

Preparation of Some Halogeno-acetones including 1-Bromo-1-chloro-1-fluoroacetone

By **G. C. Barrett, D. Muriel Hall, M. K. Hargreaves,*** and **B. Modarai**, Department of Chemistry, North East London Polytechnic, Romford Road, London E.15, and Department of Chemistry, Bedford College, Regent's Park, London N.W.1

1-Bromo-1-chloro-1-fluoroacetone has been prepared by the dibromination of monochloroacetone followed by replacement of one bromine atom by fluorine in an exchange reaction with mercuric fluoride under rigorously controlled conditions.

1-BROMO-1-CHLORO-1-FLUOROACETONE (I), hitherto unknown, was required as a source of bromochlorofluoromethane.¹ During its preparation a number of interesting reactions have been discovered and are reported here.

¹ M. K. Hargreaves and B. Modarai, *Chem. Comm.*, 1969, 16.

² F. Swarts, *Bull. Classe Sci., Acad. roy. Belg.*, 1893, (3), **26**, 102

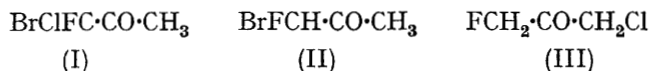
Few compounds which contain the BrClFC-group are known (*e.g.* BrClFCR; R = H,² CO₂H,^{3,4} CO₂Et,³ COF³), although a number of compounds which contain

³ F. Swarts, *Mem. Cour. Acad. roy. belg.*, 1895, **54**; *Bull. Soc. chim. France*, 1896, (3), **15**, 1134; *Bull. Classe Sci., Acad. roy. Belg.*, 1898, (3), **35**, 849.

⁴ R. N. Haszeldine, *J. Chem. Soc.*, 1952, 4259.

groups of the type CX_2Y (X and $Y = F, Cl, Br$) have been described.^{5,6} Indirect routes have frequently been used⁷⁻¹⁰ for the preparation of fluoromethylketones (see Dishart and Levine¹¹) but direct introduction of fluorine into the ketone is often preferable and was the approach used in the present work.

Stepwise halogenation of monofluoroacetone failed to give the required compound. Thus, although monofluoroacetone¹² could be brominated¹³ to give (II), chlorination with molecular chlorine under similar conditions resulted mainly in substitution in the methyl group to yield (III), as shown by the n.m.r. spectrum. Variations in the reaction conditions failed to increase the proportion of substitution in the methylene group. The chlorination appeared to proceed more rapidly (visual estimation) in less polar solvents ($CCl_4 > CHCl_3 > CH_2Cl_2$) and most rapidly in the absence of any solvent. The difference in behaviour between bromine and chlorine suggests a difference in mechanism. It is possible that bromination involves a polar mechanism while chlorination under these conditions proceeds largely by a free-radical mechanism.

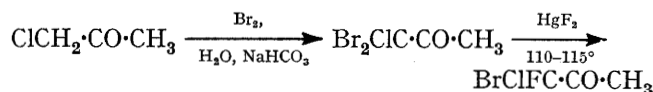


Chlorination of fluoroacetone with sulphuryl chloride in chloroform at several temperatures and with various addition rates gave small quantities of 1-chloro-1-fluoroacetone together with more of (III). Similar results were obtained by Wyman *et al.* in the absence of solvent.¹⁴ Chlorination of 1-bromo-1-fluoroacetone with molecular chlorine resulted in a complex mixture of products, all of which lacked a methyl group, as shown by their n.m.r. spectra.

Attempts were then made to replace chlorine or bromine in a dihalogenoacetone by fluorine by a halogen-exchange method. Most metallic fluorides either failed to react or caused decomposition with loss of hydrogen halide and the formation of tarry residues. When 1,1-dichloroacetone^{15,16} was heated with potassium fluoride or potassium hydrogen fluoride in diethylene glycol the major product was 1,1-difluoroacetone.¹⁷ A very small amount of 1-chloro-1-fluoroacetone was also obtained and was characterised by its n.m.r. spectrum but could not be isolated in the pure state. Other solvents such as acetamide, nitrobenzene, *p*-xylene, and acetone were found not to be satisfactory. The use of antimony trifluoride and catalysts in modifications of

Swarts' method was also unsatisfactory. Reaction of 1-bromo-1-chloroacetone¹⁸ with thallous fluoride gave low yields of 1-chloro-1-fluoroacetone (*cf.* Ray, Goswami, and Ray¹⁹).

The desired compound was eventually prepared by base-catalysed dibromination of monochloroacetone, followed by replacement of one bromine by fluorine by use of mercuric fluoride under carefully controlled conditions.



Initially, the yield in the final exchange reaction was 1–5%. However, when optimum conditions for the reaction were established, side reactions were reduced to a minimum and a yield of up to 85% (based on the HgF_2) was obtained. The efficiency of the reaction is extremely sensitive to the dryness of the mercuric fluoride which readily develops a red layer of mercuric oxide on brief exposure to atmospheric moisture. Similarly, the ketone, used in three-fold excess, must be rigorously purified and dried; the mixed reactants must be brought quickly to the threshold temperature for the reaction (with the bath at 110–112°) and stirred vigorously throughout. Slow heating to 110° greatly reduces the yield. When the mercuric fluoride was replaced by a mixture of mercurous fluoride and iodine (often used as a substitute for mercuric fluoride) the reaction failed. The use of other metallic fluorides ($KF, KHF_2, SbF_3, TlF, CaF_2$) was unsuccessful, as was the reaction with silver fluoride, even though this compound has been used to exchange fluorine for bromine in 1,1,1-tribromo-3,3,3-trifluoroacetone⁵ and in ethyl dibromochloroacetate.³ A small quantity of the desired ketone (as shown by n.m.r. and g.l.c.) was obtained with an excess of a mixture of antimony pentachloride and antimony trifluoride but repeated fractionations, followed by the use of preparative g.l.c., were necessary to purify it and this precluded preparation on a sufficient scale.

1,1-Dichloro-1-fluoroacetone was similarly prepared from 1-bromo-1,1-dichloroacetone²⁰ and mercuric fluoride; the threshold temperature for the reaction in this case was slightly higher. This compound has previously been obtained in 38% yield⁶ by the action of methylmagnesium bromide on dichlorofluoroacetic acid.

Neither (I) nor 1,1-dibromo-1-chloroacetone formed the usual derivatives (oxime, semicarbazone *etc.*), although both gave crystalline compounds with (–)

⁵ R. A. Shepard and A. A. Loisselle, *J. Org. Chem.*, 1958, **23**, 2012.

⁶ R. A. Moore and R. Levine, *J. Org. Chem.*, 1964, **29**, 1883.

⁷ F. Swarts, *Bull. Classe Sci., Acad. roy. Belg.*, 1927, **13**, 175.

⁸ R. A. Darrall, F. Smith, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 1951, 2329.

⁹ E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, *J. Amer. Chem. Soc.*, 1953, **75**, 3152; E. T. McBee, O. R. Pierce and D. D. Meyer, *ibid.*, 1955, **77**, 917.

¹⁰ A. Sykes, J. C. Tatlow, and C. R. Thomas, *J. Chem. Soc.*, 1956, 835.

¹¹ K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 2268.

¹² E. Cherbuliez, A. DePicciotto, and J. Rabinowitz, *Helv. Chim. Acta*, 1960, **43**, 1143.

¹³ E. D. Bergman, S. Cohen, E. Hoffman, and Z. Rand-Meir, *J. Chem. Soc.*, 1961, 3452.

¹⁴ D. P. Wyman, B. L. Shapiro, and P. R. Kaufman, *Canad. J. Chem.*, 1965, **43**, 2432.

¹⁵ G. Borsche and R. Fittig, *Annalen*, 1865, **133**, 111.

¹⁶ L. Glutz and E. Fischer, *J. prakt. Chem.*, 1871, [2], **4**, 52.

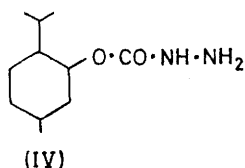
¹⁷ Jap. Pat. 8559/1956 (*Chem. Abs.*, 1958, **52**, 11927a).

¹⁸ Z. Bankowska, *Roczniki Chem.*, 1959, **33**, 1039.

¹⁹ P. C. Ray, H. C. Goswami, and A. C. Ray, *J. Indian Chem. Soc.*, 1935, **12**, 93.

²⁰ Netherlands Pat. Appl. 6,408,831/1965 (*Chem. Abs.*, 1965, **63**, 2900d).

menthyl *N*-aminocarbamate, '(–)-menthydrazone' (IV)²¹ and (I) formed a crystalline 2,4-dinitrophenylhydrazone under special conditions.



EXPERIMENTAL

The i.r. spectra were recorded with Perkin-Elmer Infra-Cord and Hilger and Watts Infra-Scan instruments, polystyrene being used as the reference standard. N.m.r. spectra for ¹H were recorded at 35° with a Perkin-Elmer R10 spectrometer at 60 MHz with Me₄Si as internal standard. The n.m.r. data are given in the table. G.l.c. separations

N.m.r. data		
	δ	J _{HF}
CH ₃ -CO-CH ₂ F	2.20(d)	4
	4.9(d)	47
CH ₃ -CO-CHF ₂	2.33(t)	1.5
	5.85(t)	53
CH ₃ -CO-CHClF	2.30(d)	3.5
	6.45(d)	51
CH ₃ -CO-CHBrF ^a	2.36(d)	3.5
	6.61(d)	51
CH ₃ -CO-CHBrCl ^b	2.45(s)	
	5.8(s)	
CH ₃ -CO-CBr ₂ Cl	2.75(s)	
CH ₃ -CO-CBrCl ₂	2.68(s)	
CH ₃ -CO-CBrClF	2.51(d)	2.0
CH ₃ -CO-CCl ₂ F	2.50(d)	2.0
CHBrClF ^c	7.64(d)	52
CHBr ₂ Cl	7.5(s)	

All data refer to the neat liquid unless a solvent is stated. δ In p.p.m. δ(Me₄Si) = 0.0 p.p.m. J Coupling constants; the units are in HZ.

^a In CDCl₃. ^b In CCl₄. ^c M. K. Hargreaves and B. Modarai, *Chem. Comm.*, 1969, 16.

were performed with a column composed of 15% Carbowax on 85–100 mesh Celite.

Monofluoroacetone.—This compound was prepared by the method of Cherbuliez *et al.*,¹² and had b.p. 72–72.5°, *n*_D²¹ 1.3685.

1-Bromo-1-fluoroacetone.¹³—This compound had b.p. 107–110°.

Chlorination of Fluoroacetone with Molecular Chlorine.—Dry chlorine was passed through a solution of fluoroacetone (22 g) in chloroform (80 g), which was protected from atmospheric moisture, and kept at 19–22° with cooling, until the gain in weight was 10 g. The mixture, freed from hydrogen chloride by the passage of nitrogen (preferable to a sodium hydrogen carbonate wash which reduced the yield), was distilled through a 30 cm vacuum-jacketed column, fractions being identified by their n.m.r. spectra. After removal of chloroform and some unchanged fluoroacetone (*ca.* 4 g), a small fraction, b.p. 80–100°, was obtained which contained some 1-chloro-1-fluoroacetone; the main fraction (*ca.* 14 g), b.p. 143–146°, *n*_D²⁵ 1.4218, did not show a methyl group (n.m.r.) and was chiefly 1-chloro-3-fluoroacetone (lit.,²² b.p. 142–144° *n*_D²⁸ 1.4195).

Reaction of 1,1-Dichloroacetone with Potassium Hydrogen Fluoride.—The potassium hydrogen fluoride was dried at 160° for 24 h, ground finely in a mortar and dried again;

before use it was again ground while still hot and kept at 160–170° for a further 30 h. Diethylene glycol (108 ml), purified by distillation to constant b.p. and *n*_D, was heated to 50° and potassium hydrogen fluoride (52 g, 0.67 mol) was added with vigorous stirring and the exclusion of moisture. The temperature was raised to 170° and 1,1-dichloroacetone (42 g, 0.33 mol) was added dropwise at such a rate that the fluoro-compound distilled, as it was formed, between 75 and 80° at a rate of 1 drop/2 s. Fractionation of the distillate gave (i) 1,1-difluoroacetone (10 g, 50% based on the chloro-compound consumed), b.p. 46–47°, *n*_D²⁰ 1.3281, in good agreement with literature values,¹⁷ *v*_{max} 1757 cm⁻¹ (C=O); (ii) 0.5 ml, b.p. 70–80°, containing some unchanged dichloroacetone and 1-chloro-1-fluoroacetone, as shown by the n.m.r. spectrum, (iii) unchanged dichloroacetone (15 g).

1,1-Difluoroacetone (–)-Menthydrazone. This compound was prepared from the ketone (1.0 g) and (–)-menthyl *N*-aminocarbamate²¹ (2.2 g) in absolute ethanol in 92% yield. It crystallised (absolute ethanol) as needles, m.p. 210–211.5°, [α]_D²² –51° (*c* 1 in Me₂CO) (Found: C, 58.1; H, 8.5; F, 13.1; N, 9.4. C₁₄H₂₄N₂O₂F₂ requires C, 57.9; H, 8.35; F, 13.1; N, 9.65%).

1-Bromo-1-chloroacetone.—Bromine (104 g) was added slowly, during 2 h, to a stirred mixture of chloroacetone (60 g) and chloroform (28 ml) kept at 0–5°. Reaction began immediately. When all the bromine had been added, the solution was washed with aqueous sodium hydrogen carbonate, dried (CaSO₄), and fractionated to give 1-bromo-1-chloroacetone (30 g, 27%), b.p. 41–42°/20 mm, *n*_D²⁴ 1.4860. The indirect method previously used¹⁸ gave a lower yield of product with the same b.p. and *n*_D.

Reaction of 1-Bromo-1-chloroacetone with Thallous Fluoride.—Bromochloroacetone (30 g), powdered anhydrous thallous fluoride (44 g), and dry diethyl ether (25 ml) were heated together under reflux with vigorous agitation and the exclusion of moisture for 48–50 h. Filtration followed by distillation gave a yellowish-green liquid (1 g, 5%), b.p. 78–85°, containing some 1-chloro-1-fluoroacetone as shown by the n.m.r. spectrum. Most of the bromochloroacetone was recovered.

1,1-Dibromo-1-chloroacetone.—Bromine (320 g, 2 mol) was added dropwise (18 h) to a vigorously stirred mixture of water (630 ml), sodium hydrogen carbonate (210 g, 2.5 mol) and chloroacetone (92 g, 1 mol), at 20–26°. After addition of the bromine, the mixture was stirred for a further 8 h, or until the bromine had disappeared. The heavy oily layer was separated, dried (CaSO₄), and fractionated to give fraction (i), b.p. 24–30°/7 mm (chloroacetone and dibromochloromethane) and fraction (ii) b.p. 57–58°/7 mm, *n*_D¹⁹ 1.5388. The second fraction was refracted and gave 1,1-dibromo-1-chloroacetone (215 g, 86%) (lachrymatory), b.p. 41–42°/1 mm, 164–165°/760 mm, *n*_D²⁰ 1.5370, *v*_{max} 1752 (C=O), 781 (C–Cl), 692 cm⁻¹ (C–Br) (Found: C, 14.5; H, 1.3; Br, 64.05; Cl, 14.25. C₃H₃Br₂ClO requires C, 14.4; H, 1.2; Br, 64.0; Cl 14.2%).

Dibromochloromethane.—Dibromochloroacetone (30 g) was added to stirred 5*N*-sodium hydroxide (70 ml) with cooling when necessary. The oil was separated and the aqueous layer was extracted with ether; the combined oil and ethereal extract were dried (CaSO₄) and distilled to give dibromochloromethane (20 g, 80%), b.p. 118–120°, *n*_D²⁰ 1.5484.

²¹ R. B. Woodward, T. P. Kohman, and G. C. Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 120.

²² E. D. Bergman and S. Cohen, *J. Chem. Soc.*, 1958, 2259.

1-Bromo-1-chloro-1-fluoroacetone.—A rigorously dried apparatus initially protected with a CaCl_2 guard-tube was used. Finely ground mercuric fluoride (30 g, 0.13 mol; from Kodak Ltd.) was added rapidly to pure 1,1-dibromo-1-chloroacetone (90 g, 0.36 mol) and the vigorously stirred mixture was quickly raised to, and maintained at, 110° ; the reaction started after 5–7 min. The temperature was kept between 110 – 115° until the reaction was complete (ca. 15 min.), as shown by a swift subsidence of the visible reaction and by a colour change of the mercuric fluoride (red-orange \rightarrow pale yellow \rightarrow grey \rightarrow brown). The CaCl_2 tube was removed and pressure in the apparatus was reduced to ca. 70–80 mm; the fluorinated product then distilled over quickly at 60 – 80° . When the b.p. rose above 80° , the receiver was changed, the pressure lowered to 50 mm and temperature of bath raised to 130° and kept at 130 – 140° until no further organic material distilled. The two distillates were separately fractionated (50 cm column), the first fractions being combined and refractionated to give 1-bromo-1-chloro-1-fluoroacetone (20 g, 85% based on HgF_2), b.p. 110 – 112° , n_D^{25} 1.4440, of 95% purity (n.m.r. and g.l.c.). Final purification was effected either by g.l.c. Autoprep or by two further fractionations with a longer column, the pure halogeno-ketone having b.p. 111 – 112° , 43 – $45^\circ/60$ mm, n_D^{25} 1.4405; d^{21} 1.7026; v_{max} 1756 (C=O),

1119 and 1079 (C–F), 777 cm^{-1} (C–Cl) (Found: C, 19.0; H, 1.7; Br, 42.1; Cl, 18.6; F, 9.8. $\text{C}_3\text{H}_3\text{BrClFO}$ requires C, 19.0; H, 1.6; Br, 42.35; Cl, 18.7; F, 10.05%).

1-Bromo-1-chloro-1-fluoroacetone 2,4-Dinitrophenylhydrazone.—The ketone (1.6 g) and 2,4-dinitrophenylhydrazine (1.0 g) in dry ether (12 ml) were stirred vigorously for 10 min; glacial acetic acid (4 drops) was added and vigorous stirring continued for 24 h in a tightly stoppered flask. The yellow *solid* (1.7 g, 91%) was collected and, after crystallisation from light petroleum (b.p. 80 – 100°), had m.p. 129 – 130° (Found: C, 29.4; H, 1.7; N, 15.2; Br, 21.5; Cl, 9.5; F, 5.35. $\text{C}_9\text{H}_7\text{BrClFN}_4\text{O}_4$ requires C, 29.2; H, 1.9; N, 15.2; Br, 21.65; Cl, 9.6; F, 5.1%).

1,1-Dichloro-1-fluoroacetone was similarly prepared from 1-bromo-1,1-dichloroacetone²⁰ and mercuric fluoride at a reaction temperature of 120 – 125° ; it had b.p. 98 – 100° , n_D^{20} 1.4049. Its (–)-*menthylhydrazone* was prepared in dry benzene; it crystallised from the same solvent, as needles, m.p. 115 – 116° (decomp.) (Found: C, 49.1; H, 6.8; Cl, 20.3; F, 5.6; N, 8.1. $\text{C}_{14}\text{H}_{23}\text{Cl}_2\text{FN}_2\text{O}_2$ requires C, 49.4; H, 6.8; Cl, 20.6; F, 5.6; N, 8.2%).

Thanks are due to the University of London for a post-graduate studentship to B. M.

[0/533 Received, April 6th, 1970]