Catalytic Hypervalent Iodine Oxidation of \textit{p}-Dialkoxybenzenes to \textit{p}-Quinones Using 4-Iodophenoxyacetic Acid and Oxone®

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A catalytic hypervalent iodine oxidation of \textit{p}-dialkoxybenzenes using 4-iodophenoxyacetic acid (1) and 2KHSO₅·KH₂SO₄·K₂SO₄ (Oxone®) was developed. Reaction of \textit{p}-dialkoxybenzenes (2) with a catalytic amount of 1 in the presence of Oxone® as a co-oxidant in 2,2,2-trifluoroethanol–water (1:2) gave the corresponding \textit{p}-quinones (3) in excellent yields without purification. This procedure was applied to synthesis of blattaquinone (9), the sex pheromone of the German cockroach, \textit{Blattella germanica}.

Key words \textit{p}-dialkoxybenzene; 4-iodophenoxyacetic acid; Oxone®; catalytic hypervalent iodine oxidation; \textit{p}-quinone; blattaquinone

Development of efficient methods for quinone synthesis is quite important in synthetic organic chemistry because they are structural components of numerous pharmacologically active compounds and useful synthetic intermediates.\textsuperscript{12} Oxidation of phenols and phenol derivatives is a common method.\textsuperscript{3–6} Among them, oxidative dearomatization of phenol ethers using metal oxidants, such as cerium(IV) ammonium nitrate (CAN)\textsuperscript{7,8} and silver(II) oxide–nitric acid \textsuperscript{9} etc., is one of the most efficient procedures for synthesis of complex natural products because phenol ethers are stable under various conditions and are easily prepared. From the perspective of the synthesis of pharmacological and agricultural active compounds, however, environmentally benign methods that are free of heavy metal waste are strongly desired. A convenient metal-free procedure to produce quinones from phenol ethers, hypervalent iodine oxidation using phenyliodi-

ne(III) trifluoroacetate (PIFA), has been reported.\textsuperscript{10} Hypervalent iodine reagents have been used extensively in recent organic synthesis because of their low toxicity, ready availability, and ease of handling.\textsuperscript{11–15} However, the reagents are expensive, moreover, stoichiometric amounts of iodine reagents are necessary during oxidation to produce equimolar amounts of iodine waste. In addition, some of them are potentially explosive. To overcome these disadvantages of these reagents, catalytic hypervalent iodine oxidations were developed recently.\textsuperscript{16–28} We also reported a catalytic hypervalent iodine oxidation of \textit{p}-alkylphenols to \textit{p}-quinones using a catalytic amount of 4-iodophenoxyacetic acid (1) with Oxone® (2KHSO₅·KH₂SO₄·K₂SO₄) as a novel system.\textsuperscript{29} This system presents the following advantages. The first is that reaction proceeds under mild conditions. The second is that Oxone® is inorganic, water-soluble, commercially available, and inexpensive with low toxicity.\textsuperscript{30} The third is that solubility of 1 in alkaline solution facilitates its recovery without special operation. As a part of our study for develop-

Table 1. Oxidative Dearomatization of 2a with 1 and Oxone®

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (eq)</th>
<th>Oxone® (eq)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%) of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>CH₃CN–H₂O (2:1)</td>
<td>1</td>
<td>Quant</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>4</td>
<td>CH₃CN–H₂O (2:1)</td>
<td>10</td>
<td>Quant</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>4</td>
<td>CH₃CN–H₂O (1:1)</td>
<td>5</td>
<td>Quant</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>4</td>
<td>CH₃CN–H₂O (1:2)</td>
<td>2</td>
<td>Quant</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>4</td>
<td>CH₃CN–H₂O (1:5)</td>
<td>3</td>
<td>33\textsuperscript{d}</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>1</td>
<td>CH₃CN–H₂O (1:2)</td>
<td>24</td>
<td>Quant</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>4</td>
<td>CH₃CN–H₂O (1:2)</td>
<td>4</td>
<td>Quant</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>4</td>
<td>CH₃CN–H₂O (1:2)</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
<td>4</td>
<td>THF–H₂O (1:2)</td>
<td>4</td>
<td>5\textsuperscript{c}</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>4</td>
<td>Acetone–H₂O (1:2)</td>
<td>5</td>
<td>d)</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>4</td>
<td>CF₃CH₂OH–H₂O (1:2)</td>
<td>1</td>
<td>Quant</td>
</tr>
<tr>
<td>12</td>
<td>0.05</td>
<td>4</td>
<td>CF₃CH₂OH–H₂O (1:2)</td>
<td>1</td>
<td>Quant</td>
</tr>
<tr>
<td>13</td>
<td>0.025</td>
<td>4</td>
<td>CF₃CH₂OH–H₂O (1:2)</td>
<td>4</td>
<td>Quant</td>
</tr>
<tr>
<td>14</td>
<td>0.01</td>
<td>4</td>
<td>CF₃CH₂OH–H₂O (1:2)</td>
<td>48</td>
<td>94</td>
</tr>
</tbody>
</table>

\textsuperscript{a) Reactions were carried out at room temperature. \textsuperscript{b) Unreacted 2a was recovered (67%). \textsuperscript{c) Unreacted 2a was recovered (95%). \textsuperscript{d) Reaction was not completed and gave 3a with unknown by-product.}

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mixture of tetrahydrofuran and water proceeded slowly to give 3a and unreacted 2a (1:20) after 4 h (entry 9). Acetone was not a suitable solvent (entry 10). In contrast, 2,2,2-trifluoroethanol\(^{21}\) was proven effective in this oxidation reaction (entries 11—14). Both reactions of 2a with 0.1 eq and 0.05 eq of 1 were finished within 1 h to give 3a (entries 11, 12). The reaction was completed within 4 h to give 3a in quantitative yield when 2a was treated with 0.025 eq of 1 and 4 eq of Oxone\(^{6}\) in CF\(_3\)CH\(_2\)OH–H\(_2\)O (1:2) at room temperature (entry 13). The reaction using 0.01 eq of 1 was finished after 48 h to afford 3a in 94% yield (entry 14). The turnover number (TON) of this reaction was calculated as 94.

We next investigated the oxidation of various \(p\)-dialkoxyarenes (2b—h, 4, 6) with 0.05 eq of 1 and 4 eq of Oxone\(^{6}\) in CF\(_3\)CH\(_2\)OH–H\(_2\)O (1:2) at room temperature as standard conditions\(^{23}\) (Chart 2). The results are presented in Table 2. Reaction of \(p\)-dimethoxybenzene (2b) gave \(p\)-benzoquinone (3b) in good yield (entry 2). \(p\)-Dioethoxybenzene (2c) was also oxidized to 3b (entry 3). Although \(p\)-\((\text{tert-butyldimethylsilyloxy})\text{methoxybenzene (2d) reacted smoothly to}

\[\text{3b}\]

give \(p\)-quinones (3b) in quantitative yield (entry 4), the electron-withdrawing acetyl group decreased the reactivity to give 3b in as low as 4% yield with the recovery of 96% of 2e after 24 h (entry 5). Reactions of 1,4-dimethoxybenzenes (2f, g) having an alkyl group, such as methyl and bulky \(\text{tert-buty1 groups at the 2-position, were oxidized to the corresponding 2-quinones (3f, g) with}

\[\text{3f, g}\]

excellent yields (entries 6, 7). The propanoate (2h) was converted to the corresponding quinone (3h) in quantitative yield (entry 8). Low solubility of the starting materials in CF\(_3\)CH\(_2\)OH–H\(_2\)O (1:2) required a change of the ratio of CF\(_3\)CH\(_2\)OH to H\(_2\)O (entries 9, 10). Anthraquinone (5) was obtained in high yield (entry 9), but the yield of 1,4-naphthoquinone (7) was low because of its low stability under the reaction conditions used for this study (entry 10). In all cases, 1 was recovered in good yield (75—85%), and can be used for oxidation again after recrystallization.

A possible catalytic cycle for this oxidation is as follows: The iodoarene (1) is oxidized by Oxone\(^{6}\) to hypervalent species,\(^{27,28,32,33}\) which oxidize \(p\)-dimethoxybenzene to give the \(p\)-quinone and an iodoarene at a lower oxidation stage. The latter would be re-oxidized by Oxone\(^{6}\) to a hypervalent species.

Finally, we applied this reaction to synthesis of \(\text{blattellaquinone (9), the sex pheromone of the German cockroach, Blattella germanica.}\}

For synthesis of 9, this catalytic oxidation was more efficient than the usual CAN oxidation.

References and Notes

1) “The Chemistry of the Quinonoid Compounds,” Vol. 2, Parts 1 and 2,
Typical reaction procedure: Compound 1 (0.050 mmol) was added to a solution of 2 (1.0 mmol) in CF<sub>3</sub>CH<sub>2</sub>OH·H<sub>2</sub>O (1 : 2, 10 mL), followed by Oxone<sup>8</sup> (4 mmol) at room temperature, the resulting mixture was stirred at the same temperature. After 2 was consumed completely, as indicated by TLC, the mixture was diluted with ethyl acetate and washed with water. The organic layer was then washed with aqueous saturated sodium bicarbonate solution and dried, then concentrated to give pure 3. If necessary, the product was purified using column chromatography on silica gel to give pure quinone. The alkaline solution was acidified by 10% hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium thiosulfate solution and dried, then concentrated to recover 1 (75—85%) which was purified by recrystallization from diethyl ether–hexane. All new compounds gave satisfactory spectroscopic data.

It remains unclear whether iodine(V) or iodine(III) species was formed during the reaction. The experiment of 1H-NMR of a mixture of 1 and an excess Oxone<sup>8</sup> in CD<sub>3</sub>CN·D<sub>2</sub>O showed no presence of hypervalent iodine species.

Many reports for the formation of hypervalent iodine species by the oxidation of iodoarene with Oxone<sup>8</sup> have appeared.\(^{36-41}\)

Compound 9: yellow crystals, mp 46—47 °C (hexane). 1H-NMR (400 MHz, CDCl<sub>3</sub>): \(\delta\) 0.99 (6H, d, \(J=6.6\) Hz), 2.07—2.22 (1H, m), 2.30 (2H, d, \(J=6.9\) Hz), 5.00 (2H, d, \(J=1.9\) Hz), 6.69 (1H, brq, \(J=2.0\) Hz), 6.77 (1H, d, \(J=10.0\) Hz), 6.80 (1H, dd, \(J=10.0, 1.0\) Hz).

13C-NMR (100 MHz, CDCl<sub>3</sub>): \(\delta\) 22.5 (2), 59.2, 131.3, 136.3, 136.4, 143.1, 171.9, 185.9, 186.7. IR (KBr) cm\(^{-1}\): 1744, 1648. MS (EI) m/z: 222 (M<sup>+</sup>). HR-MS (EI) m/z: 222.08822 (Cald for C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>: 222.08821).

Although Nojima et al. reported oxidation of 8 with CAN, that report includes no description related to detailed reaction conditions and yield.\(^{35}\)


