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(Trifluoromethyl)thiolation of 2-Alkynylbenzoates: An Efficient Route to 4-[(Trifluoromethyl)thio]-1*H*-isochromen-1-ones

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The incorporation of the (trifluoromethyl)thio group into the isocoumarin scaffold through a Lewis-acid-mediated electrophilic cyclization reaction of 2-(2-alkynyl)benzoates with trifluoromethanesulfanylamide is reported. The transformation proceeds well in the presence of $BiCl_3$ and $BF_3{\cdot}Et_2O$ under mild conditions to give 4-[(trifluoromethyl)thio]-1*H*-isochromen-1-ones regioselectively and in good yields.

Introduction

Fluorinated organic compounds often show unique and important physical, chemical, and biological properties due to the high electronegativity, low polarizability, and small size of the fluorine atom, and the strength of the C–F bond. Such compounds have been used to great effect in the pharmaceutical and agrochemical industries.[1] Statistical analysis of available data indicates that more than 20% of commercial drugs contain a fluorine group. The trifluoromethylthio group (CF_3S) has attracted increasing interest because of its strong electron-withdrawing effects and high lipophilicity.[2] The introduction of an SCF_3 group into small molecules can enhance their membrane permeability and absorption rate and also their stability. This gives an opportunity for the modification of known and new drugs (Figure 1).[3]

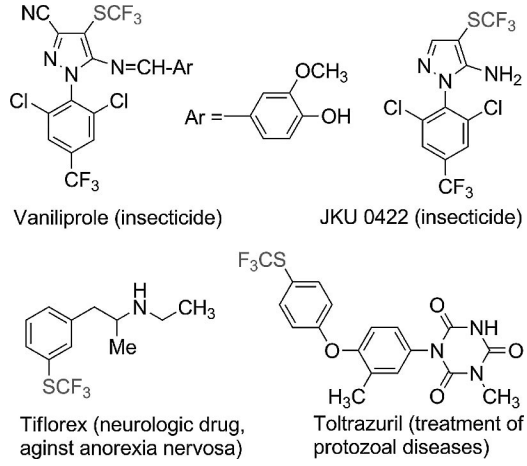

Figure 1. Examples of approved drugs containing an SCF_3 group.

Recently, several elegant approaches for the formation of C–SCF_3 bonds by direct trifluoromethylthiolation have been described. Nucleophilic trifluoromethylthiolation reagents (SCF_3^-),[4] such as $AgSCF_3$, NMe_4SCF_3, and $CsSCF_3$, have been used in combination with transition metals (especially, palladium and copper) by Buchwald and Vicic for the efficient formation of C–SCF_3 bonds. Wu and ourselves reported the introduction of the (trifluoromethyl)thio moiety into the scaffold of isoquinoline by using $AgSCF_3$ as the nucleophilic reagent.[4e] Meanwhile, several electrophilic trifluoromethylthiolation reagents (SCF_3^+), including trifluoromethanesulfanylamides,[5] trifluoromethylated thioperoxide,[6] trifluoromethanesulfonyl hypervalent iodonium ylide,[7] and *N*-trifluoromethylthiophthalimide,[8] have been developed to introduce the SCF_3 group into the target products. Recently, Qing and co-workers reported a transition-metal-free oxidative trifluoromethylthiolation of alkynes or arylboronic acids using elemental sulfur and (trifluoromethyl)trimethylsilane (CF_3TMS) as the source of the (trifluoromethyl)thio group.[9] Daugulis and co-workers reported the copper-catalysed single or double trifluoromethylthiolation of 8-aminoquinoline benzamides through the auxiliary-assisted direct functionalization of β-C–H bonds using bis(trifluoromethyl) disulfide $(CF_3S)_2$ as the electrophile.[10] Radical aryltrifluoromethylthiolation of activated alkenes using an $AgSCF_3/K_2S_2O_8$ system has also been developed.[11]

Isocoumarin and its derivatives can be found in many natural products and pharmaceuticals that show a wide

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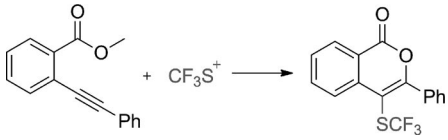
range of physiological and biological activities, such as antibacterial, anti-inflammatory, and anticancer activities, or as protease inhibitors or weedkillers.[12] Therefore, a lot of effort has been put into the synthesis of isocoumarins.[13] However, the synthesis of fluorinated isocoumarins using fluorinating reagents has not been reported. Prompted by advances in trifluoromethylthiolation, and by our interest in looking for small molecules for the inhibition of the activation and proliferation of hepatic stellate cells, and for the inhibition of extracellular matrix production,[14] we envisioned that functionalization of isocoumarin by incorporation of a trifluoromethylthio group under mild conditions would be beneficial for our biological evaluations (Scheme 1). Therefore, we initiated a program for the development of methods that could be used for the synthesis of a library of trifluoromethylthio-substituted isocoumarins.

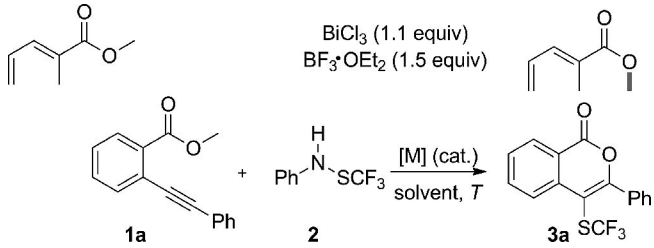


Scheme 1. Incorporation of an SCF_3 moiety into the isocoumarin core.

Results and Discussion

To examine this proposed trifluoromethylthiolation, we started to explore the practicability of this transformation, and chose the reaction of methyl 2-(phenylethynyl)benzoate (**1a**) with trifluoromethanesulfanylamide **2** as the model. Based on previous studies, which showed that Lewis acids could promote the electrophilic addition of trifluoromethanesulfanylamide,[5] the reaction was initially attempted in the presence of $BiCl_3$ (1.1 equiv.) or $BF_3{\cdot}Et_2O$ (1.5 equiv.) in $ClCH_2CH_2Cl$ (DCE) at 80 °C (Table 1, Entries 1 and 2). However, no reaction took place at all. A trace amount of the desired product (i.e., **3a**) was obtained when a combination of $Pd(OAc)_2$ (10 mol-%) and $BiCl_3$ (1.1 equiv.) was used (Table 1, Entry 3). The structure of compound **3a** was determined by X-ray diffraction analysis (Figure 2). By adjusting the amounts of the three metal salts $Pd(OAc)_2$ (10 mol-%), $BiCl_3$ (1.1 equiv.), and $BF_3{\cdot}Et_2O$ (1.5 equiv.), the expected product (i.e., **3a**) was obtained in 31% yield (Table 1, Entry 4). We next examined the effect of changing the solvent. The screening results indicated that the reaction in toluene worked more efficiently to give **3a** in 38% yield (Table 1, Entries 7–11). We found that the temperature had little impact on the outcome (Table 1, Entries 12–14). Surprisingly, the yield of **3a** increased dramatically to 97% in the absence of $Pd(OAc)_2$ (Table 1, Entry 15). The yield could not be improved further by changing the loading of $BiCl_3$ or $BF_3{\cdot}Et_2O$ (Table 1, Entries 16 and 17). No reaction occurred when 0.1 equiv. of $BiCl_3$ was used as the Lewis acid (Table 1, Entry 18).

Table 1. Initial studies for the cyclization of methyl 2-(phenylethynyl)benzoate (**1a**) with trifluoromethanesulfanylamide **2**.[a]



Entry	$Pd(OAc)_2$ [mol-%]	$BiCl_3$ [equiv.]	$BF_3{\cdot}Et_2O$ [equiv.]	Solvent[b]	T [°C]	Yield[c] [%]
1	–	1.1	–	DCE	80	n.r.
2	–	–	1.5	DCE	80	n.d.
3	10	1.1	–	DCE	80	trace
4	10	–	1.5	DCE	80	n.d.
5	10	1.1	1.5	DCE	80	31
6[d]	10	1.1	1.5	DCE	80	trace
7	10	1.1	1.5	toluene	80	38
8	10	1.1	1.5	THF	80	9
9	10	1.1	1.5	DMA	80	trace
10	10	1.1	1.5	dioxane	80	trace
11	10	1.1	1.5	CH_3CN	80	trace
12	10	1.1	1.5	toluene	60	39
13	10	1.1	1.5	toluene	50	39
14	10	1.1	1.5	toluene	25	37
15	–	1.1	1.5	toluene	25	97
16	–	1.1	1.0	toluene	25	75
17	–	0.5	1.5	toluene	25	73
18	–	0.1	1.5	toluene	25	trace

[a] Reaction conditions: methyl 2-(phenylethynyl)benzoate (**1a**) (0.2 mmol), trifluoromethanesulfanylamide **2a** (0.3 mmol), under N_2. [b] DMA = *N*,*N*-dimethylacetamide. [c] Isolated yield based on **1a**; n.r. = no reaction; n.d. = no **3a** detected. [d] Under air.

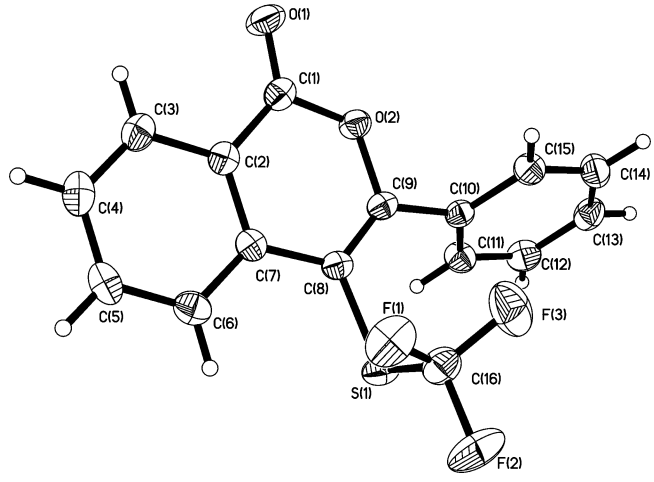
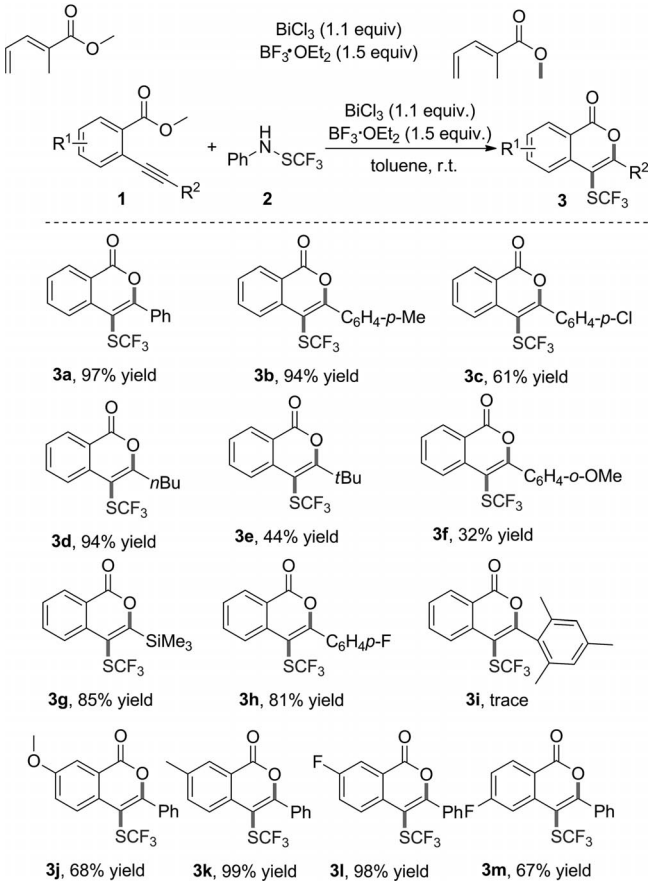


Figure 2. ORTEP representation of the structure of 4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one **3a** (30% probability ellipsoids).

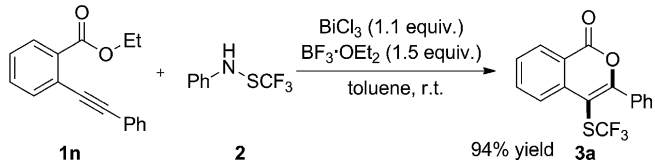
Using the optimal conditions, we then explored the substrate scope of this transformation. The results are summarized in Table 2. The substituents attached to the triple bond of 2-(2-alkynyl)benzoates **1** were tolerated well in general. For instance, when 2-alkynylbenzoate **1d**, with an *n*-

butyl group attached to the alkynyl moiety, was used as the substrate, a high yield (94%) of product **3d** was obtained. In contrast, substrate **1e**, with a *tert*-butyl group, gave a 44% yield of **3e**, probably due to steric hindrance. Interestingly, a trimethylsilyl group attached to the triple bond was tolerated under the standard conditions, and substrate **1g** gave the desired product (i.e., **3g**) in 85% yield. Additionally, various 2-alkynylbenzoates **1** with electron-withdrawing or electron-donating groups on the aromatic ring worked well under the optimized conditions. Different functional groups including fluoro, methyl, and methoxy groups were all compatible with the reaction process (leading to **3j**–**3m**). As expected, 3-phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (**3a**) was obtained in almost the same yield when methyl 2-(phenylethynyl)benzoate (**1a**) was replaced by ethyl 2-(phenylethynyl)benzoate (**1n**) under the standard conditions (Scheme 2).

Table 2. Synthesis of 4-[(trifluoromethyl)thio]-1*H*-isochromen-1-ones **3** by cyclization of 2-alkynylbenzoates **1** with trifluoromethanesulfanylamide **2**.[a]

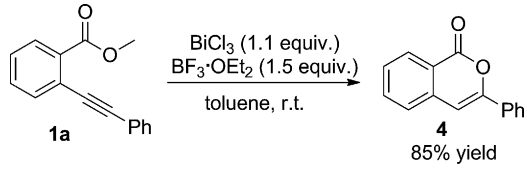


[a] Isolated yield based on 2-alkynylbenzoate **1**.

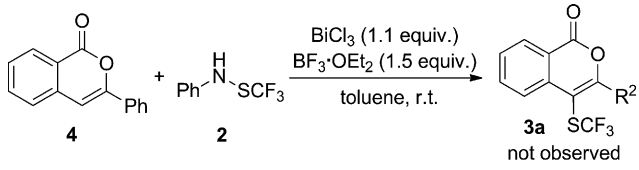


Scheme 2. Reaction of ethyl 2-(phenylethynyl)benzoate (**1n**) with trifluoromethanesulfanylamide **2**.

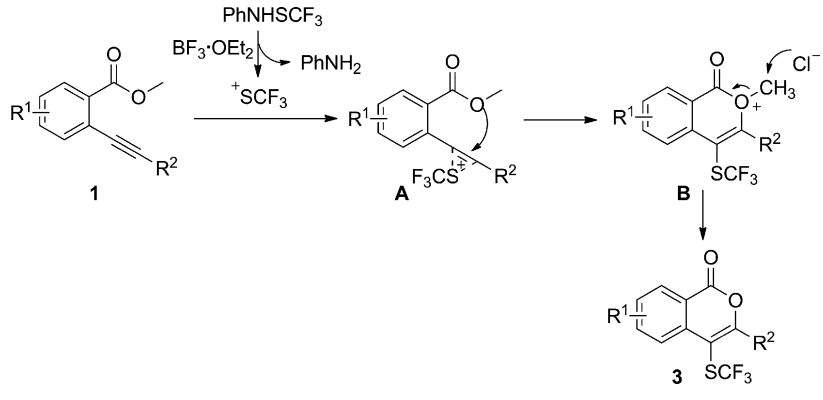
To investigate the reaction mechanism, we ran the reaction in the absence of trifluoromethanesulfanylamide **2** under the conditions shown in Table 2 (Scheme 3). Isocoumarin **4** was obtained by the Lewis acid ($BiCl_3$) catalysed intramolecular annulation of the internal alkyne in 85% yield. Isocoumarin **4** was not transformed into the desired product (i.e., **3a**) under the optimized conditions (Scheme 4). The formation of the trifluoromethylthio-substituted iso-



Scheme 3. Cyclization of methyl 2-(phenylethynyl)benzoate (**1a**) in the absence of trifluoromethanesulfanylamide **2**.



Scheme 4. Cyclization of 3-phenyl-1*H*-isochromen-1-one (**4**) with trifluoromethanesulfanylamide **2**.



Scheme 5. Proposed pathway for the formation of **3a**.

coumarin **3a** instead of **4** is probably due to the strong interaction between the trifluoromethanesulfanyl cation (CF_3S^+) and the carbon–carbon triple bond. Based on these preliminary results and previous studies,[5] we propose that the reaction involves a cascade electrophilic activation/cyclization process (Scheme 5). Initially, the additive $BF_3{\cdot}Et_2O$ promotes the generation of a reactive CF_3S^+ cation and aniline (which was observed by TLC) from trifluoromethanesulfanylamide **2**.[5d] Subsequently, intermediate **A** would be formed by coordination between the carbon–carbon triple bond and the trifluoromethanesulfanyl cation (CF_3S^+). Then, the intermediate **B** would be produced by intramolecular nucleophilic attack of oxygen. Finally, S_N2 attack of the chloride ion coming from $BiCl_3$ on the methyl group generates the desired product (i.e., **3**).[5k]

Conclusions

We have reported a trifluoromethylthiolation/cyclization protocol for the synthesis of 4-[(trifluoromethyl)thio]-1*H*-isochromen-1-ones **3** through reaction of 2-(2-alkynyl)-benzoates **1** with trifluoromethanesulfanylamide **2** in good yields under mild conditions. The Lewis acids $BiCl_3$ and $BF_3{\cdot}Et_2O$ were found to be important as activators in the transformation. The introduction of a (trifluoromethyl)thio moiety (SCF_3) into other heterocycles is currently underway in our laboratory.

Experimental Section

General Information: Unless otherwise stated, commercially sourced reagents were used as received. Solvents were dried and distilled according to standard procedures. Flash column chromatography was carried out using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was carried out using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated in rotary evaporators at ca. 20 Torr at 25–35 °C. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker DRX-400 spectrometer operating at 400, 376, or 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane on the δ scale. Coupling constants are reported in Hz. High-resolution mass spectra (HRMS) were obtained with a micrOTOF II Instrument.

General Procedure for the Synthesis of 4-[(Trifluoromethyl)thio]-1*H*-isochromen-1-ones: $BiCl_3$ (69.4 mg, 0.22 mmol) was added to a solution of 2-alkynylbenzoate **1** (0.2 mmol), trifluoromethanesulfanylamide **2** (0.3 mmol) and $BF_3{\cdot}Et_2O$ (0.3 mmol) in toluene (2.0 mL) under nitrogen. The mixture was stirred at 25 °C for 4–6 h. After TLC showed that the reaction was complete, the mixture was filtered through a thin layer of silica gel, which was then washed with EtOAc (3× 5.0 mL). The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/EtOAc, 20:1) to give product **3**.

3-Phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3a): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (dd, J = 7.9, 0.8 Hz, 1 H), 8.18 (d, J = 8.1 Hz, 1 H), 7.91–7.84 (m, 1 H), 7.68 (dd, J = 7.6, 1.8 Hz, 2 H), 7.62 (dd, J = 11.2, 4.0 Hz, 1 H), 7.48–7.50 (m, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.41 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 160.5, 137.7, 135.4, 132.3, 130.5, 129.8, 129.1, 128.9 (q, $J_{C,F}$ = 310.0 Hz), 128.1, 127.3, 125.6, 120.3, 115.0 ppm. HRMS calcd. for $C_{16}H_{10}F_3O_2S$ $[M + H]^+$ 323.0348; found 323.0322.

3-(*p*-Tolyl)-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3b): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (dd, J = 7.9, 0.9 Hz, 1 H), 8.17 (d, J = 8.1 Hz, 1 H), 7.88–7.84 (m, 1 H), 7.62–7.58 (m, 3 H), 7.29 (d, J = 8.0 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.45 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 160.7, 141.0, 138.0, 135.4, 133.9, 131.7, 130.1, 129.9, 129.8, 129.0 (q, $J_{C,F}$ = 310.0 Hz), 128.8, 125.6, 120.3, 21.5 ppm. HRMS calcd. for $C_{17}H_{12}F_3O_2S$ $[M + H]^+$ 337.0505; found 337.0483.

3-(4-Chlorophenyl)-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3c): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, J = 7.6, 0.8 Hz, 1 H), 8.18 (d, J = 8.4 Hz, 1 H), 7.90 (t, J = 7.6 Hz, 1 H), 7.65–7.63 (m, 3 H), 7.48–7.46 (m, 2 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = 42.35 (s, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 160.3, 137.6, 136.9, 135.6, 131.3, 130.7, 130.0, 129.4, 128.8 (q, $J_{C,F}$ = 311 Hz), 128.5, 125.6, 120.4 ppm. HRMS calcd. for $C_{16}H_9ClF_3O_2S$ $[M + H]^+$ 356.9958; found 356.9950.

3-Butyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3d): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, J = 7.9, 0.9 Hz, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 7.85–7.80 (m, 1 H), 7.57–7.53 (m, 1 H), 3.02 (s, 2 H), 1.79–1.72 (m, 2 H), 1.47–1.41 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.86 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 160.9, 141.3, 137.6, 135.4, 129.8, 129.1 (q, $J_{C,F}$ = 310.0 Hz), 128.5, 125.0, 120.1, 32.6, 29.4, 22.4, 13.7 ppm. HRMS calcd. for $C_{14}H_{14}F_3O_2S$ $[M + H]^+$ 303.0661; found 303.0660.

3-(*tert*-Butyl)-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3e): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 8.1 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H), 7.76 (td, J = 7.9, 1.2 Hz, 1 H), 7.63 (td, J = 7.5, 0.7 Hz, 1 H), 1.44 (s, 9 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –41.26 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 153.8, 138.9, 134.8, 131.0, 127. 8 [q, J(C,F) = 310.0 Hz], 127.4, 125.6, 118.7, 38.8, 30.4 ppm. HRMS calcd. for $C_{14}H_{14}F_3O_2S$ $[M + H]^+$ 303.0661; found 303.0664.

3-(2-Methoxyphenyl)-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3f): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, J = 7.9, 1.1 Hz, 1 H), 8.14 (d, J = 8.1 Hz, 1 H), 7.90–7.85 (m, 1 H), 7.64–7.60 (m, 1 H), 7.51–7.46 (m, 1 H), 7.41 (d, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.4 Hz, 1 H), 6.99 (d, J = 8.4 Hz, 1 H), 3.82 (s, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.40 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 156.9, 137.7, 135.3, 132.0, 130.9, 129.9, 129.1 (q, J = 310.0 Hz), 129.0, 125.5, 121.9, 120.6, 120.3, 111.0, 55.6 ppm. HRMS calcd. for $C_{17}H_{12}F_3O_3S$ $[M + H]^+$ 353.0454; found 353.0440.

4-[(Trifluoromethyl)thio]-3-(trimethylsilyl)-1*H*-isochromen-1-one (3g): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (dd, J = 8.0, 1.0 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H), 7.84 (t, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 0.46 (s, 9 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = 41.93 (s, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.64, 161.66, 136.49, 135.01, 128.74 ($J_{C,F}$ = 310.0 Hz), 124.90, 121.84, 121.21, 115.10, –0.51 ppm. HRMS calcd. for $C_{13}H_{14}F_3O_2SSi$ $[M + H]^+$ 319.0430; found 319.0434.

3-(4-Fluorophenyl)-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3h): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (dd, J =

7.9, 1.0 Hz, 1 H), 8.18 (d, J = 8.2 Hz, 1 H), 7.91–7.87 (m, 1 H), 7.72–7.68 (m, 2 H), 7.66–7.61 (m, 1 H), 7.20–7.16 (m, 2 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.42 (s), –108.99 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8 (d, J = 252.3 Hz), 162.5, 160.4, 137.7, 135.5, 132.1 (d, J = 8.7 Hz), 129.9, 129.3, 128.8 (q, J = 310.0 Hz), 128.4, 125.7, 120.3, 115.4 (d, J = 22.0 Hz) ppm. HRMS calcd. for $C_{16}H_9F_4O_2S$ $[M + H]^+$ 341.0254; found 341.0248.

7-Methoxy-3-phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3j): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.8 Hz, 1 H), 7.76 (d, J = 2.8 Hz, 1 H), 7.68–7.66 (m, 2 H), 7.50–7.43 (m, 4 H), 3.95 (s, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.43 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 160.8, 160.2, 132.3, 131.3, 130.3, 129.9, 129.0 (q, J = 310.0 Hz), 128.1, 127.5, 124.7, 123.4, 121.6, 110.4, 55.9 ppm. HRMS calcd. for $C_{17}H_{12}F_3O_3S$ $[M + H]^+$ 353.0454; found 353.0457.

7-Methyl-3-phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3k): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.1 Hz, 1 H), 7.96 (s, 1 H), 7.68–7.65 (m, 2 H), 7.51–7.42 (m, 4 H), 2.57 (s, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.45 (s) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7, 160.6, 146.8, 137.8, 132.4, 130.5, 129.9, 128.9 (q, $J_{C,F}$ = 310 Hz), 128.1, 125.7, 117.9, 22.3 ppm. HRMS calcd. for $C_{17}H_{12}F_3O_2S$ $[M + H]^+$ 337.0505; found 337.0508.

7-Fluoro-3-phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3l): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, J = 8.9, 4.9 Hz, 1 H), 8.01 (dd, J = 8.1, 2.7 Hz, 1 H), 7.67 (dd, J = 7.9, 1.7 Hz, 2 H), 7.61–7.57 (m, 1 H), 7.52–7.46 (m, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.41 (s, 3 F), –109.70 (s, 1 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 162.4 (d, J = 250.0 Hz), 159.6, 134.3, 131.9, 130.7, 129.9, 128.8 (q, J = 311.0 Hz), 128.5 (d, J = 7.8 Hz), 128.2, 123.6 (d, J = 22.9 Hz), 122.1 (d, J = 8.3 Hz), 115.4 (d, J = 23.6 Hz) ppm. HRMS calcd. for $C_{16}H_9F_4O_2S$ $[M + H]^+$ 341.0254; found 341.0252.

6-Fluoro-3-phenyl-4-[(trifluoromethyl)thio]-1*H*-isochromen-1-one (3m): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (dd, J = 8.7, 5.6 Hz, 1 H), 7.84 (dd, J = 9.9, 2.2 Hz, 1 H), 7.71–7.65 (m, 2 H), 7.55–7.46 (m, 3 H), 7.31 (ddd, J = 8.7, 8.0, 2.4 Hz, 1 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –42.4, –99.6 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3 (d, J = 257.6 Hz), 165.0, 159.6, 141.2 (d, J = 10.4 Hz), 133.3 (d, J = 10.3 Hz), 131.9 (d, J = 17.6 Hz), 130.8, 129.8, 128.8 (q, $J_{C,F}$ = 311.0 Hz), 128.7, 117.5 (d, J = 23.4 Hz), 116.8, 112.0 (d, J = 25.3 Hz) ppm. HRMS calcd. for $C_{16}H_9F_4O_2S$ $[M + H]^+$ 341.0254; found 341.0246.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds **3**.

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