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ELECTROREDUCTIVE COUPLING OF HALOFLUORO COMPOUNDS WITH ALDEHYDES[1]

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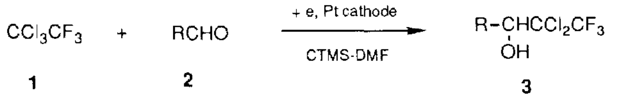
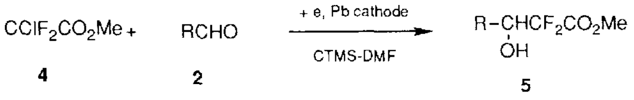
Summary: Electroreductive intermolecular coupling of halofluoro compounds such as 1,1,1-trichloro-2,2,2-trifluoroethane, methyl chlorodifluoroacetate, and perfluoroalkyl halides with aldehydes took place effectively in the presence of chlorotrimethylsilane and one of the coupling products, 2,2-dichloro-3,3,3-trifluoro-1-phenyl-1-propanol, was selectively convertible to a variety of compounds with using the electroreduction as a key reaction.

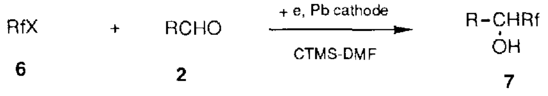
Reductive coupling of halofluoro compounds with carbonyl compounds is one of the useful methods for the synthesis of organic fluoro-compounds as exemplified by the Zn[2] or Pb[3] promoted addition reaction of 1,1,1-trichloro-2,2,2-trifluoroethane **1** to aldehydes **2**. On the other hand, the electroreduction is an effective method for the reductive coupling of polyhalogenated compounds with aldehydes as shown by our previous study on the electroreductive coupling of $CYCl_3$ (Y=Cl, CO_2Me) with aldehydes.[4] In the present study, the electroreductive method was found to be highly effective for the coupling of halofluoro compound **1** with aldehydes in the presence of chlorotrimethylsilane (CTMS) (eq 1). It was also found that one of the coupling products, **3d** ($R=C_6H_5$), was selectively transformed to a variety of compounds using electroreduction as the key reaction. The other perfluoro compounds such as methyl chlorodifluoroacetate **4** and perfluoroalkyl halides **6** ($Rf=CF_3$, n-C_4F_9) were also found to couple with **2** under similar reaction conditions (eqs 2 and 3).



$$\underset{\mathbf{1}}{CCl_3CF_3} + \underset{\mathbf{2}}{RCHO} \xrightarrow[\text{CTMS-DMF}]{+\text{ e, Pt cathode}} \underset{\mathbf{3}}{\underset{OH}{R-CHCCl_2CF_3}} \qquad (1)$$



$$\underset{\mathbf{4}}{CClF_2CO_2Me} + \underset{\mathbf{2}}{RCHO} \xrightarrow[\text{CTMS-DMF}]{+\text{ e, Pb cathode}} \underset{\mathbf{5}}{\underset{OH}{R-CHCF_2CO_2Me}} \qquad (2)$$



$$\underset{\mathbf{6}}{RfX} + \underset{\mathbf{2}}{RCHO} \xrightarrow[\text{CTMS-DMF}]{+\text{ e, Pb cathode}} \underset{\mathbf{7}}{\underset{OH}{R-CHRf}} \qquad (3)$$

The electroreductive coupling of **1** with **2** was carried out by using a Pt cathode (5 X 10 cm^2) and a carbon anode in dry DMF (40 mL) containing Et_4NOTs (10 g). The cathodic and anodic chambers were separated by a ceramic diaphragm. To the catholyte were added **1**, **2**, and CTMS (amounts are shown in Table I.). After the electricity (see Table 1) was passed at a constant current of 0.1 A, the catholyte was poured into water (200 mL) and extracted with ether. After evaporation of ether, a crude mixture of alcohol **3** and its trimethylsilyl ether was treated with 1N HCl for 30 min. The product **3** was isolated by column chromatography on silica gel (AcOEt-hexane).

Table I. Electroreductive intermolecular coupling of **1** and **2**

Run	**2**		**1** : **2**	% Yield of **3**	
1	**2a**	n-C_3H_7CHO	1 : 3[a]	**3a**	78[b]
2			1 : 3[a,c]		26[b]
3			3 : 1[d]		89[e]
4	**2b**	i-C_3H_7CHO	1 : 3[a]	**3b**	60[b]
5			1 :10[f]		88[b]
6			3 : 1[d]		68[e]
7	**2c**	$CH_3CH{=}CHCHO$	1 : 3[a]	**3c**	29[b]
8			1 :10[f]		72[b]
9			3 : 1[d]		62[e]
10	**2d**	C_6H_5CHO	1 : 3[a]	**3d**	65[b]
11			1 :10[f]		87[b]
12			3 : 1[d]		87[e]

a. **1** (5 mmol),**2** (15 mmol), CTMS (15 mmol), Electricity (10 mF).
b. Isolated yield based on **1**. c. In the absence of CTMS.
d. **1** (15 mmol), **2** (5 mmol), CTMS (5 mmol), Electricity (20 mF).
e. Isolated yield based on **2**. f. **1** (5 mmol),**2** (50 mmol), CTMS (15 mmol), Electricity (10 mF).

Table II. Electroreductive intermolecular coupling of **4** and **2**

Run	**2**[a]		% Yield of **5**[b]	
1	**2a**	n-C_3H_7CHO	**5a**	91
2	**2b**	i-C_3H_7CHO	**5b**	81
3	**2c**	$CH_3CH{=}CHCHO$	**5c**	38
4	**2d**	C_6H_5CHO	**5d**	56

a. **4** (5 mmol),**2** (25 mmol), CTMS (15 mmol), Electricity (10 mF).
b. Isolated yield based on **4**

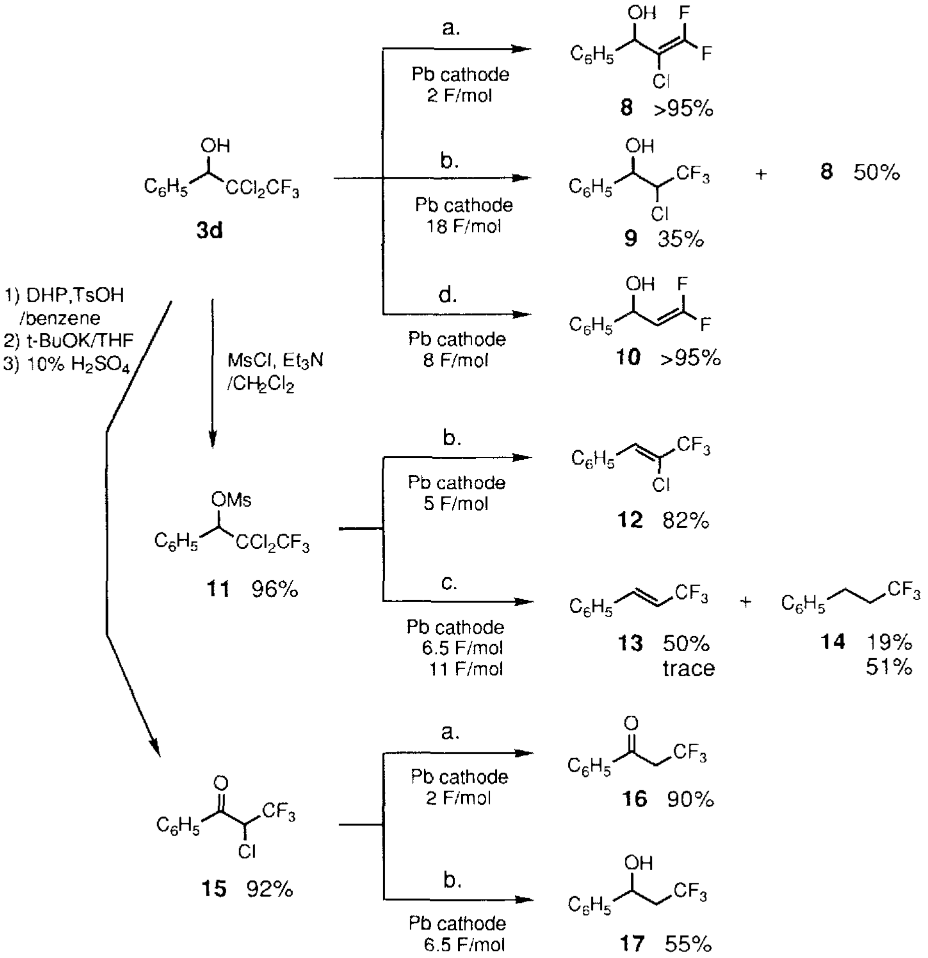
Table III. Electroreductive intermolecular coupling of **6** and **2**

Run	**6**		**2**		% Yield of **7**
1	**6a**	CF_3Br	**2e**	n-$C_7H_{15}CHO$[a]	62[b]
2			**2f**	c-$C_6H_{11}CHO$[a]	54[b]
3			**2d**	C_6H_5CHO[a]	60[b]
4			**2g**	$(C_6H_5)_2CO$[a,c]	78[b]
5	**6b**	n-C_4F_9I	**2a**	n-C_3H_7CHO[d]	49[e]
6			**2b**	i-C_3H_7CHO[d]	49[e]
7			**2d**	C_6H_5CHO[d]	47[e]

a. **6a** (ca. 25 mmol), **2** (5 mmol), CTMS (15 mmol), Electricity (20 mF). The electroreduction was carried out at -50°C, since **6a** is highly volatile compound (b. p. -57°C). b. Isolated yield based on **2** c. Hexamethyldisilazane was used in place of CTMS. d. **6b** (5 mmol),**2** (25 mmol), CTMS (15 mmol), Electricity (10 mF). e. Isolated yield based on **6b**.

The results of electroreductive coupling of **1** with **2** are shown in Table I. The yields of coupling products **3** based on either **1** or **2** were satisfactory. The absence of CTMS resulted in the decrease in the yield of **3** (run 2).[5] The electroreduction of **4** with **2** under the same conditions as above gave the corresponding coupling products **5** (Table II). In this reaction, Pb was more effective than Pt as the material of the cathode (Pt cathode: **5a**, 68%). The electroreductive coupling of **4** with aliphatic aldehydes afforded satisfactory results (runs 1 and 2), whereas the rather poor results have been reported in the Reformatsky type reactions of **4** with such aldehydes.[6] In addition, electroreduction of perfluoroalkyl halides **6** in the presence of **2** gave perfluoroalkyl carbinols **7** in moderate yields (Table III).[7]

The coupling product **3d** obtained from **1** and benzaldehyde **2d** could electroreductively be converted to a variety of compounds **8**, **9** and **10** by controlling the reaction conditions (Scheme I).[11,12] Namely, the electroreduction of **3d** was carried out under three types of reaction conditions, that is, a strongly acidic condition (condition **a**), a weakly acidic condition (condition **b**) and a basic condition (condition **d**). The reductive-elimination product **8** was selectively obtained under the condition **a**,[14] while only one chlorine atom was eliminated and a monochloro derivative **9** was formed under the weakly acidic condition **b**, though considerable amounts of **8** were also yielded. On the other hand, under the basic condition **d**, the reduction of **3d** was not terminated at the stage of the compounds **8** and **9**, but further advanced to give an unsaturated compound **10**.[15] In the electroreduction of a mesylate **11**, the condition **b** gave the elimination product while **11** was transformed to **13** and **14** under a neutral condition **c** with passing an excess amount of electricity. Ketone **15**, which was easily prepared from **3d**, was also selectively reduced to **16** or **17** by controlling the reaction conditions. Namely, **15** was selectively reduced to **16** under the strongly acidic condition **a** and it was further reduced to **17** under the weakly acidic condition **b**. These results clearly show that the control of the reaction conditions of the electroreduction is a very effective method for the selective reduction of trifluoromethyl compounds **3d**, **11**, and **15**.



(a) 0.2M Et_4OTs, 0.2M MsOH/DMF; (b) 0.2M NH_4NO_3/MeOH.; (c) 0.2M Me_4NCl/MeOH; (d) 0.2M Me_4NCl, 0.2M Et_3N/MeOH.

Scheme I

References and Notes

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2. (a) M. Fujita, T. Morita, and T. Hiyama, *Tetrahedron Lett.*, **27**, 2135 (1986). (b) R. W. Lang, *Helv. Chim. Acta*, *69*, 881 (1986).

3. H. Tanaka, S. Yamashita, Y. Katayama, and S. Torii, *Chem. Lett.*, **1986**, 2043.

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5. It seems reasonable that CTMS promoted the reaction by trapping the intermediate alkoxy anion as the corresponding silyl ether.

6. (a) E. A. Hallinan and J. Fried, *Tetrahedron Lett.*, **25**, 2301 (1984). (b) R. W. Rang and B. Schaub, *Tetrahedron Lett.*, **29**, 2943 (1988).

7. A number of methods of the generation of perfluoroalkyl anions from iodotrifluoromethane and the addition of the anions to carbonyl compounds have been studied by using Zn,[8a,b] Li,[8c] Mg,[8d] Ca,[8e] or Mn[8f] as the reducing agents so far. The generation of trifluoromethyl anion from CF_3SiMe_3 has also been reported.[9] An electrogenerated base-promoted formation of a trifluoromethyl anion equivalent from trifluoromethane has been found in our laboratory.[10]

8. Recent reports: (a) T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, **107**, 5186 (1985). (b) S. Stibille, S. Mcharex, and J. Perichon, *Tetrahedron*, **45**, 1423 (1989). (c) P. G. Gassman and N. J. O'Reilly, *J. Org. Chem.*, **52**, 2481 (1986). (d) H. Gilman, *J. Organometal. Chem.*, **100**, 83 (1975). (e) G. Stantini, M. L. Blanc, and J. G. Riess, *J. Organometal. Chem.*, **140**, 1 (1979). (f) T. Kitazume and N. Ishikawa, *Nippon Kagaku Kaishi*, **11**, 1725 (1984). Other references cited therein.

9. G. K. S. Prakash, R. Krishnamurti, and G. A. Olah, *J. Am. Chem. Soc.*, **111**, 393 (1989).

10. T. Shono, M. Ishifune, T. Okada, and S. Kashimura, *J. Org. Chem.*, **56**, 2 (1991).

11. General procedure for the electroreduction of **3d** is as follows: A 40 mL of electrolyte (see Scheme I) was placed in a cell (50 mL beaker) equipped with a Pb plate cathode (5 X 10 cm^2), a carbon rod anode, and a ceramic diaphragm. To the catholyte was added **3d** (5 mmol) and the electricity was passed at a constant current of 0.2 A. The catholyte was poured into water (200 mL) and extracted with ether. The products were isolated by distillation or column chromatography on silica gel (AcOEt-hexane).

12. Zn catalyzed formation of **8** and **12** from **1** and bezaldehyde has been reported.[13]

13. M. Fujita and T. Hiyama, *Tetrahedron Lett.*, **27**, 3655 (1986).

14. Further reduction of **8** did not take place at all, since the cathode potential was controlled by hydrogen evolution under the acidic condition and hence, it was incapable of further reduction of **8**.

15. Although the intermediate formation of **8** was detected, that of **9** could not be observed.

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