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$CeCl_3 \cdot 7H_2O$/IBX-promoted oxidation of 3-alkylindoles to 3-hydroxyoxindoles

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Abstract—3-Alkylindoles undergo smooth oxidation with IBX in the presence of $CeCl_3 \cdot 7H_2O$ in aqueous acetonitrile at ambient temperature to afford the corresponding 3-hydroxyoxindoles in high yields. This method is very useful for the direct preparation of 3-hydroxyoxindoles from 3-alkylindoles. Operational simplicity, mild and neutral reaction conditions in aqueous solution are the key features of this protocol.

The 3-hydroxyoxindole motif is a core structure in various biologically active molecules such as convolutamydines.[1] This framework exists in proteasome inhibitors like TMC-95A/B (Fig. 1).[2]

Furthermore, the 3-hydroxyindolin-2-one skeleton is also found in various alkaloids such as donaxaridine, dioxibrassinine, welwitindolinone C and 3-hydroxyglucoisatisin.[3] Therefore, there is a need to develop a simple and efficient protocol for the preparation of 3-hydroxyindolin-2-ones.[4] Iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency, easy availability, mild reaction conditions and its stability to moisture and air.[5] A wide functional group tolerance and high-yielding reactions, without over oxidation have made IBX very popular for the oxidation of alcohols even in the presence of olefins, thioethers and amino groups.[6] In recent reports, the use of IBX as a mild oxidant has been extended to many other elegant oxidative transformations.[7] Lanthanide salts are unique Lewis acids that are currently of great research interest.[8] Of various lanthanide salts, cerium(III) chloride is a relatively non-toxic, readily available at low cost, easy to handle, neutral catalyst and is fairly stable to water.[9] However, there have been no reports on the direct conversion of 3-alkylindoles into 3-hydroxyoxindoles in a single-step operation using IBX as an oxidant.

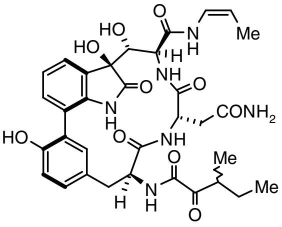
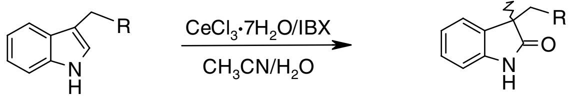


Figure 1.

As a part of our ongoing research programme on the use of rare earth metal salts for various transformations,[10] herein we disclose a novel and efficient protocol for the conversion of 3-alkylindoles into 3-hydroxyoxindoles. Accordingly, treatment of 3-methylindole with IBX in the presence of $CeCl_3 \cdot 7H_2O$ at room temperature gave the corresponding 3-hydroxyoxindole in 82% yield. Likewise, several 3-alkylindoles underwent smooth oxidation to produce 3-hydroxyindolin-2-ones in high yields (Scheme 1).



Scheme 1.

Keywords: Hypervalent iodine; Oxidation; Indoles; Cerium reagents.

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Table 1. $CeCl_3 \cdot 7H_2O$/IBX-promoted oxidation of 3-alkylindoles

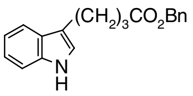
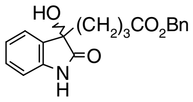
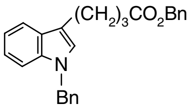
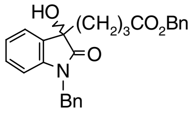
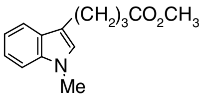
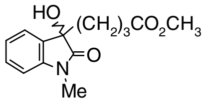
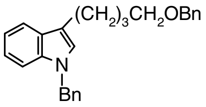
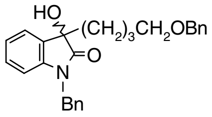
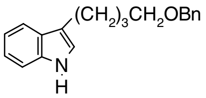
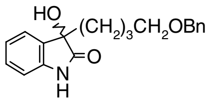
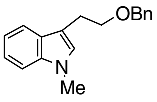
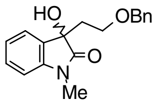
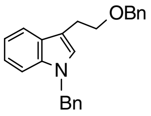
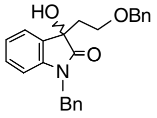
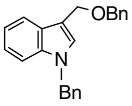
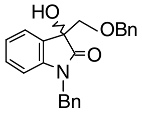
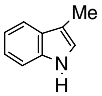
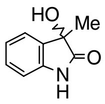
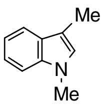
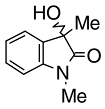
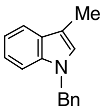
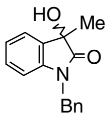
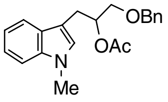
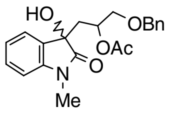
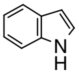
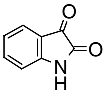
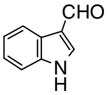
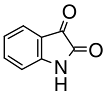
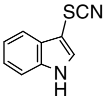
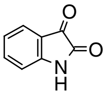
Entry	Indole (**1**)	Product[a] (**2**)	Time (h)	Yield[b] (%)
a			12.0	80
b			11.5	85
c			10.5	87
d			12.0	83
e			12.0	80
f			11.5	85
g			11.0	82
h			11.5	80
i			12.0	82
j			11.5	85
k			11.5	87
l			12.5	81

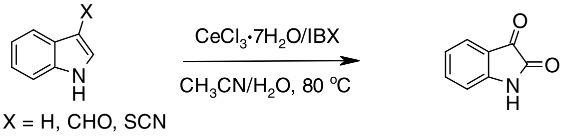
Table 1 (*continued*)

Entry	Indole (**1**)	Product[a] (**2**)	Time (h)	Yield[b] (%)
m			3.5[c]	86
n			3.0[c]	85
o			2.5[c]	87

[a] All products were characterised by ^{1}H NMR, IR, mass spectroscopy and ^{13}C NMR.

[b] Isolated and unoptimized yield.

[c] Reaction was carried at 80 °C.



Scheme 2.

Both free NH- and N-protected indoles such as *N*-alkyl or *N*-benzyl derivatives were efficiently converted into their corresponding 3-hydroxyindolin-2-ones. In all cases, the reactions proceeded very well at ambient temperature. Surprisingly, the oxidation of 3-formyl- and 3-thiocyano-indoles gave exclusively isatin instead of the desired 3-hydroxyoxindoles (Table 1, entries n and o). Isatin was also formed during the oxidation of indole with IBX/$CeCl_3{\cdot}7H_2O$ (Table 1, entry m; Scheme 2).

In the absence of $CeCl_3{\cdot}7H_2O$, the oxidation was rather slow affording the corresponding 3-hydroxyoxindoles in lower yields (15–25%). However, no oxidation was observed when the reaction was performed using 10 mol % of $CeCl_3{\cdot}7H_2O$ in the absence of IBX. Among other hypervalent iodine reagents such as the Dess–Martin periodinane, $PhI(OAc)_2$ and PhIO, IBX was found to be the best, giving good results. Of the various cerium reagents such as $Ce(OTf)_3$, and ceric ammonium nitrate which were tested, cerium(III) chloride was shown to be the most effective Lewis acid for this conversion. The products thus obtained were characterized by NMR, IR and mass spectroscopy. The scope and generality of this process is illustrated with respect to various 3-alkylindoles and the results are presented in Table 1.[11]

In conclusion, we have described an efficient protocol for the preparation of 3-hydroxyoxindoles from 3-alkyl indoles using $CeCl_3{\cdot}7H_2O$/IBX as a novel reagent system. The use of an inexpensive and water-tolerant reagent system makes this procedure simple, convenient and environmentally friendly.

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11. *Experimental procedure*: A mixture of 3-alkylindole (1 mmol), IBX (2.5 mmol) and $CeCl_3{\cdot}7H_2O$ (0.1 mmol) in CH_3CN/H_2O (9:1) was stirred at room temperature for

the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ followed by brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on a short silica gel column using a mixture of ethyl acetate–*n*-hexane (2:8) afforded pure 3-hydroxyoxindole. Spectral data for selected products. Compound **2a**: Viscous liquid, IR (KBr): ν 3299, 1740, 1698, 1622, 1471, 1187, 752, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.10 (br s, 1H), 7.18–7.30 (m, 6H), 7.10 (t, 1H, *J* = 7.4 Hz), 6.93 (t, 1H, *J* = 7.4 Hz), 6.77 (d, 1H, *J* = 8.1 Hz), 4.98 (s, 2H), 4.48 (br s, 1H), 2.22 (t, 2H, *J* = 7.4 Hz), 1.75–1.91 (m, 2H), 1.73–1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.1, 173.4, 140.7, 135.9, 130.7, 129.5, 128.1, 128.5, 124.2, 123.0, 110.7, 76.8, 66.2, 37.4, 33.9, 18.6. EIMS: *m*/*z*: 325 M^{+}, 155, 141, 91, 43. HRMS calcd for $C_{19}H_{19}NO_4Na$: 348.1198. Found: 348.1211. Compound **2b**: Mp 120–122 °C. IR (KBr): ν 3280, 2910, 1720, 1680, 1616, 1180, 730, 690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.38 (m, 12H), 7.02 (t, 1H, *J* = 7.4 Hz), 6.67 (d, 1H, *J* = 7.4 Hz), 5.06 (s, 2H), 4.95 (d, 1H, *J* = 15.6 Hz), 4.21 (d, 1H, *J* = 15.6 Hz), 3.06 (br s, 1H), 2.32 (t, 2H, *J* = 7.4 Hz), 1.87–2.12 (m, 2H), 1.48–1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 172.7, 142.5, 135.9, 135.4, 129.7, 129.6, 128.8, 128.5, 128.1, 127.6, 127.2, 124.0, 123.1, 109.5, 76.2, 66.1, 43.8, 37.8, 33.9, 18.7. FAB Mass: *m*/*z*: 416 M^{+1}, 398, 308, 290, 154, 136, 109, 95, 91, 81, 69, 55. HRMS calcd for $C_{26}H_{25}NO_4Na$: 438.1679. Found: 438.1681. Compound **2g**: Solid, mp 87–89 °C. IR (KBr): ν 3396, 2921, 2862, 1712, 1615, 1468, 1362, 1175, 1103, 748, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.36 (m, 11H), 7.18 (t, 1H, *J* = 7.7 Hz), 7.02 (t, 1H, *J* = 7.7 Hz), 6.65 (d, 1H, *J* = 7.7 Hz), 4.85 (d, 1H, *J* = 15.8 Hz), 4.74 (d, 1H, *J* = 15.8 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.41 (br s, 1H), 3.96 (td, 1H, *J* = 10.3, 3.8 Hz), 3.67 (q, 1H, *J* = 4.6 Hz), 2.37–2.53 (m, 1H), 2.08 (dt, 1H, *J* = 14.7, 4.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 142.3, 137.5, 135.6, 130.4, 129.3, 128.6, 127.7, 127.5, 127.1, 123.9, 122.8, 109.3, 75.7, 73.3, 66.0, 43.6, 37.3. FAB Mass: *m*/*z*: 374 M^{+1}, 326, 266, 250, 239, 105, 91, 83, 69, 55. HRMS calcd for $C_{24}H_{23}NO_3Na$: 396.1558. Found: 396.1575.