

## Organometallic Reactions of $\omega$ -Fluoroalkyl Halides. I.<sup>1</sup> Preparation of $\omega$ -Fluoroalkylmagnesium Halides

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Received March 13, 1956

Optimum conditions have been determined for the preparation of various  $\omega$ -fluoroalkylmagnesium halides. The effects of halogen and chain-length on the course of the reactions were investigated. A series of  $\omega$ -fluorocarboxylic acids were prepared by carbonation of the Grignard reagents.

The preparation and properties, with particular reference to toxicity, of several homologous series of  $\omega$ -fluorinated aliphatic compounds have recently been described.<sup>2,3,4</sup> During the course of this work, several chemical techniques have been examined<sup>5</sup> for their applicability to the synthesis of mono-fluorinated compounds. It has long been accepted that organic fluorides are unreactive towards metallic magnesium;<sup>5-8</sup> hence, with the ready availability of  $\omega$ -fluoroalkyl halides,<sup>9</sup> the way became clear for a study of organometallic reagents as intermediates for the preparation of  $\omega$ -fluoroalkylated derivatives. The nature of this investigation and some preliminary observations have been briefly outlined.<sup>3,10</sup>

The first attempt to prepare a fluorine-containing Grignard reagent was reported by Henne.<sup>11</sup> When 1,1-difluoro-2-iodoethane,  $F_2CHCH_2I$ , was dissolved in ether and allowed to drip onto clean magnesium, a reaction took place immediately. During the addition, a gas was evolved which was identified as vinyl fluoride. Unexpectedly, the corresponding bromo compound,  $F_2CHCH_2Br$ , did not react at all. Somewhat later, Saunders, Stacey, and Wilding<sup>12</sup> in describing the reaction between 2-fluoroethyl chloride and magnesium, observed that normal Grignard formation did not occur. The most extensive examination of the reaction between  $\omega$ -fluoroalkyl halides and magnesium has been reported by Hoffmann.<sup>13</sup> It was found that, although

$\omega$ -fluoroalkyl bromides reacted rapidly with magnesium in ether, apparently no  $\omega$ -fluoroalkylmagnesium bromides were formed. Analysis of the hydrolyzate from the reaction of 5-fluoroamyl bromide with magnesium in ether showed that over 60% of the previously organically-bound fluorine was present in the ionic state; the loss of fluorine was attributed to a process involving functional exchange with the first-formed  $\omega$ -fluoroalkylmagnesium bromide.

*Formation of  $\omega$ -fluoroalkylmagnesium halides.* In order to determine the best method for the preparation of  $\omega$ -fluoroalkylmagnesium halides, a representative  $\omega$ -fluoroalkyl halide was subjected to varied sets of experimental conditions.<sup>14</sup> 6-Fluorohexyl chloride was selected for the following reasons: chlorides are less prone to undergo exchange reactions than bromides or iodides; a six carbon chain is sufficiently long to avoid intramolecular electronic influences between the two halogen atoms; and both the rate of formation and solubility in ether of the resultant Grignard reagent are favorable, whereas both decrease with longer chain-lengths. The extent of Grignard formation was conveniently estimated by carbonation with Dry Ice;<sup>15</sup> this has frequently been used in the past for diagnostic purposes,<sup>14</sup> and the acidic nature of the products facilitated separation from the unreacted fluorohalide.

The following generalizations emerged from this preliminary work: (a) The purity of the fluorohalide is of great importance; even traces of impurities can cause complete inhibition of the reaction. (b) A concentration (volume of fluorohalide/total volume of solution) in pure anhydrous ether of about 10% is effective; higher concentrations gave lower yields, and lower concentrations resulted in slow and incomplete reactions. (c) Commercial Grignard magnesium is satisfactory if prepared for reaction by the series of washings recommended by Huber.<sup>16</sup> A large excess (40-50%) was used, to force the reaction to completion. (d) The use of a suitable cata-

(1) (a) Issued as DRB Report No. SW-26; (b) To avoid ambiguity, fluorine is not generally referred to as halogen in this communication.

(2) Pattison, *Nature*, **172**, 1139 (1953).

(3) Pattison, *Nature*, **174**, 737 (1954).

(4) Pattison, Howell, McNamara, Schneider, and Walker, *J. Org. Chem.*, **21**, 739 (1956), and subsequent papers in the series.

(5) Swarts, *Bull. soc. chim. Belg.*, **30**, 302 (1921).

(6) Bernstein, Roth, and Miller, *J. Am. Chem. Soc.*, **70**, 2310 (1948).

(7) Gilman and Heck, *J. Am. Chem. Soc.*, **53**, 377 (1931).

(8) Schiemann and Pillarsky, *Ber.*, **64**, 1340 (1931).

(9) Pattison and Howell, *J. Org. Chem.*, **21**, 748 (1956).

(10) Howell and Pattison, *Chemistry & Industry*, 949 (1955).

(11) Henne, *J. Am. Chem. Soc.*, **60**, 2275 (1938).

(12) Saunders, Stacey, and Wilding, *J. Chem. Soc.*, 773 (1949).

(13) Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).

(14) For a detailed review of this and related topics, see Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954.

(15) Hussey, *J. Am. Chem. Soc.*, **73**, 1364 (1951).

(16) Huber, *Chemist Analyst*, **41**, 62 (1952).

TABLE I  
PREPARATION, PHYSICAL CONSTANTS AND ANALYSIS OF  $\omega$ -FLUOROCARBOXYLIC ACIDS

$\omega$ -Fluoro-alkyl halide	Products of Grignard Reactions				Constants and Analysis of Fluoroacids						
	$\omega$ -Fluorocarboxylic acid	Yield, %	Dibasic acid <sup>a</sup>	Yield, %	B.P. °C.	M.P., °C.	Analyses				
							C	H	Calc'd	Found	
F(CH <sub>2</sub> ) <sub>6</sub> Cl	F(CH <sub>2</sub> ) <sub>6</sub> COOH <sup>b</sup>	64	HOOC(CH <sub>2</sub> ) <sub>6</sub> COOH	18	132-134	10	1.4207	56.76	56.93	8.78	8.97
F(CH <sub>2</sub> ) <sub>7</sub> Cl	F(CH <sub>2</sub> ) <sub>7</sub> COOH	65	HOOC(CH <sub>2</sub> ) <sub>7</sub> COOH	14	132-133	4	35-35.5	59.27	59.66	9.24	9.32
F(CH <sub>2</sub> ) <sub>8</sub> Cl	F(CH <sub>2</sub> ) <sub>8</sub> COOH <sup>c</sup>	66	HOOC(CH <sub>2</sub> ) <sub>8</sub> COOH	12	89-90	0.2	1.4289	61.34	61.46	9.72	9.69
F(CH <sub>2</sub> ) <sub>9</sub> Cl	F(CH <sub>2</sub> ) <sub>9</sub> COOH	73	HOOC(CH <sub>2</sub> ) <sub>9</sub> COOH	12	90-95	0.1	49-49.5	63.16	63.09	10.00	10.04
F(CH <sub>2</sub> ) <sub>10</sub> Cl	F(CH <sub>2</sub> ) <sub>10</sub> COOH	63	HOOC(CH <sub>2</sub> ) <sub>10</sub> COOH	12	113-115	0.25	36-36.5	64.67	64.89	10.36	10.70

<sup>a</sup> Identified by mixture melting point determinations with authentic samples. <sup>b</sup> M.p. ca. 10° and  $d_4^{20}$  1.039. <sup>c</sup> M.p. ca. 18°.

lyst to initiate the reaction is essential. Both Gilman's preactivated catalyst<sup>17</sup> and iodine alone were found to be unsatisfactory, and ethyl bromide gave variable results. Activation by *n*-butyl chloride resulted in smooth continuous reactions and high yields, so this was used for all subsequent work with fluorochlorides. Ethyl bromide was still used with the fluorobromides and fluoroiodides. (e) The reaction proceeds at room temperature; heating the mixture lowers the yield.

*Effect of chain-length.* The  $\omega$ -fluoroalkyl chlorides containing from six to ten carbon atoms reacted normally, forming the corresponding  $\omega$ -fluorocarboxylic acids in 63-73% yield, together with small amounts of the dibasic acids (12-18% yield). Results are summarized in Table I.

Under the same experimental conditions, the lower members, containing from two to five carbon atoms, produced none of the expected  $\omega$ -fluorocarboxylic acids. 5-Fluoroamyl chloride and bromide (6-10% concentration) both appeared to react normally, but the only pure compounds isolated after carbonation were the unreacted fluorohalides. 2-Fluoroethyl, 3-fluoropropyl, and 4-fluorobutyl chlorides (12.5% concentration) showed little or no tendency to react with magnesium, even with prolonged refluxing and intermittent addition of ethyl bromide or *n*-butyl chloride. In each instance, the magnesium was almost wholly unreacted and a large percentage of fluorochloride was recovered.

*Effect of halogen.* 6-Fluorohexyl bromide and iodide were subjected to conditions similar to those used for the preparation of 6-fluorohexylmagnesium

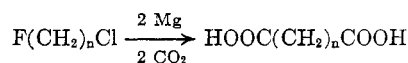
chloride. The products were then carbonated with Dry Ice as before. Results are shown in Table II.

From these results it is evident that: (1) 6-fluorohexyl chloride reacts normally with magnesium to form the desired fluorinated product; (2) 6-fluorohexyl bromide reacts with magnesium in a similar manner but with formation of approximately equivalent amounts of both  $\omega$ -fluoro and  $\omega$ -bromo products; (3) 6-fluorohexyl iodide reacts rapidly with magnesium with almost exclusive formation of the corresponding  $\omega$ -iodo product; (4) 6-fluorohexyl chloride and 6-fluorohexyl bromide form appreciable quantities of "di-Grignard" reagents.

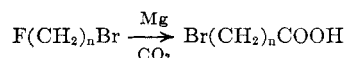
An experiment was carried out using 10-fluorodecyl bromide under the same conditions as those used for 6-fluorohexyl bromide. The following yields were obtained: 11-fluoroundecanoic acid, 42.2%; 11-bromoundecanoic acid, 22.5%; and dodecane-dioic acid, 12%. Thus the only significant difference with this longer chain-length was the higher yield of  $\omega$ -fluoro-acid.

*Discussion.* The preparation of  $\omega$ -fluoroalkylmagnesium halides produces some cleavage of the carbon-fluorine bond. The resultant losses of fluorine from the original molecule are of two types:

(1) In reactions involving  $\omega$ -fluoroalkyl chlorides and bromides, there were isolated small quantities of products formed by replacement of both fluorine and halogen:



(2) In reactions involving  $\omega$ -fluoroalkyl bromides and iodides, products were obtained which were formed by preferential replacement of fluorine:



These reactions are of considerable interest since they represent the first known examples of organic fluorides having undergone apparent Grignard formation to give moderate yields of the normal products. In view of the known lack of reactivity of alkyl fluorides, these results are unusual, especially so in those instances in which preferential loss of fluorine

TABLE II

REACTIONS OF 6-FLUOROHXYL HALIDES WITH MAGNESIUM

6-Fluorohexyl Halide, F(CH <sub>2</sub> ) <sub>6</sub> X	7-Fluoroheptanoic Acid, F(CH <sub>2</sub> ) <sub>6</sub> COOH Yield, %	7-Haloheptanoic Acid, X(CH <sub>2</sub> ) <sub>6</sub> COOH Yield, %	Suberic Acid Yield, %
F(CH <sub>2</sub> ) <sub>6</sub> Cl	64	0	18
F(CH <sub>2</sub> ) <sub>6</sub> Br	31.5	22.5	12
F(CH <sub>2</sub> ) <sub>6</sub> I	0	23.4	0

(17) Gilman and Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

took place. It is hoped that some theoretical aspects of this reaction will be described in a later paper in the series.

By analogy with the corresponding  $\omega, \omega'$ -dichloroalkanes, the failure of the short chain  $\omega$ -fluoroalkyl chlorides ( $C_2$ - $C_6$ ) to form Grignard reagents is not surprising. In general, *gem*- and *vic*-dihalides have little preparative value in Grignard syntheses.<sup>14</sup> The failure of 2-fluoroethyl chloride to react with magnesium under mild conditions conforms to Hoffmann's observation<sup>15</sup> that both the fluorine and chlorine atoms in this molecule exhibit a low and equivalent order of reactivity towards alkaline reagents. It should be mentioned however, that the lower  $\omega$ -fluoroalkyl bromides are apparently more tractable, since the two, three, and four carbon members have recently been reported<sup>18</sup> to undergo normal Grignard formation under mild conditions.

#### EXPERIMENTAL<sup>19</sup>

*Starting materials.* Ethyl ether, Merck Reagent anhydrous, dried and stored over lithium aluminum hydride, was distilled into the reaction vessels out of contact with the atmosphere. Ethyl bromide (b.p. 38°,  $n_D^{25}$  1.4219) and *n*-butyl chloride (b.p. 78°,  $n_D^{25}$  1.3998), after successive washings with conc'd sulfuric acid, water, aqueous sodium carbonate, and water, were dried over calcium chloride and fractionated twice through a 12-section Snyder column. Magnesium turnings (Baker and Adamson, Grignard Grade) were washed rapidly on a sintered glass Buchner funnel with the following reagents in the order named: 1% nitric acid (30 second contact time), water, ethyl alcohol, acetone, ethyl ether, and finally anhydrous ethyl ether containing 5 g. of paraffin wax per liter; after drying in a vacuum desiccator, the turnings were stored in a tightly stoppered bottle.<sup>16</sup> Nitrogen (Matheson Purified Grade) was used directly.  $\omega$ -Fluoroalkyl halides<sup>9</sup> were redistilled just before use. Dry Ice was obtained commercially; no improvement in yield was apparent by using pure Dry Ice prepared by freezing carbon dioxide (Matheson, Bone Dry, Reagent Grade).

*Equipment.* All reactions were conducted in a 500-ml. three-necked flask fitted with standard-taper ground glass joints. An outlet at the bottom was connected to a sintered glass filter disc and thence to a curved take-off tube which was brought up to a stopcock above the liquid level of the flask.<sup>20</sup> The reaction vessel was equipped with an efficient reflux condenser, a precision-bore stirrer, and a 250-ml. graduated dropping-funnel. The dropping-funnel was connected to a flexible joint, to allow direct distillation of ether solvent from a storage vessel. The apparatus was protected from the atmosphere and fitted for operation in an inert atmosphere in the usual manner.

In addition to the main reaction vessel, a subsidiary apparatus was used for subsequent reactions with the solution of Grignard reagent. This consisted of a three-necked flask (elongated to permit immersion in a Dewar flask) equipped with a reflux condenser, a mercury seal stirrer, and a dropping-funnel. All openings were protected by calcium chloride drying tubes.

*7-Fluoroheptanoic acid.* A stream of nitrogen was passed

(18) Kitano and Fukui, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, 58, 355 (1955).

(19) (a) The microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J.; (b) Melting points and boiling points are uncorrected, unless specified.

(20) Available commercially (M-21180) from H. S. Martin and Co., Evanston, Illinois.

through the reaction vessel, with a slight positive pressure being maintained throughout the subsequent operations. Magnesium (3.0 g., 0.124 g.-atom) was introduced and rinsed several times with ether, which had previously been distilled from the storage flask into the dropping-funnel. The washings were removed through the sintered glass disc at the bottom of the flask by increasing the nitrogen pressure, thereby removing the protective paraffin coating from the magnesium. Fresh ether (15 ml.) and *n*-butyl chloride (3 g.) were added to the clean magnesium turnings. When the reaction had subsided (*ca.* one hour), 15 ml. of a solution of 6-fluoroethyl chloride (10.0 g., 0.072 mole) in ether (90 ml., 10% concentration) was added to the still warm mixture. The mixture was not stirred until the reaction appeared to be well under way (usually 5-10 minutes after the addition of the fluorochloride). The remainder of the fluorochloride solution then was added dropwise over about two hours with constant stirring. The mixture was stirred for a further four hours after the addition was complete; by this time no more bubbles were being evolved from the surface of the magnesium. Side reactions peculiar to fluoroalkalides were minimized by slow addition and by carrying out all the operations at room temperature or lower.

The Grignard reagent then was transferred to the dropping-funnel of the subsidiary apparatus by filtration through the sintered glass filter disc under nitrogen pressure, and added over one hour to a well-stirred slush of excess powdered Dry Ice in anhydrous ether. The reaction vessel was cooled by means of a Dry Ice-acetone bath to prevent too rapid volatilization of carbon dioxide. When the addition was complete, the mixture was stirred for one hour longer and then left to stand overnight in the cold. After the excess Dry Ice had volatilized, excess 10% sulfuric acid was added to liberate the free fluoroacid, and the mixture was extracted with ether. After washing the extracts with water, the reaction product was separated into neutral and acidic fractions by extracting the ether solution with 10% sodium carbonate solution followed by water. The ether layer containing the neutral fraction was dried over sodium sulfate prior to distillation. The combined sodium carbonate extract and water washings were carefully acidified with concentrated hydrochloric acid and extracted with ether. After washing with water, the acidic ether extracts were dried over sodium sulfate.

The neutral fraction yielded 1.18 g. of unchanged 6-fluoroethyl chloride. The acid fraction gave a small forerun of *n*-valeric acid (formed from the *n*-butyl chloride used in the activation) followed by 6.03 g. of 7-fluoroheptanoic acid. The yield, based on reacted fluorochloride, was 64%. The residue from the distillation of the acidic fraction, after separation from insoluble impurities by dissolving in light petroleum ether, was recrystallized from water. Colorless, flaky crystals (2.0 g., 18%) were obtained, m.p. 139.5-140.5°, showing no depression when mixed with an authentic sample of suberic acid.

The reaction with 6-fluoroethyl bromide (13.0 g., 0.071 mole) was carried out similarly, using 133 ml. of ether (giving a 7% concentration of fluorobromide) and magnesium (3.0 g., 0.124 g.-atom). The magnesium was activated with ethyl bromide (2 g.), and the ethylmagnesium bromide was removed before the addition of the fluorobromide solution. Grignard formation was vigorous, and external cooling was necessary (cold water-bath). After isolation as described above, the acid fraction on distillation yielded 7-fluoroheptanoic acid (3.31 g., 31.5%) and then 7-bromoheptanoic acid (3.34 g., 22.5%), b.p. 165-166° (12 mm.), colorless crystals from pentane, m.p. 29-30° (*corr.*). (Heine, *et al.*<sup>21</sup> report b.p. 165-168° (11 mm.) and m.p. 29-30°). The residue consisted of suberic acid (1.5 g.).

*Anal.* Calc'd for  $C_7H_{13}BrO_2$ : C, 40.21; H, 6.27; Br, 38.22. Found: C, 40.36; H, 6.35; Br, 37.94.

(21) Heine, Becker, and Lane, *J. Am. Chem. Soc.*, 75, 4514 (1953).

The reaction with *6-fluorohexyl iodide* (16.5 g., 0.072 mole) was carried out similarly, using 133 ml. of ether (giving a 7% concentration of fluoroiodide) and magnesium (3.0 g., 0.124 g.-atom). After activation of the magnesium with ethyl bromide, the reaction vessel was immersed in an ice-bath throughout the four hours required for the addition of the fluoroiodide solution. As the reaction proceeded, a black, viscous oil settled out in the bottom of the flask; this was discarded before carbonation. After the usual isolation, concentration of the acid extract yielded 7-iodoheptanoic acid (4.3 g., 23.4%), which solidified to a pale pink mass. Several recrystallizations from pentane gave colorless plates, m.p. 45–45.5° (corr.). (Hunsdiecker and Hunsdiecker<sup>22</sup> report m.p. 48°). No 7-fluoroheptanoic or suberic acid was obtained.

(22) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

*Anal.* Calc'd for  $C_7H_{13}IO_2$ : C, 32.83; H, 5.12; I, 49.56. Found: C, 32.72; H, 4.98; I, 49.38.

*Acknowledgments.* The work described herein was carried out under Contract (DRB X-24) with the Defence Research Board of Canada, to whom grateful acknowledgment is made for financial assistance, and for permission to publish this work. The authors wish also to express their indebtedness to the National Research Council of Canada for the awards of a Studentship and a Fellowship to one of us (W.C.H.).

LONDON, ONTARIO, CANADA