

Silica Sulfuric Acid/ NaNO_2 as a Novel Heterogeneous System for the Chemoselective N-Nitrosation of Secondary Amines under Mild Conditions

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Abstract: Neat chlorosulfonic acid reacts with silica gel to give silica sulfuric acid in which sulfuric acid is immobilized on the surface of silica gel via a covalent bond. A combination of silica sulfuric acid and sodium nitrite in the presence of wet SiO_2 was used as an effective nitrosating agent for the nitrosation of secondary amines to their corresponding nitroso derivatives under mild and heterogeneous conditions in excellent yields.

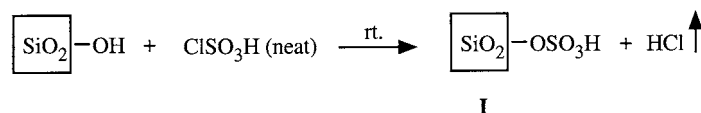
Key words: silica sulfuric acid, nitrosation, secondary amines, *N*-nitrosoamines

Nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists.¹ An effort has also been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation.^{2,3} *N*-Nitrosation chemistry of amines is an important and well-established reaction in organic synthesis. *N*-Nitrosoamines have drawn considerable interest in recent years mainly due to their strong mutagenic and carcinogenic properties, they have also been found to have vasorelaxant activity and their use as pesticides, antioxidants and lubricant additives has been described.⁴ These compounds are also useful synthetic intermediates for a preparation of various *N,N*-bonded functionalities. Furthermore, owing to their easy lithiation, followed by reaction with electrophiles and subsequent denitrosation, they can be used for the electrophilic substitution of the secondary amines at the α -carbon in a regio- and stereoselective manner.⁵ A hindered rotation about the *N-N* bond, being a consequence of a partial double-bond character between two adjacent nitrogens, results in many intriguing stereochemical features of this class of compounds.^{6,7} The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol-water solvents.⁸ Other nitrosating agents, such as Fremy's salt,⁹ bis(triphenylphosphine)nitrogen(1+) nitrite,¹⁰ *N*-haloamides and sodium nitrite under phase-transfer conditions,¹¹ oxyhy-

ponitrite,¹² dinitrogen tetroxide,¹³ oxalic acid dihydrate¹⁴ or trichloroisocyanuric acid¹⁵ and sodium nitrite have also been used. Very recently, we among many others have demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimization of chemical wastes as compared to the liquid phase counterparts.^{6,14-16} Therefore, we decided to apply a completely heterogeneous system and we have investigated a number of different reaction conditions based upon the in situ generation of HNO_2 by relatively strong inorganic acidic salts or inorganic acidic resins and sodium nitrite for the nitrosation of secondary amines.

On the other hand, any reduction in the amount of sulfuric acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection.¹⁷ In addition, there is current research and general interest in heterogeneous systems because of the importance such systems have in industry and in developing technologies.¹⁸ In continuation of our studies on the application of inorganic acidic salts¹⁶ we found that silica gel reacts with chlorosulfonic acid to give silica sulfuric acid (**I**). It is interesting to note that the reaction is easy and clean without any work-up procedure because HCl gas is evolved from the reaction vessel immediately (Scheme 1).

We hoped that the silica sulfuric acid (**I**) would be a superior proton source to all of the reported acidic solid supports or acidic resins such as polystyrene sulfonic acid and Nafion-H¹⁹ for running reactions under heterogeneous conditions. Therefore, we were interested in using this inorganic acidic resin (**I**) for the in-situ generation of HNO_2 when used in conjunction with NaNO_2 , wet SiO_2 and an organic solvent. Since the *N*-nitrosoamines are highly toxic and carcinogenic chemicals, its production with any dispersion is very interesting for organic and biological



Scheme 1

chemists. Although a key feature of the present paper is its clean work-up with easy removal of nitroso adducts due to the heterogeneous nature of the reaction, all due precaution should be taken. We wish to report a simple, cheap and chemoselective method for the effective nitrosation of secondary amines under mild and heterogeneous conditions.









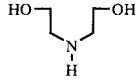
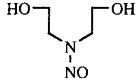
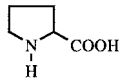
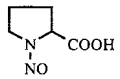
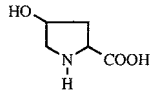
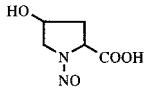
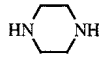
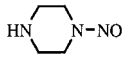
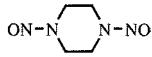
Different types of secondary amines (**1**) were subjected to the nitrosation reaction in the presence of silica sulfuric acid (**I**), NaNO₂ (**II**) and wet SiO₂ (50% w/w) in dichloromethane (Table 1). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature and take place with excellent yields (Table 2).

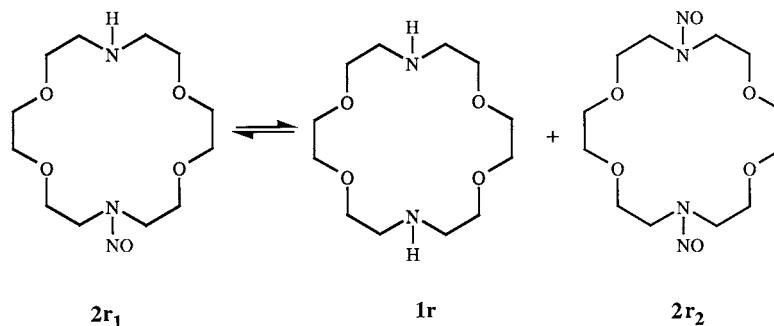
This present nitrosation reaction can be readily carried out by placing silica sulfuric acid (**I**), NaNO₂ (**II**), amine (**1**), wet SiO₂ (50% w/w) and CH₂Cl₂ as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature. The nitrosoamines (**2**) can be obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are given in Table 2.

Although selective dinitrosation of **1q** and **1r** were occurred easily by controlling the molar ratio of the reagents, selective mono nitrosation of these amines did not occur. Several attempts for producing of pure mono nitrosoamines **2q₁** and **2r₁** as the sole adducts without any separation by column chromatography failed. We think that the self transnitrosation of mono nitrosoamines **2q₁** and **2r₁** is the main reason for producing a mixture of mono and dinitroso derivatives of **1q** and **1r**, because these mixtures were formed even when using of a range of molar ratios of 0.1–1 of NaNO₂ (Scheme 2). This means that, formation of dinitrosoamines (**2q₂** and **2r₂**) began from the first time and their formation is independent of reagents. The above mentioned results are in close agreement with the transnitrosation phenomena which were reported by Singer et al.^{20,21}

In order to demonstrate the chemoselectivity of this method a competitive reaction was performed between diphenylamine (**1j**) and anisole. It was observed that amine nitrosation occurred exclusively whereas anisole remained intact in the reaction mixture after 1 hour. The nitrosation reaction of diphenylamine further shows the

Table 1 Nitrosation Reaction of Various Secondary Amines

$R^1R^2NH \xrightarrow[\text{II}]{\text{I}} R^1R^2N-N=O$			
1	2	1	2
1	Structure of substrates	2	Structure of products
a	Me ₂ NH	a	Me ₂ N-N=O
b	Et ₂ NH	b	Et ₂ N-N=O
c	(<i>i</i> -Pr) ₂ NH	c	(<i>i</i> -Pr) ₂ N-N=O
d	(<i>c</i> -C ₆ H ₁₁)CH ₃ NH	d	(<i>c</i> -C ₆ H ₁₁)CH ₃ N-N=O
e	(<i>c</i> -C ₆ H ₁₁) ₂ NH	e	(<i>c</i> -C ₆ H ₁₁) ₂ N-N=O
f		f	
g		g	
h		h	
i		i	
j	Ph ₂ NH	j	Ph ₂ N-N=O
k	(PhCH ₂) ₂ NH	k	(PhCH ₂) ₂ N-N=O
l	Ph(2-Naphtyl)NH	l	Ph(2-Naphtyl)N-N=O
m	PhCH ₃ NH	m	PhCH ₃ N-N=O
n		n	
o		o	
p		p	
q		q ₁	
		q ₂	



Scheme 2

chemoselectivity of the method as the *N*-nitrosodiphenylamine is the only product. This system thus behaves differently from some reported methods^{8,15} in that nitrosonium ion (NO⁺) attacks the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to the nitrogen atom (Scheme 3).

Table 2 Nitrosation of Secondary Amines (**1**) to their Corresponding Nitrosamines (**2**) with a Combination of Silica Sulfuric Acid (**I**), NaNO₂ (**II**) and Wet SiO₂ (50% w/w) in Dichloromethane at Room Temperature

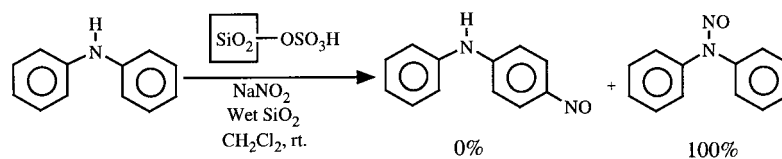
Entry	Substrate	Product ^a	Molar ratio (mmol) ^b		Time (min)	Yield ^c (%)
			Amine	NaNO ₂		
1	1a	2a	1	1.5	5	100 ^d
2	1b	2b	1	1.5	5	98
3	1c	2c	1	1.5	5	99
4	1d	2d	1	1.5	10	98
5	1e	2e	1	1.5	10	99
6	1f	2f	1	1.5	15	95
7	1g	2g	1	1.5	10	96
8	1h	2h	1	1.5	10	99
9	1i	2i	1	1.5	10	98
10	1j	2j	1	1.5	20	99
11	1k	2k	1	1.5	20	95
12	1l	2l	1	1.5	15	99
13	1m	2m	1	1.5	20	99
14	1n	2n	1	1.5	5	98
15	1o	2o	1	1.5	45	77
16	1p	2p	1	1.5	60	85
17	1q	2q₁ 2q₂	1	1.5	10	40 60
18	1q	2q₂	1	2.5	10	99
19	1r	2r₁ 2r₂	1	1.5	15	40 60
20	1r	2r₂	1	2.5	15	98

^a All of the isolated products are known and their spectra and physical data have been reported in the literature.^{1–14}

^b Wet SiO₂:substrate:silica sulfuric acid (0.2 g:1 mmol:0.2 g).

^c Isolated yields.

^d Conversion.



Scheme 3

Furthermore, the stereogenic center of L-proline (**1o**) and its derivative 4-hydroxy-L-proline (**1p**) also remained intact in the course of the reaction so that L-nitrosoproline (**2o**) was obtained with good yield (Table 1 and Table 2, entries 15 and 16). L-Nitrosoproline derivatives (**2o** and **2p**) are precursors of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties.²²

Some of the *N*-nitrosoamines reported in this paper are very important precursors for the mechanistic transnitrosation studies of **2q₂** and **2r₂**. We, therefore believe that these nitrosoamines are also very useful for synthesis of special NO releasing complexes.²³

The nitrosation reaction did not occur in the absence of wet SiO₂. This observation suggests that the water molecule is essential for such processes. The presence of wet SiO₂ thus provides an effective heterogeneous surface area for in situ generation of HNO₂. It also eases the reaction work-up. This new system effectively acts as N₂O₄ because a number of reactions are known in which nitrogen tetroxide (N₂O₄ ⇌ NO⁺NO₃⁻) acts as a nitrosating agent.^{24–26}

In conclusion, the cheapness and the availability of the reagents, easy and clean work-up, chemoselectivity and high yields make this method attractive for large-scale operations. This simple procedure is highly selective, and contamination by C-nitrosation side-products is avoided. Moreover, the new element here is that the reaction is heterogeneous. This could be worthwhile in an industrial setting.

Chemicals were purchased from Fluka, Merck and Aldrich chemicals companies. The nitrosation products were characterized by comparison of their spectral (IR, ¹H NMR), TLC and physical data with the authentic samples.

Cautions: All *N*-nitroso amines [R¹-N(NO)-R²] should be regarded as potentially powerful carcinogens, since most compounds of these types have been shown to demonstrate high in vivo carcinogenicity.^{8a}

Preparation of Silica Sulfuric Acid:

A 500 mL suction flask was used. It was equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and gas inlet tube for conducting HCl gas over an adsorbing solution, i.e., water. Into it were charged 60.0 g of silica gel. Chlorosulfonic acid was added dropwise over a period of 30 min at r.t. HCl gas evolved from the reaction vessel immediately (Scheme 1). After the addition was completed the mixture was shaken for 30 min. A white solid (silica sulfuric acid) 76.0 g was obtained.^{16a}

General Procedure for N-Nitrosation of Secondary Amines

A suspension of sodium nitrite, silica sulfuric acid (the molar ratio of silica sulfuric acid (**I**) and sodium nitrite to the substrate **1** was optimized, Table 2), amine (**1**, 5 mmol) and wet SiO₂ (1 g, 50% w/w) in dichloromethane (10 mL) were stirred vigorously magnetically at r.t. The progress of the reaction was followed by TLC. The reaction mixture was filtered after completion of the reaction. The residue was washed with CH₂Cl₂ (2 × 5 mL). Then anhyd Na₂SO₄ (10 g) was added to the filtrate when was filtered after 20 min. The solvent was evaporated and the *N*-nitroso compounds (**2**) were obtained (Table 2). If further purification was needed, flash chromatography on silica gel [eluent: acetone–petroleum ether bp 60–80 °C (10:90)] provide highly pure **2**.

N-Nitrosation of Diphenyl Amine (1j) with Silica Sulfuric Acid (I), NaNO₂ (II) and Wet SiO₂; Typical Procedure

A suspension of compound **1j** (0.338 g, 2 mmol), **I** (0.4 g 2 mmol), wet SiO₂ (50% w/w, 0.4 g) and **II** (0.207 g, 3 mmol) in dichloromethane (4 mL) was stirred at r.t. for 20 min (the progress of the reaction was monitored by TLC) and then filtered. Anhyd Na₂SO₄ (5 g) was added to the filtrate. After 15 min the resulting mixture was also filtered. Dichloromethane was removed by water bath (35–40 °C) and simple distillation. The yield was 0.361 g, (99%) of crystalline yellow solid (**2j**), mp 63–66 °C [Lit.⁸ mp 67 °C].

Acknowledgement

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