A facile trifluoromethylthiolation of 3-chloro-1*H*-inden-1-ones employing $AgSCF_3$ and KI

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.606

Abstract

An efficient method for trifluoromethylthiolation of functionalized 3-chloro-1*H*-inden-1-ones was described. Within this method, $AgSCF_3$ was employed as a nucleophilic reagent and KI was functionalized as an activator. This reaction provided the trifluoromethylthiolated indenones with excellent yields under moderate conditions.

Keywords: 3-Chloro-1*H*-inden-1-ones, trifluoromethylthiolation, $AgSCF_3$, KI

Introduction

Fluorinated compounds have received increasing attention within organic synthesis and medicinal/pharmaceutical science because of special properties of fluorine atoms, which are the most electronegative elements with a small atomic radius. Among these fluorine-containing groups, the trifluoromethylthio group (SCF_3) is of particular interest. The incorporation of the SCF_3 moiety into drug candidates can lead to the increase of compound's membrane permeability, bioavailability and metabolic stability because of its high lipophilicity and electron-withdrawing properties.[1-2] Some SCF_3 group-containing pharmaceutical products or pesticides have been reported [shown in Figure 1],[3] including toltrazuril,[4] tiflorex,[5] and fiptonil.[6] And the increasing number of the SCF_3-containing bioactive lead compounds, such as amebiasis trifloromethionine[7] and potential hypotensive agents of losartan and nifedipin analogues[8] also prove the importance of introducing the SCF_3 moiety into drug candidates.

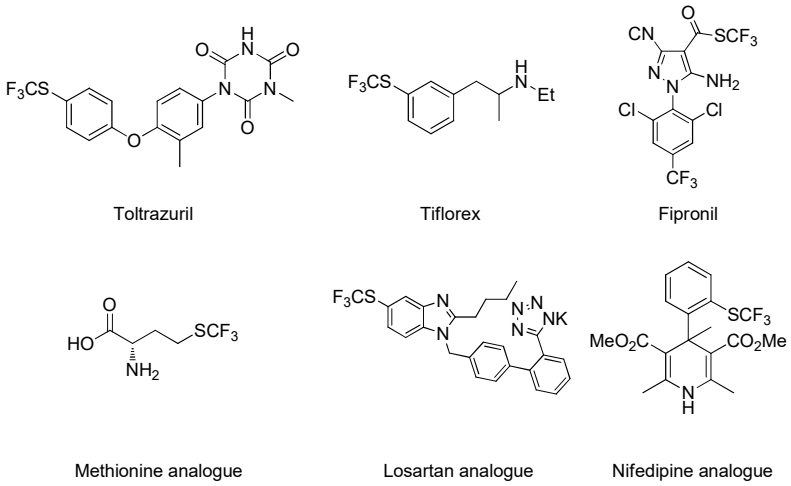


Figure 1. Bioactive agents containing SCF_3 group.

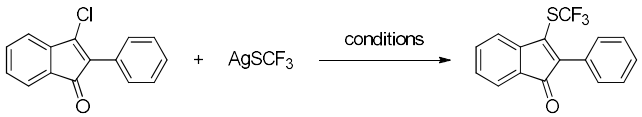
Many research groups have been managed to explore efficient methods introducing the SCF_3 group to small heterocyclic molecules.[9] Earlier trifluoromethylthiolation strategies can be classified as indirect and direct methods. The indirect methods include halogen-fluorine exchange[10] and trifluoromethylation of sulfur-containing compounds.[11] However, both of the indirect methods require harsh conditions and have a narrow substrate scope. The direct trifluoromethylthiolation methods are based on either electrophilic or nucleophilic pathways. As for heterocyclic scaffolds, such as benzofurans/ benzothiophenes,[12] isocoumarin,[13] indole[14-17] and oxidine,[18-20] they can be trifluoromethylthiolated by *N*-trifluoromethanesulfanylamides or hypervalent iodine trifluoromethanesulfenate reagent and *N*-trifluoromethylthiosaccharin. $AgSCF_3$, as the most common SCF_3^- containing nucleophilic reagent,[21] plays a key role in trifluoromethylthiolation of various bioactive structures in medicinal chemistry. And trifluoromethylthiolation of chromone derivatives using $AgSCF_3$ was achieved by our group. [22]

The indenone moiety is one of the privileged scaffolds in medicinal chemistry owing to its various biological activities. Indenone-containing compounds were widely employed as agonists for estrogen receptor[23] and peroxisome proliferator-activated receptor γ (PPARγ).[24] They also has been used as cyclooxygenase-2 (COX-2)[25] and topoisomerase I (Top I)[26] inhibitors and so on .[27] Therefore, incorporation of the SCF_3 group into the indenone moiety can lead to novel series of heterocyclic scaffolds and will bring about further advances in the pharmacological applications. Inspired by previous work,[28-29] we proposed a simple synthetic route to generate substituted indenone analogues in this work.

Results and Discussion

Compound **1a**, which was synthesized from phenylacetic acid, phthalic anhydride, and phosphorus oxychloride,[30] was selected as the model substrate for optimal conditions' screening (shown in Table1). However, reactions did not occur when $AgSCF_3$ was simply added even at different temperatures (entries1-3). This may be caused by the low activity of $AgSCF_3$ to proceed this reaction. Considering the application of KI for trifluoromethylthiolation as the addition,[31-32] KI (2 Equiv.) was introduced to accelerate reaction. Then compound **2a** was obtained at 60 °C in 51% yield (entry 4). Based on this, a series of solvents were tested. The results showed that the utilization of CH_3CN as solvent provided **2a** with the highest yield (entries 4-6). This solvent was confirmed to have a significant impact on yields. Additionally, the replacement of KI to the NaI can lead to the decease of yields (entry 7). It was also found that reactions tend to have better yields under nitrogen environment compared with no inert gas protection (entry 8).

Table 1. Optimization of Reaction Conditions[a]



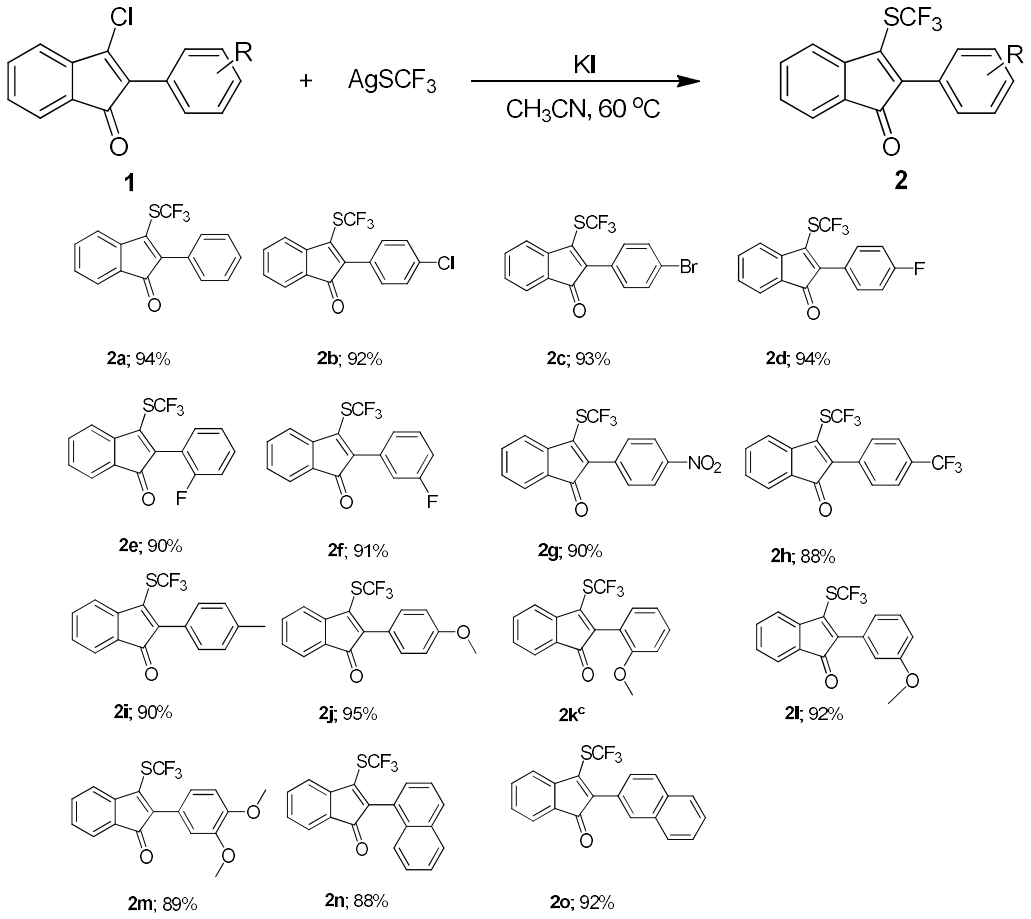
1a 2a

Entry	Additive	Solvent	Temperature (°C)	Yield (%)[c]
1	-	DMSO	20	NR[b]
2	-	DMSO	40	NR
3	-	DMSO	60	NR
4	KI	DMSO	60	51
5	KI	DMF	60	48
6	KI	CH_3CN	60	88
7	NaI	CH_3CN	60	70
8	KI	CH_3CN	60	94[d]

[a]1a (0.5mmol), $AgSCF_3$ (1mmol) and solvent (2mL) were used, [b]NR= no reaction, [c]Isolated yield, [d] Under argon atmosphere.

Under the optimized reaction conditions (2 equiv. $AgSCF_3$ and 2 equiv. KI in CH_3CN at 60 °C), a variety of indenone derivatives were applied as substrates. As shown in Figure 2, this reaction was compatible with both electron-withdrawing groups (fluoro, bromo, chloro, nitro, trifluoromethyl group) and electron-donating groups (methyl, methoxy, dimethoxy moities). The yields for different electron-withdrawing groups-containing substrates were similar. Besides, electron-withdrawing substituents at different positions of the aromatic ring provide desire

products with excellent yields (**2d**, **2e**, **2f**). However, substrates containing electron-donating groups were different (**2j**, **2k**, **2l**). Compound **2k** has the lowest yield at 60 ºC. At first we think this reaction was sensitive for steric hindrance (**2e** vs **2k**). To our surprise, the yields are almost the same when the bulkier naphthalenyl group was employed instead of the phenyl group (**2n**, **2o** vs **2a**). This result suggests that trifluoromethylthiolation of 3-chloro-1*H*-inden-1-ones *via* $AgSCF_3$ and KI to functional 2-aryl-3-((trifluoromethyl)thio)-1*H*-inden-1-ones have broader application due to its wide substrates tolerance. Compared with previous work,[28-29] the experimental conditions are milder and the synthetic method has broad scope of substrates and excellent compatibility of functional-groups for the presence of the activated chlorine atom on indenone core.



[a]Reaction condition: 1(0.5mmol), $AgSCF_3$(1mmol) and KI(1mmol) in CH_3CN at 60 ºC, 2-4 h. [b]Isolated yield. [c]Raw material recycling is more than 80%.

Figure 2. Exploration of reaction scope.[a,b]

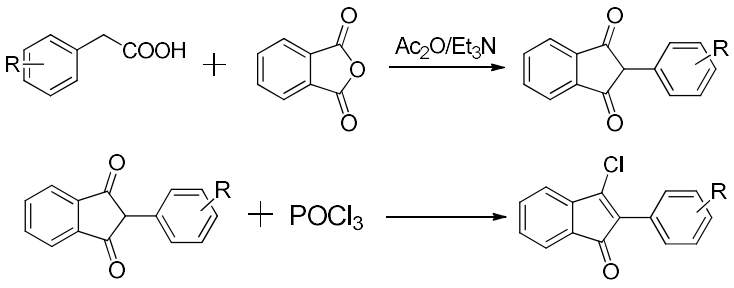
Conclusions

A novel and facile method for synthesis of SCF_3-substituted indenones *via* $AgSCF_3$/KI was discovered. This novel method only requires mild conditions and short time without employment of Pd or Ni catalysts. Moreover, this novel synthetic method was followed by simple work up and provided with superior yields.

Experimental Section

General. All reactions were performed under an argon atmosphere. Solvents and reagents are commercially available and without pretreatment. Column chromatography was employed by silica gel (200—300 mesh).^{1}H NMR spectra were recorded on a Bruker Avance 300 or a Bruker Avance 400 spectrometer in $CDCl_3$ (δ 7.26 ppm) ,respectively. ^{13}C NMR spectra were recorded on a Bruker Avance 400 or Bruker Avance 500 spectrometer in $CDCl_3$ (δ 77.16 ppm).

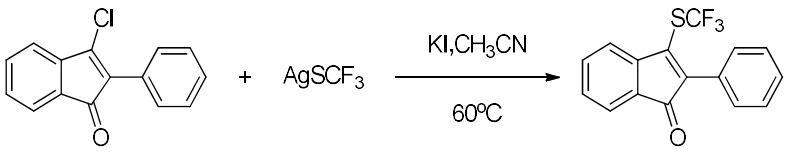
General procedure for the synthesis of compounds **1**



1

Compound **1** were prepared from corresponding unsubstituted/substituted phenylacetic acid, phthalic anhydride and phosphorus oxychloride.

General procedure for the synthesis of compounds **2a-2o**



1a **2a**

To a reaction flask were added $AgSCF_3$ (1 mmol), KI (1 mmol), compound **1**(0.5 mmol), CH_3CN (2 mL). The mixture was stirred at 60 ºC for 2-4 h. Afterward, the reaction mixture was poured into water and extracted with EtOAc and dried with Na_2SO_4. The solution was concentrated in

vacuo to get a crude mixture, which was purified by flash column chromatography on silica gel (petroleum ether: acetate 100:1) to pure products.

2-Phenyl-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2a). Yellow solid, 94% Yield; mp 107-109 °C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 4H), 7.50 – 7.42 (m, 4H), 7.34 (t, *J* 7.4 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ 193.72, 145.31, 144.42, 139.64, 135.01, 130.26, 129.71, 129.69, 129.47(q, *J* 312.1 Hz), 129.28, 129.12, 128.41, 123.50, 121.86. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.37. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OF_3NaS$) ([M+Na]$^+$): 329.0326; found: 329.0213.

2-(4-Chlorophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2b). Yellow solid, 87% Yield; mp 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* 7.1 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.48 – 7.43 (m, 3H), 7.36 (t, *J* 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.42, 144.27, 144.04, 139.94, 136.02, 135.15, 131.57, 129.90, 129.15, 128.81, 128.68(d, *J* 314.3 Hz) 127.53, 123.63, 121.99. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.32. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OClF_3S$) ([M+H]$^+$): 340.9936; found: 341.0002.

2-(4-Bromophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2c). Yellow solid, 93% Yield; mp 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* 8.4 Hz, 2H), 7.58 (d, *J* 7.1 Hz, 1H), 7.53 (t, *J* 7.4 Hz, 1H), 7.44-7.47(m, 3H), 7.35 (t, *J* 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.33, 144.25, 144.10, 140.01, 135.16, 131.77, 131.75, 129.92, 129.14, 128.60(d, *J* 311.9 Hz), 127.97, 124.43, 123.64, 122.00. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.30. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OBrF_3S$) ([M+H]$^+$): 384.9431; found: 384.9500.

2-(4-Fluorophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2d). Yellow solid, 94% Yield; mp 87-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 3H), 7.53 (t, *J* 7.5 Hz, 1H), 7.46 (d, *J* 7.3 Hz, 1H), 7.35 (t, *J* 7.4 Hz, 1H), 7.17 (t, *J* 8.7 Hz, 2H). ^{13}C NMR (125MHz, $CDCl_3$) δ193.68, 163.62(d, *J* 251.0 Hz), 144.37, 144.18, 139.37, 135.13, 132.36, 132.29, 129.77, 129.13, 128.70(d, *J* 312.1 Hz), 125.18(d, *J* 3.3 Hz), 123.59, 121.89, 115.80, 115.63. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.40, -110.34. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OF_4S$) ([M+H]$^+$): 325.0232; found: 325.0299.

2-(2-Fluorophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2e). Yellow solid, 96% Yield; mp 56-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 7.1 Hz, 1H), 7.53 (t, *J* 7.8 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.40 – 7.29 (m, 2H), 7.29 – 7.21 (m, 1H), 7.18 (t, *J* 9.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.45, 160.26(d, *J* 249.6 Hz), 143.87, 143.81, 141.28, 134.90, 131.76(d, *J* 2.1 Hz), 131.55(d, *J* 8.4 Hz), 129.99, 129.56, 128.56(q, *J* 311.5 Hz), 124.20(d, *J* 3.5 Hz), 123.61, 122.00, 117.46(d, *J* 15.3 Hz), 116.12(d, *J* 21.9 Hz). ^{19}F NMR (471 MHz, $CDCl_3$),δ -37.16 , -110.43. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OF_4S$) ([M+H]$^+$): 325.0232; found: 325.0302.

2-(3-Fluorophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2f). Yellow solid, 95% Yield; mp 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 7.1 Hz, 1H), 7.54 (t, *J* 7.5 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.36 (t, *J* 7.7 Hz, 2H), 7.30 (d, *J* 9.8 Hz, 1H), 7.15 (t, *J* 8.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.16, 162.53(d, *J* 246.3 Hz), 144.11, 143.89, 140.69, 135.13, 131.03(d, *J* 8.4 Hz), 130.02, 129.97, 129.13, 128.64(d, *J* 312.1 Hz), 126.07(d, *J* 2.6 Hz), 123.66, 122.10, 117.23(d, *J* 22.9 Hz), 116.70 (d, *J* 21.1 Hz). ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.25, -112.37. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9OF_4S$) ([M+H]$^+$): 325.0232; found: 325.0301.

2-(4-Nitrophenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2g). Yellow solid, 90% Yield; mp 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* 8.5 Hz, 2H), 7.75 (d, *J* 8.6 Hz, 2H), 7.67 – 7.55 (m, 2H), 7.51 (d, *J* 7.2 Hz, 1H), 7.41 (t, *J* 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.53, 148.18, 143.73, 142.89, 142.67, 135.53, 135.35, 131.21, 130.60, 129.02, 128.42(d, *J* 312.3 Hz), 123.92, 123.56, 122.48. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.04. HRMS-ESI(*m/z*) Calcd for ($C_{16}H_9O_3NF_3S$) ([M+H]$^+$): 352.0177; found: 352.0244.

2-(4-(Trifluoromethyl)phenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2h). Yellow solid, 88% Yield; mp 80-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* 8.3 Hz, 2H), 7.67 (d, *J* 8.2 Hz, 2H), 7.60 (d, *J* 7.2 Hz, 1H), 7.55 (td, *J* 7.5, 1.1 Hz, 1H), 7.49 (d, *J* 7.3 Hz, 1H), 7.38 (t, *J* 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.00, 143.97, 143.86, 141.54, 135.21, 132.66, 131.37(q, *J* 32.7 Hz),130.60, 130.23, 129.12, 128.57(q, *J* 312.1 Hz),125.39, 125.36, 124.05(d, *J* 272.4 Hz),123.75, 122.24. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.20, -62.88. HRMS-ESI(*m/z*) Calcd for ($C_{17}H_9OF_6S$) ([M+H]$^+$): 375.0200; found: 375.0265.

2-(p-Tolyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2i). Yellow solid, 90% Yield; mp 76-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* 7.1 Hz, 1H), 7.52 (td, *J* 7.5, 1.1 Hz, 1H), 7.48 (d, *J* 8.2 Hz, 2H), 7.45 (d, *J* 7.4 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.29 (d, *J* 7.9 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 193.95, 145.30, 144.61, 140.03, 138.64, 134.98, 130.19, 129.49, 129.32, 129.20, 128.81(d, *J* 312.0 Hz), 126.24, 123.43, 121.71, 21.65. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.45. HRMS-ESI(*m/z*) Calcd for ($C_{17}H_{11}OF_3NaS$) ([M+23]$^+$): 343.0483; found: 343.0370

2-(4-Methoxyphenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2j). Yellow solid, 95% Yield; mp 117-119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* 9.0 Hz, 2H), 7.56 (dd, *J* 7.1, 0.6 Hz, 1H), 7.51 (td, *J* 7.6, 1.1 Hz, 1H), 7.44 (d, *J* 0.9 Hz, 1H), 7.31 (td, *J* 7.4, 1.0 Hz, 1H), 7.00 (d, *J* 9.0 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.29, 160.91, 144.90, 144.70, 137.13, 135.03, 131.92, 129.30, 129.27, 128.87(d,*J* 312.1 Hz), 123.41, 121.61, 121.55, 114.03, 55.49. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.60. HRMS-ESI(*m/z*) Calcd for ($C_{17}H_{11}O_2F_3NaS$) ([M+23]$^+$): 359.0432; found: 359.0317.

2-(3-Methoxyphenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2l). Yellow solid, 92% Yield; mp 60-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* 7.1 Hz, 1H), 7.53 (td, *J* 7.5, 1.1 Hz, 1H), 7.46 (d, *J* 7.3 Hz, 1H), 7.39 (t, *J* 8.0 Hz, 1H), 7.34 (td, *J* 7.4, 1.0 Hz,1H), 7.13 (dt, *J* 7.7, 1.2 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.00 (dd, *J* 8.7, 3.0 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 193.58, 159.41, 145.17, 144.36, 139.84, 135.01, 130.29, 129.73, 129.46, 129.28, 128.76(d, *J* 311.9 Hz), 123.50, 122.75, 121.91, 115.75, 115.43, 55.44. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.30. HRMS-ESI(*m/z*) Calcd for ($C_{17}H_{12}O_2F_3S$) ([M+H]$^+$):337.0432; found: 337.0501.

2-(3,4-Dimethoxyphenyl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2m). Red solid, 94% Yield; mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* 7.2 Hz, 1H), 7.52 (td, *J* 7.6, 1.2 Hz, 1H), 7.43 (d, *J* 7.4 Hz, 1H), 7.31 (t, *J* 7.4 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.97 (d, *J* 8.2 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.24, 150.56, 148.68, 144.85, 144.55, 137.08, 135.08, 129.35, 129.21, 128.89(d, *J* 312.2 Hz) , 123.94, 123.40, 121.78, 121.57, 113.06, 110.93,

56.05, 56.03. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.60. HRMS-ESI(*m/z*) Calcd for ($C_{18}H_{14}O_3F_3S$) ($[M+H]^+$):367.0537;found: 367.0603.

2-(Naphthalen-1-yl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2n). Yellow liquid, 93% Yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* 8.3 Hz, 1H), 7.89 (d, *J* 8.1 Hz, 1H), 7.61 (d, *J* 7.1 Hz, 1H), 7.59 – 7.47 (m, 5H), 7.47 – 7.41 (m, 1H), 7.37 (t, *J* 7.5 Hz, 2H). ^{13}C NMR (125MHz, $CDCl_3$) δ 193.42, 146.76, 144.09, 143.83, 134.95, 133.67, 131.99, 130.03, 129.94, 129.63, 128.69, 128.47 (d, *J* 311.8 Hz), 128.37, 127.42, 126.56, 126.33, 125.60, 125.20, 123.67, 121.91. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.96. HRMS-ESI(*m/z*) Calcd for ($C_{20}H_{12}OF_3S$) ($[M+H]^+$):357.0483;found: 357.0551.

2-(Naphthalen-2-yl)-3-((trifluoromethyl)thio)-1*H*-inden-1-one (2o). Yellow solid, 92% Yield; mp 86-88 ºC. ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.07 (s, 1H), 7.92 (d, *J* 8.0 Hz, 2H), 7.87 (d, *J* 8.8 Hz, 1H), 7.69 (dd, *J* 8.5, 1.6 Hz,1H), 7.60 (d, *J* 7.1 Hz, 1H), 7.50-7.56 (m,3H), 7.48 (d, *J* 7.4 Hz, 1H), 7.36 (d, *J* 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.85, 145.19, 144.55, 139.61, 135.07, 133.66, 132.98, 130.80, 129.71, 129.33, 128.89, 128.79(d, *J* 312.1 Hz) 127.99, 127.85, 127.39, 126.91, 126.64, 126.56, 123.54, 121.84. ^{19}F NMR (471 MHz, $CDCl_3$), δ -37.33. HRMS-ESI(*m/z*) Calcd for ($C_{20}H_{12}OF_3S$) ($[M+H]^+$): 357.0483; found: 357.0549.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant Number 81321092) and SKLDR/SIMM (SIMM1601ZZ-03)

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