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Electrolytic Partial Fluorination of Organic Compounds. 13.[1] Selective Anodic α-Fluorination of Nitrogen-Containing Heterocyclic Sulfides and Its Application to the Synthesis of Fluorinated Fused Heterocycles

Ayman W. Erian,[2] Akinori Konno, and Toshio Fuchigami,*

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

Abstract: Highly regioselective anodic monofluorination of 2-pyridyl and 6-pyrimidinyl sulfides was successfully carried out and fluorinated fused heterocycles were readily prepared in good yields using an anodically fluorinated sulfide.

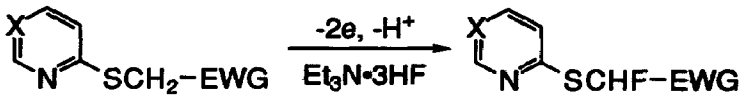
Efficient methods for the selective partial fluorination of organic compounds are becoming increasingly important in order to develop new type of medicines,[3-5] agricultural chemicals,[6] and functional materials.[7] Although a number of heterocyclic organofluorine compounds are reported to show unique biological activities,[3,5] their synthesis is not always straightforward.[8] Recently, we achieved anodic monofluorination of simple alkyl phenyl sulfides[9] and we also found that sulfides bearing electron-withdrawing groups underwent selective anodic fluorination quite efficiently.[10,11] These findings prompted us to attempt anodic fluorination of heterocyclic sulfides.

In this paper, we wish to report highly selective anodic fluorination of 2-pyridyl and 4-pyrimidinyl sulfides **1** and **2** bearing electron-withdrawing groups at the position α to the sulfur atom together with novel synthesis of fluorinated fused heterocycles using an anodically fluorinated sulfide.

Typical anodic fluorination conditions are as follows. Electrolysis was carried out at a platinum anode and cathode (2x3 cm^2) in 0.37 M $Et_3N{\cdot}3HF$/MeCN (15 ml) containing 1.5 mmol of heterocyclic sulfides **1** or **2** at ambient temperature. In order to avoid deposition of polymerized products on the anode, pulse electrolysis [applied potential (90 s)/0 V (10 s)] was performed. After the starting sulfide was completely consumed (TLC monitoring., the electrolysis solution was passed through a short column of silica gel (CH_2Cl_2). to provide almost pure monofluorinated product **3** or **4**. Results are summarized in Table 1.

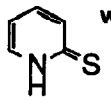
Anodic fluorination of sulfides **1** bearing electron-withdrawing groups proceeded smoothly to give the corresponding fluorinated products **3** in good yields. In these cases, the α-position to the sulfur atom of **1** was selectively monofluorinated. On the other hand, pyridyl sulfide **1c** devoid of an electron-withdrawing group gave only trace amount of a fluorinated product and a large amount of a by-product **5** due to the cleavage of a carbon-sulfur bond was formed. Although 4-pyrimidinyl sulfide **2** has a much higher oxidation potential compared to **1** and a large amount of electricity was required to complete the

Table 1. Anodic monofluorination of 2-pyridyl and 4-pyrimidinyl sulfides 1 and 2.



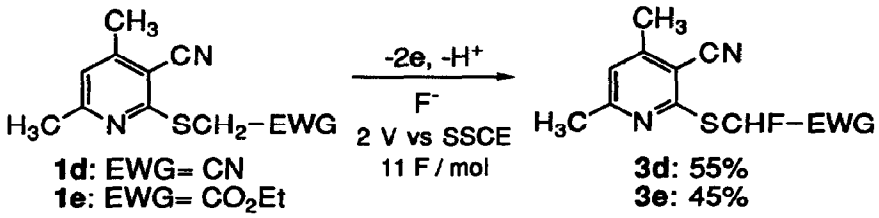
1, 2 3, 4

run		sulfide X	sulfide EWG	applied potential (V vs SSCE)	electricity (F / mol)	yield (%)
1	**1a**	CH	CN	1.6	5	**3a** (76)
2	**1b**	CH	CO_2Et	1.6	5	**3b** (76)
3	**1c**	CH	H	1.6	5	**3c** (trace)[a]
4	**2**	N	CO_2Et	2.2	11	**4** (55)

a) A large amount of by-product **5**,  was formed.

electrolysis, selective anodic fluorination of **2** was also successful (run 4). It is known that anodic fluorination of simple pyridine takes place at the pyridine ring.[12] We also found anodic fluorination at the pyridine ring of isonicotinic acid esters.[13] Therefore, it should be noted that the fluorination took place exclusively at the α-position to the sulfur atom of **1** and **2**.

Next, anodic fluorination of more complicated pyridyl sulfides **1d** and **1e** was attempted similarly as shown in Scheme 1. In these cases, the electricity required for the anodic fluorination was more than double compared to the cases of the corresponding simple pyridyl sulfides **1a** and **1b** since **1d** and **1e** have high oxidation potentials due to a strong electron-withdrawing cyano group at the pyridine ring. However, selective fluorination of these sulfides was also successful although the yield of **3e** was unsatisfactory.



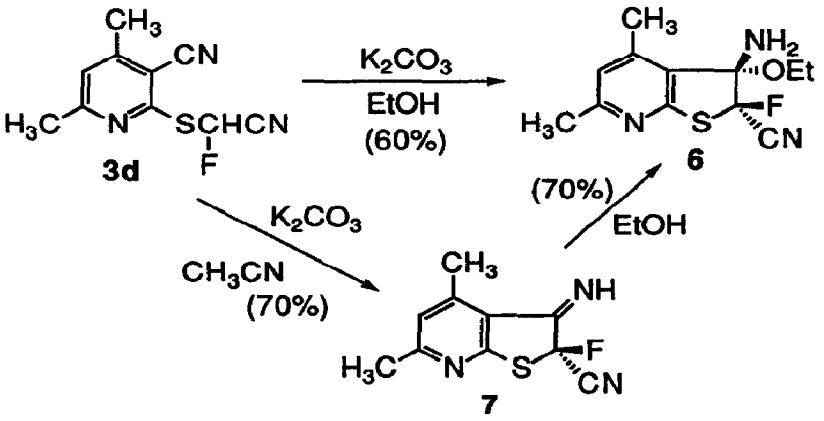
1d: EWG= CN
1e: EWG= CO_2Et

3d: 55%
3e: 45%

(Scheme 1)

Hitherto known fluorinating reagents are dangerous and/or costly, and require Teflon equipment.[8,14,15] In contrast, N-fluoropyridinium triflates have been shown to be safe and effective reagents.[16] However, fluorination of **1a** as a model compound with N-fluoropyridinium triflate and N-fluoro-3,5-dichloropyridinium triflate resulted in no formation of **3a**. Therefore, this electrochemical fluorination is much superior to a chemical method since the fluorination can be performed under mild conditions in a normal laboratory glassware without precautions .

In order to demonstrate the synthetic utility of the fluorinated products, cyclization of **3d** was attempted. It was found that treatment of **3d** with potassium carbonate in ethanol at ambient temperature afforded the fluorinated fused heterocyclic compound **6** in a relatively good yield as shown in Scheme 2. On the contrary, the cyclization in acetonitrile instead of ethanol provided the corresponding fused heterocyclic product **7** having an imino group in good yield. Since the compound **7** was readily converted into **6** by treatment of **7** in ethanol at room temperature, the fluorinated heterocyclic product **6** should be formed *via* **7** as an intermediate. N-Unsubstituted imines are usually unstable, however the imino group of **7** is relatively stable. Furthermore, the N,O-acetal moiety of **6** is also quite stable. These unusual stability seems to be owing to the strong electron-withdrawing effect of a cyano group and a fluorine atom.[17]



(Scheme 2)

Thus, we have developed novel synthesis of fluorinated fused heterocycles using anodic fluorination as a key step.

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