Nitro and related compounds

Joseph P. Adams and David S. Box

Glaxo Wellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY

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Continuing the coverage in *Contemporary Organic Synthesis*, 1997, 4, 415

1 Introduction

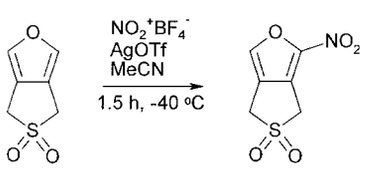
This review covers areas of current interest in the use of nitro compounds and related derivatives. It is complementary to two reviews published in *Contemporary Organic Synthesis*.[1] The research covered concentrates on new methodology, novel transformations and the intermediacy of nitro and related groups in the synthesis of biological targets.

2 Nitro compounds

2.1 Aryl nitro compounds

A wide variety of primary aromatic amines, incorporating electron donating or electron accepting substituents are oxidised by the action of *tert*-butyl hydroperoxide as oxidant, in the presence of the catalyst zirconium tetra-*tert*-butoxide, to the corresponding aromatic nitro compounds in 33–94%. The mild reaction conditions and commercial availability of the reagents make this an attractive method.[2]

1-Nitrofuranyl-3-sulfolene **2** has been prepared from furanyl-3-sulfolene **1** using the new nitration conditions of nitrosyl tetrafluoroborate and silver triflate in acetonitrile in 37% yield (Scheme 1). The substitution did not markedly reduce the performance of the furan moiety in subsequent Diels–Alder studies.[3]



1 **2**

Scheme 1

3-Nitrothiophene and other heteroaromatic nitro compounds have been synthesised by direct treatment of the corresponding organolithio or Grignard derivatives with dinitrogen tetroxide in 57–87% yields. The mechanism is believed to proceed by dinitrogen tetroxide oxidation of the anion to a radical, followed by the radical's combination with NO_2 (or N_2O_4).[4]

A new methodology for the synthesis of 3-nitropyridines, by dinitrogen pentoxide and a nucleophile (sulfur dioxide or sodium bisulfite) in tetrahydrofuran or nitromethane mixtures has been studied. The nitration proceeds *via* the *N*-nitropyridinium salt and subsequent reaction with an aqueous solution of the nucleophile to furnish the intermediate 1,4-dihydropyridine adduct which breaks down under the reaction conditions to the 3-nitropyridines in 7–68% yield.[5,6] Another approach to 3-nitropyridines is described in section 4.

The easily prepared dinitrogen tetroxide complexes of iron and nickel nitrates have been shown to selectively mono- or di-nitrate phenolic compounds in high yields. The process requires short reaction times and utilises simple work-up procedures to give the products in 62–100%.[7]

Lanthanide triflates have been used to catalyse the nitration of a range of simple aromatics with 69% nitric acid in an atom efficient process. The catalyst can be readily recycled and the only by-product is water.[8] However, the substrate range is limited to mildly electron deficient aromatics. Hydrated group IV metal triflates (*e.g.* Hf or Zr) also catalyse similar nitrations, with greater catalytic activity. Hence nitration of *o*-nitrotoluene has been achieved using a combination of the catalyst and 1 equivalent of nitric acid, giving approximately a 2 : 1 mixture of 2,6- and 2,4-dinitrotoluene in 92% yield and >95% conversion.[9]

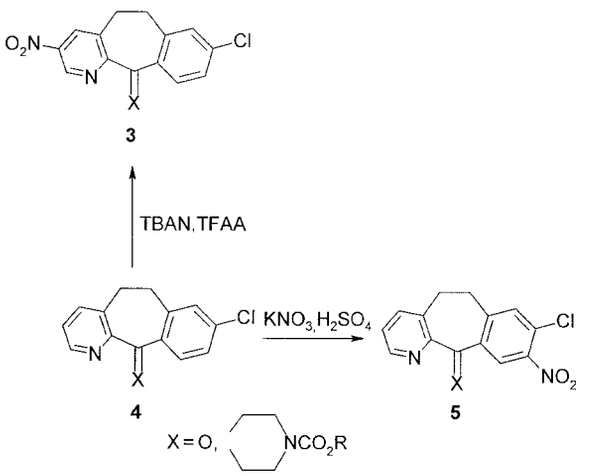
Various lanthanide nitrates have been used in the nitration of 3-substituted phenols to give regioselectively the 3-substituted 5-nitro derivatives. All the intermediates investigated had the oxygen of the phenol coordinated to the lanthanide(III) ion, and it is this effect that is thought to give the observed *meta*-selectivity in the nitration, irrespective of whether the substituent on the phenol is electron donating or withdrawing.[10]

The selective nitration of 4-hydroxybenzaldehyde to give the 3-nitro derivative has been achieved using iron(III) nitrate and a clay (dealuminated or natural) in quantitative yield. It is not necessary to support the iron(III) nitrate on the clay and it is suggested that the acidic nature of the clay acts in a catalytic role.[11]

A novel, mild system for the direct nitration of calixarenes has been developed using potassium nitrate and aluminium chloride at low temperature (0 °C). The side products of decomposition seen when using more conventional, harsher conditions, such as sulfuric acid–nitric acid mixtures, are not observed in this system and the *p*-nitrocalixarenes can be easily isolated in yields of 75–89%.[12]

Nitrating mixtures have been developed to selectively nitrate azatricyclic systems **4** in novel positions. Classical nitrations, using potassium nitrate and sulfuric acid gave mainly the 9-nitro derivatives **5**, *via* the nitrosyl cation. However, the use of tetrabutylammonium nitrate (TBAN) and trifluoroacetic

anhydride (TFAA) gives exclusively the 3-nitro compounds **3** (Scheme 2). It is suggested that the nitrating species in this case is the nitrosyl radical, generated from the homolytic decomposition of the TBAN/TFAA adduct. These 3-substituted derivatives have proved to be useful in the synthesis of potent farnesyl transferase inhibitors.[13]

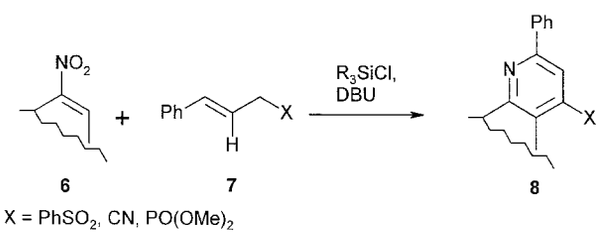


Scheme 2

Polynitrobenzene has been prepared from poly(*N*,*N*-dimethylaniline) by the action of nitric acid in acetic anhydride in 94% yield.[14]

Aryl nitro compounds are converted into *N*-monosubstituted formamides by the action of metallic tin and formic acid in toluene heated to reflux (26–86%).[15]

A silane mediated double condensation of nitroarenes **6** with allylic cations, formed from cinnamyl derivatives **7**, can be used for the synthesis of fused 6-membered nitrogen heterocycles **8**. Yields ranging from as low as 13% to as high as 87% have been obtained (Scheme 3).[16]



Scheme 3

The reductive cyclisations of 2-nitrobenzaldehydes (or 2′-nitroacetophenone) to 2,1-benzisoxazoles can be accomplished in the presence of 2-bromo-2-nitropropane and zinc in methanolic solution in yields of 38–98%.[17]

A low yielding (24%) synthesis of an indole utilizing the reaction of vinylmagnesium bromide with an arylnitro compound has been reported.[18]

A comparative study of the reaction time and yields of the nitration of selected heterocyclic compounds using microwaves and conventional heating has been reported. A range of inorganic nitrates in glacial acetic acid were investigated with copper(II) nitrate proving to be the superior reagent. In all cases the products were obtained in improved yields and in shorter reaction times using microwave radiation rather than those synthesised by heating. The procedure is cited as a safer and more convenient method for the nitration of heterocycles.[19]

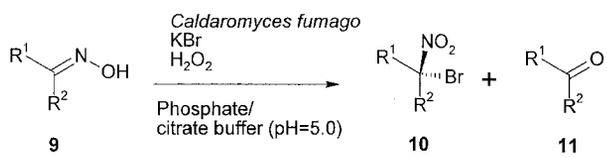
2.2 Alkyl nitro compounds

The oxidation of primary aliphatic amines has been achieved using the same catalyst system based on zirconium tetra-*tert*-butoxide and *tert*-butyl hydroperoxide on molecular sieves (50–98%) (*vide supra,* aryl nitro compounds).[20] C–H acidic nitro compounds are not epimerised under the mild reaction conditions.

A facile synthesis of fully saturated 2-nitrosugar derivatives from the corresponding amino derivatives utilises a *m*-chloroperbenzoic acid and sodium sulfate reagent system, giving the products in excellent yields (68–88%).[21]

A novel oxidation of a variety of oximes to nitroalkanes uses a molybdenum(VI) oxodiperoxo complex in acetonitrile to give the products in 50–92% yields. The only exception was fluoren-9-one oxime which gave the corresponding nitro derivative in only 25% yield, the main product being fluoren-9-one.[22]

The conversion of oximes **9** into halonitro compounds **10** has been performed in one-step using the chloroperoxidase isolated from the fungus *Caldaromyces fumago* in aqueous media in the presence of halide ions and hydrogen peroxide (Scheme 4). The reaction proceeds in 23–82% yield but is accompanied by the formation of the corresponding ketone **11**.[23]

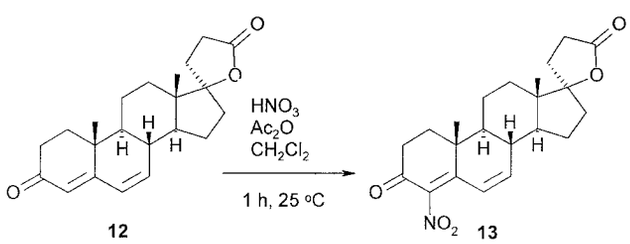


Scheme 4

The formation of a range of synthetically useful nitroalkenes has been achieved from the corresponding alkenes by their reaction with nitric oxide in the presence of zeolites with yields of 68–81%.[24] The use of the inexpensive zeolites also results in a simple work-up and ready separation of the products. The lack of corrosiveness and the ability to regenerate and re-use the catalyst make this an attractive system.

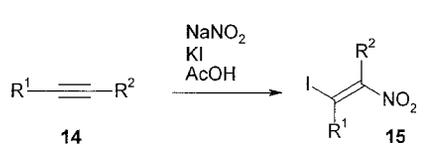
N-Hydroxyphthalimide has been shown to catalyse the nitration of adamantane, under an atmosphere of nitric oxide and dioxygen in benzonitrile.[25] In the absence of dioxygen the corresponding benzamide is formed.

Nitration of the steroid canrenone **12** using acetic anhydride with nitric acid occurs at the 4-position in 52% yield (Scheme 5). Most other reagent systems tend to react at the 6 position. The unexpected product **13** gave enhanced inhibitory activity against the target enzyme.[26]



Scheme 5

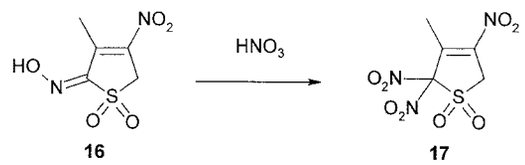
A facile, regioselective synthesis of the synthetically versatile α-iodo-β-nitroalkenes **15** from acetylenes **14** has been developed (Scheme 6) using sodium nitrate–potassium iodide mixtures. The method gives predominantly (*E*) products in 9–72% overall yield. This system is safer than the previously used, highly toxic mixture of iodine–dinitrogen tetroxide and the method can be applied to substituted and terminal alkynes.[27]



Scheme 6

A substituted 2,2,4-trinitro-2,5-dihydro-thiophene 1,1-dioxide **17** has been synthesised from the corresponding 2-oxime derivative **16** using nitric acid in 49% yield (Scheme 7).[28]

Primary nitroalkanes (or primary alkyl bromides) can be readily converted into the corresponding carboxylic acids in a novel transformation utilizing sodium nitrite in acetic acid–dimethylsulfoxide. Yields of the corresponding acids from 72 to 96% are observed.[29]



16 **17**

Scheme 7

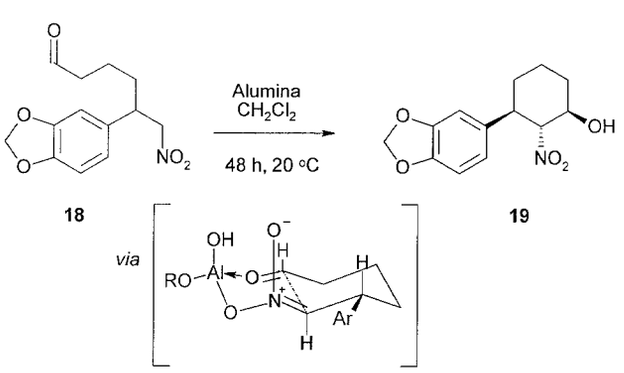
The oxidation of secondary nitro compounds to the corresponding ketones can be achieved in 52–89% using a catalytic amount of TPAP (tetrapropylammonium perruthenate) in combination with the co-oxidant *N*-methylmorpholine *N*-oxide and in the presence of silver acetate, potassium carbonate and 4 Å molecular sieves in acetonitrile.[30]

Primary nitro compounds are converted into nitriles in 51–86% yield by the action of a mixture of isocyanides with isocyanates in the presence of a base. The reaction is believed to proceed through an *in situ* formation of a nitrile oxide followed by fast oxygen transfer with the isocyanide.[31]

2.3 α- and β-Substituted nitro compounds

The nitroaldol (Henry) reaction has been performed with a variety of substrates in aqueous media to give yields of 66–94% in short reaction times. This system of sodium hydroxide and cetyltrimethylammonium chloride (CTACl) is applicable for large scale.[32] The methodology is compatible with several functional groups and has also been utilised in the conjugate addition reactions of nitroalkanes with electrophilic alkenes. Good yields (50–90%) are obtained, even with hindered substrates.[33]

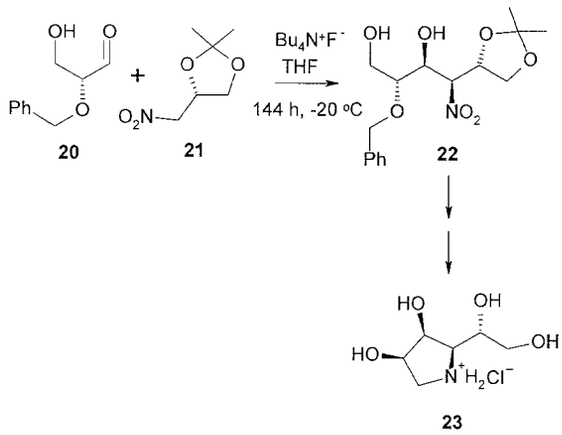
A diastereoselective modification of an intramolecular nitroaldol cyclisation has been used as the key-step in the synthesis of the C-ring of the valuable anti-tumour alkaloids pancratistatin and *trans*-dihydrolycoricidine. The desired nitroaldehyde **18** was cyclised in the presence of alumina to give the required diastereomer **19** with a diastereoselectivity of 90% de (Scheme 8), opposite to that seen in the base promoted case.[34] The mechanism is proposed to proceed *via* a chelation controlled chair-like 6-membered transition state.



18 **19**

Scheme 8

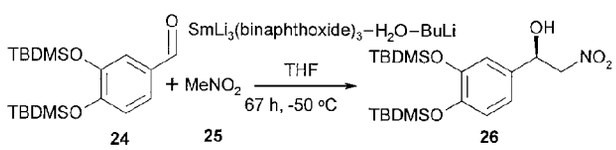
The key-step in the synthesis of 1,4-dideoxy-1,4-imino-D-mannitol (DIM) **23** and other amino analogues is the diasteroselective Henry reaction of either enantiomer of 2-*O*-benzylglyceraldehyde **20** with an optically active nitro compound **21** (Scheme 9).[35] This is a useful strategy for the synthesis of iminopolyols.



20 **21** **22** **23**

Scheme 9

A catalytic asymmetric nitroaldol reaction has been used to generate a key intermediate **26** in the synthesis of (*R*)-arbutamine, a pharmacological stress agent, in 93% yield and with an enantioselectivity of 92% ee (Scheme 10). The condensation of nitromethane **25** with a suitably protected benzaldehyde **24** is promoted by a heterobimetallic asymmetric catalyst, lanthanide lithium (binaphthoxide) (where the lanthanide is typically gadolinium or samarium).[36]

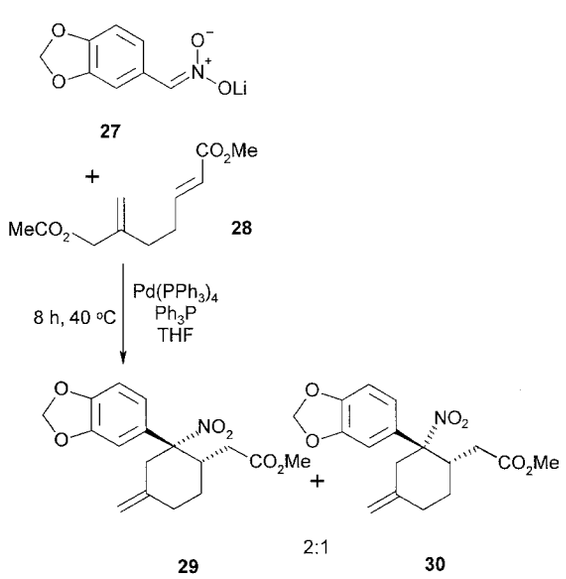


24 **25** **26**

Scheme 10

A new catalytic asymmetric approach to the Michael-addition of α-nitroesters to α,β-unsaturated esters has been developed using "Al-Li-(*R,R′*)-2,2′-dihydroxy-1,1′-binaphthyl" (AlLiBINOL) as a heterobimetallic chiral catalyst.[37] The synthetically useful products are produced in high yields (81–87%) with the enantioselectivity proving to be extremely dependent upon temperature and solvent.

Potential precursors **29** and **30** of *Erythrina* alkaloids can be assembled in a 6-membered annulation reaction, by sequential η^3-allylpalladium alkylation–Michael addition of a lithium nitronate **27** and diester **28** (Scheme 11).[38]

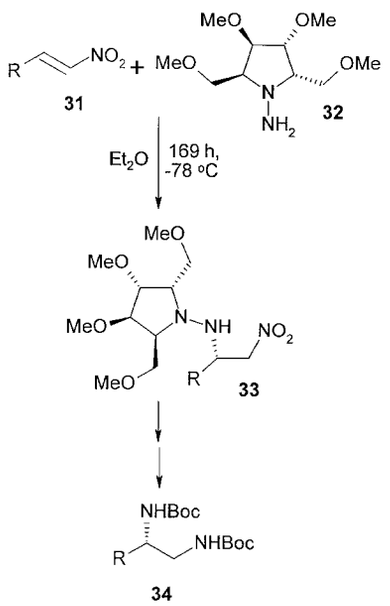


27 **28** **29** **30**

Scheme 11

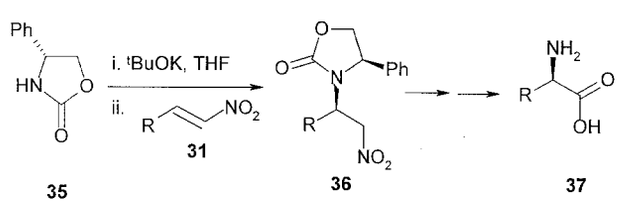
2.4 α,β-Unsaturated nitro compounds

Diastereo- and enantioselective syntheses of protected vicinal diamines **34** from α,β-unsaturated nitro compounds have been developed to give these synthetically useful compounds in 59–81% yields with high enantioselectivity (93–96% ee). The process proceeds *via* aza-Michael addition of a novel chiral ammonia equivalent **32** to nitroalkenes **31** (Scheme 12). The chiral auxiliary, a functionalised pyrrolidine, is removed by reductive N–N bond cleavage with Raney nickel, which also reduces the nitro group *in situ*.[39]



Scheme 12

In a similar strategy, a highly stereoselective conjugate addition of the potassium salt of (*R*)- or (*S*)-4-phenyl-1,3-oxazolidin-2-one **35** to various nitroalkenes **31** has been achieved.[40] The products of these additions **36** are useful precursors for the synthesis of D-α-amino acids **37** (Scheme 13), and can be easily converted to the corresponding amino acids in 6–99% yields with high enantiomeric purity (>95% ee).[41]

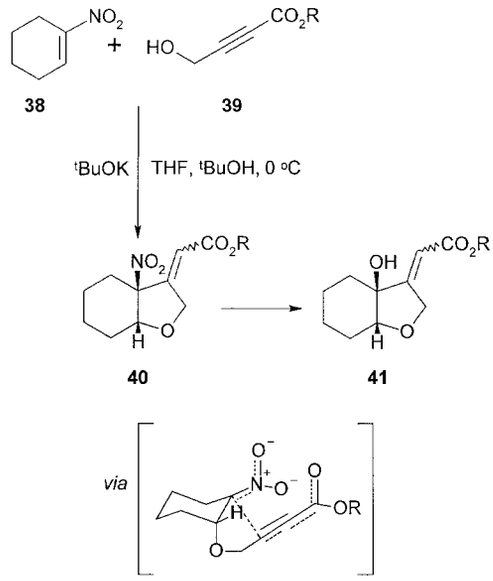


Scheme 13

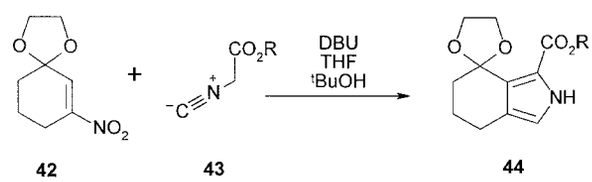
Octahydrobenzo[*b*]furans **41** have been constructed *via* tandem conjugate addition of 1-nitrocyclohex-1-ene **38** with 4-hydroxybut-2-ynoates **39** in 32–100% yields. The reaction is thought to proceed by an initial addition of alkoxide to the nitroalkene followed by a second addition of the resulting anion to the conjugated ester (Scheme 14).

Pyrroles **44** have been obtained by the cycloaddition of suitably functionalised α,β-unsaturated nitro compounds **42** and isocyanates or tosylmethyl isocyanide (TosMIC) **43** in 61–98% yields (Scheme 15).[43] The methodology affords trisubstituted pyrroles with electron withdrawing groups which are difficult to prepare directly from pyrroles. The pyrroles themselves are biologically useful compounds in their own right, and are useful intermediates for the preparation of porphyrins.

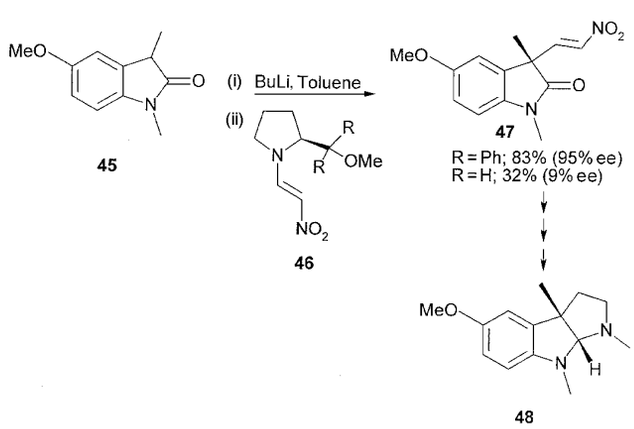
An improved method for the construction of an asymmetric quaternary carbon at the α-position of a lactone has been reported. Asymmetric nitro-olefination of α-methyl-γ-butyrolactone *via* an addition–elimination process of a chiral nitroenamine to the zinc enolate of the lactone, leads to (+)- and (−)-ethosuximide, pharmacologically active targets.[44] An extension of this work, focussing on 3-substituted 2-oxo-2,3-dihydroindoles **47**, leads to other interesting targets, notably (−)-esermethole, a precursor of the clinically important physostigmine, used to treat glaucoma. The steric bulk of the side chain on the nitroenamine **46** has a dramatic effect on the stereoselectivity of the nitro-olefination (Scheme 16).[45]



Scheme 14



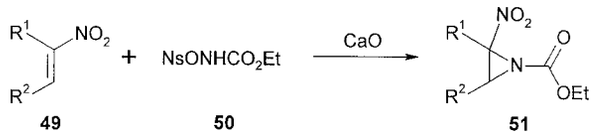
Scheme 15



Scheme 16

Various disubstituted α-nitroalkenes **49** can be converted into the corresponding aziridines **51** by the action of ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate **50**. The use of calcium oxide, in place of triethylamine, allows equimolar amounts of the reagent to be used in solvent-free, environmentally friendly conditions giving yields of 4–89% (Scheme 17).[46] It is noted that higher stereoselectivity, but poorer yields, can be achieved by thermolysis of ethyl azidoformate.

1,2-Diamines are conveniently prepared in a two step, one-pot procedure from nitro-olefins. The method initially



49 50 51

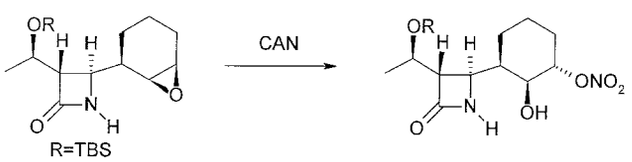
Ns = 4-nitrobenzenesulfonyl

Scheme 17

relies on a Michael addition of an *O*-alkylhydroxylamine to the nitro olefin followed by a reduction of the resultant α-nitrohydroxylamine species. This is conducted practically by treating the nitro olefin with *O*-alkylhydroxylamine hydrochloride and sodium hydrogen carbonate in tetrahydrofuran. Once the Michael addition is complete, palladium on carbon and ethanol are added and the resultant mixture stirred under an atmosphere of hydrogen. This one-pot procedure gives 1,2-diamines in 77–92% yield.[47]

3 Nitrate esters

A novel route to 4-alkoxytrinems has been devised using the intermediacy of the 4-nitrate ester as a "masked alcohol" (Scheme 18). The nitrate esters **53** were obtained by the regioselective opening of the corresponding epoxides **52** with ceric ammonium nitrate (CAN) in acetonitrile. Removal of the "nitro protecting group" by catalytic hydrogenation revealed the free hydroxy group at the end of the synthesis. This strategy was used because the direct opening of the epoxides was only successful with simple alcohols.[48]

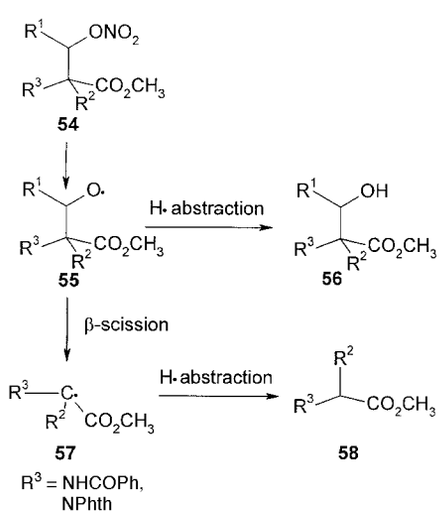


52 53

Scheme 18

The 11-nitrate esters of estrone acetates have been synthesised by CAN absorbed onto silica gel in yields of 24–39%.[49]

A study of the factors that influence the formation of α-carbon-centered amino acid radicals **57** has been reported. The radicals themselves are derived from the β-scission of β-alkoxy amino acid radicals **55** which are in turn formed by the action of tin hydrides on the corresponding β-nitrate esters **54** (Scheme 19). The rates of β-scission relative to the competing H-abstraction have been studied.[50] The new strategy could be used for the generation of radicals in peptides, where other methods would lack this regioselectivity.

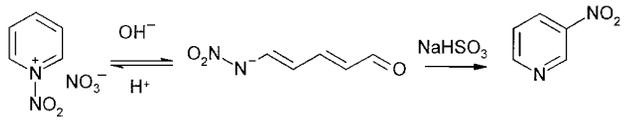


54 55 56 57 58

Scheme 19

4 Nitramines

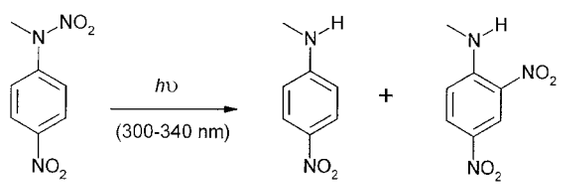
When *N*-nitropyridinium nitrate **59** is treated with sodium hydroxide then the stable sodium salt of 5-nitraminopenta-2,4-dienal **60** is formed. The reaction of this sodium salt with sodium bisulfite at pH 4 leads to the formation of 3-nitropyridine **61** (Scheme 20).[51]



59 60 61

Scheme 20

Photolysis of the nitramine **62** results in formation of the *p*-nitro-*N*-methylaniline **63** and *o*,*p*-dinitro-*N*-methylaniline **64** in approximately equimolar amounts (Scheme 21). The nature of the solvent and the presence or absence of oxygen influences the product composition range in photolysis of *N*-nitroso and *N*-nitro anilines.[52]



62 63 64

Scheme 21

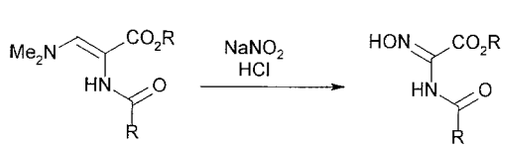
β-Nitroxyalkylnitramines have been prepared by the action of a mixture of sulfuric and nitric acids on the corresponding potassium sulfonamide salts.[53]

Dinitrogen pentoxide has been used in an inert solvent as a nitrating agent for silylamines (and silyl ethers). The resultant nitrodesilylation reaction leads to nitramines (and nitrate esters) in 37–91% yield. [**CARE!** The authors recommend the use of an armoured cupboard for these nitrodesilylation experiments].[54]

5 Nitroso compounds

A study on the nitrosation of simple aromatics has demonstrated the regioselective nature of the reaction in trifluoroacetic acid or acetic acid–sulfuric acid mixtures. The nitroso products can be simply oxidised to the corresponding nitro compounds, and hence provide a selective nitration method. The accompanying, non-selective nitrous acid catalysed nitration can be avoided by the use of nitric oxide as a purging gas.[55]

A novel method for the preparation of 5-substituted oxadiazole-3-carboxylates has been developed utilising the nitrosation of the corresponding 3-dimethylaminopropenoates **65** (Scheme 22). The resulting alkyl *N*-acyl substituted hydroximidic acids **66** afford the oxadiazoles on treatment with aqueous acid.[56]



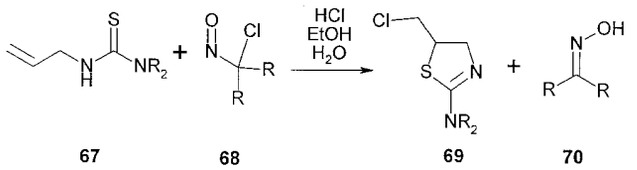
65 66

Scheme 22

Various arenesulfonyl hydrazines have been nitrosated by the new nitrosating agent sodium hexanitrocobaltate(III), $Na_3Co(NO_2)_6$, giving the corresponding azides in 60–96%

yields in aqueous solutions. Aromatic amines produced diaryltriazines (86–99%) but aliphatic amines were not nitrosated, the substrates forming a complex with the reagent.[57]

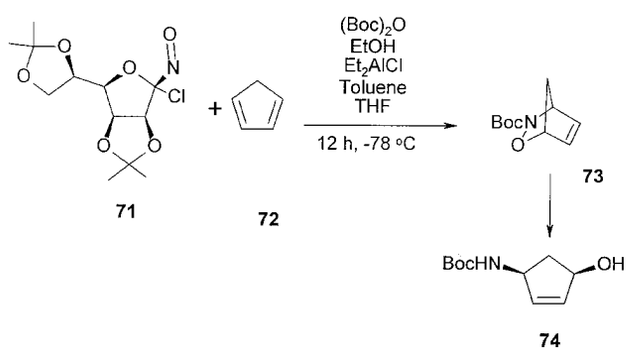
A synthesis of 2,5-disubstituted thiazolines **69** has been developed by the cyclisation of α-chloronitroso compounds **68** and *N*-allylthioureas **67**; oximes **70** are obtained as by-products (Scheme 23).[58]



67 68 69 70

Scheme 23

A novel, asymmetric synthesis of a synthetically useful amino alcohol **74** has been approached *via* the hetero Diels–Alder reaction of a chloronitroso compound derived from D-mannitol **71** and cyclopentadiene **72** (Scheme 24). The intermediate bicyclic compound **73** is produced in 64% yield with 84% ee, and is easily converted into the functionalised amino alcohol.[59]

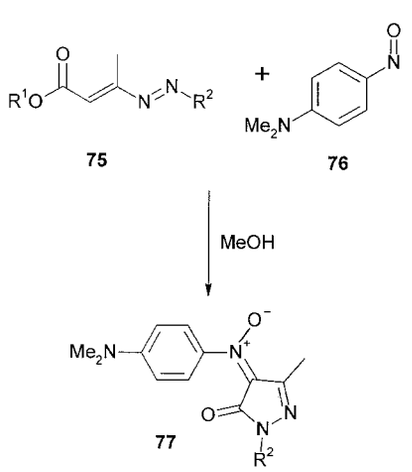


71 72 73 74

Scheme 24

The reaction of halogenated cyclopropanes with nitrosyl tetrafluoroborate furnishes the corresponding isoxazoles in good yields (43–97%). The presence of the halogen groups in the substrate leads to the formation of the fully aromatised products.[60]

The nucleophilic addition of nitroso compounds **76** to conjugated azoalkenes **75** generates the corresponding substituted pyrazol-5(4*H*)-ones **77** in one-pot, with yields of 52–93% (Scheme 25).[61]



75 76 77

Scheme 25

6 Nitrosamines

A new method for the hydrolysis of secondary amides to carboxylic acids uses a sequence of reactions based around *N*-nitrosation. Treating a polyfunctional amide with dinitrogen tetroxide leads to the nitrosamine. The nitrosamine is then treated with lithium hydroperoxide and reduced with sodium sulfite to give the carboxylic acid in 78% overall yield.[62]

N-Nitrosamides can be synthesised from the corresponding amide by a reaction with nitric oxide in aprotic and non-ethereal solvents in yields of 11–95%.[63]

7 Nitrones

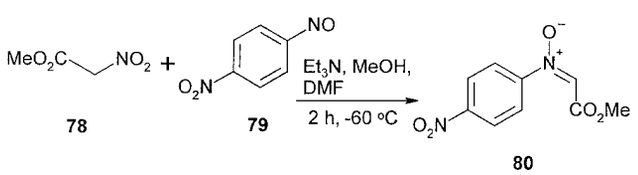
α-*N*-Diaryl nitrones have been synthesised from the Montmorillonite clay catalysed condensation of the respective aryl ketone and aryl hydroxylamines in 73–85% yields.[64] The reactions are very clean and the catalyst is easily recycled.

N-Butylidenebutylamine *N*-oxide has been synthesised by the electro-oxidation of the corresponding *N*-hydroxylamine. The system used consists of sodium tungstate–sodium bromide–di-H-sodium orthophosphate–dioxygen in water and is prepared in either divided or undivided cells with very high current efficiences (>180%).[65]

Nitrones have been generated in 69–93% yields from the corresponding aldimines by the photooxidation [6 W medium pressure mercury lamp] of a solution of the substrate in acetonitrile containing a titanium dioxide suspension.[66] Aldimines are formed from nitrones under reducing conditions, with retention of stereochemistry, when the system is purged of oxygen by nitrogen.

Secondary hydroxylamines can be selectively oxidised under mild conditions using polymer supported perruthenate. If dipolarophiles are present then isoxazolidines are produced in a one-pot process in 81–91% yields.[67]

The reaction of methyl nitroacetate **78** with 4-nitronitrosobenzene **79** has been demonstrated to effectively produce a *N*-(methoxycarbonylmethylidene)-*p*-nitrophenylamine *N*-oxide **80** in 67% yield (Scheme 26).[68]



78 79 80

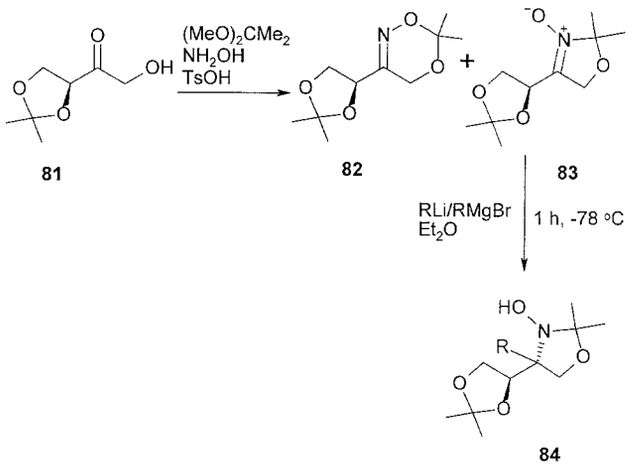
Scheme 26

Two discrete methods for the synthesis of chiral nitrones from the corresponding chiral *O*-protected α-hydroxy nitriles have been developed. The first involves the one-pot reduction–transimidation with a suitable hydroxylamine to give the aldonitrone in 82–99% yields with 97–99% ee. In the second, ketonitrones are produced by a one-pot Grignard addition–transimidation sequence (47–51% yield, 97–99% ee).[69]

The chiral, cyclic nitrone **83** is the minor component (30% yield) of the condensation of hydroxylamine, dimethyl acetonide and the isopropylidene derivative of L-erythrulose **81** *via* the (*Z*)-oxime (Scheme 27). The dioxazine **82** (35% yield) arises from the (*E*)-oxime. Organolithium and magnesium reagents add stereoselectively to the C=N bond of **83** and provide useful intermediates **84** for the synthesis of α,α-disubstituted α-amino acids.[70]

A mild method for the formation of C–N bonds has been developed *via* the ene reaction of nitrosocarbonyls with substituted olefins in yields of 10–99%. The nitrosocarbonyls are formed by the mild oxidation of the corresponding nitrile oxides.[71]

The trimethylsilyl triflate-promoted addition of a 2-silyloxyfuran to a nitrone, derived from glycolaldehyde, affords the synthetically useful tetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)-ones, after desilylation of the protected intermediate. These products can be modified to furnish polyhydroxylated lactams or piperidines, such as *rac*-fagomine.[72]

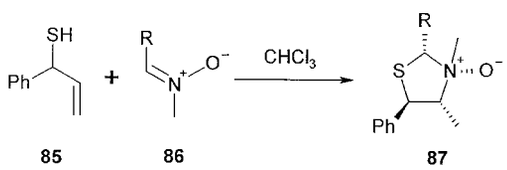


81 82 83 84

Scheme 27

Fully protected *N*-hydroxy α-amino esters have been synthesised in high selectivity in a stereodivergent process in which the key-step involves the addition of an acetylide to a nitrone. The *N*-benzyl nitrone, derived from isopropylidene-D-glyceraldehyde, undergoes the addition with high diastereoselectivity, and the subsequent hydroxylamines are converted into the desired products in three further, high yielding steps.[73]

The first direct route to 1,3-thiazolidine *N*-oxides **87** has been achieved by the reverse-Cope cyclisation of suitably substituted allylthiols **85** with nitrones **86** in 79–86% yields (Scheme 28).[74] Direct oxidation of thiazolidines normally results in the *S*-oxides.



85 86 87

Scheme 28

The regioselective [3 + 2] cycloadditions of nitroso compounds and substituted diazabutadienes or amidines afford highly functionalised cyclic nitrones in yields of 76–90%. The products can be thermolysed to imidazoles or amidines depending on the substitution pattern.[75]

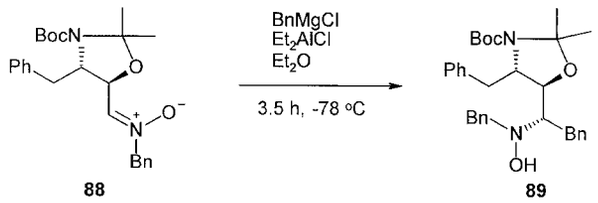
The asymmetric addition of alkyl zinc reagents to various nitrones has been achieved by the use of catalytic dicyclopentyl (*R*,*R*)-tartrate. The corresponding (*S*)-hydroxylamines are produced in good yields (84–95%) with high selectivity (63–94% ee).[76]

Stereo-complementary amino diols have been synthesised by the stereoselective addition of Grignard reagents to α-hydroxy nitrones. The use of zinc bromide and diethylaluminium chloride as precomplexing agents affords the corresponding *syn*- or *anti*- adducts respectively, which can be transformed into the required products.[77]

A similar, stereocontrolled addition of benzylmagnesium chloride to a nitrone **88** derived from phenylalanine using diethylaluminium chloride in diethyl ether gave a high yield (97%) of the desired *C*-benzylhydroxylamine **89** in excellent diastereoselectivity (94% de) (Scheme 29).[78] This product was then used as the 1,3-diaminopropan-2-ol core unit for HIV protease inhibitors.

A novel approach to β-amino acid derivatives has been developed *via* the reaction of an optically pure nitrone with a suitable ketene-acetal. (2*S*,3*S*)-*N*-Protected phenylisoserine has been synthesised using this strategy.[79]

Hydroperoxynitrones have been synthesised by a one-pot process with variable yields (20–80%). The reaction involves the tetraphenylporphyrin-sensitised photooxygenation of 2-methoxyfuran followed by the addition of an oxime to the



88 89

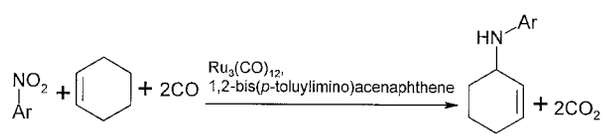
Scheme 29

resulting carbonyl oxide, the first reported addition of this kind.[80]

8 Reduction of nitro groups

A brief list of some new methods for the reduction of the nitro group is presented in Table 1. The reduction can be stopped at the hydroxylamine if borohydrides are used in conjunction with suitable catalysts (metallic antimony powder[81] or bismuth(III) chloride[82]), or it can be reduced to the amine. There are several new procedures which are generally mild, tolerate other functionality and proceed in high yields. These procedures include reductions in supercritical carbon dioxide[83] and the use of hydrazine hydrate[84,85] as the hydrogen source in addition to the use of hydrogen gas and a suitable catalyst.

A novel allylic amination of cyclohexene **91** has been shown to be catalysed by ruthenium complexes. Reduction of the aryl nitro compounds **90** to give the corresponding anilines is a competing reaction with yields of 22–77% of arylallylamine **93** contaminated with 15–42% of the aniline by-products (Scheme 30).[86]



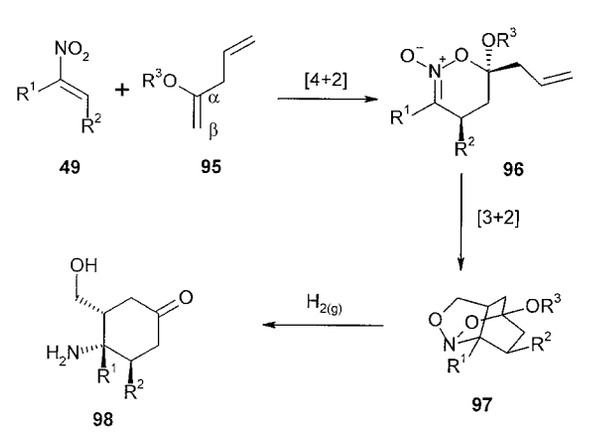
90 91 92 93 94

Scheme 30

9 Cycloadditions

9.1 Cycloadditions involving nitro groups

It is clear from Table 2 that one of the most successful uses of the nitro group in cyclisations is exemplified by the work of Denmark where a tandem [4 + 2]/[3 + 2] cycloaddition approach is used. Simple variations in the substituents on the nitroalkenes **49** and olefins **95** can lead to very different products *via* fused mode, spiro mode or bridged mode constructions. In the bridged mode (α-tether) case the inter [4 + 2]/intra [3 + 2] sequence may be followed by hydrogenation to give highly functionalised aminocyclohexanes **98** (Scheme 31).[95] A similar strategy with the β-tethered analogue leads to aminocyclopentanes **99**.[96]

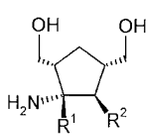


49 95 96 97 98

Scheme 31

Table 1 Reduction of nitro groups

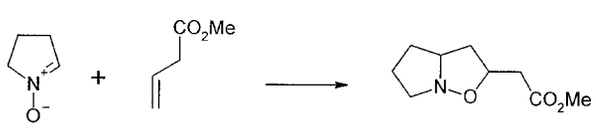
Starting material	Products	Comments	Ref.
Nitrohexane or nitroarenes	Amines	Mild procedure using diethyl chlorophosphite and a tertiary amine followed by treatment with hydrogen chloride in methanol with a subsequent work-up using sodium hydroxide. Yields are 20–95%.	87
Nitroarenes	Anilines	The Cp_2TiCl_2–samarium metal system provides mild and neutral conditions to synthesise anilines in 73–91%.	88
Nitroarenes	*N*-Arylhydroxylamines	Sodium borohydride in the presence of antimony cleanly provides hydroxylamines in 73–88% yields.	81
Nitroarenes	*N*-Arylhydroxylamines	Yields of 57–89% are obtained from this partial reduction using potassium borohydride–bismuth(III) chloride.	82
5-Nitro-1,3-benzodioxole	5-Amino-1,3-benzodioxole	Palladium–Deloxan and hydrogen gas in supercritical carbon dioxide results in a quantitative reduction.	83
Nitroarenes	Anilines	The zinc–aluminium chloride heptahydrate in tetrahydrofuran–water system provides a convenient and mild route to anilines in 75–95% yields.	89
4-Nitrophenol	4-Aminophenol	Reduction using 200 psi hydrogen over nickel supported catalysts at 110 °C in 85–94% yields.	90
Nitroarenes	Anilines	Reduction using hydrazine hydrate in the presence of iron(III) oxide–magnesium oxide catalyst. Yields are 96–100%.	84
Nitroarenes	Anilines	Activated nickel (prepared *in situ* by the reduction of nickel(II) chloride with potassium using ultrasound) in the presence of hydrazine hydrate accomplishes the reduction in 90–100% yields.	85
Nitroarenes	Anilines	A poly[*N*-(5-hydroxypentyl)pyrrole] film coated electrode incorporating palladium microparticles has been shown to be highly effective in electrocatalytic hydrogenation in 98–100% yields.	91
1,2-Dinitroaromatic	Quinoxaline	*In situ* reduction with Raney Nickel/hydrogen in the presence of the *bis*-bisulfite adduct of glyoxal resulted in the formation of the product in 79% yield.	92
6-(1-Cyanoalkyl)-5-nitropyrimidines	7-Alkyl-5*H*-pyrrolo[3,2-*d*]pyrimidines	A reductive cyclisation using sodium dithionite followed by hydrogenation on a palladium on carbon catalyst, leads to the formation of the products. If there are two alkyl groups attached to the cyanomethyl group then 6-amino-7,7-dialkyl-7*H*-pyrrolo[3,2-*d*]pyrimidines result.	93
o-Nitroaniline	Benzimidazol-2(3*H*)-one	An intramolecular reductive carbonylation with carbon monoxide under *ca.* 120 atmospheres pressure, in the presence of a solvent and a catalytic system (sulfur, or a low molecular weight derivative of sulfur, a basic medium and optionally a vanadium(v) compound). The rate of carbonylation increases with temperature and a yield of 86% is obtained after 4 h at 150 °C.	94



99

9.2 Cycloadditions involving nitrone groups

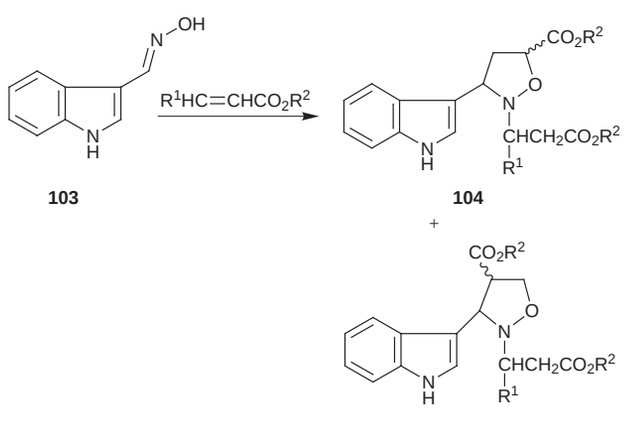
As seen from Table 3 the 1,3-dipolar cyclisation of nitrones onto olefins continues to be a tremendously powerful method for the synthesis of isoxazolines. When the nitrone **100** is part of a ring system then bicyclic systems **102** can be readily formed (Scheme 32). The 1,3-dipolar cycloadditions are usually performed by heating but alternative energy sources such as ultrasound or microwave radiation may also be employed. A comparison of these methods has been conducted by Prajapati, Sandhu and co-workers in a limited study.[107]



100 **101** **102**

Scheme 32

Indole-3-carbaldehyde oximes **103** act as Michael donors with electrophilic alkenes/alkynes affording isoxazolidines **104** and **105**, through a tandem nitrone generation–1,3-dipolar cycloaddition process. The highest yielding reaction gave 64% of the desired isoxazolidine (Scheme 33).[108]



103 **104** + **105**

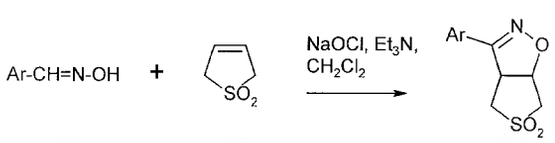
Scheme 33

Table 2 Nitro cycloadditions

Starting material	Product	Comments	Ref.
α-Nitroalkanes	6-Substituted 3,3a,4,5,6-pentahydrocyclopent[*c*]isoxazol-5-ylphosphates	Intramolecular silyl nitronate olefin cycloaddition in 45–66% yield.	97
(Fumaroyloxy)nitroalkene	(+)-Crotanecine (after further elaboration)	Lewis acid promoted tandem [4 + 2]/intra [3 + 2] cyclo-addition is the key step in the total synthesis.	98
1-Methylethyl 2-nitroethenyl but-2-enedioate	(−)-Platynecine	Tandem [4 + 2]/[3 + 2] cycloaddition of a nitroalkene with a vinyl ether in 40% yield.	99
Olefinic nitronates	Isoxazolines	Stereoselective one-pot consecutive Michael addition–1,3-dipolar cycloaddition strategy.	100
Siloxynitroalkene	(−)-Detoxinine	Tandem [4 + 2]/[3 + 2] cycloaddition is the key step in this total synthesis.	101
Functionalised nitroalkene	(−)-Mesembrine	Construction of the octahydroindole framework of mesembrine features a tandem inter [4 + 2]/intra [3 + 2] cycloaddition.	102
Nitrostyrene or 1-phenyl-2-nitropropene	5,6-Dihydro-4*H*-1,2-oxazine *N*-oxide, hexahydroisoxazolo[2,3-*b*][1,2]oxazine and tetrahydro-4*H*-furo[3,2-*e*][1,2]oxazine *N*-oxide	High pressure promoted three component one-pot tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes with enol ethers.	103
Nitroalkenes	Functionalised aminocyclopentanes	Tandem [4 + 2]/intra [3 + 2] cycloaddition as the key step.	96
Chiral carbohydrate nitroalkene	Bicyclic system	Asymmetric tandem cycloaddition of a chiral carbohydrate nitroalkene with ethyl vinyl ether in the presence of an alkene possessing electron withdrawing groups.	104
2-Nitroalkene (bearing an unsaturated ester)	Azapropellanes	The spiro mode of the tandem inter [4 + 2]/intra [3 + 2] cycloadditions.	105
Nitroethylene	(+)-Macronecine and (+)-petasinecine	Inter [4 + 2] cycloaddition with a vinyl ether followed by an inter [3 + 2] cycloaddition with an electron deficient alkene.	106

9.3 Cycloadditions involving nitrile oxide groups

Nitrile oxides provide ready access to oxazolines *via* inter- or intramolecular nitrile oxide cycloaddition (INOC) with olefins (Table 4). The nitrile oxides are usually prepared *in situ* from the corresponding nitro compound by the action of an isocyanate in the presence of an amine base (*e.g.* triethylamine). A variety of dehydration agents have also been successfully employed for the conversion of nitro to nitrile oxides (Burgess salt, DAST, acetic anhydride and oxalyl chloride).[140] Nitrile oxides have also been prepared from the action of aqueous sodium hypochlorite on oximes. One example of the INOC procedure has been used to prepare 2-isoxazoline intermediates from aryl aldoximes **106** in the synthesis of 3-arylthienoisoxazoledione **108** (Scheme 34).[141]



106 **107** **108**

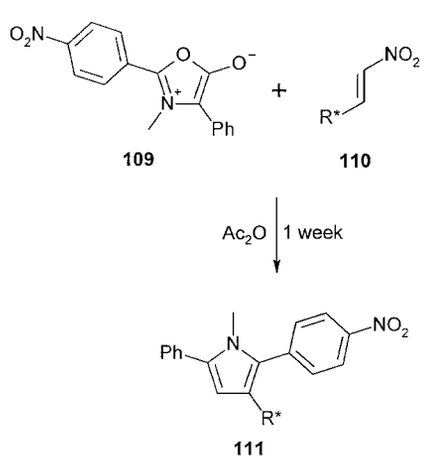
Scheme 34

10 Miscellaneous

A novel dipolar cycloaddition of the munchnone 3-methyl-2-(4-nitrophenyl)-4-phenyl-1,3-oxazolium-5-olate **109** with chiral nitroalkenes **110** derived from D-galacto- or D-manno-hept-1-enitols proceeds to give pyrrole *C*-nucleosides **111** in satisfactory yields (65–69%) (Scheme 35).[165]

Nitro heteroaromatic compounds (quinoxalines, benzathiadiazoles and benzaselenadiazoles) react with ethyl isocyanoacetate in the presence of DBU (1,8-diazabicylo[5.4.0]-undec-7-ene) to give the corresponding pyrimidine *N*-oxides in 15–32% yields. Changing the base from DBU to stronger non-nucleophilic bases (proazaphosphatane or iminophosphorane) resulted in the formation of pyrroles (30–46% yield).[166]

Novel transformations of the imidazole ring in 1-alkyl-4-nitroimidazole and 1-aryl-4-nitroimidazole following nucleophilic amination by hydroxylamine or 4-amino-1,2,4-triazole result in the formation of 3-substituted-5-alkyl/aryl-oxa-2,4-diazole ring systems in 40–87% yields.[167]



109 **110** **111**

Scheme 35

In a synthetic approach to 13-azasteroids **114** an intramolecular reductive cyclisation of a nitro group onto a ketone resulted in the formation of a conjugated nitrone **113.** This was then able to undergo a thermally induced 1,7-cyclization followed by a multistep rearrangement of the primary cycloallenic intermediate to give the corresponding 13-azasteroid **114** (Scheme 36).[168]

An improved synthesis for 1-hydroxy-4-nitro-6-trifluoromethylbenzotriazole has been demonstrated using the action of hydrazine hydrate on 1-chloro-2,6-dinitro-4-trifluoromethylbenzene in 64% yield. Similarly 1-hydroxy-4,6-dinitrobenzotriazole can be prepared from 1-chloro-2,4,6-trinitrobenzene although a reduced yield of 50% is obtained.[169]

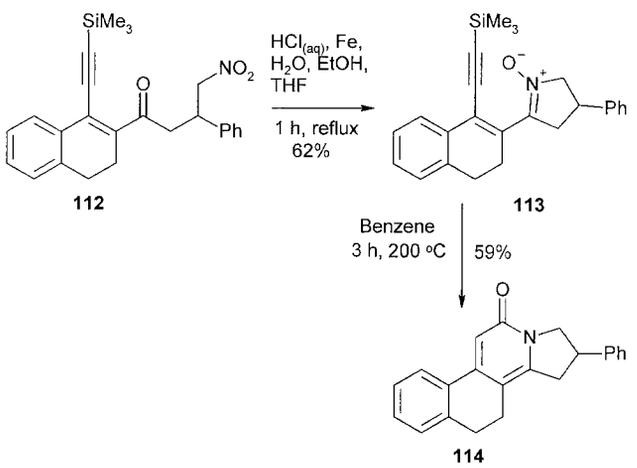
A one-pot synthesis of the benzoxazinecarboxylic acid **116**, an intermediate for the antibacterial agent Levofloxacin, from

Table 3 Nitrone cycloadditions

Starting material	Product	Comments	Ref.
Nitroalkanes	Isoxazoline fused C-60 derivatives	First example of a nitrone cycloaddition onto (60)fullerene in 42% yield.	109
Cyclic nitrone	Bicyclic isoxazolidine	1,3-Dipolar cycloaddition of chiral acrylates derived from 9-anthrylcarbinol to a cyclic nitrone (major product 52%, 4 diastereomers).	110
Chiral nitroalkane	Antifungal agent SCH-38516	1,3-Dipolar cycloaddition with maleic anhydride is the key step in this total synthesis.	111
Nitroalkane	*N*-Protected (4*S*)-4-hydroxy L-glutamic acid diester	Asymmetric 1,3-dipolar cycloaddition of a nitroalkane with a chiral enone stereoselectively provides an isoxazolidine with the desired stereochemistry.	112
Arylaldoximes	Perfluorinated isoxazolines and isoxazoles	1,3-Dipolar cycloaddition with fluorinated olefinic and acetylenic compounds in the two phase medium of chloroform–aqueous sodium perchlorate. Cyclised products are obtained in 70–85%.	113
N-Benzylidenephenylamine *N*-oxide	Primarily the *exo*-isoxazolidine	Ti-TADDOLate catalysed cycloaddition. The structure of the reactive intermediate is discussed.	114
δ- or ε-Unsaturated nitrones	Bicyclic isoxazolidines	Intramolecular 1,3-dipolar cycloaddition of nitrones to allylsilanes.	115
Cyclic nitrones	Bicyclic isoxazolidines	Asymmetric nitrone–vinyl sulfoxide cycloadditions.	116
α-Substituted cyclic nitrones	Pyrrolo[1,2-*b*]isoxazoles	Highly stereospecific 1,3-dipolar cycloaddition of cyclic nitrones with acetylenes.	117
(*S*)-5-Hydroxymethyl-1-pyrroline *N*-oxide	Isoxazolidines	The cyclic nitrone was prepared from L-(+)-prolinol with dimethyldioxirane. Complete diastereoface differentiation in the 1,3-dipolar cycloaddition is observed with several 1,2-disubstituted electron deficient olefins.	118
N-Benzylidenephenylamine *N*-oxide	Carboxamides	Improvement of the TADDOLate-titanium(IV) chloride catalysed 1,3-dipolar nitrone cycloaddition reactions by substitution of the oxazolidinone auxiliary of the alkene with succinimide. Yields of 38–76% are obtained with an *exo*:*endo* ratio of 64:36 to 95:5.	119
Various nitrones	Isoxazolidines	Asymmetric 1,3-dipolar cycloaddition reactions with chiral trifluoromethylated α,β-unsaturated arylsulfones with nitrones (58–80% yields).	120
Various nitrones	Isoxazolidines	Microwave induced 1,3-dipolar cycloaddition reactions of nitrones with styrene in yields of 76–90%.	107
Nitrones possessing an electron withdrawing group	Isoxazolidines	The asymmetric 1,3-dipolar cycloaddition of nitrones possessing electron withdrawing groups to allyl alcohol was achieved using (*R,R*)-tartrate as a chiral auxiliary.	121
N-Benzyl-α-methoxycarbonylmethanimine *N*-oxide	(−)-Bulgecinine	A short synthetic route to (−)-bulgecinine was established using a 1,3-dipolar cycloaddition of the nitrone with an allylic alcohol.	122
Various *N*-alkyl and *N*-aryl nitrones	Borane ester substituted isoxazolidines	Alkenyl boronic esters undergo regio- and stereoselective 1,3-dipolar cycloadditions with nitrones in 45–83% yields.	123
N-Benzylidenephenylamine *N*-oxide	Isoxazolidines	An examination of the hydrophobic effect on 1,3-dipolar cycloaddition reactions (45–95% yields).	124
Various nitrones	4′-Azaerythrofuranosyladenines	[3 + 2] Dipolar cycloaddition of nitrones to *N*-9-vinyladenine (5–77% yields).	125
C-Arylnitrones	Isoxazolidines	Ytterbium(III) triflate catalyses the 1,3-dipolar cycloaddition and gives the highest *endo*-selectivity. Scandium(III) triflate shows the highest rate accelerations. Chiral ligands result in moderate enantioselectivities (up to 73% ee).	126
C-Alkyl- or *C*-aryl-*N*-methylnitrones	Pyrrolidine *N*-oxides	Sequential condensation of α-lithiosulfones with nitrones to give unsaturated hydroxylamines followed by reverse Cope-elimination (68–95% over the two steps).	127
N-Allylcarbohydrate nitrones	Isoxazolidine containing heterocycles	Chiral 6- and 7-membered nitrogen containing heterocycles *via* intramolecular *N*-allyl nitrone cycloaddition (78–85%).	128
Secondary 3-oxahex-5-en-1-ylamines	Bicyclic heterocycles	Intermolecular 1,3-dipolar cycloaddition of nitrones onto allyl groups. The nitrones are prepared from secondary amines by the action of sodium tungstate and hydrogen peroxide.	129
Various nitrones	2-Oxa-3-azabicyclo[3.2.0]heptanes	Electrogenerated 1-sulfonylcyclobutenes undergo 1,3-dipolar cycloadditions to nitrones in 50–82% yields.	130
α-Alkoxy cyclic nitrones	Bicyclic isoxazolidines	Facial-, regio- and stereoselective cycloadditions with alkenes in 55–90% yields.	131

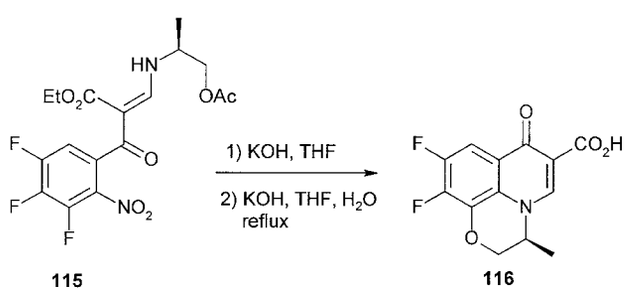
Table 3 (*Contd*)

Starting material	Product	Comments	Ref.
N-Methylhydroxylamine hydrochloride	Tetrahydropyrans and oxepanes	Intramolecular nitrone–alkene cycloaddition of acyclic 3-*O*-allylmonosaccharides (41–55% yields).	132
N-Benzylnitrone derived from D-glyceraldehyde	3-Substituted isoxazolidin-5-one	Quantitative yield of the [3 + 2] dipolar cycloaddition product obtained from the nitrone reaction with the sodium enolate of methyl acetate.	133
N-(Hydroperoxyalkyl)nitrones	2-(Hydroperoxyalkyl)-2,3-dihydroisoxazoles	Reaction of nitrones with electron deficient alkynes to give the products in good yield (30–90% yields).	134
N-Benzylidene-*N*-cyclohexyl-*C*-homoallylnitrone	*trans*, *trans* 2-Phenyl-4-hydroxy-1-azaspiro[5.5]undecane	Intramolecular [3 + 2] cycloaddition of the nitrone with the alkene in 83% yield followed by reductive cleavage of the N–O bond with zinc in acetic acid in 76% yield.	135
Pyrroline *N*-oxide	Spiro[cyclopropane-1,5′-isoxazolidines]	2-Chloro-2-cyclopropylideneacetates undergo a 1,3-dipolar cycloaddition reaction with nitrones in 70% yield.	136
Immobilised nitrones	Isoxazolidines	Hydroxylamines bound to a Rink amide resin are condensed with aldehydes to give nitrones which are then trapped with various dipolarophiles. *endo* : *exo* selectivity is 3 : 2.	137
N-Benzylidenephenylamine *N*-oxide	Isoxazolidines	[3 + 2] cycloaddition of phenylnitrone with dec-1-ene to give the desired isoxazolidine in 89% yield (with the undesired *trans* product in 3%).	138
δ,ε-Unsaturated nitrones	Fluoromethyl substituted bicyclic isoxazolidines	Intramolecular [3 + 2] cycloaddition as a technique to provide enantiomerically pure fluoromethyl substituted β-amino acids.	139



Scheme 36

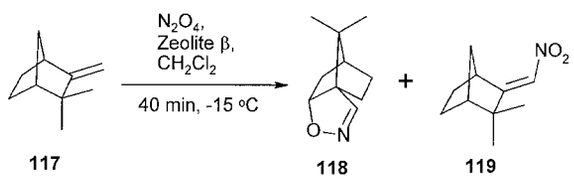
a nitrobenzoylacrylate **115** can be accomplished in 92% (Scheme 37). This one-pot sequence occurs after an addition of powdered potassium hydroxide in THF to induce the intramolecular displacement of the nitro group by the vinyl amine to form a quinoline intermediate. This is followed by the addition of an aqueous solution of potassium hydroxide to hydrolyse the acetate and induce a second cyclisation to form the desired intermediate **116**.[170]



Scheme 37

A synthesis of 2-methyl-5-(methylthio)benzothiazole from the action of acetic anhydride on 1-chloro-2-nitro-4-methylthiobenzene in the presence of sodium sulfide in acetic acid and water gives the cyclized product in 67% yield.[171]

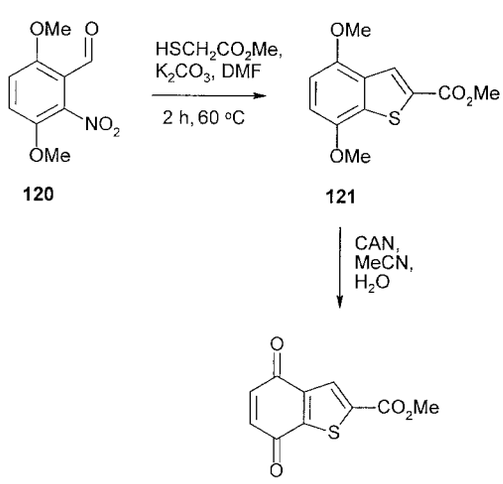
The interaction of camphene **117** with dinitrogen tetroxide in the presence of zeolites leads to a mixture of an isoxazoline **118** in 51% yield and a nitrovinylcamphene adduct **119** in 18% yield (Scheme 38).[172]



Scheme 38

2,5-Dimethoxy-6-nitrobenzaldehyde **120** undergoes a cyclisation in the presence of methyl thioglycolate to give 4,7-dimethoxybenzo[*b*]thiophene **121** in 84% yield. The same cyclisation procedure, using potassium carbonate in dimethylformamide, can also be used for 2,5-dimethoxy-6-nitroacetophenone. The benzo[*b*]thiophene adducts **121** are useful precursors for benzo[*b*]thiophene-4,7-quinones **122** (Scheme 39).[173]

The reaction of 1-ethoxycarbonyl-3-nitroindole **123** with ethyl isocyanoacetate **124** in the presence of DBU gives the



Scheme 39

Table 4 Nitrile oxide cycloadditions

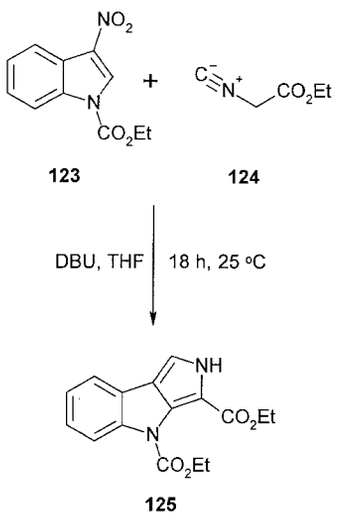
Starting material	Product	Comments	Ref.
Substituted enamidooximes	3,4-Dehydropyrrolidin-2-ones and 1,2-dehydropyrrolizidin-3-ones	Intramolecular nitrile oxide cycloaddition (INOC) followed by Raney nickel reduction.	142
Nitropropane or benzonitrile oxide	Isoxazoline containing heterocycles	Solid phase synthesis involving heterocycles linked *via* an amide bond to a resin. The heterocycles contain an allylic olefin which undergoes cycloaddition on treatment with a nitroalkane and phenylisocyanate.	143
4-Nitrobutyl phenyl selenoether	Triisoxazoline library	Iterative application of nitrile oxide 1,3-dipolar cycloaddition and selenide oxidation–elimination steps.	144
Various nitrile oxides	Ethyl isoxazoline-4-carboxylates	*N*-Protected ethyl (2*E*,4*S*)-4-amino-5-phenylpent-2-enoate undergoes cycloaddition with nitrile oxides to produce a *syn*:*anti* ratio of 2:1 of the isoxazolines in 62–66% yield.	145
2-(2′-Nitroethyl)-1,3-dioxane	C11–C24 segment of macrolactin A	An iron tricarbonyl complex of a 1,3-diene allows the reaction of a nitrile oxide, prepared from the nitro compound with phenylisocyanate and triethylamine, with a terminal olefin to give the isoxazoline intermediate. Reductive cleavage of the N–O bond results in the desired fragment.	146
1,3,3-Trimethyl-2-propylnitrocyclohexene	CDE tricyclic fragment of 12-hydroxyazadiradione	Conversion of the nitro into nitrile oxide by phenyl isothiocyanate and triethylamine allows INOC to provide the key intermediate in this anti-feedant synthesis in 73% yield.	147
Nitroalkanes	Dihydroisoxazole nucleosides and nucleotide analogues	Conversion of nitro to nitrile oxide (phenyl isocyanate and triethylamine) is followed by 1,3-dipolar cycloaddition with vinyl nucleoside bases (29–68%).	148
Alkylnitrile oxide	Substituted (60)fullerene	Addition of nitrile oxides to (60)fullerenes.	149
Methyl 4-nitrobutyrate	Dihydroisoxazoles	Nitrile oxide addition to methylenespiropentane in 44% yield. The nitrile oxide is prepared *in situ* from the nitro precursor.	150
3-Propylnitrile oxide substituted cyclohexene	Tricyclic isoxazoline	INOC in 99% yield provides the key intermediate in a (+)-pumiliotoxin C synthesis	151
Aldoximes	3-Substituted-5-phenylsulfonyl-4,5-dihydroisoxazole	Dipolar cycloadditions of nitrile oxides, isolated from the dehydrogenation of aldoximes by chloramine-T, with phenyl vinyl sulfone in 15–92% yield.	152
Primary nitro compounds	Isoxazolines	Burgess salt, DAST, acetic anhydride and oxalyl chloride were shown to be useful dehydrating agents for the formation of nitrile oxides from nitro compounds. *In situ* trapping with olefins provides an expedient route to isoxazolines.	140
1-Vinyl-2-ethylnitrocyclohexane	Tricyclic isoxazoline	INOC strategy is used to provide the key intermediate in a *trans* hydrindane synthesis.	153
Nitroalkanes	Isoxazolines	A new procedure for the generation of nitrile oxides *in situ* from nitroalkanes uses the reaction of di-*tert*-butyl dicarbonate with 4-dimethylaminopyridine catalysis in the presence of dipolarophiles at room temperature to afford the cycloadducts in 27–90%.	154
1,3-Dithiane of 2-oxopropanenitrile	Isoxazolines	1,3-Dipolar cycloaddition reactions with 1,1- and 1,2-disubstituted alkenes in 56–85% yield.	155
Alkenyl substituted nitrile oxide	A- and C-ring intermediates for Taxol	INOC strategy to provide the key intermediate in the synthesis of the desired 6- and 7-membered ring systems.	156
β-Nitroenones	6,6-Disubstituted tetrahydrothiopheno-[3,4-*c*]isoxazolines	Intramolecular silylnitronate cycloaddition whereby the nitro compound is treated with trimethylsilyl chloride and triethylamine gave greater stereoselectivity (96:4 diastereomers) than the corresponding INOC procedure (85:15 diastereomers).	157
Mesitylnitrile oxide	Isoxazolines	The addition of Lewis acids to the dipolar cycloaddition reactions of mesitylnitrile oxide with α,β-unsaturated 2-acyl-1,3-dithiane 1-oxides can reverse the sense of induced stereoselectivity.	158
Mesitylnitrile oxide	Isoxazolines	Catalytic efficiency, ligand acceleration and concentration effects in magnesium ion mediated 1,3-dipolar cycloadditions of mesitonitrile oxide to allylic alcohols have been examined.	159
Arylnitrile oxides	2-Isoxazolines	3-Sulfolene[a] undergoes a [3 + 2] cycloaddition with arylnitrile oxides (prepared *in situ* from the aryl oximes and sodium perchlorate and triethylamine) in 50–80% yields.	141
Unsymmetrical silaketals possessing a primary nitro and 1,2-disubstituted olefin	2-Isoxazoline-containing bicycle	Regiospecific INOC to give 2-isoxazolines in 60–70% yields.	160
β-Nitrostyrenes	2-Isoxazolines or isoxazoles	Treatment of β-nitrostyrenes with Grignard or organolithium reagents generates nitronates by 1,4-addition. Addition of the nitronates to ice-cold 85% sulfuric or concentrated hydrohalic acids gave 20–95% of the corresponding nitrile oxide. The nitrile oxide is then trapped with olefins or acetylenes.	161

Table 4 (*Contd*)

Starting material	Product	Comments	Ref.
3-Nitrobutylcyclohexene	Highly functionalised *cis*-decalin	A key intermediate in this functionalised *cis*-decalin synthesis is prepared by a highly diastereoselective intramolecular [3 + 2] dipolar cycloaddition of a chiral nitrile oxide.	162
Resin bound aldoximine or free aldoximine	Resin bound 2-isoxazolines	The Wang resin bound aldoximines were treated with commercial bleach in tetrahydrofuran to give the nitrile oxide *in situ* which was then trapped with the olefinic dipolarophile. The complementary strategy of using a resin bound dipolarophile was also examined.	163
Primary alkyl-bromides, -chlorides and -nitrites	2-Isoxazolines	A new route to nitrile oxides from primary alkyl halides for *in situ* dipolar cycloadditions. The procedure uses sodium nitrite and acetic acid in DMSO and gives the isoxazolines in 35–68% yield.	164

[a] IUPAC name for 3-sulfolene is 2,5-dihydrothiophene 1,1-dioxide.

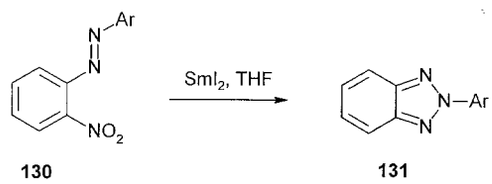
corresponding 2,4-dihydropyrrolo[3,4-*b*]indole **125** in 91% yield (Scheme 40).[174]



Scheme 40

New work on chiral nitronic acids and esters has demonstrated their use in a variety of applications. The nitronic acid **126** can be converted to the *O*-methyloxime **127** using sodium methoxide in ethanol in the presence of silica gel in 22% yield. The nitronic acid **126** has been utilized for an α,β-elimination to the butenolactone **128** in 72–86% yield and it has also been used in a 1,3-dipolar cycloaddition with ethyl acrylate giving the tricycle **129** in 53% yield (Scheme 41).[175]

o-Nitro substituted phenylazobenzenes **130** have been converted in a reductive cyclisation to 2-aryl-2*H*-benzotriazoles **131** in 84–97% yield using samarium(II) iodide (Scheme 42).[176]

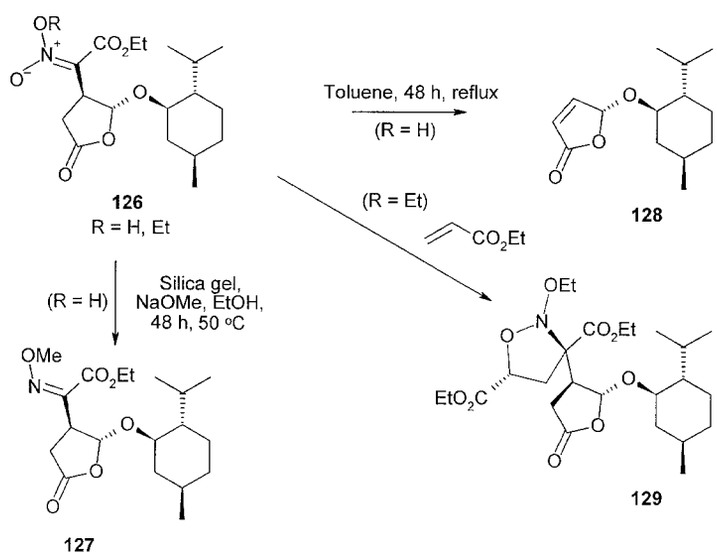


Scheme 42

In another reductive cyclization an *o*-nitroaniline **132** can be treated with isopropylsulfonyl chloride **133** in the presence of cyanogen bromide under reductive conditions to give a benzimidazole **134** in 45% yield (Scheme 43).[177]

A series of nitrofuroxanes have been prepared by subjecting unsaturated compounds to sodium nitrite and an acid with heating. Although the yields are generally low (13–37%) in one instance a yield of 95% was obtained.[178]

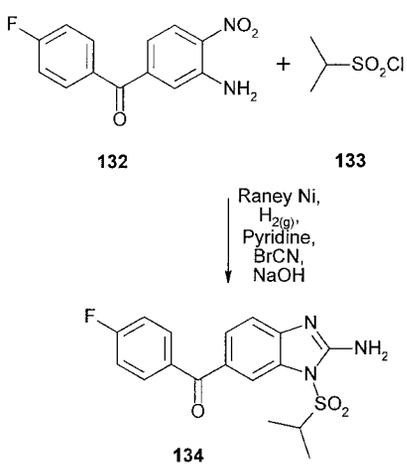
3,7-Dinitro-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene **136** has been prepared from the dinitrofuran **135** by an intramolecular Diels–Alder reaction (Scheme 44). The dinitrofuran **135** is itself prepared in a 5 step procedure from furfuraldehyde. This tricyclic intermediate was found to be a versatile synthetic tool



Scheme 41

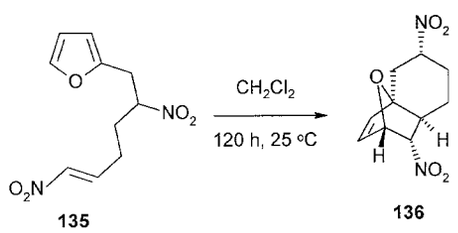
in the preparation of ergot alkaloids and valienamine bicyclic analogues.[179]

The first evidence for the ambident Diels–Alder activity of 4,6-dinitrobenzofuroxan **137** has been reported. The substrate acts as a dienophile in Normal Electron Demand D–A reactions, or as a heterodiene in the Inverse Electron Demand case. The reactivity is determined by the reaction conditions employed and the reaction partners used (Scheme 45).[180]



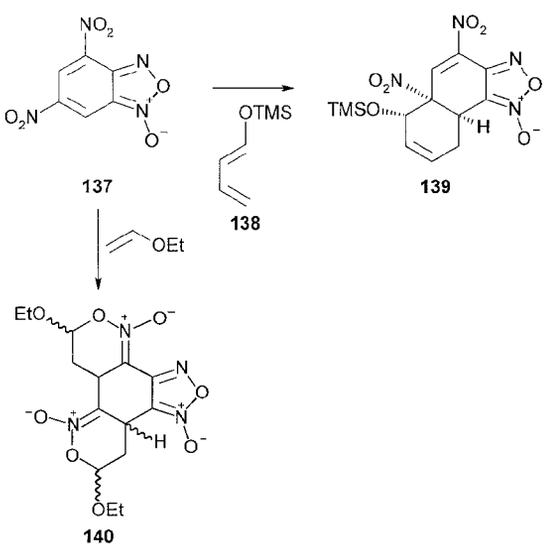
132 **133** **134**

Scheme 43



135 **136**

Scheme 44



137 **138** **139** **140**

Scheme 45

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