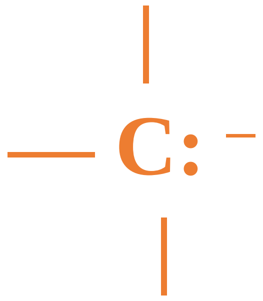
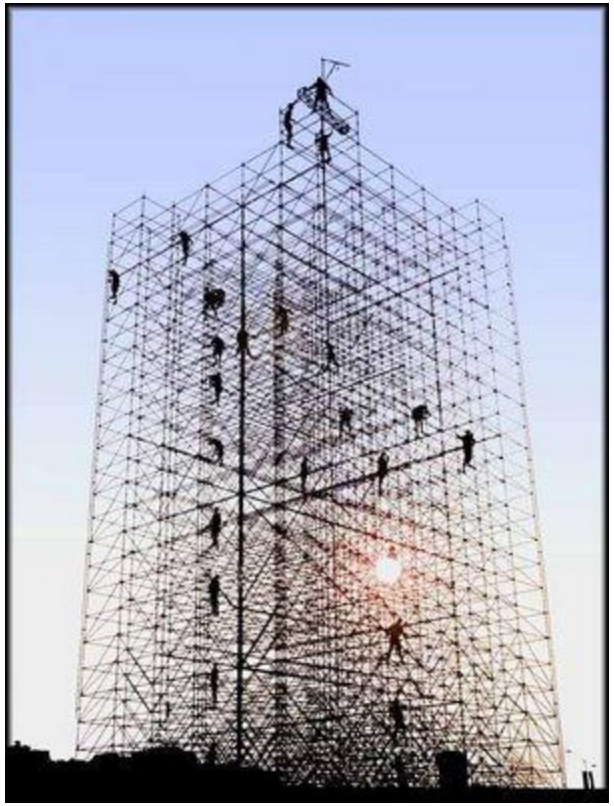
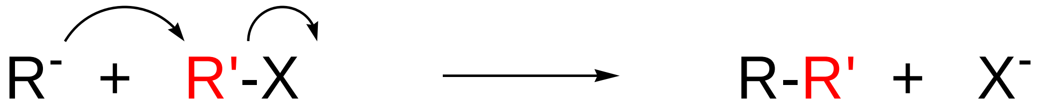
Carbanions





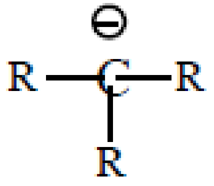
The conjugate bases of weak acids, strong bases, excellent nucleophiles.

The C-C bonds of a molecule under construction constitute its scaffolding. Reactions which form new C-C bonds are exceptionally useful synthetically. SN2 reactions, which use a carbanion as a nucleophile represent one solution to this problem.



$$R^- + R'\text{-}X \longrightarrow R\text{-}R' + X^-$$

Carbanions: are units that contain a negative charge on a carbon atom. The negative charge gives good nucleophilic properties to the unit that can be used in the formation of new carbon carbon bonds. Carbanions thus act as nucleophiles in substitution reactions, in carbonyl addition and substitution reactions, and in 1,4- addition (Michael) reactions.



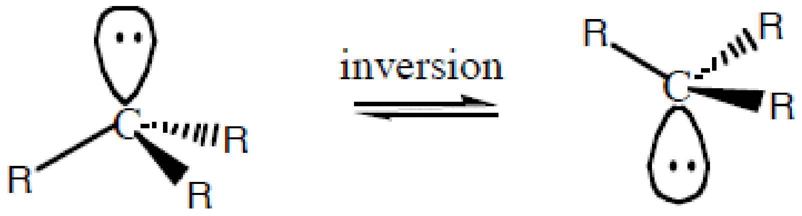
a carbanion

Carbanions bear many substituents that can affect the structure and reactivity of the carbanion, and can affect the acidity of a parent C-H precursor. Halogens stabilize carbanions in the order of Br > Cl > F. A prominent I-π repulsion between the F and Carbanionic center causes some destabilization in alpha-fluorinated carbanions. The magnitude of the destabilization depends on the carbanion structure. The destabiziation maximizes as the carbanion structure approaces a planar configuration. Thus, fluorinated carbanions possess pyramidal structues with high barriers to inversion.

Carbanion Structure

Carbanions are trivalent with sp3 hybridization. The lone pare of electrons occupies one of the sp3 orbitals. The geometery is thus tetrahedral. The tetrahedron can undergo inversion or retain its stereochemistry depending on the attached substitutents.

A methy carbanion has a barrier to inversion of about 2 kcal/ mole. The trifluoromethyl carbanion has a barrier of 120 kcal/mole. A fluorine atom is however more stabilizing than a hydrogen atom because of the fluorine electronegativity.

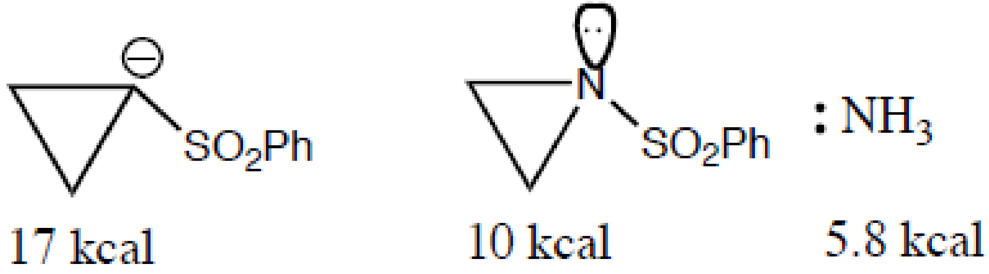


R = H; barrier = 2 kcal/mole

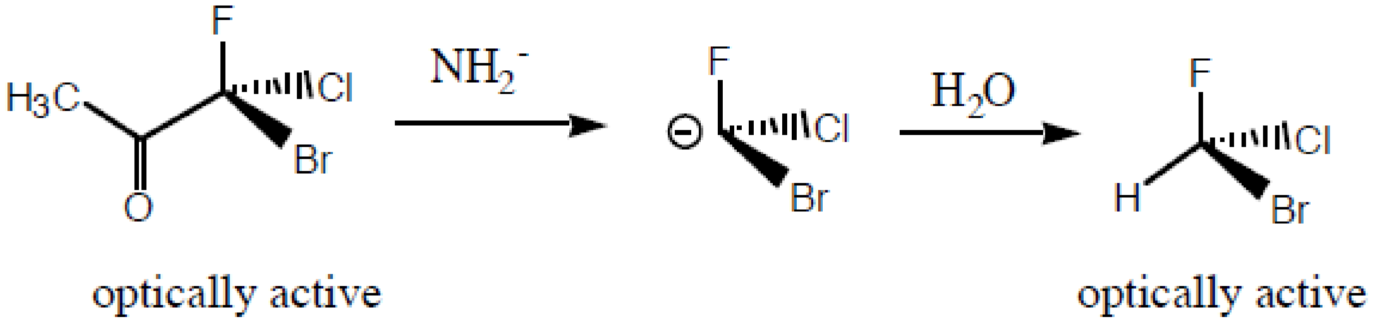
R = F; barrier = 120 kcal/mole

tetrahedral carbanion

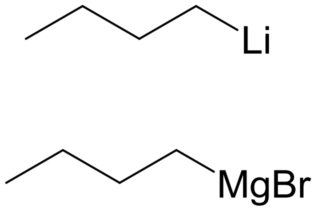
The rate of inversion in hydrocarbon system is slowed by incorporation of the carbanion into a three membered ring.



Experiments involving the use of chiral substrates aids the study of carbanion stereochemistry as inversion causes loss of optical activity. Cleavage of the methyl ketone below with amide ion give a carbanion with a slow rate of inversion. The carbanion abstracts a proton to give an optically active product. Carbanions that contain fluorine atoms often show a slow rate of inversion.



General Types of Carbanions

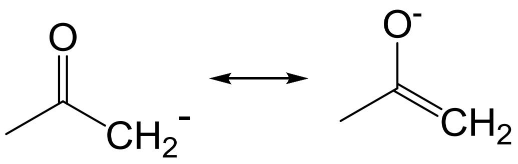


Unstabilized Carbanions
(very reactive, add readily to C=O,
not usually useful as nucleophiles in S_N2 substitution)
pKa of conjugate acid = 40 to 50.

$N\equiv C^- \ Na^+$

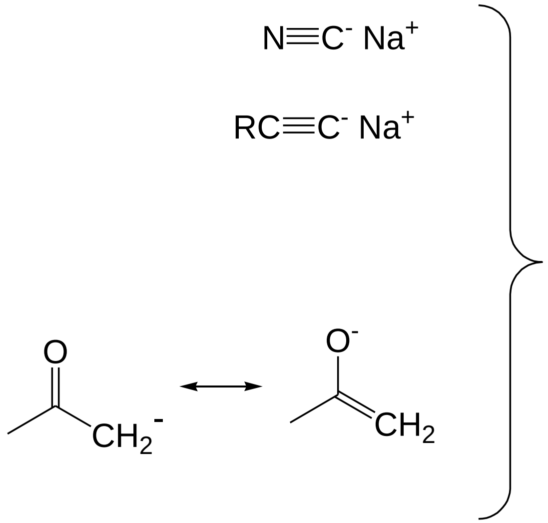
$RC\equiv C^- \ Na^+$

Stabilized by high percentage of
's' character of (sp) orbital
add readily to C=O, also useful as nucleophile in S_N2 substitution
pKa of conjugate acid = 9 to 25.



Enolate anions
Stabilized by resonance
add readily to C=O, also useful as nucleophile in S_N2 substitution
pKa of conjugate acid = 11 to 30

Formation of Stabilized Carbanions



$N\equiv C^- \; Na^+$

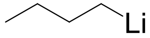
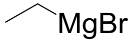
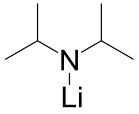
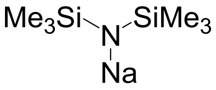
$RC\equiv C^- \; Na^+$

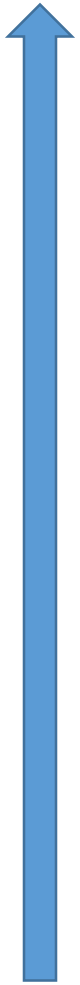
Stabilized carbanions can usually be formed
by reaction of the corresponding hydrocarbon with strong base

$$R\text{-}H + B^- \longrightarrow R^- + B\text{-}H$$

Note that, for this reaction to succeed, the carbanion must be a weaker base than the base employed to deprotonate its conjugate acid.

Bases often used to form (stabilized) carbanions

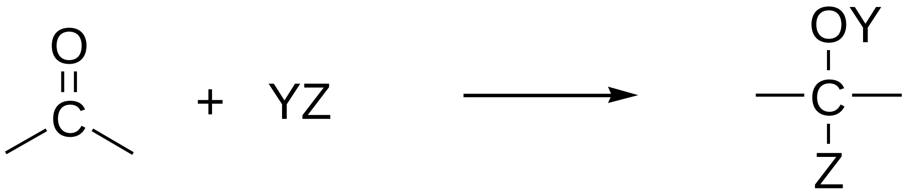
	pKa (of conjugate acid)
 	48
NaH (sodium hydride) $NaNH_2$ (sodium amide)  (Lithium Diisopropylamide) LDA	36 to 38
 (Sodium Hexamethydisilazide) NaHMDS	26
RONa (Alkoxide)	16 to 17



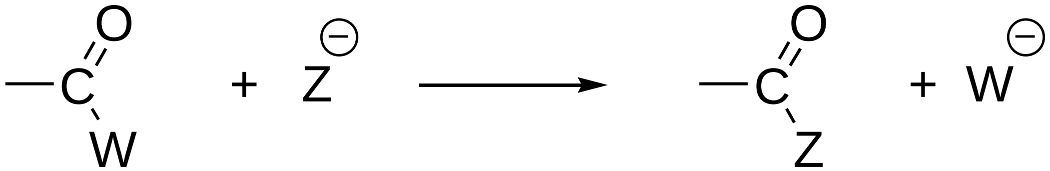
Increasing Basicity

Carbanions as the nucleophiles:

Aldehydes and ketones: **nucleophilic addition**



Esters and acid chlorides: **nucleophilic acyl substitution**



Alkyl halides: **S_N2**

Carbanions are the conjugate bases of weak acids and are therefore strong bases and excellent nucleophiles that can react with aldehydes/ketones (nucleophilic addition), esters/acid chlorides (nucleophilic acyl substitution), and alkyl halides (S_N2), etc.

Reactions involving carbanions as nucleophiles:

1. Alpha-halogenation of ketones
2. Nucleophilic addition to aldehydes/ketones
   a) aldol and crossed aldol
   b) aldol related reactions
   c) Grignard synthesis of alcohols
   d) Wittig synthesis of alkenes
3. Nucleophilic acyl substitution with esters and acid chlorides
   a) Claisen and crossed Claisen
   b) R_2CuLi + $RCOCl$

4. S_N2 with alkyl halides
    - a) Corey-House
    - b) metal acetylide
    - c) Malonate synthesis
    - d) Acetoacetate synthesis

5. Michael Addition to α,β-unsaturated carbonyl compounds

Carbanions II

Carbanions as nucleophiles in S_N2 reactions with alkyl halides.

a) Malonate synthesis of carboxylic acids

b) Acetoacetate synthesis of ketones

c) 2-oxazoline synthesis of esters/carboxylic acids

d) Organoborane synthesis of acids/ketones

e) Enamine synthesis of aldehydes/ketones

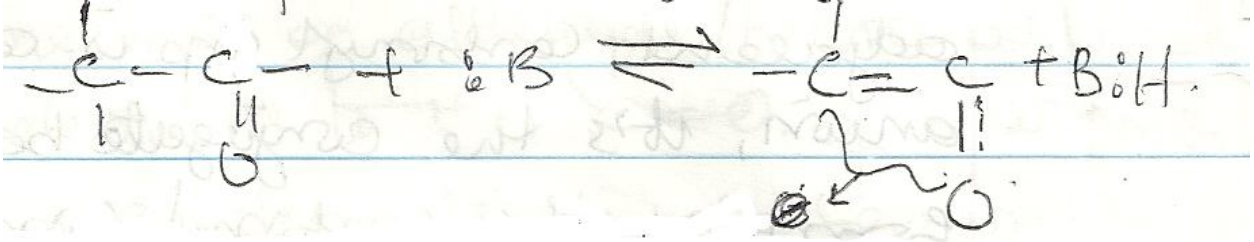
CHM 328

MECHANISM OF ORGANIC REACTIONS

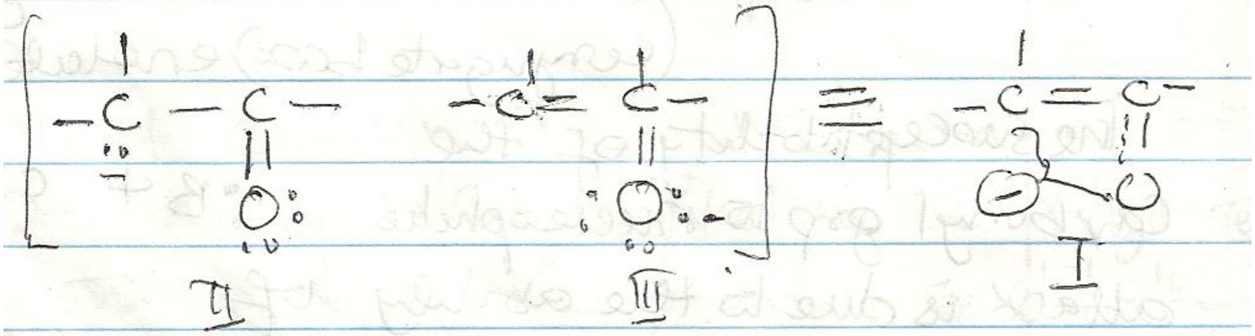
CARBANIONS

The carbonyl can play the role as a functional group as well a substituent. The carbonyl group strengthens the acidity of the hydrogen atoms attached to the α-carbon and by doing this gives rise to a whole set of chemical reactions.

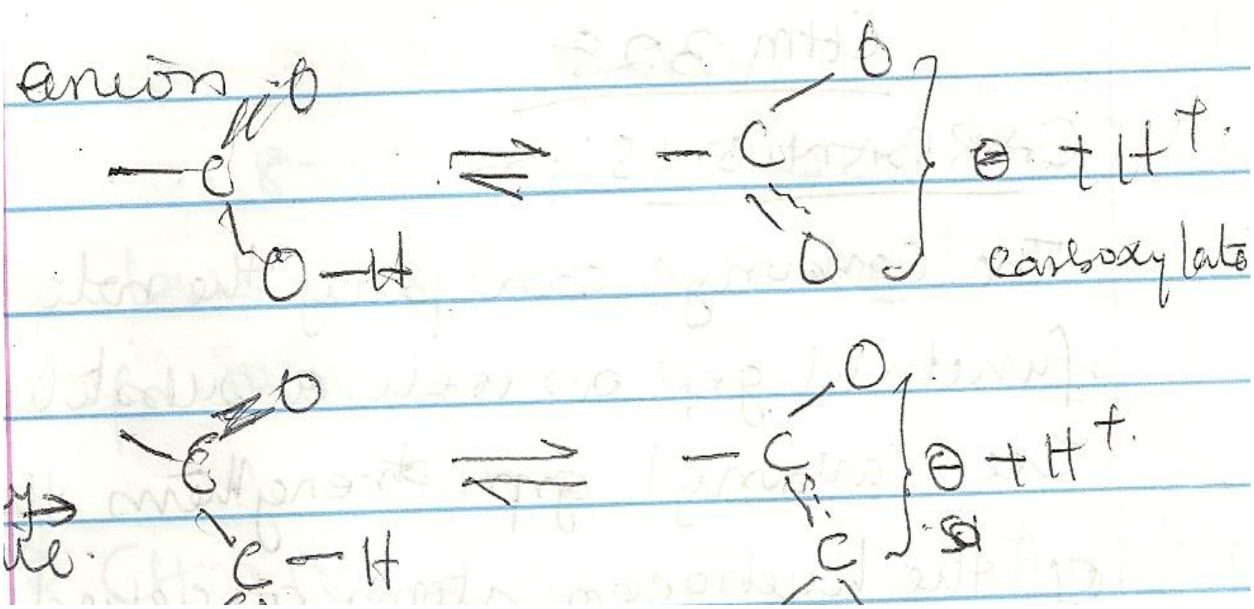
Ionization of an α-hydrogen



[Conjugate base of a carbon acid which loses its proton from carbon
Carbanion I is a resonance hybrid of two structures

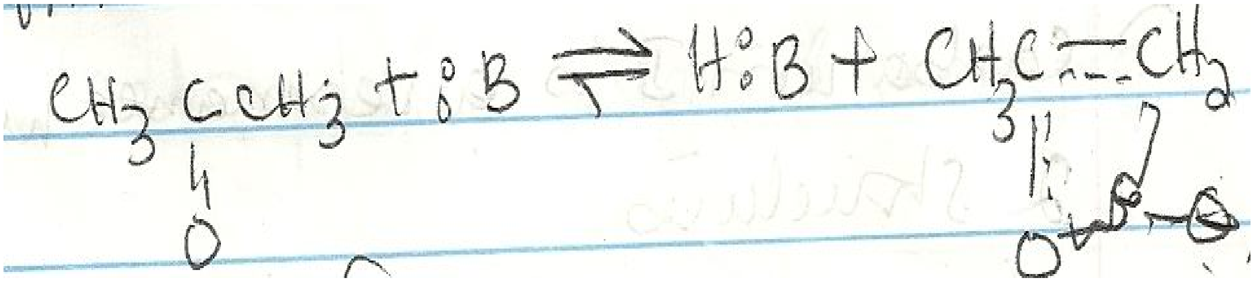


The carbonyl group effects the acidity of α-hydrogen in the same way it affects the acidity of carboxylic acids; by helping to accommodate the negative change on the anion.



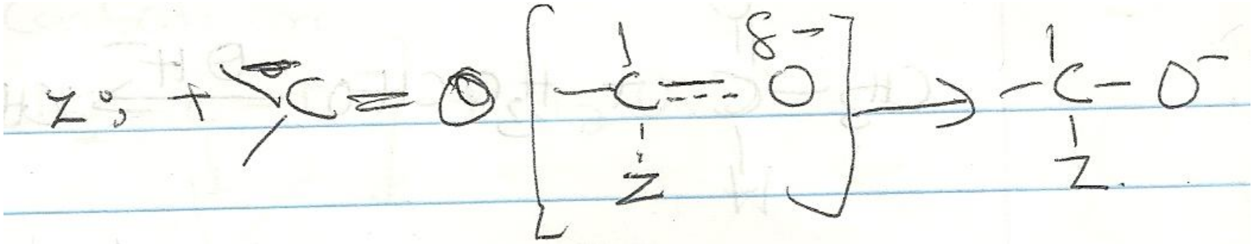
Stability is due to the fact that most of the charge is carried by oxygen and not carbon.

A carbanion which is stabilized by an adjacent carbonyl group is called an enolate anion; it is the conjugate base of the keto form of the carbonyl compound and its enolate form also.



⇌: B + $CH_3C\,(OH){=}\,CH_2$

The susceptibility of the carbonyl group to nucleophilic attack is due to the ability of oxygen to accommodate the negative charge that develops as a result of the attack.



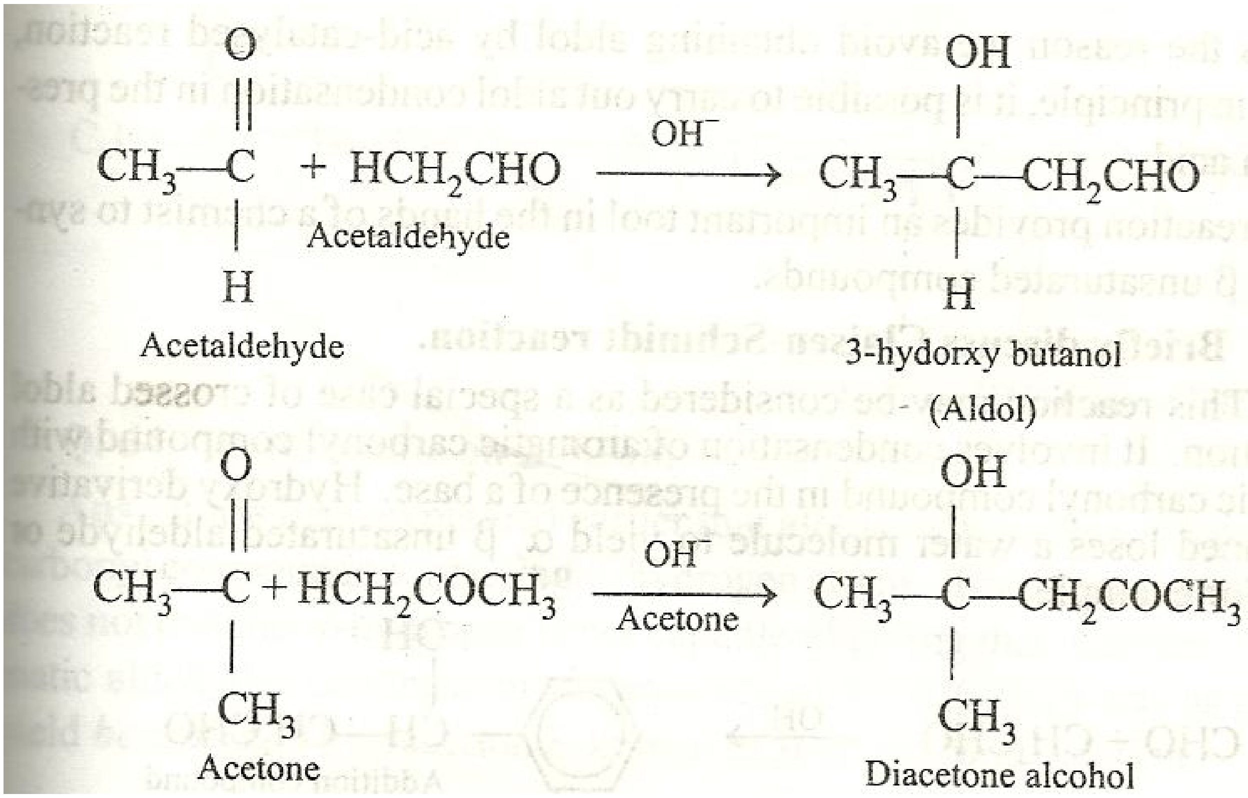
Reactions involving carbanions:

→ Carbanions are highly basic, so they behave as nucleophilic, thus they can attack carbon to form carbon-carbon bonds.

→Aldol condensation- carbanion generated from one molecule of aldehyde/ ketone add as a nucleophile to the RC=O of second molecule of a ketone/aldehyde

Mechanism of Aldol condensation:

→Two molecules of aldehyde/ ketone with α-hydrogen atoms react in the presence of dilute alkali to form β hydroxyl aldehyde or β hydroxyl ketone.

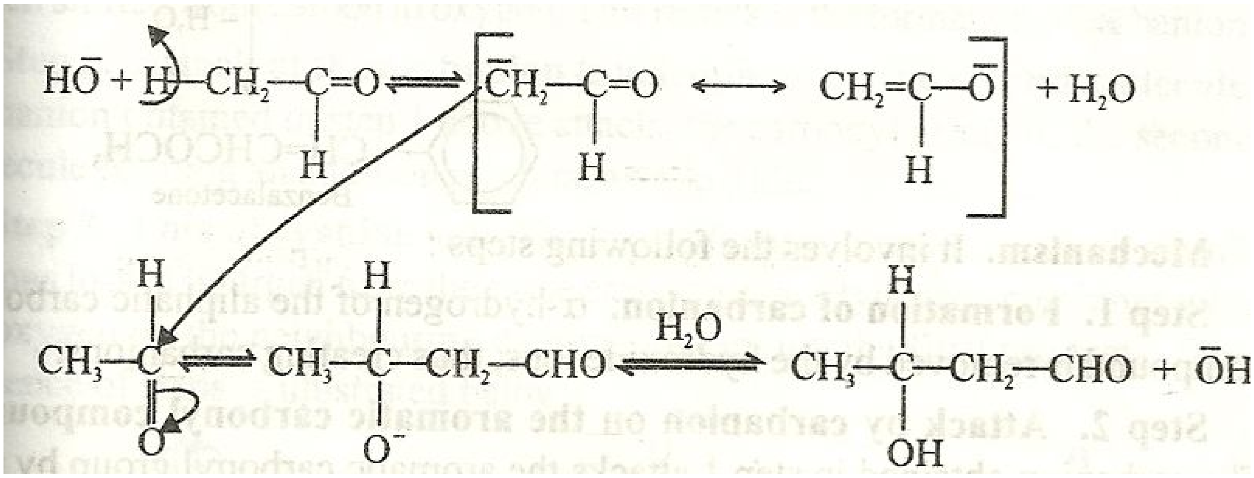


Step 1: Formation of carbanion-hydroxide from a base abstracts a proton from the α-carbon atom to a carbanion which is stabilized by resonance.

Step 2: Attack by the carbanion- the carbanion formed attacks the second molecule by nucleophilic addition mechanism to form an alkoxide ion.

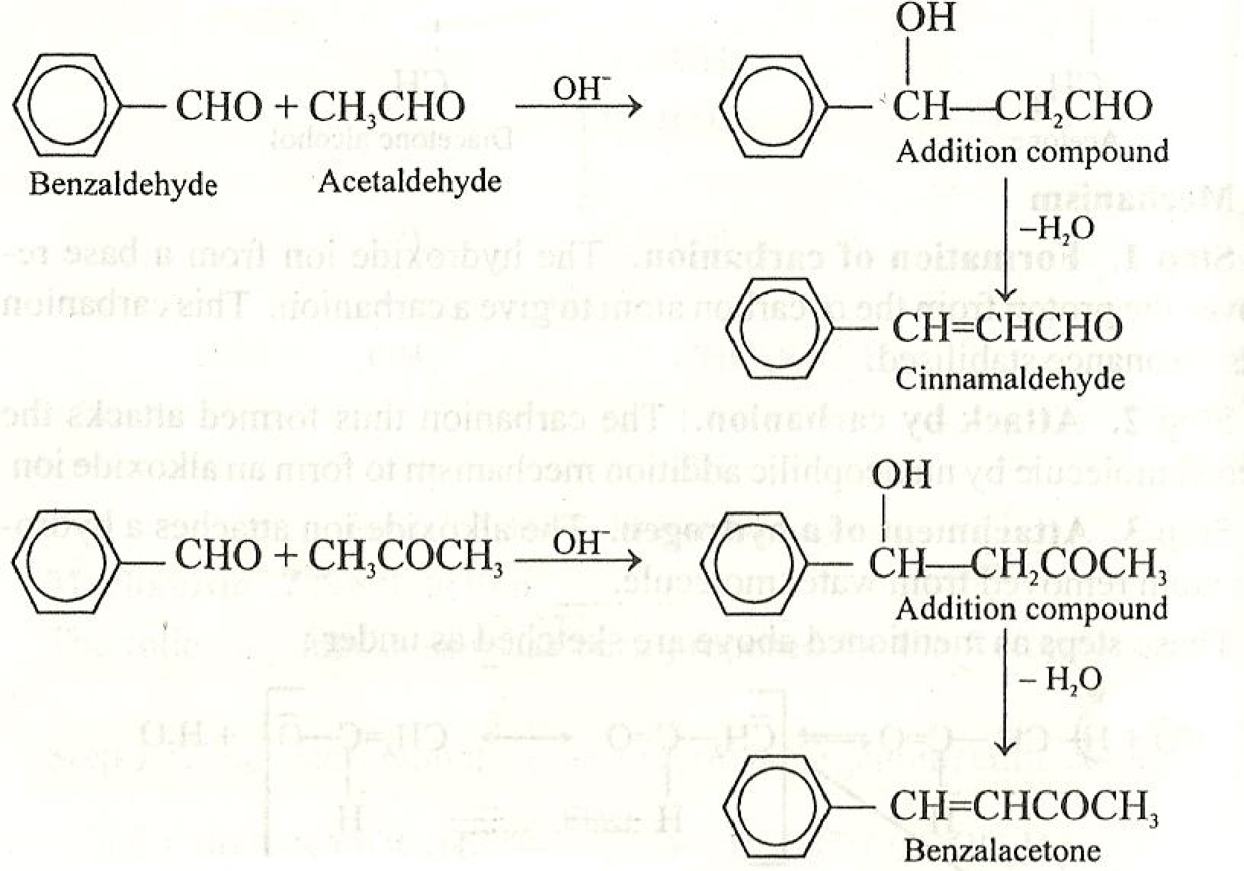
Step 3: Attachment of a hydrogen:- the alkoxide ion attaches a hydrogen atom removed from H_2O molecule.

Equation:-



Claisen- Schmidt reaction

→a crossed aldol condensation; involving condensation of aromatic carbonyl compound in the presence of a base. E.g



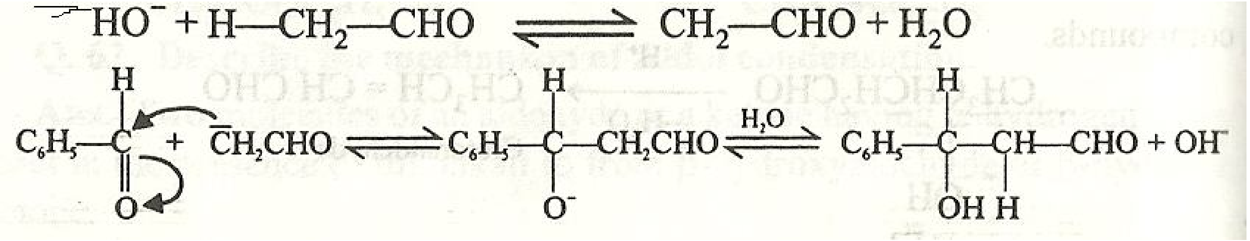
Mechanism:

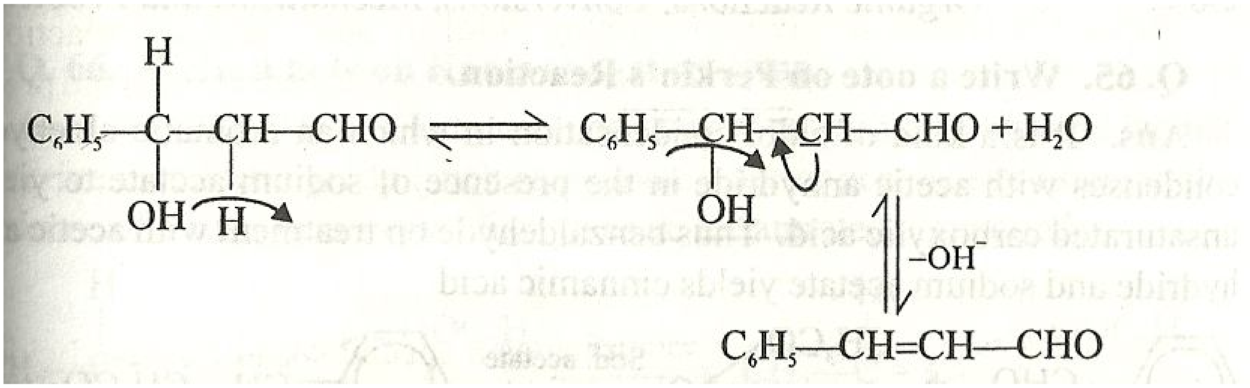
Step 1: Formation of carbanion

Step 2: Attack by carbanion on the aromatic carbonyl compound to form alkoxide ion.

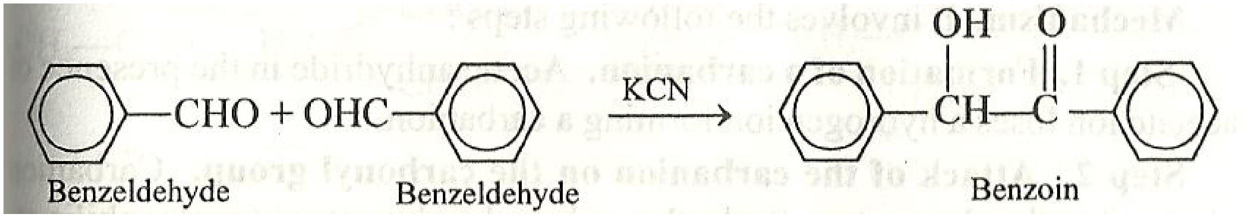
Step 3: Attachment of a proton

Step 4: α-H atom in the hydroxyl compound is removed by the base, followed by OH group and ultimately H_2O is removed



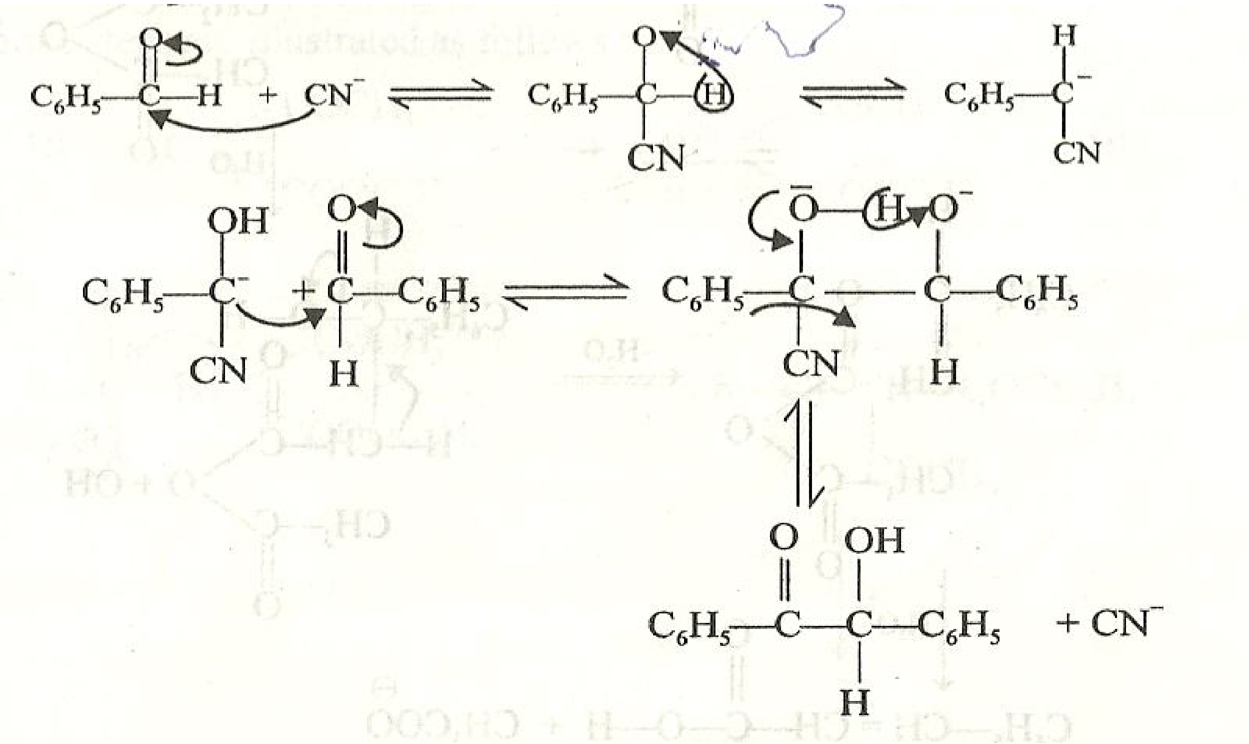


Benzoin condensation



Step 1and 2 as in other condensation reactions.

Step 3, loss of CN^- ion



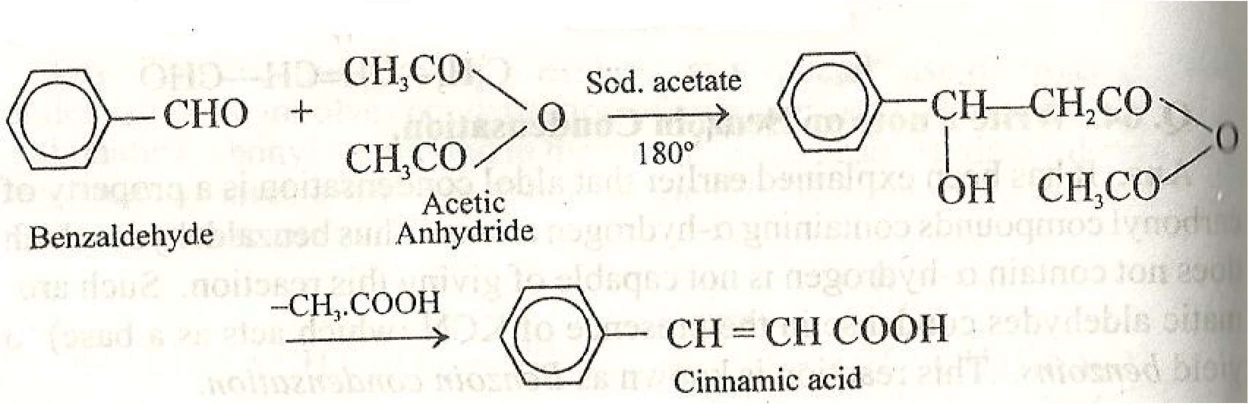
Perkins reaction

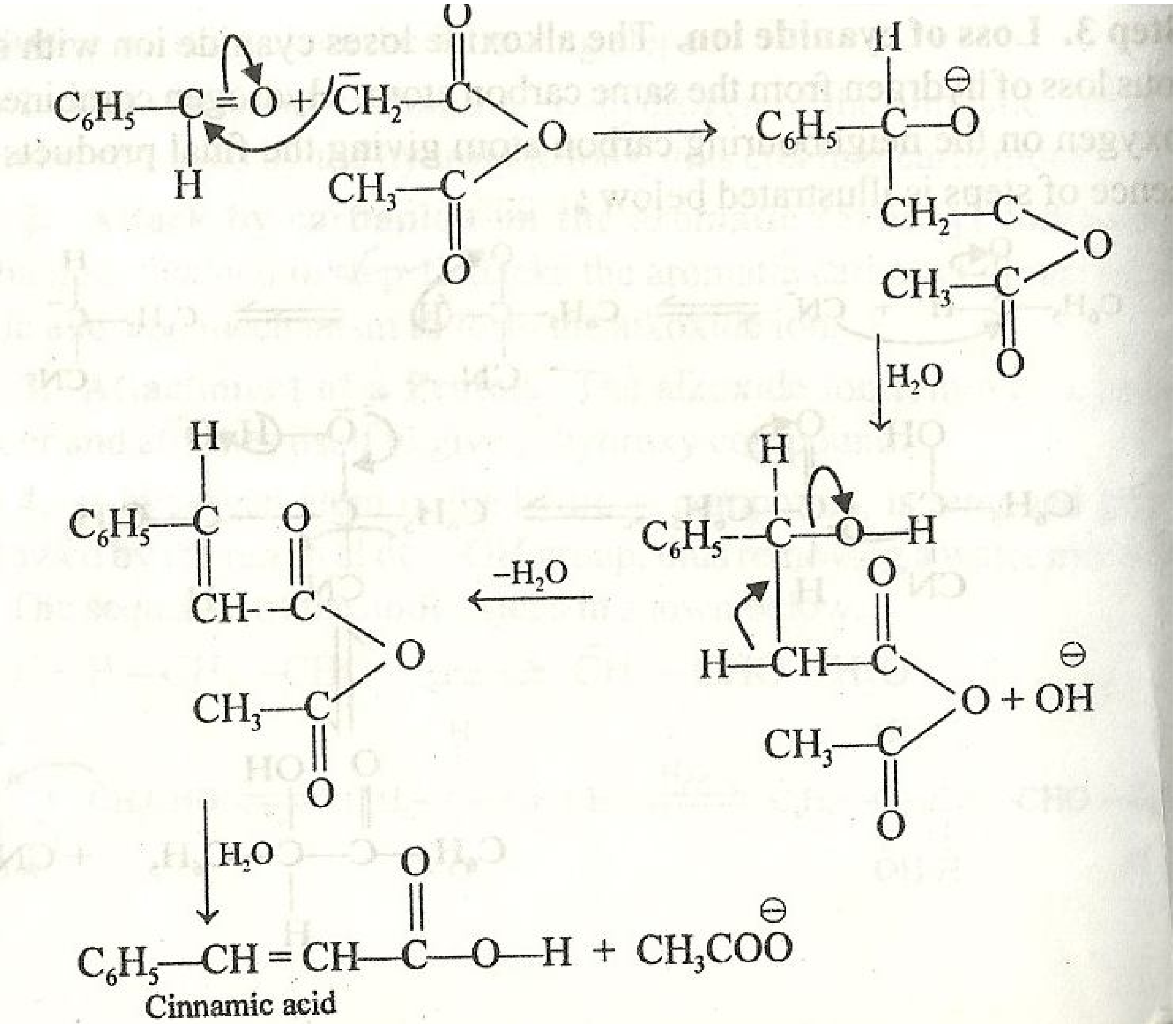
Step 1-2 as in others

Step 3: protonation of the alkoxide ion to form an aldol type compound.

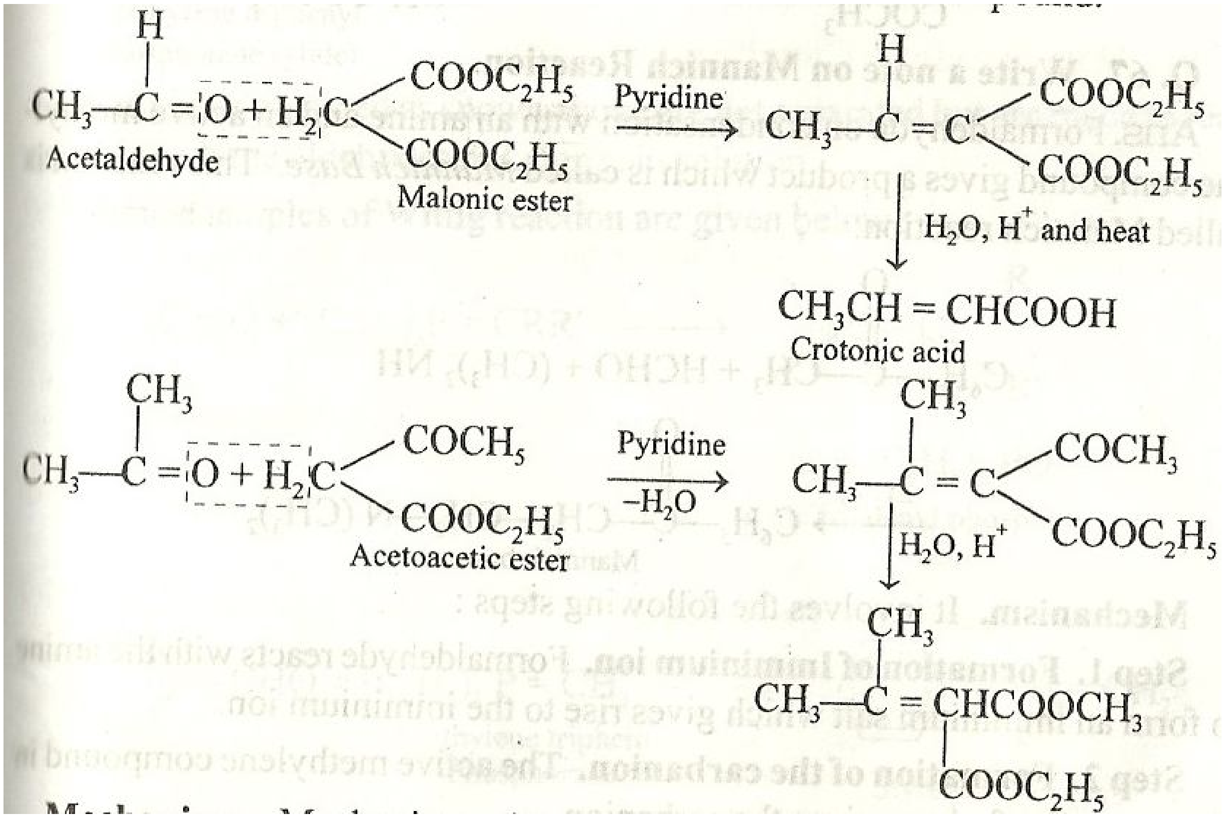
Step 4: dehydration, the hydroxyl group and neighbouring hydrogen are removed as water.

Step 5: hydration





<u>Knoevenagal reaction</u>

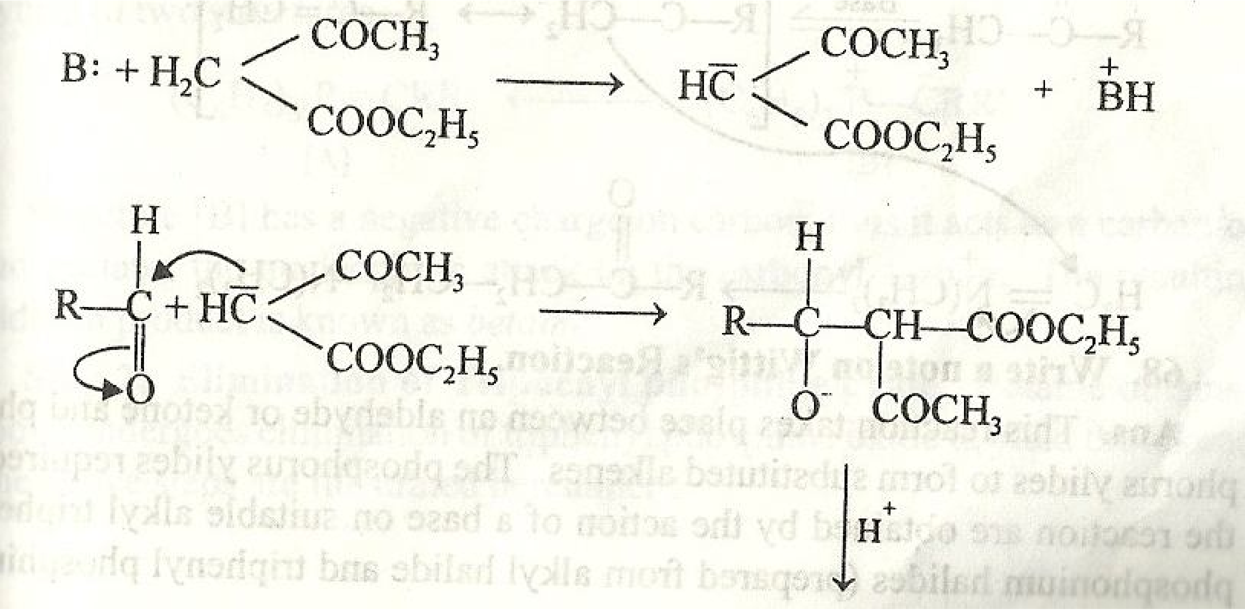


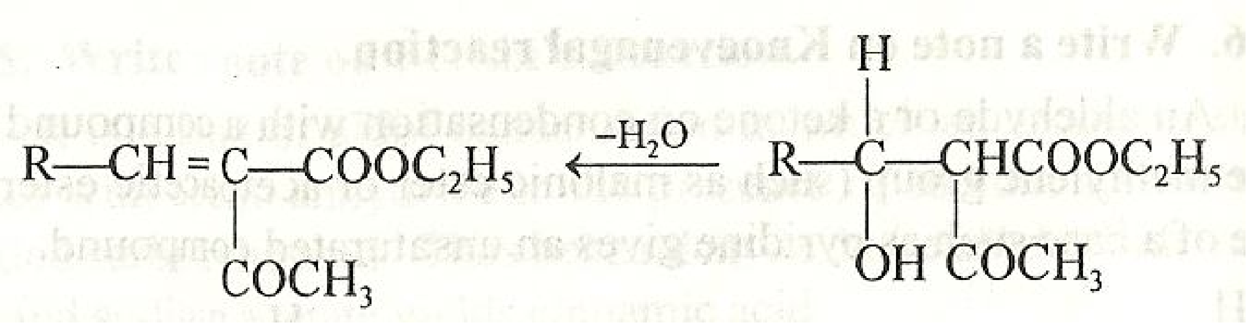
Mechanism

Step 1-2 as explained in other reactions

Step 3: protonation: - alkoxide accepts a proton to form hydroxyl compound.

Step 4: involves dehydration

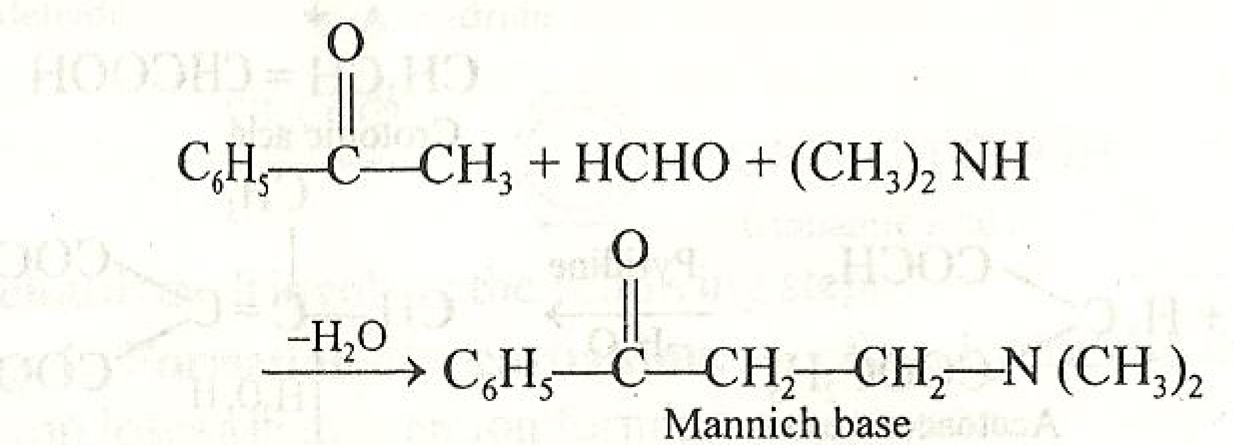




$$R-CH=\underset{\displaystyle COCH_3}{\underset{|}{C}}-COOC_2H_5 \xleftarrow{-H_2O} R-\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-\underset{\displaystyle COCH_3}{\underset{|}{C}}HCOOC_2H_5$$

Mannich reaction

Reaction involves condensation of methanol which amine p an active methylene compound to form a Mannich base.



$$C_6H_5-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 + HCHO + (CH_3)_2\,NH \xrightarrow{-H_2O} C_6H_5-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2-CH_2-N\,(CH_3)_2$$

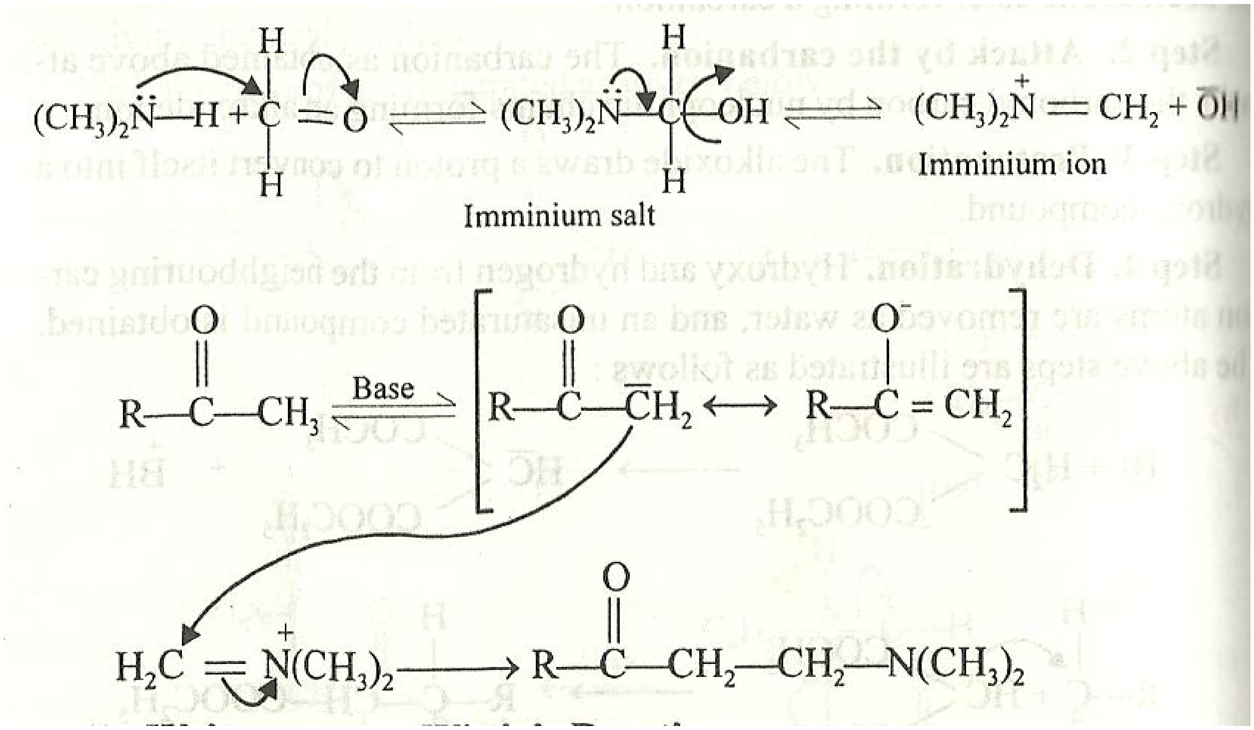
Mannich base

Mechanism:-

Step 1: formation of Imminium ion

Step 2: formation of carbanion

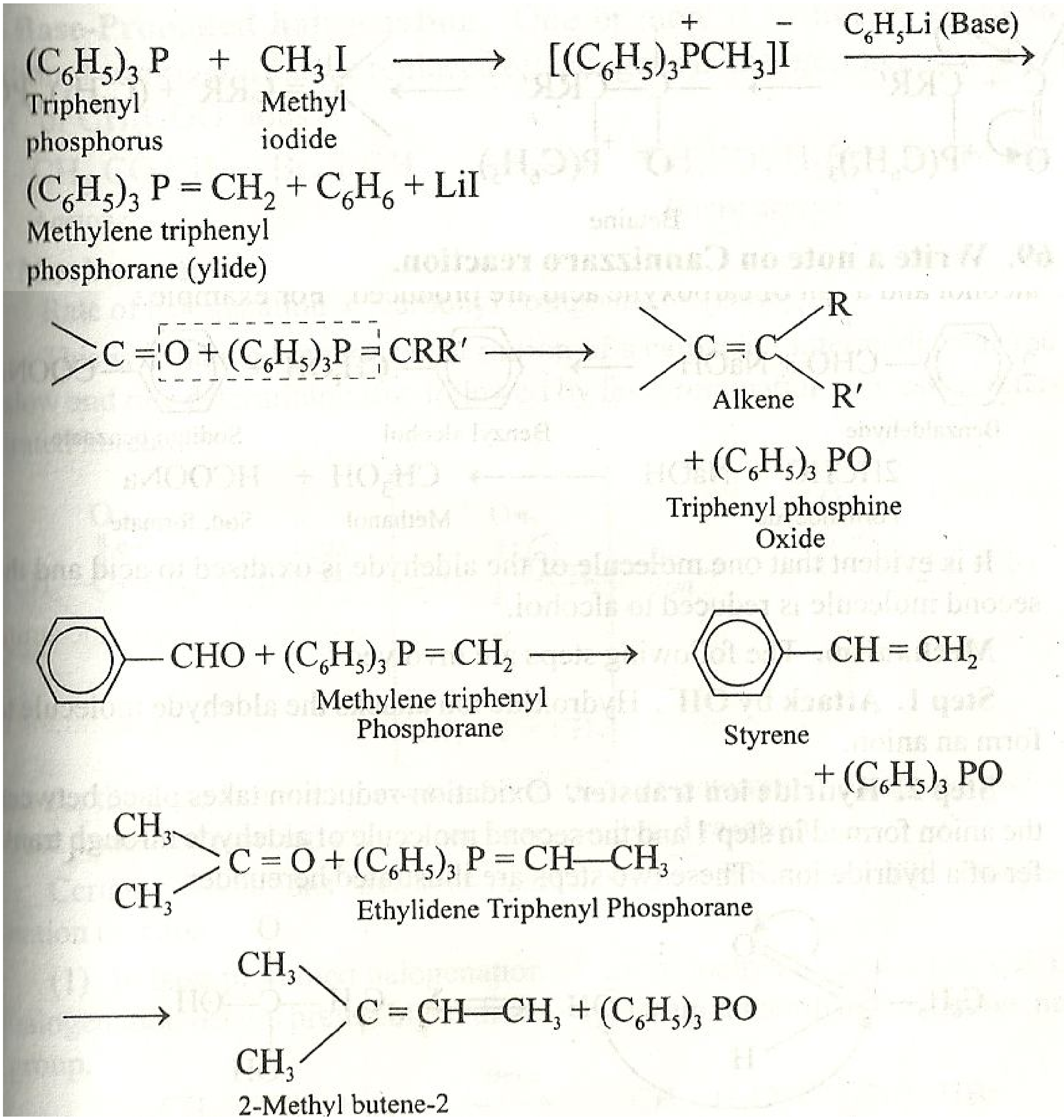
Step 3: attack by carbanion



Witting’s reaction

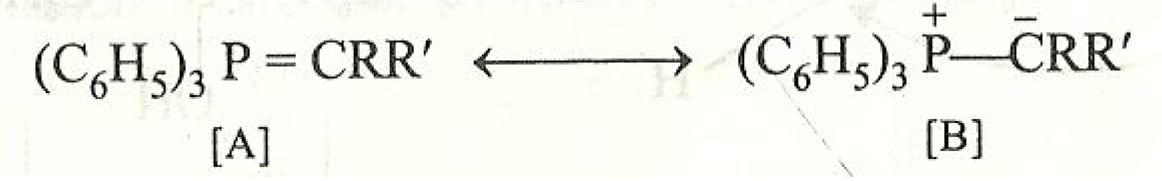
Reaction occurs between an aldehyde/ketone and phosphorous ylides to form substituted alkenes.

Phosphorous ylide is prepared by reacting a base with an alkyl triphenyl phosphonium halide as shown below



Mechanism

Step 1: attack by ylides

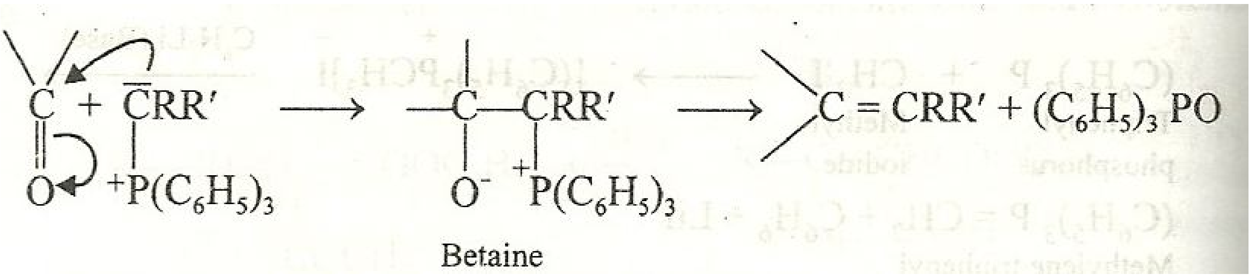


$$(C_6H_5)_3P = CRR' \longleftrightarrow (C_6H_5)_3\overset{+}{P}—\overset{-}{C}RR'$$

[A] [B]

Structure B acts as the carbanion and initiates the nucleophilic attack on the carbonyl carbon to form betaine

Step 2: elimination of triphenyl phosphate oxide to yield an alkenes



Elimination reactions 0f Alkyl halides

- In elimination reactions, atoms or groups are removed from a reactant.
- When an alkyl halide undergoes elimination reaction, the halogen X is removed from a carbon and a hydrogen is removed from an adjacent carbon, a double bond is formed below the 2 carbons from which the atoms are removed e.g.
- $CH_3CHCH_2CH_3 + CHO_3- \rightarrow CH_3CH=CH\ CH_2CH_3$
- Generally,

$$CH_3CH_2CH_2X + Y^- \rightarrow CH_3CH_2CH_2Y + X^- \quad \text{Substitution reaction}$$

$$\downarrow$$

$$CH_3CH=CH_2 + HY + X^- \text{ (elimination reaction)}$$

Factors affecting elimination reaction

- Structure of the alkyl halide (RX)
- Only secondary and primary alkyl halides undergo E1 reactions. The reaction proceeds through an intermediate of secondary carbocation which rearranges to the more stable tertiary carbocation. Base removes proton from β- carbon.
- Primary, secondary and tertiary alkyl halides undergo E2 reactions. It is a one step mechanism involving bond breaking and bond formation.

Text for further reading

Organic chemistry – Brief course by Robert Atkins and Francis. A. Carey

Organic reaction mechanism, conversions and problems by R.L Madan