



# A REVIEW ON STEREOSELECTIVITY IN ALDOL CONDENSATION REACTION

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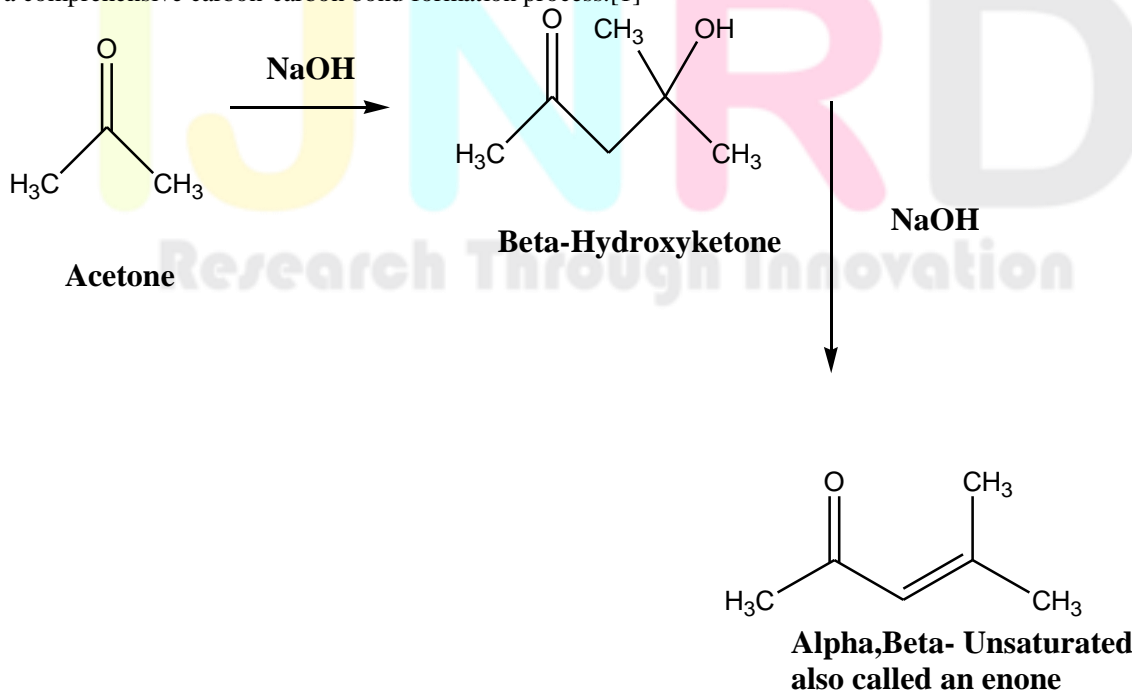
**Abstract :** In organic chemistry, aldol condensation is a basic process that forms carbon-carbon bonds and is essential to the synthesis of complex compounds. Designing and synthesizing chiral compounds with particular biological or medicinal qualities requires the capacity to manage stereoselectivity, or the relative configuration of stereocenters in the aldol process. The main ideas and current developments influencing stereoselectivity in aldol condensation processes are summarized in this abstract. The innate diastereomeric preferences during the aldol adduct's production are the source of the stereoselectivity in aldol condensation. Temperature, solvent conditions and reactant selection are a few examples of the variables that affect stereoselectivity. L-proline acts as a sustainable and beneficial substitute for standard metal-based catalysts in aldol condensation. The system that catalyzes the reaction is mild, simple to use, and frequently produces huge quantities of the desired stereoisomer. L-proline is an asset in the toolset of synthetic organic chemists, particularly for the asymmetric synthesis of complex compounds of biological and chemical effects relevance, due to its effectiveness in stereoselective aldol condensation.

**IndexTerms -** Stereoselectivity ,aliphatic aldehydes and aliphatic ketones, aromatic aldehydes and aromatic ketones ,L-proline

## 1. INTRODUCTION:

**STEREOSELECTIVITY:** It's a property of chemical reaction in which a single reactant forms an unequal mixture of stereoisomers. Stereoisomers has an identical molecular formula with 3D configuration.

**ALDOL CONDENSATION:** In 1872, Charles Wurtz invented the aldol condensation reaction, which produces  $\beta$ -hydroxy aldehyde from acetaldehyde. In an aldol condensation, an enolate ion combines with a carbonyl compound in the presence of an acid-base catalyst to generate a  $\beta$ -hydroxy aldehyde or  $\beta$ -hydroxy ketone, which is then dehydrated to provide a conjugated enone. It is a comprehensive carbon-carbon bond formation process.[1]



**STEREOSELECTIVITY IN ALDOL CONDENSATION:** Among the most crucial for natural product chemists is stereoselectivity. There has been a significant surge in the development of stereoselective organic reaction techniques in response to the growing ability to identify and assign stereogenic centers. Only a few instances of stereoselective aldol reactions were discovered in the outset of this research, primarily in relation to the complete synthesis of natural compounds.<sup>[2]</sup>

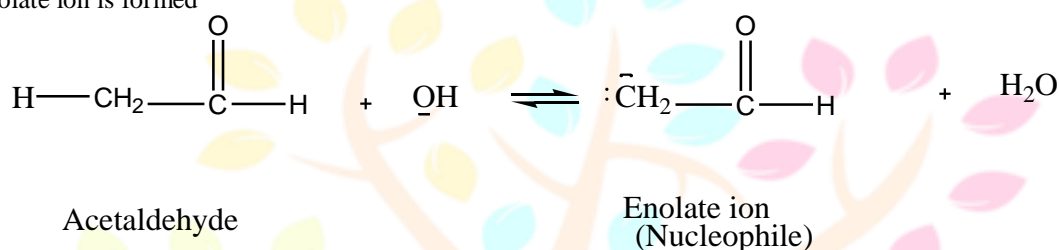
## 2. APPLICATIONS:

The biological evaluation of complex natural products is currently impeded by the manufacturing of these substances. Vinylogous aldol reactions, in contrast to biosynthesis, have the ability to add several acetate or propionate building blocks to the expanding polyketide chain. Either aldehyde or enolate activation is needed to promote such reactions. Selective methods have been proposed for both variants and have been demonstrated to be effective alternatives to conventional aldol reactions. The utilization of natural compounds like callipeltoside greatly expedites the synthetic process, as evidenced by their complete syntheses. In this context, using  $\gamma$ -substituted ketene acetals in both aldehyde and enolate activation is one of the most difficult conversions. Specifically, aliphatic aldehydes yield low amounts and preferences. Protocols for the enantioselective variation are provided with C2-symmetrical copper (II) complexes or the Tol-BINAP system.<sup>[3]</sup>

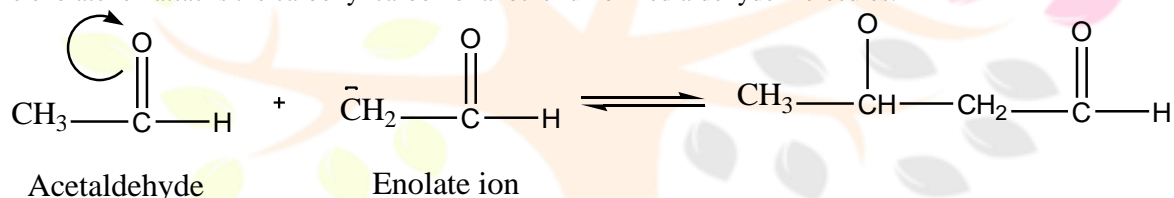
## 3. MECHANISM:

The reaction is reversible and involves the following steps:

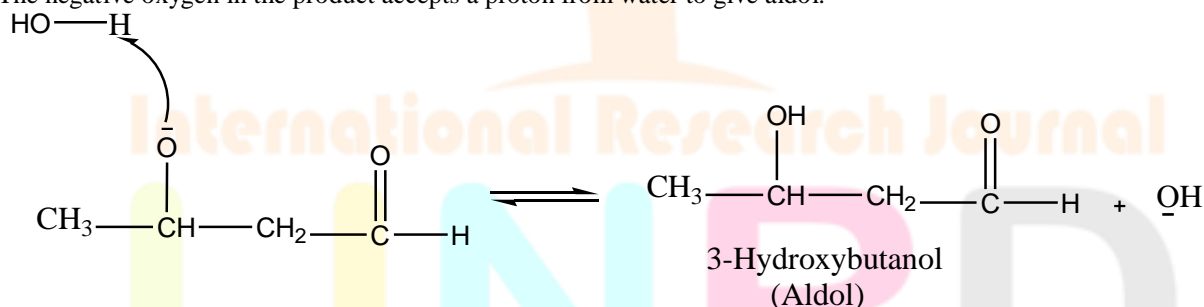
**Step 1:** The enolate ion is formed



**Step 2:** The enolate ion attacks the carbonyl carbon of another unionized aldehyde molecules.



**Step 3:** The negative oxygen in the product accepts a proton from water to give aldol.



## 5. Organo Catalyst in Aldol Condensation:

### a. L-Proline

Hajos and Parrish reported the isolation of aldol intermediates like 1 and shown that stereo differentiation takes place in the aldol phase, prior to dehydration, while investigating the proline catalyzed intermolecular aldol process. Agami subsequently discovered that there is a modest negative non-linear effect and that the reaction is second-order in proline. Studies have demonstrated that proline's pyrrolidine ring and carboxylic acid group are essential for efficient asymmetric induction. Although enantioselectivities with other amino acids and their derivatives have also been discovered, they are often not as remarkable as those with proline.<sup>[5]</sup>

### b. Magnesium hydrogen sulphate:

In the presence of magnesium hydrogen sulphate, Cross-linked aldol condensation of ketones with aromatic aldehyde gives excellent yield with no occurrence of self-condensation and can also be performed easily in solvent-free conditions.<sup>[6]</sup>

### c. Ruthenium trichloride:

Effective cross aldol condensations between ketones and aromatic aldehydes can be catalysed by anhydrous RuCl<sub>3</sub> in a sealed tube without the need of a solvent and without any occurrence of self-condensation.<sup>[7]</sup>

**d. Prolinamide urea's:**

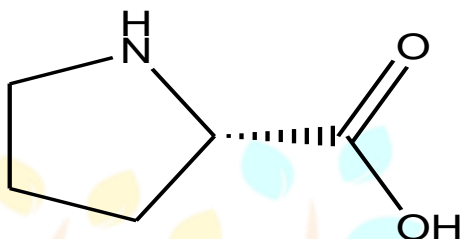
A multifunctional organocatalyst containing a prolinamide moiety, a gem diamine unit, and a urea group was effectively used. High yields (up to 98%) and excellent diastereo- (up to >98:2 dr) and enantioselectivities (up to 99% ee) were obtained from the reaction between different ketones and aldehydes. <sup>[8]</sup>

**e. Polyesterene-supported proline and prolinamides:**

Proline supported by polyesterene has been employed as an organocatalyst in the absence of any other ingredient. Reports of high yields, diastereoselectivities and enantiomeric excess has been seen. <sup>[9]</sup>

**f. L-Prolinethioamides:**

Thioamides have a greater catalytic activity than the proline alone. The inclusion of acid and slight structural modifications has a significant impact on the activity of catalysis. <sup>[10]</sup>

**6. ALIPHATIC ALDEHYDES CONCERNED ALDOL CONDENSATION**

**ALIPHATIC ALDEHYDE:** The compounds having carbonyl group with atleast one hydrogen atom which is attached to the saturated carbon atom.

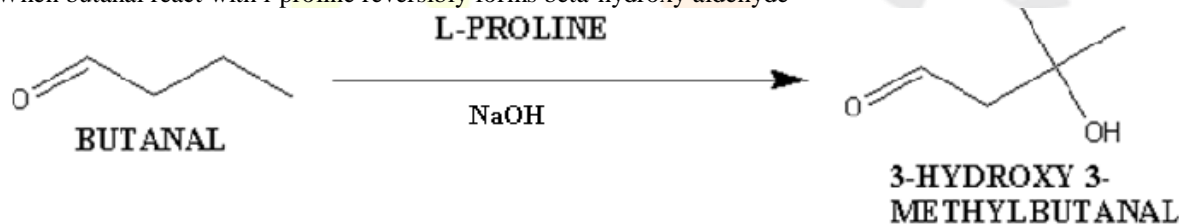
EXAMPLES: Acetaldehyde, formaldehyde, propanaldehyde, etc.....

**REACTIONS:****1. REACTION BETWEEN TWO MOLES OF METHANAL AS FOLLOWS:**

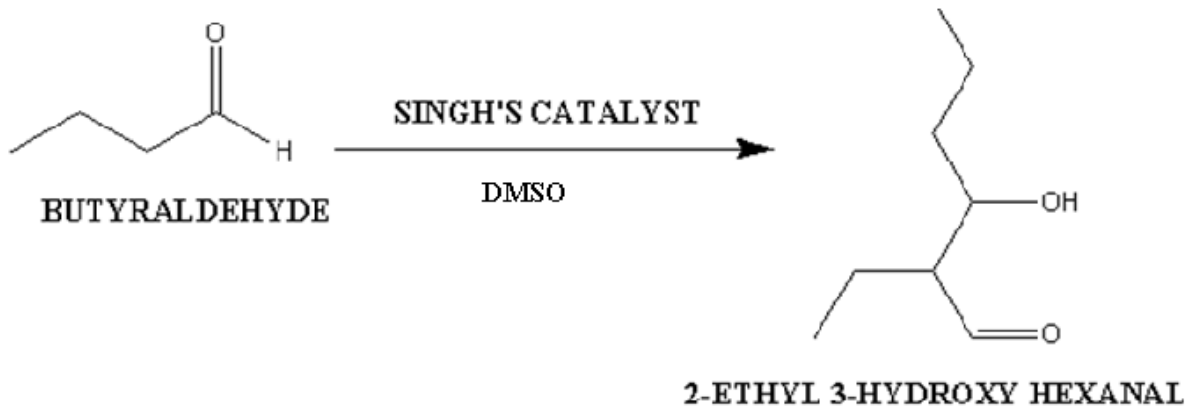
When two moles of methanal react with acid catalysis to form butanal. <sup>[11]</sup>

**2. REACTION OF BUTANAL WITH L-PROLINE AS FOLLOWS:**

When butanal react with l-proline reversibly forms beta-hydroxy aldehyde <sup>[12]</sup>

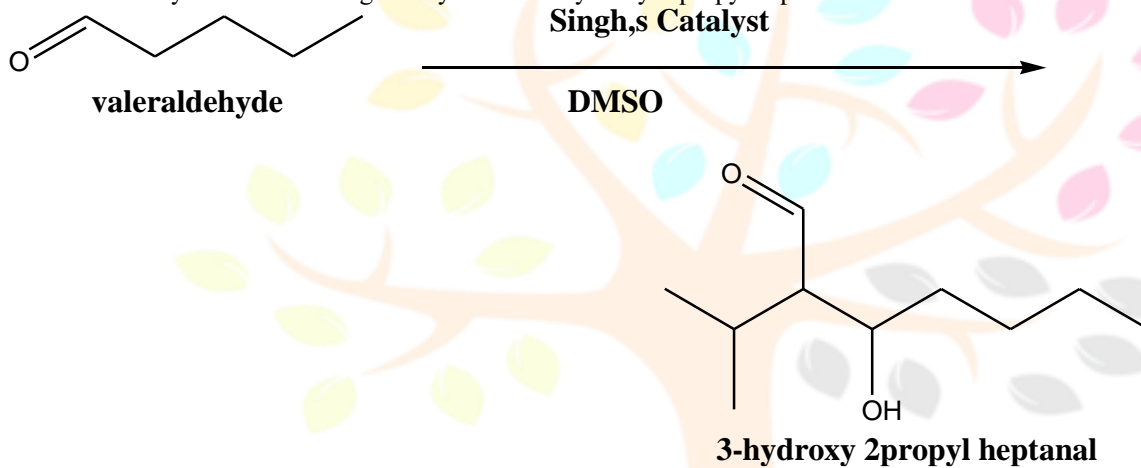
**3. REACTION OF BUTYRALDEHYDE WITH SINGH'S CATALYST AS FOLLOWS:**

When butyraldehyde react with singh's catalyst form 2-ethyl 3-hydroxy hexanal. <sup>[13]</sup>



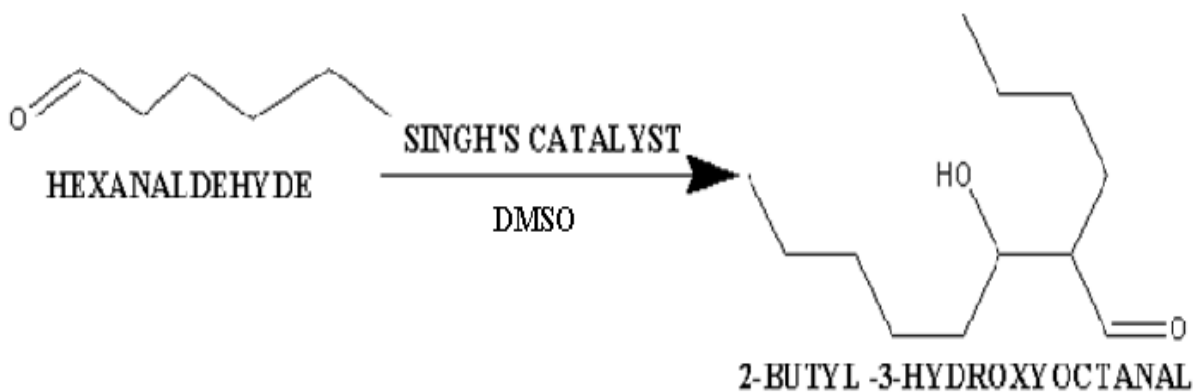
**4. REACTION OF VALERALDEHYDE WITH SINGH'S CATALYST AS FOLLOWS:**

When valeraldehyde reacts with Singh's catalyst, it forms 3-hydroxy 2-propyl heptanal.<sup>[13]</sup>



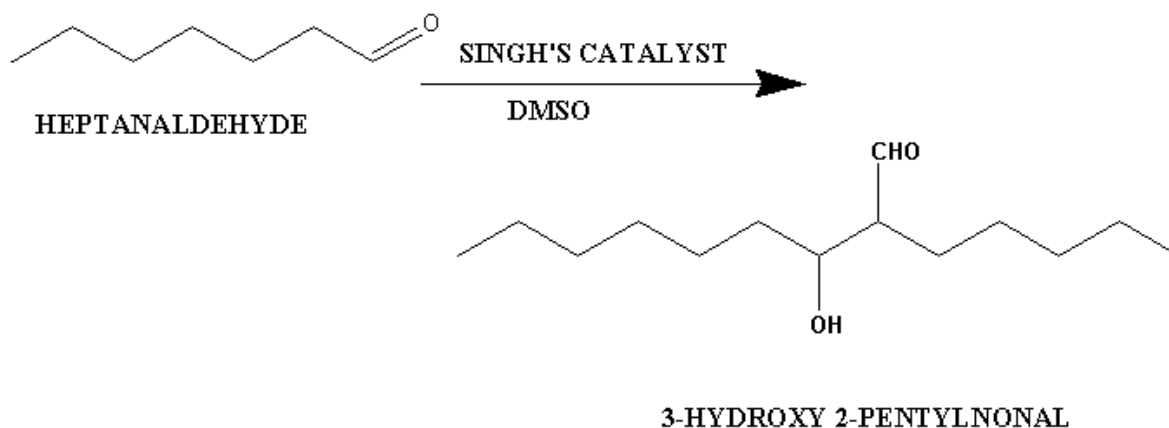
**5. REACTION OF HEXANALDEHYDE WITH SINGH'S CATALYST AS FOLLOWS:**

When hexanaldehyde reacts with Singh's catalyst, it forms 2-butyl 3-hydroxy octanal.<sup>[13]</sup>



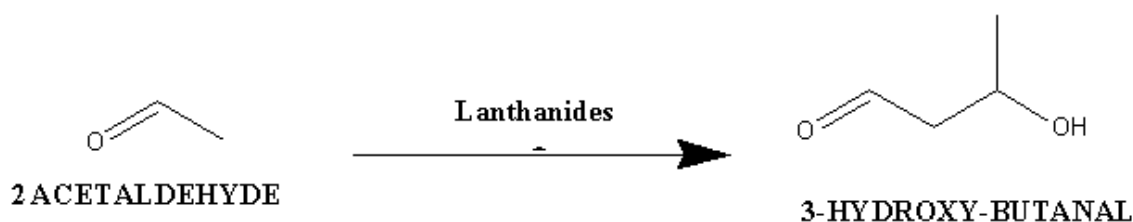
**6. REACTION OF HEXANALDEHYDE WITH SINGH'S CATALYST AS FOLLOWS:**

When heptanaldehyde reacts with Singh's catalyst, it forms 3-hydroxy 2-pentyl nonanal.<sup>[13]</sup>



### 7. REACTION OF ACETALDEHYDES WITH LANTHANIDES AS FOLLOWS:

When two molecules of acetaldehydes reacts with lanthanides to give 3-hydroxy butanal.<sup>[14]</sup>



**Table:1- aliphatic aldehydes involved in aldol condensation reaction:**

S.NO	Substrate	Reagent	Catalyst	Product
1	2 methanal	Water	Acid catalysis	Butanal
2	Butanal	NaOH	Proline	Beta Hydroxy Aldehyde
3	Butanaldehyde	DMSO	Singh's Catalyst	2-Ethyl -3-Hydroxy Hexanal
4	Valeraldehyde	DMSO	Singh's Catalyst	3-Hydroxy -2-Propyl Heptanal
5	Hexanaldehyde	DMSO	Singh's Catalyst	2-Butyl- 3-Hydroxy Octanal
6	Heptanaldehyde	DMSO	Singh's Catalyst	3-Hydroxy-2-Pentylnonal
7	2 molecules of Acetaldehyde	water	Lanthanides	3-Hydroxy butanal
8	Acetaldehyde	NaOH	No catalyst	3-Hydroxy butanal

### 8. Aliphatic Aldehydes And Aliphatic Ketones concerned aldol condensation:

#### ALIPHATIC ALDEHYDES:

The -CHO group is attached directly to sp<sup>3</sup> hybridised saturated carbon atom, such compounds are known as aliphatic aldehydes  
Eg. Formaldehyde, Acetaldehyde

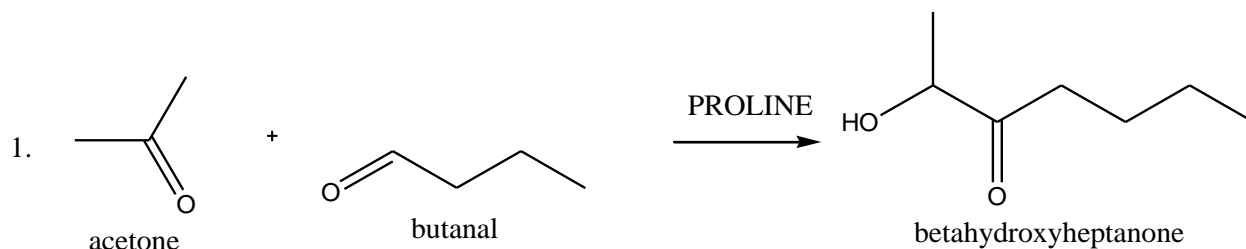
#### ALIPHATIC KETONES:

The C=O group is attached to two alkyl groups, such compounds are known as aliphatic ketones.

Eg: Acetone, Butanone

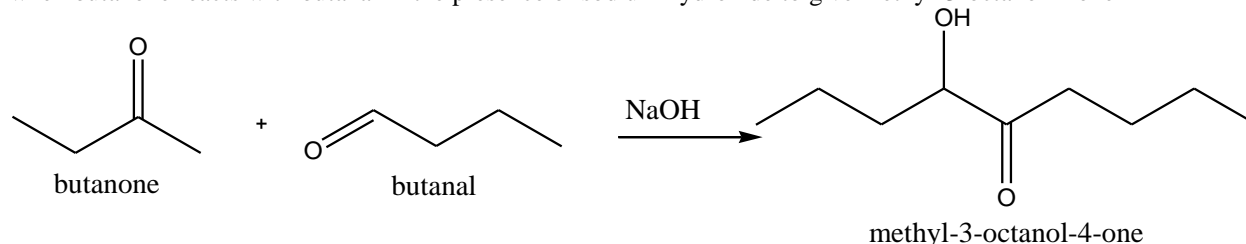
#### 1. REACTION BETWEEN ACETONE AND BUTANAL AS FOLLOWS

when acetone reacts with butanal in presence of proline to give beta hydroxyheptanone<sup>[16]</sup>



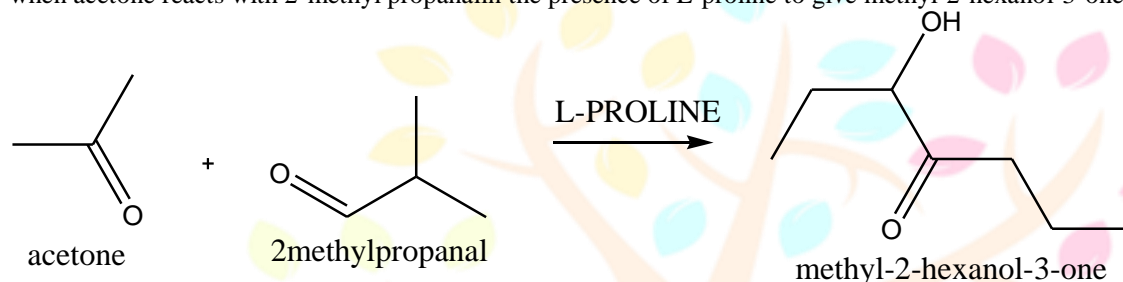
## 2. REACTION BETWEEN BUTANONE AND BUTANAL AS FOLLOWS

when butanone reacts with butanal in the presence of sodium hydroxide to give methyl-3-octanol-4-one<sup>[17]</sup>



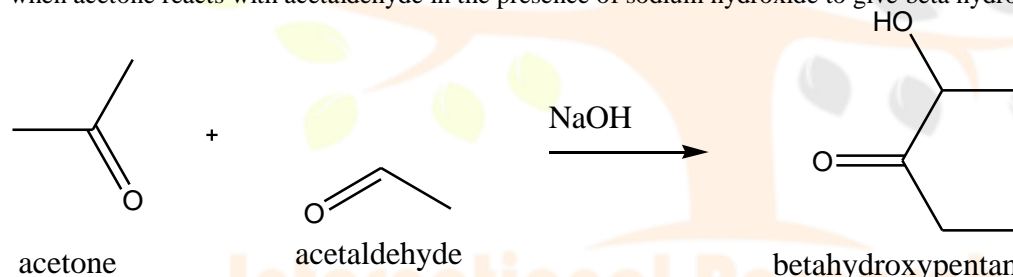
## 3. REACTION BETWEEN ACETONE AND 2-METHYL PROPANAL AS FOLLOWS

when acetone reacts with 2-methyl propanal in the presence of L-proline to give methyl-2-hexanol-3-one<sup>[18]</sup>



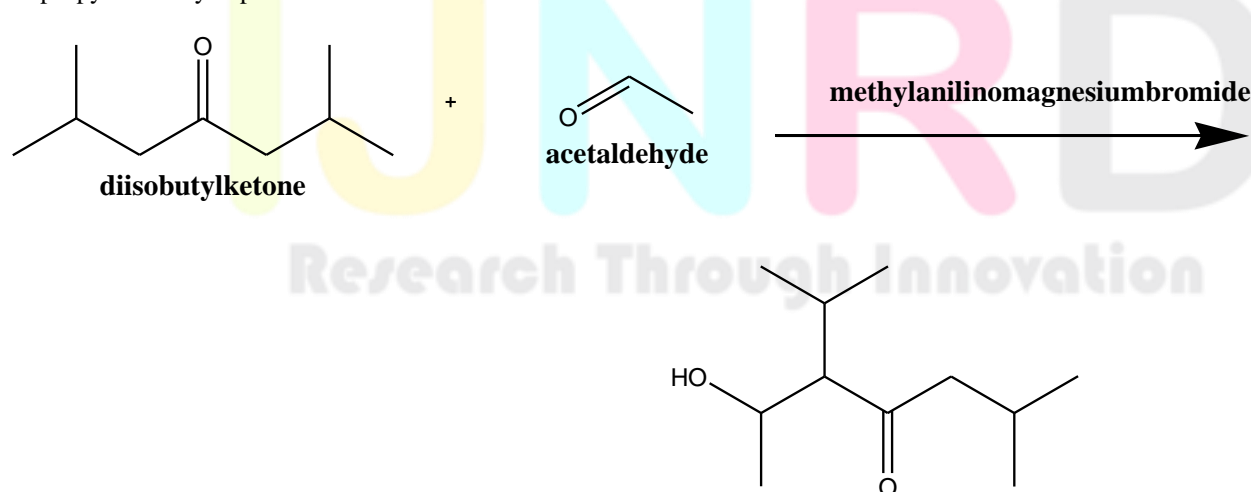
## 4. REACTION BETWEEN ACETONE AND ACETALDEHYDE AS FOLLOWS

when acetone reacts with acetaldehyde in the presence of sodium hydroxide to give beta hydroxypentanone<sup>[19]</sup>



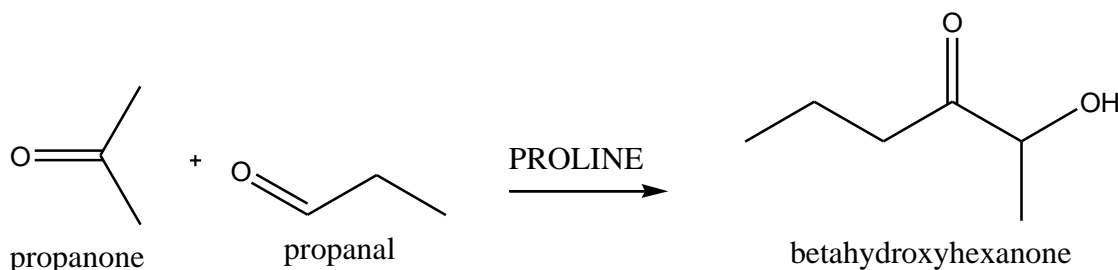
## 5. REACTION BETWEEN DIISOBUTYLKETONE AND ACETALDEHYDE AS FOLLOWS

when diisobutylketone reacts with acetaldehyde in the presence of methylanilnomagnesium bromide to give 2-hydroxy-3-isopropyl-6-methylheptanone<sup>[20]</sup>



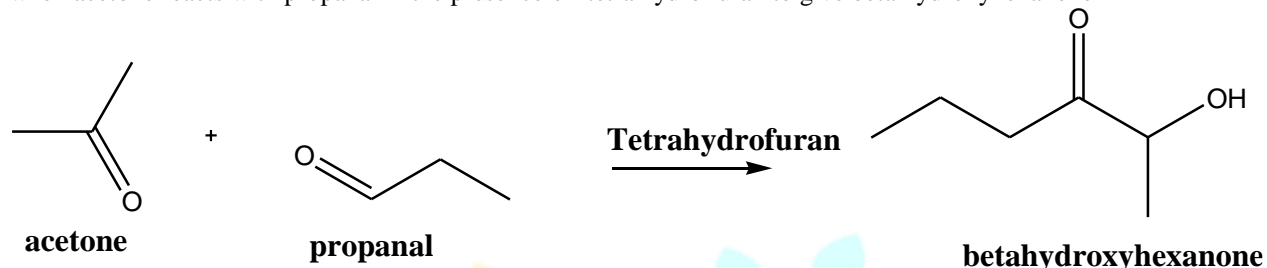
## 6. REACTION BETWEEN PROPANONE AND PROPANAL AS FOLLOWS:

when propanone reacts with propanal in the presence of proline to give beta hydroxyhexanone<sup>[21]</sup>

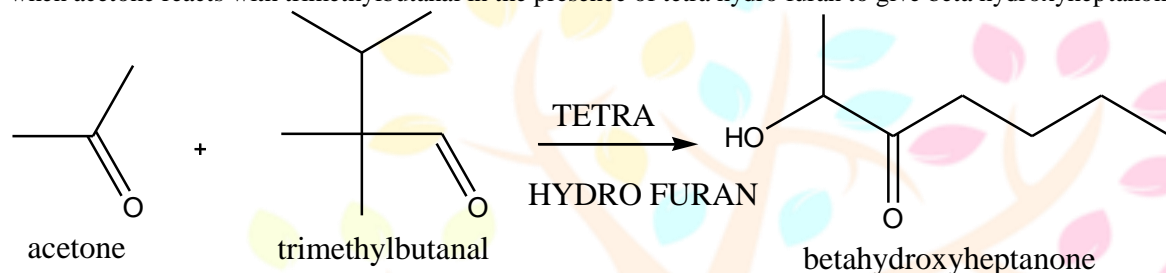


### 7. REACTION BETWEEN ACETONE AND PROPANAL AS FOLLOWS

when acetone reacts with propanal in the presence of tetrahydrofuran to give beta-hydroxyhexanone.<sup>[22]</sup>



when acetone reacts with trimethylbutanal in the presence of tetrahydrofuran to give beta-hydroxyheptanone.<sup>[23]</sup>



**Table:2-**aliphatic aldehydes and ketones involved in aldol condensation

S.NO	ALIPHATIC KETONES	ALIPHATIC ALDEHYDES	REAGENTS AND CATALYSTS USED	PRODUCT
1	Acetone	Butanal	Proline	Beta hydroxyheptanone
2	Butanone	Butanal	Sodium hydroxide	Methyl-3-octanol-4-one
3	Acetone	2-methyl propanal	L-proline	Methyl-2-hexanol-3-one
4	Acetone	Acetaldehyde	Sodium hydroxide	Beta hydroxypentanone
5	Di iso butyl ketone	Acetaldehyde	Methylanilinomagnesium bromide	2-hydroxy-3-isopropyl-6-methyl-4-heptanone
6	Propanone	Propanal	Proline	Beta hydroxyhexanone
7	Acetone	Propanal	Tetrahydrofuran	Beta hydroxyheptanone
8	Acetone	Trimethylbutanal	Tetrahydrofuran	Beta Hydroxyheptanone

### 8. AROMATIC ALDEHYDES CONCERNED ALDOL CONDENSATION:

These are a class of organic compounds having functional group of "CHO", combined to aromatic compounds to create a unique and balanced scent.

#### AROMATIC ALDEHYDES IN ALDOL CONDENSATION

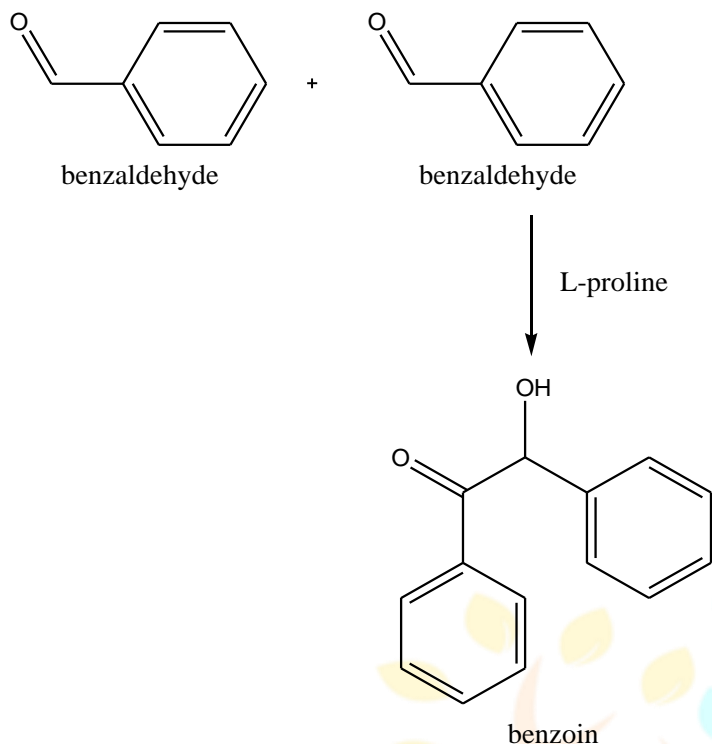
Aromatic aldehydes, such as benzaldehyde do not have alpha-hydrogens. In aldol reaction the enolate ion generated from a carbonyl compound attacks the alpha-carbon of another carbonyl compound.

The enolate ion when reacts with aromatic aldehyde, leads to the formation of beta-hydroxy carbonyl compound.

**Some of the reactions catalysed by L-proline and their derivatives:**

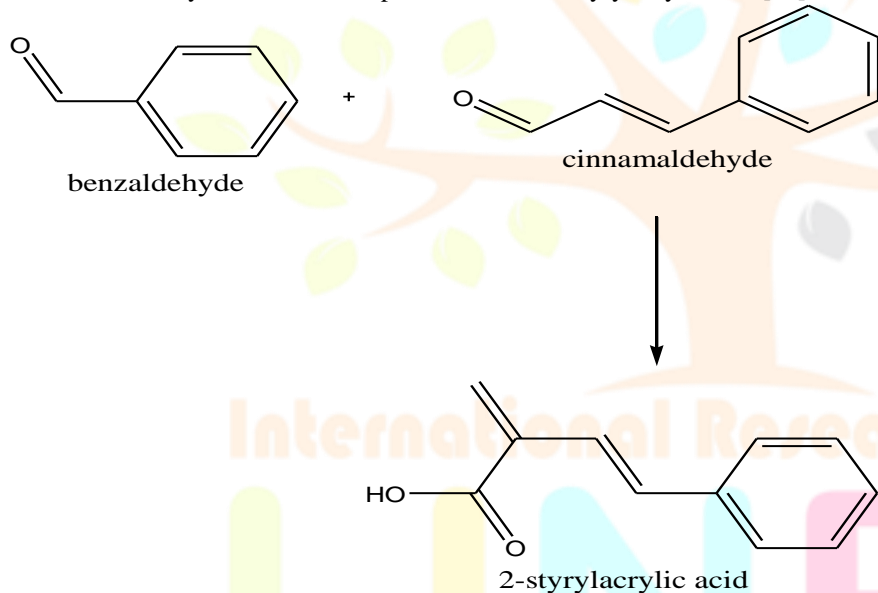
#### 1. REACTION OF BENZALDEHYDE WITH L-PROLINE AS FOLLOWS:

When benzaldehyde reacts with L-proline to form benzoin<sup>[24]</sup>



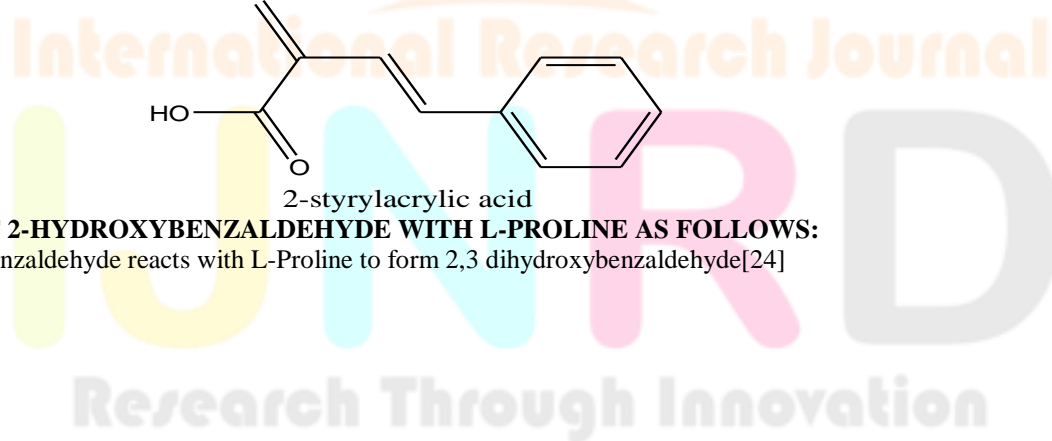
**2. REACTION OF BENZALDEHYDE WITH L-PROLINE AS FOLLOWS:**

When benzaldehyde reacts with L-proline to form 2-styrylacrylic acid [24]

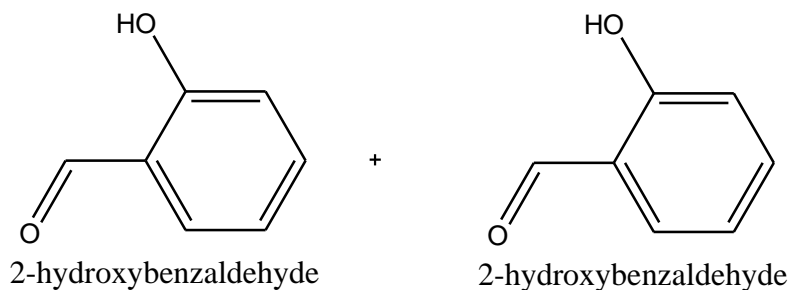


**3. REACTION OF 2-HYDROXYBENZALDEHYDE WITH L-PROLINE AS FOLLOWS:**

When 2-hydroxybenzaldehyde reacts with L-Proline to form 2,3 dihydroxybenzaldehyde[24]

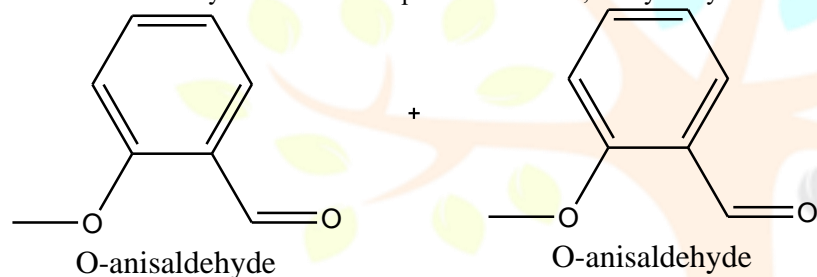






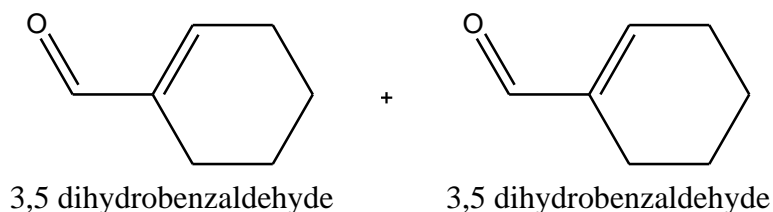
#### 4. REACTION OF O-ANISALDEHYDE WITH L-PROLINE AS FOLLOWS:

When O-anisaldehyde reacts with L-proline to form 3,4 dihydroxybenzaldehyde”24”



#### 5. REACTION OF 3,5 DIHYDROXYBENZALDEHYDE WITH L-PROLINE AS FOLLOWS:

When 3,5 dihydroxybenzaldehyde reacts with L-proline to form 1,3 dihydroxy-5-methylbenzene[24]

**Table:3-** aromatic aldehydes involved in aldol condensation:

S.no	Aromatic aldehydes	AROMATIC ALDEHYDES	CATALYST	PRODUCT
1.	Benzaldehyde	Benzaldehyde	L-proline	Benzoin
2.	Benzaldehyde	Cinnamaldehyde	L-proline	2-Styrylacrylicacid
3.	2-hydroxy benzaldehyde	2-hydroxy benzaldehyde	L-proline	2,3-dihydroxybenzaldehyde
4.	O-anisaldehyde	O-anisaldehyde	L-proline	3,4-dihydroxybenzaldehyde
5.	3,5-dihydro benzaldehyde	3,5-dihydro benzaldehyde	L-proline	1,3-dihydroxy-5-methylbenzene

### 9. AROMATIC ALDEHYDES AND AROMATIC KETONES CONCERNED ALDOL CONDENSATION

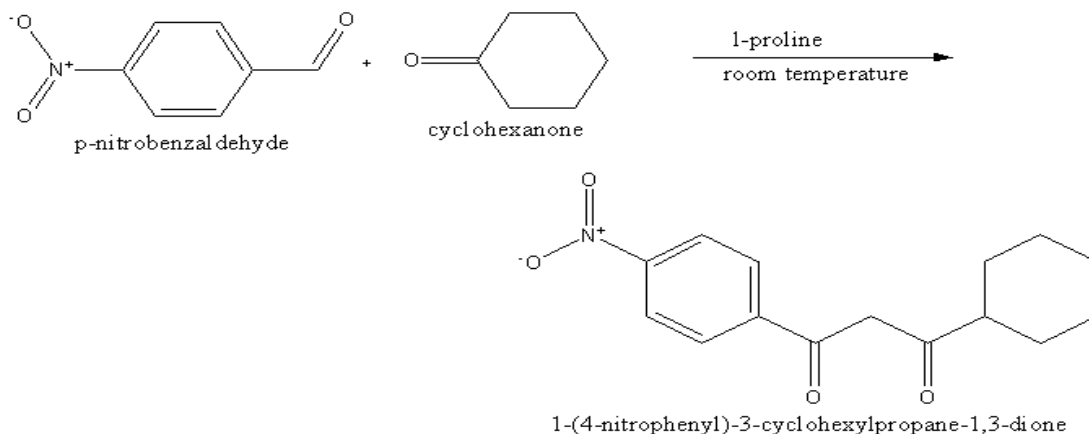
**Aromatic aldehydes:** Organic compounds with an aromatic ring and an aldehyde functional group (-CHO) are known as aromatic aldehydes. They can be made in a number of ways and are frequently seen in nature. Aromatic aldehydes are utilized in flavorings, fragrances, and medications and frequently have pleasant smells. Vanillin, which is present in vanilla beans, benzaldehyde (found in almonds), and cinnamaldehyde (found in cinnamon) are a few examples.

**Aromatic ketones:** Compounds with an aromatic ring and a ketone functional group (C=O) attached are known as aromatic ketones. These compounds are often encountered in organic chemistry and, because of the presence of both the ketone and aromatic functionalities, can display special reactivity and characteristics. They are frequently employed in synthesis, particularly for making specialized compounds, medicines, and fragrances

**Some of the reactions catalysed by proline and their derivatives are:**

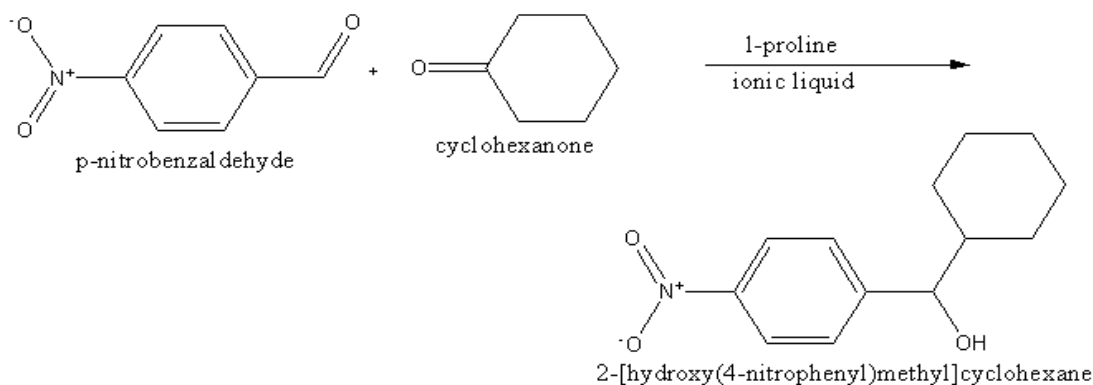
#### 1. REACTION OF P-NITRO BENZALDEHYDE AND CYCLOHEXANONE WITH L-PROLINE ARE AS FOLLOWS:

Reaction between p-nitro benzaldehyde and cyclohexanone in the presence of L-proline as a catalyst at room temperature yields 1-(4-nitrophenyl)-3-cyclohexylpropane-1,3-dione with a yield more than 92.3%. [25]



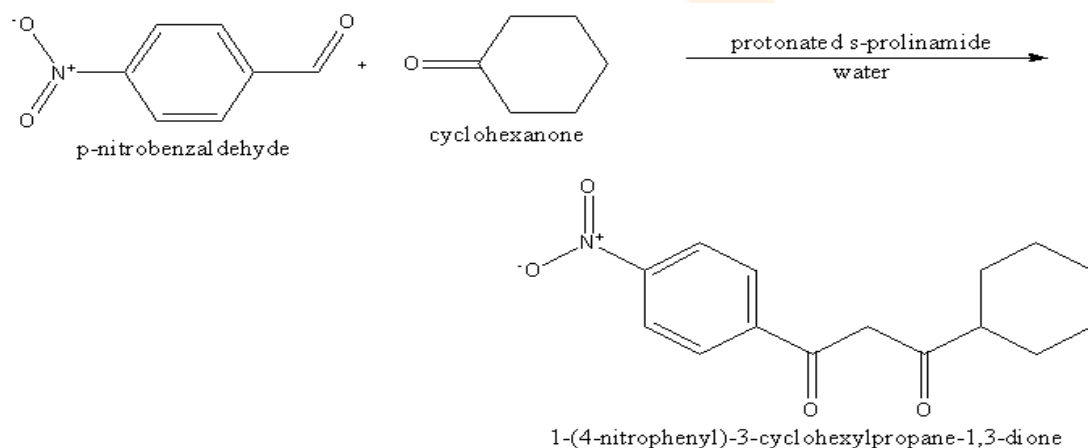
## 2. REACTION OF 4-NITRO BENZALDEHYDE AND CYCLOHEXANONE WITH L-PROLINE ARE AS FOLLOWS:

A condensation reaction between 4-nitrobenzaldehyde and cyclohexanone are combined with an ionic liquid based on camphor sulphonic acid and l-proline as a catalyst gives 2-[hydroxy(4-nitrophenyl) methyl] cyclohexanone with a high yield of 98% and 94% ee. <sup>[26]</sup>



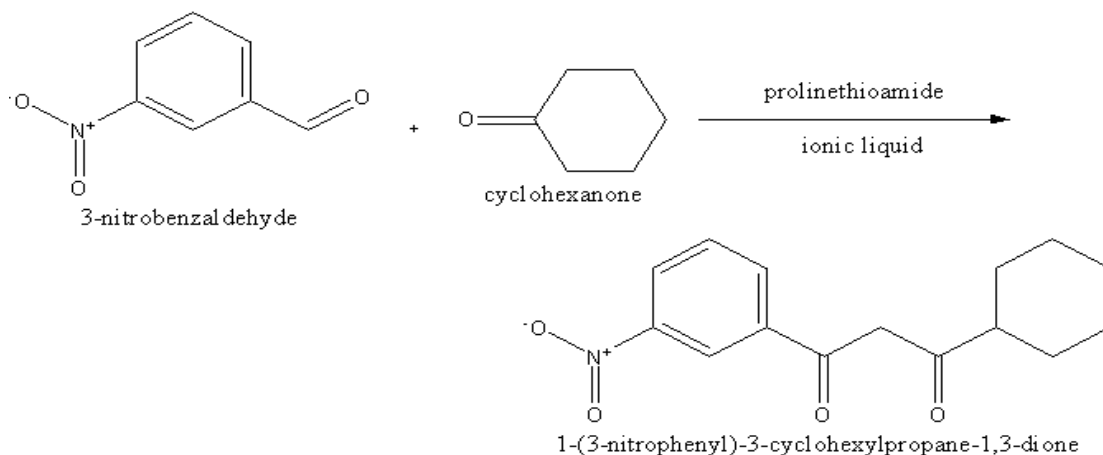
## 3. REACTION OF 4-NITRO BENZALDEHYDE AND CYCLOHEXANONE WITH S-PROLINEAMIDE ARE AS FOLLOWS:

4-nitrobenzaldehyde and cyclohexanone undergo condensation process in presence of protonated S-prolineamide to give 1-(4-nitrophenyl)-3-cyclohexylpropane-1,3-dione. <sup>[27]</sup>



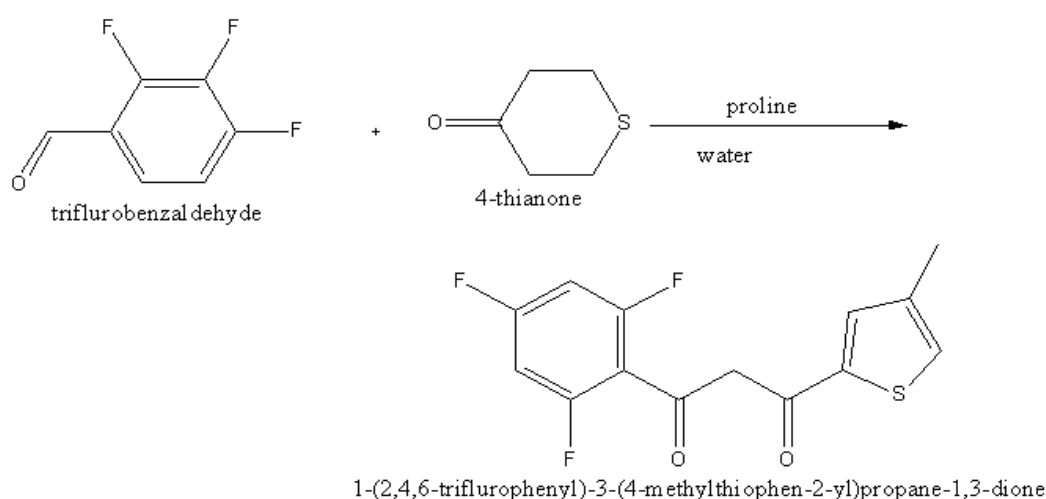
## 4. REACTION OF 3-NITRO BENZALDEHYDE AND CYCLOHEXANONE WITH PROLINETHIOAMIDE ARE AS FOLLOWS:

The reaction take place between 3-nitrobenzaldehyde and cyclohexanone in presence of prolinethioamide and ionic liquid gives 1-(3-nitrophenyl)-3-cyclohexylpropane-1,3-dione. <sup>[28]</sup>



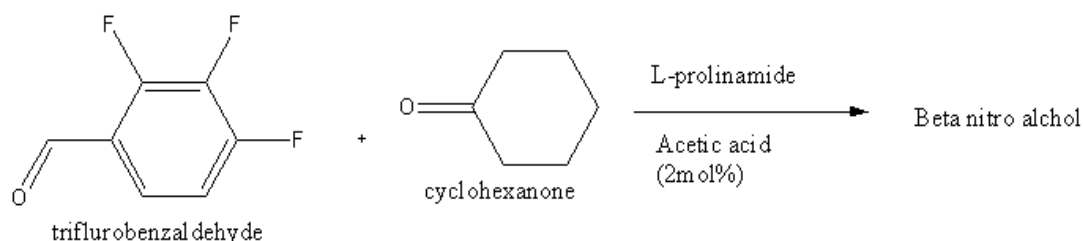
#### 5. REACTION OF TRIFLUORO BENZALDEHYDE AND 4- THIANONE WITH PROLINE ARE AS FOLLOWS:

In the presence of proline and water, a condensation reaction take place between trifluorobenzaldehyde and 4-thianone, resulting in the formation of 1-(2,4,6-trifluorophenyl)-3-(4-methylthiophen-2-yl) propane-1,3-dione. <sup>[29]</sup>



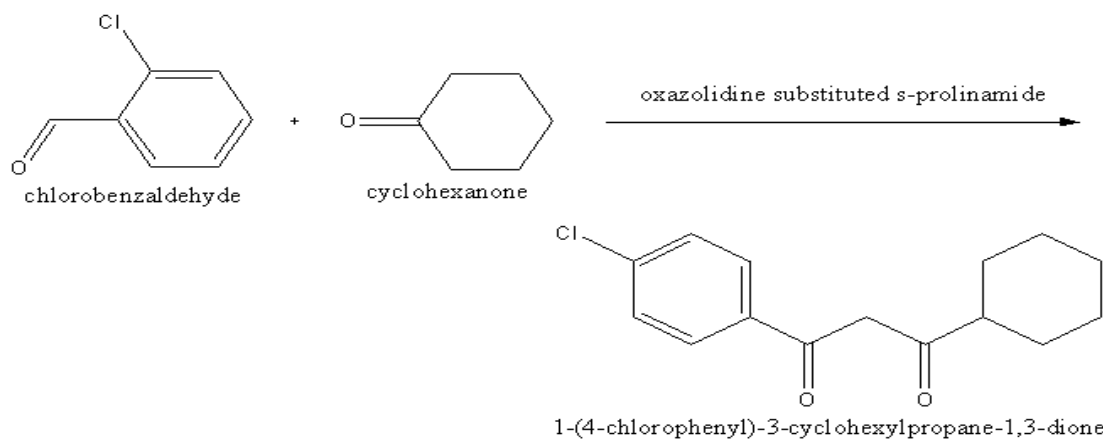
#### 6. REACTION OF TRIFLUORO BENZALDEHYDE AND CYCLOHEXANONE WITH L-PROLINAMIDE ARE AS FOLLOWS:

A reaction take place between trifluorobenzaldehyde and cyclohexanone in presence of l-prolinamide and acetic acid (2 mol%) gives beta nitro alcohol as product. <sup>[30]</sup>



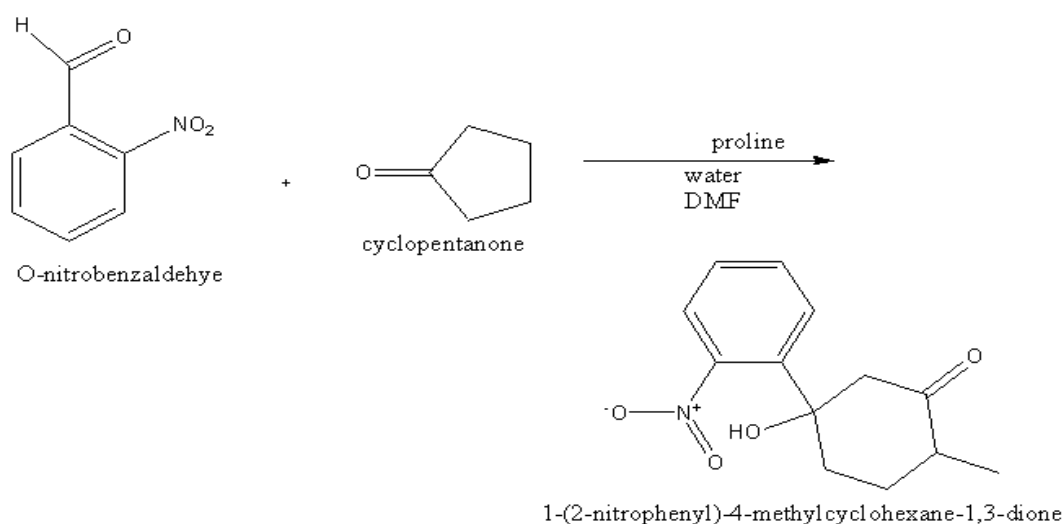
#### 7. REACTION OF CHLORO BENZALDEHYDE AND CYCLOHEXANONE WITH S-PROLINAEMIDE ARE AS FOLLOWS:

The reaction take place between chlorobenzaldehyde and cyclohexanone under the presence of oxazolidine substituted s-prolinamide gives 1-(4-chlorophenyl)-3-cyclohexylpropane-1,3-dione. <sup>[31]</sup>



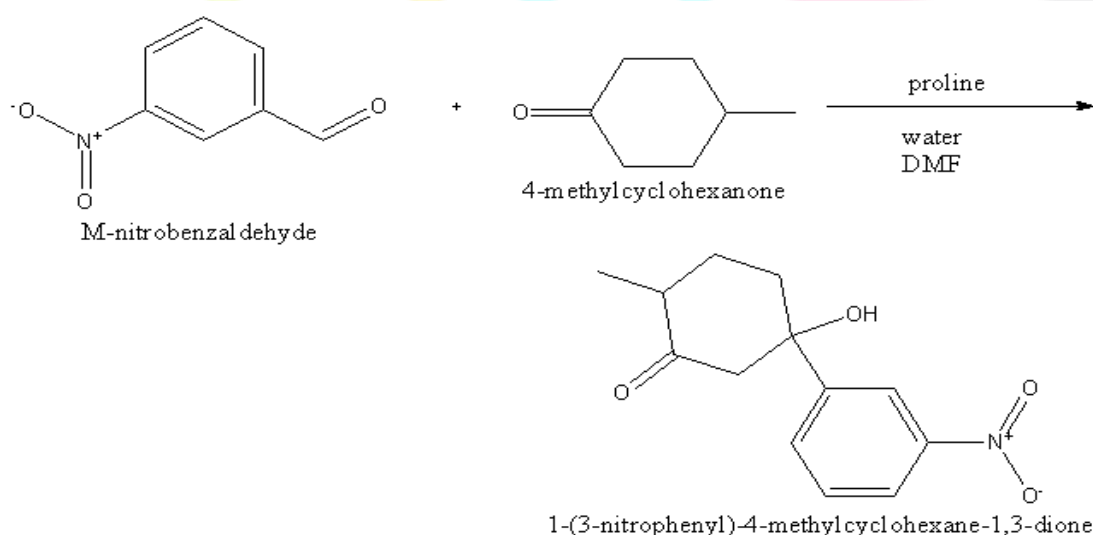
### 8. REACTION OF O-NITRO BENZALDEHYDE AND CYCLOPENTANONE WITH PROLINE ARE AS FOLLOWS:

A reaction take place between o-nitro benzaldehyde and cyclopentanone in presence of proline and under the condition of water and DMF gives 1-(2-nitrophenyl)-4-methylcyclohexane-1,3-dione. <sup>[32]</sup>



### 9. REACTION OF M-NITRO BENZALDEHYDE AND 4-METHYLCYCLOHEXANONE WITH PROLINE ARE AS FOLLOWS:

A reaction take place between m-nitrobenzaldehyde and 4-methylcyclohexanone in presence of proline and under the condition of water and DMF gives 1-(3-nitrophenyl)-4-methylcyclohexane-1,3-dione. <sup>[33]</sup>



**Table-4-** aromatic aldehydes and ketones involved in aldol condensation.

S. No	Aromatic aldehyde	Aromatic ketone	Catalyst	Product	Enantioselectivity	Conditions
1.	P-nitro benzaldehyde	Cyclohexanone	L-proline	1-(4-nitrophenyl) -3-cyclohexylpropane-1, 3-dione	>92.3%	Room temperature
2.	4-nitrobenzaldehyde	Cyclohexanone	L-proline	2-[hydroxy(4-nitrophenyl) methyl] cyclohexanone	98% yield 94% ee	Ionic liquid based on Camphor sulphonic acid
3.	4-nitrobenzaldehyde	Cyclohexanone	Protonated s-prolineamide	1-(4-nitrophenyl) -3-cyclohexylpropane-1, 3-dione	81% yield Anti-95% Syn-5% 88% ee	Solvent as water
4.	3-nitrobenzaldehyde	Cyclohexanone	Prolinethioamide	1-(3-nitrophenyl) -3-cyclohexylpropane-1, 3-dione	99% ee Anti-99% Syn-1%	Ionic liquid
5.	Trifluorobenzaldehyde	4-thianone	Proline	1-(2, 4,6-trifluorophenyl) -3-(4-methylthiophen-2-yl) propane-1, 3-dione		Water
6.	Trifluorobenzaldehyde	Cyclohexanone	L-prolineamide	Beta nitro alcohol	99% ee Anti-99.9% Syn-0.01%	Acetic acid(2mol%)
7.	Chlorobenzaldehyde	Cyclohexanone	Oxazolidine substituted s-prolineamide	1-(4-chlorophenyl) -3-cyclohexylpropane-1, 3-dione	84% ee	
8.	O-nitro benzaldehyde	Cyclopentanone	Proline	1-(2-nitrophenyl)-4-methylcyclohexane-1, 3-dione	99% yield Anti-99% Syn-1% >99% ee	Water DMF
9.	M-nitro benzaldehyde	4-methyl cyclohexanone	Proline	1-(3-nitrophenyl) -4-methylcyclohexane-1, 3-dione	99% yield Anti-99% Syn-1% >99% ee	Water DMF

**CONCLUSION:**

A crucial stage in the biosynthesis of numerous natural compounds, including steroids and terpenes, is aldol condensation. Numerous biological actions, such as antibacterial, anti-inflammatory, and anticancer effects, are exhibited by these substances. Managing stereoselectivity is essential for creating complex compounds with specific biological functions. Stereoselective aldol condensations are becoming more and more complex due to improvements in catalyst design and reaction conditions.

This reaction is still a fundamental part of organic synthesis because it makes it possible to create complex compounds with exact control over their spatial structure. In general, organic chemists must understand and regulate stereoselectivity in aldol condensation in order to produce desirable product structures and progress within the field of synthetic chemistry.

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