

Synthesis of 2-chloro-1,1-difluoroallyl mesylates through novel rearrangement and C–C bond formation by their Pd-catalyzed reaction with diethylzinc

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Abstract

Treatment of 2-chloro-3,3-difluoroprop-2-en-1-ol derivatives (**2**) with methanesulfonyl chloride in the presence of a base did not give the expected esters but 2-chloro-1,1-difluoroprop-2-enyl methanesulfonates (**4**) through a novel [3,3] sigmatropic rearrangement. Reaction of **4** with diethylzinc in the presence of tetrakis(triphenylphosphine) palladium gave 1-alkyl- or 1-aryl-2-chloro-3-fluoropenta-1,3-dienes in moderate to good yields through a C–C bond formation followed by dehydrofluorination.

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1. Introduction

Nowadays, many fluorine compounds have attracted much attention in the various fields, such as medicines, agricultural chemicals and liquid crystals, based on their interesting properties. Therefore, various researches are continued for development of the new synthetic method for a fluorine compound. Previously, we have reported several new reactions of halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**), using it as a building block for the syntheses of some fluorine compounds [1–3]. Further, we reported that β -chloro- γ,γ -difluoroallyl alcohols (**2**) were obtained with satisfactory yields when **1** was treated with 2.2 equiv. of BuLi in the presence of carbonyl compounds (Scheme 1) [4].

We also reported that ethyl 4-chloro-3,3-difluoropent-4-enoates (**3**) were obtained by the reaction of **2** with triethyl orthoacetate in the presence of a catalytic amount of propanoic acid at 140 °C [5]. This reaction proceeded through the Claisen or [3,3] sigmatropic rearrangement. Thus, a ketene acetal must be formed first, then rearranged to

3. On the other hand, methanesulfonylation of **2** with methanesulfonyl (mesyl) chloride in the presence of an amine gave allyl mesylates (**4**) with moderate to good yields. In this reaction, the primary mesylates underwent a [3,3] sigmatropic rearrangement probably due to high electron withdrawing effect of the fluorine atoms or/and the sulfonyl group (Scheme 2).

A mesyloxy group is a good leaving group in nucleophilic reactions. However, the carbon–oxygen bond attached to a difluoromethylene group in **4** is highly stable and difficult to be replaced with a nucleophile. On the other hand, allyl alcohol derivatives react with a nucleophilic reagent through a π -allyl palladium complex to give substitution products. Thus, we examined the palladium-catalyzed reaction of **4** with a carbon nucleophile. In this paper, we would like to report formation of β -chloro- α,α -difluoroallyl mesylates **4** through a novel sigmatropic rearrangement and the reaction of **4** with diethylzinc in the presence of palladium catalyst.

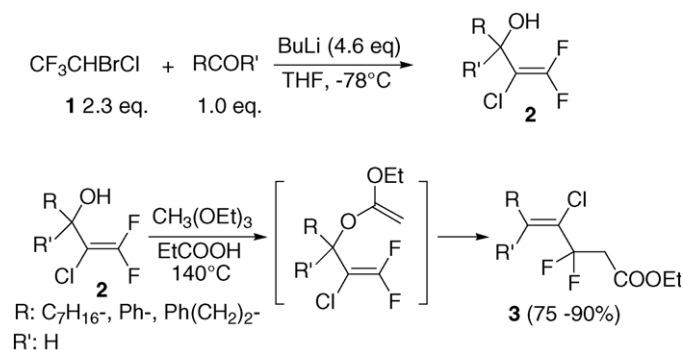
2. Results and discussion

The reaction of halothane with carbonyl compounds in the presence of 2.2 equiv. of BuLi gave **2** in the yield of 61–

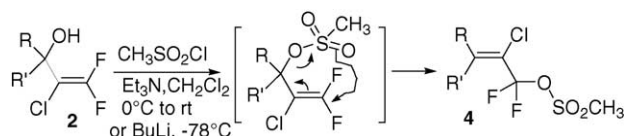
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Scheme 1.



Scheme 2.

83% at -78°C [4]. The products **2** were found to be rather unstable. Thus, we tried protection of the hydroxyl group of **2** by mesylation. Surprisingly, mesylates obtained by this reaction were not the simple mesylates, but [3,3] sigmatropic rearrangement products **4**.

The reaction of **2b** from 4-methoxybenzaldehyde with mesyl chloride in the presence of triethylamine in several minutes gave the product **4b** in the yield of 87%. The same reaction of **2e** obtained from acetophenone, a ketone, was much slower than those of the corresponding allyl alcohols obtained from aldehydes, as shown in Table 1.

This reaction proceeds with **2** derived from either aldehydes or ketones, in other words, secondary or tertiary allylic alcohols. Thus, mesyl chloride was added to a solution of **2a–f** in CH_2Cl_2 at 0°C , and triethylamine was added slowly, then the mixture was allowed to warm up to room temperature. The reaction was monitored by GLC analysis. Reactions of **2a–d** were completed in a few

Table 1
Reaction of **2** with $\text{CH}_3\text{SO}_2\text{Cl}$ in the presence of Et_3N

R	R'		Temperature ($^\circ\text{C}$)	Time (h)	Yield (%) ^a	Z/E ^c ratio
C_6H_5-	H-	(2a)	0	<1	65	>99/<1
4- $\text{CH}_3\text{OC}_6\text{H}_4-$	H-	(2b)	0	<1	87	>99/<1
4- ClC_6H_4-	H-	(2c)	0	<1	77	>99/<1
$\text{C}_7\text{H}_{15}-$	H-	(2d)	0	<1	86	>99/<1
C_6H_5-	CH_3-	(2e)	0 to rt	2	50 (33) ^b	87/13
$-(\text{CH}_2)_5-$		(2f)	0 to rt	2	36 (41) ^b	-

^a Isolated yield.

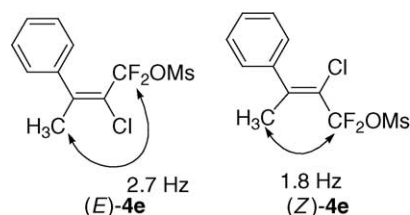
^b In parenthesis: recovery of **2**.

^c Determined by ^1H NMR.

minutes after addition of triethylamine. The reaction of **2e** or **2f** needed several hours at the same condition, while primary mesylates were not observed in both cases. These results show that the mesylates rearranged as soon as they were formed and that the mesylation of tertiary alcohols (**2e** and **2f** obtained from ketones) proceeded much slower than those of secondary alcohols (**2a–d**) obtained from aldehydes. Large amounts of **2e** or **2f** were recovered even after prolonged reaction times. The reaction of **2a–d** must have proceeded promptly at 0°C to room temperature. When pyridine was used as a base, reaction of both types of alcohols needed a few days probably due to its low basicity. On the other hand, BuLi accelerated the reaction. The mesylate **2e** is a mixture of *E/Z* isomers. The coupling constants between the methyl protons and the fluorine in the isomers of **2e** were 1.8 and 2.7 Hz. Generally, *trans* configuration of CH_3 and CF_2 showed a large coupling constant [6]. Therefore, we tentatively assigned the isomer showing the large coupling constant as *E*-form as shown in Fig. 1.

These results were the same as the result that Yamazaki et al. reported on the reaction of non-chlorinated 3,3-difluoroallyl alcohol and methanesulfonyl chloride [7]. This fact supports a hypothesis that the fluorine atoms must play an important role in this [3,3] sigmatropic rearrangement.

It is known that cleavage of the carbon–oxygen bond bound to a CF_2 group as that in **4** is very difficult. A nucleophilic reagent, an alkoxide or an amine, attacked the sulfur atom of mesylates to give a mesyl ester or a mesyl amide [7a,8]. On the other hand, allyl derivatives generally react with a carbon nucleophile through a π -allyl palladium complex, giving a substitution product [9]. Therefore, we examined the reaction of **4** with a carbon nucleophile in the

Fig. 1. Coupling constants of **4e**.

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