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Chemoselective *N*-nitrosation of secondary amines under heterogeneous and mild conditions via *in situ* generation of HNO_2

Arash Ghorbani-Choghamarani [a,*], Hamid Goudarziafshar [a], Somaieh Rezaee [b], Saiedeh Shima Mortazavi [a]

[a] *Department of Chemistry, Faculty of Science, Ilam University, P.O. Box 69315516, Ilam, Iran*
[b] *Islamic Azad University, Science and Research, Branch-Ahvaz, Ahvaz, Iran*

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Abstract

A wide variety of secondary amines are chemoselectively subjected to *N*-nitrosation reaction with treatment of citric acid and $NaNO_2$ in the presence of wet SiO_2 (50%, w/w) in dichloromethane at room temperatture under heterogeneous conditions. The *N*-nitrosation method is very simple and products can be easily isolated with good to high yields.

Keywords: *N*-Nitrosation; Secondary amines; Heterogeneous; Citric acid; $NaNO_2$

N-Nitrosation chemistry of amines is an important and well-established reaction in organic synthesis; nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists [1]. Nitrosation reactions are of wide and varied significance. *N*-Nitroso compounds are of biological interest and are used as 'transnitrosating agents', *i.e.* NO-donor drugs [2]. An effort has also been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation [3,4]. These compounds are also useful synthetic intermediates for the preparation of various *N*-*N*-containing functionalities. *N*-Nitrosamines have been prepared by various approaches such as the reaction of amines by $NaNO_2$ and an acid [5–15], Fremy's salt [16], bis(triphenylphosphine) nitrogen nitrite [17], *N*-haloamides and sodium nitrite under phase-transfer conditions [18], oxyhyponitrite [19] and dinitrogen tetroxide [20].

In the last few years, heterogeneous systems [21–26], have become increasingly used in organic synthesis, mainly because the reactions are carried out under mild conditions, the organic products are easily isolated and the chemical wastes are minimized. Therefore we decided to design a new heterogeneous system for the chemoselctive *N*-nitrosation of secondary amines by *in situ* generation of HNO_2 *via* treatment of citric acid, as organic solid acid, and sodium nitrite.

Herein, we have shown that different types of *N*-nitroso secondary amines **2** can be easily obtained by the reaction of citric acid (**I**), sodium nitrite (**II**) and wet SiO_2 (50%, w/w) with secondary amines **1** in CH_2Cl_2 at room temperature with good to excellent yields (Scheme 1).

N-Nitrosation of secondary amines was easily carried out by mixing of a secondary amine with citric acid, $NaNO_2$ and wet SiO_2 (50%, w/w) at room temperature under completely heterogeneous and mild conditions. The notable point

* Corresponding author.
E-mail address: arashghch58@yahoo.com (A. Ghorbani-Choghamarani).

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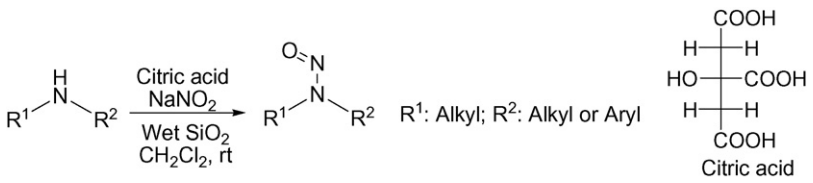
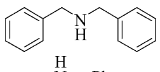
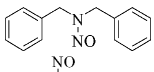
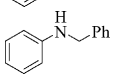
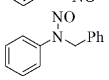
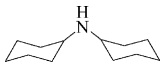
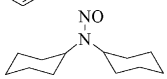
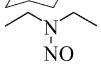
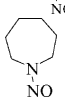
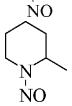
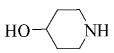
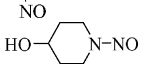
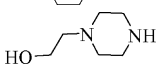
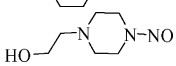
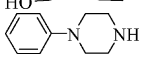
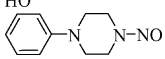
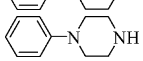
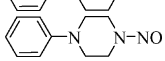
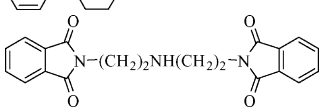
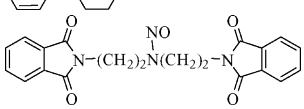
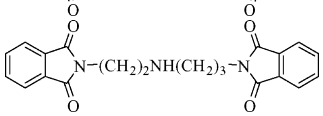
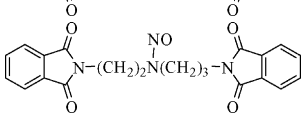


Scheme 1.

is that highly pure products can be easily isolated from the reaction media by simple filtration and evaporation of dichloromethane. The results for this transformation are summarized in Table 1.

To investigate the role of wet SiO_2 (50%, w/w), as source of water, *N*-phenyl-piperazine was subjected to nitrosation reaction in the absence of wet SiO_2, however the reaction did not occur and *N*-nitroso-*N*-phenyl-piperazine was not observed after 7 h, which means that water is necessary for this heterogeneous transformation (Table 1, entry 11).

Table 1
N-Nitrosation of secondary amines **1** to the corresponding *N*-nitrosamines **2** by combination of citric acid (**I**), $NaNO_2$ (**II**) and wet SiO_2 (50%, w/w) in dichloromethane at room temperature.

Entry	Substrate	Product	Substrate/reagents (mmol)[a]		Time (min)	Yield (%)[b]
			I	II		
1			0.67	2	35	97
2			0.67	2	40	98
3			0.67	2	40	99
4			0.67	2	30	47
5			0.67	2	20	84
6			0.67	2	50	88
7			0.67	2	45	88[c]
8			0.67	2	40	98
9			0.67	2	110	91
10			0.67	2	115	93[c]
11			0.67	2	7 h	–[d,e]
12			0.67	2	90	99
13			0.67	2	160	98