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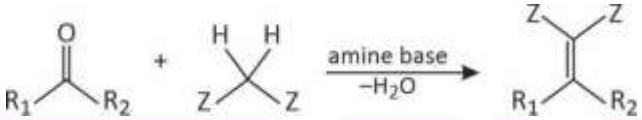
Study Notes On Knoevenagel Reaction

KNOEVENAGEL REACTION

In this reaction, an aldehyde or a ketone with an active hydrogen compound undergoes condensation in presence of basic catalyst (usually a basic amine) to yield α, β-unsaturated compound as a product.
This is a Nucleophilic Addition reaction in which the compound with an active hydrogen is followed by removal of water.

- The active hydrogen compound is supposed to be bearing electron-withdrawing groups, such as- CN, NO_2, CHO, COR, CO_2R, etc.
- These electron withdrawing groups make the hydrogen atoms of methylene group *acidic* which can be easily removed by adding a suitable base. Such hydrogens are referred to as *active hydrogen atoms*.
- Solvent for reaction is Aprotic solvent, such as- DMF, MeCN, pyridine or piperidine.
- Pyridine plays a dual role in this reaction. It acts as both solvent and catalyst.
- In this reaction, a mild base is used.

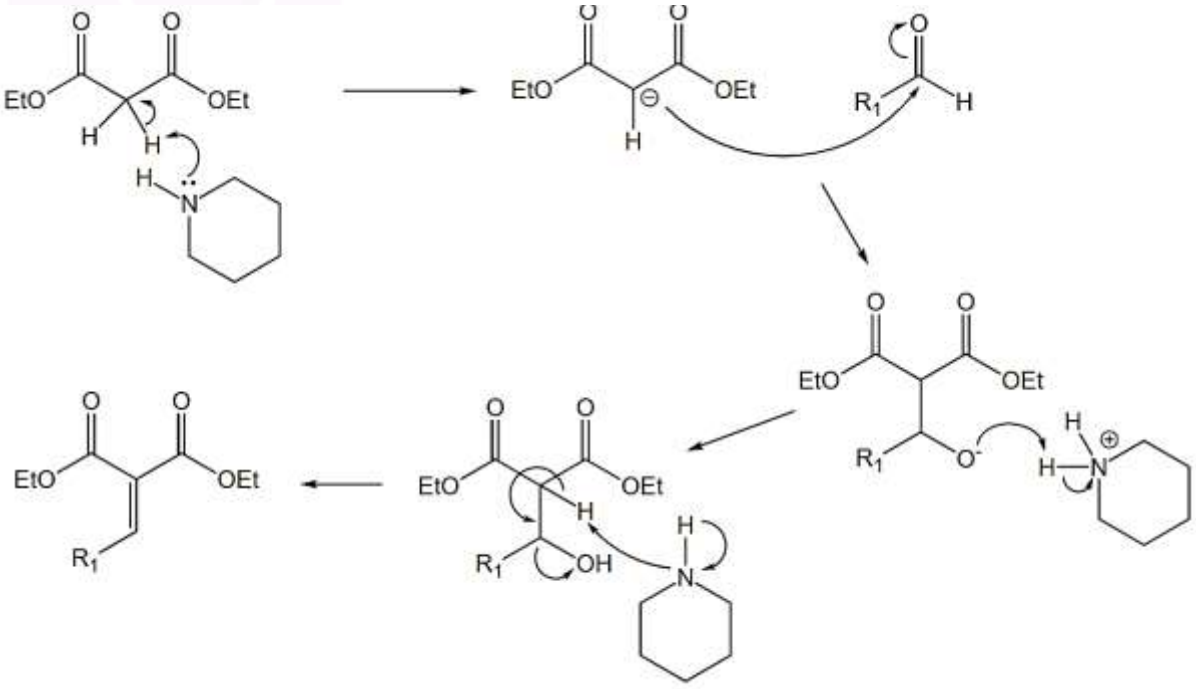
General reaction-



Z: electron withdrawing group

(Example- diethyl malonate, Meldrum's acid, ethyl acetoacetate, malonic acid or nitromethane)

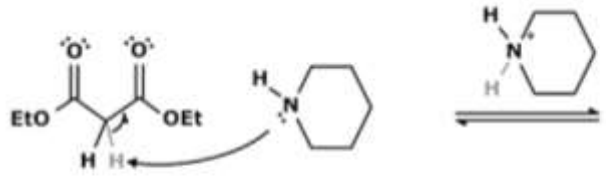
Reaction mechanism- It can be studied like Crossed Aldol Reaction.

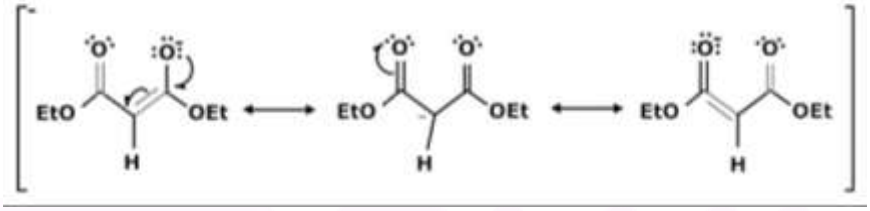


Step by step Mechanism-

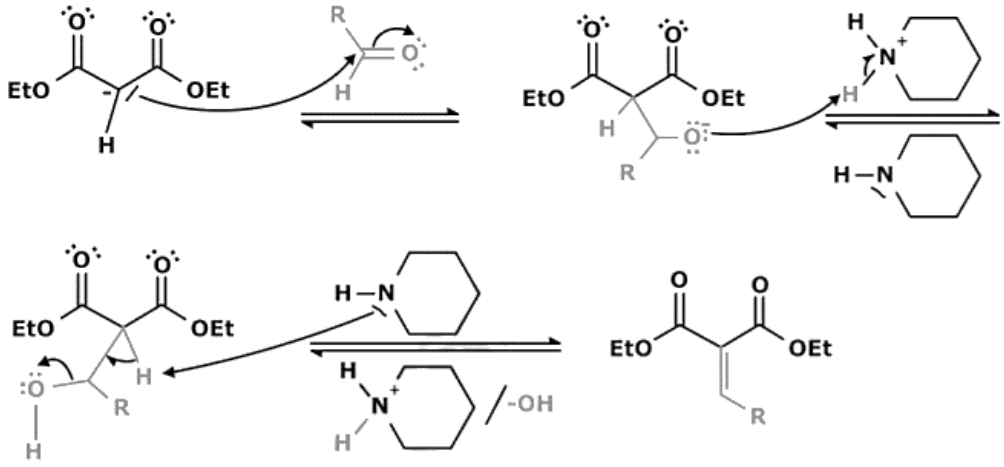
The mechanism is very similar to aldol condensation where a carbanion is generated which attacks as nucleophile on the electrophilic center of the other molecule leading to condensation.

Step 1: Deprotonation of the activated methylene by the base (piperidine) to give a carbanion which is resonance stabilized via enolate ion.



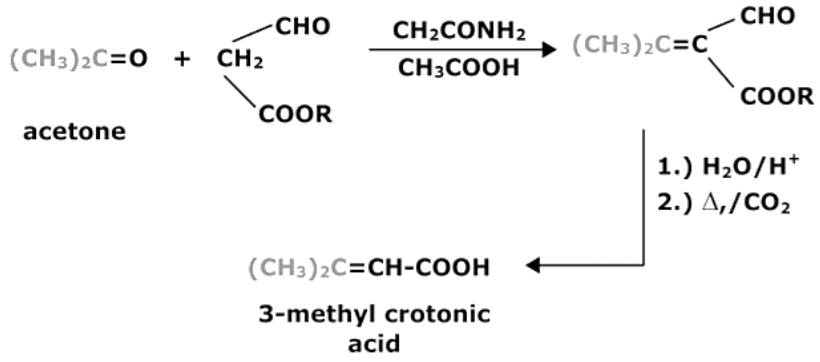


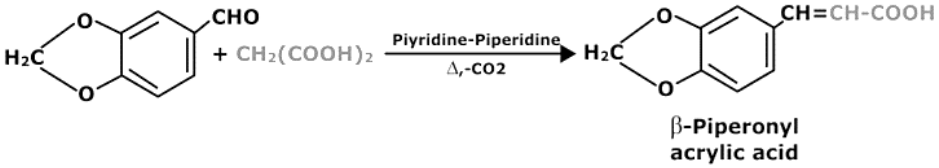
This enolate ion attacks as nucleophile via the carbon of carbanion on the carbonyl carbon of the aldehyde (or ketone). Unlike aldol, the resulting intermediate rather than taking proton undergoes base-induced elimination.



Note: Knoevenagel condensation reaction is involved as an important step in production of an antimalarial drug, lumefantrine.

Few examples of Knoevenagel reaction-





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