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FLUOROHALOGENO COMPOUNDS. I. THE GRIGNARD REACTION OF SOME
FLUOROHALOGENOETHANES

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SUMMARY

An extension of the scope of the Grignard reaction of fluorinated compounds is reported. Fluorohalogenoethanes of the general formula CF_3CXYZ (X = F,Cl,Br ; Y,Z = Cl,Br) were found to undergo smoothly the metal-halogen exchange reaction with alkyl- or aryl-magnesium halides at low temperature to yield organometallic compounds $CF_3CXMYMgHal$. The Grignard compounds were reacted with a series of aldehydes and ketones to give the corresponding alcohols in good to moderate preparative yields.

INTRODUCTION

Fluorinated organometallic compounds have become useful synthetic intermediates for introducing fluorinated units into organic molecules. The metal-halogen exchange reaction [1] has been widely used as a convenient route for the preparation of intermediate Grignard reagents. Low temperature is the necessary pre-requisite for the stability of perfluoroalkylmagnesium halides [2,3,4]. Many reports [1-21] deal with the preparation and synthetic applications of perfluoroalkyl Grignard reagents. So far, only perfluoroalkyl iodides and bromides have been used for this reaction.

The chemistry of α -halogenoalkylmagnesium reagents was reviewed [22], but none of the compounds reported contained

fluorine or fluorinated group. Organometallic compounds derived from fluorohalogenoalkanes⁺ containing more than one halogen atom other than fluorine on the same carbon atom have received little attention. The halogen atoms (Cl, Br, I) will apparently decrease the chemical stability of the organometallics and subsequent products, but, on the other hand, their reactivity may be utilized in further synthetic steps [23]. The readily available fluorohalogenoethanes seemed to be suitable compounds to initiate the study of the preparation and the reactivity of fluorinated α -halogenoalkylmagnesium halides.

We wish to report further extension of the metal-halogen exchange reaction which have facilitated the synthesis of some α -halogeno-fluoroalkylmagnesium halides of the general formula CF_3CX_2MgHal , where $X = F, Cl, Br$ and $Y = Cl, Br$. As a proof of their structure and synthetic utility, the Grignard compounds were reacted with a series of aldehydes and ketones to yield the corresponding alcohols.

RESULTS AND DISCUSSION

The metal-halogen exchange reaction [1] between an alkyl- or aryl-magnesium halide and perfluoroalkyl iodide or bromide is a generally applied method of preparation of perfluoroalkylmagnesium halides. We have found that 1,1-dihalogeno-tetrafluoro- and 1,1,1-trihalogenotrifluoro-ethanes undergo smoothly this exchange reaction in diethylether to give α -halogeno-fluoroalkylmagnesium halides. The results were not substantially influenced by the nature of alkyl or aryl in the hydrocarbon Grignard reagent. Isopropylmagnesium bromide was used in most reactions.

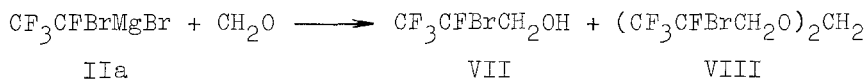
The fluorohalogenoethanes which were converted successfully into organomagnesium compounds according to Scheme 1 are listed in Table 1. They all contain the trifluoromethyl group that appeared to be the necessary structural feature for the formation of the Grignard reagent.

⁺ 'halogeno' in this connection means any halogen atom with the exception of fluorine

solution of alkylmagnesium halide were the signs of the intermediate formation of the fluorinated Grignard reagent. Attempts to accomplish the exchange reaction at room temperature resulted in exothermic decompositions of fluorohalogenoethanes with no higher boiling products isolable.

The well established reaction of the Grignard reagents with various types of aldehydes and ketones proceeded smoothly giving the corresponding alcohols. For illustration, results of reactions of 1-bromo-1,2,2,2-tetrafluoroethylmagnesium bromide (IIa) with a series of carbonyl compounds are listed in Table 2.

The reaction of the Grignard compound IIa with formaldehyde [25] gave two major products, the expected primary alcohol VII and its formal VIII which is the common by-product of this reaction [26].



Compounds CF_3CFClBr (I), CF_3CFBr_2 (II), $\text{CF}_3\text{CClBr}_2$ (V) and CF_3CBr_3 (VI) were all prepared by the reaction of 1,2-dibromotetrafluoroethane (IX) with anhydrous aluminium chloride. This reaction was reported [27] to give only II, VI and X. The recent patent application [28] and the paper cited therein [29] describe aluminium chloride as not promoting the isomerization of 1,2-dibromotetrafluoroethane (IX).

In our experiments, the reaction of IX with AlCl_3 on a laboratory scale proceeded smoothly to yield products of isomerization (II), disproportionation (VI and X) and exchange (I and V) [30] reactions, provided it was monitored by glc analysis or infrared spectroscopy, and quenched by the addition of diluted hydrochloric acid as soon as all of the 1,2-dibromotetrafluoroethane (IX) was converted. Unless the reaction is quenched in time, the yield of the isomerization product II falls and products of disproportionation and chlorination prevail. Careful distillation of the product mixture afforded fluorohalogenoethanes I, II, V, VI and X.

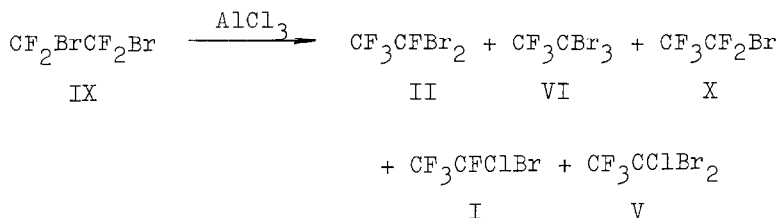
TABLE 1
The Grignard reaction of fluorohalogenoethanes with acetone

Starting ethane	Product $CF_3CX_2Y-C(CH_3)_2OH$					
	X	Y	No.	Boiling point $^{\circ}C$	Yield %	Elemental analysis (%) found (calc d)
No.						C H F Cl Br
I	F	Cl	X	112	34.3	31.12 3.68 39.29 17.94 (30.86) (3.60) (39.09) (18.21)
II	F	Br	XI	128	81.7	25.36 3.03 31.43 33.10 (25.12) (2.95) (31.80) (33.43)
III	Cl	Cl	XII	123	4.7	28.71 3.58 27.12 33.25 (28.46) (3.34) (27.01) (33.60)
IV	Cl	Cl	XII	123	19.7	28.55 3.60 27.26 33.41 (28.46) (3.34) (27.01) (33.60)
V	Cl	Br	XIII	137	19.0	23.32 2.91 21.98 14.17 30.95 (23.51) (2.76) (22.31) (13.88) (31.28)
VI	Br	Br	XIV	152	20.3	19.69 2.36 19.02 53.66 (20.02) (2.35) (19.00) (53.29)

TABLE 2
The reaction of $\text{CF}_3\text{CFBrMgBr}$ (IIa) with aldehydes and ketones

Carbonyl compound		Product ^a $\text{CF}_3\text{CFBr-C(R}^1\text{R}^2\text{)OH}$		Elemental analysis (%)				
R^1	R^2	No.	Boiling point $^{\circ}\text{C/mm Hg}$	Yield %	C	H	F	Found (calc'd)
CH_3	CH_3	XI	128	81.7	25.36 (25.12)	3.03 (2.95)	31.43 (31.80)	33.10 (33.43)
CH_3	$\text{i-C}_4\text{H}_9$	XV	91/50	54.5	34.26 (34.18)	4.70 (4.66)	27.36 (27.04)	28.25 (28.43)
	cyclo- $(\text{CH}_2)_4$	XVI	70/14	40.9	31.49 (31.72)	3.57 (3.42)	28.79 (28.57)	30.40 (30.15)
CH_3	C_6H_5	XVII	105/15	24.9	40.12 (39.89)	3.20 (3.01)	25.42 (25.24)	26.50 (26.54)
H	H	VII	97	27.6	17.20 (17.08)	1.63 (1.43)	36.37 (36.02)	37.54 (37.88)
		VIII	92/28	13.1	19.67 (19.37)	1.61 (1.39)	34.85 (35.03)	37.00 (36.83)
H	CH_3	XVIII	112	71.1	21.61 (21.35)	2.46 (2.24)	34.09 (33.78)	35.85 (35.52)
H	C_6H_5	XIX	85/11	46.5	37.62 (37.66)	2.47 (2.46)	26.34 (26.47)	27.49 (27.84)

^a all products were the corresponding alcohols, only the reactor with formaldehyde yielded the alcohol VII and its formal VIII



Scheme 2

Further research of the reactivity of fluorinated α -halogenoalkylmagnesium halides and their synthetic utility is in progress.

EXPERIMENTAL

General comments

All boiling points are uncorrected. Gas chromatography was performed on a Chrom 4 (Laboratorní přístroje Praha) analytical chromatograph (FID, stainless steel columns 0.3 x 360 cm, packed with 10 % SE-30 or 10 % polypropylene sebacate on Chromaton N-AW-DMCS). All new compounds were characterized by NMR (^{19}F and ^1H) and infrared spectroscopy and by elemental analysis. The physical measurements and analyses of the products of the reactions are summarized in Tables 1, 2 and 3. NMR spectra were recorded in deuteriochloroform on Varian XL-100/15 and Tesla BS 567 spectrometers. ^1H chemical shifts are quoted in δ units using tetramethylsilane, and ^{19}F chemical shifts in ppm positive to high field of trichlorofluoromethane, both internal references. NMR data are summarized in Table 3. Infrared spectra were obtained by use of the Perkin-Elmer 325 instrument.

Materials

All reactions were carried out under an atmosphere of dry nitrogen. Diethylether was distilled from LiAlH_4 prior to use. The carbonyl compounds were all of commercial grade quality and were distilled and dried over molecular sieves.

TABLE 3
NMR spectra of new compounds

Compound number	^{19}F			^1H		
	Chemical shift	Relative intensity	Type of signal ^a and J in Hz	Chemical shift	Relative intensity	Type of signal ^a and J in Hz
VII	78.7	3	d J=8.5	2.92	1	s (-OH)
	136.4	1	tq $J_q=8.5$ $J_t=17$	4.11	2	d J=17
VIII	78.9	3	d J=8.6	4.17	4	d J=17.2
	135.3	1	tq $J_q=8.6$ $J_t=17.2$	4.90	2	s
X	75.6	3	broad d J=6	1.51	6	broad s
	133.8	1	broad q J=6	2.52	1	s (-OH)
XI	73.0	3	d J=8.6	1.51	6	s
	132.6	1	q J=8.6	2.80	1	s (-OH)
XII	71.1	-	broad s	1.59	6	q J=1.1
				2.64	1	s (-OH)
XIII	69.1	-	broad s	1.62	6	broad s
				2.72	1	s (-OH)

XIV	67.1	-	broad s	1.71 2.59	6 1	broad s s (-OH)
XV ^b	72.7 134.0; 134.1	3 1	broad d J=8.6 c J(F-P)=8.6	0.99; 1.02 1.50 1.60 - 2.05 2.07	6 3 3 1	2xd J=7 broad s c s (-OH)
XVI	74.0 130.8	3 1	d J=8.5 q J=8.5	1.57 - 2.47	-	c
XVII ^b	72.0; 72.1 128.5; 130.1	3 1	2xd J=8.7 2xq J=8.7	1.91 7.02 - 7.73	3 5+1	s c
XVIII ^b	76.5; 77.5 131.7; 132.5	3 1	2xd J=9.4 c	1.43 2.69 4.17	3 1 1	d J=6 s (-OH) q J=6
XIX ^b	75.5; 77.2 132.2 135.3	3 0.5 0.5	2xd J=9.4 quintet J=9.4 dq J _q =9.4 J _d =18.8	2.72 5.12 7.43	1 1 5	s (-OH) c c

^a c = complex, s = singlet, d = doublet, t = triplet, q = quartet
^b mixture of diastereomers

Formaldehyde was obtained by thermal decomposition [25] of paraformaldehyde (Lachema Brno) dried for 3 days over P_2O_5 .

The fluorohalogenoethanes were purchased or prepared according to known procedures and were distilled prior to use. CF_2BrCF_2Br (IX) (PCR Ventron), $CF_2ClCFCl_2$ (Spolek Ústí n.L.) and $CF_3CHClBr$ (Spofa Praha) were the commercial products. $CF_2BrCFClBr$ was prepared by the addition of bromine to chlorotrifluoroethylene (Spolek Ústí n.L.). $CF_3CFClBr$ (I), CF_3CFBr_2 (II), CF_3CClBr_2 (V) and CF_3CBr_3 (VI) were prepared by the action of anhydrous aluminium chloride on IX. In the reference experiment, CF_3CClBr_2 (V) was prepared by the rearrangement of $CF_2BrCFClBr$ [31]. CF_3CCl_3 (III) was prepared by the aluminium chloride induced isomerization of $CF_2ClCFCl_2$ [32]. $CFCl_2CFCl_2$ was purchased as a by-product of the production of $CF_2ClCFCl_2$ (Spolek Ústí n.L.), and $CF_2ClOCCl_3$ was prepared by its rearrangement by means of aluminium chloride [32]. CF_3CCl_2Br (IV) was prepared by chlorination of $CF_3CHClBr$ [33].

Reaction of CF_2BrCF_2Br (IX) with $AlCl_3$

A 1000-ml three-necked flask fitted with a mechanical stirrer, a thermometer and a reflux condenser connected with a dry-ice cooled trap and a H_2SO_4 hydraulic valve, was charged with 1526.0 g (5.87 mol) of CF_2BrCF_2Br (IX) (previously dried by P_2O_5) and 77.3 g (0.58 mol) of anhydrous aluminium chloride. The flask was heated to reflux in an oil bath maintained at 50-55°C with continuous stirring. Glc analysis of samples of the reaction mixture hydrolyzed by water and neutralized by $NaHCO_3$ solution showed total disappearance of the starting CF_2BrCF_2Br (IX) after 22 hours. The flask was then cooled in an ice bath and the reaction was quenched by the addition of diluted (1:5) hydrochloric acid. The heavy organic layer was separated, neutralized and dried over $CaCl_2$. Fractionation on a column (100 x 2 cm) packed with porcelain saddles (size 3 mm) gave 183.5 g (14.5 % yield) of $CF_3CFClBr$ (I), 767.2 g (50.3 %) of CF_3CFBr_2 (II), 181.4 g (11.2 %) of CF_3CClBr_2 (V) and 260.4 g (13.8 %) of CF_3CBr_3 (VI). In the dry-ice trap condensed 15.5 g of the mixture of lower-boiling products, in which CF_3CF_2Br (X) (48 % by glc, 0.3 % yield) prevailed.

General procedure for the Grignard reactions

To a stirred solution of isopropylmagnesium bromide prepared from 1.58 g (65 mmol) of Mg and 8.0 g (65 mmol) of *i*-PrBr in 150 ml of diethylether, cooled to -70°C , a solution of 60 mmol of a fluorohalogenoethane in 30 ml of ether was added dropwise at a rate sufficient to keep the temperature below -60°C . After 30 minutes of stirring at -70°C , a solution of 65 mmol of a carbonyl compound in 30 ml of ether was added within 1 hour. After an additional 1 hour stirring at -70°C , the reaction mixture was allowed to warm up to room temperature over a 2 h period, and hydrolyzed by 2N HCl (50 ml). The ether layer was washed with water and dried over anhydrous MgSO_4 . Distillation provided the crude alcohol which was purified by fractionation. The results of reactions and characterization of products are summarized in Tables 1,2,3.

Reaction of $\text{CF}_3\text{CFBrMgBr}$ (IIa) with formaldehyde

The Grignard reagent $\text{CF}_3\text{CFBrMgBr}$ (IIa) was prepared as described in the General procedure from 60 mmol of CF_3CFBr_2 (II). Formaldehyde obtained by heating of 10.0 g (333 mmol) of pre-dried paraformaldehyde in a flask at 180°C [25] was introduced into the reaction flask cooled to -70° just above the surface of the stirred slurry by the flow of dry nitrogen over a 2 h period. After an additional 1 hour stirring at -70° , the reaction mixture was allowed to warm up to room temperature and hydrolyzed by 2N HCl (50 ml). A part of the unreacted formaldehyde in the form of paraformaldehyde remained undissolved and was removed by filtration. The ether solution was washed with water and dried over anhydrous MgSO_4 . The crude product was obtained by distillation, and repeated fractionation provided 3.5 g (16.6 mmol, 27.6 % yield) of 2-bromo-2,3,3,3-tetrafluoropropanol (VII), boiling point 97°C , and 1.7 g (3.9 mmol, 13.1 % yield) of 2,8-dibromo-1,1,1,2,8,9,9,9-octafluoro-4,6-dioxanonane (VIII), b.p. $92^{\circ}/28$ mm Hg.

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