Facile Synthesis of 3-Aryl-3-hydroxy-2-oxindoles from 2-Arylindoles

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3-Aryl-3-hydroxy-2-oxindoles have been found in many biologically important compounds,1 as shown in Figure 1. As some examples, orally active potent growth hormone secretagogue SM-136086,1a potent antimicrobial lead drug EC18,1b,c and potent opener of maxi-K channels MaxiPost and its lead compound1d,2a have been reported. In addition, 3-aryl-3-hydroxy-2-oxindoles have been used as intermediates for the synthesis of many oxindole derivatives such as 3-halo-, 3-alkoxy-, 3-thialkoxyl-, 3-aryl, and 3-acetamido-2-oxindole derivatives.2 Thus, various synthetic approaches for these valuable compounds have been reported.1e,6 The reactions of isatin with aryllithium or arylmagnesium halides have been reported.3 The reaction of aryloboronic acids and isatin in the presence of transition metal catalysts has also been used frequently.1e,4 In addition, cyclization of α-ketoamides1b,5 and Friedel-Crafts type reaction of isatin with electron-rich arenes also provided these valuable compounds.6

Recently, we reported an aerobic transition metal-free synthesis of 2,3-diarylindoles via an oxidative nucleophilic substitution of hydrogen (ONSH) pathway from 2-arylindoles and nitroarenes.7 As an example, the reaction of 2-phenylindole (1a) and 1,3-dinitrobenzene in DMSO in the presence of Cs2CO3 under O2 balloon atmosphere afforded 2,3-diarylindole in good yield (78%) in short time, as shown in Scheme 1. During the study, we found the formation of 3-phenyl-3-hydroxy-2-oxindole (2a), albeit in moderate yield (41%), under the same reaction condition for a long time (8 h) without 1,3-dinitrobenzene.

Encouraged by the unusual formation of synthetically useful 3-phenyl-3-hydroxy-2-oxindole, we examined the optimum condition for the conversion of 1a to 2a, as summarized in Table 1. The yield of 2a was improved to 73% when we replaced Cs2CO3 to KOH under the same reaction condition (90°C, 8 h), as shown in entry 1. The yield of 2a was further improved to 84% at lower temperature (65°C) with lesser amount of KOH (1.5 equiv), although a long reaction time (20 h) was required (entry 2).8 When we used lesser amount of KOH (0.5 equiv), 2a was formed in low yield (12%) and most of 1a was recovered (entry 3).

The use of 3.0 equiv of KOH (entry 4) does not increase the yield, although reaction time was shortened. DMF (entry 5) or THF (entry 6) was found to be less efficient solvent. The use of NaOH (entry 7) or tetrabutylammonium hydroxide (entry 9) showed a similar result to that of KOH, while LiOH (entry 8) or DBU (entry 10) was ineffective. KOtBu (entry 11) or potassium trimethylsilanolate (entry 12) showed a similar reactivity to that of KOH. The reaction under N2 balloon atmosphere (entry 13) did not produce 2a as expected.

Various 2-substituted indoles 1b–1n were prepared according to the reported methods.9 The reactions of 2a–1a were carried out under the optimized condition (KOH, DMSO, 65°C, O2 balloon), and the results are summarized in Table 2. The reactions of 5-chloro-2-phenylindole (1b) and 5-methyl-2-phenylindole (1c) afforded the corresponding products 2b (79%) and 2c (86%) in good yields. However, the reaction of 5-nitro derivative 1d did not produce 2d, presumably due to delocalization of the indole anion to the nitro group (vide infra, Scheme 3). The reactions of 2-(4-chlorophenyl)indole (1e), 2-(4-methoxyphenyl)indole (1f), 2-(2-naphthyl)indole (1g), and 2-(2-thienyl)indole (1h) afforded the corresponding products 2e–2h in good yields (77–87%). It is interesting to note that the reaction of 1f was completed in short time (10 h) than other entries. The result implied that a facile migration of electron-rich 4-methoxyphenyl moiety would reduce the reaction time (vide infra). The reaction of 2-(2-benzofuranyl)indole (1i) was very slow, and 2i was isolated in low yield (39%) after 48 h along with recovered 1i (8%). The reaction of 2-(4-nitrophenyl)indole (1j) was also ineffective, and the reason might be attributed to difficult migratory aptitude of electron-deficient 4-nitrophenyl moiety (vide infra, Scheme 3). In addition, the reactions of 2-tert-butylindoles 1k–1m afforded 2k–2m in good yields (84–90%) in short time (10 h). However, the reaction of 2-benzylindole (1n) showed the formation of many intractable side products. The only isolable compound was 2-benzoylindole (2n).

Based on the experimental results, the reaction mechanism for the conversion of 1a to 2a is proposed, as shown in...
Scheme 2. The indole anion I was converted to 3-hydroxyindolenine intermediate III via the hydroperoxide intermediate II.\textsuperscript{11} Subsequently, III was changed to an epoxide intermediate IV under basic condition, and a following semipinacol type rearrangement of IV would produce 3-phenyloxindole VI.\textsuperscript{12} A subsequent aerobic oxidation of VI would produce 2a.\textsuperscript{13}

As noted above, the reactions of 1d and 1i did not produce the corresponding 3-aryl-3-hydroxy-2-oxindoles. As shown in Scheme 3, an electron delocalization of the indole anion I renders the formation of a hydroperoxide intermediate II difficult. For the reaction of 1i, a rearrangement of 4-nitrophenyl group might be difficult during the conversion of epoxide intermediate IV to V.

As a synthetic application, the reduction of 2a to 3-phenylindole (3a) was examined. Actually we could obtain 3a in good yield (74%) by the reaction of 2a under the reported condition using BH\textsubscript{3}THF (3.0 equiv),\textsuperscript{14} as shown in Scheme 4. Thus, our protocol could provide an easy way of two-step synthesis of 3-arylindole from 2-arylindole.

In summary, an efficient synthetic route of 3-aryl-3-hydroxy-2-oxindoles has been developed from 2-arylindoles. The procedure provides a brand-new synthetic method of 3-aryl-3-hydroxy-2-oxindoles from readily available starting materials in high yields.

**Experimental**

**Typical procedure for the synthesis of 2a.** A stirred solution of 1a (97 mg, 0.5 mmol) and KOH (85%, 50 mg, 0.75 mmol) in DMSO (1.0 mL) was heated to 65°C for 20 h under O\textsubscript{2} balloon atmosphere. After the usual aqueous extractive workup and column chromatographic purification process (CH\textsubscript{2}Cl\textsubscript{2}/EtOAc, 3:1), 2a was isolated as a white solid, 95 mg (84%). Other compounds were synthesized similarly, and the selected spectroscopic data of 2a and 2k are as follows.\textsuperscript{2e,15}

**Compound 2a.** 84%; white solid, mp 210–212°C (Ref. 2e 207–209°C); IR (KBr) 3414, 3176, 1697 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz) δ 6.62 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.21–7.35 (m, 6H), 10.40 (br s, 1H); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 75 MHz) δ 77.32, 109.88, 122.08, 124.79, 125.43, 127.44, 131.50, 142.34, 178.50; ESIMS m/z 226 [M+H].

**Compound 2k.** 90%; white solid, mp 222–224°C (Ref. 15 224–225°C); IR (KBr) 3358, 1716 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) δ 0.94 (s, 9H), 5.65 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 10.11 (br s, 1H); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) δ 23.95, 36.74, 79.84, 108.98, 120.71, 125.67, 128.54, 131.50, 142.34, 179.50; ESIMS m/z 206 [M+H].
**Table 2.** Synthesis of 3-substituted-3-hydroxy-2-oxindoles."^a^  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indoles 1</th>
<th>Products 2 (%)</th>
<th>Entry</th>
<th>Indoles 1</th>
<th>Products 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a (84)</td>
<td>8</td>
<td>1h</td>
<td>2h (77)^c</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b (79)</td>
<td>9</td>
<td>1i</td>
<td>2i (39)^c,a</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c (86)</td>
<td>10</td>
<td>1j</td>
<td>2j (0)^f</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d (0)^b</td>
<td>11</td>
<td>1k</td>
<td>2k (90)^d</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e (81)^c</td>
<td>12</td>
<td>1l</td>
<td>2l (87)^c,d</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f (87)^c,d</td>
<td>13</td>
<td>1m</td>
<td>2m (84)^d</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g (78)^e</td>
<td>14</td>
<td>1n</td>
<td>2n (26)^d</td>
</tr>
</tbody>
</table>

^a^ Conditions: Indole 1 (0.5 mmol), KOH (1.5 equiv), DMSO, 65°C, O2 balloon, 20 h.  
^b^ Indole 1d was recovered in 91%, and some polar side products were formed.  
^c^ Ar1 = 4-chlorophenyl, Ar2 = 4-methoxyphenyl, Ar3 = 2-naphthyl, Ar4 = 2-thienyl, Ar5 = 2-benzofuranyl, Ar6 = 4-nitrophenyl.  
^d^ Reaction time was 10 h.  
^e^ Reaction time was 48 h, and 1i was recovered in 8%.  
^f^ Indole 1j was recovered in 52%, and some polar side products were formed.

**Scheme 2.** Proposed mechanism.

**Scheme 3.** Plausible reason for the failure of 1d and 1j.

**Scheme 4.** Two-step conversion of 1a to 3a.


For selected synthesis using Friedel-Crafts reactions, see: (e) R. J. S. Beer, T. Donovanik, A. Robertson, J. Chem. Soc. 1954, 4139. The conversion of IIa to III might proceed by DMSO11a or N-methyl-2-phenylindole showed completely no reaction.


