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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_2COOH) [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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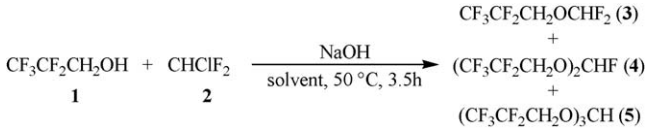
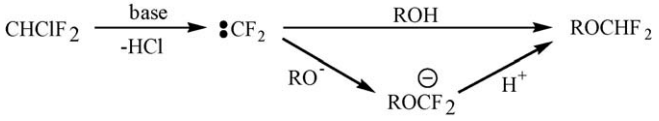
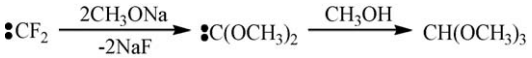


Scheme 1. Solvent effect.



Scheme 2. Mechanism for difluoromethylation.



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

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).

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.