Epoxide Opening with Tetrabutylammonium Fluoride (TBAF)

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Positron emission tomography (PET) has been used to assess the fundamental and neurochemical parameters in normal and diseased human organisms.[1] Measuring these parameters with PET requires the preparation of specific molecular imaging probes labeled with positron-emitting radioisotopes. Labeling pharmaceuticals with [^{18}F]fluorine often enables the fluorine-substituted analogue to be used to trace biochemical processes while maintaining favorable interaction with the target.[2] Thus, a rapid and effective method for the introduction of ^{18}F is a great concern in organofluorine and radiopharmaceutical chemistry.

The typical method for introduction of a fluorine atom in an aliphatic molecule is the nucleophilic substitution of the corresponding sulfonates or halides by a fluoride ion.[3] For example, the reaction of 2-(3-methanesulfonyloxypropoxy)-naphthalene with CsF in *t*-BuOH gave 2-(3-fluoropropoxy)naphthalene in 92% yield along with the corresponding ether.[4]

Epoxide opening with a fluoride ion has been widely used in the preparation of fluorohydrins, which were often found in a certain bioactive molecules such as steroids, amino acids, carbohydrates, and prostaglandins.[5] Anhydrous hydrogen fluoride is a good reagent for cleavage of the epoxide ring, but it is not easy to handle due to its toxicity and corrosiveness.[6] To avoid this problem, some reagents have been developed; HF-amine complex,[7] potassium hydrogen difluoride,[8] silicon tetrafluoride,[9] tetrabutylammonium dihydrogen trifluoride,[10] and so on. Although these reagents gave successful results to some extent, most cases require heating at high temperature for a long period. In consequences, byproducts were often resulted from elimination, rearrangements or polymerization.[6]

Metal fluoride[^{18}F] or tetrabutylammonium fluoride[^{18}F] (TBA^{18}F) is a good source of the fluorinating agent to prepare radiopharmaceuticals containing ^{18}F,[11] but they were rarely used in the epoxide ring opening reaction.[12]

In this report, we examined epoxide opening reactions with metal fluoride or TBAF for introducing [^{18}F]fluorine to fluorohydrins.

Results and Discussion

TBAF is a typical desilylation agent for breaking oxygen-silicon or carbon-silicon bonds, and plays a role as a base or an oxidant, in addition to a nucleophilic fluorination reagent.[13] Among metal fluorides, KF was widely used, but CsF was employed in this study because of the better solubility in organic solvents.

Some epoxides were examined. 1,2-Epoxy-4-phenylbutane is a typical one, and *p*-chlorophenyl glycidyl ether, and cyclohexyl glycidyl ether were chosen as aromatic and aliphatic glycidyl ethers, respectively. Solvent effect was also examined. DMF was employed as an aprotic polar solvent, and *t*-BuOH as a polar one, and toluene as a non-polar one. *t*-BuOH was also chosen because it was reported to give a special effect in the S_N2 type reaction for introducing a fluorine atom.[4]

As shown in Table 1, those epoxides were treated with 5 equiv. of CsF or TBAF at 80 °C for 3 h. The reaction mixture was subjected to a short path column chromatography to remove TBAF and analyzed by NMR. The primary fluoro compound was given as a major compound and the regio-isomer was not observed. Although intermediate oxyanions were known to react with the starting epoxide to yield dimeric or oligomeric products,[13] those by-products were hardly observed under these reaction conditions. TBAF provided much better yield than CsF. The reaction was sensitive to the reaction media. Nonpolar solvents are better

Table 1. Epoxide ring opening reactions

entry	SM[a]	MF	solvent	yield[b]
1	A	CsF	DMF	4
2	A	CsF	*t*-BuOH	5
3	A	TBAF	*t*-BuOH	22
4	A	TBAF	toluene	30
5	B	CsF	DMF	2
6	B	CsF	*t*-BuOH	7
7	B	TBAF	*t*-BuOH	39
8	B	TBAF	toluene	92(72)
9	C	CsF	DMF	1
10	C	CsF	*t*-BuOH	8
11	C	TBAF	*t*-BuOH	18
12	C	TBAF	toluene	38

[a]Starting material. A, Y= $PhCH_2$-; B, Y= *p*-ClC_6H_4O-; C, Y= *c*-$C_6H_{11}O$-. [b]The fluorinating agent was 1.0 M solution of TBAF in THF. The reaction took place with 5 equiv. of the reagent at 80 °C for 3 h, and the relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis. The remainder was mainly the unreacted starting material.

Table 2. Ring opening reactions of various phenyl glycidyl ethers[a]

entry	X	TBAF (eq)	solvent	additive (1 equiv)	temp (°C)	yield
1[b]	Cl	5	toluene		80	87
2	Cl	3	toluene		80	82
3	Cl	1	toluene		80	43
4	Cl	5	toluene		50	20
5	Cl	5	THF		80	73
6	Cl	5	CH_3CN		80	58
7[c]	Cl	5	toluene	AcOH	80	–
8	Cl	5	toluene	*p*-TsOH	80	74
9	Cl	5	toluene	TFA	80	89(67)
11	H	5	Toluene		80	91
12	CH_3	5	Toluene		80	92
13[d]	NO_2	5	toluene		80	–

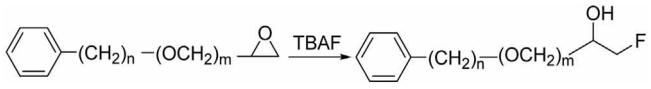
[a]The fluorinating agent was 1.0 M solution of TBAF in THF, and the relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis. [b]The reaction took place with TBAF·3H_2O in toluene. [c]The major product was 3-*p*-chlorophenoxy-2-hydroxypropyl ethanoate. [d]The major product was *p*-nitrophenol.

than protic or aprotic polar solvents, and *t*-BuOH showed no special effect in this case.[4] Among the epoxides, *p*-chlorophenyl glycidyl ether reacted with TBAF in toluene to give the corresponding fluorohydrin in the best yield (entry 8). The difference between the aromatic glycidyl ether and the aliphatic ether was not understood at this moment (entries 8 and 12).

Next, we examined the reaction with *p*-chlorophenyl glycidyl ether in detail. As shown in Table 2, either source of TBAF was not so different in yield (entries 1 and 2). The better yield was given under the conditions of 5 equiv. of TBAF, 3 h of reaction time, 80 °C of reaction temperature, and toluene as a solvent. The reaction generally completed within 1.5 h. The opening of the epoxides usually gave terminally fluorinated compounds. Although the regioselectivity was known to depend upon the reaction conditions,[15] the regioselectivity in the present study was neither influenced by the addition of an acid catalyst (entries 8 and 9) nor the electronic effect of the substituents on the phenyl ring (entries 1, 11 and 12). In the presence of acetic acid, the major product was 3-*p*-chlorophenoxy-2-hydroxypropyl ethanoate, indicating that the acetoxy anion attacked the epoxide (entry 7). The cleavage of the glycidyl group took place instead of the ring opening, in the case of *p*-nitrophenyl glycidyl ether (entry 13).

As shown in Table 3, the reaction of various aromatic epoxides was carried out under the same reaction conditions. The reaction of styrene oxide gave 1-phenyl-2-fluoro-1-ethanol in 13% yield (entry 1). In the reaction of 1,2-epoxy-3-phenylpropane, 1-fluoro-3-phenyl-2-propanol was given in 31% yield along with 3-phenylpropane-1,2-diol and 3-phenylprop-2-en-1-ol as major byproducts, presumably because the hydroxide ion attacked the epoxide and the

Table 3. Ring opening reactions of various epoxides[a]



entry	n	m	yield
1	0	0	13
2[b]	1	0	31
3	1	1	45
4	2	1	37

[a]The fluorinating agent was 1.0 M solution of TBAF in THF. The reaction took place with 5 equiv. of the reagent in toluene at 80 °C for 3 h, and the relative yields were calculated by integrations of NMR data. [b]The remainder was mainly 3-phenylpropane-1,2-diol and 3-phenylprop-2-en-1-ol.

fluoride ion abstracted the benzylic proton, respectively (entry 2). Benzyl glycidyl ether was converted to the corresponding fluorohydrin in 45% yield (entry 3). The reaction of phenylethyl glycidyl ether gave the corresponding fluorohydrin in moderate yield (entry 4).

In conclusion, the epoxide opening reaction proceeded faster with TBAF than CsF. Aryl glycidyl ether type compounds gave the corresponding fluorohydrins in higher yield with an exclusive regioselectivity. However, the epoxide opening reaction of other epoxides proceeded in lower yield. Therefore this method could be useful in the preparation of fluorohydrin radiopharmaceuticals derived from aryl glycidyl ether type compounds. A certain biologically active compound contains phenolic functional groups, and it can be converted to aryl glycidyl ether type compounds.[14] Since the starting epoxide and the resulting fluorohydrin were easily separable by column chromatography, this reaction might be useful in a certain case. Otherwise, the alcohol moiety in fluorohydrins may be protected and deprotected during the S_N2 process by [^{18}F]fluorine.

Experimental Section

General. Compounds such as tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) and solvents were purchased from Aldrich. Chromatography was performed with E. Merck silica gel 60 (63-200 μm). ^{1}H NMR spectra were recorded on a Varian Jemini 2000 (200 MHz). ^{13}C NMR spectra were recorded on a Varian Unity Inova 400 (100 MHz). All NMR data were obtained in $CDCl_3$ solutions. Some spectral data of the following compounds were reported in literatures or commercially available; 1-(4-chlorophenoxy)-3-fluoro-2-propanol,[15] 1-fluoro-3-*p*-tolyoxy-2-propanol,[16] 1-fluoro-3-phenoxy-2-propanol,[16] 1-benzyloxy-3-fluoro-2-propanol,[15] 1-fluoro-3-phenethyloxy-2-propanol,[17] 1-fluoro-3-phenyl-2-propanol,[18] 3-phenylpropane-1,2-diol,[19] and 3-phenylprop-2-en-1-ol,[20] 1-fluoro-4-phenyl-2-butanol.[21]

Typical procedure for the epoxide opening reaction of *p*-chlorophenyl glycidyl ether with TBAF. To a 1.0 M solution of TBAF in THF (5.0 mL, 5.0 mmol) was added a solution of *p*-chlorophenyl glycidyl ether (0.185 g, 1.00 mmol) in toluene (10 mL), and the mixture was allowed to

stir at 80 °C for 3 h. The mixture was subjected to a short path column chromatography on silicagel (hexane:EtOAc = 7:3) to remove TBAF. The solvent was evaporated and the crude product was analyzed by NMR. Purification by column chromatography gave 1-(4-chlorophenoxy)-3-fluoro-2-propanol (0.147 g, 72%). All spectral data were the same as reported in literature.[15]

1-Cyclohexyloxy-3-fluoro-2-propanol. ^{1}H NMR ($CDCl_3$, 400 Hz) δ 4.54-4.51 (m, 1H), 4.40-4.37 (m, 1H), 4.04-3.93 (m, 1H), 3.58-3.48 (m, 2H), 3.31-3.25 (m, 1H), 1.93-1.83 (m, 2H), 1.77-1.68 (m, 2H), 1.58-1.49 (m, 1H), 1.37-1.19 (m, 5H); ^{13}C NMR δ 84.7, 83.0, 78.1, 69.3, 67.5, 32.0, 25.7, 23.9; MS calcd. for $C_9H_{17}FO_2$ ($M+H^+$) 177.12, found 177.10.

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