SHORT PAPER

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Chemoselective N-nitrosation of secondary amines under mild and heterogeneous conditions via *in situ* generation of NOCl†

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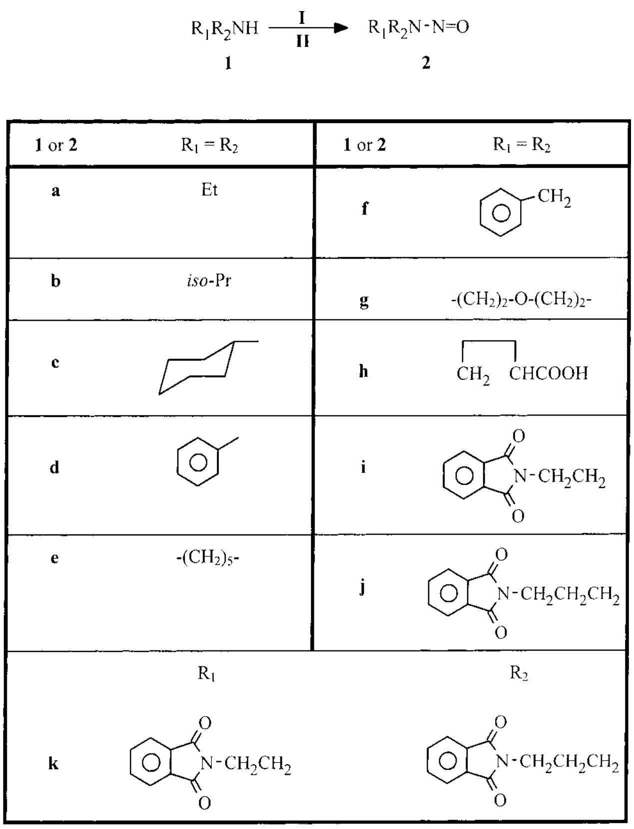
A combination of inorganic chloride salts [e.g. WCl6 , $AlCl_3$ and $ZnCl_2$] and sodium nitrite in the presence of wet SiO_2 were used as an effective nitrosating agent for the nitrosation of secondary amines to their corresponding nitroso derivatives under mild and heterogeneous conditions in moderate to excellent yields.

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. The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alchohol-water solvents.[1,2] 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] oxalic acid dihydrate or inorganic acidic salts [e.g. NaHSO4.H2O and $Mg(HSO_4)_2$] and sodium nitrite have also been used.[8,9] Very recently, we among many others have demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimisation 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,[10] urazoles,[11] dihydropyridines[12] and phenols.[13] Therefore, we decided to apply a heterogeneous system and we have investigated a number of different reaction conditions based upon the *in situ* generation of NOCl (as an efficient nitrosating agent) by one of the inorganic chloride salts [e.g. WCl_6, $AlCl_3$ and $ZnCl_2$] 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.

Different types of secondary amines (**1**) were subjected to the nitrosation reaction in the presence of inorganic chloride salts [e.g. WCl_6 (**I**), $AlCl_3$ (**II**) and $ZnCl_2$ (**III**)], $NaNO_2$ (**IV**) and wet SiO_2 (50% w/w) in dichloromethane (Scheme 1). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature and take place with moderate to excellent yields (Table 1).

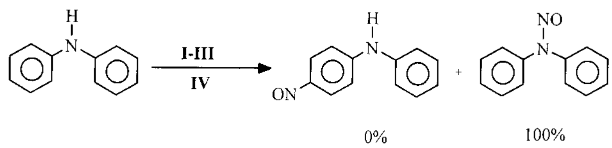
This present nitrosation reaction can be readily carried out by placing one of the inorganic chloride salts [e.g. WCl_6 (**I**), $AlCl_3$ (**II**) and $ZnCl_2$ (**III**)], $NaNO_2$ (**II**) , amine (**1**), wet SiO_2 (50% w/w) and CH_2Cl_2 as the inert solvent in a reaction vessel and efficiently stirring 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 1.



Scheme 1

The nitrosation reaction of diphenylamine (**2d**) shows the chemoselectivity of the method as *N*-nitrosodiphenylamine is the only product. This system thus behaves differently from some reported methods[2] 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 2).

Furthermore, the chiral center of L-proline (**1h**) also remained intact in the course of reaction so that L-nitrosoproline (**2h**) was



Scheme 2

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Nitrosation of secondary amines (1) to their corresponding nitrosoamines (**2**) with a Combination of WCl_6 (**I**), $AlCl_3$ (**II**) and $ZnCl_2$ (**III**)], $NaNO_2$ (**IV**) and wet SiO_2 (50% w/w) in dichloromethane at room temperature.

Entry	Substrate	Product[a]	(Reagent/substrate)[b]				Time	Yield[c]
			I	II	III	IV	(h)	(%)
1	**1a**	**2a**[6,7,14]	0.33	—	—	2	2	98
2	**1a**	**2a**[6,7,14]	—	1	—	3	0.5	98
3	**1a**	**2a**[6,7,14]	—	—	3	3	1.25	98
4	**1b**	**2b**[14]	0.25	—	—	1.5	0.5	95
5	**1b**	**2b**[14]	—	1	—	3	2	88
6	**1b**	**2b**[14]	—	—	3	3	2	98
7	**1c**	**2c**[5]	0.25	—	—	1.5	0.5	98
8	**1c**	**2c**[5]	—	1	—	3	0.5	99
9	**1c**	**2c**[5]	—	—	3	3	0.75	68[e]
10	**1d**	**2d**[2]	0.25	—	—	1.5	1	98
11	**1d**	**2d**[2]	—	0.5	—	3	1	94
12	**1d**	**2d**[2]	—	—	3	3	3	98
13	**1e**	**2e**[7,14]	0.25	—	—	1.5	0.5	93
14	**1e**	**2e**[7,14]	—	1	—	3	0.75	90
15	**1e**	**2e**[7,14]	—	—	3	3	1	98
16	**1f**	**2f**[5]	0.25	—	—	1.5	0.5	96
17	**1f**	**2f**[5]	—	1	—	3	0.5	99
18	**1f**	**2f**[5]	—	—	3	3	2.75	96
19	**1g**	**2g**[3]	0.25	—	—	1.5	1	93
20	**1g**	**2g**[3]	—	1	—	3	1	99
21	**1g**	**2g**[3]	—	—	3	3	0.75	99
22	**1h**	**2h**[6]	0.25	—	—	1.5	0.5	93
23	**1h**	**2h**[6]	—	1	—	3	2	23[e]
24	**1h**	**2h**[6]	—	—	3	3	3	—[e]
25	**1i**[16]	**2i**	0.25	—	—	1.5	2	80
26	**1i**[16]	**2i**	—	1	—	3	1.5	72
27	**1i**[16]	**2i**	—	—	3	3	3	32[e]
28	**1j**[16]	**2j**	0.25	—	—	1.5	1	99
29	**1j**[16]	**2j**	—	1	—	3	2	50
30	**1j**[16]	**2j**	—	—	3	3	4	32[e]
31	**1k**[16]	**2k**	0.25	—	—	1.5	0.5	99
32	**1k**[16]	**2k**	—	1	—	3	1	65
33	**1k**[16]	**2k**	—	—	3	3	1.25	8[e]

[a]Those products which are known are indicated by their own references. [b]Wet S_1O_2 : substrate (0.2 g : 1 mmol). [c]Isolated yields. [e]Complexation occurred.

obtained in excellent yields (Table 1, Scheme 1, Entries 22-24). L-Nitrosoproline (**2h**) 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 1, entries 25–33).[16]

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 NOCl (Scheme 3). It also eases the reaction work-up. WCl_6 and $AlCl_3$ are superior to $ZnCl_2$ in convenience, yield and purity of the isolated nitroso products (Table 1).

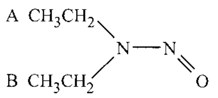
The most interesting feature of our results is the ^{1}H-NMR spectra of N-nitroso products that were given in the Table 2. They clearly show, in all cases the diastereotopic nature of the adjacent N–CH protons which is due to the bent nature of the N=O bond and its mutual exchange. Therefore in proton NMR the symmetrical dialkyl or diaryl N-nitroso amines (**2a–g** and **2i–j**) such as diethyl N-nitroso amines (**2a**) give two distinct methyl or methylene signals [Scheme 4, **3** (A and B)] of equal intensity, separated *ca* 0.34 and 0.77 ppm respectively. The higher frequency peaks are attributed to the protons of the ethyl group *trans* to the nitroso oxygen. This is in agreement with the spectra data in the literature.[17] N-Nitroso amines which have different alkyl moieties (**2k**) give two series proton signals for one of the alkyl moiety but these are of different intensity (**4** and **5**), the low-frequency signal being the

Table 2 ^{1}H-NMR data of N-nitroso amines (**2**)

Entry	Compound	^{1}H-NMR ($CDCl_3$)/TMS) δ (ppm)
1	**2a**	3.87 (q, 2H), 3.33 (q, 2H), 1.16 (t, 3H), 0.85 (t, 3H)
2	**2b**	4.96 (septet, 1H), 4.19 (septet, 1H), 1.41 (d, 6H), 1.07 (d, 6H)
3	**2c**	4.76 (quintet, 1H), 3.65 (quintet, 1H), 1.85–142 (m, 20H)
4	**2d**	7.31–704 (m, 10)
5	**2e**	4.06 (br s, 2H), 3.64 (t, 2H), 1.66 (m, 6H)
6	**2f**	7.33–7.08 (m, 10H), 5.19 (s, 2H), 4.45 (s, 2H)
7	**2g**	3.02 (m, 2H), 2.61–2.43 (m, 6H)
8	**2h**	10.83 (s, 4H), 5.24 (t, 2H), 4.35 (m, 8H), 3.62 (t, 3H), 2.12 (m, 10H)
9	**2i**	7.67 (m, 8H), 4.39 (dd, 2H), 3.81 (m, 6H)
10	**2j**	7.76 (m, 8H), 4.24 (t, 2H), 3.65 (m, 6H), 2.17-195 (m, 4H)
11	**2k**	7.68 (m, 8H), 4.42-3.62 (m, 8H), 2.13 (q, 1H), 1.95 (q, 1H)

$$MCl_n + nH_2O \rightarrow M(OH)_n + nHCl$$
$$HCl + NaNO_2 \rightarrow NaCl + HNO_2$$
$$HCl + HNO_2 \rightarrow NOCl + H_2O$$

Scheme 3



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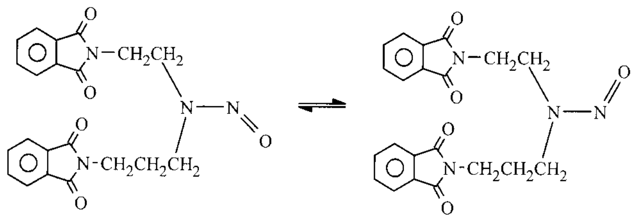

4 **5**

Scheme 4

more intense. The intensity ratio leads immediately to information about the relative concentrations of the rotamers and hence to the equilibrium constant 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.

Experimental

General: Chemicals were purchased from Fluka, Merck and Aldrich chemicals companies. The nitrosation products were characterized by comparison of their spectral (IR, ^{1}H-NMR, ^{13}C-NMR), TLC and physical data with the authentic samples.

Caution: All N-nitroso amines [here R_1-N(NO)-R_2] should be regarded as potentially powerful carcinogens, since most compounds of this type have been shown to possess high activity in experimental animals.[2a]

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 in the Table 1), amine (**1**, 5 mmol) and wet SiO_2 (50% w/w) in dichloromethane (10 ml for entries 1–24 and 50 ml for entries 25–33) 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 15 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 WCl_6 (I), $NaNO_2$ (II) and wet SiO_2 : a typical procedure:* A suspension of compound **1d** (0.338 g, 2 mmol), **I** (0.198 g 0.5 mmol), wet SiO_2 (50% w/w, 0.4 g) and **II** (0.207 g, 3 mmol) in dichloromethane (4 ml) was stirred at room temperature for 1 hour (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 minutes the resulting mixture was also filtered. Dichloromethane was removed by water bath (35–40 °C) and simple distillation. The yield was 0.340 g, (93%) of crystalline yellow solid (**2d**), m.p. 63–65 °C [Lit.[2] m.p. 67 °C].

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