Fluorocyclization of Unsaturated Aldehydes to Five- or Six-membered Cyclic Fluoroalcohols

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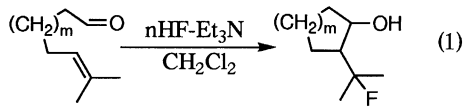
In the presence of HF-Et_3N complexes, the stereoselective cyclization of 5- and 6-alkenals takes place to give five- and six-membered cyclic fluoroalcohols, respectively.

Recently, HF-amine complexes such as HF-pyridine and HF-Et_3N have been used as the fluorinating reagents for the hydrofluorination and the halofluorination of alkenes, alkynes, or oxiranes instead of anhydrous hydrogen fluoride which is less selective and more hazardous.[1] However, as for the fluorination reaction accompanying carbon-carbon bond formation, only a few successful studies have been reported.[2] We would like to report here that nHF-Et_3N complexes (n=4-6) caused the fluorocyclization of unsaturated aldehydes to produce cyclic fluoroalcohols stereoselectively (Eq.1).

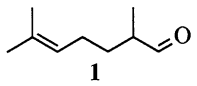
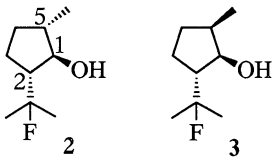
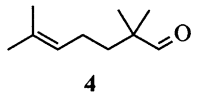
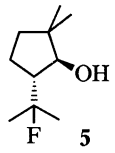
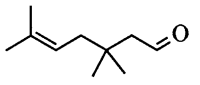
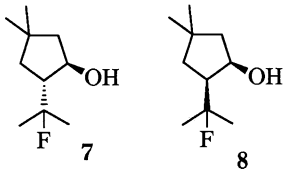


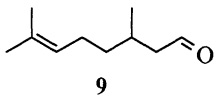
(1)

m = 1, 2 n = 4-6

Among the HF-amine complexes, 3HF-Et_3N, which is commercially available and most commonly used, showed no reactivity towards 2,6-dimethyl-5-heptenal (**1**). On the other hand, more acidic reagents such as 4HF-Et_3N[3], 5HF-Et_3N[3], and 6HF-Et_3N[3], could cause the fluorocyclization reaction of **1** to produce a fluoroalcohol having a five-membered ring (**2**) stereoselectively with only a slight amount of its stereoisomer (**3**) as shown in Table 1 (Entries 1-4).[4] When 9HF-pyridine (Olah's reagent) was used, **1** was completely consumed but the desired fluoroalcohol could not be obtained at all (Entry 5). The selectivity for **2** was slightly improved by carrying out the reaction at -78 °C (Entry 6). From the reaction of 2,2,6-trimethyl-5-heptenal (**4**) and 3,3,6-trimethyl-5-heptenal (**6**) with 5HF-Et_3N, the fluorocyclization products (**5** and **7**) were also obtained selectively (Entries 7-9). The fluorocyclization reaction of 6-alkenals took place less selectively under the same

Table 1. Fluorocyclization Reaction of 5-Alkenals and 6-Alkenals

Entry	Aldehyde	nHF-Et_3N	React. Cond.	Yield/%[a]	Products[b]
	 **1**				 **2** : **3**
1		3HF-Et_3N	25°C, 1h	0	
2		4HF-Et_3N	25°C, 1h	50	90 : 10
3		5HF-Et_3N	25°C, 1h	78	89 : 11
4		6HF-Et_3N	25°C, 1h	69	83 : 17
5		9HF-Pyridine	25°C, 1h	0	
6		5HF-Et_3N	-78°C, 3h	71	93 : 7
	 **4**				 **5**
7		5HF-Et_3N	-78°C, 3h	72	
8		5HF-Et_3N	25°C, 1h	77	
	 **6**				 **7** : **8**
9		5HF-Et_3N	-78°C, 3h	55	92 : 8



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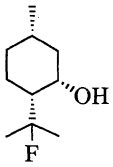

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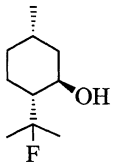

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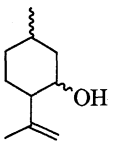

12

10	$5HF\text{-}Et_3N$	25°C, 1h	78	52	:	35	:	13
11	$5HF\text{-}Et_3N$	-78°C, 3h	80	70	:	24	:	6
12	$5HF\text{-}Et_3N$	-94°C, 3h	81	77	:	20	:	3

a Glpc yields based on aldehydes. b The stereochemistry of the products was determined from NOE of NMR.

conditions to provide fluoroalcohols having a six-membered ring.[5] For instance, citroneral (**9**) gave two fluoroalcohols (**10** and **11**) as well as isopulegols (**12**) derived from the intramolecular ene-type reaction (Entry 10).[7] By carrying out the reaction at low temperature, the selectivity could be improved and **10** was selectively obtained (Entries 11 and 12).[8]

A typical procedure for the synthesis of **2** is as follows. To a CH_2Cl_2 solution (2 ml) of $5HF\text{-}Et_3N$ complex (2 mmol, 402 mg) in a Teflon vessel, was added dropwise at -78 °C 2,6-dimethyl-5-heptenal (1 mmol, 126 mg) in CH_2Cl_2 (1 ml). The mixture was stirred at this temperature for 3 h and then poured into aqueous sodium bicarbonate. The products were extracted with ether and then isolated by column chromatography (silica gel / hexane-ether). The products were identified by NMR, IR, and high resolution mass spectra and the yield of the products were obtained by GC analysis using nonane as an internal standard.

References and Notes

1 N. Yoneda, *Tetrahedron*, **47**, 5329 (1991). C. Bonini, G. Righi, *Synthesis*, **1994**, 225. M. R. C. Gerstenberger, A. Haas, *Angew. Chem. Int. Ed. Engl.*, **20**, 647 (1981).

2 M. Shimizu, H. Yoshioka, *Tetrahedron Lett.*, **28**, 3119 (1987). S. Kanemoto, M. Shimizu, H. Yoshioka, *Bull. Chem. Soc. Jpn.*, **62**, 2024 (1989).

3 These reagents were prepared by mixing anhydrous HF and Et_3N under nitrogen at -78 °C.

4 The assignment of the configuration of the substitutents on the C-1, C-2, and C-5 of the cyclopentane ring of **2** was made by NOE experiments which show the NOE enhancements of 1.4% between H on C-1 and CH_3 on C-5 and of 2.6% between H on C-1 and CH_3 of $-CF(CH_3)_2$ on C-2.

5 It was reported that the ene-type cyclization reaction of 6-alkenals takes place more quickly than that of 5-alkenals and in the cyclization reaction of **9** induced by alkylaluminum chlorides, **12** was obtained exclusively without the formation of any chlorocyclization products.[6]

6 B. B. Snider, M. Karras, R. R. Price, and D. J. Rodini, *J. Org. Chem.*, **47**, 4538 (1982).

7 Since isopulegols (**12**) did not react with $5HF\text{-}Et_3N$ under the same reaction conditions, they are not the precursors of **10** and **11**.

8 Under the same reaction conditions, the endocyclization of 4-methyl-4-pentenal did not take place.