REVIEW

Nitro and related groups

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Received (in Cambridge, UK) 16th September 2002,
First published as an Advance Article on the web 12th November 2002

Covering: the literature published between January 2000 and January 2002. Previous review: *J. Chem. Soc., Perkin Trans. 1*, 2000, 3695.

1 Introduction

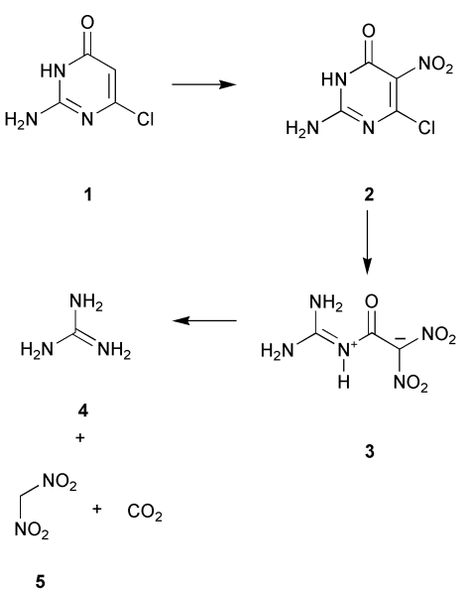
This review describes the use of nitro compounds and related derivatives. The research covered concerns the use of nitro compounds in new methodology and novel transformations. It continues the coverage in four previous reviews in the area.[1] A host of reviews covering different aspects of nitro chemistry have been published in the 2000–2001 period including those dealing with the hydrogenation of aromatic nitro compounds[2,3] and other nitrogen-containing compounds on palladium,[4] the application of heterogeneous catalysts in the nitration of aromatic compounds,[5] nitro and nitroso transformations in superacids,[6] and nitrone and nitro compound cycloadditions aided by Lewis acid catalysis.[7] Among the reviews on nitrone chemistry are those covering asymmetric 1,3-dipolar cycloadditions,[8] nucleophilic addition to nitrones,[9] and the application of nitrones in the total synthesis of natural products.[10]

2 Nitration of aliphatics

A simple one-pot synthesis of aliphatic nitro compounds from the corresponding alcohols using a sodium nitrite–acetic acid–hydrochloric acid system has been reported to proceed in 70–93%.[11] Treatment of a tetranitrocubane with sodium hexamethyldisilazide and nitrogen tetroxide in THF–2-methyltetrahydrofuran–isopentane at low temperature, −130 °C to −78 °C, followed by an acidic work-up results in the formation of heptanitrocubane in 74% yield. Further nitration to give the octanitrocubane is performed using the same lithium hexamethyldisilazide base but quenching with NOCl and ozone in dichloromethane to give the product in 45–55% yield.[12] An efficient catalytic alkane nitration using nitrogen dioxide and air, with *N*-hydroxyphthalimide as catalyst, proceeds in 44–66% yields.[13] A useful modification of this procedure uses nitric acid in place of the nitrogen dioxide to provide a more practical method with slightly improved yields (32–91%).[14] The key to this nitration was determined to be the *in situ* formation of nitrogen dioxide and the phthalimide *N*-oxyl radical by the reaction of the *N*-hydroxyphthalimide with nitric acid.

3 Nitration of heterocycles

The difficulties encountered in the preparation of the widely used heterocyclic precursor 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidone **2** by nitration of 2-amino-6-chloro-4(3*H*)-pyrimidone **1** using mixtures of concentrated fuming nitric acid and sulfuric acid have been found to be due to the formation of an open-chain *gem*-dinitro compound **3** (diaminomethyleneaminocarbonyldinitromethane). This *gem*-dinitro compound decomposes by loss of carbon dioxide in dimethyl sulfoxide, or in aqueous potassium hydroxide, to give guanidine **4** and dinitromethane **5** (Scheme 1). Use of potassium nitrate in



Scheme 1

sulfuric acid gives the desired 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidone **2** in 72% yield.[15] The nitration of 6-substituted purine nucleosides with tetrabutylammonium nitrate and trifluoroacetic anhydride proceeds to give the 2-nitrated products. The method is limited to those substrates which do not possess NH or OH substituents.[16]

Selective β-polynitration of zinc 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin has been achieved using a controlled titration with a system comprising nitric acid–trifluoromethanesulfonic acid–trifluoromethanesulfonic anhydride.[17]

 DOI: 10.1039/b009711j

2-Trimethylstannylated benzo[*b*]furan, benzo[*b*]thiophene, *N*-substituted indoles and pyridine afford, regioselectively, the corresponding nitro derivatives in highly variable yields, 2–86%, *via* treatment with tetranitromethane. Irradiation is required from a sun-lamp in the case of *N*-containing heterocycles.[18]

A series of faujasite zeolites, with varying amounts of aluminium present, were used in the nitration of substituted 1-chloro-2-nitrobenzene, 2-nitrotoluene and pyrazole with dinitrogen pentoxide. The rates for the reactions are not only dependent upon the mass of the faujasite zeolite used but also increase with increasing aluminium content.[19]

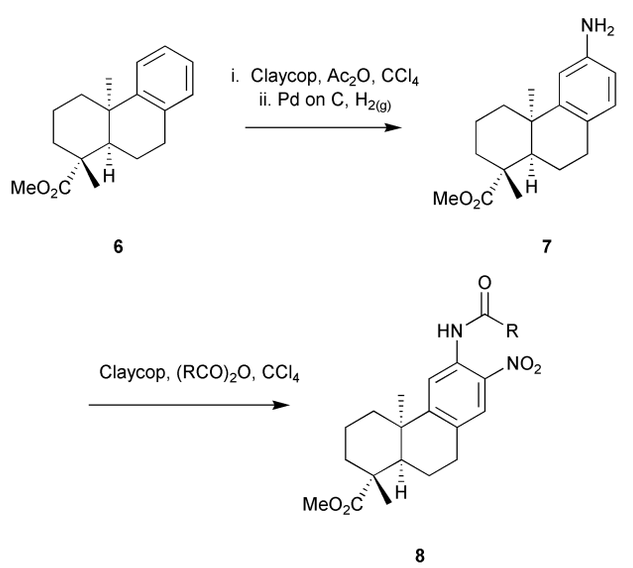
A low yielding, 5%, nitration of an osmabenzene (a metallobenzene) has been achieved using copper(II) nitrate in acetic anhydride.[20]

4 Nitration of aromatics

A solution of nitric acid in dichloromethane can be prepared by the action of 96% sulfuric acid on potassium nitrate. The resultant solution can subsequently be used for nitration of aromatics in 92–97% yield.[21]

Cerium(IV) ammonium nitrate (CAN) is a convenient reagent for the nitration of coumarins. Higher regioselectivities are observed using CAN in hydrogen peroxide in aqueous media as compared to CAN in acetic acid for the nitration of 7-hydroxycoumarin, 7-hydroxy-4-methylcoumarin and their derivatives (80–92% yields).[22] High yielding (92–99%) nitration of aromatics can be performed using metal nitrates (CAN, potassium–or tributylammonium nitrate) suspended in dichloromethane in the presence of two equivalents of sulfuric acid. Dispersing the sulfuric acid on silica gel allows the nitration products to be isolated by a simple filtration and removal of the solvent.[23]

Impregnation of montmorillonite with bismuth nitrate provides the basis for the efficient regioselective nitration of aromatic compounds in 72–99% yields.[24] Methyl *cis*-deisopropyldehydroabietate **6** is selectively nitrated at the 12-position by reaction with Claycop [a K-10 montmorillonite clay impregnated with copper(II) nitrate]. Reduction of the nitro group to give the amino derivative **7** followed by acetylation with trifluoroacetic anhydride allows a second treatment with the Claycop in carbon tetrachloride to provide the product from *ortho* nitration **8** (Scheme 2). The acetylation–nitration procedure has been shown to work with other anilines in 59–70% yield.[25] These acetylation–nitration products allow ready access to 2-substituted benzimidazoles from aniline. A high degree of *para* regioselectivity is achieved in the nitration of aromatic compounds when nitric acid is used with a zeolite possessing a low Si/Al ratio, with yields of 67–90% of the *para* products.[26] Mononitration of aromatic compounds using a zeolite catalyst in combination with dinitrogen tetroxide and air in a sealed system achieves 76–97% yields of the *para* nitro aromatics as the major products under solvent-free conditions.[27] In the presence of molecular oxygen and the zeolite H-ZSM-5, neat, liquid nitrogen dioxide reacted with toluene to give predominantly 4-nitrotoluene; chlorobenzene performed similarly to toluene. Although the *para*-predominant products are obtained the overall yields are low (5%).[28]



Scheme 2

A variety of nitrating systems have been used in ionic liquids (*e.g.* ammonium nitrate and trifluoroacetic anhydride in 1-ethyl-3-methylimidazolium trifluoroacetate). Yields vary from 50 to 100%, and do not require the use of strong acids.[29]

Dialkoxybenzenes are smoothly nitrated to afford the dinitro or trinitro derivatives, in 52–88% yields, by treatment with an excess of nitrogen dioxide followed by oxidation with ozone at low temperature.[30]

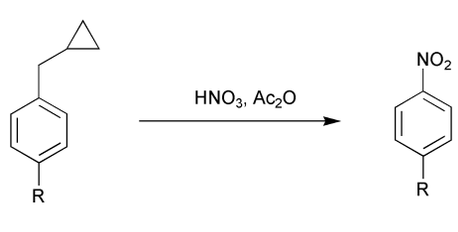
A simple and convenient *ipso*-nitration of arylboronic acids uses ammonium nitrate and trifluoroacetic anhydride to give the aromatic nitro compounds in 52–78% yields.[31] The use of excess ammonium nitrate leads to dinitration.

Treatment of fluoren-9-ylmethoxycarbonyl amino acids with 100% nitric acid in dichloromethane gives ready access to (2-nitrofluoren-9-yl)methoxycarbonyl amino acids in 92–95%.[32]

Nitration of *N*-acetyl-2,3-dichloroaniline with potassium nitrate and sulfuric acid was used to provide the 4-nitro product in 42% yield, regioselectively.[33]

An efficient method for the nitration of phenols uses the inorganic acidic salts $Mg(HSO_4)_2$ or $NaHSO_4{\cdot}H_2O$ with sodium nitrite and wet silica gel in dichloromethane. The nitration proceeds by a process whereby the nitrosation and oxidation occur simultaneously, without any additional oxidants for the oxidation of nitrosophenol, to give the desired nitrophenols in 33–95% yields.[34] Alternatively Oxone™ may be used in place of the magnesium or sodium bisulfates to give the nitrophenols *via* nitrosation–oxidation.[35]

Nitrodealkylation of *para* substituted benzylcyclopropanes **9** using standard nitration conditions of nitric acid in acetic anhydride occurs to give the nitroarenes **10** in 78–92% yields (Scheme 3),[36] the driving force being the loss of the stable methylcyclopropyl carbocation from the *ipso* attack.



Scheme 3

Aromatic rings can be rapidly and mildly nitrated using dinitrogen pentoxide in the presence of an iron(III) catalyst [$Fe(acac)_3$]. Yields of 91–100% are obtained in 4 min, but regioselective control is poor, as would be expected from such a highly reactive nitrating system. The iron catalyst activates the system sufficiently that toluene is nitrated at −100 °C.[37]

The nitration of phenol by peroxynitrite has been achieved using sodium nitrate in the presence of the cobalt substituted polyoxometalate $K_7[CoAlW_{11}O_{39}]{\cdot}15H_2O$ under pH 7.4 buffered conditions.[38]

A convenient one-pot, one-step synthesis of *para*-nitrocalix[*n*]arenes is demonstrated when *p*-*tert*-butylcalix[*n*]arenes are treated with a mixture of nitric acid and acetic acid in dichloromethane in 85–89% yields.[39]

The ammonium nickel sulfate mediated nitration of aromatic compounds with nitric acid works efficiently at room temperature to give the mononitro adducts in 85–94% yields and high regioselectivity.[40]

Nitration of spiroannulated benzazepines has been conducted in 44–80% yields using a mixture of sulfuric acid and nitric acid.[41] [*ring*-C-14]Toluene has also been nitrated with this system in 83% yield.[42]

5 Reduction of the nitro group

A selective, catalytic reduction of aromatic nitro-compounds containing highly reactive functional groups utilises hydrogenation over a platinum–alumina catalyst at *ca.* 10–30 atm pressure of hydrogen in 89–96% yields.[43]

The solvent-free reduction of aromatic nitro-compounds with alumina-supported hydrazine under microwave irradiation in the presence of iron(III) chloride, iron(III) oxide hydroxide or iron(III) oxides proceeds in 81–97% yields.[44] Microwave radiation is also used in the alumina–iron(II) sulfate–sodium hypophosphite, solvent-free nitro reduction system, which gives the corresponding amino derivatives in 69–88% yields.[45]

Reduction of aromatic nitro-compounds to anilines, in 55–95% yields, with hydroiodic acid under non-refluxing conditions (90 °C, 24 h) proceeds with excellent chemoselectivity, leaving untouched nitrile, ester, halide, carbonyl, amide, sulfonamide, imidazole and methylthio groups.[46]

The reduction of nitrobenzenes to anilines with decaborane ($B_{10}H_{14}$) in the presence of palladium-on-carbon and two drops of acetic acid at reflux occurs in 81–97% yields.[47]

Aryl nitro-compounds are readily reduced to the corresponding anilines by the action of sulfurated calcium borohydride [$Ca(BH_2S_3)_2$] in tetrahydrofuran at reflux in 82–90% yields. This new modified borohydride reagent is prepared by a metathetical reaction between calcium chloride and $NaBH_2S_3$. The reagent has also been demonstrated to effectively reduce aryl azides to anilines.[48] Barium and strontium sulfurated borohydrides can also be prepared in a similar manner using a metathesis reaction with $NaBH_2S_3$. The barium sulfurated borohydride is more stable and more reactive than the corresponding strontium species and has been used to reduce a variety of different functionalities including the nitro group in 80–98% yields.[49] Zirconium(IV) chloride–sodium borohydride is an effective system for the reduction of aromatic and primary nitro compounds to the corresponding primary amines in 78–92% yields.[50]

Aliphatic and aromatic nitro compounds are selectively reduced to the corresponding amino derivatives using Raney nickel and formic acid (or ammonium formate). This chemoselective reduction procedure proceeds in 45–92% yields and is tolerant of a large number of sensitive functionalities.[51] 5% Platinum-on-charcoal can also be used in place of Raney nickel (80–93% yields) and in this case the ammonium formate is a more efficient hydrogen donor than formic acid.[52] Commercial zinc dust also works with ammonium formate to reduce aliphatic and aromatic nitro compounds to their amino derivatives in 45–95% yields, while being compatible with a variety of sensitive functionalities including halogens, aldehydes, ketones, carboxylic acids, esters, amides, nitriles and acetamides.[53]

An indium–ammonium chloride in aqueous ethanol system has been used for the reduction of aromatic and heteroaromatic nitro compounds in 70–90% yields.[54] Similarly an ultrasound promoted, samarium–ammonium chloride system has proved to be efficient in the reduction of aromatic nitro compounds to anilines, 56–92% yields.[55] Indium itself can be used in conjunction with hydrochloric acid in aqueous media for the reduction of nitro and azide groups in 60–99% yields.[56]

Urushibara nickel catalysts are non-pyrophoric, easily prepared and can be used for many of the same reactions as Raney nickel. The Urushibara nickel-catalysed hydrogenation of aromatic nitro compounds proceeds efficiently at 1 atmosphere to give the aniline products in 80–91% yields.[57]

Samarium(0) metal in conjunction with a catalytic amount of 1,1′-dioctyl-4,4′-bipyridinium dibromide has been developed as a chemoselective reduction system for aromatic nitro compounds. The 1,1′-dioctyl-4,4′-bipyridinium dibromide acts as an electron-transfer catalyst and is essential in the activation of the Sm(0) metal. The anilines are formed in 78–99% yield.[58]

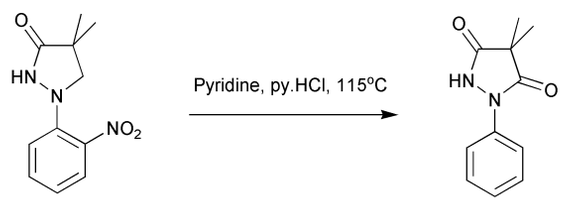
Porphyrinatoiron–sodium borohydride and phthalocyanatoiron–sodium borohydride systems have been investigated for the reduction of nitroarenes. The phthalocyanatoiron–sodium borohydride system was found to be more effective. The rate of the reduction to the anilines has been shown to increase by the addition of 2-bromoethanol, and this reduction proceeds in 67–98% yields.[59]

An amino(2.2)paracyclophane has been prepared from the corresponding nitro compound by reduction using $Fe_3(CO)_{12}$, 18-crown-6 and potassium hydroxide in toluene in 95% yield.[60]

6 Denitration

Nitrates (*e.g.* nitroglycerin) are clinically important vasodilators which are believed to be transformed into NO *in vivo via* a three-electron reduction. Molybdenum hydrotris(3,5-dimethylpyrazol-1-yl)borate complex is an efficient catalyst for the denitration of nitrates, using triphenylphosphine as a reducing cofactor, producing NO and thereby acting as an enzyme model system.[61]

Heating 4,4-dimethyl-1-(2-nitrophenyl)pyrazolidin-3-one **11** in pyridine containing pyridine hydrochloride results in a transformation to 4,4-dimethyl-1-phenylpyrazolidine-3,5-dione **12**, in which the methylene group has been oxidised and the nitro group has effectively disappeared (Scheme 4). A possible



11 **12**

Scheme 4

mechanism for this new acid-catalysed redox–denitration reaction has been proposed by the authors but further work is required to confirm the mechanism and scope of the chemistry.[62]

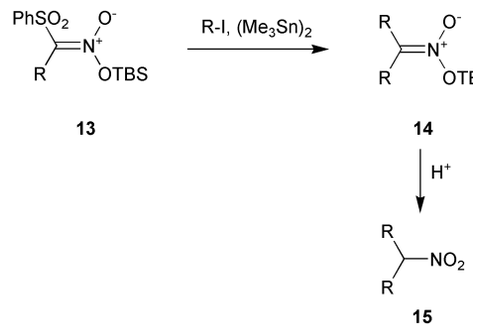
7 Nitroalkylation

The radical reaction of alkyl iodides with phenylsulfonyl substituted silyl nitronates **13** in the presence of hexamethylditin, with irradiation at 300 nm, affords *C*-alkylated nitro compounds **15** in 42–62% yields *via* the intermediacy of the dialkyl silyl nitronates **14** (Scheme 5).[63]

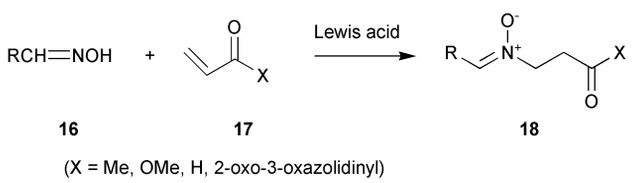
In the presence of Lewis acid catalysts, particularly the mixed zinc(II) iodide–boron trifluoride–ether system, aldoximes **16** react with α,β-unsaturated carbonyl compounds **17** to give *N*-alkylnitrones **18** in 79–100% yields (Scheme 6).[64]

8 *N*-Nitroso compounds

Oxazolidinones **21** have been prepared from *N*-carbamoylamino alcohols **19** by treatment with nitrous acid, *via* an *N*-nitroso compound intermediate **20**, in 30–100% yield (Scheme 7).[65]

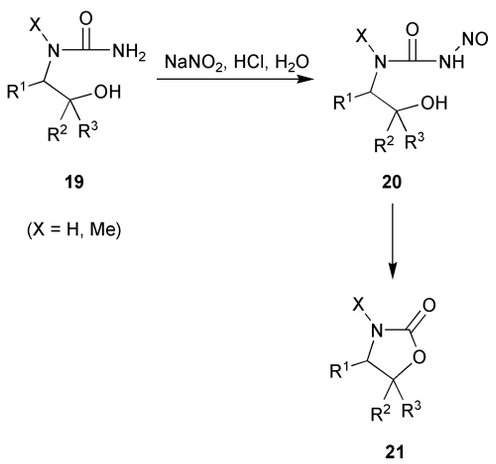


Scheme 5



(X = Me, OMe, H, 2-oxo-3-oxazolidinyl)

Scheme 6



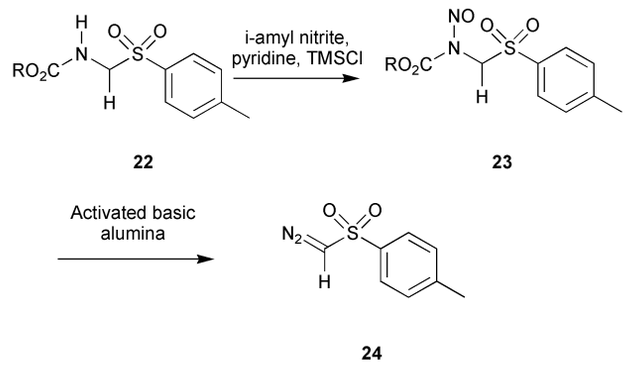
Scheme 7

Potassium monopersulfate (Oxone™), or other relatively strong inorganic Lewis acidic salts (*e.g.* tungsten chloride, aluminium chloride, zinc chloride) react with sodium nitrite in the presence of wet silica gel to give an effective nitrosation system. This *in-situ* generation of nitrous acid allows the nitrosation of secondary amines to the corresponding nitroso derivatives to occur in 92–99% yields.[66] The inorganic salts are less effective than potassium monopersulfate.[67] Replacing the potassium monopersulfate with iodic or periodic acids similarly works well to give the nitroso derivatives in 82–99% yields.[68] The *N*-nitrosation of secondary amines with NO(18-crown-6)$^{+}$·$H(NO_3)_2^{-}$ and silica gel is reported to give quantitive yields of the desired nitroso derivatives.[69]

N-Nitrosonornicotine and 4-hydroxy-1-(3-pyridyl)butan-1-one (used as a biological marker to differentiate tobacco smokers and passive smokers) are prepared in a one-step reaction by *N*-nitrosation of the nicotinoid mysomine. Mysomine is found in nut products as well as tobacco. This research suggests that exposure to nicotinoid nitrosation products seems not to be restricted exclusively to tobacco.[70]

A preparation of *N*-amino-*N*-demethylcodeine uses a nitrosation of codeine, with sodium nitrite and sulfuric acid, to give the corresponding *N*-nitroso-*N*-demethylcodeine intermediate in 30% yield. The *N*-nitroso-*N*-demethylcodeine intermediate is then reduced to the *N*-amino-*N*-demethylcodeine using zinc in acetic acid in 67% yield.[71]

A preparation of tosyldiazomethane **24** uses the treatment of the carbamate **22** with amyl nitrite and trimethylsilyl chloride in the presence of pyridine to form the resulting nitroso derivative **23** in 90% yield. This nitroso derivative **23** was then treated with activated alumina to give the desired tosyldiazomethane **24** in 67% yield (Scheme 8).[72]



Scheme 8

Lithium dialkylamides react with NO at atmospheric pressure to generate *N*-nitrosoalkylamines in 40–100% yields. This is the first report of NO insertion into an N–Li bond.[73]

Nitration of imidazolidin-2-one using nitric acid and acetic anhydride followed by hydrolysis leads to the formation of 1-amino-2-nitroaminoethane in 49% yield.[74]

9 Oxidation to give nitro compounds

Aromatic primary amines can be directly converted into the corresponding nitro compounds by treatment with titanium superoxide polymer (prepared by the action of hydrogen peroxide on titanium tetraisopropoxide in anhydrous methanol) and hydrogen peroxide.[75]

10 Vicarious nucleophilic substitution

Nitroarenes are good substrates for vicarious nucleophilic substitution (VNS) of hydrogen using the carbanion formed from 2-phenylthio-1,3-dithiane and potassium *tert*-butoxide, in 61–95% yields and high regioselectivity. The resulting nitroaryl dithianes are readily unmasked to give the corresponding aldehydes.[76] (*p*-Nitroaryl)diarylmethanes are also readily prepared *via* VNS of hydrogen in nitroarenes with carbanions of diarylmethyl *p*-chlorophenyl sulfide. The (*p*-nitroaryl)diarylmethanes are formed in 52–98% yields regioselectively at the *para* position (the *ortho* position is sterically hindered).[77]

11 Henry reaction on nitro compounds

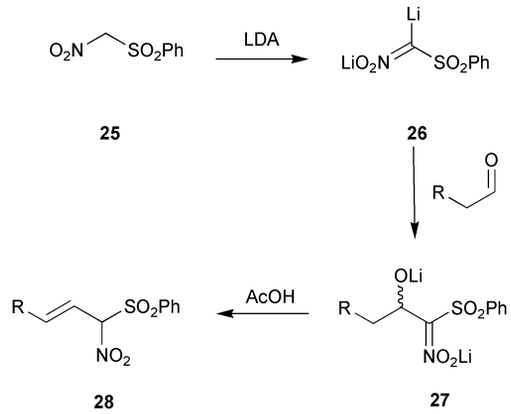
The synthesis of conjugated nitroalkenes can be performed using a gel entrapped base catalysed Henry reaction. The base consists of an agar-agar aqua gel containing 10% potassium hydroxide and has achieved yields of 40–96% in the nitroaldol condensation reaction.[78]

The reaction of phenylsulfonyl(nitro)methane **25** with more than two equivalents of LDA afforded the dilithium salt of phenylsulfonyl(nitro)methane **26**. This dilithium salt **26** readily underwent a nitroaldol reaction with unbranched aldehydes but the resultant nitroaldol product **27** dehydrated to afford unconjugated β,γ-unsaturated α-nitrosulfones **28** in 52–88% yield (Scheme 9).[79]

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) and its 7-methyl derivative (MTBD) are effective catalysts for the nitroaldol reaction, achieving yields of 70–98%. The reaction proceeds after a few minutes at 0 °C. Polymer-supported TBD is also an effective promoter of the Henry reaction.[80]

12 Miscellaneous nitro reactions

Catalytic enantio- and diastereoselective Michael addition reactions of aldehydes to conjugated nitro olefins using the chiral

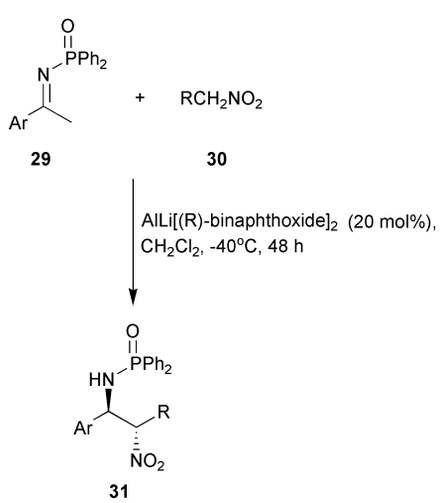


25 26 27 28

Scheme 9

catalyst (*S*)-2-(morpholinomethyl)pyrrolidine proceed in 67–96% yield, are *syn*-selective (up to 98:2) and give enantioselectivities up to 78% ee.[81]

A new route to chiral vicinal diamines *via* an enantioselective and diastereoselective catalytic nitro-Mannich reaction has been discovered. A second-generation heterobimetallic complex, LiAl[(*R*)-BINOL]$_2$, catalyses the reaction of nitroalkanes **30** with diphenylphosphinoyl imines **29** to give the nitro Mannich products **31** in 75–98% yield with 74–83% ee and diastereoselectivity of up to 7:1 (Scheme 10).[82] Reduction of the



29 30 31

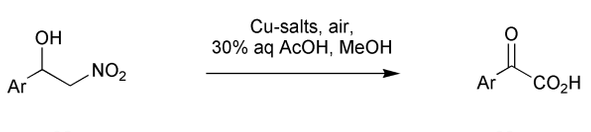
Scheme 10

nitro group using Sm(II) chemistry and treatment with hydrochloric acid to remove the diphenylphosphinoyl group led to the desired chiral vicinal diamines.

The catalytic enantioselective addition of nitro compounds to imines provides a simple approach for the synthesis of optically active β-nitro-α-amino esters. The chiral catalyst Cu{2,2-bis[(4*R*)-phenyloxazolin-2-yl]propane}(OTf)$_2$ is used in the presence of triethylamine to give the β-nitro-α-amino esters in 38–81% yields and with 74–99% ee.[83]

Copper(II) salts (copper sulfate or copper acetate) catalyse the conversion of aryl nitroaldol products **32** into the corresponding aryl α-keto acids **33** in 41–97% yield using 30% aqueous acetic acid–methanol (1:1) (Scheme 11).[84]

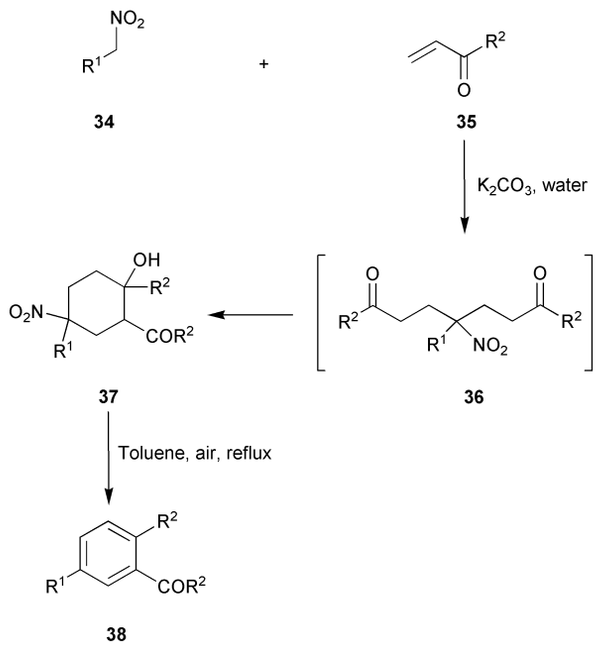
A two-step procedure for the formation of 1-acyl-2,5-dialkylbenzene drivatives **38** from nitroalkanes **34** proceeds



32 33

Scheme 11

through a double Michael addition using 2 equivalents of enone **35** to 1 equivalent of nitroalkane **34** (70–95% yield). The resultant diketone **36** undergoes a cyclisation and the cyclic products **37** readily undergo loss of water and nitrous acid, and then aerial oxidation to give the 1-acyl-2,5-dialkylbenzene products **38** in 50–80% yields using tosic acid in toluene and a Dean–Stark apparatus with simultaneous injection of air (Scheme 12).[85]

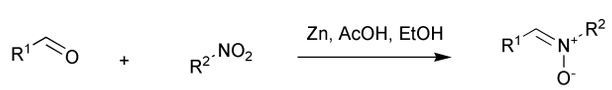


34 35 36 37 38

Scheme 12

13 Preparation of nitrones

Functionalised nitrones **41** have been prepared from nitro compounds **40** in 45–96% yields by a zinc-mediated reduction of nitroalkanes **40** in the presence of aldehydes **39** (Scheme 13).[86]



39 40 41

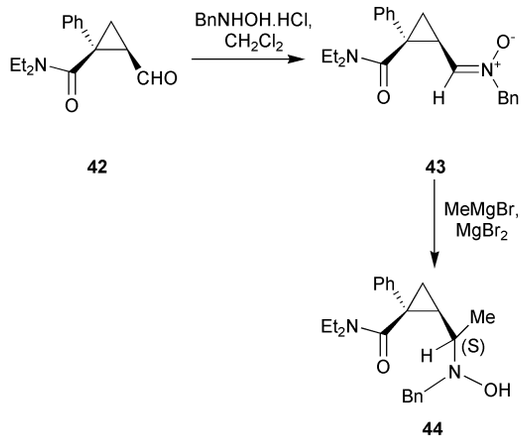
Scheme 13

The manganese dioxide oxidation of *N*,*N*-dialkylhydroxylamines to nitrones is a mild and efficient procedure proceeding at ambient temperature in 85–96% yield.[87]

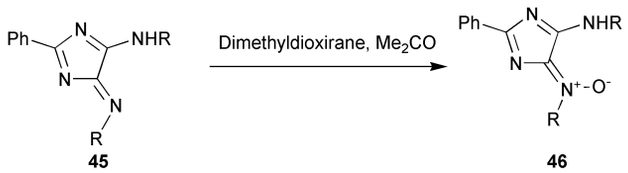
N-Methylhydroxylamine hydrochloride reacts with substituted benzaldehydes in the presence of powdered molecular sieves to give the corresponding *C*-aryl-*N*-methylnitrones in 80–100% yield.[88] Similarly the reaction of *N*-benzylhydroxylamine hydrochloride with a cyclopropyl aldehyde has been show to give the corresponding *C*-cyclopropylnitrone in 100% yield.[89] The *C*-cyclopropylnitrone was then treated with methylmagnesium bromide to give the corresponding hydroxylamine in 81% yield and with a de of 96% (Scheme 14).

β-Aminonitrones **46** have been synthesised by an oxidative modification of 4*H*-imidazoles **45**, using dimethyldioxirane as the oxidant, in 86–96% yields (Scheme 15).[90]

Two differing methods for nitrone formation have been reported in the same paper by Katritzky.[91] The first method uses a condensation of *N*-substituted hydroxylamines with aromatic aldehydes to give the nitrone products in 60% yield. The second method involved the oxidation of secondary amines to nitrones using sodium tungstate with hydrogen peroxide in similar yields. The sodium tungstate–hydrogen peroxide system has also been used to oxidise perhydroindole **47** to the correspond-

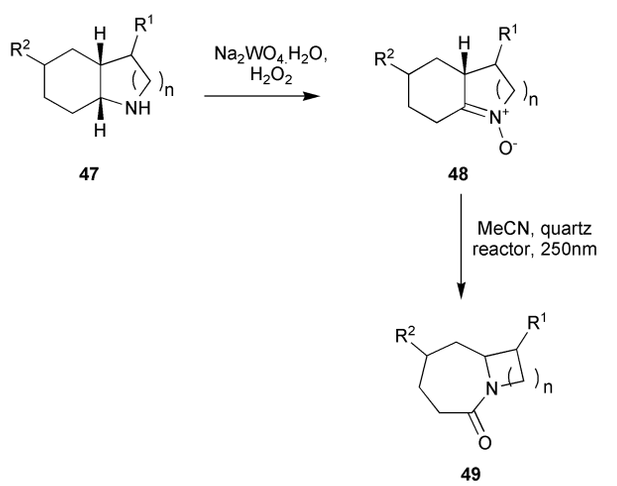


Scheme 14



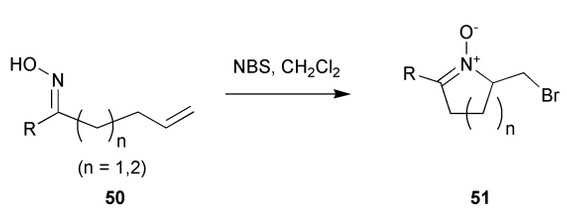
Scheme 15

ing nitrone **48** which was then irradiated at 250 nm to give fused bicyclic lactams **49** in 20–40% yields (Scheme 16).[92]



Scheme 16

Oximes **50** possessing γ- and δ-alkenyl substitutents are cyclised by *N*-bromo- or *N*-iodosuccinimide, iodine or iodine monochloride to the corresponding cyclic nitrones **51** (Scheme 17), or dimeric H-bonded hydroiodide salts, in essentially

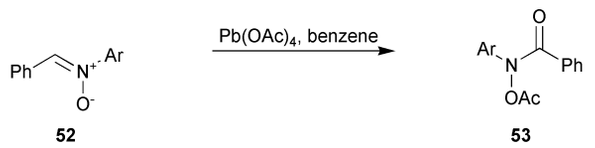


Scheme 17

quantitiative yield. The resultant cyclic nitrones **51** were then used in 1,3-dipolar cycloadditions.[93]

14 Oxidation of nitrones

α-Phenyl-*N*-arylnitrones **52** have been oxidised by lead tetraacetate in benzene to give the corresponding *O*-acetyl-*N*-benzoyl-*N*-arylhydroxylamines **53** in 89–93% yields (Scheme 18).[94]



Scheme 18

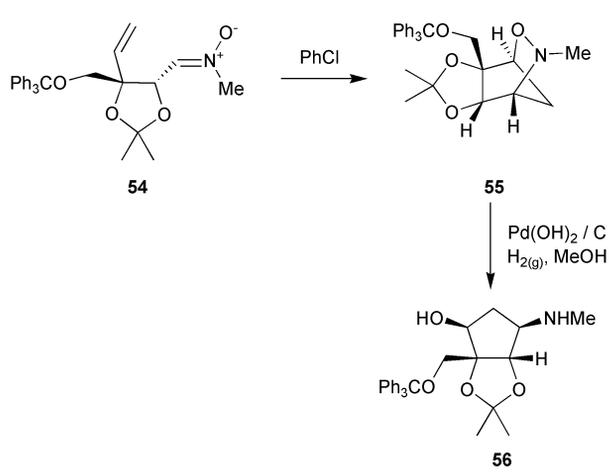
15 Deoxygenation of nitrones

Nitrones can be readily converted into their imine counterparts by a deoxygenation procedure using aluminium chloride hexahydrate–potassium iodide in acetonitrile–water in 70–92% yield.[95] An indium–ammonium chloride deoxygention of nitrones to imines also proceeds in high yields (85–98%).[96]

Treatment of nitrones under less forcing reduction conditions leads to *N*-hydroxylamines. Optically active *N*-hydroxylamines have been prepared by the asymmetric hydrogenation of nitrones with an iridium catalyst system {prepared from [IrCl(cod)]$_2$, (*S*)-BINAP, tetrabutylammonium borohydride} under a hydrogen atmosphere in 82% yield and up to 86% ee.[97] Rhodium and other iridium catalyst systems were found to be less effective.

16 Nitrone cyclisation

The 1,3-dipolar cycloaddition of nitrones to alkenes to form isoxazolidines followed by the reductive cleavage of the N–O bond is a common strategy for many different syntheses. A 1,3-dipolar cycloaddition of furfuryl nitrones with acrylates to give isoxazolidines in 75–96% yields followed by the reductive cleavage of the N–O bond has been used as the key step in an approach to protected 4-hydropyroglutamic acids.[98] A second example of this type of strategy has been used in the total synthesis of pentenomycin (which shows antibacterial activity). The nitrone **54** is prepared from an L-arabinose derived aldehyde and subsequently undergoes an intramolecular nitrone cycloaddition in 53% to give the isoxazolidine **55**. This is then treated with palladium hydroxide-on-carbon under a hydrogen atmosphere to cleave the N–O bond and give the amino-alcohol **56** in 52% yield (Scheme 19).[99] Similarly, in a concise synthesis



Scheme 19

of seven-membered iminocyclitols, nitrone cycloadditions are used to form spiro isoxazolidines which are then subjected to reductive opening of the isoxazolidine ring by Raney nickel.[100]

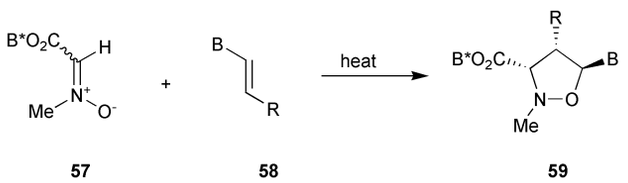
Highly diastereo- and enantioselective 1,3-dipolar cycloaddition reactions of nitrones containing an amide group to allyl alcohol have been achieved using a catalyst system comprised of diisopropyl (*R*,*R*)-tartrate, diethylzinc, iodine and an amine *N*-oxide. The amine oxide (*e.g.* pyridine *N*-oxide) was

essential to ensure a high enantioselectivities. Yields were 20–79% with 57–98% ee.[101]

Nitrones have been used to form 5-fluoroalkyl substituted isoxazolidines as a mixture of *c*is *an*d trans diastereoisomers in 83–100% yields using ethyl 2-hydropoly(per)fluoroalk-2-enoates as the alkene partner for the cycloadditions.[102]

The nitrone cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide with several acetals of γ-oxo-α,β-unsaturated esters has been studied and the reactions all showed complete regioselectivity and a high preference for the *endo* products, (43–93% yields).[103]

A stereoselective approach to isoxazolidinyl nucleosides **59** has been developed whereby the 1,3-dipolar cycloaddition of a *C*-chiral nitrone **57** with purine and pyrimidine nucleobases **58** produces thymidine and adenosine *N*,*O*-nucleosides **59**, respectively (Scheme 20).[104]



57 **58** **59**

(B = purine, pyrimidine; R = H, CO_2Et; B* = 15-endo-(-)-borneolyl)

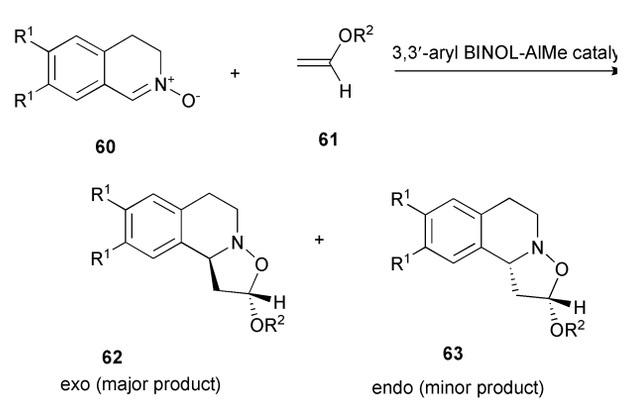
major product when
B = purine, R = H or
B = pyrimidine, R = CO_2Et

Scheme 20

An *N*-chiral nitrone was used in a 1,3-dipolar nitrone cycloaddition with but-3-enol to give all four diastereoisomers of the resultant isoxazolidine in a 1:1:1:1 ratio with 98% yield.[105]

The regioselective and diastereoselective intramolecular cycloaddition of *N*-methyl nitrones derived from 3-(allylamino)-propionaldehydes has been investigated and it has been determined that methyl substitution at the 3-position results in predominantly the *syn–cis* fused adducts whereas substitution at the 2-position is less selective and results in *syn–cis*-, *anti–cis*-fused and *syn*- and *anti*-bridge adducts.[106]

The 1,3-dipolar cycloaddition of *C*,*N*-diphenylnitrone to *tert*-butyl vinyl ether in the presence of chiral boron complexes results predominantly in *trans* cycloadducts. This is a reversal of the *endo*/*exo* diastereoselectivity as compared to the uncatalysed reaction. Although fast and sometimes high yielding (31–96%) the enantioselectivities remained low at 6–40% ee.[107] A highly diastereo- and enantioselective catalytic 1,3-dipolar cycloaddition reaction of cyclic nitrones **60** activated by chiral 3,3′-aryl BINOL–AlMe complexes is especially effective with alkyl vinyl ethers **61**, giving predominantly the *exo* diastereoisomer **62** of the isoxazolidine in 24–92% yields, 90–100% de and 10–85% ee (Scheme 21).[108] A lanthanide-catalysed



60 **61**

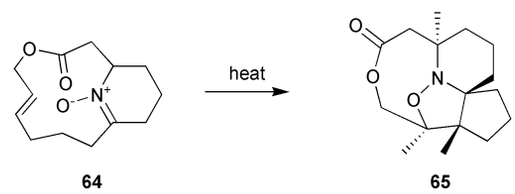
62 **63**

exo (major product) endo (minor product)

Scheme 21

asymmetric 1,3-dipolar cycloaddition of nitrones with alkenes using 3,3′-bis(2-oxazoyl)-1,1′-bi(2-naphthol) (BINOL-BOX) ligands proceeds in up to 94% yield and 94% de, 87% ee.[109]

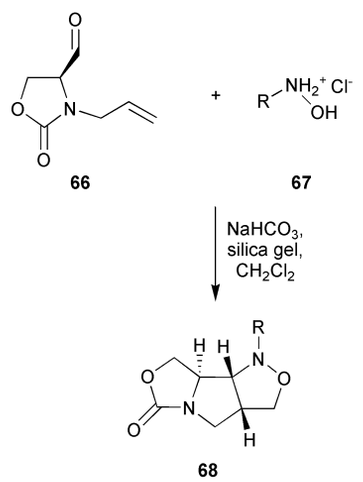
A stereocontrolled entry to the spirocyclic core of pinnaic acid *via* a transannular nitrone cycloaddition of the bicyclic nitrone-alkene **64** has been used to give a tetracycle **65** in 64% yield (Scheme 22).[110]



64 **65**

Scheme 22

Solvent-free microwave-induced intramolecular cyclisation of unsaturated nitrones prepared from the aldehyde **66** (or oximes and azomethine ylides) on the surface of silica gel produces functionalised tricyclic isoxazolidines **68** fused with a pyrrolidine or piperidine ring in 79–82% yield (Scheme 23).[111]



66 **67**

68

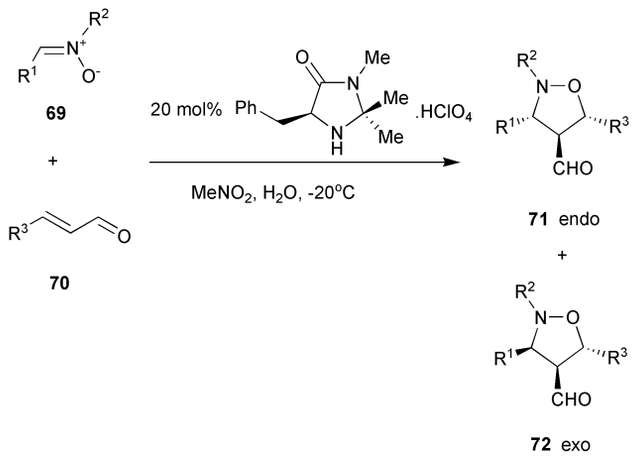
Scheme 23

A concise enantioselective synthesis of antimalarial febrifugine alkaloids has been developed which uses the reaction of (*S*)-2-(*tert*-butyldiphenylsilyloxy)-5-(mesyloxy)pentanal with hydroxylamine to form a cyclic nitrone, which undergoes a simultaneous 1,3-dipolar cycloaddition with allyl alcohol to give three diastereoisomeric isoxazolidine bicyclic adducts.[112] Further manipulation of these products led to (+)-febrifugine and (+)-isofebrifugine.

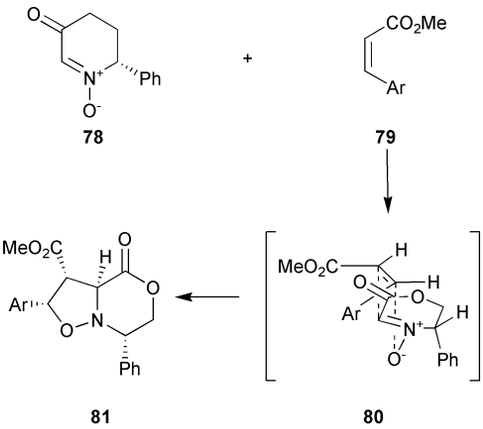
The first example of an enantioselective organocatalytic 1,3-dipolar cycloaddition between nitrones **69** and olefins **70** uses the (5*S*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidinium perchlorate catalyst in water and nitromethane to give the isoxazolidine products **71** and **72** in 66–98% yields with *endo*:*exo* ratios of 81:19 to 98:2 and with 90–99% ee (Scheme 24).[113]

The alkylidenecyclopropane nitrone **74**, prepared from the corresponding aldehyde **73**, undergoes a diastereoselective intramolecular 1,3-dipolar cycloaddition to give three diastereoisomeric spirocyclopropane isoxazolidines **75**–**77** in 70% yield (Scheme 25). The major diastereoisomer **75** is formed in 46% yield.[114]

A stereocontrolled synthesis of multi-functional β-substituted α-amino-acids utilises a nitrone cycloaddition approach. The stereochemistries were controlled *via* a (*Z*)-nitrone-*exo* transition state for the *syn*-amino acid and *via* an (*E*)-nitrone-*exo* transition state (see transition state **80**) for the *anti*-amino



Scheme 24

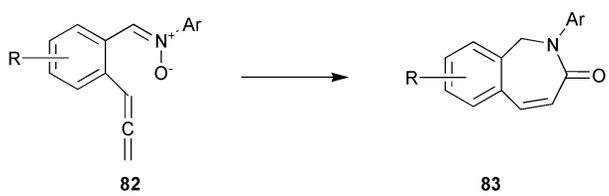


Scheme 26

acid where the (*E*)-nitrone geometry is enforced by the use of a cyclic nitrone **78** (Scheme 26).[115] N–O reductive cleavage of the product **81** obtained from the cycloaddition followed by further synthetic transformations led to the desired amino acid derivatives.

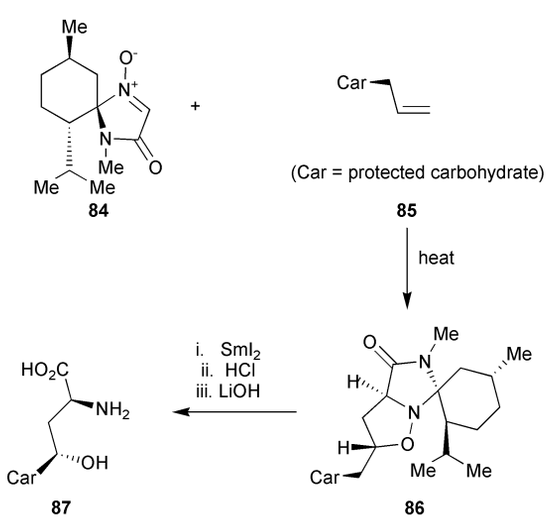
A stereoselective synthesis of L-isoxazolidinyl thymidine from *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldhyde nitrone (BIGN) *via* a 1,3-dipolar cycloaddition of BIGN with vinyl acetate, or vinylthymine, has been demonstrated. The cycloaddition proceeds in up to 88% yields, the product being formed as three diastereoisomers.[116]

Dihydro[*c*]benzazepin-3-ones **83** have been prepared from conjugated nitrone–allene precursors **82** *via* a multistep rearrangement, involving a 1,7-dipolar electrocyclisation process, in 24–93% yields (Scheme 27).[117]



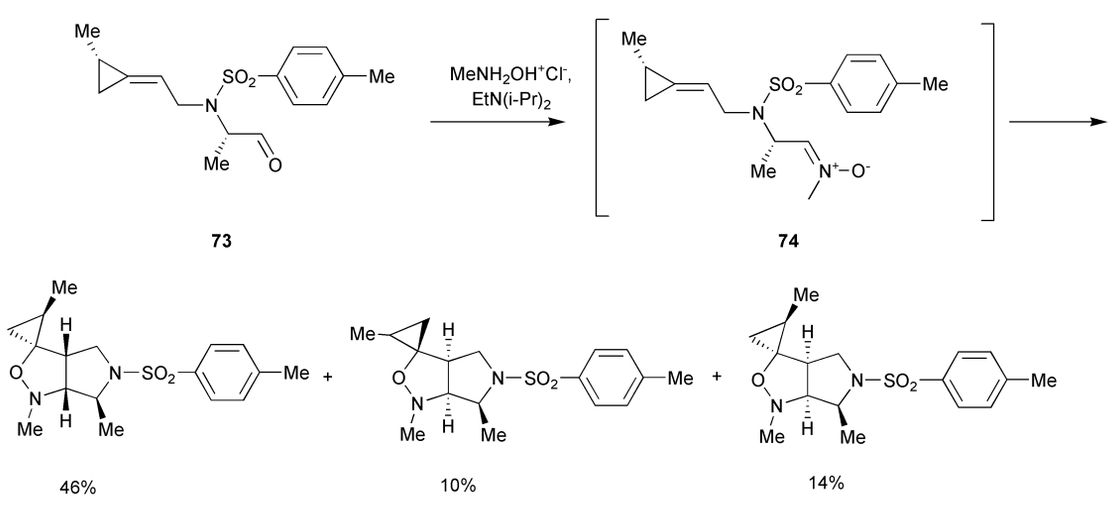
Scheme 27

The reaction of a 1,3-diploar cycloaddition of a chiral glycine equivalent **84** and *C*-allyl or vinyl derived carbohydrate **85** leads to the formation of isoxazolidines **86** in 82–92% yields (Scheme 28). Reductive cleavage of the N–O bond followed by removal of the chiral auxillary gave *C*-glycosylated amino-acids **87**.[118]



Scheme 28

Nitrones react with but-3-enylmagnesium bromide to give alkenylhydroxylamines that cyclise by retro-Cope elimination. Heating the diastereoisomeric mixtures of pyrrolidine *N*-oxides, in the absence of solvents, effected a highly diastereoselective isomerisation to provide *cis*-2,5-disubstituted products in 52–96% yield and 66–96% de.[119] Similarly the addition of Grignard reagents to D-*erythro*-pent-4-enose *N*-benzyl nitrone furnishes hydroxylamines that readily undergo Cope–House

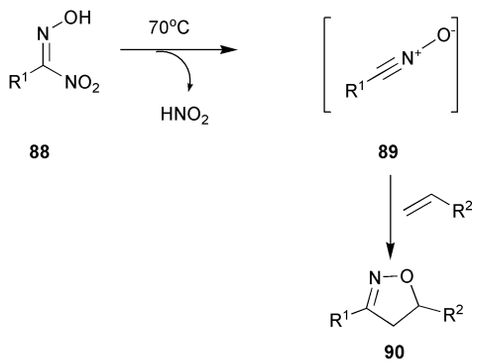


Scheme 25

cyclisation to afford pyrrolidine *N*-oxides in 12–91% as a mixture of diastereoisomers.[120]

17 Nitrile oxide cyclisations

Nitrolic acids **88** are easily prepared from nitroalkanes and are readily converted into nitrile oxides **89** upon heating. Trapping of the resultant nitrile oxides **89** with alkenes generates the isoxazolidines **90** in 40–95% yields (Scheme 29).[121]



Scheme 29

The regioselective 1,3-dipolar cycloaddition of nitrile oxides to 3-arylidene-4-chromanone has been used to prepare spiro-dihydroisoxazoles (spiroisoxazolines) in 77–90% yield.[122] The nitrile oxides themselves are formed from the action of a base on the corresponding hydroximinoyl chloride.

A total synthesis of 8,14-secostereoids used as a key step a nitrile oxide cycloaddition with enones, or enol derivatives of 1,3-diketones, to give the isoxazolines in 50–63% yields.[123] Reductive cleavage of the N–O bond of the isoxazolines was achieved with Raney nickel.

The magnesium-ion-mediated diastereoface-selective 1,3-dipolar cycloaddition of nitrile oxides with chiral 3-acryloyloxazolidin-2-ones leads to the highly diastereoselective formation of 2-isoxazolines. These asymmetric reactions are examples of Lewis-acid-mediated stereocontrol in the nitrile oxide cycloaddition to electron deficient dipolarophiles.[124]

An example of an antibody-catalysed asymmetric 1,3-dipolar cycloaddition of an arylnitrile oxide with *N*,*N*-dimethylacrylamide has been performed with 98% ee.[125]

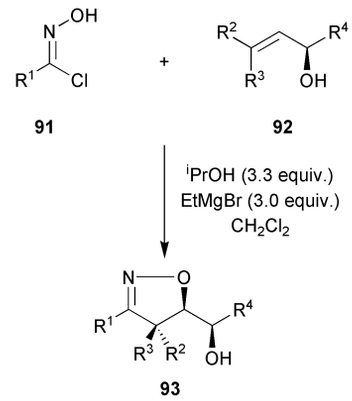
An approach to L-(+)-furanomycin uses furoisoxazoline intermediates as key intermediates. The furoisoxazolines are prepared by the cycloaddition of the dipolarophile 2-methylfuran with a chiral nitrile oxide in 67% yield as a mixture of two diastereoisomers.[126]

3-Aryl-4-methoxycarbonylisoxazoles have been synthesised from the reaction of various benzonitrile oxides with methyl 3-(4-nitrobenzoyloxy)acrylate in 43–96% yields.[127]

Kanemasa had previously demonstrated that treatment of benzohydroximinoyl chloride with organometallic compounds resulted in *O*-metallation followed by 1,3-elimination of a metal chloride. The liberated benzonitrile oxide forms a complex with the Lewis acidic metal salts. These complexes then undergo high yielding 1,3-dipolar cycloadditions to the magnesium alkoxides of allylic alcohols with high *syn* selectivity.[128] These Kanemasa magnesium–alkoxy directed nitrile oxide cycloadditions have recently been extended to aliphatic nitrile oxides to prepare *syn* isoxazolines, in 68–87% yields, as aldol equivalents for polyketide building blocks.[129] Hence the aliphatic hydroximinoyl chlorides **91** react with allylic alcohols **92** (in the presence of a Grignard reagent to form the corresponding nitrile oxides and magnesium alkoxides *in situ*) to form the *syn* isoxazolines **93** (Scheme 30).

Nitrile oxides derived from carbohydrates (D-galactose, D-mannose and D-xylose) undergo a cycloaddition with dipolarophiles (alkenes or alkynes) in 30–98% yields.[130]

The 1,3-dipolar cycloaddition of stannyl alkynes and nitrile oxides proceeds regioselectively and in 35–80% yield to the 4-stannylisoxazoles. No reaction is observed when vinyl- or allylstannanes are used.[131]



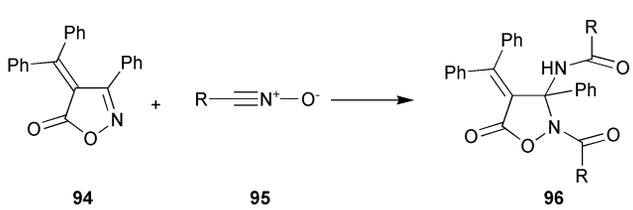
Scheme 30

Alk-2-enylphosphonates react with nitrile oxides to give the corresponding isoxazoline derivatives in 67–88% yields. The nitrile oxides were generated by the action of 4-chlorophenyl isocyanate with nitroalkanes and trapping the nitrile oxide with the alk-2-enylphosphonates *in situ*.[132]

The reaction of resin-bound alkynes with nitrile oxides, prepared *in situ* from the chlorination of oximes and subsequent elimination of hydrogen chloride, gives resin-bound oxazoles in high yields (as demonstrated by cleavage of the oxazoles from the resin in 60–90% overall yield for the cycloaddition–cleavage procedure).[133]

The intramolecular cycloaddition of 4-*O*-allyl nitrone or nitrile oxide species attached to 1,2-isopropylidene furanoside rings bearing an allyl ether side chain leads to isoxazolidines or isoxazolines. These products were further transformed into chiral oxepinopyran and oxepinooxepane systems.[134]

The reaction between nitrile oxides **95** and 4-diphenylmethylene-3-phenylisoxazol-5-one **94** does not proceed *via* a cyclisation but gives instead an unprecedented rearrangement to yield 4-diphenylmethylene-2,3,3-trisubstituted derivatives **96** in 15–16% yield (Scheme 31).[135]

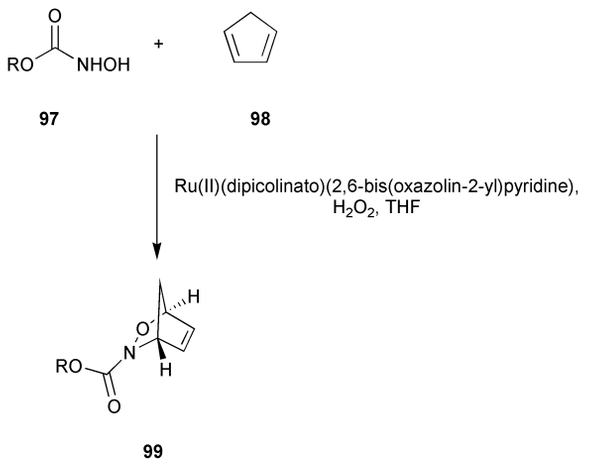


Scheme 31

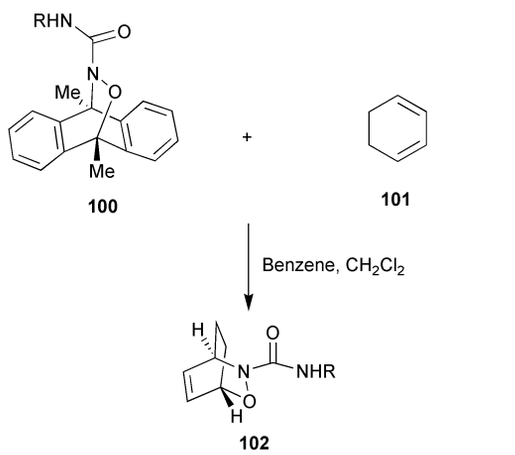
18 Acyl nitroso compounds

Oxidation of hydroxamic acids, *N*-hydroxyureas or *N*-hydroxycarbamates with Dess–Martin periodinane generates the corresponding acyl nitroso compounds. These acyl nitroso compounds undergo a hetero Diels–Alder reaction with conjugated dienes to produce the corresponding cycloadducts in 11–76% yields.[136] Similarly, the ruthenium(II)–pyridine-2,6-dicarboxylate or 2,6-bis(oxazolinyl)pyridineruthenium(II) complex catalysed the hydrogen peroxide oxidation of hydroxamic acid **97** in the presence of cyclopentadiene **98** to give acyl nitroso adducts **99** in 74–99% yields (Scheme 32).[137]

Retro Diels–Alder reaction of *N*-hydroxyurea-derived acyl nitroso-9,10-dimethylanthracene **100** produces acyl nitroso compounds which can be trapped *in situ* with cyclohexa-1,3-diene **101** to give the Diels–Alder products **102** (Scheme 33).[138]



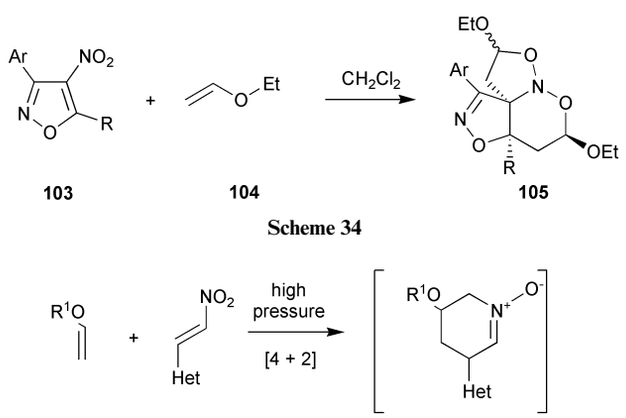
Scheme 32



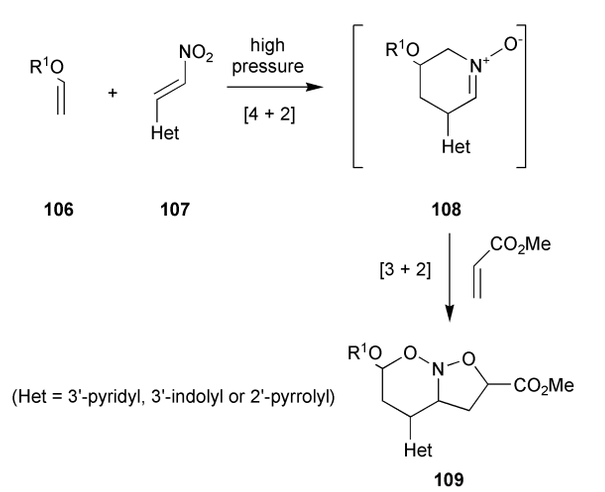
Scheme 33

4-Nitroisoxazoles **103** undergo a highly diastereoselective pericyclic reaction with ethyl vinyl ether **104** affording spiro tricyclic nitroso acetals **105** in 52–90% yields (Scheme 34).[139]

1-Nitro-2-heteroarylethenes **107** react with vinyl ethers **106** (4-methoxybenzyl vinyl ether) and methyl acrylate at high pressure (15 kbar) in a three-component reaction *via* tandem [4 + 2]/[3 + 2] cycloaddition to give novel heteroaromatic substituted five- or six-membered bicyclic nitroso acetals **109** (Scheme 35).[140]



Scheme 34



Scheme 35

The ease with which many compounds can be converted into nitro, nitroso or nitrone derivatives and the versatility of these compounds for simple transformations or cycloadditions ensures that this highly active area of chemistry will continue to be a topic of considerable interest for synthetic chemists.

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