FLUORO-KETONES. I REACTIONS OF HYDROCARBON GRIGNARDS WITH PERFLUOROALKYLACID FLUORIDES

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SUMMARY

The reaction between Grignard reagents and perfluoroacid fluorides provides a convenient synthesis procedure for ketones $R_fOR_fC(O)R'$, where R_fOR_f is a perfluoroalkylether group and R' is either an aromatic or aliphatic group. Reaction temperature is an important factor in producing higher yields of ketones. Meta and para-bromophenyl Grignard reagents, which thus far have not been prepared as pure mono Grignards, present secondary competing reactions which detract from their synthetic utility.

INTRODUCTION

Polyfluoroaliphatic ketones have been synthesized by various procedures [1,2]. One of the most widely used is the reaction between an organometallic compound (RM where M = Li, MgX, Zn, Cd) with a variety of substrates, e.g. acids, anhydrides, esters, nitriles and acid halides. With the acids and anhydrides a two to three mole excess of organometallic reagent (RMgX) must be used. Reactions between acid halides and RLi or

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RMgX reagents [3, 4, 5, 6] generally have been reported to give low yields of ketones due to a secondary reaction between the RM compound and ketone to yield tertiary alcohols.

$$RM + R_fC(O)X \xrightarrow{\ r_1\ } R_fC(O)R + MX \tag{1}$$

$$R_fC(O)R + RM \xrightarrow{\ r_2\ } R_fC(OH)R_2 \tag{2}$$
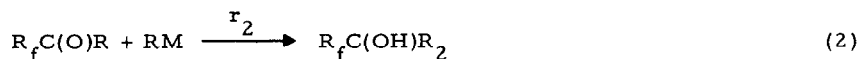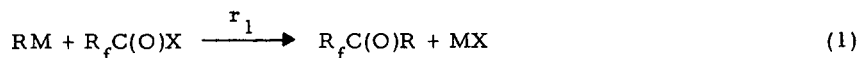
Recently [7] a reaction between a perfluoro Grignard, C_6F_5MgBr and $C_3F_7C(O)Cl$ has been reported to produce $\cdot C_6F_5C(O)C_3F_7$ in 66% yield. No mention of any by-product tertiary alcohol was indicated.
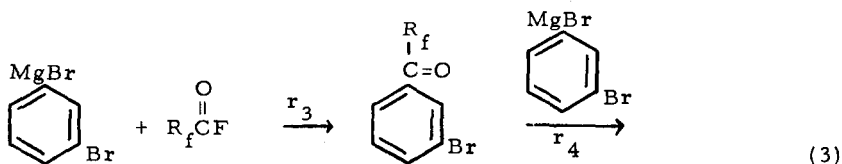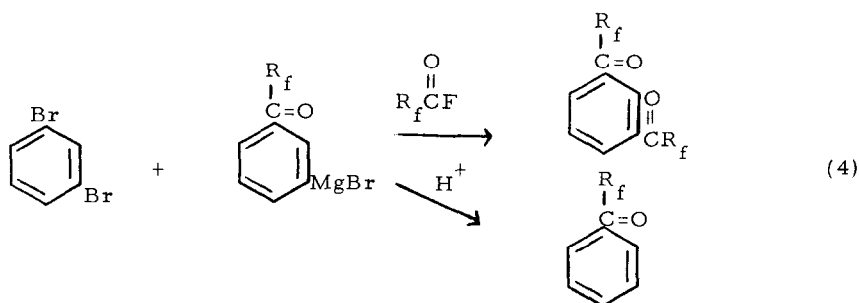
RESULTS AND DISCUSSION

In our studies on the reactions between organometallic compounds with acid halides we have found that in most instances perfluoroalkyl containing ketones, $R_fC(O)R$, could be synthesized in varying yields depending on the organometallic specie (organo-magnesium, -lithium, -cuprate), solvent and reaction temperature. This report is concerned with reactions between hydrocarbon Grignard reagents and perfluoroalkylacid halides of the type $C_3F_7O[CF(CF_3)CF_2O]_nCF(CF_3)C(O)F$ [8], and $C_2F_5O(CF_2CF_2O)_n$ $CF_2C(O)F$ [9].

Phenylmagnesium bromide in diethyl ether between $-20°$ to $0°$ reacts with secondary acid fluorides, $C_3F_7O[CF(CF_3)CF_2O]_nCF(CF_3)C(O)F$ to produce the ketones $C_3F_7O[CF(CF_3)CF_2O]_nCF(CF_3)C(O)C_6H_5$ in yields of 93-97% (n = 0→4). No evidence for any tertiary alcohols was indicated. Our initial assumptions on the lack of tertiary alcohol formation were attributed to the possible steric hindrance offered by the pendant $-CF_3$ on the alpha carbon to the carbonyl function. Reactions of C_6H_5MgBr with primary acid fluorides e.g. $C_2F_5O(CF_2CF_2O)_nCF_2C(O)F$ produced high yields of ketone ($\sim 90\%$) under equivalent conditions. With these primary acid fluorides, however, small yields ($\sim 5\%$), of the tertiary alcohols $C_2F_5O(CF_2CF_2O)_nCF_2C(OH)(C_6H_5)_2$ were formed. At lower reaction

temperatures (-30°) the only product formed was the ketone $(>94\%)$. Even though the R_fOR_f group activates the carbonyl towards nucleophilic substitution by the organometallic reagents, with the perfluoroalkyletheracid fluorides studied, and with the particular reaction conditions used (see experimental) ketone formation is the principal reaction product. Apparently rate 1 is much faster than rate 2 (equations 1-2) and is favored by lower reaction temperatures. We have noted that at lower reaction temperatures, the $R_fOR_fC(O)F$ compounds have limited solubility in diethyl ether and as expected decrease solubility is observed with increase of molecular weight. Sufficient solvent must be present so that a homogeneous reaction medium is present. Insufficient solvent results in a two liquid phase system at lower temperatures and high yields of ketones cannot be obtained.

p-BrC_6H_4MgBr and m-BrC_6H_4MgBr were similarly reacted with $R_fOR_fC(O)F$ to yield the bromophenyl ketones in lower yields than C_6H_5MgBr. The reduction in yield is attributed to two factors; inability to prepare a pure mono Grignard and a competing secondary reaction between the product ketone and Grignard reagent. The conventional method of preparing Grignard reagents, that of reacting the halide with magnesium in diethyl ether produces a mixture of two Grignard reagents when applied to the para and meta dibromobenzenes. Although the mono Grignard predominates, $\sim 85\text{-}90\%$, smaller quantities of the di-Grignard, $\sim 2\text{-}9\%$, are also formed. In addition, unreacted dibromobenzene remains when equivalent mole ratios of dihalide and magnesium are used. The di-Grignard compound on reaction with the acid halides yields the diketone. The competing secondary reaction that also takes place for the meta bromo Grignard is indicated in equations 3-4.
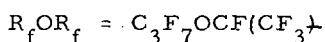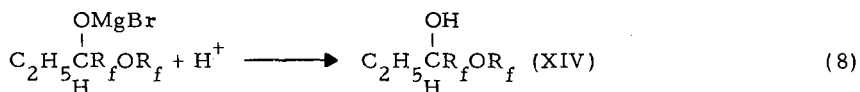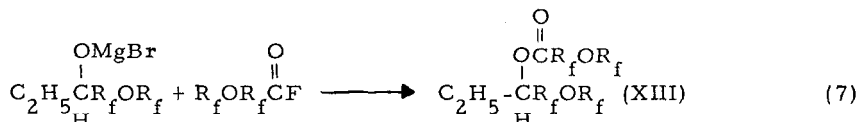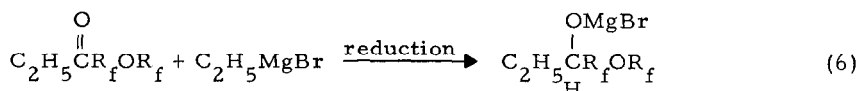

(3)

$$
\underset{\substack{\text{Br} \\ \text{Br}}}{\bigcirc} \;+\; \underset{\substack{\text{MgBr}}}{\overset{\overset{\displaystyle R_f}{\underset{\displaystyle C=O}{|}}}{\bigcirc}} \;\;\xrightarrow[\;\;H^+\;\;]{\;R_fCF\;(O)\;}\;\; \underset{\substack{R_f \\ C=O}}{\overset{\overset{\displaystyle R_f}{\underset{\displaystyle C=O}{|}}}{\bigcirc}}\; \overset{O}{\underset{CR_f}{\parallel}} \tag{4}
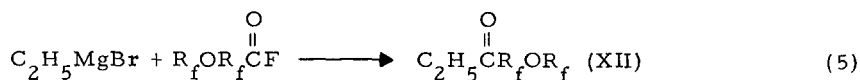$$

Addition of the Grignard to the acid fluoride favors r_3 over r_4. Because of these two reasons a multiplicity of products are formed and difficulty in separation of products was noted resulting in reduced practical yields of the mono ketones. In the preparation of p-BrC_6H_4MgBr, tetrahydrofuran was the preferred solvent since yields of the mono Grignard were ~90%. In diethyl ether as the solvent, yields of the mono Grignard were considerably lower, 70-75%, and an insoluble lower layer formed consisting primarily of the para di-Grignard. In the preparation of m-BrC_6H_4 MgBr the highest yield (85%) of the mono Grignard was obtained in diethyl ether. Considerable unreacted m-$Br_2C_6H_4$ was present even in attempted reactions using excess (20%) magnesium. No attempts were made in the synthesis of the O-BrC_6H_4MgBr due to the instability of this compound.

In our limited studies on hydrocarbon Grignard reagents with R_fOR_f-$C(O)F$ compounds, again solvent and reaction temperature were found to be important factors in obtaining high yields of ketone. At $0°$ for example, the reaction between C_2H_5MgBr and $C_3F_7OCF(CF_3)C(O)F$ leads to three products XII (67%), XIII (30%) and XIV (3%). By lowering the reaction temperature to $-78°$, with sufficient solvent to solubilize the acid fluoride, the rates of the various reactions are altered in favor of producing the ketone in excellent yield XII (91%), XIII (6.3%) and XIV (2.4%). With beta hydrogen containing hydrocarbon alkyl Grignard reagents, previous investigators [10, 11] noted formation of secondary alcohols with carbonyl containing substrates. Various mechanisms have been proposed for the reduction process leading to the secondary alcohol formation. In these studies as well

as ours, no tertiary alcohols as indicated by equation 2 have been found. The three products formed in the reaction are consistent with equations 5-8.

$$C_2H_5MgBr + R_fOR_f\overset{O}{\overset{\|}{C}}F \longrightarrow C_2H_5\overset{O}{\overset{\|}{C}}R_fOR_f \quad (XII) \tag{5}$$

$$C_2H_5\overset{O}{\overset{\|}{C}}R_fOR_f + C_2H_5MgBr \xrightarrow{\text{reduction}} C_2H_5\underset{H}{\overset{OMgBr}{\overset{|}{C}}}R_fOR_f \tag{6}$$

$$C_2H_5\underset{H}{\overset{OMgBr}{\overset{|}{C}}}R_fOR_f + R_fOR_f\overset{O}{\overset{\|}{C}}F \longrightarrow C_2H_5-\underset{H}{\overset{O\overset{O}{\overset{\|}{C}}R_fOR_f}{\overset{|}{C}}}R_fOR_f \quad (XIII) \tag{7}$$

$$C_2H_5\underset{H}{\overset{OMgBr}{\overset{|}{C}}}R_fOR_f + H^+ \longrightarrow C_2H_5\underset{H}{\overset{OH}{\overset{|}{C}}}R_fOR_f \quad (XIV) \tag{8}$$

$$R_fOR_f = C_3F_7OCF(CF_3)-$$

EXPERIMENTAL

General Comments

Reactions involving organometallic reagents were carried out under dry nitrogen with usual precautions for rigorous exclusion of moisture and air. Tetrahydrofuran was dried by refluxing over metallic sodium followed by distillation from calcium hydride prior to use. Anhydrous diethyl ether (Mallinckrodt) was used without further purification. All new compounds were characterized by NMR (^{19}F and ^{1}H), IR, mass spectral and combustion analysis (except VI). GLC analysis was performed on an F&M Model 700 instrument using 6 ft. and 12 ft., 10% SE-30 on Chromosorb W and a 10% Apiezon L on Chromosorb W columns. Yields of products were determined by GLC analysis. Isolated yields were always lower and depended on the complexity of the reaction mixture.

Mass spectral analysis was performed using an electron impact spectrometer for the arylalkyl ketones. The phenylalkyl ketones did not indicate any parent ion peaks. The highest peaks observed were for the $(M-F)^+$. The bromophenylalkyl ketones did indicate weak $(M)^+$. The 100% base peak for both arylalkyl ketones generally was the $(ArCO)^+$. Since the bisalkyl ketone XII fragmented extensively, chemical ionization spectrometry was used. Under these conditions $(M)^+$ and $(M-F)^+$ ions were readily detectable.

Synthesis of p-Bromophenylmagnesium Bromide

Into a flame-dried four neck flask equipped with a stirrer, nitrogen inlet, thermometer and addition funnel was added p-dibromobenzene (10.6g; 45.0 mmol.) and magnesium (1.09g; 45.0 mmol.). To this stirred mixture was added a few milliliters of anhydrous THF. As soon as an exothermic reaction began, the remaining THF was added (100 ml) and the temperature of the exothermic reaction was controlled by external cooling with an ice bath. Most of the magnesium was consumed in 2 hr. and the last traces were consumed in stirring for an additional 20 hr. at room temperature. An aliquot sample after hydrolysis with saturated NH_4Cl solution gave on GLC analysis (6 ft. SE-30 column) benzene (2.4%), bromobenzene (94.2%) and dibromobenzene (2.4%). The remaining Grignard solution was filtered through glass wool and analyzed by acid-base titration. A 98.2% total base was obtained. This Grignard solution was used immediately for subsequent reactions with various acid fluorides. We have found that on storage of this Grignard solution at room temperature for 20 days, that the Grignard content decreases from 94% to 84%. At higher reflux temperatures, for example, the stability of the Grignard solution decreases much faster. A GC-MS analysis of the decomposition products indicated the presence of biphenyl, bromobiphenyl, dibromobiphenyl, terphenyl, bromoterphenyl and dibromoterphenyl.

TABLE I

$$R_fOR_fC(O)F + RMgX \longrightarrow R_fOR_fC(O)R$$
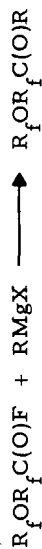
R_fOR_f	R	$R_fOR_fC(O)R$	By-Products
$C_3F_7OCF(CF_3)$	C_6H_5	I	--
$C_3F_7O[CF(CF_3)CF_2O]CF(CF_3)$	C_6H_5	II	--
$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$	C_6H_5	III	--
$C_2F_5O[CF_2CF_2O]_2CF_2$	C_6H_5	IV	--
$C_2F_5O[CF_2CF_2O]_3CF_2$	C_6H_5	V	$R_2C(OH)R_fOR_f$ (VI)
$C_3F_7OCF(CF_3)$	$p-BrC_6H_4$	VII	$C_6H_5C(O)R_fOR_f$ (I)
$C_3F_7O[CF(CF_3)CF_2O]CF(CF_3)$	$p-BrC_6H_4$	VIII	$C_6H_5C(O)R_fOR_f$ (II)
$C_2F_5O[CF_2CF_2O]_3CF_2$	$p-BrC_6H_4$	IX	$C_6H_5C(O)R_fOR_f$ (V)
$C_3F_7OCF(CF_3)$	$m-BrC_6H_4$	X	$m-[R_fOR_fC(O)]_2C_6H_4$ (XI), 1,$m-Br_2C_6H_4$
$C_3F_7OCF(CF_3)$	C_2H_5	XII	$RCOC(O)R_f$ (XIII) (with H and R_f); $RCOH$ (XIV) (with H and R_f)

m-Bromophenylmagnesium Bromide

m-Bromophenylmagnesium bromide was prepared in a similar fashion to the p-bromophenylmagnesium bromide except that the magnesium (5.86g; 241 mmol.) was added to a rapidly stirred solution of m-dibromobenzene (56.9g; 241 mmol.) dissolved in diethyl ether (1000 ml). The reaction was stirred until all the magnesium was consumed. The mixture was filtered through glass wool and analyzed by GLC which indicated benzene (6.3%), bromobenzene (85%) and unreacted dibromobenzene (8.7%). Diethyl ether was the preferred solvent since in THF or mixture of diethyl ether and THF a non-uniform, turbid mixture resulted. Use of 20% excess magnesium did not consume the unreacted dibromobenzene. In this case a higher percentage of the di-Grignard was formed.

General Procedure for the Reactions of Various Grignards with Acid Halides

A flame dried, four neck flask, equipped with a nitrogen inlet, thermometer, stirrer and addition funnel was used. A diethyl ether or THF solution of the Grignard (one molar equivalent) was rapidly added to a cooled rapidly stirred diethyl ether solution of the acid halide (one molar equivalent). Sufficient diethyl ether must be present to ensure complete solubility of the acid fluoride at reaction temperature. Temperature of the reaction was adjusted by cooling with an ice bath or for the lower temperature reactions by an acetone-CO_2 bath. The reaction was followed by GLC analysis of aliquot samples hydrolyzed by NH_4Cl solution.

After completion of reaction, a small quantity of methanol was added followed by hydrolysis with NH_4Cl (25%) solution. The upper diethyl ether layer was separated, dried ($MgSO_4$) and solvent removed by distillation or aspiration under vacuum. In reactions yielding low boiling products (XII, XIII, XIV) the reaction mixture was worked up without methanol.

The results of the various reactions between the Grignard reagents and acid fluorides are summarized in Tables I and II.

TABLE II*

	Yield[a]	B.P./mm	Combustion Data (Calc./Found)			IR (C=O) cm^{-1}	M.S. (found)
			C	H	Br		
I	95	80°/18 mm	36.94 / 37.10	1.29 / 1.16	--	1710	(M)$^+$ (b)
II	96	112°/20 mm	32.4 / 32.4	0.90 / 0.90	--	1710	(M-19)$^+$ (c)
III	97	114°/5 mm	29.9 / 29.8	0.70 / 0.62	--	1710	(M-19)$^+$ (c)
IV	98	116°/28 mm	32.2 / 32.1	0.97 / 1.02	--	1725	(M-19)$^+$ (c)
V	97	119°/17 mm	30.1 / 30.1	0.79 / 0.81	--	1725	(M-19)$^+$ (c)
VI	3	(d)	--	--	--	--	(M)$^+$ (b)
VII	77	80°/10 mm	30.7 / 30.9	0.86 / 0.83	17.0 / 17.0	1710	(M)$^+$ (b)

(a) yields determined by G.C. analysis; (b) M.S. by chemical ionization; (c) M.S. by electron impact; (d) isolated by preparative G.C.
* all new compounds

TABLE II* (Continued)

	Yield[a]	B.P./mm	Combustion Data (Calc./Found)			IR (C=O) cm^{-1}	M.S. (found)
			C	H	Br		
VIII	76	120°/8 mm	28.4/28.3	0.63/0.40	12.6/12.7	1710	$(M)^+$ (b)
IX	74	123°/10 mm	26.8/26.9	0.56/0.42	11.1/11.4	1710	$(M)^+$ (b)
X	69	71°/16 mm	30.7/30.7	0.86/0.70	17.0/17.3	1710	$(M)^+$ (b)
XI	8	(d)	30.8/30.8	0.57/0.59	--	1718	$(M-19)^+$ (c)
XII	91(-78°) 67(0°)	105•	28.1/27.9	1.47/1.50	--	1760	$(M)^+$ (b)
XIII	6.6(-78°) 30(0°)	168°	25.6/25.4	0.92/0.98	--	1798	$(M)^+$ (b)
XIV	2.4(-78°) 3(0°)	(d)	27.9/28.0	2.03/1.86	--	--	$(M)^+$ (b)

(a) yields determined by G.C. analysis; (b) M.S. by chemical ionization; (c) M.S. by electron impact; (d) isolated by preparative G.C.

* all new compounds

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