Organocatalytic C3-Selective Friedel-Crafts Alkylation of Indoles with $\alpha, \beta$-Unsaturated Ketones

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Electronic Supplementary Information (ESI)

General Information. Material were purchased from commercial suppliers and used without further purification. Solvents were dried according to standard procedures. Reactions were monitored by thin-layer chromatography (TLC) analysis. Flash column chromatography was performed using 200-300 mesh silica gel. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. $^1$HNMR spectra were recorded on Varian Mercury 400 (400 MHz) spectrophotometers. Chemical shifts are reported in ppm from the solvent resonance as the internal standard (CDCl$_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad single), coupling constants (Hz) and integration. $^{13}$C NMR spectra were recorded on Varian Mercury 400 (100 MHz) with complete proton decoupling spectrophotometers (CDCl$_3$: 77.0 pm). Mass spectra analysis was performed on API 200 LC/MS system. Elementary analysis was taken on a Vario EL III elementary analysis instrument. 1-methylindole, 1,2-dimethylindole were prepared as described in the literature.$^1$

General Procedure: To a round bottom flask equipped with a magnetic stir bar and charged with pyrrolidine was added the solvent, and the approrite acid, then placed in room temperature. The solution was stirred for 10 min before addition of enone. After stirring for an additional 10 min the indole substrate was added in one portion. The resulting suspension was stirred at room temperature until complete consumption of the indole substrate as determined by TLC. The reaction mixture was diluted with ether and washed with brine. The organic layer was dried with...
MgSO₄ and concentrated in vacuo. The resulting residue was purified by silica gel chromatography to afford the title compounds.

4-(3-Indolyl)-5-methyl-2-hexanone (Table 2, entry 1). Prepared according to the general procedure from indole (58.6 mg, 0.50 mmol), 5-methyl-3-hexene-2-one (198 µL, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 6h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow oil (92% yield). ¹HNMR (400MHz, CDCl₃) δ : 0.87 (d, J=6.8Hz, 3H), 0.92 (d, J=6.4Hz, 3H), 1.97 (s, 3H), 2.02-2.09 (m, 1H), 2.82-2.92 (m, 2H), 3.31-3.36 (m, 1H), 6.94 (s, 1H), 7.08 - 7.19 (m, 2H), 7.33 - 7.37 (m,1H), 7.65(dm, J=7.6Hz, 1H), 8.01(bs,1H). ¹³CNMR (100 MHz, CDCl₃) δ :20.3, 20.5, 30.0, 32.6, 39.3, 47.0, 111.2, 117.3, 119.0, 119.3, 121.7, 121.9, 127.1, 136.2, 209.6. MS(El)m/z: 229(M⁺),215,186,172,142. Anal calcd for C₁₅H₁₉NO: C,78.56; H,8.35; N,6.11; Found: C,78.71; H,8.31; N,6.21.

4-(3-(2-Methylindolyl))-5-methyl-2-hexanone (Table 2, entry 2). Prepared according to the general procedure from 2-methylindole (65.6 mg,0.50 mmol), 5-methyl-3-hexene-2-one (198 µL,1.50 mmol), pyrrolidine (12.5 µL,0.15 mmol), HClO₄ (12 µL,0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 10h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow oil (90% yield). ¹HNMR (400MHz, CDCl₃) δ : 0.71 (d, J=6.8Hz, 3H), 1.02 (d, J=6.4Hz, 3H), 1.84 (s, 3H), 2.13 (m, 1H), 2.28 (s, 3H), 2.87 (dd, J=14,3.6Hz, 1H), 3.04(dd, J=9.6, 4.0Hz, 1H), 3.10 (m, 1H), 7.01-7.07 (m,2H), 7.16-7.19 (m,1H), 7.55 (dm, J=8.0Hz, 1H), 7.95 (bs, 1H). ¹³CNMR (100MHz,CDCl₃) δ :12.0, 21.3, 21.4, 30.7, 32.4, 40.0, 46.6, 110.4, 112.8, 118.6, 119.0, 120.3, 127.2, 131.9,135.5,209.7. MS(El)m/z:243(M⁺),214,200,171. Anal calcd for C₁₆H₂₁NO: C,78.97; H,8.70; N,5.76; Found:C,78.93; H,8.79; N,5.80.

4-(3-(1,2-Dimethylindolyl))-5-methyl-2-hexanone (Table 2, entry 3). Prepared according to the general procedure from 1,2-Dimethylindole (72.6 mg,0.50 mmol), 5-methyl-3-hexene-2-one (198 µL,1.50 mmol), pyrrolidine (12.5 µL,0.15 mmol), and HClO₄ (12 µL,0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 15h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow solid (87% yield). ¹HNMR (400MHz, CDCl₃) δ : 0.71(d,J=6.8Hz,3H),1.03(d,J=6.8Hz,3H), 1.86(s,3H), 2.17(m,1H), 2.28(s,3H), 2.88-2.91(m,1H), 3.07-3.13(m,2H), 3.63(s,3H), 7.02-7.26(m,3H), 7.58(dm,J=8.0Hz,1H). ¹³CNMR (100MHz,CDCl₃) δ : 10.5, 21.4, 21.5, 29.5, 30.7, 32.5, 40.2, 46.9, 108.6, 112.4, 118.2,119.1,120.0,126.3, 133.8, 136.9, 209.3.
4-(3(1-Methylindolyl))-5-methyl-2-hexanone (Table 2, entry 4). Prepared according to the general procedure from 1-methylindole (65.6 mg, 0.50 mmol), 5-methyl-3-hexene-2-one (198 µL, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 20h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow oil (83% yield).

1HNMR (400MHz, CDCl₃) δ: 0.86(d, J=6.4 Hz, 3H), 0.91(d, J=6.8 Hz, 3H), 1.96(s, 3H), 2.05(m, 1H), 2.82-2.85(m, 2H), 3.30-3.32(m, 1H), 7.08(tm, J=7.4 Hz, 1H), 7.17-7.26(m, 2H), 7.62(dm, J=8.0 Hz, 1H). 13 CNMR (100MHz, CDCl₃) δ: 20.1, 20.3, 30.0, 32.4, 32.6, 39.0, 47.0, 109.2, 116.0, 118.6, 119.5, 121.3, 126.7, 127.7, 137.0, 209.4. MS(EI) m/z: 243(M⁺), 200, 186, 157, 143. Anal calcd for C₁₆H₂₁NO: C, 78.97; H, 8.70; N, 5.76; Found: C, 78.75; H, 8.76; N, 5.75.

4-(3-Indolyl)-4-phenyl-2-butanone (Table 2, entry 5). Prepared according to the general procedure from indole (58.6 mg, 0.50 mmol), benzalacetone (219 mg, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 12h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale brown oil (80% yield).

1HNMR (400MHz, CDCl₃) δ: 2.07(s, 3H), 3.18(dd, J=16.0, 7.6 Hz, 1H), 3.23(dd, J=16.1, 7.2 Hz, 1H), 4.83(t, J=7.6 Hz, 1H), 6.98-7.33(m, 9H), 7.42(dm, J=8.4 Hz, 1H), 8.05(bs, 1H). 13 CNMR (100MHz, CDCl₃) δ: 30.3, 38.4, 50.3, 111.1, 118.8, 119.4, 121.3, 122.2, 126.3, 136.5, 127.7, 128.4, 136.5, 144.0, 207.7. MS(EI) m/z: 263(M⁺), 221, 206, 143. Anal calcd for C₁₈H₁₇NO: C, 82.10; H, 6.51; N, 5.32; Found: C, 82.19; H, 6.52; N, 5.27.

4-(3-(2-Methylindolyl))-4-phenyl-2-butanone (Table 2, entry 6). Prepared according to the general procedure from 2-methylindole (65.6 mg, 0.50 mmol), benzalacetone (219 mg, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 12h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow solid (87% yield).

1HNMR (400MHz, CDCl₃) δ: 1.95(s, 3H), 2.35(s, 3H), 3.26(dd, J=16.8, 6.4 Hz, 1H), 3.38(dd, J=16.0, 8.4 Hz, 1H), 4.80(t, J=7.6 Hz, 1H), 6.92-7.25(m, 8H), 7.40(dm, J=7.6 Hz, 1H), 7.74(bs, 1H). 13 CNMR (100MHz, CDCl₃) δ: 12.1, 30.8, 36.8, 48.2, 110.4, 113.1, 119.1, 119.2, 120.8, 125.9, 127.3, 128.3, 131.8, 135.4, 144.0, 207.9. MS(EI) m/z: 277(M⁺), 234, 218, 204, 157. Anal calcd for C₁₉H₁₉NO: C, 82.28; H, 6.90, N, 5.05; Found: C, 82.08; H, 7.00; N, 5.36.
4-(3-(1,2-Dimethylindolyl))-4-phenyl-2-butanone (Table 2, entry 7). Prepared according to the general procedure from 1,2-dimethylindole (72.6 mg, 0.50 mmol), benzalacetone (219 mg, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 4 days and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow solid (69% yield).

¹H NMR (400 MHz, CDCl₃) δ: 1.98 (s, 3H), 2.40 (s, 3H), 3.33 (dd, J=16, 6.4 Hz, 1H), 3.44 (dd, J=16.0, 8.0 Hz, 1H), 3.60 (s, 3H), 4.89 (t, J=7.2 Hz, 1H), 6.97 (tm, J=8.0 Hz, 1H), 7.10-7.14 (m, 2H), 7.20-7.24 (m, 3H), 7.29 (dm, J=7.2 Hz, 2H), 7.47 (dm, J=7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 10.5, 29.5, 30.7, 37.0, 48.4, 108.8, 112.4, 118.7, 119.0, 120.3, 125.8, 126.3, 127.3, 128.2, 133.6, 136.8, 144.3, 207.8. MS (EI) m/z: 291 (M⁺), 248, 232, 217, 144. Anal. calcd for C₂₀H₂₁NO: C, 82.44; H, 7.26; N, 4.81; Found: C, 82.61; H, 7.23; N, 4.87.

4-(3-(1-Methylindolyl))-4-phenyl-2-butanone (Table 2, entry 8). Prepared according to the general procedure from 1-methylindole (65.6 mg, 0.50 mmol), benzalacetone (219 mg, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 2 days and worked up in the general procedure, after silica gel chromatography, the title compound as a brown oil (79% yield).

¹H NMR (400 MHz, CDCl₃) δ: 2.07 (s, 3H), 3.15 (dd, J=16.0, 7.6 Hz, 1H), 3.24 (dd, J=16.0, 7.6 Hz, 1H), 3.73 (s, 3H), 4.82 (t, J=7.6 Hz, 3H), 6.82 (s, 1H), 7.00 (tm, J=7.5 Hz, 1H), 7.12-7.41 (m, 7H), 7.42 (dm, J=8.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 30.3, 32.6, 38.3, 50.4, 109.2, 117.2, 118.8, 119.4, 121.6, 126.1, 126.3, 126.8, 127.6, 128.4, 137.2, 144.1, 207.6. MS (EI) m/z: 277 (M⁺), 220, 217, 202, 158. Anal. calcd for C₁₉H₁₉NO: C, 82.28; H, 6.90; N, 5.05; Found: C, 82.43; H, 6.80; N, 5.00.

4-(3-(1-Methylindolyl))-2-pentanone (Table 3, entry 9). Prepared according to the general procedure from 1-methylindole (65.6 mg, 0.50 mmol), 3-penten-2-one (146 µL, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and HClO₄ (12 µL, 0.15 mmol) in CH₂Cl₂ (1.00 mL) at room temperature for 20 h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow oil (90% yield).

¹H NMR (400 MHz, CDCl₃) δ: 1.37 (d, J=6.8 Hz, 3H), 2.10 (s, 3H), 2.70 (dd, J=16.4, 8.4 Hz, 1H), 2.93 (dd, J=16.0, 6.0 Hz, 1H), 3.64 (m, 1H), 3.74 (s, 3H), 6.84 (s, 1H), 7.11 (tm, 7.8 Hz, 1H), 7.21-7.31 (m, 2H), 7.64 (dm, J=8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 21.4, 27.0, 30.4, 32.6, 51.6, 109.3, 118.6, 119.2, 119.4, 121.6, 125, 126.5, 137.1, 208.7. MS (EI) m/z: 216 (M⁺), 172, 157, 143, 115. Anal. calcd for C₁₄H₁₇NO: C, 78.10; H, 7.96; N, 6.51; Found: C, 78.39; H, 7.90; N, 6.55.

4-(3-indolyl)-2-pentanone (Table 3, entry 10). Prepared according to the general procedure from indole (58.6 mg, 0.50 mmol), 3-penten-2-one (146 µL, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and HClO₄ (12 µL, 0.15
mmol) in CH$_2$Cl$_2$ (1.00 mL) at room temperature for 10h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow oil (82% yield), $^1$HNMR (400MHz,CDCl$_3$) $\delta$: 1.37 (d, J=1.37Hz, 3H), 2.08(s, 3H), 2.71(dd, J=16.4, 8.4Hz), 2.93(dd, J=16.0, 6.0Hz), 3.64(m, 3H), 6.90(S, 1H), 7.11-7.64(m,4H),8.14(s,1H). $^{13}$CNMR (100MHz,CDCl$_3$) $\delta$: 21.0, 26.7,30.2,51.3,111.4,119.0,119.2,120.3,120.7,122.0,126.6,136.5,209.4. MS(EI) m/z: 201(M$^+$),158,144,116,85. Anal calcd for C$_{13}$H$_{15}$NO: C, 77.58; H, 7.51; N, 6.96; Found: C, 77.51; H, 7.52; N, 6.99.

**4-(3-(2-Methylindolyl))-2-pentanone (Table3, entry 11).** Prepared according to the general procedure from 2-methylindole (65.6 mg, 0.50 mmol), 3-penten-2-one (146 µL, 1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and HClO$_4$ (12 µL, 0.15 mmol) in CH$_2$Cl$_2$ (1.00 mL) at room temperature for 14h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow oil 89% yield), $^1$HNMR (400MHz,CDCl$_3$) $\delta$: 0.82(d,3H), 1.53(s, 3H), 1.92(s, 3H), 2.39(dd, J=16.4,6.4Hz, 1H), 2.55(dd, J=16.0, 6.0Hz,1H), 3.1(m, 1H), 6.61-6.77(m,3H),7.17(m,1H),7.64(s,1H). $^{13}$CNMR (100MHz,CDCl$_3$) $\delta$:11.6, 20.8, 26.8, 30.4, 50.2, 110.5, 114.6, 118.7, 118.8, 120.5, 126.8, 130.5, 135.5, 209.6. MS(EI) m/z: 215(M$^+$),172,158,130,115. Anal calcd for C$_{14}$H$_{17}$NO: C, 78.1; H, 7.96; N, 6.51; Found: C, 78.5; H, 7.92; N, 6.53.

Reference:

3a racemic

Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

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