Indium(III) Chloride/2-Iodoxybenzoic Acid: A Novel Reagent System for the Conversion of Indoles into Isatins

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Abstract: Indoles and azaindoles undergo smooth oxidation with 2-iodoxybenzoic acid (IBX) in the presence of indium(III) chloride at 80 °C to afford the corresponding isatins in excellent yields. This method is very useful for the direct preparation of isatins from indoles. The reaction proceeds smoothly in aqueous media and the products are obtained in excellent yields.

Keywords: indole, indium(III) reagents, isatin, hypervalent iodine

Isatins (1H-indole-2,3-diones) are versatile building blocks for the synthesis of a large variety of heterocyclic compounds such as indoles, isatoic anhydride, and quinolines, and as precursor for convolutamydines (Figure 1) and proteasome inhibitors. Isatins have also been found in mammalian tissue where they act as a modulator of biochemical processes. The versatility of isatins stems from their pharmacological and biological properties. Therefore, much attention has been paid to the preparation of isatins. As a result, there have been reports on the conversion of indoles into isatins. However, the conditions used may cause modification of the substituents and yields are generally low, particularly when the indole is unsubstituted at nitrogen. Hypervalent iodine reagents have attracted increasing interest as oxidants in organic synthesis due to their mild, selective, and environmentally benign oxidizing properties. Among various hypervalent iodine reagents, 2-iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency, ready availability, mild reaction conditions, and its stability to moisture and air. Wide functional group tolerance and high yielding reactions without over oxidation, has made the use of 2-iodoxybenzoic acid synthetically useful for the oxidation of alcohols, even in the presence of alkenes, sulfides, and amino groups. In recent reports, the use of 2-iodoxybenzoic acid as a mild oxidant has been extended to many other elegant oxidations.

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sence of indium(III) chloride resulted in low yield of product (21%) even after a long reaction time (24 h). However, no oxidation of indole was observed when the reaction was performed using 10 mol% of indium(III) chloride in the absence of 2-iodoxybenzoic acid. Both indium(III) chloride and 2-iodoxybenzoic acid are essential for the success of the reaction. Among other hypervalent iodine reagents studied [i.e., Dess–Martin periodinane, PhI(OAc)₂, PhIO], 2-iodoxybenzoic acid was found to be the best, giving good results. Of various indium reagents tested [i.e., In(OTf)₃, In(ClO₄)₃], indium(III) chloride was shown to be the most effective Lewis acid for this conversion. The scope and generality of this process is illustrated with respect to various indoles and the results are presented in the Table 1.

Table 1  Indium(III) chloride/2-Iodoxybenzoic Acid Promoted Oxidation of Indoles to Isatins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product¹</th>
<th>Time (h)</th>
<th>Yieldb (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Indole 1a" /></td>
<td><img src="image2" alt="Product 2a" /></td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Indole 1b" /></td>
<td><img src="image4" alt="Product 2b" /></td>
<td>2.5</td>
<td>79</td>
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<tr>
<td>3</td>
<td><img src="image5" alt="Indole 1c" /></td>
<td><img src="image6" alt="Product 2c" /></td>
<td>1.5</td>
<td>90</td>
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<tr>
<td>4</td>
<td><img src="image7" alt="Indole 1d" /></td>
<td><img src="image8" alt="Product 2d" /></td>
<td>1.5</td>
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<tr>
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<td><img src="image9" alt="Indole 1e" /></td>
<td><img src="image10" alt="Product 2e" /></td>
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<tr>
<td>6</td>
<td><img src="image11" alt="Indole 1f" /></td>
<td><img src="image12" alt="Product 2f" /></td>
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<td>91</td>
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<tr>
<td>7</td>
<td><img src="image13" alt="Indole 1g" /></td>
<td><img src="image14" alt="Product 2g" /></td>
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<td>85</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Indole 1h" /></td>
<td><img src="image16" alt="Product 2h" /></td>
<td>1.5</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Indole 1i" /></td>
<td><img src="image18" alt="Product 2i" /></td>
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<tr>
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<td><img src="image20" alt="Product 2j" /></td>
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</table>
In conclusion, we have described a novel and efficient protocol for the conversion of indoles into isatins using indium(III) chloride/2-iodoxybenzoic acid as a novel reagent system. The use of an inexpensive and water-tolerant reagent system makes this procedure quite simple, more convenient, and environmentally friendly for the preparation of synthetically and biologically potent isatins in a one-pot operation.

All known compounds were characterized by $^1$H NMR, IR, and MS and their spectroscopic data was identical to that reported in the literature. All new compounds were characterized by $^1$H NMR, $^{13}$C NMR, IR, and MS.

**Indole-2,3-diones 2; General Procedure**

Indole or azaindole (1 mmol), IBX (2.5 mmol), and InCl$_3$ (0.1 mmol) in MeCN–H$_2$O (9:1) were stirred at 80 °C for the appropriate time (Table 1). When the reaction was complete (TLC), the mixture was filtered through Celite and washed with EtOAc (2 × 10 mL). The combined organic extracts were washed with NaHCO$_3$ soln and then with brine and dried (anhyd Na$_2$SO$_4$). Removal of solvent followed by purification on a short chromatography column (silica gel, EtOAc–$n$-hexane, 2:8) afforded pure 2.

**1-Benzyl-1H-indole-2,3-dione (2c)**

Orange needles; mp 133–135 °C.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 7.55 (d, $J$ = 7.4 Hz, 1 H), 7.51 (t, $J$ = 7.4 Hz, 1 H), 7.09 (t, $J$ = 7.4 Hz, 1 H), 7.37–7.24 (m, 5 H), 6.87 (d, $J$ = 8.1 Hz, 1 H), 4.91 (s, 2 H).

MS (EI): $m$/z (%) = 237 (M$^+$, 70), 180 (40), 146 (100), 104 (12), 91 (85), 57 (10).

**1-Methyl-1H-indole-2,3-dione (2d)**

Orange needles; mp 130–132 °C.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 7.72 (d, $J$ = 8.1 Hz, 1 H), 7.65 (s, 1 H), 6.91 (d, $J$ = 8.1 Hz, 1 H), 3.22 (s, 3 H).

MS (EI): $m$/z (%) = 241 (M$^+$ + 2, 98), 239 (98), 213 (85), 211 (88), 185 (88), 183 (100), 158 (24), 156 (26), 104 (100), 77 (50), 63 (50).

**Methyl 2,3-Dioxo-2,3-dihydro-1H-indole-5-carboxylate (2k)**

Orange needles; mp 258–259 °C.

IR (KBr): 3055, 2927, 1730, 1606, 1466, 1324, 1251, 1104, 1090, 951, 863, 758, 692 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 7.55 (t, $J$ = 7.4 Hz, 1 H), 7.49 (d, $J$ = 7.4 Hz, 1 H), 7.07 (t, $J$ = 7.4 Hz, 1 H), 6.88 (d, $J$ = 8.1 Hz, 1 H), 3.18 (s, 3 H).

MS (EI): $m$/z (%) = 205 (M$^+$, 30), 177 (100), 146 (60), 119 (25), 90 (20), 63 (25).

**Table 1** Indium(III) chloride/2-Iodoxybenzoic Acid Promoted Oxidation of Indoles to Isatins (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product$^a$</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
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<td><img src="image" alt="Indole structure 2c" /></td>
<td><img src="image" alt="Isatin structure 2k" /></td>
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<tr>
<td>12</td>
<td><img src="image" alt="Indole structure 1l" /></td>
<td><img src="image" alt="Isatin structure 2l" /></td>
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<td>87</td>
</tr>
<tr>
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<td><img src="image" alt="Indole structure 1m" /></td>
<td><img src="image" alt="Isatin structure 2m" /></td>
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<td>80</td>
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<tr>
<td>14</td>
<td><img src="image" alt="Indole structure 1n" /></td>
<td><img src="image" alt="Isatin structure 2n" /></td>
<td>3.5</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$ All products were characterized by $^1$H NMR, IR, and MS.

$^b$ Isolated and unoptimized yields.
Acknowledgment

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References

(b) Stang, P. J.; Zhdankin, V. V. Chem. Rev. 1996, 96, 1123.