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# Synthesis of Alkyl Fluorides from Alcohols *via* Fluoroformate Esters[1]

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Treatment of an alkyl chloroformate with anhydrous thallous fluoride yields the corresponding alkyl fluoroformate which, on warming with pyridine, eliminates carbon dioxide to produce the alkyl fluoride. This sequence of reactions provides a convenient synthesis of alkyl fluorides from alcohols applicable to primary and secondary alcohols and cyclohexanol but failing with cyclopentanol.

The common methods heretofore available for the transformation of alcohols into alkyl fluorides have involved either the conversion of the alcohol to the corresponding chloride or bromide followed by treatment with an appropriate metal fluoride[2a,b] or else conversion to the *p*-toluenesulfonate ester which then is heated with potassium fluoride in a high-boiling solvent.[2c] In connection with studies of fluorinated derivatives of steroid hormones, a convenient and apparently general procedure has been developed for the replacement of the hydroxyl group of a primary or secondary alcohol by a fluorine atom. The method consists of three steps: reaction of the alcohol with phosgene to form the chloroformate ester, conversion of the chloroformate ester to a fluoroformate by treatment with anhydrous thallous fluoride and, finally, elimination of carbon dioxide from the fluoroformate by warming in the presence of pyridine. This sequence of reactions has been carried out successfully with ethyl, isopropyl, *s*-butyl and cyclohexyl alcohols. In the case of cyclopentanol, the fluoroformate was prepared without difficulty, but the decomposition of the latter material to yield cyclopentyl fluoride has not proved successful as yet. The preparation of the fluoroformates is summarized in Table I and of the alkyl fluorides in Table II.

TABLE I

PREPARATION OF FLUOROFORMATES

| ROCOCl | | | ROCOF[a] | | Fluorine, % | |
|---|---|---|---|---|---|---|
| R | G. used | Yield, % | B.p., °C. | $n^{25}$D | Calcd. | Found |
| Ethyl | 35 | 58 | 55.6–57[b] | 1.3295 | ... | ... |
| Isopropyl | 27 | 51 | 81–82 | 1.3619 | 17.92 | 17.94 |
| *s*-Butyl | 15 | 64 | 92–93 | 1.3669[c] | 15.83 | 15.80 |
| Cyclopentyl | 54 | 61 | 50–51.5[d] | 1.4119 | 14.39 | 14.34 |
| Cyclohexyl | 40 | 67 | 64–65[d] | 1.4350 | 13.01 | 12.98 |

[a] Yield and constants after redistillation. [b] Reported[4] b.p. 57°. [c] At 28°. [d] 25 mm.

The conversion of simple alcohols to their chloroformate esters by treatment with phosgene, either in the presence or absence of a base, is a well known reaction and needs no elaboration. In a previous study[3] of the feasibility of preparing alkyl fluorides by the decomposition of fluoroformate esters, it was found that the conversion of thiodiglycol to 2-chloroethyl-2-fluoroethyl sulfide could be carried out in fair yield by treatment of the bis-chloroformate of thiodiglycol with liquid hydrogen fluoride with subsequent heating to eliminate carbon dioxide from the monofluoroformate which apparently was formed. However, this procedure did not prove successful when applied to certain other primary and secondary alcohols, and it is somewhat inconvenient since the use of liquid hydrogen fluoride requires special apparatus. In the search for more suitable reagents for the conversion of chloroformates to fluoroformates it was found, in confirmation of the results of Goswami and Sarker,[4] that thallous fluoride is a highly satisfactory reagent for this purpose. Replacement of chlorine by fluorine takes place smoothly on stirring the chloroformate with an equimolar amount of anhydrous thallous fluoride at room temperature for several hours followed by a brief period of warming on a steam-bath.

Since variable results were obtained with different batches of commercial thallous fluoride, a reagent which gave uniformly good results was prepared very simply from thallous formate as described in the Experimental section. Since thallous salts are moderately expensive reagents, the thallous chloride formed in the exchange reaction is recovered and reconverted to thallous fluoride by the same procedure.

TABLE II

PREPARATION OF ALKYL FLUORIDES

| ROCOF | | | | | Mol. wt.[a] | | Fluorine, % | |
|---|---|---|---|---|---|---|---|---|
| R | G. used | Yield, % | B.p., °C. | $n^{25}$D | Calcd. | Found | Calcd. | Found |
| Ethyl | 9.2 | 63 | ............. | ..... | 48.0 | 47.9 | ... | ... |
| Isopropyl | 5.0 | 75 | ............. | ..... | 62.0 | 62.4 | ... | ... |
| *s*-Butyl | 2.8 | 61 | ............. | ..... | 76.0 | 76.5 | ... | ... |
| Cyclohexyl | 7.5 | 58[b] | 73–75[c] (300 mm.) | 1.4142[c] | .. | .. | 18.62 | 18.63 |

[a] By vapor density. [b] After redistillation. [c] Reported b.p. 71–74.5° (300 mm.), $n^{20}$D 1.4147; A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938).

The elimination of carbon dioxide from a fluoroformate to yield an alkyl fluoride was investigated using heat alone and by heating in the presence of

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[1] This investigation was supported by a grant from the American Cancer Society, as recommended by the Committee on Growth of the National Research Council.

[2] (a) A. L. Henne, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 49; (b) W. Bockemüller, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 244; (c) W. F. Edgell and L. Parts, Abstracts of Papers, 125th Meeting of A.C.S., Spring, 1954, p. 4N.

[3] M. S. Kharasch, S. Weinhouse and E. V. Jensen, THIS JOURNAL, **77**, 3145 (1955).

[4] H. C. Goswami and P. B. Sarker, *J. Indian Chem. Soc.*, **10**, 537 (1933).

pyridine. The best results were obtained when the fluoroformate was heated at 70–100° in the presence of an equimolar amount of dry pyridine. The alkyl fluorides thus produced were free of olefin, inasmuch as they did not reduce neutral potassium permanganate.

## Experimental

**Preparation of Thallous Fluoride.**—Thallous formate (100 g., 0.4 mole), obtained from the Eastman Kodak Co., was dissolved in 150 ml. of water and the solution made alkaline with ammonia. Hydrogen sulfide was passed into this solution until no further precipitation took place, whereupon the insoluble thallous sulfide was removed by filtration, thoroughly washed with water and dissolved in an excess of 50% aqueous hydrofluoric acid (Merck and Co., Inc.). A small residue of sulfur was removed by filtration (using a fluted filter and polyethylene funnel) and the clear solution of thallous fluoride evaporated to dryness on the steam-bath. The residue was dissolved in 33% aqueous hydrofluoric acid and the solution filtered once more and evaporated to dryness. The residue was dried at 110° for 8 hours and stored in a desiccator. The yield of thallous fluoride was 87.0 g. (97.5%).

Thallous fluoride suitable for use in the exchange reaction can be prepared by subjecting thallous acetate (Eastman Kodak Co.) or thallous nitrate (Fairmount Chemical Co.) to the same procedure as described for the formate. However, thallous formate is the cheapest starting material.

**Preparation of Thallous Fluoride from Recovered Thallous Chloride.**—The solid residue remaining from the fluorine exchange reaction consists of thallous chloride with some thallous fluoride and organic material. This solid was heated on a steam-bath for a few hours with alcohol and then cooled, filtered, washed on the filter with acetone and dissolved in boiling water. The hot solution was filtered; the filtrate was made alkaline with ammonia and subjected to the procedure described in the preceding section.

**Chloroformates.**—Commercial ethyl chloroformate (U.S.I.) was redistilled before use. The other chloroformate esters were prepared according to the procedure of Kenyon, *et al.*[5] Isopropyl, *s*-butyl and cyclohexyl chloroformates are known compounds, but cyclopentyl chloroformate (b.p. 69–70.5° (25 mm.), $n^{25}$D 1.4461, yield 89%) has not been reported heretofore. Its identity was checked by chlorine analysis (calcd. 23.86, found 23.81) and by reaction with aniline to form cyclopentylphenylurethan which, after recrystallization from carbon tetrachloride, melted at 131–132° and did not depress the melting point of an authentic sample of the derivative prepared from cyclopentanol.[6]

**Fluoroformates.**—All apparatus was dried in an oven before use and anhydrous conditions were maintained throughout. The chloroformate ester was treated with an equimolar amount of dry thallous fluoride added with stirring in several portions over a period of a few hours. After the addition was complete, the mixture was stirred at room temperature overnight and then warmed on a steam-bath for one-half hour. The product was distilled from the solid thallous salt under reduced pressure and purified by redistillation. All the fluoroformates thus prepared are colorless, mobile liquids, mildly lachrymatory with a pungent odor.

**Fluorides.**—The conversion of fluoroformate esters to alkyl fluorides was carried out under anhydrous conditions. The outlet of the condenser was connected through two soda lime tubes to a Dry Ice trap. The fluoroformate under helium (or nitrogen) was treated with an equimolar amount of pyridine (redistilled and stored over barium oxide). A white solid formed at first which later dissolved as the color of the reaction mixture changed to bright pink and then to brown. In the case of ethyl, isopropyl and *s*-butyl fluoroformates, the pyridine was added at room temperature and then the bath temperature was raised gradually and maintained at 100–110° for several hours until no more alkyl fluoride condensed in the cold trap. In case of cyclohexyl fluoroformate, the temperature of the reaction mixture was maintained at 70–75° during the addition of the pyridine and for 20 hours thereafter. Then water was added and the organic layer separated, washed with water, dried over calcium chloride and distilled; the product was purified by redistillation. Attempts to convert cyclopentyl fluoroformate to cyclopentyl fluoride have been unsuccessful. In the absence of pyridine this fluoroformate decomposes slowly at 100° to yield carbon dioxide and cyclopentene. In the presence of either a catalytic amount or an equimolar amount of pyridine, evolution of carbon dioxide takes place at about 70° to yield a high-boiling product whose structure has not been established.

**Fluorine Analysis.**—The determination of fluorine was carried out by an adaptation to organic compounds[7] of previously described procedures.[8] A 200-mg. sample of the compound to be analyzed was fused with sodium peroxide and potassium perchlorate in an electrically ignited Parr bomb. The fluorine was distilled from the acidified melt as silicon tetrafluoride and titrated in a chloroacetate buffer of *p*H 3 with thorium nitrate using a sodium alizarin sulfonate indicator.

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(5) J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935).

(6) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 163, 226.

(7) M. S. Kharasch, S. Weinhouse and E. V. Jensen, unpublished results.

(8) H. H. Willard and O. B. Winter, *Ind. Eng. Chem.*, *Anal. Ed.*, **5**, 7 (1933); W. M. Hoskins and C. A. Ferris, *ibid.*, **8**, 6 (1936); W. D. Armstrong, *ibid.*, **8**, 385 (1936); R. J. Rowley and H. V. Churchill, *ibid.*, **9**, 551 (1937).