Direct Coupling of Pyrroles with Carbonyl Compounds: Short, Enantioselective Synthesis of (S)-Ketorolac

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SUPPORTING INFORMATION

General Procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), triethylamine, benzene, and dimethoxyethane were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an ethanolic solution of phosphomolybdic acid or p-anisaldehyde in ethanol/aqueous H$_2$SO$_4$/CH$_3$CO$_2$H and heat as developing agents. NMR spectra were recorded on either Bruker DRX 500 or AMX 400 or Varian Inova-400 instruments, and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, b = broad. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. High resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter.

Pyrrole 2: Yield = 54% bsm; yellow oil; R$_f$ = 0.55 (silica gel, 3:1 hexane:EtOAc); [$\alpha$]$_D$ = -88 (CH$_2$Cl$_2$, c = 10.6); IR (film) $\nu_{max}$ 3378, 3029, 2919, 1654, 1602, 1553, 1494, 1452, 1378, 1354, 1286, 1187, 1097, 1034, 896, 806, 790, 702 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (bs, 1 H, D$_2$O exchangeable), 7.05 – 7.10 (m, 3 H), 6.72 (s,
1 H), 6.50 (s, 1 H), 6.48 (s, 1 H), 6.40 (d, J = 5.6 Hz, 1 H), 6.06 – 6.08 (m, 1 H), 5.84 (m, 1 H), 5.03 (s, 1 H), 4.67 (s, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 3.12 (d, J = 13.6 Hz, 1 H), 2.93-2.97 (m, 1 H), 2.77 (d, J = 3.0 Hz), 2.22 (dd, J = 19.2, 5.6 Hz, 1 H), 1.82 (s, 3 H), 1.73 (s, 3 H); 13C NMR (100MHz,CDCl3)δ 200.8, 145.0, 142.4, 137.7, 134.9, 128.1, 127.4, 126.2, 117.9, 115.1, 108.3, 108.1, 53.3, 45.6, 40.4, 29.6, 24.0, 16.8 IRMS (ESI-TOF) calcd. for C12H17NO [M + H'] 306.1852, found 306.1855.

**Pyrrrole 3:** Yield = 53%; colorless cubes; m.p. = 121-122 °C; Rf = 0.34 (silica gel, 3:1 hexane:EtOAc); [α]D = −49 (CH2Cl2, c = 1.79); IR (film) νmax 3366, 3337, 2915, 1667, 1567, 1436, 1373, 1240, 1202, 1101, 1073, 1029, 903, 886, 777, 718 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 8.58 (bs, 1 H, D2O exchangeable), 6.74 (s, 1 H), 6.72 (s, 1 H), 6.14 (s, 1 H), 6.05 (s, 1 H), 4.82 (s, 1 H), 4.79 (s, 1 H), 3.73 (d, J = 7.5 Hz, 1 H), 3.14 (dd, J = 7.0, 11.5 Hz, 1 H), 2.60 – 2.63 (m, 1 H), 2.50 – 2.54 (m, 1 H), 1.81 (s, 3 H), 1.71 (s, 3 H); 13C NMR (125 MHz, CDCl3) δ 198.6, 145.8, 143.8, 124.7, 127.0, 117.4, 112.6, 107.6, 106.1, 49.4, 46.2, 30.1, 19.9, 15.9; HRMS (ESI-TOF) calcd. for C14H17NO [M + H'] 216.1383, found 216.1384.

**Pyrrrole 4:** Yield = 67% bsm; brown oil; Rf = 0.53 (silica gel, 3:1 hexane:EtOAc); [α]D = −85 (CH2Cl2, c = 0.2); IR (film) νmax 3369, 2920, 1662, 1449, 1364, 1228, 1157, 1070, 892, 778, 730 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.90 (bs, 1 H, D2O exchangeable), 6.67 – 6.70 (m, 1 H), 5.81 (d, J = 2.8 Hz, 1 H), 4.83 (s, 1 H), 4.76 (s, 1 H), 3.64 (d, J = 7.2 Hz, 1 H), 3.08 (q, J = 6.4, 12.8 Hz, 1 H), 2.67 – 2.73 (m, 1 H), 2.45 – 2.51 (m, 1 H), 2.12 (s, 3 H), 1.97 (s, 3 H), 1.79 (s, 3 H), 1.73 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 199.0, 146.5, 144.2, 135.0, 124.5, 123.9, 114.1, 112.8, 108.1, 49.5, 45.6, 29.9, 21.0, 16.5, 11.3 (2 C); HRMS (ESI-TOF) calcd. for C16H17NO [M + H'] 244.1696, found 244.1689.
Pyrrole 5: Yield = 54%; green oil; Rf = 0.50 (silica gel, 1:1 hexane:EtOAc); [α]D = −170 (CH₂Cl₂, c = 0.1); IR (film) νmax 2927, 1707, 1670, 1438, 1185, 1120, 900, 837, 770, 721 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.13 (bs, 1 H, D₂O exchangeable), 6.75-6.77 (m, 1 H), 4.71-4.73 (m, 2 H), 3.65 (d, J = 14.5 Hz, 1 H), 2.88 – 2.94 (m, 1 H), 2.53 – 2.56 (m, 1 H), 2.40 – 2.46 (m, 1 H), 2.34 (dd, J = 9.5, 19.0 Hz, 2 H), 2.10 (s, 3 H), 1.88 (s, 3 H), 1.55 (s, 3 H), 1.03 (t, J = 9.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 199.3, 146.2, 143.7, 135.8, 121.7, 120.7, 120.3, 115.7, 112.3, 49.9, 48.8, 31.6, 20.0, 18.0, 16.4, 15.8, 11.3, 9.7; HRMS (ESI-TOF) calcd. for C₁₈H₂₅NO [M + H⁺] 272.2009, found 272.2011.

Pyrrole 6: Yield = 42% bsm; brown solid; m.p. = 114-115 °C; Rf = 0.52 (silica gel, 3:1 hexane:EtOAc); [α]D = −81 (CH₂Cl₂, c = 1.5); IR (film) νmax 3358, 2968, 2922, 1660, 1588, 1450, 1374, 1230, 1074, 1036, 891, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.12 (bs, 1 H, D₂O exchangeable), 6.70 (s, 1 H), 5.94 – 5.95 (m, 1 H), 5.79 – 5.80 (m, 1 H), 4.82 (s, 1 H), 4.76 (s, 1 H), 3.68 (d, J = 6.4 Hz, 1 H), 3.11 (dd, J = 5.6, 10.4 Hz, 1 H), 2.64 – 2.70 (m, 1 H), 2.58 (dd, J = 6.0, 12.0 Hz, 2 H), 2.46 – 2.52 (m, 1 H), 1.79 (s, 3 H), 1.72 (s, 3 H), 1.22 (t, J = 6.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 198.9, 146.3, 144.1, 134.9, 134.4, 125.6, 112.7, 106.1, 104.0, 49.4, 45.6, 29.9, 21.0, 20.6, 16.3, 13.6; HRMS (ESI-TOF) calcd. for C₁₆H₂₁NO [M + H⁺] 244.1696, found 244.1699.

Pyrrole 7: Yield = 42%; colorless cubes; m.p. = 131-133 °C; Rf = 0.27 (silica gel, 3:1 hexane:EtOAc); [α]D = −160 (CH₂Cl₂, c = 0.3); IR (film) νmax 3412, 2960, 1696, 1561, 1458, 1412, 1376, 1328, 1268, 1236, 1212, 1165, 1133, 1056, 1028, 972, 774, 721 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.88 (bs, 1 H, D₂O exchangeable), 6.65 – 6.67 (m, 1 H), 6.10 – 6.11 (m, 2 H), 4.37 (dd, J = 6.8, 13.6 Hz, 1 H), 3.88 – 3.91 (m, 1 H), 3.56 (d, J = 14.0 Hz, 1 H), 3.52 (d, J = 14.0 Hz, 1 H), 1.77 – 1.97 (m, 6 H), 1.58 (s, 1 H), 1.54 (d, J = 7.2 Hz, 3 H), 1.32 – 1.41
(m, 3 H), 1.16 – 1.17 (m, 1 H), 0.95 (s, 3 H), 0.94 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.7, 129.5, 117.7, 108.7, 106.1, 65.6, 53.6, 48.8, 48.0, 44.7, 39.5, 38.3, 33.0, 26.8, 20.8, 20.2, 16.3; HRMS (ESI-TOF) calcd. for C$_{13}$H$_{24}$N$_2$O$_3$S [M + H$^+$] 337.158, found 337.158.

**Pyrrrole 8:** Yield = 57%; brown solid; m.p. = 85-87 °C; R$_f$ = 0.29 (silica gel, 1:1 hexane:EtOAc); Mixture of two diastereomers, major presented; IR (film) ν$_{max}$ 3376, 2960, 2926, 2866, 1763, 1589, 1452, 1387, 1343, 1263, 1185, 1107, 1047, 948, 809, 772, 726 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.36 (bs, 1 H, D$_2$O exchangeable), 4.59 – 4.64 (m, 1 H), 3.97 – 4.02 (m, 1 H), 2.85 – 2.90 (m, 1 H), 2.35 (dd, $J$ = 2.0, 8.0 Hz, 2 H), 2.16 (s, 3 H), 1.92-1.99 (m, 4 H), 1.46 (t, $J$ = 4.8 Hz, 3 H), 1.06 (t, $J$ = 6 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.5, 122.3, 121.2, 118.6, 115.2, 75.8, 39.8, 38.8, 21.2, 18.0, 15.9, 11.2, 9.7; HRMS (ESI-TOF) calcd. for C$_{13}$H$_{19}$NO$_2$ [M + H$^+$] 222.1488, found 222.1487.

**Pyrrrole 9:** A modified procedure as follows was required for the ester couplings: tert-butylacetate (79.8 µL, 0.625 mmol) and 2,4-dimethyl-3-ethylpyrrole (16.9 µL, 0.125 mmol) were dissolved in THF (7.5 mL). The solution was cooled to −78 °C and a solution of LDA (0.50 M, 1.58 mL) was added. The reaction was allowed to stir for 30 minutes, after which time it was warmed to 0 °C. The septum was removed and copper(II)-2-ethylhexanoate (91.9 mg, 0.262 mmol) was rapidly added as a solid and then the septum was replaced. The reaction was stirred until the blue color dissipated (approximately 2 min.), then it was quenched by pouring into 5% aqueous NH$_4$OH (15 mL). The aqueous layer was partitioned with EtOAc (20 mL). The organic layer was separated and washed successively with water (15 mL) then brine (15 mL), dried (MgSO$_4$), filtered, and the solvent removed in vacuo. Flash chromatography (silica gel) of the crude reaction afforded pure coupled product. Yield = 41% bsm (estimated by NMR); unstable light brown oil; R$_f$ = 0.67 (silica gel, dichloromethane); IR (film) ν$_{max}$ 3378, 2960, 2927, 1719, 1603, 1456, 1392, 1368, 1316, 1220, 1148, 1122,
951, 836, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.12 (bs, 1 H, D₂O exchangeable), 3.47 (s, 2 H), 2.37 (dd, J = 7.5, 15 Hz, 2 H), 2.16 (s, 3 H), 1.94 (s, 3 H), 1.47 (s, 9 H), 1.06 (t, J = 7.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 122.0, 120.5, 117.3, 114.5, 81.2, 32.4, 28.3, 17.8, 15.9, 11.1, 9.1. HRMS (ESI-TOF) calcd. for C₁₀H₁₇NO₂ [M + H⁺ - tBu] 182.1181, found 182.1179.

Pyrrole 10: Yield = 42%; unstable red oil; Rₜ = 0.21 (silica gel, 1:1 hexane:EtOAc); Mixture of two diastereomers, major presented; IR (film) νmax 3301, 2960, 2922, 1671, 1606, 1547, 1530, 1433, 1400, 1378, 1251, 1087, 956, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (bs, 1 H, D₂O exchangeable), 3.85 (t, J = 9.6 Hz, 1 H), 3.63 (m, 1 H), 2.86 (s, 1 H), 2.36 (dd, J = 7.6, 15.2 Hz, 2 H), 2.26 – 2.32 (m, 2 H), 2.14 (s, 3 H), 1.96 (s, 3 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.05 (t, J = 7.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 122.0, 121.5, 121.1, 54.3, 37.9, 34.8, 28.0, 19.0, 17.8, 16.0, 11.2, 9.8. HRMS (ESI-TOF) calcd. for C₁₄H₂₃N₂O [M + H⁺] 235.1805, found 235.1808.

Scheme S1: Synthetic pathway to ketorolac.

Pyrrole Sultam 13: Compound 11 (460 mg, 3.00 mmol) was dissolved in benzene (3
mL) and the solvent removed in vacuo. The compound was then dissolved in anhydrous THF (15 mL, 0.2 M) and cooled to 0 °C. Triethylamine (433 µL, 3.25 mmol) was then added, followed by methyl chloroformate (232 mL, 3.00 mmol), and stirring was continued for 60 minutes. In a separate flask, (S)-2,10-camphorsultam (538 mg, 2.50 mmol) was dried in vacuo for 30 minutes, was dissoled in THF (12.5 mL, 0.2 M) and cooled to –78 °C. A 2.50 M solution of butyl lithium (1.05 mL, 2.63 mmol) was then added and the solution stirred for 20 minutes. The anhydride solution was then filtered through a medium porosity glass frit under a blanket of nitrogen to remove the triethylamine hydrochloride salt. The filtrate was then canulated into a solution of the lithiate (12) at –78 °C. The reaction was allowed to immediately warm to room temperature, and was quenched in 20% potassium carbonate solution (20 mL), and partitioned with EtOAc (30 mL). The organic layer was washed with water (20 mL) then brine (20 mL) and dried over MgSO₄. Removal of the solvent in vacuo gave pure pyrrole sultam 13, 876 mg (100%) as a light brown oil; R_f = 0.316 (silica gel, 3:1 hexane:EtOAc); [α]_D = –49 (CH₂Cl₂, c = 10.6); IR (film) ν_max 2958, 1813, 1734, 1693, 1500, 1456, 1412, 1390, 1327, 1279, 1237, 1215, 1167, 1118, 1089, 1052, 1035, 987, 948, 866, 813, 772, 727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.65 (t, J = 2 Hz, 2 H), 6.13 (t, J = 2.4 Hz, 2 H), 3.90 – 3.99 (m, 2 H), 3.84 – 3.87 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 120.5, 108.1, 65.1, 52.8, 48.4, 47.7, 44.6, 38.4, 32.8, 32.3, 26.4, 26.3, 20.8, 19.8; LRMS (ESI) [M + H⁺] 351, [M + Na⁺] 373.

**Annulation Product 16:** Compound 13 (39.5 mg, 0.113 mmol) was dried in vacuo for 30 minutes, dissolved in anhydrous THF (8.0 mL), and cooled to –78 °C. Triethylamine (30 µL, 0.225 mmol) was added to the reaction mixture, followed by LHMDS solution (1.0 M, 135 µL). Stirring was continued for 20 minutes, after which time the reaction was warmed to 12 °C. After 15 minutes the septum was removed and solid ferrocenium hexafluorophosphate (28.0 mg, 0.0845 mmol) was added rapidly, after which the septum was replaced. The reaction was vigorously stirred for approximately 5 minutes, until the reaction was yellow and all the ferrocenium salt was
consumed. After this time, the reaction was diluted with 3:1 hexane:EtOAc (15 mL) and filtered through a short plug of silica gel. The solvent was removed in vacuo to give 54.8 mg of the crude reaction mixture with 65% bsm yield of product based on NMR (4.5:1 dr). (See attached $^1$H NMR spectra of purified 15). This compounds was quite unstable and was reacted immediately after preparation. Thus, the crude mixture was dissolved in benzoyl chloride (200 µL) and stirred at 70 °C for 4 hours. The reaction was then cooled to ambient temperature, diluted with dichloromethane (10 mL) and washed three times with 2 N NaOH (10 mL), water, then brine (10 mL). The organic layer was dried (MgSO$_4$) and the solvent removed in vacuo. The crude reaction mixture was then subjected to preparative TLC purification (silica gel, dichloromethane), which gave pure annulation product 16 (5.6 mg, 56% yield, 65% yield bsm) and recovered starting material (1.0 mg). At this point, the two diastereomers were also successfully separated (3.9 mg major, 1.7 mg minor). Pyrrole 16 was a stable compound unlike its precursor.

**Ketorolac (1):** The major diastereomer of 15 (3.9 mg, 0.00860 mmol) was dissolved in dimethoxyethane (35 µL) and cooled to −10 °C. Isobutylene (2.7 µL, 0.0258 mmol) was then added to the reaction mixture, followed by 30% hydrogen peroxide solution (1.9 µL, 0.0172 mmol) then 40% tetrabutylammoniumhydroxide solution (11.2 µL, 0.0172 mmol). Stirring was continued at −10 °C for 3 hours then quenched with four drops of 1.5 M Na$_2$SO$_3$, followed by stirring for 1 hour. The reaction was then acidified with 1 M HCl (5 mL) and extracted three times with EtOAc (5 mL). The organic layers were combined, dried with MgSO$_4$, and the solvent removed in vacuo. Ketorolac was isolated by preparative TLC (silica gel, EtOAc) to give material (1.2 mg, 58%) that was spectroscopically identical with an authentic sample. The ee (90%) was determined by HPLC analysis (chiralpak AD, hexane:isopropanol:trifluoroacetic acid = 90:10:0.1 v/v%, 310 nm, 0.8 mL/min); retention times of enantiomers: 12.6 min (R isomer) and 13.9 min (S isomer). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, $J = 7.2$ Hz, 2 H), 7.51 (t, $J = 7.2$ Hz, 1 H), 7.43 (t, $J = 7.6$ Hz, 2 H), 6.81 (d, $J = 4$ Hz, 1 H), 6.13 (d, $J = 4$ Hz, 1 H), 4.53-4.58 (m, 1 H), 4.43-4.48 (m, 1 H), 4.08-4.12 (m, 1 H), 2.79-2.92 (m, 2 H).