An Improved Synthesis of α -Carbolines Under Microwave Irradiation

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Supporting Information

(10 pages)

General methods. Comparative microwave experiments were performed on Samsung M1719N and Panasonic NN-F359WBE domestic microwave ovens and Synthrowave 402 (from Prolabo) and Explorer (from CEM-Biotage) focused microwave instruments. Methylene chloride was dried and distilled from calcium hydride. Commercial reagents were purchased from Aldrich and used without further purification. Proton nuclear magnetic resonance (^1H NMR) was measured on Varian Gemini 200 or Varian Unity 300 instruments. Infrared spectra (IR-FT) were recorded on a Spectrum 2000 instrument from Perkin-Elmer. Mass Spectra (MS) were obtained on an Automass Multi Finningan instrument using EI and APCI techniques. Microanalyses were performed on a Leco CHNS-932 instrument. Melting points were measured using a Gallenkamp instrument.

Synthesis of N-azinylbenzotriazoles 1. General procedure. Benzotriazoles **2** (2 mmol), azines **3** (2 mmol) and a magnetic stirring bar were added to a reactor tube of an Explorer monomode microwave apparatus (CEM-Biotage). The tube was capped and irradiated for 10 min at 50 W and 180 °C. The reaction mixture was chromatographed on silica gel using methylene chloride as the eluent.

1a. Yield: 72%. Mp 92-93 °C; white powder. IR (KBr) ν 1614, 1577, 1490, 1462, 1050, 786, 740 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3) δ 8.66 (apdt, 1H; $J = 8.4$ Hz, $J = 0.9$ Hz); 8.09 (apt, 2H; $J = 8.1$ Hz, $J = 8.4$ Hz); 7.80 (t, 1H; $J = 8.1$ Hz, $J = 7.5$ Hz); 7.58 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz); 7.43 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 0.9$ Hz); 7.16 (d, 1H; $J = 7.5$ Hz); 2.66 (s, 3H). MS (EI) m/z 210 (M^+ , 27) 182 (M-28,

100) 181 (72) 92 (50). Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.48; H, 4.70; N, 26.27.

1b. Yield: 87%. Mp 112-113 °C; white powder. IR (KBr) ν 1476, 1441, 1073, 1062, 785, 768, 752 cm^{-1} . 1H -NMR (300 MHz, $CDCl_3$) δ 8.65 (ddd, 1H; $J = 8.4$ Hz, $J = 0.9$ Hz, $J = 0.9$ Hz); 8.61 (ddd, 1H; $J = 4.9$ Hz, $J = 1.8$ Hz, $J = 0.7$ Hz); 8.30 (ddd, 1H; $J = 8.2$ Hz, $J = 1.1$ Hz, $J = 0.7$ Hz); 8.11 (ddd, 1H; $J = 8.4$ Hz, $J = 0.9$ Hz, $J = 0.9$ Hz); 7.93 (ddd, 1H; $J = 8.2$ Hz, $J = 7.5$ Hz, $J = 1.8$ Hz); 7.59 (ddd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 0.9$ Hz); 7.44 (ddd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 0.9$ Hz); 7.32 (ddd, 1H; $J = 7.5$ Hz, $J = 4.9$ Hz, $J = 1.1$ Hz). MS (EI) m/z 196 (M^+ , 26) 168 (100) 78 (67). Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.24; H, 3.99; N, 28.20.

1c. Yield: 85%. Mp 148-149 °C; Lit.^{1b}; white powder. IR (KBr) ν 1594, 1507, 1082, 1085, 1034, 828, 782, 743 cm^{-1} . 1H -NMR (300 MHz, $CDCl_3$) δ 8.97 (apdt, 1H; $J = 8.4$ Hz, $J = 0.9$ Hz); 8.50 (d, 1H; $J = 8.8$ Hz); 8.38 (d, 1H; $J = 8.8$ Hz); 8.16 (d, 1H; $J = 8.4$ Hz); 8.15 (apdt, 1H; $J = 8.4$ Hz, $J = 0.9$ Hz); 7.89 (d, 1H; $J = 8.1$ Hz); 7.79 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.5$ Hz); 7.68 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 0.9$ Hz); 7.58 (aptd, 1H; $J = 8.1$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz); 7.49 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 0.9$ Hz). MS (EI) m/z 246 (M^+ , 19) 218 (87) 128 (100). Anal. Calcd for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 72.81; H, 4.08; N, 22.61.

1c

1d. Yield: 94%. Mp 164-166 °C; Lit.^{1b}; pink prisms. IR (KBr) ν 1597, 1473, 1446, 1085, 1050, 772, 751 cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.87 (d, 1H; $J = 8.1$ Hz); 8.24 (s, 1H); 8.08 (apt, 2H; $J = 8.4$ Hz); 7.94 (d, 1H; $J = 8.4$ Hz); 7.70 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.5$ Hz); 7.61 (apt, 1H; $J = 8.4$ Hz); 7.51 (aptd, 1H; $J = 8.1$ Hz, $J = 1.1$ Hz); 7.44 (apt, 1H; $J = 7.3$ Hz, $J = 7.0$ Hz); 2.74 (s, 3H). MS (EI) m/z 260 (M^+ , 27) 232 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.79; H, 4.78; N, 21.24.

1d

1e. Yield: 72%. Mp 120-122 °C; yellow powder. IR (KBr) ν 1593, 1474, 1448, 1064, 781 cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.60 (dd, 1H; $J = 4.8$ Hz, $J = 1.8$ Hz, $J = 0.7$ Hz); 8.38 (s, 1H); 8.25 (d, 1H; $J = 8.4$ Hz); 7.90 (aptd, 1H; $J = 8.4$ Hz, $J = 7.3$ Hz, $J = 1.8$ Hz); 7.82 (s, 1H); 7.28 (ddd, 1H; $J = 7.3$ Hz, $J = 4.8$ Hz, $J = 1.1$ Hz); 2.46 (s, 3H); 2.42 (s, 3H). MS (EI) m/z 224 (M^+ , 30) 195 (72) 78 (100). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.81; H, 5.45; N, 24.73.

1e

1f. Yield: 67%. Mp 139-141 °C; yellow prisms. IR (KBr) ν 1484, 1459, 1096, 997, 847, 795 cm^{-1} . ^1H -NMR (200 MHz, CDCl_3) δ 8.36 (s, 1H); 8.02 (d, 1H; $J = 8.1\text{ Hz}$); 7.80 (s, 1H); 7.76 (apt, 1H; $J = 8.1\text{ Hz}$, $J = 7.3\text{ Hz}$); 7.12 (d, 1H; $J = 7.3\text{ Hz}$); 2.66 (s, 3H); 2.45 (s, 3H); 2.40 (s, 3H). MS (EI) m/z 238 (M^+ , 23) 92 (100). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.74; H, 6.04; N, 23.26.

1f

1g. Yield: 73%. Mp 168-169 °C; white powder. IR (KBr) ν 1505, 1479, 1087, 1028, 829, 746 cm^{-1} . ^1H -NMR (200 MHz, CDCl_3) δ 8.69 (s, 1H); 8.47 (d, 1H; $J = 9.2\text{ Hz}$); 8.35 (d, 1H; $J = 9.2\text{ Hz}$); 8.18 (d, 1H; $J = 8.4\text{ Hz}$); 7.88 (d, 1H; $J = 8.1\text{ Hz}$); 7.87 (s, 1H); 7.78 (aptd, 1H; $J = 8.4\text{ Hz}$, $J = 7.0\text{ Hz}$, $J = 1.5\text{ Hz}$); 7.57 (aptd, 1H; $J = 8.1\text{ Hz}$, $J = 7.0\text{ Hz}$, $J = 1.1\text{ Hz}$); 2.53 (s, 3H); 2.45 (s, 3H). MS (EI) m/z 274 (M^+ , 18) 246 (30) 128 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.23; H, 4.99; N, 20.32.

1g

1h. Yield: 79%. Mp 166-167 °C; white powder. IR (KBr) ν 1601, 1475, 1448, 1406, 1083, 1042, 912, 757 cm^{-1} . ^1H -NMR (200 MHz, CDCl_3) δ 8.68 (s, 1H); 8.32 (d, 1H; $J = 0.7\text{ Hz}$); 8.17 (d, 1H; $J = 7.7\text{ Hz}$); 8.03 (dd, 1H; $J = 8.1\text{ Hz}$, $J = 1.1\text{ Hz}$); 7.86 (s, 1H);

7.77 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.5$ Hz); 7.58 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz); 2.82 (d, 3H; $J = 0.7$ Hz); 2.52 (s, 3H); 2.44 (s, 3H). MS (EI) m/z 288 (M^+ , 50) 260 (83) 142 (100). Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.03; H, 5.72; N, 19.34.

1i. Yield: 70%. Mp 198-199°C; yellow powder. IR (KBr) ν 1477, 1462, 1067, 775 cm^{-1} . 1H -NMR (200 MHz, $CDCl_3$) δ 8.88 (s, 1H); 8.61 (aptd, 1H; $J = 4.8$ Hz, $J = 1.8$ Hz, $J =$ Hz); 8.27 (d, 1H; $J = 8.4$ Hz); 8.21 (s, 1H); 7.95 (aptd, 1H; $J = 8.4$ Hz, $J = 7.7$ Hz, $J = 1.8$ Hz); 7.36 (ddd, 1H; $J = 7.7$ Hz, $J = 4.8$ Hz, $J = 1.1$ Hz). MS (EI) m/z 264 (M , 16) 266 (11) 268 (2) 236 (52) 238 (33) 240 (4) 78 (100). Anal. Calcd for $C_{11}H_6N_4Cl_2$: C, 49.84; H, 2.28; N, 21.13. Found: C, 49.91; H, 2.34; N, 20.79.

1j. Yield: 40%. Mp 183-184 °C; white powder. IR (KBr) ν 1472, 1292, 1091, 1044, 787 cm^{-1} . 1H -NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H); 8.21 (s, 1H); 8.06 (d, 1H; $J = 8.2$ Hz); 7.82 (apt, 1H; $J = 8.2$, $J = 7.5$ Hz); 7.20 (d, 1H; $J = 7.5$ Hz); 2.68 (s, 3H). MS (EI) m/z 278 (M^+ , 10) 280 ($M+2$, 6) 282 ($M+4$, 1) 92 (100). MS (APCI) m/z 279 ($M+1$, 100) 281 (77) 283 (15). Anal. Calcd for $C_{12}H_8N_4Cl_2$: C, 51.64; H, 2.89; N, 20.07. Found: C, 51.52; H, 2.92; N, 19.71.

1k. Yield: 82%. Mp 250-252 °C; white powder. IR (KBr) ν 1506, 1449, 1092, 1031, 827 cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 9.14 (s, 1H); 8.45 (d, 1H; $J = 8.8$ Hz); 8.39 (d, 1H; $J = 8.8$ Hz); 8.25 (s, 1H); 8.18 (d, 1H; $J = 8.4$ Hz); 7.90 (d, 1H; $J = 8.1$ Hz); 7.81 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.5$ Hz); 7.61 (aptd, 1H; $J = 8.1$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz). MS (EI) m/z 314 (M^+ , 5) 316 (3) 318 (1) 286 (25) 288 (17) 290 (3) 128 (100). Anal. Calcd for $\text{C}_{15}\text{H}_8\text{N}_4\text{Cl}_2$: C, 57.16; H, 2.56; N, 17.78. Found: C, 57.04; H, 2.74; N, 17.54.

1l. Yield: 91%. Mp 213-214 °C; white powder. IR (KBr) ν 1601, 1474, 1452, 1045, 908, 754 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 9.14 (s, 1H); 8.31 (d, 1H; $J = 0.9$ Hz); 8.24 (s, 1H); 8.18 (d, 1H; $J = 8.4$ Hz); 8.06 (dd, 1H; $J = 8.2$ Hz, $J = 1.1$ Hz); 7.80 (aptd, 1H; $J = 8.4$ Hz, $J = 7.0$ Hz, $J = 1.5$ Hz); 7.62 (aptd, 1H; $J = 8.2$ Hz, $J = 7.0$ Hz, $J = 1.3$ Hz); 2.84 (d, 3H; $J = 0.9$ Hz). MS (EI) m/z 328 (M^+ , 10) 330 (6) 332 (1) 300 (43) 302 (28) 304 (5) 142 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{Cl}_2$: C, 58.38; H, 3.06; N, 17.02. Found: C, 58.29; H, 3.10; N, 16.95.

11

Synthesis of α -carbolines 4. General procedure. Pyridylbenzotriazole **1** (1 mmol), $\text{H}_4\text{P}_2\text{O}_7$ (16 mmol) and a magnetic stirring bar were placed in a reactor tube of an Explorer monomode microwave apparatus (CEM-Biotage). The tube was capped and irradiated for 30 s at 150 W and 170 °C. The reaction mixture was taken up in water and 15% NaOH was added to give a basic pH. The solid was filtered off, air dried and chromatographed on silica gel using hexanes/ethyl acetate 1:1 as eluent.

4a. Yield: 45%. Mp 258-259 °C; white powder. IR (KBr) 1604, 1461, 1417, 1275, 1223, 779, 733 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3) δ 9.72 (s, 1H); 8.21 (d, 1H; $J = 7.7$ Hz); 8.00 (d, 1H; $J = 7.9$ Hz); 7.51 (d, 1H; $J = 8.2$ Hz); 7.43 (aptd, 1H; $J = 8.2$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz); 7.24 (aptd, 1H; $J = 8.2$ Hz, $J = 7.0$ Hz, $J = 1.1$ Hz); 7.06 (d, 1H; $J = 7.9$ Hz); 2.75 (s, 3H). MS (EI) m/z 182 (M^+ , 100) 181 (55) 181 (13) 154 (10). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.74; H, 5.43; N, 14.99.

4a

4b. Yield: 34%. Mp 219-220 °C; Lit.^{11b} 210 °C; white powder. IR (KBr) 1602, 1456, 1417, 1276, 768, 740 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3) δ 9.93 (s, 1H); 8.50 (dd, 1H; $J = 4.9$ Hz, $J = 1.5$ Hz); 8.34 (dd, 1H; $J = 7.7$ Hz, $J = 1.7$ Hz); 8.06 (d, 1H; $J = 7.9$ Hz); 7.50 (m, 2H); 7.24 (m, 2H). MS (EI) m/z 168 (M^+ , 100) 140 (19) 114 (10) 84 (8). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{N}_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.20; H, 4.67; N, 16.59.

4c. Yield: 19%. Mp 355-356 °C; Lit.^{11c} >300 °C; yellow powder. IR (KBr) 1616, 1460, 1406, 1230, 787, 736 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) δ 8.74 (s, 1H); 8.56 (s, 1H); 8.14 (d, 1H; *J* = 7.7 Hz); 8.05 (d, 1H; *J* = 8.8 Hz); 8.02 (d, 1H; *J* = 8.1 Hz); 7.72 (aptd, 1H; *J* = 8.4 Hz, *J* = 6.8 Hz, *J* = 1.5 Hz); 7.52 (m, 3H); 7.30 (aptd, 1H; *J* = 8.2 Hz, *J* = 7.7 Hz, *J* = 1.3 Hz). MS (EI) *m/z* 218 (M⁺, 100) 190 (8) 109 (7). Anal. Calcd for C₁₅H₁₀N₂: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.76; H, 4.49; N, 12.73.

4d. Yield: 27%. Mp 278-279 °C; Lit.^{11c} 270-272 °C; white powder. IR (KBr) 1613, 1402, 1251, 1230, 741, 727 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) δ 9.69 (s, 1H); 8.27 (d, 2H; *J* = 8.4 Hz); 8.11 (dd, 1H; *J* = 8.4 Hz, *J* = 0.7 Hz); 7.74 (aptd, 1H; *J* = 8.2 Hz, *J* = 6.8 Hz, *J* = 1.3 Hz); 7.51 (m, 3H); 7.30 (m, 1H); 3.22 (s, 3H). MS (EI) *m/z* 232 (M⁺, 100) 231 (49). Anal. Calcd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.45; H, 5.13; N, 11.70.

4e. Yield: 36%. Mp 232-234 °C; white powder. IR (KBr) 1604, 1588, 1465, 1438, 1413, 1276, 1242, 760 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) δ 9.65 (s, 1H); 8.43 (d, 1H; *J*

= 3.7 Hz); 8.24 (d, 1H; J = 6.6 Hz); 7.80 (s, 1H); 7.29 (s, 1H); 7.14 (dd, 1H; J = 7.5 Hz, J = 4.9 Hz); 2.43 (s, 3H); 2.41 (s, 3H). MS (EI) m/z 196 (M^+ , 100) 195 (66) 181 (71). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.46; H, 6.07; N, 13.90.

4f. Yield: 37%. Mp 243-244 °C; white powder. IR (KBr) 1610, 1468, 1432, 1411, 1277, 1224 cm^{-1} . 1H -NMR (200 MHz, $CDCl_3$) δ 9.74 (s, 1H); 8.13 (d, 1H; J = 7.7 Hz); 7.75 (s, 1H); 7.29 (s, 1H); 7.01 (d, 1H; J = 7.7 Hz); 2.73 (s, 3H); 2.42 (s, 3H); 2.40 (s, 3H). MS (EI) m/z 210 (M , 100) 209 (62) 195 (62). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.58; H, 6.61; N, 12.99.

4g. Yield: 24%. Mp 317-319 °C; yellow powder. IR (KBr) 1628, 1486, 1468, 1409, 1270, 748 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H); 8.54 (s, 1H); 8.03 (d, 1H; J = 8.6 Hz); 7.98 (d, 1H; J = 8.6 Hz); 7.88 (s, 1H); 7.69 (aptd, 1H; J = 8.4 Hz, J = 1.5 Hz); 7.45 (aptd, 1H; J = 7.9 Hz, J = 7.1 Hz); 7.26 (s, 1H). MS (EI) m/z 246 (M^+ , 100) 245 (46) 231 (35). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.52; H, 5.57; N, 11.26.

4h. Yield: 38%. Mp 318-320 °C; yellow powder. IR (KBr) 1610, 1473, 1409, 1290, 1272, 744 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.53 (s, 1H); 8.23 (d, 1H; $J = 9.5$ Hz); 8.02 (d, 2H; $J = 7.5$ Hz); 7.69 (aptd, 1H; $J = 8.2$ Hz, $J = 1.3$ Hz); 7.48 (aptd, 1H; $J = 8.2$ Hz, $J = 1.3$ Hz); 7.26 (s, 1H); 3.18 (s, 3H); 2.44 (s, 3H); 2.43 (s, 3H). MS (EI) m/z 260 (M^+ , 100) 259 (44) 245 (37). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 79.96; H, 6.06; N, 10.48.

4j. Yield: 16%. Mp 295-296 °C; white powder. IR (KBr) 1606, 1442, 1410, 1244, 1101, 765 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.93 (s, 1H); 8.49 (d, 1H; $J = 3.7$ Hz); 8.27 (d, 1H; $J = 7.7$ Hz); 8.11 (s, 1H); 7.60 (s, 1H); 7.21 (m, 1H). MS (EI) m/z 236 (M^+ , 86) 238 (67) 240 (17) 237 (100) 239 (64) 241 (11). Anal. Calcd for $\text{C}_{11}\text{H}_6\text{N}_2\text{Cl}_2$: C, 55.73; H, 2.55; N, 11.82. Found: C, 55.60; H, 2.56; N, 11.48.