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1,3-Dihalo-5,5-dimethylhydantoin or citric acid/NaNO$_2$ as a heterogeneous system for the selective mononitration of phenols under mild conditions

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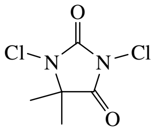
Direct nitration of phenols was performed using 1,3-dichloro-5,5-dimethylhydantoin, 1,3-dibromo-5,5-dimethylhydantoin or citric acid/NaNO$_2$ in the presence of wet SiO$_2$ at room temperature.

The nitration of aromatic compounds is an important industrial process.[1] However, the nitration of aromatic rings involves unsolved problems of regioselectivity, overnitration and competitive oxidation of substrates.[2] The nitration of phenol under various conditions has been studied.[3] Recently, three procedures have been reported for the nitration of phenols with the use of microemulsion and surface-mediated systems for regioselective nitration[4] or an enzymatic method.[5] We have reported the reactions of hydrated metal nitrates and their dinitrogen tetroxide complex analogues, as well as ionic metal nitrates or nitrites, in the presence of inorganic acidic salts, for the nitration of phenols under various conditions.[6] The nitration of phenols using nitric acid under phase-transfer and ultrasonic conditions is also known.[7,8]



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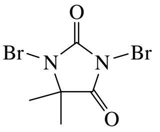

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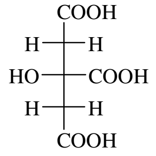

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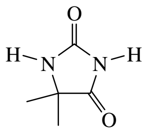
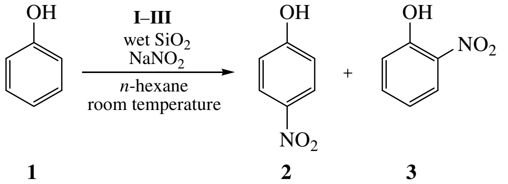


IV

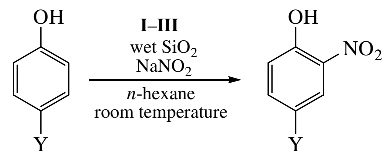
We found that commercially available 1,3-dichloro(bromo)-5,5-dimethylhydantoin (**I** or **II**)[9,10] and citric acid (**III**) can be used as a green source of H$^+$. Therefore, we report a simple, cheap and convenient method for the effective mononitration of phenols using 1,3-dichloro-5,5-dimethylhydantoin (DCH, **I**), 1,3-dibromo-5,5-dimethylhydantoin (DBH, **II**) or citric acid (CA, **III**) with NaNO$_2$ in the presence of wet SiO$_2$ under mild and heterogeneous conditions (Schemes 1 and 2).[†]



1 **2** **3**

Scheme 1

A range of 4-substituted phenols (**4**) were also nitrated using **I**–**III**/NaNO$_2$ in the presence of wet SiO$_2$ (50%, w/w) in *n*-hexane (Scheme 2). The nitration reactions were performed at room temperature with moderate to good yields (Schemes 1 and 2, Table 1). They can be readily carried out by placing the nitrating agents, phenols (**1** or **4**) and the solvent in a reaction vessel and stirring the resulting heterogeneous mixture at room temperature. Highly pure mono nitrophenols can be obtained by filtration and subsequent evaporation of the solvent.



4a–m **5a–m**

a Y = F
b Y = Cl
c Y = Br
d Y = CN
e Y = Ph
f Y = Me
g Y = OMe
h Y = COMe
i Y = CHO
j Y = CH$_2$Ph
k Y = NHOAc
l Y = 4-HOC$_6$H$_4$
m Y = COOH

Scheme 2

A combination of sodium nitrite and one of the **I**–**III** can act as a solid nitrating agent, which can be readily weighed, handled and used in the presence of moist SiO$_2$.

Phenol nitration did not occur in the absence of **I**–**III** (Table 1, entry 15). On the other hand, water molecules or wet SiO$_2$ are necessary for the nitration of phenols (Table 1, entry 16). Therefore, we think that wet SiO$_2$ acts as a heterogeneous effective surface area for *in situ* generation of HNO$_2$, efficiently making work-up easy. DCH or DBH (slightly soluble in *n*-hexane) was used for the *in situ* generation of HOX in the presence of wet SiO$_2$.[11] It was converted to 5,5-dimethylhydantoin (**IV**) as a highly polar compound, which is completely insoluble in *n*-hexane, adsorbed by silica gel (Scheme 3). However, highly

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[†] Chemicals from Fluka, Merck and Aldrich were used. Yields refer to isolated pure products. Silica gel (70–230 mesh) from Merck was used. The nitration products were characterised by a comparison of their spectral (IR, ^{1}H NMR), TLC and physical data with those of authentic samples.[12,13]

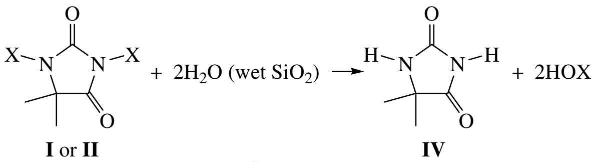
A typical procedure for mononitration of phenol **1** *with 1,3-dibromo-5,5-dimethylhydantoin* **I**, *NaNO$_2$ and wet SiO$_2$*. A suspension of compound **1** (0.188 g, 2 mmol), **I** (0.572 g, 2 mmol), NaNO$_2$ (0.276 g, 4 mmol) and wet SiO$_2$ (50% w/w, 0.4 g) in *n*-hexane (10 ml) was magnetically stirred at room temperature. The reaction was complete after 45 min. The reaction mixture was filtered; the residue was washed with *n*-hexane (20 ml). Anhydrous Na$_2$SO$_4$ (3 g) was added to the filtrate. After 15 min, the resulting mixture was also filtered; *n*-hexane was removed in a water bath (35–40 °C) by distillation. The residue is a mixture of 2- and 4-nitrophenol. 4-Nitrophenol (**2**) is insoluble in *n*-pentane, yield 0.077 g (28%), mp 111–113 °C (lit.,[13] mp 114 °C). The *n*-pentane fraction was evaporated in a water bath (35–40 °C) to give 2-nitrophenol (**3**), yield 0.166 g (60%), mp 44–46 °C (lit.,[13] mp 44 °C) (Table 1, Scheme 1).

A typical procedure for mononitration of 4-chlorophenol **4b** *with 1,3-dibromo-5,5-dimethylhydantoin* **I**, *NaNO$_2$ and wet SiO$_2$*. A suspension of compound **4b** (0.257 g, 2 mmol), **I** (0.572 g, 2 mmol), wet SiO$_2$ (50% w/w, 0.4 g) and NaNO$_2$ (0.138 g, 2 mmol) in *n*-hexane (10 ml) was stirred at room temperature for 30 min (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na$_2$SO$_4$ (3 g) was added to the filtrate. After 15 min, the resulting mixture was also filtered; *n*-hexane was removed by distillation in a water bath. The yield of **5b** 0.312 g (90%), crystalline pale yellow solid, mp 88–89 °C, (lit.,[13] mp 91 °C).

Table 1 Mononitration of phenols with a combination of **I**/$NaNO_2$ (A), **II**/$NaNO_2$ (B) or **III**/$NaNO_2$ (C) and wet SiO_2 (50%, w/w) in *n*-hexane at room temperature.

Entry	Substrate	Product	Substrate:reagents/mmol[a]			Time/min			Yield (%)[b]			Mp/°C	
			A	B	C	A	B	C	A	B	C	Found	Reported
1	**1**	**2**	2:2	2:2	2:4	45	45	90	28	23	38	111–113	115[12]
		3							60	47	41	44–46	44[12]
2	**4a**	**5a**	1:1	1:1	0.5:1	25	40	150	95	55	97	73	73–74[13]
3	**4b**	**5b**	1:1	1:1	2.5:5	30	45	120	90	75	57	88–89	91[12]
4	**4c**	**5c**	1:1	1:1	3:6	45	30	45	84	75	98	87	84[12]
5	**4d**	**5d**	1:1	1:1	3:6	45	45	420	91	75	93	140–142	145[13]
6	**4e**	**5e**	1:1	1:1	1:2	45	45	180	88	60	99	61–63	66[12]
7	**4f**	**5f**	1:1	1:1	1:2	45	45	60	89	60	94	29–31	31[12]
8	**4g**	**5g**	1:1	1:1	1:2	45	45	45	85	75	63	57–58	54–56[12]
9	**4h**	**5h**	1:1	1:1	1:2	45	45	16 h	86	80	82	122–124	123[12]
10	**4i**	**5i**	1:1	1:1	1:2	45	45	18 h	90	55	90	143–145	140–142[13]
11	**4j**	**5j**	1:1	1:1	1:2	45	45	75	80	70	87	63–65	61–66[12]
12	**4k**	**5k**	1:1	1:1	3.5:7	60	60	135	—[c]	—[c]	98	63–65	61–66[12]
13	**4l**	**5l**	1:1	1:1	1:2	45	45	60	88	70	45	183–186	183–184[12]
14	**4m**	**5m**	1:1	1:1	1:2	45	45	48	86	80	20	180–182	180–184[12]
15	**1**	**2**, **3**	0:2	0:2	0:4	12 h	12 h	12 h	no reaction[d]				
16	**1**	**2**, **3**	2:2	2:2	2:4	12 h	12 h	12 h	no reaction[e]				

[a] Wet SiO_2:substrate (**1** and **5**) (0.2g:1 mmol). [b] Isolated yields. [c] No reaction. [d] Reaction did not occur in the absence of **I–III**. [e] Reaction did not occur in the absence of wet SiO_2.

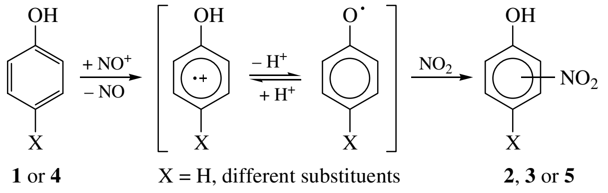


Scheme 3

pure mononitrophenols were obtained by the filtration and subsequent evaporation of the solvent.

These new systems *in situ* generated HNO_2 and NO^+. Therefore, the nitrous acid-catalysed mechanism (NAC) may be proposed (Scheme 4).[12]

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



Scheme 4

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