Preparations of *C*-Nitroso Compounds

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Preparations of *C*-Nitroso Compounds

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1. Introduction

The discovery of important roles of *C*-nitroso compounds in various biological metabolic processes has generated a renewed interest in the general chemical properties of nitrosoalkanes (R−N=O; R = alkyl) and nitrosoarenes (ArNO; Ar = aryl), two important subsets of this general class of compounds. For example, the identification of the nitrosobenzene adduct of hemoglobin as a product of nitrobenzene poisoning[1,2] and the realization that some amine-containing drugs may be metabolized to nitroso derivatives[3−6] led to an increased desire to study the fundamental biochemical properties of this fascinating class of *C*-nitroso compounds. To this end, many studies have been reported on the fundamental chemistry of *C*-nitroso compounds under conditions that either stabilize the *C*-nitroso functionality or enhance their reactivity toward isomerization or reactivity with substrates.

A major difficulty in *C*-nitroso chemistry, however, is that the high reactivity of these compounds necessarily imposes constraints upon the methods employed for their preparation, particularly with regard to the yield of the desired product. For example, the ease of oxidation of the desired nitroso compound (if oxidation of a suitable precursor is the chosen synthetic route) to its nitro derivative can significantly reduce the yield of the nitroso product. Similarly, the ease of isomerization of $R_2C(H)NO$ compounds to the corresponding oximes R_2C=NOH can restrict the choice of solvent for the preparation of primary and secondary nitrosoalkanes. A further consideration to be borne in mind is the possibility of reaction of the *C*-nitroso compound with the starting material and/or preparative reagents. There is, however, a considerable variety of synthetic routes available for the high-yield preparations of *C*-nitroso compounds (monomers or dimers; Figure 1), some of which have been in regular use for well over 100 years.

Some earlier reviews of this area have been published. Book chapters by Sandler and Karo (in 1986)[7] and by Williams (in 1988)[8] present the most detail to date on the experimental techniques for preparations of *C*-nitroso compounds. Other useful earlier reviews are those by Touster,[9] Boyer,[10] Metzger and

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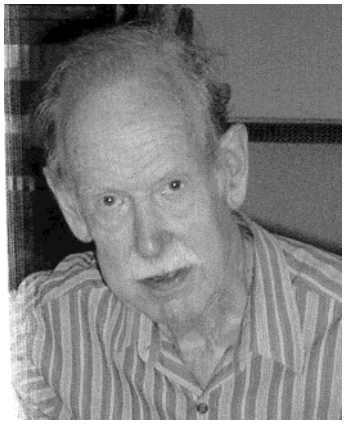


Brian Gowenlock was born in Oldham, Lancashire, England, in 1926. He studied at the University of Manchester and received his B.Sc., M.Sc., and Ph.D. degrees in 1946, 1947, and 1949, respectively. His Ph.D. studies in gas-phase kinetics were carried out under the direction of Dr. Ernest Warhurst and Professor Michael Polanyi. He moved to the University of Wales, Swansea, as an Assistant Lecturer in 1948, and his entry into nitroso compound chemistry was an unplanned byproduct of using nitric oxide as a radical trap. His further academic posts were at the University of Birmingham (1955–1966) and as Professor at Heriot–Watt University, Edinburgh (1966–1990). He has been an honorary member of the University of Exeter since 1992, where he is a Visiting Professor. He is a Fellow of the Royal Society of Edinburgh (FRSE) and served on the University Grants Committee from 1976 to 1985 for services to which he was appointed Commander of the Order of the British Empire (CBE) in 1986. He continues to be fascinated by the wide-ranging subtleties of the chemistry of *C*-nitroso compounds.

George Richter-Addo was born in Glasgow, Scotland, to a Ghanaian father and German mother. He received his Honors B.Sc. and Dip. Ed. degrees (1982) from the University of Cape Coast in Ghana (West Africa). He obtained his Ph.D. degree in 1988 under the direction of Peter Legzdins (in organometallic chemistry) at the University of British Columbia in Canada and subsequently did postdoctoral work at the University of Alberta (with Allen Hunter), UBC (with Legzdins), and University of Utah (with John Gladysz). He joined the faculty at the University of Oklahoma in 1993, where he is a University of Oklahoma Presidential Professor. His research lies at the interface of chemistry and biology and mainly deals with the interactions of organic nitroso compounds and nitric oxide with metalloporphyrins and heme proteins such as myoglobin and cytochrome P450.

Meier,[11] Seidenfaden,[12] and Katritzky et al.[13]

Given the renewed interest in the study of the biological and environmental consequences of *C*-nitroso compound formation, it is not surprising that many new and/or improved procedures for the preparations of these compounds have been developed over the last two decades. In this review, we present a comprehensive review of the synthetic procedures for the preparation of *C*-nitroso compounds and place these procedures in proper historical context. We also include a small number of routes to the production of *C*-nitroso compounds that may have preparative possibilities or which require improved workup methods. We indicate, when known, whether the method of preparation is applicable to all types of *C*-nitroso compounds or only to separate classes such as nitrosoarenes, nitrosoalkanes, nitrosohomocycles, or nitrosoheterocycles. Nitrosoalkenes are considered in a separate section. The coordination chemistry of *C*-nitroso compounds with metals has been reviewed recently.[6,14]

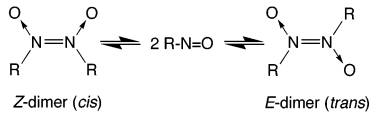


Figure 1.

2. Synthetic Methods

2.1. Direct Substitution of –H by –NO

2.1.1. Hydrocarbons

A very successful direct nitrosation of some polymethyl-substituted benzenes was reported by Bosch and Kochi.[15] The nitrosations of the arenes were achieved using solutions of nitrosonium tetrafluoroborate in acetonitrile under argon; the arenes employed included 1,3-dimethylbenzene, 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, and 1,2,3,4-tetramethylbenzene (eq 1).

$$\mathrm{ArH} + \mathrm{NO}^+ \rightarrow \mathrm{ArNO} + \mathrm{H}^+ \qquad (1)$$

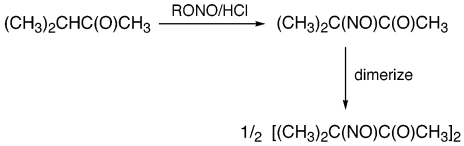
Atherton et al.[16] extended this electrophilic nitrosation reaction to other arenes such as toluene, 1,2-dimethylbenzene, and 1,3-dimethylbenzene using degassed trifluoroacetic acid under a nitric oxide atmosphere. The nitrosoarenes produced under the latter conditions are unstable, but the method ensures reaction with the nitrosonium ion.

For the nitrosations of alkanes and cycloalkanes, the preparative method employed is a radical trapping reaction with nitric oxide and as such is discussed in section 2.7.

2.1.2. Compounds with Activated CH Groups

The nitrosation of aliphatic compounds requires that electron-withdrawing groups be situated adjacent to the carbon atom to be nitrosated; for preparative purposes it is important for this carbon to be a 3° carbon atom, as the nitrosation of 1° or 2° carbon atoms frequently leads to the production of the isomeric oximes. The activating groups include the carbonyl, alkoxycarbonyl, nitro, cyano, and aryl moieties. The nitrosating agent used in the nitrosation of ketones is an alkyl nitrite in the presence of acetyl chloride or HCl. The preparation of dimeric 3-methyl-3-nitroso-2-butanone (Scheme 1) from 3-

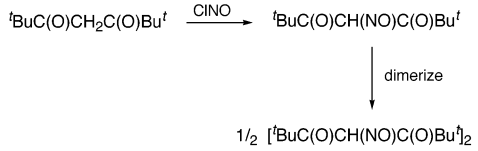
Scheme 1



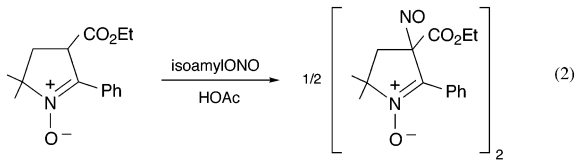
methyl-2-butanone by Aston et al.[17,18] is a good example of this approach.

Other examples are provided by Pritzkow and Rösler.[19] An early preparation[20] of dimeric 4-nitrosomenthon employed pentyl nitrite and HCl as the nitrosating agent, and such nitrosations have been extended using pentyl nitrite and acetyl chloride.[21] An extension of this synthetic route is provided by the direct nitrosation of the diketone, dipivaloylmethane, by nitrosyl chloride in ether or acetic acid to give a 50% yield of the dimeric 4-nitroso-2,2,6,6-tetramethylheptane-3,5-dione product (Scheme 2).[22]

Scheme 2



A further example is provided by the reaction of 3-methylbutyl nitrite (isoamyl nitrite) in glacial acetic acid under reflux with 3-ethoxycarbonyl-5,5-dimethyl-2-phenyl-1-pyrroline-1-oxide to give dimeric 3-ethoxycarbonyl-5,5-dimethyl-3-nitroso-2-phenyl-1-pyrroline-1-oxide (eq 2).[23]



(2)

A variation is provided by the nitrosation of cyclohexanone in acetic anhydride by dinitrogen tetraoxide to give a high yield of dimeric 2-nitroso-2-nitrocyclohexanone.[24]

Nitrosation of secondary nitro compounds such as 2-nitropropane to give 2-nitro-2-nitrosopropane is noteworthy in that the first aliphatic nitroso compound was prepared by this method by Meyer and Locher in 1874.[25]

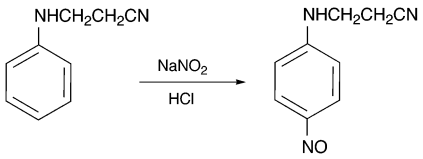
2.1.3. Phenols and Aromatic Ethers

The nitrosation of phenol by nitrous acid was first studied by Baeyer and Caro in 1874,[26] the product being *p*-quinone monoxime, a tautomer of *p*-nitrosophenol. Substituted phenols and naphthols with *para* H-atoms behave similarly. The direct nitrosation of anisole was realized well over a century later using sodium nitrite in dichloromethane/trifluoroacetic acid[27] and then extended[15] by using nitrosonium tetrafluoroborate in acetonitrile under argon. Nitrosation of anisole has also been accomplished using acetic acid/nitrosyl sulfuric acid/sulfuric acid mixtures under a stream of nitric oxide.[28] Bosch and Kochi's synthetic route has been applied successfully to substituted anisoles with 2-methyl, 3-methyl, 2,6-dimethyl, 3,5-dimethyl, 2-bromo, 3-bromo, and 2-mesityl substituents.[15,29] The 4-nitrosoanisole was obtained in very high yield, whereas very little or no nitroso products were obtained when 4-substituted anisoles were used in the nitrosation reactions.[15]

Interestingly, nitrosation of anisole by nitrosonium ethyl sulfate ($EtOSO_2O^-NO^+$) is reported to result in the generation of both 4-nitrosoanisole (major) and 4-$EtOC_6H_4NO$ (minor).[30]

2.1.4. Aromatic Amines

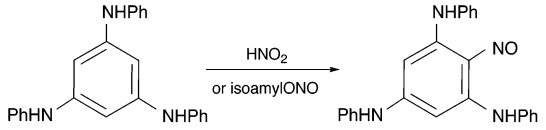
The direct nitrosation by nitrous acid of tertiary aromatic amines is a long established method for the preparation of *para*-nitroso-*N*,*N*-disubstituted anilines,[31] and a standard detailed method is available.[32] The nitrosation of secondary aromatic amines occurs at the nitrogen, giving an *N*-nitrosoamine. In the presence of hydrochloric or hydrobromic acid, a Fischer−Hepp rearrangement occurs to give the *para*-nitroso-monosubstituted amine.[33] An example of this is the nitrosation of *N*-(2-cyanoethyl)aniline in methanolic sodium nitrite/HCl yielding the *para*-nitroso-*N*-(2-cyanoethyl)aniline (eq 3).[34]



(3)

Willenz[35] extended this to the preparation of a number of *N*-alkyl- and *N*,*N*-dialkyl-*p*-nitrosoanilines, although poor yields were obtained from *N*-*n*-hexylaniline, and no *C*-nitroso compound resulted from *N*-*n*-octadecylaniline. Morgan and Evens[36] nitrosated 2-methylaminonaphthalene to give the *N*-nitroso product; stirring this product in cold ethanolic hydrochloric acid produced 1-nitroso-2-methylaminonaphthalene in good yields. Nitrosation of *N*,*N*-dialkylanilines by nitrosonium ethyl sulfate yielded the 4-nitroso-*N*,*N*-dialkylaniline products; the ionic (protonated) nitroso intermediates could be isolated as well, since they precipitated out of solution.[30]

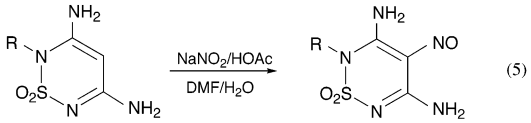
An interesting ring nitrosation of a secondary aromatic amine without the apparent formation of an intermediary *N*-nitroso compound is provided by the formation of 2,4,6-tris(phenylamino)nitrosobenzene when 1,3,5-tris(phenylamino)benzene is reacted with nitrous acid (eq 4),[37] although the reported NO bond length in the product (1.13 Å) is unusually short.



(4)

2.1.5. Heteroaromatic Compounds

Only electron-rich heterocyclic ring systems are subject to electrophilic attack by nitrosating agents: examples include pyrroles,[38,39] pyrazoles,[40] antipyrine (2,3-dimethyl-1-phenylpyrazol-5-one),[41] imidazoles,[42] fused benzimidazoles,[43−45] 1*H*-pyrrolo[1,2-a]imidazoles,[46,47] imidazo[2,1-b]thiazoles,[48−51] indolizines,[52,53] indoles,[54−57] 8-thia-1,4-diazacycl[3,3,2]azines,[58] and thiazoles.[59] Nitrosation of four 3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides with sodium nitrite and acetic acid in a DMF/water solution at 0−5 °C gives good yields of the corresponding 4-nitroso derivatives (eq 5; R = CH_2Ph, CH_2CH_2Ph, Bu, Ph).[60]



(5)

2.2. Substitution of a Functional Group by the Nitroso Group

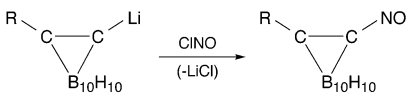
2.2.1. Nitrosation of Organometallic Compounds

The use of nitroso demetalation reactions for the generation of *C*-nitroso compounds has a long history. In 1874, Baeyer[61] prepared nitrosobenzene from the reaction of nitrosyl bromide with diphenylmercury. A similar reaction by Oddo using phenylmagnesium bromide and nitrosyl chloride also produced nitrosobenzene,[62] but Waters and Marsh,[63] in attempting to repeat this work, reported that the predominant product was diphenylamine. A range of methyl-substituted nitrosobenzenes was obtained from the reaction of the arylmercuriacetate with nitrosyl chloride generated in situ from a mixture of ethyl nitrite and hydrochloric/acetic acids.[64] Beginning in the 1960s, the use of nitrosative demetalation has been considerably extended both with and beyond the use of organomercury and organomagnesium compounds. Robson et al.[65] prepared two nitrosoalkynes by reaction of bis(*tert*-butylethynyl)- and bis(*n*-butylethynyl)mercury with nitrosyl chloride at −40 °C, the yields being better with the mercury compounds than with the magnesium or lithium analogues. Motte and Viehe[66] also prepared *tert*-butylnitrosoacetylene from reaction of *tert*-butyltrimethylstannylacetylene with dinitrogen tetroxide at −60 °C (eq 6).

$$^{t}\mathrm{Bu{-}C{\equiv}C{-}SnMe_3} \xrightarrow[-60\ ^\circ\mathrm{C}]{N_2O_4} {}^{t}\mathrm{Bu{-}C{\equiv}C{-}NO} + \mathrm{Me_3SnONO_2} \quad (6)$$

Prickett[67] prepared nitrosocyclopropane from dicyclopropylmercury and nitrosyl chloride. This method has also been used for halogenated nitroso compounds by Tarrant and O'Connor[68] in the preparation of $CF_3CFClNO$, CF_3CCl_2NO, and $(CF_3)_2CFNO$ from reaction of the corresponding difluoroalkylmercury with nitrosyl chloride in DMF. Near-quantitative yields of the nitrosoperfluoroalkanes $C_nF_{2n+1}NO$ (n = 1, 2, 3, 6) are realized from the reaction of nitrosyl chloride with the corresponding $Cd(C_nF_{2n+1})_2$glyme reagent.[69]

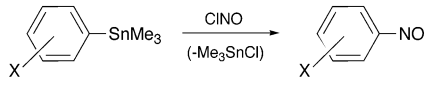
The successful use of organolithium compounds in *C*-nitroso compound syntheses is illustrated by the preparation of 1-nitroso-*ortho*-carborane and 1-methyl-2-nitroso-*ortho*-carborane (eq 7) from reaction of the corresponding lithium compounds with excess nitrosyl chloride in ether−hexane at low temperatures (−70/−125 °C).[70,71]



(7)

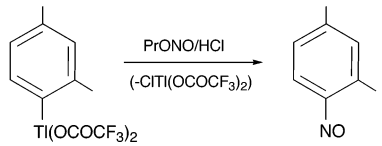
Extension to the preparation of 1-nitroso-*m*-carborane, 1-methyl-7-nitroso-*m*-carborane, and 1-nitroso-*p*-carborane has been reported by Zakharkin.[72]

Other preparations using organotin compounds have been reported.[73] Several monosubstituted phenyltrimethylstannanes give good yields of the corresponding substituted nitrosobenzenes (eq 8) when the reactions with nitrosyl chloride in anhydrous dichloromethane are performed at −20 °C; when a halogen substituent is present, the reaction is much slower even at the higher reaction temperature of 0 °C.



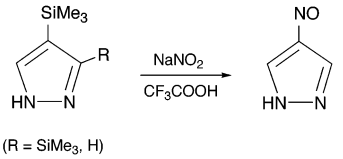
(8)

Preparation of various arylnitroso compounds in good yields using organothallium precursors has been reported (e.g., eq 9).[74]



(9)

In a similar vein, 4-nitrosopyrazole has been prepared from the reaction of both 4-trimethylsilylpyrazole and 3,4-bis(trimethylsilyl)pyrazole with sodium nitrite/trifluoroacetic acid at 0 °C (eq 10).[75]



(10)

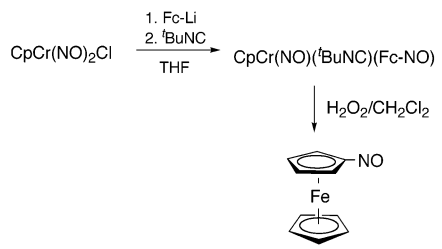
The method has been extended to prepare 3(5)-nitroso-4-trimethylsilylpyrazole and 3(5)-nitrosopyrazole. The reaction between tridodecylaluminum and nitrosyl chloride in THF under nitrogen at −10 °C gives *trans*-dimeric 1-nitrosododecane (eq 11).[76]

$$\mathrm{Al(C_{12}H_{25})_3} + 3\mathrm{ClNO} \rightarrow \mathrm{C_{12}H_{25}NO} + \mathrm{AlCl_3} \quad (11)$$

All of these preparations are based upon the observation that the leaving group that results is a relatively stabilized metal cation. In view of the considerable number of organolithium and organomercury compounds that can be synthesized in good yields, it seems likely that the preparation of a wide range of nitroso compounds should prove possible by the increased use of nitrosative demetalations.

The synthesis of nitrosoferrocene from ferrocenyllithium (FcLi) has been reported using the reaction sequence shown in Scheme 3.[77] FcLi reacted with $CpCr(NO)_2Cl$ by nucleophilic addition of the ferrocenyl moiety to the nitrogen atom of a nitrosyl group.

Scheme 3



The resulting intermediate, on reaction with *tert*-butyl isocyanide, formed a nitrosoferrocene complex, which on controlled oxidative degradation with hydrogen peroxide in dichloromethane gave nitrosoferrocene.

The insertion of the nitrosonium cation into the chromium−carbon bond of $CpCr(NO)_2Ph$ gives the cationic nitrosobenzene complex $[CpCr(NO)_2\{N(O)Ph\}]^+$, which upon further reaction with chloride ion releases PhNO in fair yields.[78] Stoichiometric carbon−nitrogen bond formation mediated by metal complexes, in which the *C*-nitroso compounds remain coordinated to the metal centers, has been reviewed.[6,14]

2.2.2. Nitrosation by Replacement of Other Functional Groups

There are a number of examples of such replacements in which nitrosyl chloride is used as the source of nitric oxide. Sutcliffe[79,80] used the reaction between nitrosyl chloride and sodium trichloromethylsulfinate to prepare trichloronitrosomethane, for which the reaction pathway in Scheme 4 is suggested.

Scheme 4

$$ClNO \rightleftharpoons NO + Cl\cdot$$
$$CCl_3SO_2Na + Cl\cdot \longrightarrow CCl_3SO_2\cdot + NaCl$$
$$CCl_3SO_2 + ClNO \longrightarrow CCl_3SO_2NO + Cl\cdot$$
$$CCl_3SO_2NO \longrightarrow CCl_3NO + SO_2$$

Tattershall[81] used the mercury arc photolysis of equimolar quantities of chloroform and nitrosyl chloride to prepare solutions of trichloronitrosomethane in chloroform. The reaction between nitrosyl chloride and peroxyphenylacetic acid in petroleum ether at 0 °C produces dimeric *ω*-nitroso-toluene (Scheme 5).[82]

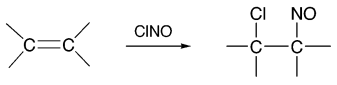
Scheme 5

$$PhCH_2COOOH \xrightarrow{ClNO} PhCH_2NO + HCl + CO_2 + 1/2O_2$$
$$\downarrow \text{dimerize}$$
$$1/2\,[PhCH_2NO]_2$$

2.3. Addition Reactions to C═C Double Bonds

2.3.1. Addition of Nitrosyl Halides

The addition of nitrosyl halides to alkenes is a very useful approach to the synthesis of *C*-nitroso compounds (eq 12).



(12)

The addition of nitrosyl chloride to the C═C double bond of various terpenes played an important role in the early studies of the structure of terpenes.[83] An early review[84] of the chemistry of nitrosyl chloride includes a summary of reactions with compounds containing C═C bonds. A later review by Kadzyauskas and Zefirov[85] on the nitrosochlorination of alkenes was published in 1968. A series of papers by Ogloblin and co-workers gives details of the reactions with alkenes and cycloalkenes,[86,87] ketene acetals,[88] vinyl ethers,[89] α,*β*-unsaturated ketones containing a substituted vinyl group,[90] acyclic α,*β*-unsaturated ketones,[91] chloroalkenes,[92] cyclopropene derivatives,[93] and enamines.[94] In some cases the nitroso compounds formed are unstable (e.g., from some vinyl ethers[89] and some α,*β*-unsaturated ketones[90]), but even where the majority of products formed are the result of disproportionation of the resulting nitroso chlorides, in the case of 1-acetoxy-1-chloro-2-nitroso-2-methylpropane a crystalline dimer was formed.[95] The papers by Ogloblin and co-workers describe the use of IR spectroscopy to distinguish between the *E*- and *Z*-dimers; however, questions concerning the stereochemistry of the nitrosyl chloride addition to the C═C bonds and the nature of the chirality of the compounds produced were not addressed. Rogic and co-workers[96] considered these in detail and demonstrated that as the addition of nitrosyl chloride to cyclohexene can occur both cis and trans with respect to the ring, there is the possibility that three different *Z*-dimers and three different *E*- dimers can form (Figure 2).

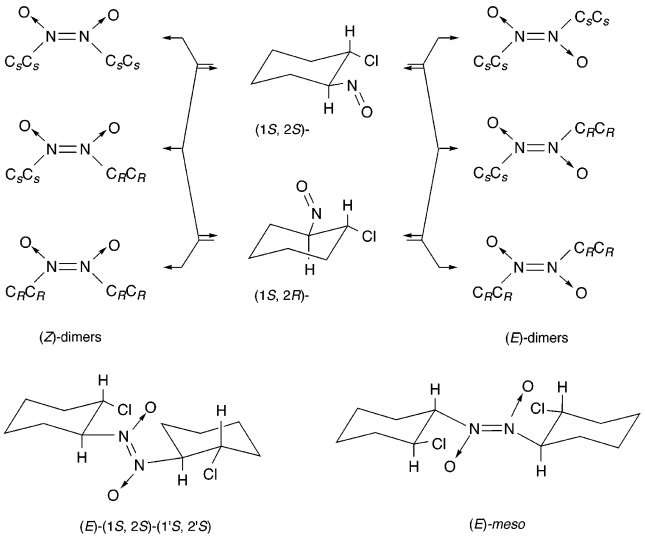


Figure 2.

Similar considerations have been applied to the reaction products of nitrosyl chloride and 1,5-cyclooctadiene and *trans,trans,trans*-cyclododecatriene.[97] Ponder and Wheat[98] studied the dimeric nitrosochloride products of the addition to the strained bicyclic olefins norbornene, norbornadiene, 5-methylene-2-norbornene, 5-ethylidene-2-norbornene, and bicyclo[2,2,2]octene-2. Other authors have given careful consideration to the stereochemistry of nitrosyl chloride addition products to various terpenes, e.g., *γ*-terpinene,[99] sylvestrene,[100] *p*-menth-1-ene, limonene and α-pinene,[101] (±)-α-terpinyl acetate,[102] (+)-car-3-ene,[103] and *trans*-*β*-terpineol.[104]

Tkachev and Vorobjev[105] have shown that nitrosyl chloride reacts with the diterpenoid cembreme at −50 °C in dichloromethane to give a blue solution, whereas at −5 °C a tar-like product forms within 1 s. Subsequent reaction of the blue solution with morpholine confirms the formation of the nitrosochloride. Markova and Tkachev[106] isolated a crystalline dimeric

nitrosochloride of the acyclic monoterpenoid linalylacetate from the interaction of a gaseous stream of nitrosyl chloride in nitrogen slowly passed over a dichloromethane solution of the terpenoid at −15/−5 °C, the product being a 1:1 mixture of diastereomers.

Nitrosyl chloride has been shown to react readily and with a high degree of stereospecificity with three acetylated glycals at −40/−80 °C in either ethyl acetate or dichloromethane to produce *trans*-dimeric acetylated 1,2-*cis*-2-deoxy-2-nitroso-α-D-aldopyranosyl chlorides (Figure 3).[107]

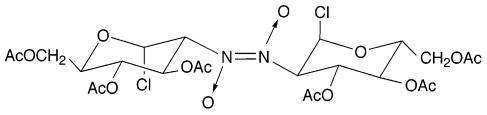
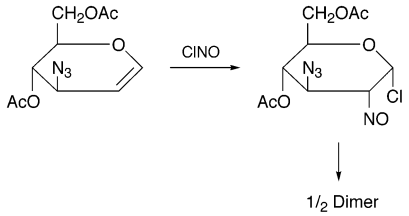


Figure 3.

Similar reactions of glycals have also been reported,[108,109] and further examples of the preparation of such dimeric nitrosochloride derivatives are provided by Heyns and Hohlweg (Scheme 6).[110]

Scheme 6



The rates of addition of nitrosyl chloride to C=C double bonds are subject to wide variation depending upon the structure of the alkene, cycloalkene, or substituted styrene concerned,[111,112] and these studies are obviously relevant to the successful use of this addition reaction for synthetic purposes. The patent literature[113] gives details of the production of dimeric nitroso chlorides of propene and ethene from the metal-catalyzed reaction in a chlorinated hydrocarbon solvent within the temperature range −25/40 °C.

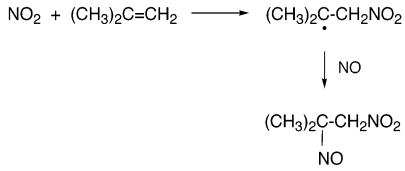
Although nitrosyl bromide has been less frequently employed than nitrosyl chloride in these addition reactions, it has been shown that the ethyl nitrite/phosphorus tribromide system is a good source of nitrosyl bromide and gives high yields of dimeric nitrosobromides from norbornene and benzonorbornene, the addition occurring as a *syn-exo* process.[114]

The reaction of nitrosyl fluoride with C=C double bonds has received some attention. The review by Knunyants et al.[115] gives the major references to the Russian preparative work. Andreades[116] obtained 2-nitrosoheptafluoropropane and *tert*-nitrosononafluorobutane from reaction of nitrosyl fluoride with hexafluoropropene and octafluoroisobutene, respectively. He also prepared heptafluorocyclobutyl nitrite from reaction of nitrosyl fluoride with hexafluorocyclobutanone; thermal decomposition of this product yielded γ-nitrosohexafluorobutyryl fluoride together with the corresponding nitro compound.[117]

2.3.2. Addition of Oxides of Nitrogen

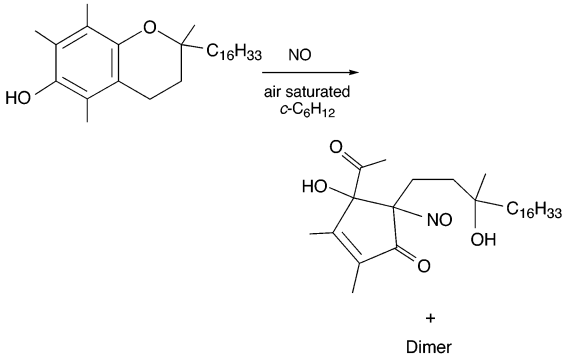
These addition reactions can be carried out with nitric oxide or dinitrogen trioxide or dinitrogen tetraoxide. An early study by Bunge[118] showed that the reaction of a terpene once ascribed to nitric oxide addition was, in fact, due to dinitrogen trioxide addition. Almost a century later, Brown[119] showed that when highly purified nitric oxide was used in an attempted reaction with 2-methylpropene, no addition occurred; the reaction occurred when trace quantities of nitrogen dioxide were present (e.g., Scheme 7).

Scheme 7



Park and Walton[120] used EPR spectroscopy to demonstrate that small amounts of nitrogen dioxide were necessary to produce β-nitroalkyl radicals, which can react further with nitric oxide.

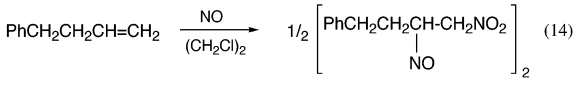
The reaction of nitric oxide with α-tocopherol (vitamin E) in air-equilibrated cyclohexane gave a variety of products including a colorless oil in ∼10% yield for which the structure 2,3-dimethyl-4-acetyl-4-hydroxy-5-nitroso-2-cyclopentenone is proposed (eq 13) based on UV−vis, IR, and ^{1}H NMR spectroscopic evidence.[121]



(13)

The absence of any blue color is, however, surprising. It is not clear what, if any, inferences can be drawn regarding the biological relevance of this NO−vitamin E reaction. However, vitamin E has antioxidant properties, and it will be interesting to determine the in vivo relevance of vitamin E in protection against NO-induced cell damage.

Dimeric 1-nitro-2-nitroso-4-phenylbutane (eq 14) has been identified as the reaction product from the room-temperature reaction of 4-phenyl-1-butene, dissolved in 1,2-dichloroethane, with nitric oxide at atmospheric pressure.[122]



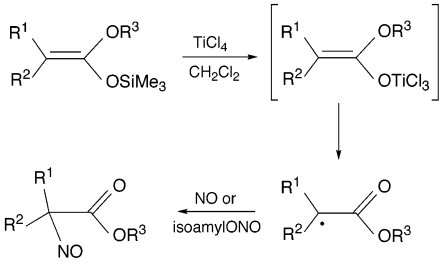
(14)

The reaction of nitric oxide with benzene solutions of chloroprene and 2,3-dichlorobutadiene yields dimer-

ic 2-chloro-1-nitro-4-nitrosobut-2-ene and 2,3-dichloro-1-nitro-4-nitrosobut-2-ene, respectively.[123]

Ketene *O*-alkyl-*O′*-silyl acetals react with nitric oxide or 3-methylpentyl nitrite in the presence of titanium(IV) chloride to give good yields (>65%) of α-nitroso esters (Scheme 8).[124] When R^2 = H in

Scheme 8



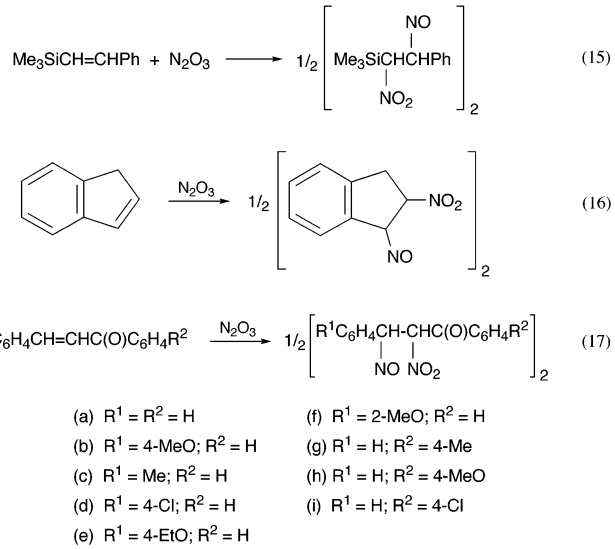
(a) $R^1 = R^2$ = Me; R^3 = Et
(b) $R^1 = R^3$ = Et; R^2 = Me
(c) $R^1 = R^2$ = Ph; R^3 = Me

Scheme 8, the isomeric oximes are the final products.

The study of the addition of dinitrogen trioxide to alkenes is over a century old, examples being the addition to styrene[125] and 2-methylbut-2-ene.[126,127] The product was named 'trimethylethylene nitrosite' and shown to exist as a blue monomer in solution or as a colorless dimer in the solid state. The term *nitrosite* is a shortened form of nitrosonitrite, whereas the term *pseudonitrosite* is used for the isomeric nitronitroso addition compound. Preparative details for addition of dinitrogen trioxide to C=C compounds to give dimeric nitronitroso (pseudonitrosite) derivatives are given for but-2-ene, dimethylbutadiene, styrene, 4-methoxy-propenylbenzene (anethole), 4-propenyl-1,2-methylenedioxybenzene (isosafrole), stilbene, cyclohexene, cyclooctene, and cycloocta-1,5-diene.[127−129] Details are also given for nitronitroso derivatives from L-α-phellandrene[130] and for cinnamyl acetate[131] and for initial nitrosonitrites from propene, 2-methylpropene, 3-chloropropene, and 2,3-dimethylbut-2-ene.[132] Pfab[133] showed that the addition of dinitrogen trioxide to 2-methylpropene produced the *trans*-dimer of 1-nitro-2-methyl-2-nitrosopropane together with other products from oxidation of the monomeric nitroso compound.

It should be noted that there are considerable differences in the melting point values recorded for dimeric 1-nitroso-2-nitro-1-phenylethane, and these may be accounted for in terms of the geometric isomerism of the azodioxy group together with conformational isomerism. The crystal structure[134] identifies a *trans*-dimer of melting point 108.4 °C, but other preparations using different solvents and recrystallization procedures give values of 112,[127] 122,[129] 129,[135] 130,[131] and 158 °C.[135] Detailed studies of these wide divergences have not been carried out.

Other preparations of dimeric nitronitroso compounds by dinitrogen trioxide addition include the products resulting from the addition to seven silanes containing an ethylenic bond (e.g., eq 15),[136] seven indenes (e.g., eq 16),[137] and nine α,β-unsaturated ketones of the chalcone class (eq 17).[138]



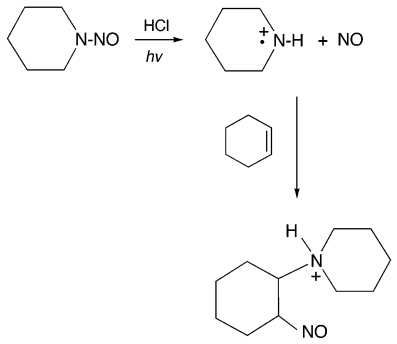
(a) $R^1 = R^2$ = H
(b) R^1 = 4-MeO; R^2 = H
(c) R^1 = Me; R^2 = H
(d) R^1 = 4-Cl; R^2 = H
(e) R^1 = 4-EtO; R^2 = H
(f) R^1 = 2-MeO; R^2 = H
(g) R^1 = H; R^2 = 4-Me
(h) R^1 = H; R^2 = 4-MeO
(i) R^1 = H; R^2 = 4-Cl

Preparative details are available for two distinct conformers of blue crystalline humulene nitrosite[139,140] and caryophyllene nitrosite.[141]

2.3.3. Addition of N-Nitroso Compounds

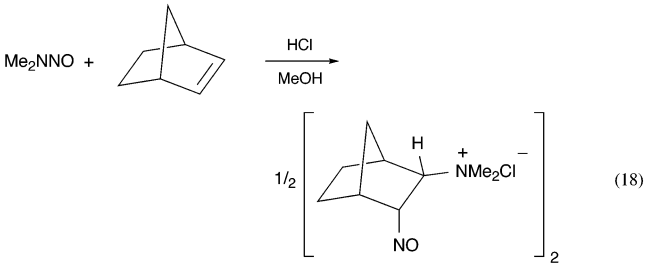
The photoaddition of *N*-nitroso compounds to compounds containing C=C bonds in acidified solvents such as methanol has been reviewed by Chow,[142] who proposed that formation of an aminium radical was followed by its addition to (by electrophilic radical attack at) a π bond and subsequent capture of the resultant radical by nitric oxide (e.g., Scheme 9). The

Scheme 9



resultant 1:1 adduct isomerizes to the oxime if there is an α-H atom present, and only in the absence of this α-H atom can the nitroso compound be isolated. In a series of published reports it was shown that the majority of products were oximes; however, preparative details for *C*-nitroso compounds from photolysis of nitrosamines using 0.05 mol of nitrosamine and 1−3 mol equiv of alkene in methanol and concentrated HCl have been described.[143] Interestingly, the photolysis of *N*-nitroso-*N*-hexylacetamide or *N*-nitroso-*N*-methylhexanamide in cyclohexane yielded small quantities of dimeric nitrosocyclohexane.[144] *Trans*-dimeric nitroso compounds are obtained from the reaction of *N*-nitrosopiperidine with 3,3-dimethylbut-1-ene and 1-hexene[145] and cyclohex-

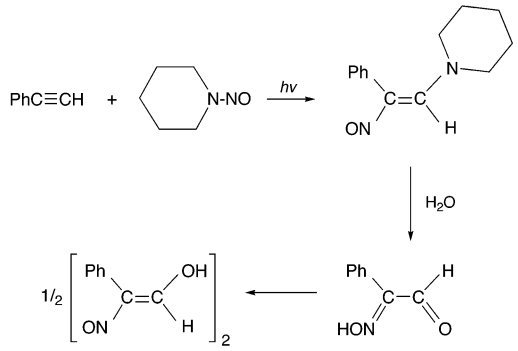
ene.[146] Similarly, dimethylnitrosamine undergoes photoaddition to norbornene (eq 18).[147]



(18)

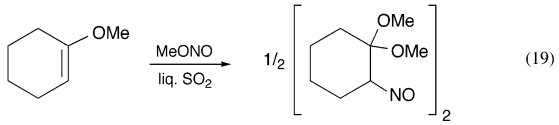
An interesting analogous synthesis is provided by the photoaddition of *N*-nitrosopiperidine to phenylacetylene followed by hydrolysis to form phenylglyoxal ketoxime, which tautomerizes to give the dimer of 1-nitroso-2-hydroxystyrene (Scheme 10),[148] a compound which merits a full structural study.

Scheme 10



2.3.4. Addition of O-Nitroso Compounds

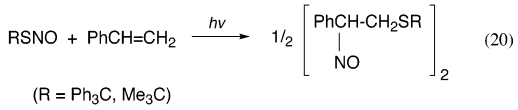
The addition of 1-methoxycyclohexene to a solution of methyl nitrite in liquid sulfur dioxide at −40 °C in the presence of a catalytic amount of sulfur trioxide, sulfuric acid, or boron trifluoride etherate yields the *trans*-dimer of 1,1-dimethoxy-2-nitrosocyclohexane quantitatively (eq 19).[149] The method has been extended (using methyl or ethyl nitrite) to produce eight other α-nitroso ketone acetal dimers in yields of >70%.



(19)

2.3.5. Addition of S-Nitroso Compounds

The photolysis of tritylthionitrite and *tert*-butylthionitrite in the presence of styrene produces diastereomeric dimeric nitroso compounds (eq 20).[150]

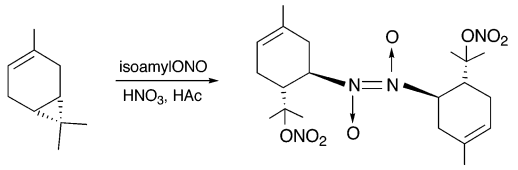


(20)

2.3.6. Addition of Other Nitrosyl Compounds

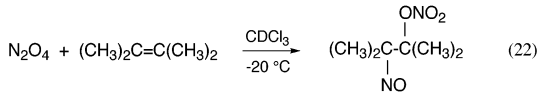
Hamann and Swern[151] showed that nitrosyl formate, prepared in situ from isoamyl nitrite and formic acid, added readily to a number of acyclic-, alicyclic-, and aryl-substituted unsaturated compounds yielding formoxy nitroso compounds. Dimeric crystalline products were obtained from cyclohexene, norbornene, styrene, and α- and *trans*-β-methylstyrene, whereas 2,3-dimethylbut-2-ene and Δ^9-octalin yielded blue monomeric oils; upon purification, the latter product gave blue needles of *cis*- and *trans*-9-formoxy-10-nitrosodecalin. The addition of nitrosyl acetate and of nitrosyl benzoate to 2,3-dimethylbut-2-ene was also shown to give high yields of 2,3-dimethyl-2-acetoxy-3-nitrosobutane and 2,3-dimethyl-2-benzoyloxy-3-nitrosobutane, respectively. In a similar study, Sharpe[152] showed that nitrosyl benzoate and dinitrosyl terephthalate added to 2,3-dimethylbut-2-ene and that nitrosyl benzoate added to Δ^9-octalin giving high yields of the nitroso product.

The presumed 3-carene nitrosate studied by Simonsen[153] has been shown to be an unsymmetrical *trans*-dimeric nitroso compound formed by a reaction of isoamyl nitrite and nitric acid in acetic acid with the (+)-3-carene, in which *the double bond is left intact* and the cyclopropane ring is cleaved.[154] The two identical units of the compound give rise to separate ^{1}H NMR spectroscopic signals due to the dissymmetry of the molecule which is named as (3*R*,3′*R*,4*R*,4′*R*)-(*E*)-di(8-nitrooxy-6-menthen-3-yl)diazene *N*,*N*′-dioxide (eq 21).



(21)

Heterolytic addition of dinitrogen tetraoxide to tetramethylethylene in the absence of oxygen at −20 °C using deuteriochloroform as solvent has been shown to produce the unstable blue nitrosonitrate (eq 22).[155]



(22)

Perrotti and De Malde[156] isolated a dimeric nitrosonitrate in quantitative yield from reaction of dinitrogen tetraoxide with 2-methylpropene in the presence of concentrated nitric acid and suggested an ionic mechanism for the addition reaction.

2.4. Oxidation of Other Nitrogen-Containing Functional Groups

2.4.1. Primary Amines

A wide variety of oxidizing agents is available for the oxidation of 1° amines to nitroso derivatives. The period from 1970 onward was marked by an increase in the number of possible synthetic routes for high-yield preparations of aromatic, aliphatic, and homocyclic nitroso compounds.

(1) Caro's Acid. There are a number of suitable oxidizing agents for the syntheses of nitrosoarenes, nitrosoalkanes, and nitrosocycloalkanes, of which the first to be employed was Caro's acid (peroxomono-

sulfuric acid, H_2SO_5).[157] Experimental details for the preparations using Caro's acid are to be found in the paper by Mijs et al.[158] for nitrosobenzenes with the following substituents: 2,6-dimethyl, 2,6-dimethyl-4-iodo, 2-methyl-4-iodo, 4-methoxy, 2,6-dimethyl-4-methoxy, 2,6-dimethyl-4-bromo, and 2-nitro. Mijs[159] extended the syntheses to nitrosobenzene itself and to nitrosobenzenes with the following substituents: 4-nitro, 2-methoxy, 3-methoxy, 2-methyl-4-bromo, and 2,4,5-trimethyl. In an earlier study by Schors et al.,[160] the syntheses of the following substituted nitrosobenzenes by Caro's acid oxidation were reported: 3-chloro-4-nitrosoanisole, 2,4-diethoxynitrosobenzene, 4-chloronitrosobenzene, 4-bromonitrosobenzene, 4-iodonitrosobenzene, 3-nitroso-ethylbenzoate, 4-nitroso-ethylbenzoate, and nitrosomesitylene. Other substituted nitrosobenzenes have been obtained by this method.[161,162] Many of the preparations by Bamberger and co-workers in the 1898−1910 period made use of Caro's acid as the oxidant for reaction with aromatic amines.[163] Langley[164,165] gives preparative details for 2-methyl-4-nitro-nitrosobenzene. Hirota and Otano[166] also used Caro's acid oxidation to prepare nitrosobenzenes with the following substituents: 2-isopropyl, 2-*tert*-butyl, 2-fluoro, 2,6-diisopropyl, 3,4-dibromo, 4-ethyl, 4-*n*-propyl, 4-isopropyl, and 4-*tert*-butyl.

Caro's acid oxidation of primary aminoalkanes to give dimeric nitrosoalkanes was first achieved by Bamberger and Seligman[167] for the cases of $Me_2C(CH_2X)NH_2$ (X = H, Me, COMe). Caro's acid oxidation of amines has been used to prepare the *trans*-dimers of 1-methyl-1-nitrosocyclohexane and 2-nitroso-2-phenylpropane.[128] Commercially available *Oxone* (with acetone as solvent in a biphasic oxidation process) has been used to prepare the *trans*-dimers of nitrosocyclohexane, 1-nitrosobutane, and 1-nitrosodecane.[168] In these cases, the isomeric oximes were also formed.

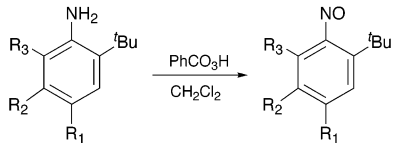
(2) Peracetic Acid. Holmes and Bayer[169] used 30% hydrogen peroxide/acetic acid to prepare several disubstituted and trisubstituted nitrosobenzenes with the following substituents: 2,6-dichloro, 2,6-dibromo, 2,4,6-trichloro, 2,4,6-tribromo, 2,3,6-trichloro-4-methyl, 2,6-dibromo-4-chloro, 2,6-dichloro-4-bromo, 2,6-dichloro-4-methyl, 2,6-dibromo-4-methyl, 2,6-dibromo-4-COOEt, 2,6-dichloro-4-COOEt, 2,6-dichloro-4-cyano, and 2,6-dibromo-4-cyano. Gorrod[170] used this method to prepare nitrosobenzene, 2-nitrosobiphenyl, 4-nitrosobiphenyl, 1-nitrosonaphthalene, 2-nitrosonaphthalene, and 2-nitrosofluorene.

There are further examples of the use of peracetic acid as the oxidizing agent in the preparation of 2-nitrosobenzamide[171] and 2-nitrosoaniline[172] from the corresponding amino compounds. Dimeric 4-nitrosotetrafluoropyridine has been prepared by oxidation of the amine using a mixture of trifluoroacetic anhydride and 85% hydrogen peroxide in methylene chloride.[173]

Emmons[174] prepared several dimeric nitrosoalkanes (alkyl = propyl, tolyl, octadecyl, *tert*-butyl, cyclohexyl) by oxidation of the amines using peroxyacetic acid (prepared from 90% hydrogen peroxide and acetic anhydride in dichloromethane). Similarly, Meister[175] prepared nitrosocyclododecane using a 20% solution of peroxyacetic acid in ethyl acetate, and Corey and Gross[176] prepared three *tert*-alkylnitroso compounds by this method (*tert*-alkyl = *tert*-butyl, *tert*-octyl, and 1-adamantyl).

(3) Potassium Permanganate. Bamberger and Tschirner[177] used potassium permanganate together with formaldehyde in sulfuric acid for the oxidation of aniline to nitrosobenzene. 2,4,6-Tri-*tert*-butylnitrosobenzene was isolated from the products obtained by potassium permanganate oxidation of the corresponding amine in a chloroform/water mixture at 20 °C.[178] Similarly, nitrosocyclohexane was prepared from cyclohexylamine using potassium permanganate and formaldehyde in sulfuric acid.[179]

(4) 3-Chloroperoxybenzoic Acid (MCPBA) and Peroxybenzoic Acid. From the late 1960s onward, there have been many reports of the use of 3-chloroperoxybenzoic acid for the synthesis of nitroso compounds. A particular example is the oxidation of 3-aminobenzamide by 3-chloroperoxybenzoic acid in DMF at 0−5 °C to give 3-nitrosobenzamide.[180] Preparation of 6-nitroso-1,2-benzopyrone, 5- nitroso-1(2*H*)-isoquinolinone, 7-nitroso-1(2*H*)-isoquinolinone, and 8-nitroso-1(2*H*)-isoquinolinone was also reported. These aryl nitroso compounds were prepared to test their suitability as specific inactivators of retroviral zinc fingers and as antitumor agents.[180] The preparation of 2,6-dimethyl- and 2,6-diethylnitrosobenzene and 2-ethyl-6-methylnitrosobenzene using dichloromethane as solvent has been reported[181] and extended using acetonitrile-d_3 as solvent to prepare the same products and 2-methyl-6-*tert*-butylnitrosobenzene (very low yields of <5% were obtained upon oxidation of the 2-chloro-4-methylaniline and 2,4-dimethylaniline precursors).[182] Okazaki[183] used peroxybenzoic acid oxidation to produce five sterically encumbered *tert*-butyl-substituted nitrosobenzenes (eq 23); these nitrosobenzenes were proposed to exist as monomers even in the solid state due to the presence of bulky *tert*-butyl substituents in the 2-positions.



(23)

a) $R_1 = R_3 = t$-Bu; R_2 = H
b) $R_1 = t$-Bu; R_2 = H; R_3 = Me
c) $R_1 = R_3$ = H; $R_2 = t$-Bu
d) R_1 = OC(O)Ph; R_2 = H; $R_3 = t$-Bu
e) $R_1 = t$-Bu; $R_2 = R_3$ = H

Peroxybenzoic acid was also used to produce nitrosobenzenes with 2,6-di-fluoro, 2,6-dichloro, 2,6-dibromo, 2,6-dibromo-4-methyl, and 2-nitro-4-methyl substituents.[184]

The reaction of 3-chloroperoxybenzoic acid with aliphatic primary amines (2-butylamine, 1-hexylamine, 1-propylamine, 2-phenylethylamine, and cyclohexylamine) in dichloromethane at room temperature has been shown to give excellent yields of the dimeric nitroso compounds.[185] Baer and Chiu[186] prepared a number of dimeric nitroso sugars, the chloroform or chloroform−methanol solution of the amino

sugar being added dropwise to a refluxing solution of 3-chloroperoxybenzoic acid in chloroform; *trans*-dimeric 2-nitrosocyclohexanol was also prepared by the same method. Several *C*-nitroso compounds such as nitrosomesitylene, 2-nitrosotoluene, nitrosocyclohexane, 1-alkyl-1-nitrosocyclohexane (alkyl = Me, Et, cyclohexyl), 1-ethyl-1-nitrosocyclopentane, nitroso-*tert*-butane, 2-nitrosoisocamphane, and 2,2,4-trimethyl-4-nitrosopentane have been prepared using 3-chloroperoxybenzoic acid as the oxidant.[187] Eleven *trans*-dimeric aralkyl *C*-nitroso compounds have been prepared by addition of the oxidant to a chloroform solution of the amine at 0−5 °C.[188] An interesting variant[189] is provided by passing a stream of *tert*-butylamine in dry nitrogen through a tube packed with 3-chloroperoxybenzoic acid in sodium chloride maintained at 4 °C, the effluent gas being passed through a trap at −80 °C where a blue liquid condensed. Slow conversion to the colorless dimer in the presence of unreacted amine took place at −30 °C. Another synthesis by this method is that of nitrosocyclopropane; commercial cyclopropylamine is slowly distilled through a plug of 3-chloroperbenzoic acid suspended on sodium chloride, the blue product being condensed out with subsequent dimerization.[190]

(5) Hydrogen Peroxide in the Presence of a Catalyst. Sakaue et al.[191] used 35% hydrogen peroxide in the presence of peroxotungstophosphate ($H_3PW_{12}O_{40}$) to oxidize aromatic amines such as aniline, 4-methylaniline, and 4-chloro-aniline to give the respective nitroso compounds. Another catalyst for the hydrogen peroxide oxidation of 1° aromatic amines is $[Mo(O)(O_2)_2(H_2O)(hmpa)]$;[192] high yields for a wide range of substituted nitrosobenzenes RC_6H_4NO (R = H, 4-Me, 4-Et, 4-*tert*-Bu, 4-OMe, 4-CO_2Me, 4-NHCOMe, 4-F, 4-Cl, 4-Br, 3-Me, 3-Cl, 3-OMe, 2-Me, 2-Et, 2-OMe) were obtained. In a later development,[193] 14 substituted anilines $RC_6H_4NH_2$ (R = 2-Me, 2-Et, 2-Cl, 2-Br, 3-Me, 3-Cl, 3-Br, 4-Me, 4-Et, 4-isopropyl, 4-*tert*-butyl, 4-F, 4-Cl, and 4-Br) were oxidized by hydrogen peroxide in the presence of *cis*-$Mo(O)_2(acac)_2$ (acacH = $MeC(O)CH_2C(O)Me$) to give, in most cases, high yields of the nitroso products. Another example of the catalytic oxidation of substituted anilines 4-$RC_6H_4NH_2$ (R = H, Me, OMe, CO_2Et, COMe, F, Cl, Br, CF_3, and CN) to give the corresponding nitroso derivatives is provided by the catalyst oxoperoxo(pyridine-2,6-dicarboxylato)(hmpa)molybdenum(VI).[194] Methylrhenium trioxide has also been used as a catalyst for the hydrogen peroxide oxidation of some anilines $RC_6H_4NH_2$ (R = H, 2-Me, 3-Me, 4-Me, 4-cyclohexyl, 4-Cl).[195]

(6) Peroxyformic Acid. Peroxyformic acid has been used in the oxidation of precursor substituted anilines in refluxing dichloromethane to give C_6F_5NO,[196,197] 4-BrC_6F_4NO,[198] 4-$(HOOC)C_6F_4NO$,[198] and 4-$CF_3C_6F_4NO$.[199]

(7) Other Peroxy Compounds. Dimeric nitrosocyclohexane was prepared from oxidation of the amine by a sodium tungstate−hydrogen peroxide mixture.[200] Burckard and co-workers[201] reported the use of the same reagents in the oxidation of aromatic amines to their nitroso derivatives. Stowell[202] similarly prepared the *trans*-dimers of 2-methyl-2-nitrosopropane (nitroso-*tert*-butane) and 2,4,4-trimethyl-2-nitrosopentane (nitroso-*tert*-octane). Baldwin et al.[187] also reported the preparation of nitroso-*tert*-octane from octylamine using a mixture of sodium tungstate, the sodium salt of EDTA, and 15% hydrogen peroxide. Details of this methodology for the preparation of nitroso-*tert*-octane are given by Corey and Gross.[203] Stowell and Lau[204] prepared dimeric 2,6-dimethylnitrosobenzene by the sodium tungstate-30% hydrogen peroxide oxidation of the precursor amine.

Zajac and co-workers used two different peracid salts as the source of oxidants to prepare nitrosoalkanes and nitrosocycloalkanes from the corresponding amines in high yields. Both of these synthetic pathways avoid the use of added hydrogen peroxide solutions. The first example[205] used sodium percarbonate (as the source of hydrogen peroxide), sodium bicarbonate, and *N*,*N*,*N*′,*N*′-tetraacetylethylenediamine in a biphasic system of ethyl acetate or dichloromethane and water to prepare the dimers of 1-nitrosododecane, 1-nitroso-2-phenylethane, 2-nitrosomethyl-*endo*-norbornane, nitrosocyclohexane, 1-nitrosoadamantane, 2-nitrosoadamantane, 3-nitrosonoradamantane, 2-nitroso-*endo*-norbornane, and 2-nitroso-*exo*-norbornane. Following the success of the above syntheses, Zajac[206] used sodium perborate in place of sodium percarbonate and obtained good yields of 1-nitrosododecane, 1-nitroso-2-phenylethane, nitrosocyclohexane, 2-nitroso-*endo*-norbornane, 1-nitrosoadamantane, 2-nitrosoadamantane, and 3-nitrosonoradamantane.

Crandall and Reix[168] used dimethyldioxirane to oxidize aliphatic primary amines, the products including not only dimeric nitrososalkanes but also oximes, nitroalkanes, nitrones, and oxaziridines. Good yields of the nitroso dimers could be isolated from the initial reaction mixture in the cases of nitrosocyclohexane, 1-nitrosobutane, and 1-nitrosodecane, but benzylamine gave only the benzaldoxime.

(8) Oxaziridines and Oxaziridinium Salts. The synthesis of dimeric nitroso compounds in low yields from the reaction of 2-(phenylsulfonyl)-3-oxaziridine (Davis' reagent) with benzylamine, *endo*-2-norbornylmethylamine, cyclohexylamine, *endo*- and *exo*-2-norbornylamine, *tert*-butylamine, 1-adamantylamine, 2-adamantylamine, and 3-noradamantylamine has been reported.[207] Hanquet and Lusinchi[208] prepared dimeric nitroso compounds from *n*-butylamine, *tert*-butylamine, benzylamine, and 1-phenyl-2-propylamine using the oxaziridinium tetrafluoroborate derived from dihydroisoquinoline.

(9) Oxygen Difluoride. Oxygen difluoride oxidation of *tert*-butylamine, *tert*-octylamine, and cyclopropylamine at temperatures below −42 °C to obtain the corresponding dimeric nitroso compounds has been reported.[209] The production of two different dimers of nitroso-*tert*-butane and nitrosocyclopropane was claimed; however, no other reports of the cis dimers of these have appeared to date in the literature.

(10) Nitrous Acid. An unusual oxidation of an amino group by an equivalent of nitrous acid to form the corresponding nitroso compound is provided by

Table 1. Preparations of Substituted Nitrosobenzenes from Ferric Chloride Oxidation of the Corresponding Hydroxylamines

substituent	ref	substituent	ref	substituent	ref	substituent	ref
2-Cl	213	3-Me	213, 214, 221	4-CO_2Me	216	2,3-di-Me	221
2-Br	213	3-Et	213	4-CH=C(CN)$_2$	216	2,4-di-Me	221
2-I	158, 213	3-CH=CHCO$_2$Et	214	4-C(Ph)=C(CN)$_2$	216	2,5-di-Me	213, 221
2-Me	158, 213	4-F	213, 214	4-*tert*-Bu	166	2,6-di-Me	213, 222[a]
2-Et	213	4-Cl	158, 213, 214	2,4-di-Cl	217[a]	3,4-di-Me	74, 214, 221
2-Ph	158	4-Br	160, 213, 214	2,5-di-Cl	218[a]	3,5-di-Me	213, 214, 222
3-F	214	4-I	158, 213, 214	3,4-di-Cl	219[a]	2,4,5-tri-Me	163
3-Cl	213, 214	4-NO_2	216	3,5-di-Cl	220	2,4,6-tri-Me	159, 213, 223
3-Br	213, 214	4-CN	216	2,4,6-tri-Cl	158, 159		
3-I	158, 213, 214	4-Me	158, 213−215[a]	3,5-di-Cl-4-I	158		

[a] Oxidation using acidified dichromate.

the formation of dimeric tris(nitromethyl)nitrosomethane from tris(nitromethyl)methylamine at 0−5 °C (eq 24).[210]

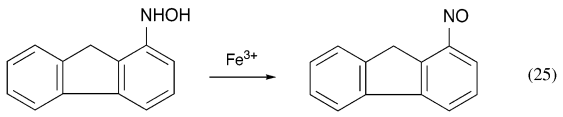
$$(O_2NCH_2)_3CNH_2 \xrightarrow{HNO_2} 1/2[(O_2NCH_2)_3CNO]_2 \quad (24)$$

2.4.2. Hydroxylamines

The controlled oxidation of *N*-aryl- and *N*-alkylhydroxylamines (RNHOH) is a common method for the production of nitroso compounds, there being a wide variety of oxidizing agents available for this purpose. The *N*-substituted hydroxylamines are usually obtained by partial reduction of the nitro precursors RNO_2; in most cases, the favored reagents for this step are powdered zinc together with ammonium chloride as in the case of the formation of *N*-1-adamantylhydroxylamine from 1-nitroadamantane.[211] Preparative details are given for the reduction of nitrobenzene to *N*-phenylhydroxylamine followed by acidified dichromate oxidation to nitrosobenzene.[212] Oxidizing agents used are listed below.

(1) Ferric Chloride. The oxidation of aromatic hydroxylamines has been used in the preparation of substituted nitrosobenzenes for over 100 years, and Table 1 lists the major references for the preparation of many monosubstituted, disubstituted, and trisubstituted nitrosobenzenes using ferric chloride.

A related ferric ion oxidation reaction is provided by the oxidation of 2-hydroxylaminofluorene by ferric ammonium sulfate (eq 25).[224]



(25)

(2) Sodium or Potassium Dichromate and Sulfuric Acid. The use of acidified dichromates as an alternative to ferric chloride to prepare substituted nitrosobenzenes has been employed for many years, and many examples are available.[225−230] This method has been extended to the syntheses of dimeric 3-nitrosopyridine[231] and to *trans*-dimeric 2-methyl-2-nitrosobutane and 2-methyl-2-nitroso-1-acetoxypropane from the *N*-alkylhydroxylamines.[232] A related method uses chromium trioxide in the attempted oxidation of 1,3-dihydroxylamino-4,6-dinitrobenzene to the corresponding dinitroso compound.[233] The presence of a bright green color suggests that some of the desired product was obtained, but the reported further oxidation to the 1,3,4,6-tetranitrobenzene product suggests that a milder oxidant might be needed for the preparation of high yields the desired nitroso compound.

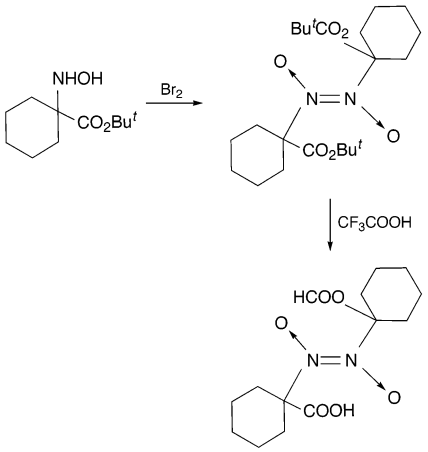
(3) Potassium Ferricyanide in Sodium Hydroxide. The preparation of *trans*-dimeric α-alkyl-substituted 2-nitroso-1-phenylethanes ($PhCH_2CH(R)NO)_2$ (R = H, Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, and *tert*-Bu) by this method has been described.[234,235]

(4) Periodates and Periodic Acid. In 1960, Emery and Neilands[236] discovered that periodic acid oxidation of *N*-methylhydroxylamine and of *N*-methylacethydroxamic acid produced *cis*-dimeric nitrosomethane in high yield. Although they did not attempt to extend this method to other *N*-alkylhydroxylamines, they suggested that such an extension was likely to succeed. In 1964, Sklarz and co-workers[237,238] introduced the use of tetraethylammonium periodate as an oxidant for hydroxylamines, and this was developed from 1973 onward by Kirby and co-workers[239] for the oxidation of a range of hydroxylamines to produce short-lived nitroso compounds, which were then trapped by dienes to produce dihydrooxazines. Later studies[240−242] added the compounds ROC(O)NHOH, RR′NC(O)NHOH and RCH(OR′)C(O)NHOH (R and R′ = alkyl or aryl) to the list of hydroxylamines used to produce short-lived *C*-nitroso compounds. A further development took place in the use of tetraethylammonium periodate for the oxidation of chloroform solutions of sugar hydroxylamines of the general structure R_3CNHOH to the corresponding monomeric R_3CNO. The same product can also be obtained using the oxidant dichlorodicyanobenzoquinone (DDQ). The use of periodate for the oxidation of sugar hydroxylamines RCH_2NHOH and $R_2CHNHOH$ gives only the isomeric oximes. In contrast, the use of DDQ with RCH_2NHOH gives both the oxime and the dimeric nitroso compound, whereas only the dimeric nitroso compound is produced when $R_2CHNHOH$ is used.[243,244]

(5) Halogens and Hypohalites. Oxidation of *tert*-butylhydroxylamine by bromine in sodium hydroxide (as a source of NaOBr) at 0 °C gives good yields of the corresponding nitrosoalkane.[174,245] This has been extended to prepare dimeric 1-nitroso-1-carboxylic acid-*tert*-butyl ester-cyclohexane (Scheme 11).[246]

Oxidation using bromine water together with a solution of the hydroxylamine in 2 M HCl gave good yields of dimeric nitroso compounds $(RNO)_2$ (R = cyclohexyl, 4-heptyl, cycloheptyl, cyclooctyl, 2-meth-

Scheme 11



ylcyclohexyl).[247,248] Further extension to the *trans*-dimers of 1-nitroso-*trans*-decalin, 2-nitroso-*trans*-decalin, and 2-nitroso-*cis*-decalin followed.[249] Oxidation of 1-cyano-1-hydroxylaminocyclohexane by chlorine yields the corresponding nitroso compound,[250] and an ethanol solution of 3-chloro-4-methyl-phenylhydroxylamine was oxidized to the dimeric nitroso compound by stirring with iodine, sodium iodide, and sodium acetate in water.[251]

(6) Silver Carbonate. Maassen and de Boer[252] showed that when silver carbonate, precipitated on Celite, was added to a dichloromethane solution of RNHOH (R = Ph, 4-ClC_6H_4, cyclohexyl, isopropyl, *cyclo*-C_3H_5CHMe, and 2-adamantyl) at room temperature, 84−95% yields of the dimeric nitroso compounds were obtained within a few minutes, thereby avoiding the danger of coupling between the nitroso compound and the unreacted hydroxylamine to form azoxy derivatives. Lower yields (57−66%) were obtained for R = *tert*-butyl (in dry $CFCl_3$) and benzyl (in dry CH_2Cl_2 at 0 °C). With the exception of nitrosobenzene, the dimers obtained were the *trans*-dimers, and the 1-cyclopropyl-1-nitrosoethane was a mixture of the racemic and *meso* forms of the dimer. Further details are given by Maassen.[253]

(7) Lead Dioxide. The oxidation of five *N*-hydroxycarbamates (ROC(O)NHOH; R = Me, Et, *i*-Pr, Ph, CH_2Ph) with freshly prepared lead dioxide in dichloromethane at −10 °C showed the presence of the corresponding nitrosoformates ROC(O)NO, as judged by the further reaction with alcohols to yield carbonate products.[254]

(8) Other Oxidizing Agents. *tert*-Butylhydroperoxide oxidizes *N*-alkylhydroxylamines $R(Me)_2CNHOH$ (R = Me, Et, CH_2OCOMe) and the nitroso compounds were detected by visible absorption spectroscopy.[255] Good yields of *C*-nitroso compounds result from the rapid oxidation of both phenyl- and *tert*-butylhydroxylamine by phenylseleninic anhydride ($(PhSeO)_2O$) in dry THF at room temperature.[256] Oxidation of 4-hydroxylaminopyridine-1-oxide by potassium permanganate is an easy route to the nitroso derivative.[257] Other oxidizing agents employed in such oxidations include phenyliodine ditrifluoroacetate,[258] diethyl azodicarboxylate,[259] 2,6-dichloro-3,5-dicyanobenzoquinone (DDQ),[244] peroxyformic acid,[260] MCPBA,[261] and pyridinium chlorochromate with arylhydroxylamines in THF.[262] Diethyl azodicarboxylate oxidizes cyclopropylhydroxylamine to give the *trans*-dimer of nitrosocyclopropane at −24 °C, the hydroxylamine having been obtained by controlled reduction of nitrocyclopropane.[263] Potassium ferrate(VI) has recently been reported to oxidize *N*-phenylhydroxylamine to nitrosobenzene.[264]

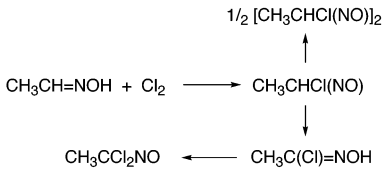
2.4.3. Oximes

Rheinboldt and Dewald[265,266] showed that nitrosyl chloride reacted with both ketoximes and aldoximes to give geminal chloronitroso compounds (eq 26).

(26)

A further study[267] showed that only some oximes yielded chloronitroso compounds when treated with nitrosyl chloride (nitrimines and ketones were produced in some cases). The successful cases included camphor oxime and pinacolone oxime: the statement that the IR spectra of both monomeric and dimeric 2-chloro-2-nitroso-3,3-dimethylbutane are identical is obviously incorrect. The preferred method for the preparation of chloro- and bromo-nitroso compounds is the reaction of halogen or alkylhypohalite with oxime. This method, based upon the early work of Piloty and Schmidt, has been reviewed by Kosinski[268] and Kresze et al.[269] and was employed by several groups in the 1950s.[248,250,270−272] Diekman and Lüttke[273] used *tert*-butylhypochlorite as the chlorinating agent for oximes (RR′C=NOH) to give geminal chloronitroso compounds in high yield (>90%) and purity (R/R′ = H/Me, H/Ph, Me/Me, Me/*t*-Bu, Me/*n*-Bu, Me/CH_2Ph, and $(CH_2)_5$). The same reagent was used to oxidize five *para*-substituted phenylhydroxylamines to their nitroso derivatives.[216] High yields (>70%) of chloronitroso compounds were obtained from the reaction of chlorine with five different ketoximes in ether.[248] The bromination of acetaldoxime was shown by Piloty and Stock[274] to give 1-bromo-1-nitrosoethane, which could be isolated as the dimer; chlorination of some oximes yielded the 1-chloro-1-nitrosoalkanes.[275] The further reactions giving 1,1-dichloro-1-nitrosoethane are shown in Scheme 12.

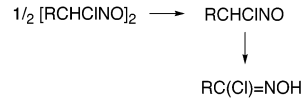
Scheme 12



Chiang[276] reported similar results on chlorination of various benzaldoximes. The chlorination of aldoximes to aldehydo−sugar oximes has been studied by Tronchet et al.;[277] the white solid dimer of RCHClNO dissociates in solution to form the monomer, which subsequently isomerizes to the oxime (Scheme 13).

It has been reported[278] that hexafluoroacetoxime $(CF_3)_2C$=NOH reacts with chlorine at −78 °C to give $(CF_3)_2C(Cl)NO$; 2-nitrosoheptafluoropropane has been prepared from the same oxime by reaction with

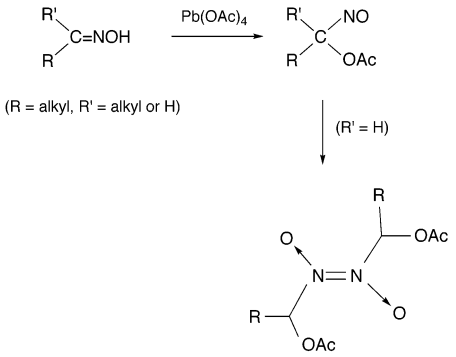
Scheme 13



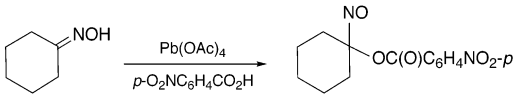
hydrogen fluoride/chromium trioxide.[279] Bromination of 2-pentanone oxime by *N*-bromosuccinimide in sodium carbonate yields the bromonitroso product.[270]

Lead tetraacetate reacts with ketoximes to give geminal nitrosoacetates.[280] Extension of these studies[281] showed that geminally substituted nitroso compounds resulted from the reaction of aliphatic and alicyclic ketoximes with lead tetraacetate and lead tetrabenzoate in inert solvents such as ether, benzene, dichloromethane, and tetrachloroethylene (Scheme 14).

Scheme 14



It was also shown that when cyclohexanone oxime reacted with lead tetraacetate in ethereal 4-nitrobenzoic acid, pale blue crystals of 1-nitroso-1-(4-nitrobenzoxy)cyclohexane were formed (eq 27).

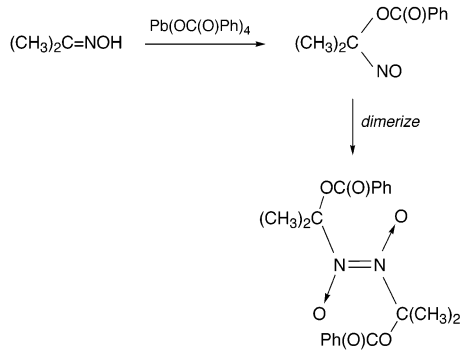


(27)

Extension to reaction of lead tetraacetate with aldoximes resulted in the isolation of four different *trans*-dimeric nitroso acetoxyalkanes $(RCH(OAc)NO)_2$ (R = propyl, pentyl, heptyl, and benzyl). Similarly, Lown[282] showed that geminal nitroso acetoxy derivatives were obtained in 23−72% yields from the reactions of lead tetraacetate with the ketoximes of acetone, cyclopentanone, cyclohexanone, 4-*tert*-butylcyclohexanone, heptan-2-one, and heptan-4-one. Dimeric 1-*equatorial*-1-acetoxy-1-nitroso-4-*tert*-butylcyclohexane and monomeric 1-*axial*-1-acetoxy-1-nitroso-4-*tert*-butylcyclohexane were obtained. White and Considine[283] were the first to study the reaction between lead tetrabenzoate and both aliphatic and alicyclic ketoximes. Dimeric 2-nitroso-2-benzoyloxypropane was isolated from the reaction with acetoxime (Scheme 15).

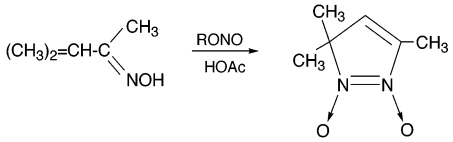
The reaction of lead tetraacetate with aliphatic *anti*-aldoximes[284] and steroid ketoximes[285] yielded geminal nitrosoacetates. Isolation of the colorless *trans*-dimer of 1-acetoxy-1-nitrosoheptane was achieved from reaction with *anti*-heptanaldoxime, whereas the colorless reaction product (with a blue tinge) from *syn*-trimethylacetaldoxime did not yield

Scheme 15



a pure sample of the spectroscopically indicated dimeric 1-acetoxy-1-nitroso-2,2-dimethylpropane. The light blue color of the solid 3β,6β-diacetoxy-6α-nitroso-5α-cholestane suggested the presence of both monomeric and dimeric forms. Two short reviews of the reactions of lead tetraacetate with oximes have appeared.[286,287]

Extension to the oxidation of the dioximes of aliphatic and alicyclic diketones has been made;[288,289] pyrazoline1,2-dioxides are formed, and geminal acetoxynitroso compounds are probable precursors. The reaction of mesityl oxide oxime with nitrite ester in acetic acid produces 3,5,5-trimethyl-3-pyrazoline *N*,*N*′-dioxide (eq 28).[290]



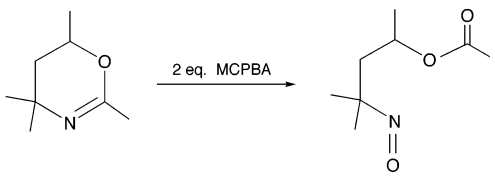
(28)

Ozonolysis of *N*-phenylbenzaldoxime and *N*-*tert*-butylbenzaldoxime produced nitrosobenzene and 2-methyl-2-nitrosopropane intermediates, respectively, which were further oxidized to their nitro derivatives.[291]

2.4.4. Other N-Containing Functional Groups

Lee and Keana[261] showed that oxidation of an oxazoline with 3-chloroperoxybenzoic acid gave the oxaziridine (Scheme 16), which upon further manipulation gave the nitroso ester as the final product.

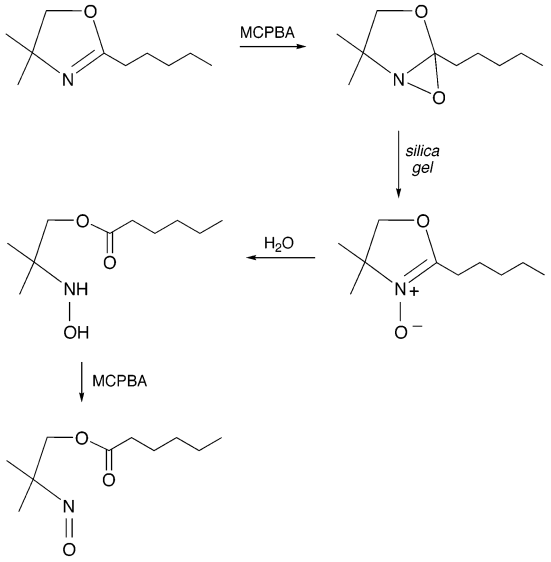
Similar oxidation of a dihydrooxazine with 2 equiv of 3-chloroperoxybenzoic acid produced 2-nitroso-2-methyl-4-acetoxypentane as a blue oil which crystallized as the colorless dimer at −20 °C (eq 29).



(29)

The ozonation of two nitrones using 1 mol equiv of ozone produced their nitroso products; nitro compounds were the final products of ozonation.[291] The oxidation of the amines *N*-pentachlorophenylpiperidine and *N*-pentachlorophenylpyrrolidine with peroxyformic acid gave pentachloronitrosobenzene.[260] The intermediate *N*-pentachlorophenyl-2-formoxypi-

Scheme 16



peridine similarly gave pentachloronitrosobenzene. In a similar manner, tetrachloro-4-nitrosopyridine was obtained from tetrachloro-4-methylaminopyridine on reaction with peroxytrifluoroacetic acid.[292]

2.5. Preparation from Nitro Compounds

2.5.1. Direct Reduction

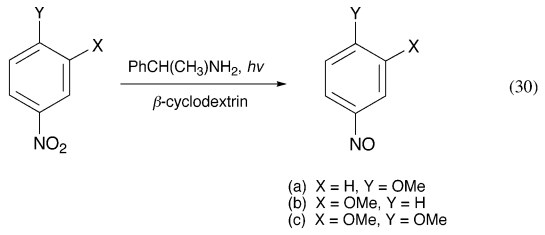
The direct reduction of nitrobenzene to give nitrosobenzene has attracted the attention of chemists for about 100 years. Early examples are provided on the reduction of nitrobenzene by barium oxide[293] and by sodium, potassium, calcium, strontium, barium, magnesium, zinc, and aluminum amalgams in dry organic solvents.[294] A related reduction of *m*-dinitrobenzene by zinc to give *m*-nitro-nitrosobenzene was reported in 1905.[295] The more recent studies by Ponec and co-workers have provided essential insight into the conditions necessary for selective surface-catalyzed deoxygenation of nitrobenzene. The catalysts used were carefully characterized,[296,297] and by using various oxides of manganese it has been shown[298] that the steady-state catalyst for the reduction is the spinel Mn_3O_4 in a slightly reduced form, the mechanism for this selective reduction being that proposed by Mars and Van Krevelen for vanadium oxide catalysts.[299] Further studies have investigated the role of Li^+, Na^+, and K^+ ions on the activity and selectivity of Mn_3O_4 and similarly of the mixed oxide catalyst $PbO-Mn_3O_4$.[296,300−302] The deoxygenation reaction is carried out at 573 K using an open-flow system with a fixed bed reactor and using helium as the carrier gas. A further variation of the catalyst is shown in the use of a series of mixed cobalt aluminum oxides with spinel structures, the rate of production of nitrosobenzene increasing almost linearly with increasing concentration of cobalt in the surface.[303] The importance of these studies lies in the potential for producing nitrosobenzene from nitrobenzene on an industrial scale without the formation of the waste products that result from the batch process involving reduction to the hydroxylamine and subsequent oxidation.

In a series of papers, Moinet reported the development of direct synthetic methods for the high-yield production of substituted 2-nitrosobenzoic acids and other substituted nitrosobenzenes from their nitrobenzene precursors using a "redox" cell. In general, the solution was allowed to flow through two consecutive porous electrodes of opposite polarity; at the first porous cathode the nitro compound was reduced to the hydroxylamine, and at the second porous anode this was oxidized to the nitroso compound.[304−307] High-yield syntheses of *ortho*-substituted nitrosobenzenes RC_6H_4NO (R = CO_2H, CO_2Me, $CONH_2$, CONHMe, $CONEt_2$, CON(Me)Ph, CH_2CO_2H, $CHOHCO_2H$, $NHCO_2Me$) were achieved by this method.[305]

An efficient electrochemical synthesis of nitrosobenzene from nitrobenzene has been reported;[308] a THF−0.2 M tetrabutylammonium perchlorate solution in the presence of 6 equiv of benzoic acid was used. When the oxidation step (after the four-electron reduction of $PhNO_2$ to PhNHOH) was carried out at −30 °C, the isolated yield of nitrosobenzene was 90%.

Optimum conditions for the electrosyntheses of *meta*- and *para*-substituted nitrosobenzenes from nitrobenzenes $RC_6H_4NO_2$ with the electron-withdrawing substituents (R = CN, COO^-, COOMe, CHO, COMe) have been described.[309] Extension of this technique to nitroheterocyclic compounds has yet to be attempted.

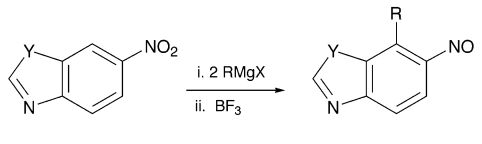
It has been shown that photoreduction (by irradiation with a medium-pressure mercury lamp with a Pyrex filter) of the ternary complexes of β-cyclodextrin, some nitrophenyl ethers, and 1-phenylethylamine in the solid state gave >95% yields of the corresponding nitroso compounds (eq 30).[310]



(30)

(a) X = H, Y = OMe
(b) X = OMe, Y = H
(c) X = OMe, Y = OMe

The reaction of mononitroarenes with alkyl Grignard reagents has been investigated extensively;[311] it has been shown that conjugate addition of the alkyl RMgX system occurs and that nitroso compounds can be obtained from a number of bicyclic aromatic systems such as naphthalenes, quinolines, indoles, benzothiophenes, benzoxazoles, and benzothiazoles (e.g., eq 31).[312]



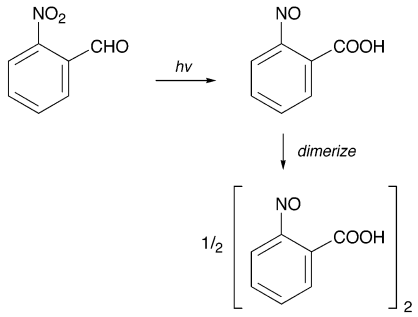
(31)

(X = halogen; Y = O, S)

2.5.2. Redox Reactions

Light-catalyzed intramolecular rearrangements of nitroaromatic compounds containing an *ortho* sub-

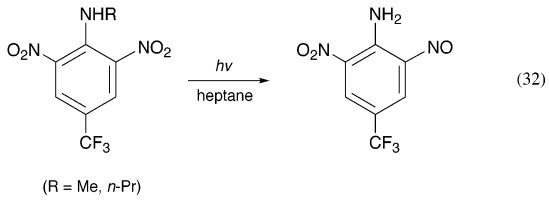
Scheme 17



stituent in which a C−H bond is attached to the *ortho* ring carbon have long been known. Ciamician and Silber[313] found that *o*-nitrobenzaldehyde rearranged photolytically to *o*-nitrosobenzoic acid (Scheme 17), and Sachs and Hilpert[314] suggested that "all aromatics which have a hydrogen *ortho* to a nitro group will be light sensitive".

These rearrangements occur for the nitroaromatics containing the *ortho* groups CH=NPh,[315] C(CN)H(OH),[314] $CH(OEt)_2$,[316] CH_2OH,[316,317] and $CHPh_2$.[318] The quantum yield of the *o*-nitrobenzaldehyde intramolecular rearrangement in acetone is 0.5,[319] which was found to be in good agreement with the unweighted value of 0.46 for the isomerization reaction in the solid state.[320] This photolytic oxygen-transfer rearrangement[321] has been employed as a chemical actinometer using a dispersion of *o*-nitrobenzaldehyde in a thin film of poly(methyl methacrylate).[322] γ-Irradiation of solid *o*-nitrobenzaldehyde results in the formation of *o*-nitrosobenzoic acid in >90% yield.[323] In all these examples the products are the *trans*-dimeric nitroso compounds.

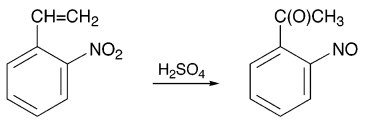
Other developments of the photoredox reaction are shown in the production of *o*-4-pyridylnitrosobenzenes from the light-sensitive *o*-4-(1,4-dihydropyridyl)nitrobenzene precursors,[324] in the production of *o*-nitrosophenols from *o*-nitrophenoxyacetic acids,[325] and in the formation of *o*-nitrosoanilines from *o*-nitro-*N*-alkylanilines (eq 32).[326]



(32)

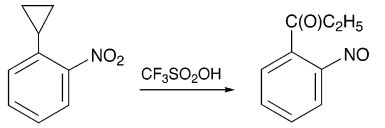
(R = Me, *n*-Pr)

In addition to these photochemical reactions, thermal rearrangements have been observed; *o*-nitrocyclopropylbenzene in the presence of concentrated sulfuric acid at low temperatures gives *o*-nitrosopropiophenone, and *o*-nitrostyrene similarly produces *o*-nitrosoacetophenone (eq 33).[327]



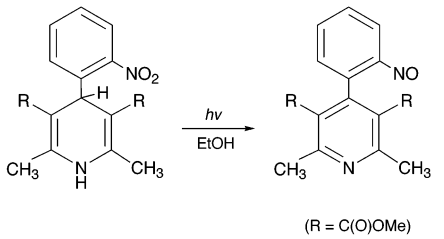
(33)

The rearrangement of *o*-cyclopropylnitrobenzene in trifluoromethane sulfonic acid gives *o*-nitrosopropiophenone in 79% yield (eq 34).[328]



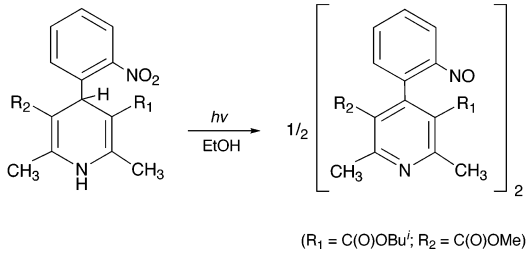
(34)

Some *o*-nitrobenzene derivatives are of pharmaceutical importance and can form nitroso compounds on irradiation of their solutions by sunlight or by ultraviolet light. Examples are provided by the irradiation of nifedipine, an antihypertensive drug and calcium channel blocker, which gives high yields of an apparently monomeric nitroso compound (eq 35),[324,329,330] and by the irradiation of the structurally similar nisoldipine, also a calcium channel blocker, which gives a monomeric and two dimeric nitroso compounds (eq 36).[331]



(35)

(R = C(O)OMe)

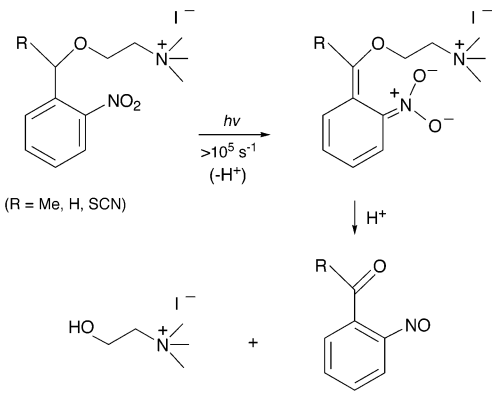


(36)

(R_1 = C(O)OBu^i; R_2 = C(O)OMe)

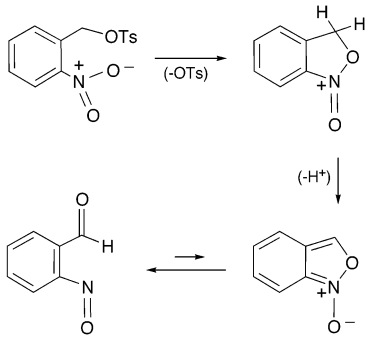
Three *o*-nitrobenzyl ethers of choline, when subjected to laser flash photolysis at 351 nm, give *ortho*-substituted nitrosobenzenes with release of choline (Scheme 18).[332]

Scheme 18



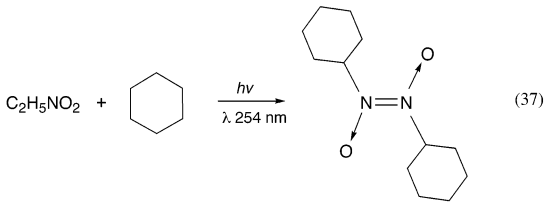
Photolysis of *o*-nitrobenzyl alcohol has been shown to generate *o*-nitrosobenzaldehyde.[317] Hydrolysis of *o*-nitrobenzyl tosylate in 1:1 acetonitrile/water gives *o*-nitrobenzyl alcohol and *o*-nitrosobenzaldehyde by an intramolecular nucleophilic substitution reaction (Scheme 19).[333]

Scheme 19



2.5.3. Photochemical Synthesis from Nitroalkanes in Solution

Reid and Wilcox[334] found that the *trans*-dimer of nitrosocyclohexane was the major product from the irradiation (at 254 nm) of nitroethane in degassed cyclohexane (eq 37); the same product was obtained from photolysis of nitromethane in degassed cyclohexane.[335]



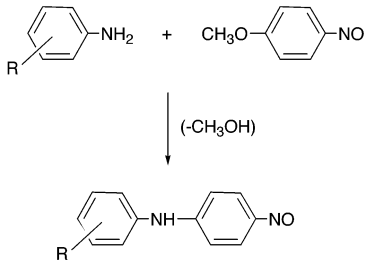
(37)

Co-60 γ-irradiation of liquid nitromethane resulted in the formation of *cis*-dimeric nitrosomethane.[336]

2.6. Preparation from Other Nitroso Compounds

Ingold[337] prepared the *para*-substituted nitrosobenzenes 4-RC_6H_4NO (R = Cl, Br, NO_2) by reaction of the elemental halogens (reaction temperature of ~5 °C) or concentrated nitric acid (reaction temperature of 0 °C) with nitrosobenzene in carbon disulfide. Hammick and Illingworth[338] showed that the production of 4-bromonitrosobenzene did not occur when glacial acetic acid was the solvent. 4-Nitrosophenyl ethers can be aminated with primary aromatic amines to give 4-nitrosodiphenylamines (Scheme 20).[339]

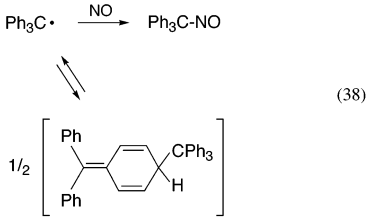
Scheme 20



(R = H, *o*-Me, *m*-Me, *p*-Me, *p*-OMe, *p*-OEt, *p*-Cl, *p*-NH_2, *p*-NMe_2)

2.7. Reaction of Free Radicals with Nitric Oxide

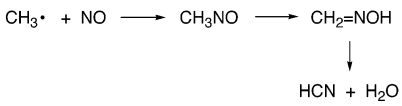
The formation of a nitroso compound by the reaction described in eq 38 was first proposed in 1911 to explain the blue coloration obtained when nitric oxide (itself a radical) was passed into a solution of the equilibrium mixture of the trityl dimer (at the time believed to be "hexaphenylethane", but now known to have an unsymmetrical quinoid structure)[340] and triphenylmethyl.[341]



(38)

Staveley and Hinshelwood[342−344] found that addition of small quantities of nitric oxide to the reaction vessel during the pyrolytic decomposition of diethyl ether brought about a considerable reduction of the decomposition reaction rate (by trapping of radicals with NO) and ascribed this to the reactions in Scheme 21, although no experimental detection of nitrosomethane or formaldoxime was presented.

Scheme 21



It is, however, possible that the unidentified white solid obtained from the photolysis of gaseous dimethylmercury in the presence of nitric oxide was (or contained) a dimer of nitrosomethane.[345]

Dimeric nitrosomethane was first isolated in 1948 by Coe and Doumani[346] from the photolysis of gaseous *tert*-butyl nitrite, the overall reaction (eq 39) being followed by deposition of the dimeric nitrosomethane at the unirradiated wall of the reaction vessel.

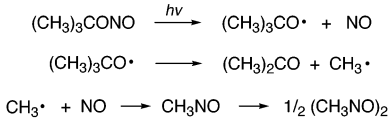
$$(CH_3)_3CONO \xrightarrow{h\nu} (CH_3)_2CO + CH_3NO \quad (39)$$

A possible reaction mechanism (Scheme 22) consists of the production of *tert*-butoxy radicals, followed by their decomposition to give acetone and methyl radicals, the latter then being trapped by the nitric oxide liberated in the first step.

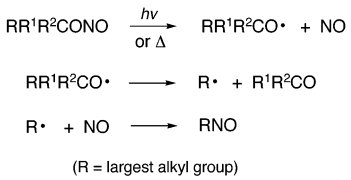
However, the absence of ethane production in the actual experiments suggested to the authors that an *intramolecular* formation of nitrosomethane was likely instead.

The formation of 2-nitrosopropane in the flow-system pyrolysis of gaseous diisopropylmercury in the presence of nitric oxide[347] led the way to the subsequent production of a range of nitrosoalkanes by the pyrolysis or photolysis of alkyl nitrites (Scheme 23).[348,349]

Scheme 22



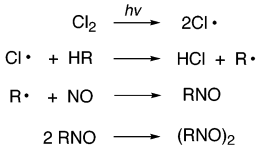
Scheme 23



The optimum temperature for the flow pyrolysis was 320 ± 5 °C. A preparative apparatus for the photolytic production of dimeric nitrosomethane from *tert*-butyl nitrite has been described.[350]

A series of investigations by Müller and co-workers into the photonitrosation and photooximation of hydrocarbons under various conditions led to the production of the following nitroso compounds: 1-chloro-1-nitrosocyclohexane,[351] 1-chloro-1-nitroso-2-methylcyclohexane,[352] dimeric nitrosocyclohexane,[247] dimeric *ω*-nitrosotoluene,[247] dimeric 4-nitrosoheptane,[247] 1-chloro-1-nitrosocycloheptane,[248] 1-chloro-1-nitrosocyclooctane,[248] dimeric nitrosocycloheptane,[248] dimeric nitrosocyclooctane,[248] and dimeric 1-nitroso-2-methylcyclohexane,[248] the general scheme being that described in Scheme 24.

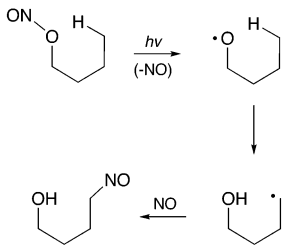
Scheme 24



Müller's major interest, as developed in a series of papers and reviews,[353,354] lay in the exploitation of the above syntheses followed by isomerization of the secondary nitroso compounds to achieve photooximation of a wide variety of cycloalkanes. Donaruma[355] also described the preparation of dimeric nitrosocyclohexane from an irradiated solution of cyclohexane in benzene through which was passed a stream of nitrosyl chloride entrained in nitrogen.

An important application of the photolysis of nitrites to give *C*-nitroso compounds (in an intramolecular process) is provided by the Barton reaction.[356] Photolysis of some steroidal nitrites in either benzene or toluene produces an alkoxy radical (shown in Scheme 25), which then undergoes an intramolecular isomerization by hydrogen-atom transfer involving a six-membered ring transition state. This is then followed by the trapping of this second radical by the nitric oxide produced in the initial photolysis, resulting in a net 1,5-migration of NO from O to C (Scheme 25); the mechanism is also given by other authors.[357,358]

Scheme 25



The initial studies were made using steroidal nitrites, and Figure 4 illustrates the range of applicability for functionalization at either of the methyl groups (C-18 and C-19).[359]

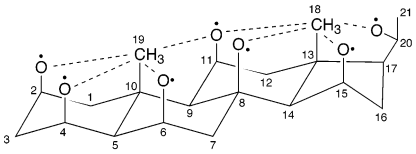


Figure 4.

C-18 can undergo hydrogen abstraction by an alkoxy radical at C-8, C-11, C-15, or C-20. For C-19, the abstraction is possible from an alkoxy radical at C-2, C-4, C-6, or C-11.[359] The main interest of these syntheses was not the preparation of the *trans*-dimeric steroid nitroso compounds but rather their oxime isomers.

Photolysis of an alkyl nitrite carborane-CH_2ONO, derived from the nitrosation (by ClNO in pyridine) of deca-*B*-methyl-1-hydroxymethyl-1,12-dicarba-*closo*-dodecaborane(12), gave the dimeric 2-nitrosomethyl carborane derivative, which was isolated as a coloress solid.[360]

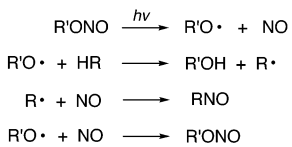
The radical rearrangement reactions of alkoxy radicals has been exploited by Kabasakalian and Townley[361−367] in a series of papers dealing with the room-temperature photolysis of alkyl and alicyclic nitrites in deoxygenated solvents such as heptane and benzene, which have poor radical chain transfer characteristics. In addition to the Barton-type radical rearrangement reactions, some cases involved the alkoxy radical decomposition reaction followed by trapping of the resultant alkyl radical by nitric oxide as shown above. The cases where there are reasonable yields of nitroso compounds[361−367] are listed in Table 2.

An analogous intramolecular hydrogen abstraction reaction is presented by the photolysis of *N*-nitroso-*N*-hexylacetamide in degassed benzene giving *trans*-dimeric *N*-(4-nitrosohexyl)acetamide.[144] This has been extended[368] to the photolysis of *N*-nitroso-*N*-acetyldehydroabietylamine in benzene under helium, yielding the *anti*-dimer of 6α-nitroso-*N*-acetyldehydroabietylamine in 40% yield.

The low-temperature (−80 to +20 °C) decomposition of several substituted cyclopropyl nitrites gave *C*-nitroso derivatives in a number of cases (Table 3).[369]

The photochemical nitrosation of hydrocarbons using alkyl nitrites was explored in detail by de Boer and co-workers. The method was based upon the reaction series described in Scheme 26, where the

Scheme 26



best yields resulted when R′ = *tert*-butyl and R = cyclobutyl, cyclopentyl, cyclohexyl, cyclododecyl, *n*-butyl, *iso*-butyl, benzyl, $PhCH_2CH_2$, and Ph_2CH.

Table 2. Photolysis (λ > 300 nm) of Nitrite Esters (RONO) in Benzene[a]

R group	dimeric nitroso products	ref
n-octyl	4-nitroso-1-octanol, "mixed dimer" γ-nitrosoheptane-4-nitroso-1-octanol, γ-nitrosoheptane	361[b]
2-phenyl-1-ethyl	ω-nitrosotoluene	362
4-phenyl-1-butyl	4-nitroso-4-phenyl-1-butanol	362
5-phenyl-1-pentyl	4-nitroso-5-phenyl-1-pentanol	362
4-heptyl	1-nitroso-4-heptanol	363
2-hexyl	2-nitroso-5-hexanol	363
3-heptyl	2-nitroso-5-heptanol	363
4-octyl	2-nitroso-5-octanol	363
5-nonyl	2-nitroso-5-nonanol	363
2-methyl-2-butyl	nitrosoethane	363
2-methyl-2-pentyl	1-nitrosopropane	363
2-methyl-2-hexyl	5-nitroso-2-methyl-2-hexanol	363
2,5-dimethyl-2-hexyl	5-nitroso-2,5-dimethyl-2-hexanol (monomer)	363
3-methyl-2-butyl	2-nitrosopropane	364
2,2-dimethyl-1-propyl	2-nitroso-2-methylpropane (monomer)	364
3,3-dimethyl-2-butyl	2-nitroso-2-methylpropane (monomer)	364
2-cyclohexyl-1-ethyl	2-(-1-nitroso-1-cyclohexyl)-1-ethanol	365
3-cyclohexyl-1-propyl	3-(1-nitroso-1-cyclohexyl)-1-propanol	365
4-cyclohexyl-1-butyl	4-(1-nitroso-1-cyclohexyl)-1-butanol	365
2-cyclohexyl-1-cyclohexyl		365
2-ethyl-1-cyclohexyl		365
cyclobutyl	4-nitrosobutanal	366
cyclopentyl	5-nitrosopentanol	366
cycloheptyl	6-nitrosohexanol and 4-nitroso-1-cycloheptanol	366
cyclooctyl	4-nitroso-1-cyclooctanol	366
DL-1-isobornyl	DL-1-nitroso-α-campholanaldehyde	367[c]

[a] In degassed solution using a mercury arc. [b] In heptane [c] 300 nm < λ < 400 nm; the compound is destroyed by sunlight.

Table 3. *C*-Nitroso Compounds Prepared from Low-Temperature Decomposition of Some Methyl-Substituted Cyclopropyl Nitrites[a]

ring substituent	temp (°C)	product
1-methyl	20	1-nitrosobutan-3-one (dimer)
1,2,2-trimethyl	−25	2-methyl-2-nitrosopentan-4-one (dimer)
cis,*trans*- and *trans*,*trans*-2,3-dimethyl-1-phenyl	−5	2-nitroso-3-methyl-1-phenyl-butan-1-one (dimer)
pentamethyl	−45	2-nitroso-2,3,3-trimethylpentan-4-one (monomer)
2,2,3,3-tetramethyl	−55	3-nitroso-2,2,3-trimethylpentanal (monomer)
1-methoxy-2,2,3,3-tetramethyl	<−80	methyl 3-nitroso-2,2,3-trimethylbutyrate (monomer)

[a] Reference 369.

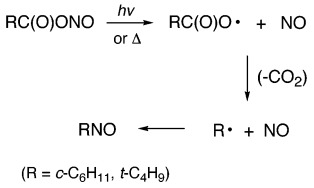
Both *trans*- and *cis*-dimers were obtained by this method;[370−372] also, monomeric *C*-nitroso compounds were obtained when R = *tert*-butyl and $(Me)_2CHC(Me)_2$.[373]

The radical trapping reaction by nitric oxide has been successfully used by Haszeldine[374] and Banus[375] in the production of perfluorinated nitrosoalkanes. The perfluoroalkyl radical is produced by photolysis of gaseous perfluoroalkyliodide and trapped by nitric oxide (eq 40).

$$R_FI \xrightarrow[h\nu]{NO} R_FNO + I \qquad (40)$$

Improvements in the technique give enhanced yields.[376,377] Both hydrocarbon and fluorinated radicals can be prepared from the photolytic or pyrolytic decomposition of acyl nitrites as shown by Pritzkow and Nitzer[378] (Scheme 27; R = cyclohexyl and *tert*-butyl), Stump et al.[379] (R = $MeO_2C(CF_2)_n$; n = 2 or 3), and Umemoto and Tsutsumi (R = CF_3).[380]

Scheme 27



2.8. Preparation of Unsymmetrical "Mixed-Dimer" RN_2O_2R' Azodioxy Compounds

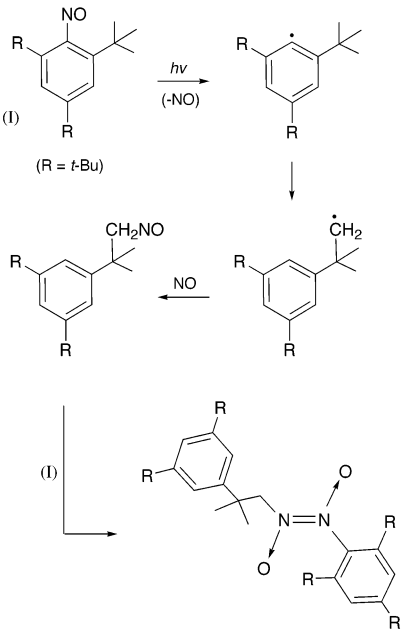
It is apparent that the bonding possibilities of the *trans*- and *cis*-N_2O_2 groups are not confined to the production of symmetrical $(RNO)_2$ dimers, but it was not until 1933 that evidence for the formation of such compounds was produced,[381] when solid−liquid equilibria studies showed that *unsymmetrical* 1:1 products were formed from mixtures of 2,4,6-trimethylnitrosobenzene (nitrosomesitylene) with 2-nitronitrosobenzene or 2,4-dimethylnitrosobenzene. In addition, cryoscopic measurements in benzene solution showed that 2-methylnitrosobenzene, 2-methoxynitrosobenzene, and phenylnitrosomethane also formed mixed dimers with 2,4,6-trimethylnitrosobenzene.

Further examples of mixed dimers, $R-N_2O_2-R'$, are given by Fornstedt and Lindquist (R = Me, R′ = Et)[382] and Wajer (R = Me, R′ = Me-d_3; R = cyclohexyl, R′ = cyclohexyl-d_{11})[383] in which equivalent mixtures of the *cis*-dimers of the two symmetrical components were placed in an organic solvent such that slow

dissociation to monomers occurred, followed by recombination to give the three *trans*-dimers $(RNO)_2$, $R-N_2O_2-R'$, and $(R'NO)_2$ in the relative molar ratio of 1:2:1.

A mixed dimer has been obtained from the photolysis ($\lambda > 320$ nm) of 2,4,6-tri-*tert*-butylnitrosobenzene dissolved in benzene;[384] the reaction pathway described in Scheme 28 demonstrates the formation

Scheme 28



of the mixed aromatic/aralkanyl dimer.

Another route to the formation of mixed dimers has been demonstrated[222] for mixtures of nitrosobenzene with 2,6-dimethylnitrosobenzene, 2,6-dimethylnitrosobenzene, and 3,5-dimethylnitrosobenzene; each pair was dissolved in $CDCl_3$ and studied by variable-temperature NMR spectroscopy to obtain detailed kinetic and thermodynamic data for the mixed *trans*- and *cis*-dimers. This method shows much promise for extending our knowledge of mixed dimers.

2.9. Nitrosyl Cyanide

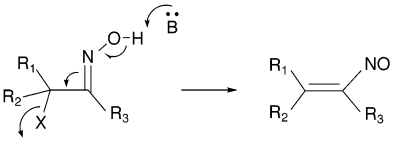
The chemistry of this interesting compound has been reviewed by Kirby.[239] Nitrosyl cyanide is similar to nitrosoalkynes in that it contains a nitroso group bonded to an sp-C atom. The usual preparative method of ONCN is by the reaction of nitrosyl chloride with silver cyanide;[385] careful attention to conditions is necessary in order to avoid explosions. A detailed description on how to avoid this hazard during the preparation of ONCN in milligram quantities has been reported, and the preparation of eight isotopically labeled species was also given.[386]

2.10. Nitrosoalkenes

Although the transient existence of nitrosoalkenes was first invoked over a century ago,[387] sustained interest in the preparation of these compounds is essentially a post-1960 development. Two reviews of the chemistry of nitrosoalkenes have been published.[388,389] Many of the nitrosoalkenes exist in solution as unstable intermediates, and some of these have been identified spectroscopically and/or by their characteristic blue color. In other cases, the existence of nitrosoalkenes was inferred from trapping reactions.

2.10.1. Dehydrohalogenation of α-Halooximes and Chloronitrosoalkanes

Gilchrist[388] described the reaction of α-halooximes with bases (eq 41) as "by far the most important method for the generation of vinyl-nitroso compounds", and this judgment is emphasized by the great majority of the papers that have appeared in this area since that statement was made two decades ago.



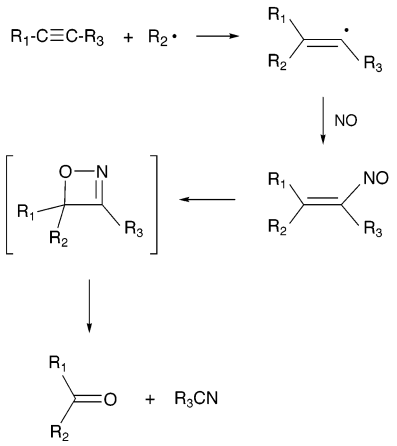
The nitrosoalkenes formed may often be highly reactive and have only a transient existence at room temperature, but there are also some that are stable monomeric solids which have been fully characterized. Others have been prepared in the gaseous state using flow techniques, and the identification of the short-lived nitrosoethenes has been accomplished by microwave spectroscopy.[390−394] The bases used for dehydrohalogenation of the chlorooximes include triethylamine,[395] 1,5-diaza-bicyclo[4,3,0]non-5-ene,[396] sodium alkoxides,[397] stirring a suspension of freshly ground sodium carbonate suspended in dry *tert*-butyl methyl ether[398] (or in diethyl ether[399] or methylene chloride[400]), a two-phase system of aqueous sodium carbonate and methylene chloride,[401] stirring with sodium bicarbonate in alcohol,[402] and stirring with calcium hydroxide suspended in ethyl acetate containing 0.5% water.[403] For the synthesis of gaseous nitrosoalkenes, the chlorooxime is passed over sodium bicarbonate or potassium carbonate at room temperature,[392,394] although direct dehydrochlorination by pyrolysis at 450 °C is preferred.[390−393] Dehydrochlorination of chlorooximes by triethylamine in organic solvents such as benzene,[404] DMF,[395] or acetonitrile[405] results in rapid generation of nitrosoalkenes. Dehydrochlorination of dimeric vicinal chloronitroso compounds by triethylamine has been employed by Pritzkow[406−411] for the preparation of a wide variety of β-nitrosostyrenes. The majority of these β-nitrosostyrenes were isolated as orange-red dimeric solids. Some dimeric carbohydrate nitrosochlorides undergo dehydrochlorination upon treatment with triethylamine[412] and methanol−pyridine.[109] A variant is provided by the reaction of fluoride ions (from CsF, KF, AgF, or $[n\text{-Bu}]_4NF$) with *O*-trialkylsilyl derivatives of α-halooxime compounds in weakly nucleophilic aprotic solvents such as acetonitrile.[413] Lyapkolo and Ioffe[389] provide details of the preparative methods for the production of α-halooximes.

Blue crystals of monomeric 6-nitrosocholesteryl acetate have been isolated in >60% yield from the dehydrochlorination of the chlorooxime precursor with triethylamine.[395]

2.10.2. Reaction of Vinylic Radicals with Nitric Oxide

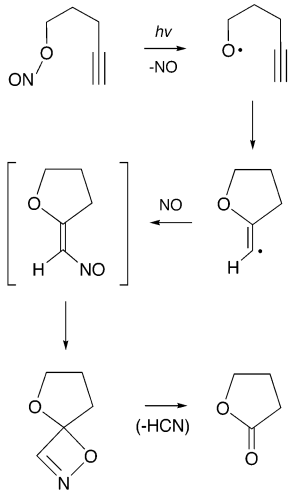
It has been claimed[414] that trifluoronitrosoethylene was obtained by the photolysis of trifluoroiodoethylene in the presence of nitric oxide (compare with eq 40); however, the reported spectroscopic properties were not conclusive. This is apparently the only example of the isolation of a nitrosoalkene by this method, although Sherwood and Gunning[415] presented evidence for the formation of unstable nitrosoalkenes when photolytically generated radicals are added to alkynes in the presence of nitric oxide at room temperature in the gas phase (Scheme 29).

Scheme 29



Similarly, Heicklen[416] photolyzed trifluoroiodoethylene in the presence of nitric oxide and found that the only carbon-containing products were difluoroformaldehyde and cyanogen fluoride (an intermediate trifluoronitrosoethylene C_2F_3NO was proposed for this reaction). An example of a nitrosoalkene formed as an intermediate in a radical trapping reaction (albeit an extremely low yielding one!) is shown in Scheme 30.[417]

Scheme 30

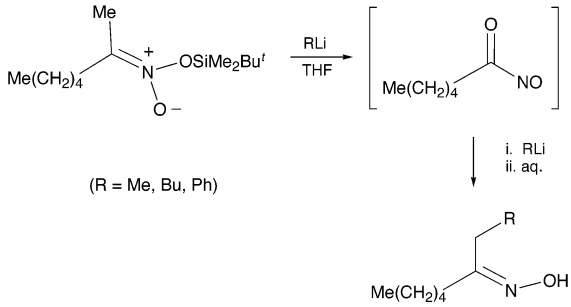


Further investigations of radical trapping of vinylic radicals with nitric oxide should be carried out preferably using flow systems and low-temperature trapping of the reaction products.

2.10.3. 1,3-N,C-Elimination of Trialkylsilanols from Silyl Nitronates

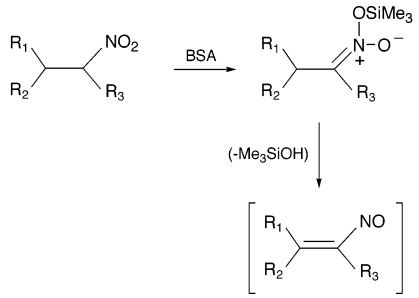
2-Nitrosohept-1-ene is a probable intermediate[418] in the reaction of *tert*-butyldimethylsilylnitronate with an excess of organolithium reagent in THF (Scheme 31).

Scheme 31



In similar fashion, β-substituted nitrosoalkenes are intermediates[419−421] that form during the trimethylsilylation reaction of nitroalkanes, where the initial product is a silyl nitronate (Scheme 32). A further

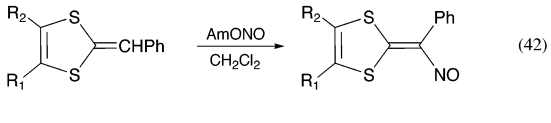
Scheme 32



example of a nitrosoalkene intermediate is found in the silylation of methyl 3-nitropropionate.[422]

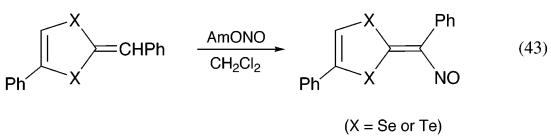
2.10.4. Nitrosation of C═C Bonds

There are a limited number of stable nitrosoalkenes that can be prepared by reaction of an alkyl nitrite with a C═C moiety linked to a heterocyclic fragment. In these cases, the stabilization is the result of O···X (X = S, Se, Te) interactions. Two examples are shown in eq 42,[423] and extensions to the related selenium[424,425] and tellurium[426] compounds are shown in eq 43.



(42)

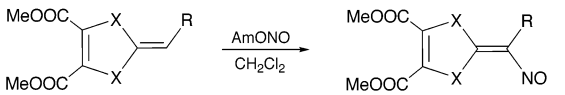
(a) R_1 = Ph; R_2 = H
(b) R_1 = R_2 = CO_2Me



(43)

(X = Se or Te)

Developments are listed in a review,[427] which gives details of the production of four analogous nitroso compounds shown in eq 44.

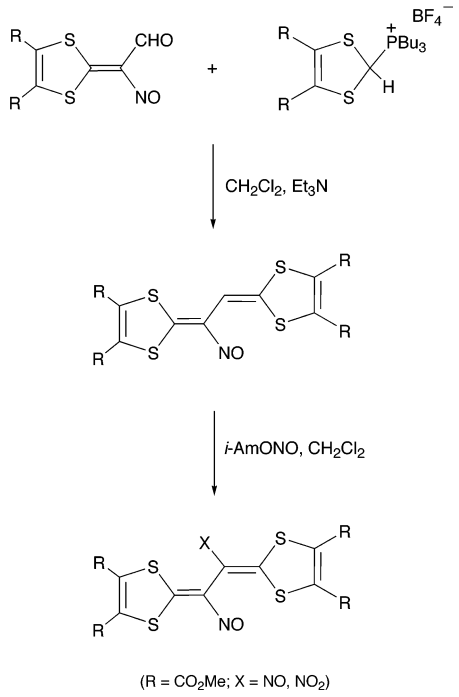


(44)

(a) X = S; R = CHO
(b) X = Se; R = CHO
(c) X = Se; R = *o*-$C_6H_4CF_3$
(d) X = Se; R = C(O)Me

Other nitroso derivatives containing dithiafulvene rings have been prepared using the Wittig reaction (Scheme 33).[428]

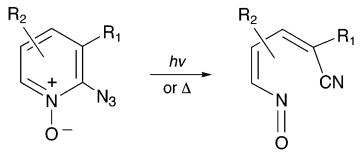
Scheme 33



Bryce and co-workers[429−431] provided further examples of such alkyl nitrite additions to C=C bonds. An unstable dimeric 1-nitroso-2-acetoxycyclohexene compound is formed from the reaction of an acetic acid solution of cyclohexenyl acetate (containing a few drops of sulfuric acid) with isopropyl nitrite at 0−5 °C.[432]

2.10.5. Other Methods

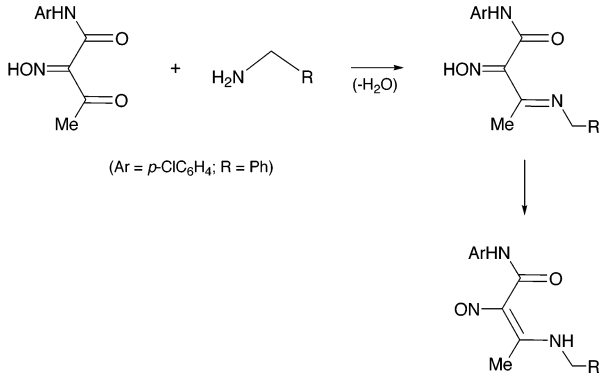
Abramovitch[433−435] has shown that 2-azidopyridine *N*-oxides undergo chemical change when heated at temperatures >85 °C in benzene, methanol, or aniline or when irradiated at 350 nm at room temperature in benzene. The intermediate formation of a nitrosoalkene (eq 45) is proposed to account for the variety of products obtained.



(45)

Other authors[436−439] provide examples of reactions for which the production of nitrosoalkene intermediates is postulated. Addition of gaseous nitrosyl chloride in methylene chloride at 0 °C to alkynes produces β-chloronitrosoalkenes (eq 46).[440]

Scheme 34



$$RC{\equiv}CR' \xrightarrow{ClNO} RC(Cl){=}C(R')NO + RC(NO){=}C(Cl)R' \quad (46)$$

(R = H (a), alkyl (b); R′ = $(CH_2)_nCO_2Me$)

Veronese et al.[441,442] prepared crystalline specimens of some monomeric nitrosoalkenes from reaction of a monoxime with allylamine or benzylamine (Scheme 34), and crystal structural studies[441,443] of some of these compounds confirm their structures (Figure 5).

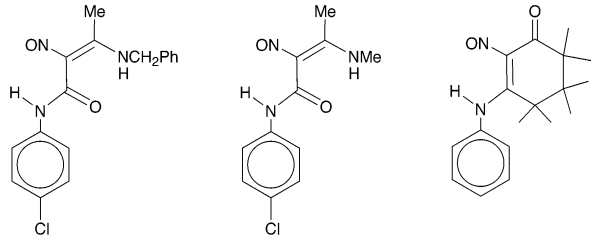
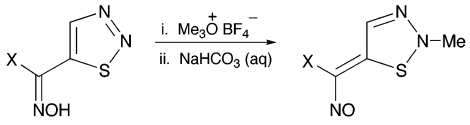


Figure 5.

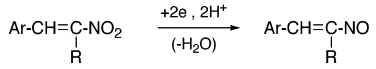
A low yield of a stable nitrosoalkene is reported to form[444] from methylation of 5-hydroxyiminomethyl-1,2,3-thiadiazole and subsequent treatment with aqueous sodium bicarbonate (eq 47).



(47)

(a) X = H
(b) X = Me

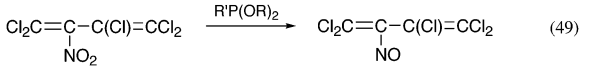
There are a few examples of the formation of nitrosoalkenes from nitroalkenes. The cathodic reduction of some 1-nitro-2-arylalkenes to the corresponding oximes is presumed[445] to occur via an initial two-electron reduction step (eq 48).



(48)

The surface-promoted formation (by Fe or Ni) of nitrosoethene by a low-pressure pyrolytic (at 883 K) deoxygenation of nitroethene using mass spectrometric detection techniques has been reported.[446] Deoxy-

genation of perchloro-2-nitrobuta-1,3-diene by reaction with $(MeO)_2PNCO$ produces the corresponding nitrosoalkene (eq 49).[447]

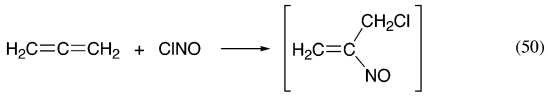


(49)

It should be noted, however, that when ethyl phosphites react with β-nitrostyrenes, the formation of a nitrosoalkene intermediate is judged to be unlikely.[448]

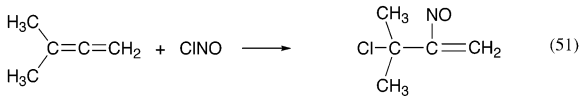
Other possible routes for the synthesis of nitrosoalkenes that are analogous to those well established for nitrosoalkanes and nitrosoarenes may be considered. The low-temperature reaction between nitrosyl chloride and alkenylmetal compounds,[449−451] dilithioalkenes,[452] and the isomeric 2-chlorovinylmercuric chlorides[453] may provide further routes to nitrosoalkenes.

The room-temperature reaction of nitrosyl chloride with propadiene in chloroform in the presence of catalytic amount of stannous chloride gave a transitory greenish-blue color (λ_{max} 650 nm), which was ascribed to the formation of a reactive nitrosoalkene intermediate (eq 50).[454]



(50)

The isolation of 2-nitroso-3-chloro-3-methylbutene from reaction of nitrosyl chloride with 3-methylbuta-1,2-diene in ether at 0 °C followed by vacuum sublimation of the product to a liquid-nitrogen-cooled thimble has been reported (eq 51).[455]



(51)

2.11. Nitrosodienes

Apart from the example noted in eq 49, studies of such compounds do not appear in the literature, although potential precursors are known. For example, 2-lithio-1,3-butadiene has been prepared,[456] but its reaction with nitrosyl chloride has not been reported.

3. Epilogue

Knowledge of the successful preparative methods for the generation of *C*-nitroso compounds provides new avenues for the study of their reactions and coordination chemistry as a function of the R groups attached to the nitroso functionality. In particular, studies aimed at elucidating the influence of the nitroso moiety on the chemistry of the R group and the complementary influence of the R group on the nitroso moiety (e.g., C−N bond cleavage, N−O bond rupture, oxidation and reduction, etc.) should provide researchers with information that they need to begin to decipher the roles of these *C*-nitroso compounds in environmental biology.

4. Abbreviations

AcO	acetate
Am	amyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
Cp	η^5-cyclopentadienyl
DDQ	dichlorodicyanobenzoquinone
DMF	dimethylformamide
EDTA	ethylenediaminetetraacetic acid
Et	ethyl
hmpa	hexamethylphosphoramide
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Ph	phenyl
Pr	propyl
THF	tetrahydrofuran

5. Acknowledgments

BGG thanks his research collaborators from 1953 onward who have consistently stimulated his interests in the problems apparent in the chemistry of *C*-nitroso compounds. GBR-A is grateful to the National Institutes of Health for financial support. We thank Timothy R. Demmin for author permission to re-draw a scheme (Figure 2) from ref 96.

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