

Selectfluor-Mediated Tandem Cyclization of Enaminones for the Synthesis of 3-Fluorochromones

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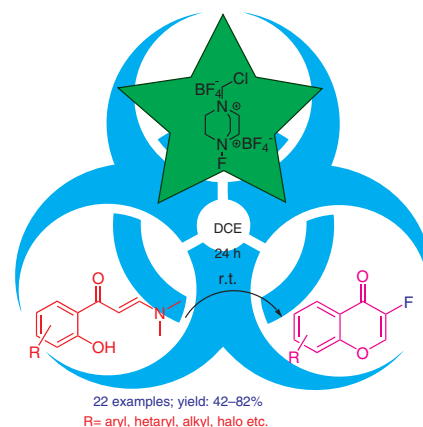
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Abstract An efficient synthesis of various 3-fluorochromones (3-fluoro-4*H*-chromene-4-ones) from enaminones by using Selectfluor is described. The key step in the synthesis involves tandem fluorination and cyclization to form 3-fluorochromones in good yields. The significant features of this method include simple operational procedures, a high purity of the product, and excellent regioselectivity.

Keywords fluorochromones, enamino ketones, fluorination, Selectfluor

Chromone derivatives have a wide range of applications in medicinal chemistry.¹ Their biological activities include tyrosine and protein kinase inhibitory,^{2,3} antiinflammatory,⁴ antiviral,⁵ antioxidant, and antihypertensive activities,⁶ as well as activities toward benzodiazepine receptors,⁷ lipoxygenases, and cyclooxygenases.⁸ Chromone derivatives have been used as anticancer agents⁹ and in the treatment of cystic fibrosis, as they activate the cystic fibrosis transmembrane conductance regulator.¹⁰ The vast range of biological effects associated with chromones has led to the chromone ring system being considered a privileged structure.¹¹ Examples of bioactive molecules derived from chroman-4-ones that have a range of applications in medicinal chemistry are shown in Figure 1.¹²

Organic compounds in which hydrogen atoms are replaced by fluorine atoms have unique physical, chemical, and biological properties. Such fluorocarbon compounds play a central role in drug development due to their greater probability of transformation into drug candidates.^{13,14} Moreover, fluorine-18 is used in radiolabeling of biomolecules for positron emission tomography.¹⁵ For these rea-

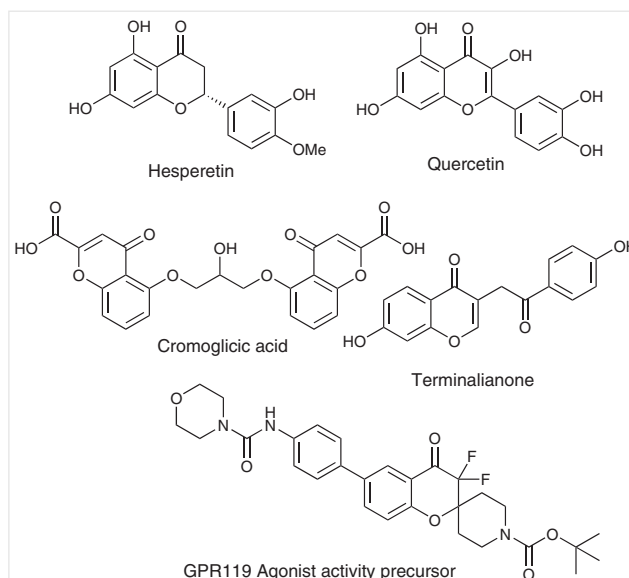


Figure 1 Biologically active chroman-4-one derivatives

sons, synthetic methods for the efficient installation of fluorine onto organic compounds have attracted considerable attention. In particular, the Kirk group has shown that many fluorine-containing compounds have significant biological activities,¹⁶ and they have been actively pursuing research on organofluorine chemistry over recent decades.¹⁷

The preparation of chromone derivatives has also generated great interest.¹⁸ Generally, 3-substituted chromones are synthesized by two different methods.¹⁹ The first approach involves addition of a substituent to a preformed chromone moiety. The second method commences with a *o*-hydroxyacetophenone, with subsequent cyclization to

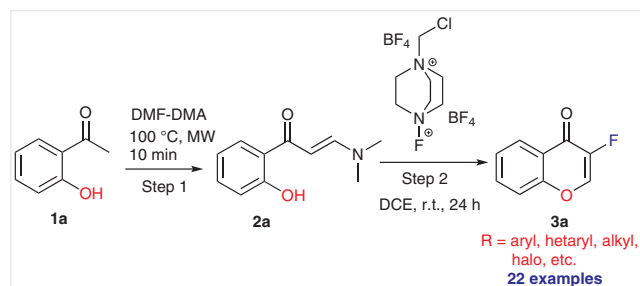
form the pyranone ring. Nevertheless, there is still a need for novel synthetic methods for the manipulation of the core structure of chromones.

Due its ease of introduction and its biological effects, the CF_3 group is widely used in medicinal chemistry,²⁰ moreover, it can be regarded as a bioisostere for a chloro or a methyl group. Fluorine has a high electronegativity, a relatively small size, and very low polarizability.^{13b} Installation of one or more fluorine atoms into an organic molecule usually improves its binding, absorption, and transportation properties in biological situations.²¹

There are several indirect methods for preparing 3-fluorinated chromones (Scheme 1).^{22,23} A general approach involves condensing an *o*-hydroxyacetophenone derivative^{10,11} with an aldehyde and an aniline containing a difluorochloro moiety.²⁴ Fuchigami and co-workers adopted a different approach of electrochemically fluorinating flavones with $\text{Et}_3\text{N}\cdot 3\text{HF}$ or $\text{Et}_4\text{N}\cdot 4\text{HF}$;²⁵ however, yields were relatively low and the synthetic route was not universally applicable. Rozen and co-workers demonstrated that one should not be intimidated by diluted F_2 ,²⁶ and they reported the preparation of 3-fluorochromone by using elemental fluorine in a two-step synthetic sequence.²⁷ The difluoro derivatives obtained in the first step were dehydrofluorinated in the second step to form the corresponding 3-fluo-

rochromones. An expedient and mild strategy for the synthesis of 3,3-difluorochroman-4-ones using Selectfluor has recently been reported.²⁸

In our work on hybrid molecules,²⁹ we needed to synthesize a number of chromone derivatives. Inspired by the work of Song and co-workers,²⁸ we surmised that Selectfluor {1,4-bis(chloromethyl)-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}³⁰ might be used for both the cyclization and fluorination of enamino ketones to give 3-fluorochromones, taking advantage of a suitably positioned hydroxy group on the aromatic ring. Here, we report the synthesis of chromone analogues by using Selectfluor (Scheme 2). This is the first example of the use of Selectfluor in the synthesis of 3-fluorochromones from enaminones.



Scheme 2 Preparation of 3-fluorochromones by using Selectfluor

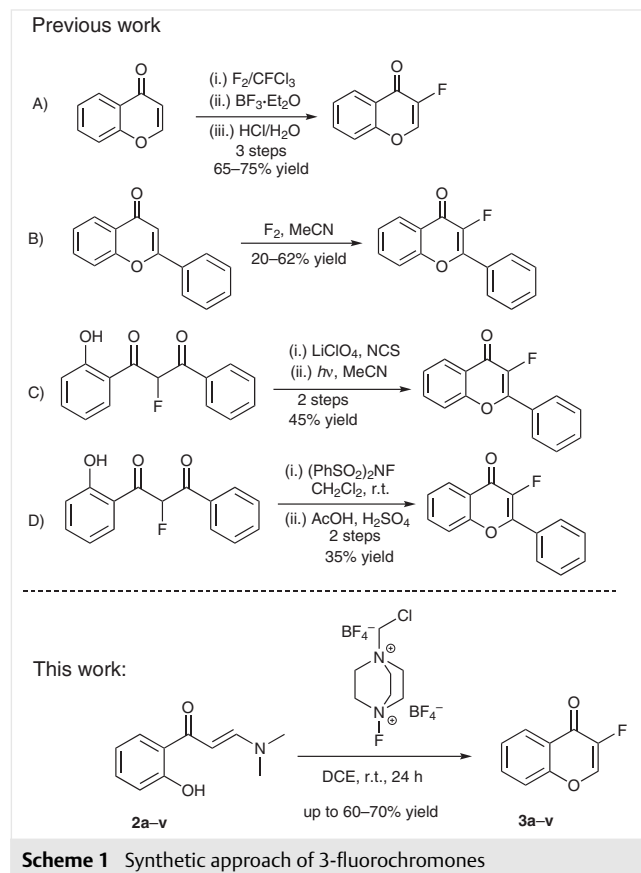
Initially, we prepared the enaminone **2a** by treating *o*-hydroxyacetophenone (**1a**) with *N,N*-dimethyl formamide dimethyl acetal (DMF-DMA) in toluene under reflux. Compound **2a** was fully characterized by ^1H NMR and LC-

Table 1 Screening of the Optimal Conditions^a

| Entry | Reaction conditions | Yield ^a (%) |
|-------|--|------------------------|
| 1 | DCE, r.t., 24 h | – |
| 2 | Selectfluor (1.0 equiv), DCE, r.t., 24 h | 46 |
| 3 | Selectfluor (1.0 equiv), DCE, r.t., 48 h | 48 |
| 4 | Selectfluor (1.0 equiv), DCE, 70 °C, 24 h | 39 |
| 5 | Selectfluor (2.0 equiv), DCE, r.t., 24 h | 82 |
| 6 | Selectfluor (3.0 equiv), DCE, 70 °C, 24 h | 36 |
| 7 | Selectfluor (2.0 equiv), DCE, 100 °C, 24 h | 30 |
| 8 | Selectfluor (2.0 equiv), DMF, 70 °C, 24 h | 61 |
| 9 | Selectfluor (2.0 equiv), 1,4-dioxane, 70 °C, 24 h | 37 |
| 10 | Selectfluor (2.0 equiv), MeCN, 70 °C, 24 h | 32 |
| 11 | Selectfluor (2.0 equiv), MeCN, r.t., 24 h | 62 |
| 12 | Selectfluor (2.0 equiv), MeCN, r.t., 48 h | 77 |
| 13 | Selectfluor (2.0 equiv), H_2O , 70 °C, 24 h | 62 ^b |
| 14 | Selectfluor (2.0 equiv), CH_2Cl_2 , r.t., 24 h | 25 |
| 15 | Selectfluor (2.0 equiv), CH_2Cl_2 , r.t., 24 h | 31 |

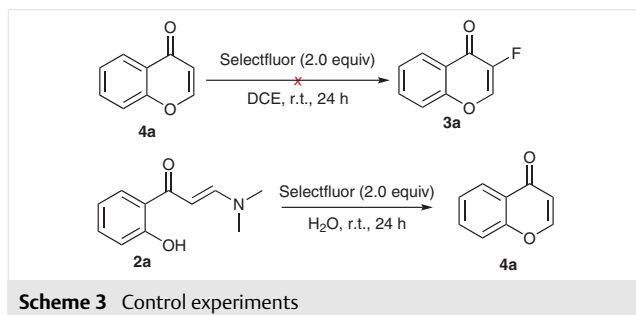
^a Yield of the isolated product.

^b The nonfluorinated chromone **4a** was obtained (see below).



Scheme 1 Synthetic approach of 3-fluorochromones

MS analysis. In particular, a resonance at $\delta = 8.2$ ppm in the ^1H NMR spectrum corresponded to the olefinic proton. The conversion of enamino ketone **2a** into 3-fluoro-4H-chromen-4-one (**3a**) in the presence of Selectfluor was chosen as a model reaction for the purpose of optimizing the conditions (Table 1). When enaminone **2a** (1 mmol) was treated with Selectfluor (1 equiv) in dichloroethane at room temperature for 24 hours, we were pleased to find that Selectfluor did indeed mediate the desired fluorocyclization (Table 1, entry 2). Under these conditions, the reaction provided a 46% conversion of **2a** into the desired chromone product **3a** after 24 hours. Compound **3a** was fully characterized by standard spectroscopic techniques (IR and ^1H and ^{13}C NMR). Because no other byproducts were formed, as evidenced by LC-MS analysis, the reaction was allowed to continue at room temperature; however, even after 48 hours, there was little increase in the yield of the product (48%; entry 3). Encouraged by these result, we attempted to optimize the reaction condition by changing the amount of Selectfluor, the reaction temperature, the solvent, and the duration of reaction (Table 1). A 77% yield of product **3a** was obtained by using two equivalents of Selectfluor in MeCN as the solvent at room temperature for 48 hours.



Finally, to demonstrate that the reaction proceeds via the enaminone, we conducted a control experiment (Scheme 3). As expected, treating the chromone **4a** with Selectfluor in DCE did not give any **3a**. Interestingly, however,

chromone **4a** was obtained when enaminone **2a** was treated with Selectfluor in water as the solvent (see also Table 1, entry 13).

To establish the generality of this method, the reactions of various substituted aryl and hetaryl ketones were examined, and the results are summarized in Table 2. High yields were obtained for substrates having alkyl (**3b**, **3f**, **3p**, **3q**) or halo groups (**3c**, **3d**, **3o**) in the 6-position. More importantly, the previously inaccessible naphthalene analogue **3e** and the substituted pyrazole analogue **3r** were synthesized in yields of 62 and 52%, respectively. The pyridochromone derivative **3n** was also synthesized in 42% yield. Among these 3-fluorochromone derivatives, three molecules²⁷ (**3a**, **3c**, and **3d**) are known molecules; all the others are new.

To demonstrate the versatility of the fluorocyclization reaction, we next explored the possibility of employing our method to synthesize a chroman–chromone hybrid, starting with resorcinol (**5**) (Scheme 4). The reaction of **5** with 2-methylbut-3-en-2-ol (**6**) in HCO_2H gave the chromanol **7**, which was treated with acetyl chloride at -10°C to afford the 6-acetylchromanol **8** in 70% yield.³¹ Treatment of **8** with DMF-DMA at 100°C under microwave conditions gave enaminone **9**, which underwent fluorocyclization with Selectfluor in DCE to give the novel chroman–chromone hybrid **3v** in 51% yield. The product was characterized by ^1H NMR, ^{13}C NMR, and LC-MS analyses.

In summary, we have developed a novel, efficient, and reproducible Selectfluor-mediated reaction for the synthesis of 3-fluorochromones from readily available *o*-hydroxyacetophenones.³² This approach offers an alternative to the use of elemental fluorine, which had previously been used for the fluorination of chromones. The reaction conditions are sufficiently mild to tolerate a range of functional groups, providing the potential for further functionalization of the chromone products.

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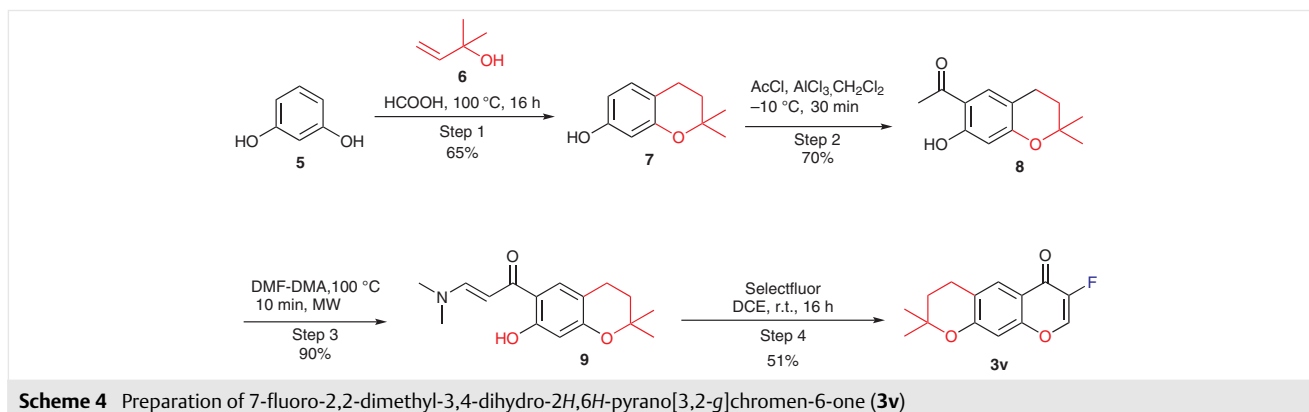
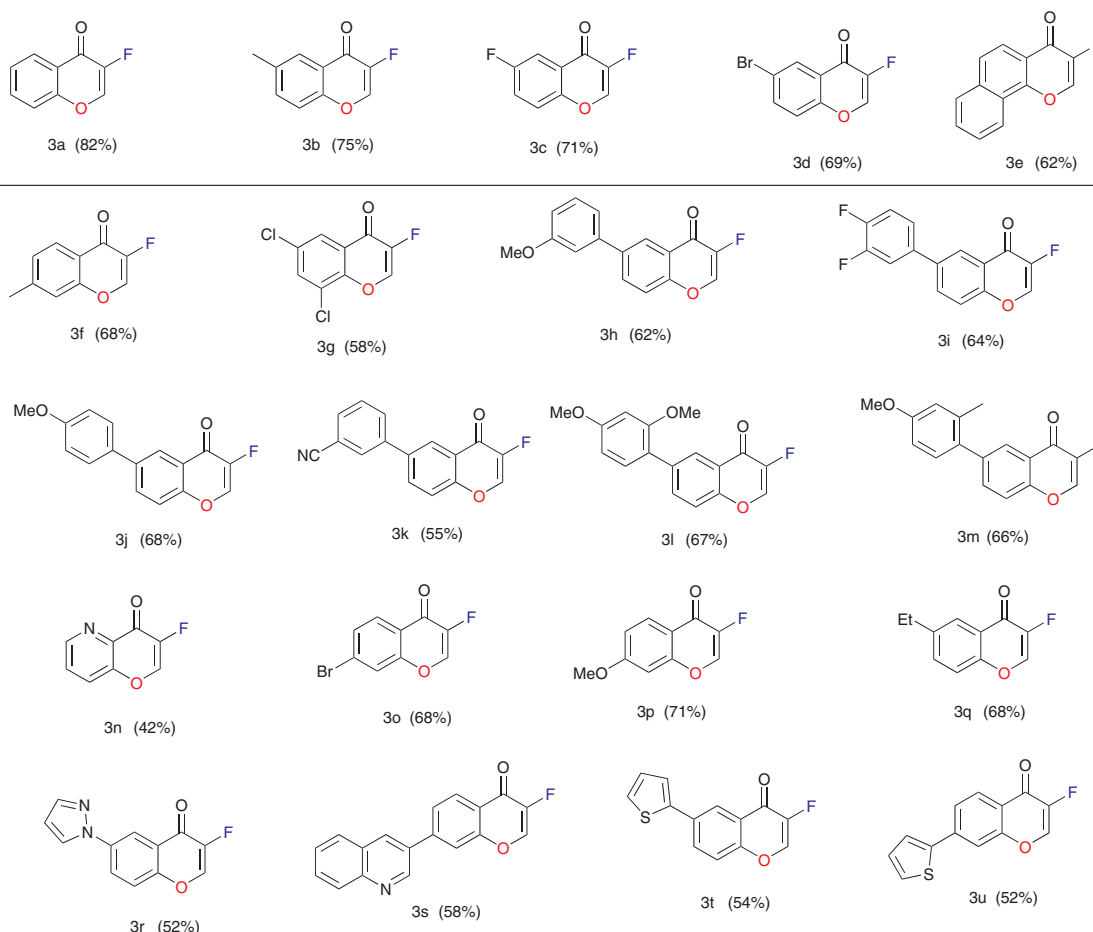


Table 2 3-Fluorochromones Synthesized



^a Reaction conditions: enamionone **2** (1.0 equiv), Selectfluor (2 equiv), DCE, r.t., 24 h.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1691489>.

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- (32) **3-Fluoro-4H-chromen-4-one (3a); Typical Procedure**
Selectfluor (708 mg, 2 mmol) was added to a stirred solution of enaminone **2a** (191 mg, 1 mmol) in DCE (5 mL) at 0 °C, and the mixture (a white suspension) was stirred at r.t. for 24 h. When the reaction was complete (TLC, 30% EtOAc-PE), the mixture was poured into ice-cold water and stirred for 10 min. The mixture was then extracted with EtOAc (3 ×) and the combined organic layers were washed with water and brine, then dried (Na₂SO₄), filtered, and concentrated. The resulting crude product was purified by flash column chromatography [silica gel (100–200 mesh), 15–20% EtOAc-PE] to give an off-white solid; yield: 135 mg (82%); mp 158–162 °C.
IR (KBr): 3084, 2967, 1814, 1709, 1587, 1483, 1395, 1194, 955, 753 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 8.96 (d, *J* = 4 Hz, 1 H), 8.16 (d, *J* = 8 Hz, 1 H), 7.87 (t, *J* = 8.5 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 169.4 (d, *J* = 15.5 Hz), 155.3, 149.6 (d, *J* = 242.2 Hz), 147.7, 145.1 (d, *J* = 40.6 Hz), 134.5, 125.5, 124.2, 118.7. ¹⁹F NMR (470 MHz, CDCl₃): δ = -165.7. MS (EI): *m/z* (%) = 165 [M + 1]⁺ (100).