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PREPARATION OF HALO-F-METHANES VIA POTASSIUM FLUORIDE-HALOGEN CLEAVAGE OF HALO-F-METHYLPHOSPHONIUM SALTS

D.J. BURTON, S. SHIN-YA and H.S. KESLING

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242 (U.S.A)

SUMMARY

Treatment of halo-F-methylphosphonium salts with potassium fluoride and halogen (I_2, Br_2, ICl, IBr) gives modest yields of halo-F-methanes. This method of preparation augments the classical Hunsdiecker approach to these materials.

INTRODUCTION

Fluoromethyl iodides have generally been prepared from silver salts of carboxylic acids via the Hunsdiecker reaction [1,2] or from acid halides and potassium iodide [3]. The utility of this method is limited by the availability of the appropriate acid or acid chloride or by the cost of the Hunsdiecker reaction in large scale preparation.

Halo-F-methylphosphonium salts have been demonstrated to be versatile synthetic precursors. They have been employed as precursors to the nucleophilic fluoromethylene ylides [4] and the electrophilic difluorocarbene [5]. We have also shown that these salts can serve as halomethyl transfer agents [6] with subsequent transfer of the halomethyl group to substrates such as F-olefins, F-pyridine, aroyl fluorides, and halogen. In this report we address the capture of the halo-F-methyl groups with halogens.

RESULTS AND DISCUSSION

When bromodifluoromethyltriphenylphosphonium bromide, 1, was treated with anhydrous potassium fluoride in triglyme in the presence of iodine, 41% of bromodifluoroiodomethane, 2, and 9% of difluorodiiodomethane, 3, were isolated. Similarly, trihalomethylphosphonium salts 4, 5, and 6 were treated with potassium fluoride in the presence of I_2, ICl, Br_2, or IBr.

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TABLE 1

Preparation of halo-F-methanes

$$[R_3\overset{+}{P}CFXY]Z^{-} + \text{halogen} + KF \xrightarrow{\text{solvent}} \text{halo-}F\text{-methanes}$$

Entry	Phosphonium salt	Halogen^{a}	Solvent	Products (%)^{b}
1	$[Ph_3\overset{+}{P}CF_2Br]Br^{-}$, 1	I_2^{c}	TG	CF_2BrI(41), CF_2I_2(9)
2	$[Ph_3\overset{+}{P}CFBr_2]Br^{-}$, 4	I_2	TG	$CFBr_2I$^{d} 31, $CFBr_3$^{e} 12, $CHFBr_2$^{f} 10
3	4	I_2	DMF	$CFBr_2I$^{d} 52, $CFBr_3$^{e} 20, $CFBrI_2$^{d} 15
4	4	I_2	Tet. G	$CFBr_2I$^{d} 57, $CFBr_3$^{e} 15, $CFBrI_2$^{d} 13, $CHFBr_2$^{f} 10
5	4	IBr	Tet. G	$CFBr_2I$^{d} 32, $CFBr_3$^{e} 31, $CHFBr_2$^{f} 9
6	$[(Me_2N)_3\overset{+}{P}CF_2Cl]Cl^{-}$, 5	I_2	TG	CF_2ClI 53(34)^{g}
7	5	ICl	Tet. G	CF_2ClI 18, CF_2Cl_2^{h} 28
8	5	Br_2^{i}	TG	CF_2BrCl^{j} 5, CF_2Br_2^{j} 3

9	$[(Me_2N)_3\overset{+}{P}CFCl_2]Cl^-$, 6	I_2	TG	$CFCl_2I^g$ 63(31), $CFCl_3{}^j$ 27
10	6	ICl	Tet. G	$CFCl_2I$ 43, $CFCl_3{}^j$ 24
11	6	$Br_2{}^k$	TG	$CFCl_2Br^l$ 42, $CFCl_3{}^j$ 15, $CFClBr_2{}^l$ 5, $CFHCl_2{}^f$ 25

(a) Unless otherwise noted, a slight excess of halogen and a three-fold excess of KF was used; (b) ^{19}F NMR yield *vs*. $PhCF_3$. Isolation yield in parentheses. Products were identified either by spiking with an authentic sample or by combination of IR and mass spectral data of the isolated products; (c) 45% excess of (1) and a two-fold excess of KF used; (d) assignment was made based on ^{19}F NMR data by comparison to related methanes; (e) isolated by GLPC; mass spectrum and/or ^{19}F NMR spectrum in agreement with authentic sample; (f) not isolated, but ^{19}F NMR data was in agreement with reported values; (g) 20% excess of (5) and three-fold excess of KF used; (h) chemical shift in the ^{19}F NMR spectrum was identical with an authentic sample; (i) major products (not isolated) observed in the ^{19}F NMR spectrum were found at Φ^* 16.0 (s); Φ^* 67.7 (s); Φ^* 75.3 (s); Φ^* 64.3 (d), J = 55 Hz; Φ^* 71.2 (d), J = 60 Hz; and Φ^* 72.9 (d), J = 55 Hz; (j) not isolated but identified by spiking with an authentic sample; (k) unidentified peaks in the ^{19}F NMR spectrum were also observed at: Φ^* 60.0 (d), J = 55 Hz and Φ^* 68.0 (d), J = 55 Hz; (l) isolated by preparative GLPC and identified by ^{19}F NMR, IR, and mass spectrum.

TABLE 2

Spectral data of halo-_F_-methanes

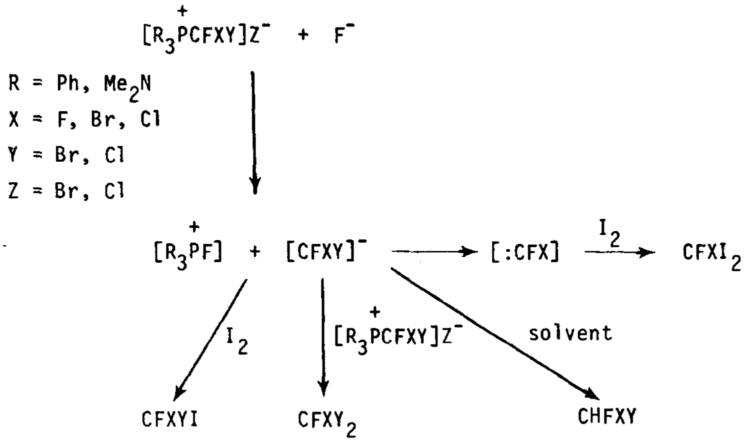
Methane	^{19}F (ppm)	IR (cm^{-1})[a]	Mass spectrum (m/e)
CF_2BrI	-13.8 ($CDCl_3$)	1110 (s), 1060 (vs), 765 (vs) (neat)	258, 256 (M^+)
	- 1.8 (TG as Rx. mix.)		131, 129 (base)
CF_2I_2	-19.1 ($CDCl_3$)	1100 (s), 1045 (vs), 720 (vs) (neat)	304 (M^+)
	+18.4 (TG as Rx. mix)		177 (base)
$CFBr_2I$	+ 3.8 (Tet. G as Rx. mix.)		
$CFBrI_2$	+ 9.0 (Tet. G as Rx. mix.)		
CF_2ClI	- 7.4 (CCl_4)	1125 (vs), 1080 ~ 1060 (vs), 905 (m)	214, 212 (M^+)
	+ 6.9 (TG as Rx. mix.)	870 (s), 840 ~ 740 (vs), (CCl_4)	87, 85 (base)
$CFCl_2I$	- 5.9 (CCl_4)	1045 (vs), 870 (w), 810 ~ 730 (vs),	232, 230, 228 (M^+)
	+11.4 (TG as Rx. mix.)	(CCl_4)	105, 103, 101 (base)
$CFCl_2Br$	- 3.2 (CCl_4)	1075 (vs), 900 (m), 840 ~ 750 (vs),	105, 103, 101 (base)
		(CCl_4)	
$CFClBr_2$	- 5.6 (CCl_4)	1065 (vs), 890 (w), 880 (w), 810 ~	230, 228, 226, 224 (M^+)
		720 (s), (CCl_4)	149, 147, 145 (base)

(a) Peaks of greater than _ca_. 10% absorption are reported.

$$\underset{\underline{1}}{[Ph_3\overset{+}{P}CF_2Br]Br^-} + KF + I_2 \xrightarrow[RT]{triglyme} \underset{\underline{2},\ 41\%}{CF_2BrI} + \underset{\underline{3},\ 9\%}{CF_2I_2}$$

The results of these reactions are tabulated in Table 1, and the spectral data of the products of these reactions is summarized in Table 2. Similar results were obtained with either pregenerated and isolated phosphonium salt or _in situ_ generated phosphonium salt.

The observed products can be most easily rationalized _via_ ejection of the halo-_F_-methyl anion from the phosphonium salt by fluoride ion attack on the salt. Capture of the anion by halogen, solvent (protonation), or the original salt [7] accounts for most of the observed products [8]. The remaining products can be rationalized by α-elimination from the initial anion to form carbene with subsequent capture of carbene with halogen (cf. Scheme 1).



Scheme 1

As noted in Table 1, capture of the halo-_F_-methyl group by iodine gives the best preparative results and provides a reasonable one-pot preparation of the halo-_F_-methanes. Salt _4_ gave a reasonable yield of $CFBr_2I$, but we were unable to isolate this material without extensive decomposition. Despite the modest yields, the ease of reaction scale-up and the commercial availability of the precursors make this route a new and attractive entry to several halo-_F_-methanes.

EXPERIMENTAL

Preparation of dibromofluoromethyltriphenylphosphonium bromide, 4

A 250 ml flask equipped with an addition funnel, mechanical stirrer, and condenser was flame dried under a nitrogen flow. The flask was charged with 68.0 g (0.25 mole) of $CFBr_3$ and 15 ml of dry THF. Then, 65.5 g (0.25 mole) of triphenylphosphine, dissolved in 100 ml of dry THF, was added via the addition funnel over 8.5 hours. The temperature was maintained at 0-5°C during the addition. After the addition of the tertiary phosphine was completed, the reaction mixture was heated at reflux for seven hours. Then, the reaction mixture was cooled to 0°C and the solid product was filtered (Schlenk funnel) under nitrogen. The solid product was washed with cold dry THF (3 x 60 ml) and then dried at room temperature under vacuum (0.05 mm Hg) to give 116.5 g (88%) of tan powder, mp 206.5° (decomp.); ^{19}F NMR ($CDCl_3$) Φ^* 74.2 ppm (d) J = 78 Hz; ^{31}P NMR ($CHCl_3$) δ = -36.0 (d); ^1H NMR ($CDCl_3$) δ = 7.9 (m).

Preparation of chlorodifluoromethyltris(dimethylamino)phosphonium chloride, 5

To a similarly equipped apparatus described in the previous reaction was charged 16.3 g (0.10 mole) of tris(dimethylamino)phosphine and 150 ml of dry triglyme. The reaction flask was cooled to 0°C and 25 g (0.20 mole) of CF_2Cl_2 was condensed (Dry-Ice condenser) into the reaction solution. The reaction mixture was stirred at ambient temperature for twelve hours followed by subsequent addition of an additional 12.6 g (0.10 mole) of CF_2Cl_2 at twelve hour intervals until a total of 0.80 mole of CF_2Cl_2 had been added. Then, the flask was cooled to 0°C and the white solid product was filtered (Schlenk funnel) under nitrogen, washed with dry Et_2O (3 x 100 ml), and dried at room temperature under vacuum (0.05 mm Hg) to give 25.1 g (88%) of white powder, mp 218° (decomp.); ^{19}F NMR ($CDCl_3$) Φ^* = 51.6 ppm (d) J = 92 Hz; ^{31}P NMR ($CDCl_3$) δ = -40.1 (t); ^1H NMR ($CDCl_3$) δ = 3.1 (d) J = 10.5 Hz. Although the salt is hygroscopic, it is stable to exposure to ethanol and water.

Preparation of 6

Details for the preparation of 6 have been previously described [9].

General procedure for the reaction of 1, 4, 5, or 6 with halogen and potassium fluoride

A mixture of either *in situ* formed or pregenerated phosphonium salt and solvent was cooled to 0°C and halogen was added in one portion by either syringe or *via* a solids addition tube. After stirring at 0°C for 15 minutes, potassium fluoride was added *via* a solids addition tube. The reaction mixture was stirred at 0°C for 2 hours, overnight at RT; filtered, washed with solvent, and the filtrate subjected to flash distillation. Products were purified by a second fractional distillation or by GLPC.

Reaction of 1 with KF and I_2

1, prepared *in situ* from 341 g (1.3 moles) of triphenylphosphine and 294 g (1.4 moles) of CF_2Br_2 in 1.5 liters of dry triglyme [10], was treated with 228 g (0.9 mole) of iodine and 151 g (2.6 moles) of dry potassium fluoride. The flash distillate was fractionated on a teflon spinning band column to give 93.9 g (41%) of 2, bp 64.5 to 65.5°/746 mm Hg. Crude 3 was purified by preparative GLPC to give 24.6 g (9%) of 3, bp 92°/744 mm Hg [11].

Reaction of 4 with KF and I_2

Salt 4 (25 g, 0.047 mole) in tetraglyme (100 ml) was treated with iodine (17.9 g, 0.070 mole) and dry potassium fluoride (8.2 g, 0.141 mole). ^{19}F NMR analysis of the reaction mixture indicated the formation of 57% $CFBr_2I$, 15% $CFBr_3$, 13% $CFBrI_2$, and 10% $CHFBr_2$. Isolation of pure $CFBr_2I$ or $CFBrI_2$ by either distillation or GLPC, however, was unsuccessful.

Reaction of 5 with KF and I_2

Salt 5, prepared *in situ* from 16.4 g (0.10 mole) of *tris*(dimethylamino) phosphine and excess CF_2Cl_2 in triglyme (150 ml) was treated with iodine (20.3 g, 0.080 mole) and dry potassium fluoride (17.4 g, 0.30 mole). ^{19}F NMR analysis of the reaction mixture showed the formation of CF_2ClI (53%). Flash distillation of the reaction mixture followed by simple room temperature distillation (reduced pressure) of the flash distillate gave 6.8 g of *ca*. 90% pure CF_2ClI (34%). An analytical sample was obtained by GLPC.

Reaction of 6 with KF and I_2

Salt 6 (16.0 g, 0.053 mole) in triglyme (80 ml) was treated with iodine (14.9 g, 0.059 mole) and potassium fluoride (9.3 g, 0.16 mole). ^{19}F NMR analysis of the reaction mixture showed the formation of $CFCl_2I$ (63%) and $CFCl_3$ (27%). The reaction mixture was flash distilled; the distillate was washed with water, and the organic layer was dried over 4 Å molecular sieves. The aqueous layer was extracted with ether, dried over 4 Å molecular sieves and combined with the dry organic layer. After removal of ether, distillation at room temperature (reduced pressure) gave 4.3 g of $CFCl_2I$ (31%) [12]. An analytical sample was obtained by GLPC.

Reaction of 6 with KF and Br_2

Salt 6 (2.0 g, 0.0067 mole) in triglyme (10 ml) was treated with bromine (1.6 g, 0.010 mole) and dry potassium fluoride (1.2 g, 0.020 mole). ^{19}F NMR analysis showed the formation of 42% $CFCl_2Br$, 15% $CFCl_3$, 5% $CFClBr_2$, and 25% $CHFCl_2$. Analytical samples of $CFCl_2Br$ and $CFClBr_2$ were obtained by GLPC.

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7 We have observed these salts to be good positive halogen donors to carbanions in other work in our laboratory.

8 The main product of these reactions, the halo-*F*-methane, could also be rationalized by formation of a pentavalent phosphorane intermediate with subsequent transfer of the halo-*F*-methyl group from the phosphorane. We have no evidence to rule out such a pathway. Consequently, for simplicity sake we rationalize the product formation *via* the common type of intermediate shown in Scheme 1, keeping in mind this is merely a convenient mechanistic interpretation.

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10 Distilled from sodium-benzophenone ketyl.

11 Compound **3** can also be obtained by washing the distillation residue (after separation of **2**) with aqueous $NaHSO_3$, drying with 4 Å molecular sieves, and distillation at reduced pressure.

12 GLPC indicated the $CFCl_2I$ contained *ca*. 10% of Et_2O. For best results, washing of the aqueous layer with Et_2O should be omitted.