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ELECTROLYTIC PARTIAL FLUORINATION OF ORGANIC COMPOUNDS. 3.[1] REGIOSELECTIVE ANODIC MONOFLUORINATION OF ORGANOSELENIUM COMPOUNDS AND THEIR SYNTHETIC APPLICATION

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Summary : Regioselective anodic α-monofluorination of selenides bearing electron-withdrawing groups such as cyano, ester, and amide groups was successfully performed. Highly stereoselective synthesis of α-fluoro α,β-unsaturated esters was achieved by using an α-fluoro α-selenoester prepared.

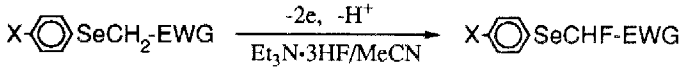
Recently, much interest has been paid to partially fluorinated compounds in the fields of material science and medicinal chemistry.[2] However, methodes for their preparation are limited in many cases.[3] Therefore, the development of methods for the partial fluorination of organic molecules are becoming greatly important. Electrochemical fluorination is attractive because fluorine atoms can be introduced into organic molecules in one step. Although anodic perfluorination is well-established, anodic partial fluorination has been undeveloped.[4]

Most recently, we[1,5] and Laurent *et al.*[6] have reported the anodic fluorination of sulfides at the α-position in the presence of the Et_3N·3HF complex which is rather stable to air and moisture. Although fluorinated sulfides are versatile building blocks, their oxidative desulfurization leading to fluoroolefines requires relatively high temperature.[7]

Here, we describe the first regioselective anodic fluorination of organoselenium compounds and its synthetic application to α-monofluoro α,β-unsaturated esters. Although the fluoroselenenylation of alkenes is well-known,[8] electrochemical fluorination of selenides has been unknown so far.[9]

In a typical anodic fluorination, constant potential electrolysis was carried out at platinum electrodes (3x4 cm) at room temperature in 0.37M Et_3N·3HF/MeCN (50 ml) containing 5 mmol of selenide **1** using an undivided or divided cell. After the starting selenide **1** was almost consumed (monitoring unreacted **1** by TLC and/or MS), the electrolysis solution was worked up by two ways as follows.
Method A: the electrolysis solution was neutralized with 12% aqueous ammonia immediately after the electrolysis.
Method B: the solution was left overnight and then concentrated under reduced pressure followed by neutralization with aqueous ammonia. After these procedures, extraction with CH_2Cl_2 and chromatography on silicagel (Hexane-AcOEt, 9:1-8:2) provided α-fluorinated selenide **2**. The results are summarized in Table 1.

Table 1. Anodic Monofluorination of Selenides



1 **2**

Run	Selenides			Type of Cell[a]	Anodic Potential (V vs SCE)	Charge Passed (F/mol)	Work up	Yield of **2** (%)
	No	X	EWG					
1	**1a**	H	CN	U	1.6-1.8	6.6	A	**2a** (71)
2	**1b**	H	COOEt	U	1.5	5.8	A	**2b** (70)
3	**1c**	Cl	COOEt	U	1.8-1.9	6.5	A	**2c** (81)
4	**1d**	MeO	COOEt	U	1.4-1.5	6.1	B	**2d** (51)
5	**1e**	H	$CONH_2$	U	1.6	4.0	A	**2e** (0)[b]
6	**1e**	H	$CONH_2$	Dg	1.6-1.7	2.4	A	**2e** (19)
7	**1e**	H	$CONH_2$	Di	1.5-1.6	3.5	B	**2e** (60)

a) U : undivided. Dg : divided with a sintered glass.
Di : divided with anion-exchange membrane (ACH-45T,Tokuyama Soda)
b) Considerable amount of diphenyl diselenide was formed.

Selenides bearing electron-withdrawing groups underwent anodic fluorination and a fluorine atom was introduced into α to the selenium atom selectively. On the other hand, compounds lacking an electron-withdrawing group such as benzyl phenyl selenide and methyl phenyl selenide failed to give fluorinated products. The former gave benzyl phenyl selenoxide and diphenyl diselenide as major products together with small amount of benzaldehyde. These results clearly indicate that an electron-withdrawing substituent α to the site of fluorination is necessary for the successful fluorination.

Substituent effect on the fluorination of α-selenoesters was remarkable. At the end of electrolysis, selenides **1b** and **1c** provided the corresponding α-fluorinated products **2b** and **2c** in good yields (run 2 and 3), while **1d** gave only trace amount of α-fluorinated product **2d**. However, interestingly after the electrolytic solution of **1d** was left overnight, a large amount of **2d** was formed (run 4).

Moreover, this fluorination was greatly affected by the type of cells as follows. In an undivided cell, α-selenoamide **1e** provided no α-fluorinated products. In this case, diphenyl diselenide was formed considerably and the electrolysis was not completed. When a divided cell equipped with a sintered glass diaphragm was used, desired fluorinated product **2e** could be obtained. However, the yield was still low and a large amount of diphenyl diselenide (26%) was formed. It should be notable that in this case, starting **1e**, diphenyl diselenide, and **2e** were detected considerably from the catholyte by TLC and MS. Without electrolysis, permeation of the substrate **1e** into the cathode chamber was not observed at all. These results suggest that anodic oxidation of **1e** generates relatively stable cationic intermediates[10], which permeates from the anodic chamber into the cathodic one, and then is subjected to cathodic reduction to regenerate **1e**. In order to avoid their permeation, an anion-exchange membrane was used as a diaphragm for the anodic fluorination of **1e** resulted in a satisfactory yield of **2e** (run 7).

Next, we have attempted anodic fluorination of selenides **1 f** and **1g** bearing an additional electron-withdrawing group such as an ester group and chlorine atom as shown in Scheme 1. Both selenides provided the corresponding fluorinated selenides **2 f** and **2g** in moderate yields.

$$PhSeCHRCOOEt \xrightarrow[Et_3N\cdot 3HF/MeCN]{-2e,\ -H^+} PhSeCFRCOOEt$$

(Cell = Di)

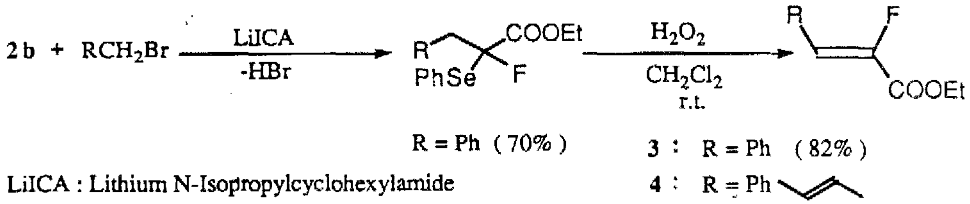
1f : R = COOEt (1.8V, 2.7F/mol) **2f** 55%

1g : R = Cl (2.3V, 3.0F/mol) **2g** 65%

(Scheme 1)

The products, **2 f** and **2 g** have a multi functional carbon structure therefore, they seem to be highly useful in theoretical and synthetic chemistry.[12]

Finally, in order to demonstrate the synthetic utility of the fluorinated selenides, we have carried out the stereoselective synthesis of α-fluoro α,β-unsaturated esters, which are useful for the preparation of monofluorinated retinoides, insect sex pheromones, and pyrethdroides.[13] For example, benzylation of **2b** followed by oxidative deselenenylation with hydrogen peroxide at room temperature provided Z-type of α-fluoro α,β-unsaturated ester **3**[14] in high yield (Scheme 2).[15] Furthermore, we successfully carried out the highly stereoselective synthesis of α-fluoro dienic esters such as (E,Z)-ethyl 2-fluoro-5-phenyl-2,4-pentadienoate **4**[16] as shown in Schem 2.



LiICA : Lithium N-Isopropylcyclohexylamide

(Sheme 2) (75% besed on **2b**)

Thus, this work illustrates the first successful example of electrochemical partial fluorination of organoselenium compounds and their application to the highly stereoselective synthesis of α-fluoro α,β-unsaturated esters.

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9) Anodic α-substitution of selenides has never been reported.

10) Cationic intermediates generated anodically from selenides **1d** and **1e** seem to be rather stable since their transformation into α-fluorinated products **2d** and **2e** requires long time. Thus, after electrolysis, standing the electrolytic solution over night was quite effective for obtaining **2d** and **2e** in good yields as shown in runs 4 and 7. On the contrary, cationic intermediates from **1a**~**1c** are unstable and their transformation into **2a**~**2c** is very fast. These facts can be explained as follows. In the case of simple methyl phenyl selenide, the ion peaks m/e 191 and 189 which correspond to the intermediate, $[PhSeFMe]^+$ were detected from the electrolytic solution. Therefore, the cationic intermediates seem to be $[p\text{-}XC_6H_4SeFCH_2\text{-}EWG]^+$, **C** which may be transformed into α-fluorinated products through a Pummerer type mechanism as proposed in the case of anodic fluorination of sulfides1). A stronger EWG facilitates deprotonation from the methylene group of **C** more efficiently while an electron-donating methoxy group (X=OMe) suppresses the deprotonation. Therefore, the effect of both substituents, X and EWG is understandable11).

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14) ^{19}F NMR ($CDCl_3$, ext CF_3COOH), δ -43.7 (d, $J_{F,Htrans}$= 36Hz)

15) Burton *et al.*13) also reported the preparation of α-fluoro α,β-unsaturated esters using $[(EtO)_2P(O)CFC(O)OEt]^- Li^+$ and esters in the presence of diisobutylaluminum hydride (DIBAL). However, their stereochemistry is completely reversed and E-type unsaturated esters were preferentially formed.

16) ^{19}F NMR ($CDCl_3$, ext CF_3COOH), δ -48.6 (d,$J_{F,Htrans}$= 31Hz)

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