6.04

1,2-Oxazines and their Benzo Derivatives

THOMAS L. GILCHRIST
University of Liverpool, UK

JANE E. WOOD
Glaxo Wellcome Medicines Research Centre, Stevenage, UK

6.04.1 INTRODUCTION
6.04.2 THEORETICAL METHODS
6.04.3 EXPERIMENTAL STRUCTURAL METHODS
  6.04.3.1 X-Ray Crystal Structures
  6.04.3.2 NMR Spectra
  6.04.3.3 UV Spectra
  6.04.3.4 IR Spectra
6.04.4 THERMODYNAMIC ASPECTS
  6.04.4.1 Aromaticity of Conjugated Rings
  6.04.4.2 Conformations of Nonconjugated Rings
6.04.5 REACTIVITY OF FULLY CONJUGATED RINGS
6.04.6 REACTIVITY OF NONCONJUGATED RINGS
  6.04.6.1 4H-1,2-Benzoxazines and 4H-1,2-Oxazines
  6.04.6.2 6H-1,2-Oxazines and 6H-1,2-Oxazin-6-ones
  6.04.6.3 3,6-Dihydro-2H-1,2-oxazines
  6.04.6.4 5,6-Dihydro-2H-1,2-oxazines
  6.04.6.5 5,6-Dihydro-4H-1,2-oxazines
    6.04.6.5.1 Unimolecular reactions
    6.04.6.5.2 Reactions with electrophiles
    6.04.6.5.3 Reaction with nucleophiles
    6.04.6.5.4 Reduction and reductive cleavage
    6.04.6.5.5 1,3-Dipolar cycloaddition reactions of 5,6-dihydro-4H-oxazine 2-oxides
6.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS
  6.04.7.1 Ring Hydrogen Atoms
  6.04.7.2 Other Substituents
6.04.8 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT
  6.04.8.1 Intramolecular Cyclization
  6.04.8.2 Combination of 4-Atom and 2-Atom Components
    6.04.8.2.1 [4 + 2] Cycloaddition leading to 3,6-dihydro-2H-1,2-oxazines
    6.04.8.2.2 [4 + 2] Cycloaddition leading to 5,6-dihydro-4H-1,2-oxazines
6.04.1 INTRODUCTION

1,2-Oxazines and their benzo derivatives were described, along with other oxazines and thiazines, by Sainsbury 〈84CHEC-I(3)995〉. Since 1984 the main developments have been in the preparation of 3,6- and 5,6-dihydro-1,2-oxazines and in their subsequent use as synthetic intermediates, particularly by reductive ring cleavage. Several research groups have investigated the asymmetric synthesis of 3,6-dihydro-2H-1,2-oxazines by cycloaddition of chiral nitrosocarbonyl compounds to dienes. There have also been significant advances in the characterization of salts of the fully conjugated 1,2-oxazinium cation bearing a variety of ring substituents and in the chemistry of transient 1,2-oxazinium cations.

The nomenclature of some of the ring systems containing the 1,2-oxazine skeleton is shown in Figure 1. Examples of all the monocyclic systems, and of partially or fully hydrogenated analogues, are known. The fused-ring systems shown in Figure 1 are also all represented in the literature, although 2H-1,2-benzoxazines and 2H-naphth[1,2-d]oxazines occur only as partially reduced derivatives. The naphth[1,8-de]-1,2-oxazine ring system is unique because it is the only fully conjugated, neutral 1,2-oxazine derivative apart from those containing carbonyl functions, such as (1) and (2). There are a few examples of the naphth[1,8-de]-1,2-oxazine ring system in the literature and these have been briefly reviewed 〈90AHC(51)1〉.

![Chemical Structures](image)

**Figure 1** Examples of well-known 1,2-oxazine ring systems.
The properties of the 1,2-oxazine ring system are described following the general pattern adopted in other chapters of this volume. Most of the information refers to the monocyclic systems but benzo fused-ring systems and carbonyl derivatives of the monocyclic systems are discussed where there are significant differences (for example, in methods of preparation). The balance of the coverage differs from that in some other chapters because the overwhelming majority of the literature citations concern partially or fully reduced 1,2-oxazines rather than the conjugated systems. The aim has been to include all significant developments up to mid-1994.

### 6.04.2 THEORETICAL METHODS

The geometry, heat of formation, ionization potential, and charges on the atoms of the 1,2-oxazinium cation have been calculated by the MINDO/3 method \( \langle 87\text{ZOR717} \rangle \). The calculated geometry and atomic charges are shown in Figure 2(a); the bond distances can be compared with those from the x-ray crystal structure of the tetramethyl-1,2-oxazinium cation shown in Figure 2(b) \( \langle 85\text{JA5722} \rangle \). The heat of formation of the 1,2-oxazinium cation was calculated as 162.9 kcal mol\(^{-1} \) and the ionization potential as 15.32 eV.

Calculations by SCF-MO LCAO methods have also been carried out on the oxazinones (1) and (2) \( \langle 85\text{ZOR2445} \rangle \). The effective charges at the ring atoms have been calculated in order to correlate these with the experimentally observed position of alkylation (the ring nitrogen or the oxygen of the carbonyl group).

A molecular mechanical (MM2 force field) parameter set has been obtained for compounds containing N—O bonds and this has been applied to calculations of the geometries and energies of tetrahydro-2H-1,2-oxazine and of its 2-methyl derivative \( \langle 93\text{MI604-01} \rangle \). The geometrical parameters compare well with previously obtained experimental values.

![Figure 2](image)

Figure 2  (a) Bond distances (Å) and charges at the atoms (q) in the 1,2-oxazinium cation, calculated by the MINDO/3 method; (b) bond distances in the 3,4,5,6-tetramethyl-1,2-oxazinium cation determined by x-ray crystallography.

### 6.04.3 EXPERIMENTAL STRUCTURAL METHODS

#### 6.04.3.1 X-Ray Crystal Structures

Crystal structure data have been obtained not only for the 1,2-oxazinium cation shown in Figure 2(b) and for perhydro-1,2-oxazines referred to above, but also for several partly saturated 1,2-oxazines. The C—N and N—O bond distances in 6H-1,2-oxazines \( \langle 80\text{SCS523}, 93\text{CS(P1)2507} \rangle \) and in 5,6-dihydro-4H-1,2-oxazines \( \langle 88\text{HCA822}, 89\text{AX(C)976}, 92\text{CPB1921} \rangle \) are within the range expected for oxime ethers.

#### 6.04.3.2 NMR Spectra

The \(^{13}\text{C} \) chemical shift values for the tetramethyl-1,2-oxazinium salt (3) and for some 6H-1,2-oxazines and dihydro-1,2-oxazines (4)–(8) are given in Table 1.
1,2-Oxazines and their Benzo Derivatives

\[
\text{Me} - \text{O} - \text{N} - \text{Me}
\]

(3)

\[
\text{Me} - \text{O} - \text{N} - \text{Me}
\]

AlCl\(_7\)^{-}

(3)

\[
\text{Me} - \text{O} - \text{N} - \text{Me}
\]

(4)

\[
\text{EtO} - \text{O} - \text{N} - \text{Et}
\]

(5)

\[
\text{Ph}
\]

(6)

\[
\text{Me}_3\text{Si}
\]

(7)

\[
\text{NMe}
\]

(8)

Table 1 13C NMR shifts of 1,2-oxazines (3)-(8)^a.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3)</td>
<td>165.1</td>
<td>157.3</td>
<td>139.7</td>
<td>197.5</td>
<td>85JA5772</td>
</tr>
<tr>
<td>(4)</td>
<td>156.8</td>
<td>110.9</td>
<td>141.4</td>
<td>66.5</td>
<td>89S908</td>
</tr>
<tr>
<td>(5)</td>
<td>156.2</td>
<td>112.9</td>
<td>127.8</td>
<td>94.7</td>
<td>94CB685</td>
</tr>
<tr>
<td>(6)</td>
<td>155.8</td>
<td>19.6</td>
<td>23.7</td>
<td>64.9</td>
<td>91LA851</td>
</tr>
<tr>
<td>(7)</td>
<td>146.8</td>
<td>19.1</td>
<td>22.4</td>
<td>75.5</td>
<td>92JOC339</td>
</tr>
<tr>
<td>(8)</td>
<td>56.6</td>
<td>123.5</td>
<td>125.8</td>
<td>68.5</td>
<td>77JCS(P2)619</td>
</tr>
</tbody>
</table>

^a Spectra in CDCl\(_3\) except for compound (3) (CD\(_2\)Cl\(_2\)).

The \(^1\)H NMR spectra of a variety of 1,2-oxazines have proved useful in determining the lowest energy conformations of the rings. The ring systems adopt chair or half-chair conformations; substituents normally occupy equatorial or pseudoequatorial positions. The exception is that alkoxy and other electronegative substituents attached to C-6 occupy axial or pseudoaxial positions; this can be accounted for by the influence of a pronounced anomic effect of the ring oxygen atom. For example, the spectrum of 3-acetyl-6-ethoxy-5,6-dihydro-4H-1,2-oxazine (9) shows H-6 as a triplet (J 2.8 Hz) at \(\delta\) 5.20, consistent with the conformation shown \(\langle 83JCS(P1)1281\rangle\). This is a general feature which has been observed with many other such dihydrooxazines including compounds (10) \(\langle 88BCJ461\rangle\) and (11) \(\langle 90LA217\rangle\). In the case of 3,6-dihydro-2H-1,2-oxazines \(^{13}\)C NMR spectra were used for conformational analysis \(\langle 77JCS(P2)619\rangle\).

\[
\text{Me}_2\text{SiO} - \text{O} - \text{N} - \text{Ph}
\]

(11)

6.04.3.3 UV Spectra

The UV spectrum of the tetramethyloxazinium salt (3) (counterion AlCl\(_4^-\)) in 0.1 M acetic anhydride–AlCl\(_3\) complex in dichloromethane shows a maximum absorption at 270 nm (log \(\varepsilon\) 3.92) \(\langle 85JA5722\rangle\). This has been ascribed to the \(\pi-\pi^*\) band and was taken as evidence that the cation is an aromatic ring system. UV spectra were earlier taken as evidence for the formation of aromatic oxazinium cations when 3,5-diphenyl-1,2-oxazinone (12) and related oxazinones are alkylated or protonated (Equation (1)) \(\langle 73ZOR1987, 74ZOR1513\rangle\). For example, the UV spectrum of compound (12) in methanol (\(\lambda_{\text{max}}\) 239 and 303 nm; log \(\varepsilon\) 4.20 and 4.10) is substantially different to that in concentrated sulfuric acid (\(\lambda_{\text{max}}\) 340 and 392 nm; log \(\varepsilon\) 4.02 and 4.26) \(\langle 73ZOR1987\rangle\).
An unusual effect of halogen substitution has been observed in the UV spectra of 4-halooxazines (13) \langle 86JJ33 \rangle. The absorption maximum of compound (6) in hexane is at 212 nm (log \( \varepsilon \) 2.95); both the intensity and wavelength of the absorption maximum increases in compounds (13) in the sequence 234 (3.13) (X = F), 239 (3.43) (X = Cl), 247 (3.38) (X = Br) and 255 (3.55) (X = I). It has been suggested that the changes are due to the polarization of the substituent.

\[
\text{RX} = \text{Et}_2\text{O}^+\text{BF}_4^-, \text{Me}_2\text{SO}_4, \text{H}_2\text{SO}_4
\]

6.04.3.4 IR Spectra

The IR absorption which is of most diagnostic value is the C–N stretching frequency, which occurs at about 1590 cm\(^{-1}\) in a wide range of 5,6-dihydro-4\(H\)-1,2-oxazines \langle 83JCS(P1)1275, 83JCS(P1)1283, 88BCJ461, 90LA217 \rangle and at a slightly lower frequency in 6\(H\)-1,2-oxazines \langle 91LA553, 92CB2243 \rangle. The C–C stretching frequency of 6\(H\)-1,2-oxazines appears at about 1660 cm\(^{-1}\). The stretching frequency of the carbonyl group in a conjugated oxazine, 5-methyl-3-phenyl-6\(H\)-1,2-oxazin-6-one, is 1730 cm\(^{-1}\) \langle 92CB2243 \rangle. Values between 1730 and 1760 cm\(^{-1}\) have been recorded for the C–O stretching frequency of 5,6-dihydro-4\(H\)-1,2-oxazin-6-ones \langle 91JCS(P1)3153 \rangle.

6.04.4 THERMODYNAMIC ASPECTS

6.04.4.1 Aromaticity of Conjugated Rings

The conclusion reached by the authors of the theoretical and experimental studies discussed in Section 6.04.2 is that the 1,2-oxazin-4-ylium cation is a planar, aromatic cation, although the x-ray structure shown in Figure 2(b) reveals that the bond distances tend to alternate (for example, the C–N bond distance is not significantly greater than that in oximes and imines). The ring system is very susceptible to nucleophilic attack because of the high positive charge and for this reason only heavily substituted cations are so far available for experimental study.

6.04.4.2 Conformations of Nonconjugated Rings

Experimental work carried out in the 1970s established that tetrahydro-1,2-oxazines adopt a chair conformation \langle B-80MI 604-01 \rangle; in the 1990s, molecular mechanics calculations have been carried out which are in accord with the experimental results \langle 93MI 604-01 \rangle.

The evidence from \(^1\)H NMR spectra of many 5,6-dihydro-4\(H\)-1,2-oxazines is that they adopt half-chair conformations (see Section 6.04.3.2) and this is supported by molecular mechanics calculations \langle 90LA217 \rangle. 3,6-Dihydro-2\(H\)-1,2-oxazines also adopt a half-chair conformation \langle 77JCS(P2)619 \rangle.
6.04.5 REACTIVITY OF FULLY CONJUGATED RINGS

Because of the highly electrophilic nature of the 1,2-oxazinium cation, virtually no studies have been carried out on isolated salts; no general chemistry has been developed comparable to that of the pyrulium salts. There are, however, some reports of reactions in which 1,2-oxazinium salts are likely to be transient intermediates. Early work on 3,5,6-triaryl-1,2-oxazinium cations indicated that on hydration they are converted into the corresponding 6-hydroxy-6H-oxazinium cations (Equation (2)) \( \langle \text{74ZOR1513} \rangle \). A more general pattern of reactivity towards nucleophiles has been established by Reissig and his co-workers. They have shown that the 6-methoxy group of the 6H-oxazines (14) is readily replaced by nucleophiles in the presence of boron trifluoride etherate, and have suggested a mechanism (Scheme 1) involving the 1,2-oxazinium cations as intermediates \( \langle \text{89JOC508} \rangle \). This is quite a general reaction in that a wide range of nucleophiles, including silyl enol ethers, allylsilanes and even activated aromatic compounds such as furan, can be used to give the corresponding 6-substituted oxazines in good yield. There are, however, some exceptions: when Lewis acid-catalyzed reactions of the oxazine (14a) were attempted with trimethylsilyl cyanide or with triethyl phosphite as nucleophiles, products of ring contraction were isolated \( \langle \text{92LA621} \rangle \). It is suggested that these result from ring contraction of the oxazine (14a) instead of elimination to the oxazinium cation.

\[
\text{Scheme 1}
\]

6.04.6 REACTIVITY OF NONCONJUGATED RINGS

6.04.6.1 4H-1,2-Benzoxazines and 4H-1,2-Oxazines

It is known that several types of 1,2-oxazine undergo thermal pericyclic reactions in which the N-O bond is cleaved \( \langle \text{84CHEC-I(3)995} \rangle \). A more recent reaction of this type is the thermal retro-Diels–Alder reaction of 3-substituted 4H-1,2-benzoxazines (15; \( \text{R} = \text{Me, Ph} \)). These compounds decompose on heating at, or below, 90°C to give the corresponding nitrile and \( \alpha \)-benzoquinone methide, which can be intercepted by alkenes (Scheme 2) \( \langle \text{90JOC5341, 94TL7273} \rangle \). A similar reaction of the bicyclic 5,6-dihydro-4H-1,2-oxazine (16) in the presence of traces of acid has been ascribed to the formation and decomposition of a transient 4H-1,2-oxazine (17) \( \langle \text{90LA469} \rangle \). A monocyclic 4H-1,2-oxazine has been postulated as an intermediate in a related fragmentation \( \langle \text{95H(40)531} \rangle \).

\[
\text{Scheme 2}
\]
6.04.6.2 6H-1,2-Oxazines and 6H-1,2-Oxazin-6-ones

3-Phenyl-6H-1,2-oxazine undergoes HCl-catalyzed conjugate addition of benzyl alcohol (Equation (3)) \(<91LA189\). This reaction is presumably initiated by protonation on nitrogen. Alkylation of the benzoxazinones (18) by triethylxonium tetrafluoroborate also takes place on nitrogen \(<82ZOR662, 85ZOR2445\>). In the case of 6-methoxy-6H-1,2-oxazines (14) replacement of the 6-substituent by nucleophiles (Scheme 1) is initiated by attack of a Lewis acid on the methoxy group \(<92LA621, 95H(40)531\); however, in other cases the Lewis acid can coordinate to the ring oxygen and this leads to cleavage of the ring \(<92LA621\).

Other reactions of 6H-1,2-oxazines also result in ring cleavage. The oxazines (19) are converted by reaction with DBU into 2-acetylpyridines, the key step being eliminative cleavage of the ring (Scheme 3) \(<87JCS(P1)2505\). A wide range of reductive cleavage reactions has also been observed (Scheme 4) \(<92CB2243, 93LA1155\>.

Benzoxazinones of type (12) have been subjected to electrochemical reduction in the presence of strychnine and other optically active bases to give optically active 2-(aminoalkyl)benzoic acids, but the optical yields are generally low \(<82MI604-01\>.

6.04.6.3 3,6-Dihydro-2H-1,2-oxazines

The most common reaction of 3,6-dihydro-2H-1,2-oxazines is reductive cleavage of the N—O bond, this being an important step in several synthetic schemes which are based on Diels–Alder
reactions of nitroso compounds. The chemoselective cleavage of the N—O bond in the presence of the carbon–carbon double bond can be achieved by means of sodium amalgam if the N—O bond is activated. For example, the N—O bond of the oxazine (20) was selectively cleaved in good yield using sodium amalgam (Equation (4)) and the method has been used with other chiral oxazines. A milder reagent, which is suitable only for activated N—O bonds, is aluminum amalgam. For dihydrooxazines in which the N—O bond is not activated the bond can be cleaved using zinc and acetic acid. Reductive cleavage of the N—O bond by bacteria in the presence of mediators (methylviologen and hydrogen gas) has been recommended as a very mild chemoselective alternative.

Another synthetically useful reaction of 3,6-dihydro-1,2-oxazines is cis dihydroxylation of the carbon–carbon double bond. It is often possible to achieve good diastereoselectivity, especially in bicyclic oxazines with an asymmetric ring junction, such as compound (21) (Equation (5)).

Some reactions of specific types of 3,6-dihydro-1,2-oxazines are worthy of note. The oxazine (22) and related compounds are converted into pyrroloindoles such as (23) when warmed in ethanol at 40–50°C.
being a [3,3] sigmatropic rearrangement in which the N—O bond is cleaved. The pyrrole (25) was produced in moderate yield when the 6-methoxyoxazin (24) was treated with boron trifluoride etherate and methanol (Equation (6)) [91JOC850]. In this reaction, which was investigated as a model for a step in a projected route to mitomycins, acid-catalyzed ring opening is accompanied by nucleophilic attack on the benzene ring at the position ortho to nitrogen by methanol. This unusual process is apparently initiated by the Lewis acid-catalyzed cleavage of the N—O bond, the developing positive charge on nitrogen being sufficient to activate an ortho carbon atom to nucleophilic attack. A different type of ring contraction occurs when N-Boc-3,6-dihydro-1,2-oxazines are treated with LDA: 2,5-dihydrofuranylamines are formed after cleavage of the N—O bond [93TL961].

Scheme 5

6.04.6.4 5,6-Dihydro-2H-1,2-oxazines

This ring system is known to be unstable: the N—O bond is cleaved by a retro-Diels–Alder process under very mild conditions (Equation (7)) [84CHEC-II(3)995]. Further examples of this reaction have been reported [83LA897] and there are several other fragmentation reactions of 1,2-oxazines in which ring cleavage probably occurs in this way [85HCA1998, 88BCJ461, 89TL3471]. The formation of 2-phenylpyrrole (44%) from 5,6-dihydro-3-phenyl-4H-1,2-oxazine and base can be explained by the sequence shown in Scheme 6 [89TL3471] and the cleavage of the oxazine N-oxides (26) is similar (Scheme 7) [88BCJ461].

Scheme 6
6.04.6.5 5,6-Dihydro-4H-1,2-oxazines

6.04.6.5.1 Unimolecular reactions

There are several thermal ring cleavage reactions of 4H-1,2-oxazines \( \langle 79CC1090, 81TL2557, 83JCS(P1)1479, 84CHEC-I(3)995 \rangle \) but the type of ring opening varies according to the substituents. The 3-carboxyl group acetic acid, with loss of carbon dioxide and opening of the ring, below 100°C \( \langle 79CC1090 \rangle \). 4H-Oxazines which are formed by cycloaddition of nitrosoalkenes to 1-methyltetrahydrocarbazole undergo the reverse reaction when heated in xylene \( \langle 83JCS(P1)1479 \rangle \) and 5,6-dihydro-6,6-dimethyloxazin-4-ones undergo ring contraction to pyrrolinone \( \text{N-oxides under the same conditions} \langle 81TL2557 \rangle \). 5,6-Dihydro-3-phenyl-4H-1,2-oxazines also undergo photoinduced cleavage of the \( \text{N-O bond} \langle 81CL1561 \rangle \).

6.04.6.5.2 Reactions with electrophiles

5,6-Dihydro-4H-1,2-oxazines which bear substituents at C-6 capable of stabilizing a positive charge are readily cleaved in acidic media. An example is the conversion of the dihydrooxazine \( 27; \text{R} = \text{Ph} \) to the pyrrolinone \( \text{N-oxide} \) \( 28 \) by reaction with HCl in methanol (Scheme 8) \( \langle 85JCS(P1)2769 \rangle \). The corresponding 3-acetiloxazin \( 27; \text{R} = \text{COMe} \) is converted into 3-carboxylic acid-2-methylpyridine \( \text{N-oxide} \) \( 29 \) under the same conditions. Ring contractions analogous to those of \( 27; \text{R} = \text{Ph} \) to \( 28 \) also occur with 6-trimethylsilyloxy substituted oxazines \( \langle 90LA469 \rangle \).

\[
\text{Scheme 8}
\]

Oxazines of the general structure \( 29 \) are also easily cleaved by acid catalysts (Equation (8)). The ability of the trimethylsilyl group to stabilize an adjacent cation undoubtedly promotes the ring opening reaction, which leads to the unsaturated ketones shown in Equation (8) for \( \text{R} = \text{Ph} \) \( \langle 87S77 \rangle \) and \( \text{R} = \text{CO}_2\text{Et} \) \( \langle 86CC30 \rangle \), or to the corresponding oxime for \( \text{R} = \text{CF}_3 \) \( \langle 92JC339 \rangle \). Oxazines \( 30 \) bearing both alkoxy and trimethylsilyloxy groups at C-6 are hydrolyzed by HCl to oxazinones \( 31 \) and to open chain oximes \( \langle 91JCS(P1)13153 \rangle \). Dihydrooxazin \( \text{N-oxides are easily cleaved to give carbonyl compounds by acids under Nef type conditions} \langle 86HCA1971, 91TL5607 \rangle \).

Simple 5,6-dihydro-4H-1,2-oxazines can be alkylated on nitrogen by reaction with triethylxonium tetrafluoroborate to give the corresponding \( \text{N-ethyloxazine tetrafluoroborates} \) \( \langle 83LA897 \rangle \); benzyl iodide has also been used as an alkylating agent \( \langle 91LA161 \rangle \).

Several useful C-substitution reactions of 5,6-dihydro-4H-1,2-oxazines have been achieved after removal of a proton from C-4 with a strong base: these reactions are described in Section 6.04.7.1.
6.04.6.5.3 Reaction with nucleophiles

The 3-position of 5,6-dihydro-4H-1,2-oxazines is electrophilic, and, when additional activation is present, a variety of nucleophiles can attack at this position. A 3-nitro substituent can be displaced by nucleophiles \(<84\text{CHEC-I}3995>\) and N-alkyloxazinium salts are attacked by nucleophiles including cyanide \(<87\text{JOC}877>\) and diphenyl hydrogen phosphate (Equation (9)) \(<91\text{LA}161>\). A halogen substituent at the 4-position of 5,6-dihydrooxazines can undergo S\(_n2\) displacement by nucleophiles such as amines and azide, fluoride, and malonate anions \(<86\text{JJ}33, 94\text{CB}685>\).

\[
\text{Me} \quad \overset{\text{P(O)(OPh)}_{2}}{\text{O}} \quad \overset{\text{Ph}}{\text{N}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \\
\text{Me} \quad \overset{\text{P(O)(OPh)}_{2}}{\text{O}} \quad \overset{\text{Ph}}{\text{N}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}} \quad \overset{\text{Ph}}{\text{O}}
\]

6.04.6.5.4 Reduction and reductive cleavage

One of the most useful features of the chemistry of 5,6-dihydro-4H-1,2-oxazines is that, by careful control of the reagent and the conditions, they can be cleanly reduced to a variety of heterocyclic and open-chain compounds. A systematic survey of these reactions has been published \(<90\text{LA}475>\) and there are several other examples of synthetic applications.

Reductive deoxygenation of oxazines bearing alkoxy, trimethylsilyloxy, or dialkylamino substituents at the 6-position can be carried out using either Fe\(_3\)(CO)\(_{12}\) \(<90\text{BCJ}3595>\) or Mo(CO)\(_6\) \(<90\text{LA}469>\) and the reaction leads to the formation of pyrroles in good yield (Equation (10)). It is possible to prepare pyrroles in a “one-pot” procedure starting from \(\alpha\)-haloalkanes and enamines, the dihydrooxazine being generated and then reduced by Fe\(_3\)(CO)\(_{12}\) \(<90\text{BCJ}3595>\). The methodology has also been applied to the synthesis of the pheromone methyl 4-methylpyrrole-2-carboxylate (34) from the oxazine (33) \(<92\text{LA}709>\).

\[
\text{Me} \quad \overset{\text{Z = OAlk, OSiMe}_{3}, N(Alk)_{2}}{\text{O}} \quad \overset{\text{Fe}_{3}(CO)_{12} \text{ or Mo(CO)}_{6}}{\text{N}} \quad \overset{\text{Z = OAlk, OSiMe}_{3}, N(Alk)_{2}}{\text{O}} \quad \overset{\text{Me}}{\text{CO}_{3}Me} \quad \overset{\text{Me}}{\text{CO}_{3}Me} \quad \overset{\text{Me}}{\text{CO}_{3}Me} \quad \overset{\text{Me}}{\text{CO}_{3}Me}
\]
Dihydrooxazines of type (33) can be reduced to pyrrolidines by catalytic hydrogenation \(^{(87CR(S)180, 89S265, 90LA475, 95LA667)}\) or by reaction with aluminum amalgam. For example, the proline derivative (35) was prepared in good yield by catalytic hydrogenation (Equation (11)). Both aluminum amalgam and catalytic hydrogenation methods are effective for the reduction of 3-ethoxycarbonyloxazines of this type, but the mechanisms may differ because the stereoselectivity of the reduction depends on the choice of reagent \(^{(87CR(S)180)}\). Sodium borohydride, LAH, and DIBAL-H have also been used for the reductive cleavage of several dihydrooxazines \(^{(90LA475)}\); an example of a useful reductive cleavage is the formation of the benzylamine (36) (87%) by LAH reduction of the oxazine (29; R = Ph) \(^{(87S777)}\). The C=N bond can be reduced without cleavage of the ring by reaction with sodium cyanoborohydride in acetic acid \(^{(94S1050)}\).

\[
\text{Me} \quad \text{N} \quad \text{CO}_2\text{Et} \quad \text{Me}_3\text{SiO} \quad \text{H}_2, \text{Pd/C}, \text{HCl} \quad 74\% \quad \text{Me} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

\[
(35)
\]

**6.04.6.5.5 1,3-Dipolar cycloaddition reactions of 5,6-dihydro-4H-oxazine 2-oxides**

5,6-Dihydro-4H-oxazine 2-oxides can be regarded as cyclic nitronic esters, and as such they can act as 1,3-dipoles in cycloaddition reactions with electron-deficient alkenes. The intermolecular reaction has been known since the 1960s and the reactions can show good regioselectivity and diastereoselectivity. For example, the structure of the adduct formed from 4-bromophenyl acrylate and an oxazine N-oxide (Equation (12)) was established as (37) by x-ray crystallography \(^{(86JA1306, 86HCA1971)}\). Intramolecular 1,3-dipolar cycloadditions of this type have also been studied \(^{(93JOC1853)}\).

\[
\text{H} \quad \text{N} \quad \text{CO}_2\text{Ar} \quad \text{H} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{CO}_2\text{Ar}
\]

\[
(37) \quad (\text{Ar} = 4\text{-BrC}_6\text{H}_4)
\]

**6.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS**

**6.04.7.1 Ring Hydrogen Atoms**

Some useful reactions of 5,6-dihydro-4H-1,2-oxazines are based on their selective deprotonation followed by reaction of the carbanions with electrophiles. The deprotonation reactions of 3-methyl-5,6-dihydro-4H-1,2-oxazine (6) have been investigated by Shatzmiller and co-workers. They showed that it was possible to selectively deprotonate the oxazine either at the 3-methyl group (by using lithium \(\text{t}-\text{butylisopropylamide}\)) or at the 4-position (by using butyllithium in a nonpolar solvent) \(^{(81JA5916)}\). Deprotonation at the 4-position is achieved cleanly and rapidly at \(-65^\circ\text{C}\) with butyllithium in hexane and THF \(^{(91LA381)}\). The 4-lithio species can be methylated with iodomethane.
1,2-Oxazines and their Benzo Derivatives

(81JA5916, 91LA381) and halogenated by reaction with chlorine, bromine, or iodine (86IJ33). When the halogens are rapidly added to a solution of the lithium salt, the dimer (38) is formed as the major product (91LA851). The 3-lithiomethyl compound (39) reacts with diiodomethane to give the 3-(2-iodoethylidene) derivative (40) (Scheme 9); a radical mechanism has been suggested for this process (91LA381).

\[
\begin{align*}
\text{BuLi} & \quad \text{Me} \quad \text{BuLi} \\
\text{Me} & \quad \text{Me} \\
\text{N} = \text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

(38)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

(39)

\[
\begin{align*}
\text{Me} & \quad \text{CH}_2\text{Li} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

(40)

Scheme 9

The scope of the chemistry of lithiated 1,2-oxazines has been greatly extended by Reissig and his co-workers (91CB115, 91CB2279, 95LA667). They have explored reactions with a wide range of electrophiles and with several 5,6-dihydrooxazines. The lithiation of the oxazine (29; R = Ph) is, unexpectedly, highly diastereoselective, the proton at C-4 which is cis to the 6-substituent being removed exclusively (91CB115). The selectivity is ascribed to coordination of butyllithium to the ring oxygen atom. Reaction of the intermediate with electrophiles then takes place mainly with retention of configuration (Scheme 10). The delocalized carbanion (42) formed by deprotonation of the oxazine (41) reacts with electrophiles either at C-4 (iodoalkanes) or at the terminus of the methylene group (deuterium oxide, carbonyl compounds, and dimethyl disulfide) (91CB2279).

\[
\begin{align*}
\text{Li}^+ & \quad \text{MeO} \quad \text{Ph} \\
\text{MeO} & \quad \text{Ph} \\
\end{align*}
\]

(41)

\[
\begin{align*}
\text{Li} & \quad \text{Me}_3\text{Si} \quad \text{Ph} \\
\text{Me}_3\text{Si} & \quad \text{Ph} \\
\end{align*}
\]

(42)

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{Ph} \\
\text{Li} & \quad \text{Me}_3\text{Si} \quad \text{Ph} \\
\text{E}^+ & \quad \text{Me}_3\text{Si} \\
\end{align*}
\]

Scheme 10

An example of a deprotonation at C-4 by a much weaker base (DBU) is the eliminative rearrangement of the oxazines (43) (Equation (13)) (87JCS(P1)2505). It is also possible to substitute the 4-
position of dihydrooxazines directly (and diastereoselectively) by radical bromination (NBS and dibenzoyl peroxide) \( \langle 94CB685 \rangle \).

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\text{N} \\
\text{R} \\
\end{array}
\xrightarrow{\text{DBU}}
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\text{N} \\
\text{R} \\
\end{array}
\]

\[ (43) \]

6.04.7.2 Other Substituents

Nucleophilic displacement reactions of halogen substituents at C-4, and various reactions of substituents attached to C-6, have been described in Section 6.04.6. The 3-ethoxycarbonyl substituent, rather than the C\(=\)N bond, of ethyl 5,6-dihydro-\(4H\)-1,2-oxazine-3-carboxylate is reduced by sodium borohydride \( \langle 79\text{JOC}2487 \rangle \).

6.04.8 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

6.04.8.1 Intramolecular Cyclization

A standard synthetic approach to 1,2-oxazines of various types is the cyclization of an oxime bearing a side chain with an appropriate electrophilic centre. In most cases the oxime is isolated and cyclized in a separate step, but in some the oxime is made \textit{in situ}, usually from the corresponding carbonyl compound. All such methods are described together in this section.

An example of this type of synthesis is the preparation of 3-phenyl-5,6-dihydro-1,2-oxazine shown in (Equation (14)) \( \langle 81\text{CL}1561, 89\text{TL}3471 \rangle \). A disadvantage of the route, which applies to all types of oxime cyclizations, is that cyclic nitrones can also be produced if the nitrogen atom of the oxime acts as the nucleophile. The ratio of products seems in some cases to be determined more by the cyclization conditions than by the stereochemistry of the starting oxime \( \langle 92\text{CC}1537 \rangle \). The same approach has been applied to the synthesis of oxazine N-oxides: for example, compound (45) was prepared in high yield by cyclization of the nitroalcohol (44) under Mitsunobu conditions (dead and triphenylphosphine) \( \langle 92\text{TL}6723 \rangle \).

\[
\begin{array}{c}
\text{X} \\
\text{Ph} \\
\end{array}
\xrightarrow{\text{NaOH (X = OTs) or KOBu}^+ (X = Cl)}
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{N} \\
\end{array}
\]

\[ (X = \text{OTs, Cl}) \]

\[
\begin{array}{c}
\text{Me} \\
\text{CO}_2\text{Et} \\
\text{NO}_2 \\
\end{array}
\]

\[ (44) \]

\[
\begin{array}{c}
\text{Me} \\
\text{CO}_2\text{Et} \\
\text{N}^+ \\
\text{O}^- \\
\end{array}
\]

\[ (45) \]

1,2-Oxazines can also be synthesized by intramolecular addition of oximes to carbon–carbon double bonds. These reactions are not general: nitrones and other products can be formed in competition with oxazines. There are examples of conjugate addition to activated alkenes \( \langle 81\text{TL}2557, 91\text{CPB}2830 \rangle \) and of acid or Lewis acid-catalyzed addition to simple alkenes \( \langle 88\text{TL}6805 \rangle \) or alkenes \( \langle 89\text{JCS(P1)2415} \rangle \). 3-Methyl-6-vinyl-5,6-dihydro-\(4H\)-1,2-oxazine was isolated in moderate yield from
a cyclization of this type (Equation (15)) \( \langle 89 \text{JCS(P1)}2415 \rangle \). Cyclization of 1,4-diketone monooximes was described previously as a route to 1,2-oxazines \( \langle 84 \text{CHEC-I}(3)995 \rangle \) and there are several more examples \( \langle 85 \text{JFC}(28)139, 91 \text{ZN(B)}809, 92 \text{JHC}255 \rangle \). A variant is the preparation of 1,2-oxazin-6-ones (47) by reaction of the unsaturated ketones (46) with hydroxylamine (Equation (16)) \( \langle 80 \text{ZC}19 \rangle \).

\[ \text{Cl}_3\text{C} = \text{C}(\text{Ar})\text{O} \xrightarrow{\text{NH}_2\text{OH}} \text{Ar} \xrightarrow{\text{Me}} \text{Ar} \]

\( \text{(46)} \) - \( \text{(47)} \)

\( \beta \)-Nitrostyrenes have been used as precursors of benzoazines. Conjugate addition of diethyl phosphite to the compounds PhCH=\( \equiv \text{C}(\text{R})\text{NO}_2 \) (\( \text{R} = \text{Me}, \text{Ph} \)) gives nitronic acids which are cyclized to the benzoazines (48) in moderate yield when added to 85% sulfuric acid \( \langle 92 \text{JOC}6508 \rangle \). A mechanism has been proposed for the reaction involving cyclization of an intermediate nitroso alcohol (Scheme 11). Other examples \( \langle 86 \text{HC}(79), 90 \text{T759} \rangle \) of the cyclization of nitronic acid derivatives to 1,2-oxazines include the preparation of the 6-hydroxy-5,6-dihydro-4\( H \)-1,2-oxazine (50) (50%) by reduction of the nitronic anhydride (49) with zinc–copper couple (Equation (17)) \( \langle 90 \text{T759} \rangle \). Derivatives of the 1,2-benzoazin-4-one and the naphth[1,8-\( de \)]-1,2-oxazine ring systems have been prepared by cyclization of oximes onto aromatic rings bearing hydroxy or methoxy groups \( \langle 86 \text{MI} 604-01, 90 \text{AHC}(51)1 \rangle \). The process is exemplified by the preparation of 3-methylnaphth[1,8-\( de \)]-1,2-oxazine by heating the oxime of 8-acetyl-1-naphthol in ethylene glycol (Equation (18)) \( \langle 71 \text{JCS(C)}747 \rangle \).

\[ \text{P(O)(OEt)}_2 \xrightarrow{\text{H}^+} \text{P(O)(OEt)}_2 \]

\( \text{R} \)

\[ \text{Ph} \xrightarrow{\text{OH}_2\text{H}^+} \text{Ph} \]

\( \text{P(O)(OEt)}_2 \xrightarrow{\text{R}^+} \text{P(O)(OEt)}_2 \)

\( \text{R} \)

\( \text{OH}_2\text{H}^+ \)

\( \text{R} \)

\[ \text{Ph} \xrightarrow{\text{Zn/Cu}} \text{Ph} \xrightarrow{\text{Me}} \text{Ph} \]

\( \text{O} \)

\( \text{N} \)

\( \text{O} \)

\[ \text{Me} \xrightarrow{\text{Me}} \text{Me} \]

\( \text{OH} \)

\[ \text{HOCH}_2\text{CH}_2\text{OH}, \text{heat} \xrightarrow{66\%} \text{Me} \]

(15) - (18)
6.04.8.2 Combination of 4-Atom and 2-Atom Components

6.04.8.2.1 [4 + 2] Cycloaddition leading to 3,6-dihydro-2H-1,2-oxazines

The well-established Diels–Alder reaction between nitroso compounds and conjugated dienes has continued to be refined over the last decade. The most important advances have been in the development of chiral nitroso dienophiles useful for asymmetric synthesis and in the exploitation of the intramolecular Diels–Alder reaction in synthesis 〈94S1107〉.

Several cycloaddition reactions of nitrosobenzenes to acyclic, electron-rich dienes have been described 〈91JOC850, 93JA6094〉; an example is illustrated in Scheme 12. α-Chloronitrosoalkanes are particularly useful dienophiles because the cycloadducts are easily cleaved by acid to the N-unsubstituted 1,2-oxazines. Two chiral α-chloronitroso compounds which have been used in Diels–Alder reactions are compounds (51) 〈84TL5377〉 and (52) 〈86LA1360, 90LA267, 93LA261, 94TL5653〉. The latter, which is derived from D-mannose, has been shown to add to several cyclic and acyclic dienes with high regioselectivity and diastereoselectivity.

\[
\text{Me}_3\text{SiO} \equiv \text{O} + \text{MeO} \quad \rightarrow \quad \begin{array}{c}
\text{Me}_3\text{SiO} \\
\text{N} \\
\text{Ph}
\end{array}
\]

\[
\text{Scheme 12}
\]

The more reactive acylnitroso compounds, which were originally introduced by Kirby 〈77CSR1〉, are now widely used in both intermolecular and intramolecular Diels–Alder reactions. These compounds are not isolable but are generated in situ by oxidation of the corresponding hydroxamic acids. Sodium periodate or tetraalkylammonium periodates are usually used as the oxidants but other reagents, such as oxalyl chloride/DMSO 〈92TL3583〉 can be used. A new route to acylnitroso compounds has also been discovered: rhodium(II)-catalyzed decomposition of the diazo compound CF₂C(N₂)NO₂ gave CF₂CONO which was intercepted by cycloaddition to 9,10-dimethylanthracene 〈88TL5719〉.

The chiral compounds (53)–(58) have been used as dienophiles in order to assess their use in asymmetric synthesis. Chiral induction is more difficult than for chiral α-chloronitroso compounds because of the greater separation between the nitroso group and the chiral substituent. It is for this reason that compounds such as (53), derived from mandelic acid and other hydroxy acids, have been studied, on the basis that intramolecular hydrogen bonding might improve the rigidity of the dienophile 〈91JA5089, 93JCS(P1)1397〉. This prediction is partly borne out by the higher diastereoselectivities achieved with dienophiles bearing a free hydroxy group compared with the analogous methyl ethers. Several dienophiles bearing chiral pyrrolidine substituents, including (54) 〈90TA363〉, (55) 〈91TA1209〉, and (56) 〈92HCA109〉 have been generated; high diastereoselectivities were achieved in the cycloadditions with compounds (54) and (55), which possess C₂ symmetry. In these, and other cycloadditions of acylnitroso compounds, the major products are formed by enediyne addition of the dienes to nitroso compounds in the cisoid conformation (Figure 3). The more bulky acylnitroso compounds (57) 〈91TA1173〉 and (58) 〈92TL3583〉 also react with simple dienes to give adducts in high yield and with excellent diastereoselectivity. The alternative approach, the addition of an achiral acylnitroso compound to a chiral diene, has also been explored 〈93T2123〉.
Several intramolecular Diels–Alder reactions of acylnitroso compounds have been investigated, particularly as steps in target synthesis. When the tethering chain contains an asymmetric carbon centre, the cycloaddition results in the formation of diastereoisomers. In the case of the reaction shown in (Equation 19), the selectivity was much higher when the reaction was carried out in water rather than in an organic solvent.

![Chemical Structures](image)

**Figure 3** Preferred transition state (endo approach to the cis-acylnitroso compound) in Diels–Alder reactions with dienes.

\[
\begin{array}{c}
\text{O} \\
\text{Bn} \\
\end{array} \xrightarrow{89\%} \begin{array}{c}
\text{O} \\
\text{Bn} \\
\end{array} + \begin{array}{c}
\text{O} \\
\text{H} \\
\end{array}
\]

**Equation 19**

H₂O: 4:1  
CHCl₃: 1.3:1

### 6.04.8.2.2 [4 + 2] Cycloaddition leading to 5,6-dihydro-4H-1,2-oxazines

Conjugated nitrosoalkenes are unlike other nitroso compounds in that they act as dienes, rather than as dienophiles, in the Diels–Alder reaction. Even with conjugated dienes such as cyclopentadiene, nitrosoalkenes normally act as the 4π components in such reactions. This Diels–Alder reaction is now the best general method for the preparation of 5,6-dihydro-4H-1,2-oxazines.

The nitrosoalkenes which are used in the reaction are transient species. They are usually generated *in situ* from an α-haloketoxime, by reaction with a heterogeneous base such as sodium carbonate in an organic solvent (dichloromethane, diethyl ether, or methyl tert-butyl ether) at room temperature. In the presence of simple enol ethers and other electron-rich alkenes, dihydrooxazines are formed in good yield (Scheme 13). Nitrosoalkenes which have been generated and used in this way are listed in Table 2. A longer-lived nitrosoalkene, 1,2,2-trichloronitrosoethylene (59), also reacts with electron-rich alkenes to give dihydrooxazines. The nitrosoalkenes (61; R = H, Me) have been generated from the O-silyloximes (60) by reaction with fluoride, and products of intramolecular cycloaddition have been isolated (Equation (20)).
1,2-Oxazines and their Benzo Derivatives

Scheme 13

Table 2 3-Substituted 5,6-dihydro-4H-1,2-oxazines by Diels–Alder addition of nitrosoalkenes to alkenes (Scheme 13).

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>83JCS(P1)1275, 90CB2403, 90LA217, 91JCS(P1)3153</td>
</tr>
<tr>
<td>4-O$_2$NC$_2$H$_4$</td>
<td>H</td>
<td>83JCS(P1)1275</td>
</tr>
<tr>
<td>1-Adamantyl</td>
<td>H</td>
<td>84CPB143</td>
</tr>
<tr>
<td>Bu</td>
<td>H</td>
<td>92MIP9209587</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>H</td>
<td>92JOC339</td>
</tr>
<tr>
<td>CHO</td>
<td>H</td>
<td>83JCS(P1)1283</td>
</tr>
<tr>
<td>COMe</td>
<td>H</td>
<td>83JCS(P1)1283</td>
</tr>
<tr>
<td>CH==CHCO$_2$Me</td>
<td>H</td>
<td>92LA709</td>
</tr>
<tr>
<td>CO$_2$Me</td>
<td>H</td>
<td>92LA709</td>
</tr>
<tr>
<td>CO$_2$Et</td>
<td>H</td>
<td>83JCS(P1)1283, 86CC30, 90LA217, 90CB2403</td>
</tr>
<tr>
<td>o-C$_6$H$_4$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>

Cycloaddition reactions of α-nitrosostyrene (Scheme 13; $R^1 = \text{Ph, } R^2 = \text{H}$) have been investigated the most. Earlier examples of these reactions have been reviewed briefly $\langle 83\text{CSR}53\rangle$. The intermediate adds to conjugated alkenes in moderate to good yield, but not to simple alkenes $\langle 83\text{JCS(P1)1275}\rangle$. Enol ethers give dihydrooxazines in good yield $\langle 83\text{JCS(P1)1479}\rangle$; dihydrooxazines can also be obtained by cycloaddition to electron-rich heterocycles such as furans $\langle 79\text{JCS(P1)249}\rangle$ and 3-substituted indoles $\langle 83\text{JCS(P1)1479}\rangle$. In publications from the late 1980s and early 1990s examples have been published of dihydroxazine synthesis by cycloaddition of α-nitrosostyrene to silyl enol ethers $\langle 87\text{S77, 90BCJ3595, 90CB2403, 90LA217, 90S26, 92LA709}\rangle$, ketene trimethylsilyl acetal $\langle 91\text{JCS(P1)3153}\rangle$, allylsilanes $\langle 86\text{CC30, 87S77, 90LA217}\rangle$, chiral enol ethers $\langle 90\text{SL514, 92AG(E)1033}\rangle$, enamines $\langle 90\text{BCJ3595}\rangle$, methoxyallene $\langle 91\text{LA553}\rangle$, and the enolate anion of ethyl cyanoacetate $\langle 87\text{AP(320)776}\rangle$.

With other nitrosoalkenes there is a general trend towards greater reactivity as the α-substituent becomes more electron withdrawing in character. This is particularly so for 3-nitrosobut-3-en-2-one (Scheme 13; $R^1 = \text{COMe, } R^2 = \text{H}$) $\langle 83\text{JCS(P1)1283}\rangle$ and for 1,1,1-trifluoro-2-nitrosopropene ($R^1 = \text{CF}_3, R^2 = \text{H}$) $\langle 92\text{JOC339}\rangle$, but even the introduction of a $p$-nitro substituent into α-nitrosostyrene significantly improves the efficiency of the cycloaddition process $\langle 83\text{JCS(P1)1275}\rangle$. For example, in contrast to α-nitrosostyrene, both 3-nitrosobut-3-en-2-one and 4-nitro-α-nitrosostyrene react with simple alkenes to produce dihydrooxazines in moderate yield.
The outcome of extensive investigations of the mechanism of these reactions is a consensus that they are concerted Diels–Alder reactions with inverse electron demand \( \langle 83 \text{JCS(P1)1275}, 90 \text{CB2403}, 90 \text{LA217}, 91 \text{LA553}, 92 \text{JOC339}, 93 \text{JCS(P1)1391} \rangle \). The cycloaddition is stereospecific with respect to the alkene component and it is usually regioselective, the more electron-rich substituent of the alkene becoming the 6-substituent of the dihydrooxazine as shown in Scheme 13. With indoles, the terminal carbon of the nitrosoalkene invariably attacks at C-3, and with furans and pyroles, at C-2, even if these positions are blocked by substituents: this is shown in the reaction of 2,5-dimethylpyrrole with ethyl 2-nitrosopropenoate (Scheme 14) \( \langle 93 \text{JCS(P1)1391} \rangle \). The cycloaddition is, however, subject to stereic effects and these influence the diastereoselectivity of the process \( \langle 90 \text{CB2403} \rangle \). A striking example of selectivity is provided by the reaction of \( \alpha \)-nitrosostyrene with silyl enol ethers as (E)/(Z) mixtures: the reactivity is so much greater for the (E) isomers that the procedure can be used as a practicable means of separation of the (E) and (Z) isomers \( \langle 90 \text{OS26} \rangle \).

\[
\text{Me} \quad \text{HN} \quad \text{Me} \quad + \quad \text{BrC} \quad \text{CO}_2 \quad \text{Et} \quad \xrightarrow{\text{Na}_2\text{CO}_3} \quad \text{Me} \quad \text{HN} \quad \text{O} \quad \text{N} \quad \text{CO}_2 \quad \text{Et} \quad \quad 70\% \]

Scheme 14

There are two methods of preparing dihydrooxazines which are closely related to the cycloaddition of nitrosoalkenes; both were known before the 1980s but have been subject to more recent investigation. The first is the cycloaddition of nitroalkenes to alkenes. Denmark and co-workers have described both intermolecular \( \langle 86 \text{HCA1971}, 93 \text{JOC1853}, 93 \text{JOC1859} \rangle \) and intramolecular \( \langle 86 \text{JA1306} \rangle \) Lewis acid-catalyzed versions of the reaction. 1-Nitrocyclohexene reacts with cyclohexene and other cycloalkenes in the presence of tin(IV) chloride at \(-78^\circ\text{C} \langle 86 \text{HCA1971} \rangle \). The major product of the reaction with cyclohexene is the oxazine 2-oxide (62) (Equation (21)) although isomeric compounds are also isolated in low yield. A stepwise mechanism with a zwitterionic intermediate has been suggested for the reaction.

\[
\text{C} \quad + \quad \text{C} \quad \xrightarrow{\text{SnCl}_4, -78^\circ\text{C}} \quad \text{H} \quad \text{O} \quad \text{N} \quad \text{O} \quad \quad 43\% \]

(62) Equation (21)

Cycloaddition reactions of nitroalkenes to enamines, enolate anions, and silyl enol ethers are well established. Reactions with simple enol ethers have also been described \( \langle 88 \text{BC}3461, 93 \text{JOC1853} \rangle \). Chiral enol ethers have been used as partners in the cycloaddition process \( \langle 93 \text{JOC1859}, 94 \text{JOC4576}, 94 \text{JOC5672}, 95 \text{JOC3221} \rangle \). 2-Nitro-1,3-dienes have also been added to enol ethers \( \langle 91 \text{TL5607} \rangle \) and to enamines (including a chiral enamine) \( \langle 92 \text{TL5641} \rangle \) to give dihydrooxazine 2-oxides.

The second method related to nitrosoalkene cycloaddition is the reaction of vinylnitrosoum cations with alkenes. Several intramolecular cycloaddition reactions of this type have been described \( \langle 87 \text{JOC877} \rangle \); one example is illustrated in Scheme 15.

\textbf{6.04.8.2.3 Other syntheses involving 4-atom and 2-atom combinations}

Methods in which hydroxylamine acts as the 2-atom component have been described in Section 6.04.8.1. The reactions of nitroalkenes with enolate anions and with electron-rich alkenes (see Section 6.04.8.2.2) can also be regarded as examples of this class since some at least of these processes
1,2-Oxazines and their Benzo Derivatives

Scheme 15

take place through detectable intermediates. There are few new methods in this category, but the synthesis of the benzoxazines (15) is one of this type. Compound (15; R = Me) was prepared in 77% yield by the reaction of 2-nitropropene with TFSA and benzene \( \langle 90 \text{T7539} \rangle \). Other nitroalkenes react similarly. A mechanism was proposed in which the nitroalkene is doubly protonated and the dication is then intercepted by benzene (Scheme 16).

Scheme 16

6.04.8.3 Combination of Two 3-Atom Components

An unusual synthesis of 4,5-dichloro-6,6-dimethyl-6\(H\)-1,2-oxazines is provided by the reaction of nitrile oxides with 1,2-dichloro-3,3-dimethylcyclopropene \( \langle 93 \text{JCSP12507} \rangle \). This reaction apparently involves an acyclic vinylcarbene isomer of the cyclopropene (Scheme 17).

Scheme 17

6.04.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

The most important synthesis in this class is that leading to the oxazinium salts such as (3). These compounds are formed by the reaction of nitrosyl chloride with dialuminum hexahalide \( \sigma \) complexes of alkyl-substituted cyclobutadienes. A mechanism has been proposed involving the formation and rearrangement of a bicyclic cation (63) and, since isomeric oxazinium salts are formed in some cases, further rearrangement (Scheme 18), possibly through a benzene type structure \( \langle 85 \text{JA5722, 86PAC89} \rangle \). Calculations have been carried out on the energies of the various structures possible for a nitroscyclobuteny1 cation \( \langle 87 \text{ZOR717} \rangle \).

A 5,6-dihydro-4\(H\)-1,2-oxazine has also been formed by the titanium bromide-catalyzed ring expansion of an isoxazoline N-oxide (Equation (22)) \( \langle 92 \text{CPB1921} \rangle \).
6.04.10 IMPORTANT COMPOUNDS AND APPLICATIONS

The main application of 1,2-oxazine derivatives has been as intermediates in synthesis. As described in Section 6.04.6, the weak N—O bond allows oxazines having a defined substitution pattern to be constructed and then cleaved. Examples include the asymmetric synthesis of mannostatin A \( \langle 91JA5089 \rangle \) and of amino sugars \( \langle 90LA267, 94TL5653 \rangle \) as potentially useful glycosidase enzyme inhibitors, and the target synthesis of piperidine and indolizidine alkaloids \( \langle 93JOC6083, 94TL595 \rangle \). In the 5,6-dihydro-4H-1,2-oxazine series, the reductive cleavage reaction has been used in the synthesis of lipophilic analogues of proline; these compounds are useful as inhibitors of angiotensin converting enzyme \( \langle 89S265 \rangle \). The acid-catalyzed and reductive cleavage of 6-silyloxy substituted dihydrooxazines has been used in the target synthesis of precursors to the macrolide pyrenophorin and of (Z)-jasmone \( \langle 92LA709 \rangle \). 3-\( t \)-Butyl-5,6-dihydrooxazines have been prepared as potential herbicides \( \langle 92MIP9209587 \rangle \).

Denmark and co-workers have developed a versatile route to pyrrolizidine alkaloids and other natural products which is based on successive \([4 + 2]\) and \([3 + 2]\) cycloaddition of nitroalkenes to alkenes followed by N—O bond cleavage \( \langle 94JOC5672, 94PAC2041, 95JOC3205, 95JOC3574, 96CRV137 \rangle \).