Facile Synthesis of Isoindigo Derivatives from 3-Indolyl-2-Oxindoles with DDQ

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Isoindigo (3,3’-biindolylidene-2,2’-dione) and its derivatives have received much attention due to their biological activity such as anti-leukemia, antiproliferative, and anti-inflammatory activity (Figure 1).1 For example, meisoindigo has been used for the treatment of chronic myeloid leukemia in China2 and Natura (1-digonzo has been used for the treatment of chronic myeloid leukemia3) and key intermediates for the synthesis of spirooxindole1 which have been used as electron acceptor units for the synthesis of natural products.4

In general, isoindigo derivatives have been synthesized by an acid-catalyzed condensation reaction of isatin with oxindole,5–25 tris(diethylamino)phosphine-mediated carbene dimerization of isatin,5a–25b palladium-catalyzed cascade dual annihilations of diarybut-2-ynamides,5c and other methods.5d–n

Recently, we were interested in the synthesis of spirooxindole derivatives.5 As a continuing study, we examined the synthesis of spirooxindole 3 from 3,3-diindolyl-2-oxindole 1a’. Similar intramolecular oxidative coupling of bis-indolyl derivatives has been carried out with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in the presence of p-TsOH or trifluoroacetic acid (TFA).7 The reaction of 1a’ and DDQ in refuxing TFA showed complete decomposition of 1a’. Thus, the reaction of 1a’ and DDQ in the presence of p-TsOH (5 mol%) in refluxing toluene was examined; however, the formation of 3 was not observed. Instead, meisoindigo 2a was formed in low yield (5–10%). When we carried out the reaction of 1a’ and DDQ (2.0 equiv) in the presence of TFA (20 mol%) in refluxing toluene for 18 h, the yield of 2a increased to 31%, as shown in Scheme 1.8 However, the reaction is less atom-economic due to loss of valuable one molecule of indole. Thus, we examined the reaction of 3-indolyl-2-oxindole 1a under the same reaction conditions, and 2a was obtained in better yield (52%) in short time (2 h). To the best of our knowledge, such procedure toward the synthesis of isoindigo derivative from 3,3-diindolyl-2-oxindoles or 3-indolyl-2-oxindoles has not been reported.5,9

Thus, the synthesis of 2a from 1a was examined under various reaction conditions, and the results are summarized in Table 1. The yield of 2a decreased to 44% without TFA (entry 2). The use of AcOH as an acid catalyst was less effective (entry 3). The reaction in 1,2-dichloroethane (DCE, entry 4) was similar to the one in toluene. When we used 1,4-dioxane as a reaction medium (entry 5), the yield was improved to 62%. To our delight, the highest yield (82%) was obtained when carrying out the reaction in aqueous dioxane (entry 6),10 and the remaining 1a was not observed. The result strongly stated that water molecule must be involved in the transformation of 1a to 2a (vide infra). The use of an excess amount (3.0 equiv) of DDQ (entry 7) does not increase the yield, and the yield decreased when an equivalent amount of DDQ was used (entry 8). The use of tetrachloro-1,4-benzoquinone (chloranil, entry 9), Oxone (2KHSO5/KHSO4/K2SO4, entry 10), or pyridinium chlorochromate (PCC, entry 11) was less effective in the reaction.

Encouraged by the successful result, we synthesized various isoindigo derivatives 2b–2l, and the results are summarized in Table 2.

The reactions of 1b–1d under the standard condition gave 2b–2d in good yields (71–79%). The reactions of N,N-disubstituted derivatives 1e–1k afforded the corresponding isoindigo derivatives 2e–2k in good yields (73–83%). In addition, the reaction of N-unsubstituted derivative 1l also gave isoindigo 2l in moderate yield (67%).

As shown in Table 2, compound 2h was synthesized from 1h in good yield (76%). It is interesting to note that 2h could also be synthesized from 1m in good yield (80%), as shown in Scheme 2.

The reaction mechanism could be proposed as shown in Scheme 3. An acid-catalyzed dehydration of 1a would generate resonance-stabilized cation intermediate I (path a).9a Addition of water at the 2-position of the indole ring generated a cyclic hemiaminal intermediate II. A subsequent oxidation of II with DDQ would afford 2a.11 Another plausible reaction mechanism is also suggested in Scheme 3. The reaction of DDQ and 1a in the presence of an acid catalyst would form an intermediate III via a charge-transfer complex (path b).12,13 Subsequent addition of water to form IV and following elimination of DDQH2 produced V.12
Final acid-catalyzed dehydration of V produced 2a. When we added DDQ to a stirred solution of 1a, green color appeared presumably due to the formation of a charge-transfer complex between 1a and DDQ. The green color turned to deep red by the reaction progress. Based on the experimental observations, both pathways might contribute to the formation of isoindigo. As expected according to the suggested mechanism, the reaction of N,N-dimethyl-3-(2-methylindolyl)-2-oxindole, prepared from N-methylisatin and 1,2-dimethylindole, under the standard reaction condition showed a complete decomposition to intractable polar compounds.

In summary, various isoindigo derivatives were synthesized in good yields from 3-indolyl-2-oxindoles. Further studies to probe the scope of the reaction and reaction mechanism are currently underway.

Table 1. Optimization of reaction conditions for the synthesis of 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>2a Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ (2.0 equiv), TFA, toluene, reflux, 2 h</td>
<td>52%</td>
</tr>
<tr>
<td>2</td>
<td>DDQ (2.0 equiv), toluene, reflux, 3 h</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>DDQ (2.0 equiv), AcOH, toluene, reflux, 2 h</td>
<td>46%</td>
</tr>
<tr>
<td>4</td>
<td>DDQ (2.0 equiv), TFA, DCE, reflux, 2 h</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>DDQ (2.0 equiv), TFA, dioxane, reflux, 2 h</td>
<td>62%</td>
</tr>
<tr>
<td>6</td>
<td>DDQ (2.0 equiv), TFA, aaq, dioxane, reflux, 2 h</td>
<td>82%</td>
</tr>
<tr>
<td>7</td>
<td>DDQ (3.0 equiv), TFA, aaq, dioxane, reflux, 2 h</td>
<td>79%</td>
</tr>
<tr>
<td>8</td>
<td>DDQ (1.0 equiv), TFA, aaq, dioxane, reflux, 2 h</td>
<td>56%</td>
</tr>
<tr>
<td>9</td>
<td>chloranil (2.0 equiv), TFA, aaq, dioxane, reflux, 2 h</td>
<td>9%</td>
</tr>
<tr>
<td>10</td>
<td>Oxone (1.0 equiv), TFA, aaq, dioxane, reflux, 4 h</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td>PCC (2.0 equiv), aaq, dioxane, reflux, 2 h</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Substrate 1a (0.5 mmol), 20 mol% of TFA or AcOH, aaq dioxane is dioxane/H2O = 10:1. *Isolated yield (%).
Experimental

Typical Synthetic Procedure of 2a. 3-Indolyl-2-oxindole 1a was prepared from N-methylisatin and indole according to the reported method.\textsuperscript{14} To a stirred solution of 1a (139 mg, 0.5 mmol) and DDQ (227 mg, 1.0 mmol) in aqueous 1,4-dioxane (1,4-dioxane/H\textsubscript{2}O = 10:1) was added TFA (11 mg, 20 mol\%). The reaction mixture was heated to reflux for 2 h. After removal of solvents and column chromatographic purification process (n-hexane/EtOAc, 2:1), meisoindigo 2a\textsuperscript{15} was isolated as a dark red solid, 113 mg (82%). Other compounds were synthesized similarly, and the selected spectroscopic data of unknown compound 2f are as follows.

Compound 2f: 73%; dark purple solid, mp 224–226°C; IR (KBr) 1687, 1606, 1468, 1338 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 2.31 (s, 3H), 2.51 (s, 3H), 3.27 (s, 3H), 3.52 (s, 3H), 6.76 (d, \(J = 7.7\) Hz, 1H), 6.91 (s, 1H), 7.04 (t, \(J = 7.7\) Hz, 1H), 8.89 (s, 1H), 9.09 (d, \(J = 8.0\) Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 19.2, 21.0, 26.1, 29.7, 107.6, 118.6, 121.8, 122.2, 122.5, 128.0, 129.5, 131.3, 132.1, 132.7, 134.1, 137.2, 140.9, 144.9, 167.9, 168.6; ESIMS m/z 319 [M + H]\textsuperscript{+}. Anal. Calcd for C\textsubscript{20}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.74; H, 6.02; N, 8.59.

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Supporting Information. Additional supporting information including experimental procedure and spectroscopic data is available in the online version of this article.

References


In contrast, the reaction of 1a’ afforded 2a in low yield (39%) even under the optimized reaction conditions (DDQ,aq. dioxane, TFA, reflux, 2 h).


