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Route for the Generation of Trifluoromethyl-Substituted Pyrrplo[3,2-*c*]quinolines

Danqing Zheng,[†,‡] Tong Liu,[‡] Xia Liu,[†] Xiaona Fan,*[,†] and Jie Wu*[,‡,§]

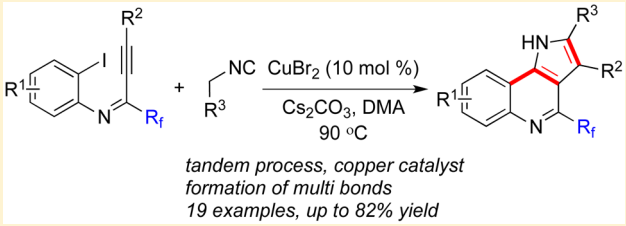
[†]Gannan Medical University Collaborative Innovation Center for Gannan Oil-tea Camellia Industrial Development, 1 Yixueyuan Road, Ganzhou, Jiangxi 341000, China

[‡]Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Generation of trifluoromethyl-substituted pyrrolo[3,2-*c*]quinolines via a copper(II)-catalyzed tandem reaction of *N*-(*σ*-iodoaryl)alkynylimines with 2-isocyanoacetates is reported. The process involves a [3 + 2] cycloaddition and intramolecular C−C bond coupling, leading to the fluorine-containing *N*-heterocycles under mild conditions with high efficiency.



It is well-known that quinolines hold an important position among natural products and small molecule chemotherapeutics due to their diverse pharmacological properties.[1] Thus, much attention has been paid to the development of methodologies for the construction of quinolines.[2,3] Among the family of quinolines, pyrrolo[3,2-*c*]quinolone is an important class of compounds and distributes in many biologically active natural products such as isocryptolepine,[4] martinelline, and martinellic acid (Figure 1).[5] The natural

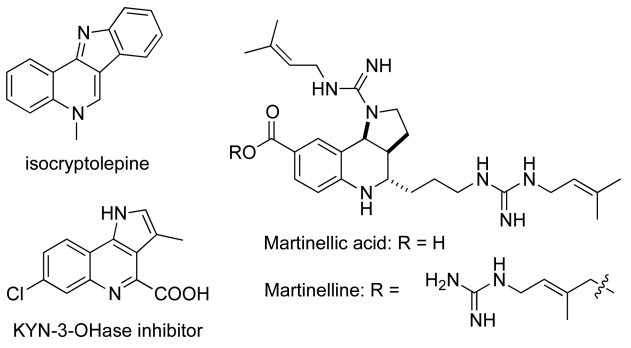


Figure 1. Examples of natural products and bioactive compounds featuring the pyrrolo[3,2-*c*]quinolone scaffold.

alkaloid isocryptolepine has been used traditionally to treat a range of diseases and now has shown to be a potential new antimalarial agent.[4,6] Martinelline and martinellic acid are two guanidine alkaloids isolated from root extracts of the Martinellaiquitosensis vine, which have been indicated as modest antibiotics and effective inhibitors for several G-protein coupled receptors.[5,7] The pyrrolo[3,2-*c*]quinolone is also one of the most broadly used frameworks in medicinal chemistry for developing KYN-3-OHase inhibitors,[8] ATPase inhibitors,[9] antitumors,[10] hypotensive agents,[11] etc. In the meantime, it is well recognized that introduction of the fluorine atom into small molecules could lead to great changes in their pharmacological properties due to the unique impact of fluorine.[12] However, there are few methods for incorporating fluorinated moieties into pyrrolo[3,2-*c*]quinolones. Hence, we report our recent efforts for the generation of fluorinated pyrrolo[3,2-*c*]quinolones via a copper(II)-catalyzed reaction of *N*-(*σ*-iodoaryl)alkynylimines with 2-isocyanoacetates under mild conditions.

2-Isocyanoacetate is a useful building block in tandem reactions because of its unusual reactivity in generating multiple bonds in a single-pot process.[13−15] In the past decades, significant progress has been achieved in the pursuit of novel methods for the construction of structurally diverse nitrogen-containing heterocycles with 2-isocyanoacetate. We were also attracted by this versatile synthon and developed several efficient routes for the formation of nitrogen-containing heterocycles employing 2-isocyanoacetate as the substrate.[16] For instance, we reported the generation of tetrahydroindeno-[2,1-*b*]pyrroles via a base-promoted reaction of (*E*)-2-alkynylphenylchalcones with 2-isocyanoacetates.[16a] Based on our recent studies on 2-isocyanoacetates and prompted by the importance of fluorine-containing pyrrolo[3,2-*c*]quinolones, we conceived that fluorinated pyrrolo[3,2-*c*]quinolones **3** could be prepared via a copper-catalyzed tandem reaction of *N*-(*σ*-iodoaryl)alkynylimines with 2-isocyanoacetates, as presented in Scheme 1. We envisioned that the copper-catalyzed [3 + 2] cycloaddition of 2-isocyanoacetate with the triple bond of *N*-(*σ*-

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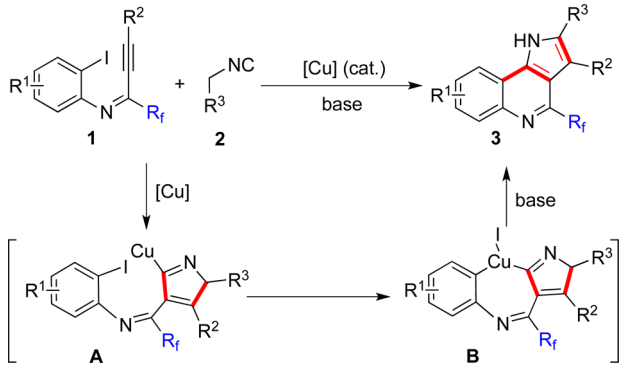
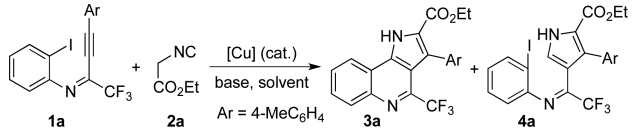
Scheme 1. Proposed Route for the Copper(Ii)-Catalyzed Reaction of *N*-(σ-Iodoaryl)alkynylimines with 2-Isocyanoacetates



iodoaryl)alkynylimine would occur first to generate the organocopper intermediate **A**. The following intramolecular insertion of copper into the C−I bond would lead to the intermediate **B**, which would undergo reductive elimination and aromatization to provide the expected product **3**. To verify the feasibility of this proposed route, we therefore started to explore the possibility of this copper(II)-catalyzed tandem reaction of *N*-(σ-iodoaryl)alkynylimines with 2-isocyanoacetates.

Initially, the reaction between *N*-(σ-iodoaryl)alkynylimine **1a** and ethyl 2-isocyanoacetate **2a** was performed as the model for the optimization of the reaction conditions (Table 1). The reaction was catalyzed by CuI in the presence of 1.5 equiv of Cs_2CO_3 in DMF at room temperature. To our delight, the expected product of 4-(trifluoromethyl)pyrrolo[3,2-*c*]-quinolone **3a** was isolated in 17% yield (Table 1, entry 1). The structure of product **3a** was proved by X-ray diffraction analysis (Figure 2). The byproduct pyrrole **4a** was also detected in 39% yield, which was generated from the protonation of the organocopper intermediate. This result confirmed the practicability of the deigned route in Scheme 1. It was found that only the protonated byproduct **4a** was observed in the absence of the copper catalyst, which demonstrated that the copper catalyst was essential in this transformation (Table 1, entry 2). Next, the reaction temperature was evaluated, and the yield was increased to 39% when the reaction was performed at 90 °C (Table 1, entry 4). No better result was obtained when the reaction temperature was elevated to 110 °C (Table 1, entry 5). Other solvents were next screened, such as DMSO, DMA, 1,4-dioxane, and CH_3CN (Table 1, entries 6−9). The reaction proceeded smoothly when DMA was applied, which gave rise to the desired product **3a** in 47% yield. The reaction did not take place in 1,4-dioxane or CH_3CN. Utilization of CuOAc as the catalyst also failed to provide the desired product (Table 1, entry 10). The examination of other copper catalysts indicated that $CuBr_2$ was the best choice, leading to the desired product **3a** in 82% yield (Table 1, entries 11−14). A similar yield was obtained when the amount of Cs_2CO_3 was decreased to 1.0 equiv (Table 1, entry 15). The yield was lower in the presence of 0.7 equiv of Cs_2CO_3 (Table 1, entry 16). The results were inferior when other bases were employed (Table 1, entries 17−19). We also tested the less active substrate *N*-(σ-bromoaryl)-alkynylimine under the conditions. However, only a trace amount of the desired product **3a** was detected. This transformation still failed when the reaction was performed at 110 °C (data not shown in Table 1).

Table 1. Initial Studies for the Reaction of *N*-(σ-Iodoaryl)alkynylimine1a with 2-Isocyanoacetate2a[a]



					yield[b] (%)	
entry	[Cu]	solvent	base	temp (°C)	3a	4a
1	CuI	DMF	Cs_2CO_3	rt	21 (17)	39 (36)
2		DMF	Cs_2CO_3	rt	0	37
3	CuI	DMF	Cs_2CO_3	60	32	38
4	CuI	DMF	Cs_2CO_3	90	39	31
5	CuI	DMF	Cs_2CO_3	110	35	27
6	CuI	DMSO	Cs_2CO_3	90	41	35
7	CuI	DMA	Cs_2CO_3	90	47	25
8	CuI	Dioxane	Cs_2CO_3	90	ND	40
9	CuI	CH_3CN	Cs_2CO_3	90	ND	34
10	CuOAc	DMA	Cs_2CO_3	90	ND	20
11	CuBr	DMA	Cs_2CO_3	90	58	27
12	$CuBr_2$	DMA	Cs_2CO_3	90	82	10
13	CuCl	DMA	Cs_2CO_3	90	44	18
14	$CuCl_2$	DMA	Cs_2CO_3	90	70	12
15[c]	$CuBr_2$	DMA	Cs_2CO_3	90	82 (78)	7
16[d]	$CuBr_2$	DMA	Cs_2CO_3	90	68	10
17[c]	$CuBr_2$	DMA	K_2CO_3	90	75	7
18[c]	$CuBr_2$	DMA	K_3PO_4	90	63	trace
19[c]	$CuBr_2$	DMA	NaOH	90	43	trace

[a]Reaction conditions: [Cu] (0.02 mmol), *N*-(σ-iodoaryl)alkynylimine **1a** (0.2 mmol), 2-isocyanoacetate **2a** (0.24 mmol), base (0.3 mmol), solvent (2.0 mL), 1 h. [b]Yields detected by ^{19}F NMR based on *N*-(σ-haloaryl)alkynylimine **1a** using trifluorotoluene as the standard. Isolated yields in parentheses. [c]Base (1.0 equiv). [d]Base (0.7 equiv).

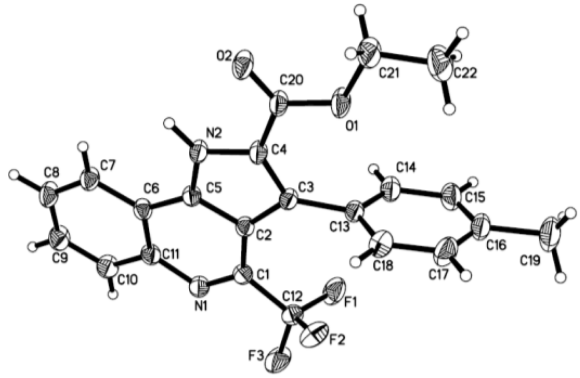


Figure 2. X-ray ORTEP illustration of 4-(trifluoromethyl)pyrrolo[3,2-*c*]quinolone **3a** (30% probability ellipsoids).

The scope of the copper-catalyzed tandem reaction of *N*-(σ-iodoaryl)alkynylimines **1** and 2-isocyanoacetates **2** was subsequently investigated under the above optimized reaction conditions (Table 2). The results revealed that in most cases *N*-(σ-iodoaryl)alkynylimines **1** reacted with ethyl 2-isocyanoacetate **2a**, leading to the desired products **3** in good yields. Other isocyanides such as methyl 2-isocyanoacetate and tosylmethyl isocyanide could also participate in this transformation to produce the corresponding products **3b,c** in good yields. The reaction was complex when (isocyanomethyl)benzene was applied. Reactions of *N*-(σ-iodoaryl)alkynylimines **1** bearing

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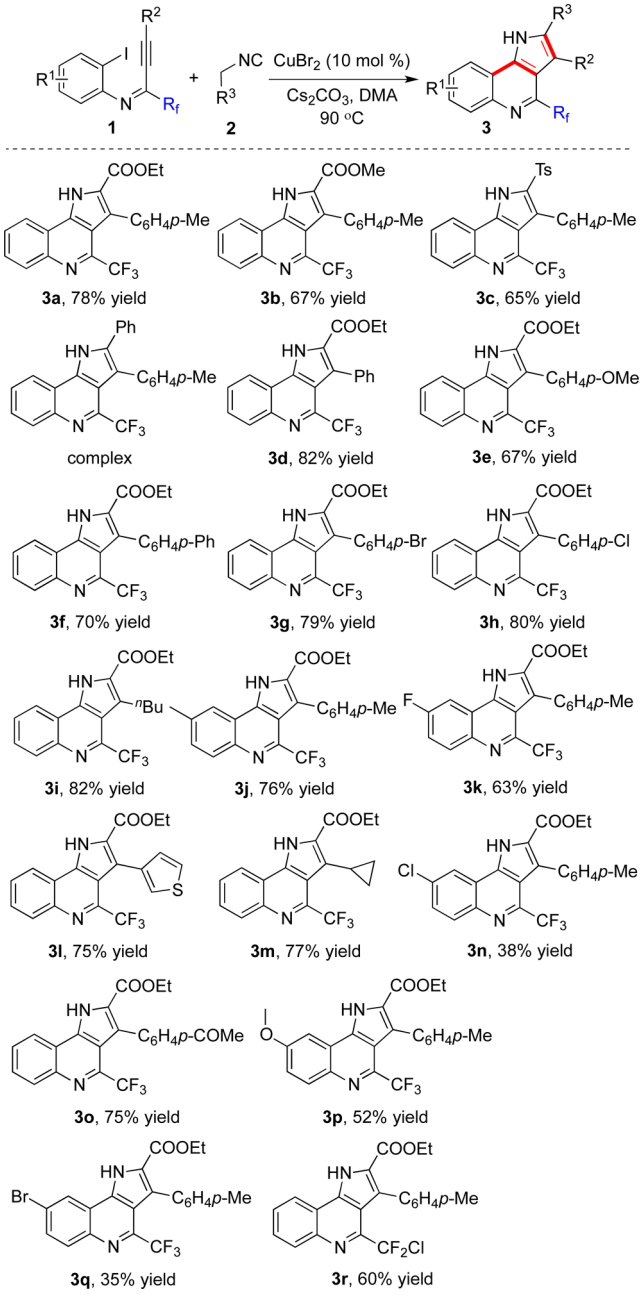
Table 2. Scope Investigation of the Copper-Catalyzed Tandem Reaction of *N*-(σ-Iodoaryl)alkynylimine 1 with 2-Isocyanoacetate 2[a,b]



[a]Reaction conditions: $CuBr_2$ (0.02 mmol), *N*-(σ-iodoaryl)-alkynylimine **1** (0.2 mmol), 2-isocyanoacetate **2**(0.24 mmol), Cs_2CO_3 (0.2 mmol), DMA (2.0 mL), 1 h. [b]Isolated yields based on *N*-(σ-iodoaryl)alkynylimines **1**.

methyl, methoxy, chloro, fluoro, bromo, or acetyl substituents with ethyl 2-isocyanoacetate **2a** worked smoothly to afford the desired products **3**. Moreover, alkyl and heterocyclic substituents attached to the triple bond in *N*-(σ-iodoaryl)-alkynylimines **1** could also be tolerated under the conditions, and the corresponding products were generated as expected. Reactions of electron-donating groups such as methyl and methoxy substituents on the σ-iodophenyl ring worked efficiently as well, leading to the desired products. On the contrary, most electron-withdrawing groups such as bromo and chloro led to rather lower yields, although the fluoro substituent gave a moderate yield of 63%. We suspected that the lower isolated yields were ascribed to the poor solubility of the products. Furthermore, the CF_2Cl substituent was applied as the fluoroalkyl group in this transformation, and the corresponding product **3r** was successfully generated in 60% yield.

On the basis of the experimental observations and previous reports,[5e,14b] the reaction process was consistent with our proposed mechanism in Scheme 1. Initially, a α-metalated isocyanide would be formed via the reaction of copper catalyst and 2-isocyanoacetate in the presence of a base. Subsequent [3 + 2] cycloaddition with the triple bond of *N*-(σ-iodoaryl)-alkynylimine would afford the organocopper intermediate **A**. As mentioned above, the intermediate **B** would be produced through intramolecular insertion of copper into the C−I bond. Further reductive elimination and aromatization would lead to the final outcome.

In conclusion, we have described an approach for the synthesis of fluorinated pyrrolo[3,2-*c*]quinolones via a copper-catalyzed tandem reaction of *N*-(σ-iodoaryl)alkynylimines **1** with 2-isocyanoacetates **2**. It can be expected that the potential biological activities of the fluorine-containing heterocycles are attractive. Moreover, this transformation takes place under mild conditions with high efficiency and shows a wide range of functional group tolerance.

EXPERIMENTAL SECTION

General Experimental Procedure for the Copper-Catalyzed Tandem Reaction of *N*-(σ-Iodoaryl)alkynylimine 1 with 2-Isocyanoacetate 2. 2-Isocyanoacetate **2** (0.24 mmol) was added to a solution of $CuBr_2$ (0.02 mmol), Cs_2CO_3 (0.2 mmol), and *N*-(σ-iodoaryl)alkynylimine **1** (0.2 mmol) in DMA (2.0 mL). The mixture was stirred at 100 °C for 10−15 h. After completion of reaction as indicated by TLC, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:3) to give the desired product **3**. (*N*-(σ-Iodoaryl)alkynylimines **1** were prepared according to the previous report.[12e])

*Ethyl 3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3a**):* white solid (62.1 mg, 78%); mp 266−267 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 13.59 (s, 1H), 8.95−8.97 (m, 1H), 8.13−8.15 (m, 1H), 7.77−7.79 (m, 2H), 7.12−7.16 (m, 4H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −62.08; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 142.0 (q, *J* = 36.2 Hz), 141.8, 137.7, 136.5, 131.3, 130.7, 130.2, 129.3, 128.9, 127.8, 126.5, 123.9, 122.8, 121.4 (q, *J* = 274.2 Hz), 118.5, 115.6, 60.8, 21.3, 13.8; HRMS calcd for $C_{22}H_{18}F_3N_2O_2$ (M + H^+) 399.1315, found 399.1317.

*Methyl 3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3b**):* white solid (51.4 mg, 67%); mp 242−243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 10.59 (s, 1H), 8.28−8.34 (m, 2H), 7.70−7.79 (m, 2H), 7.18−7.27 (m, 4H), 3.76 (s, 3H), 2.45 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.41; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 143.3 (q, *J* = 36.2 Hz), 142.4, 137.2, 137.1, 130.8, 130.1, 130.0, 129.0, 128.3, 127.8, 125.8, 124.7, 120.8 (q, *J* = 274.1 Hz), 120.2, 117.6, 116.3, 52.2, 21.3; HRMS calcd for $C_{21}H_{16}F_3N_2O_2$ (M + H^+) 385.1158, found 385.1159.

*3-p-Tolyl-2-tosyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]quinoline (**3c**):* white solid (62.4 mg, 65%); mp 259−260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 11.37 (s, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H),7.73 (t, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.12−7.18 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 2H), 2.48 (s, 3H), 2.38 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.64; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.9 (q, *J* = 36.3 Hz), 142.3, 138.0,

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137.1, 136.7, 132.6, 131.1, 130.6, 129.4, 129.2, 128.6, 127.9, 127.8, 127.3, 123.6, 120.8 (q, J = 274.1 Hz), 120.7, 117.6, 116.2, 21.5, 21.4. HRMS calcd for $C_{26}H_{20}F_3N_2O_2S(M + H^+)$ 481.1192, found 481.1194.

*Ethyl 3-phenyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3d**):* white solid (62.9 mg, 82%); mp 231−232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.64 (s, 1H), 8.95−8.98 (m, 1H), 8.14−8.16 (m, 1H), 7.79−7.81 (m, 2H), 7.36−7.37 (m, 3H), 7.27−7.28 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.15; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 142.0 (q, J = 35.3 Hz), 141.8, 137.8, 134.3, 130.9, 130.2, 129.4, 129.1, 127.6, 127.2, 126.5, 123.9, 122.9, 121.4 (q, J = 273.8 Hz), 118.5, 115.5, 60.8, 13.8; HRMS calcd for $C_{21}H_{16}F_3N_2O_2$ $(M + H^+)$ 385.1158, found 385.1165.

*Ethyl 3-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3e**):* white solid (55.4 mg, 67%); mp 253−254 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.59 (s, 1H), 8.94−8.99 (m, 1H), 8.15−8.17 (m, 1H), 7.79−7.81 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.08; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 158.9, 142.0 (q, J = 33.4 Hz), 141.8, 137.7, 131.9, 130.2, 129.4, 129.0, 126.6, 126.2, 123.7, 122.8, 121.4 (q, J = 274.3 Hz), 118.5, 115.5, 112.7, 60.8, 55.4, 13.9; HRMS calcd for $C_{22}H_{18}F_3N_2O_3$ $(M + H^+)$ 415.1264, found 415.1264.

*Ethyl 3-(biphenyl-4-yl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3f**):* white solid (64.4 mg, 70%); mp 231−233 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 10.78 (s, 1H), 8.38 (d, J = 7.2 Hz. 1H), 8.32 (d, J = 8.0 Hz. 1H), 7.66−7.82 (m, 6H), 7.50 (t, J = 8.0 Hz, 2H), 7.37−7.44 (m, 3H), 4.22 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.36; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 143.3 (q, J = 35.6 Hz), 142.2, 141.0, 140.2, 137.2, 132.6, 130.9, 129.0, 128.7, 128.3, 127.2, 127.0, 125.7, 125.4, 124.9, 120.9 (q, J = 274.3 Hz), 120.3, 117.7, 116.2, 61.4, 13.5; HRMS calcd for $C_{27}H_{20}F_3N_2O_2$ $(M + H^+)$ 461.1471, found 461.1469.

*Ethyl 3-(4-bromophenyl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3g**):* white solid (72.9 mg, 79%); mp 259−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.70 (s, 1H), 8.95−8.98 (m, 1H), 8.15−8.17 (m, 1H), 7.80−7.82 (m, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.08; ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 141.9, 141.8 (q, J = 35.8 Hz), 137.8, 133.8, 133.1, 130.3, 129.5, 129.1, 126.5, 122.8, 122.4, 121.3 (q, J = 274.2 Hz), 121.1, 118.5, 115.2, 61.0, 13.8; HRMS calcd for $C_{21}H_{15}BrF_3N_2O_2$ $(M + H^+)$ 463.0264, found 463.0256.

*Ethyl 3-(4-chlorophenyl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3h**):* white solid (66.8 mg, 80%); mp 252−253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.68 (s, 1H), 8.94−8.96 (m, 1H), 8.13−8.15 (m, 1H), 7.78−7.80 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.11; ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 141.8, 141.7 (q, J = 33.5 Hz), 137.8, 133.4, 132.7, 132.5, 130.2, 129.4, 129.1, 127.3, 126.5, 122.8, 122.3, 121.3 (q, J = 274.0 Hz), 118.4, 115.3, 61.0, 13.8; HRMS calcd for $C_{21}H_{15}ClF_3N_2O_2$ $(M + H^+)$ 419.0769, found 419.0778.

*Ethyl 3-butyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3i**):* white solid (59.6 mg, 82%); mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.24 (s, 1H), 8.90−8.92 (m, 1H), 8.11−8.13 (m, 1H), 7.74−7.76 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 3.08 (t, J = 8.0 Hz, 2H), 1.36−1.50 (m, 7H), 0.90 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −63.00; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 141.6, 141.4 (q, J = 34.9 Hz), 138.0, 130.1, 129.2, 128.8, 125.4, 124.9, 122.8,122.3 (q, J = 273.3 Hz), 118.5, 114.7, 61.2, 33.8, 24.7, 23.0, 14.5, 13.9; HRMS calcd for $C_{19}H_{20}F_3N_2O_2$ $(M + H^+)$ 365.1471, found 365.1466.

*Ethyl 8-methyl-3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3j**):* white solid (62.6 mg, 76%); mp 270−271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 10.49 (s, 1H), 8.17 (d, J = 8.8 Hz. 1H), 8.05 (s, 1H), 7.59 (d, J = 8.8 Hz. 1H), 7.20−7.27 (m, 4H), 4.20 (q, J = 7.2 Hz, 2H), 2.62 (s, 3H), 2.44 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.29; ^{13}C NMR (100 MHz, $CDCl_3$) 161.7, 142.8 (q, J = 33.6 Hz), 140.7, 138.7, 137.0, 136.7, 131.0, 130.5, 130.2, 127.7, 125.5, 123.9 (q, J = 273.8 Hz), 122.4, 119.6, 119.4, 117.5, 116.3, 61.2, 21.8, 21.3, 13.5; HRMS calcd for $C_{23}H_{20}F_3N_2O_2$ $(M + H^+)$ 413.1471, found 413.1470.

*Ethyl 8-fluoro-3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3k**):* white solid (53.4 mg, 63%); mp 265−266 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 13.56 (s, 1H), 8.72−8.75 (d, J = 10.0 Hz, 1H), 8.17−8.21 (m, 1H), 7.62−7.67 (t, J = 8.8 Hz, 1H), 7.13−7.18 (m, 4H), 4.09 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −62.12 (s, 3F), −109.68 (m, 1F); ^{13}C NMR (100 MHz, DMSO-d_6) 161.5 (d, $^1J_{CF}$ = 245.8 Hz), 161.0, 141.5 (q, J = 34.6 Hz), 138.8, 137.3, 136.6, 133.3 (d, $^3J_{CF}$ = 9.6 Hz), 131.0, 130.7, 127.8, 126.8, 123.9, 121.3 (q, J = 274.1 Hz),119.5 (d, $^3J_{CF}$ = 11.1 Hz), 118.7 (d, $^2J_{CF}$ = 25.0 Hz), 115.6, 107.4 (d, $^2J_{CF}$ = 24.6 Hz), 60.9, 21.3, 13.8; HRMS calcd for $C_{22}H_{17}F_4N_2O_2$ $(M + H^+)$: 417.1221, found 417.1225.

*Ethyl 3-(thiophene-3-yl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3l**):* white solid (58.5 mg, 75%); mp 234−235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.63 (s, 1H), 8.92−8.95 (m, 1H), 8.12−8.14 (m, 1H), 7.75−7.77 (m, 2H), 7.49−7.50 (m, 1H), 7.36 (s, 1H), 7.06 (d, J = 4.4 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.75; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 141.9 (q, J = 35.2 Hz), 141.8, 137.8, 133.2, 130.8, 130.2, 129.3, 128.9, 127.0, 125.3, 123.8, 122.8, 121.4 (q, J = 274.0 Hz), 118.4, 115.8, 60.8, 13.8; HRMS calcd for $C_{19}H_{14}F_3N_2O_2S$ $(M + H^+)$ 391.0723, found 391.0739.

*Ethyl 3-cyclopropyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3m**):* white solid (53.5 mg, 77%); mp 224−225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (s, 1H), 8.86−8.88 (m, 1H), 8.13−8.15 (m, 1H), 7.75−7.77 (m, 2H), 4.43 (q, J = 7.2 Hz, 2H), 1.97 (s, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.01 (d, J = 7.2 Hz, 2H), 0.52 (d, J = 7.2 Hz, 2H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −61.85; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 142.0 (q, J = 36.6 Hz), 141.8, 137.7, 130.1, 129.1, 128.7, 128.2, 124.6, 122.6, 121.9 (q, J = 273.1 Hz), 118.4, 116.5, 61.4, 14.5, 9.2, 7.8; HRMS calcd for $C_{18}H_{16}F_3N_2O_2$ $(M + H^+)$ 349.1158, found 349.1163.

*Ethyl 8-chloro-3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3n**):* white solid (32.8 mg, 38%); mp 273−274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 10.97 (s, 1H), 8.43 (d, J = 2.0 Hz. 1H), 8.24 (d, J = 8.8 Hz. 1H), 7.70−7.73 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 7.24 (s, 4H), 4.30 (q, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.51; ^{13}C NMR (100 MHz, $CDCl_3$) 160.8, 142.3 (q, J = 35.7 Hz), 140.2, 136.7, 136.6, 133.5, 132.2, 130.9, 130.7, 129.6, 127.8, 126.9, 123.9, 122.1, 121.2 (q, J = 274.2 Hz), 119.4, 116.0, 60.9, 21.3, 13.9; HRMS calcd for $C_{22}H_{17}ClF_3N_2O_2$ $(M + H^+)$ 433.0925, found 433.0916.

*Ethyl 3-(4-acetylphenyl)-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3o**):* white solid (55.4 mg, 75%); mp 277−278 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.73 (s, 1H), 8.96−8.99 (m, 1H), 8.15−8.17 (m, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.80−7.82 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 2.64 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −62.12; ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.2, 160.8, 141.9, 141.6 (q, J = 35.0 Hz), 139.7, 137.9, 136.1, 131.3, 130.2, 129.5, 129.1, 127.2, 126.4, 122.9, 122.7, 121.3 (q, J = 274.1 Hz), 118.4, 115.1, 61.0, 27.1, 13.8; HRMS calcd for $C_{23}H_{18}F_3N_2O_3$ $(M + H^+)$ 427.1264, found 427.1278.

*Ethyl 8-methoxy-3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3p**):* white solid (44.5 mg, 52%); mp 273−274 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.38 (s, 1H), 8.86 (d, J = 9.2 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.43−7.46 (m, 1H), 7.14−7.19 (m, 4H), 4.08 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 2.38 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −61.91; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 160.2, 143.8, 142.2 (q, J = 35.1 Hz), 138.2, 136.5, 131.4, 130.7, 127.8, 126.0, 124.1, 123.9, 121.4 (q, J = 274.3 Hz), 120.4, 114.8, 112.7, 109.7, 60.7, 55.9, 21.3, 13.9; HRMS calcd for $C_{23}H_{20}F_3N_2O_3$ $(M + H^+)$ 429.1421, found 429.1412.

*Ethyl 8-bromo-3-p-tolyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3q**):* white solid (33.3 mg, 35%); mp 276−277 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 11.07 (s, 1H), 8.57 (d, J = 2.0 Hz. 1H), 8.16 (d, J = 8.8 Hz. 1H), 7.84 (dd, J = 2.0 Hz, 8.8 Hz,

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1H), 7.23 (s, 4H), 4.29 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.53; ^{13}C NMR (100 MHz, $CDCl_3$) 162.0, 143.7 (q, J = 35.9 Hz), 140.9, 137.2, 136.1, 132.4, 132.3, 130.1, 127.7, 125.9, 125.7, 123.0, 122.4, 122.1, 120.8 (q, J = 274.3 Hz), 119.1, 116.8, 61.7, 21.3, 13.4; HRMS calcd for $C_{22}H_{17}BrF_3N_2O_2$ (M + H^+) 477.0420, found 477.0422.

Ethyl 4-(chlorodifluoromethyl)-3-p-tolyl-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (3r): white solid (49.7 mg, 60%); mp 269−270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 13.58 (s, 1H), 8.95−8.98 (m, 1H), 8.12−8.14 (m, 1H), 7.76−7.79 (m, 2H), 7.13 (s, 4H), 4.05 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{19}F NMR(376 MHz, DMSO-d_6) δ −49.0; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 146.3 (t, J = 29.5 Hz), 141.6, 138.0, 136.4, 131.8, 131.0, 130.1, 129.3, 128.8, 127.7, 126.7, 126.1 (q, J = 290.1 Hz), 124.1, 122.8, 118.4, 114.6, 60.8, 21.3, 13.8; HRMS calcd for $C_{22}H_{18}ClF_2N_2O_2$ (M + H^+) 415.1019, found 415.1016.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01669.

^{1}H and ^{13}C NMR spectra of compounds **3** (PDF)

X-ray crystal data of compound **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jie_wu@fudan.edu.cn.

*E-mail: fxn918@126.com.

Notes

The authors declare no competing financial interest.

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