Elaboration of 2-Trifluoromethylindoles via a Cascade Coupling-Condensation-Deacylation Process

Yu Chen¹, Yuji Wang¹, Zheming Sun¹ and Dawei Ma²*

¹Department of Chemistry, Fudan University, Shanghai, 200433, China
²State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute Of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Supporting Information

Table of Contents

Experimental---------------------------------------------S2-S9
Copies of ¹H NMR and ¹³C NMR spectrum of 7a-7s-------------------S10-S47
Copies of ¹H NMR and ¹³C NMR spectrum of 8 and 9-----------------S48-S51
Experimental

**General methods.** $^1$H NMR or $^{13}$C NMR spectra were recorded on JEOL ECA-400, Bruker DPX-300, Bruker DMX-500. Proton chemical shifts were given in relative to tetramethylsilane (δ 0.00 ppm) in CDCl$_3$. Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl$_3$ (δ 77.00 ppm). Mass spectra were recorded on a HP 5989A mass spectrometer. High resolution mass spectra were recorded on a Finnigan MAT mass spectrometer.

**Material.** All solvents and CuI were purified according to *Purification of Laboratory Chemicals (4th edition)*. Others were used as received. Silica gel plate GF254 were used for thin layer chromatography (TLC) and silica gel H were used for flash column chromatography.

**General procedure for synthesis of 2-trifluoromethylindoles.** A Schlenk tube was charged with aryl iodide (0.25 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and Cs$_2$CO$_3$ (326 mg, 1 mmol). Then β-keto ester (0.5 mmol) and DMSO (0.5 mL) were successively injected. After the reaction mixture was stirred at corresponding temperature for 12-18 h, it was partitioned between ethyl acetate and saturated NH$_4$Cl. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 20:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

![Chemical structure of 7a](image)

**Methyl 5-nitro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7a).** $^1$H NMR (400 MHz, d$_6$-acetone) δ 3.98 (s, 3H), 7.77 (d, $J$ = 8.7 Hz, 1H), 8.22 (dd, $J$ = 2.3, 8.7 Hz, 1H), 9.04 (d, $J$ = 2.3 Hz, 1H); $^{13}$C NMR (100 MHz, d$_6$-acetone) δ 51.48, 109.27, 113.88, 119.17, 120.08, 120.25 (d, $J$ = 268 Hz), 125.65, 131.90 (q, $J$ = 38 Hz), 137.41, 144.10, 162.15; ESI-MS $m/z$ 306 (M + NH$_4$)$^+$; HRMS calcd for C$_{11}$H$_7$N$_2$O$_4$F$_3$ 288.0358 (M)$^+$, found 288.0359.
Ethyl 5-nitro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7b). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.48 (t, $J$ = 7.3 Hz, 3H), 4.49 (q, $J$ = 7.3 Hz, 2H), 7.59 (d, $J$ = 8.7 Hz, 1H), 8.29 (dd, $J$ = 2.3, 8.7 Hz, 1H), 9.23 (d, $J$ = 2.3 Hz, 1H), 9.64 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 13.58, 60.75, 109.52, 113.74, 119.10, 119.97, 120.26 (d, $J$ = 269 Hz), 125.74, 131.73 (q, $J$ = 39 Hz), 137.40, 143.96, 161.59; ESI-MS m/z 320 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_9$N$_2$O$_4$F$_3$ 302.0514 (M)$^+$, found 302.0518.

tert-Butyl 5-nitro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7c). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.67 (s, 9H), 7.58 (d, $J$ = 8.7 Hz, 1H), 8.27 (dd, $J$ = 2.3, 8.7 Hz, 1H), 9.25 (d, $J$ = 2.3 Hz, 1H), 9.69 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 28.25, 82.80, 111.83, 112.96, 119.99 (d, $J$ = 268 Hz), 120.23, 120.43, 126.26, 131.63 (q, $J$ = 39 Hz), 136.91, 143.98, 161.58; ESI-MS m/z 348 (M + NH$_4$)$^+$; HRMS calcd for C$_{14}$H$_{13}$N$_2$O$_4$F$_3$ 330.0827 (M)$^+$, found 330.0825.

Cyclohexyl 5-nitro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7d). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.25-2.10 (m, 10H), 5.14 (m, 1H), 7.65 (d, $J$ = 8.7 Hz, 1H), 8.26 (dd, $J$ = 2.3, 8.7 Hz, 1H), 9.25 (d, $J$ = 2.3 Hz, 1H), 10.54 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.64, 25.40, 31.58, 74.14, 110.69, 113.07, 119.96 (d, $J$ = 268 Hz), 120.27, 120.49, 126.15, 132.05 (q, $J$ = 39 Hz), 136.99, 144.08, 161.95; ESI-MS m/z 374 (M + NH$_4$)$^+$; HRMS calcd for C$_{16}$H$_{15}$N$_2$O$_4$F$_3$ 356.0984 (M)$^+$, found 356.0988.
Benzyl 5-nitro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7e). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.48 (s, 2H), 7.35-7.58 (m, 6H), 8.28 (dd, $J = 2.3$, 8.7 Hz, 1H), 9.21 (d, $J = 2.3$ Hz, 1H), 9.67 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) δ 66.58, 109.24, 113.89, 119.23, 120.08, 120.25 (d, $J = 268$ Hz), 125.81, 128.32, 128.46, 128.61, 132.08 (q, $J = 39$ Hz), 136.17, 137.50, 144.11, 161.54; ESI-MS m/z 382 (M + NH$_4$)$^+$; HRMS calcd for C$_{17}$H$_{11}$N$_2$O$_4$F$_3$ 364.0671 (M)$^+$, found 364.0672.

Ethyl 2-(trifluoromethyl)-1H-indole-3-carboxylate (7f). $^1$H NMR (400 MHz, $d_6$-acetone) δ 1.39 (t, $J = 7.3$ Hz, 3H), 4.38 (q, $J = 7.3$ Hz, 2H), 7.25-7.58 (m, 3H), 8.22 (d, $J = 8.2$ Hz, 1H), 11.89 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) δ 13.70, 60.09, 107.55, 112.80, 120.99 (d, $J = 267$ Hz), 122.42, 122.82, 125.11, 126.62, 128.64 (q, $J = 39$ Hz), 134.85, 162.59; ESI-MS m/z 275 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_{10}$NO$_2$F$_3$ 257.0664 (M)$^+$, found 257.0665.

Methyl 2-(trifluoromethyl)-1H-indole-3-carboxylate (7g). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.98 (s, 3H), 7.32-7.49 (m, 3H), 8.25 (d, $J = 7.8$ Hz, 1H), 9.34 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 51.79, 108.16, 112.14, 120.51 (d, $J = 270$ Hz), 122.87, 123.30, 125.56, 126.54, 129.11 (q, $J = 44$ Hz), 133.95, 163.82; ESI-MS m/z 261 (M + NH$_4$)$^+$; HRMS calcd for C$_{11}$H$_8$NO$_2$F$_3$ 243.0507 (M)$^+$, found 243.0510.
Methyl 5-acetyl-2-(trifluoromethyl)-1H-indole-3-carboxylate (7h). \(^1\)H NMR (400 MHz, \textit{d}_6\text{-acetone}) \(\delta\) 2.64 (s, 3H), 3.96 (s, 3H), 7.65 (d, \(J = 8.7\) Hz, 1H), 7.99 (dd, \(J = 0.9, 8.7\) Hz, 1H), 8.85 (d, \(J = 0.9\) Hz, 1H); \(^1\)C NMR (100 MHz, \textit{d}_6\text{-DMSO}) \(\delta\) 27.16, 52.21, 108.16, 113.75, 120.79 (d, \(J = 269\) Hz), 124.13, 124.95, 125.75, 130.43 (q, \(J = 39\) Hz), 132.42, 137.41, 162.96, 197.78; ESI-MS \(m/z\) 303 (M + NH\(_4\))\(^+\); HRMS calcd for C\(_{13}\)H\(_{10}\)NO\(_3\)F\(_3\) 285.0613 (M)\(^+\), found 285.0613.

![Image of 7h](image)

**Eethyl 5-chloro-2-(trifluoromethyl)-1H-indole-3-carboxylate (7i).** \(^1\)H NMR (400 MHz, \textit{d}_6\text{-acetone}) \(\delta\) 1.39 (t, \(J = 7.3\) Hz, 3H), 4.39 (q, \(J = 7.3\) Hz, 2H), 7.35 (dd, \(J = 1.8, 8.7\) Hz, 1H), 7.59 (d, \(J = 8.7\) Hz, 1H), 8.18 (d, \(J = 1.8\) Hz, 1H), 12.01 (br s, 1H); \(^1\)C NMR (100 MHz, \textit{d}_6\text{-acetone}) \(\delta\) 13.65, 60.35, 107.26, 114.50, 120.64 (d, \(J = 268\) Hz), 121.57, 125.55, 127.59, 128.34, 129.91 (q, \(J = 38\) Hz), 133.25, 162.14; ESI-MS \(m/z\) 309 (M + NH\(_4\))\(^+\); HRMS calcd for C\(_{12}\)H\(_9\)NO\(_2\)ClF\(_3\) 291.0274 (M)\(^+\), found 291.0271.

![Image of 7i](image)

**3-Allyl 5-methyl 2-(trifluoromethyl)-1H-indole-3,5-dicarboxylate (7j).** \(^1\)H NMR (400 MHz, \textit{d}_6\text{-DMSO}) \(\delta\) 3.85 (s, 3H), 4.83 (d, \(J = 5.5\) Hz, 2H), 5.26-5.29 (m, 1H) 5.38-5.43 (m, 1H), 5.95-6.10 (m, 1H), 7.63 (d, \(J = 8.7\) Hz, 1H), 7.92 (d, \(J = 8.7\) Hz, 1H), 8.76 (s, 1H); \(^1\)C NMR (100 MHz, \textit{d}_6\text{-DMSO}) \(\delta\) 52.58, 65.37, 107.73, 113.90, 118.39, 120.77 (d, \(J = 270\) Hz), 124.74, 124.89, 125.86, 125.92, 130.56 (q, \(J = 39\) Hz), 132.94, 137.47, 162.13, 166.97; ESI-MS \(m/z\) 345 (M + NH\(_4\))\(^+\); HRMS calcd for C\(_{15}\)H\(_{12}\)NO\(_4\)F\(_3\) 327.0718 (M)\(^+\), found 327.0723.
Methyl 6-acetyl-2-(trifluoromethyl)-1H-indole-3-carboxylate (7k). $^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 2.62 (s, 3H), 3.93 (s, 3H), 7.93 (d, $J = 1.4$ Hz, 1H), 8.20-8.28 (m, 2H), 12.20 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 26.01, 51.11, 107.60, 113.85, 120.57 (d, $J = 269$ Hz), 122.31, 122.35, 129.57, 131.55 (q, $J = 37$ Hz), 134.32, 134.44, 162.64, 196.59; ESI-MS m/z 303 (M + NH$_4$)$^+$; HRMS calcd for C$_{13}$H$_{10}$NO$_3$F$_3$ 285.0613 (M)$^+$, found 285.0614;

Methyl 5-methyl-2-(trifluoromethyl)-1H-indole-3-carboxylate (7l). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.49 (s, 3H), 3.98 (s, 3H), 7.20 (d, $J = 8.7$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 8.03 (s, 1H), 9.13 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.73, 51.74, 107.68, 111.71, 120.51 (d, $J = 268$ Hz), 122.19, 126.84, 127.38, 128.90 (q, $J = 39$ Hz), 132.26, 133.02, 163.91; ESI-MS m/z 275 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_{10}$NO$_2$F$_3$ 257.0664 (M)$^+$, found 257.0660;

Methyl 6-methoxy-2-(trifluoromethyl)-1H-indole-3-carboxylate (7m). $^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 3.82 (s, 3H), 3.90 (s, 3H), 6.95 (d, $J = 8.7$ Hz, 1H), 7.02 (s, 1H), 8.03 (d, $J = 8.7$ Hz, 1H), 11.68 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 50.85, 54.92, 94.40, 107.65, 114.03, 120.59, 120.99 (d, $J = 279$ Hz), 123.16, 127.36 (q, $J = 40$ Hz), 135.85, 158.62, 163.07; ESI-MS m/z 291 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_{10}$NO$_3$F$_3$ 273.0613 (M)$^+$, found 273.0615.
Methyl 5-iodo-6-methyl-2-(trifluoromethyl)-1H-indole-3-carboxylate (7n).

$^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 2.49 (s, 3H), 3.91 (s, 3H), 7.54 (s, 1H), 8.65 (s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 28.12, 51.07, 94.38, 106.22, 113.11, 120.67 (d, $J = 268$ Hz), 126.71, 129.55 (q, $J = 39$ Hz), 132.32, 135.13, 137.14, 162.67; ESI-MS $m/z$ 401 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_9$NO$_2$IF$_3$ 382.9630 (M)$^+$, found 382.9625.

Methyl 7-chloro-5-iodo-2-(trifluoromethyl)-1H-indole-3-carboxylate (7o).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.98 (s, 3H), 7.66 (s, 1H), 8.49 (s, 1H), 9.29 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 51.38, 85.44, 107.89, 118.92, 120.20 (d, $J = 269$ Hz), 129.66, 130.09, 130.59 (q, $J = 39$ Hz), 131.62, 132.53, 162.18; ESI-MS $m/z$ 421 (M + NH$_4$)$^+$; HRMS calcd for C$_{11}$H$_6$NO$_2$ClI F$_3$ 402.9084 (M)$^+$, found 402.9083.

3-Ethyl 7-methyl 5-iodo-2-(trifluoromethyl)-1H-indole-3,7-dicarboxylate (7p).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.44 (t, $J = 7.3$ Hz, 3H), 4.02 (s, 3H), 4.44 (q, $J = 7.3$ Hz, 2H), 8.31 (s, 1H), 8.88 (s, 1H), 10.52 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.16, 52.74, 61.13, 85.85, 107.83, 115.25, 119.88 (d, $J = 269$ Hz), 129.55, 130.26 (q, $J = 39$ Hz), 132.66, 135.72, 137.11, 162.27, 165.95; ESI-MS $m/z$ 459 (M + NH$_4$)$^+$; HRMS calcd for C$_{14}$H$_{11}$NO$_4$IF$_3$ 440.9685 (M)$^+$, found 440.9683.
Benzyl 5-(2-hydroxyethyl)-2-(trifluoromethyl)-1H-indole-3-carboxylate (7q). $^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 2.92 (t, $J = 7.3$ Hz, 2H), 3.80 (t, $J = 7.3$ Hz, 2H), 5.42 (s, 2H), 7.21-7.58 (m, 7H), 8.09 (s, 1H), 11.87 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 39.75, 63.44, 65.88, 106.90, 112.57, 120.99 (d, $J = 268$ Hz), 122.12, 126.91, 128.08, 128.09, 128.25, 128.52, 128.78 (q, $J = 39$ Hz), 133.62, 134.44, 136.73, 162.56; ESI-MS $m/z$ 381 (M + NH$_4$)$^+$; HRMS calcd for C$_{19}$H$_{16}$NO$_3$F$_3$ 363.1082 (M)$^+$, found 363.1083.

3-Ethyl 5-methyl 2-(trifluoromethyl)-1H-indole-3,5-dicarboxylate (7r). $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.31 (t, $J = 7.3$ Hz, 3H), 3.84 (s, 3H), 4.31 (q, $J = 7.3$ Hz, 2H), 7.58 (d, $J = 8.7$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 8.31 (s, 1H), 13.31 (br s, 1H); $^{13}$C NMR (100 MHz, $d_6$-DMSO) $\delta$ 14.45, 52.58, 60.87, 108.12, 113.85, 120.82 (d, $J = 270$ Hz), 124.66, 124.89, 125.83, 125.96, 130.35 (q, $J = 39$ Hz), 137.47, 162.44, 167.00; ESI-MS $m/z$ 333 (M + NH$_4$)$^+$; HRMS calcd for C$_{14}$H$_{12}$NO$_4$F$_3$ 315.0718, found 315.0714.

Methyl 5-methoxy-2-(trifluoromethyl)-1H-indole-3-carboxylate (7s). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.88 (s, 3H), 3.97 (s, 3H), 7.02 (dd, $J = 2.3$, 8.7 Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.68 (d, $J = 2.3$ Hz, 1H), 9.24 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 51.72, 55.77, 103.03, 107.61, 113.04, 116.99, 120.46 (d, $J = 268$ Hz), 127.61, 128.90, 128.91 (q, $J = 39$ Hz), 156.60, 164.05; ESI-MS $m/z$ 291 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_{10}$NO$_3$F$_3$ 273.0613 (M)$^+$, found 273.0615.
Methyl 4-methyl-3-oxo-2-(2,2,2-trifluoroacetamido)phenyl)pentanoate (8). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.95-1.15 (m, 6H), 2.25-2.32 (m, 0.8H), 2.55-2.70 (m, 0.2H), 3.69, 3.79 (s, s, 3H), 4.89 (s, 0.2H), 7.17-8.22 (m, 4.8H), 10.26 (br s, 0.2H), 13.32 (br s, 0.8H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 17.43, 18.72, 19.25, 19.68, 31.50, 39.67, 52.28, 53.32, 62.55, 95.20, 115.49 (q, J = 287 Hz), 121.44, 125.91, 126.33, 126.42, 127.42, 129.24, 129.88, 132.40, 132.59, 134.38, 154.65 (q, J = 37 Hz), 170.75, 172.39, 184.38, 208.48; ESI-MS m/z 349 (M + NH$_4$)$^+$; HRMS calcd for C$_{15}$H$_{16}$NO$_4$F$_3$ 331.1031 (M)$^+$, found 331.1035.

\[
\begin{array}{c}
\begin{array}{c}
\text{NHCOCF}_3 \\
\text{CO}_2\text{Et}
\end{array}
\end{array}
\]

Ethyl 2-(2,2,2-trifluoroacetamido)phenyl)acetate (9). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.29 (t, J = 7.3 Hz, 3H), 3.66 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 7.19-7.40 (m, 3H), 7.88 (d, J = 7.8 Hz, 1H), 10.16 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.03, 38.94, 62.33, 116.15 (q, J = 287 Hz), 124.66, 126.41, 126.97, 128.80, 131.24, 134.31, 155.64 (q, J = 37 Hz), 173.05; ESI-MS m/z 293 (M + NH$_4$)$^+$; HRMS calcd for C$_{12}$H$_{12}$NO$_3$F$_3$ 275.0769 (M)$^+$, found 275.0766.