REVIEW

Nitro and related compounds

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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 described in three previous reviews in this area.[1] Other recent reviews in this area include aromatic nitration,[2] aromatic nitrosation,[3] cyclic nitrones,[4] aliphatic nitro compounds,[5] and nitroalkane radicals.[6]

2 Nitration

Nitration of 2-nitrotoluene, 1-chloro-2-nitrobenzene and 1-chloro-4-nitrobenzene has been achieved using dinitrogen pentaoxide in dichloromethane at 0 °C. It has been shown that some zeolites, notably H-faujasite 720, catalyse this transformation and also increase the regioselectivity to the 4-position when nitrating 2-nitrotoluene or 1-chloro-2-nitrobenzene with respect to those reactions uncatalysed by the zeolites. The catalysed reaction gives yields of 93–96%.[7]

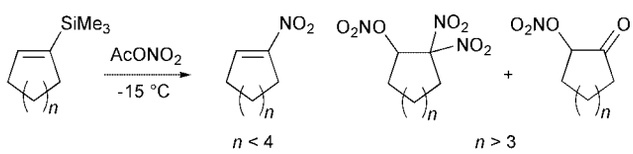
Dinitrogen tetraoxide interacts with 18-crown-6 to give the stable ionic crystalline complex $NO^+ \cdot 18\text{-crown-6} \cdot H(NO_3)_2^-$. This can then be used as a selective nitrating agent for phenol and substituted phenols with yields of 35–94%.[8]

Various polynitro musks have been prepared from the corresponding aromatic materials by ozone-mediated polynitration using nitrogen dioxide (Kyodai-nitration) in 40–82% yield.[9]

Nitration of *N*-protected indoles has been achieved with acetyl nitrate, prepared from 90% nitric acid and acetic anhydride, affording the corresponding 3-nitroindoles in 41–86% yield.[10]

A new methodology for the one-step conversion of olefins into α-nitro ketones has been studied. The nitration is achieved using a trimethylsilyl nitrate–DMSO reagent system (or chromium trioxide–trimethylsilyl nitrate) and proceeds in 45–73% yield.[11]

A facile method for the conversion of cyclic vinylsilanes **1** into α,β-unsaturated 1-nitrocycloalkenes **2** using acetyl nitrate has been studied. It was found that medium and large ring vinylsilanes gave novel 1,1-dinitro-2-nitrates **3** as the major products in 56–75% yield. In the case of the cyclooctyl derivative the keto nitrate **4** was also formed in 32% yield (Scheme 1).[12]

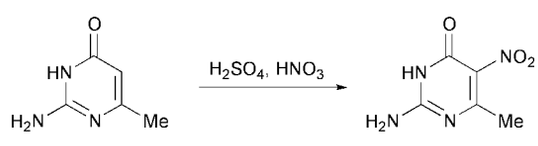


Scheme 1

Benzocrown-ethers can be efficiently nitrated using nitric acid in carbon tetrachloride at 45 °C in 96% yield.[13]

The direct synthesis of *p*-nitrocalix[4]arene from *p-tert*-butylcalix[4]arene has been achieved by using either concentrated nitric acid (82% yield) or potassium nitrate and aluminium chloride as a nitrating agent in the same yield.[14] The preparation of tetranitrotetrapropoxycalix[4]arene from the *tert*-butyltetrapropoxycalix[4]arene has been achieved using a mixture of trifluoroacetic acid and nitric acid at room temperature. A yield of 98% is achieved in dichloromethane.[15,16]

A high yield nitration of a pyrimidinone **5**, used in the synthesis of a novel *C*-nucleoside has been developed using a nitric–sulfuric acid reagent system to give the product **6** in 80% yield (Scheme 2).[17]



Scheme 2

The high regioselectivity achieved in the ring nitration of many methoxyphenyl derivatives has been studied using cerium ammonium nitrate coated on silica. It was found that nitration occurred only when there were at least two electron donating groups giving yields of 39–93%. *ipso*-Nitration and competition with oxidative demethylation leading to benzoquinones in the cases of easily oxidised substrates can be limitations.

Nitration of 1-methyluracil **7** uses copper nitrate in acetic anhydride at room temperature to give the 3-nitro derivative **8** in 77% yield. Subsequent treatment with sulfuric acid results in

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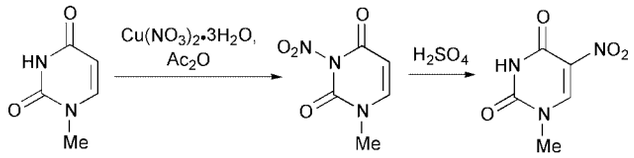
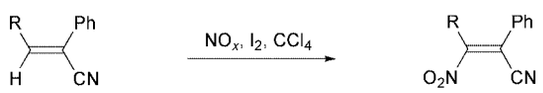


7 8 9

Scheme 3

a rearrangement to the 5-nitroderivative **9** (Scheme 3). Direct nitration at the 5′-position of uracil nucleosides has been achieved using *N*-nitropyrazole with triflic acid in acetonitrile in 73–96% yield.[18]

A facile site selective nitration of α,β-unsaturated nitriles **10** using a mixture of nitrogen monooxide and nitrogen dioxide has been investigated. The treatment of such compounds with nitrogen oxides in the presence of iodine in carbon tetrachloride at −5 °C gave the corresponding products **11** exclusively with the *Z*-geometry about the double bond in yields of 75–90% (Scheme 4).[19]



10 11

Scheme 4

3-Acetylindole and its derivatives can be regioselectively nitrated using nitronium tetrafluroborate in the presence of tin(IV) chloride. At −15 to −10 °C only 3-acetyl-5-nitroindole is formed (85% yield), while at 60 °C only 3-acetyl-6-nitroindole is formed.[20]

A procedure for the nitration of fullerenes has been developed using a mixture of nitric acid and copper powder in benzene (nitrogen dioxide is created *in situ*). The degree of nitration is dependent on the concentration of nitrogen dioxide, temperature and the reaction time. Selective synthesis of hexanitro[60]fullerenes is possible using extended reaction time (17 hours at 30 °C). The allylic *tert*-nitro groups are excellent leaving groups for nucleophilic substitution with aniline to produce hexaanilino[60]fullerenes in 94% yield.[21]

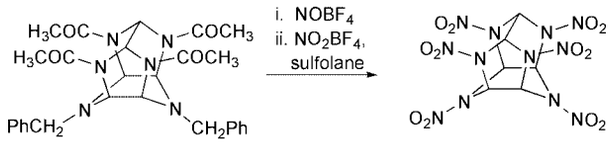
Nitration of 3,4-dihydro-2(1*H*)-quinoline has been achieved regioselectively using a mixture of nitric and sulfuric acid. By carrying the reaction out at low temperature and diluting the acid the yield of the mononitrated product can be raised to 90%.[22]

In the preparation of the anticancer drug 9-nitrocamptothecin, the nitration of camptothecin was studied using 19 different inorganic nitrate salts in a series of different solvents. Conversion was optimised using sulfuric acid as the solvent. A combination of potassium nitrate and thallium(I) nitrate allowed 9-nitrocamptothecin to be produced in 29% yield, (with 12-nitrocamptothecin as the major product—41%).[23]

Nitrate salts doped into clay (Clayfen–iron(III) nitrate on clay, and Clayan–ammonium nitrate on clay) are suitable for the solvent-free nitration of styrenes. Either Clayfen or Clayan converts both styrene and its *p*-substituted derivatives into the corresponding β-nitrostyrene with yields of 13–68%. A considerable amount of the corresponding aldehyde (9–21%) was also seen. [**EXTREME CAUTION** should be taken when heating the clays to above 70 °C in an oil bath or microwave].[24]

Sequential reaction of 4,10-dibenzyl-2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane **12** with nitrosonium tetrafluoroborate and nitronium tetrafluroborate in sulfolane† has been shown to give the corresponding caged polynitramine **13** in 90% yield (Scheme 5).[25]

† The IUPAC name for sulfolane is tetrahydrothiophene 1,1-dioxide.

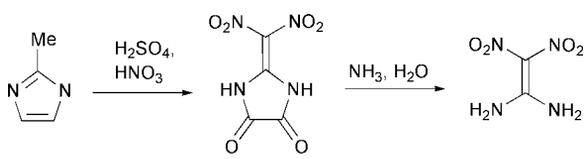


12 13

Scheme 5

An efficient and selective mono and dinitrating agent has been developed using a combination of dinitrogen tetraoxide and chromium nitrate ($Cr(NO_3)_3 \cdot 2N_2O_4$) which is prepared by passing N_2O_4 gas through a chromyl chloride solution in nitropropane. The complex can perform mononitration in a range of solvents at room temperature giving a mixture of the *ortho* and predominantly *para* products in a combined yield of 39–97%.[26]

In an approach to the synthesis of 1,1-diamino-2,2-dinitroethylene *via* the hydrolytic cleavage of nitrated heterocycles, imidazole derivatives were nitrated using nitric and sulfuric acid. It was found that the nitration of 2-methylimidazole **14** gave a product **15** that could then undergo a displacement reaction with ammonia to give the 1,1-diamino-2,2-dinitroethylene **16** in an 87% yield. (Scheme 6).[27]

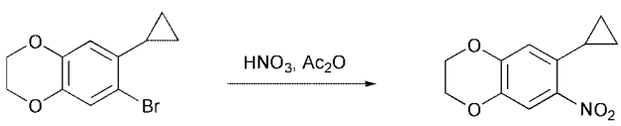


14 15 16

Scheme 6

The mononitration of electron rich aromatics and its associated problems of regioselectivity, over-nitration and the competitive oxidation of substrates has been studied and led to the use of either nitronium tetrafluoroborate or Claycop (copper nitrate impregnated on K10 Montmorillonite). The reactions proceeded rapidly, with substitution mainly occurring *ortho* to the directing group, with yields of 31–89%.[28]

Nitration of 6-bromo-7-cyclopropyl-2,3-dihydro-1,4-benzodioxine **17** using nitric acid in acetic anhydride gave 6-nitro-7-cyclopropyl-2,3-dihydro-1,4-benzodioxine **18** in 72% yield (Scheme 7).[29]



17 18

Scheme 7

In a stereospecific synthesis of a 9-substituted benzolactam from L-tyrosine, aromatic nitration was initially achieved using lanthanum nitrate as a phase transfer catalyst and sodium nitrate with hydrochloric acid as the nitrating agent in dichloromethane. The nitro group was then reduced and protected as an acetamide to achieve the correct electronic distribution on the benzene ring. Further nitration into the correct position on the ring was then achieved using nitric acid and acetic anhydride, followed by removal of the acetamide group.[30]

Vanadium oxynitrate is a powerful new reagent for nitrating aromatic rings at room temperature in dichloromethane under non-acidic conditions. High yields are reported with varying degrees of regioselectivity and mono- and dinitration.[31]

The nitration of polyaromatic hydrocarbons can have many problems associated with it, including insolubility of substrates and polynitration. Sulfuric acid supported on silica in the

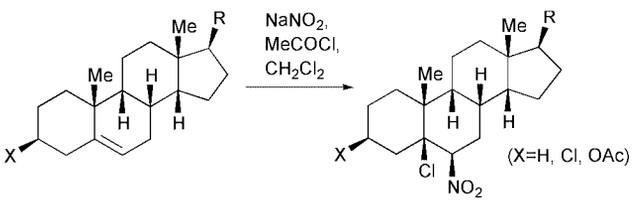
presence of nitric acid proved to be suitable for the regioselective nitration of polyaromatics, with a simple work-up procedure, giving yields of 45–82%.[32]

The electron deficient nature of the pyridine ring makes nitration difficult even when electron donating groups are attached. The problem has been circumvented by the use of nitrogen pentaoxide and a buffered solution of sodium bisulfite, which gives 3-nitro-4-acylaminopyridines products from 4-acylaminopyridines in 63–72% yield.[33]

The employment of modified clays and zeolites with nitric acid has been shown to be suitable for the regioselective nitration of aromatics with combined yields of 30–98% for *o*-, *m*- and *p*-nitration.[34]

Mixtures of highly nitrated cubanes (including heptanitrocubane) have been accessed from 1,3,5,7-tetranitrocubane using sodium bis(trimethylsilyl)amide followed by addition of dinitrogen tetraoxide. The previously elusive octanitrocubane can then be synthesised in 45–55% yield by addition of nitrosyl chloride to a solution of the lithium salt of heptanitrocubane.[35]

A facile method for the nitration of steroidal olefins **19** employs a sodium nitrite–acetyl chloride reagent system to furnish the nitrated steroids **20** in a 45–70% yield (Scheme 8).[36]

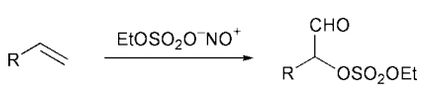


19 **20**

Scheme 8

3 Nitrosation

Nitrosonium ethyl sulfate, prepared *in situ* from ethyl nitrite and sulfur trioxide, is a highly reactive nitrosating reagent for the conversion of terminal olefins **21** and dienes into substituted aldehydes and ketones. Terminal olefins **21** furnish the corresponding α-ethylsulfato substituted aldehydes **22** in 70–75% yield (Scheme 9). The reaction with isoprene gives



21 **22**

Scheme 9

4-hydroxy-2-methylbut-2-enal in 78% yield with the *E*-configuration. Adding aqueous ethanol at −55 °C gave a reversal to predominantly the *Z*-configuration about the double bond.[37]

During a study into the formation and reactivity of *S*-nitrosothiols, the use of a two-phase system has been employed in order to circumvent the problems associated with the use of dinitrogen tetraoxide. The method involves addition of the thiol to an acidic solution of sodium nitrite followed by precipitation forced by addition of methanol at −10 °C.[38]

An efficient method of *S*-nitrosothiol preparation has also been reported employing a combination of oxalic acid and sodium nitrite in *tert*-butyl alcohol at room temperature.[39] A combination of oxalic acid and sodium nitrite has also been used in the preparation of the nitroso derivatives of secondary amines in 90–100% yields.[40]

Nitrosation of the ketoxime 2,6-dimethylhepta-2,5-dien-4-one oxime furnishes the *N*,*N*′-dioxygenated pyrazole 3,3-dimethyl-5-(2-methylprop-1-enyl)-3*H*-pyrazole 1,2-dioxide in 80% yield using butyl nitrite as the nitrosating reagent.[41]

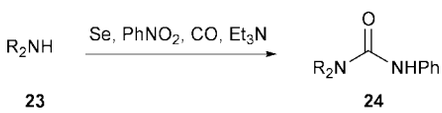
Secondary amines have been allowed to react with nitric oxide in the presence of oxygen to furnish *N*-nitrosoamines in yields of 26–100%. Investigation led to the conclusion that the reaction proceeds by two distinct pathways to yield the same nitroso adducts. One pathway involves oxygen as a catalyst and the other requires stoichiometric amounts of oxygen.[42]

Olefins (styrenes, α,β-unsaturated carbonyl compounds and α,β,γ,δ-unsaturated carbonyl compounds) have been directly converted into oximes in 31–94% yields using a cobalt(II) porphyrin catalysed reduction–nitrosation methodology using triethylsilane and *tert*-butyl nitrite.[43]

4 Reduction of nitro compounds

The reduction of aryl nitro compounds into the corresponding anilines has been reported to proceed smoothly using aluminium and ammonium chloride in methanol. The reaction rate was greatly enhanced by irradiating in an ultrasonic bath giving the product in 70–90% yields.[44]

It has been shown that selenium catalyses the reductive carbonylation of nitrobenzene to selectively afford unsymmetrical phenylureas **24** in 0–80% yields with secondary amines **23** (Scheme 10). When primary amines are used, mixed products



23 **24**

Scheme 10

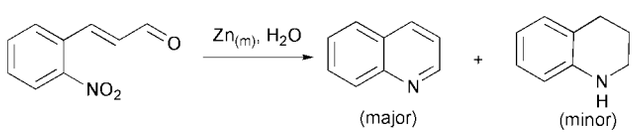
were obtained comprising of RNHCONHR, RNHCONHPh and PhNHCONHPh.[45]

Hydrazoarenes can be prepared in yields of 32–95% from the corresponding nitroarene with aluminium and potassium hydroxide in methanol, at ambient temperature. The coupling is proposed to proceed by a single electron transfer mechanism. In most cases traces of anilines were also formed. 4-Nitroanisole gave mainly the corresponding azoarene.[46]

Ultrasonically activated nickel (UAN) is obtained from the reduction of anhydrous nickel chloride with ultrasonically dispersed potassium. UAN produces azoxyarenes as the major products from nitroarenes. The azoxyarenes can then be converted into the corresponding azo- or azoxy compounds by hydrazine hydrate using the same catalyst. Yields of 25–59% were reported.[47]

In the presence of a catalytic amount of iodine, the reduction of nitroarenes into primary amines and hydrazines proceeds in yields of 56–70% with a THF solution of samarium and aqueous ammonium chloride. Amido and halogen substituents on the ring are unaffected.[48]

Quinoline **26** is produced when functionalised *o*-nitroarene **25** is treated with zinc powder in near-critical water at 250 °C (Scheme 11). The process is thought to proceed *via* a reduction of the nitro group followed by *in situ* cyclisation with a carbonyl or alcohol moiety, giving yields of 62–85%. Indoles can also be prepared in 80–91% yield using phenylacetaldehyde derivatives by this method.[49]



25 **26** **27**

Scheme 11

The reduction of 2- and 4-substituted nitrobenzenes to the corresponding anilines has been effected using electrogenerated nickel, without affecting various other substituents (alkenyl, alkynyl, halo, acetyl, methoxy, cyano, ethoxycarbonyl, formyl, benzyloxy and phenylsulfonylamino) at room temperature. The nickel can be easily prepared and gives various anilines in yields

of 22–92%. The highly activated nickel is prepared by electrolysis using a platinum cathode and nickel anode in DMF with tetrabutylammonium tetrafluoroborate under constant current.[50]

A rapid and inexpensive method for reduction of nitroarenes to anilines has been developed using ferric chloride and zinc in DMF and water, giving yields of 71–92%.[51] This system has also been used for the reduction of carbonyl compounds to alcohols.[52]

An isolable complex formed using palladium on carbon and ethylenediamine was found to catalyse the chemoselective hydrogenation of a nitro group (in addition to olefin, acetylenic, benzyl ester and azido groups) in 98% yield. *N*-Benzyl and *N*-benzyloxycarbonyl groups are untouched under these conditions.[53]

Secondary and tertiary amines have been selectively prepared in 66–77% and 72–88% yields, respectively, by a one-pot reduction–alkylation procedure. Aromatic nitro compounds are treated with an olefin (styrene, cyclic olefins or heterofunctionalised olefins) and $[Rh(cod)Cl]_2$ catalyst under an atmosphere of carbon monoxide (30 bar) and hydrogen (60 bar). If 3:1 nitro compound:olefin is used, monoalkylation predominates. If excess olefin is used then bisalkylation is preferred.[54]

High activity and selectivity for the reduction of aromatic nitro compounds under mild reaction conditions has been reported using hydrazine hydrate in the presence of an iron(III) oxide–magnesium oxide catalyst with 96–100% conversion.[55]

Nitrobenzene derivatives have been reduced to the corresponding aromatic amines by using 4 equivalents of samarium and a catalytic amount of iodine in methanol or THF. The yields ranged from 60–95%.[56]

The Ni(0) complex $Ni[P(OPh)_3]_4$ has been used in catalytic transfer hydrogenation with ammonium formate to reduce a variety of functionalities, including the reduction of 4-nitrotoluene to 4-aminotoluene in 68% yield.[57]

The conversion of *o*-carboran-1-ylsodium compounds into the nitro derivatives of *o*-carboranes‡ *via* 1,4-addition to unsaturated nitro compounds has been studied. The products can then be reduced with lithium aluminium hydride in ether, to furnish primary *o*-carboran-1-ylalkylamines in 30–40% yields.[58]

A mild hydrogenation of nitro aromatics, in the presence of γ-Al_2O_3 supported palladium(II)–pyrazol-5-one complexes, has been reported to give anilines in 95–98% yield.[59] Nitrobenzenes have also been chemoselectively reduced to anilines using decaborane in the presence of palladium on carbon and a trace amount of acetic acid and methanol at reflux in 81–97% yield.[60]

5 Synthesis of nitrones

Oximes have been oxidised to nitroalkanes by using oxone in acetonitrile, buffered to pH 7.5, in 52–75% yields.[61]

A one-pot, solvent-free synthesis of cyclic α-nitroketones has been realised in 68–86% yield *via* a Henry reaction on neutral alumina followed by an *in situ* oxidation of the intermediate nitroalkanol using chromium(VI) oxide supported on alumina.[62]

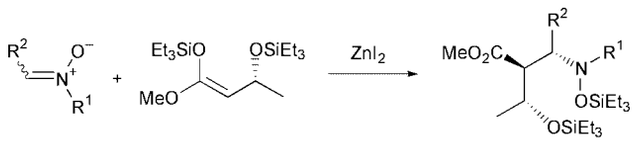
Hydroxylamines have been oxidised to nitrones in 50–92% yield using sodium hypochlorite and potassium bisulfate in dichloromethane.[63] *N*,*N*-Disubstituted hydroxylamines have also been oxidised to nitrones using hydrogen peroxide, sodium hypochlorite or iodosylbenzene as the stoichiometric oxidant in the presence of Jacobsen's catalyst (Mn(III) (salen) complexes).[64]

6 Addition to nitrones

Enantiopure 5-substituted-3-pyrrolin-2-ones have been readily prepared from *N*-benzyl-2,3-diisopropylidene-D-glyceraldehyde nitrone using the lithium salt of methyl propiolate. The *syn*:*anti* ratio is dependent upon the nature of the Lewis acid used as an additive.[65]

N-Benzylpyrrolidin-2-yl nitrones derived from L-proline, undergo highly diastereoselective nucleophilic addition of Grignard and organolithium compounds with high *syn* selectivity to give enantiomerically pure pyrrolidinylbenzyl hydroxylamines in 72–95% yields and with *syn*:*anti* ratios from 3:1 to 25:1.[66]

A chiral ketene silyl acetal **29** has been shown to undergo a highly diastereoselective addition to nitrones **28** using zinc diiodide in acetic acid to give the hydroxylamine derivative **30** in 60–89% yields (Scheme 12).[67]



28 **29** **30**

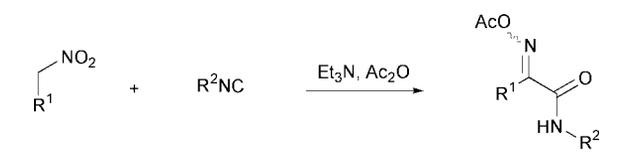
Scheme 12

Addition of (trifluoromethyl)trimethylsilane to α,*N*-diarylnitrones using potassium butoxide in THF at −78 °C has produced a series of α-(trifluoromethyl)-*N*-hydroxylamines protected as their *O*-trimethylsilyl derivatives in 37–54% yields. Conducting the chemistry at 25 °C results in the α-(trifluoromethyl)imine being formed (35–63% yields).[68]

Grignard addition to the *N*-benzylnitrones derived from β-amino-α-hydroxy aldehydes has been shown to proceed to the corresponding α-substituted hydroxylamines in 62–96% yield. *syn* Selectivity predominated but a reversal of diastereoselectivity was observed when Lewis acids were added to the complex with the nitrones.[69]

7 Conversion to oximes

A multicomponent reaction between nitro compounds **31**, isocyanides **32** and acylating agents provides an original route to α-oximinoamides **33** in 30–65% yields (Scheme 13).[70] Higher



31 **32** **33**

Scheme 13

yields are obtained in DMSO than when toluene is used as solvent.[71]

C-Glycopyranosylnitromethanes have been converted into the corresponding methanal oximes using tributyltin hydride and a catalytic amount of azobiscyclohexylcarbonitrile in 84–97% as a mixture of *E*- and *Z*-isomers.[72]

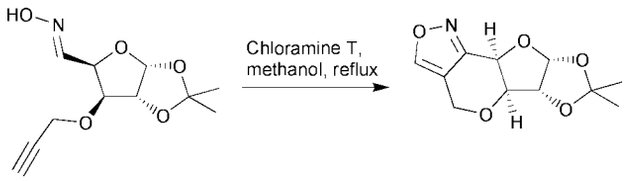
1-Bromo-1-nitroalkanes react with trialkylphosphites to give dialkyl (1-hydroxyiminoalkyl)phosphonates in 52–62% yields as a mixture of *E*- and *Z*-isomers.[73]

8 Nitrile oxide cycloadditions

Intramolecular cycloaddition of 3-*O*-alkynyl carbohydrate nitrile oxides has been used in an approach to the synthesis of enantiomerically pure isoxazole derivatives **35**. The nitrile oxide is prepared *in situ* by the action of Chloramine T on the oxime **34** with the subsequent cycloaddition proceeding in an 84% overall yield (Scheme 14).[74]

2-Isoxazolines and oxazoles possessing phosphonate groups can be prepared by the 1,3-dipolar cycloaddition reaction of

‡ The IUPAC name for *o*-carborane is 1,2-dicarbadodecacarborane.



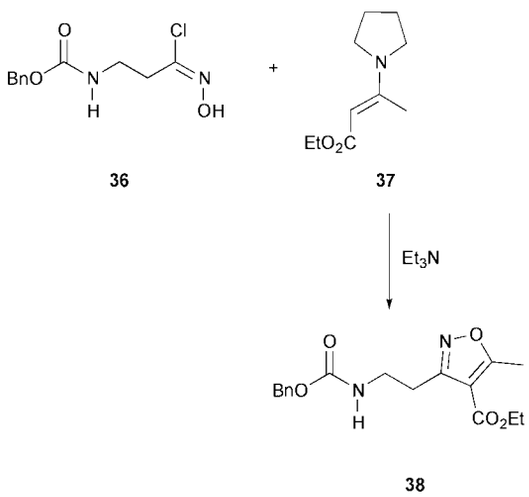
34 35

Scheme 14

nitrile oxides with unsaturated phosphonates in 67–88% yields.[75]

The oxidative action of manganese(IV) oxide on aldoximes generates nitrile oxides *in situ* at ambient temperature, which can themselves be trapped with dipolarophiles to form 2-oxazoles in 41–92% yields. This procedure proved to be ineffective when dodecanal oxime was used.[76]

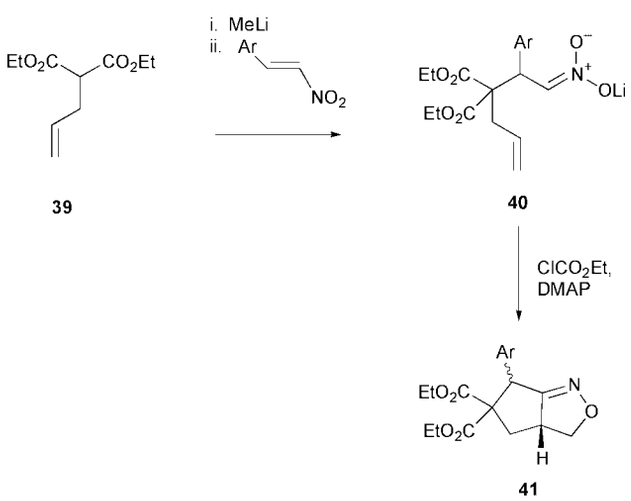
A β-aminonitrile oxide, formed from an oxime derivative of β-alanine **36**, has been treated with an enamine of a β-ketoester **37** to afford the 3-(2-aminoalkyl)isoxazole-4-carboxylic ester **38** in 69% yield (Scheme 15).[77]



36 37 38

Scheme 15

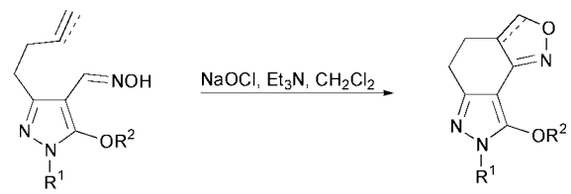
The anion prepared from the action of methyllithium on diethyl allylmalonate **39** undergoes a Michael addition to β-nitrostyrenes to give the corresponding nitronates **40**. Treatment of the nitronates **40** with ethyl chloroformate in the presence of 4-dimethylaminopyridine, as catalyst, generates the nitrile oxides, which then undergo intramolecular nitrile oxide–olefin cycloadditions (INOCs) in 41–76% yields to give the isoxazoline products **41** (Scheme 16).[78]



39 40 41

Scheme 16

An INOC procedure has been used to prepare 3a,4,5,7-tetrahydro-3*H*-isoxazolo[3,4-*e*]indazole **43** and pyrazolo(3,4-γ)(2,1)-dihydrobenzoisoxazoles **43** by utilising NaOCl to oxidise oximes **42** containing alkenyl- and alkynyl functionality respectively (Scheme 17).[79] Chloramine T has been used for the

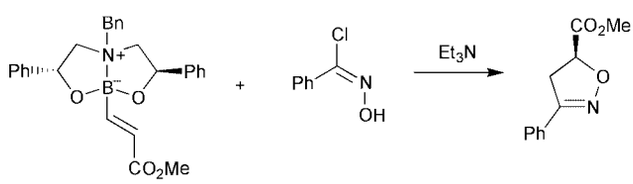


42 43

Scheme 17

oxidation of a steroidal oxime such that a subsequent INOC resulted in a steroidal isoxazoline.[80]

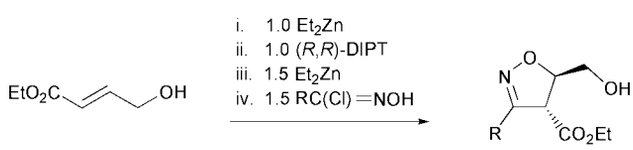
Chiral vinyldioxazaborocines **44** undergo 1,3-dipolar cycloadditions with benzonitrile oxide, itself prepared *in situ* by the action of triethylamine on the chloro oxime **45**, to furnish enantiomerically enriched 5-substituted 2-isoxazolines **46** in 43–65% yields (Scheme 18).[81]



44 45 46

Scheme 18

The asymmetric 1,3-dipolar cycloaddition of nitrile oxides, prepared from hydroximoyl chlorides, to γ-substituted allylic alcohols **47** has been demonstrated using the chiral additive diisopropyl (*R*,*R*)-tartrate to furnish 3,4,5-trisubstituted 1,2-isoxazolines **48** in high regio- and enantioselectivities (89–98% ee) (Scheme 19).[82]



47 48

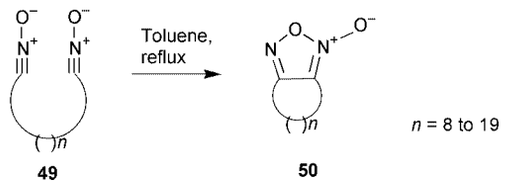
Scheme 19

1,4-Diisocyanatobenzene has been used for the *in situ* preparation of nitrile oxides from nitro groups. The nitrile oxides then underwent cycloadditions with alkenes or alkynes to furnish isoxazolines or isoxazoles respectively.[83]

Isoxazolines have been prepared in 62–94% yields from oximes by *in situ* formation of the nitrile oxide using sodium hypochlorite or calcium hypochlorite and subsequent reaction with olefins. The yields are enhanced by the use of sonication over more "classical" stirring under the same conditions.[84]

An intramolecular nitrile oxide dimerisation has been used to furnish medium and large rings **50** in 80–85% yield in an efficient C–C bond-forming ring-closing reaction. The nitrile oxides **49** are prepared in a one-pot procedure from aldehydes by reaction with hydroxylamine to form oximes that then undergo oxidation with sodium hypochlorite (Scheme 20).[85]

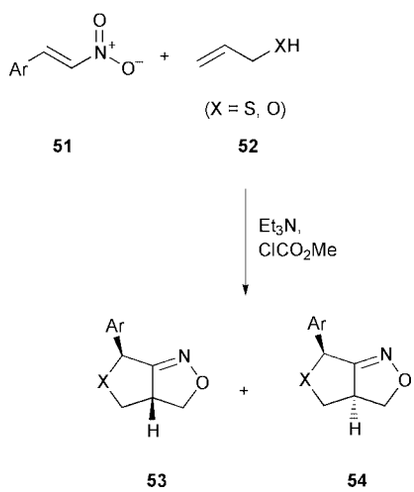
A one-pot synthesis of 5-membered cyclic thioethers or ethers *via* INOC or IAOC (intramolecular alkoxycarbonyl nitronate-olefin cycloaddition) has been demonstrated. Michael addition of prop-2-enethiol **52** to β-nitrostyrenes **51**, in the presence of triethylamine is followed by treatment of this



49 50

Scheme 20

solution with methyl chloroformate in THF or diethyl ether at reflux to give the desired bicyclo products in 39–99% *via* INOC. These intermediates can undergo IAOC to give the *trans* bicyclo product or INOC to give the products **53** and **54** as a *cis–trans* mixture (Scheme 21). The nitronates prepared by the action of allyl alcohol **52** and a base on β-nitrostyrenes **51** can be converted into methoxycarbonyl nitronates using methyl chloroformate in the presence of DMAP and triethylamine.[86]



51 52 53 54

Scheme 21

Nitrile oxides can also be generated from α-hydroxyimino carboxylic acid derivatives with ammonium hexanitratocerate(IV) (CAN). The resultant nitrile oxides can undergo 1,3-cycloaddition with olefinic and acetylenic dipolarophiles to give the cycloaddition products in 12–98% yields.[87]

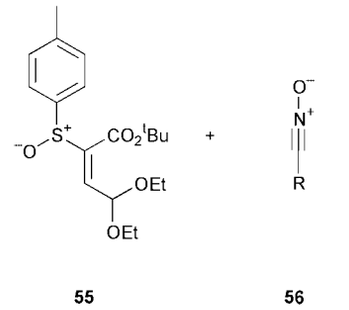
The 1,3-cycloaddition of nitrile oxides **56** to *tert*-butyl (*E*)-4,4-diethoxy-2–*p*-tolylsulfinylbut-2-enoate **55** yield isoxazoles **57** and **58**, with 69–71% yields of the major products **57** (Scheme 22). 5-Ethoxy-3-*p*-tolylsulfinylfuranones react to give isoxazolines by retaining the sulfinyl group.[88]

The 1,3-dipolar cycloadditions of mesitonitrile oxide **60** to β-hydroxy-α-methylene esters **59** (Bayliss–Hillman adducts) proceed with good regioselectivity to give the isoxazolines **61** and **62** (Scheme 23). Formation of the Mg-alkoxide reverses the diastereoselectivity of the cycloaddition. This reversal in diastereoselectivity is believed to be due to the magnesium forming a chelated intermediate. Subjecting the reaction mixture to microwave irradiation strongly accelerates the rate of reaction with only small changes to diastereoisomeric excesses.[89]

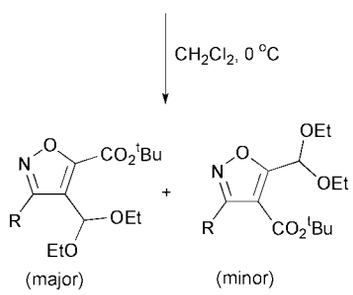
9 Nitrone cycloaddition

The 1,3-dipolar cycloaddition between diphenyl nitrone and 4-(*S*)-benzyl-3-[(*E*)-but-2′-enoyl]-1,3-oxazolidin-2-one was demonstrated to give differing ratios of diastereoisomers in the presence of different inorganic salts (Lewis acids). The conformations adopted by the 4-(*S*)-benzyl-[(*E*)-but-2′-enoyl)-1,3-oxazolidin-2-one, **63** and **64**, when co-ordinated to the cations, can be used to rationalise the diastereoselectivity (Fig. 1).[90]

A proline-derived nitrone has been shown to readily undergo [3+2] cycloadditions with a variety of alkenes and alkynes to give isoxazolidines and isoxazolines respectively in 14–84% yield.[91]

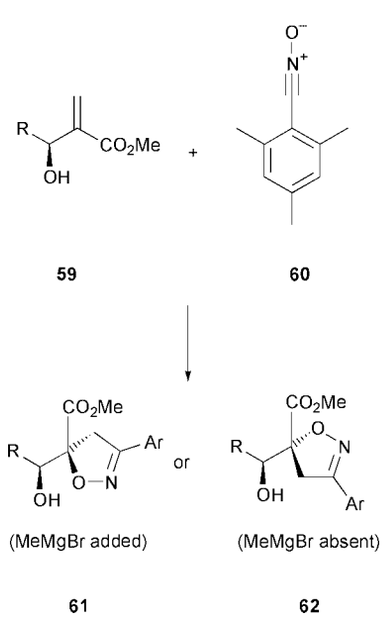


55 56



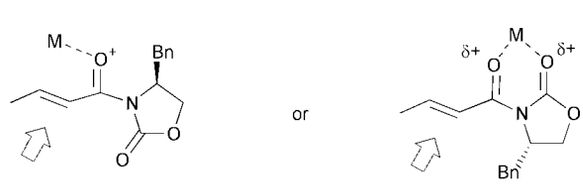
57 58

Scheme 22



59 60 61 62

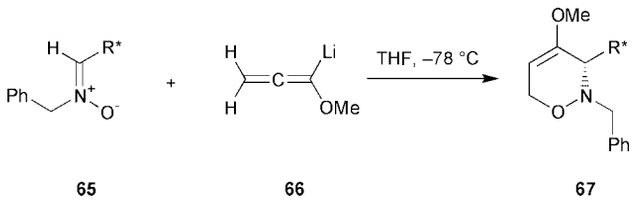
Scheme 23



63 64

Fig. 1

A new diastereoselective synthesis of enantiomerically pure 1,2-oxazine derivatives **67** by the addition of lithiated methoxyallene **66** to chiral nitrones **65** in yields of 35–82% has been achieved. *Syn*:*anti* Ratios of 90:10 to 98:2 were observed (Scheme 24). Precomplexation of the nitrones **65** with diethylaluminium chloride results in excellent *anti* selectivity.[92]



65 66 67

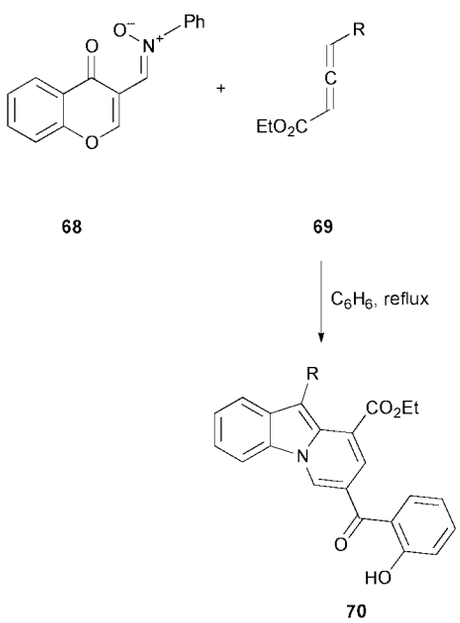
Scheme 24

The use of copper (II)- and zinc(II) bisoxazolines as catalysts for the diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between electrophilic nitrones and electron rich olefins has been developed. The nitrones coordinate to the catalysts in a bidentate fashion and react smoothly with the alkenes at room temperature to give the isoxazolidines in 43–83% yields with high diastereoselectivity and with enantioselectivities of up to 94% ee. The reactive intermediate is proposed to consist of both the nitrone and alkene coordinated to the chiral catalyst.[93]

Control of enantiofacial selectivity in 1,3-dipolar cycloaddition reactions has been achieved using a chiral ytterbium catalyst, prepared from ytterbium triflate, (*S*)-BINOL and the amine (*R*)-MNEA (*N*-methyl-bis[(*R*)-1-(naphthyl)ethyl]amine) while choosing different achiral additives and different nitrones. 4 Å molecular sieves were shown to both increase the yields and reverse the enantiofacial selectivity.[94]

The intramolecular 1,3-dipolar cycloaddition reactions of (*Z*)-*N*-alk-4-enylnitrones possessing various alkenyl substituents has been investigated and the regiochemistries of the resulting isoxazolidines determined. Bromo- and silyl-substituents effect significant regiocontrol on the intramolecular nitrone dipolar cycloaddition reaction.[95] An intramolecular (*Z*)-*N*-alk-4-enylnitrone cycloaddition reaction was used as the key step in the synthesis of the indolizidine core of the allopumiliotoxins.[96]

Functionalised 1-benzoindolizines **70** have been prepared in 35–60% yield by the regioselective 1,3-dipolar cycloaddition of *N*-(4-oxo-4*H*-1-benzopyran-3-ylmethylidone)phenylamine *N*-oxide **68** to allenic esters **69**. The cycloadducts undergo a series of intramolecular rearrangements including an intramolecular [4+2] cycloaddition *in situ* to give the products **70** (Scheme 25).[97]



68 69 70

Scheme 25

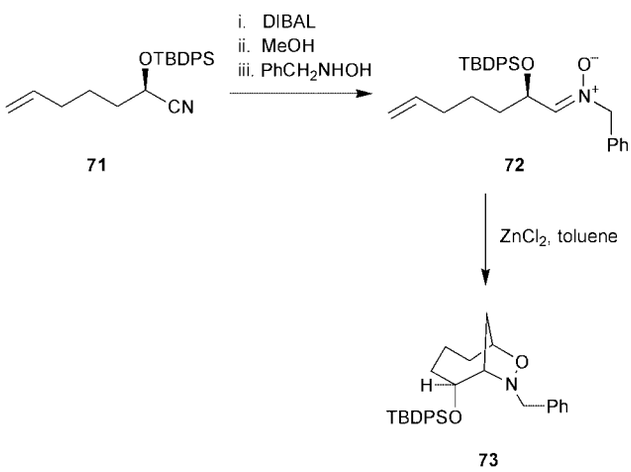
Synthetic polyoxoaluminium Keggin ion pillared Buserite (KPB) is an effective catalyst for the 1,3-diploar cycloadditions of α-*N*-diaryl nitrones with electron deficient olefins. The 4-substituted isoxazolidine products are exclusively *trans*.[98]

The intramolecular cycloadditions of nitrones derived from 1-allylpyrrole-2-carbaldehyde have provided a route to racemic and enantiopure pyrrolizidines and indolizidines.[99]

A synthetic strategy towards the stereoselective synthesis of 2′-amino-2′,3′-dideoxynucleosides relies upon a 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones to allyl acetate.[100]

Enantiopure hydroxylated nitrones undergo a 1,3-dipolar cycloaddition to glycals in a reaction which is strongly accelerated under high pressure. At 10 kbar pressure tricyclic isoxazolidines are obtained in 56–100% yields.[101]

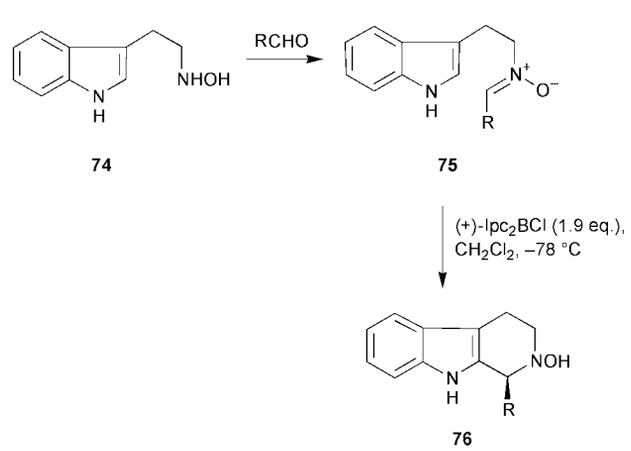
Intramolecular 1,3-dipolar cycloaddition of an ω-unsaturated chiral nitrone **72** using one equivalent of zinc chloride in toluene has led to an isoxazolidine **73** in high yield (85%) and high enantiomeric purity (94% ee). The nitrone **72** was prepared in a one-pot procedure by the action of DIBAL-H on an *O*-protected chiral cyanohydrin **71** followed by the addition of methanol to liberate the free imine. Subsequent addition of *N*-benzylhydroxylamine resulted in the formation of the chiral nitrone **72** in 90% yield and 96% ee (Scheme 26).[102]



71 72 73

Scheme 26

The use of diisopinocampheylchloroborane as a chiral Lewis catalyst in the Pictet–Spengler reaction of *N*-hydroxytryptamine **74** with aldehydes furnishes the corresponding 2-hydroxytetrahydro-β-carbolines **76** in 39–94% yields with 15–90% ee *via* nitrones **75**. Chiral binaphthol derived Brønsted acid-assisted Lewis acids have also been used to give enantiomeric excesses up to 91% (Scheme 27).[103]



74 75 76

Scheme 27

In a synthesis of the nonproteinogenic amino acid (2*S*,-3*S*,4*S*)-3-hydroxy-4-methylproline, a constituent of antifungal echinocandins, a cycloaddition of *N*-(methylidene)methyl-

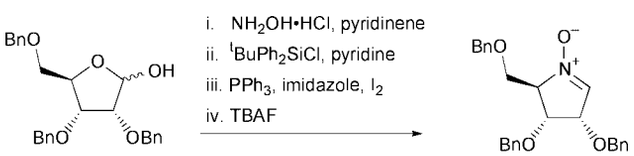
amine *N*-oxide to an α,β-unsaturated lactam derived from (*S*)-pyroglutaminol was conducted in 70% yield.[104]

Cyclic nitrones react with γ-oxo-α,β-unsaturated esters with a strong preference (*ca*. 20:1) for those bicyclic isoxazolidine regioisomers with the oxygen atom of the nitrone becoming attached to the β-ester position. This high regioselectivity is attributed to steric factors.[105]

The palladium(II) catalysed 1,3-dipolar cycloadditions of nitrones with enol ethers proceeds smoothly in 71–100% yield with 50:50 to 91:9 mixtures of diastereoisomers.[106] The 1,3-dipolar cycloaddition reactions of *trans*-2-methylene-1,3-dithiolane 1,3-dioxide with nitrones furnish spiro isoxazolidines in 64–86% yields.[107]

In the ytterbium trifluoromethanesulfonate catalysed diastereoselective 1,3-dipolar cycloaddition reactions of *N*-(benzylidene)phenylamine *N*-oxide with *N*-crotonoyloxazolone or *N*-crotonoylpyrrolid-2-inone the *endo* product is predominant in toluene while the *exo* product predominates when acetonitrile is used as solvent. However, when *N*-crotonoylimidazolinone or *N*-crotonoylsuccinimide are subjected to the same reaction conditions, the *exo* adducts are the major products in both solvents.[108]

Nitrones derived from D-ribose have been used for 1,3-dipolar cycloadditions and for nucleophilic additions. The chiral cyclic nitrones **78** were prepared in a 4-step procedure by ring opening of the functionalised D-ribose **77** with hydroxylamine followed by the protection of the resultant oxime with the *tert*-butyldiphenylsilyl group, conversion of the secondary hydroxy to an iodide and then treatment of the silyl oxime with tetrabutylammonium fluoride (Scheme 28).[109].



Scheme 28

A study of the [3 + 2] cycloaddition of nitrones to dec-1-ene has shown that the isoxazolidine regioisomers with the oxygen attached to the 2-position of the dec-1-ene and with the *syn* diastereoisomer predominates.[110]

The 1,3-dipolar cycloaddition of allylic and homoallylic alcohols to *N*-(benzylidine)methylamine *N*-oxide, in toluene at 80 °C, occur much more rapidly in the presence of the Lewis acid magnesium bromide–diethyl ether and with stereoselectivities in the range 5:1 to >95:5. The purely thermal reactions are largely stereorandom and require over 48 hours.[111]

In a total synthesis of (−)-histrionicotoxin an intermolecular nitrone [3 + 2] cycloaddition with styrene gave a masked nitrone which was later revealed by a retro reaction at 190 °C in toluene in a sealed tube. The revealed nitrone was then able to undergo an intramolecular cycloaddition with an α,β-unsaturated nitrile.[112]

10 Miscellaneous

β-Nitro oximes have been prepared by the C–C cross coupling of terminal *N*,*N*-bis(silyloxy)enamine nitronate anions formed from the action of base on the corresponding nitro compound in 42–94% yield. Conjugated nitroso alkenes generated from the *N*,*N*-bis(silyloxy)enamines are believed to be the intermediates in the reaction pathway.[113]

The oxidative *N*-dealkylation of secondary *N*-aryl-*N*-alkylamines proceeds cleanly with zirconium(IV) butoxide and *tert*-butyl hydroperoxide to give nitroarenes in 49–76% yields. Applying similar conditions to nitrones results in cleavage of the C–N bond to give the corresponding carbonyl compounds in quantitative yields.[114]

The Michael addition of nitroalkanes to α,β-unsaturated carbonyl compounds has been conducted at room temperature in the presence of potassium fluoride supported on a natural phosphate as a catalyst to give 51–98% yields of the desired γ-nitro carbonyl compounds.[115] The conjugate addition of a nitroalkane to an enedione using DBU as base in acetonitrile, followed by elimination of nitrous acid, leads to alk-2-enyl 1,4-diketones in yields of 32–99%.[116]

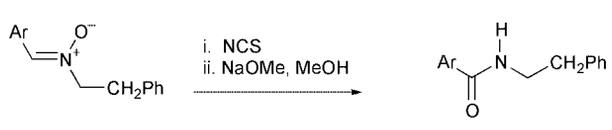
The trimethylsilyl bromide mediated silylation of nitro compounds at −30 °C in dichloromethane in the presence of triethylamine leads to 2-*N*,*N*-bis(trimethylsilyloxy)amino-2,3-dihydrofurans *via* *N*,*N*-bis(trimethylsilyloxy)iminium cations in high yields (83–87%). Similarly, *N*,*N*-bis(trimethylsilyloxy)-aminocyclopropanes can be prepared using the same synthetic conditions with substrates bearing a more acidic proton γ to the nitro group.[117]

Aryl nitroso derivatives have been prepared by the action of *tert*-butyl hypochlorite at −78 °C on aryl hydroxylamines in yields of 82–99%.[118]

Zinc in a mixture of acetic acid and methanol reduces γ-*N*-hydroxylamino-α,β-acetylenic esters bearing a methoxy-substituted benzyl group on the N-atom to *Z*-γ-amino-α,β-ethylenic esters in 51–62% yields.[119]

A zinc sulfate controlled regioselective nitration of 3,4-dihydronitrostyrene with tetranitromethane leads to 6-nitro-3,4-dihydronitrostyrene in 70% yield. Sodium hydrosulfite and zinc sulfate then induce a reductive cyclisation, in 52% yield, to 5,6-dihydroxyindole at pH 4 (using a phosphate buffer).[120]

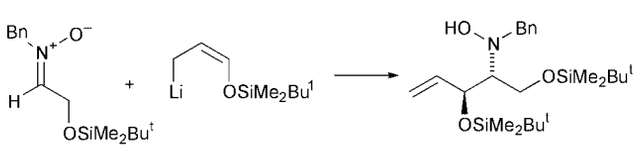
Treatment of α-aryl-*N*-(β-phenylethyl)nitrones **79** with thionyl chloride and triethylamine or *N*-chlorosuccinimide and sodium methoxide gives rise to an unexpected rearrangement resulting in the formation of amides **80** in 80–88% yield (Scheme 29).[121]



Scheme 29

α-Nitroalkyl and α-perfluoroalkylamines have been prepared in 14–78% yield *via* the *in situ* reduction of products resulting from the condensation of perfluoroalkyl nitriles with α-nitrocarbanions using sodium borohydride in acetic acid.[122]

Addition of the anion **82** derived from *tert*-butyldimethylsilyl protected allyl alcohol to a nitrone **81** derived from *N*-benzylhydroxylamine afforded an *anti*-selective α-silyloxyallylation to give the hydroxylamine product **83** in 55% yield as a single diastereoisomer (Scheme 30).[123]



Scheme 30

Phenylacetonitrile or benzyl phenyl sulfones form carbanions with DBU which react with nitroarenes in the presence of magnesium bromide to give 2,1-benzisoxazole derivatives in 13–83% yields.[124]

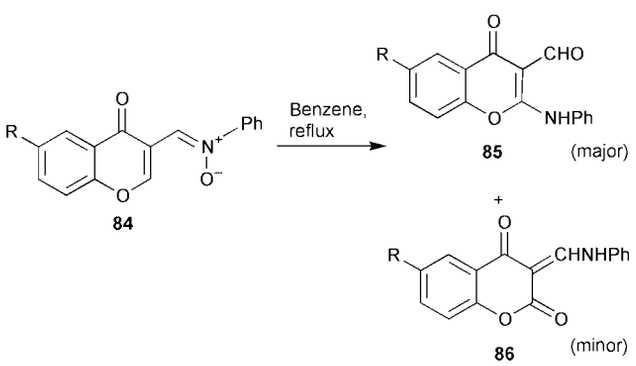
N-(Benzylidene) *tert*-butylamine *N*-oxide reacts with activated olefins to give two types of spin adduct by electron paramagnetic resonance. One adduct corresponds to the reductive coupling of *N*-(benzylidene) *tert*-butylamine *N*-oxide and the

olefin. The second adduct corresponds to the coupling product of the olefin with 2-methyl-2-nitrosopropane (a degradation product of *N*-*tert*-butylmethylidene)phenylamine *N*-oxide).[125]

Nitrones are reduced to aldimines by treatment with titanium dioxide in acetonitrile while irradiating with a 6 W medium pressure mercury vapour lamp in 79–88% yields. Conversely aldimines are oxidised to nitrones when treated with titanium dioxide in acetonitrile in the presence of oxygen while irradiating with a 6 W medium pressure mercury vapour lamp in 69–93% yields.[126]

Treatment of an *N*-benzylamine with sodium tungstate and hydrogen peroxide in acetone gave the corresponding *N*-benzylideneamino *N*-oxide product in 43% yield.[127]

A thermal rearrangement of *N*-(4-oxo-4*H*-1-benzopyran-3-ylmethylidene)phenylamino *N*-oxide **84** occurs in refluxing benzene to afford 2-(*N*-phenylamino)-4-oxo-4*H*-1-benzopyran-3-carbaldehydes **85** as the major products (70%) and 3-(phenyliminomethylene)chroman-2,4-diones **86** as the minor products (25%) (Scheme 31).[128]

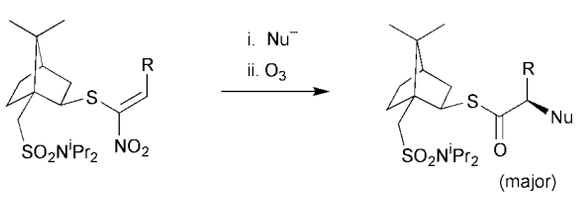


84 **85** **86**

Scheme 31

A remarkable direct substitution of a nitro by a hydroxy group has been observed. *in situ* Oxidation with dimethyldioxirane of the Meisenheimer complex derived from nitroarenes and the carbanion of 2-phenylpropionitrile affords the phenols as the major products, in up to 47% yield, with little of the expected nitroarene products. Addition of 0.5 to 1.0 equivalents of water to the reaction mixture at the start of the reaction results in a higher yield (69–87%) of the phenol.[129]

Diastereoselective tandem conjugate addition of oxygen- and nitrogen-centred nucleophiles to nitroalkenes **87** bearing a (1*S*)-10-camphorsulfonic acid derivative α to the nitro group, followed by ozonolysis has given rise to α-hydroxy and α-amino thiol acid derivatives **88** with the (*R*)-epimers predominating (33–71% de) (Scheme 32).[130]

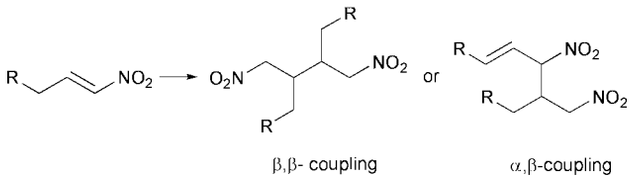


87 **88**

Scheme 32

Electrochemical reductive coupling of aliphatic nitroalkenes **89** has been controlled such that the β,β-coupling (electrohydrodimerisation) products **90** or the more common α,β-coupling products **91** can be obtained selectively (Scheme 33). In the case of the β,β-coupling, aliphatic nitroalkenes possessing acidic protons at the β-centre were used to give the dimerised products in 41–95% yields.[131]

Conjugate addition of nitroalkanes to enedione derivatives under basic conditions (DBU) is accompanied by nitrous acid elimination to give 2-alkylidene-1,4-diesters. Chemoselective

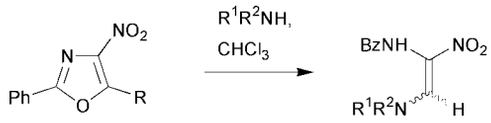


89 **90** **91**

Scheme 33

reduction with lithium aluminium hydride of the carbonyls in the Michael adducts gives 2-alkylidene-1,4-diones in 68–95% yields.[132]

Addition of amino nucleophiles to 2-phenyl-4-nitro-1,3-oxazole **92** results in ring-opening to afford polyfunctionalised nitroenamines **93** in 70–98% yields, (Scheme 34).[133] The process



92 **93**

Scheme 34

has been used in highly diastereoselective cascade reactions to provide novel polycyclic systems.

A mild and efficient Nef reaction for the conversion of nitroalkanes to the corresponding carbonyl derivatives utilises dimethyldioxirane to oxidise nitronate anions, generated *in situ* from nitroalkanes, in 73–99% yield.[134] Benzylic and secondary nitro compounds, under a modified Nef reaction, are converted into the corresponding carbonyl compounds upon treatment with bis(trimethylsilyl)peroxide in the presence of sodium hydride in 60–84% yields.[135]

The conjugate addition of diethylzinc to α,β-unsaturated nitroacetates in the presence of an asymmetric copper(I) phosphoramidite catalyst gave the 1,4-adducts in high yields but low ee's. When structurally rigid 3-nitrocoumarins were used enantioselectivities up to 92% could be obtained.[136]

Tetraorganogallate complexes, prepared *in situ* by the action of an organolithium reagent on a triorganogallium reagent, undergo Michael additions to α,β-unsaturated nitro compounds to give 1,4-products in high yields (up to 98%).[137]

The use of nitro and related compounds within organic chemistry continues to provide effective solutions to synthetic problems. The plethora of nitration and nitrosation techniques coupled with the facile conversion of these compounds into active intermediates will ensure that the current high degree of interest in this area of chemistry will be maintained in the future.

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