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4-Isoxazolines: Scaffolds for Organic Synthesis

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This review provides coverage of the more relevant contributions to the synthesis and reactivity of 4-isoxazolines (2,3-dihydroisoxazoles). The richness of the reactivity of these heterocycles makes them interesting building blocks for the synthesis of both cyclic and acyclic compounds.

1. Introduction

4-Isoxazolines (2,3-dihydroisoxazoles, **1**) are interesting synthons for cyclic and acyclic compounds[1,2] and are also known for their biological activities.[3–7] These heterocyclic compounds have attracted considerable interest due to their readiness to undergo rearrangement reactions, making them of interest from both synthetic and mechanistic points of view. The reactivity of this ring system is mainly due to the relatively low thermochemical stability of the N–O bond associated with the π system.

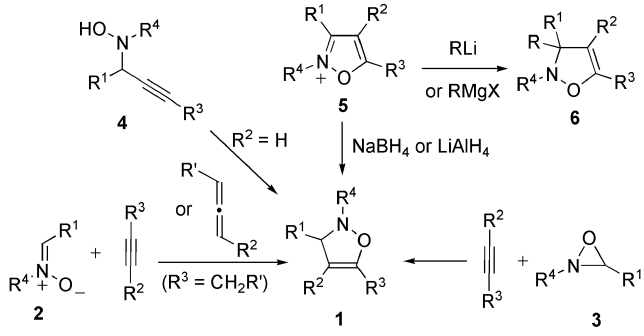
1

4-Isoxazolines
(2,3-dihydroisoxazoles)

The aim of this review is to cover the more relevant synthetic approaches to 4-isoxazoline derivatives as well as their reactivity, which make these heterocycles an interesting scaffold for organic synthesis.

2. Synthesis of 4-Isoxazolines

The main strategy used to obtain the 4-isoxazole ring system has been 1,3-dipolar cycloaddition between nitrones **2** (Scheme 1) and alkynes or allenes. Other methods include cycloaddition of oxaziridines **3** with alkynes, cyclization of propargylic *N*-hydroxylamines **4**, addition of Grignard reagents or organolithium compounds to isoxazolium salts **5** or their reduction with hydride reagents.



Scheme 1.

2.1. 1,3-Dipolar Cycloadditions between Nitrones and Alkynes or Allenes

Cycloadditions between nitrones and asymmetrically substituted alkynes can yield regioisomers.[1,2–8] With monosubstituted alkynes such as alkyl- or phenylacetylene, however, 5-substituted 4-isoxazolines are obtained regiospecifically. On the other hand, electron-deficient acetylenes (e.g., methyl propiolate or cyanoacetylene) give mixture of regioisomers or lead to the selective synthesis of 4-substi-

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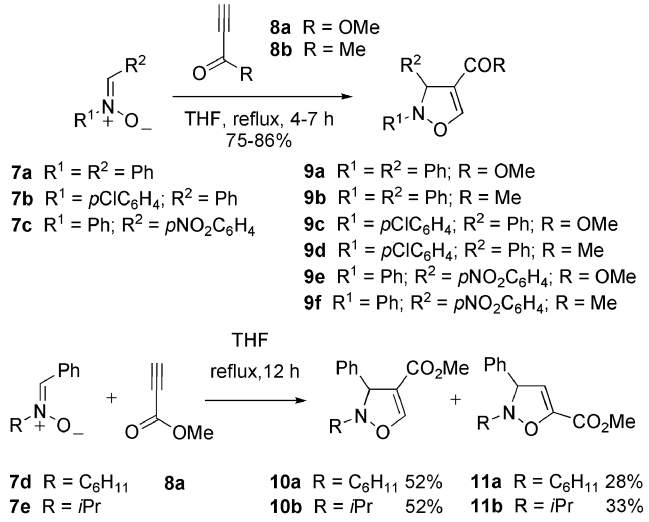
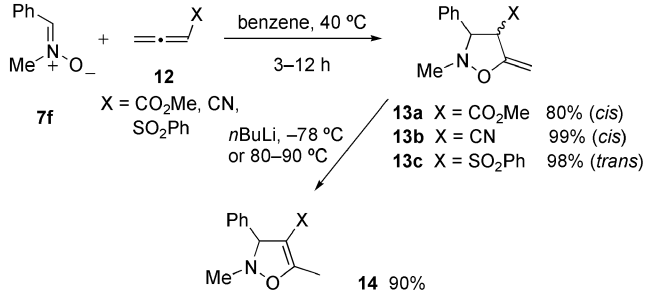
tuted 4-isoxazolines. The regiochemistry of these 1,3-dipolar cycloaddition reactions has been interpreted by FMO analysis.[2,9]

Efficient regioselective formation of 4-substituted 4-isoxazolines can be illustrated by the reactions between the *N*-arylnitrones **7a**–**7c** (Scheme 2) and methyl propiolate or but-2-yn-2-one.[10] However, nitrones bearing a cyclohexyl or an isopropyl group on the nitrogen (**7d** and **7e**) afford the two possible regioisomers, the 4-substituted derivative being the major product in each case.



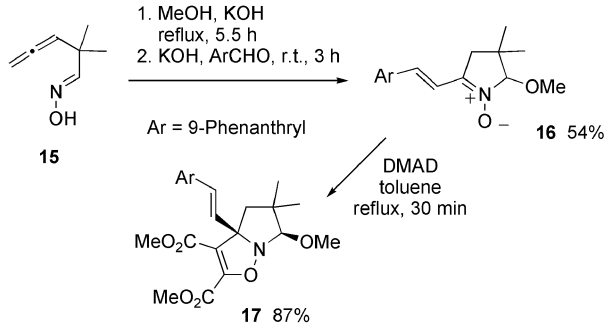
Scheme 2.

1,3-Dipolar cycloadditions between nitrones and the electron-deficient allenes **12** take place regioselectively to give the 5-methylene-isoxazolidines **13**, which can be converted into the corresponding 4-isoxazolines **14** upon treatment with base or through thermolysis, by 1,3-hydrogen shifts (Scheme 3).[11–15]



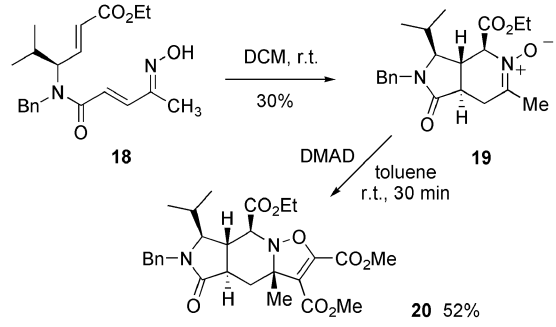
Scheme 3.

The five-membered cyclic nitrone **16** (Scheme 4), prepared through a one-pot allenyloxime domino reaction, participates in 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to give the 4-isoxazoline **17** in high yield and as a single diastereoisomer.[16]



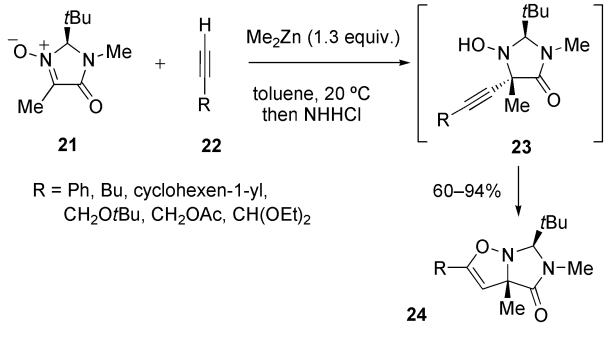
Scheme 4.

Chiral polycyclic 4-isoxazolines have also been obtained by the 1,3-dipolar cycloaddition approach (Scheme 5).[17] The intramolecular [4+2] cycloaddition of the α,β-unsaturated oxime **18** leads to the chiral nitrone **19** via an endocyclic 2-piperidine enamine. This nitrone acts as a 1,3-dipole in the reaction with dimethyl acetylenedicarboxylate, affording the 4-isoxazoline **20** in a stereoselective fashion.



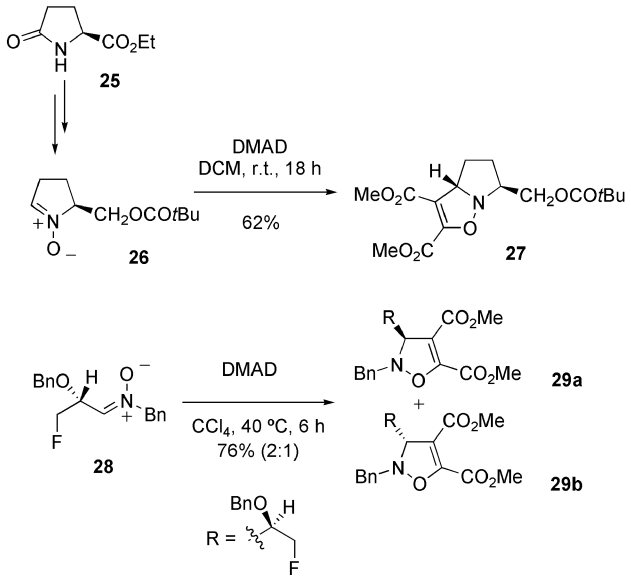
Scheme 5.

Treatment of the chiral cyclic nitrone **23** (Scheme 6) with alkynylzinc reagents led to a tandem addition/cyclization process giving the bicyclic 4-isoxazolines **24** regio- and diastereoselectively.[18] Although the outcome of the reaction is the expected 1,3-dipolar cycloadducts the reaction follows a two-step pathway, as demonstrated by the authors by TLC analysis of hydrolysed aliquots of the reaction mixture, showing the formation and disappearance of the intermediate **23**.



Scheme 6.

The chiral nitrone **26** (Scheme 7) can be prepared through the use of ethyl L-pyroglutamate (**25**) as the source of chirality and subsequently reacts with DMAD to afford the chiral 4-isoxazoline **27**.[19] However, the 1,3-dipolar cycloaddition between the chiral nitrone **28** and DMAD gives a 2:1 ratio of the two diastereoisomeric fluorinated 4-isoxazolines **29** in 76% overall yield.[20]



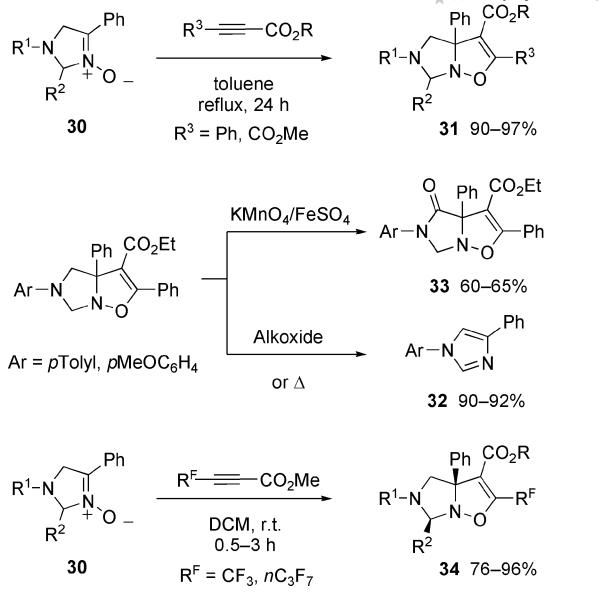
Scheme 7.

The tetrahydroimidazo[1,5-*b*]isoxazoles **31** (Scheme 8) were obtained from cycloadditions between the cyclic nitrones **30** and phenylpropiolates or DMAD. These heterocycles were converted into imidazoles (e.g., **32**) when treated with alkoxide or heated under vacuum. On the other hand, oxidation with $KMnO_4/FeSO_4$ gave the 4-oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **33**.[21] The 2-perfluoroalkyl-tetrahydroimidazo[1,5-*b*]isoxazoles **34** can be obtained from the cyclic nitrones and methyl 2-perfluoroalkynoates in a highly diasteroselective and regioselective fashion.[22]

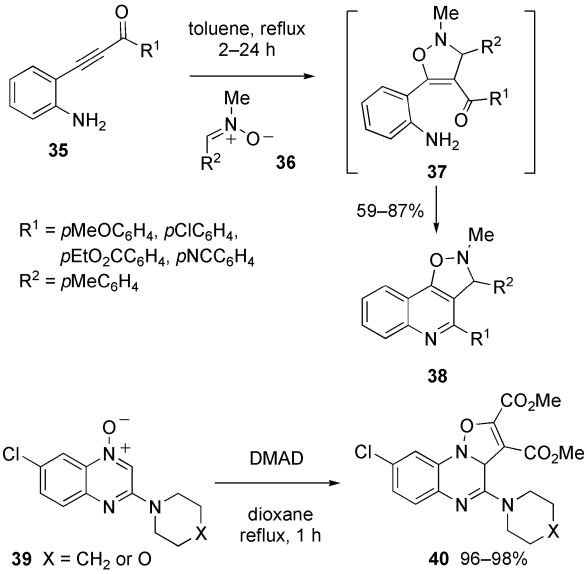
The isoxazolino[4,5-*c*]quinoline ring system has been prepared by sequential double annulation starting from the acyclic β-(2-aminophenyl)-α,β-ynones **35** (Scheme 9) and the *N*-methylnitrones **36**.[23] The initial regioselective 1,3-dipolar cycloaddition reactions lead to the 4-isoxazolines **37**, which undergo condensation to give the quinoline nucleus.

Treatment of quinoxaline 4-oxides (Scheme 9) with DMAD in dioxan at reflux affords isoxazolo[2,3-*a*]quinoxalines (e.g., **40**) in high yields.[24,25]

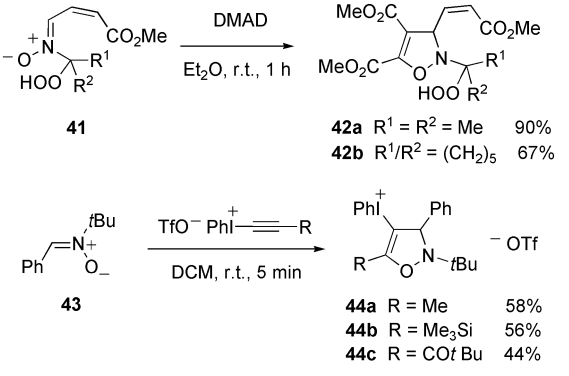
The (hydroperoxyalkyl)nitrones **41** (Scheme 10) react with acetylenes to give 2-(hydroperoxyalkyl)-4-isoxazolines (e.g., **42**) under mild conditions.[26] The authors observed that derivatives other than the 4-isoxazoline **42a** are not very stable, significant decomposition being observed during column chromatography. Although the estimated yield of the crude 4-isoxazoline **42b** as judged from the ^1H spectrum was 90%, this product was isolated after silica gel chromatography only in 67% yield.



Scheme 8.



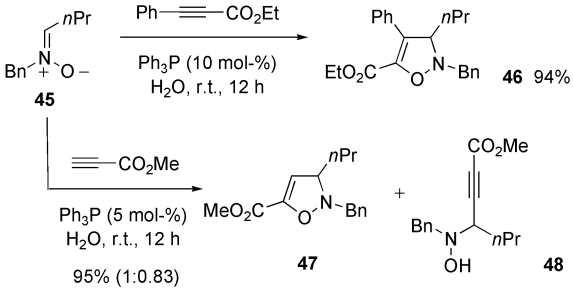
Scheme 9.



Scheme 10.

Cycloaddition of the nitrone **43** (Scheme 10) with (alkynyl)phenyliodonium triflates has also been reported, leading to the corresponding iodonium-substituted 4-isoxazolines **44** regioselectively and in moderate yields.[27]

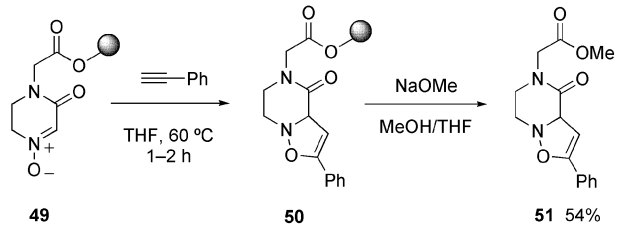
A study on the reactivity of alkynoates towards nitrones "on water" in the presence of tertiary amines and phosphanes as organocatalysts has been reported.[28,29] The reactivity pattern is characterized by the formation of mixtures of 2,3,5-trisubstituted 4-isoxazolines (e.g., **47**, Scheme 11) and *N*-propargylic hydroxylamines (e.g., **48**) from terminal alkynoates, whereas reactions with internal alkynoates lead to the chemo- and regioselective synthesis of 2,3,4,5-tetrasubstituted 4-isoxazolines as illustrated by the reaction between the nitrone **45** and methyl propiolate. The 4-isoxazoline synthesis proceeds via zwitterionic allenoates, generated from the addition of the catalyst to the alkynoates, which participate in regioselective 1,3-dipolar cycloaddition with nitrones, followed by the elimination of the catalyst.



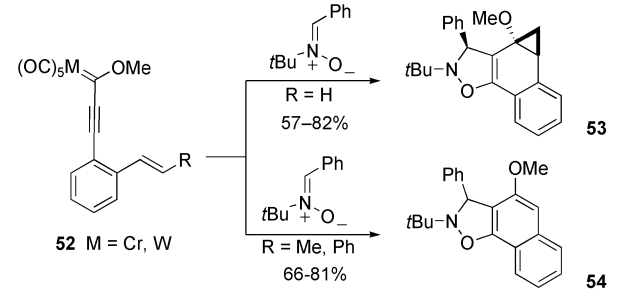
Scheme 11.

1,3-Dipolar cycloadditions of nitrones and monosubstituted alkynes on solid supports are known.[30,31] With the starting polymer-supported cyclic nitrone 4-isoxazoline **49** (Scheme 12), cycloaddition was carried out in THF at 60 °C. The cycloadduct **51** was isolated in 54% overall yield after basic cleavage from the resin.

The alkynyl Fischer carbene complexes **52** (R = H, Scheme 13) undergo a cascade cycloaddition/cyclopropanation process in the presence of a nitrone to afford 4-isoxazolines (e.g., **53**) in good yield. Under the same conditions, complexes **52** with substituents at the pendant olefin group (R = Me, Ph) undergo a cycloaddition/metathesis process leading to the naphthalenes **54**.[32]

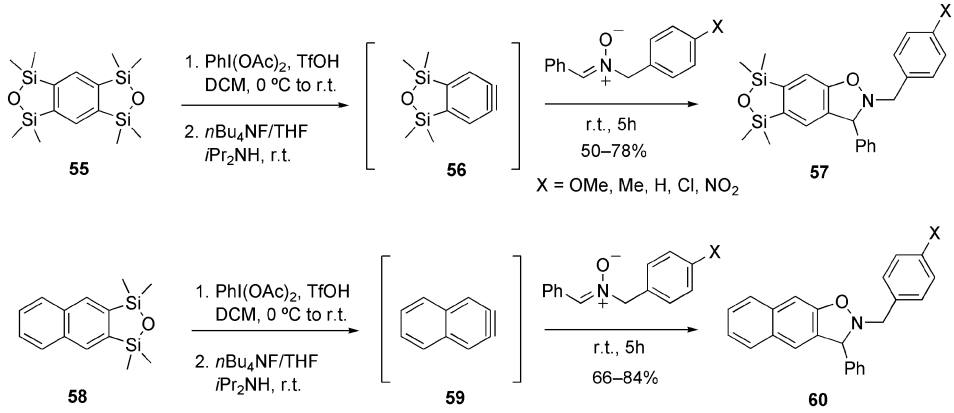


Scheme 12.



Scheme 13.

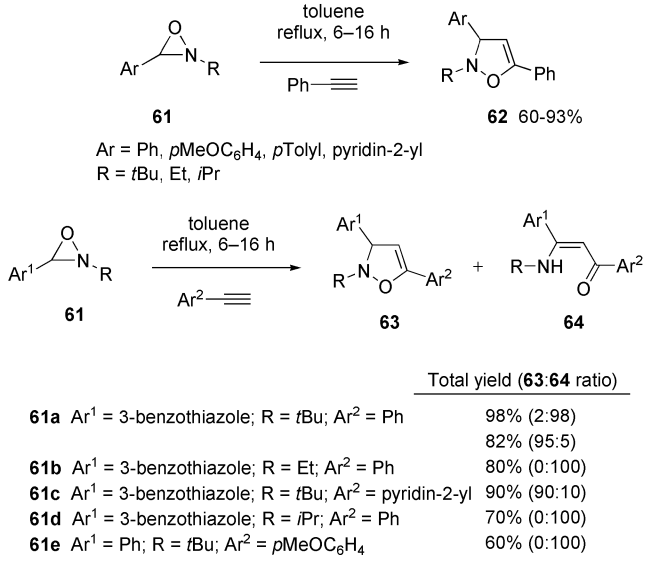
Benzo[*d*]isoxazoline and naphtho[2,3-*d*]isoxazoline derivatives have been prepared through cycloadditions between nitrones and arynes. The arynes **56** and **59** (Scheme 14) were generated from the benzobisoxadisilole **55** and the 2,3-naphthoxadisilole **58**, respectively, by a phenyliodination/fluoride-induced desilylation process. Cycloadditions of the benzyne **56** with diarylnitrones gave the benzo[*d*]isoxazolines **57** in 50–78% yields, whereas the naphthyne **59** reacted with the same nitrones to give the naphtho[2,3-*d*]isoxazolines **60** in good yields.[33]



Scheme 14.

2.2. Cycloadditions of Oxaziridines with Alkynes

Troisi et al. described the synthesis of 3,5-diaryl-2-alkyl-4-isoxazolines from aryl alkynes and 2-alkyl-2-aryloxaziridine (Scheme 15).[34] The oxaziridines **61** were prepared by oxidation of the corresponding imines with *m*-chloroperbenzoic acid.

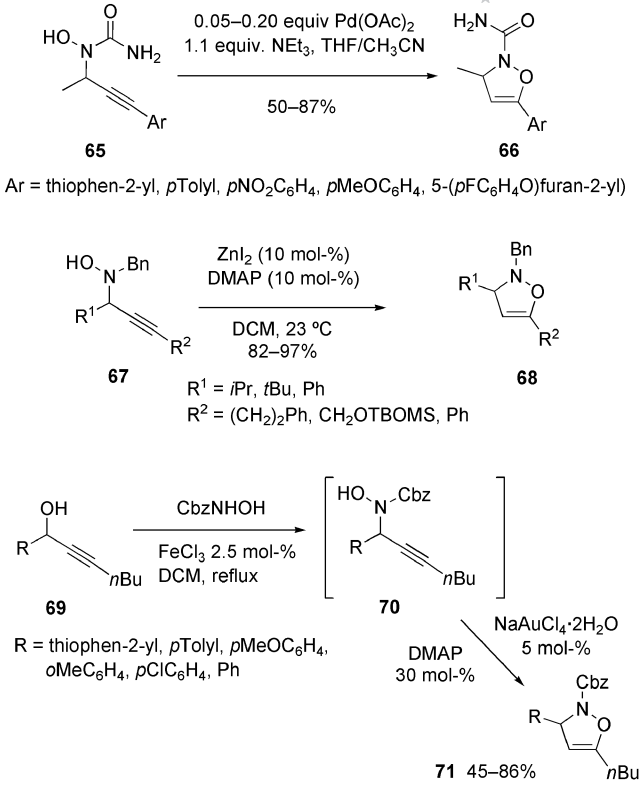


Scheme 15.

The thermolysis of solutions of the oxaziridines **61** and alkynes in toluene affords 4-isoxazolines. The regioselectivity of the cycloaddition reaction can be explained by considering steric interactions, which is also consistent with unsuccessful attempts to carry out the reactions with internal alkynes such as 1-phenylpropyne. The authors observed that several 4-isoxazolines were unstable under the experimental conditions and were converted into the corresponding β-amino enones through N–O bond cleavage. The presence of an electron-withdrawing group at C-5 and/or an electron-donating group at C-3 favours the 4-isoxazoline rearrangement. Nevertheless, this methodology is useful for the synthesis of 4-isoxazolines, which are difficult to prepare by other methods.

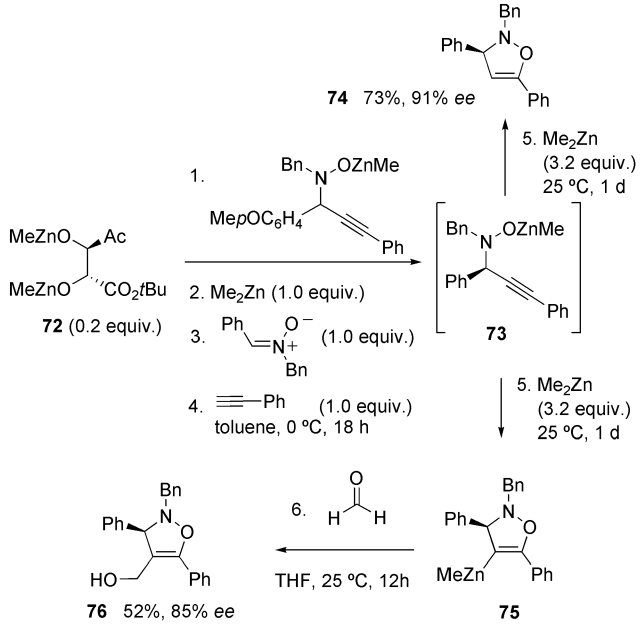
2.3. Cyclization of Propargylic *N*-Hydroxylamines

The aryl-substituted propargylic *N*-hydroxyureas **65** (Scheme 16) undergo palladium-mediated cyclization to give the 4-isoxazolines **66** in good yields.[35] The 2,3,5-trisubstituted 4-isoxazolines **68** were also obtained efficiently from 5-*endo*-dig cyclizations of the propargylic *N*-hydroxylamines **67** in the presence of catalytic amounts of ZnI_2 and DMAP.[36] A one-pot approach to 4-isoxazolines from the propargylic *N*-hydroxylamine **69**, through dual gold/iron catalysis, has been reported.[37] Through the use of a bisnucleophilic protected hydroxylamine, the first iron(III)-promoted propargylic substitution is followed by the gold(III)-promoted cyclization in the presence of DMAP as co-catalyst to furnish the 4-isoxazolines **71**.



Scheme 16.

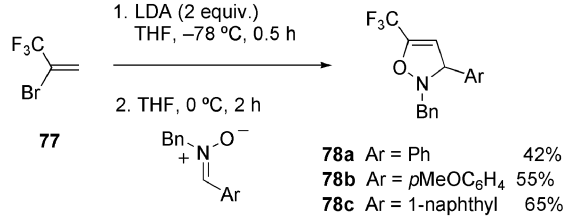
One-pot catalytic asymmetric additions of alkynylzinc to nitrones in the presence of di-*tert*-butyl (*R*,*R*)-tartrate as a chiral auxiliary, followed by cyclization, afford the corresponding (*S*)-4-isoxazolines (e.g., **74**, Scheme 17) with high enantioselectivity. In these addition reactions, the presence of the methylzinc salt of a product-like racemic hydroxylamine as an additive leads to enantiomeric enhancement.



Scheme 17.

On the other hand, the cyclization step is accelerated by the addition of dimethylzinc. The initially formed cyclization product **75** could be trapped with formaldehyde to give the 4-isoxazoline **76**.[38]

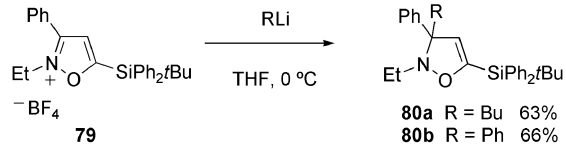
Aryl nitrones undergo nucleophilic additions with fluoroalkylated acetylides, generated from 2-bromo-3,3,3-trifluoropropene through treatment with LDA. Subsequent cyclization gives the fluoroalkylated 4-isoxazolines **78** in moderate yields (Scheme 18).[39]



Scheme 18.

2.4. Addition of Organolithium Reagents to Isoxazolium Salts

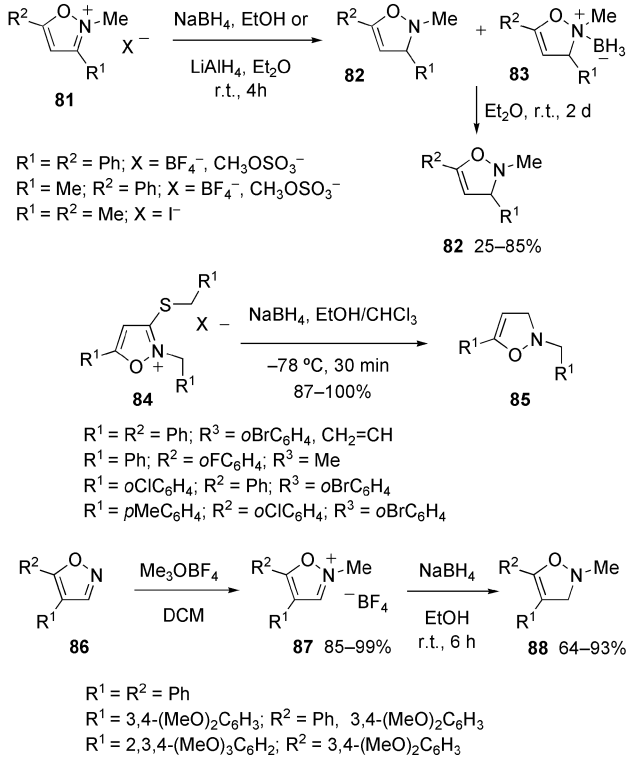
Silylated 4-isoxazolines (e.g., **80**) have been prepared from the starting 5-silylated 3-phenylisoxazolium salt **79** by regioselective alkylation with organolithium reagents (Scheme 19).[40]



Scheme 19.

2.5. Reduction of Isoxazolium Salts with Hydride Reagents

Alberola et al. reported that 3,4-disubstituted *N*-alkylisoxazolium salts undergo lithium aluminium hydride or sodium borohydride reduction to give 4-isoxazolines. In some cases, depending on the anion of **81** (Scheme 20) involved and the hydride used, mixtures of 4-isoxazolines and their borane complexes were obtained; these could be converted into the 4-isoxazolines **82** by treatment with ether.[41]



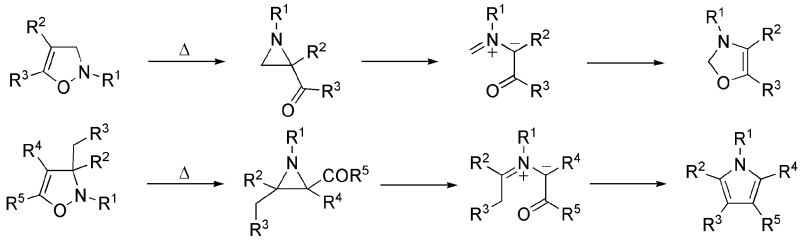
Scheme 20.

The synthesis of 3-unsubstituted 4-isoxazolines by treatment of the 3-alkylthio-5-aryl-2-(arylmethyl)isoxazolium halides **84** (Scheme 20) with sodium borohydride has also been reported. The 5-aryl-2-(arylmethyl)isoxazolines **85** are obtained in this way in high yields.[42] On the other hand, 4,5-diaryl-4-isoxazolines (e.g., **88**) have been prepared by subjecting the isoxazoles **86** to tandem *N*-quaternization/sodium borohydride reduction conditions.[4,43]

3. Reactivity of 4-Isoxazolines

3.1. 4-Isoxazolines as Building Blocks for Cyclic Compounds

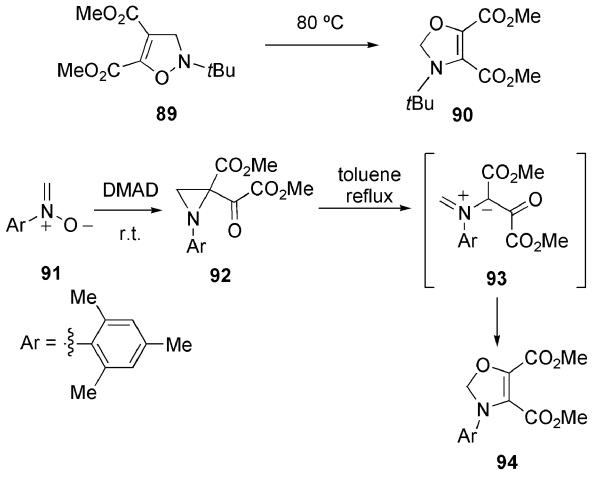
4-Isoxazolines have attracted considerable interest as a result of their readiness to undergo rearrangement reactions. The reactivity of this ring system is mainly due to the relatively low thermochemical stability of the N–O bond associated with the π system. The most general reactivity



Scheme 21.

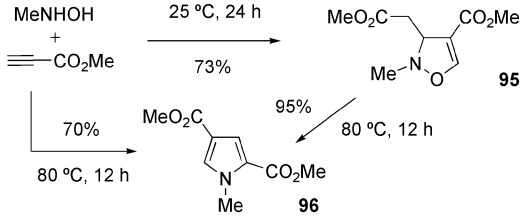
pattern involves thermal isomerization to 2-acylaziridines. The corresponding azomethine ylides generated by conrotatory aziridine ring opening can either undergo ring closure to oxazolines or undergo a proton shift followed by cyclization to afford pyrroles (Scheme 21). 4-Isoxazolines unsubstituted at C-3 usually provide exclusive formation of 4-oxazolines, whereas the rearrangements of 4-isoxazolines bearing a methyl or RCH_2 substituent at C-3 afford pyrroles.[1,2]

Baldwin et al. showed that the 4-isoxazoline **89** (Scheme 22) isomerized at 80 °C to the 4-oxazoline **90**. On the other hand, it was observed that the aziridine **92**, obtained directly from the reaction between the nitrone **91** and DMAD, undergoes thermolysis to give the 4-oxazoline **94**, presumably via the azomethine ylide **93** (NMR-monitored experiments).[44] The key intermediates in these reactions are therefore the acylaziridines, which undergo further rearrangement to give the 4-oxazolines.



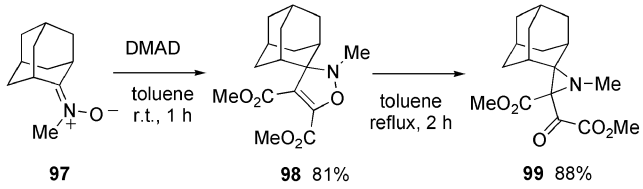
Scheme 22.

Padwa et al. studied the reaction between methylhydroxylamine and methyl propiolate (Scheme 23). The reaction of a 1:2 mixture of the two reactants at 25 °C for 24 h gave the 4-isoxazoline **95** in 73% yield. The process involves the generation of the nitrone in situ, followed by the 1,3-dipolar cycloaddition. When the reaction was carried out at 80 °C for 12 h, the *N*-methyl-1*H*-pyrrole **96** was obtained. The same pyrrole could be isolated in high yield from the thermolysis of the 4-isoxazoline **95** at 80 °C.[45]



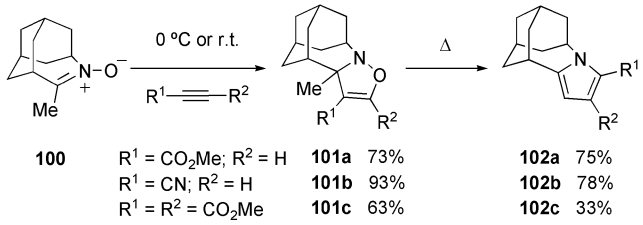
Scheme 23.

Georgiev et al. reported the isolation of an intermediate aziridine from a 4-isoxazole/pyrrole rearrangement. The thermolysis of the spiro[adamantane-4-isoxazoline] **98** (Scheme 24) gave the corresponding spiro[adamantane-aziridine] **99** in 88% yield. This result provides evidence that similar 4-isoxazole/pyrrole rearrangements proceed with an initial ring contraction to an aziridine ring.[46]



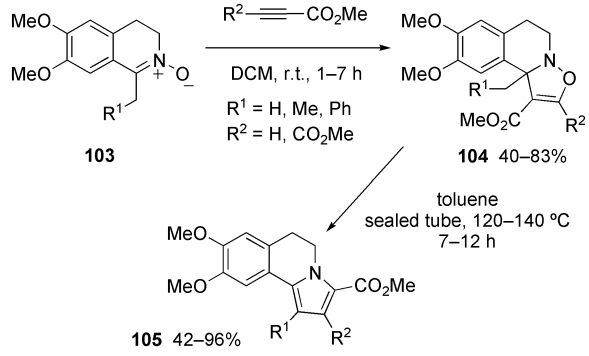
Scheme 24.

1,3-Dipolar cycloaddition reactions between nitrones incorporated in homoadamantane systems and electron-deficient alkynes proceed at or below room temperature to give the 4-isoxazolines **101** (Scheme 25). These cycloadducts were further converted into homoadamantane-fused pyrroles on heating in toluene.[47]



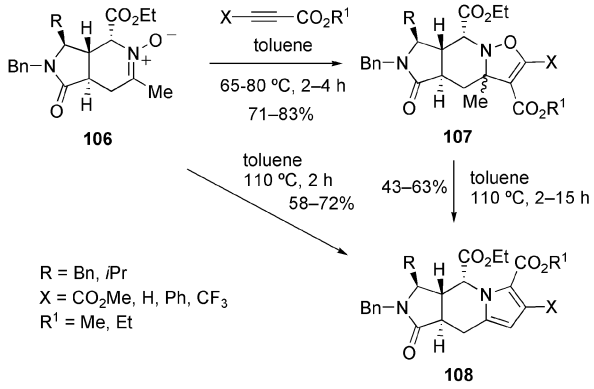
Scheme 25.

The synthesis of 4-isoxazoline and pyrrole derivatives fused to a 3,4-dihydroisoquinoline ring system has been reported. Cycloadditions between 3,4-dihydroisoquinoline *N*-oxide and alkynes provided the corresponding 1,3-cycloadducts (e.g., **104**; Scheme 26) and the sealed tube thermolysis of these 4-isoxazolines afforded the 5,6-dihydropyrrolo[2,1-*a*]isoquinolines (e.g., **105**).[48]



Scheme 26.

The thermolysis of the amino-acid-derived nitrones **106** (Scheme 27) in the presence of DMAD at temperatures in the 65–80 °C range produces the corresponding 4-isoxazolines **107**, whereas in toluene at reflux the pyrroles **108** are isolated as single enantiomers. The same pyrrole derivatives were obtained upon heating the 4-isoxazolines **107** in toluene at reflux.[49]

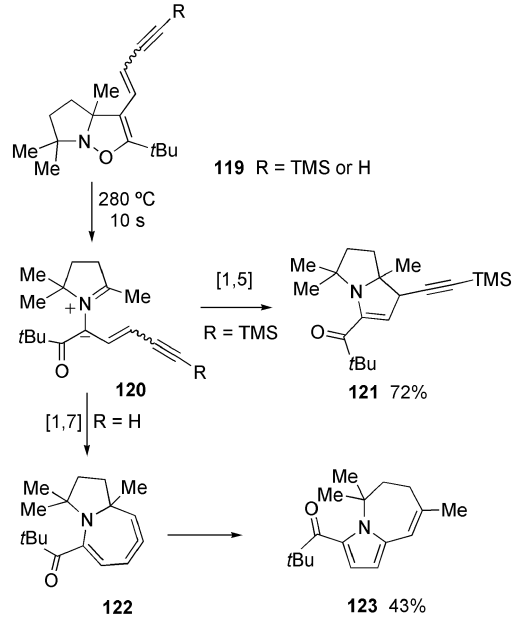


Scheme 27.

The azomethine ylides generated from 4-isoxazoles can be trapped by intramolecular 1,3-dipolar cycloaddition or can undergo 1,5- and 1,7-ring closure to give five- and seven-membered heterocycles. The 4-isoxazoline **110** (Scheme 28), obtained from the intermolecular 1,3-dipolar cycloaddition between the nitrone **109** and DMAD, is converted into the tricyclic compound **113** in 50% yield through the intramolecular cycloaddition of the azomethine ylide **112**.[50]

The reactivity of 4-isoxazolines bearing butadienyl groups (e.g., **114**, Scheme 28) under short-time thermolysis conditions (280–320 °C with a contact time of ca. 10 s) has been studied. Dihydroazepines are obtained as the major products, together with the formation of pyrroles. The process can be explained in terms of the involvement of intermediary azomethine ylides, which undergo 1,5- and 1,7-electrocyclization to give five-membered (e.g., **117** with loss of methane from **116**) and seven-membered heterocycles (e.g., **118**), respectively.[51]

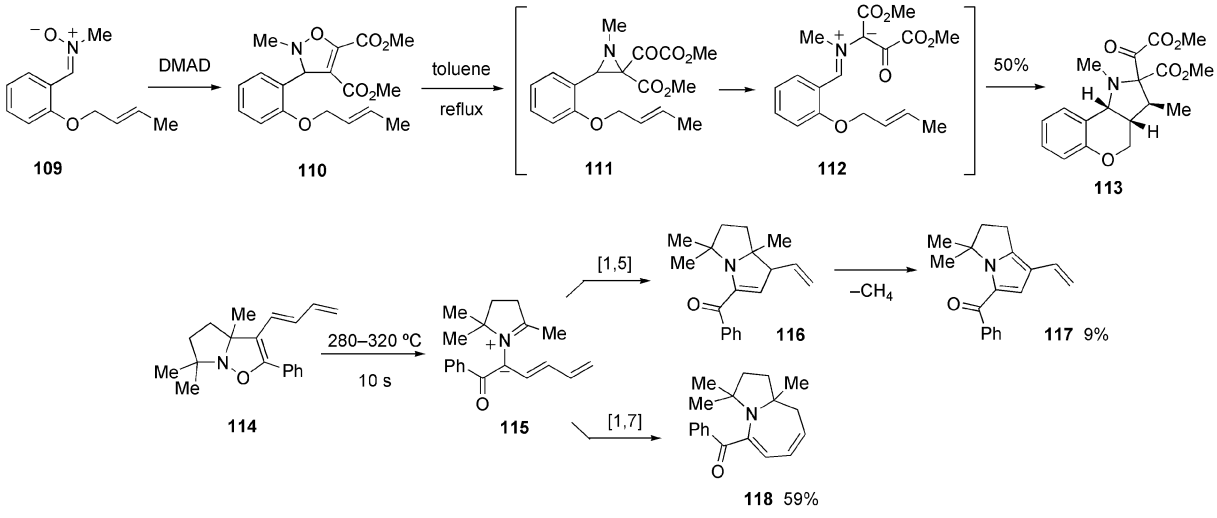
The reactivity of enynyl-substituted 4-isoxazolines has also been explored. The TMS derivatives (e.g., **119**, R = TMS; Scheme 29) undergo short-time thermolysis giving rise to annulated pyrrolines (e.g., **121**). In contrast, derivatives bearing a terminal alkyne (e.g., **119**, R = H) lead to bicyclic compounds (e.g., **123**). The 4-isoxazolines thus act as masked azomethine ylides, which undergo either 1,5-electrocyclization or 1,7-electrocyclization to give cycloallene intermediates followed by rearrangement to afford azepinopyrrole derivatives.[52]



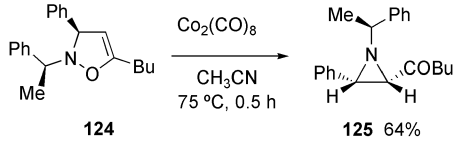
Scheme 29.

Ring contraction of 4-isoxazoles to 2-acylaziridines can also be achieved through a $Co_2(CO)_8$-promoted rearrangement[53] (Scheme 30). The optically pure isoxazoline **124** was converted by this methodology into the aziridine ketone **125** in a diastereoselective process.

Stable azomethine ylides (e.g., **129**, Scheme 31) have been prepared by photochemical excitation of annulated 4-isoxazoles. The proposed mechanism is based on the photochemically induced N–O bond cleavage to the correspond-



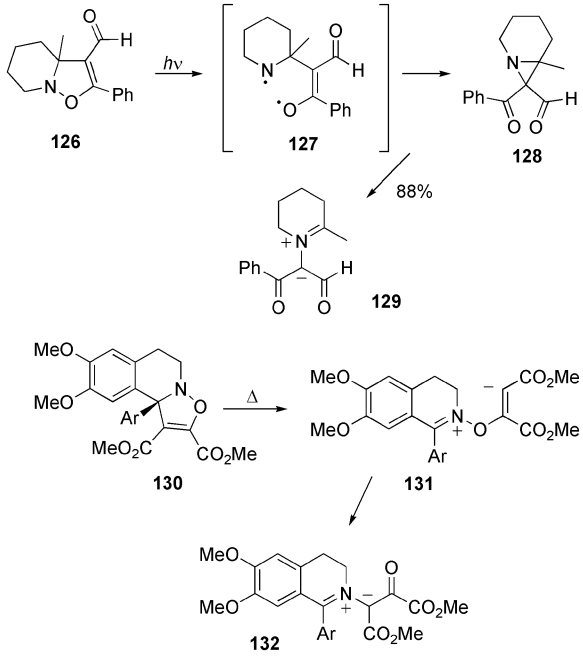
Scheme 28.



124 **125** 64%

Scheme 30.

ing diradical followed by bond reorganization to an aziridine, which undergoes C–C cleavage to afford the isolable azomethine ylide.[54,55]



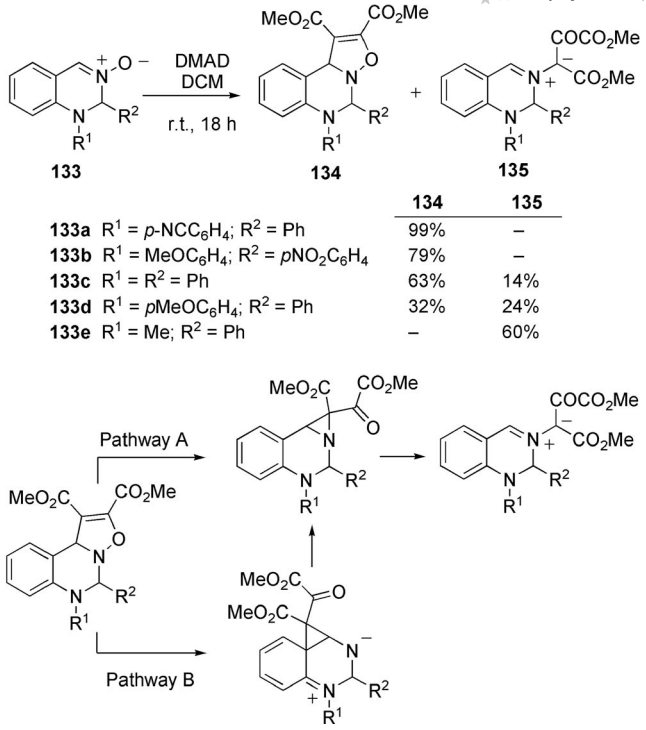
126 **127** **128** **129** **130** **131** **132**

Scheme 31.

The isoxazolo[3,2-*a*]isoquinolines **130** (Scheme 31) are also converted into stable azomethine ylides **132** upon heating.[56] However, the authors propose a mechanism involving consecutive C3–C4 bond heterolysis and 1,3-sigmatropic shift rather than the accepted mechanistic pathway involving acylaziridines as intermediates.

The reactivity of the 1,2-disubstituted 1,2-dihydroquinazoline 3-oxides **133** (Scheme 32) towards DMAD has been studied. The reaction outcome varied with the nature of the *N*-substituent. The dipoles **133a**–**133d** gave the corresponding 4-isoxazolines **134**, accompanied in the cases of **133c** and **133d** by the stable azomethine ylides **135**. The *N*-methyl derivative only gave azomethine ylide **135e**.

The rearrangement of 4-isoxazolines to azomethine ylides could occur in a concerted fashion by way of an acylaziridine intermediate (Pathway A, Scheme 32). However, with this interpretation it is difficult to explain the relative stability of the *N*-aryl-4-isoxazolines with respect to the *N*-methyl derivative. The authors thus proposed an alternative pathway (Pathway B) involving a cyclopropyl-fused intermediate as the aziridine precursor, which could account for the increased lability of the isoxazoline ring with increasing electron-releasing power of the *N*-substituent.[57]

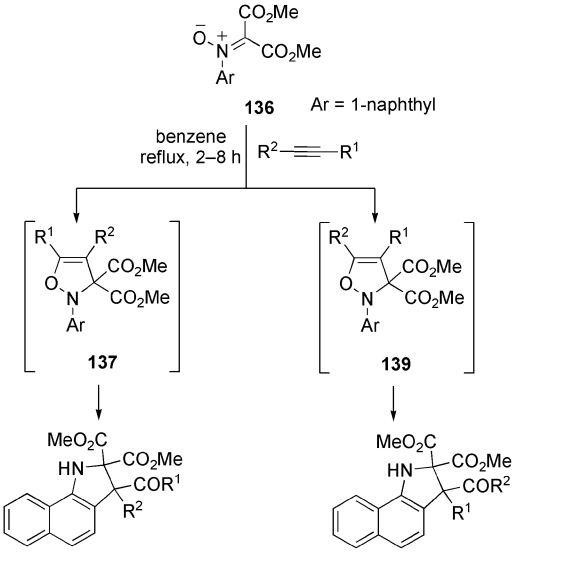


133 **134** **135**

	134	135
133a R^1 = *p*-NCC_6H_4; R^2 = Ph	99%	–
133b R^1 = $MeOC_6H_4$; R^2 = *p*-$NO_2C_6H_4$	79%	–
133c R^1 = R^2 = Ph	63%	14%
133d R^1 = *p*-$MeOC_6H_4$; R^2 = Ph	32%	24%
133e R^1 = Me; R^2 = Ph	–	60%

Scheme 32.

N-(1-Naphthyl)-*C*,*C*-dimethoxycarbonylnitrone (**136**, Scheme 33) reacts with acetylenes to give the 1*H*-benz[*g*]-indoline derivatives **138** in high yields. The synthesis of these heterocycles was interpreted in terms of the generation of the expected 4-isoxazolines as intermediates, followed by rearrangement to the final products. From the reactions between nitrone **136** and propiolates, compounds **140**, resulting from the regioisomeric 4-isoxazolines, were also isolated in low yields.[58]



136 **137** **139**

138a R^1 = R^2 = CO_2Me 89%
138b R^1 = Me; R^2 = CO_2Me 81%
138c R^1 = Ph; R^2 = CO_2Et 92%

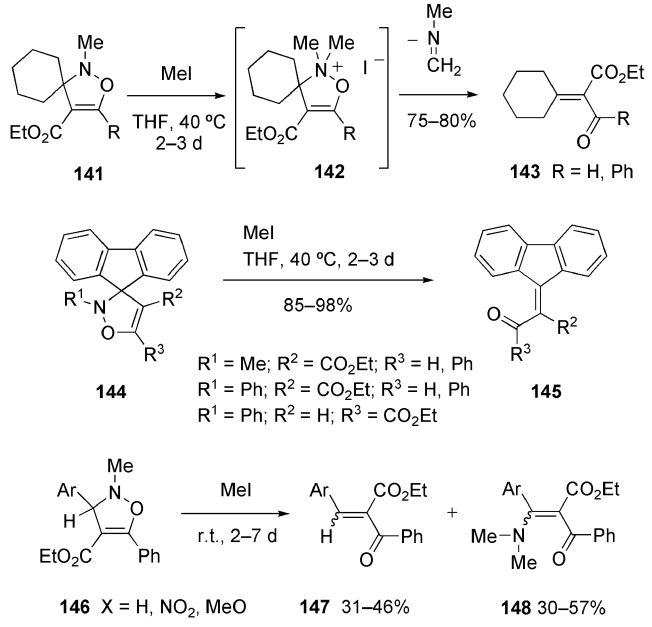
140a R^1 = Me; R^2 = CO_2Me 3%
140b R^1 = Ph; R^2 = CO_2Et 2%

Scheme 33.

3.2. 4-Isoxazolines as Building Blocks for Acyclic Compounds

N-Oxidation or quaternization of the nitrogen atom of a 2-substituted 4-isoxazole activates the system towards ring-opening reactions.

4-Isoxazoles react with iodomethane to form α,β-unsaturated ketones via isoxazolium salt intermediates.[59,60] In line with this observation, the thermolysis of the 3,3-disubstituted 4-isoxazolines **141** and **144** (Scheme 34) in THF at 40 °C with excess methyl iodide afforded the corresponding α,β-enones **143** and **145** in good yields.[55]

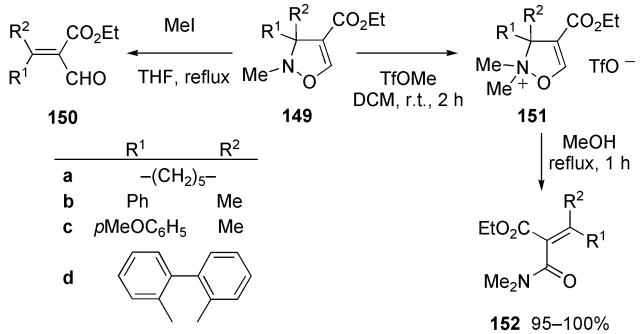


Scheme 34.

The presence of an abstractable hydrogen at the 3-position in the isoxazoline ring opens the way to a competitive reaction route with formation of enamino derivatives.[60] This can be illustrated by the reaction of the 4-isoxazolines **146** (Scheme 34), bearing abstractable benzylic hydrogen. These compounds react with iodomethane to give α,β-unsaturated ketones and enamines.

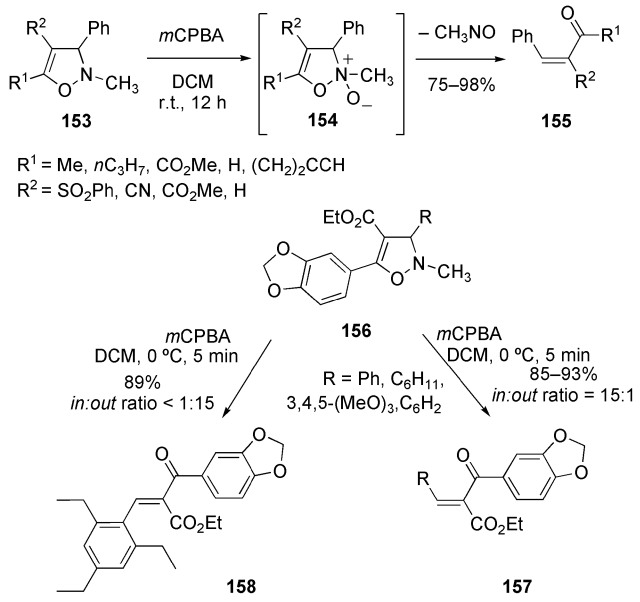
On the other hand, the 3,3-disubstituted 4-isoxazolines **149** (Scheme 35) are converted into the α,β-enals **150** upon treatment with MeI in THF at reflux. The quaternization of nitrogen in the 3,3-disubstituted 4-isoxazoles **149** to give the isoxazolium salts **151**, followed by thermolysis in MeOH, however, leads to the α,β-unsaturated amides **152** in high yields through solvent-assisted heterocyclic C3–N bond cleavage.[61]

Oxidation of the 4-isoxazole ring with *m*CPBA affords α,β-unsaturated carbonyl compounds with cheletropic extrusion of nitrosomethane (Scheme 36).[62–65] The 4-isoxazolines **153** are smoothly converted in high yields into the α,β-unsaturated ketones **155** upon treatment with the peroxyacid.[62,63] Houk et al. have demonstrated that the oxidation of 4-isoxazolines with *m*CPBA is followed by stereoselective cheleotropic extrusion of nitrosomethane at low



Scheme 35.

temperature to give "in" alkenes (e.g., **157**). The stereoselectivity is reversed, however, in the oxidation of 4-isoxazolines with a bulky group at C-3, leading to the synthesis of "out" alkenes as the major products (e.g., **158**).[64,65]



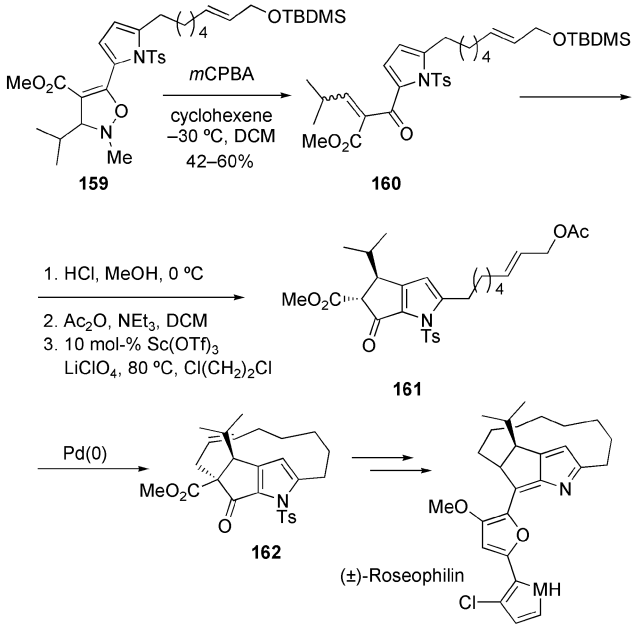
Scheme 36.

This reactivity feature of 4-isoxazolines has been used in the formal synthesis of (±)-roseophilin. The pyrrolyl vinyl ketone **160** (Scheme 37), prepared by oxidation of the 4-isoxazoline **159**, underwent Nazarov cyclization to give the 5,5′-fused keto pyrrole **161**. π-Allyl palladium macrocyclization afforded **162**, which can be converted into the target molecule.[66]

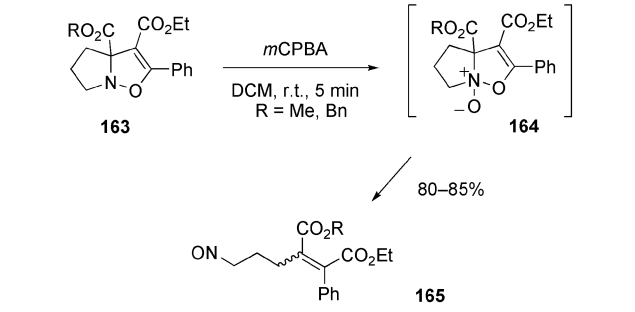
The proline-derived bicyclic 4-isoxazolines **163** (Scheme 38), each bearing a carboxylic substituent at C-3, afford the acyclic nitrosoalkyl-substituted α,β-unsaturated ketones **165** upon treatment with *m*CPBA.[67]

Reduction of 4-isoxazoles can lead to β-amino ketones or β-amino alcohols.[68–70] Hootelé et al. reported that β-amino ketones are obtained in good yields by hydrogenolysis in the presence of Pd/C in ethanol (e.g., **167**, Scheme 39).[68]

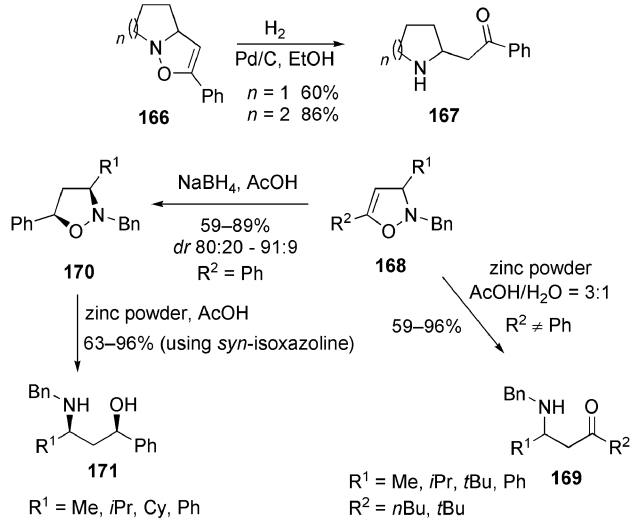
Hydrogenolysis of 4-isoxazolines has also been used to prepare β-amino ketones, which are key intermediates in



Scheme 37.



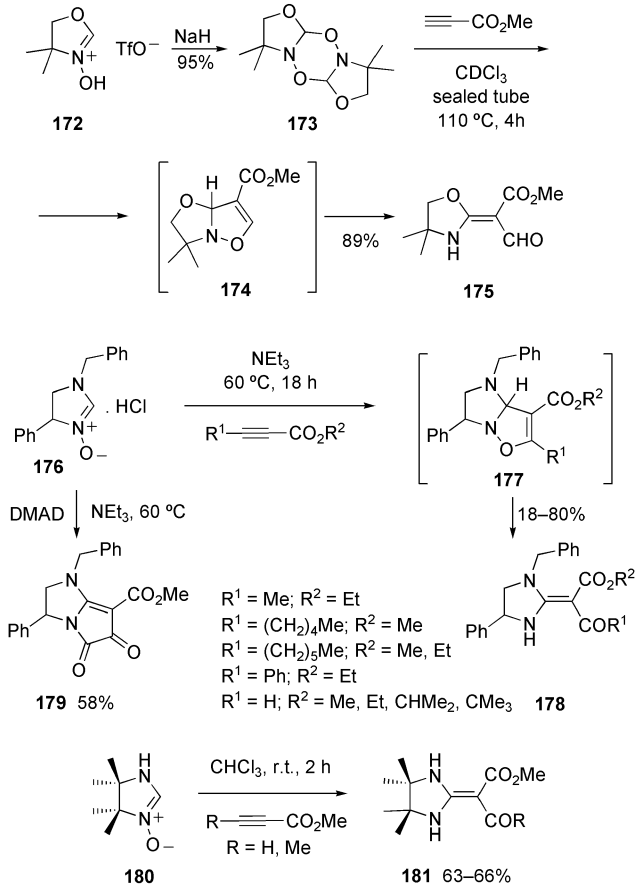
Scheme 38.



Scheme 39.

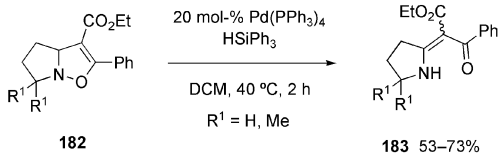
the reported synthesis of tetraponerine alkaloids.[69] The synthesis of β-amino ketones from the 4-isoxazolines **168** ($R^2 \neq$ Ph, Scheme 39) upon treatment with a suspension of Zn powder in glacial acetic acid has also been reported.[70] When 4-isoxazolines bearing a phenyl group at C-5 were subjected to the same reaction conditions, β-amino alcohols were obtained instead of β-amino ketones, although with limited scope. However, more efficient processes are observed on carrying out the reduction with sodium borohydride in acetic acid followed by N–O bond cleavage with Zn powder in acetic acid. This synthetic strategy leads to the diastereoselective synthesis of the *syn*-β-amino alcohols **171**[70].

4-Isoxazoles with a hydrogen at the 3-position can undergo a rearrangement involving cleavage of this C–H bond, together with N–O bond cleavage induced by the prototropic process, affording enamine β-carbonyl compounds.[71–73] The dimer **173** (Scheme 40), which in solution exists in equilibrium with the monomer, a *C*-alkoxynitrone, reacts with methyl propiolate to give the enamine β-carboxaldehyde **175** via the bicyclic 4-isoxazoline **174**.[72] On the other hand, the 2-imidazoline nitrone **176** (Scheme 40) reacts with propiolates to afford the ene-1,1-diamines **178** through rearrangement of the initially formed 4-isoxazoline cycloadducts **177**. In the presence of acetylenedicarboxylates as dipolarophiles, the nitrone **176** is converted into the 2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole-5,6-diones (e.g., **179**).[72] Similar chemistry can be carried out by starting with the 4,5-dihydro-1*H*-imidazole 3-oxide **180**[73].



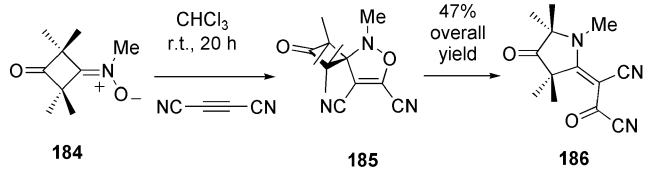
Scheme 40.

The $Pd(PPh_3)_4$-promoted N–O bond cleavage of proline-derived bicyclic 4-isoxazolines in the presence of silanes also furnished enamine β-carbonyl compounds (e.g., **183**, Scheme 41).[67]



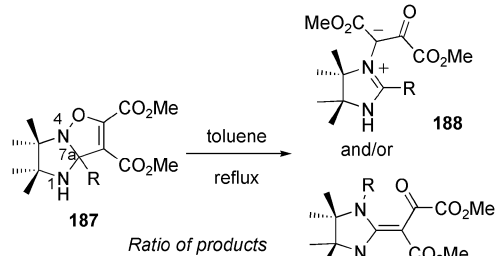
Scheme 41.

Alternatively, the cleavage of the N–O bond can be accompanied by the migration of a substituent from the 3-position of the isoxazole ring to the nitrogen atom.[73] Huisgen et al. described the rearrangement of the 4-isoxazoline **185** (Scheme 42) to the enamine β-carbonyl compound **186**, a process involving a ring expansion reaction.[74]



Scheme 42.

The reactivity pattern for the thermal rearrangement of the bicyclic 4-isoxazolines **187** is shown in Scheme 43.[75] The outcome of the reaction is determined by the nature of the C-7a substituent. When R is an alkyl group only the pathway leading to the ylides **188** is observed. On the other hand, a competing pathway is observed in the case of conjugated π-systems (Ar or CH=CHPh) involving the migration of the R group to N-4, with the formation of the ene-1,1-diamines **189**. With aryl groups such as phenyl or *p*-methoxyphenyl groups, both products are formed, whereas with *p*-dimethylaminophenyl or styryl groups exclusive formation of the ene-1,1-diamines **189** is observed.

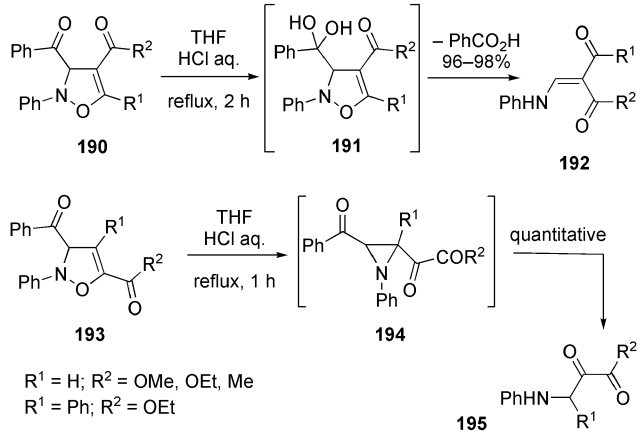


Ratio of products

R	188	189
Me	100	–
*t*Bu	100	–
p$NO_2C_6H_4$	100	–
Ph	85	15
p$MeOC_6H_4$	25	75
p$Me_2NC_6H_4$	–	100
CH=CHPh	–	100

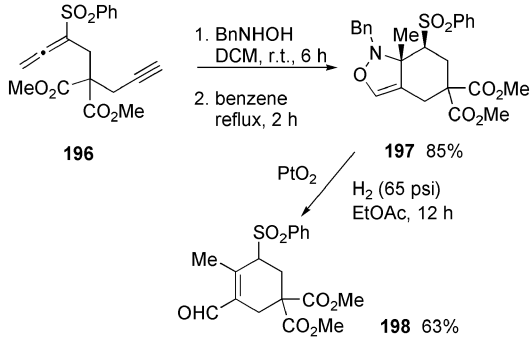
Scheme 43.

The acid-catalysed rearrangements of the regioisomeric 4-isoxazolines **190** and **193** (Scheme 44) lead to different outcomes, yielding the enamino derivatives **192** and the amines **195**, respectively. In the case of the 4-isoxazolines **190** the process involves the initial addition of water to the carbonyl group at C-3, providing benzoic acid as a good leaving group. The extended conjugation of the 4-acyl-4-isoxazolines stabilized the heterolytic N–O cleavage with 1,7-H migration. The cross conjugation in the N,O-vinyl system of **193** causes a lower electron density on C-4 of the 5-acyl regioisomer than in the 4-acyl derivative, making the reaction pathway to the enamine unfavourable. The 4-isoxazolines **193** are therefore converted into the amines **195** via aziridine intermediates.[76]



Scheme 44.

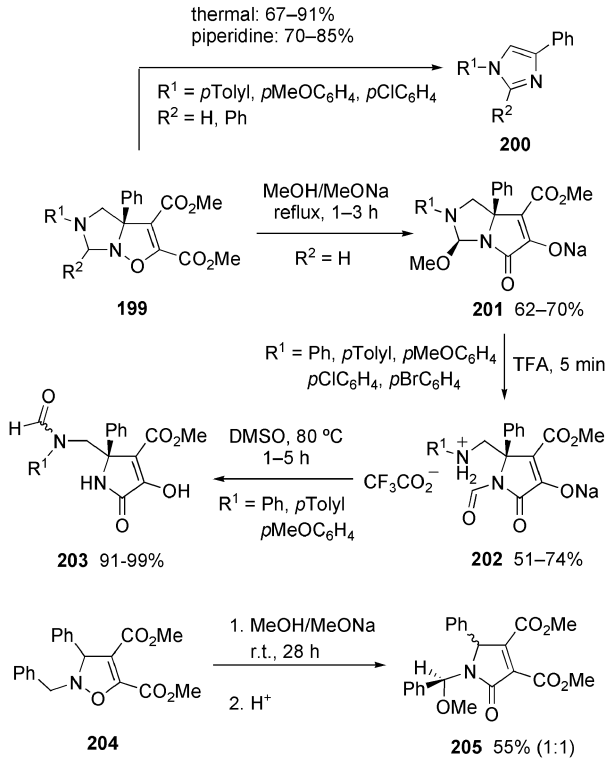
The acetylenic allene **196** (Scheme 45) reacts with benzylhydroxylamine to produce the 4-isoxazoline **197** in good yield. Catalytic hydrogenation of this heterocycle leads to N–O bond cleavage followed by benzylamine elimination and formation of the cyclohexenyl aldehyde **198**.[77]



Scheme 45.

The tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylates **199** (Scheme 46) undergo thermal or amine-induced ring-opening to give the imidazole derivatives **200**.[78,79] On the other hand, diastereoselective rearrangement of **199** in the presence of methoxide gives the tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-6-olates **201**. Acidic hydrolysis of these heterocycles followed by intramolecular transformylation affords the 2,5-dihydro-1*H*-pyrrole derivatives **203**.[80] A

similar rearrangement was observed when the monocyclic isoxazoline derivative **204** was treated with methoxide[81] (Scheme 46).



Scheme 46.

Conclusions

The reactions discussed in this review demonstrate that 4-isoxazoles are interesting building blocks for organic synthesis. Their readiness to undergo rearrangement reactions makes them suitable for use as building blocks for a range of cyclic and acyclic compounds. Pyrroles, oxazolines and aziridines are examples of heterocyclic compounds that can be obtained from the thermal rearrangement of 4-isoxazolines. The *N*-oxidation or quaternization of nitrogen in 4-isoxazoles activates the systems to undergo ring-opening reactions and provides routes to α,β-unsaturated carbonyl compounds and α,β-unsaturated amides. The reduction of 4-isoxazoles allows the synthesis of β-amino carbonyl compounds and β-amino alcohols. Acyclic compounds can also be obtained through thermal and base-induced rearrangement of 4-isoxazolines.

Despite the progress already achieved, the scope of 4-isoxazoline chemistry, as well as mechanistic studies on their rearrangements, still remains a field that warrants further exploration.

Acknowledgments

Thanks are due to the Fundação para a Ciência e a Tecnologia (FCT) (Project PTDC/QUI/64470/2006) and the Fundo Europeu de Desenvolvimento Regional (FEDER) for financial support.

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