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LETTERS

Electrochemical Synthesis of Ethyl Pentafluoroacetoacetate.

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Abstract: Electrochemical reduction of ethyl trifluoroacetate in the presence of chlorotrimethylsilane (TMSCl) is followed by a Claisen condensation to produce the ethyl (trimethylsilyl)ketal of ethyl pentafluoroacetoacetate (**1**). Ethyl pentafluoroacetoacetate is available in high yield by the hydrolysis of (**1**) under mild conditions.

Keywords: Fluorine and compounds, Electrochemistry, Keto acids and derivatives.

Ethyl pentafluoroacetoacetate has been prepared in 20% yield by the condensation of difluoro- and trifluoroacetates [1]. Although little is known about it's chemistry, it has interest as a precursor of biologically active compounds. The reduction of ethyl trifluoroacetate with sodium sand leads to γ,γ,γ-trifluoroacetoacetate *via* the intermediate formation of ethyl pentafluoroacetoacetate [2]. Electrochemical reduction of trifluoroacetic acid esters is believed to take place as a two electron process at a high cathodic potential -2.65 V. Preparative scale electrolysis in the presence of a proton donor shows no carbonyl group reduction, instead substitution of two fluorine atoms by hydrogen with a yield 70 - 90 % [3]. So, it was reasonable to expect, that the electrochemical reduction of ethyl trifluoroacetate in aprotic media could provide a route to ethyl pentafluoroacetoacetate (**5**).

We carried out preparative electrochemical reduction of ethyl trifluoroacetate in acetonitrile (undivided cell, stainless steel cathode, sacrificial Al anode) and obtained ethyl pentafluoroacetoacetate in low yield (<10%). The low yield is probably due to the difference in the reduction potentials: the potential of the starting compound is 0.5 V more cathodic than that of the product, the initially formed acetoacetate undergoing further reduction [4].

Electrolysis under the same conditions, but with an excess of chlorotrimethylsilane (TMSCl) provided ethyl pentafluoroacetoacetate ethyl(trimethylsilyl)ketal (**1**) in 51% yield. Obviously, difluorocarboxylate anion (**2**), generated after two-electron transfer [5,6], adds to the molecule of starting ester (see scheme 1). Silylation of the intermediate anion (**3**) is more rapid than elimination of ethoxide, and the resulting ketal (**1**) was not electroactive under the reaction conditions.

Silylation of the anion (**2**) also occurs to small extent, but contrary to the silylation of (**2**) generated by reduction of ethyl iododifluoroacetate with Zn [7], C-silylation was observed to give (**4**) [8].

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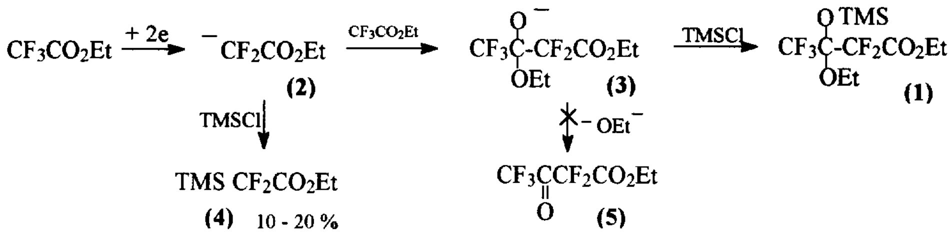
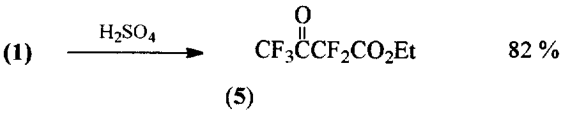
Scheme 1.



A typical experiment is as follows: into the electrochemical cell, equipped with a stainless steel cathode (50 cm^2), sacrificial Al anode, magnetic stirrer and inert gas inlet, 60 ml dry acetonitrile, 0.1 g Et_4NBF_4 and 8.6 g (79 mM, 10 ml) TMSCl were charged and pre-electrolysis was carried out for 30 min at current density of 4 mA·cm^{-2}. Then 10.7 g (75 mM, 9 ml) of ethyl trifluoroacetate was added and electrolysis continued at a current density of 12 mA·cm^{-2} until 2F had been consumed. The electrolyte was poured on ice and extracted with 50 ml hexane. The hexane extract was washed with 10 ml of water, dried over anhydrous $MgSO_4$, and distilled to obtain 6.9 g of **(1)** [9].

Ethyl pentafluoroacetoacetate is readily available by mild hydrolysis of the ketal **(1)**: it may be achieved, for instance, by heating under reflux in ethanol or by stirring with $NaHF_2$ in acetonitrile, but in this case it is difficult to separate the product **(5)**. If hydrolysis is carried out in concentrated sulphuric acid at ambient temperature, pure product may be condensed into a cold trap at reduced pressure [10].



$$\mathbf{(1)} \xrightarrow{H_2SO_4} CF_3\overset{O}{\overset{\|}{C}}CF_2CO_2Et \qquad 82\,\%$$

(5)

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4. The reduction potentials were determined on the "Polarografic analyzer PA-2" (Praha) in 0.1 M acetonitrile solution of Et_4NBF_4 at the glassy carbon electrode *vs* SCE. Potentials of the reduction peaks for CF_3CO_2Et, CF_3CO_2Me and $CF_3COCF_2CO_2Et$ were correspondingly: -2.58, -2.37, -1.96 V.
5. On the basis of voltammetric data two electron transfer was verified by the analysis of the Randles-Ševcik equation. The average diffusion coefficient obtained from it was $1 \cdot 10^{-4}$.
6. The possibility of the initial TMSCl reduction was not taken into account because of it's high reduction potential: Martynov, B.I.; Stepanov, A.A. *J. Fluor. Chem.* **1997**; 85: 127 - 8
7. Kitagawa, O; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**; 29: 1803 - 1806
8. $TMSCF_2CO_2Et$ structure was confirmed by NMR^{19}F (δ_F *vs* external CF_3COOH is 46.4, s) and ethyl difluoroacetate formation by acidic hydrolysis.
9. Ketal **(1)** is a liquid with b.p. 94 - 7°C at 15 mm Hg; δ_F (external CF_3COOH): -1.3 (3F, t, J = 11.0 Hz); 35.73 and 37.77 (2F, J_{AB} = 262.5 Hz). Found: C, 39.10; H, 5.58; F, 27.83; Si, 8.34. Calc. for $C_{11}H_{19}F_5O_4Si$: C, 39.05; H, 5.66; F, 28.08; Si, 8.30%.
10. Boiling point of the obtained ester **(5)** is 105 - 7°C (lower than reported in [1]). δ_F (external CF_3COOH): 4.8 (3F, t, J = 9 Hz); 42.3 (2F, q, J = 9 Hz). Found: C, 32.59; H, 2.24; F, 43.16. Calc. for $C_6H_5F_5O_2$: C, 32.74; H, 2.29; F, 43.16 %.