Tetrahedron 66 (2010) 2746–2751

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

p-TsOH promoted Fischer indole synthesis of multi-substituted 2-trifluoromethyl indole derivatives

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ARTICLE INFO

Article history:
Received 20 November 2009
Received in revised form 8 January 2010
Accepted 22 January 2010
Available online 10 February 2010

Keywords:
Fluorinated indoles
Fluorinated ketoesters
Fischer indole synthesis

ABSTRACT

A *p*-TsOH promoted one-pot synthesis of multi-substituted 2-trifluoromethyl indole derivatives, for instance, 2-trifluoromethyl-3-phenylindoles, 2-trifluoromethyl-indole-3-propanoates, and 2-trifluoromethyl-indole-3-butanoates from reactions of 1,1,1-trifluoro-3-phenylacetone and simply prepared ω-trifluoromethyl substituted δ and ε-ketoesters with arylhydrazines via Fischer indole synthesis has been developed.

1. Introduction

The replacement of hydrogen or halogen atom or alkyl group in organic molecules by CF_3 group has received wide attention in pharmaceuticals, agrochemicals, and material sciences due to the specific properties of the trifluoromethyl group.[1] Recent results showed that the introduction of CF_3 group at specific position in organic skeletons could enhance the relatively physiological stability, modulate the physical, chemical, and biological properties, and improve the pharmacokinetic properties as well.[2,3] Indole scaffold exists in variety of natural products with biological significance and was widely employed as pharmaceutical and agrochemical intermediate.[4] Indoles that have functional substituents at the C-2 and C-3 positions are capable of binding to many receptors with high affinity especially for electron-withdrawing substituent at C-2 position,[3,5] in addition, indole-3-carboxylates also have potential biological activities.[6] Therefore, simultaneously having both trifluoromethyl group at C-2 position and carboxylate group at C-3 position of indole skeleton is well worth to be expected to be a core structure in pharmaceutically and agrochemically important molecules.[7]

Construction of such indole skeleton, however, still remains a challenge due to the lack of sources of fluorinated substrates or efficient ways to install both CF_3 group and carboxylate group to indole skeleton in one process.[2a,8] To the best of our knowledge, there was even no report in literature regarding to the synthesis of fluorinated indole skeletons via traditional Fischer indole synthesis by using fluorinated ketone substrates.[2f,9]

In this paper, we wish to reveal the *p*-TsOH promoted Fischer indole synthesis toward the biologically interesting multi-substituted 2-trifluoromethyl indole derivatives including 2-trifluoromethyl-3-carboxylates in one-pot manner directly from the reaction of 1,1,1-trifluoro-3-phenylacetone and simply prepared ω-trifluoromethyl δ and ε-ketoesters building blocks with arylhydrazines.[10] This synthesis is facile, scalable, and transition metal free process. The reaction is typically passing through the hydrazone intermediate **3** followed by indolization to generate indole product **4** (Scheme 1).

2. Results and discussion

Our previous results about the synthesis of trifluoromethyl substituted 1,2-diaza-3-one heterocycles from ω-fluoroalkylated ketoesters has revealed that the reactions of arylhydrazines with ω-trifluoromethyl ketoesters that have shorter chain length, such as β and γ-ketoesters provided a major formation of 1,2-diaza-3-one heterocycle compounds by a tandem condensation/ring-closure reaction, but our preliminary result showed that the reaction with ketoesters that have longer chain length, such as δ-ketoester, could go through Fischer indolization.[10] To reveal in-depth coverage of 2-trifluoromethyl indole derivatives via Fischer indole synthesis, 1,1,1-trifluoro-3-phenylacetone (**1a**) was initially tested in this process and 2-trifluoromethyl 3-phenylindole (**4aa**) could be obtained successfully via Fischer indole synthesis under the catalysis of $ZnCl_2$. However, the reaction of trifluoromethyl δ-ketoester

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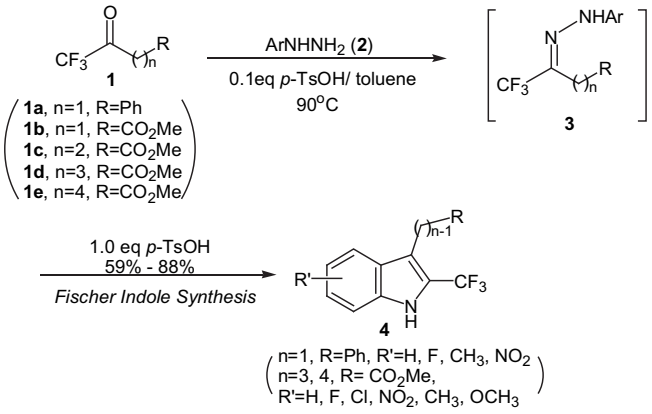
doi:10.1016/j.tet.2010.01.080



Scheme 1. *p*-TsOH promoted one-pot synthesis of 2-trifluoromethyl indole derivatives.

(**1d**) with phenylhydrazine (**2a**) under the catalysis of $ZnCl_2$ mainly resulted in the formation of hydrazone (**3da**), only trace amount of indole product was detected by ^{19}F NMR even using excess amount of $ZnCl_2$ (entry 1, Table 1). Other Lewis acids, such as $Ti(OEt)_4$ showed ability to catalyze the same condensations of ketoester **1** with hydrazine **2**, and obtained hydrazones **3** in high ratios (entry 2, Table 1). However, both of them encountered a great difficulty to achieve the subsequential indolization. Protonic acids, such as H_2SO_4, HCl, AcOH, and TFA were also able to promote such condensation in water, MeOH, or toluene media, and provided arylhydrazone intermediates in good ratios (Table 1). However, they also weren't suitable to carry out the Fischer indole synthesis properly. Reactions under such conditions only yielded indole-3-carboxylates **4** in lower yields or a complex mixture if reaction temperature was raised. Instead, *p*-TsOH was found to be a proper promoter to push the indolization to form desired 2-trifluoromethyl indole-3-carboxylate (**4da**) in excellent ratios (entry 5, Table 1). The condensation of arylhydrazine with ketoester could be terminated at stage of formation of hydrazone if catalytic amount of *p*-TsOH was employed (entry 3, Table 1). Reaction promoted by stoichiometric *p*-TsOH resulted in the formation of corresponding indole-3-carboxylate (**4da**) as major products (entries 5–7, Table 1). After screening and optimizing the reaction conditions, stoichiometric *p*-TsOH in toluene at 90 °C was selected to be a prior condition for this one-pot synthesis of indole derivatives (**4**).

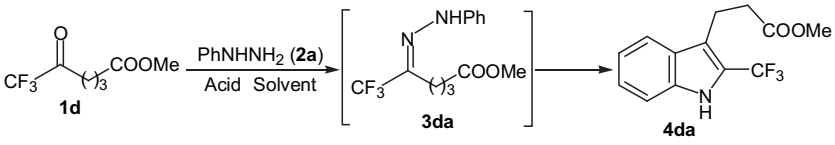
The Fischer indolizations of trifluoromethyl δ and ε-ketoesters (**1d** and **1e**) with phenylhydrazine (**2a**) were successfully carried out to form 2-trifluoromethyl indole-3-carboxylates (**4da**, **4ea**) under the promotion of stoichiometric *p*-TsOH in toluene (entries 7 and 18, Table 2). However, the reaction of γ-ketoester with phenylhydrazine under the same reaction conditions provided 4,5-dihydro-6-trifluoromethyl pyridazinone as dominated product rather than the formation of indole product, only trace amount of indole product could be detected by ^{19}F NMR. It's clear that the final products from the reactions of γ-ketoester and phenylhydrazines were dominated by the chain length of ω-trifluoromethyl ketoesters. The formation of five-membered pyrazol-3-ols and six-membered pyridazinones via condensation/ring-closure reaction of trifluoromethyl β,γ-ketoesters (shorter chain length) with phenylhydrazine are thermodynamically favored. Whereas, to longer chain length δ,ε-ketoesters, the reactions with phenylhydrazines were preferred to undergo the typical Fisher indolization process

Table 2
Synthesis of trifluoromethylated indole derivatives **4** from ω-trifluoromethyl ketones or ketoesters

Entry	**1** $CF_3CO(CH_2)_nR$	**2** $ArNHNH_2$	Temp/time (°C/h)	**4**	Yield[a] (%)
1	**1a** (*n*=1, R=Ph)	**2a** (R′=H)	80/8	**4aa**	83
2	**1a**	**2b**(R′=4-F)	80/8	**4ab**	79
3	**1a**	**2c** (R′=4-CH_3)	80/8	**4ac**	88
4	**1a**	**2d** (R′=4-NO_2)	80/8	**4ad**	71
5	**1b** (*n*=1, R=COOMe)	**2a**	Reflux/12	**4ba**	0[b]
6	**1c** (*n*=2, R=COOMe)	**2a**	Reflux/12	**4ca**	0.01[b]
7	**1d** (*n*=3, R=COOMe)	**2a**	90/12	**4da**	79
8	**1d**	**2b** (R′=4-F)	90/12	**4db**	75
9	**1d**	**2c** (R′=4-CH_3)	90/12	**4dc**	81
10	**1d**	**2d** (R′=4-NO_2)	90/15	**4dd**	60
11	**1d**	**2e** (R′=4-Cl)	90/12	**4de**	71
12	**1d**	**2f** (R′=4-OCH_3)	70/20	**4df**	20
13	**1d**	**2g** (R′=2-F)	90/18	**4dg**	61
14	**1d**	**2h** (R′=3-F)	90/15	**4dh** (4-F)	15
				4dh′(6-F)	44
15	**1d**	**2i** (R′=3-Cl)	90/15	**4di** (4-Cl)	25
				4di′(6-Cl)	40
16	**1d**	**2j** (R′=2,4-NO_2)	90/20	**3dj**	87[c]
17	**1e** (*n*=4, R=COOMe)	**2a**	90/15	**4ea**	68
18	**1e**	**2b**	90/15	**4eb**	70

[a] Isolated yield.
[b] Determined by ^{19}F NMR analysis to the crude reaction mixtures.
[c] Only hydrazone **3dj** was obtained.

Table 1
Optimization of reaction conditions for the synthesis of 2-trifluoromethy 3-indole carboxylic ester **4da**



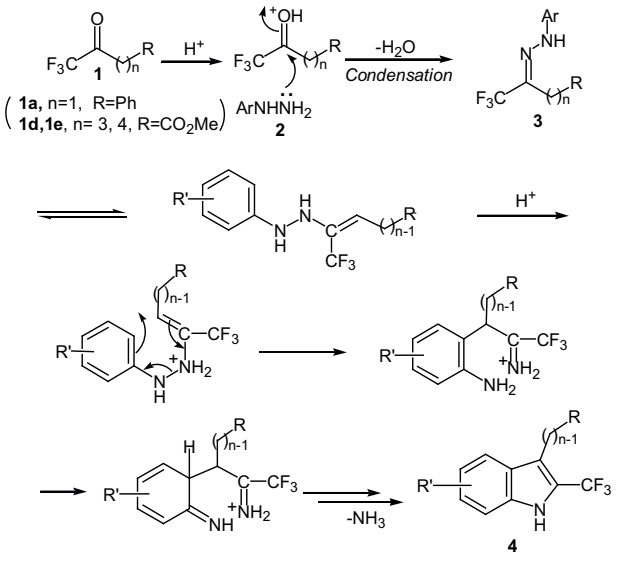
Entry	Solvent	Acid	Temp (°C)	**3da**:**4da**[a]
1	Toluene	$ZnCl_2$ (0.2 equiv)	Reflux	99[b]:1
2	Toluene	$Ti(OEt)_4$ (0.2 equiv)	Reflux	93[b]:0
3	Toluene	*p*-TsOH (0.1 equiv)	Reflux	82:16
4	Toluene	*p*-TsOH (0.2 equiv)	Reflux	75:22
5	Toluene	*p*-TsOH (1.1 equiv)	90	1:95
6	Toluene	*p*-TsOH (1.1 equiv)	Reflux	1:86
7	Toluene	*p*-TsOH (1.5 equiv)	90	1:93
8	Toluene	CF_3COOH (0.2 equiv)	Reflux	94[b]:0
9	MeOH	98% H_2SO_4	Reflux	67:28
10	AcOH	AcOH/AcONa	Reflux	100:0
11	MeOH	HCl	Reflux	65:13

[a] Ratio determined by ^{19}F NMR analysis to the crude reaction mixtures after stirring 12 h.
[b] Indole product **4da** was only detected by ^{19}F NMR as a minor product even using excess amount of acid.

through tautomerization, [3,3]-sigmatropic rearrangement, cyclization, and aromatization. Moreover, the reactions of δ or ε-ketoesters with aliphatic hydrazines only resulted in the formations of cyclic trifluoromethylated dihydrodiazepinone or 1,2-diazocinone.[10]

The reactions of 1,1,1-trifluoro-3-phenylacetone with arylhydrazines could provide higher yield of 2-trifluoromethyl 3-phenylindoles under the promotion of stoichiometric *p*-TsOH than the reactions catalyzed by $ZnCl_2$ (entries 1–4, Table 2).

Reactions toward methyl 2-trifluoromethyl-indole-3-propanoates and methyl 2-trifluoromethyl-indole-3-butanoates from ω-trifluoromethyl δ-ketoester and ε-ketoester were carried out via typical Fischer indole synthesis mechanism (Scheme 2). In general, *para*- and *ortho*-electron releasing group substituted arylhydrazines exhibited higher reactivities and provided better yields of products in comparison with those electron-withdrawing group substituted hydrazines (entries 10 and 11). *p*-Methoxyphenylhydrazine (**2f**), however, is unstable,[11] the condensation of **2f** with ketoester **1d** was quite difficult to be controlled and resulted in complex mixture, thus, the isolated yield of indole product **4df** was low. Regioisomers caused by stronger electronegative effect of substituent group on phenyl ring of hydrazines was also observed in the cases of using *m*-F and *m*-Cl-phenylhydrazines (entries 14 and 15, Table 2). Products (**4dh′** and **4di′**) from electron richer position of phenylhydrazines were much favored. Moreover, *m*-F-phenylhydrazines provided relatively higher regioselectivities (**4dh**/**4dh′**) than *m*-Cl-phenylhydrazines (**4di**/**4di′**) due to stronger electronegativity of fluorine atom.



Scheme 2. Plausible reaction mechanism from ketones or ketoesters to indoles **4**.

The structure of the product **4dc** was confirmed by X-ray diffraction studies (Fig. 1). In the diagram of crystal structure of **4dc**, crystal structure is stabilized by intermolecular and intramolecular hydrogen bonds (Table 3). The supramolecular aggregation is completed by the presence of π–π interactions, intermolecular hydrogen bonds, and intermolecular van der Waals.

3. Conclusion

In conclusion, multi-substituted biologically significant 2-trifluoromethyl indole derivatives, such as 2-trifluoromethyl-3-phenylindoles, 2-trifluoromethyl-indole-3-propanoates, and 2-trifluo romethyl-indole-3-butanoates, were synthesized through one-pot process from the reactions of 1,1,1-trifluoro-3-phenylacetone and simply prepared ω-trifluoromethyl substituted δ and ε-ketoesters with hydrazines via *p*-TsOH promoted Fischer indole synthesis. Variation of the arylhydrazines and suitable fluorinated ketoester or ketone can provide the desired 2-trifluoromethyl indole derivatives.

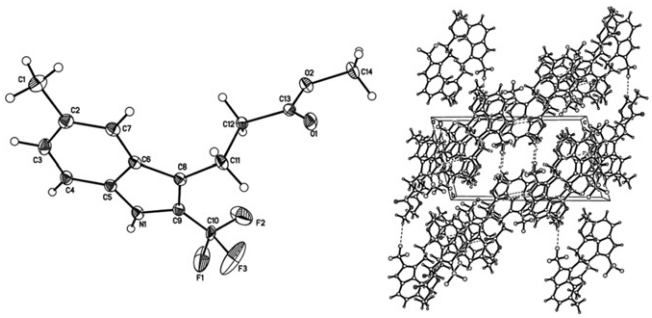


Figure 1. An ORTEP plot of **4dc** and its packing diagram.

Table 3
Hydrogen-bond geometry

D–H···A	D–H	H···A	D···A	D–H···A
N1–H1···O4	0.86	2.07	2.925(5)	170.0
N2–H2···O1	0.86	2.07	2.925(5)	170.4
C25–H25A···F6	0.97	2.35	2.958(6)	120

Symmetry codes: (i) $-x+1, -y, -z$; (ii) $x+1/2, -y+1/2, z+1/2$.

4. Experimental section

4.1. General

Reactions were conducted in an appropriate round bottom flask equipped with magnetic stirring bar and condenser under nitrogen protection. Thin layer chromatography (TLC) was performed on a silica gel. All melting points were taken on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China, and were uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AV-500 spectrometer. Chemical shifts for ^1H NMR spectra are reported in parts per million downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in parts per million relative to internal chloroform (δ 77.2 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in parts per million downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants (J) are given in hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartet, respectively, br refers to a broad signal. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer, absorbance frequencies are given at maximum of intensity in cm^{-1}. Elemental analyses were performed with Elemental Vario EL III instrument.

4.2. General procedure for the 2-trifluoromethyl indoles 4

A 25 mL three-necked flask equipped with a condenser and magnetic stir bar was charged with hydrazine (10 mmol), ketone or ketoester (10 mmol), toluene-4-sulfonic acid (11 mmol), and toluene (10 mL) at 90 °C under nitrogen atmosphere. After the solution stirring for about 0.5 h, phenylhydrazone was produced. The mixture was maintained for 3–18 h. Solvent was evaporated under reduced pressure, and the residue was then purified by flash column chromatography on silica gel to yield the product **4**.

*4.2.1. 3-Phenyl-2-(trifluoromethyl)-1H-indole (**4aa**).* Pale yellow crystal (5:1 petroleum ether/acetone); mp 63–64 °C (lit.[12] 63–64 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.65 (d, 1H, J=8.0 Hz), 7.54–7.53 (m, 2H), 7.49–7.46 (m, 3H), 7.42–7.36 (m, 2H), 7.22–7.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.1, 132.3, 130.0, 128.5, 127.7, 127.4, 125.3, 121.8 (q, $^1J_{C-F}$=267.5 Hz), 121.4, 121.3 (q, $^2J_{C-F}$=37.5 Hz), 121.2, 119.9 (q, $^3J_{C-F}$=2.5 Hz), 111.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ −56.80 (s, 3F). IR (cm^{-1}): ν 3450, 3058, 1606, 1495, 1448, 1325, 1130, 1109, 749, 703. Anal. Calcd for $C_{15}H_{10}F_3N$: C, 68.96; H, 3.86; N, 5.36. Found: C, 69.25; H, 4.32; N, 5.05.

*4.2.2. 5-Fluoro-3-phenyl-2-(trifluoromethyl)-1H-indole (**4ab**).* White solid (5:1 petroleum ether/acetone); mp 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 7.55–7.50 (m, 4H), 7.46–7.43 (m, 1H), 7.41–7.38 (m, 1H), 7.32 (dd, 1H, J=9.0, 2.0 Hz), 7.14 (td, 1H, J=9.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (d, $^1J_{C-F}$=236.3 Hz), 131.8, 131.6, 129.9, 129.8, 128.7, 127.9, 122.9 (q, $^2J_{C-F}$=36.3 Hz), 121.5 (q, $^1J_{C-F}$=267.5 Hz), 119.9 (q, $^3J_{C-F}$=2.5 Hz), 114.3 (d, $^2J_{C-F}$=27.5 Hz), 112.9 (d, $^3J_{C-F}$=9.5 Hz), 105.9 (d, $^2J_{C-F}$=23.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −57.03 (s, 3F), −121.84 to −121.89 (m, 1F); IR (cm^{-1}): ν 3453, 3063, 1609, 1570, 1457, 1250, 1164, 1123, 863, 800, 767, 703.

*4.2.3. 5-Methyl-3-phenyl-2-(trifluoromethyl)-1H-indole (**4ac**).* White solid (5:1 petroleum ether/acetone); mp 74–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (br s, 1H), 7.54–7.48 (m, 4H), 7.43–7.40 (m, 2H), 7.36 (d, 1H, J=8.5 Hz), 7.20 (d, 1H, J=8.5 Hz), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.4, 132.4, 130.9, 130.1, 128.5, 127.6, 127.1, 121.8 (q, $^1J_{C-F}$=267.5 Hz), 121.4 (q, $^2J_{C-F}$=37.5 Hz), 120.5, 119.5 (q, $^3J_{C-F}$=2.5 Hz), 118.6, 111.5, 21.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −56.76 (s, 3F); IR (cm^{-1}): ν 3381, 3086, 1609, 1568, 1326, 1171, 1111, 699. Anal. Calcd for $C_{16}H_{12}F_3N$: C, 69.81; H, 4.39; N, 5.09. Found: C, 69.72; H, 4.58; N, 4.99.

*4.2.4. 5-Nitro-3-phenyl-2-(trifluoromethyl)-1H-indole (**4ad**).* Yellow solid (4:1 hexane/ethyl acetate); mp 108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 8.60 (d, 1H, J=2.0 Hz), 8.28 (dd, 1H, J=9.0, 2.0 Hz), 7.57–7.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 137.8, 130.5, 129.9, 129.0, 128.6, 127.0, 124.3 (q, $^2J_{C-F}$=37.5 Hz), 122.2 (q, $^3J_{C-F}$=2.5 Hz), 121.0 (q, $^1J_{C-F}$=267.5 Hz), 120.6, 118.9, 112.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ −57.41 (s, 3F); IR (cm^{-1}): ν 3360, 3090, 1525, 1478, 1337, 1173, 1129, 818, 750, 704. Anal. Calcd for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96; N, 9.15. Found: C, 58.57; H, 3.24; N, 8.95.

*4.2.5. Methyl 3-(2-(trifluoromethyl)-1H-indol-3-yl) porpanoate (**4da**).* White solid (5:1 petroleum ether/acetone); mp 151–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 7.68 (d, 1H, J=8.0 Hz), 7.41 (d, 1H, J=8.0 Hz), 7.33 (dd, 1H, J=8.0, 8.0 Hz), 7.20 (ddd, 1H, J=8.0, 8.0, 1.0 Hz), 3.68 (s, 3H), 3.24 (td, 2H, J=8.0, 1.0 Hz), 2.67 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 135.5, 127.0, 124.8, 122.1 (q, $^1J_{C-F}$=266.3 Hz), 121.8 (q, $^2J_{C-F}$=37.5 Hz), 120.6, 120.0, 116.4 (q, $^3J_{C-F}$=2.5 Hz), 112.0, 51.9, 35.4, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.44 (s, 3F); IR (cm^{-1}): ν 3363, 3044, 1718, 1592, 1458, 1201, 1155, 742. Anal. Calcd for $C_{13}H_{12}F_3NO_2$: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.34; H, 4.70; N, 5.07.

*4.2.6. Methyl 3-(5-fluoro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4db**).* White solid (5:1 petroleum ether/acetone); mp 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 7.35–7.30 (m, 2H), 7.10–7.06 (m, 1H), 3.69 (s, 3H), 3.18 (td, 2H, J=8.0, 1.0 Hz), 2.65 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 158.2 (d, $^1J_{C-F}$=235.0 Hz), 131.9, 127.4 (d, $^3J_{C-F}$=10.0 Hz), 123.5 (q, $^2J_{C-F}$=37.5 Hz), 121.8 (q, $^1J_{C-F}$=267.5 Hz), 116.4 (q, $^3J_{C-F}$=2.5 Hz), 113.8 (d, $^2J_{C-F}$=25.0 Hz), 113.0 (d, $^3J_{C-F}$=10.0 Hz), 104.8 (d, $^2J_{C-F}$=25.0 Hz), 51.9, 35.2, 19.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.73 (s, 3F), −122.22 to −122.31 (m, 1F). IR (cm^{-1}): ν 3359, 3017, 1713, 1571, 1465, 1200, 1115, 859, 807, 730. Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84. Found: C, 53.94; H, 3.71; N, 4.90.

*4.2.7. Methyl 3-(5-methyl-2-(trifluoromethyl)-1H-indol-3-yl)propanoate (**4dc**).* Yellow solid (5:1 petroleum ether/acetone); mp 156–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (br s, 1H), 7.43 (s, 1H), 7.28 (d, 1H, J=8.0 Hz), 7.15 (dd, 1H, J=8.0, 1.0 Hz), 3.69 (s, 3H), 3.20 (td, 2H, J=8.0, 1.0 Hz), 2.66 (t, 2H, J=8.0 Hz), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 133.8, 130.1, 127.2, 126.7, 122.1 (q, $^1J_{C-F}$=267.5 Hz), 121.8 (q, $^2J_{C-F}$=37.5 Hz), 119.4, 116.0 (q, $^3J_{C-F}$=2.5 Hz), 111.7, 51.8, 35.4, 21.5, 19.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.42 (s, 3F); IR (cm^{-1}): ν 3346, 3035, 1725, 1570, 1472, 1208, 1155, 1109, 794. Anal. Calcd for $C_{14}H_{14}F_3NO_2$: C, 58.95; H, 4.95; N, 4.91. Found: C, 58.75; H, 4.84; N, 4.80.

*4.2.8. Methyl 3-(5-nitro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4dd**).* White solid (5:1 petroleum ether/acetone); mp 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (br s, 1H), 8.69 (d, 1H, J=2.0 Hz), 8.23 (dd, 1H, J=9.0, 2.0 Hz), 7.47 (d, 1H, J=9.0 Hz), 3.70 (s, 3H), 3.29 (td, 2H, J=8.0, 1.0 Hz), 2.70 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ 173.0, 143.2, 139.6, 127.1, 125.6 (q, $^2J_{C-F}$=37.5 Hz), 122.6 (q, $^1J_{C-F}$=267.5 Hz), 120.5, 119.9 (q, $^3J_{C-F}$=2.5 Hz), 118.6, 113.8, 51.8, 35.8, 19.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ −59.07 (s, 3F); IR (cm^{-1}): ν 3349, 3080, 1725, 1587, 1520, 1355, 1181, 1150, 741. Anal. Calcd for $C_{13}H_{11}F_3N_2O_4$: C, 49.37; H, 3.51; N, 8.86. Found: C, 49.15; H, 3.34; N, 8.73.

*4.2.9. Methyl 3-(5-chloro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4de**).* White solid (5:1 petroleum ether/acetone); mp 153–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 7.64 (d, 1H, J=1.5 Hz), 7.33 (d, 1H, J=8.0 Hz), 7.27 (dd, 1H, J=8.0, 1.5 Hz), 3.69 (s, 3H), 3.19 (td, 2H, J=8.0, 1.0 Hz), 2.65 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 133.6, 128.2, 126.7, 125.6, 123.2 (q, $^2J_{C-F}$=37.5 Hz), 121.7 (q, $^1J_{C-F}$=267.5 Hz), 119.7, 116.5 (q, $^3J_{C-F}$=2.5 Hz), 113.1, 51.9, 35.2, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.71 (s, 3F); IR (cm^{-1}): ν 3324, 3063, 1725, 1588, 1456, 1148, 1114, 900, 797, 721. Anal. Calcd for $C_{13}H_{11}ClF_3NO_2$: C, 51.08; H, 3.63; N, 4.58. Found: C, 51.16; H, 3.77; N, 4.31.

*4.2.10. Methyl 3-(5-methoxy-2-(trifluoromethyl)-1H-indol-3-yl) pro panoate (**4df**).* Brown oil (4:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (br s, 1H), 7.29 (d, 1H, J=9.0 Hz), 7.05 (d, 1H, J=2.0 Hz), 6.99 (dd, 1H, J=9.0, 2.0 Hz), 3.87 (s, 3H), 3.69 (s, 3H), 3.20 (td, 2H, J=8.0, 1.0 Hz), 2.66 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 154.9, 129.8, 127.5, 122.4 (q, $^2J_{C-F}$=37.5 Hz), 122.0 (q, $^1J_{C-F}$=267.5 Hz), 116.4 (q, $^3J_{C-F}$=2.5 Hz), 115.4, 112.9, 100.9, 56.0, 51.9, 35.2, 19.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.47 (s, 3F); IR (cm^{-1}): ν 3408, 1718, 1610, 1513, 1470, 1217, 1159, 1113, 804, 727.

*4.2.11. Methyl 3-(7-fluoro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4dg**).* White solid (5:1 petroleum ether/acetone); mp 110–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (br s, 1H), 7.44 (dd, 1H, J=8.0, 5.0 Hz), 7.10 (ddd, 1H, J=8.0, 8.0, 5.0 Hz), 7.02 (dd, 1H, J=11.0, 8.0 Hz), 3.68 (s, 3H), 3.22 (td, 2H, J=8.0, 1.0 Hz), 2.66 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 149.8 (d, $^1J_{C-F}$=243.8 Hz), 130.6, 124.1 (d, $^2J_{C-F}$=13.8 Hz), 122.8 (q, $^2J_{C-F}$=37.5 Hz), 121.7 (q, $^1J_{C-F}$=267.5 Hz), 121.1 (d, $^3J_{C-F}$=5.0 Hz), 117.5 (q, $^3J_{C-F}$=2.5 Hz), 115.9 (d, $^3J_{C-F}$=5.0 Hz), 109.5 (d, $^2J_{C-F}$=16.3 Hz), 51.9, 35.2, 19.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.71 (s, 3F), −134.22 (dd, 1F, J=11.0, 5.0 Hz); IR (cm^{-1}): ν 3342, 3026, 1722, 1578, 1424, 1200, 1146, 1112, 800, 746. Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84. Found: C, 53.83; H, 3.91; N, 4.78.

*4.2.12. Methyl 3-(4-fluoro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4dh**).* White solid (5:1 petroleum ether/acetone); mp 105–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (br s, 1H), 7.20–7.26

(m, 1H), 7.16 (d, 1H, J=8.0 Hz), 6.82 (ddd, 1H, J=11.0, 8.0, 0.5 Hz), 3.70 (s, 3H), 3.28 (td, 2H, J=8.0, 1.0 Hz), 2.72–2.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 157.7 (d, $^1J_{C-F}$=247.5 Hz), 137.8 (d, $^3J_{C-F}$=10.0 Hz), 125.6 (d, $^3J_{C-F}$=7.5 Hz), 122.1 (q, $^2J_{C-F}$=37.5 Hz), 121.7 (q, $^1J_{C-F}$=267.5 Hz), 116.3 (d, $^2J_{C-F}$=20.0 Hz), 115.6 (q, $^3J_{C-F}$=2.5 Hz), 108.0 (d, $^4J_{C-F}$=3.8 Hz), 105.9 (d, $^2J_{C-F}$=20.0 Hz), 51.8, 35.8, 20.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.38 (s, 3F), −122.53 (dd, 1F, J=11.0, 5.0 Hz); IR (cm^{-1}): ν 3309, 3051, 1724, 1643, 1581, 1439, 1207, 1165, 1119, 785, 734.

*4.2.13. Methyl 3-(6-fluoro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4dh′**).* Pale yellow solid (5:1 petroleum ether/acetone); mp 117–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (br s, 1H), 7.59 (dd, 1H, J=9.0, 5.0 Hz), 7.02 (dd, 1H, J=9.0, 2.0 Hz), 6.95 (td, 1H, J=9.0, 2.0 Hz), 3.68 (s, 3H), 3.21 (td, 2H, J=8.0, 1.0 Hz), 2.67 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 161.4 (d, $^1J_{C-F}$=241.3 Hz), 135.5 (d, $^3J_{C-F}$=12.5 Hz), 123.7, 122.2 (q, $^2J_{C-F}$=37.5 Hz), 121.8 (q, $^1J_{C-F}$=267.5 Hz), 121.3 (d, $^3J_{C-F}$=10.0 Hz), 116.8 (q, $^3J_{C-F}$=2.5 Hz), 110.1 (d, $^2J_{C-F}$=25.0 Hz), 98.1 (d, $^2J_{C-F}$=25.0 Hz), 51.9, 35.4, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.56 (s, 3F), −116.76 (dd, 1F, J=11.0, 5.0 Hz); IR (cm^{-1}): ν 3319, 1715, 1631, 1576, 1442, 1268, 1157, 1114, 847, 805, 730. Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84. Found: C, 53.81; H, 3.85; N, 4.91.

*4.2.14. Methyl 3-(4-chloro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4di**).* White solid (5:1 petroleum ether/acetone); mp 91–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (br s, 1H), 7.30 (dd, 1H, J=8.0, 1.0 Hz), 7.20 (dd, 1H, J=8.0, 8.0 Hz), 7.15 (dd, 1H, J=8.0, 1.0 Hz), 3.72 (s, 3H), 3.43 (td, 2H, J=8.5, 1.0 Hz), 2.75–2.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 136.7, 127.5, 125.4, 123.5 (q, $^2J_{C-F}$=37.5 Hz), 122.8, 122.1, 121.7 (q, $^1J_{C-F}$=267.5 Hz), 117.1 (q, $^3J_{C-F}$=2.5 Hz), 110.8, 51.8, 36.6, 20.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.41 (s, 3F); IR (cm^{-1}): ν 3323, 3071, 1719, 1583, 1458, 1265, 1161, 1120, 780, 744, 684. Anal. Calcd for $C_{13}H_{11}ClF_3NO_2$: C, 51.08; H, 3.63; N, 4.58. Found: C, 51.01; H, 3.72; N, 4.47.

*4.2.15. Methyl 3-(6-chloro-2-(trifluoromethyl)-1H-indol-3-yl) propanoate (**4di′**).* White solid (5:1 petroleum ether/acetone); mp 78–79 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (br s, 1H), 7.58 (d, 1H, J=8.5 Hz), 7.36 (d, 1H, J=2.0 Hz), 7.15 (dd, 1H, J=8.5, 2.0 Hz), 3.67 (s, 3H), 3.21 (td, 2H, J=8.0, 1.0 Hz), 2.65 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 135.6, 131.0, 125.7, 122.5 (q, $^2J_{C-F}$=37.5 Hz), 121.8, 121.7 (q, $^1J_{C-F}$=267.5 Hz), 121.2, 117.0 (q, $^3J_{C-F}$=2.5 Hz), 111.8, 51.9, 35.3, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.66 (s, 3F); IR (cm^{-1}): ν 3323, 3035, 1723, 1589, 1441, 1201, 1160, 1112, 920, 802, 716. Anal. Calcd for $C_{13}H_{11}ClF_3NO_2$: C, 51.08; H, 3.63; N, 4.58. Found: C, 51.06; H, 3.62; N, 4.59.

*4.2.16. Methyl 4-(2-(trifluoromethyl)-1H-indol-3-yl)butanoate (**4ea**).* White solid (5:1 petroleum ether/acetone); mp 156–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 7.68 (d, 1H, J=8.0 Hz), 7.38 (d, 1H, J=8.0 Hz), 7.31 (ddd, 1H, J=8.0, 8.0, 1.0 Hz), 7.18 (ddd, 1H, J=8.0, 8.0, 1.0 Hz), 3.67 (s, 3H), 2.94 (t, 2H, J=7.5 Hz), 2.38 (td, 2H, J=7.5, 1.0 Hz), 2.03 (t, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 135.5, 127.4, 124.8, 122.2 (q, $^1J_{C-F}$=267.5 Hz), 121.8 (q, $^2J_{C-F}$=37.5 Hz), 120.6, 120.3, 117.6 (q, $^3J_{C-F}$=2.5 Hz), 111.9, 51.7, 33.6, 25.8, 23.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.15 (s, 3F); IR (cm^{-1}): ν 3341, 3062, 1720, 1590, 1454, 1382, 1200, 1161, 1115, 746.

*4.2.17. Methyl 4-(5-fluoro-2-(trifluoromethyl)-1H-indol-3-yl) butanoate (**4eb**).* White solid (5:1 petroleum ether/acetone); mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.33–7.29 (m, 2H), 7.07 (dd, 1H, J=9.0, 2.5 Hz), 3.68 (s, 3H), 2.89 (td, 2H, J=7.5, 1.0 Hz), 2.38 (t, 2H, J=7.5 Hz), 2.00 (t, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 158.2 (d, $^1J_{C-F}$=235.0 Hz), 131.9, 127.9 (d, $^3J_{C-F}$=10.0 Hz), 123.4 (q, $^2J_{C-F}$=37.5 Hz), 121.9 (q, $^1J_{C-F}$=267.5 Hz), 117.8 (q, $^3J_{C-F}$=2.5 Hz), 113.9 (d, $^2J_{C-F}$=26.3 Hz), 112.8 (d, $^3J_{C-F}$=10.0 Hz), 105.2 (d, $^2J_{C-F}$=22.5 Hz), 51.7, 33.5, 25.7, 23.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.47 (s, 3F), −122.51 to −122.53 (m, 1F); IR (cm^{-1}): ν 3357, 3010, 1723, 1568, 1470, 1208, 1147, 1103, 895, 803, 690. Anal. Calcd for $C_{14}H_{13}F_4NO_2$: C, 55.45; H, 4.32; N, 4.62. Found: C, 55.57; H, 4.21; N, 4.57.

*4.2.18. Methyl 5-(2-(2,4-dinitrophenyl)hydrazono)-6,6,6-trifluorohexanoate (**3dj**).* Yellow solid (4:1 petroleum ether/ethyl acetate); mp 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.33 (br s, 1H), 9.15 (d, J=2.5 Hz, 2H), 8.44–8.42 (m, 1H), 8.06 (d, J=9.5 Hz, 1H), 3.74 (s, 3H), 2.70–2.67 (m, 2H), 2.52 (t, J=7.0 Hz, 2H), 2.07–2.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 144.4, 143.2 (q, $^2J_{C-F}$=33.8 Hz), 140.2, 131.4, 130.5, 123.1 120.9 (q, $^1J_{C-F}$=272.5 Hz), 117.4, 52.2, 33.3, 24.9, 20.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ −69.8 (s, 3F); IR (cm^{-1}): ν 3313, 3094, 1725, 1616, 1594, 1335, 1196, 1132, 849, 743.

4.3. X-ray crystal structure data of compound 4dc

Single-crystal XRD was performed with graphite-monochromatic Mo Kα radiation (λ=0.71073 Å) on a Bruker Smart ApexII CCD diffractometer at T=273(2) K. The structures were solved by direct method with SHELXS-97 program and refined by full matrix least-squares on F^2 with SHELXL-97 program. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located and included at their calculated position.

CCDC 755245 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Acknowledgements

This work was financially supported by National Natural Science Foundation of China (20772079), Science and Technology Commission of Shanghai Municipality (07JC14020, 07ZR14040, 08JC1409900) and Shanghai Municipal Education Commission.

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