SHORT PAPER

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One-pot nitration of phenols under mild and heterogeneous conditions

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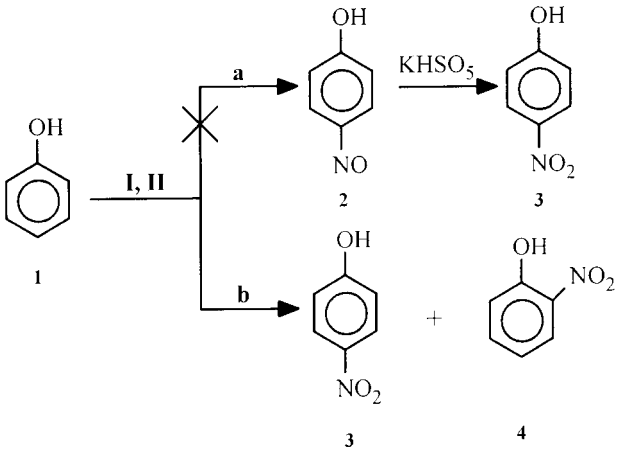
Nitrophenols can be obtained via nitrosation–oxidation of phenols with Oxone® , $NaNO_2$ and wet SiO_2 at room temperature in moderate to high yields. *In situ* generation of HNO_2 and the radical cation mechanism via the nitrous acid catalysed (NAC) pathway or hydrogen abstraction involving NO_2 appear to be applicable to phenol nitration using these reagents.

Keywords: nitrophenols, Oxone®, nitrous acid catalysis

The nitration of aromatic compounds may be achieved with many nitrating reagents and is a very useful method in organic synthesis. Nitration of phenol as a special case has been studied using various nitrating agents under different conditions.[1–17] Recently, in this connection we have reported the applications and mechanism of reaction of some hydrated metal nitrates and their dinitrogen tetroxide complex analogues for the nitration of phenols under various conditions.[18] We have also demonstrated that *in situ* formation of HNO_3 is a major factor for effective nitration of phenols with metal nitrates (containing covalent nitrato groups).[18a] Our goal, in undertaking this line of work, was two-fold: (a) to overcome the limitations and drawbacks of the reported methods such as : tedious work-up,[9, 11] strongly acidic media (H_o~ -8),[4b] oxidation ability of the reagents and safety problems (storage, handling, using and also presence of toxic transition metal cations such as Cr^{3+}, Hg^{2+}, Cu^{2+},... within molecular structure of the reagents), [19, 20] (b) to send a high-yielding one-pot synthesis of nitrophenols using a novel combination of reagents. 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 their liquid phase counterparts. We have reported simple procedures for *in situ* generation of the nitrosonium ion (NO^+) under mild and heterogeneous conditions and also applications of it for different purposes.[21] 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 the relatively strong *solid inorganic acidic salt* [Oxone® (**I**), pK_a~2] with sodium nitrite. We wish to report here a one-pot heterogeneous procedure for the nitration of phenols.

During the course of our studies on the utilisation of NO^+ in functional groups transformations, we thought that phenol (**1**) must be converted into the *p*-nitrosophenol selectively by Oxone® (**I**) [(2 eq), one equivalent of **I** was needed for the oxidation step], $NaNO_2$ [(**II**), (1 eq)] and wet SiO_2 (50% *w/w*) in CH_2Cl_2 as solvent via *in situ* generation of HNO_2. We also thought that phenol nitrosation is rapid and yields almost entirely the *para* isomer which can be readily converted into *p*-nitrophenol *via* a mild oxidation with HNO_3,[22] H_2O_2/Na_2WO_4[23] *etc*. Therefore, we decided to produce *p*-nitrophenol *via* a nitrosation-oxidation strategy[22–24] in a one-pot reaction under mild and heterogeneous conditions. We chose Oxone® because it is an acid source (a proton source for the *in situ* generation of HNO_2 and NO^+) as well as being a very mild oxidant which is needed for second step i.e. the oxidation of *p*-nitrosophenol. (Scheme 1, path **a**). In contrast to the reported procedures in aqueous media,[22–24] we observed the apparently direct formation of *o*-nitrophenol (**4**) and *p*-nitrophenol (**2**), (Scheme 1, Table, path **b**).



Scheme 1

Different kinds of 4-substituted phenols (**5**) were also subjected to nitration in the presence of Oxone® (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% *w/w*) in dichloromethane (Scheme 2). The nitration reactions were performed under mild and completely heterogeneous conditions at room temperature in moderate to excellent yields (Scheme 2, Table). The present nitration reactions can be readily 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. This method provides nitrated phenols directly, in short reaction times and good yields.

In fact, a combination of sodium nitrite and solid acids can act as solid HNO_2 which can be readily weighed, handled and used for different purposes in the presence of moist SiO_2.[21]

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 hours (Scheme 3). Selective mononitration of 4,4′-

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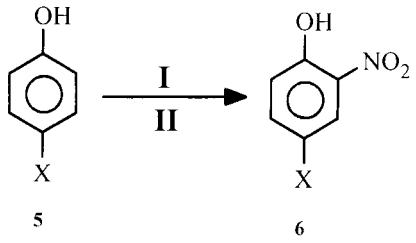
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Mononitration of phenols to their corresponding nitro derivatives with a combination with [$KHSO_4.2KHSO_5.K_2SO_4$] (**I**), $NaNO_2$ (**II**) and wet SiO_2 (50% *w/w*) in dichloromethane at room temperature.

Entry	Substrate	Product	Reag. /Subst/mmol[a]		Time/h	Yields[b]/%	M.p./°C	
			I	II			Found	Reported
1	**1**	**3** **4**	1.5	4	3	39 40	110-113 44-45	115[7] 44[7]
2	**5a**	**6a**	0.5	1	2	75	73	73–74[4c]
3	**5b**	**6b**	1	1	2	97	89	91[11, 28]
4	**5c**	**6c**	0.5	1	2	95	87	84[11, 28]
5	**5d**	**6d**	1	2	2	65	140–142	145[4c, 28]
6	**5e**	**6e**	0.5	1	2	88	61–63	66[31]
7	**5f**	**6f**	1	2	2	86	29–31	31[11, 28]
8	**5g**	**6g**	1	2	2	59	54–56	—[28, 32]
9	**5h**	**6h**	4	12	0.5	60	122–124	123[11, 28]
10	**5i**	**6i**	1	2	2	88	61–66	—[33]
11	**5j**	**6j**	2.5	7.5	5	58	180	—[13, 34]
12	**5k**	**6k**	0.5	1	2	80	180–184	—[31]
13	**1**	**3, 4**	–	1	24(h)	No Reaction[c]		

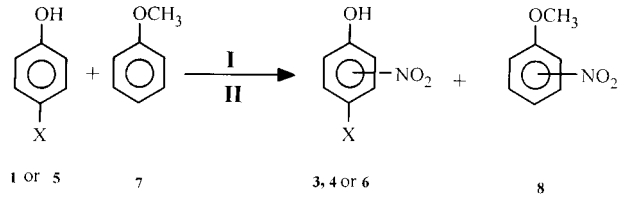
[a]Wet SiO_2: substrate (1) (0.2 g: 1 mmol); [b]isolated yields; [c]reaction did not occur in the absence of [$KHSO_4.2KHSO_5.K_2SO_4$] (**I**).



5 **6**

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

Scheme 2



1 or **5** **7** **3, 4** or **6** **8**

100% 0%

Scheme 3

dihydroxybiphenyl (**5k**) was also achieved by controlling the stoichiometry of reagents (Table 1, entry 12).

Although the reaction occurs without wet SiO_2 the reaction time period is very long and reaction is completed only after several days. Therefore, we think that the presence of wet SiO_2 will act as a heterogeneous effective surface area for *in situ* generation of HNO_2. It will also make work-up easy.

This new system *i.e.* a combination of inorganic acidic salts **I** and sodium nitrite is similar to N_2O_4 ($N_2O_4 \rightleftharpoons NO^+NO_3^-$)[27] as a nitrosating agent via *in situ* generation of HNO_2 (eq 1) and NO^+ (eq 2). Therefore on the basis of our observations, the previously reported results concerning the applications of N_2O_4,[25, 26] metal nitrate dinitrogen tetroxide complexes [$M(NO_3)_m.nN_2O_4$],[17a] oxidation of HNO_2 with oxygen and production of N_2O_4 (eq 3–6),[27] the recent reported mechanism for nitration of phenols[28–29] and the products which are obtained, the following nitrous acid catalysed mechanism (NAC) or hydrogen abstraction involving an NO_2 pathway[30] may be proposed (Schemes 4 and 5).

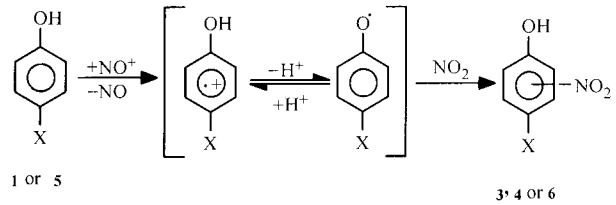
In conclusion, the cheapness and the availability of the reagents, easy and clean work-up, and good yields make this method attractive for large-scale operations. Moreover, the new element here is that the reaction is heterogeneous. This could be useful in an industrial setting.[17]

Experimental

General: Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated pure products. The commercial potassium monopersulfate (tradename Oxone®) for synthesis [from Merck, chemical formula ($KHSO_4.2KHSO_5.K_2SO_4$)] was used. The nitration products were characterised by comparison of their spectral (IR, ^{1}H-NMR, ^{13}C-NMR), TLC and physical data with the authentic samples.[4, 18]

Mononitration of phenol (1) with Oxone® (I), $NaNO_2$ (II) and wet SiO_2: a typical procedure: A suspension of compound **1** (0.188g, 2 mmol), **I** (1.842 g, 3 mmol), **II** (0.552g, 8 mmol) and wet SiO_2 (50% *w/w*, 0.4 g) in CH_2Cl_2 (6ml) was stirred magnetically at room temperature. The reaction was completed after 10 minutes 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 minutes the resulting mixture was also 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, 0.106 g, 39%, m.p. 110–113°C [lit[7] m.p. 114°C]. The *n*-pentane was

$$H^+ + NO_2^- \rightarrow HNO_2 \quad (1)$$
$$HNO_2 + 2H^+ \rightarrow NO^+ + H_3O^+ \quad (2)$$
$$2HNO_2 \rightarrow N_2O_3 + H_2O \quad (3)$$
$$N_2O_3 \rightarrow NO + NO_2 \quad (4)$$
$$2NO_2 \rightarrow N_2O_4 \quad (5)$$
$$2NO \rightarrow N_2O_2 \quad (6)^{27}$$
$$N_2O_2 + O_2 \rightarrow N_2O_4 \quad (6)^{27}$$



Scheme 4

$$4\text{-}XC_6H_4OH + NO_2^{\cdot} \Leftrightarrow 4\text{-}XC_6H_4O^{\cdot} + HNO_2$$

$$4\text{-}XC_6H_4O^{\cdot} + NO_2^{\cdot} \rightarrow \text{Products}^{30}$$

Scheme 5

evaporated by water bath (35–40°C), to give 2-nitrophenol (**4**), 0.110 g, 40%, m.p. 44–45 °C [lit[7] m.p. 44°C] (Table , Scheme 1).

*Mononitration of 4-chlorophenol (**5b**) with Oxone® (**I**), $NaNO_2$ (II) and wet SiO_2: a typical procedure:* A suspension of compound **5b** (0.257g, 2mmol), **I** (1.228g 2 mmol), wet SiO_2 (50% *w/w*, 0.2g) and **II** (0.138g, 2mmol) in dichloromethane (6ml) was stirred at room temperature for 2 hours (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (3g) 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 0.336 g, (97%) of crystalline pale yellow solid (**6b**), m.p. 89°C, [Lit.[4c] 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.[4c]

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