# A Green Reagent for the Iodination of Phenols

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Abstract: A new reagent  $(I_2/NaNO_2)$  for the iodination of the aromatic ring of phenols has been discovered. The reaction proceeds at room temperature in 1.5–6 hours. In the presence of this reagent, iodinated compounds are regioselectively formed in significant yields from the corresponding substrates.

Key words: iodination, phenols, sodium nitrite, Lewis acid, ecofriendly

Iodination of a functionalized aromatic species is an example of an electrophilic substitution. Many such aromatic substitution reactions are the key routes to introduce many other functional groups besides iodine in the aromatic ring. Direct iodination of aromatic compounds is difficult due to the low electrophilicity of molecular iodine compared to the other halogens, and also due to the reducing effect of the hydrogen iodide produced.<sup>1</sup> However, arenes have previously been successfully iodinated in the presence of either a Lewis acid or an oxidizing agent.<sup>1,2</sup> Several iodination methods have been reported using various reagents, such as tetramethylammonium  $\begin{array}{l} \mbox{dichloroiodide,}{}^{3a}\ GeI_2, {}^{3b}\ I_2/AgNO_3, {}^{3c}\ INO_3, {}^{3d}\ I_2/Al_2O_3, {}^{3e}\ I_2/\\ Cu(OMe)_2, {}^{3f}\ I_2/H_2O_2, {}^{3g}\ NH_4I/Oxone^{\circledast}, {}^{3h}\ I_2/CAN, {}^{3i}\ ICI/\\ \end{array}$ Lewis acid,<sup>3j</sup> I<sub>2</sub>/HgO,<sup>3k</sup> I<sub>2</sub>/Ag<sub>2</sub>SO<sub>4</sub>,<sup>31</sup> n-BuLi/CF<sub>3</sub>CH<sub>2</sub>I,<sup>3m</sup> I<sub>2</sub>/NaHCO<sub>3</sub>,<sup>3n</sup> and ICl/ZnO.<sup>30</sup> Although these procedures provide some improvement relative to other methods, most of them still suffer from long reaction times, the necessity of drastic reaction conditions, and tedious workups. Some of them require an excess of reagents, and the catalysts from them are toxic. Many of these reagents also are expensive, which effectively limits their application.

Despite the great importance of aromatic iodinated compounds as precursors for organic transformation via ionic, radical and metal-catalyzed intermediates,<sup>4</sup> as well as for the preparation of pharmaceutical and bioactive compounds,<sup>5</sup> there is still a great need for the discovery of a simple, inexpensive and nontoxic reagent system for the introduction of iodine into an aromatic ring. Today, the preparation and regiospecific modification of polysubstituted aromatic molecules is a fundamental problem for both synthetic and industrial chemists.<sup>6</sup>

In our work on the development of useful synthetic methodologies for the synthesis of ellipticine,<sup>7</sup> an approach for the synthesis of carbazole derivatives from 2,5-dimethylphenol by preparing its iodinated product **6a** with  $I_2/CAN^{3i}$  was unsuccessful. Preparation of its iodinated product, however, was reported in good yields in the presence of benzyltrimethylammonium dichloroiodate/ $CaCO_3^{8a}$  and benzyltriphenylphosphonium peroxymonosulfate/KI.<sup>8b</sup> During an attempt to develop this work with inexpensive and eco-friendly reagents, we accidentally observed that iodine and sodium nitrite together work as an effective iodination reagent for the aromatic ring of phenol (Scheme 1).



Scheme 1

Sodium nitrite, a naturally occurring chemical, a meat preservative, and an antidote for cyanide poisoning, has many other medicinal applications.<sup>9</sup> However, apart from its use to convert amines into diazo compounds<sup>10</sup> and preparation of aryl halide in the presence of halotrimethylsilane,<sup>11</sup> its full synthetic utility is yet to be exploited. Its low price, nontoxicity and eco-friendly nature make it an ideal reagent for the iodination of phenol and its derivatives.

Although the hydroxyl group is an *ortho/para* director in the aromatic electrophilic substitution of phenols, iodination of phenols with I<sub>2</sub>/NaNO<sub>2</sub> in H<sub>2</sub>O-MeOH occurs predominantly in the *ortho* position and 2-iodophenol is the major product (Table 1, entries 1 and 17). When a phenol has an ortho substituent, the iodine substitution primarily takes place at the para position (Table 1, entries 2, 3, 6, and 14), but 4,6-diiodo-2-nitrophenol is formed in the case of o-nitrophenol (Table 1, entry 7). In p-methylphenol and p-nitrophenol, the corresponding ortho-monoiodinated products are formed exclusively (Table 1, entries 5 and 9). With an aldehyde function at the *para* position, only the ortho/ortho'-diiodinated phenol is obtained (Table 1, entry 12). With a methyl, nitro, or formyl substituent at the *meta* position of the phenol, however, *ortho/ortho'*double iodination occurred (Table 1, entries 4, 8, and 11). Surprisingly, 2-hydroxybenzaldehyde and 3-hydroxyphenol did not undergo iodination even after 24 hours (Table 1, entries 10 and 15). Interestingly 4-hydroxyphenol readily oxidized almost quantitatively to the corre-

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PAPER successful in iodinating both electron-activated and

-deactivated phenols. In all the reactions, some unreacted

starting material was recovered, and 10-20% of undetec-

ted by-products were formed. Reaction at room tempera-

ture with equimolar amounts of phenols, I2, and NaNO2 is

recommended for optimal results.

sponding *p*-quinone  $(16a)^{12}$  instead of undergoing iodination.<sup>13</sup> Generally, phenols with an electron-donating substituent easily underwent iodination in less time (Table 1, entries 3, 4, and 5), in comparison to those substituted with an electron-deactivating group (Table 1, entries 7, 8, 9, 11, 12, and 13). But I<sub>2</sub>/NaNO<sub>2</sub> is quite

Table 1	Iodination	of Phenols
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Entry	Substance	Product; yield (%)				Time (h) <sup>a</sup>
		ortho	para	meta	others	
1	OH	OH 1a (78) <sup>b</sup>	_c	-	OH Ib (7) <sup>b</sup>	4
2	OH Br	_	OH Br	-	-	3.5
3	OH	_		-	_	4
4	OH	OH 4a (13) <sup>d</sup>	<b>3a</b> (23) <sup>a</sup>	-	_	3
5	OH	5 c (50)d	_	-		4
6	OH	<b>5a</b> (59) <sup>5</sup>	OH 6a (68) <sup>d</sup>	-	OH 6 <b>b</b> (8) <sup>d</sup>	6
7	OH NO <sub>2</sub>	_	_	_		2 6
8	OH NO <sub>2</sub>	$\mathbf{Ba} (63)^d$	-	-	7 <b>a</b> (78)° -	6

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Entry	Substance	Product; yield (%)				Time (h) <sup>a</sup>
		ortho	para	meta	others	
9	OH NO <sub>2</sub>		_	-	-	6
10	ОНСНО	<b>-</b>	-	-	-	24
11	ОН	OH I CHO 11a (24) <sup>d</sup>	_	-	_	4.5
12	OH CHO	OH I CHO	_	-	_	6
13	OH CHO	12a (23) <sup>d</sup> OH CHO 13a (66) <sup>d</sup>	_	-	-	6
14	ОН	-	OH	-	-	1.5
15	ОН	-	<b>14a</b> (53) <sup>a</sup>	-	-	24
16	ОН	-	-	-		0.5
17	ОН	ОН 17а (52) <sup>d</sup>	-	_	<b>102</b> (94)" -	6

 Table 1
 Iodination of Phenols (continued)

<sup>a</sup> Reactions were conducted at r.t. and the reaction time was determined by TLC after the addition of the corresponding phenol.

<sup>b</sup> GPC yields.

<sup>c</sup> No such product.

<sup>d</sup> Isolated yields are reported (a single run).

An increase in temperature to the reflux point did not improve the product yield. A change of the solvent from methanol to ethanol had no discernible solvent effect. The time sequence of the addition of the phenol was found to be critical to the outcome of the reaction. By stirring the mixture of phenols,  $I_2$ , and NaNO<sub>2</sub> led to the formation of more by-products and less of the main iodinated product. On the other hand, when phenol was added after stirring a mixture of  $I_2$ /NaNO<sub>2</sub> in  $H_2O$ –MeOH for 30 minutes, the yield of the iodinated product increased to a satisfactory level. No other specific reaction was observed when simple phenol was allowed to react with molecular  $I_2$  or NaNO<sub>2</sub> individually in  $H_2O$ –MeOH for six hours. This suggests that NaNO<sub>2</sub> initially reacts with molecular iodine and helps to generate the active I<sup>+</sup> electrophile.

Although any mechanistic discussion is speculative at this point, a pathway for this reaction may be proposed based on the experimental results and available literature.<sup>3e,j,o,14a,b</sup> The ionic nature of Na<sup>+</sup>NO<sub>2</sub><sup>-</sup> appears to act as an effective catalyst for electrophilic iodination. It can polarize and activate I<sub>2</sub> for the generation of HOI,<sup>14a</sup> which can subsequently function as a source of the I<sup>+</sup> electrophile.<sup>3e</sup> The nitrosonium ion (NO<sup>+</sup>) produced from NaNO<sub>2</sub> under acidic conditions<sup>14c</sup> acts as a Lewis acid.<sup>15a</sup> Generally, Lewis acids polarize I<sub>2</sub> to a more effective I<sup>+</sup> electrophile.<sup>3e,15b,c</sup>

In conclusion, a new eco-friendly methodology for the regiospecific iodination of phenols at room temperature using an inexpensive, nontoxic green reagent  $(I_2/NaNO_2)$  is reported. Predominantly, mono ortho iodination occurs in unsubstituted and *para*-substituted phenols, and *para* iodination results with *ortho*-substituted ones. With *meta*substituted substrates, ortho/ortho' double iodination takes place. Further, this reagent works successfully for the iodination of both electron-activated and -deactivated phenols and also for nearly quantitative oxidation of 1,4dihydroxybenzene to the corresponding quinone. This reagent is also effective for the iodination of a phenol with a formyl group without affecting its formyl functionality in significant yields. Although the literature enumerates a number of reagents for the iodination of phenols, the simplicity, environmental acceptability and inexpensiveness of this reagent makes it more practical. Further investigation is underway in our laboratory to explore the scope and limitations of this procedure.

The melting points were determined by Yanaco micro melting point apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JNM ECP-500 (500 and 125 MHz), using CDCl<sub>3</sub> as a solvent with TMS as an internal standard. Mass spectra were recorded on a JMS GCmate II GC-mass spectrometer.

#### **Iodination of Aromatic Species; General Procedure**

A mixture of NaNO<sub>2</sub> (69 mg, 1 mmol) and I<sub>2</sub> (254 mg, 1 mmol) in a 1:1 mixture of H<sub>2</sub>O (5 mL) and MeOH (5 mL) was stirred for 0.5 h. To this stirred solution, the respective phenol (1 mmol) was added directly at 5–10 °C. The resultant mixture was stirred at r.t. for 1.5–6 h (Table 1) under atmospheric air. The progress of the reaction was monitored using TLC. After completion of the reaction, the organic product was extracted with CHCl<sub>3</sub> ( $3 \times 15$  mL). The combined organic extracts were washed with of 0.1 M aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL) to remove the unreacted I<sub>2</sub>, followed by extraction with CHCl<sub>3</sub> ( $3 \times 10$  mL). The combined CHCl<sub>3</sub> extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure in a rotary evaporator. The residue obtained was purified by silica gel chromatography with CHCl<sub>3</sub>–MeOH to obtain the corresponding pure aryl iodides (Table 1). For the iodination of phenol (Table 1, entry 1), however, purification was accomplished using a Recycling Preparative HPLC equipped with a gel permeation chromatography column (with CHCl<sub>3</sub> as the eluent).

#### 2-Iodophenol (1a)<sup>30</sup>

Mp 39–41 °C (Lit.<sup>16a</sup> mp 43 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.51 (s, 1 H, OH), 7.50 (t, *J* = 8.0 Hz, 1 H, ArH), 7.64 (d, *J* = 6.5 Hz, 1 H, ArH), 7.79 (t, *J* = 8.0 Hz, 1 H, ArH), 8.28 (d, *J* = 6.5 Hz, 1 H, ArH).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 87.4, 116.2, 123.4, 128.4, 139.3, 155.5.

### 2,4-Diiodophenol (1b)<sup>16b</sup>

Mp 72-74 °C (Lit.<sup>16b</sup> mp 73.5-74.0 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.52 (d, *J* = 6 Hz, 1 H, ArH), 7.69 (dd, *J* = 6.5, 2.0 Hz, 1 H, ArH), 8.02 (d, *J* = 2.5 Hz, 1 H, ArH).

### 2-Bromo-4-iodophenol (2a)<sup>16c</sup>

Mp 49–51 °C (Lit.<sup>16d</sup> mp 51 °C).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.53 (s, 1 H, OH), 6.80 (d, *J* = 8.7 Hz, 1 H, ArH), 7.51 (d, *J* = 9.1 Hz, 1 H, ArH), 7.75 (s, 1 H, ArH).

#### 4-Iodo-2-methylphenol (3a)<sup>16b</sup>

Mp 65-66 °C (Lit.16b mp 68.5-69.0 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.32 (s, 3 H, CH<sub>3</sub>), 6.52 (d, *J* = 9.5 Hz, 1 H, ArH), 6.87 (d, *J* = 9.5 Hz, 1 H, ArH), 7.56 (d, *J* = 2.5 Hz, 1 H, ArH).

### 2,6-Diiodo-3-methylphenol (4a)<sup>16e</sup>

Black oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 2.17 (s, 3 H, CH<sub>3</sub>), 7.04 (m, 1 H), 8.43 (d, J = 6.5 Hz, 1 H).

#### 2-Iodo-4-methylphenol (5a)<sup>16f</sup>

Light-brown oil (Lit.<sup>16f</sup> mp 34.5–35.5 °C; Lit.<sup>16g</sup> light-brown oil).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta = 2.21$  (s, 3 H), 5.42 (br s, 1 H, OH), 6.75 (d, J = 8.0 Hz, 1 H), 6.88 (dd, J = 8.5, 2.0 Hz, 1 H), 7.03 (d, J = 2.5 Hz, 1 H).

#### 4-Iodo-2,5-dimethylphenol (6a)<sup>8a</sup>

Mp 99 °C (Lit.<sup>8a</sup> mp 95–96 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.04, (s, 3 H, CH<sub>3</sub>), 2.19 (s, 3 H, CH<sub>3</sub>), 6.34 (s, 1 H, ArH), 7.60 (s, 1 H, ArH), 9.54 (br s, 1 H, OH). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 16.0, 17.0, 99.9, 121.4, 129.0, 132.6, 139.8, 145.9.

#### 4,6-Diiodo-2,5-dimethylphenol (6b)<sup>16h</sup>

Mp 63-64 °C (Lit.<sup>16h</sup> mp 63 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 2.12 (s, 3 H, CH<sub>3</sub>), 2.47 (s, 3 H, CH<sub>3</sub>), 7.58 (s, 1 H, ArH).

#### 4,6-Diiodo-2-nitrophenol (7a)<sup>3d</sup>

Mp 98 °C (Lit.<sup>8a</sup> mp 98 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.33 (d, *J* = 1.5 Hz, 1 H, Ar-H), 8.40 (d, *J* = 1.5 Hz, 1 H, Ar-H), 11.26 (br s, 1 H, OH).

# 2,6-Diiodo-3-nitrophenol (8a)<sup>16e</sup>

Mp 72–73 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.33 (d, *J* = 2.5 Hz, 1 H, ArH), 8.41 (d, *J* = 3 Hz, 1 H, ArH).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 81.1, 88.5, 116.2, 133.6, 153.8, 154.1.

### 2-Iodo-4-nitrophenol (9a)<sup>16b</sup>

Mp 83 °C (Lit.<sup>16b</sup> mp 90.0–91.5 °C, Lit.<sup>16j</sup> mp 86–87 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.08 (d, *J* = 9.0 Hz, 1 H, ArH), 8.19 (dd, *J* = 2.5, 3.0 Hz, 1 H, ArH), 8.60 (d, *J* = 1.5 Hz, 1 H, ArH). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 91.2, 99.9, 121.5, 134.3, 152.0, 156.1.

# 2,4-Diiodo-3-hydroxybenzaldehyde (11a)

Brown oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 6.34$  (d, J = 4.5 Hz, 1 H, ArH), 7.02 (d, J = 8.0 Hz, 1 H, ArH), 9.98 (s, 1 H, CHO). GC-MS: m/z = 374 (100% M<sup>+</sup>)

GC-MS:  $m/z = 374 (100\%, M^+)$ .

## 3,5-Diiodo-4-hydroxybenzaldehyde (12a)<sup>16k</sup>

Mp 194–195 °C (Lit.<sup>16k</sup> mp 197 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.19 (s, 2 H, ArH), 9.67 (s, 1 H, CHO).

### **3-Iodo-4-hydroxy-2,5-dimethylbenzaldehyde (13a)** Mp 132–134 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.34 (s, 3 H, CH<sub>3</sub>), 2.78 (s, 3 H, CH<sub>3</sub>), 6.11 (s, 1 H, OH), 7.58 (s, 1 H, ArH), 10.06 (s, 1 H, CHO). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 16.7, 24.0, 97.7, 122.5, 128.6, 135.0, 142.8, 157.1, 190.7.

GC-MS:  $m/z = 276 (100\%, M^+)$ .

## 4-Iodo-2-hydroxyphenol (14a)<sup>161</sup>

Mp 94–96 °C (Lit.<sup>161</sup> mp 90–92 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.93 (br s, 2 H, 2 × OH), 6.86 (d, J = 9 Hz, 1 H, ArH), 7.64 (d, J = 2.5 Hz, 1 H, ArH), 7.68 (dd, J = 2.5, 3.0 Hz, 1 H, ArH).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 91.4, 115.5, 117.6, 141.7, 146.5, 153.6.

# 1,4-Benzoquinone (16a)<sup>16m</sup>

Mp 114–116 °C (Lit.<sup>16m</sup> mp 112.9 °C).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta = 6.72$  (s, 4 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 136.4, 187.1.

# 1-Iodo-2-naphthol (17a)<sup>16b</sup>

Mp 94 °C (Lit.16b mp 91-92 °C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.23 (d, *J* = 8.0 Hz, 1 H, ArH), 7.73 (m, 2 H, ArH), 7.62 (t, *J* = 7.5 Hz, 1 H, ArH), 7.39 (d, *J* = 8.0 Hz, 1 H, ArH), 7.21 (d, *J* = 9.5 Hz, 1 H, ArH).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 85.3, 115.7, 125.2, 127.2, 127.8, 129.1, 130.0, 131.3, 137.6, 147.1.

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