THE GRIGNARD REACTION

A Senior Thesis

presented by

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for the degree of

Bachelor of Science

Washington and Lee University

Lexington, Virginia

May 10, 1948

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INTRODUCTION

The Grignard reagent, with its variety of useful reactions, has long been recognized as one of the fundamental tools of organic synthesis.[11] It should, for this reason, be of interest to inspect the topic as a compact and rather complete subject in itself, rather than to assume the usual textbook approach, which mentions it only from time to time as it is encountered in other phases of organic chemistry.

Although a detailed study of each individual reaction and reaction product derived from the Grignard reagent would not be practical in a paper of this length, an attempt will be made to classify these reactions in general groupings, illustrated with specific examples, in order to show the broad scope and importance of the topic. The means used to accomplish this will be to give the historical background leading up to the use of the Grignard reaction first, then the methods of preparing various Grignard reagents, and after this some of the properties, mechanisms, reactions, and uses of the reagent itself. An important part of the discussion of both preparations and uses is that which deals with the limitations and shortcomings of the reaction.

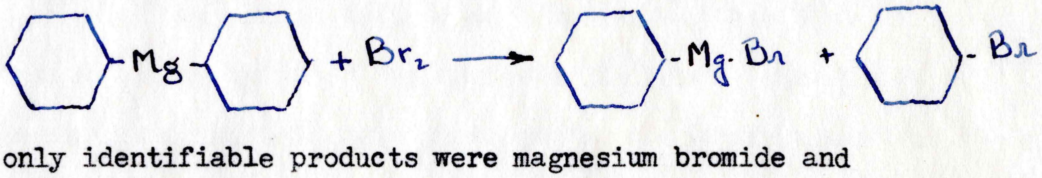
Finally, the purpose of the experimental work involved has been to determine ,to some extent, the part which the solvent plays in influencing reactions of the Grignard reagent.

THE GRIGNARD REACTION

A. Historical Background.

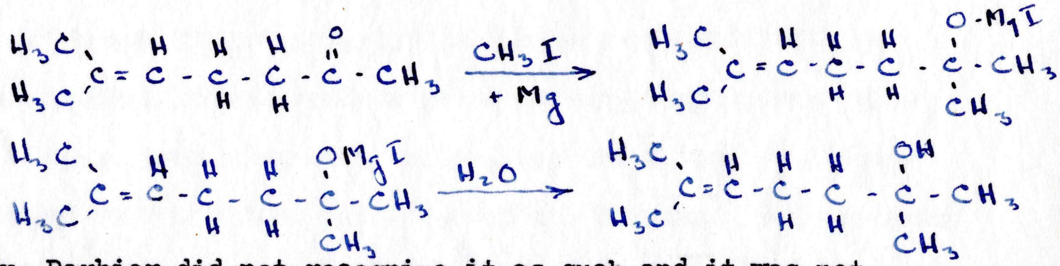
Although the Grignard reaction, as we know it today, was not properly formulated until 1900, it had its origin as far back as 1849, when Frankland produced diethyl zinc in an unsuccessful attempt to make the free ethyl radical from the reaction between zinc metal and ethyl iodide.[27] Ten years later, W. Hallwachs and A. Schafarik repeated the experiment using magnesium instead of zinc, and concluded that their product contained traces of a diethyl magnesium compound.[53] This was the first recorded instance of any experimental work with magnesium and an alkyl halide, which was later to form the basis for Grignard's work.

In 1861, Frankland called attention to the lack of knowledge concerning organomagnesium compounds, in a long article[28] on the organic compounds of other metals, but it was 1893 before the next step was taken. Then a Philadelphian named Hermann Fleck, working in the laboratory of Lothar Meyer, prepared and identified diphenylmagnesium, using bromobenzene and magnesium metal. Afterwards he treated this with excess bromine, expecting the following reaction:[26]



but the only identifiable products were magnesium bromide and bromobenzene, so he concluded that if an organomagnesium halide were formed, it was only as an intermediate product and could not be isolated. Some years later, Gilman and Brown demonstrated that the excess bromine had destroyed the phenylmagnesium halide as it was formed.[43]

It was 1899 before the next application of magnesium in an organic synthesis was made. This was by Barbier, who treated 6-methyl-5-hepten-2-one with methyl iodide and magnesium metal in an ethereal solvent, and isolated 2,6-dimethyl-5-hepten-2-ol as an end product of water hydrolysis. The reaction, as it would be formulated in the light of present-day evidence, was:[32]



However, Barbier did not recognize it as such and it was not until a year later that Grignard, a student of Barbier, showed it to be the two separate reactions, and it was Grignard who was the first to realize the possibilities of this new reaction, and who laid the foundation for its future expansion. Grignard was awarded the Nobel prize in 1912 for his work, which has resulted in one of the most general synthetic methods of organic chemistry.[5]

B. Preparation of the Reagent, and Limitations Involved Therein.

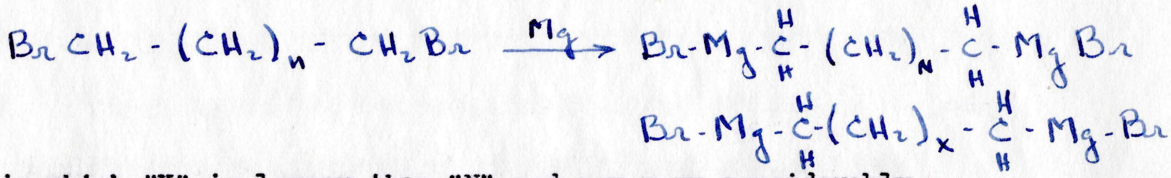
The Grignard reagent is defined as a moderately reactive[29] metalloorganic halide in which the magnesium is bound to both the organic radical and the halogen. Representing the organic radical by R- , the magnesium by -Mg- , and the halogen by -Hal, the structure is most simply conceived as R-Mg-Hal. At present the Grignard is the most versatile of the organic compounds of metals which include lithium, zinc, tin, lead, bismuth, antimony, and mercury.[57] The reagent is prepared most simply by the interaction of an alkyl iodide or bromide with magnesium turnings, in dry ether. Diethyl ether is most generally used for this purpose, although a recent trend is away from this highly inflammable material to less volatile ethers of higher molecular weights. Conditions essential to success are purity of reagents and absence of water, which inhibits the reaction.[33] If the ether to be used is not dry, special methods of purification must be applied. These include brine washing, drying over calcium chloride, refluxing with sodium, and distilling over phosphorous pentoxide. Since isolation of the Grignard is unnecessary before its use in synthesis, the general procedure is to form the Grignard in the ether solvent, and afterwards to add the other reactant or reactants directly to this ethereal solution. Indeed, the ether is generally thought to be an essential part of the compound, although Gilman reports[30] that the reagent may sometimes be prepared with no solvent, or with tertiary amines, benzene, or other inert solvents.

This description of the formation of a Grignard reagent applies to many different organic halides, both aryl and alkyl. However, there are some difficulties which depend on the structure of the halide.

First of all, none of the aromatic chlorides have been known to react with magnesium at the chlorine atom to form the reagent. Another limitation is that dihalogen-substituted paraffins, in which the halogens are adjacent to one another, yield olefins upon treatment with magnesium.[57] Also, unsaturated halides of the type R-CH::CHBr form substituted acetylenes by the elimination of hydrogen bromide.

The vinyl radical does not yield a Grignard reagent due to inactivity of the halogen atom caused by the bond structure of the molecule.[10] Also, unsaturated groups like the allyl radical often cause difficulty due to rearrangement.[58]

Tertiary compounds give only small quantities of Grignard reagent, which might be expected from their other reactions. Butylene, for example, is a product of the reaction of magnesium with tertiary butyl bromide. And dihalogen paraffins in which the halogens are widely separated undergo a reaction analogous to a Wurtz-Fittig, resulting in a mixture of magnesium compounds of varying chain length, such as the following:[58]



$$BrCH_2-(CH_2)_n-CH_2Br \xrightarrow{Mg} Br-Mg-\overset{H}{\underset{H}{C}}-(CH_2)_N-\overset{H}{\underset{H}{C}}-MgBr$$

$$Br-Mg-\overset{H}{\underset{H}{C}}-(CH_2)_X-\overset{H}{\underset{H}{C}}-Mg-Br$$

in which "X" is larger than "N" and may vary considerably.

There is, in every case, some loss if yield in preparing a Grignard by reaction between the reagent formed and the unused organic halide. For example:

Table I indicates the average yields[47] of Grignard compounds from some of the alkyl and aryl bromides, under strictly comparable conditions. These percentage yields, however, are independent of the rate at which the reagents are formed.

TABLE I.

Percentage Yields of Grignard Compounds from Some Bromides

Ethyl	93%	tert-Amyl	24%
n-Propyl	92%	n-Hexyl	92%
iso-Propyl	84%	n-Heptyl	89%
n-Butyl	94%	n-Octyl	88%
iso-Butyl	87%	Bromobenzene	95%
sec-Butyl	78%	o-Bromotoluene	93%
tert-Butyl	25%	m-Bromotoluene	88%
n-Amyl	89%	p-Bromotoluene	87%
iso-Amyl	88%	a-Bromonapthalene	95%
sec-Amyl	67%	b-Bromonapthalene	84%

C. Properties of the Reagent, Physical and Chemical.

The physical properties of the Grignard reagent are rather similar, regardless of their composition. All are colorless or grey solids,[31] which undergo disproportionation before any melting points may be determined, as follows:

$$2\,R\text{-}Mg\text{-}Hal \longrightarrow R\text{-}Mg\text{-}R + MgHal_2$$

Some of the lower-weight alkyl reagents may be distilled in ether solution, but since the corresponding R-Mg-R and $MgHal_2$ compounds may also be ether-distilled,[44] the vapor composition of the reagent is still uncertain.

The characteristic equilibria are known, however:[46]

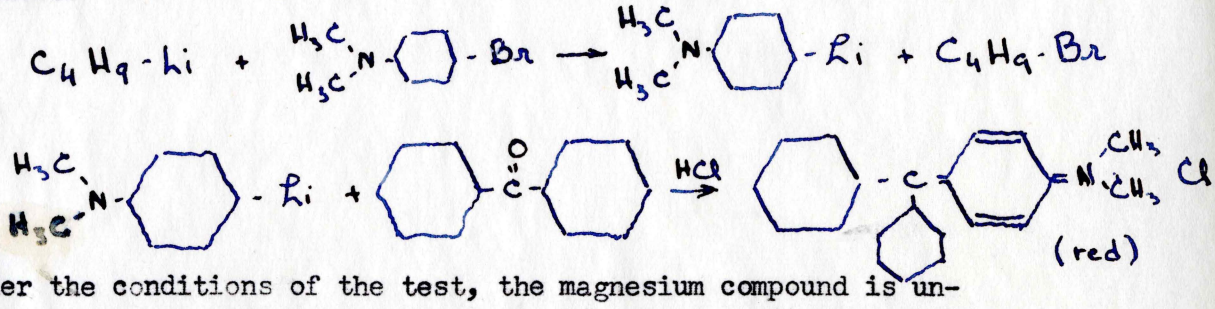
$$2\ R\text{-}Mg\text{-}Hal \rightleftharpoons R\text{-}Mg\text{-}R + MgHal_2$$

$$R\text{-}Mg\text{-}Hal \rightleftharpoons R^{-} + MgHal^{+}$$

so the reagent is really a mixture. But since the reactions of R-Mg-R and R-Mg-Hal differ appreciably only in their rates,[32] and the equilibria are reversible, there is no essential difference in product or yield.

From the second equilibrium above, it would be expected that the Grignard reagent would act as R- and -MgHal units in addition reactions, and this is almost invariably the case. The R- grouping adds to the less acidic element, and the -MgHal to the more acidic,[31] according to Gilman, who lists some elements according to their decreasing acidities as follows, $C < S < N < O$. This is not strictly true, however, since the carbon atom can be either acidic or basic, depending on its position in a radical.

In analysis, true alkyl Grignards may be distinguished from the organolithium compounds which resemble them by treatment with p-bromodimethylaniline in the presence of benzophenone,[50] as follows:



Under the conditions of the test, the magnesium compound is unaffected, while the lithium compound gives a bright red color. The less reactive aryl compounds of both metals give no test.

A more complete, although a more exacting, analysis may be obtained by the mixture of one milliliter of Grignard with one milliliter of a one per cent solution of Michler's ketone[49] in dry benzene, followed by hydrolysis with ice water, and addition of two drops of a two-tenths per cent solution of iodine in acetic acid. A characteristic blue-green color is noticed. The reaction is recognized as a dye reaction: thus, if phenylmagnesium bromide were the compound under investigation, Malachite Green would be the end product. The analysis depends upon the carbon-to-metal bond in the Grignard, and the formation of an intermediate carbinol which yields the dye on hydrolysis. It is useful in testing for completeness of reaction of Grignards. Acid chlorides and pyrrole interfere.[31]

Another test may be obtained by using triphenylbismuth dichloride, in the same concentrations, instead of Michler's ketone. This gives a deep-purple color with Grignards, especially the aryl compounds, which is similar to the phenol-ferric chloride test, and whose reaction mechanism is similarly unknown.[40]

The quantitative analysis for Grignards may be readily obtained by water hydrolysis of an aliquot portion of reagent solution, and titration with a standard acid,[60] according to the reaction:

$$\mathrm{R{-}Mg{-}Hal} + \mathrm{H_2O} \longrightarrow \mathrm{R{-}H} + \mathrm{Mg(OH)Hal}$$

$$\mathrm{Mg(OH)Hal} + \mathrm{H^+ . X^-} \longrightarrow \mathrm{H_2O} + \mathrm{MgX(Hal)}$$

In practice, of course, there may be some disproportionation of the type:

$$2\,\mathrm{MgHal(OH)} \rightarrow \mathrm{Mg(OH)_2} + \mathrm{Mg(Hal)_2}$$

However, this will not affect the results of the titration.

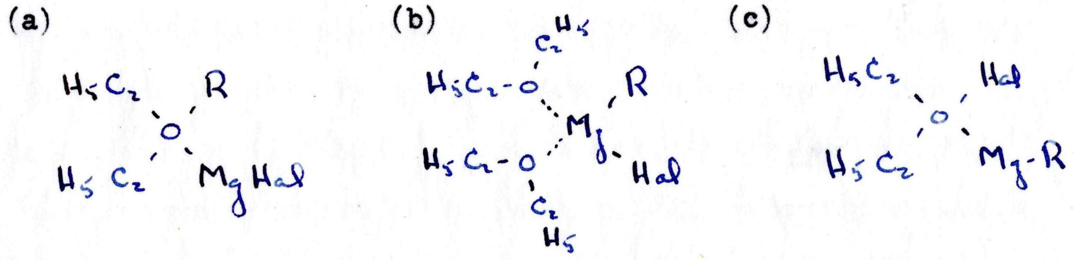
D. Structure and Mechanism of Grignard Reagents.

Since the structure and mechanism of the Grignard reagent are so interdependent, it will be well to consider them at the same time. The structure of the reagent has not, at the present time, been satisfactorily determined. Although it is certain that the main skeleton is of the form R-Mg-Hal, there is reason to believe that the ethereal solvent plays a part in the reactions,[3] and is therefore more or less bound up with the reagent. Evidence toward this is that evaporation of solvent from Grignards, under varied conditions, always leaves either one or two molecules of ether for each molecule of reagent.[57] Whether this ether influences the reactions themselves, or acts only upon the rate of reactivity can not be definitely said; however, several of the best-known formulations of Grignard structures are presented below.

Grignard himself proposed that the ether, in a one-to-one ratio with the halide, is attached so that the oxygen of the ether is the central binding atom of the entire complex, as in Figure 1 (a).

Meisenheimer, on the other hand, contended that the magnesium is the central atom holding the entire structure together, as shown in Figure 1 (b), while Baeyer and Villiger[1] jointly proposed a structure in which the oxygen of the ether is the central atom, as in Grignard's formulation, but asserted that the organic radical -R is attached directly to this oxygen, rather than through the magnesium, as Grignard had diagrammed. This Baeyer-Villiger molecule, shown in Figure 1 (c), is unreasonable in terms of electronic structure.

Figure 1.


(a) (b) (c)

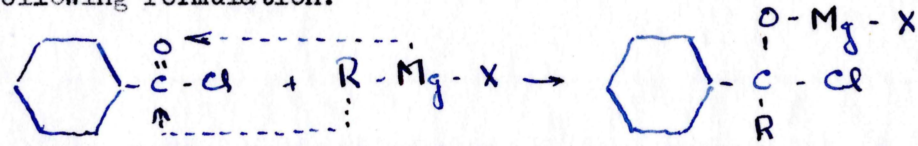
As the situation stands at present, the Meisenheimer concept serves best to explain the presence of solvent. Other structures have been proposed, but most of these resemble one of the above.[61]

Whatever the actual structure of the compound, it is generally accepted that coordination does occur in the metalloorganic compounds. The varying reactivities of these compounds, the reducing action of the less active ones, and the very slow reaction rates in ester and ketone additions, all are probably due to coordinate formation, in which the less reactive of the reagents are those in which the coordinate bonds are the stronger. This leads directly to the conclusion that the solvent in a Grignard reaction affects the reaction by a solvation process, and it is this branch of the subject which is under investigation in the experimental work of this thesis.

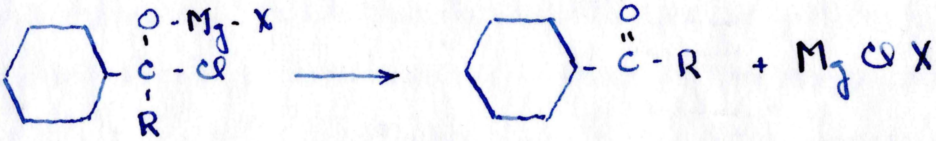
Gilman states[35] that there is evidence that the primary reaction complex, which is the initial prodcut formed in a Grignard addition, reacts by means of an intramolecular coordination, or chelation effect, but gives no examples.

For purposes of illustrating the proposed concepts of mechanism, several common examples will be taken. The first is the reaction of a Grignard with an acid halide, either alkyl or aryl.

If this were a direct replacement reaction, the fluoride would be the least reactive of the halides, and their reactivity would increase down the periodic table, in the general order of F, Cl, Br, and I. However, since the acid fluorides were found[4] to be the most reactive of the halides, all tested under similar conditions, the reaction must be an addition. This would permit the following formulation:



since the -R grouping has previously been shown to attach itself to the less acidic element of the double bond. Subsequent separation of MgXCl, of course, yields the ketone:



The relative reactivities of some functional groups with phenylmagnesium bromide, in the order of decreasing reactivity, are,[4] from left to right: $-CHO > -COCH_3 > -NCO > -COF > -COC_6H_5 > -COCl > -COBr > -COC_2H_5 > -CN$.

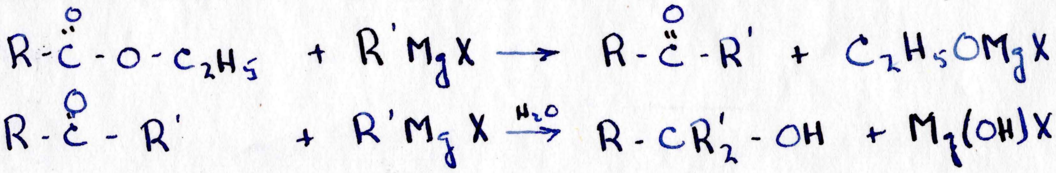
Since the acid halide reaction is an addition, the halogen will influence the speed and ease of reaction only to the extent that it modifies the additive power of the carbonyl group. This consideration is probably partly a spatial one, in which the size of the halogen atom hinders the access of the carbonyl center to the Grignard reagent.[12] Supporting evidence for this spatial theory is given by the figures in Table II.[12]

TABLE II

ATOMIC DIMENSIONS

Bond	Center-to-center Bond Distance	Halogen Atom Radius
C-C	1.54 A	----
C-F	1.41	0.64 A
C-Cl	1.76	0.99
C-Br	1.91	1.14
C-I	2.10	1.33

In the mechanism of addition of Grignard reagents to esters, it is possible that addition to the double bond is not always the initial step,[33] particularly in the more unreactive metallo-organic compounds. It has been established that ketones are a transitory product in this reaction, which follows the course:



$$R-\overset{O}{\ddot{C}}-O-C_2H_5 + R'MgX \rightarrow R-\overset{O}{\ddot{C}}-R' + C_2H_5OMgX$$
$$R-\overset{O}{\ddot{C}}-R' + R'MgX \xrightarrow{H_2O} R-CR'_2-OH + Mg(OH)X$$

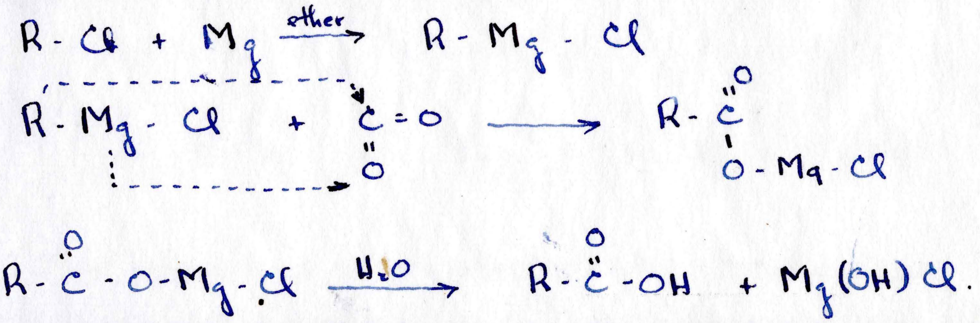
However, the complete mechanism is uncertain, although magnesium complex formation may be the correct solution. Gilman[34] proposes a preliminary addition to form oxonium compounds as a possible explanation. Regardless of the exact mechanical arrangement, though, the solvation theory is further supported by consideration[38] of the fact that in ether solution, Michler's ketone and phenylmagnesium bromide do react, but will re-form the ketone to a large extent upon water hydrolysis. In benzene solution, however, the carbinol formation is more pronounced, and a lowered solvation effect seems the best explanation.[38]

Thus while the mechanism of even the simplest Grignard reaction is not definitely known, there is some strong evidence available which indicates that the solvation effect is of consequence.

E. Reactions of the Grignard Reagent.

1. Synthesis of Acids.

The Grignard is widely used in the synthesis of the carboxylic acids. The preparation consists of the addition of carbon dioxide to the Grignard reagent, with subsequent hydrolysis of the resulting addition product, and separation of the acid from the water and magnesium salts. The overall synthesis is formulated as follows:[8]



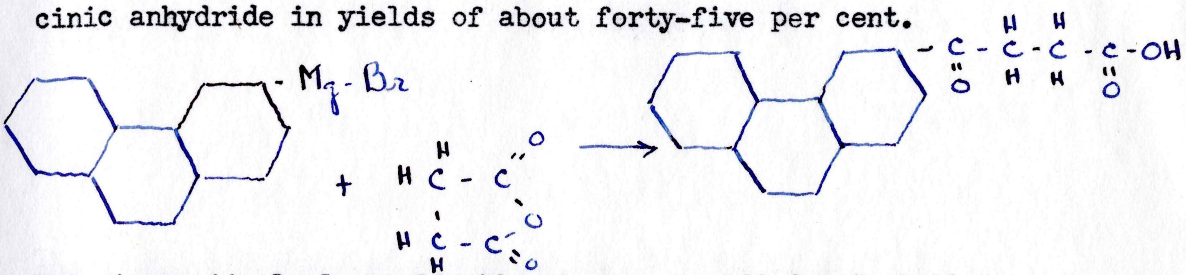
$$R\text{-}Cl + Mg \xrightarrow{\text{ether}} R\text{-}Mg\text{-}Cl$$

$$R\text{-}Mg\text{-}Cl + \underset{\overset{\|}{O}}{C}{=}O \longrightarrow R\text{-}\underset{|\atop O\text{-}Mg\text{-}Cl}{\overset{O}{\overset{\|}{C}}}$$

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}Mg\text{-}Cl \xrightarrow{H_2O} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + Mg(OH)Cl.$$

The most convenient method is to pour the ethereal Grignard solution over dry ice. This reduces the secondary reactions which produce ketones and tertiary alcohols.[35] If dry ice is not available or convenient, similar results may be obtained by adding gaseous carbon dioxide to a cooled reaction mixture.

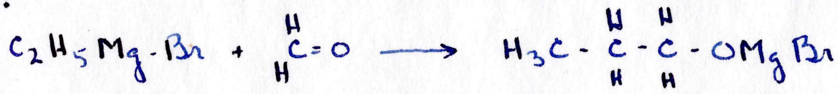
An interesting deviation from normal acid formation is the synthesis of keto-acids,[19] which also goes easily. For example, the unusual b-phenanthroylpropionic acid is readily formed by the interaction of 9-phenanthrylmagnesium bromide and succinic anhydride in yields of about forty-five per cent.



This is particularly applicable when a specified orientation can not be achieved by other means.

2. Synthesis of Alcohols and Hydroxyl Compounds.

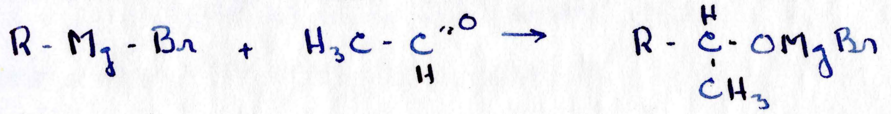
In general, in the Grignard synthesis of alcohols, it is found that formaldehyde plus a Grignard yields a primary alcohol, other aldehydes plus a Grignard yield secondary alcohols, and ketones and esters plus a Grignard yield tertiary alcohols.[42] The first reaction, that with formaldehyde, takes place accordingly:



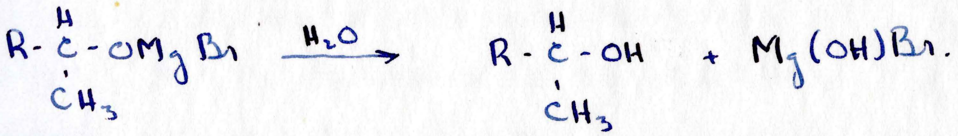
$$C_2H_5Mg\text{-}Br + \begin{matrix}H\\ \\ H\end{matrix}C{=}O \longrightarrow H_3C-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OMgBr$$

$$C_3H_7-O-Mg-Br \xrightarrow{H_2O} C_3H_7OH + Mg(OH)Br.$$

This is seldom used in the preparation of the alcohols of low molecular weight because they are so readily available elsewhere. The general reaction of aldehydes with Grignards is similar:

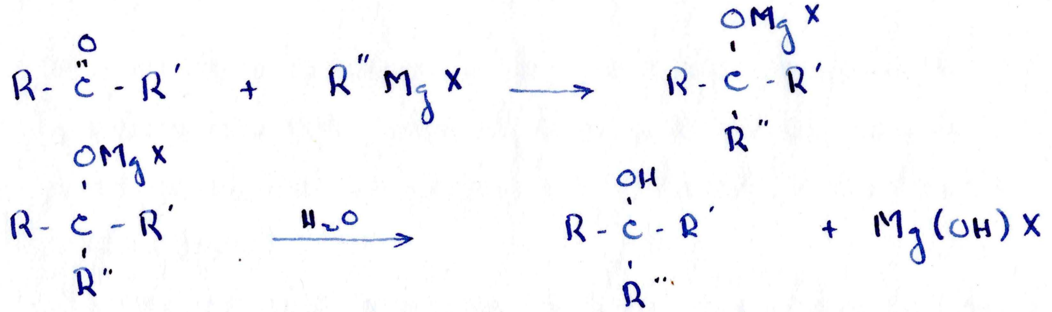


$$R-Mg-Br + H_3C-\underset{H}{C}{=}O \rightarrow R-\overset{H}{\underset{CH_3}{C}}-OMgBr$$



$$R-\overset{H}{\underset{CH_3}{C}}-OMgBr \xrightarrow{H_2O} R-\overset{H}{\underset{CH_3}{C}}-OH + Mg(OH)Br.$$

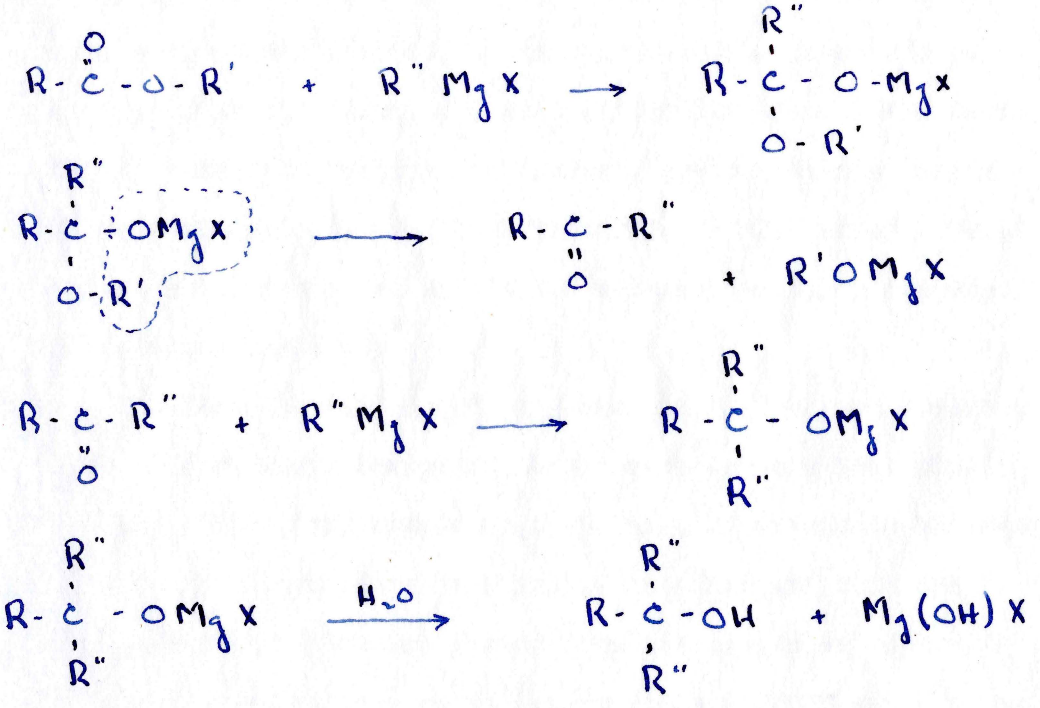
while ketones react as follows:



$$R-\overset{O}{\overset{\|}{C}}-R' + R''MgX \longrightarrow R-\underset{R''}{\overset{OMgX}{C}}-R'$$

$$R-\underset{R''}{\overset{OMgX}{C}}-R' \xrightarrow{H_2O} R-\underset{R''}{\overset{OH}{C}}-R' + Mg(OH)X$$

The stepwise reaction with esters is:[8]



$$R-\overset{O}{\overset{\|}{C}}-O-R' + R''MgX \longrightarrow R-\underset{O-R'}{\overset{R''}{C}}-O-MgX$$

$$R-\underset{O-R'}{\overset{R''}{C}}-OMgX \longrightarrow R-\underset{\underset{O}{\|}}{C}-R'' + R'OMgX$$

$$R-\underset{\underset{O}{\|}}{C}-R'' + R''MgX \longrightarrow R-\underset{R''}{\overset{R''}{C}}-OMgX$$

$$R-\underset{R''}{\overset{R''}{C}}-OMgX \xrightarrow{H_2O} R-\underset{R''}{\overset{R''}{C}}-OH + Mg(OH)X$$

It is noticed that the reaction of the Grignard with a ketone is a means of attaching three separate hydrocarbon groups in a carbinol formation, which makes possible the synthesis of many carbinols otherwise difficult to obtain.

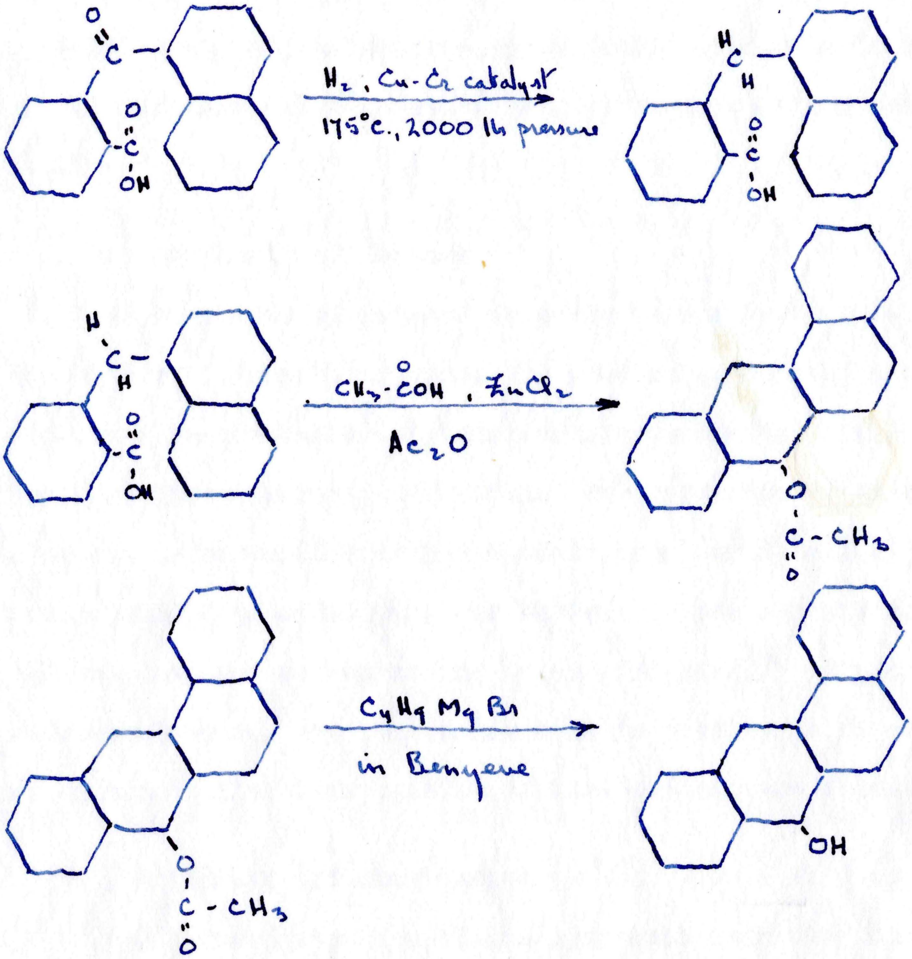
One obstacle which may occur is incomplete formation of the tertiary alcohol. It can be seen that the second step of the reaction with an ester is an intermediate ketone synthesis, and, depending on the ketone formed and the Grignard being used, the reaction may be halted at this point.

In addition to esters and ketones, the following groups of compounds will form tertiary alcohols with a Grignard reagent: acids, acid anhydrides, salts of acids, amides, and acid halides.[33]

The principal exceptions to alcohol formation come from steric considerations. Di-tertiary-butyl ketone is a good example, because the active Grignard is unable to reach the carbon-oxygen double bond, so that no reaction takes place. Outside of steric cases, the main difficulty lies in the fact that if there are carboxyl or hydroxyl groups at other parts of the reacting molecule, the Grignard will also attack them, and either be destroyed or give a secondary addition compound at the wrong position.[14]

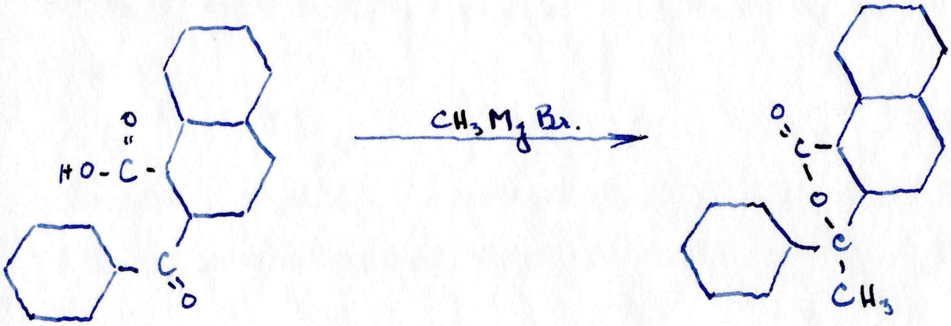
The direct oxidation of Grignards will give good yields of alcohols from alkyl compounds, but generally very poor yields of phenols from aryl compounds. Addition of oxygen is believed to be due to a secondary reaction of the Grignard with the ether peroxides which are formed from the oxygen and ether,[66] but as yet a completely satisfactory explanation remains to be given.

The synthesis of anthranol will be given here because it is a case in which benzene may be substituted for the ether solvent.[22] 2-a-napthylmethylbenzoic acid, which is made by hydrogenating 2-a-napthoylbenzoic acid, is converted to the ester 1,2-benzanthryl-10-acetate, and this is split by the Grignard in a typical ester cleavage as follows:



The product is 1,2-benz-10-anthrol.

The lactone synthesis is another example of the Grignard formation of hydroxyl compounds. An example is shown below, in the preparation of a lactone which would be difficult to obtain by other means.[23]



It is of interest to note that in addition to the insertion of a methyl group at the carbon-oxygen double bond, The Grignard in this instance also caused a ring closure, a rather unusual result.

3. Synthesis of Ketones.

The synthesis of ketones properly belongs as a sub-heading under alcohol formation, since the same reagents can be used for each, and the ketone is an intermediate product in alcohol formation. The preparation of ketones in preference to tertiary alcohols is accomplished by the addition of acyl halide, in small amount, to a Grignard, or better, to the less reactive cadmium compound corresponding to the Grignard.[12] By using this cadmium compound, and reasonable care to keep it in excess at all times, satisfactory yields of most ketones are obtainable.

4. Synthesis of Hydrocarbons.

The Grignard reaction allows hydrocarbons to be formed quite easily, and when made in this manner, they will be free of other hydrocarbons of similar boiling or melting-points,[29] which is advantageous, since it is not always easy to accomplish fractional distillation of hydrocarbon mixtures. The most easily diagrammed reaction of this type is the hydrogen cleavage of a Grignard, which requires one mole of hydrogen for each mole of Grignard:

$$2\,R\text{-}Mg\text{-}X + 2H_2 \longrightarrow 2\,R\text{-}H + MgH_2 + MgX_2$$

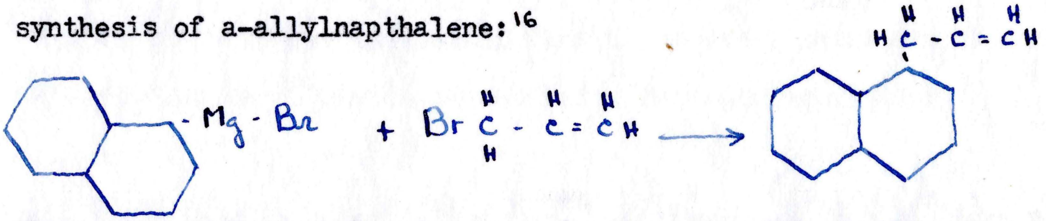
The ease of reaction is dependent upon the relative reactivity of the magnesium compound, which was discussed along with mechanism.

A simpler way than direct hydrogenation, however, is the reaction with active hydrogen compounds, of which water is the most common. This particular reaction occurs with such ease and speed that in all Grignard reactions precautions about dryness of reagents and apparatus is necessary.[5] The equation is:

$$R-Mg-X + H_2O \longrightarrow R-H + Mg(OH)X$$

with some disproportionation of MgOHX into $Mg(OH)_2$ and MgX_2.

The synthesis of mixed aryl-alkyl compounds is accomplished by use of the Grignard reaction. A typical example is the synthesis of a-allylnapthalene:[16]



although a wide variety of compounds are made with similar ease.

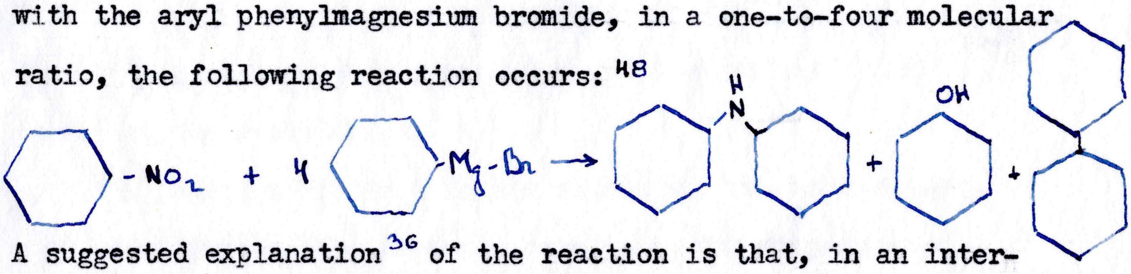
Other active hydrogen compounds than water, such as alcohols and acids give hydrocarbons with the Grignard:[5]

$$R-Mg-X + R'-OH \longrightarrow R-H + MgX(O-R')$$

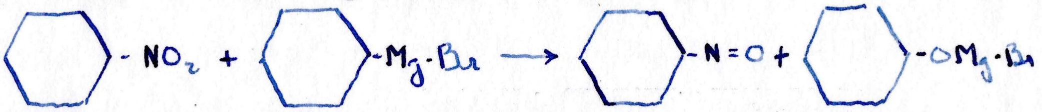
By varying the solvent ether according to the product desired, a considerable difference in boiling-points may be obtained between solvent and product, which facilitates separation. For example, if n-pentane is the hydrocarbon being synthesized, a higher-boiling ether than the diethyl, such as n-butyl or n-hexyl, would be used.

5. Reactions with Nitrogen Compounds.

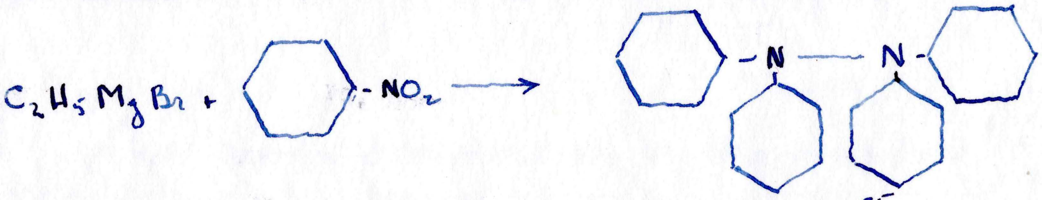
The most common of the nitrogen compounds which react with the Grignard reagent are the nitro compounds, typical of which is nitrobenzene. This gives several different products, depending largely upon the particular Grignard used. For instance, with the aryl phenylmagnesium bromide, in a one-to-four molecular ratio, the following reaction occurs:[48]



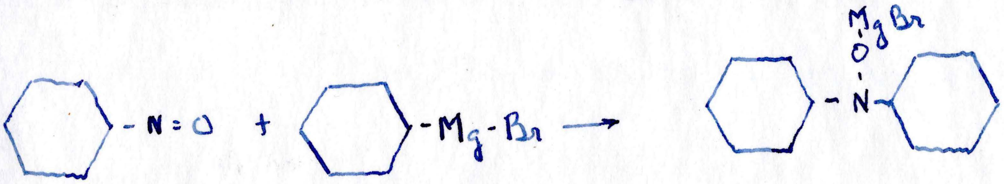
A suggested explanation[36] of the reaction is that, in an intermediate step, the following occurs to some extent:

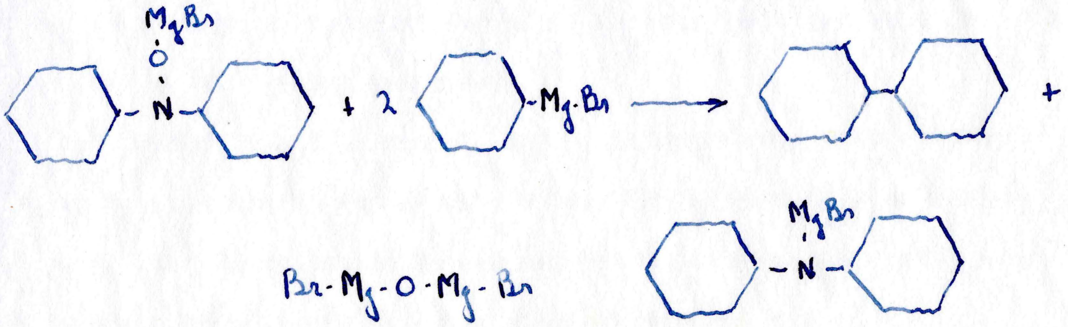


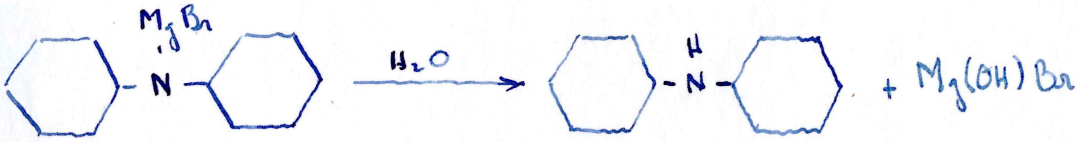
With the use of an alkyl Grignard, however, tetrasubstituted hydrazines[48] are found among the reaction products:



Nitrosobenzene has been found to undergo the reactions:[35]

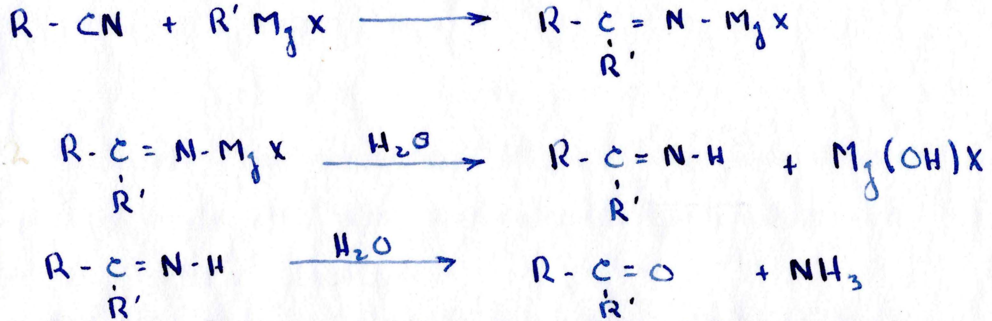






This is not the complete formulation, but shows the chief course of the reaction.

The reaction of the Grignard with cyanides, with subsequent hydrolysis of the product, results in the formation of ketones. The reaction yields a transitory ketimine derivative:[34]



$$R-CN + R'MgX \longrightarrow \underset{R'}{R-C}=N-MgX$$

$$\underset{R'}{R-C}=N-MgX \xrightarrow{H_2O} \underset{R'}{R-C}=N-H + Mg(OH)X$$

$$\underset{R'}{R-C}=N-H \xrightarrow{H_2O} \underset{R'}{R-C}=O + NH_3$$

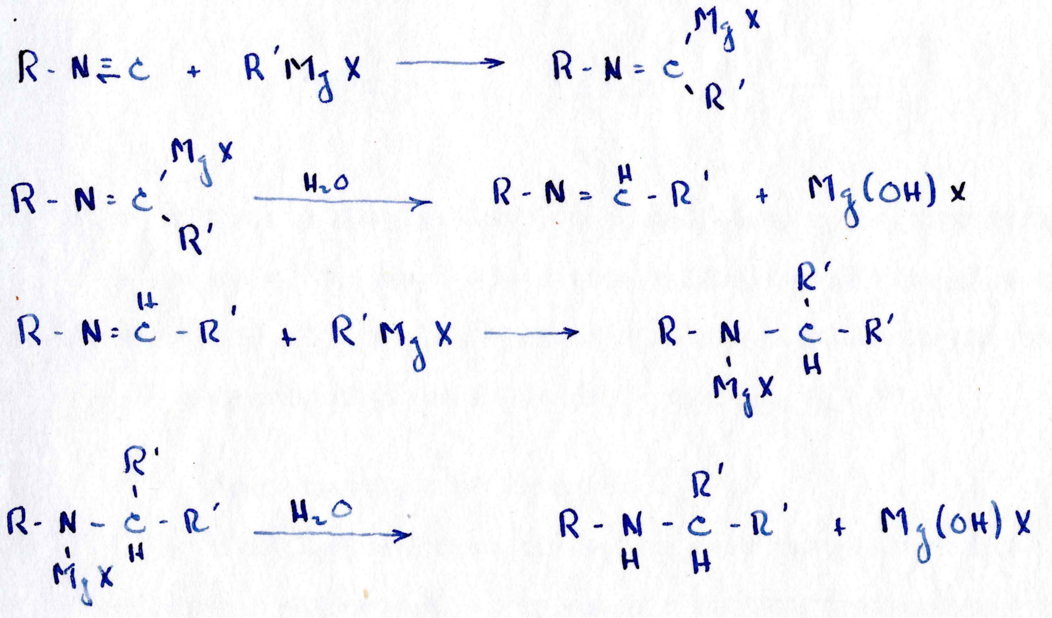
Cyanogen cleavage of Grignards, and the halogen-cyanogen cleavage, both occur readily:[33]

$$R\cdot Mg-X + (CN)_2 \longrightarrow R-CN + MgX(CN)$$

$$2R-Mg-X + 2X-CN \longrightarrow R-CN + R-X + MgX_2 + MgX(CN)$$

The proportion of cyanide to halide depends upon the relative reactivity of the halogen used.

Isocyanides, in general, add to Grignard reagents to form addition compounds, which are further hydrolyzed to azomethylene compounds. These azomethylene compounds in turn react with more Grignard reagent to yield secondary amines.



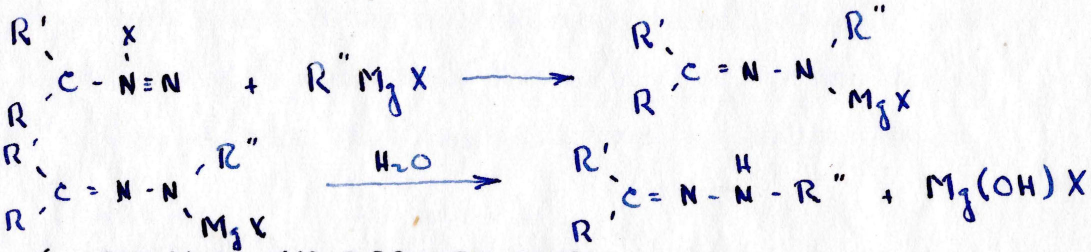
$$R-N\equiv C + R'MgX \longrightarrow R-N=C\begin{smallmatrix}MgX\\ R'\end{smallmatrix}$$

$$R-N=C\begin{smallmatrix}MgX\\ R'\end{smallmatrix} \xrightarrow{H_2O} R-N=\overset{H}{C}-R' + Mg(OH)X$$

$$R-N=\overset{H}{C}-R' + R'MgX \longrightarrow R-\underset{MgX}{N}-\overset{R'}{\underset{H}{C}}-R'$$

$$R-\underset{MgX}{N}-\overset{R'}{\underset{H}{C}}-R' \xrightarrow{H_2O} R-\underset{H}{N}-\overset{R'}{\underset{H}{C}}-R' + Mg(OH)X$$

Aliphatic diazo compounds[32] yield nitrogen-substituted compounds, while aryl diazo compounds show noticeably less tendency toward any reaction:



$$\begin{smallmatrix}R'\\ R\end{smallmatrix}C-\overset{X}{N}\equiv N + R''MgX \longrightarrow \begin{smallmatrix}R'\\ R\end{smallmatrix}C=N-N\begin{smallmatrix}R''\\ MgX\end{smallmatrix}$$

$$\begin{smallmatrix}R'\\ R'\end{smallmatrix}C=N-N\begin{smallmatrix}R''\\ MgX\end{smallmatrix} \xrightarrow{H_2O} \begin{smallmatrix}R'\\ R\end{smallmatrix}C=N-\overset{H}{N}-R'' + Mg(OH)X$$

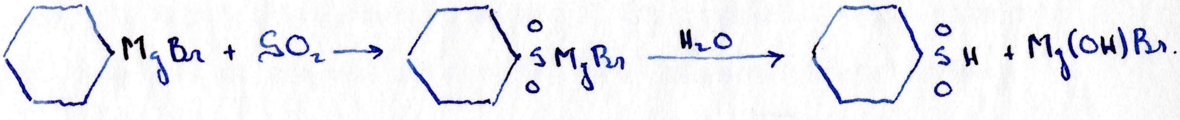
6. Reactions with Sulfur Compounds.

Addition of free sulfur to a Grignard reagent, and subsequent hydrolysis of the addition product gives a mercaptan, or thio-alcohol, in a reaction analogous to oxidation of Grignards to alcohols.[37]

$$R-Mg-X + S \longrightarrow R-S-Mg-X$$

$$R-S-MgX \xrightarrow{H_2O} R-SH + Mg(OH)X$$

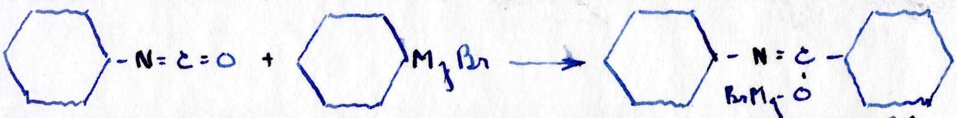
The reaction with sulfur dioxide[41] to form sulfinic acids is demonstrated with phenylmagnesium bromide:



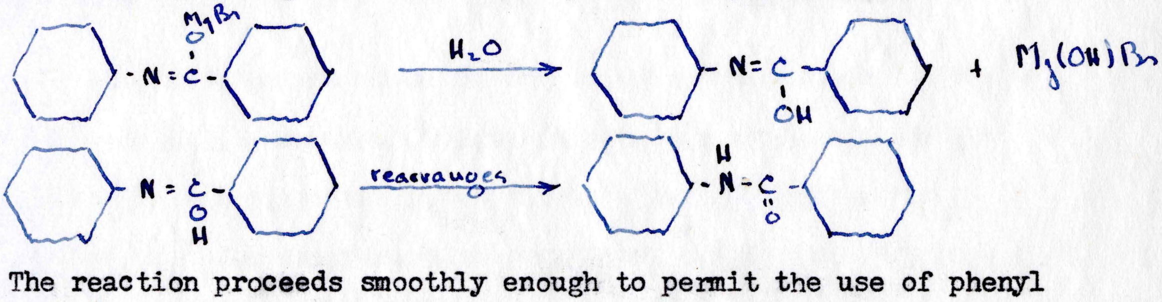
These sulfinic acids are useful intermediates in the preparation of thiophenols[41] by reduction of the sulfinic acid with zinc and sulfuric acid, followed by steam distillation, which in the case of the benzenesulfinic acid yields thiophenol, C_6H_5SH.

7. Other Reactions of Interest.

The remaining reactions of the Grignard reagent are discussed from the viewpoint of types of structure, rather than of functional groups. The first of these structures is the terminal cumulated unsaturated compounds, which include the ketenes, isocyanates, isothiocyanates, and thionylamines. In general, these compounds will react at the terminal unsaturated linkage,[45] and not at the second unsaturation. For example, in the reaction of phenyl isocyanate with phenylmagnesium bromide, the reaction is:

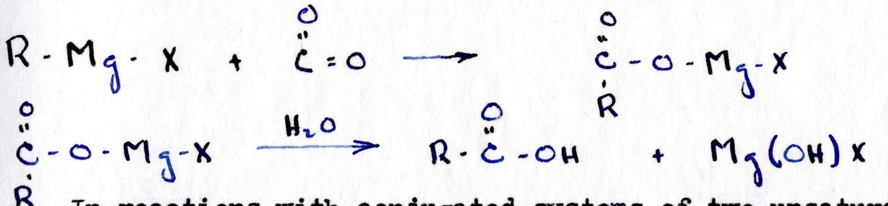


The usual rearrangement then takes place on hydrolysis:[36]



The reaction proceeds smoothly enough to permit the use of phenyl and alpha-napthyl isocyanates in the preparation of derivatives for the identification of Grignard compounds.[67]

With non-terminal cumulated systems, which are those systems in which there are two adjacent unsaturated links, neither of which is at the end of a chain, the Grignard reagent gives reactions which are similar to those of the isolated independent linkages, except that with the simpler systems, such as carbon dioxide, carbon disulfide, and sulfur dioxide, only one of the two double bonds is broken, as in the reaction:[36]



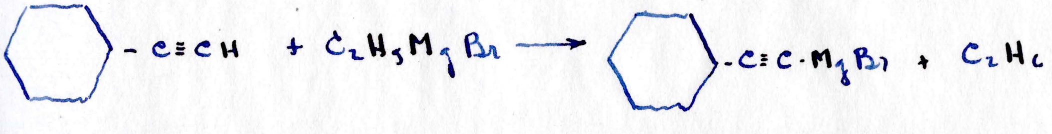
$$R\text{-}Mg\text{-}X + \overset{O}{\overset{\|}{C}}=O \longrightarrow \underset{R}{\overset{O}{\overset{\|}{C}}}\text{-}O\text{-}Mg\text{-}X$$

$$\underset{R}{\overset{O}{\overset{\|}{C}}}\text{-}O\text{-}Mg\text{-}X \xrightarrow{H_2O} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + Mg(OH)X$$

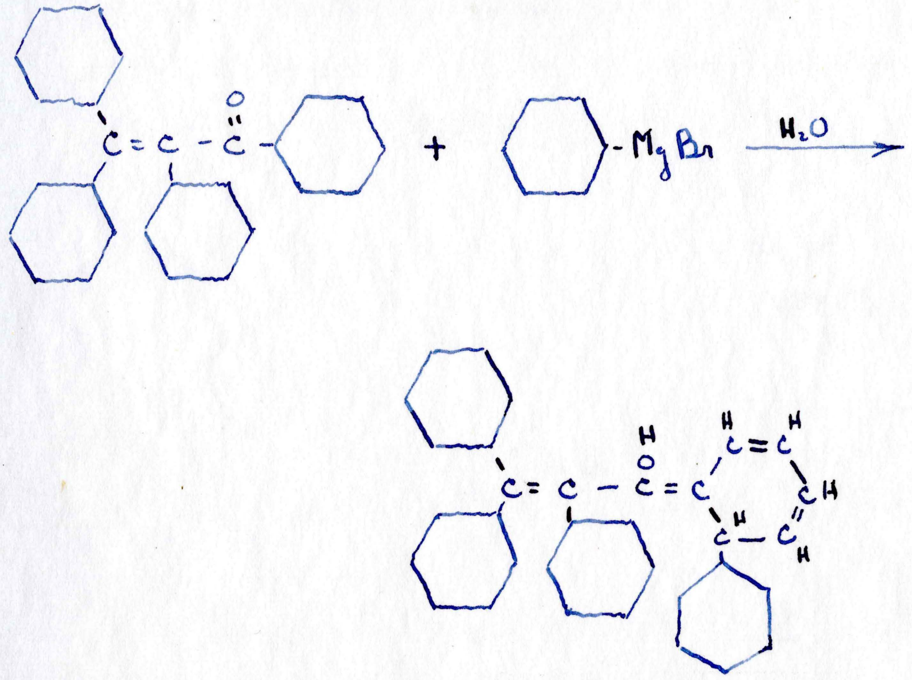
In reactions with conjugated systems of two unsaturated linkages, separated by one or more carbon atoms, usually 1,2-addition occurs, as in the simpler systems. However, there is no 1,2-addition to ethylenic or acetylenic linkages,[36] because of the acidic nature of the hydrogen attached to the group. Instead, the following take place:[6, 30]

$$H\text{-}C\equiv C\text{-}H + C_2H_5\text{-}MgBr \longrightarrow H\text{-}C\equiv C\text{-}MgBr + C_2H_6$$

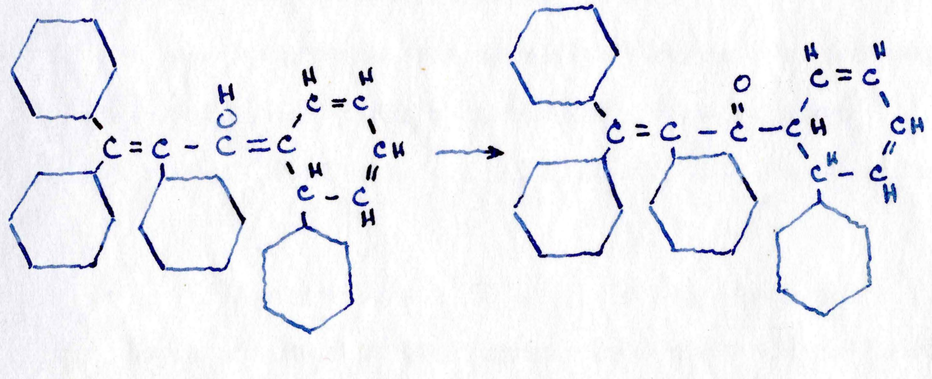
$$H\text{-}C\equiv C\text{-}H + 2\,C_2H_5MgBr \longrightarrow Br\text{-}Mg\text{-}C\equiv C\text{-}MgBr + 2\,C_2H_6$$



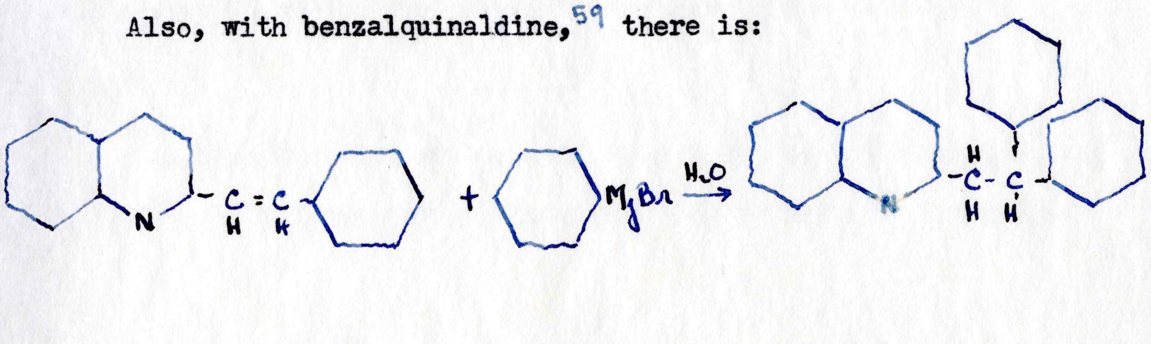
1,4-addition reactions of the Grignard reagent are interesting and fairly common. Grignards have the unusual property of unlocking a conjugated system which is part nuclear and part lateral.[36] For example, with phenylated unsaturated ketones, the following type reaction occurs:[23]



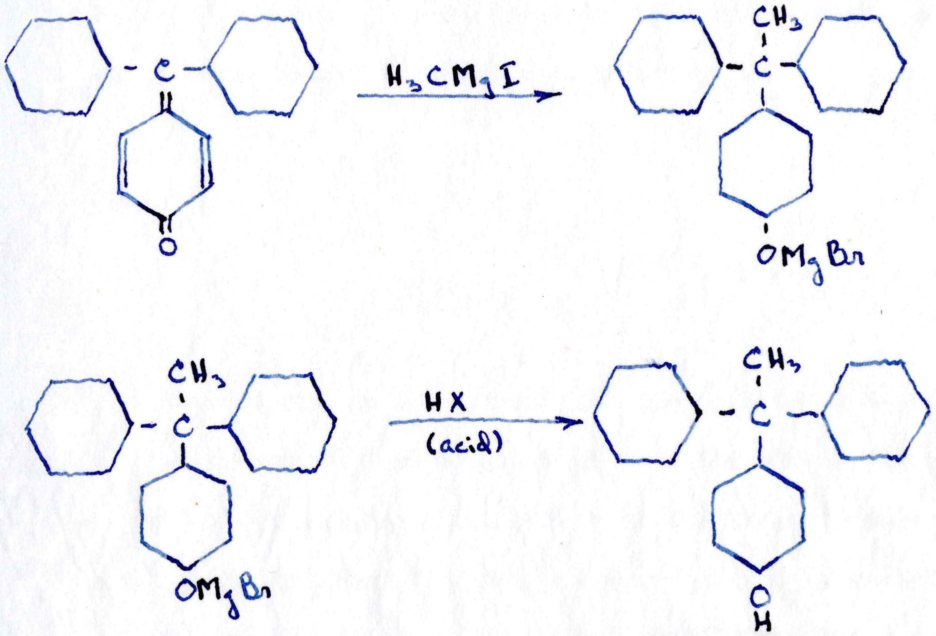
and the unstable enol form subsequently tautomerizes:



Also, with benzalquinaldine,[59] there is:

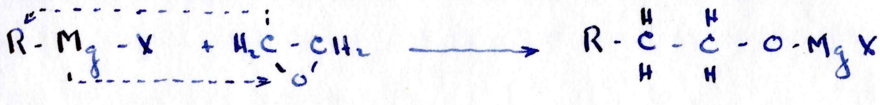


1,6-Additions have been found to occur with derivatives of fuchsone,[62] the reaction being:



The reaction of quinones with Grignard reagents yields mixtures of 1,4- and 1,6-carbonyl addition products,[21] and is consequently of little preparative value.

The use of ethylene oxide with a Grignard to increase the length of a carbon chain by two atoms is well-known:[8]



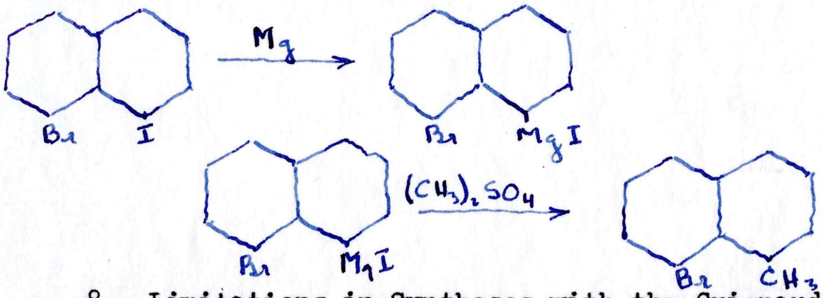
$$R-Mg-X + \underset{O}{H_2C-CH_2} \longrightarrow R-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-MgX$$

$$R-CH_2-CH_2-OMgX \xrightarrow{H_2O} R-CH_2-CH_2-OH + Mg(OH)X$$

and halogen cleavage of a Grignard is another simple reaction.[33] Addition of free halogen gives rise to an organic halide.

$$R-Mg-I + I_2 \longrightarrow R-I + MgI_2$$

The reaction between magnesium and a peri-dihalonapthalene, in which the halogens are dissimilar, illustrates the difference in reactivities of the halogens. 1-bromo-9-iodonapthalene undergoes a reaction with magnesium metal in which the iodine linkage is disrupted. If this product is treated with dimethyl sulfate, 1-bromo-9-methylnapthalene results:[16]

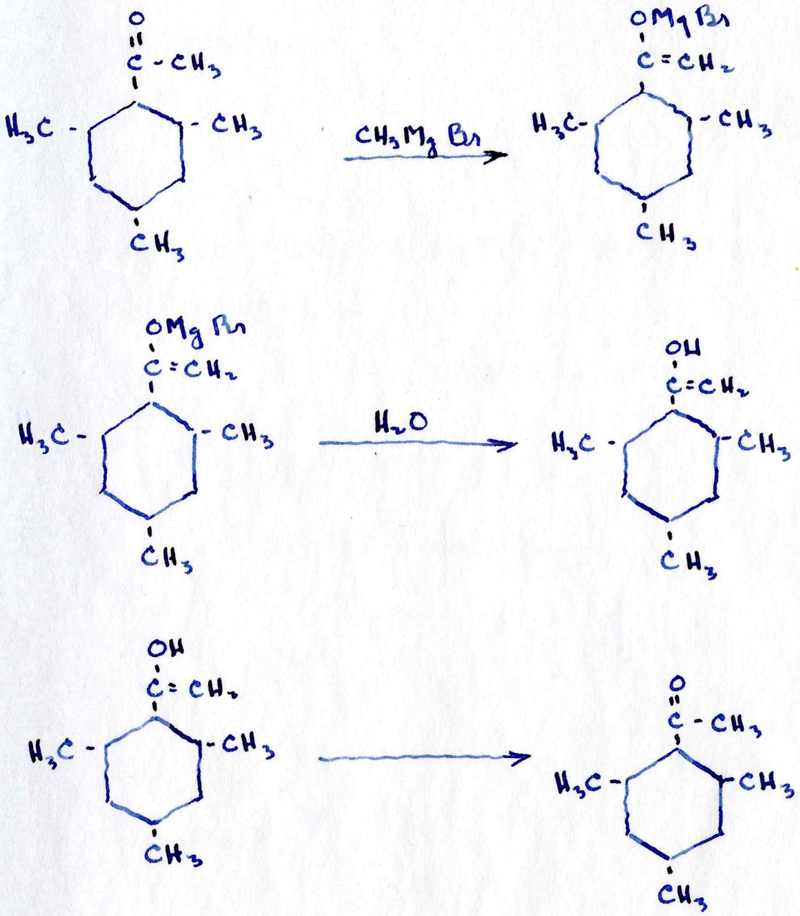


8. Limitations in Syntheses with the Grignard Reagent.

Perhaps the most common limitation in the use of the Grignard reagent is that atmospheric oxidation of the reagent proceeds so rapidly in many cases that exclusion of air is necessary. Mercury sealing of apparatus is sufficient protection in the more rapid reactions, but an atmosphere of nitrogen is often required.

Another disadvantage is that compounds which contain several functional groups capable of reacting with the Grignard frequently cannot be made to react at one group and not at another, which eliminates the Grignard as a means of introducing many groups into a molecule.[9]

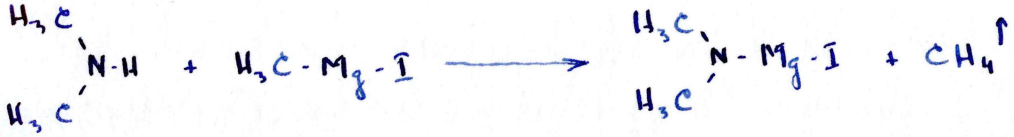
Other limitations are caused by steric hindrance. In general, for example, a bromine atom, flanked in the two ortho-positions is unreactive. Methyl groups in the ortho-positions often give rise to abnormal addition, as in the reaction of acetomesitylene with methylmagnesium bromide:[20]



in which the final product is identical with the starting material.

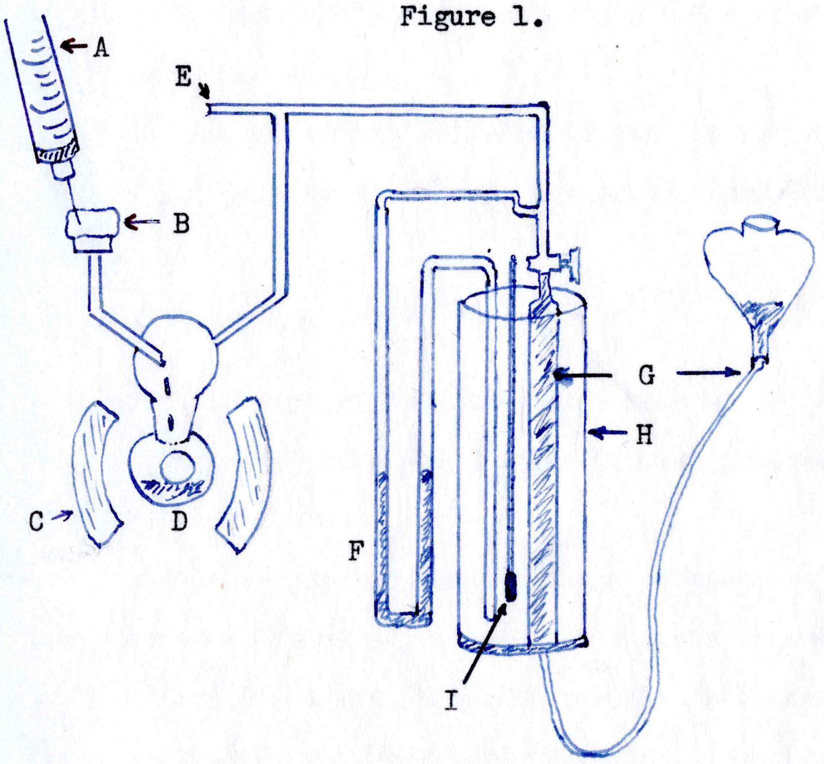
F. Uses of the Grignard Reagent.

The Grignard reagent has several uses, other than those in connection with pure organic synthesis, which are of interest. First among these is the Tschugaeff-Zerewitinoff analysis for active hydrogen,[33] which gives the number of active hydrogen atoms per molecule of a known compound. The procedure is to add an excess of methylmagnesium iodide, usually in diisoamyl ether,[62] to a known quantity of sample, and to measure the volume of methane liberated. A sample reaction is that of dimethylamine:



A so-called "Grignard Machine", used in this determination, is shown in Figure 1.[13]

Figure 1.



A. Calibrated hypodermic for adding Grignard reagent.

B. Rubber stopple to permit air-tight injection.

C. Intermittent electromagnet to vibrate steel ball in sample container.

D. Sample with glass-covered steel ball for uniform mixing.

E. Inlet for nitrogen atmosphere.

F. Manometer apparatus used to determine volume of methane.

G. Levelling burette.

H. Water bath for constant temperature control.

I. Thermometer.

A measured volume of solution is injected into the system from the hypodermic, and complete reaction with the weighed sample is insured by vibrating the glass-covered steel ball through the sample by means of the electromagnet. The remainder of the apparatus is for collection and measurement of the liberated methane.

Another use of the Grignard reagent is the synthesis of tetraethyl lead, or so-called "anti-knock" compound. The reaction is:[7]

$$4\ C_2H_5MgBr + 2PbCl_2 \longrightarrow Pb(C_2H_5)_4 + 4MgClBr + Pb.$$

This is of laboratory interest only, because of prohibitive cost. A cheaper sodium-lead alloy process is used exclusively in industry.

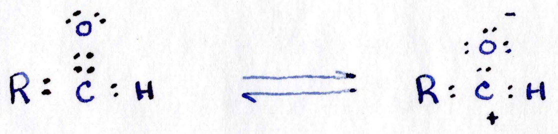
Another use not employed because of economic limitations is the vulcanization of rubber.[15] Sulfur is the commercially used vulcanizing agent, but good results have been obtained, in laboratory lots, with Grignard reagents. The high reactivity of the Grignard in addition at unsaturated links is involved.

An important use for the Grignard reagent at present is in the synthesis of otherwise scarce and expensive biologically useful compounds. For example, the reaction is used in the synthesis of progesterone and other hormones[23] where their isolation and purification from body excretions is expensive and difficult. The reagents are also useful in making carcinogens for cancer research. These carcinogens are polynuclear hydrocarbons which induce cancer and malignant tumors when impregnated in animals. These are two examples illustrating a large field in which the Grignard reagent may be considered indispensable.

EXPERIMENTAL WORK

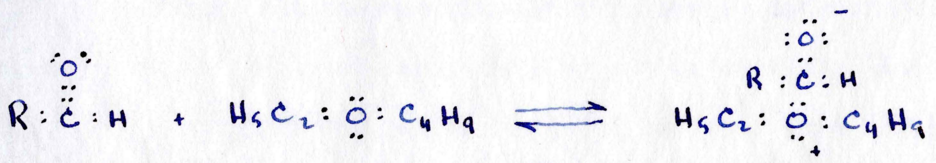
A. Introduction.

The purpose of the experimental work is to determine whether an optically active ether solvent will have sufficient solvation effect upon the reaction between a Grignard reagent and an aldehyde to cause the resulting alcohol to rotate the plane of polarized light.* Since the ether solvent forms complexes with the Grignard reagent, the solvated Grignard molecule will, in effect, be optically active. At the same time, because of resonance of the aldehyde molecule between the structures: .



$$\mathrm{R}:\overset{\mathrm{O}}{\ddot{\mathrm{C}}}:\mathrm{H} \rightleftharpoons \mathrm{R}:\overset{:\ddot{\mathrm{O}}:^{-}}{\underset{+}{\mathrm{C}}}:\mathrm{H}$$

there should also be solvation of the aldehyde:



$$\mathrm{R}:\overset{\mathrm{O}}{\ddot{\mathrm{C}}}:\mathrm{H} + \mathrm{H_5C_2}:\ddot{\mathrm{O}}:\mathrm{C_4H_9} \rightleftharpoons \mathrm{H_5C_2}:\overset{\overset{:\ddot{\mathrm{O}}:^{-}}{\mathrm{R}:\mathrm{C}:\mathrm{H}}}{\underset{+}{\ddot{\mathrm{O}}}}:\mathrm{C_4H_9}$$

which would make the aldehyde similarly active. The reaction between these two activated molecules should then result in an optically active product.

---

* Tarbell and Paulson, J. Am. Chem. Soc., <u>64</u>, 2842 (1942), found that d-methyl-sec-butyl ether solvent gave an inactive product with this reaction, and suggested that two molecules of the ether had coordinated with each molecule of Grignard reagent to form a complex containing a plane of symmetry.

The work may be divided into five phases: resolution of the alcohol, preparation of the racemic ether to determine the ease of reaction and percentage yield, Grignard reactions in the racemic ether to determine ease and yield of reaction, preparation of the active ether, and Grignard reactions in the active ether.

B. Reactions Accomplished.

1. Resolution of the Alcohol.

The resolution of 2-butanol was carried out in the following manner.[64] Five hundred fifty grams of phthalic anhydride and 285 grams of 2-butanol were heated with constant stirring on a water bath for eleven hours. The resulting crude sec-butyl hydrogen phthalate was dissolved in eighteen liters of dilute sodium carbonate solution, and the unchanged alcohol extracted with ether. The ester was then re-precipitated with excess hydrochloric acid, washed with water, and recrystallized. The recrystallization was carried out in two parts; half of the ester was treated with glacial acetic acid, and the other half with low-boiling petroleum ether. The glacial acetic acid caused loss of yield due to the high solubility of the ester, and the petroleum ether gave poor results because of the slight solubility of the ester even when the petroleum ether was heated to boiling.

The brucine salt of the ester was prepared in three stages, because of the limited amount of brucine. In the first trial, 191 grams of the ester was dissolved in 0.88 liters of warm acetone, 339 grams of brucine alkaloid were added, and the mixture refluxed at 40° for one hour, after which it was filtered hot, and the filtrate placed in the ice box. Approximately 0.30 liters of excess acetone were required during the filtration to cause complete solution of the brucine salt. This necessitated removal of the excess acetone before fractional crystallization. A water bath was used for this purpose, and too much of the solvent was evaporated, resulting in the crystallization of a portion of the brucine salt of the l-ester along with the brucine salt of the d-ester. The product, after recrystallization from hot methanol, was treated with a slight excess of dilute aqueous sodium hydroxide and steam distilled. The alcohol was salted out with potassium carbonate, and distilled. The boiling point at 744 mm. pressure was 98.0°. The boiling point of the pure alcohol at 760 mm. pressure is recorded as 99.5°.[64] The specific rotation of pure d-sec-butanol is recorded as +12.0°, using the d-line of sodium at 20°.[64] The specific rotation of the resolved alcohol was +2.8°, using the d-line of sodium at 23°. About twenty milliliters of d-alcohol were obtained.

The remaining solution of the brucine salt of the l-ester in acetone was dried over a water bath, treated with excess aqueous sodium hydroxide, and steam distilled. Due to removal of some l-alcohol along with the d-alcohol in the fractional crystallization, insufficient l-alcohol was obtained to permit investigation with the polarimeter.

The alkaline brucine suspensions remaining after steam distillation were recovered by treatment with excess dilute hydrochloric acid, and filtration. The filtrate was then treated with a slight excess of ammonia solution, after which it was again filtered, and the free brucine washed with small amounts of pure water. The brucine was dried by passing air through it, and afterwards by standing in a desiccator. This recovered brucine was then used in the second and third trials.

In the second trial, 243 grams of ester were dissolved in 1.10 liters of acetone, and 431 grams of brucine added.

In the third trial, 337 grams of ester were dissolved in 1.40 liters of acetone, and 536 grams of brucine added. During the evaporation of excess acetone from these solutions, a considerable amount of water, from an open condenser attachment, was accidentally run into the acetone solutions. This resulted in a thick, viscous mass, which could not be filtered or crystallized. Attempts to remove the water by continued standing, in small portions in calcium chloride desiccators, were unsuccessful; therefore, no resolved alcohol was obtained from either the second or third trial.

2. Preparation of the Racemic Ether.

Racemic sec-butyl ethyl ether was prepared by the Williamson synthesis to determine the ease of reaction and percentage yield of ether.[55]

Eight grams of freshly-cut sodium metal were added to 100 milliliters of 2-butanol, and allowed to stand until no further reaction was noticed. To this was added 17.5 grams of ethyl bromide, and the mixture was allowed to stand for three days. The mixture was then distilled, and the fraction coming over between 80° and 85° was collected, mixed with 100 milliliters of water, and redistilled. This time the fraction distilling between 67° and 72°, consisting of an azeotropic mixture of alcohol and water,[56] was collected, redistilled, and the fraction in the range 71° to 72° collected, separated, and the ether dried over calcium chloride, refluxed with sodium, and distilled. The first trial of this synthesis yielded 1.2 grams of pure ether, and the second trial 1.5 grams. In a third trial the amount of ethyl bromide was doubled, and the time of reaction increased to four days, with intermittent agitation. This raised the yield from 100 milliliters of alcohol to 6.7 grams of ether, but this was still insufficient for use with the antipode alcohol.

Next the ether was prepared in benzene solvent,[65] by adding 4.6 grams of freshly-cut sodium metal to 100 milliliters of dried benzene, and adding 26.0 grams of 2-butanol. This mixture was refluxed over a water bath until solution was complete, after which 38.5 grams of ethyl bromide were added, and the solution allowed to stand overnight. Distillation of this mixture was unsuccessful because of the similarity in boiling points of the ether and the benzene.

The ether could probably be prepared in diethyl ether solvent,[65] but this was not done.

Due to failure to prepare the active ether, no Grignard reactions were run.

C. Summary and Conclusions.

The problem has not been solved to date. However, if the active ether could be prepared in diethyl ether solvent, in sufficient yield, the remainder of the problem should follow without much difficulty.

Since no activity was noticed with reactions in d-methyl-sec-butyl ether solvent, however, it is doubtful whether any activity would be obtained using the d-ethyl-sec-butyl ether.

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