N,N-Bond Forming Heterocyclization: Synthesis of 3-Alkoxy-2*H*-Indazoles

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General Procedures:

Organic solvents, anhydrous solvents and reagents were purified by the appropriate standard procedures. Thin layer chromatography (TLC) used aluminium sheets coated with silica gel 60 F254 visualized under 254 nm light. Flash chromatography was conducted using silica gel 60 of particle size 0.040-0.063 mm. Melting points were uncorrected. Infrared spectra were recorded neat. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 , and d_6 -DMSO at 399.77 MHz and ^{13}C NMR at 100.53 MHz with solvent signals used for reference at 7.24 ppm for ^1H and 77.0 for ^{13}C NMR, δ values are given in ppm, the coupling constants J are expressed in Hz. HPLC was accomplished with a Nova-Pak C_{18} column (3.9 x 150 mm). Mobile phases were 99.9% CH_3CN with 0.1% TFA and 99.9% water with 0.1% TFA. The separation gradient was 0 to 100% organic over 15 min, 100% organic for 10 min, and 100% to 0% organic over 1 min. Samples were run over at a constant flow rate of 1 mL/min and a temperature of 25 °C. Detection was at 254 nm. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy.

2-Benzyl-3-methoxy-2H-indazole (14). Benzyl(2-nitrobenzyl)amine (**3**) was synthesized according to the literature method.¹⁰ Crude amine **3** (0.300 g, 1.239 mmol) gave **14** (R_f = 0.37 (2:5 hexane / ethyl acetate) as a light yellow oil (61%): ^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, J = 8.7 Hz, 1.2, 1H), 7.57 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.32-7.18 (m, 6H), 6.92 (dt, J = 6.6 Hz, 0.9 Hz, 1H), 5.44 (s, 2H), 4.21 (s, 3H); ^{13}C NMR δ 147.3, 146.6, 136.3, 128.6, 127.7, 127.5, 126.1, 119.6, 119.4, 117.7, 106.8, 60.4, 52.0; IR (neat) 1624, 1526, 1510, 1406, 1385, 1113, 737, 701 cm^{-1} ; HPLC purity = 97%; HREIMS calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ (M^+) 238.1106, found: 238.1104.

2-Benzyl-3-(2-methoxy-ethoxy)-2H-indazole (15). Benzyl(2-nitrobenzyl)amine (**3**) was synthesized according to the literature method.¹⁰ Crude amine **3** (0.300 g, 1.239 mmol) gave **15** (R_f = 0.32, 40% EtOAc in hexanes) as a light yellow oil (0.262 g, 75%): ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.54 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 7.30-7.28 (m, 5H), 7.18 (dt, J = 2.8 Hz, 0.8 Hz, 1H), 6.91 (dt, J = 2.8 Hz, 0.8 Hz, 1H), 5.46 (s, 2H), 4.49 (t, 2H), 3.64 (t, 2H), 3.37 (s, 3H); ¹³C NMR δ 147.3, 145.6, 136.4, 128.6, 127.8, 127.7, 126.1, 119.9, 119.2, 117.7, 107.5, 77.5, 70.8, 59.0, 52.0; IR (neat) 3060, 3031, 2983, 2929, 2880, 2815, 1624, 1549, 1523, 1385, 1266, 1110, 1028, 738, 702 cm⁻¹. HPLC purity = 98%; HREIMS calcd for C₁₇H₁₈N₂O₂ (M⁺) 282.1368, found: 282.1372.

2-(2-Benzyl-2H-indazol-3-yloxy)ethanol (16). Benzyl(2-nitrobenzyl)amine (**3**) was synthesized according to the literature method.¹⁰ Crude amine **3** (0.286 g, 1.18 mmol) gave **16** (R_f = 0.19, 50% EtOAc in hexanes) as a light yellow oil (0.228 g, 71%): ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.53 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 7.16-7.27 (m, 5H), 6.90 (dt, J = 7.6 Hz, 0.8 Hz, 1H), 5.34 (s, 2H), 4.46 (t, 2H), 3.78 (t, 2H), 2.67 (s, 1H); ¹³C NMR δ 147.3, 136.4, 128.8, 128.0, 127.5, 126.5, 120.2, 119.3, 117.7, 107.5, 75.1, 69.1, 61.3, 52.3; IR (neat) 3285, 3065, 3030, 2945, 2868, 1732, 1624, 1525, 1384, 1244, 1117, 1081, 1043, 883, 739 cm⁻¹. HPLC purity = 96.6%; HREIMS calcd for C₁₆H₁₆N₂O₂ (M⁺): 268.1212, found: 268.1213.

3-Ethoxy-2-(4-methoxybenzyl)-2H-indazole (17). Using the general 2H-indazoles procedure, crude amine **4** [¹H NMR (400 MHz, CDCl₃) δ 7.85 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 7.53-7.45 (m, 2H), 7.30 (dt, J = 8.4, J = 1.2, 1H), 7.16 (d, J = 6.8 Hz, 2H), 6.76 (d, J = 6.8 Hz, 2H), 3.95 (s, 2H), 3.70 (s, 3H), 3.68 (s, 3H); ¹³C NMR δ 158.8, 149.2, 135.5, 133.2, 131.8, 131.4, 129.4, 128.1, 124.8, 113.9, 55.3, 52.8, 50.1, (0.321 g, 1.176 mmol)] gave **17** (R_f

= 0.36, 40% EtOAc in hexanes) as a light yellow oil (0.262 g, 60%): ^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.45 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.1 (dd, J = 6.8 Hz, 1.2 Hz, 1H), 6.82 (dd, J = 6.4 Hz, 0.8 Hz, 1H), 6.75 (dd, J = 6.8 Hz, 0.8 Hz, 2H), 5.3 (s, 2H), 4.4 (q, 2H), 3.67 (s, 3H), 1.36 (t, 3H); ^{13}C NMR δ 159.3, 147.3, 129.3, 128.7, 126.1, 119.7, 119.5, 117.8, 114.1, 107.4, 107.5, 69.4, 55.3, 51.7, 51.6; IR (neat) 3060, 2978, 2934, 2834, 1623, 1511, 1384, 1244, 1174, 1114, 1030, 738 cm^{-1} . HPLC purity = 96.2%; HREIMS calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 282.1368, found: 282.1363.

3-Ethoxy-2-(4-methoxyphenyl)-2H-indazole (18). 4-Methoxyphenyl(2-nitrobenzyl)amine (**5**) was synthesized using the literature method.¹⁶ Crude amine **5** (0.36 g, 1.394 mmol) gave **18** (R_f = 0.47, 40% EtOAc in hexanes) as a light brown oil (0.086 g, 23%): ^1H NMR (400 MHz, CDCl_3) δ 7.72 (dd, J = 9.2 Hz, 0.8 Hz, 2H), 7.65 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 7.57 (dd, J = 9.2 Hz, 1.2 Hz, 1H), 7.24 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.0 (dd, J = 7.2 Hz, 2.4 Hz, 2H), 6.97 (dt, J = 6.4 Hz, 0.8 Hz, 1H), 4.5 (q, 2H), 3.8 (s, 3H), 1.43 (t, 3H); ^{13}C NMR δ 159, 147.7, 126.9, 125.5, 122.8, 120.3, 119.8, 117.9, 114.2, 108.5, 69.9, 69.1, 55.6, 15.5; IR (neat) 3052, 2981, 2935, 2834, 1622, 1512, 1377, 1246, 1170, 1104, 1027, 736 cm^{-1} . HPLC purity = 96.0%; HREIMS calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ (M^+) 268.1212, found: 268.1217.

2-Isopropyl-3-methoxy-2H-indazole (20). Using the general 2H-indazoles procedure, crude amine **7** [^1H NMR (400 MHz, CDCl_3) δ 7.93 (dd, J = 8.1 Hz, 0.6 Hz, 1H), 7.63-7.53 (m, 2H), 7.38 (dt, J = 8.4, J = 1.8, 1H), 4.00 (s, 3H), 2.84 (m, 1H), 1.08 (d, 6H); (0.254 g, 1.307 mmol)] gave **20** (R_f = 0.55, 40% EtOAc in hexanes) as a light yellow oil (0.176 g, 71%): ^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.55 (dd, J = 8.7 Hz, 1.2 Hz, 1H), 7.16 (dt, J = 6.6 Hz, 1.2 Hz, 1H), 6.84 (dt, J = 6.6 Hz, 0.6 Hz, 1H), 4.77 (m, 1H), 4.20 (s, 3H), 1.51 (d, 6H); ^{13}C NMR δ 147.4, 145.7, 125.5, 119.3, 119.2, 117.6, 106.8, 60.7, 49.5, 22.2; IR

(neat) 3063, 2978, 2936, 2878, 1623, 1522, 1380, 1271, 1221, 1108, 1070, 738 cm^{-1} . HPLC purity = 96.7%; HREIMS calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ (M^+) 190.1106, found: 190.1103.

2-Cyclopropyl-3-methoxy-6-methyl-2H-indazole (22). Using the general 2H-indazoles procedure, crude amine **8** [^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.17 (dd, J = 8.0, J = 1.6, 1H), 4.03 (s, 3H), 2.40 (s, 3H), 2.10 (m, 1H), 0.46-0.38 (m, 4H); ^{13}C NMR δ 146.8, 144.5, 135.7, 132.5, 128.6, 125.1, 51.1, 30.1, 21.6, 6.6; (0.314 g, 1.522 mmol)] gave **22** (R_f = 0.44, 40% EtOAc in hexanes) as a light yellow oil (0.126 g, 41%): ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H), 7.35 (s, 1H), 7.00 (d, J = 7.6 Hz, 1.2 Hz, 1H), 4.27 (s, 3H), 3.67 (m, 1H), 2.34 (s, 3H), 1.31 (m, 2H), 1.06 (m, 2H); ^{13}C NMR δ 147.4, 145.7, 128.9, 128.7, 127.9, 117.3, 117.2, 107.4, 60.5, 29.7, 21.7, 6.6; IR (neat) 3060, 3014, 2919, 2861, 1692, 1530, 1516, 1409, 1346, 1197, 1104, 1022, 797 cm^{-1} . HPLC purity = 97.1%; HREIMS calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}^+$ ($\text{M}+\text{H}$) 203.1179, found: 203.1169.

2-Butyl-3-methoxy-6-methyl-2H-indazole (23). Using the general 2H-indazoles procedure, crude amine **9** [^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 3.97 (s, 3H), 2.65 (t, 2H), 2.41 (s, 2H), 1.48 (m, 2H), 1.32 (m, 2H), 0.89 (t, 3H); ^{13}C NMR δ 144.5, 135.9, 131.9, 128.4, 125.1, 51.2, 49.4, 32.2, 21.5, 20.4, 13.9; (0.189 g, 0.851 mmol)] gave **23** (R_f = 0.59, 50% EtOAc in hexanes) as a light yellow oil (0.111 g, 60%): ^1H NMR (400 MHz, CDCl_3) δ 7.42 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.24 (s, 3H), 4.18 (t, 2H), 2.35 (s, 3H), 1.86 (m, 2H), 1.36 (m, 2H), 0.93 (t, 3H); ^{13}C NMR δ 146.1, 145.7, 128.7, 128.5, 117.3, 106.8, 94.3, 60.4, 47.8, 31.9, 21.7, 19.9, 13.6; IR (neat) 3019, 2956, 2935, 2872, 1633, 1530, 1454, 1407, 1347, 1082, 798 cm^{-1} . HPLC purity = 99%; HREIMS calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ (M^+) 218.1419, found: 218.1423.

2-Benzyl-5,6-dimethoxy-3-propoxy-2H-indazole (25). Using the general 2*H*-indazoles procedure, crude amine **10** [¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H), 7.25-7.13 (m, 5H), 7.02 (s, 1H), 3.96 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 2H); ¹³C NMR δ 153.2, 147.5, 140.8, 139.9, 131.2, 128.4, 128.1, 127.1, 112.5, 108.1, 56.3, 56.2, 53.4, 50.6; (0.328 g, 1.086 mmol)] gave **25** (R_f = 0.15, 40% EtOAc in hexanes) as a light yellow oil (0.039 g, 11%): ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.25 (m, 5H), 6.84 (s, 1H), 6.77 (s, 1H), 5.36 (s, 2H), 4.3 (t, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 1.81 (m, 2H), 1.03 (t, 3H); IR (neat) 2997, 2963, 2937, 2879, 2832, 1637, 1513, 1489, 1470, 1433, 1370, 1230, 1208, 1163, 1021, 829 cm⁻¹. HPLC purity = 99%; HREIMS calcd for C₁₉H₂₂N₂O₃ (M⁺) 326.1630, found: 326.1629.

2-Allyl-3,5,6-trimethoxy-2H-indazole (26). Using the general 2*H*-indazoles procedure, crude amine **11** [¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 1H), 7.03 (s, 1H), 5.86 (m, 1H), 5.13 (m, 2H), 4.08 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.27 (d, 2H); (0.240 g, 0.794 mmol)] gave **26** (R_f = 0.10, 40% EtOAc in hexanes) as a light yellow oil (0.130 g, 55%): ¹H NMR (400 MHz, CDCl₃) δ 6.81 (s, 2H), 6.01 (m, 1H), 5.2 (dd, J = 10.4 Hz, 1.2 Hz, 1H), 5.12 (dd, J = 15.6 Hz, 1.2 Hz, 1H), 4.76 (dd, J = 5.6 Hz, 1.6 Hz, 2H), 4.19 (s, 3H), 3.88 (d, 6H); ¹³C NMR δ 151.5, 146.5, 144.2, 132.8, 117.8, 100.8, 96.5, 96.1, 60.9, 56.1, 56.0, 55.8, 50.4; IR (neat) 2998, 2934.6, 2830, 1641, 1528, 1488, 1362, 1229, 1209, 1194, 1163, 1019, 991, 826 cm⁻¹. HPLC purity = 99%; HREIMS calcd for C₁₃H₁₆N₂O₃ (M⁺) 248.1161, found: 248.1157.

2-Butyl-6-chloro-3-methoxy-2H-indazole (27). Using the general 2*H*-indazoles procedure, crude amine **12** [¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 1H), 7.63-7.53 (m, 2H), 3.99 (s, 2H), 2.91 (t, 2H), 1.61 (m, 2H), 1.34 (m, 2H), 0.85 (t, 3H); (0.295 g, 1.068 mmol)] gave **27** (R_f = 0.55, 40% EtOAc in hexanes) as a light yellow oil (0.194 g, 67%): ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 8.4 Hz, 1H), 7.46 (m, 1H), 6.80 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 4.27 (s, 3H),

3.67 (m, 2H), 2.34 (s, 3H), 1.31 (m, 2H), 1.06 (m, 2H); ^{13}C NMR δ 147.1, 146.8, 131.9, 120.8, 117.9, 116.5, 105.2, 60.4, 48.0, 31.8, 19.9, 13.6; IR (neat) 3011, 2958, 2934, 2872, 1615, 1526, 1406, 1379, 1250.5, 1085, 1049, 914, 782 cm^{-1} . HPLC purity = 98.9%; HREIMS calcd for $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{O}$ (M^+) 238.0873, found: 238.0874.

2-Butyl-3-methoxy-2*H*-indazole-6-carboxylic acid (28). The crude amine **13** (0.264 g, 0.923 mmol) was added to a solution of 5% KOH in methanol. The reaction was allowed to stir for 6 h at 60 $^{\circ}\text{C}$ and then concentrated. The crude reaction mixture was taken up with EtOAc (100 mL), made acidic (100 mL 1N HCL), washed with water (100 mL), brine (100 mL), then dried over sodium sulfate, concentrated in vacuum and the product was crystallized from chloroform-methanol to give **28** as a light red solid (0.249 g, 96%): ^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H), 8.41 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0, 1H), 4.04 (s, 2H), 2.92 (t, 2H), 1.62 (m, 2H), 1.36 (m, 2H), 0.86 (t, 3H); ^{13}C NMR δ 171.2, 148.7, 137.8, 137.1, 133.7, 131.2, 125.5, 50.7, 39.9, 30.4, 19.8, 13.6. Further purification by recrystallization from chloroform-ethanol gave a pink solid, mp 162-164 $^{\circ}\text{C}$: ^1H NMR (400 MHz, CDCl_3) δ 8.0 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 4.3 (s, 3H), 4.2 (t, 2H), 1.8 (m, 2H), 1.2 (m, 2H), 0.8 (t, 3H); ^{13}C NMR δ 171.7, 146.6, 146.4, 130.0, 121.3, 119.9, 119.2, 108.2, 60.4, 48.2, 31.8, 19.9, 13.6; IR (neat) 3387, 3019, 2955, 2935, 2872, 1696, 1552, 1532, 1519, 1491, 1381, 1123, 1078, 1010 cm^{-1} ; HPLC purity = 99%; HREIMS calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$ (M^+) 248.1161, found: 248.1165.

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