Synthesis of New 2,3-Disubstituted 4-Chloro-1-hydroxyindoles

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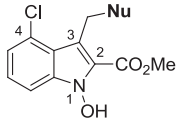
The syntheses of new 2,3-disubstituted 4-chloro-1-hydroxyindoles were described. The conjugate nitro ketoester was reacted with various thiol and alcohol nucleophiles by the action of stannous chloride dihydrate through the unique processes of reduction of nitro group, intramolecular condensation, and addition of nucleophiles in one pot, to provide multisubstituted 1-hydroxyindoles. The reactions with thiol nucleophiles provided better results than those with alcohols, and, in particular, secondary and tertiary thiols provided best yields.

Keywords: Heterocycles, Nucleophilic addition, Reduction, Tin, Cyclization

Introduction

1-Hydroxyindoles contain a hydroxy group at N(1) instead of the hydrogen in indoles, and are thus supposed to retain slightly but meaningfully different physical and chemical properties compared with indoles. Earlier studies have revealed the general features and properties of this unique structure.[1] Because of the presence of the hydroxy group, 1-hydroxyindoles are more polar and acidic (pK_a 8.1–9.8) than indoles.[1a] Although they are rarely found in natural products, their alkoxy forms, 1-alkoxyindoles, are found in some of the natural products.[2,3] In addition, they could be useful building blocks for complex molecules and serve as surrogates of indoles.[4] Recent studies have shown that these compounds display several types of biological activities such as antiproliferative,[5,6] antibiotic,[4] and platelet aggregation inhibitory activities.[7] However, much remains unknown regarding their chemistry and biological properties, and the studies on these compounds have been somewhat limited by the scarcity of tolerable synthetic methods and a narrow range of diversity of the reported compounds. Because of the growing interest, we previously reported the synthesis of 1-hydroxyindole derivatives and their application to more elaborate molecules, which demonstrated the potential significance of 1-hydroxyindoles.[8–10] Thus, as part of our continued efforts to generate novel multisubstituted 1-hydroxyindoles, we here report the synthesis of new 2,3-disubstituted 4-chloro-1-hydroxyindoles **1**. This method comprises a one-pot reaction involving reduction of a nitro group, condensation to give a conjugate nitrone, and addition of a nucleophile. To the best of our knowledge, these types of reactions are rarely reported except a few cases in our previous investigations.[8–10]



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Experimental

General. Melting points were measured in open capillary tubes using Buchi B-545 (Buchi Corp., Flawil, CH, Switzerland) melting point apparatus and are uncorrected. Fourier transform-infrared spectroscopy (FT-IR) spectra were measured on a Perkin-Elmer Spectrum GX spectrometer (Perkin-Elmer, Waltham, MA, USA) and frequencies (ν) are given in reciprocal centimeters (cm^{-1}). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on a Bruker DRX 300 spectrometer (Bruker Inc., Madison, WI, USA) and the δ values for chemical shift are expressed as units relative to tetramethylsilane (TMS). Mass spectra were obtained by EI or ESI method. Analytical thin layer chromatography (TLC) was conducted on glass plates (0.25 mm) coated with silica gel (20 × 20 cm; Aldrich No. Z12272-6) (Sigma-Aldrich, St. Louis, MO, USA). Column chromatography was performed using Merck silica gels (230–400 mesh; Merck Corp., Kenilworth, NJ, USA). Most of the chemicals were purchased commercially and, if needed, distilled before use. HPLC analyses were conducted using the following Waters Associate Units: 515 A pump, 515 B pump, dual λ absorbance 2487 detector, 717 plus autosampler, and Hypersil ODS column (4.6 × 300 mm). The product analyses were performed using linear gradient condition: from 100% A (aqueous 0.025 M triethylammonium acetate, pH 6.5), 0% B (acetonitrile) to 80% A, 20% B in 1 min, then to 10% A, 90% B in 30 min. The flow rate was 1 mL/min, and the eluent was monitored at 254 nm. The HPLC solvents were filtered (aqueous solution with Millipore high-volume and low-pressure (HVLP), 0.45 mm; acetonitrile with Millipore high-volume (HV), 0.45 mm) and degassed before use.

Methyl 3-(2′-Chloro-6′-nitrophenyl)-2-oxopropanoate (4).[6] To a mixture of NaH (60% in mineral oil, 0.56 g, 14 mmol, 4.0 equiv) in anhydrous N,N-Dimethylmethanamide (DMF) (20 mL) at 0 °C, a solution of 2-chloro-6-nitrotoluene (**3**, 0.58 g, 3.4 mmol, 1.0 equiv) in anhydrous

DMF (5 mL) was added. After stirring for 5 min at 0 °C, a solution of dimethyl oxalate (2.0 g, 17 mmol, 5.0 equiv) in anhydrous DMF (5 mL) was added, and stirring was continued for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 3.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) at 0 °C, extracted with EtOAc (2 × 30 mL), and washed with H_2O (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (1:6 → 1:1 EtOAc/hexanes) to give the title compound **4** (0.67 g, 76%) as a yellow solid. Mp 58–59 °C; R_f 0.46 (1:2 EtOAc/hexanes); HPLC t_R 21.2 min; IR (KBr) 3081, 2923, 1735, 1582, 1531, 1359, 803 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 7.97 (dd, J = 8.2, 1.2 Hz, 1H), 7.82 (dd, J = 8.0, 1.2 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 4.65 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 190.2, 162.0, 152.2, 138.3, 135.8, 131.0, 128.9, 125.2, 54.4, 42.0; MS *m/z* 258 $[M + H]^+$; HRMS (+ESI) calcd for $C_{10}H_8ClNNaO_5$ $[M + Na]^+$ 279.9989, found 279.9983.

Methyl 3-(2′-Chloro-6′-nitrophenyl)-2-oxobut-3-enoate (2). To a mixture of NaH (60% in mineral oil, 0.18 g, 4.4 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (THF) (90 mL) at 0 °C, a solution of ketoester (**4**, 1.0 g, 4.0 mmol, 1.0 equiv) in anhydrous THF (43 mL) was added. After stirring for 1 h, dimethylmethyleneammonium chloride (1.1 g, 12 mmol, 3.0 equiv) was added and stirring was continued for 15 h at 25 °C. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (2 × 40 mL), and washed with H_2O (2 × 40 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (1:5 → 1:1 EtOAc/hexanes) to give the title compound **2** (0.76 g, 72%) as a yellow solid. Mp 67–68 °C; R_f 0.44 (1:2 EtOAc/hexanes); HPLC t_R 21.7 min; IR (KBr) 3444, 2923, 2849, 1682, 1533, 1492, 1028 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.01 (dd, J = 8.3, 1.2 Hz, 1H), 7.85 (dd, J = 8.1, 1.2 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 6.73 (s, 1H), 6.40 (s, 1H), 3.92(s, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 186.2, 164.6, 151.3, 141.0, 137.2, 136.8, 135.9, 132.1, 131.0, 124.6, 54.3; MS *m/z* 270 $[M + H]^+$; HRMS (+ESI) calcd for $C_{11}H_8ClNNaO_5$ $[M + Na]^+$ 291.9989, found 291.9983.

General Procedure for 2,3-Disubstituted 4-Chloro-1-hydroxyindoles (1). To a stirred mixture of $SnCl_2{\cdot}2H_2O$ (2.5–3.3 equiv) and 4 Å molecular sieves (10 wt %) in DME (0.5 mL), nucleophile (5.0 equiv) was added, and the mixture was stirred for 30 min at room temperature. Then, the conjugate ketoester (**2**, 27 mg, 0.10 mmol, 1.0 equiv) was added at 25 °C and the reaction mixture was warmed to 45 °C. After stirring for 1.5–6.5 h in the dark, the reaction mixture was cooled to room temperature and purified by preparative thin layer chromatography (PTLC) or column chromatography to afford the title compounds **1**.

Methyl 3-[(Benzylthio)methyl]-4-chloro-1-hydroxy-1H-indole-2-carboxylate (1a). Use of benzyl mercaptan (60 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2{\cdot}2H_2O$ (52 mg, 0.25 mmol, 2.5 equiv) in general procedure (1.5 h) afforded the title compound **1a** (27 mg, 75%) as a yellow solid. Mp 101–102 °C; R_f 0.55 (1:2 EtOAc/hexanes); HPLC t_R 28.0 min; IR (KBr) 2924, 1600, 1451, 1265, 1028, 841, 749 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 9.30 (br s, 1H), 7.41 (dd, J = 8.3, 0.9 Hz, 1H), 7.37–7.16 (m, 6H), 7.12 (dd, J = 7.5, 0.9 Hz, 1H), 4.43 (s, 2H), 3.85 (s, 3H), 3.79 (s, 2H); ^{13}C NMR (75 MHz, CD_3CN) δ 163.0, 140.4, 138.3, 130.2, 129.8, 129.0, 128.2, 127.7, 125.8, 123.6, 119.6, 118.1, 110.3, 53.2, 37.8, 27.7; MS *m/z* 362 $[M + H]^+$; HRMS (+EI) calcd for $C_{18}H_{16}ClNO_3S$ $[M]^+$ 361.0539, found 361.0537.

Methyl 3-[(n-Butylthio)methyl]-4-chloro-1-hydroxy-1H-indole-2-carboxylate (1b). Use of 1-butanethiol (54 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2{\cdot}2H_2O$ (52 mg, 0.25 mmol, 2.5 equiv) in general procedure (1.5 h) afforded the title compound **1b** (25 mg, 75%) as a yellow solid. Mp 53–54 °C; R_f 0.46 (2:98 EtOAc/$CHCl_3$); HPLC t_R 22.4 min; IR (KBr) 3393, 2924, 1713, 1492, 1252, 756 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 9.24 (br s, 1H), 7.41 (dd, J = 8.3, 0.9 Hz, 1H), 7.28 (dd, J = 8.3, 7.5 Hz, 1H), 7.13 (dd, J = 7.5, 0.9 Hz, 1H), 4.45 (s, 2H), 3.93 (s, 3H), 2.48 (t, J = 7.3 Hz, 2H), 1.55–1.40 (m, 2H), 1.39–1.20 (m, 2H), 0.87 (t, J = 9.6 Hz, 3H); ^{13}C NMR (75 MHz; CD_3CN) δ 162.9, 138.4, 128.8, 127.6, 125.8, 123.4, 119.4, 119.1, 110.2, 53.1, 33.1, 32.3, 26.8, 23.1, 14.3; MS *m/z* 328 $[M + H]^+$; HRMS (+EI) calcd for $C_{15}H_{18}ClNO_3S$ $[M]^+$ 327.0696, found 327.0697.

Methyl 4-Chloro-3-[(n-hexylthio)methyl]-1-hydroxy-1H-indole-2-carboxylate (1c). Use of 1-hexanethiol (75 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2{\cdot}2H_2O$ (52 mg, 0.25 mmol, 2.5 equiv) in general procedure (4 h) afforded the title compound **1c** (26 mg, 74%) as a yellow solid. Mp 47–48 °C; R_f 0.63 (1:2 EtOAc/hexanes); HPLC t_R 31.8 min; IR (KBr) 3444, 3025, 1711, 1492, 757 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 9.20 (br s, 1H), 7.42 (dd, J = 8.3, 0.9 Hz, 1H), 7.29 (dd, J = 8.3, 7.5 Hz, 1H), 7.14 (dd, J = 7.5, 0.9 Hz, 1H), 4.42 (s, 2H), 3.94 (s, 3H), 2.49 (t, J = 7.3 Hz, 2H), 1.55–1.43 (m, 2H), 1.40–1.20 (m, 6H), 0.87 (t, J = 9.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 163.0, 138.5, 128.9, 127.7, 125.8, 123.5, 119.5, 119.3, 110.3, 53.2, 32.8, 32,6. 31.0, 29.8, 27.0, 23.7, 14.7; MS *m/z* 356 $[M + H]^+$; HRMS (+EI) calcd for $C_{17}H_{22}ClNO_3S$ $[M]^+$ 355.1009, found 355.1011.

Methyl 4-Chloro-3-[(cyclohexylthio)methyl]-1-hydroxy-1H-indole-2-carboxylate (1d). Use of cyclohexanethiol (63 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2{\cdot}2H_2O$ (52 mg, 0.25 mmol, 2.5 equiv) in general procedure (1.5 h) afforded the title compound **1d** (30 mg, 84%) as a yellow solid. Mp 96–97 °C; R_f 0.64 (3:97 EtOAc/$CHCl_3$); HPLC t_R 30.0 min; IR (KBr) 3435, 3025, 2923, 1601, 1492, 701 cm^{-1}; ^1H NMR (300 MHz; CD_3CN) δ 9.24 (br s, 1H), 7.43 (dd, J = 8.3, 0.9 Hz, 1H), 7.29 (dd, J = 8.3, 7.5 Hz, 1H), 7.14 (dd, J = 7.5, 0.9 Hz, 1H), 4.45 (s, 2H), 3.94 (s, 3H), 2.72–2.60 (m, 1H), 1.80–1.15 (m, 10H); ^{13}C NMR (75 MHz, CD_3CN) δ 163.0, 138.4, 128.9, 128.7, 127.6, 125.7, 123.5, 119.4, 110.3, 53.3, 44.7, 35.2, 27.4, 27.0, 25.6; MS *m/z* 354 [M +

H]$^+$; HRMS (+EI) calcd for $C_{17}H_{20}ClNO_3S$ [M]$^+$ 353.0852, found 353.0850.

Methyl 3-[(t-Butylthio)methyl]-4-chloro-1-hydroxy-1H-indole-2-carboxylate (1e). Use of *t*-butanethiol (56 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (52 mg, 0.25 mmol, 2.5 equiv) in general procedure (1.5 h) afforded the title compound **1e** (27 mg, 83%) as a yellow solid. Mp 126–128 °C; R_f 0.61 (2:98 EtOAc/$CHCl_3$); HPLC t_R 27.2 min; IR (KBr) 3444, 3025, 2924, 1601, 1492, 756 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.20 (br s, 1H), 7.46 (dd, J = 8.3, 0.9 Hz, 1H), 7.34 (dd, J = 7.5, 0.9 Hz, 1H), 7.20 (dd, J = 8.3, 7.5 Hz, 1H), 4.52 (s, 2H), 3.95 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.9, 138.2, 128.8, 127.6, 126.0, 123.5, 119.7, 117.6, 110.3, 53.3, 43.9, 31.5, 24.1; MS *m*/*z* 328 [M + H]$^+$; HRMS (+EI) calcd for $C_{15}H_{18}ClNO_3S$ [M]$^+$ 327.0696, found 327.0699.

Methyl 4-Chloro-1-hydroxy-3-[(phenylthio)methyl]-1H-indole-2-carboxylate (1f). Use of thiophenol (52 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (5.5 h) afforded the title compound **1f** (20 mg, 57%) as a yellow solid. Mp 35–38 °C; R_f 0.36 (1:2 EtOAc/hexanes); HPLC t_R 26.4 min; IR (KBr) 3435, 3025, 2923, 1492, 1258, 756 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.25 (br s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.18–7.31 (m, 6H), 7.12–7.18 (m, 1H), 4.80 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.5, 138.2, 136.9, 133.4, 130.2, 128.8, 128.5, 127.6, 126.1, 123.5, 119.3, 116.9, 110.3, 53.1, 31.0; MS *m*/*z* 348 [M + H]$^+$; HRMS (+EI) calcd for $C_{17}H_{14}ClNO_3S$ [M]$^+$ 347.0383, found 347.0381.

Methyl 3-[(Benzyloxy)methyl]-4-chloro-1-hydroxy-1H-indole-2-carboxylate (1g). Use of benzyl alcohol (52 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1g** (16 mg, 45%) as a yellow solid. Mp 96–97 °C; R_f 0.41 (1:2 EtOAc/hexanes); HPLC t_R 26.2 min; IR (KBr) 3444, 3161, 2923, 2849, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.40–7.22 (m, 6H), 7.17 (d, J = 7.5 Hz, 1H), 5.11 (s, 2H), 4.60 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 140.5, 137.8, 129.6, 129.3, 128.9, 128.8, 127.4, 127.1, 123.7, 120.3, 116.2, 110.2, 73.2, 62.9, 53.4; MS *m*/*z* 346 [M + H]$^+$; HRMS (+ESI) calcd for $C_{18}H_{16}ClNNaO_4$ [M + Na]$^+$ 368.0666, found 368.0661.

Methyl 3-[(n-Butyloxy)methyl]-4-chloro-1-hydroxy-1H-indole-2-carboxylate (1h). Use of *n*-butanol (46 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1h** (15 mg, 47%) as a yellow solid. Mp 61–63 °C; R_f 0.44 (1:2 EtOAc/hexanes); HPLC t_R 23.4 min; IR (KBr) 3445, 3025, 1493, 700 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.37 (br s, 1H), 7.41 (dd, J = 8.3, 0. 9 Hz, 1H), 7.31–7.23 (m, 1H), 7.15 (dd, J = 7. 5, 0.9 Hz, 1H), 5.01 (s, 2H), 3.94 (s, 3H), 3.52 (t, J = 6.4 Hz, 2H), 1.51–1.49 (m, 2H), 1.49–1.20 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 161.3, 136.4, 127.4, 125.8, 125.6, 122.1, 117.3, 115.2, 108.7, 69.4, 61.4, 51.9, 31.7, 19.2, 13.1; MS *m*/*z* 312 [M + H]$^+$; HRMS (+EI) calcd for $C_{15}H_{18}ClNO_4$ [M]$^+$ 311.0924, found 311.0926.

Methyl 4-Chloro-1-hydroxy-3-[(n-pentyloxy)methyl]-1H-indole-2-carboxylate (1i). Use of *n*-pentanol (54 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1i** (14 mg, 43%) as a yellow solid. Mp 59–61 °C; R_f 0.50 (1:2 EtOAc/hexanes); HPLC t_R 27.0 min; IR (KBr) 3445, 2924, 1451, 757 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.27 (br s, 1H), 7.42 (dd, J = 8.3, 0.8 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.16 (dd, J = 7.5, 0.8 Hz, 1H), 5.01 (s, 2H), 3.95 (s, 3H), 3.51 (t, J = 6.5 Hz, 2H), 1.64–1.46 (m, 2H), 1.40–1.17 (m, 4H), 0.95–0.80 (m, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.8, 137.8, 128.9, 127.3, 127.1, 123.6, 120.3, 116.7, 110.1, 71.2, 62.9, 53.3, 30.7, 29.7, 23.6, 14.8; MS *m*/*z* 326 [M + H]$^+$; HRMS (+EI) calcd for $C_{16}H_{20}ClNO_4$ [M]$^+$ 325.1081, found 325.1080.

Methyl 4-Chloro-1-hydroxy-3-[(n-octyloxy)methyl]-1H-indole-2-carboxylate (1j). Use of *n*-octanol (79 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1j** (18 mg, 48%) as a yellow solid. Mp 52–54 °C; R_f 0.48 (3:97 EtOAc/$CHCl_3$); HPLC t_R 33.1 min; IR (KBr) 3445, 3925, 1718, 1492, 757 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.33 (br s, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 5.00 (s, 2H), 3.93 (s, 3H), 3.50 (t, J = 6.4 Hz, 2H), 1.59–1.45 (m, 2H), 1.40–1.15 (m, 10H), 0.93–0.80 (m, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.7, 137.7, 129.8, 128.7, 127.1, 123.4, 120.1, 116.6, 109.9, 70.9, 62.7, 53.1, 32.8, 30.8, 30.3, 30.2, 27.2, 23.6, 14.6; MS *m*/*z* 368 [M + H]$^+$; HRMS (+EI) calcd for $C_{19}H_{26}ClNO_4$ [M]$^+$: 367.1550, found 367.1553.

Methyl 4-Chloro-1-hydroxy-3-[(isopropyloxy)methyl]-1H-indole-2-carboxylate (1k). Use of isopropanol (38 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1k** (19 mg, 63%) as a yellow solid. Mp 93–95 °C; R_f 0.47 (1:2 EtOAc/hexanes); HPLC t_R 26.0 min; IR (KBr) 3444, 3001, 1666, 1600, 701 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.27 (br s, 1H), 7.39 (dd, J = 8.3, 0.9 Hz, 1H), 7.25 (dd, J = 8.3, 7.5 Hz, 1H), 7.14 (dd, J = 7.5, 0.9 Hz, 1H), 5.02 (s, 2H), 3.94 (s, 3H), 3.79 (septet, J = 6.1 Hz, 1H), 1.18 (d, J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.8, 137.8, 128.8, 127.3, 127.0, 123.6, 120.2, 116.9, 110.1, 72.4, 60.7, 53.3, 23.0; MS *m*/*z* 298 [M + H]$^+$; HRMS (+ESI) calcd for $C_{14}H_{16}ClNNaO_4$ [M + Na]$^+$ 320.0666, found 320.0660.

Methyl 4-Chloro-3-[(cyclohexyloxy)methyl]-1-hydroxy-1H-indole-2-carboxylate (1l). Use of cyclohexanol (52 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (1.5 h) afforded the title compound **1l** (14 mg, 41%) as a yellow solid. Mp 101–104 °C; R_f 0.43 (1:2 EtOAc/hexanes); HPLC t_R 27.3 min; IR (KBr) 3444, 2924, 1493, 757 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 9.43 (br s, 1H), 7.36 (dd, J =

7.9 Hz, 1H), 7.12 (dd, J = 7.5, 0.8 Hz, 1H), 5.05 (s, 2H), 3.93 (s, 3H), 3.40–3.50 (m, 1H), 1.13–1.80 (m, 10H); ^{13}C NMR (75 MHz, CD_3CN) δ 162.8, 137.8, 128.9, 127.2, 127.1, 123.6, 120.3, 117.0, 110.1, 78.3, 60.5, 53.3, 33.6, 27.2, 25.3; MS *m/z* 338 $[M+H]^+$; HRMS (+EI) calcd for $C_{17}H_{20}ClNO_4$ $[M]^+$ 337.1081, found 337.1082.

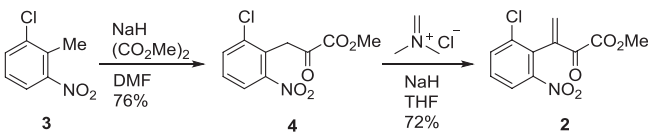
Methyl 4-Chloro-1-hydroxy-3-(4-hydroxybenzyl)-1H-indole-2-carboxylate (1m). Use of phenol (44 μL, 0.50 mmol, 5.0 equiv) and $SnCl_2·2H_2O$ (69 mg, 0.33 mmol, 3.3 equiv) in general procedure (4 h) afforded the title compound **1m** (13 mg, 40%) as a yellow solid. Mp 154–156 °C; R_f 0.34 (1:2 EtOAc/hexanes); HPLC t_R 24.6 min; IR (KBr) 3434, 2924, 1654, 1260, 1181, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (br s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 4.58 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 156.3, 140.3, 134.2, 130.5, 127.5, 126.6, 123.3, 120.9, 120.6, 120.1, 116.3, 110.3, 53.1, 30.7; MS *m/z* 332 $[M+H]^+$; HRMS (+ESI) calcd for $C_{17}H_{14}ClNNaO_4$ $[M+Na]^+$ 354.0509, found 354.0504.

Results and Discussion

Synthesis of 2,3-Disubstituted 4-Chloro-1-hydroxyindoles 1. Prior to the synthesis of the intended multisubstituted 1-hydroxyindoles **1**, we needed to prepare the appropriate substrate. We applied our previous procedure[8] with minor modifications to the synthesis of new conjugate ketoester **2** that contains an *o*-chloro substituent, as shown in Scheme 1. A toluene derivative **3** was treated with NaH and dimethyl oxalate to give ketoester compound **4**.[6] Subsequent reaction of **4** and dimethylmethyleneammonium chloride in the presence of NaH produced a new substrate, conjugate ketoester **2**.

In order to synthesize new derivatives **1**, we set out to expand the scope of the reaction with *o*-chloro substrate. As depicted in Scheme 2, we initially presumed that these reactions occur through the reduction of the nitro group and condensation to give conjugate nitrone **5**, which would then undergo 1,5-addition[8] with nucleophile, leading to the generation of 1-hydroxyindoles **1**. We also presumed that this pathway could not be the only way and therefore speculated other pathways to produce **1**. For example, we might suggest another plausible pathway in which 1,4-addition occurs first and then reduction and condensation follow. Although we were interested in the mechanistic aspects and are presently investigating the related pathways, the identification of the pathways was inconclusive, due to the reversibility of the 1,4-addition and the related complexities.

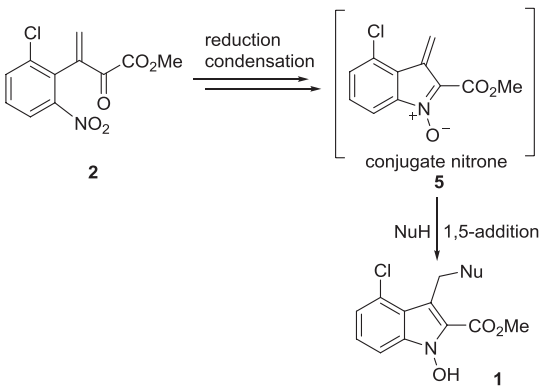
For the synthesis of target compounds, we chose stannous chloride ($SnCl_2$) considering its appropriate reducing power[11]



Scheme 1. Synthesis of conjugate ketoester **2**.

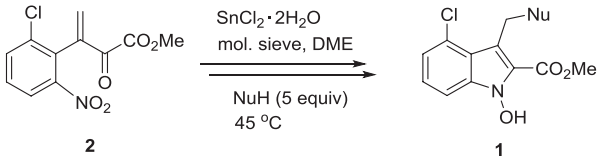
for aromatic nitro group and our previous results.[8] So, we performed the reactions employing **2** and various nucleophiles in the presence of $SnCl_2·2H_2O$ (2.5–3.3 equiv) and 4 Å molecular sieve in DME in the dark, leading to the generation of new 2,3-disubstituted 4-chloro-1-hydroxyindoles **1**, as summarized in Table 1. Given that the presumed intermediate (*e.g.*, **5**) is a highly reactive electrophile, we also tried to employ nucleophiles of high hindrance and/or low reactivity to construct new multisubstituted 1-hydroxyindoles that would be otherwise difficult to prepare.

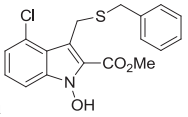
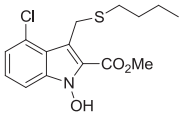
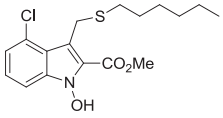
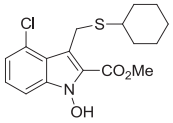
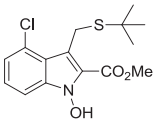
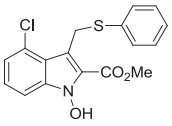
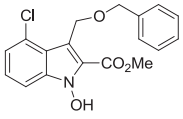
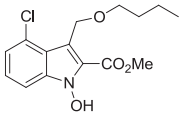
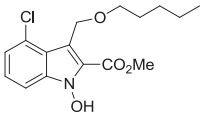
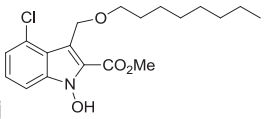
We first examined thiols as nucleophiles and obtained products **1a–1f** in good to modest yields. The reactions with primary thiols (entries 1–3) provided good yields (74–75%). Surprisingly, the reactions with secondary and tertiary thiols (entries 4 and 5) provided better yields than those with primary thiols (entries 1–3), and in particular, the reaction with *t*-butanethiol afforded good yield (83%). Based on these observations, it was believed that the electronic effect on nucleophilicity by the alkyl groups in secondary and tertiary thiols was more significant than the steric effect. When thiophenol was used (entry 6), the reaction provided *S*-alkylated adduct **1f** without *C*-alkylated adduct. Then, we used alcohols as nucleophiles and obtained **1g–1m** (entries 7–13). The reactions with primary and secondary alcohol nucleophiles provided the products in modest yields. Among these alcohol nucleophiles, isopropyl alcohol (entry 11) provided the best yield (63%), which again implied the significance of the electronic effect on nucleophilicity. However, the reaction with tertiary alcohol (*e.g.*, *t*-BuOH) did not provide appreciable amount of product in similar reaction conditions, and the result was inconclusive (data not shown), which differ from that with *t*-butanethiol (entry 5). Interestingly, the reaction with phenol (entry 13) afforded *C*-alkylated adduct **1m** without *O*-alkylated adduct, which is consistent with the previous observation.[8] This result was also found to be different from that with thiophenol, which was attributed to the lower reactivity of alcohols than thiols. When comparing these results of thiol and alcohol nucleophiles, we found that thiol nucleophiles provided better results than alcohol nucleophiles, and the striking difference was observed between *t*-butanethiol and



Scheme 2. Presumed pathway for the formation of 1-hydroxyindoles **1**.

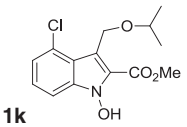
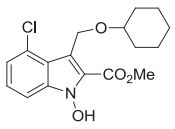
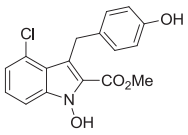
Table 1. Synthesis of 1-hydroxyindoles **1**.[a]



Entry	$SnCl_2 \cdot 2H_2O$ (equiv)	NuH	Time (h)	Product	Yield[b] (%)
1	2.5	BnSH	1.5	 **1a**	75
2	2.5	BuSH	1.5	 **1b**	75
3	2.5	HexSH	1.5	 **1c**	74
4	2.5	*c*-HexSH	1.5	 **1d**	84
5	2.5	*t*-BuSH	1.5	 **1e**	83
6	3.3	PhSH	5.5	 **1f**	57
7	3.3	BnOH	5.0	 **1g**	45
8	3.3	BuOH	6.5	 **1h**	47
9	3.3	PenOH	6.5	 **1i**	43
10	3.3	OctOH	5.0	 **1j**	48

(*continued overleaf*)

Table 1 (*continued*)

Entry	$SnCl_2·2H_2O$ (equiv)	NuH	Time (h)	Product	Yield[b] (%)
11	3.3	*i*-PrOH	5.0	 **1k**	63
12	3.3	*c*-HexOH	5.0	 **1l**	41
13	3.3	PhOH	5.0	 **1m**	40

[a] All reactions were run in 27 mg (0.10 mmol) scale of **2**.
[b] Isolated yields were given.

t-butanol. Taken together, these results demonstrated the broad applicability and tolerance of this method.

Conclusion

We report the synthesis of new 2,3-disubstituted 4-chloro-1-hydroxyindoles **1**. Using substrate **2** obtained by a two-step synthetic sequence, we performed the reactions in one pot with nucleophiles in the presence of $SnCl_2·2H_2O$ and 4 Å molecular sieves, through the unique pathways of reduction, condensation, and addition, finally affording 1-hydroxyindoles **1**. The presumed intermediate (*e.g.*, nitrone **5**) was found to be electrophilic enough to react with hindered thiols and alcohols. The reactions with thiols afforded better results than those with alcohols and, in particular, *t*-butanethiol and cyclohexanethiol provided the best yields (83 and 84%, respectively).

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Supporting Information. Additional supporting information is available in the online version of this article.

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