Synthesis of fluorinated β-carbolines by one-pot reaction

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This paper describes a new strategy for the synthesis of 1-trifluoromethyl-9*H*-pyrido [3,4-b]indole **2** by one-pot reaction of tryptophan methyl ester hydrochloride **1** and trifluoroacetic anhydride (TFAA) in the presence of $POCl_3$ with satisfactory yield. Additionally, the structure of **2b** was confirmed by X-ray crystallographic analysis.

Keywords: fluorinated β-carbolines, 9*H*-pyrido[3,4-b]indoles, one-pot reaction

9*H*-Pyrido[3,4-b]indoles, commonly known as β-carbolines, have received significant attention because they show various biological and pharmaceutical properties. Some of them have been shown to possess central nervous system (CNS) activities, for instance, ethyl β-carboline-3-carboxylated (β-CCE), is known to bind with high affinity to the central benzodiazepine receptors (BZR)[1-4] and recent reports reveal that some β-carboline compounds, for example, β-carboline (norharman) and 1-methyl-β-carboline (harman) are potent inhibitors of monoamine oxidase which plays a significant physiological role in the CNS and peripheral organs.[5,6] Some β-carboline derivatives also exhibit antitumour,[7] anti-HIV,[8] antiviral,[9] antimicrobial,[10] antiplasmodial[11] and insecticidal activities.[12] As a result, studies on synthetic methods of varoius β-carbolines still remain an attractive topic. Many synthetic methods have been developed for the preparation of these compounds, such as Pictet–Spengler reaction of tryptamines and aldehydes,[13] Bischler–Napieralski reaction,[14-17] aza-Wittig reaction,[18] [4 + 2] cycloaddition of electron deficient 1,2,4-triazines with enamines,[19] intramolecular Michael addition,[20] thermal electrocyclic reaction of 3-alkenylindole-2-aldoxime,[21] modified intramolecular Goldberg amide arylation,[22] and palladium-catalysed annulation.[23-24]

Trifluoromethyl compounds have attracted much attention because of their important applications as biologically active agents and liquid crystalline materials, which exhibit specific biological and physical properties.[25-27] In addition, in our recent studies, we found that some β-carbolines with trifluoromethyl group at position-1 not only exhibited good inhibitory activities on monoamine oxidase but also good antitumor activities on tumor lung cell A-549.[28] As a consequence, trifluoromethylated compounds have attracted very broad attention. Much current effort has been devoted to the development of methods for trifluoromethylated analogues.[29-31] However, to our knowledge, examples of trifluoromethylated β-carbolines were scarcely reported. Bergman and co-workers synthesised fluorinated β-carbolines by intramolecular cyclisation of 5(4*H*)-oxazolones derived from tryptophan.[32] Kimoto and co-workers reported the synthesis of fluorinated β-carbolines,[33] but the method of these compounds suffered from multistep routes compared to recent reports in which trifluoromethylated β-carbolines were synthesised from tryptophan methyl ester hydrochloride and trifluoroacetic acid by one-pot reaction involved trifluoroacetimidoyl halides.[34-35]

Earlier mechanistic reports suggest that trifluoromethylated β-carbolines **2** might be synthesised from tryptophan methyl ester hydrochloride **1** and trifluoroacetic anhydride (TFAA) by one-pot reaction in the presence of $POCl_3$.[34-36] As expected, our initial experiment demonstrated that a one-pot approach was feasible. Reaction of tryptophan methyl ester hydrochloride **1** with TFAA in the presence of $POCl_3$ in xylene at 125 °C for 6 h directly afforded the corresponding product β-carboline **2a** in 61% isolated yield (Scheme 1). Compared with the previous reports,[34-35] this route avoided the using of highly toxic CCl_4 and the production of a large amount of the by-product triphenylphosphine oxide which caused difficulty in purification of the desired products. This exciting result prompted us to investigate further reaction conditions to increase the yield. Investigations into the optimisation of the reaction conditions, such as solvent, reaction temperature, and base for the synthesis of **2a** are listed in Table 1.

As shown in Table 1, bases played an important role in this reaction. When K_2CO_3 and pyridine were used as base, no product could be obtained, but Et_3N gave **2a** in 61% yield (Table 1, entries 1–3). On the basis of the results, a gradual increase in yield was observed when the reaction temperature was increased from 70 to 135 °C and 125 °C generated the highest yield (Table 1, entries 3 and 9–13). The examination of solvent effects revealed that xylene was the solvent of choice (Table 1, entries 3–8).

Table 1 Optimisation of the synthesis of **2a** by one-pot reaction

Entry	Temperature/°C	Solvent	Base	Time/h	Yield/%[a]
1	125	Xylene	K_2CO_3	6	0
2	125	Xylene	pyridine	6	0
3	125	Xylene	Et_3N	6	61
4	Reflux	Toluene	Et_3N	6	48
5	Reflux	Dioxane	Et_3N	6	0
6	Reflux	Carbon tetrachloride	Et_3N	6	Trace
7	Reflux	Ethyl acetate	Et_3N	6	0
8	Reflux	Acetonitrile	Et_3N	6	0
9	135	Xylene	Et_3N	6	60
10	110	Xylene	Et_3N	6	51
11	90	Xylene	Et_3N	6	43
12	80	Xylene	Et_3N	6	21
13	70	Xylene	Et_3N	6	Trace

[a]Isolated yield.

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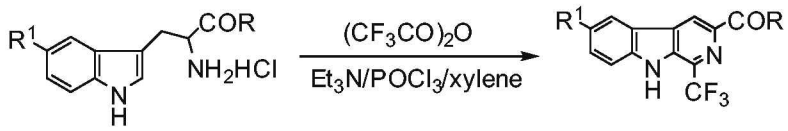

1 2

R = OMe; OEt; OPr^n; OPr^i; OBu^n; OBu^i; OPent^n; OPent^i.
R^1 = H, Br.

Scheme 1

Having determined the optimal reaction conditions, we were interested in determining the scope of this one-pot reaction. Various fluorinated β-carbolines have been synthesised in moderate yield and all the products were identified by MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The results are summarised in Table 2. Based on the results, it could be concluded that the change of R or R^1 had little influence on the yields of the target compounds **2a–i** because these compounds were obtained in similar yields.

Meanwhile, In order to further confirm the structure of the product **2**, the X-ray diffraction analysis was carried out. The crystal structure of compound **2b** as a representative example is shown in Figure 1.[37]

In conclusion, an efficient new synthetic method of β-carbolines with CF_3 at C_1 and substituted groups at C_3 has been developed by one-pot reaction in the present of $POCl_3$. The one-pot method has easily accessible starting materials, mild conditions, separation of convenience and a satisfactory yield compared to the previous reports. Further study in this area is under investigation in our laboratory.

Experimental

Melting points were recorded on Digital Melting Point Apparatus WRS-1B and uncorrected. TLC was performed using precoated silica gel 60 GF_{254} (0.25 mm) and column chromatography was performed using silica gel (300–400 mesh). IR spectra were taken on an EQUINOX-55 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a AVANCE-300 instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as the solvent at room temperature. Chemical shifts are given in δ relative to TMS, coupling constants (*J*) are expressed in Hz. Mass spectra were measured with Thermo Finnigan LCQ-Advantage.

General procedure for preparation of the fluorinated β-carbolines

A 100 ml, three-necked flask equipped with a condenser with Et_3N (2.20 ml, 16 mmol), xylene (20 ml), tryptophan amide (8 mmol). After the solution was stirred for about 10 min (ice bath), TFAA (1.1 ml, 8 mmol) was added. The mixture was then stirred for 20 min at room temperature. Subsequently, $POCl_3$ (7.2 ml, 80 mmol) was added and heated at 125 °C for 6 hour. The solvent was evaporated under reduced pressure and the resulting crude product was purified through silica gel column chromatography eluting with petroleum ether and ethyl acetate (15:1, v/v) to give the corresponding fluorinated β-carbolines. The physical and spectra data of all compounds are as follows.

Methyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2a**): Pale yellow solid; m.p. 250–251 °C (Lit.[33] m.p. 250–251 °C);

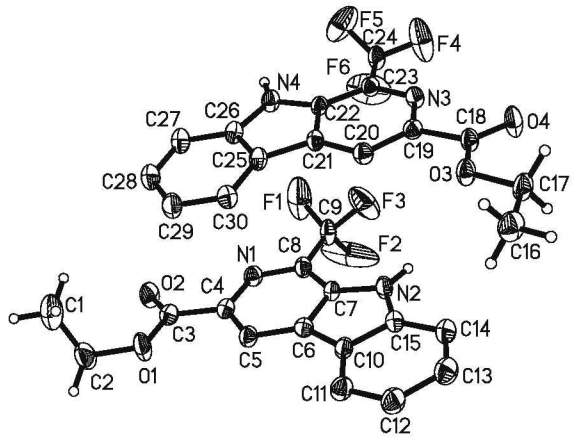

Fig. 1

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.98 (s, 3H), 7.42 (t, *J* = 6.8 Hz, 1H), 7.79–7.69 (m, 2H), 8.53 (d, *J* = 7.4 Hz, 1H), 9.21 (s, 1H), 12.36 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.45, 112.99, 120.46, 120.75, 121.33, 122.05 (q, $J_{C\text{-}F}$ = 272.3 Hz, CF_3), 122.56, 128.99 (q, $J_{C\text{-}C\text{-}F}$ = 35.9 Hz, C–CF_3), 130.12, 131.93, 132.98, 135.91, 142.04, 165.06. IR (cm^{-1}): 3363, 1694.

Ethyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2b**): Pale yellow solid; m.p. 217–218 °C (Lit.[32] m.p. 217–218 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.37 (t, *J* = 7.0 Hz, 3H), 4.41 (q, *J* = 6.9 Hz, 2H). 7.38 (t, *J* = 7.0 Hz, 1H), 7.71–7.65 (m, 2H), 8.50 (d, *J* = 7.5 Hz, 1H), 9.18 (s, 1H), 12.32 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.75, 61.46, 112.99, 120.46, 120.73, 121.33, 122.05 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 122.57, 129.01 (q, $J_{C\text{-}C\text{-}F}$ = 35.9 Hz, C–CF_3), 130.13, 131.95, 132.97, 135.93, 142.01, 165.30. IR (cm^{-1}): 3360, 1719.

Propyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2c**): Pale yellow solid; m.p. 207–208 °C (Lit.[33] m.p. 207–208 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.04 (t, *J* = 7.4 Hz, 3H), 1.88–1.79 (m, 2H), 4.36 (t, *J* = 6.7 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.79–7.69 (m, 2H), 8.53 (d, *J* = 7.9 Hz, 1H), 9.19 (s, 1H), 12.34 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.69, 22.09, 66.87, 113.25, 120.72, 120.94, 121.58, 122.31 (q, $J_{C\text{-}F}$ = 272.1 Hz, CF_3), 122.86, 129.29 (q, $J_{C\text{-}C\text{-}F}$ = 36.4 Hz, C–CF_3), 133.22, 136.41, 142.29, 164.82. IR (cm^{-1}): 3358, 1719.

Isopropyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2d**): Pale yellow solid; m.p. 232–233 °C (Lit.[33] m.p. 232–233 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.41 (d, *J* = 6.2 Hz, 6H), 5.28–5.24 (m, 1H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.78–7.68 (m, 2H), 8.52 (d, *J* = 7.9 Hz, 1H), 9.17 (s, 1H), 12.32 (s, 1H). ^{13}C NMR (75 MHz,

Table 2 Synthesis of several fluorinated β-carbolines from the one-pot reaction[a]

Entry	R	R^1	Product	Yield/%[b]	M.p./°C
1	OMe	H	**2a**	61	250-251
2	OEt	H	**2b**	62	217-218
3	OPr^n	H	**2c**	60	207-208
4	OPr^i	H	**2d**	63	232-233
5	OBu^n	H	**2e**	63	168-169
6	OBu^i	H	**2f**	61	214-215
7	$O(CH_2)_4CH_3$	H	**2g**	63	155-156
8	$O(CH_2)_2CH(CH_3)_2$	H	**2h**	62	155-156
9	OMe	Br	**2i**	61	297-298

[a]Amount of reagents: tryptophan amide (8 mmol), TFAA (8 mmol), $POCl_3$ (80 mmol), triethylamine (16 mmol), xylene (20 ml).
[b] Isolated yields based on tryptophan amide.

DMSO-d_6): δ = 21.98, 68.92, 113.11, 120.58, 120.79, 121.41, 122.21 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 122.69, 128.88, 129.11 (q, $J_{C\text{-}C\text{-}F}$ = 35.6 Hz, C–CF_3), 130.22, 131.98, 133.05, 136.57, 142.15, 164.12. IR (cm^{-1}): 3343, 1715.

Butyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2e**): Pale yellow solid; m.p. 168–169 °C (Lit.[33] m.p. 168–169 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.51–1.39 (m, 2H), 1.80–1.70 (m, 2H), 4.37 (t, J = 6.6 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.76–7.65 (m, 2H), 8.49 (d, J = 7.9 Hz, 1H), 9.15 (s, 1H), 12.30 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.84, 18.95, 30.59, 65.01, 113.08, 120.54, 120.74, 121.32 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 121.37, 122.64, 129.12 (q, $J_{C\text{-}C\text{-}F}$ = 35.9 Hz, C–CF_3), 130.18, 131.96, 133.05, 136.21, 142.12, 164.65. IR (cm^{-1}): 3369, 1717.

Isobutyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2f**): Pale yellow solid; m.p. 214–215 °C (Lit.[33] m.p. 214–215 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 2.10–2.06 (m, 1H), 4.15 (d, J = 6.7 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.75–7.65 (m, 2H), 8.54 (d, J = 8.0 Hz, 1H), 9.16 (s, 1H), 12.33 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.09, 27.62, 70.88, 113.00, 120.46, 120.57, 121.25, 122.05 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 122.56, 129.09 (q, $J_{C\text{-}C\text{-}F}$ = 35.7 Hz, C–CF_3), 130.07, 131.88, 132.97, 136.12, 142.04, 164.48. IR (cm^{-1}): 3362, 1725.

Pentyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2g**): Pale yellow solid; m.p. 155–156 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.92 (t, J = 6.9 Hz, 3H), 1.45–1.35 (m, 4H), 1.81–1.75 (m, 2H), 4.38 (t, J = 6.8 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.78–7.68 (m, 2H), 8.53 (d, J = 7.9 Hz, 1H), 9.19 (s, 1H), 12.34 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.11, 22.07, 27.85, 28.22, 65.32, 113.11, 120.57, 120.86, 121.44, 122.17 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 122.75, 129.12 ($J_{C\text{-}C\text{-}F}$ = 36.1 Hz, C–CF_3), 130.26, 132.00, 133.07, 136.21, 142.13, 164.68. EI-MS (*m/z*): 350 (M^+, 6), 236 (100), 216 (14); IR (cm^{-1}): 3365, 1732. Elemental Anal. Calcd for $C_{18}H_{17}F_3N_2O_2$: C, 61.71; H, 4.89; N, 8.00; Found: C, 61.92; H, 4.94; N, 8.21.

Isopentyl 1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2h**): Pale yellow solid; m.p. 155–156 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.95 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.65–1.77 (m, 2H), 4.14–4.24 (m, H), 4.39 (t, J = 6.8 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.75–7.65 (m, 2H), 8.51 (d, J = 8.0 Hz, 1H), 9.16 (s, 1H), 12.32 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.63, 24.99, 37.29, 63.86, 113.12, 120.59, 120.75, 121.41, 122.18 (q, $J_{C\text{-}F}$ = 272.0 Hz, CF_3), 122.68, 127.63, 129.17 (q, $J_{C\text{-}C\text{-}F}$ = 35.7 Hz, C–CF_3), 130.22, 132.01, 133.09, 136.28, 142.16, 164.65. EI-MS (*m/z*): 350 (M^+, 7), 236 (100), 216 (13); IR (cm^{-1}): 3365, 1732. Elemental Anal. Calcd for $C_{18}H_{17}F_3N_2O_2$: C, 61.71; H, 4.89; N, 8.00; Found: C, 61.89; H, 4.96; N, 7.91.

Methyl 6-bromo-1-(trifluoromethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**2i**): Brown solid; m.p. 297–298 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.97 (s, 3H), 7.71 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.87 (s, 1H), 9.32 (s, 1H), 12.51 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.68, 113.61, 115.11, 121.55, 121.98 (q, $J_{C\text{-}F}$ = 272.3 Hz, CF_3), 122.43, 125.36, 129.45 (q, $J_{C\text{-}C\text{-}F}$ = 36.3 Hz, C–CF_3), 131.04, 132.78, 133.31, 136.27, 140.81, 165.05. ESI-MS (*m/z*): 373 ([M + 2]$^+$, 100), 371 (M^+, 96); IR (cm^{-1}): 3443, 1637. Elemental Anal. Calcd for $C_{14}H_8BrF_3N_2O_2$: C, 45.07; H, 2.16; N, 7.51. Found: C, 45.25; H, 2.03; N, 7.64.

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37 CCDC-697284 contains the supplementary crystallographic data for **2b**, which is available free of charge via www.ccdc.cam.ac.uk.