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## The Grignard Reagents: Their Preparation

Flora Cooke

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THE GRIGNARD REAGENTS: THEIR PREPARATION

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BY Flora Cooke.

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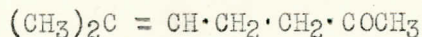
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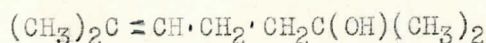
DEPARTMENT OF CHEMISTRY

## GRIGNARD REAGENTS; THEIR PREPARATION

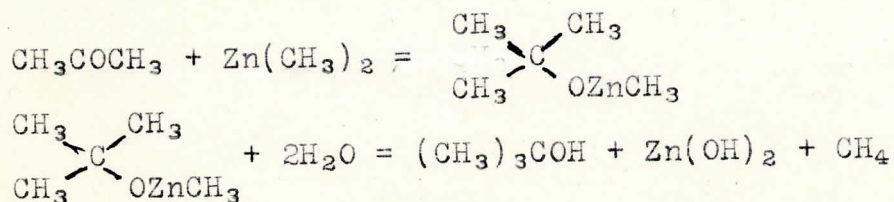
In 1899 it was found by Barbier that when methyl heptenone,



is brought into contact with methyl iodide,  $\text{CH}_3\text{I}$ , in the presence of magnesium and ether, a reaction occurs and dimethyl heptenol,



can be isolated after the product has been treated with acid. These observations suggested that magnesium methyl iodide,  $\text{CH}_3\text{MgI}$ , had been formed and had subsequently reacted with the methyl heptenone in the same manner as zinc methyl was known to react with ketones.\* <sup>1</sup>



As it was also known that zinc methyl unites with anhydrous ether to form a compound  $\text{Zn}(\text{CH}_3)_2(\text{C}_2\text{H}_5)_2\text{O}$ . Barbier's observations led Victor Grignard, Professor at the Chemical Institute of Lyons, France, in 1903, to investigate the action of magnesium on methyl iodide and similar compounds in the presence of ether. The magnesium alkyl halides which were thus discovered and analogous aryl compounds are known as the Grignard reagents.\*<sup>2</sup> They react easily with many types of substances and have been extensively used in organic syntheses. Since this reaction has been applied in so many directions, it will be impossible to do more than indicate the nature of the principle applications. Their main reactions will be summarized subsequently.

\*<sup>1</sup> Frankland and Duppa's Method, pp. 246, Cohen Organic Chemistry.

\*<sup>2</sup> In recognition of this discovery, Grignard was awarded one-half the Nobel Prize for the year 1912.

In many cases the actual preparation of the Grignard reagent is unnecessary and the desired synthesis may be brought about by the method employed by Barbier. It is also possible in many cases to use zinc instead of magnesium, a method which was employed by Reformatsky. But although the behavior of the magnesium alkyl compounds will be seen to resemble in many respects that of the zinc alkyls, their greater reactivity, owing, no doubt, to the more electropositive character of the metal as well as the convenience of their preparation, offer great advantages over the use of zinc compounds. Moreover, aromatic halogen compounds, such as bromo- and iodobenzene and toluene may be used in addition to the alkyl halides.

In all those reactions in which a Grignard reagent is employed, it is <sup>not</sup> necessary to isolate the crystalline compound. An ethereal solution of the reagent is used and as the combined ether appears to play no part in the chemical change, it is not represented in the equations for the reactions.

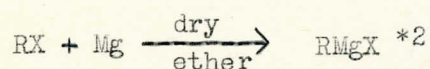
According to F. Stanley and F. Barry Kipping in their "Organic Chemistry",\*<sup>1</sup> the solution is prepared as follows: "Clean dry magnesium (1 gram atom) in the form of powder or filings is placed in a flask provided with a reflux condenser and is covered with 5 to 10 times its weight of pure, dry ether; a small quantity (1 to 2 c.c.) of the alkyl halogen compound (1 g. mol) is then added. If, after one to five minutes, a visible reaction sets in, it is then only necessary to continue the addition of the alkyl halide at such a rate that the reaction does not become too violent; but it is often advisable and sometimes essential to keep the solution at 0° to 10°C. during the operation. If a reaction does not set in spontaneously, the flask is gently warmed,

\*<sup>1</sup>  
p. 208



or a small quantity of a solution of magnesium ethyl bromide,  $C_2H_5MgBr$ , prepared in a test tube \*1 is poured into the flask; the reaction having been started, the addition of the requisite alkyl halogen compounds is then continued as before. In order to ensure success, all the reagents and the apparatus must be perfectly dry and the end of the condenser should be fitted with a calcium chloride tube."

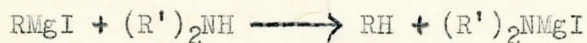
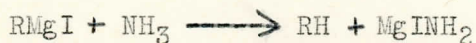
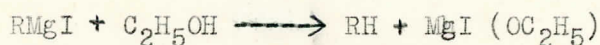
A general expression of the formation of a Grignard Reagent is as follows:



The principle type reactions of the Grignard Reagents are the following:

#### 1. Hydrocarbons

The magnesium alkyl or aryl halide is decomposed by water, by alcohols, by acids, by ammonia and by primary and secondary amines yielding hydrocarbons.



\*1

Magnesium reacts almost immediately with ethyl bromide. A trace of iodine may also be used to start the reaction which, with some halides, does not commence readily.

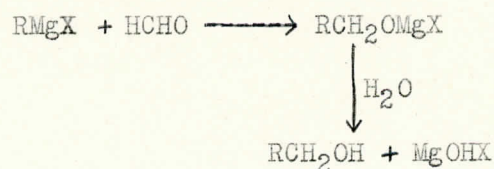
\*2

In this general equation, RX stands for any alkyl or aryl halide and  $RMgX$  for any Grignard reagent

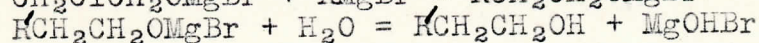
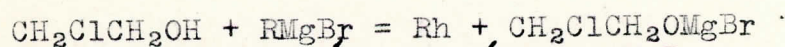
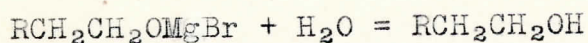
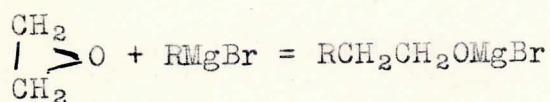
## 2. Alcohols

Alcohols may be obtained from aldehydes, ketones, acid chlorides, esters, etc.

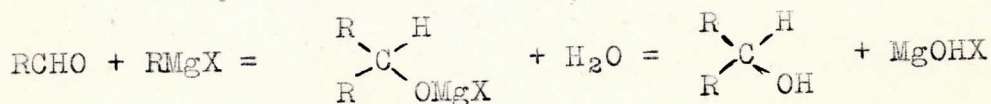
a. Synthesis of a primary alcohol from formaldehyde and the Grignard Reagent.



Its polymeric form, trioxymethylene, may be used more conveniently. They have also been prepared from ethylene oxide and ethylene chlorhydrin.

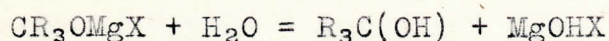
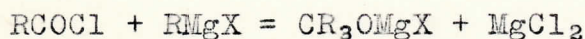
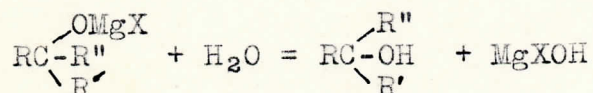
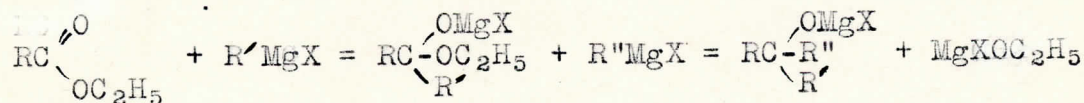
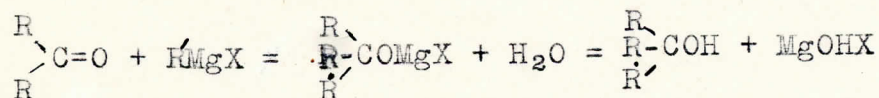


b. Synthesis of a secondary alcohol.



### c. Synthesis of a tertiary alcohol.

Tertiary alcohols are readily prepared from ketones, esters, and acid chlorides.



Anhydrides and lactones also give tertiary alcohols.

### 3. Aldehydes

A number of methods have been elaborated for producing aldehydes of which the following are the most important.

a. The action of HCN on a Grignard reagent and hydrolysis of the product yields an aldehyde

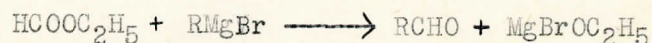


b. Bouveault's method.



c. Gattermann's method

Gattermann found that by using three molecules of ester and keeping the temperature low, an aldehyde could be formed from formic ester.

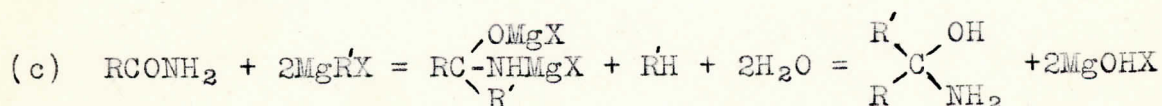
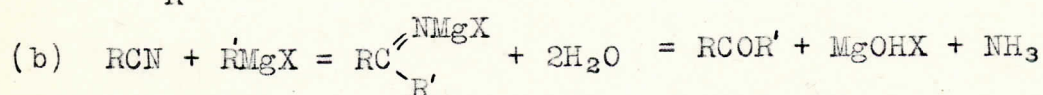
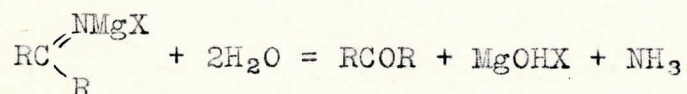
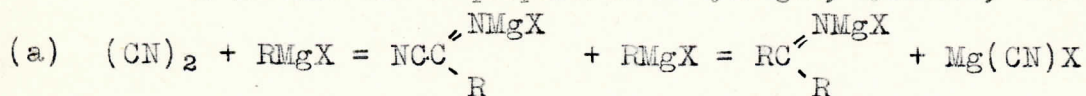




d. Another method which also yields aldehydes is that of Sachs and Doevy in which isocyanides are used.

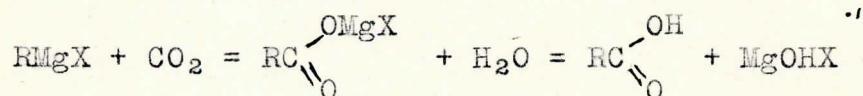


4. Ketones can be prepared from cyanogen, cyanides, and amides.



## 5. Acids and Esters

Acids are obtained by passing carbon dioxide into the ethereal solution of the magnesium alkyl compound and decomposing the product with water or sulphuric acid, or if the sodium salt is required, with sodium hydroxide solution.

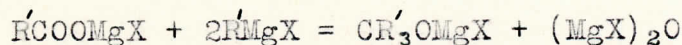


\*1

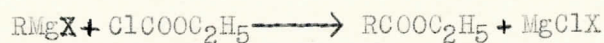
Sulphur dioxide reacts like carbon dioxide and forms sulphuric acids.



If the intermediate compound is further acted upon by two molecules of magnesium alkyl compound and the product decomposed with water, a tertiary alcohol is formed.

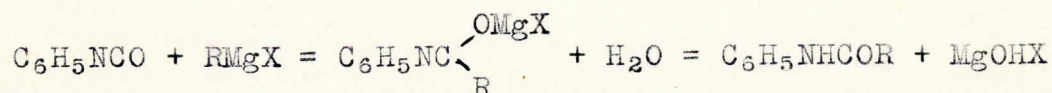


By using chloroformic ester with the Grignard reagent, esters are obtained.\* <sup>1</sup>



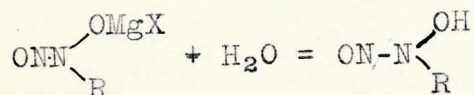
#### 6. Amides

Amides of the aromatic series may be obtained from aryl carbimides.



#### 7. Hydroxylamine derivatives.

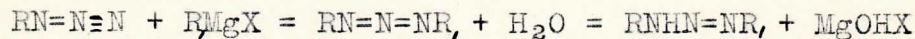
Both nitric oxide and nitrogen peroxide react with the Grignard reagent, the former giving nitroso hydroxylamines and the latter, dialkyl hydroxylamines.



The mechanism of the second reaction has not as yet been explained.

#### 8. Diazo amino compounds.

Aliphatic as well as aromatic diazo amino compounds can be prepared from alkyl and aryl azides.

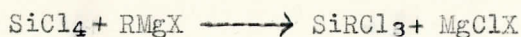


9. Grignard reagents react with the halides of many metals and of many non-metals yielding alkyl or alkyl halogen derivatives of the element.

\* <sup>1</sup>

Houben's method.

Compounds of this kind have been obtained from the halides of phosphorus, arsenic, antimony, silicon, tin, lead, mercury, thallium, gold, and other elements.



#### 10. Additive compounds.

Kohler has made a careful study of the action of the Grignard reagent on the unsaturated aldehydes and ketones containing the group  $\text{C}=\text{C}.\text{CR}=\text{O}$ . Several reactions are possible. Addition may occur at the double bond or with the ketone or aldehyde group or again following Thiele's rule,<sup>\*1</sup> in the 1,4 position. All these effects have been observed and are found to depend upon the nature of the attached radicals and may be summarized as follows:

a. In aldehydes and ketones in which R is hydrogen or an alkyl group, a normal reaction with the CO group takes place with the formation of a tertiary alcohol.

b. If the attached radical is aromatic, addition occurs in position 1,4, and a ketone is formed.

c. If the attached radical is an alkyl-oxy group, addition takes place either as in (b) or the alkyl-oxy group is replaced by the radical of the reagent. The former takes place with an aryl magnesium halide and the latter with an alkyl compound.

These reactions may be applied indifferently to the formation of aliphatic and aromatic compounds.

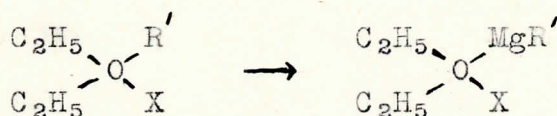
These equations and principles do not exhaust the many changes which may be wrought by the Grignard reagent, but they will serve to illustrate the general character of the processes.

Rather, these ten general type reactions of the Grignard reagent are a limited expression of the unlimited number of compounds which may be synthesized by their means.

<sup>\*1</sup> Thiele's theory of partial valencees.



It has been suggested by Tschelinzeff that the ether which appears to form a compound with the magnesium alkyl halide acts catalytically at low temperatures, for although interaction between the magnesium and alkyl halide takes place in benzene or xylene it is necessary to boil the liquid, whereas the presence of a little ethyl ether causes combination at the ordinary temperature. He considers the effect of the ether is to dissociate the alkyl halide by forming the oxonium compound thus assisting union with the metal.



This makes the presence of ether a very important factor. It has also been noted that this reaction, the formation of a Grignard reagent, is completely retarded if the ether used is not pure. Both alcohol and water which are always found in the commercial product must be removed. To the ordinary science student, this has offered much difficulty and I have endeavored to find the most efficient method within the limits of the supplies offered to laboratory students at Ursinus. A brief description of the method and result obtained in each trial will be given, along with my reaction to the efficiency shown. In each case a sample of 50 c.c. of ordinary ether was used, and the sample was considered pure when a reaction with an alkyl halide, magnesium and iodine was obtained.

#### METHOD I - METALLIC SODIUM

Metallic sodium was added to the ether in very thin pieces with special care taken that active surfaces of the metal were exposed to the liquid. It was impossible to get the ether dry within a reasonable length of time (10 days) by simply adding additional active sodium as the first became inactive. It was found that sodium alone would purify the ether if after a reasonable length of time the ether was distilled off of the old sodium and



fresh metal added. It was necessary to do this three times. In all cases where sodium was used, slight refluxing in warm water materially aided the process. The time required for drying 50 c.c. of ether by repeated distillation and addition of sodium was one week.

#### METHOD 2

Preliminary shaking with  $\text{CaCl}_2$  and addition of sodium according to the same method as described above. This process showed no material difference from method 1. The ether was dried but there was no material saving in time or labor.

#### METHOD 3

Prolonged standing with  $\text{CaCl}_2$  (24 hours) and then addition of metallic sodium. In this case there was a saving of both time and labor as compared with the use of sodium alone. The ether, when poured off of the  $\text{CaCl}_2$  onto metallic sodium showed just a slight reaction with the metal. It was necessary to distil the ether from the sodium two times but it was not necessary to add as much sodium nor was the time interval necessary to render the sodium inactive as long. It required approximately five days to purify the ether by this method.

#### METHOD 4

Shaking with saturated sodium chloride solution and addition of metallic sodium. The results obtained by this procedure were entirely unfavorable.

#### METHOD 5

Prolonged standing with saturated sodium chloride solution and addition of metallic sodium. This method also proved unsatisfactory.

#### METHOD 6

Preliminary shaking with  $\text{CaCl}_2$  and addition of phosphorus pentoxide. This method proved unsatisfactory. There was no evidence that the ether was dry within two weeks although the method of distilling the solution from the drying agent and adding fresh as in the sodium method was not tried because

of the fact that there was evidence that there was still unreacted, active phosphorus pentoxide in the container. Also, if the method did prove satisfactory, there would be no evidence of increased efficiency over the use of sodium and efficiency is the aim of these experiments.

#### METHOD 7

Prolonged standing with  $\text{CaCl}_2$  (24 hours) and addition of phosphorus pentoxide. This method proved the most efficient. Dry ether was obtained within 24 hours of the addition of the pentoxide. In fact, the ether was so dry that it was difficult to preserve the sample. Spontaneous evaporation occurring much more rapidly than with ordinary commercial ether. Only one distillation was necessary and a relatively small amount of  $\text{P}_2\text{O}_5$  as compared with the amount of sodium used in other trials was necessary.

#### METHOD 8

$\text{CaCl}_2$  alone. Commercial ether was allowed to stand with  $\text{CaCl}_2$  for approximately three weeks with no evidence of the ether being wholly dry. Its reactivity with metallic sodium or  $\text{P}_2\text{O}_5$  was greatly decreased, however, and a sample of 25 c.c. which was left at the end of the three weeks became totally dry with  $\text{P}_2\text{O}_5$  within 8 hours. This proves that  $\text{CaCl}_2$  takes very nearly all the water and alcohol out of the ether.

The following table summarizes the relative efficiency of the methods tried.

REAGENT	TOTAL TIME
1. $\text{CaCl}_2$ (24 hours), $\text{P}_2\text{O}_5$ -----	2 days
2. $\text{CaCl}_2$ (24 hours), Na -----	5 days
3. $\text{CaCl}_2$ (Preliminary shaking), Na -----	7 days
4. Na -----	7 days
5. $\text{CaCl}_2$ -----	Inefficient in wholly drying but very efficient in removing a large percentage of impurities.



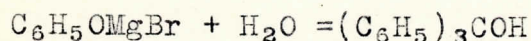
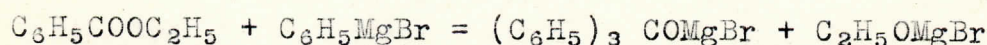
# REAGENT

6.  $\text{CaCl}_2$  (Preliminary shaking),  $\text{P}_2\text{O}_5$  ----- Inefficient
7.  $\text{NaCl}$  (24 hours),  $\text{Na}$  ----- Inefficient
8.  $\text{NaCl}$  (Preliminary shaking),  $\text{Na}$  ----- Inefficient

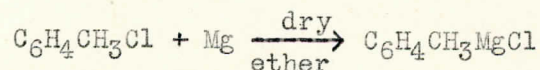
## CONCLUSION -

The most efficient method to purify ether for the Grignard reagent is to allow the solution to stand for a prolonged length of time with  $\text{CaCl}_2$  (24 hours, or longer if time permits), followed by addition of phosphorus pentoxide. Within a short time the ether will be dry as proved by the fact that an additional amount of phosphorus pentoxide added will not be discolored. One distillation will suffice. If  $\text{P}_2\text{O}_5$  is not available, sodium may be used but in the use of sodium it is necessary to keep active surface of the metal in contact with the solution and several distillations and subsequent additions of new metal may prove necessary.

After the acquirement of a sufficient amount of dry ether triphenyl carbinol was prepared according to the procedure as outlined in Adams and Johnson "Laboratory Experiments in Organic Chemistry", page 289-291. The following equations illustrate the reaction.



Several attempts were made to make a Grignard reagent with chlorotoluene and pure, dry ether. However, all attempts proved unsuccessful. This apparently was due to the impurity of the aryl halide rather than to the incomplete dryness of the ether which proved successful in test tube tests on other reagents.



Grignard reagents were also made with ethyl bromide and benzyl chloride.



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