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Fluorination of Flavones and Chromones Using Elemental Fluorine

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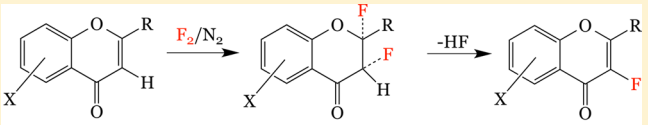
Supporting Information

ABSTRACT: Flavonoids are abundant micronutrients in our diet, possessing various biological activities. Fluorine was successfully added across the double bond of various flavones and chromones. The difluoro derivative products were easily dehydrofluorinated to form the corresponding 3-fluoroflavones and 3-fluorochromones.



X = H, Br, Cl, OAc; R= Ph, H

INTRODUCTION

Introducing the fluorine atom into organic molecules is important since quite frequently such compounds possess unique physical, chemical, and biological properties. They also play a significant role in drug development because fluorinated bioactive molecules can have significantly higher chances of becoming drug candidates and eventually drugs.[1,2] Many such compounds made with $[18]F_2$ are also valuable for positron emission tomography (PET).[3] No wonder there is an ever-increasing demand for new and selective methods for preparation of organic materials containing one or more fluorine atoms.

Flavones and chromones occur in many different plants and are abundant in our diet,[4] having numerous health effects such as a decreased risk of cardiovascular diseases[5] and are efficacious in the treatment of chronic inflammatory pain[6] and in anticancer activities.[7] They also exhibit antiviral activity,[8] serve as antioxidants[9] and anti-HIV agents,[10] act as bactericidals,[11] and much more. Studies indicate, however, that many such compounds can last in the body for only about 10 h before they are metabolized.[12]

Naturally, an efficient synthesis of fluoroflavones and chromones is very desirable since there is a good chance they would outperform the natural starting materials. What's more, because numerous fluoro derivatives have proven to be more stable toward metabolic decomposition, it is reasonable to assume that this might also be the case here. This led to several attempts to prepare 3-fluoroflavones and 3-fluorochromones, but usually the results were obtained by several indirect methods. Some have used a total synthesis approach requiring α-hydroxy acetophenone derivatives[13,14] or condensation between aldehydes and dimethylanilines containing a difluoro-chloro moiety.[15] A different approach was taken by Fuchigami, who electrochemically fluorinated some flavones with $Et_3N\cdot 3HF$ or $Et_4NF\cdot 4HF$.[16] In most cases, the yields were quite low and the synthetic routes not of general nature. The reasons these methods were so indirect were in part the unjustified fears associated with elemental fluorine (even though diluted) and the readiness to take extra steps to avoid working with it.

We have been using nitrogen-diluted fluorine for many types of reactions without any problems for years. It was successfully employed for activation of "impossible" sites of organic molecules by the unique electrophilic "front side" substitution of remote tertiary sp^3 CH bonds,[17] by adding it across some simple olefins[18] and acetylenes,[19] or by using it for creating secondary useful reagents such as acetyl hypofluorite,[20] $HOF\cdot CH_3CN$,[21] MeOF,[22] halogen fluorides,[23] BrF_3,[24] and much more. We present here yet another use of this element for one-step general and efficient synthesis of fluoroflavones and fluorochromones from the parent flavonoids.

RESULTS AND DISCUSSION

Adding chlorine and bromine across various double bonds is a process almost as old as organic chemistry itself. Adding fluorine to olefins, however, has almost no precedence. We concluded from our only work on the reaction of F_2 with some simple double bonds that there are two main reasons for this situation. The first reason is the very high enthalpy of any reaction between a double bond and F_2. This issue could be addressed by using quite diluted F_2 and conducting the reactions at low temperatures. The second reason is the low polarizability and the weak bond between the two fluorine atoms encouraging non specific radical reactions. In order to decrease the chances of following such routes, one has to offer a relatively polar solvent (see details in the Experimental Section). If, however, the polarity is too high, fluorine seems to leave the reaction vessel unreacted probably because of its complete insolubility. We found that a mixture of very nonpolar solvents such as $CFCl_3$ and chloroform gives better results than one of these solvents alone, but what has even a better effect is the addition of ethanol in various proportions. This solvents' combination increases solubility,[25] and the EtOH serves as a good acceptor for the negative pole of the F−F molecule. Generally speaking, addition of too much alcohol prevented the reaction from taking its desirable course, and most of the substrate remains unreacted as fluorine escapes the reaction vessel without doing much. Too little ethanol, however, allows formation of fluorine radicals that destroy slowly the organic substrate.[18]

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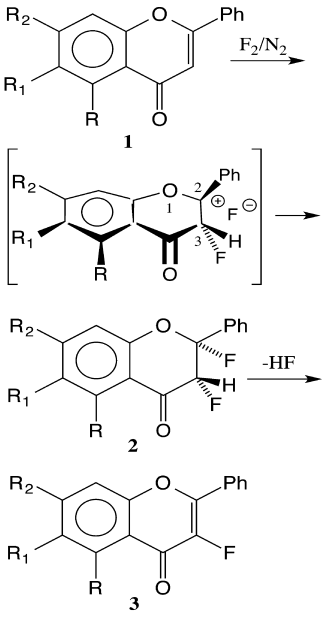
The addition of fluorine to flavonoids presents yet another challenge. These compounds possess a unique double bond. On one hand, it is a conjugated enone, which naturally is less reactive than an isolated double bond, while on the other hand, it is an enol derivative making it quite sensitive to ring-opening forming potentially α-fluorocarbonyl moieties. These two opposing effects must be balanced, something which could be achieved mainly through varying the alcohol concentration in the solvent mixture.

When diluted fluorine (7−10% F_2 in N_2) was bubbled slowly through a cold (−78 °C) and well-stirred solution of flavone **1a** in a mixture of $CHCl_3$/$CFCl_3$/EtOH (usually in 5:4:1 ratio), *cis*-2,3-difluoro-4-flavanone (**2a**)[16] was formed in 76% yield (Scheme 1). The *cis* configuration is revealed by the $^2J_{HF}$ coupling constants of 46 Hz and $^3J_{HF}$ of 28 Hz, in accordance with the H−C−C−F dihedral angle of about 60°. In addition, the J_{FF} coupling constant of 15 Hz is in line with the gauche conformation. Similar results were obtained when 6-chloroflavone (**1b**) was reacted with fluorine, forming *cis*-2,3-difluoro-6-chloro-4-flavanone (**2b**)[16] in 70% yield. Flavones containing the phenolic moiety did not usually react cleanly with fluorine, but the situation improved when the hydroxyl groups were acetylated. Thus, 6-acetoxyflavone (**1c**)[26] reacted with elemental fluorine to form the desired *cis*-2,3-difluoro-6-acetoxy-4-flavanone (**2c**) in 65% yield, and the 5,7-diacetoxyflavone (**1d**)[27] produced the *cis*-2,3-difluoro-5,7-diacetoxy-4-flavanone **2d** in about 70% yield, although it was not isolated in analytical purity and was reacted as is in the planned consecutive step (see below).

Scheme 1. Fluorination of Flavones



	1	2	3
a	$R = R_1 = R_2 = H$	76%	92%
b	$R = R_2 = H$; $R_1 = Cl$	70%	95%
c	$R = R_2 = H$; $R_1 = OAc$	65%	85%
d	$R = R_2 = OAc$; $R_1 = H$	70%[a]	63%[b]
e	$R = OH$; $R_1 = H$; $R_2 = OAc$		49%[b]

[a]Not analytically purified. [b]Yield based on the starting flavone **1d**.

It is of interest to compare this to the addition mechanism. A well-known fact concerning the reaction of most members of the halogen family with double bonds is the *anti* mode addition. With fluorine, however, the situation is reversed. It is a small atom which cannot form a bridged fluoronium ion as is the case with the other halogens. It is bound to create a transition cage containing a fluoride and the extremely unstable α-fluoro carbonium ion. The two ions in this cage collapse rapidly before the fluoride has a chance to move toward the opposite face of the ring, resulting in the *syn* addition (Scheme 1). It should be emphasized that a four center addition of moieties containing electrophilic fluorine to the π system of the olefin had been discredited in the past.[28]

The difluorinated product **2a** was easily dehydrofluorinated to 3-fluoroflavone (**3a**)[16] in higher than 90% yield, simply by adsorbing it on a silica gel column. HF elimination occurred readily due to the anti configuration of the two atoms. Dehydrofluorination of **2b** on silica-gel similarly led to a formation of 3-fluoro-6-chloroflavone (**3b**)[16] in 95% yield. The dehydrofluorination of *cis*-2,3-difluoro-6-acetoxy-4-flavanone (**2c**), however, could not be conveniently carried on silica since part of the acetate was simultaneously hydrolyzed. Nevertheless, dehydrofluorination could be achieved by treating **2c** with BF_3·OEt_2 for about 3 h to produce 3-fluoro-6-acetoxyflavone (**3c**) in 85% yield. The difluoro diacetoxy flavonoid **2d**, which as mentioned above was not isolated in analytical purity, was also treated with BF_3·OEt_2 which after three hours caused dehydrofluorination, but this time the acetoxy group at 5 was also hydrolyzed forming 3-fluoro-5-hydroxy-7-acetoxyflavone (**3e**) in 49% yield (based on **1d**). When the same crude **2d** was slowly passed through a silica chromatographic column using petroleum ether/EtOAc (as with **2a** and **2b**) it formed a complicated mixture. If however, **2d** was fast eluted, it did result, as anticipated, in a complete dehydrofluorination, and without affecting any of the acetate groups thus obtaining the diacetoxy fluoroflavone **3d** in 63% overall yield based on the starting flavone **1d**.

Chromones were treated with fluorine as well. The basic chromone **4a** formed a mixture of difluorinated product **5a** and **6a**, the latter as a result of partial spontaneous HF elimination. To complete the elimination, the mixture was absorbed on silica gel leading eventually to 3-fluorochromone (**6a**)[29] in overall yield of 75% (Scheme 2).

2,3-Difluoro-6-bromo-4-chromanone (**5b**) and 2,3,6-trifluoro-4-chromanone (**5c**) were made by adding F_2 to the corresponding 6-bromo- and 6-fluorochromones **4b** and **4c** in 80%, and 82% yield (GC), respectively. They were not isolated in analytical purity but dehydrofluorinated by flash chromatography to provide 3-fluoro-6-bromochromone (**6b**) and 3,6-difluorochromone (**6c**) almost quantitatively. The fluorination with F_2 was also successful when the double bond was trisubstituted as in 3-methylchromone (**4d**), which formed 2,3-difluoro-3-methyl-4-chromanone (**5d**) in 65% yield. When the fluorination reaction was performed under the standard conditions described above on derivatives possessing an electron-withdrawing group attached to the double bond as in 3-bromochromone (**4e**), the conversion did not exceed 60% and the yield of 2,3-difluoro-3-bromo-4-chromanone (**5e**) was only 36%. In order to improve the outcome of the reaction, the amount of the ethanol had to be significantly reduced until a full conversion and 64% yield of **5e** was achieved. In the last two cases (**5d** and **5e**), neither silica gel nor BF_3·OEt_2 could induce dehydrofluorination since the proton α to etheric

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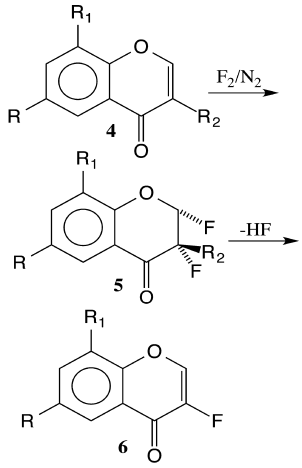
Scheme 2. Fluorination of Chromones



(When R_2 = H)

a	**4**	$R = R_1 = R_2 = H$;	**5**	- ;	**6**	75%
b	**4**	$R = Br$; $R_1 = R_2 = H$;	**5**	80% ;	**6**	95%
c	**4**	$R = F$; $R_1 = R_2 = H$;	**5**	82% ;	**6**	98%
d	**4**	$R = R_1 = H$; $R_2 = Me$;	**5**	65% ;	**6**	-
e	**4**	$R = R_1 = H$; $R_2 = Br$;	**5**	64% ;	**6**	-

oxygen is not acidic enough, and harsh conditions such as prolonged treatment with NaOH[30] resulted in destruction of the molecule so at the present we were unable to induce HF elimination in such cases.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded using a 400 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 376.8 MHz with $CFCl_3$ serving as an internal standard. The proton broadband-decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. Here, too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. IR spectra were recorded with an FTIR ATR spectrometer. MS were measured with a Q-TOF (synapt) mass analyzer.

General Fluorination Procedure. Fluorine is a strong oxidant and corrosive material. In organic chemistry, it is used after dilution with nitrogen or helium (generally from 1−20% depending on the reaction type). Such dilution can be achieved by using either an appropriate copper or monel vacuum line or by purchasing prediluted fluorine. A detailed description of a simple setup appeared in the previous literature.[31] The reactions themselves are carried out in standard glassware. If elementary precautions are taken, work with F_2 (which is less toxic than chlorine[32]) proceeds smoothly, and we have had no bad experience working with it. Still, the work with this reagent requires a well-ventilated area and good common sense as thousands of other reagents in chemistry do.

The reactions were usually carried out on scales of 1−5 mmol flavone or chromone derivatives, monitored by TLC, GC, or NMR. The starting flavones and chromones are commercially available, and we have acetylated the hydroxyl groups where relevant. Fluorine, at concentrations of 7−10% in N_2, was slowly passed through a cold (−78 °C) and vigorously stirred solution of the enone dissolved in 100 mL of $CFCl_3$, 125 mL of $CHCl_3$, and 25 mL of EtOH. An efficient mixing was achieved by using a vibromixer, which also ensured a fine dispersion of the gas bubbles. In most cases, the reactions were completed within 1.5−4 h. They were terminated by pouring into 200 mL water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The crude product was usually purified by vacuum flash chromatography using silica gel with various proportions of petroleum ether/EtOAc as eluent or by recrystallization.

Dehydrofluorination Procedures. Two methods were employed for the described HF elimination. (A) The corresponding fluoro derivative was dissolved in benzene and cooled to about 10 °C. Excess $BF_3{\cdot}OEt_2$ was added in one portion, and the reaction mixture allowed to warm to room temperature and stirred for an additional 3 h. Cold diluted HCl solution was added, and the organic layer washed with bicarbonate and worked up as usual. The resulting enones were usually recrystallized. (B) HF elimination was achieved simply by adsorbing the crude difluorinated product on a silica gel column (60-H, Merck) and eluted the organic substances with various proportions of petroleum ether/EtOAc.

2,3-Difluoro-4-flavanone (2a)[16] was prepared from flavone (**1a**) (0.76 g, 3.4 mmol) as described above: off-white solid; mp 108−109 °C (0.68 g, 76% yield); ^{1}H NMR 7.98 (dd, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1 H), 7.73−7.71 (m, 2 H), 7.65 (t, J = 7.7 Hz, 1 H), 7.53−7.52 (m, 3 H), 7.27−7.23 (m, 1 H), 7.16 (d, J = 8.3 Hz, 1 H), 5.45 (dd, J_1 = 28.0 Hz, J_2 = 45.6 Hz, 1 H); ^{13}C NMR 185.9 (d, J = 16.4 Hz), 156.3, 137.5, 134.1 (d, J = 25.5 Hz), 130.7, 128.8, 127.2, 126.1 (d, J = 6.7 Hz), 124.1, 119.7, 118.5, 113.9 (dd, J_1 = 22.3 Hz, J_2 = 236.8 Hz), 90.4 (dd, J_1 = 33.4 Hz, J_2 = 203.0 Hz); ^{19}F NMR −129.1 (dd, J_1 = 28.1 Hz, J_2 = 15.3 Hz), −212.8 (dd, J_1 = 45.5 Hz, J_2 = 16.0 Hz).

3-Fluoroflavone (3a).[16] Compound **2a** was flash chromatographed resulting in a pale yellow solid, mp 85−86 °C (0.57 g, 92% yield).

2,3-Difluoro-6-chloro-4-flavanone (2b)[16] was prepared from 6-chloroflavone (**1b**) (0.72 g, 2.8 mmol) as described above: white solid; mp 157−159 °C (0.58 g, 70% yield).

3-Fluoro-6-chloroflavone (3b).[16] Compound **2b** was flash chromatographed resulting in a white solid: mp 169−172 °C (0.51 g, 95% yield).

6-Acetoxyflavone (1c)[26] was prepared by reacting a solution of 6-hydroxyflavone (1.30 g, 5.5 mmol) in pyridine with acetic anhydride, and the mixture was stirred overnight: white solid; mp 157−158 °C (1.01 g, 66% yield).

5,7-Diacetoxyflavone (1d)[27] was prepared in a similar manner (as for **1c**) using chrysin (1.27 g, 5.0 mmol) as a starting material: white solid; mp 203−205 °C (1.5 g, 88% yield).

2,3-Difluoro-6-acetoxy-4-flavanone (2c) was prepared from 6-acetoxyflavone (**1c**) (0.43 g, 1.5 mmol) as described above: white solid; mp 148−149 °C (0.32 g, 65% yield); ^{1}H NMR 7.71−7.69 (m, 2 H), 7.68 (d, J = 2.8 Hz, 1 H), 7.52−7.53 (m, 3 H), 7.37 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1 H), 7.18 (d, J = 8.9 Hz, 1 H), 5.44 (dd, J_1 = 28.0 Hz, J_2 = 45.5 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR 185.2 (d, J = 16.9 Hz), 169.4, 153.8, 146.7, 133.8 (d, J = 25.2 Hz), 131.0, 130.8, 128.8, 126.1 (d, J = 6.6 Hz), 120.2, 119.7, 119.6, 114.0 (dd, J_1 = 21.9 Hz, J_2 = 237.5 Hz), 90.4 (dd, J_1 = 33.1 Hz, J_2 = 203.1 Hz), 21.1; ^{19}F NMR −129.1 (dd, J_1 = 28.1 Hz, J_2 = 15.2 Hz), −213.2 (dd, J_1 = 45.4 Hz, J_2 = 15.8 Hz); HRMS with atmospheric solid analysis probe (ASAP) m/z calcd for $C_{17}H_{12}F_2O_4$ 319.0782 $(M + H)^+$, found 319.0779; IR 1759, 1719 cm^{-1}. Anal. Calcd for $C_{17}H_{12}F_2O_4$: C, 64.15; H, 3.80; F, 11.94. Found: C, 63.86; H, 3.49; F, 12.27.

3-Fluoro-6-acetoxyflavone (3c) was formed by treating **2c** with $BF_3{\cdot}OEt_2$: white solid; mp 184−185 °C (0.25 g, 85% yield); ^{1}H NMR 8.04−8.01 (m, 2 H), 7.99 (d, J = 2.7 Hz, 1 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.58−7.56 (m, 3 H), 7.48 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1 H), 2.36 (s, 3 H); ^{13}C NMR 170.4 (d, J = 16.9 Hz), 169.3, 152.8, 151.3 (d, J = 24.2 Hz), 147.7, 146.2 (d, J = 248.8 Hz), 131.8, 129.1, 128.8 (d, J = 4.9 Hz), 128.5, 128.3 (d, J = 7.7 Hz), 125.2 (d, J = 7.5 Hz), 119.7, 118.0 (d, J = 3.2 Hz), 21.1; ^{19}F NMR −161.5; HRMS (ASAP) m/z calcd for $C_{17}H_{11}FO_4$ 299.0720 $(M + H)^+$, found 299.0725; IR 1764, 1645 cm^{-1}. Anal. Calcd for $C_{17}H_{11}FO_4$: F, 6.37. Found: F, 6.07.

3-Fluoro-5,7-diacetoxyflavone (3d) was prepared from 2,3-difluoro-5,7-diacetoxyflavone (**2d**) whose stability did not permit analytical purification and therefore was used immediately upon formation from **1d** (0.58 g, 1.7 mmol) as described above. Compound **3d** (0.38 g) is a white solid, mp 205−207 °C, 63% yield based on **1d**; ^{1}H NMR 7.98−7.96 (m, 2 H), 7.57−7.55 (m, 3 H), 7.38 (d, J = 2.1 Hz, 1 H), 6.88 (d, J = 1.9 Hz, 1 H), 2.47 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR 169.6, 169.3 (d, J = 18.4 Hz), 168.0, 156.7, 154.4, 150.6 (d, J = 2.7 Hz), 150.3(d, J = 25.0 Hz), 146.3 (d, J = 247.3 Hz), 131.9, 129.1, 128.4 (d, J = 5.5 Hz), 128.1 (d, J = 7.6 Hz), 115.4 (d, J = 6.3 Hz), 113.9, 109.2, 21.3, 21.2; ^{19}F NMR −161.6; HRMS (ESI) m/z calcd for

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$C_{19}H_{13}FO_6$ 379.0594 (M + Na)$^+$, found 379.0596; IR 1768, 1649 cm^{-1}.

3-Fluoro-5-hydroxy-7-acetoxyflavone (3e) was formed by treating the crude **2d** with BF_3·OEt_2. The determination of which acetate was hydrolyzed was made by comparing ^{1}H NMR spectra of **3d** and **3e**. Hydrolysis of acetate in position 5 did not affect the aromatic hydrogen in position 8, and the methyl of the acetate in this position disappeared: beige solid; mp 184−186 °C (0.26 g, 49% yield); ^{1}H NMR 8.00−7.98 (m, 2 H), 7.58−7.56 (m, 3 H), 6.89 (d, J = 2.0 Hz, 1 H), 6.61 (d, J = 2.0 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR 174.9 (d, J = 17.6 Hz), 168.4, 161.9 (d, J = 3.0 Hz), 156.5, 155.8, 152.2 (d, J = 23.3 Hz), 144.6 (d, J = 248.9 Hz), 132.2 (d, J = 1.3 Hz), 129.2, 128.3 (d, J = 7.8 Hz), 109.5 (d, J = 6.4 Hz), 105.5, 101.4, 21.3; ^{19}F NMR −163.7; HRMS (ESI) m/z calcd for $C_{17}H_{11}FO_5$ 337.0488 (M + Na)$^+$, found 337.0486; IR 1767, 1651 cm^{-1}.

3-Fluorochromone (6a)[29] was prepared from chromone (**4a**) (0.69 g, 4.7 mmol) as described above: white solid; mp 138−140 °C (0.58 g, 75% yield); ^{1}H NMR 8.30 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1 H), 8.16 (d, J = 3.4 Hz, 1 H), 7.71 (t, J = 7.8 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 1 H); ^{13}C NMR 170.7 (d, J = 15.6 Hz), 156.0, 149.5 (d, J = 248.9 Hz), 143.0 (d, J = 39.9 Hz), 134.2, 126.2, 125.4, 125.0 (d, J = 7.6 Hz), 118.5; ^{19}F NMR −166.2; HRMS (ASAP) m/z calcd for $C_9H_5FO_2$ 165.0352 (M + H)$^+$, found 165.0357; IR 1652 cm^{-1}.

2,3-Difluoro-6-bromo-4-chromanone (5b) was prepared from 6-bromochromone (**4b**) (0.81 g, 3.6 mmol) as described above. A crude oil containing the product in 80% yield (GC, 0.76 g) was immediately characterized without any purification since it tends to eliminate HF spontaneously: HRMS (ASAP) m/z calcd for $C_9H_5BrF_2O_2$ 262.9519 (M + H)$^+$, found 262.9515.

3-Fluoro-6-bromochromone (6b) was prepared from **5b** (0.81 g, 3.6 mmol) as described above: white solid; mp 163 °C dec (0.66 g, 95% yield); ^{1}H NMR 8.43 (d, J = 2.4 Hz, 1 H), 8.16 (d, J = 3.3 Hz, 1 H), 7.79 (dd, J_1 = 8.9, J_2 = 2.4 Hz, 1 H), 7.42 (d, J = 8.9 Hz, 1 H); ^{13}C NMR 169.4 (d, J = 14.3 Hz), 154.7, 149.5 (d, J = 250.5 Hz), 143.3 (d, J = 40.0 Hz),137.3, 128.7 (d, J = 3.2 Hz), 126.3 (d, J = 8.1 Hz), 120.5, 119.1; ^{19}F NMR −165.3; HRMS (ASAP) m/z calcd for $C_9H_4BrFO_2$ 242.9457 (M + H)$^+$, found 242.9453; IR 1651 cm^{-1}. Anal. Calcd for $C_9H_4BrFO_2$: F, 7.82. Found: F, 7.95.

2,3,6-Trifluoro-4-chromanone (5c) was prepared from 6-fluorochromone (**4c**) (0.75 g, 4.6 mmol) as described above. A crude oil containing the product in 82% yield (GC, 0.76 g) was immediately characterized without any purification since it tends to eliminate HF spontaneously: HRMS (ASAP) m/z calcd for $C_9H_5F_3O_2$ 203.0320 (M + H)$^+$, found 203.0322.

3,6-Difluorochromone (6c) was prepared from **5c** (0.75 g, 4.6 mmol) as described above: white solid; mp 170−172 °C (0.67 g, 98% yield); ^{1}H NMR 8.17 (d, J = 3.3 Hz, 1 H), 7.93 (dd, J_1 = 8.1 Hz, J_2 = 3.1 Hz, 1 H), 7.55−7.52 (m, 1H), 7.47−7.42 (m, 1H); ^{13}C NMR 169.8 (dd, J_1 = 16.0 Hz, J_2 = 2.3 Hz), 159.7 (d, J = 247.9 Hz), 152.2, 149.2 (dd, J_1 = 249.0 Hz, J_2 = 1.6 Hz),143.3 (d, J = 40.0 Hz), 126.3 (t, J = 8.1 Hz), 122.7 (d, J = 25.7 Hz), 120.7 (d, J = 8.3 Hz), 111.0 (dd, J_1 = 24.2 Hz, J_2 = 3.8 Hz); ^{19}F NMR −115.0, −166.6; HRMS (ESI) m/z calcd for $C_9H_4F_2O_2$ 183.0258 (M + H)$^+$, found 183.0253; IR 1640 cm^{-1}. Anal. Calcd for $C_9H_4F_2O_2$: C, 59.35; H, 2.21; F, 20.86. Found: C, 58.96; H, 1.90; F, 20.98.

2,3-Difluoro-3-methyl-4-chromanone (5d) was prepared from 3-methylchromone (**4d**) (0.82 g, 3.6 mmol): white solid; mp 87−90 °C (0.62 g, 65% yield); ^{1}H NMR 7.82 (d, J = 2.5 Hz, 1 H), 7.68 (d, J = 2.5 Hz, 1 H), 6.07 (dd, J_1 = 52.9 Hz, J_2 = 0.7 Hz, 1 H), 1.70 (dd, J_1 = 21.4 Hz, J_2 = 1.1 Hz, 1 H); ^{13}C NMR 186.7 (d, J = 18.0 Hz), 149.5, 137.2, 129.9, 125.5 (d, J = 1.7 Hz), 124.8, 121.0 (d, J = 2.2 Hz), 109.2 (dd, J_1 = 240.7 Hz, J_2 = 27.9 Hz), 91.0 (dd, J_1 = 198.0 Hz, J_2 = 24.8 Hz), 19.1 (dd, J_1 = 24.0 Hz, J_2 = 4.7 Hz),; ^{19}F NMR −145.2 (dd, J_1 = 52.8 Hz, J_2 = 16.4 Hz), −178.3 (m); HRMS (ASAP) m/z calcd for $C_{10}H_6Cl_2F_2O_2$ 266.9791 (M + H)$^+$, found 266.9787; IR 1720 cm^{-1}. Anal. Calcd for $C_{10}H_6Cl_2F_2O_2$: C, 44.98; H, 2.26; Cl, 26.55. Found: C, 45.04; H, 2.30; Cl, 26.48.

2,3-Difluoro-3-bromo-4-chromanone (5e) was prepared from 3-bromochromone (**4e**) (0.64 g, 2.8 mmol): colorless liquid (0.48 g, 64% yield); ^{1}H NMR 8.01 (dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1 H), 7.69−7.65 (m, 1 H), 7.29−7.25 (m, 1 H), 7.13 (dd, J_1= 8.4 Hz, J_2 = 0.6 Hz, 1 H), 6.29 (d, J = 53.8 Hz, 1 H); ^{13}C NMR 179.9 (d, J = 20.0 Hz), 154.3, 138.1, 128.3 (d, J = 1.5 Hz), 124.7, 118.6, 117.5, 108.0 (dd, J_1 = 239.6 Hz, J_2 = 28.0 Hz), 91.0 (dd, J_1 = 277.0 Hz, J_2 = 33.2 Hz); ^{19}F NMR −138.3 (dd, J_1 = 54.0 Hz, J_2 = 17.6 Hz), −147.6 (d, J = 17.6 Hz); HRMS (ASAP) m/z calcd for $C_9H_5BrF_2O_2$ 262.9519 (M + H)$^+$, found 262.9524; IR 1718 cm^{-1}. Anal. Calcd for $C_9H_5BrF_2O_2$: C, 41.10; H, 1.92; F, 14.45. Found: C, 40.86; H, 2.11; F, 14.64.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra and GC data. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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