→ Organic synthesis via enolates :-

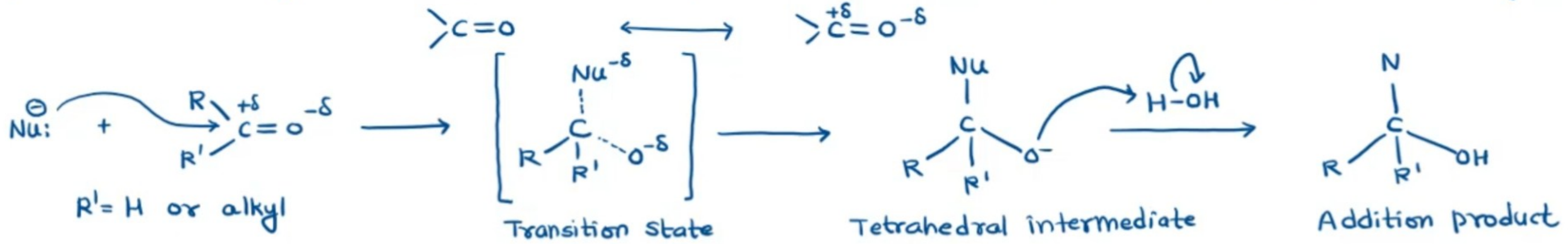
- Introduction:-

- Carbonyl compounds (aldehydes and ketones) show following two important chemical characteristics -

1. Polarity of carbonyl carbon   2. Acidic character of α- hydrogens.

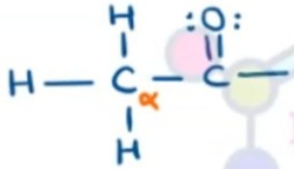
1. Polarity of carbonyl carbon:-

- Due to difference in electronegativities of carbon and oxygen, the π electron density around oxygen is more than that at the carbon atom.
- As a result oxygen bears partial negative charge and carbon bears partial positive charge.
- As a consequence, the carbonyl carbon can be attacked directly by a nucelophile to give a tetrahedral intermediate in which O bears a negative charge. This species get protonated to give final product. The proton needed is obtained from solvent or reagent.



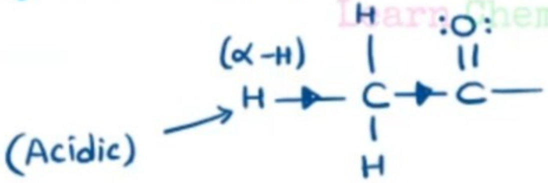
- The carbonyl carbon of >C=O group is sp^2 hybridised. So >C=O group is planar and hence can be attacked by the nucleophile from either side (top or bottom) with an equal probability.
- When the nucleophile attacks the carbonyl carbon, the hybridisation of carbon changes from sp^2 to sp^3 and new bond is formed between nucleophile and carbon
- The π electrons of the C=O bond completely transfered to the oxygen atom.

2. Acidity of α-hydrogens : Formation of Enolates:-



- The acidic character of α-hydrogen is due to following reasons-

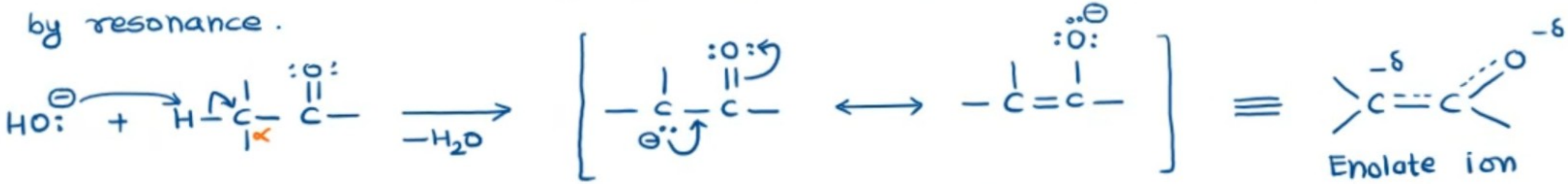
(i) Electron withdrawing effect (–I) of carbonyl group :-



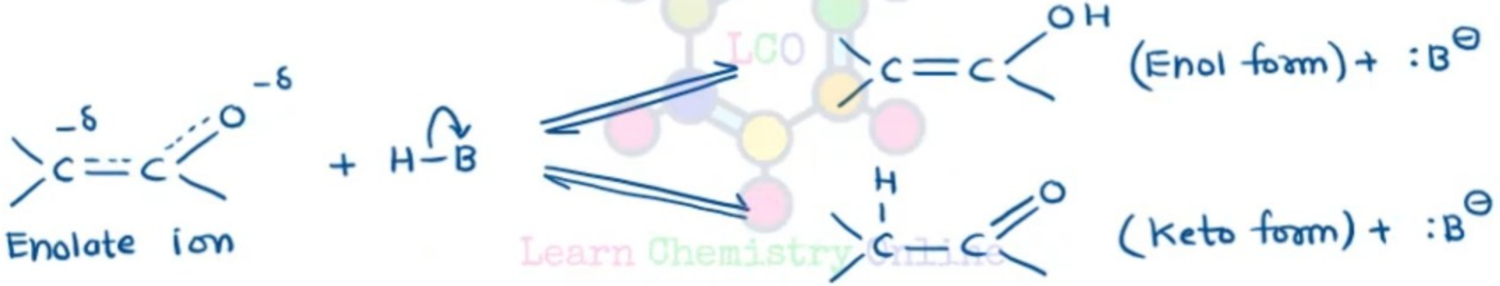
- Due to electronic imbalance, the carbonyl group tends to withdraw electrons from the adjacent C–C bond. This makes α-carbon more electron-deficient.
- The α-carbon, in turn, withdraw electrons from C_α–H bond and hence the α-hydrogen(s) are weakly held and hence can be easily attracted by strong bases.

(ii) Resonance stabilisation of the resulting carbanion:-

- After the removal of α-hydrogen by a strong base, the resulting carbanion is stabilised by resonance.



- Due to above mentioned resonance structures, this enolate ion can accept a proton at carbon atom to produce the keto form or at oxygen atom to produce the enol form.

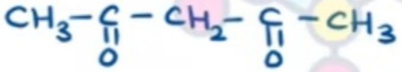


- Because of this behaviour the anion is called enolate ion.
- It may be noted that only α-hydrogens are acidic. β, γ, δ ... etc hydrogens are not acidic because inductive effect decreases with distance and also the resulting carbanion cannot be stabilised by resonance.
- α-hydrogens of carboxylic acids and its derivatives not not acidic. because $>C=O$ group is in conjugation with lone pair of adjacent heteroatom.

- α-hydrogens of aldehydes and ketones are acidic but the acidic character is very weak. hence these compounds cannot be converted into enolate ions by the reaction with bases such as alkali metal hydroxides.
- Aldehydes and ketones are far less acidic than water and alcohols. Therefore, strong bases such as sodium amide should be used to generate high concentration of the enolates.
- The acidic characters of carbonyl compound can be increased in the following cases:-

(i) when a hydrogen is placed α to two carbonyl groups.

- In this case, negative charge on the anion can be delocalised by both carbonyl groups which make the compound more acidic. e.g. acetyl acetone

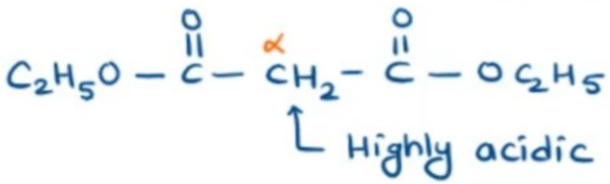


$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

(ii) In addition to $>C=O$ group, presence of some other strongly electron withdrawing group. e.g. acetonitrile (CH_3-CN)

- Conclusion:-
- The enolates obtained from the dicarbonyl compounds such as malonic ester or aceto acetic ester are very important in the organic synthesis because their enolates are easily formed by reacting these esters with sodium ethoxide.

→ Alkylation of Diethyl malonate : Malonic ester synthesis :-



$$C_2H_5O-\overset{O}{\overset{\|}{C}}-\overset{\alpha}{CH_2}-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

Highly acidic

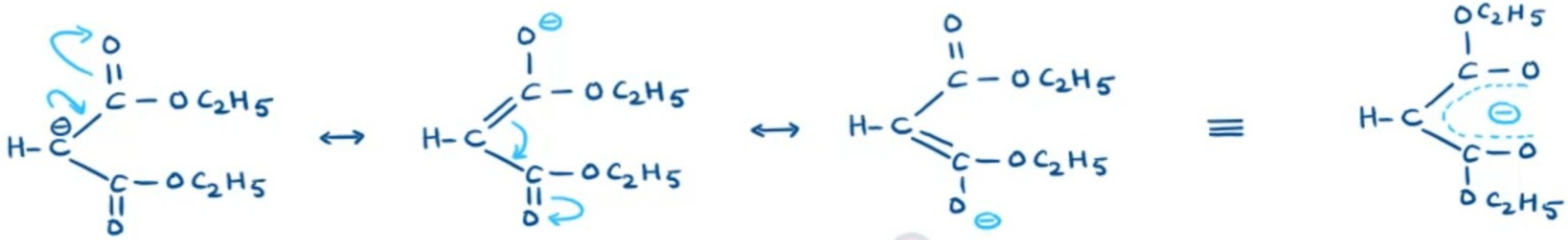
- The α-hydrogen atoms of methylene group in diethyl malonate are highly acidic it is surrounded by two electron withdrawing groups. This is the reason why this compound is called as active methylene compounds.
- Due to strong acidic nature of hydrogens of methylene group, it has become a versatile reagent in organic synthesis.
- In general the synthetic procedure utilising diethyl malonate consists of the following three different steps :-

(i) Formation of enolate anion:-

- Due to higher acidic character it is easily converted into enolate ion when treated with ethoxide ion.

$$2Na + 2C_2H_5OH \longrightarrow \underset{\text{Base}}{2C_2H_5\overset{\ominus}{O}\overset{\oplus}{Na}} + H_2O$$

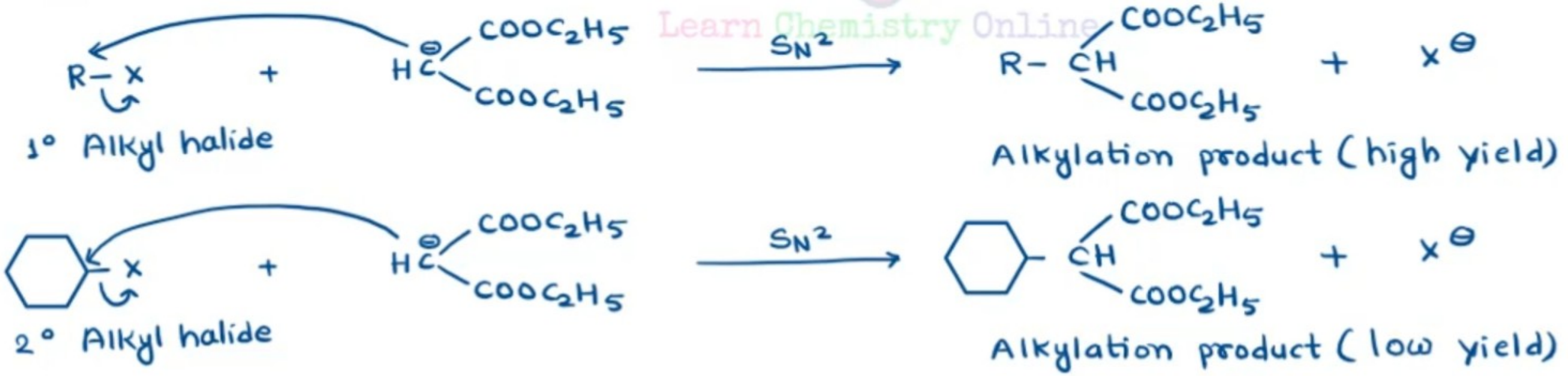
- The enolate ion is stabilised by resonance

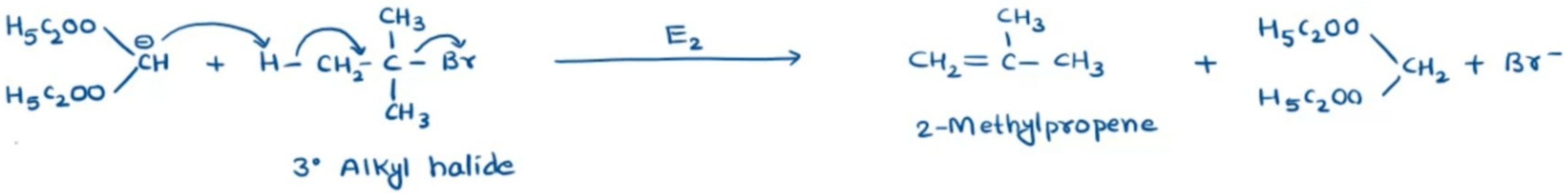


Resonance hybrid

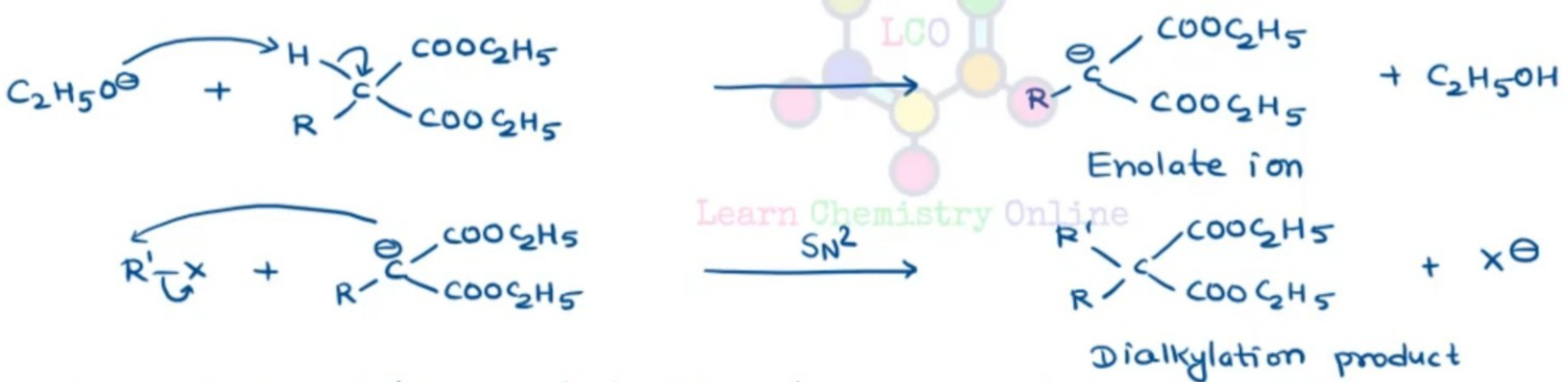
(ii) Alkylation of enolate ion (S_N2 substitution)

- Enolate ion attakes on primary alkyl halide to form alkylation product.
- The yields are low for secondary alkyl halides. However, the tertiary alkyl halides undergo elimination reaction to form alkene.





- Aryl halides cannot be used for alkylation as they fail to undergo S_N2 reaction.
- As the product after monoalkylation still has an acidic hydrogen, it can further react with sodium ethoxide to give corresponding enolate ion which may react with another molecule of alkyl halide to give dialkyl malonic ester.

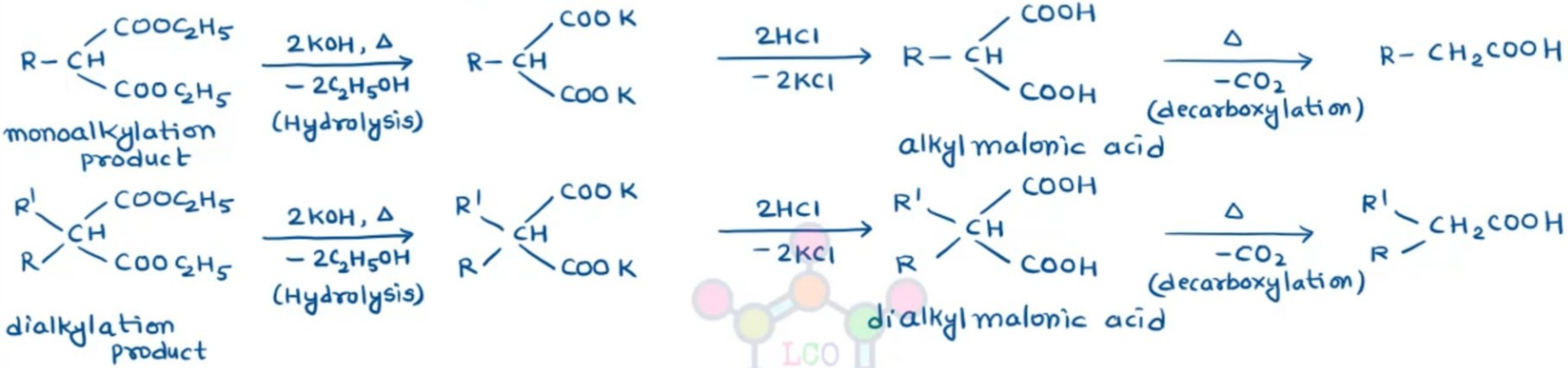


- formation of dialkylation product can be represented as-

$$CH_2(COOC_2H_5)_2 \xrightarrow[2.\ RX]{1.\ C_2H_5ONa} RCH(COOC_2H_5)_2 \xrightarrow[2\ R'X]{1.\ C_2H_5ONa} RR'(COOC_2H_5)_2$$

- α-haloketones and α-haloester can also be used for alkylation of malonic ester.

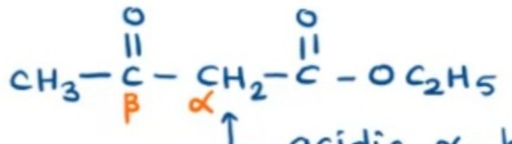
(iii) Hydrolysis and decarboxylation:-



- The above three step procedure is called Malonic ester synthesis (MES) and used to synthesise a large variety of organic compounds.
  e.g. synthesis of monocarboxylic acids, dicarboxylic acids, diols etc.

→ Alkylation of ethyl acetoacetate : Acetoacetic ester synthesis :-

- Ethyl acetoacetate or acetoacetic ester is a β-keto ester having two α-hydrogens.



$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$

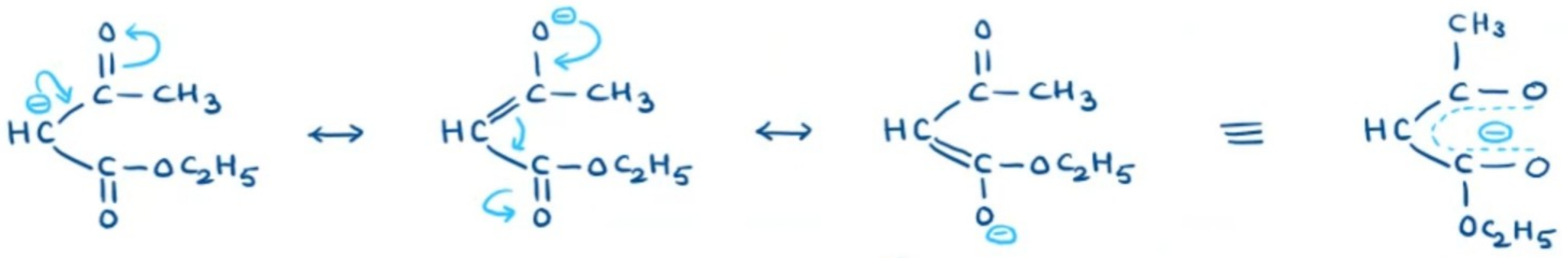
acidic α-hydrogens

- like malonic ester it also has a CH_2 group (methylene group) surrounded by two carbonyl groups(one keto carbonyl and one ester carbonyl) and hence it is also called an active methylene compound.
- It is also an important reagent in organic chemistry.
- Its synthetic utility depends upon the following three steps:-

(1) Formation of enolate ion:-

- Due to its acidic character (acidic α-hydrogens) it is easily converted in to enolate ion when react with ethoxide ion.

- The enolate ion is stabilised by resonance.



Resonance structures

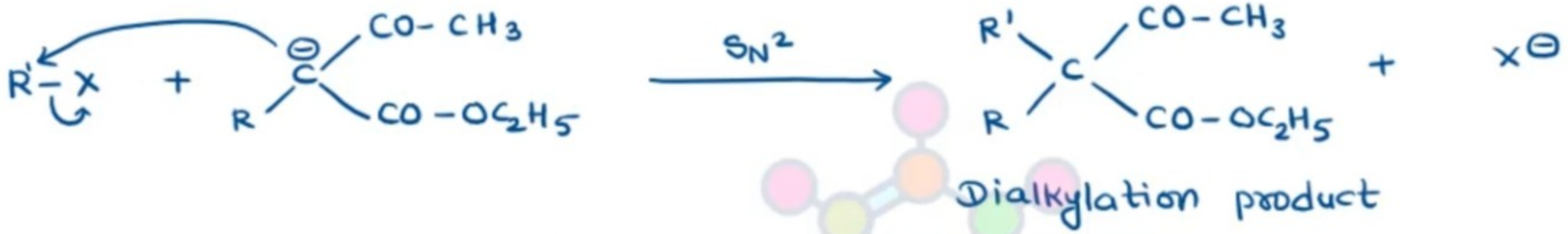
Resonance hybrid

(ii) Alkylation of enolate ion (S_N2 substitution):-

- Enolate ion of acetoacetic ester behaves as nucleophile and attaks on unhindered primary alkyl halide to give high yields of the monoalkylation products.

Monoalkylated acetoacetic ester.

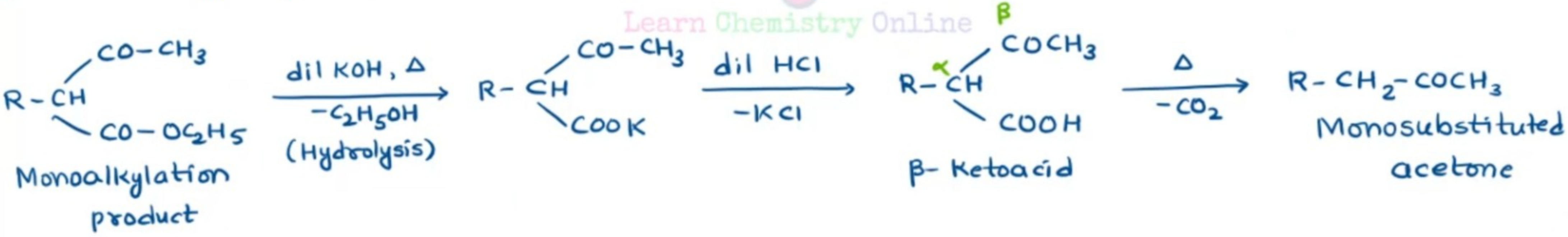
- As the monoalkylation product still has one more acidic hydrogen, it undergoes further reaction with sodium ethoxide to form corresponding enolate anion which reacts with alkyl halide to give dialkylated product.

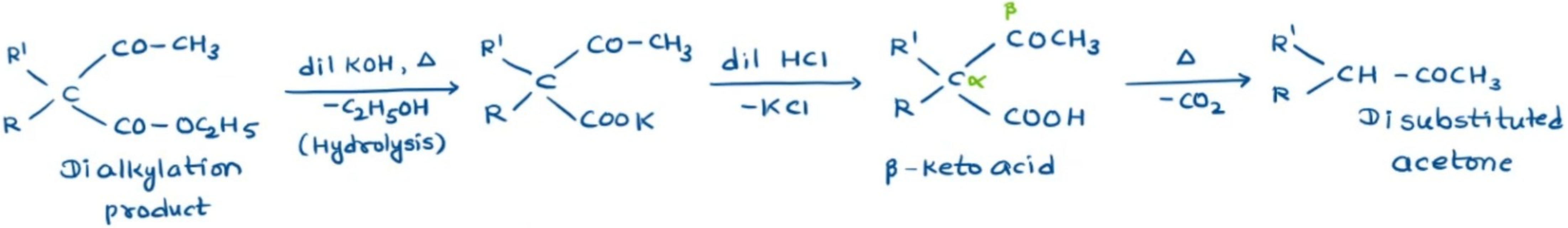


ii) Hydrolysis and decarboxylation:-

- The alkylated ester can undergo hydrolysis in two different ways:-

ⓐ Ketonic hydrolysis (Formation of Ketone):-





ⓑ Acidic hydrolysis (Formation of Acid):-

$$CH_3-\overset{O}{\overset{\|}{C}}-\overset{R}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[\Delta]{\text{Conc. KOH}} CH_3COOK + R\text{-}CH_2COOK + C_2H_5OH$$

- It may be noted that both ketonic and acid hydrolysis takes place simultaneously under both conditions (dilute as well as conc. KOH). The difference is that with dilute aqueous or ethanolic KOH solution ketones can be obtained as predominat products, whereas with conc. aqueous or ethanolic KOH solution mainly acids are the products.

- The above three step procedure is called acetoacetic ester synthesis (AES) which is used to synthesise a large variety of organic compound.

example. synthesis of ketones, carboxylic acids etc.

→ Synthesis of Ethyl acetoacetate : Claisen condensation:-

- Ethyl acetate can be converted to ethyl acetoacetate in presence of sodium ethoxide and ethanol.

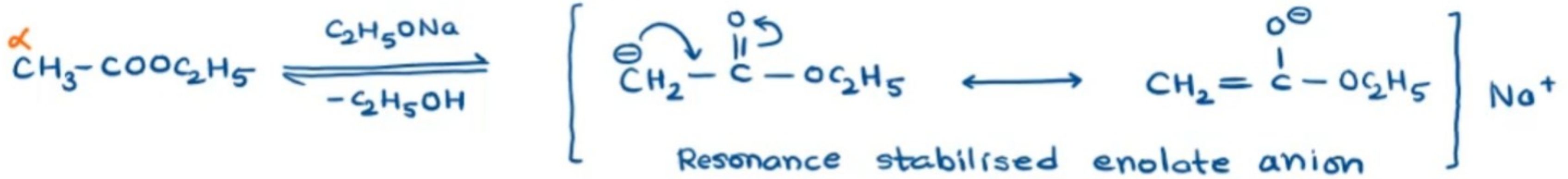
$$\underset{\text{Ethyl acetate}}{2\ CH_3COOC_2H_5} \xrightarrow[-C_2H_5OH]{C_2H_5\bar{O}\overset{+}{Na}} \underset{\text{Sod. salt of ethylacetoacetate}}{[CH_3COCHCOOC_2H_5]^-Na^+} \xrightarrow{H^\oplus} \underset{\text{Ethyl acetoacetate}}{CH_3COCH_2COOC_2H_5}$$

- The above reaction is known as claisen condensation.
- This reaction covers various condensation between a carboxylic ester and the ester containing an α-hydrogen, a ketone or a nitrile. These reactions are usually carried out by treating ester with sodium ethoxide in ethanol solution. other bases such as sodium hydride (NaH) or sodium methoxide have also been used.

- Mechanism:-

- The mechanism of Claisen condensation is similar to Aldol condensation.
- The reaction involves the following two steps-

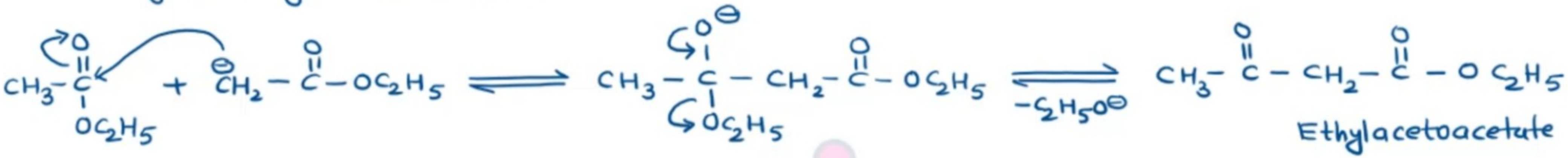
Step-I Loss of acidic α-hydrogen to form resonance stabilised enolate anion.



$$\overset{\alpha}{CH_3}-COOC_2H_5 \underset{-C_2H_5OH}{\overset{C_2H_5ONa}{\rightleftharpoons}} \left[\overset{\ominus}{C}H_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longleftrightarrow CH_2=\overset{O^\ominus}{\overset{|}{C}}-OC_2H_5 \right] Na^+$$

Resonance stabilised enolate anion

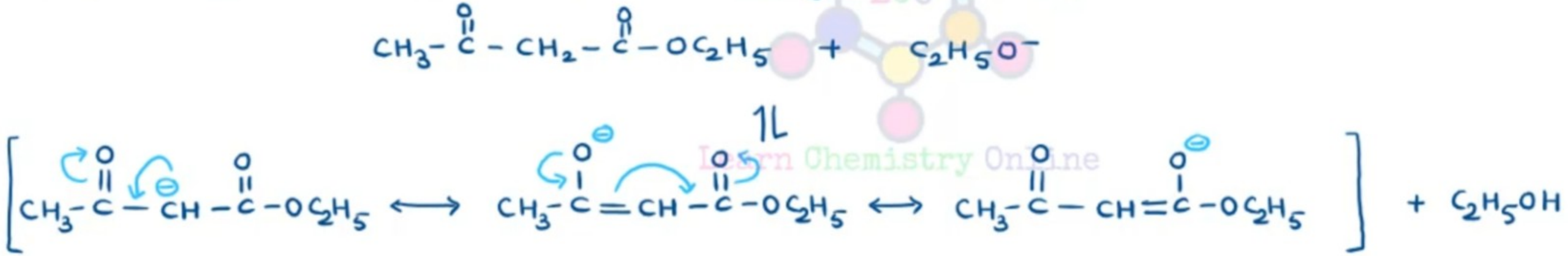
Step-II - Nucleophilic addition of the enolate ion on the carbonyl carbon of second molecule of ethyl acetate to give addition product which eliminates an ethoxide ion to give ethyl acetoacetate



$$CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5 + \overset{\ominus}{C}H_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \rightleftharpoons CH_3-\underset{OC_2H_5}{\overset{O^{\ominus}}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightleftharpoons[-C_2H_5O^{\ominus}]{} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

Ethylacetoacetate

- Finally in the presence of full equivalent of ethoxide, ethylacetoacetate is converted in to its enolate salt which is relatively more stable.



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5O^-$$

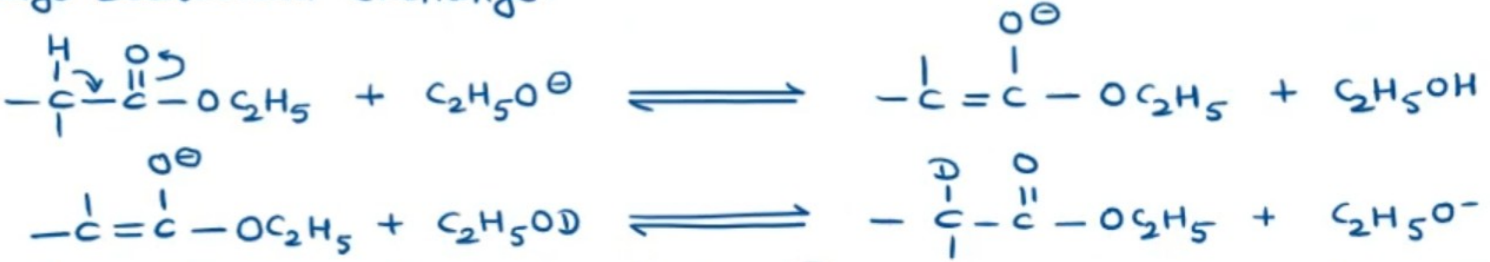
$$\Updownarrow$$

$$\left[CH_3-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longleftrightarrow CH_3-\overset{O^{\ominus}}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longleftrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH=\overset{O^{\ominus}}{\overset{|}{C}}-OC_2H_5\right] + C_2H_5OH$$

- Evidences:-

- Following two evidences are in favour of the above mechanism involving reversible formation of the enolate anion in claisen condensation.

(i) The esters having acidic α-hydrogens on treatment with $C_2H_5O^-$ in C_2H_5OD (Deuterated alcohol) readily undergo deuterium exchange.



$$-\overset{H}{\underset{|}{\overset{|}{C}}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5O^{\ominus} \rightleftharpoons -\overset{|}{C}=\overset{O^{\ominus}}{\overset{|}{C}}-OC_2H_5 + C_2H_5OH$$

$$-\overset{|}{C}=\overset{O^{\ominus}}{\overset{|}{C}}-OC_2H_5 + C_2H_5OD \rightleftharpoons -\overset{D}{\underset{|}{\overset{|}{C}}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5O^-$$

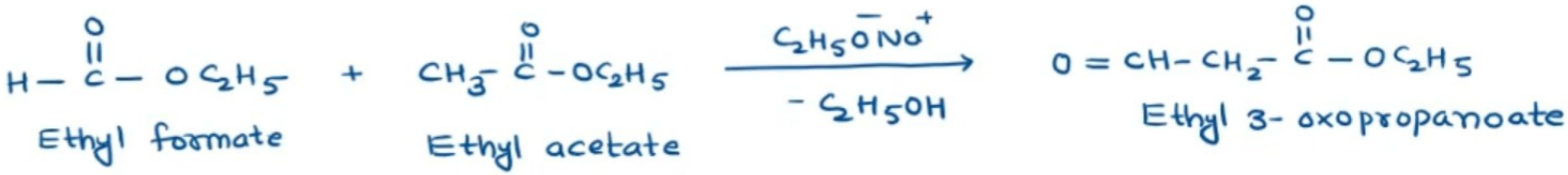
- The rate of exchange of these hydrogens are comparable to reactivity of these esters in Claisen condensation.

(ii) Due to reversible formation of enolate ion, optically active esters undergoes racimisation.

- Importance of Claisen condensation:-
- This reaction is not only limited to esters having α-hydrogens to form β-ketoesters, but may also be carried out on an ester and a Ketone or a nitrile to give β-diketones and β-ketonitriles. Further, besides sodium ethoxide, other bases such as sodium hydroxide, sodamide, triphenylmethylsodium may also be used.
- Cross Claisen condensation:-
- When Claisen condensation takes place between two different esters having α-hydrogens, a mixture of four possible β-ketoesters is formed which are difficult to separate and purify. Cross Claisen condensation of this type has no synthetic utility.

- when one ester does not possess α- hydrogens (e.g. ethyl formate, ethyl oxalate, ethyl benzoate etc.) then it has great synthetic utility.

e.g.



$$H-\overset{O}{\overset{\|}{C}}-OC_2H_5 + CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[-C_2H_5OH]{C_2H_5\bar{O}\overset{+}{Na}} O=CH-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

Ethyl formate

Ethyl acetate

Ethyl 3- oxopropanoate

→ Keto-Enol tautomerism of Ethyl acetoacetate :-

→ Tautomerism :-

- The structural isomers, which differ in the relative positions of their atoms and are in rapid equilibrium with each other, are called as tautomers and the phenomenon is termed as tautomerism.
- The interconversion of tautomers is a chemical reaction which involves making and breaking of sigma bonds.
- The tautomers aries due to 1,3 migration of proton or anion from polyvalent atom to the other atom within same molecule. Migration of proton is called prototropy and migration of anion is called aniontropy.
- The most important type of tautomerism is keto-enol tautomerism where keto and enol forms of a compound are in equilibrium.

Keto form

Enol form (ene+ol)

- Keto-enol tautomerism is represented by the compound containing a methylene ($-CH_2-$) or a methine group ($=CH-$) adjacent to a carbonyl group. e.g. ethyl acetoacetate

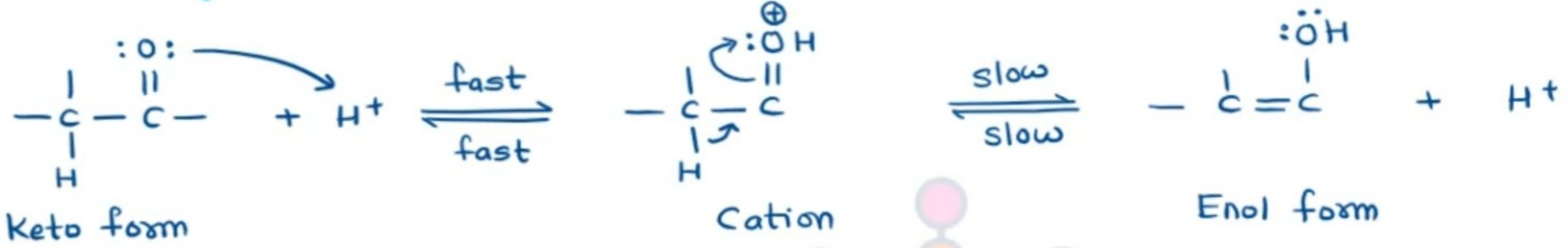
Ethyl acetoacetate
(Keto form)

Enol forms

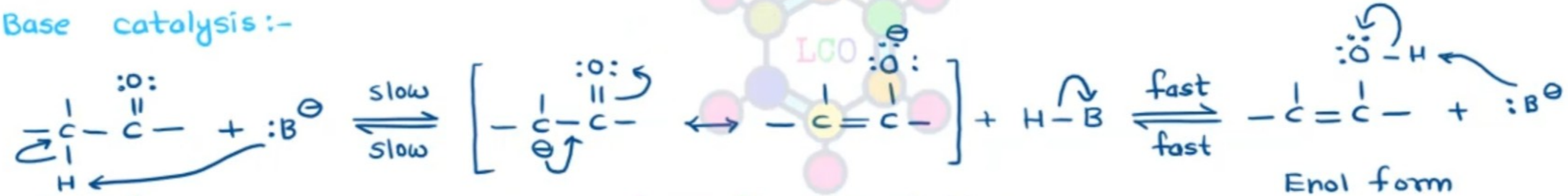
→ Mechanism of Keto-enol tautomerism:-

- Keto-enol interconversion is catalysed by both acids as well as bases-

ⓐ Acid catalysis:-



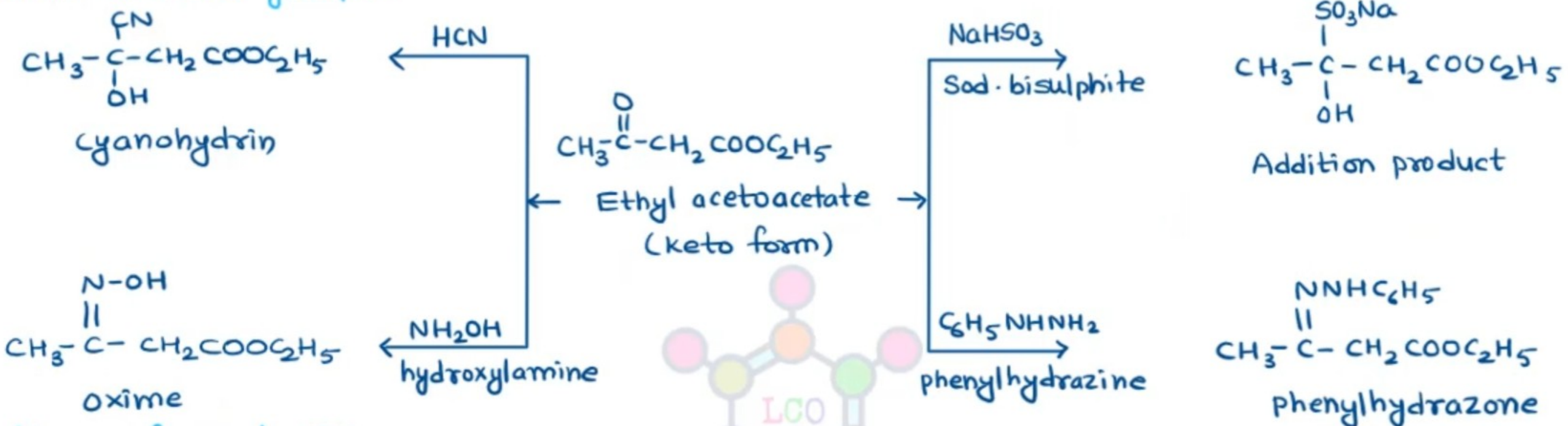
ⓑ Base catalysis:-



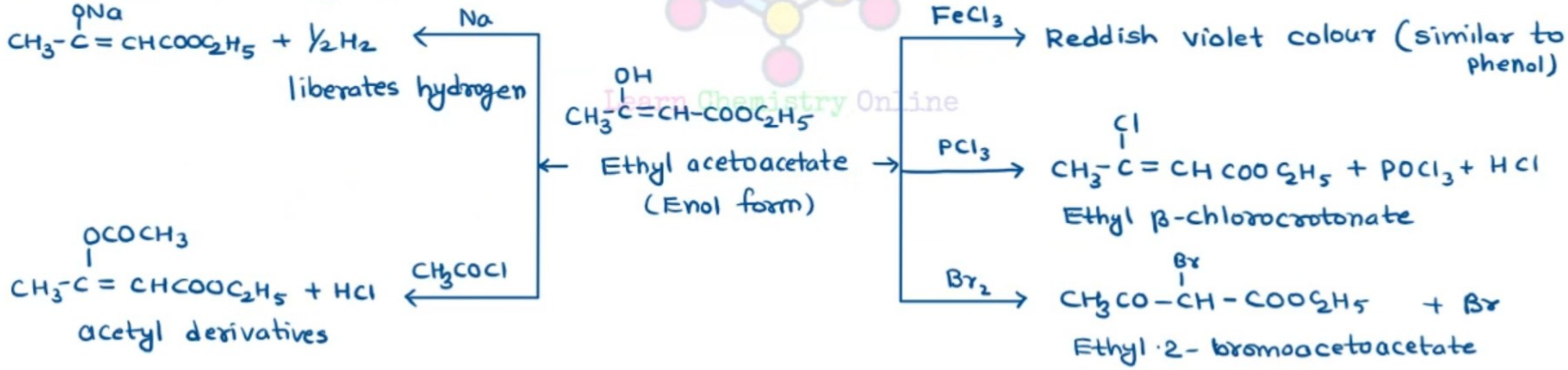
- Evidence in support of Keto-enol tautomerism in ethyl acetoacetate:-

- Ethyl acetoacetate undergoes due to both the keto and enol groups-

① Reactions of keto group:-



② Reactions of enol group:-



→ Isolation of tautomers:-

- Knorr (1911) separates keto and enol forms using petroleum ether.
- Meyer (1920), separated the two forms by Aseptic distillation (Fractional distillation in the absence of dust, moisture etc.)

→ Factors affecting the composition of keto-enol tautomeric mixture:-

① stability of enol form:-

- Keto form is more stable than enol form because C=O bond is stronger than C=C bond. Hence in simple aldehydes and ketones, amount of enol form is less than 1% i.e. negligible.
- The percentange of enol form increases in the following cases-

(i) When the ethylenic double bond is in conjugation with a carbonyl group.

(ii) Intramolecular H-bond is formed between the enolic hydroxyl group and second carbonyl group.

- In case of ethylacetoacetate, both the above conditions are satified, hence percentage of enol form is 7.5%.

② Polarity of solvent:- Polarity of solvent $\propto$ stability of keto form

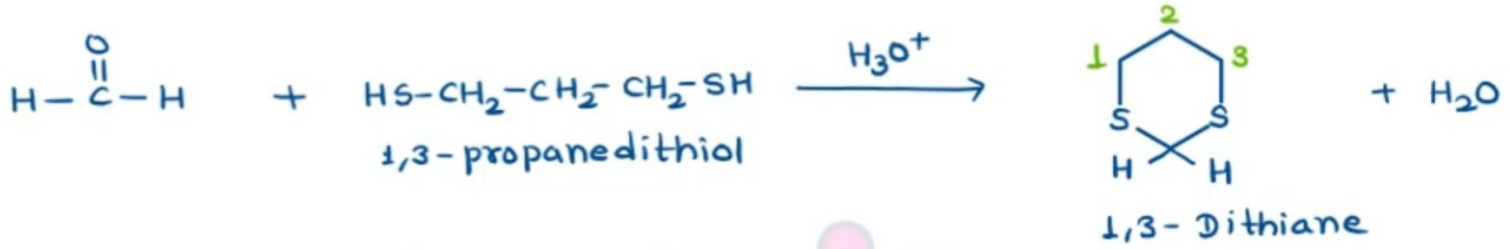
- Polar solvents stabilise the keto form by H-bond. hence % of keto form is high.

water as solvent → Keto (99.6%) + Enol (0.4)

Hexane (non polar) → Keto (53.6%) + Enol (46.4)

→ Alkylation of 1,3-dithiane :-

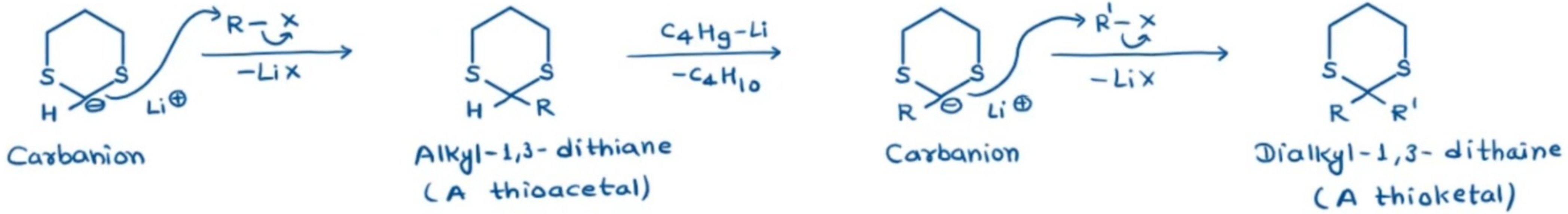
- 1,3-dithianes are prepared by reaction of formaldehyde with 1,3-propanedithiol in presence of acid.



- 1,3-Dithiane behave as a weak protonic acid as the hydrogen atoms of methylene group are surrounded by two sulphur atoms.
- In the presence of a strong base such as n-butyllithium, 1,3-diathiane can be converted into the corresponding anions which are stabilised by two sulphur atoms.

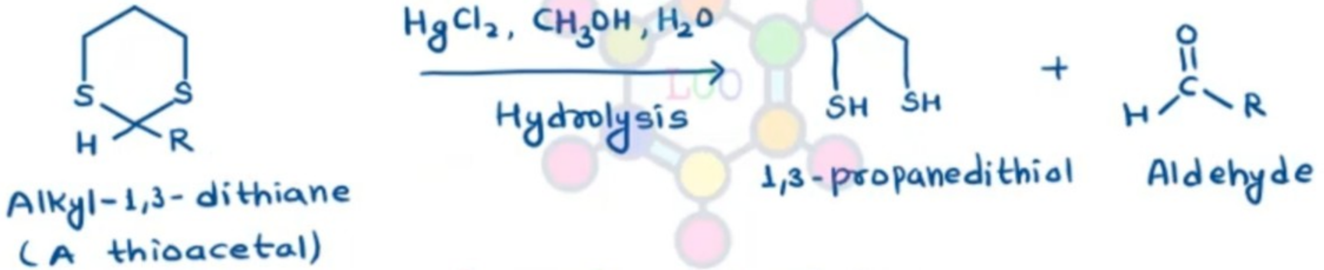
- Alkylation:-

- The carbanion of 1,3-dithiane behaves as a neucleophile and attacks on alkyl halide to form mono and dialkyl derivatives of 1,3-dithiane

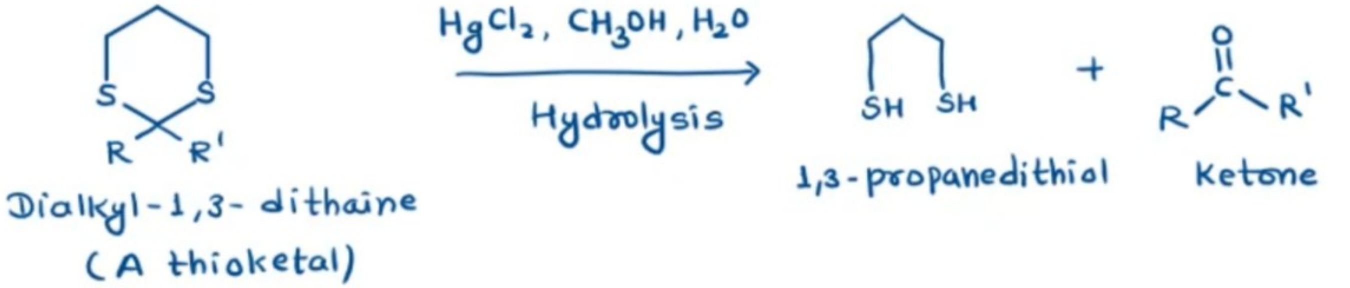


→ Synthetic utility of 1,3-dithiane:-

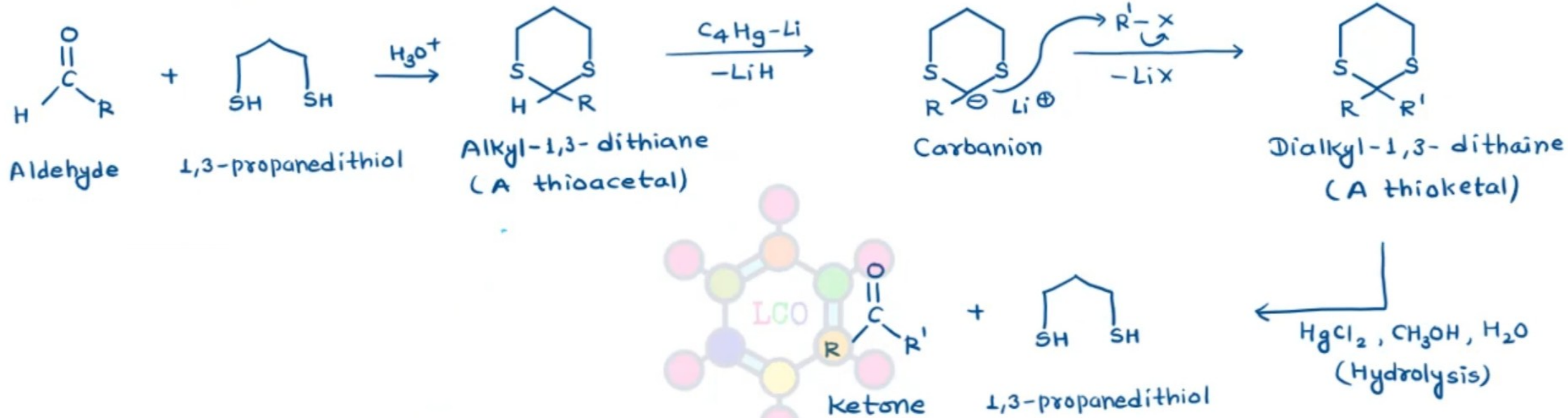
① Preparation of Aldehyde:-



② Synthesis of Ketone:-



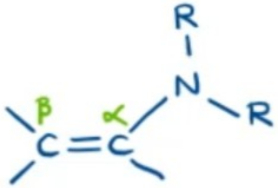
③ Conversion of Aldehydes into Ketones:-



→ Alkylation and Acylation of enamines:-

→ Enamines:-

- An enamine is a tertiary amine with a double bond in the α, β-position with respect to nitrogen.
- The term "enamine" comes from ene + amine by omitting 'e' from 'ene'.
- Enamine contains a nucleophilic carbon and undergo alkylation reaction.
- α, β-unsaturated amines are called enamines which are nitrogen analoues of enols.



Enamine

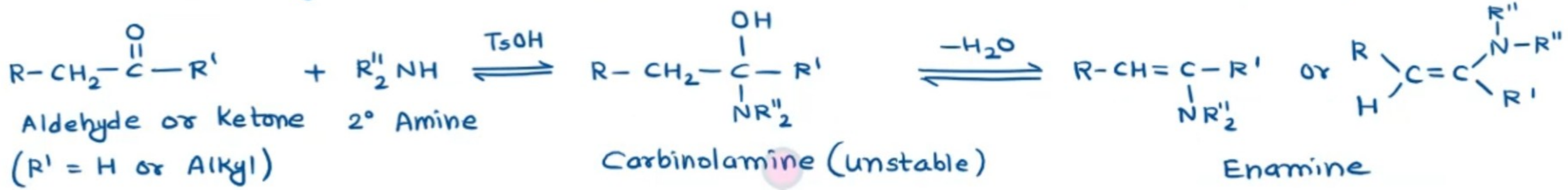
Enol

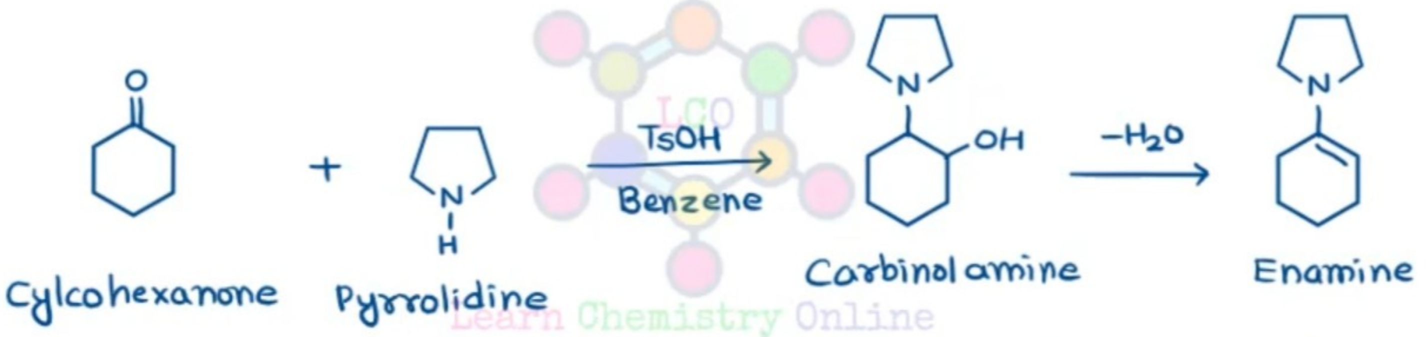
- Enamines are regarded as a resonance hybrid of the following two contributing forms.

- Due to anionic nature of β-carbon, enamines act as strong nucleophile.

→ Formation:-

- Enamines are obtained when an aldehyde or ketone having α-hydrogen atom(s) is treated with a secondary amine in the presence of an acid such as p-toluenesulphonic acid (TsOH).





- Water is removed as a azeotrope with benzene to shift the equilibrium forward. Most commonly cyclic 2° amines for this purpose are as follows-

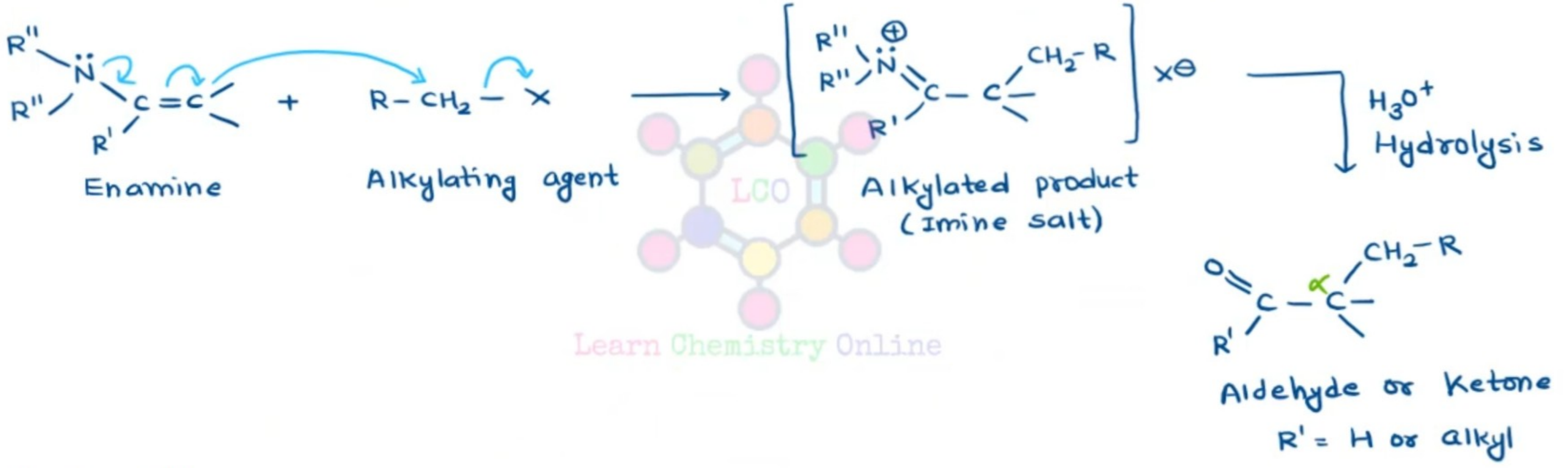
Pyrrolidine

piperidine

Morpholine

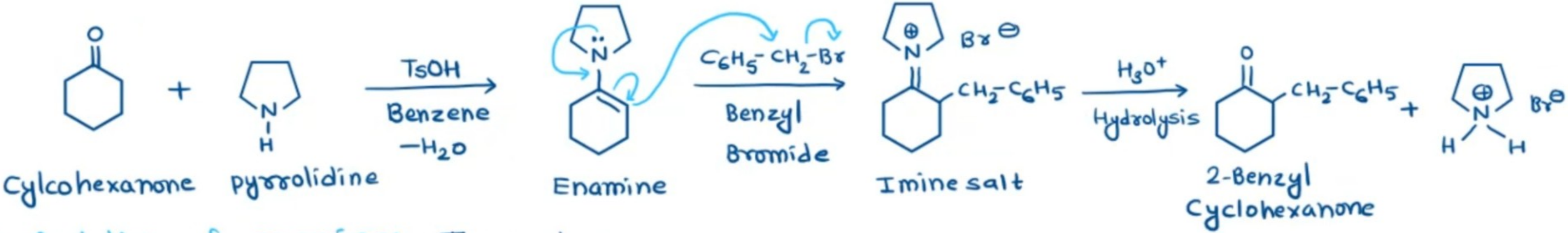
→ Alkylation of enamines:-

- Due to nucleophilic character, enamines undergo S_N2 reaction with primary alkyl halide or some other active alkyl halides such as allylic, benzylic etc. to form imine salts which on hydrolysis give alkylated aldehydes or ketones.
- α-haloethers and α-haloesters can also be used as alkylating agents.



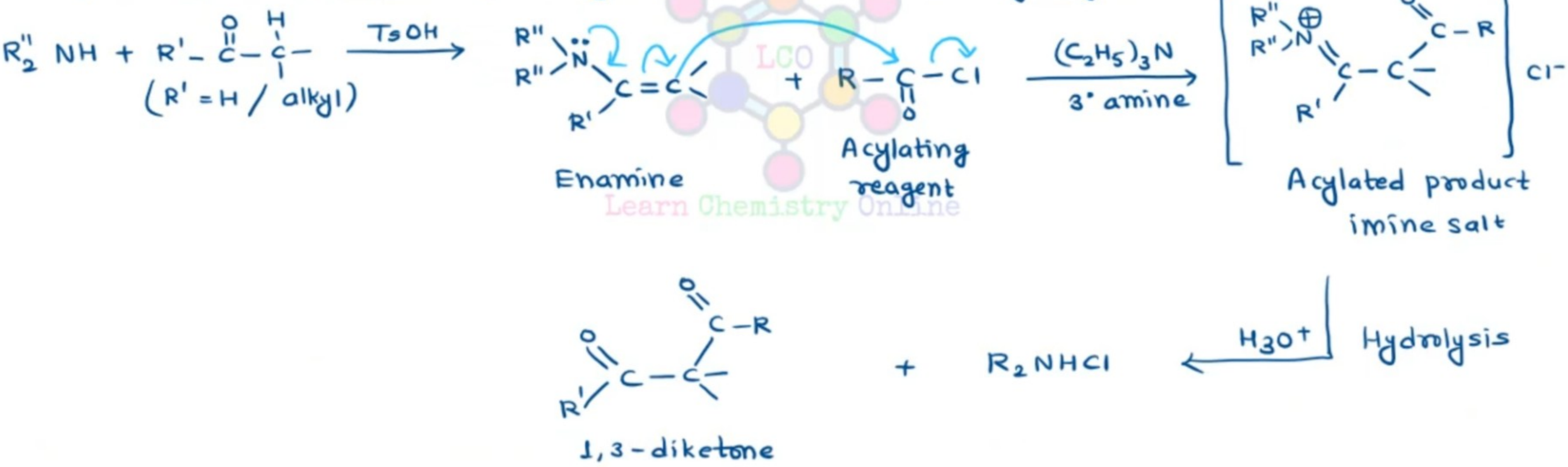
- Synthetic utility:-

- The procedure involving alkylation of enamines followed by hydrolysis has been used for α-alkylation of aldehydes and ketones. The α-alkylation of aldehydes or ketone is known as Stork-enamine synthesis.



→ Acylation of enamine:- Three steps-

(i) Preparation of enamine (ii) Acylation reaction (iii) hydrolysis



→ Synthetic Utility :- 1,3-dicarbonyl compounds can be prepared by acylation of enamine.