



# Electrolytic partial fluorination of organic compounds. Part 45: Highly regioselective anodic monofluorination of (*E*)-3-benzylidene-2,3-dihydrochroman-4-ones<sup>†</sup>

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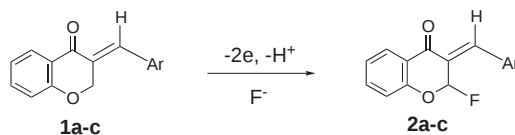
Received 9 January 2001; revised 29 January 2001; accepted 2 February 2001

**Abstract**—Anodic monofluorination at the position  $\alpha$  to the oxygen atom of chroman-4-one derivatives was successfully carried out: this is the first selective electrochemical fluorination of fused-type, oxygen-containing heterocyclic compounds. © 2001 Elsevier Science Ltd. All rights reserved.

Chroman-4-one derivatives have been known as inhibitors of HIV-1 that causes AIDS.<sup>2</sup> They have also drawn much attention due to their broad range of pharmacological activities.<sup>3</sup> Moreover, the biological potency of fluorinated heterocycles has been widely documented.<sup>4</sup> Therefore, considerable efforts have been made to explore new synthetic routes to fluorinated heterocycles. The electrochemical method was found

to be more applicable than the conventional, hazardous chemical methods.<sup>5</sup> Recently, we developed selective anodic fluorination of flavones<sup>6</sup> and arylthioethylenecarbonates<sup>7</sup> as examples of oxygen-containing heterocycles. Crown ethers were also anodically fluorinated; however,  $\alpha,\omega$ -difluoro products were formed due to ring opening.<sup>8</sup> On the other hand, furan, benzofuran,<sup>9</sup> and morpholines<sup>10</sup> were anodically fluori-

**Table 1.** Anodic fluorination of (*E*)-3-benzylidene-2,3-dihydrochroman-4-ones (**1a–c**)



**1,2;**    **a:** Ar = C<sub>6</sub>H<sub>5</sub>;    **b:** Ar = 4-ClC<sub>6</sub>H<sub>4</sub>;    **c:** Ar = 4-BrC<sub>6</sub>H<sub>4</sub>

| Run | Substrate | Supporting electrolyte/solvent            | Charge passed (F/mol) | Yield (%) <sup>a</sup> |
|-----|-----------|-------------------------------------------|-----------------------|------------------------|
| 1   | <b>1a</b> | Et <sub>4</sub> NF·4HF/DME                | 6.5                   | 72 (64)                |
| 2   | <b>1a</b> | Et <sub>4</sub> NF·4HF/DME <sup>b,c</sup> | 5.5                   | 17                     |
| 3   | <b>1a</b> | Et <sub>4</sub> NF·4HF/MeCN               | 3.0                   | 21                     |
| 4   | <b>1a</b> | Et <sub>4</sub> NF·3HF/DME                | 7.0                   | 68                     |
| 5   | <b>1a</b> | Et <sub>3</sub> N·4HF/DME                 | 8.5                   | 52                     |
| 6   | <b>1a</b> | Et <sub>3</sub> N·3HF/DME                 | 8.5                   | 35                     |
| 7   | <b>1b</b> | Et <sub>4</sub> NF·4HF/DME                | 7.0                   | 60 (56)                |
| 8   | <b>1c</b> | Et <sub>4</sub> NF·4HF/DME                | 6.5                   | 59 (58)                |

<sup>a</sup> Calculated on the basis of <sup>19</sup>F NMR spectra and the figures in parentheses are isolated yields.

<sup>b</sup> An undivided cell was used.

<sup>c</sup> A considerable amount of an unidentified, insoluble white polymeric product was formed.

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<sup>†</sup> For Part 44, see: Ref. 1.

nated; however, their fluorinated products were either not isolable due to their instability or were isolable in very low yields with less selectivity. Therefore, a successful selective anodic direct fluorination at position  $\alpha$  to a ring-oxygen atom has not yet been reported.

In this work, we successfully performed, for the first time, a highly regioselective anodic direct fluorination at the position  $\alpha$  to the ring-oxygen atom of the biologically active chroman-4-one derivatives **1a–c**. Anodic fluorination of (*E*)-3-benzylidene-2,3-dihydrochroman-4-one (**1a**), as a typical example, was conducted with platinum plate electrodes (2×2 cm<sup>2</sup>) in a 0.3 M solution of a fluoride salt in dimethoxyethane (30 ml) using a divided cell under a nitrogen atmosphere at room temperature. A constant current (6 mA/cm<sup>2</sup>) was applied until the starting material was completely consumed. The electrolysis results are summarized in Table 1. Only one fluorinated product was obtained and it was identified as (*E*)-3-benzylidene-2,3-dihydro-2-fluorochroman-4-one (**2a**) on the basis of its elemental analysis and spectral data.<sup>11</sup>

As shown in Table 1, a highly regioselective anodic monofluorination of **1a** took place regardless of the electrolytic conditions. It was found that a fluorine atom attacked selectively the position  $\alpha$  to the ring-oxygen atom of **1a** to furnish **2a** in moderate to good yields. Among various electrolytic conditions, Et<sub>4</sub>NF·4HF/DME using a divided cell (run 1) was the most effective for the formation of the fluorinated product **2a**.

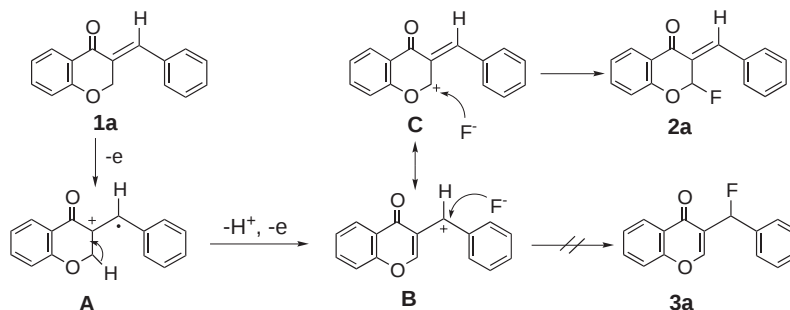
An undivided cell (run 2) was not suitable for anodic synthesis of **2a**. In this case, the fluorination yield decreased drastically due to the formation of an undesirable, insoluble white polymeric product. Acetonitrile (run 3) and Et<sub>3</sub>N·3HF (run 6) were also not effective. The regioselective monofluorination of **1a** is depicted in Scheme 1. It was reported that isomerization occurs

readily when the migrating double bond moves into conjugation with an aromatic benzene nucleus.<sup>12</sup> Therefore, it is conceivable that intermediate **B** isomerizes into **C**, followed by preferential attack of a fluoride ion to the cationic intermediate **C** to give **2a**. Benzylic nucleophilic substitution takes place easily; however, there was no evidence for the formation of the benzylic fluorinated product **3a**.

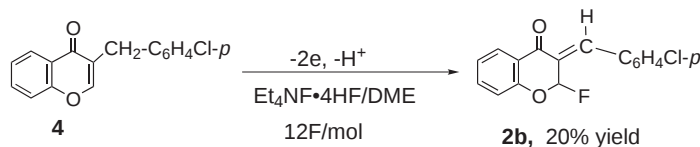
To generalize this interesting finding, we extended the anodic fluorination to other chroman-4-one derivatives **1b,c** and similar results were obtained, as shown in Table 1 (runs 7 and 8). In both cases, a fluorine atom was inserted selectively at the position  $\alpha$  to the ring-oxygen atom of **1b,c** to afford the corresponding 2-fluorochroman-4-ones **2b,c** in moderate yields.<sup>13,14</sup>

Furthermore, anodic fluorination of 3-(4-chlorobenzyl)chromone (**4**) was similarly attempted as shown in Scheme 2. Interestingly, **2b** was obtained in a reasonable yield, but the corresponding fluorinated product **5** was not formed. This result is in sharp contrast to our previous report for the anodic fluorination of flavones.<sup>6</sup> In the case of flavones, 3-fluoroflavones were formed. Thus, anodic fluorination of chromanone **1b** and homoisoflavone **4** provided the same fluorinated product **2b**. This result is quite interesting from a mechanistic point of view. A proposed mechanism for the anodic formation of **2b** from **4** is outlined in Scheme 3. A fluoride ion is assumed to attack the radical cation **D** to form **E**, which is further oxidized to give the fluorocarocation **F**, followed by elimination of a proton from the benzylic methylene group of **F** to afford the thermodynamically more stable<sup>15</sup> 2-fluorochroman-4-one derivative **2b** rather than its isomer **5**.

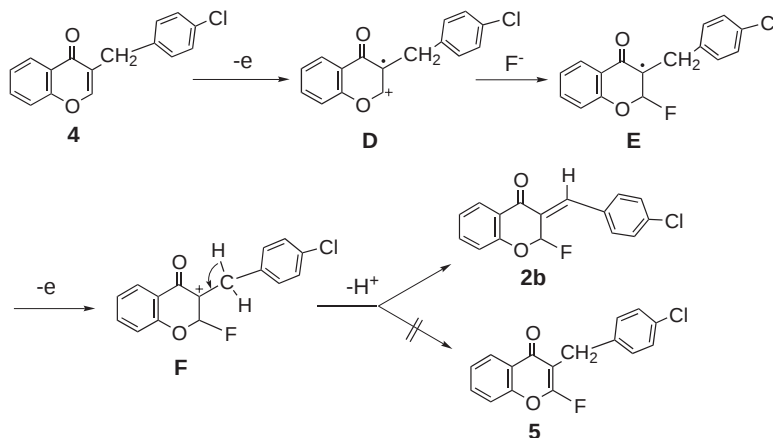
In conclusion, we have successfully conducted anodic fluorination at the position  $\alpha$  to the ring-oxygen atom of chroman-4-ones. This is the first report of successful



Scheme 1.



Scheme 2.



Scheme 3.

regioselective electrochemical direct fluorination of fused-type, oxygen-containing heterocyclic compounds where the methodology is of potential synthetic value.

### Acknowledgements

The authors would like to thank the Japan Society for the Promotion of Science (JSPS) for financial support (Grant-in-Aid for Scientific Research No. 1299307). They are also grateful to the Kato Foundation for financial support.

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- Compound **2a**: mp 69–70°C (AcOEt/hexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.76 (d, 1H,  $J=45.20$  Hz), 7.33–7.49 (m, 7H), 7.63 (dd, 1H,  $J=8.58$ , 7.26 Hz), 7.96 (s, 1H), 8.17 (d, 1H,  $J=7.92$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  87.75 (d,  $J=173.3$  Hz), 118.06, 123.77, 124.06, 125.33, 125.71, 126.19, 128.44, 128.68, 133.87, 137.48, 137.79, 153.53, 153.69, 156.15, 175.54;  $^{19}\text{F}$  NMR  $\delta$  -101.40 (d,  $J=45.04$  Hz); MS ( $m/z$ ) 254 ( $\text{M}^+$ ). Anal. calcd for  $\text{C}_{16}\text{H}_{11}\text{FO}_2$ : C, 75.58; H, 4.36. Found: C, 75.92, H, 4.55.
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- Compound **2b**: mp 93–94°C (AcOEt/hexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.69 (d, 1H,  $J=45.19$  Hz), 7.29–7.42 (m, 6H), 7.62 (dd, 1H,  $J=8.58$ , 6.93 Hz), 7.98 (s, 1H), 8.14 (d, 1H,  $J=7.91$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) (DEPT)  $\delta$  87.25 (d,  $J=173.3$  Hz), 118, 125.33, 125.53, 127.6, 127.7, 128.53, 133.89, 153.15, 153.33 ( $\text{CH}'\text{s}$ ), 123.29, 123.6, 134.44, 136.17, 156.04, 175.33 ( $\text{C}'\text{s}$ );  $^{19}\text{F}$  NMR  $\delta$  -102.50 (d,  $J=45.04$  Hz); MS ( $m/z$ ) 288 ( $\text{M}^+$ ). Anal. calcd for  $\text{C}_{16}\text{H}_{10}\text{ClFO}_2$ : C, 66.56; H, 3.49. Found: C, 66.74, H, 3.77.
- Compound **2c**: mp 80–81°C (AcOEt/hexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.69 (d, 1H,  $J=45.19$  Hz), 7.34–7.52 (m, 6H), 7.67 (dd, 1H,  $J=7.91$ , 6.93 Hz), 7.99 (s, 1H), 8.17 (d, 1H,  $J=7.92$  Hz);  $^{19}\text{F}$  NMR  $\delta$  -102.76 (d,  $J=45.04$  Hz); MS ( $m/z$ ) 333 ( $\text{M}^+$ ). Anal. calcd for  $\text{C}_{16}\text{H}_{10}\text{BrFO}_2$ : C, 57.68; H, 3.03. Found: C, 57.59, H, 3.25.
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