A Direct Access to 3-(2-Oxoalkyl)indoles *via* Aluminium Chloride Induced C-C Bond Formation[†]

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Experimental Section

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^1H NMR and ^{13}C NMR spectra were determined in CDCl_3 , $\text{DMSO}-d_6$ or $\text{MeOH}-d_4$ solution on 200 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] was generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Dry 1,2-dichloromethane was prepared by distilling it over phosphorous pentoxide. Fused AlCl_3 (13-15g) was prepared by heating commercially available AlCl_3 (20g) at 130-140 °C for 3-5 h under anhydrous condition.

Typical procedure for the preparation of 1-(1*H*-3-Indolyl)-2-propanone (3a): To a solution of 3-methylindole **1** (3g, 22.9 mmol) in dry 1,2-dichloroethane (40 mL) was added fused AlCl_3 (9.1g, 68.6 mmol) at 0 °C. The mixture was warmed to 25 °C with vigorous stirring and the stirring continued for 30 minutes at the same temperature. After cooling the mixture to 0 °C acetyl chloride **2a** (2.0g, 25.6 mmol) was added slowly and drop-wise. The mixture was stirred at 25 °C for 48 h. and then poured into crushed ice (80g) slowly and portion wise. The mixture was stirred until it reaches to room temperature and extracted with methylene chloride (4 x 25 mL). The organic layers were collected, combined, washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography using petroleum ether-ethyl acetate to give the title compound (2.3g, yield 58%).

Spectral and analytical data for the indole derivatives synthesized:

1-(1H-3-Indolyl)-2-propanone (3a): light brown solid; DSC 115.38 °C; mp 114-115 °C (lit¹ 115-117.5 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H, D₂O exchangeable, NH), 7.54 (d, *J* = 6.9 Hz, 1H), 7.38 (d, *J* = 6.2 Hz, 1H), 7.23 (t, *J* = 6.2 Hz, 1H), 7.19 (t, *J* = 6.9 Hz, 2H), 3.82 (s, 2H, CH₂), 2.16 (s, 3H, CH₃). ¹³C NMR (50 MHz, CDCl₃) δ 207.6 (C=O), 136.1, 127.1, 123.2, 122.1, 119.6, 118.5, 111.2, 108.5, 40.7 (CH₂), 28.8 (CH₃); IR (KBr, cm⁻¹) 3327.1, 1709.7 (C=O), 755.3; *m/z* (DIP CI Method) 174 (100, M+1); HPLC 99 %, HICHROM RPB (250 x 4.6 mm), mobile phase 0.01M KH₂PO₄: CH₃CN (70:30), 1.0 mL/min, 220 nm, retention time 19.6 min., VU (MeOH, nm), 280, 220; Elemental analysis found C, 76.37; H, 6.25; N, 8.23; C₁₁H₁₁NO requires C, 76.28; H, 6.40; N, 8.09.

1-(1H-3-Indolyl)-2-butanone (3b): yellow solid; mp 45-46 °C (lit² 45 - 46.5 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H, D₂O exchangeable, NH), 7.54 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.11 (m, 2H), 3.81 (s, 2H, CH₂), 2.52 (t, *J* = 7.3 Hz, 2H, CH₂), 1.03 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (50 MHz, CDCl₃) δ 210.7 (C=O), 135.9, 126.8, 123.3, 121.5, 119.0, 118.1, 111.2, 107.6, 39.1 (CH₂), 34.2 (CH₂), 7.4 (CH₃); IR (Neat, cm⁻¹) 3405.1, 1707.3 (C=O), 1620.2, 743.6; *m/z* (DIP CI Method) 188 (100, M+1); HPLC: 98 %; HICHROM RPB (250 x 4.6 mm), mobile phase A:0.01M KH₂PO₄, B: CH₃CN, T/%B :0/20, 10/20, 45/85, 55/85, 65/20, 70/20, 1.0 mL/min, 280 nm, retention time 27 min.; VU (MeOH, nm) 280, 220. Elemental analysis found C, 76.77; H, 6.95; N, 7.53; C₁₂H₁₃NO requires C, 76.98; H, 7.00; N, 7.48.

1-(1H-3-Indolyl)-2-pentanone (3c): light yellow solid; DSC 54.42 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H, D_2O exchangeable, NH), 7.54 (d, $J = 7.3$ Hz, 1H), 7.37 (d, $J = 6.9$ Hz, 1H), 7.20 (t, $J = 6.9$ Hz, 1H), 7.15 – 7.11 (m, 2H), 3.80 (s, 2H, CH_2), 2.45 (t, $J = 7.3$ Hz, 2H, CH_2), 1.59 – 1.53 (m, 2H, CH_2), 0.85 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, CDCl_3) δ 210.0 (C=O), 136.0, 127.0, 123.3, 121.8, 119.3, 118.3, 111.2, 108.0, 43.2 (CH_2), 39.7 (CH_2), 17.1 (CH_2), 13.4 (CH_3); IR (KBr, cm^{-1}) 3344, 1712.3 (C=O), 1633.1, 742.6; m/z (DIP CI Method) 202 (100, $\text{M}+1$); HPLC: 97 %, HICHROM RPB (250 x 4.6 mm), mobile phase KH_2PO_4 : CH_3CN (50:50), 1.0 mL/min, 220 nm, retention time 9.9 min., VU (MeOH, nm) 280, 220; Elemental analysis found C, 77.60; H, 7.61; N, 7.18; $\text{C}_{13}\text{H}_{15}\text{NO}$ requires C, 77.58; H, 7.51; N, 6.96.

1-(1H-3-indolyl)-2-hexanone (3d): low melting solid; ^1H NMR (400 MHz, CDCl_3) δ 8.22 (s, 1H, D_2O exchangeable 1H, NH), 7.55 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.23 – 7.21 (m, 1H), 7.16-7.12 (m, 2H), 3.82 (s, 2H, CH_2), 2.37 (t, $J = 7.3$ Hz, 2H, CH_2), 1.59 – 1.52 (m, 2H, CH_2), 1.29 – 1.22 (m, 2H, CH_2), 0.86 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (50MHz, CDCl_3) δ 209.9 (C=O), 136.1, 127.2, 123.2, 122.0, 119.5, 118.5, 111.2, 108.4, 41.1 (CH_2), 39.8 (CH_2), 25.8 (CH_2), 22.1 (CH_2), 13.7 (CH_3); IR (Neat, cm^{-1}) 3407.9, 1707 (C=O), 1619.8, 742.6; m/z (DIP CI Method) 216 (100, $\text{M}+1$); HPLC: 97 %, INERTSIL ODS 3V (250 x 4.6 mm); mobile phase 0.01M KH_2PO_4 : CH_3CN (30:70), 1.0 mL/min, 220 nm, retention time 10.5 min.; VU (MeOH, nm) 281, 220; Elemental analysis found C, 78.21; H, 7.91; N, 6.38; $\text{C}_{14}\text{H}_{17}\text{NO}$ requires C, 78.10; H, 7.96; N, 6.51.

1-(1H-3-Indolyl)-2-heptanone (3e): low melting solid; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, D_2O exchange 1H, NH), 7.53 (d, $J = 6.8$ Hz, 1H), 7.34 (d, $J = 6.8$ Hz, 1H), 7.17 (t, $J = 6.8$ Hz, 1H), 7.14 -7.09 (m, 2H), 3.79 (s, 2H, CH_2), 2.46 (t, $J = 7.3$ Hz, 2H), 1.59 – 1.51 (m, 2H), 1.29 -1.17 (m, 4H), 0.83 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 209.9 (C=O), 136.1, 127.2, 123.2, 122.0, 119.5, 118.5, 111.2, 108.4, 41.4 (CH_2), 39.8 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 22.3 (CH_2), 13.8 (CH_3); IR (Neat, cm^{-1}) 3404.8, 1707.6 (C=O), 1620.1, 742.2; m/z (DIP CI Method) 230 (100, $\text{M}+1$); HPLC: 98 %, HICHROM RPB (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN (30:70), 1.0 mL/min, 220 nm, retention time 38.8 min., VU (MeOH, nm) 281, 220; Elemental analysis found C, 78.80; H, 8.41; N, 6.08; $\text{C}_{15}\text{H}_{19}\text{NO}$ requires C, 78.56; H, 8.35; N, 6.11.

1-(1H-3-Indolyl)-2-octanone (3f): low melting solid; ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, D_2O exchangeable, 1H, NH), 7.54 (d, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.2 (t, $J = 6.8$ Hz, 1H), 7.15 – 7.11 (m, 2H), 3.8 (s, 2H, CH_2), 2.47 (t, $J = 7.3$ Hz, 2H), 1.58 – 1.51 (m, 3H), 1.25-1.19 (m, 5H), 0.85 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, CDCl_3) δ 209.6 (C=O), 136.1, 127.3, 123.1, 122.1, 119.6, 118.6, 111.2, 108.7, 41.4 (CH_2), 39.8 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 23.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3); IR (Neat, cm^{-1}) 3377.1, 1709.3 (C=O), 1600.3, 741.2; m/z (DIP CI Method) 244 (100, $\text{M}+1$); HPLC: 97 %, HICHROM RPB (250 x 4.6 mm), mobile phase A: 0.01M KH_2PO_4 , B: CH_3CN , gradient T/%B: 0/30, 10/30, 35/80, 45/80, 55/30, 60/30, 1.0 mL/min, 225 nm, retention time 33.4 min.; VU (MeOH, nm) 280, 221; Elemental analysis found C, 78.90; H, 8.61; N, 5.88; $\text{C}_{16}\text{H}_{21}\text{NO}$ requires C, 78.97; H, 8.70; N, 5.76.

1-(1H-3-indolyl)-2-nonanone (3g): light brown solid, mp 44 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, D_2O exchangeable 1H, NH), 7.54 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.15 - 7.11 (m, 2H), 3.8 (s, 2H, CH_2), 2.46 (t, $J = 7.3$ Hz, 2H, CH_2), 1.58-1.53 (m, 4H, 2 CH_2), 1.27 – 1.20 (m, 6H, 3 CH_2), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, CDCl_3) δ 209.7 (C=O), 136.1, 127.2, 123.1, 122.1, 119.6, 118.6, 111.2, 108.6, 41.4 (CH_2), 39.8 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 13.9 (CH_3); IR (Neat, cm^{-1}) 3407.5, 1708.5 (C=O), 1619.8, 741.3; m/z (DIP CI Method) 258 (100, $\text{M}+1$); HPLC: 97 %, HICHRON RPB (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN (30:70), 1.0 mL/min, 220 nm, retention time 13.3 min.; VU (MeOH, nm), 280, 220; Elemental analysis found C, 79.49; H, 9.09; N, 5.14; $\text{C}_{17}\text{H}_{23}\text{NO}$ requires C, 79.33; H, 9.01; N, 5.44.

4-Cyclopentyl-1-(1H-3-indolyl)-2-butanone (3h): light yellow solid, DSC 66.80 °C; mp 60-62 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, D_2O exchangeable, 1H, NH), 7.54 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.22 (m, 1H), 7.15-7.13 (m, 2H), 3.8 (s, 2H), 2.49 (t, $J = 7.6$ Hz, 2H), 1.69 – 1.42 (m, 9H), 1.0 (m, 2H), ^{13}C NMR (50 MHz, CDCl_3) δ 209.8 (C=O), 136.1, 127.2, 123.1, 122.1, 119.6, 118.5, 111.2, 108.5, 40.7, 39.8, 39.5, 32.3 (2C), 30.0, 25.0 (2C). IR (Neat, cm^{-1}) 3357.0, 1708.3 (C=O), 758.9; m/z (DIP CI Method) 256 (100, $\text{M}+1$); HPLC: 98 %, HICHRON RPB (250 x 4.6 mm); mobile phase A: 0.01M KH_2PO_4 ; B: CH_3CN ; flow rate 1.0 mL/min, 281 nm, retention time 42.7 min., VU (MeOH, nm), 281, 221; Elemental analysis found C, 79.68; H, 8.42; N, 5.61; $\text{C}_{17}\text{H}_{21}\text{NO}$ requires C, 79.96; H, 8.29; N, 5.49.

1-(3-Methyl-1H-2-indolyl)ethanone (4): DSC 147.57 °C; mp 147-148 °C; (lit³ 149 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.8 (s, D₂O exchangeable, 1H, NH), 7.69 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.16-7.12 (m, 2H), 2.65 (s, 3H, CH₃), 2.63 (s, 3H, CH₃); ¹³C NMR (50 MHz, CDCl₃) δ 190.4 (C=O), 136.0, 132.6, 128.7, 126.4, 121.1, 119.9, 118.7, 111.8, 28.9 (CH₃), 11.0 (CH₃); IR (KBr, cm⁻¹) 3443.8, 1635.7 (C=O), 742.0, 707.9; *m/z* (DIP CI Method) 174 (100, M+1). HPLC: 99 %, INERTSIL ODS 3V (250 x 4.6 mm), mobile phase A: 0.01M KH₂PO₄; B: CH₃CN, gradient (T/%B): 0/40, 5/40, 20/80, 30/80, 35/40, 40/40, flow rate: 1.0 mL/min, 210 nm, retention time 14.7 min.; VU (MeOH, nm), 311, 236, 206, Elemental analysis found C, 76.40; H, 6.46; N, 7.99; C₁₁H₁₁NO requires C, 76.28; H, 6.40; N, 8.09.

1-(3,3'-Dimethyl-2,3-dihydro-1H, 1'H-[2,2']biindolyl-5-yl)ethanone (5): DSC 180.56 °C; mp 179-180 °C; ¹H NMR (200 MHz, CDCl₃) δ 8.59 (s, D₂O exchangeable, 1H, NH), 8.22 (s, D₂O exchangeable, 1H, NH), 7.84 (d, *J* = 8.8 Hz, 1H), 7.32-6.72 (m, 5H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.18-4.12 (m, 1H), 3.32- 3.24 (m, 1H), 2.68 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 1.41 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (50 MHz, CDCl₃) δ 198.4 (C=O), 149.7, 138.0, 136.3, 132.6, 129.1, 128.9, 127.7, 123.2, 122.4, 120.4, 119.6, 110.3, 109.8, 109.5, 64.0, 45.2, 26.5, 16.5, 8.6; IR (Neat, cm⁻¹) 3325.8, 1650.1, 1612.0, 743.4; *m/z* (DIP CI Method) 305 (100, M+1); HPLC 98 %, column: INERTSIL ODS 3V (250 x 4.6 mm), mobile phase A:0.01M KH₂PO₄, B: CH₃CN, gradient T/%B: 0/40, 5/40, 20/80, 30/80, 35/40, 40/40, flow rate: 1.0 mL/min., 260 nm, retention time: 21.2 min., VU (MeOH, nm) 260, 203; Elemental analysis found C, 78.69; H, 6.66; N, 9.39; C₂₀H₂₀N₂O requires C, 78.92; H, 6.62; N, 9.20.

1-(2-Acetyl-3-methyl-1H-5-indolyl)ethanone (6): brown Solid, DSC 233.79 °C; mp 230-232 °C; (lit⁴ 228-228.5 °C); ¹H NMR (400 MHz, CDCl₃) δ 9.1 (s, D₂O exchangeable, 1H, NH), 8.37 (s, 1H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 2.7 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 2.65 (s, 3H, CH₃); ¹³C NMR (50 MHz, CDCl₃) δ 197.2 (C=O), 190.6 (C=O), 138.5, 133.6, 129.2, 127.4, 124.7, 123.6, 119.6, 112.3, 29.0 (CH₃), 26.5 (CH₃), 10.4 (CH₃); IR (KBr, cm⁻¹) 3418.8, 3310.1, 1667.5 (C=O), 1632.7 (C=O), 1614.1, 767.5, 722.6; m/z (DIP CI Method) 216 (100, M+1); HPLC 99 %, INERTSIL ODS 3V (250 x 4.6 mm), mobile phase A:0.01M KH₂PO₄; B: CH₃CN, gradient (T/%B): 0/30, 5/30, 20/80, 30/80, 35/30, 40/30; flow rate 1.0 mL/min, 279 nm, retention time 14.3 min., VU (MeOH, nm) 325, 279, 220; Elemental analysis found C, 72.43; H, 5.94; N, 6.53; C₁₃H₁₃NO₂, requires C, 72.54; H, 6.09; N, 6.51.

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