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ELECTROLYTIC TRANSFORMATION OF FUNCTIONAL GROUPS OF FLUORO-ORGANIC COMPOUNDS. I. ANODIC METHOXYLATION AND ACETOXYLATION OF TRIFLUOROETHYL SULFIDE

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Summary: Anodic methoxylation and acetoxylation of phenyl trifluoroethyl sulfide were successfully performed to give the corresponding α-methoxy and α-acetoxy sulfides in good to excellent yields, respectively. These products were found to be useful building blocks for the synthesis of fluoroorganic compounds.

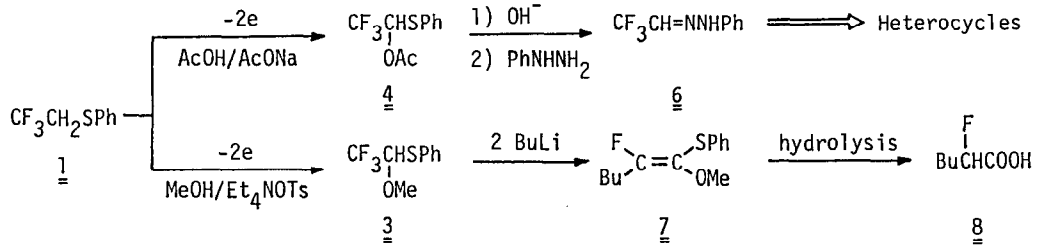
Although much attention has recently been paid to trifluoromethylated compounds because of their remarkable biological activities,[1] methods for their preparation are limited in many cases.[2] For example, nucleophilic substitution hardly occurs at a position adjacent to a trifluoromethyl group due to its strong electron-withdrawing effect.[3]

In recent years, electrochemical reactions have been shown to be very useful for organic synthesis.[4] However, very few electrosynthetic studies on fluoroorganic compounds, except for well-known electrofluorination and anodic oxidation of trifluoroacetic acid, have been reported.[4]

From these view points, novel transformation of functional groups of trifluoromethylated compounds was examined using electrochemical technique.

We wish to report successful anodic methoxylation and acetoxylation of trifluoroethyl sulfide, which is readily available from cheap trifluoroethanol, to trifluoroacetaldehyde equivalents[5] together with their synthetic utilization as a building block as shown in Scheme 1.

First of all, the anodic methoxylation of phenyl trifluoroethyl sulfide (1) was successfully performed as follows: using an undivided cell, constant current electrolysis of 1 (2 mmol) was carried out in methanol (30 ml) containing Et_4NOTs (0.07 M) at room temperature. After passing



[Scheme 1]

10 F mol^{-1} of electricity (monitering unreacted 1), usual work-up followed by chromatography on silica gel (hexane-AcOEt, 9:1) provided α-methoxy sulfide 3[6] almost quantitatively.

Contrary, non-fluorinated ethyl phenyl sulfide (2) did not give any methoxylated product under the same electrolytic conditions.[7] It was also found that a graphite anode was unsuitable compared to a platinum one.

Next, the anodic acetoxylation of 1 and 2 was performed similarly in acetic acid containing sodium acetate. As shown in Table 1, the acetoxylation of 1 proceeded smoothly to give α-acetoxy sulfide (4)[8] in 60% yield (Run 4) whereas any acetoxylated sulfide was not obtained from 2 under the same electrolytic conditions (Run 6). It was observed that the anodic acetoxylation of 2 could proceed to give 5[9] only when the concentration of the substrate 2 and the electrolyte was extremely high[10,11] (Run 7). It was also found that the yield of 4 increased to 70%, although the amount of the consumed electricity decreased (Run 5).

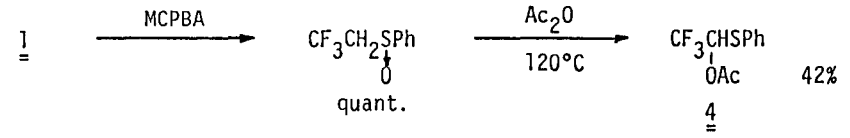
Table 1. Anodic Methoxylation and Acetoxylation of Sulfides 1 and 2

RCH_2SPh (1,2) $\xrightarrow[M-Y]{-2e}$ RCHSPh (3-5), Y

Run	R	Y	Anode material	Electrolyte[a)]	Current density (A dm-2)	Electricity passed (F mol-1)	Product yield (%)
1	CF_3	OMe	Pt	A	3.3	10.0	93 (3)
2	CF_3	OMe	C	A	3.3	10.0	13 (3)
3	Me	OMe	Pt	A	3.3	10.0	0
4	CF_3	OAc	Pt	B	1.2	4.0	60 (4)
5	CF_3	OAc	Pt	B'	5.0	3.0	70 (4)
6	Me	OAc	Pt	B	1.2	5.0	0 (5)
7	Me	OAc	Pt	B'	5.0	2.5	45 (5)

a) A: 0.2M Et_4NOTs/MeOH(30 ml) containing 2 mmol of 1 or 2. B: 0.2M AcONa/AcOH(30 ml) containg 2 mmol of 1 or 2. B': 1.2M AcONa/AcOH(5 ml) containing 17 mmol of 1 or 2.

Pummerer rearrangement is a well-known reaction for the preparation of α-acetoxy sulfides from sulfoxides which are easily derived from the corresponding sulfides. Preparation of 4 from the sulfoxide[12] of 1 was attempted by Pummerer rearrangement. However, the sulfoxide provided 4 in a low yield after heating at 120°C for 24 h in acetic anhydride.



[Scheme 2]

Thus, the electrochemical acetoxylation was found to be superior to the Pummerer reaction since the acetoxylation proceeded under mild conditions and the yield was also higher.

It should be noticeable that a trifluoromethyl group promoted remarkably the anodic substitution with methoxy and acetoxy groups although nucleophilic substitution of trifluoromethylated compounds generally takes place at their α-positions with difficulty. Although the reaction mechanism is unclear, the reaction may proceed *via* an electrogenerated cationic species, e. g. $CF_3CH=\overset{+}{S}Ph$ or $CF_3\overset{+}{C}HSPh$, similarly to the case of the anodic substitution of non-fluorinated sulfides.[7,11,13]

Finally, in order to demonstrate the synthetic utility of 3 and 4 as a trifluoroacetaldehyde equivalent, we first attempted transformation of 4 into hydrazone derivatives since they are known to be useful building blocks for the preparation of heterocyclic compounds bearing a trifluoromethyl group.[14] Thus, 4 was easily converted into trifluoroacetaldehyde phenylhydrazone (6)[14] (*ca.* 70% yield) without any defluorination in the course of alkali hydrolysis.

Furthermore, we successfully attempted the transformation of 3 into α-fluoroalkanoic acids, a class of compounds which have currently received biological interest.[1] For example, treatment of 3 with two equiv of butyllithium in THF at -78°C ~ room temperature for 3 h provided monofluoroketene hemithioacetal (7)[15] in 70% yield and quantitative transformation of 7 into α-fluorohexanoic acid (8)[16] was achieved by hydrolysis in 90% sulfuric acid at 60°C for 3 h.

Thus, this work serves to illustrate an example of the potential utility of electrochemical technique in the synthesis of fluoroorganic compounds.

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References and Notes

1) a) "Carbon-Fluorine Compounds," (A CIBA Foundation Symposium), Elsevier, Amsterdam, 1972. b) M. Schlosser, Tetrahedron, 34, 3 (1978). c) "Biomedical Aspects of Fluorine Chemistry," ed. by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo (1983).

2) For example, M. Hudlicky, "Chemistry of Organic Fluorine Compounds," 2nd. ed. John Wiley & Sons, New York (1976).

3) a) T. Umemoto, J. Synth. Org. Chem. Soc. Jpn., 41, 251 (1983). b) T. Umemoto and Y. Gotoh, J. Fluorine Chem., 28, 235 (1985). c) T. Umemoto and Y. Goto, J. Fluorine Chem., 31, 231 (1986).

4) a) "Organic Electrochemistry," 2nd ed, ed by M. M. Baizer and H. Lund, Marcel Dekker, New York (1983). b) T. Shono, "Electroorganic Chemistry as a New Tool in Organic Synthesis," Springer-Verlag, Berlin (1984).

5) Trifluoroethanol is much cheaper than trifluoroacetaldehyde. However, the oxidative transformation of trifluoroethanol into trifluoroacetaldehyde has been unsuccessful so far.

6) 3: ^{19}F NMR($CDCl_3$, ext CF_3COOH), δ -3.1(d); ^{1}H NMR($CDCl_3$, TMS), δ 3.60(s, 3H, Me), 4.80(q, 1H, CH, J_{H-H}=6 Hz), and 7.1-7.7(m, 5H, Ph); IR, 980 cm^{-1} (C-O); MS, m/e 222(M^+).

7) Hitherto, only one successful anodic methoxylation of a special type of sulfur compounds such as cephalosporines has been reported: S. Torii, H. Tanaka, N. Satoh, T. Siroi, M. Sasaoka, N. Tada, and J. Nokami, Bull. Chem Soc. Jpn., 56, 2185 (1983).

8) 4: ^{19}F NMR($CDCl_3$, ext CF_3COOH), δ -3.5(d); ^{1}H NMR($CDCl_3$, TMS), δ 2.10(s, 3H, Me), 6.30(q, 1H, CH, J_{H-H}=6 Hz), and 7.1-7.6(m, 5H, Ph); IR, 1770 cm^{-1} (C=O); MS, m/e 250(M^+).

9) 5: ^{1}H NMR($CDCl_3$, TMS), δ 1.50(d, 3H, Me, J_{H-H}=7 Hz), 2.00(s, 3H, Ac), 6.20 (q, 1H, CH, J_{H-H}=6 Hz), and 7.2-7.6(m, 5H, Ph); IR, 1775 cm^{-1}(C=O); MS, m/e 196(M^+).

10) The electrolysis was carried out at *ca.* 50°C.

11) Nokami *et al.* have successfully carried out anodic acetoxylation of sulfides in high concentrations: J. Nokami, M. Hatate, S. Wakabayashi, and R. Okawara, Tetrahedron Lett., 21, 2557 (1980).

12) The sulfoxide was easily prepared by the reaction of 1 with *m*-chloroperbenzoic acid: ^{1}H NMR($CDCl_3$, TMS), δ 3.50(q, 2H, CH_2, J_{H-F}=10 Hz) and 7.4-7.9(m, 5H, Ph); MS, m/e 208(M^+).

13) S. Torii, "Electroorganic Synthesis, Part 1, Oxidation Method and Application," Kodansha & Verlarg Chemie, Tokyo & Weinheim (1985), p. 214.

14) K. Tanaka, S. Maeno, and K. Mitsuhashi, Chem. Lett., 1982, 543; J. Heterocyclic Chem., 22, 565 (1985).

15) 7: ^{1}H NMR($CDCl_3$, TMS), δ 0.6-1.8(m, 7H, C_3H_7), 2.50(t.d, 2H, CH_2CF=, J_{H-H}= 6 Hz and J_{H-H}=22 Hz), 3.50(s, 3H, OMe), and 7.1-7.5(m, 5H, Ph); IR, 1660 cm^{-1}(C=O); MS, m/e 240(M^+).

16) The product 8 was identified by spectroscopic comparison with the authentic sample.[17]

17) K. Tanaka, T. Nakai, and N. Ishikawa, Chem. Lett., 1979, 175.

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