Mild microwave-assisted synthesis of dipyrromethanes and their analogues

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**General Procedures.** $^1$H NMR (300 MHz, 400 MHz or 500 MHz) and $^{13}$C NMR (75 MHz, 100 MHz or 125 MHz) spectra were recorded on a Varian 300 MHz, a Varian or a Bruker 400 MHz, or a Bruker 500 MHz instrument, respectively. Chemical shifts were referenced to residual solvent peaks and are given as follows: chemical shift (δ, ppm), multiplicity [s, singlet; br; d, doublet, t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. IR experiments were performed on a Perkin Elmer Spectrum-100 FT-IR spectrometer equipped with an ATR accessory. HR-ESI-MS analyses were performed on a Bruker MicroTOF ESI mass spectrometer or by the mass spectrometry service of the Ecole Polytechnique Federale de Lausanne. Compounds 1e, 1f, and 1h were synthesized following literature methods, the synthesis of 1g was modelled on those of analogous compounds. All other chemicals and solvents were from commercial sources and used as received. Microwave heating was performed with a Biotage Initiator instrument.

**Chromatography.** Preparative chromatography was performed using silica gel [Davisil chromatographic silica media (35–70 micron)]. Thin layer chromatography was performed on silica-coated glass plates. Samples were visualized by UV-light (254 nm), or staining with KMnO$_4$/NaOH or cerium-ammonium-molybdate.

**Synthetic procedures and characterization data**

**General procedure for the Mannich reaction.** A sample of the heterocycle was dissolved in CH$_2$Cl$_2$ or CH$_3$CN (as shown in Tables 1 and 2, 0.15–0.2 M). Dimethylmethylideneammonium iodide (Eschenmoser’s salt, 2 equiv.) was added in a single portion. The reaction mixture was stirred at room temperature or at 60 °C until TLC analysis indicated the complete consumption of the starting material (20 min–26 h). The reaction mixture was diluted with CH$_2$Cl$_2$ or EtOAc (for CH$_3$CN as reaction medium) and saturated aqueous NaHCO$_3$. The phases were separated, and the aqueous layer was extracted once. The
The organic layer was dried (Na$_2$SO$_4$), and the solvent was evaporated. The crude product was used without further purification in the next step.

**General procedure for dipyrrromethane synthesis.** The N,N-dimethylaminomethylated substrate obtained in the first step was placed in a microwave vial. Pyrrole was added to afford a 0.2–0.3 M solution, and the vial was capped. The vial was placed in a microwave reactor, and was heated at 150 °C for 30 min. The reaction mixture was cooled to room temperature, the pyrrole was evaporated, and the dark brown oily residue was purified by column chromatography (silica, petroleum ether/EtOAc) to afford the products.

Known compound.$^5$ Green-brown oil (88%): IR (ν, cm$^{-1}$, thin film) 3676, 2988, 2902, 2817, 2770, 1455, 1394, 1384, 1359, 1256, 1076, 1057, 1016; $^1$H NMR (300 MHz, CDCl$_3$, complex spectrum due to the presence of multiple protonated species, all peaks reported) δ 2.20 (s, 2.5H), 2.24 (s, 3H), 2.26 (s, 2.5H), 3.45 (s, 2H), 4.56 (s, 1H), 5.99–6.14 (m, 2H), 6.67–6.74 (m, 1H), 9.58 (br, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, complex spectrum due to the presence of multiple protonated species, all peaks reported) δ 42.6, 44.9, 45.1, 55.6, 56.6, 69.2, 106.3, 107.5, 107.8, 109.8, 118.0, 122.5, 128.7, 130.0.

Known compound.$^6$ Yellow oil (51%): IR (ν, cm$^{-1}$, thin film) 3676, 2938, 2813, 2766, 2729, 2700, 1495, 1478, 1450, 1419, 1406, 1395, 1361, 1298, 1254, 1076, 1052, 1023, 1012; $^1$H NMR (400 MHz, CDCl$_3$) δ 2.17 (s, 6H), 3.24 (s, 2H), 5.23 (s, 2H), 6.05 (br, 1H), 6.07–6.10 (m, 1H), 6.12–6.16 (m, 1H), 6.69 (dd, $J$ = 2.9, 1.6 Hz, 1H), 7.05–7.11 (m, 2H), 7.26–7.30 (m, 1H), 7.30–7.37 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 54.1, 50.4, 55.7, 106.8, 109.6, 122.2, 126.7, 127.2, 128.6, 129.9, 139.0.
The ammonium salt of this compound is known. Pale brown oil (40%): IR (ν, cm⁻¹, thin film) 3676, 3224, 2988, 2902, 2820, 2775, 1454, 1406, 1394, 1383, 1250, 1230, 1057, 1028; ¹H NMR (400 MHz, CDCl₃) δ 2.23 (s, 6H), 3.39 (s, 2H), 5.74 (s, 1H), 5.88 (s, 1H), 8.69 (br, 1H); ¹³C NMR (100 MHz, CDCl₃, only product peaks reported) δ 13.0, 44.7, 56.6, 105.2, 108.1, 126.9, 127.9; HR-ESI-MS calcd 139.1230 obsd 139.1228 [(M + H)⁺, M = C₈H₁₄O₂].

Brown oil (quant.): IR (ν, cm⁻¹, thin film) 3224, 2923, 2857, 2821, 2775, 1591, 1498, 1457, 1412, 1352, 1256, 1173, 1097, 1059, 1005; ¹H NMR (300 MHz, CDCl₃) δ 2.10 (s, 1H), 2.20 (s, 1H), 2.23 (s, 5H), 2.28 (s, 1H), 2.30 (s, 1H), 3.38–3.52 (m, 1H), 3.56 (s, 1.5H), 4.65 (s, 0.5H), 6.11 (d, J = 2.7 Hz, 0.2H), 6.16 (d, J = 2.9 Hz, 0.2H), 6.28 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 2.7 Hz, 1H), 7.10–7.20 (m, 2H), 7.61 (d, J = 8.3 Hz, 0.4H), 7.67 (dd, J = 7.6, 6.0 Hz, 2H), 9.30 (br, 1H). HR-ESI-MS calcd 327.0353 obsd 327.0351 [(M + H)⁺, M = C₁₃H₁₅N₂I].

Yellow oil (62%): IR (ν, cm⁻¹, thin film) 3003, 2945, 2866, 2709, 1568, 1481, 1463, 1417, 1406, 1298, 1262, 1225, 1172, 1133, 1051, 1016; ¹H NMR (400 MHz, CDCl₃) δ 1.08 (d, J = 7.4 Hz, 18H), 1.43 (septet, J = 7.4 Hz, 3H), 2.25 (s, 6H), 3.42 (s, 2H), 6.23–6.27 (m, 1H), 6.64–6.69 (m, 1H), 6.70–6.74 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 11.6, 17.8, 44.6, 56.2,
111.7, 121.4, 123.6, 124.3; HR-ESI-MS calcd 281.2363 obsd 281.2406 [(M + H)$^+$, M = C$_{16}$H$_{32}$N$_2$Si].

Colorless oil (quant.): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.17 (t, $J = 7.2$ Hz, 3H), 2.02 (s, 1.5H), 2.17 (s, 4H), 2.31 (s, 1.5H), 3.33 (d, $J = 11.9$ Hz, 2H), 4.12 (q, $J = 7.6$ Hz 1H), 4.67 (s, 0.5H), 7.01 (dd, $J = 15.3$, 8.2 Hz, 2H), 7.38 (d, $J = 10.6$ Hz, 1H), 7.66 (dd, $J = 9.3$, 7.7 Hz, 2H). 10.4 (br, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.2, 14.4, 42.7, 44.8, 52.5, 54.0, 59.4, 70.4, 92.1, 114.2, 123.2, 124.4, 127.7, 128.1, 132.6, 132.8, 134.3, 136.4, 136.6, 164.6; HR-ESI-MS calcd 456.0888 obsd 456.0894 [(M + MeOH + Na)$^+$, M = C$_{16}$H$_{19}$N$_2$O$_2$I].

Light yellow oil (87%): $^1$H NMR (400 MHz, CDCl$_3$, all peaks are reported) $\delta$ 2.23 (s, 6H), 2.253-2.294 (m, 3H), 3.37 (d, $J = 2.5$ Hz, 0.2H), 3.41 (d, $J = 2.5$ Hz, 1.5H), 3.45 (d, $J = 2.8$ Hz, 0.5H), 3.76–3.80 (m, 0.6H), 4.58 (d, $J = 2.6$ Hz, 0.6H), 5.26 (d, $J = 2.4$ Hz, 0.6H), 6.44–6.49 (m, 0.7H), 6.52–6.57 (m, 0.5H), 6.58–6.71 (m, 0.8H), 6.76–6.81 (m, 0.2H), 7.23–7.31 (m, 0.9H), 7.41 (d, $J = 2.3$ Hz, 0.4H), 9.67 (dt, $J = 3.6$, 2.1 Hz, 1.0H), 9.73 (s, 0.3H), 9.87 (d, $J = 3.1$ Hz, 0.4H), 10.90 (br, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, all peaks are reported) $\delta$ 42.0, 42.5, 42.6, 44.3, 44.4 44.8, 45.0, 45.1, 45.2, 52.0, 54.0, 55.3, 55.4, 56.0, 70.2, 71.2, 71.9, 72.4, 106.7, 107.8, 108.6, 109.1, 109.6, 118.9, 123.4, 124.1, 124.7, 126.5, 128.3, 129.6, 131.2, 131.6, 137.4, 185.3, 185.5, 185.7, 185.9; HR-ESI-MS calcd 175.0842 obsd 175.0839 [(M + Na)$^+$, M = C$_8$H$_{12}$N$_2$O].
Known compound. Gray solid (from dimethylaminomethyl-imidazole: 57%; from pyrrole via dimethylaminomethyl-pyrrole: 64%): IR (\(\nu\), cm\(^{-1}\), thin film) 3330, 1562, 1471, 1441, 1333, 1245, 1183, 1120, 1097, 1026; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.96 (s, 1H), 6.01–6.08 (m, 1H), 6.12–6.19 (m, 1H), 6.60–6.68 (m, 1H), 7.62–7.96 (br, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 26.4, 106.4, 108.3, 117.3, 129.1; HR-ESI-MS calcd 169.0737 obsd 169.0770 [(M + Na\(^+\), M = C\(_9\)H\(_{10}\)N\(_2\)].

Pale gray solid (64%): IR (\(\nu\), cm\(^{-1}\), thin film) 3676, 2988, 2902, 1452, 1406, 1394, 1383, 1250, 1242, 1230, 1057, 1028; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.90 (s, 1H), 4.99 (s, 1H), 6.00–6.07 (m, 1H), 6.11–6.16 (m, 1H), 6.16–6.28 (m, 2H), 6.64–6.78 (m, 2H), 7.02 (d, \(J = 7.6\) Hz, 2H), 7.28–7.46 (m, 3H), 7.83 (br, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 25.5, 50.4, 105.9, 107.3, 108.4, 116.9, 122.1, 126.6, 128.8, 129.8, 138.3; HR-ESI-MS calcd 237.1386 obsd 237.1383 [(M + H\(^+\), M = C\(_{16}\)H\(_{16}\)N\(_2\)].

Known compound. Dark yellow oil (13%): IR (\(\nu\), cm\(^{-1}\), thin film) 3676, 3363, 2988, 2901, 1660, 1590, 1566, 1509, 1395, 1308, 1250, 1181, 1113, 1086, 1066, 1037, 1026; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.20 (s, 3H), 3.93 (s, 2H), 5.79 (s, 1H), 5.90 (s, 1H), 6.04 (s, 1H), 6.16 (s, 1H), 6.67 (s, 1H), 7.57 (br, 1H), 7.91 (br, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 13.0, 26.5, 105.8, 106.4, 108.3, 117.1, 127.5, 129.4; HR-ESI-MS calcd 183.0893 obsd 183.0885 [(M + Na\(^+\), M = C\(_{16}\)H\(_{12}\)N\(_2\)].
Pale brown oil (42%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.10 (s, 2H), 6.07 (as, 1H), 6.17 (as, 1H), 6.32–6.34 (m, 1H), 6.67–6.68 (m, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.79–7.97 (br, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 25.4, 90.5, 107.0, 108.7, 108.8, 117.0, 117.6, 120.5, 125.3, 128.3, 129.5, 136.0, 137.5; HR-ESI-MS calcd 372.0049 obsd 372.0044 [(M + Na)$^+$, M = C$_{15}$H$_{13}$N$_2$I].

Colorless oil (54%): IR (v, cm$^{-1}$, thin film) 3676, 3341, 2959, 2867, 1563, 1534, 1464, 1407, 1394, 1383, 1272, 1258, 1236, 1210, 1116, 1067, 1016; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.19 (d, $J = 7.6$ Hz, 18H), 1.50 (sept, $J = 7.6$ Hz, 3H), 3.95 (s, 2H), 5.97 (s, 1H), 6.18–6.24 (m, 1H), 6.25–6.29 (m, 1H), 6.65–6.73 (m, 2H), 6.79–6.87 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.8, 17.9, 25.5, 105.0, 108.3, 111.3, 116.0, 122.2, 122.7, 124.7, 132.2; HR-ESI-MS calcd 303.2251 obsd 303.2247 [(M + H)$^+$, M = C$_{18}$H$_{30}$N$_2$Si].

Pale solid (32 mg, 52%): $^1$H NMR (400 MHz, CDCl$_3$/CD$_3$OD) $\delta$ 1.14 (dt, $J = 7.1$, 1.2 Hz, 3H), 3.76 (s, 1H), 4.08 (q, $J = 7.2$ Hz 2H), 5.72–5.81 (m, 1H), 5.94–6.05 (m, 1H), 6.58–6.63 (m, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.33–7.39 (m, 1H), 7.61 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$/CD$_3$OD) $\delta$ 13.7, 24.0, 59.4, 91.3, 105.6, 107.5, 113.3, 116.8, 121.1, 124.1, 128.8, 129.0, 132.4, 134.8, 136.4, 165.8; HR-ESI-MS calcd 456.0888 obsd 456.0894 [(M + MeOH + Na)$^+$, M = C$_{16}$H$_{19}$N$_2$O$_2$I].
Colorless oil (6mg, 6%): $^1$H NMR (400 MHz, CDCl₃) δ 3.97 (s, 2H), 6.00–6.08 (m, 1H), 6.11–6.19 (m, 1H), 6.44–6.49 (m, 1H), 6.67–6.74 (m, 1H), 7.27–7.30 (m, 1H), 9.70 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl₃) δ 26.2, 104.8, 106.9, 108.6, 117.9, 127.2, 127.3, 127.5, 132.4, 185.7; HR-ESI-MS calcd 197.0685 obsd 197.0687 [(M + Na)$^+$, $M = C_{10}H_{10}N_2O$].

\[ \text{Known compound.} \]

Colorless oil (92%): $^1$H NMR (400 MHz, CDCl₃) δ 2.31 (s, 6H), 3.66 (s, 2H), 7.09–7.19 (m, 3H), 7.33 (d, $J = 7.3$ Hz, 1H), 7.71 (d, $J = 7.7$ Hz, 1H), 8.56 (br, 1H); $^{13}$C NMR (100 MHz, CDCl₃) δ 45.3, 54.5, 111.1, 119.2, 119.5, 121.9, 123.8, 127.9, 128.1, 132.2; HR-ESI-MS calcd 197.1049 obsd 197.1027 [(M + Na)$^+$, $M = C_{11}H_{14}N_2$].

\[ \text{Known and commercially available compound. NMR spectra previously recorded in DMSO-$d_6$.} \]

Pale pink gum (82%): $^1$H NMR (400 MHz, CDCl₃, peaks for product reported) δ 2.29 (s, 6H), 3.59, 3.60 (2 x s, 2H), 3.85 (s, 3H), 6.83–6.88 (m, 1H), 7.05–7.13 (m, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 8.35 (br, 1H); $^{13}$C NMR (100 MHz, CDCl₃, all peaks reported) δ 42.7, 45.3, 54.5, 55.9, 68.9, 101.1, 110.7, 111.7, 112.1, 112.9, 124.5, 128.3, 128.7, 131.4, 132.5, 154.0; ESI-MS calcd 205.13 obsd 205.15 [(M + H)$^+$, $M = C_{12}H_{16}N_2O$].

\[ \text{Known compound and commercially available compound, spectra not available. Bright yellow solid (53%):} \]

$^1$H NMR (400 MHz, CDCl₃) δ 2.30 (s, 6H), 3.63, 3.65 (2 x s, 2H), 7.36 (d, $J = 9.2$ Hz 1H), 7.39–7.49 (m, 1H), 8.06–8.13 (m, 1H), 8.67 (dd, $J = 8.7, 2.1$ Hz, 1H),
8.91 (br, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, all peaks reported) δ 42.6, 45.3, 54.2, 69.2, 104.1, 105.0, 110.2, 111.0, 115.2, 116.1, 116.8, 116.9, 117.4, 117.5, 117.6, 117.7, 117.9, 118.0, 126.5, 127.2, 127.4, 127.8, 130.6, 131.6, 139.2, 140.0, 141.5, 141.7; HR-ESI-MS calcd 220.1081 obsd 220.1100 [(M + H)$^+$, M = C$_{11}$H$_{13}$N$_3$O$_2$].

Known compound.$^{10}$ Dark green solid (89%): $^1$H NMR (400 MHz, CDCl$_3$, contains ~33% N-alkylated product, for which peaks are not reported) δ 2.29 (s, 6H), 2.35 (s, 3H), 3.57 (s, 2H), 7.07–7.23 (m, 3H), 7.61–7.64 (m, 1H), 8.22 (br, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, peaks reported for both C- and N-alkylated products) δ 10.6, 11.8, 42.8, 45.4, 53.3, 65.9, 110.1, 118.4, 119.4, 120.9, 128.7, 129.4, 133.5, 135.1; HR-ESI-MS calcd 189.1386 obsd 180.1364 [(M + H)$^+$, M = C$_{11}$H$_{16}$N$_2$].

Brown solid (77% from dimethylaminomethyl indole): $^1$H NMR (400 MHz, CDCl$_3$) δ 4.14 (s, 2H), 6.11 (s, 1H), 6.19 (d, $J$ = 3.0 Hz, 1H), 6.61 (s, 1H), 6.98 (s, 1H), 7.12 (at, $J$ = 7.5 Hz, 1H), 7.23 (at, $J$ = 8.7 Hz, 1H), 7.37 (d, $J$ = 8.1 Hz, 1H), 7.54 (d, $J$ = 7.9 Hz, 1H). 7.91 (br, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.8, 105.6, 108.3, 111.2, 113.8, 116.4, 119.0, 119.6, 122.2, 122.4, 127.4, 131.0, 134.4; HR-ESI-MS calcd 219.0893 obsd 219.0886 [(M + Na)$^+$, M = C$_{13}$H$_{12}$N$_2$].

Brown oil (80% from dimethylaminomethyl-indole): $^1$H NMR (400 MHz, CDCl$_3$) δ 3.80 (s, 3H), 4.10 (s, 2H), 6.08 (s, 1H), 6.16 (d, $J$ = 3.0 Hz, 1H), 6.62 (s, 1H), 6.86 (d, $J$ = 8.8 Hz,
1H), 6.92 (s, 1H), 6.99 (s, 1H), 7.24 (s, 1H), 7.91 (br, 2H); 13C NMR (100 MHz, CDCl3) δ 23.8, 55.9, 100.7, 105.5, 108.9, 111.9, 112.5, 113.5, 116.3, 123.2, 127.8, 130.9, 131.5, 154.1; HR-ESI-MS calcd 249.0998 obsd 249.0996 [(M + Na)+, M = C14H14N2O].

Known compound.11 Yellow oil (29 mg, 40% from dimethylaminomethy-indole): 1H NMR (400 MHz, CDCl3/CD3OD) δ 4.10 (s, 2H), 5.86–5.93 (m, 1H), 5.98–6.05 (m, 1H), 6.58–6.65 (m, 1H), 7.17 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.93–8.05 (m, 1H), 8.39–8.45 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 23.3, 105.3, 107.2, 111.0, 116.1, 116.4, 116.5, 116.6, 125.9, 126.6, 130.2, 139.9, 140.7; HR-ESI-MS calcd 264.0743 obsd 264.0761 [(M + Na)+, M = C13H11N3O2].

Known compound.12 Colorless oil (67%): 1H NMR (400 MHz, CDCl3, complex spectrum, all peaks reported) δ 2.28 (s, 6H), 4.65 (s, 2H), 5.44 (s, 0.7H), 5.52 (br, 1.5H), 6.95 (s, 1H), 7.02–7.09 (m, 2.5H), 7.48 (s, 1H), 7.55 (br, 0.3H), 7.68 (br, 0.5H); 13C NMR (100 MHz, CDCl3, spectrum more complex than expected, all peaks recorded) δ 41.9, 63.4, 70.1, 119.8,
121.8, 128.9, 129.0, 137.5; HR-ESI-MS calcd 148.0845 obsd 148.0841 \([M + \text{Na}]^+, M = \text{C}_6\text{H}_{11}\text{N}_3\), calcd 183.1604 obsd 183.1599 \([M + \text{H}]^+, M = \text{C}_9\text{H}_{18}\text{N}_4\) (for dialkylated compound).

References


