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

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Abstract  An efficient synthesis of various 3-fluorochromones (3-fluoro-4H-chromene-4-ones) from enamino ketones 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.\textsuperscript{1} Their biological activities include tyrosine and protein kinase inhibitory,\textsuperscript{2,3} antiinflammatory,\textsuperscript{4} antiviral,\textsuperscript{5} antioxidant, and antihypertensive activities,\textsuperscript{6} as well as activities toward benzodiazepine receptors,\textsuperscript{7} lipoxigenases, and cyclooxygenases.\textsuperscript{8} Chromone derivatives have been used as anticancer agents\textsuperscript{9} and in the treatment of cystic fibrosis, as they activate the cystic fibrosis transmembrane conductance regulator.\textsuperscript{10} The vast range of biological effects associated with chromones has led to the chromone ring system being considered a privileged structure.\textsuperscript{11} Examples of bioactive molecules derived from chroman-4-ones that have a range of applications in medicinal chemistry are shown in Figure 1.\textsuperscript{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.\textsuperscript{13,14} Moreover, fluorine-18 is used in radiolabeling of biomolecules for positron emission tomography.\textsuperscript{15} For the these reasons, 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,\textsuperscript{16} and they have been actively pursuing research on organofluorine chemistry over recent decades.\textsuperscript{17}

The preparation of chromone derivatives has also generated great interest.\textsuperscript{18} Generally, 3-substituted chromones are synthesized by two different methods.\textsuperscript{19} The first approach involves addition of a substituent to a preformed chromone moiety. The second method commences with a 3-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 CF₃ 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 transporta-
tion 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 α-hydroxyacetophenone derivative¹⁰,¹¹ with an aldehyde and an aniline containing a difluoro or chloro moiety.²⁴ Fuchigami and co-workers adopted a different approach of electrochemically fluorinating flavones with Et₃N·3HF or Et₄NF·4HF;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 F₂,²⁶ 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-fluorochromones. 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 syn-
thesize 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 cycliza-
tion and fluorination of enamino ketones to give 3-fluoro-
chromones, taking advantage of a suitably positioned hy-
droxy group on the aromatic ring. Here, we report the syn-
thesis 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 enamines.

Initially, we prepared the enamino ketone 2a by treating α-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>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>DCE, r.t., 24 h</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Selectfluor (1.0 equiv), DCE, r.t., 24 h</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Selectfluor (1.0 equiv), DCE, r.t., 48 h</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor (1.0 equiv), DCE, 70 °C, 24 h</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>Selectfluor (2.0 equiv), DCE, r.t., 24 h</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Selectfluor (3.0 equiv), DCE, 70 °C, 24 h</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Selectfluor (2.0 equiv), DCE, 100 °C, 24 h</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>Selectfluor (2.0 equiv), DMF, 70 °C, 24 h</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>Selectfluor (2.0 equiv), 1,4-dioxane, 70 °C, 24 h</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>Selectfluor (2.0 equiv), MeCN, 70 °C, 24 h</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>Selectfluor (2.0 equiv), MeCN, r.t., 24 h</td>
<td>62</td>
</tr>
<tr>
<td>12</td>
<td>Selectfluor (2.0 equiv), MeCN, r.t., 48 h</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>Selectfluor (2.0 equiv), H₂O, 70 °C, 24 h</td>
<td>62b</td>
</tr>
<tr>
<td>14</td>
<td>Selectfluor (2.0 equiv), CH₂Cl₂, r.t., 24 h</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>Selectfluor (2.0 equiv), CH₂Cl₂, r.t., 24 h</td>
<td>31</td>
</tr>
</tbody>
</table>

⁹ Yield of the isolated product.
³⁰ The nonfluorinated chromone 4a was obtained (see below).
and 13C NMR). Because no other byproducts were formed, 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 enamino 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 fluoroacyclization (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 13C 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 results, 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 enamino, 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 enamino 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 molecules (3a, 3c, and 3d) are known molecules; all the others are new.

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

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References and Notes

(21) 3-Fluoro-4H-chromen-4-one (3a); Typical Procedure Selectfluor (708 mg, 2 mmol) was added to a stirred solution of enamino 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.
(22) 1H NMR (500 MHz, DMSO-d6); 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 (t, J = 7.5 Hz, 1 H). 13C NMR (125 MHz, DMSO-d6); δ = 169.4 (d, J = 15.5 Hz), 153.9, 149.6 (d, J = 242 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 (ESI): m/z (%) = 165 [M + 1]+ (100).

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