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Electrochemically Induced Fluorinative Ring Expansion of Cycloalkylideneacetates

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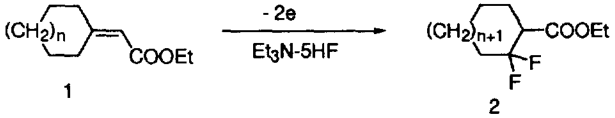
Abstract: The electrochemical oxidation of cyclic unsaturated esters (1) was carried out using Et_3N-5HF as the electrolyte. The ring expansion and fluorination took place to give β,β-difluorocycloalkanecarboxylic esters (2) selectively.

Recently we showed that the Et_3N-5HF complex is an excellent electrolyte and a fluorine source for the partial fluorination of aliphatic aldehydes[1] and cyclic ketones.[2] It is more stable than the commercially available Et_3N-3HF complex under the electrochemical oxidation conditions of carbonyl compounds which require a relatively high oxidation potential.[3] We wish to report here a novel fluorinative ring expansion reaction of cycloalkylideneacetates (1) induced electrochemically in the Et_3N-5HF complex (Eq 1).

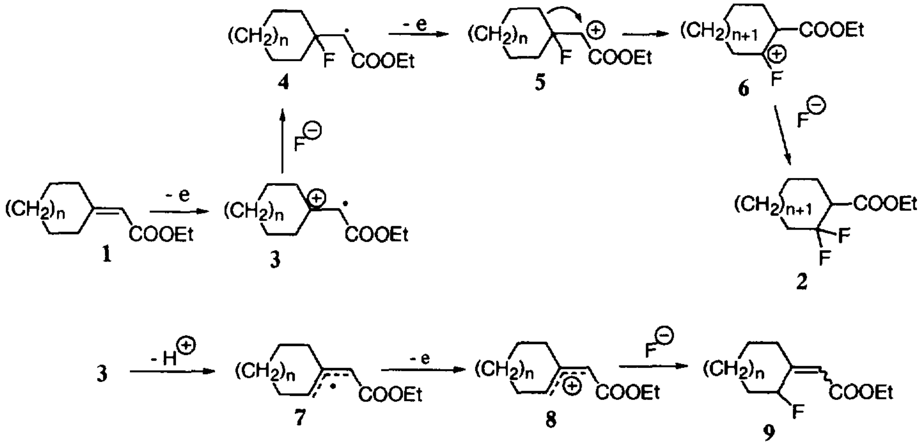


(1)

Recently, Meurs et al. reported[4] that the electrochemical oxidation of simple alkenes such as styrene in Et_3N-3HF gave *vic*-difluoroalkane. On the other hand, the *gem*-difluorination and the ring expansion took place in the electrochemical oxidation of the cycloalkylideneacetates (1) in Et_3N-5HF.[5] When unsaturated esters having 5- and 6-membered rings (1, n = 0 and 1) were used, the 6- and 7-membered difluorocycloalkanecarboxylic esters (2, n = 0 and 1) were obtained, respectively, in good to moderate yields (Entries 1-9 in Table 1). However, in the reaction of cycloheptylideneacetate (1, n = 2), a simple monofluorination at the α-position of the double bond took place competitively and the expected cyclooctanecarboxylic ester (2, n = 2) was obtained only in lower yield (Entry 10).[6] For the unsymmetrically substituted substrates, a preference for the migration of the more substituted carbon was observed.[7] The selectivity was moderate for the mono-substituted substrate (Entry 3), while the exclusive migration of the substituted carbon was observed when two methyl groups were attached to the same carbon (Entry 5). The reaction was carried out in Et_3N-5HF or a mixture of CF_3COOEt and Et_3N-5HF (1:3)[8] using platinum electrodes (2 x 2 cm) and an undivided cell (30 ml) made of Teflon PFA. The electrolysis was performed at the controlled potentials after measuring the oxidative potential of each ester (vs. Ag/Ag$^+$) by cyclic voltammetry. The anode and cathode were exchanged every two seconds to avoid the formation of polymer films on the electrode.

The following procedure for the synthesis of ethyl 2,2-difluorocycloheptanecarboxylate is representative (Entry 1). Under an inert atmosphere of nitrogen, ethyl cyclohexylideneacetate (0.336g, 2 mmol) and Et_3N-5HF (15 ml) were introduced into the cell. The mixture was cooled to -20 °C and the electrolysis was carried out at 2.3 V until the starting material was consumed. The reaction mixture was then poured into ice-water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After the removal of $MgSO_4$ by filtration, the product was isolated by column chromatography (silica gel / hexane : ether = 50 : 1) and identified by ^1H NMR, ^{19}F NMR, IR, and mass spectra.

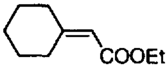
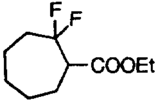
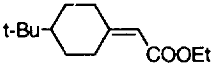
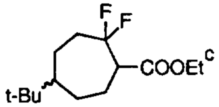
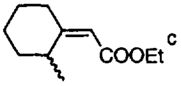
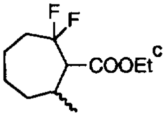
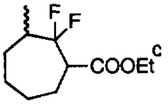
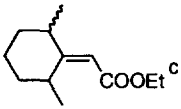
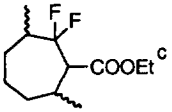
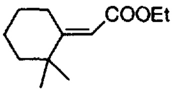
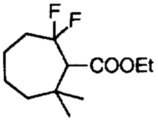
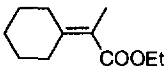
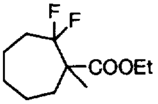
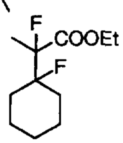
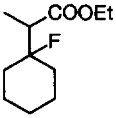
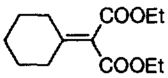
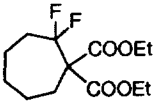
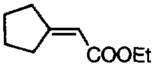
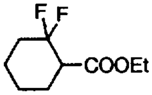
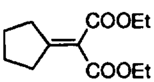
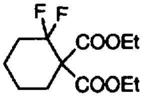
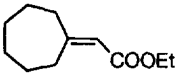
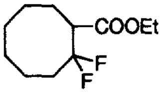
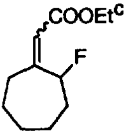
The reaction probably proceeds as follows: One-electron oxidation of the substrate (**1**) gave the radical cation species (**3**), which was fluorinated by Et_3N-5HF to afford a fluoroalkyl radical (**4**). The subsequent oxidation of **4** yielded the unstable carbocation (**5**), which rearranged to the more stable intermediate (**6**). Finally, the product (**2**) was formed by the attack of the fluoride to **6**. The mono-fluorinated by-product (**9**), obtained in the reaction of cycloheptylideneacetate (n=2), was formed from the intermediate **3** by the deprotonation, oxidation, and fluorination sequences (**Scheme 1**).



Scheme 1

This unusual ring expansion reaction seems to be induced by the formation of the carbocation intermediate **5** which is destabilized by the electron-withdrawing ester substituent, and isomerizes to the more stable intermediate **6**. When the carbocation intermediate corresponding to **5** is stabilized by a methyl group attached to the same carbon as the ester group, the formation of the non-expanded product was observed (Entry 6).

Table 1. Electrochemical Oxidation of Unsaturated Esters 1 in Et_3N-5HF[a]

Entry	Ester 1	Applied potential (V vs. Ag/Ag^+)	Electricity (F/mol)	Products (Distribution)	Yield (%)[b]
1		2.30	4.0		71(63)
2		2.30	5.5		60[d]
3		2.25	4.0	 70  30	61
4		2.20	3.0		63
5		2.30	4.0		42
6		1.80	2.8	 73  20  7	83
7		2.40	4.0		(55)
8		2.20	4.0		56
9		2.40	7.0		(55)
10		2.30	4.2	 48  52	67[e]

a. If not mentioned otherwise, the reaction was carried out in Et_3N-5HF at -20 °C. b.Glc yields based on 1 used and in prentheses, isolated yields. c. A mixture of stereoisomers. d. The reaction was carried out in a mixture of CF_3COOEt and Et_3N-5HF (1:3). e. The reaction was carried out at -40 °C.

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References and Notes

1. Yoneda, N.; Chen, S.-Q.; Hatakeyama, T.; Hara, S.; Fukuhara, T. *Chem. Lett.*, **1994**, 849-850.
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4. Meurs, J. H. H.; Eilenberg, W. *Tetrahedron*, **1991**, *47*, 705-714.
5. Replacement of Et_3N-5HF by Et_3N-3HF resulted in the competitive oxidation of Et_3N-3HF and a significant decrease in the yield of **2** under the reaction conditions.
6. From the substrate of the 8-membered ring, a complex mixture of the products was obtained.
7. Wovkulich, P. M. *Comprehensive Organic Synthesis Volume 1*; Schreiber, S. Ed.; Pergamon Press: Oxford, 1991; pp. 843-899.
8. When the substrate is insoluble in Et_3N-5HF alone, the additional use of CF_3COOEt as co-solvent is effective.

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