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A mild and fast continuous-flow trifluoromethylation of coumarins with the CF_3 radical derived from CF_3SO_2Na and TBHP†

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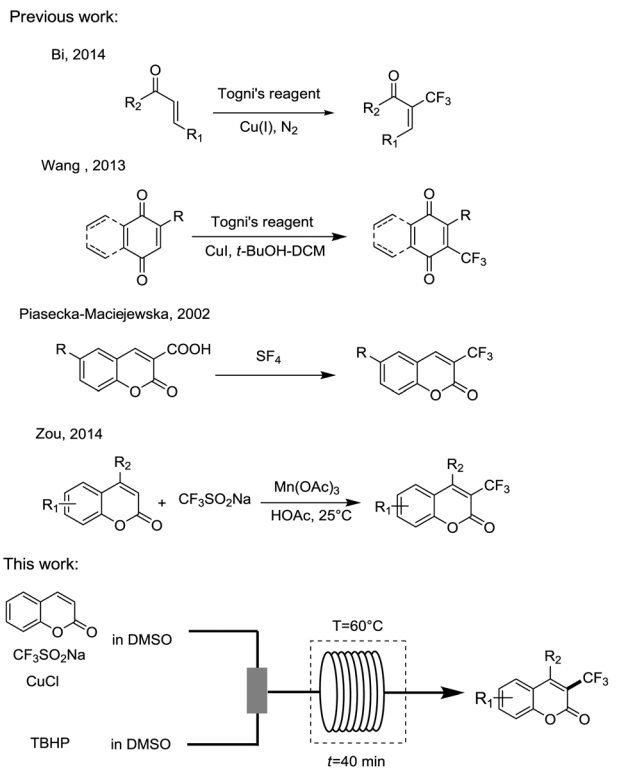
A mild and fast Cu(I)-catalyzed trifluoromethylation of coumarins with CF_3SO_2Na and TBHP in a continuous-flow reactor has been developed. This method is experimentally simple and carried out under mild conditions, affording the corresponding products in moderate to good yields, and showing wide substrate tolerance. The scale-up flow process results in an isolated yield of 68% and a productivity of 305 mg h^{-1} of 3-trifluoromethyl-7-diethylamino-4-methyl coumarin when the concentration was increased five-fold. Given these features and the widespread applications of coumarins, this method may find use from laboratory to manufacturing.

Introduction

Coumarin derivatives represent a vast family of compounds which are mostly extracted and isolated from traditional Chinese herbs.[1] They have emerged as promising and valuable natural products with significant and high biological activities,[2] such as anti-inflammatory,[3] anti-oxidant,[3b,4] and anti-coagulant activities.[5] Meanwhile, coumarin is also very suitable to act as fluorescent chromospheres, and has been widely utilized in photosensitive polymeric materials,[6] lasers,[7] and fluorescent probes for metal ions.[8]

The trifluoromethyl group is highly electron withdrawing, and its introduction can remarkably improve molecular properties.[9] Trifluoromethylation has recently been adopted as a tool for improving the desired molecular characteristics. The trifluoromethyl group is becoming an increasingly versatile component and common trait among the molecules found in pharmaceuticals, agrochemicals, dyes, polymers and organic

regioselective C–H α-trifluoromethylation of α,β-unsaturated carbonyl compounds, and this reaction allowed diverse substrates (Scheme 1). In 2013, Wang[14] developed a copper-catalytic trifluoromethylation of quinone. Coumarin compounds



Scheme 1 Synthesis of unsaturated α-trifluoromethyl ketones and 3-trifluoromethyl coumarins.

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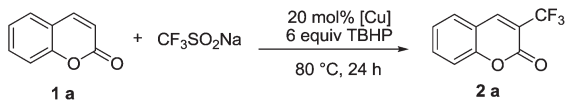
contain the α,β-unsaturated carbonyl subunit. Piasecka-Maciejewska[15] reported the preparation of 3-trifluoromethyl-coumarin with 3-carboxylic acid coumarin and sulfur tetrafluoride. In 2014, Zou[16] reported a straightforward method of $Mn(OAc)_3$ mediated trifluoromethylation by coumarins with CF_3SO_2Na.

Continuous flow reaction has attracted much attention of industry and academia for safety and sustainability.[17] Recent studies have demonstrated that economic savings can be realized in certain cases by transforming a batch reaction into a continuous process. Herein, we report a mild and fast method for Cu(I)-catalyzed trifluoromethylation of coumarins by using CF_3SO_2Na–TBHP partners in a continuous-flow system.

Results and discussion

Initially, trifluoromethylation of coumarin (**1a**) with CF_3SO_2Na was selected as the model to screen the reaction parameters in a batch (Table 1). Firstly, $CuCl_2$ as the catalyst gave 3-trifluoromethyl coumarin (**2a**) in 30% GC yield (entry 1). Next, when CuI, CuSCN or CuCl was used as the catalyst, the yield of the product increased to 38%, 45% and 65% respectively (entries 2–4). Screening copper catalysts revealed that CuCl could promote the yield in the case of DMSO as the solvent, and then several solvents were investigated. For the better dissolution of CF_3SO_2Na, a solvent mixture DMSO/H_2O was examined. However, the yield of **2a** dropped from 45% to 35% as the proportion of DMSO to water decreased from 2 : 1 to 1 : 1 (entries 5 and 6), the DCM and H_2O mixture also gave poor yield (13%, entry 7). Other solvents like MeOH, THF, DMF and acetone failed to lead to a better conversion as well (entries 8–12). With the CuCl catalyst and DMSO solvent, the yield of **2a** still remained at 65% while shortening the time to 6 h (entry 13). If the time is further shortened to 2 h, the yield would decrease to 52% (entry 14). When 2 equiv. of CF_3SO_2Na was applied, the trifluoromethylation reaction only gave 34% yield (entry 15). Finally, when carrying out this reaction at 120 °C, there is no beneficial effect on **2a** (59%, entry 16).

Table 1 Optimization of the reaction conditions in batch[a]



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Entry	Catalysis	Solvent	Time (h)	Yield[b] (%)
1	$CuCl_2$	DMSO	24	30
2	CuI	DMSO	24	38
3	CuSCN	DMSO	24	45
4	CuCl	DMSO	24	65
5	CuCl	DMSO : H_2O (2 : 1)	24	45
6	CuCl	DMSO : H_2O (1 : 1)	24	35
7	CuCl	DCM : H_2O (2 : 1)	24	13
8	CuCl	CH_3CN	24	53
9	CuCl	MeOH	24	10
10	CuCl	THF	24	21
11	CuCl	DMF	24	15
12	CuCl	Acetone	24	22
13	CuCl	DMSO	6	65
14	CuCl	DMSO	2	52
15[c]	CuCl	DMSO	6	34
16[d]	CuCl	DMSO	6	59

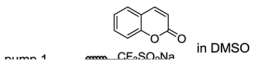
[a] Reaction conditions: coumarin (**1a**, 0.1 mmol), CF_3SO_2Na (0.4 mmol), Cu salt (0.02 mmol), TBHP 70% in water (0.6 mmol), solvent (1.5 mL) at 80 °C under air, reaction time (24 h). [b] Yields were determined by GC analysis using *n*-dodecane as an internal standard. [c] CF_3SO_2Na (0.2 mmol). [d] Temperature 120 °C.

With the optimized batch conditions in hand, a continuous-flow microreactor was assembled as described in Scheme 2(a). Initially, we investigated the amount of CF_3SO_2Na used in the reaction in a continuous-flow system, keeping the reaction time at 60 min at a flow rate of 66 μL min^{-1} (reactor volume 4 mL, reaction time 60 min). With 2 equiv. of CF_3SO_2Na, the yield of **2a** increased to 66%, further with 4 equiv. of CF_3SO_2Na, the yield of **2a** increased slightly to 70% (Scheme 2(b)). Therefore, 2 equiv. of CF_3SO_2Na were applied in the following experiments considering the cost of CF_3SO_2Na. However, in a batch process 4 equiv. of CF_3SO_2Na must be taken and reacted for 6 h to achieve 65% yield of **2a**. Subsequently, optimization of the amount of TBHP in this reaction showed that 4 equiv. of TBHP gave the highest yield in trifluoromethylation (Scheme 2(c)).

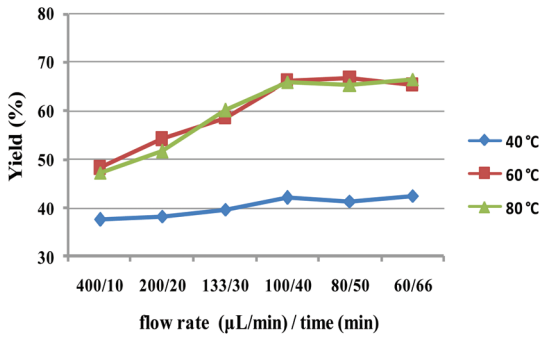
Due to the high surface-to-volume ratio of the microreactor, heat transfer and mass transfer take place rapidly.[18] Hence, we hoped to further optimize the flow rate (reaction time) and temperature in the continuous-flow reactor. The results showed that there were no big differences in **2a** yields (about 68%) when the reaction was carried out at 60 °C or at 80 °C. The yield decreased significantly when the temperature was decreased to 40 °C (Scheme 3). On the other hand, the yield of **2a** increased from 48% to 68% as the flow rate decreased from 400 to 100 μL min^{-1} (the reaction time ranged from 10 to 40 min) at either 60 °C or 80 °C. Further decreasing the flow rate to 80, even to 66 μL min^{-1}, the yield of **2a** remained around 68% (extending the reaction time to 50 or 60 min). Finally, we established the optimal reaction conditions: using 2 equiv. of CF_3SO_2Na, the trifluoromethylation of coumarin was performed at a flow rate of 100 μL min^{-1} at 60 °C for 40 min in a continuous-flow reactor.

With the optimized reaction conditions in hand, we next investigated the substrate scope of a series of substituted coumarins with a continuous-flow reactor. As shown in Table 2, both electron-rich and electron-deficient functional groups at coumarins could be tolerated. Alkyl-substituted coumarins provided the target products in moderate yields (56–66%, **2b**–**2d**), among these, *tert*-butyl coumarin (**2e**) was better than methyl-coumarins. Good yields could also be obtained with a 7-methoxyl substituted derivative, giving a relatively higher 63% yield (**2f**). In the case of a weak electron-withdrawing group acetoxyl or bromo at the 6-position, moderate yields of 59% and 55% were obtained respectively (**2g** and **2h**). However, the strong electron-withdrawing group nitro at the 6-position afforded a poor yield (39%, **2i**). Since 4-phenyl-coumarins as the family members of coumarin derivatives are

a

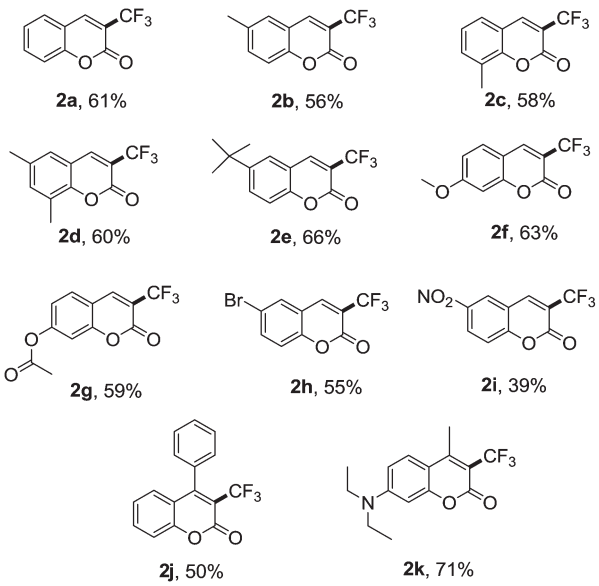


Scheme 2 Optimization of the amounts of CF_3SO_2Na and TBHP in a continuous-flow reactor. Reaction conditions: coumarin (0.1 mmol), CuCl (0.02 mmol), flow rate (66 μL min^{-1}, 60 min), yields were determined by GC analysis using *n*-dodecane as an internal standard. (a) Schematic diagram of trifluoromethylation of coumarin in a continuous-flow reactor. (b) The yield of **2a** *vs.* 0.1, 0.2, 0.3 and 0.4 mmol of CF_3SO_2Na, TBHP 70% in water (0.6 mmol); (c) the yield of **2a** *vs.* 0.1, 0.2, 0.4 and 0.8 mmol of TBHP 70% in water, CF_3SO_2Na (0.2 mmol).

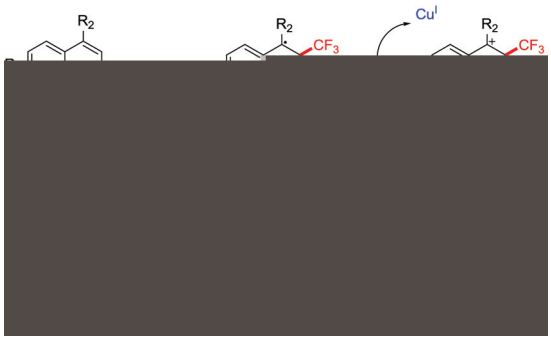


Scheme 3 Optimization of the flow rate (reaction time) and temperature in a continuous-flow reactor. Reaction conditions: coumarin (0.1 mmol), CuCl (0.02 mmol), CF_3SO_2Na (0.2 mmol), TBHP 70% in water (0.4 mmol), yields were determined by GC analysis using *n*-dodecane as an internal standard.

Table 2 Substrate scope of trifluoromethyl coumarin[a]



[a] Reaction conditions: coumarin (0.4 mmol), CF_3SO_2Na (0.8 mmol), CuCl (0.08 mmol) as the catalyst, TBHP 70% in water (1.6 mmol).

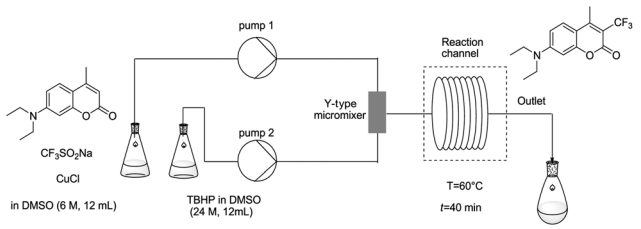


Scheme 4 Proposed mechanism for coumarin trifluoromethylation.

widely distributed in natural products and used in biological studies,[19] 3-trifluoromethyl-4-phenyl-coumarin **2j** was obtained in moderate yield of 50%. The 3-trifluoromethyl-7-diethylamino-4-methyl coumarin derivative afforded a higher yield of 71% (**2k**).

Based on our experiment and others' work,[11,13,14,20] a plausible mechanism (Scheme 4) for the synthesis of 3-trifluoromethyl-coumarin was proposed. Firstly, CF_3SO_2Na was reduced by Cu(I) to generate a CF_3 radical *via* a single-electron-transfer process, with oxidation of Cu(I) to Cu(II). Then the CF_3 radical attacked at the α-position of coumarin (**A**) so that the more stable free radical intermediate (**B**) was formed. Afterwards the electron at the C4-position of the carbocation intermediate (**B**) was oxidized by Cu(II), with reduction of Cu(II) to Cu(I). After that, the carbocation intermediate (**C**) was produced *via* another single-electron-transfer process. Finally 3-trifluoromethyl-coumarin (**D**) was obtained in a process of deprotonation.

In order to investigate the applicability of this trifluoromethyl reaction on the industrial scale beyond the laboratory scale, the developed gram-scale procedure was scaled-up (Scheme 5). The 7-diethylamino-4-methyl coumarin derivative is highly fluorescent, which makes this fluorophore attractive for use in biological studies, and the 7-diethylamino-4-methyl coumarin derivative has also been incorporated into ligands used for studies of γ-aminobutyric acid type A ($GABA_A$) receptors.[21] 7-Diethylamino-4-methyl coumarin (6 mmol, 1.386 g) was used in a scale-up experiment under the optimized



Scheme 5 Procedure for scale-up trifluoromethylation reaction of 7-diethylamino-4-methyl coumarin.

conditions at 100 μL min^{-1} flow rate in a continuous-flow system. The scale-up flow process was run continuously for 240 min to obtain 1.22 g of **2k** in 68% yield when the concentration was increased five-fold (0.5 M) compared to the optimization conditions (0.1 M). This corresponded to a product output of 305 mg h^{-1}.

Conclusion

In conclusion, we have developed a fast and mild conversion of coumarin to 3-trifluoromethyl-coumarin in a continuous flow reactor, using a smaller amount of the trifluoromethylation reagent and taking a shorter reaction time than the batch reaction. The reactions are easy to set up at 60 °C under air, using CuCl as the catalyst and a stable and inexpensive CF_3SO_2Na as the trifluoromethyl reagent. This reaction proceeds well for a wide range of substituent coumarins. The scale-up reaction results in a productivity of 305 mg h^{-1} of 3-trifluoromethyl-7-diethylamino-4-methyl coumarin with an isolated yield of 68%. Given these features and the widespread applications of coumarins, this method may find use in laboratory to manufacturing.

Experiment

General information

All reagents unless otherwise noted were obtained from commercial sources and used without further purification. DMSO (98.0%) and CF_3SO_2Na (>95.0%) were used without any purification. All these reactions were monitored by TLC with silica gel GF_{254} precoated plates. The products were isolated by column chromatography on silica gel (200–300 mesh size). ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on INOVA 400 or 500 instruments with operating frequencies of 400 or 500, 100 or 126 and 377 or 470 MHz, respectively. Chemical shifts for ^1H NMR were reported in ppm relative to TMS. All ^{13}C NMR spectra were reported in ppm relative to deuterated chloroform (77.00 ppm). The following abbreviations are used to set multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, and m = multiplet. Coupling constants (*J*) were reported in Hertz (Hz). Gas chromatography analyses were performed with an FID detector. GC-MS data were also recorded. High-resolution mass spectrometry data were recorded on a high-resolution mass spectrometer in the ESI mode.

Procedure for the synthesis of 3-trifluoromethyl-coumarin in batch

A flame-dried reaction vessel with a magnetic stirring bar was charged with coumarin (0.1 mmol, 14.6 mg), CF_3SO_2Na (0.4 mmol, 62.4 mg), CuCl (0.02 mmol, 2 mg), and DMSO (1.5 mL) in sequence. An aqueous solution of TBHP (70% solution in water, 0.6 mmol, 82 μL) was added dropwise into the reaction mixture with stirring at room temperature. The mixture was stirred at 80 °C under air for 24 h. The reaction mixture was cooled to ambient temperature and poured into deionized water. The resulting mixture was extracted with ethyl acetate, analyzed by GC using *n*-dodecane as an internal standard for yields.

Procedure for the synthesis of 3-trifluoromethyl-coumarin in the continuous-flow reactor

General optimized reaction condition procedure. A solution **1** of coumarin (0.1 mmol), CF_3SO_2Na, and CuCl (0.02 mmol) in DMSO (1.0 mL) was injected into the 1 mL PTFE-FEP sample loop 1. The other 1 mL sample loop 2 was loaded with a solution **2** of TBHP (70% in water) in 1 mL DMSO. The valves of the both loops were set to load and the reagents pumped through the system using DMSO as a system solvent at a given same flow rate. The reagents were combined in a Y-type mixer before entering a 4 mL convection flow coil (CFC) reactor (1/32 inner diameter), which was maintained at a given temperature. The product stream exiting the reactor was collected in a test tube, diluted with deionized water, extracted with ethyl acetate, and analyzed by GC using *n*-dodecane as an internal standard.

General substituted-coumarin reaction procedure. A solution **1** of substituted coumarins (0.4 mmol), CF_3SO_2Na (0.8 mmol, 124.8 mg), and CuCl (0.08 mmol, 8 mg) in DMSO (4 mL) was injected into one of the 1 mL PTFE-FEP sample loop 1. The other 1 mL sample loop 2 was loaded with a solution **2** of TBHP (70% in water, 1.6 mmol, 218 μL) in 4 mL DMSO. The solutions **1** and **2** in both needles were separately injected into the sample loops 1 and 2 four times, with 1 mL each time (when the previous 1 mL of solution flowed into the reactor, the following 1 mL of solution was immediately injected into the sample loop). The valves of the both loops were then set to load and the reagents pumped through the system using DMSO as a system solvent at the same flow rate of 50 μL min^{-1} (the residence time = 40 min). The reagents were combined in a Y-type mixer before entering a 4 mL convection flow coil (CFC) reactor (1/32 inner diameter), which was maintained at 60 °C (residence time = 40 min). The product stream exiting the reactor was collected in a test tube, diluted with deionized water, and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried with Na_2SO_4 and then concentrated under vacuum. After evaporation, the residue was purified by column chromatography on silica gel

(200–300 mesh size) using petroleum ether/EtOAc as the eluent to give the product.

Procedure for scale-up trifluoromethylation reaction of 7-diethylamino-4-methyl coumarin. A test tube was filled with 12 mL of DMSO, in which 7-diethylamino-4-methyl coumarin (6 mmol, 1.386 g), CF_3SO_2Na (12 mmol, 1.872 g), CuCl (0.6 mmol, 60 mg) were dissolved. Another test tube was filled with 12 mL of DMSO containing TBHP (24 mmol, 3.27 mL). The concentrations of 7-diethylamino-4-methyl coumarin and reagents in DMSO were both increased five-fold (0.5 M) compared to the optimization conditions (0.1 M). The reagent solutions were separately pumped into PTFE-FEP tubes (1/32 inner diameter) using two pumps (Syrris Ltd) at a flow rate of 50 μL min^{-1}. The two solution streams flowed and mixed into a Y-type mixer, and then immediately entered a 4 mL convection flow coil (CFC) reactor (1/32 inner diameter) at a flow rate of 100 μL min^{-1}., which was maintained at 60 °C (residence time = 40 min). The flow process was run continuously for 240 min. The product stream exiting the reactor was collected in a test tube, diluted with deionized water, and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried with Na_2SO_4 and then concentrated under vacuum. After evaporation, the residue was purified by column chromatography on silica gel (200–300 mesh size) using petroleum ether/EtOAc as the eluent to give 1.22 g of the product. This flow process gave a product output of 305 mg h^{-1}.

3-(Trifluoromethyl)-2H-1-benzopyran-2-one ***(2a)***.[16,22] White powder (52.2 mg, 61%); mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.89 (s), 154.59 (s), 143.33 (q, J = 4.6 Hz), 134.43 (s), 129.46 (s), 125.31 (s), 121.31 (q, J = 271.1 Hz), 117.67 (q, J = 33.0 Hz), 116.98 (s), 116.74 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.19(s, 3F); GC-MS (EI, m/z): 214(M^+, 100), 186(57), 136(52), 63(34).

6-Methyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2b)***.[16] White powder (51.0 mg, 56%); mp 122–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.28 (d, J = 8.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.19 (s), 151.73 (s), 142.38 (q, J = 4.8 Hz), 134.56 (s), 134.24 (s), 128.14 (s), 120.42 (q, J = 271.9 Hz), 116.38 (q, J = 33.3 Hz), 115.65 (s), 115.48 (s), 19.67 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.13 (s, 3F); GC–MS (EI, m/z): 228(M^+, 100), 200(48), 199(43), 131(43).

8-Methyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2c)***.[16] White powder (52.9 mg, 58%), mp 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.06 (s), 153.02 (s), 143.64 (q, J = 4.9 Hz), 135.68 (s), 127.12 (s), 126.70 (s), 124.81 (s), 121.44 (q, J = 271.9 Hz), 117.33 (q, J = 33.3 Hz), 116.55 (s), 15.36 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.10 (s, 3F). GC-MS (EI, m/z): 228(M^+, 100), 200(54), 199(52), 131(95).

6,8-Dimethyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2d)***. White powder (57.4 mg, 60%); mp 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.34 (s, 1H), 7.22 (s, 1H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.26 (s), 151.24 (s), 143.56 (q, J = 4.8 Hz), 136.90 (s), 134.60 (s), 126.77 (s), 126.30 (s), 121.55 (q, J = 271.8 Hz), 117.19 (q, J = 32.8 Hz), 116.37 (s), 20.59 (s), 15.23 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.20 (s, 3F); HRMS (ESI) m/z: [M + Na]$^+$ Calcd For $C_{12}H_9F_3O_2Na$ 265.0452; found 265.0456.

6-tert-Butyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2e)***. White powder (71.2 mg, 66%); mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.66 (dd, J = 8.8, 2.2 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.26 (s), 152.63 (s), 148.57 (s), 143.84 (q, J = 4.5 Hz), 132.25 (s), 125.67 (s), 121.53 (q, J = 271.3 Hz), 117.25 (q, J = 32.9 Hz), 116.51 (s), 116.20 (s), 34.61 (s), 31.18 (s); ^{19}F NMR (377 MHz, $CDCl_3$) δ −66.56 (s, 3F); HRMS (ESI) m/z: [M + Na]$^+$ Calcd For $C_{14}H_{13}F_3O_2Na$ 293.0765; found 293.0759.

7-Methoxyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2f)***.[16] White powder (60.5 mg, 63%); mp 124–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 6.93 (dd, J = 8.7, 2.4 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.93 (s), 156.78 (s), 156.36 (s), 143.22 (q, J = 4.2 Hz), 130.53 (s), 121.67 (q, J = 277.7 Hz), 113.74 (s), 113.71 (q, J = 33.6 Hz), 110.31 (s), 100.67 (s), 56.00 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −65.68 (s, 3F); GC-MS (EI, m/z): 244(M^+, 78), 216(73), 201 (100), 69(40).

7-Acetyloxy-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2g)***.[16] White powder (64.1 mg, 59%); mp 146–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.17 (dd, J = 8.5, 2.1 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.32 (s), 155.55 (d, J = 0.6 Hz), 155.33 (s), 155.18 (s), 142.74 (q, J = 4.8 Hz), 130.30 (s), 121.28 (q, J = 272.0 Hz), 119.34 (s), 116.98 (q, J = 33.4 Hz), 114.44 (s), 110.48 (s), 21.08 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.13 (s, 3F); GC-MS (EI, m/z): 230(M^+, 26), 202(27), 43(100), 32(38).

6-Bromo-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2h)***. White powder (66.1 mg, 55%); mp 162–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.76 (m, 2H), 7.30 (d, J = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.29 (s), 153.65 (s), 142.16 (q, J = 3.9 Hz), 137.34 (s), 131.78 (s), 121.21 (q, J = 272.4 Hz), 118.96 (q, J = 34.2 Hz), 118.93 (s), 118.41 (s), 118.01 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.34 (s, 3F); GC-MS (EI, m/z): 292(M^+, 71), 294(70), 157(89), 87(100).

6-Nitro-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2i)***.[16] Yellow powder (41.6 mg, 39%); mp 188–189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 2.6 Hz, 1H), 8.54 (dd, J = 9.1, 2.6 Hz, 1H), 8.26 (s, 1H), 7.56 (d, J = 9.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.80 (s), 154.15 (s), 144.43 (s), 142.07 (q, J = 4.9 Hz), 128.85 (s), 125.24 (s), 120.66 (q, J = 272.9 Hz), 120.05 (q, J = 34.1 Hz), 118.40 (s), 116.77 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.51 (s); GC-MS (EI, m/z): 256(M^+, 59), 157(100), 87(83), 62(55).

4-Phenyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one ***(2J)***.[16,22] White powder (57.5 mg, 50%); mp: 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.59 (m, 1H), 7.57–7.51 (m, 3H), 7.41 (d, J = 8.3 Hz, 1H), 7.28–7.24 (m, 2H), 7.21 (t, J = 7.7 Hz, 1H), 7.02

(d, J = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) 156.85 (d, J = 2.1 Hz), 156.37 (s), 153.38 (s), 134.09 (s), 132.79 (s), 129.26 (d, J = 5.5 Hz), 128.46 (s), 127.23 (d, J = 1.6 Hz), 124.76 (s), 121.82 (q, J = 275.3 Hz), 119.43 (s), 116.82 (s), 114.98 (q, J = 30.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) 57.46 (s); GC-MS (EI, m/z): 190(M^+, 71), 262(63), 165(100), 82(38).

7-(Diethylamino)-4-methyl-3-(trifluoromethyl)-2H-1-benzopyran-2-one (2k).[23] Yellow powder (86.2 mg, 71%); mp: 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (d, J = 9.2 Hz, 1H), 6.64 (dd, J = 9.2, 2.1 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.44 (q, J = 7.1 Hz, 4H), 2.56 (d, J = 2.0 Hz, 3H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 157.39 (d, J = 0.7 Hz), 155.95 (s), 155.06 (d, J = 0.6 Hz), 151.98 (s), 127.22 (s), 123.84 (q, J = 274.0 Hz), 109.39 (s), 108.02 (s), 107.97 (q, J = 30.2 Hz), 96.92 (s), 44.96 (s), 15.31 (s), 12.50 (s); ^{19}F NMR (470 MHz, $CDCl_3$) 55.47 (s); GC-MS (EI, m/z): 299(M^+, 34), 284(100), 256(43).

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