Supporting Information

A novel method for the synthesis of 2-trifluoromethylindoles from N-(o-haloaryl)alkynylimines

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Table of contents

General information .......................................................... S2
General procedure for 2-trifluoromethylindoles synthesis .............. S2
Characterization data for compounds 2a-2n .......................... S2-S6
NMR spectra for compounds 2a-2n ................................. S7-S20
General:

Melting points were measured on a Melt-Temp apparatus and uncorrected. $^1$HNMR spectra were recorded in CDCl$_3$ and d-DMSO on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. $^{19}$F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using CFCl$_3$ as external standard. $^{13}$C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Elemental analysis was performed by the Analytical Laboratory of Shanghai Institute of Organic Chemistry. Mass spectra were recorded by EI methods, HRMS (EI) was measured on Waters Micromass GCT Premier mass spectrometer.

Solvents and reagents were purchased from commercial sources and used as received. All reactions were carried out under a nitrogen atmosphere in a Schlenk tube and monitored by TLC with silica gel coated plates. Flash column chromatography was carried out using 300-400 mesh silica gel at increased pressure and petroleum ether/ethyl acetate combination was used as the eluent.

General procedure for $N$-(o-haloaryl)alkynylimine 1 synthesis

Terminal alkyne (3.6 mmol 1.2 equiv) was added to a solution of fluoroalkylimidoyl chloride (3 mmol), K$_3$PO$_4$ (3.6 mmol, 1.2 equiv), CuI (1 mmol, 30 mol %), and KI (3 mmol, 1 equiv) in CH$_3$CN (6.0 ml). The solution was then stirred at 60°C. After completion of reaction as indicated by TLC, the solvent was evaporated. The residue was purified by flash chromatography on silica gel to provide the desired product 1.

General procedure for 2-trifluoromethylindoles synthesis

A schlenk tube was charged with Pa(PPh$_3$)$_2$Cl$_2$ (10 mol %) and K$_3$PO$_4$ (2 equiv), evacuated and backfilled with nitrogen. DME (2 ml), N-(o-haloaryl)alkynylimine 1 (0.3 mmol), and H$_2$O (1.0 equiv) was successively added. The mixture was stirred at 60 °C until the completion of the reaction. Then the reaction crude was filtered and the filtrate evaporated. The residue was purified by column chromatography on silica gel to yield products 2.

Characterization data for compounds

3-benzoyl-2-trifluoromethylindole (2a)

White solid, mp 138-140 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.73 (br, 1H), 7.89 (d, $J = 7.6$ Hz, 2H), 7.67 – 7.07 (m, 7H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -58.75; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.7, 138.9, 134.6, 133.3, 129.8, 128.5, 127.1 (q, $J = 39.0$ Hz), 126.4, 125.5, 122.5, 122.0, 120.7 (q, $J =
269.7 Hz), 117.1, 112.3; LRMS (EI) m/z (relative intensity) 289 (60) [M⁺], 212 (100); Anal. Calcd. for C₁₆H₁₀F₃NO: C, 66.44; H, 3.48; N, 4.84. Found: C, 66.33; H, 3.65; N, 4.78. IR(KBr): 3246, 3077, 1598, 1495, 1122, 1080, 930, 750, 697, 626 cm⁻¹

2-trifluoromethyl-3-benzoyl-5-methylindole (2b)

White solid, mp 156-158 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.47 (br, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.67 – 7.10 (m, 6H), 2.33 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃) δ -58.58. ¹³C NMR (100 MHz, CDCl₃) δ 191.7, 138.9, 133.2, 132.9, 129.8, 128.4, 127.3, 126.7 (q, J = 38.9 Hz), 126.7, 121.3, 120.7 (q, J = 270.0 Hz), 116.7, 111.8, 21.5. LRMS (EI) m/z (relative intensity) 303 (54) [M⁺], 226 (100), 77 (24). Anal. Calcd. for C₁₇H₁₂F₃NO: C, 67.32; H, 3.99; N, 4.62. Found: C, 67.18; H, 4.17; N, 4.54. IR(KBr): 3164, 3071, 1622, 1599, 1549, 1464, 1346, 1264, 1231, 1201, 909, 791, 702 cm⁻¹.

6-methoxy-2-trifluoromethyl-3-benzoylindole (2c)

Light yellow solid, mp 125-127 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.44 (br, 1H), 7.88 (d, J = 7.4 Hz, 2H), 7.66 – 7.41 (m, 3H), 7.21 (d, J = 9.1 Hz, 1H), 6.93 – 6.76 (m, 2H), 3.80 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃) δ -58.46. ¹³C NMR (100 MHz, CDCl₃) δ 191.6, 158.6, 138.9, 135.6, 133.2, 129.8, 128.5, 125.7 (q, J = 38.9 Hz), 122.7, 120.7 (q, J = 269.2 Hz), 120.6, 117.2, 113.6, 94.3, 55.6. LRMS (ESI) m/z (relative intensity) 320.1 [M+H]⁺. Anal. Calcd. for C₁₇H₁₂F₃NO₂: C, 63.95; H, 3.79; N, 4.39. Found: C, 63.77; H, 3.88; N, 4.29. IR(KBr): 3186, 1620, 1585, 1546, 1460, 1434, 1264, 1231, 1201, 925, 814, 658 cm⁻¹.

5-fluoro-2-trifluoromethyl-3-benzoylindole (2d)

White solid, mp 149-151 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.86 (br, 1H), 7.86 (d, J = 7.9 Hz, 2H), 7.70 – 7.36 (m, 4H), 7.16 – 6.92 (m, 2H). ¹⁹F NMR (282 MHz, CDCl₃) δ -59.04 (s, 3H), -119.75 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 191.0, 159.1 (q, J = 239.3 Hz), 138.6, 133.4, 131.0, 129.7, 128.6, 128.5 (q, J = 39.0 Hz), 126.9 (q, J = 10.4 Hz), 120.3 (q, J = 270.2 Hz), 117.2, 114.7 (q, J = 27.0 Hz), 113.4 (q, J = 9.6 Hz), 106.9 (q, J = 25.4 Hz). LRMS (EI) m/z (relative intensity) 307 (52) [M⁺], 303 (31), 230 (100), 212 (50), 105 (24), 77 (27). HRMS-EI (m/z) calcld for C₁₆H₉F₄NO 307.0620; found 307.0620. IR(KBr): 3174, 1628, 1599, 1543, 1493, 1470, 1141, 1116, 904, 701, 629, 511 cm⁻¹.
2,5-bistrifluoromethyl-3-benzoylindole (2e)

[Chemical structure image]

White solid, mp 170-172 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.71 (br, 1H), 7.88 (d, $J$ = 7.9 Hz, 2H), 7.77 - 7.44 (m, 6H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -58.87 (s, 3H), -61.62 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.7, 138.3, 135.8, 133.8, 129.7, 128.6, 128.1 (q, $J$ = 39.0 Hz), 125.8, 125.3 (q, $J$ = 32.1 Hz), 124.4 (q, $J$ = 271.4 Hz), 122.3 (q, $J$ = 2.6 Hz), 120.2 (q, $J$ = 270.5 Hz), 120.0 (q, $J$ = 4.3 Hz), 118.0, 112.8. LRMS (EI) m/z (relative intensity) 357 (48) [M$^+$], 280 (100), 105 (36), 77 (35). Anal. Calcd. for C$_{17}$H$_9$F$_6$NO: C, 57.15; H, 2.54; N, 3.92. Found: C, 57.02; H, 2.72; N, 3.87. IR(KBr): 3198, 1626, 1598, 1551, 1470, 1451, 1329, 1133, 1110, 904, 809 cm$^{-1}$.

2-trifluoromethyl-3-(4-methylbenzoyl)indole (2f)

[Chemical structure image]

Light yellow solid, mp 130-132 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.72 (br, 1H), 7.80 (d, $J$ = 7.9 Hz, 2H), 7.52 - 7.08 (m, 6H), 2.44 (s, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -58.70. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 191.2, 144.3, 136.2, 134.6, 130.1, 129.2, 126.8 (q, $J$ = 38.9 Hz), 126.3, 125.3, 122.3, 121.9, 120.7 (q, $J$ = 270.0 Hz), 117.3, 112.3, 21.7. LRMS (EI) m/z (relative intensity) 303 (63) [M$^+$], 212 (100), 119 (32), 91 (27). Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO: C, 67.15; H, 2.54; N, 3.92. Found: C, 67.02; H, 2.72; N, 3.87. IR(KBr): 3198, 1626, 1598, 1551, 1470, 1451, 1329, 1133, 1110, 904, 809 cm$^{-1}$.

2-trifluoromethyl-3-(4-methoxybenzoyl)indole (2g)

[Chemical structure image]

Brown solid, mp 128-130 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.61 (br, 1H), 7.90 (d, $J$ = 8.8 Hz, 2H), 7.51 - 7.11 (m, 4H), 6.95 (d, $J$ = 8.8 Hz, 2H), 3.88 (s, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -58.68. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.2, 163.9, 134.6, 132.4, 131.6, 126.4, 126.3 (q, $J$ = 38.9 Hz), 125.3, 122.3, 121.9, 120.8 (q, $J$ = 269.9 Hz), 117.5, 113.8, 112.2, 55.5. LRMS (EI) m/z (relative intensity) 319 (100) [M$^+$], 212 (80), 135 (64). Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO$_2$: C, 63.95; H, 3.79; N, 4.39. Found: C, 63.55; H, 3.82; N, 4.32. IR(KBr): 3211, 1640, 1610, 1546, 1495, 1444, 1292, 1169, 1130, 908, 741, 606 cm$^{-1}$.

2-trifluoromethyl-3-(3-methoxybenzoyl)indole (2h)

[Chemical structure image]
White solid, mp 110-111 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.65 (br, 1H), 7.53 – 7.11 (m, 8H), 3.82 (s, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -58.72. $^{13}$C NMR (100 MHz, CDCl$_3$) δ 191.4, 159.8, 140.2, 134.6, 129.5, 127.0 (q, $J$ = 38.9 Hz), 126.4, 125.5, 122.9, 122.5, 122.0, 120.7 (q, $J$ = 270.0 Hz), 120.0, 117.1, 113.6, 112.2. LRMS (EI) m/z (relative intensity) 319 (58) [M$^+$], 212 (100). Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO$_2$: C, 63.95; H, 3.79; N, 4.39. Found: C, 63.83; H, 3.82; N, 4.36. IR(KBr): 3255, 1649, 1597, 1554, 1464, 1335, 1291, 1258, 1124, 1041, 814, 742 cm$^{-1}$.

**2-trifluoromethyl-3-(4-chlorobenzoyl)indole (2i)**

White solid, mp 171-173 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.50 (br, 1H), 7.83 (d, $J$ = 8.5 Hz, 2H), 7.57 – 7.13 (m, 6H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -58.7. $^{13}$C NMR (100 MHz, CDCl$_3$) δ 189.9, 139.7, 137.1, 134.4, 131.2, 128.9, 127.0 (q, $J$ = 39.6 Hz), 126.2, 125.7, 122.8, 121.9, 120.5 (q, $J$ = 270.0 Hz), 116.8, 112.2. LRMS (EI) m/z (relative intensity) 323 (42) [M$^+$], 212 (100). Anal. Calcd. for C$_{16}$H$_9$ClF$_3$NO: C, 59.37; H, 2.80; N, 4.33. Found: C, 59.17; H, 2.96; N, 4.24. IR(KBr): 3221, 1640, 1592, 1543, 1495, 1445, 1444, 1291, 907, 744 cm$^{-1}$.

**2-trifluoromethyl-3-(4-fluorobenzoyl)indole (2j)**

White solid, mp 156-158 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.34 (br, 1H), 7.92 (dd, $J$ = 8.4, 5.6 Hz, 2H), 7.56 – 7.07 (m, 6H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -58.72 (s, 3H), -105.08 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 189.7, 166.0 (q, $J$ = 255.1 Hz), 135.1 (q, $J$ = 3.2 Hz), 134.5, 132.5 (q, $J$ = 9.5 Hz), 126.8 (q, $J$ = 38.9 Hz), 126.3, 125.6, 122.7, 121.9, 120.6 (q, $J$ = 269.4 Hz), 116.9, 115.7 (q, $J$ = 22.3 Hz), 112.2. LRMS (EI) m/z (relative intensity) 307 (62) [M$^+$], 212 (100), 123 (24), 95 (26). HRMS-EI (m/z) calcd for C$_{16}$H$_9$F$_4$NO 307.0620; found 307.0619. IR(KBr): 3216, 3075, 1627, 1601, 1545, 1494, 1445, 1351, 1291, 1233, 1135, 909, 746, 603 cm$^{-1}$.

**2-trifluoromethyl-3-(2-chlorobenzoyl)indole (2k)**
2-trifluoromethyl-3-(2-naphthoyl)indole (2l)

Light yellow solid, mp 159-161 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 10.02 (br, 1H), 7.55 – 7.07 (m, 8H). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -59.79. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 189.6, 140.1, 134.2, 131.7, 131.7, 130.3, 129.4, 128.7 (q, \(J = 39.0\) Hz), 126.9, 126.3, 125.6, 123.5, 121.6, 120.4 (q, \(J = 270.3\) Hz), 116.8, 112.4. LRMS (EI) m/z (relative intensity) 32 3 (42) [M\(^+\)], 212 (100). Anal. Calcd. for C\(_{16}\)H\(_9\)ClF\(_3\)NO: C, 59.37; H, 2.80; N, 4.33. Found: C, 59.33; H, 2.90; N, 4.23. IR(KBr): 3174, 1644, 1591, 1542, 1494, 1438, 1290, 1164, 930, 739, 627 cm\(^{-1}\).

2-trifluoromethyl-3-(2-thienyl)indole (2m)

Light yellow solid, mp 95-97 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.54 (br, 1H), 8.36 (s, 1H), 8.08 – 7.80 (m, 4H), 7.67 – 7.07 (m, 6H). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -58.61. \(^{13}\)C NMR (100 MHz, d-DMSO) \(\delta\) 191.3, 136.1, 135.8, 134.6, 132.4, 132.2, 129.7, 128.6, 128.5, 127.9, 127.0 (q, \(J = 38.9\) Hz), 126.8, 126.5, 125.5, 125.1, 122.6, 122.0, 120.7 (q, \(J = 270.2\) Hz), 117.3. LRMS (EI) m/z (relative intensity) 339 (92) [M\(^+\)], 212 (100), 155 (25), 127 (47). HRMS-EI (m/z) calcd for C\(_{20}\)H\(_{12}\)F\(_3\)NO 339.0871; found 339.0870. IR(KBr): 3274, 1645, 1625, 1548, 1498, 1447, 1289, 1175, 1126, 808, 749 cm\(^{-1}\).

2-trifluoromethyl-3-pivaloylindole (2n)

Light yellow solid, mp 148-150 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.22 (br, 1H), 7.81 – 7.06 (m, 7H). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -58.5. \(^{13}\)C NMR (100 MHz, d-DMSO) \(\delta\) 182.7, 145.0, 136.3, 135.8, 135.6, 129.1, 125.7, 125.5, 125.4 (q, \(J = 38.1\) Hz), 122.4, 121.4 (q, \(J = 270.0\) Hz), 121.3, 116.2, 113.5. LRMS (EI) m/z (relative intensity) 295 (100) [M\(^+\)], 212 (94), 111 (46). Anal. Calcd. for C\(_{16}\)H\(_7\)F\(_3\)NOS: C, 56.95; H, 2.73; N, 4.74. Found: C, 56.59; H, 2.88; N, 4.66. IR(KBr): 3244, 1620, 1554, 1513, 1451, 1411, 1284, 1180, 1143, 825, 742 cm\(^{-1}\).
White solid, mp 153-154 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.85 (br, 1H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.42 – 7.15 (m, 3H), 1.31 (s, 9H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -58.7. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.4, 134.9, 125.4, 125.1, 121.8, 121.6, 121.6 (q, $J = 38.9$ Hz), 120.8 (q, $J = 268.5$ Hz), 118.7, 45.4, 27.1. LRMS (EI) m/z (relative intensity) 269 (8) [M$^+$], 212 (100). HRMS-EI (m/z) calcd for C$_{14}$H$_{14}$F$_3$NO 269.1028; found 269.1023. IR(KBr): 3295, 2975, 1658, 1548, 1449, 1334, 1175, 1139, 947, 741 cm$^{-1}$.

NMR spectra for compounds

$2a$
2n