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An efficient synthesis of *N*-nitrosamines under solvent, metal and acid free conditions using *tert*-butyl nitrite

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Synthesis of various *N*-nitroso compounds from secondary amines is reported using *tert*-butyl nitrite (TBN) under solvent free conditions. Broad substrate scope, metal and acid free conditions, easy isolation procedure and excellent yields are the few important features of this methodology. The acid labile protecting groups such as *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyloxycarbonyl (Boc) as well as sensitive functional groups such as phenols, olefins and alkynes are found to be stable under the standard reaction conditions. Besides the *N*-nitrosation, TBN is also found to be an efficient reagent in few other transformations including aryl hydrazines to aryl azides and primary amides to carboxylic acids under mild conditions.

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

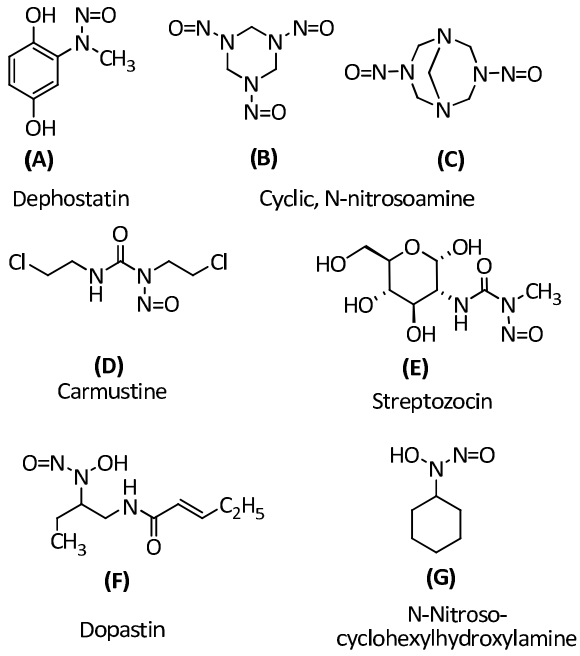

Figure 1. Biologically important *N*-nitroso compounds.

Besides the biological importance, *N*-nitrosamine compounds have become valuable intermediates in organic synthesis.[7] Preparations of biologically important α-disubstituted hydrazines[8] and mesoionic-heterocyclic compound sydnones[9] are the traditional applications of *N*-nitrosamines (Scheme 1). Aryl C-nitroso compounds can be obtained in good yield from *N*-nitrosamines through Fischer–Hepp rearrangement.[10] 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.[11] Recently, *N*-nitrosamine functional groups have emerged as a traceless directing group for

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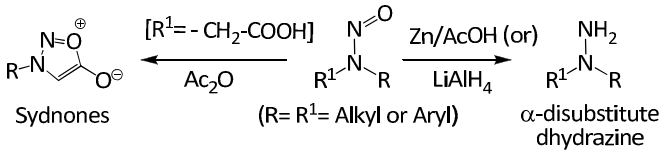
† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x. NMR Spectra is available for all the products. CIF file of compound **2f** with CCDC number 1444786 is available as supplementary information

the activation of inert C-H bond in aryl rings by associating with transition metals.[12] These C-H activation reactions provide a fruitful way to construct various biologically important heterocyclic compounds.



Scheme 1. Some traditional applications of *N*-nitrosamines

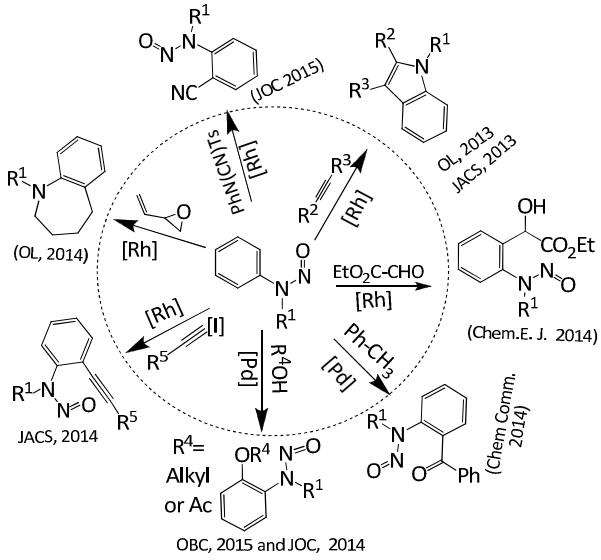
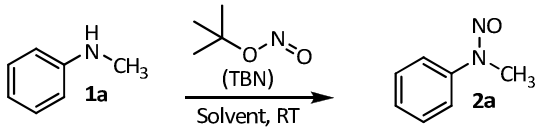


Figure 2. Recent applications of *N*-nitrosamines as a directing group for inert C-H bond activation.[12]

The chemical syntheses of *N*-nitrosamines are well-established reaction in organic synthesis.[7a] 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). Besides this traditional reagent, nitrosyl chloride,[13] nitrosonium tetrafluoroborate,[14] nitroso-crown ether adduct [NO^+,Crown, $H(NO_3)_2^-$],[15] Fremy's salt[16] and nitrogen oxides (e.g. N_2O_3, N_2O_4, etc)[17] were used to accomplish various *N*-nitroso compounds from corresponding secondary amines. In addition, various heterogeneous systems have been developed in the last decade using a combination of sodium nitrite with solid acids[18] or nitrogen oxide with different solid supports.[19] However, most of these methods proceed through a strong acidic condition which limits their use in a complex synthesis, particularly, when there is an acid-labile group on the substrate. Moreover, preparation, handling and storing of some of these reagents are very difficult which further limit their extensive uses in organic synthesis. Dealkylative nitrosation of *tert*-amines have been performed previously using some alkyl nitrites.[20] Very recently, nitromethane (CH_3NO_2) has been employed as an alternative source for generating nitrosyl (NO) moiety in the presence of various oxidizing systems (e.g. IBX or KI/TBHP or [Cu]/O_2).[21] However, these methods are not practical on a parallel synthesis due to poor yields and harsh reaction conditions. In this context, development of an acid free and metal free nitrosating reagent which will work efficiently under mild conditions remains an important goal. 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.[22]

tert-Butyl nitrite (TBN) is a very useful synthetic reagent frequently used for diazotization reactions.[23] In addition, TBN is also explored in a regiospecific C-nitration of phenols, azoarenes, arylboronic acids, anilides, aromatic sulfonamides, olefins and alkynes.[24] Recently, a regioselective C-nitrosation of imidazoheterocycles has been accomplished by using *tert*-butyl nitrite under catalyst free condition.[25] As a metal-free reagent, *tert*-butyl nitrite has many advantages like commercial availability, inexpensiveness, easy handing, medium volatility, good solubility in common solvents, etc. In this context, here we would like to report an important application of *tert*-butyl nitrite *i.e.* *N*-nitrosation of secondary amines under solvent free conditions.

Table 1. Nitrosation of *N*-methyl aniline using *tert*-butyl nitrite.[a]



Entry	Solvent	TBN (equiv.)	Time (min)	Yiled (%)[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	CH_3CN	1.5	30	90
7	Diethyl Ether	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]

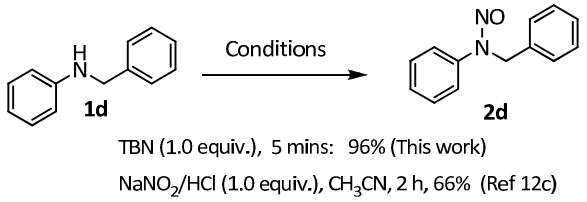
[a]Reaction conditions: Amine (1 mmol) and TBN was stirred in the respective solvents (2 mL) at room temperature. [b]Isolated yields. [c]Crude yield (seen in ^{1}H NMR). [d]n-Butyl nitrite was employed. [e]Isoamyl nitrite was employed.

At the outset, commercially available *N*-methylaniline (**1a**) was used as a model substrate for *N*-nitrosation reaction with *tert*-butyl nitrite (TBN). The reactions were performed at room temperature in various protic and aprotic solvents (Table 1). Dichloromethane provides the desired product **2a** in 81% with one equiv. of TBN after 40 minutes (Table 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 1, entry 2). Similarly, other aprotic solvents such as chloroform, dichloroethane, diethyl ether,

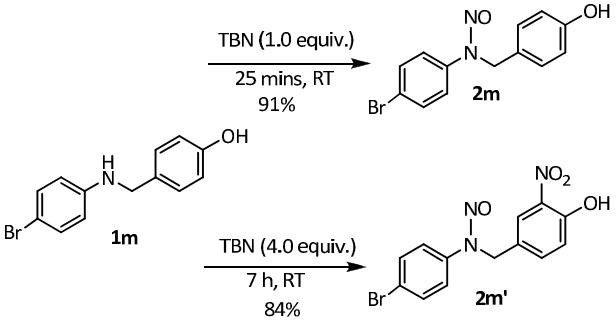
tetrahydrofuran and acetonitrile took around 20-30 minutes and provide the desired product in good to excellent yields (Table 1, entries 3-7). However, the protic solvents such as methanol, ethanol and H_2O took slightly longer reaction time (45-90 mins) for completion which may be due to the interaction of nucleophilic solvents with TBN (Table 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 gets an 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 chemical reaction should be favored under solvent free conditions.[22] Development of solvent free protocols appears to be an ideal case, because, solvent free reactions not only reduce the environmental pollution but also high yielding and cost effective.[26] However, to best of our knowledge so far there is no convenient solvent free protocol has been described for the preparation of *N*-nitrosamines. Hence, the *N*-nitrosation of methylaniline (**1a**) was attempted under solvent free condition using one equiv. of *tert*-butyl nitrite at room temperature (Table 1, entry 11). We were pleased to see a quantitative formation of *N*-nitroso-*N*-methylaniline (**2a**) within 5 minutes. Although, the other frequently used alkyl nitrites such as n-butyl nitrite and isoamyl nitrite provide the desired product in comparable yield (Table 1, entries 12 and 13), *tert*-butyl nitrite offers some important advantages over others. For example, *tert*-butanol *i.e.* the resulted byproduct of tert-butyl nitrite during the *N*-nitrosation, is less susceptible to further reactions (e.g. oxidation, nucleophilic substitution, etc.) when compared with primary alcohols which is resulted from n-butyl nitrite and isoamyl nitrite. In addition, *tert*- butanol is completely miscible with water while n-butanol and isoamyl alcohol has limited water solubility (e.g. water solubility of isoamyl alcohol: 28 g/L and n-butanol: 73 g/L) which increases the difficulty in isolation of pure products through simple aqueous work up procedures. 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 exposures of chemists to the carcinogenic *N*-nitroso compounds.

Prompted, *N*-nitrosation of various secondary amines was studied using TBN under solvent free conditions and the results are summarized in Table 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, **2b**-**2i**). In all the cases quantitative conversion (>94%) was observed irrespective of substituents 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*-benzylanilines to corresponding nitrosamines.[12c] For example, *N*-benzyl *N*-nitrosoaniline (**2d**) was obtained only in 66% from corresponding secondary amine using the traditional procedure while the current method (*i.e.* TBN) provides 96%, which clearly distinguish the efficiency of TBN over $NaNO_2$/HCl (Scheme 2). On the other hand, TBN is also found to be very efficient in nitrosating sterically hindered anilines where *N*-nitroso *N*-isopropylaniline was accomplished from corresponding secondary amine in high yield within 60 minutes (Table 2, **2j**).



Scheme 2. Conversion of *N*-benzylaniline to corresponding *N*-nitrosoaniline using $NaNO_2$-HCl and TBN.

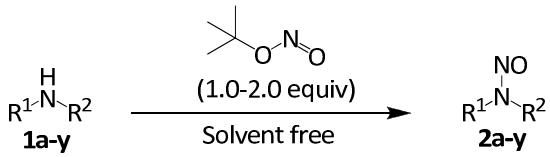


Scheme 3. Nitrosation reaction with N-(4-Hydroxybenzyl) 4-bromoaniline (**1m**).

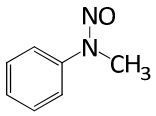
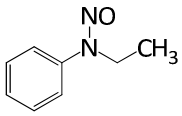
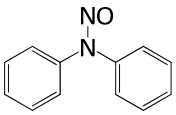
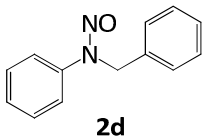
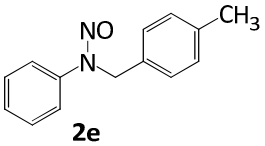
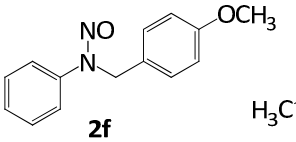
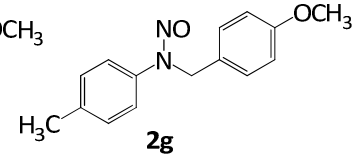
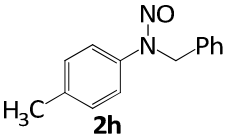
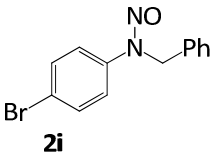
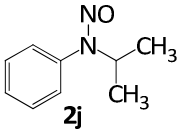
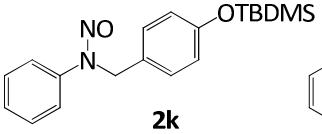
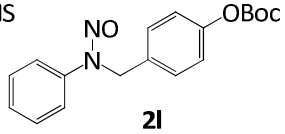
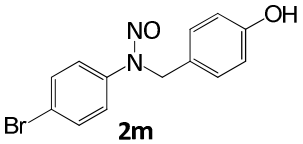
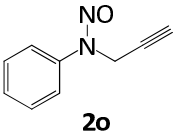
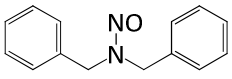
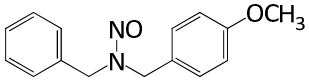
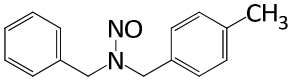
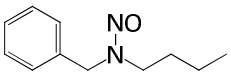
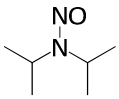
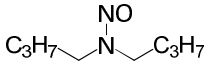
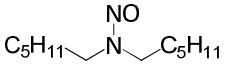
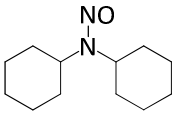
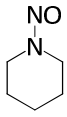
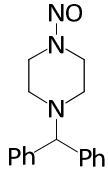
Functional group and protecting group tolerance is one of the most important aspects in multistep organic synthesis. In order to test the compatibility of commonly used acid labile protecting groups such as *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyloxycarbonyl (Boc), compounds **1k** and **1l** have been synthesized and subjected for *N*-nitrosation reactions under optimized condition. It was found that both TBDMS and Boc protecting groups remain stable during the reaction and 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,[24d, 24m, 24n] *N*-(4-Hydroxybenzyl)4-bromoaniline (**1m**), *N*-allyl aniline (**1n**) and *N*-propargyl aniline (**1o**) (*i.e.* substrates containing secondary amine with phenol, olefin and alkyne functionalities) were subjected for 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 show the broad scope of this methodology. Moreover, with an excess amount of TBN (≈4 equiv.) 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 3).

Further to extend the scope of this methodology, *N*-nitrosation of various dibenzyl, benzyl alkyl, dialkyl and cyclic secondary amines were carried out under optimized conditions (**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 (**2p**-**2s**). On the other hand, dialkyl and cyclic secondary amines (**1t**-**1y**) undergo *N*-nitrosation within the period of 4-5 hrs to provide 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.

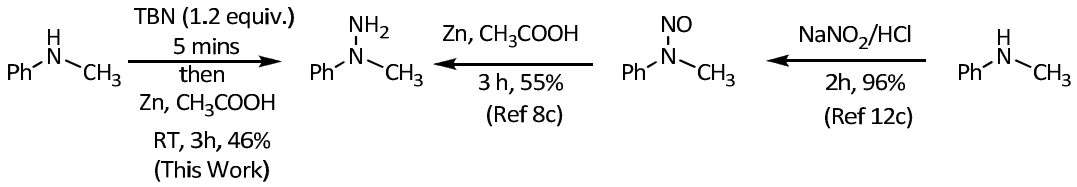
Table 2. Nitrosation of secondary amines using *tert*-butyl nitrite under solvent free conditions.[a,b]



1a-y **2a-y**

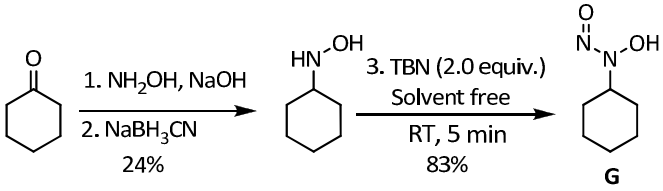
 **2a** (<5 min, 97%)	 **2b** (<5 min, 95%)	 **2c** (10 min, 98%)	 **2d** (5 min, 96%)
 **2e** (15 min, 95%)	 **2f** (15 min, 94%)	 **2g** (15 min, 94%)	 **2h** (15 min, 95%)
 **2i** (10 min, 95%)	 **2j** (60 min, 91%)	 **2k** (20 min, 92%)	 **2l** (20 min, 95%)
 **2m** (25 min, 91%)[c]	 **2n** (<5 min, 94%)	 **2o** (10 min, 91%)	 **2p** (1 h, 97%)[d]
 **2q** (1 h, 95%)[d]	 **2r** (45 min, 96%)[d]	 **2s** (1 h, 91%)[d]	 **2t** (8 h, 91%)[e]
 **2u** (8 h, 94%)[e]	 **2v** (8h, 80%)[e]	 **2w** (8 h, 90%)[e]	 **2x** (8 h, 82%)[e]	 **2y** (8 h, 82%)[e]

[a]Reaction conditions: Amine (1 mmol) and t-BuONO (1.0 equiv.) was stirred at room temperature or 45 °C. [b]Isolated yields. [c] Reaction was started at 0°C and allowed to stir at RT. [d]Reactions were carried out at 45 °C with 1.5 equiv. TBN. [e]Reactions were carried out at 45 °C with 2 equiv. TBN.



Scheme 5. One-pot synthesis of 1-methyl-1-phenylhydrazine directly from *N*-methylaniline.

The scope of this methodology was further investigated by attempting the synthesis of biologically important *N*-nitroso-*N*-cyclohexylhydroxylamine (Figure 1, **G**). The synthesis of compound **G** was accomplished from cyclohexanone in three steps as shown in Scheme 4. The reaction of cyclohexanone with hydroxylamine hydrochloride followed by sodium cyanoborohydride reduction provides the *N*-cyclohexylhydroxylamine in 24% yield[27] which was subjected for the *N*-nitrosation under solvent free condition using *tert*-butyl nitrite. The *N*-nitrosation reaction underwent smoothly at room temperature to provide the desired product in 83% yield.



Scheme 4. A synthetic route for the preparation of compound **G.**

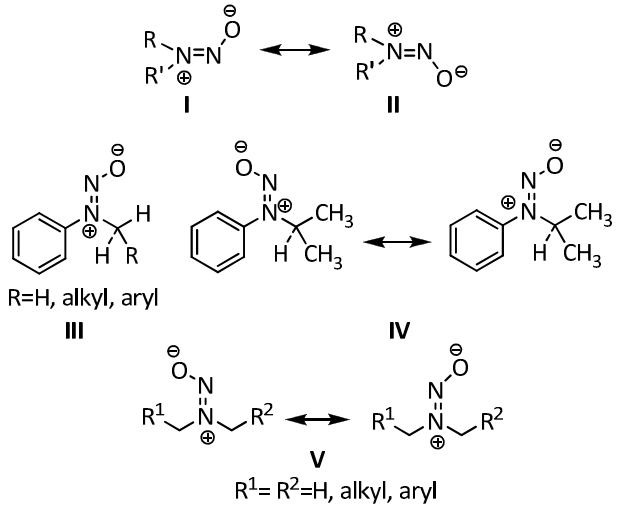


Figure 3. Different orientations of N-nitrosamines.

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 3, **I** and **II**).[7a] 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, 2k-2m**). The orientation of *N*-nitroso group in these compounds is expected to be less hindered side (*i.e.* alkyl side, Figure 3, **III**) and this was further confirmed by single crystal XRD analysis of the product **2f** (Figure 4).[28] 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 3, **IV** and **V**, see ESI).

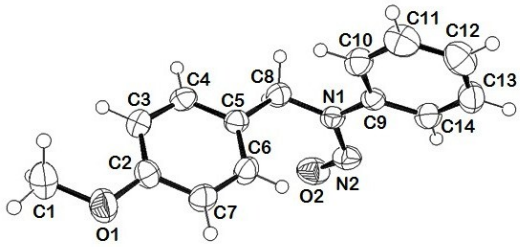


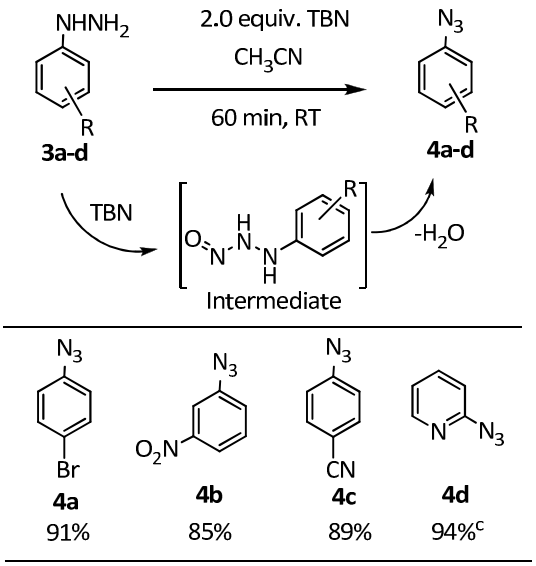
Figure 4. ORTEP (at 50% ellipsoid) diagram of **2f.** [28]

α-Disubstituted hydrazines and their derivatives exhibit a wide range of biological properties.[29] In addition, they are also used as building blocks for the construction of various biologically important heterocyclic compounds.[29] One-pot syntheses of α-disubstituted hydrazines directly from secondary amines (*via N*-nitrosamine intermediate) is not well-established reaction in organic synthesis. Nevertheless, it is expected that the development of such protocol will reduce the time and labor as well as prevent the exposure of chemists to *N*-nitrosoamines. In a representative reaction, we have attempted one-pot synthesis of 1-methyl-1-phenylhydrazine directly from *N*-methylaniline, *i.e.* nitrosation followed by reduction using TBN and zinc-acetic acid, respectively (Scheme 5). The reaction provides 46% (under non-optimized conditions) of the desired product while the usual two step protocol provides 53% (overall yield) which basically require workup procedures, isolation of intermediates, etc. (Scheme 5).[8c]

Aryl azides have found growing applications in organic synthesis especially for the assembly of heterocyclic compounds and dendrimers.[30] 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 3) from which a water molecule is removed to yield the corresponding azide. This transformation was previously explored with $NaNO_2$/HCl,[31] N_2O_4,[32] nitrosyl tetrafluoroborate[33] and Ph_3P/Br_2/n-Bu_4NNO_2[34] where these reactions proceed through an acidic medium. 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 3). 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 high yield (>85%) under the same conditions. Moreover, heterocyclic azide *i.e.* 2-pyridyl azide (**4d**) was obtained in a

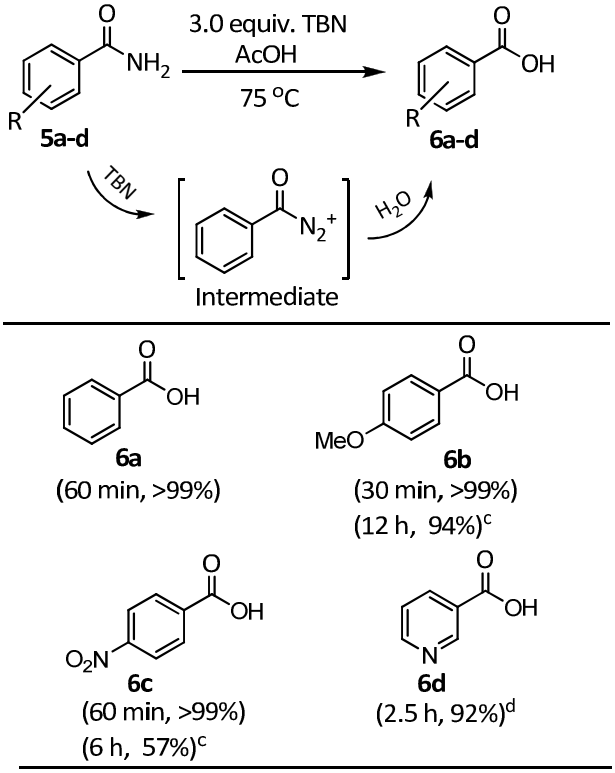
quantitative yield (94%) from 2-hydrazinopyridine which shows the broad synthetic utility of this methodology.

Table 3. Conversion of aryl hydrazines into corresponding azides.[a,b]



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

Table 4. Conversion of benzamides into benzoic acids. [a,b]



[a]Reaction conditions: Amide (1 mmol) and TBN (3.0 equiv.) was stirred in acetic acid (3mL) at 75 °C. [b]Isolated yield. [c]Reactions with *iso*-amyl nitrite (ref. 35c). [d]5.0 equiv. of TBN is used.

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.[35] The efficiency of TBN in this transformation was examined using benzamide as a model substrate. The reaction was performed using three equiv. of TBN in acetic acid at 75°C. The reaction provides benzoic acid (**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 is also compatible with heterocyclic amides where nicotinamide is 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.[35c] For example, conversion of 4-methoxybenzamide to corresponding acid was achieved within 30 mins using TBN while 12 hrs 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 6hrs while TBN provides quantitative yield in one hour. It is also worthy to mention that this transformation basically doesn't need any work-up procedures or column chromatography. Simple evaporation of acetic acid provides the desired products in enough purity. Overall, the *tert*-butyl nitrite is found to be a versatile reagent in organic synthesis.

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. One-pot synthesis of α-disubstituted hydrazine from secondary amine was successfully demonstrated using TBN as nitrosating reagent. Besides the *N*-nitrosation, TBN is 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. The scope and limitations of these preliminary reports will be explored in due course.

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