Aldehyde and Ketone

Bayer-Villiger Oxidation:

The treatment of ketones with paracids such as perbenzoic acid or peracetic acid or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by insertion of oxygen. The reaction is called Bayer-Villiger oxidation.

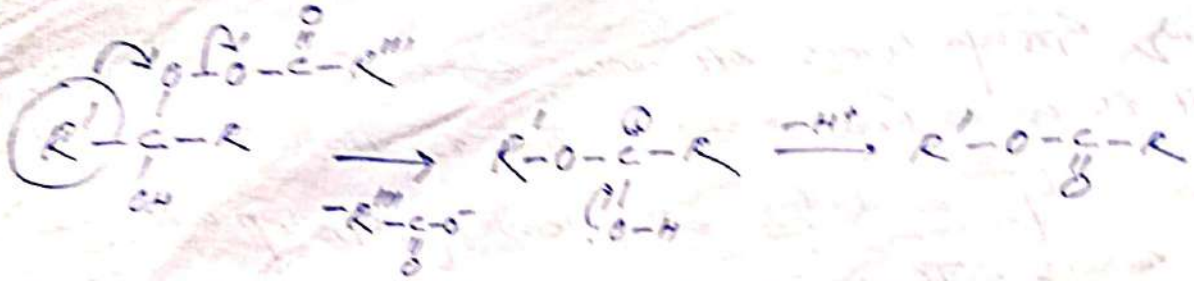
$$R-\overset{\overset{O}{\|}}{C}-R' + R-\overset{\overset{O}{\|}}{C}-OOH \longrightarrow R-\overset{\overset{O}{\|}}{C}-OR'$$

A particularly good reagent is peroxytrifluoro acetic acid. For unsymmetrical ketones the approximate order of migration is tertiary alkyl > 2nd alkyl ≈ aryl > primary alkyl > methyl.

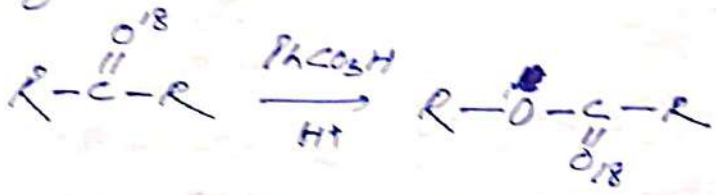
Enolizable β-diketone ($R-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-R$) do not react. α-diketones ($R-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-R$) can be converted to anhydride. With aldehyde migration of hydrogen gives the carboxylic acid.

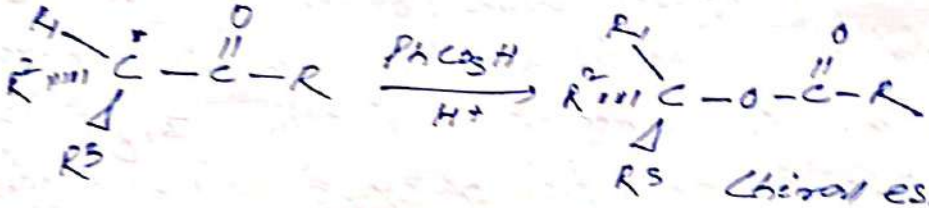
Mechanism:

$$R'-\overset{\overset{O}{\|}}{C}-R \xrightarrow{H^+} R'-\overset{\overset{\oplus O-H}{\|}}{C}-R \equiv R-\overset{\overset{\oplus}{O}H}{\overset{|}{C}}-R \xrightarrow{R'''CO_3H} \longrightarrow$$



One important piece of evidence for this mechanism was that benzophenone-^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxy oxygen.





Chiral ester with retention of configuration

This suggests that discrete carbanion formation is not involved during the migration of the group.

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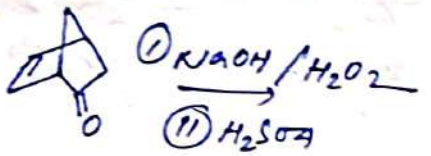
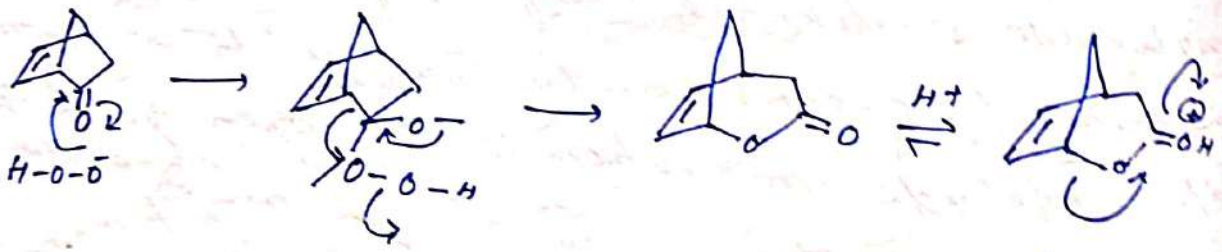
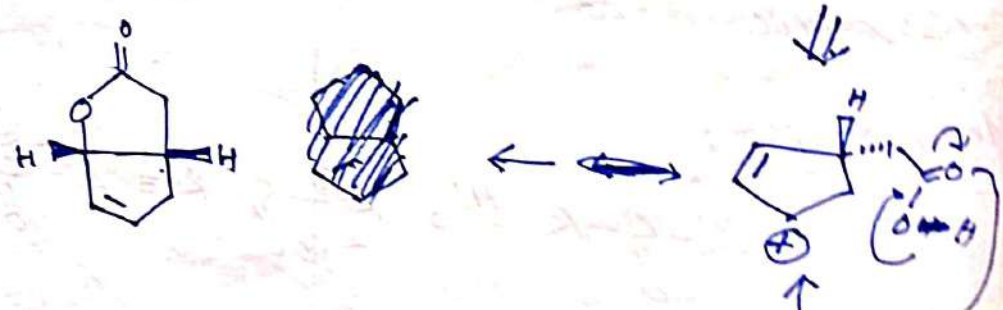






Wittig reaction:

In the Wittig reaction an aldehyde and ketone is treated with phosphorous ylide to give an olefin. Phosphorous ylids are usually prepared by treatment of phosphonium salt with a base, and phosphonium salt are usually prepared from the phosphine and alkyl halid.

$$Ph_3P + X-\underset{R'}{\underset{|}{CH}}-R \longrightarrow Ph_3\overset{\oplus}{P}-\underset{R'}{\underset{|}{CH}}-R \; X^{\ominus}$$

$$\downarrow BuLi$$

$$\left[Ph_3\overset{\oplus}{P}-\underset{R'}{\underset{|}{\ddot{C}^{\ominus}}}-R \longleftrightarrow Ph_3P=\underset{R'}{\underset{|}{C}}-R \right]$$

ylide.

$$-\underset{O}{\underset{\|}{C}}- + Ph_3\overset{\oplus}{P}-\underset{R'}{\underset{|}{\ddot{C}^{\ominus}}}-R \longrightarrow -\underset{R'}{\underset{|}{C}}=C-R$$

The phosphonium salts are most often converted to the ylides by treatment with a strong base such as butyl lithium, Sodium amide, Sodium hydride or a Sodium alkoxide.

An important advantage of the Wittig reaction is that the position of the new double bond is always certain, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensation.

The reaction is very general. The aldehyde or ketone may be aliphatic, alicyclic or aromatic; it may contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_3, aromatic nitro or halo, acetal or even ester group. Double or triple bonds conjugated with carbonyl also do not interfere.

Role of Solvent in S_N2 reaction:

S_N2 reaction rate increases with increasing polarity of solvent:

Nucleophilic displacement reactions involve ion either as nucleophiles or as products, as a consequence relatively polar solvents are required. A polar solvent has a relatively high dipole moment and dielectric constant. Both hydroxylic as well as polar aprotic solvents (eg. DMSO, DMF) are used. Aprotic solvents cannot form hydrogen bonds, thus they do not solvate anions to any appreciable extent. Consequently with anionic nucleophiles, reaction rates are far greater in the polar aprotic solvents.

A polar aprotic solvent dissolves ionic compounds, and it solvate cations, the way similar to protic solvents by orienting the negetive end of its dipole around the cation. It is ~~unable~~ however, Unable to solvate the anion by H-bonding.

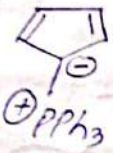
→

Simple ylides are highly reactive, reacting with oxygen, water, HCl and alcohols, as well as carbonyl compounds and carboxylic esters., so the reaction runs under conditions where these materials are absent.

$$Ph_3\overset{+}{P}-\bar{C}H-\underset{\underset{O}{\|}}{C}-R \longleftrightarrow Ph_3\overset{+}{P}-CH=\underset{\underset{O^-}{|}}{C}-R$$

Stable ylide

The ylide of type ① does not react with ketone or aldehydes.



Special example

① $R''OCH_2Cl \xrightarrow{PPh_3} R''OCH_2\overset{+}{P}Ph_3\,Cl^- \xrightarrow[2.\,RCOR']{1.\,base} R''OCH=\underset{\underset{R}{|}}{C}-R'$

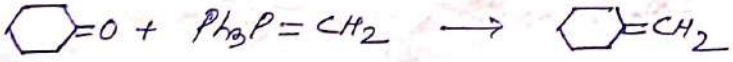
↓ hydrolysis

$R'-\underset{\underset{R}{|}}{C}=CH-OH$

⇌

$R-\underset{\underset{R}{|}}{CH}-CHO$

(ii) $-\underset{|}{C}=O + Ph_3\overset{+}{P}-\bar{C}HCH_2COO^- \rightarrow -\underset{|}{C}=CHCH_2COO^-$

(222) 

ylides are usually prepared from triphenyl phosphine, but phosphonate esters may also been used:

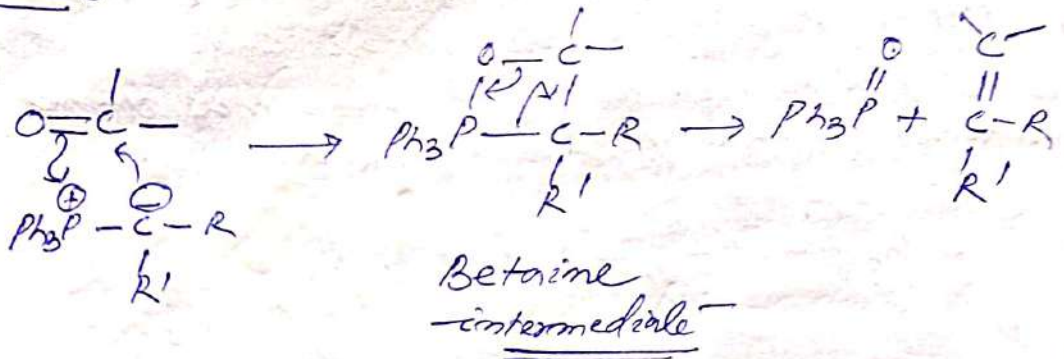
$$(RO)_2\overset{\overset{O}{\|}}{P}-\underset{\underset{R'}{|}}{CH}-R'' \xrightarrow{base} (RO)_2\overset{\overset{O}{\|}}{P}-\underset{\underset{R'}{|}}{\bar{C}}-R''$$

↓ $-C=O$

$$-\underset{|}{C}=\underset{\underset{R'}{|}}{C}-R''$$

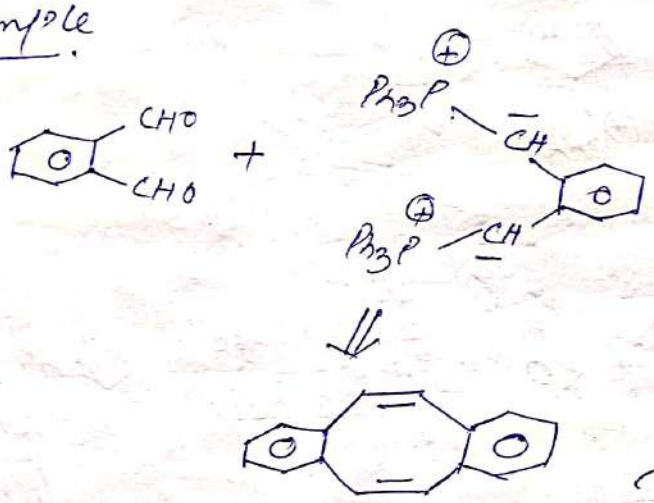
$$* (EtO)_3P + RCH_2X \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}-CH_2R$$

Mechanism:



Betaine intermediate

Special example



* What is ylide?

A ylide is a neutral dipolar molecule containing a formally negetively charged atom directly attached to a hetero atom with a formal positive charge, and in which both atoms have full octet of electrons.

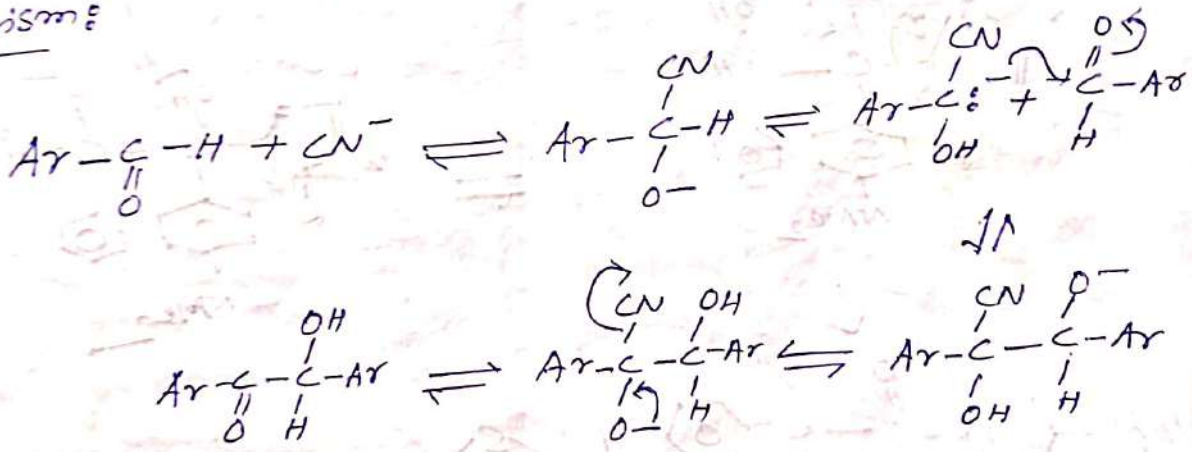
* ✓ $Ph_3\ddot{N}$ cannot be used as a substituted for Ph_3P in Wittig reaction. Give reason—

Benzoin condensation:

When certain aldehydes are treated with cyanide ion, benzoins are produced in a reaction called the Benzoin condensation. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction can be accomplished only for aromatic aldehydes, though not for all of them, and for glyoxals RCOCHO. The one that no longer has a C-H bond in the product is called the donor, because it has "donated" its hydrogen to the oxygen of the other molecule, the acceptor.

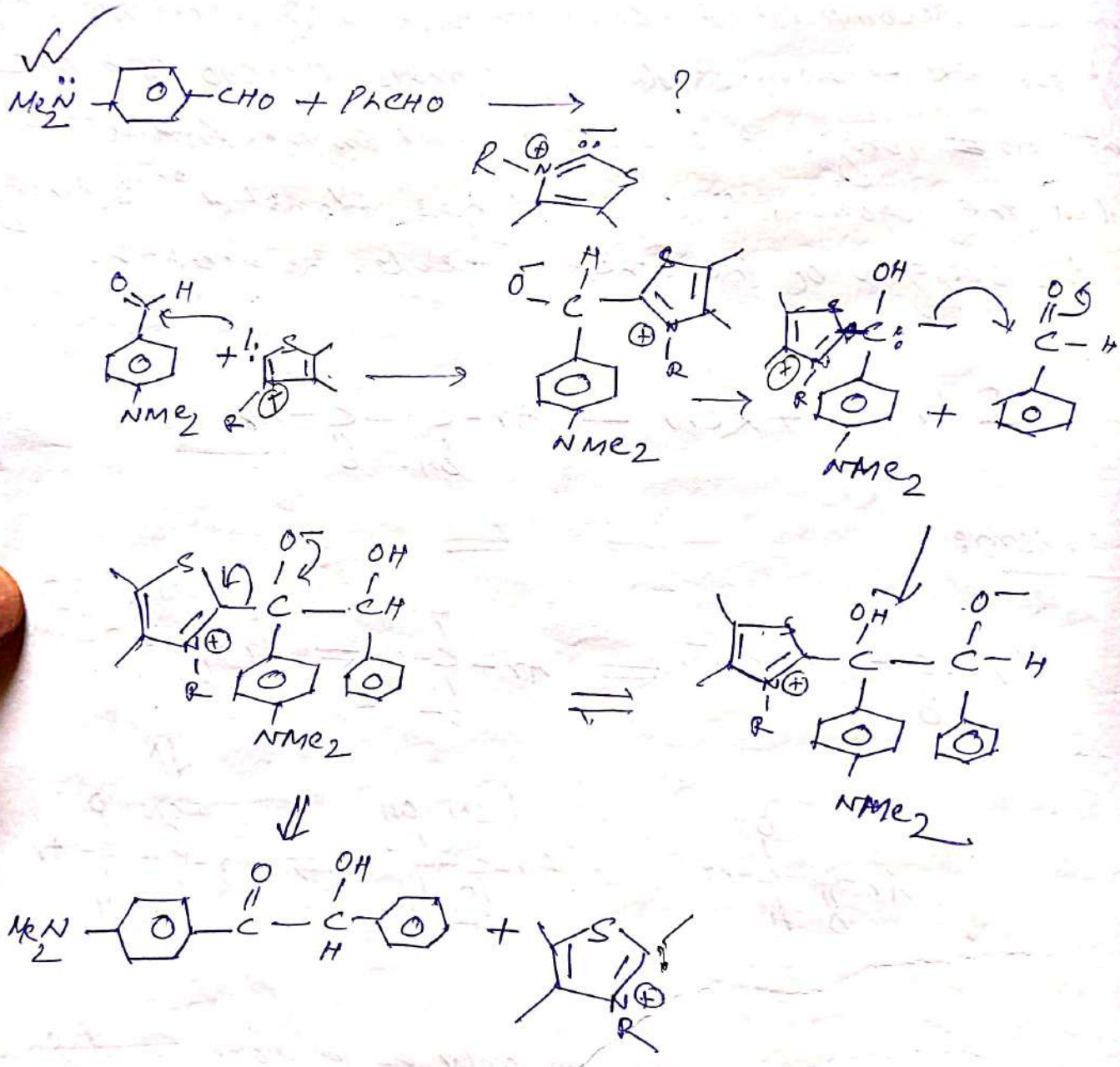
$$2\,ArCHO + KCN \longrightarrow Ar-\underset{OH}{CH}-\underset{O}{C}-Ar$$

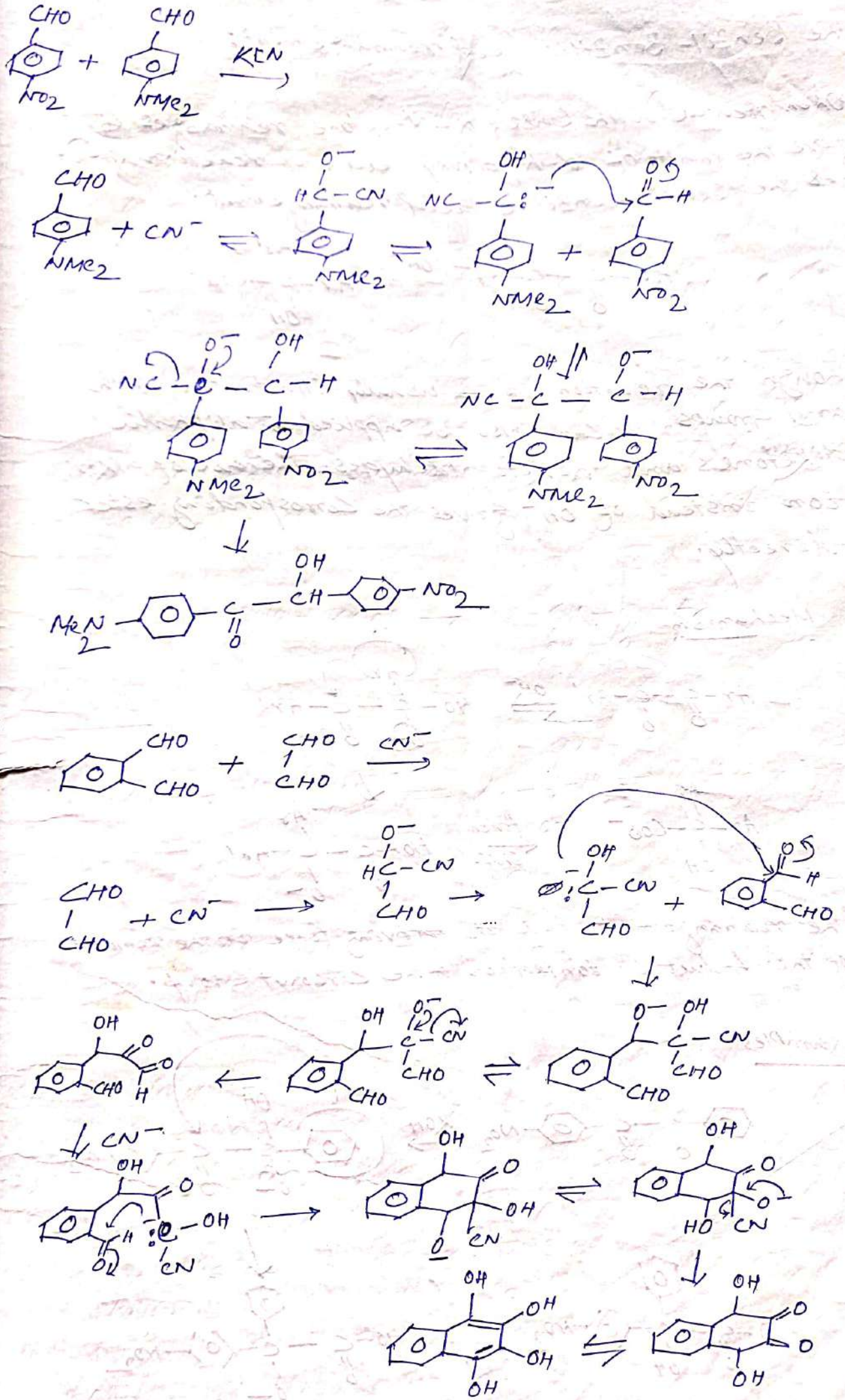
Mechanism:



Some aldehydes can perform only as a donor and some only as an acceptor and hence cannot be self-condensed, though they can be condensed with different aldehyde. For example p-dimethylaminobenzaldehyde is only acts as a donor. Thus it can not condense with itself, but it can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor.

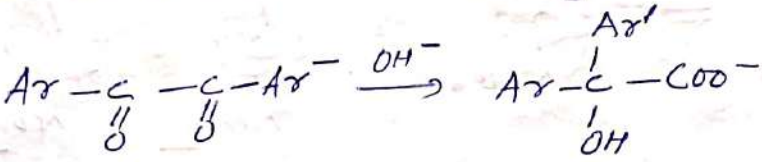
CN^- is a highly specific catalyst for this reaction, because it can perform three function ① it acts as a nucleophile ② its electron-withdrawing ability permit loss of the aldehydic protons and ③ having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze this reaction.





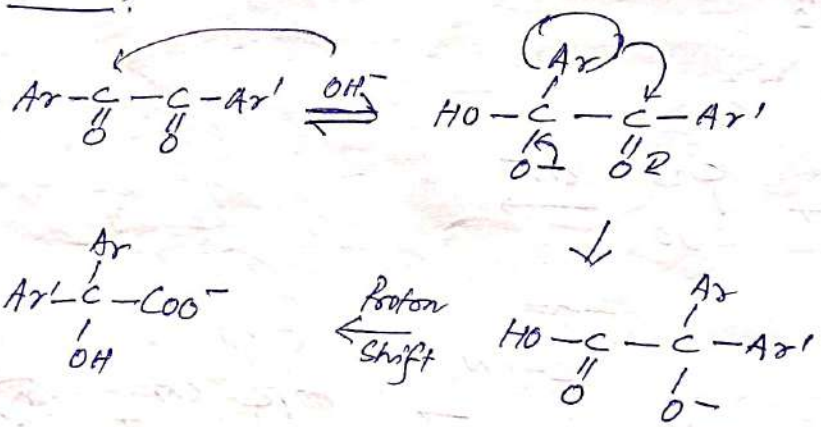
The Benzil-Benzilic acid rearrangement:-

When treated with base, α-diketone rearranges to give the salt of α-hydroxy acid, a reaction known as the benzil-benzilic acid rearrangement.



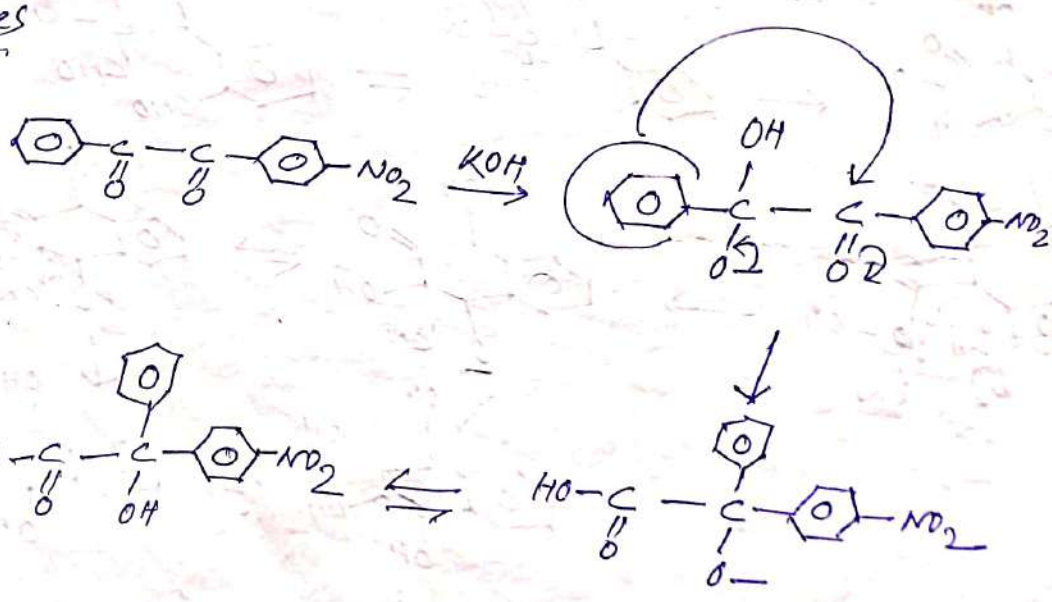
Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones and α-keto aldehydes. The use of alkoxide ion instead of OH^- gives the corresponding ester directly.

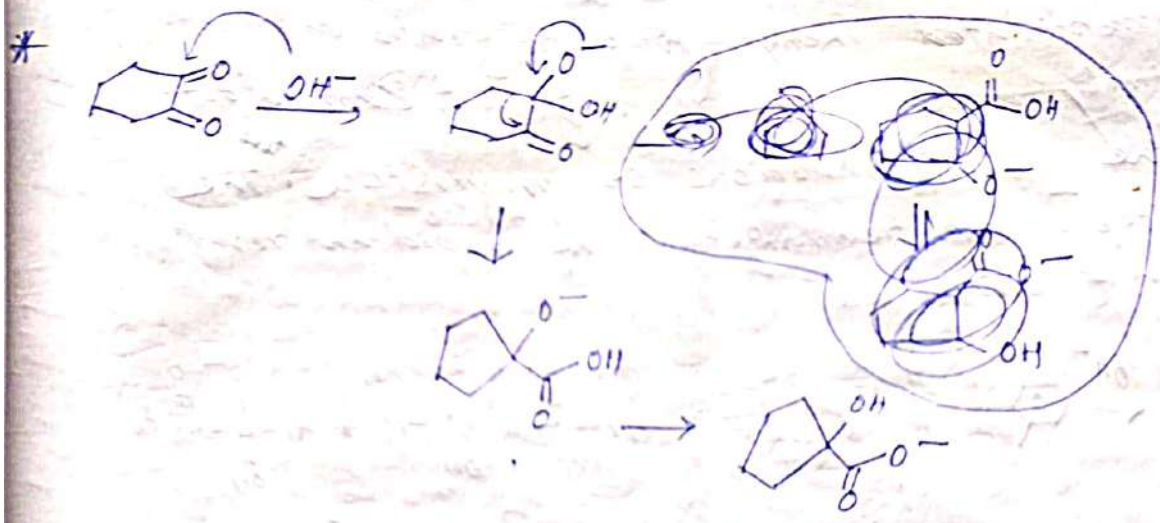
Mechanism

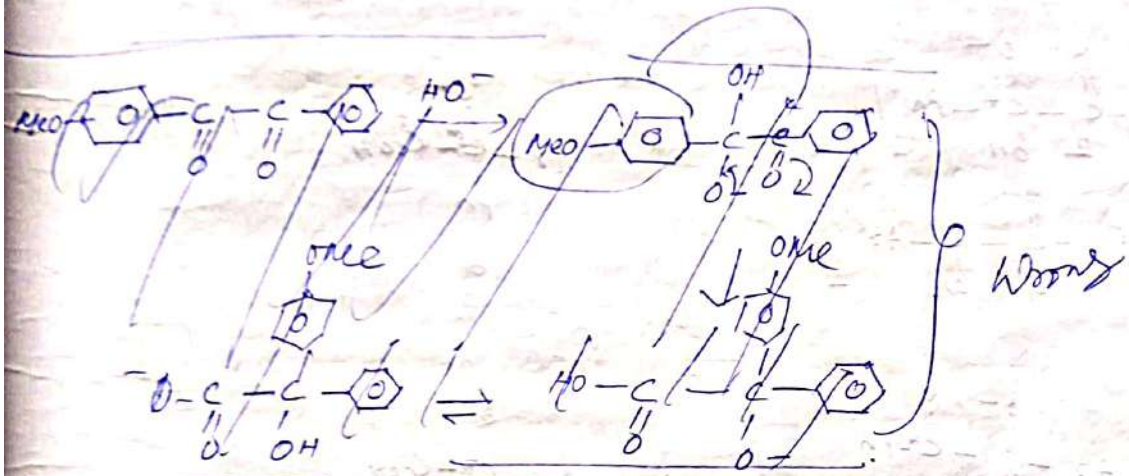


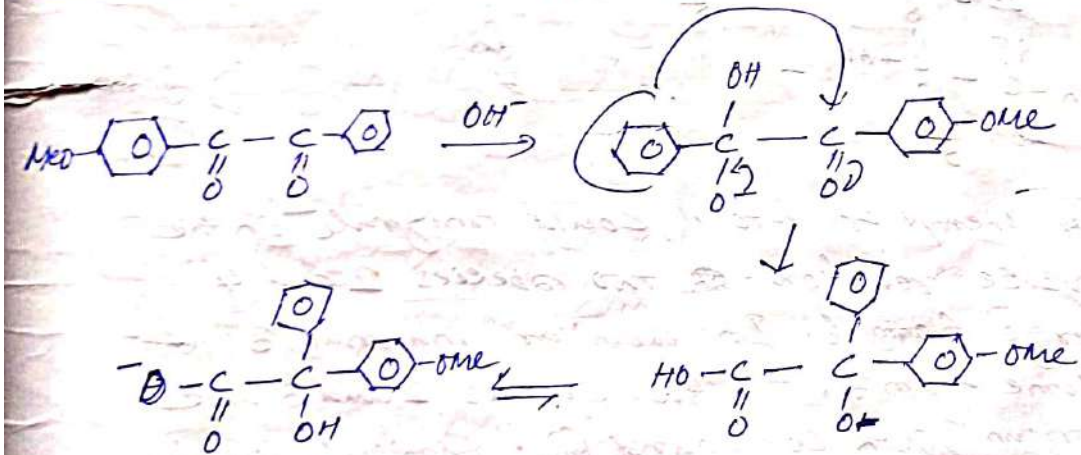
The rearrangement has its driving force in the removal of the product by ionisation of the carboxyl group.

Examples



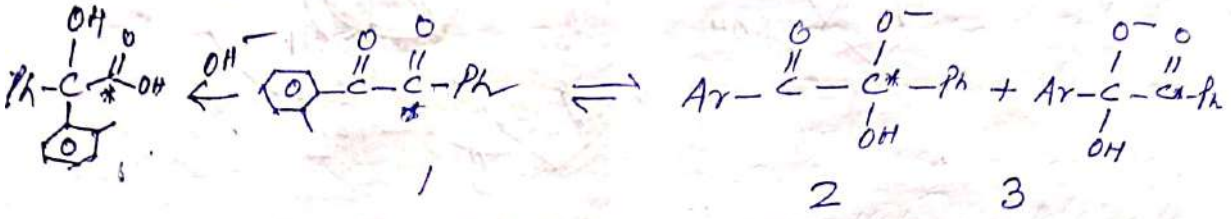




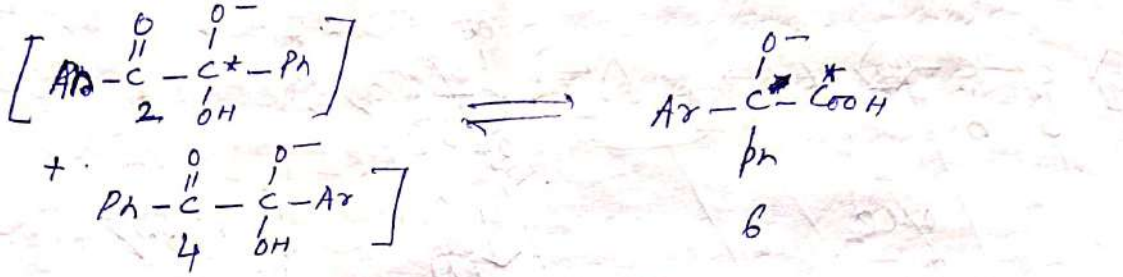


That the rearrangement is generally irreversible has been shown by several experiments in their studies of the relative migratory aptitudes of aryl groups in unsymmetrical benzil. In most recent study it was found that the rearrangement of 2-methylbenzil labeled with ~~C=14~~ Carbon-14 in the carbonyl groups adjacent to unsubstituted phenyl ring, produces 2-methylbenzilic acid with over 97% of the ~~labelling~~ labeling in the carbonyl groups. This indicates that in the rearrangement

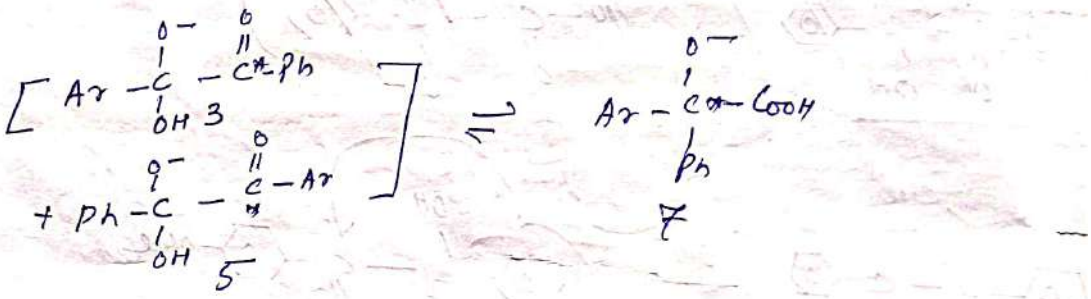
the Unsubstituted Phenyl Group migrates almost exclusively and that the rearrangement carried out Under the Usual conditions is irreversible. The First step of the rearrangement, the rapid and reversible addition of OH^-



1 2 3

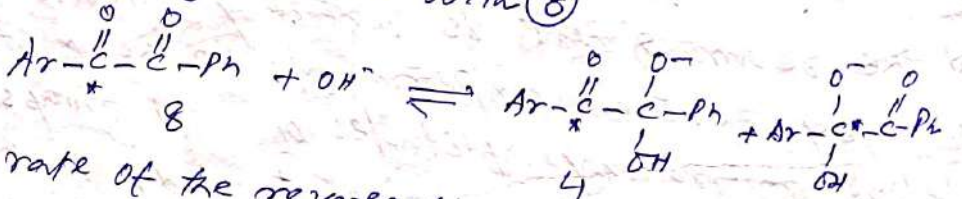


2 4 6



3 5 7

Since either Phenyl or p-tolyl could migrate in the proposed reverse reaction, two species 2 and 4 would emerge from 6. In similar manner 3 and 5 would come from 7. The two species 2 and 3 are in equilibrium with compound (1). Similarly 4 and 5 would be in equilibrium with (8)



8 4 5

If the rate of the reverse benzilic acid rearrangement were insignificant then 8 and 1 would eventually be present in approximately equal amounts of 2-methyl benzilic acid-1-C^{14} and 2-methyl benzilic acid-2-C^{14}. In all the rearrangement of labelled benzils studied, not one has yielded equal amount of the two isomeric acids

Knoevenagel Condensation:

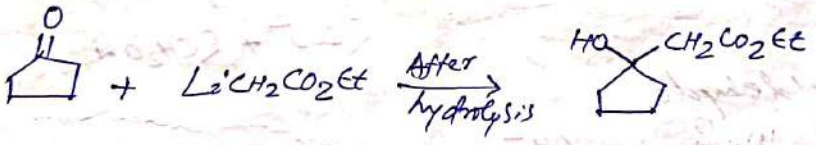
The condensation of aldehydes or ketones, usually not containing an α-hydrogen with compounds of the form $Z-CH_2-Z'$ or $Z-CHR-Z'$ is called Knoevenagel reaction. Z and Z' may be CHO, COR, COOH, COOR, CN, NO_2, SOR, SO_2R or similar group. When Z = COOH, decarboxylation of product take place in situ. If a strong enough base is used, the reaction can be performed on compounds possessing only a single 'Z', e.g. CH_3Z or RCH_2Z. Other active hydrogen compounds can also be employed, among them $CHCl_3$, 2-methylpyridine, terminal acetylene, cyclopentadienes.

$$PhCHO + CH_3COCH_2CO_2Et \xrightarrow[0^\circ C]{Et_2NH} Ph-CH=C(COCH_3)-CO_2Et$$

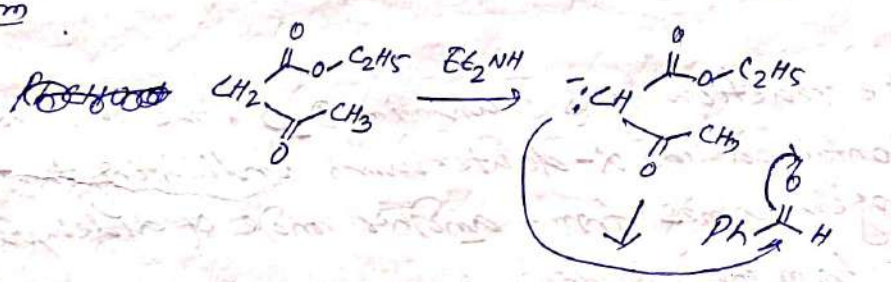
$$PhCHO + CH_3NO_2 \xrightarrow{n\text{-}C_5H_{11}NH_2} Ph\,CH=CH-NO_2$$

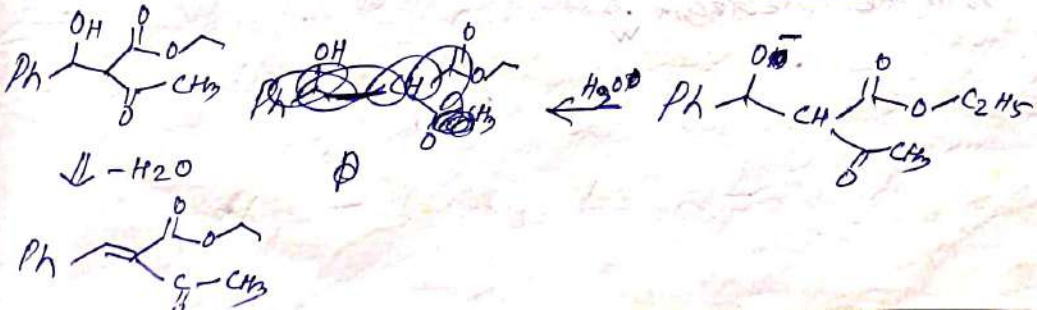
$$PhCHO + CH_2(COOH)_2 \xrightarrow[Piperidine]{Pyridine} Ph\,CH=CHCOOH$$

$$\Delta$$



Mechanism



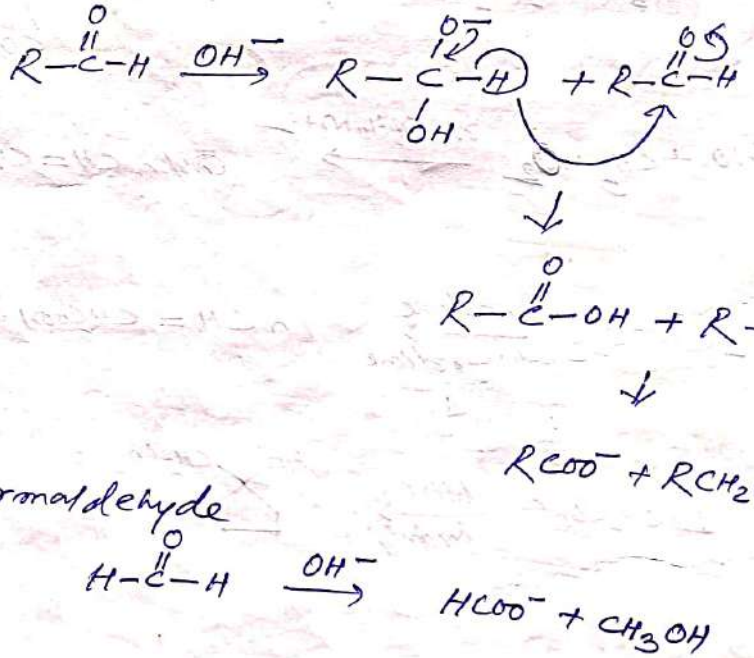


Cannizzaro reaction

$$2\,ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

Aromatic aldehydes and aliphatic aldehydes with no α-H, give the Cannizzaro reaction when treated with NaOH or other strong base. In this reaction one molecule of aldehyde oxidise another to the acid and it itself reduce to primary alcohol. Aldehyde with an α-H do not give the reaction, because when these compounds are treated with base the aldol reaction is much faster.

In the case where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called crossed Cannizzaro reaction.



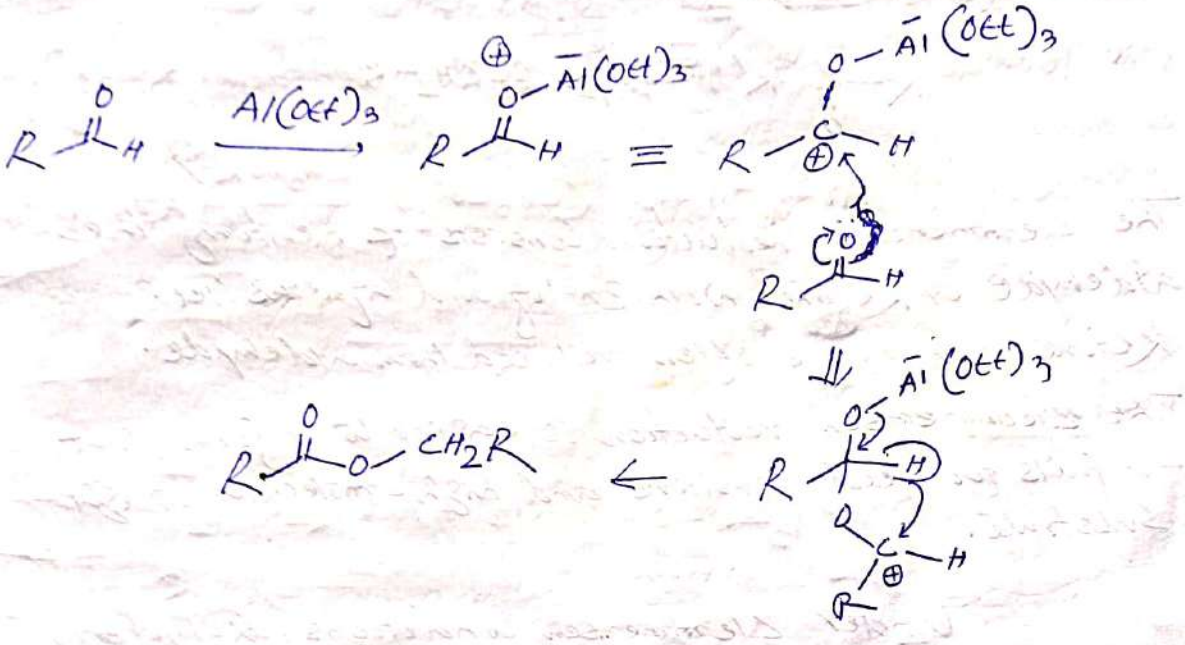
For formaldehyde

$$H-\overset{O}{\overset{\|}{C}}-H \xrightarrow{OH^-} HCOO^- + CH_3OH$$

* When the reaction was run in D_2O, the recovered alcohol contained no α-deuterium, indicating that the hydrogen comes from another mole of aldehyde and not from the medium.

When aldehydes with or without α-H, are treated with $Al(OEt)_3$, one molecule is oxidized and another reduced but in ~~Tiche~~ Tischchenko reaction they are found as the ester

$$2RCHO \xrightarrow{Al(OEt)_3} RCOOCH_2R$$

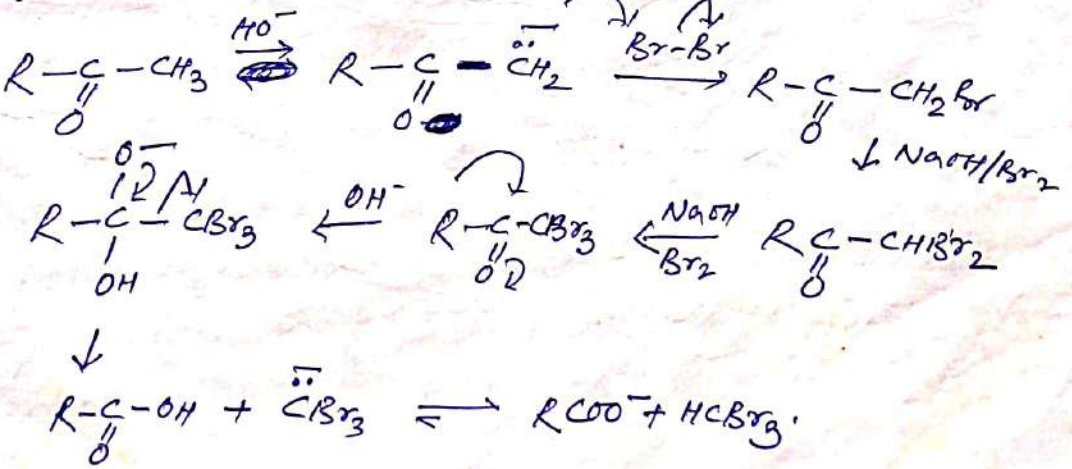


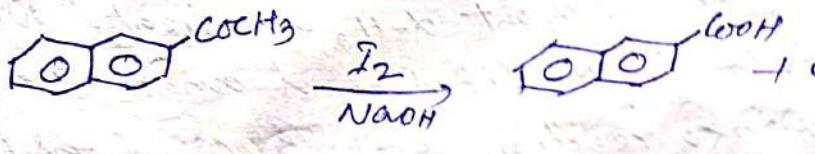
Haloform reaction

In the haloform reaction, methyl ketones are cleaved with halogen and a base. The halogen can be bromine, Chlorine or iodine. What takes place is actually a combination of two reactions. The first ~~is an~~ is the trihalogenation of methyl group of methyl keton. Then the ~~resulting~~ resulting trihaloketone is attacked by hydroxide ion:

$$R-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow[NaOH]{3Br_2} R-\underset{\underset{O}{\|}}{C}-CBr_3 \xrightarrow{HO^-} HCBr_3 + RCOO^-$$

Mechanism:





Clemmensen reduction:

$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[HCl]{Zn-Hg} R-CH_2-R'$$

The Clemmensen reduction consists of heating the aldehyde or ketone with Zn-Hg and aqueous HCl. Ketone are more often reduced than aldehyde. The Clemmensen reduction is easier to perform, but it fails for acid sensitive and high-molecular weight substrate.

Under Clemmensen conditions, α-hydroxy ketones gives either ketones or olefins and 1,3-diones usually undergo rearrangement.

$$Me-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-Me \xrightarrow[HCl]{Zn/Hg} Me-\underset{\underset{O}{\|}}{C}-CHMe_2$$

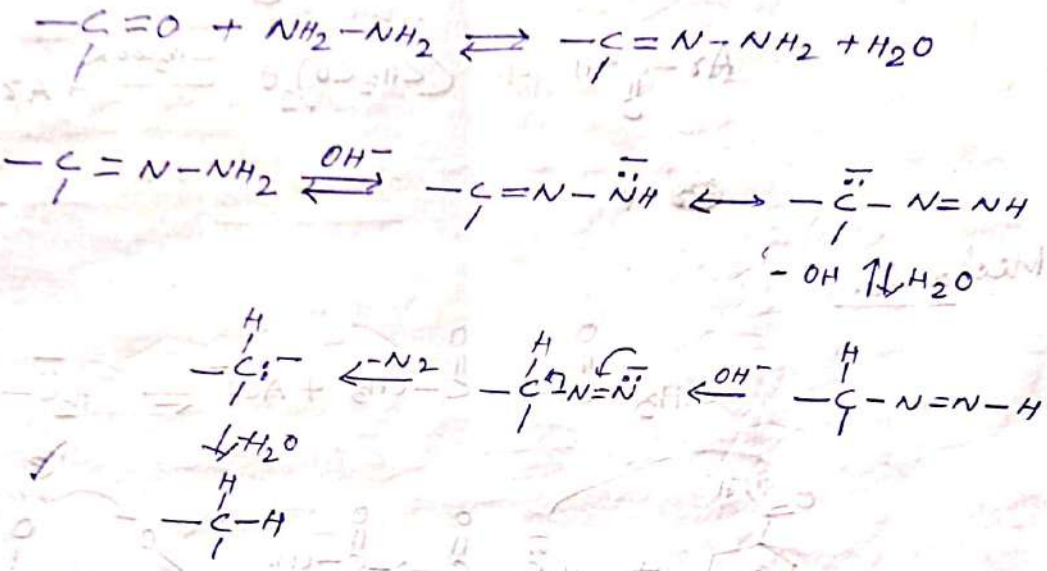
For α,β-Unsaturated ketones Clemmensen reduction gives both reduced products or olefine reduced products.

$$CH_3-CH=CH-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow[HCl]{Zn/Hg} CH_3-CH_2-CH_2-CH_2\,CH_3$$

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

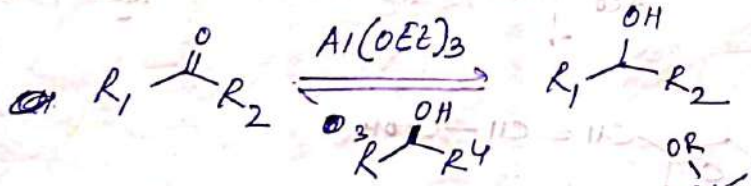
The Wolff-Kishner reduction:

The reaction involves the reduction of carbonyl group to methylene by base catalysed decomposition of hydrazone of the carbonyl compound. Alkyl diimides are believed to be formed which collapse with loss of nitrogen. The loss of the especially stable molecule of nitrogen provides the driving force of the reaction.

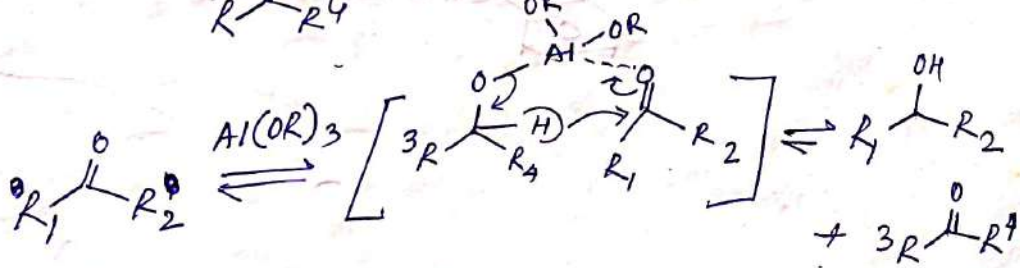


Meerwein-Ponndorf-Verley reduction:

The Meerwein-Ponndorf-Verley reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohol utilizing aluminium alkoxide catalyst in the presence of isopropanol (or a 2° alcohol)



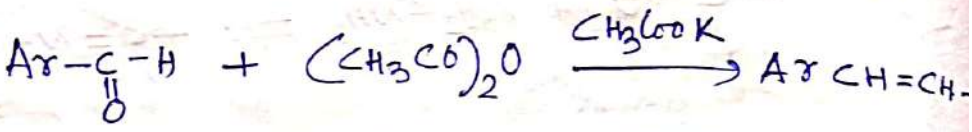
Mechanism:



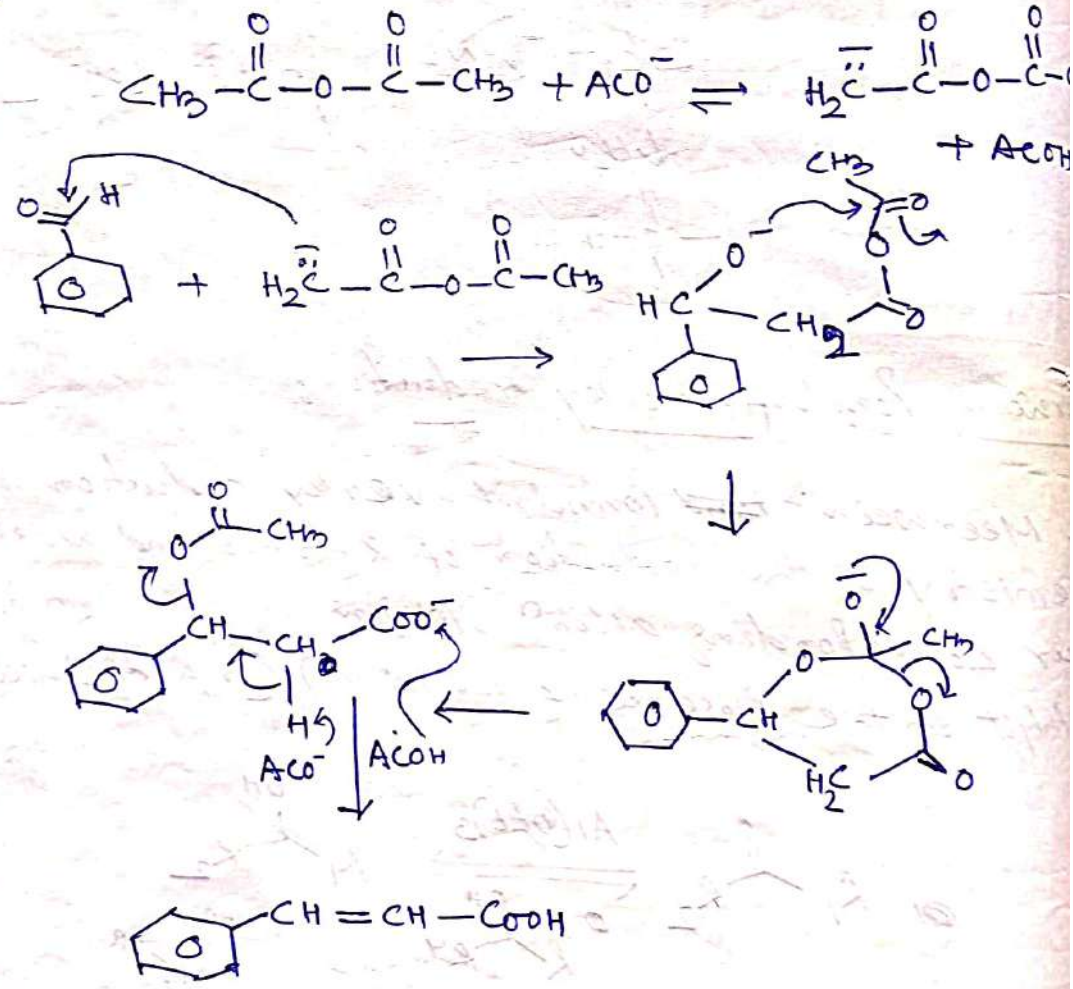
Isopropanol is useful as a hydride donor because the resulting acetone may be continuously removed from the reaction mixture by distillation.

Perkin reaction:

The reaction is used for the synthesis of α, Unsaturated acids, and is an aldol type condens between aromatic aldehyde and a carboxylic acid anhydride $(RCO)_2O$ catalyzed by a carboxylate (the potassium salt of the carboxylic acid, RCOOK)

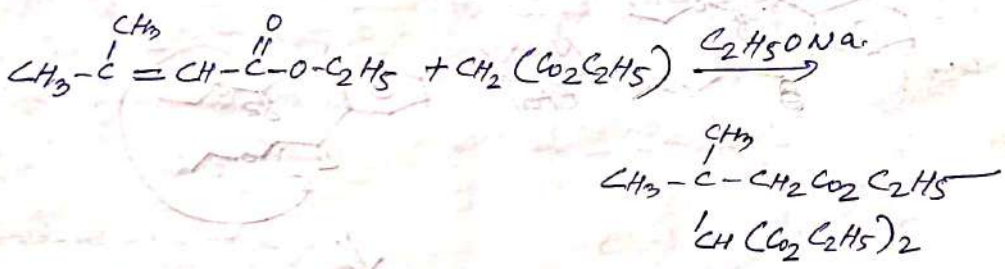


Mechanism

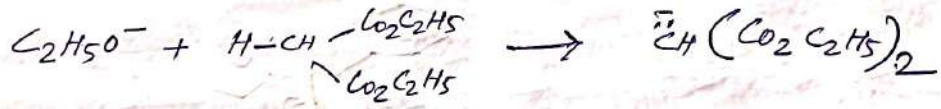


The Michael reaction:

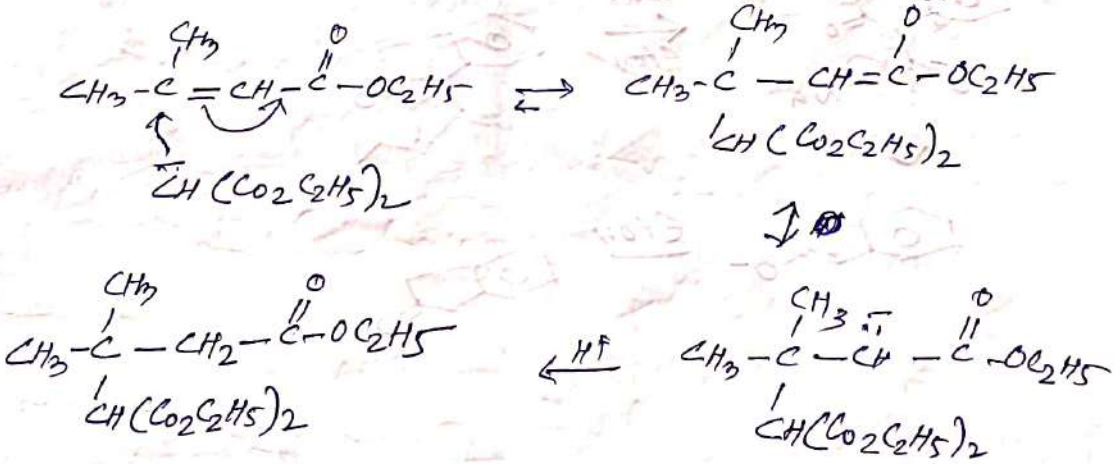
This is conjugate addition of enolate ions to α,β-Unsaturated Carbonyl compounds ie. to activated olefins. Like other nucleophiles, the enolates do not react with simple olefins. The name Michael reaction is infact applied to a reaction between enolate forming component and an alkene which is not only activated by conjugation to a Carbonyl group but to other groups of -M type. e.g. ester, cyano, nitro and nitrile. With these structural features, the anion formed after addition is stabilized sufficiently by the delocalization of the charge on to an electronegative element and the addition therefore, occours at a particular rate.

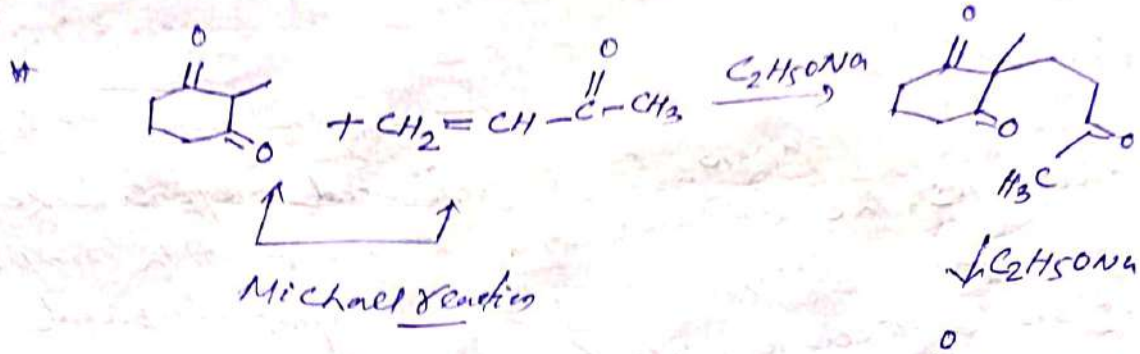


Step-1



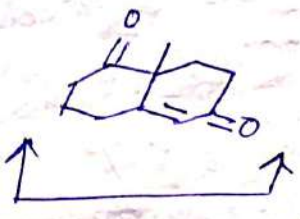
Step-2





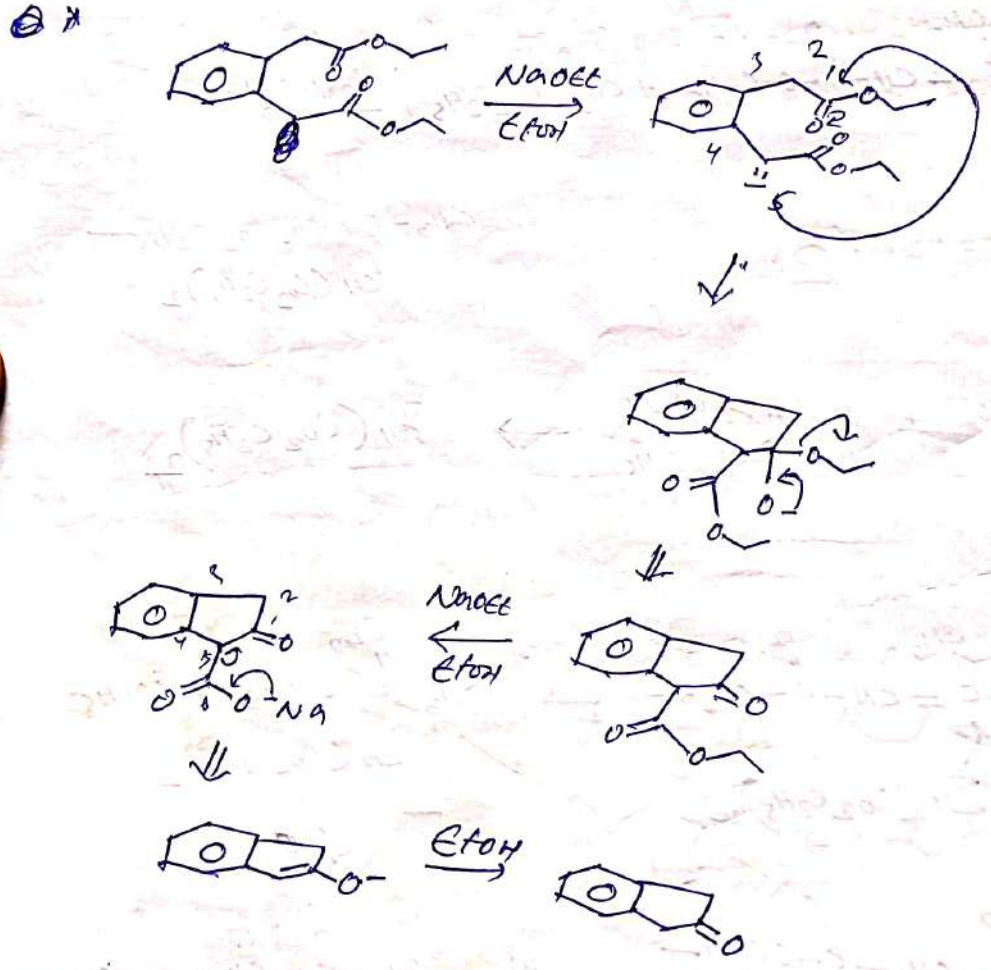
Michael reaction

$\downarrow C_2H_5ONa$



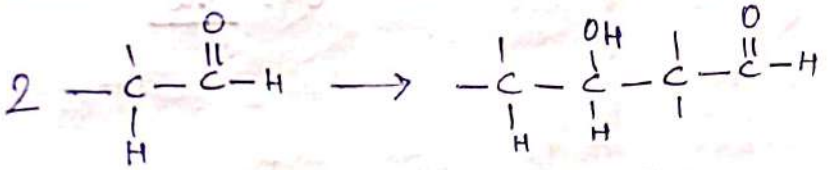
A simple aldol condensation

Robinson Annulation reaction

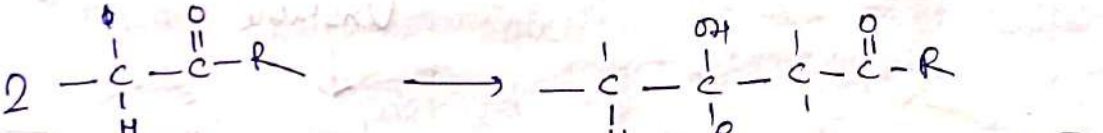


Aldol Condensation:

When a dilute base is used a condensation reaction involving two molecules of carbonyl compound occurs. The process is the addition of the nucleophilic carbanion enolate usually of an aldehyde to the C=O of its parent compound and is termed an aldol condensation. In a mixed aldol addition, the carbanion enolate adds to the C=O of the molecule other than its parent.



Aldehyde — β-hydroxy aldehyde

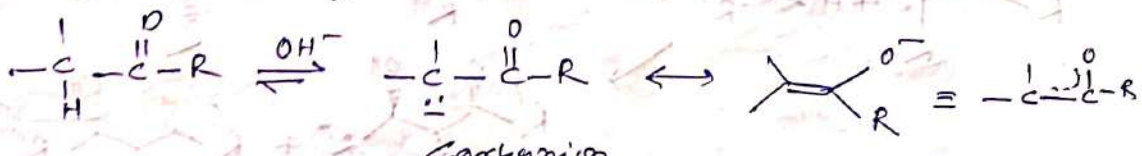


Ketone — β-hydroxy ketone

Simple aldol condensations occurs both under basic as well as acidic conditions. Under acidic conditions, one ends up with an α,β-unsaturated compound.

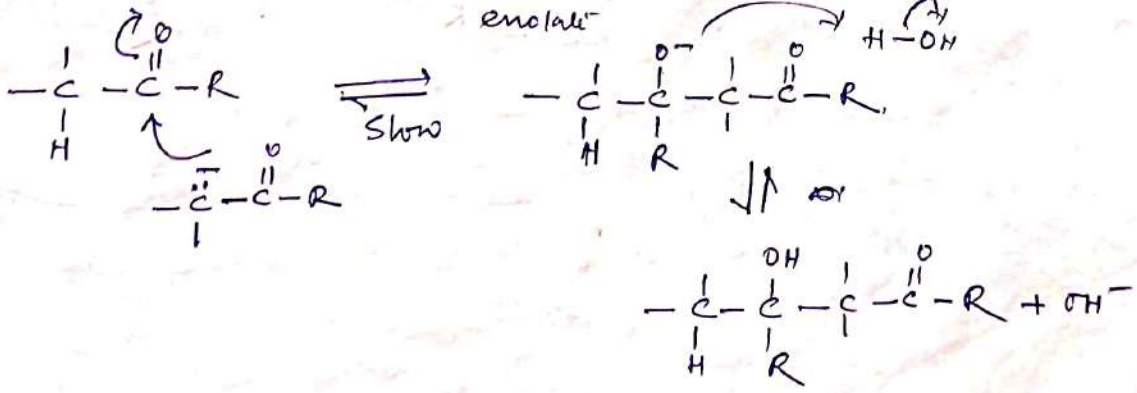
Mechanism: (Base Catalyzed)

Step-1



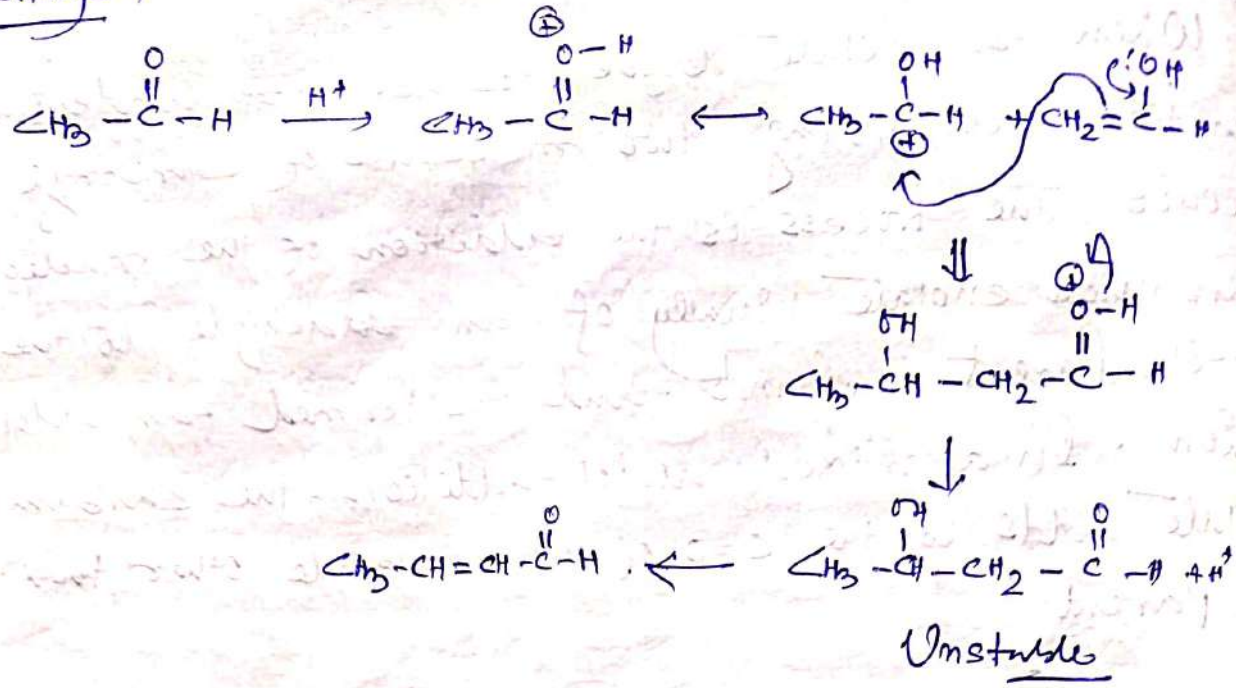
Carbanion enolate

Step-2



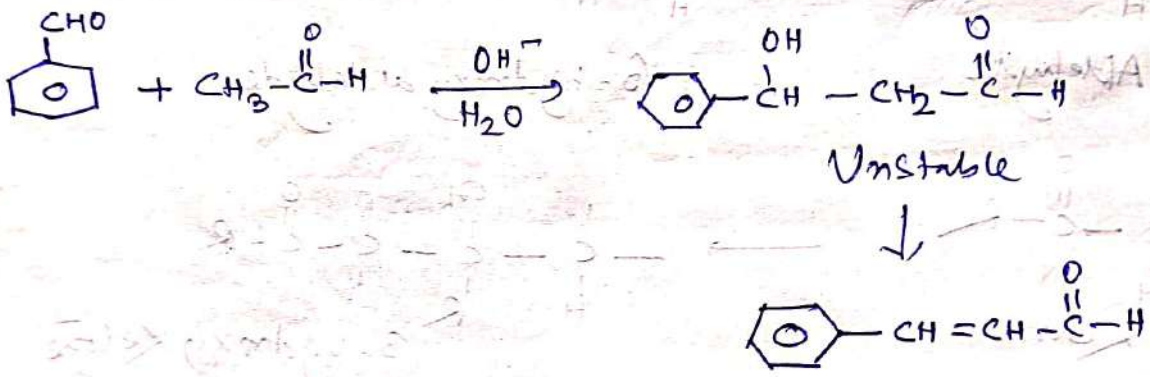
Slow

Acid Catalyzed



Unstable

*



Unstable

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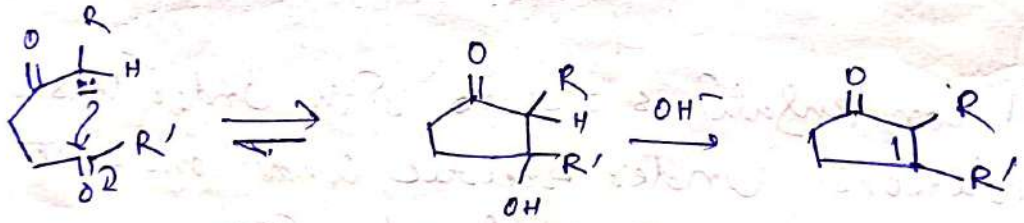

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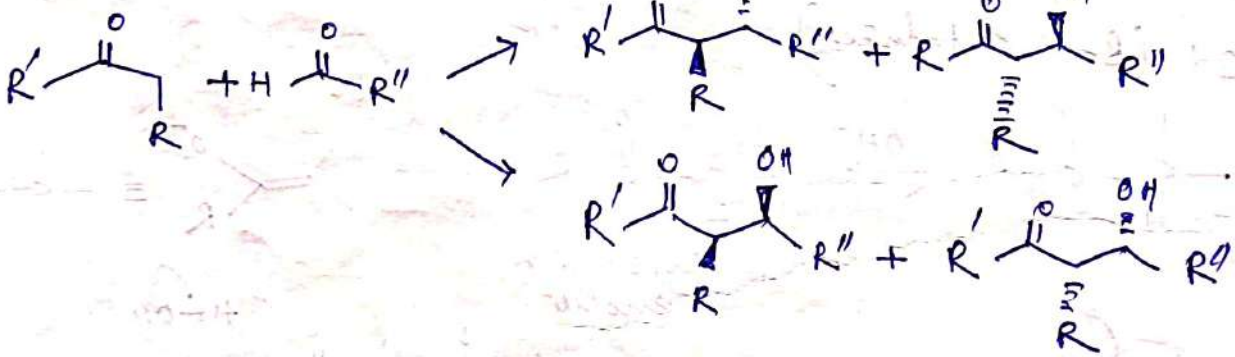
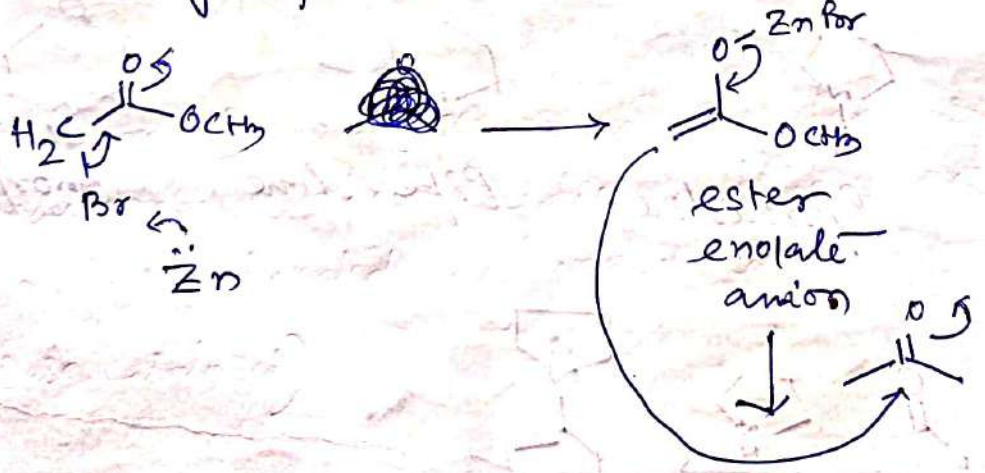


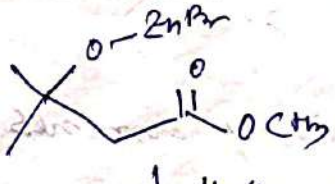
$$PhCHO + CH_3NO_2 \xrightarrow{OH^-} PhCH=CH-NO_2$$

$$C_6H_5CHO + C_6H_5CH_2CN \xrightarrow[EtOH]{EtO^-} C_6H_5CH=\underset{\underset{C_6H_5}{|}}{C}-CN$$

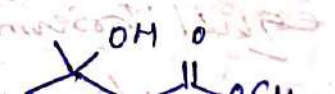
Reformatsky reaction:

This is crossed condensation reaction and leads to aldol type products. The Reformatsky reaction involves the addition of an organozinc reagent to the carbonyl group of an aldehyde or ketone. This reaction extends the carbon skeleton of an aldehyde or a ketone and yields β-hydroxy esters. In this regard the mechanism of Reformatsky reaction resembles a grignard reaction e.g. with a ketone. The organozinc reagent is less reactive than a grignard reagent, therefore it does not add to the ester group.



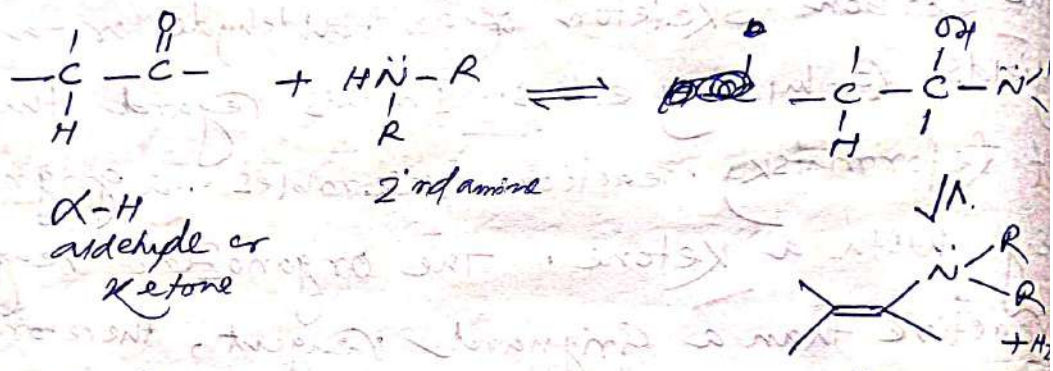


$\downarrow H_2O$



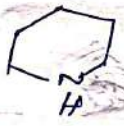
Stork enamine reaction:

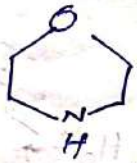
The name enamine usually refers to α, β-unsa amines. These can be prepared by reaction of a aldehyde or a ketone which contains atleast on α-H atom and a secondary amine under acid catalysis. Most stable enamines are those der from ketones rather than aldehydes. Moreover, the enamines derived from cyclic secondary amines, a further more stable, heterocyclic secondary amines

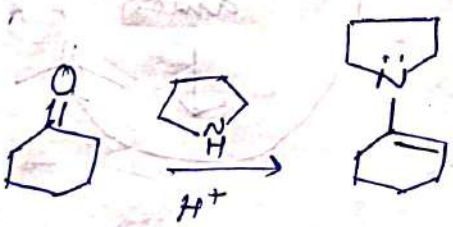


2ird amine (Cyclic) are

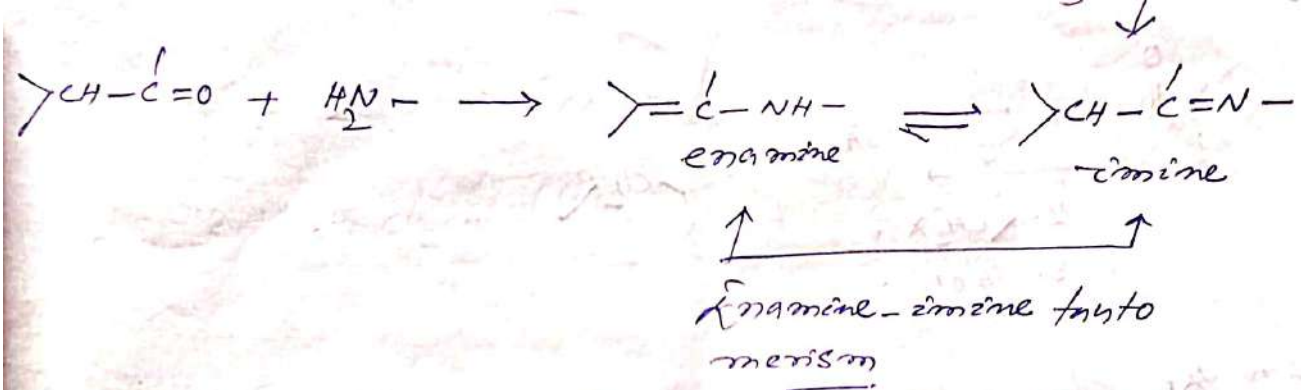

Pyrrolidine


Piperidine

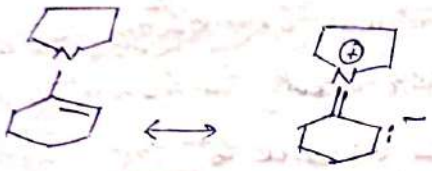

morpholine



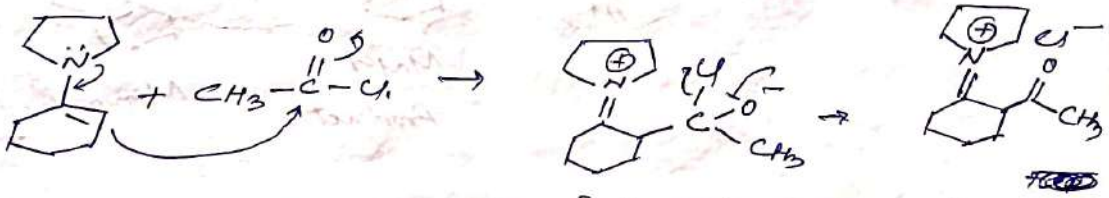
* Primary amines also form enamines, however, in their case, enamine–imine tautomerism is possib The equilibrium lies virtually completely on the imine side, it being more stable than enami Thus an enamine from a



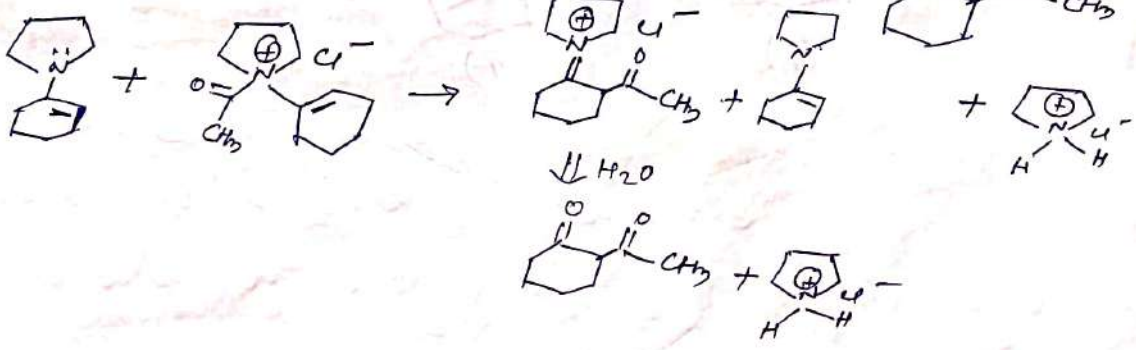
Imp:

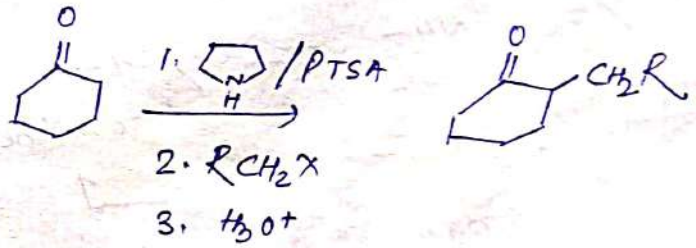


An examination of the resonance structures shows that β-carbon is a nucleophilic center. The enamines can be acylated with an acyl halide or an Ac_2O. The iminium ion is hydrolysed and the net result is the removal of the original amine and the formation of β-diketone. During acylation N-acylation may also take place, however a N-acyl product is unstable and instead acts as an acylating agent itself. Consequently the yields of C-acylated products are high.

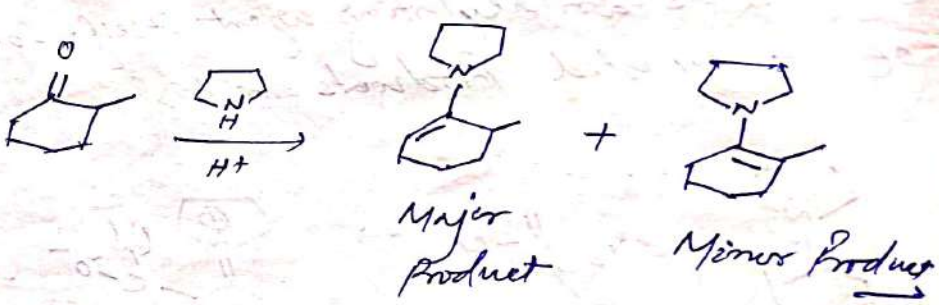


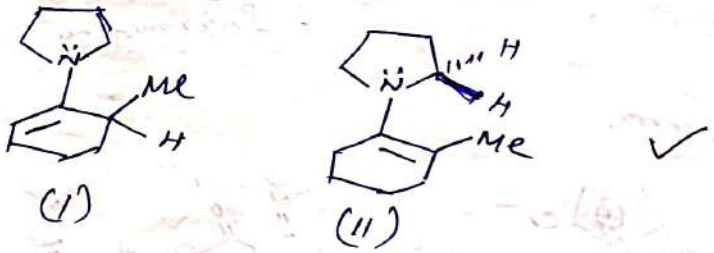
N-acyl product form:





In the case of unsymmetrical ketones, that can react at two sites, the enamine formation occurs predominantly at the less substituted position. The stabilization in an enamine is due to interaction of the alkene π-system with the ~~Unsaturated~~ unshared electron pair on a p-orbital on nitrogen. Consequently a coplanarity of the bonds on the unsaturated carbon atoms and those to nitrogen is necessary. This coplanarity can be achieved in (I) but not in (II) due to steric repulsions. Thus the enamine from 2-methyl cyclo-hexanone, gives the C-alkylation predominantly on the less substituted carbon.

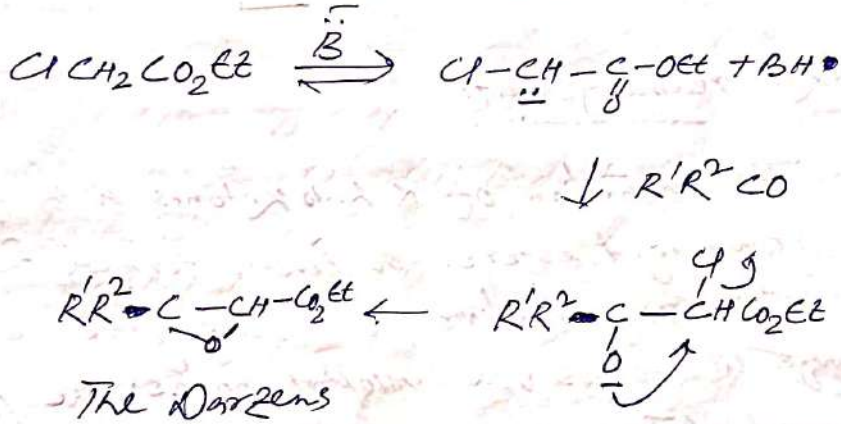




(I) (II) ✓

Darzens reaction:

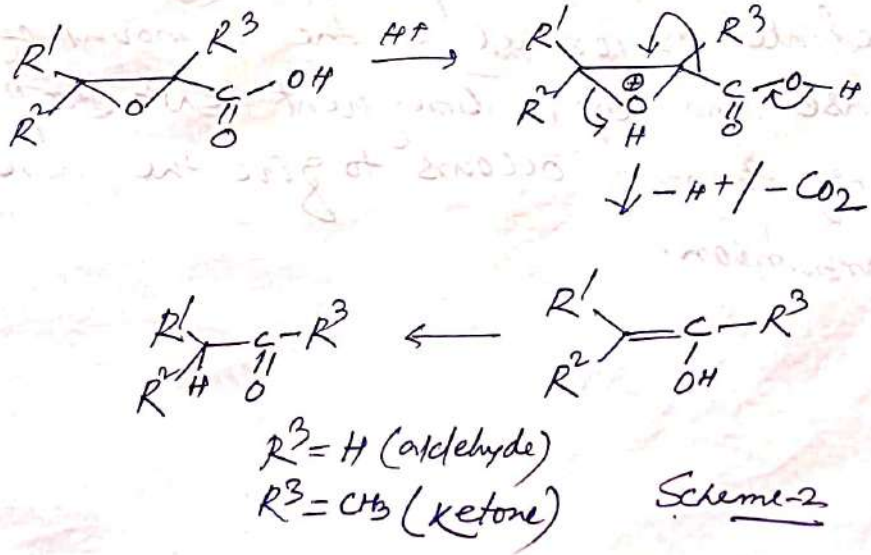
Aldehydes and Ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters called glycidic esters. The reaction called Darzens condensation involves the addition of the enolate to the carbonyl group to give an oxidation, this displaces the halide ion by an internal SN2 reaction. On alkaline hydrolysis these esters gives glycidic acids which undergo a decarboxylative rearrangement when warmed in the presence of acids to give an aldehyde if $R^3 = H$ or a ketone if R^3 = alkyl group (scheme-2)



The Darzens reaction

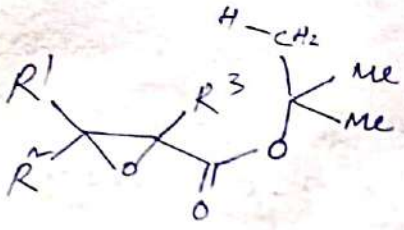
Scheme-1

When t-butyl Glycidates are used, the ester on hydrolysis eliminates isobutene to give an aldehyde or ketone (~~St~~ scheme 3)

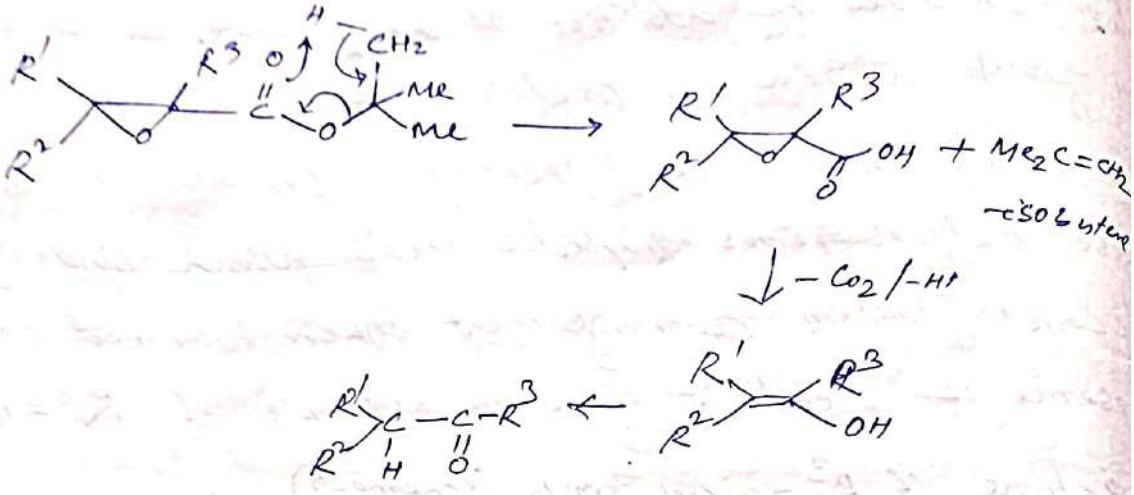


$R^3 = H$ (aldehyde)
$R^3 = CH_3$ (ketone)

Scheme-2



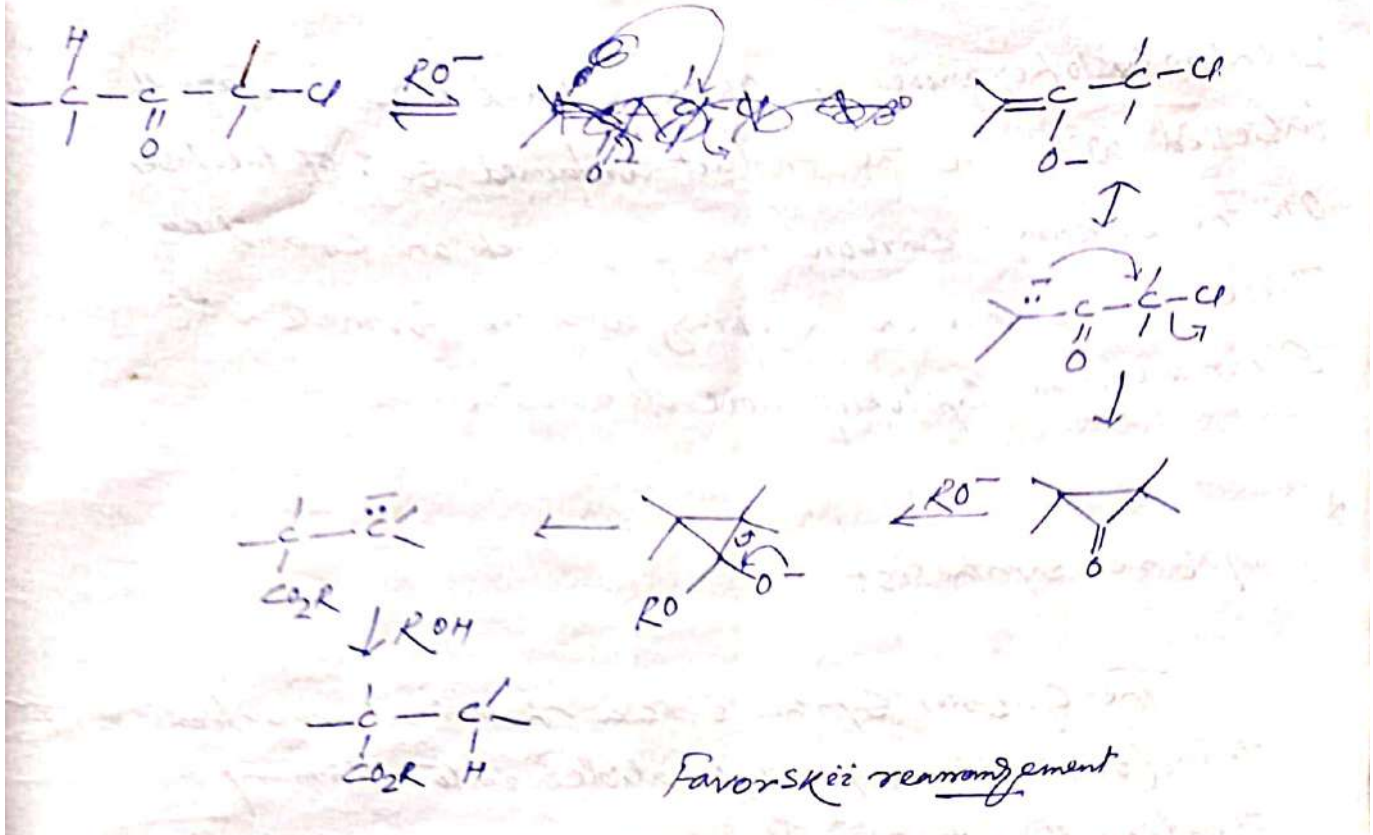
III



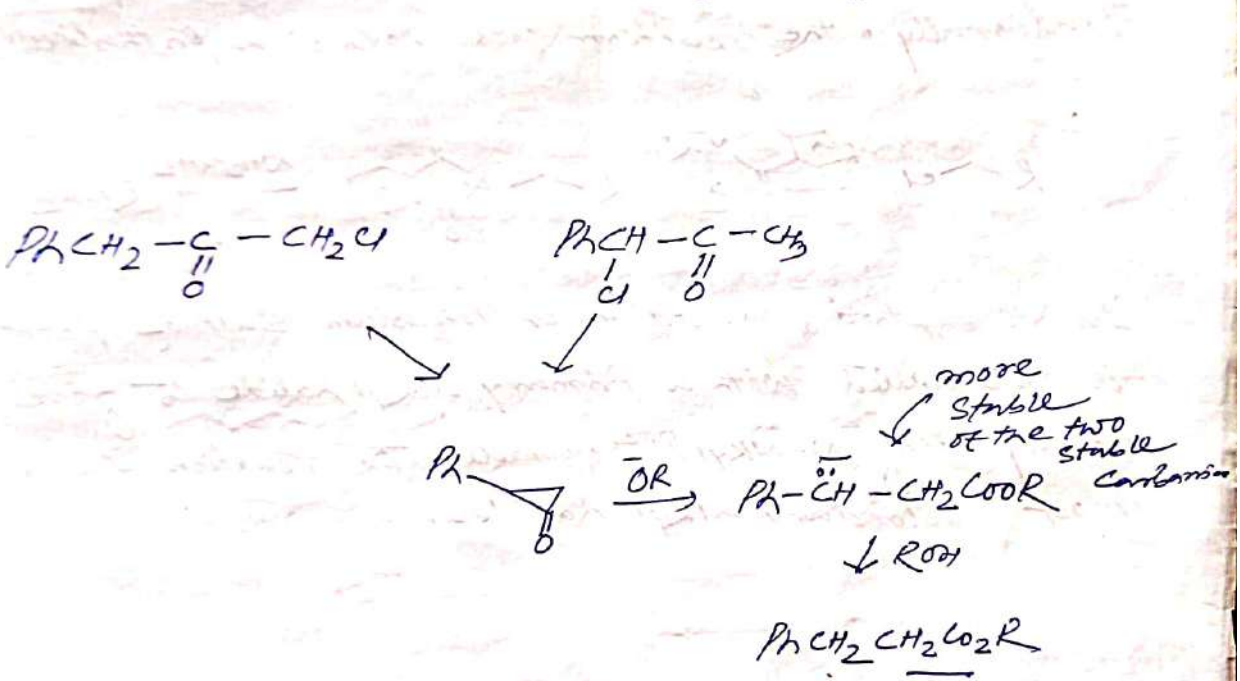
Scheme-3

Favorskii rearrangement:

The reaction of α-halo ketones with alkoxide
give rearranged esters, a process termed favorskii re
angement. The reaction with base gives enolates wh
rearrange to esters via cyclopropanones. The cyclopropano
intermediate opens in such a way so as to give the
more stable of the two possible carbanions. Alkyl grou
destabilize carbanions while aryl groups stabilize th
by delocalization of the negative charge. Thus bot
the compound give the same product and this reac
a common cyclopropanone intermediate. This int
-mediate is formed by the removal of an α-H
base and by subsequent S_N2-displacement
Ring opening occurs to give the more stable
carbanion.



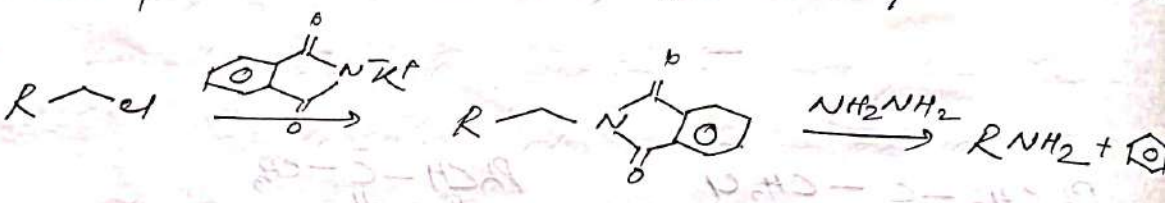
Favorskii rearrangement



2-Chloro Cyclohexanone in which C-1 and C-2 were equally labelled with ^{14}C the Product contained 50% of the label on the carbonyl carbon and 25% each on C1 and C2. These results are in keeping with the formation of Symmetrical Cyclopropanone derivative.

* Gabriel Synthesis:

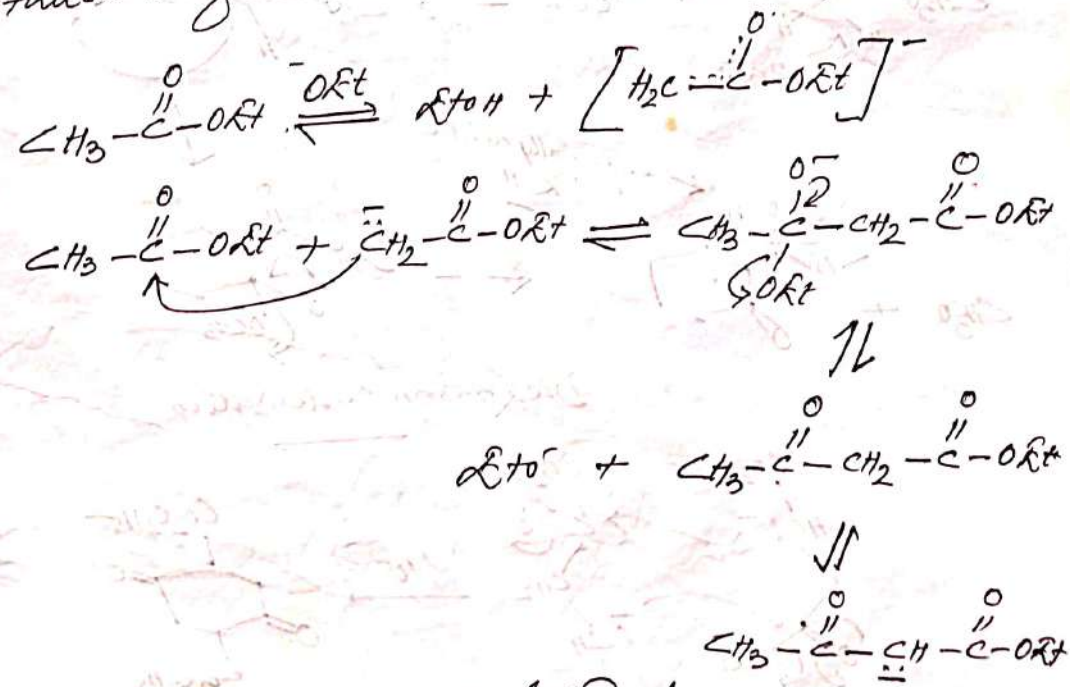
The Gabriel Synthesis is a chemical reaction that transforms primary alkyl halides into primary amines. Traditionally, the reaction uses potassium phthalimide



In this method, the sodium or potassium salt of phthalimide is N-alkylated with a primary alkyl halide to give the corresponding N-alkylphthalimide. The reaction fails with most secondary alkyl halides.

The Claisen Condensation:

On treatment with strong base like sodium ethoxide, ester which contain an α-H undergo self condensation; termed Claisen Condensation. The mechanism involves the conversion of one molecule of ester to a nucleophile by the base and the second molecule serves as a substrate. The Claisen Condensation reaction involves a series of equilibria i.e. each step in the condensation is reversible. One may note that the formation of the new carbon–carbon bond is not thermodynamically favorable. The formation of the α-carbanion is not a favorable equilibrium reaction as alkoxide is a weaker base than enolate and consequently only a low concentration of enolate forms. Attack of the α-carbanion on the second molecule of ester, however, gives the product. The reaction is predicted to have an equilibrium constant around 1 and is reversible. In the final step, β-keto ester reacts with the alkoxide generated from substitution to give the enolate anion of the product.



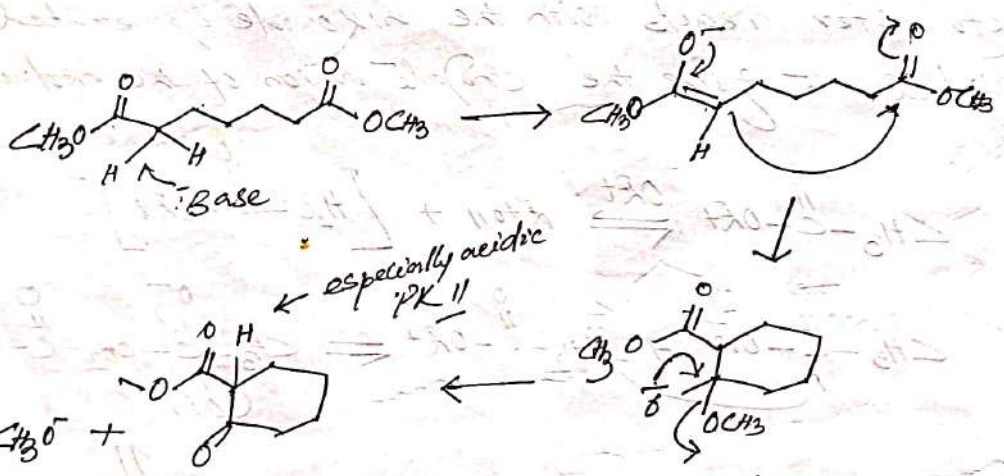
The equilibrium reactions are shifted toward this anion due to its stability since two carbonyl groups stabilize the common α-carbanion. The neutral β-keto ester product is isolated via acidification of the reaction

$CH_3C(=O)CH_2CO_2Et$

acetoacetic ester

The Dieckmann reaction:

It is an intramolecular Claisen condensation by way of which certain cyclic ketones can be obtained. It is most successful on diesters of 6 and 7 di-basic acids where it gives the high yields of cyclic β-keto esters. The primary driving force of the Dieckmann condensation as with Claisen condensation is the formation of the anion of the product β-keto ester by deprotonation of the hydrogen bonded to the carbon between two carbonyl groups of the product-β-keto ester. the diesters of shorter chain dibasic acids due to the strain that would result in the small rings react differently. Thus ethyl succinate undergoes, an intermolecular condensation between two molecules to give a cyclohexane dione system.



Dieckmann condensation