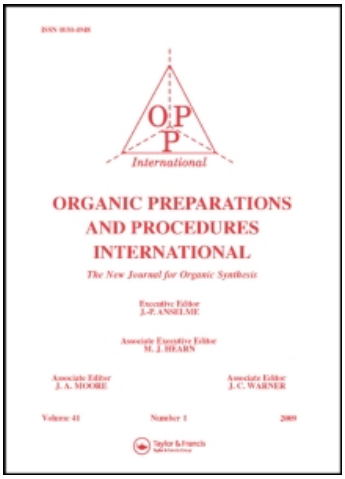

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RECENT SYNTHETIC APPLICATIONS OF N-NITROSAMINES AND RELATED COMPOUNDS

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INTRODUCTION

N-Nitroso compounds are an important class of chemical carcinogens and mutagens. Although we lack direct evidence that these compounds produce cancer in man, they are considered a hazard to human health.[1] In spite of the fact that nitrosamines have been known since 1863,[2] their biological importance was not recognized until 1956, when Magee and Barnes[3] reported that N-nitrosodimethylamine was a liver carcinogen. Eleven years later, Druckrey et al.[4] demonstrated that many other nitrosamines are potent carcinogens, showing pronounced organ specificity. These early findings led to extensive structure-activity relationship studies of N-nitroso compounds.[5] They were shown to exhibit a high degree of organ specificity, with the target organ varying from one species to another.[6] To explain the carcinogenic action and organ specificity of nitrosamines, extensive research into their metabolic fate is being carried out, including studies on the ability of tissues to activate these compounds into alkylating, or other cellular damaging, agents.[7]

Humans are exposed to trace amounts of N-nitroso compounds through various sources, and work in this area has resulted in outstanding developments in analytical instrumentation and techniques to detect these low levels. A milestone in this area was the development of the Thermal Energy Analyzer (TEA),[8] which uses a chemiluminescence detector

specific for compounds that release nitric oxide. In the TEA nitric oxide is oxidized by ozone, and the light in the far-visible and near-infrared regions emitted by the activated NO_2 is quantified as it decays to the ground state. N-Nitroso compounds can be measured in less than 1 ng amounts. With the addition of colorimetric techniques a sensitivity of better than one part per billion in the analysis of volatile nitrosamines[9] can be reached. The selective determination of nitrosamines in air has been accomplished with gas chromatography/low-resolution mass spectrometry, with detection limits in the 0.1-0.2 $\mu g/m^3$ range.[10] Mass spectrometry is the most reliable method for structure identification of nitrosamines in environmental samples, and is sensitive to sub- $\mu g/kg$ levels.[11,12] Although these advances in analytical chemistry have made the trace analysis of volatile nitrosamines in environmental samples a routine process, the methods are not always suited to the detection of non-volatile nitrosamines. Recently, the use of a new type of chemiluminescence detector combined with capillary GC or HPLC chromatography for analysis of non-volatile N-nitroso compounds has been reported.[13] As a result, there will be an increase of data on environmental non-volatile N-nitroso compounds. This is an important development, since it allows the detection of N-nitrosoamides[13] including nitrosoureas, nitrosocarbamates, nitrosoguanidines,[14] and nitrosoamino acids.[15,16]

Advances in trace analysis of nitrosamines have enabled us to categorize the sources of human exposure to these compounds.[17] This exposure can often be from exogenous sources depending on personal habits in such matters as diet,[18,19] tobacco product use,[20,21] cosmetics,[22] pesticides,[23] drugs,[24,25] rubber products for infant care,[26,27] automobile interiors[28] and household products.[29] Exogenous exposure may also be of an occupational nature.[17] Most of the data available for exposure

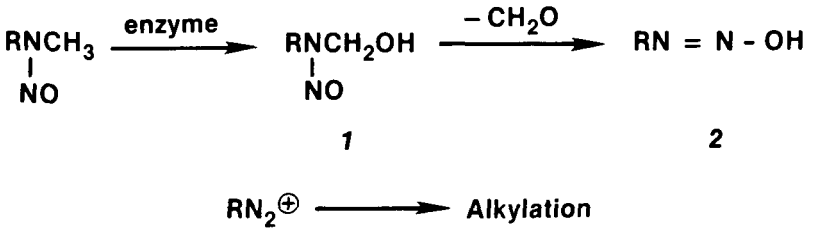
in the work place come from the metal[30,31] and rubber,[32,33] industries. Exposure to exogenous N-nitroso compounds is also known to occur in pesticide and detergent production, the chemical and leather industries, and in mining and fisheries.[17] In vivo formation of N-nitroso compounds by reaction of nitrosatable amino compounds and nitrosating agents is responsible for the endogenous exposure to many carcinogens.[1,17] Sander et al.[34] were the first to demonstrate that sufficient amounts of a nitroso compound could be formed in vivo to induce cancer when rats were fed methylbenzylamine and morpholine together with nitrite. Subsequent studies with alkylureas fed to rats together with nitrite gave rise to nervous system tumors, which indicated that the corresponding alkylnitrosoureas were formed in vivo.[35] Tumor induction by nitrite interaction with a number of drugs containing amino groups in vivo has also been studied extensively.[36,37] Mechanistic studies of N-nitrosation and nitrosating agents leading to the formation of N-nitrosamines, and nitrosamides is another area of research that has received vigorous attention.[38,39,40] These studies also include trans-nitrosation[41] and the search for substances which either facilitate, or inhibit, the N-nitrosation reaction.[1] The major emphasis in these investigations has been to explain how environmental carcinogens originate.

The nitroso group is a reactive functionality, which contains four pairs of non-bonded electrons. There is extensive delocalization of the amino nitrogen lone-pair of electrons into the π system of the N=O group. The N-O bond of the nitrosamine function is angular, and the delocalization of electrons produces a double-bond character in the N-N bond. This barrier-of-rotation gives rise to (E) and (Z) rotamers. Nuclear magnetic resonance spectroscopy has been an important tool in studying the restricted rotation about the N-N bond and structural assignments of

E and Z rotamers.[42] N-Nitrosamines are potential Lewis bases due to the four lone-pairs of electrons. They are known to trap one proton: that is they form 1:1 adducts when treated with concentrated sulfuric acid, 72% perchloric acid, trifluoroacetic acid, and trifluorosulfuric acid.[43] Complexation with metal salts to give 1:1 and 1:2 adducts has been reported.[44] Complexation is also known to take place with Lewis acids,[44a,45] and between nitrosamines and alcohols, phenols and amines[46] as well as with chiral alcohols.[47] Alkylation with strong electrophiles takes place at the oxygen atom of the nitroso group to form salts. Alkylating agents such as triethyloxonium tetrafluoroborate,[48] hexafluoroantimonate[49] and dimethyl sulfate[49] have been used for this purpose. Acylation reactions generally result in N-N bond fission giving the corresponding amide, carbonate or sulfonamide.[50] Intramolecular acylation at oxygen results in sydnone formation.[51] Grignard reagents[52] and lithium reagents[53] add across the N=O group giving a variety of coupling and decomposition products. The nitroso group can be reduced to form the corresponding hydrazine with either Zn in acetic acid,[54] titanium trichloride,[55] or lithium aluminum hydride.[56] Catalytic hydrogenations on Raney-Nickel,[57] cuprous chloride in acidic ethanol,[58] and aluminum nickel alloy in aqueous alkaline solution[59] have been used to reduce nitrosamines to the parent amine. Oxidation reactions of the nitroso group to the nitro group are also well known.[60] Chow and co-workers have probed into the photochemistry of N-nitrosamines[61] and established that, in acid solutions, the primary photoprocess involves generation of nitric oxide and aminium radicals ($R_2NH^{\bullet+}$). Although, N-nitrosamines are relatively stable to photolysis in neutral solution, they have been known to undergo photolytic decomposition in neutral solvents[62] and in the gas phase.[63] Nitrosoamides behave as the amine counterparts in acidic solution. In neutral solution, these com-

pounds decompose to amidyl and nitric oxide radicals.[64]

The known chemistry of N-nitrosamines and related compounds is not restricted to their formation and reactions involving only the nitroso group. Because of the electronic structure of the nitrosamine function, a positive as well as a negative charge on the α-carbon can be stabilized.[65] Thus, via the nitroso group, an amine has the ability to undergo nucleophilic or electrophilic reaction at the α-position. Anion stabilization of the α-carbon gives rise to the development of "umpolung" of amine reactivity.[65a] The effect of the nitrosamine function on remote functional groups in the molecule has been studied in relation to its anchimeric assistance in solvolysis reactions,[66] in ring expansions,[67] and in elimination reactions.[68] Loeppky et al.[69] have made considerable progress in the study of chemical and biochemical transformations of β-oxidized nitrosamines. This type of compound plays an important role in environmental carcinogenesis and metabolism of dialkyl nitrosamines. The synthesis and chemistry of α-hydroxylated nitrosamines, and derivatives thereof, have received considerable attention.[68a,70] This interest has arisen because nitrosamines in general require metabolic activation to promote cancer. The first step in activation is the α-hydroxylation process.[71] Although, the enzymatic oxidation is a detoxification step, the resulting α-hydroxynitrosamine 1 is quite unstable. The intermediate breaks down to a diazohydroxide 2, or some other species responsible for the alkylation of nucleic acids (Eq. 1). Although it is by no means certain that nucleic acid alkylation is responsible for tumor induction, α-hydroxynitrosamines are critical metabolites that may behave as a transportable form of an alkylating agent.[72] In addition to α-hydroxylation, enzymatic β-[69], γ-[73] and ω-[74] oxidation can occur. Thus, the preparation and chemical properties of these metabolites are also of interest.



A great deal of the basic organic chemistry of N-nitroso compounds remains unexplored. Yet, sound organic chemical knowledge of N-nitrosamines is essential if we are to unravel the mechanisms involved in carcinogenesis. Ironically, it is precisely because of their carcinogenic properties that exhaustive exploration of the usefulness of N-nitroso compounds as important synthetic intermediates has been neglected. Several review articles dealing with different aspects of the chemistry of nitrosamines have been published. Fridman et al.[40] wrote one of the earliest articles, where they discuss the advances in the chemistry of aliphatic N-nitrosamines. Formation, inhibition and destruction of nitrosamines were reviewed by Douglass et al.[75] A recent chapter by Challis and co-worker[38b] gives a thorough survey on the formation and decomposition of N-nitrosamines and N-nitrosoimines. A brief review on the organic chemistry of N-nitroso compounds was presented by Anselme.[76] Recent reviews by Olajos et al.[1a] and Digenis et al.[1b] cover some aspects of the organic chemistry of N-nitrosamines, and N-nitrosoamides; however, their main focus is on the biochemistry of these compounds. Ridd[39a] and Williams[39b] have written two excellent reviews on the mechanism of nitrosation. It is our purpose in this review to center attention on the organic chemistry of N-nitroso compounds, their syntheses and reactions, rather than to focus on their biochemistry, carcinogenic properties or environmental implications. Basically, only proven synthetic methods and

reactions are discussed here, therefore, in most cases no critical evaluation of each procedure is given.

I. SYNTHESIS OF N-NITROSO COMPOUNDS

N-nitrosamines have been formed in the reaction of various nitrosating agents with primary, secondary, and tertiary amines, as well as from amides.[38-40] They can be formed in the gas phase, in acidic or basic media[77] and in organic solvents. There are agents which catalyze, or inhibit the nitrosation reaction. Yields, ranging from quantitative to trace amounts have been reported. We will limit ourselves, in this section, to nitrosation reactions of synthetic value suitable for the preparation of quantities useful for further studies.

1. Nitrous Acid in Aqueous Media

The most commonly used nitrosating agent is sodium nitrite in aqueous acidic solutions at pH 2-5. Kinetics and mechanism studies of N-nitrosamine-formation from secondary amines using sodium nitrite in aqueous buffers indicate that the actual nitrosating species at moderate pH is (NOX). This nitrosating agent is formed from the interaction of protonated nitrous acid (H_2O^+-NO) and a nucleophilic catalyst (X^-). When the nucleophilic catalyst is the nitrite in itself, the reactive nitrosating species is nitrogen trioxide (N_2O_3). Other common catalysts (X^-) are chloride ions (Cl^-) and thiocyanate ions (SCN^-). Mirvish[78] has reported that amines of pKa > 5, show a pH-dependence during nitrosation, with an optimum value at pH 3.4, that is, the amine basicity determines the proportion of unprotonated amine available for nitrosation. Thus, the reaction rate depends on the concentration of non-ionized amine as well as the nitrosating agent, and it is represented by the equation rate = k $[R_2NH]$ $[HNO_2]$.[2] For weakly basic amines, the reaction rates are independent of the amine concentration, but proportional to the nitrosating

agent. Since weakly basic amines are not protonated to a large extent at low pH, the ease of nitrosation increases as the basicity decreases.[78c] However, many weak bases are too unreactive to form nitroso compounds with N_2O_3. Therefore, at high acidity the reaction pathway follows the rate equation, rate = k $[R_2NH]$ $[HNO_2]$ $[H_3O^+]$, where the neutral amine or amide reacts directly with nitrosonium ion (NO^+) or nitrous acidium ion.[79] Typically, aqueous media nitrosation of amines and amides are carried out at 0° to 25° in sulfuric,[80] acetic,[81] hydrochloric,[81] formic,[82] or nitric acid[83] and sodium nitrite. A yellow oil generally separates out indicating the formation of the nitrosamine, which may be purified by column chromatography or, if volatile, by vacuum distillation. Configurational isomers in substituted cyclic nitrosamines have been purified and separated by preparative HPLC.[84] Nitrosation of some ureas often results in the precipitation of the nitrosourea, which may then be purified by recrystallization.[80] The nitrosation of amides,[85] including ureas and carbamates[85b] can be carried out effectively at pH 1 with nitrous acid in a two phase system, usually a water-methylene chloride mixture.

2. Nitrosyl Chloride and Nitrosyl Tetrafluoroborate in Organic Solvents

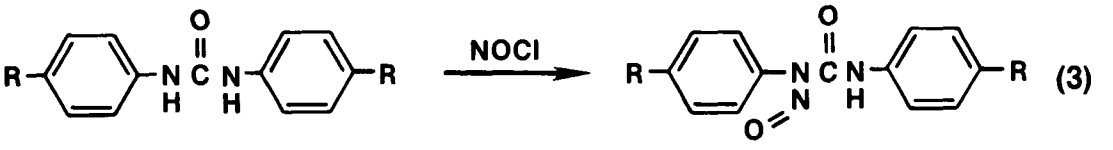
Nitrosyl chloride is formed in aqueous media when nitrite salts and aqueous hydrochloric acid are used in nitrosation reactions. However, gaseous nitrosyl chloride can be bubbled into an organic solution of an amine to form a mixture of the corresponding nitrosamine and the amine hydrochloride[86]. To avoid the formation of the amine hydrochloride, the starting amine is converted to its sodium salt 3 in tetrahydrofuran which is, in turn, treated with NOCl at -70°C. Simple isolation procedures, followed by purification gave sometimes to quantitative yields of nitrosamines[87] (Eq. 2). Pyridine was also employed as a scavenger for hydrogen

chloride giving high yields of N-nitrosamines.[87] A hitherto difficult synthesis of 2,2-disubstituted nitrosooxazolidines[88] became possible by using NOCl in methylene chloride-potassium carbonate media at 0°C.[89]

$$R_2NH \xrightarrow[THF]{NaH} R_2NNa \xrightarrow[-70°]{NOCl} R_2NNO + NaCl \qquad (2)$$

3

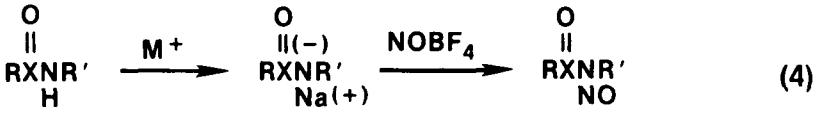
N-arylamides[90] and N-(sec-butyl)amides[91] have been nitrosated with NOCl. However, in these cases, N_2O_4 gives much better results.[91] Nitrosation of 1,3-diarylureas 4 with nitrosyl chloride in dimethylformamide at 0°C gave 1,3-diarylnitrosoureas 5 in 59-96% yields[92] (Eq. 3).



(3)

4 **5**

Nitrosamino acids have been prepared in large quantities by nitrosation with nitrosyl tetrafluoroborate ($NOBF_4$) in acetonitrile and pyridine.[93] This nitrosating agent, a source of the nitrosonium ion (NO^+), is also effective in the synthesis of N-nitrosoamides 6a and N-nitrososulfonamides 6b under basic conditions.[94] The amide or sulfonamide in ether is first converted to the sodium or lithium salt, then nitrosated with $NOBF_4$ at 0° (Eq. 4).



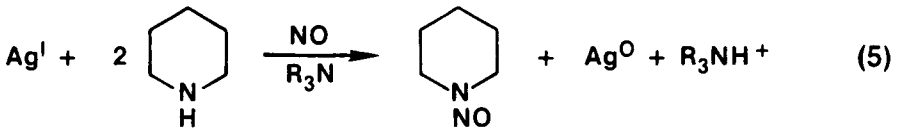
(4)

6a; X = C
b; X = SO

3. Nitrosation by Oxides of Nitrogen in Organic Media

The oxides of nitrogen involved in amine or amide nitrosation are nitric oxide (NO), dinitrogen trioxide (N_2O_3) and dinitrogen tetraoxide (N_2O_4).[38] Dinitrogen trioxide (N_2O_3) in organic solvents gives high yields of nitrosamines;[95] it also nitrosates 1,3-diarylureas 4 in good yields (Eq. 3). The latter nitrosation is carried out in DMF at 0°C.[92] Amides in carbon tetrachloride and acetic acid are effectively nitrosated with gaseous N_2O_3.[96] The best reagent for the preparation of nitrosoamides is nitrogen tetraoxide (N_2O_4). The reaction is carried out at 0°C in carbon tetrachloride-acetic acid, and it goes to completion within 10 min.[91] To avoid denitrosation caused by nitric acid formed during the reaction, sodium acetate is used as a base. N_2O_4 in methylene chloride at 0°C is a good nitrosating agent for secondary amines; however at -80°, this reagent becomes a nitrating agent.[97] At 0°C in DMF, N_2O_4 nitrosates 1,3-diarylureas 4 (Eq. 3).[92] However, when the aryl rings were substituted with methoxy groups, 4 (R = OMe), dinitrogen tetraoxide gave nitro and dinitro derivatives on the meta positions of the aromatic rings. Demethylation of aliphatic acyclic and cyclic tertiary amines, followed by *in situ* nitrosation, was accomplished with N_2O_4 in carbon tetrachloride at 0-45°C. The yields of nitrosamine ranged from 42-89%.[98] Acetic anhydride may be used as a solvent in this reaction, but the yields of nitrosamine were much lower. Nitric oxide (NO) alone is inactive as a nitrosating agent. In the presence of oxygen, NO, is oxidized to the reactive species N_2O_3 and N_2O_4.[99] Rapid nitrosation by nitric oxide in the absence of oxygen does occur where catalyzed by iodide, or Ag(I), Cu(I), Cu(II), Zn(II), Fe(III), and Co(II) salts.[38] Equimolar concentrations of Ag(I) salts and piperidine, containing triethylamine or 2,2,6,6-tetramethylpiperidine, gave 100% yield of nitrosopiperidine 7

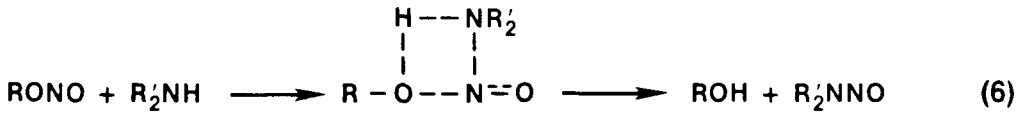
(Eq. 5). The reaction proceeds via the interaction of NO with the amino radical cation intermediate derived from the Ag(II)-amine complex.[100] N-Nitrosamines have been formed quantitatively with NO and iodine (I_2) in basic aqueous solutions.[101] Ethanol or acetonitrile are used as co-solvents to increase the solubility of the iodine. The reaction proceeds via the interaction of nitrosyl iodide with the unprotonated amine. Nitrosation by NO in organic solvents is catalyzed by iodide salts in the presence of hydrogen iodide. Nitrosyl iodide is generated under these reaction conditions, and is the actual nitrosating species.[100]



7

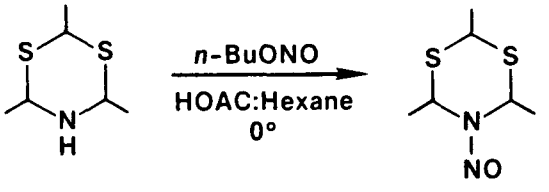
4. Nitrosation with Nitrite Esters in Organic Solvents

Alkyl nitrites derived from monohydric alcohols are reactive under acidic, thermal and photolytic conditions.[38b] Compounds of this type bearing electron-withdrawing β-substituents[102] nitrosate amines rapidly in alkaline aqueous solutions.[103] In organic solvents, nitrite esters are convenient nitrosating agents due to their pronounced solubility in these media. Oae et al.[104] investigated the kinetics and mechanism of the aminolysis of phenethyl nitrite in 61% dioxane-water. The reaction involves a nucleophilic substitution on the sp^2 hybridized trivalent nitrogen. A proton transfer occurs in the rate-determining step, and it probably proceeds through a concerted mechanism, as shown in Eq. 6. The reactions in this report were not carried out on a preparative scale. However, product analysis by gas chromatography indicated that N-nitrosopiperidine was formed in 100% yield.



(6)

Quantitative formation of N-methyl-N-nitrosoaniline and N-nitrosodiphenylamine were observed upon treatment of the corresponding amines with t-butyl nitrite in acetic acid-hexane at 0° (Eq. 7). These compounds could not be obtained in either aqueous, or non-aqueous, nitrosating systems.[106]

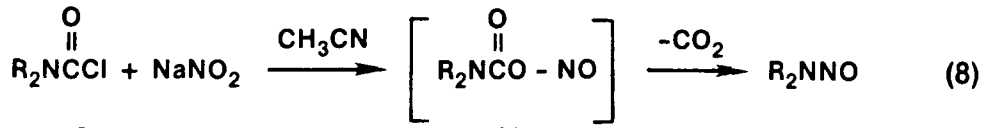


(7)

8 *9*

5. Miscellaneous Nitrosations of Synthetic Value

An indirect route to nitrosamines under neutral conditions has been reported where carbamoyl chlorides 10 with sodium nitrite in acetonitrile give the corresponding nitrosamine in 76% to 100% yields.[107] The reaction proceeds through a carbamoyl nitrite intermediate 11 (Eq. 8). The reaction depicted in Eq. 8 was at first thought to occur via a homolytic cleavage of the N-O bond to give aminyl radicals and nitric oxide, which on recombination would form the corresponding nitrosamine. However, the high yields of pure nitrosamines obtained from this reaction probably rule out the free radical mechanism favoring a concerted or an ion-pair dissociation process.



(8)

10 *11*

N-Chlorodialkylamines 12 can be converted to the corresponding nitrosamines with two equivalents of sodium nitrite suspended in acetonitrile at reflux.[108] The reaction takes place via nucleophilic displacement of nitrite ion on chlorine and the generation of N_2O_4 which acts as the nitrosating agent (Eq. 9).

$$R_2NCl + 2NaNO_2 \xrightarrow[CH_3CN]{\Delta} R_2NNO + NaNO_2 + NaCl \qquad (9)$$

12

Under phase transfer conditions, amines are converted to the corresponding N-nitrosamines in the presence of N-chlorosuccinimide, two equivalents of sodium nitrite and a quaternary ammonium salt.[109] The reaction of N-chlorosuccinimide with nitrite forms nitryl chloride (NO_2Cl) which, upon reaction with a second mole of nitrite, produces the actual nitrosating agent, in this case N_2O_4 (Eq. 10). Halogenating agents, other than N-chlorosuccinimide are also effective in mediating nitrosation reactions.

$$R_2NH + \text{(N-chlorosuccinimide)} + 2NaNO_2 \xrightarrow[H_2O/CH_2Cl_2]{(+)\ R'_4NCl^{(-)}} R_2NNO \qquad (10)$$

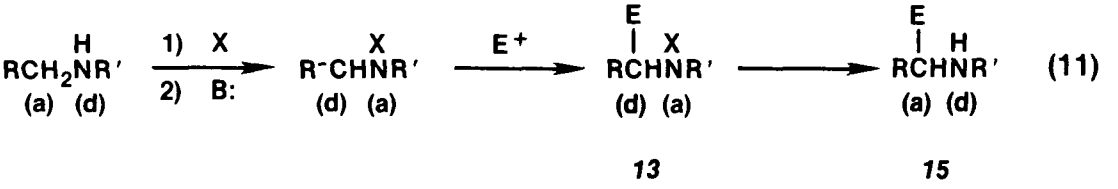
A mixture of sodium nitrite in acetic acid-acetic anhydride nitrosates amides in good yield within 15 hr at 0°C.[91] A synthetic route to nitrosoamides has been developed in order to introduce a nitroso moiety containing nitrogen-13. This isotope is cyclotron produced and it is obtained in the form of $^{13}NO_3^-$. The reaction involves copper reduction of NO_3^- to NO_2^- in glacial acetic acid with concomitant nitrosation of the amide.[110] The reaction is carried out at 25°C and it goes to completion within 5 min. This pathway has provided good yields of ^{13}N-labeled strep-

tozotocin, nitrosocarbaryl and N-nitroso-2-pyrrolidone to be used in distribution studies. Potassium nitrosodisulfonate (Fremy's salt) reacts with secondary and tertiary amines in aqueous sodium carbonate or pyridine solution to form the corresponding nitrosamine in moderate yields.[112] High yields of nitrosamines were obtained when a secondary amine was treated with Fremy's salt in aqueous sodium carbonate solution in the presence of hydroxylamine.[112] 2-Cyano-2-propyl nitrate has been used in the phase-transfer catalyzed nitrosation of 2-aryl-3-nitroindoles, but its use is limited to these compounds.[113]

II. N-NITROSAMINES AS SYNTHETIC EQUIVALENTS OF α-SECONDARY AMINO AND α-PRIMARY AMINO CARBANIONS

The formation of carbon-carbon bonds is, in general, a polar process involving the interaction of a nucleophilic and an electrophilic center. The electronic environment conferred by the activating group attached to the carbon is what determines the "philicity" of that carbon.[114] Many target molecules in organic synthesis contain nitrogen and thus α-nitrogen-substituted carbanions are valuable intermediates to react with electrophiles to form new bonds.[115] Nitrogen normally behaves as a nucleophilic center, that is, a donor (d) heteroatom,[116] and thus is unable to stabilize an α-carbanion ($^-$CHNHR). For that nitrogen to stabilize an adjacent carbanion, its normal reactivity mode must be reversed through a temporary heteroatom modification to 13. It is now possible to carry out reactions with electrophiles on the α-carbon, which is now a donor (d) or nucleophilic center, to form a new compound 14. Removal of the modifying group (X) to 15 will restore the normal reactivity as outlined in Eq. 11. This process is universally known as "umpolung", and in the case of nitrogen it is specifically called "umpolung of amine reactivity".[65a] Generally, all that it requires to reverse the polarity of the

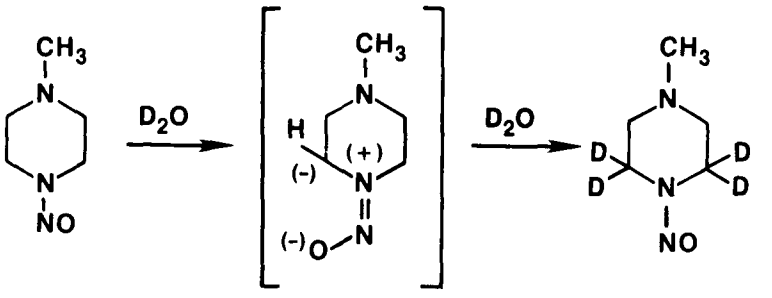
amino nitrogen is to give it a partial positive charge. This is accomplished by the introduction of an electron-withdrawing group which will then promote the formation of an α-carbanion 13, where dipole polarization factors contribute to its stabilization.[117]



13 15 (11)

1. α-Secondary Amino Carbanions. Reaction with Electrophiles

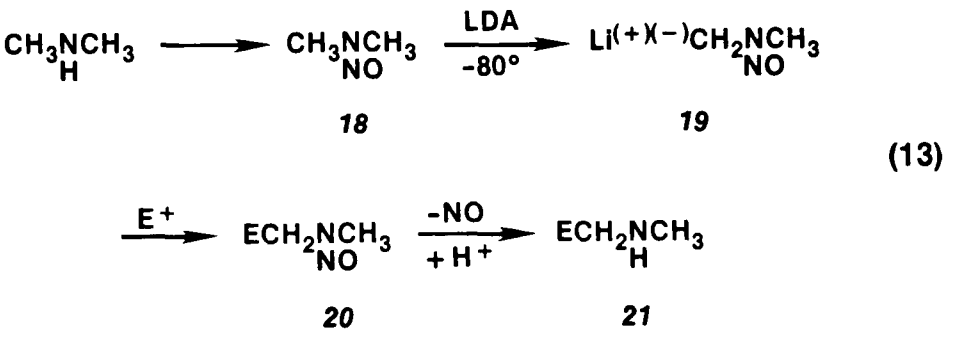
The first indication that nitrosamines were potentially useful as α-secondary amino carbanionic synthons was reported by Keefer et al.[65a] They observed that a number of aliphatic nitrosamines undergo base-catalyzed hydrogen-deuterium exchange. A typical example is that of N-nitroso-4-methylpiperazine 16, which on exposure to sodium deuteroxide in deuterium oxide at 100°C gave the tetradeuterated derivative 17 within 115 min. This exchange, therefore, gave evidence for the involvement of an α-nitrosamino carbanion 16a in the exchange reaction (Eq. 12). Moreover, this procedure has become the standard method for the synthesis of numerous deuterium-,[65a,68b,81,119] and tritium-labeled nitrosamines.[120] The effects of stereochemistry and the stereoelectronic control on the



16 16a 17 (12)

rates of hydrogen-deuterium exchange of α-protons in cyclic nitrosamines have been studied.[65d,121]

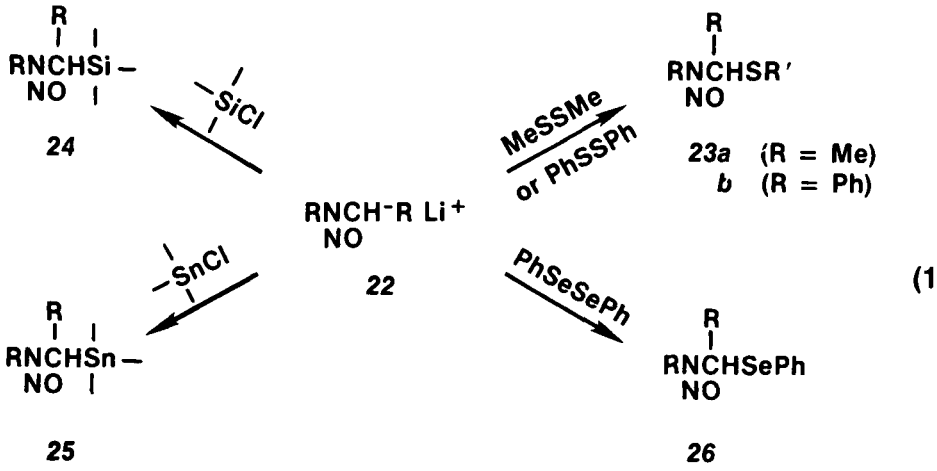
In 1972, Seebach et al.[122] reported that metalation of dimethylnitrosamine 18 with lithium diisopropylamide at -80°C converted it quantitatively to the corresponding lithionitrosamine 19. The lithionitrosamine 19 then undergoes alkylation or acylation with various electrophiles to form the corresponding adduct 20. Denitrosation of 20 provided a new secondary amine 21.[122b,123] The entire process, from the nitrosation of dimethylamine to dimethylnitrosamine 18 to the formation of a new amine 21, established N-nitrosamines as umpolung synthons for α-secondary amino carbanions (Eq. 13). Treatment of the lithionitrosamine 19 with an



(13)

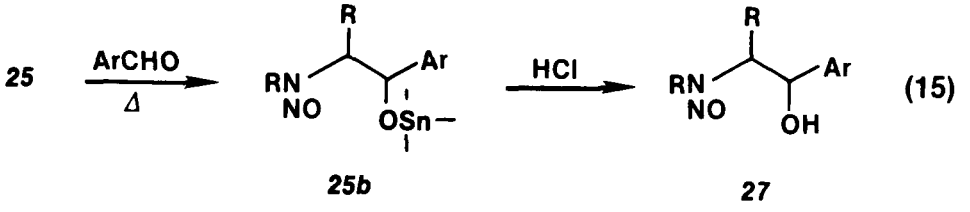
alkylating agent such as methyl iodide gave methylethylnitrosamine 20 (E = CH_3) in 75% yield. Benzylating agents such as benzyl bromide formed 20 (E = CH_2Ph) in 95% yield, and hydroxyalkylating agents, i.e. n-butyraldehyde, produced 20 (E = CHOHn-C_3H_7) in 80% yield.[122] Metalated nitrosamines also react with heteroatom-containing electrophiles to form α-heterosubstituted nitrosamines.[124] A lithionitrosamine 22 reacts with dimethyl disulfide, and with diphenyl disulfide in THF at -78°C to form the corresponding α-methylthiodialkyl-, 23a (R'= Me) and the α-phenylthiodialkylnitrosamine 23b (R'= Ph) respectively (Eq. 14). Trimethylsilylchloride, and trimethylstannyl chloride add to 22 forming the corresponding α-tri-

methylsilyl 24 and the α-trimethylstannyldialkylnitrosamine 25. For the introduction of a phenylseleno group on the α-position, diphenyl diselenide was used to form 26 (Eq. 14). α-Thio nitrosamines 23a and 23b can be further converted to their corresponding sulfoxides on oxidation



(14)

with potassium periodate in aqueous media.[124] The α-trimethylstannylnitrosamine 25 can undergo reaction with aromatic aldehydes at 60-80°C for 9-18 hrs to give, after acid hydrolysis of the stannyl ether 25b, the corresponding N-nitrosoarylethanolamine 27 in 40-72% yields, (Eq. 15).[125] The α-phenylselenonitrosamines 26 are useful reagents in the synthesis of vinylic nitrosamines upon oxidative elimination of phenylselenic acid.[68a]



(15)

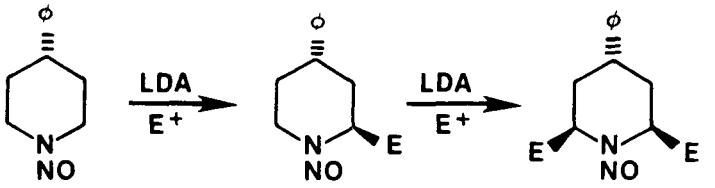
Addition of carboxylic acid chlorides, anhydrides, or esters to lithioanions 28 give α-acylated nitrosamines 29 in poor yields.[122b] However, the yields of 29 can be improved by using acyl cyanides as the acylating electrophiles (Eq. 16).[125] Addition of CO_2 to the lithionitrosamine 28 gives N-nitroso-α-aminoacids 29c in 20-90% yields.[121b,126] The methyl esters of N-nitroso-α-aminoacids 29d are isolated in yields of 59-97% when the electrophile used is methyl chloroformate (Eq. 16).[127]

$$\underset{\text{NO}}{\text{RNCH}_2^-\text{Li}^+} \xrightarrow{\text{R'CX}} \underset{\text{NO}}{\text{RNCH}_2\text{CR'}} \qquad (16)$$

28

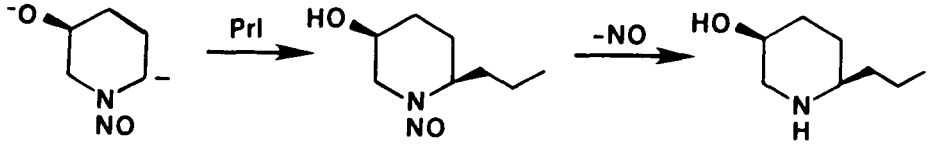
29a R′ = CH_3 (22%)
b R′ = Ph (54%)
c R′ = OH (20-90%)
d R′ = OCH_3 (59-97%)

There is considerable regio- and stereospecificity in electrophilic reactions with cyclic nitrosamines.[121c,128] The anion of N-nitroso-4-phenylpiperidine 30 gives only the axial-substituted product 31 upon reaction with an electrophile. A second lithiation with lithium diisopropylamide gives the 2,6-diaxial derivative 32 (Eq. 17).[121b] The conformational stereospecificity in electrophilic reaction is also illustrated in the synthesis of the cis-isomer 35 of the naturally occurring pseudoconhydrin, which has the trans configuration.[129] Metalation of the nitroso derivative of 3-piperidinol followed by alkylation with n-propyl iodide gave the axial adduct 34. Reductive cleavage of the nitroso group in 34 gave the amine 35 in 52% yield, (Eq. 18).



(17)

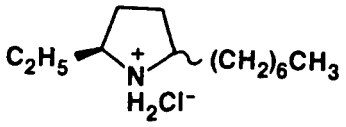
30 *31* *32*



(18)

33 *34* *35*

In addition to hemlock alkaloids such as pseudoconhydrine 35, other naturally occurring compounds have been synthesized via nitrosamine anions. 2-Ethyl-5-heptylpyrrolidine hydrochloride 36, a constituent of South African fire ant venom was prepared by way of its α-amino carbanionic synthon, N-nitrosopyrrolidine.[130] The α-lithioanion of nitrosopyrrolidine has also been used to synthesize macrostomine 37, the main alkaloid of papaver macrostomum Boiss et Huet.[131]



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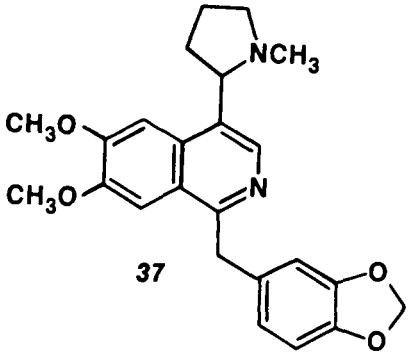
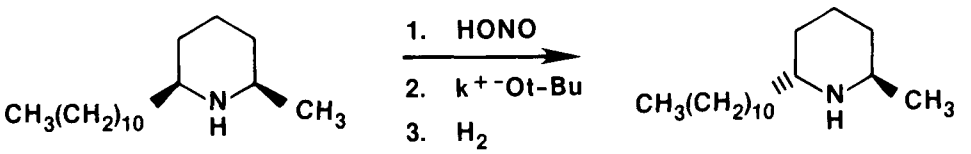


37

Another fire ant venom, selenopsin A 39, was obtained from its readily available cis-isomer 38. Compound 38 was nitrosated, then treated with potassium t-butoxide in dimethyl sulfoxide at 90-100° for 60 hrs followed by reductive denitrosation over Raney-Ni to give (±) 39 in 94% yield (Eq. 19).132



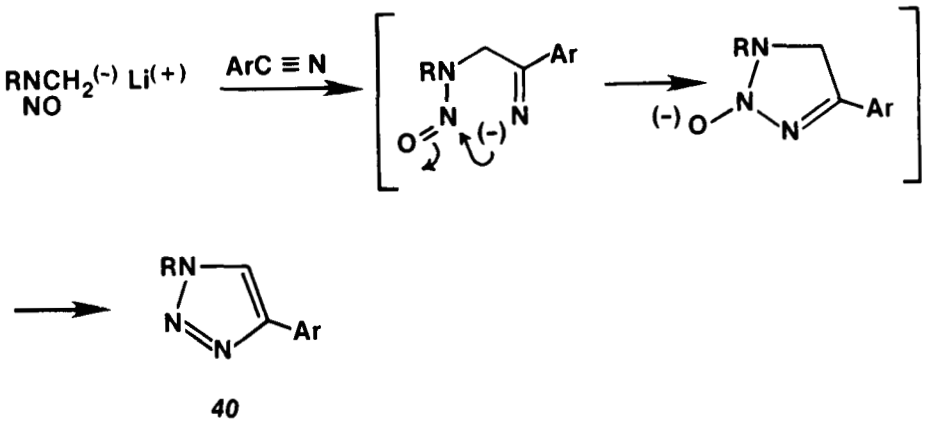
(19)

38 39

The use of alkyl- or aryllithiums for nitrosamine anion formation should be avoided since the resulting lithium salts undergo elimination to give azomethine imines intermediates.[53b] Carbon-carbon bond formation between nitrosamines and non-enolizable carbonyl compounds can be carried out using potassium t-butoxide.[125] Metalation of nitrosamines with potassium t-butoxide/butyllithium/diisopropylamine (KDA) takes place more rapidly than with lithium diisopropylamide (LDA) and gives more reactive potassium derivatives.[125] In order to avoid exposure to carcinogenic nitrosamines, "one-pot procedures" have been developed where the intermediate products are not isolated.[122b,133] Denitrosation takes place on cleavage with hydrochloric acid in benzene, or reductively with Raney-Ni in tetrahydrofuran. Aluminum-nickel alloy rapidly reduces nitrosamines to the corresponding secondary amine in aqueous alkali.[134] Removal of the nitroso group by its sequential reduction with lithium aluminum hydride followed by Raney-Nickel has also proven to be an effective "one-pot procedure".[133b] Sodium borohydride-$TiCl_4$ in glyme is also a convenient system for the reductive denitrosation of amines.[134b]

2. α-Secondary Amino Carbanions. Formation of 1,2,3,-Triazoles and Sydnones

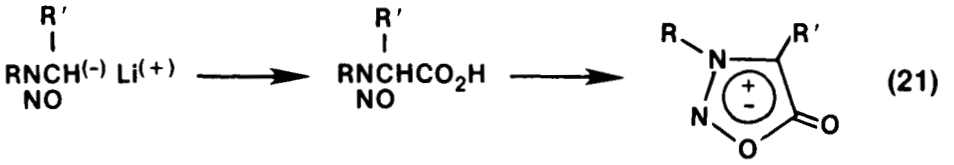
Lithionitrosamines react with non-enolizable nitriles to form 1,2,3-triazoles 40 in 45-90% yields, as shown in Eq. 20.[135]



(20)

40

Although some nitrosamino acids are readily accessible from their corresponding secondary aminoacids,[136] a much more varied series of these compounds can be obtained from α-lithionitrosamines[121b,126,127] as described in the previous section. N-nitrosamino acids on treatment with acetic anhydride give sydnones 41,[51] thus α-lithionitrosamines provide an access route to the synthesis of sydnones (Eq. 21).



(21)

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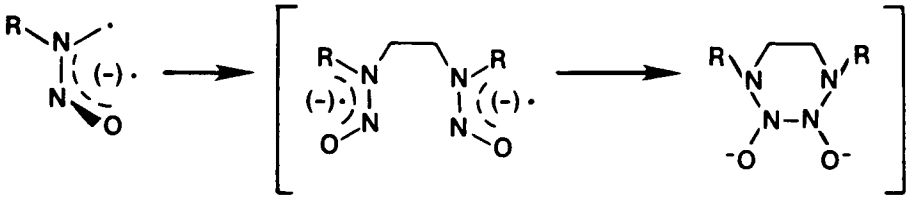
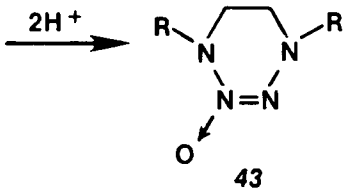
3. α-Secondary Amino Carbanions. Dimerization Reactions

Tetrahydro-ν-tetrazine oxides 48 are formed upon decomposition of lithionitrosamines at -73° under nitrogen.[137] A head-to-head dimerization takes place via a nitrosamine radical anion 42 formed by lithium reduction of the anion. A probable mechanism is shown in Eq. 22. N,N'-Dimethyl-N,N'-dinitrosethylenediamine, a representative acyclic N-nitroso compound, gives the corresponding ν-tetrazine oxide 44 in 50% yield. Cyclic nitrosamines can also dimerize to the corresponding oxides; lithionitrosopiperi-

dine, for example, gives the corresponding oxide 45 in 32% yield. N-Nitrosopyrrolidine, N-nitrosohexamethyleneimine and N-nitroso-4-methylpiperazine give the corresponding tricyclic dimers in 2%, 5% and 22% yields, respectively. These oxides can be reduced with Raney-nickel, in good yields, to the corresponding diamines. In the presence of iodine, lithionitrosamines undergo oxidative coupling to form dinitroso compounds.[137]





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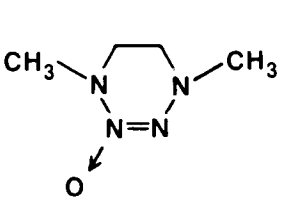

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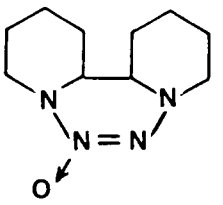

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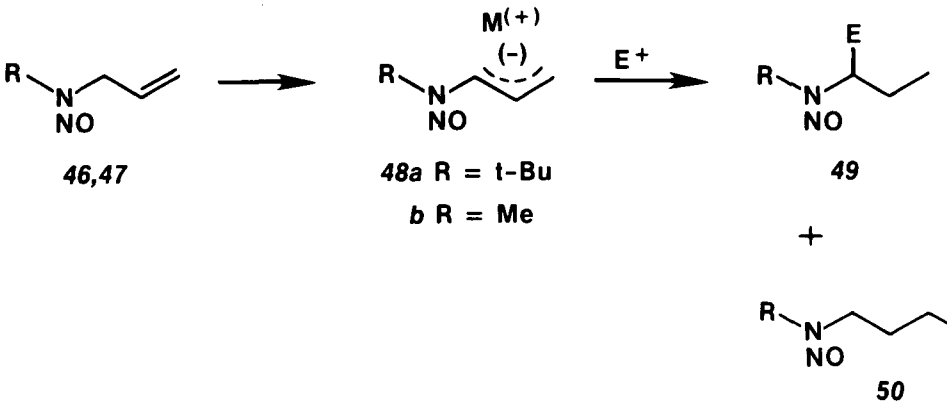
4. α-Secondary Amino Carbanions with an Additional Activating Group

Lithiation of methylalkylnitrosamines is known to occur selectively at the primary carbon. However, metalation of methylbenzylnitrosamine is not selective, due to additional activation of the secondary carbon by the phenyl group.[122b] Allyl-t-butyl- 46 (R = t-Bu) and allylmethylnitrosamine 47 (R = Me) form the anion 48 on the allylic side of the molecule with lithium diisopropylamide or with potassium-t-butoxide.[138] Alkylation

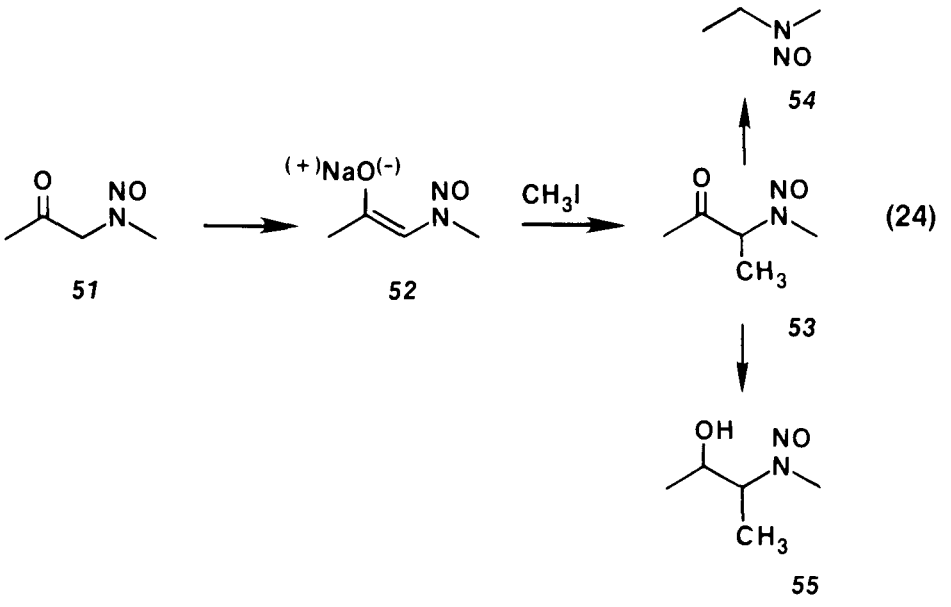
of 48 leads exclusively to the α-product 49. Carbonyl compounds add to 48a to give the α-adducts (49) and the δ-adducts 50. However, under thermodynamic control, the δ-adduct 50 is formed exclusively; the methyl analog 48b favors α-addition to 49 (Eq. 23).



46,47 — 48a R = t-Bu, b R = Me — 49 + 50 (23)

The use of β-ketonitrosamines as anionic synthons is under current investigation.[139] N-Nitroso-N-methyl-2-oxopropylnitrosamine 51 is a representative compound in this series. The α-methylene group is activated, both by the nitroso and the carbonyl group. Moreover, the carbonyl offers a versatile functionality that can be converted either to a different group (C=O → C-NH, C-OH), or used to further elaborate the molecule (C=O → C-C). The enolate anion 52 was formed at 25°C with sodium hydride, and alkylated with methyl iodide to give 53 in 60% yield. This compound undergoes a retro-Claisen condensation to methylethylnitrosamine 54 in near quantitative yield (Eq. 24). This indicates that 51 is a synthetic equivalent of α-methylene-methylamino anion ($^{-}CH_2NHCH_3$). Sodium borohydride reduction of 53 gives the corresponding alcohol 55 in good yield, demonstrating, in turn, the equivalency of 51 to the α-(β-alkanol)amine anion [$CH_3(HO)CHCH^{-}NHCH_3$]. Anselme et al.[139b] have investigated a system analogous to the one described in Eq. 24. The additional activating group in their sequence is a carboxylic ester [R'O2CCH-N(NO)R]. Alkylation

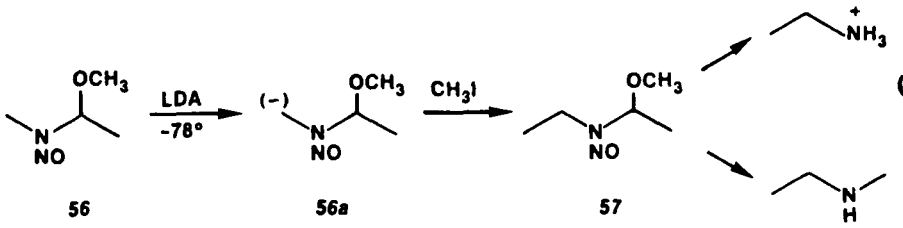
with an electrophile (E^+) occurs at the α-position to give [$R'O_2CCHEN(NO)R$], which upon decarboxylation forms the corresponding nitrosamine [$CH_2EN(NO)R$].



(24)

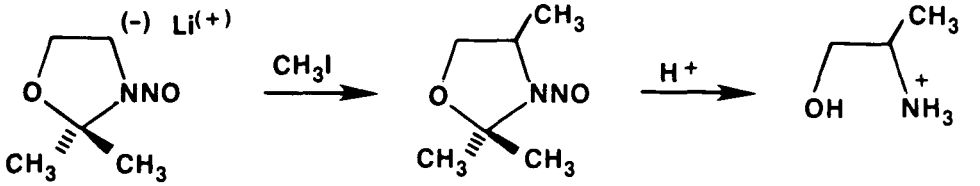
5. α-Primary Amino Carbanions

Primary amines are readily converted to α-nitrosaminoalkyl ethers.[70a,140] These compounds are versatile synthetic equivalents of α-primary amino carbanions.[141] A representative example is N-nitroso-N-methyl-1-methoxyamine 56. It forms anion 56a upon metalation with lithium diisopropylamide at -80°C within 5 min. Alkylation with methyl iodide gives N-nitroso-N-ethyl-1-methoxyethylamine 57 in 80% yield. Regeneration of the primary amine functionality is carried out upon treatment of the nitrosaminoalkyl ether with ethyl chloroformate in boiling acetone, followed by acid hydrolysis of the intermediate urethane. In the case of 57, an 80% yield of ethylamine hydrochloride was obtained (Eq. 25). Reduction of 57 over aluminum-nickel alloy in aqueous alkali gave diethylamine in 86% yield.[141]



56 56a 57 (25)

An efficient preparation of N-nitroso-2,2-disubstituted oxazolidines was reported recently.[89] The use of these compounds for use as umpolung synthons for β-alkanolamines[142] is being studied. The lithioanion 58 of N-nitroso-2,2-dimethyloxazolidine reacts with methyl iodide to form N-nitroso-2,2,4-trimethyloxazolidine 59 which upon hydrolytic demasking gives 2-aminopropanol 60 (Eq. 26).



58 59 60 (26)

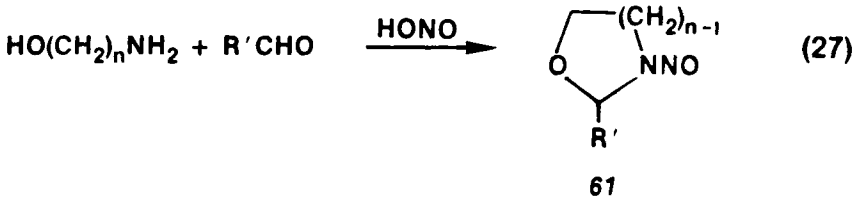
III. α-OXYGENATED NITROSAMINES

N-Nitrosamines, in vivo and in vitro, undergo cytochrome P-450-dependent dealkylation.[143] By the action of tissue-specific microsomal oxygenases,[71] they are converted into α-oxygenated intermediates. The highly reactive α-hydroxynitrosamine breaks down to a diazoic acid or a similar species capable of alkylating cellular nucleophiles (Eq. 1). α-Hydroxynitrosamines, their esters and ethers are important in studies of the metabolism of nitrosamines and their carcinogenic action. α-Hydroxylation appears to be a critical step in the metabolism of acyclic,[143,144]

as well as cyclic nitrosamines.[145] The extent of metabolic α-hydroxylation can be measured from the amount of molecular nitrogen formed during treatments.[146] This technique requires doubly [^{15}N] labeled nitrosamines. Farrelly[147] has developed a general assay for measuring microsomal oxidative dealkylation. The assay traps and measures carbonyl compounds which result from the breakdown of the α-hydroxy nitrosamines formed during metabolism. Because of the biological implications concerning α-hydroxylation, there has been a concentrated effort to study the chemistry of α-hydroxynitrosamines and their derivatives and to develop synthetic methods for their preparation.

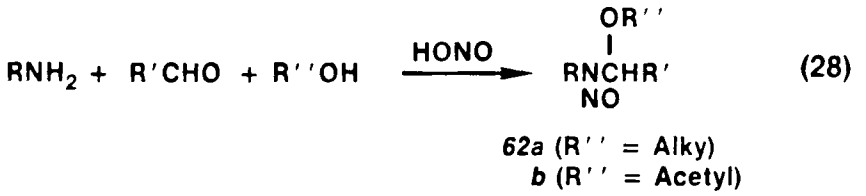
1. Synthesis of α-Hydroxynitrosamines and Derivatives

Due to the anticipated instability of α-hydroxynitrosamines, most of the early efforts were directed towards the synthesis of their corresponding ethers and esters. These derivatives are relatively stable, and upon hydrolysis generate the desired α-hydroxy compound. Cyclic and open chain α-nitrosaminoalkyl ethers, 61 and 62, were first synthesized by Eiter et al.[88a] The cyclic compound 61 was synthesized in a one-step reaction using α-, β- and δ-alkanolamines with aldehydes in the presence of nitrous acid (Eq. 27). The open-chain analog 62 required a primary amine, an aldehyde, an alcohol (R"= alkyl) and nitrous acid, (28). The modification of the latter method, involving the replacement of the alcohol (R"OH) with acetic acid, gave the corresponding α-acetoxynitrosamine 62b (R"= acetyl).[71c] Mochizuki et al.[148] developed a method where the alkyl ether 62a could be readily converted to the α-acetoxy derivative with acetic acid heated at reflux for 1.5-6 hr.



(27)

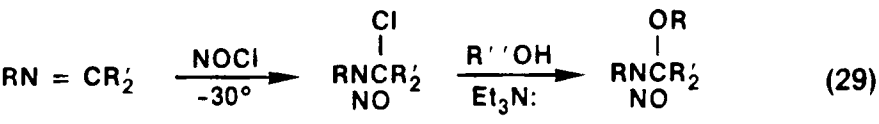
61



(28)

62a (R'' = Alky)
b (R'' = Acetyl)

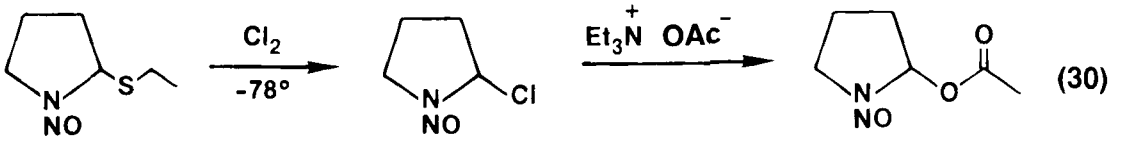
Addition of nitrosyl chloride to Schiff bases 63 gives the α-chloronitrosamine 64, which is stable at -30°C. Addition of methanol, acetic acid or p-nitrobenzoic acid in triethylamine gave the corresponding methyl ether 65a (R"= Me), the acetoxy 65b (R"= acetyl) or the p-nitrobenzoate ester 65c (R"= p-$NO_2C_6H_5CO$) (Eq. 29).[70a] Benzyl and n-butyl ethers, substituted benzoic, trifluoroacetic, dichloroacetic acid esters and α-D-glucuronides of α-hydroxynitrosamines have also been prepared by this method.[70b,149]



(29)

63 65 a,b,c

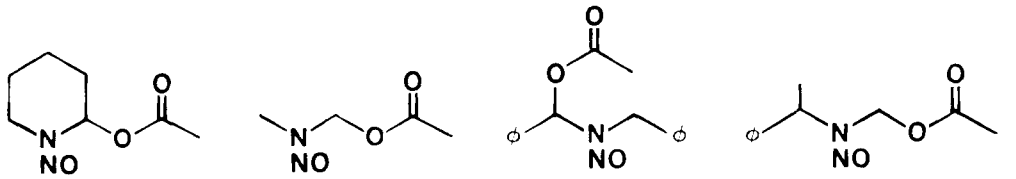
Cyclic α-chloronitrosamines, such as α-chloro-N-nitrosopyrrolidine 67, are prepared by chlorinating α-thioethylnitrosopyrrolidine 66 at -78°C. The intermediate 67 is not isolated, but treated in situ at -78° with triethylammonium acetate to give α-acetoxy-N-nitrosopyrrolidine 68 in 24% yield (Eq. 30).[150]



(30)

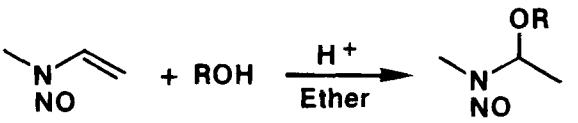
66 67 68

The oxidative decarboxylation with lead tetraacetate of N-nitroso-proline, N-nitrosopipecolic acid, N-nitrososarcosine, N-nitroso-N-benzyl-α-phenylglycine, and N-nitroso-N-phenethylglycine gave α-acetoxy-N-nitrosopyrrolidine 68, α-acetoxy-N-nitrosopiperidine 69, N-(α-acetoxymethylene)-N-methylnitrosamine 70, α-acetoxybenzylbenzylnitrosamine 71 and N-(α-acetoxymethylene)-N-(1-phenylethyl)nitrosamine 72, respectively.[70h,72c,151]



69 70 71 72

N-Nitrosoenamines, such as methylvinylnitrosamine 73, undergo rapid electrophilic addition across the double bond, and thus, they are excellent reagents for the preparation of α-methoxy and α-acetoxynitrosamines[152]. Acid-catalyzed addition of acetic acid to 73 at 0°C gave methyl (1-acetoxyethyl)nitrosamine 74a in 86% yield, while addition of methanol gave 74b in 98% yield (Eq. 31).

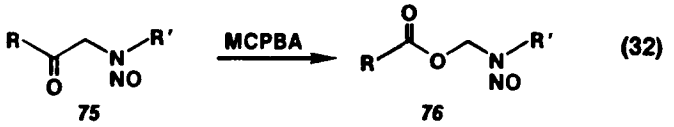


(31)

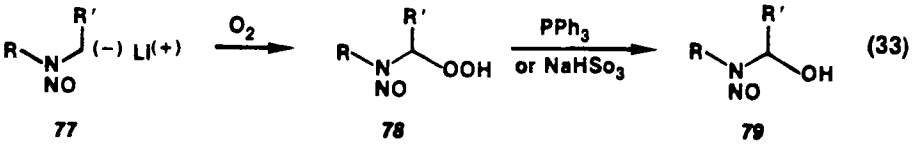
73

74a R = CH_3CO
b R = CH_3

The Baeyer-Villiger oxidation of β-ketonitrosamines 75 with m-chloroperbenzoic acid (MCPBA) in methylene chloride gave the corresponding α-acetoxy derivative 76 (Eq. 32).[153] Electrophilic addition of oxygen to a lithionitrosamine 77 gives the corresponding α-hydroperoxynitrosamine 78.[70e] These hydroperoxides are excellent precursors of α-hydroxynitrosamines.[70f] This conversion takes place upon reduction of the peroxide 78 with triphenylphosphine in chloroform under nitrogen, or with aqueous sodium bisulfite, to produce the corresponding α-hydroxynitrosamine 79 (Eq. 33). This is the first report of an unprotected α-hydroxynitrosamine being prepared and characterized.[70f]



75 76 (32)

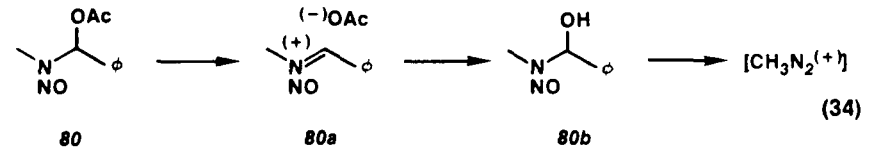


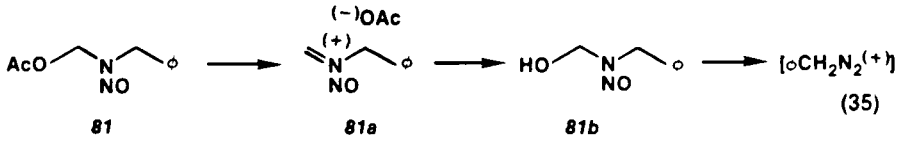
77 78 79 (33)

2. Properties of α-Oxygenated Nitrosamines

Baldwin and co-workers[70g] discovered pronounced differences in chemical reactivity between two structural isomers, N-methyl-N-(α-acetoxybenzyl)nitrosamine 80 and N-(α-acetoxymethyl)-N-benzylnitrosamine 81. The former isomer was hydrolyzed at a rate 32-fold faster than 81 at pH 8, and it was a powerful bacterial mutagen.[144b] Even at neutral pH, isomer 80 decomposed rapidly, (t 1/2 = 19 min), while 81 was stable. It was proposed that hydrolysis of α-acetoxynitrosamines undergo O-acyl fission to nitrosoimminium ions, which act as electrophiles. However, a hydrolysis

is not in line with the mechanism involved in the decomposition of these compounds. dissociation rather than hydrolysis is a more accurate term. The α-acetoxy compound 80 upon dissociation gives the resonance stabilized benzylnitrosoimminium ion 80a (Eq. 34); imminium ion 80a, is much more stable than 81a, which is derived from the dissociation of 81 (Eq. 35), and thus conversion of 80 to 80b is a much more rapid reaction. In aqueous media, the nitrosoimminium ion 80a will give N-methyl-n-(α-hydroxybenzyl)nitrosamine 80b which will rapidly decompose to benzaldehyde and an alkylating species, likely to be the methyldiazonium ion $[CH_3N_2^+]$ or the carbocation (Eq. 34). Similarly, but at a much slower rate, the structural isomer 81 will go through 81a and form the α-hydroxynitrosamine 81b, which in turn breaks down to a benzylating agent and formaldehyde (Eq. 35).

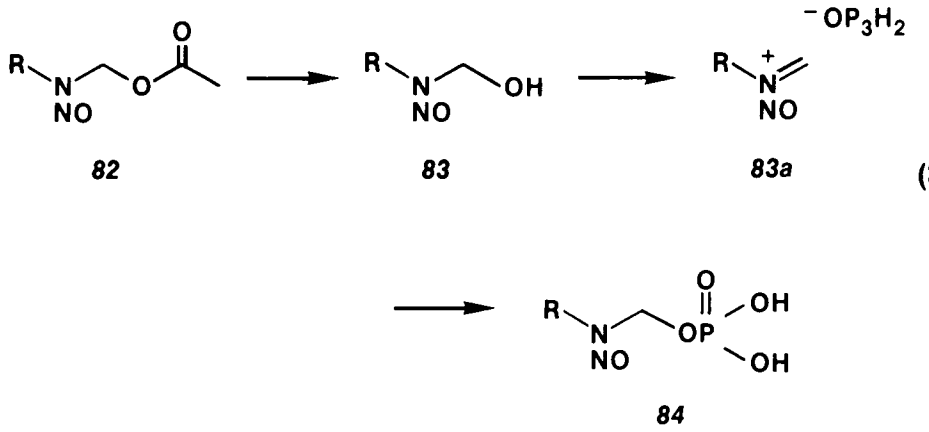




Wiessler et al.[72a] investigated the stability of a series of α-acetoxynitrosamines in aqueous medium (pH 7, 37°C). The stability of these compounds was monitored by the decrease in the UV absorbance at λ_{max} 230 nm as a function of time. The German authors found that anchimeric assistance of the nitroso group favors dissociation. Thus, the higher the ratio of Z/E rotamers, the greater the rate of hydrolysis. It was

also found that secondary acetates were dissociated 44 to 350 times faster than primary acetates. This gives an indication that carbonium ion species are formed and secondary acetates give rise to more stable nitrosoimminium ions than do the primary ones. These studies clearly indicate that the chemical behavior of α-hydroxynitrosamines and derivatives, in solvolysis reactions, is governed by the intermediacy of the N-nitrosoimminium ion. It may even be possible that nitrosoimminium ions act as electrophiles which alkylate cellular nucleophiles.[72a] The role of nitrosoimminium ions in the oxidative decarboxylation of nitrosoamino acids with lead tetraacetate to α-acetoxynitrosamines has been reported.[70h] It has also been demonstrated that the thermal decomposition of α-acetoxynitrosamines is governed by the intermediacy of nitrosoimminium ions.[72a]

As previously mentioned, α-hydroxynitrosamines are extremely reactive. However, it has been found that these intermediates are sufficiently stable, *in vivo*, to form conjugated products. This has come to light through the isolation of glucuronides of α-hydroxynitrosamines from rat urine.[154] Solvolysis of α-acetoxynitrosamines 82 in aqueous phosphate has been investigated. Compound 82 underwent O-CO fission to give the corresponding α-hydroxy derivative 83. This intermediate in turn decomposed to the imminium ion 83a which was trapped by the phosphate ion, to give N-nitroso-N-(α-phosphoroxyalkyl)alkylamines 84 (Eq. 36).[155] The reduction of peroxides 78 in the presence of hydrogen phosphate also gave the α-phosphoroxynitrosamines 84. The reduction was also carried out in the presence of other nucleophiles, such as, thiosulfate and dithiocarbonate. It was proposed from these studies that the amount of addition at the α-position is directly related to the extent of equilibrium between the α-hydroxylated species and the nitrosoimmonium ion.[156]

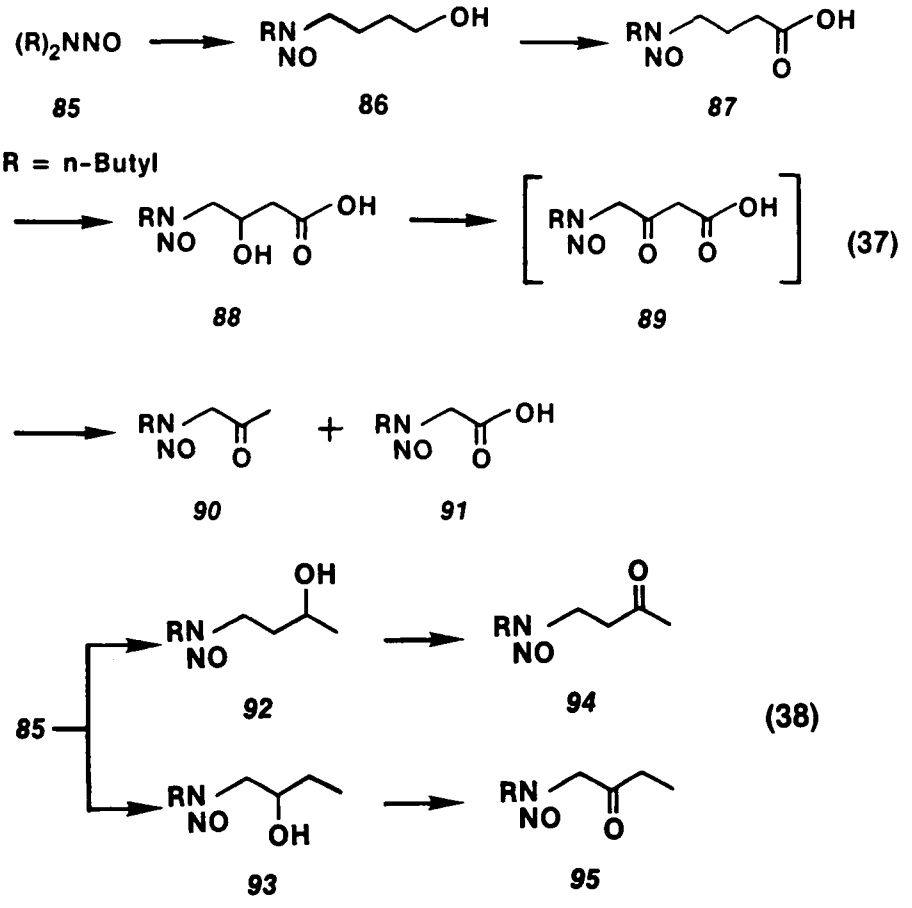


IV. β-, γ- AND ω-OXIDIZED NITROSAMINES

There has been much interest in the study of the chemistry of "oxidized" nitrosamines as they relate to the human exposure, carcinogenesis and metabolism.[69a] The compounds are defined as N-nitroso compounds containing an hydroxyl, a carbonyl, carboxylic acid group or derivatives thereof on the β-, γ- or ω-carbon. A number of β-oxidized nitrosamines have been found in the environment, e.g. N-nitrosodiethanolamine [$(HOCH_2CH_2)_2NNO$]. This carcinogen[157] is a contaminant of metal cutting fluids,[30,158] cosmetics, lotions and shampoos,[159] and is present in antifreeze,[160] and in snuff and other tobacco products.[161] β-Hydroxynitrosopyrrolidine has been found in cooked bacon,[162] and other β-oxidized nitrosamines derived from common drugs have been reported.[163] In some regions of China, β-ketonitrosamines are found in corn bread and pickle juice,[164] and this may be related to the region's high incidence of esophageal cancer.

Oxidized nitrosamines have been isolated as stable metabolites of cyclic and dialkylnitrosamines, originally containing no oxygen functionality.[69d,73,165] Long-chain N-nitrosodialkylamines are metabolically degraded by a chain-shortening process involving oxidation of the terminal carbon as the initial step, and retaining the nitroso group. The metabolic fate of di-n-butylnitrosamine 85 illustrates well this degradation.[166] After oral administration to rats, the metabolites were isolated and charact-

erized. The three main pathways through which 85 is oxidatively metabolized are shown in Eqs. 37 and 38. Dibutylnitrosamine 85 undergoes ω-oxidation to give compound 86 with a terminal hydroxyl group. Further oxidation gives the carboxylic acid 87, the major metabolite isolated in this study.



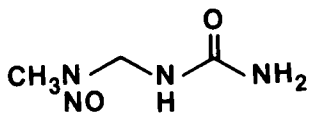
β-Hydroxylation of 87 yields N-n-butyl-N-(2-hydroxy-3-carboxypropyl)-nitrosamine 88 which on oxidation and degradation through the corresponding ketone 89 forms N-n-butyl-N-(2-oxopropyl)nitrosamine 91 (Eq. 37). An ω-1 oxidation of 85 gives the γ-hydroxy compound 92. The other pathway involves a ω-2 hydroxylation to form the β-hydroxy derivative 93. These hydroxy compounds undergo further oxidation to the corresponding γ-keto-, 94 and β-keto- nitrosamines 95 (Eq. 38). The hydroxy compounds were iso-

lated as the glucuronic acid conjugates, but for simplicity sake the metabolites have been shown in the equation as the free hydroxy compound.

Methylation of nucleic acids by long-chain dialkylnitrosamines is a direct result of chain degradation. The main reaction product found in nucleic acid of rat liver after exposure to dibutylnitrosamine 85 was 7-methylguanine. A metabolite such as 93 forms methylbutylnitrosamine, which allows the formation of methylating agents by subsequent α-hydroxylation of the n-butyl group.[165a,167] In many cases, the β-, γ- and ω-oxidized metabolites have a carcinogenic effect which is not identical to that of the parent compound.[168] Moreover, the carcinogenic potency and tumor spectrum also varies according to the oxidation state of the oxygen-bearing carbon (i.e. hydroxy, oxo).[169] Because β-, γ- and ω-hydroxylations are also pathways of nitrosamine activation in carcinogenesis and metabolism, the study of their chemistry and syntheses has been greatly stimulated.

1. Neighboring Group Participation by the Nitroso Function in Solvolysis Reactions

Michejda et al.[170] prepared and studied α-ureidonitrosdimethylamine 96 and α-ureidonitrosopyrrolidine 97 in relation to their structural similarities to α-acetoxynitrosamines. The kinetics of hydrolysis of these compounds revealed a strong N-nitroso group participation. The discovery of this anchimeric effect prompted the study of the solvolysis of p-toluenesulfonate derivatives of β- and γ-hydroxynitrosamines.[66a,171]



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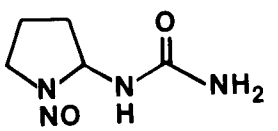
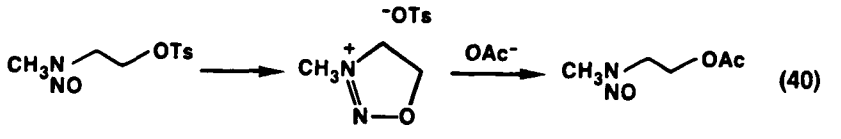


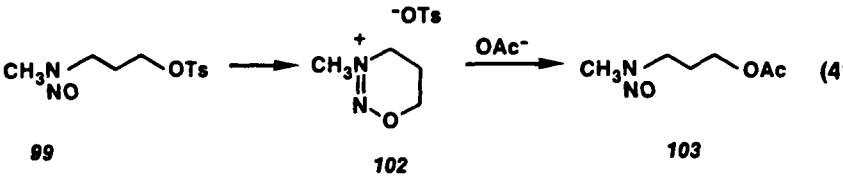
97

(39)

Acetolysis of two representative examples, N-methyl-N-nitroso-2-

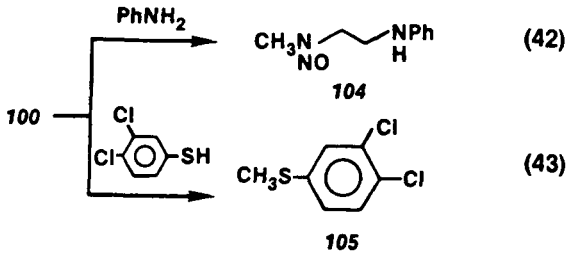
(tosyloxy)ethylamine 98 and N-methyl-N-nitroso-3-(tosyloxy)propylamine 99 were carried out in glacial acetic acid buffered with potassium acetate. The tosylate 98 solvolyzed 200 times faster than benzyl tosylate to give the 2-acetoxy product 101. The kinetic data support the concept of neighboring group participation by the nitroso group. The reaction proceeds through the cyclic intermediate 100 which, upon nucleophilic attack by the acetate ion, forms 101 (Eq. 40). This cyclic compound, or oxadiazolium ion, can actually be isolated in quantitative yield when the parent tosylate 98 is warmed in a non-nucleophilic solvent (i.e. CH_2Cl_2).[172] The tosyloxypropylamine 99 passes through the six-membered intermediate 102 to give the 3-acetoxy product 103 (Eq. 41). The acetolysis of 99 is slower than for the tosyloxyethylamine 98, since the latter has fewer degrees of freedom, and thus a less negative entropy of activation.[66a]





The oxadiazolium ion 100 is an alkylating agent, both in organic solvents and in neutral aqueous solution. Treatment of this compound with aniline results in quantitative formation of methyl-(2-anilinoethyl)-nitrosamine 104 (Eq. 42), which results from an attack on the 2-ethyl group, as is the case with the acetate ion (Eq. 40). However, when 3,4-dichlorothiophenol is used as the nucleophile, the site of attack is the methyl

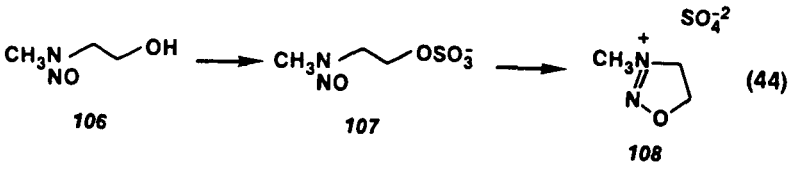
group giving a quantitative yield of 3,4-dichlorothioanisole 105 (Eq. 43). The reaction of 100 with guanine and guanosine also involve an attack on the methyl group.[172,173]



(42)

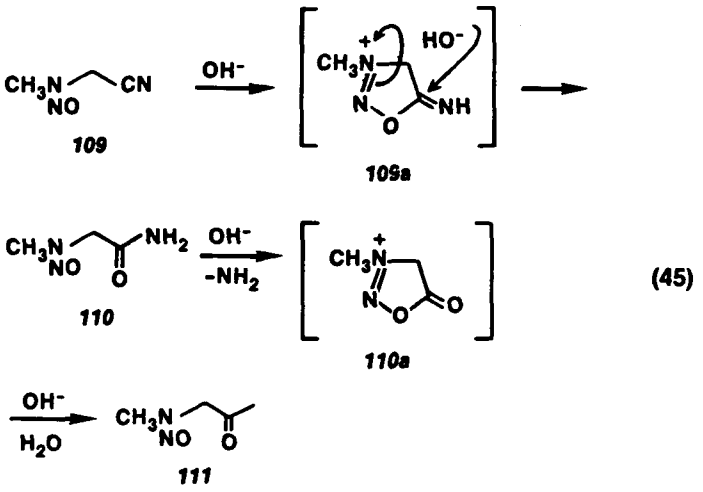
(43)

The involvement of the oxadiazolium ion in carcinogenesis has been proposed by Michejda et al.[172-174] For example, the strong liver carcinogen N-nitrosomethyl-2-hydroxyethylamine 106 may undergo a sulfate conjugation of the hydroxyl group to give 107. This sulfate conjugate undergoes intramolecular nucleophilic displacement to the cyclic sulfate 108 which in turn interacts, as a methylating agent, with cellular nucleophiles (Eq. 44).



(44)

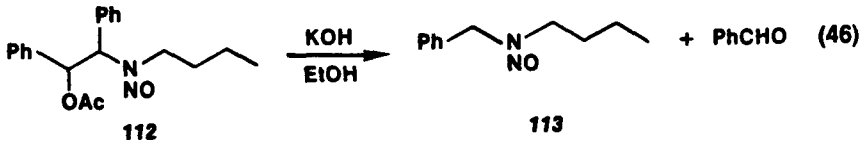
Anchimeric assistance by the nitroso group is also involved in the hydrolysis of N-nitroso-2-(methylamino)acetonitrile 109 to N-nitrososarcosine 111.[175] Although nitriles do not hydrolyze rapidly at room temperature in basic medium (pH 13), the nitrile 109 undergoes two unusually fast hydrolytic changes. The reaction proceeds to the amide 110 via the cyclic intermediate 109a, followed by hydroxide ion attack. The amide intermediate 110 is rapidly hydrolyzed to N-nitrososarcosine 111, via the five-membered ring 110a (Eq. 45).



(45)

2. Base-induced Fragmentation of β-Oxidized Nitrosamines

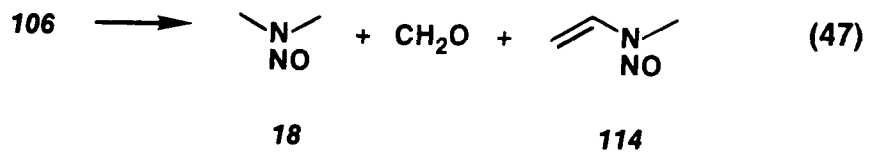
Loeppky et al.[163] discovered the base-induced retro-aldol condensation of β-hydroxynitrosamines during the attempted ester hydrolysis of 112 in ethanolic potassium hydroxide. The fragmentation products derived from this particular compound were benzaldehyde and N-nitroso-N-butylbenzylamine 113 (Eq.46). A systematic study of this fragmentation reaction was carried out with a variety of β-hydroxynitrosamines.[69] The reaction was generally carried out at 70°C in THF-t-butyl alcohol and potassium t-butoxide. Most of the compounds studied followed the pathway described in Eq. 46 giving two clean products.



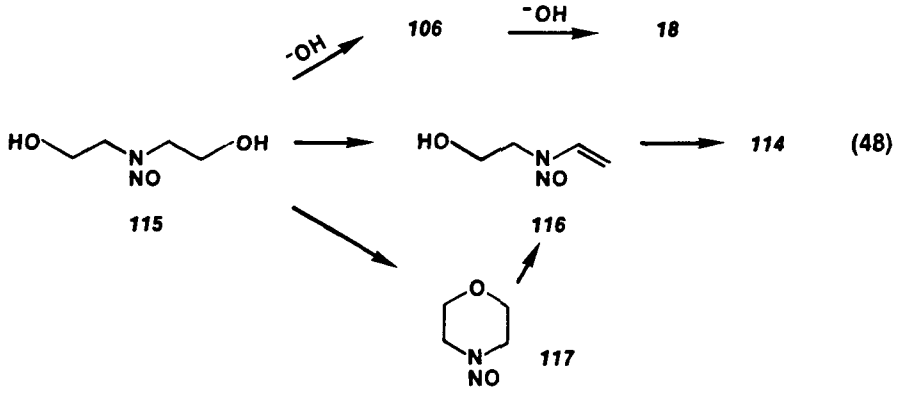
(46)

N-Methyl-N-hydroxyethylamine 106 not only underwent fragmentation to the expected dimethylnitrosamine 18 and formaldehyde but also gave N-methyl

vinylnitrosamine 114 (Eq. 47).

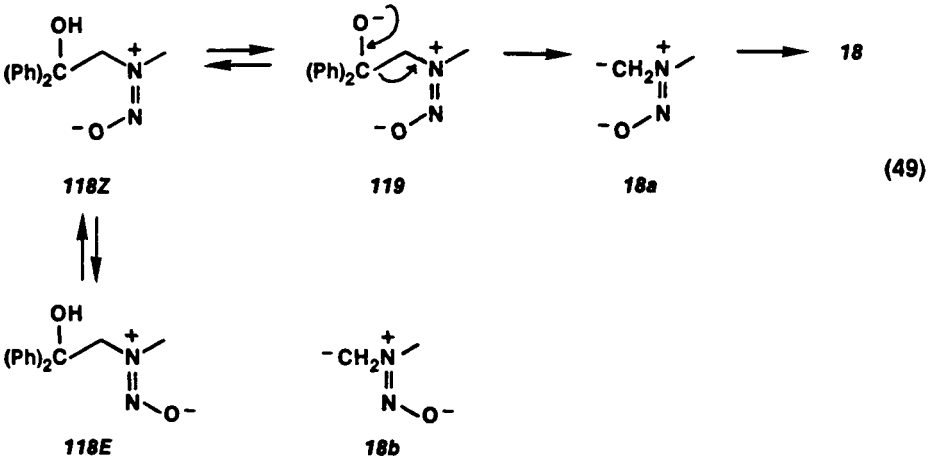


As we discussed previously, N-nitrosodiethanolamine 115 is a very important compound because of its carcinogenic properties, and its occurrence in the environment. Investigation of the retro-aldol type fragmentation of this compound indicated that other base-induced fragmentations were also taking place.[69] The retro-aldol fragmentation of 115 to N-nitrosomethylethanolamine is a slow reaction, and thus other fragmentations become important. The base-catalyzed elimination of water gives N-nitroso-2-hydroxyethylvinylnitrosamine 116 which upon retroaldol cleavage gives N-nitrosomethylvinylamine 114. N-nitrosomorpholine 117 is also formed upon elimination of water, and it can further fragment to 116 (Eq. 48).



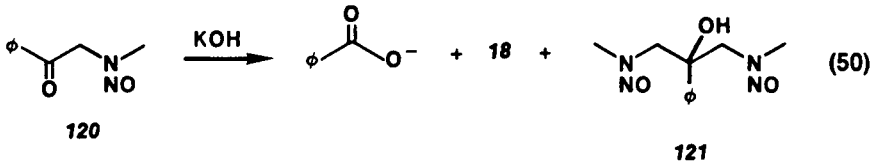
Detailed mechanistic studies of the base-induced fragmentation rate of β-hydroxynitrosamines and, in particular, the kinetic demonstration of the "syn-effect" in the fragmentation reaction have been reported.[69c]

This investigation ties in remarkably well with the stability studies of the α-nitrosamino carbanions discussed in Section II. (2-Hydroxy-1,1-diphenylethyl)methylnitrosamine 118 exists as an equilibrium mixture of 118E and 118Z where the E rotamer predominates. The minor rotamer 118Z was synthesized in pure form from the lithio anion addition of dimethylnitrosamine 18 to benzophenone, and its rate of decomposition to dimethylnitrosamine 18 and benzophenone (Eq. 49) was compared with that of the equilibrium mixture (containing mostly 118E). This reaction occurs 287 times faster than for rotamer 118E (87%). Loeppky et al.[69c] proposed and experimentally supported a mechanism where the fragmentation of 118E proceeds by ratedetermining isomerization of 118E to 118Z prior to rapid retro-aldol cleavage. Fragmentation of the alkoxide 119 gives the anion 18a of dimethylnitrosamine 18, indicating significant stereoelectronic control by the N-NO function. The incipient syn-carbanion is perpendicular to the N-NO plane and able to delocalize through a 4-atom 6-π-electron system;[121,128] the anti-carbanion 18b would not be as stable.



(49)

It has been shown that under basic conditions, β-ketonitrosamines undergo a retro-Claisen-type cleavage. In alcoholic potassium hydroxide at room temperature, 2-oxopropylpropylnitrosamine produces potassium acetate and methylpropylnitrosamine.[176] Under basic conditions 2-phenyl-2-oxoethylmethylnitrosamine 120 decomposes to potassium benzoate, dimethylnitrosamine and also the bis-nitrosamino alcohol 121 (Eq. 50).[69a]

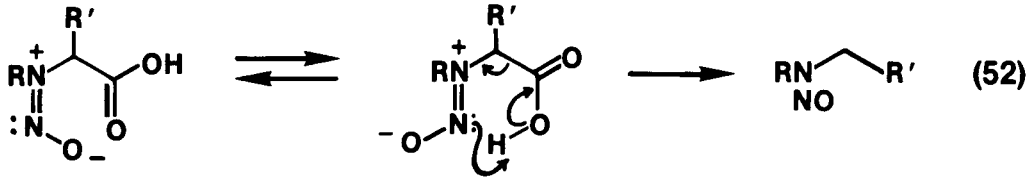


120 121 (50)

Preliminary studies of the retro-Claisen condensation of N-nitroso-N-methyl-2-oxopropylamine 51 have been reported.[177] Analysis of 51 by NMR indicate that at equilibrium it exists in 1.5:1 ratio of 51Z:51E rotamers which are separable on HPLC. In aqueous alkali at 25°C, 51Z undergoes cleavage to form the acetate anion, and dimethylnitrosamine via the syn anion 18a. Rotamer 51E does not react under these conditions, but it is necessary for it to epimerize to 51Z to undergo fragmentation. The "syn effect" associated with the retro-aldol fragmentation in β-hydroxynitrosamines is also encountered in the retro-Claisen cleavage of β-ketonitrosamines. Thus the more rapid fragmentation of the Z isomer is due to the greater stability of the incipient syn carbanion.

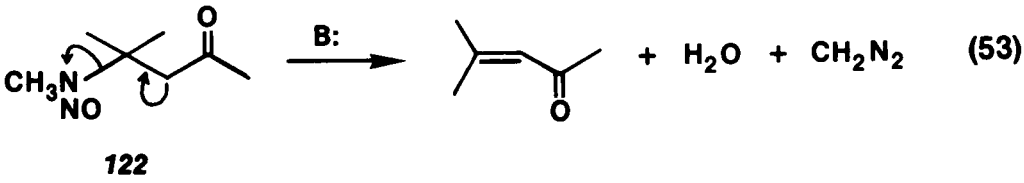
51Z 51E (51)

Thermal decarboxylation of α-nitrosamino acids give the corresponding nitrosamines in high yields.[178] The reaction occurs via a cyclic concerted mechanism that is only possible with the E rotamer (Eq. 52).



(52)

The γ-oxidized nitrosamine 122 when treated with sodium isopropoxide at 70-75°C constitutes a large scale preparation of diazomethane (Eq. 53).[179]

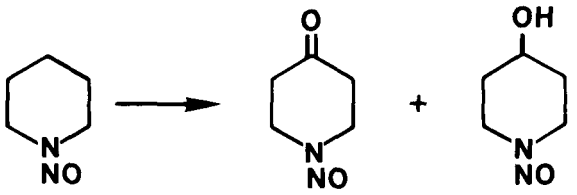


(53)

122

3. Chemical Oxidation of N-Nitrosamines at the β and γ-Carbons

The most commonly known oxidation reaction of N-nitrosamines occurs at the nitroso-nitrogen to form the corresponding nitramine. Peroxytrifluoroacetic acid has been found to be a unique reagent for this purpose.[60,180] However, since enzymatic oxidations occur at different carbon atoms in the nitrosamine molecule, there has been an interest in the oxidation of these compounds in purely chemical systems. An enzyme-free model system that has been used in the oxidation of nitrosamines[181] is the Udenfriend system,[182] which requires molecular oxygen, ascorbic acid, Fe^{+2} and EDTA. Oxidation of N-nitrosopiperidine 123 in this system, and by rat-liver microsomes gave N-nitroso-4-piperidone 124 and N-nitroso-4-hydroxypiperidine 125 (Eq. 54).[181b]



(54)

123 **124** **125**

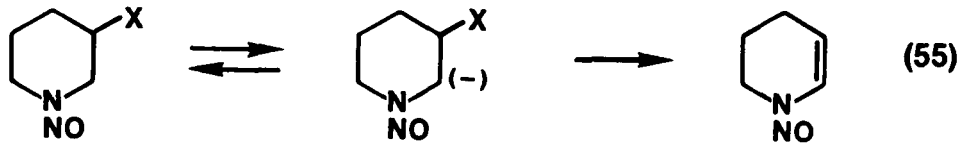
Electrochemical oxidation of N-nitrosodialkylamines such as N-nitroso-di-n-butylamine 85 was carried out in acetonitrile in the presence of dissolved oxygen. Cyclic voltametry at ambient temperature converted 85 to the corresponding nitramine and N-n-butyl-N-(2-oxobutyl)nitrosamine 95.[183]

V. N-NITROSOENAMINES

Prior to 1979, very little was known about the chemistry and carcinogenicity of vinylic nitrosamines (N-nitrosoenamines). Only three members of this class of compounds had been reported,[184] mainly because of the lack of a general synthetic method for their preparation. In 1979 three practical methods for the synthesis of α,β-unsaturated nitrosamines were described.[68a] This has resulted in increased investigations of their biological activities[185] and their versatility as synthetic intermediates.[68,152]

1. Synthesis of N-Nitrosoenamines

The reaction of 3-(tosyloxy)-N-nitrosopiperidine 126a or 3-chloro-N-nitrosopiperidine 126b with potassium hydroxide suspended in ether and catalyzed with 18-crown-6-ether gave the corresponding 2,3-dehydro-N-nitrosopiperidine 128 in quantitative yield (Eq. 55).[68a] The loss of the tosyl or chloro group occurs via a classical $E_{1c}B$ mechanism, i.e. there is a reversible formation of carbanion 127 prior to elimination.

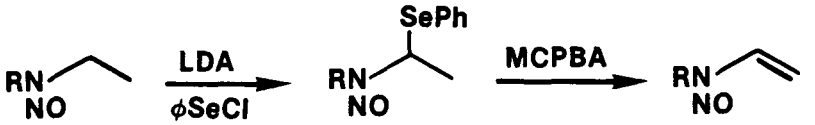


(55)

126a, X = TsO **127** **128**

b, X = Cl

Another method, which involves an oxidative elimination reaction, requires the formation of an α-phenylselenonitrosamine 130. This compound is made from the α-nitrosaminocarbanion of 129 with phenylselenyl chloride or diphenyl diselenide. Treatment of 130 with a two-fold excess of m-chloroperbenzoic acid (MCPBA) at 30-35° gives the corresponding α,β-unsaturated nitrosamine 131 in 64-71% yield (Eq. 56), upon elimination of phenylselenenic acid. If the allylic unsaturated nitrosamine is available,



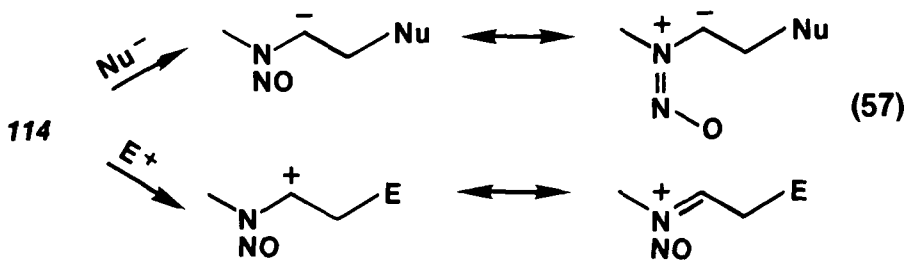
(56)

129 **130** **131**

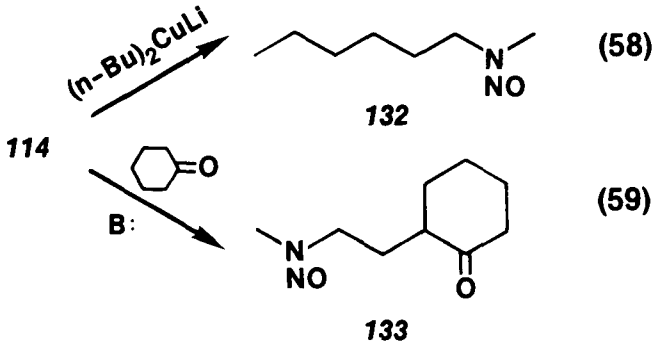
it can readily be converted to the N-nitrosoenamine upon equilibration by heating in methanolic potassium hydroxide.

2. Reactions of N-Nitrosoenamines with Nucleophiles

The N-nitroso function has the ability to stabilize a positive as well as a negative charge on the α-carbon. Thus, N-nitrosoenamines are reactive towards nucleophiles as well as electrophiles, as shown in Eq. 57, in which methylvinylnitrosamine 114 is used as a representative example.[152]



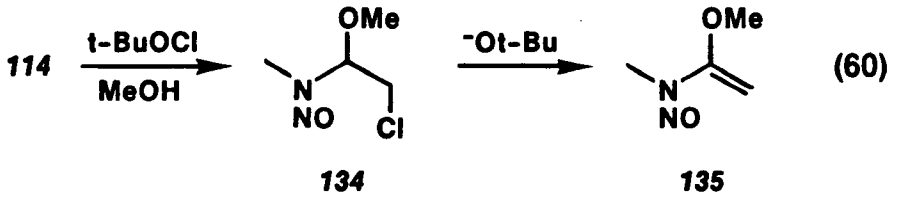
N-nitrosoenamines are reactive toward nucleophilic reagents such as alkylcopperlithiums and enolate anions. A Michael-type addition of di-n-butylcopperlithium to 114 gives N-methylhexylnitrosamine 132 in 88% yield (Eq. 58). When the nucleophile is an enolate anion such as that of cyclohexanone, the corresponding adduct 133 is obtained in 45% yield (Eq. 59). Aryl- and alkyllithiums are not very useful in this system since attack on the nitroso group competes with Michael-type addition. Cyclic N-nitrosoenamines in base-catalyzed reaction with alcohols form the corresponding 3-alkyoxy adduct.[152]



3. Reactions of N-Nitrosoenamines with Electrophiles

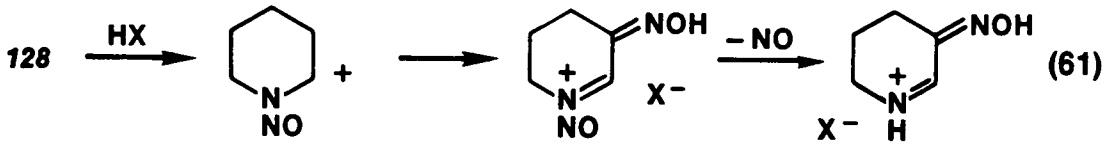
As discussed in section III, N-nitrosoenamines are excellent sources of α-methoxy and α-acetoxynitrosamines (Eq. 31). These are good examples of electrophilic additions across the double bond. Electrophilic addition of t-butyl hypochlorite to methylvinylnitrosamine 114 in methanol gave

the corresponding β-chloro-α-methoxy adduct 134 in 82% yield. Treatment of 134 with potassium-t-butoxide in ether with catalytic amounts of 18-crown-6-ether gave the enol ether 135, which was until now an unknown class of N-nitroso compound (Eq. 60).[152]



134 135 (60)

The reaction of 2,3-dehydro-N-nitrosopiperidine 128 with strong mineral acids gives the oxime salt 137. This probably results from the protonation of 128 at C-3 to form the cationic species 128a which in turn nitrosates the N-nitrosoenamine 128 at C-3 to form intermediate 136. Denitrosation of 136 gives the oxime salt 137 (Eq. 61).[65b]

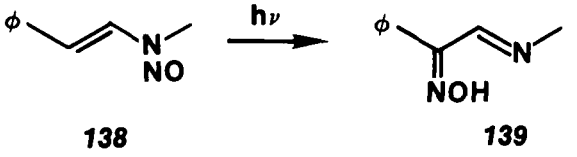


128a 136 137 (61)

4. Oxidation Reactions

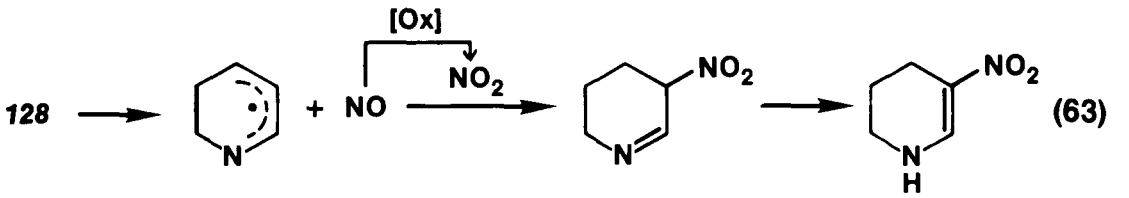
Seebach and Enders[122b] reported that, in the absence of oxygen, methyl-p-styrylnitrosamine 138 formed the oxime 139 under radical producing conditions (Eq. 62). Similarly, Michejda et al.[186] reported that 2,3-dehydro-N-nitrosopiperidine 128 was photolabile, and that photolysis in the absence of oxygen gave the oxime 137. However, in the presence of oxygen, the nitroenamine 141 was obtained. The reaction proceeds by photodissociation of the N-N bond to give nitric oxide and the enaminyl radical 140. The nitric oxide is oxidized to nitrogen dioxide, which couples

with radical 140 to give 141 (Eq. 63). Oxidation of the α,β-unsaturated nitrosamine 128 with iodosobenzene or m-chloroperbenzoic acid also gave the nitroenamine 141.



(62)

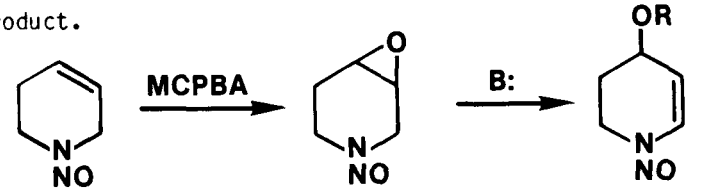
138 139



(63)

140 141

Oxidation of the β,γ-unsaturated nitrosamine 142 with m-chloroperbenzoic acid (MCPBA) gave the corresponding 3,4-oxide 143. Under mild basic conditions, 143 was converted to the allylic alcohol 4-hydroxy-2,3-dehydro-N-nitrosopiperidine 144, (Eq. 64).[68b] This alcohol was also obtained in the microsomal reaction of 128[187]. Oxidation of 128 with lead tetraacetate gave 4-acetoxy-2,3-dehydro-N-nitrosopiperidine 145 as the major product.



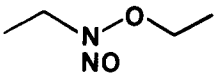
(64)

142 143 144 R = H
145 R = Ac

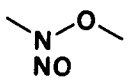
VI. THE CHEMISTRY OF N-NITROSO-N,O-DIALKYLHYDROXYLAMINES

The carcinogenic activity of N-nitroso-O,N-diethylhydroxylamine 146 and N-nitroso-O,N-dimethylhydroxylamine 147 has been studied.[187] Metabolic studies on these and other compounds of this type are currently underway in our laboratory and should provide some interesting information about their biological activity.[188] Although the nitrosation of N,O-dialkyl-

hydroxylamines was described in 1931 as the simplest way for preparing the corresponding nitroso compound[189-190] very little is known about the chemistry of this class of N-nitrosamines. ^{14}C-labeled compounds of this type[191] have been synthesized using this same basic method. Details of synthetic methods for the preparation of the amine precursors of the title compounds is beyond the scope of this review. However, it should be pointed out that their synthesis is well established. The preparation involves the selective alkylation of hydroxyurethane[192] or hydroxyurea[193] with subsequent hydrolysis. Catalytic reductions of N-nitroso-O,N-dialkylhydroxylamines have been reported,[189,194] and their properties under hydrolytic conditions have also been studied.[190] The use of these compounds as intermediates in the synthesis of azoxyalkanes has been explored.[195]



146



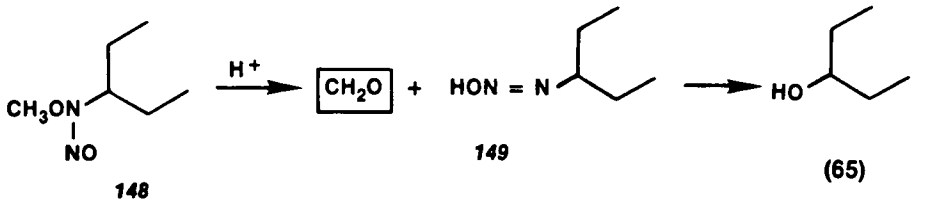
147

1. Catalytic Reduction and Hydrolysis

Catalytic hydrogenation of 147 in glacial acetic acid over Adams catalyst under 1.3 atmosphere of hydrogen gave methylammonium acetate and methanol within 6 hours.[189] The reduction takes place in two stages. Reductive cleavage of the nitroso group to ammonia is the first step in the formation of N,O-dimethylhydroxylammonium acetate ($CH_3ONHCH_3 \cdot HOAc$). The substituted hydroxylamine then undergoes an N-O cleavage to the primary amine and the alcohol. Reduction of 147 in aqueous basic media proceeded rapidly over aluminum-nickel to give methylamine in 93% yield.[194]

When N-nitroso-N,O-diethylhydroxylamine 146 was hydrolyzed in concentrated hydrochloric acid, ethanol and acetaldehyde were formed. Under similar conditions, N-nitroso-N,O-dimethylhydroxylamine 147 gave methanol

and formaldehyde. The proposed mechanism consists in the oxidative cleavage of the alkoxy group to give the corresponding aldehyde, leaving the diazohydroxide which upon loss of nitrogen gives the alcohol.[190a] N-Nitroso-O-methyl-N-3-amylhydroxylamine 148 gives upon acid hydrolysis, formaldehyde and 3-pentanol. Initial N-O cleavage forms the diazohydroxide 149 which upon loss of nitrogen gives the corresponding alcohol (Eq. 65).



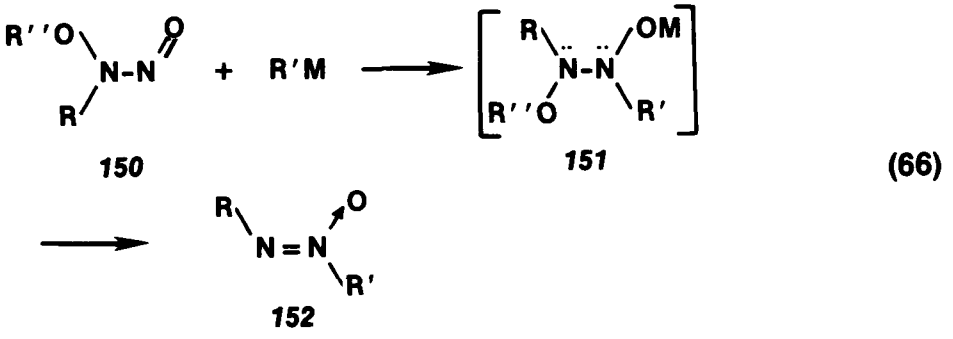
148 149 (65)

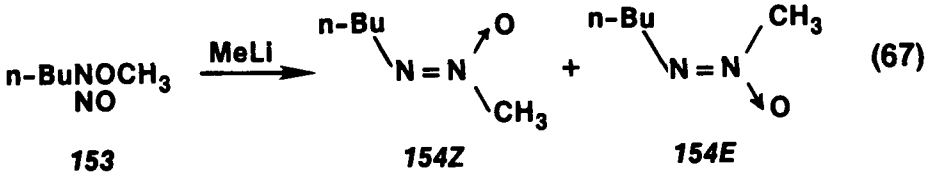
Anselme and Kano[190] investigated the hydrolysis of larger and more reactive compounds than 148, such as N-(p-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine, [p-$CH_3C_6H_4CH_2N(NO)OCH_2Ph$]. Different products were obtained from those predicted by the work of Major et al.,[189] even though the same reaction conditions were used. The predominant product from the acid hydrolysis, instead of the expected p-methylbenzyl alcohol, was the hydrochloride salt of N-(p-methylbenzyl)-O-benzylhydroxylamine. This discrepancy prompted these authors to re-investigate the acid hydrolysis of 148. Although, 3-pentanol was isolated as one of the major products, no formaldehyde was detected as implied in Eq. 65. The major component of the hydrolysis was the denitrosation product, N-(3-pentyl)-O-methyl-hydroxylamine hydrochloride. It appears from this work, that the mechanism of hydrolysis and the products proposed by Major et al.[189] cannot be correct.

2. Synthetic Applications

Nucleophilic addition of alkyllithiums, alkyl Grignard reagents, and dialkylcopper lithiums to N-nitroso-N,O-dialkylhydroxylamines 150 forms the Z-azoxyalkanes 152 according to the mechanism described in Eq.

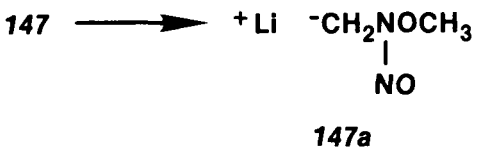
66.[195] Although this reaction appears to be useful as a regioselective synthesis of unsymmetrical azoxyalkanes, it has some serious limitations. The yields are low, there is always "over-reaction", and it is limited to primary aliphatic organometallic reagents. In most cases the (Z)-azoxymethane is isolated; however, in the reaction of methyllithium with N-nitroso-O-methyl-N-n-butylhydroxylamine 153 both the 154 Z, and the 154 E isomers are obtained, the latter being the predominant one (Eq. 67).





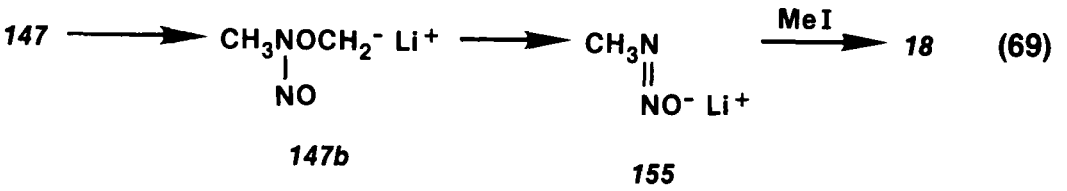
N-Nitroso-O,N-dimethylhydroxylamine 147 undergoes rapid H-D exchange in deuterium oxide/$^{-}$OD at room temperature. The exchange occurred at the N-methyl group to give N-nitroso-O-methyl-N-methyl-d3-hydroxylamine [$CD_3N(NO)OCH_3$]. This finding, and the fact that these compounds are catalytically reduced to the primary amine, prompted the evaluation of these compounds as α-primary amino carbanion synthons. Metalation of 147 with lithium diisopropylamide followed by addition of methyl iodide unexpectedly gave dimethylnitrosamine 18 in very small quantities, with no other nitroso-compound being formed.[142] These results indicate that metalation on the N-methyl group leads to a very unstable anionic species, 147a (Eq. 68).

However, metalation also occurs on the oxygen-bearing carbon forming a short-lived intermediate 147b that breaks down into the E-diazotate 155, which, in turn, is alkylated to form 18 (Eq. 69). Base-catalyzed decomposition of N,O-disubstituted-N-nitrosohydroxylamines has been studied by Anselme and Kano.[190] Their work supports the intermediacy of diazotates, provided that aprotic solvents are used.



(68)

147a

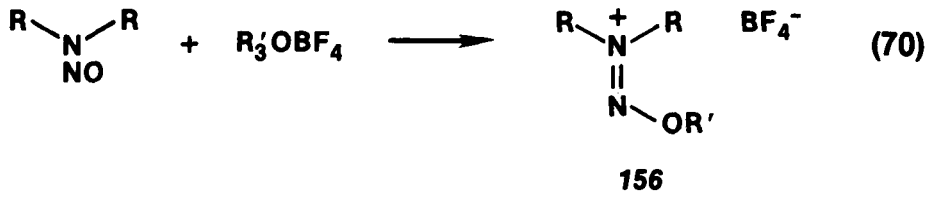


(69)

147b 155

VII. O-ALKYLATION OF N-NITROSAMINES

The oxygen atom of the N-nitroso group bears a partial negative charge; thus it can interact with electrophilic reagents. Some aspects of the nucleophilic character of this oxygen were touched upon in section IV-1 under the discussion of the role of oxadiazolium ions in neighboring-group participation by the nitroso function. Oxygen alkylation is of interest in nitrosamine chemistry for, upon reaction, the latter becomes an electrophilic intermediate. O-Alkylated nitrosamines were discovered by Hünig et al.[196] and are commonly known as alkoxydiazenium ions of general structure 156. These compounds are formed on reaction of a dialkylnitrosamine and a trialkyloxonium tetrafluoroborate (Eq. 70). The salts are also accessible by alkylation of the nitrosamine with alkyl halides in the presence of silver perchlorate. Magic methyl or ethyl readily alkylate the nitrosamine oxygen to form the corresponding alkoxydiazenium fluorosulfonates ($R_2^+N{=}NOR'\ FSO_3^-$).[146]

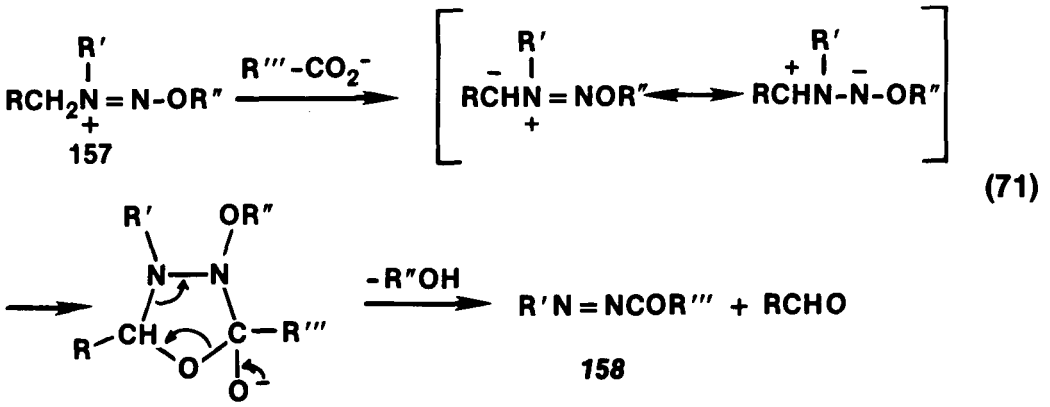


(70)

156

Alkylation Reactions of Alkoxydiazenium Ions

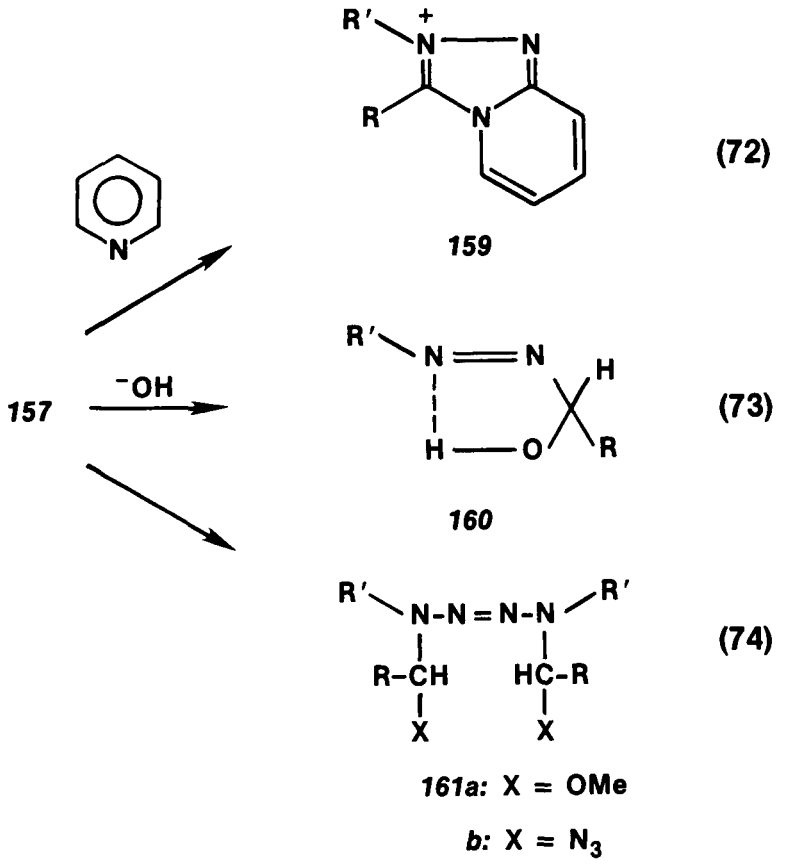
Alkoxydiazenium cations, of the general structure 157, react with carboxylates to give the α-carbonylazo compound 158 in high yield.[196a] The reaction works well as shown in Eq. 71 provided that R' is either an aromatic or a tertiary alkyl group.



(71)

158

The synthesis of s-triazolium cations (i.e. 159) can be achieved by reaction of the alkoxydiazenium ion 157 with nitrogen heterocycles (i.e. pyridine) (Eq. 72).[196b] The reaction of 157 with hydroxide ion gives α-hydroxydialkyldiazenes 160 (Eq. 73). This hydroxy compound has been shown to exist in the trans stereochemistry about the azo double bond with intramolecular hydrogen bonding.[197] The cis-isomers can be prepared only in solution by irradiation of the trans-isomer and it cannot be isolated.[198] Notice that the trans stereochemistry about the azo bond, in 160, is determined by hydrogen bonding as shown in Eq. 73. Nucleophiles such as methoxide or azide ions with 157 give α α'-dimethoxy and α α'-diazidotetrazenes 161a and 161b respectively (Eq. 74).[199]



The reaction of alkoxydiazenium fluorosulfonate salts with various nucleophiles has been examined.[146,173] In contrast to fluoroborate salts, the fluorosulfonates are soluble in organic solvents. These salts generally react with nucleophiles by displacement of the O-alkyl group. However, their reaction with 3,4-dichlorothiophenol in organic solvents results in the formation of thioethers from O- and N-dealkylation.

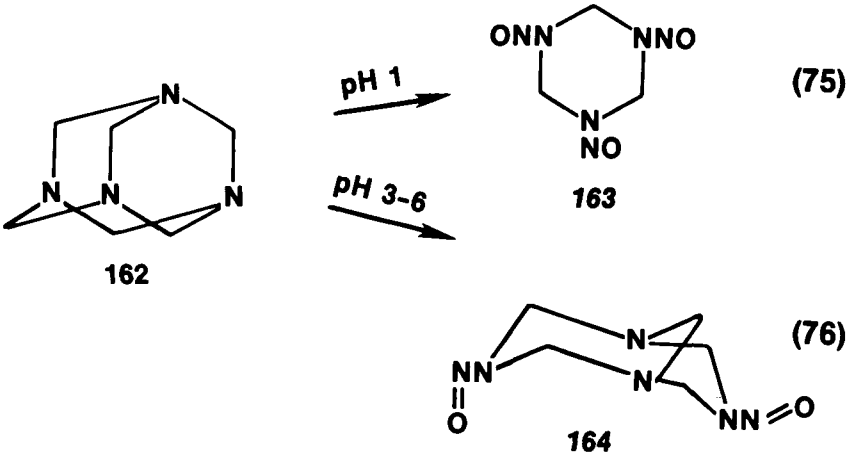
VIII. NITROGEN HETEROCYCLES WITH MULTIPLE NITROSO GROUPS

Limited aspects of the chemistry of heterocyclic di-, tri- and tetranitrosamines have been studied in connection with the structure and the chemistry of aldehyde-ammonia adducts.[200] Heterocyclic 1,3-dinitrosamines have also been prepared as intermediates for the synthesis of cyclic 1,3-

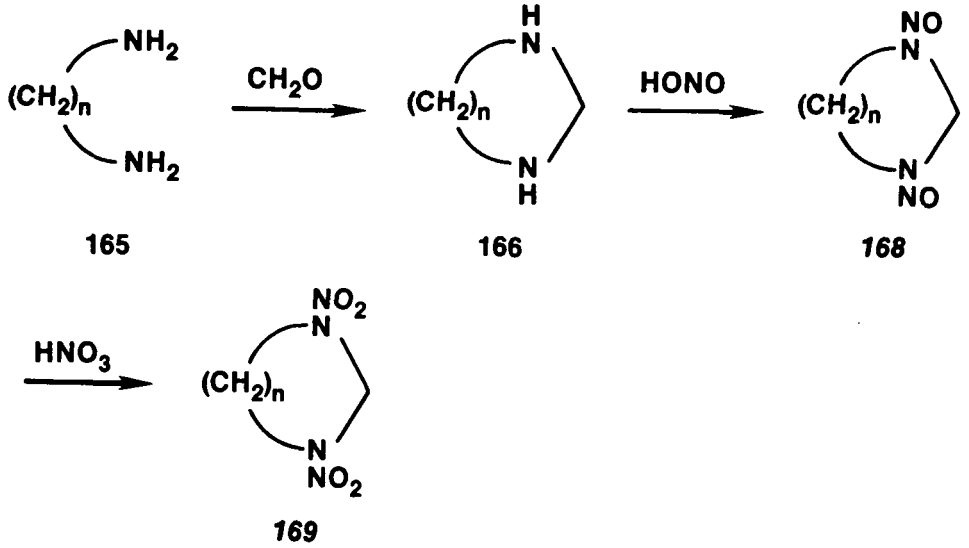
dinitramines, which are a potentially important class of energetic materials.[201] A few examples dealing with α-alkylation of polynitrosamines have been reported.[202]

1. Nitrosation of Hexamethylenetetramine and Related Compounds

The reaction between hexamine 162 and nitrous acid at pH 1 gives exclusively the trinitroso compound 163 in 50% yield. In the pH range of 3-6, the dinitroso compound 164 is formed in 76% yield. At pH 2, a mixture of the dinitroso and the trinitroso compounds is obtained.[200a,203] The stereochemistry of these products has been studied in detail by proton- and carbon-NMR.



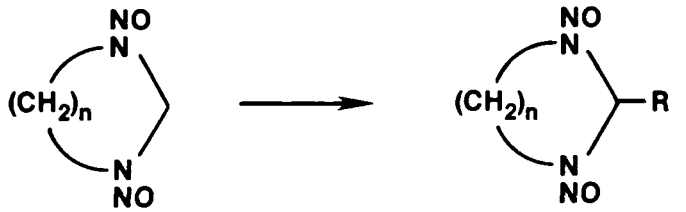
Cyclic 1,3-dinitrosamines 167 are prepared from α,ω-diamines 165 and formaldehyde to form the cyclic aminal 166 followed by in situ nitrosation (Eq. 77). This offers an alternate method for the preparation of cyclic 1,3-dinitramines 168, important in the study of energetic materials.[201]



165 166 168 169 (77)

2. Alkylation of Cyclic gem-Dinitrosamines

The first examples of α-alkylation of polynitrosamines were reported recently by Boyer and Kumar.[202] This work is related to the α-nitrosamino carbanion investigations discussed in section II. Potassium-t-butoxide catalyzed the addition of benzaldehyde to 1,3-dinitrosoimidazolidine 169a, and 1,3-dinitrosohexahydropyrimidine 169b to give the 2-hydroxybenzyl derivatives 170a and 170b in 88 and 76% yields, respectively (Eq. 78). Monobenzylations of 169a and 169b with benzyl bromide can be accomplished in aqueous sodium hydroxide solutions with catalytic amounts of triethylbenzylammonium chloride to give the corresponding adducts 171a and 171b.



(78)

169a: n = 2
b: n = 3

170a: n = 2; R = φCHOH
b: n = 3; R = φCHOH
171a: n = 2; R = φCH$_2$
b: n = 3; R = φCH$_2$

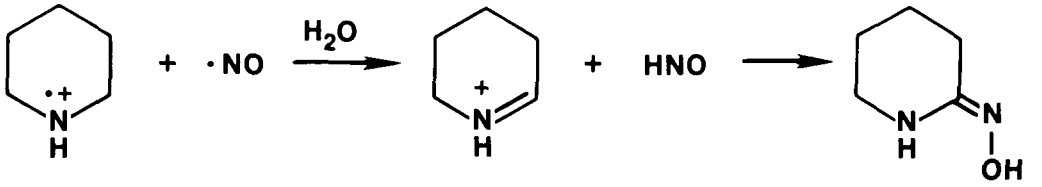
IX. PHOTOCHEMISTRY OF NITROSAMINES

The kinetics and mechanism of nitrosamine and nitrosoamide photochemistry have been studied extensively and are the main subject of two review articles.[61,64] We will limit ourselves to a brief introduction to this subject. Photolysis of nitrosoamides generates amido radicals together with NO. In the presence of dilute acid, N-nitrosamines undergo photoreaction to generate primarily nitric oxide and aminium radicals ($R_2NH\cdot+$). Recently Chow et al.[204] reported that the decomposition of nitrosamines to aminium radicals occurs from the singlet excited state, and it is too rapid for intersystem crossing to the triplet state to occur. Basically, photoreaction of nitrosamines involves the chemistry of an aminium radical in the presence of nitric oxide. Several competing processes take place in the photochemistry of nitrosamines which determine the fate of the aminium ion. The main types of processes in photoreactions are photoelimination, photoreduction and photoaddition reactions. Photolysis of nitrosopiperidine 123 to the piperidinium radical 172 under different conditions gives different product patterns representative of the different photoprocesses. In the case of N-nitrosoamino acids, oxidative decarboxylations occur.[205]

1. Photoelimination

The photoelimination process in water, or in other poor hydrogen atom-donating solvents, is the favored reaction pathway. The piperidinium radical 172 undergoes radical disproportionation to the tetrahydropyridine 173 and HNO. Nucleophilic attack of HNO on 173 gives the photoelimination product 174 (Eq. 79). The tetrahydropyridine 173 and HNO also polymerize to isotripiperidine and $H_2N_2O_2$, which are relatively stable compounds.[61,206] The production of HNO is only a postulated pathway, and it involves the initial formation of a nitrosamine - acid complex, followed by a photochem-

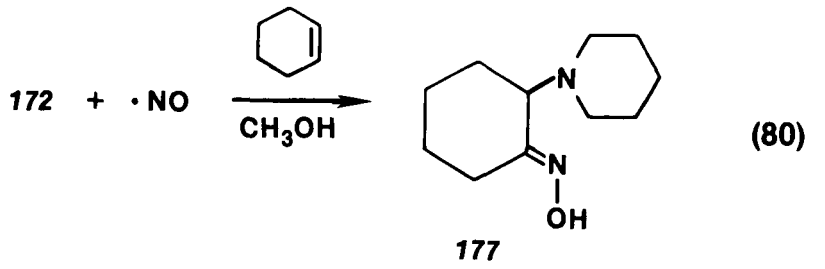
ical homolysis of the N-N bond. However, there is mounting evidence that photolysis does occur in neutral media,[207] and thus, the existence of hyponitrous acid is questionable, along with its ability to add across a double bond, i.e. 173.



172 173 174

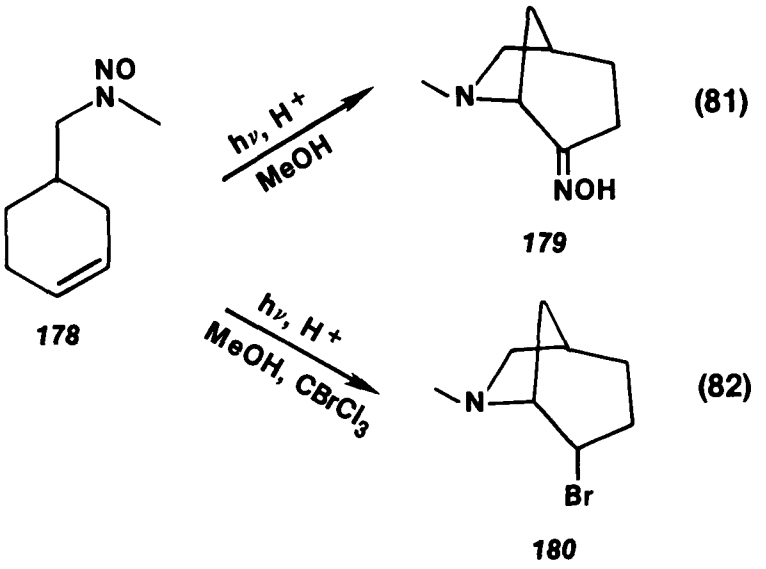
2. Photoreduction

Photolysis of nitrosopiperidine 123 in the presence of cyclohexene in acidic media results in addition of 172 and NO radicals across the double bond. The tautomeric oxime 177 is isolated in this reaction (Eq. 80).



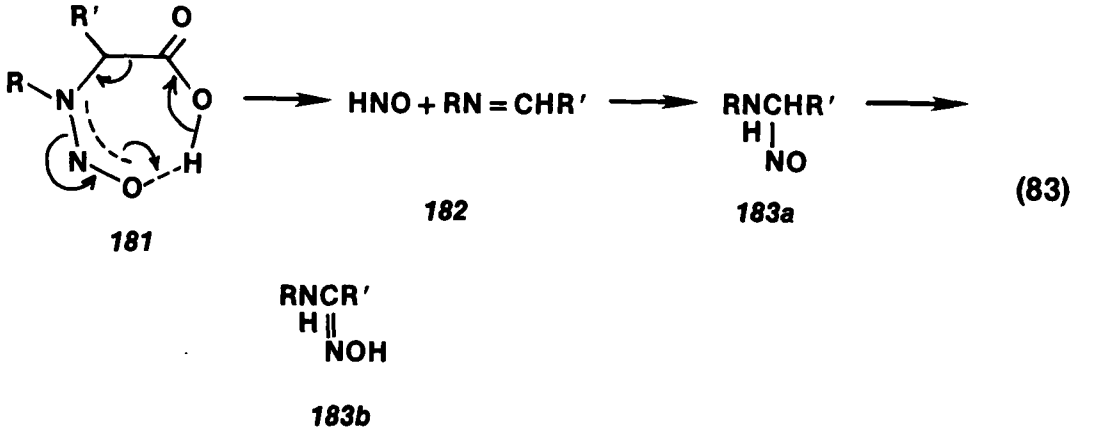
177

In organic synthesis, nitrosamine photoaddition is the most useful of all the photo processes mentioned. It is a very practical method for preparing nitrogen-containing compounds from olefins, as 1:1 adducts are obtained (Eq. 80). Intramolecular cycloadditions to form azacyclic and azabicyclic compounds have been carried out successfully.[61] For example, photolysis of nitrosamine 178 in acidic methanol gives the azabicyclic oxime 179 (Eq. 81). Photolysis of 178 in the presence of bromotrichloromethane gives endo-6-bromo-2-azabicyclo[3.2.1]octane 180 (Eq. 82).



3. Oxidative Decarboxylation

α-Nitrosamino acids are photosensitive due to the proton donating ability of the α-carboxyl group. The reaction pathway falls in the category of a photoelimination. The photolabile compound may require the Z-configuration 181 for maximum hydrogen bonding. Upon loss of NO radical and carbon dioxide, the alkylideneimine 182 is formed. The addition of HNO to 183 gives the C-nitroso compound 183a or the tautomeric oxime 183b.



X. CONCLUSIONS

This survey was intended to give the reader an insight into the frontiers of nitrosamine chemistry. It is our purpose to stress that sound organic chemical knowledge of these compounds is important in the unravelling of their mechanism of action in carcinogenesis. It is also important to note that N-nitrosamine can be useful reagents in organic synthesis. The preparation of these compounds can be achieved in high yields *via* numerous routes, and thus they are readily available reagents. N-Nitrosamines are widely used in "umpolung" chemistry as synthetic equivalents of α-secondary amino and α-primary amino carbanions. The importance of α-oxidized nitrosamines in carcinogenesis has stimulated a great deal of synthetic research into methods for their preparation, and has led to the discovery of some interesting aspects of nitrosoimminium ion chemistry. The chemistry of β-, γ- or ω-oxidized nitrosamines has attracted much attention due to metabolic and environmental concerns. Solvolysis reactions of these compounds have taught us much about neighboring group participation by the nitroso group. Base-induced fragmentation of β-hydroxy and β-oxonitrosamines lead to *retro*-aldol and *retro*-Claisen type cleavages. These reactions explain the degradation of long-chain nitrosamines to lower alkyl compounds. Although the chemistry of β-ketonitrosamines is still in the early stage of development, these compounds have proven to be potentially good anionic synthons with multiple activating groups. The development of new syntheses of vinylic nitrosamines or N-nitrosoenamines has sparked renewed interest in the chemistry of these compounds. These are versatile synthetic intermediates for they can interact effectively with nucleophilic as well as electrophilic reagents. N-Nitrosoenamines also undergo interesting oxidation as well as photochemical reactions. The chemistry of N-nitroso-N,O-dialkylhydroxylamines is virtually a

wide-open field for chemical research. Although many aspects of their basic chemistry are known, i.e. decomposition, hydrolysis, reduction, their application as synthetic intermediates remains to be explored. Some attention has been given to the interaction of the nitroso oxygen of nitrosamines with electrophilic reagents. Oxygen alkylation converts the nitrosamine into an electrophilic intermediate. Several biochemical studies have attempted to relate the nucleophilic character of the oxygen to the formation of alkylating agents active toward cellular nucleophiles. Nitrogen heterocycles with multiple nitroso groups have been examined in the study of aldehyde-ammonia adducts and in the search for new energetic materials. The synthetic use of these compounds as anionic reagents has begun to receive some attention. Photochemical research of N-nitrosamines and N-nitrosamides has been actively pursued for more than 20 years. A great deal of information has been accumulated on the kinetics and mechanism of the photoreactions involving these types of compounds. We have only touched upon the nitrosation of amides to give the corresponding nitrosoamides, these compounds include nitrosoureas, nitrosocarbamates, nitrosocarboxylic acid amides, and nitrosoamidines. Since they are structurally different from N-nitrosamines, their chemical properties differ a great deal. A separate review article dealing strictly with N-nitrosamides would be necessary if a fair survey of their chemistry were to be given.

ACKNOWLEDGEMENT

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