SUPPORTING INFORMATION

A Versatile Synthesis of 3,5-Disubstituted 2-Fluoropyridines and 2-Pyridones

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General comments.

All solvents were purified and dried, as required, according to standard literature procedures. 5-bromo-2-fluoropyridine (**3**) was purchased from Aldrich and used without further purification. BuLi refers to *n*-BuLi. Light petroleum refers to the fraction boiling in the range 40-60 °C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass Spectra were obtained on a Fisons VG Analytical Autospec spectrometer using CI (CH₄ as reagent gas). ¹H, ¹³C, ¹⁹F NMR spectra were recorded on a JEOL JNM-GX270, JEOL JNM-LA300 or JEOL JNM-GX400 spectrometer. Chemical shift values are given in parts per million and *J* values are reported in Hz, and proton and carbon assignments are based on two-dimensional (COSY) and DEPT experiments.

2-Fluoro-3-phenylpyridine (8).¹ This compound was isolated using the above procedure except that the reaction mixture was heated under reflux for 6 h. IR (film) ν (cm^{-1}): 3060, 1600, 1449, 1423, 1413, 1242, 1204, 848, 770, 695. ^1H NMR (400 MHz, CDCl_3): 8.21 (1 H, br d, $J = 4.8$ Hz, 6-H), 7.88 (1 H, ddd, $J = 9.3, 7.4, 2.0$ Hz, 4-H), 7.60-7.38 (5 H, m, Ph), 7.28 (1 H, ddd, $J = 7.4, 4.8, 1.9$ Hz, 5-H). ^{13}C NMR (100.5 MHz, CDCl_3): 161.3 (d, $J = 234.3$ Hz, C), 146.4 (d, $J = 14.6$ Hz, CH), 140.7 (d, $J = 4.6$ Hz, CH), 134.2 (C), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.5 (CH), 124.0 (d, $J = 9.0$ Hz, CH), 121.8 (CH). HRMS: calcd for $\text{C}_{11}\text{H}_9\text{NF}$ (MH^+), 174.0719; found, 174.0715.

5-Bromo-2-fluoro-3-phenylpyridine (4a). IR (film) ν (cm^{-1}): 3062, 1588, 1554, 1455, 1420, 1241, 1198, 1015, 899, 773, 730, 695. ^1H NMR (400 MHz, CDCl_3): 8.23 (1 H, br s, 6-H), 7.98 (1 H, dd, $J = 8.8, 2.4$ Hz, 4-H), 7.59-7.41 (5 H, m, Ph). ^{13}C NMR (100.5 MHz, CDCl_3): 159.4 (d, $J = 242.1$ Hz, C), 146.8 (d, $J = 15.4$ Hz, CH), 142.8 (d, $J = 4.6$ Hz, CH), 132.9 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.8 (CH), 125.8 (d, $J = 30.0$ Hz, C), 116.7 (d, $J = 4.6$ Hz, C). HRMS: calcd for $\text{C}_{11}\text{H}_8\text{NF}^{79}\text{Br}$ (MH^+), 251.9824; found, 251.9823.

5-Bromo-2-fluoro-3-(4'-nitrophenyl)pyridine (4b). mp 115-117 °C (from diethyl ether / hexane). IR (neat) ν (cm^{-1}): 3077, 1601, 1510, 1441, 1403, 1346, 1028, 858, 850, 739, 695. ^1H NMR (400 MHz, CDCl_3): 8.38-8.33 (3 H, m, 6-H, 3'-H and 5'-H), 8.40 (1 H, dd, $J = 8.4, 2.6$ Hz, 4-H), 7.75 (1 H, br d, $J = 7.7$ Hz, 2'-H and 6'-H). ^{13}C NMR (100.5 MHz, CDCl_3): 159.0 (d, $J = 242.0$ Hz, C), 148.6 (d, $J = 16.1$ Hz, CH), 148.2 (C), 142.8 (d, $J = 3.9$ Hz, CH), 138.9 (C), 129.83 (CH), 129.8 (CH), 124.1 (CH), 123.4 (d, $J = 30.0$ Hz, C), 117.1 (d, $J = 4.6$ Hz, C). HRMS: calcd for $\text{C}_{11}\text{H}_7\text{N}_2\text{O}_2\text{F}^{79}\text{Br}$ (MH^+), 296.9675; found, 296.9683.

5-Bromo-2-fluoro-3-(2'-methylphenyl)pyridine (4c). IR (film) ν (cm^{-1}): 3062, 1592, 1553, 1421, 1276, 1240, 1192, 1018, 902, 770, 727. ^1H NMR (270 MHz, CDCl_3): 8.28 (1 H, br s, 6-H), 7.82 (1 H, dd, $J = 8.3, 2.6$ Hz, 4-H), 7.39-7.16 (4 H, m, Ar-H), 2.22 (3 H, s, Me). ^{13}C NMR (100.5 MHz, CDCl_3): 159.5 (d, $J = 239.8$ Hz, C), 147.4 (d, $J = 14.6$ Hz, CH), 144.1 (d, $J = 5.3$ Hz, CH), 136.5 (C), 132.5 (d, $J = 3.8$ Hz, C), 130.5 (CH), 129.9 (CH), 129.2 (CH), 126.1 (CH), 125.7 (d, $J = 30.0$ Hz, C), 116.3 (C), 19.8 (CH_3). HRMS: calcd for $\text{C}_{12}\text{H}_{10}\text{NF}^{79}\text{Br}$ (MH^+), 265.9981; found, 265.9975.

5-Bromo-2-fluoro-3-(4'-methoxyphenyl)pyridine (4d). mp 66-68 $^{\circ}\text{C}$ (from diethyl ether / hexane). IR (neat) ν (cm^{-1}): 2934, 1608, 1516, 1437, 1407, 1245, 1179, 1037, 1021, 831, 705. ^1H NMR (270 MHz, CDCl_3): 8.18 (1 H, dd, $J = 2.4, 1.3$ Hz, 6-H), 7.95 (1 H, dd, $J = 8.6, 2.4$ Hz, 4-H), 7.50 (2 H, m, 3'-H and 5'-H), 7.00 (2 H, m, 2'-H and 6'-H), 3.86 (3 H, s, OMe). ^{13}C NMR (100.5 MHz, CDCl_3): 159.6 (d, $J = 241.6$ Hz, C), 146.1 (d, $J = 15.4$ Hz, CH), 142.3 (d, $J = 4.6$ Hz, CH), 138.3 (C), 130.1 (CH), 130.0 (CH), 125.3 (d, $J = 30.0$ Hz, C), 125.1 (C), 116.4 (d, $J = 4.6$ Hz, C), 114.5 (CH), 55.4 (OMe). HRMS: calcd for $\text{C}_{12}\text{H}_{10}\text{NOF}^{79}\text{Br}$ (MH^+), 281.9923; found, 281.9930.

5-Bromo-2-fluoro-[3,3']bipyridyl (4e). mp 119-121 $^{\circ}\text{C}$ (from ethyl acetate / hexane). IR (neat) ν (cm^{-1}): 3019, 1590, 1553, 1484, 1449, 1396, 1340, 1244, 1010, 808, 746, 708. ^1H NMR (270 MHz, CDCl_3): 8.80 (1 H, br s, 2'-H), 8.69 (1 H, br d, $J = 4.6$ Hz, 4'-H), 8.31 (1 H, br m, 6-H), 8.02 (1 H, dd, $J = 8.2, 2.3$ Hz, 4-H), 7.89 (1 H, ddd, $J = 7.9, 3.9, 2.0$ Hz, 6'-H), 7.44 (1 H, dd, $J = 7.9, 4.6$ Hz, 5'-H). ^{13}C NMR (67.9 MHz, CDCl_3): 159.3 (d, $J = 241.8$ Hz, C), 150.2 (CH), 149.4 (CH), 149.3 (CH), 147.9 (d, $J = 16.0$ Hz, CH), 142.7 (d, $J = 4.7$ Hz, CH), 136.1 (d, $J = 4.0$ Hz, C), 128.7 (C), 123.6 (CH), 117.0 (d, $J = 5.2$ Hz, C). HRMS: calcd for $\text{C}_{10}\text{H}_7\text{N}_2\text{F}^{79}\text{Br}$ (MH^+), 252.9777; found, 252.9776.

2-Fluoro-5-(4''-methylphenyl)-3-(4'-nitrophenyl)pyridine (5a). mp 170-172 °C (from diethyl ether / hexane). IR (neat) ν (cm⁻¹): 2923, 1602, 1519, 1454, 1346, 1204, 852, 815, 741, 697. ¹H NMR (400 MHz, CDCl₃): 8.46 (1 H, br m, 6-H), 8.35 (2 H, br d, J = 8.7 Hz, 3'-H and 5'-H), 8.06 (1 H, dd, J = 9.2, 2.4 Hz, 4-H), 7.82 (2 H, br d, J = 9.2 Hz, 2'-H and 6'-H), 7.49 (2 H, d, J = 8.3 Hz, 3''-H and 5''-H), 7.32 (2 H, d, J = 8.3 Hz, 2''-H and 6''-H), 2.43 (3 H, s, Me). ¹³C NMR (100.5 MHz, CDCl₃): 159.4 (d, J = 240.6 Hz, C), 147.9 (C), 145.8 (d, J = 14.6 Hz, CH), 140.5 (d, J = 5.4 Hz, CH), 139.1 (d, J = 3.1 Hz, C), 138.7 (C), 135.9 (d, J = 5.4 Hz, C), 133.2 (C), 130.1 (CH), 129.8 (CH), 127.0 (CH), 124.0 (CH), 121.5 (C), 121.3 (C), 21.2 (CH₃). HRMS: calcd for C₁₈H₁₄N₂O₂F (MH⁺), 309.1039; found, 309.1040.

2-Fluoro-3-(4'-methoxyphenyl)-5-phenylpyridine (5b). mp 119-121 °C (from diethyl ether / hexane). IR (neat) ν (cm⁻¹): 3035, 1610, 1516, 1447, 1408, 1252, 1180, 1030, 832, 766, 697. ¹H NMR (400 MHz, CDCl₃): 8.34 (1 H, br s, 6-H), 8.01 (1 H, dd, J = 9.2, 2.2 Hz, 4-H), 7.61-7.39 (7 H, m, 3'-H, 5'-H and Ph), 7.02 (2 H, d, J = 8.4 Hz, 2'-H and 6'-H), 3.87 (3 H, s, OMe). ¹³C NMR (100.5 MHz, CDCl₃): 160.0 (C), 159.9 (d, J = 239.8 Hz, C), 143.6 (d, J = 14.6 Hz, CH), 138.9 (d, J = 4.6 Hz, CH), 136.9 (C), 135.5 (d, J = 5.3 Hz, C), 130.1 (CH), 129.2 (CH), 128.3 (CH), 127.2 (CH), 126.2 (CH), 123.4 (d, J = 30.2 Hz, C), 114.4 (CH), 55.4 (OMe). HRMS: calcd for C₁₈H₁₅NOF (MH⁺), 280.1138; found, 280.1136.

2-Fluoro-5-(naphthalen-2''-yl)-3-(4'-nitrophenyl)pyridine (5c). mp 139-141 °C (from diethyl ether / hexane). IR (neat) ν (cm⁻¹): 3057, 1602, 1517, 1449, 1346, 1206, 854, 819, 740. ¹H NMR (400 MHz, CDCl₃): 8.60 (1 H, br s, 6-H), 8.33 (2 H, d, J = 8.7 Hz, 3'-H and 5'-H), 8.20 (1 H, dd, J = 9.2, 2.2 Hz, 4-H), 8.05 (1 H, br s, 1''-H), 7.98 (1 H, d, J = 8.6 Hz, 4''-H), 7.91 (2 H, m, 6''-H and 9''-H), 7.83 (2 H, d, J = 8.7 Hz, 2'-H and 6'-H), 7.71 (1 H, dd, J = 8.6, 1.4 Hz, 3''-H), 7.56 (2 H, m, 7''-H and

8''-H). ^{13}C NMR (100.5 MHz, CDCl_3): 159.6 (d, $J = 241.4$, C), 147.9 (C), 146.1 (d, $J = 15.4$ Hz, CH), 140.3 (d, $J = 5.4$ Hz, C), 139.4 (d, $J = 3.8$ Hz, CH), 135.9 (C), 133.6 (C), 133.3 (C), 133.1 (C), 129.8 (CH), 129.2 (CH), 128.2 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 126.3 (CH), 124.7 (CH), 124.0 (CH), 121.5 (d, $J = 28.4$, C). HRMS: calcd for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{F}$ (MH^+), 345.1039; found, 345.1034.

2-Fluoro-3-(4'-methoxyphenyl)-5-(4''-trifluoromethylphenyl)pyridine

(5d). mp 129-131 °C (from diethyl ether / hexane). IR (neat) ν (cm^{-1}): 2937, 1610, 1517, 1454, 1325, 1255, 1173, 1131, 1113, 906, 836, 731. ^1H NMR (270 MHz, CDCl_3): 8.35 (1 H, dd, $J = 2.3, 1.4$ Hz, 6-H), 8.03 (1 H, dd, $J = 9.2, 2.3$ Hz, 4-H), 7.76 (2 H, d, $J = 8.2$ Hz, 3''-H and 5''-H), 7.70 (2 H, d, $J = 8.2$ Hz, 2''-H and 6''-H), 7.57 (2 H, m, 3'-H and 5'-H), 7.03 (2 H, m, 2'-H and 6'-H), 3.88 (3 H, s, OMe). ^{13}C NMR (100.5 MHz, CDCl_3): 160.4 (d, $J = 241.3$, C), 160.2 (C), 143.8 (d, $J = 15.4$ Hz, CH), 140.4 (C), 139.0 (d, $J = 3.9$ Hz, CH), 134.2 (d, $J = 4.6$ Hz, C), 130.1 (CH), 130.1 (CH), 127.5 (CH), 126.2 (q, $J = 3.8$ Hz, C), 125.8 (C), 125.5 (C), 114.4 (CH). HRMS: calcd for $\text{C}_{19}\text{H}_{14}\text{NOF}_4$ (MH^+), 348.1012; found, 348.1007.

2-Fluoro-5-(N-Boc-indol-2''-yl)-3-(4'-nitrophenyl)pyridine (5e). IR (film)

ν (cm^{-1}): 2930, 1733, 1602, 1521, 1445, 1347, 1324, 1223, 1158, 1131, 853, 768, 741. ^1H NMR (400 MHz, CDCl_3): 8.36 (3 H, m, 3'-H, 5'-H and 6-H), 8.19 (1 H, br d, $J = 8.3$ Hz, 8''-H), 7.99 (1 H, dd, $J = 9.2, 2.4$ Hz, 4-H), 7.80 (2 H, br d, $J = 8.8$ Hz, 2'-H and 6'-H), 7.60 (1 H, br d, $J = 7.9$ Hz, 5''-H), 7.39 (1 H, t, $J = 7.3$ Hz, 6''-H), 7.31 (1 H, t, $J = 7.3$ Hz, 7''-H), 6.70 (1 H, s, 3''-H), 1.47 (9 H, s, Boc). ^{13}C NMR (100.5 MHz, CDCl_3): 172.1 (C), 159.4 (d, $J = 242.2$ Hz, C), 153.5 (C), 150.0 (C), 147.9 (C), 147.1 (d, $J = 15.4$ Hz, CH), 141.1 (d, $J = 3.8$ Hz, CH), 140.1 (d, $J = 5.4$ Hz, C), 137.4 (C), 134.5 (C), 130.8 (C), 129.8 (CH), 129.8 (CH), 128.9 (CH), 125.3 (CH), 124.1 (CH), 123.5 (CH), 120.9 (CH), 120.5 (d, $J = 28.4$ Hz, C), 115.8 (CH), 112.1 (CH),

84.6 (C), 28.0, (C(CH₃)₃). HRMS: calcd for C₂₄H₂₁N₃O₄F (MH⁺), 434.1516; found, 434.1517.

2-Fluoro-3-(4'-methoxyphenyl)-5-(N-Boc-pyrrol-2''-yl)pyridine (5f). IR (film) ν (cm⁻¹): 2980, 1741, 1611, 1517, 1442, 1315, 1251, 1181, 1144, 834, 730. ¹H NMR (400 MHz, CDCl₃): 8.11 (1 H, br s, 6-H), 7.84 (1 H, dd, J = 9.2, 1.9 Hz, 4-H), 7.54 (2 H, br d, J = 7.3 Hz, 3'-H and 5'-H), 7.41 (1 H, br t, J = 2.5 Hz, 5''-H), 7.01 (2 H, br d, J = 7.3 Hz, 2'-H and 6'-H), 6.28 (2 H, m, 3''-H and 4''-H), 3.86 (3 H, s, OMe), 1.41 (9 H, s, Boc). ¹³C NMR (100.5 MHz, CDCl₃): 159.9 (C), 159.5 (d, J = 239.9 Hz, C), 149.1 (C), 145.3 (d, J = 14.6 Hz, CH), 141.2 (d, J = 4.6 Hz, C), 130.0 (d, J = 3.1 Hz, CH), 129.0 (C), 123.4 (CH), 122.1 (d, J = 28.4 Hz, C), 115.7 (CH), 114.3 (CH), 110.9 (CH), 84.3 (C), 55.4 (OMe), 27.8 (C(CH₃)₃). HRMS: calcd for C₂₁H₂₂N₂O₃F (MH⁺), 369.1614; found, 369.1618.

2-Fluoro-3-(4'-methoxyphenyl)pyridine (9). This compound was isolated using the above procedure except that the reaction mixture was heated under reflux for 6 h. mp 47-49 °C (from diethyl ether / hexane). IR (neat) ν (cm⁻¹): 2836, 1604, 1518, 1435, 1406, 1292, 1249, 1242, 1182, 1035, 1001, 831, 805, 795, 762. ¹H NMR (270 MHz, CDCl₃): 8.15 (1 H, dt, J = 4.7, 1.4 Hz, 6-H), 7.84 (1 H, ddd, J = 9.9, 7.6, 2.0 Hz, 4-H), 7.51 (2 H, m, 3'-H and 5'-H), 7.25 (1 H, ddd, J = 7.6, 4.7, 1.4 Hz, 5-H), 7.00 (2 H, m, 2'-H and 6'-H), 3.86 (3 H, s, OMe). ¹³C NMR (100.5 MHz, CDCl₃): 160.4 (d, J = 240.3 Hz, C), 159.6 (C), 145.4 (d, J = 14.6 Hz, CH), 139.8 (d, J = 4.6 Hz, CH), 129.7 (CH), 125.9 (C), 123.3 (d, J = 27.7 Hz, C), 121.4 (d, J = 4.6 Hz, CH), 113.9 (CH), 113.9 (CH), 55.1 (OMe). HRMS: calcd for C₁₂H₁₀NOF (M⁺), 203.0746; found, 203.0743.

5-(4''-Methylphenyl)-3-(4'-nitrophenyl)-2-pyridone (6a). mp 238-240 °C (from chloroform / hexane). IR (neat) ν (cm^{-1}): 2859, 1647, 1622, 1593, 1555, 1516, 1346, 1248, 1110, 851, 815, 735, 694. ^1H NMR (400 MHz, CDCl_3): 8.32 (2 H, d, J = 8.8 Hz, 3'-H and 5'-H), 7.99 (3 H, m, 6-H, 2'-H and 6'-H), 7.69 (1 H, d, J = 2.4 Hz, 4-H), 7.37 (2 H, d, J = 8.3 Hz, 3''-H and 5''-H), 7.26 (2 H, d, J = 8.3 Hz, 2''-H and 6''-H), 2.40 (3 H, s, Me), 1.59 (1 H, br s, NH). ^{13}C NMR (75.5 MHz, CDCl_3): 162.5 (C), 147.2 (C), 142.9 (C), 140.6 (CH), 137.8 (C), 132.9 (C), 132.2 (CH), 130.0 (CH), 129.4 (CH), 125.8 (CH), 123.6 (CH), 121.8 (C), 21.1 (CH_3). HRMS: calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_3$ (MH^+), 307.1083; found, 307.1081.

3-(4'-Methoxyphenyl)-5-phenyl-2-pyridone (6b). mp 203-205 °C (from chloroform / hexane). IR (neat) ν (cm^{-1}): 2839, 1643, 1609, 1598, 1516, 1479, 1249, 835, 757, 729. ^1H NMR (400 MHz, CDCl_3): 7.86 (1 H, d, J = 2.1 Hz, 6-H), 7.74 (2 H, d, J = 8.8 Hz, 3'-H and 5'-H), 7.61 (1 H, d, J = 2.1 Hz, 4-H), 7.48-7.31 (5 H, m, Ph), 6.99 (2 H, d, J = 8.8 Hz, 2'-H and 6'-H), 3.86 (3 H, s, OMe), 1.63 (1 H, br s, NH). ^{13}C NMR (75.5 MHz, CDCl_3): 163.4 (C), 159.5 (C), 138.5 (CH), 136.6 (CH), 131.6 (C), 130.5 (C), 129.9 (CH), 129.1 (CH), 128.9 (C), 127.3 (CH), 125.8 (CH), 121.3 (C), 113.9 (CH), 55.4 (OMe). HRMS: calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_2$ (MH^+), 278.1181; found, 278.1180.

References

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