CHAPTER-1

INTRODUCTION

1.1 Brief Introduction

In organic chemistry, "nitroso" refers to a distinct functional group where nitric oxide (NO) is attached to an organic moiety. Organic nitroso compounds can be categorized as *C*-nitroso compounds, *S*-nitroso compounds, *O*-nitroso compounds and *N*-nitroso compounds (Figure 1.1) [1]. The chemical and biological significance of *C*-, *S*- *O*- and *N*-nitroso compounds are discussed below as separate section.

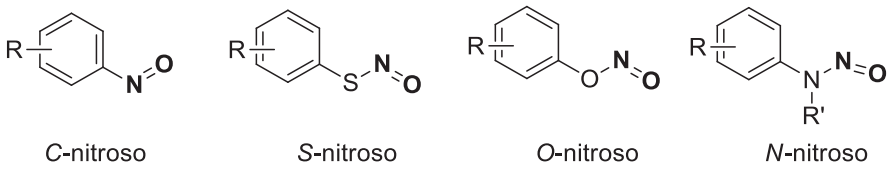
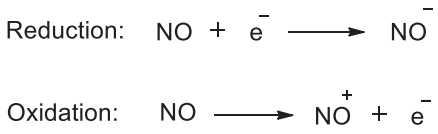


Figure 1.1 *C, S, O, N*-nitroso compounds.

On the other hand, nitrosyls refers to a compound in which NO moiety is attached to non-organic compounds, for example, metal centre (i.e. metal-NO) or halogen centre (nitrosyl chloride, Cl-N=O). Nitric oxide is a stable radical, having an unpaired electron which gives hyponitrite anion upon reduction while oxidation yields the nitrosonium cation (Scheme 1.1) [2].



Scheme 1.1 Reduction and Oxidation of nitric oxide.

Nitric oxide serves as ligand in metal complexes, known as metal nitrosyl complexes, where NO is bonded to a metal centre in two different ways, as NO^+ and NO^-. In general, it is assumed that NO^+ coordinates linearly (i.e. M-N=O) with

bond angle 180°, whereas NO^- forms a bent geometry, with bond angle 120°. Metal nitrosyl complexes have gained considerable interest in the past two decades owing to their biological significances. For example, metal nitrosyl compound sodium nitroprusside is used as a medicine to lower blood pressure in human beings (Figure 1.2) [3].

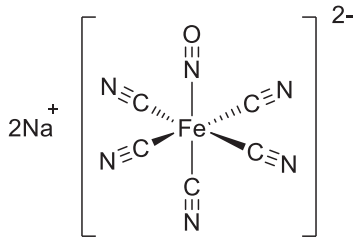
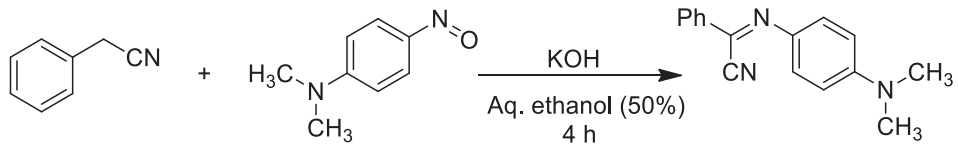


Figure 1.2 Biological significant metal nitrosyl compound sodium nitroprusside.

1.2 *C*- Nitroso Compounds

In 1874, the first well known example of *C*-nitroso compound i.e. *p*-nitroso dimethylaniline, was reported by Baeyer from the reaction of nitrosyl chloride with diphenyl- mercury. Later, in 1899 Elrich and Sachs disclosed the synthetic utility of *p*-nitroso dimethylaniline in organic synthesis. They have demonstrated the preparation of *N*-phenylimines by reacting *p*-nitroso dimethylaniline with active methylene compound 2-phenyl acetonitrile in the presence of a base. Later, this reaction is known as Ehrlich-Sachs reaction (Scheme 1.2) [4, 5].



Scheme 1.2 Ehrlich-Sachs reaction.

In general, the monomeric nitroso-compounds are blue (aliphatic) or green (aromatic) in colour whereas the dimers are colourless (Figure 1.3). The monomeric aliphatic RC-NO compounds display N-O bond lengths and C-N-O angles in the range of 1.1-1.22 Å and 103-121° respectively [6]. The dimeric compounds display N-N bond distances of 1.22-1.33 Å, which are significantly shorter than a formal N-N single bond distance of 1.42 Å; this indicates double-bond character is present [6]. On the other hand, these compounds can be detected through UV spectroscopy where the band around 6300-7900 Å was observed in all monomeric nitrosamines. The characteristic bands of aliphatic *C*-nitrosamines were identified around 2700-2900 Å and <2200 Å. Bathochromic (towards longer wavelength) or Hypsochromic (towards shorter wavelength) shift will depend on the nature of the substitutents, *i.e.* electron donating or withdrawing, present on the aryl ring [6].

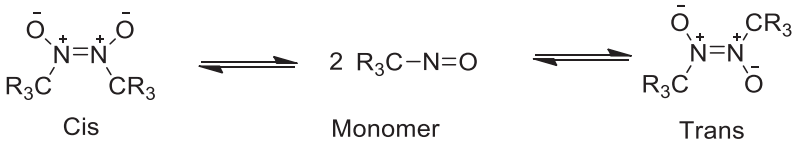
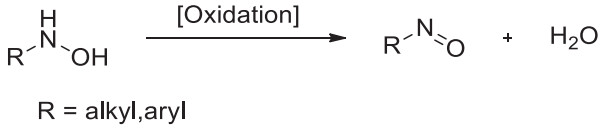


Figure 1.3 Dimerization of *C*- nitroso compounds

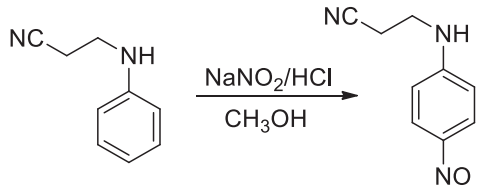
When the nitroso group is attached to primary or secondary carbon, they were found unstable and tautomerise to oxime formation. Therefore, it is important to have tertiary carbon atom for the synthesis of stable *C*-nitroso compounds [7]. The successful synthesis of *C*-nitroso compounds has been achieved through several synthetic methods including oxidation reaction, nitrosation, Fischer-Hepp rearrangement, photochemical reaction, etc. and few of them are described below.

Alkyl or aryl *C*-nitroso compounds are typically prepared by the oxidation of hydroxylamine in the presence of various oxidants including ferric chloride [8], acidified dichromates (potassium dichromate and sulphuric acid) [9], periodic acid [10], etc. (Scheme 1.3).



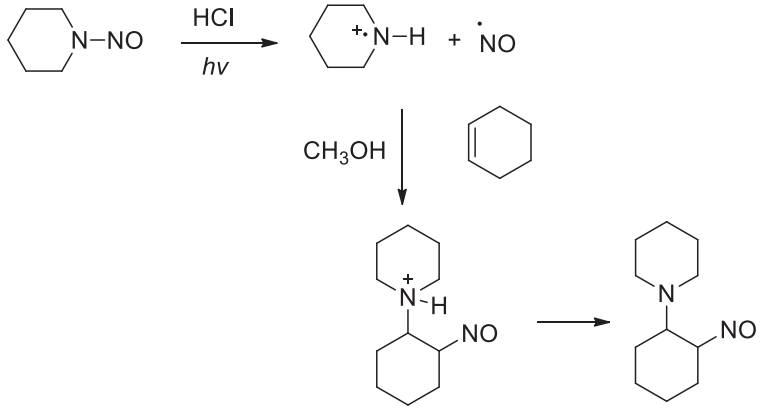
Scheme 1.3 Synthesis of *C*-Nitrosamines *via* oxidation

On the other hand, nitroso group can be introduced into the aryl ring, for example in aromatic amines, phenols, ethers, heterocyclic ring systems such as pyrroles, pyrazoles, imidazoles, indolizines, indoles, etc., using different nitrosating agents [7]. The different nitrosating sources are sodium nitrite with different acids (HCl, CF_3COOH, Caro's acid and CH_3COOH), alkyl nitrite (*iso*-amyl nitrite), nitrogen oxides (N_2O_3, N_2O_4) and nitrosyl chloride (NOCl) [4]. In some cases, rearrangement of *N*-nitroso aniline provides aryl *C*-nitroso compounds in the presence of hydrochloric acid, which is known as Fischer-Hepp rearrangement (Scheme 1.4). For example, the nitrosation of *N*-(2-cyanoethyl) aniline in methanolic sodium nitrite/HCl leads to the *para*-nitroso-*N*-(2-cyanoethyl) aniline [11].



Scheme 1.4 Synthesis of *para*-nitroso aniline.

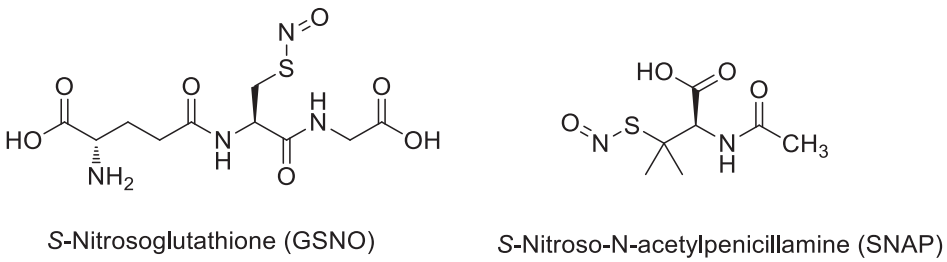
Nevertheless, the researchers were also focussed on the photochemical route for the synthesis of different *C*-nitroso compounds (Scheme 1.5). *N*-Nitroso compounds can be dissociated and added across the C-C double bonds in the presence of photo light. This reaction yields various alkylnitroso compounds. For instance, *N*-nitrosopiperidine dissociates to aminium radical and nitric oxide radical in the presence of light which is added to cyclohexene. This photochemical reaction results into the formation of cyclohexyl *C*-nitroso compound [12].



Scheme 1.5 Synthesis of *C*-nitrosamines *via* photochemical route.

1.3 *S*-Nitroso Compounds

S-Nitroso compounds (RSNOs) received great attention in biological science, since they act as NO donors [13]. For example, thionitrites such as *S*-nitrosoglutathione (GSNO) and *S*-nitroso-*N*-acetyl penicillamine (SNAP) (Figure 1.4) has received much attention in biochemistry since they act as a signalling molecule in living systems [13, 14]. GSNO and NO concentrations in the human body regulate the respiratory function and anti-inflammatory responses in the respiratory tract [13, 14].

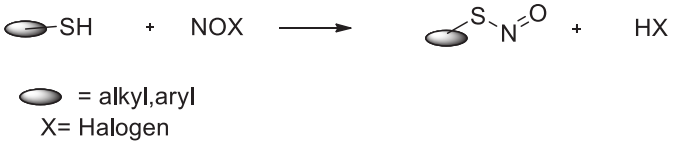


S-Nitrosoglutathione (GSNO) *S*-Nitroso-N-acetylpenicillamine (SNAP)

Figure 1.4 *S*-nitroso containing biological compounds.

In general, *S*-nitrosothiols are green, red or pink in color and found stable up to 37 °C. In the infrared spectra (IR), the N-O and the C-S bond stretching frequencies were identified at 1480-1530 cm^{-1} and 600-730 cm^{-1} respectively. The UV-visible spectra show bands in the 330-350 nm region (n_o-π^*) and also at 550-600 nm (n_N-π^*). These observations are useful for the monitoring the decomposition of *S*-nitrosothiols in biological systems [13].

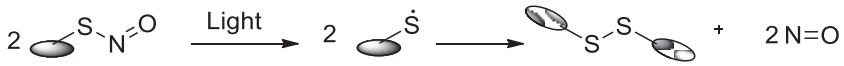
Nitrosation of thiols, both aliphatic as well as aromatic, is achieved using different source of nitrosating agents including $NaNO_2/H^+$, nitrogen oxides, nitrosyl chloride, organic nitrites (e.g. *tert*. butyl nitrite), etc. *S*-nitrosation is a very reactive process and the addition of nitrosating source to the acidic solution of respective thiol resulting into the transient red colour which indicates the formation of *S*-nitrosothiol (Scheme 1.6) [15].



Scheme 1.6 Synthesis of nitrosothiols.

Nitrosothiols are mostly unstable species since S-NO bond is labile which undergoes decomposition to disulphide under light by releasing nitroso (NO) group.

The RS-NO bond (31-32 kcal/mol) is relatively weaker than S-S bond i.e. disulfide (65-66 kcal/mol) resulting in short life span (Scheme 1.7) [16, 17]. *S*-Nitrosothiols exhibit *cis-trans* isomerisation with an S-N rotation barrier of >10kcal/mol indicates of partial double-bond character of the S-N linkage (Figure 1.5) [17, 18].



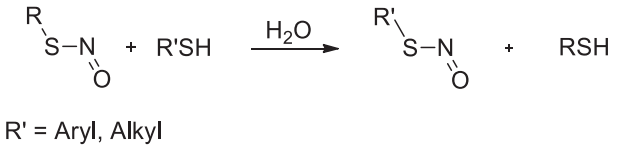
Scheme 1.7 Decomposition of *S*-nitrosothiols.

Figure 1.5 *Cis-trans* isomerisation of RSNOs.

On the other hand, the stabilities of RSNOs depends upon on R group that is attached with sulfur, generally it follow R=3 °C > R=2 °C > R=1 °C [16]. In this context, aromatic nitrosothiols (ArSNOs) are more stable than aliphatic nitrosothiols. M. Flister *et al.,* reported that in *cis*-PhSNO, the -SNO group is found to be perpendicular with the aromatic ring, with the C-C-S-N dihedral angle ~90°. In the *trans*-ArSNOs seems to have even more tilted -SNO group with C-C-S-N dihedral in the 85°-50° range (Figure 1.6) [17, 18].

Figure 1.6 Variation in dihedral angle of *S*-nitrosothiols.

Among the different reactions of *S*-nitrosothiols, transnitrosation is well known in which the transfer of nitrosonium ion (NO^+) from one thiol to another thiol takes place without the generation of nitric oxide (Scheme 1.8) [19].



Scheme 1.8 Transnitrosation *via* thiols.

1.4 *O*-Nitroso Compounds

O-Nitroso compounds are based upon the chemical structure R-ONO, they are known as alkyl nitrites [20]. Alkyl nitrites are relatively stable liquids with low or medium boiling points (17-105 °C) and generally soluble in most of the solvents. There are three main types of nitrites (Figure 1.7), which are basically used in organic chemistry: *n*-pentyl nitrite (*n*-amyl nitrite) [21] **1a**, the *iso*-pentyl nitrite [21] **1b** and the *t*-butyl nitrite (*t*-BuONO or TBN) **1c** [22].

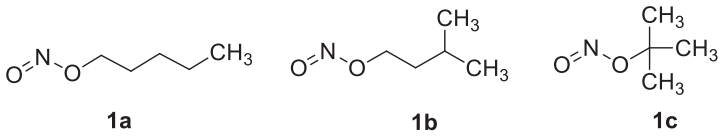
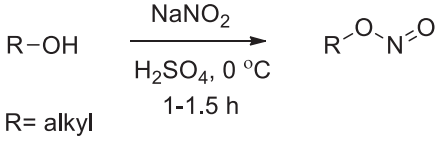


Figure 1.7 Different alkyl nitrites.

Alkyl nitrites are commercially available but they can be easily prepared from the corresponding alcohols and sodium nitrite in sulfuric acid solution (Scheme 1.9) [20].



Scheme 1.9 Synthesis of alkyl nitrites.

Various applications of alkyl nitrites are well explored in organic synthesis. Generally, alkyl nitrites were found efficient alternative to $NaNO_2$ and used in many organic transformations such as diazotization of anilines, nitration of phenols, arylboronic acid and acetanilide, oxidation reactions, etc [20, 21, 22].

1.5 *N*-Nitroso Compounds

N-Nitrosamines are the chemical compounds with direct N-N bond in which nitroso group is directly attached to the amine. The preparation of *N*-nitrosamine was first described by Geuther in 1863. He demonstrated the synthesis of *N*-nitroso dimethylamine by the reaction dimethylamine hydrochloride with sodium nitrite. Later, in 1956 the tumorigenic property of *N*-nitroso dimethylamine (NDMA) was explored by Magee and Barnes [23, 24].

Nitrosamines represent a family of potent carcinogens which are readily formed from ubiquitous secondary amines and nitrite [23, 24]. They possess unique carcinogenic and mutagenic properties which gathered a great attention from biological perspective. Most of the *N*-nitrosamines are carcinogenic and induces cancer in animals [23, 24]. Naturally, *N*-nitroso compounds exist in latex products such as balloons, foods, cosmetics and natural products [23].

On the other hand, *N*-nitrosamines are the versatile class of organic compounds which has wide applications in different fields. *N*-Nitroso dimethylamine (NDMA) is an industrial by-product used in the preparation of rocket fuel 1,1-dimethylhydrazine [25]. They are widely used as reactive intermediates which can be further transformed to obtain valuable compounds such as dialkylhydrazines, nitramines, sydnones and sydnoneimines. Recently, the nitroso group has emerged as directing group for

activation of inert C-H bond which gave variety of *ortho*-functionalized aniline compounds.

1.5.1 Properties and Spectroscopic Discussion

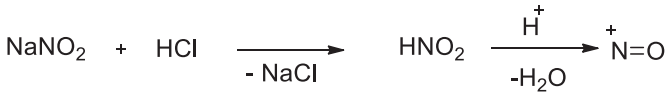
The aliphatic nitrosamines are yellow or yellow-green and white in color while aromatic nitrosamines appear as yellow or reddish-yellow. Both *N*-nitrosamines exist in liquid as well as solid state. The solid nitrosamines are found to be more stable than the liquid ones. The stability of these compounds depending upon the substituents attached to the amine nitrogen. Nevertheless, the temperature as well as pH also affects the stability of these compounds [26, 27]. They are stable in the dark, in neutral or alkaline solution but are less stable in more acidic solutions or in light. They are partially soluble in water but soluble in common organic solvents such as alcohols and halogenated hydrocarbons. The densities of the majority of nitrosamines are usually in the range 0.9 to 1.2 gcm^{-3} [26, 27]. All *N*-nitrosamines exhibit three relatively intense bands in the infrared spectra. From which the two absorption bands in ranges 1410 to 1350 cm^{-1} and 1320 to 1160 cm^{-1} corresponds to N-N vibrations whereas the band 1095 to 1045 cm^{-1} corresponds to N=O stretching [26].

The nitrosamine (N-N=O) exists in two isomers (rotamers), i.e., *syn* and *anti.* This is due to the delocalization of lone-pair on nitrogen atom with N=O bond in *N*-nitrosamines. Two isomers can be easily detected and distinguished through NMR spectroscopy (Figure 1.8) [28].

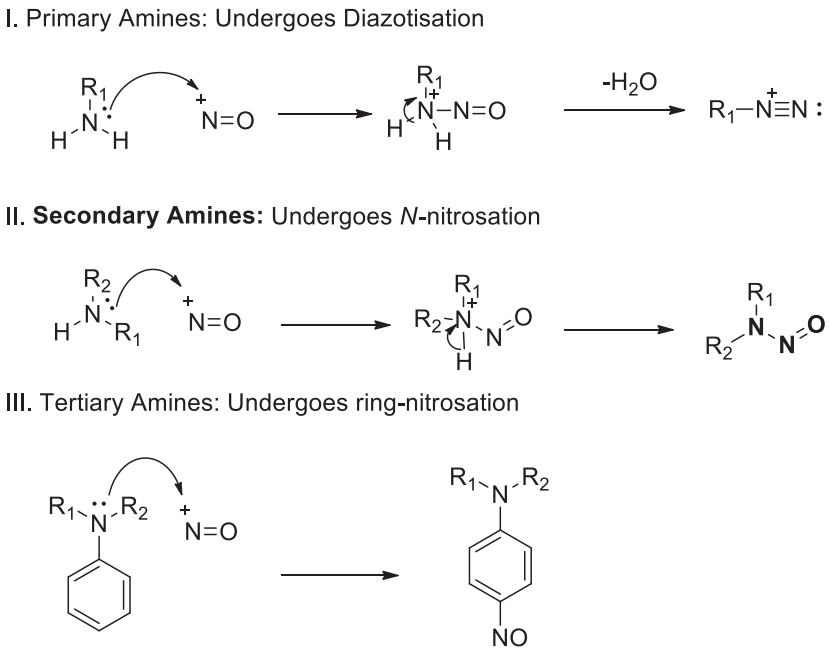
Figure 1.8 Restricted rotation of *N*-nitrosamines.

1.5.2 Synthesis of *N*-nitrosamines

Typically, *N*-nitrosation of secondary amines is achieved using sodium nitrite and aqueous hydrochloric acid or H_2SO_4. The reaction of sodium nitrite with acid generates the nitrosonium ion (Scheme 1.10) [29]. However, under the nitrosation condition, primary amines undergo diazotisation reaction while alkyl tertiary amines do not react. On the other hand, aromatic tertiary amines proceed for the ring nitrosation (Scheme 1.11).



Scheme 1.10 Generation of nitrosonium ion**.**



Scheme 1.11 Reactions of different amines with nitrosonium ion.

N-Nitrosamines have vast applications in synthetic organic chemistry (Figure 1.9). *N*-nitrosamines undergo oxidation, reduction, rearrangement, cyclization,

photochemical reactions, etc [29]. Some transformations involving nitrosamine is discussed below.

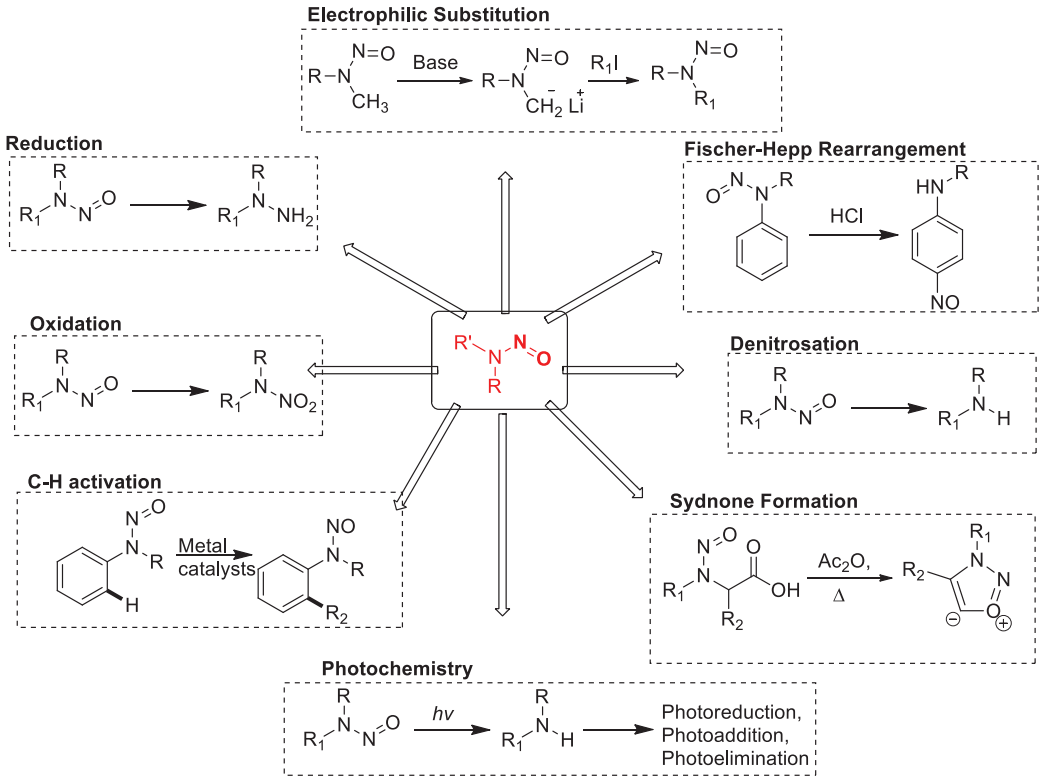
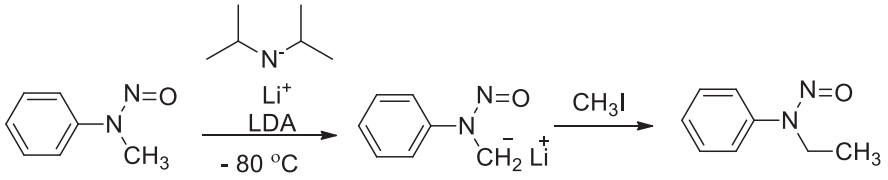


Figure 1.9 Applications of *N*-nitrosamines**.**

1.5.3 Electrophilic Substitution at the α-carbon of *N*-Nitrosamines

Electrophilic functionalization of α-carbon in secondary amines represents an important problem in organic synthesis. Generation and stabilization of carbanion at α-carbon of secondary is difficult due to the presence of adjacent nitrogen atom. In this context, *N*-nitrosation facilitates the formation of carbanion with strong base such as *n*-BuLi and LDA, because carbanion is stabilized through resonance. This lithiated compound undergoes electrophilic substitution with various electrophiles and provides valuable synthetic intermediates. [30, 31]. For example, *N*-nitroso *N*-ethylaniline was

prepared from *N*-nitroso *N*-methylaniline using lithium diisopropylamide (LDA) and iodomethane (Scheme 1.12) [30].



Scheme 1.12 Electrophilic substitution at α-carbon of *N*-nitrosamine.

Similarly, electrophilic substitution of lithionitrosamine has been demonstrated with different electrophilic reagents such as disulfides, diselenides, trimethylchlorosilane and trimethylchlorostannane (Figure 1.10) [32, 33].

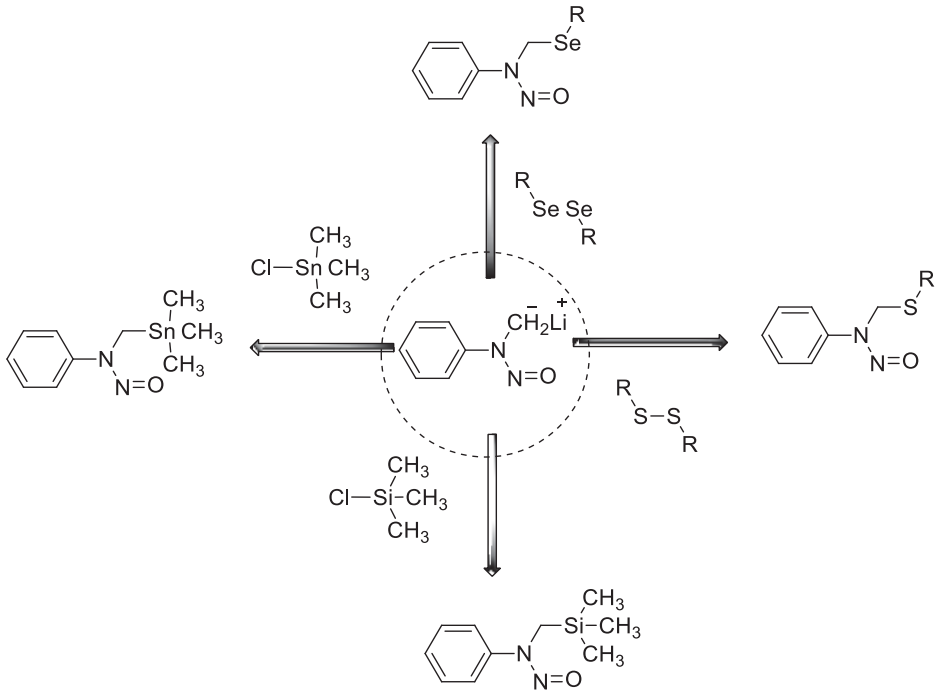
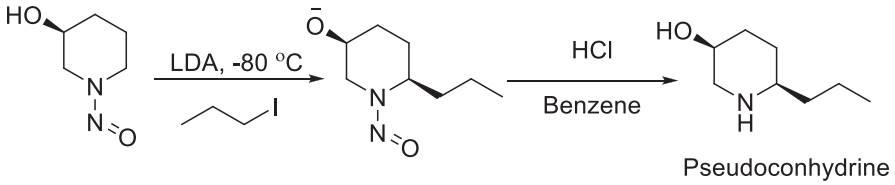


Figure 1.10 Different lithionitrosamine mediated electrophilic substitution.

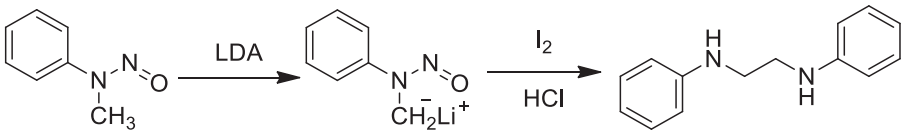
Synthesis of epimer of naturally occurring alkaloid Pseudoconhydrine was demonstrated using *N*-nitrosation protocol [32]. Lithiation of *N*-nitroso 3-piperidinol

with LDA provides α-lithiated piperidinol which undergoes subsequently undergoes *C*-alkylation and yields the desired alkaloid epimer as shown Scheme 1.13.



Scheme 1.13 Alkylation of *N*-nitrosamine through α-lithiation.

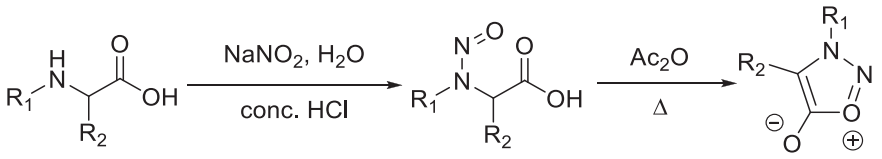
In addition, it was also found that *α*-halo nitrosamines are obtained on reaction of metalated nitrosamines with chlorine, bromine and iodine but they are unable to isolate. In case of iodine, it leads to oxidative dimerization (Scheme 1.14) [31, 32].



Scheme 1.14 Oxidative coupling *via* lithionitrosamine.

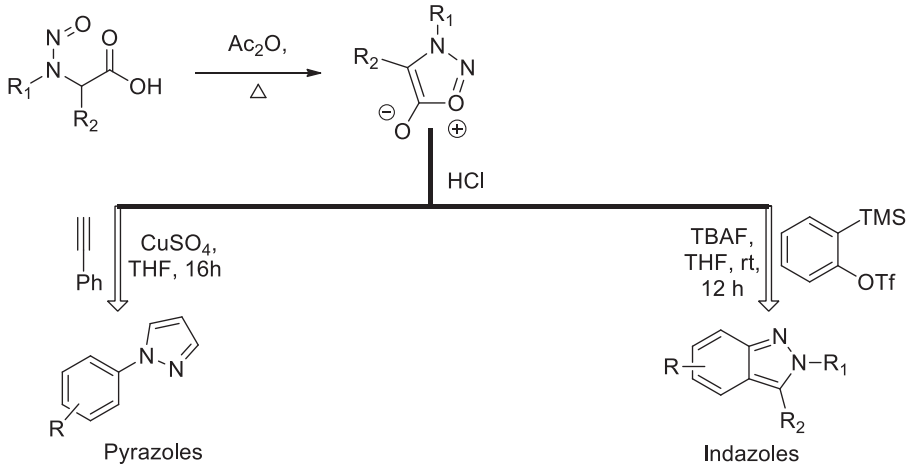
1.5.4 Sydnone formation

Sydnones are a class of heterocycles known as mesoionic compounds. They have gained significant interest due to their biological activities such as antibacterial, anti-inflammatory and antineoplastic agents [34]. Azarifar *et al*., have synthesized sydnones through reaction of secondary amino acids with sodium nitrite and hydrochloric acid with the acetic anhydride under aqueous conditions (Scheme 1.15) [35, 36]. The formation of the sydnones relies on the nucleophilic nature of the oxygen of the nitroso group and takes place in the presence of the acetic anhydride. The usage of trifluoroacetic anhydride (TFAA) has superseded over the use of acetic anhydride, largely due to an increased rate of cyclization.



Scheme 1.15 Classical method for assessment of sydnones.

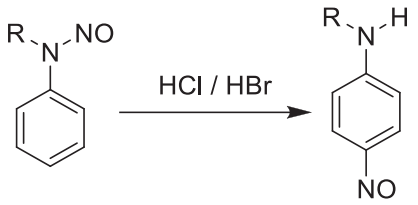
Sydnones were also used as starting materials for the preparation of biologically relevant indazole and pyrazole heterocycles (Scheme 1.16) [37, 38]. Many reviews have been published on the synthesis as well as physical, chemical and biological properties of different sydnones.



Scheme 1.16 Applications of sydnones in synthesis of heterocycles.

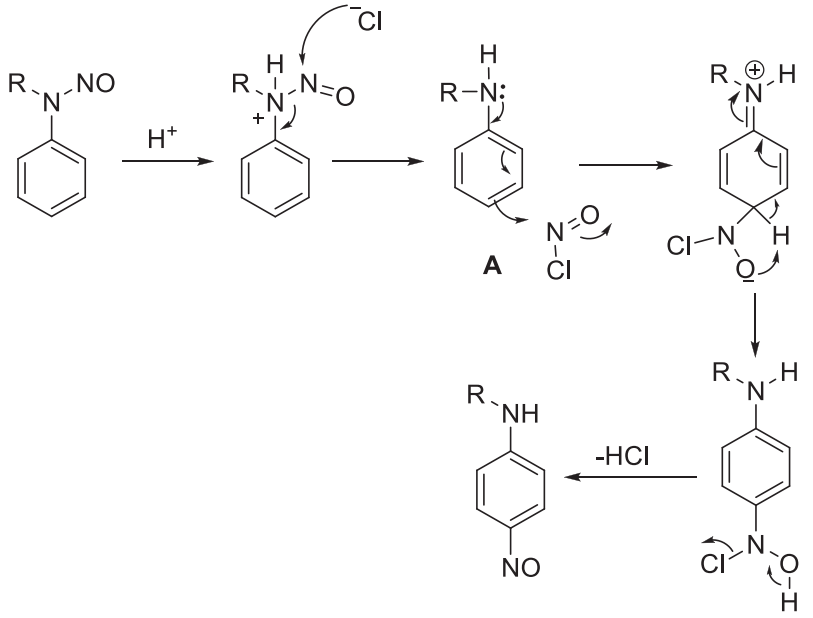
1.5.5 Fischer-Hepp rearrangement

Fischer-Hepp rearrangement was reported in 1886 which involves conversion of *N*-nitroso aromatic amines into *p*-nitroso aromatic amines in the presence of hydrochloric or hydrobromic acid (Scheme 1.17) [39]. Instead of HCl or HBr, sulphuric acid can also be used, but the reaction provides low yield. The specificity of HCl and HBr in the Fischer-Hepp rearrangement, unlike other acids, can be attributed to the formation of nitrosyl halide which actively participates in the reaction [39, 40].



Scheme 1.17 Fischer-Hepp rearrangement.

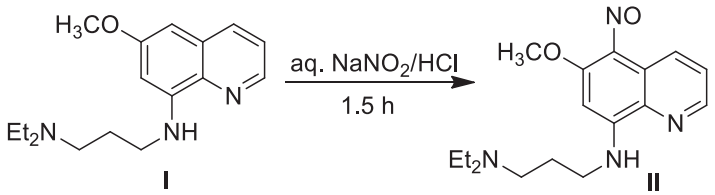
The mechanism for the rearrangement of *N*-alkyl *N*-nitrosoaniline is given below. The reaction of *N*-nitrosamine with HCl leads to the generation of nitrosyl chloride and *N*-alkyl aniline. The lone pair of electrons in amine (**A**) undergoes delocalization and allows the electrophilic nitrosation at the *p*-position. Further, the re-aromatization followed by subsequent HCl elimination provides *p*-nitroso *N*-alkyl *N*-aniline (Scheme 1.18) [40].



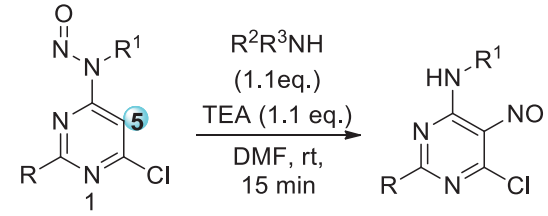
Scheme 1.18 Mechanism for Fischer-Hepp rearrangement.

Fischer-Hepp rearrangement reaction is very useful tool for the synthesis of *p*-nitroso aryl amines. Quinoline derivative (**I**) was nitrosated in the presence of aqueous sodium nitrite and HCl which undergoes rearrangement to form *C*-nitrosamine product

II (Scheme 1.19) [41]. Similar to quinoline derivatives, 5-nitroso pyrimidines derivatives were also synthesized using Fischer-Hepp rearrangement (Scheme 1.20) [42].



Scheme 1.19 Synthesis of *C*-nitroso of quinoline derivative **I**.



R^1= H, Bn
R = SMe, Bn
R^2 =H, R^3= alkyl

Scheme 1.20 *C*-nitrosation of pyrimidines.

1.5.6 Reduction of *N*-Nitrosamines

Hydrazine derivatives are widely used in the pharmaceutical, agricultural and dye industries. On the other hand, arylhydrazines are the precursors for the synthesis of heterocyclic compounds such as indoles, pyrazines, pyrazoles, etc. [43]. Indeed, hydrazines are the direct starting materials for the synthesis of biologically relevant hydrazides and hydrazones (e.g. atazanavir [44] and benserazide [45]) (Figure 1.11).

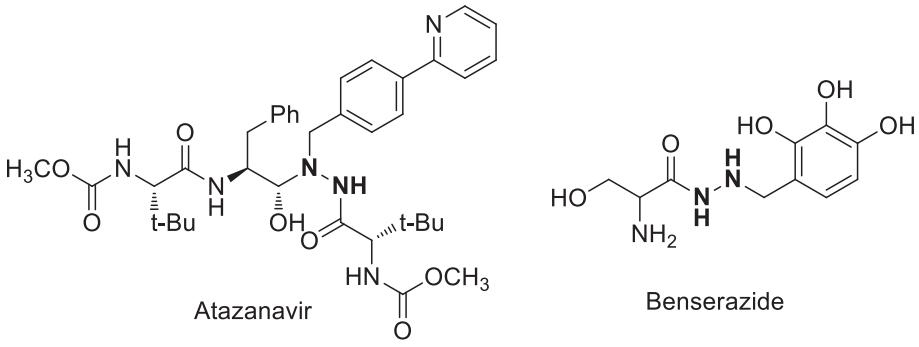
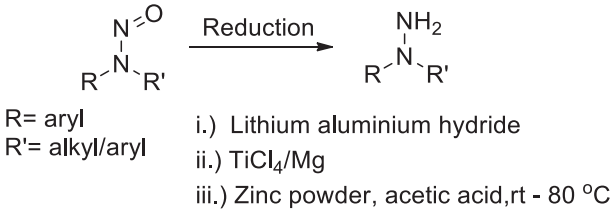


Figure 1.11 Hydrazine-based active pharmaceutical ingredients.

The reduction of *N*-nitroso group provides valuable *N*,*N*-disubstituted hydrazine. Considerable attention has been paid for the reduction of the nitroso compounds using different metal based reducing agents such as Lithium aluminium hydride [46], low-valent titanium reagent [47] and Zn/AcOH [48]. Among them, zinc mediated reduction is widely used for the reduction of *N*-nitrosamines (Scheme 1.21). Broad discussion on the reduction of *N*-nitrosamines is described in chapter 5.

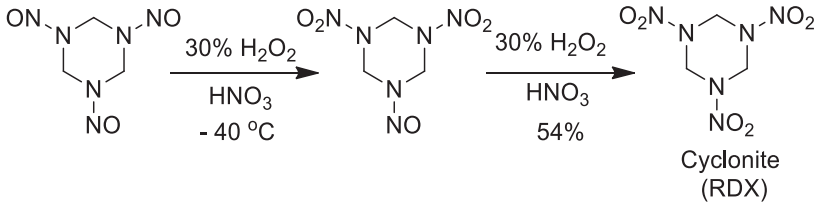


Scheme 1.21 Reduction of *N*-nitrosamines.

1.5.7 Oxidation of *N*-Nitrosamines

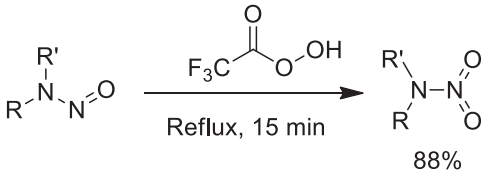
N-Nitrosamines are the precursor for the preparation of *N*-nitro-amines which is achieved through oxidation. Literature survey revealed that the variety of oxidising agents such as hydrogen peroxide with nitric acid, nitric acid and ammonium persulfate and trifluoroperacetic acid can be used for the oxidation reaction [49, 50, 51]. For, instance, the powerful explosive, 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX) is

prepared through oxidation of 1,3,5-trinitroso-1,3,5-triazacyclohexane using hydrogen peroxide (30%) and nitric acid (99%) (Scheme 1.22) [52].



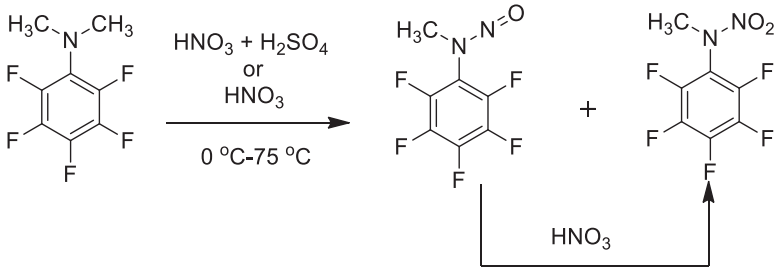
Scheme 1.22 Oxidation of *N*-nitrosamines with hydrogen peroxide and nitric acid.

Trifluoroperacetic acid found very efficient for the oxidation of *N*-nitrosamine to *N*-nitramine. This method provides high purity of the products in quantitative yields (Scheme 1.23) [51].



Scheme 1.23 Oxidation of *N*-nitrosamines with trifluoroperacetic acid.

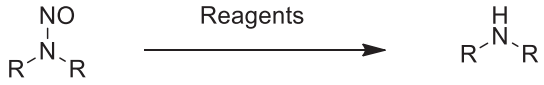
Dealkylative *N*-Nitration of *N*,*N*-dialkyl perfluoroarylamines with HNO_3/H_2SO_4 results *N*-nitroso and nitro derivative (Scheme 1.24). The oxidation of *N*-nitroso with nitric acid alone leads to the corresponding *N*-nitro compound [53].



Scheme 1.24 Synthesis of *N*-nitro amine using HNO_3/H_2SO_4.

1.5.8 Denitrosation of *N*-Nitrosamines

Denitrosation of *N*-nitrosamine is an important process not only in organic synthesis but also in biological sciences (Scheme 1.25) [54, 55, 56]. From the discovery of carcinogenicity and mutagenicity of nitrosamines, significant research has been focused on the quantitative determination of nitrosamines present in food and other human care products. Reliable methods for the determination of volatile nitrosamines are well-established using different analytical techniques like GC-MS [54]. However, only limited methods were developed for measuring non-volatile nitrosamines. Chemical denitrosation is one of the reliable methods used for the quantification of total *N*-nitroso compounds present in various products [54]. During denitrosation, the evolved nitric oxide (NO) is oxidized with ozone to form electronically excited nitrogen dioxide which emits a photon while decays back to the ground state and that is measured by a photomultiplier tube [54]. The common reagents, HBr in glacial AcOH, freshly prepared HI from NaI and H_2SO_4, and copper chloride in HCl are widely used in the determination of total *N*-nitroso compounds (Scheme 1.25) [54].



Scheme 1.25 Chemical denitrosation of *N*-nitrosamine.

Denitrosation reaction is also received considerable attention in organic synthesis. As mentioned earlier, *N*-nitrosamines are used as starting materials, masking groups, directing groups, etc. in organic synthesis. While many chemical reactions employ *N*-nitrosamine intermediates, they are also often formed as major side products. For instance, *N*-nitrosamine is obtained as the major side product during the synthesis

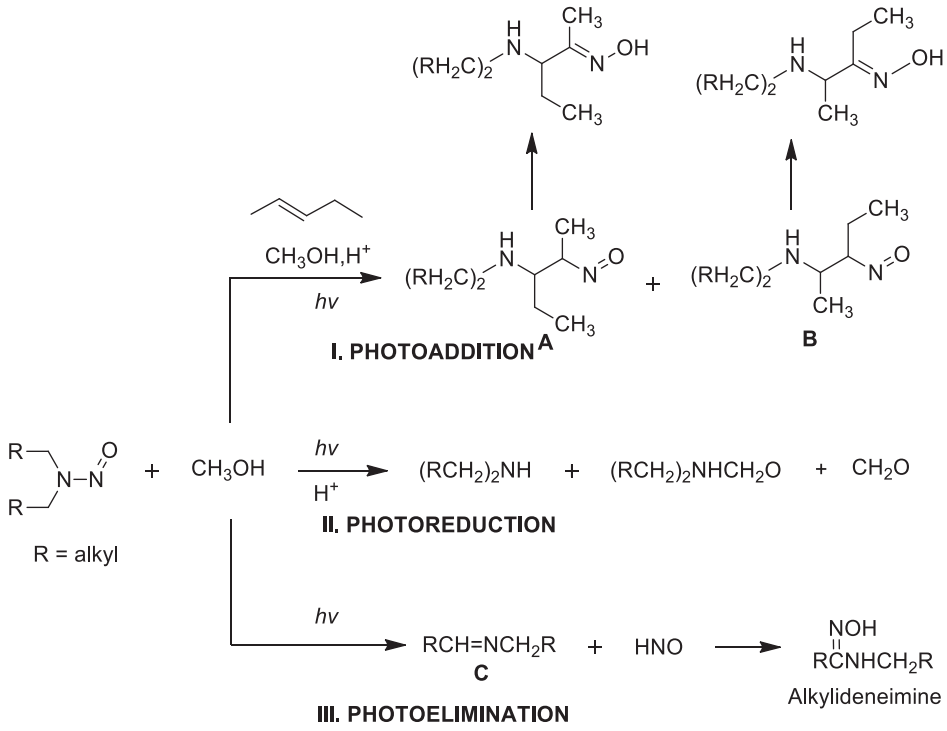
of an important herbicide, pendimethalin (Figure 1.12) [55, 56]. Pendimethalin is an herbicide of the dinitroaniline class used in premergence and postemergence applications to control annual grasses and prevents weeds from emerging during the development of crops [55, 56]. Denitrosation is key step used for the generation of active amine compounds in all these reactions. Different reagent systems such as CuCl/HCl [57], $NiCl_2/NaBH_4$ [58], $Fe(CO)_5$ [59], Raney-Ni/H_2 [60], Fe/NH_4Cl [61] and Zn/NH_4Cl [62] have been utilized for the denitrosation of *N*-nitrosamines. Further, the broad discussion about the denitrosation of *N*-nitrosamine will be mentioned in chapter 3.

Figure 1.12 Pendamethalin and its *N*-nitroso derivative.

1.5.9 Photochemistry of *N*-nitrosamines

N-nitroso dialkylamines show a band around 350 *mμ* which is attributed to n-π* transition. This band shows several peaks in the aprotic solvents such as ether and cyclohexene and a smooth maxima peak at 340-350 *mμ* in protic solvents [63]. The scission of N-N bond of nitrosamine will be determined through photolysis with the disappearance of N-NO stretching. Chow *et al.,* performed the experiments in solution phase where they have done the prolonged irradiation under nitrogen atmosphere in

various solvents such as water, alcohol, etc., with the mercury lamp where no appreciable change was observed in the UV spectrometry. Later, in the presence of catalytic amount of hydrochloric acid in the pyrex flask containing the *N*-nitroso compound, when irradiated with the mercury lamp leads to disappearance of 340-350 *mμ* peaks [64]. They have also studied the different photochemical reactions of alkyl nitrosamines such as photoreduction, photoaddition and photoelimination (Scheme 1.26).



Scheme 1.26 Photolysis of N-NO of nitrosamines leads to photoaddition, photoreduction and photoelimination.

Chow *et al.,* demonstrated the photoaddition reaction of *N*-nitrosamines to the C=C bond which results in the formation of *C*-nitroso compounds (Scheme 1.26 **I**) [65-67]. However, alkyl *C*-nitroso compounds are unstable which rearranges to oxime

products. Photoreduction of *N*,*N*-dialkyl *N*-nitrosamine in methanol solution with an acid leads to the formation of parent amine, formaldehyde and *N*-amino formamide (Scheme 1.26 **II**) [67, 68]. The photoelimination of *N*,*N*-dialkyl *N*-nitrosamine gave iminium intermediate **C** and azanone which converts into alkylideneimine (Scheme 1.26 **III**) [67, 68].

1.5.10 *N*-Nitroso Directed C-H Activation

In general C-H bonds possess high energy, hence, the formation of a carbon-carbon or carbon-heteroatom bond by breaking C-H bonds is considered to be a difficult task. Metal-catalyzed C-H activation enables the preparation of complex molecules from simple starting materials. Selective C-H functionalization at a single site in the presence of multiple C-H bonds is achieved using different directing groups. These directing groups provide support to the transition metals for the co-ordination and enable the C-H activation at the specific site [69].

Among the different directing groups, *N*-nitroso groups have been well explored in different C-H activation reactions. *N*-nitrosamines are capable of co-ordinating with different transition metals like palladium, rhodium, ruthenium, etc. Different modes of binding of the metal compounds to *N*-nitrosamines are illustrated in Figure 1.13 [1].

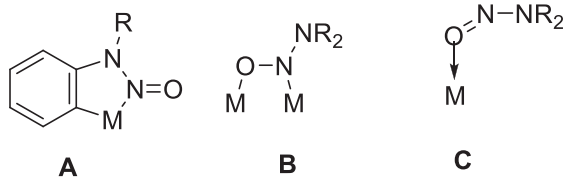
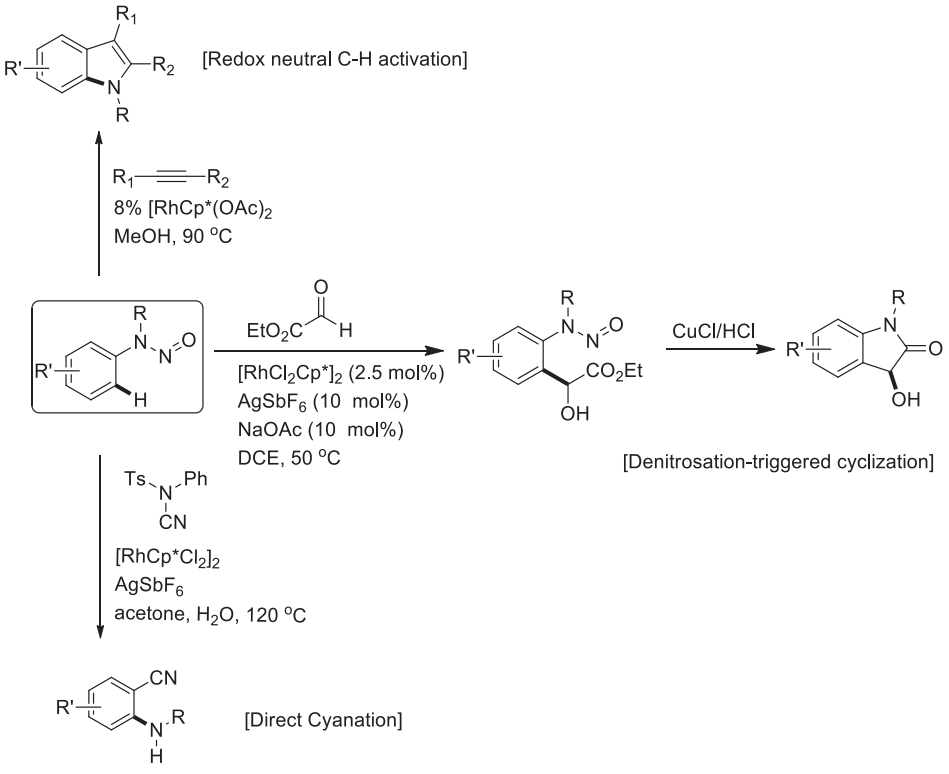


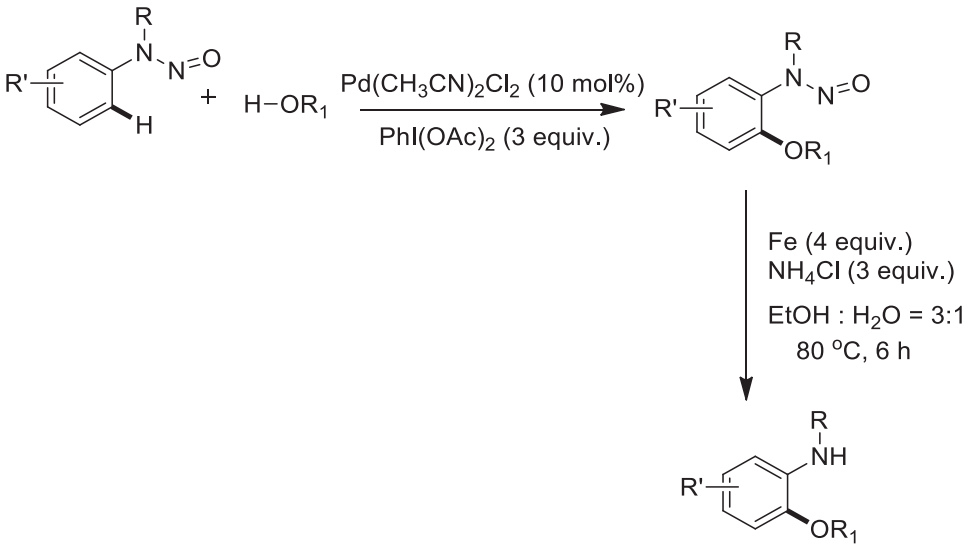
Figure 1.13 Binding modes in interaction of metal-nitrosamine.

In 2013, Wang *et al*., described synthesis of functionalized indoles through C-H annulations of *N*-alkyl *N*-nitrosoaniline in presence of rhodium catalyst at 90 °C. The *N*-nitroso group served as both a directing group and an internal oxidant (Scheme 1.27) [70]. Later, Chen *et al*., reported the synthesis of 3-hydroxy-2-oxindoles by Rh (III)-catalyzed *N*-nitroso-directed C-H addition to ethyl 2-oxoacetate, followed by subsequent denitrosation-triggered cyclization [71]. These methods are found to be advantageous for the development of heterocyclic molecules. Rh (III)-catalyzed *ortho*-cyanation of *N*-alkyl *N*-nitroso arylamines provides 2-(alkylamino) benzonitriles using *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (NCTS) as "CN" source [72].



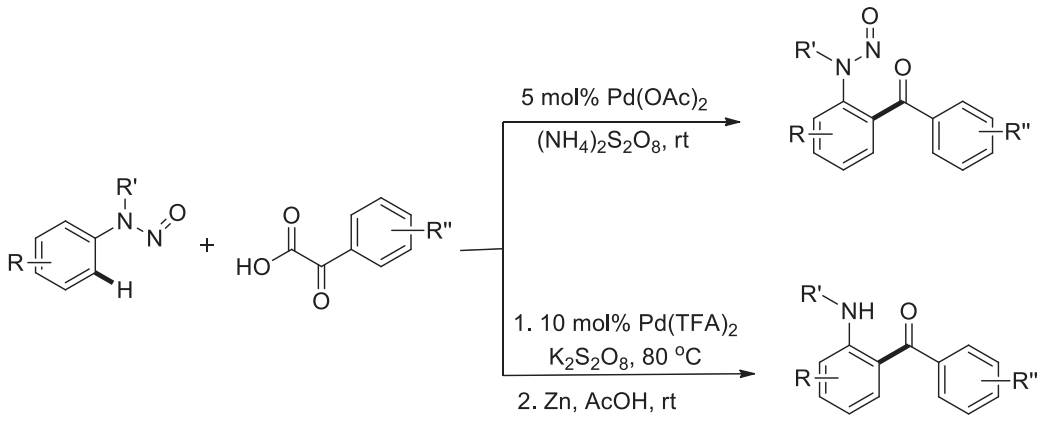
Scheme 1.27 Rhodium catalyzed *N*-nitroso directed C-H activation.

Besides the rhodium-catalyzed C-C bond formation, different palladium catalysed reactions were also explored. Gao *et al*., have described the *o*-alkoxylation of nitrosamines using primary as well as secondary alcohols as the alkoxylating reagents. Palladium salts were used as catalysts and diacetoxy iodobenzene [$PhI(OAc)_2$] served as an oxidant. Subsequent removal of nitroso group using Fe/ammonium chloride gave *o*-alkoxyanilines (Scheme 1.28) [61].

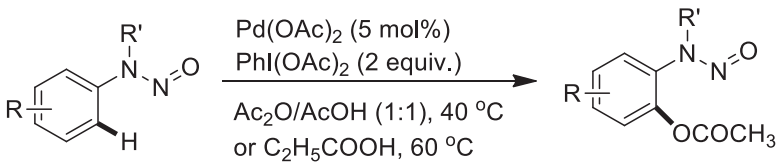


Scheme 1.28 *o*-Alkoxylation of *N*-Nitrosamines.

Palladium catalysed decarboxylative *ortho*-acylation of *N*-nitrosoanilines using α-oxocarboxylic acids was demonstrated in the presence of different oxidants such as ammonium persulfate [73] and potassium persulfate [74] (Scheme 1.29). Both reactions were performed under mild conditions which provide *N*-alkyl-2-aminobenzophenones in good yields. Recently, palladium-catalyzed *o*-acyloxylation of *N*-nitroso anilines with Ac_2O and acetic acid was also explored (Scheme 1.30) [62].



Scheme 1.29 Palladium catalyzed nitroso-directed *ortho*-acylation.



Scheme 1.30 Palladium catalyzed *o*-acyloxylation of *N*-nitrosoanilines.

1.6 Conclusion

The above discussion provides the significance of nitroso compounds in various fields. The *C*-nitroso and *O*-nitroso compounds were found wide applications in synthetic organic chemistry while *S*-nitroso compounds display some interesting biological activity. In this context, *N*-nitrosamines possess both chemical as well as biological applications. *N*-Nitrosamines are carcinogenic which induce cancers in animals. On the other hand, *N*-nitrosamines are the versatile class of organic compounds explored in organic synthesis as starting material, reagents, masking groups, directing groups, etc. Chemical denitrosation of *N*-nitrosamine has been considered as an important transformation for the quantification of total *N*-nitrosamines present in the biological system as well as to regenerate the amines. *N*-Nitrosamines

also display interesting stereochemistry (*syn* and *anti*, E:Z) due to electronic arrangements. In this context, our interest was to explore the chemistry of *N*-nitrosamine in different organic transformations.

1.7 The objectives of the present work

1. To synthesize the *N*-nitrosamines with environment-friendly aspect having efficient, selective and high yields (i.e., atom and step economy) using *tert*-butyl nitrite (TBN) metal-free reagent from secondary amines. Also, applications of *tert*-butyl nitrite; such as the transformation of amides to acids and hydrazines to azides.
2. A straightforward approach for the regioselective nitration of *N*-alkyl anilines using *tert*-butyl nitrite under mild condition.
3. The denitrosation protocol for the removal of nitroso moiety to form secondary amines under metal-free conditions using iodine and triethylsilane.
4. The reduction of nitroso group of *N*-nitrosamines to synthesize α-disubstituted hydrazines using ecofriendly reagent thiourea dioxide (TDO).

The transformations with complete atom economy and no waste or innocuous by-product represents the high synthetic efficiency. Therefore, our intension was to identify mild, efficient and practical methods for the transformation of *N*-nitrosamines to different useful products. In the next chapters, we have introduced synthesis and different applications of *N*-nitrosamines.

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