

A REVIEW ON GRIGNARD FUNCTIONALISATION OF CHALCONES : A PLATFORM FOR BIO ACTIVE MOLECULE DISCOVERY

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ABSTRACT:

Grignard reagents are organo magnesium halides with its general formula R-Mg-X are cornerstone reagents in organic synthesis. It was discovered by victor Grignard in 1900 and recognized with the Nobel Prize in the year 1912, they are typically generated by reacting alkyl or aryl halides with magnesium metal in anhydrous ethereal solvents such as diethyl ether and tetrahydrofuran. The carbon-magnesium bond is highly polarized, giving Grignard reagents strong nucleophilic and basic character. This property makes them invaluable for carbon-carbon bond formation, particularly in the synthesis of alcohols and other functionalized organic compounds. Due to their high reactivity towards protic substances like water, alcohols, and amines, these reagents must be handled under strictly anhydrous conditions to prevent decomposition.

This study explores chalcones, naturally occurring alpha, beta -unsaturated ketones that form the C₆ – C₃ - C₆ – core of the flavonoids family. The chalcones are widely distributed in plants and contribute to plant growth and defense. They are recognized for diverse pharmacological properties, including anti inflammatory, anti cancer, antioxidant, and antimicrobial activities. Structural modifications like incorporation of thiophene rings enhance their electronic and the biological properties

Key words:

Grignard reagent, Organo magnesium halides, Victor Grignard, alkyl/aryl halides + halides + magnesium metal

INTRODUCTION:

GRIGNARD REAGENT:

Grignard reagent constitutes a significant organo metallic compound. This reaction was first discovered by French chemist Victor Grignard in 1900. In 1912 Victor Grignard was awarded Nobel Prize for his invention.

The general formula of Grignard reagent is generally represented as $R-Mg-X$. In this general formula the R corresponds to an organic moiety such as an alkyl [or] aryl group, while X is denoted by halogen atom. Common examples of Grignard reagents are methyl magnesium chloride [CH_3MgCl] and phenyl magnesium bromide [C_6H_5MgBr].

Generally Grignard reagents are rarely handled in solid state. Commonly employed as solutions in ethereal solvents like diethyl ether and tetrahydrofuran. Their stability in solution is maintained only under strictly anhydrous conditions because even traces of moisture can rapidly decompose the reagent.

This preparation involves the reaction of haloalkanes with metallic magnesium in dry ether. The carbon - magnesium bond present in the reagent is highly polarized because magnesium is strongly electropositive magnesium halides exhibit predominantly ionic behavior.

The ability of Grignard reagent to react readily with proton donating substance such as alcohols, water, and amines provides acidic hydrogen atoms that leads to conversion of Grignard reagents into the corresponding hydrocarbons. Due to this, the exclusion of moisture is essential throughout their synthesis, storage, applications. This reaction mainly used for the construction of carbon-carbon bonds and the preparation of a wide variety of valuable organic compounds.^[1]

CHALCONES:

The name chalcone originates from a Greek word associated with a bronze like appearance. They are synthesized in the 19th century. Chalcones gained significant attention due to their chemical structure and biological properties.

They are commonly found in different tissues and plant parts. Chalcones play a major role in plant growth and defense mechanism. Variations in the substitution pattern on the aromatic ring gives rise to large number of chalcone derivatives with distinct physico chemical and biological characteristics.

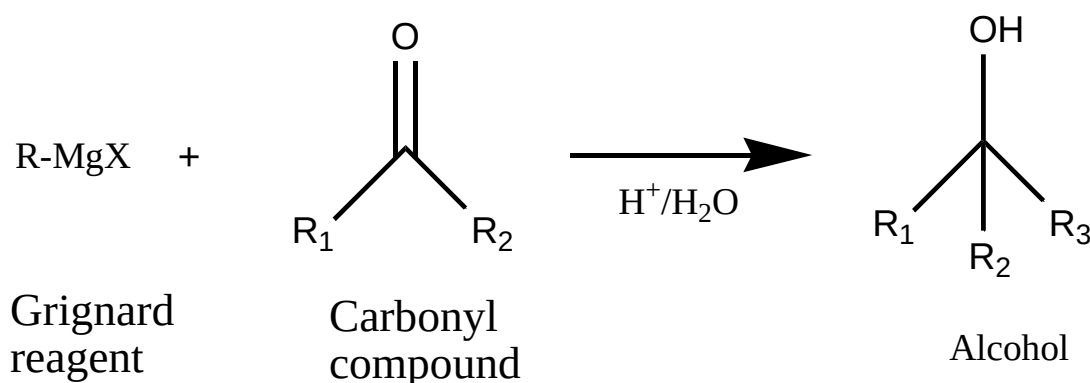
Chalcones are naturally occurring compounds. Chalcones have two aromatic rings and are connected with 3 carbon alpha – unsaturated carbonyl system. Chalcones are prepared by claisen-schmidt condensation reaction, in this reaction aldehyde and ketone reacts and forms chalcones.

Chalcones are used to absorb light in photodynamic therapy. Thiophene chalcones are a type of chalcones, they are present in normal chalcone structure because of this pharmacological electronic properties are improved. In the research of chalcones new thiophene - containing chalcones were synthesized and also studied on UV absorption by using DFT(computer calculations) they analyzed molecular behavior in this study sulfur containing chalcones thiophene chalcones are synthesized .

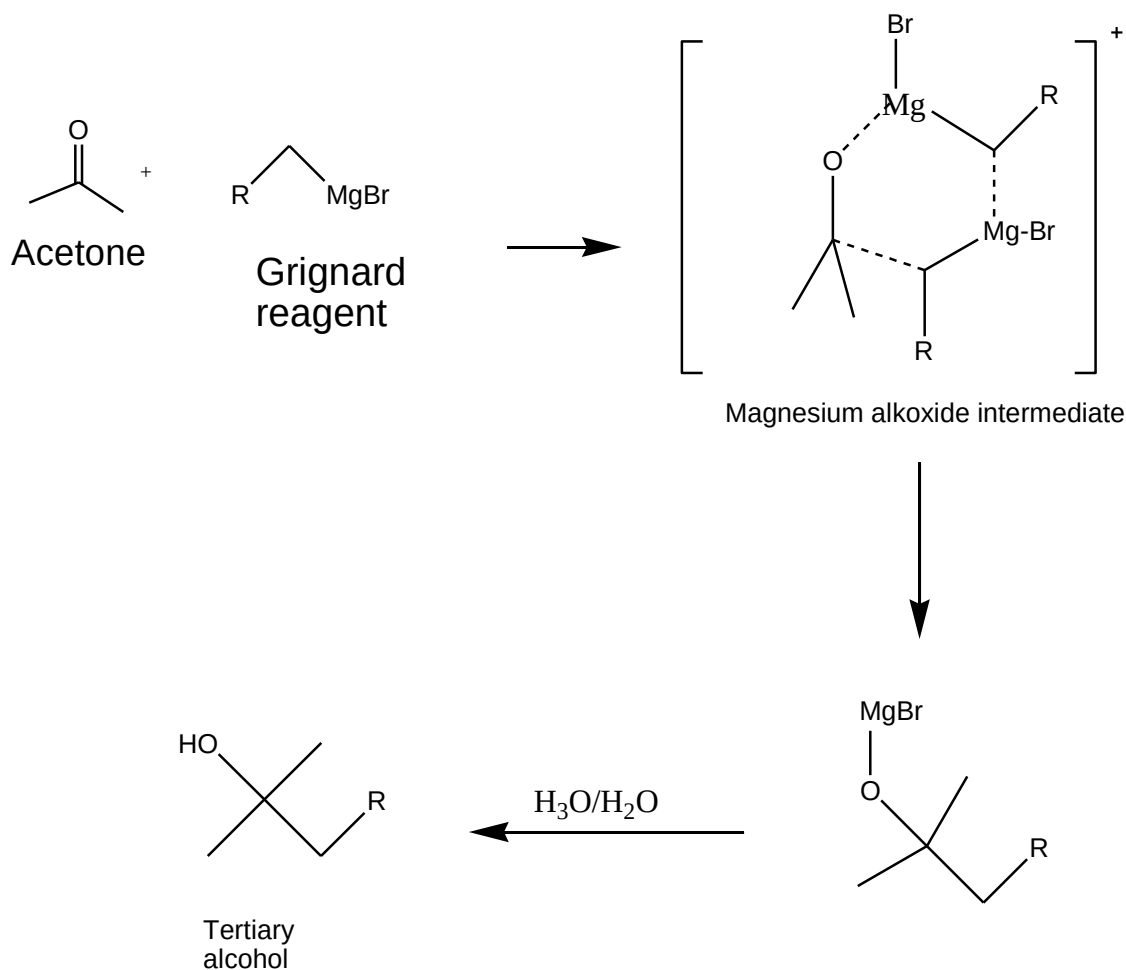
This reaction is done under the temperature between 50 degree Celsius to 100 degree Celsius for a few hours using a suitable solvent. This reaction rarely occurs in solid phase but generally it occurs in liquid phase ^[2]

MECHANISM:

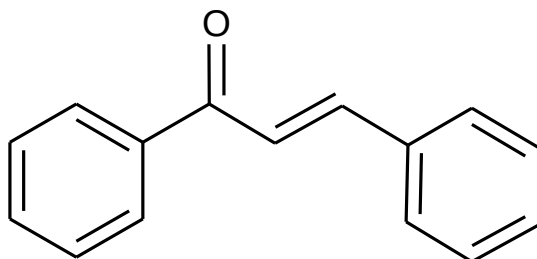
REACTION:



MECHANISM OF GRIGNARD REAGENT:^[3]

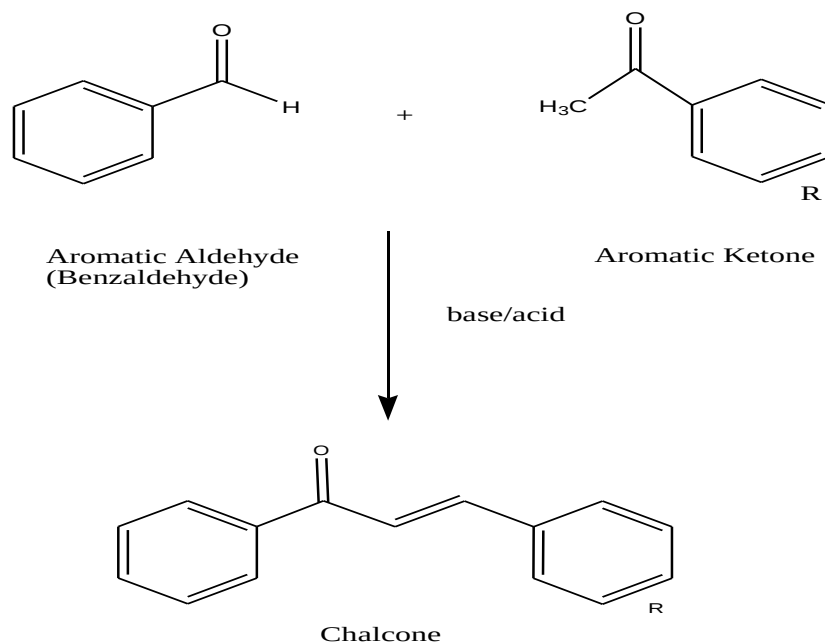


GENERAL STRUCTURE OF CHALCONE:

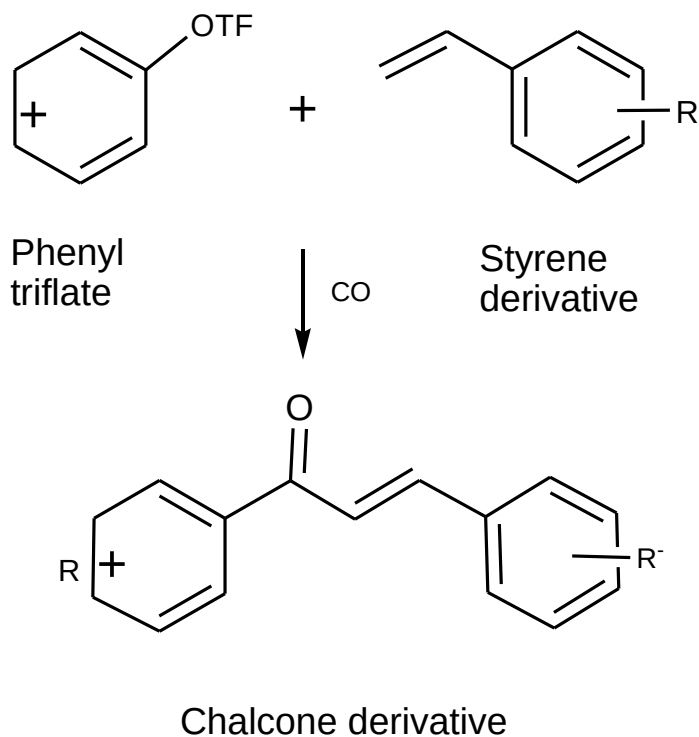


Structure of chalcones

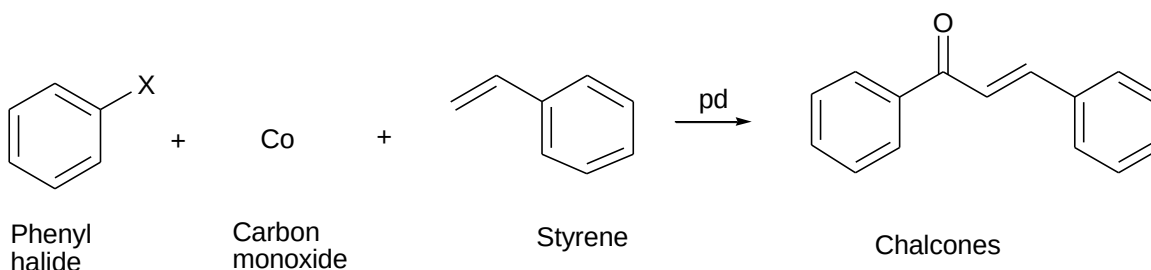
CLAISEN-SCHEMIDT'S CONDENSATION:



SCHEME-1: CLAISEN SCHEMIDT CONDENSATION ^[4]

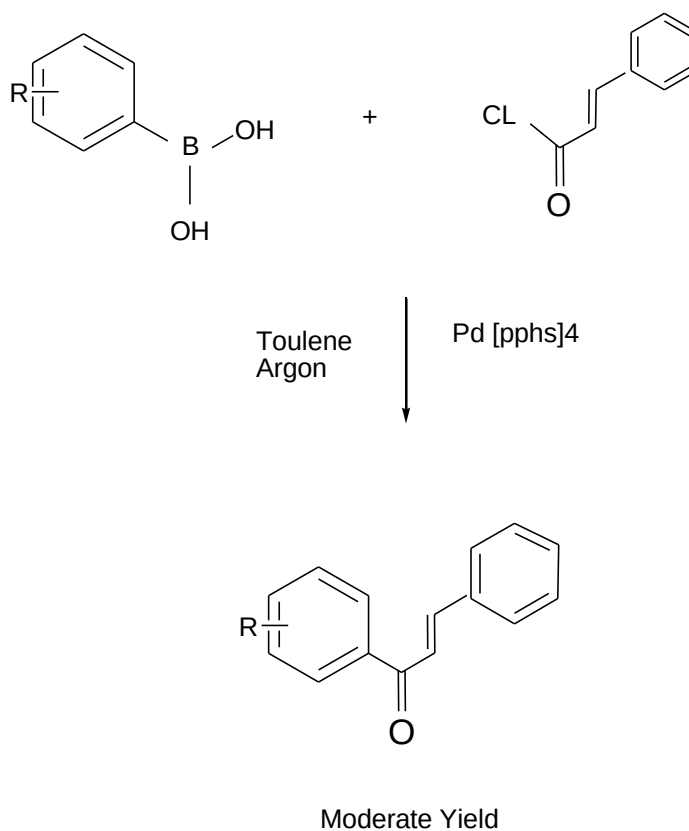


SCHEME- 2: CARBONYLATIVEHECK'S COUPLING REACTION

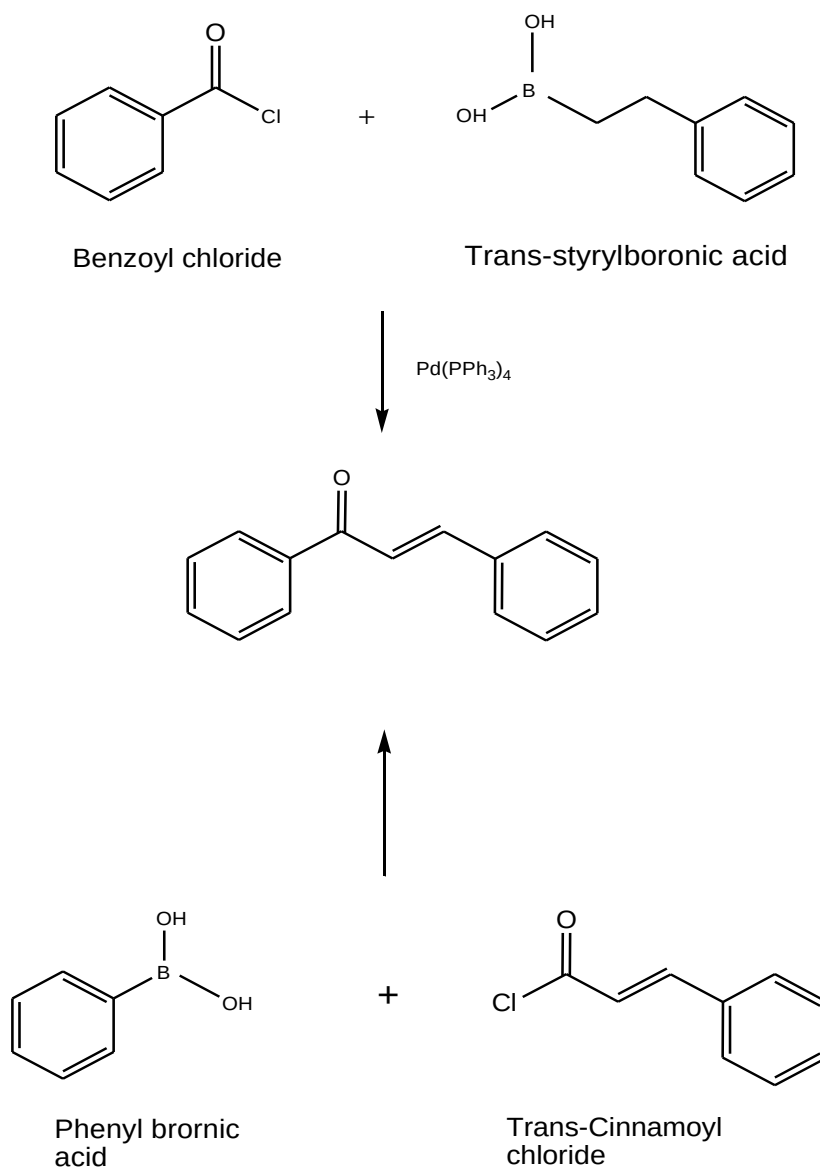


SCHEME-3:

SUZUKI-MIYAUURA COUPLING REACTION:^[4]



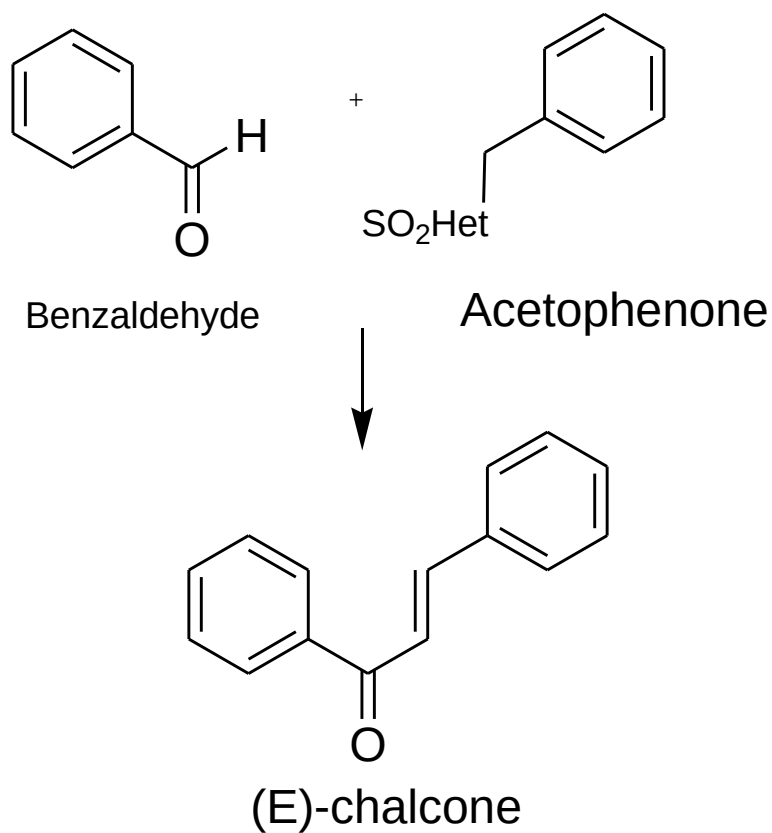
SCHEME-4: SUZUKI –MIYAYURA COUPLING REACTION



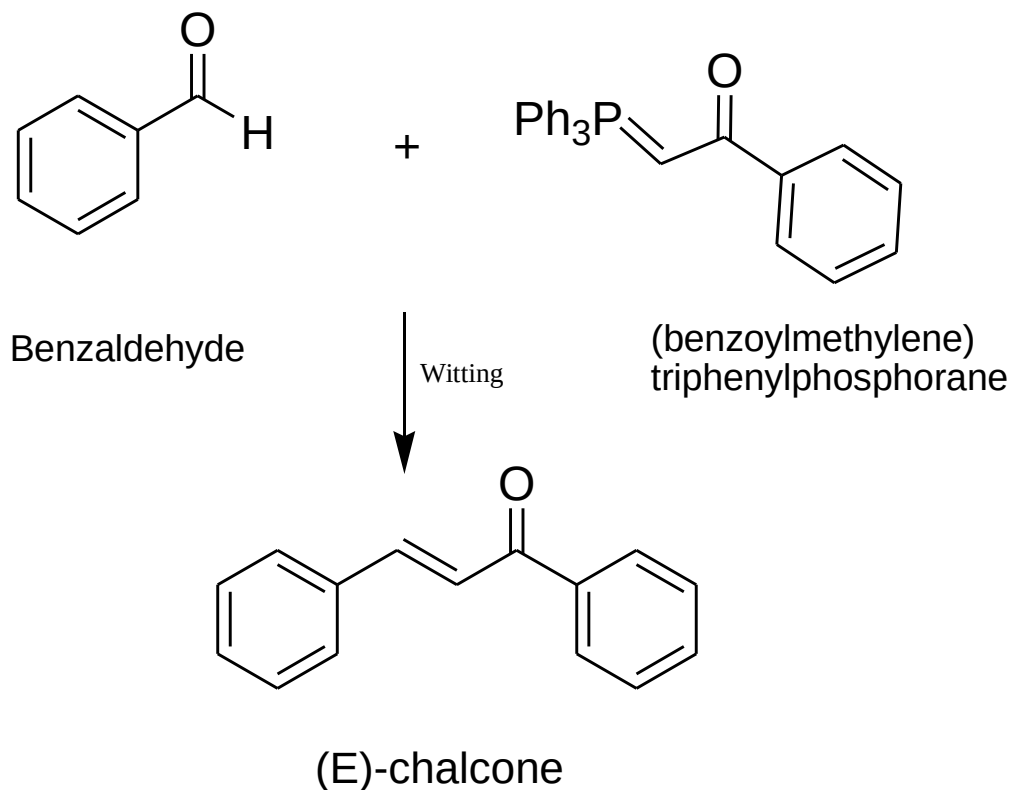
SUZUKI COUPLING REACTION ^[4]

SCHEME-5:

JULIA-KOJENSKI OLEFINATION ^[4]



SCHEME-6: Synthesis of chalcones through the Julia kociencki olefination reaction ^[4]



MAIN BODY:

GRIGNARD REACTION MECHANISM:

The synthesis of Grignard reagent is highly nucleophilic. This reagent attacks the electrophilic carbon in the polar bond of carbonyl group. Mechanism of Grignard reaction is a six-membered transition state.

Some reactions of Grignard reagents may proceed through single electron transfer process. Some process involves the formation of carbon-silicon bond, and carbon-carbon bond.

The Grignard reagent co-ordinates with the ketone on the simultaneous displacements of an ether molecule of salvation. This is followed by a rapid reaction with a second monomeric Grignard reagent for the formation of alcohol through a six membered transition state. It been proposed that reaction can be proceed with Rmg, RmgX or both organo metallic compounds.^[5]

Chalcones:

Chalcones are plant derived polyphenolic compounds. These are belonged to the flavonoids family, and are characterized by distinct $C_6-C_3-C_6$ molecular framework.

The pharmacological properties in the chalcones include anticancer, anti-inflammatory, antioxidant and anti microbial activities. Chalcones consists of two aromatic rings and these are interconnected by a highly electrophilic three carbon α, β unsaturated carbonyl system [1, 3-diphenyl-2-propen-1-one]^[5]

METHODS AND MATERIAL OF THE CHALCONES:

For the preparation of chalcones this undergoes claisen-schmidt condensation method.

SCHEME 1: claisen-schmidt condensation.

For the formation of carbon-carbon bonds the heck reaction is used. In the presence of palladium catalyst and a base unsaturated ketones react with aryl halides or aryl iodides.

Heck reaction is used to prepare Steichen and chalcones is used in the reaction. It converts into a carbonylative heck reaction to form substituted chalcones.

For the activation of reactants bases are used, whereas palladium acts as the main catalyst. Under similar reaction conditions by reaction with aryl halides or aryl triplets with styrene derivatives the substituted chalcones and aromatic olefins can be synthesized.

SCHEME 2: Synthesis of chalcones

Carbonylative heck's coupling reaction is simplified version. In this chalcones preparation involved in the reaction between an aryl halide like phenyl halide with styrene and palladium acts as catalyst in the presence of carbon monoxide. The catalyst palladium plays an important role in carbonylative coupling reaction.

SCHEME 3: Suzuki – miyaura coupling reaction

Akira Suzuki was first introduced this reaction in 1979. For the formation of carbon-carbon bonds between two different chemical fragments, this method is most widely used. For synthesis of chalcone derivatives and other aromatic compounds this reaction plays an important role. In the presence of catalyst palladium the anhydrous toluene as the solvent and cesium carbonate as the base. Acyl chlorides or aryl halides reacts with aryl boronic acids in this method under the

argon atmosphere. Under the reflux conditions for the few hours, this reaction is generally carried out in moderate to high yields of the desired chalcones under reflux conditions

This coupling is highly efficient due to the joining of two different organic groups for the formation of new C - C bonds. It may vary by depending on the type of halides used.

SCHEME 4: Suzuki reaction

This Suzuki coupling reaction was applied for the formation of carbon – carbon bonds in the presence of palladium as catalyst for the synthesis of chalcones.

It is proved to be one of the very most efficient synthetic routes for the construction of chalcones. The two main approaches for the synthesis of chalcones via Suzuki coupling involve

Reaction of benzyl chloride with phenyllinyl boric acid

Coupling of cinnamoyl chloride with phenyl boric acid

SCHEME 5: Suzuki coupling reaction

Julia – kaisenski olefination

Here, chalcones are formed through the condensation reaction. Involving a Julia coupling reagent and aromatic aldehydes.

It typically employs heteroaryl sulfones reagents such as sulfonyl phenylethanone along with bases.

Phenylethanone is found to be the most effective combinations for the chalcones productive

SCHEME 6: Synthesis of chalcones through the Julia – locienski olefination reaction

Witting reaction by utilizing the basic functional property of chalcones as alpha, beta – unsaturated carbonyl compounds. Chalcones can be synthesized through this witting reaction. Chalcones are obtained by the condensation of triphenyl methylenephosphorone with benzaldehyde in THF over 30 hours under reflux conditions or alternatively in benzene over 3 days, producing moderate

SCHEME 7: Synthesis of chalcones via witting reaction solid acid catalyst – mediated reaction.

By using a solid catalyst chalcones can be efficiently synthesized which is heterogeneous nature. This method involves the condensation of aromatic aldehydes with ethyl benzene in ethylene dichloride solvent under microns radiation. The reaction proceeds smoothly using ion-exchange resins. Which serves as effective solid acid catalyst.^[6]

REACTION OF GRIGNARD REAGENT WITH CHALCONES:

The Grignard reagent reacts with alpha, beta unsaturated ketones it carries in two different ways

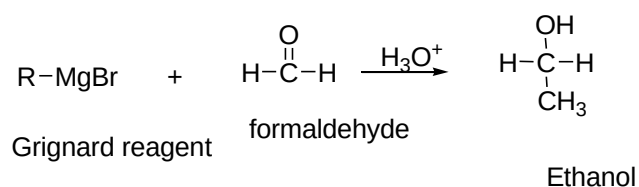
1, 2- addition: - The Grignard reagent attacks mainly the carbonyl carbon [C=O] bond for the formation of an alcohol after hydrolysis.

1, 4- addition: - Grignard reagent attacks the beta carbon of double bond followed by protonation to give alcohol.

Various reactions of Grignard reagents:

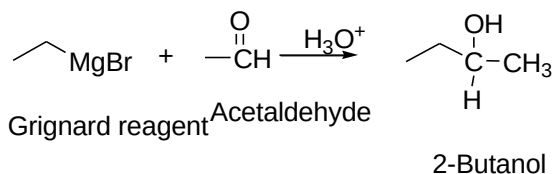
1. Reaction with formaldehyde:

Grignard reagent reacts with formaldehyde which is followed by acid hydrolysis to give primary alcohol.



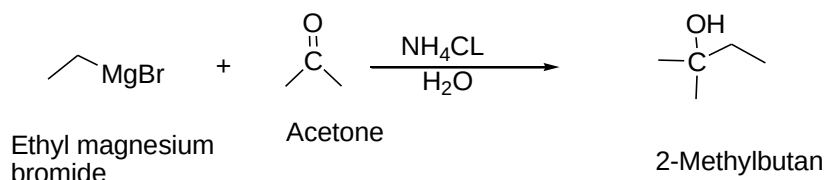
2. Reaction with other aldehydes:

Grignard reagent reacts with aldehydes except formaldehyde which is followed by hydrolysis to give secondary alcohol.



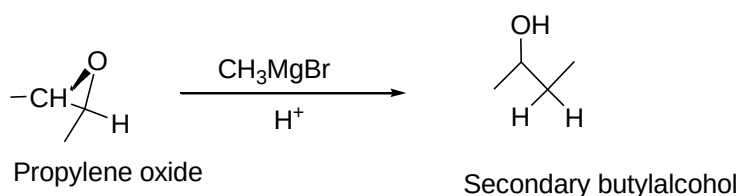
3. Reaction with ketones:

Grignard reagent react with ketones which is followed by hydrolysis to give tertiary alcohols



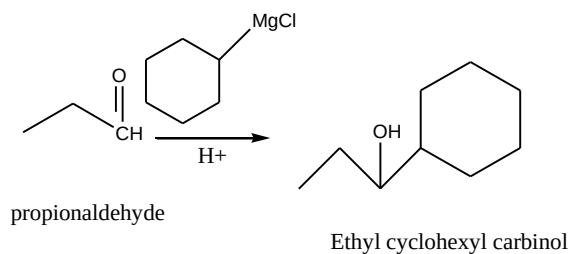
4. Reaction with epoxides:

Grignard reagent reacts with epoxides by opening of the epoxide ring. The newly formed c-c bond which is followed by acidic hydrolysis to for an alcohol with chain extension.



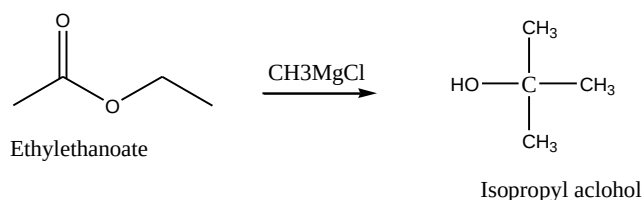
5. Reaction with propionaldehyde:

To give ethyl cyclohexyle carbinol Grignard reagent react with propionaldehyde which is followed by acidic hydrolysis.



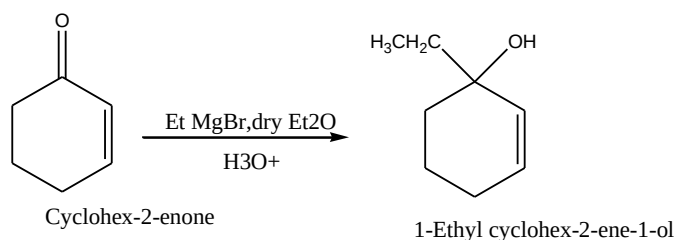
6. Reaction with esters:

Grignard reagent reacts with esters followed by hydrolysis to give isopropyl alcohol.



7. Reaction with alpha, beta unsaturated ketones:

Grignard reagent reacts with alpha, beta unsaturated ketones followed by acidic hydrolysis to give 1- ethyl cyclohex- 2 – en – 1-ol ^[7].



APPLICATIONS:

1. Formation of alkenes and alkynes:

Grignard reagent plays an important role in the synthesis of alkenes and alkynes by involving in reactions with alkyl halides or terminal alkynes, generally followed substitutions or eliminations steps. ^[8]

2. Synthesis of bioactive compounds:

In the preparation of pharmaceuticals, fragrances, natural products and other fine chemicals, the alcohols and related derivatives produced from reactions involving chalcones and Grignard reagents acts as important intermediates. ^[8]

3. Pharmaceutical applications:

In medicinal chemistry and industrial chemistry drugs synthesis Grignard reactions plays an important role, like preparation of the drug 'Tamoxifen' which is highly prescribed for the treatment of breast cancer.^[8]

4. Carboxylic acids preparations:

Carboxylic acids are synthesized by Grignard reagent reacting with carbon dioxide, and followed by acidic hydrolysis. An additional carbon atom is introduced into the final product in this process.^[8]

5. Coupling reactions:

In the presence of organo-magnesium reagents, transition metal catalysts involve in cross-coupling reactions, then complex organic molecules take place with new C-C linkages.^[8]

LIMITATIONS FOR GRIGNARD REAGENT:

1. Moisture sensitivity is the biggest limitation



Immediately reaction failed

2. Incompatible with acidic functional groups compounds containing

-OH, -NH₂, -COOH, -SH

They donate H⁺ & quench the reagent

3. Cannot be used in protic solvents. It is only used in dry ether or THF.

4. Different with sterically hindered substrates bulky ketones react slowly.

5. Poor functional groups tolerance. Cannot co-exist with many groups in same molecules.^[9]

LIMITATIONS OF CHALCONES

1. Chalcones are hydrophobic and limiting dissolution so, they have poor aqueous solubility.
2. At the higher dosage it has possible toxicity.
3. It has no bio availability.
4. It is having poor stability in biological system^[10]

CONCLUSION:

The reaction of chalcones with Grignard reagent is an organic Transformation involving the addition of organo magnesium compound to the carbonyl system of the chalcone. Chalcones alpha, beta unsaturated ketones which undergo 1, 2 addition or 1, 4 addition depending on the nature of Grignard reagent and the reaction conditions

This may lead to the formation of different alcohol derivatives such as tertiary alcohols and unsaturated alcohols. This reaction shows the strong nucleophilic character of the Grignard reagents and the ability to form new c-c bond. This is one of the most important applications in organic synthesis.

The products that are obtained from these reactions can serve as the intermediates that are useful for the preparation of various complex organic molecules.

This provides a valuable method for modifying the chalcone structure, introducing new carbon groups, and synthesizing structurally diverse compounds. Due to this importance in carbon- carbon bond formation, the Grignard reactions have significant applications in the development of biologically active compounds.

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