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The use of Nafion-H®/$NaNO_2$ as an efficient procedure for the chemoselective *N*-nitrosation of secondary amines under mild and heterogeneous conditions

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Abstract—A combination of Nafion-H® and sodium nitrite in the presence of wet SiO_2 was used as an effective agent for the *N*-nitrosation of secondary amines under mild and heterogeneous conditions in good to excellent yields.

Acids are widely used as catalysts in industry for producing more than 1×10^8 mt/year of products. The most commonly used are HF, H_2SO_4, $HClO_4$ and H_3PO_4 (in liquid form or supported on Keiselguhr). Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems and environmentally safe disposal.[1,2] In addition, waste and by-products can be minimized or avoided by developing cleaner synthetic routes.[3] On the other hand, reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection. 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.[4] Among reported solid acids, Nafion-H® has been used for a wide variety of reactions ranging from alkylation with olefins, alkyl halides, alkyl esters, isomerization, transalkylation, acylation, nitration, ether and ester synthesis, acetal formation, and rearrangement chemistry.[5]

Nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists.[6] An effort has also been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation.[7,8]

N-Nitrosation of amines is an important and well-established reaction in organic synthesis. *N*-Nitrosoamines have attracted 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.[9] These compounds are also useful synthetic intermediates for the 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 secondary amines at the α-carbon in a regio- and stereoselective manner.[10] Hindered rotation about the *N*–*N* bond in nitrosoamines, as a consequence of a partial double-bond character between two adjacent nitrogens, results in many intriguing stereochemical features.[11,12]

The most general reagent for synthesis of nitrosoamines is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol–water solvents.[13] Other nitrosating agents, such as frémy's salt,[14] bis-(triphenylphosphine)nitrogen(1+) nitrite,[15] *N*-haloamides and sodium nitrite under phase-transfer conditions,[16] oxyhyponitrite,[17] dinitrogen tetroxide,[18] oxalic acid dihydrate,[19] silica sulfuric acid, trichloroisocyanuric acid[20] with 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

Keywords: Nafion-H®; chemoselective *N*-nitrosation; secondary amines; *N*-nitrosoamines.

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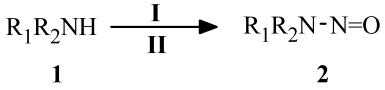
reaction conditions and minimization of chemical waste as compared to the liquid phase counterparts.[19–23] Therefore, we decided to search for a completely heterogeneous system for *N*-nitrosation and investigated a number of different reaction conditions based upon the in situ generation of HNO_2 by Nafion-H® resins.

Different types of secondary amines **1** were subjected to nitrosation in the presence of Nafion-H® **I**, $NaNO_2$ **II** and wet SiO_2 (50% w/w) in dichloromethane (Scheme 1). The nitrosation reactions were performed at room temperature and took place with good to excellent yields (Table 1). Thus, the Nafion-H® **I**, $NaNO_2$ **II**, amine **1**, and wet SiO_2 (50% w/w) were stirred efficiently in CH_2Cl_2 as the solvent at room temperature. The nitrosoamines **2** were isolated simply by filtration and evaporation of the solvent. The results and reaction conditions are given in Table 1.



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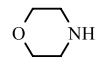
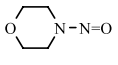
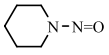
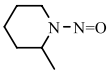
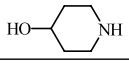
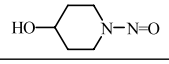
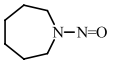
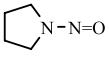
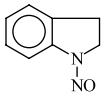
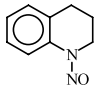
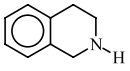
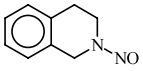
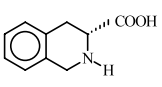
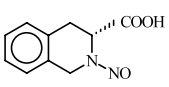
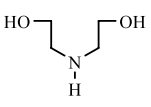
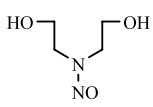
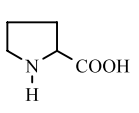
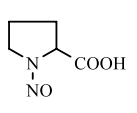
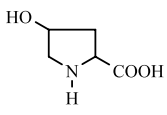
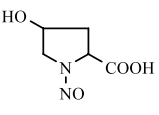
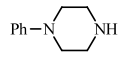
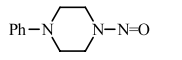
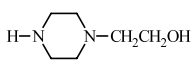
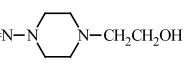
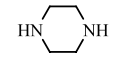
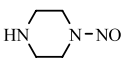
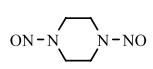
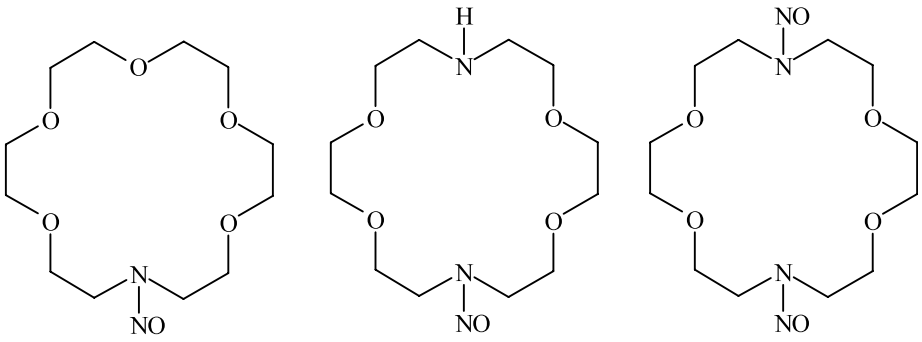
a	Me_2NH	a	Me_2N-N=O
b	Et_2NH	b	Et_2N-N=O
c	(*iso*-Pr)$_2$NH	c	(*iso*-Pr)$_2$N-N=O
d	(*c*-C_6H_{11})CH_3NH	d	(*c*-C_6H_{11})CH_3N-N=O
e	(*c*-C_6H_{11})$_2$NH	e	(*c*-C_6H_{11})$_2$N-N=O
f		f	
g		g	
h		h	
i		i	
j		j	
k		k	
l		l	
m		m	
n		n	
o		o	

1	Structure of substrates	2	Structure of products
p	Ph_2NH	p	Ph_2N-N=O
q	Ph(PhCH_2)NH	q	Ph(PhCH_2)N-N=O
r	(PhCH_2)$_2$NH	r	(PhCH_2)$_2$N-N=O
s	Ph(2-Naphthyl)NH	s	Ph(2-Naphthyl)N-N=O
t	$PhCH_3NH$	t	$PhCH_3$N-N=O
u		u	
v		v	
w		w	
x		x	
y		y	
z		z_1	
		z_2	
A	Kryptofix® 22	$2A_1$ $2A_2$	Mononitroso Kryptofix® 22 Dinitroso Kryptofix® 22
B	Kryptofix® 21	B	Nitroso Kryptofix® 21

Scheme 1.



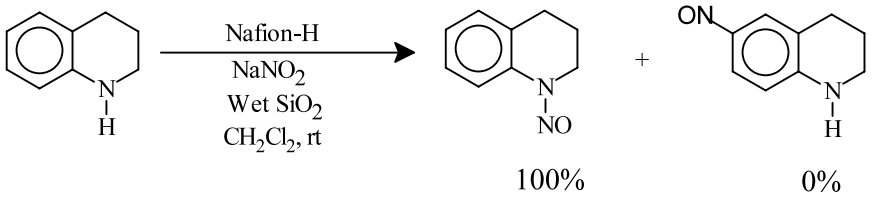
2B **$2A_1$** **$2A_2$**

Table 1. Nitrosation of secondary amines **1** to their corresponding nitrosoamines **2** with a combination of Nafion-H® **I**, $NaNO_2$ **II** and wet SiO_2 (50% w/w) in dichloromethane at room temperature

Entry	Substrate	Product[a]	Molar ratio amine:$NaNO_2$ (mmol)[b]	Time (min)	Yield[c] (%)
1	**1a**	**2a**	1:2	10	100[d]
2	**1b**	**2b**	1:2	20	90
3	**1c**	**2c**	1:2	30	85
4	**1d**	**2d**	1:2	40	80
5	**1e**	**2e**	1:2	30	85
6	**1f**	**2f**	1:2	30	70
7	**1g**	**2g**	1:2	20	85
8	**1h**	**2h**	1:2	45	80
9	**1i**	**2i**	1:2	90	50
10	**1j**	**2j**	1:2	30	85
11	**1k**	**2k**	1:2	30	85
12	**1l**	**2l**	1:2	45	65
13	**1m**	**2m**	1:2	45	72
14	**1n**	**2n**	1:2	45	70
15	**1o**	**2o**	1:2	60	63
16	**1p**	**2p**	1:2	45	80
17	**1q**	**2q**	1:2	30	85
18	**1r**	**2r**	1:2	30	90
19	**1s**	**2s**	1:2	30	75
20	**1t**	**2t**	1:2	40	78
21	**1u**	**2u**	1:2	45	65
22	**1v**	**2v**	1:2	90	60
23	**1w**	**2w**	1:2	90	50
24	**1x**	**2x**	1:2	30	80
25	**1y**	**2y**	1:2	90	60
26	**1z**	**$2z_1$**	1:2	40	15
	1z	**$2z_2$**	1:2	40	85
27	**1z**	**$2z_2$**	1:3	35	85
28	**1A**	**$2A_1$**	1:2	50	10
	1A	**$2A_2$**	1:2	50	90
29	**1A**	**$2A_2$**	1:3	30	75
30	**1B**	**2B**	1:2	45	70

[a] All of the isolated products are known and their spectra and physical data have been reported in the literature.[6–19]
[b] Wet SiO_2:substrate:Nafion-H® (0.5 g:1 mmol:0.2 g).
[c] Isolated yields.
[d] Conversion.

Dinitrosation of **1A** and **1z** occurred easily using the appropriate molar ratio of the reagents, but mononitrosation only of these amines could not be achieved. Several attempts at producing pure mononitrosoamines **$2A_1$** and **$2z_1$** as the sole adducts, without any separation by column chromatography, failed. We think that the self transnitrosation of mononitrosoamines **$2A_1$** and **$2z_1$** is the main reason for formation of a mixture of mono- and dinitroso- derivatives of **1A** and **1z**, because mixtures were formed even when using a range of molar



Scheme 2.

ratios of 0.1–1 of $NaNO_2$ (Table 1, entries 26–29). This means that formation of dinitrosoamines (**2A$_2$** and **2z$_2$**) began in the early stages of the reaction and their formation is independent of the ratio of reagents. These results are in close agreement with transnitrosation phenomena which have been reported by Singer et al.[24,25]

In order to assess the chemoselectivity of this method a competitive reaction was performed between diphenylamine **1p** and anisole. It was observed that amine nitrosation occurred exclusively whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation of a mixture of *N*-arylamine and *N*,*N*-diarylamines shows further the chemoselectivity of the method as the *N*-nitrosoarylamine was the only product. Thus, this system behaves differently to some other reported methods[13,20] in that the nitrosonium ion (NO^+) attacks only the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to the nitrogen atom (Table 1, entries 12, 13, 15–20 and 24. A typical example is shown in Scheme 2).

Furthermore, the chiral center of L-proline **1v**, 4-hydroxy-L-proline **1w** and D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1o** also remained intact during the course of the reaction (Table 1, Scheme 1, entries 22, 23 and 15). Amino acid derivatives **2v**, **2w** and **2o** are precursors of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties.[25]

Some of the *N*-nitrosoamines such as **2A$_2$** and **2z$_2$** reported in this paper are very important precursors for the mechanistic transnitrosation studies and some could be useful for synthesis of special NO releasing complexes.[26,27]

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 for in situ generation of HNO_2. It also facilitates 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 large-scale operations. This simple procedure is highly selective and *C*-nitrosation and hydroxy oxidation side-products are avoided.

General procedure for *N*-nitrosation of secondary amines

A suspension of sodium nitrite, Nafion-H® (the molar ratio of Nafion-H® **I** and sodium nitrite to the substrate **1** was optimized, Table 1), amine **1** (5 mmol) and wet SiO_2 (2.5 g, 50% w/w) in dichloromethane (10 mL) was stirred vigorously 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 washing and separated by filtration after 20 min. The solvent was evaporated and the *N*-nitroso compounds **2** was obtained. If further purification was needed, flash chromatography on silica gel [eluent: acetone/petroleum ether bp 60–80°C, (10:90)] provide highly pure **2**.[28,29]

Acknowledgements

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References

1. Corma, A. *Current Opinion in Solid State and Materials Science*; Current Chemistry Ltd, 1997; Vol. 2, pp. 63–75.
2. Corma, A.; Garcia, H. *Catal. Today* **1997**, *38*, 257–308.
3. Sikdar, S. K.; Howell, S. G. *J. Cleaner Production* **1998**, *6*, 253–259.
4. Sheldon, R. A.; Downing, R. S. *Appl. Catal. A: General* **1999**, *189*, 163–183.
5. Harmer, M. A.; Sun, Q. *Appl. Catal. A: General* **2001**, *221*, 45–62.
6. (a) Williams, D. L. H. *Nitrosation*; Cambridge University Press, 1988; pp. 77–149; (b) Williams, D. L. H. *Supplement F2: The Chemistry of Amino, Nitroso, Nitro and Related Groups*; John Wiley and Sons, 1996; pp. 665–682; (c) Keefer, L. K.; Williams, D. L. H. *Methods in Nitric Oxide Research*; John Wiley and Sons, 1996; pp. 509–519 and references cited therein.
7. Garcia-Rio, L.; Leis, J. R.; Moreira, J. A.; Norberto, F. *J. Org. Chem.* **2001**, *66*, 381.

8. Garcia-Rio, L.; Leis, J. R.; Iglesias, E. *J. Org. Chem.* **1997**, *62*, 4712.
9. Nudelman, N. S.; Bonatti, A. E. *Synlett* **2000**, 1825 and references cited therein.
10. Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Matuszynska, H.; Potonski, T. *J. Org. Chem.* **2001**, *66*, 501.
11. Zolfigol, M. A.; Shirini, F.; Ghorbani Choghamarani, A.; Taqian-nasab, A.; Keypour, H.; Salehzadeh, S. *J. Chem. Res. (S)* **2000**, 420.
12. Rivera, A.; Gallo, G. I.; Joseph-Nathan, P. *Synth. Commun.* **1997**, *27*, 163.
13. (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Text Book of Practical Organic Chemistry*; 5th ed; Longman: London and New York, 1989; (b) Sheriner, R. L.; Reynold, T. L.; Fuson, C.; Curtin, D. Y.; Morrill, T. C. *The Systematic Identification of Organic Compounds*; 6th ed; John Wiley and Sons, 1980; pp. 220–223.
14. Castedo, L.; Riguera, R.; Vezquez, M. P. *J. Chem. Soc., Chem. Commun.* **1983**, 301.
15. Fanning, J. C.; Keefer, L. K.; Larry, K. *J. Chem. Soc., Chem. Commun.* **1987**, 955.
16. Nakajima, M.; Warner, J. C.; Anselme, J. P. *Tetrahedron Lett.* **1984**, *25*, 2619.
17. Chang, S. K.; Harrington, G. W.; Rothstein, M.; Shergalis, W. A.; Swern, D.; Vohra, S. K. *Cancer Res.* **1979**, *39*, 3871.
18. Makhova, N. N.; Karpov, G. A.; Mikhailyuk, A. N.; Bova, A. E.; Khamel′nitskii, L. I.; Novikov, S. S. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, *1*, 226.
19. Zolfigol, M. A. *Synth. Commun.* **1999**, *29*, 905.
20. (a) Zolfigol, M. A.; Ghorbani-Choghamarani, A.; Hazarkhani, H. *Synlett* **2002**, 1002; (b) Zolfigol, M. A.; Bamoniri, A. *Synlett* **2002**, 1621.
21. (a) Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509 and references cited therein; (b) Zolfigol, M. A.; Torabi, M.; Mallakpour, S. E. *Tetrahedron* **2001**, *57*, 8381; (c) Shirini, F.; Zolfigol, M. A.; Mallakpour, B.; Mallakpour, S. E.; Hagipour, A. *Tetrahedron Lett.* **2002**, *43*, 1555.
22. Riego, J. M.; Sedin, Z.; Zaldivar, J. M.; Marziano, N. C.; Tortato, C. *Tetrahedron Lett.* **1996**, *37*, 513.
23. Turro, N. J. *Tetrahedron* **1987**, *43*, 1589.
24. Singer, S. S.; Lijinsky, W.; Singer, G. M. *Tetrahedron Lett.* **1977**, *19*, 1613.
25. Singer, S. S. *J. Org. Chem.* **1978**, *43*, 4612.
26. Turnbull, K. *J. Heterocycl. Chem.* **1985**, *22*, 965.
27. Richter-Addo, G. B. *Acc. Chem. Res.* **1999**, *32*, 529.
28. The nitrosation products were characterized by comparison of their spectral (IR, ^{1}H NMR), TLC and physical data with authentic samples.
29. **Caution**: All *N*-nitroso amines [R^1-N(NO)-R^2] should be regarded as potentially powerful carcinogens, since most compounds of these types have been shown to possess high activity in experimental animals.[13a]