Tetrahedron Letters, Vol. 34, No. 8, pp. 1311-1312, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Difluorophenylselenomethylation of Ethers

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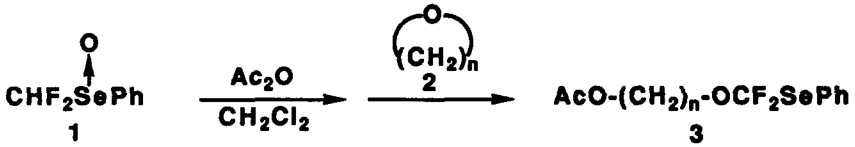
Summary; Pummerer reaction of difluoromethyl phenyl selenoxide with acetic anhydride proceeds at refluxing temperature of CH_2Cl_2, generating difluorophenylselenomethyl carbocation equivalent which can be trapped with cyclic ethers to give ω-(difluorophenylselenomethoxy)alkyl acetates 3.

Introduction of the difluoromethylene unit into organic compounds has proved attractive due to the unique biological activities of the difluoromethylene-containing compounds.1) The most widely used method for the introduction of the difluoromethylene functionality has been the nucleophilic reactions of substituted difluoromethyl carbanions (XCF_2^-) such as metal induced reactions of halodifluoroacetates,2) chlorodifluoromethyl ketones,3) difluoroallyl halides,4) and halodifluoromethylphosphonates.5) Although the chemistry of difluorocarbene generated from CF_2Br_2 and other halodifluoromethanes6) is well known, there has been no report on the electrophilic reactions of substituted difluoromethyl carbocations (XCF_2^+)7) in spite of their potentiality for the syntheses of difluoromethylene compounds. Here, we describe a first formal generation of difluorophenylselenomethyl carbocation via Pummerer rearrangement of difluoromethyl phenyl selenoxide (1)8) and its electrophilic reaction with ethers.

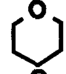
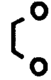


The Pummerer reaction of 1 with acetic anhydride proceeds smoothly via tetravalent selenium intermediate 4 at refluxing temperature of CH_2Cl_2 in contrast to high temperature reaction of sulfoxides.9) The electron-deficient intermediate can be trapped with cyclic ethers to give difluorophenylselenomethoxy compounds 3. On adding Ac_2O to 1 in THF-$CDCl_3$ at 20 °C, two sets of double-doublets (J_1 = 52.9 Hz, J_2 = 250.0 Hz, δ = 48.32 and δ = 49.23 in ^{19}F-NMR) due to geminal hydrogen-fluorine and fluorine-fluorine couplings of CHF_2 group of 1 disappeared within 1 h and one doublet (J = 53.9 Hz, δ = 61.58) of 4 appeared.10) The time-dependent product distribution and consumption of 4 in $CDCl_3$ observed in ^{19}F-NMR revealed the figure 1. The fact that the rates of the consumption of both oxirane and pyran are almost same suggests that the formation of the carbocation intermediate would be rate-determining in the overall reaction.

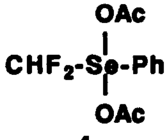
Most of cyclic ethers provided 3 in moderate to good yields. Reaction of oxirane 2a was accompanied by the formation of oligomer. The regiochemistry of the ring opening follows the Markovnikov's rule (3.5 : 1 for 2a). It is noteworthy that even carbon-oxygen bond of diethyl ether can be cleaved at about 40 °C. Although the reaction mechanism is not clear at present, it is interesting that in contrast to the very clean reaction of THF, tetrahydrothiophene, pyrrole, and *N*-acetyl pyrrole provided none of the desired products.[11]

Deselenation can be performed very smoothly by Bu_3SnH-AIBN-benzene system, affording the desired difluoromethyl ether (86 % in the case of 3c).

Table 1. Difluorophenylselenomethylation of Ethers.

	Ether 2		Solvent (ml)	Yield 3 (%)
2a		(5.0 eq)	CH_2Cl_2 (2.0)	3a (34)[a)]
2b		(5.0 eq)	CH_2Cl_2 (2.0)	3b (60)
2c		(2.0 ml)	none	3c (87)
2d		(1.0 ml)	CH_2Cl_2 (1.0)	3d (74)
2e		(1.0 ml)	CH_2Cl_2 (1.0)	3e (63)
2f	$(CH_3CH_2)_2O$	(1.0 ml)	CH_2Cl_2 (1.0)	3f (36)[b)]

Conditions; 1 (0.5 mmol), Ac_2O (2.5 mmol), reflux for 2~4 hours.
a) Yield of regioisomers. b) NMR yield of $CH_3CH_2OCF_2SePh$.



$$CHF_2\text{-}\underset{OAc}{\overset{OAc}{Se}}\text{-}Ph$$

4

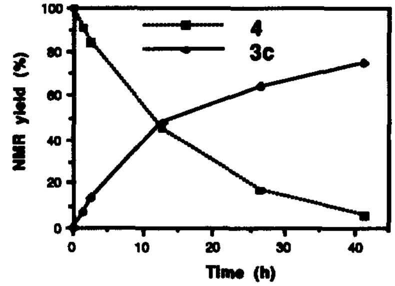


Fig. 1. Reaction of 1 with Ac_2O in $CDCl_3$-THF (2c).

References and Notes

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7) Generations and ^{19}F-NMR spectra of alkyl, aryl, and halodifluoromethyl carbocations in SbF_5-SO_2ClF were discussed. G. A. Olah and Y. K. Mo, chapter 36 in " Carbonium Ions ", Ed. by G. A. Olah and P von R. Schleyer, Wiley-Interscience (1976). Trifluoromethyl cation is less stable than the corresponding chloro and bromo species. C. H. Reynolds, *J. Chem. Soc., Chem. Commun.*, **1991**, 975.

8) The selenoxide **1** was prepared in CH_2Cl_2 by H_2O_2 oxidation of difluoromethyl phenyl selenide which was derived from reaction of sodium benzeneselenolate with CF_2Br_2 in EtOH-DMF. Details will be described elsewhere.

9) We observed that Pummerer reaction of 2,2,2-trifluoroethyl phenyl selenoxide completed at 0 °C within 0.5 h. Whereas, Fuchigami reported the sulfur analog necessitates 24 h at 120 °C. T. Fuchigami, Y. Nakagawa, and T. Nonaka, *Tetrahedron Lett.*, **27**, 3869 (1986).

10) The signal of one doublet would arise from the tentatively assigned tetravalent selenium intermediate **4**. J. P. Marino and R. D. Larsen, Jr, *J. Am. Chem. Soc.*, **103**, 4642 (1981); H. Togo, N. Miyagawa, and M. Yokoyama, *Chem. Lett.*, **1992**, 1677. The chemical shift is indicated by δ (ppm) down field from C_6F_6.

11) Difluoromethyl phenyl selenide as a major product and difluorophenylselenomethyl acetate as a minor product were obtained.

12) Financial support (Priority Area of Organic Unusual Valency No. 03233219) from the Ministry of Education, Science and Culture of Japan and ^{19}F-NMR analysis in SC-NMR Laboratory of Okayama University are gratefully acknowledged.

(Received in Japan 15 October 1992)