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Reactions of aliphatic fluoro-alcohols with $CHClF_2$ at atmospheric pressure

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Abstract

The reactions of aliphatic fluoro-alcohols with chlorodifluoromethane ($CHClF_2$) at atmospheric pressure were examined. In the reaction of $CF_3CF_2CH_2OH$, the difluoromethylated ether was obtained in moderate yield by using ethers such as 1,4-dioxane, diglyme and THF, or their mixtures with water as a reaction solvent. While acetal and orthoformate were also produced, the selectivity of the difluoromethylated ether could be improved by adding water to the reaction. The effect of water could be explained by the reaction mechanism.

Keywords: Difluoromethylation; Difluorocarbene; Chlorodifluoromethane; Fluorinated ether

1. Introduction

Fluorinated ethers containing some hydrogen atoms have been expected as environmental friendly alternatives to CFCs and HCFCs due to their low environmental effect, non-flammability, low toxicity, thermal stability and excellent physical properties [1]. Especially, some $ROCHF_2$-type fluorinated ethers have a short tropospheric life time, and can be a new alternative with low global warming effect [2].

$ROCHF_2$-type fluorinated ethers are usually synthesized by the insertion of difluorocarbene to O–H bond of alcohol. In this reaction, chlorodifluoromethane ($CHClF_2$) [3,4], dibromodifluoromethane (CF_2Br_2) [5], sodium trifluoroacetate (CF_3COONa) [6], fluorosulfonyldifluoroacetic acid (FO_2SCF_2-COOH) [7] and hexafluoropropylene oxide [8] could be employed as a difluorocarbene source. $CHClF_2$ is one of the most convenient and inexpensive difluorocarbene sources, because it is commercially available as an alternative refrigerant R-22. As for the reactions using $CHClF_2$, it was reported that the reactions with some phenols and pyridinols proceeded efficiently at atmospheric pressure to afford the difluoromethylated ether in good yield [9–11]. While, in the reaction of aliphatic fluoro-alcohols with $CHClF_2$, it was necessary to carry out the reaction at higher pressure to prepare the difluoromethylated ether satisfactorily [4].

In a present study, the reactions of aliphatic fluoro-alcohols with $CHClF_2$ at atmospheric pressure were examined. Actually, the reaction was proceeded efficiently even at atmospheric pressure by employing ethers such as 1,4-dioxane, diglyme and THF as a reaction solvent. In the reactions using $CF_3CF_2CH_2OH$, the difluoromethylated ether was obtained along with acetal and orthoformate. We found that the selectivity of the products was affected by the amount of water in the reaction. To clarify the effect of water, the reaction mechanism was investigated. Moreover, the reactions of various alcohols with $CHClF_2$ were examined.

2. Results and discussion

2.1. *Solvent effect ~ reaction of $CF_3CF_2CH_2OH$ with $CHClF_2$*

Initially, the reactions of $CF_3CF_2CH_2OH$ (**1**) with $CHClF_2$ (**2**) at atmospheric pressure were carried out using various solvents (Scheme 1, Table 1). The reactions were carried out by bubbling **2** to the solution of **1**, NaOH and the solvent through a glass-filter. The feeding rate of **2** was controlled by a mass flow controller at about 10 ml/min. If the reaction proceeded satisfactorily, almost of **2** was absorbed to the solvent during feeding **2**. The ether-type solvents such as 1,4-dioxane, diglyme

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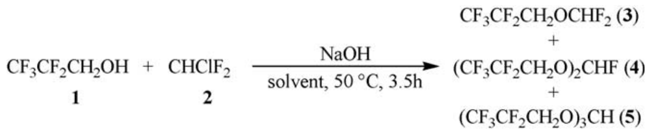


Scheme 1. Solvent effect.

Table 1
Solvent effect[a]

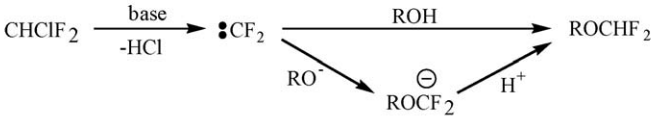
Entry	Solvent (ml)	Yield from **1** (%)[b]		
		3	**4**	**5**
1	1,4-Dioxane (60)	42	22	30
2	1,4-Dioxane (40) + H_2O (20)	43	17	5
3	Diglyme (60)	41	26	24
4	Diglyme (40) + H_2O (20)	52	32	11
5	THF (40) + H_2O (20)	42	21	7
6	NMP (60)	11	14	13
7	NMP (40) + H_2O (20)	0	0	0
8	DMF (40) + H_2O (20)	0	0	0
9	$(CH_3)_2CHOH$	5	0	Trace
10	$(CH_3)_2CHOH$ (40) + H_2O (20)	10	1	2
11[c]	Excess of **1**	16	0	15

[a] Reaction conditions; **1**: 40 mmol, **2**: 60 mmol, NaOH: 200 mmol, reaction temperature: 50 °C, reaction time: 3.5 h.

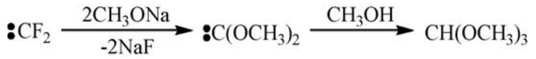
[b] Yields were determined by NMR.

[c] **1**: 600 mol, **2**: 40 mmol. Yields were based on **2**.

and THF, and also their mixtures with water were efficient for this reaction (Table 1, Entries 1 ~ 5). The difluoromethylated ether (**3**) was obtained as a main product along with the acetal (**4**) and the orthoformate (**5**). While NMP was one of the proper reaction solvents in the reaction of CF_3CH_2OH with $CHClF_2$ under pressure [4], it was not favorable to carry out the reaction at atmospheric pressure (Table 1, Entries 6 and 7). It was considered that the low solubility of **2** and NaOH to this solvent inhibited the reaction. In the reactions of substituted phenols with **2**, the mixture of isopropanol and water was reported to be a good solvent for difluoromethylation [9,10]. However, using isopropanol as a reaction solvent, the yield of **3** was low, since the reaction of isopropanol with **2** proceeded to afford $(CH_3)_2CHOCHF_2$ (Table 1, Entries 9 and 10). Although **3** and **5** were obtained in using excess of **1** as a reaction solvent, the yields were low (Table 1, Entry 11).



Scheme 2. Mechanism for difluoromethylation.



Scheme 3. Mechanism for formation of orthoformate in the reaction of methanol with $CHClF_2$.

The results of solvent effect showed that water in the solvent was affected the yield and the selectivity of products. Therefore, the effect of adding water to the reaction was observed in detail. The results using 1,4-dioxane or diglyme as a basal solvent were shown in Table 2. As the amount of water increased, the selectivity of **3** increased, and the yield of **5** decreased in the case of both solvents.

2.2. Reaction mechanism

The difluoromethylation of alcohol with $CHClF_2$ was reported to be proceeded via generation of difluorocarbene. The difluorocarbene was inserted to the OH bond of the alcohol to afford the difluoromethylated ether (Scheme 2) [12]. Here, it was natural to consider another pathway of the difluoromethylation, which was the protonation of $ROCF_2^-$ generated by the reaction of alkoxide with the difluorocarbene (Scheme 2).

In the reactions of $CF_3CF_2CH_2OH$ (**1**) with $CHClF_2$, the acetal (**4**) and the orthoformate (**5**) were also obtained as products. In the case of CH_3OH (or CH_3ONa), the mechanism for the formation of the orthoformate had been proposed by Hine and Porter [12], and been verified by Lee et al. [13]. The

Table 2
Effect of adding water[a]

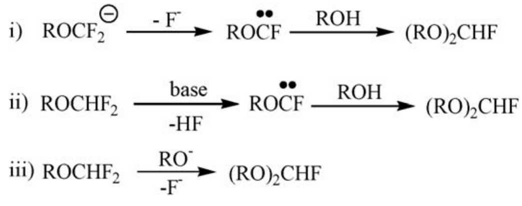
Entry	Solvent	Amount of water (g)	Yield from **1** (%)[b]			Selectivity of **3** (%)[c]
			3	**4**	**5**	
1	1,4-Dioxane	0	42	22	30	45
2	1,4-Dioxane	3.6	52	25	22	53
3	1,4-Dioxane	7.2	54	26	20	54
4	1,4-Dioxane	14.4	56	24	11	62
5	1,4-Dioxane	21.6	48	18	6	67
6[d]	Diglyme	0	41	26	24	45
7	Diglyme	20	52	32	11	55
8	Diglyme	30	53	29	7	60

[a] Reaction conditions; **1**: 40 mmol, **2**: 60 mmol, solvent (1,4-dioxane: 60 ml or diglyme: 40 ml), NaOH: 200 mmol, reaction temperature: 50 °C, reaction time: 3.5 h.

[b] Yields were determined by NMR.

[c] Selectivity of **3** = (yield of **3**)/(sum of yields of **3**, **4** and **5**) ×100.

[d] Diglyme: 60 ml.

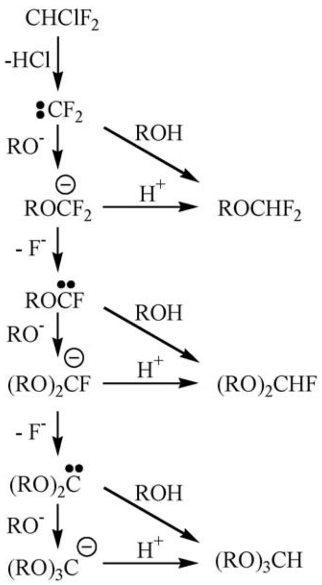


Scheme 4. Mechanism for formation of acetal (R = $CF_3CF_2CH_2$–).

mechanism was shown in Scheme 3. However, the production of the acetal like **4** had never been reported. Three mechanisms could be considered for the formation of **4**, and listed in Scheme 4. In order to make sure the possibility of the mechanisms (ii) and (iii), the reaction of $CF_3CF_2CH_2OCHF_2$ (**3**) and **1** was examined under the same condition as the reaction with $CHClF_2$. As a result, **3** was recovered quantitatively, and neither **4** nor **5** was detected. Therefore, the mechanisms (ii) and (iii) were not acceptable under this condition, and the mechanism (i) was considered to be reasonable.

In the same way, the reaction of **4** with **1** had been attempted to confirm the mechanism for the production of **5**. However, the isolation of **4** could not be achieved, because this compound was unstable. Then, the reaction of **4** with **1** was examined using the crude products. After the reaction of **1** with $CHClF_2$, $CHClF_2$ dissolved in the crude products was removed by bubbling of N_2. After that, **1**, sodium hydroxide and benzotrifluoride as an internal standard were added to the crude products, and kept at 50 °C for 3.5 h. As a result, it was confirmed that the amount of **4** and **5** was not changed by NMR analysis. This result meant that **5** was formed not via the formation of **4**, but by the reaction of **1** with $(CF_3CF_2CH_2O)_2C$ carbene, which was similar to the mechanism for the production of **4**. The reaction mechanism was summarized in Scheme 5.

The effect of adding water could be explained by the reaction mechanism. The water worked as a proton donor and contributed to the protonation of the anion intermediate. Then, the selectivity of **3** was increased, and the yield of **5** was decreased by adding water to the reaction.



Scheme 5. Mechanism of the reaction of $CF_3CF_2CH_2OH$ with $CHClF_2$ (R = $CF_3CF_2CH_2$–).

Table 3
Reactions of various alcohols with $CHClF_2$[a]

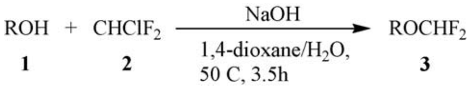
Entry	**1**	**3**	Yield of **3** from **1** (%)[b]
1	$CF_3CF_2CH_2OH$ (**1a**)	$CF_3CF_2CH_2OCHF_2$ (**3a**)	56
2	$CHF_2CF_2CH_2OH$ (**1b**)	$CHF_2CF_2CH_2OCHF_2$ (**3b**)	55
3	CHF_2CH_2OH (**1c**)	$CHF_2CH_2OCHF_2$ (**3c**)	36
4	$CF_3CH_2CH_2OH$ (**1d**)	$CF_3CH_2CH_2OCHF_2$ (**3d**)	17
5	$CH_3CH_2CH_2OH$ (**1e**)	$CH_3CH_2CH_2OCHF_2$ (**3e**)	4
6	$CF_3CH(CH_3)OH$ (**1f**)	$CF_3CH(CH_3)OCHF_2$ (**3f**)	38
7	$(CF_3)_2CHOH$ (**1g**)	$(CF_3)_2CHOCHF_2$ (**3g**)	0
8	$(CH_3)_2CHOH$ (**1h**)	$(CH_3)_2CHOCHF_2$ (**3h**)	0

[a] Reaction conditions; **1**: 40 mmol, **2**: 60 mmol, NaOH: 200 mmol, 1,4-dioxane: 60 ml, H_2O: 14.4 g, reaction temperature: 50 °C, reaction time: 3.5 h.
[b] Yields were determined by NMR.

2.3. *Reaction of various alcohols with $CHClF_2$*

The difluoromethylations of various alcohols were examined under the same conditions as Table 2, Entry 4 (Scheme 6, Table 3). In the cases of $CF_3CF_2CH_2OH$ (**1a**) and $CHF_2CF_2CH_2OH$ (**1b**), the yields of **3** were almost same (Table 3, Entries 1 and 2). The yield of **3** was lower than that of **3a** and **3b** in the reaction of CHF_2CH_2OH (**1c**) and $CF_3CH_2CH_2OH$ (**1d**) (Table 3, Entries 3 and 4). The reaction of $CH_3CH_2CH_2OH$ (**1e**) gave only small amount of **3e** (Table 3, Entry 5). It was reported that the difluorocarbene was generated by the reaction of alkoxide and $CHClF_2$ (Scheme 7) [12]. In the cases of **1c**, **1d** and **1e**, the alkoxide would not be formed efficiently due to the low acidity of alcohols compared with **1a** and **1b**. In the reaction of alcohols with low acidity, the pressured reaction might be preferable to carry out the reaction smoothly [13].

With regard to the difluoromethylations of isopropyl-type alcohols, the reactions of $CF_3CH(CH_3)OH$ (**1f**), $(CF_3)_2CHOH$ (**1g**) and $(CH_3)_2CHOH$ (**1h**) were examined (Table 3, Entries 6 ~ 8). Although the reaction of neither **1g** nor **1h** proceeded, only the reaction of **1f** proceeded to afford **3f**. The basicity of the alkoxide of **1g** might be too low to abstract a proton from $CHClF_2$ due to the two trifluoromethyl groups. For this reason, no product was obtained in the case of **1g**. On the other hand, the reaction of **1h** did not proceed due to the low acidity of **1h** like **1e**.



Scheme 6. Reactions of various alcohols with $CHClF_2$.

$$CHClF_2 + RO^- \longrightarrow :CF_2 + ROH + Cl^-$$

Scheme 7. Generation of difluorocarbene.

3. Conclusion

The reactions of aliphatic fluoro-alcohols with $CHClF_2$ proceeded at atmospheric pressure in ethereal solvents such as 1,4-dioxane, diglyme and THF, and afforded difluoromethylated ether accompanied by acetal and orthoformate. Addition of water in the solvents was effective to improve the selectivity of the difluoromethylated ether. It was considered that the effect of adding water was derived from the promotion of the protonation of the anion intermediate. The results of the reactions with various alcohols showed that the acidity of the alcohol had an effect on the reaction.

4. Experimental

4.1. General

All of the reagents were used without further purification. ^{1}H- (300 MHz) and ^{19}F NMR (282 MHz) were measured with JEOL ECA-300S using TMS and $CFCl_3$ as internal standards and $CDCl_3$ as a solvent. MS (EI, 70 eV) spectra were measured using the Shimazu GCMS-QP2010 system equipped with GC-2010. HRMS (EI, 70 eV) spectra were measured using Hitachi M-80B.

4.2. A typical experimental procedure for the reaction of $CHClF_2$ with alcohol (Table 1, Entry 1)

2,2,3,3,3-Pentafluoropropanol (40 mmol), sodium hydroxide (200 mmol) and 1,4-dioxane (60 ml) were placed into a 100 ml flask equipped with a cooled condenser, a thermocouple and a gas inlet bubbler tube (Kinoshita glass-filter G-4, 5–10 μm). After the solution was heated at 50 °C, chlorodifluoromethane was introduced at 10 ml/min for about 2.5 h (total: 60 mmol), and the reactor was kept at 50 °C for 1 h. After cooling, the mixture was poured into 200 ml cooled water, and the products were extracted with chloroform. Benzotrifluoride (7.0 mmol) was added to the extraction as an internal standard, and the structure and the ratio of the products were determined by GC–MS, ^{1}H NMR and ^{19}F NMR spectra.

4.3. 1,1,1,2,2-Pentafluoro-3-difluoromethoxypropane (**3a**)

^{1}H NMR: δ 4.27 (2H, t, $J = 12.7$ Hz, CH_2), 6.33 (1H, t, $J = 71.1$ Hz, CHF_2); ^{19}F NMR: δ −84.3 (3F, s, CF_3), −87.2 (2F, d, $J = 71.1$ Hz, CHF_2), −124.5 (2F, t, $J = 12.7$ Hz, CF_2). MS: m/z, 181 (M^+-F), 133 ($CF_3CF_2CH_2^+$), 81 ($CHF_2OCH_2^+$), 69 (CF_3^+), 51 (CHF_2^+).

4.4. Bis(2,2,3,3,3-pentafluoropropoxy)fluoromethane (**4**)

This compound is new, but could not be isolated because it was decomposed during distillation.

^{1}H NMR: δ 4.19 (4H, t of d, $J = 12.6$ Hz, 6.6 Hz, CH_2), 6.02 (1H, d, $J = 75.3$ Hz, CHF); ^{19}F NMR: δ −84.2 (6F, s, CF_3), −95.2 (1F, d, $J = 75.3$ Hz, CHF), −124.3 (4F, t, $J = 12.6$ Hz, CF_2); MS: m/z, 311 (M^+-F), 211 ($CF_3CF_2CH_2OCHFOCH_2^+$), 182, 181 ($CF_3CF_2CH_2OCHF^+$), 133 ($CF_3CF_2CH_2^+$), 113, 83, 69 (CF_3^+), 64, 51, 49, 45, 29.

4.5. Tris(2,2,3,3,3-pentafluoropropoxy)methane (**5**)

^{1}H NMR: δ 4.07 (6H, t, $J = 13.1$ Hz, CH_2), 5.53 (1H, s, CH); ^{19}F NMR: δ −84.2 (9F, s, CF_3), −124.2 (6F, t, $J = 13.1$ Hz, CF_2); HRMS calcd. for $C_{10}H_6F_{15}O_3$, 459.0077; found, 459.0038; MS: m/z, 459 (M^+-H), 311 ($(CF_3CF_2CH_2O)_2CH^+$), 179, 159, 133 ($CF_3CF_2CH_2^+$), 113, 111, 83, 69 (CF_3^+), 64, 51.

4.6. 2,2,3,3-Tetrafluoro-1-difluoromethoxypropane (**3b**) [7,14]

^{1}H NMR: δ 4.22 (2H, t, $J = 12.3$ Hz, CH_2), 5.92 (2H, t of t, $J = 53.0$ Hz, 4.2 Hz, CHF_2CF_2), 6.32 (1H, t, $J = 72.2$ Hz, CHF_2O); ^{19}F NMR: δ −86.3 (2F, d, $J = 72.2$ Hz, CHF_2O), −124.9 (2F, t, $J = 12.3$ Hz, CF_2), −138.7 (2F, d, $J = 53.0$ Hz, CHF_2CF_2); MS: m/z, 163 (M^+-F), 115 ($CHF_2CF_2CH_2^+$), 95, 83, 82, 81 ($CHF_2CH_2^+$), 65, 51 (CHF_2^+), 33, 31, 29.

4.7. 1,1-Difluoro-2-difluoromethoxyethane (**3c**)

^{1}H NMR: δ 4.04 (2H, t of d, $J = 13.1$ Hz, 4.1 Hz, CH_2), 5.93 (1H, t of t, $J = 55.0$ Hz, 4.1 Hz, CHF_2CH_2), 6.30 (1H, t, $J = 72.6$ Hz, CHF_2O); ^{19}F NMR: δ −86.1 (2F, d, $J = 72.6$ Hz, CHF_2O), −126.1 (2F, d of t, $J = 55.0$ Hz, 13.1 Hz, CHF_2CH_2); MS: 81 ($CHF_2OCH_2^+$), 65 ($CHF_2CH_2^+$), 51 (CHF_2^+), 45, 31, 29.

4.8. 1,1,1-Trifluoro-3-difluoromethoxypropane (**3d**)

^{1}H NMR: δ 2.49 (2H, q of t, $J = 10.3$ Hz, 6.5 Hz, CF_3CH_2), 4.09 (2H, t, $J = 6.5$ Hz, CH_2O), 6.23 (1H, t, $J = 73.3$ Hz, CHF_2); ^{19}F NMR: δ −65.7 (3F, t, $J = 10.3$ Hz, CF_3), −86.3 (2F, d, $J = 73.3$ Hz, CHF_2); HRMS calcd. for $C_4H_4F_5O$, 163.0182; found, 163.0180; MS: m/z, 115, 97 ($CF_3CH_2CH_2^{+}$), 95, 81 ($CHF_2OCH_2^+$), 77, 69 (CF_3^+), 65, 64, 51 (CHF_2^+), 49, 47, 45, 33, 31, 29, 27.

4.9. Difluoromethoxypropane (**3e**)

^{1}H NMR: δ 0.96 (3H, t, $J = 7.4$ Hz, CH_3), 1.67 (2H, q of t, $J = 7.4$ Hz, 6.6 Hz, CH_3CH_2), 3.80 (2H, t, $J = 6.6$ Hz, CH_2O), 6.19 (1H, t, $J = 75.3$ Hz, CHF_2); ^{19}F NMR: δ −84.2 (d, $J = 75.3$ Hz); MS: 110 (M^+), 109 (M^+-H), 81 ($CHF_2OCH_2^+$), 63, 51 (CHF_2^+), 43 ($CH_3CH_2CH_2^+$), 42, 41, 31, 29 ($CH_3CH_2^+$), 27.

4.10. 1,1,1-Trifluoro-2-difluoromethoxypropane (**3f**)

^{1}H NMR: δ 1.47 (3H, d, $J = 6.6$ Hz, CH_3), 4.59 (1H, q of q, $J = 6.6$ Hz, 6.6 Hz, =CH-), 6.32 (1H, t, $J = 72.6$ Hz, CHF_2); ^{19}F NMR: δ −79.8 (3F, d of m, $J = 6.6$ Hz, CF_3), −84.3 (2F, d of m, $J = 72.6$ Hz, CHF_2); HRMS calcd. for $C_4H_4F_5O$, 163.0182; found, 163.0157; MS: 149 (M^+-CH_3), 97 ($CF_3CHCH_3^+$), 95 (M^+-CF_3), 79, 77, 69 (CF_3^+), 51 (CHF_2^+), 49, 47, 45, 43, 29, 27.

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