B. Sc. (CHEMISTRY) SEM V : US05CCHE21 :

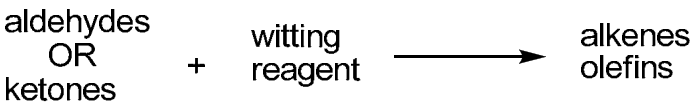
ORGANIC CHEMISTRY

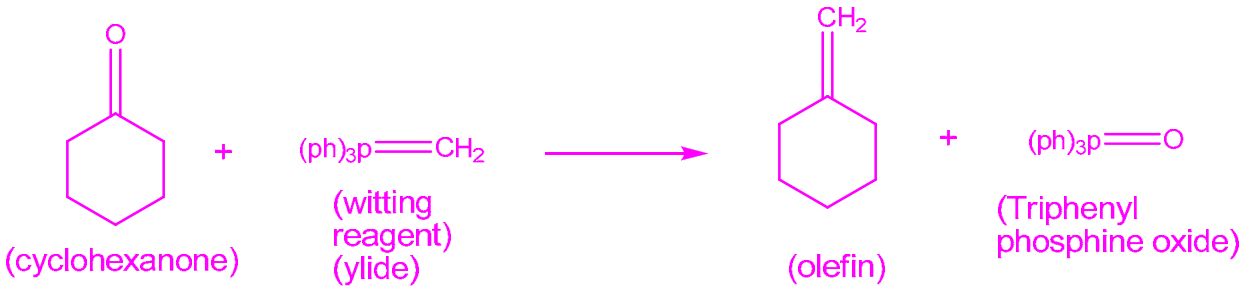
[Compiled by Dr. B. C. Dixit, V P & R P T P SCIENCE COLLEGE, VALLABH VIDYANAGAR-388120]

UNIT : II : REACTION MECHANISM :

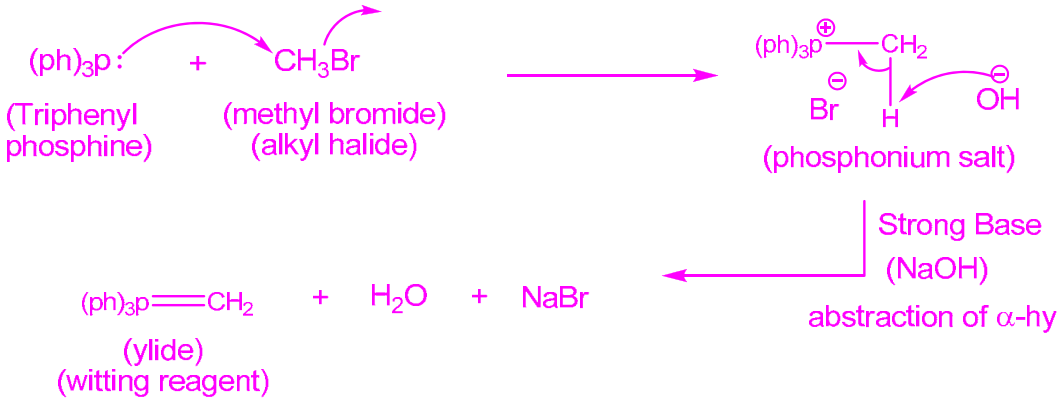
(i) Wittig reaction, **(ii)** Perkin reaction, **(iii)** Benzoin condensation, **(iv)** Birch reduction, **(v)** Curtius–Schmidt rearrangement, **(vi)** Hofmann rearrangement, **(vii)** Mannich reaction, **(viii)** Benzilic acid rearrangement, **(ix)** Sommlet rearrangement, **(x)** Favorskii rearrangement, **(xi)** Beckmann rearrangement, **(xii)** Baeyer-Villiger oxidation.

(i) Wittig reaction : Reaction of an aldehyde or keton with alkyllidene triphenyl phosphoranes (witting reagent) to give an alkenes is known as witting reaction. It is also know as coupling reaction and was discovered by Georg Wittig. (German chemist: Wittig olefination)





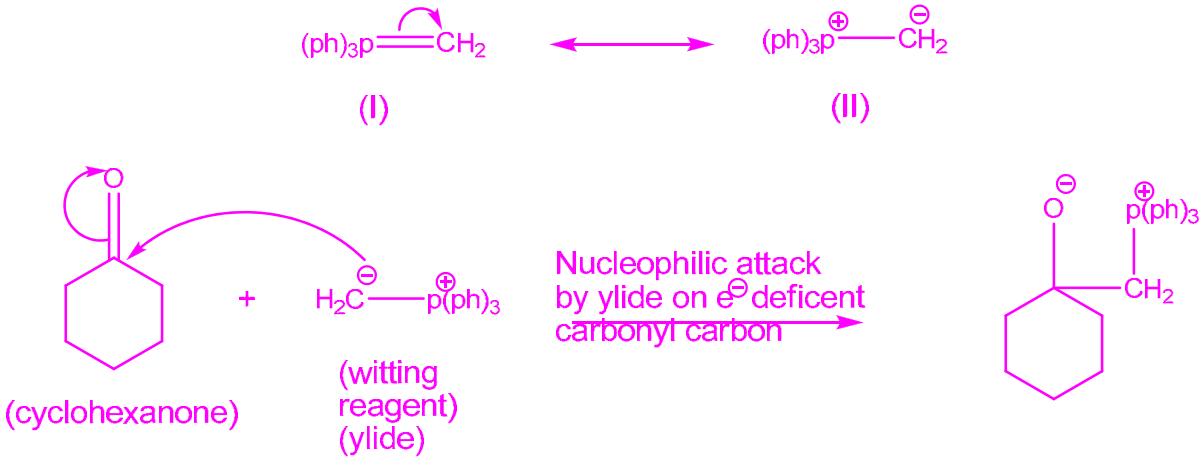
Witting reagent preparation :



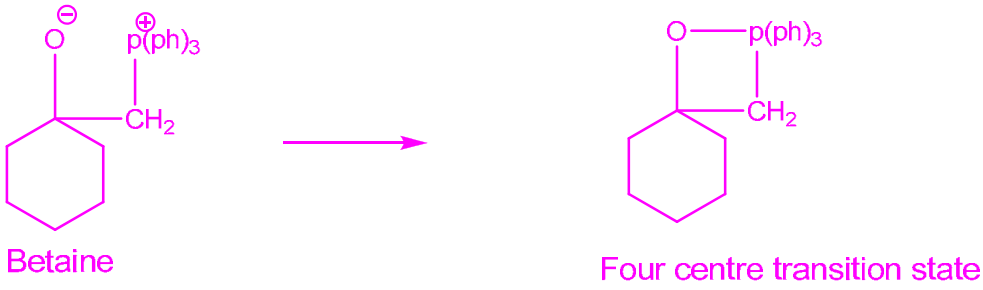
The witting reagent i.e alkylliene tripphenyl phosphoranes is also known as ylide. It is prepared by reacting triphenyl phosphine $(ph)_3p$ with an alkyl halide and then removing an α-hydrogen from the intermediate phosphonium salt by the action of strong base ($NaNH_2$, NaOH etc).

Mechanism:

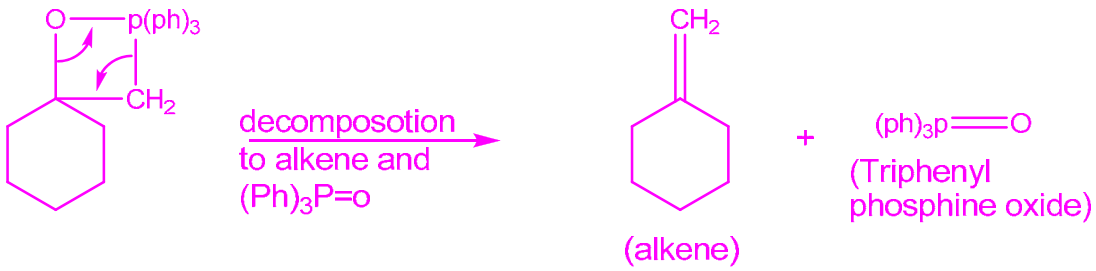
(i) The key step in the mechanism is the nucleophilic attack by alkylidene triphenyl phosphorane (Wittig reagent) (II) on the electron deficient carbonyl carbon of carbonyl compounds. This leads to formation of charge separated intermediate called a Betaine.



(ii) The betaine intermediate is now subject to formation of a new oxygen phosphorous bond, yielding an another intermediate (oxaphosphetanes), which has a four membered ring structure.



(iii) In the four membered ring intermediate, the carbon-oxygen bond and the carbon-phosphorus bonds are cleaved. The oxygen forms a new double bond with the phosphorus atom to form triphenyl phosphine oxide, while carbon- carbon double also formed yielding a required alkene product.

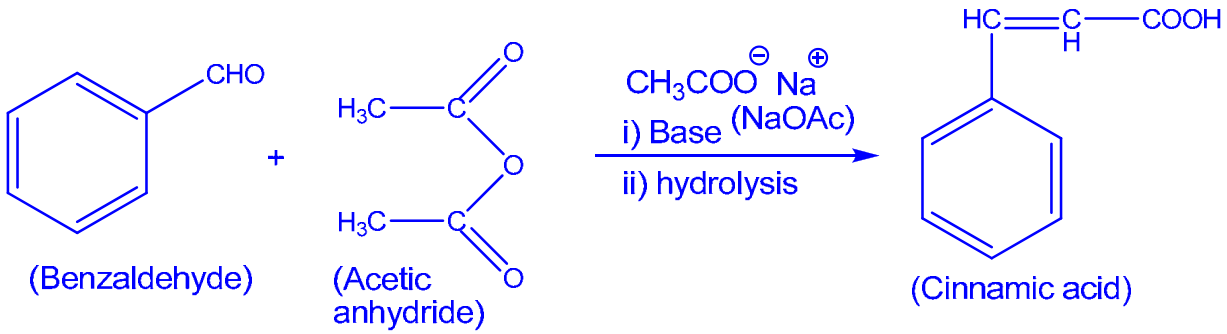


(ii) Perkin Condensation:

An aromatic aldehyde is condensed with acid anhydridc in the presence of base to form an α, β-unsaturated acid is known as Perkin condensation reaction.

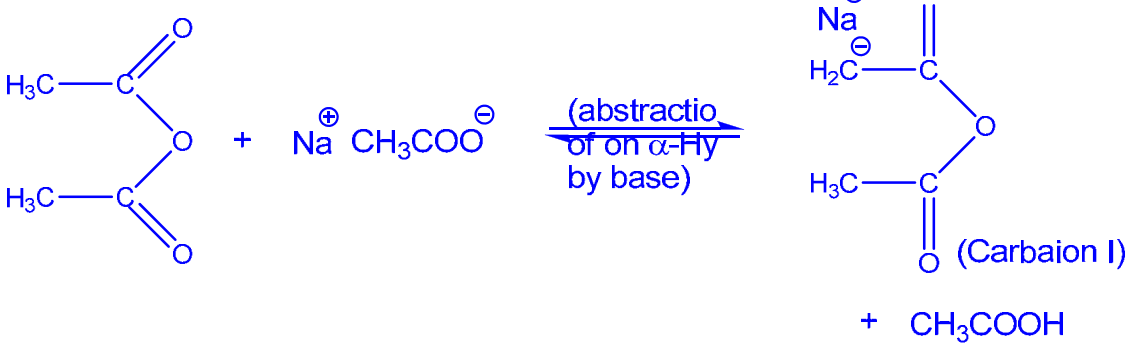
aromatic aldehydre + acid anhydride —Base→ α,β–unsaturate acid

Condensation of benzaldehyde with acetic anhydride in the presence of sodium acetate as a base catalyst give cinnamic acid as a product.



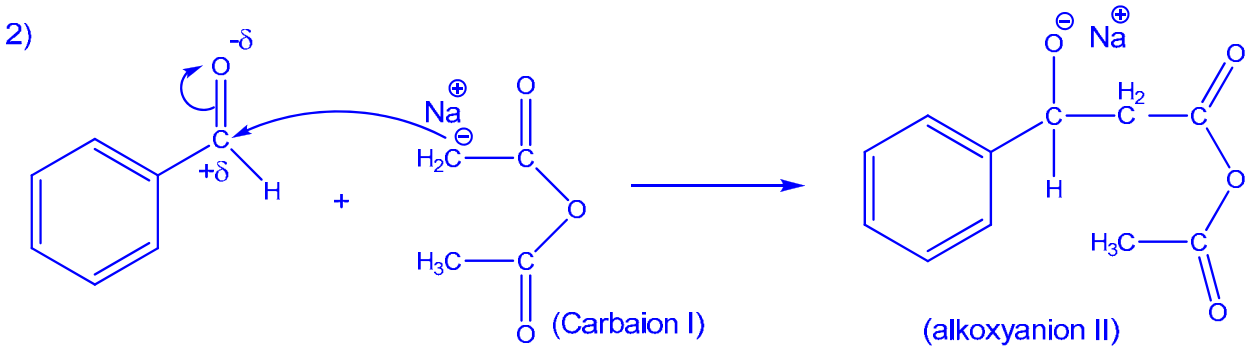
Mechanism:

1)



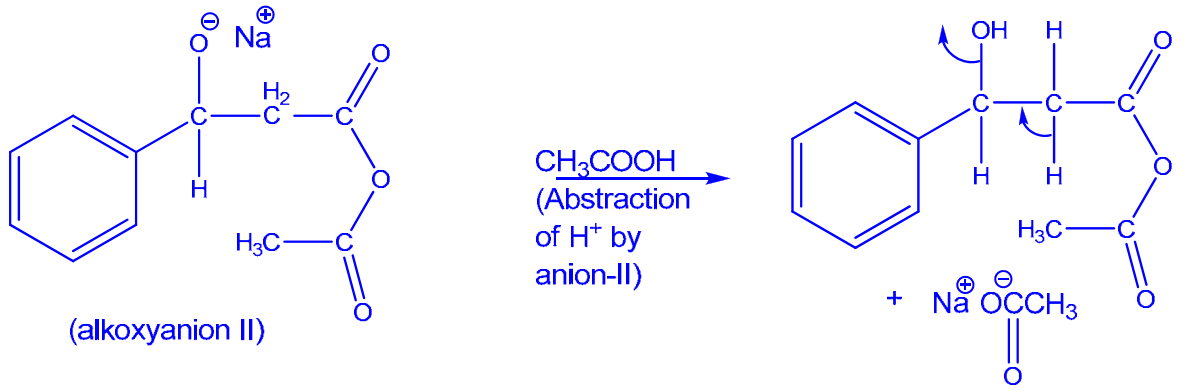
In first step base (sodium acetate) abstract proton from acetic anhydride to generate a carbanion (I).

2)



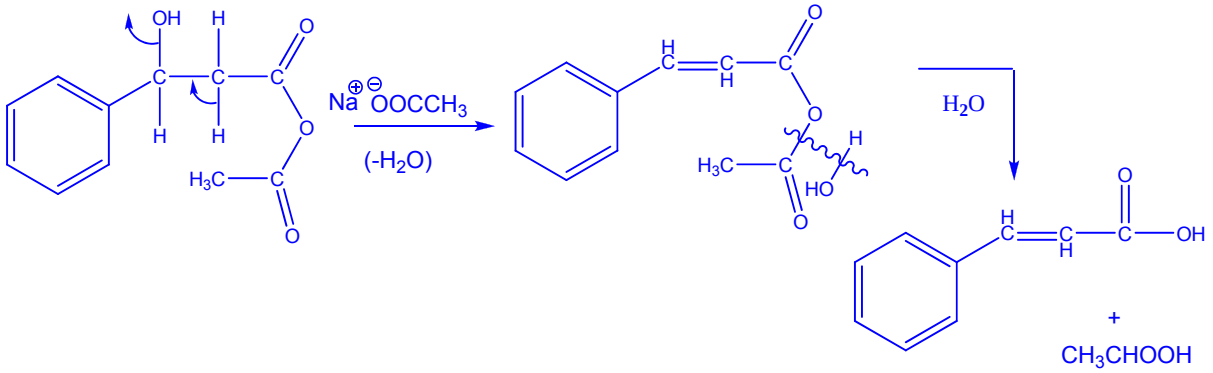
In the second step carbanion-I undergo nucleophilic attack on carbonyl group of benzaldehyde to generate alkoxy anion-II.

3)



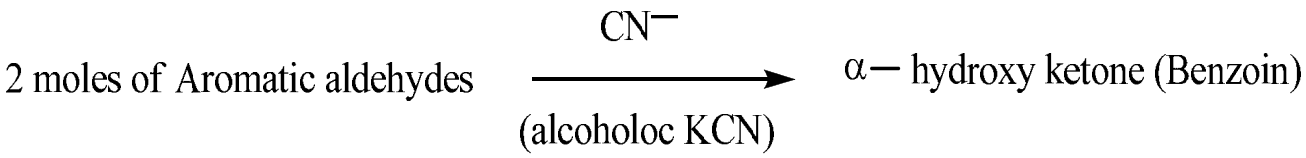
Protonation of alkoxy anion-II takes place by abstract H^+ ion from acetic acid to generate hydroxyl anhydride.

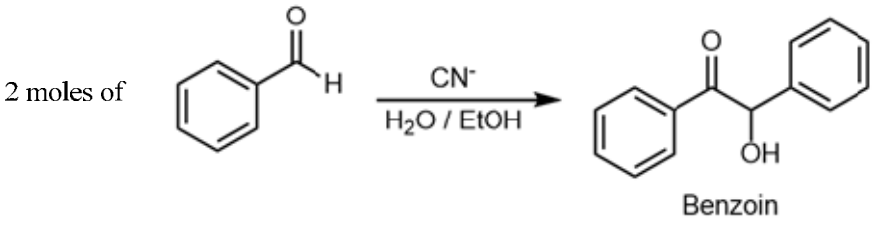
4)



In final step, dehydration take place in presence of sodium acetate, followed by hydrolysis to generate cinnamic acid.

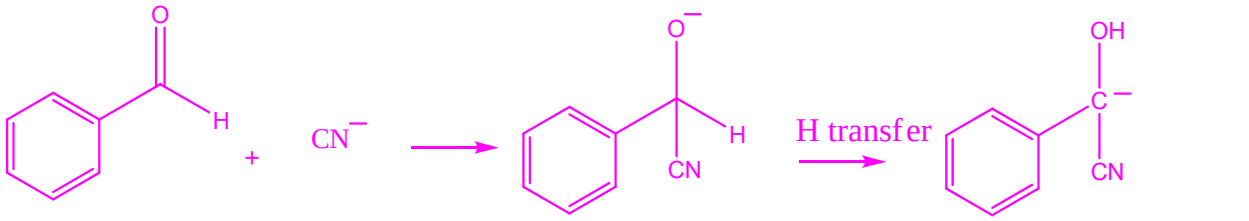
(iii) Benzoin condensation : Aromatic aldehydes can be condensed in the presence of CN^{---} ion (cyanide ions) as a catalyst to give α-hydroxy ketone (Benzoin). This reaction is known as Benzoin condensation reaction.





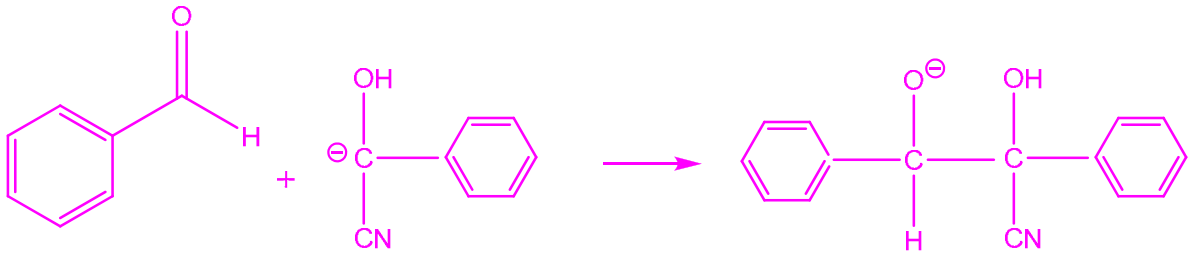
Mechanism :

(i) In the first step CN^{--} ion (weak base) (KCN or NaCN) undergo nucleophilic attack on electron deficient carbonyl carbon of benzaldehyde to form cyanohydrin anion (I).



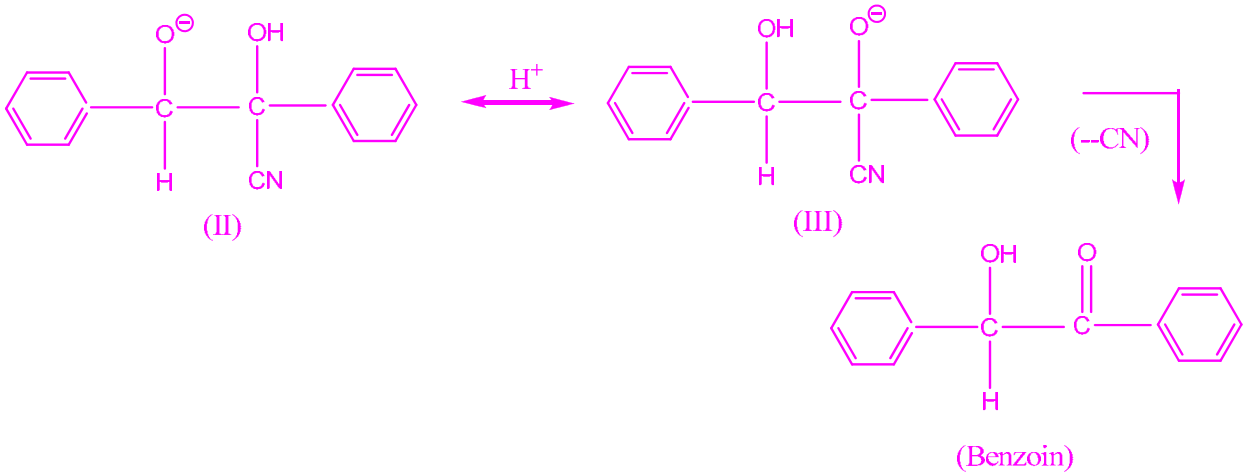
(Cyanohydrin anion) (I)

(ii) Cyanohydrin anion (I) undergo nucleophilic attack on carbonyl carbon of benzaldehyde to form alkoxy anion (II).



(II)

(iii) Alkoxide anion (II) undergo exchange of proton to produce another alkoxide anion (III), which finally undergo loss of CN^{---} ion to give α-hydroxy ketone (Benzoin).



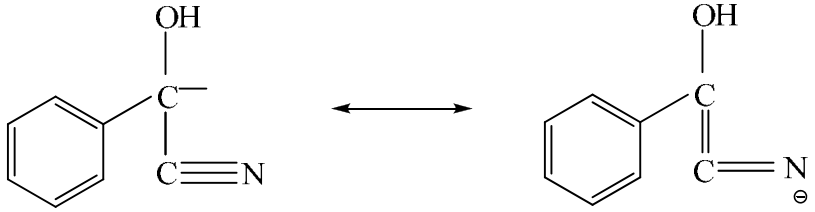
(II) (III) (Benzoin)

The CN^{---} (cyanide ion) is a very specific catalyst for Benzoin condensation reaction due to following reason :(Explain)

(i) The CN^{---} is not strong enough to abstract aldehyde proton because it is not sufficiently basic. But it attacks on electron deficient carbonyl carbon and give intermediate cyanohydrins anion.

(ii) CN^{---} is an electron withdrawing group. Because of its electron withdrawing properties, it helps in the removal of proton from the carbon and that is gained by –ve ly charged 'O' atom to give cyanohydrins anion.

(iii) It also stabilized the intermediate cyanohydrins anion by withdrawing electrons.

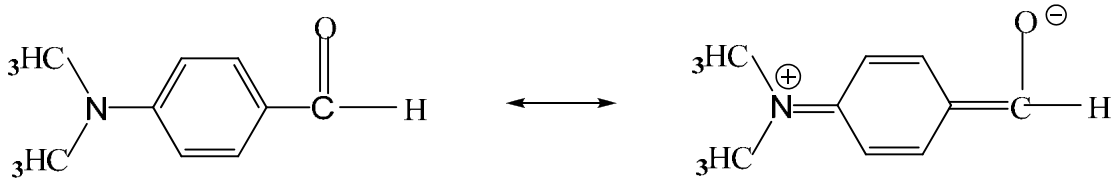


(iv) It (CN^{---} ion) is a weakly basic and hence it is good leaving group. It can be easily removed in the last step.

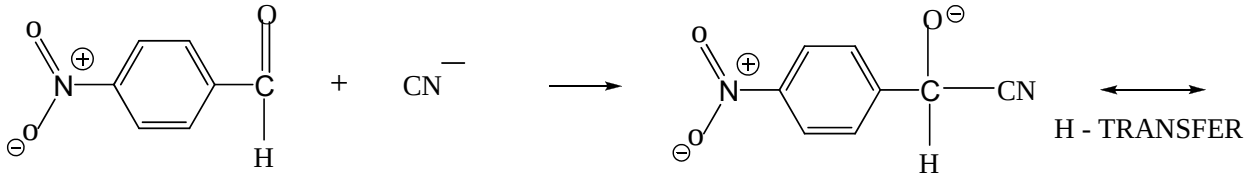
(iv) In absence of catalyst (CN^{---} ion), reaction does not occurs.

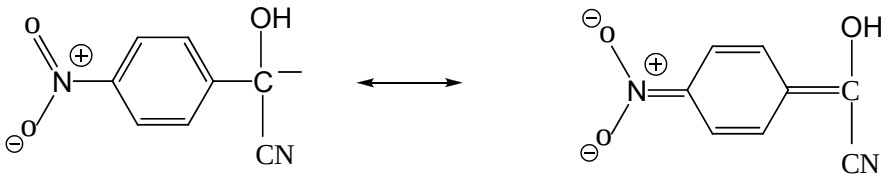
Q : Explain : *p- N, N* – Dimethylaminobenzaldehyde and *p*-nitrobenzaldehyde do not undergo self condensation under benzoin condensation.

Due to resonance in *p- N, N* – Dimethylaminobenzaldehyde the carbonyl carbon is not sufficiently electrophilic and hence it cannot attacked by CN^{---} ion.



Similarly, because of resonance the cyanohydrin anion of *p*-nitrobenzaldehyde is not nucleophilic enough to attack on another aldehyde molecules.

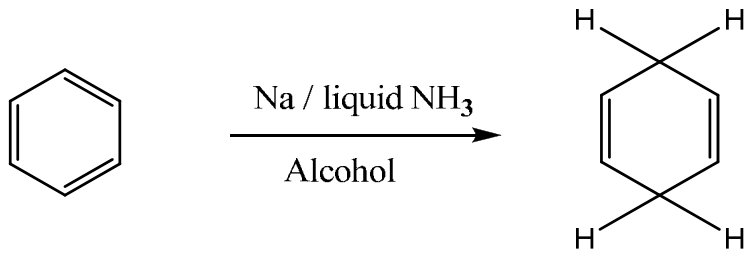




(iv) Birch reduction :

In Birch reduction aromatic compound having a benzenoid ring are converted into 1,4-cyclohexadiene in which two hydrogen atoms are attached at opposite ends of the molecule. Here, partial reduction of aromatic compound takes place into non-conjugated cyclic diene in presence of alkali metal, liquid ammonia and alcohol (proton donor).

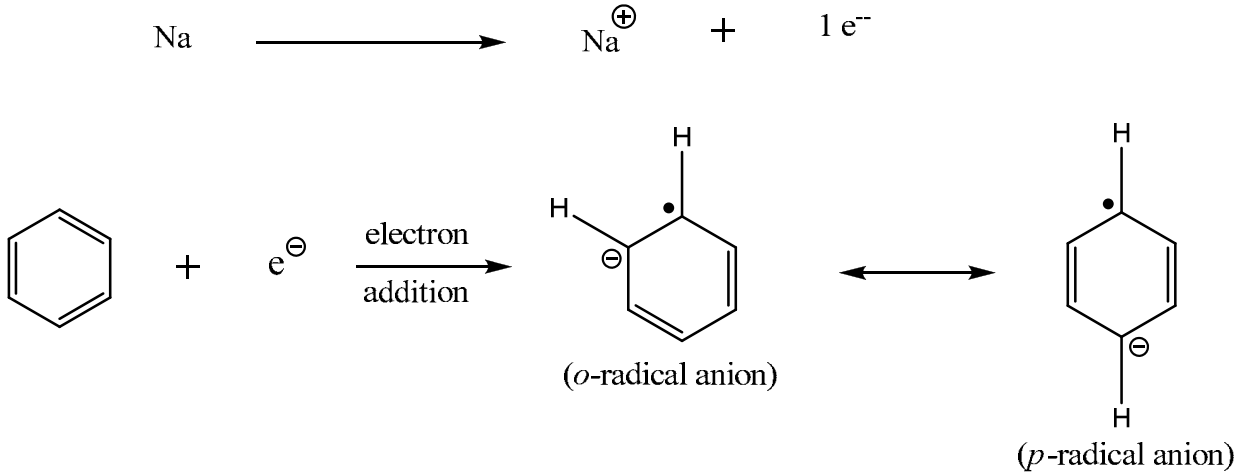
Aromatic compound $\xrightarrow[\text{alcohol}]{\text{Alkali metal, liquid } NH_3}$ non-conjugated cyclic diene



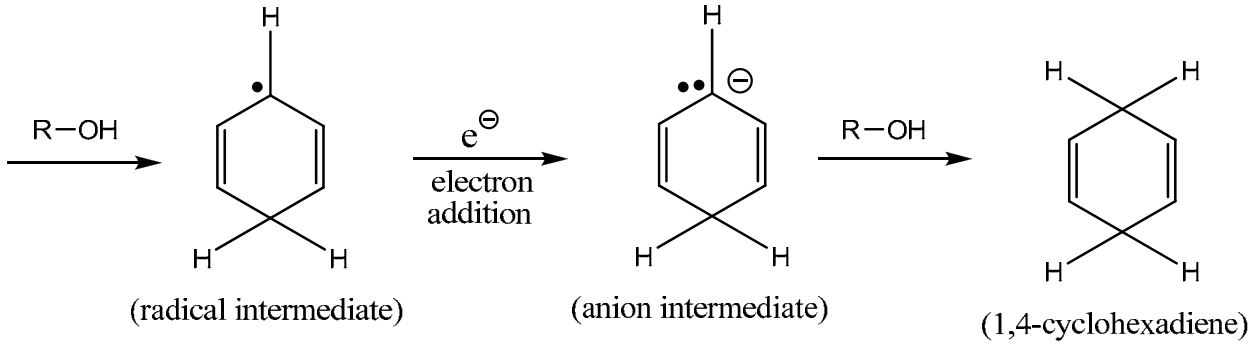
Benzene (1,4-cyclohexadiene)

Mechanism :

(i) In the first step an electron produced from sodium metal, undergo free radical attack on any one carbon of benzene ring to produce o-radical anion, that undergo resonance to produce more stable p-radical anion.

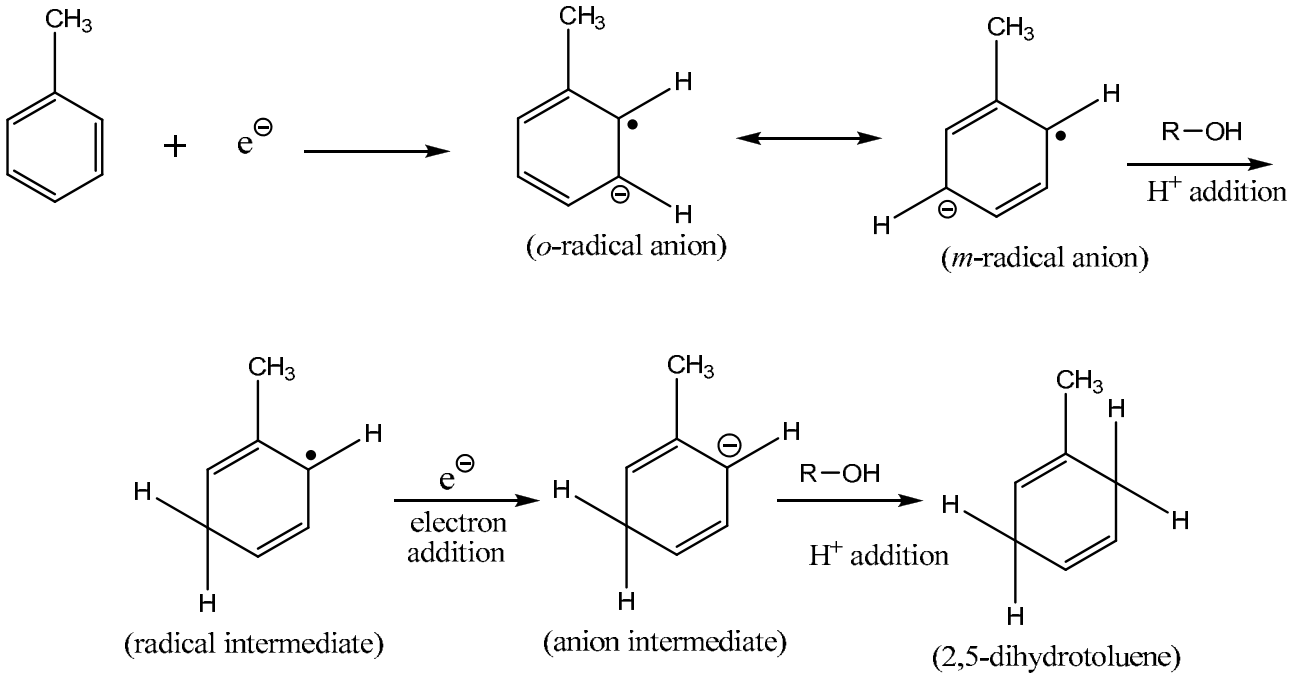


(ii) p-radical anion abstract H^+ ion (proton) from alcohol to generate radical intermediate, which further undergo free radical addition to produce anion intermediate which upon abstraction of proton from alcohol gives 1,4-cyclohexadiene.

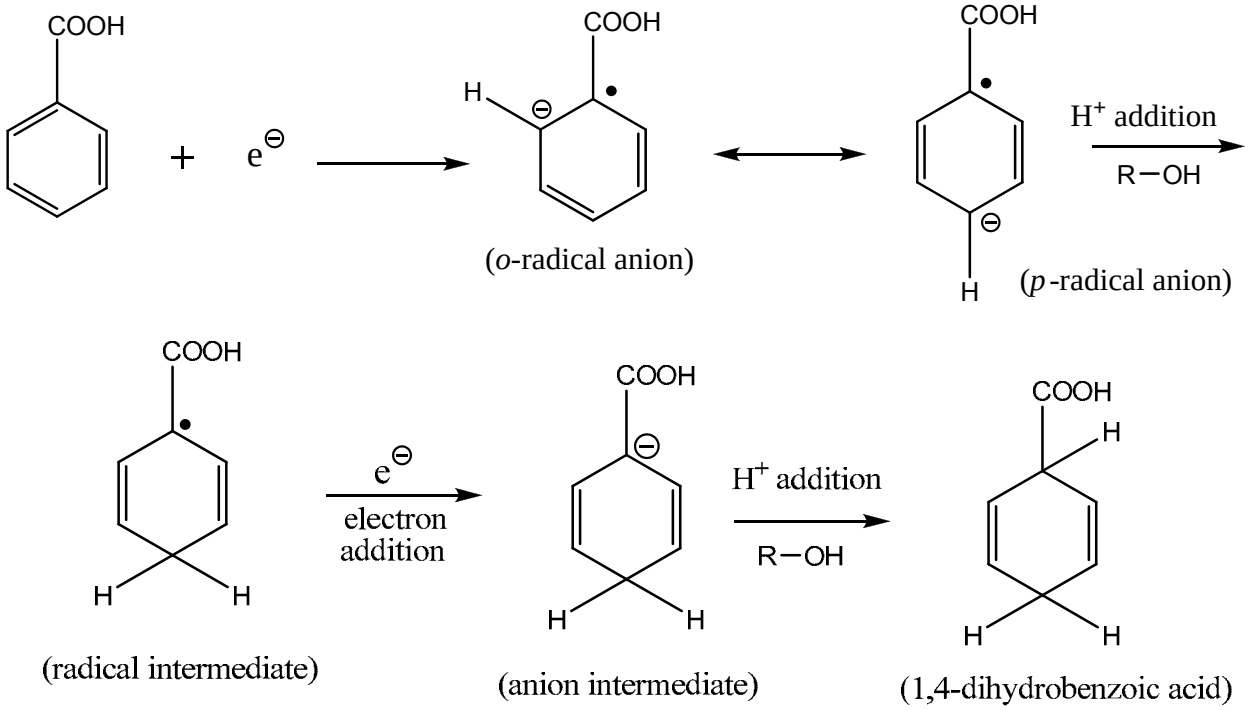


Birch reduction of toluene give 2,5-dihydrotoluene, where as benzoic acid gives 1,4-dihydobenzoic acid.(Explain)

Calculation by molecular orbital method of the electron density in the radical – anion showed that the electron density is the greatest at ortho and para position to the electron donating group ($-CH_3$) and hence Birch reduction of toluene or any benzenoid compound having an electron donating group should gives 2,5-dihydrotoluene or 2,5-dihydroderivatives.

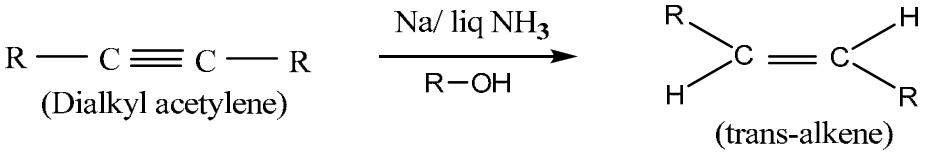


On the other hand calculation on the radical anion of a benzenoid compound with on electron withdrawing group showed that the *para* position to the group has the maximum electron density and hence compound like benzoic acid give 1,4-dihydro benzoic acid.

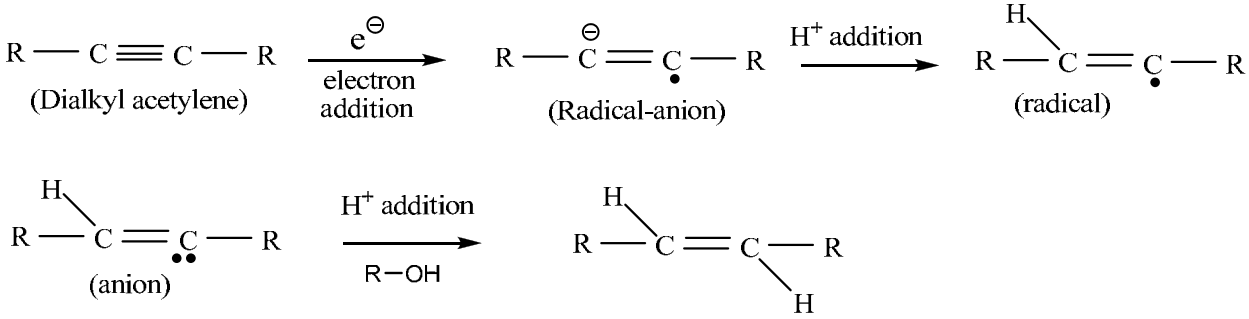


Birch reduction of acetylene:

Acetylene derivative undergo birch reduction to give *trans* alkene.



Mechanism :



(v) Curtius–Schmidt rearrangement :

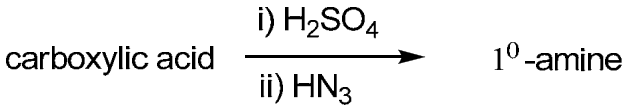
Using Curtius–Schmidt rearrangement carbonyl derivatives can be converted in to different products.

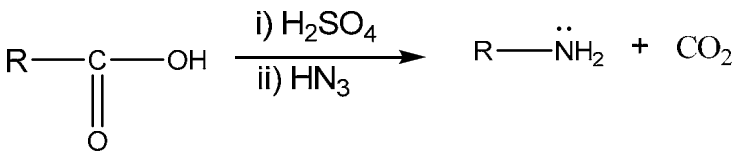
(a) carboxylic acid in to primary amine

(b) ketone into N-substituted amide

(c) aldehyde into N-formaldehyde derivative and Nitrile

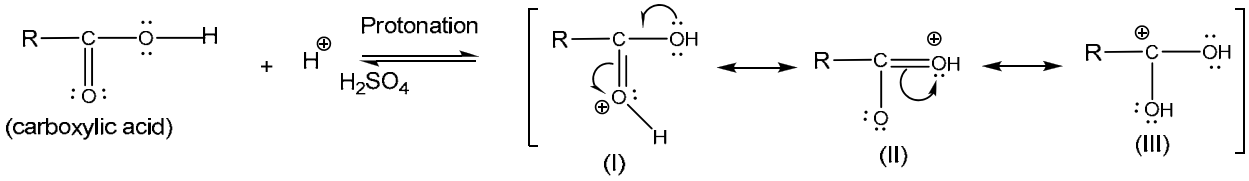
(a) The conversion of carboxylic acid into 1^0-amine in the presence of H_2SO_4 and hayrazoic acid (NH_3) is know as curtius- Schidt rearrangement.



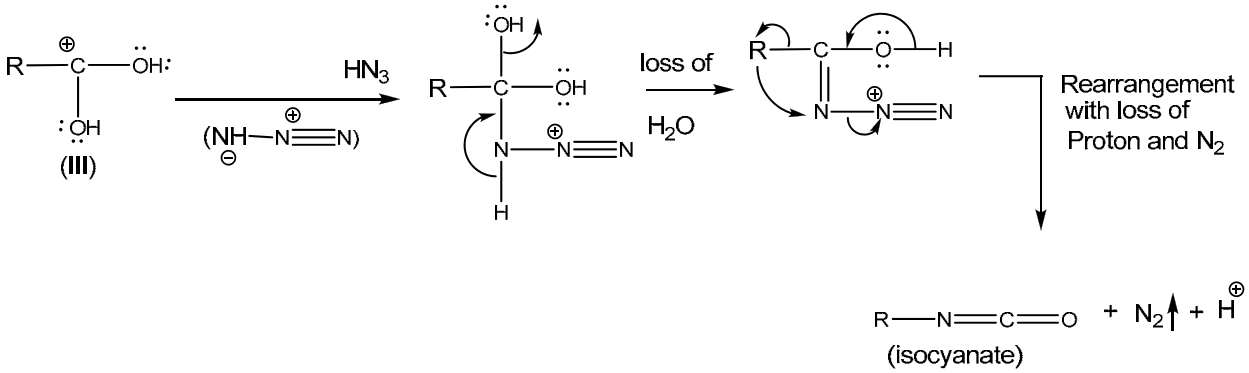


Mechanism:

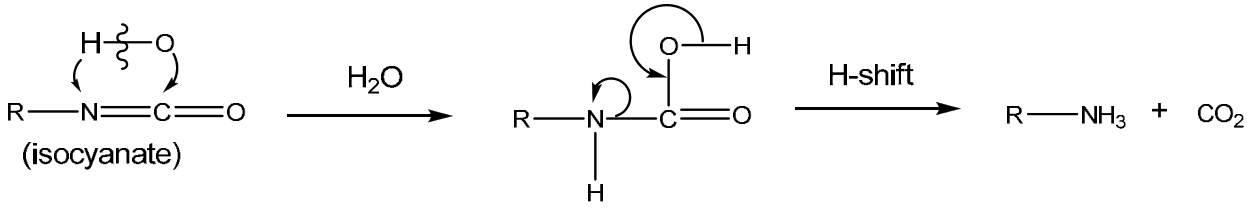
(i) In the first step carboxylic acid undergo protonation to generate carbocation.



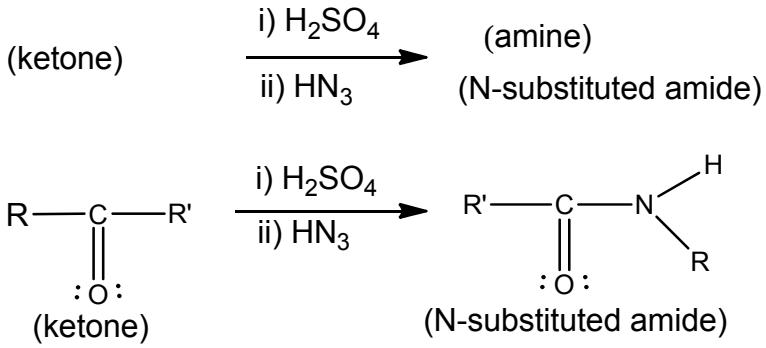
(ii) In the second step carbocation undergo nucleophilic attack by hydrazoic acid followed by loss of water and rearrangement to generates isocyanate derivative.



(iii) Isocyanate derivative undergo hydrolysis to produce primary amine.

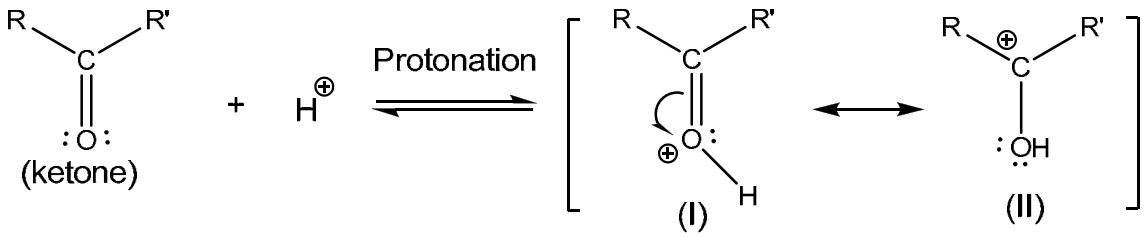


(b) Carbonyl compounds also undergo curtius- Schmidt rearrangement. Keton produce amides.

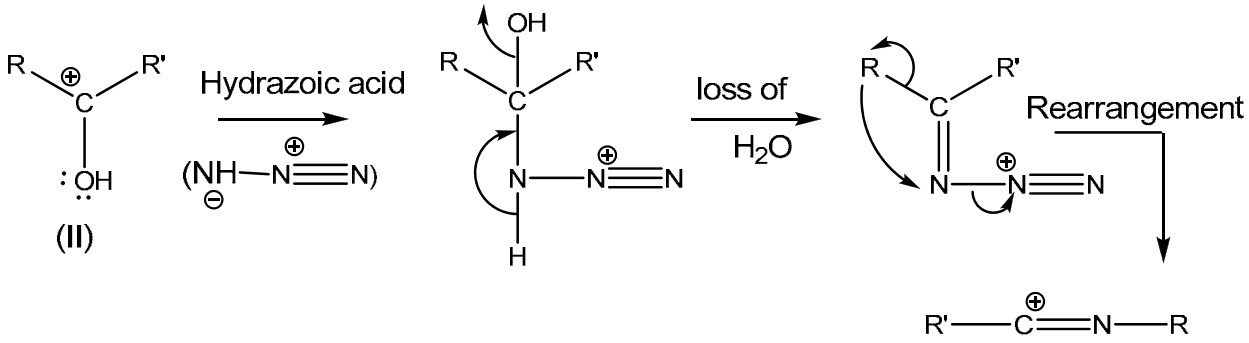


Mechanism:

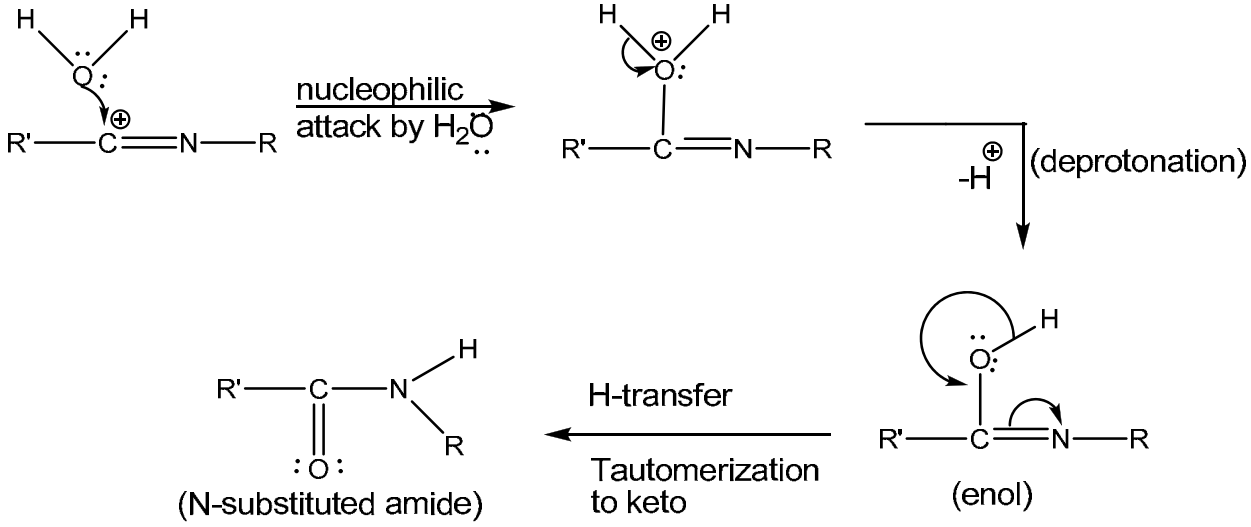
(i) In the first step ketone undergo protonation to generate carbocation (II).



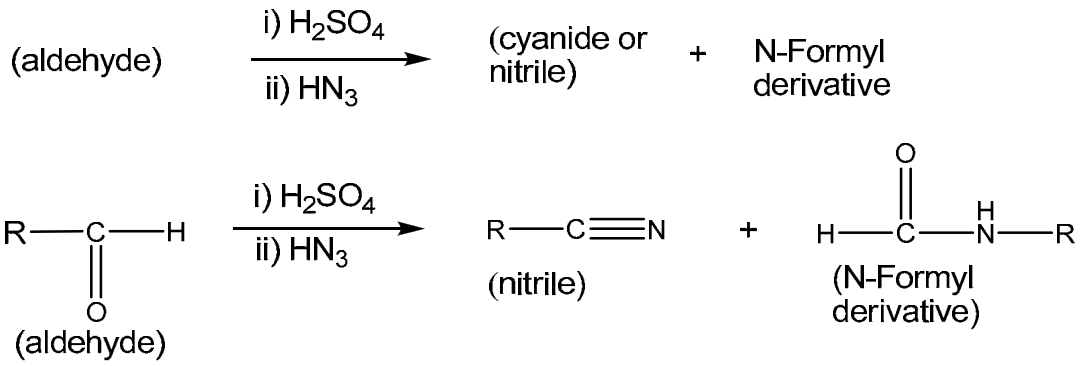
(ii) In the second step carbocation (II) undergo nucleophilic attack by hydrazoic acid followed by loss of water and rearrangement to generates isocyanate derivative.



(iii) Isocyanate derivative undergo nucleophilic attack by water followed by deprotonation and tautomerization to produce N-substituted amide.

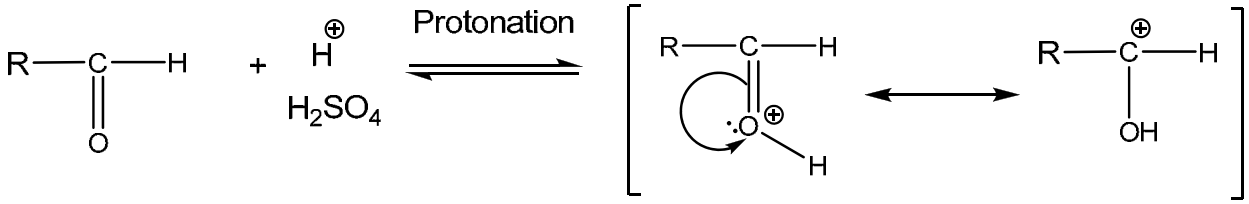


(c) Aldehyde compounds also undergo curtius- Schmidt rearrangement. Aldehyde generally gives a mixture of the corresponding nitrile (cyanide) and N-formyl derivatives.

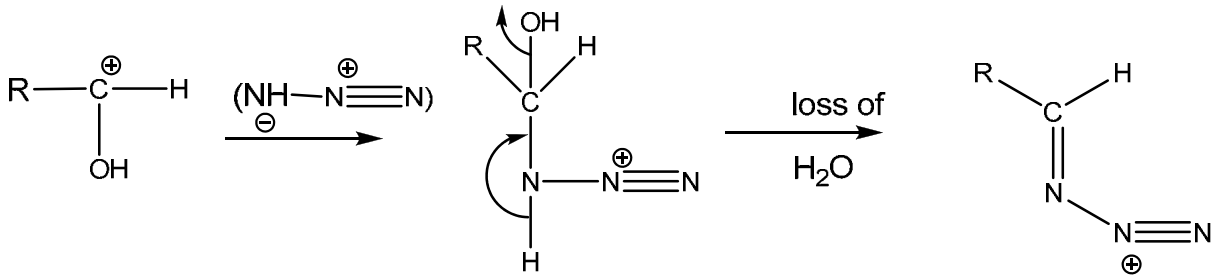


Mechanism:

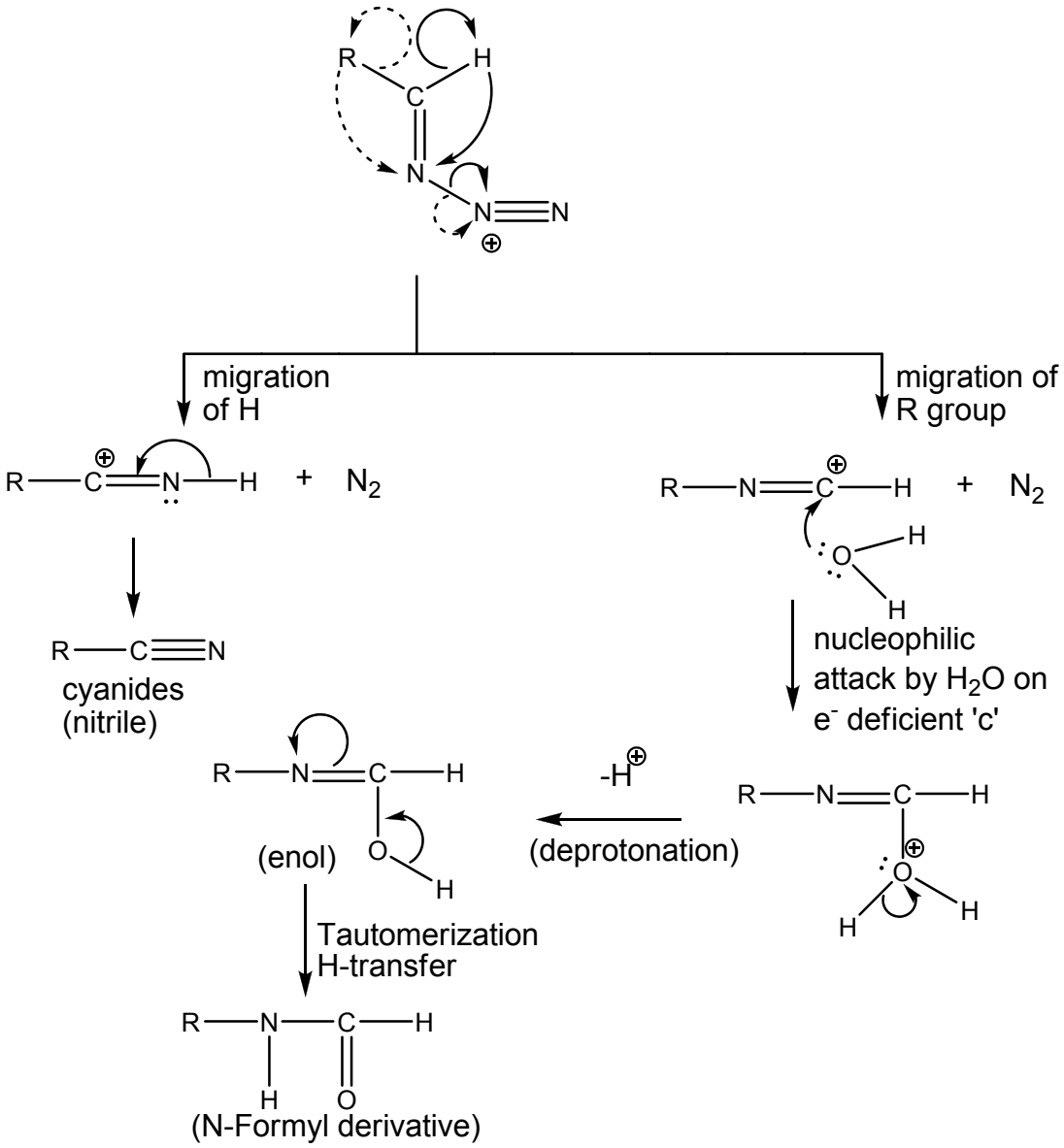
(i) In the first step aldehyde undergo protonation to generate carbocation.



(ii) In the second step carbocation undergo nucleophilic attack by hydrazoic acid followed by loss of water to generates azide derivative.

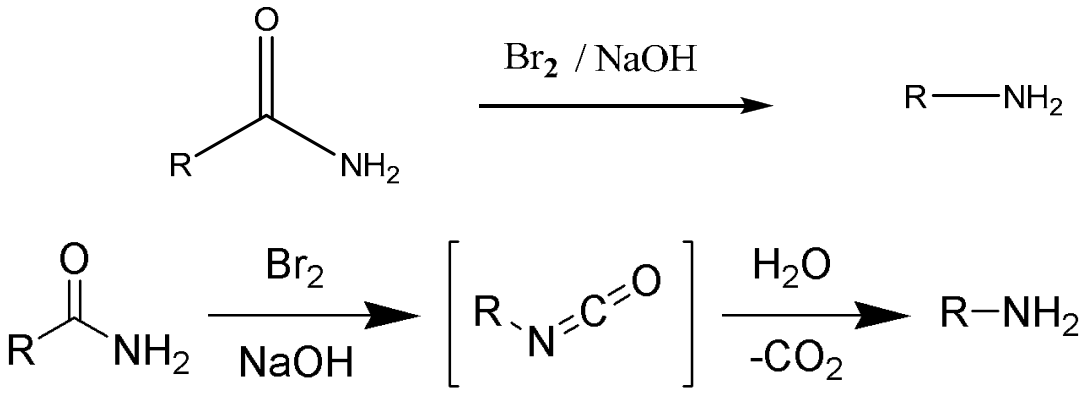


(iii) Finally azide derivative undergo rearrangement. Upon migration of 'H' it gives nitrile derivative, while upon migration of R group followed by nucleophilic attack by water and deprotonation it gives N-formyl derivatives.



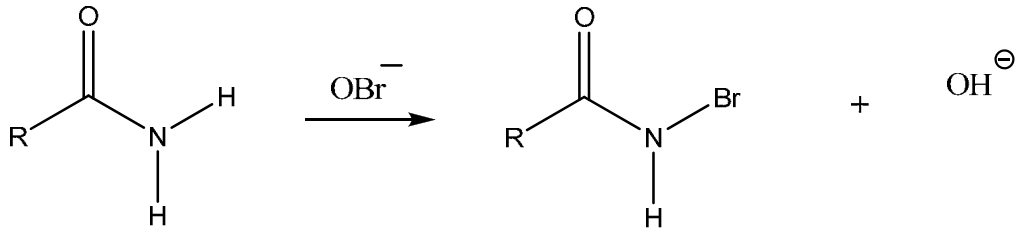
(vi) Hofmann rearrangement :

In Hofmann rearrangement a primary amide is converted in to a primary amine with one less (fewer) carbon atom. The reaction is named after its discoverer – August Wilhelm von Hofmann. This reaction is also sometimes called the Hofmann degradation.

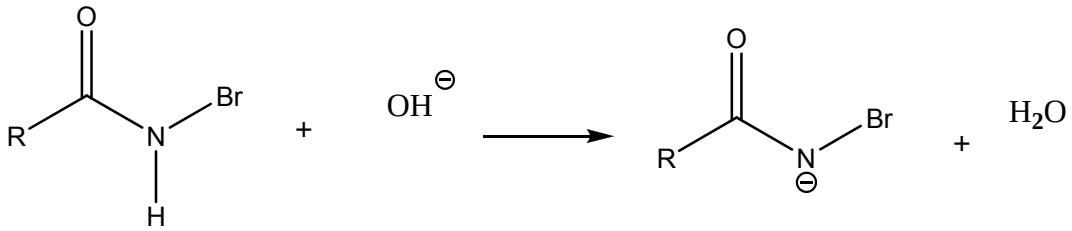


Mechanism :

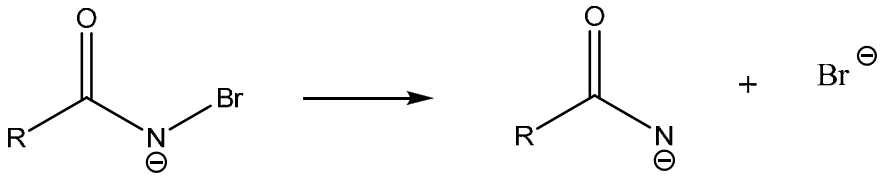
1. In the first step halogenation (bromination) of amide takes place in presence of sodium hypobromide (NaOBr) to generate N-bromoamide.

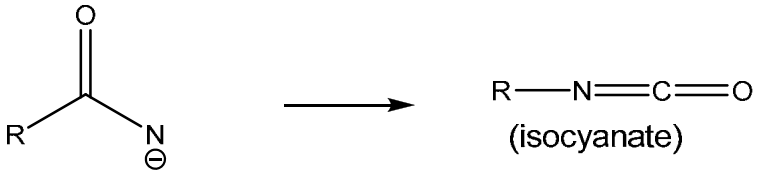


2. In the second step base abstract proton from N-bromoamide to form anion of *N*-bromoamide.

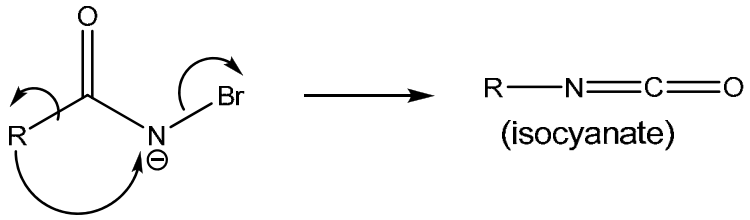


In step 3, loss of bromide ion take place to produce an electron deficient nitrogen atom derivatives. In step 4 'R' group migrates to an electron deficient nitrogen atom to generate isocyanate.

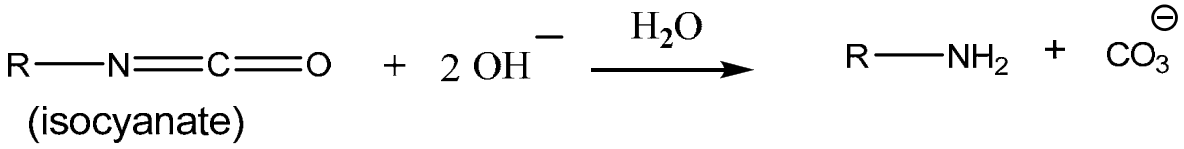
3) 

4) 

Step 3 and 4 are believed to occur simultaneous, in which, the attachment of R group to nitrogen helping to push out halide ion.

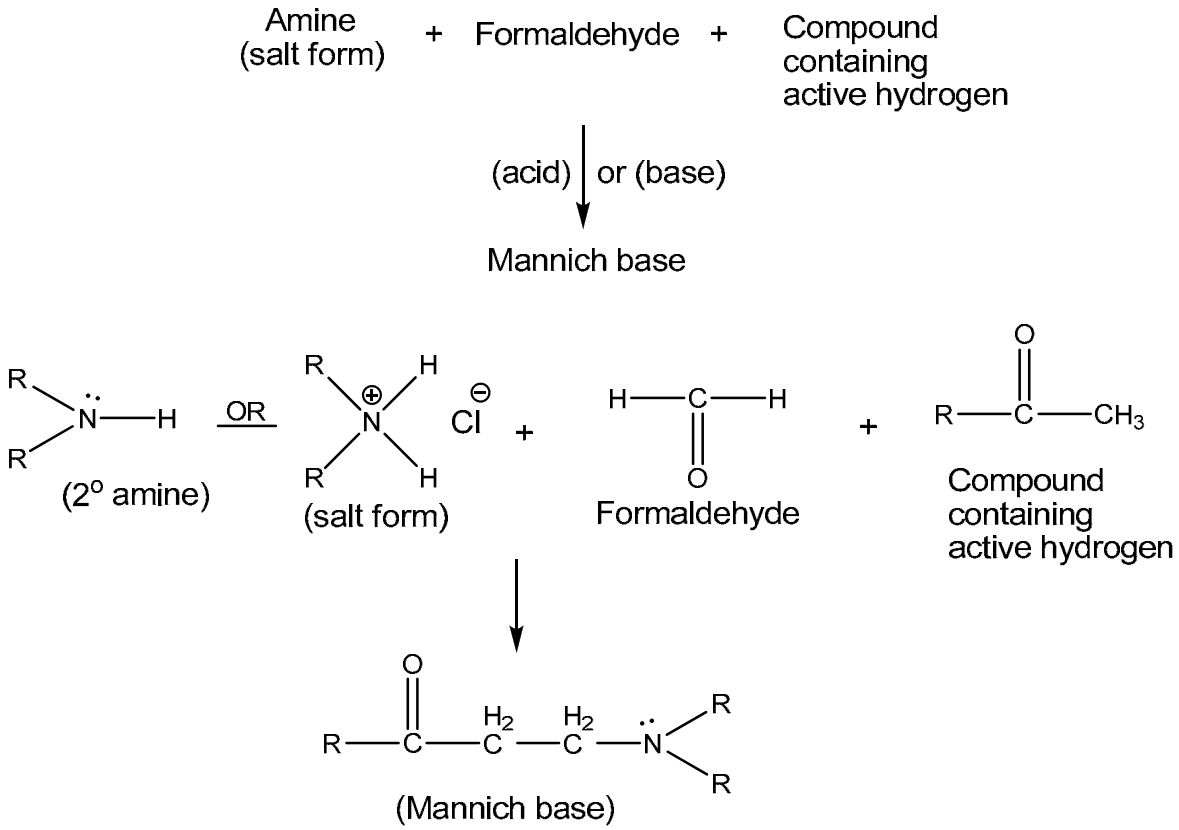


Step 5 is the hydrolysis of isocyanate to form primary amine and carbonate ion.



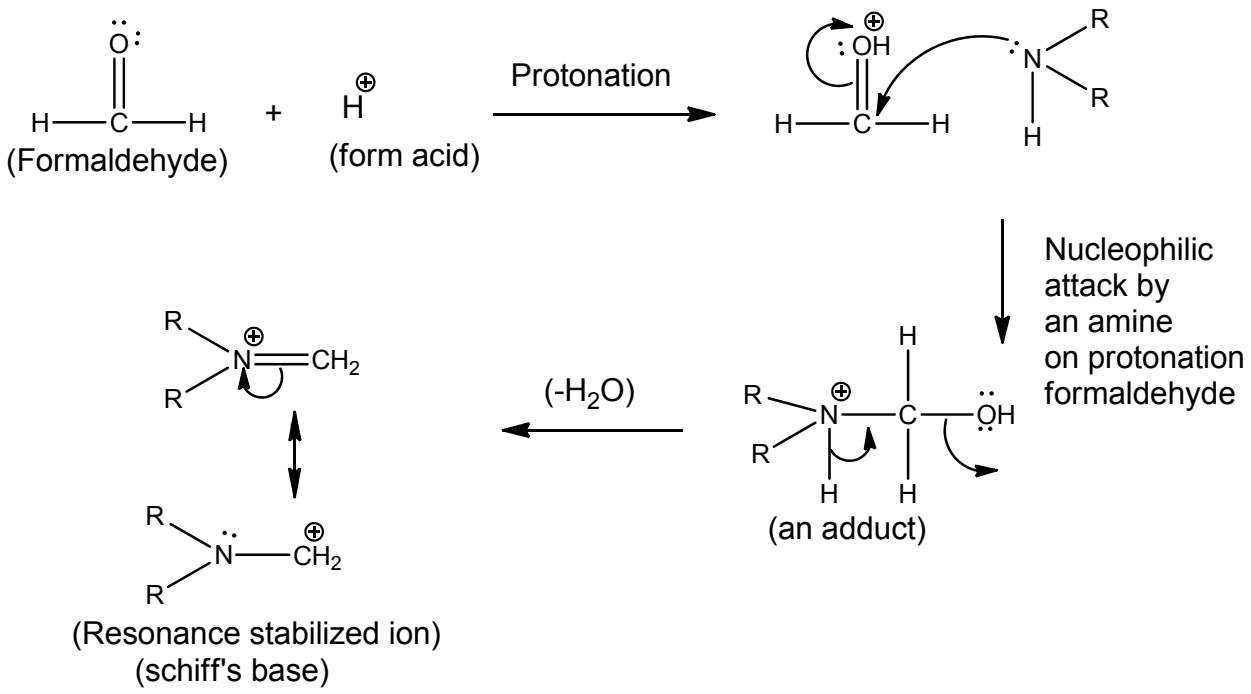
(vii) Mannich reaction :

The formation of Mannich bases by condensing an amine, formaldehyde and a compound containing an active hydrogen atom is known as Mannich reaction. An acidic or basic medium is needed for the chemical reaction. The final product is a β-amino-carbonyl compound and is known as a **Mannich** base.

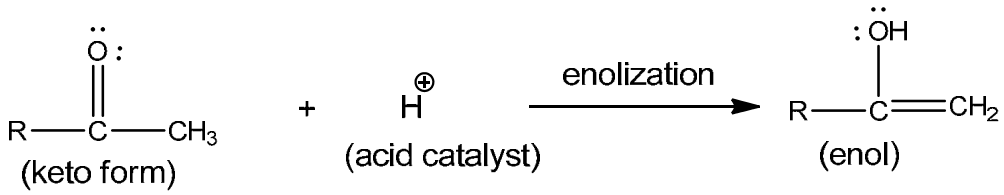


Mechanism:

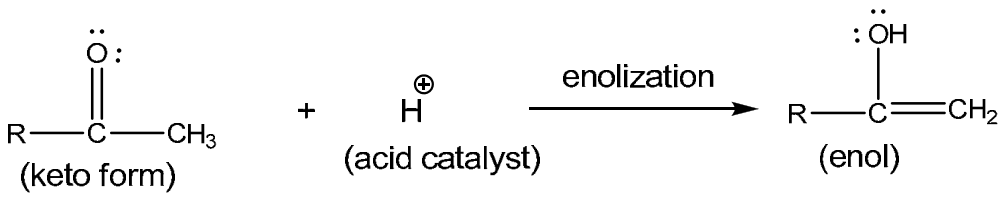
Step (i) : In the first step addition of amine to fromaldehyde in the presence of acid to give an adduct which loses water to form the resonance stabilized ion (Schiff base).

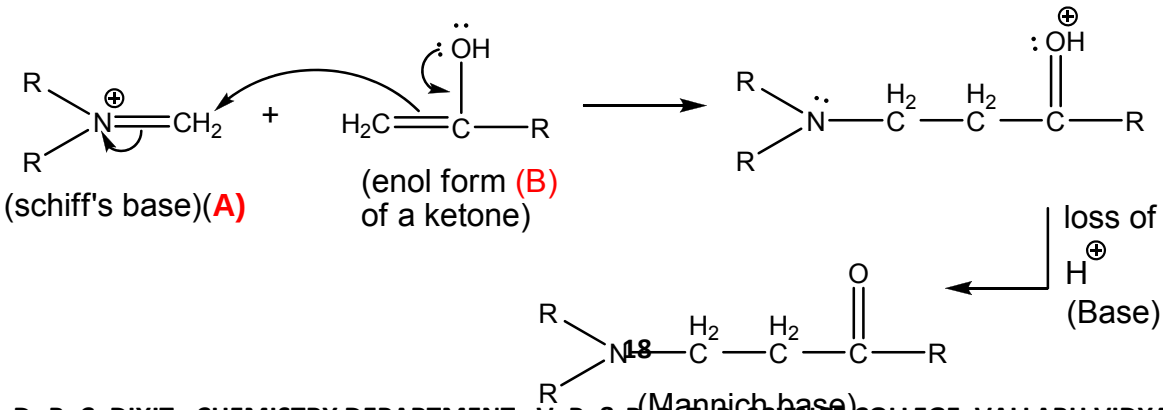


Step (ii) : The acid converts keton (compound containing active hy.) into enolic form.



Step (iii) : The resonance stabilized ion and enolic form of ketone react to form Mannich base.



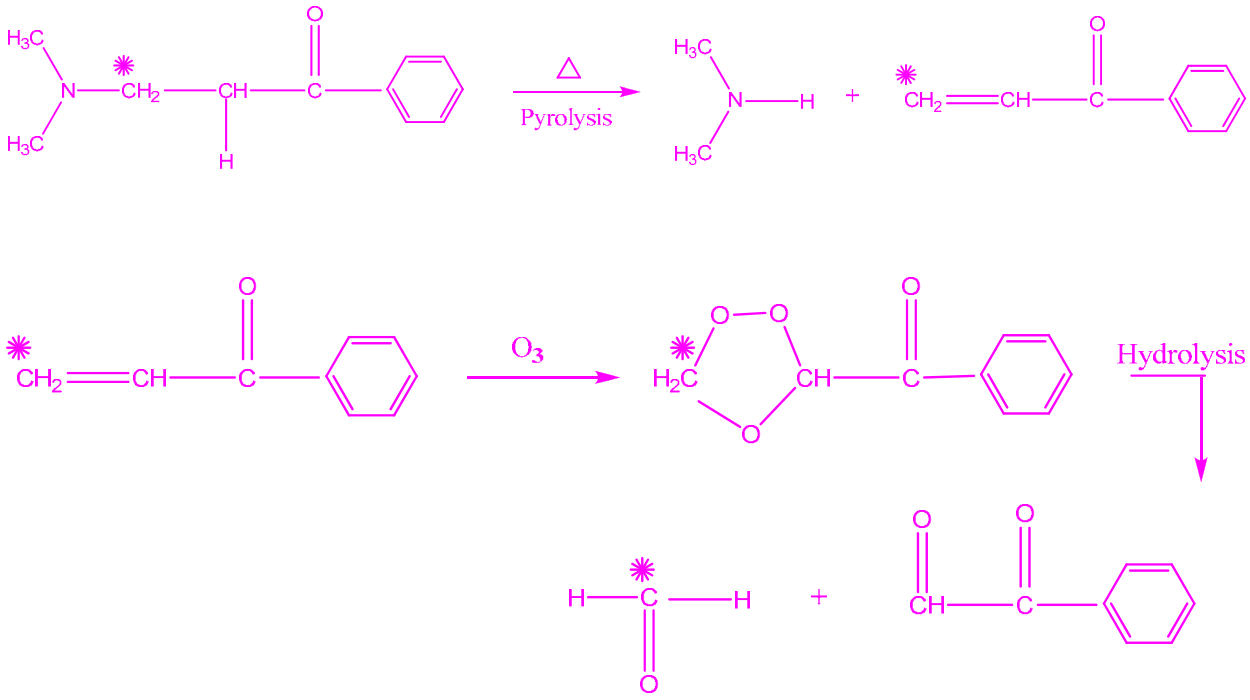


Explain : Out of two --CH_2-- groups in Mannich base, one is coming from formaldehyde.

In Mannich reaction, the resulting Mannich base contains two --CH_2 – group, one is coming from formaldehyde and the other from ketone.

It can be demonstrated by carbon – 14 labeling studies and it indicated that no rearrangement takes place.

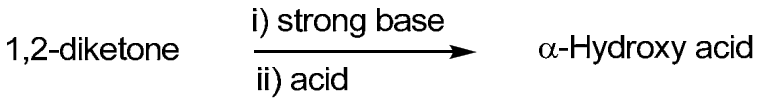
β-^{14}C- β-dimethyl amino propiophenone was prepared according to above reaction, which on pyrolysis and then followed by Ozonolysis give formaldehyde containing all the ^{14}C content.



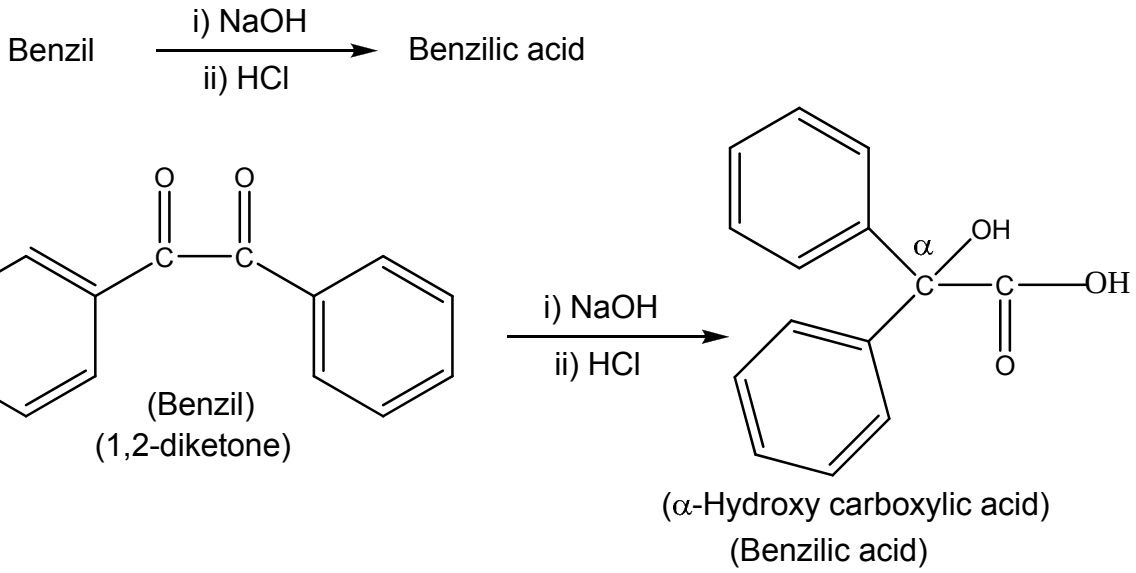
From the above experimental data we can say that out of two --CH_2 – groups, one --CH_2 – is coming from formaldehyde as it retains labeled carbon upon pyrolysis, followed by ozonolysis/hydrolysis.

(viii) Benzilic acid rearrangement :

The rearrangement of 1,2-diketones in the presence of strong base of α-Hydroxy acid is known as Benzilic acid rearrangement.

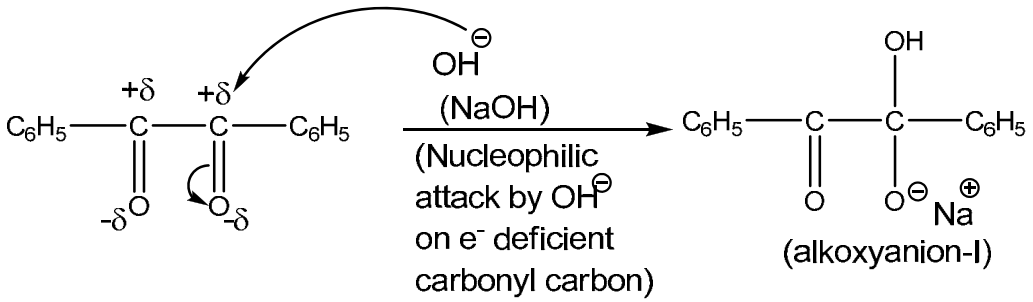


Benzil under these condition give benzilic acid

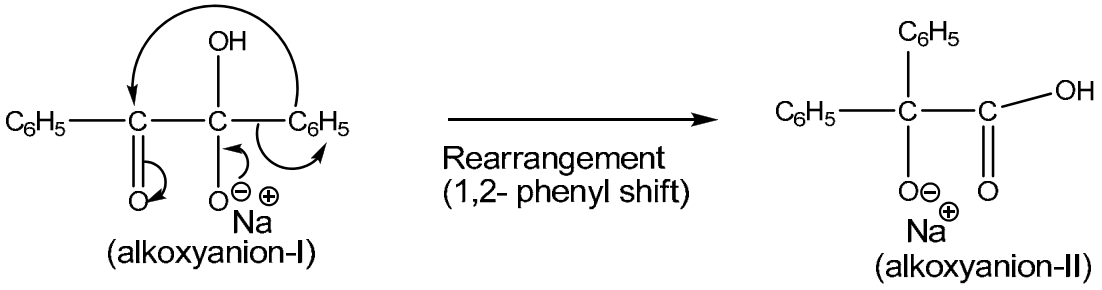


Mechanism :

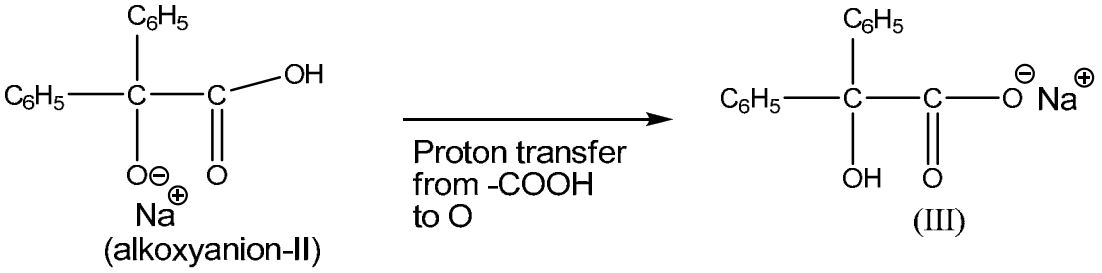
(i) In the first step, OH ion undergo nucleophilic attack on electron deficient carbonyl carbon to produce alkoxy anion-I.



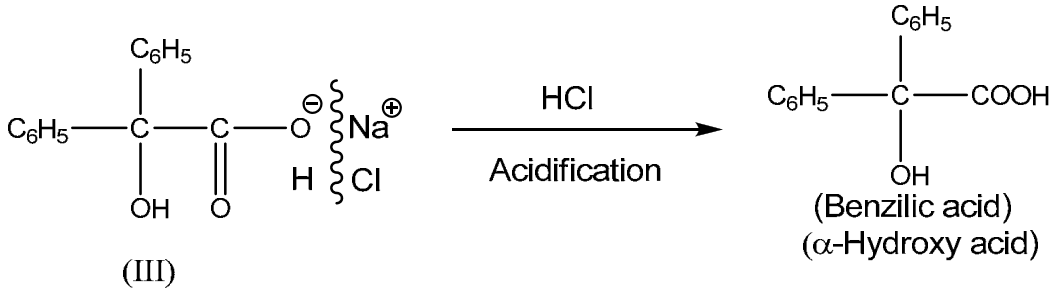
(ii) In the second step, rearrangement takes place via 1,2- phenyl shift to produce alkoxy anion-II.



(iii) In the third step, proton transfer takes place from carboxylic acid to oxygen of alkoxy anion-II.



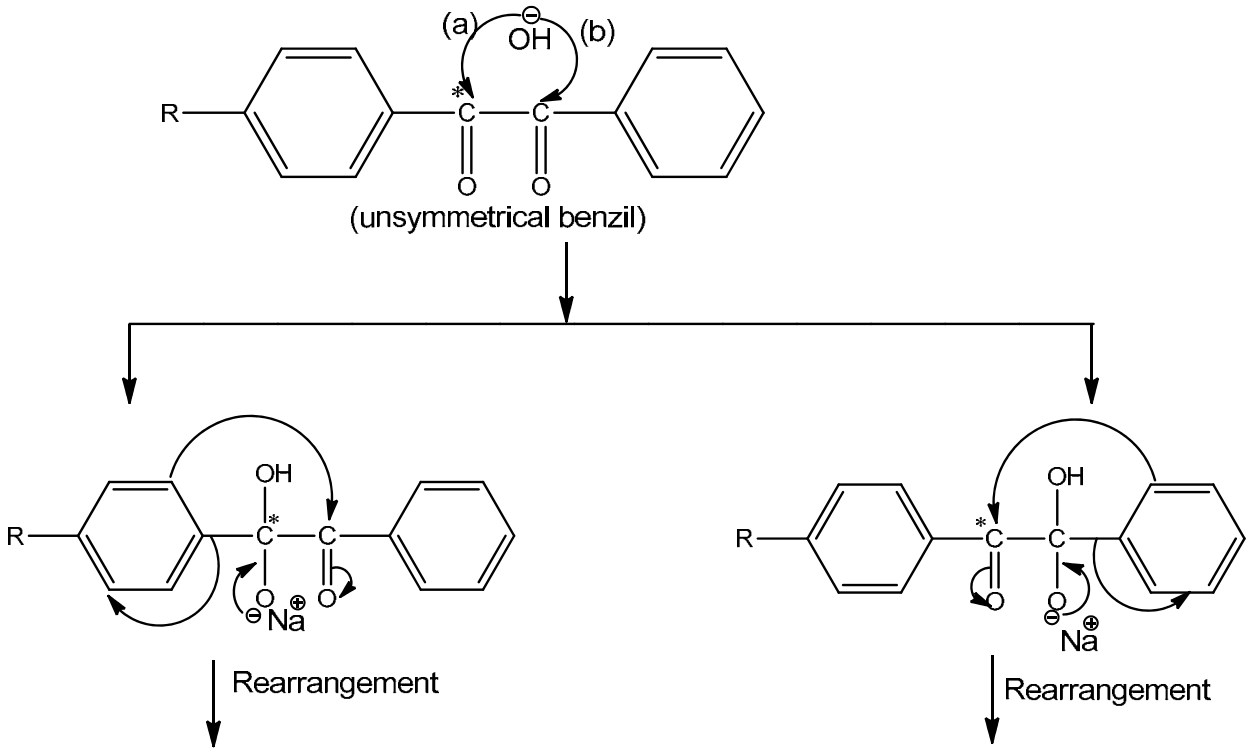
(iv) Finally upon acidification in the third step, proton transfer takes place from carboxylic acid to oxygen of alkoxy anion-II.

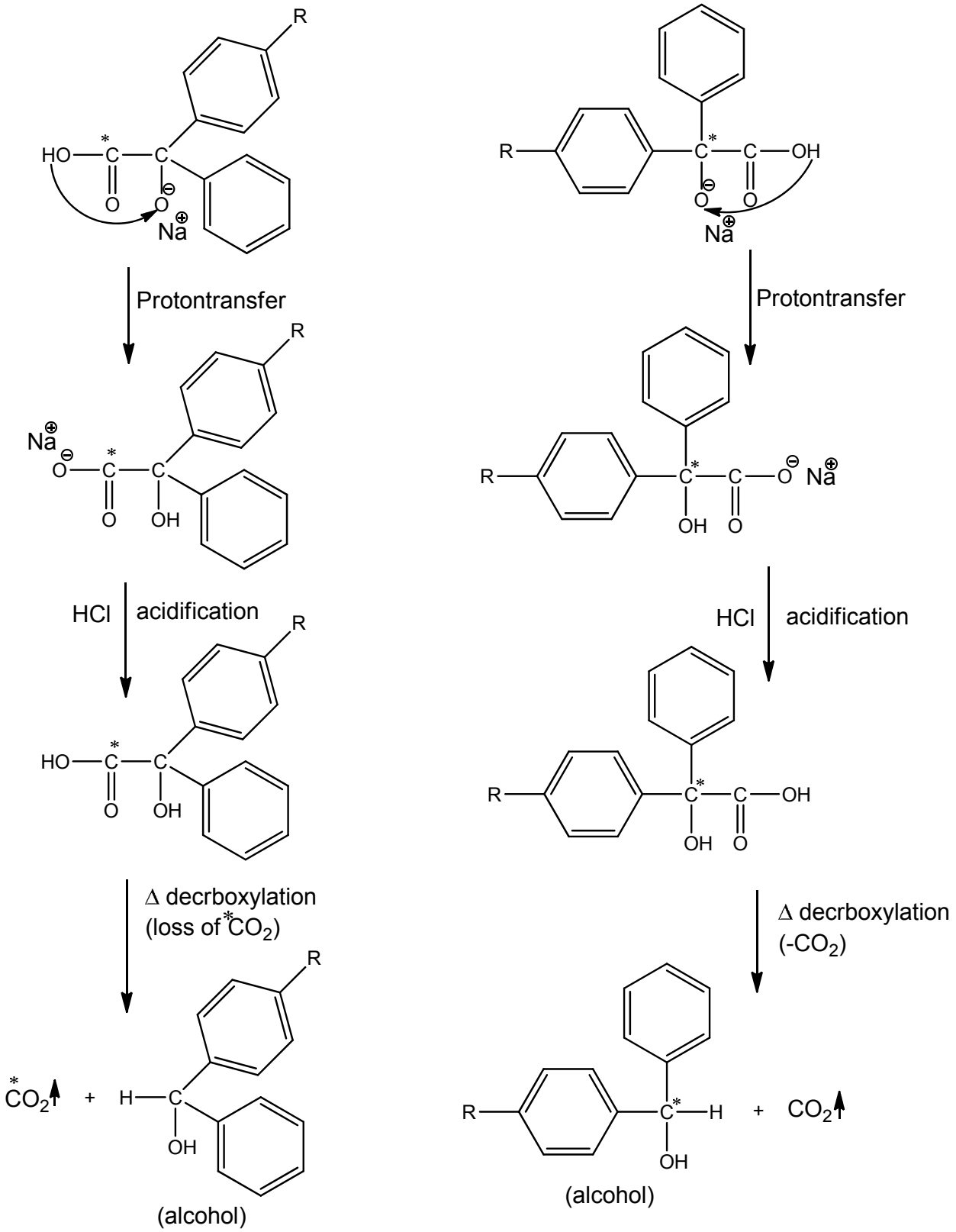


Preference for migration:-

Which of the two aryl groups migrates in unsymmetrical benzyls. It has been answered by C^{14}- labeling studies.

The product of the above unsymmetrical benzil after the rearrangement was decarboxylated and analyzed for C^{14} content. All the C^{14} content was found in the carbon dioxide and none in the alcohol derivative. This indicates that the migration of the aryl group containing an electron releasing group. We can say that in unsymmetrical benzil the aryl group with electron donating group migrates faster than the simple phenyl or aryl group.


(a)
OH
(b)
R
C
C
O
O
(unsymmetrical benzil)
OH
R
C
C
O
Na
O
Rearrangement
OH
R
C
C
O
O
Na
Rearrangement

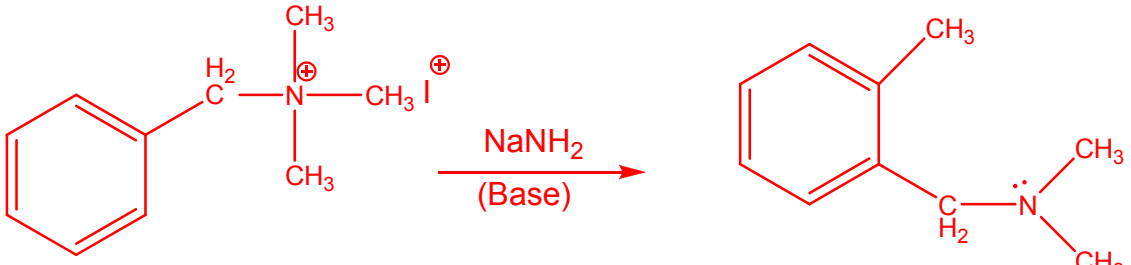

Protontransfer
HCl
acidification
Δ decrboxylation
(loss of *CO2)
(alcohol)
Protontransfer
HCl
acidification
Δ decrboxylation
(-CO2)
(alcohol)

(ix) Sommlet rearrangement :

The reaction of tetraalkyl ammonium halides containing a benzyl hydrogen to 3°-amine in the presence of strong base ($NaNH_2$. Sodamide) is called Sommelet rearrangement.

Tetra alkyl ammonium halide containing a benzyl hydrogen $\xrightarrow[(NaNH_2)]{\text{Base}}$ 3°-amine

Conversion of benzyltrimethyl ammonium iodide to ortho-methylbenzldimethyl amine.

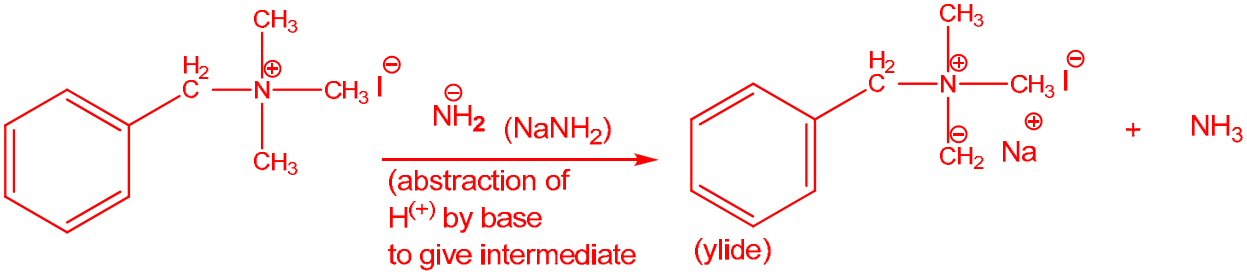


(Benzyl trimethyl ammonium iodide)

(o-Methylbenzyl dimethyl amine) (3°-amine)

Mechanism:-

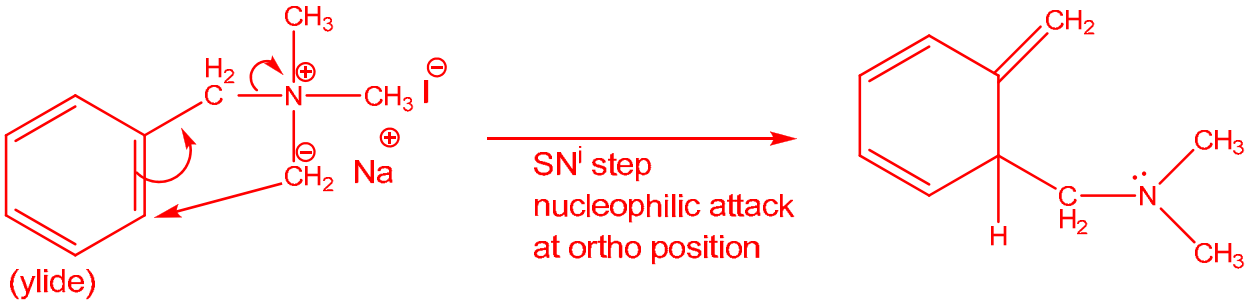
(i) In the first step, base abstract proton from quaternary alkyl group to produce ylide intermediate.



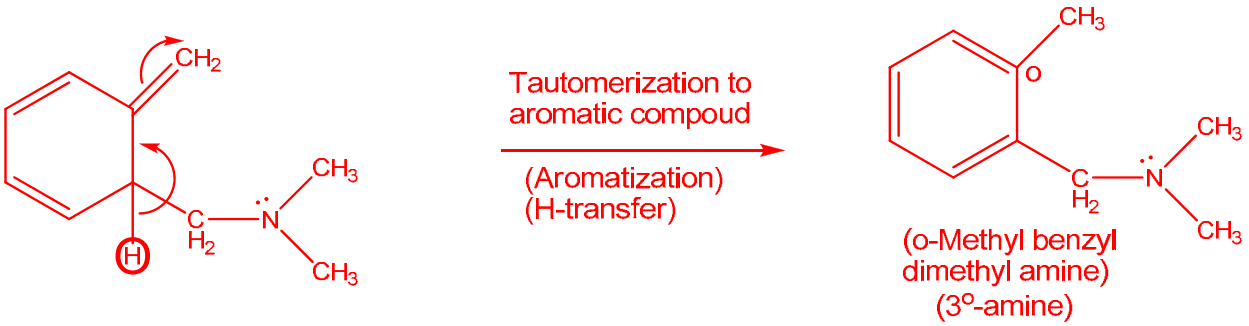
(abstraction of $H^{(+)}$ by base to give intermediate ylide)

(ylide)

(ii) In the second step, rearrangement takes place by nucleophilic attack of carbanion (ylide) of quaternary alkyl group to ortho position of benzene ring to produce non-aromatic intermediate.

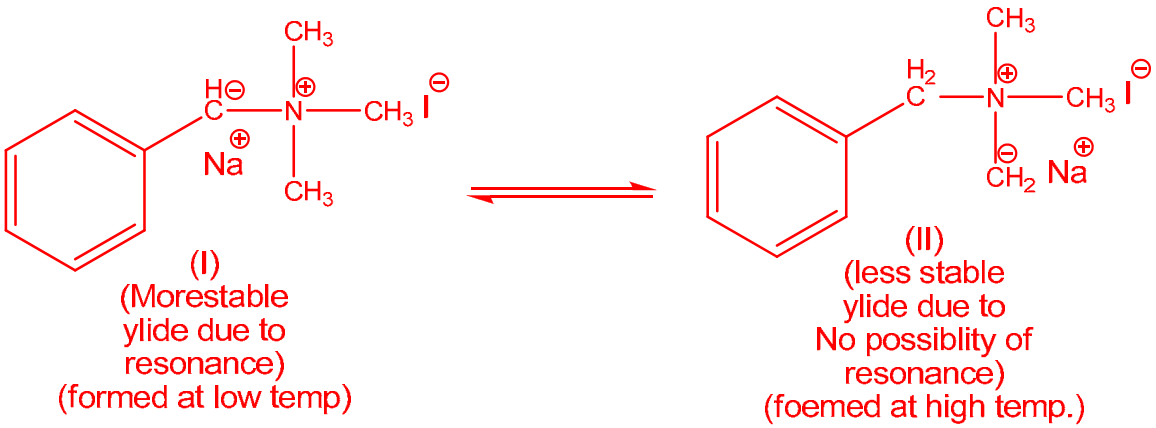


(iii) In the final step, upon exchange of proton (tautomerization) it gives aromatic compound 3^0 amine (o-Methyl benzyl dimethyl amine).



……

The rearrangement proceeds via the formation of less stable ylide (II).

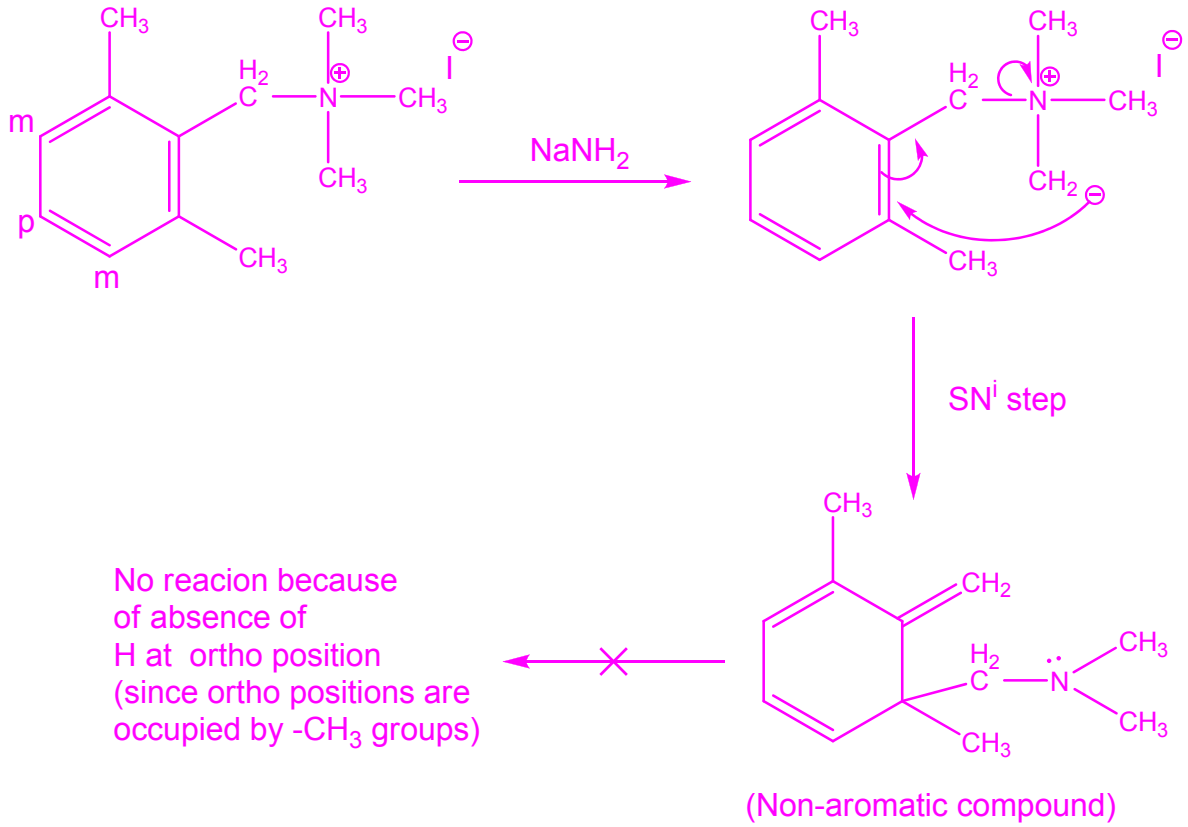


During Sommlet rearrangement, both ylides (I) & (II) exist in equilibrium. Out of that ylide (I) is more stable than ylide (II) because of the possibilities of resonance of benzyl anion. However, ylide (I) formed at low temperature, while in actual reaction progresses at higher temperature, and at higher temperature, equilibrium is displaced to the less stable ylide (II). Hence we can say that Sommlet rearrangement proceeds via the formation of less stable ylide (II).

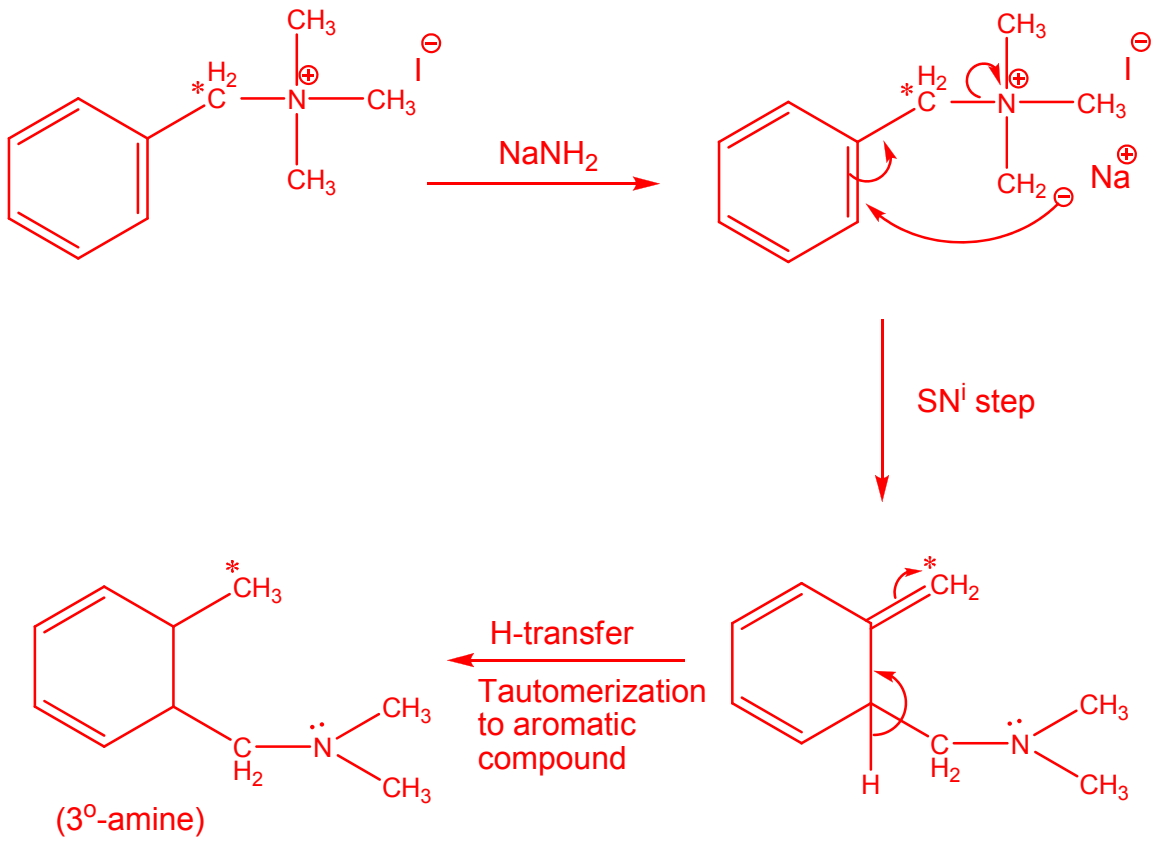
Evidence for the mechanism:

Scientist Hauser has provided some independent support for the mechanism. He argued that if the Sommelet rearrangement really proceeded via an intermediate ylide (less stable) (II) compound, than the compound in which ortho- positions are occupied by some groups should be isolated without aromatization.

This has been found to be true experimentally:



According to Sommelet rearrangement mechanism the benzyl carbon becomes the $-CH_3$ group in the product. When this carbon was labeled $\{C_6{}^{14}\}$ in the reactant, the ortho methyl carbon in the product retained all radioactivity.



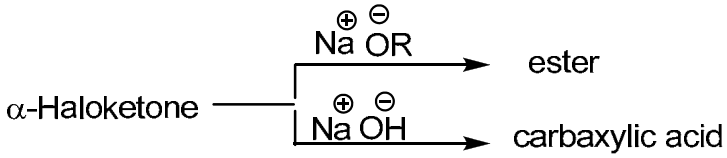
From the above experimental data, we can say that sommelet rearrangement proceeds through ylide intermediate compounds.

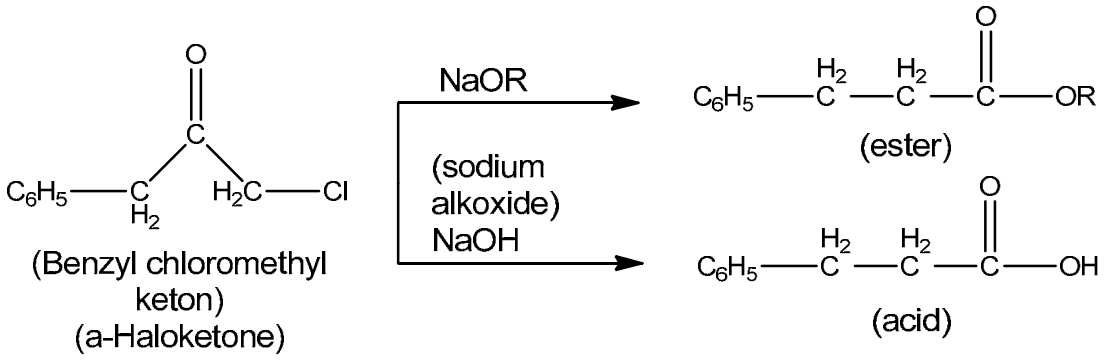
(10) Favorskii Rearrangement:-

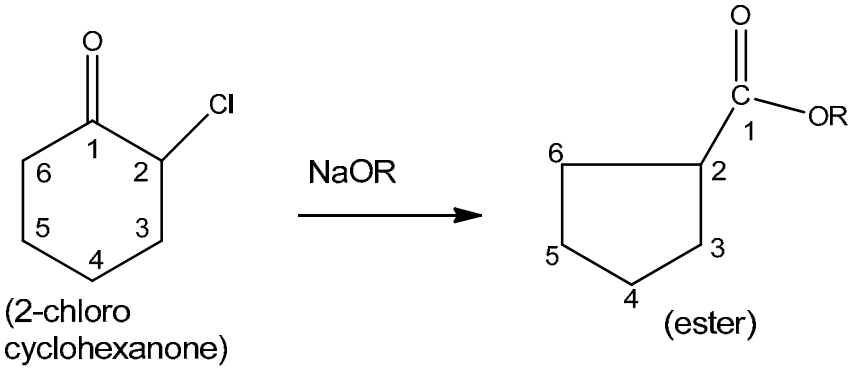
α-haloketon upon treatment with an alkoxide ion gives an ester product. In this reaction the product has a rearranged carbon skeleton, having same number of carbon atoms as the reactant. This reaction is called the Favorskii rearrangement.

Similar α-haloketones upon treatment with NaOH gives a carboxylic acid.

In cyclic α-haloketone the process leads to ring contraction.

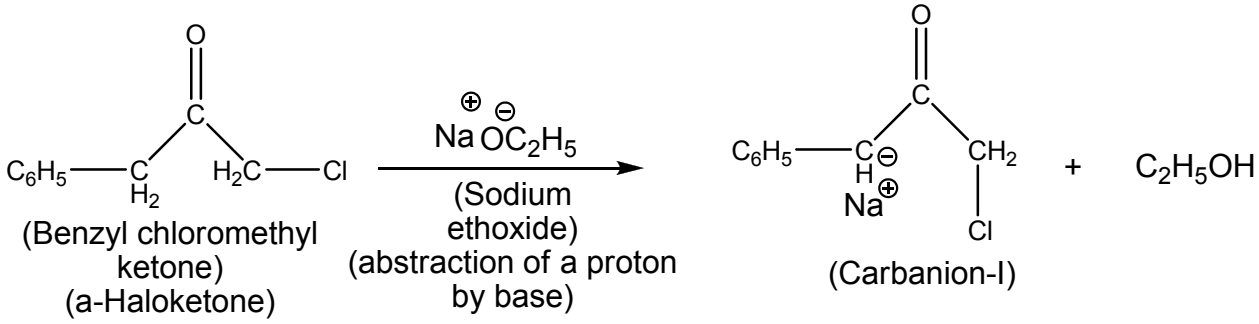




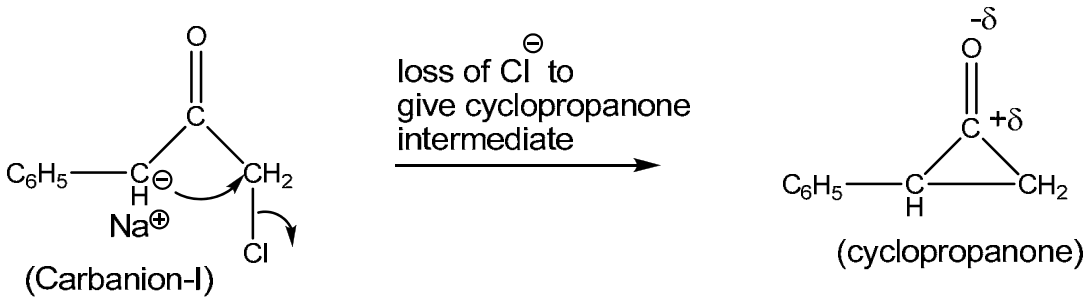


Mechanism:

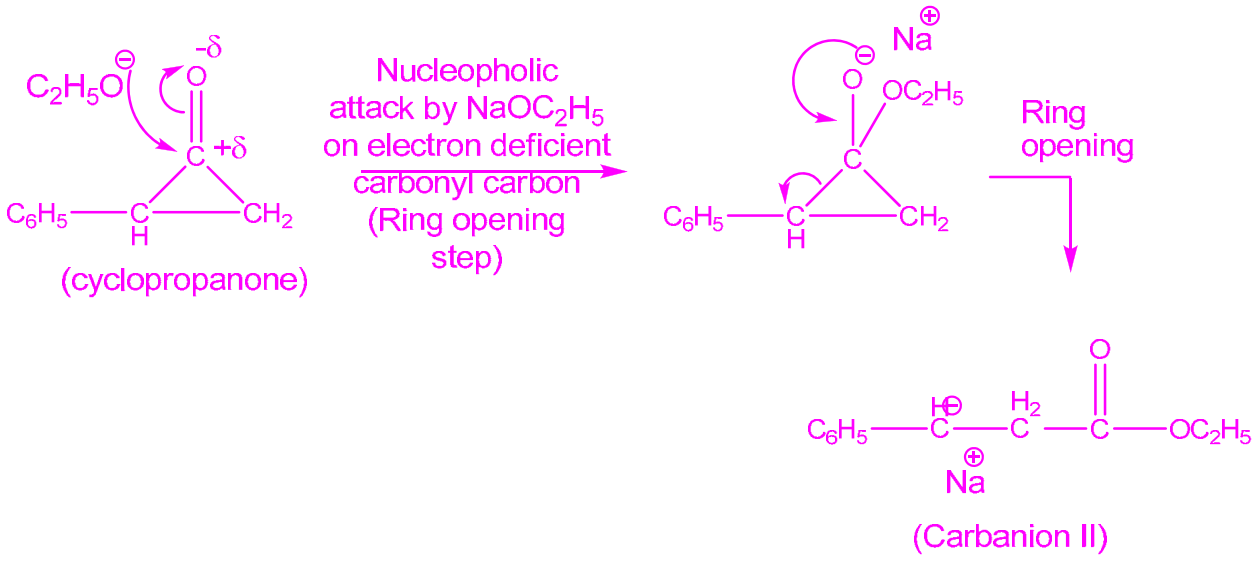
(i) In the first step, base abstract proton from α-haloketone to produce carbanion-I.



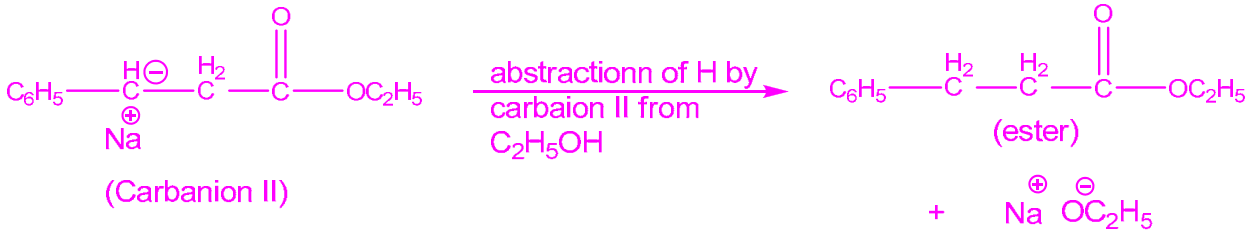
(ii) In the second step, carbanion undergo nucleophilic attack on halogen containing carbon to produce cyclopropanone intermediate.



(iii) In the third step, base undergo nucleophilic attack on carbony carbon to produce carbanion II via ring opening reaction.

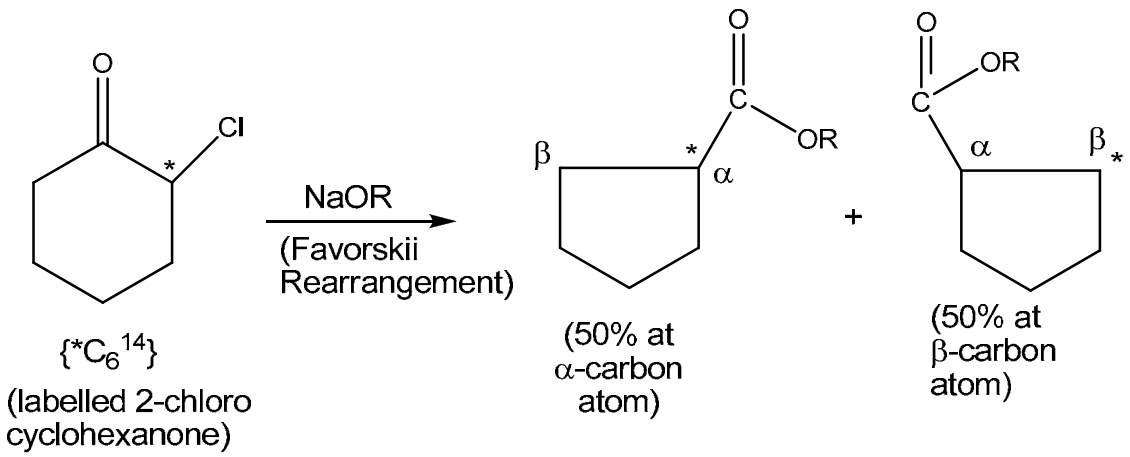


(iv) In the final step, carbanion-II abstract proton from alcohol to produce ester.

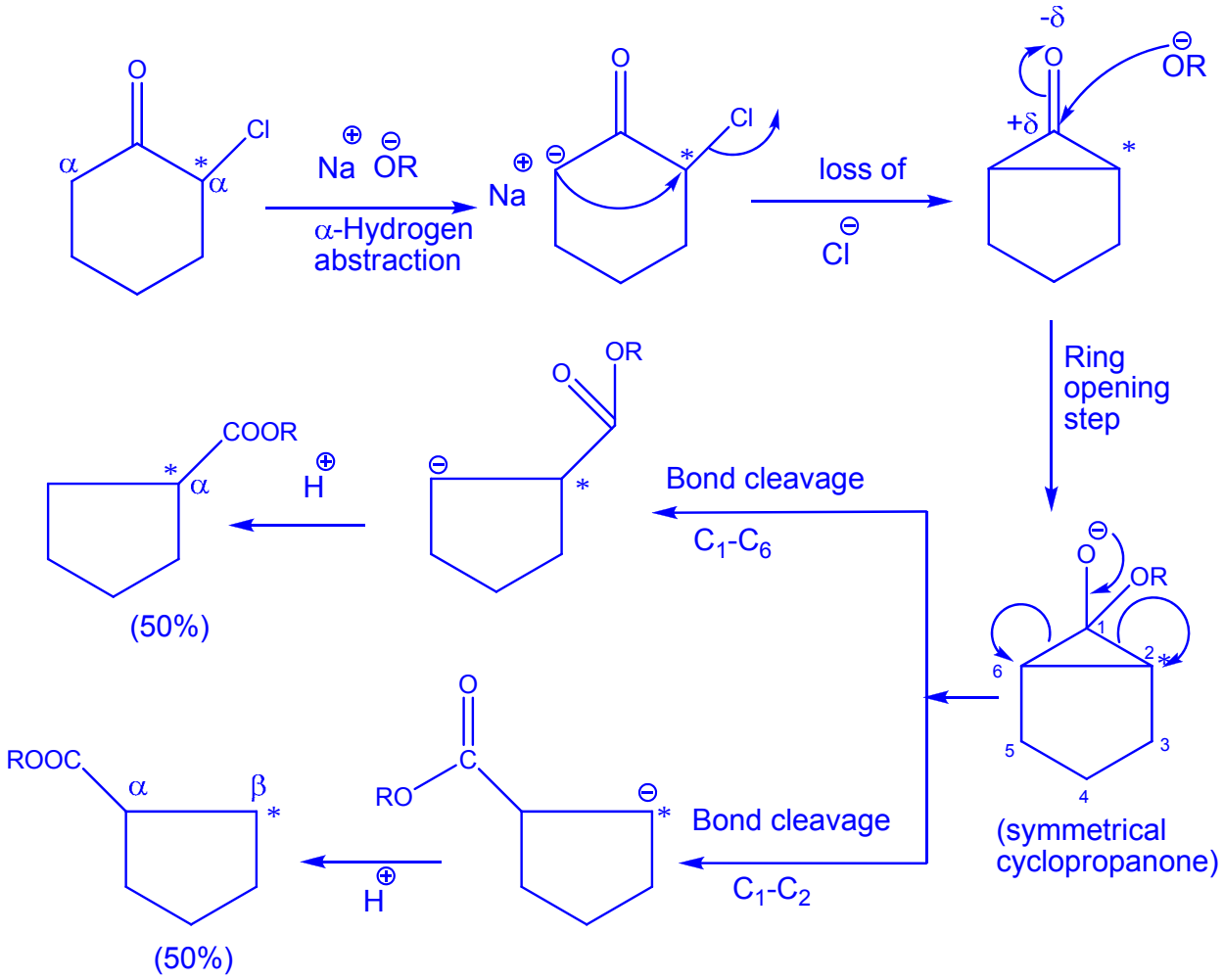


Explain : Favorskii rearrangement involves symmetrical cyclopropanone intermediate compound. Give evidence for the Favorskii rearrangement.

To explain it we will take 2-chlorocyclohexanone labelled with C^{14} at the –Cl containing carbon, and was allowed to react with NaOR. Mass spectroscopy analysis shows that the product was found to contain half the $^{14}C_6$ at the α-carbon and half $_6C^{14}$ at the β-carbon atom.

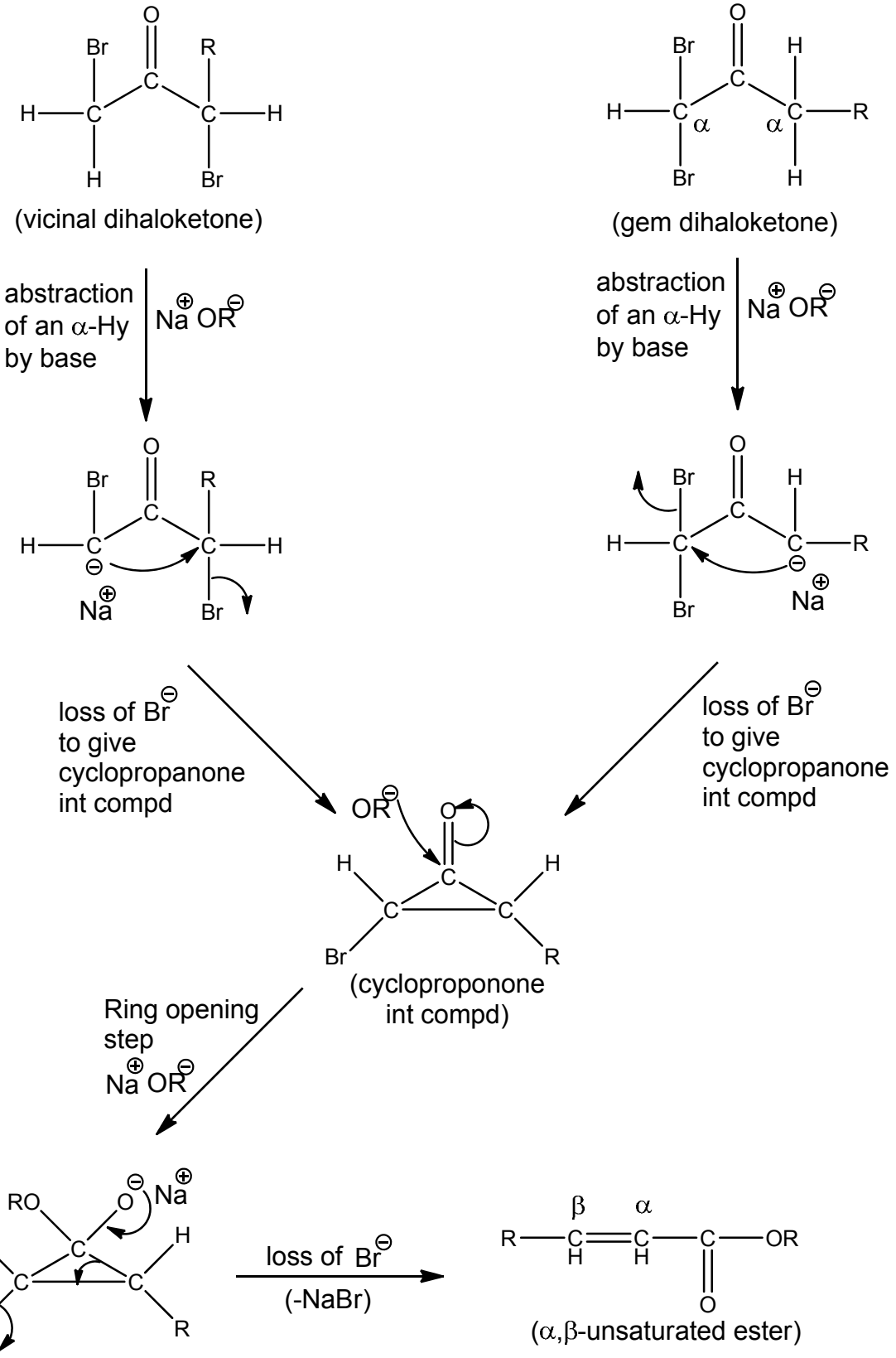


This is only possible when two carbon atoms that are alpha (α) to the carbonyl group i.e C_2 and C_6 become equivalent at some stage during the course of the rearrangement. Intermediacy of a symmetrical cyclopropanone which opens up with equal probability on either side of the carbonyl group only fits the above experimental observation.



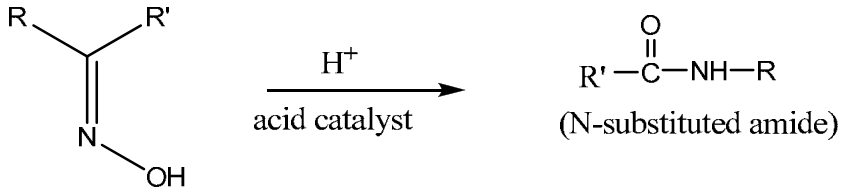
Favorskii Rearrangement of gem and vicinal dihaloketone:

Favorskii rearrangement of gem and vicinal dihaloketones gives the same product i.e α,β-unsaturated ester.


(vicinal dihaloketone)
(gem dihaloketone)
abstraction of an α-Hy by base
Na OR
abstraction of an α-Hy by base
Na OR
loss of Br to give cyclopropanone int compd
loss of Br to give cyclopropanone int compd
(cyclopropononе int compd)
Ring opening step
Na OR
loss of Br
(-NaBr)
(α,β-unsaturated ester)

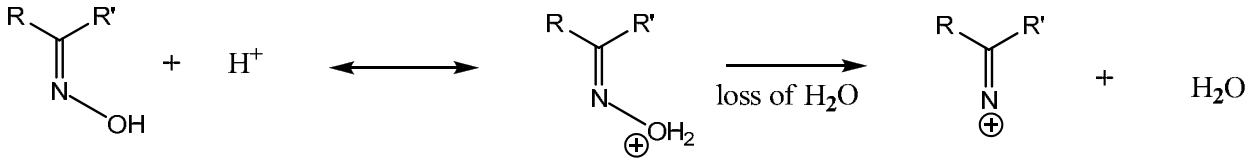
(xi) Beckmann rearrangement :

Conversion of ketoxime to nitrogen substituted amide in the presence of acid catalyst is known as Beckmann rearrangement.

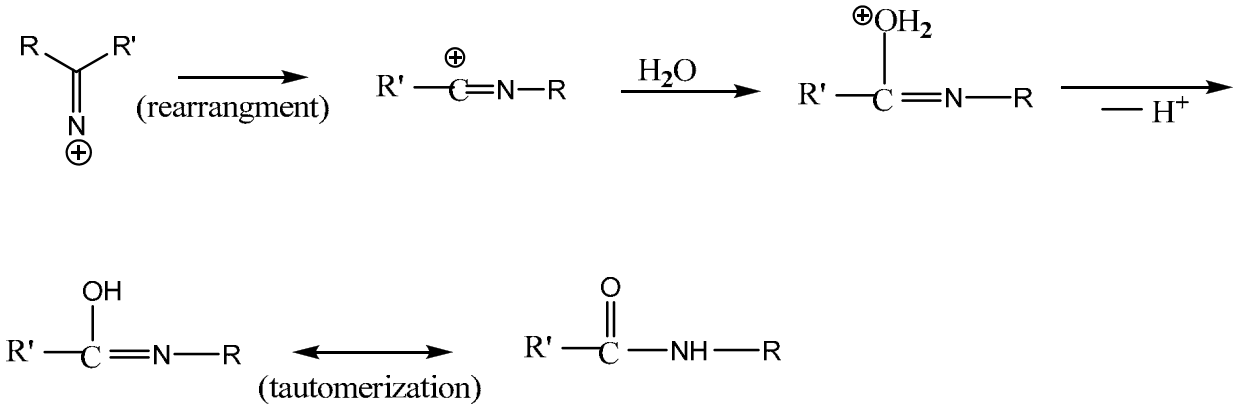


Mechanism :

(i) First step is the protonation of ketoxime, followed by loss of water to produce electron deficient nitrogen.



(ii) In the second step electron deficient nitrogen undergo rearrangement to produce carbocation, which upon nucleophilic attack by water followed by tautomerization to give N-substituted amide.



Beckmann rearrangement is highly stereospecific :

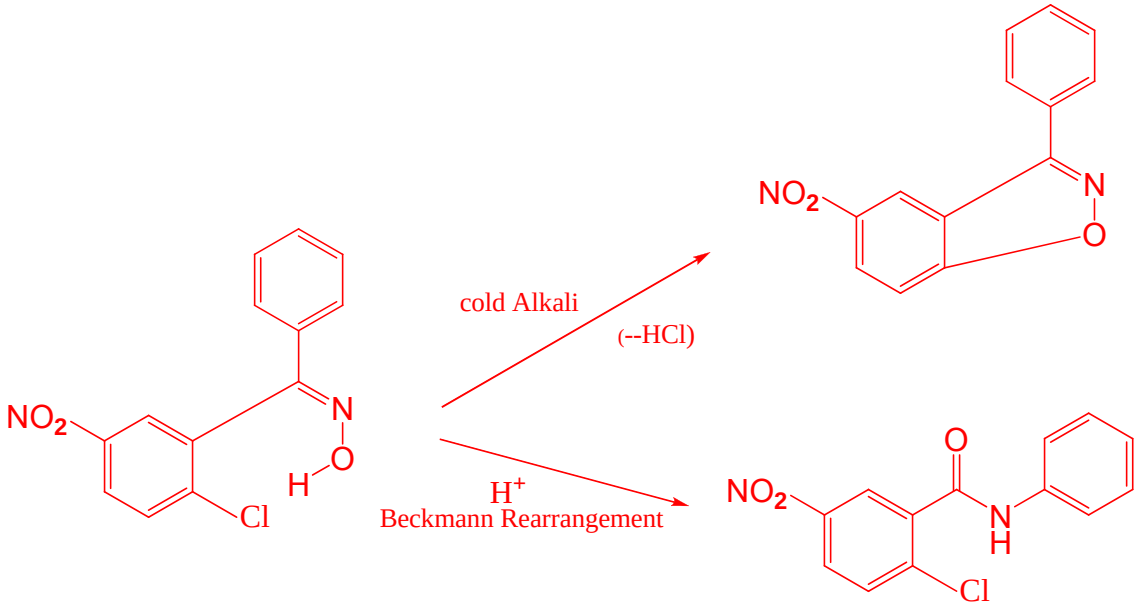
Beckmann rearrangement is highly stereospecific in that the migrating group always approaches to the nitrogen atom from the opposite side of oxygen atom. Only 'R' group migrates because it is on the opposite side of the leaving group (H_2O or oxygen atom)

i.e. the group which is anti or trans to the –OH group migrates to the electron deficient 'N' atom.

The exclusive migration of the anti group has been confirmed by the conversion of 2-chloro-5-nitrobenzophenone oxime in to chloronitrobenzanilide.

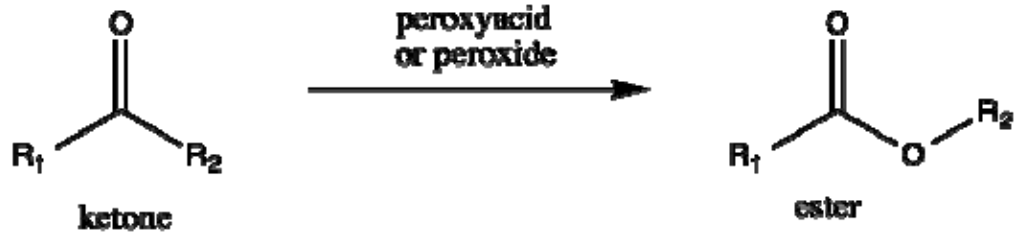
The configuration of this oxime has been established by its ready conversion to a nitro substituted phenyl benzisoxazole showing that the nitrated benzene ring present on the same side of the C=N linkage as the –OH group.

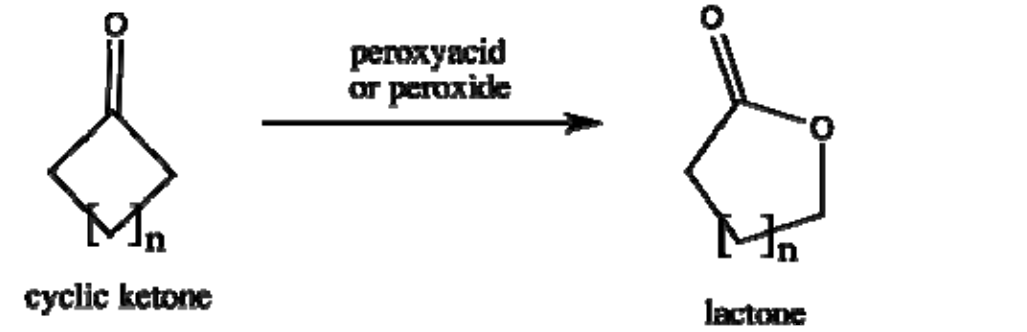
When this oxime undergoes Beckmann rearrangement, it is found that the phenyl group rather than the nitrated benzene ring migrates to the nitrogen.

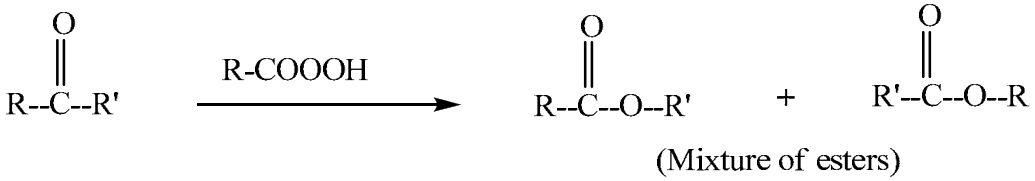


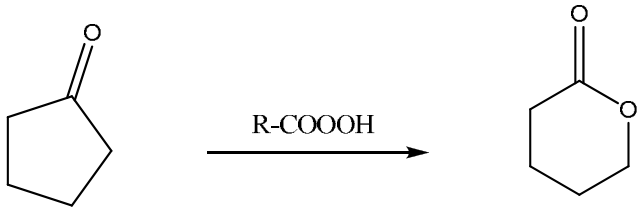
(xii) Baeyer-Villiger oxidation:

Oxidation of ketones to an esters and a cyclic ketones to an cyclic esters (lactones) using a peroxy acid (RCO_3H) is known as Baeyer-Villiger oxidation.

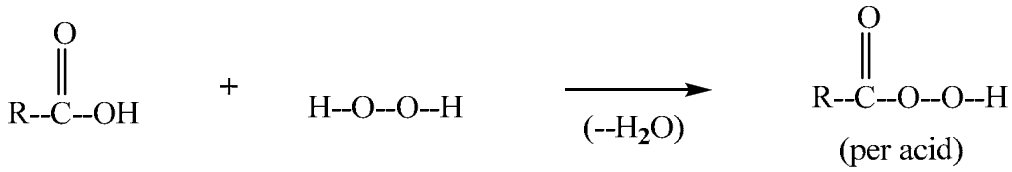








Peracids can be prepared by the reaction of carboxylic acid and hydrogen peroxide:



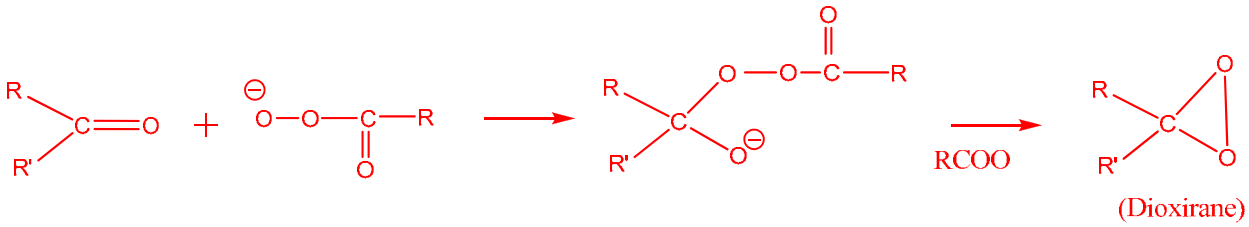
Various per acids are perbenzoic acid ($PhCO_3H$), per acetic acid (CH_3CO_3H), trifluoroperacetic acid (CF_3CO_3H) etc.

Mechanism : There are two mechanism for Baeyer-Villiger oxidation.

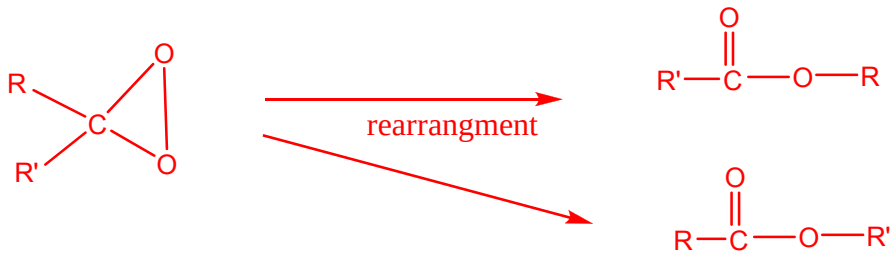
(i) Mechanism for Baeyer-Villiger oxidation:

Baeyer-Villiger oxidation suggested the formation of a dioxirane as an intermediate compound by the attack of the peroxy anion on the carbonyl carbon, followed by the rearrangment in dioxirane ring to gives a mixture of esters.

(i) In the first step, peroxy anion attack on the carbonyl carbon to form dioxirane as an intermediate compound.



(ii) In the first second step, dioxirane ring undergo rearrangment to gives a mixture of esters.



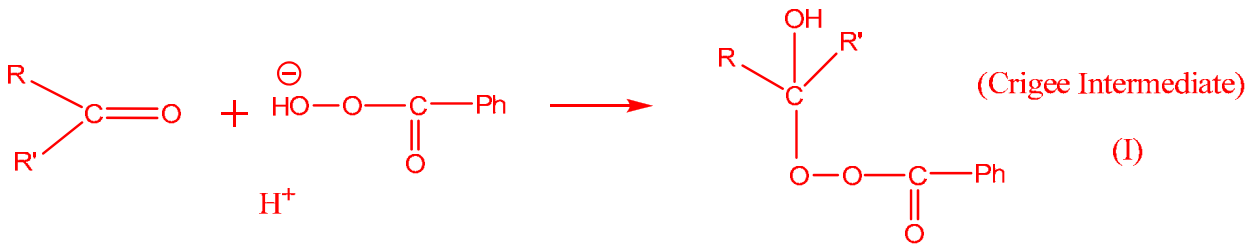
[The more electron rich 'R' group migrates to the oxygen in this concerted process, allowing for accurate prediction of the stereochemistry of the product.]

(ii) <u>Crigee and Kasper Mechanism :</u>

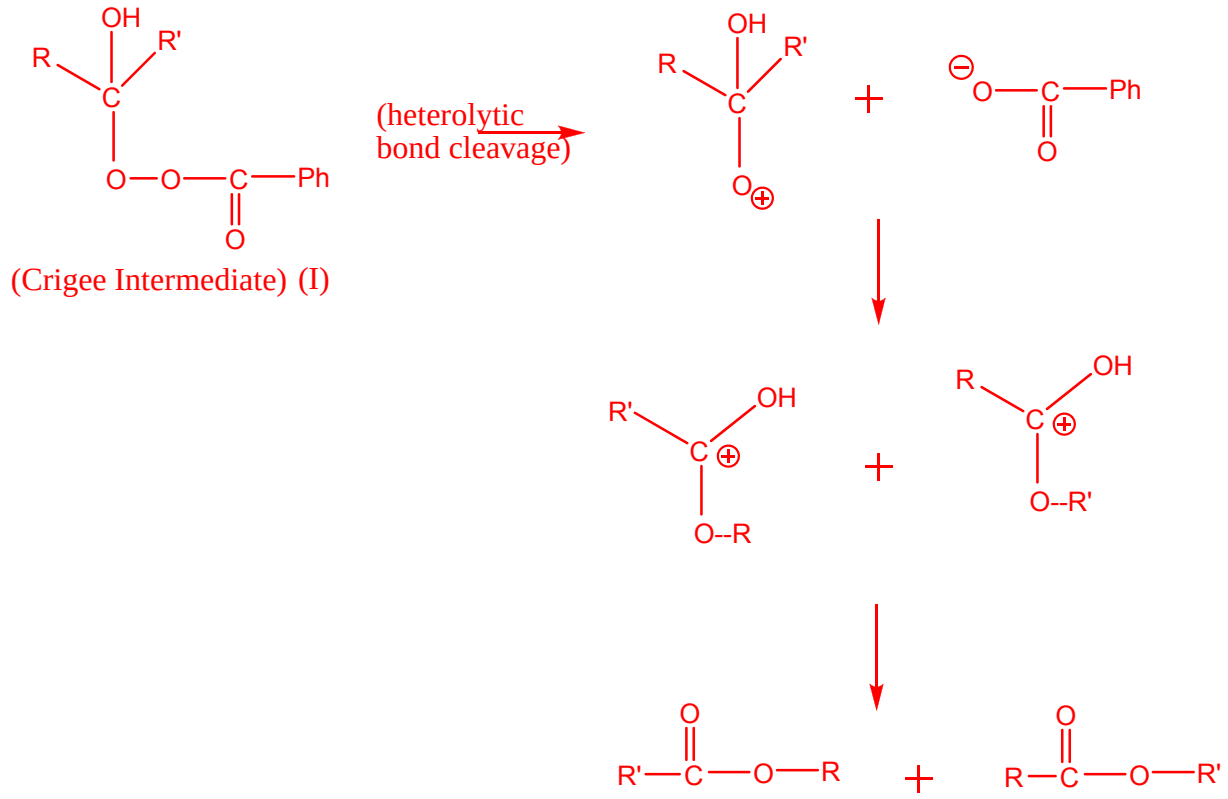
It was proposed by Crigee and Kasper. This mechanism involves a nucleophilic attack by the per acid on the carbonyl carbon to form an intermediate (I), which is also known as Crigee intermediate (I).

Mechanism:

(i) In the first step, peroxy anion attack on the carbonyl carbon to from Crigee intermediate (I).

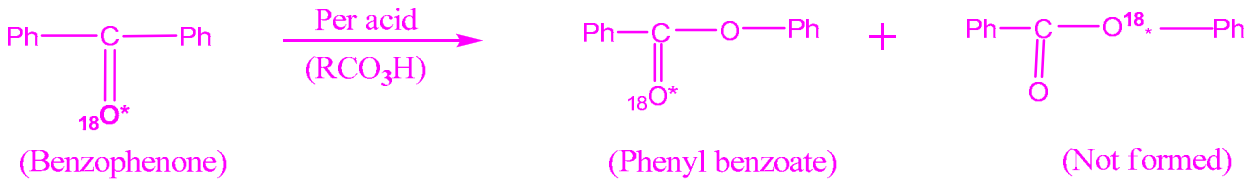


(ii) In the second step, Crigee intermediate (I) undergo heterolytic bond cleavage to produce alkoxy anion and carboxylate ion. Further alkoxy anion undergo rearrangement by R or R' shift to give esters.

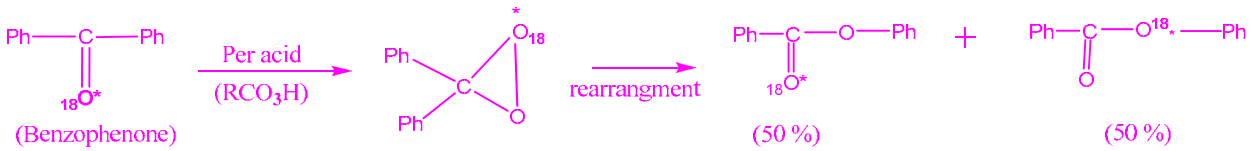


Evidence for the Crigee mechainsm:

Doering and Dorfmann subjected benzophenone labelled with O^{18} to oxidation with per acid. The isolation of the product phenyl benzoate and its oxygen analysis, showed that all the labelled O^{18} was retained in the carbonyl oxygen and none in the alkoxy oxygen.



This experiment rules out the first mechanism i.e. Baeyer-Villiger Mechanism. Because according to Baeyer-Villiger Mechanism the product should have 50 % O^{18} in carbonyl oxygen and 50 % O^{18} in the alkoxy oxygen, base the intermediate dioxirane compound is symmetrical.

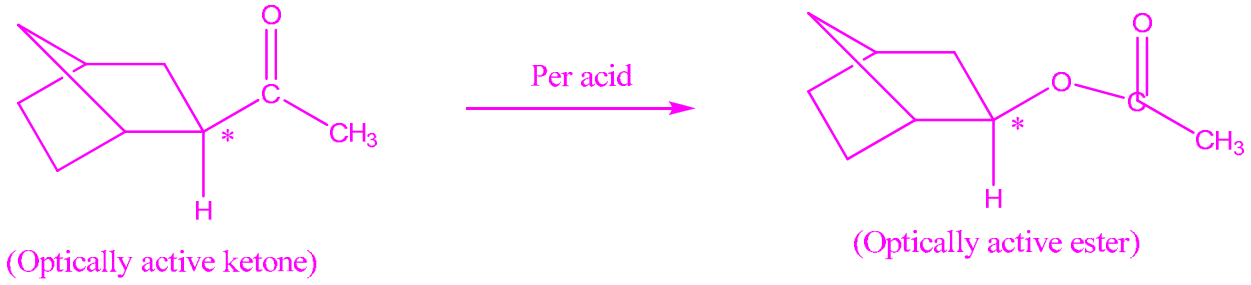


The data (experimental data) fit the second mechanism i.e. Crigee-Kasper mechanism. Therefor, we can say that Bayer-Villiger oxidation reaction reaction proceeds through Crigee-Kasper mechanism. In an unsymmetrical ketones the order of migration of an alkyl group is :

$3^0 > 2^0 > 1^0 > CH_3$

The reason is that the migration terminus 'O' (+Ve charged) is an electron deficient and hence the group which is better in supplying electrones (--Ve charged) to positively charged oxygen atom migrates faster than other group.

Explain : Bayer-Villiger oxidation reaction proceeds through complete retention in the configuration in the migrating group.



During migration of the group, the migrating group never becomes completely free from the remainder of the molecule. i.e. the bond breakage between C—C and bond formation between C—O takes synchronomously (occurring at the same time) and hence reaction proceeds through complete retention in the configuration in the migrating group and hence we can say that the migration of the group i.e. rearrangement step is an intramolecular step. All the above facts supports the Crigee-Kasper mechanism.

REFERENCE BOOK :

1. Reaction mechanism in Organic Chemistry by S. M. Mukherji.
2. Organic reaction mechanism by R.K. Bansal, 3rd ed.
3. Reaction mechanism in Organic Chemistry S. M. Mukherji and S. P. Singh.