

Module-5 Learning Material

Learning Material

Course: B. Pharmacy 4th Sem

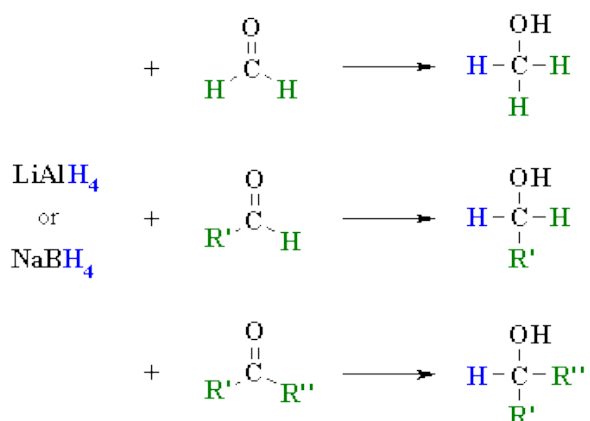
MODULE-5: REACTIONS OF SYNTHETIC IMPORTANCE



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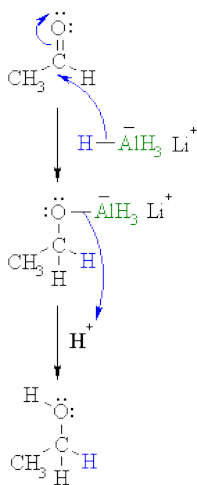
Metal hydride reduction (NaBH_4 and LiAlH_4)

Reduction of various carbonyl compounds is done by using reagents that transfer a hydride from boron or aluminium. The most common sources of the hydride nucleophile are lithium aluminium hydride and sodium borohydride. The hydride anion is not present during this reaction rather these reagents serve as a source of hydride due to the presence of a polar metal hydrogen bond. Because aluminium is less electronegative than boron the Al-H bond in LiAlH_4 is more polar, thereby making LiAlH_4 a stronger reducing agent.



Step1:

The nucleophilic H in the hydride reagent adds to the electrophilic C in the polar carbonyl group in the aldehyde, electrons from the $\text{C}=\text{O}$ move to the O creating an intermediate metal alkoxide complex.

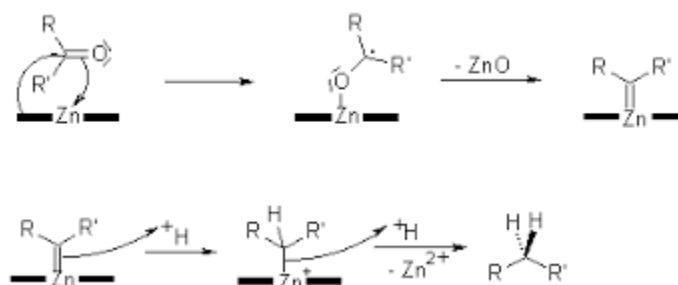


Step2:

This is the work-up step, a simple acid/base reaction. Protonation of the alkoxide oxygen creates the primary alcohol product from the intermediate complex.

COURSE: B. PHARMACY, 4 Sem Module-5: REACTIONS OF SYNTHETIC IMPORTANCE

CLEMMENSEN REDUCTION:- The Clemmensen reduction is a reaction that is used to reduce aldehydes or ketones to alkanes using hydrochloric acid and zinc amalgam. The Clemmensen reduction is named after a Danish chemist, Erik Christian Clemmensen. This reaction is particularly effective in aryl-alkyl ketones reduction formed in Friedel-Crafts acylation. The reaction is more effective in reduction of cyclic ketones or aliphatic and zinc metal.

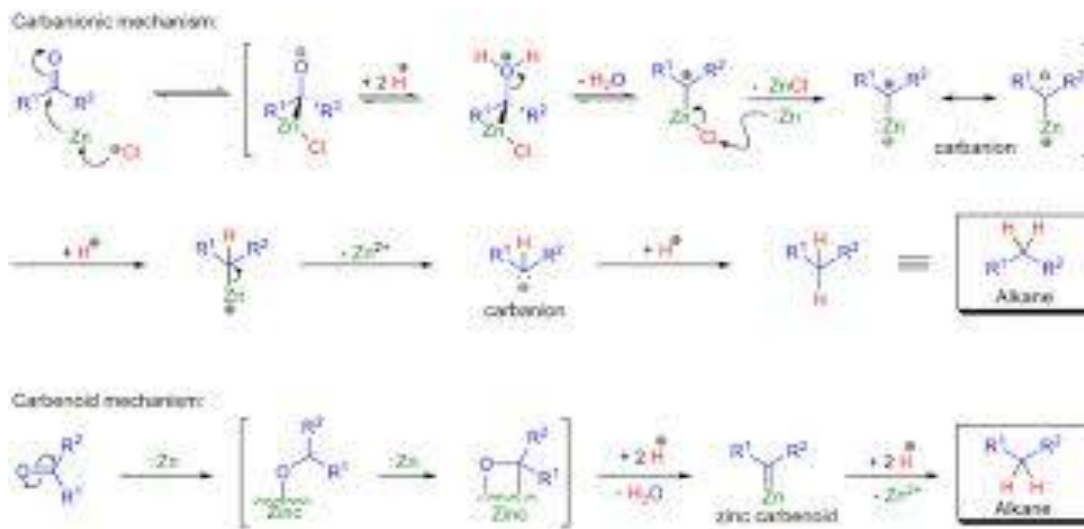


Mechanism of Clemmensen Reduction Reaction:

The mechanism of this reaction is not completely understood, but there are two proposals;

- Carbanionic mechanism: The carbanionic mechanism of reaction shows that the zinc attacks directly to the protonated carbon.
- Carbenoid mechanism: While the carbenoid mechanism is a radical process and reduces the happenings on zinc metal surface. The reduction takes place at the surface of the zinc catalyst. In this reaction, alcohols are not postulated as intermediates, because subjection of the corresponding alcohols to these same reaction conditions does not lead to alkanes.

The following proposal employs the intermediacy of zinc carbenoids to rationalize the mechanism of the Clemmensen Reduction:



COURSE: B. PHARMACY, 4 Sem Module-5: REACTIONS OF SYNTHETIC IMPORTANCE

The underlying substance must not react to the acidic conditions. The acid sensitive base substance reacts in the Wolff-Kishner reduction that has a strong base if it is milder than it is Mozingo reduction. The reaction is not for the substances that are sensitive to acids.

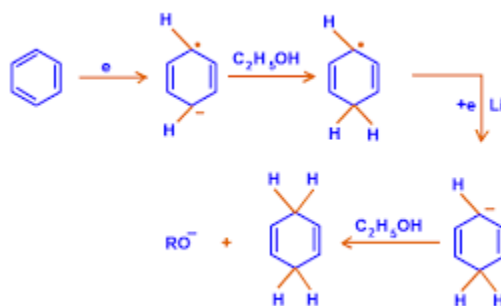
The heterogeneous nature makes the mechanism remains obscure, in spite of its antiquity and the studies on mechanism are difficult. There are only a few studies on the particular reaction proposed like possibly zinc carbenoids and organozinc intermediates.

BIRCH REDUCTION:

The Birch reduction is an organic chemical reaction where aromatic compounds which have a benzenoid ring are converted into 1,4-cyclohexadiene which have two hydrogen atoms attached at opposite ends of the molecule. It is a very useful reaction in synthetic organic chemistry. The Birch reduction can be classified as an organic redox reaction. Here, an organic reduction of aromatic rings in liquid ammonia with sodium, lithium or potassium and alcohol occurs. An example of a Birch reduction reaction is the reduction of naphthalene.

Mechanism of Birch Reduction

The solvated electrons (the free electrons in the solution of sodium in liquid ammonia which are responsible for the intense blue colour) add to the aromatic ring, giving a radical anion. This radical anion is supplied with a proton by the alcohol. The alcohol also supplies another proton to the penultimate carbanion. Now, with the alcohol present, the products – cyclohexadiene and an alkoxide ion are formed. The Birch reduction mechanism is illustrated below.

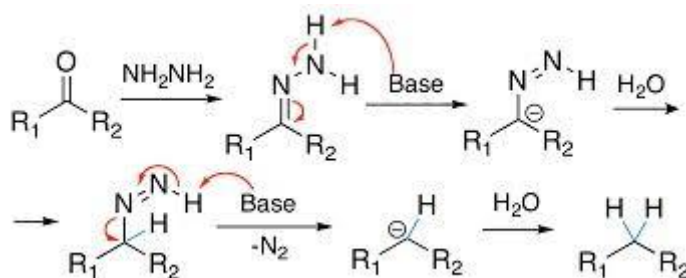


Thus, the required 1,4 cyclohexadiene where two hydrogen atoms are attached on opposite ends of the molecule is formed. Alternative organic solvents such as tetrahydrofuran can be employed instead of ammonia since liquid ammonia must be condensed into a flask and left to evaporate overnight post the completion of the reaction.

WOLFF KISHNER REDUCTION

Wolff-Kishner reduction is a most common reduction used to convert carbonyl groups into methylene groups. This reduction is generally used for removing a carbonyl group after it has served its synthetic purpose. It involves reduction of the hydrazones of the aldehydes and ketones in alkaline medium at high temperature to give hydrocarbons.

Mechanism:- The formation of hydrazones anion by deprotonation of the terminal nitrogen by a base. Hydrazone anion undergoes rearrangement and the carbon atom gets protonated. Again deprotonation of nitrogen occurs and carbon gets protonated. If strong base and highly polar medium is used then this reduction can be carried out at room temperature. This reduction is used for the decomposition of hydrazones of aldehydes and ketones.



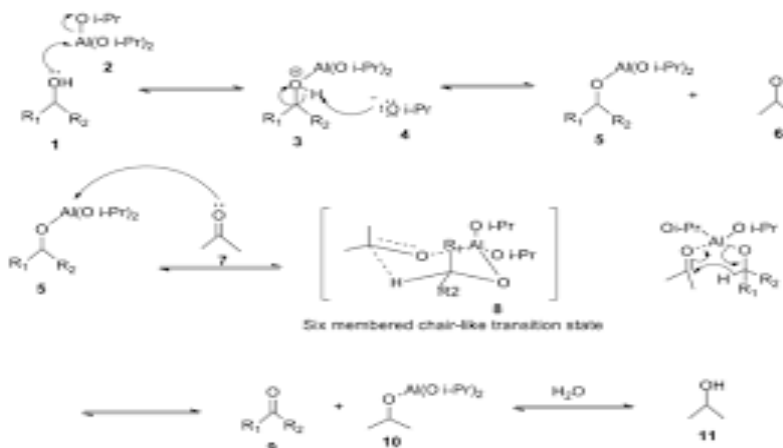
OPPENAUER OXIDATION

Oppenauer Oxidation is the process of conversion of secondary alcohols to ketones by selective oxidation. This reaction is named after Rupert Viktor Oppenauer. Oxidation reaction takes place in the presence of $[\text{Al}(\text{i-Pro})_3]$ in excess of acetone.

It is an aluminium alkoxide catalyzed the oxidation of a secondary alcohol to the corresponding ketone. This is reverse of the Meerwein Ponndorf Verley reduction. It is a very good method to oxidise allylic alcohols to α , β -unsaturated ketones.

Oppenauer Oxidation Mechanism

1. In the first step, alcohol coordinates with aluminium isopropoxide to form a complex
2. This complex reacts with ketone to form a six-membered transition complex
3. The α -carbon of the alcohol is converted to the carbonyl carbon from the aluminium-catalyzed hydride shift.
4. The acetone proceeds over a six-membered transition state.
5. The desired ketone is formed after the hydride transfer



This reaction is used to oxidize alcohols to carbonyl compounds. For example, simple ketone acetone or cyclohexanones is used as the hydride acceptor in the presence of aluminium alkoxide usually isopropoxide or t-butoxide. **The oxidation is the exact reverse of Meerwein-Ponndorf-Verley reduction and involves deprotonation of the alcohol by equilibration with the alkoxide followed by hydride transfer.** This equilibrium is generally displaced to the right by using a large excess of the hydride acceptor.

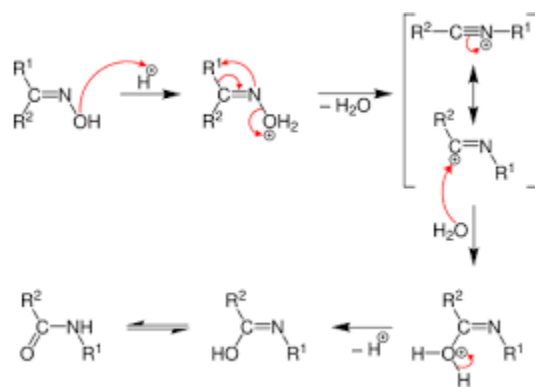
BECKMANN REARRANGEMENT:- The Beckmann Rearrangement is a reaction of the oximes that can bring about either nitriles or amides, contingent upon the beginning material. These Oximes that obtained from the ketones develop into amides; oximes got from the aldehydes shape into nitriles.

The Beckmann Rearrangement process is a natural reaction that is useful in changing an oxime to that of an amide under some acidic conditions. The reaction eventually starts by the process of protonation of the alcohol group gather shaping a preferred leaving group.

The R group transition to that of the leaving species then moves to the nitrogen, bringing about a carbocation and the arrival of a water particle. The water atom attacks the carbocation, and after the process of deprotonation and tautomerization, the amide is obtained.

In simple, Beckmann Rearrangement is a reaction where oxime is changed over to an amide. The oxime is processed by treating an aldehyde or a ketone with hydroxylamine. This Beckmann Rearrangement reaction, named after Ernst Otto Beckmann, a German scientist.

Mechanism:



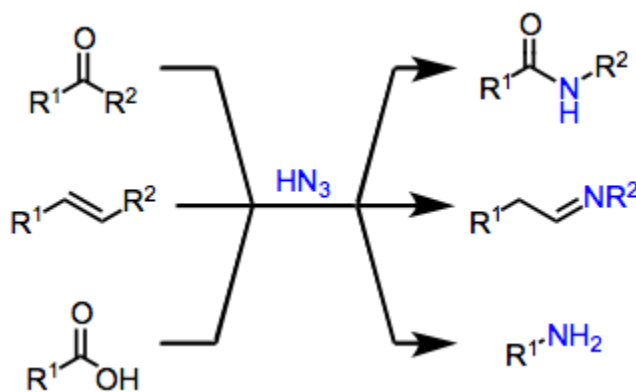
The process of Beckmann Rearrangement is as shown below-

1. The oxime is shaped when cyclohexanone responds with the hydroxylamine.
2. The Protonation of hydroxyl of oxime happens after the change of the alkyl substituent “trans” to the nitrogen

3. At the same time, the N-O bond is severed with the expulsion of water.
4. Later, Isomerization process happens which protonates the molecule of nitrogen and then prompts to the production of amine.

SCHMIDT REACTION

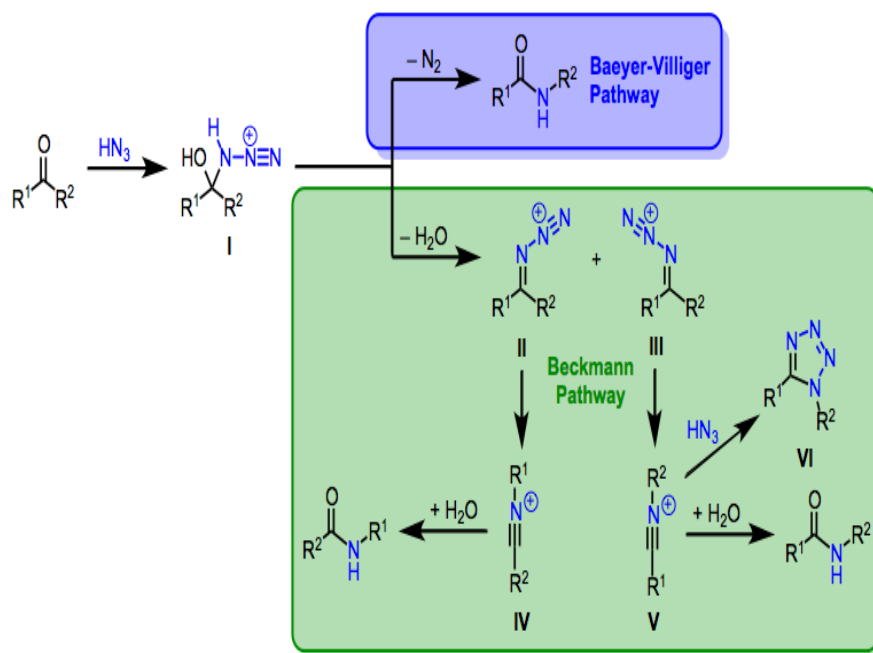
The **Schmidt reaction** is the reaction of hydrazoic acid or an alkyl azide with a carbonyl compound, alkene, or alcohol, often in the presence of a Brønsted or Lewis acid. Although the family of Schmidt reactions includes a number of variants, they all result in the migration of a substituent from carbon to nitrogen with loss of a molecule of dinitrogen. This reaction has considerable utility for the synthesis of hindered or cyclic Azides are nucleophilic at their terminal nitrogen atoms, and may add to suitably activated electrophiles in the presence of a Brønsted or Lewis acid. Upon addition, the newly bound nitrogen atom becomes electron-deficient and is subject to 1,2-migration of a carbon or hydrogen substituent with loss of a molecule of dinitrogen. Historically, carbonyl compounds were the first electrophiles successfully employed in this context. Since the initial discovery of the Schmidt reaction, many variants employing alternative electrophiles and hydrazoic acid have been developed. Related reactions of alkyl azides may yield substituted amides, lactams, or amines (after reduction of iminium ions). However, the scope of alkyl azides in the Schmidt reaction is limited compared to hydrazoic acid.



Generally, intramolecular Schmidt reactions are more useful than their intermolecular counterparts, which are limited by poor site selectivity and sensitivity to steric hindrance. The Schmidt reaction of carboxylic acids, which produces amines, is in direct competition with the milder Curtius rearrangement, and is rarely used in practice. Nonetheless, the Schmidt reaction has been applied extensively for the synthesis of medium-sized lactams and hindered amides. For these applications, the Schmidt reaction exhibits advantageous site selectivity and atom economy.

Reactions of Ketones

The mechanisms of reactions of ketones with hydrazoic acid begin with addition of HN_3 to the carbonyl group to form adizohydrin intermediate **I**. At this stage, one can envision two mechanistic pathways that lead to amides. In a process analogous to the mechanism of the Baeyer-Villiger reaction, the azidohydrin may rearrange to afford amides directly after loss of a proton. A second possibility is analogous to the mechanism of the Beckmann rearrangement. Elimination of water from the azidohydrin affords isomeric diazoiminium ions **II** and **III**, which undergo synchronous, antiperiplanar 1,2-rearrangement to yield nitrilium ions **IV** and **V**. Subsequent addition of water and tautomerization lead to the amide products. The observation of tetrazole side products at high concentrations of hydrazoic acid and similar product ratios in conceptually related Beckmann and Schmidt reactions provide evidence of the Beckmann-type mechanism in reactions of hydrazoic acid. However, it should be noted that alkyl azides must react via the Baeyer-Villiger mechanism to avoid the formation of adjacent positive charges.

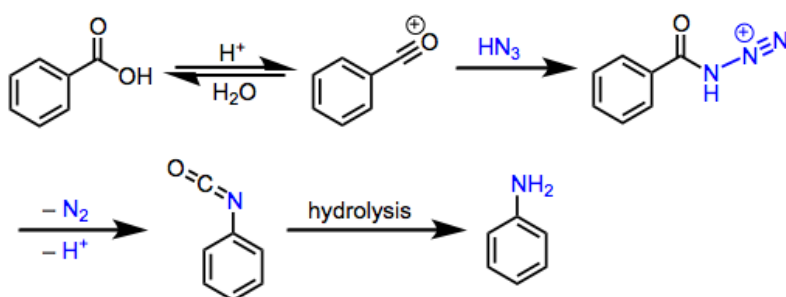


The product of the migration step is determined by the configuration of the diazoiminium ion, and it has thus been proposed that the observed amide product ratio is directly related to the ratio of diazoiminium ions. In support of this idea, calculations have shown that the barrier to direct conversion between **II** and **III** is quite high. However, **II** and **III** may interconvert rapidly via the addition of water followed by elimination, and a Curtin-Hammett situation cannot be ruled out. Under Curtin-Hammett conditions, the amide product ratio is not determined by the ratio of

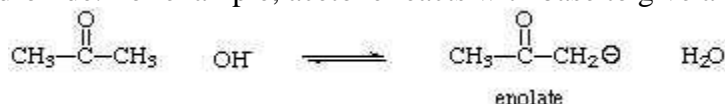
diazoiminium ions, but by their relative rates of conversion to nitrilium ions. In any case, preferential migration of the larger R group is overwhelmingly observed, suggesting the predominant intermediacy of the less hindered diazoiminium ion. Stereogenic centers migrate with retention of configuration.

Reactions of Carboxylic Acids

The mechanism of the reaction of carboxylic acids with hydrazoic acid is well understood. Initial formation of an acylium ion is followed by the addition of hydrazoic acid to form an acyl azide intermediate. The only possible migration event produces an isocyanate, which undergoes hydrolysis to yield an amine and carbon dioxide.



CLAISEN-SCHMIDT CONDENSATION:- A reaction of the vesatile enolate ion. Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide. For example, acetone reacts with base to give an enolate.



When an enolate forms from an aldehyde, the enolate will normally react with unreacted aldehyde to undergo the "aldol addition" or "aldol condensation" reaction. Since ketones are less reactive toward nucleophilic addition, the enolate formed from a ketone can be used to react with an aldehyde, a modification called the Claisen-Schmidt reaction. In cases where the product formed still has a reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.

