MANNICH REACTION AND ALDOL CONDENSATION

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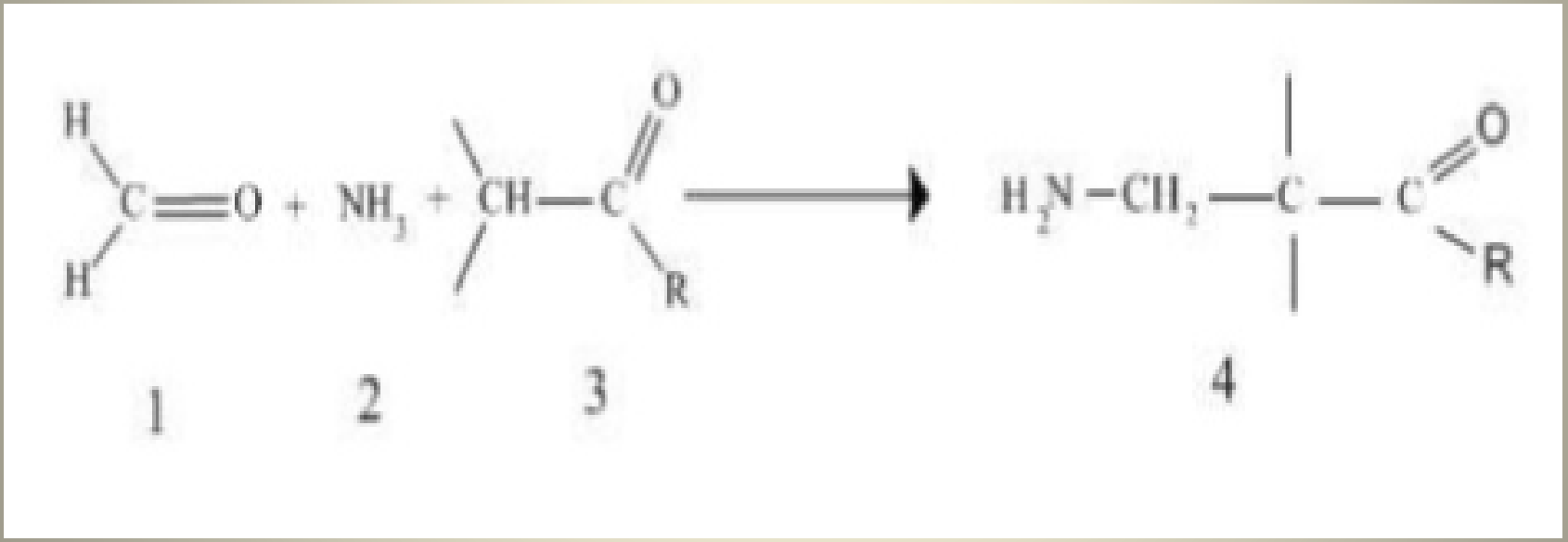
MANNICH REACTION

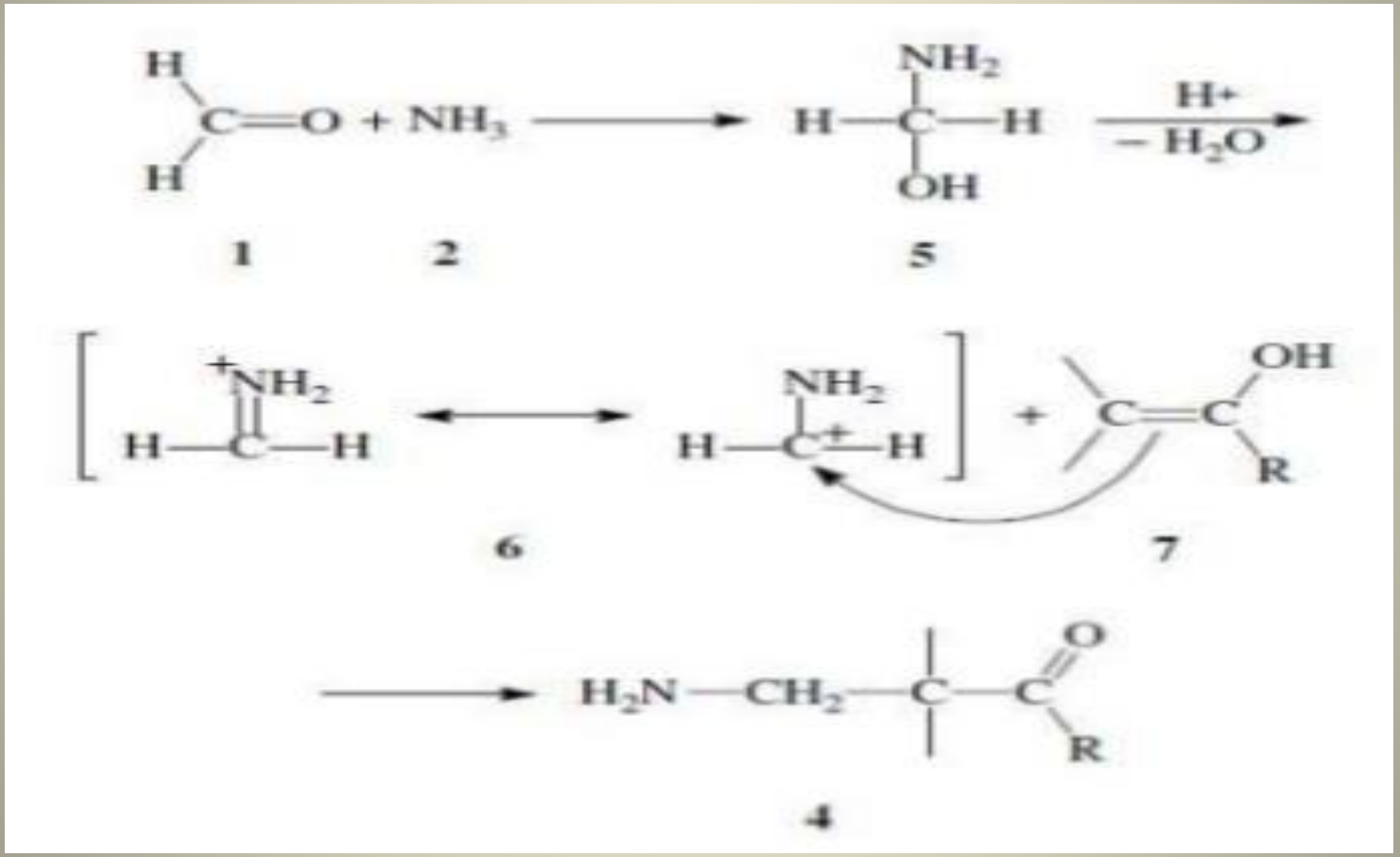
Mannich Reaction

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.

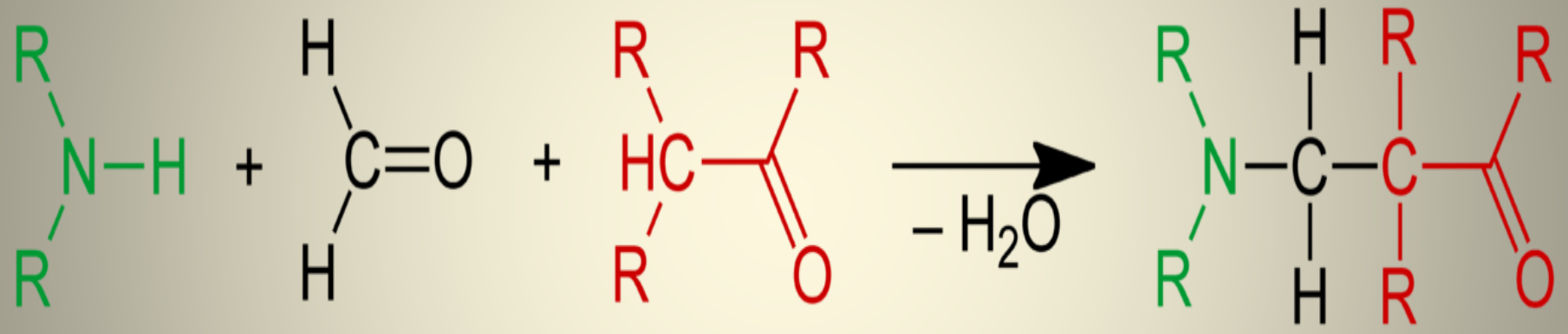
The condensation reaction of CH- acidic compound e.g a ketone with formaldehyde and Ammonia is called the Mannich reaction. The product 4 is called the MannichBase.



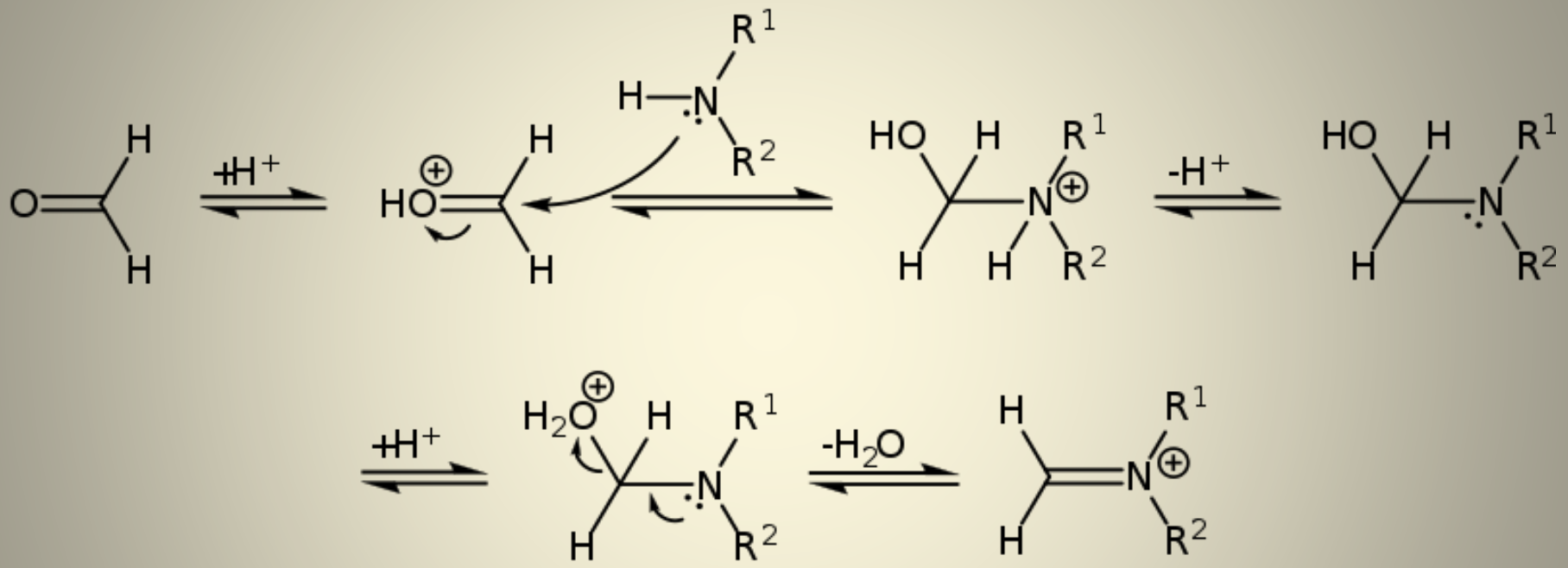
MECHANISM


H
C=O + NH3
H
NH2
H—C—H
OH
H+
– H2O
1
2
5
+NH2
H—C—H
NH2
H—C+—H
OH
C=C
R
6
7
H2N—CH2—C—C
O
R
4

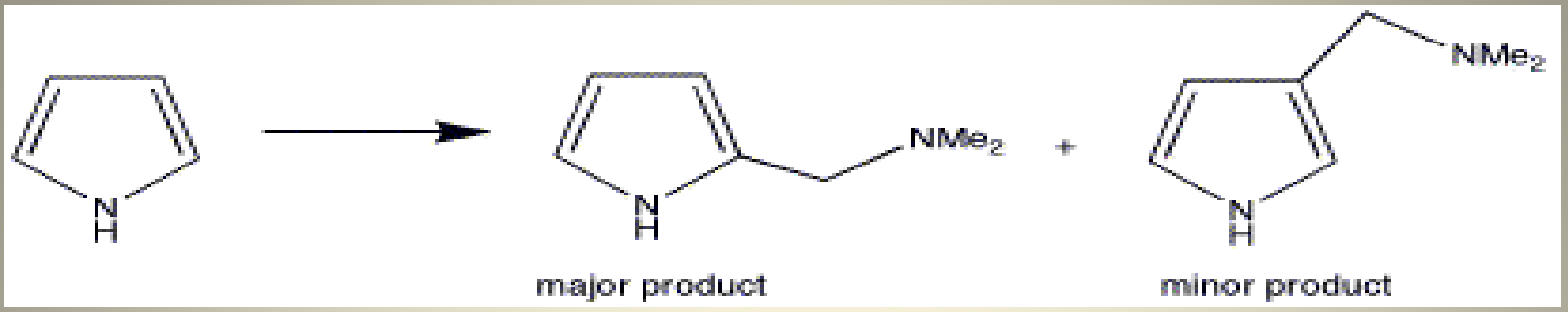
Reaction with primary amines

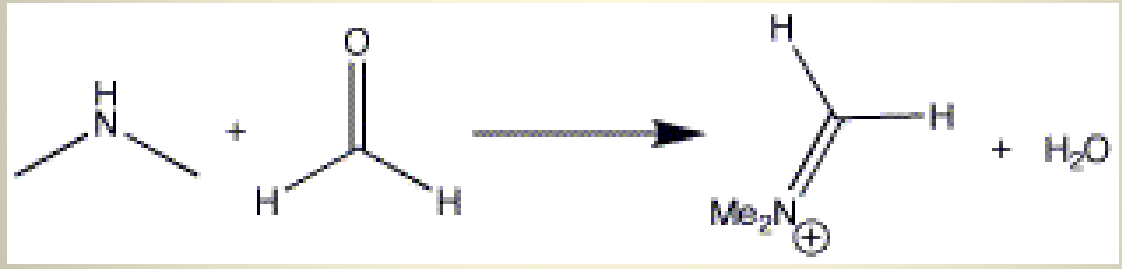


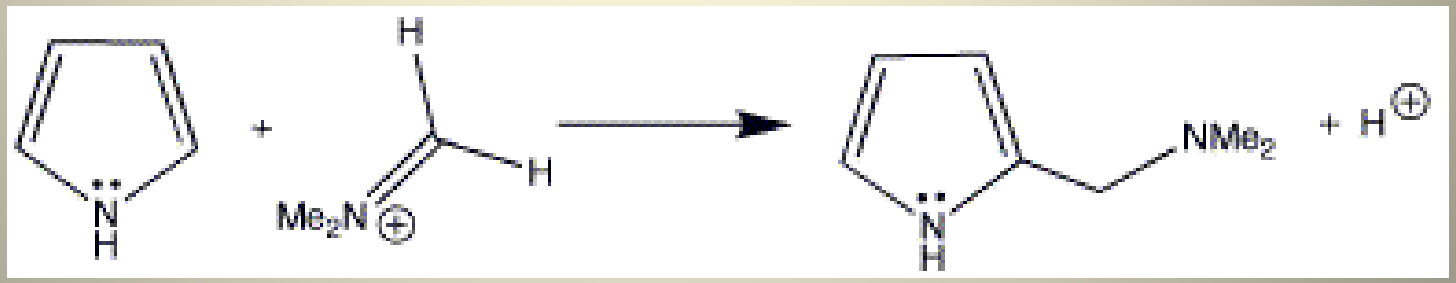
MECHANISM



Pyrrole—Mannich reaction







Limitations

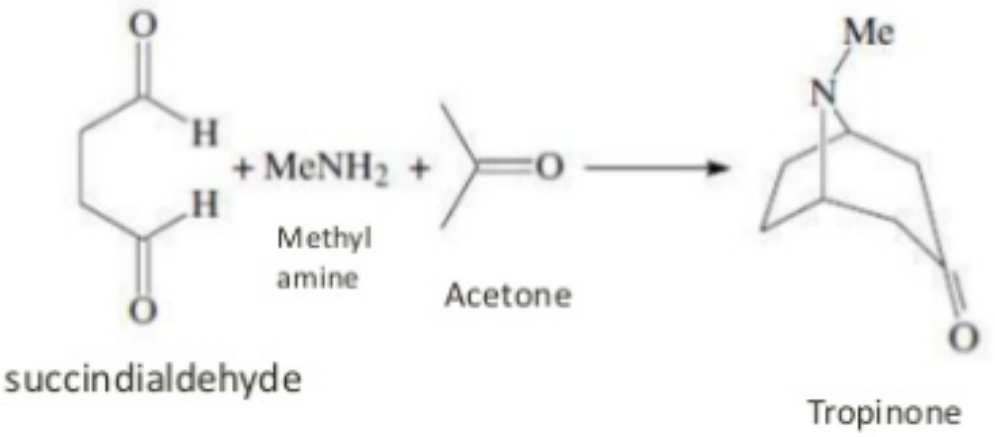
- Thus the range of application is limited (e.g. confined to amino methylation)
- In many cases undesired side products are formed
- The ability to control regio- and stereoselectivity is generally unsatisfactory

Applications

The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators, paint- and polymer chemistry, catalysts and main mechanism of formalin tissue crosslinking. The Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol, and tolmetin (anti-inflammatory drug)and azacyclophanes. The Mannich reaction is employed to synthesize alkyl amines, converting non-polar hydrocarbons into soap or detergents. This is used in a variety of cleaning applications, automotive fuel treatments, and epoxy coatings. Similar methods of substituted branched chain alkyl ethers into polyetheramines are achieved via a number of reactions.

Applications

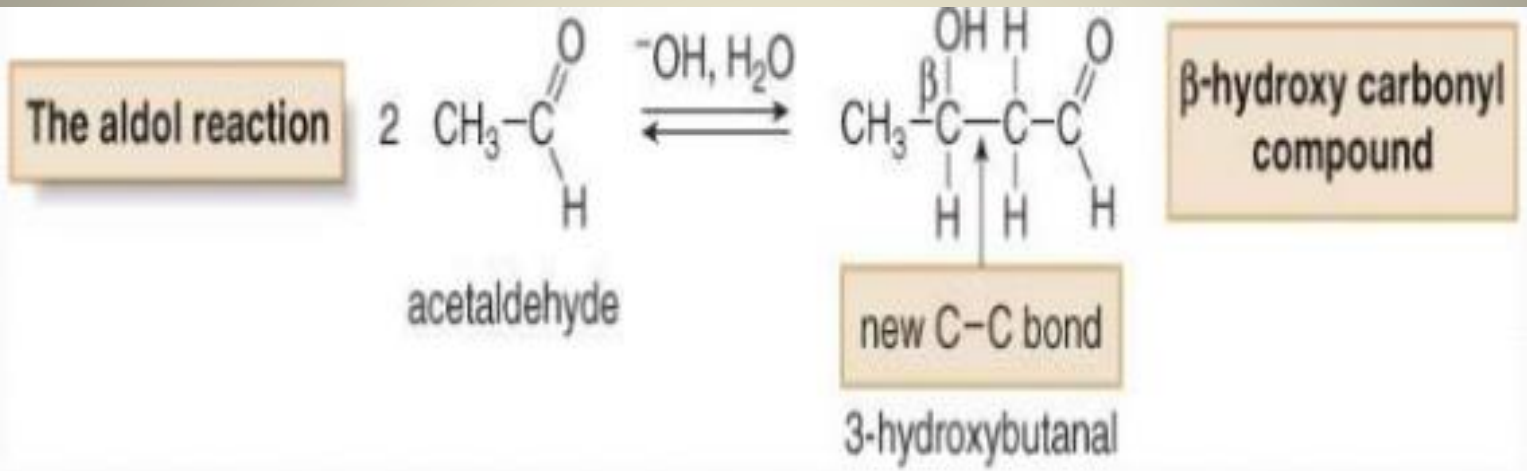
- The synthesis of tropinone, a precursor of atropine and related compounds, is a classical example. In 1917 Robinson has prepared tropinone by a Mannich reaction of succindialdehyde and methylamine with acetone; better yields of tropinone were obtained when he used the calcium salt of acetonedicarboxylic acid instead of acetone.



ALDOL
CONDENSATION

ALDOL CONDENSATION

An **aldol condensation** is a condensation reaction in organic chemistry in which an enol or an enolate ion reacts with a carbonyl compound to form a β-hydroxyaldehyde or β-hydroxyketone, followed by dehydration to give a conjugated enone.



Thus the following Aldehydes or ketones having no α-hydrogen atom do not undergo Aldol Condensation.

Conditions regarding Aldol condensation

- A reversible equilibrium
- OH is the base typically used in an aldol reaction.
- Aldol reactions can be carried out with either aldehydes or ketones.
- With aldehydes, the equilibrium favors products
- With ketones the equilibrium favors the starting materials.

MECHNISM OF

ALDOL CONDENSATION

Step 1:

First, an acid-base reaction. Hydroxide functions as a base and removes the acidic a-hydrogen giving the reactive enolate.

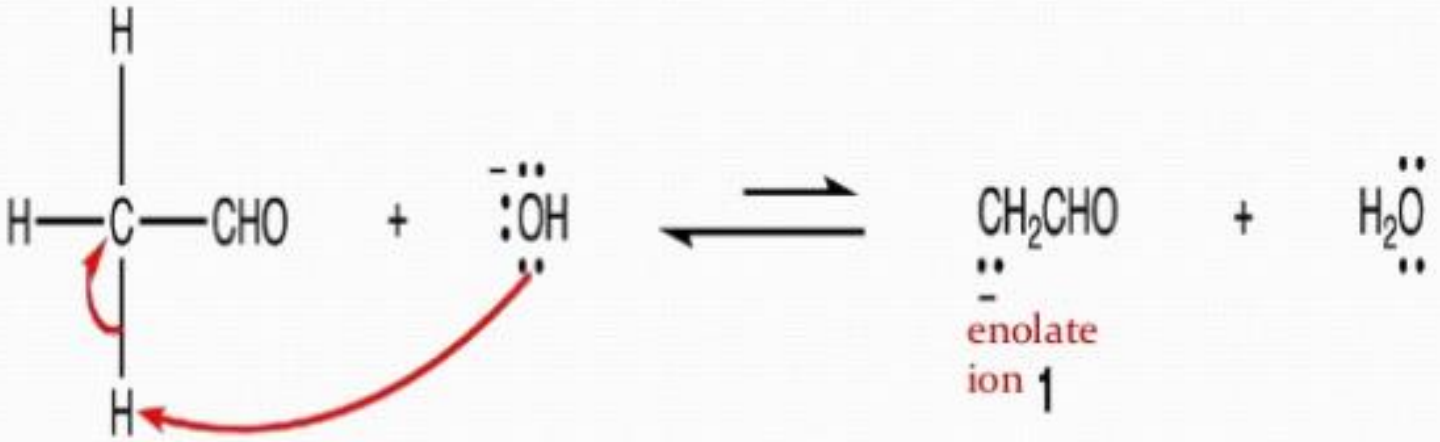
Step 2:

The nucleophilic enolate attacks the aldehyde at the electrophilic carbonyl **C** in a nucleophilic addition type process giving an intermediate alkoxide.

Step 3:

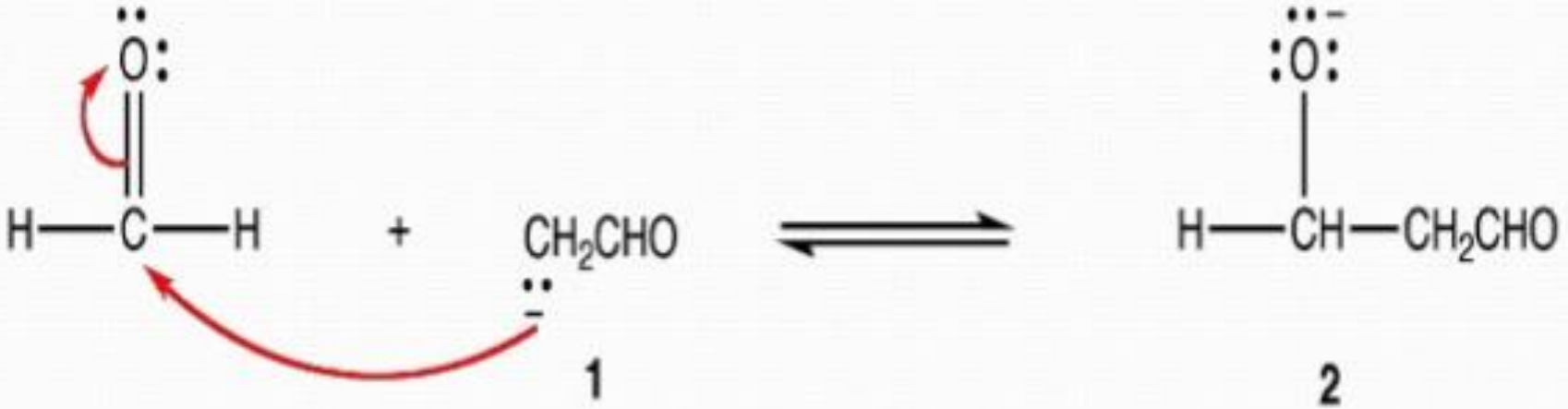
An acid-base reaction. The alkoxide deprotonates a water molecule creating hydroxide and the β-hydroxyaldehydes or **aldol** product.

Step:1



❖An enolate ion is the anion formed when an alpha hydrogen in the molecule of an aldehyde or a ketone is removed as a hydrogen ion.

Step:2



The alkoxide ion is the conjugate base of alcohols.

Step:3

2

3

aldol product

Alkoxide ion is protonated by water.

LIMITATIONS:

Aldol products,as such, are not always isolated from the reaction mixture.eg:acetaldol readily forms a cyclic hemi-acetol.

EXTENSIONS:

Aldol condensation can occur between

- Two identical or different aldehydes
- Two identical or different ketones
- An aldehyde and a ketone

REFERENCES

1 Chem.libretext.org

2 www.organic-chemistry.org

3 Organic chemistry –Francis A Carey

THANK YOU