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Chemoselective N-Nitrosation of Secondary Amines under Mild and Heterogeneous Conditions with $ZrCl_4/NaNO_2$

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A combination of zirconium tetrachloride 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.

INTRODUCTION

Nitroso compounds in general are quite well-known compounds, and their reactions have been extensively studied from different points of view. Among them, N-nitrosation chemistry of amines is an important reaction in organic synthesis. Many nitrosating agents have been examined including alkyl nitrites, nitrosothiols, nitrogen oxides, nitrosyl salts, etc. and a number of catalysts identified and quantified.[1,2] The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alchohol water solvents. Other nitrosating agents such as Fremy's salt, bis(triphenylphosphine)nitrogen(1+) nitrite, N-haloamides and sodium nitrite under phase-transfer conditions, oxyhyponitrite, oxalic acid dihydrate or inorganic acidic salts [*e.g.*, $NaHSO_4 \cdot 2H_2O$ and $Mg(HSO_4)_2$] and sodium nitrite have been used.[3,4]

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. It has been also shown that any carrier of NO^+ would suffice for the nitrosation reaction of suitable compounds such as thiols,[5] urazoles,[6] dihydropyridines[7] and phenols.[8] 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 NOCl by $ZrCl_4$ and sodium nitrite for nitrosation of secondary amines. We wish to report a simple, chemoselective and convenient method for the effective nitrosation of secondary amines under mild and heterogeneous conditions.

RESULTS AND DISCUSSION

Different types of secondary amines (**1**) were subjected to nitrosation reaction in the presence of $ZrCl_4$ (**I**), $NaNO_2$ (**II**) and wet SiO_2 (50% w/w) in dichlorometh-

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ane (Scheme-1). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature with excellent yields (Table-1).

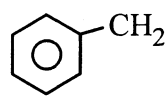
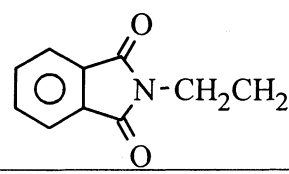
TABLE-1
NITROSATION OF SECONDARY AMINES (1) TO THEIR CORRESPONDING NITROSOAMINES (2) WITH A COMBINATION OF $ZrCl_4$ (I), $NaNO_2$ (II) AND WET SiO_2 (50% w/w) IN DICHLOROMETHANE AT ROOM TEMPERATURE

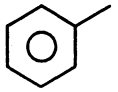
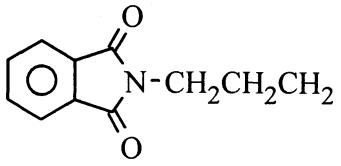
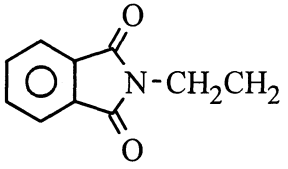
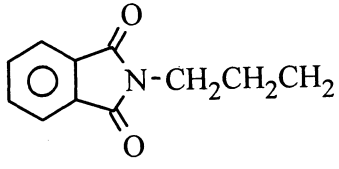
Entry	Substrate	Product	(Reagent/Substrate)[a]		Time (h)	Yield[b] (%)
			I	II		
1.	**1a**	**2a**	1	3	0.50	98
2.	**1b**	**2b**	1	3	1.25	85
3.	**1c**	**2c**	1	3	1.00	98
4.	**1d**	**2d**	1	3	1.50	97
5.	**1e**	**2e**	1	3	0.50	90
6.	**1f**	**2f**	1	3	0.75	96
7.	**1g**	**2g**	1	3	1.00	93
8.	**1h**	**2h**	1	3	3.00	99
9.	**1i**	**2i**	1	3	1.50	95

[a]Wet SiO_2 : substrate (0.2 g : 1 mmol). [b]Isolated yields.

The present nitrosation reaction can be readily carried out by placing $ZrCl_4$ **(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 resultant 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 Scheme-1.

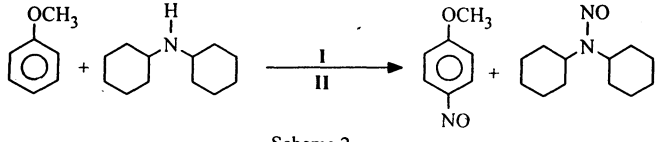
$$\underset{\mathbf{1}}{R_1R_2NH} \xrightarrow[\mathbf{II}]{\mathbf{I}} \underset{\mathbf{2}}{R_1R_2N{-}N{=}O}$$

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

1 or 2	$R_1 = R_2$	1 or 2	$R_1 = R_2$
d		h	
	R_1		R_2
i			

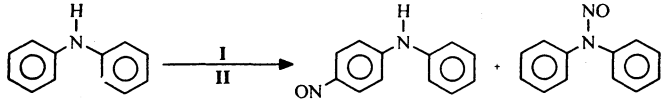
Scheme-1

In order to show the chemoselectivity of this method a competitive reaction was performed between dicyclohexylamine (**1c**) and anisole (**3**). It was observed that amine exclusively nitrosation was proceeded; whereas anisole remained intact in the reaction mixtures after 2 h (Scheme-2).



3 Scheme 2 0% 100%

The nitrosation reaction of diphenylamine further supports the chemoselectivity of the represented method so that the N-nitrosodiphenylamine is the only product. Therefore, this system behaves differently from some reported methods[9] so that nitrosonium ion (NO^+) attacks the nitrogen sites of the secondary amines wherein an aromatic moiety is connected directly to nitrogen atom (Scheme-3).



Scheme 3 0% 100%

Meanwhile, one of us showed that some of the presented amines are very important precursors for the synthesis of symmetrical and asymmetrical tripodal tetraamines (Table-1, Entries 7–9).[10] Therefore, we believed that their nitroso derivatives are also very useful for synthesis of special NO releasing complexes.

The nitrosation reactions were not occurred in the absence of wet SiO_2. This fact indicate that the water molecule is essential for such processes. Therefore, as a consequence, the presence of wet SiO_2 will act as a media and provide an

effective heterogeneous surface area for *in situ* generation of NOCl (Scheme 4). It also eases the reaction's work-up.

$$ZrCl_4 + 4H_2O \rightarrow Zr(OH)_4 + 4HCl$$

$$HCl + NaNO_2 \rightarrow NaCl + HNO_2$$

$$HCl + HNO_2 \rightarrow NOCl + H_2O$$

Scheme-4

In conclusion, the low cost 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 deprotection and C-nitrosation side-products is avoided. Moreover, the new element here is that the reaction is heterogeneous. This could be worth while in an industrial setting. We believe that the present methodology would be an important addition to existing ones. The scope and limitations of this method are under investigation in our laboratory.

EXPERIMENTAL

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, ^{1}H-NMR, ^{13}C-NMR and TLC) and physical data with the authentic samples. The protected amines **(1g–i)** were synthesized according to our previously reported procedure.[10]

General Procedure for N-Nirosation of Secondary Amines

A suspension of sodium nitrite-zirconium tetrachloride (the molar ratio of zirconium tetrachloride and sodium nitrite to the substrate **1** was optimized (Table-1), amine (**1**, 2 mmol) and wet SiO_2 (50% w/w) in dichloromethane (4 mL for Entries 1–6 and 20 mL for Entries 7–9) 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 (5 g) was added to the filtrate and filtered after 20 min. 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)] to give extra pure **2**.

N-Nirosation of Diphenyl Amine (1d) with $ZrCl_4$ (I), $NaNO_2$ (II) and wet SiO_2 : A Typical Procedure: A suspension of compound **1d** (0.338 g, 2 mmol), **I** (0.466 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 1.5 h (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 min the resulting mixture was also filtered. Dichloromethane was removed by keeping the reaction mixture at water bath (35–40°C) and simple distillation. The yield was 0.355 g (97%) of crystalline yellow solid **(2d)**, mp 64–66°C [Lit.[9] mp 67°C.]

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