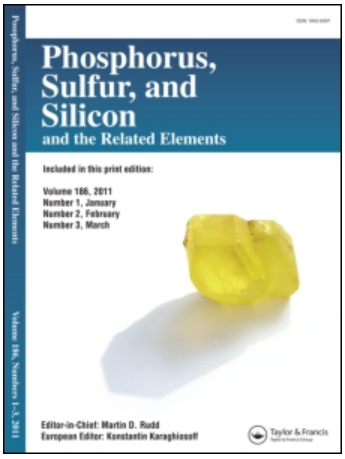

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Silica Chloride/NaNO 2 as a Novel Heterogeneous System for Production of Thionitrites and Disulfides Under Mild Conditions

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SILICA CHLORIDE/$NaNO_2$ AS A NOVEL HETEROGENEOUS SYSTEM FOR PRODUCTION OF THIONITRITES AND DISULFIDES UNDER MILD CONDITIONS

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*Thiols can be readily converted to their corresponding thionitrites with a combination of silica chloride (**I**), wet SiO_2 and sodium nitrite in dichloromethane at room temperature. Disulfides result from the homolytic cleavage of the sulfur-nitrogen bond of the unstable thionitrite and subsequent coupling of the resultant thiyl radicals.*

Keywords: Disulfides; silica chloride; thiols; thionitrites (S-nitrosothiols)

There currently is a general interest in heterogeneous systems because of the importance that such systems have in industry and in developing technologies.[1,2] In continuation of our studies on the application of heterogeneous systems we found that silica chloride[3,4] (**I**) is an excellent source for generation of HCl. It is interesting to note that the addition of wet SiO_2 to the reaction mixture containing silica chloride generates HCl in situ. Therefore, We used it for a different purpose.[5,6] We also were interested in using reagent (**I**) for the nitrosation of thiols via in situ generation of HNO_2 and NO^+, respectively, when used in conjunction with $NaNO_2$, wet SiO_2 in an organic solvent (Scheme 1). On the other hand thionitrites have not been as widely studied as their oxygen counterparts alkyl nitrites, generally because of their reduced

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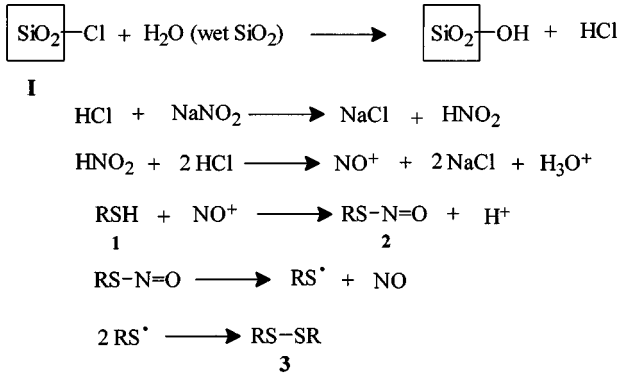

1, 2, 3	R	1, 2, 3	R
a	$PhCH_2$	f	Ph
b	*n*-C_8H_{17}	g	C_3H_6SH
c	Cyclohexyl	h	$C_2H_4COOCH_3$
d	C_2H_4COOH	i	4-FC_6H_4
e	C_2H_4OH		

SCHEME 1

stability.[7] However, in recent years there has been much interest generated in the chemistry and biochemistry of nitrosothiols,[7–14] since (a) they are being examined as possible drugs to effect vasodilatation and to reduce platelet aggregation, (b) they are now believed to play an important part in some of the physiological processes involving nitric oxide, (c) they are being used as a source of thiyl radicals[7] or as nitrosating agents. The vital role of thiols and disulfides in living systems has focused on their interconversion reactions. Intense interest in the chemistry of thionitrites has been generated in connection with the newly discovered remarkable physiological roles of nitric oxide, including particularly vasodilation and cytotoxic action of macrophages. Thiols and thionitrites (S-nitrosothiols) are believed to be involved in in vivo processes, possibly in the mechanism of NO transfer reactions.[11]

The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol-water solvents. Other nitrosating agents have been used successfully to synthesize thionitrites, notably alkyl nitrites, nitrosyl salts, dinitrogen trioxide, dinitrogen tetroxide,[7–10] trichloronitromethane,[11] oxalic acid dihydrate,[12]

inorganic acidic salts,[13] or silica sulfuric acid[14] and sodium nitrite. 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.[13–16] Therefore, we decided to apply silica chloride (**I**)/$NaNO_2$ as a new heterogeneous system for the nitrosation of thiols. We wish to report a simple, cheap and convenient method for the effective nitrosation of thiols and production of disulfides under mild and heterogeneous conditions (Scheme 1).

Different kinds of thiols were subjected to the nitrosation reaction in the presence of $NaNO_2$, wet SiO_2 (50% w/w), and silica chloride (**I**) in dichloromethane. The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature. A bright-red heterogeneous solution was obtained immediately due to the formation of thionitrite. Disulfides result from the homolytic cleavage of the sulfur-nitrogen bond of the unstable thionitrite and subsequent coupling of the resultant thiyl radicals.[11] Therefore, this method also could be used for conversion of thiols to their corresponding disulfides quantitatively with increasing temperature (Scheme 1 and Table I).

Although the reaction occurs without wet SiO_2, the reaction time is very long and the reaction is completed only after several days. Therefore we think that the presence of wet SiO_2 will act as a media and will

TABLE I Nitrosation of Thiols to Their Corresponding Unstable Nitrosothiols (2) and Production of Disulfides (3) with a Combination of Silica Chloride (**I**), $NaNO_2$ (**II**), and Wet SiO_2 (50% *w/w*) in Dichloromethane at Room Temperature

			Reagent/Substrate[a]			
Entry	Substrate	Product	**I** (g)	**II** (mmol)	Time (min)	Yields[b] (%)
1	**1a**	**3a**	0.27	2	60	99
2	**1b**	**3b**	0.27	2	60	92
3	**1c**	**3c**	0.27	2	60	90
4	**1d**	**3d**	0.27	2	30	60
5	**1e**	**3e**	0.27	2	45	99
6	**1f**	**3f**	0.27	2	20	98
7	**1g**	**3g**	0.27	2	35	95
8	**1h**	—[c]	0.54	2	35	—[c]
9	**1i**	**3i**	0.27	2	25	91

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

provide a heterogeneous effective surface area for in situ generation of HNO_2. It also will make easy work-up.

In conclusion, practical and efficient nitrosation-oxidation of thiols were achieved by the present methodology. The low cost and availability of the reagents, easy procedure, and easy work-up make this method attractive for the organic chemists.

EXPERIMENTAL SECTION

General

Chemicals were purchased from Fluka, Merck, Riedel-deHaen AG and Aldrich Chemical companies. Silica chloride was synthesised according to the reported procedures.[3,4] Disulfides were characterized by comparison of their spectral (IR, ^{1}H-NMR, UV, and TLC) and physical data with authentic samples.[8–14,17,18]

A Typical Experimental Procedure

To a solution of thiophenol [(**1f**) 0.220 g, 2 mmol] in CH_2Cl_2 (10 mL), **I** (0.54 g), wet SiO_2 (50% *w/w*) (0.4 g) and $NaNO_2$ (0.257 g, 4 mmol) were added. The resulting mixture was stirred at room temperature; a bright-red heterogeneous solution was obtained immediately. Thionitrites were characterized by comparison of their UV spectra with those reported in the literature.[17,18] Typical spectra are as follows: λ_{max} (CH_2Cl_2): PhSNO, 380, 529, 570 nm]. A pale yellow solution was also obtained after 20 min and then filtered. The residue was washed with CH_2Cl_2 (2 × 10 ml). Anhydrous Na_2SO_4 (3 g) was added to the filtrate. After 15 min, the resulting mixture was filtered again. Dichloromethane was evaporated. The yield was 0.213 g (98%) of crystalline brownish solid (**3f**), m.p. 58–59°C [Lit.[17,18] m.p. 58–60°C].

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