

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

Petros G. Tsoungas

Ministry of Development, Department of Research and Technology, Messogion

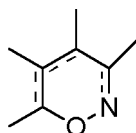
Ave. 14-18, Athens, GR-115 10, Greece, e-mail : pgt@gsrt.gr

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.

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1. INTRODUCTION

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



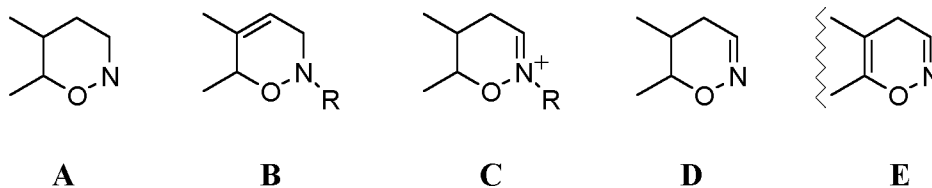
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The partially saturated analogues have been extensively studied and their synthetic potential has been explored by Kresze,³ Eschenmoser,⁴ Gilchrist,⁵ Denmark⁶ and Reissig.⁷ In contrast, their aromatic fused counterparts have received relatively limited attention.⁸ Elegant reviews by Kirby⁹ and Gilchrist⁵ and later by Boger,¹⁰ Streith-Defoin,¹¹ Waldmann¹² and Dell¹³ focus mainly on the synthetic potential of the reactive precursors of **1** in connection with the Hetero-Diels-Alder (HD-A) reaction.

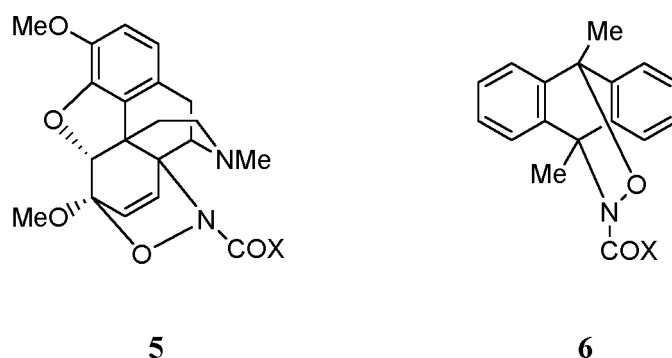
It appears that the 1,2-oxazine heterocycle has not enjoyed an autonomous treatment, in its own merit, as the subject of a review article. The present account, thus, aims at highlighting the major synthetic routes to **1**, up to date, in accord with the reactive precursors used, isolated or *in situ*, 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 *N-O* moiety either donated by one of the reactants or contributed by both each bearing one of the constituent *N* or *O* atoms. The facile *N-O* bond cleavage^{5,11} renders the ring a potentially useful intermediate in synthesis.¹¹⁻²² **1** can be described by the known fully or partially saturated structures **A-D**.

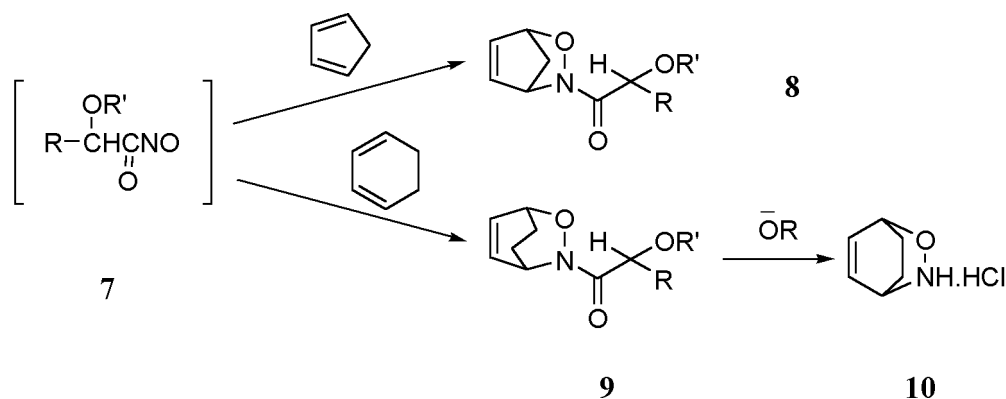


Type **A** is the least investigated, though interesting biological activity, among other useful properties, might be anticipated.²³ 3,6-Dihydro-2*H*-1,2-oxazines **B** have demonstrated considerable synthetic potential.^{3,10} The synthesis and chemistry of 5,6-dihydro-4*H*-1,2-oxazin-4-ium salts **C** have been advanced



Similar reactions with the ester or urea derivatives of intermediate (**3**) give structures corresponding to the above.^{9,41} A variety of oxidants have been employed for the generation of **3**, most commonly the tetraethylammonium periodate.^{35,36} Phosphine oxide nitroso species, generated from their precursor hydroxamic acid derivatives, have been recently employed as N-O heterodienophiles to give 3,6-dihydro-2*H*-1,2-oxazine analogues.⁴⁰

Chiral α -amino or α -hydroxy derivatives (**7**) have been used as dienophiles with achiral dienes such as cyclopenta (hexa)diene (Scheme 2).⁴²

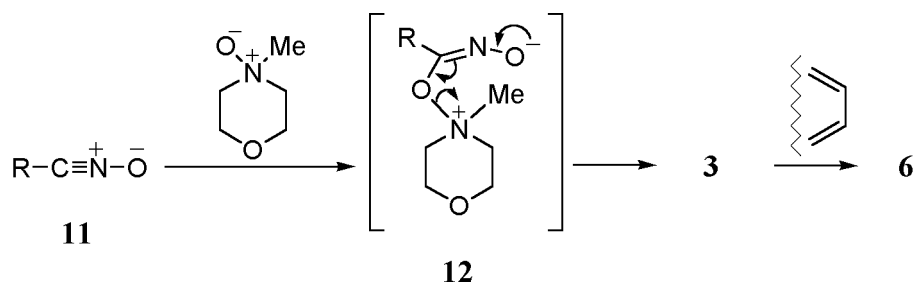


Scheme 2

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.*⁴³ in the synthesis of oxazine (**10**) when an α -chloro nitroso derivative $RR^1C(Cl)NO$ was used.

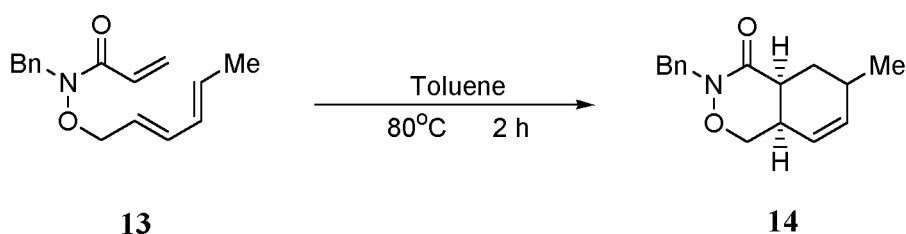
Nitrosocyanides, prepared *in situ*, have also been used as dienophiles and structures analogous to **5** and **6** have been isolated.^{44,45}

Nitrile oxides (**11**) can be a very interesting and efficient source of **3**, (Scheme 3).⁴⁶



Scheme 3

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).



Scheme 4

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

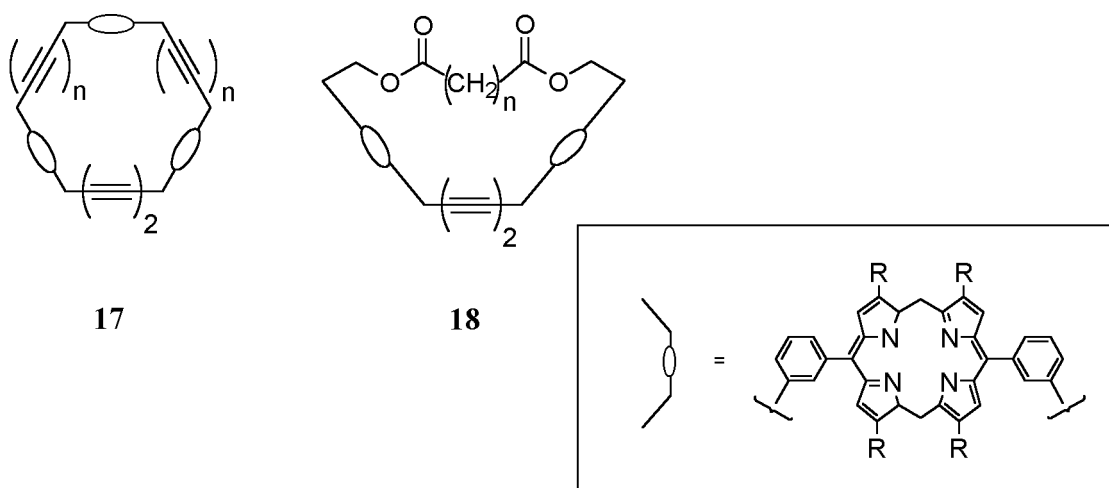
2.2 Nitrosoarenes

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).



Scheme 5

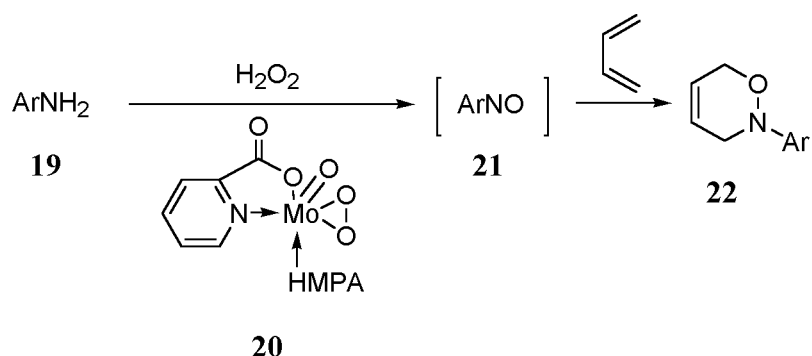
Kirby,⁹ in his review, has given a concise account of the main features of this reaction with representative examples. Streith and Defoin,¹¹ on the other hand, have perceptively reviewed the use of this reaction in natural product synthesis with selected examples. Cyclic metalloporphyrins (**17**) or (**18**) are recently under investigation for their catalytic role in D-A reactions incorporating **15** (Scheme 6).⁵²



Scheme 6

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.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-dihydro-2H-1,2-oxazines (**22**) (Scheme 7).⁵³



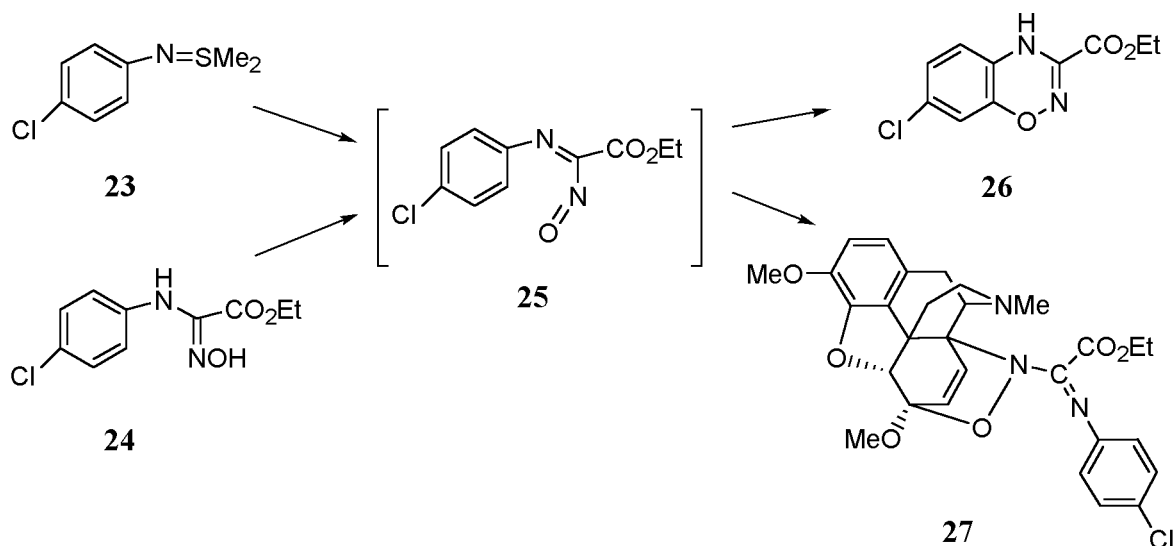
Scheme 7

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 cyanofornate *N*-oxide (Scheme 8).⁵⁶



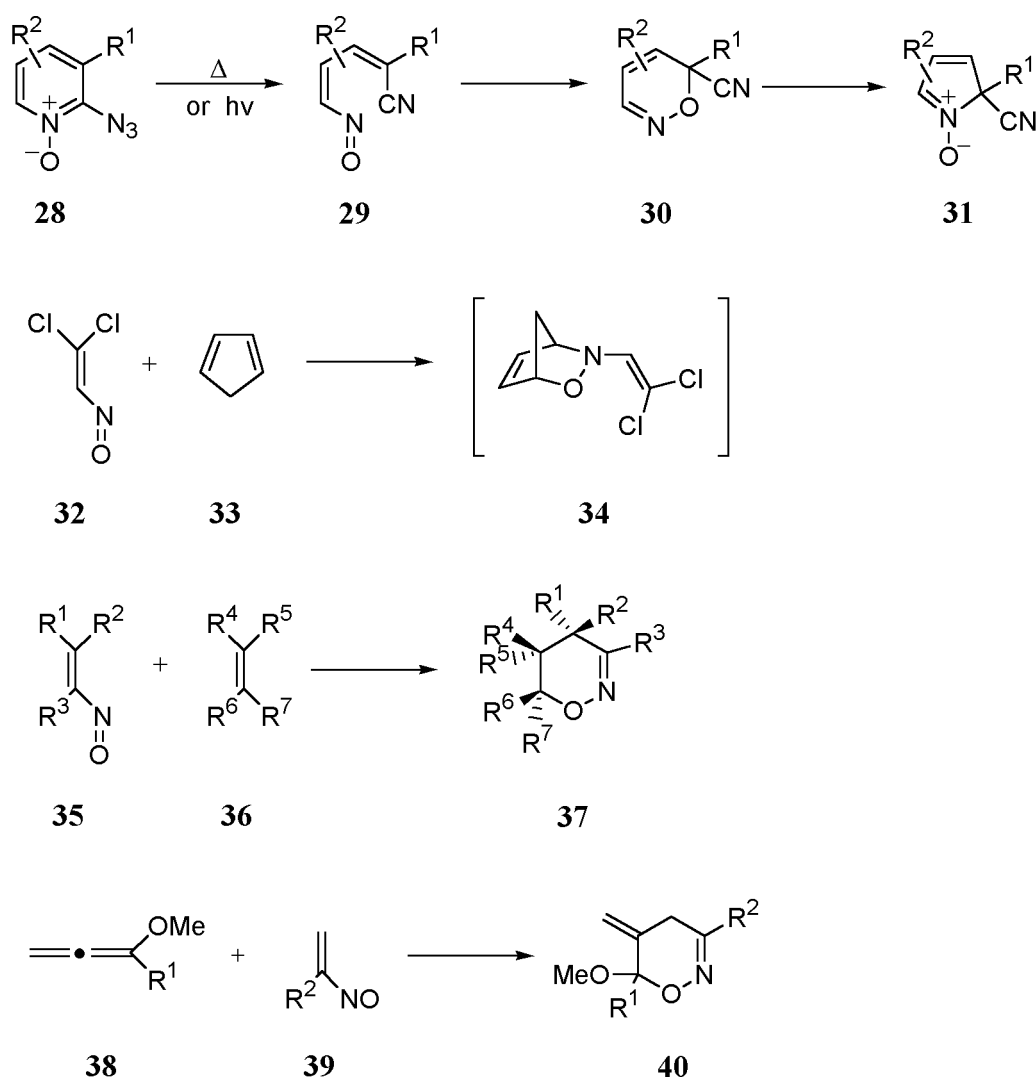
Scheme 8

Both reactions give the benzoxadiazine (**26**). However, when **25** is intercepted by thebaine, the 1,2-oxazine (**27**) has been isolated.

2.4 Nitrosoalkenes

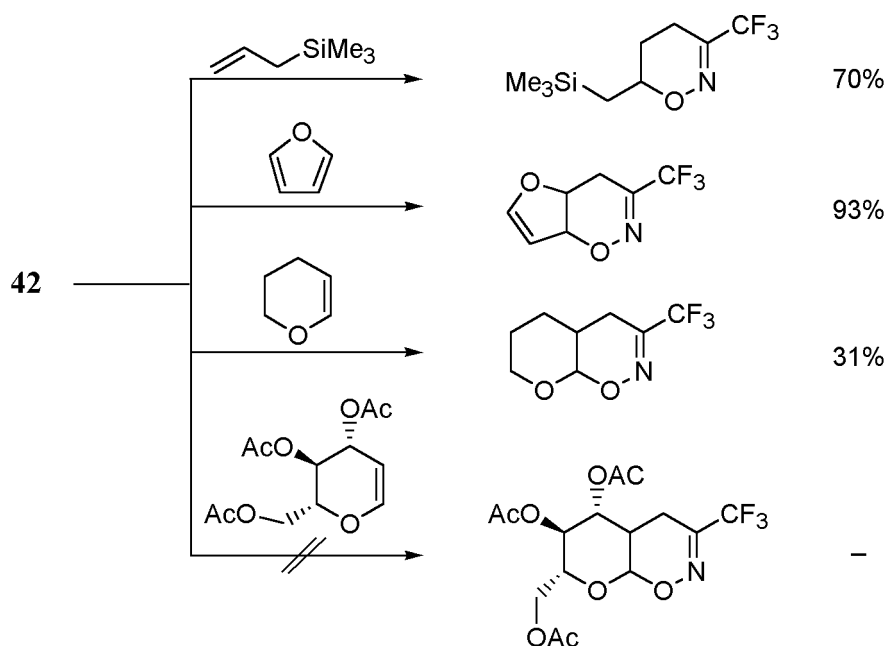
These reactive species along with nitrosocarbonyls constitute the two major sources for the construction of the 1,2-oxazine structure.

Cyclisation or cycloaddition (the nitrosoalkene acting as either a 2π or a 4π component) with dienes, among other important aspects, has been extensively covered by Gilchrist⁵ and recently by Lyapkalo and Ioffe.⁵⁷ Some representative examples are elucidated (Scheme 9).



Scheme 9

The conjugated nitrosoalkenes (**29**), (**32**), (**35**) and (**39**) undergo a cyclisation or a cycloaddition to the

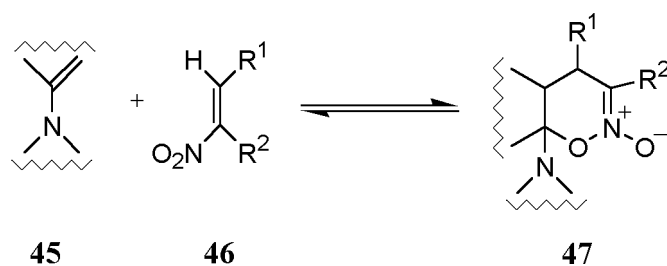


Scheme 11

2.5 Nitroalkenes

Several interesting approaches to 1,2-oxazines have appeared, where a nitroalkene reacts with another alkene or a derivative of it.

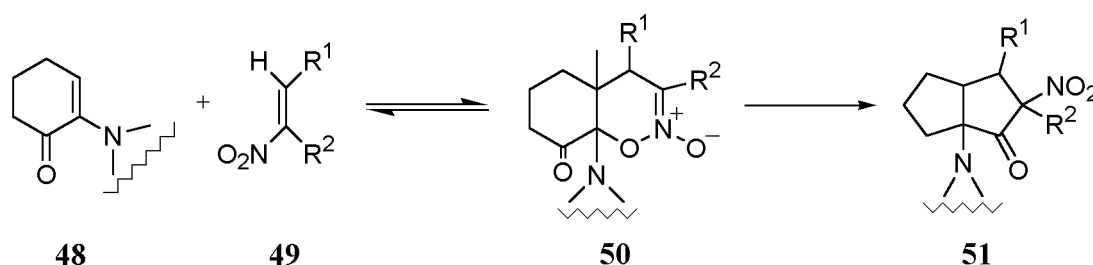
Obvious advantages in the use of nitroalkenes are their facile synthesis⁶⁷⁻⁷⁰ and stability. The *N*-oxide (**47**) of 1,2-oxazines has been formed, isolated or *in situ*, by a [4+2] cycloaddition of **46** with cyclic or acyclic enamines (**45**) (Scheme 12).⁷¹



Scheme 12

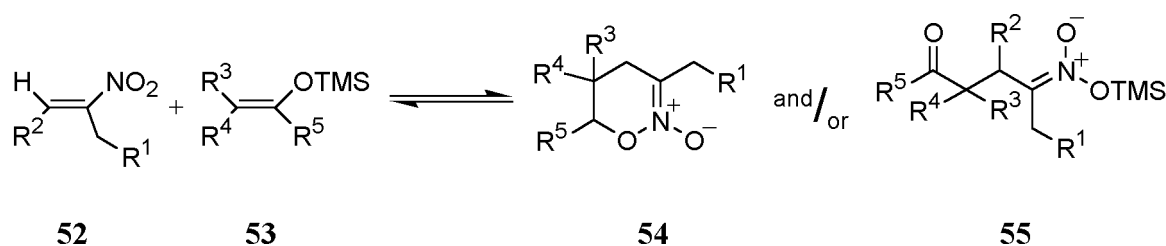
The stability of **47** has been found to depend on the structure of **45**, the substitution of **46** and the experimental conditions used. Even when isolated, 1,2-oxazine *N*-oxides (**47**) are usually stored at

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

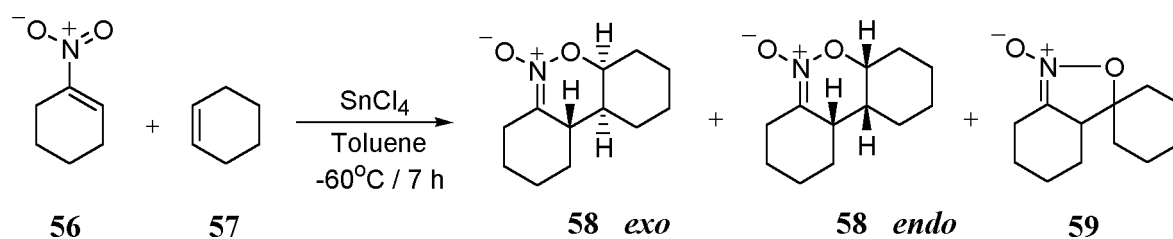
The reaction proceeds upon thorough mixing of the reactants without solvent. In solution there is no reaction. If taken in a solvent, the *N*-oxide (**50**) partly reverts to the reactants and partly isomerizes to **51**. Conjugate addition of silyl enol ethers (**53**) to nitroalkenes has proved to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



Scheme 14

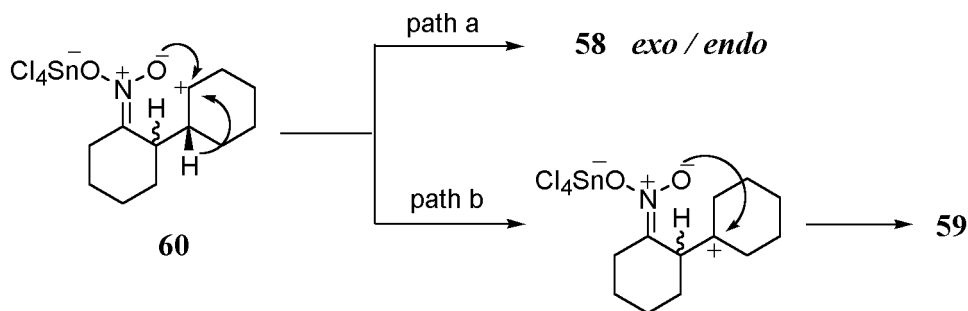
The reaction is promoted by Lewis acids, of which TiCl_4 or SnCl_4 have been found to give best yields,^{72,73} on account of the stability of nitroalkenes towards them and the synthetic equivalence of silyl enol ethers to keto-enolates.⁷⁵

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



Scheme 15

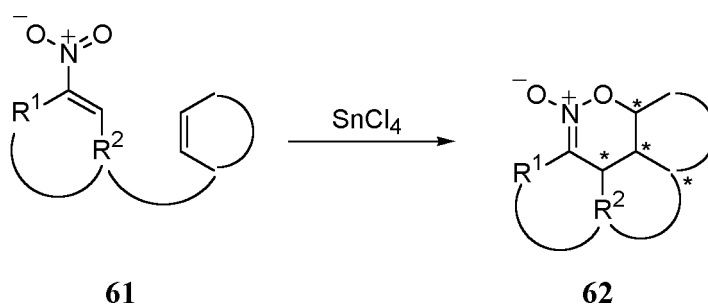
A common intermediate (**60**) has been proposed for the formation of the cyclic nitronates (**58**) *exo/endo* and the *spiro* molecule (**59**) (Scheme 16).⁷⁶ **60** collapses *via* two separate pathways, *a* by charge annihilation and *b* by a Wagner-Meerwein shift and capture of the tertiary carbocation.



Scheme 16

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

Intramolecular [4+2] cycloaddition of nitroalkenes (**61**) to *N*-oxides (cyclic nitronates) (**62**) in the presence of SnCl₄ has been investigated (Scheme 17).^{27,77}

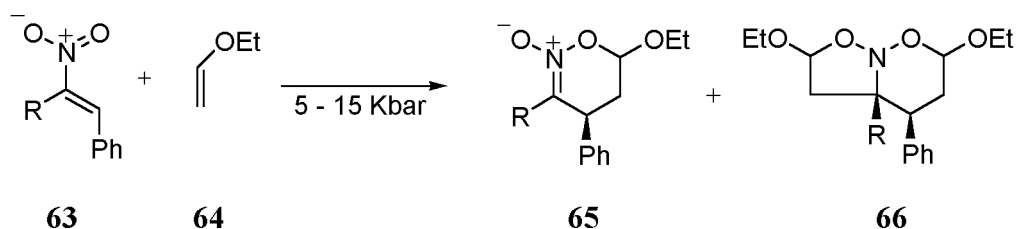


Scheme 17

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

Cycloadditions of this type have also been reported under pressure.⁸⁶ It is known that cycloadditions are accelerated, in general, by high pressure.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

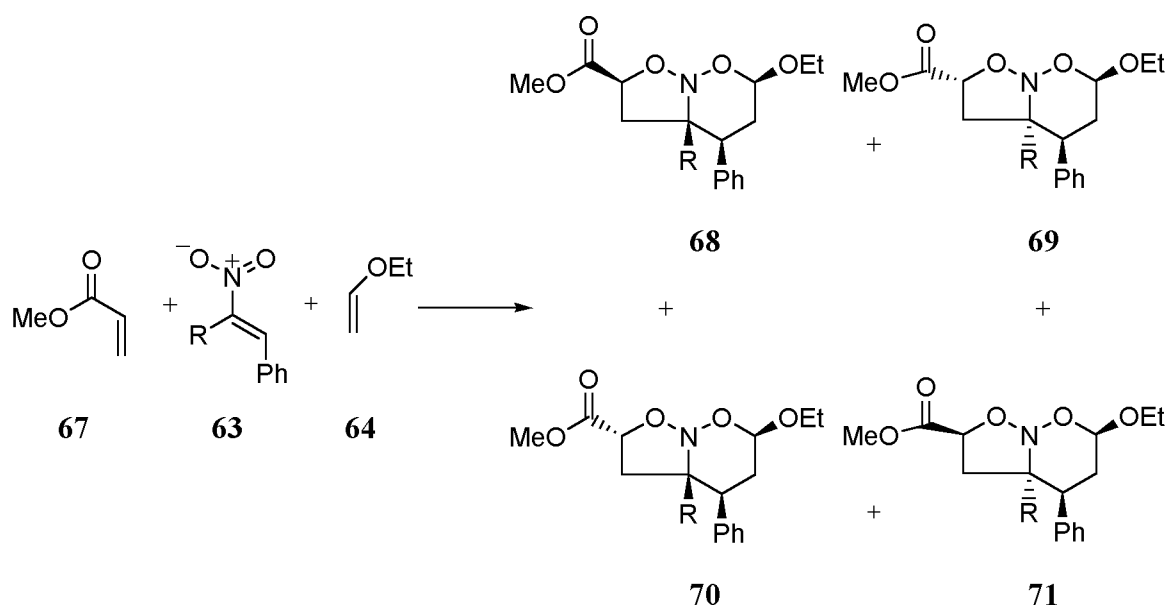
nitronate (**65**), thus, generated, reacts with another alkene in a [3+2] cycloaddition leading to a nitroso acetal, in presence of a Lewis acid catalyst (Scheme 18). Without the latter, large excess of enol ether, long reaction times or a strongly activated nitroalkene are required.



Scheme 18

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).

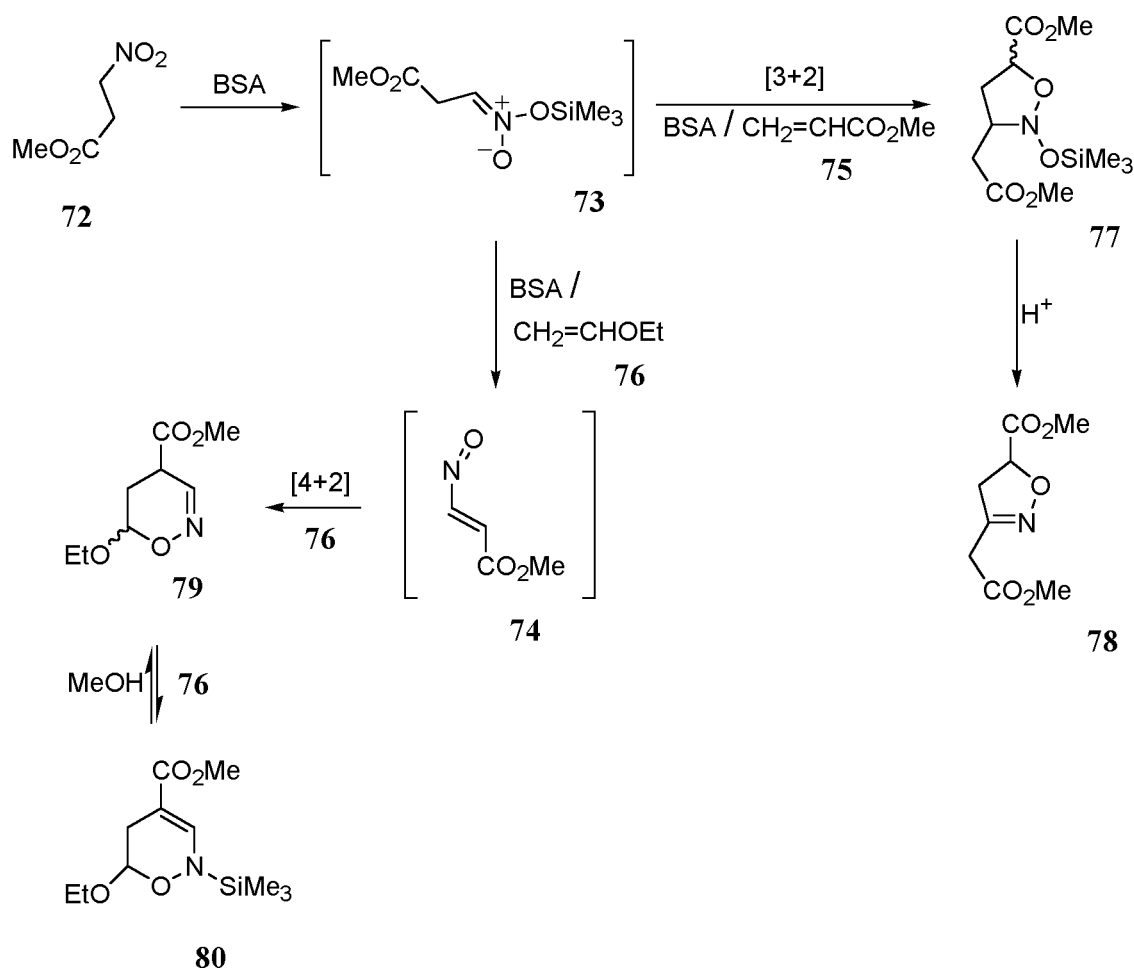


Scheme 19

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

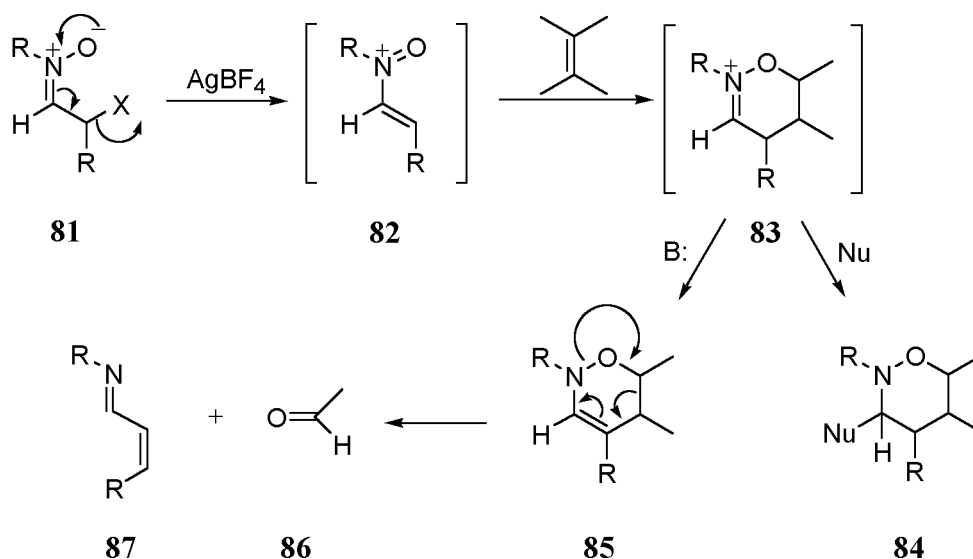
Aliphatic nitro compounds (nitroalkanes) have found an ever-increasing significance in synthesis with the advances of their silylation and the participation of the resultant silylnitronates in various well-known reactions as modified substrates.⁶¹ Nitrosoalkenes (**74**) are, thus, generated through 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

2.7 Vinylnitrosonium Cations (VNC's)

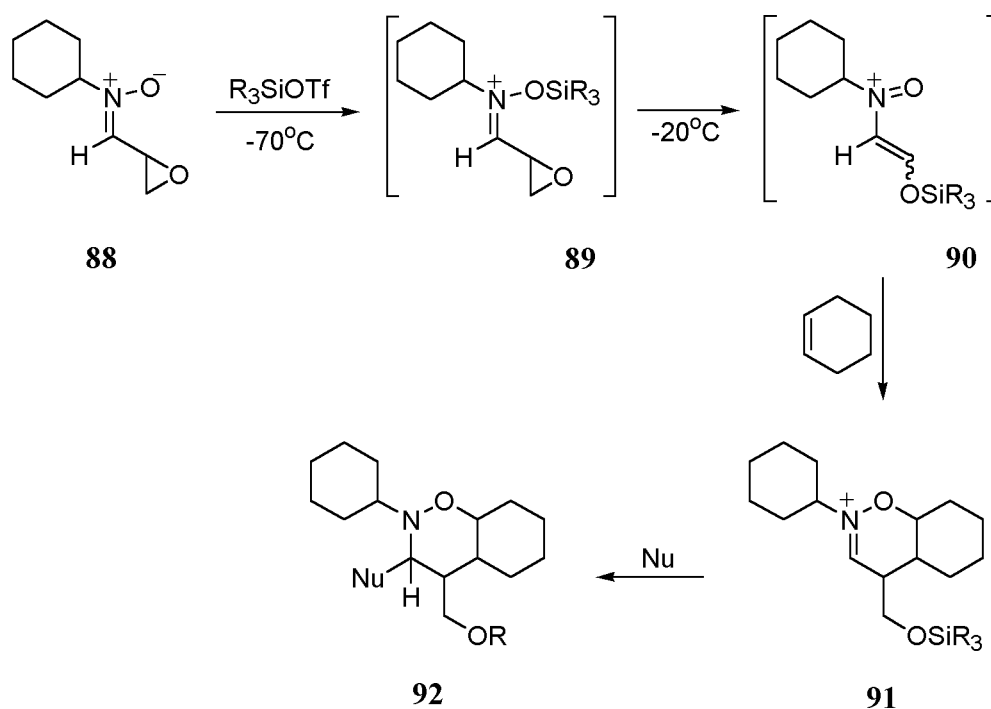
These are highly reactive heterodienes (**82**)^{89,90} and have been used as 4π components in stereoselective cycloadditions with unactivated alkenes⁹¹ to give 1,2-oxazinium cycloadducts (**83**) (Scheme 21).



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.⁹²

The high electrophilicity of **82** has been clearly demonstrated by Eschenmoser⁹⁰ who used them in connection with the selective hydrolysis of amides in the final stages of the total synthesis of vitamin B₁₂. Subsequent extensive studies were carried out by the Eschenmoser group⁹⁰ 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-2H-1,2-oxazine (**85**) by a [4+2] cycloreversion generates aldehyde (**86**) and imine (**87**) (Scheme 21). Graf and Riediker⁹³ have extended the chemistry of VNC's by using α,β -epoxyaldonitrones (**88**) as their precursors (Scheme 22).



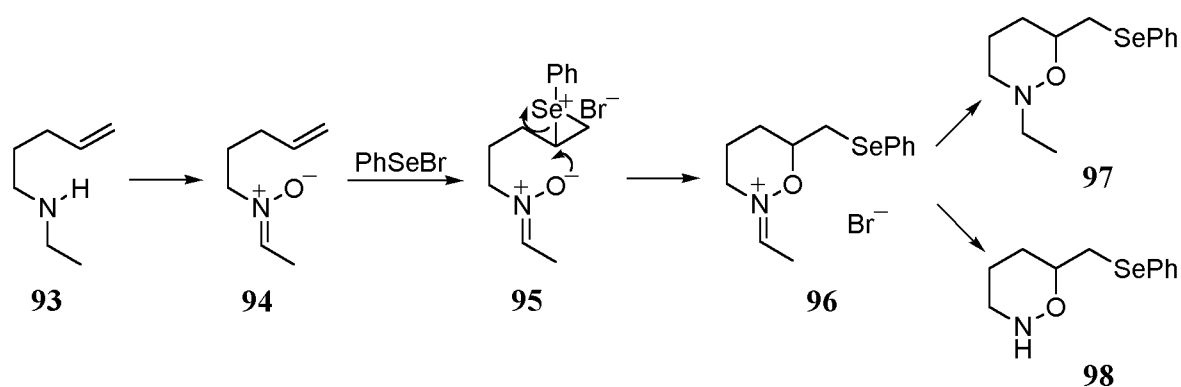
Scheme 22

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**),⁹⁴ undergo electrophile-induced ring closure by phenylselenenyl bromide to the 6-membered iminium salt (**96**), treatment of which with nucleophiles leads to the tetrahydro-1,2-oxazines (**97**), (**98**) (Scheme 23).⁹⁵

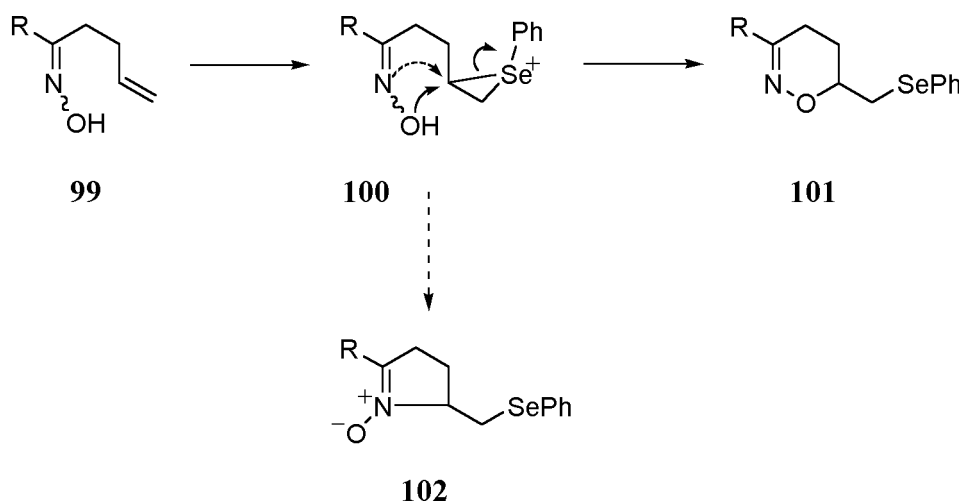


Scheme 23

2.9 Alkenyl Oximes

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

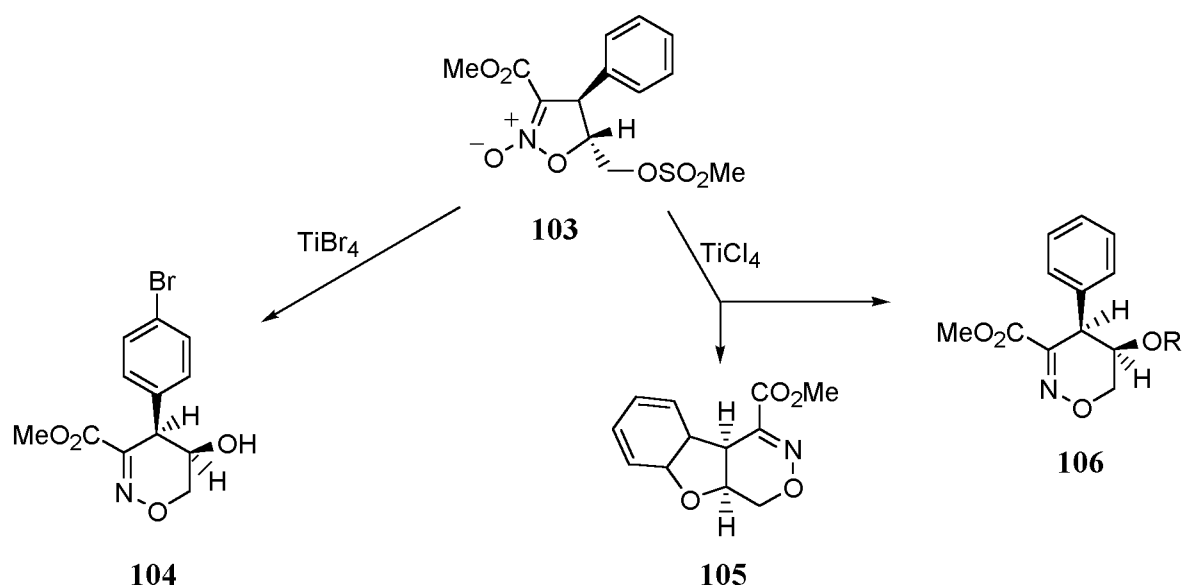
The seleniranium intermediate (**100**) is intramolecularly trapped by the internal oxime nucleophile either through its *O* to give 5,6-dihydro-4*H*-1,2-oxazines (**101**) or through the *N* to give the cyclic nitron (**102**) (Scheme 24). Clearly, it is the geometry of the oxime that determines the 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

2.10 Isoxazoline 2-Oxides

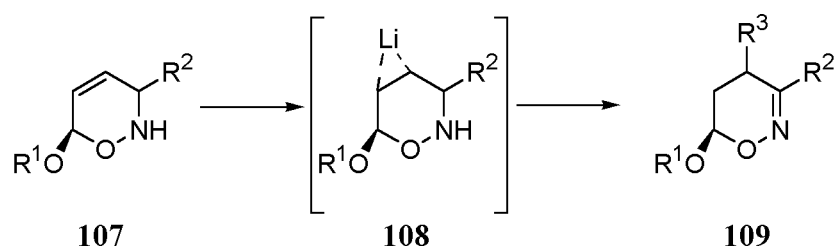
Isoxazoline 2-oxides, as their methanesulphonate derivatives (**103**), on treatment with TiBr_4 or TiCl_4 give rise to 1,2-oxazines (**104**), (**105**) and (**106**) respectively, by ring expansion (Scheme 25).⁹⁷



Scheme 25

2.11 1,2-Oxazines

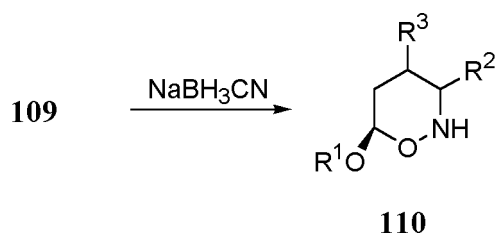
6*H*-1,2-oxazines (**107**) may serve as precursors to their 4*H*-counterparts (**109**) (Scheme 26).^{98,99}



Scheme 26

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

2*H*-1,2-oxazines (**110**) can be obtained by NaBH₃CN reduction of **109** (Scheme 27).¹⁰¹



Scheme 27

3.0 CARBO(HETERO)CYCLO-FUSED 1,2-OXAZINES

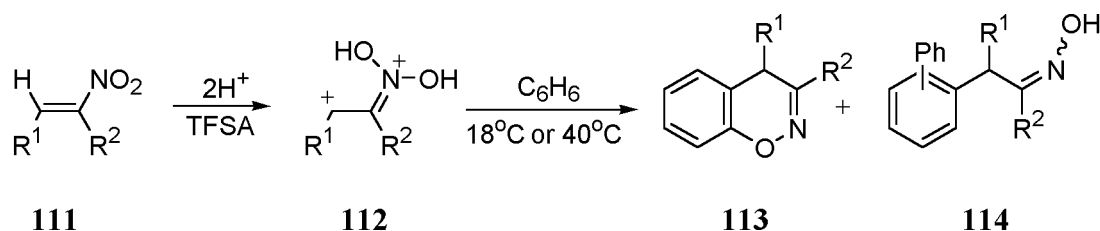
Access to these heterocycles **E** and their *N*-oxides is limited at present. The methods available are not of general applicability with respect to tailor-made substitution on either or both rings. Clearly, additional versatile routes to this heterocyclic structure are required as its potential to 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 (**112**), generated from diprotonation of β -nitrostyrenes (**111**) with TFSA, upon reaction with benzene, give 4*H*-1,2-benzoxazines (**113**) (Scheme 28).¹⁰⁴⁻¹⁰⁶



Scheme 28

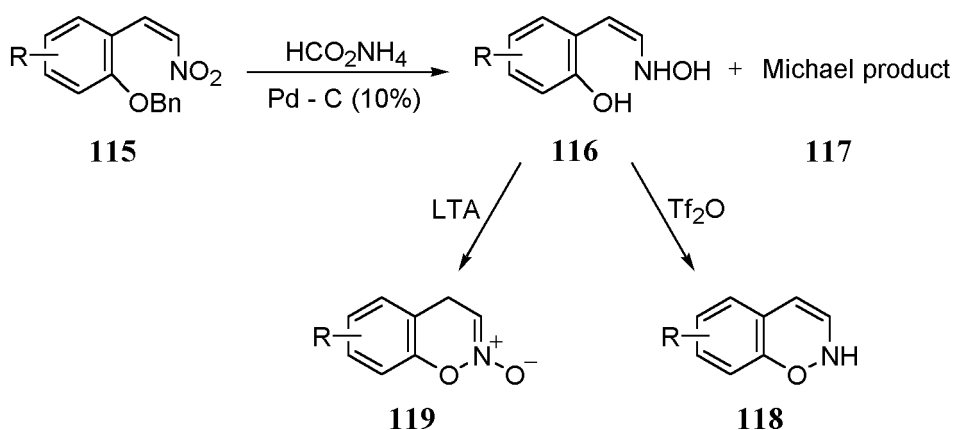
Large excess of TFSA and prolonged reaction are required to obtain **113** in good yield, as the major product.

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

The reaction conditions (time, temperature and work-up) determine the predominance of **113** over **114**.

The reaction has been found to give **113** only with benzene itself, although variable substitution on the nitroalkenes is comfortably tolerated.

Nitroalkenes (**115**) offer an alternative versatile route to 4*H*-1,2-benzoxazines (Scheme 29).¹⁰⁷

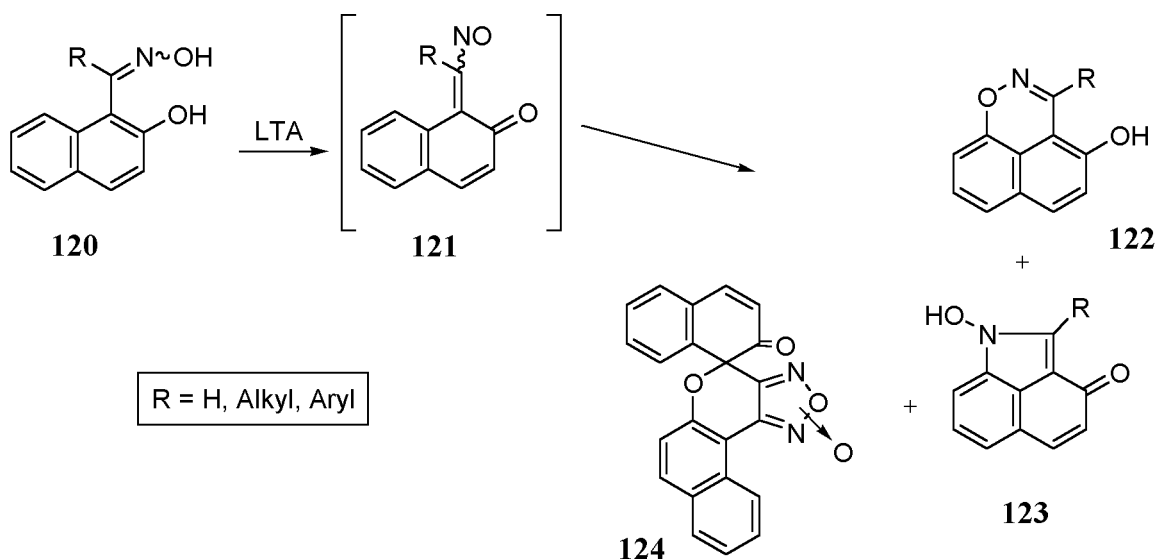


Scheme 29

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_2O 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).¹⁰⁸

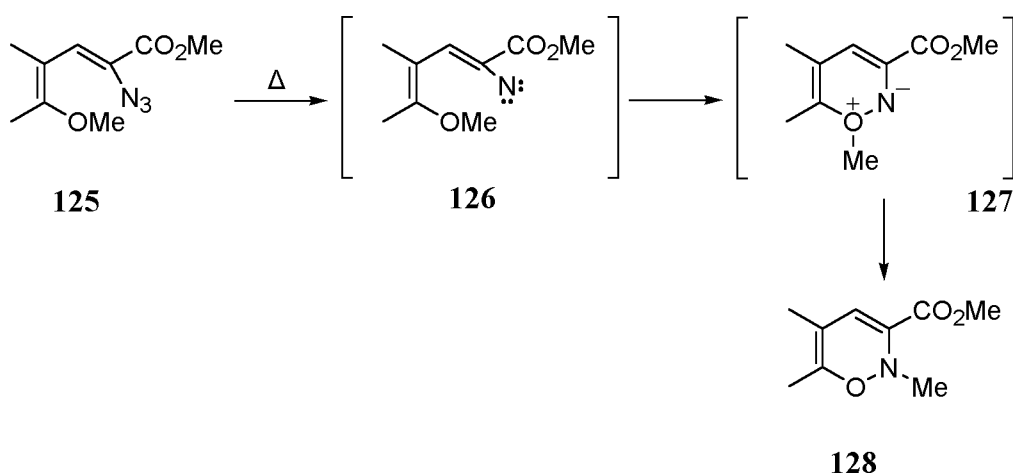


Scheme 30

The formation of **122** has been rationalized by a *peri* cyclisation/annulation of the *o*-NQM (**121**).¹⁰⁸ 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(ophilic) 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).¹⁰⁹

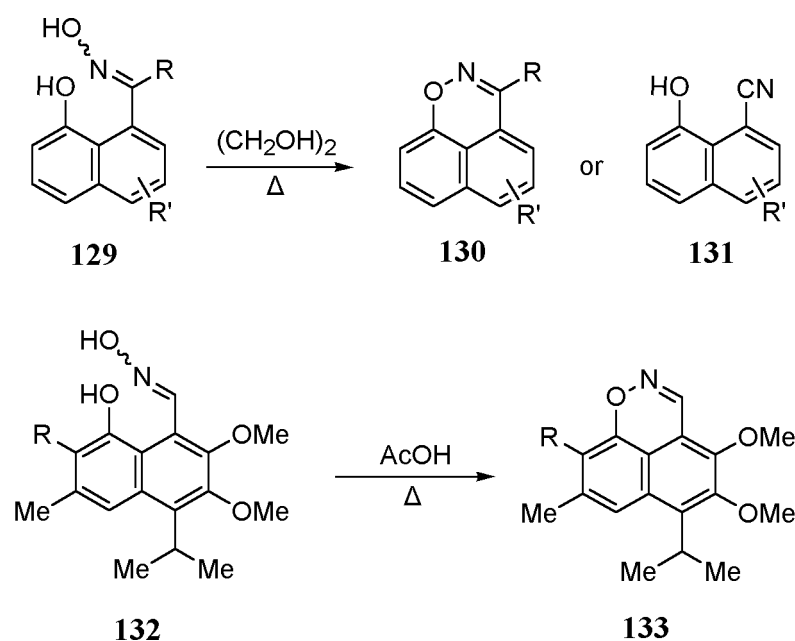


Scheme 31

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.¹⁰⁹ 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-acylnaphthalenes (**129**) upon heating (Scheme 32).¹¹⁰

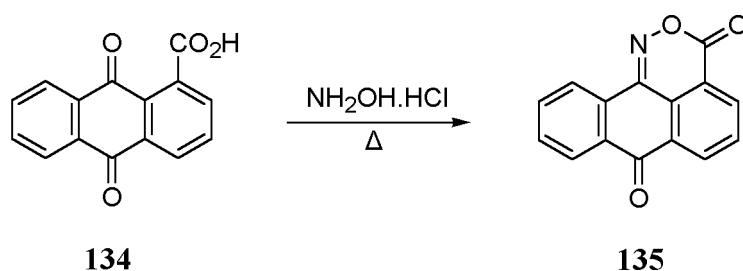


Scheme 32

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).^{111,112}

Peri-annulated 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).¹¹³



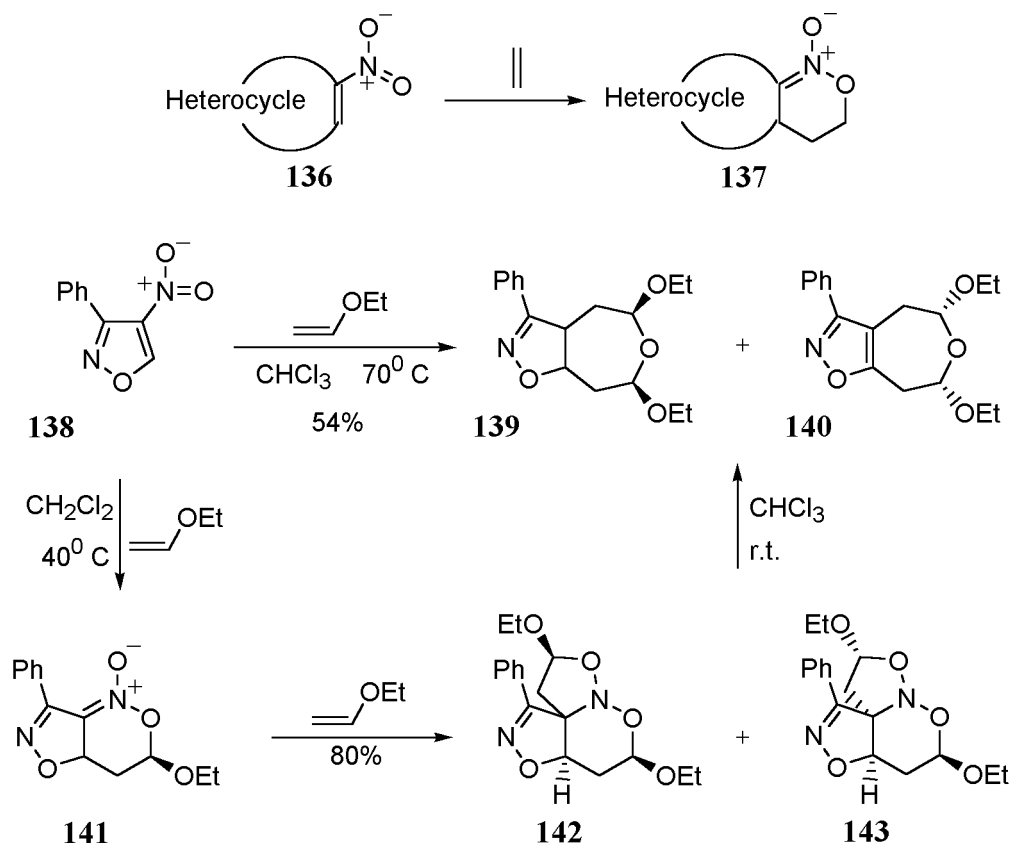
Scheme 33

135 has also been obtained by acid-catalysed rearrangement of 1-nitromethylantraquinone.¹¹⁴

3.6 Nitro-substituted Heterocycles

3,5-dinitropyridones,¹¹⁵ 3-nitro-2,5-dihydrofuran derivatives,¹¹⁶ 4,6-dinitrobenzofuroxan,¹¹⁷ 4-nitro-2-phenyloxazole-5-carboxylate¹¹⁸ and very recently 4-nitroisoxazoles¹¹⁹ have been reported as effective nitro-heterodienes, leading to the corresponding heterocyclo-fused adducts 1,2-oxazine N-oxides, with

high diastereoselectivity (Scheme 34)

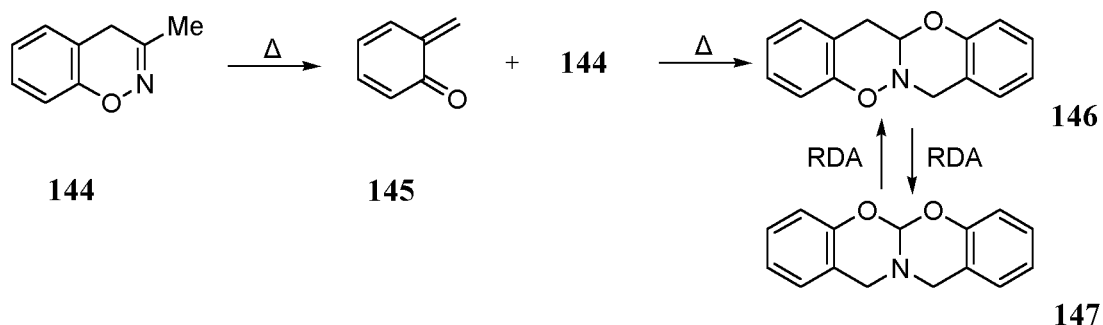


Scheme 34

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.

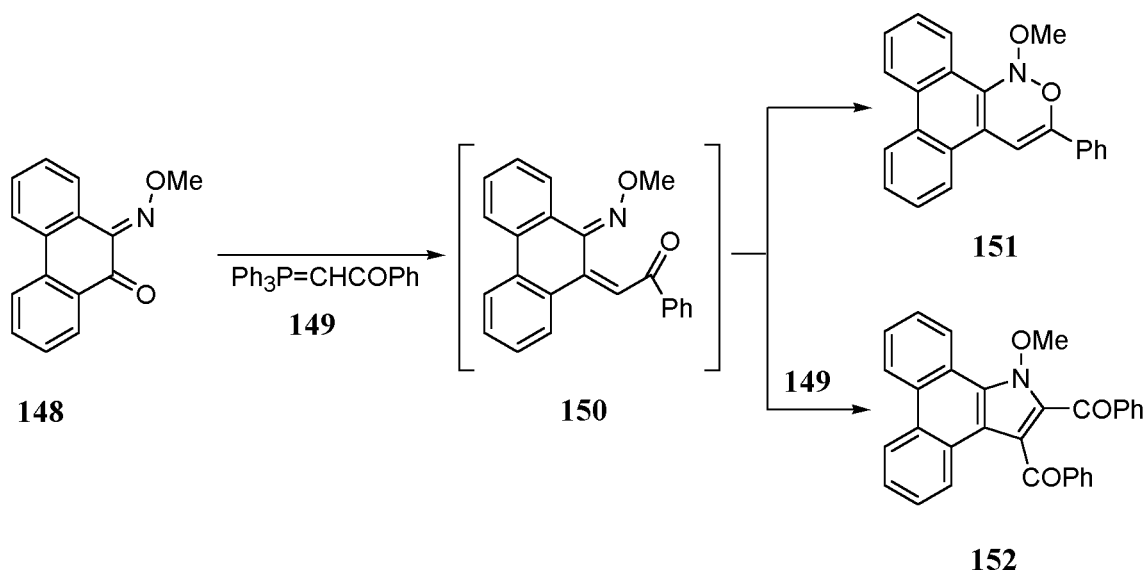
3.7 Miscellaneous

Thermolysis of 1,2-oxazine (**144**) leads to the highly reactive *ortho*-quinonemethide (**145**).^{8b} 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).



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

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.

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