Facile Synthesis of 6-Hydroxyindole and 6-Methoxyindole via Regioselective Friedel–Crafts Acylation and Baeyer–Villiger Oxidation

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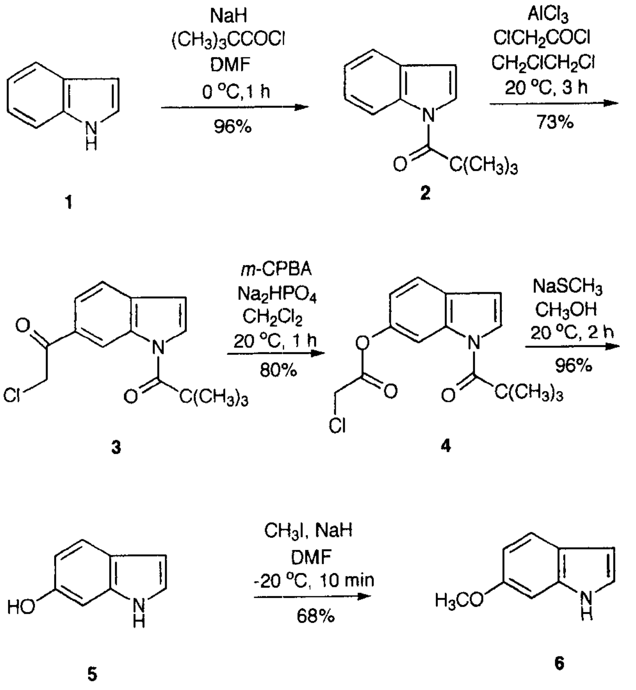
A facile synthesis of 6-hydroxyindole and 6-methoxyindole starting from indole is described. Regioselective chloroacetylation of 1-pivaloylindole followed by Baeyer–Villiger oxidation offers introduction of an oxygen function into the 6-position of the indole ring. Deacylation of 6-chloroacetyl-1-pivaloylindole gives 6-hydroxyindole which is converted to 6-methoxyindole by methylation. The overall yield of 6-hydroxyindole and 6-methoxyindole from indole is 54 and 37 %, respectively.

6-Hydroxyindoles and 6-methoxyindoles have interesting pharmacological activities and are valuable precursors to some important indoles and indole alkaloids.[4] However, no efficient chemical method for the synthesis of 6-hydroxyindole (**5**) has been established, although the syntheses of substituted 6-hydroxyindole derivatives have been reported in a few cases starting from methyl tyrosinate,[5] 4-hydroxybenzaldehyde[6] or an appropriate *p*-benzoquinone derivative.[7] On the other hand, 6-methoxyindole (**6**) has been synthesized via three different routes. Woodward effected the Meerwein arylation of 4-methoxy-2-nitrobenzene diazonium chloride with formaldoxime to afford 2-nitroanisaldehyde, which was condensed with nitromethane and reductively cyclized to give 6-methoxyindole.[8] Raucher and Koolpe reported the Meerwein arylation of 6-methoxy-2-nitrobenzenediazonium chloride with vinyl acetate and subsequent reduction of the resulting adducts to afford the 6-methoxyindole.[9] Feldman and Rapoport[10] prepared 6-methoxyindole from 4-methoxy-2-nitrotoluene by condensation with *N*,*N*-dimethylformamide dimethyl acetal[11,12] followed by reduction of the resulting β-dimethylamino-4-methoxy-2-nitrostyrene.

The regioselective oxidation of indole and indole derivatives at the 6-position of indole has not been reported. Oxidation of the indole derivatives with peracid,[13] singlet oxygen,[14] MoO_5–HMPA,[15] etc has always occurred at the pyrrole ring of indole. Much higher nucleophilicity of the pyrrole ring than that of the benzene ring prevents the direct oxidation on the benzene part.

We felt that an attractive approach for the facile synthesis of unsubstituted 6-hydroxyindole and 6-methoxyindole would be available by the regioselective Friedel–Crafts acylation at the 6-position of 1-acylindole, derived from indole, followed by oxidation and deacylation. Accordingly, in this paper we describe an efficient method to synthesize simple 6-hydroxyindole and 6-methoxyindole.

The acylation of indoles has been considerably studied, and has been a rather widely used synthetic procedure for some time.[16] However, the regioselective acylation at position-6 of 2,3-unsubstituted indoles has not been reported. We searched for a good regioselective acylation procedure to oxidize the 6-position of indole. We found that the reaction of 1-pivaloylindole (**2**), which was prepared from indole with pivaloyl chloride and sodium hydride in dimethylformamide in 96 % yield, with chloroacetyl chloride and aluminum chloride gave good yield of 6-chloroacetyl-1-pivaloylindole (**3**) without formation of 2- or 3-chloroacetylated indoles.[17] The best yield was obtained when compound **2** was added to 1,2-dichloroethane solution of 4.7 equivalents of chloroacetyl chloride and 4.5 equivalents of aluminum chloride over 3 hours at 20 °C. The yield of **3** was lowered, when **2** was added at a stretch to chloroacetyl chloride/aluminum chloride complex or when more aluminum chloride was added than chloroacetyl chloride. This procedure could be processed on a large scale. Compound **3** was efficiently crystallized after standard extractive workup. The structure **3** was supported by ^{1}H NMR data. In the ^{1}H NMR spectrum of compound **2**, the protons at $\delta = 8.51$ and 7.55 were unambiguously identified as H-7 and H-4 protons respectively. The chemical shift of H-7 proton of compound **3** must be shifted downfield, compared with that of compound **2**. In fact, that of compound **3** was shifted downfield at $\delta = 9.12$. On the other hand, the chemical shift ($\delta = 7.62$) of H-4 proton of compound **3** was not shifted. Furthermore, the H-7 proton signal appeared as a broad singlet. The presented spectral evidence supports the structure **3**.



The introduction of an oxygen function into the 6-position of **3** was performed by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane in the presence of anhydrous sodium hydrogen phosphate at 20 °C for 1 hour to afford 6-chloroacetoxy-1-pivaloylindole **(4)** in 80% yield.[18] In contrast, when anhydrous sodium hydrogen phosphate was not added, no reaction occurred and **3** was recovered.

The deacylation has been carried out by using a variety of basic reagents, including potassium carbonate/methanol and sodium hydroxide/methanol. We found that these deacylation conditions for **4** gave low yield of 6-hydroxyindole **(5)** on account of the undesirable reactions such as oxidation. Then sodium thiomethoxide was used in converting **4** into **5**. This reagent gave excellent yield (96%) of **5** in methanol at 20 °C under an argon atmosphere. Subsequent conversion of **5** to 6-methoxyindole **(6)** was achieved by treatment with 1.0 equivalent of sodium hydride and 1.0 equivalent of iodomethane in dimethylformamide at − 20 °C under an argon atmosphere in 68% yield.

In summary, a facile synthesis of 6-hydroxyindole **(5)** and 6-methoxyindole **(6)** has been carried out. Our method seems to be very efficient for the synthesis of indole derivatives containing an oxygen function at the 6-position of indole.

Melting points were determined on a Mitamura Riken mp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-FX200 spectrometer. Chemical shifts (δ) are given in ppm from internal TMS and coupling constants (J) in Hz. IR spectra were taken on a JASCO IR-A-3 infrared spectrometer. UV spectra were obtained on a JASCO UVDEC-505 spectrometer. Mass spectra were measured on a JEOL JMS-DX300 instrument. Column chromatography was performed with 230–400 mesh silica gel. Unless otherwise noted materials were obtained from commercial suppliers and used without further purification. DMF was treated with molecular sieves 4A. For all new compounds satisfactory microanalyses obtained: C ± 0.24, H ± 0.11, N ± 0.13.

1-Pivaloylindole (2):
To a suspension of 60% NaH (8.84 g, 0.221 mol) in DMF (200 mL) was added indole (20.0 g, 0.171 mol) over 30 min at 0 °C and the mixture was stirred for 15 min. To the mixture was added pivaloyl chloride (23.0 mL, 0.187 mol) dropwise at 4 °C. After stirring at 4 °C for 15 min, the mixture was added to ice-cold H_2O (1000 mL) and benzene (300 mL) and extracted with benzene (3 × 300 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The product was crystallized from hexane to give **2** (32.0 g) as white prisms. A second crop (1.0 g) was obtained from the mother liquor by silica gel column chromatography; total yield: 33.0 g (96%); mp 68–69 °C.

MS: $m/z = 201$ (M$^+$).

UV (MeOH): λ_{max} (ε) = 299 (6330), 290 (5770), 254 (10500), 238 nm (20400).

IR (KBr): ν = 3180, 2980, 2920, 2860, 1690, 1535, 1470, 1440, 1405, 1320, 1190, 1160, 1100, 1080, 910, 760 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 1.50 (9 H, s), 6.61 (1 H, d, J = 3.9 Hz), 7.25 (1 H, ddd, J = 1.3, 7.3, 7.3 Hz), 7.34 (1 H, ddd, J = 1.5, 7.3, 8.2 Hz), 7.55 (1 H, dd, J = 1.7, 7.3 Hz), 7.72 (1 H, d, J = 3.9 Hz), 8.51 (1 H, d, J = 8.2 Hz).

6-Chloroacetyl-1-pivaloylindole (3):
To a suspension of $AlCl_3$ (89.3 g, 0.672 mol) in 1,2-dichloroethane (600 mL) was added chloroacetyl chloride (55.9 mL, 0.701 mol) dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min and heated to 20 °C. To this solution was added **2** (30.0 g, 0.149 mol) over 3 h at 20 °C. The resulting mixture was stirred for an additional 15 min, then poured into ice-cold H_2O (1000 mL) and extracted with 1,2-dichloroethane (2 × 600 mL). The combined extracts were thoroughly washed with H_2O (3 × 500 mL) and 5% aq $NaHCO_3$ (3 × 200 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The product was crystallized from MeOH to give **3** (28.0 g) as white needles. A second crop (2.0 g) was obtained from the mother liquor by silica gel column chromatography; total yield: 30.0 g (73%); mp 108–109 °C.

MS: $m/z = 277$ (M$^+$).

UV (MeOH): λ_{max} (ε) = 323 (11800), 291 (16500), 233 (23300), 221 nm (23300).

IR (KBr): ν = 3100, 2980, 2920, 1690, 1600, 1520, 1480, 1430, 1405, 1315, 1300, 1260, 1220, 1185, 1090, 920, 905, 815, 800, 750 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 1.52 (9 H, s), 4.82 (2 H, s), 6.67 (1 H, d, J = 3.9 Hz), 7.62 (1 H, d, J = 8.5 Hz), 7.91 (1 H, dd, J = 1.58, 8.5 Hz), 7.92 (1 H, d, J = 3.9 Hz), 9.12 (1 H, br s).

6-Chloroacetoxy-1-pivaloylindole (4):
To a suspension of anhydr. Na_2HPO_4 (5.0 g) and **3** (2.34 g, 8.45 mmol) in CH_2Cl_2 (25.0 mL) was added 80% *m*-CPBA (2.20 g) at 20 °C and the mixture was stirred for 1 h. The mixture was poured into ice-cold H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with 5% aq $NaHCO_3$ (3 × 25 mL); dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/hexane) to give **4** as white prisms; yield: 1.90 g (80%); mp 66–67 °C (hexane).

MS: $m/z = 293$ (M$^+$).

UV (MeOH): λ_{max} (ε): 297 (4600), 288 (5340), 260 (11800), 238 nm (21900).

IR (KBr): ν = 3160, 2980, 1780, 1685, 1530, 1470, 1430, 1410, 1315, 1210, 1190, 1170, 1150, 1085, 960, 930, 910, 820, 810, 790 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 1.51 (9 H, s), 4.31 (2 H, s), 6.61 (1 H, d, J = 4.0 Hz), 7.05 (1 H, dd, J = 2.2, 8.4 Hz), 7.54 (1 H, d, J = 8.4 Hz), 7.75 (1 H, d, J = 4.0 Hz), 8.32 (1 H, d, J = 2.2 Hz).

6-Hydroxyindole (5):
To a solution of **4** (1.20 g, 4.10 mmol) in MeOH (36.0 mL) was added 15% aq NaSMe (3.70 mL) at 20 °C. After 2 h, the mixture was dissolved in EtOAc, neutralized with aq 1 N HCl, and extracted with EtOAc (3 × 50 mL). The extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The product was crystallized from $CHCl_3$ and EtOAc to give **5** (0.46 g) as white plates. A second crop (0.060 g) was obtained from the mother liquor by silica gel column chromatography; total yield: 0.52 g (96%); mp 128–129 °C.

MS: $m/z = 133$ (M$^+$)

UV (MeOH): λ_{max} (ε) = 294 (6130), 269 (4720), 218 nm (35000).

IR (KBr): ν = 3400, 1625, 1505, 1425, 1240, 1170, 950, 830, 820, 720 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 4.55 (1 H, s), 6.46 (1 H, m), 6.66 (1 H, dd, J = 2.5, 8.5 Hz), 6.82 (1 H, br s), 7.07 (1 H, dd, J = 2.5, 4.0 Hz), 7.45 (1 H, d, J = 8.5 Hz), 7.95 (1 H, br s).

6-Methoxyindole (6):
60% NaH (0.060 g, 1.5 mmol) was added to a solution of **5** (0.2 g, 1.5 mmol) and MeI (0.10 mL, 1.6 mmol) in DMF (0.80 mL) at − 20 °C under an Ar atmosphere and the mixture was stirred for 10 min. The mixture was poured into ice-cold H_2O (10 mL) and benzene (10 mL) and extracted with benzene (2 × 10 mL). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/hexane) to give **6** as white plates; yield: 0.15 g (68%); mp 93–94 °C (MeOH) (Lit.[8] mp 91–92 °C).

MS: $m/z = 147$ (M$^+$).

UV (MeOH): λ_{max} (ε): 291 (5760), 264 (4850), 218 nm (31200).

IR (KBr): ν = 3400, 1625, 1500, 1450, 1295, 1250, 1200, 1165, 1025, 940, 810, 710 cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 3.84$ (1 H, s), 6.47 (1 H, ddd, $J = 0.9$, 2.2, 3.3 Hz), 6.79 (1 H, dd, $J = 2.5$, 8.5 Hz), 6.83 (1 H, br d, $J = 2.5$ Hz), 7.07 (1 H, dd, $J = 2.3$, 3.3 Hz), 7.50 (1 H, br d, $J = 8.5$ Hz), 7.99 (1 H, br s).

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