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Functional Group Transformation of α-Trifluoromethylated Alcohol Derivatives

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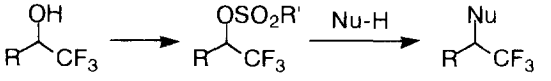
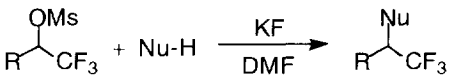
Abstract: Functional group transformation of α-trifluoromethylated alcohols was investigated. Nucleophilic substitutions of their sulfonates was achieved in the presence of metal fluoride as a base with complete inversion of the configuration. Copyright © 1996 Elsevier Science Ltd

In recent years, the introduction of fluorine-containing groups such as a trifluoromethyl group to organic compounds has been widely investigated because of their unique biologically activities and physical properties.[1] For example, the nucleophilic addition of trifluoromethyl anion equivalents (e.g., R_3Si-CF_3/F^-,[2] CF_3X/Zn[3]) to carbonyl compounds gives α-trifluoromethylated alcohols in good yields under the mild conditions. However, the difficulty of the transformation of the resultant hydroxyl group to other functional groups has hindered further extensive development in this field. In general, a hydroxyl group can easily undergo nucleophilic substitutions by the conversion into a good leaving group such as sulfonate,[4] but potent electronegativity of a trifluoromethyl group prevents even sulfonates of α-trifluoromethylated alcohols from nucleophilic substitution.[5] Therefore, there has been few reports about the functional group transformation of α-trifluoromethylated alcohols: To our knowledge, only one example, where sulfur nucleophile can be introduced *via* sulfonate,[6] has appeared in the literature, and the introduction of other nucleophiles has not been reported. In this paper, we wish to report nucleophilic substitutions of their sulfonates in the presence of metal fluoride as a base with complete inversion of the configuration.



Fluorine-containing mesylates, 2,2,2-trifluoro-1-phenylethyl methanesulfonate (**1**) and 1,1,1-trifluoro-2-octyl methanesulfonate (**2**) were easily prepared by the usual method.[7] Initially, we examined the nucleophilic substitution of these mesylates with benzoic acid. As was expected, only small amounts of the desired products were obtained by the reactions with sodium benzoate, which is commonly used for nucleophilic substitution of non-fluorinated sulfonates.[4,8] In the reaction of non-fluorinated mesylate, Sato and Otera reported that secondary mesylates undergo the S_N2 reaction with various nucleophiles in the presence of CsF.[9] We applied the CsF promoted substitution reaction of mesylates **1** with benzoic acid, and found that the desired substitution proceeded at elevated temperature and benzoate **3a** was formed in 35.3%

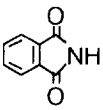
yield.[10] In order to increase the yield, a variety of basic materials were examined as a reaction promoter. Common base such as NaOH or K_2CO_3 gave only low yields of the products, but KF exhibited higher reactivity and afforded the substituted products in good yields.[10] The representative results were summarized in Table 1.[11] Aliphatic mesylate **2** was much less reactive than benzylic derivative **1** (entry 3). Next, thiophenol and phthalimide were also examined as nucleophiles. Reactivity of phthalimide was much lower than that of benzoic acid, and the desired product was obtained in poor yields. On the other hand, the substitution with thiophenol proceeded even at room temperature, and best result (71.1%) was obtained at 60 °C by using five equivalents of the nucleophile and KF (entries 4,5 and 6).



1 : R = Ph
2 : R = *n*-C_6H_{13}

3a : R = Ph, Nu = PhCOO-
3b : R = Ph, Nu = PhS-
3c : R = Ph, Nu = (Phthaloyl)N-
4a : R = *n*-C_6H_{13}, Nu = PhCOO-

Table 1. Reaction of Mesylates and Nucleophiles (Nu-H) in the Presence of KF.[a]

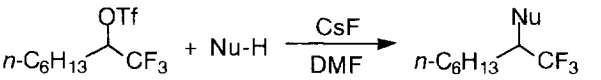
Entry	Substrate	Nu-H	(equiv.)	KF (equiv.)	Conditions	Product and Yield (%) [b]		
1	**1**		(2.0)	2.0	120 °C, 87 h	**3a**	51.3	(79.6)
2	**1**			5.0	120 °C, 87 h	**3a**	61.0	(94.5)
3	**2**			5.0	120 °C, 87 h	**4a**	24.0	(49.9)
4	**1**		(2.0)	5.0	r.t., 20 h	**3b**	43.3	(40.6)
5	**1**		(5.0)	5.0	r.t., 18 h	**3b**	66.9	(42.9)
6	**1**		(5.0)	5.0	60 °C, 6 h	**3b**	71.1	(84.3)
7	**1**		(2.0)	2.0	120 °C, 92 h	**3c**	8.2	(58.6)
8	**1**			5.0	120 °C, 92 h	**3c**	11.2	(71.7)

a : In all reactions, 0.5 mmol of substrate and 2.0 ml of DMF were used.
b : Conversion yield. Convertions of substrates were shown in the parentheses.

Next, the substitutions of trifluoromethanesulfonates (triflates), having higher leaving ability than mesylates, were investigated. 1,1,1-Trifluoro-2-octyl trifluoromethanesulfonate (**5**) could be prepared as a stable compound,[12] but the preparation of 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate was failed because of its low stability. This fact suggests that the reactivities of the fluorine-containing triflates are also very high, and they may easily undergo the substitution reactions. Indeed, the substitution of **5** with benzoic acid proceeded at room temperature by using CsF as a base, and the yield of benzoate **4a** (Table 2, entry 1) was much higher than that from mesylate **2** (Table 1, entry 3). The reaction with thiophenol took place rapidly and smoothly at room temperature, and thioether **4b** was obtained in excellent yield (entry 3). Even

on using phthalimide with low nucleophilic reactivity, the yield of the product was also increased, though higher reaction temperature was required (entry 5).

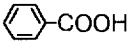
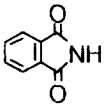
Finally, optically active triflate was applied to the present substitution reactions, and the configuration of the products was investigated. Optically active triflate *(R)*-**5** prepared from *(R)*-1,1,1-trifluoro-2-octanol (97% ee) underwent the substitutions with benzoic acid and thiophenol in reasonable yields under the same reaction conditions as above (Table 2, entries 2 and 4). HPLC analyses of the products using chiral columns[13] showed that both **4a** and **4b** had *S*-configurations in at least 96% ee. These results clearly indicate that the present substitutions proceed with complete inversion (S_N2 type reaction).



5

4a : Nu = PhCOO-
4b : Nu = PhS-
4c : Nu = (Phthaloyl)N-

Table 2. Reaction of **5** and Nucleophiles (Nu-H) in the Presence of CsF.[a]

Entry	Substrate	Nu-H	Conditions	Product and Yield (%) [b]
1	**5**		r.t., 41 h	**4a** 50.5 (82.2)
2	*(R)*-**5**		r.t., 40 h	*(S)*-**4a**[c] 57.1 (78.7)
3	**5**		r.t., 24 h	**4b** 84.4 (100)
4	*(R)*-**5**		r.t., 24 h	*(S)*-**4b**[c] 84.1 (100)
5	**5**		60 °C, 16 h	**4c** 21.3 (100)

a : In all reactions, 0.5 mmol of **5**, 1.0 mmol of nucleophile, 1.0 mmol of CsF and 2.0 ml of DMF were used.
b : Conversion yield. Convertions of **5** were shown in the parentheses.
c : Configuration was determined by chiral HPLC.

In conclusion, functional group transformation of α-trifluoromethylated alcohols, which has been thought to be difficult, was achieved by means of the nucleophilic substitution of their sulfonates in the presence of metal fluoride as a base. It was revealed that these substitutions were S_N2 type reaction and proceeded with complete inversion of the configuration. Further investigations of the transformation and wide application are now in progress.

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5. This low reactivity of the α-trifluoromethylated alcohols derivatives is also observed in the preparation of their methanesulfonates (mesylates): For example, the mesylate from 1-phenylethanol is unstable and easily decomposed at room temperature, whereas that from 2,2,2-trifluoro-1-phenylethanol is a very stable compound.[7]
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7. 2,2,2-Trifluoro-1-phenylethyl methanesulfonate (**1**) was prepared in 96% yield from 2,2,2-trifluoromethyl-1-phenylethanol and methanesulfonylchloride in the presence of triethylamine and 4-dimethylaminopyridine in ether. 1,1,1-Trifluoro-2-octyl methanesulfonate (**2**) was also prepared from 1,1,1-trifluoro-2-octanol in 69% yield.
8. This fact makes a sharp contrast with the reaction of sodium benzenethiolate,[6] and shows that the introduction of oxygen nucleophiles is much difficult by the usual manners.
9. Sato, T.; Otera, J. *Synlett* **1995**, 336-338.
10. A mixture of mesylate **1** (0.5 mmol), benzoic acid (1.0 mmol) and base (1.0 mmol) in DMF (2.0 ml) was stirred at 120 °C. Results were as follows: base, reaction time, conversion of **1**, conversion yield of **3a**; CsF, 115 h, 78.0%, 35.3%; NaOH, 39 h, 40.2%, 16.9%; K_2CO_3, 65 h, 84.2%, 19.5%; KF, 87 h, 79.6%, 51.3%. When CsF was used as a base, the hydrolysis of fluorinated mesylates was a severe side reaction because of the hygroscopicity of CsF, however, no hydrolysis of non-fluorinated mesylates took place at all under the similar reaction conditions. Therefore, a spray-dried KF is thought to be a most suitable base for the reaction of fluorinated mesylates in spite of its lower solubility.
11. Typical procedure: To a mixture of potassium fluoride (58 mg, 1.0 mmol), benzoic acid (122 mg, 1.0 mmol) and DMF (2.0 ml), mesylate **1** (127 mg, 0.5 mmol) was added under argon atmosphere. The mixture was stirred at 120 °C for 87 h. The reaction was quenched by adding water and products were extracted by ethyl acetate. Dodecane was added to the organic layer as an internal standard, and the conversion of **1** and the yield of the product were determined by GLC. 2,2,2-Trifluoro-1-phenylethyl benzoate (**3a**) was obtained in 51.3% yield: ^{1}H-NMR (TMS, $CDCl_3$): δ= 6.37 (q, *J*= 6.9 Hz, 1H), 7.40-7.66 (m, 8H), 8.11-8.15 (m, 2H); ^{19}F-NMR ($CFCl_3$, $CDCl_3$): δ= -76.34 (d, *J*= 6.9 Hz).
12. 1,1,1-Trifluoro-2-octyl trifluoromethanesulfonate (**5**) was prepared from 1,1,1-trifluoro-2-octanol and trifluoromethanesulfonic anhydride in the presence of triethylamine in 70% yield.
13. Configurations of **4a** and **4b** were determined by comparing with *(R)*-**4a** prepared from *(R)*-1,1,1-trifluoro-2-octanol and benzoyl chloride. HPLC conditions: For **4a**, Column: CHIRALPAK AD (DAISEL), Eluent: Hexane:2-Propanol = 400:1, Flow rate: 0.8 ml/min. For **4b**, Column: CHIRALCEL OD (DAISEL), Eluent: Hexane:2-Propanol = 1000:1, Flow rate: 0.8 ml/min.

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