Expanding the [1,2]-Aryl Migration to the Synthesis of Substituted Indoles

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Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds (30 pages).

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Experimental

General Methods. Reagents and solvents obtained from commercial suppliers were used without purification or drying unless otherwise noted. All reactions were conducted in standard RB-flasks under a nitrogen atmosphere. NMR spectra were obtained on Burker DPX-400 and DPX-500 spectrometer. Flash column chromatography was performed employing 200-400 mesh silica gel (Aldrich) eluting with mixtures of hexanes and ethyl acetate. HPLC was performed on an Agilent 1100 series machine using a Agilent ZORBAX (Eclipse Plus C18) column (4.6 x 50 mm, 1.8 Micron, 600 Bar), 1.50 mL/min flowrate, 215 nm detection, 28 °C column temperature; mobile phase MeCN /0.1 wt% aqueous H3PO4 10/90 ramp to 95/5 over 9 min and stay for 1 min.

Acylation of anilines: A modified procedure of Sugasawa reaction \[1\] was used to react anilines with nitriles.

1-(2-Amino-3-chlorophenyl)-2-chloroethanone (3). 2-Chloroaniline (12.76 g, 100 mmol) and chloroacetonitrile (8.88 g, 250 mmol) were added sequentially to a mixture of AlCl3 pellets (16.0 g, 120 mmol) and BCl3 solution (1.0 M in dichloromethane, 120 mL, 120 mmol) with extra 60 mL dichloromethane cooled in ice bath. The cloudy solution was stirred for 0.5 h at room temperature before being heated at reflux for 14 h. The reaction mixture was then cooled in ice bath, quenched with 2N HCl 150 mL, heated at reflux for 20 min, cooled, and extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over MgSO4, concentrated, and chromatographed to give 1-(2-Amino-3-chlorophenyl)-2-chloroethanone (3, 13.05 g, 64%) as a bright yellow solid. mp 104-106 °C.

\[1^H \text{NMR} (500 MHz, CDCl3): \delta 7.61 (dd, J = 8.2, 1.2 Hz, 1H), 7.46 (dd, J = 7.8, 1.2 Hz, 1H), 6.85 (bs, 2H), 6.63 (m, 1H), 4.68 (s, 2H). \]

\[1^3C \{^1H\} \text{NMR} (125 MHz, CDCl3): \delta 192.3, 147.2, 134.8, 129.5, 121.0, 116.0, 115.5, 46.5. \]

Anal. calcd (found) for C8H7Cl2NO: C, 47.09 (46.95); H, 3.46 (3.29); N, 6.86 (6.78).

The remaining substituted 1-(2-aminophenyl)-2-chloroethanones were synthesized analogous to that employed in the synthesis of 3.

1-(2-Amino-4,5,6-trifluorophenyl)-2-chloroethanone (6d): white solid, mp 105-106 °C. \[1^H \text{NMR} (500 MHz, CDCl3): \delta 6.39 (bs, 2H), 6.28 (ddd, J = 11.6, 6.0, 2.3 Hz, 1H), 4.68 (d, J = 4.7 Hz, 2H); \]

\[1^3C \{^1H\} \text{NMR} (125 MHz, CDCl3): \delta 190.1 (m), 156.5 (dd, J = 11.1, 6.8 Hz), 154.5 (dd, J = 11.1, 3.2 Hz), 153.8 (dd, J = 10.8, 6.5 Hz), 151.8 (dd, J = 11.8, 6.5 Hz), 148.0 (dd, J = 7.4, 12.9 Hz), 132.4 (m), 130.5 (dd, J = 17.2, 16.0 Hz), 103.0 (dt, J = 14.2, 2.5 Hz), 99.4 (ddd, J = 20.3, 3.1, 1.2 Hz), 50.6 (d, J = 18.4 Hz); \]

\[1^9F \{^1H\} \text{NMR} (470 MHz, CDCl3): \delta -124.7 (dd, J = 22.9, 13.7 Hz), -128.9 (dd, J = 22.9, 15.3 Hz), -175.6 (m). \]

Anal. calcd (found) for C8H5ClF3NO: C, 42.98 (42.64); H, 2.25 (2.09); N, 6.26 (6.78).

The remaining substituted 1-(2-aminophenyl)-2-chloroethanones were synthesized analogous to that employed in the synthesis of 3.

1-(2-Amino-3-chlorophenyl)-2-chloropropanone (8): yellow solid, mp 54-55 °C. \[1^H \text{NMR} (500 MHz, CDCl3): \delta 7.75 (dd, J = 8.2, 1.2 Hz, 1H), 7.47 (dd, J = 7.7, 1.3 Hz, 1H), 6.89 (bs, 2H), 6.65 (m, 1H), 5.30 (q, J = 6.6 Hz, 1H), 1.74 (d, J = 6.6 Hz, 3H). \]

NMR (125 MHz, CDCl₃): δ 195.0, 147.7, 134.6, 129.8, 121.0, 115.7, 115.3, 53.0, 20.3. Anal. calcd (found) for C₉H₅ClNO: C, 49.57 (49.35); H, 4.16 (4.07); N, 6.42 (6.35).

7-Chloro-2-propylindole (5a). To a solution of 1-(2-Amino-3-chlorophenyl)-2-chloroethanone (3) (204 mg, 1.00 mmol) in 2.0 mL toluene at −10 °C was added dropwise a solution of propylmagnesium chloride (2.0M in diethyl ether, 1.25 mL, 2.50 mmol). The reaction was kept <10 °C during addition and stirred in cold bath for 15 min before removal of the bath. After 20 min at room temperature, the mixture was quenched with diluted aqueous NH₄Cl, extracted with MTBE, washed with brine, and dried over MgSO₄. After concentration, the crude residue was chromatographed to give 7-chloro-2-propylindole (5a, 157 mg, 81%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.08, (bs, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.03 (m, 1H), 6.31 (s, 1H), 2.78 (t, J = 7.5 Hz, 2H), 1.80 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H). ¹³C ¹H NMR (125 MHz, CDCl₃): δ 137.9, 134.4, 133.4, 130.3, 120.7, 120.5, 118.6, 117.7, 116.0, 101.4, 32.8. HRMS calcd (found) for C₁₉H₁₉ClN (M+H⁺): 298.1206 (298.1198).

The remaining indoles were synthesized analogous to that employed in the synthesis of 5a.

2-Allyl-7-chloroindole (5b): pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.13 (bs, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.18 (dd, J = 7.6, 0.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.37 (m, 1H), 6.06 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 5.28 (m, 2H), 3.58 (m, 2H). ¹³C ¹H NMR (125 MHz, CDCl₃): δ 137.9, 133.4, 130.3, 120.7, 120.5, 118.6, 117.7, 116.0, 101.4, 32.8. HRMS calcd (found) for C₁₉H₁₉ClN (M+H⁺): 298.1206 (298.1198).

7-Chloro-2-(2-[1,3]-dioxan-2-ylethyl)indole (5c): pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.41 (m, 1H), 2.05 (m, 2H), 2.20 (m, 1H), 2.95 (t, J = 7.1 Hz, 2H), 3.82 (m, 2H), 4.20 (m, 2H), 4.66 (t, J = 4.8 Hz, 1H), 6.27 (d, J = 1.8 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 8.72 (br s, 1H). ¹³C ¹H NMR (100 MHz, CDCl₃): δ 140.1, 133.2, 130.2, 120.2, 120.2, 118.4, 115.9, 100.2, 100.5, 67.0, 34.1, 25.7, 22.2. HRMS calcd (found) for C₁₇H₁₇ClINO (M+H⁺): 286.0994 (286.0954).

2-Trimethylsilylmethylindole (5f): pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 0.11 (s, 9H), 2.21 (s, 2H), 6.11 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 7.37 (m, 1H), 7.85 (br s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 138.8, 132.9, 131.0, 120.3, 118.3, 115.8, 100.5, 31.6, 29.1, 29.0, 28.3, 22.7, 14.1. HRMS calcd (found) for C₁₉H₁₉ClN (M+H⁺): 290.1626 (290.1618).

2-Trimethylsilylmethylindole (5f): pale yellow solid, mp 118-120 °C. ¹H NMR (400 MHz, CDCl₃): δ 9.68 (bs, 1H), 8.62 (m, 1H), 7.79 (m, 1H), 7.73 (td, J = 7.3, 1.7 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.21 (m, 2H), 7.06 (t, J = 7.8 Hz, 1H), 7.04 (d,
7-Chloro-2-pyridin-3-ylindole (5j): white solid, mp 86-88°C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.38 (bs, 1H), 7.52 (d, \(J = 7.9\) Hz, 1H), 7.34 (m, 2H), 7.22 (dd, \(J = 7.6, 0.6\) Hz, 1H), 7.12 (dd, \(J = 5.0, 3.7\) Hz, 1H), 7.06 (t, \(J = 7.9\) Hz, 1H), 6.81 (d, \(J = 2.2\) Hz, 1H), 0.31 (s, 9H). \(^{13}\)C \(^1\)H NMR (100 MHz, CDCl\(_3\)): \(\delta\) 133.1, 128.7, 122.7, 121.1, 119.4, 119.3, 116.1, 109.8, 99.2, 96.1, −0.3. Anal. calcd (found) for C\(_{13}\)H\(_{14}\)ClN\(_3\): C, 61.01 (61.01); H, 5.65 (5.65).

7-Chloro-2-thien-2-ylindole (5j): white solid, mp 145-147°C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.15 (bs, 1H), 7.62 (m, 2H), 7.43 (m, 3H), 7.30 (s, 1H), 6.94 (s, 1H), 6.84 (d, \(J = 2.0\) Hz, 1H), 2.49 (s, 3H), 2.48 (s, 3H). \(^{13}\)C \(^1\)H NMR (125 MHz, CDCl\(_3\)): \(\delta\) 134.3, 131.5, 131.0, 128.6, 128.5, 127.7, 125.9, 122.8, 119.7, 118.5, 118.1, 109.0, 92.4, 82.3, 21.4, 16.6. HRMS calcd (found) for C\(_{18}\)H\(_{16}\)ClN (M+H): 246.1283 (246.1278).

7-Fluoro-5-methyl-2-pyridin-3-ylindole (7f): white solid, mp 145-147°C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.37 (bs, 1H), 7.68 (d, \(J = 7.2\) Hz, 2H), 7.47 (t, \(J = 7.7\) Hz, 2H), 7.37 (t, \(J = 7.4\) Hz, 1H), 7.21 (s, 1H), 6.79 (m, 2H), 2.47 (s, 3H). \(^{13}\)C \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 148.7, 145.3, 135.1, 135.0, 134.8, 130.5, 129.6, 124.7, 122.6, 121.1, 119.5, 117.0, 102.4. HRMS calcd (found) for C\(_{13}\)H\(_{16}\)ClN\(_2\) (M+H): 229.0533 (229.0533).

7-Chloro-2-pyridin-3-ylindole (5i): white solid, mp 207-209°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.93 (dd, \(J = 2.3, 0.7\) Hz, 1H), 8.40 (dd, \(J = 5.0, 1.5\) Hz, 1H), 8.13 (dt, \(J = 8.0, 2.0\) Hz, 1H), 7.43 (m, 1H), 7.40 (m, 1H), 7.10 (dd, \(J = 7.6, 1.0\) Hz, 1H), 6.95 (t, \(J = 7.7\) Hz, 1H), 6.84 (s, 1H). \(^{13}\)C \(^1\)H NMR (100 MHz, CDCl\(_3\) & CD\(_2\)COD): \(\delta\) 146.7, 145.3, 135.1, 135.0, 134.8, 130.5, 129.6, 124.7, 122.6, 121.1, 119.5, 117.0, 102.4. HRMS calcd (found) for C\(_{13}\)H\(_{10}\)ClN\(_2\) (M+H): 229.0533 (229.0533).
NMR (125 MHz, CDCl₃): δ 149.0 (d, J = 243.0 Hz), 138.8, 132.9 (d, J = 4.9 Hz), 132.0, 130.5 (d, J = 5.6 Hz), 129.1, 128.0, 125.2, 123.3 (d, J = 12.9 Hz), 115.9 (d, J = 3.1 Hz), 108.7 (d, J = 16.0 Hz), 100.1 (d, J = 2.4 Hz), 21.5. 

7-Chloro-3-methyl-2-propylindole (9a): pale yellow oil. 

1H NMR (500 MHz, CDCl₃): δ 7.95 (bs, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 7.5, 0.6 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 2.77 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.77 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H). 

13C {1H} NMR (125 MHz, CDCl₃): δ 136.1, 132.4, 131.0, 120.4, 119.8, 116.8, 115.8, 108.2, 28.2, 23.0, 13.9, 8.7. 

HRMS calcd (found) for C₁₃H₁₂FN: C, 79.98 (79.71); H, 5.37 (5.32); N, 6.22 (6.06).

7-Chloro-3-methyl-2-thien-2-ylindole (9b): off-white solid; mp 111-112 °C; 

1H NMR (400 MHz, CDCl₃): δ 2.49 (s, 3H), 7.08 (m, 1H), 7.18 (m, 2H), 7.30 (m, 1H), 7.40 (m, 1H), 7.48 (d, J = 7.9 Hz, 1H), 8.17 (br s, 1H). 

13C NMR (125 MHz, CDCl₃): δ 134.6, 133.0, 131.3, 129.2, 127.7, 125.4, 124.7, 121.9, 120.5, 117.6, 116.0, 110.4, 10.0. 

HRMS calcd (found) for C₁₃H₁₁ClN (M+H): 208.0893 (208.0889).

2-(N-trimethylacetyl-2-aminophenyl)indole (15): pale brown oil; 

1H NMR (500 MHz, CDCl₃): δ 1.22 (s, 9H), 6.65 (s, 1H), 7.20 (m, 2H), 7.26 (m, 1H), 7.39 (m, 1H), 7.45 (m, 2H), 7.68 (d, J = 7.9 Hz, 1H), 8.22 (br s, 1H), 8.39 (d, J = 7.9 Hz, 1H), 8.44 (br s, 1H). 

13C NMR (125 MHz, CDCl₃): δ 177.2, 136.6, 135.8, 134.2, 129.3, 128.7, 124.3, 123.7, 122.8, 121.7, 120.7, 120.6, 120.5, 111.1, 102.6, 39.9, 27.5. 

HRMS calcd (found) for C₁₉H₁₉N₂O (M+H): [293.1654 (293.1660)].

1-(2-Amino-3-chlorophenyl)-2-chloro-1-D-ethan-1-ol (16). To a solution of 1-(2-amino-3-chlorophenyl)-2-chloroethan-1-ol (3, 1.02 g, 5.0 mmol) in 1,4-dioxane (9.0 mL) and water (1.0 mL) was added NaBD₄ (256 mg, 6.0 mmol) at room temperature, aged for 1 h, quenched with saturated NH₄Cl, extracted with MTBE, washed with brine, and dried over MgSO₄. After concentration, the crude residue was chromatographed to give alcohol 16 (0.78g, 75%) as a white solid. 

mp 61-63 °C; 

1H NMR (500 MHz, CDCl₃): δ 7.24 (dd, J = 7.9, 1.5 Hz, 1H), 6.97 (dd, J = 7.7, 1.4 Hz, 1H), 6.66 (m, 1H), 4.01 (d, J = 11.3 Hz, 1H), 3.74 (d, J = 11.3 Hz, 1H). 

13C {1H} NMR (125 MHz, CDCl₃): δ 142.0, 129.6, 126.8, 123.6, 120.9, 118.1, 74.6 (t, J = 22.5 Hz), 47.8. 

HRMS calcd (found) for C₈H₆Cl₂NO (M+H): [207.0202 (207.0201)].

7-Chloro-2-D-indole (17). To a solution of 1-(2-amino-3-chlorophenyl)-2-chloro-1-D-ethan-1-ol (16, 207 mg, 1.0 mmol) in THF (2.0 mL) cooled at −10 °C was added tPrMgCl (2.0 M in THF, 1.25 mL, 2.5 mmol), warmed to room temperature, aged for 1 h, quenched with saturated NH₄Cl, extracted with MTBE, washed with brine, and dried over MgSO₄. After concentration, the crude residue was chromatographed to give indole 17 (105 mg, 69%) as a white solid. 

mp 52-54 °C; 

1H NMR (500 MHz, CDCl₃): δ 8.35, 7.61 (d, J = 7.9 Hz, 1H), 7.27 (dd, J = 7.6, 0.9 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H). 

13C {1H} NMR (125 MHz, CDCl₃): δ 133.2, 129.4, 124.6 (t, J = 28.0 Hz), 121.4, 120.7, 119.4, 116.7, 103.6. 

HRMS calcd (found) for C₈H₆DCIN (M+H): [153.0330 (153.0325)].
1-(2-Amino-3-chlorophenyl)-2-chloroethanone (3).
7-Chloro-2-propylindole (5a).
2-Allyl-7-chloroindole (5b).
2-Chloro-2-(2-[1,3]-dioxan-2-ylethyl)indole (5c).
7-Chloro-2-cyclopropylindole (5d).
7-Chloro-2-hexan-1-ylindole (5e):
7-Chloro-2-pyridin-2-ylindole (5h).
7-Chloro-2-pyridin-3-yldole (5i).
7-Chloro-2-thien-2-ylindole (5j).
7-Chloro-2-(2-trimethylsilylacetyln-1-yl)indole (5k).
7-Chloro-2-hexyn-1-ylindole (5l).
1-(2-Amino-4,5,6-trifluorophenyl)-2-chloroethanone (6d).
1-(2-Amino-3-fluoro-5-methylphenyl)-2-chloroethanone (6f).
4,5,6-Trifluoro-2-propylindole (7d).
5,7-Dimethyl-2-phenylethynylindole (7e).
7-Fluoro-5-methyl-2-phenylnindole (7f).
1-(2-Amino-3-chlorophenyl)-2-chloropropan-1-one (8).
7-Chloro-3-methyl-2-propylindole (9a).
7-Chloro-3-methyl-2-thien-2-ylindole (9b).
2-((N-trimethylacetyl-2-aminophenyl)indole (15):
1-(2-Amino-3-chlorophenyl)-2-chloro-1-D-ethan-1-ol (16).
7-Chloro-2-D-indole (17).