

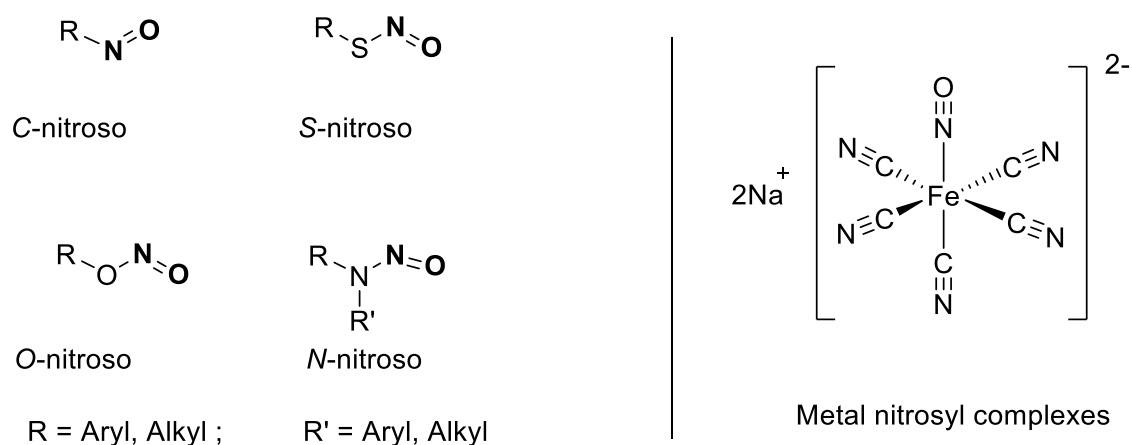
## **CHAPTER-1**

**Introduction, Synthesis and Application**



## 1.1 Introduction

The class of organic compounds with a nitroso (“NO”) moiety in their structure is known as “nitroso compounds” [1]. The physical and chemical properties of a nitroso compound are largely depending on the type of atom or group to which the “NO” group is bonded. Organic nitroso compounds can be broadly categorized into four types, namely C-nitroso compounds (e.g., nitrosoalkanes:  $R-N=O$  and nitrosoarenes:  $Ar-N=O$ ), S-nitroso compounds (nitrosothiols;  $RS-N=O$ ), O-nitroso compounds (alkyl nitrites;  $RO-N=O$ ), and N-nitroso compounds (e.g., nitrosamines,  $R_1N(-R_2)-N=O$ ) [1]. Moreover, nitric oxide is used as a ligand in metal complexes, known as metal nitrosyl complexes. In these cases, NO is bonded to a metal centre in two different ways, namely  $NO^+$  and  $NO^-$  (Figure 1.1) [2].



**Figure 1.1** C, S, O, N-nitroso compounds and Metal nitrosyl complexes.

Nitroso compounds are used in several chemical reactions and chemical industries for different purposes. Fischer-Hepp rearrangement and Barton reaction are the two useful transformations in organic synthesis that involve nitroso compounds [3, 4]. Organonitroso

compounds are used as ligands for synthesizing transition metal complexes [2]. Nitroso compounds such as nitrosodimethylaniline and nitrosophenols are usually blue or green in colour and are used in the dye industries [5]. The nitroso derivatives of amides (*N*-nitroso compounds) decompose when heating with the formation of nitrogen and hence they are used as foam-producing agents in industries [6].

### 1.2 Stability and reactivities of different nitroso compounds

As mentioned earlier, nitroso compounds are four types, namely *C*-nitroso compounds, *S*-nitroso compounds, *O*-nitroso compounds, and *N*-nitroso compounds [1]. Among these compounds, *C*-nitroso compounds and *N*-nitroso compounds are relatively stable when compared with *O*- and *S*-nitroso compounds [7]. In this context, the synthesis and applications of *C*-nitroso and *N*-nitroso compounds (*N*-nitrosamines and *N*-nitrosamides) compounds have been well investigated in organic chemistry [6]. On the other hand, *O*-nitroso compounds are relatively less stable when compared with *C*-nitroso and *N*-nitroso compounds [7]. Among the different *O*-nitroso compounds, the synthesis and applications of primary, secondary, and tert-alkyl nitrites are well-studied in the literature [8, 9, 10]. However, only limited literature is available for the synthesis, isolation, characterization, and applications of the *S*-nitroso compounds due to their poor stability in ambient conditions. Short descriptions of these compounds are given below [11, 12].

### 1.3 *C*-Nitroso compounds

In general, *C*-nitroso compounds are two types, i) Aryl-*C*-nitroso compounds, and ii) Alkyl-*C*-nitroso compounds. Both, alkyl or aryl *C*-nitroso compounds are usually prepared by the oxidation of hydroxylamine using various oxidants including ferric

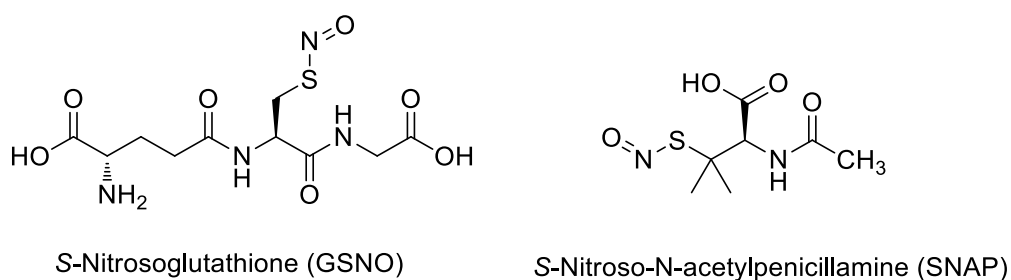
chloride, acidified dichromates (potassium dichromate and sulphuric acid), periodic acid, etc. [13, 14, 15] (**Scheme 1.1**). On the other hand, Aryl-*C*-nitroso compounds can be synthesized using different nitrosating agents (e.g. NaNO<sub>2</sub>/HCl, (N<sub>2</sub>O<sub>3</sub>, N<sub>2</sub>O<sub>4</sub>) and nitrosyl chloride (NOCl)) [16]. In general, primary or secondary *C*-nitroso compounds were found to be unstable and tautomerise to oxime formation. On the other hand, tertiary or aryl *C*-nitroso compounds are more stable [7].



**Scheme 1.1** Synthesis of *C*-Nitrosamines *via* oxidation

#### 1.4 *S*-Nitroso Compounds

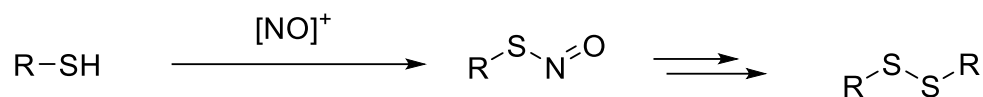
*S*-Nitroso compounds are compounds that possess direct *S*-NO bonds. *S*-Nitroso compounds act as NO donors, hence receiving special attention in biological chemistry [13]. For instance, *S*-nitrosoglutathione (GSNO) and *S*-nitroso-*N*-acetyl penicillamine (SNAP) (**Figure 1.2**) act as a signalling molecules in living systems [13, 14].



**Figure 1.2** *S*-nitroso containing biological compounds.

Nitrosation of alkyl and aryl thiols is usually achieved using a different source of nitrosating agents including NaNO<sub>2</sub>/H<sup>+</sup>, nitrogen oxides, nitrosyl chloride, organic nitrites (e.g. *tert.* butyl nitrite), etc. Nitrosothiols are mostly unstable species since the *S*-NO bond

is labile and undergoes decomposition to disulfide under light by releasing the nitroso (NO) group (**Scheme 1.2**) [11, 18].



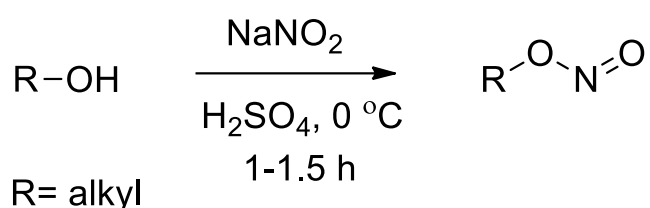
R = alkyl, aryl

**Scheme 1.2** Synthesis of nitrosothiols.

The stabilities of RSNOs depend upon on R group on sulphur. In general, the stability follows as R=3 °C > R=2 °C > R=1 °C [11]. In this context, aromatic nitrosothiols (ArSNOs) are more stable than aliphatic nitrosothiols.

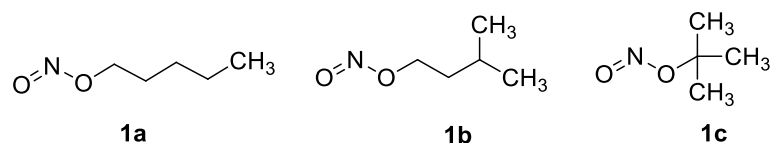
### 1.5 O-Nitroso Compounds

O-Nitroso compounds are those that have direct RO-NO bonds and are known as alkyl nitrites [8]. Alkyl nitrites are relatively stable liquids and are found soluble in most solvents and water. Alkyl nitrites are commercially available but they can be easily prepared from the corresponding alcohols and sodium nitrite in the presence of acids (**Scheme 1.3**) [8].



**Scheme 1.3** Synthesis of alkyl nitrites.

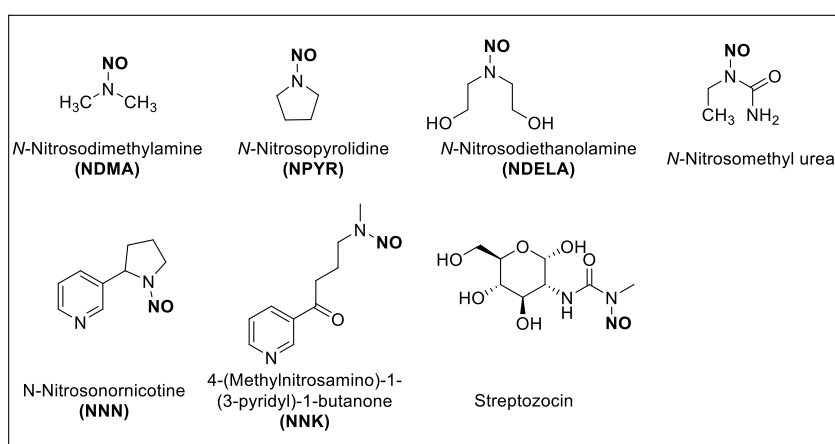
There are three alkyl nitrites including *n*-pentyl nitrite (*n*-amyl nitrite) [9] **1a**, the *iso*-pentyl nitrite [9] **1b**, and the *t*-butyl nitrite (*t*-BuONO or TBN) **1c** [10] have been frequently used in organic synthesis (**Figure 1.3**).



**Figure 1.3** Different alkyl nitrites.

### 1.6 *N*- Nitroso Compounds

*N*-Nitrosamines are chemical compounds, where the “nitroso” (NO) group is directly attached to the nitrogen of amines. *N*-Nitroso compounds and their derivatives occur in a wide range of foods, natural products, fluids, rubber additives, agricultural chemicals, tobacco, detergents, rust solvents, plastics, leather products, textiles, cosmetics, and drugs [19]. Also, 1,1-dimethylhydrazine obtained from *N*-nitroso-dimethylamine (NDMA) is used as rocket fuel [20]. They are occasionally used as solvents or synthetic intermediates in organic chemistry and act as a directing group for inert C-H bond activation to give *ortho*-functionalized aniline compounds. Nitroso group on primary and *tert*-amines are not stable. Nitroso group on secondary amines are stable and used in various fields. In general, *N*-Nitroso compounds are of two types, namely *N*-Nitrosamine and *N*-Nitrosamide (**Figure 1.4**).

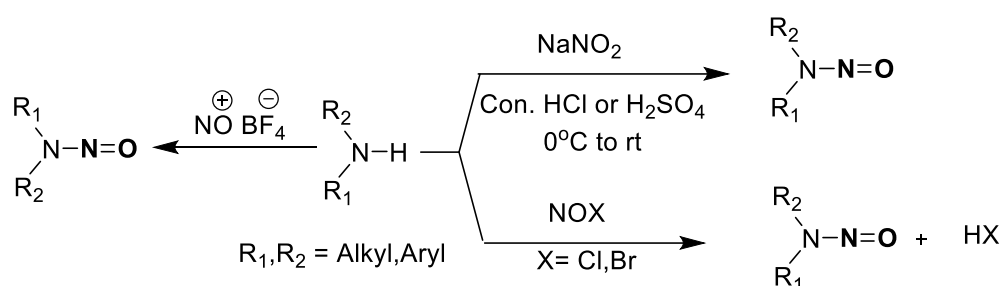


**Figure 1.4** Some examples of Nitrosamines and Nitrosamides.

## 1.7 Synthesis of *N*-Nitrosamines and *N*-Nitrosamides

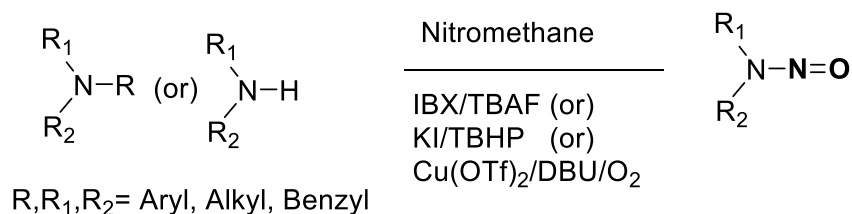
### 1.7.1 Synthesis of *N*-Nitrosamines

The synthesis of *N*-Nitrosamines is typically achieved from secondary amines and nitrous acid [6]. Nitrosyl chloride [21], Nitrogen oxides (*e.g.* N<sub>2</sub>O<sub>3</sub>, N<sub>2</sub>O<sub>4</sub>, *etc*) [22], Nitrosonium tetrafluoroborate [23], and fremy's salt [24] were also used occasionally for the preparation of *N*-Nitrosamines (**Scheme 1.4**).



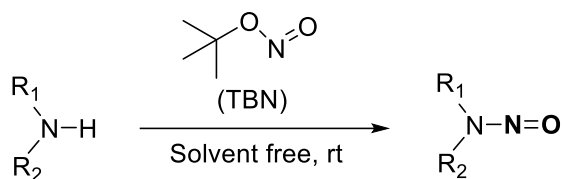
**Scheme 1.4** Synthesis of *N*-Nitrosamines with a different reagent.

Recently, nitromethane (CH<sub>3</sub>NO<sub>2</sub>)-mediated *N*-Nitrosation of secondary and tertiary amines has been achieved in the presence of oxidizing agents such as IBX/TBAF [25], KI/TBHP [26], and Cu(OTf)<sub>2</sub>/DBU/O<sub>2</sub> [27] (**Scheme 1.5**). On the other hand, our research group recently reported the *N*-Nitrosamines preparation from secondary amines using tert-butyl nitrite (**Scheme 1.6**) [28].



**Scheme 1.5** Synthesis of *N*-Nitrosamines using nitromethane.



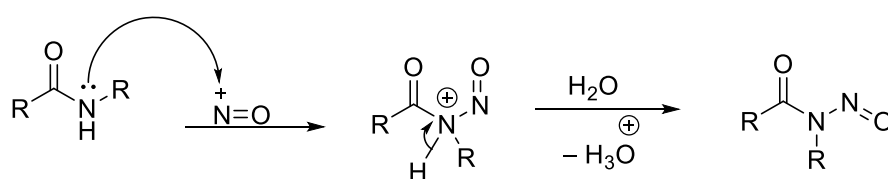


$R_1, R_2 = \text{Aryl, Alkyl, Benzyl}$

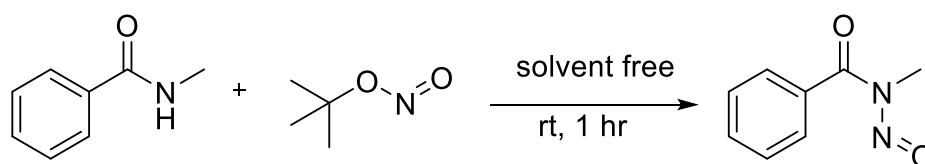
**Scheme 1.6** *N*-Nitrosamines preparation from secondary amines using tert-butyl nitrite.

### 1.7.2 Synthesis of *N*-Nitrosamides: *N*-Nitroso acyl amides and *N*-Nitroso sulfonamides

In general, *N*-Nitrosamides are two types namely, *N*-Nitroso acyl amides and *N*-Nitroso sulfonamides. These *N*-Nitrosamides are relatively less stable than *N*-Nitrosamines. Nevertheless, *N*-Nitrosamines are important intermediates in organic synthesis. *N*-Nitroso acyl amides can be prepared from secondary amides in the presence of different nitrosating agents including nitrosyl chloride, nitrogen oxides, etc. [29] (**Scheme 1.7**). Recently, *tert*-butyl nitrite (TBN) mediated *N*-Nitrosylation of secondary amides was achieved under solvent-free conditions at room temperature (**Scheme 1.8**).

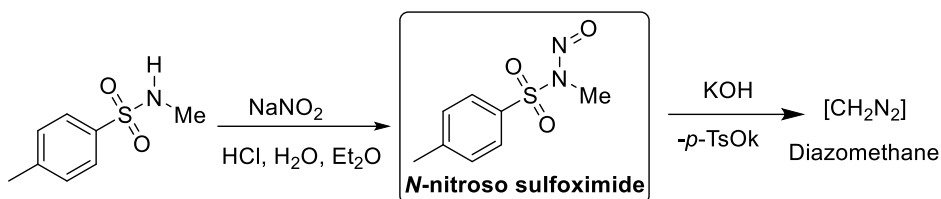


**Scheme 1.7** Reactions of the amide with nitrosonium ion



**Scheme 1.8** Synthesis of *N*-Nitroso amide with TBN

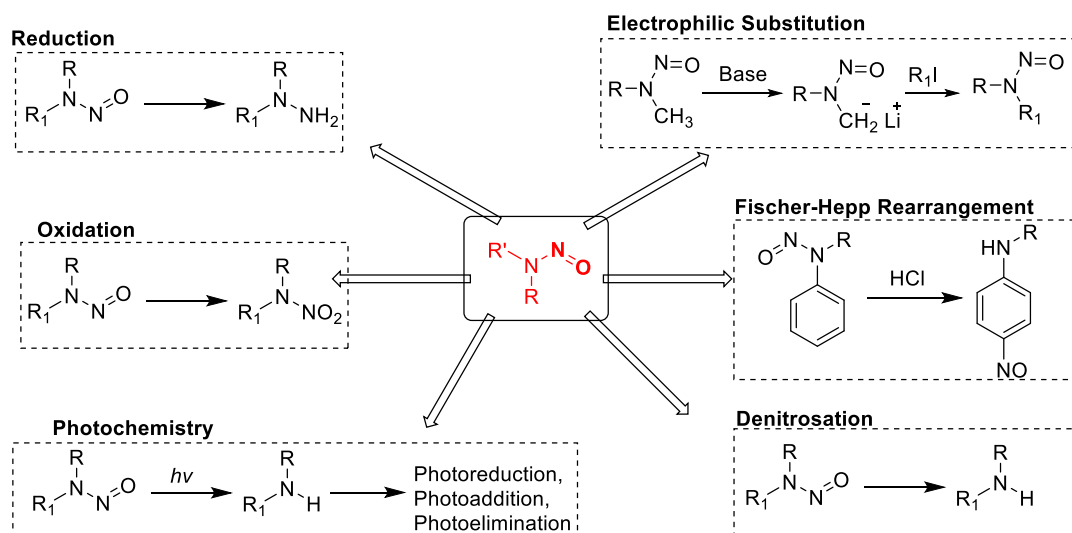
On the other hand, *N*-Nitroso sulfoximides have been synthesised from corresponding amides via *N*-Nitrosation using  $\text{NaNO}_2/\text{HCl}$ . For instance, *N*-Methyl-*N*-Nitroso benzenesulfonamide is prepared from *N*-Methyl-*N*-Nitroso benzenesulfonamide and used as the diazomethane precursors (**Scheme 1.9**) [30].



**Scheme 1.9** Synthesis of *N*-Nitroso sulfoximide.

### 1.8 Reactions of *N*-Nitrosamines:

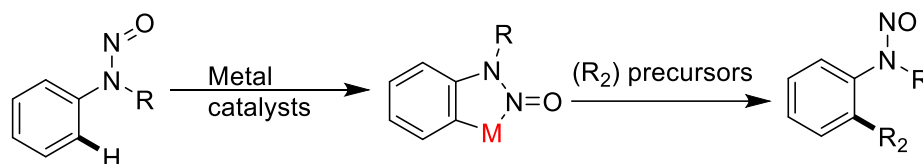
*N*-Nitrosamines have vast applications in synthetic organic chemistry. *N*-Nitrosamines undergo oxidation, reduction, rearrangement, cyclization, photochemical reactions, etc [31]. Formation of carbanion at the  $\alpha$ -carbon (i.e.  $\alpha$ -lithiation) of *N*-Nitrosamines with bases like *n*-BuLi and LDA is facile due to the resonance. Such lithiated compounds undergo electrophilic substitution with various electrophiles and provide valuable synthetic intermediates [32, 33]. Reduction of *N*-Nitrosamines provides hydrazine in good yields while oxidation provides *N*-Nitro compounds. Some aromatic *N*-Nitrosamines undergo Fischer-Hepp rearrangements and dinitrosation reactions under acidic conditions. Moreover, *N*-Nitrosamines undergo various types of reactions under photochemical conditions [31] (**Figure 1.5**).



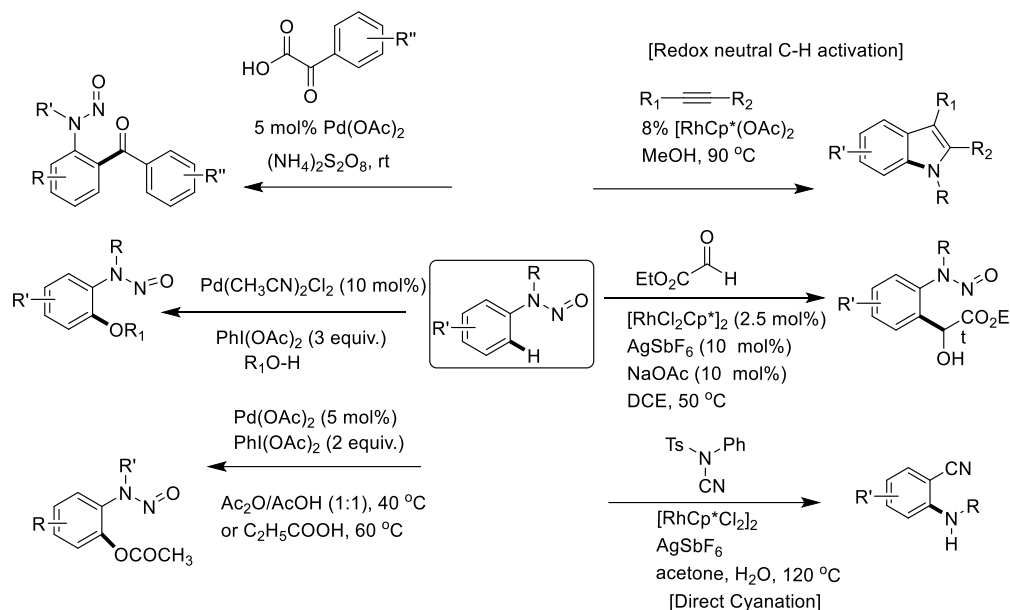
**Figure 1.5** Reactions of *N*-Nitrosamines.

### 1.9 *N*-Nitroso Directed C-H Activation of aryl amines:

Recently, the *N*-Nitroso group has been well explored as a “directing group” in different C-H activation reactions (**Figure 1.6**). *N*-Nitrosamines are capable of coordinating with different transition metals like palladium, rhodium, ruthenium, etc, and allow *ortho*-C-H insertion and activations (**Scheme 1.10**) [34]. For instance, Rh (III)-catalyzed *N*-Nitroso-directed C-H activation reactions and Pd (II)-catalyzed *N*-Nitroso-directed C-H activation reactions have been explored [1].



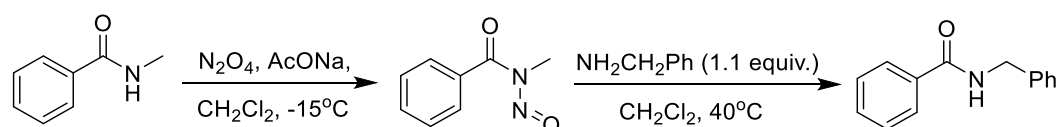
**Figure 1.6** Binding mode and C-H activations.



**Scheme 1.10** Rhodium and palladium-catalyzed *N*-Nitroso directed *C*-H activation.

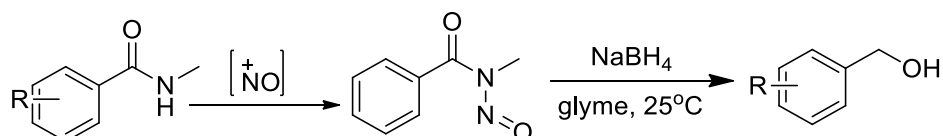
### 1.10 Reactions of *N*-Nitrosamides:

*N*-Nitrosamides are two types, namely *N*-Nitroso *N*-Acyl amides and *N*-Nitroso *N*-Sulfonyl amides. *N*-Nitroso *N*-Acyl amides are less stable than *N*-Nitrosamines and usually get decomposed by thermal, photolytic, or acidic conditions. Therefore, unlike *N*-Nitrosamines, the synthetic applications of *N*-Nitroso *N*-Acyl amides are limited in the literature. *N*-Nitroso *N*-Acyl amides have been used as the intermediates in transamidation reactions. For instance, *N*-Methylbenzamide is converted into *N*-Nitroso-*N*-Methylbenzamide in the first step using some nitrosating reagents and was subjected to nucleophilic substitution with an external amine. These reactions provide a library of amides via transamidation reactions (**Scheme 1.11**) [35].



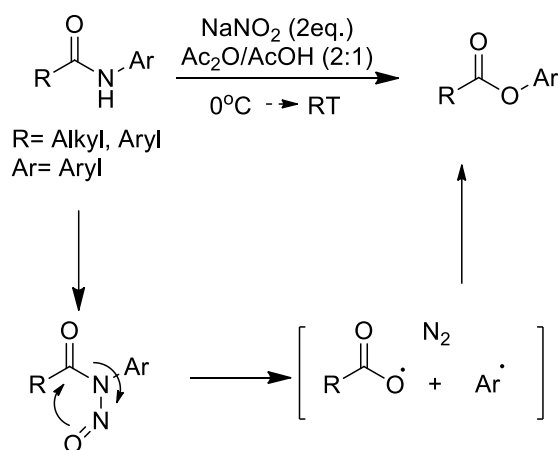
**Scheme 1.11** Transamidation of secondary amides *via N*-Nitrosamide

On the other hand, *N*-Nitrosamines undergo facile reduction to corresponding alcohols. For example, Rudinger *et al.* (1955) reported the reduction of secondary amides with  $\text{NaBH}_4$  via *N*-Nitrosamide intermediate at room temperature using glyme as a solvent (**Scheme 1.12**) [36].



**Scheme 1.12** Reduction of *N*-Nitrosamide

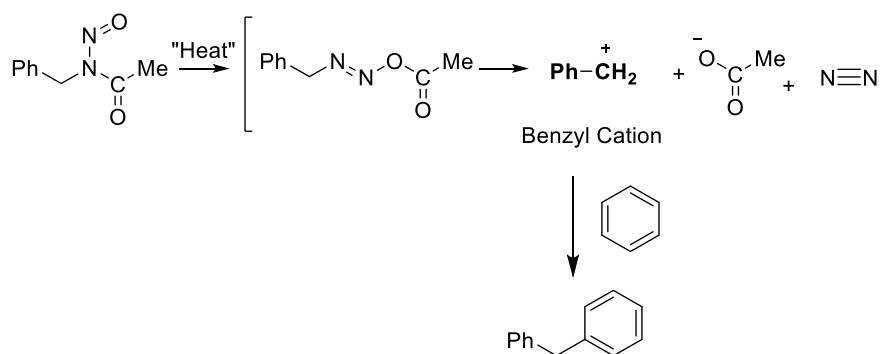
It was also observed that *N*-Aromatic secondary amides converted into *O*-Aromatic esters via *N*-Nitrosamide intermediate as shown in (**Scheme 1.13**) [37]. The mechanism of the reaction proceeds through the radical formation and recombination steps.



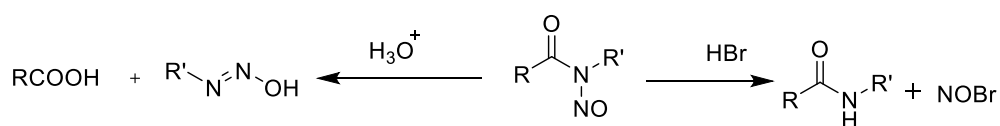
**Scheme 1.13** Formation of *O*-Aromatic esters via *N*-Nitrosamide

*N*-Benzyl-*N*-Nitrosamine was used as a source of benzylic cation in Friedel-Crafts alkylation reaction under thermal conditions (**Scheme 1.14**) [38, 39]. On the other hand,

*N*-Nitroso *N*-Acyl amides can be converted into corresponding acids or amides with suitable reaction conditions (**Scheme 1.15**) [40, 41].



**Scheme 1.14** *N*-Nitrosoamide mediated benzylation of benzene and toluene



**Scheme 1.15** Acid catalysed hydrolysis of *N*-Nitrosamides

## 1.11. Conclusions

The above discussion provides the significant features of nitroso compounds in different fields, including synthetic organic chemistry, medicinal chemistry, coordination chemistry and biology. In general, the *C*-Nitroso, *N*-Nitroso and *O*-Nitroso compounds were found wide applications in synthetic organic chemistry while *S*-Nitroso compounds display some interesting biological activity. On the other hand, *N*-Nitrosamines are carcinogenic and mutagenic which induce cancers in animals. In this context, our interest was to explore the synthesis and applications of *N*-Nitrosamines and *N*-Nitrosamides in different organic transformations.

### 1.12 The objectives of the present work

1. To develop a route for the preparation of uronamides (amides derived from carbohydrates) under transamidation strategy using *N*-Nitrosamides intermediates.
2. To develop a protocol for the denitrosation of *N*-Nitrosamines under metal-free conditions.
3. To develop a route for the synthesis of *N*-Nitroso sulfonamides under mild reaction conditions and investigate their applications in nitroso transfer reactions.
4. To use the *N*-Nitrosamines as directing groups for the stereoselective *O*-glycosylation reactions.

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**1.13 References**

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