Electronic Supplementary Information

Synthesis of 2-Trifluoromethyl Quinoline by the Reaction of Fluorinated Imine with Alkyne Catalyzed by Indium(III) Triflate

Haibo Xie, Jiangtao Zhu, Zixian Chen, Shan Li, Yongming Wu*

a Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345LingLing Road, Shanghai 200032, P. R. China.
Fax: (+86) 21-54925192; E-mail: ymwu@sioc.ac.cn

b Department of Chemistry, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China

Table of contents

General information............................................................ S2

General procedure for 2-trifluoromethylquinolines synthesis......... S2

Characterization data for compounds 6a – 6o ......................

NMR spectra for compounds 6a – 6o .................................
General:
Melting points were measured on a Melt-Temp apparatus and uncorrected. \(^1\)HNMR spectra were recorded in CDCl\(_3\) on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. \(^1\)9F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using CFCl\(_3\) as external standard. \(^1\)3C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Solvents and reagents were purchased from commercial sources and used as received. CH\(_3\)CN was distilled from calcium hydride. All reactions were carried out under a nitrogen atmosphere in a Schlenk tube, with a stir bar and caps with a Teflon screw-cap. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300-400) and petroleum ether/ethylacetate combination was used as the eluent.

General procedure for 2-trifluoromethylquinolines synthesis

A schlenk tube was charged with In(OTf)\(_3\) (56 mg, 0.1 mmol), BQ (216 mg, 2 mmol), evacuated and backfilled with nitrogen. toluene (5 ml), Phenylacetylene (2 mmol) and 4-methoxy-N-(2,2,2-trifluoroethylidene)aniline (4a) (203 mg, 1 mmol) was successively added. Then the reaction mixture was stirred at 60°C for 3 h. The mixture was partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography on silica and then recrystallized from petroleum (boiling range 60~90°C) provide 6a as a white solid.

1.1) 6-methoxy-4-phenyl-2-(trifluoromethyl)quinoline, 6a.

White solid, mp 68°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.18 (d, \(J = 9.1\) Hz, 1H), 7.62 (s, 1H), 7.57-7.53 (m, 5H), 7.47 (dd, \(J_1 = 9.1\) Hz, \(J_2 = 2.8\) Hz, 1H), 7.22 (d, \(J = 2.8\) Hz, 1H), 3.81 (s, 3H); \(^1\)9FNMR (282 MHz, CDCl\(_3\)) \(\delta\) -67.7 (s); \(^1\)3CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.3, 148.9, 145.0 (q, \(J = 35.2\) Hz), 143.8, 137.4, 131.8, 129.1, 128.8, 128.6, 123.3, 121.8 (q, \(J = 275.5\) Hz), 117.3, 103.3, 55.4; IR(KBr): 3022, 2975, 1621, 1494, 1479, 1386, 1369, 1284, 1179, 1127, 1096, 1031, 830, 706; MS (EI) m/z (relative intensity) 303 (100) [M\(^+\)], 272 (8), 268 (25), 218 (11), 190 (13), 134 (7); Anal.Calcd. For C\(_{17}\)H\(_{12}\)F\(_3\)NO: C, 67.32; H, 3.99; N, 4.62. Found: C, 67.41; H, 3.94; N, 4.63

1.2) 2-(bromodifluoromethyl)-6-methoxy-4-phenylquinoline, 6b.
White solid, mp 94°C; $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 8.17 (d, $J = 9.1$ Hz, 1H), 7.61 (s, 1H), 7.57-7.52 (m, 5H), 7.46 (dd, $J_1 = 9.1$ Hz, $J_2 = 2.8$ Hz, 1H), 7.22 (d, $J = 2.8$ Hz, 1H), 3.81 (s, 3H); $^{19}$FNMR (282 MHz, CDCl$_3$) $\delta$ -50.3 (s); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 150.7 (t, $J = 26.2$ Hz), 148.9, 143.4, 137.5, 131.8, 129.2, 128.8, 128.3, 123.2, 117.5 (t, $J = 306.0$ Hz), 116.3, 103.4, 55.5; IR(KBr): 3078, 2963, 1620, 1587, 1509, 1492, 1474, 1431, 1223, 1148, 1085, 1030, 940, 760, 702; MS (EI) m/z (relative intensity) 363 (8) [M$^+$], 284 (100), 268 (6), 241 (6), 190 (10), 134 (6); Anal.Calcd. For C$_{17}$H$_{12}$BrF$_2$NO: C, 56.07; H, 3.32; N, 3.85. Found: C, 56.11; H, 3.32; N, 3.74.

1.3) 6-methyl-4-phenyl-2-(trifluoromethyl)quinoline, 6c.

White solid, mp 36°C; $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 8.18 (d, $J = 8.7$ Hz, 1H), 7.72 (s, 1H), 7.76-7.63 (m, 2H), 7.58-7.50 (m, 5H), 2.50 (s, 3H); $^{19}$FNMR (282 MHz, CDCl$_3$) $\delta$ -67.7 (s); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 150.0, 146.6 (q, $J = 34.4$ Hz), 146.4, 139.0, 137.3, 132.9, 130.1, 129.5, 128.9, 128.8, 127.4, 124.5, 121.8 (q, $J = 275.7$ Hz), 117.1, 21.9; IR(KBr): 3061, 2923, 1621, 1591, 1588, 1566, 1506, 1495, 1472, 1446, 1387, 1326, 1264, 1181, 1136, 1094, 984, 827, 766, 701, 623; MS (EI) m/z (relative intensity) 287 (100) [M$^+$], 272 (28), 266 (11), 252 (19), 218 (16), 202 (12), 189 (9), 133 (8), 108 (8); Anal.Calcd. For C$_{17}$H$_{12}$F$_3$N: C, 71.07; H, 4.21; N, 4.88. Found: C, 71.24; H, 4.44; N, 4.91.

1.4) 6-chloro-4-phenyl-2-(trifluoromethyl)quinoline, 6d.

White solid, mp 86°C; $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J = 9.1$ Hz, 1H), 7.94 (d, $J = 2.1$ Hz, 1H), 7.75-7.70 (m, 2H), 7.58-7.55 (m, 3H), 7.52-7.49 (m, 2H); $^{19}$FNMR (282 MHz, CDCl$_3$) $\delta$ -67.9 (s); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 150.2, 147.7 (q, $J = 34.2$ Hz), 146.1, 136.4, 134.9, 132.0, 131.6, 129.4, 129.0, 128.1, 124.7, 121.5 (q, $J = 275.7$ Hz), 117.8; IR(KBr): 3061, 1601, 1591, 1489, 1456, 1382, 1284, 1263, 1183, 1132, 1094, 1070, 893, 790, 704; MS (EI) m/z (relative intensity) 307 (100) [M$^+$], 288 (7), 272 (56), 252 (11), 252 (47), 202 (40), 176 (11), 126 (10), 101 (9); Anal.Calcd. For C$_{16}$H$_{12}$ClF$_3$N: C, 62.45; H, 2.95; N, 4.55. Found: C, 62.55; H, 3.24; N, 4.55.

1.5) 6-fluoro-4-phenyl-2-(trifluoromethyl)quinoline, 6e.
White solid, mp 91°C; ¹H NMR (300 MHz, CDCl₃) δ 8.28-8.23 (m, 1H), 7.69 (s, 1H), 7.59-7.47 (m, 7H); ¹⁹FNMR (282 MHz, CDCl₃) δ -67.8 (s, 3F), -109.2 (m, 1F); ¹³CNMR (100 MHz, CDCl₃) δ 161.8 (d, J = 251.7 Hz), 150.3 (d, J = 5.9 Hz), 147.7 (qd, J₁ = 34.7 Hz, J₂ = 2.8 Hz), 144.8, 136.6, 133.1 (d, J = 9.4 Hz), 129.3, 129.0, 128.4 (d, J = 9.6 Hz), 121.6 (q, J = 275.1 Hz), 120.0 (d, J = 25.6 Hz), 117.5, 109.3 (d, J = 23.2 Hz); IR(KBr): 3081, 3060, 1786, 1624, 1594, 1566, 1514, 1495, 1472, 1386, 1286, 1268, 1233, 1095, 1028, 925, 838, 705, 625; MS (EI) m/z (relative intensity) 291 (100) [M⁺], 270 (22), 250 (5), 222 (43), 221 (16), 220 (19), 194 (9), 136 (7), 111 (8); Anal.Calcd. For C₁₆H₉F₄N: C, 65.98; H, 3.11; N, 4.81. Found: C, 65.90; H, 2.98; N, 4.74.

1.6) 4-phenyl-2,6-bis(trifluoromethyl)quinoline, 6f.

White solid, mp 94°C; ¹H NMR (300 MHz, CDCl₃) δ 8.41 (d, J = 8.9 Hz, 1H), 8.32 (s, 1H), 8.00 (dd, J₁ = 8.9 Hz, J₂ = 1.9 Hz, 1H), 7.79 (s, 1H), 7.62-7.52 (m, 5H); ¹⁹FNMR (282 MHz, CDCl₃) δ -63.1 (s, 3F), -68.2 (s, 3F); ¹³CNMR (100 MHz, CDCl₃) δ 152.2, 149.5 (q, J = 35.1 Hz), 148.7, 136.1, 131.8, 130.4 (q, J = 23.2 Hz), 129.6, 129.4, 129.2, 126.6, 126.2 (d, J = 2.8 Hz), 123.9 (q, J = 4.6 Hz), 123.7 (d, J = 272.7 Hz), 121.3 (q, J = 276.0 Hz), 118.2; IR(KBr): 3071, 2954, 1618, 1575, 1504, 1477, 1437, 1389, 1367, 1301, 1269, 1178, 1126, 1098, 1038, 832, 693; MS (EI) m/z (relative intensity) 341 (100) [M⁺], 322 (13), 320 (10), 272 (93), 252 (38), 232 (9), 203 (19), 202 (27), 176 (7), 126 (7); Anal.Calcd. For C₁₇H₁₄F₆NO₂: C, 59.83; H, 2.66; N, 4.10. Found: C, 59.89; H, 2.64; N, 4.12.

1.7) 6-methoxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)quinoline, 6g.

White solid, mp 60°C; ¹H NMR (300 MHz, CDCl₃) δ 8.12 (d, J = 9.5 Hz, 1H), 7.58 (s, 1H), 7.47-7.44 (m, 2H), 7.41 (dd, J₁ = 9.5 Hz, J₂ = 2.7 Hz, 1H), 7.25 (d, J = 2.7 Hz, 1H), 7.08-7.05 (m, 2H), 3.87 (s, 3H), 3.79 (s, 3H); ¹⁹FNMR (282 MHz, CDCl₃) δ -67.5 (s); ¹³CNMR (100 MHz, CDCl₃) δ 160.1, 159.2, 148.7, 144.9 (q, J = 34.8 Hz), 143.8, 131.7, 130.4, 129.6, 128.8, 123.1, 121.8 (q, J = 275.0 Hz), 117.1, 114.2, 103.3, 55.4, 55.2; IR(KBr): 3004, 2954, 1618, 1575, 1504, 1477, 1437, 1389, 1367, 1301, 1269, 1178, 1126, 1098, 1038, 832, 693; MS (EI) m/z (relative intensity) 333 (100) [M⁺], 318 (9), 268 (25), 303(7), 298 (13), 275 (8), 149 (5); Anal.Calcd. For C₁₈H₁₄F₆NO₂: C, 64.86; H, 4.23; N, 4.20. Found: C, 64.79; H, 4.43; N, 4.12.
1.8) 6-methoxy-4-p-tolyl-2-(trifluoromethyl)quinoline, 6h.

![Structure of 6h](image)

White solid, mp 136°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.15 (d, $J = 9.5$ Hz, 1H), 7.61 (s, 1H), 7.45-7.34 (m, 5H), 7.25 (d, $J = 2.8$ Hz, 1H), 3.80 (s, 3H), 2.45 (s, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -67.5 (s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.2, 149.0, 145.0 (q, $J = 34.5$ Hz), 138.9, 134.5, 131.8, 129.0, 128.7, 125.9, 123.2, 121.8 (q, $J = 275.1$ Hz), 117.2, 103.3, 55.4, 21.2; IR(KBr): 3013, 2960, 1619, 1505, 1477, 1390, 1368, 1286, 1178, 1126, 1098, 1026, 845, 693; MS (EI) m/z (relative intensity) 317 (100) [M$^+$], 302 (11), 282 (19), 232 (8), 151 (5); Anal. Calcd. For C$_{18}$H$_{14}$F$_3$NO: C, 68.13; H, 4.45; N, 4.41. Found: C, 68.10; H, 4.53; N, 4.30.

1.9) 4-(4-chlorophenyl)-6-methoxy-2-(trifluoromethyl)quinoline, 6i.

![Structure of 6i](image)

White solid, mp 98°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.18 (d, $J = 9.2$ Hz, 1H), 7.59 (s, 1H), 7.57-7.46 (m, 5H), 7.14 (d, $J = 2.7$ Hz, 1H), 3.83 (s, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -67.7 (s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.5, 147.6, 145.0 (q, $J = 33.8$ Hz), 143.8, 135.8, 135.0, 131.9, 130.5, 129.1, 128.4, 123.4, 121.7 (q, $J = 275.3$ Hz), 117.2, 102.9, 55.5; IR(KBr): 3020, 1789, 1620, 1598, 1479, 1385, 1283, 1175, 1134, 1099, 1025, 843, 731; MS (EI) m/z (relative intensity) 337 (100) [M$^+$], 302 (23), 287 (11), 252 (9), 239 (16), 190 (9); Anal. Calcd. For C$_{17}$H$_{11}$ClF$_3$NO: C, 60.46; H, 3.28; N, 4.15. Found: C, 60.37; H, 3.27; N, 4.02.

1.10) 4-(4-fluorophenyl)-6-methoxy-2-(trifluoromethyl)quinoline, 6j.

![Structure of 6j](image)

White solid, mp 102°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.14 (d, $J = 9.4$ Hz, 1H), 7.59 (s, 1H), 7.54-7.49 (m, 2H), 7.44 (dd, $J_1 = 9.4$ Hz, $J_2 = 2.7$ Hz, 1H), 7.15 (d, $J = 2.7$ Hz, 1H), 7.29-7.23 (m, 2H), 3.82 (s, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -67.5 (s, 3F), -112.7 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 163.0 (d, $J = 249.4$ Hz), 159.4, 147.8, 144.9 (q, $J = 35.4$ Hz), 143.8, 133.3 (d, $J = 3.0$ Hz), 131.9, 130.9 (d, $J = 8.3$ Hz), 128.6, 123.3, 121.7 (q, $J = 274.7$ Hz), 117.3, 115.9 (d, $J = 21.7$ Hz), 103.3, 55.4; IR(KBr): 3021, 2974, 1774, 1621, 1504, 1478, 1389, 1289, 1178, 1100, 1025, 842, 729; MS (EI) m/z (relative intensity) 321 (100) [M$^+$], 286 (32), 236 (12), 208 (12); Anal. Calcd. For C$_{17}$H$_{11}$F$_3$NO: C, 63.55; H, 3.45; N, 4.36. Found: C, 63.62; H, 3.65; N, 4.31.
1.11) 6-methoxy-4-(3-methoxyphenyl)-2-(trifluoromethyl)quinoline, 6k.

White solid, mp 57°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 9.1\) Hz, 1H), 7.63 (s, 1H), 7.50-7.45 (m, 2H), 7.26-7.25 (m, 1H), 7.12-7.05 (m, 3H), 3.88 (s, 3H), 3.82 (s, 3H); \(^{19}\)FNMR (282 MHz, CDCl\(_3\)) \(\delta\) -67.7 (s); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 163.0 (d, \(J = 249.4\) Hz), 159.8, 159.3, 148.8, 145.0 (q, \(J = 34.8\) Hz), 138.7, 131.1, 129.8, 128.6, 123.3, 121.7 (q, \(J = 275.0\) Hz), 121.5, 117.2, 114.8, 114.3, 103.3, 55.5, 55.3; IR(KBr): 3020, 1622, 1585, 1493, 1478, 1384, 1288, 1233, 1180, 1097, 1033, 833, 714; MS (EI) m/z (relative intensity) 333 (100) [M\(^+\)], 318 (7), 302 (9), 287 (6), 275 (7), 258 (8), 149 (6); Anal.Calcd. For C\(_{18}\)H\(_{14}\)F\(_4\)NO\(_2\): C, 64.86; H, 4.23; N, 4.20. Found: C, 63.77; H, 4.16; N, 4.11.

1.12) 4-(2-chlorophenyl)-6-methoxy-2-(trifluoromethyl)quinoline, 6l.

White solid, mp 84°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.19 (d, \(J = 9.2\) Hz, 1H), 7.61-7.35 (m, 6H), 6.78 (d, \(J = 2.8\) Hz, 1H), 3.78 (s, 3H); \(^{19}\)FNMR (282 MHz, CDCl\(_3\)) \(\delta\) -67.6 (s); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.4, 146.3, 144.8 (q, \(J = 34.6\) Hz), 143.6, 136.0, 133.0, 131.8, 131.1, 130.2, 130.0, 128.8, 127.0, 123.5, 121.7 (q, \(J = 274.8\) Hz), 117.9, 103.2, 55.4; IR(KBr): 3016, 1620, 1600, 1485, 1438, 1385, 1286, 1224, 1181, 1097, 1030, 838, 768; MS (EI) m/z (relative intensity) 337 (100) [M\(^+\)], 302 (94), 287 (61), 282 (35), 267 (17), 239 (30), 190 (14); Anal.Calcd. For C\(_{18}\)H\(_{13}\)ClF\(_3\)NO: C, 60.46; H, 3.28; N, 4.15. Found: C, 60.61; H, 3.27; N, 4.12.

1.13) 6-methoxy-4-(naphthalen-2-yl)-2-(trifluoromethyl)quinoline, 6m.

White solid, mp 88°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 9.3\) Hz, 1H), 8.04-7.92 (m, 4H), 7.72 (s, 1H), 7.65-7.58 (m, 3H), 7.48 (dd, \(J_1 = 9.3\) Hz, \(J_2 = 2.7\) Hz, 1H), 7.25 (d, \(J = 2.3\) Hz, 1H), 3.76 (s, 3H); \(^{19}\)FNMR (282 MHz, CDCl\(_3\)) \(\delta\) -67.5 (s); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.4, 148.9, 145.1 (q, \(J = 33.6\) Hz), 143.9, 134.9, 133.3, 133.1, 131.9, 128.8, 128.6, 128.4, 128.2, 127.8, 126.9, 126.8, 126.6, 123.4, 121.8 (q, \(J = 274.0\) Hz), 117.6, 103.3, 55.5; IR(KBr): 3042, 3002, 1622, 1594, 1508, 1482, 1439, 1391, 1368, 1276, 1231, 1185, 1096, 1033, 927, 836, 740; MS (EI) m/z (relative intensity) 353 (100) [M\(^+\)], 337 (32), 322 (19), 302 (30), 287 (16), 239 (12), 159 (15), 152 (21); Anal.Calcd. For C\(_{21}\)H\(_{14}\)F\(_3\)NO: C, 71.38; H, 3.99; N, 3.96. Found: C, 71.17; H, 4.02; N, 3.96.
1.14) 6-methoxy-4-(thiophen-2-yl)-2-(trifluoromethyl)quinoline, 6n.

![Chemical structure of 6-methoxy-4-(thiophen-2-yl)-2-(trifluoromethyl)quinoline](image)

White solid, mp 94°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.09 (d, \(J = 9.1\) Hz, 1H), 7.70 (s, 1H), 7.58 (d, \(J = 2.7\) Hz, 1H), 7.53 (d, \(J = 5.0\) Hz, 1H), 7.42-7.38 (m, 2H), 7.24-7.21 (m, 2H), 3.85 (s, 3H); \(^1\)^13\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.8, 144.9 (q, \(J = 34.5\) Hz), 144.1, 141.3, 138.2, 131.9, 128.7, 128.3, 128.1, 127.9, 123.5, 121.8 (q, \(J = 275.4\) Hz), 117.6, 103.1, 55.5; IR(KBr): 3068, 3025, 2964, 1619, 1590, 1478, 1435, 1340, 1279, 1225, 1176, 1098, 1027, 833, 741; MS (EI) m/z (relative intensity) 309 (100) [M\(^+\)], 274 (37), 246 (5), 224 (5), 196 (8); Anal.Calcd. For C\(_{15}\)H\(_{10}\)F\(_3\)NOS: C, 58.25; H, 3.26; N, 4.53. Found: C, 58.54; H, 3.60; N, 4.55.

1.15) 6-methoxy-4-phenyl-3-deuterium-2-(trifluoromethyl)quinoline, 6o

![Chemical structure of 6-methoxy-4-phenyl-3-deuterium-2-(trifluoromethyl)quinoline](image)

White solid, mp 68°C; \(^1\)HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 9.1\) Hz, 1H), 7.56-7.52 (m, 5H), 7.46 (dd, \(J_1 = 9.1\) Hz, \(J_2 = 2.4\) Hz, 1H), 7.22 (d, \(J = 2.4\) Hz, 1H), 3.81 (s, 3H); \(^1\)^13\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.5, 149.0, 145.1 (q, \(J = 34.5\) Hz), 144.0, 137.5, 132.0, 129.3, 129.0, 128.9, 128.8, 123.4, 121.9 (q, \(J = 275.6\) Hz), 117.2 (t, \(J = 25.8\) Hz), 103.4, 55.5; MS (EI) m/z (relative intensity) 304 (100) [M\(^+\)], 273 (8), 269 (20), 219 (8), 191 (9), 134 (5); Anal.Calcd. For C\(_{17}\)H\(_{11}\)F\(_3\)NO: C, 67.10; H, 4.31; N, 4.60. Found: C, 67.45; H, 4.18; N, 4.45.
6b
6c