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A mild ring opening fluorination of epoxide with ionic liquid 1-ethyl-3-methylimidazorium oligo hydrogenfluoride (EMIMF(HF)$_{2.3}$)

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Abstract

Ring opening fluorination of epoxides with hydrogen fluoride in ionic liquid 1-ethyl-3-methylimidazorium oligo hydrogenfluoride EMIMF(HF)$_{2.3}$ was demonstrated. This ionic liquid released hydrogen fluoride graduately to make mild conditions without oligomerization of epoxides.

Keywords: Fluorohydrin; Epoxide ring opening; Hydrogen fluoride; Ionic liquid

1. Introduction

Ring opening fluorination of epoxide has been a convenient method for preparation of fluorohydrin [1]. The direct way may be treatment of epoxides with anhydrous hydrogen fluoride [2,3], but in some cases, it has a drawback due to its toxicity and difficulty for handle. Alternative fluorine sources have been employed successfully to avoid this problem. HF-amine complex [4–6], potassium dihydrogen trifluoride or potassium hydrogen difluoride [7–9], silicon tetrafluoride [10], titanium tetrafluoride [11], tetrabutylammonium dihydrogen trifluoride [12], were reported as effective reagents for ring opening fluorination of epoxide. In a previous paper [13], we reported halofluorination of alkenes in the presence of ionic liquid 1-ethyl-3-methylimidazorium oligo hydrogenfluoride EMIMF(HF)$_{2.3}$ (Fig. 1) [15] and proved that this ionic liquid was available as fluoride ion source with easy-handling. In this paper, we wish to report ring opening fluorination of epoxides with the ionic liquid as hydrogen fluoride source.

2. Results and discussion

Styrene oxide (**1a**) in CH_2Cl_2 was added EMIMF(HF)$_{2.3}$ at room temperature and stirred vigorously at ambient temperature to obtain 2-fluoro-2-phenyl-ethanol (**2a**) in 72% yield (Scheme 1). The reaction mixture is biphase which consist of CH_2Cl_2 phase and ionic liquid phases. In order to increase the rate of releasing hydrogen fluoride into CH_2Cl_2 phase, methanol was added as an additive. The addition of proton source will carry fluoride ion from ionic liquid like phase transfer catalyst. 2-Fluoro-2-phenyl-ethanol (**2a**) was sole product and the region isomer 1-fluoro-2-phenyl-2-ethanol was not detected by ^{1}H and ^{19}F NMR in the obtained crude product. As shown in entry 2 of Table 1, when catalytic amount of methanol was added, the yield was improved. The use of methanol as a solvent instead of CH_2Cl_2 accelerated the consumption of epoxide, but formation of 2-methoxy-2-phenyl ethanol which was arisen from attack of methoxide anion was predominant (entry 4).

Ring opening fluorination of various epoxide with EMIMF(HF)$_{2.3}$ and methanol catalyst are summarized in Table 2. In all cases, regioselectivity was high. Aryl and cyclic epoxides were converted to fluorohydrins in moderate yield (entry 1–4). Mono-alkyl substituted epoxide resulted in recovery of the starting material (entry 8). These results indicated that stabilization effect of carbocation which was formed by epoxide ring opening at the intermediate played an important role (Scheme 2).

If epoxides react with aqueous hydrogen fluoride in methanol solution, epoxides were consumed rapidly, but oligomerization occurred and no flurohydrin was obtained. This ionic liquid generated hydrogen fluoride to organic

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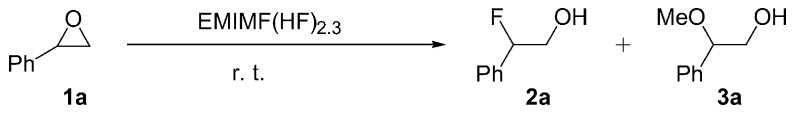


Scheme 1.

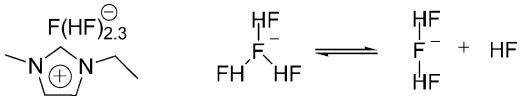
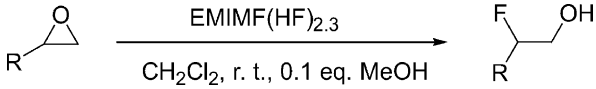


Fig. 1. EMIMF(HF)$_{2.3}$.

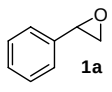
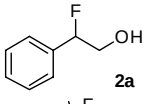
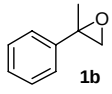
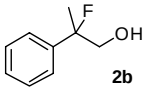
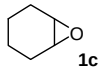
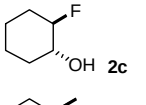
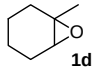
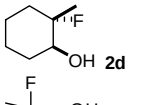
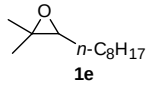
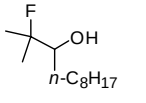
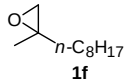
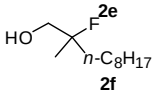
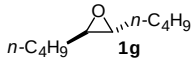
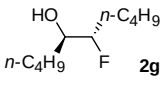
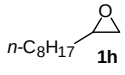


Scheme 2.

Table 1
Ring opening fluorination of styrene oxide

Entry	Solvent	Time (h)	**2a** (%)	**3a** (%)
1	CH_2Cl_2	24	72	–
2	CH_2Cl_2/0.1 eq. MeOH	16	81	–
3	CH_2Cl_2/1.0 eq. MeOH	12	74	17
4	MeOH	4	4	75

Table 2
Ring opening fluorination of various epoxides

Entry	Epoxide	Time (h)	Product	Yield (%)
1	 **1a**	16	 **2a**	81
2	 **1b**	16	 **2b**	74
3	 **1c**	16	 **2c**	55
4	 **1d**	6	 **2d**	65
5	 **1e**	24	 **2e**	37[a]
6	 **1f**	24	 **2f**	28[b]
7	 **1g**	48	 **2g**	7[c]
8	 **1h**	120	–	0[d]

[a] 50% of starting material was recovered.
[b] 47% of starting material was recovered.
[c] 83% of starting material was recovered.
[d] Starting material was only recovered.

phase graduately and effectively that concentration of hydrogen fluoride was kept appropriate, which realized mild fluorination condition.

In summary, we demonstrated ring-opening fluorination of epoxide with mild and safe fluorinating reagent EMIMF(HF)$_{2.3}$ which makes the non-aqueous work-up possible.

3. Experimental

Reagents were purchased from Wako, Tokyo Kasei, or Aldrich, and used without further purification. Epoxides were prepared by oxidation of olefines with *m*CPBA or addition of (bromometyl) lithium to carbonyl compounds [14]. Reactions were monitored by thin-layer chromatography using 25 mm E. Merck silica-gel plates (Silica Gel F_{254}). Silica-gel was purchased from Kanto Chemical Co. The polypropylene tube used was a centrifuge tube (15 ml) with a screw cap, and is available from Corning. NMR spectra were recorded on a Varian Gemini 300 or Mercury 2000 in $CDCl_3$. EMIMF(HF)$_{2.3}$ was prepared according to [15].

3.1. General procedure for ring opening fluorination of epoxides

In a 15 mm polypropylene tube, epoxide (1 mmol), CH_2Cl_2 (500 μl), and methanol (4 μl) were placed. Ionic liquid EMIMF(HF)$_{2.3}$ (600 μl) was added to the mixture at room temperature, and stirred. When the reaction finished, ethyl acetate (1 ml) was added and the whole was stirred vigorously. The stirring was stopped, the mixture was separated into two phases. The upper layer was collected by decantation. This extraction with ethyl acetate was repeated twice more. The crude product was purified by a short silica-gel column chromatography. Yield was determined by ^{19}F NMR in comparison with internal standard.

*3.1.1. 2-Fluoro-2-phenyl-ethanol (**2a**)*

^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.34 (m, 5H), 5.57 (ddd, $J = 3.0$, 7.5, 48.3 Hz, 1H), 4.01–3.76 (m, 2H), 2.02

(bs, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −186.8 (ddd, J = 48.6, 29.6, 17.8 Hz).

*3.1.2. 2-Fluoro-2-phenyl-propan-1-ol (**2b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.32 (m, 5H), 3.92–3.69 (m, 2H), 1.83 (bs, 1H), 1.75 (d, J = 22.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −157.2 (m).

*3.1.3. 2-Fluorocyclohexane-1-ol (**2c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (dm, J = 51.3 Hz, 1H), 3.67–3.57 (m, 1H), 2.45 (bs, 1H), 2.13–1.99 (m, 2H), 1.77–1.69 (m, 2H), 1.51–1.20 (m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −181.4 (d, J = 51.3 Hz).

*3.1.4. 2-Fluoro-2-methyl-cyclohexanol (**2d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76–3.67 (m, 1H), 2.17 (bs, 1H), 1.94–1.21 (m, 11H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.0 (m).

*3.1.5. 2-Fluoro-2-methyl-decan-3-ol (**2e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (t, J = 7.5 Hz, 1H), 1.98 (s, 1H), 1.36 (d, J = 3.9 Hz, 6H), 1.35–1.24 (m, 14H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.5 (d, J = 163.4 Hz), 77.2 (d, J = 23.3 Hz), 32.2, 31.6, 31.5, 30.0, 29.9, 24.2, 23.0, 21.3 (d, J = 24.5 Hz, 2C), 14.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.7 (m). Anal. Calcd for $C_{12}H_{25}FO$: C, 70.54; H, 12.33. Found: C, 70.48; H, 12.28.

*3.1.6. 2-Fluoro-2-methyl-decan-1-ol (**2f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67–3.47 (m, 2H), 1.76–1.56 (m, 2H), 1.36 (s, 3H), 1.34–1.22 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.0 (d, J = 165.3 Hz), 68.43 (d, J = 23.4 Hz), 36.6 (d, J = 22.2 Hz), 32.2, 30.4, 29.8, 29.6, 23.8 (d, J = 6.3 Hz), 23.0, 21.1 (d, J = 24.5 Hz), 14.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −154.8 (m). Anal. Calcd for $C_{11}H_{23}FO$: C, 69.43; H, 12.18. Found: C, 69.68; H, 11.88.

*3.1.7. 6-Fluoro-decan-5-ol (**2g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37 (ddt, J = 47.7, 9.3, 3.9 Hz, 1H), 3.77–3.69 (m, 1H), 1.77–1.25 (m, 12H), 0.92 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.6 (d, J = 167.9 Hz), 73.0 (d, J = 21.6 Hz), 31.4, 29.2 (d, J = 20.7 Hz), 28.0, 27.6, 22.7, 22.6, 14.1, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −190.8 (m). Anal. Calcd for $C_{10}H_{21}FO$: C, 68.14; H, 12.01. Found: C, 68.21; H, 11.72.

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