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N-NITROSATION OF SECONDARY AMINES UNDER MILD AND HETEROGENEOUS CONDITIONS

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ABSTRACT

A combination of potassium monopersulfate 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.

N-Nitrosation chemistry of amines is an important and well-established reaction in organic synthesis.[1,2] The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol-water solvents.[3,4] Other nitrosating agents, such as Fremy's salt,[5] bis(triphenylphosphine)nitrogen(1+) nitrite,[6] N-haloamides and sodium nitrite under phase-transfer conditions,[7] oxyhyponitrite,[8] dinitrogen

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tetroxide,[9] oxalic acid dihydrate, and sodium nitrite have also been used.[10] Very recently, we among many others have demonstrated that the heterogeneous reagent systems have many advantages, such as simple experimental procedures, mild reaction conditions, and minimization of chemical wastes, as compared to their liquid phase counterparts.[10–13]

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 salt*, e. g., potassium monopersulfate ($KHSO_5$, $_pK_a \approx 1$), and sodium nitrite for the nitrosation of secondary amines. We 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 $KHSO_5$ (**I**), $NaNO_2$ (**II**) and wet SiO_2 (50% *w*/*w*) in dichloromethane (Scheme). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature and took place with excellent yields (Tab.).

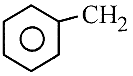
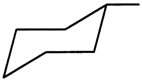
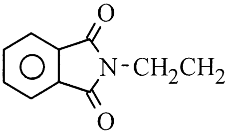
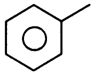
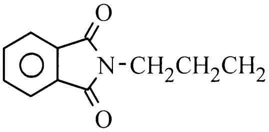
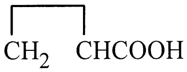
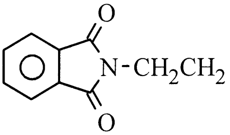
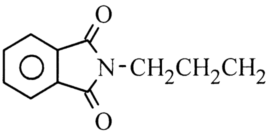
This present nitrosation reaction can be readily carried out by placing $KHSO_5$ (**I**), $NaNO_2$ (**II**), amine (**1**), wet SiO_2 (50% *w*/*w*), and CH_2Cl_2 as the inert solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature. The nitrosoamines (**2**) can be obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are given in the Table.

To demonstrate the chemoselectivity of this method, a competitive reaction was performed between dicyclohexylamine (**1c**) and anisole. It was observed that amine nitrosation occurred exclusively, whereas anisole remained intact in the reaction mixture after 2 h. The nitrosation reaction of diphenylamine further shows the chemoselectivity of the method as the N-nitrosodiphenylamine is the only product. This system thus behaves differently from some reported methods[3,4] 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.

Furthermore, the chiral center of L-proline (**1e**) also remained intact in the course of the reaction so that L-nitrosoproline (**2e**) was obtained in excellent yields (Table, Scheme 1, Entry 5). L-Nitrosoproline (**2e**) is a precursor of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties.[15]

Some of the amines used are very important precursors for the synthesis of symmetrical and asymmetrical tripodal tetraamines (Table, Entries 8–10) [16–18.] We therefore believe that their nitroso derivatives are also very useful for synthesis of special NO-releasing complexes.

$$\underset{\mathbf{1}}{R_1R_2NH} \xrightarrow[\mathbf{II}]{\mathbf{I}} \underset{\mathbf{2}}{R_1R_2N\text{-}N{=}O}$$

1 or **2**	$R_1 = R_2$	**1** or **2**	$R_1 = R_2$
a	Et	**f**	
b	*iso*-Pr	**g**	$-(CH_2)_5-$
c		**h**	
d		**i**	
e			
j	R_1 		R_2 

Scheme.

The nitrosation reaction did not occur in the absence of wet SiO_2. This observation suggests that the water molecule is essential for such processes. The presence of wet SiO_2 thus provides an effective heterogeneous surface area for in situ generation of HNO_2 (Scheme 4). It also eases the reaction work-up.

In conclusion, the low cost and 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 deprotection and C-nitrosation side-products is avoided.

Table. Nitrosation of Secondary Amines (**1**) to Their Corresponding Nitrosoamines (**2**) with a Combination of [$KHSO_4.2KHSO_5.K_2SO_4$] (**I**), $NaNO_2$ (**II**) and Wet SiO_2 (50% *w*/*w*) in Dichloromethane at Room Temperature

Entry	Substrate	Product[a]	(Reagent/Substrate)[b] I	II	Time (h)	Yield[c] (%)
1	**1a**	**2a**[8,9,14]	1	3	0.75	92
2	**1b**	**2b**[14]	1	3	1	94
3	**1c**	**2c**[7]	1	3	1	98
4	**1d**	**2d**[3,4]	1	3	0.5	98
5	**1e**	**2e**[8]	1	3	2.5	93
6	**1f**	**2f**[7]	1	3	2	92
7	**1g**	**2g**[9,14]	1	3	2.5	99
8	**1h**[16–18]	**2h**	1	3	3	99
9	**1i**[16–18]	**2i**	1	3	4.5	99
10	**1j**[16–18]	**2j**	1	3	2	97

[a]All of the isolated products are known and their spectra and physical data have been reported in the literature; [b]Wet SiO_2: substrate (0.2 g : 1 mmol); [c]Isolated yields.

Moreover, the new element here is that the reaction is heterogeneous. This could be worthwhile in an industrial setting.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. The commercial potassium monopersulfate for synthesis [from Merck company, chemical formula ($KHSO_4 \cdot 2KHSO_5 \cdot K_2SO_4$)] was used. Yields refer to isolated pure products. The nitrosation products were characterized by comparison of their spectral (IR, ^1H NMR, ^{13}C NMR), TLC, and physical data with the authentic samples.

General Procedure for N-Nitrosation of Secondary Amines

A suspension of sodium nitrite, inorganic acidic salt (the molar ratio of inorganic acidic salt and sodium nitrite to the substrate **1** was optimized; see Table), amine (**1**, 5 mmol), and wet SiO_2 (50% *w*/*w*) in dichloromethane (10 mL for Entries 1–7 and 50 mL for Entries 8–10) was stirred vigorously magnetically at room temperature. The progress of the reaction was followed by TLC. The reaction mixture was filtered after completion of the reaction. The residue was washed with CH_2Cl_2 (2×5 mL). Then anhydrous Na_2SO_4 (10 g) was added to the filtrate and filtered after 20 m. The solvent was evaporated and the N-nitroso compounds (**2**) were obtained (Tab.). If further purification is needed, flash chromatography on silica gel [eluent: acetone/petroleum ether (10:90)] provides pure **2**.

N-Nitrosation of Diphenyl Amine (**1d**) with [$KHSO_4 \cdot 2KHSO_5 \cdot K_2SO_4$] (**I**), $NaNO_2$ (**II**), and Wet SiO_2: A Typical Procedure

A suspension of compound **1d** (0.338 g, 2 mmol), **I** (1.228 g, 2 mmol), wet SiO_2 (50% *w*/*w* 0.4 g), and **II** (0.414 g, 6 mmol) in dichloromethane (4 mL) was stirred at room temperature for 30 m (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (5 g) was added to the filtrate. After 15 m, the resulting mixture was also filtered. Dichloromethane was removed by water bath (35°–40°C) and simple distillation. The yield was 0.358 g, (98%) of crystalline yellow solid (**2d**), m.p. 64°–66°C [Lit. m.p. 67°C].

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