Synthesis of benzimidazoles by potassium tert-butoxide-promoted intermolecular cyclization reaction of 2-iodoanilines with nitriles

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General Remarks

General: All manipulations were conducted with Schlenk tube. $^1$H NMR spectra were recorded on the Varian 400 MHz WB spectrometers. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) as an internal standard in CDCl$_3$ and DMSO-d$_6$. $^{13}$C NMR spectra were obtained by the same NMR spectrometers and were calibrated with CDCl$_3$ ($\delta = 77.00$ ppm) or DMSO-d$_6$ ($\delta = 39.50$ ppm). Mass spectra were obtained using electrospray ionization (ESI) mass spectrometer. All nitriles and solvents were freshly distilled over CaH$_2$ (This operation is very important for these reactions). Unless otherwise noted, other materials obtained from commercial suppliers were used without further purification.

Experimental Section

2-Phenyl-benzimidazole (3a)$^1$

Typical Procedure: General procedure for the synthesis of 2-phenyl-benzimidazole 3a: 2-iodoaniline 1a (65.7 mg, 0.3 mmol), KOBu' (102 mg, 0.9 mmol), DMAc (1.0 mL) were mixed in a Schlenck tube under Ar. To the mixture was added benzonitrile 2a (61.8 mg, 0.3 mmol) under Ar. The reaction mixture was stirred for 24 h at 120 °C under Ar. The solution was cooled to room temperature and cold saturated aqueous solution of NaCl was added slowly. The crude product was purified by column chromatography on silica gel. (eluent: petroleum ether / acetone = 5:1) to afford 54.2 mg (93%) white solid 3a; mp: 294-295°C; IR:(KBr) $\nu$ max 3047, 1622, 1591, 1463, 1277, 1005, 687, 495 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$, ppm) $\delta$ 12.96 (br s, 1H), 8.21-8.18 (m, 2H), 7.68 (br s, 1H), 7.59-7.45 (m, 4H), 7.26-7.17 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm) $\delta$ 151.3, 143.8, 135.0, 130.2, 129.9 (broad peak), 129.0 (broad peak), 126.5 (broad peak), 122.6 (broad peak), 121.8 (broad peak), 118.9, 111.5 (broad peak); MS (ESI) m/z: [M+H]$^+$ 195.1.

5-Methyl-2-phenyl-benzimidazole (3b)$^2$

The reaction of 2-iodo-5-methylaniline 1c (69.9 mg, 0.3 mmol), benzonitrile 2a (61.9 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 56.5 mg (91%) white solid 3b; mp: 294-295°C; IR:(KBr) $\nu$ max 3047, 1622, 1591, 1463, 1400, 1112, 766 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$, ppm) $\delta$ 12.78 (br s, 1H), 8.21-8.18 (m, 2H), 7.68 (br s, 1H), 7.59-7.45 (m, 4H), 7.26-7.17 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm) $\delta$ 151.3, 143.8, 135.0, 130.2, 129.9 (broad peak), 129.0 (broad peak), 126.5 (broad peak), 122.6 (broad peak), 121.8 (broad peak), 118.9, 111.5 (broad peak); MS (ESI)m/z: [M+H]$^+$ 209.1.
5-Chloro-2-phenyl-benzimidazole (3c)

The reaction of 4-chloro-2-iodoaniline (1d) (75.9 mg, 0.3 mmol), benzonitrile (2a) (61.9 mg, 0.6 mmol), KOBu (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 80 °C afforded 56.3 mg (82%) white solid (3c); mp: 294-295°C; IR: (KBr) ν max 3043, 1624, 1451, 1439, 1384, 1107, 1062 cm⁻¹; ¹H NMR (400 MHz, DMSO-d6, ppm) δ 13.16 (br s, 1H), 8.20-8.18 (m, 2H), 7.76-7.51 (m, 5H), 7.27-7.22 (m, 1H); ¹³C NMR (100 MHz, DMSO-d6, ppm) δ 152.9, 152.5, 144.8, 142.7, 135.8, 133.9, 132.6, 130.2, 129.7, 129.2, 129.0, 128.7, 128.4, 126.9, 126.6, 126.1, 122.7, 122.1, 120.1, 118.3, 112.7, 111.1; MS (ESI) m/z: [M+H]+ 229.1.

5-Bromo-2-phenyl-benzimidazole (3d)

The reaction of 4-bromo-2-iodoaniline (1f) (69.9 mg, 0.3 mmol), benzonitrile (2a) (61.9 mg, 0.6 mmol), KOBu (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 100 °C afforded 68.5 mg (84%) brown solid (3d); mp: 206-208°C; IR: (KBr) ν max 1621, 1467, 1444, 1422, 1397, 1304, 1277, 1109 cm⁻¹; ¹H NMR (400 MHz, DMSO-d6, ppm) δ 13.16 (br s, 1H), 8.19 (d, J = 6.8 Hz, 2H), 7.88 (br s, 1H), 7.71-7.50 (m, 4H), 7.37 (m, 1H); ¹³C NMR (100 MHz, DMSO-d6, ppm) δ 152.7, 152.4, 145.3, 143.0, 136.3, 134.1, 130.2, 129.7, 129.2, 129.0, 126.9, 126.6, 125.2, 124.8, 121.3, 120.6, 114.8, 114.0, 113.1; MS (ESI) m/z: [M+H]+ 273.1.

5-Iodo-2-phenyl-benzimidazole (3e)

The reaction of 2,4-diiodoaniline (1h) (103.5 mg, 0.3 mmol), benzonitrile (2a) (61.9 mg, 0.6 mmol), KOBu (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 100 °C afforded 71.9 mg (75%) beige solid (3e); mp: 209-210°C; IR: (KBr) ν max 1464, 1394 cm⁻¹; ¹H NMR (400 MHz, DMSO-d6, ppm) δ 13.08 (br s, 1H), 8.17 (d, J = 6.8 Hz 2H), 7.95 (br s, 1H), 7.60-7.38 (m, 5H); ¹³C NMR (100 MHz, DMSO-d6, ppm) δ 152.1, 151.9, 145.9, 143.3, 136.9, 134.5, 130.7, 130.3, 130.2, 129.6, 129.0, 127.3, 126.6, 121.0, 119.8, 113.6, 86.3, 85.3; MS (ESI) m/z: [M+H]+ 321.0.

5-Fluoro-2-phenyl-benzimidazole (3f)

The reaction of 4-fluoro-2-iodoaniline (1i) (71.1 mg, 0.3 mmol), benzonitrile (2a) (61.9
mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 80 °C afforded 26.1 mg (41%) brown solid 3f; mp: 245-246°C; IR:(KBr) νmax 3043, 1467, 1407 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, ppm) δ 13.07 (br s, 1H), 8.18-8.16 (m, 2H), 7.70-7.32 (m, 5H), 7.12-7.03 (m, 1H); ¹³C NMR (100 MHz, DMSO-d₆, ppm) δ 159.8, 157.6, 153.0, 144.2, 140.5, 135.2, 131.7, 130.1, 129.9, 129.0, 126.5, 119.8, 112.1, 110.4, 104.4, 97.8; MS (ESI) m/z: [M+H]⁺ 213.1.

2-(2-Methylphenyl)-benzimidazole (3g)⁴

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 2-methylbenzonitrile 2b (70.3 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 22.0 mg (35%) white solid 3g; mp: 226-227°C; IR:(KBr) νmax 2876, 1605, 1541, 1445, 1409, 1366, 1315, 1273, 1227, 1091, 766, 747, 733, 455 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, ppm) δ 12.62 (br s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.41-7.36 (m, 3H), 7.24-7.19 (m, 2H), 2.61 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆, ppm) δ 151.9, 143.7, 137.0, 134.4, 131.3, 130.1, 129.5, 129.3, 126.0, 122.4, 121.4, 118.9, 111.3, 21.1; MS (ESI) m/z: [M+H]⁺ 209.1.

2-(3-Methylphenyl)-benzimidazole (3h)²

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 3-methylbenzonitrile 2c (70.3 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 52.4 mg (84%) white solid 3h; mp: 224-225°C; IR:(KBr) νmax 2878, 1624, 1447, 1404, 1359, 1316, 1275, 1228 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, ppm) δ 12.87 (br s, 1H), 8.04-8.03 (m, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.65-7.52 (m, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.33-7.30 (m, 1H), 7.21-7.19 (m, 2H), 2.42 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆, ppm) δ 151.4, 138.2, 130.5, 130.1, 128.8, 127.0, 123.0, 122.1, 118.5, 111.5, 21.1; MS (ESI) m/z: [M+H]⁺ 209.1.

2-(4-Methylphenyl)-benzimidazole (3i)¹

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 4-methylbenzonitrile 2d (70.3 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 57.4 mg (92%) white solid 3i; mp: 279-280°C; IR:(KBr) νmax 3052, 2962, 2914, 1619, 1588, 1500, 1446, 1430, 1273 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆,
ppm) δ 12.84 (br s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.64-7.52 (m, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.20-7.18 (m, 2H), 2.38 (s, 3H); 13C NMR (100 MHz, DMSO-d6, ppm) δ 151.4, 139.6, 129.5, 127.5, 126.4, 122.0, 21.0; MS (ESI) m/z: [M+H]+ 209.1.

2-(4-Methoxyphenyl)-benzimidazole (3j)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 4-methoxybenzonitrile 2e (79.8 mg, 0.6 mmol), KOBu’ (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 61.2 mg (91%) white solid 3j; mp: 232-233°C; IR:(KBr) νmax 3052, 1611, 1581, 1454, 1233, 764, 694 cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d6, ppm) δ 12.77 (br s, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.20-7.10 (m, 4H), 3.84(s, 3H); 13C NMR (100 MHz, DMSO-d6, ppm) δ 160.6, 151.4, 128.1, 122.7, 121.8, 114.4, 55.3; MS (ESI) m/z: [M+H]+ 225.1.

2-(4-Chlorophenyl)-benzimidazole (3k)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 4-chlorobenzonitrile 2f (82.2 mg, 0.6 mmol), KOBu’ (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 40.8 mg (60%) white solid 3k; mp: 304-305°C; IR:(KBr) νmax 3051, 1586, 1491, 1273, 1108, 1016, 765, 288, 471, 434 cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d6, ppm) δ 13.02 (br s, 1H), 8.22-8.19 (m, 2H), 7.70-7.63 (m, 3H), 7.55 (br s, 1H), 7.27-7.18 (m, 2H); 13C NMR (100 MHz, DMSO-d6, ppm) δ 150.2, 143.8, 135.0, 134.5, 129.1, 129.07, 128.2, 122.8, 121.9, 119.0, 111.4; MS (ESI) m/z: [M+H]+ 229.1.

2-(4-Iodophenyl)-benzimidazole (3l)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 4-iodobenzonitrile 2g (137.4 mg, 0.6 mmol), KOBu’ (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 120 °C afforded 55.1mg (57%) white solid 3l; mp: 303-304°C; IR:(KBr) νmax 2970, 1447, 1424, 1315, 1059, 828, 742 cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d6, ppm) δ 13.00 (br s, 1H), 7.98-7.92 (m, 4H), 7.67 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.24-7.19 (m, 2H); 13C NMR (100 MHz, DMSO-d6, ppm) δ 150.4, 143.7, 137.8, 135.0, 129.7, 128.3, 122.8, 121.9, 119.0, 111.5, 96.8; MS (ESI) m/z: [M+H]+ 321.0.
2-(4-Fluorophenyl)-benzimidazole (3m)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), 4-fluorobenzonitrile 2h (72.6 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 80 °C afforded 38.5 mg (61%) orange solid 3m; mp: 254-255°C; IR:(KBr) \( \nu_{\text{max}} \) 3053, 1603, 1397, 1228, 795, 747 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\), ppm) \( \delta \) 12.93 (br s, 1H), 8.24-8.20 (m, 2H), 7.68-7.65 (m, 2H), 7.55-7.39 (m, 2H), 7.22-7.21 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\), ppm) \( \delta \) 163.1 (d, \( J = 246.5 \) Hz), 150.5, 143.8, 135.1, 128.8, 128.7, 126.9 (d, \( J = 2.3 \) Hz), 122.2 (d, \( J = 81.2 \) Hz); 118.9, 116.1 (d, \( J = 21.6 \) Hz), 111.4; MS (ESI) m/z: [M+H]\(^{+}\) 213.1.

2-(Furan-2-yl)-benzimidazole (3n)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), furan-2-carbonitrile 2i (55.8 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 100 °C afforded 34.2 mg (62%) white solid 3n; mp: 279-280°C; IR:(KBr) \( \nu_{\text{max}} \) 3058, 1631, 1525, 1417, 1364, 1279, 1234 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\), ppm) \( \delta \) 12.94 (br s, 1H), 7.96-7.95 (m, 1H), 7.63 (d, \( J = 8.0 \) Hz, 1H), 7.50 (d, \( J = 7.2 \) Hz, 1H), 7.24-7.17 (m, 3H), 6.75-6.73 (m, 1H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\), ppm) \( \delta \) 145.6, 144.7, 143.7, 134.3, 122.7, 121.8, 118.8, 112.4, 111.4, 110.5; MS (ESI) m/z: [M+H]\(^{+}\) 185.1.

2-(Thien-2-yl)-benzimidazole (3o)

The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), thiophene-2-carbonitrile 2j (65.4 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 100 °C afforded 45.8 mg (76%) yellow solid 3o; mp: 312-313°C; IR:(KBr) \( \nu_{\text{max}} \) 3047, 3009, 1571, 1451, 1424, 1314, 1276, 1235 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\), ppm) \( \delta \) 12.94 (br s, 1H), 7.84 (d, \( J = 2.8 \) Hz, 1H), 7.73 (d, \( J = 4.8 \) Hz, 1H), 7.59-7.52 (m, 2H), 7.25-7.19 (m, 3H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\), ppm) \( \delta \) 147.1, 133.7, 128.8, 128.7, 128.33, 128.28, 126.73, 126.68, 122.2 (broad peak), 118.5 (broad peak), 111.1 (broad peak); MS (ESI) m/z: [M+H]\(^{+}\) 201.1.

N-(2-Iodophenyl)benzimidamide (5a)
The reaction of 2-iodoaniline 1a (65.7 mg, 0.3 mmol), benzonitrile 2b (70.3 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 25 °C afforded 87.1 mg (90%) white solid 5a; mp: 110-112°C; IR:(KBr) ν_{max} 3446, 3296, 3147, 3051, 1632, 1564, 1386, 1014, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6, ppm) δ 8.02 (d, J = 5.6 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 7.2 Hz, 3H), 7.35-7.31 (m, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.78-6.74 (m, 1H), 6.42 (br s, 2H); ^13C NMR (100 MHz, DMSO-d6, ppm) δ 154.0, 151.8, 138.6, 135.5, 130.3, 129.4, 128.0, 127.4, 121.8, 94.0; MS (ESI) m/z: [M+H]^+ 323.0.

6-Methyl-2-(p-tolyl)-benzimidazole (3p)^7

The reaction of 2-iodo-4-methylaniline 1c (69.9 mg, 0.3 mmol), 4-methylbenzonitrile 2d (70.3 mg, 0.6 mmol), KOBu' (101.1 mg, 0.9 mmol), DMAc (1.0 mL) under Ar at 100°C afforded 53.0 mg (80%) white solid 3p; mp: 168-169°C; IR:(KBr) ν_{max} 3024, 2955, 2855, 1911, 1717, 1660, 1631, 1447, 803 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6, ppm) δ 12.69 (br s, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.49-7.33 (m, 4H), 7.02 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H), 2.38 (s, 3H); ^13C NMR (100 MHz, DMSO-d6, ppm) δ 151.1, 139.4, 131.1, 129.5, 127.6, 126.4, 123.4, 114.9, 21.4, 21.0; MS (ESI) m/z: [M+H]^+ 223.1.

N,N-Dimethyl-2-(6-methyl-2-(p-tolyl)-benzimidazol-1-yl)acetamide and N,N-Dimethyl-2-(5-methyl-2-(p-tolyl)-benzimidazol-1-yl)acetamide (7 and 7')^7

The compounds 7 and 7' were synthesized according to literature’s method^7 with yield of 66% (7/7' = 1:1, the ratio was determined by ^1H NMR on the crude products); white solid; mp: 110-113°C; IR:(KBr) ν_{max} 3030, 2920, 1653, 1449,1146, 807 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6, ppm) δ 7.69 (d, J = 8.8 Hz, 1H), 7.59-7.56 (m, 5H), 7.30-7.28 (m, 4H), 7.13-7.07 (m, 3H), 7.01 (s, 1H), 4.88 (s, 2H), 4.87 (s, 2H), 3.05-2.30 (m, 12H), 2.48 (s, 6H), 2.42 (s, 6H); MS (ESI) m/z: [M+H]^+ 308.2.

Reference:
716-719.


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[Diagram of a molecule with peaks labeled 7.597, 7.542, 7.239, 7.197 in ppm]

[Diagram of a molecule with peaks labeled 4.03, 1.00, 2.04 in ppm]
and

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