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SYNTHESIS AND REACTIONS OF A PERFLUOROALKYLETHER GRIGNARD REAGENT CONTAINING A FUNCTIONAL ESTER GROUP

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SUMMARY

The first perfluoroalkylether magnesium bromide containing a functional ester group, $ROC(O)(CF_2)_4OCF_2CF_2MgBr$(I) has been synthesized through the metal-halogen exchange reaction between a perfluoroalkylether iodide ester and ethylmagnesium bromide. The thermal stability in diethyl ether of the Grignard reagent and the products of the Grignard's intermolecular reaction at higher temperatures have been established. Reactions of the Grignard reagent with various substrates such as water, diethyl oxalate, ethyl formate, diethyl carbonate, ethyl acetate, ethyl benzoate and ethyl trifluoroacetate indicate the synthetic utility of this Grignard reagent.

INTRODUCTION

Perfluorinated Grignard reagents have been previously synthesized by a halogen-metal exchange reaction (eqn. 1) in diethyl ether as the solvent at low reaction temperature [1-5].

$$R_fX + RMgBr \xrightarrow[-70° \text{ to } -78°C]{C_2H_5OC_2H_5} RX + R_fMgBr \qquad (1)$$

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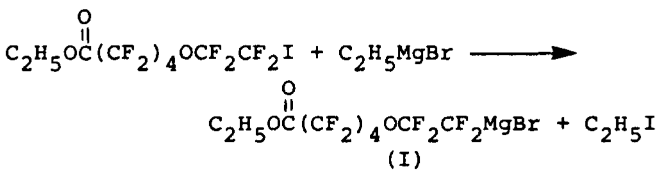
In various studies it has been found that the thermal stability of perfluoro Grignard reagents is dependent on temperature, solvent and structural properties of the R_f group [2,4,5,6]. The Grignard reagents exhibit stability at -78°C for approximately a day, but will slowly decompose to an olefin, $R_fCF{=}CF_2$, at some higher temperature (~-40°C). In tetrahydrofuran solvent the Grignard is less stable than in diethyl ether. A special type of perfluoro Grignard $F(CF_3)_2COCF_2CF_2MgBr$ is more stable than the perfluoroalkyl Grignard reagent [6]. Reactions between perfluoroorganometallic compounds and ketones and esters have been previously reported as a means of synthesizing alcohols [2], ketones [6,7], acids [8], and esters [6,8].

We have expanded our continuing studies on perfluoroaliphatic Grignard reagents to the synthesis of a perfluoroalkylether Grignard reagent containing an ester functional group. The thermal stability of $ROC(O)(CF_2)_4OCF_2CF_2MgBr$(I) has been investigated. In addition, reactions with various carboxylic esters have also been performed to determine what structural effects the substrates have on the synthetic utility of the Grignard.

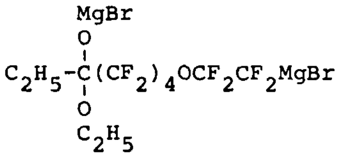
DISCUSSION

A perfluoroalkyl Grignard compound containing a functional group has not been previously reported. We have found that the metal-halogen exchange reaction as shown in eqn. 2 is much faster than the addition reaction to the carbonyl group of the



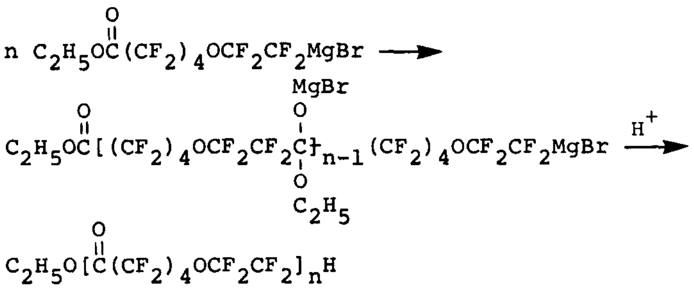
$$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4OCF_2CF_2I + C_2H_5MgBr \longrightarrow \underset{(I)}{C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4OCF_2CF_2MgBr} + C_2H_5I \qquad (2)$$

ester. In diethyl ether as the solvent, the ethylmagnesium bromide reacts with a stoichiometric amount of $C_2H_5OC(O)(CF_2)_4$-OCF_2CF_2I to give a high yield (~95 GC area %) of I. An excess of C_2H_5MgBr over stoichiometric quantity reacts with the carbonyl group of the ester to yield the hemiketal



$$C_2H_5-\underset{\underset{C_2H_5}{O}}{\overset{\overset{MgBr}{O}}{C}}(CF_2)_4OCF_2CF_2MgBr$$

which on hydrolysis would produce $C_2H_5C(O)(CF_2)_4OCF_2CF_2H$. Due to the functional ester group present in the molecule, the thermal sensitivity of I is different than other Grignard reagents. The decomposition reaction is an intermolecular reaction (see eqn. 3). The rate of reaction is a function of time,



$$n\ C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4OCF_2CF_2MgBr \longrightarrow C_2H_5O\overset{O}{\overset{\|}{C}}[(CF_2)_4OCF_2CF_2\underset{\underset{C_2H_5}{O}}{\overset{\overset{MgBr}{O}}{C}}]_{n-1}(CF_2)_4OCF_2CF_2MgBr \xrightarrow{H^+} C_2H_5O[\overset{O}{\overset{\|}{C}}(CF_2)_4OCF_2CF_2]_nH \qquad (3)$$

temperature, and solvent. The yield of $C_2H_5O[C(O)(CF_2)_4OCF_2CF_2]_nH$ was determined by GC/MS analysis of the hydrolyzed reaction. Table 1 lists the results obtained for the thermal stability of I under different reaction conditions. From Table 1, it can be seen that the low reaction temperature, e.g. -75° and -110°C, has a stabilizing effect on the Grignard reagent. In diethyl ether as a solvent, the Grignard reagent is more stable than in tetrahydrofuran. At -20°C in diethyl ether the decomposition

TABLE 1

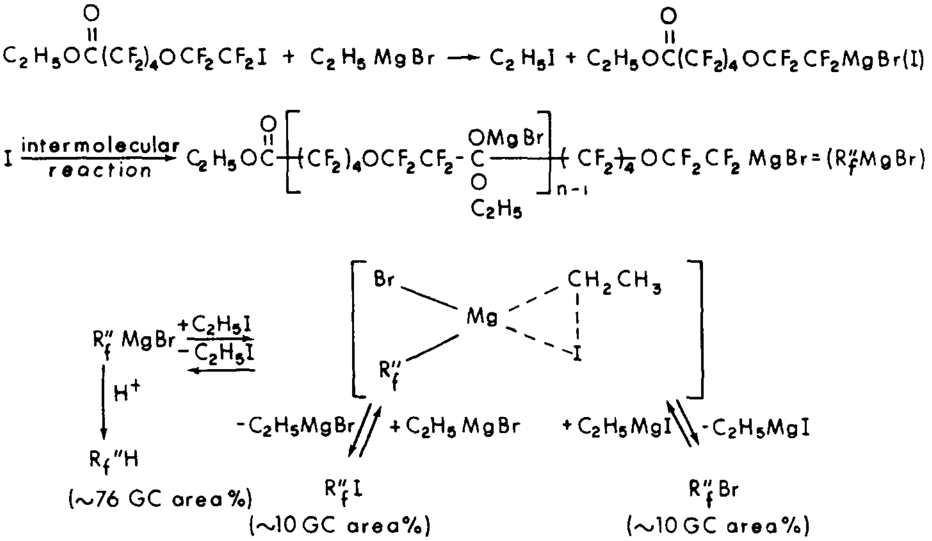
Stability of $C_2H_5O\overset{\overset{O}{\|}}{C}(CF_2)_4OCF_2CF_2MgBr$

Solvent	Temperature (°C)	Time (h)	Decomposition Products - GC Area % $C_2H_5O[\overset{\overset{O}{\|}}{C}(CF_2)_4O(CF_2)_2]_nH$ n=1	n=2	n=3	n=4
Et_2O	-110	0.5	96	trace	-	-
Et_2O	- 75	1	95	3	trace	-
Et_2O	- 75	3	91	4	trace	-
Et_2O	- 75	24	89	5	trace	-
Et_2O	- 45	4.5	26[a]	45[a]	14[a]	3[a]
Et_2O	- 20	1	b			
THF	- 75	1	77	11	1	trace
THF	- 75	3	70	15	3	trace

[a] Products characterized by GC/MS analysis

[b] Three homologous series of products were found as follows: $C_2H_5O[\overset{\overset{O}{\|}}{C}(CF_2)_4O(CF_2)_2]_nH$, $C_2H_5O[\overset{\overset{O}{\|}}{C}(CF_2)_4O(CF_2)_2]_nBr$, and $C_2H_5O[\overset{\overset{O}{\|}}{C}(CF_2)_4O(CF_2)_2]_nI$, n = 1,2,3,4. These products were characterized by GC/MS analysis. The approximate ratio of $R_f''H:R_f''Br:R_f''I$ = 76:10:10 (GC area %, $R_f'' = C_2H_5O[\overset{\overset{O}{\|}}{C}(CF_2)_4O(CF_2)_2]_n$).

products contained three homologous series of compounds which have not been fully characterized. A partial identification by GC/MS analysis indicated the following to be present: $C_2H_5O[C(O)(CF_2)_4OCF_2CF_2]_nH$, $C_2H_5O[C(O)(CF_2)_4OCF_2CF_2]_nBr$, and $C_2H_5O[C(O)(CF_2)_4OCF_2CF_2]_nI$, $n = 1$ to 4. The approximate ratio of (GC area %)-$R_f''H:R_f''Br:R_f''I$ = 76:10:10. No cyclic compounds due to an intramolecular cyclization reaction have been noted. A possible mechanism leading to the various products is suggested in Scheme 1. If the Grignard I is allowed to reach ambient temperature and then hydrolyzed, a complex mixture of products results.



SCHEME 1

Reactions with Various Substrates

As mentioned above, in the absence of another reactive substrate, the Grignard I can react intermolecularly. If, however, a substrate containing a carbonyl group is added to the Grignard, a reaction with it may occur depending on its reactivity towards the Grignard. The rate of addition reaction to the substrate depends on two properties, electronic and steric effects. In order to better understand these effects, reactions between the Grignard reagent I and carboxylic esters were investigated. Table 2 is a summation of the reaction products (in GC area %) based on various substrates. From Table 2 it can be seen that the rate of reaction order is $C_2H_5OC(O)>H>C_2H_5O>CH_3>C_6H_5>>>CF_3$, where these are groups R in a series of compounds $RC(O)OC_2H_5$. In $CF_3C(O)OC_2H_5$, the CF_3 group has a strong inductive effect on the carbonyl group of the carboxylic ester. This fluorinated ester, however, does not react with the Grignard reagent in diethyl ether at -75°C. To further substantiate the greater reactivity of the $CH_3C(O)OC_2H_5$ over $CF_3C(O)OC_2H_5$, a competition reaction between one equivalent of the Grignard I with one equivalent each of $CH_3C(O)OC_2H_5$ and $CF_3C(O)OC_2H_5$ was performed. The only product that was formed was $C_2H_5OC(O)(CF_2)_4OCF_2CF_2C(O)$-$CH_3$. From the study of a molecular model of the compound, it is concluded that steric effects due to the CF_3 group must be an important consideration.

The physical properties of the various products prepared from the interaction between Grignard I and carboxylic esters (at -75°C, 24 hours) are listed in Table 3.

As has previously been reported [10,11], highly fluorinated carbonyl compounds tend to hold water and form the stable hydrate derivatives quite readily. We have found that compounds V and VII (see Table 3) formed the monohydrate very readily. The hydrates of VI and VIII could easily be dehydrated by reaction with phosphorous pentoxide at temperatures of 150°C.

TABLE 2

Reaction of $C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4OCF_2CF_2MgBr$ **with carboxylic esters,** $R\overset{O}{\overset{\|}{C}}OC_2H_5$[a]

R (in $R\overset{O}{\overset{\|}{C}}OC_2H_5$)	Time (h)	GC Area %		
		Unreacted $C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2H$	Intermolecular Reaction $C_2H_5O[\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2]_2H$	Product $C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}R$
$C_2H_5O\overset{O}{\overset{\|}{C}}$	0.5	15	trace	81
"	2	12	1	84
"	22	8	1	91
H	0.5	42	trace	55
"	2	26	1	70
"	20	10	1	86
"	48	10	1	86
C_2H_5O	0.5	75	trace	23
"	2	46	1	50
"	24	13	2	80
"	48	13	2	80
CH_3	0.5	84	trace	13
"	2	64	1	32
"	20	14	2	80
"	48	14	2	80
C_6H_5	0.5	96	trace	2
"	2	85	2	11
"	20	47	4	44
"	48	45[b]	5[b]	46[b]
CF_3	0.5	97	trace	trace
"	2	92	3	trace
"	22	87	7	1
"	48	84	9	1

[a] Reactions at -75°C in diethyl ether; an aliquot sample removed at time period, hydrolyzed with 2N HCl and analyzed by GC

[b] Products characterized by GC/MS only

TABLE 3

Characterization of new compounds

Compound	% Yield[a] A	% Yield[a] B	b.p. (°C)	IR[b] (cm^{-1})	M.S.	Combustion Data (Calc'd/Found) C	Combustion Data (Calc'd/Found) H
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2H$ (III)	95	80	156	1775(C=O)	390(M^+)	$\frac{27.70}{27.70}$	$\frac{1.55}{1.56}$
$CH_3O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2H$ (IVa)	26	-	150	1775(C=O)	376(M^+)	-	-
$CH_3O\overset{O}{\overset{\|}{C}}[(CF_2)_4O(CF_2)_2]_2H$ (IVb)	45	-	230	1775(C=O)	720(M^+)	$\frac{25.01}{24.67}$	$\frac{0.56}{0.61}$
$CH_3O\overset{O}{\overset{\|}{C}}[(CF_2)_4O(CF_2)_2]_3H$ (IVc)	14	-	131/0.12 mm	1775(C=O)	c	-	-
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OC_2H_5$ (V)	91	76	255	1775(C=O)[d] 1745(C=O)	490(M^+)	$\frac{31.85}{31.85}$	$\frac{2.06}{2.18}$
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OC_2H_5 \cdot H_2O$ (VI)	-	94	-	1775(C=O)[d] 1745(C=O) 3460(OH)	490$(M-H_2O)^+$	$\frac{30.72}{30.29}$	$\frac{2.38}{2.39}$
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}H$ (VII)	86	78	193	1775(C=O)	418(M^+)	$\frac{28.72}{28.64}$	$\frac{1.45}{1.51}$
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}H \cdot H_2O$ (VIII)	-	92	-	1775(C=O) 3470(OH)	418$(M-H_2O)^+$	$\frac{27.54}{27.43}$	$\frac{1.85}{1.89}$
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}OC_2H_5$ (IX)	80	68	220	1775(C=O)	462(M^+)	$\frac{31.18}{31.07}$	$\frac{2.18}{2.17}$
$C_2H_5O\overset{O}{\overset{\|}{C}}(CF_2)_4O(CF_2)_2\overset{O}{\overset{\|}{C}}CH_3$ (X)	80	72	209	1775(C=O) 1755(C=O)[e]	432(M^+)	$\frac{30.57}{30.31}$	$\frac{1.86}{1.78}$

[a] A = GC area %, B = isolated yield; [b] Neat liquid; [c] The M^+ is beyond the limit of the MS instrument;

[d] Adjacent to CF_2; [e] Adjacent to CH_3

TABLE 4

^1H AND ^{19}F chemical shifts*

				Structure							
Compound	CH_3	CH_2	COO	CF_2	CF_2	CF_2	CF_2	O	CF_2	CF_2	X
III	1.0	4.1		-120.0	-124.2	-126.6	-84.2		-90.1	-139.5	H 5.6
V	1.0	4.1		-119.8	-123.9	-126.2	-84.3		-84.3	-122.0	$COCOOCH_2$ 4.1 CH_3 1.0
VI	1.2	4.2 or 4.3		-119.4	-123.6	-125.7	-83.6		-81.9	-125.3	$COCOOCH_2$ 4.2 or 4.3 CH_3 1.2 H_2O 4.8
VII	1.0	4.1		-119.8	-124.1	-126.4	-84.1		-85.9	-129.3	CHO 9.3
VIII	1.0	4.1		-119.5	-123.7	-126.0	-84.0		-84.7	-132.6	CHO 5.3 H_2O 5.0
IX	1.1	4.2		-119.7	-123.7	-126.3	-84.1		-86.5	-122.8	$COOCH_2$ 4.2 CH_3 1.1
X	1.0	4.1		-120.0	-124.1	-126.3	-84.4		-85.8	-124.6	$COCH_3$ 2.1
IVa	3.7	-		-119.9	-124.4	-126.7	-84.2		-90.1	-139.6	H 5.6
Dimer IVb	3.7	-		-119.8 -118.2	-124.2 -122.5	-126.3 -126.3	-84.1 -84.1		-85.0 -90.1	-121.5 -139.5	CO - H 5.6
Trimer IVc	3.7	-		-119.8 -118.4 -118.4	-124.2 -122.6 -122.6	-126.3 -126.3 -126.3	-84.4 -84.4 -84.4		-85.2 -85.2 -90.1	-121.5 -121.5 -139.5	CO - CO - H 5.6

*^1H and ^{19}F chemical shifts measured from external TMS and $CFCl_3$, respectively.

Studies on the synthesis, stability and reactions of the organolithium compound, $C_2H_5OC(O)(CF_2)_4OCF_2CF_2Li$, are in progress and will be presented at a later date.

EXPERIMENTAL

General Comments

All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Anhydrous diethyl ether was distilled from $LiAlH_4$ prior to use. Tetrahydrofuran was dried over sodium wire and was distilled from sodium benzophenoneketyl. Diethyl oxalate, ethyl formate, diethyl carbonate, ethyl acetate, ethyl benzoate, and ethyl trifluoroacetate were dried over $MgSO_4$ and were distilled from $MgSO_4$ prior to use. All boiling points are uncorrected. Gas chromatographic analyses (GC) were performed on a Perkin-Elmer Sigma 1 chromatograph using a six-foot stainless steel column (1/4" d.) packed with 10% SE-30 on Chromosorb W. Mass spectra were obtained on a duPont Model 21-490 mass spectrometer using a chemical ionization and electron impact mode. Infrared spectra were recorded on a Perkin-Elmer Model 600 computing infrared spectrophotometer The isolated yields were always lower due to isolation procedures by distillation. NMR spectra were recorded on a Varian A56/60 spectrometer. Spectra were obtained without using any solvent. Chemical shifts were measured from TMS and $CFCl_3$ by substitution of a tube containing the standards (Table 4).

Preparation of I in Diethyl Ether

Anhydrous diethyl ether (500 ml) and $C_2H_5OC(O)(CF_2)_4O(CF_2)_2I$ [12] (20.0 g, 38.8 mmol) were placed into a 1000 ml four-necked flask, equipped with a stirrer, low-temperature thermometer, a dropping funnel, and a nitrogen gas inlet and maintained under a nitrogen atmosphere. The contents were cooled to -75°C and ethylmagnesium bromide (13.6 ml of 2.85 M in diethyl ether solution, 38.8 mmol) was added over a 10-minute period while maintaining the internal reaction temperature between -75°C to -72°C. The solution was stirred at -75°C for an additional 20 minutes, an aliquot sample removed, hydrolyzed with 2N HCl and analysis by GC indicated a 95% yield of $C_2H_5OC(O)(CF_2)_4\text{-}O(CF_2)_2H$ (III). The reaction solution was hydrolyzed with 2N HCl (300 ml), phase separated, dried over $MgSO_4$, and the solvent removed by a rotary evaporator. Distillation of the concentrated mixture yielded the product III (12.1 g, 80%). See Table 3.

Stability of $C_2H_5OC(O)(CF_2)_4O(CF_2)_2MgBr$(I) (at -75°C-100°C)

The Grignard reagent I, prepared as described above, was synthesized at two temperatures, -110° and -75°C. After 30 minutes the reaction mixture at -110°C was hydrolyzed with precooled solution of conc. HCl and analyzed by GC. From the Grignard I, aliquot samples were removed periodically, hydrolyzed with 2N HCl, and analyzed by GC (see Table 1). The stability of I is inferred by the amount of III detected.

The synthesis of the Grignard I was performed in an identical manner to the one in diethyl ether at -75°C except that THF was used as the solvent. GC results are reported in Table 1.

Stability of $CH_3OC(O)(CF_2)_4O(CF_2)_2MgBr$ (at -45°C)

The Grignard reagent, $CH_3OC(O)(CF_2)_4OCF_2CF_2MgBr$, was synthesized as described above for the Grignard I. After 20 minutes, the reaction temperature was allowed to warm to -45°C. After

4.5 hours, the reaction mixture at -45°C was hydrolyzed with conc. HCl (10 ml). The reaction mixture was then poured into 2N HCl (300 ml), phase separated, and dried ($MgSO_4$). A GC/MS analysis indicated three major products - IVa, IVb, and IVc. Distillation of the mixture yielded the three oligomeric compounds. Analytical samples were isolated by gas chromatographic separations since the distilled fractions were not pure.

Reaction of I with Ethyl Acetate

To a diethyl ether solution of I (38.8 mmol) at -75°C was added freshly distilled ethyl acetate (6.83 g, 77.6 mmol) over two minutes. The reaction solution was stirred at -75°C, and aliquot samples removed at 0.5, 2, 20, and 48 hour periods, hydrolyzed with 2N HCl, and analyzed by GC (see Table 2). The whole reaction solution was hydrolyzed with conc. HCl (20 ml) at -75°C, poured into 2N HCl (200 ml), phase separated, and dried over $MgSO_4$. Distillation of the concentrated mixture yielded the product X (12.0 g, 72%). See Table 3.

Synthesis of Compounds V, VII, and IX

These compounds were synthesized by the same general procedure as outlined above for compound X.

Synthesis of Monohydrates VI and VIII

To a diethyl ether (5 ml) solution of V (1.07 g, 2.18 mmol) was added water (0.5 ml). The reaction was stirred for one day at room temperature, phase separated, and dried ($MgSO_4$). The solvent was removed by a rotary evaporator leaving a viscous liquid product (94% yield).

The hydrate VIII was produced from VII by the same procedure.

Dehydration of VI and VIII

Compounds VI and VIII were prepared from V and VII respectively by heating the hydrates over phosphorous pentoxide for 30 minutes at 150°C. Distillation from the dehydrating agent produced the anhydrous compounds (see Table 3).

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