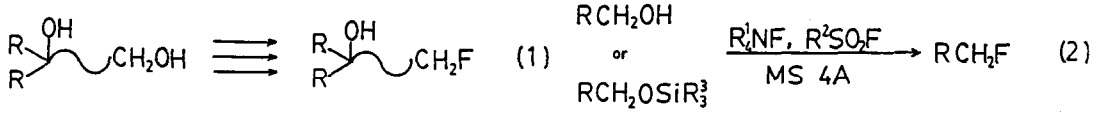
Tetrahedron Letters,Vol.26,No.35,pp 4207-4210,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

CHEMOSELECTIVE FLUORINATION FOR PRIMARY ALCOHOLS

Makoto Shimizu,* Yuko Nakahara, and Hirosuke Yoshioka*
The Institute of Physical and Chemical Research (RIKEN)
Wako, Saitama 351-01 Japan

Summary: Primary alcohols and their silylated derivatives are selectively fluorinated by tetraalkylammonium fluoride and aryl(or alkyl)sulfonyl fluoride.

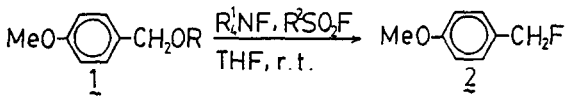
Increasing interests in fluorine-containing medicines and pesticides stimulate the development of new methodologies for the preparation of specifically fluorinated compounds.[1] One of the most important and straightforward strategies for the introduction of a limited number of fluorine into a target molecule is the conversion of a hydroxyl group into fluorine. For this purpose certain reagents have been devised.[2] However, most of them have innegligible drawbacks due to formation of by-products derived from poly-fluorination, olefination, etherification , etc, and/or tedious preparation and handling of reagents. We have been exploring mild fluorination methods for alcohols especially associated with the molecule designs for the bio-controlling agents specifically fluorinated, and now found a selective fluorination method for primary alcohols, which involves the use of tetraalkylammonium fluoride and aryl(or alkyl)sulfonyl fluoride.[3]



Treatment of p-methoxybenzyl alcohol with 1.1 equiv of tetra-*n*-butylammonium fluoride (TBAF) and 1.1 equiv of p-toluenesulfonyl fluoride (TsF) in THF in the presence of molecular sieves 4A[4] at room temperature gave p-methoxybenzyl fluoride in 46% yield (Run 1). A satisfactory result was obtained when TBAF (3.0 eq) and methanesulfonyl fluoride (MsF, 2.0 eq) were employed, and the desired product was obtained in 81% (Run 2).[5] This fluorination method is also applicable to silylated primary alcohols. p-Methoxybenzyl trimethylsilyl ehter underwent clean fluorination reaction to give the fluorinated product in 70% where a

combination of benzyltrimethylammonium fluoride (BTAF)[6] and MsF was found to work better (Run 3). *t*-Butyldimethylsilylated analogue was also fluorinated although the yields were somewhat lower (Runs 5 and 6). Primary aliphatic alcohols needed higher reaction temperatures for the completion of the reaction, and the fluorination was performed in refluxing THF. BTAF was superior in the case of trimethylsilylated compounds (Run 11), whereas BTAF did not effect the reaction with *t*-butyldimethylsilyl ether, and TBAF appears to be essential in this case (Runs 12 and 13).

Table 1[a]

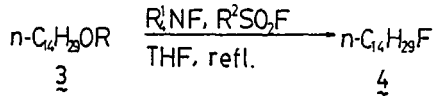


1 2

Run	R	R^1_4NF (eq)	R^2SO_2F (eq)	2/Yield (%)[b,c]
1	H	TBAF(1.1)	TsF(1.1)	46
2	H	TBAF(3.0)	MsF(2.0)	81
3	$SiMe_3$	BTAF(2.0)	MsF(1.2)	70
4	$SiMe_3$	TBAF(3.0)	MsF(1.5)	61
5	$SiMe_2$ *t*-Bu	TBAF(3.0)	MsF(1.5)	57
6	$SiMe_2$ *t*-Bu	BTAF(2.0)	MsF(1.5)	52

[a]Detailed procedure, see ref. 9. [b]Ref. 7.
[c]Yield determined by NMR using a calibrated internal standared.

Table 2[a]



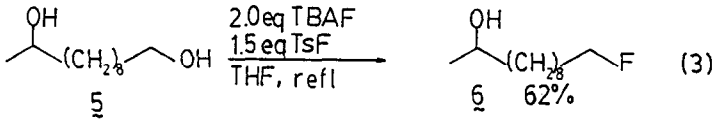
3 4

Run	R	R^1_4NF (eq)	R^2SO_2F (eq)	4/Yield (%)[b,c]
7	H	TBAF(3.0)	TsF(2.0)	83
8	H	TBAF(3.0)	MsF(2.0)	72
9	H	BTAF(2.0)	MsF(1.5)	36
10	$SiMe_3$	TBAF(3.0)	TsF(2.0)	49
11	$SiMe_3$	BTAF(3.0)	TsF(2.0)	87
12	$SiMe_2$ *t*-Bu	TBAF(3.0)	TsF(2.0)	76
13	$SiMe_2$ *t*-Bu	BTAF(3.0)	TsF(2.0)	0

[a]Detailed procedure, see ref. 9. [b]Ref. 7.
[c]Yield determined by NMR using a calibrated internal standard.

Examination into chemoselectivity of the present method has revealed that the fluorination is specific for primary alcohols. Under the fluorination conditions (3.0 eq TBAF, 2.0 eq MsF, THF, r.t., 24 hr) secondary and tertiary alcohols were quantitatively recovered. Under more forcing conditions (3.0 eq TBAF, 2.0 eq MsF, THF, refl, 17 hr), secondary alcohols afforded dehydrated olefins (10-30 %) along with the recovered stating materials (70-90 %), whereas tertiary alcohols were almost unaffected[8] (>95 % recovery). For preferential fluorination for primary hydroxyl groups we considered that the steric and electronic effects of R group in RSO_2F were very important factors, and therfore screened a variety of RSO_2F, e.g., R=camphor, *p*-bromophenyl, 2,4,5-trichlorophenyl, 2,4,6-triisopropylphenyl, 2,4,6-trimethylphenyl, *p*-tolyl, methyl, and so on,[9] for the selective fluorination of primary alcohols using dodecane-1,10-diol (5) as substrate, and as

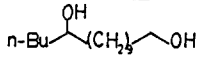
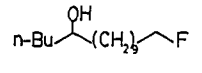
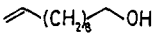
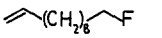
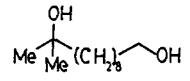
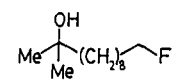
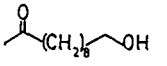
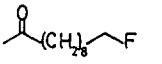
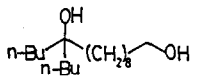
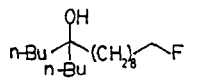
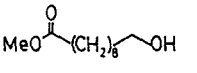
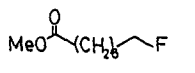
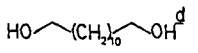
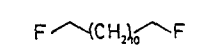
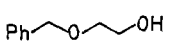
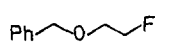
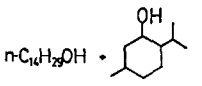
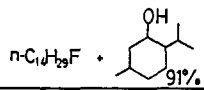
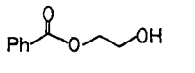
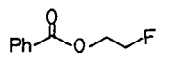
a result, p-tosyl fluoride gave the best result (*vide infra*).



(3)

Several primary alcohols possessing secondary or tertiary hydroxyl group, or other functionalities were subjected to the present reaction,[10] and Table 3 summarizes the result. In the presence of secondary or tertiary hydroxyl groups primary alcohols underwent selective fluorination to give mono-fluorinated products in good yield. Olefins, ketones, esters, and ethers remained unaffected by the present procedure.

Table 3. Selective Fluorination for Primary Alcohols[a]

Run	ROH	RF	Yield(%)[b,c]	Run	ROH	RF	Yield(%)[b,c]
14			69	19			81
15			80	20			65
16			73	21			86
17	 [d]		71	22			89
18			80	23			66

[a]The reaction was carried out in refluxing THF in the presence of molecular sieves 4A with alcohol:TBAF:TsF=1.0:3.0:2.0. [b]Ref. 7. [c]Isolated yield. [d]Alcohol:TBAF:TsF=1.0:6.0:4.0.

Thus demonstrated in the above examples, by the present method the primary alcohols and their silylated derivatives are cleanly converted to mono-fluorinated compounds by simple operation where the formation of ethers and olefins is in most cases negligible or in a few per cent order, if any. Furthermore, the chemoselectivity of this procedure may offer wide applicability to the selective fluorination requisite for newer approaches dealing with poly-functionalized intermediates.

References and Notes

1. H. Yoshioka, C. Takayama, and N. Matsuo, *J. Synth. Org. Chem. Jpn.*, **42**, 770 (1984); N. Ishikawa, *ibid.*, **42**, 809 (1984); T. Fuchikami, *ibid.*, **42**, 775 (1984); I. Kumadaki, *ibid.*, **42**, 786 (1984); K. Bannai and S. Kurozumi, *ibid.*, **42**, 794 (1984); R. Filler and Y. Kobayashi, Eds. "Biomedical Aspects of Fluorine Chemistry", Kodansha Ltd., Elsevier Biomedical Press: Tokyo, New York 1982.
2. G. A. Boswess, Jr., W. C. Ripka, R. M. Scribner, and C. W. Tullock, *Org. Reactions*, **21**, 1 (1974); C. M. Sharts and W. A. Sheppard, *ibid.*, **21** 125 (1974); Y. Kobayashi and C. Akashi, *Chem. Pharm. Bull.*, **16**, 1009 (1968); Y. Kobayashi, C. Akashi, and K. Morinaga, *ibid.*, **16**, 1784 (1968); G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. I. Kerekes , and J. A. Olah, *J. Org. Chem.*, **44**, 3872 (1979); A. Takaoka, H. Iwakiri, and N. Ishikawa, *Bull. Chem. Soc. Jpn.*, **52**, 3377 (1980); T. Asai, A. Yasuda, M. Kato, K. Uchida, and M. Yamabe,*The 1984 International Chemical Congress of Pacific Basin Societies, Honolulu*, (1984); Abstract 10F03.
3. Conversion of alkyl sulfonates to alkyl fluorides by tetra-*n*-butylammomium fluoride has been known; see for example, A. B. Foster, R. Hems, and J. M. Webber, *Carbohyd. Res.*, **5**, 292 (1967).
4. Molecular sieves 4A dried in a microwave oven under vaccum were used.
5. We consider that the reaction proceeds via initial deprotonation of alcohol with F^- followed by sulfonylation and replecement by F^-. The ability of fluoride ion to deprotonate; see for a review, J. H. Clark, *Chem. Rev.*, **80**, 429 (1980).
6. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **104**, 1025 (1982).
7. All compounds gave satisfactory spectral data.
8. The selectivity of the present methods is explained in terms of the sulfonylating ability of RSO_2F; faster for primary alcohols than for secondary ones and practically no reaction with tertiary hydroxyl groups.
9. Sulfonyl fluorides were usualy prepared from the corresponding chlorides via exchange reaction with KF in toluene-water. cf. W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).
10. The following example is a typical experimental procedure: To a solution of TBAF·$3H_2O$ (purchased from Aldrich Chemical Co., and used without further purification, 391 mg, 1.24 mmole) in 3 ml of THF in the presence of molecular sieves 4A (1 g)[4] was added a mixture of p-TsF (144 mg, 0.83 mmole) and 2-methyl-dodecane-2-11-diol (83 mg, 0.41 mmole) in 2 ml of THF at room temperature. After stirring at reflux for 17 hrs, the reaction mixture was filtered through a pad of silica gel with the aid of a small amount of ethyl acetate. The filtrate was concentrated to give an oil (84 mg), which was purified by flash silica gel column chromatography to afford 11-fluoro-2-hydroxy-2-methyldodecane (67 mg, 80%).

(Received in Japan 20 April 1985)