CHAPTER-2

AN EFFICIENT SYNTHESIS OF *N*-NITROSAMINES UNDER SOLVENT, METAL AND ACID FREE CONDITIONS USING *TERT*-BUTYL NITRITE

2.1 Introduction

N-Nitroso compounds are present in a wide range of foods, cosmetics and natural products [1, 2]. More attention is being paid to the chemistry of *N*-nitroso compounds owing to their unique carcinogenic and mutagenic properties [2-4]. These compounds have been used in various treatments including cancer, cardiovascular diseases, central nervous disorders and diseases related to immunity and physiological disorders (Figure 2.1) [1-4]. For instance, a derivative of *N*-nitrosoaniline, dephostatin **A** is known to be a potential inhibitor of cysteine-containing enzymes such as protein tyrosine phosphatases, papain and caspase [5,6]. The cyclic *N*-nitrosamines **B** and **C** have been found to inhibit thrombus formation in the arterioles and venules of rats [3]. Although *N*-methyl-*N*-nitrosourea is a cancer inducer, its derivatives were found to be potent antitumor agents. For example, carmustine **D** and related compounds (e.g. lomustine and semustine) are widely used as alkylating agents in chemotherapy [7-8]. Streptozocin **E** is a sugar derived *N*-methylnitrosourea used as an antibiotic and antineoplastic agent [8]. In addition, streptozocin is also a well known diabetogenic agent currently used in medical research to produce animal models for hyperglycemia and Type 1 diabetes [9]. The *N*-nitrosohydroxylamine derivative dopastin **F** is used as an experimental antihypertensive agent that inhibits copper-dependent dopamine *β*-hydroxylase efficiently [3, 10]. Similarly, *N*-nitroso-*N*-cyclohexylhydroxylamine **G** is used as a synergistic agent which increases the insecticidal activity of chlordane [3].

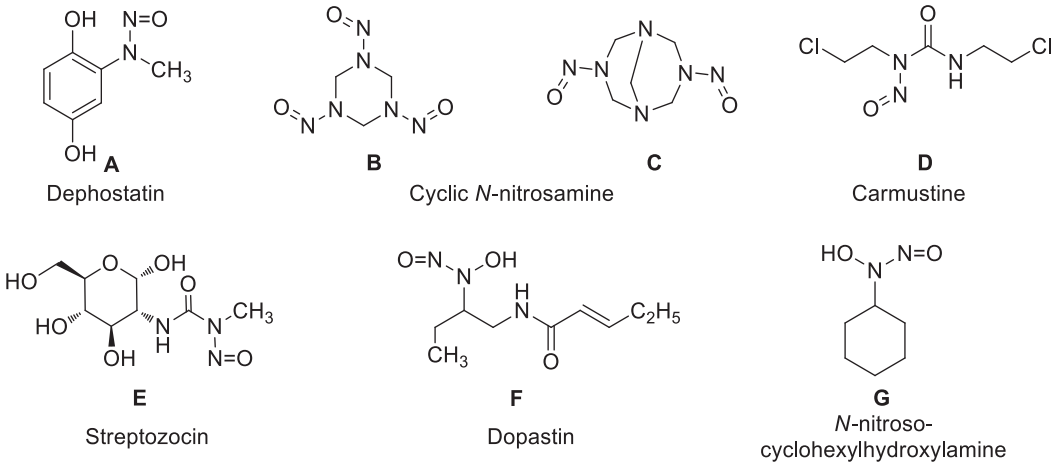
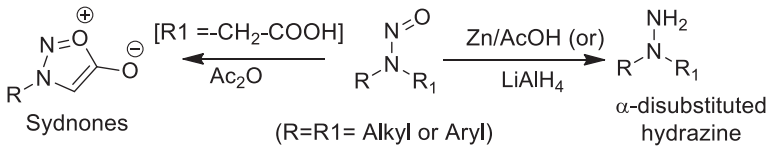


Figure 2.1 Biologically important *N*-nitroso compounds.

Besides being biologically important, *N*-nitrosamine compounds have become valuable intermediates in organic synthesis [11, 12]. Preparations of biologically important α-disubstituted hydrazines [13-16] and mesoionic-heterocyclic compound sydnones [17, 18] are the traditional applications of *N*-nitrosamines (Scheme 2.1). Aryl *C*-nitroso compounds can be obtained in good yield from *N*-nitrosamines through the Fischer-Hepp rearrangement [19, 20].



Scheme 2.1 Some traditional applications of *N*-nitrosamines.

Moreover, the electrophilic substitutions at the α-carbon of the secondary amines have been performed in a regio- and stereoselective manner by masking the secondary

amines as *N*-nitrosamines [21]. Recently, *N*-nitrosamine functional groups have emerged as traceless directing groups for the activation of inert C-H bonds in aryl rings by associating with transition metals (Figure 2.2) [22-31]. These C-H activation reactions provide fruitful ways to construct various biologically important heterocyclic compounds as discussed in Chapter 1.

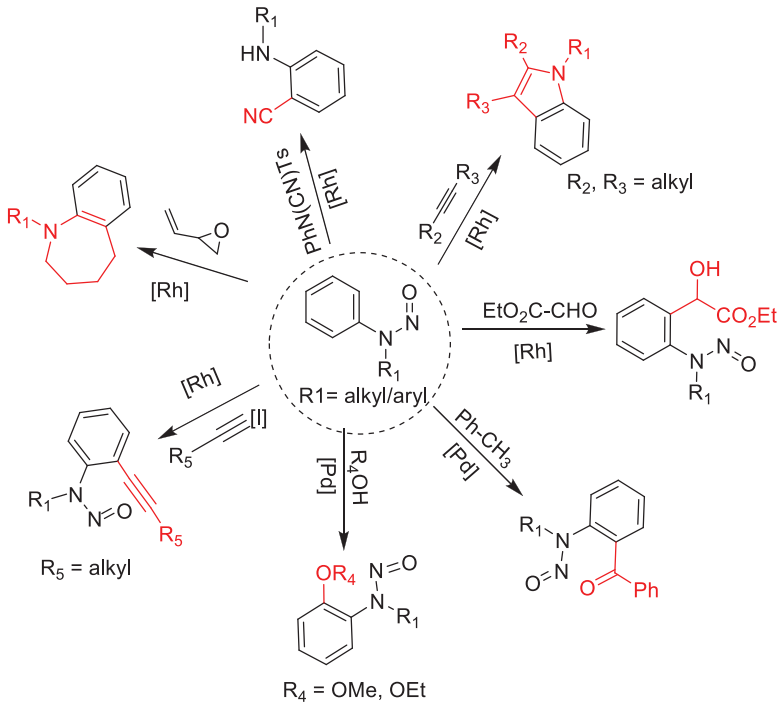
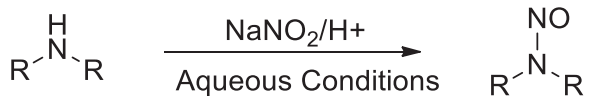


Figure 2.2 Recent applications of *N*-nitrosamines as a directing group for inert C-H bond activation.

The chemical syntheses of *N*-nitrosamines are well-established reactions in organic synthesis [11]. The most common procedure involves the use of nitrous acid generated (*in situ*) from sodium nitrite and concentrated mineral acid (e.g. HCl, H_2SO_4) (Scheme 2.2).



Scheme 2.2 Traditional method of *N*-nitrosation of secondary amine.

Besides this traditional reagent, nitrosyl chloride [32], nitrosonium tetrafluoroborate [33], nitroso-crown ether adduct [NO^+, Crown, $H(NO_3)^{2-}$] [34], Fremy's salt [35] and nitrogen oxides (e.g. N_2O_3, N_2O_4, etc.) [36, 37] were used to synthesize various *N*-nitroso compounds from the corresponding secondary amines. In addition, various heterogeneous systems have been developed in the last decade using a combination of sodium nitrite with solid acids [38-41] or nitrogen oxide with different solid supports acids [42-44]. However, most of these methods proceed through strong acidic conditions which limits their use in complex synthesis, particularly, when there is an acid-labile group on the substrate.

Moreover, the preparation, handling and storing of some of these reagents are very difficult which further limits their extensive uses in organic synthesis. Dealkylative nitrosation of *tert*-amines has been performed previously using some alkyl nitrites [45, 46]. Very recently, nitromethane (CH_3NO_2) has been employed as an alternative source for generating the nitrosyl (NO) moiety in the presence of various oxidizing systems (e.g. IBX or KI/TBHP or [Cu]/O_2) [47-49]. However, these methods are not practical on parallel synthesis due to poor yields and harsh reaction conditions.

With the increase in environmental awareness with respect to green chemistry, there is also a pressing need to develop eco-friendly approaches for the preparation of various

fine chemicals [50-51]. In this context, development of an acid free and metal free nitrosating reagent which will work efficiently under mild conditions remains an important goal.

tert-Butyl nitrite (TBN) is a very useful synthetic reagent frequently used for diazotization reactions [52, 53] TBN is found to be a reliable source of NO and NO_2 radicals and explored in the regiospecific *C*-nitration of phenols, azoarenes, arylboronic acids, anilides, aromatic sulfonamides, olefins and alkynes [54-67]. Recently, the regioselective *C*-nitrosation of imidazoheterocycles has been accomplished by using *tert*-butyl nitrite under catalyst free conditions [68]. As a metal-free reagent, *tert*-butyl nitrite has many advantages like commercial availability, inexpensiveness, easy handling, medium volatility, good solubility in common solvents, etc. In this context, we would like to report an important application of *tert*-butyl nitrite i.e. *N*-nitrosation of secondary amines under solvent free conditions.

2.2 Results and Discussions

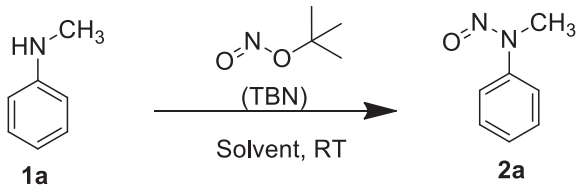
2.2.1 Optimization for *N*-nitrosation under different reaction conditions

At the outset, commercially available *N*-methyl aniline (**1a**) was used as a model substrate for the *N*-nitrosation reaction with *tert*-butyl nitrite. The reactions were performed at room temperature in various protic and aprotic solvents (Table 2.1). Dichloromethane provides the desired product **2a** in 81% yield with one equiv. of TBN after 40 minutes (Table 2.1, entry 1). Further, no improvement was observed in the yield with increase in

time. However, by increasing TBN to 1.5 equiv. the reaction leads to completion (92%, isolated yield) in 25 minutes (Table 2.1, entry 2). Similarly, other aprotic solvents such as chloroform, dichloroethane, diethyl ether, tetrahydrofuran and acetonitrile took around 20-30 minutes and provided the desired product in good to excellent yields (Table 2.1, entries 3-7). However, the protic solvents such as methanol, ethanol and H_2O took a slightly longer reaction time (45-90 min) for completion which may be due to the interaction of the nucleophilic solvents with TBN (Table 2.1, entries 8-10). Overall, TBN is found to be an efficient nitrosating reagent in most of the commonly used organic solvents.

From the environmental perspective, green chemistry has got immense appreciation in recent years. According to one of the principles of green chemistry, toxic solvents in organic synthesis should be replaced with greener alternatives (e.g. water, ionic liquids, supercritical CO_2, bio-based green solvents, etc.) or the chemical reaction should be favored under solvent free conditions [50, 51]. Development of solvent free protocols appears to be an ideal case, because, solvent free reactions not only reduce the environmental pollution but are also high yielding and cost effective [69]. However, to the best of our knowledge so far no convenient solvent free protocol has been described for the preparation of *N*-nitrosamines. Hence, the *N*-nitrosation of *N*-methylaniline (**1a**) was attempted under solvent free conditions using one equiv. of *tert*-butyl nitrite at room temperature (Table 2.1, entry 11). We were pleased to see a quantitative formation of *N*-nitroso-*N*-methylaniline (**2a**) within 5 minutes.

Table 2.1 Nitrosation of *N*-methyl aniline using *tert*-butyl nitrite.[a,b]



1a **2a**

S.No.	Solvent	TBN (equiv.)	Time (min)	Yield[b] (%)
1	CH_2Cl_2	1.0	40	81
2	CH_2Cl_2	1.5	25	92
3	$CHCl_3$	1.5	30	92
4	DCE	1.5	25	89
5	THF	1.5	20	93
6	Diethyl ether	1.5	30	90
7	CH_3CN	1.5	30	80
8	CH_3OH	1.5	45	93
9	C_2H_5OH	1.5	60	87
10	H_2O	1.5	90	87
11	**Solvent-free**	**1.0**	**>5**	**95 (>99)[c]**
12	Solvent-free	1.0	>5	93[d]
13	Solvent-free	1.0	>5	90[e]

[a]Reaction conditions: Amine (1 mmol) and TBN was stirred in the respective solvents (2 mL) at room temperature. [b]Isolated yields. [c]Crude yield (seen in ^{1}H NMR). [d]*n*-Butyl nitrite was employed. [e]*iso*-Amyl nitrite was employed.

Although, the other frequently used alkyl nitrites such as *n*-butyl nitrite and *iso*-amyl nitrite provided the desired product in comparable yield (Table 2.2, entries 12 and

13), *tert*-butyl nitrite offers some important advantages over the others. For example, *tert*-butanol i.e. the resulting byproduct of *tert*-butyl nitrite during *N*-nitrosation is less susceptible to further reactions (e.g. oxidation, nucleophilic substitution, etc.) when compared with primary alcohols which result from *n*-butyl nitrite and *iso*-amyl nitrite. In addition, *tert*-butanol is completely miscible with water while *n*-butanol and *iso*-amyl alcohol have limited water solubility (e.g. water solubility of *iso*-amyl alcohol: 28 g L^{-1} and *n*-butanol: 73 g L^{-1}) which increases the difficulty in the isolation of pure products through simple aqueous work up procedures (Figure 2.3). In the case of *tert*-butyl nitrite, the product was obtained in high purity by aqueous work-up or filtering the crude product through a short silica pad without any work-up procedures. To some extent, this solvent free and easy isolation procedure minimizes the exposure of chemists to the carcinogenic *N*-nitroso compounds.

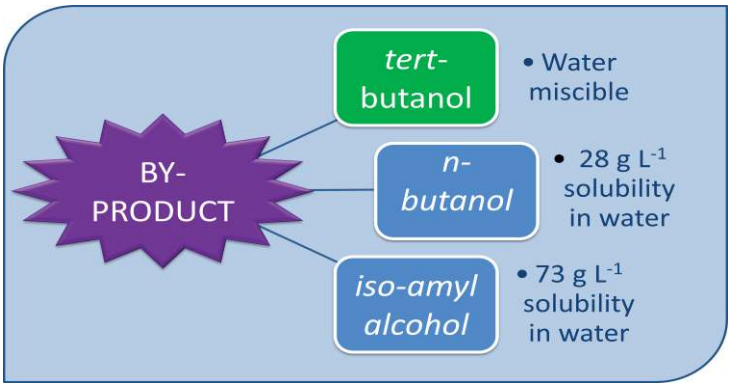
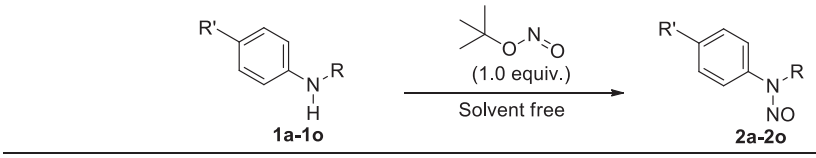
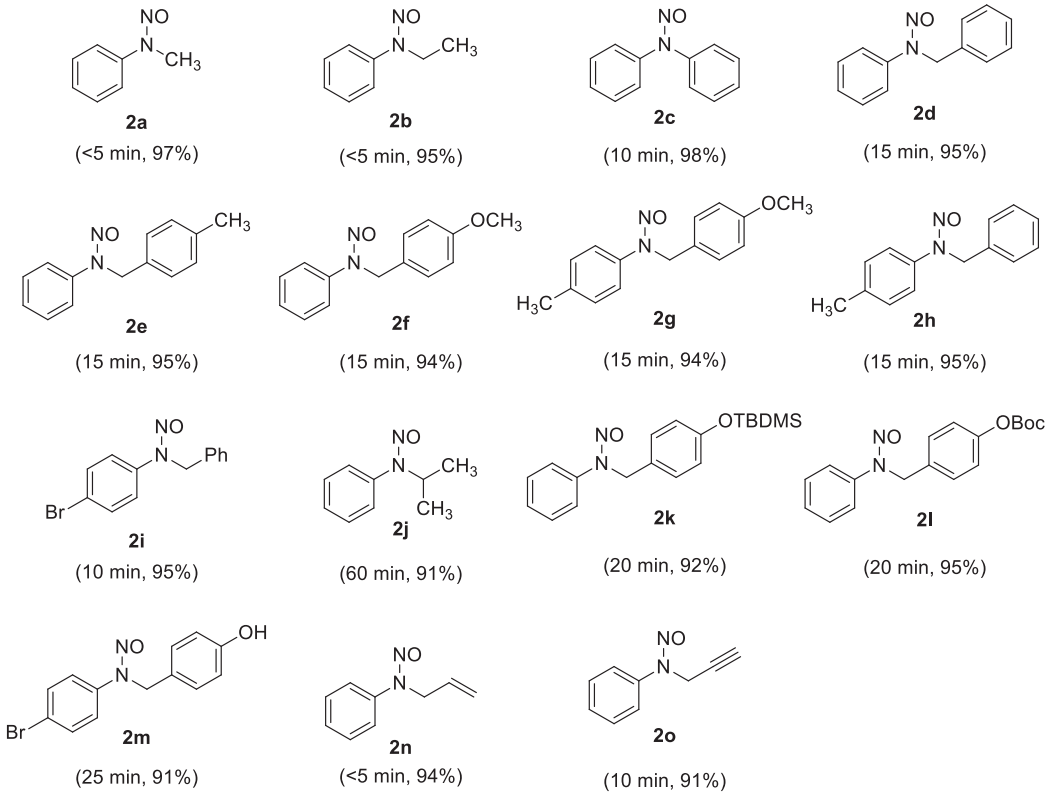


Figure 2.3 Solubility of byproducts in aqueous work-up.

2.2.2 Substrate scope

Table 2.2 Nitrosation of aromatic secondary amines using *tert*-butyl nitrite under solvent free conditions.[a,b]



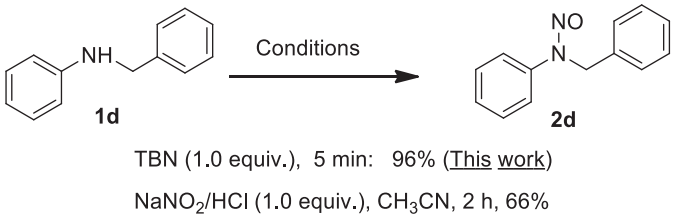


[a]Reaction conditions: Amine (1 mmol) and *t*-BuONO (1.0 equiv.) was stirred at room temperature. [b]Isolated yields.

Promptly, *N*-nitrosation of various secondary amines was studied using TBN under solvent free conditions and the results were summarized in Table 2.2. Similar to *N*-methyl aniline (**1a**), *N*-ethyl, phenyl and benzyl anilines underwent nitrosation smoothly at room

temperature in a chemo-selective manner (Table 2.2, **2b**-**2i**). In all the cases quantitative conversion (>94%) was observed irrespective of the substituent on the substrate.

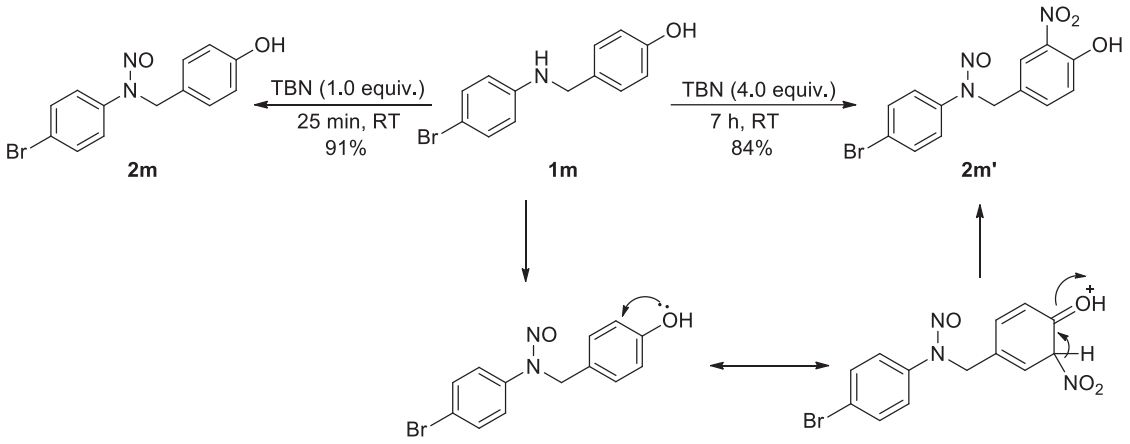
In this context, the traditional procedure (i.e. $NaNO_2$/HCl) was found to be inferior, particularly observed in the case of conversion of *N*-benzyl anilines to the corresponding nitrosamines [24]. For example, *N*-benzyl *N*-nitrosoaniline (**2d**) was obtained only in 66% yield from the corresponding secondary amine using the traditional procedure while the current method (i.e. TBN) provides 96% yield, which clearly distinguishes the efficiency of TBN over $NaNO_2$/HCl (Scheme 2.3). On the other hand, TBN was also found to be very efficient in nitrosating sterically hindered anilines where *N*-nitroso *N*-isopropylaniline was synthesized from the corresponding secondary amine in high yield within 60 minutes (Table 2.2, **2j**).



Scheme 2.3 Conversion of *N*-benzylaniline to corresponding *N*-nitrosoaniline using $NaNO_2$/HCl and TBN.

Functional group and protecting group tolerance is one of the most important aspects in multistep organic synthesis. In order to test the compatibility of commonly used acid labile protecting groups such as *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyloxycarbonyl (Boc) compounds **1k** and **1l** have been synthesized and subjected to *N*-

nitrosation reactions under optimized conditions. It was found that both the TBDMS and Boc protecting groups remain stable during the reaction and the desired products (**2k** and **2l**) were obtained in good yields. By considering the previous reports on *C*-nitration of phenols, olefins and alkynes with *tert*-butyl nitrite [58, 67, 68], *N*-(4-hydroxybenzyl)-4-bromoaniline (**1m**), *N*-allyl aniline (**1n**) and *N*-propargyl aniline (**1o**) (i.e. substrates containing the secondary amine with phenol, olefin and alkyne functionalities) were subjected to the nitrosation reaction under optimized conditions. Remarkably, in all three cases the desired *N*-nitroso products (**2m**, **2n** and **2o**) were obtained in high yields, which showed the broad scope of this methodology. Moreover, with an excess amount of TBN (≈4 equiv.) the alkene and alkyne functionalities remained intact while interestingly, *ortho*-nitrated *N*-nitroso phenol (**2m′**) was obtained from the phenolic substrate **1m** in 84% yield (Scheme 2.4). This clearly indicates that the hydroxyl group which has electron-donating tendency shares the lone pair of the oxygen to the aromatic ring where the resonance opens the *ortho* position for the attack of NO_2^+ through electrophilic substitution for the formation of the respective **2m'**.



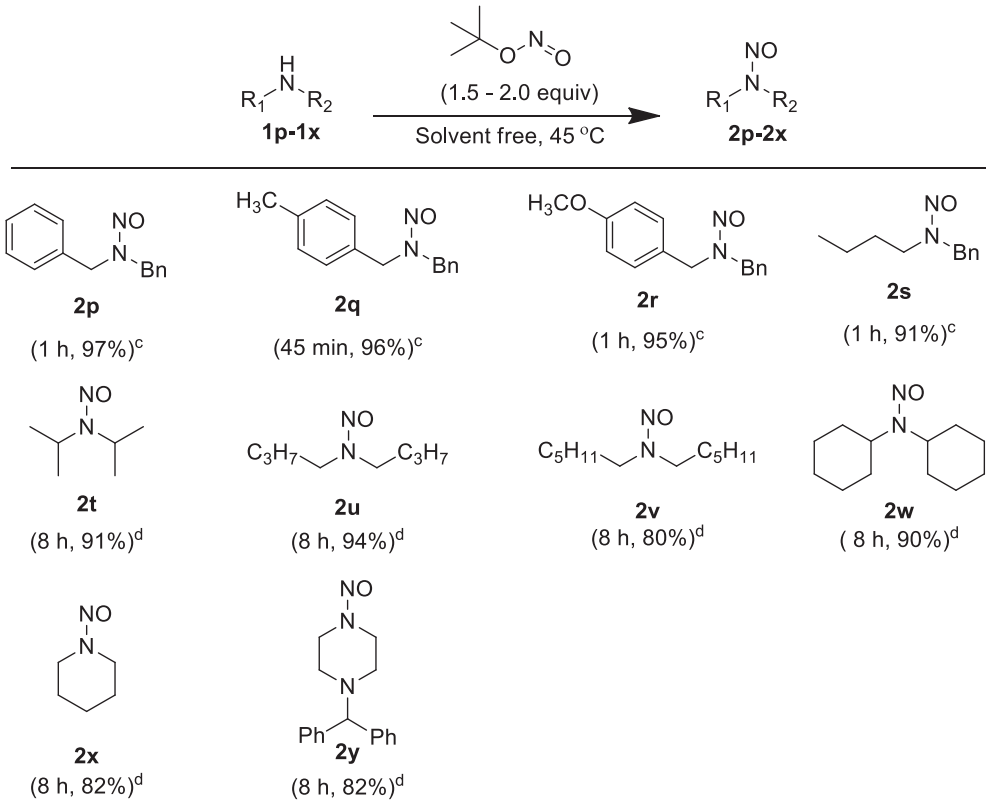
Scheme 2.4 Nitrosation reaction with *N*-(4-Hydroxybenzyl) 4-bromoaniline (**1m**).

To further extend the scope of this methodology, *N*-nitrosation of various dibenzyl, benzyl alkyl, dialkyl and cyclic secondary amines were carried out under optimized conditions (Table 2.3, **1p**-**1y**). During the nitrosation of dibenzyl amine (**1p**), a slower rate of conversion was observed at room temperature, thus, the reaction was performed at 45 °C with 1.5 equiv. of *tert*-butyl nitrite. Under this elevated temperature, dibenzyl and benzyl alkyl amines underwent nitrosation in high yields (>91%) within the period of one hour (Table 2.3, **2p**-**2s**).

On the other hand, dialkyl and cyclic secondary amines (**1t**–**1y**) undergo *N*-nitrosation within 8 h to provide the desired products (**2t**–**2y**) in good yields (>80%), however with 2.0 equivalents of *tert*-butyl nitrite. Overall, the reactivities of different types of secondary amines were found in the following order: aryl amines > benzyl amines > alkyl amines. This clearly indicates that the resonance effect on the reactivities of the

aromatic anilines as well as on the aliphatic amines which helps in proposing the mechanism.

Table 2.3 Nitrosation of aliphatic secondary amines using *tert*-butyl nitrite under solvent free conditions.[a,b]

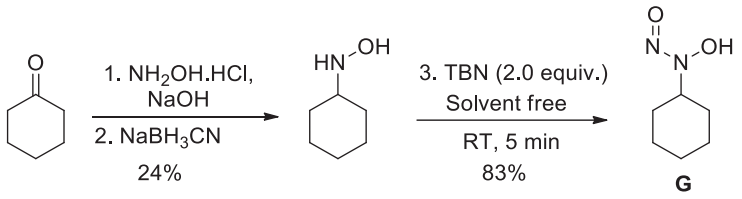


[a]Reaction conditions: Amine (1 mmol) and *t*-BuONO (1.5-2.0 equiv.) was stirred 45 °C. [b]Isolated yields. [c]Reactions were carried out with 1.5 equiv. TBN. [d]Reactions were carried out with 2 equiv. TBN.

2.2.3 Synthesis of *N*-cyclohexylhydroxylamine

The scope of this methodology was further investigated by attempting the synthesis of the biologically important *N*-nitroso *N*-cyclohexylhydroxylamine (Figure 2.1, **G**). The

synthesis of compound **G** was accomplished from cyclohexanone in three steps as shown in Scheme 2.5.



Scheme 2.5 A synthetic route for the preparation of compound **G**.

The reaction of cyclohexanone with hydroxylamine hydrochloride followed by sodium cyanoborohydride reduction provides the *N*-cyclohexylhydroxylamine in 24% yield [70] which was subjected to *N*-nitrosation under solvent free conditions using *tert*-butyl nitrite (current protocol). The *N*-nitrosation reaction underwent smoothly at room temperature to provide the desired product in 83% yield.

2.2.4 Restricted rotation of *N*-nitrosamines

It is well known that *N*-nitrosamines exhibit two orientations (i.e. *syn* and *anti*) due to restricted rotation of the N-N bond resulting from nitrogen lone-pair delocalization (Figure 2.4, **I** and **II**) [11]. During the *N*-nitrosation with TBN, the *α*-unsubstituted and mono-substituted *N*-alkyl anilines gave predominantly one isomer (observed in NMR for the products **2a, 2b, 2d-2i, and 2k-2m**). For example, the orientation of *N*-nitroso group in 4-methoxy *N*-nitroso *N*-benzylaniline (**2f)** was confirmed by single crystal XRD analysis (Table 2.4) [71], which revealed that the nitroso group is towards the *N*-benzylaniline (Figure 2.4, **III**). This result clearly explained the existence of single isomer which is *anti*

form. On the other hand, α-di-substituted *N*-alkyl anilines (e.g. **2j**) and unsymmetrical benzyl amines (e.g. **2q**-**2s**) gave two rotamers approximately in 1:1 ratio (Figure 2.4, **IV** and **V**) [71]. The barrier to rotation about this bond is estimated at approximately 24 kcal mole^{-1}.

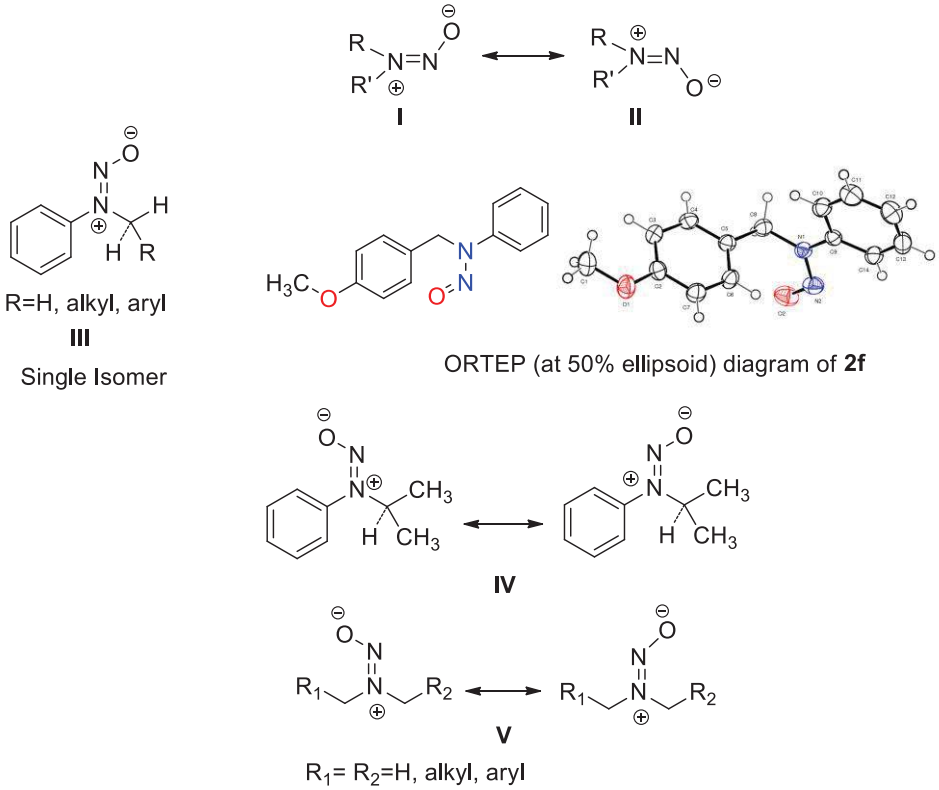


Figure 2.4 Different orientations of *N*-nitrosamines.

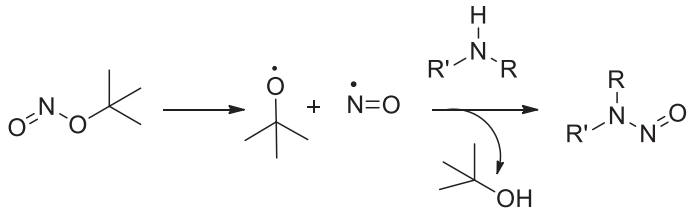
Table 2.4 Crystal refinement parameters for **2f**.

Parameters	2f
CCDC	**1444786**
Empirical formula	$C_{14}H_{14}N_2O_2$
Formula weight	242.27
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	7.5292(5)
b/Å	5.7936(3)
c/Å	13.9668(9)
α/°	90
β/°	93.766(4)
γ/°	90
Volume/Å^3	607.93(6)
Z	2
ρ_{calc} mg/mm^3	1.324
μ/mm^{-1}	0.090
F(000)	256
Crystal size/mm^3	0.3 × 0.3 × 0.2
2Θ range for data collection	2.123 to 22.890°
Index ranges	-8<=h<=8, -6<=k<=6, --16<=l<=16
Reflections collected	6532
Independent reflections	2141 [R(int) = 0.02]
Data/restraints/parameters	2141 / 1 / 164
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0299, wR_2 = 0.652
Final R indexes [all data]	R_1 = 0.381, wR_2 = 0.0712
Largest diff. peak/hole / e Å^{-3}	0.11 and -0.12

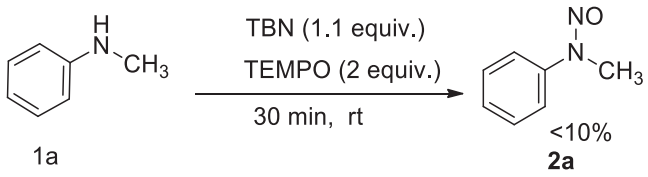
$^aR_1=\Sigma||F_o| -|F_c||/\Sigma|F_o|$, $^bwR_2=|\Sigma_w(|F_o|^2-|F_c|^2)|/\Sigma|w|(F_o)^2|^{1/2}$

2.2.5 Plausible mechanism

Plausible mechanism for the *tert*-butyl nitrite mediated *N*-nitrosation was shown is Scheme 2.6. TBN undergoes homolytic cleavage to form nitrosyl radical and alkoxy radical. The alkoxy radical abstracts the proton from amine and allows formation of N-NO bond. *t*-Butanol released as the byproduct of reaction (Scheme 2.6). To support our radical mechanistic hypotheses, the nitrosation of *N*-methyl aniline was carried out with a radical trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) (Scheme 2.7). As expected, the *N*-nitrosation was inhibited by TEMPO, and only less than 10% of the desired product (i.e. *N*-nitroso *N*-methyl aniline) was obtained which supports our assumption.



Scheme 2.6 Plausible mechanism of *N*-nitrosation.



Scheme 2.7 Control experiment with TEMPO.

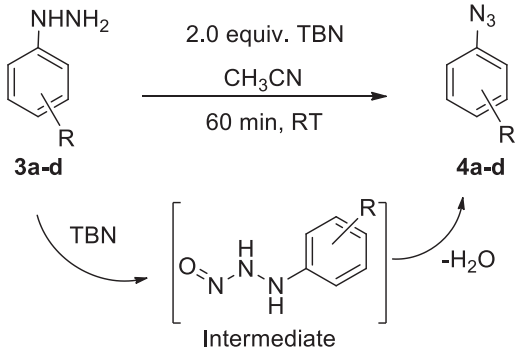
2.3 Other Related Applications of *tert*-Butyl Nitrite (TBN)

We further explored applications of TBN in two different transformations, *i.e.* i) aryl hydrazines into aryl azides and ii) benzamides into benzoic acids, under mild reaction conditions.

2.3.1 Conversion of hydrazides into aryl azides

Aryl azides have found growing applications in organic synthesis especially for the assembly of heterocyclic compounds and dendrimers [72]. Aryl azides are usually prepared by the nucleophilic displacement of aryl halides with sodium azide. Alternatively, mono-substituted aryl hydrazines can be converted to corresponding aryl azides using a nitrosating reagent under mild conditions. Basically, this transformation proceeds through a formation of terminal *N*-nitroso intermediate (Table 2.5) from which a water molecule is removed to yield the corresponding azide. This transformation was previously explored with $NaNO_2$/HCl [73], N_2O_4 [74], nitrosyl tetrafluoroborate [75] and Ph_3P/Br_2/n-Bu_4NNO_2 [76] where these reactions proceed through an acidic medium.

Table 2.5 Conversion of aryl hydrazines into corresponding azides.[a,b]



4a	**4b**	**4c**	**4d**
91%	85%	89%	94%[c]

[a]Reaction conditions: Hydrazine (2 mmol) and TBN (2.0 equiv.) was stirred in acetonitrile (3 mL) at room temperature [b]Isolated yield. [c]5.0 equiv. of TBN is used.

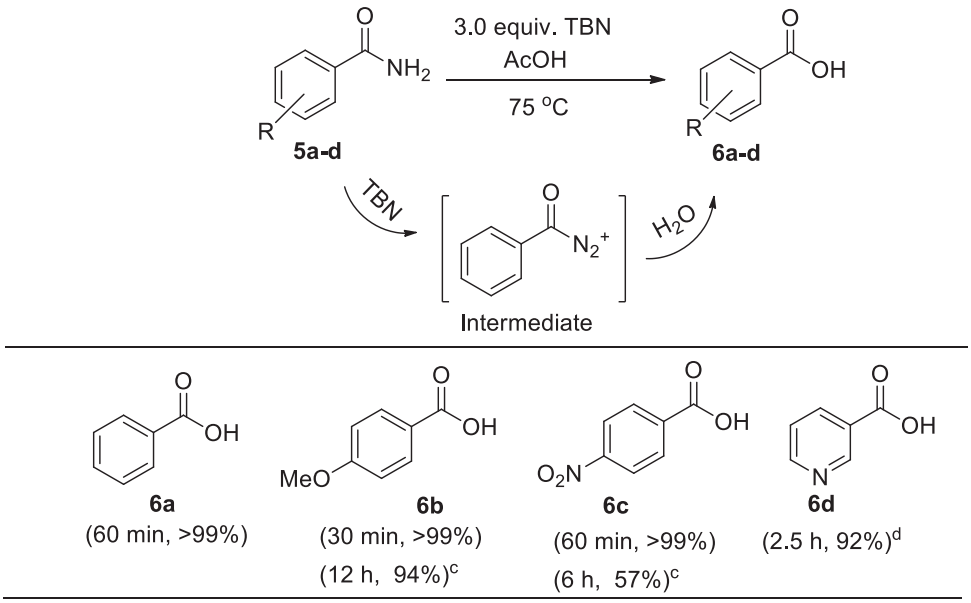
The efficiency of TBN in this transformation was studied using 4-bromophenyl hydrazine (**3a**) as a model substrate with 2.0 equiv. of TBN in acetonitrile (Table 2.5). We were glad to see a clean reaction that provides 91% of 4-bromophenyl azide (**4a**) within 60 minutes at room temperature. Similarly, 3-nitrophenyl azide (**4b**) and 4-cyanophenyl azide (**4c**) was obtained in quantitative yield (>85%) under the same conditions. Moreover, heterocyclic azide, *i.e.* 2-pyridyl azide (**4d**) was obtained in high yield (94%) from 2-hydrazinopyridine which shows the broad synthetic utility of this methodology.

2.3.2 Synthesis of carboxylic acid from corresponding primary amides

Similarly, the conversion of primary amides into corresponding carboxylic acids is an important transformation typically achieved under strong acidic or basic conditions. Hydrolysis of primary amides *via* diazotization is another simple approach, but less explored in organic synthesis [77-79]. The efficiency of TBN in this transformation was examined using benzamide (**5a**) as a model substrate. The reaction was performed using three equiv. of TBN in acetic acid at 75 °C. The reaction provides benzoic acid (Table 2.6, **6a**) as a single product in quantitative yield within 60 minutes. Likewise, 4-methoxy and 4-nitrobenzamides (electron-rich and poor amides) were converted to corresponding benzoic acids (**6b** and **6c**, respectively) in quantitative yield within a short time. Interestingly, this protocol was also compatible with heterocyclic amides where nicotinamide was successfully converted to nicotinic acid (**6d**) in an excellent yield.

As a matter of fact, TBN is found to be a superior diazotizing reagent when compared with *iso*-amyl nitrite which requires not only longer reaction time but also provides lower yields [79]. For example, conversion of 4-methoxybenzamide to corresponding acid was achieved within 30 min using TBN while 12 h required with *iso*-amyl nitrite, although the yields of both reactions are approximately same (>94%). On the other hand, 4-nitrobenzoic acid was obtained only in 57% using *iso*-amyl nitrite after 6 h while TBN provides quantitative yield in one hour. Overall, the *tert*-butyl nitrite is found to be a versatile reagent in organic synthesis.

Table 2.6 Conversion of benzamides into benzoic acids. [a,b]



[a]Reaction conditions: Amide (1 mmol) and TBN (3.0 equiv.) was stirred in acetic acid (3 mL) at 75 °C. [b]Isolated yield. [c]Reactions with *iso*-amyl nitrite. [d]5.0 equiv. of TBN is used.

2.4 Conclusion

In conclusion, we have demonstrated here an efficient and greener method for the *N*-nitrosation of secondary amines using *tert*-butyl nitrite under solvent free, metal free and acid free conditions. A number of aryl, benzyl and alkyl secondary amines were nitrosated in excellent yields under mild conditions. Remarkably, the acid labile protecting groups such as *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyloxycarbonyl (Boc) as well as sensitive functional groups such as phenols, olefin and alkyne were found to be remain intact under the standard reaction conditions. Besides the *N*-nitrosation, TBN was also

found to be an efficient reagent in the transformation of aryl hydrazines to aryl azides and primary amides into carboxylic acids under mild conditions.

2.5 Experimental Section

2.5.1. Experimental procedure for *N*-nitrosation of secondary amines (2a-2w)

Secondary amine (1.0 mmol) and *tert*-butyl nitrite (1.0 equiv for anilines, 1.5 equiv. for benzyl amines and 2.0 equiv. for alkyl amines) was mixed carefully at room temperature and allowed to stir in appropriate temperature for appropriate time. After completion (as seen by TLC), *t*-BuOH was evaporated in vacuum to obtain desired products in good purity. In other hand, products were obtained in high purity through short silica purification.

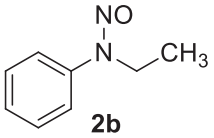
2.6 Analytical Data for the *N*-Nitrosamines

2.6.1 *N*-Methyl-*N*-nitrosoaniline (2a)

2a

The title compound was obtained as yellow oil. Yield: 97% (131 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.52. IR (neat): 3342, 2932, 1678, 1478, 1320, 878 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.47-7.43 (m, 2H), 7.36-7.32 (m, 1H), 3.45 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 142.5, 129.6, 127.5, 119.4, 31.6. HRMS: Calc. for $C_7H_9N_2O_3$ $[M+H]^+$: 137.0715, Obser.: 137.0697.

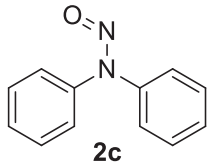
2.6.2 *N*-Ethyl-*N*-nitrosoaniline (2b)



2b

The title compound was obtained as yellow oil. Yield: 95% (143 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3420, 2978, 1782, 1456, 1346, 786 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.1 Hz, 2H), 7.48 (t, 2H), 7.39-7.34 (t, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 141.6, 129.7, 127.5, 119.7, 39.4, 11.9. HRMS: Calc. for $C_8H_{11}N_2O$ $[M+H]^+$: 151.0871, Obser.: 151.0871.

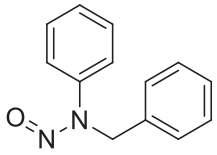
2.6.3 *N*-Nitrosodiphenyl amine (2c)



2c

The title compound was obtained as yellow crystals. M.p. 68 °C. Yield: 98% (194 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.47. IR (neat): 3210, 1567, 1487, 1380, 1176, 785 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.5-7.43 (m, 3H), 7.43-7.37 (m, 4H), 7.32 (dq, *J* = 8.6, 4.2 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 142.7, 136.9, 129.9, 129.6, 129.4, 127.5, 127.1, 119.8. HRMS: Calc. for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0871, Obser.: 199.0867.

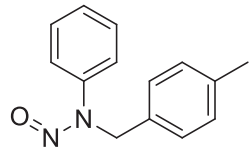
2.6.4 *N*-Benzyl-*N*-nitrosoaniline (2d)



2d

The title compound was obtained as yellowish orange crystals. M.p. 57-58 °C. Yield: 95% (201 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3187, 1578, 1477, 1287, 785 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.29-7.14 (m, 5H), 7.02 (d, *J* = 7.2 Hz, 2H), 5.18 (s, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 141.9, 134.4, 129.6, 128.9, 127.7, 127.5, 127.1, 119.7, 47.4. HRMS: Calc. for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1028, Obser.: 213.1019.

2.6.5 *N*-(4-Methylbenzyl)-*N*-nitrosoaniline (2e)

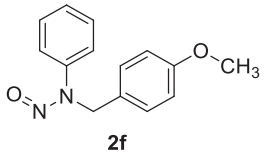


2e

The title compound was obtained as yellowish orange crystals. M.p. 68 °C. Yield: 95% (214 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3267, 1592, 1483, 1232, 776 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.43-7.38 (m, 2H), 7.32 (td, *J* = 7.1, 3.4 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.20 (s, 2H), 2.29 (s, 3H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 141.9, 137.5, 131.4, 129.6,

129.6, 127.5, 127.1, 119.7, 47.2, 21.2. HRMS: Calc. for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, Obser.: 227.1184.

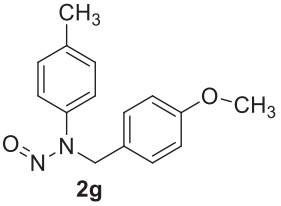
2.6.6 *N*-(4-Methoxybenzyl)-*N*- nitrosoaniline (2f)



2f

The title compound was obtained as yellowish orange crystals. M.p. 83 °C. Yield: 94% (227 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.53. IR (neat): 3245, 1588, 1498, 1189, 778 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.45-7.40 (m, 2H), 7.36-7.31 (m, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.19 (s, 2H), 3.76 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 159.1, 141.9, 129.5, 128.7, 127.5, 126.5, 119.9, 114.3, 55.4, 46.9. HRMS: Calc. for $C_{14}H_{15}N_2O_2$ $[M+Na]^+$: 265.1134, Obser.: 265.0957.

2.6.7 *N*-[(4-Methoxy)benzyl]-*N*-nitroso-(4-methyl)aniline (2g)

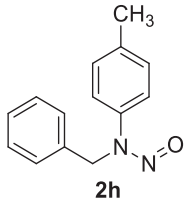


2g

The title compound was obtained as yellow solid. M.p. 78 °C. Yield: 94% (240 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3345, 1567, 1482, 1187, 878 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.26-7.20 (m, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.82-6.77 (m, 2H), 5.16 (s, 2H), 3.76 (s, 3H), 2.37 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$)

δ 159.2, 139.5, 137.6, 130.2, 128.8, 126.7, 120.2, 114.3, 55.4, 47.1, 21.1. HRMS: Calc. for $C_{15}H_{17}N_2O_2$ $[M+Na]^+$: 279.1109, Obser.: 279.1109.

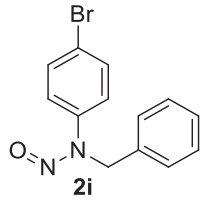
2.6.8 *N*-Benzyl-*N*-nitroso-(4-methyl)aniline (2h)



2h

The title compound was obtained as yellow oil. M.p. 52 °C. Yield: 94% (240 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.49. IR (neat): 3346, 1678, 1476, 1357, 1182, 879 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.29-7.19 (m, 5H), 7.08-7.04 (m, 2H), 5.21 (s, 2H), 2.35 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 139.5, 137.5, 134.5, 130.1, 128.9, 127.7, 127.2, 119.8, 47.6, 21.0. HRMS: Calc. for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, Obser.: 227.1187.

2.6.9 *N*-Benzyl *p*-bromo *N*-nitrosoaniline (2i)

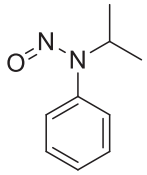


2i

The title compound was obtained as yellow crystals. M.p. 121 °C. Yield: 95% (276 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3345, 2908, 1678, 1485, 1009, 768 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 15.1, 7.8 Hz, 4H), 7.05 (d, *J* = 7.2 Hz, 2H), 5.22 (s, 2H). ^{13}CNMR (125 MHz, $CDCl_3$) δ

140.9, 134.1, 132.7, 129.1, 128.0, 127.1, 120.9, 47.0. HRMS: Calc. for $C_{13}H_{11}BrN_2O$ $[M+H]^+$: 291.0133, Obser.: 291.0127.

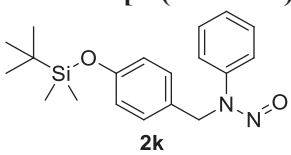
2.6.10 *N*-Isopropyl-*N*-nitrosoaniline (2j)



2j

The title compound was obtained as yellow oil. Yield: 91% (149 mg); (mixture of two isomers in ≈6:4 ratio). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.48. IR (neat): 3486, 2987, 1688, 1492, 1328 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.49-7.36 (m, 5H), 7.32 (dd, *J* = 5.3, 3.0 Hz, 2H), 5.20 (hept, *J* = 6.9 Hz, 1H), 5.03 (hept, *J* = 6.8 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 139.4, 136.5, 129.4, 129.2, 129.16, 128.8, 127.7, 125.9, 56.1, 46.3, 22.0, 19.7. HRMS: Calc. for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1028, Obser.: 165.1021.

2.6.11 *N*-[4-(TBDMS)Benzyl]-*N*-nitrosoaniline (2k)

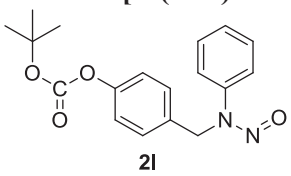


2k

The title compound was obtained as yellow oil. Yield: 92% (310 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3378, 2981, 1690, 1409, 1345, 1007, 890 cm^{-1}.^{1}HNMR (500 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.43-7.38 (m, 2H), 7.34-7.29 (m, 1H), 6.94 (t, *J* = 5.7 Hz, 2H), 6.74-6.70 (m, 2H),

5.16 (s, 2H), 0.94 (s, 9H), 0.14 (s, 6H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 155.1, 141.8, 129.4, 128.5, 127.3, 127.0, 120.3, 119.8, 46.9, 25.6, 18.1, -4.4. HRMS: Calc. for $C_{19}H_{27}N_2O_2Si$ $[M+Na]^+$: 365.1842, Obser.: 365.1654.

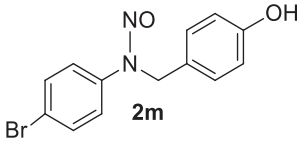
2.6.12 *N*-[4-(Boc)Benzyl]-*N*- nitrosoaniline (2l)



2l

The title compound was obtained as yellow solid. M.p. 89 °C. Yield: 95 % (314 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3457, 2932, 1689, 1478, 1378, 1253 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 5.4, 3.5 Hz, 2H), 7.44-7.39 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.08 (s, 4H), 5.21 (s, 2H), 1.52 (s, 9H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 151.9, 150.7, 141.8, 131.9, 129.7, 128.4, 127.6, 121.9, 119.8, 83.9, 46.9, 27.8. HRMS: Calc. for $C_{18}H_{21}N_2O_4$ $[M+H]^+$: 329.1501, Obser.: 329.1500.

2.6.13 *N*-Nitroso (4-Hydroxybenzyl)-4-bromoaniline (2m)

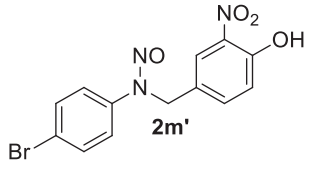


2m

The title compound was obtained as red crystals. M.p. 131.4 °C. Yield: 91% (279 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.55. IR (neat): 3492, 3356, 2986, 1686, 1438, 1326, 1009, 587 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5

Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 5.12 (s, 2H), 4.85 (s, 1H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 140.9, 132.7, 128.9, 121.2, 115.9, 46.6. HRMS: Calc. for $C_{13}H_{11}BrN_2O_2$ $[M+Na]^+$: 328.9902 Obser.: 328.9896.

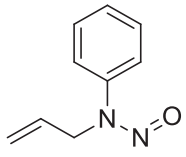
2.6.14 *N*-Nitroso (4-Hydroxy-3-nitrobenzyl)-4-bromoaniline (2m')



2m'

The title compound was obtained as yellow crsytals. M.p. 152 °C. Yield: 84% (296 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.38. IR (neat): 3387, 2897, 1675, 1465, 1378, 1025, 573 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 5.14 (s, 2H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 154.8, 140.3, 136.5, 133.6, 133.0, 126.5, 123.8, 121.5, 121.1, 121.1, 45.9. Calc. for $C_{13}H_{10}BrN_3O_4$ $[M+H]^+$: 351.9933 Obser.: 351.9927.

2.6.15 *N*-Allyl-*N*-nitrosoaniline (2n)

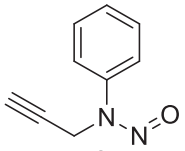


2n

The title compound was obtained as dark brown oil. Yield: 94% (152 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5,

R_f = 0.54. IR (neat): 3542, 3410, 1634, 1438, 1332, 1241 cm^{-1} ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 2H), 7.47-7.42 (m, 2H), 7.36-7.31 (m,1H), 5.74 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.17 (m, *J* = 10.4, 2.5, 1.6 Hz, 1H), 5.10-5.04 (m, 1H), 4.62 (dt, *J* = 5.2, 1.7 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 141.9, 129.6, 129.5, 127.4, 119.5, 118.1, 46.8. HRMS: Calc. for $C_9H_{11}N_2O$ $[M+H]^+$: 163.0691, Obser.:163.0862.

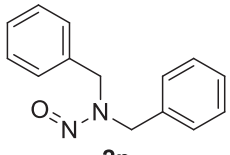
2.6.16 *N*-Propargyl *N*-nitrosoaniline (2o)



2o

The title compound was obtained as dark brown oil. Yield: 91% (145 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.52. IR (neat): 3598, 2357, 1657, 1478, 1359, 1298 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H), 7.50-7.45 (m, 2H), 7.39-7.35 (m, 1H), 4.70 (dd, *J* = 2.5, 1.2 Hz, 2H), 2.18 (t, *J* = 2.6 Hz, 1H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 140.9, 129.6, 127.8, 119.8, 75.8, 72.2, 32.8. HRMS: Calc. for $C_9H_9N_2O$ $[M+H]^+$: 161.0715, Obser.: 161.0711.

2.6.17 *N*-Nitroso dibenzylamine (2p)

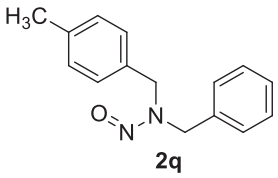


2p

The title compound was obtained as yellow crystals. M.p. 60-61 °C. Yield: 97% (219 mg). The residue was purified by column chromatography in silica gel eluting with

hexane:EtOAc 95:5, R_f = 0.54. IR (neat): 3450, 3100, 2988, 1499, 1531, 1322, 1105 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 3H), 7.33-7.27 (m, 3H), 7.26-7.22 (m, 2H), 7.07-7.02 (m, 2H), 5.20 (s, 2H), 4.66 (s, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 134.4, 133.8, 129.0, 128.8, 128.5, 128.4, 128.3, 127.8, 54.9, 44.8. HRMS: Calc. for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, Obser. 227.1163.

2.6.18 *N*-(4-Methylbenzyl)-*N*-nitroso benzylamine (2q)

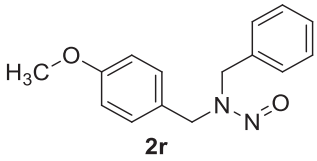


2q

The title compound was obtained as yellow oil. Yield: 96% (231 mg); (mixture of two isomers in ≈1:1 ratio). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.52.The title compound was obtained as yellow oil. Yield: 96% (231 mg). IR (neat): 3480, 3101, 2974, 1369, 1539, 1324, 1109 cm^{-1}.^{1}HNMR (500 MHz, $CDCl_3$) δ 7.45-7.37 (m, 3H), 7.35-7.30 (m, 3H), 7.28 (dt, *J* = 7.8, 4.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.15 (m, 4H), 7.10-7.06 (m, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.20 (s, 2H), 5.18 (s, 2H), 4.68 (s, 2H), 4.65 (s, 2H), 2.40 (s, 3H), 2.36 (s, 3H).^{13}CNMR (125 MHz, $CDCl_3$) δ 138.6, 137.8, 134.7, 134.1, 131.5, 131.0, 129.8, 129.6,

129.1, 128.9, 128.7, 128.6, 128.5, 128.0, 54.9, 54.8, 44.8, 44.7, 21.3, 21.3. HRMS: Calc. for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, Obser.: 241.1340.

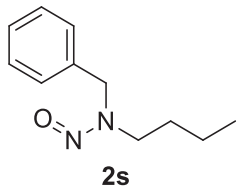
2.6.19 *N*-(4-Methoxybenzyl)-*N*-nitroso benzylamine (2r)



2r

The title compound was obtained as dark yellow liquid. Yield: 95% (244 mg); (mixture of two isomers in ≈1:1 ratio) The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.50. IR (neat): 3185, 2985, 1586, 1478, 1345, 1123 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 3H), 7.20 (qdd, *J* = 9.3, 4.8, 2.2 Hz, 6H), 7.11-7.06 (m, 2H), 6.97 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.92-6.87 (m, 2H), 6.85-6.80 (m, 2H), 6.78-6.72 (m, 2H), 5.09 (s, 2H), 5.06 (s, 2H), 4.57 (s,2H), 4.52 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 160.0, 159.4, 134.7, 134.1, 130.2, 129.9, 129.2, 129.0, 128.6, 128.5, 128.0, 126.4, 126.1, 114.6, 114.3, 55.5, 55.0, 54.6, 44.8, 44.6. HRMS: Calc. for $C_{15}H_{17}N_2O_2$ $[M+Na]^+$: 279.1108, Obser.: 279.1109.

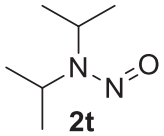
2.6.20 *N*-Nitroso *N*-butylbenzylamine (2s)



2s

The title compound was obtained as yellow oil. Yield: 91% (174 mg); (mixture of two isomers in ≈1:1 ratio) The residue was purified by column chromatography in gel eluting with hexane:EtOAc 95:5, R_f = 0.49. IR (neat): 3145, 2879, 1652, 1478, 1356, 1002 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 1H), 7.26-7.17 (m, 2H), 7.06-7.02 (m, 1H), 5.18 (s, 1H), 4.72 (s, 1H), 3.97 (t, *J* = 7.3 Hz, 1H), 3.38-3.35 (m, 1H), 1.66-1.58 (m, 1H), 1.32-1.10 (m, 4H), 0.89-0.74 (m, 3H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 135.0, 134.4, 129.1, 128.9, 128.6, 128.3, 128.3, 127.9, 56.2, 51.4, 46.1, 43.0, 30.2, 28.0, 20.4, 19.8, 13.7, 13.6. HRMS: Calc. for $C_{11}H_{17}N_2O$ $[M+H]^+$: 193.1341, Obser.: 193.1331.

2.6.21 *N*-Nitroso diisopropylamine (2t)

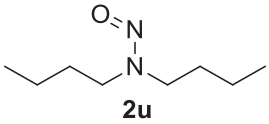


2t

The title compound was obtained as off-white crystals. M.p. 48 °C. Yield: 91% (118 mg); (mixture of two isomers in ≈1:1 ratio) The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.51. IR (neat): 2894, 2946, 1478, 1389, 1345, 1032. cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.04-4.96 (m, 1H), 4.26-4.18 (dh, *J* = 13.0, 6.6 Hz, 1H), 1.48 (dd, *J* = 6.7, 1.4 Hz, 6H), 1.13 (dd, *J*

= 6.9, 1.2 Hz, 6H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 50.6, 44.6, 23.8, 19.2. HRMS: Calc. for $C_6H_{15}N_2O$ $[M+H]^+$: 131.1184, Obser.: 131.1183.

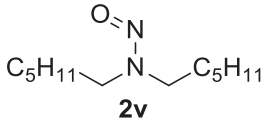
2.6.22 *N*-Nitroso dibutylamine (2u)



2u

The title compound was obtained as pale yellow oil. Yield: 94% (148 mg); The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.49. IR (neat): 2847, 2857, 1475, 1332, 1387, 1034 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 3.97 (t, *J* = 7.3 Hz, 2H), 3.44 (t, *J* = 9.8, 5.5 Hz, 2H), 1.69-1.60 (m, 2H), 1.42-1.34 (m, 2H), 1.33-1.24 (m, 2H), 1.24-1.15 (m, 2H), 0.90-0.85 (t, 3H), 0.84-0.80 (t, 3H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 51.9, 43.3, 30.2, 28.0, 20.3, 19.6, 13.5, 13.4. HRMS: Calc. for $C_8H_{19}N_2O$ $[M+H]^+$: 159.1497, Obser.: 159.1490.

2.6.23 *N*-Nitroso dihexylamine (2v)

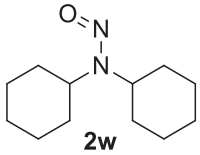


2v

The title compound was obtained as yellow oil. Yield: 80% (171 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.48. IR (neat): 2952, 2752, 1465, 1358, 1398, 1024 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.04-4.01 (m, 3H), 3.51-3.47 (m, 3H), 1.72-1.68 (m, 2H), 1.48-1.40 (m, 2H),

1.22-1.22 (m, 12H), 0.88-0.83 (m, 6H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 52.5, 43.8, 31.5, 31.4, 28.4, 27.0, 26.3, 26.1, 22.6, 14.1. HRMS: Calc. for $C_{12}H_{27}N_2O$ $[M+H]^+$: 215.2123, Obser.: 215.2121.

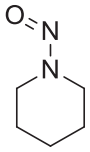
2.6.24 *N*-Nitroso dicyclohexylamine (2w)



2w

The title compound was obtained as off-white crystals. M.p. °C. Yield: 90% (189 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.51. IR (neat): 2876, 2975, 1448, 1376, 1123 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.92-4.75 (m, 2H), 3.78-3.61 (m, 2H), 1.94-1.84 (m, 6H), 1.69 (m, 4H), 1.56 (dd, *J* = 5.5, 4.2 Hz, 1H), 1.45-1.07 (m, 9H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 58.5, 52.2, 34.3, 29.3, 26.0, 25.4, 25.3, 25.2. HRMS: Calc. for $C_{12}H_{22}N_2O$ $[M+H]^+$: 211.1810, Obser.: 211.1790.

2.6.25 *N*-Nitrosopiperidine (2x)

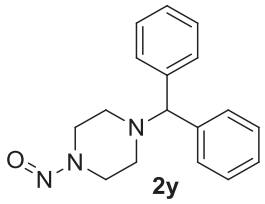


2x

The title compound was obtained as yellow crystals. M.p. 167 °C Yield: 82% (93 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.51. IR (neat): 2947, 2854, 1465, 1338, 1090 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.16-4.12 (m,

2H), 3.75-3.72 (m, 2H), 1.77-1.72 (m, 4H), 1.53-1.51 (m, 1H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 51.0, 39.9, 26.5, 24.9, 24.3. HRMS: Calc. for $C_5H_{10}N_2O$ $[M+H]^+$: 115.0871, Obser.: 115.0859.

2.6.26 1-Benzhydryl-*N*-nitrosopiperazine (2y)



2y

The title compound was obtained as yellow oil. Yield: 82% (230 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.53. IR (neat): 2940, 2870, 1678, 1458, 1342, 1102 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 4H), 7.29 (dd, *J* = 10.4, 4.8 Hz, 4H), 7.20 (ddt, *J* = 6.2, 5.0, 2.5 Hz, 2H), 4.30 (s, 1H), 4.25-4.22 (m, 2H), 3.81 (dd, *J* = 12.6, 7.1 Hz, 2H), 2.59 (dd, *J* = 12.5, 7.2 Hz, 2H), 2.40-2.27 (m, 2H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 141.9, 128.9, 127.9, 127.5, 52.0, 50.6, 50.0, 39.9, 29.8. HRMS: Calc. for $C_{17}H_{19}N_3O$ $[M+H]^+$: 282.1606, Obser.: 282.1607.

2.7 Procedure for Preparation of *N*-nitroso Cyclohexylhydroxylamine

<u>Step 1</u>: Synthesis of *N*-cyclohexylhydroxylamine

The round-bottom flask was charged with 1.67 g of $NH_2OH.HCl$ and (24 mmol, 1.2 equiv) and 0.96 g of NaOH (24 mmol, 1.2 equiv.) solution in 10 mL of water at 0 °C and subsequently, 2.24 g of cyclohexylhydroxylamine (20 mmol) added dropwise. Then, it was

allowed to stir for approximately for 2 h at 0 °C. The cyclohexanone oxime intermediate formation was monitored *via* TLC and then to it 15 mL of methanol along with a drop of methyl orange. The solution was acidified to a pink colour with addition of 2 M HCl in methanol. $NaBH_3CN$ (0.73 g, 11.6 mmol, 0.67 equiv.) was added portion wise at 0 °C. The reaction was monitored through TLC and the product was formed with 1 h. The reaction mixture was neutralized with NaOH (2 × 10 mL) and extracted with ethyl acetate (2 × 15 mL).The organic layer was dried over sodium sulfate and evaporated in vacuo under reduced pressure. The title product was obtained as white solid. (0.542 g, 24%). [M.p. 137 °C], IR (neat): 3054, 2950, 2850, 1460, 1330, 1010 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$+CD_3OD) δ 3.79 (s, 2H), 2.67 (tt, *J* = 10.8, 3.6 Hz, 1H), 1.80 (d, *J* = 10.7 Hz, 2H), 1.65 (d, *J* = 13.3 Hz, 2H), 1.54 (d, *J* = 12.7 Hz, 1H), 1.22-1.12 (m, 2H), 1.10-1.02 (m, 1H), 1.01-0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$+ CD_3OD) δ 60.5, 49.4, 49.2, 49.0, 48.9, 48.7, 30.1, 26.0, 24.6.

Step 2: *N*-nitrosation of *N*-cyclohexylhydroxylamine:

N-cyclohexylhydroxylamine (1.0 mmol) and *tert*-butyl nitrite (2.0 equiv.) was added at room temperature and allowed to stir for 5 min. After completion (as seen by TLC), *t*-BuOH was evaporated in vacuum to obtain desired product in good purity. The desired product was obtained in high purity through short silica purification as off-white to pale yellow solid. (95 mg, 83%). [M.p. 45 °C] IR (neat): 2942, 2853, 1452, 1330, 1089 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (tt, *J* = 11.4, 3.7 Hz, 1H), 1.88 (dd, *J* = 44.4, 12.3 Hz,

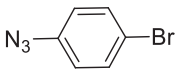
4H), 1.69-1.56 (m, 3H), 1.42-1.29 (m, 2H), 1.26-1.16 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.9, 28.4, 25.2, 24.8.

2.8 Procedure for the Synthesis of Aryl Azides from Aryl Hydrazines (4a-4d)

To a stirred solution of aryl hydrazine (2 mmol) in acetonitrile (2 mL), *tert*-butyl nitrite (2.0 equiv. for **3a-3c** and 5.0 equiv. for **3d**) was added drop-wise at room temperature. Further, the reaction mixture was allowed to stir at room temperature for appropriate time while the reaction progress was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL). The companied organic layer was dried over sodium sulphate, evaporated and the residue was subjected to column chromatography to obtain the desired products.

2.9 Analytical Data of Aryl Azides

2.9.1 4-Bromophenyl azide (4a)

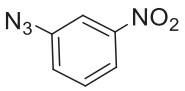


4a

The title compound was obtained as yellow oil. M.p. 20 °C. Yield: 91% (360 mg); The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.67. IR (neat): 2108, 2092 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 133.0, 120.8, 117.9. HRMS: Calc. for $C_6H_5BrN_3$ $[M+H]^+$: 197.9667,

Obser.: 197.9665.

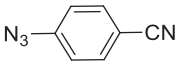
2.9.2 3-Nitrophenyl azide (4b)



4b

The title compound was obtained as dark orange solid. M.p. 54 °C. Yield: 85% (278 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.56. IR (neat): 2124, 2106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.87 (t, *J* = 2.1 Hz, 1H), 7.55-7.49 (m, 1H), 7.32 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 142.2, 130.8, 125.1, 119.9, 114.3. HRMS: Calc. for $C_6H_5N_4O_2$ $[M+H]^+$: 165.0413, Obser.: 165.0411.

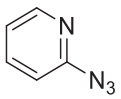
2.9.3 4-Cyanophenyl azide (4c)



4c

The title compound was obtained as yellow crystals. M.p. 60 °C. Yield: 89% (256 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.59. IR (neat) 2154, 2108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 2H), 7.11-7.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 134.0, 119.9, 118.5, 108.5. HRMS: Calc. for $C_7H_5N_4$ $[M+H]^+$: 145.0514, Obser.: 145.0512.

2.9.4 2-Azido pyridine (4d)



4d

The title compound was obtained as yellowish red crystals. M.p. 79 °C. Yield: 94% (224 mg). The residue was purified by column

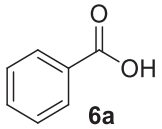
chromatography in silica gel eluting with hexane:EtOAc 95:5, R_f = 0.69. IR (neat): 2144, 2113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 6.9 Hz, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.72 (ddd, *J* = 8.9, 6.8, 0.8 Hz, 1H), 7.30-7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 132.0 125.6, 116.7, 116.2. HRMS: Calc. for $C_5H_5N_4$ $[M+H]^+$: 121.0514, Obser.: 120.0512.

2.10 Procedure for the Synthesis of Substituted Benzoic Acids from Corresponding Amides (6a-6d)

To a stirred solution of primary amide (1 mmol) in acetic acid (2 mL), *tert*-butyl nitrite (3 equiv.) was added slowly under N_2 atmosphere. Then the reaction mixture was allowed to stir for 60 min at 75 °C while the progress was monitored by TLC. After completion, the reaction mixture was evaporated to dryness to obtain corresponding benzoic acids in quantitative yield. However, to obtain high purity for NMR analysis, the crude products were subjected to short silica filtration using a mixture of ethyl acetate and hexane.

2.11 Analytical Data of Carboxylic Acids

2.11.1 Benzoic acid (6a)

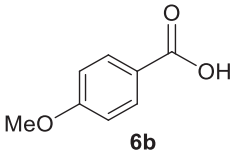


6a

The title compound was obtained as white crystalline solid. {Crude yield, >120 mg (>99%); After purification, 115 mg (95%)}. M. p. 122 °C. The residue was purified by column chromatography in silica gel

eluting with hexane:EtOAc 80:20, R_f = 0.25. IR (neat): 3300, 2547 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 12.43 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 133.8, 130.2, 129.3, 128.5. HRMS: Calc. for $C_7H_7N_2$ $[M+H]^+$: 123.0446, Obser.: 123.0424.

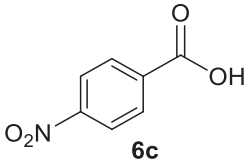
2.11.2 4-Methoxy benzoic acid (6b)



6b

The title compound was obtained as white crystals. {(Crude yield, >150 mg, (>99%); After purification, 144 mg (95%)}. M. p. 183 °C. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 80:20, R_f = 0.27. IR (neat): 3350, 2509 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 163.6, 132.1, 122.7, 113.7, 55.5. HRMS: Calc. for $C_8H_9N_3$ $[M+H]^+$: 153.0552, Obser.: 153.0551.

2.11.3 4-Nitrobenzoic acid (6c)

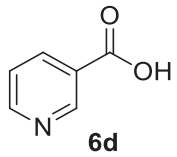


6c

The title compound was obtained as white to yellow crystals. {(Crude yield, >165 mg, (>99%); After purification, 155 mg (93%)}. M. p. 237 °C. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 70:30, R_f = 0.25. IR (neat): 3347, 2500 cm^{-1}. ^1H NMR (500 MHz, DMSO) δ 13.59 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 8.21 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz,

DMSO) δ 165.8, 149.9, 136.6, 130.6, 123.6. HRMS: Calc. for $C_7H_6NO_4$ $[M+H]^+$: 167.0219, Obser.: 167.0218.

2.11.4 Nicotinic acid (6d)



6d

The title compound was obtained as white crystals. (113 mg, 92%). M. p. 143 °C. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 75:25, R_f = 0.23. IR (neat): 3342, 1652 cm^{-1}. ^1H NMR (500 MHz, DMSO) δ 13.41 (s, 1H), 9.07 (s, 1H), 8.8-8.76 (m, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.56-7.50 (m, 1H). ^{13}C NMR (125 MHz, DMSO) δ 166.2, 153.2, 150.2, 136.9, 126.5, 123.7. HRMS: Calc. for $C_6H_6NO_2$ $[M+H]^+$: 124.0339, Obser.: 124.0337.

2.12 Spectral Data for Few Products

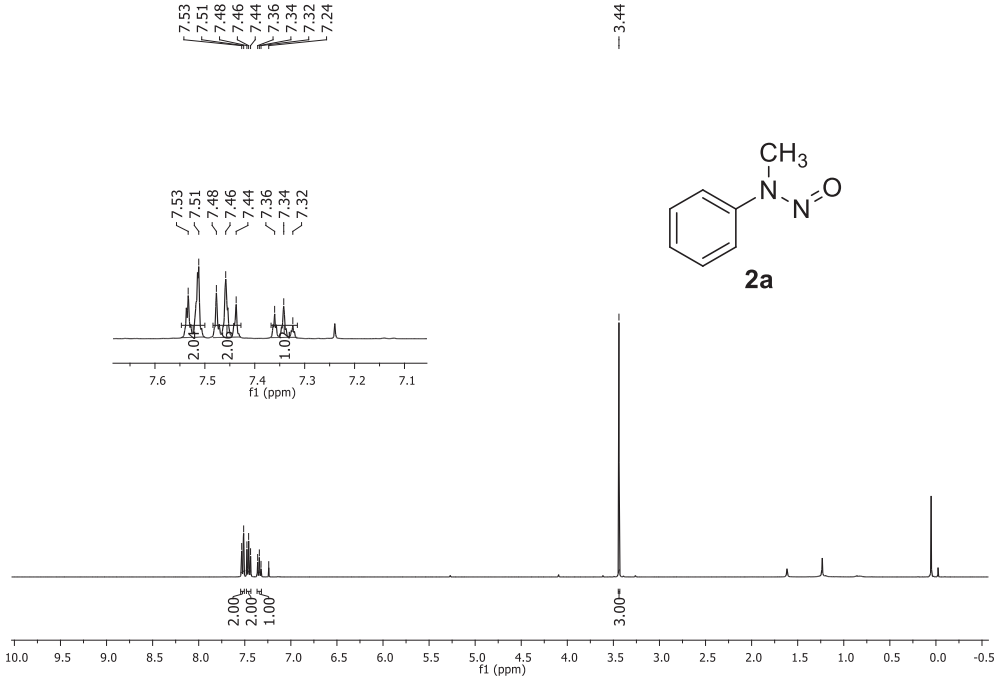


Figure 2.5 ^{1}H NMR of product **2a** in $CDCl_3$.

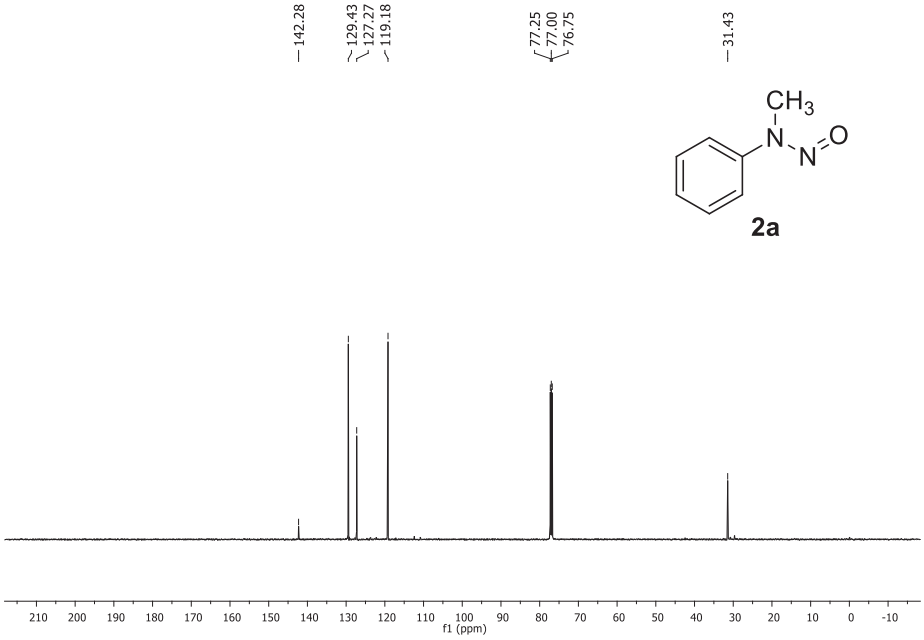


Figure 2.6 ^{13}C NMR of product **2a** in $CDCl_3$.

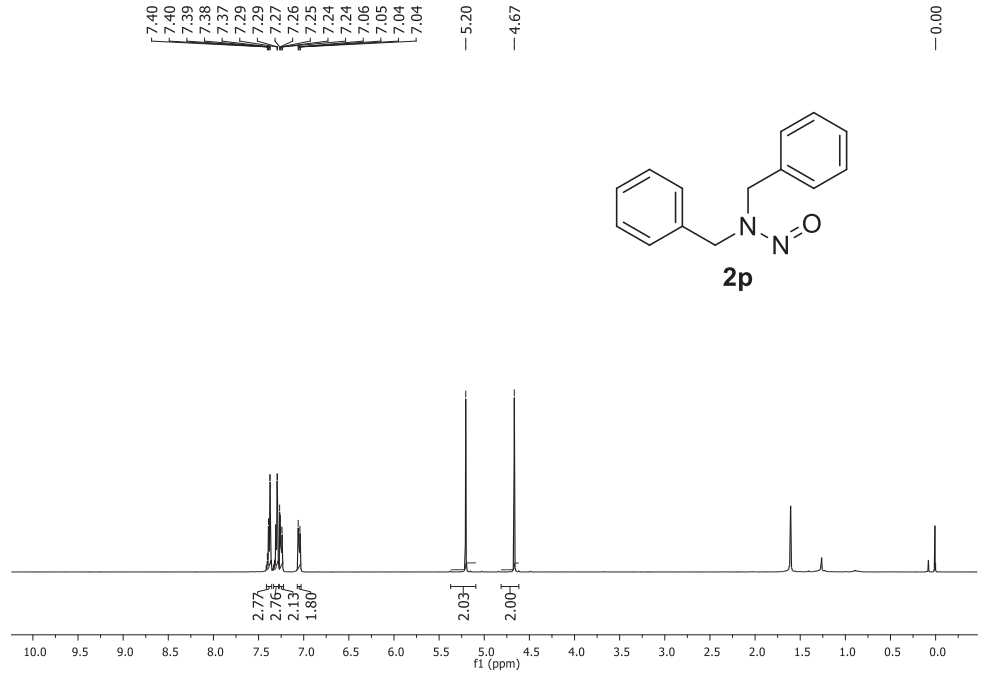


Figure 2.7 ^{1}H NMR of product **2p** in $CDCl_3$.

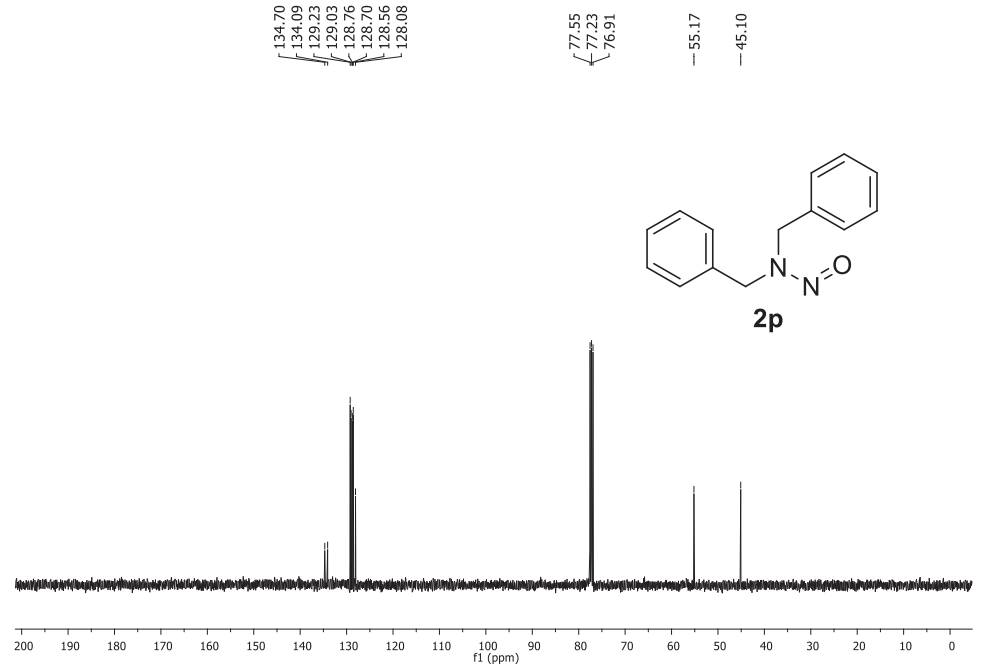


Figure 2.8 ^{13}C NMR of product **2p** in $CDCl_3$.

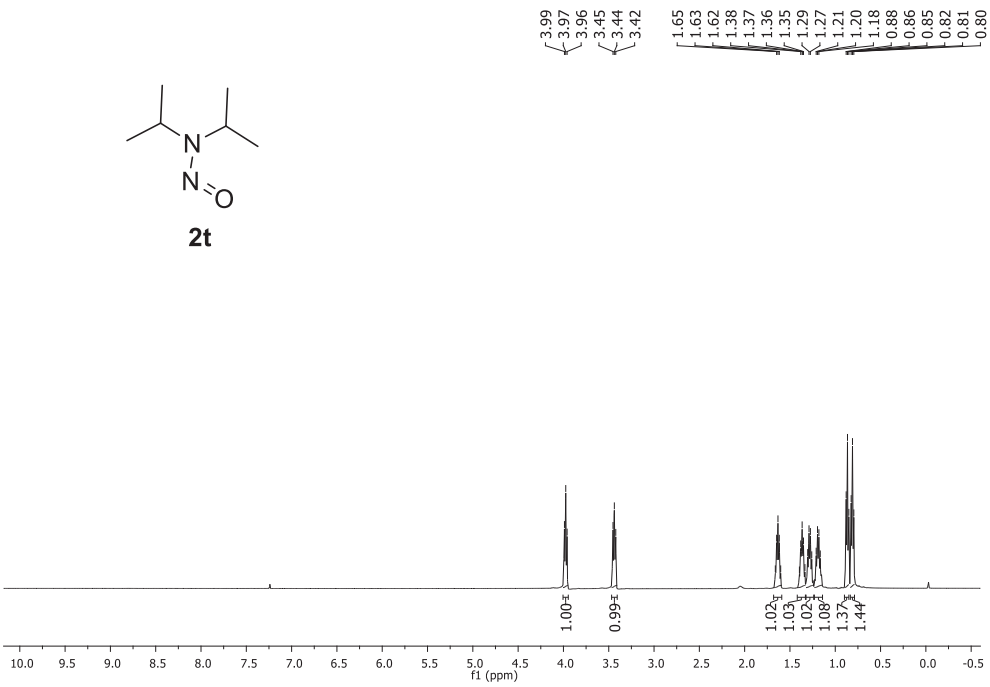


Figure 2.9 ^{1}H NMR of product **2t** in $CDCl_3$.

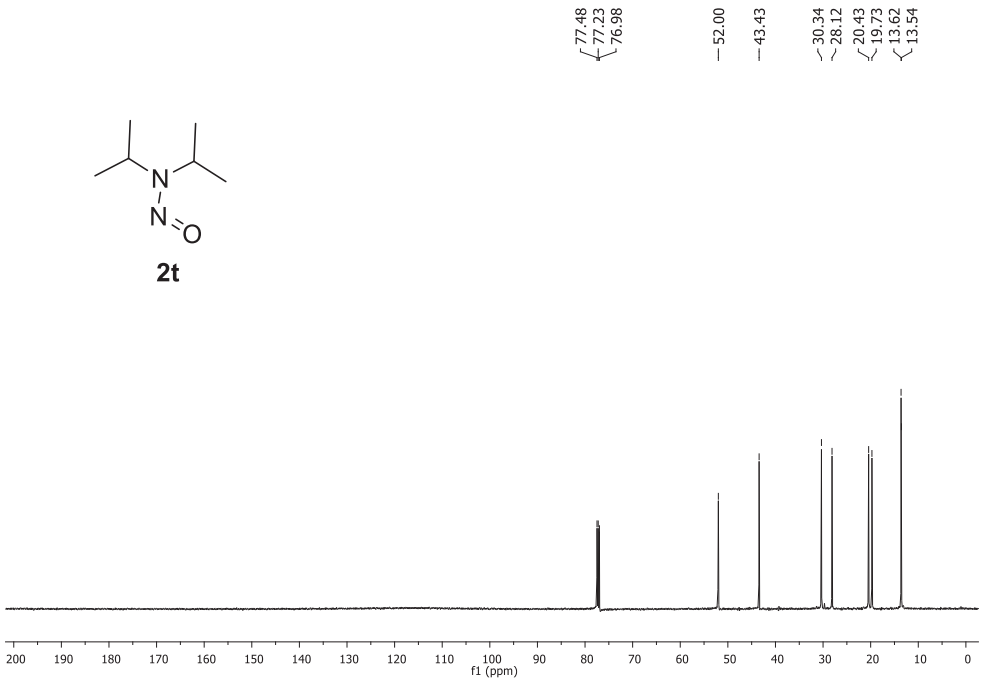


Figure 2.10 ^{13}C NMR of product **2t** in $CDCl_3$.

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