Samarium(II) Iodide-promoted Hydroxyalkylations of Indole-3-carbonyls. An Expedient Approach to Pyrrolidino[1,2-*a*]indoles and Furo[3,4-*b*]indoles

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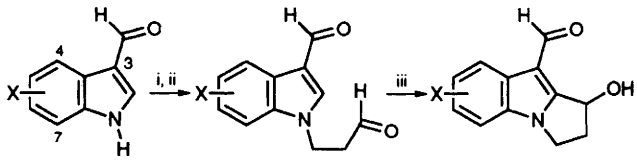
3-Formyl-, 3-acetyl-1-methylindole and their 2-cyano analogues undergo intra- and inter-molecular hydroxyalkylations on treatment with samarium(II) iodide in the presence of a cosolvent hexamethylphosphoramide; the intramolecular coupling products have the structure prototype of mytomycins and the intermolecular coupling products are readily converted to furoindoles as synthetic equivalents of indole-2,3-quinodimethanes.

In addition to extensive applications of samarium(II) iodide in organic synthesis,[1] we recently carried out dimerizations of benzaldehydes and intramolecular phenyl–carbonyl coupling reactions promoted by SmI_2/HMPA (HMPA = hexamethylphosphoramide).[2] The role of cosolvent HMPA is crucial to prevent reduction or pinacol coupling of aromatic carbonyl compounds.[3] We report here that the method was utilised successfully to effect coupling reactions of indoles and carbonyl compounds, either intra- or inter-molecularly. This is a new method for hydroxyalkylations at the C-2 of indoles, it also provides a route to the mytomycin skeleton[4] (*e.g.* **3**) and to furoindoles[5] (*e.g.* **9**).

The indoledialdehydes **2a–2c** were prepared by alkylation of the 3-formylindoles **1a–1e** individually with 2-(2-bromoethyl)-1,3-dioxane followed by hydrolysis as shown in Scheme 1. Under an argon atmosphere, a tetrahydrofuran (THF) solution (8 cm^3) of **2a** (0.67 mmol) was added dropwise over a period of 30 min to a violet solution of SmI_2 (1.7 mmol, prepared from Sm metal and 1,2-diiodoethane) and HMPA (1.5 cm^3) in THF (20 cm^3) at 0 °C. The light-green mixture was stirred at 0 °C for 10 min and warmed to room temp. The reaction mixture was worked up to yield a single product **3a**.† Intramolecular cyclisations of **2b** and **2c** were carried out by similar procedures to give the pyrrolidino[1,2-*a*]indolecarboxaldehydes **3b** and **3c**, respectively.

As shown in Scheme 2, the intermolecular coupling reaction of 3-acetyl-1-methylindole **1d** and *p*-methoxybenzaldehyde was carried out by treatment with SmI_2/HMPA to afford a 2,3-dihydroindole **4**, whereas attempted reaction of **1d** with acetophenone failed owing to competitive dimerization of acetophenone.[2] The ^1H NMR spectrum of **4** showed a large coupling constant of 8.7 Hz between 2-H and 3-H, indicating the 2,3-*cis* configuration.[6] On the other hand, the coupling reaction of acetophenone with the 3-formyl indole **1e** having a cyano substituent at C-2 was successfully carried out, giving **5**. By similar procedures, **1e** reacted with *p*-methoxybenzaldehyde and butan-2-one to give the corresponding 3-formyl-2-hydroxyalkylindoles **6** and **7**, and 2-cyano-3-acetyl-1-methylindole **1f** reacted with *p*-methoxybenzaldehyde to afford **8**. These reactions demonstrated a novel method for reductive hydroxyalkylations in indole system. The products **5–8** served as precursors of furo[3,4-*b*]indoles as exemplified by the acid-catalysed condensation of **8** to **9** in 82% yield.[5] Furo[3,4-*b*]indoles have been employed successfully as equivalents to indole-2,3-quinodimethane in Diels–Alder reactions.[5]

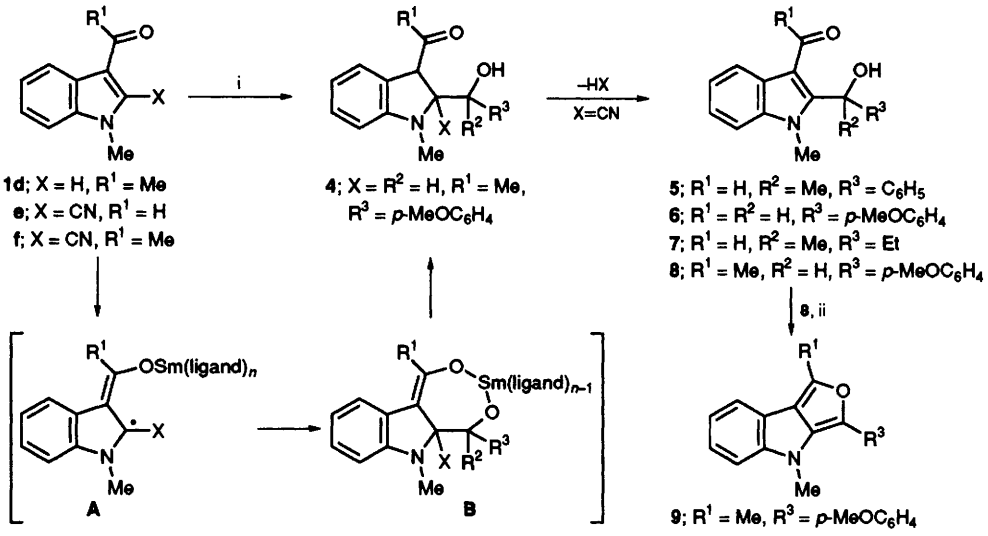
The coupling reaction was presumably initiated by one-electron transfer from SmI_2 to the more reactive indolecarbonyl group. The intermediate C-2 radical, or the anion derived by further SmI_2 reduction, added to the other carbonyl group and followed by protonation to give the 2,3-dihydroindole **4**, by autoxidation to give the pyrrolidino[1,2-*a*]indoles **3** or by elimination of HCN to give the indoles **5–8**. The cyano group was believed to exert a



1a; X = H **2a** (81%) **3a** (64%)
b; X = 5-OMe **b** (78%) **b** (78%)
c; X = 7-Et **c** (75%) **c** (76%)

Scheme 1 *Reagents and conditions*: i, NaH, THF; $BrCH_2CH_2CH[O(CH_2)_3O]$, room temp., 48 h; ii, 70% aqueous AcOH, reflux 1 h; iii, SmI_2, THF, HMPA, 0 °C (10 min) to room temp., (1 h)

† The new compounds had compatible IR, MS, HRMS, ^1H and ^{13}C spectra. Some pertinent data are listed: **3a**, solid, m.p. 113–115 °C; ^1H NMR ($CDCl_3$) δ 2.58–2.72 (1 H, m), 2.98–3.09 (1 H, m), 4.01–4.14 (1 H, m), 4.28–4.39 (1 H, m), 5.59 (1 H, dd, *J* 7.7, 6.2 Hz), 7.23–7.35 (3 H, m), 7.94–8.00 (1 H, m), 10.10 (1 H, s). **3c**, solid, m.p. 168–169 °C. **4**, oil; ^1H NMR ($CDCl_3$) δ 1.84 (3 H, s), 2.77 (1 H, br s, OH), 2.87 (3 H, s), 3.79 (3 H, s) 4.07 (1 H, dd, *J* 8.7, 2.4 Hz), 4.26 (1 H, d, *J* 8.7 Hz), 5.07 (1 H, d, *J* 2.4 Hz), 6.59 (1 H, d, *J* 8 Hz), 6.70 (1 H, t, *J* 8 Hz), 6.88 (2 H, d, *J* 8.7 Hz), 6.95 (1 H, d, *J* 7.5 Hz), 7.14 (1 H, t, *J* 7.5 Hz), 7.30 (2 H, d, *J* 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 29.8 (q), 35.2 (q), 53.8 (d), 55.2 (q), 69.6 (d), 75.2 (d), 108.9 (d), 113.8 (d, 2 C), 119.1 (d), 123.3 (d), 126.8 (s), 127.0 (d, 2 C), 128.6 (d), 131.5 (s), 152.8 (s), 159.0 (s), 205.9 (s). **8**, oil; ^1H NMR ($CDCl_3$) δ 2.72 (3 H, s), 3.74 (3 H, s), 3.76 (3 H, s), 6.23 (1 H, br s), 6.78 (2 H, d, *J* 8.7 Hz), 7.17 (2 H, d, *J* 8.7 Hz), 7.31–7.42 (3 H, m), 7.91–7.94 (1 H, m). **9**, oil; ^1H NMR ($CDCl_3$) δ 2.49 (3 H, s), 3.63 (3 H, s), 3.85 (3 H, s), 6.50 (2 H, d, *J* 8.8 Hz), 6.87 (2 H, d, *J* 8.8 Hz), 7.26–7.39 (3 H, m), 7.90–7.94 (1 H, m).



Scheme 2 *Reagents and conditions*: i, R^2R^3CO, SmI_2, THF, HMPA, 0 °C (30 min) to room temp., (1 h); ii, *p*-$MeC_6H_4SO_3H$, toluene, reflux 5 h. Yields: **4**, 42; **5**, 75; **6**, 82; **7**, 67; **8**, 85 and **9**, 82%.

beneficial effect to stabilise the intermediate radical or anion,[6] and thus facilitate the electron-transfer process. Treatment of aromatic and α,β-unsaturated aldehydes with SmI_2 usually leads to pinacols or polymeric mixtures.[7] Our current study demonstrates that the presence of HMPA causes a different process to effect aryl–carbonyl coupling reactions.[2] Introduction of a cyano group at an appropriate position in the indole system appears to promote this type of coupling reaction.

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