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A COMPREHENSIVE REVIEW ON GREGANARD REACTION

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Abstract: The Grignard reaction is a key approach in making hydro carbons. It is very important when planning and carrying out such experiment to know how much mount of the main product will form and what kind of byproducts might appear. Reliable information has been collected about how Grignard reagent (Mg compounds) reacts with different carbonyl compounds. Using this data, it is possible to make good predictions about the results. When Grignard reagent reacts with saturated carbonyl compounds, scientists can usually predict the product yield quite accurately. But, with unsaturated carbonyl compounds, the available data is limited, unclear and often conflicting. Because of this, it is very hard sometimes impossible to predict the product yield correctly. This research was done to help to fill that knowledge gap. The experiments used normal laboratory methods & equipment. Joseph. A Dixon.et.al revealed that unsaturated carbonyl compounds (crotonaldehyde & mesityl oxide) are easy to buy commercially. The other two (3,4 -dimethyl -3- pentene-2- one & 4- pentene-3-one) can be made in large amounts. The reaction of Grignard reagent with cinnamaldehyde is not reported to our knowledge. So, in this article we explore the similar reactions of Grignard reagent with alpha, beta unsaturated aldehydes as a reference.

INTRODUCTION:

The Grignard reaction was an important discovery made by French chemist Francois August Victor Grignard. He received the noble prize in chemistry in the year 1912 for this invention. Grignard reaction creates bond between Grignard reagent and carbonyl atoms. Generally, it happens between a compound which contain carbonyl groups.

Eg: Aldehydes and ketones.

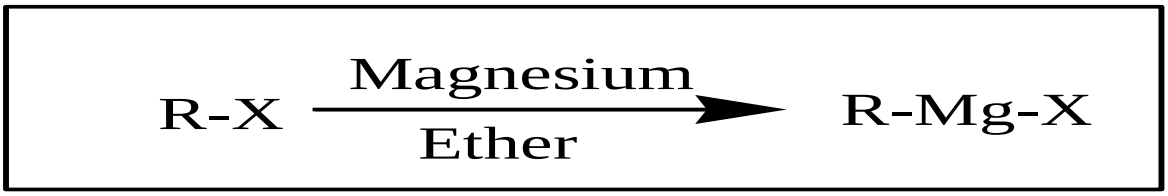
Basically, Grignard reagent is an organic compound that contain magnesium. The Grignard reaction is widely applicable in various sectors like laboratories, industries, to produce various organic compounds such as ketones, carbonyl compounds, and alcohols. The composition of Grignard reagent is aryl/alkyl halides. It reacts with magnesium metal in the presence of solvent like ether/tetra hydro furan. This reaction should be conducted in dry conditions.[1]

The problems that elucidating with this mechanism is that ethereal solution of Grignard reagent having different chemical species. The main reactant RMg-X is condensed that it was a proof of number of mono poly metallic molecules that should be in equilibrium. It Largely depends on nature of experimental conditions.[2] One application of this reaction involves the interaction of Grignard reagents with alpha, beta unsaturated carbonyl compounds: Alpha& beta unsaturated substances are very important in chemistry because of their special structure & wide range of uses, they are used as building blocks in making medicines and other biological materials. In the past, chemist used older more traditional methods to make alpha beta unsaturated carbonyl compounds.These methods did not use transition-metal catalysts. People used methods like adding and removal of halogens (or) use strong chemicals like organosulfur, organ selenium (or) benzo quinone to trigger the reactions.[3] One of the best method to prepare alpha beta unsaturated carbonyl compounds is carboxylation.[4]

SYNTHESIS OF GRIGNARD REAGENT:

Haloalkanes are the compounds which contain halogen atom which are bonded with sp^3-hybridized or sp^2 hybridized carbon atoms that are (aryl and vinyl halides). when haloalkanes are reacts with Magnesium metal produces organo magnesium halides 1°& 2° and 3° alkyl halides easily produced by Grignard reagents but their reactivities are different from each other Alkyl halides, Aryl and vinyl halides are slowly react. In haloalkanes, the halogens' order of reactivity is I> Br > Cl >> F. Grignard reagent is not suitable to preparation of organofluorides due their un reactivity. Organo halogen compounds which contain bromine & Chlorine are mostly used to prepare the Grignard reagent. Grignard reagent synthetically produces a new carbon- carbon bonds. The polarity of carbon-magnesium bond is different to the carbon-halogen bond of haloalkanes. The Grignard reagent contain an atom which is partially negative charge as like carbanion will easily react with the electrophilic centers like carbonyl carbon atoms of aldehydes and ketones & esters. Grignard reagent quickly reacts with acid hydrogen atom in the molecule, which contains an alcohol and water.[5]

Chemical reaction:



Solvents used in Grignard reagent are:

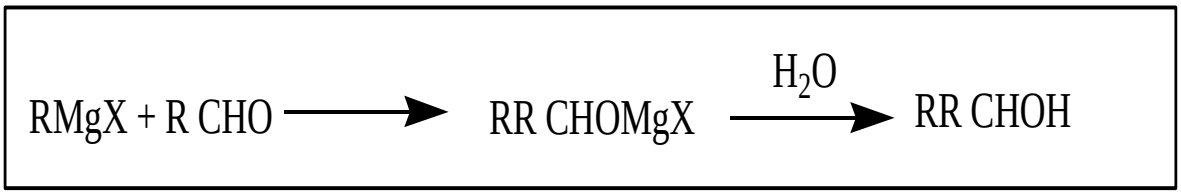
The most important solvents used in Grignard synthesis are diethyl ether and tetrahydrofuran. These are solvents in which either reagent reacts with the protons from a protic solvent. For example: Grignard reagent.

It can be made from aryl letters and haloalkanes and is expressed as R-Mg-X. The magnesium in the Grignard reagent and the oxygen atom in diethyl ether combine to form a complex. Grignard reagents are helpful in organic synthesis.[6]

General mechanism of action of grignard reagent:

The grignard reagents are chemical compounds that consist of magnesium. They have a general formula of "RMgX". Where: R is an organic group (alkyl or allyl), and X is a halide (like chlorine, bromine, or iodine). An alkyl or allyl halide is reacted with magnesium metal in an ether solvent to create Grignard reagents. These reagents are very reactive and acts as nucleophiles (electron donors) or bases in organic reactions.

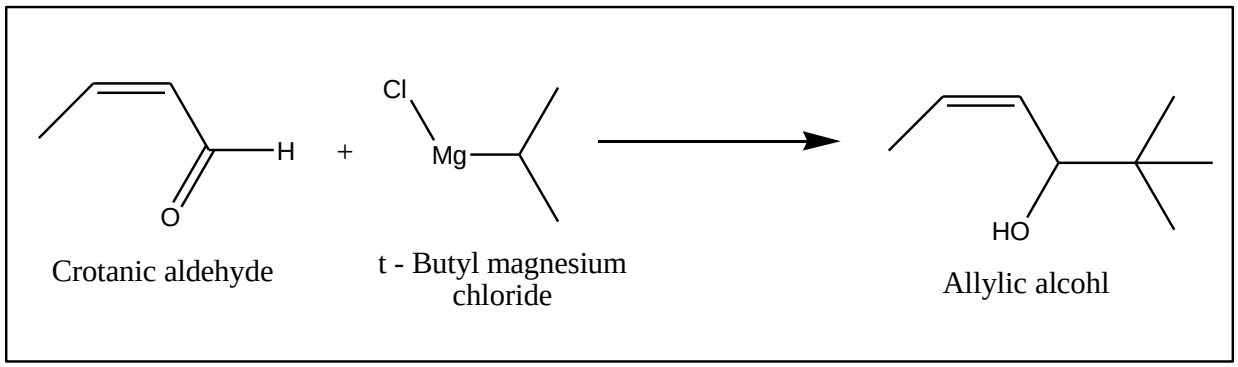
How they react: Grignard reagents react with compounds containing a carbonyl group (like aldehydes or ketones). The carbon in The other compound's carbonyl carbon is attacked by RMgX. When the combination is handled with water, it forms a new carbon-carbon bond and eventually produces alcohol.[7]



Until now, it has been generally believed that Alpha and beta unsaturated aldehydes react with the Grignard reagent uniquely at the carbonyl group, resulting in a 1, 2 additions. For example: Recent findings show that “t- butyl magnesium chloride” reacts with “crotonic aldehyde” to give 1,2 addition products (allylic alcohols) &1,4 addition products (saturated alcohols) in nearly equal proportions (approx. 25% each). Initial tests with other Grignard reagents such as ethyl-, propyl-, and iso propyl magnesium bromide, also suggest that formation of 1,4- addition products, through these occurs a much smaller extent. One of the reaction products, aldehyde with the formula {C8H16O}, forms a semi carbazone melting at 166^0csemicarbazone is easily oxidized by Tollen’s reagent to yield an acid {C8H16O2} which forms an amide melting at 163-164^0c. Further chemical modification of this acid using the Hell-Volhard–zelinsky reaction followed by treatment with methanol produced an alpha- bromo ester{C9H17O2Br}. Heating this ester with diethyl aniline lead to the formation of an alpha, beta unsaturated ester {C9H16O2}. when this ester underwent ozonolysis, it produced pinacolone, which was identified by converting it to semi carbazone, melting at 155^0c. Thus, it can be concluded that the original aldehyde was successfully transformed through a sequence of reactions confirming the presence of both 1,2 & 1,4- addition products in the reaction with Grignard reagents.[8]

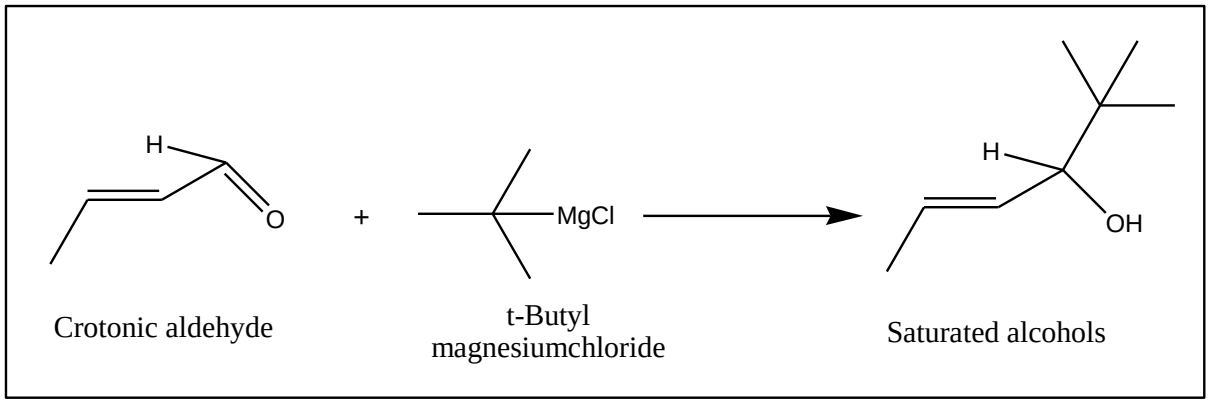
Chemical reaction:

When the t-butyl magnesium chloride reacts with crotonic aldehyde to give 1,2 addition product that is allylic alcohol



Chemical reaction:

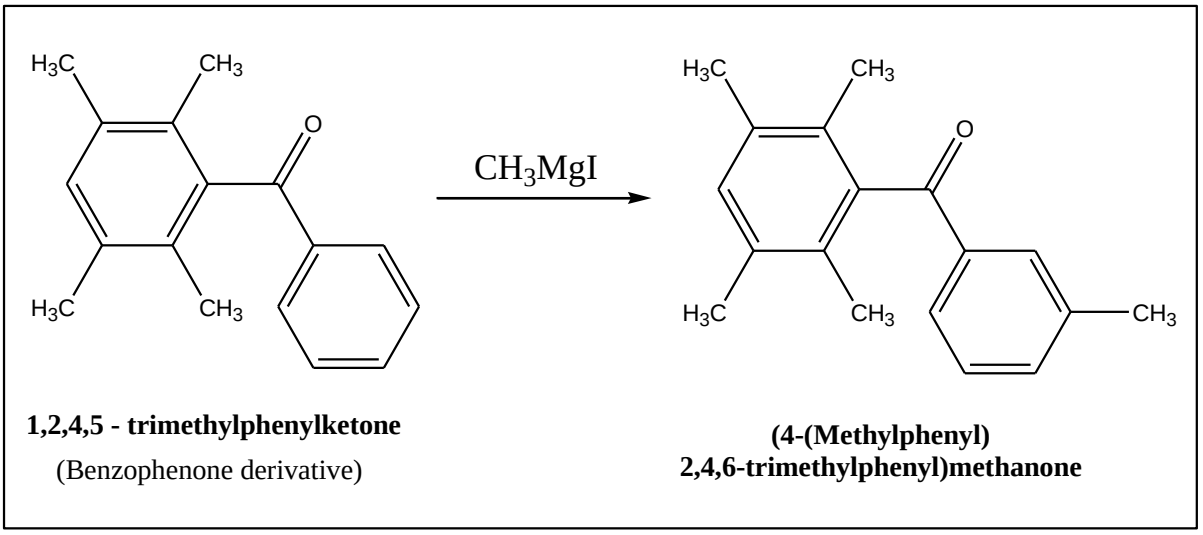
When the t-butyl magnesium chloride reacts with crotonic aldehyde to give 1,4 addition product that is saturated alcohols via conjugate addition.



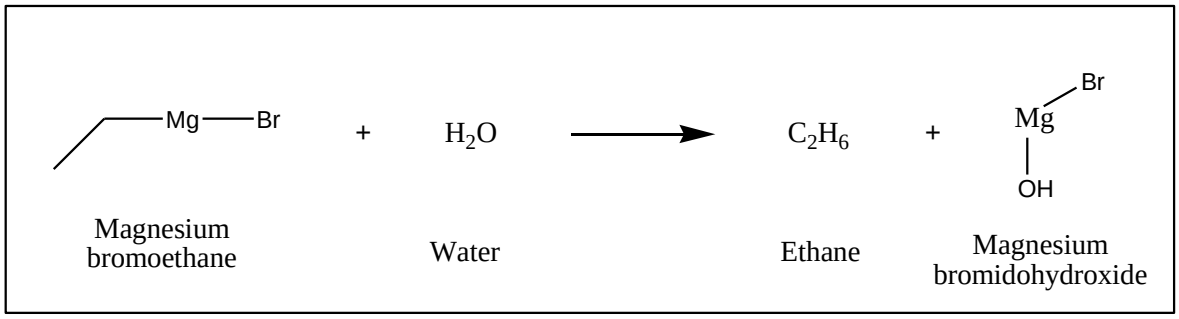
The Grignard reagent's interaction with alpha and beta unsaturated ketones:

Soon after the discovery of Grignard reagent E.P Kohler. Etal. Found that they could react with unsaturated ketones by adding either in the 1,2 position (or) 1,4 position. Through the continued research, Kohler and his co -workers helped to understand the conjugated addition reaction. This work is evidence& especially valuable because ofeasy study, how Grignard reagents are added to different compounds. Grignard reagent mainly plays an important role in conjugate addition mechanism. When Grignard addition product was examined at low temperature. It was determined that resulting alcohol which produced converted into more stable ketones. Whenever the Grignard addition to the penta dienones. In this condition one mole of Grignard reagent reacts with one mole of ketones forms an intermediate product that will decompose and regenerate a carbonyl group i.e, new ketone is formed will again react with another molecule of the Grignard reagent. Some exterior factors such as solvent (or) temperature have a less influence on whether the reaction favors 1,2 (or) 1,4 addition& the amount of product formed remains nearly same under different condition. When alpha, beta unsaturated ketones react with Grignard reagent i.e, RMgX product formed depends on mode of addition, Conjugate addition is 1,2 addition or 1,4 addition. It has been discovered that the more reactive carbonyl group have an greater tendency to undergo 1,2 addition the carbonyl group will influence the other substituents.[9]

Chemical reaction:



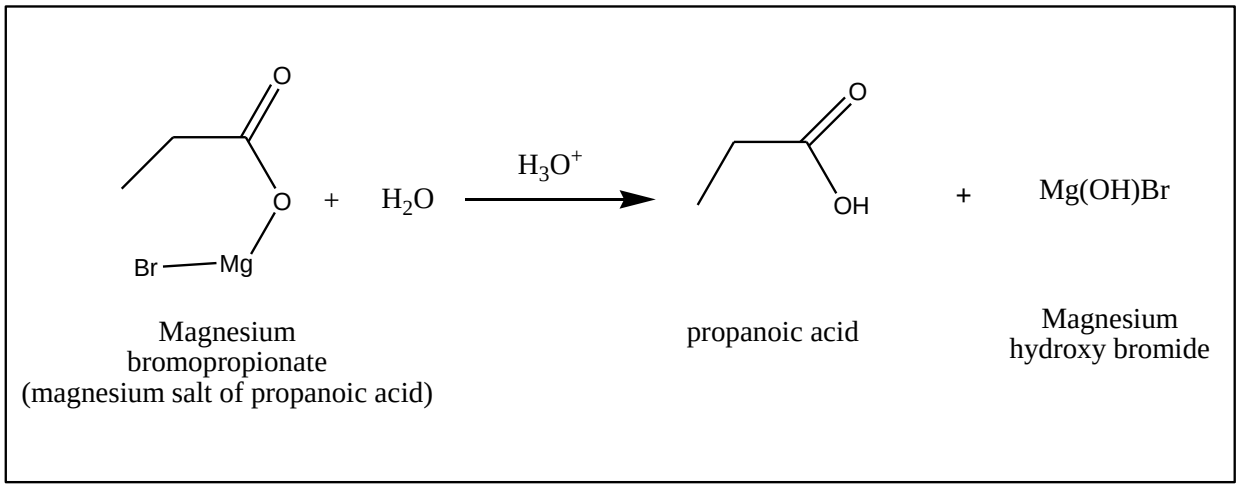
Alkane synthesis:
Grignard reagents react quickly with water and get destroyed, forming alkanes. Because of this, all equipment and chemicals must be kept completely dry when preparing a Grignard reagent. The inorganic residue formed, Mg(OH)Br, is called a “basic bromide.” It represents a halfway form between magnesium bromide and magnesium hydroxide.
Chemical reaction:



Carboxylic acid synthesis:

Carbon dioxide goes through two stages with Grignard reagents. First, carbon dioxide is combined with a Grignard reagent. Bubbles form in dry carbon dioxide and Grignard reagent dissolved in diethyl ether. Afterwards, hydrolysis occurs using water and diluted acid (which could be dilute sulfuric acid or dilute hydrochloric acid). The reaction will yield a carboxylic acid that contains Compared to the Grignard reagent, one more carbon atom that was used as the starting material.[10]

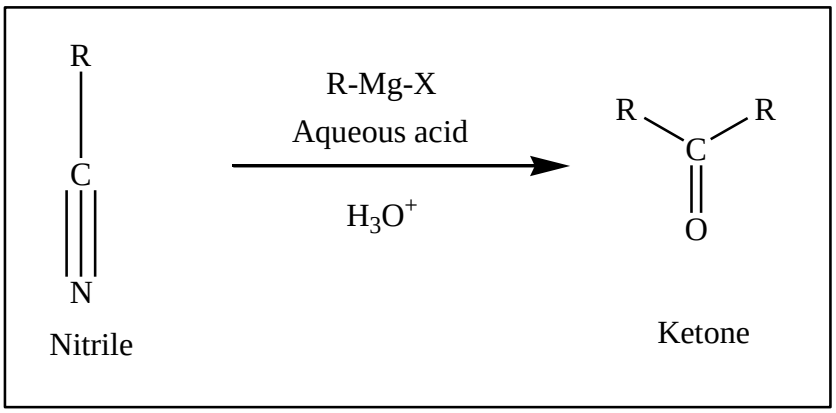
chemical reaction:



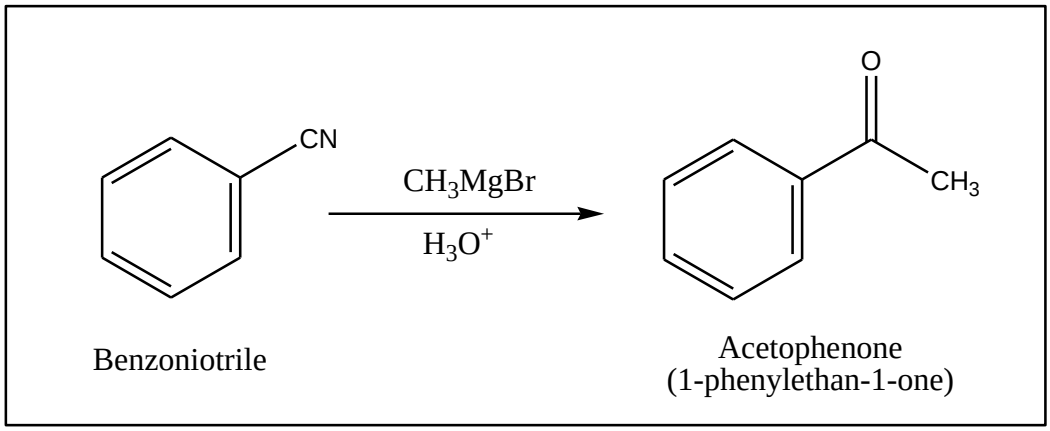
Addition of grignard reagent to nitriles to give ketones:

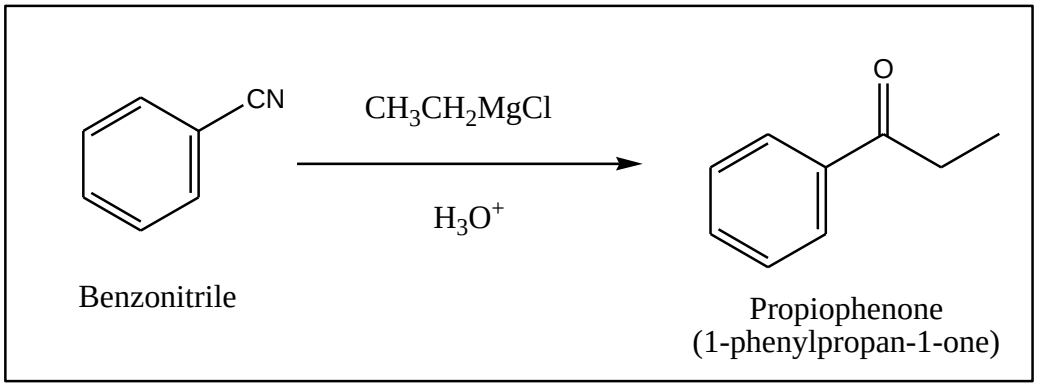
The addition of Grignard reaction to the nitriles to give imines. The imines react with aqueous acid to form ketones. The water can be used for this change, but using a bit of acid with water for better work.[11]

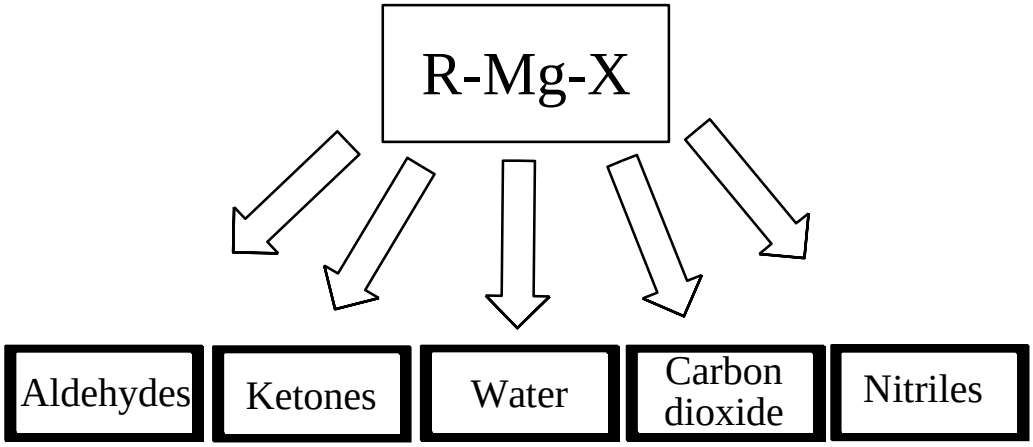
Chemical reaction:



Example:







Applications of grignard reagent:

Making of Tamoxifen:
Tamoxifen is a medicine used to treat breast cancer. To make it, scientists use a Grignard reagent reacts with a ketone compound to form the main structure of tamoxifen.

Making of Atrovastatin:
Atrovastatin is a statin medicine that helps lower cholesterol. One of the steps in making it also uses a Grignard reaction. Showing how important this reaction is in making complex medicines. Grignard reagents have many benefits in making drugs: Versatile: They can take part in many types of reactions, helping to make a wide range of different molecules. Efficient: Grignard reactions are usually easy and quick, making it faster to build complex molecules. Atom economy: These reactions use atoms efficiently. Creating less waste and making better use of the starting materials.[7] Grignard reagents are used to make important natural products like polyketides, terpenoids, and amino acids.[12] Grignard reagents are made from organic halides. They are very reactive and work well in chemical reactions.[13]

CONCLUSION: Alcohols, alkanes, carboxylic acids, ketones, and the formation of carbon-carbon bonds are all made possible by the Grignard reaction, an essential tool in organic synthesis. While reactions with saturated carbonyl compounds generally give predictable product yields, reactions with α, β-unsaturated carbonyl compounds are more complex due to competing 1,2- and 1,4-

addition pathways. Experimental evidence with compounds such as crotonaldehyde, mesityl oxide, 3,4-dimethyl-3-pentene-2-one, and 4-pentene-3-one shows that both types of addition products can form, though their proportions vary depending on the Grignard reagent and reaction conditions. These findings underscore the importance of understanding reaction mechanisms and controlling experimental variables when working with unsaturated carbonyls. Furthermore, the study highlights the unreported reaction of Grignard reagents with cinnamaldehyde as a potential avenue for further research. Overall, the work reinforces the versatility and industrial relevance of Grignard reagents are especially important in the preparation of natural products, pharmaceuticals, & other biologically active molecules

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