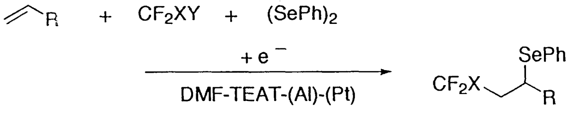
A New Entry to Difluoromethylene Compounds; An Electrochemical Method

Hideki Asai and Kenji Uneyama*
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700

(Received September 1, 1995)

Electroreduction of dibromodifluoromethane in the presence of diphenyldiselenide and olefins in a DMF-(Pt)-(Al) system provided adducts of in situ generated bromodifluoromethyl radical and phenylselenenyl group to olefins. One electron transfer from benzeneselenolate to CF_2Br_2 induces the formation of $CF_2Br\cdot$ radical. This system is also useful for generation of $\cdot CF_2CO_2Et$ radical from ethyl bromodifluoroacetate.

The introduction of difluoromethylene group into organic compounds has been currently investigated[1] since compounds bearing this group often show unique biological activities.[2] Dibromodifluoromethane (CF_2Br_2) is one of the easily available reagents so that selective generations of difluoromethyl carbene ($:CF_2$) and bromodifluoromethyl radical ($CF_2Br\cdot$) from CF_2Br_2 have been the subjects of current fluorine chemistry. Two-electron-reduction with metals such as Zn[3] or Pb[4] and one-electron-reduction with CuCl[5] or $CrCl_3/Fe$[6] have been demonstrated. Electrochemical reduction would be one of the promising candidates for the purpose. However, direct electrochemical reduction of CF_2Br_2 leads to the formation of difluorocarbene[7,8] via two-electron-reduction. Therefore, some kind of mediators must be employed for selective generation of $CF_2Br\cdot$ via single-electron-transfer (SET) process.[9,10] Benzeneselenolate anion[11] is a good SET reagent.[12] Cyclic voltammetry showed that $(PhSe)_2$ was more easily reduced than CF_2Br_2.[13] Therefore, bromodifluoromethyl-selenation of olefins should be realized electrochemically and the products would be precursors of functionalized allylic difluoromethylene compounds. This approach has proved to be successful.



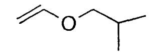
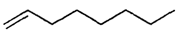
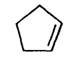
1

Scheme 1.

The reaction was conducted under the following conditions : A solution of $(PhSe)_2$ (0.5 mmol), CF_2Br_2 (1.5 mmol) and isobutyl vinyl ether (10 mmol) in DMF (8 ml) containing tetraethylammonium tosylate (TEAT) as the supporting electrolyte was electrolyzed under a constant current (25 mA) and argon atmosphere in an undivided beaker-type cell fitted with two plate electrodes of Pt (cathode 3.0 cm^2) and Al (anode 3.0 cm^2). Reaction temperature, electricity charged and other details are given under the column of the table.

When the substrate is an electron rich olefin such as isobutyl vinyl ether, bromodifluoromethyl radical reacts smoothly at 0 °C to give the selenated adduct in a moderate yield. The concentration of olefin affected the yield of the major product. When lower concentration of olefin was employed, the major product was $PhSeCF_2Br$[14] which formed either by coupling between in situ generated $CF_2Br\cdot$ and $PhSe\cdot$ or reaction of $CF_2Br\cdot$ with $PhSe^-$. This result suggests that the reaction of $CF_2Br\cdot$ with olefin is slower than that with $PhSe^-$ and that the use of excess amount of olefin is necessary. Under the condition employed for isobutyl vinyl ether, the yields of **1** from the both 1-octene and cyclopentene were unsatisfactory and the selenide **3** (X=Br) was a major product because of the lower reactivity of these olefins to $CF_2Br\cdot$ radical. The desired seleno-bromodifluoromethylated products increased, when reaction temperature was elevated to room temperature and dibromodifluoromethane was added every 2 h for 6 h.[15] Ethyl bromodifluoroacetate and nonafluorobutyl iodide were less volatile than CF_2Br_2 and thus electrolysis could be carried out at higher temperature. The temperatures of ca. 20, 40 and 50 °C were of choice for isobutyl vinyl ether, cyclopentene and 1-octene, respectively. The reaction of $BrCF_2CO_2Et$ with olefins provided the desired adducts in quite reasonable yields which were interesting precursors for the functionalized difluoromethylene compounds. The reaction sequence is proposed as shown in Scheme 2.

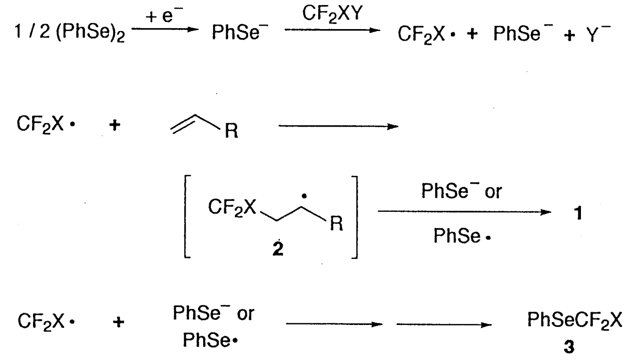
Table 1. Yields/% of **1** in bromodifluoromethyl-selenation and the related reactions of olefins[a]

	CF_2XY		
Olefins	CF_2Br_2	$BrCF_2CO_2Et$	C_4F_9I
	45[b]	80[c]	73[c]
	57[d]	58[e]	71[e]
	68[d]	45[f]	77[f]

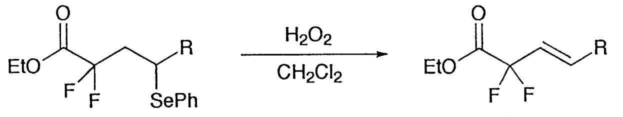
general conditions : DMF (8 ml) / Et_4NOTs (0.1 mmol) / olefin (10 mmol) / $(PhSe)_2$ (0.5 mmol) under a constant corrent (25 mA), Pt (cathode 3.0 cm^2) Al (anode 3.0 cm^2) , argon atmosphere.

[a] isolated yields/% based on $(PhSe)_2$. [b] at 0 °C CF_2XY (1.5 mmol) for 3 h. [c] at r.t. CF_2XY (1.5 mmol) for 3.5 h. [d] at r.t. CF_2XY (4.5 mmol) for 6 h. [e] at 50 °C CF_2XY (1.5 mmol) for 5 h. [f] at 40 °C CF_2XY (1.5 mmol) for 5 h.

Oxidative deselenation (H_2O_2 in CH_2Cl_2) of **1a** proceeded regioselectively and stereoselectively to give ethyl trans-2,2-difluoro-3-decenoate (J = 15.8 Hz in ^1H NMR) in almost quantitative yield. The predominant regioselectivity may arise from the higher acidity of difluoroalkylated methylene protons.

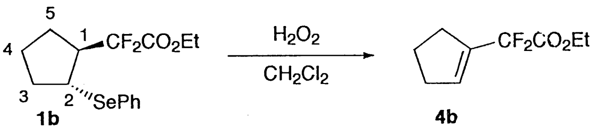


Scheme 2.



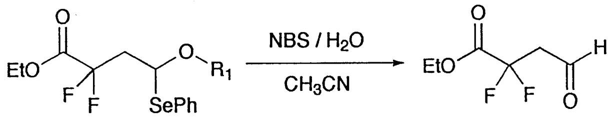
1a R = n-C_6H_{13} **4a**

Similarly, oxidative deselenation of **1b**[16] afforded **4b** regioselectively in 92% yield.



1b **4b**

Since the selenated compound **1c** derived from the vinyl ether is an acetal type compound, it provided the corresponding aldehyde **5c** in 62% yield by NBS-promoted deselenation in aqueous acetonitrile.



1c R_1 = i-C_3H_7 **5c**

References and Notes

1 K. Uneyama, *J. Synth. Org. Chem. Jpn.*, **51**, 232 (1993).

2 a) R. Filler and T. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, 1982. b) R. Filler, *Organofluorine Chemistry and Its Industrial Applications*. c) R. E. Banks and E. Horwood, *Chichester*, 1979. d) M. Schlosser, *Tetrahedron*, **34**, 3 (1987). e) J. Fried, E. A. Hallinan, and M. J. Szwedo Jr., *J. Am. Chem. Soc.*, **106**, 3871 (1984). f) F. Tellier and R. Sauvetre, *Tetrahedron Lett.*, **33**, 3643 (1992).

3 a) W. R. Dolbier, Jr., H. Wojtowicz, and C. R. Burkholder, *J. Org. Chem.*, **55**, 5420 (1990). b) J. Gonzaler, C. J. Foti, S. Elsheimer, *J. Org. Chem.*, **56**, 4322 (1991).

4 Y. Besserd, U. Muller, and M. Schlosser, *Tetrahedron*, **46**, 5213 (1990).

5 J.Gonzalez, C. J. Foti, and S. Elsheimer, *J. Org. Chem.*, **56**, 4322 (1991).

6 C.-M. Hu and J. Chen, *J. Chem. Soc., Chem. Commun.*, **1993**, 72.

7 H. P. Fritz and W. Kornrumpf, *J. Electroanal. Chem.*, **100**, 217 (1979).

8 Amatore privately informed us the direct electroreduction of CF_2Br_2 also generated $CF_2Br\cdot$ radical. We also examined direct electroreduction under the same conditions shown in this paper without $(PhSe)_2$ and observed only 8% of the dimer of the radical **2** and a mixture of unidentified oligomeric products.

9 Generation of $CF_2Br\cdot$ radical by the electrooxidatively recycled Mn(III) as a mediator is known. K. Nohair, I. Lachaise, J.-P. Paugam, and J.-Y. Nédélec, *Tetrahedron Lett.*, **33**, 213 (1992).

10 Recently, Médebielle et. al. demonstrated that anion radicals of some nitrobenzenes can act as a mediator to transfer one electron to CF_2Br_2 in an electroreduction system. The abstract (4C04) of the 14th International Symposium on Fluorine Chemistry, Yokohama July 31 - Aug. Studies on both direct and indirect electrochemical reduction of perfluoroalkyl halides have been reported. a) M. Médebielle, J. Pinson, and J.-M. Savéant, *Tetrahedron Lett.*, **33**, 7351 (1992). b) M. Médebielle, M. A. Oturan, J. Pinson, and J.-M. Savéant, *Tetrahedron Lett.*, **34**, 3409 (1993). M. Médebielle, *Tetrahedron Lett.*, **36**, 2071 (1995).

11 Electroreductive generation of benzeneselenolate from $(PhSe)_2$; T. Inokuchi, M. Kusumoto, and S. Torii, *J. Org. Chem.*, **55**, 1548 (1990).

12 We previously reported the generation of perfluoroalkyl radical by SET from chemically generated phenyl selenorate anion. But, this system could not be satisfied in the case of CF_2Br_2. K. Uneyama and K. Kitagawa, *Tetrahedron Lett.*, **32**, 375 (1991).

13 Likewise, $(PhSe)_2$ was more reducable than C_4F_9I and $BrCF_2CO_2Et$.

14 The corresponding coupling between thiophenoxy radical and $Rf\cdot$ was reported. C. Wakselman, *J. Fluorine Chem.*, **59**, 367 (1992).

15 Boiling point of CF_2Br_2 is 24 °C.

16 Stereochemistry of **1b** was assigned by the coupling constant (J = 5.4 Hz). [The coupling constant was obtained by decoupling methylene protons on C_3.]

17 The authors are grateful to the Ministry of Education, Science, Sports, and Culture of Japan for financial support Grant-in Aid for Priority Area (Organic Electrochemistry No. 05235102) and SC-NMR Laboratory of Okayama University for ^{19}F NMR analysis.