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银介导的自由基三氟甲硫化环化: 含 CF_3S 苯并咪唑[2,1-*a*]异喹啉的合成

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摘要 开发了一种实用的银催化三氟甲硫化环化反应, 合成了各种结构多样的含 CF_3S 的苯并咪唑[2,1-*a*]异喹啉, 产率中等至良好. 机理研究表明, 催化反应通过 CF_3S 自由基引发的串联环化途径进行.
关键词 三氟甲硫化; 自由基; 环化; 氮杂环

Silver-Mediated Radical Trifluoromethylthiolation Cyclization: Synthesis of CF_3S-Containing Benzimidazole[2,1-*a*]isoquinolines

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Abstract A practical Ag-catalyzed trifluoromethylthiolation cyclization reaction was developed. Various structurally diverse CF_3S-containing benzimidazo[2,1-*a*]isoquinolines were obtained for the first time in moderate to good yields. Mechanistic studies suggested that the catalytic reaction proceeds via a CF_3S-radical-triggered cascade cyclization pathway.
Keywords trifluoromethylthiolation; radical; cyclization; *N*-heterocycles

1 Introduction

N-Heterocycles are important scaffolds in medicinal and synthetic chemistry. They occur in a range of bioactive molecules and are valuable synthetic building blocks that can be converted into a wide range of valuable structures.[1] The development of methods for the concise construction of *N*-heterocycles is therefore an important topic in research on organic synthesis.[2] Structurally diverse tetracyclic benzimidazole[2,1-*a*]isoquinolines are important synthetic intermediates. They are also key structural scaffolds in antidiabetic, anti-inflammatory, and antitumor compounds, and have powerful biological properties.[3] Many methods have been established for constructing these polycyclic frameworks, but they mainly involve multistep condensation reactions and pre-functionalized materials.[4] The development of more concise routes, especially one-pot strategies, for accessing these tetracyclic frameworks from readily available substrates is therefore desirable.

Compounds bearing fluorine atoms have been widely used as agrochemicals, pharmaceuticals, and materials because of their specific physical, chemical, and biological properties.[5] Among fluorinated moieties, the trifluoromethylthio group (SCF_3) has attracted sustained interest because of its special properties, particularly its strong electron-withdrawing effect and high lipophilicity.[6] Radical cascade cyclization strategies have emerged as versatile tools for constructing heterocyclic compounds, and are opening up new methods for rapidly building up molecular complexity.[7] In 2014, Wang's group reported the first $AgSCF_3$-mediated trifluoromethylthiolation cyclization of activated alkenes via a radical process to produce valuable trifluoromethylthio-containing oxindoles (Scheme 1a).[8] In

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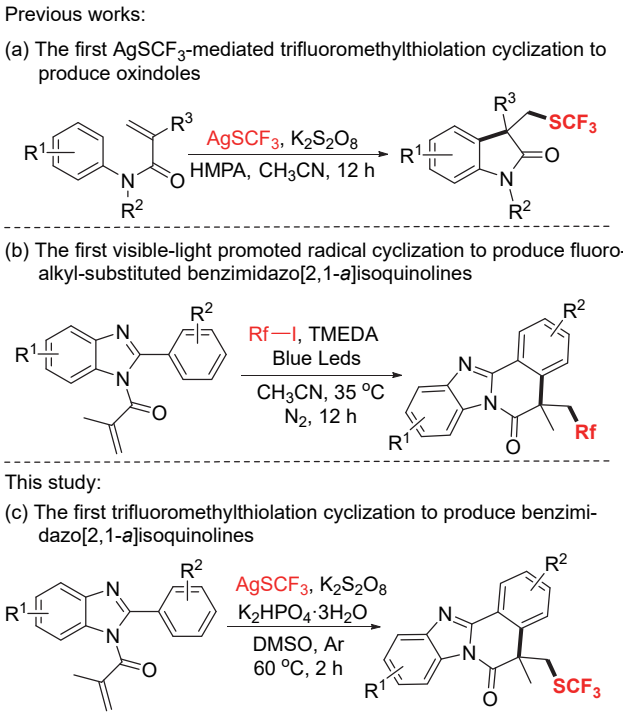
2019, Chen *et al.*[9] reported a visible-light-promoted radical cyclization for accessing perfluoroalkyl-substituted benzimidazo[2,1-*a*]isoquinolines. This involved adding a stoichiometric amount of a base (Scheme 1b). Recently, Li's group reported a similar copper-catalyzed trifluoromethylarylation cycloaddition of imidazoles and alkenes with CF_3SO_2Cl as the radical source for synthesizing highly functionalized tricyclic imidazoles.[10] As part of our ongoing interest in heterocycle modification,[11] we have developed a one-pot formal trifluoromethylthiolation cyclization strategy for constructing a series of structurally diverse trifluoromethylthio-containing benzimidazo[2,1-*a*]-isoquinolines (Scheme 1c). Gram-scale synthesis, and selective diversification via oxidation and reduction were achieved. This shows the practicability of this reaction and its potential use in industrial applications.

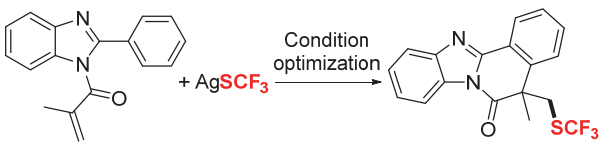


Scheme 1 Strategies for construction of fluoro-containing *N*-heterocycles.

2 Results and discussion

To test the feasibility of this idea, our initial experiments mainly focused on the trifluoromethylthiolation cyclization of *N*-methacryloyl-2-phenylbenzoimidazole (**1a**) with $AgSCF_3$ as trifluoromethylthio radical source. Initially, **1a** (0.3 mmol) reacted with $AgSCF_3$ (1.1 equiv.) with $K_2S_2O_8$ (2.0 equiv.) as the oxidant, in DMSO (2.0 mL) at 60 °C in an air atmosphere. After 2 h, the substrate **1a** had been consumed, and the desired product **2a** was isolated in 52% yield (Table 1, Entry 1). Other solvents, namely MeCN, 1,2-dichloroethane (DCE), and tetrahydrofuran (THF), were less effective than dimethyl sulfoxide (DMSO) (Table 1, Entries 2～4). Decreasing the amount of $K_2S_2O_8$ to 1 equiv. did not significantly affect the yield of **2a** (Table 1, Entry 5). Use of the oxidants (diacetoxy)iodobenzene (PIDA), Selectfluor, *tert*-butyl hydroperoxide (TBHP) (70% in water), and $(NH_4)_2S_2O_8$ was then investigated; $K_2S_2O_8$ was the best choice (Table 1, Entries 6～9). To further improve the reaction efficiency, different additives, *i.e.*, KH_2PO_4, hexamethylphosphoramide (HMPA), Li_2CO_3, $NaHCO_3$, $KHCO_3$, Na_2CO_3 and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), were investigated (Table 1, Entries 10～16). KH_2PO_4 improved the reaction efficiency, and 62% of **2a** was obtained. Use of just 1 equiv. of $KH_2PO_4·3H_2O$ gave **2a** in an isolated yield of 83% (Table 1, Entries 17～19). Further screening showed that a higher reaction temperature, i.e., 80 °C, would cause more side reactions, or a lower temperature, i.e., 40 °C would result in longer reaction time, which did not improve the yield compared with that obtained at 60 °C (Table 1, Entries 20 and 21).

Table 1 Optimization of the reaction conditions[a,b]



1a 2a

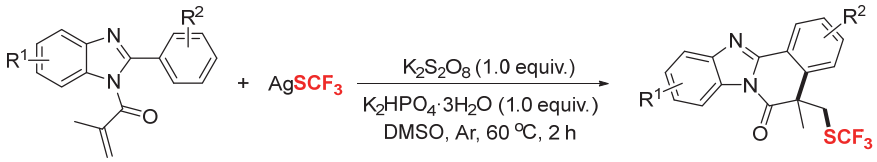
Entry	Oxidant/equiv.	Additive/equiv.	*V*(solvent)/mL	Yield/%
1	$K_2S_2O_8$ (2.0)	None	DMSO	52
2	$K_2S_2O_8$ (2.0)	None	MeCN	17
3	$K_2S_2O_8$ (2.0)	None	DCE	0
4	$K_2S_2O_8$ (2.0)	None	THF	21
5	$K_2S_2O_8$ (1.0)	None	DMSO	50
6	PIDA (1.0)	None	DMSO	38
7	Selectfluor (1.0)	None	DMSO	0
8	TBHP (1.0)	None	DMSO	Trace
9	$(NH_4)_2S_2O_8$ (1.0)	None	DMSO	51
10	$K_2S_2O_8$ (1.0)	KH_2PO_4 (1.5)	DMSO	62
11	$K_2S_2O_8$ (1.0)	HMPA (1.5)	DMSO	Trace
12	$K_2S_2O_8$ (1.0)	Li_2CO_3 (1.5)	DMSO	35
13	$K_2S_2O_8$ (1.0)	$NaHCO_3$ (1.5)	DMSO	48
14	$K_2S_2O_8$ (1.0)	$KHCO_3$ (1.5)	DMSO	47
15	$K_2S_2O_8$ (1.0)	Na_2CO_3 (1.5)	DMSO	50
16	$K_2S_2O_8$ (1.0)	DBU (1.5)	DMSO	53
17	$K_2S_2O_8$ (1.0)	$KH_2PO_4·3H_2O$ (1.5)	DMSO	65
18	$K_2S_2O_8$ (1.0)	$KH_2PO_4·3H_2O$ (1.0)	DMSO	83
19	$K_2S_2O_8$ (1.0)	$KH_2PO_4·3H_2O$ (0.5)	DMSO	64
20	$K_2S_2O_8$ (1.0)	$KH_2PO_4·3H_2O$ (1.0)	DMSO	56[c]
21	$K_2S_2O_8$ (1.0)	$KH_2PO_4·3H_2O$ (1.0)	DMSO	70[d]

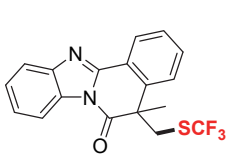
[a] Reaction conditions: **1a** (0.3 mmol), $AgSCF_3$ (1.1 equiv.), oxidant (1.0～2.0 equiv.), additive (0.5～1.5 equiv.) in solvent (2 mL), under Ar for 2 h. [b] Yield of isolated product. [c] Reaction performed at 40 ℃; [d] Reaction performed at 80 °C.

After the optimized reaction conditions had been established, the generality of this oxidative radical cascade cy-

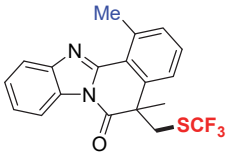
clization was investigated (Table 2). Substrates **1** with substituents at various positions on the benzene ring, namely *o*-methyl, *m*-methyl, and *p*-methyl, were all efficiently transformed into the corresponding products **2b**, **2d**, and **2f**. Electron-donating (Me, OMe, SMe, and Ph) or electron-withdrawing (F, Cl, Br, I, CF_3, OCF_3, COOMe, CN, and SO_2Me) groups on the benzene ring performed well in the cascade process, and afforded the desired products in

Table 2 Substrate scope[a,b]

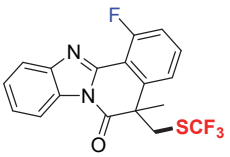




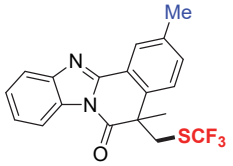
2a, 83%



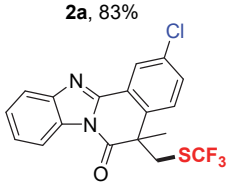
2b, 46%



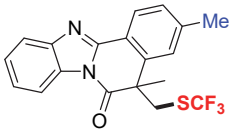
2c, 40%



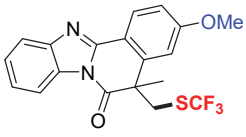
2d, 69%



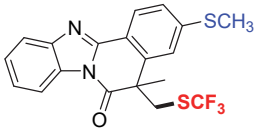
2e, 63%



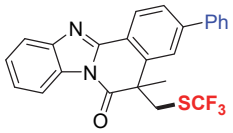
2f, 71%



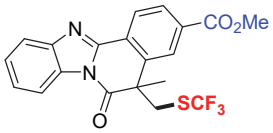
2g, 70%



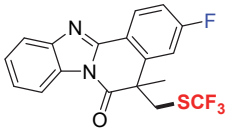
2h, 63%



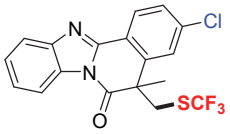
2i, 82%



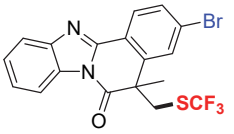
2j, 58%



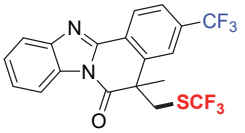
2k, 74%



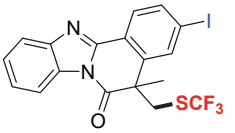
2l, 80%



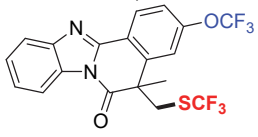
2m, 69%



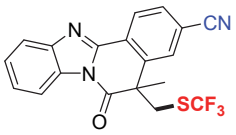
2n, 55%



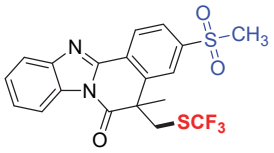
2o, 73%



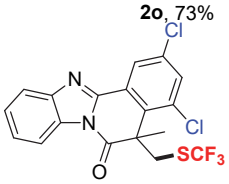
2p, 48%



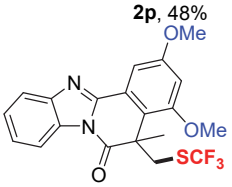
2q, 82%



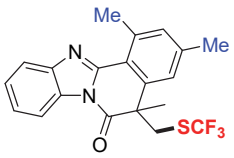
2r, 84%



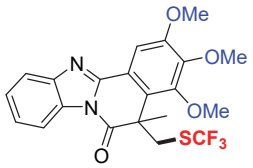
2s, 32%



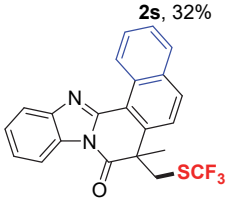
2t, 76%



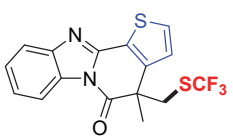
2u, 72%



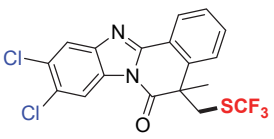
2v, 73%



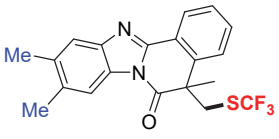
2w, 85%



2x, 67%



2y, 75%

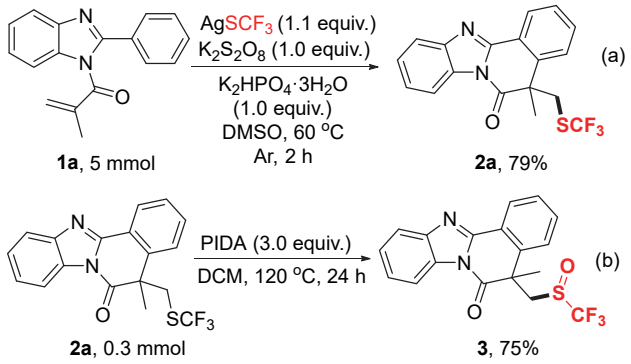


2z, 74%

[a] Reaction conditions: **1** (0.3 mmol), $AgSCF_3$ (1.1 equiv.), $K_2S_2O_8$ (1.0 equiv.), $KH_2PO_4·3H_2O$ (1.0 equiv.) in DMSO (2 mL), under Ar for 2 h. [b] Yield of isolated product.

moderate to good yields (**2b**～**2r**). Halo substituents on the phenyl ring were well tolerated, and provided a handle for further transformations. Notably, SMe, COOMe, and CN were easily converted to other useful functional groups. This significantly expands the synthetic utility of the current protocol. Substrates with multiple substituents, e.g., **1s**～**1v**, were also converted to the corresponding products **2s**～**2v** in moderate to high yields (32%～76%). The naphthalene- and 2-thiophene-substituted 1*H*-benzo[*d*]imidazoles **1w** and **1x** were also smoothly converted in this reaction, and the corresponding products **2w** and **2x** were obtained in 85% and 67% yields, respectively. The multiply substituted 1*H*-benzo[*d*]imidazoles **1y** and **1z** were generally reactive, and gave the corresponding products **2y** and **2z** in 75% and 74% yields, respectively.

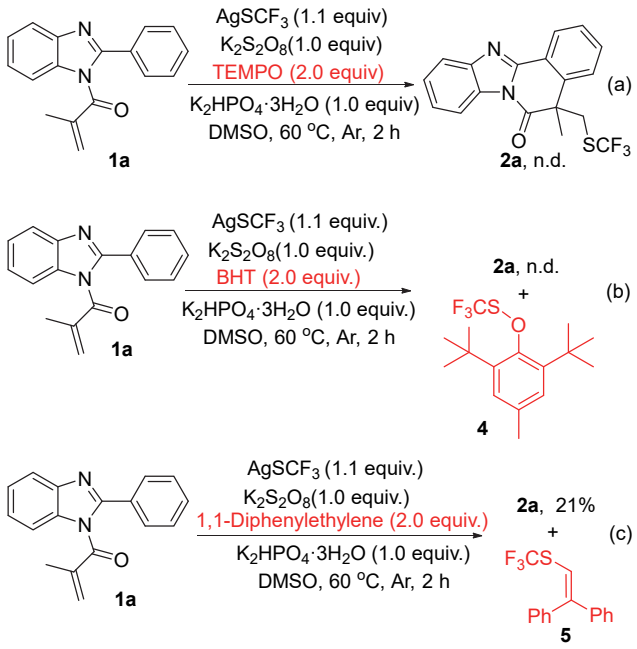
The reaction was scaled up to evaluate the synthetic utility of this protocol. When the reaction of **1a** was performed on a 5 mmol scale, **2a** was isolated in 79% yield (Scheme 2a). This enabled further synthetic transformations. Product **2a** could also be oxidized to CF_3S-containing sulfoxide **3** in good yield; which is valuable core in drug molecules (Scheme 2b).



Scheme 2 Application investigation

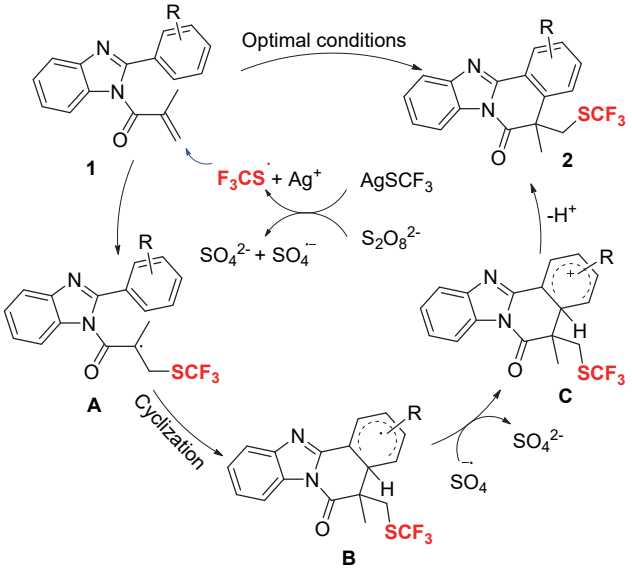
Control experiments were performed to determine the possibility of a radical pathway (see Supporting Information for details). The addition of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.0 equiv.) as radical scavengers under the standard reaction conditions failed to give **2a**, and adduct **4** was detected by HRMS analysis (Schemes 3a and 3b). When 1,1-diphenylethylene was added, the reaction was significantly inhibited, and the radical-trapping product **5** was detected by HRMS (Scheme 3c). These results indicate that a radical pathway was involved in these systems, and this radical trifluoromethylthiolation cascade cyclization is generally initiated by formation of a SCF_3 radical from $AgSCF_3$.

On the basis of the control experiment results and a literature survey[12], a plausible mechanism for the formation of product **2** is proposed (Scheme 4). Initially, $AgSCF_3$ is oxidized by $K_2S_2O_8$ and generates $SO_4^{\cdot-}$ and SCF_3 radical. The SCF_3 radical then attacks the activated alkenyl moiety in substrate **1** to give radical intermediate **A**, which under



Scheme 3 Mechanistic study

goes intramolecular cyclization to give radical intermediate **B**. Next, the reaction of intermediate **B** with $SO_4^{\cdot-}$ gives the cationic intermediate **C**. Finally, according to the proposed mechanism, loss of a proton from **C** affords the desired product **2**.



Scheme 4 Proposed reaction mechanism

3 Conclusions

We have developed a $AgSCF_3$-mediated oxidative radical cascade cyclization for synthesizing various structurally diverse SCF_3-substituted tetracyclic benzimidazole[2,1-*a*]isoquinolines. This simple radical cascade strategy features ease of handling, a wide substrate scope, good functional group compatibility (Me, OMe, SMe, Ph, F, Cl, Br, I, CF_3, OCF_3, COOMe, CN, and SO_2Me), easily scaled-up

operation, and facile derivatization. A mechanistic study proved that the reaction proceeds via a SCF_3-radical-triggered cascade cyclization process, which avoids the direct influence of electronic effects and enhances the application scope of some particular functional groups (Br, I, COOMe, and CN). Further use of this strategy in the synthesis of more complicated drug candidates is being investigated in our laboratory.

4 Experimental section

4.1 General conditions

All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR, ^{13}C NMR spectra were recorded on Bruker Ascend™ 400, Bruker Ascend™ 500, Bruker Ascend™ 600 spectrometer in deuterated solvents containing TMS as an internal reference standard. All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization orthogonal acceleration time-of-flight (ESI-OA-TOF), and the purity of all samples used for HRMS (> 95%) was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using GF254 silica gel-coated TLC plates. Purification by flash column chromatography was performed over SiO_2 (silica gel 200～300 mesh).

4.2 General procedure for the synthesis of 1

Step 1: In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a mixture of benzaldehydes (5.0 mmol, 508 μL) and $NaHSO_3$ (11.0 eq, 5.73 g) in H_2O (20.0 mL) was added. When the mixture reached refluxing temperature, *o*-phenylenediamines (5.0 mmol, 541 mg) were added. After completion of the reaction (monitored by TLC), the mixture was vacuum filtered after cooling to room temperature by a glass funnel. The residues were washed by water (20 mL×2), and then recrystallized to give the corresponding 2-phenyl-1*H*-benzo[*d*]imidazoles.

Step 2: To the solution of 2-phenyl-1*H*-benzo[*d*]imidazoles (3 mmol, 583 mg) and DMAP (0.6 mmol, 73 mg) in DCM (0.5 mol//L), Et_3N (6 mmol, 834 μL) was added at 0 °C. After stirring for 20 min, methacryloyl chloride (6 mmol, 581 μL) was added to the mixture drop by drop. The solution was then warmed up to room temperature and stirred for 12 h. The reaction was complete according to TLC analysis, and water (20 mL) was added to the mixture, which was extracted with CH_2Cl_2 (15 mL×3). Then the organic solvent was concentrated *in vacuo*. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluent to give **1**.

4.3 General procedure for the synthesis of 2

With precautions to exclude air and moisture, the screw-cap test tube (15 mL) with a stir bar was charged with substrates **1** (0.3 mmol), $AgSCF_3$ (1.1 equiv., 69.3 mg), $K_2S_2O_8$ (1.0 equiv., 81.1 mg), $K_2HPO_4·3H_2O$ (1.0 equiv., 68.5 mg) and DMSO (2 mL). Then the mixture was stirred at 60 °C under Ar atmosphere for 2 h. After the completion of the reaction, the mixture was quenched by $NaHCO_3$ (sat. aq. 15 mL) and extracted with CH_2Cl_2 (5 mL×3). Then the organic solvent was concentrated *in vacuo* and residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluent to give products **2**.

5-Methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]-imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2a**): White solid, 89.9 mg, 83% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.31. m.p. 97～98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.51 (m, 1H), 8.35 (m, 1H), 7.83 (m, 1H), 7.61 (m, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.46 (m, 3H), 3.93 (d, J=12.9 Hz, 1H), 3.60 (d, J=12.9 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.71, 149.23, 144.03, 138.51, 133.78, 132.18, 131.26, 128.81, 128.79 (t, J= 329.0 Hz), 126.28 (d, J=12.6 Hz), 125.99 (d, J=9.7 Hz), 126.46, 123.28, 120.01, 115.74, 49.36, 39.70 (d, J=1.6 Hz), 29.07; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.01. HRMS (ESI) calcd for $C_{18}H_{14}F_3N_2OS$ $[M+H]^+$: 363.0773, found 363.0768.

1,5-Dimethyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**2b**): Yellow solid, 52.1 mg, 46% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.49. m.p. 106～107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43～8.36 (m, 1H), 7.89～7.81 (m, 1H), 7.46 (m, 3H), 7.38 (d, J=7.5 Hz, 1H), 7.34 (d, J=7.8 Hz, 1H), 3.95 (d, J=12.7 Hz, 1H), 3.60 (d, J=12.7 Hz, 1H), 3.06 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.82, 149.42, 144.18, 140.37, 139.53, 132.11, 130.81, 130.42, 130.22 (q, J=306.7 Hz), 125.98, 125.93, 123.86, 121.81, 120.30, 115.75, 49.27, 39.87, 29.67, 24.69; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.03. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$: 377.0930, found 377.0924.

1-Fluoro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2c**): White solid, 45.9 mg, 40% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.17. m.p. 138～139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.39～8.34 (m, 1H), 7.96～7.90 (m, 1H), 7.58 (m, 1H), 7.50～7.45 (m, 2H), 7.30 (t, J=9.3 Hz, 2H), 3.94 (d, J=13.1 Hz, 1H), 3.57 (d, J=13.1 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.07, 160.53 (d, J=263.6 Hz), 145.35 (d, J=8.7 Hz), 144.29 (d, J=1.8 Hz), 140.97, 132.80 (d, J=9.5 Hz), 131.23 (t, J= 307.1 Hz), 130.23, 126.42 (d, J=22.8 Hz), 122.03 (d, J= 3.7 Hz), 120.76, 116.76 (d, J=21.5 Hz), 115.63, 112.71 (d, J=10.0 Hz), 49.40, 39.84 (d, J=1.5 Hz), 29.36; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.94, −106.22. HRMS (ESI) calcd for $C_{18}H_{13}F_4N_2OS$ $[M+H]^+$: 381.0679, found 381.0673.

2,5-Dimethyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2d**): Yellow solid, 78.3 mg, 69% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.36. m.p. 119～120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38～8.31 (m, 2H), 7.82 (m, 1H), 7.49～7.39 (m, 3H), 7.34 (d, J=8.1 Hz, 1H), 3.91 (d, J=12.7

Hz, 1H), 3.57 (d, J=12.7 Hz, 1H), 2.47 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.91, 149.44, 144.01, 138.97, 135.64, 130.18 (q, J=306.9 Hz), 133.26, 131.29, 126.45, 126.18, 125.92, 125.85, 122.95, 119.92, 115.73, 49.08, 39.70 (d, J=1.5 Hz), 29.10, 21.01; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.03. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$: 377.0930, found 377.0924.

2-Chloro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2e**): Yellow liquid, 75.2 mg, 63% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.35. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.49 (d, J=2.2 Hz, 1H), 8.37～8.30 (m, 1H), 7.87～7.79 (m, 1H), 7.55 (m, 1H), 7.49～7.43 (m, 2H), 7.39 (d, J=8.5 Hz, 1H), 3.91 (d, J=13.0 Hz, 1H), 3.55 (t, J=12.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.18, 147.92, 143.90, 136.71, 135.20, 132.16, 131.25, 128.39 (t, J=212.7 Hz), 127.62, 126.40 (d, J=10.5 Hz), 126.01, 124.94, 120.24, 115.77, 49.28, 39.61 (d, J=1.6 Hz), 28.97; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.90. HRMS (ESI) calcd for $C_{18}H_{13}ClF_3N_2OS$ $[M+H]^+$: 397.0384, found 397.0380.

3,5-Dimethyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2f**): White solid, 79.8 mg, 71% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.35. m.p. 113～114 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (d, J=8.0 Hz, 1H), 8.36～8.32 (m, 1H), 7.81 (m, 1H), 7.44 (m, 2H), 7.36 (d, J=8.0 Hz, 1H), 7.24 (s, 1H), 3.91 (d, J=12.8 Hz, 1H), 3.59 (d, J=12.8 Hz, 1H), 2.49 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.85, 149.47, 144.09, 142.91, 138.52, 131.40 (t, J=306.9 Hz), 131.23, 129.88, 126.40, 126.28, 126.14, 125.69, 120.60, 119.83, 115.68, 49.26, 39.65, 29.10, 21.96; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.05. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$: 377.0930, found 377.0923.

3-Methoxy-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2g**): White solid, 82.3 mg, 70% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.22. m.p. 101～102 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (d, J=8.7 Hz, 1H), 8.31 (d, J=7.2 Hz, 1H), 7.78 (d, J=7.4 Hz, 1H), 7.46～7.37 (m, 2H), 7.08 (m, 1H), 6.92 (d, J=2.3 Hz, 1H), 3.91 (d, J=10.8 Hz, 4H), 3.55 (d, J=12.8 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.71, 162.81, 149.42, 144.16, 140.55, 131.17, 130.17 (q, J=306.9 Hz), 128.31, 126.10, 125.42, 119.58, 116.02, 115.58, 114.28, 111.89, 55.68, 49.47, 39.70 (d, J=1.5 Hz), 29.14; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.01. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2O_2S$ $[M+H]^+$: 393.0879, found 393.0872.

5-Methyl-3-(methylthio)-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2h**): White solid, 86.9 mg, 63% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.19. m.p. 119～120 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43～8.28 (m, 2H), 7.83～7.75 (m, 1H), 7.43 (m, 2H), 7.36 (m, 1H), 7.25 (d, J=1.6 Hz, 1H), 3.91 (d, J=13.0 Hz, 1H), 3.56 (d, J=12.9 Hz, 1H), 2.58 (s, 3H), 1.83 (d, J=10.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.44, 149.11, 144.76, 144.13, 138.96, 131.22, 130.12 (d, J=307.0 Hz), 126.62, 126.22, 125.76, 125.65, 122.89, 119.82, 119.69, 115.65, 49.40, 39.61, 29.02, 15.17; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.95. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS_2$ $[M+H]^+$: 409.0651, found 409.0645.

5-Methyl-3-phenyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2i**): Yellow solid, 107.9 mg, 82% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.45. m.p. 148～149 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.47 (d, J=8.2 Hz, 1H), 8.30～8.24 (m, 1H), 7.78～7.71 (m, 1H), 7.69～7.64 (m, 1H), 7.58～7.51 (m, 3H), 7.44～7.37 (m, 2H), 7.39～7.31 (m, 3H), 3.88 (d, J=13.0 Hz, 1H), 3.58 (d, J=13.0 Hz, 1H), 1.86～1.75 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.73, 149.13, 145.22, 144.20, 139.68, 139.02, 131.32, 130.19 (q, J=307.0 Hz), 129.16, 128.55, 127.80, 127.27, 126.84, 126.27, 125.94, 124.69, 122.07, 120.00, 115.74, 49.62, 39.66 (d, J=1.4 Hz), 29.19; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.87. HRMS (ESI) calcd for $C_{24}H_{18}F_3N_2OS$ $[M+H]^+$: 439.1086, found 439.1081.

Methyl 5-methyl-6-oxo-5-(((trifluoromethyl)thio)methyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline-3-carboxylate (**2j**): White solid, 73.3 mg, 58% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.18. m.p. 123～124 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.58 (d, J=8.2 Hz, 1H), 8.40～8.34 (m, 1H), 8.22～8.13 (m, 2H), 7.88～7.83 (m, 1H), 7.52～7.45 (m, 2H), 3.99 (s, 3H), 3.95 (d, J=13.1 Hz, 1H), 3.65 (d, J=13.1 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.22, 164.78, 147.15, 143.02, 137.61, 132.13, 130.24, 128.93 (q, J=307.2 Hz), 128.57, 126.52, 126.03, 125.53, 125.45, 125.37, 119.32, 114.81, 51.67, 48.58, 38.74, 27.84; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.84. HRMS (ESI) calcd for $C_{20}H_{16}F_3N_2O_3S$ $[M+H]^+$: 421.0828, found 421.0820.

3-Fluoro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2k**): White solid, 84.7 mg, 74% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.35. m.p. 111～112 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.52 (m, 1H), 8.36～8.31 (m, 1H), 7.83～7.79 (m, 1H), 7.49～7.41 (m, 2H), 7.26 (m, 1H), 7.15 (m, 1H), 3.92 (d, J=13.1 Hz, 1H), 3.52 (d, J=13.1 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.13, 165.05 (d, J=253.9 Hz), 148.44, 143.96, 141.19 (d, J=7.6 Hz), 131.21 (t, J=307.2 Hz), 131.14, 128.88 (d, J=9.1 Hz), 126.17 (d, J=41.3 Hz), 119.97, 119.82, 119.80, 116.83 (d, J=22.5 Hz), 115.70, 113.19 (d, J=23.4 Hz), 49.59, 39.76 (d, J=1.6 Hz), 28.86; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.92, −105.42. HRMS (ESI) calcd for $C_{18}H_{14}F_4N_2OS$ $[M+H]^+$: 381.0679, found 381.0674.

3-Chloro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2l**): White solid, 94.6 mg, 80% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.39. m.p. 101～102 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (d, J=8.4 Hz, 1H), 8.37～8.31 (m, 1H), 7.84～7.79 (m, 1H), 7.52 (m, 1H), 7.45 (m, 3H), 3.91 (d, J=13.1 Hz, 1H), 3.54 (d, J=13.1 Hz, 1H), 1.83

(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.00, 148.32, 143.97, 140.17, 138.41, 131.19, 131.20 (d, J=614.3 Hz), 129.41, 127.69, 126.39, 126.35, 126.19, 121.93, 120.09, 115.74, 49.47, 39.72 (d, J=1.6 Hz), 28.80; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.88. HRMS (ESI) calcd for $C_{18}H_{14}ClF_3N_2O_2S$ $[M+H]^+$: 397.0384, found 397.0376.

3-Bromo-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2m**): White solid, 91.2 mg, 69% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.13. m.p. 70～71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.41～8.30 (m, 2H), 7.85-7.79 (m, 1H), 7.68 (m, 1H), 7.60 (d, J=1.7 Hz, 1H), 7.49-7.43 (m, 2H), 3.91 (d, J=13.1 Hz, 1H), 3.54 (d, J=13.1 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.95, 148.39, 143.96, 140.29, 132.30, 131.20, 129.57 (t, J=460.6 Hz), 129.30, 127.71, 126.71, 126.41, 126.22, 122.34, 120.11, 115.74, 49.42, 39.72 (d, J=1.6 Hz), 28.79; ^{19}F NMR (471 MHz, $CDCl_3$) δ: − 40.86. HRMS (ESI) calcd for $C_{18}H_{13}BrF_3N_2OS$ $[M+H]^+$: 440.9879, found 440.9878.

5-Methyl-3-(trifluoromethyl)-5-(((trifluoromethyl)thio)-methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2n**): White solid, 70.9 mg, 55% yield. R_f(petroleum ether/ethyl acetate, V∶V = 20∶1): 0.43. m.p. 127～128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.65 (d, J=8.2 Hz, 1H), 8.36 (m, 1H), 7.86 (m, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.70 (s, 1H), 7.54～7.46 (m, 2H), 3.96 (d, J=13.4 Hz, 1H), 3.59 (d, J=13.4 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.92, 147.75, 143.95, 139.14, 133.69 (q, J=33.2 Hz), 131.24, 129.87 (d, J=307.2 Hz), 126.97, 126.67, 126.58, 125.65 (d, J=3.6 Hz), 124.35 (t, J=243.3 Hz), 123.25 (d, J=3.9 Hz), 120.42, 115.85, 49.76, 39.68, 28.84; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.84, -63.01. HRMS (ESI) calcd for $C_{19}H_{13}F_6N_2OS$ $[M+H]^+$: 431.0647, found 431.0643.

3-Iodo-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2o**): White solid, 106.9 mg, 73% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.13. m.p. 156～157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36～8.31 (m, 1H), 8.20 (d, J=8.3 Hz, 1H), 7.88 (m, 1H), 7.81 (m, 2H), 7.49～7.42 (m, 2H), 3.90 (d, J=13.1 Hz, 1H), 3.53 (d, J=13.1 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.88, 148.52, 143.96, 140.16, 138.11, 135.24, 131.23, 129.99 (q, J=307.2 Hz), 127.50, 126.41, 126.24, 122.86, 120.13, 115.75, 98.69, 49.24, 39.68, 28.81; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.85. HRMS (ESI) calcd for $C_{18}H_{13}F_3IN_2OS$ $[M+H]^+$: 488.9740, found 488.9732.

5-Methyl-3-(trifluoromethoxy)-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2p**): White solid, 64.3 mg, 48% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.21. m.p. 90～91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.56 (d, J=8.7 Hz, 1H), 8.34 (m, 1H), 7.83 (m, 1H), 7.51～7.44 (m, 2H), 7.41 (d, J=8.7 Hz, 1H), 7.28 (s, 1H), 3.93 (d, J=13.3 Hz, 1H), 3.53 (d, J=13.3 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.99, 151.83, 148.03, 143.96, 140.70, 131.16, 129.90 (d, J=307.1 Hz), 128.34, 126.44, 126.27, 122.02, 121.23, 120.33 (q, J=259.2 Hz), 120.17, 118.50, 115.75, 49.70, 39.74, 28.83; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.93, -57.65. HRMS (ESI) calcd for $C_{19}H_{13}F_6N_2O_2S$ $[M+H]^+$: 447.0596, found 447.0590.

5-Methyl-6-oxo-5-(((trifluoromethyl)thio)methyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline-3-carbonitrile (**2q**): White solid, 95.1 mg, 82% yield. R_f(petroleum ether/ethyl acetate, V∶V = 10∶1): 0.19. m.p. 214～215 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.62 (d, J=8.1 Hz, 1H), 8.37～8.33 (m, 1H), 7.88～7.84 (m, 1H), 7.81 (m, 1H), 7.77 (s, 1H), 7.50 (m, 2H), 3.95 (d, J=13.4 Hz, 1H), 3.55 (d, J=13.4 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.46, 147.24, 143.97, 139.42, 131.95, 131.24, 130.32, 129.79 (q, J=307.5 Hz), 127.31, 127.02, 126.98, 126.74, 120.58, 117.71, 115.88, 115.38, 49.56, 39.71, 28.67; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.74. HRMS (ESI) calcd for $C_{19}H_{13}F_3N_3OS$ $[M+H]^+$: 388.0726, found 388.0719.

5-Methyl-3-(methylsulfonyl)-5-(((trifluoromethyl)thio)-methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2r**): White solid, 110.9 mg, 84% yield. R_f(petroleum ether/ethyl acetate, V∶V = 20∶1): 0.36. m.p. 222～223 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.72 (d, J=8.2 Hz, 1H), 8.39～8.33 (m, 1H), 8.11～8.04 (m, 2H), 7.87 (m, 1H), 7.51 (m, 2H), 3.98 (d, J=13.6 Hz, 1H), 3.63 (d, J=13.6 Hz, 1H), 3.13 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.71, 147.28, 143.98, 143.33, 139.72, 131.25, 129.87 (q, J=307.6 Hz), 128.19, 127.50, 127.47, 127.00, 126.74, 125.71, 120.60, 115.89, 50.12, 44.46, 39.57, 28.91; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.57. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2O_3S_2$ $[M+H]^+$: 441.0549, found 441.0543.

2,4-Bichloro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2s**): White solid, 41.3 mg, 32% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.44. m.p. 139～140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (d, J=2.3 Hz, 1H), 8.35 (m, 1H), 7.84 (m, 1H), 7.61 (d, J=2.2 Hz, 1H), 7.54～7.45 (m, 2H), 4.53 (d, J=13.8 Hz, 1H), 4.00 (d, J=13.8 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.47, 147.20, 143.94, 135.65, 134.45, 134.12, 132.77, 131.21, 128.02 (d, J=193.9 Hz), 126.72, 126.60, 125.54, 120.35, 115.94, 51.10, 35.89, 25.18; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.66. HRMS (ESI) calcd for $C_{18}H_{12}Cl_2F_3N_2OS$ $[M+H]^+$: 430.9994, found 430.9990.

2,4-Dimethoxy-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2t**): White solid, 96.3 mg, 76% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.42. m.p. 164～165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (m, 1H), 7.83 (m, 1H), 7.67 (d, J=2.4 Hz, 1H), 7.48～7.41 (m, 2H), 6.68 (d, J=2.4 Hz, 1H), 4.32 (d, J=12.8 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.88 (d, J=12.8 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.13, 160.79, 158.49, 149.66, 143.99, 131.35, 130.45 (q, J=306.8 Hz), 126.16, 125.85, 125.32, 119.85, 118.85, 115.87, 103.57, 100.48, 55.87, 55.74, 49.35, 36.64, 25.82; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −

40.96. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_2O_3S$ $[M+H]^+$: 423.0985, found 423.0979.

1,3,5-Trimethyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2u**): White solid, 84.3 mg, 72% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.47. m.p. 117～118 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (m, 1H), 7.86～7.81 (m, 1H), 7.47～7.40 (m, 2H), 7.19 (s, 1H), 7.12 (s, 1H), 3.94 (d, J=12.7 Hz, 1H), 3.60 (d, J=12.7 Hz, 1H), 3.03 (s, 3H), 2.44 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.95, 149.65, 144.25, 141.29, 140.20, 139.61, 133.10, 130.43, 130.31 (q, J=306.8 Hz), 125.85, 125.72, 124.41, 120.12, 119.16, 115.69, 49.18, 39.86, 29.67, 24.48, 21.62; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.06. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_2OS$ $[M+H]^+$: 391.1086, found 391.1081.

2,3,4-Trimethoxy-5-methyl-5-(((trifluoromethyl)thio)-methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2v**): White solid, 99.4 mg, 73% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.43. m.p. 94～95 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.34 (m, 1H), 7.83～7.77 (m, 2H), 7.46～7.39 (m, 2H), 4.20 (d, J=12.6 Hz, 1H), 4.08 (s, 3H), 4.03 (s, 3H), 3.93～3.88 (m, 4H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.93, 154.33, 152.28, 149.42, 145.25, 144.07, 131.33, 130.34 (q, J=306.7 Hz), 126.15, 125.65, 123.63, 119.65, 119.05, 115.82, 103.75, 61.10, 60.76, 56.32, 49.43, 37.48, 26.60; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.86. HRMS (ESI) calcd for $C_{21}H_{20}F_3N_2O_4S$ $[M+H]^+$: 453.1090, found 453.1083.

7-Methyl-7-(((trifluoromethyl)thio)methyl)benzo[h]benzo[4,5]imidazo[2,1-*a*]isoquinolin-8(7*H*)-one (**2w**): White solid, 105.3 mg, 85% yield. R_f(petroleum ether/ethyl acetate, V∶V=20∶1): 0.21. m.p. 197～198 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.53 (d, J = 8.8 Hz, 1H), 8.47～8.42 (m, 1H), 8.08 (d, J=8.7 Hz, 1H), 7.97～7.91 (m, 2H), 7.84 (m, 1H), 7.70～7.64 (m, 1H), 7.55～7.48 (m, 3H), 4.04 (d, J=12.8 Hz, 1H), 3.72 (d, J=12.8 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.80, 149.41, 144.10, 138.75, 133.28, 133.14, 130.24, 130.16 (d, J=306.8 Hz), 129.11, 128.52, 128.26, 127.35, 126.27, 126.15, 122.36, 120.36, 118.82, 115.80, 49.55, 39.55, 29.23; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.97. HRMS (ESI) calcd for $C_{22}H_{16}F_3N_2OS$ $[M+H]^+$: 413.0930, found 413.0924.

4-Methyl-4-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[1,2-*a*]thieno[2,3-*c*]pyridin-5(4*H*)-one (**3x**): Yellow solid, 74.2 mg, 67% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.42. m.p. 97～98 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.33～8.28 (m, 1H), 7.79～7.74 (m, 1H), 7.64 (d, J=5.1 Hz, 1H), 7.46～7.39 (m, 2H), 7.10 (d, J=5.1 Hz, 1H), 3.81 (d, J=12.9 Hz, 1H), 3.49 (d, J=12.9 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.28, 146.13, 144.23, 143.87, 131.60, 130.64, 130.11 (q, J=306.9 Hz), 126.18, 125.94, 125.13, 125.08, 119.88, 115.28, 49.21, 39.67 (d, J=1.6 Hz), 27.69; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.97. HRMS (ESI) calcd for $C_{16}H_{12}F_3N_2OS_2$ $[M+H]^+$:369.0338, found 369.0333.

9,10-Dichloro-5-methyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**2y**): White solid, 97.1 mg, 75% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.43. m.p. 144～145 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.49～8.42 (m, 2H), 7.88 (s, 1H), 7.65 (m, 1H), 7.58～7.53 (m, 1H), 7.47 (d, J=7.9 Hz, 1H), 3.90 (d, J=13.0 Hz, 1H), 3.59 (d, J=13.0 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.53, 150.78, 143.45, 138.67, 132.79, 130.33, 130.20, 130.00 (q, J=307.1 Hz), 129.82, 128.99, 126.58, 126.12, 122.69, 121.17, 117.10, 49.51, 39.83 (d, J=1.5 Hz), 28.94; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −40.92. HRMS (ESI) calcd for $C_{18}H_{12}Cl_2F_3N_2OS$ $[M+H]^+$: 430.9994, found 430.9990.

5,9,10-Ttrimethyl-5-(((trifluoromethyl)thio)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**2z**): White solid, 86.9 mg, 74% yield. R_f(petroleum ether/ethyl acetate, V∶V=10∶1): 0.51. m.p. 121～122 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.39 (m, 1.0 Hz, 1H), 8.05 (s, 1H), 7.52～7.47 (m, 2H), 7.44 (m, 1.0 Hz, 1H), 7.36 (d, J=7.7 Hz, 1H), 3.84 (d, J=12.8 Hz, 1H), 3.50 (d, J=12.8 Hz, 1H), 2.34 (d, J=9.1 Hz, 6H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.60, 148.47, 142.50, 138.27, 135.32, 135.24, 131.78, 129.58, 128.71, 126.09, 125.96, 123.55, 120.20, 116.00, 49.20, 39.72 (d, J=1.5 Hz), 29.03, 20.51 (d, J=7.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ: −41.04. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_2OS$ $[M+H]^+$: 391.1086, found 391.1079.

5-Methyl-5-(((trifluoromethyl)sulfinyl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (**3**): White solid, 79.6 mg, 75% yield. R_f(petroleum ether/ethyl acetate, V∶V=5∶1): 0.26. m.p. 101～102 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.53 (d, J=6.9 Hz, 1H), 8.30 (d, J=7.2 Hz, 1H), 7.84 (d, J=8.3 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.57 (m, 2H), 7.50～7.43 (m, 2H), 4.10 (d, J=13.8 Hz, 1H), 3.70 (d, J=13.8 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.61, 148.97, 144.15, 137.27, 132.16, 131.15, 129.16, 128.46 (d, J=220.5 Hz), 127.00, 126.78, 126.50, 126.11, 122.59, 120.22, 115.61, 59.13 (d, J=2.6 Hz), 47.33, 30.71; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −73.74. HRMS (ESI) calcd for $C_{18}H_{14}F_3N_2O_2S$ $[M+H]^+$: 379.0723, found 379.0719.

Supporting Information Control experiments, application investigation and NMR spectra of products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/

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