SYNTHESIS OF 1,2-OXAZINES AND THEIR N-OXIDES

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Abstract - The available routes to the synthesis of partially saturated 1,2-oxazine isomers or their N-oxides as well as those of their aromatic counterparts are presented.

1. INTRODUCTION

2.0 DI(TETRA)HYDRO-1,2-OXAZINES

2.1 Nitrosocarbonyls
2.2 Nitrosoarenes
2.3 Nitrosoimines
2.4 Nitrosoalkenes
2.5 Nitroalkenes
2.6 Nitroalkanes
2.7 Vinylnitrosonium Cations
2.8 Alkenyl nitrones
2.9 Alkenyl oximes
2.10 Isoxazoline 2-oxides
2.11 1,2-Oxazines

3.0 CARBO(HETERO)CYCLO 1,2-OXAZINES

3.1 Nitrosoalkenes
3.2 Nitroalkenes
3.3 o-Nitrosonaphthoquinone methides
3.4 Arylvinyl Azides
3.5 Peri-Hydroxynaphthyl Ketoximes
3.6 Nitro-substituted Heterocyles
3.7 Miscellaneous

CONCLUSION
REFERENCES
1. INTRODUCTION

The heterocyclic structure (1) represents the 1,2-isomer of the oxazine group.\textsuperscript{1,2}

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

1

The partially saturated analogues have been extensively studied and their synthetic potential has been explored by Kresze,\textsuperscript{3} Eschenmoser,\textsuperscript{4} Gilchrist,\textsuperscript{5} Denmark\textsuperscript{6} and Reissig.\textsuperscript{7} In contrast, their aromatic fused counterparts have received relatively limited attention.\textsuperscript{8} Elegant reviews by Kirby\textsuperscript{9} and Gilchrist\textsuperscript{5} and later by Boger,\textsuperscript{10} Streith-Defoin,\textsuperscript{11} Waldmann\textsuperscript{12} and Dell\textsuperscript{13} focus mainly on the synthetic potential of the reactive precursors of 1 in connection with the Hetero-Diels-Alder (HD-A) reaction.

It appears that the 1,2-oxazine heterocycle has not enjoyed an autonomous treatment, in its own merit, as the subject of a review article. The present account, thus, aims at highlighting the major synthetic routes to 1, up to date, in accord with the reactive precursors used, isolated or \textit{in situ}, through selected representative examples. Interesting features, in the author’s opinion, are briefly discussed.

Some overlapping of reactions and other data already covered in the earlier reviews has been inevitable, nonetheless it is helpful in maintaining the clarity of presentation.

Pertinent to the construction of 1 is the incorporation of the \textit{N-O} moiety either donated by one of the reactants or contributed by both each bearing one of the constituent \textit{N} or \textit{O} atoms. The facile \textit{N-O} bond cleavage\textsuperscript{5,11} renders the ring a potentially useful intermediate in synthesis.\textsuperscript{11-22} 1 can be described by the known fully or partially saturated structures A-D.

\[
\begin{array}{cc}
\text{A} & \text{B} \\
\text{C} & \text{D} \\
\end{array}
\]

Type A is the least investigated, though interesting biological activity, among other useful properties, might be anticipated.\textsuperscript{23} 3,6-Dihydro-2\textit{H}-1,2-oxazines B have demonstrated considerable synthetic potential.\textsuperscript{3,10} The synthesis and chemistry of 5,6-dihydro-4\textit{H}-1,2-oxazinium salts C have been advanced.
by Eschenmoser et al.\textsuperscript{4} whereas their uncharged analogues D have been obtained by inverse electron demand Diels-Alder (IED/D-A) reaction of alkenes and nitrosoalkenes.\textsuperscript{10,24} This approach was first realized by Bravo et al.\textsuperscript{25} and was later developed further by Viehe\textsuperscript{26} and mainly by Gilchrist.\textsuperscript{5} Aromatic analogues of D conform to structure E (or its tautomer). The bulk of the 1,2-oxazine literature is dominated by type D structures and their N-oxides.

2. DI(TETRA)HYDRO-1,2-OXAZINES

All reported methods aim at generating the N-O bearing, usually transient, reactive species. This is, then, trapped inter-or intramolecularly\textsuperscript{27-31} by unsaturated moieties to give the target 1,2-oxazine ring.

2.1 Nitrosocarbyols

These species have been proposed as transient intermediates in the oxidative cleavage of hydroxamic acids (2) (or their derivatives)\textsuperscript{9, 32-36} (Scheme 1) in the pyrolysis of alkyl nitrites in the presence of aldehydes,\textsuperscript{37} in the thermal or photochemical cleavage of 1,2,4-oxadiazole 2-oxides\textsuperscript{38} or in the thermal cycloreversion of their HD-A adducts.\textsuperscript{9,39}

![Scheme 1](image)

3, generated \textit{in situ}, enters a [4+2] cycloaddition with a diene to form the cycloadduct 1,2-oxazine (4) (type B).\textsuperscript{40} Thebaine or 9,10-dimethylantracence (DMA) have been frequently used as reactive dienes\textsuperscript{9,40} to give 5 or 6 respectively. An asymmetric variant of HD-A reaction with 1-sulphonyldienes and nitrosocarbyl derivatives has been reported recently.\textsuperscript{40}
Similar reactions with the ester or urea derivatives of intermediate (3) give structures corresponding to the above. A variety of oxidants have been employed for the generation of 3, most commonly the tetraethylammonium periodate. Phosphine oxide nitroso species, generated from their precursor hydroxamic acid derivatives, have been recently employed as N-O heterodienophiles to give 3,6-dihydro-2H-1,2-oxazine analogues. Chiral α-amino or α-hydroxy derivatives (7) have been used as dienophiles with achiral dienes such as cyclopenta (hexa)diene (Scheme 2).

Scheme 2

Moderate asymmetric induction has been observed in the mixture of diastereoisomers (8) and (9). However, high asymmetric induction has been achieved by Kresze et al. in the synthesis of oxazine (10) when an α-chloro nitroso derivative RR'C (Cl)NO was used. Nitrosocyanides, prepared in situ, have also been used as dienophiles and structures analogous to 5 and 6 have been isolated.
Nitrile oxides (11) can be a very interesting and efficient source of 3, (Scheme 3).46

\[
R\equiv N\equiv O
\]

11

The reaction is a synthetically useful protocol offering a variety of 1,2-oxazines analogous to 6. An interesting and synthetically promising intramolecular D-A reaction of hydroxamates has been recently reported.47 Thus, suitably tethered hydroxamates (13) undergo intramolecular cycloaddition to 14 upon heating (Scheme 4).

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

13

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

14

Theoretical calculations have been called in to elucidate the conformation effects on the proximity of the diene and dienophile centers in 13 and thus its reactivity. The efficiency and general applicability of the approach have been demonstrated with selective and predictable stereochemical requirements. An analogous intramolecular D-A reaction, used for the synthesis of marine alkaloid (-)-lepadin B, has been reported.48

2.2 Nitrosoarenes

The HD-A cycloaddition of these species with dienes has been reported49 first by Wichterle and Arbuzov. Hamer50 and Kresze51 have studied kinetically the reaction of various \( p \)-substituted nitrosobenzenes (15) with cyclohexa-1,3-diene and 2,3-dimethylbut-1,3-diene to oxazines (16) (Scheme 5).
Kirby,\textsuperscript{9} in his review, has given a concise account of the main features of this reaction with representative examples. Streith and Defoin,\textsuperscript{11} on the other hand, have perceptively reviewed the use of this reaction in natural product synthesis with selected examples. Cyclic metalloporphyrins (17) or (18) are recently under investigation for their catalytic role in D-A reactions incorporating 15 (Scheme 6).\textsuperscript{52}

Acceleration and catalysis of this reaction by artificial receptors, antibodies and RNA is well documented but no structure data of synthetic hosts are available to shed light on features responsible for success or failure of the catalytic action. A detailed structure analysis of geometry changes imposed on the accelerating agent, upon binding to a D-A product, has been reported.\textsuperscript{52} The significance of the host flexibility for acceleration of the D-A reaction, within the cavity of a cyclic metalloporphyrin receptor, has been confirmed.

A molybdenum-catalysed oxidative D-A reaction of aromatic primary amines (19) and conjugated dienes with hydrogen peroxide provide an efficient access to 3,6-dihydro2\textit{H}-1,2-oxazines (22) (Scheme 7).\textsuperscript{53}
The pivotal element in the reaction is the *in situ* generation of 21 in the presence of the metal complex (20). The success of this approach stems from the chemoselectivity of the oxidation reaction leaving the diene and the substituents of the aromatic amine unaffected. Consequently, this is a good route to a variety of 1,2-oxazines (22) otherwise difficult to access or non accessible at all.\(^{54}\)

The nature of transition state (TS) and the mechanism of the HD-A reaction of nitrosoarenes (and nitrosocarbonyls) have been investigated by Houk *et al.*\(^{55}\) Accordingly, the cycloaddition proceeds through a highly asynchronous TS, in a strongly *endo* mode, by diradical or zwitterionic pathways competing only when the nitroso species bearing a small *N* substituent reacts with a diene substituted with a radical-stabilizing group.

### 2.3 Nitrosoimines

Two characteristic reactions, generating the reactive intermediate (25) are the oxidation of amidoxime (24) with lead(IV) acetate (LTA) or the treatment of sulfimide (23) with cyanoformate *N*-oxide (Scheme 8).\(^{56}\)
Both reactions give the benzoxadiazine (26). However, when 25 is intercepted by thebaine, the 1,2-oxazine (27) has been isolated.

2.4 Nitrosoalkenes

These reactive species along with nitrosocarbonyls constitute the two major sources for the construction of the 1,2-oxazine structure. Cyclisation or cycloaddition (the nitrosoalkene acting as either a $2\pi$ or a $4\pi$ component) with dienes, among other important aspects, has been extensively covered by Gilchrist and recently by Lyapkalo and Ioffe. Some representative examples are elucidated (Scheme 9).

![Scheme 9](image)

The conjugated nitrosoalkenes (29), (32), (35) and (39) undergo a cyclisation or a cycloaddition to the...
1,2-oxazines (30), (34), (37) and (40), respectively. Substitution R¹ on 28 determines the predominance of 30 or 31.³⁸ Cycloaddition of 32 to 33 is typical of the dienophilic character of nitrosocarboxyls (3).⁵⁹ Cycloaddition of 35, acting as a 4π conjugated heterodiene, is, perhaps, the most important reaction of nitrosoalkenes that dominated their chemistry quite a few years.⁶⁰,⁶¹ Allenes (38), upon reaction with nitrosoalkenes (39), give the cycloadduct 1,2-oxazine (40).

The exo/endo selectivity and stereospecificity of the cycloaddition, the E/Z selectivity of nitrosoalkenes and the relative reactivities of silyl enol ethers or other alkenes have been investigated.⁶²

1,2-oxazines, halo-substituted at C-4, analogous to 37, have recently been prepared by an intermolecular D-A reaction of the corresponding nitrosoalkene with a variety of dienophiles.⁶³ The C-4 substitution allows for high stereoselectivity.

Extending the [4+2] cycloaddition chemistry of nitrosoalkenes,⁶⁴,⁶⁵ that of 1,1,1-trifluoro-2-nitroso-propene (42) with silyl enol ethers (43) offers a flexible and efficient access to a large variety of 1,2-oxazines (44) (Scheme 10).⁶⁶

![Scheme 10](image)

The results demonstrate that 42 is a powerful heterodiene, remarkably more than nitrosostyrene or other alkyl bearing analogues. The reactivity of the species is apparently due to the electronic effects of the CF₃ group. Comparison of HOMO and LUMO energies of 42 with those of nitrosoethylene or nitrosostyrene by MNDO calculations support the electronic accelerative effect of the group.⁶⁶

Dienophiles (43) bearing substituents larger than ethyl have been found to give no cycloadducts with nitrosostyrene. In contrast 42 has readily been added to those unreactive silyl enol ethers in low to moderate yields. Other dienophiles have also been used and the corresponding 1,2-oxazines have been obtained in good to excellent yields (Scheme 11).
2.5 Nitroalkenes

Several interesting approaches to 1,2-oxazines have appeared, where a nitroalkene reacts with another alkene or a derivative of it. Obvious advantages in the use of nitroalkenes are their facile synthesis\textsuperscript{67-70} and stability. The N-oxide (47) of 1,2-oxazines has been formed, isolated or \textit{in situ}, by a [4+2] cycloaddition of 46 with cyclic or acyclic enamines (45) (Scheme 12).\textsuperscript{71}

The stability of 47 has been found to depend on the structure of 45, the substitution of 46 and the experimental conditions used. Even when isolated, 1,2-oxazine N-oxides (47) are usually stored at
temperatures as low as -15°C. A variant of this reaction has been studied with ketoenamines (48) to give 1,2-oxazine N-oxides (50) (Scheme 13).72

Scheme 13

The reaction proceeds upon thorough mixing of the reactants without solvent. In solution there is no reaction. If taken in a solvent, the N-oxide (50) partly reverts to the reactants and partly isomerizes to 51. Conjugate addition of silyl enol ethers (53) to nitroalkenes has proved to be an efficient route to 1,2-oxazine N-oxides (54) (Scheme 14).73,74

Scheme 14

The reaction is promoted by Lewis acids, of which TiCl$_4$ or SnCl$_4$ have been found to give best yields,72,73 on account of the stability of nitroalkenes towards them and the synthetic equivalence of silyl enol ethers to keto-enolates.75

[4+2] Cycloaddition of nitrocycloalkenes with cycloalkenes leads to the N-oxides (58) (Scheme 15).76

Scheme 15
A common intermediate (60) has been proposed for the formation of the cyclic nitronates (58) \textit{exo/endo} and the \textit{spiro} molecule (59) (Scheme 16).\textsuperscript{76} 60 collapses via two separate pathways, \textit{a} by charge annihilation and \textit{b} by a Wagner-Meerwein shift and capture of the tertiary carbocation.

![Scheme 16](image)

Alternatively two independent competing mechanisms have been proposed; a concerted cycloaddition to 58 \textit{exo/endo} and a zwitterionic pathway leading only to 59.\textsuperscript{76}

Intramolecular [4+2] cycloaddition of nitroalkenes (61) to \textit{N}-oxides (cyclic nitronates) (62) in the presence of SnCl\textsubscript{4} has been investigated (Scheme 17).\textsuperscript{27,77}

![Scheme 17](image)

Consecutive [4+2]/[3+2] cycloadditions of nitroalkenes have been intensively investigated by Denmark \textit{et al.}\textsuperscript{6,14,78-83} Their inter/intra tandem strategy, in all possible permutations, has been developed and its synthetic potential has been demonstrated.\textsuperscript{84} A DFT study of these reactions has been carried out.\textsuperscript{83,85}

Cycloadditions of this type have also been reported under pressure.\textsuperscript{86} It is known that cycloadditions are accelerated, in general, by high pressure.\textsuperscript{87} It was reasoned that under these conditions short reaction times, no need for a catalyst and no large excess of enol ether would suffice. In these reactions a nitroalkene (63) is allowed to react with an electron rich alkene (64) under IED/D-A conditions. The
nitronate (65), thus, generated, reacts with another alkene in a [3+2] cycloaddition leading to a nitroso acetal, in presence of a Lewis acid catalyst (Scheme 18). Without the latter, large excess of enol ether, long reaction times or a strongly activated nitroalkene are required.

\[
\begin{align*}
\text{Scheme 18} \\
\begin{array}{c}
\text{63} \quad \text{64} \quad 5 - 15 \text{ Kbar} \\
\end{array}
\end{align*}
\]

At a 10 kbar pressure and after 23 h the tandem adduct (66) is isolated exclusively whereas at higher 15 kbar pressure and only after 2 h the conversion was complete. At 10 kbar after 2 h the [4+2] adduct (65) was isolated in good yield.

The regio- and stereochemistry of the cycloaddition, studied by COSY/NOESY NMR, showed that a [4+2] process takes place with regio- and endo-selectivity while the subsequent [3+2] one with regio- and exo-selectivity and anti-with respect to the phenyl group. Three component tandem cycloadditions have also been investigated.\(^{86}\) Accordingly, nitroalkenes have been reacted with enol ethers and electron poor alkenes. Nitronates react faster with electron-deficient alkenes than with their electron-rich counterparts. Thus, the generated nitronate is intercepted selectively by an electron-deficient in the presence of both (Scheme 19).

\[
\begin{align*}
\text{Scheme 19} \\
\begin{array}{c}
\text{67} \quad \text{63} \quad \text{64} \quad 68 \quad 69 \quad 70 \quad 71 \\
\end{array}
\end{align*}
\]
A very interesting asymmetric synthesis of 1,2-oxazine N-oxides by a D-A reaction in water has been very recently reported.88

2.6 Nitroalkanes

Aliphatic nitro compounds (nitroalkanes) have found an ever-increasing significance in synthesis with the advances of their silylation and the participation of the resultant silylnitronates in various well-known reactions as modified substrates.61 Nitrosoalkenes (74) are, thus, generated through silylnitronates (73) (Scheme 20). The latter is trapped with dienophiles (75) or (76), in the presence of \(N,O\)-bis(trimethylsilyl)acetamide (BSA) as the silylating agent, to give cycloadducts (77) and (79) and ultimately the stable isoxazoline (78) and the substituted 5,6-dihydro-2\(H\)-1,2-oxazine (80).

![Scheme 20](image-url)
2.7 Vinylnitrosonium Cations (VNC’s)

These are highly reactive heterodienes (82)\textsuperscript{89,90} and have been used as 4π components in stereoselective cycloadditions with unactivated alkenes\textsuperscript{91} to give 1,2-oxazinium cycloadducts (83) (Scheme 21).

The choice of VNC’s (82) has been dictated, to bypass some serious limitations experienced with nitrosoalkenes, such as: (a) nucleophilic dienophiles (e.g. enol ethers and thioenol ethers) are required in cycloaddition with unactivated alkenes (b) cycloaddition is strongly dependent on dienophile geometry due to secondary orbital overlap. (c) an \(O\) functionality into the allylic position of the heterodiene, desirable in some target molecules, hampers the reaction with the nitrosoalkenes used.\textsuperscript{92}

The high electrophilicity of 82 has been clearly demonstrated by Eschenmoser\textsuperscript{90} who used them in connection with the selective hydrolysis of amides in the final stages of the total synthesis of vitamin B\textsubscript{12}. Subsequent extensive studies were carried out by the Eschenmoser group\textsuperscript{90} on the generation of VNC’s and their facile cycloaddition with unactivated alkenes (Scheme 21). A major drawback of these species is their extreme reactivity. Thus, electrophilic substitution with tri(tetra)-substituted alkenes as well as arenes is preferred. When cycloaddition occurs the oxazinium (83) can be efficiently trapped by nucleophiles (e.g Nu=CN, Scheme 21) to give the functionalized tetrahydrooxazine (84). Alternatively, 83 can be deprotonated and the resulting 5,6-dihydro-2\textit{H}-1,2-oxazine (85) by a [4+2] cycloreversion generates aldehyde (86) and imine (87) (Scheme 21). Graf and Riediker\textsuperscript{93} have extended the chemistry of VNC’s by using \(\alpha,\beta\)-epoxyaldonitrones (88) as their precursors (Scheme 22).
The O-silyl nitronium ether (89) suffers a Si migration to oxirane O with concomitant opening of the latter to the ether VNC (90). This species being extremely unstable is rapidly intercepted by a dienophile to 1,2-oxazinium (91), which, in turn, by a nucleophilic attack (e.g. KCN) allows the isolation of the 1,2-oxazine (92) as before.

Using these protocols a number of 1,2-oxazines have been prepared.

2.8 Alkenyl Nitrones

Nitrones (94), obtained as the sole products of the oxidation of amines (93), undergo electrophile-induced ring closure by phenylselenyl bromide to the 6-membered iminium salt (96), treatment of which with nucleophiles leads to the tetrahydro-1,2-oxazines (97), (98) (Scheme 23).
2.9 Alkenyl Oximes

γ-Alkenyl oximes (99) can be cyclised by phenyl selenenyl sulphate (PhSe)$_2$SO$_4$. The latter is a strong electrophilic selenenylalating agent and has found wide application in synthesis$^{14,78-80}$ and ring closures.$^{81-83}$

The seleniranium intermediate (100) is intramolecularly trapped by the internal oxime nucleophile either through its O to give 5,6-dihydro-$4H$-1,2-oxazines (101) or through the N to give the cyclic nitrone (102) (Scheme 24). Clearly, it is the geometry of the oxime that determines the nature of the product. Furthermore, the nature of the R substituent was found to effect the course of the cyclisation reaction. It was also found that 102 partly isomerises to 101 during the reaction.$^{96}$

![Scheme 24](image)

2.10 Isoxazoline 2-Oxides

Isoxazoline 2-oxides, as their methanesulphonate derivatives (103), on treatment with TiBr$_4$ or TiCl$_4$ give rise to 1,2-oxazines (104), (105) and (106) respectively, by ring expansion (Scheme 25).$^{97}$
2.11 1,2-Oxazines

$6H$-1,2-oxazines (107) may serve as precursors to their $4H$-counterparts (109) (Scheme 26).$^{98,99}$

The organolithio-intermediate (108) is easily alkylated with a variety of reagents and a series of derivatives of 109 are thus obtained.$^{100}$

$2H$-1,2-oxazines (110) can be obtained by NaBH$_3$CN reduction of 109 (Scheme 27).$^{101}$
3.0 CARBO(HETERO)Cyclo-FUSED 1,2-OXAZINES

Access to these heterocycles \( \mathbf{E} \) and their \( \mathbf{N} \)-oxides is limited at present. The methods available are not of general applicability with respect to tailor-made substitution on either or both rings. Clearly, additional versatile routes to this heterocyclic structure are required as its potential to synthetic transformations appears to be promising (e.g. precursors to ortho-quinonemethides, see later).

3.1 Nitrosoalkenes

These species, as presented in 2.4, add to various heterocycles in a D-A mode leading to heterocyclo-fused 1,2-oxazines.\(^{102,103}\)

3.2 Nitroalkenes

Dications (\( \mathbf{112} \)), generated from diprotonation of \( \beta \)-nitrostyrenes (\( \mathbf{111} \)) with TFSA, upon reaction with benzene, give 4\( \mathbf{H} \)-1,2-benzoxazines (\( \mathbf{113} \)) (Scheme 28).\(^{104-106}\)

![Scheme 28](image)

Large excess of TFSA and prolonged reaction are required to obtain \( \mathbf{113} \) in good yield, as the major product.

The formation and reactivity of nitroalkene-derived diprotonated species (\( \mathbf{112} \)) have been investigated.\(^{104-106}\) When reacted with benzene, this undergoes one intramolecular 6\( \pi \) electrocyclisation to \( \mathbf{113} \) and an intermolecular electrophilic reaction among two molecules of benzene leading to \( \mathbf{114} \) as a mixture of the two geometrical isomers. The \( \text{aci} \)-nitro intermediate (\( \mathbf{112} \)) has been invoked.\(^{104}\)

The reaction conditions (time, temperature and work-up) determine the predominance of \( \mathbf{113} \) over \( \mathbf{114} \). The reaction has been found to give \( \mathbf{113} \) only with benzene itself, although variable substitution on the nitroalkenes is comfortably tolerated.

Nitroalkenes (\( \mathbf{115} \)) offer an alternative versatile route to 4\( \mathbf{H} \)-1,2-benzoxazines (Scheme 29).\(^{107}\)
Reductive cyclisation of 115, through O-formylation, leads to the unsaturated hydroxylamine (116), as one of the major products. The Michael reaction to 117 can be suppressed by using a catalytic amount of TFA. LTA oxidative cyclisation or Tf$_2$O cyclodehydration of 116 may lead to the N-oxide (119) or the parent heterocycle (118) respectively. The approach suffers from the following limitations: (a) no substitution is possible on the oxazine ring and (b) no reduction-sensitive substitution is allowed on the benzene ring. The advantages on the other hand are: (a) diverse substitution (with the previous exception) can be tolerated on the carbocycle, (b) various heterocycles can be isolated from a common source and c) ring transformations are feasible leading to diverse structures.

3.3 o-Nitrosoquinone methides (NQM's)

Oxidation of 2-hydroxy-1-naphthaldoxime (120) with LTA gives fused 1,2-oxazines (122) as one of three products (Scheme 30).
The formation of 122 has been rationalized by a peri cyclisation/annelation of the o-NQM (121). Interestingly, the latter encompasses a nitrosoalkene and an ortho-quinonemethide. Its efficient trapping, therefore, with suitable alkenic or alkynic molecules or nucleophiles should demonstrate its heterodien(ophil)ic character in cycloadditions and its overall potential in synthesis. Work on these lines is currently in progress in our group.

3.4 Arylvinyl Azides

Thermolysis of o-methoxy- substituted aryl azides (125) gives rise to fused 1,2-oxazines (128) (Scheme 31).

Scheme 31

Insertion of a nitrene-like intermediate (126) on to the adjacent methoxyl group to dipolar species (127) and subsequent rearrangement to 1,2-oxazine (128) has been invoked. The method is a useful access to 1,2-benzoxazines (128). However, its synthetic potential is limited by the resultant substitution of the heterocyclic ring, which, in turn, reduces the potential of 128 for further transformations.

3.5 Peri-Hydroxynaphthyl Ketoximes

Naphtho[de]-1,2-oxazines (130) have been obtained by cyclisation of the oximes of 8-hydroxy-1-acynaphthalenes (129) upon heating (Scheme 32).
1,2-Oxazines (130) are isolable only when $R \neq H$. If $R = H$, nitriles (131) have been isolated instead. Gossypol and its oxime derivatives (132) are easily cyclised to the corresponding 1,2-oxazines (133) (Scheme 32).\textsuperscript{111,112}

Peri-annelated 1,2-oxazines (135) with inverse heteroatom orientation have been obtained by heating anthraquinone-1-carboxylic acid (134) in aqueous solution of $\text{NH}_2\text{OH} \cdot \text{HCl}$ (Scheme 33).\textsuperscript{113}

$\text{135}$ has also been obtained by acid-catalysed rearrangement of 1-nitromethylanthraquinone.\textsuperscript{114}

### 3.6 Nitro-substituted Heterocycles

3,5-dinitropyridones,\textsuperscript{115} 3-nitro-2,5-dihydrofuran derivatives,\textsuperscript{116} 4,6-dinitrobenzofuroxan,\textsuperscript{117} 4-nitro-2-phenyloxazole-5-carboxylate\textsuperscript{118} and very recently 4-nitroisoxazoles\textsuperscript{119} have been reported as effective nitro-heterodienes, leading to the corresponding heterocyclo-fused adducts 1,2-oxazine N-oxides, with
high diastereoselectivity (Scheme 34)

Interestingly, 138 shows a temperature-dependent reactivity pattern. The oxepines (139) and (140) are rationalized by ring expansion of nitroso acetals (142) and (143), followed by HNO expulsion.

3.7 Miscellaneous

Thermolysis of 1,2-oxazine (144) leads to the highly reactive ortho-quinonemethide (145). The latter is intercepted by 144 to give the tetracyclic 1,2-oxazine (146). This, in turn, may undergo a further retro-D-A reaction to the isomer (147) (Scheme 35).
A "Wittig" type reaction of $o$-quinone oxime $O$-alkyl methide (148) with a phosphorane (149) also leads to fused 1,2-oxazines (151) as the major product (Scheme 36).^{120}

![Scheme 36](image)

**CONCLUSION**

Versatile and efficient routes are available for the various partially saturated 1,2-oxazines. Similar endeavours are needed for their aromatic counterparts. Convergent access to these heterocycles will offer a wealth of interesting transformations, possibly of synthetic utility too.

**REFERENCES**


1802.
64. (a) C. Hippeli and H.-U. Reissig, *Synthesis*, 1987, **77**, (b) C. Hippeli and H.-U. Reissig, *Liebig's,*


107. P.G. Tsoungas and M. Searcey, manuscript to be submitted.


