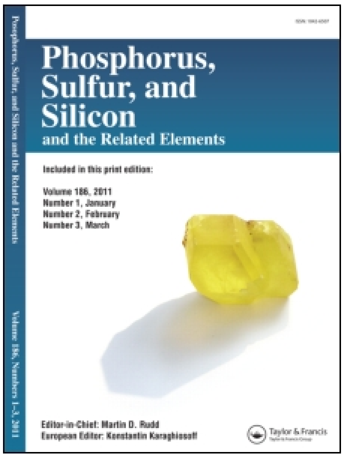

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SILICA CHLORIDE/NaNO$_2$ AS A NOVEL HETEROGENEOUS SYSTEM FOR THE NITRATION OF PHENOLS UNDER MILD CONDITIONS

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Nitrophenols can be obtained via direct nitration of phenols with silica chloride, NaNO$_2$, and wet SiO$_2$ at room temperature in moderate to high yields.

Keywords: Heterogeneous conditions; nitration; phenols; silica chloride

The nitration of aromatic compounds may be achieved with many nitrating reagents and is a very useful way in organic synthesis. The nitration of phenol as a special case has been studied under various conditions.[1–18] Very recently, three excellent procedures have been reported for the nitration of phenols, two of them using microemulsion and surface-mediated systems for the regioselective nitration of phenols.[19] The third one reported an enzymatic method for the nitration of phenols.[20] Recently, we have reported on the applications and mechanism of the reaction of some hydrated metal nitrates and their dinitrogen tetroxide complex analogues, as well as ionic metal nitrates or nitrites in the presence of solid acids for the nitration of phenols under various conditions.[21]

Our goal, in undertaking this line of work, was threefold: a) to overcome the limitations and drawbacks of the reported methods such as overnitration,[1] tedious work-up,[10,12] strongly acidic media ($H_o \sim -8$),[5b] oxidation ability of the reagents and safety problems (storage, handling,

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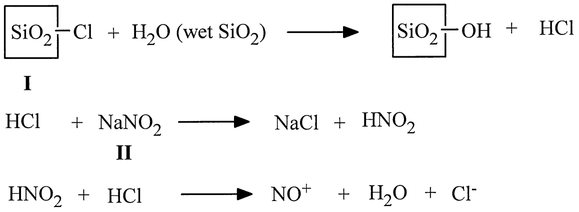
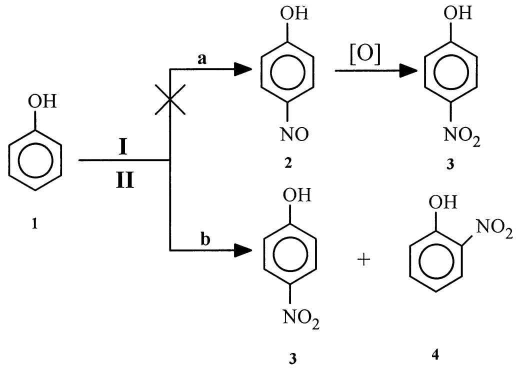
and the presence of toxic transition metal cations such as Cr^{+3}, Hg^{+2}, Cu^{+2}, ... within the molecular structure of the reagents);[22,24] b) solvent-free organic synthesis, which seems to be a highly useful technique, especially for industry and it many advantages such as reduced pollution, low costs, and simplicity in process and handling;[25] and c) high-yielding one-pot synthesis of nitrophenols using a novel combination of reagents are our main interest.

Any reduction in the amount of liquid acids needed and/or any simplification in handling procedures would be highly convenient in terms of risk reduction, economic advantage, and environment protection.[1] On the other hand, there is intense current research and general interest in heterogeneous systems in industry and in developing technologies. In continuation of our studies on the application of heterogeneous systems,[26,27] we found that the silica chloride[28,29] (**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 of silica chloride could in situ generate HCl and original SiO_2. Therefore, we decided to seek a heterogeneous system for the nitration of phenols, and we have investigated a number of different reaction conditions based upon the in situ generation of HNO_2 by using silica chloride (**I**), sodium nitrite, and wet SiO_2 (Scheme 1). We report here a one-pot heterogeneous procedure for the mono nitration of phenols (Schemes 2 and 3).



SCHEME 1

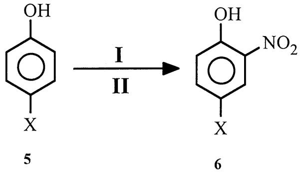
During the course of our studies on the utilization of NO^+ in functional groups transformations, we thought that phenol (**1**) could be converted into the 4-nitrosophenol (**2**) selectively by silica chloride (**I**), $NaNO_2$ [(**II**), and wet SiO_2 (50% *w/w*) in CH_2Cl_2 via in situ generation of HNO_2. In addition, phenol nitrosation is rapid and yields almost entirely the *para* isomer, which can be converted readily to 4-nitrophenol (the desired product which is the precursor of acetaminophene) via a mild oxidation with HNO_3,[30] H_2O_2/Na_2WO_4,[31] etc. (Scheme 2, path **a**). Therefore, we decided to produce 4-nitrophenol via a nitrosation-oxidation strategy[27–29] in a one pot reaction under mild



SCHEME 2

and heterogeneous conditions. We chose silica chloride (**I**)/wet SiO_2 system for the nitrosation of phenol. In contrast to the reported procedures in aqueous media,[31,32] we observed that apparently direct formation of 2-nitrophenol (**4**) and 4-nitrophenol (**3**) occured (Scheme 2, path **b**).

Different kinds of 4-substituted phenols (**5**) also were subjected to nitration reaction in the presence of silica chloride (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% *w/w*) in dichloromethane (Scheme 3). The nitration reactions were performed under mild and completely heterogeneous conditions at room temperature in moderate to excellent yields (Scheme 3,



5, 6	X	**5, 6**	X
a	F	**g**	OCH_3
b	Cl	**h**	$COCH_3$
c	Br	**i**	CHO
d	CN	**j**	CH_2Ph
e	Ph	**k**	NHOAc
f	CH_3	**l**	4-HOC_6H_4

SCHEME 3

TABLE I Mononitration of Phenols to Their Corresponding Nitro Derivatives with a Combination of Silica Chloride (**I**), $NaNO_2$ (**II**), and Wet SiO_2 (50% *w/w*) in Dichloromethane at Room Temperature

			Subst./Reagents[a]		Time	Yields[b]	m.p. (°C)	
Entry	Substrate	Product	**I**(g)	**II**(mmol)	(h)	%	Found	Reported
1	**1**	**3**	0.2	1.5	1	31	111–113	115[8]
		4				32	44–46	44[8]
2	**5a**	**6a**	0.2	1.5	0.5	67	73	73–74[5c]
3	**5b**	**6b**	0.2	1.5	0.75	90	89	91[12,36]
4	**5c**	**6c**	0.6	4.5	1.25	96	87	84[12,36]
5	**5d**	**6d**	0.6	4.5	1.75	96	140–142	145[5c,36]
6	**5e**	**6e**	0.2	1.5	2	99	61–63	66[39]
7	**5f**	**6f**	0.2	1.5	1.5	90	29–31	31[12,36]
8	**5g**	**6g**	0.4	3	1	88	54–56	—[36,41]
9	**5h**	**6h**	0.4	3	3	87	122–124	123[12,36]
10	**5i**	**6i**	0.75	5.5	1.5	97	143–145	140–142[5c]
11	**5j**	**6j**	0.2	1.5	2	99	61–66	—[41]
12	**5k**	**6k**	1.1	8.25	5	93	180	—[14,42]
13	**5l**	**6l**	0.4	3	0.5	45	180–184	—[39]
14	**1**	**3, 4**	—	1.5	24 (h)		No reaction[c]	

[a] Wet SiO_2:substrate (1) (0.134 g:1 mmol).
[b] Isolated yields.
[c] Reaction did not occur in the absence of silica chloride (**I**).

Table I). The present nitration reactions readily can be carried out by placing the nitrating agents, phenols (**1** or **5**) and the solvent used in a reaction vessel and efficiently stirring the resultant heterogeneous mixture at room temperature. The mono nitrophenols can be obtained by simple filtration and then evaporation of the solvent.

In fact, a combination of sodium nitrite and silica chloride (**I**) can act as a solid nitrating agent which readily can be weighed, handled, and used for different purposes in the presence of moist SiO_2. Unexpectedly, overnitration occurred under solvent free conditions.

A competitive reaction was performed between phenol and anisole. It was observed that exclusive phenol nitration proceeded, anisole remaining intact in the reaction mixtures after 24 h. Selective mononitration of 4,4′-dihydroxybiphenyl (**5l**) also was achieved by controlling the stoichiometry of reagents (Table I, entry 13). Phenol nitration did not occur in the absence of the silica chloride (Table I, entry 14).

This new system, i.e., a combination of silica chloride (**I**) and sodium nitrite, is similar to N_2O_4 ($N_2O_4 \Leftrightarrow NO^+NO_3^-$).[35] Therefore, on the basis of our observations, the previously reported results concerning the applications of N_2O_4,[27,33,34] metal nitrate dinitrogen tetroxide complexes

$[M(NO_3)_m \cdot nN_2O_4]$,[21a] oxidation of HNO_2 with oxygen and production of N_2O_4,[35] the very recent reported mechanism for nitration of phenols,[36–39] and the products which are obtained, the nitrous acid catalyzed mechanism (**NAC**) may be proposed.[21f]

In conclusion, the low cost, availability of the reagents, easy and clean work-up, generation of reuseable silica gel without any toxic metal cations, and good yields make this method attractive for organic chemists.

EXPERIMENTAL SECTION

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Yields refer to isolated pure products. Silica chloride was synthesized according to the reported procedure.[43,44] The nitration products were characterized by comparison of their spectral (IR, ^{1}H-NMR), TLC, and physical data with authentic samples.

Mononitration of Phenol (1) with Silica Chloride (I), $NaNO_2$ (II), and Wet SiO_2: A Typical Procedure

A suspension of compound **1** (0.188 g, 2 mmol), **I** (0.4 g), **II** (0.207 g, 3 mmol), and wet SiO_2 (50% *w/w*, 0.4 g) in CH_2Cl_2 (10 ml) was stirred magnetically at room temperature. The reaction was completed after 1 h 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. Dichloromethane was removed by water bath (35–40°C)* and simple distillation. The residue is a mixture of 2 and 4-nitrophenols. 4-Nitrophenol (**3**) is insoluble in n-pentane, 0.084 g, 31% m.p. 112–113°C [lit.[5] m.p. 114°C]. The n-pentane was evaporated by water bath (35–40°C),[45] to give 2-nitrophenol (**4**), 0.088 g, 32%, m.p. 43–45°C [lit.[5] m.p. 44°C] (Table I, Scheme 2).

Mononitration of 4-Chlorophenol (5b) with Silica Chloride (I), $NaNO_2$ (II), and Wet SiO_2: A Typical Procedure

A suspension of compound **5b** (0.257 g, 2 mmol), **I** (0.4 g), wet SiO_2 (50% *w/w*, 0.4 g), and **II** (0.207 g, 3 mmol) in dichloromethane (10 ml)

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*Dichloromethane is the best solvent for the nitration of phenols due to its low boiling points. We know that the 2-nitrophenols are very volatile and should be distilled with low boiling point solvents and the yield of reaction will be decreased.

was stirred at room temperature for 30 min (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (3 g) was added to the filtrate. After 15 min the resulting mixture was filtered. Dichloromethane was removed by water bath (35–40°C) and simple distillation. The yield was, 0.232 g, (67%) of a crystalline pale yellow solid (**6b**), m.p. 89–90°C [lit.[5c] m.p. 91°C]. ^{1}H-NMR (FT-90 MHz, $CDCl_3$, TMS): δ 7.12 (dd, 1H), 7.42 (dd, 1H), 8.02 (s, 1H), 10.31 (b, 1H). ^{1}H-NMR spectra were identical with reference spectra.[5c]

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