

774. *Studies on Organic Fluorine Compounds. Part I. Some Esters of Monofluoroacetic Acid and Related Compounds.*

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Ethyl fluoroacetate is obtained from the chloroacetate and potassium fluoride at ordinary pressure, if acetamide or its *N*-methyl derivative is used as solvent. Replacement of chlorine or bromine by fluorine under these conditions is also possible in some other cases. Some higher alkyl fluoroacetates have been prepared by transesterification reactions.

THE known methods for the preparation of esters of fluoroacetic acid are based on the interaction between a derivative of chloro- or bromo-acetic acid and potassium or some other fluoride (see Henne, "Organic Reactions," 1948, Vol. 2, p. 49). This reaction is slow at atmospheric pressure, and the yields are unsatisfactory, especially in the case of chloroacetic acid derivatives. *E.g.*, by refluxing ethyl bromoacetate with potassium fluoride during 16 hr., Bacon, Bradley, Hoegberg, Tarrant, and Cassaday (*J. Amer. Chem. Soc.*, 1948, **70**, 2653) obtained only a 45% yield of ethyl fluoroacetate. A more practical method involves use of pressure autoclaves and higher temperatures, yields reported varying, for ethyl fluoroacetate, from 20% (Jenkins and Kohler, *Chem. Ind.*, 1948, Feb., p. 232) to 75% (Gryszkiewicz-Trochimovski, Sporzynski, and Wnuk, *Rec. Trav. chim.*, 1947, **66**, 413, 419). Work under pressure with these poisonous and almost completely odourless compounds is however hazardous, especially as the reaction is sometimes accompanied, owing to unknown factors, by dangerous pressure increase; furthermore, the reaction mixture is highly corrosive.

Attempts to accelerate the reaction by increasing the temperature, by using high-boiling esters of chloroacetic acid and potassium fluoride in an efficient column, failed; *e.g.*, with butyl chloroacetate, the rate of the reaction, low even at the beginning, quickly approached zero, and the result with *n*-octyl chloroacetate (b. p. 247°) was no better. It can be assumed that the potassium fluoride is quickly covered with a film of the chloride

which prevents further reaction. Recently (*Bull. Soc. chim.*, 1953, 20, 462), it was observed by E. Gryszkiewicz-Trochimovski, O. Gryszkiewicz-Trochimovski, and Levy that satisfactory yields (75%) can be obtained by heating potassium fluoride with cyclohexyl bromoacetate.

A possibility of overcoming the difficulties caused by the heterogeneous character of the reaction mixture was indicated by our observation (cf. Bacon *et al.*, *loc. cit.*) that chloroacetamide (b. p. 222°) but not chloroacetanilide (b. p. 228°), when heated with potassium fluoride, gave a 65% yield of fluoroacetamide. It was assumed that potassium fluoride was more soluble in the amide than in the anilide. Sodium fluoride, which is insoluble in chloroacetamide, does not react with it.

A suitably high-boiling, readily available solvent for potassium fluoride and esters of chloroacetic acid was found in acetamide, which at 120° dissolved 5% (by weight) of potassium fluoride. Anhydrous conditions proved essential, in order to prevent hydrolytic side reactions. The yield thus obtained was 60–63%. Sodium and ammonium fluorides, which are practically insoluble in acetamide, gave negligible results. Addition of xylene or nitrobenzene to the reaction mixture had an inhibitory effect. Of other amides tested, benzamide and dimethylformamide were ineffective, methoxyacetamide gave low yields, and only *N*-methylacetamide afforded results similar to those obtained with acetamide. It must be concluded that at least one hydrogen atom in the amide group is necessary for the dissolution of potassium fluoride, presumably by the formation of hydrogen bonds.

In the same way, *n*-butyl and *isobutyl* fluoroacetate could be prepared (see Table 2). For higher esters, acetamide is too volatile and part of it is carried over with the distillate. In these cases, transesterification of ethyl fluoroacetate with the desired alcohol is preferable (cf. Bacon *et al.* and Gryszkiewicz-Trochimovski *et al.*, *loc. cit.*); thus, *n*-amyl, *n*-hexyl, and *n*-octyl fluoroacetate have been prepared (see Table 2).

A cursory investigation of the applicability of the acetamide method to other halogen-replacement reactions is reported in Table 1. In view of the known reactivity of benzyl

TABLE 1. Reactions of alkyl halides with potassium fluoride in boiling acetamide.

Halide	Yield (%)	B. p. of fluoride		Halide	Yield (%)	B. p. of fluoride	
		obs.	lit.			obs.	lit.
Pentyl chloride	0	—	—	Octyl bromide	19	141–143°	142.5°*
Pentyl bromide	23	62°	62.8°*	Benzyl bromide	0	—	139.8 ^b
<i>iso</i> Pentyl bromide ...	18	52	53.5°*	2-Chloroethyl acetate	20	116–118	119.3°*
Octyl chloride	27	141–143	142.5°*				

* Swarts, *Bull. Acad. roy. Belg.*, 1921, 7, 442. ^b Ingold and Ingold, *J.*, 1928, 2257. • Swarts, *Rec. Trav. chim.*, 1914, 33, 252.

bromide, it must be concluded that it reacts preferentially with the acetamide, thus escaping fluorination.

EXPERIMENTAL

Materials.—Potassium fluoride (water content of the commercial product, 6%) was dried at 120°. Finely ground and coarse potassium fluoride gave the same results. Acetamide was purified by distillation (b. p. 215–220°). Methylacetamide was prepared according to Hofmann (*Ber.*, 1881, 14, 2729) (b. p. 206°), methoxyacetamide according to Kilpi (*Z. physikal. Chem.*, 1912, 80, 182) (m. p. 96°), and chloroacetamide (m. p. 119.5°) and chloroacetanilide (m. p. 134°) according to Scholl (*Ber.*, 1896, 29, 2417) and Tommasi (*Bull. Soc. chim.*, 1873, 19, 400).

Apparatus.—A three-necked ground-joint flask of 1 l. capacity was mounted with an efficient stirrer (mercury seal) and a heated Vigreux column (30-cm.), which was connected to a reflux head with variable take-off and a condenser. Redistillation of the products was carried out in a packed column (glass helices), 85 cm. long and 2 cm. in diameter (7 theor. plates).

Ethyl Fluoroacetate.—A ratio 1 : 2 : 3 for acetamide, potassium fluoride, and the ester permits, with a suitable reflux ratio, constant take-off of ethyl fluoroacetate. A mixture of ethyl chloroacetate (300 g.), potassium fluoride (200 g.), and acetamide (100 g.) was heated with stirring. After 3 min. refluxing began, the temperature at the head of the column being 117°; it was kept at 117–121° during the reaction, which required about 2 hr.; at the end, the temperature fell gradually to 70°. The crude distillate weighed 216 g. Redistillation gave ethanol (about

16 g.), ethyl fluoroacetate (137 g.), b. p. 117—118°, n_D^{20} 1.37, d_{20}^{20} 1.092, $[M]_D^{20}$ 22.00 (calc., 22.09), and ethyl chloroacetate (52 g.). The ethyl fluoroacetate contained only 0.4% of chlorine.

Pentyl Fluoroacetate (by Trans-esterification).—Ethyl fluoroacetate (0.47 mole), *n*-pentyl alcohol (0.52 mole), and concentrated sulphuric acid (1 g.) were heated in an efficient column during 1 hr. The product (41.5 g., 59%) boiled at 170—172°.

TABLE 2. *Higher esters of fluoroacetic acid* ($\text{CH}_2\text{F}\cdot\text{CO}_2\text{R}$).

(A = acetamide method; B = transesterification.)

R	B. p.	n_D^{20}	d_4^{20}	$[M]_D^{20}$		Method	Yield * (%)	Found (%)		Reqd. (%)	
				Found	Calc.			C	H	C	H
Bu ^l	150°	1.392	1.0184	31.05	31.41	A	29	54.1	8.5	53.7	8.2
Bu ⁿ	154	1.392	1.0200	31.00	31.41	A	42	54.2	8.4	53.7	8.2
<i>n</i> -C ₅ H ₁₁	171	1.398	0.9980	36.00	36.03	B	59	56.5	8.4	56.8	8.8
<i>n</i> -C ₆ H ₁₃	189	1.410	0.9650	41.50	40.65	B	56	59.4	9.5	59.3	9.3
<i>n</i> -C ₈ H ₁₇	223	1.417	0.9460	50.20	49.89	B	58	63.8	10.2	63.3	10.0

* Based on the chloroacetate employed.

Butyl Fluoroacetate (without a Solvent).—Butyl chloroacetate (130 g.) (Gehring, *Bull. Soc. chim.*, 1886, 46, 147) and dry potassium fluoride (100 g.) were heated with stirring. Only a small fraction boiled at 150—160°, then the temperature rose above 170° and remained constant at this level even after 2 hr. On redistillation, only 8 g. (7%) of a product were obtained which boiled at 153—155° (b. p. of butyl fluoroacetate 154°).

Reaction in Methylacetamide.—Ethyl chloroacetate (100 g.), potassium fluoride (100 g.), and methylacetamide (40 g.) were heated as above. 67 G. of crude distillate were obtained within 90 min. and afforded, on redistillation, fractions, b. p. 75—80° (14 g.), b. p. 117—119° (25 g., 34%; ethyl fluoroacetate), and b. p. 140—142° (13 g.; ethyl chloroacetate).

Reaction in Methoxyacetamide.—Ethyl chloroacetate (100 g.), potassium fluoride (72 g.), and methoxyacetamide (36 g.) were heated with stirring. Within 6 hr. 23 g. of distillate were collected. Redistillation gave 10 g. (11%) of ethyl fluoroacetate, b. p. 115—120°.

2-Fluoroethyl Acetate.—2-Chloroethyl acetate (Bogert and Slocum, *J. Amer. Chem. Soc.*, 1924, 46, 766) (123 g.), potassium fluoride (87 g.), and acetamide (59 g.) were heated with stirring as described above during 2 hr. The product, b. p. 115—120°, upon redistillation, gave the pure fluorine compound (20%), b. p. 116—118° (Swarts, *Rec. Trav. chim.*, 1914, 33, 255, gives b. p. 119.3°).

The data concerning the new *esters* of fluoroacetic acid are summarised in Table 2.