Decarboxylative Formation of *N*-Alkyl Pyrroles From 4-Hydroxyproline

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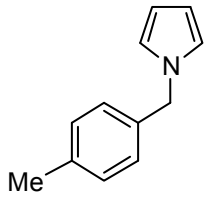
Supporting Information

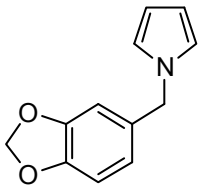
General Information: All reagents and solvents were purchased from commercial sources. Toluene was distilled prior to use. Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and DMP and PMA stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and a Varian VNMRS-400 MHZ and were reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and a Varian VNMRS-400 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. *trans*-4-Hydroxy-*L*-proline and (*S*)-(-)-indoline-2-carboxylic acid were purchased from commercial sources and used as received. The aldehydes were purified either by distillation or by recrystallization prior to use. Products **2a**[2], **2b**[3], **2c**[3], **2e**[2], **2j**[2], **2l**[1], **2m**[5], **2p**[6], **2q**[4], **8a**[4] were previously reported and their published characterization data matched ours in all respects.

General Procedure: A 10 mL microwave reaction tube was charged with aldehyde (1.0 mmol, 1.0 equiv), *trans*-4-hydroxy-*L*-proline (0.157 g, 1.2 mmol, 1.2 equiv), toluene (0.5 M, 2.0 mL), and benzoic acid (0.024 g, 0.2 mmol, 0.2 equiv). A 10 x 8 mm SiC passive cylindrical heating element was carefully added on its side to the reaction tube. The reaction tube was sealed with a Teflon-lined snap cap, and heated in the microwave reactor at 240 ºC (200 W, 50–170 psi) for the appropriate time. After cooling with compressed air flow, the crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 5 mL). The aqueous layers were extracted with EtOAc (3 x 5 mL) and the combined organic layers dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the product was purified by flash silica gel column chromatography.

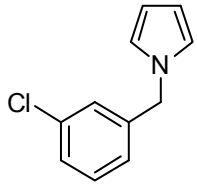
1-(4-Methylbenzyl)-1*H*-pyrrole (2d): Following the general procedure, compound **2d** was obtained from *trans*-4-hydroxy-*L*-proline and 4-tolyl carboxaldehyde as a colorless liquid in 58% yield (99 mg); R_f = 0.47 (Hexanes/EtOAc 9:1 v/v); IR (neat) 3099, 2921, 1516, 1497, 1439, 1352, 1308, 1278, 1087, 1067, 969, 799, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J*= 7.7 Hz, 2H), 6.73 (dd, *J*= 2.0, 3.9 Hz, 2H), 6.23 (dd, J= 2.0, 3.9 Hz, 2H), 5.06 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.1, 129.3, 127.0, 121.0, 108.3, 53.1, 21.0; *m/z* (ESI-MS) 172.1 $[M + H]^+$.



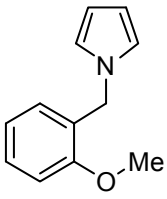
1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1*H*-pyrrole (2f): Following the general procedure, compound **2f** was obtained from *trans*-4-hydroxy-*L*-proline and piperonal as a white solid in 66% yield (133 mg); R_f = 0.38 (Hexanes/EtOAc 9:1 v/v); mp = 43–45 °C; IR (KBr) 3101, 2930, 2789, 1850, 1499, 1440, 1259, 924, 865, 735, 605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (app d, *J* = 7.9 Hz, 1H), 6.70 (app t, *J* = 2.1 Hz, 2H), 6.66–6.64 (m, 1H), 6.63–6.62 (m, 1H), 6.20 (app t, *J* = 2.1 Hz, 2H), 5.95 (s, 2H), 4.98 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.1, 131.9, 120.9, 120.5, 108.5, 108.2, 107.7, 101.1, 53.1; *m/z* (ESI-MS) 202.4 $[M + H]^+$.



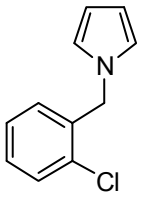
1-(3-Chlorobenzyl)-1*H*-pyrrole (2g): Following the general procedure, compound **2g** was obtained from *trans*-4-hydroxy-*L*-proline and 3-chlorobenzaldehyde as a yellow liquid in 68% yield (130 mg); R_f = 0.47 (Hexanes/EtOAc 9:1 v/v); IR (neat) 2957, 2871, 1708, 1599,1576, 1498, 1433, 1289, 1203, 1088, 969, 864, 779, 725, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (app t, *J* = 1.0 Hz, 1H), 7.28–7.27 (m, 1H), 7.14–7.13 (m, 1H), 7.04–6.99 (m, 1H), 6.72 (app t, *J* = 2.1 Hz, 2H), 6.26 (app t, *J* = 2.1 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 134.6, 129.9, 127.8, 127.0, 125.0, 121.1, 108.8, 52.6; *m/z* (ESI-MS) 192.3 $[M + H]^+$.



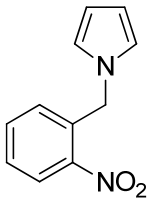
1-(2-Methoxybenzyl)-1*H*-pyrrole (2h): Following the general procedure, compound **2h** was obtained from *trans*-4-hydroxy-*L*-proline and 2-methoxybenzaldehyde as a colorless liquid in 67% yield (125 mg); R_f = 0.43 (Hexanes/EtOAc 9:1 v/v); IR (neat) 3099, 3001, 2937, 2835, 1602, 1587, 1491, 1455, 1437, 1281, 1261, 1150, 1087, 1068, 1050, 969, 877, 781, 725, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (app t, *J* = 7.9 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.79–6.76 (m, 1H), 6.76 (app t, *J* = 2.1 Hz, 2H), 6.72–6.71 (m, 1H), 6.26 (app t, *J* = 2.1 Hz, 2H), 5.09 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 139.7, 129.7, 121.1, 119.2, 112.8, 112.6, 108.4, 55.1, 53.1; *m/z* (ESI-MS) 188.1 $[M + H]^+$.



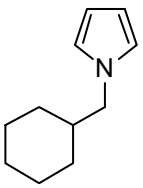
1-(2-Chlorobenzyl)-1*H*-pyrrole (2i): Following the general procedure, compound **2i** was obtained from *trans*-4-hydroxy-*L*-proline and 2-chlorobenzaldehyde as a colorless liquid in 70% yield (134 mg); R_f = 0.53 (Hexanes/EtOAc 9:1 v/v); IR (neat) 3099 3063, 2928, 1574, 1498, 1473, 1445, 1473, 1351, 1292, 1277, 1087, 1069, 1040, 969, 747, 725, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (comp, 2H), 7.26–7.18 (comp, 2H), 6.75–6.73 (comp, 2H), 6.27–6.24 (comp, 2H), 5.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.3, 129.3, 128.8, 128.3, 127.2, 121.3, 108.7, 50.8; *m/z* (ESI-MS) 192.1 $[M + H]^+$.



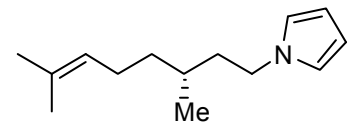
1-(2-Nitrobenzyl)-1*H*-pyrrole (2k): Following the general procedure at 150 °C, compound **2k** was obtained from *trans*-4-hydroxy-*L*-proline and 2-nitrobenzaldehyde as yellow liquid in 61% yield (123 mg); R_f = 0.36 (Hexanes/EtOAc 9:1 v/v); IR (neat) 2921, 2844, 2360, 1578, 1523, 1338, 1289, 1088, 858, 788, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (app d, *J* = 1.3, 8.2 Hz, 1H), 7.53 (app t, *J* = 7.6 Hz, 1H), 7.43 (app t, *J* = 7.8 Hz, 1H), 6.71 (app t, *J* = 2.1 Hz, 2H), 6.60 (app d, *J* = 7.9 Hz, 1H), 6.26 (app t, *J* = 2.1 Hz, 2H), 5.5 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 134.2, 128.4, 128.3, 124.9, 121.7, 109.3, 50.7; *m/z* (ESI-MS) 203.1 $[M + H]^+$.



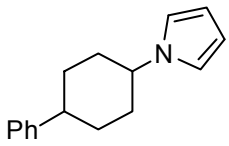
1-(Cyclohexylmethyl)-1*H*-pyrrole (2o): Following the general procedure, compound **2o** was obtained from *trans*-4-hydroxy-*L*-proline and 1-cyclohexane carboxaldehyde as a clear liquid in 51% yield (83 mg); R_f = 0.71 (Hexanes/EtOAc 9:1 v/v); IR (neat) 2924, 2852, 1499, 1449, 1283, 1089, 1061, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (app t, *J* = 2.0 Hz, 2H), 6.18 (app t, *J* = 1.99 Hz, 2H), 3.73 (d, *J* = 7.0 Hz, 2H), 1.80–1.63 (comp, 6H), 1.32–1.15 (comp, 3H), 1.02–0.93 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0, 107.5, 56.3, 39.9, 30.8, 26.3, 25.7; *m/z* (ESI-MS) 163.7 $[M + H]^+$.



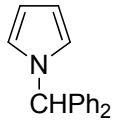
(*R*)-1-(3,7-Dimethyloct-6-en-1-yl)-1*H*-pyrrole (2r): Following the general procedure, compound **2r** was obtained from *trans*-4-hydroxy-*L*-proline and (*R*)-citronellal as a faded green liquid in 42% yield (86 mg); R_f = 0.72 in (Hexanes/EtOAc 9:1 v/v); IR (neat) 3101, 2963, 2923, 2864, 2360, 1500, 1452, 1377, 1283, 1088, 1063, 967, 720, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (app t, 2.1 Hz, 2H), 6.15 (app t, 2.1Hz, 2H), 5.12–5.07 (m, 1H), 3.96–3.85 (comp, 2H),2.05–1.92 (comp, 2H), 1.86–1.79 (m, 1H), 1.70 (s, 3H), 1.61 (s, 3H), 1.64–1.57 (m, 1H), 1.51–1.43 (m, 1H), 1.41–1.34 (m, 1H), 1.25–1.17 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.4, 124.5, 120.4, 107.8, 47.6, 38.6, 36.8, 30.0, 25.7, 25.3, 19.4, 17.6; *m/z* (ESI-MS) 206.3 $[M + H]^+$.



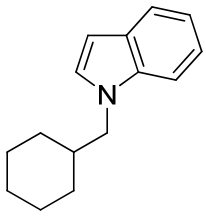
1-(4-Phenylcyclohexyl)-1*H*-pyrrole (2s): Following the general procedure, compound **2s** was obtained from *trans*-4-hydroxy-*L*-proline and 4-phenyl cyclohexanone as a yellow semi solid in 31% yield (70 mg) as a 10:1 mixture of stereoisomers; R_f = 0.53 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3097, 3029, 2938, 2353,1602, 1494, 1449, 1273, 1087, 763, 722, 631 cm^{-1}; ^1H NMR of the major diastereomer (500 MHz, $CDCl_3$) δ 7.25–7.20 (comp, 2H), 7.18–7.11 (comp, 3H), 6.70 (app t, *J* = 2.1 Hz, 2H), 6.10 (app t, *J* = 2.1 Hz, 2H), 3.87 (tt, *J* = 23.8, 11.9 Hz, 1H), 2.55 (tt, *J* = 24.4, 12.2 Hz, 1H), 2.19–2.14 (m, 2H), 2.00–1.98 (m, 2H), 1.82–1.74 (m, 2H), 1.63–1.55 (m, 2H); ^{13}C NMR of the major diastereomer (125 MHz, $CDCl_3$) δ 146.3,128.4, 126.7, 126.2, 118.5, 107.5, 58.2, 43.5, 34.6, 33.3; *m/z* (ESI-MS) 224.7 $[M + H]^+$.



1-Benzhydryl-1*H*-pyrrole (2t): Following the general procedure, compound **2t** was obtained from *trans*-4-hydroxy-*L*-proline and benzophenone as a white solid in 52% yield (121 mg); mp = 70–74 °C; R_f = 0.61 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3061, 3028, 1601, 1486, 1450, 1268, 1086, 1030, 968, 724, 698, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (comp, 6H), 7.15–7.12 (comp, 4H), 6.67 (app t, *J* = 2.1 Hz, 2H), 6.54, (s, 1H), 6.25 (app t, *J* = 2.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 128.5, 128.2, 127.8, 121.1, 108.2, 66.8; *m/z* (ESI-MS) 235.9 $[M + H]^+$.



1-(Cyclohexylmethyl)-1*H*-indole (8b): A 10 mL microwave reaction tube was charged with cyclohexane carboxaldehyde (0.028g, 0.25 mmol, 1.0 equiv.), (*S*)-(-)-indoline-2-carboxylic acid (0.049 g, 0.30 mmol, 1.2 equiv.), toluene (0.5 M, 0.50 mL), and benzoic acid (0.061 g, 0.05 mmol, 0.2 equiv.). A 10 x 8 mm SiC passive cylindrical heating element was carefully added on its side to the reaction tube. The reaction tube was sealed with a Teflon-lined snap cap, and heated in the microwave reactor at 240 ºC (200 W, 170 psi) for 15 min. After cooling with compressed air flow, the crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 5 mL). The aqueous layers were extracted with EtOAc (3 x 5 mL) and the combined organic layers dried over anhydrous Na_2SO_4. Compound **8b** was isolated as a colorless liquid in 64% yield (34 mg); R_f = 0.55 (Hexanes/EtOAc 9:1 v/v); IR (neat) 2923, 2851, 1512, 1463, 1442, 1310, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (app d, *J* = 7.9 Hz, 1H), 7.34 (app d , *J* = 8.2 Hz, 1H), 7.20 (app t, *J* = 7.5 Hz, 1H), 7.09 (app t, *J* = 7.5 Hz, 1H), 7.06 (app d, *J* = 3.1 Hz, 1H), 6.47 (app d, *J* = 3.1 Hz, 1H), 3.94 (app d, *J* = 7.2 Hz, 2H), 1.90–1.81 (m, 1H), 1.74–1.69 (comp, 4H), 1.22–1.14 (comp, 4H), 1.00 (app q, *J* = 24.3, 11.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 128.5, 121.2, 120.8, 119.1, 109.6, 108.8, 100.6, 53.0, 38.8, 31.1, 26.3, 25.7; *m/z* (ESI-MS) 213.7 $[M + H]^+$.



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