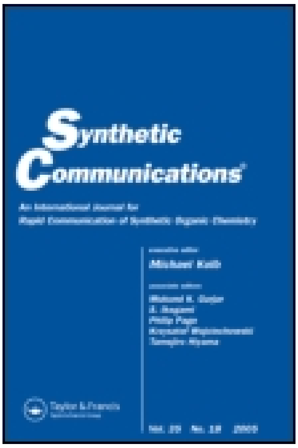

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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N-Nitrosation of Secondary Amines Using p-TSA-$NaNO_2$ as a Novel Nitrosating Agent Under Mild Conditions

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Version of record first published: 04 Feb 2010.

To cite this article: Sanjay P. Borikar & Vincent Paul (2010): N-Nitrosation of Secondary Amines Using p-TSA-$NaNO_2$ as a Novel Nitrosating Agent Under Mild Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:5, 654-660

To link to this article: http://dx.doi.org/10.1080/00397910903009448

Synthetic Communications®, 40: 654–660, 2010
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903009448

N-NITROSATION OF SECONDARY AMINES USING *p*-TSA-NaNO$_2$ AS A NOVEL NITROSATING AGENT UNDER MILD CONDITIONS

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A combination of p-toluenesulfonic acid (p-TSA) and sodium nitrite was used as a novel effective nitrosating agent for the N-nitrosation of secondary amines to their corresponding nitroso derivatives under mild and heterogeneous conditions in moderate to excellent yields.

Keywords: *N*-nitrosation; nitroso amines; secondary amines; *p*-toluenesulfonic acid

INTRODUCTION

N-Nitrosation chemistry has been an interesting area for mechanistic organic and biological chemists.[1] An effort has been made to combine both the synthetic and mechanistic aspects of nitrosation and transnitrosation.[2,3] However, *N*-nitroso compounds have also been reported to have strong carcinogenic and mutagenic properties.[4] The nitrosation of secondary (and tertiary) amines has been thoroughly studied, mainly because of the possible in vivo formation of nitrosoamines from naturally occurring secondary amines and sources of nitrous acid in the environment (foods, water, atmosphere, etc.). They have been used as pesticides, lubricants, and antioxidants.[5] The *N*-nitrosation of amines is an important and well-established reaction in organic synthesis.

These compounds are useful synthetic intermediates for the preparation of various *N,N*-bonded functionalities. Lithiation was followed by reaction with electrophiles and subsequent denitrosation, which could be applied to the electrophilic substitution of the secondary amines at the α-carbon in a regio- and stereoselective manner.[6] A partial double bond between two adjacent nitrogens in nitroso compounds, due to hindered rotation between the *N*-*N* single bond, results in many intriguing stereochemical features.[7] *N*-Nitroso compounds are generally synthesized by *N*-nitrosation of the corresponding NH-containing compounds (amines, amides, urea, etc.) by reaction with nitrosating agents.[8] The most common reagent for the synthesis of nitrosoamines is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol–water solvents.[9] In acidic medium ($pH < 4$), the main nitrosating species are nitrosonium ion, dinitrogen trioxide (N_2O_3) and nitrosyl

Received February 5, 2009.

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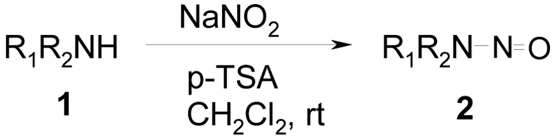
halides.[10,11] In basic or neutral medium, nitroprusside[12,10b,11] and alkyl nitrites[13] are effective nitrosating agents. Other nitrosating agents, such as *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS),[14] moist $SiO_2/NaNO_2$ in the presence of an acid (mostly solid acids or inorganic halides),[15] [NO^+-crown-$H(NO_3)^{2-}$],[16] and more recently charcoal impregnated with N_2O_4,[17] tin(IV) chloride,[18] combination of alumina with methane sulfonic acid (AMA),[19] tungstate sulfuric acid (TSA),[20] and acetic anhydride,[21] have also been reported. Several other nitrosating agents, such as Angeli's salt,[12] have also been used. There are some disadvantages such as poor yield, harsh reaction conditions, and the need for large amounts of reagent or catalyst. In *N*-nitrosation with AMA, the reactivity of methane sulfonic acid is low; therefore they were reported with the combination of alumina, and the yield is very poor compared to our method.

With regard to wide application of *p*-toluenesulfonic acid as reagent or catalyst in organic chemistry, the new nitrosating agent can be introduced and is useful in this direction. We think that the *p*-toluenesulfonic acid would be a proton source superior to all of the reported acidic solid supports or acidic resins such as polystyrene sulfonic acid and Naflon-H[22] for running reactions under heterogeneous conditions. In recent years, heterogenation of chemical systems is an active field in industrial and laboratorial chemistry because of simplification in handling procedures, reduction of corrosion, green chemistry, avoidance of by-products, easy and clean reaction, and simple workup.

RESULTS AND DISCUSSION

We hereby report a new nitrosating agent. The generation of NO^+ in the nitrosation reaction is the well-known key step. We have found that *p*-toluenesulfonic acid is a cheap, commercially and readily available reagent used in many organic synthesis. Therefore, we decided to apply *p*-toluenesulfonic acid–sodium nitrite as the new nitrosating agent for secondary amines. We report a simple and chemoselective method for the effective nitrosation of secondary amines under mild and heterogeneous conditions. Because, the *N*-nitrosoamines are highly toxic and carcinogenic, their production and dispersion are of interest to organic and biological chemists alike. A key feature of the present article is simple workup with easy removal of nitroso adducts as a result of the heterogeneous nature of the reaction. The different types of secondary amines **1** were subjected to the nitrosation reaction in the presence of *p*-toluenesulfonic acid and sodium nitrite in dichloromethane at room temperature (Scheme 1).

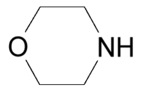
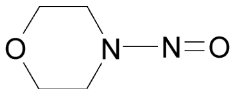
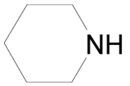
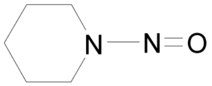
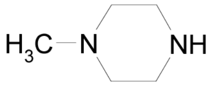
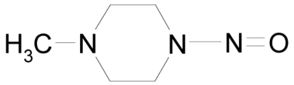
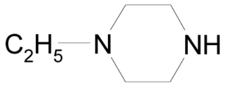
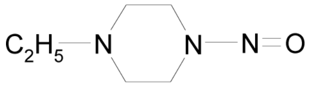
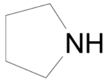
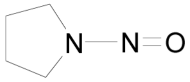
The nitrosation reaction was performed under mild and completely heterogeneous conditions at room temperature with moderate to excellent yields.

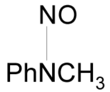
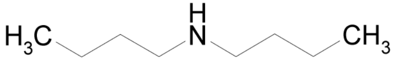
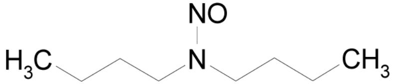
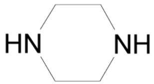
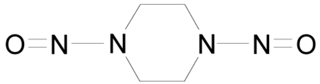
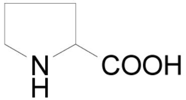
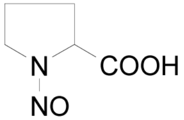


$$\underset{\mathbf{1}}{R_1R_2NH} \xrightarrow[\text{p-TSA}\ CH_2Cl_2,\ rt]{NaNO_2} \underset{\mathbf{2}}{R_1R_2N{-}N{=}O}$$

Scheme 1. *N*-Nitrosation of secondary amines.

Table 1. *N*-Nitrosation of secondary amines **1** at room temperature using *p*-toluenesulfonic acid and $NaNO_2$ in CH_2Cl_2

Entry	Substrate 1	Product 2	Time (min)	Yield[b] (%)
1	Et_2NH	$Et_2N-N=O$	20	93
2	$(iso\text{-}Pr)_2NH$	$(iso\text{-}Pr)_2N-N=O$	90	95
3	$(c\text{-}C_6H_{11})_2NH$	$(c\text{-}C_6H_{11})_2N-N=O$	2	95
4			5	97
5			3	92
6			20	95
7			15	85
8			5	97

9	$PhNHCH_3$	 $Ph\overset{NO}{N}CH_3$	4	91
10			4	95
11			5	95
12			720	90

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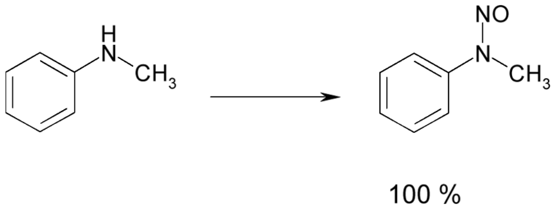
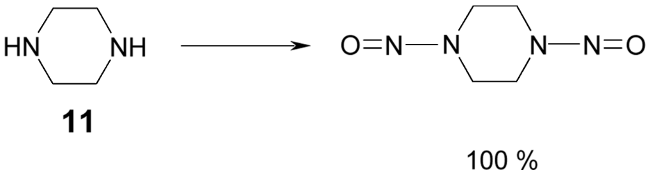
[a] All products are known, and their spectral and physical data are in accordance with authentic samples.

[b] Isolated yields.



Scheme 2. Chemoselective *N*-nitrosation of *N*-methyl aniline.



Scheme 3. Di-*N*-nitrosation of piperazine (**1K**).

This reaction can be efficiently carried out by placing sodium nitrite, secondary amine, *p*-toluenesulfonic acid, and dichloromethane into a reaction vessel and vigorous stirring the resulting heterogeneous mixture at room temperature. The *N*-nitrosoamines **2** can be obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are given in Table 1.

To access the chemoselectivity of this method, a competitive reaction was performed between *N*-methyl aniline and anisole. It was observed that the secondary amine nitrosation occurred exclusively, whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation reaction of *N*-methyl aniline further shows the chemoselectivity of the method as *N*-nitroso-*N*-methyl aniline is the only product. Thus, this system behaves differently than some other reported methods.[19] The nitrosonium ion (NO^+) attacks only the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to nitrogen atom (Scheme 2).

Dinitrosation of **11** occurred easily using the appropriate molar ratio of the reagents, but unfortunately mononitrosation of this amine **11** could not be achieved even after altering the molar ratio of the reactants (Scheme 3).

The nitrosation of L-proline **12** furnished L-nitrosoproline in good yield, and the stereocenter remained intact. This reaction was very slow as compared to others.

CONCLUSION

In conclusion, a mild and efficient methodology has been developed employing an inexpensive, commercially and readily available p-toluenesulfonic acid. The procedure is easy to operate, with clean workup. The high yield, highly chemo- and regioselective reactions and lack of *C*-nitrosation side product make this methodology simple and attractive for large-scale operations.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker system (200 MHz for ^{1}H and 75 MHz for ^{13}C) using tetramethylsilane (TMS) as an internal standard. The reaction were monitored by thin-layer chromatography (TLC) using 0.25-mm Merck silica-gel plates (60F-254), and the products were purified by column chromatography on silica gel (60–120 mesh) obtained from M/s Spectrochem India Ltd. IR spectra were recorded on a Perkin-Elmer Fourier transform (FT)–IR 16 PC spectrometer.

Typical Experimental Procedure for *N*-Nitrosation of Secondary Amines

p-Toluenesulfonic acid (1.14 g, 6.0 mmol) was slowly added to a stirred suspension of sodium nitrite (0.416 g, 6.0 mmol) and morpholine (0.5 g, 5.7 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was efficiently stirred for 5 min, and the completion of the reaction was monitored by TLC. After completion of the reaction, the insoluble solid was removed by filtration, and the filtrate was concentrated under reduced pressure to afford *N*-nitrosomorpholine (0.630 g, 97% yield, mp 29°C) as a pale yellow powder.

ACKNOWLEDGMENT

This work was carried out under Indo-Hungarian Inter-Governmental joint project (P90807) and is gratefully acknowledged.

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