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

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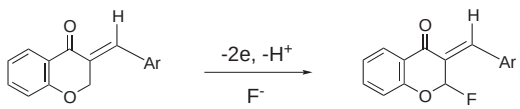
Abstract—Anodic monofluorination at the position α to the oxygen atom of chroman-4-one derivatives was successfully carried out: this is the first selective electrochemical fluorination of fused-type, oxygen-containing heterocyclic compounds.

Chroman-4-one derivatives have been known as inhibitors of HIV-1 that causes AIDS.[2] They have also drawn much attention due to their broad range of pharmacological activities.[3] Moreover, the biological potency of fluorinated heterocycles has been widely documented.[4] 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.[5] Recently, we developed selective anodic fluorination of flavones[6] and arylthioethylenecarbonates[7] as examples of oxygen-containing heterocycles. Crown ethers were also anodically fluorinated; however, α,ω-difluoro products were formed due to ring opening.[8] On the other hand, furan, benzofuran,[9] and morpholines[10] were anodically fluori-

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



1a-c **2a-c**

1,2; **a**: Ar = C_6H_5; **b**: Ar = 4-ClC_6H_4; **c**: Ar = 4-BrC_6H_4

Run	Substrate	Supporting electrolyte/solvent	Charge passed (F/mol)	Yield (%)[a]
1	**1a**	$Et_4NF{\cdot}4HF$/DME	6.5	72 (64)
2	**1a**	$Et_4NF{\cdot}4HF$/DME[b,c]	5.5	17
3	**1a**	$Et_4NF{\cdot}4HF$/MeCN	3.0	21
4	**1a**	$Et_4NF{\cdot}3HF$/DME	7.0	68
5	**1a**	$Et_3N{\cdot}4HF$/DME	8.5	52
6	**1a**	$Et_3N{\cdot}3HF$/DME	8.5	35
7	**1b**	$Et_4NF{\cdot}4HF$/DME	7.0	60 (56)
8	**1c**	$Et_4NF{\cdot}4HF$/DME	6.5	59 (58)

[a] Calculated on the basis of ^{19}F NMR spectra and the figures in parentheses are isolated yields.
[b] An undivided cell was used.
[c] A considerable amount of an unidentified, insoluble white polymeric product was formed.

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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 α 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 α 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^2) 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^2) 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.[11]

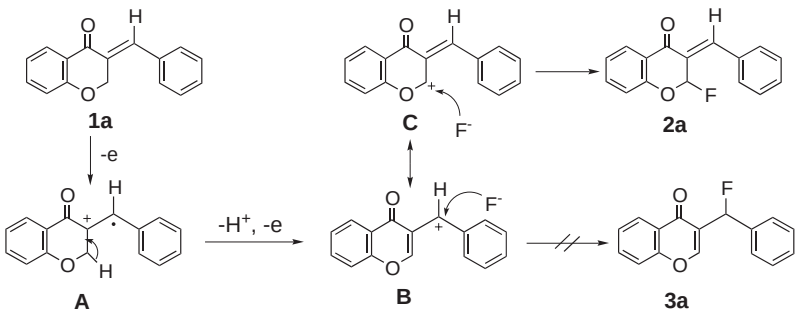
As shown in Table 1, a highly regioselective anodic monofluorination of **1a** took place regardless of the electrolytic conditions. It was found that a fluorine atom attacked selectively the position α to the ring-oxygen atom of **1a** to furnish **2a** in moderate to good yields. Among various electrolytic conditions, $Et_4NF{\cdot}4HF$/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 $Et_3N{\cdot}3HF$ (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.[12] 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**.

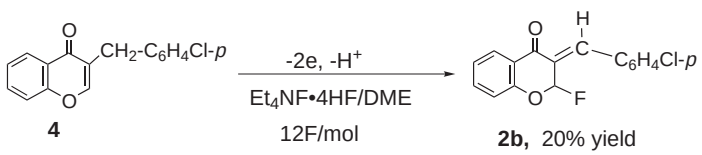
To generalize this interesting finding, we extended the anodic fluorination to other chroman-4-one derivatives **1b**,**c** and similar results were obtained, as shown in Table 1 (runs 7 and 8). In both cases, a fluorine atom was inserted selectively at the position α to the ring-oxygen atom of **1b**,**c**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

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.[6] 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 fluorocarbocation **F**, followed by elimination of a proton from the benzylic methylene group of **F** to afford the thermodynamically more stable[15] 2-fluorochroman-4-one derivative **2b** rather than its isomer **5**.

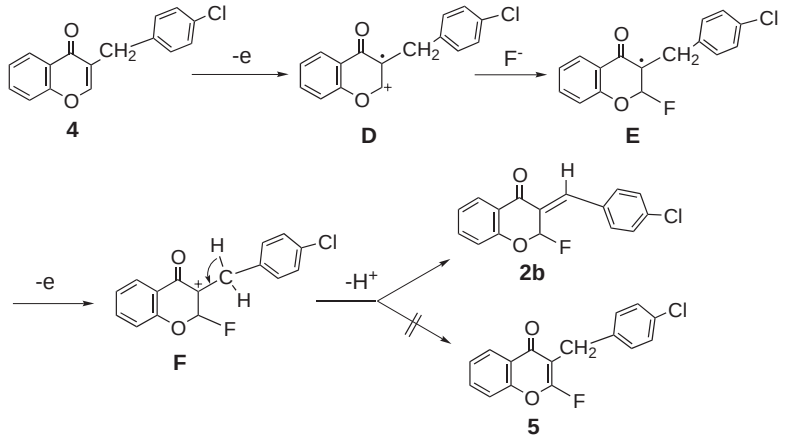
In conclusion, we have successfully conducted anodic fluorination at the position α to the ring-oxygen atom of chroman-4-ones. This is the first report of successful



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

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11. Compound **2a**: mp 69–70°C (AcOEt/hexane); ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) δ 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}F NMR δ −101.40 (d, J=45.04 Hz); MS (m/z) 254 (M^+). Anal. calcd for $C_{16}H_{11}FO_2$: C, 75.58; H, 4.36. Found: C, 75.92, H, 4.55.
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13. Compound **2b**: mp 93–94°C (AcOEt/hexane); ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) (DEPT) δ 87.25 (d, J=173.3 Hz), 118, 125.33, 125.53, 127.6, 127.7, 128.53, 133.89, 153.15, 153.33 (CH's), 123.29, 123.6, 134.44, 136.17, 156.04, 175.33 (C's); ^{19}F NMR δ −102.50 (d, J=45.04 Hz); MS (m/z) 288 (M^+). Anal. calcd for $C_{16}H_{10}ClFO_2$: C, 66.56; H, 3.49. Found: C, 66.74, H, 3.77.
14. Compound **2c**: mp 80–81°C (AcOEt/hexane); ^{1}H NMR ($CDCl_3$) δ 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}F NMR δ −102.76 (d, J=45.04 Hz); MS (m/z) 333 (M^+). Anal. calcd for $C_{16}H_{10}BrFO_2$: C, 57.68; H, 3.03. Found: C, 57.59, H, 3.25.
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