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Synthesis of Isochromenes

Facile Synthesis of 4-(Trifluoromethyl)-1*H*-isochromenes from Alkynols

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Abstract: Isochromene derivatives are important structural motifs found in various biologically active compounds as well as important natural products. A method to generate CF_3-containing isochromene derivatives has been developed, which gives moderate to good yields by using Togni's reagent as the trifluoromethyl source. The key step involves alkynol cyclization and subsequent trapping by a reactive electrophilic trifluoromethyl species generated in situ from Togni's reagent.

Introduction

Oxygen-containing heterocycles are ubiquitous in drugs, natural products, and other compounds of tremendous importance.[1] For example, isochromenes and related cyclic ether structures are ubiquitous structural motifs found in various biologically active compounds as well as important natural products.[2] Numerous efforts have been made to develop methods to prepare isochromene and related cyclic ether structures,[3] but available approaches suffer from low yield or require complex starting materials.

A potentially simpler alternative for generating enol ethers and diverse oxygen-containing heterocycles is inter- or intramolecular addition of an O-H nucleophile to alkynes activated by a cationic fragment via the common π-activation mode.[4,5] This is considered a part of hydrofunctionalization.[4] Metal-catalyzed alkynol cyclization offers a reliable and atom-economic method of obtaining highly functionalized, oxygen-containing heterocycles,[6] but this cyclization approach often leads to protonation products without further derivatization.[7]

Since incorporating a trifluoromethyl group into a potentially useful organic molecule can dramatically enhance its chemical and physical properties, numerous efforts have been invested in developing facile and efficient syntheses of CF_3-containing organic compounds.[8,9] Many electrophilic or nucleophilic trifluoromethyl reagents and trifluoromethanesulfinate salts act as efficient CF_3 sources.[10] $TMSCF_3$ or Togni's reagent can introduce CF_3 onto various carbocycles and heterocycles.[11]

To the best of our knowledge, incorporation of the CF_3 group into isochromene and related cyclic ether structures has not been reported. Besides, there are only a few reports on construction of compounds with olefinic trifluoromethyl groups,[12] which are useful in synthetic applications. Therefore we aimed to develop a facile and efficient synthetic strategy to furnish CF_3-substituted isochromene derivatives. Based on our previous successes in identifying synthetic applications of alkynols[13] and construction of heterocycles ,[14] here we report the cyclization of alkynols and their subsequent trapping by an active electrophilic trifluoromethyl species generated in situ from Togni's reagent. This process provides a facile route to CF_3-substituted isochromene derivatives.

Results and Discussion

Initially we focused on screening parameters to optimize reaction conditions. We commenced our study by mixing the internal alkynol **1a**, $[PdCl_2(PPh_3)_2]$, and $ZnCl_2$ in toluene (Table 1). The reaction mixture was then stirred at 40 °C, and the reaction was monitored by thin layer chromatography (TLC). Once the starting alkynol **1a** was consumed, Togni's reagent and CuI were added directly under Ar, and the mixture was stirred for another 0.5 h at 40 °C. The desired product **2a** was not obtained when toluene, DMSO, or *N*,*N*-dimethylacetamide (DMA) served as the solvent. Traces of **2a** were obtained by extending the reaction time and using EtOH as the solvent. The desired product **2a** was formed in 72% isolated yield using $CHCl_3$ as solvent, which encouraged us to screen other solvents (entries 1–6). The reaction in DCM was found to give the best yield of all other solvents (entry 7).

Screening copper salts showed that the reaction with CuI gave the best yield, although the yield did not vary substantially among the salts tested (entry 7 vs 8–12). Increasing the ratio of internal alkynol **1a** to Togni's reagent from 1:1.2 to 1:1.5 and then to 1:2 increased the yield to 87% (entry 7 vs 13–14). The reactions were then carried out in the presence of 0, 5, and 10 mol% of CuI, respectively, giving the desired product in 36%, 51%, and 57% isolated yields (entries 15–17).

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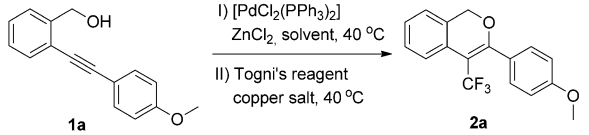
Table 1. Investigation of reaction conditions.[a]



1a 2a

Entry	Solvent	Copper salt/mol%	*t* [h]	Yield [%][b]
1	toluene	CuI/20	6	NR
2	DMSO	CuI/20	6	NR
3	DMA	CuI/20	6	NR
4	EtOH	CuI/20	12	<5
5	$CHCl_3$	CuI/20	6	72
6	1,2-DCE	CuI/20	6	73
7	DCM	CuI/20	6	79
8	DCM	CuBr/20	6	66
9	DCM	CuCN/20	6	69
10	DCM	$Cu(ClO_4)_2{\cdot}6H_2O$/20	6	52
11	DCM	$Cu(OTf)_2$/20	6	58
12	DCM	$Cu(OAc)_2$/20	6	63
13[c]	DCM	CuI/20	6	57
14[d]	**DCM**	**CuI/20**	**6**	**87**
15[d]	DCM	none	6	36
16[d]	DCM	CuI/5	6	51
17[d]	DCM	CuI/10	6	57
18[e]	DCM	CuI/20	6	26
19[f]	DCM	CuI/20	6	0

[a] Unless indicated otherwise, reactions were carried out under Ar for 6 h in sealed tubes containing **1a** (0.3 mmol), $[PdCl_2(PPh_3)_2]$ (0.015 mmol), $ZnCl_2$ (0.12 mmol), and solvent (2 mL) at 40 °C. Togni's reagent (0.6 mmol) and CuI (0.06 mmol) were added directly under Ar and stirred for another 0.5 h at 40 °C. [b] Isolated yield. [c] Ratio of internal alkynol **1a** to Togni's reagent = 1:1.2. [d] Ratio of internal alkynol **1a** to Togni's reagent = 1:2. [e] Without $[PdCl_2(PPh_3)_2]$. [f] Without $ZnCl_2$. DCE = 1,2-dichloroethane; DCM = dichloromethane; NR = no reaction.

Lastly, control experiments were carried out, finding that the alkynol cyclization gave only 26% isolated yield in the absence of $[PdCl_2(PPh_3)_2]$, and the reaction did not proceed without $ZnCl_2$ (entries 18 and 19). The results confirmed the critical roles both of $[PdCl_2(PPh_3)_2]$ and $ZnCl_2$ in the reaction. It is noteworthy that the desired product was not obtained if the reaction process was integrated into one step.

After optimizing the conditions for generating CF_3-bearing isochromene and related cyclic ether structures, we explored the generality of the reaction. This approach tolerated a wide range of alkynols bearing either an electron-withdrawing or electron-donating substituent, furnishing the desired compound in moderate to good yields (Figure 1). Internal alkynols **1** containing electron-donating groups, such as Me and MeO at positions R^2, R^3, or R^4 were converted into the corresponding products in moderate to good yields under the developed reaction conditions (**2b–d**, **2m**, and **2n**). The molecular structure of **2b** in the solid state was unambiguously confirmed by single crystal X-ray crystallographic analysis (Figure 2).[15] Our strategy was also able to generate products bearing Cl (**2i** and **2j**), which may undergo subsequent coupling reactions.[16] Internal alkynols **1** bearing F or CF_3 groups at positions R^1, R^2, R^3, or R^4 reacted smoothly to give the desired products (**2e–2h**, **2k**, and **2l**).

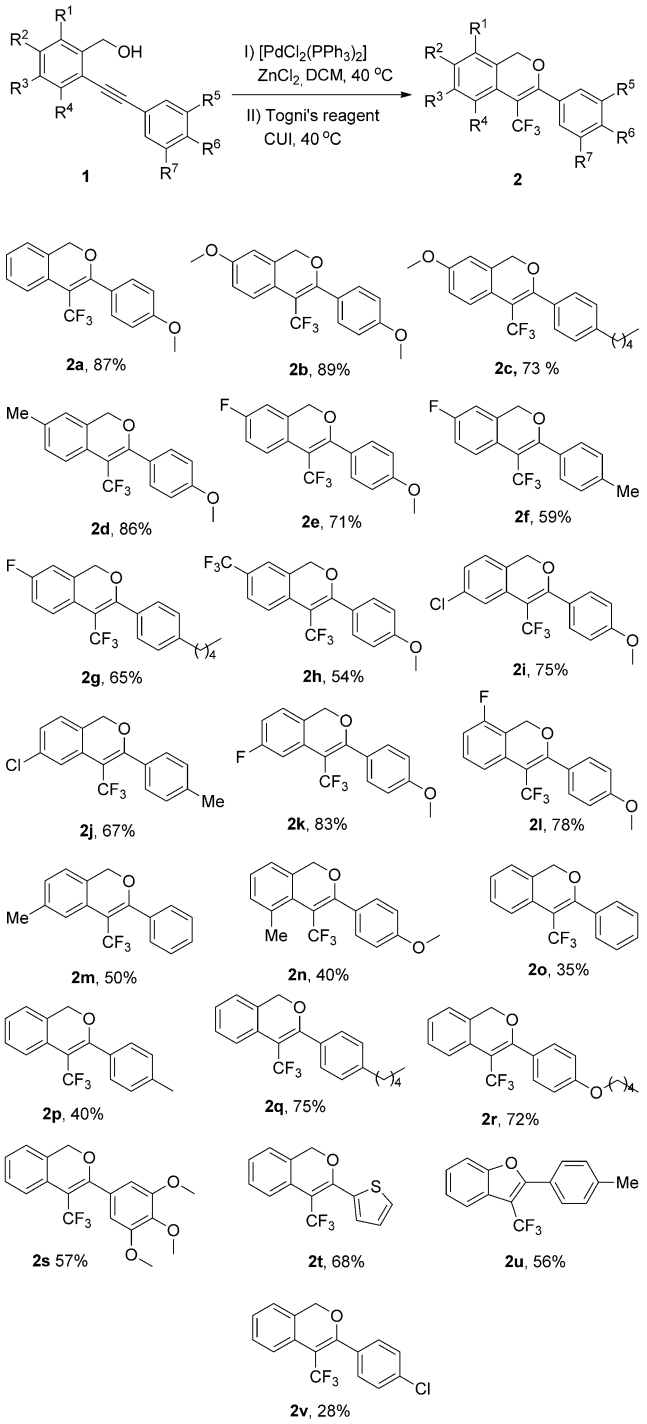


Figure 1. Exploration of substrate scope. Reaction conditions: Internal alkynol **1** (0.3 mmol), $[PdCl_2(PPh_3)_2]$ (0.015 mmol), $ZnCl_2$ (0.12 mmol), and DCM (2 mL) were added to a sealed tube under Ar. The reaction mixture was stirred at 40 °C and monitored by TLC. Once the starting alkynol **1** was consumed, Togni's reagent (0.6 mmol) and CuI (0.06 mmol) were added directly under Ar, and the mixture was stirred a further 0.5 h at 40 °C. Isolated yields are shown.

The reactions of internal alkynols **1** bearing hydrogen or electron-donating groups at positions R^5, R^6, or R^7 proceeded smoothly (**2c**, **2f**, **2g**, **2j**, and **2o–2s**), whereas the reactions of alkynols **1** carrying electron-withdrawing chloride at the posi-

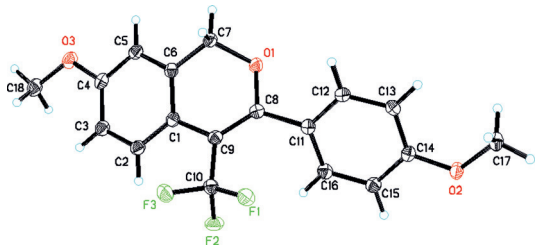
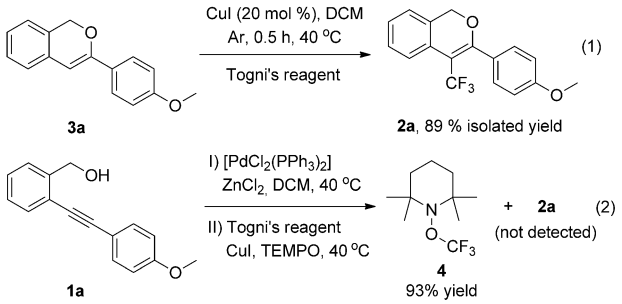


Figure 2. X-ray crystal structure of **2b**.

tion R^6 generated the corresponding product **2v** in a lower 28% yield. Encouraged by these results, we proceeded to generate the desired product **2t** from an alkynol substituted with a heterocyclic thiophenyl group. However, the reactions of alkynols bearing an aliphatic substituent, such as hexyl or 1-cyclohexene, did not afford the desired products. In contrast, the reaction was able to generate the benzofuran derivative **2u** in 56% yield.

We carried out some experiments to elucidate the reaction mechanism. Treating 3-(4-methoxyphenyl)-1*H*-isochromene (**3a**) with Togni's reagent and CuI in DCM at 40 °C under Ar furnished the CF_3-group-containing product **2a** in 89% isolated yield (Scheme 1, Eq. (1)). This result suggests that **3a** is involved in the reaction. When the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction under the developed conditions, the desired product **2a** did not form, and the CF_3 radical-trapping product **4** was detected in 93% yield (Scheme 1, Eq. (2)). These results suggest that the reaction may involve a CF_3 radical intermediate.

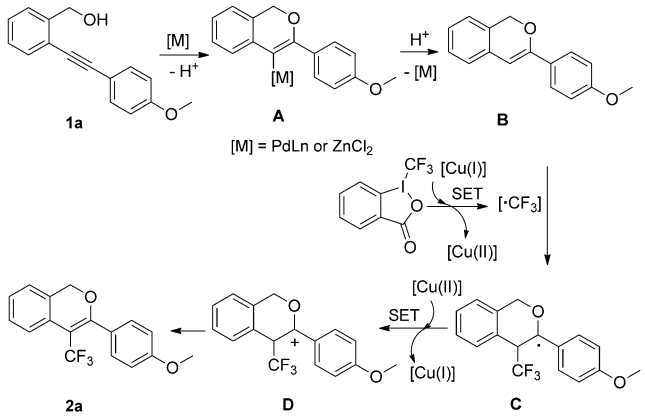


Scheme 1. Investigation of the reaction mechanism.

We propose a plausible mechanism based on these experimental results and the literature (Scheme 2).[7,16] The Lewis acid $[PdCl_2(PPh_3)_2]$ and $ZnCl_2$ coordinates to the triple bond and activates it to produce intermediate **A**, which is protonated to give enol ether intermediate **B**. This intermediate reacts with the trifluoromethyl radical generated in situ from Togni's reagent in the presence of CuI to form intermediate **C**. This then undergoes single electron transfer (SET)[17] followed by deprotonation to generate the product **2a**.

Conclusions

In conclusion, we have demonstrated alkynol cyclization followed by trapping by a reactive electrophilic trifluoromethyl species generated in situ from Togni's reagent, affording CF_3-substituted isochromene derivatives. The reaction occurs in a short time under mild conditions and moderate to good yields are obtained. As an example of incorporation CF_3 group into the isochromene, this protocol may demonstrate great value in future synthetic applications in fine chemical preparation and drug development.



Scheme 2. Plausible reaction mechanism to form **2a** from **1a**.

Experimental Section

Typical Experimental Procedure for Product 2a

To a sealed tube were added internal alkynol **1** (0.3 mmol), $[PdCl_2(PPh_3)_2]$ (0.015 mmol), $ZnCl_2$ (0.12 mmol), and DCM (2 mL) under an Ar atmosphere. The reaction mixture was stirred at 40 °C and the reaction was monitored by TLC. Once the starting alkynol **1** was consumed, Togni's reagent (0.6 mmol) and CuI (0.06 mmol) were added directly under an Ar atmosphere and stirred for another 0.5 h at 40 °C. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel to afford the desired product **2a**.

3-(4-Methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2a). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (87%), m.p. 54.6–56.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, J = 8.72 Hz, 2H), 7.44 (d, J = 7.92 Hz, 1H), 7.35–7.39 (m, 1H), 7.25–7.30 (m, 1H), 7.15 (d, J = 7.40, 1H), 6.92 (d, J = 8.84, 2H), 5.13 (s, 2H), 3.84 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.26 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.5, 159.7, 131.7, 131.6, 128.8, 128.4, 127.3, 126.8, 125.7, 125.0 (q, J = 269.3 Hz), 124.1, 122.3, 122.2, 113.3, 69.7, 55.2 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{17}H_{13}O_2F_3$ $[M]^+$: 306.0868; found: 306.0869.

7-Methoxy-3-(4-methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2b). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (89%), m.p. 75.5–78.2 °C;^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 7.52 (d, J = 8.72 Hz, 2H), 7.36 (dd, J_1 = 2.00 Hz, J_2 = 8.68 Hz, 1H), 6.90–6.93 (m, 3H), 6.70 (d, J = 2.56 Hz, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 3.83 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.49 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.4, 158.9, 131.7, 131.6, 129.3, 126.0, 125.1 (q, J = 269.4 Hz), 123.8, 121.5, 113.7, 113.4, 110.0, 105.2,

69.7, 55.5, 55.3 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{15}O_3F_3$ $[M]^+$: 336.0973; found: 336.0975.

7-Methoxy-3-(4-pentylphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2c). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a colorless liquid (73%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, J = 8.04 Hz, 2H), 7.36 (dd, J_1 = 1.68 Hz, J_2 = 8.60 Hz, 1H), 7.21 (d, J = 8.04 Hz, 2H), 6.91 (dd, J_1 = 1.68 Hz, J_2 = 8.68 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 5.12 (s, 2H), 3.83 (s, 3H), 2.64 (t, J = 7.64 Hz, 2H), 1.63 (m, 2H), 1.34 (m, 4H), 0.89 ppm (t, J = 6.92 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.52 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.9, 158.2, 145.7, 131.0, 129.9, 129.3, 128.0, 125.0 (q, J = 269.4 Hz), 123.9, 121.3, 113.7, 110.0, 69.7, 55.5, 35.9, 31.5, 30.9, 22.5, 14.0 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{15}O_2F_3$ $[M]^+$: 376.1850; found: 376.1651.

3-(4-Methoxyphenyl)-7-methyl-4-(trifluoromethyl)-1*H*-isochromene (2d). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (86%), m.p. 89.5–90.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.53 (d, J = 8.64 Hz, 2H), 7.33 (d, J = 7.96 Hz, 2H), 7.18 (d, J = 8.04 Hz, 2H), 7.97 (s, 1H), 6.92 (d, J = 8.72 Hz, 2H), 5.10 (s, 2H), 3.85 (s, 3H), 2.37 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.38 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.5, 159.1, 159.0, 137.0, 131.7, 129.1, 127.6, 126.1, 126.0, 125.1 (q, J = 269.3 Hz), 124.8, 123.8, 122.4, 122.3, 113.4, 69.8, 55.3, 21.1 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{15}O_2F_3$ $[M]^+$: 320.1024; found: 320.1025.

7-Fluoro-3-(4-methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2e). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (71%), m.p. 88.8–90.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.53 (d, J = 8.72 Hz, 2H), 7.37–7.41 (m, 1H), 7.04–7.10 (m,1H), 6.93 (d, J = 8.88 Hz, 2H), 6.89 (dd, J_1 = 2.56 Hz, J_2 = 8.20 Hz, 1H), 5.11 (s, 2H), 3.86 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.55 (CF_3), −114.74 ppm (F);^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.8 (d, J = 245.6 Hz), 161.7, 159.3, 131.8, 131.7, 129.6 (d, J = 7.38 Hz), 126.3, 125.5, 125.0 (q, J = 269.4 Hz), 124.2, 124.1, 123.6, 115.3 (d, J = 21.6 Hz), 113.5, 111.4 (d, J = 22.6 Hz), 104.6 (d, J = 31.5 Hz), 69.2, 55.3 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{17}H_{12}O_2F_4$ $[M]^+$: 324.0773; found: 324.0774.

7-Fluoro-3-(p-tolyl)-4-(trifluoromethyl)-1*H*-isochromene (2f). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a colorless liquid (59%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, J = 7.56 Hz, 2H), 7.40 (s, 1H), 7.22 (d, J = 7.56 Hz, 2H), 7.07 (t, J = 8.64 Hz, 1H), 6.88 (d, J = 8.04 Hz, 1H), 5.12 (s, 2H), 2.40 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.59, −114.52 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.8 (d, J = 245.7 Hz), 159.6, 141.2, 130.4, 130.0, 129.9, 129.6 (d, J = 7.3 Hz), 128.8, 124.8 (q, J = 269.4 Hz), 124.3 (d, J = 2.0 Hz), 124.2 (d, J = 2.0 Hz), 123.5, 115.4 (d, J = 21.6 Hz), 111.5 (d, J = 22.5 Hz), 105.7, 105.2 (d, J = 31.7 Hz), 69.3 (d, J = 1.9 Hz), 21.5 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{15}O_2F_3$ $[M]^+$: 308.0824; found: 308.0826.

7-Fluoro-3-(4-pentylphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2g). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a colorless liquid (65%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.47 (d, J = 7.84 Hz, 2H), 7.40 (s, 1H), 7.23 (d, J = 7.88 Hz, 2H), 7.07 (t, J = 8.44 Hz, 1H), 6.89 (d, J = 8.04 Hz, 1H), 5.13 (s, 2H), 2.65 (t, J = 7.68 Hz, 2H), 1.64 (m, 2H), 1.33 (s, 4H), 0.89 ppm (t, J = 6.36 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.60, −114.55 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 163.0, 160.6, 159.7, 146.2, 130.6, 130.0, 129.6 (d, J = 7.3 Hz), 128.1, 124.8 (q, J = 269.4 Hz), 124.7, 124.3 (d, J = 5.9 Hz), 123.5, 115.5, 115.2, 111.4 (d, J = 22.5 Hz), 105.4, 105.1, 69.3 (d, J = 1.7 Hz), 35.9, 31.5, 30.9, 22.5, 14.0 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{15}O_2F_3$ $[M]^+$: 364.1450; found: 364.1451.

3-(4-Methoxyphenyl)-4,7-bis(trifluoromethyl)-1*H*-isochromene (2h). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) as a faint-yellow solid (54%), m.p. 87.2–89.0 °C; 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.63 (d, J = 8.08 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 9.2 Hz, 1H), 7.43 (s, 1), 6.94 (d, J = 8.84 Hz, 2H), 5.18 (s, 2H), 3.87 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.49 (CF_3), −62.41 ppm (CF_3), ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 162.1, 161.7, 132.5, 131.9, 131.8, 129.0, 128.7, 127.6, 125.6, 125.5, 125.4, 125.1, 124.8 (q, J = 269.3 Hz), 122.7, 122.6, 121.2, 121.1, 113.5, 104.5 (d, J = 32.1 Hz), 69.4, 55.4 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{18}H_{12}O_2F_6$ $[M]^+$: 374.0741; found: 374.0742.

6-Chloro-3-(4-methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2i). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (75%), m.p. 67.3–69.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, J = 8.78 Hz, 2H), 7.41 (s, 1H), 7.25 (dd, J_1 = 1.92 Hz, J_2 = 4.96 Hz, 1H), 7.09 (d, J = 8.04 Hz, 1H), 6.93 (d, J = 8.88 Hz, 2H), 5.10 (s, 2H), 3.85 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.45 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.9, 160.8, 134.5, 131.9, 131.8, 130.6, 126.8, 125.6, 125.4, 125.3, 124.8 (q, J = 269.3), 122.6, 122.5, 113.5, 69.3, 55.4 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{17}H_{12}O_2F_3Cl$ $[M]^+$: 340.0478; found: 340.0475.

6-Chloro-3-(p-tolyl)-4-(trifluoromethyl)-1*H*-isochromene (2j). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (67%), m.p. 67.5–69.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.47 (d, J = 8.12 Hz, 2H), 7.42 (t, J = 1.76 Hz, 1H), 7.22–7.27 (m, 3H), 7.09 (d, J = 8.04 Hz, 1H), 5.12 (s, 2H), 2.41 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.51 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.3, 141.5, 134.5, 130.4, 130.3, 130.0, 128.9, 128.8, 127.0, 126.0, 125.5, 125.4, 124.6 (q, J = 269.3 Hz), 122.6, 122.5, 105.2, 104.8, 69.4, 21.6 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{17}H_{12}O_2F_3Cl$ $[M]^+$: 324.0529; found: 324.0530.

6-Fluoro-3-(4-methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2k). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) as a white solid (83%), m.p. 70.4–72.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, J = 8.72 Hz 2H), 7.08–7.15 (m, 2H), 6.97 (dd, J_1 = 2.36 Hz, J_2 = 8.40 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 3.84 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.60 (CF_3), −112.92 ppm (F); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 162.9 (d, J = 243.2 Hz), 161.9, 160.8 (d, J = 3.5 Hz), 131.9, 131.8, 130.9 (d, J = 8.8 Hz), 125.6, 125.5, 125.4, 124.8 (q, J = 269.3 Hz), 123.0, 122.9, 113.7, 113.6, 113.5, 109.9 (d, J = 1.7 Hz), 109.7 (d, J = 1.7 Hz), 104.6 (d, J = 32.0 Hz), 69.4, 55.4 ppm; HRMS (EI, TOF): *m/z*: calcd for $C_{17}H_{12}O_2F_4$ $[M]^+$: 324.0773; found: 324.0775.

8-Fluoro-3-(4-methoxyphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2l). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a faint-yellow oily liquid (78%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, J =

8.76 Hz, 2H), 7.30–7.35 (m, 1H), 7.20–7.22 (m, 1H), 7.00 (t, J= 8.48 Hz, 1H), 6.91–6.95 (m, 2H), 5.24 (s, 2H), 3.85 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.45 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.8, 160.6, 157.4 (d, J = 243.7 Hz), 131.8, 131.7, 131.1, 131.0, 129.5 (d, J = 8.3 Hz), 125.5, 124.8 (q, J = 269.1 Hz), 118.2, 114.5 (d, J = 17.9 Hz), 113.7 (d, J = 20.7 Hz), 113.5, 63.2 (d, J = 3.6 Hz), 55.4 ppm; HRMS (EI, TOF): m/z: calcd for $C_{17}H_{12}O_2F_4$ $[M]^+$: 324.0775; found: 324.0773.

6-Methyl-3-phenyl-4-(trifluoromethyl)-1*H*-isochromene (2m). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) as a white solid (50%), m.p. 94.1–95.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.57 (d, J = 6.92 Hz, 2H), 7.39–7.49 (m, 3H), 7.11 (d, J = 7.60 Hz, 1H), 7.25 (s, 1H), 7.05 (d, J = 7.60 Hz, 1H), 5.14 (s, 2H), 2.40 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.20 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 160.0, 138.4, 133.8, 130.6, 130.1, 130.0, 128.3, 128.0, 127.9, 124.9 (q, J = 269.6 Hz), 124.6, 124.1, 123.1, 69.8, 21.6 ppm; HRMS (EI, TOF): m/z: calcd for $C_{17}H_{13}OF_3$ $[M]^+$: 290.0918; found: 290.0919.

3-(4-Methoxyphenyl)-5-methyl-4-(trifluoromethyl)-1*H*-isochromene (2n). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a faint-yellow solid (40%), m.p. 106.9–108.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.67 (d, J = 8.84 Hz, 2H), 7.17–7.23 (m, 2H), 7.03 (d, J = 6.72 Hz, 1H), 6.95 (d, J = 8.88 Hz, 2H), 5.04 (s, 2H), 3.87 (s, 3H), 2.52 ppm (d, J = 1.28 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −47.73 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 164.1, 162.0, 133.3, 132.3, 132.0, 131.4, 128.8, 126.8, 126.0, 125.4 (q, J = 269.4 Hz), 120.0, 113.6, 71.6, 55.4, 21.6 ppm; HRMS (EI, TOF): m/z: calcd for $C_{18}H_{15}O_2F_3$ $[M]^+$: 320.1024; found: 320.1026.

3-Phenyl-4-(trifluoromethyl)-1*H*-isochromene (2o). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a faint-yellow oily liquid (35%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.58 (d, J = 6.96 Hz, 2H), 7.37–7.50 (m, 5H), 7.28–7.32 (m, 1H), 7.17 (d, J = 7.36 Hz, 1H), 5.18 ppm (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.40 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 133.6, 130.7, 130.0, 128.6, 128.4, 128.0, 127.3, 127.2, 124.8 (q, J = 269.1 Hz), 124.2, 122.5, 69.9 ppm; HRMS (EI, TOF): m/z: calcd for $C_{16}H_{11}OF_3$ $[M]^+$: 276.0762; found: 276.0764.

3-(*p*-Tolyl)-4-(trifluoromethyl)-1*H*-isochromene (2p). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (40%), m.p. 54.6–56.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.48 (d, J = 8.08 Hz, 2H), 7.44 (s, 1H), 7.35–7.40 (m, 1H), 7.25–7.31 (m, 1H), 7.22 (d, J = 7.92 Hz, 2H), 7.16 (d, J = 7.36 Hz, 1H), 5.15 (s, 2H), 2.40 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.35 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 141.1, 130.7, 130.0, 128.8, 128.7,128.5, 127.4, 127.1, 125.0 (q, J = 269.2 Hz), 124.2, 122.4, 69.8, 21.5 ppm; HRMS (EI, TOF): m/z: calcd for $C_{17}H_{13}OF_3$ $[M]^+$: 290.0918; found: 290.0919.

3-(4-Pentylphenyl)-4-(trifluoromethyl)-1*H*-isochromene (2q). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a colorless liquid (75%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.49 (d, J = 8.08 Hz, 2H), 7.45 (d, J = 7.88 Hz, 1H), 7.38 (dt, J_1 = 1.12 Hz, J_2 = 7.6 Hz, 1H), 7.28 (dt, J_1 = 1.04 Hz, J_2 = 7.44 Hz, 1H), 7.22 (d, J = 8.20 Hz, 2H), 7.16 (d, J = 7.44 Hz, 1H), 5.15 (s, 2H), 2.65 (t, J = 7.60 Hz, 2H), 1.60–1.67 (m, 2H), 1.30–1.37 (m, 4H), 0.89 ppm (t, J = 6.88 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.34 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 160.2, 146.1, 130.9, 130.7, 130.1, 130.0, 129.7, 128.7, 128.5, 128.1, 128.0, 127.4, 127.1, 125.0 (q, J = 269.4 Hz), 124.2, 122.8, 122.5, 122.4, 101.6, 69.9, 35.9, 31.5, 30.9, 30.8, 22.5, 14.0 ppm; HRMS (EI, TOF): m/z: calcd for $C_{21}H_{21}OF_3$ $[M]^+$: 346.1545; found: 346.1544.

3-(4-(Pentyloxy)phenyl)-4-(trifluoromethyl)-1*H*-isochromene (2r). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a faint-yellow oily liquid (72%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.53 (d, J = 8.76 Hz, 2H), 7.44 (d, J = 7.92 Hz, 1H), 7.35–7.39 (m, 1H), 7.25–7.30 (m, 1H), 1.15 (d, J = 7.40 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.13 (s, 2H), 3.99 (t, J = 3.99 Hz, 2H), 1.77–1.84 (m, 2H), 1.34–1.49 (m, 4H), 3.94 ppm (t, J = 7.12, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.29 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 161.3, 160.0, 131.7, 129.0, 128.5, 127.4, 127.0, 125.5, 125.1 (q, J = 269.4 Hz), 124.1, 122.4, 113.9, 105.2, 104.9, 69.8, 68.1, 28.9, 28.2, 22.5, 14.0 ppm; HRMS (EI, TOF): m/z: calcd for $C_{21}H_{12}O_2F_3$ $[M]^+$: 362.1494; found: 362.1496.

4-(Trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-isochromene (2s). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a light-yellow solid (57%), m.p. 134.4–135.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, J = 7.84 Hz, 1H). 7.37–7.41 (m, 1H), 7.28- 7.33 (m, 1H), 7.18 (d, J = 7.44 Hz, 1H), 5.17 (s, 2H), 3.90 (s, 3H), 3.89 ppm (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.24 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 152.7, 140.3, 128.6, 127.3, 127.2, 125.0 (q, J = 269.4 Hz), 124.2, 122.4, 107.5, 70.0, 61.0, 56.2 ppm; HRMS (EI, TOF): m/z: calcd for $C_{19}H_{17}O_4F_3$ $[M]^+$: 366.1079; found: 366.1078.

3-(Thiophen-2-yl)-4-(trifluoromethyl)-1*H*-isochromene (2t). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a colorless liquid (68%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (dd, J_1 = 1.00 Hz, J_2 = 5.04 Hz, 1H), 7.52 (d, J = 3.76 Hz, 1H), 7.44 (d, J = 7.92 Hz, 1H), 7.36–7.40 (m, 1H), 7.27–7.31 (m, 1H), 7.17 (d, J = 7.00 Hz, 1H), 7.10 (dd, J_1 = 3.80 Hz, J_2 = 5.00 Hz, 1H), 5.11 ppm (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −54.13 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 153.1, 134.7, 131.5, 131.4, 128.7, 128.6, 127.8, 127.4, 127.2, 124.8 (q, J = 269.6 Hz), 124.3, 123.5, 122.8, 122.7, 69.8 ppm; HRMS (EI, TOF): m/z: calcd for $C_{14}H_9OF_3S$ $[M]^+$: 282.0326; found: 282.0327.

2-(*p*-Tolyl)-3-(trifluoromethyl)benzofuran (2u). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a white solid (56%), m.p. 148.0–149.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, J = 7.84 Hz, 1H), 7.72 (d, J = 8.12 Hz, 2H), 7.55 (d, J = 7.48 Hz, 1H), 7.34–7.40 (m, 2H), 7.31 (d, J = 7.96 Hz, 2H), 2.44 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −55.24 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 153.5, 140.7, 129.3, 128.6, 128.5, 126.0, 124.8 (q, J = 269.2 Hz), 124.0, 120.6, 111.4, 21.5 ppm; HRMS (EI, TOF): m/z: calcd for $C_{16}H_{11}OF_3$ $[M]^+$: 276.0762; found: 276.0763.

3-(4-Chlorophenyl)-4-(trifluoromethyl)-1*H*-isochromene (2v). The compound was prepared by following the typical procedure and obtained after column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) as a faint-yellow oily liquid (28%); 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.52 (d, J = 8.48 Hz, 2H), 7.37–7.45 (m, 4H), 7.29–7.33 (m, 1H), 7.17 (d, J = 7.36 Hz, 1H), 5.17 ppm (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −53.41 ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 136.9, 132.0, 131.4, 131.3, 128.7, 128.3, 128.2, 127.5, 127.3, 124.7 (q, J = 269.4 Hz), 124.2, 122.5, 69.9 ppm; HRMS (EI, TOF): m/z: calcd for $C_{16}H_{10}OF_3Cl$ $[M]^+$: 310.0372; found: 310.0371.

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