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### AROMATIC HYDROXYLATION BY A NEW CUPRIC NITRATE-H<sub>2</sub>O<sub>2</sub>-PHOSPHATE BUFFER SYSTEM

Aayesha Nasreen<sup>a</sup> & Srinivas R. Adapa<sup>a</sup>

<sup>a</sup> Inorganic Division, Indian Institute of Chemical Technology, Hyderabad, 500 007, INDIA

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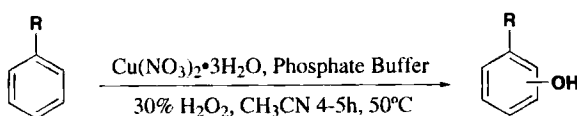
## OPPI BRIEFS

AROMATIC HYDROXYLATION BY A NEW CUPRIC NITRATE-H<sub>2</sub>O<sub>2</sub>-PHOSPHATE  
BUFFER SYSTEM<sup>†</sup>

Submitted by                      Aayesha Nasreen and Srinivas R. Adapa\*  
(03/02/00)

*Inorganic Division, Indian Institute of Chemical Technology  
Hyderabad - 500 007, INDIA*

The replacement of hydrogen on aromatic ring with a variety of substituents by electrophilic aromatic substitution is one of the most important processes in organic synthesis.<sup>1</sup> The hydroxylation of aromatics has received considerable attention during the last 20 years and the utility of H<sub>2</sub>O<sub>2</sub> as source of electrophilic oxygen has gained increasing importance. There have been a few reports on direct hydroxylation of aromatic compounds,<sup>2-13</sup> However, most of these systems are not easy to handle, and introduction of the hydroxyl group activates the ring for further reaction and oxidation. Since H<sub>2</sub>O<sub>2</sub> can be an effective hydroxylating agent, this serves as an impetus for the development of new hydroxylating systems based on H<sub>2</sub>O<sub>2</sub>. In continuation of our efforts to develop a new and more effective catalyst, several catalysts were studied for hydroxylation. This paper reports an efficient one-pot direct hydroxylation procedure involving the use of cupric nitrate<sup>14</sup> in conjunction with hydrogen peroxide and phosphate buffer to give phenols.



We found that 30% H<sub>2</sub>O<sub>2</sub> is an efficient and mild reagent for the hydroxylation of aromatic compounds in 90-95% yields (Table 1). The products were characterized by <sup>1</sup>H NMR, mass spectra, IR spectroscopy and the percentage of *o/p* isomers was determined by HPLC. The reaction of the alkylbenzenes shows predominant *o/p* orientation in accordance with typical electrophilic aromatic substitution.<sup>15</sup>

**TABLE.** Yields and Relative Ratio of Hydroxylation of Aromatic Compounds

Substrate	Time (h)	Yield <sup>a</sup> (%)	<i>para</i> Isomer <sup>b</sup>			<i>ortho</i> Isomer <sup>b</sup>		
			Yield (%)	mp <sup>c</sup> (°C)	<i>lit</i> <sup>d</sup>	Yield (%)	mp <sup>c</sup> (°C)	<i>lit</i> <sup>d</sup>
Ethylbenzene	4	92	96	46	47	4	194-195	195-197
<i>t</i> -Butylbenzene	4	94	95	97-98	99	5	223	224
Isobutylbenzene	4	90	94	59-61	61	6	224-226	226-228
Toluene	4	95	94	201	202	6	191	191-192
Anisole	3	94	89	55	56	11	104-105	106
Acetanilide	3	90	88	167-168	168	12	205-207	207-210
Chlorobenzene	4	92	92	216	217	8	174-175	175-176
Naphthalene	4	94	85 ( $\alpha$ )	92-93	94	15 ( $\beta$ )	121	122-123
Bromobenzene	4	92	88	63-64	64	12	194	195
<i>p</i> -Xylene	4	95	-	-	-	96	73-75	75-77

a) Actual yield of product(s) isolated. b) Yield refer to the ratio of *para* to *ortho* isomer.

c) bps are in parenthesis. d) reference 17.

The reaction failed when the solvent was changed from acetonitrile to methyl isobutyl ketone, acetone or methanol. No product was observed in absence of phosphate buffer. There was no reaction, when  $\text{AlCl}_3$ ,  $\text{FeCl}_3$ , or  $\text{FeSO}_4$  was used instead of cupric nitrate. The reaction proceeded very slowly with  $\text{CuCl}_2$  or  $\text{Cu}(\text{OAc})_2$  when compared to cupric nitrate. Longer reaction times and high temperatures resulted in the formation of polymerized product. Unexpectedly *o*-xylene underwent dimerization after the hydroxylation resulting 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl [ $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.92 (6H, s,  $\text{CH}_3$ ), 2.20 (6H, s,  $\text{CH}_3$ ), 6.70 (4H, s, aromatic), 7.92 (2H, s, exchangeable OH), yield 92%, mp. 198-200°, *lit* mp.199-201°. <sup>16</sup> Benzene gave hydroquinone (yield 95%, mp. 172°, *lit.* <sup>17</sup> mp.172-175°) while nitrobenzene gave 2,4-dihydroxynitrobenzene (yield 93%, mp. 82°, *lit.* <sup>17</sup> mp. 81-83°).

It is difficult to define the precise mechanism of the reaction, but our preliminary experiments indicate that the reaction is proceeding by the formation of peroxocuprate complex which in principle, can transfer the hydroperoxide species to the either substrate directly or by radical cation intermediate. It is also believed that the mechanism is similar to  $\text{CAN}^{8b}$  mediated reaction and that of the literature reports. <sup>18,19</sup>

In conclusion, the present system is a highly effective hydroxylating system for aromatic compounds providing the corresponding phenols in high yields. Since cupric nitrate,  $\text{H}_2\text{O}_2$  and phosphate buffer are easily handled, inexpensive reagents, this new procedure is ecofriendly with high regioselectivity is a significant improvement in direct aromatic hydroxylation.

## EXPERIMENTAL SECTION

All chemicals and solvents were obtained from commercial sources and used without further purification.  $^1\text{H}$  NMR were recorded at 90 MHz in  $\text{CDCl}_3$  solvent, IR spectra were obtained on G.C. FTIR using Vartan Nicolet USA apparatus and EI mass spectra were determined by using V.G. Micromass 7070H and Finnigan mal 1020B apparatus. Melting points were determined on Veego digital automatic melting point apparatus and are uncorrected.

**Typical Procedure.**- In a typical experimental procedure, to a solution of anisole (1.08 g, 0.01 mole) in acetonitrile (10 mL), was added neutral phosphate buffer (997 mg, 3.6 mmol) in 10 mL of water [the phosphate buffer is an equimolar mixture of disodium hydrogen orthophosphate ( $\text{Na}_2\text{HPO}_4$ , 510 mg, 3.6 mmol) and potassium dihydrogen orthophosphate ( $\text{KH}_2\text{PO}_4$ , 488 mg, 3.6 mmol)], cupric nitrate (0.5 g, 2.1 mmol) in 2 mL of water followed by the addition of 30%  $\text{H}_2\text{O}_2$  (7 mL, 0.0618 mole) in three portions. The reaction mixture was heated at  $50^\circ$  for 4 hr. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (15 mL). The organic layer was washed with water and dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated under reduced pressure. The crude product was chromatographed over silica gel column using chloroform:ethyl acetate (3:1) as eluent to yield pure products 1.165 g (94%), which was analysed by HPLC as 1.104 g (89%) of *p*-hydroxyanisole and 0.136g, (11%) of *o*-hydroxyanisole.

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#### A CONVENIENT PREPARATION OF METHYL 4-(2-AMINOETHYL)BENZOATE

Submitted by                      Stephen W. Wright  
(05/05/00)

*Pfizer Central Research  
Eastern Point Road, Groton, CT 06340*

Methyl 4-(2-aminoethyl)benzoate (**1**) is an intermediate in the preparation of a variety of pharmaceuticals, including the antidiabetics Meglitide<sup>1</sup> and S15261,<sup>2</sup> the leukotriene D<sub>4</sub> antagonist LM-1376,<sup>3</sup> and the antiarteriosclerotic BM-15766.<sup>4</sup> It is also of value as a doubly functionalized template for the synthesis of combinatorial chemistry products. Remarkably, few preparations of **1** have been reported in the literature. These suffer from several disadvantages, including the use of starting materials that are not commercially available,<sup>5</sup> low yields of one or more steps, the use of