〔Chem. Pharm. Bull.
16(6)1009—1013(1968)〕

UDC 547.26.04 : 547.221.07

Studies on Organic Fluorine Compounds. III.[1] Conversion of Alcohols to Fluorides by Difluorotriphenylphosphorane[2]

Yoshiro Kobayashi[3a] and Chigen Akashi

Research Laboratories, Yawata Chemical Industry Co., Ltd.[3]

(Received July 28, 1967)

The reactions of difluorotriphenylphosphorane with alcohols were studied, and the former substance was found to be an excellent one-step flourinating reagent for substituting the hydroxyl group of primary and secondary alcohols. When more than one mole equivalent of alcohols were added to the reagent, the corresponding ethers were also obtained.

The common method for the transformation of alcohols into alkyl fluorides substituting the hydroxyl group with the fluorine atom is the one in which the hydroxyl group is first substituted with chlorine or bromine and then with fluorine using alkali fluorides.[4] This method is not applicable when the alcohol has any part in the structure which should not be halogenated, for instance, double bonds. There is another method, similar to the one mentioned above, where the hydroxyl group is tosylated and treated with potassium fluoride.[5] The third method is to decompose fluoroformate derived from alcohols by warming it in the presence of pyridine.[6] And the fourth is by the pyrolysis of 2-alkylpseudouromiumfluoride, which has also been derived from alcohols, and fluoroborates.[7] But all these methods, starting with alcohols, require two steps or more.

Yarovenko and Raksha found that primary and secondary alcohols can be transformed to the corresponding fluorides by one step using 2-chloro-1,1,2-trifluorotriethylamine,[8] which is applied in the fluorination of hydroxy-steroids.[9,10] Considering the complexity of this reagent, we think it significant of find more one-step reagents of this kind.

A reaction whose formula is shown below[11] attracted our attention and prompted us to apply it to fluorination.

$$R_3P + X_2 + R'OH \longrightarrow (R_3PX_2 + R'\text{-}OH) \longrightarrow R_3PO + R'X + HX$$

$$(R, R' = \text{aryl or alkyl};\ X = Cl, Br, I)$$

The yield of alkylhalide from this reaction was 50—98%, but in the case of fluorine, the method could not, of course, be directly applied owing to its high reactivity. The mechanism of this reaction has been studied; first, R_3PX_2 was produced as intermediate,

---

[1] Part II: *Chem. Pharm. Bull.* (Tokyo), **15**, 1901 (1967)

[2] Most part of this work was presented at the Annual Meeting of the Chemical Society of Japan, Kyoto, April 1966.

[3] Location: *46 Sakinohama, Nakabaru, Tobata-ku, Kitakyushu-shi.* a) Present Address: *Tokyo College of Pharmacy, Kashiwagi, Shinjuku-ku, Tokyo.* All communication and requests are to be sent to this author.

[4] A.L. Henne, "Organic Reactions," Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1944, p. 49.

[5] W.F. Edgell and L. Parts, *J. Am. Chem. Soc.*, **77**, 4899 (1955).

[6] S. Nakanishi, T.C. Myers, and E.V. Jensen, *J. Am. Chem. Soc.*, **77**, 3099 (1955).

[7] J.H. Amin, J. Newton, and F.L.M. Pattison, *Can. J. Chem.*, **43**, 3173 (1965).

[8] N.N. Yarovenko and M.A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959).

[9] D.E. Ayer, *Tetrahedron Letters*, **1962**, 1065.

[10] L.H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A.D. Cros, *Tetrahedron Letters*, **1962**, 1249.

[11] G.A. Wiley, F.L. Hershkowitz, B.M. Rein, and B.C. Chung, *J. Am. Chem. Soc.*, **86**, 965 (1964).

which reacted with the alcohol, although this substance could not be separated because of its instability.

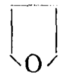
Difluorotriphenylphosphorane was synthesized by Smith,[12] treating triphenylphosphin or triphenylphosphin oxide with sulfur tetrafluoride. And another preparation of treating triphenylphosphin with N_2F_4 is also known,[13] but nothing is known about any reaction of this compound.

The authors synthesized difluorotriphenylphosphorane using Smith's method improved by us, and washed it with ether, recrystallized it from dimethylformamide, and purified it by sublimation.

According to the literature,[12] the reaction had been carried out in two different stages of heating; the yield was 69%. In our case, 98% yield was obtained by heating at 140—150° for 8—10 hours. In nitrogen atmosphere this crystalline substance is stable, and can be handled and stored; it is not extremely hygroscopic as described in the literature. We found that this substance is an excellent one-step fluorinating agent for alcohols. We heated alcohols with two mole equivalents of difluorotriphenylphosphorane at 150—170° for 5—7 hours in a Hastelloy-C-lined autoclave using acetonitrile as solvent with stirring. The reaction condition was somewhat more drastic than in the cases where other halogens were involved,[11] but below 120°, almost all the unchanged material was obtained. After being cooled to room-temperature, the autoclave was opened and crystals, phosphorous compounds, were filtered off. The filtrate was carefully distilled in the presence of sodium fluoride to make hydrogen fluoride inert ($NaF+HF \rightarrow NaHF_2$), and the alkyl-fluoride fraction was purified using the preparative gas chromatography. Glass apparatus can be used for the reaction without solvent, but it is necessary to neutralize the generated hydrogen fluoride by adding tertiary amines such as triethylamine in advance.

This fluorination reaction was successfully carried out for the representative of primary-, secondary-, ω-substituted, and dialcohols, and gave the results as shown in Table I. The yield of alkyl fluoride based on alcohol was derived from gas chromatographic analysis of the reaction mixture. The conditions in these reactions are not necessarily optimum, and we believe that the yield can be increased by using more reagent.

TABLE I

Alcohol	Mole Ratio Ph_3PF_2/alc.	Main Product	Compd. No.	Yield (% based on alcohol)
n-octyl-	2.02	*n*-$C_8H_{17}F$	I	78.2
n-amyl-	1.85	*n*-$C_5H_{11}F$	II	60.3
isoamyl-	2.00	$(CH_3)_2CHCH_2CH_2F$	III	52.6
isoamyl-	0.32	$[(CH_3)_2CHCH_2CH_2]_2O$	X	64.0[a]
benzyl-	2.00	$C_6H_5CH_2F$	IV	32.8
phenetyl-	2.05	$C_6H_5CH_2CH_2F$	V	72.8
3-chloropropyl	2.00	$ClCH_2CH_2CH_2F$	VI	64.2
hexamethylenglycol	2.81	$FCH_2(CH_2)_4CH_2F$	VII	12.0
sec-amyl-	1.87	$CH_3CH_2CH_2CHFCH_3$	VIII	52.2
neopentyl-	1.90	$(CH_3)_2CH=CHCH_3$	IX	48.0
tetramethylenglycol	0.35		XI	91.0[a]
cyclohexyl-	0.38		XII	66.0[a]

[a] % based on Ph_3PF_2

---

12) W.C. Smith, *J. Am. Chem. Soc.*, **82**, 6176 (1960).
13) W.C. Firth, Jr., S. Frank, M. Gruber, and V.P. Wystrach, *Inorg. Chem.*, **4**, 765 (1965).

The main products were identified by comparing with the corresponding authentic samples in the refractive index, infrared spectrum, and retention time in gas chromatography. In some cases, peaks of what seemed to be olefins formed as by-products were noticed in gas chromatogram, but the quantity was small.

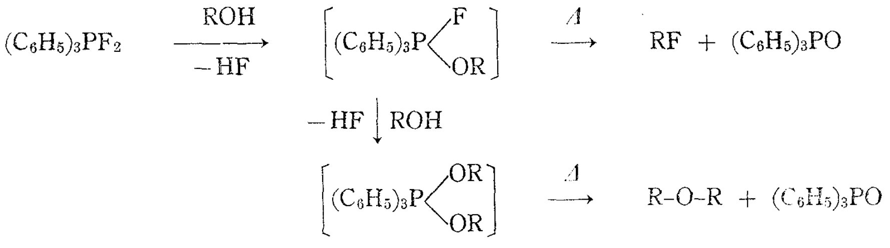


Chart 1

We deduce that the reaction has proceeded according to the above formula; for, when more than one mole equivalent of alcohols to the reagent was used, the corresponding ethers were produced as by-products, and when more than two mole equivalents were used ethers were the main products, alkyl fluoride not being produced at all.

In the case of neopentylalcohol, 2-methylbutene-2 was obtained as the main product, and Wagner-Meerwein rearrangement as in the following formula was due to the production.

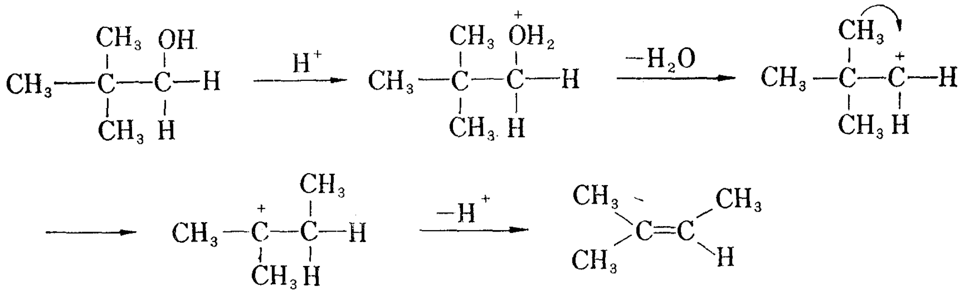
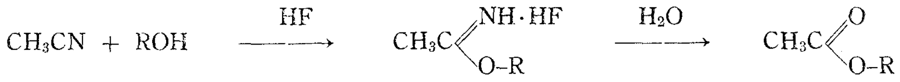


Chart 2

On the gas chromatogram, there were small peaks which were presumed to be of alkyl fluoride, but we could not verify the fact as the authentic sample was not available.

In the case of cyclohexanol, the main product was cyclohexene; since this was obtained when the reaction temperature was as low as 60°, it is more reasonable to think that cyclohexanol was dehydrated than that fluoride which had been produced was dehydrofluorinated.

At an early stage of this work, to know how the hydrogen fluoride generated in the course of reaction contributed to the fluorination, we treated isoamyl alcohol with the corresponding hydrogen fluorides and acetonitrile under the same reaction conditions as mentioned above. The main product was isoamyl acetate, while very little isoamyl fluoride was obtained, thereby suggesting the following formula for the reaction.



As this substance could not be obtained from the reaction using difluorotriphenylphosphorane, we assumed that the first fluorine atom of the reagent was entirely substituted with the alcohol very fast and the generated hydrogen fluoride had not affected the fluorination, which was also observed in the cases of the reaction of other halogens with triphenylphosphin.[14] A further proof for this is that the yield was not much different from that of the reaction with triethylamine.

As this reagent and its reaction products are liable to be toxic, caution should be used not to touch or inhale them directly.

Experimental

Difluorotriphenylphosphorane——In a 100 ml autoclave, distilled triphenylphosphine (60.0 g, 0.17 mole), SF_4 (53.8 g, 0.50 mole), and dry benzene (90 ml) were heated at 150° for 10 hr. with stirring. After the conclusion of reaction, the autoclave was cooled to room-temperature and the valve was opened to discharge the unchanged SF_4. The autoclave was again heated to 40—50° under the reduced pressure (20—30 mmHg) to remove benzene thoroughly, and pale yellow crystals were obtained from the autoclave in a dry nitrogen atmosphere.

The crystalline substance was washed in anhydrous ethyl ether, sublimated at 160—170° (10^{-4} mmHg), and recrystallized from dimethylformamide, and colorless prisms (63.4 g) of mp 134—142° were obtained. The yield based on triphenylphosphine was 92.5%. Though the substance was not completely pure, elemental analysis and infrared-absorption spectra[12] indicating that it was evidently difluorotriphenylphosphorane, it was used in the following reaction.

***n*-Octyl Fluoride (I)**——A mixture of $(C_6H_5)_3PF_2$ (12.63 g, 0.042 mole), *n*-octylalcohol (2.84 g, 0.022 mole), and CH_3CN (25 ml) was heated at 170° with stirring for 8 hr in a Hastelloy-C-lined autoclave. After being cooled to room temperature, the autoclave was opened and crystals, phosphorous compounds, were filtered off. The filtrate was carefully distilled in the presence of NaF (3.0 g), and the main fraction (*ca.* 2 g) which was purified using a preparative gas chromatography,[15] *n*-octyl fluoride (bp 145—146°, $n_D^{24.5}$ 1.3939), was identical with a sample ($n_D^{24.5}$ 1.3936) prepared from *n*-octyl bromide and KF[16] on refractive index, IR spectrum, and the retention time of gas chromatogarphy. (Identification of all the following products was done in the same manner.)

Any peak corresponding to either olefin or the starting material, *n*-octyl alcohol, was not found on the gas chromatogram.

The gas chromatographic analysis was carried out using a Yanagimoto GCG-220 Special type with the whole system made of Monel. The conditions were as follows:

Column: silicone grease 20% on Diasolid 80%; 2 m.

Column temp.: 50°; Flow rate: H_2, 40 ml/min.

The yields of alkyl fluorides in Table I were obtained by gas chromatographic analysis of the reaction mixture, and corrected using inner standards whose relative sensitivitis to the authentic samples were known.

***n*-Amyl Fluoride (II)**——$(C_6H_5)_3PF_2$ (13.26 g, 0.044 mole), *n*-amyl alcohol (2.20 g, 0.025 mole) and CH_3CN (30 ml) were heated at 150° for 8 hr and worked up as above, yielding *n*-amyl fluoride (bp 64°) identical with a sample prepared from *n*-amyl bromide and KF.[16]

Isoamyl Fluoride (III)——$(C_6H_5)_3PF_2$ (13.79 g, 0.046 mole), isoamylalcohol (2.01 g, 0.023 mole), and CH_3CN (40 ml) were treated as above, yielding isoamyl fluoride (bp 56°, $n_D^{25.5}$ 1.3527) identical with a sample ($n_D^{25.5}$ 1.3525) prepared from isoamyl bromide and KF.[16] A peak assignable to olefin was also shown on gas chromatogram (*ca.* 6%).

Benzyl Fluoride (IV)——$(C_6H_5)_3PF_2$ (11.12 g, 0.037 mole), benzyl alcohol (2.02 g, 0.019 mole), and CH_3CN (40 ml) were treated as above, yielding benzyl fluoride (bp 140°, $n_D^{24.5}$ 1.4916) identical with a sample (n_D^{21} 1.4912) prepared from benzyl bromide and KF.[16]

Phenethyl Fluoride (V)——$(C_6H_5)_3PF_2$ (11.07 g, 0.037 mole), phenethylalcohol (2.21 g, 0.018 mole), and CH_3CN (30 ml) were treated as above, yielding phenethyl fluoride (bp 160°, $n_D^{24.5}$ 1.4902) identical with a sample ($n_D^{24.5}$ 1.4916) prepared from phenethyl bromide and KF.[17]

3-Chloropropyl Fluoride (VI)——$(C_6H_5)_3PF_3$ (12.54 g, 0.042 mole), 3-chloropropanol (2.08 g, 0.022 mole), and CH_3CN (40 ml) were treated as above, yielding 3-chloropropyl fluoride (bp 82°) identical with a sample prepared from 3-chloropropyl bromide and KF.[18] A small peak assignable to olefin was found on the gas chromatogram.

1,6-Difluorohexane (VII)——$(C_6H_5)_3PF_3$ (18.56 g, 0.062 mole), hexamethyleneglycol (2.70 g, 0.022 mole), and CH_3CN (30 ml) were treated as above, yielding 1,6-difluorohexane (bp 130°) identical with a sample prepared from 1,6-dibromohexane and KF.[19]

---

14) G.A. Wiley, B.M. Rein, and R.L. Hershkowitz, *Tetrahedron Letters*, **1964**, 2509.
15) Beckman, "MEGACHROM."
16) H. Kitano and K. Fukui, *J. Chem. Soc. Japan*, *Ind. Chem. Sect.*, **58**, 352 (1955).
17) I.L. Knunyants, O.V. Kildisheva, and I.P. Petrov, *Zh. Obshch. Khim.*, **19** (1949).
18) F.W. Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).
19) F.W. Hoffmann, *J. Org. Chem.*, **14**, 105 (1949).

sec-Amyl Fluoride (VIII)——$(C_6H_5)_3PF_2$ (13.04 g, 0.043 mole), *sec*-amyl alcohol (2.01 g, 0.023 mole), $(C_2H_5)_3N$ (3.70 g, 0.037 mole), and CH_3CN (35 ml) were treated as above, yielding *sec*-amyl fluoride ($n_D^{25.5}$ 1.3539) identical with a sample ($n_D^{25.5}$ 1.3538) prepared from *sec*-amyl bromide and KF.[20]

2-Methylbutene-2 (IX)——$(C_6H_5)_3PF_2$ (13.08 g, 0.044 mole), neopentylalcohol (2.23 g, 0.025 mole), and CH_3CN (25 ml) were heated at 140° for 8 hr and worked up as above, yielding 2-methylbutene-2 identical with the authentic sample. A small peak assumed to be that of neopentyl fluoride was found on the gas chromatogram, but it was not identified as the authentic sample could not be synthesized.

Di-isoamylether (X)——$(C_6H_5)_3PF_2$ (4.33 g, 0.014 mole), isoamyl alcohol (3.87 g, 0.044 mole), and CH_3CN (20 ml) were heated at 130° for 5 hr, and worked up as above, yielding di-isoamylether (bp 172°) identical with the authentic sample.

Tetrahydrofuran (XI)——$(C_6H_5)_3PF_2$ (4.27 g, 0.014 mole), tetramethyleneglycol (3.66 g, 0.040 mole), and CH_3CN (20 ml) were treated as above, yielding tetrahydrofuran in good yield identical with the authentic sample.

Cyclohexene (XII)——$(C_6H_5)_3PF_2$ (3.37 g, 0.011 mole), cyclohexanol (2.85 g, 0.028 mole), and CH_3CN (25 ml) were heated at 60° for 6 hr and treated as above, yielding cyclohexene identical with the authentic sample.

Isoamyl Acetate——Isoamyl alcohol (3.63 g), HF (1.5 ml), CH_3CN (30 ml) were heated at 130° for 6 hr and worked up as above. The main product separated by using preparative gas chromatography was identified with isoamyl acetate ($n_D^{21.8}$ 1.4003) by elemental analysis and comparing with the authentic sample ($n_D^{21.8}$ 1.4001).

Acknowledgement We wish to thank Yawata Chemical Industry Company, Ltd. for permission of publishing the work.

---

20) N.B. Chapman and J. L. Levy, *J. Chem. Soc.*, **1952**, 1673.