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$Ph_3P/Br_2/n\text{-}Bu_4NNO_2$ as an efficient system for the preparation of *N*-nitrosamines and azides

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ABSTRACT

The combination $PPh_3/Br_2/n\text{-}Bu_4NNO_2$ was developed as a new reagent system for the efficient preparation of *N*-nitrosamines and azides from the corresponding amines and hydrazine derivatives, respectively, at 0 °C to room temperature, in excellent yields.

Nitroso compounds and their reactions have been studied extensively. Their pharmaceutical applications have been studied[1] and many of their uses for the treatment of cardiovascular and central nervous system diseases, and diseases related to immunity and physiological disorders have been reported.[2]

Different nitrosating agents as sources of nitrosonium ions (NO^+), including nitrous acid (HNO_2), nitrosyl chloride (NOCl), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), nitrosonium tetrafluoroborate ($NO^+BF_4^-$) and alkyl nitrites have been applied widely.[3] Fremy's salt (potassium nitrosodisulfonate),[4] bis(triphenylphosphine)nitrogen(1^+) nitrite,[5] *N*-haloamides and sodium nitrite under phase-transfer conditions,[6] oxyhyponitrite,[7] oxalic acid dihydrate[8] or trichloroisocyanuric acid[9] and sodium nitrite, silica sulfuric acid/$NaNO_2$,[10] $NO^+\cdot Crown\cdot H(NO_3)_2^-$],[11] inorganic chloride salts/$NaNO_2$[12] and PVP-N_2O_4[13] have also been used as efficient nitrosating agents. Due to the instability and inconvenient handling of aqueous solutions of NO, there is an increasing interest in using compounds capable of generating NO in situ, that is, NO donors. Organic nitrates and nitrites, metal NO-complexes, nitrosamines and nitrosimines are the most well-known NO donors.

In addition to the interesting biological properties of nitrosamines, due to their strong mutagenic and carcinogenic properties,[14] the development of new reagents for their practical synthesis is of interest. Previously, we reported that triphenylphosphine in mixed reagent systems was capable of converting alcohols, thiols, and trimethylsilyl and tetrahydropyranyl ethers to alkyl halides, nitriles, azides, thiocyanates and isothiocyanates. The formation of 1,2-benzisoxazoles and nitration of aromatic compounds were also carried out with Ph_3P mixed reagent systems.[15] In continuation of our studies on the use of Ph_3P, we now report $PPh_3/Br_2/n\text{-}Bu_4NNO_2$ as a new mixed reagent system for the generation of nitrosonium ions under mild and efficient reaction conditions.

Different secondary amines were subjected to reaction with this reagent with a ratio of 1.2/1.2/1.2/1.0 of $Ph_3P/Br_2/n\text{-}Bu_4NNO_2$/amine in CH_2Cl_2 at room temperature (Scheme 1).

The reactions were found to be complete almost immediately and high to excellent yields of the corresponding nitrosamines were obtained. The results of the *N*-nitrosation of amines are shown in Table 1 (entries 1–10).

In a typical experiment, to a flask containing a stirred mixture of Ph_3P (1.2 mmol, 0.314 g) and Br_2 (1.2 mmol, 0.07 mL) in dry dichloromethane (5 mL) was added $n\text{-}Bu_4NNO_2$ (1.2 mmol, 0.348 g) at room temperature. *N*-Benzylethylamine (1.0 mmol, 0.15 mL) was then added to the reaction mixture. TLC monitoring showed

$$R^1R^2NH \xrightarrow[CH_2Cl_2,\ rt.]{Ph_3P/Br_2/\ n\text{-}Bu_4NNO_2} R^1R^2NNO$$

Scheme 1.

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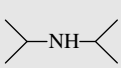
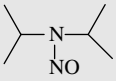
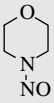
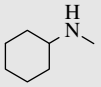
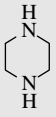
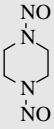
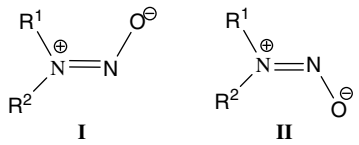
Table 1
Nitrosation of amines in CH_2Cl_2 at room temperature[a]

Entry	Compound	Product	Yield[b] (%)
1	$(PhCH_2)_2NH$	$(PhCH_2)_2NNO$	95
2	$PhCH_2NHCH_2CH_2Ph$	$PhCH_2N(NO)CH_2CH_2Ph$	95
3	$PhCH_2NHCH_2CH_3$	$PhCH_2N(NO)CH_2CH_3$	91
4	$PhCH_2NHCH_3$	$PhCH_2N(NO)CH_3$	94
5	Et_2NH	Et_2NNO	91
6			90
7			92
8			89
9			94
10			90[c]
11	$(PhCH_2)_3N$	$(PhCH_2)_2NNO$	90[c]
12	Et_3N	Et_2NNO	92[c]

[a] Quantitative conversion was obtained almost immediately.
[b] Isolated yields.
[c] The stoichiometry of $Ph_3P/Br_2/n\text{-}Bu_4NNO_2$/amine was 2.4/2.4/2.4/1.

completion of the reaction after 1 min. The solvent was evaporated and the residue was chromatographed on a silica gel column using *n*-hexane–ethyl acetate (3:1) as eluent. Benzyl ethylnitrosamine was obtained in 91% yield as an equal mixture of two isomers. [^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.9 (3H, t; J = 7.2 Hz), 1.3 (3H, t; J = 7.2 Hz), 3.5 (2H, q; J = 7.2 Hz), 4.0 (2H, q; J = 7.2 Hz), 4.8 (2H, s), 5.2 (2H, s), 7.3 (10H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 10.94, 13.90, 38.22, 45.69, 46.56, 55.73, 127.78, 128.09, 128.16, 128.48, 128.79, 128.96, 134.30, 134.83].

Due to the existence of π-bonding between the adjacent nitrogen atoms in nitrosamines, there is restricted rotation around the N–N bond, as represented by the geometric resonance contributors (**I**) and (**II**).



I **II**

These isomers were readily observed in the NMR spectra of these systems. Thus, depending on the orientation of the nitroso-oxygen atom relative to the alkyl substituents, the chemical shifts for the protons of R^1 and R^2 showed considerable differences. In the ^{1}H NMR spectrum of symmetrical dialkyl nitrosamines such as diethyl *N*-nitrosamine, two distinct methyl and methylene signals were observed for the two different ethyl groups. This is in agreement with spectroscopic data in the literature.[16]

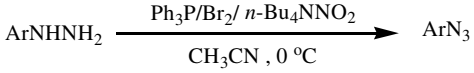
We also studied the application of our system for the nitrosation of two tertiary amines. It was observed that under our reaction conditions, dealkylation of tertiary amines occurred accompanied by *N*-nitrosation (Table 1, entries 11 and 12). In comparison with related methods for this conversion which usually achieve moderate yields under strongly acidic conditions,[17] the present method proceeds under mild reaction conditions in excellent yields.

This reagent system was also applicable for the preparation of various azides through nitrosation of their corresponding hydrazines and hydrazides (Scheme 2). Treatment of phenylhydrazine as a model compound with the mixed reagent system in acetonitrile at 0 °C rapidly gave the corresponding azide in 94% isolated yield through the intermediacy of the corresponding β-nitroso hydrazine.

The efficiency of this method is compared with some reported methods in Table 2.

As is evident from Table 2, our method for the conversion of hydrazines and hydrazides to azides avoids long reaction times, low and high temperatures and the use of gaseous dinitrogen tetroxide[19] which is not easy to handle.

This method was then applied successfully for the preparation of various azides. All the reactions occurred rapidly at 0 °C with high yields (Table 3).



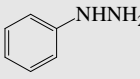
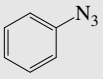
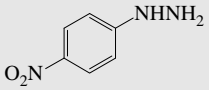
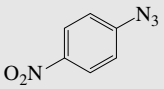
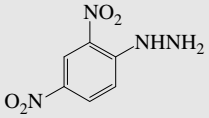
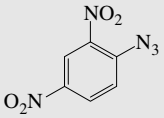
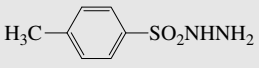
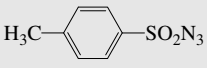
Scheme 2.

Table 2
Comparison of the reaction conditions of the present method with those reported in the literature

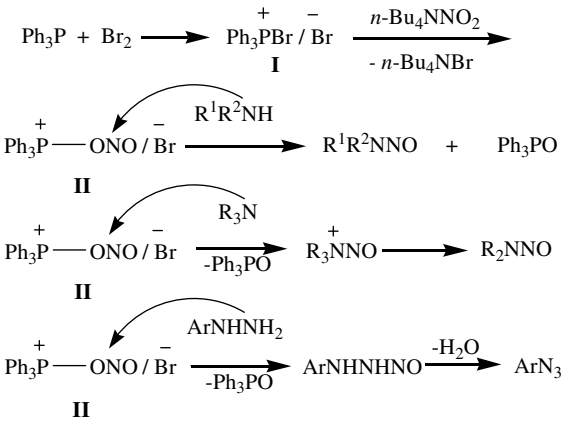
Entry	Reagent	Conditions	Time	Yield%
1	**$Ph_3P/Br_2/n\text{-}Bu4NNO_2$**	**0 °C**	**Immediately**	**94**
2	$NaNO_2$/HCl	−5 °C[18]	25–30 min	65–68
3	N_2O_4/CH_3CN	−20 °C[19]	20 min	87
4	Clay supported ferric nitrate	Reflux in CH_2Cl_2[20]	2 h	63
5	$NOBF_4$	−40 °C[21]	~10 min	—[a]

[a] Yield is not reported in the literature.

Table 3
Conversion of hydrazines and hydrazides to azides in acetonitrile at 0 °C[a]

Entry	Reactant	Product	Yield[b] (%)
1			94
2			90[c]
3			87
4			95
5			92

[a] When the reactions were carried out at room temperature, an unidentified side product was also formed and the yield of azide decreased.
[b] Isolated yield.
[c] Spectral data for 4-nitrophenyl azide; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.07 (2H, m), 8.15 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 119.38, 125.56, 144.55, 146.85.



Scheme 3.

A typical procedure for this transformation is as follows. To an efficiently stirred solution of Ph_3P (1.2 mmol, 0.314 g) Br_2 (1.2 mmol, 0.07 mL) and n-Bu_4NNO_2 (1.2 mmol, 0.348 g), in dry CH_3CN (5 mL) at 0 °C was added 4-nitrophenylhydrazine (1 mmol, 0.153 g). The reaction was monitored by TLC. After the disappearance of the starting material, the solvent was evaporated. Column chromatography of the crude mixture on silica gel using n-hexane as eluent gave 4-nitrophenyl azide in 90% yield.

We propose a mechanism in which, in the first stage, triphenylphosphine reacts with bromine to form the phosphonium bromide **I**. Then, addition of n-Bu_4NNO_2 to **I** produces the intermediate **II** and n-Bu_4NBr. This intermediate reacts with R^1R^2NH, R_3N or $ArNHNH_2$ via substitution at the nitrogen atom of **II** according to Scheme 3. Generation of triphenylphosphine oxide in these reactions is considered a strong driving force.

We were also interested in using another source of bromine for these reactions, however, when we used NBS, similar reactions with Ph_3P/NBS/n-Bu_4NNO_2 gave no reaction even after a long reaction time.

To summarize, we have described a highly efficient method for the preparation of nitrosamines and azides. The $Ph_3P/Br_2/n$-Bu_4NNO_2 system acts as a source for the delivery of NO^+ under very mild reaction conditions. The ready availability of the reagents, excellent yields and short reaction times are advantages worthy of mention for the present method.

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