Electrolytic Partial Fluorination of Organic Compounds. 54.[1] Anodic Mono- and Trifluorination of Thiochroman-4-one Derivatives and the Factors Affecting Product Selectivity

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Anodic fluorination of (*E*)-3-benzylidene-2,3-dihydrothiochroman-4-one and 3-benzyl-1-thiochromone derivatives under a variety of electrolytic conditions was found to provide selectively or exclusively the same fluorinated products: (*E*)-3-benzylidene-2,3-dihydro-2-fluorothiochroman-4-ones. In addition, di- and trifluorinated derivatives were also obtained depending on the starting heterocycles and electrolytic conditions. The factors affecting the product selectivity were also examined.

Introduction

Fluorine closely mimics hydrogen with respect to steric requirements. Due to its high electronegativity and the the lipophilicity of the carbon−fluorine bond, insertion of fluorine atom(s) in organic compounds has significant beneficial effects in modifying their physical and biological properties.[2−5] Consequently, there is a growing interest in the synthesis of fluorine-containing heterocycles. Recently, electrochemical fluorination methodology has been established as a unique and useful tool for selective direct fluorination of organic molecules.[6,7] The anodic α-fluorination of organic sulfur compounds, which have electron-withdrawing groups at the α-position, has been extensively studied by our group.[8] However, very limited examples have been reported for the selective anodic α-fluorination of benzo-fused sulfur-containing heterocycles.[9]

Thiochroman-4-one and 1-thiochromone derivatives are interesting classes of heterocycles due to their broad pharmacological and medicinal importance.[10,11] In this work, we successfully performed anodic fluorination of (*E*)-3-benzylidene-2,3-dihydrothiochroman-4-ones **1** to provide the corresponding mono- and trifluorinated products. Anodic fluorination of an isomer of **1**, a 1-thiochromone derivative, also provided the same fluorinated products derived from **1**. Moreover, the factors affecting the product selectivity were investigated.

Results and Discussion

Oxidation Potentials of the Starting Substrates 1a,b and 2. The oxidation peak potentials E_p^{ox} of thiochroman-4-ones **1a**,**b** and a thiochromone derivative **2** were measured by means of cyclic voltammetry using a divided cell at a platinum anode in 0.1 M $Bu_4N{\cdot}BF_4$/anhydrous acetonitrile. These heterocycles exhibited irreversible oxidation peaks, and the first peak potentials (E_p^{ox}) are listed in Table 1. Thiochromone derivative **2** was found to be oxidized at a more positive potential than its isomer **1**.

Anodic Fluorination of Thiochroman-4-one Derivatives 1a,b. (*E*)-3-Benzylidene-2,3-dihydrothiochroman-4-one (**1a**) was first subjected to anodic fluorination under various conditions, and the electrolysis results are

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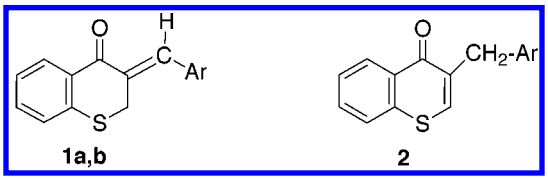
Table 1. Oxidation Potentials (E_p^{ox}) of Starting Substrates



compd no.	Ar	E_p^{ox} (V vs SSCE)[a]
1a	C_6H_5	1.70
1b	4-ClC_6H_4	1.77
2	4-ClC_6H_4	1.90

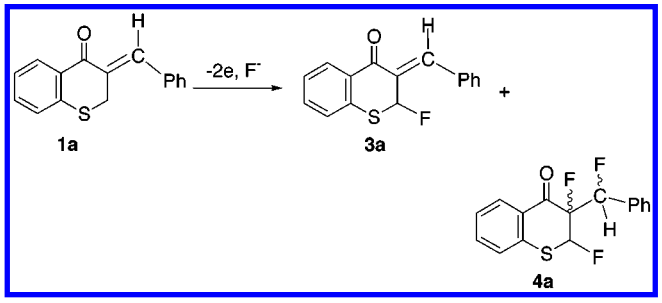
[a] In 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Sweep rate = 100 mV s^{-1}.

Table 2. Anodic Fluorination of (*E*)-3-Benzylidene-2,3-dihydrothiochroman-4-one (1a)

run	supp electrolyte/ solvent	charge passed[a] (F mol^{-1})	yield (%)[b] **3a**	yield (%)[b] **4a**	selectivity % of **3a**
1	$Et_4NF{\cdot}4HF$/DME	2.5	81 (63)	5	94
2	$Et_4NF{\cdot}4HF$/DME[c]	2.5	48	10	83
3	$Et_4NF{\cdot}4HF$/MeCN	2.5	58	12	83
4	$Et_4NF{\cdot}3HF$/DME	2.5	73	13	85
5	$Et_4NF{\cdot}3HF$/DME[d]	2.2	78 (65)		100
6	$Et_3N{\cdot}4HF$/DME	4.0	42	20	68
7	$Et_3N{\cdot}3HF$/DME	4.0	35	11	76

[a] Constant current electrolysis using a divided cell was applied until the starting material was almost consumed. [b] Calculated on the basis of ^{19}F NMR; isolated yields are shown in parentheses. [c] An undivided cell was used. [d] Controlled potential electrolysis (1.70 V vs SSCE) was applied.

Scheme 1



summarized in Table 2. When the electrolysis was conducted at constant current, two fluorinated products **3a** and **4a** (Scheme 1) were obtained in all cases (Table 1, runs 1−4 and 6 and 7). Under these conditions, the use of $Et_4NF{\cdot}4HF$/DME in a divided cell resulted in a high product selectivity (run 1); 2-fluorothiochroman-4-one derivative **3a** was obtained selectively in an 81% yield along with its trifluoro analogue **4a** as a minor product (5%). The overall fluorinated yield decreased significantly when an undivided cell (run 2) or acetonitrile (run 3) was used. Furthermore, the use of other fluoride salts (runs 4, 6, and 7) under similar conditions gave moderate to high overall fluorinated yields but the product selectivity was low.

The oxidation potential (E_p^{ox}) of the monofluorinated product **3a** was measured by cyclic voltammetry under similar conditions as described in Table 1. It was found that the oxidation potential (E_p^{ox}) of **3a** is 2.01 V vs SSCE (saturated NaCl calomel electrode), which is more positive than that of **1a** by 0.31 V. This finding prompted us to carry out controlled potential electrolysis (1.7 V vs SSCE) of **1a** in $Et_4NF{\cdot}3HF$/DME (run 5). Notably, the product selectivity was optimized so that a highly regioselective α-monofluorination was achieved under the potentiostatic electrolysis to solely give **3a**. On the other hand, further anodic fluorination of 2-fluorothiochromanone derivative **3a** was performed using $Et_3N{\cdot}4HF$/DME in a divided cell to furnish the trifluorinated product **4a** predominantly in a moderate yield as shown in Scheme 2.

Scheme 2

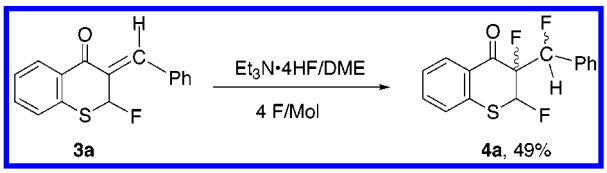


Table 3. Anodic Fluorination of (*E*)-3-Arylidene-2,3-dihydrothiochroman-4-ones 1a,b

run	Ar	charge passed[a] (F mol^{-1})	yield (%)[b] **3**	yield (%)[b] **4**
1	C_6H_5 (**1a**)	2.5	81 (63)	5
2	4-ClC_6H_4 (**1b**)	3.0	49	37
3	4-ClC_6H_4 (**1b**)	2.2[c]	89 (77)	
4	4-ClC_6H_4 (**1b**)	5.0	16	80 (53)

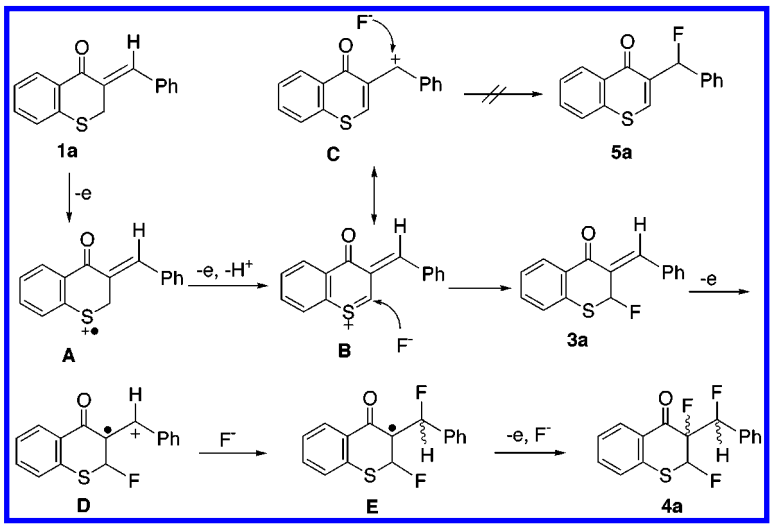
[a] Constant current electrolysis was applied using an H-type divided cell. [b] Calculated on the basis of ^{19}F NMR; the isolated yields are shown in parentheses. [c] Controlled potential electrolysis (1.77 V vs SSCE) was applied.

A possible reaction mechanism for anodic mono- and trifluorination of thiochroman-4-one **1a** is depicted in Scheme 3. The one-electron oxidation should take place on sulfur and then be followed by deprotonation to generate the sulfonium intermediate **B**, which reacts with a fluoride ion at the position that is α to the sulfur atom to give 2-fluorothiochroman-4-one derivative **3a**. Further oxidation of **3a** is assumed to take place at the olefin moiety to generate the radical cation intermediate **D**, which reacts with a fluoride ion followed by further oxidation and a successive reaction with a fluoride ion to afford the trifluorinated product **4a**. The expected benzylic fluorinated product **5a** could not be detected. This fact excludes the formation of the benzylic carbocation **C** during the electrolysis.

In addition, the anodic behavior of (*E*)-3-(4-chlorobenzylidene)-2,3-dihydrothiochroman-4-one (**1b**) toward $Et_4NF{\cdot}4HF$/DME using a divided cell was also investigated (Table 3, runs 2−4). Galvanostatic electrolysis of **1b** was carried out by passing a 3 F mol^{-1} charge until **1b** was completely consumed. The mono- and trifluorinated derivatives **3b** and **4b** (Scheme 4) were formed in a high overall yield with very low product selectivity (run 2). Continuation of the electrolysis, by passing a 5 F mol^{-1} charge, directed the product selectivity toward trifluorination (run 4). On the other hand, when the electrolysis was carried out under controlled potential conditions, the corresponding monofluorinated product **3b** was obtained exclusively in a high yield with good current efficiency (run 3). Therefore, potentiostatic electrolysis using $Et_4NF{\cdot}4HF$/DME in a divided cell was found to be suitable for the regioselective monofluorination at the position α to the sulfur atom of the thiochroman-4-one derivatives **1a**,**b**.

Anodic Fluorination of 3-(4-Chlorobenzyl)thiochromone (2). Next, constant current anodic fluorination of 3-(4-chlorobenzyl)-1-thiochromone (**2**), an isomer of **1b**, was attempted. The fluorination proceeded smoothly to afford three fluorinated products as shown in Table 4

Scheme 3



Scheme 4

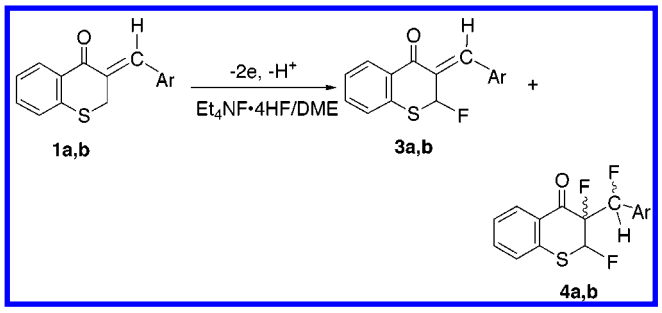
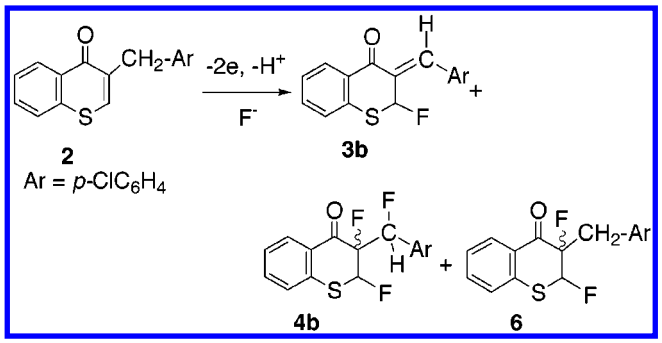


Table 4. Anodic Fluorination of 3-(4-Chlorobenzyl)-1-thiochromone (2)

run	supp electrolyte	charge passed[a] (F mol^{-1})	yield%[b] 3b	4b	6
1	Et_4NF•4HF/DME	2.5[c]	61	14	13
2	Et_4NF•4HF/DME	5.0	6	51	17
3	Et_4NF•4HF/DME	2.5[c,d]	59		17
4	Et_3N•3HF/DME	3.0[c]	56	19	

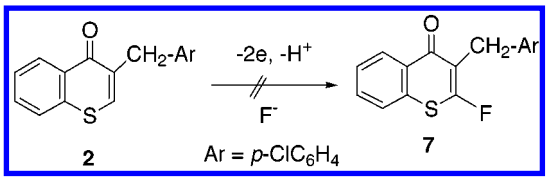
[a] Constant current electrolysis (6 mA cm^{-2}) was applied using an H-type divided cell. [b] Calculated on the basis of ^{19}F NMR. [c] The starting material was completely consumed. [d] Controlled potential electrolysis (1.90 V vs SSCE) was applied.

Scheme 5

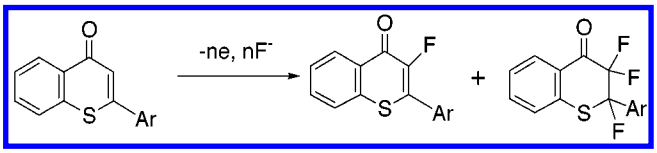


and Scheme 5. Surprisingly, two of these fluorinated products were found to be identical with the mono- and trifluorinated derivatives **3b** and **4b**, respectively, and were formed in a high overall yield. The third product was established as the 3-(4-chlorobenzyl)-2,3-difluoro-2,3-dihydrothiochroman-4-one (**6**) on the basis of its elemental analysis and spectral data (cf. Experimental Section). The product selectivity in this case was greatly dependent upon the amount of charge passed and the electrolysis conditions. When the electrolysis was conducted until the complete consumption of **2** occurred, a monofluorinated product **3b** was formed as the major product in 61% yield; the overall fluorination yield was excellent (run 1). On the other hand, when 5 F mol^{-1} of electricity was passed, the trifluoro **4b** became the major product (run 2). Furthermore, controlled potential electrolysis of 1-thiochromone derivative **2** at 1.90 V vs SSCE resulted in the formation of mono- and difluorinated products **3b** and **6** in 59 and 17% yields, respectively (run 3). In sharp contrast, Et_3N•3HF/DME afforded **3b** and **4b**, but **6** was not formed (run 4).

Scheme 6



Scheme 7



Anodic fluorination of the 1-thiohomoisoflavone derivative **2** provides an interesting alternate stereoselective pathway to (*E*)-3-(4-chlorobenzylidene)-2-fluoro-2,3-dihydrothiochroman-4-one (**3b**). The corresponding 2-fluoro-1-thiohomoisoflavone derivative **7** was not formed (Scheme 6). This result is in sharp contrast to Laurent's report on the anodic fluorination of thioflavones as shown in Scheme 7.[12] In the case of thioflavones, 3-fluorothioflavones and 2,3,3-trifluorothioflavones were formed; however, no such products were obtained in our case.

The behavior of 1-thiohomoisoflavone derivative **2** toward anodic fluorination is quite different from that of thioflavones. A proposed mechanism for the anodic formation of **3b**, **4b**, and **6** from **2** is outlined in Scheme 8. Oxidation can take place either at the sulfur atom (route a) or at the olefin moiety (route b) to generate a

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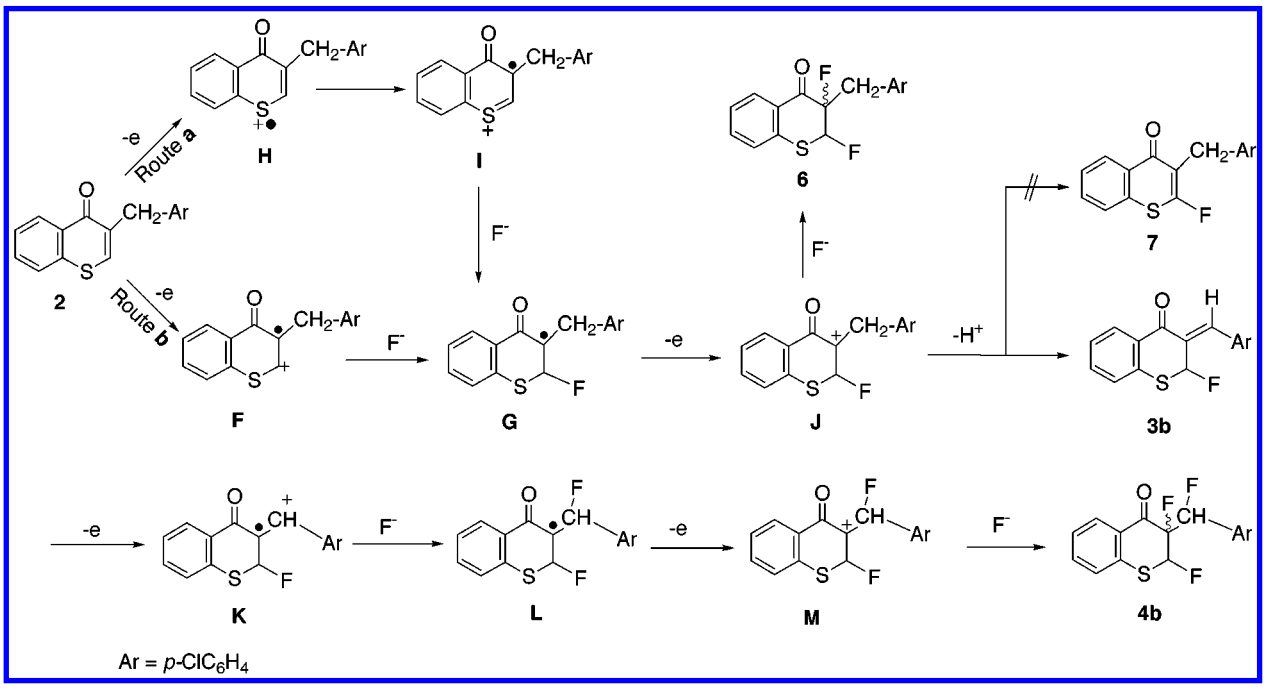
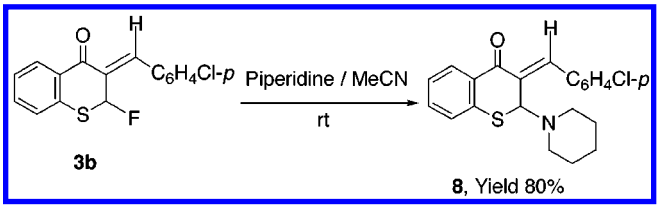
Scheme 8

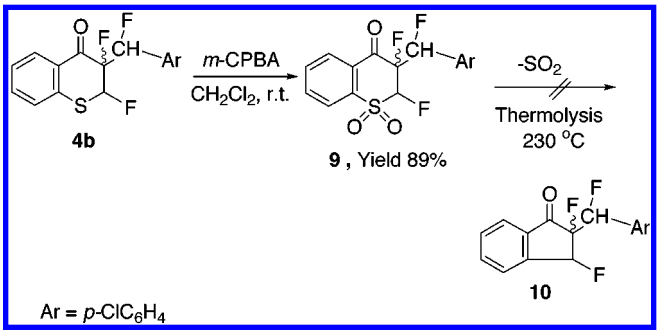


radical cation **H** or **F**. A fluoride ion reacts with the radical cation **F** or **I** to form **G**, which is further oxidized to give the α-fluorocarbocation **J**. Successive reaction with a fluoride ion gives the 2,3-difluoro derivative **6**. On the other hand, elimination of a proton from **J** preferentially gives the monofluoro product **3b** rather than **7**. This preference is consistent with facts reported in the literature: (i) isomerization takes place readily when the migrating double bond moves into conjugation with an aromatic benzene nucleus,[13] (ii) an exocyclic double bond is energetically more stable than an endocyclic one,[14] and (iii) the E-form of 3-benzylidene-2,3-dihydrothiochroman-4-ones is generally more predominant when compared with its Z-form.[15−17] From these viewpoints, we conclude that the elimination of a proton took place from the benzylic methylene group of **J** to afford the thermodynamically more stable 2-fluorothiochroman-4-one derivative **3b** rather than its isomer **7**. This finding is similar to our recent report for anodic fluorination of 3-benzylchromone derivatives.[18] The use of $Et_4NF{\cdot}4HF$ gave **3b**, **4b**, and **6**, while the use of $Et_3N{\cdot}3HF$ gave **3b** and **4b**, but **6** was not formed at all. $Et_3N{\cdot}3HF$ is known to contain a considerable amount of free Et_3N.[19] Et_3N should promote deprotonation in the cationic intermediate **J** to form **3b**. Thus, the lack of formation of **6** by using $Et_3N{\cdot}3HF$ can be reasonably explained. Further oxidation of **3b** followed by reaction with a fluoride ion gives the trifluorinated product **4b**, similar to the reaction shown in Scheme 2.

Scheme 9



Scheme 10



The synthetic utility of the fluorinated products was also studied. Treatment of **3b** with piperidine in acetonitrile at room temperature afforded 2-piperidylthiochroman-4-one derivative **8** in a high yield, as shown in Scheme 9. However, similar treatment of **4b** with piperidine resulted in no reaction and the the trifluoro derivative **4b** was completely recovered. Furthermore, chemical oxidation of **4b** with *m*-chloroperbenzoic acid in dichloromethane at room temperature gave the trifluorosulfone **9** in good yield as shown in Scheme 10. Attempts to synthesize the trifluoroindanone derivative **10** through thermal SO_2 extrusion from the sulfone **9**, similar to our previous report,[20] were unsuccessful.

Conclusions

In conclusion, we have successfully established two stereoselective routes for the anodic synthesis of (*E*)-3-

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benzylidene-2-fluoro-2,3-dihydrothiochroman-4-ones **3**. This is the first report of successful stereoselective electrochemical direct α-fluorination of fused type, sulfur-containing heterocyclic compounds.

Experimental Section

3-Benzylidene-2,3-dihydrothiochroman-4-one and 3-benzylthiochromone derivatives **1a**,**b** and **2** were synthesized according to procedures reported in the literature.[21,22]

Anodic Fluorination of Thiochroman-4-one and 1-Thiochromone Derivatives. Electrolysis was conducted at a platinum anode and cathode (2 × 2 cm^2) in 0.3 M solution of a fluoride salt in dimethoxyethane (30 mL) containing thiochromanone **1** or thiochromone **2** derivative (1 mmol) by using an H-type divided cell with a glass diaphragm under a nitrogen atmosphere at an ambient temperature. Constant current (6 mA cm^{-2}) or controlled potential was applied until a complete consumption of the starting substrate was achieved (monitored by TLC and GC-MS). After the electrolysis, the resulting electrolytic solution was passed through a short column of silica gel using ethyl acetate as eluent. The collected solution was evaporated under vacuum. Then, the yield of the fluorinated product was calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. The yield was calculated on the basis of the integral ratios between the monofluorobenzene and the fluorinated product. After that, the product was isolated by column chromatography on silica gel using a hexane/ethyl acetate eluent (5:1).

***(E)*-3-Benzylidene-2,3-dihydro-2-fluorothiochroman-4-one (3a).** Mp 64−65 °C; ^1H NMR δ 6.80 (d, 1H, J = 45.86 Hz), 7.30−7.49 (m, 8H), 8.02 (s, 1H), 8.43 (dd, 1H, J = 7.58, 1 Hz); ^{13}C NMR (DEPT) δ 90.26 (d, CH, J = 173.30 Hz), 126.38, 126.56, 126.65, 127.67, 128.18, 128.32, 128.55, 128.61, 131.32, 131.46 (CH), 134.43, 134.74, 136.64, 137.79, 177.26 (C); ^{19}F NMR δ −98.30 (d, J = 45.96 Hz); MS *m/e* 270 (M^+), 249, 238, 221, 108. Anal. Calcd for $C_{16}H_{11}FSO$: C, 71.09; H, 4.10. Found: C, 71.09; 4.37.

***(E)*-3-(4-Chlorobenzylidene)-2,3-dihydro-2-fluorothiochroman-4-one (3b).** Mp 81−82 °C; ^1H NMR δ 6.76 (d, 1H, J = 45.53 Hz), 7.32 (d, 2H, J = 8.25 Hz), 7.42 (d, 2H, J = 8.25 Hz), 7.50−7.62 (m, 3H), 8.10 (s, 1H), 8.49 (d, 1H, J = 7.59 Hz); ^{19}F NMR δ −99.39 (d, J = 45.97 Hz); MS *m/e* 304 (M^+), 285, 249, 221, 167, 149, 108. Anal. Calcd for $C_{16}H_{10}ClFSO$: C, 63.06; H, 3.31. Found: C, 63.07; 3.56.

2,3-Difluoro-3-(α-fluorobenzyl)-2,3-dihydrothiochroman-4-one (4a). Yellow oil; ^1H NMR δ 5.38 (dd, 1H, J = 50.15, 7.92 Hz), 6.07 (ddd, 1H, J = 43.38, 22.10, 1.89 Hz), 7.24−7.61 (m, 8H), 8.16 (dd, 1H, J = 7.92, 1.32 Hz); ^{19}F NMR δ −98.14 (dddd, 1F, J = 50.56, 21.14, 10.11, 1.84 Hz), −109.24 (dt, 1F, J = 43.20, 10.11 Hz), −112.15 (m, 1F); MS *m/e* 308 (M^+), 288 (M^+ − HF), 180, 136, 109. Anal. Calcd for $C_{16}H_{11}F_3SO$: C, 62.33; H, 3.60. Found: C, 62.30; H, 3.64.

2,3-Difluoro-3-(α-fluoro-4-chlorobenzyl)-2,3-dihydrothiochroman-4-one (4b). Yellow oil; ^1H NMR δ 5.39 (dd, 1H, J = 50.15, 7.92 Hz), 5.93 (ddd, 1H, J = 43.22, 21.44, 1.89 Hz), 7.23−7.42 (m, 4H), 7.52−7.60 (m, 3H), 8.14 (d, 1H, J = 7.91 Hz); ^{19}F NMR δ −98.15 (dddd, 1F, J = 50.56, 21.14, 10.11, 1.84 Hz), −109.10 (dt, 1F, J = 43.20, 10.11 Hz), −111.94 (m, 1F); MS *m/e* 342 (M^+), 322 (M^+ − HF), 180, 136, 108. Anal. Calcd for $C_{16}H_{10}ClF_3SO$: C, 56.07; H, 2.94. Found: C, 55.96; H, 2.82.

3-(4-Chlorobenzyl)-2,3-difluoro-2,3-dihydrothiochroman-4-one (6). Mp 136−137 °C; ^1H NMR δ 3.32 (d, 2H, J = 21.76 Hz), 5.63 (dd, 1H, J = 49.79, 6.59 Hz), 7.25−7.38 (m, 6H), 7.57 (ddd, 1H, J = 8.90, 7.91, 1.48 Hz), 8.15 (dd, 1H, J = 7.91, 1.48 Hz); ^{19}F NMR δ −94.62 (m, 1F), −100.24 (dd, 1F, J = 49.94, 20.34 Hz); MS (FAB^+) (*m/e*) 325 (M^+ + H), 304, 289, 197, 154, 126. HRMS (FAB^+): Calcd for $C_{16}H_{12}ClF_2OS$: 325.0265. Found: 325.0320. Anal. Calcd for $C_{16}H_{11}ClF_2SO$: C, 59.17; H, 3.41; S, 9.87. Found: C, 58.93; H, 3.46; S, 9.87.

3-(4-Chlorobenzylidene)-2-(1-piperidyl)-2,3-dihydrothiochroman-4-one (8). To a solution of 2-fluorothiochroman-4-one derivative **3b** (0.152 g, 0.5 mmol) in acetonitrile (10 mL) was added piperidine (0.1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under vacuum, and the residue was chromatographed using hexane/ethyl acetate (3:1) as eluent to afford 0.147 g (80%) of pure **8**. Mp 46−47 °C; ^1H NMR δ 1.44−1.58 (m, 6H), 2.32−2.43 (m, 4H), 4.87 (s, 1H), 7.23 (d, 2H, J = 8.24 Hz), 7.37 (d, 2H, J = 8.24 Hz), 7.47−7.58 (m, 3H), 8.31 (s, 1H), 8.49 (d, 1H, J = 7.58 Hz); ^{13}C NMR (DEPT) δ 24.65, 26.33, 53.03 (CH_2), 67.84, 126.31, 127.40, 128.25, 128.84, 129.72, 130.88, 134.54 (CH), 131.79, 132.42, 136.75, 139.41, 161.57, 178.03 (C); MS *m/e* 369 (M^+), 326, 312, 286, 250, 221, 149, 108, 84. Anal. Calcd for $C_{21}H_{20}ClNSO$: C, 68.19; H, 5.45; N, 3.79; S, 8.67. Found: C, 67.98; H, 5.65; N, 3.60; S, 8.49.

2,3-Difluoro-3-(α-fluoro-4-chlorobenzyl)-2,3-dihydrothiochroman-4-one-1,1-dioxide (9). A mixture of the trifluorothiochroman-4-one derivative **3b** (0.171 g, 0.5 mmol) and *m*-chloroperbenzoic acid (0.207 g, 1.2 mmol) in dichloromethane (20 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water, and the product was extracted with dichloromethane. The organic phase was collected, washed with aqueous Na_2CO_3 solution, then dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the solid product was recrystallized from ethanol to give 0.167 g (89% yield) of pure trifluorosulfone **9**. Mp 173−175 °C; ^1H NMR δ 5.22 (dd, 1H, J = 48.30, 6.60 Hz), 6.30 (dd, 1H, J = 43.03, 24.24 Hz), 7.46 (d, 2H, J = 8.58 Hz), 7.63 (d, 2H, J = 8.58 Hz), 7.90−8.12 (m, 3H), 8.34 (d, 1H, J = 7.92 Hz); ^{19}F NMR δ −101.69 (m, 1F), −107.71 (dt, 1F, J = 43.20, 8.27 Hz), −109.42 (ddd, 1F, J = 47.80, 8.27, 2.76 Hz); MS (FAB^+) *m/e* 375 (M^+ + H), 359, 307, 289, 273, 242, 187, 154, 136, 107. Anal. Calcd for $C_{16}H_{10}ClF_3SO_3$: C, 51.28; H, 2.69. Found: C, 51.36; H, 2.96.

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