

Regioselective Synthesis of 1-Alkyl or 1-Aryl-1*H*-indazoles via Copper-Catalyzed Cyclizations of 2-haloarylcarbonylic compounds.

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Supporting Information

Experimental Section

¹H NMR

¹³C NMR

Experimental Section

General Experimental Details.

All NMR spectra were recorded on Bruker WP 200 SY (200 MHz for ^1H and 50.3 MHz for ^{13}C) or Bruker Avance 400 DRX (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometers in CDCl_3 and $\text{DMSO}-d_6$ using TMS as internal reference. Chemical shift (δ) values are expressed in ppm and coupling constants (J) are reported in Hz. GCMS spectra were measured on a Hewlett-Packard 5890 series II gas chromatograph (5971 series mass selective detector) and electron impact (EIMS) were run in a VG-MICROMASS ZAB-2F. High resolution mass spectra (HRMS) and the corresponding low resolution spectra (EIMS and FABMS) were obtained on a VG TS-250 spectrometer by EI and fast atom bombardment (FAB) working at 70 eV and using nitrobenzyl alcohol as the matrix with xenon as the fast atom. Column chromatography (CC) was performed on silica gel (Merck no. 9385). TLCs were carried out on silica gel 60 F₂₅₄ (Merck, 0.25 mm thick) and were detected by UV. Solvents and reagents were purified by standard procedures as necessary.

Representative procedure for the synthesis of 1,3-dialkyl or 3-aryl-1-methyl-1H-indazoles: 1,3-dimethyl-1H-indazole (2a): An oven-dried resealable Schlenk tube was charged with CuO (4 mg, 2 mol %) and K₂CO₃ (150 mg, 1.5 mmol), evacuated, and back filled with argon. 2-chloroacetophenone (0.13 mL, 1 mmol) and methylhydrazine (0.35 mL, 6.4 mmol) were added under argon. The Schlenk tube was sealed, and the reaction was stirred magnetically at 110 °C for 20 h. The resulting suspension was cooled to room temperature, filtered, diluted with ethyl acetate and washed with water. The organic phase was concentrated. Purification of the residue by flash chromatography on silica gel (Hexane/EtOAc, 95:5) gave the desired product (34 mg, 54 % yield). Other compounds (**2c-2g**) were prepared similarly in 30-80 % yield. (Table 1)

1,3-dimethyl-1H-indazole (2a): Light yellow oil. ¹H NMR (200 MHz, CDCl₃) δ 7.66 (dd, *J* = 1.1, 8.0 Hz, 1H, ArH), 7.36 (ddd, *J* = 1.1, 7.6, 8.0 Hz, 1H, ArH), 7.35 (dd, *J* = 1.1, 8.0 Hz, 1H, ArH), 7.12 (ddd, *J* = 1.8, 7.6, 8.0 Hz, 1H, ArH), 3.99 (s, 3H, CH₃), 2.57 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 141.2, 129.4, 126.2, 124.1, 120.4, 119.6, 108.8, 35.1, 11.9. HRMS (*m/z*): calculated for C₉H₁₁N₂ [M+H]⁺, 147.0916; found, 147.0922.

3-ethyl-1-methyl-1H-indazole (2c): Light yellow oil. ¹H NMR (200 MHz, CDCl₃) δ 7.68 (d, *J* = 1.6, 8.0 Hz, 1H, ArH), 7.38 (ddd, *J* = 1.1, 7.7, 8.0 Hz, 1H, ArH), 7.31 (dd, *J* = 1.1, 8.3 Hz, 1H, ArH), 7.11 (ddd, *J* = 1.6, 7.7, 8.3 Hz, 1H, ArH), 4.00 (s, 3H, CH₃), 3.01 (q, *J* = 7.7 Hz, 2H, CH₂), 1.42 (t, *J* = 7.7 Hz, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 146.8, 141.0, 126.2, 122.5, 120.5, 119.5, 108.9, 35.1, 20.5, 13.8. HRMS (*m/z*): calculated for C₁₀H₁₃N₂ [M+H]⁺, 161.1073; found 161.1069.

1-methyl-3-phenyl-1H-indazole (2d): White crystals, m.p. 62-64 °C. ¹H NMR (200 MHz, CDCl₃) δ 8.07-7.98 (m, 3H, ArH), 7.58-7.44 (m, 4H, ArH), 7.42-7.19 (m, 2H, ArH), 4.14 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 143.8, 141.5, 133.8, 128.9, 127.9, 127.5, 126.3, 121.7, 121.4, 121.0, 109.3, 35.6. HRMS (*m/z*): calculated for C₁₄H₁₃N₂ [M+H]⁺, 209.1073; found 209.1081.

5-methoxy-1,3-dimethyl-1H-indazole (2e): White crystals, m.p. 66-68 °C. ¹H NMR (200 MHz, CDCl₃) δ 7.47 (d, *J* = 8.8 Hz, 1H, ArH), 6.74 (dd, *J* = 1.8, 8.8 Hz, 1H, ArH), 6.62 (d, *J* = 1.8 Hz, 1H, ArH), 3.91 (s, 3H, CH₃), 3.87 (s, 3H, CH₃), 2.50 (s, 3H, CH₃).

¹³C NMR (50.3 MHz, CDCl₃) δ 159.6, 142.0, 141.3, 121.2, 118.2, 111.6, 89.9, 55.5, 35.0, 11.8. HRMS (*m/z*): calculated for C₁₀H₁₃N₂O [M+H]⁺, 177.1022; found 177.1010.

5-chloro-1,3-dimethyl-1*H*-indazole (2f): Light yellow oil. ¹H NMR (200 MHz, CDCl₃) δ 7.60 (s, 1H, ArH), 7.31 (dd, *J* = 1.8, 8.8 Hz, 1H, ArH), 7.23 (d, *J* = 8.8 Hz, 1H, ArH), 3.98 (s, 3H, CH₃), 2.52 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 140.8, 139.3, 126.9, 125.3, 124.1, 119.7, 110.0, 35.3, 11.8. HRMS (*m/z*): calculated for C₉H₁₀N₂Cl [M+H]⁺, 181.0527; found 181.0529.

5-amino-1-methyl-3-phenyl-1*H*-indazole (2g): Brown crystals, m.p. 112-114 °C. ¹H NMR (200 MHz, CDCl₃) δ 7.92 (ddd, *J* = 1.5, 1.5, 8.8 Hz, 1H, ArH), 7.91 (d, *J* = 8.8 Hz, 1H, ArH), 7.51-7.20 (m, 4H, ArH), 7.24 (d, *J* = 1.8 Hz, 1H, ArH), 6.89 (dd, *J* = 1.1, 1.8 Hz, 1H, ArH), 4.06 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 140.7, 137.3, 134.2, 128.7, 127.4, 127.2, 122.5, 118.4, 110.0, 104.0, 35.6. HRMS (*m/z*): calculated for C₁₄H₁₄N₃ [M+H]⁺, 224.1182; found 224.1174.

1-*t*-butyl-3-methyl-1*H*-indazole (2h): Light yellow oil (40 mg, 22% yield). ¹H NMR (200 MHz, CDCl₃) δ 7.62 (dd, *J* = 1.1, 8.0 Hz, 1H, ArH), 7.22 (dd, *J* = 1.1, 7.6 Hz, 1H, ArH), 7.08 (m, 2H, ArH), 2.56 (s, 3H, CH₃), 1.76 (s, 9H, C-CH₃). ¹³C NMR (50.3 MHz, CDCl₃) 139.7, 130.8, 129.5, 125.4, 120.5, 119.2, 112.1, 47.2, 29.8, 12.0.

3-methyl-1-phenyl-1*H*-indazole (2i): Obtained following the general procedure by increasing the temperature at 200 °C. Light yellow oil (83 mg, 40% yield) ¹H NMR (200 MHz, CDCl₃) δ 7.75-7.18 (m, 9H, ArH), 2.67 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 144.1, 140.3, 139.5, 129.5, 127.3, 126.2, 124.9, 122.5, 120.9, 120.7, 110.4, 12.0. HRMS (*m/z*): calculated for C₁₄H₁₃N₂ [M+H]⁺, 209.1073; found 209.1071.

1-hydroxyethyl-3-methyl-1*H*-indazole (2j): Light brown crystals, m.p. 48-50 °C (53 mg, 30% yield). ¹H NMR (200 MHz, CDCl₃) δ 7.61 (dd, *J* = 1.1, 8.0 Hz, 1H, ArH), 7.35 (m, 2H, ArH), 7.13 (ddd, *J* = 1.1, 7.6, 8.0 Hz, 1H, ArH), 4.34 (t, *J* = 5.1 Hz, 2H, CH₂), 4.03 (t, *J* = 5.1 Hz, 2H, CH₂), 3.55 (s, 1H, OH), 2.49 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 142.0, 141.0, 126.6, 123.2, 120.5, 120.0, 109.0, 61.8, 50.2, 11.9. HRMS (*m/z*): calculated for C₁₀H₁₂N₂ONa [M+Na]⁺, 199.0842; found 199.0848.

Synthesis of 4: 1-chloroanthraquinone (242 mg, 1 mmol) was dissolved in 10 mL THF/DMA (1:1) and methylhydrazine (0.22 mL, 4 mmol) was dropwisely added under N₂. The reaction mixture was heated at 80 °C for 16h, then concentrated under vacuum, dissolved into EtOAc, washed with water, dried over Na₂SO₄, evaporated and the residue flash chromatographed on silica gel (Hexane/EtOAc, 9:1), affording **4** (200 mg, 83% yield). Yellow crystals, m.p. 184-185 °C. ¹H NMR (200 MHz, CDCl₃) δ 8.45 (dd,

$J = 1.1, 7.7$ Hz, 1H, ArH), 8.20 (dd, $J = 1.1, 7.7$ Hz, 1H, ArH), 8.04 (dd, $J = 1.8, 5.8$ Hz, 1H, ArH), 7.53 (ddd, $J = 1.1, 7.7, 7.7$ Hz, 1H, ArH), 7.50- 7.32 (m, 3H, ArH), 4.24 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 183.7, 139.5, 138.8, 133.3, 131.9, 129.3, 128.3, 126.5, 123.7, 122.6, 121.7, 120.7, 114.7, 36.4. HRMS (m/z): calculated for C₁₅H₁₁N₂O [M+H]⁺, 235.0865; found 235.0867.

Synthesis of 1-methyl-1*H*-indazol-3-ol (6a): An oven-dried resealable Schlenk tube was charged with CuO (4 mg, 2 mol %) and K₂CO₃ (150 mg, 1.5 mmol), evacuated, and back filled with argon. 2-chlorobenzoic acid or 2-bromobenzoic acid (1 mmol) was added and dissolved in benzene. Methylhydrazine (0.35 mL, 6.4 mmol) was added under argon. The Schlenk tube was sealed, and the mixture stirred magnetically at 110 °C for 20 h. The resulting suspension was cooled to room temperature, filtered and evaporated under vacuum. Purification by flash chromatography on silica gel (Cl₂CH₂/MeOH/AcOH, 95:5) gave the desired product (32 mg, 22% yield). ¹H NMR (200 MHz, CDCl₃) δ 8.12 (bs, 1H, OH), 7.76 (d, $J = 8.0$ Hz, 1H, ArH), 7.45 (t, $J = 8.0$ Hz, 1H, ArH), 7.27-7.20 (m, 1H, ArH), 7.09 (t, $J = 7.3$ Hz, 1H, ArH), 3.77 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 157.0, 142.3, 128.8, 121.4, 119.4, 112.8, 108.8, 34.8. HRMS (m/z): calculated for C₈H₈N₂ONa [M+Na]⁺, 171.0528; found 171.0542.

Compounds **6c-6e** and **8** were prepared similarly in 16-54% yield (Table 2)

5-methoxy-1-methyl-1*H*-indazol-3-ol (6c): ¹H NMR (200 MHz, CDCl₃) δ 7.12 (m, 3H, ArH), 3.85 (s, 3H, OCH₃), 3.77 (s, 3H, CH₃-N), 3.13 (s, 1H, OH). ¹³C NMR (50.3 MHz, CDCl₃) δ 157.0, 139.6, 129.8, 121.5, 112.4, 110.5, 100.6, 55.8, 35.7. HRMS (m/z): calculated for C₉H₁₀N₂O₂Na [M+Na]⁺, 201.0634; found 201.0645.

5-chloro-1-methyl-1*H*-indazol-3-ol (6d): ¹H NMR (200 MHz, CDCl₃) δ 7.74 (d, $J = 2.2$ Hz, 1H, ArH), 7.39 (dd, $J = 9.1$ and 2.2 Hz, 1H, ArH), 7.16 (d, $J = 9.1$ Hz, 1H, ArH), 3.84 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 151.3, 143.5, 143.2, 134.8, 131.3, 120.8, 110.2, 35.2. HRMS (m/z): calculated for C₈H₇N₂ONaCl [M+Na]⁺, 205.0139; found 205.0143.

5-amino-1-methyl-1*H*-indazol-3-ol (6e): ¹H NMR (200 MHz, CD₃OD) δ 7.04 (dd, $J = 1.8, 8.0$ Hz, 1H, ArH), 6.93 (d, $J = 8.04$ Hz, 1H, ArH), 6.92 (d, $J = 1.8$ Hz, 1H, ArH), 4.84 (bs, 3H, NH₂ and OH), 3.29 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CD₃OD) δ 161.0, 143.6, 142.4, 123.2, 117.4, 112.4, 106.6, 37.4. HRMS (m/z): calculated for C₈H₉N₃ONa [M+Na]⁺, 186.0638; found 186.0666.

1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-ol (8): Light brown crystals, m.p. 136-138 °C. ¹H NMR (200 MHz, CDCl₃) δ 8.46 (dd, $J = 1.8, 4.8$ Hz, 1H, ArH), 8.03 (dd, $J = 1.8, 7.7$

Hz, 1H, ArH), 7.77 (bs, 1H, OH), 6.94 (dd, $J = 4.8, 7.7$ Hz, 1H, ArH), 3.87 (s, 3H, CH₃). ¹³C NMR (50.3 MHz, CDCl₃) δ 154.9, 151.0, 150.4, 130.6, 115.1, 105.4, 32.9. HRMS (m/z): calculated for C₇H₈N₃O [M+H]⁺, 150.0662; found 150.0658.





























