A REVIEW ON GRIGNARD REACTION WITH EMPHASIS ON ALPHA, BETA UNSATURATED KETONES

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Abstract : The reaction between Grignard reagents and alpha beta-unsaturated ketones is a fundamental transformation in organic chemistry that demonstrates the dual reactivity of conjugated carbonyl systems. Grignard reagents (RMgX), which are highly reactive organo-magnesium compounds, can participate in two distinct modes of nucleophilic addition the 1, 2-addition (quickest addition to the carbonyl carbon) and the 1,4-addition (coupled addition to the beta carbon of the alpha beta-unsaturated system). The pathway taken is largely influenced by several factors including the reaction temperature, solvent, nature of the Grignard reagent, and the structure of the substrate. At low temperatures and in non-polar solvents such as diethyl ether, the reaction is governed by kinetic control, favoring 1,2-addition, further leads to the preparation of allylic alcohols after hydrolysis. It occurs because carbonyl-carbon is more electrophilic, cause increased susceptible for rapid attack by the nucleophilic carbon of the Grignard reagent. In contrast, under higher temperatures or in the presence of more stabilized or less reactive organometallic reagents such as organocuprates (Gilman reagents), the reaction proceeds via 1,4-addition. This pathway yields saturated carbonyl compounds after protonation, due to nucleophilic attack at the β-position of the conjugated system, which is thermodynamically more stable.

***Index Terms* - Aldol condensation, chalcones, formaldehyde, Grignard reagent, ketones, primary alcohol.**

INTRODUCTION

François Auguste Victor Grignard, a French organic chemist, first reported the discovery of organo-magnesium compounds in 1899, characterized by the presence of a carbon–magnesium covalent bond. His pioneering contributions to organometallic chemistry led to his receiving the Nobel Prize in Chemistry in 1912.[1]

Grignard reagents have since become indispensable tools in organic synthesis. They are extensively used for carbon–carbon bond formation, enabling the preparation of diverse functionalized organic molecules and facilitating carbon chain homologation. Their versatility and reactivity make them highly significant even in modern organic chemistry.[2]

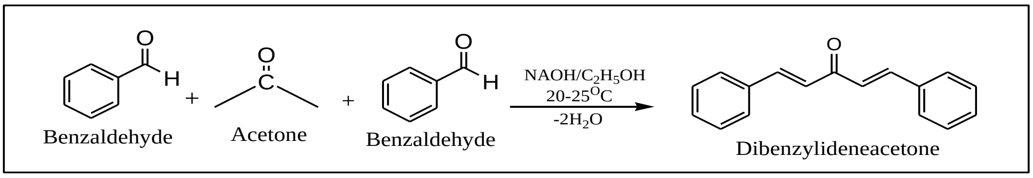
One of the most fundamental classes of organic reactions involves nucleophilic addition to the carbonyl group. When a carbon–carbon double bond is conjugated with a carbonyl group, the electrophilic nature of the carbonyl carbon extends to the beta carbon through delocalization. Such compounds are called enones or chalcones. This ability makes Grignard reagents extremely useful in constructing complex molecular frameworks under relatively mild conditions.[3]

Among naturally occurring enones, chalcones are of particular importance. Structurally, they are α, β-unsaturated ketones that serve as key components in the generation of flavonoids and iso flavonoids, widely distributed in plants and foods such as soy, fruits, vegetables, spices, and tea.[4]

Both natural and synthetic chalcones display diverse pharmacological properties, including antimicrobial, antioxidant, anticancer, antidiabetic, and anti-inflammatory activities. Typically appearing as yellow-colored pigments, chalcones play a vital role in organic synthesis, drug discovery, and biological research.[5]

Reaction involved in Chalcones

Claisen–Schmidt condensation is the reaction between an aldehyde or ketone having an alpha hydrogen with an aromatic carbonyl compound which is having no alpha hydrogen. It can be described as a unique type of aldol condensation.[6]



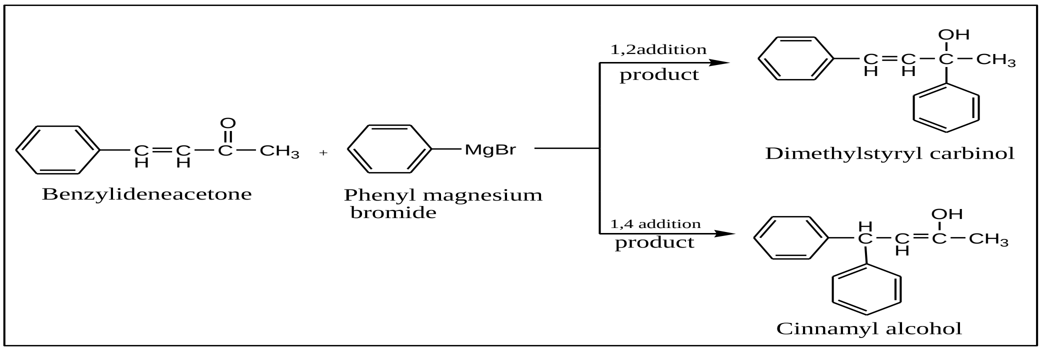
Preparation & synthesis of Grignard reagent

- A Round Bottom Flask was taken with Magnesium ribbon and cut into small pieces and dry ether was added
- 1:1 alkyl halide mixture was taken and dry ether was added in dropping funnel
- 2-3 ml of solution from dropping funnel was added into flask
- When reaction started ether becomes cloudy & also began to boil gently

- If reaction doesn't start add one or two drops of crystal iodine in flask
- When solution from dropping funnel maintain such a rate of ether refluxes occurs. Grignard reagent was prepared.[7]

Reaction of Grignard reagent with α, β-unsaturated ketones

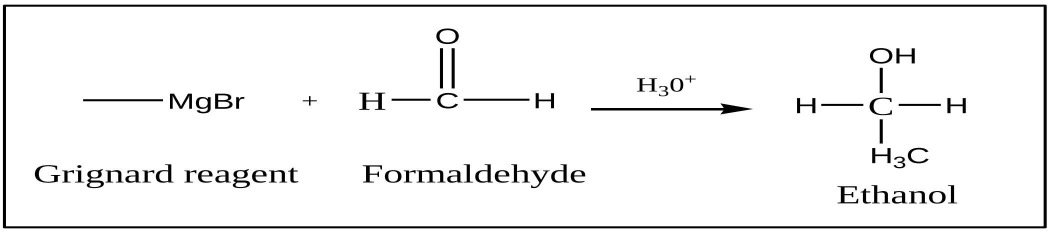
Phenyl magnesium bromide reacts with Benzylideneacetone gives 1,2 addition products as Dimethyl styryl carbinol and 1,4 addition products as cinnamyl alcohol.[8]



Various reactions

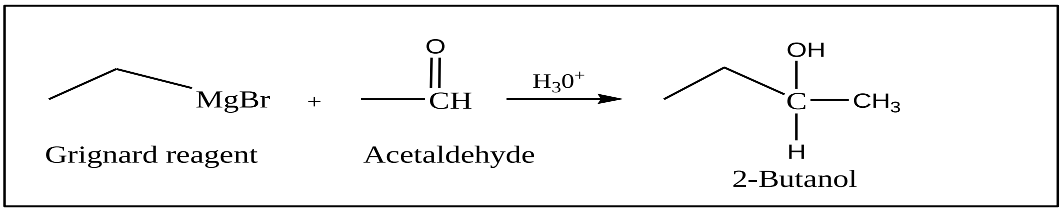
❖ Formation of Ethanol

- Methyl magnesium bromide reacts with Formaldehyde to give an Ethanol.[8]



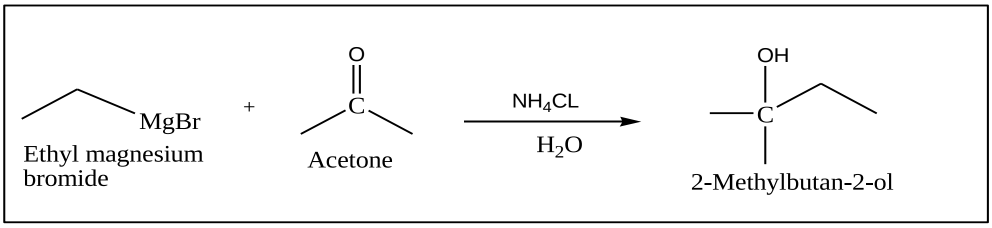
❖ Formation of 2-Butanol

- Ethyl magnesium bromide reacts with all other aldehydes to give 2-Butanol.[8]



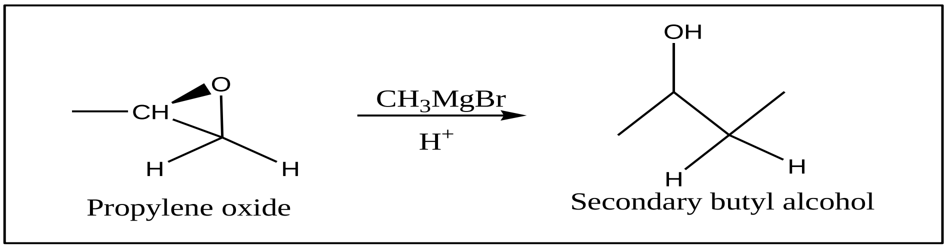
❖ Formation of 2-Methylbutan-2-ol

- Ethyl magnesium bromide reacts with ketones to give 2-Methylbutan-2-ol.[8]



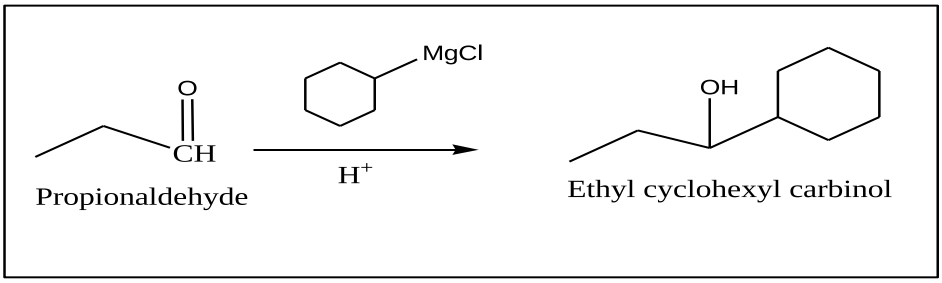
❖ Formation of Secondary butyl alcohol

- Methyl magnesium bromide reacts with epoxides & generate new carbon-carbon bond and this c-c bond reacts with acid - base reagent & forms alcohols.[9]



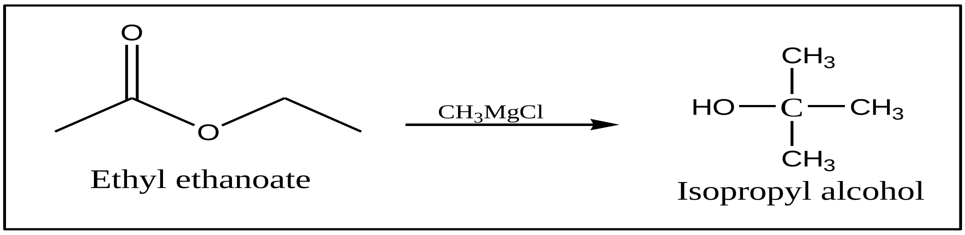
❖ **Formation of Ethyl cyclohexyl carbinol**

- Cyclohexyl magnesium chloride reacts with propionaldehyde to give Ethyl cyclohexyl carbinol.[9]



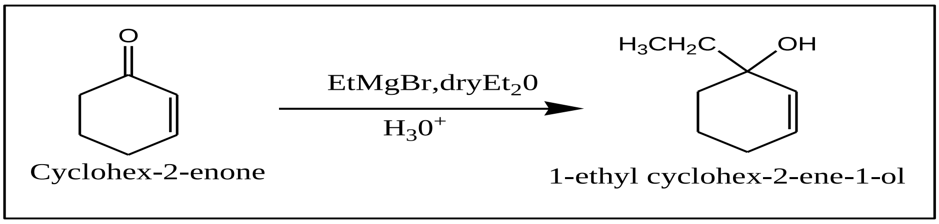
❖ **Formation of Isopropyl alcohol**

- Methyl magnesium bromide reacts with ethyl ethanoate to give isopropyl alcohol.[9]



❖ **Formation of 1-ethyl cyclohex-2-ene-1-ol**

- Ethyl magnesium bromide reacts with cyclohex-2-enone to give 1-ethyl cyclohex-2-ene-1-ol.[9]



APPLICATION & USES

a) Formation of New Carbon–Carbon Bonds:

- One of the most significant uses of Grignard reagents is in constructing new C–C bonds through nucleophilic addition, a reaction commonly known as the Grignard reaction.[10]

b) Synthesis of Alcohols:

- By reacting with different carbonyl compounds, Grignard reagents can be used to prepare:
  - Primary alcohols (derived from formaldehyde)
  - Secondary alcohols (derived from aldehydes)
  - Tertiary alcohols (derived from ketones or esters).[10]

c) Preparation of Carboxylic Acids:

- Grignard reagent reacts with carbon dioxide and followed by acid hydrolysis to give carboxylic acid.[10]

d) Alkene and Alkyne Formation:

- Grignard reagents can help synthesize alkenes and alkynes through reactions with alkyl halides or terminal alkynes, often followed by elimination or substitution steps.[11]

e) Coupling Reactions:

- Under the influence of transition metal catalysts, organo-magnesium reagents participate in cross-coupling reactions (such as the Negishi coupling) to form complex organic molecules with new C–C linkages.[11]

f) Production of Bioactive Compounds:

- The alcohol products and other related derivatives generated from chalcone and Grignard reagents can serve as intermediates in the synthesis of pharmaceuticals, natural products, fragrances, and fine chemicals.[11]

g) Pharmaceutical Development:

- Specific examples involve the use of Grignard reactions in the manufacturing process of drugs such as Tamoxifen; a medication used to treat and prevent breast cancer.[11]

CONCLUSION

The interaction of Grignard reagent with chalcones remain a foundational element of modern synthetic chemistry, demonstrating the intricate interplay between reagent structure, substrate electronics, and reaction conditions. Their ability to undergo both 1,2- and 1,4-nucleophilic addition reflects their dual nature as potent nucleophiles and strong bases, providing chemists with a versatile platform for achieving selective functionalization. Chalcones, as prototypical α, β-unsaturated ketones, further highlight the significance of these transformations. Their natural abundance, pharmacological relevance, and structural adaptability make them important synthetic targets as well as valuable intermediates in the preparation of bioactive molecules. The application of Grignard reagents in modifying chalcone frameworks underscores their relevance in medicinal chemistry, natural product synthesis, and industrial organic processes. Taken together, the studies reviewed affirm the enduring importance of Grignard chemistry. Although discovered over a century ago, Grignard reagents continue to offer remarkable versatility, operational simplicity, and effectiveness in constructing complex molecular architectures. Their wide applicability—from alcohol and carboxylic acid formation to cross-coupling reactions and pharmaceutical synthesis—ensures their lasting relevance in both academic and industrial settings. Ongoing developments, particularly in catalytic, eco-friendly, and selectively controlled Grignard-based methodologies, promise to further expand their potential in carbon–carbon bond formation and the synthesis of biologically significant compounds.

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