Monatshefte für Chemie 136, 1579–1582 (2005)
DOI 10.1007/s00706-005-0296-9

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Practical and General Method for Direct Synthesis of Alkyl Fluorides from Alcohols under Mild Conditions

Babasaheb P. Bandgar*, **Vinod T. Kamble,** and **Ankush V. Biradar**

Organic Chemistry Research Laboratory, School of Chemical Sciences,
Swami Ramananad Teerth Marathwada University, Nanded-431 606, Maharashtra, India

Received November 11, 2004; accepted (revised) January 26, 2005
Published online August 22, 2005

Summary. A variety of alcohols were treated with Ph_3P and KF in CCl_4-*DMF* at room temperature to afford the corresponding fluorides in very good yields.

Keywords. Alcohols; Alkyl fluorides; Triphenyl phosphine; Potassium fluoride; Chemoselective.

Introduction

Increasing interest 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 fluorine into a target molecule is the conversion of a hydroxyl into a fluorine group. The common method for the transformation of alcohols into alkyl fluorides is substituting the hydroxyl group first with chlorine or bromine and then with fluorine using alkali fluorides. This method is not applicable when the alcohol contains substituents which should not be halogenated, for instance, double or triple bonds. Other limitations associated with this method are high temperatures and/or long reaction times generally necessary due to the low solubility and nucleophilicity of the fluoride ion. Furthermore, significant amounts of alkenes and alcohols are concomitantly formed because the fluoride ion also behaves as a strong base and hydrolyzing agent. In another method the hydroxyl group is first tosylated and then treated with potassium fluoride [2]. The third method is to decompose fluoroformates derived from alcohols by warming it in the presence of pyridine [3]. The fourth one is by pyrolysis of 2-alkylpseudouromium fluorides derived from alcohols and fluoroborates [4]. However, all these methods starting from alcohols require two steps or more.

* Corresponding author. E-mail: vtkd@rediffmail.com

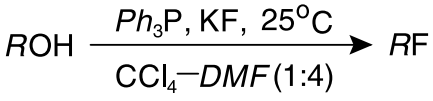
Alkyl fluorides are also prepared in one step from alcohols by heating with difluorotriphenyl phosphorane [5a] or diphenyltrifluoro phosphorane [5b] at 140–150°C. However, drastic conditions, long reaction times, poor to low yields, and requirement of specially prepared reagents by heating at 150°C for longer periods make this process less attractive. Expensive reagents such as diethylaminosulfur trifluoride (*DAST*) [6] and bis(2-methoxyethyl)aminosulfur trifluoride [7] are also reported. However, these reagents are hazardous, thermally unstable, and therefore utilization of these reagents for large scale applications is limited. Primary and secondary alcohols can be transformed to the corresponding fluorides in one step using 2-chloro-1,1,2-trifluorotriethylamine [8]. Considering the complexity of this reagent and its unsatisfactory yields with tertiary alcohols, a more practical, mild, one-step, and general reagent for this kind of transformation should increase the synthetic potential of the reaction. Recently, Ph_3P and NaN_3 in CCl_4-*DMF* (1:4) have been used as a mild reagent for the direct conversion of alcohols into azides/amines [9].

Results and Discussions

We report in this communication our results for the direct conversion of alcohols into fluorides using triphenyl phosphine and KF in CCl_4-*DMF* (1:4) under mild conditions (Scheme 1).

When alcohols were treated with Ph_3P and KF in CCl_4-*DMF* (1:4) at room temperature, the corresponding fluorides were obtained in very good yields. The results are summarized in Table 1. The method appears to be general, as a variety of alcohols such as primary, secondary, tertiary, benzylic, allylic and propargylic alcohols underwent smooth fluorination. It is important to note that any C=C and C≡C bonds present elsewhere in the molecule remained unaltered under these reaction conditions (Table 1, entries 14, 15, 16). Thus, the reaction is highly chemoselective and the functional groups in the substrate such as phenol (entry 1), chloro (entry 2), *Me*O (entry 4), methylenedioxy (entry 5), ketone (entry 8), and tosyl (entry 18) were tolerated under the reaction conditions. Benzyl alcohol is selectively converted into corresponding fluoride in the presence of phenol (entry 1) and primary alcohol. Diols (entries 7, 11) are also smoothly transformed into the corresponding difluorides with two equivalents of Ph_3P and KF. Methods reported so far gave unsatisfactory yields of fluorides in the case of secondary and tertiary alcohols. In this context, the present procedure is noteworthy because even secondary and tertiary alcohols furnished very good yields of the corresponding fluorides.

In conclusion, we have found a convenient, mild, and general procedure for the direct conversion of alcohols into the corresponding fluorides in very good yields.



Scheme 1

Table 1. Preparation of alkyl fluorides

Entry	Alcohol	Fluoride	Time / h	Yield[a,b] / %
1	4-HO–C_6H_4–CH_2OH	4-HO–C_6H_4–CH_2F	0.5	92
2	4-Cl–C_6H_4–CH_2OH	4-Cl–C_6H_4–CH_2F	0.75	93
3	3-O_2N–C_6H_4–CH_2OH	3-O_2N–C_6H_4–CH_2F	1.5	90
4	4-*Me*O–C_6H_4–CH_2OH	4-*Me*O–C_6H_4–CH_2F	1.5	88
5	3,4-$CH_2(O)_2C_6H_3$–CH_2OH	3,4-$CH_2(O)_2C_6H_3$–CH_2F	2.5	91
6	Furfuryl alcohol	Furfuryl fluoride	2.0	90
7	4-HOH_2C–C_6H_4–CH_2OH	4-FH_2C–C_6H_4–CH_2F	3.5	90
8	*Ph*–CO–CHOH–*Ph*	*Ph*–CO–CHF–*Ph*	4.0	84
9	$CH_3(CH_2)_6OH$	$CH_3(CH_2)_6F$	3.0	86
10	Tetrahydrofurfuryl alcohol	Tetrahydrofurfuryl fluoride	2.5	86
11	$HO(CH_2)_6OH$	$F(CH_2)_6F$	3.0	91
12	Cyclohexanol	Cyclohexyl fluoride	3.5	89
13	Menthol	Menthyl fluoride	4.0	87
14	Cinnamyl alcohol	Cinnamyl fluoride	2.0	85
15	Citronellol	Citronellyl fluoride	2.0	87
16	*Ph*–CH_2–CH(OH)–CH≡CH	*Ph*–CH_2–CH(F)–CH≡CH	4.5	89
17	*Ph*–CH(OH)–$(CH_2)_2OH$	*Ph*–CH(F)–$(CH_2)_2F$	1.0	80
18	4-*Ts*O–C_6H_4–CH_2OH	4-*Ts*O–C_6H_4–CH_2F	1.0	86

[a] Yield of isolated pure product; [b] products are characterized by IR, ^{1}H NMR, elemental analysis, and comparison with authentic samples

Tolerance of other functional groups present elsewhere in the molecule is superior compared to the reported ones.

Experimental

All chemicals were of analytical grade and used as obtained. IR spectra were recorded on a Bomem MB 104 FT-IR spectrometer and ^{1}H NMR spectra were recorded on an AC 300F NMR spectrometer (300 MHz).

General Procedure

KF (10 mmol) was added to a mixture of 5 mmol alcohol, and 12.5 mmol triphenyl phosphine dissolved in 5 cm^3 CCl_4-*DMF* (1:4). The mixture was stirred at room temperature. After completion of the reaction (TLC), the mixture was extracted with 2×5 cm^3 of *n*-pentane. The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to isolate the crude product, which was further purified by column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:9).

References

[1] a) Mascaretti DA (1993) Aldrichimica Acta **26**: 47; b) Wilkinson JA (1992) Chem Rev **92**: 505; c) Albanese D, Landini D, Penso M (1998) J Org Chem **63**: 9587; d) Resnati G (1993) Tetrahedron **49**: 9385; e) Welch JT (1987) Tetrahedron **43**: 3123
[2] Edgell WF, Parts L (1955) J Am Chem Soc **77**: 4899
[3] Nakanishi S, Myers TC, Jensen EV (1955) J Am Chem Soc **77**: 3099
[4] Amin JH, Newton J, Pattison FLM (1965) Can J Chem **43**: 3173

[5] a) Kobayashi Y, Akashi C (1968) Chem Pharm Bull **16**: 1009; b) Kobayashi Y, Akashi C, Morinaga K (1968) Chem Pharm Bull **16**: 1784
[6] Middleton WJ (1975) J Org Chem **40**: 574
[7] Lal GS, Pez GP, Pesaresi RJ, Prozonic FM (1999) Chem Commun 215
[8] a) Yarovenko NN, Raksha MA (1959) Zh Obshch Khim **21**: 2159; b) Ayer DE (1862) Tetrahedron Lett 1065; c) Knox LH, Yelarde E, Berger S, Cuadriello D, Cros AD (1962) Tetrahedron Lett 1249
[9] Reddy GVS, Rao GV, Subramanyam RVK, Iyengar DS (2002) Synth Commun **30**: 2223