

Notes

Chemoselective *N*-Nitrosation of Secondary Amines under Mild and Heterogeneous Conditions

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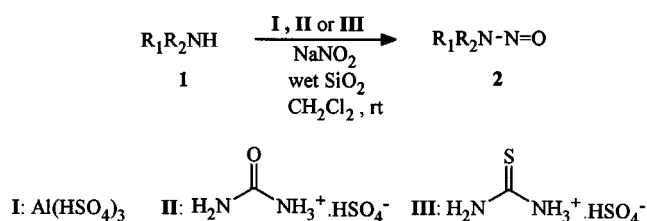
N-Nitrosation of amines is an important and well-established reaction in organic synthesis.¹ The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol-water solvents.² Other nitrosating agents, such as Fremy's salt,³ bis(triphenylphosphine)nitrogen(1+) nitrite,⁴ *N*-haloamides and sodium nitrite under phase-transfer conditions,⁵ oxyhyponitrite,⁶ dinitrogen tetroxide,⁷ solid acids and sodium nitrite have also been used.⁸ Very recently, we 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 the liquid phase counterparts.^{8,9}

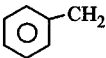


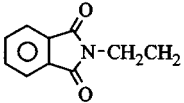
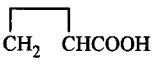
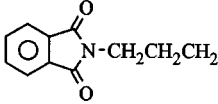
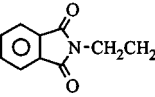
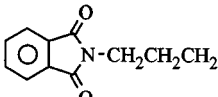
Therefore, we have investigated a number of different reaction conditions based upon the *in situ* generation of HNO₂ by relatively strong *inorganic acidic salt I* (i.e. Al(HSO₄)₃, pK_a ≈ 1) or organic acidic salts (**II** and **III**) and sodium nitrite (**IV**) for the nitrosation of secondary amines. 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 a solid acid, **I**, **II** or **III**, NaNO₂ (**IV**) and wet SiO₂ (50% w/w) in dichloromethane (Scheme 1). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature and took place with excellent yields (Table 1).

This present nitrosation reaction can be readily carried out by placing a solid acid, NaNO₂, amine, wet SiO₂ (50% w/w) and CH₂Cl₂ into a reaction vessel and efficiently 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 the Table 1.

In order to demonstrate the chemoselectivity of this method a competitive reaction was performed between



1 or 2	R ₁ = R ₂	1 or 2	R ₁ = R ₂
a	Et	f	
b	<i>iso</i> -Pr	g	-(CH ₂) ₅ -
c		h	-(CH ₂) ₂ -O-(CH ₂) ₂ -
d		i	
e		j	
	R ₁		R ₂
k			

Scheme 1

dibenzylamine (**1f**) and anisole. It was observed that amine nitrosation occurred exclusively whereas anisole remained intact in the reaction mixture after one hour. The nitrosation reaction of diphenylamine (**1d**) further showed the chemoselectivity of the method as the *N*-nitrosodiphenylamine is the only product. This system thus behaves differently from

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Table 1. Nitrosation of secondary amines (**1**) by a combination of solid acid (**I**, **II**, or **III**), NaNO₂ (**IV**) and wet SiO₂ (50% w/w) in dichloromethane at room temperature

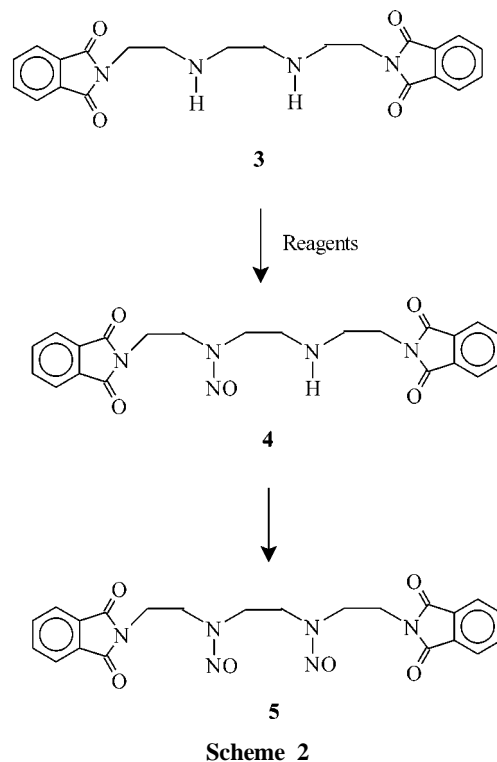
Entry	Substrate	Product ^a	(Reagent/Substrate) ^b				Time (h)	Yield ^c (%)
			I	II	III	IV		
1	1a	2a ^{6,7,10}	0.5	–	–	1.5	0.5	98
2	1a	2a ^{6,7,10}	–	1.5	–	1.5	0.5	54
3	1a	2a ^{6,7,10}	–	–	1.5	1.5	1	54
4	1b	2b ¹⁰	0.5	–	–	1.5	0.5	88
5	1b	2b ¹⁰	–	1.5	–	1.5	1	94
6	1b	2b ¹⁰	–	–	1.5	1.5	1	96
7	1c	2c ⁵	0.5	–	–	1.5	0.5	98
8	1c	2c ⁵	–	1.5	–	1.5	0.5	90
9	1c	2c ⁵	–	–	1.5	1.5	0.5	90
10	1d	2d ²	0.5	–	–	1.5	0.5	99
11	1d	2d ²	–	1.5	–	1.5	2	85
12	1d	2d ²	–	–	1.5	1.5	1	93
13	1e	2e ⁶	0.5	–	–	1.5	1	86
14	1e	2e ⁶	–	1.5	–	1.5	2	78
15	1e	2e ⁶	–	–	1.5	1.5	2	89
16	1f	2f ⁵	0.5	–	–	1.5	0.5	98
17	1f	2f ⁵	–	1.5	–	1.5	0.5	94
18	1f	2f ⁵	–	–	1.5	1.5	1	98
19	1g	2g ^{7,10}	0.5	–	–	1.5	0.5	98
20	1g	2g ^{7,10}	–	1.5	–	1.5	1.25	46
21	1g	2g ^{7,10}	–	–	1.5	1.5	1	58
22	1h ¹²	2h ³	0.5	–	–	1.5	0.5	90
23	1h ¹²	2h ³	–	1.5	–	1.5	0.75	80
24	1h ¹²	2h ³	–	–	1.5	1.5	0.75	99
25	1i	2i ^{8c}	0.5	–	–	1.5	1.5	52
26	1i	2i ^{8c}	–	1.5	–	1.5	1.5	86
27	1i	2i ^{8c}	–	–	1.5	1.5	2.75	85
28	1j	2j ^{8c}	0.5	–	–	1.5	0.75	68
29	1j	2j ^{8c}	–	1.5	–	1.5	1	84
30	1j	2j ^{8c}	–	–	1.5	1.5	0.5	81
31	1k	2k ^{8c}	0.5	–	–	1.5	1	48
32	1k	2k ^{8c}	–	1.5	–	1.5	1	43
33	1k	2k ^{8c}	–	–	1.5	1.5	2	88

^aAll of the isolated products are known and their spectra and physical data have been reported in the literature. ^bWet SiO₂: substrate (0.2 g: 1 mmol). ^cIsolated yields.

some reported methods² 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 good yields (Table 1, Scheme 1, Entries 13-15). L-Nitrosoproline (**2e**) is a precursor of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties.¹¹

Some of the amines used are very important precursors for the synthesis of symmetrical and asymmetrical tripodal tetraamines (Table 1, Entries 25-33),^{12,13} we therefore, believe that their nitroso derivatives were also very useful for the synthesis of special NO releasing complexes.^{14,15}



Several attempts for the selective mono and dinitrosation of tetraamines (**3**) in order to produce its mono and dinitroso derivatives (**4** and **5**) were unsuccessful. This may be due to instability of these compounds in solution (Scheme 2).

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.

In conclusion, the cheapness and the availability of the reagents, easy and clean work-up, chemoselectivity and high yields make this method attractive for organic chemists. This simple procedure is highly selective, and contamination by deprotection and C-nitrosation side-products is avoided.

Experimental Section

General. Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated pure products. The nitrosation products were characterized by comparison of their spectral (IR, ¹H-NMR, ¹³C-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 as shown in Table 1), amine (**1**, 2 mmol) and wet SiO₂ (50% w/w, 0.4 g) in dichloromethane (4 ml for Entries 1-24 and 20 mL for Entries 25-33) was vigorously stirred 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 CH₂Cl₂ (2 × 5 mL). Then

anhydrous Na₂SO₄ (5 g) was added to the filtrate, and the solution was filtered after 20 minutes. The solvent was evaporated and the N-nitroso compounds (**2**) were obtained (Table 1). 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 Al(HSO₄)₃ (I), NaNO₂ (IV) and wet SiO₂: A typical procedure. A suspension of compound **1d** (0.338 g, 2 mmol), **I** (0.318 g 1 mmol), wet SiO₂ (50% w/w, 0.4 g) and **IV** (0.414 g, 6 mmol) in dichloromethane (4 mL) was stirred at room temperature for 30 minutes, while the progress of the reaction was monitored by TLC, and then filtered. Anhydrous Na₂SO₄ (5 g) was added to the filtrate. After 15 minutes the resulting mixture was also filtered. Dichloromethane was removed by water bath (35-40 °C) and simple distillation. The yield was 0.360 g, (99%) of crystalline yellow solid (**2d**), mp 65-67 °C [Lit.² mp 67 °C].

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