



A Review on Grignard Reagent

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Abstract: Grignard reagents are highly reactive organomagnesium halides formed by the reaction of magnesium metal with alkyl or alkenyl halides. They are very strong bases and react with acidic hydrogens such as alcohols, water and carboxylic acids. They are generally produced by reacting an aryl halide or an alkyl halide with magnesium. Grignard compounds are popular reagents in organic synthesis for creating new carbon-carbon bonds. For example, when reacted with another halogenated compound R'-X' in the presence of a suitable catalyst, they typically yield R-R' and the magnesium halide Mg-XX' as a by-product; and the latter is insoluble in the solvents normally used. Pure Grignard reagents are extremely reactive solids. They are normally handled as solutions in solvents such as diethyl ether or tetrahydrofuran; which are relatively stable as long as water is excluded. In such a medium, a Grignard reagent is invariably present as a complex with the magnesium atom connected to the two ether oxygens by coordination bonds. Grignard reagents react with a variety of carbonyl derivatives. The most common application of Grignard reagents is the alkylation of aldehydes and ketones, i.e., the Grignard reaction.

Keywords: Grignard reagents, alkylation, aldehydes, ketones.

Introduction:

An important class of organo-metallic compounds discovered by Victor Grignard in 1900 is alkyl magnesium halide, RMgX, referred as Grignard Reagents. ¹

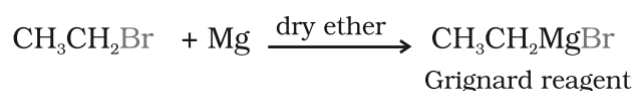
A **Grignard reagent** or **Grignard compound** is a chemical compound with the general formula R-Mg-X, where X is a halogen and R is an organic group, normally an alkyl or aryl.

Two typical examples are methylmagnesium chloride Cl-Mg-CH₃ and phenylmagnesium bromide (C₆H₅)-Mg-Br. They are a subclass of the organomagnesium compounds.

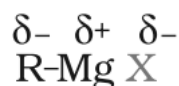
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Grignard reagents are obtained by the reaction of haloalkanes with magnesium metal in dry ether.



In the Grignard reagent, the carbon-magnesium bond is covalent but highly polar, with carbon pulling electrons from electropositive magnesium; the magnesium halogen bond is essentially ionic.



Grignard reagents are highly reactive and react with any source of proton to give hydrocarbons. Even water, alcohols, amines are sufficiently acidic to convert them to corresponding hydrocarbons.

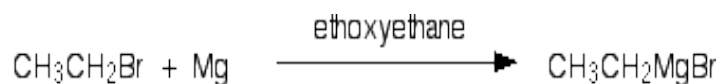


It is therefore necessary to avoid even traces of moisture from a Grignard reagent. On the other hand, this could be considered as one of the methods for converting halides to hydrocarbons.ⁱ

The preparation of a Grignard reagent

General synthesis

Grignard reagents are made by adding the halogenoalkane to small bits of magnesium in a flask containing ethoxyethane (commonly called diethyl ether or just "ether"). The flask is fitted with a reflux condenser, and the mixture is warmed over a water bath for 20 - 30 minutes.



Everything must be perfectly dry because Grignard reagents react with water.ⁱⁱⁱ

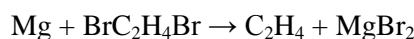
From Mg metal

Traditionally Grignard reagents are prepared by treating an organic halide (normally organobromine) with magnesium metal. Ethers are required to stabilize the organomagnesium compound. Water and air, which rapidly destroy the reagent by protonolysis or oxidation, are excluded using air-free techniques.ⁱⁱ Although the reagents still need to be dry.^{iv}

As is common for reactions involving solids and solution, the formation of Grignard reagents is often subject to an induction period. During this stage, the passivating oxide on the magnesium is removed. After this induction period, the reactions can be highly exothermic. This exothermicity must be considered when a reaction is scaled-up from laboratory to production plant.^v Most organohalides will work, but carbon-fluorine bonds are generally unreactive, except with specially activated magnesium (through Rieke metals).

Magnesium

Typically the reaction to form Grignard reagents involves the use of magnesium ribbon. All magnesium is coated with a passivating layer of magnesium oxide, which inhibits reactions with the organic halide. Many methods have been developed to weaken this passivating layer, thereby exposing highly reactive magnesium to the organic halide. Mechanical methods include crushing of the Mg pieces in situ, rapid stirring, and sonication.^{iv} Iodine, methyl iodide, and 1,2-dibromoethane are common activating agents. The use of 1,2-dibromoethane is advantageous as its action can be monitored by the observation of bubbles of ethylene. Furthermore, the side-products are innocuous:

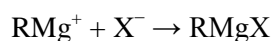
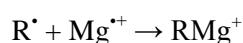
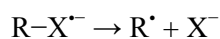
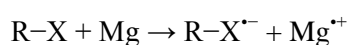


The amount of Mg consumed by these activating agents is usually insignificant. A small amount of mercuric chloride will amalgamate the surface of the metal, enhancing its reactivity. Addition of preformed Grignard reagent is often used as the initiator.

Specially activated magnesium, such as Rieke magnesium, circumvents this problem.^{vi} The oxide layer can also be broken up using ultrasound, using a stirring rod to scratch the oxidized layer off,^{vii} or by adding a few drops of iodine or 1,2-Diiodoethane. Another option is to use sublimed magnesium or magnesium anthracene.^{viii}

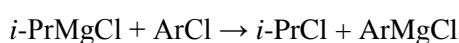
Mechanism

In terms of mechanism, the reaction proceeds through single electron transfer:^{ix-x-xi}



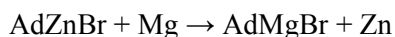
Mg transfer reaction (halogen–Mg exchange)

An alternative preparation of Grignard reagents involves transfer of Mg from a preformed Grignard reagent to an organic halide. Other organomagnesium reagents are used as well.^{xii} This method offers the advantage that the Mg transfer tolerates many functional groups. An illustrative reaction involves isopropylmagnesium chloride and aryl bromide or iodides:^{xiii}



From alkylzinc compounds (reductive transmetalation)

A further method to synthesize Grignard reagents involves reaction of Mg with an organozinc compound. This method has been used to make adamantane-based Grignard reagents, which are, due to C-C coupling side reactions, difficult to make by the conventional method from the alkyl halide and Mg. The reductive transmetalation achieves:^{xiv}



Testing Grignard reagents

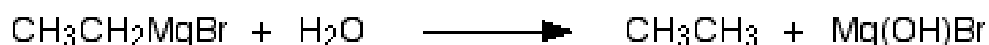
Because Grignard reagents are so sensitive to moisture and oxygen, many methods have been developed to test the quality of a batch. Typical tests involve titrations with weighable, anhydrous protic reagents, e.g. menthol in the presence of a color-indicator. The interaction of the Grignard reagent with phenanthroline or 2,2'-biquinoline causes a color change.^{xv}

Application of Grignard reagents

Alkane synthesis:

Grignard reagents react with water to produce alkanes. This is the reason that everything has to be very dry during the preparation of Grignard reagent.

For example:



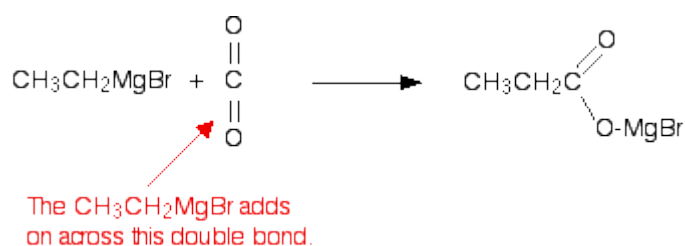
The inorganic product, Mg(OH)Br, is referred to as a "basic bromide". It is a half-way stage between magnesium bromide and magnesium hydroxide.

Carboxylic synthesis:

Grignard reagents react with carbon dioxide in two stages. In the first stage, an addition of the Grignard reagent to the carbon dioxide.

Dry carbon dioxide is bubbled through a solution of the Grignard reagent in ethoxyethane (Diethyl ether).

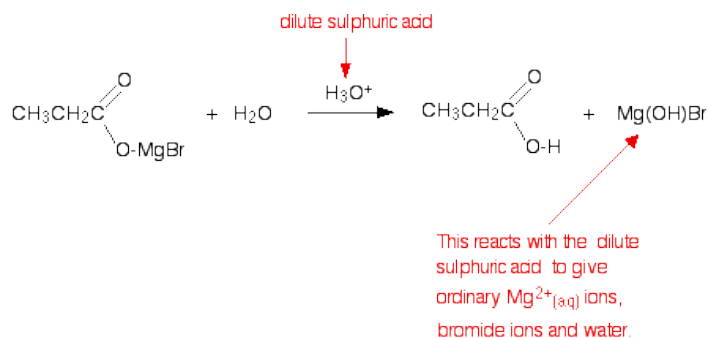
For example:



The product is then hydrolysed (reacted with water) in the presence of a dilute acid. Typically dilute sulphuric acid or dilute hydrochloric acid is used.

A carboxylic acid is produced with one more carbon than the original Grignard reagent.

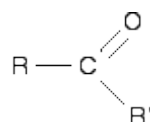
The usually quoted equation is:



Almost all sources quote the formation of a basic halide such as Mg(OH)Br as the other product of the reaction.

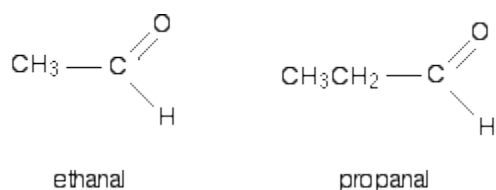
Alcohol synthesis:

Carbonyl compounds contain the C=O double bond. The simplest ones have the form:

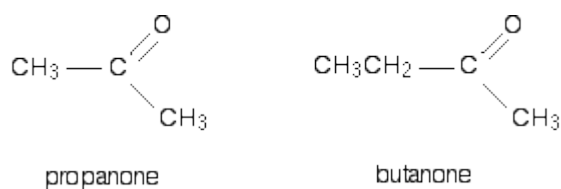


R and R' can be the same or different, and can be an alkyl group or hydrogen.

If one (or both) of the R groups are hydrogens, the compounds are called *aldehydes*. For example:



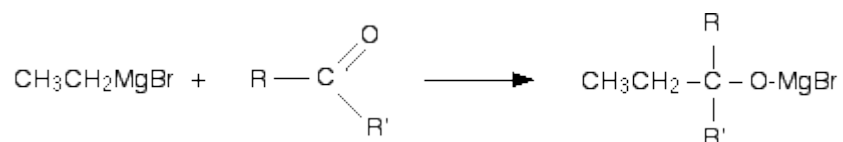
If both of the R groups are alkyl groups, the compounds are called *ketones*. Examples include:



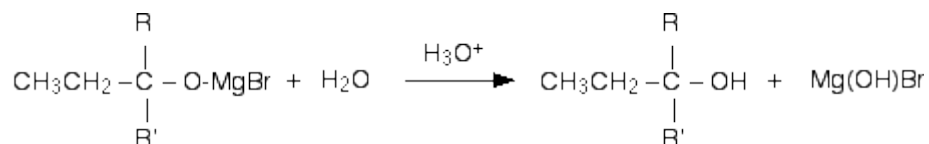
The general reaction between Grignard reagents and carbonyl compounds

The reactions between the carbonyl compounds and Grignard reagents can look quite complicated, but they all react in the same way - all that changes are the groups attached to the carbon-oxygen double bond.

In the first stage, the Grignard reagent adds across the carbon-oxygen double bond:



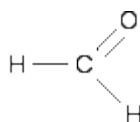
Dilute acid is then added to this to hydrolyse it.



An alcohol is formed. One of the key uses of Grignard reagents is the ability to make complicated alcohols easily.

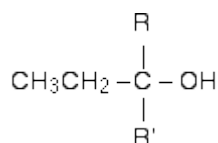
The reaction between Grignard reagents and methanal

In methanal, both R groups are hydrogen. Methanal is the simplest possible aldehyde.



methanal

Assuming that you are starting with $\text{CH}_3\text{CH}_2\text{MgBr}$ and using the general equation above, the alcohol you get always has the form:



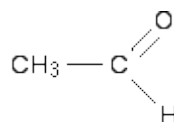
Since both R groups are hydrogen atoms, the final product will be:



A primary alcohol is formed. A primary alcohol has only one alkyl group attached to the carbon atom with the -OH group on it.

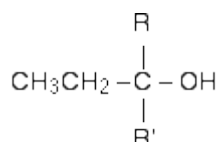
The reaction between Grignard reagents and other aldehydes

The next biggest aldehyde is ethanal. One of the R groups is hydrogen and the other CH_3 .



ethanal

Again, think about how that relates to the general case. The alcohol formed is:



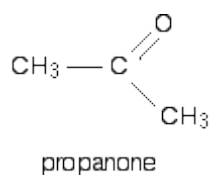
So this time the final product has one CH_3 group and one hydrogen attached:



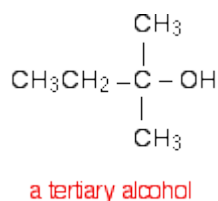
A secondary alcohol has two alkyl groups (the same or different) attached to the carbon with the -OH group on it.

The reaction between Grignard reagents and ketones

Ketones have two alkyl groups attached to the carbon-oxygen double bond. The simplest one is propanone.



This time when you replace the R groups in the general formula for the alcohol produced you get a tertiary alcohol.



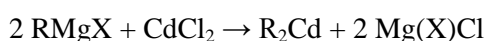
A tertiary alcohol has three alkyl groups attached to the carbon with the -OH attached. The alkyl groups can be any combination of same or different.ⁱⁱⁱ

Salicylaldehyde synthesis:

Grignard reagents serve as a base for protic substrates (this scheme does not show workup conditions, which typically includes water). Grignard reagents are basic and react with alcohols, phenols, etc. to give alkoxides (ROMgBr). The phenoxide derivative is susceptible to formylation by paraformaldehyde to give salicylaldehyde.^{xvi}

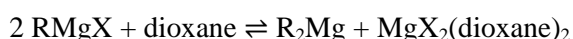
Dialkylcadmium synthesis:

Like organolithium compounds, Grignard reagents are useful for forming carbon-heteroatom bonds. Grignard reagents react with many metal-based electrophiles. For example, they undergo transmetallation with cadmium chloride (CdCl₂) to give dialkylcadmium:^{xvii}



Schlenk equilibrium

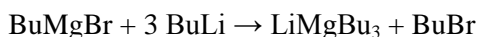
Most Grignard reactions are conducted in ethereal solvents, especially diethyl ether and THF. Grignard reagents react with 1,4-dioxane to give the diorganomagnesium compounds and insoluble coordination polymer $MgX_2(dioxane)_2$ and (R = organic group, X = halide):



This reaction exploits the Schlenk equilibrium, driving it toward the right.

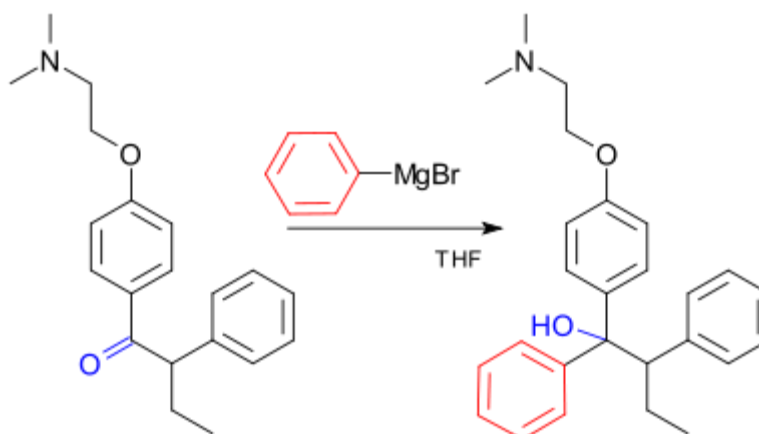
Precursors to magnesiates

Grignard reagents react with organolithium compounds to give ate complexes (Bu = butyl):^{xviii}



Industrial use

An example of the Grignard reaction is a key step in the (non-stereoselective) industrial production of Tamoxifen^{xix} (currently used for the treatment of estrogen receptor positive breast cancer in women):^{xx}



Conclusion:

Grignard reagents are one of the most common building blocks in organic synthesis of pharmaceutical products. One of the example is Tamoxifen as mentioned above. Tamoxifen is a non-steroidal antiestrogen used to treat breast cancer as well as prevent the incidence of breast cancer in high risk population. Grignard reagent also useful in synthesis of alcohols i.e. with aldehydes and ketones they gives primary alcohol, secondary alcohol and tertiary alcohol. Grignard reagent plays significant role



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in organic synthesis so basic knowledge about it, useful during usage because it is very unstable in open atmosphere (interact with atmospheric oxygen, carbon dioxide and water that degrades Grignard reagent), nobody knows the exact strength of Grignard reagent. So this writeup just provides the details about Grignard reagent.

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