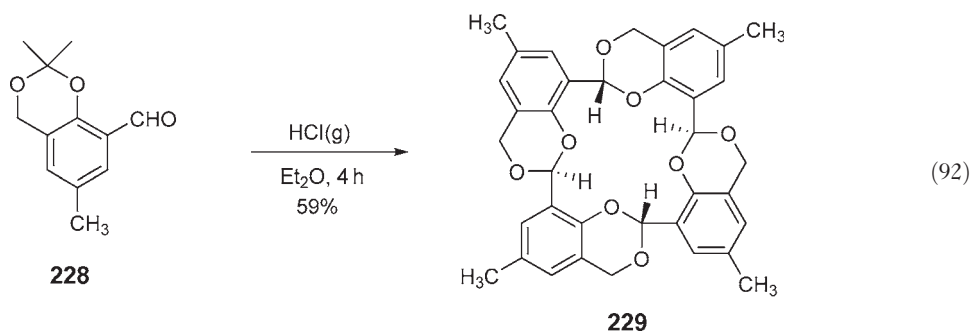
The synthesis of 1,3-dioxanes and congeners by transformation of a ring of the same size is not highly developed. Only a few examples of such reactions, typically transacetalizations, have been reported. An important issue of 1,3-dithiane formation, namely the stench of the 1,3-propanedithiol, has been addressed by Liu and co-workers. They found that

1,3-dithianes may be synthesized from ketones or aldehydes by transacetalization of odorless 2-alkylidene-1,3-dithianes, such as **226** or **227** <2005S85>, using dodecylbenzenesulfonic acid (DBSA) <2005JOC4535>, or MeOH <2003JOC9148>, or MeOH/McCOCl <2005CHJ1060> for mediation (**Scheme 108**).



Scheme 108

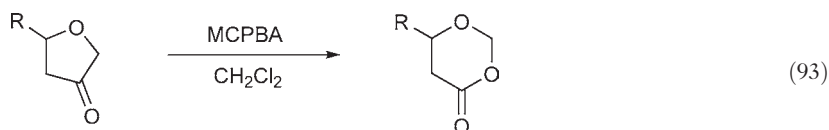
Another interesting example of a transacetalization is the tetramerization of 1,3-dioxane **228** to the macrocycle **229** (**Equation 92**). This cyclooligomerization was promoted by dry HCl in Et₂O and the tetrameric product was formed in 59% yield <2000OL4125>.



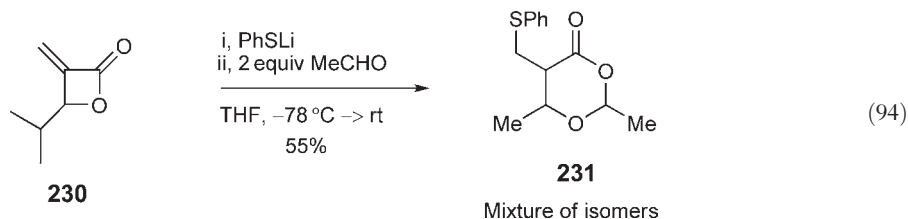
8.11.10.2 Ring Expansion of Smaller Ring Systems

Ring expansion of a four- or five-membered ring is a more common route for the preparation of 1,3-dioxanes, 1,3-dithianes, and 1,3-oxathianes and various methods have been developed.

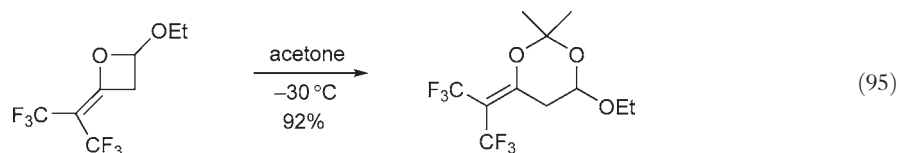
The Baeyer–Villiger reaction of 3-tetrahydrofuranones with MCPBA gave exclusively the 1,3-dioxan-4-ones in preparative useful yields (**Equation 93**) <2001TL4713, 2004CC816>.



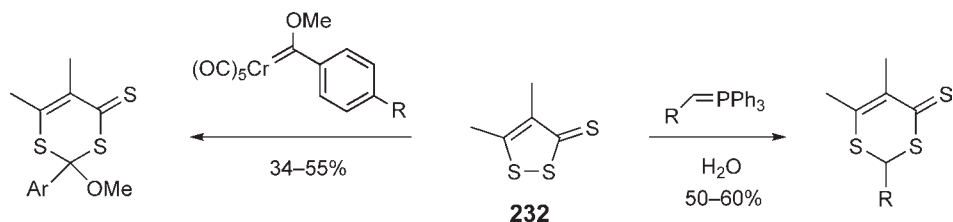
Ring expansion of four-membered rings to 1,3-dioxan-4-ones was achieved using 3-methylene-4-isopropyl- β -lactone **230** as starting material. Michael addition of PhSLi to **230** gave the enolate *in situ*, which further reacted with 2 equiv of acetaldehyde to 1,3-dioxan-4-one **231** as a mixture of isomers in 55% yield. Interestingly, a 1,3-dioxan-4-one containing the initial isopropyl group was obtained only when less than 2 equiv of acetaldehyde were employed (**Equation 94**) <2000EJO2529>. Apparently, a retro-aldol–aldol reaction sequence occurred in the initial stages of dioxanone formation.



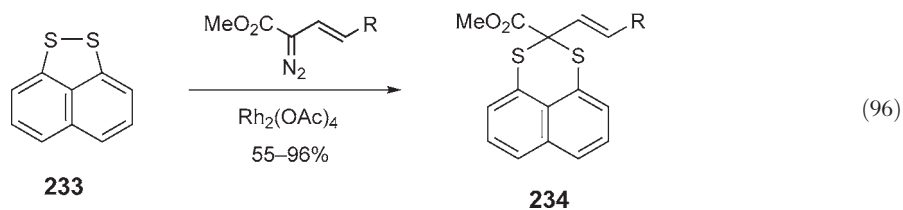
An activated 4-alkylidene-2-ethoxyoxetane reacted smoothly with acetone at -30°C to give 6-alkylidene-4-ethoxy-1,3-dioxane in 92% yield (Equation 95) <2003JA14446>.



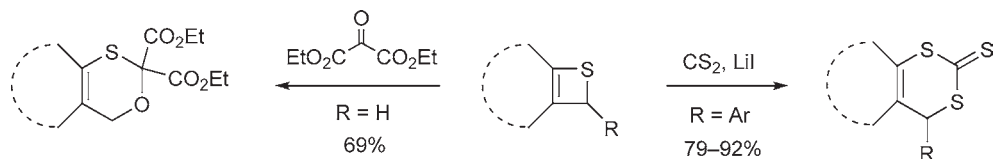
The 1,2-dithiol-3-thiones, such as **232**, react with either phosphorus ylides <2004HCO217, 2005JHC103> or with Fischer carbenes <2006JOC808> with ring expansion, providing 2-substituted- or 2,2-disubstituted-1,3-dithianes in moderate yields (Scheme 109). Similarly, cyclic naphthalene-1,8-disulfide **233** gave the 1,3-dithiane **234** in good to excellent yields in a rhodium acetate-catalyzed carbene insertion using diazo ester precursor <1998TL7113> (Equation 96).



Scheme 109

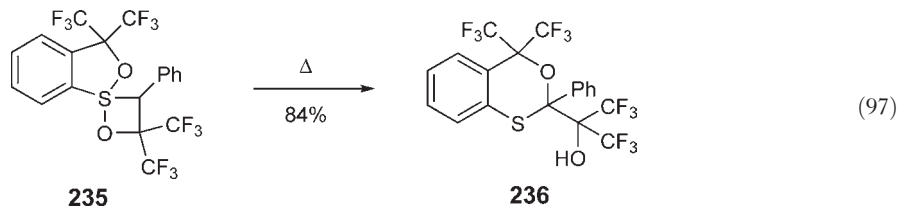


Thietes, four-membered precursors for the synthesis of 1,3-dithianes or 1,3-oxathianes, provide access to the target heterocycles by reacting with either carbon disulfide and LiI <2002IJB1234, 2003S340> or, when the ring system denoted in Scheme 110 is aromatic, with diethyl 2-oxomalonate via a [4+2] cycloaddition pathway <1998JHC1505>.



Scheme 110

One of the rare examples of an intramolecular ring expansion leading to a 1,3-oxathiane is depicted in Equation (97). The sulfurane precursor **235** thus upon heating rearranged to 1,3-oxathiane **236** <1996JA697>.



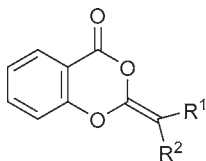
8.11.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Reports on the new syntheses of six-membered ring systems with two oxygen and/or sulfur atoms in 1,3-positions are rather limited and are covered already in Sections 8.11.9 and 8.11.10. Often, only one really successful synthetic path has been described or the derivatives obtained were simply by-products. Thus, a comparison of various synthetic strategies for obtaining certain dioxane/oxathiane/dithiane derivatives is not meaningful.

8.11.12 Important Compounds and Applications

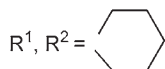
The position of Meldrum's acid in this chapter is outstanding; due to its high acidity ($pK_a = 4.97$, *vide supra*) and rigid cyclic structure, it has been frequently employed in the organic syntheses of a large number of key building blocks <2004SL1649>. Thus, practical applications of the reaction products frequently appeared and were quite interesting; for example, a photoinduced decomposition of 5-diazo Meldrum's acid in a polymer matrix has been published <1997MI43> (hereby a diazo ketone has been developed which is sensitive to far UV (200–260 nm), making it suitable for high-resolution lithographic applications) and a dye derived from Meldrum's acid was synthesized which proved sensitive to both dipolarity-polarizability and the acidity of the medium <2004DP(62)277>.

A new class of compounds, 2-alkylidenebenzo-1,3-dioxin-4-ones **237**, was synthesized <2001TL5231> for which the members act as a prodrug for aspirin and have proved to be useful intermediates in the synthesis of a completely new class of aspirin prodrugs.

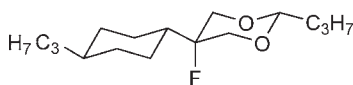


237

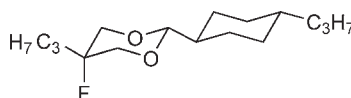
$R^1 = H$; $R^2 = H, Me, CH=CH_2, OMe, m-C_6H_4Me$



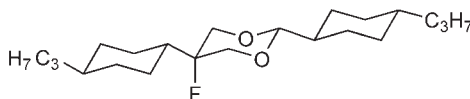
A new class of liquid crystals with strongly negative dielectric anisotropy was explored by employing the ambivalent characteristics of the 1,3-dioxane moiety <2006EJO4819>; due to both the polarity of 1,3-dioxane and axial fluorination, compounds **238–240** proved to have very useful mesogenic and electrooptical properties.



238



239



240

Liquid crystal polymers having 1,3-dithiane or 1,3-oxathiane rings as mesogenic side groups exhibit the extremely important liquid crystal phase at around room temperature <1999MI335>. 1,3-Oxathianes have also been applied as perfumery and flavoring ingredients; other derivatives exhibit excellent herbicidal activity and 1,3-oxathiane derivatives have been employed as corrosion inhibitors for steel.

Application of the new but already widely employed MS technique of ESI readily allowed the detection of weak noncovalent interactions of antitumor drug–DNA complexes <1999RCM2489, 2002CC556>; ESI data were used to derive a semi-quantitative estimate of the relative stability of the DNA complexes formed with 1,3-dithiane analogs.

A variety of natural products that contain the 1,3-dioxane moiety as elements of their molecular framework have been isolated. Their structures have been determined and very often they exhibited antitumor and antifungal activities <1997NN403, 1997CCC957, 1997TL1697, 2001CJC1786>. New fungicidal fluorine-containing thiazolo-1,3-dithiins have also been synthesized and were found to display strong *in vitro* fungicidal activities <1998IJB306>.

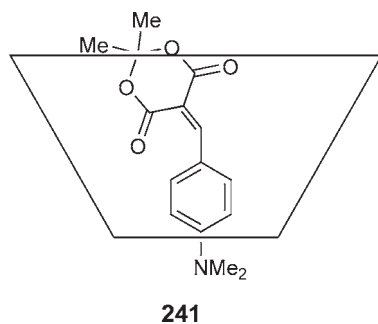
2-Vinyl-4*H*-1,3-dithiin was identified together with 2-vinyl-4*H*-1,2-dithiin to be the major organosulfur compounds in fresh garlic oil (*A. sativum*) <2004MI235, 2006MI287>. Both compounds decompose during the separation and structure elucidation procedure and form many different sulfur compounds; but all of these organic sulfur compounds (OSCs) proved to be heavily involved in the protection mechanism by garlic against cardiovascular disorders and carcinogenesis. Thus, OSCs were quantified by a new high-performance liquid chromatography (HPLC) method with respect to garlic source, variability, and different stability of these OSCs, and showed their general sulfur dependence to have a positive effect on cardiovascular disorders and carcinogenesis <2005JPB963>.

8.11.13 Further Developments

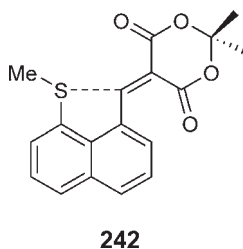
8.11.13.1 1,3-Dioxane and Meldrum's Acid Derivatives

The effect of the substituent on the conformational equilibria of 2-substituted 1,3-dioxanes proved to be of continuous interest. First, high level *ab initio* calculations demonstrated the Gibbs free energies of the axial conformers to be more stable than the corresponding equatorial conformers if the substituents are electron withdrawing groups (OMe, F, Cl, Br) <2007CAR(342)1202>; CH/*n* hydrogen bonds were presumed to be an important factor in stabilizing the axial conformer. And second, the conformational equilibrium of 5-hydroxy-1,3-dioxane was studied experimentally in CHCl₃ and calculated in vacuo at two different levels of theory (*ab initio* and DFT methods) <2007JOC4156>; the calculations agreed well with the experimental findings in solution, the equatorial position of the hydroxyl group is preferred by 1.9 kcal mol⁻¹ and the bifurcated hydrogen bond contribute 3.6 kcal mol⁻¹ to the lowest energy conformer which is consequently 2-axial-OH-1,3-dioxane.

In the course of a host-guest study of γ -cyclodextrin with solvatochromic dyes, the interaction with the Meldrum's acid dye **241** was studied by NMR and UV-VIS spectroscopy <2006JPO786>. ¹H NMR evidence pointed to the inclusion of the whole molecule into the γ -cyclodextrin moiety.



Studying further the 1,5-interactions in peri-substituted naphthalenes (which culminated in the complete formation of a single bond in zwitterion **63** (Section 8.11.3.1.1) the corresponding methylthio derivative **242** was investigated <2006CEJ7724>; also in this case the MeS...sp²-C attractive interaction controls the solid state structure of compound **242**.



A kinetic and computational study of the hydrolysis of α -R- α -SMe-methylene Meldrum's acid (R = H, Me, Et, *s*-Bu, *t*-Bu) has been published <2006JOC4795> and confirmed that crowding at the transition state is an important factor on the rate of nucleophilic attack; no intermediate accumulated to detectable level.

Finally, a number of further X-ray structures of a 5,6-ring anellated 2-phenyl-1,3-dioxane derivative (in chair conformation) <2006AXEo3115> and a number of 5-exo-methylene Meldrum's acid derivatives (envelope conformation with C-2 as flap atom) <2007AXEo1913; 2006AXEo1722, 2006AXEo3215, 2006AXEo3477, 2006AXEo3581, 2007AXEo1915> were published.

Also inositol-orthoformate and -orthoacetate were of continuing interest: the conformation <2006CL868, 2007CAR(342)1182>, X-ray structures <2007CAR(342)1182, 2007EJO1153> and hydrogen bonding in a number of derivatives <2007H(72)469> were investigated.

8.11.13.2 1,3-Oxathiane Derivatives

The enthalpy of formation of 1,3-oxathiane sulfone in the gaseous state at 298.15 K was derived from the respective enthalpy of combustion in oxygen and also *ab initio* calculated at the G3 level of theory: $\Delta_f H^\circ_m(g) = -469.4 \pm 1.19$ kJ mol⁻¹ (calc. -468.5 kJ mol⁻¹) <2007JOC1143>.

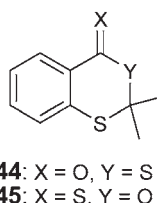
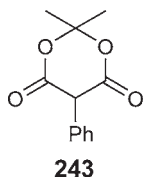
The equatorial conformation of the CH=O group in 2 position of the oxathiane chair conformer was studied at HF/6-31G* and B3LYP/6-31G* levels of theory <2006JOC4178>; the anti-to-S conformer (dihedral angle axial-2-H/carbonyl oxygen = 35.1–41.0°) proved to be 2.54 and 1.34 kcal mol⁻¹, respectively, more stable than the syn-to-S conformer (dihedral angle axial-2-H/carbonyl oxygen = 117.2–120.6°); also the transition states of the two conformers in nucleophilic addition reactions were calculated and the anti-to-S addition found to be predominant in agreement with the experiment.

8.11.13.3 1,3-Dithiin and 1,3-Dithiane Derivatives

In the 1,3-dithiane series by measurement of ¹J_{C,H} coupling constants in their anancomeric sulfoxides, sulfones, and sulfilimines, the corresponding orbital interactions were studied employing the NBO method <2007CEJ4273>; both the interaction of axial S=O bonds with antiperiplanar C–H bonds and the one of equatorial S=O bonds with β -C–H bonds (homoanomeric effect) proved strongest. Further, the X-ray analysis of an 2-exo-methylene-1,3-dithiane derivative in half chair conformation has been published <2006AXEm3295> and the occurrence of 2-allyl-4,5-dihydro-1,3-dithiin in garlic oils <2006MI135, 2007MI29, 2007MI332> and allium species was quantitatively estimated <2006MI351>.

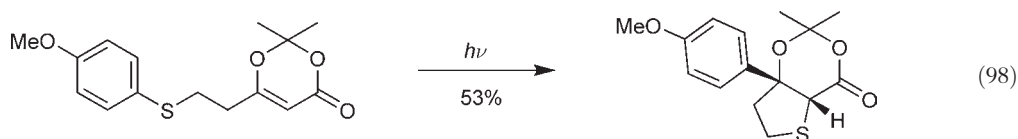
8.11.13.4 Thermal and Photochemical Reactions

5-Phenyl Meldrum's acid **243** <2007JOC1399> and other acetals, such as **244** and **245** <2006HCA991>, have been subjected to flash vacuum pyrolysis (FVP). As displayed in **Scheme 11** (Section 8.11.6.1.1), acylketenes are the major products.



Some advancement toward the understanding of the reactivity of 5-diazo Meldrum's acid (**33**, **Scheme 15**, Section 8.11.6.1.1) has been reported. Thus, the photo- and thermolytic properties of this compound have been studied in detail <2006RJO815, 2006RJO1213>. The carbene, generated from diazo Meldrum's acid **33** and rhodium catalysts, reacted with nucleophiles to afford various products <2006RJO1741> and with alkenes to yield cyclopropanes <2006BK503>. Photolysis of salicylic acid acetals, such as those shown in **Equation (18)** (Section 8.11.6.1.1), have been used for initiating free radical polymerization <2006PLM7611, 2007MAR72>. Aryl-substituted salicylidene acetals have been introduced as photolabile protecting groups for aldehydes and ketones <2007OL1533, 2007OL2831>. New results have been reported with respect to the photolytic properties of oxathiin **172** (**Scheme**

24, Section 8.11.6.2.1) <2007ARK(viii)7>, and to the ‘*tert*-amino effect’ <2006RCB384>. The intramolecular photocycloaddition of novel sulfur-substituted 1,3-dioxin-4-ones (Equation 98) has been described <2006JA9040>.



8.11.13.5 Reactions with Electrophiles

The reaction of O,O-/ S,O-/ S,S-1,3-heterocycles with electrophiles is focused on two substrates: Meldrum's acid (Scheme 29, Section 8.11.6.2.2) and 2,2-dimethyl-1,3-dioxan-5-one (Scheme 42, Section 8.11.6.3.2). The Knoevenagel reaction of Meldrum's acid has been studied in the following fields: method development <2006MI868, 2007SL874>, reaction with unusual electrophiles <2007NJC691>, and natural product synthesis <2007JOC1039>. Domino Knoevenagel/reduction reactions <2006OBC4436> and Knoevenagel/nucleophilic addition reactions <2006QSA921> have been described as well. The three component synthesis of Meldrum's acid with aldehydes and nucleophiles was extended to novel heterocyclic product classes <2006SL1835, 2006RJO509, 2006MI843>. The condensation of Meldrum's acid with carbon atoms at the carboxyl oxidation state has been carried out with orthoesters <2007JOC2232> and iminoesters <2007JOC2477>. 5-Alkylidene Meldrum's acid derivatives have also been obtained by reacting Meldrum's acid with thiolium salts <2007SL1470>. Imidazole-containing allylic alcohols have been used in a palladium catalyzed double alkylation of Meldrum's acid (Scheme 29, Section 8.11.6.2.2) <2006T10555>.

2,2-Dimethyl-1,3-dioxan-5-one has been reacted with electrophiles either in auxiliary controlled transformations or in catalytic asymmetric processes which are actually most prominent (Scheme 42, Section 8.11.6.3.2). The auxiliary-controlled diastereoselective methodology has been adopted for the preparation of natural products <2007SL1021>, intermediates <2007TL751>, or analogs <2007EJO1085>. The proline (or analogs) catalyzed catalytic asymmetric aldol addition of 2,2-dimethyl-1,3-dioxan-5-one with aldehydes was recently discovered and some new insights into the reaction have been reported <2006SL2387, 2006CEJ5383>. Other electrophiles, such as nitroalkenes <2006EJO4578>, amins <2006S4060>, imines <2007TA1033, 2007JOC1417>, and *in situ* prepared imines <2006S3597> have been employed as electrophiles. The reaction was applied to the synthesis of natural product analogs <2006S2155, 2006SL3507>. An interesting one pot double alkylation at C-4 and C-6 of 2,2-dimethyl-1,3-dioxan-5-one, though not proline catalyzed, was developed using 2-nitro-enals as electrophiles, providing cyclitols in one step (Equation 99) <2006CC4239>.



Electrophiles, such as aldehydes <2006TL9089> or activated lactones (addition occurs at C-5) <2006SC3249>, have been reacted with silylketene acetals of 1,3-dioxin-4-ones according to Scheme 28 (Section 8.11.6.2.2). Alkylation at C-2 of 1,3-dithianes <2007ARK(x)29> and 1,3-oxathiane-dioxides <2006H(70)619> were reported. The successful use of the linchpin strategy depicted in Scheme 65 (Section 8.11.6.4.2) in natural product synthesis <2007JOC4280> as well as the electrophilic displacement of the silyl group in 2-silyl-1,3-dithianes (cf. Scheme 64, Section 8.11.6.4.2) <2006TL7525> was demonstrated. Method development was the focus in studies toward the single oxidation of 1,3-dithianes <2006MCL(456)85, 2006CAJ136>.

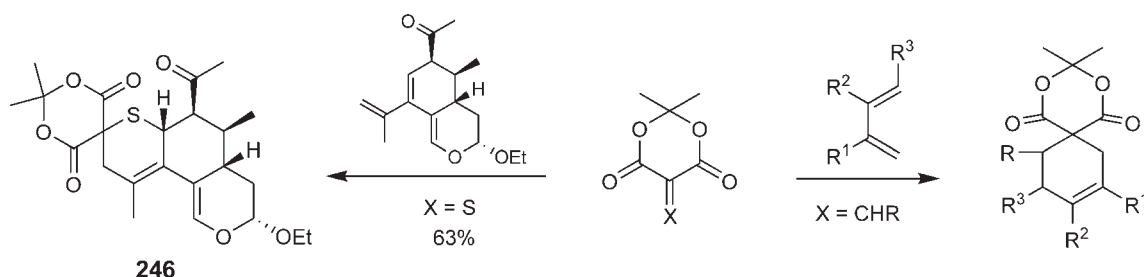
8.11.13.6 Reactions with Nucleophiles

(Stereoselective) additions of nucleophiles to 5-alkylidene Meldrum's acid as displayed in Scheme 17 (Section 8.11.6.1.3) <2006TA2957, 2007AGE4964> and to the carbonyl group of 2,2-dimethyl-1,3-dioxan-5-one (Scheme 47, Section 8.11.6.3.3) either in a three component transformation <2006OL3689> or in a nickel-catalyzed reaction

<2006JA8559> have been described. The use of 1,3-dioxin-4-ones as masked β -ketoacids (Scheme 31, Section 8.11.6.2.3) <2006TL4061>, of 2-alkylidene-1,3-dithiane 1-oxides as Michael acceptors (cf. Scheme 48, Section 8.11.6.3.3) <2007SL1622>, and chiral 4-acetoxy-1,3-dioxanes as precursors for the initial reaction of a multi component synthesis (cf. Equation (44), Section 8.11.6.4.3) <2006JA16480> have also been successfully demonstrated.

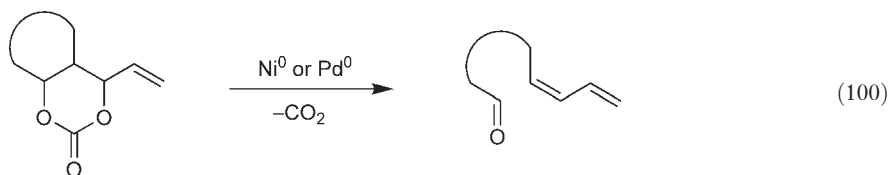
8.11.13.7 Radical, Cyclic Transition State and Ring-Opening Reactions

The chemistry of 5-methylene-2,2-dimethyl-1,3-dioxane derivatives in radical cyclizations (Equation 36, Section 8.11.6.3.4) <2007TL1645> and of 1,3-dithiane-2-yl in zirconocene-catalyzed dimerization reactions (cf. Scheme 71, Section 8.11.6.4.4) <2007JOM(692)3110> has been further explored. A new application of chiral 1,3-dioxins (Scheme 54, Section 8.11.6.3.6) is the aziridination followed by rearrangement to Garner-type aldehydes <2007ARK(x)245>. The Diels–Alder reaction of 5-alkylidene Meldrum's acid (Scheme 1, X = CR¹R²) <1999RJO1457, 2004RJO854> or *in situ* prepared from active precursors <2003AGE4233, 2004CEJ5323> with various dienes has been explored in the past. Most recent studies are devoted to the application in natural product chemistry <2003OL4983, 2007JOC1717> and in pharmaceutical chemistry <2007BML1362>, and to the synthesis of tetrahydrofluorenones <2006JOC9899>. Interestingly, the 5-thione of Meldrum's acid (Scheme 111, X = S) react with a diene in a hetero-Diels–Alder reaction providing intermediate 246 of quassinoid synthesis <2006OL4385>.



Scheme 111

The cyclodextrin-supported cleavage of 1,3-oxathianes with IBX (cf. Scheme 76, Section 8.11.6.4.6) <2006SC3771>, as well as the copper-catalyzed aminolysis of 1,3-dithianes <2006OL2547> has been published. 1,3-Dioxane-2-ones readily undergo a Grob fragmentation (Equation 100) <2006CC4303>. This reaction is catalyzed by Ni- (24–99% yield) or by Pd-complexes (42–93% yield).



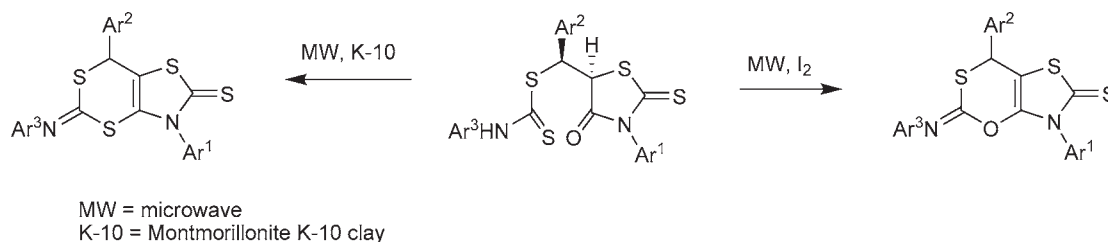
8.11.13.8 Reactions in the Side Chain of 1,3-Heterocycles

The functionalization of 2-alkylidene-1,3-dithianes is actively studied by Liu *et al.* Substitutions at the double bond, related to those described in Scheme 79 (Section 8.11.7) <2006CHJ1431, 2007SC703>, and condensation <2006T10111> or addition reactions <2007SL37, 2007JOC4985> (cf. Scheme 80, Section 8.11.7) have been reported from this group. The application of 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (Scheme 86, Section 8.11.7) as auxiliary in diastereoselective reactions <2006H(69)303, 2007AGE2314> and as ligand in catalytic asymmetric epoxidations <2007T5386> was of continuing interest as well as the S_NV reaction of functionalized 5-alkylidene Meldrum's acid derivatives (Scheme 90, Section 8.11.7) <2006CJC1979, 2006JOC4795, 2006JPO647, 2007JOC3302>. The gold-catalyzed cyclization of 5,5-diallyl Meldrum's acid derivatives (Scheme 88, Section

8.11.7) <2007CEJ1358> and the ruthenium mediated isomerization of double bonds (cf. **Scheme 89**, Section 8.11.7) <2007TL137> are recent examples of transition metal catalyzed manipulations at the side chain carbon atoms of 1,3-heterocycles. A novel side-chain addition reaction of aldehydes to 6-alkylidene-1,3-dioxin-4-ones was used for the construction of intermediates of lophotoxin <2006CJC1226>. An acid-catalyzed intramolecular cycloaddition of a hydroxy group to an alkene has been effected by the presence of an adjacent 1,3-dithiane moiety <2006TL4549>.

8.11.13.9 Synthesis of 1,3-Heterocycles

Acid-catalyzed acetalizations (**Scheme 96**, Section 8.11.9.1) have been employed for the synthesis of pharmaceuticals <2007BMC4775> and for chiral 2-alkyl-5-alkylidene-1,3-dioxane-4,6-diones <2006OBC3822>. A new catalyst for acetalization reactions has been reported <2006MI921>. New strategies for the synthesis of 1,3-benzodioxin-4-ones (Equation 71, Section 8.11.9.1) <2007ARK(vi)6> and the analogous 1,3-benzoxathian-4-ones <2006EJO3554, 2006S3195>, and for 1,3-dioxane-2-ones (cf. Equation 72, Section 8.11.9.1) <2006MI111> as well as for 1,3-oxathiin-6-ones (Equation 76, Section 8.11.9.2) <2006OBC2745> have been published. The Baylis–Hillman reaction of an N-acryloyl Oppolzer sultam with aldehydes is used for the synthesis of chiral 5-methylene-1,3-dioxane-4-ones (cf. **Scheme 102**, Section 8.11.9.3.1) <2006EJO4731>. The gold(I)-catalyzed cyclization of *tert*-butyloxycarbonyl (BOC)-protected homopropargylic substrates displayed in **Scheme 105** (Section 8.11.9.3.3) can also be effected with inexpensive mercury salts in short times and good yields <2006TL8369>. A novel cyclization reaction providing either 1,3-dithiins or 1,3-oxathiins from one precursor has been discovered by Yadav and Rai (**Scheme 112**) <2006T8029>.



Scheme 112

New reaction conditions for the odorless transacetalization providing 1,3-dithianes from aldehydes or ketones, as depicted in **Scheme 108** (Section 8.11.10.1), have been published <2006S3801, 2007SC993>.

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Biographical Sketch



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Michael Sefkow (born 1966, Berlin, Germany) studied chemistry at the Technical University of Berlin. He obtained his Ph.D degree in 1994 from the ETH Zürich under the guidance of Professor Seebach. After a postdoctoral study at the Harvard University with Professor D. A. Evans (1994–95), he went to the GBF (1996–97) working on the epothilones. In 1998, he started his independent research at the University of Potsdam funded by a DFG-fellowship. He finished his habilitation in 2002. In 2004 and 2005, he was appointed at the University of Leipzig. His research interests include the stereoselective synthesis of lignans and neolignans, the transition metal-catalyzed cycloadditions, and the reactivity of nonsolvated carbenium ions.

8.12

1,4-Dioxins, Oxathiins, Dithiins, and their Benzo Derivatives

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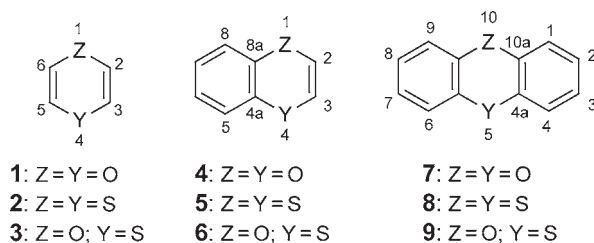
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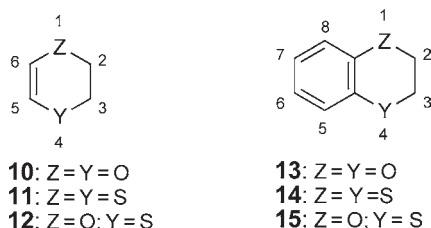
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8.12.1 Introduction

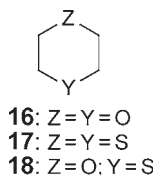
The present chapter consists of an update (1995–2006) of a particularly wide variety of ring systems described in CHEC-II(1996) (Chapter 6.09) <1996CHEC-II(6)447>. In the fully unsaturated compounds, the more comprehensively studied include 1,4-dioxin **1** and 1,4-dithiin **2**. Examples of 1,4-oxathiins **3** are rarer. The monobenzo-fused derivatives of all three rings, namely 1,4-benzodioxin **4**, 1,4-benzodithiin **5**, and 1,4-benzoxathiin **6**, have been investigated but it is the dibenzo analogs, dibenzo[*b,e*][1,4]dioxin or oxanthrene **7**, thianthrene **8**, and phenoxathiin **9**, which are perhaps the best known. Ring numbering is as shown in the formulae **1–9**, with oxygen taking priority over sulfur, when both heteroatoms are present.



Most partially saturated ring systems, 2,3-dihydro-1,4-dioxin **10** (sometimes named as 1,4-dioxene), 2,3-dihydro-1,4-dithiin **11**, 2,3-dihydro-1,4-oxathiin **12**, 2,3-dihydro-1,4-benzodioxin or 1,4-benzodioxane **13**, 2,3-dihydro-1,4-benzodithiin **14**, and 2,3-dihydro-1,4-benzoxathiin **15** are well investigated. Ring numbering for compounds **10–12** is followed as shown, independently of the presence of substituents.



Saturated rings like 1,4-dioxane **16**, frequently used as a solvent, 1,4-dithiane **17**, and 1,4-oxathiane **18** were first prepared at the turn of the twentieth century.



The International Agency for Research on Cancer (IARC) has classified 1,4-dioxane as a possible human carcinogen <1999MI1> and the World Health Organization (WHO) has suggested 50 ng/ml as the maximum contaminant level since 2002 <2000MI1>. A critical review of the information pertaining to the potential carcinogenicity of 1,4-dioxane indicates that a formal reevaluation of the carcinogenic potency of 1,4-dioxane is warranted <2003MI183>.

As polychlorinated 1,4-dibenzodioxins (PCDDs) are highly toxic chemicals, and well-known environmental pollutants and environmental estrogens, a lot of attention has been paid to 1,4-dibenzodioxins and their halogenated derivatives. Optical spectra and photophysical properties of PCDD derivatives have been thoroughly reviewed <2000RCR1037>.

1,4-Dioxins, 1,4-oxathiins, 1,4-dithiins, and annulated derivatives have been reviewed in 1997 <1997HOU(9a)1>. More recently, synthetic methods for preparing 1,4-dioxins and their benzo- and dibenzofused derivatives <2004SOS(16)15, 2004SL2449>, 1,4-dithiins <2004SOS(16)57> and 1,4-oxathiins, and their annulated analogs <2004SOS(17)19> have been reviewed.

8.12.2 Theoretical Methods

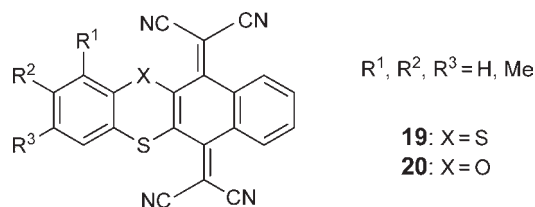
Although numerous theoretical studies were done in the past, theoretical attempts to model structural and physico-chemical properties are still an active field of research. These calculations are often compared with experimental data (see Section 8.12.3). Due to the toxicity of PCDDs, many theoretical investigations have been done on these compounds, otherwise known as oxanthrenes. Theoretical values for ionization energy (IE) were obtained with the best suitable AM1 Hamiltonian for chlorinated 1,4-dibenzodioxins and compared with experimental values. The ionization energy increases by approximately 100 meV for each additional chlorine substituent up to 2,8-dichloro-1,4-dibenzodioxin <1995IJM97>. PCDD IR spectra, simulated by *ab initio* calculations, reproduce the experimental IR spectra, including intensities, very well and allow unknown isomer identification <1995JA4167, 1997ANC1113, 2001JA3584>. Semi-empirical calculations for electronically excited states on PCDDs carried out in the Pariser–Parr–Pople (PPP), complete neglect of differential overlap/spectroscopic (CNDO/S), and intermediate neglect of differential overlap/screened (INDO/S) approximations taking into account singly excited electronic configurations were in good agreement with observed electronic spectra <1978JOM(146)235, 1998ZFK1251, 2000OPS42, 2000OPS339, 2000JST(553)243>. On the same family, a quantum structure–property relationship (QSPR) model for a nonpolar DB-5 fused silica-bonded phase capillary column has been developed to predict the retention times <2002MI451>.

Quantum chemistry calculations were performed using the INDO/S approximation of the electronic states and spin-orbital interactions, and experimental estimations were made for the fluorescence and phosphorescence rate constants. The substitution of Cl for H in the β -positions of 1,4-dibenzodioxin weakly affects the magnitude of the $3B_{1u}(\pi\pi^*)$ S_0 transition dipole moment which is lower in 2,3,7,8-tetrachloro-1,4-dibenzodioxin <1998PJP1251>. A theoretical investigation of the conformational change of tetrachlorinated 1,4-dibenzodioxins in the binding site of a dioxin receptor model was performed using the semiempirical AM1 method. Furthermore, a correlation between dioxins' toxicity and their absolute molecular 'hardness' was found <1999JST(475)203>. Full *ab initio* optimizations

were also performed on fluorinated 1,4-dibenzodioxins and theoretical calculations of HOMO coefficients of the unsubstituted 1,4-dibenzodioxin gave a good explanation for the observed regioselective metabolic attack at the 2,3,7,8-positions <1997ZNB1418>. Theoretical *ab initio* calculations using the Hartree–Fock (HF), B3LYP, and configuration interaction singles (CIS) methods have been done on the $S_1 \leftarrow S_0$ transitions of PCDDs <2003JMT(622)229> and have shown that 1,4-dibenzodioxin exists in a planar form whereas thianthrene exist as a puckered form <2003JST(655)451>. This was in accordance with the structural study on oxanthrene **7**, phenoxathiine **9**, and thianthrene **8**, calculated using MM3 and *ab initio* (3-21G* basis set) methods. Indeed, **7** was found to be planar although compounds **8** and **9** showed different degrees of nonplanarity, respectively 145.0° and 125.2° <1997JST(413)1>. Thianthrene derivatives were also studied in the context of doping-controlled spin alignment in a thianthrene-based molecular magnet <2005SM(152)469>.

Vibrational frequencies of 1,4-benzodioxin using the density functional theory (DFT) method, as well as the conventional HF and MM3 force-field methods, were calculated to evaluate the frequency prediction capability of each computational method and get a better understanding of the vibrational spectra <1998MI173>.

Molecular orbital calculations have been performed on compounds **19** and **20** <1994JOC4618>. The calculated PM3 equilibrium geometric structures show that these compounds are severely distorted from planarity in accordance with X-ray structural analysis (see Section 8.12.3.1). On the other hand, PM3 calculations performed on both neutral and oxidized/reduced compounds show that oxidation and reduction induce a clear gain of aromaticity. Predictions using the nonempirical valence effective Hamiltonian (VEH) method have shown that the electronic charge density in the highest occupied molecular orbital (HOMO) is localized on the benzodithiin **19** or benzoxathiin **20** rings.



For 1,4-dithiane **17**, the chair structure is more stable than the corresponding boat structure by 10.3 kcal mol⁻¹. The corresponding radical cation is calculated to be more stable in the boat form <2002JA8321>.

A theoretically estimated enthalpy of formation of 1,4-dithiane 1,1-dioxide was calculated from high-level *ab initio* molecular orbital calculations at the G2(MP2) level. The theoretical calculations appear to be in very good agreement with experiment (enthalpy of formation ($T = 298.15$ K) of 1,4-dithiane sulfone = -333.0 kJ mol⁻¹) <2006JOC2581>.

Concerning 1,4-dioxane **16**, its inversion has been studied by using *ab initio* molecular orbital theory at the HF/6-31G* and BLYP/6-31G* levels. The chair conformation is the lowest in energy, followed by the two twist-boats. The transition state connecting the chair and the twist-boats is a half-chair structure, in which four atoms in the ring are planar <1997PCA3382>.

8.12.3 Experimental Structural Methods

Optical spectra and photophysical properties of PCDD derivatives have been thoroughly reviewed <2000RCR1037>.

8.12.3.1 X-Ray Diffraction and Electron Diffraction

Many crystal structures of host compounds or solvate compounds with 1,4-dioxane as well as a wide range of organic structures bearing a 1,4-dioxin, 1,4-oxathiin, or 1,4-dithiin core have been determined by single crystal X-ray diffraction.

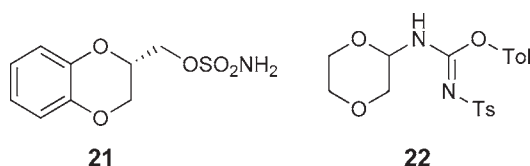
X-Ray diffraction studies on oxanthrene **7** have revealed a planar structure in the solid state. Thianthrene **8** and phenoxathiin **9** are both folded about the axis containing the two heteroatoms with dihedral angles of 138° and 128°, respectively <1996CHEC-II(6)447>. In many (poly)substituted thianthrenes, the dithiin ring is bent along the line passing through the sulfur bridges <1996JOC3041>. This 'butterfly angle' can be compared with typical values of 128–130° for simpler thianthrenes <1996T4745, 1997JCM272>. In the case of 1,4,6,9-tetraisopropylthianthrene, X-ray crystal structure determination revealed that bulky substituents such as *i*-Pr groups scarcely affected the structure of the parent dithiin framework <2006BCJ460>.

For 2,3-dihydro-1,4-dithiino[5,6-*c*]quinoline, the conformation of the 1,4-dithiin ring is a half-chair <1995JCX171>. The molecular structures of acenaphto[1,2-*b*][1,4]dithiine and 8,9-bis(methylsulfanyl)acenaphto[1,2-*b*][1,4]dithiine are folded along the S(1)⋯S(2) vector by 48° and 54°, respectively <1996J(P1)2451, 1999J(P2)755>. This conformation is in sharp contrast to the conformation of bis-acenaphto[1,2-*b*:1,2-*e*][1,4]dithiine, which, remarkably for an uncharged 1,4-dithiine derivative, is planar <1985JOC1550>. X-Ray geometric parameters obtained for compound **20** support theoretical calculations on molecular structure <1994JOC4618>.

Although substituted 1,4-dithiins revealed a boat structure in the solid state <1996CHEC-II(6)447>, the first isolation and X-ray structural analysis of the radical cation salt of non-benzo-annelated 1,4-dithiin derivatives indicated that the dithiin ring radical cation is planar in agreement with the theoretical prediction <1999TL4375>. The structure of the *cis,syn,cis*-photodimer obtained after irradiation of 1,4-dithiin has been unequivocally established by X-ray crystallographic methods as well as that of the tetrathiatetraasterane obtained by a further irradiation of the aforementioned dimer <1998TL9125>.

On the basis of differential scanning calorimetry (DSC) and X-ray analysis, two polymorphic forms of 2,6-diphenyl-1,4-dithiin were assigned: a metastable form (m.p. = 62–63 °C) in which the benzene ring and the double bond are nearly coplanar and a stable form (m.p. = 79–80 °C) where the benzene ring and the double bond are far from being coplanar <2004HAC424>. The molecular arrangement of 1,4-dioxane in the pure liquid phase has been investigated by X-ray and neutron diffraction methods. The liquid structure is similar to that of cyclohexane and is characterized by a long-range structure due to the periodicity in the molecular centers and a weak orientational correlation between adjacent molecules, in keeping with the behavior for a van der Waals molecule <1999MP(96)743>.

For compound **22**, X-ray analysis demonstrates that the dioxane ring adopts the chair conformation and that the imidoil amino group prefers an axial conformation <2002T2621>. For (1,4-benzodioxin-2(3*H*)-yl)methyl sulfamic acid ester **21**, the conformation of the dihydrodioxin ring is close to an ideal half-chair and for 1,2,4,6,7,9-hexafluoro-1,4-dibenzodioxin, an X-ray crystal structure has shown that the molecule is essentially planar and possesses a center of inversion <1995JFC(73)265>.



8.12.3.2 NMR Spectroscopy

The ¹H and ¹³C nuclear magnetic resonance (NMR) chemical shift of all the parent structures are fully reported in CHEC-II(1996) <1996CHEC-II(6)447>. Since then, the complete proton and carbon chemical shift assignments have been made for 2- and 3-formyl, acetyl, or methyl phenoxathiin <1996PJC36>.

Using one-dimensional (1-D) and 2-D ¹H and ¹³C NMR, the structure of substituted 2-vinyl-2,3-dihydrobenzo-1,4-dioxin regioisomers was unambiguously determined <1999EJO2665>. In the last decade, NMR spectroscopy has been extensively used to characterize polyhalogenated 1,4-dioxin and 1,4-dibenzodioxin derivatives and to predict or to verify their environmental and biological implications.

Several structural isomers of 2,5- and 2,6-disubstituted 1,4-dioxanes were identified using strong ¹H–¹H coupling effects in 2-D *J*, δ NMR spectra. The identification was achieved by measuring the coupling constants between the ring protons and then using (1) the Karplus relationship to determine whether the substituent was axial or equatorial, and (2) the planar–zigzag coupling to differentiate the 2,6-isomer and the 2,5-isomer <1997MI359>. ¹H NMR was also used to evaluate the hydration of the C–H groups in 1,4-dioxane, characterized by a small increase in δ_{CH} with increasing water mole fraction <2003PCB3972>. The NMR ²H spin-lattice relaxation times were measured to reveal the dynamics of water and 1,4-dioxane molecules in 1,4-dioxane-*d*₆–water and 1,4-dioxane–D₂O binary solutions <1999JML163>.

Conformational evidence of thianthrene, thianthrene 5-oxide, and *cis*- and *trans*-thianthrene 5,10-dioxides has been reported by studying ¹H NMR spectra in different solvents (CD₂Cl₂, toluene-*d*₈, THF-*d*₈; THF = tetrahydrofuran) and at various temperatures (from 25 to –130 °C) (see Section 8.12.4.3) <2005JOC3450>.

Another study from low-temperature ¹⁹F NMR spectra showed that the inversion of octafluoro-1,4-dithiane has $\Delta H^\ddagger = 8.2 \text{ kcal mol}^{-1}$, $\Delta G^\ddagger (25^\circ\text{C}) = 10.7 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -8.4 \text{ e.u.}$ The geminal coupling, ²*J*_{AB}, is 231 Hz <1998JFC(90)97>.

8.12.3.3 UV Spectroscopy

Representative ultraviolet (UV) spectra of nonaromatic but fully conjugated 1,4-dioxin and its sulfur analogs are given in CHEC-II(1996) <1996CHEC-II(6)447>. UV absorption spectra of PCDDs show a weak broad band at ~ 300 nm and a strong narrower band at ~ 230 nm <1995MI105, 1989JP2125>. In order to evaluate the limit for single frequency resonance-enhanced two-photon ionization, ultraviolet/visible (UV/Vis) solution spectra of 1,4-dibenzodioxin and tetrachloro-1,4-dibenzodioxin were measured <1995IJM97>. The kinetics of hydrolysis of dihydro-1,4-oxathiin derivatives were investigated by UV spectrophotometry <1996JK128> and complex stability constant ($\log K = 9.16 \pm 0.1$) was determined by UV/Vis titration experiments with thianthrene as ligand in a 1:2 aggregate $[\text{Ag}(\text{thianthrene})_2]\text{ClO}_4$ <2004OBC2897>.

8.12.3.4 IR, Raman, Fluorescence, and Phosphorescence Spectroscopy

The observed and calculated (on the basis of the modified many-body model) wave numbers, the Raman intensities, and the polarization ratios for 1,4-dioxane **16** have been fully reported <1996MI401>. Further studies have shown that the frequencies of infrared (IR) C–H stretching vibration modes of **16** increase and the absorption intensities of the modes decrease with increasing water concentration <2003PCB3972>.

The IR and Raman spectra of vapor-phase and liquid-phase 1,4-benzodioxan have been measured in the $4000\text{--}50\text{ cm}^{-1}$ range with the complete assignments of all vibrational modes <1998MI173, 2003JST(661–662)23>. The low-frequency vapor-phase (295°C) Raman spectrum of 1,4-benzodioxan show two A_2 out-of-plane ring twisting modes and two B_2 out-of-plane modes (ring bending and ring flapping) <2003JST(650)57>. A comparison of experimental and theoretical IR absorption frequencies was made on polychlorinated 1,4-benzodioxanes <1997ANC1113, 2000OPS(88)339>. The IR spectra of 76 dioxin congeners with zero to eight chlorines have been calculated by the DFT (B3LYP) methods. Simple rules for IR spectral analysis were provided and a characteristic IR peak around 1392 cm^{-1} is unique to all toxic congeners <2001JA3584>.

Fluorescence was used to investigate the excited-state dynamics of the radical cation of thianthrene (TH^+) <2001PCA6594>. The frequencies of the fundamental modes of the molecules of some dioxins in the ground electronic state were also determined by analysis of their fine-structure phosphorescence spectra <1999OPS(86)239, 1997OPS(83)92, 2000OPS(89)42, 2000OPS(88)339>.

The phosphorescence spectra of chlorinated 1,4-dibenzodioxins, in hexane solutions at 77 and 4.2 K, have a well-resolved vibronic structure with distinctions in quasi-linear phosphorescence spectra even for closely related isomers of polychlorinated dioxins <1998MI129>.

Emission electronic spectra of dioxins are characterized by phosphorescence and very low intensity fluorescence. The phosphorescence lifetime was found to change slowly as the number of the chlorine atoms varies in a dioxin molecule <2000JST(553)243>.

8.12.3.5 Mass Spectrometry

To complete the fragmentation patterns described in CHEC-II(1996) <1996CHEC-II(6)447>, ions formed by losses of S, HS, and H_2S are usually diagnostic of six-membered sulfur heterocycles. The relative abundance of ions in the spectra of 1,4-dithiins and 1,4-dithiafulvalenes allows unambiguous isomer differentiation <2003RCM547>. The typical behavior of PCDD/PCDFs in tandem mass spectrometry (MS/MS) is fragmentation with loss of COCl , 2COCl , COCl_2 , COCl_3 , and $(\text{CO})_2\text{Cl}$ <2004MI193>.

The effect of successive introductions of chlorine substituents on the IE of 1,4-dibenzodioxin was evaluated using the method of resonance-enhanced two-color two-photon ionization (REMPI) in a cold molecular jet combined with time-of-flight (TOF) mass spectrometry and comparison with other dioxins and theoretical values <1995IJM97, 1994IJM101>.

Mass spectra for clusters formed by the adiabatic expansion of liquid droplets of different mole fraction (χ_{dio}) 1,4-dioxane–water mixtures have been studied. For $\chi_{\text{dio}} = 0.01$, the hydrogen-bonded networks of water are predominant in the water-rich region with 1,4-dioxan molecules probably being captured in the network to form clathrates, but decrease exponentially with increasing χ_{dio} <1999JML163>.

8.12.3.6 Photoelectron Spectroscopy

The UV photoelectron spectra of 1,4-dioxin, 1,4-dithiin, 1,4-oxathiin, and their dibenzo derivatives as well as the saturated compounds were detailed in CHEC(1984) <1984CHEC(3)958>.

8.12.4 Thermodynamic Aspects

8.12.4.1 Intramolecular Forces

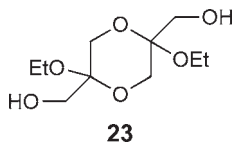
Boiling points and melting points of main compounds are reported in CHEC-II(1996) <1996CHEC-II(6)447>. Separation and thermal condensation of both pure regioisomers of 6- and 7-carboxy-2-hydroxymethyl-1,4-benzodioxane lead to infusible crystalline cyclic dimers having a very high melting point (>350 °C) <1996CL131>. When the orthorhombic form of 2,3,7,8-tetramethoxythianthrene is heated to 150 °C, an enantiotropic (reversible) phase transition into the monoclinic phase occurs. This phase transition was characterized by DSC, temperature-resolved X-ray powder diffractometry (TXRD), and thermally stimulated depolarization current (TSDC) measurements <1997BBG1889>.

Measurement of enthalpies of formation in the condensed and gas phase have shown that 1,4-dithiane 1,1-dioxide is 6.7 kJ mol⁻¹ more stable than 1,3-dithiane 1,1-dioxide <2006JOC2581>.

A few gas chromatography (GC) and liquid chromatography (LC) studies have been reported. For example, PCDDs have been separated on a 50 m × 0.25 mm polar fused silica capillary GC column (CP Sil-88, Chrompack) with helium as carrier gas and Fourier transform infrared (FTIR)/MS detectors <1997ANC1113>. Furthermore, a highly sensitive and accurate GC–MS method for rapid quantitative analysis of 1,4-dioxane in water has been described <1997JCH(787)283>.

Structure and dynamics of 1,4-dioxane–water binary solutions were also studied by X-ray diffraction, mass spectroscopy, and NMR relaxation. The structure of 1,4-dioxane–water mixtures changes with 1,4-dioxane mole fraction (χ_{dio}): in the range of $\chi_{\text{dio}} < 0.1$, the hydrogen-bonded network of water predominates in the mixtures; in a very narrow range of $0.1 < \chi_{\text{dio}} < 0.3$ small aggregates of water and 1,4-dioxane molecules are formed; and an ordered structure of 1,4-dioxane observed for pure liquid is evolved in the mixtures over a wide range of $\chi_{\text{dio}} > 0.3$ <1999JML163, 2003JML143>. The hydration of the CH groups in organic solutes having a polar group is indicated by the formation of blue-shifting C–H...OH₂ hydrogen bonds <2003PCB3972>. Salt-induced phase separation of 1,4-dioxane–water mixtures with NaCl has been investigated from the microscopic to mesoscopic scale by large-angle X-ray scattering (LAXS) and small-angle neutron scattering (SANS) methods. The X-ray radial distribution functions have shown that before phase separation the preferential hydration structures of Na⁺ and Cl⁻ are enhanced with increasing NaCl concentration and that after phase separation the structures of the organic and aqueous phases are practically similar to those of 1,4-dioxane–water mixtures at the corresponding solvent compositions. The higher the NaCl concentration the more the phase separation of the 1,4-dioxane–water–NaCl mixtures progresses, because hydrogen bonds between 1,4-dioxane and water molecules are gradually disrupted by the strong electrostatic field of the ions with increasing NaCl concentration; thus, the 1,4-dioxane mole fraction and volume of the 1,4-dioxane-rich phase increase with added NaCl concentration <2001PCB10101>. Finally, 1,4-dioxane is decomposed by combining sonolysis and photocatalysis in the presence of HF-treated TiO₂ powder. This synergistic effect is attributable to effective enhancement of photocatalysis by sonolysis <2004JPH75>.

For **23**, both hydroxyl groups in the *cis*- and *trans*-isomer act as donors in intermolecular two-center and three-center O–H...O hydrogen bonding, which may be classified as medium strong and weak. Additionally, there are C–H...O hydrogen-bonding interactions in each crystal: that in the *cis*-isomer is intramolecular <2003JST(647)223>.



From a coordination chemistry point of view, it is noteworthy that thianthrene has been used as a ligand for transition metals such as silver, palladium, platinum, and mercury <1986JCM2801, 1998ICA145>.

8.12.4.2 Aromaticity in the Unsaturated Series

1,4-Dithiins were first described as formally antiaromatic with some *ab initio* calculations starting to show that it could be classified as nonaromatic <1996CHEC-II(6)447>. However, more recently, on the basis of computational predictions of magnetic susceptibility and nuclear shielding constants, 1,4-dithiine and thianthrene behave as ordinary nonaromatic systems in response to an external magnetic field <2003CPL(375)583, 1999JMT(461–462)553>. On the other hand, experimental and theoretical evidence of aromaticity in 1,4-dithiin dication annelated with bicyclo[2.2.2]octene units was reported <1999CC777>.

8.12.4.3 Conformations

As reported in CHEC-II(1996), the conformation of 1,4-dioxin is planar (D_{2h} symmetry) and oxanthrenes have structures ranging from folded to near planar. 1,4-Dithiin seems to adopt the boat-like form rather than the planar. For thianthrene, the molecule exists as a folded C_2 shape. Finally, 2,3-dihydro-1,4-dioxin is more stable in the half-chair (twisted) conformation with C_2 symmetry <1996CHEC-II(6)447>. The chair conformation was claimed to be that preferred for 1,4-dioxane on the basis of semi-rigid model <1977JCP2874>, quantum-chemical AM1 and PM3 calculations <1990JMT(208)179>, and many NMR studies. This conformational analysis as applied to substituted 1,4-dioxanes has been thoroughly developed <1998AHC(69)251>. The *cis*- and *trans*-isomers of 2,5-diethoxy-2,5-bis(hydroxymethyl)-1,4-dioxane **23** crystallize in the monoclinic and orthorhombic system, respectively. The 1,4-dioxane ring of the *cis*-isomer molecule adopts a twist-boat conformation, while the ring of the *trans*-isomer is a chair. The two ethoxy groups in the *trans*-isomer are in more crowded axial positions, due to the anomeric effect. The anomeric effect, stronger in the *cis*-isomer, influences its stability, despite the presence of two bulky hydroxymethyl groups in the equatorial orientation and the low-energy chair conformation of the *trans*-isomer <2003JST(647)223>. Furthermore, X-ray crystallographic analysis has shown that the *endo*-anomeric effect controls the axial preference of the imidoyl amino group of dioxane ring conformers or anomers in compound **20** <2002T2621>.

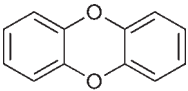
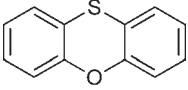
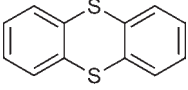
The potential energy barrier of 1,4-benzodioxan **13** to ring inversion is 1–2 kcal mol^{−1} lower than that of 1,4-dioxene **10**, typically 6.9 and 8.7 kcal mol^{−1} (HF/6-31G*) and 7.5 and 8.8 kcal mol^{−1} (B3LYP/6-31G*), respectively <1998MI173>.

The structure of phenoxathiin was studied based on photographic X-ray data <1991AXC381> and with *ab initio* calculations at the B3LYP/(6-31+G)+d level <2005JST(723)223>, at 3-21G* <1997JST(413)1> and with semi-empirical PM3 methods <1993OM775>. The puckering angle between the two halves of the heterocyclic ring was found around 142.3–160.0°.

A computational study of conformational interconversions in 1,4-dithiane has shown that the 1,4-boat transition state structure was 9.53–10.5 kcal mol^{−1} higher in energy than the chair conformer and 4.75–5.82 kcal mol^{−1} higher in energy than the 1,4-twist conformer <2003JCC909>. At the MP2/6-31G* level, the half-chair conformer of 2,3-dihydro-1,4-dithiin is 5.6 kcal mol^{−1} more stable than its eclipsed boat conformer <1998JCC1064>. Surprisingly, the most typical conformational behavior for substituted 1,4-dithianes has been shown to be the predominance of the axial conformer owing to intramolecular dipolar and steric interactions <1997PS(120/121)181>.

Calculated conformations, bond lengths, and bond angles which reproduce correctly the experimental values have shown that compound **7** is planar while molecules **8** and **9** show different degrees of nonplanarity (Table 1) <1997JST(413)1>.

Table 1 Conformations of compounds **7**, **8**, and **9**

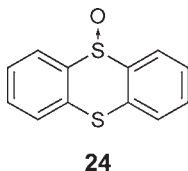
Molecule	Conformation ^a	Method	Reference
 7	Planar	X-Ray	1978AXB2956
	Planar	<i>Ab initio</i>	1990JMT(204)41
	Planar	MM3(96)	1997JST(413)1
	Planar	<i>Ab initio</i> (3-21G*)	1997JST(413)1
 9	147.7(1)	X-Ray	1991AXC381
	145.0	<i>Ab initio</i> (3-21G*)	1997JST(413)1
 8	131.4(3)	ED	1975J(F2)1173
	127.1(7)	X-Ray	1984AXC103
	140.6	NMR	1982J(P2)1209
	130	MM3(96)	1997JST(413)1
	125.2	<i>Ab initio</i> (3-21G*)	1997JST(413)1

^aIf a quantitative measure for nonplanar conformation is available, the dihedral angle (in degrees) is simply given.

Adapted from V. S. Mastryukov, K.-H. Chen, S. H. Simonsen, N. L. Allinger, and J. E. Boggs, *J. Mol. Struct.*, 1997, 413–414, 1.

Data on the apparent dipole moment and ¹H NMR spectra of thianthrene-5-oxide **24** under different conditions of solvent and temperature support the rapid conformational equilibrium of **24**, which flaps between two limit boat conformations with the sulfoxide group in a pseudoaxial or pseudoequatorial position, respectively. Variable-temperature

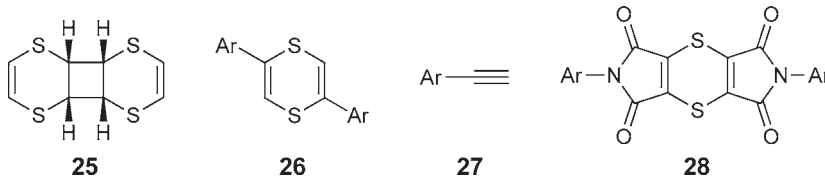
^1H NMR spectra have established the interconversion barrier of *trans*-thianthrene 5,10-dioxides and confirmed that the conformational equilibrium of *cis*-thianthrene 5,10-dioxides is strongly displaced toward the conformation with both sulfinyl groups in the pseudoequatorial position <2005JOC3450>.



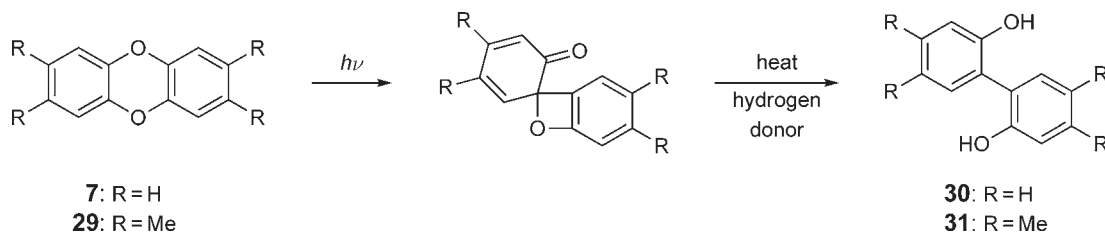
8.12.5 Reactivity of Fully Conjugated Rings

8.12.5.1 Unimolecular Thermal and Photochemical Reactions

In CHEC-II(1996), thermal stabilities of 1,4-dioxins and mainly 1,4-dithiin derivatives have been discussed <1996CHEC-II(6)447>. Since then, reports on unimolecular thermal and photochemical reactions on 1,4-oxathiins and their benzo derivatives are very rare. Concerning 1,4-dithiin derivatives, the photodimer **25** obtained by irradiation of 1,4-dithiin **2**, first reported by Gollnick and Hartmann <1982TL2651>, has been unequivocally established to have *cis,syn,cis*-stereochemistry <1998TL9125>. For 2,5-diaryl-1,4-dithiins **26**, irradiation in benzene solution with short wavelength UV light led to a novel fragmentation forming the corresponding aryl alkynes **27**. <1997SUL15> Heating 1,4-dithiintetracarboxydiimide structures **28** above their melting temperature caused decomposition of the dithiine ring with elimination of one sulfur atom to give a thiophene <2005RRC601>.



Irradiation of 1,4-dibenzodioxins **7** and **29** in aqueous ($\text{CH}_3\text{CN-H}_2\text{O}$) and organic solutions (CH_3CN , THF, 1,4-dioxane, 2-propanol, and methanol) gives 2,2'-dihydroxybiphenyls **30** and **31**, respectively, as the major products <1994JPH199, 1993CC409>. Evidence of 2-spiro-6'-cyclohexa-2',4'-dien-1'-one and subsequent 2,2'-biphenylquinone intermediates have been reported (Scheme 1) <2005PPS876>. Under similar conditions, chlorinated 1,4-dibenzodioxins gave the corresponding 2,2'-biphenols via the singlet excited state <2006CL348>.

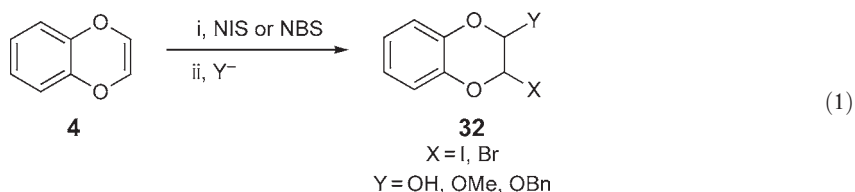


Scheme 1

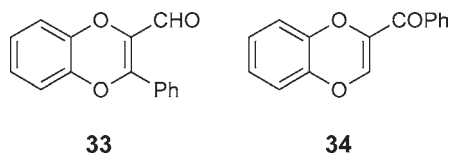
8.12.5.2 Electrophilic Attack at Carbon

8.12.5.2.1 At carbon of the heterocyclic ring

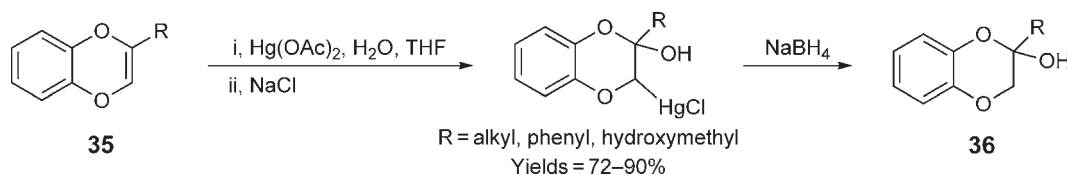
Since the publication of CHEC-II(1996), only a few papers deal with the reactivity of 1,4-benzodioxin. For example, as shown in Equation (1), treating **4** with *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) followed by an appropriate nucleophile gave various 2,3-disubstituted-1,4-benzodioxanes **32** in a simple one-pot procedure <2001HCO135>.



Subjected to a mixture of nitric acid/acetic acid, ethyl 1,4-benzodioxin-2-carboxylate did not lead to the expected 6-substituted product but led to a complicated mixture from which 52% of ethyl 3-nitro-1,4-benzodioxin-2-carboxylate was isolated <1997SC431>. Under acidic conditions, addition of water at the double bond of 2-phenyl-3-formyl-1,4-benzodioxin **33** afford an hemiketal which recycled. After dehydration, the 2-benzoyl-1,4-benzodioxin **34** was isolated in very good yield <2000CHE351>.

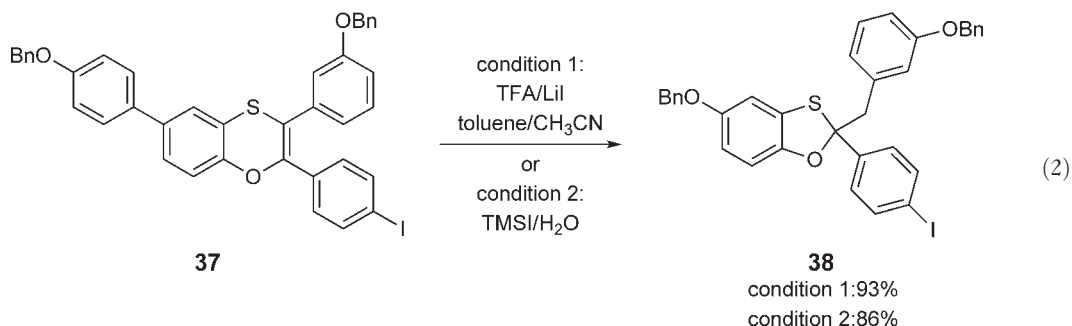


The oxymercuration reaction of various 2-substituted 1,4-benzodioxin derivatives **35** in the presence of a suspension of mercuric acetate in water/THF followed by treatment *in situ* with sodium chloride and then with sodium borohydride as a reducing agent provided in excellent yields the expected hemiketals **36** (Scheme 2) <1997T2061>.



Scheme 2

An interesting rearrangement was observed when 2,3,6-trisubstituted-1,4-benzoxathiin **37** was reacted with HI or TMSI/H₂O (TMSI = trimethylsilyl iodide). As shown in Equation (2), a selective 1,2-migration of the sulfur atom affords 1,3-benzoxathiole **38** <2004TL3729>.

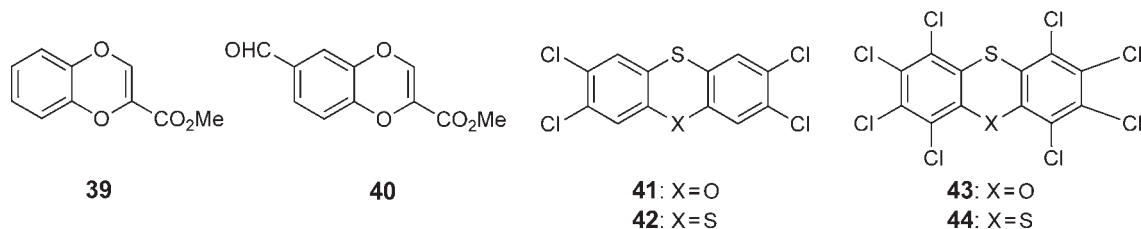


8.12.5.2.2 At carbon of an aromatic ring

In addition to the reactivity reported in CHEC-II(1996) <1996CHEC-II(6)447>, 2-substituted-1,4-benzodioxins were reacted in a solvent-free Friedel-Crafts acylation employing AlCl₃-DMA, AlCl₃-DMSO, or AlCl₃-DMF reagents with acyl halides or anhydrides to provide the 6-acyl compounds as the major products (DMA = dimethylacetamide; DMSO = dimethyl sulfoxide; DMF = dimethylformamide) <1997SC1291, 1999TL3523>. The electrophilic

formylation of the ester **39**, performed with dichloromethyl methyl ether in the presence of aluminium trichloride, gave 75% of methyl 6-formyl-1,4-benzodioxin-2-carboxylate **40** <1997SC431>.

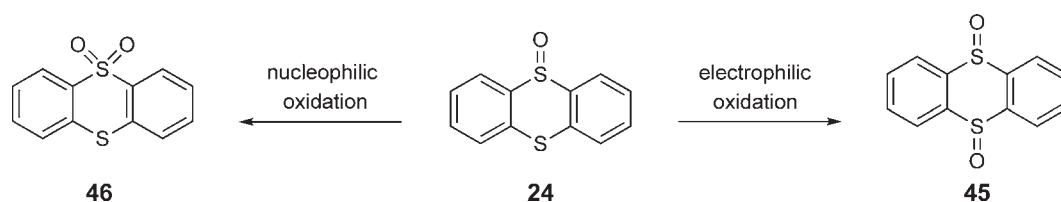
Phenoxathiin and thianthrene can be chlorinated without oxidation into the corresponding sulfoxides using sulfuryl chloride and AlCl_3 to form the 2,3,7,8-tetrachloro derivatives **41** and **42**, respectively. Use of BMS reagent – a mixture of sulfur monochloride, sulfuryl chloride, and aluminium chloride – results in exhaustive chlorination of phenoxathiin and thianthrene with formation of perchlorinated products **43** and **44**. It is noteworthy that using sulfuryl chloride in dichloromethane, the sulfoxides were isolated as the major products <1997CHE333>.



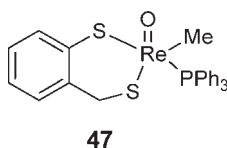
8.12.5.3 Electrophilic Attack at Sulfur

Many oxidizing agents have been used to afford almost all the possible oxide derivatives of 1,4-dithiin, 1,4-benzoxathiin, 1,4-benzodithiin, thianthrene, and phenoxathiin <1984CHEC(3)943, 1996CHEC-II(6)447>.

It is noteworthy that thianthrene-5-oxide **24** was introduced in 1984 as a general mechanistic probe for determining the electrophilic or nucleophilic character of a given oxidant. Thus, electrophilic oxidants should prefer to react with the sulfide moiety of **24** to yield disulfoxide **45**, while nucleophilic oxidants should preferably react at the sulfoxide site of **24** to give sulfone **46** (Scheme 3) <1991JA6202, 1986AGE101, 1986AGE188, 1984JA5020>. Nevertheless, this application could lead to misleading interpretations because of the oxidation mechanism involved as well as the conformational mobility of **24** <2004JOC9090, 2005JOC3450>. Oxidation of thianthrene **8** continues to be studied. The mono- and dioxide products have been isolated in very high yields (>96%) using *t*-BuOOH (1 equiv and 3 equiv, respectively) with 1 mol% of the oxorhenium(v) dithiolate catalyst **47** without any traces of sulfone derivatives <2002IC1272>. Substrate **24** is oxidized at the sulfide site to give **45** with >99:1 selectivity using an equimolar amount of H_2O_2 and a tungstate catalyst <2001T2469>. Furthermore, air oxidation of phenoxathiin and thianthrene catalyzed by nitrogen oxides allow the chemoselective formation of phenoxathiin and thianthrene sulfoxides (yields >93%) <1995J(P1)1057>. Finally, thianthrene 5,5,10,10-tetraoxide can be obtained by full oxidation of thianthrene **8** with 8 equiv of H_5IO_6 and 2 mol% of CrO_3 <2003JOC5388>.

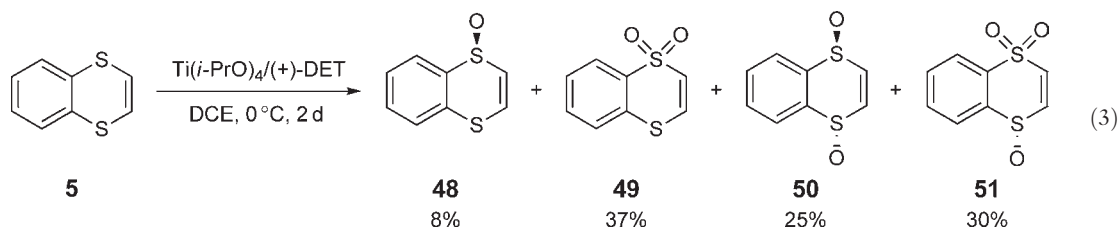


Scheme 3

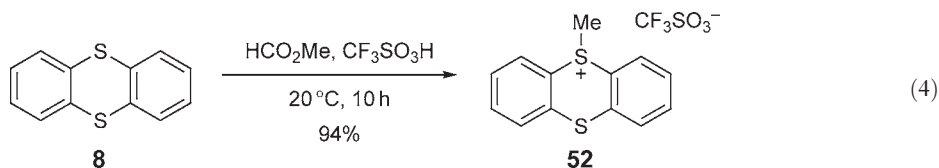


Dioxygenase-catalyzed sulfoxidation of 1,4-benzodithiin and its dihydro analog using whole cells of *Pseudomonas putida* gave the corresponding monosulfoxides with high ee values (>98%) and was enantioselective. Single enantiomers of 1,4-benzodithiin sulfoxide **48** had already been isolated, in a separable mixture with the corresponding achiral sulfone

49, *trans*-bis-sulfoxide **50**, and the sulfone-sulfoxide **51**, by direct asymmetric oxidation of the parent 1,4-benzodithiin with the modified Sharpless reagent [Ti(IV)/(+)-diethyltartrate/*t*-butyl hydroperoxide] (Equation 3) <1996TA369>.

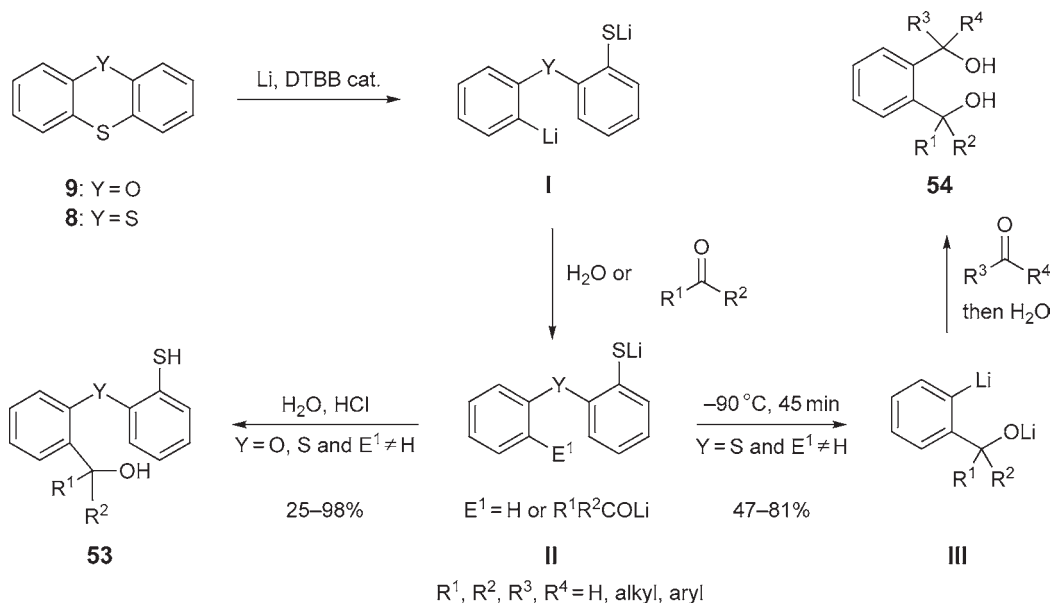


Another aspect of the reactivity of the sulfur atom is illustrated by a reaction done on thianthrene. Indeed, **8** is not sufficiently nucleophilic to be alkylated by methods that work well with dialkyl and alkyl aryl sulfides, although Saeva was able to alkylate it by reaction with *p*-cyanobenzyl bromide and silver triflate <1986T6123>. The sulfonium salt **52** bearing a methyl group can be obtained by an acid-promoted reaction with methyl formate (Equation 4) <1998JOC7522>.



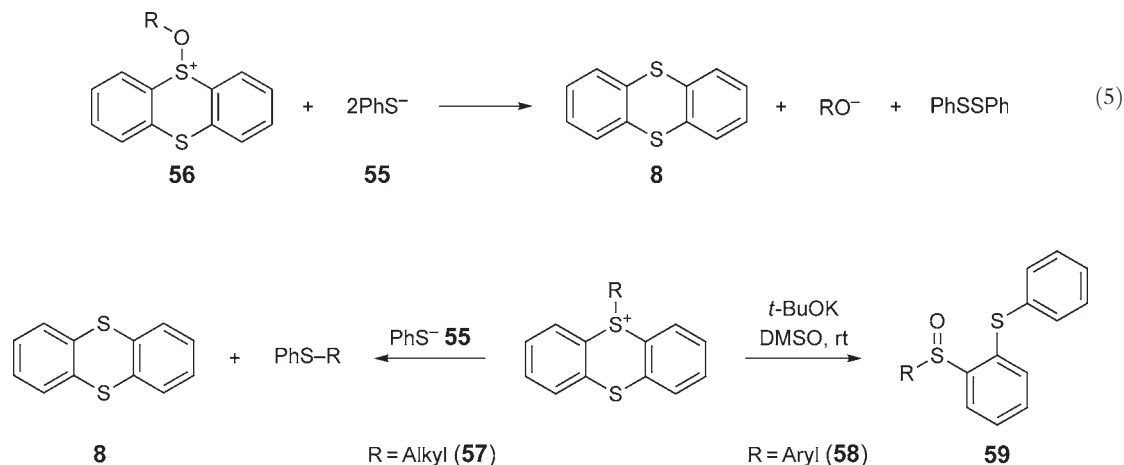
8.12.5.4 Nucleophilic Attack at Sulfur

In addition to the few examples of nucleophilic attack at the sulfur atom of thianthrene, phenoxathiin oxide, and thianthrene oxide, described in CHEC-II(1996) <1996CHEC-II(6)447>, the arene-catalyzed lithiation methodology was applied to the reductive ring opening of phenoxathiin **9** and thianthrene **8**. The lithiation of these heterocycles with lithium and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB, 7.5 mol%) in THF at temperatures ranging from -90 to -78°C gives the corresponding functionalized organolithium intermediate **I**, which by reaction with different electrophiles, followed by hydrolysis, furnishes the expected functionalized thiols **53**. In the case of thianthrene, intermediate **II** can be lithiated again and react with a second electrophile (carbonyl derivative) to afford diols **54** (Scheme 4) <2003T2083, 2002CL726>.



Scheme 4

Reaction of thiophenoxide ion **55** with 5-alkoxythianthrenium salts **56** occurred exclusively at the 5-thianthrene sulfur atom. The alkoxy group was displaced and thianthrene was formed while thiophenoxide was converted into diphenyl disulfide (Equation 5). In contrast, reactions of thiophenoxide with 5-alkylthianthrenium salts **57** were deduced to follow an S_N2 pathway (or an elimination pathway, if R = cycloalkyl) while 5-aryl thianthreniums **58** lead mainly to diaryl sulfides **59** via a ring opening in the presence of *t*-BuOK in DMSO (Scheme 5) <2002JPO139, 2001JPO81, 1999JPO827, 1999JHC617>.

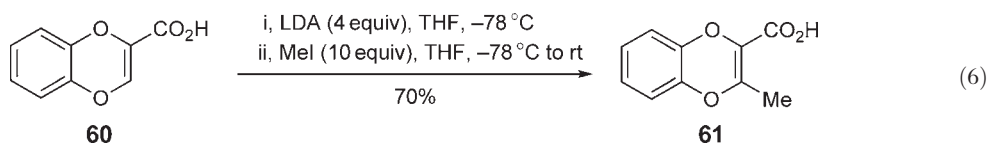


Scheme 5

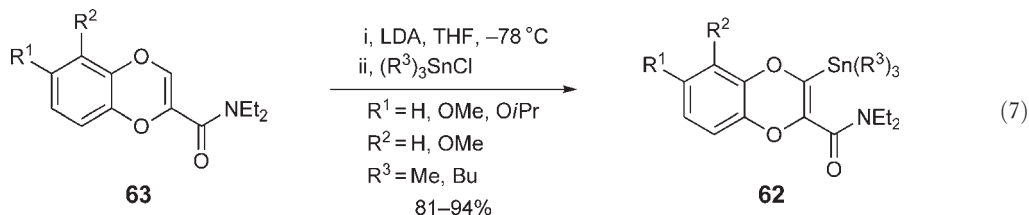
8.12.5.5 Nucleophilic Attack at Hydrogen

8.12.5.5.1 At hydrogen of the heterocyclic ring

1,4-Dithiin, 1,4-benzodioxin, and its 2-substituted derivatives can be readily deprotonated and trapped with electrophiles although the reaction is more problematic with 1,4-dioxin. Oxanthrene and phenoxathiin are cleaved with lithium <1996CHEC-II(6)447>. A more recent example deals with the metallation at C-3 of the 1,4-benzodioxane **60** bearing a carboxylic acid function at C-2, with lithium diisopropylamide (LDA) and subsequent quench with iodomethane. The corresponding 3-methylated benzodioxane **61** was isolated in 70% yield (Equation 6) <2000EJM663>.

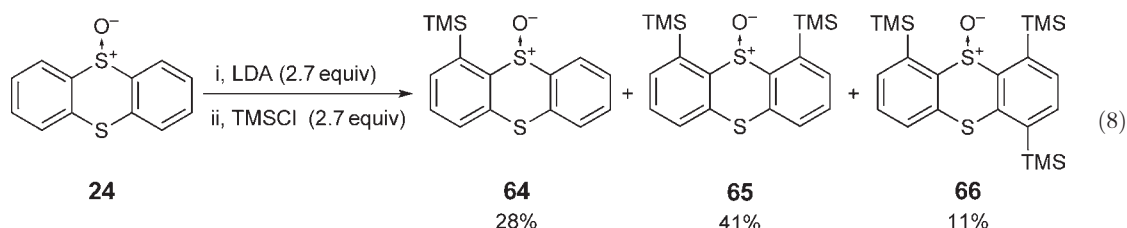


Concerning the synthesis of 3-stannylbenzo[1,4]dioxin-2-carboxamides **62**, when compounds **63** were treated with LDA (2 equiv) at -78 °C, the corresponding metallated heterocycles were reacted with the trimethyltin or tributyltin chloride providing vinylstannanes **62** in high yields (Equation 7) <1997TL5635>. In the naphtho[2,3-*b*][1,4]dioxin series, the 2-diethylamido derivative can be metallated with LDA at -78 °C and quenched with aldehydes <2002T1533>.



8.12.5.5.2 At hydrogen of an aromatic ring

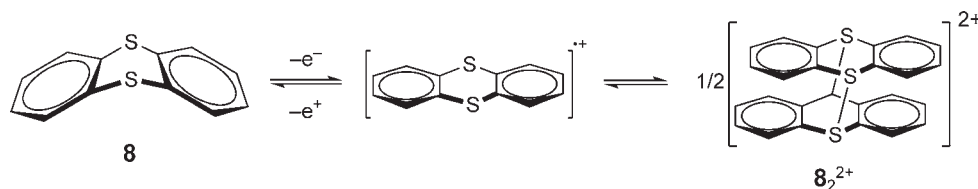
Metallation of the aromatic ring of 1,4-benzodioxin, oxanthrene, phenoxathiin, and thianthrene have been reported with butyllithium. The monolithiation occurs respectively at position 5, position 1, and position 4. When phenoxathiin was reacted with excess of *n*-butyllithium, followed by quenching with carbon dioxide, the 4,6-diacid was obtained in satisfactory yield <1996CHEC-II(6)447>. 4,6-Dilithiation of thianthrene seems difficult; however, starting from the 5,5-dioxide derivatives, synthesis of the 4,6-diacid was achieved by metallation <1957JA208>. More recently, lithiation of thianthrene 5-oxide, then trapping with chlorotrimethylsilane, gave 4-mono-, 4,6-di-, and 4,6,9-tri-TMS derivatives **64**, **65**, and **66** (Equation 8). Reduction of the sulfoxide afforded the corresponding substituted thianthrenes <1996T4745>. Dilithiation of the 3,7-dimethylphenoxathiin has been reported for the synthesis of new chiral ligands <1998AGE3116>.



8.12.5.6 Reactions with Radicals, Carbenoid, Electron-Deficient Species

The preparation of a number of 5-(alkyl)thianthrenium perchlorates has been performed from the thianthrene cation radical with dialkylmercurials and tetraalkyltins (R_4Sn) <1983JOC143>. Thianthrene as well as phenoxathiin cation radical perchlorates react with alkenes. The former add stereospecifically to cycloalkenes although the latter afforded a mixture of mono- and bis-adducts in which the configuration of the alkene was retained <2003JOC8910>.

The one-electron oxidation of thianthrene under superdry conditions is followed by a planarization of the ring system and a dimerization via the sulfur atoms to give 8_2^{2+} (Scheme 6) <2004OBC2897>.

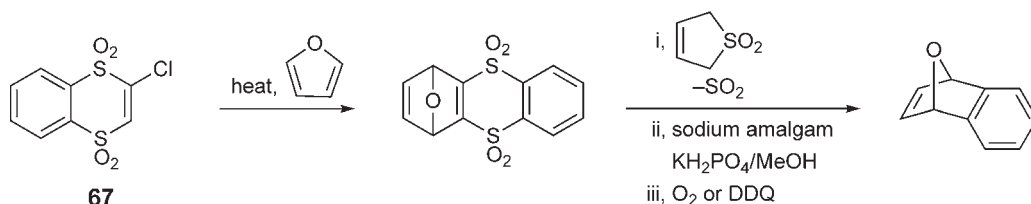


Scheme 6

Furthermore, thianthrene react with 2-diazo(fluoroalkyl)acetoacetates under mild conditions in the presence of catalytic $Rh_2(OAc)_4$ to afford the corresponding sulfonium ylides as the major products <2004JFC(125)1071>. In addition to all the desulfurization conditions reported in CHEC-II(1996) <1996CHEC-II(6)447>, a new efficient reagent was developed. Introduction of the sodium salt of 3-hydroxy-*N*-methylpiperidine into the aggregates of NiCRA's ($NaH-RONa-NiX_2$) led to 83% yield of desulfurized thianthrene in 30 min <1998TL8987>.

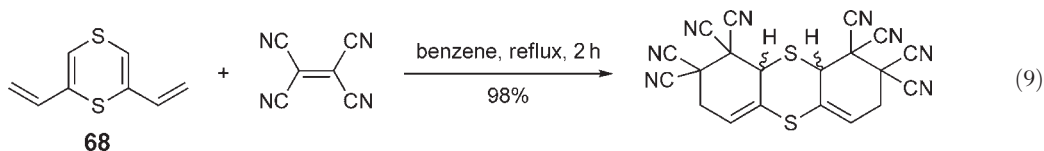
8.12.5.7 Cyclic Transition State Reactions with a Second Molecule

Photooxygenations of 1,4-dioxins and their benzo- and naphtho derivatives as well as the ozonolyses of 1,4-benzodioxins and the cycloaddition of dithiins and 1,4-benzodithiins have been reported <1996CHEC-II(6)447>. In more recent reports, 2-chloro-1,4-benzodithiin-1,1,4,4-tetraoxide **67** was employed as a very reactive dienophile <1997G393, 2005JOC5221> and was suggested as a mild alternative to the use of benzyne in [4+2] cycloaddition reactions (Scheme 7) <1996T14247>.



Scheme 7

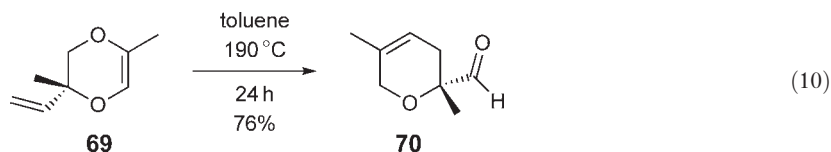
Furthermore, the synthetic utility of 2,6-divinyl-1,4-dithiin **68** as a reactive diene in Diels–Alder reactions was reported with tetracyanoethylene, maleic anhydride, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate (DMAD) and allowed the preparation of various dihydrothianthrene derivatives (Equation 9) <2003S849>.



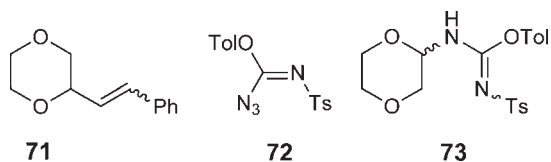
8.12.6 Reactivity of Nonconjugated Rings

8.12.6.1 Unimolecular Thermal Reactions and Photochemical Reactions

A Claisen rearrangement of the 1,4-dioxene **69** provided the pyran **70** asymmetrically (Equation 10) <1998JA12702>.



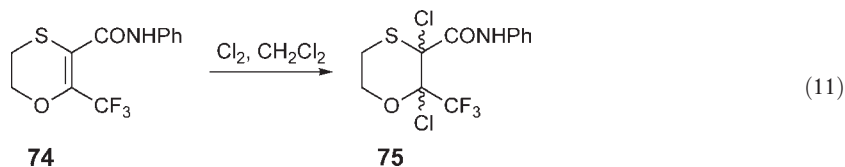
Under microwave irradiation, 1,4-dioxane directly adds to phenylacetylene to generate styryldioxane **71**. The best result was obtained without using any catalyst <2004TL7581>. Furthermore, thermal decomposition of *O*-(*p*-methylphenoxy) *N*-(*p*-methylbenzenesulfonyl)azidoformimidate **72** in refluxing 1,4-dioxane affords isourea **73** <2002T2621>.



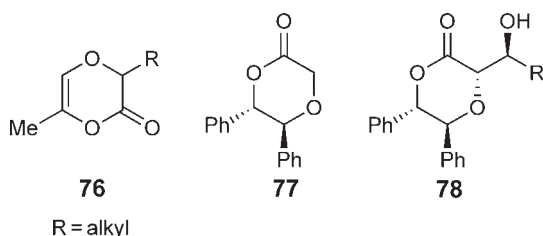
8.12.6.2 Electrophilic Attack at Carbon

8.12.6.2.1 At carbon of the heterocyclic ring

Bromination of 2,3-dihydro-1,4-dithiin **11** gave the unstable 2,3-dibromo-1,4-dithiane <1998JOC3952>. Chlorination of trifluoromethylated dihydro-1,4-oxathiin **74** in a methylene chloride solution at room temperature gives a 1:1 mixture of *trans*- and *cis*-dichloro-1,4-oxathianes **75**. The mixture of stereoisomers is explained by the strong electron-withdrawing effect of the trifluoromethyl group which leads to increased ionic character by involvement of the lone-pair electron of oxygen to form an oxonium ion intermediate (Equation 11) <1999BKC1218>. When nonfluorinated dihydro-1,4-oxathiins were used, no chlorinated intermediates were isolated, and an isomeric dihydro-1,4-oxathiin was observed <1995H(39)921>. Bromination of 1,4-oxathiane **18** affords the labile *trans*-2,3-dibromo-1,4-oxathiane in quantitative yield. The bromination probably proceeds via 2,3-dihydro-1,4-oxathiin **12** as intermediate <1996S198>.

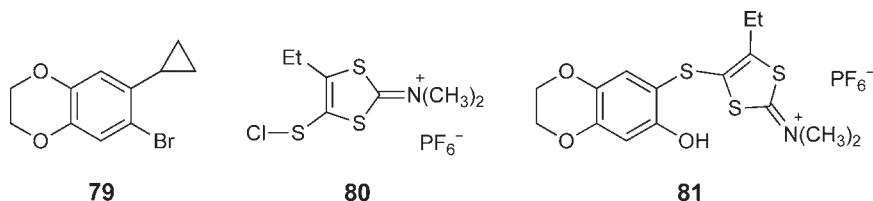


The formylation of phenoxathiin through the Duff reaction afforded 2-formylphenoxathiin <1998MI85>. 1,4-Dioxane reacts with *N*-chlorobenzotriazole in 54% yield in the presence of 20 mol% of TiCl_4 to afford the corresponding α -(benzotriazol-1-yl)alkyl ether <1999H(51)1877>. 1,4-Dioxane is also chlorinated with SO_2Cl_2 at 80 °C for 1 h to give 92% of 2,3-dichloro-1,4-dioxane <1998JPP10067773> and monofluorinated in $\text{Et}_4\text{NF} \cdot 4\text{HF}$ by direct electrochemical fluorination <2002TL1503>. 1,4-Dioxene **11** reacts with triphenylmethanethiosulfonyl chloride at room temperature under nitrogen atmosphere to give *trans*-2-chloro-3-(triphenylmethyldithio)-1,4-dioxane <1998JOC8654>. 3-Alkyl-6-methyl-2,3-dihydro-1,4-dioxin-2-ones **76** undergo an acetylation reaction in position 5 with acetyl chloride in the presence of zinc(II) chloride <2003RJO707>. In the saturated series, boron enolates of 1,4-dioxan-2-one **77** were found to undergo an asymmetric aldol addition to afford protected *anti*-1,2-diols **78** <2000OL3035, 2002TL1789>.



8.12.6.2.2 At carbon of an aromatic ring

As already mentioned in CHEC-II(1996), several electrophilic substitution reactions (acylation, formylation, halogenation, sulfonation, chlorosulfonation, amination) have been reported on 2,3-dihydro-1,4-benzodioxin **13** as well as the bromination of 1,4-benzodithiane <1996CHEC-II(6)447>. In the recent literature, most attention was paid to **13**. Thus, bromination using (diacetoxyiodo)benzene and lithium bromide as electrophilic Br^+ source afforded 6-bromo-2,3-dihydro-1,4-benzodioxin in 74% yield <2004SL461>. Reaction of β -ethylsulfanypropionyl tetrafluoroborate with 1,4-benzodioxane and subsequent elimination results in formation of the vinyl ketone group at C-6 <1998SRI89>. Nitration at position 6 of 7-cyclopropyl-1,4-benzodioxane has proved to be possible without ring opening of the cyclopropane substituent by the bromine atom *ipso*-substitution mechanism of the 6-bromo derivatives **79** with N_2O_4 <1999CHE281>. 6-Hydroxy-1,4-benzodioxane undergoes aminomethylation with poor regioselectivity <2000H(53)197> and also reacts with electrophile **80** to afford **81** as a single regioisomer <2004EJO1455>. Acylation of 2-substituted-1,4-benzodioxin derivatives using AlCl_3 -DMSO, AlCl_3 -DMF, or AlCl_3 -DMA affords the 7-acyl regioisomers as the main compounds <1997SC1291, 1999TL3523>. Spectroscopic studies show the presence of coordination compounds as reaction intermediates, thus explaining the observed regioselectivity <2000MOL319>.

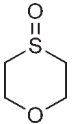
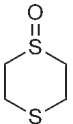


8.12.6.3 Electrophilic Attack at Sulfur

One of the main research interests in this area is to find new oxidizing agents having the highest chemoselectivity to obtain the sulfoxide derivatives without overoxidation to sulfones. 1,4-Oxathiane **18** was often used as a model sulfur-containing compound to afford **82** (Table 2) and **17** similarly gave **83**. *cis*-2,6-Dimethyl-1,4-dithiane was oxidized to the

corresponding sulfones and sulfoxides using various oxidants: NaIO₄, H₂O₂, Jones' reagent, and *t*-pentyl hydroperoxide in the presence of Mo(CO)₆ or MoCl₅. Configurations of the oxidation products were determined <1999RJO1073>.

Table 2 Chemoselective oxidation of sulfides to sulfoxides

Sulfides	Sulfoxides	Oxidizing agent	Experimental conditions	Isolated yield (%)	Reference
 18	 82	H ₂ O ₂ (1 equiv)/F ₂₀ TPPFe (0.09%) ^a	EtOH, rt, 4 min	85	2004JOC3586
		Hydroperoxy sultams (1 equiv)	MeOH, rt, 1 h	95	2002JOC8400
		CAN, hydrated silica gel	CH ₂ Cl ₂ , rt, 50 min	100	1998SC2969
		Ca(OCl) ₂ (0.6 equiv), moist alumina	CH ₂ Cl ₂ , rt, 50 min	85	1997S1161
		H ₅ IO ₆ (1.1 equiv)/FeCl ₃ (0.03 equiv)	CH ₃ CN, rt, 1 h	64	2002S2484
		MMPP ^b (0.55 equiv), wet silica gel	CH ₂ Cl ₂ , rt, 1 h	94	1997S764
		Br ₂ (1.05 equiv), hydrated silica gel	CH ₂ Cl ₂ , 0 °C, 50 min	100	1998S1238
		BAAOD ^c (1.2 equiv)	CH ₃ CN, reflux, 1 h	89	2003PS(178)2441
 17	 83	65% HNO ₃ , P ₂ O ₅ /silica gel (64% w/w) (1 equiv)	neat, rt, 6 min	89	2005TL5503
		<i>N</i> - <i>t</i> -Butyl- <i>N</i> -chloro-cyanamide (1 equiv)	CH ₃ CN/H ₂ O, rt	90	2005CL1230

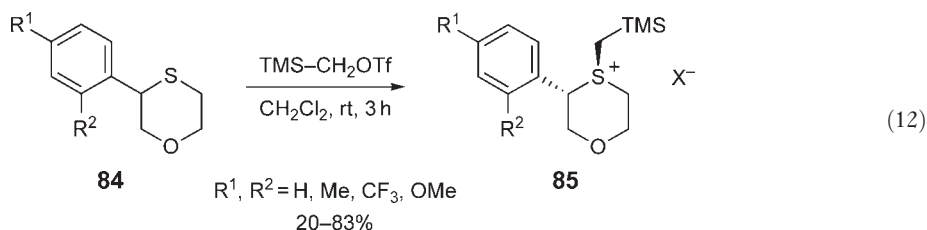
^aF₂₀TPPFe = iron tetrakis(pentafluorophenyl)porphyrin.

^bMMPP = magnesium monoperoxyphthalate.

^cBAAOD = 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate.

Oxidation of 2,5,7-trisubstituted 2,3-dihydrobenzoxathiin affords a mixture of *cis*- and *trans*-sulfoxides with the *trans*-isomer dominant and the aryl group in position 2 being pseudoequatorial in both isomers <2001CC551, 2004MI317>. Enantioselective oxidation of 2,3-dihydro-1,4-benzodithiin **14** and 2,3-dihydro-1,4-benzoxathiin **15** has been performed using a fungal biocatalyst. The enantiomeric excesses of the resulting chiral sulfoxides were moderate (54% and 88%, respectively) but recrystallization of the latter afforded the enantiopure (*R*)-material <1999CJC463>.

Moreover, the sulfur atom of 1,4-oxathianes can be alkylated. Thus, reaction of 3-aryl-1,4-oxathianes **84** with (trimethylsilyl)methyl trifluoromethanesulfonate gave a mixture of *cis*- and *trans*-isomers of 3-aryl-4-(trimethylsilyl)-methyl-1,4-oxathanium triflates **85** (Equation 12) <1997J(P1)715>.



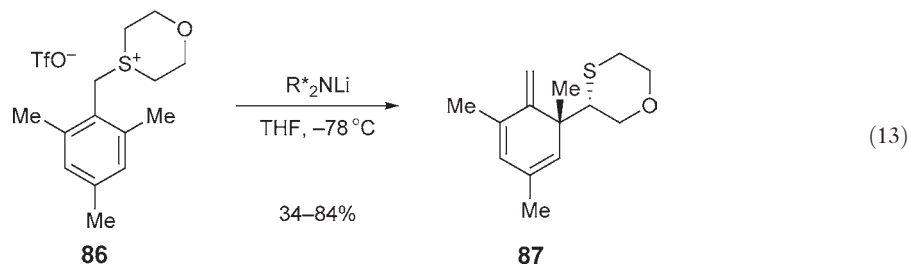
8.12.6.4 Nucleophilic Attack at Hydrogen

8.12.6.4.1 At hydrogen of the heterocyclic ring

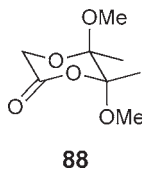
Metallation of 2,3-dihydro-1,4-dioxins and 2,3-dihydro-1,4-dithiins has been extensively studied and allows useful functionalization of the heterocycles. However, treatment of oxathiane and dithiane with LDA provided the ring-opened products. Similarly, 2,3-dihydro-1,4-benzodioxins, 2,3-dihydro-1,4-benzodithiins, and 2,3-dihydro-1,4-benzoxathiins were described to give ring modification under anionic conditions <1996CHEC-II(6)447>. Metallation of 2,3-dihydro-1,4-dioxins is still widely employed. Thus, 2-metallo-1,4-dioxene has been quenched by various electrophiles such as selenium <1998JMC1945>, aminoallenes <2002T10329>, and bulky ketones <2002JOC4904>. In the case of 2,3-dihydro-1,4-benzodioxins, the difficulty of direct metallation has led to alternative approaches going through a halogen–metal exchange being reported (see Section 8.12.7.2). Metallation of 2,3-dihydro-1,4-dithiin **11**

with 2 equiv of LDA afforded the 5,6-dilithio-2,3-dihydro-1,4-dithiin which was reacted with selenium followed by titanocene dichloride for the synthesis of selenafulvalene derivatives <1991SM(41)2093>.

Chiral bis-lithium amide bases have been used for enantiotopic deprotonation of the sulfonium salt of 1,4-oxathiane **86**. The anion undergoes an enantioselective thia-Sommelet rearrangement to afford the 3-substituted-1,4-oxathiane **87**. Only bis-lithium amide bases were effective, giving products with high diastereoselectivity and with low to moderate enantioselectivity (Equation 13) <2003TL8203>.

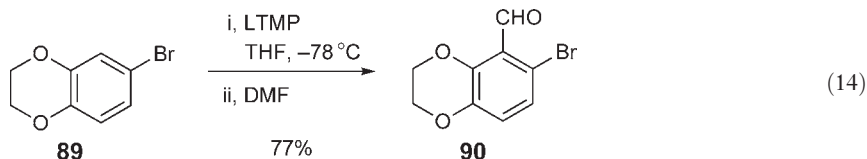


5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-one **88** (or butane-2,3-diacetal desymmetrized glycolic acid) is deprotonated and reacted with various electrophiles such as alkyl halides, ketones, aldehydes, and α,β -unsaturated carbonyls or nitro olefins to give the corresponding alkylated products with excellent selectivity in all cases <2003S1598, 2001AGE2906, 2001OL3749, 2002S1973, 2001OL3753, 2001AGE4763>.



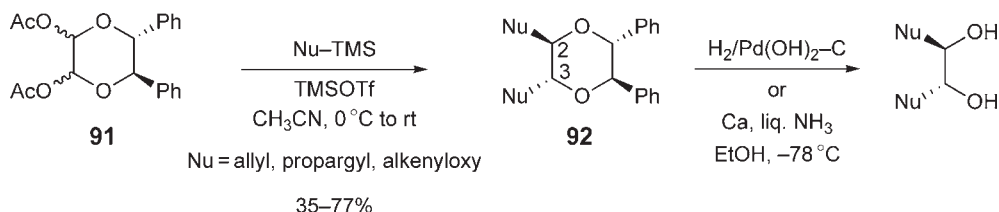
8.12.6.4.2 At hydrogen of an aromatic ring

As already mentioned in CHEC-II(1996) <1996CHEC-II(6)447>, substituted 2,3-dihydro-1,4-benzodioxins can be lithiated by butyllithium in THF at low temperatures although attempted lithiation of 1,4-benzodioxane **13** gave only the ring-opened product catechol monovinyl ether <1978CIL234>. To investigate whether an additional halogen atom would increase the thermodynamic acidity of the *ortho*-hydrogen and shift the reaction with lithium bases from ring opening to *ortho*-lithiation, deprotonation of 6-bromo-2,3-dihydro-1,4-benzodioxane **89** was studied. A rapid deprotonation occurred with 1.1 equiv of either LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at -78°C . Subsequent quenching of the aryllithium with DMF gave the expected benzaldehyde product **90** in good yields (>68%) (Equation 14) <1999JOC8004>. A similar sequence of *ortho*-lithiation/iodination with LDA on 6-diphenylphosphino-1,4-benzodioxane via a thermodynamically controlled process, instead of the generally used iodination with diiodoethane, gave 6-diphenylphosphino-5-iodo-1,4-benzodioxane in 75% isolated yield <2002TL2789>.



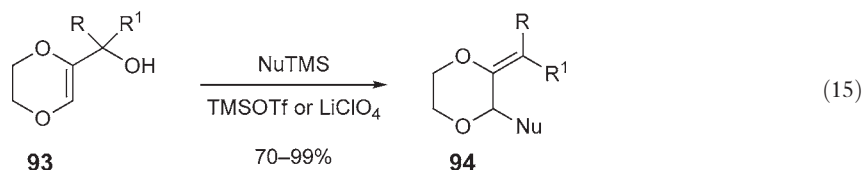
8.12.6.5 Nucleophilic Attack at Carbon

Nucleophilic additions have been performed on 2,3-diacetoxy-5,6-diphenyl-1,4-dioxane **91**. Thus, allyltrimethylsilanes, propargylsilane, and silyl enol ether in the presence of Lewis acid afforded, in a one-pot operation, the tetrasubstituted 1,4-dioxane **92** in good yields and in a highly stereoselective manner with respect to the stereochemistry at the C-2 and C-3 carbons (Scheme 8) <1995TA2113>. A similar approach allowed successive nucleophilic addition of two different nucleophiles. Further cleavage of the benzyl ether functions gave the corresponding chiral 1,2-disubstituted-1,2-diols <1995TA2117>.



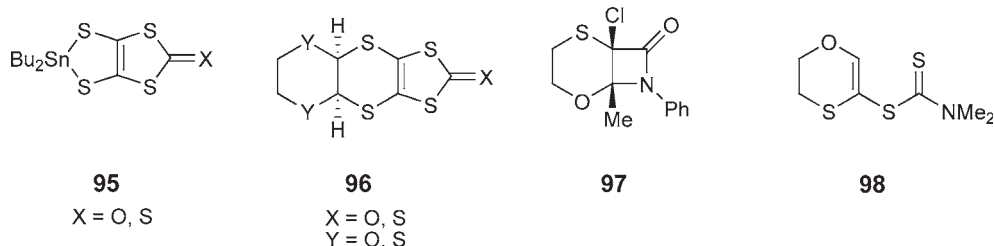
Scheme 8

Allylic alcohols **93**, obtained from the metallation reaction of 1,4-dioxene (see Section 8.12.6.4.1), undergo substitution reactions by carbon nucleophiles in the presence of a Lewis acid resulting in a new carbon–carbon bond formation. This transformation, which is assisted by the neighboring dioxene ring, probably proceeds via an oxocarbenium intermediate. Thus, various silyl enol ethers in the presence of lithium perchlorates or a catalytic amount of TMSOTf led to substitution products **94** in high yields (Equation 15) <1999TL863, 2000OL1141, 2001TL231>.



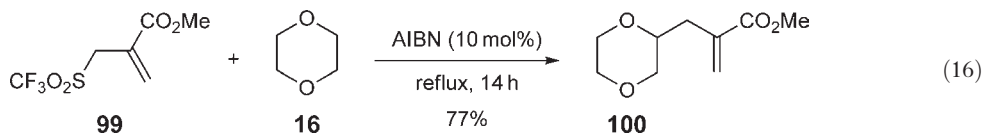
2,3-Dichloro-1,4-dioxane and 2,3-dibromo-1,4-dithiane react smoothly with tin dithiolates **95** in the presence of BF₃·Et₂O to give the corresponding tricyclic adducts **96** as single *cis*-diastereoisomers in good yields <1998JOC3952>.

Halogen displacement in 2,3-dihalogeno-1,4-oxathiins has been exploited. An intramolecular approach with a carboxamide function as nucleophile affords the bicyclic β -lactam **97** <1999H(50)713>. An intermolecular substitution with sodium *N,N*-dimethyldithiocarbamate in acetonitrile was also reported to give **98** after HBr elimination <1996S198>.

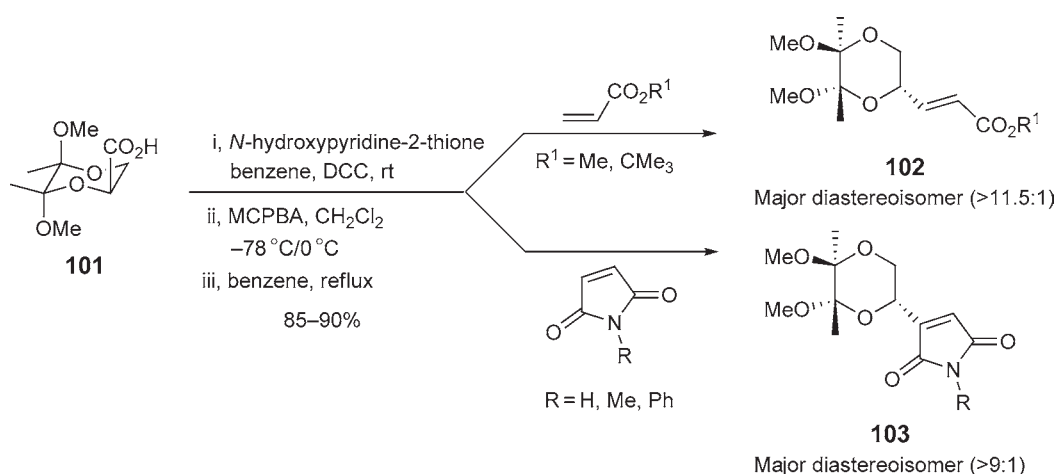


8.12.6.6 Reactions with Radicals, Carbenoid, and Electron-Deficient Species

1,4-Dioxane **16** show a good ability to undergo a radical C–H abstraction to afford the corresponding α -oxyradical. The radical source can come from allylic trifluoromethyl sulfones **99** via the trifluoromethyl radical. Thus, 1,4-dioxane is allylated in 77% yield using 2,2'-azobisisobutyronitrile (AIBN) (10 mol%) as radical initiator (Equation 16) <1998TL4163>. In a similar approach, the α -oxy radical (generated from a stoichiometric amount of benzoyl peroxide) underwent addition to fluorinated vinylsulfones giving access to new families of fluorinated compounds <1999JFC(99)73, 2000SC4309>.



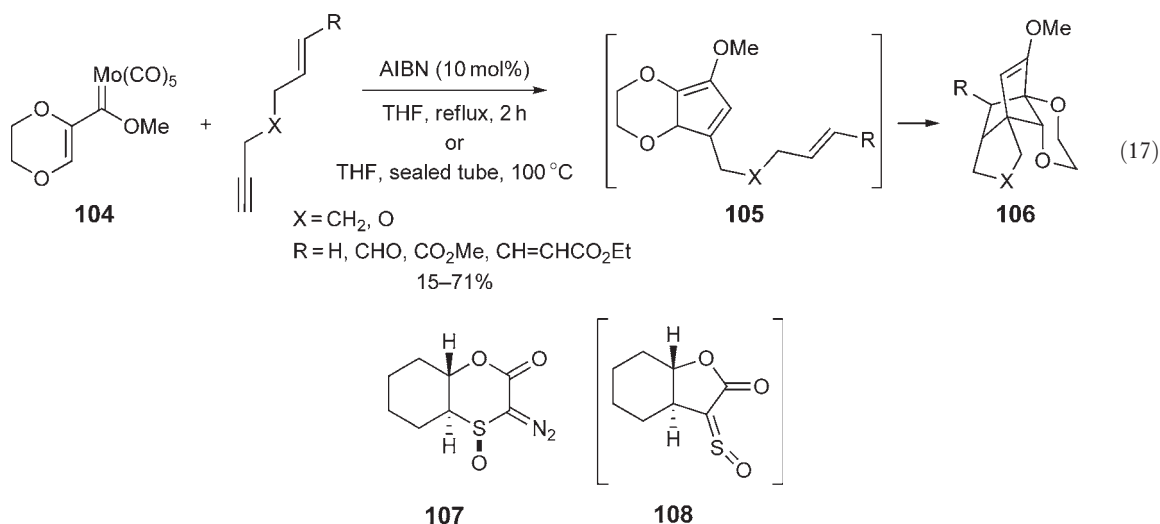
Following a radical process, radiation induced chain addition of allylbenzene to 1,4-dioxane **16**. Efficiency of the addition depends on the concentration of the monomer <1999JRN953>. Alcohols also react, albeit in low yields (10%), with **16** in the presence of (diacetoxyiodo)benzene, probably via a radical pathway, to afford 2-alkoxy-1,4-dioxanes <2004SL2291>. Free radicals have also been generated by decarboxylation of dimethoxydioxanecarboxylic acids **101** and added to some maleimides and acrylates with high stereoselectivity (Scheme 9) <2002OL2035>.



Scheme 9

The desulfurization of 1,4-oxathiane with sodium in refluxing hydrocarbon solvent, which allows the formation of diethyl ether in very good yield (>95%), can be reported here [<1998TL2671>](#). Furthermore, 6-hydroxy-1,4-benzodithiin undergoes a reductive cleavage with lithium in liquid ammonia, provided the 3,4-dimercaptophenol [<2004BML3753>](#).

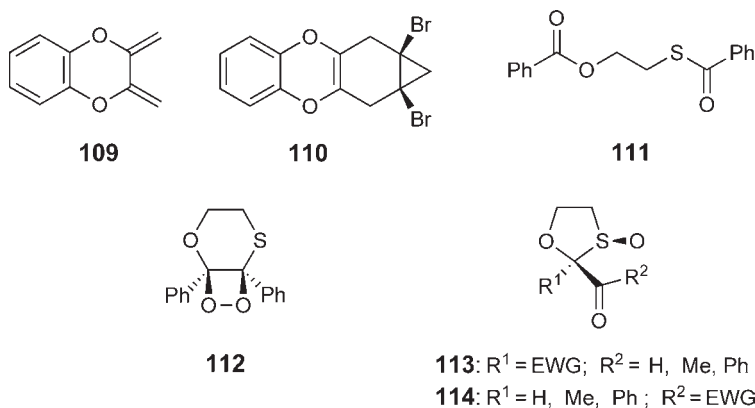
Rare examples of reactions with carbenoids have been reported in the last decade. Dioxenylmolybdenum carbene complex **104** reacts with 1,6-enynes to afford tetracyclic products with the general structure **106**. This reaction clearly occurs via formation of methoxycyclopentadiene fused to the starting 1,4-dioxane ring **105** (Equation 17) [<1996JOC159>](#). Another example deals with the decomposition of the α -diazosulfonides **107** using rhodium acetate catalyst. The formation of the α -oxosulfine intermediate **108** via a Wolff-type rearrangement can be demonstrated by its trapping as a cycloadduct with dienes [<1998TL3849>](#).



8.12.6.7 Cyclic Transition State Reactions with a Second Molecule

Most of the examples previously reported involve the cycloaddition reaction or photooxidation of 2,3-dihydro-1,4-dioxin [<1996CHEC-II\(6\)447>](#). A more recent Diels–Alder cycloaddition was done between the dimethylidenedihydrobenzodioxin **109** and the reactive 1,2-dibromocyclopropene. Reaction of the cyclopropene (generated *in situ*

from 1,1,2-tribromo-2-trimethylsilylcyclopropane) with **109** leads to the dibromodioxacyclopropanthracene **110** as a stable pale yellow crystalline compound in a modest 45% yield <1996AJC533>. Photosensitized oxygenation of 2,3-dihydro-1,4-oxathiins depends on the nature of the substituents and the solvent. In alcohols, especially in methanol, oxygenation of sulfides to sulfoxides by singlet oxygen readily occurs. Photooxygenation in CH₂Cl₂ of 2,3-diphenyl-5,6-dihydro-1,4-oxathiin affords the dicarbonyl compound **111** via the thermally unstable dioxetane **112**. However, the presence of an electron-withdrawing group at C-5 of the 1,4-oxathiin system induces the exclusive and highly stereoselective formation of the ketosulfoxides **113** and **114** <2002JOC4937>.

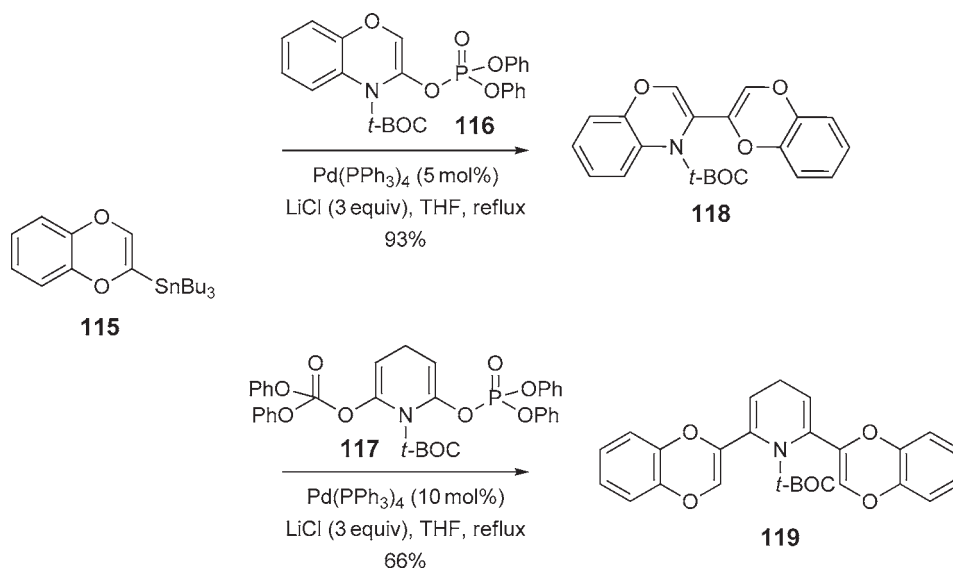


8.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

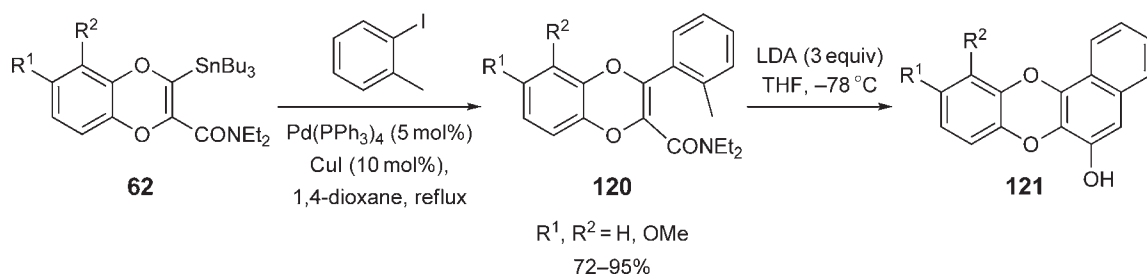
8.12.7.1 Fully Conjugated Rings

Many examples of metal-catalyzed reactions are reported on thianthrene derivatives. Thus, the thianthren-1-ylboronic acid was reacted in a Suzuki–Miyaura cross-coupling reaction with different aryl halides. The reaction took place in water in the presence of a resin-supported palladium complex and potassium carbonate to give uniform and quantitative yields of the corresponding biaryls <2002OL2997>. Using an heteroaryl halide like 4-amino-2-chloro-5-nitropyrimidine, the Pd(OAc)₂-catalyzed (5 mol%) cross-coupling reaction occurred in the presence of the sterically hindered and electron-rich 1,1'-bis(di-*tert*-butylphosphino)ferrocene (D-*t*-BPF) ligand and K₃PO₄ (2 equiv) in refluxing 1,4-dioxane to give the coupled product in good yield (72%) <2004ASC1859>. The same boronic acid was homocoupled in high-intensity ultrasound and under microwave irradiation with heterogenous catalysis using Pd/C <2005TL2267, 2005MI91>. On the other hand, 2-bromo-1,4-benzodioxin <1997T2061> and 4,6-bromothianthrene <1996T4745>, obtained by replacement of the silicon substituents of 4,6-bis(trimethylsilyl)thianthrene (see Section 8.12.5.5.2) with bromine, couple smoothly with phenylboronic acid using tetrakis(triphenylphosphine)palladium(0) as a catalyst. 2-Tributylstannyl-1,4-benzodioxin **115** has been coupled with vinylphosphonate **116** and bis-vinylphosphate **117** in the presence of LiCl and a catalytic amount of Pd(PPh₃)₄ (5 mol%) to afford **118** and **119**, respectively, in very good yield (Scheme 10) <1999TL701, 2005TL3703>. Vinylstannane **62** was successfully cross-coupled with various aryl halides in a Pd-catalyzed approach with a catalytic amount of CuI (10 mol%) in refluxing 1,4-dioxane <1997TL5635>. When 2-iodotoluene was used as electrophile, further treatment of the initial product **120** with LDA (3 equiv) at –78 °C led to the 7,12-dioxabenzodioxanthracene **121** bearing at C-6 a hydroxyl group (Scheme 11) <1998TL989>.

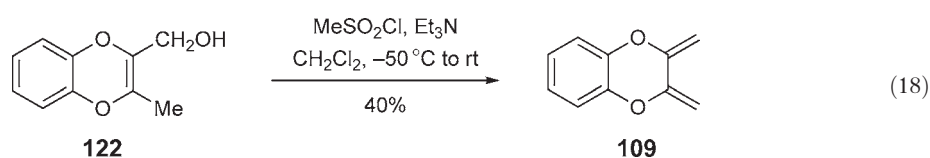
2-Cyano-1,4-benzodioxin can be reduced to the corresponding amino derivative using LiAlH₄ in THF. 2-Hydroxymethyl-1,4-benzodioxin, obtained by LiAlH₄ reduction of the corresponding ethyl ester, was tosylated and subsequently substituted by various amines <2000EJM663>. Synthesis of the dimethylidene-1,4-benzodioxin **109** required seven steps (described in detail) from ethyl 2,3-dihydro-1,4-benzodioxin-2-carboxylate. The last step starts with the benzodioxinylmethanol **122** which is converted into the corresponding mesylate derivative for *in situ* 1,4-elimination to diene **109** (Equation 18) <1996AJC533, 1992TL2965>.



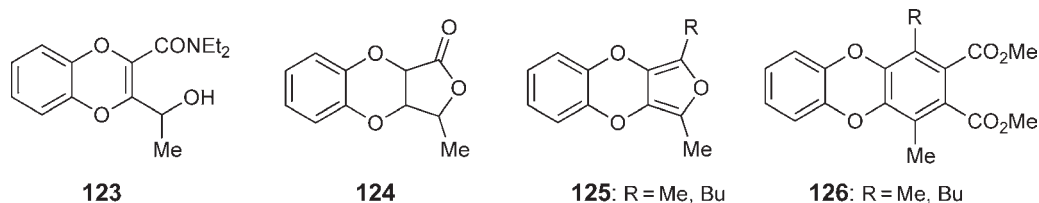
Scheme 10



Scheme 11

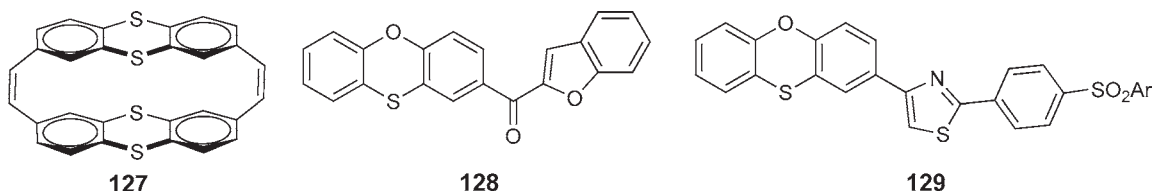


2,3-Disubstituted-1,4-benzodioxins **123** were converted using acidic conditions (catalytic amount of TsOH in refluxing THF) into lactone **124**. In a subsequent step, the lactone was converted in the corresponding furobenzodioxins **125** which undergo Diels–Alder reactions to prepare regioselectively substituted dibenzodioxins **126** <1996SC2057>.



6-Amino-1,4-benzodioxin-2-carboxylic acid ethyl ester was prepared in excellent yield from the corresponding 6-formyl derivative **40** via a Curtius rearrangement <1997SC431>. Finally, the tertiary hydroxyl group in 2,3-dihydro-1,4-benzodioxinic hemiketals **36** has been substituted by a cyano or an allyl group using the corresponding

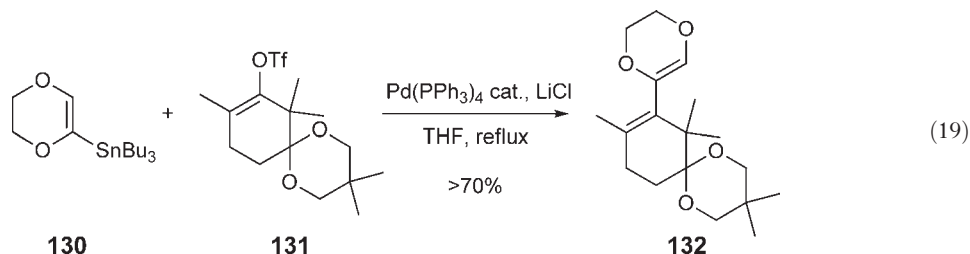
silylated reagents in the presence of boron trifluoride diethyl etherate in 40–76% yields <1997T2061>. Thianthren-1-boronic acid reacts with sodium methanesulfinate in a cross-coupling reaction mediated by cupric acetate (1.1 equiv) in the presence of K_2CO_3 (2 equiv) and 4 Å molecular sieves in DMSO to afford the corresponding methyl sulfones in 42% yield <2004TL3233>. 2,7-Diacetylthianthrene was subjected to a McMurry coupling ($TiCl_4/Zn$ /pyridine in THF) using high-dilution techniques. The resulting thianthrenophane **127** was isolated in very low yield (3%) <2004OBC2897>.



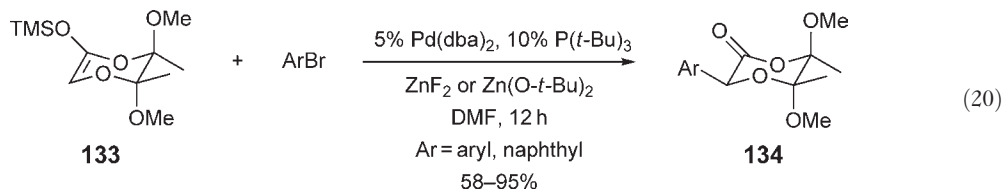
Finally, 4-acetylphenoxathiin is converted in 2- ω -bromoacetylphenoxathiin using bromine in acetic acid. Displacement of the bromine with pyridine or tetrahydrothiophene afforded the corresponding pyridinium and sulfonium salts which were reacted with *p*-nitrosodimethylaniline, under basic conditions, leading to the corresponding nitrones. 2- ω -Bromoacetylphenoxathiin was also condensed with *o*-hydroxybenzaldehydes to obtain new benzofuran derivatives like **128** <2002CHE242> and with certain *p*-(arylsulfonyl)thiobenzamides to lead to the formation of the corresponding 2,4-disubstituted thiazoles **129** <2001CHE353>.

8.12.7.2 Saturated and Partially Saturated Compounds

Palladium-catalyzed reactions are the most studied. For example, 5-tributylstannyl-1,4-dioxene **130** underwent a cross-coupling reaction with the enol triflate **131** in refluxing THF in the presence of LiCl and a catalytic amount of $Pd(PPh_3)_4$ (Equation 19) <1996TL7013>.

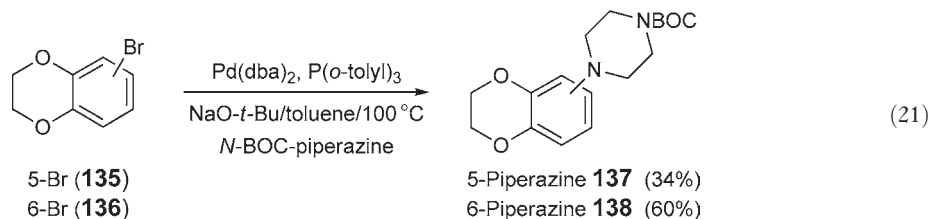


An interesting arylation of the silyl enolate of Ley's dioxanone **133** in the presence of a catalytic amount of $Pd_2(dba)_3$ (5 mol%) and $P(t-Bu)_3$ (10 mol%) with 0.5 equiv of ZnF_2 or $Zn(O-t-Bu)_2$ provides a single diastereoisomer of the coupled products **134** (dba = dibenz[*a,h*]anthracene). A variety of electronically and sterically distinct aryl halides, including those containing electrophilic functional groups, have been introduced (Equation 20) <2004JA5182>.

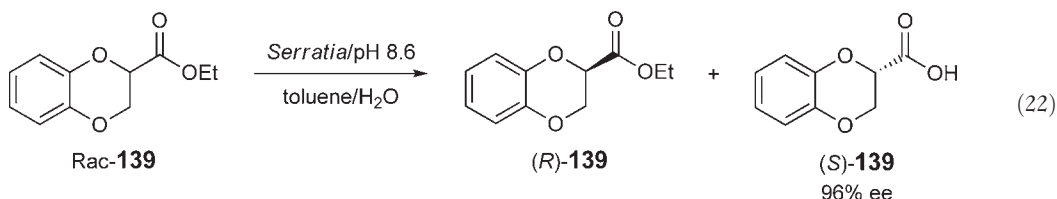


1,4-Benzodioxanes bearing an iodine or a boronic acid group at position 6 have been used in cross-coupling reactions. The former was subjected to carbonylative amination with piperidine in the presence of $Pd(PPh_3)_4$ under $[^{11}C]$ carbon monoxide pressure to produce new radiotracers <2002NMB845>. The latter was used in a Suzuki cross-coupling reaction using reverse-phase glass beads in an aqueous medium <2003TL5095>. It is noteworthy that 6-metallo-1,4-benzodioxane can be obtained from lithium/bromine <2002TL2789> or magnesium/bromine exchange <2002TL8621> and subsequently quenched by different electrophiles (e.g., DMF) <2001T8297>. 6-Amino-1,4-benzodioxane undergoes N-arylation with aryllead and arylbismuth reagents in the presence of copper acetate (10 mol%) at room temperature in dichloromethane <2000H(53)2535>. A complementary approach involves the

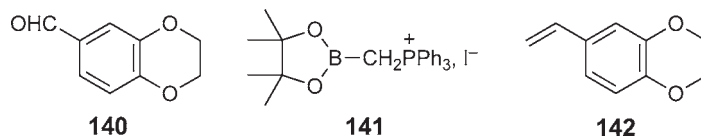
palladium-catalyzed aromatic amination reaction of 5-bromo- and 6-bromo-1,4-benzodioxanes **135** and **136** with *N*-tert-butoxycarbonylpiperazine. Conditions developed by Buchwald, that is, Pd(dba)₂ (2 mol%) with 4 mol% of tri(*o*-tolyl)-phosphine and sodium *t*-butoxide (1.4 equiv) in toluene at 100 °C, were very efficient (60% yield) to produce the corresponding *t*-butoxycarbonyl (BOC)-protected arylpiperazines **137** and **138** (Equation 21) <1998TL2219>.



Reactivity of carboxylic acid, acid chloride, or ester functions attached at the heterocyclic or aromatic ring of 1,4-benzodioxane was reported for addition–elimination reactions with amines and alcohols and reduction reactions <1998JOC10015, 2002MI49, 2000EJM663>. Various studies have been described on the synthesis of enantiomerically pure 2-substituted- 1,4-benzodioxanes. Their preparation typically involves the use of building blocks from the ‘chiral pool’, such as glycerol or glycidol <1999JME3342, 2001JOC1018>, or enzymatic resolution of ethyl 1,4-benzodioxane-2-carboxylate Rac-**139** with an esterase (*Serratia*) (Equation 22) <2001TA2169>, or was accomplished after conversion of the enantiomers into diastereoisomers <1999JME4214>. Efficient chemical resolution methods affording both enantiomers of 1,4-benzodioxane-2-carboxylic acids are also reported <1996JME2253, 2003TA3779, 2005TA1639>.

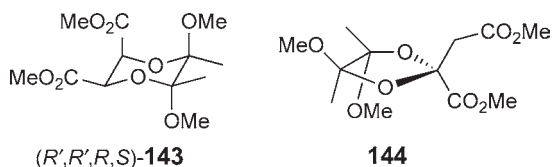


2-Cyano-1,4-benzodioxane can be reduced to the corresponding amino derivatives using hydrogenation conditions (H₂, Pd/C) <2000EJM663> or transformed into thioimidates (as its hydrobromide salt) by condensation with thiophenol <1999S927>. 1,4-Benzodioxane-6-carbaldehyde **140** was implicated in numerous reactions. An electrochemically driven coupling reaction with organic halides in the presence of catalytic amounts of Cr(II) salts and Pd(0) allows the formation of the corresponding secondary alcohol <1997TL6307>. Reaction with solid-supported triphenylphosphine under Wittig conditions, using microwave irradiation, gave the expected alkenes <2001OL3745> and reaction with pinacolboratamethylenetriphenylphosphonium iodide **141** produces the 6-vinyl-1,4-benzodioxane **142** <2002SC2575>. 1,4-Benzodioxane-6-carbaldehyde **140** was also investigated in a solid-phase synthesis of benzamide and butylamine-derived hydantoin libraries <1998MI129>. Conventional aldehyde reduction and addition reactions were also reported <2001T8297>.



2-Hydroxymethyl-1,4-benzodioxane was efficiently acetylated under microwave irradiation <2004BKC1295>, by transesterification mediated by N-heterocyclic carbene catalysts <2003JOC2812>, by lipase-catalyzed transesterification <2002TL2979>, and using enol esters catalyzed by iminophosphoranes <1999JOC9063>. Tosylation <1999JME3342, 2000TL9617, 2002JA3578>, silylation <1997JOC5057>, desilylation of the *t*-butyldimethylsilyl ethers <2000JOC2065> as well as perfluoro-*t*-butyl ether synthesis <1996JOC361> are also reported.

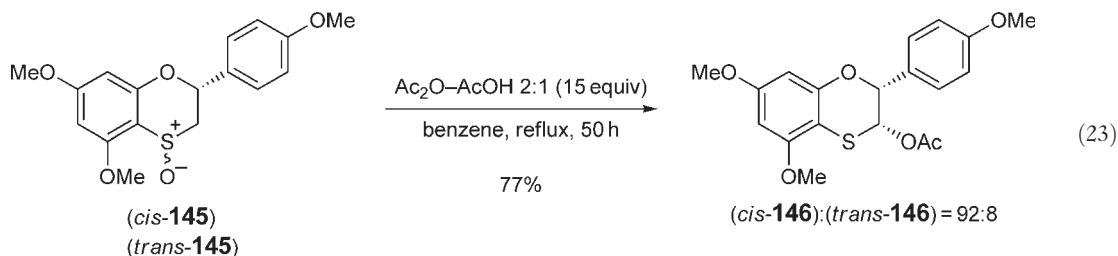
The 1,4-dioxane (*R',R',R,S*)-**143**, developed by Ley, allows many reactions on the ester moiety. Thus, reduction and further selective silylation, alkylation, acetalization, oxidation, and nucleophile addition of the spatially different hydroxyl termini <1999J(P1)1627, 1999J(P1)1635, 2001J(P1)2516> as well as the selective transesterification and aminolysis of the spatially different carboxylate termini <1999J(P1)1631> were described. Upon treatment with lithium amide bases, alkylation of **143** failed and it was shown to undergo an unexpected rearrangement to give the chiral dioxolane **144** <1999TL1583>.



8.12.8 Reactivity of Substituents Attached to Ring Heteroatoms

In the rings containing sulfur, reduction of sulfoxides of phenoxathiin and thianthrene can be performed in excellent yield with the aluminium chloride/sodium iodide or zinc dust/1,4-dibromobutane systems <1996CHEC-II(6)447>.

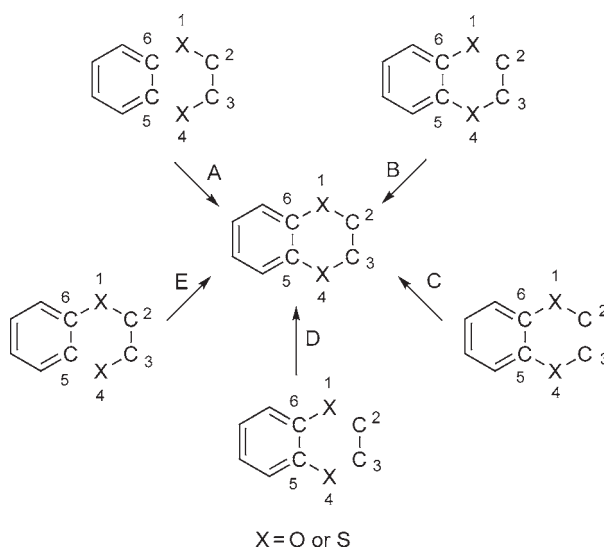
Pummerer reactions of both isomers of sulfoxide **145** with an excess of Ac₂O–AcOH in boiling benzene afforded the same mixture of *cis*- and *trans*-acetoxyderivatives **146**; the former is the major product (*cis*-**146**:*trans*-**146** = 92:8), with the 2-aryl group being pseudoequatorial and the 3-acetoxy moiety pseudoaxial (Equation 23) <2004MI317>.



8.12.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

8.12.9.1 Benzo-Fused Ring Systems

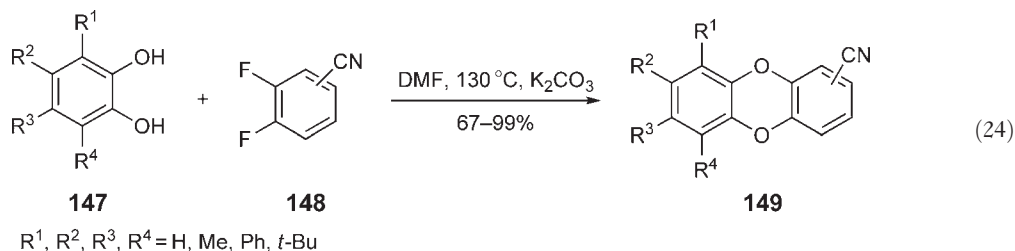
The six-membered ring synthesis for benzo-fused ring systems can be divided in five combinations of bond formation. One or simultaneously two C–C and/or C–X bonds can be formed. These are the following: X(1)C(6) and X(4)C(5) (A); X(1)C(2) (B); C(2)C(3) (C); X(1)C(2) and C(3)X(4) (D); X(1)C(6) (E) (Scheme 12). Examples of the five combinations were discussed in CHEC-II(1996) <1996CHEC-II(6)447>.



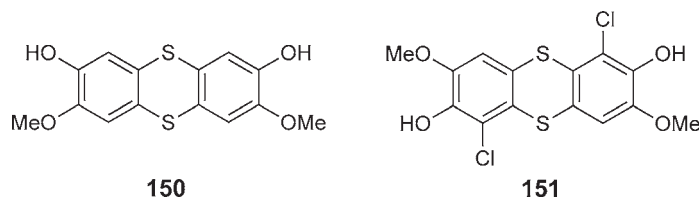
Scheme 12

8.12.9.1.1 Combination A (bond formation X(1)C(6) and X(4)C(5))

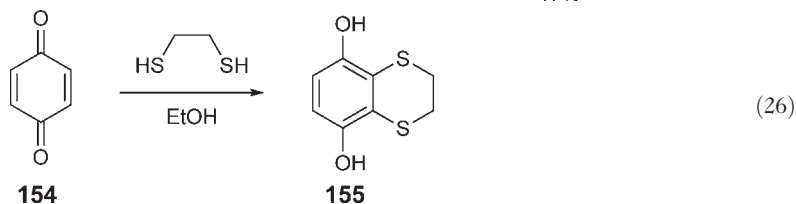
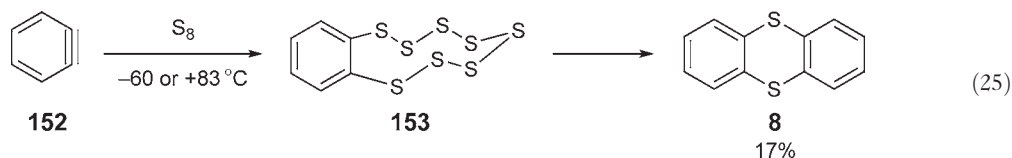
Cyanooxanthrenes **149** were quantitatively prepared for the first time from catechols **147** by nucleophilic fluorine displacement from 2,3- and 3,4-difluorobenzonitriles **148** (Equation 24) <1999CL479, 2001NJC379>. Various aryldioxins and aryldithiins were obtained by one-pot reaction between *o*-dihydroxyarenes and 1,2-diols or dithiols in the presence of *p*-toluenesulfonic acid (PTSA) through the addition of the diol or dithiol to the protonated keto tautomer of the phenol <2004TL1343>. Another synthesis of oxanthrenes and thianthrenes by nucleophilic substitution can be performed using Cp^*Ru^+ π -complexes of 1,2-dihaloaromatics with the dipotassium salts of catechols and 1,2-benzenedithiol <1996OM1319, 1996JOM(507)1>.



Activated *o*-methoxyphenol reacts with sulfur dichloride to give, depending on the addition speed of the reactant, 2,8-dihydroxy-3,7-dimethoxythianthrene **150** or 1,6-dichloro-2,7-dihydroxy-3,8-dimethoxythianthrene **151** <1997JCM272>.

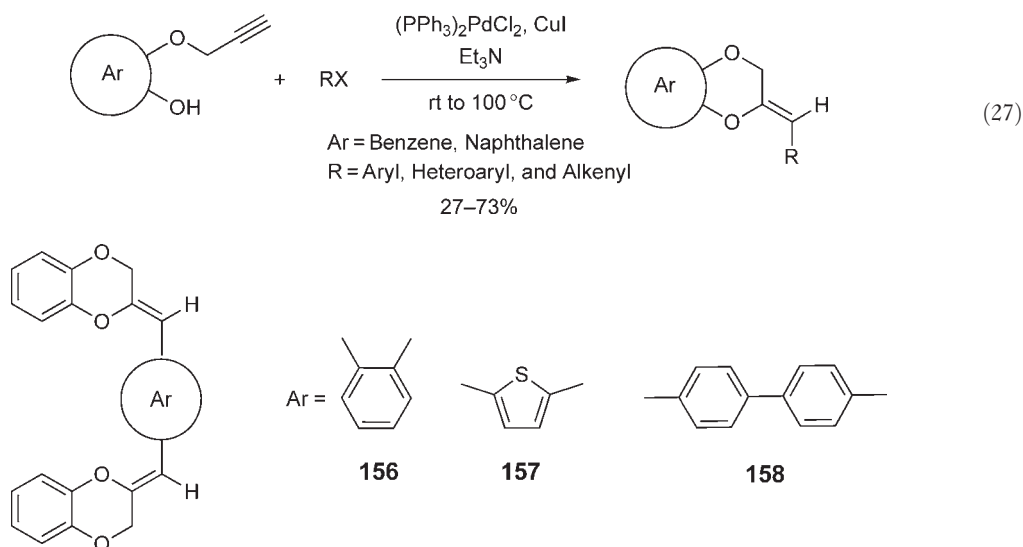


Thianthrene **8** is formed utilizing *o*-benzyne **152** as precursor <1994SR61> via the decomposition of an initial *o*-C₆H₄S₈ intermediate **153** (Equation 25) <2004JOC5483>. 1,2-Ethanedisulfenyl chloride has been utilized as an electrophilic reagent only with highly activated aromatics for the preparation of substituted 2,3-dihydro-1,4-benzodithiins <2001SM(120)1061>. Finally, 5,8-dihydroxy-2,3-dihydro-1,4-benzodithiin **155** was synthesized by conjugate addition of ethane-1,2-dithiol to 1,4-benzoquinone **154** (Equation 26) <2005BML3463>.

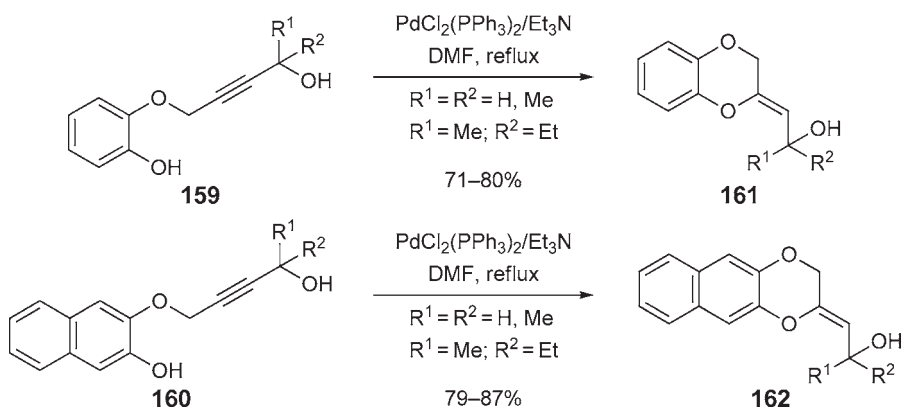


8.12.9.1.2 Combination B (bond formation X(1)C(2))

In the past, 2-methylene-1,4-benzodioxane has been synthesized through multistep procedures with poor overall yield starting from catechol <1966T931, 1965JME446>. More recently, monoprop-2-ynylated catechol and 2-hydroxy-3-(prop-2-yloxy)naphthalene reacted with aryl halides in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI in triethylamine to give regio- (*exo*) and stereoselectively (*Z*) the corresponding 2-alkylidene-2,3-dihydro-1,4-benzo- and naphthodioxins in good yields. Electron-withdrawing groups present in aryl halide moieties facilitated the reaction compared to electron-donating groups (Equation 27) <1996CC1067, 1998JOC1863>. Diiodo compounds were found to be equally effective and led to the novel bisheteroannulated products **156–158** with good regio- and stereoselectivity <1998JOC1863>.

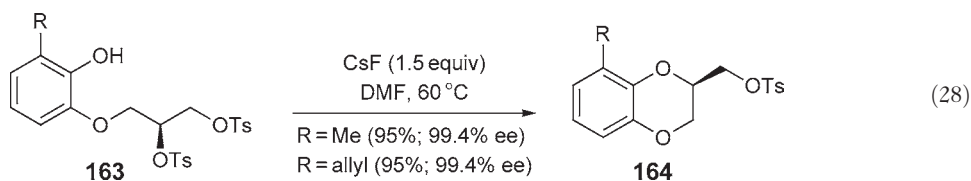


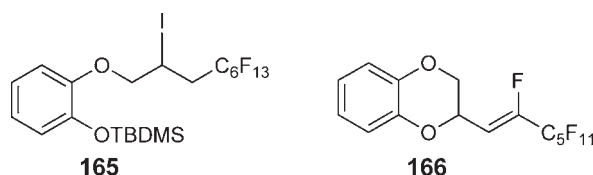
In a similar approach, monopropargyl derivatives of both catechol **159** and 2,3-dihydroxynaphthalene **160** were cyclized to the corresponding alkylidene benzo- and naphthodioxanes **161** and **162** in DMF in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ as the catalyst (Scheme 13). The *endo*-cyclization was observed only for the catechol with $\text{R}^1 = \text{R}^2 = \text{H}$. The stereoselectivity of the *exo*-cyclization was extremely high and only the (*Z*)-isomers were formed as confirmed by nuclear Overhauser effect (NOE) difference experiments <1997SC367>.



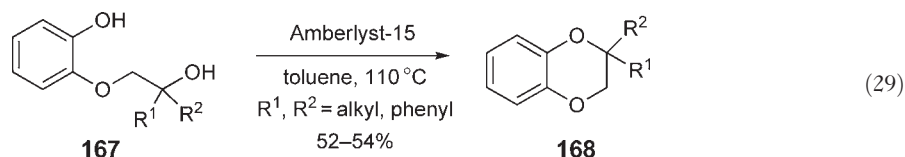
Scheme 13

Cyclizations of *o*-(ω -haloalkoxy)phenols have been widely studied and were used to afford an expedient synthesis of 5-alkyl-2,3-dihydro-1,4-benzodioxins <2004SC2487>. This approach via a nucleophilic substitution was used for the synthesis of 8-substituted-2-hydroxymethyl-1,4-benzodioxane derivatives **164** in an enantiopure form. Use of CsF instead of more basic conditions allowed higher yields and enantiomeric excess (Equation 28) <2001ASC95>. Dry tetrabutylammonium fluoride (TBAF) in THF was required and was basic enough to initiate an intramolecular S_{N}' substitution from the protected phenol **163** to the fluoro-1,4-benzodioxane **166** <1996T6187>.

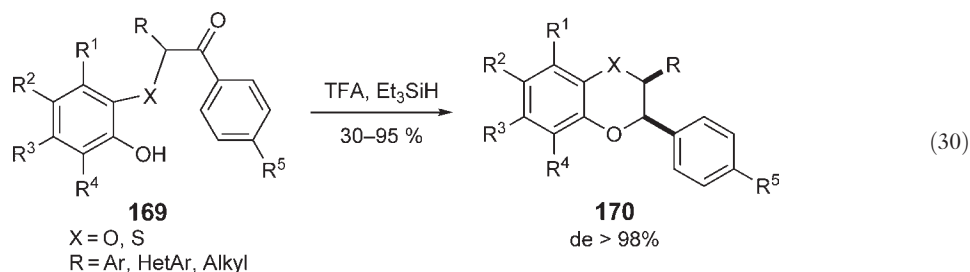




The 1,4-benzodioxane ring can be formed by an intramolecular nucleophilic attack on an oxirane by a phenol hydroxy under alkaline conditions <1998SC3121>. An asymmetric and regioselective total synthesis application to 1,4-benzodioxane lignans was reported <2000TL6079>. Using the ion exchanger Amberlyst-15 in toluene, the cyclization of the hydroxyphenols **167** gave the expected 2,3-dihydro-1,4-analogs **168** (Equation 29) <1997T2061>.



Although several methods are known to afford the *anti*-2,3-diaryl-2,3-dihydrobenzoxathiins and benzodioxanes <2000TL6079, 1997JOC2611, 2001JME261>, only a limited number lead to the *syn*-isomer. For this purpose, Kim *et al.* developed a dehydrative reduction of ketones **169** using TFA/Et₃SiH to afford *syn* 2,3-bisaryl-2,3-dihydrobenzoxathiins and benzodioxanes **170** with total diastereoselectivity and in excellent yields (Equation 30) <2003OL685>. Previous reduction of the ketone followed by an acidic treatment afforded the *anti*-isomer <2004JME2171>.

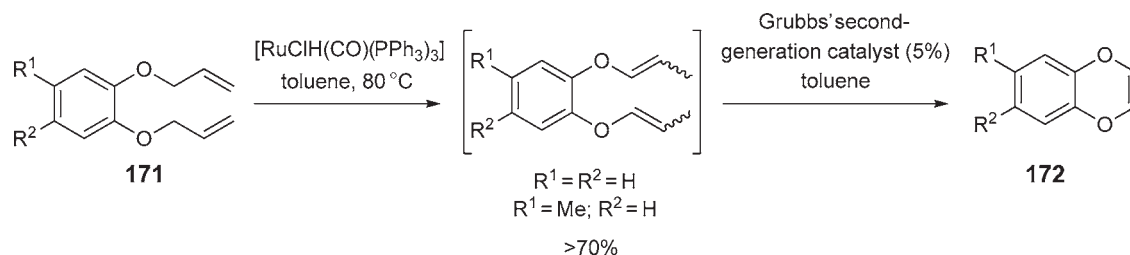


Dicyanodibenzodioxin as well as tetracyano derivatives of thianthrene and phenoxathiin have been synthesized by aromatic nucleophilic substitution reaction of the bromine atom and nitro group in 4-bromo-5-nitrophthalonitrile <2001H(55)1161>.

A simple and flexible synthesis of benzoxathiin-2-one from phenols has been reported. The key step in this synthesis is a hitherto unknown anionic rearrangement under direct metallation conditions <2004T5215, 2003SL1474>.

8.12.9.1.3 Combination C (bond formation C(2)C(3))

This combination is probably the least studied and was only used for the synthesis of 1,4-benzodioxins. For this purpose, various bis(vinyloxy)aryl precursors **171** were subjected to a ring-closing metathesis (RCM) with Grubbs' second-generation catalyst. To avoid the hazardous synthesis of the vinyloxy starting materials, the authors developed a new allylation/isomerization/RCM procedure allowing the formation of 1,4-benzodioxin structures **172** in good yields (Scheme 14) <2003TL6483>.

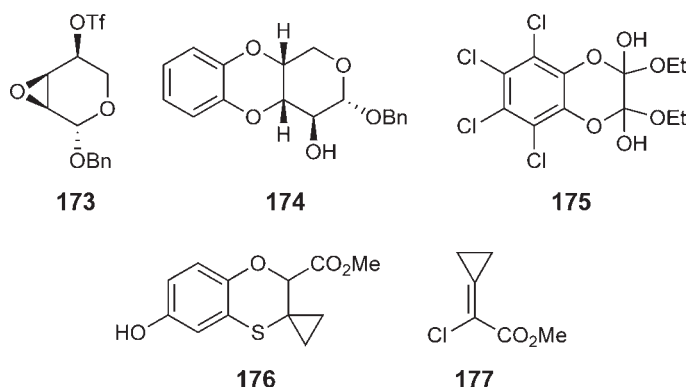


Scheme 14

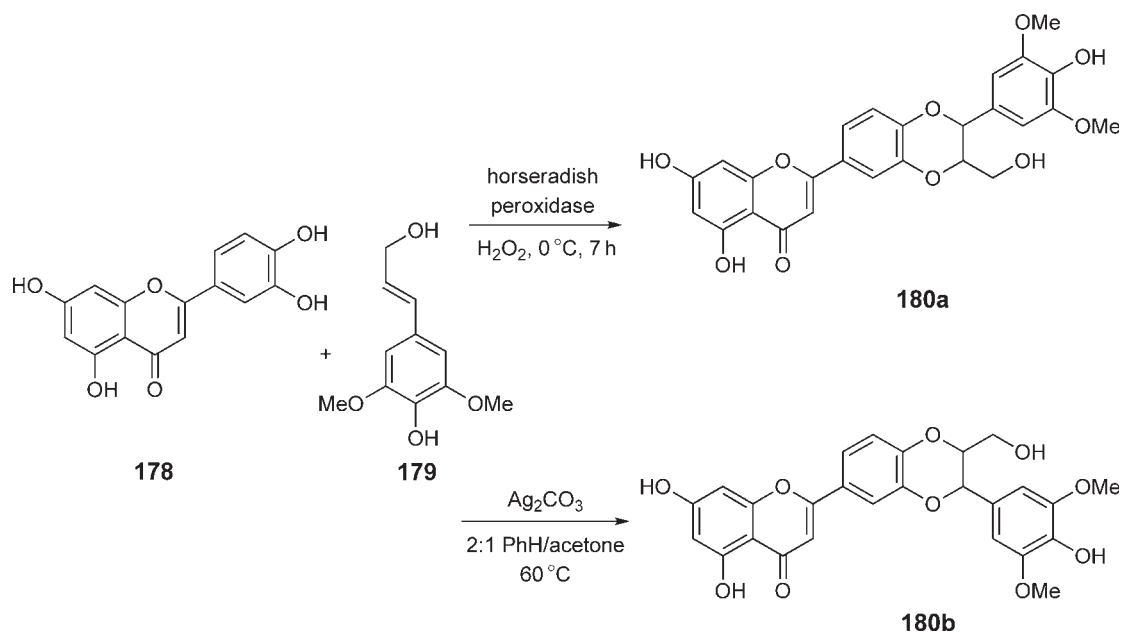
8.12.9.1.4 Combination D (bonds formation X(1)C(2) and C(3)X(4))

This combination is by far the most studied and used. For example, 2-chloro-1,4-benzodithiins <1998EJO2775>, 1,4-dithianone, its benzo derivative, and 2,3-dihydro-1,4-benzodithiin <2004BCJ1897> have been synthesized by double nucleophilic substitution, starting from benzene-1,2-thiol. Similarly, catechols led to various 1,4-benzodioxans, depending on the nature of the electrophile. Thus, dibromoethane was used in an aqueous basic solution in the presence of a catalytic amount of methyltriocetylammmonium chloride (phase-transfer catalyst) in the absence of any organic solvent <2001SC1>, α -bromoketones afforded 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxane derivatives using polymer-supported reagents <1999J(P1)2425>, epoxy triflates **173** yielded chiral 1,4-benzodioxans **174** <2005MI238>, and diethyl oxalate undergoes a nucleophilic addition to lead to compound **175** <1999JCM626>.

Spirocyclopropane-annelated 1,4-benzoxathiane **176** has been obtained through Michael addition of binucleophilic *o*-hydroxythiophenol onto methyl 2-chloro-2-cyclopropylideneacetate **177**, followed by ring closure through nucleophilic substitution of the chlorine atom <2003EJO985>.



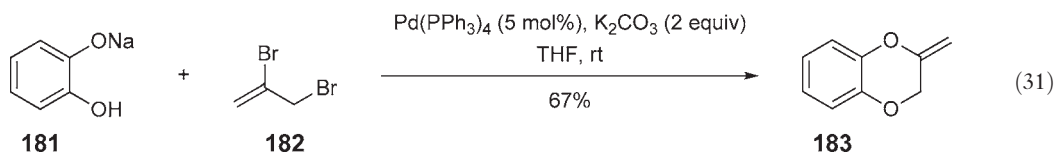
An alternative approach, again starting from catechol derivatives **178**, allows the formation of the 1,4-benzodioxan core **180** by using horseradish peroxidase (HRP) <1999TL3185, 2001JME261>, Ag_2CO_3 <2000JNP1140>, or $\text{K}_3\text{Fe}(\text{CN})_6$ <1999TL4567> in reaction with the cinnamyl alcohol **179** (Scheme 15).



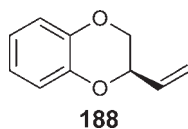
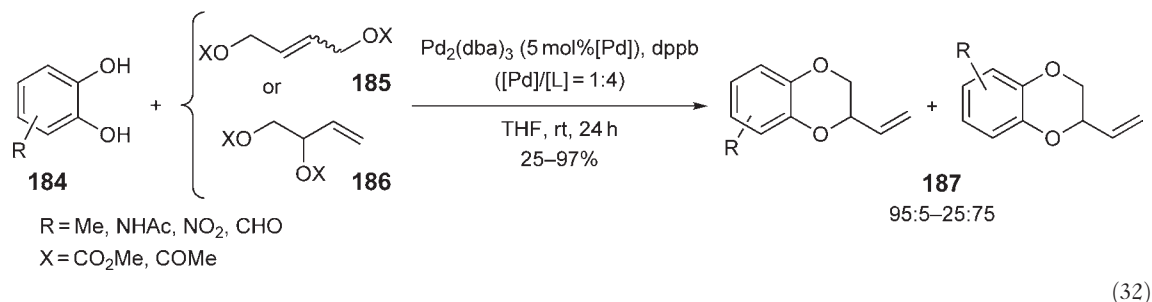
Scheme 15

Linear annulated dioxins' synthesis were reported by analogy with that of the 1,4-benzodioxin series <2002T1533> or in a modification of the Ullmann ether synthesis <2004T8899>.

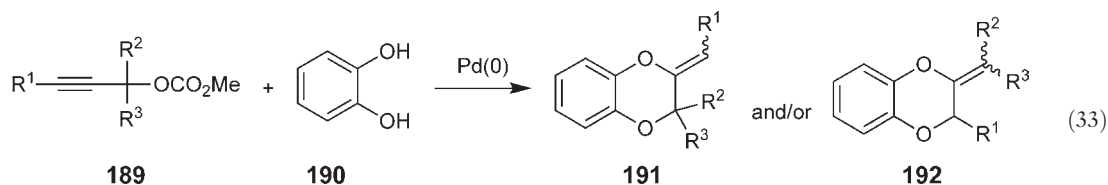
Palladium-catalyzed approaches have been described and studied for the oxygenated series. Thus, treatment of 2,3-dibromo-1-propene **182** with the monoanion of catechol **181**, generated with NaH, in the presence of Pd(PPh₃)₄ and anhydrous potassium carbonate, afforded 2,3-dihydro-2-methylene-1,4-benzodioxin **183** in 67% yield (Equation 31) <1998JA9283>.



The reaction of 1,4-bis(methoxycarbonyloxy)but-2-ene **185** or 3,4-bis(methoxycarbonyloxy)but-1-ene **186** with various substituted benzene-1,2-diols **184** was catalyzed by a palladium(0) complex to give substituted 2-vinyl-2,3-dihydro-1,4-benzodioxins **187** in good yields via a tandem allylic substitution reaction. In the case of 4-substituted benzene-1,2-diols, the ratio of regioisomers was determined by the relative acidity of the two phenolic protons. For 3-substituted benzene-1,2-diols, this ratio was determined only by steric effects in the case of alkyl substituents, although it is determined mainly by the relative stabilities of the corresponding phenoxides for other substituents; however, for 3-nitrobenzene-1,2-diol, this ratio was determined by the relative leaving-group ability of 2-nitro- or 3-nitrophenoxide (Equation 32). When the cyclization was performed in the presence of an optically active phosphine, chiral 2-vinyl-2,3-dihydro-1,4-benzodioxin **188** was obtained with enantioselectivity of up to 45% using 2,2-bis(diphenyl-phosphanyl)-1,1'-binaphthyl (BINAP) as the chiral phosphine <1999EJO2665, 1994TL6093>. With chiral 2-(phosphinophenyl)pyridine ligand, the enantiomeric excess goes up to 71% <2004TL7277>.

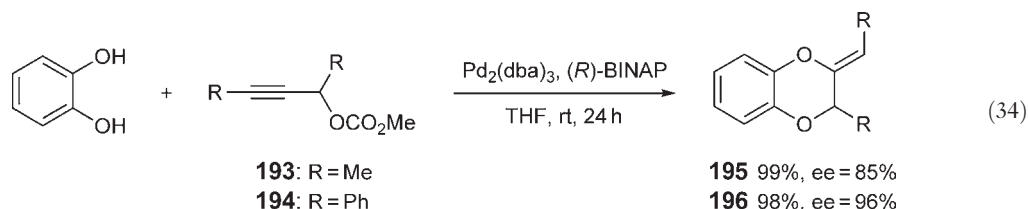


Moreover, the palladium-catalyzed condensation of benzene-1,2-diol **190** with various propargylic carbonates **189** provides a versatile and easy access to a wide variety of 2-alkylidene-3-alkyl-2,3-dihydro-1,4-benzodioxins **191** and **192** with quite good yields (Equation 33) <2001JOC6634, 1999TL9025, 2002ARK(v)102>. The process is often quite regio- and stereoselective, the major regioisomer being formed by the intramolecular attack of the phenoxide ion on the more electrophilic termini of the (η³-allyl)palladium intermediate. The stereochemistry of the double bond in the resulting heterocycle depends on the substitution pattern of the propargylic carbonate. Primary and secondary carbonates afforded mainly, if not exclusively, the (Z)-alkene, while tertiary carbonates gave predominantly the (E)-isomer.

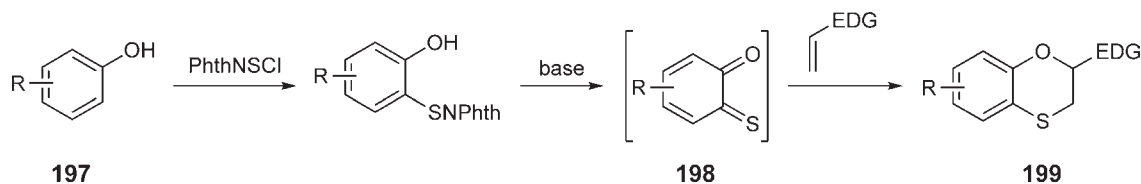


R¹, R², R³ = H, Me, Et, *i*-Pr, *t*-Bu, cycloalkyl, CF₃, Ph, Bn, or CH₂OTBS

An asymmetric version of this palladium-catalyzed annulation of benzene-1,2-diol with various propargylic carbonates [<2000OL527, 2002EJO1966>](#) and racemic secondary propargylic carbonates and acetates [<2003TL557, 2005T2589>](#) was developed. The highest chemical yields and enantioselectivities (up to 97%) are obtained using atropisomeric diphosphines such as BINAP, (6,6'-dimethylbiphenyl-2,2'-diyl)bis(diphenylphosphine) (BIPHEMP), or MeOBIPHEP (BIPHEP = biphenylphosphine), as the chiral ligands ([Equation 34](#)).

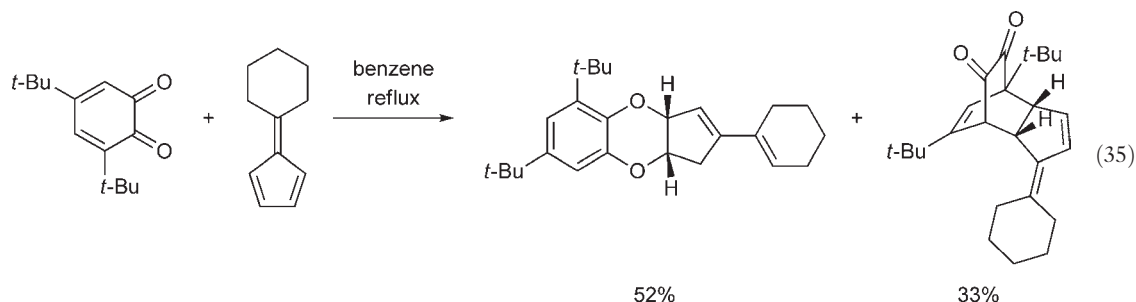


o-Hydroxy-*N*-thiophthalimides, prepared by *N*-phthalimidesulfonylation of activated phenols **197**, are suitable precursors of *o*-thioquinones **198**, a synthetically useful class of electron-poor heterodienes, which react with styrenes [<2005OBC3066, 1997JOC2611>](#), vinyl ethers, [<1996T12247>](#), arylalkenes [<2002H\(56\)471>](#), pentafulvenes [<2002T3235, 2000TL6919>](#), cyclic dienes [<2001T8349>](#), and acyclic dienes [<2001J\(P1\)3020>](#), giving rise to the formation of substituted 2,3-dihydro-1,4-benzoxathiin cycloadducts **199** with complete regioselectivity ([Scheme 16](#)) [<B-2003MI\(7\)108>](#). Examples with alkynes led to the 1,4-benzoxathiin derivatives [<2002H\(56\)471>](#). It is noteworthy that under kinetic control, *o*-thioquinones react as dienophile via the thione with acyclic 1,3-dienes to afford spiro cycloadducts [<2003T5523>](#).

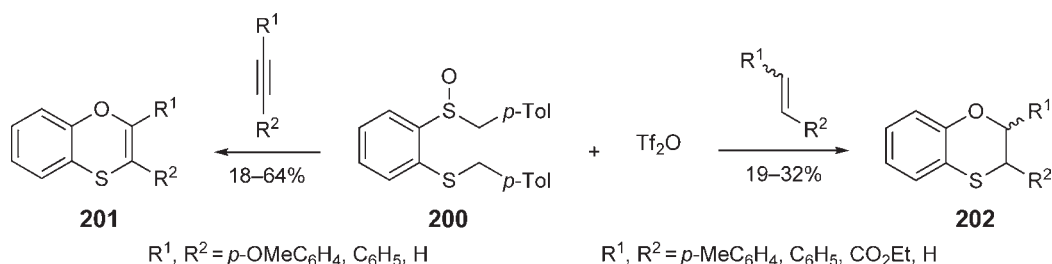


Scheme 16

o-Benzoquinones undergo cycloaddition reactions with heterocyclic dienes and some carbocyclic dienes to give 1,4-benzodioxanes ([Equation 35](#)) [<1995J\(P1\)443, 1996SL1143, 1996T4029, 1999T11017>](#). A photochemical reaction of *o*-benzoquinones with 1,3-diketones also afforded 1,4-benzodioxanes in low yields [<1998BKC917>](#).



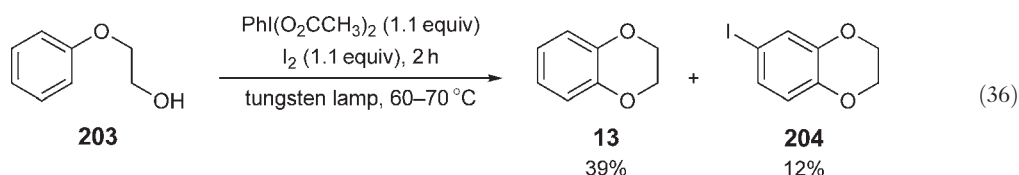
Finally, in this section, the reaction of 1,2-bis(4-methylbenzylthio)benzene mono-*S*-oxide **200** with TiF_2O in the presence of alkynes and alkenes produces 1,4-benzodithiins **201** and 2,3-dihydro-1,4-benzodithiins **202**, respectively ([Scheme 17](#)) [<2000CC1667>](#).



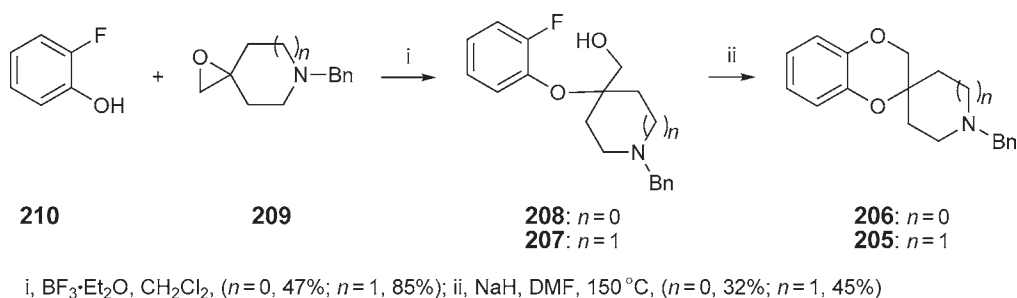
Scheme 17

8.12.9.1.5 Combination E (bond formation X(1)C(6))

Numerous different mechanistic approaches have been applied for this combination. First, cyclization of phenoxy-ethanols **203**, in the presence of (diacetoxyiodo)benzene and iodine, gave a mixture of 1,4-benzodioxane **13** and 6-iodo-1,4-benzodioxane **204** via alkoxy radicals (Equation 36) <1997J(P1)787, 1996TL2441>.

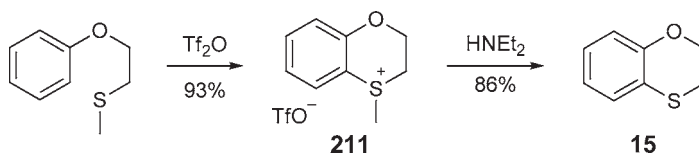


Then, nucleophilic aromatic substitution was applied for the synthesis of 1,2,4,6,7,9-hexafluoro-1,4-dibenzodioxin from 2,3,4,6-tetrafluorophenol in the presence of sodium *t*-butylate <1995JFC(73)265>. In a similar way, cyano-1,4-dibenzodioxins and cyano-1,4-dibenzodithiins have been synthesized by fluorine displacement reactions with catechols <2001NJC379, 2001NJC385>. In accordance with a similar mechanism, the synthesis of spiro (1,4-benzodioxin-2,4'-piperidines) **205** and spiro (1,4-benzodioxin-2,3'-pyrrolidines) **206** have been developed from alcohols **207** and **208**, respectively, both of them being obtained from 2-fluorophenol **210** with the corresponding epoxide **209** (Scheme 18) <2003SL813>.



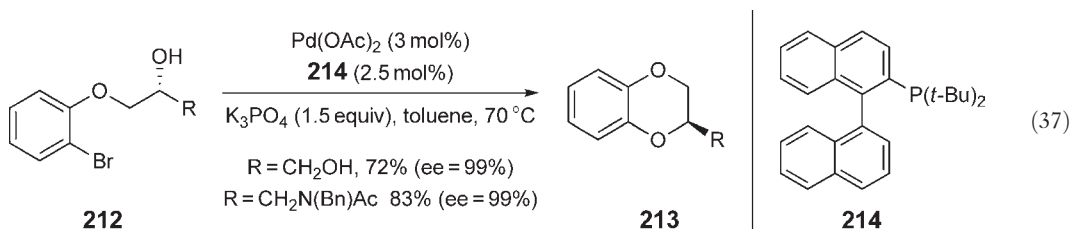
Scheme 18

Another approach to 2,3-dihydro-1,4-benzoxathiin is based on the electrophilic cyclization of sulfenyl chlorides <1995JPR283> or aryl-substituted aliphatic sulfides <2003S1191>. In the latter case, subsequent demethylation of the sulfonium salt **211** can be carried out using diethylamine (Scheme 19). $\text{S}_{\text{E}}\text{Ar}$ was applied to form 1,4-benzodioxane from alcohol in the presence of polyphosphoric acid <1998MI1550>. Furthermore, dibenzothiophene, phenoxathiin, and thianthrenes can be easily obtained by reaction of octasulfur in the presence of aluminium chloride with biphenyl, diphenyl ether, and diphenyl sulfides, respectively, under focused microwave irradiation <1998SUL199>. *syn*-2,3-Disubstituted-2,3-dihydro-1,4-benzoxathiin rings have been produced by Michael addition of a 2-mercaptoethanol to a quinone ketal, followed by cyclization of the initial Michael adduct, and subsequent aromatization <2004TL5429>.



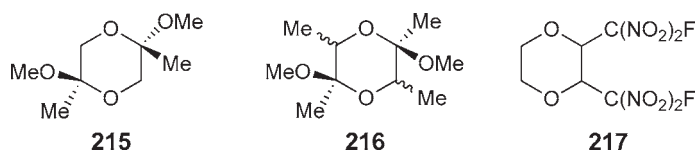
Scheme 19

Finally, Buchwald and co-workers developed a high-yield, general method for the palladium-catalyzed formation of 1,4-benzodioxane. Bulky, electron-rich *o*-biphenylphosphines of type **214** together with $\text{Pd}(\text{OAc})_2$ have proved to be the most general catalytic system to avoid the β -hydride elimination side reaction [<2000JA12907>](#). This strategy was extended to the synthesis of enantiomerically pure 2-substituted-1,4-benzodioxanes **213** from **212** (Equation 37) [<2001JA12202>](#).

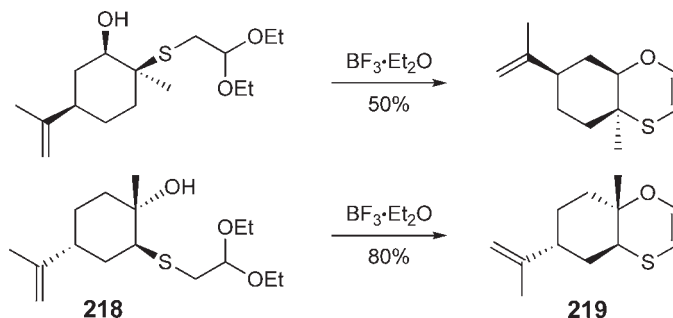


8.12.9.2 Non-Benzo-Fused Ring Systems

Due to environmental concerns, finding new catalysts for the synthesis of 1,4-dioxane by cyclodehydration has been of continuing interest. For this purpose, HZSM-5 [<1996JMO\(109\)149>](#), sulfated zirconia [<1999JCM326>](#), and metal(IV) phosphates [<2001GC143>](#) have been used. A continuous acid catalysis in supercritical fluids is also reported [<1999JA10711>](#). Substituted 1,4-dioxanes **215** and **216** have been obtained from propargyl alcohol and but-1-yn-3-ol with a cationic gold(I) complex in the presence of methanol [<1998AGE1415>](#). Compound **215** (stereochemistry was not assigned in this case) has also been isolated under palladium-catalyzed conditions [<1997JOM\(535\)77>](#).



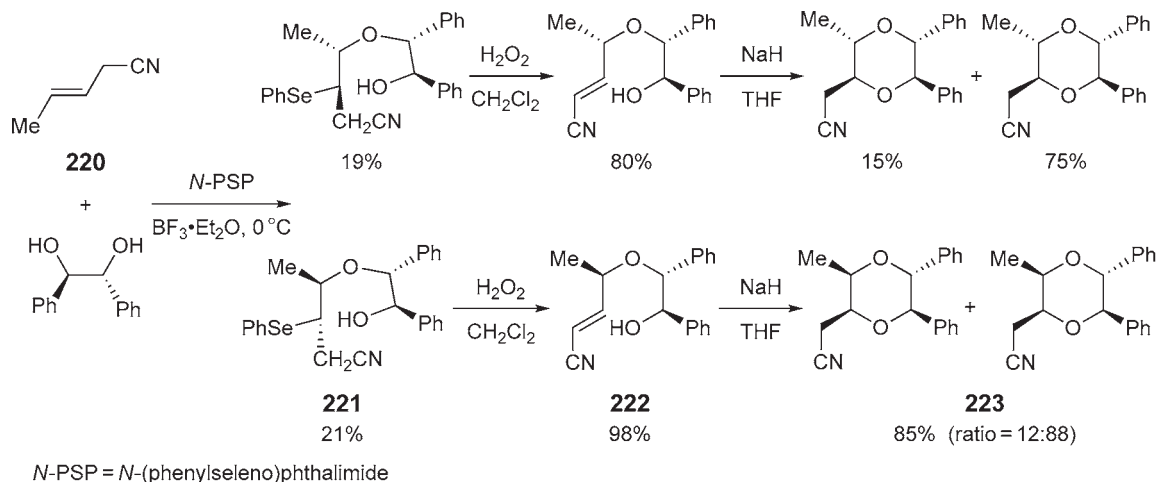
As already reported in CHEC(1984) [<1984CHEC\(3\)943>](#) and CHEC-II(1996) [<1996CHEC-II\(6\)447>](#), syntheses of 1,4-dioxanes, 1,4-oxathianes, and 1,4-dithianes utilize the nucleophilicity of negatively charged or neutral oxygen and sulfur atoms. Some new examples of 1,4-dioxane-bearing aryls, [<2003RJO1206>](#) aminomethyl [<1999RCB2299>](#) and fluorodinitromethyl groups **217** [<2002CHE385>](#) follow this approach as do methods for the synthesis of camphor-derived 1,4-oxathianes [<2001TA999>](#). Hydroxyacetals **218** treated with an excess of boron trifluoride–diethyl ether furnished compounds **219** in moderate to good yields (Scheme 20) [<2001JP12604>](#).



Scheme 20

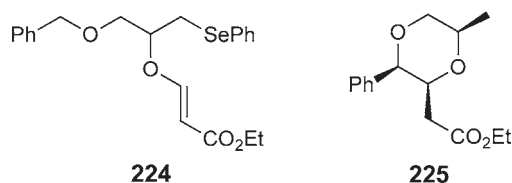
For 1,4-dithianes, montmorillonite K10 promoted the reaction of β , β' -dichlorosulfides with hydrogen sulfide <2001S2397>.

In the case of perfluoro compounds, the cyclization proceeds through an elimination reaction followed by an S_N' process instead of a direct nucleophilic substitution <1996T6187>. A few other approaches deal with a hetero-Michael addition. Thus, substituted 1,4-dithiane 1,1-dioxides were prepared by conjugate addition of hydrogen sulfide to bisvinylsulfonfyl derivatives <1998PS(134/135)171, 2000IJB406> and enantiomerically pure 1,4-dioxanes **223** were obtained via an alkoxyseleenylation of alkene **220** <1998TL6471> followed by the attack of the nucleophilic oxygen on the Michael acceptor **222** (resulting from the elimination of the intermediate selenoxide) (Scheme 21) <2003TA1095>. An intramolecular and stereoselective O-heterocyclization involving S-shaped (η^5 -dienyl)tricarbonyliron (1+) generated *in situ* provides a useful access to chiral-functionalized *trans*-2,3-substituted 1,4-dioxanes <1996JOC1914>.

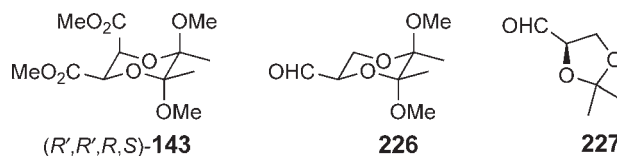


Scheme 21

In a radical process from the organoselenium **224** and in the absence of carbon monoxide, only one diastereoisomer of 1,4-dioxane **225** was isolated (82% yield) <2002OL3>.



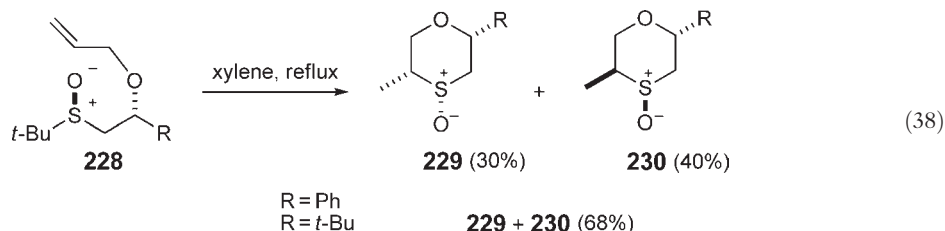
The 1,4-dioxane ring is also described as the resulting structure from the direct protection of 1,2-diols with α -diketones <1996SL793, 1996JOC3897, 1996AGE197>. The synthesis and utility of a particular example, compound (*R',R',R,S*)-**143**, has been described for a general and efficient synthesis of enantiopure anti-1,2-diols <1999J(P1)1627, 1999J(P1)1631, 1999J(P1)1635, 2001J(P1)2516>. Similarly, substituted 1,4-dioxane **226**, readily obtain in both pure enantiomeric forms, is a useful and stable alternative to glyceraldehyde acetone **227** <2002AGE3898>.



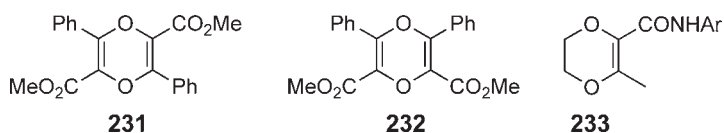
In a similar way, 1,4-oxathian-2-one and 1,4-dioxan-2-one were obtained from the condensation of thioglycolic acid and glycolic acid, respectively <1979J(P1)1893, 1998T11445>, and from palladium-catalyzed <1999JOC6750> or oxoammonium salt <2004JOC5116> oxidations of 2,2'-thiodiethanol or diethylene glycol. Asymmetric syntheses

were also developed by reacting an α -halogeno ester with a diol <1999OL71, 1981J(P1)1796>, glyoxylic acid, or glyoxal with chiral hydrobenzoin <1995TA2117> or via a three-step route from 3-halopropane-1,2-diols <2004OBC3608>.

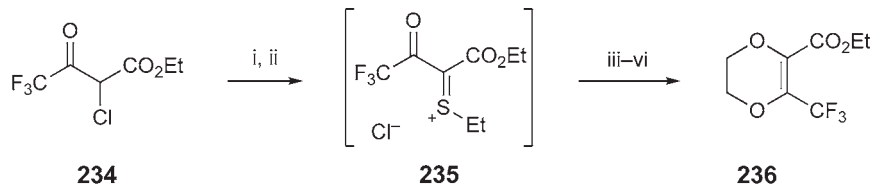
Taking advantage of a tandem sulfoxide elimination–sulfenic acid addition approach to cyclic sulfoxides <1977J(P1)1574>, the synthesis of a number of novel 1,4-oxathiane oxides **229** and **230** based on the intramolecular addition of sulfenic acids to alkenes or alkynes tethered through an ether linkage has been reported (Equation 38) <2005OBC404>.



In the fully and partially unsaturated oxygenated series, the syntheses of 2,5-dimethoxycarbonyl-3,6-diphenyl-1,4-dioxin **231** and 2,6-dimethoxycarbonyl-3,5-diphenyl-1,4-dioxin **232** were recently reported from methyl phenylchloropyruvate with potassium phthalimide and sodium imidazolidine <2000CHE911>.



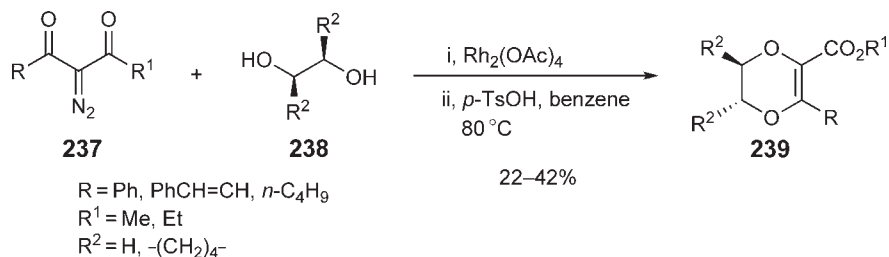
2,3-Dihydro-1,4-dioxincarboxanilide **233** was synthesized from propargyl chloride and 1,2-ethanediol <1998JFA2827>. An analog **236** bearing a CF_3 group, was obtained from an α -halogeno keto ester **234** in a five-step sequence probably via an activated thionium ion **235** (Scheme 22) <2001BKC149, 2000JHC1003>.



i, ethanethiol, Et_3N , C_6H_6 , rt, 4 h; ii, SO_2Cl_2 , CH_2Cl_2 , rt, 1 h; iii, ethylene glycol, rt, 38 h, 82% from **234**; iv, Raney-Ni, EtOH, reflux, 17 h, 70%; v, SOCl_2 , C_6H_6 , 1 h, rt; vi, Et_3N , reflux, 62% over 2 steps

Scheme 22

Another approach to substituted 2,3-dihydro-1,4-dioxins **239** involves the reaction between 1,2-diols **238** and rhodium carbenoids generated from α -diazo- β -ketoester **237** (Scheme 23) <1999H(51)1073>. This method complements the intramolecular reactions described earlier <1997JOC3902>.



Scheme 23

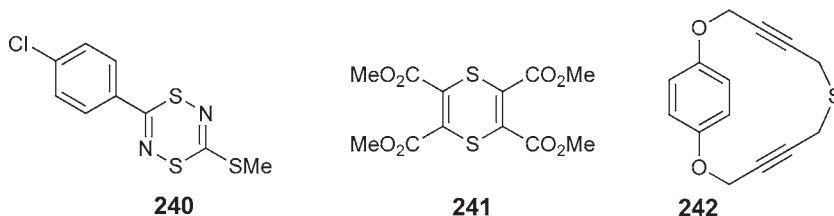
The thermal intramolecular dimerization of some group 6 bis-carbene complexes yield 1,4-dioxenes <1996JA2166, 2001JA851>. 2,3-Dihydro-1,4-oxathiins have also been produced from α -halogeno keto esters and 2-mercaptoethanol <2001BKC149> as well as from a Mn(III)- based reaction of alkenes with α -mercaptoketones <1998T11445>. An inverse electron demand cycloaddition approach between α,α' -dioxothiones and electron-rich alkenes like ethyl vinyl ether gives 2,3-dihydro-1,4-oxathiin cycloadducts with complete regio- and chemoselectivity <1996AGE777, 1997CC2291, 1999JOC6490>. Finally, an improved synthesis of 2,3-dihydro-1,4-dithiin **11** (38% yield), compared to the previous one <1996CHEC-II(6)447>, involves stoichiometric amounts of 2-bromo-1,1-diethoxyethane and 1,2-ethanedithiol in toluene with traces of PTSA <1998NJC585>.

8.12.10 Ring Synthesis by Transformation of Another Ring

8.12.10.1 Fully Unsaturated Compounds

8.12.10.1.1 Non-benzo-fused ring systems

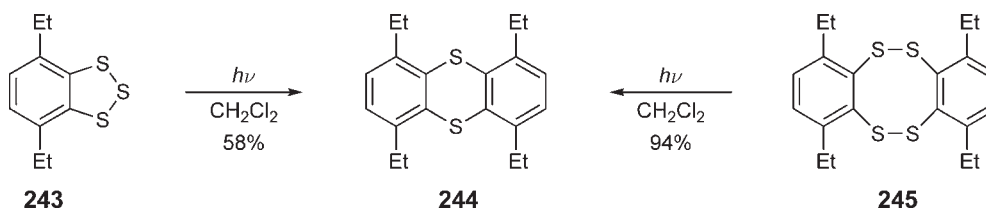
1,4-Dioxins, 1,4-oxathiins, and 1,4-dithiins have often been prepared by elimination reactions from saturated analogs as described in CHEC-II(1996) <1996CHEC-II(6)447>. Since then, a synthesis of tetramethyl 1,4-dithiin-2,3,5,6-tetracarboxylate **241** has been reported in low yield (12%) by thermal decomposition of the 1,4,2,5-dithiadiazine system **240** in refluxing *o*-dichlorobenzene in the presence of DMAD <1997J(P1)1157>. Recently, 2,6-divinyl-1,4-dithiin **68** has been isolated from the reaction of 1,4-bis(4-bromobut-2-ynyloxy)benzene with an excess of alumina-supported sodium sulfide. The formation of **68** has been presumed to take place via cyclic sulfide **242** <2003S849>.



8.12.10.1.2 Benzo-fused ring systems

As already mentioned in CHEC-II(1996), 1,4-benzodioxins are often obtained from the corresponding dihydro compounds <1996CHEC-II(6)447>. Thus, elimination reactions of monoiodo and monobromo <2001HCO135> or dibromo benzodioxanes <2000EJM663> allow the formation of various 2-substituted-1,4-benzodioxins in good yields. 6-Methyl-1,4-benzoxathiin was prepared from the saturated derivatives by reaction with SOCl_2 , then quinoline <2003BML2083>.

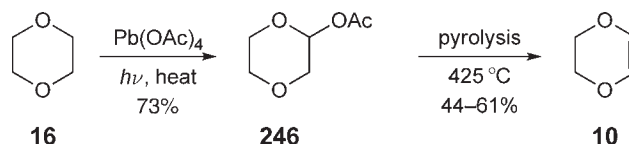
Typically, photolysis of **243** was performed by 100 W high-pressure Hg lamp in CH_2Cl_2 under argon. Dibenzotetrathiocin **245** was photolyzed in similar conditions. In these photolyses, desulfurization-cyclization and ring-contraction reactions proceeded to give thianthrene **244** in 58% and 94% yields, respectively (Scheme 24) <1999PS(153/154)369, 1999TL9101, 2000TL1801>. Acenaphtho[1,2-*b*][1,4]dithiin and acenaphtho[1,2-*b*][1,4]oxathiin derivatives have been reported by oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) from the corresponding saturated heterocycles <1996J(P1)2451, 1999J(P2)755>.



Scheme 24

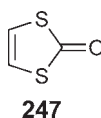
8.12.10.2 Saturated and Partially Saturated Compounds

Recently, a clean formation of 2,3-dihydro-1,4-dioxane **10** has been described in a two-step process starting from 1,4-dioxane. This approach takes advantage of the capability of lead tetraacetate to engage in the acetoxylation of C–H bonds adjacent to etheral oxygen centers (**Scheme 25**) <2005OS99>.

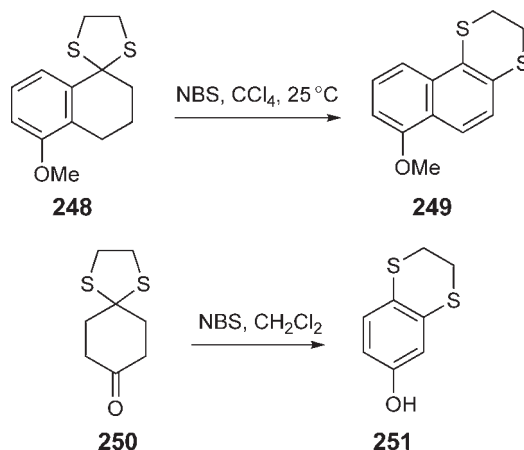


Scheme 25

Synthesis of 2,3-dihydro-1,4-dithiin **11** was accomplished from 1,3-dithiol-2-one **247** in the presence of dibromoethane and potassium hydroxide <1998JOC3952>, while reaction of 2,3-dichloro-1,4-dioxane with powdered Zn in hexamethylphosphoramide (HMPA) was used for the synthesis of 1,4-dioxene **10** <1998JPP1006773>. To obtain substituted 1,4-oxathianes, the hydrogenation of the corresponding partially saturated compounds has been employed <2001J(P1)2604>.



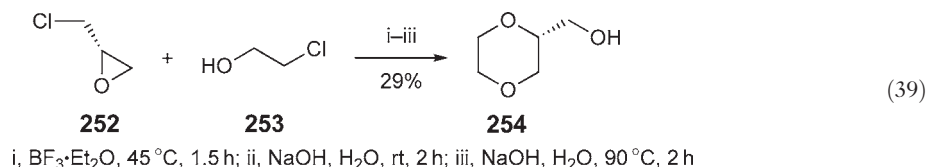
Saturated acenaphtho[1,2-*b*][1,4]dithiin and acenaphtho[1,2-*b*][1,4]oxathiin derivatives have been described via a ring expansion of the corresponding dithioketal and oxothioketal going through a diazo intermediate <1996J(P1)2451, 1999J(P2)755>. Another ring expansion of *S,S*-acetals **248** and **250** in the Mitsunobu conditions <1999T801> or in the presence of NBS <1997H(45)1921, 2004BML3753> allows the formation of substituted 2,3-dihydro-1,4-benzodithiins **249** and **251** (**Scheme 26**).



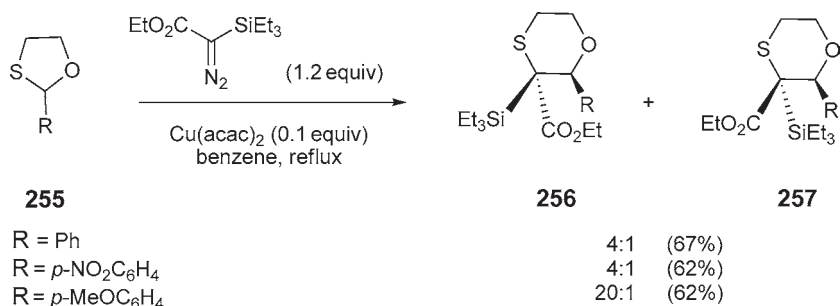
Scheme 26

Cyclodimerization of thiirane over acidic molecular sieves afforded 1,4-dithiane **17** <2001CAL95>, and epoxide opening by ethanedithiol in the presence of Zeolite HSZ-360 gave substituted 1,4-dithiane <1999SC767>. Similarly, the reaction of episulfides in non-nucleophilic solvents such as dichloromethane furnishes the corresponding substituted 1,4-dithianes in good yields <2002T7037>. Intramolecular ring opening of epoxides and epithiochlorohydrin by thiolates and alcohols, respectively, allowed the formation of substituted 1,4-oxathianes <2000TL2621, 2004MI116>. This strategy was applied to the synthesis of substituted 1,4-dioxanes from substituted epoxides

<1995JMO(104)L5, 1999RCB2086, 2000RJO757> and to the synthesis of enantiomerically pure 1,4-dioxane **254** from chiral epichlorhydrin **252** with 2-chloroethanol **253** (Equation 39) <2005BML3207>.

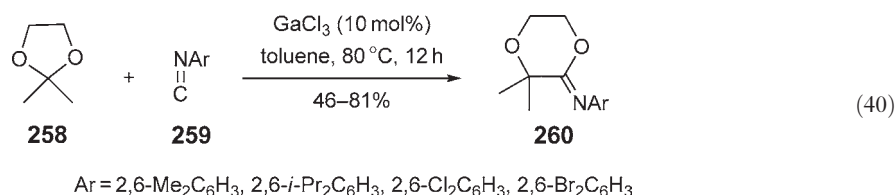


Furthermore, 1,3-oxathiolanes **255** are efficiently converted, via sulfur ylide intermediates, to 1,4-oxathianes **256** and **257** by ring expansion with a silylated diazoacetate in the presence of copper catalyst (Scheme 27) <2002CC346, 2005T43>.

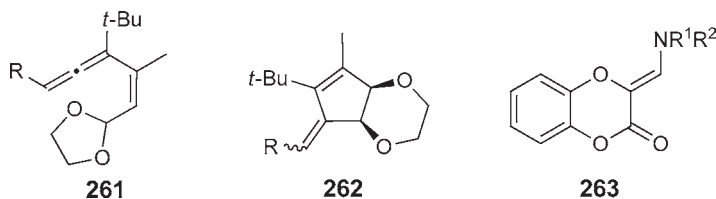


Scheme 27

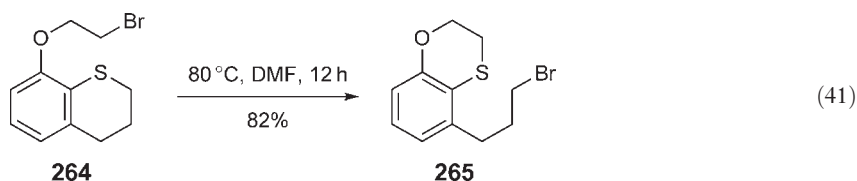
A similar approach for the synthesis of 1,4-dioxanes from unsymmetrical 2,4-disubstituted-1,3-dioxolanes is reported with methyl diazoacetate in the presence of $\text{Rh}_2(\text{OAc})_4$, CuSO_4 , and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <2002DOC207, 1992ZOR2320>. 1,3-Dioxolanes bearing an electron-rich aromatic <2005JOC6111> or heteroaromatic ring <1999TL5439> also react readily with carbenoid species to afford 2,3-polysubstituted-1,4-dioxanes. GaCl_3 was reported to catalyze insertion of isocyanides **259** into a C–O bond in 1,3-dioxolanes **258** (Equation 40) <2005OL3697> and torquoselectivity in the cationic cyclopentannulation of (2*Z*)-hexa-2,4,5-trienal acetals **261** afforded 1,4-dioxane **262** <1997TL7425, 2000CEJ4021>.



Finally, 1,4-benzodioxin-2-carboxylic esters or carboxamides react with nucleophilic amines to give access to 3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamides and 3-aminomethylene-1,4-benzodioxin-2(3*H*)-one **263** <2003T1227>.



1,4-Benzoxathiins **265** can be prepared by rearrangement of the 8-(2-bromoethoxy)-2,3-dihydro-2H-1-benzothio-pyran **264** in DMF at 80 °C (Equation 41) <2003MI187>.



8.12.11 Synthesis of Particular Classes of Compounds

The diverse range of different structures prepared over the period in question together with the small number of publications on any given system preclude any meaningful comparison of the various methods available.

8.12.12 Important Compounds and Applications

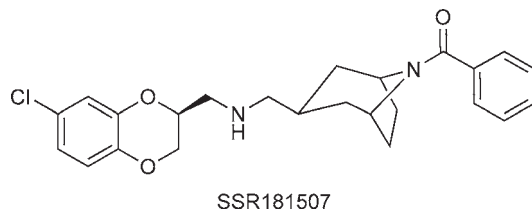
One of the most known oxanthrene derivatives, tragically known as the ‘Seveso poison’ after an explosion at Seveso in northern Italy in July 1976, is the 2,3,7,8-tetrachlorooxanthrene (TCDD), or dibenzo[*b,e*][1,4]dioxin. Studies on the TCDD receptor (or aryl hydrocarbon (Ah) receptor protein) have been reviewed <1996MI55, 1995MI307, 1994MI226>. Degradation and environmental implication of this highly toxic compound as well as other PCDDs were investigated <1984CHEC(3)943, 1996CHEC-II(6)447, 2001MI495, 2003AGE3718>.

The oxanthrene ring system has shown biological activities against wild-type P388 leukemia *in vitro* and *in vivo* <1996CHEC-II(6)447>.

Phenoxathiins were intensely studied in order to obtain new antifungal, antibiotic, anti-inflammatory, antiedema, antidiabetic, choleric, cytostatic, and tranquilizer drugs, or insecticides <1984CHEC(3)943, 1996CHEC-II(6)447>.

Thianthrene derivatives are implicated in early treatment of skin infections, in cosmetics, and are employed as solvents and plasticizers for polyvinyl chloride (PVC) <1984CHEC(3)943, 1996CHEC-II(6)447>. Physical and chemical properties and reactivity of thianthrene cation radical perchlorate have been extensively studied <2003JPO142, 2002JOC4030, 1996JOC4716, 1991JOC1332>. Thianthrenes have also gained new interest as components of conducting organic materials, for example, charge-transfer salts <1987SM(20)357, 1991AGE714, 1993CB465, 1994CB2043>.

Numerous derivatives of 2,3-dihydro-1,4-benzodioxin have been studied in the field of medicinal chemistry as selective α_1 -adrenoreceptor antagonists (WB4191, Doxazosin, Phendioxan), selective α_2 -adrenoreceptor antagonists (Idazoxan), selective 5-HT_{1A} receptor agonists (Spiroxatrine, MDL72832, Flesinoxan), 5-HT_{1B} receptor agonists (Eltoprazine), 5-HT₄ receptor antagonists (SB204070A). The pharmacological activity of the above-mentioned compounds varies greatly, depending on their specific observed affinities. Thus, these derivatives can be anti-hypertensive agents, antidepressant agents, anxiolytic agents, serenic agents, etc. The 2,3-dihydro-1,4-benzodioxin framework has often been found in biologically active lignans. Silybin and Americanin are antihepatotoxic, and Haedoxan has insecticidal activity <1996CHEC-II(6)447, 2001JME261>. More recently, WB4101-related benzodioxanes were synthesized. Depending on the configuration of a cyclopentane unit, the affinity for α_1 -adrenoreceptor subtypes and the affinity for 5-HT_{1A} receptors was differentiated <1999JME4214>. Benzodioxanes bearing a benzylpiperidine unit have been described to possess a remarkable affinity for both σ and 5-HT_{1A} receptors <2005JME266>. On the other hand, some benzodioxanes bearing an amide, urea, or imidazolidinone moiety have proved to be potent α_2 -adrenergic and D2-dopamine receptors <2000JME3653>.



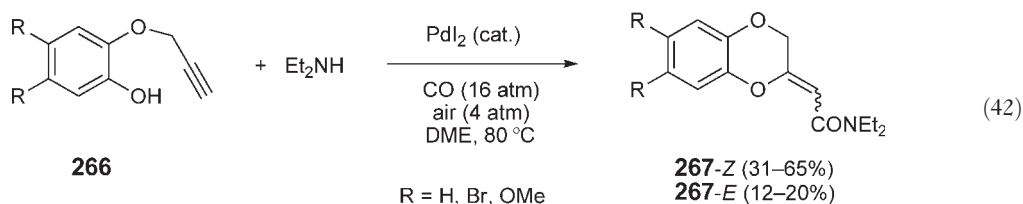
Compound (SSR181507) is a dopamine D₂ receptor antagonist and 5-HT_{1A} receptor agonist <2003MI2604>, although benzodioxanypiperazine derivatives (such as Lecozotan) possess 5-HT_{1A} antagonist activity *in vitro* <2005JME3467>. Furthermore, 1,4-benzodioxanes bearing a 2-pyrrolidinyl substituent at the 5- and 2-position bind at $\alpha 4\beta 2$ nicotinic acetylcholine receptor <2006BML5610>. The 1,4-benzodioxane ring system was also implicated as a potent vanilloid receptor-1 (TRPV1 or VR1) antagonist <2005JME71>, as potent calcium channel antagonist <2000EJM663>, and have insecticidal activity against *Spodoptera litura* F <2002MI49>. From a non-therapeutic point of view, a new atropoisomeric ligand bearing a 1,4-benzodioxane core (SYNPHOS[®]) has been synthesized and applied in ruthenium-mediated hydrogenation reactions <2003TL823, 2004PNA5799>. Recently, some 1,4-dioxanes were found to display a moderate antiviral effect <2005BML3207>.

Derivatives of 2,3-dihydro-1,4-oxathiin and 1,4-benzoxathiins have been patented as agrochemicals with the discovery of so-called systemic fungicides <1984CHEC(3)943>. Thus, 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbox-anilide or Carboxin is a well-known systemic fungicide used for seed treatment. 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 <1996CHEC-II(6)447>. Dihydrobenzoxathiins were discovered as a novel class of selective estrogen receptor alpha modulators (SERAMs) <2004JME2171>. Many variations were investigated on this scaffold <2005BML3912>. Dihydrobenzodithiin compounds were also evaluated as SERAMs. They maintained a high degree of selectivity for Er_a over Er_b; however, they lacked the *in vivo* antagonism/agonism activity exhibited by dihydrobenzoxathiins <2004BML3753>.

1,4-Benzoxathiins, considered as 4-thiaflavans, have shown antimicrobial <2004MI317> and antioxidant activity and seem to operate by both the flavonoid-like and the tocopherol-like mechanisms <2001CC551, 2005OBC3066>.

8.12.13 Further Developments

Very recently, 2,3-dihydro-1,4-benzodioxins have been synthesized from allylic catechol derivatives using a domino Wacker–Heck reaction with α,β -unsaturated ketones or esters <2007H(70)309>. Benzodioxanes **267** was synthesized from 2-prop-2-ynyloxyphenols **266** through tandem oxidative aminocarbonylation of the triple bond-intramolecular conjugate addition. The reaction showed a significant degree of selectivity, the *Z* isomers being formed preferentially <2006JOC7895>. New substituted derivatives containing the 1,4-benzodioxane nucleus were also described for their *in vitro* and *in vivo* anti-inflammatory activity <2007BMC4876>. Furthermore, novel 5-benzyl and 5-benzylidenethiazolidine-2,4-diones carrying 2,3-dihydro-1,4-benzodioxin pharmacophore have shown glycogen phosphorylase inhibitor activity <2007BMC4048> and new benzodioxinic lactones have been reported with potential anticancer activity <2007JME294>.



In the sulfur series, 2,3-disubstituted-1,4-benzodithiins were isolated by reacting fused aromatic 1,2,3,4,5-pentathiepins with triphenylphosphine and alkynes bearing electron-withdrawing groups <2006OL4529>. A novel access to 1,4-dithiins and 1,4-benzodithiins has been described from the acyclic ketones and cyclic ketones, respectively, using 1,1'-(ethane-1,2-diyl)dipyridinium bis tribromide (EDPBT) <2007TL1007>.

Thianthrene sulfilimines were readily prepared by the reaction of substituted thianthrene derivatives with chloramine T or O-mesitylenesulfonylhydroxylamine (MSH). On *N*-tosylation or oxidation of 1- or 2-substituted thianthrene derivatives, the regioselectivities toward the attacking site of the reagents whether 5- or 10-position of sulfur atom were observed as *ca.* 3:1 and 1.8 to 1.5:1, respectively. The photolysis of thianthrene sulfilimines and their oxides occurred with SN- and SO-bond cleavage to afford the corresponding thianthrene derivatives, and in the photolysis of *trans*-5-(*N*-*p*-tosyl)iminothianthrene 10-oxide *trans*–*cis* isomerization was observed <2007T7708>. Concerning the thianthrene tetraoxide, the ring inversion barrier of the 2,7-diisopropyl derivatives was determined by making use of the variable temperature ¹³C NMR spectra ($\Delta G^\ddagger = 6.5 \text{ kcal mol}^{-1}$) <2006JOC6248>.

A comprehensive review of recent chemistry of thianthrene cation radical has appeared <2006MI617> and thianthrene cation radical tetrafluoroborate (Th^+BF_4^-) was found to add to 2,3-dimethyl-2-butene (DMB) at 0 °C and –15 °C. The adduct was stable in CD_3CN solution at –15 °C but decomposed slowly at 0 °C and quickly at 23 °C <2006JOC3737>.

Finally, enantioselective reduction of 2-substituted-1,4-benzoxathiins to 2-substituted-1,4-dihydrobenzoxathiins was undertaken using an enantioselective sulfur oxidation and sulfoxide directed reduction sequence <2006S3389>.

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Biographical Sketch



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