Organic Chemistry

Semester-4, CBCS

Course: CEMG CC-4/GE-4

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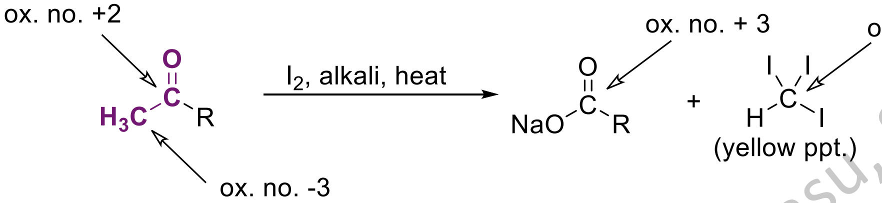
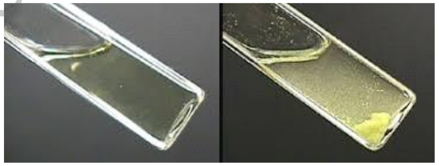
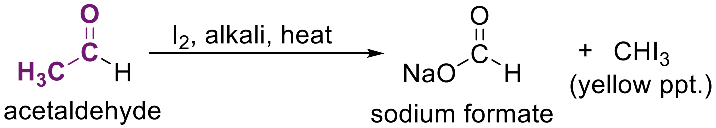
Chemistry of Carbonyl: Iodoform reaction:

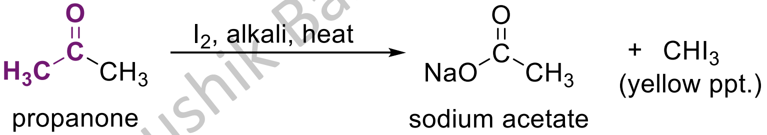
An oxidation reaction of aldehydes or ketones bearing a ketomethyl group in their structure or for compounds that under the reaction condition of the test, generates such carbonyl compounds *in situ.*

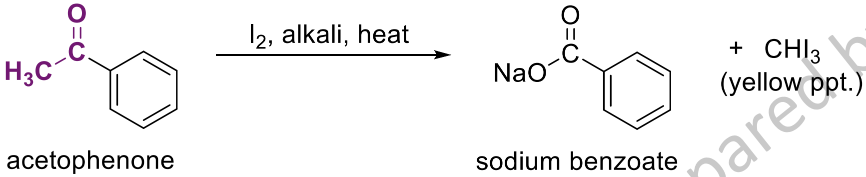
Reagent: I_2 in alkali, with Br_2 in alkali, we have bromoform reaction; commonly known as the haloform test.

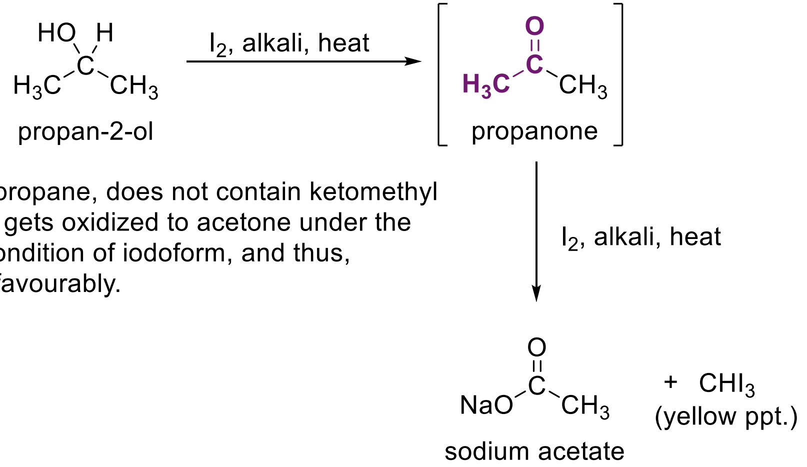






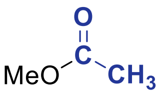




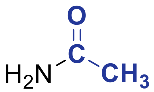


2-hydroxypropane, does not contain ketomethyl group but, gets oxidized to acetone under the reaction condition of iodoform, and thus, responds favourably.

Not all compounds conatining ketomethyl group respond to this test, e.g.

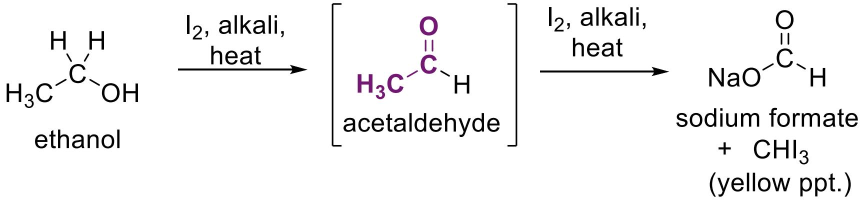


methyl acetate, contains ketomethyl group but it is an ester; undergoes base-induced ester hydrolysis under the reaction condition of iodoform reaction.



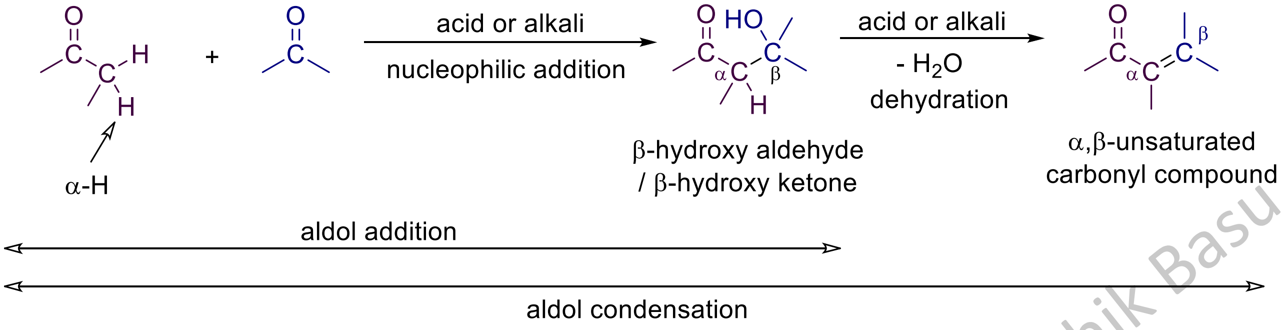
acetamide, contains ketomethyl group but it is amide; undergoes Hofmann degradation under reaction condition of iodoform.

Similarly:



Chemistry of Carbonyl: Aldol reaction / addition / condensation:

An aldol condensation reaction is a C-C bond forming reaction between carbonyl compounds possessing α-hydrogens and affords β-hydroxyketone which may eventually dehydrate to an α,β-unsaturated carbonyl compound.



One component acts as the nucleophile - deprotonation of carbonyl α-H to enolate

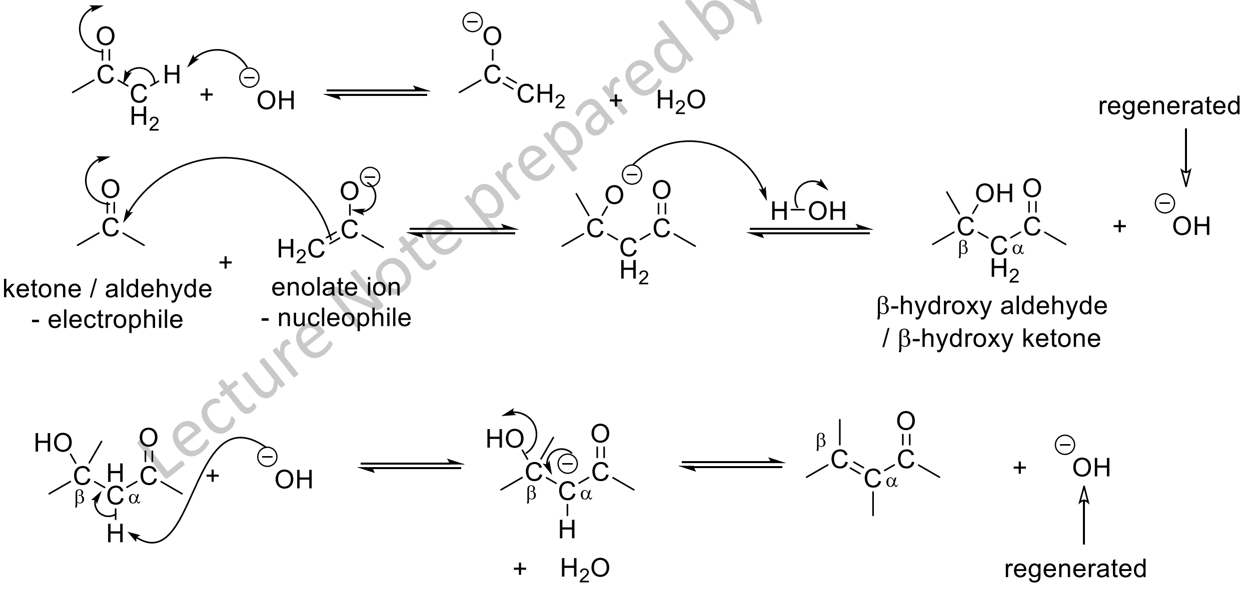
The other component acts as the electrophile

Mechanism in alkali:

1. Generation of enolate:

2. Nucleophilic addition:

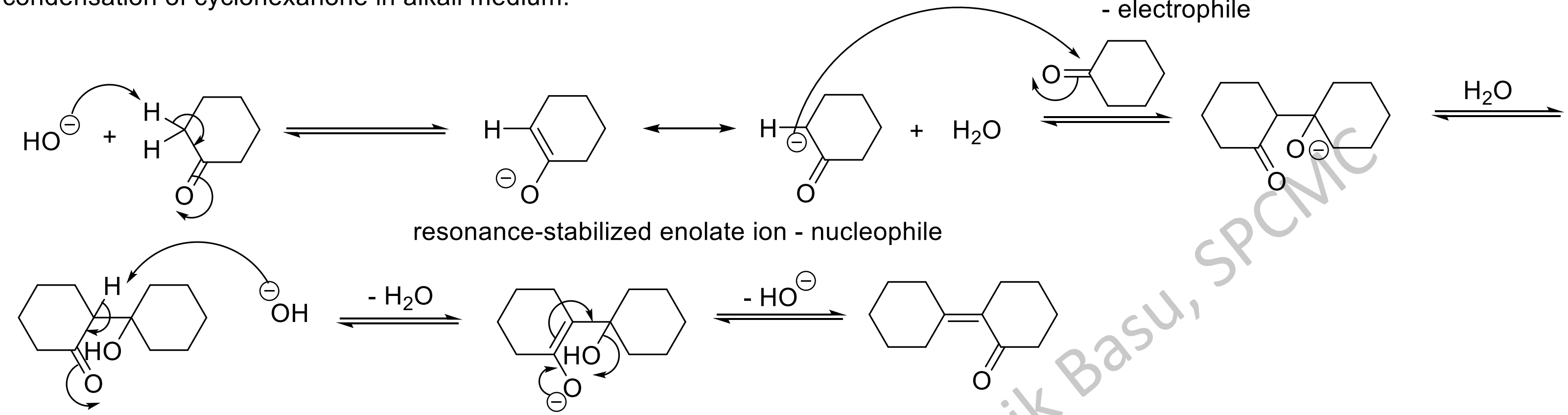
3. Dehydration:



1. Must have at least two α-Hs to complete condensation process
2. Reaction is reversible
3. Catalytic in alkali
4. Dehydration requires forcing condition
5. Condensation b/w same carbonyls - self-condensation
6. Condensation b/w two different carbonyls - cross-condensation

Chemistry of Carbonyl: Aldol reaction / addition / condensation:

Self-condensation of cyclohexanone in alkali medium:



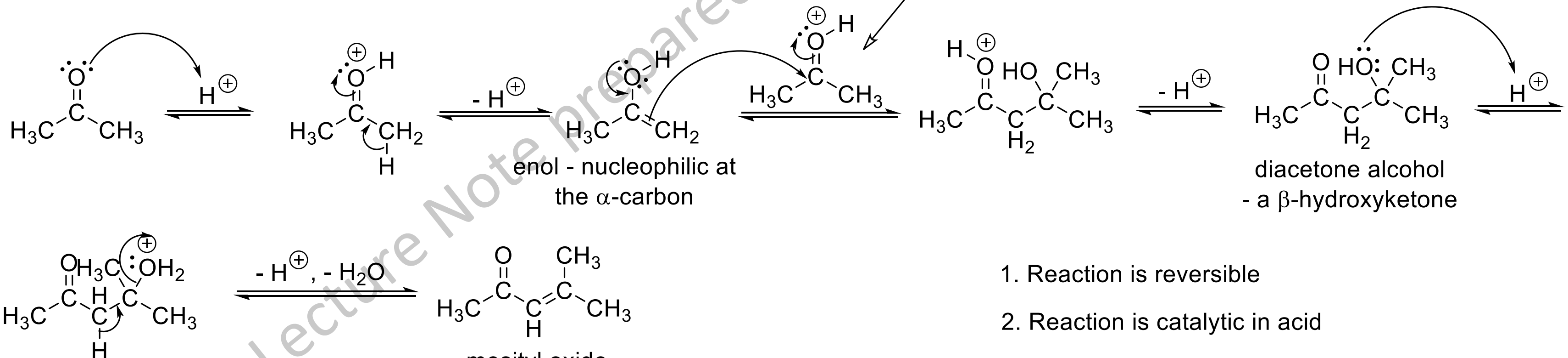
cyclohexanone
- electrophile

resonance-stabilized enolate ion - nucleophile

β-hydroxyketone

α,β-unsaturated ketone

Self-condensation of acetone in acid medium:



protonated acetone
- electrophile

enol - nucleophilic at
the α-carbon

diacetone alcohol
- a β-hydroxyketone

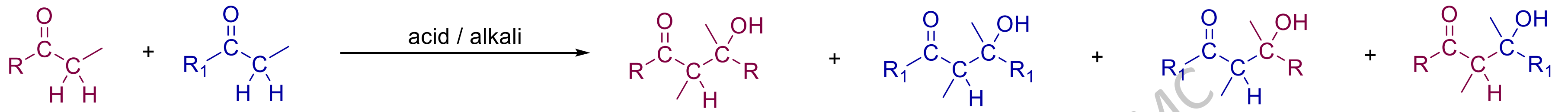
mesityl oxide
- an α,β-unsaturated ketone

1. Reaction is reversible

2. Reaction is catalytic in acid

Chemistry of Carbonyl: Aldol reaction / addition / condensation:

Cross-aldol condensation: A possibility of mixture of products -



self-aldol products

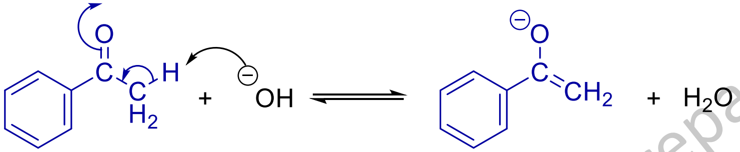
cross-aldol products

For successful cross-aldol avoiding mixture of products:

1. only one of the partners must have α-H, not the other (self-aldol of second component not a problem then)
2. the partner without α-H must be more electrophilic than the one which has the α-H (self-aldol of first component not a problem then)

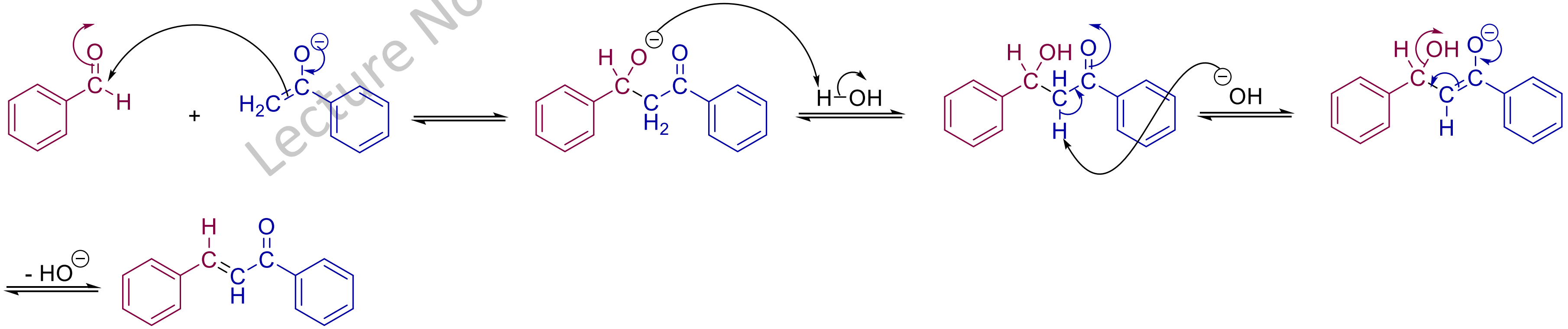
Enolate only from first component, nucleophilic attack of that enolate only on second component

Acetophenone has α-H, benzaldehyde does not, enolate forms from acetophenone only.



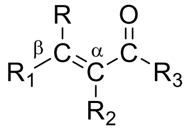
The basicity of hydroxide is such that a small portion of acetopheone forms enolate, most of it remains in unenolized form; this can add the enolate leading to self-aldol reaction, but...

...benzaldehyde is more electrophilic than acetophenone towards nucleophilic addition due to both electronic and steric factors, hence, the enolate preferentially attacks benzaldehyde (cross-aldol promoted) and not unenolized acetophenone (self-aldol prevented)

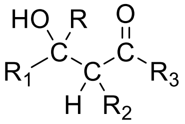


Chemistry of Carbonyl: Aldol reaction / addition / condensation:

Finding out the structure of the parent carbonyls from the product aldol / unsatuarted carbonyl:



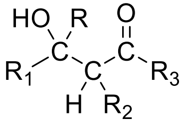
... can come from dehydration of ...



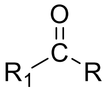
an α,β-unsaturated carbonyl, can be considered as an alkene, which...

a β-hydroxycarbonyl compound

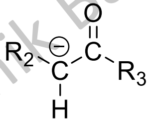
i.e., add a H at the α-carbon and a OH at the β-carbon



... can come from nucleophilic addition to ...



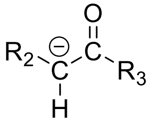
... of...



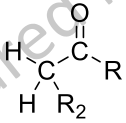
a β-hydroxycarbonyl compound can be considered as an alcohol, which...

ketone / aldehyde - electrophile

enolate - nucleophile



... must come from ...

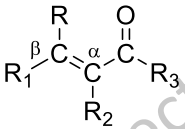


and a base

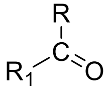
carbonyl compound with α-H

i.e., break the C-C between C_α-C_β, form a =O to C_β and one H to C_α

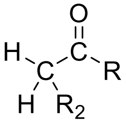
Overall:



... must come from ...

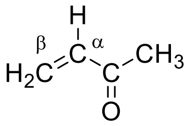


and

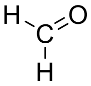


(and a base)

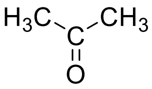
i.e., break the C=C between C_α-C_β, add =O to C_β and two Hs to C_α



must have come from



and



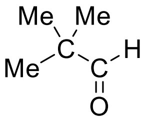
(and a base)

but-3-en-2-one

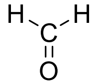
formaldehyde

propanone

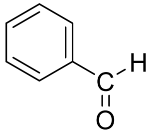
Compounds that do not participate in self-aldol condensation:



pivalaldehyde

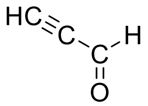


formaldehyde



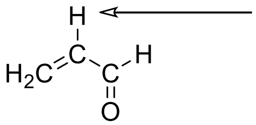
and other aromatic aldehydes

benzaldehyde



No α-H present for these

propiolaldehyde



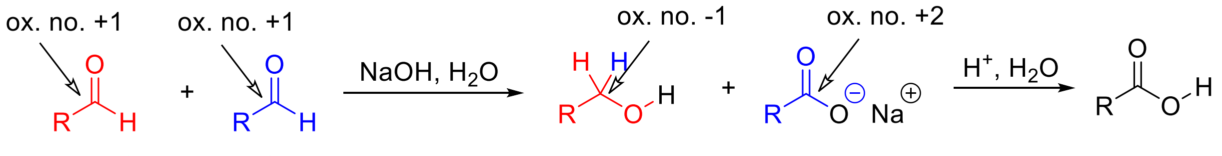
α-H present but it is not enolizable, hence no self-aldol

acrylaldehyde

These compounds undergo Cannizzaro disproportionation when heated with strong alkali

Chemistry of Carbonyl: Cannizzaro Reaction:

When reacted with concentrated NaOH (50 wt%) or other strong bases (e.g., alkoxides), aliphatic and aromatic aldehydes with no α-hydrogen undergo an intermolecular hydride-transfer reaction known as the Cannizzaro reaction.

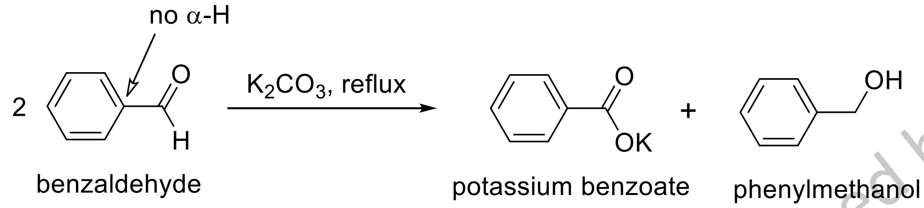


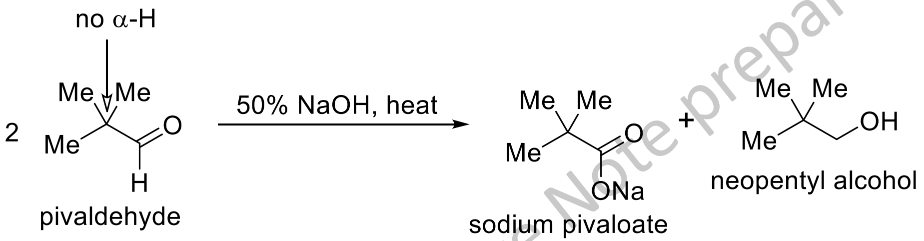
[R = alkyl (without α-H), aryl]

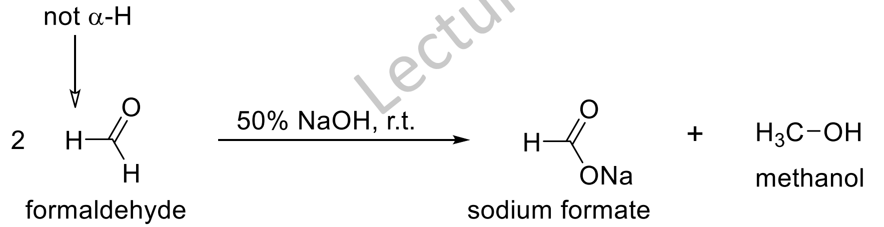
In this base-mediated disproportionation reaction, one molecule of aldehyde oxidizes another to the corresponding carboxylic acid and is reduced to the corresponding primary alcohol in a maximum 50% yield.

If the aldehyde has α-Hs, the aldol reaction will take place faster than the Cannizzaro reaction.

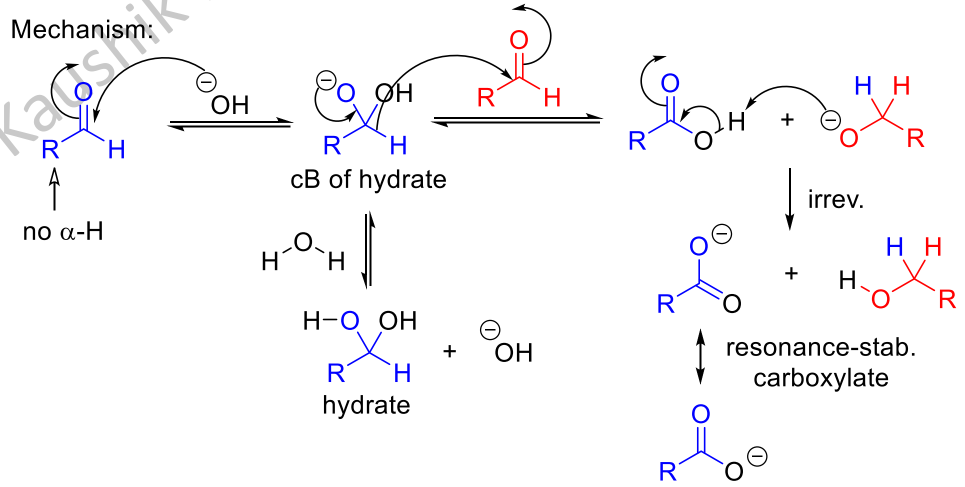
Examples:



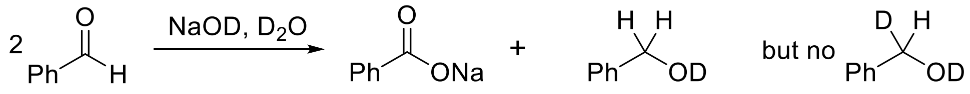




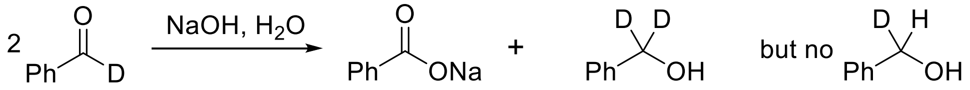
Mechanism:



Using D_2O, ^{-}OD there is no incorporation of D at the carbinol carbon :



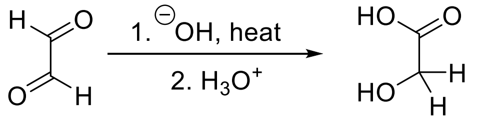
Using H_2O, ^{-}OH on PhCDO there is no incorporation of H at the carbinol carbon :



Chemistry of Carbonyl: Cannizzaro Reaction:

When reacted with concentrated NaOH (50 wt%) or other strong bases (e.g., alkoxides), aliphatic and aromatic aldehydes with no α-hydrogen undergo an intermolecular hydride-transfer reaction known as the Cannizzaro reaction.

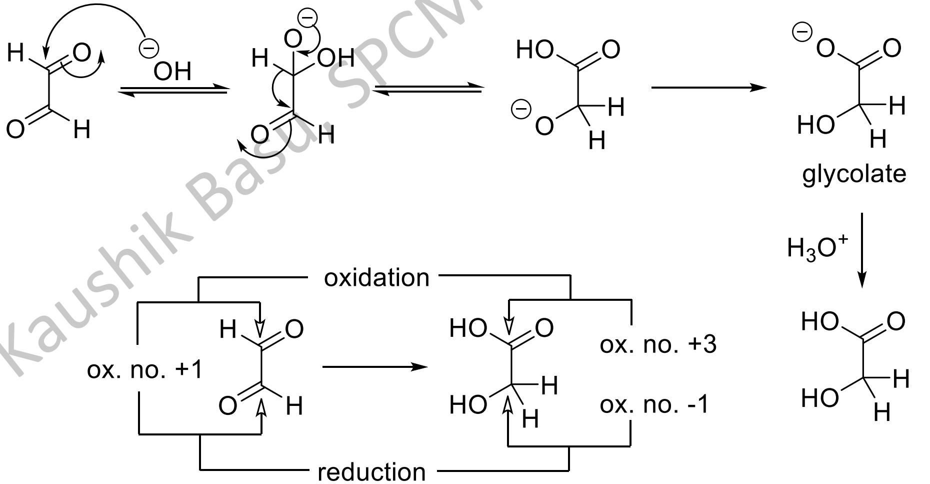
Intramolecular Cannizzaro reaction: For dialdehydes - heating with conc. alkali;

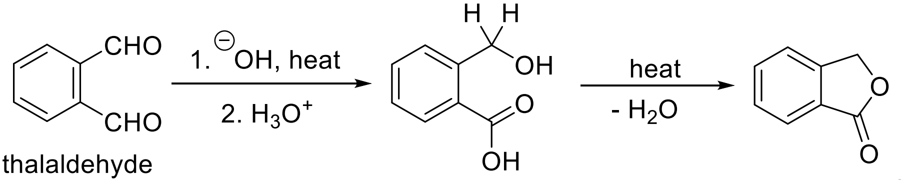


glyoxal

2-hydroxyacetic acid
aka glycolic acid

Mechanism: with glyoxal:





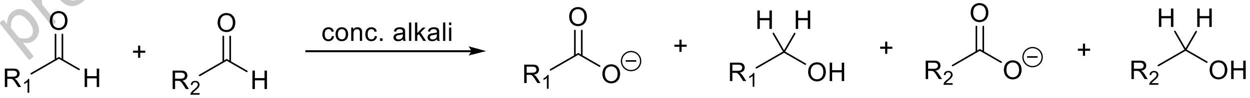
phthalaldehyde

2-(hydroxymethyl)benzoic acid

lactone - intramolcular variant of ester

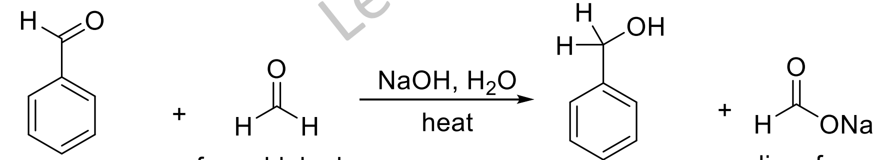
Crossed Cannizzaro reaction:

In general, a mixture of two different aldehydes undergoes Cannizzaro Reaction to yield all possible, i.e. four products. The process is not very useful due to formation of mixture of products.



[R_1 and R_2 lack α-H]

However, when one of the components is formaldehyde, the reaction becomes synthetically useful as the formaldehyde almost exclusively reduces the other aldehyde and itself gets oxidized to formate. This method is partiularly important for crossed Cannizzaro reactions b/w formaldehyde and an aromatic aldehyde.



benzaldehyde

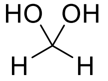
formaldehyde

benzyl alcohol

sodium formate

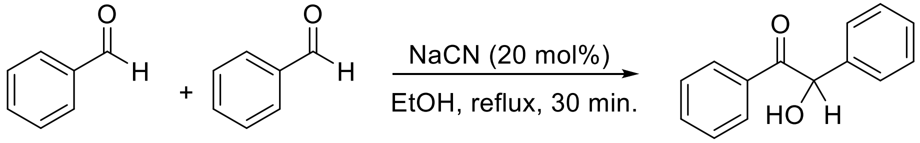
Why does formaldehyde always acts as the hydride donor?

i) Formaldehyde exists in aq. medium as hydrate: which can donate hydride



ii) Has two hydrides to donate, donation statistically more favourable.

Chemistry of Carbonyl: Benzoin condensation:



benzaldehyde

benzoin -
an α-hydroxyketone

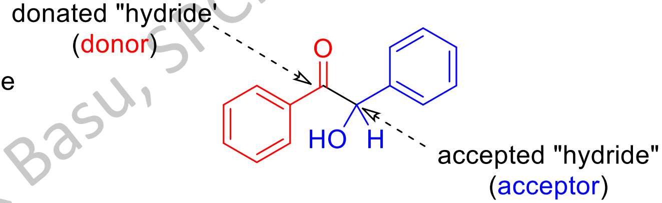
Cyanide catalysed union of two aldehydes (generally aromatic) into an α-hydroxyketone.

Successful for certain (but not all) aromatic / heteroaromatic aldehydes and α-ketoaldehydes (glyoxals).

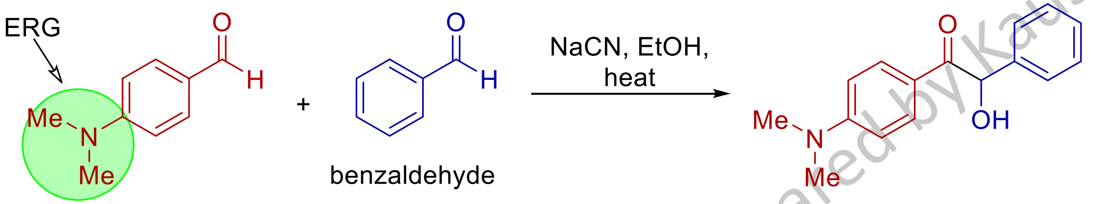
Cyanide-catalysed process generally does not work for aldehydes with α-H.

Understanding benzoin condensation in terms of donor-acceptor approach - as if one of the carbonyl compounds has donated a hydride to the other:

Trick to recognize donor-acceptor:

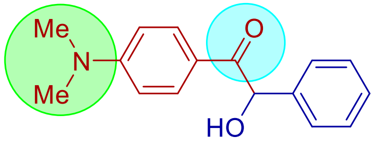


Cross-benzoin condensation:



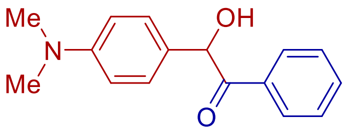
4-(dimethylamino)benzaldehyde

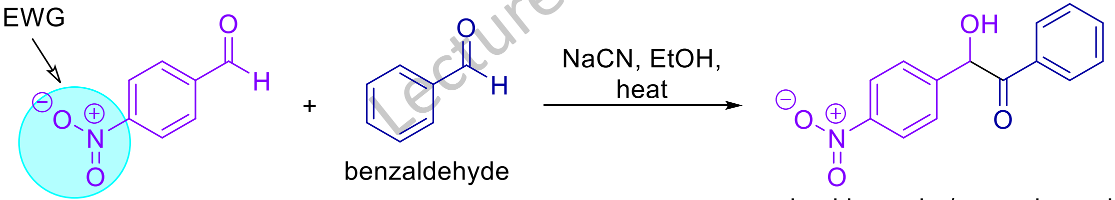
mixed benzoin / cross-benzoin /
heterobenzoin



(ERG conjugated to C=O)

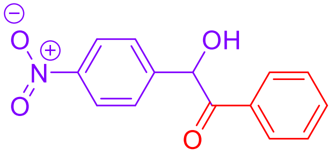
is more stable than



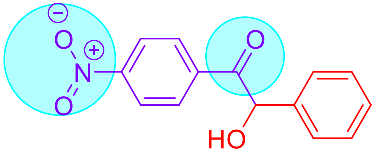


4-nitrobenzaldehyde

mixed benzoin / cross-benzoin /
heterobenzoin



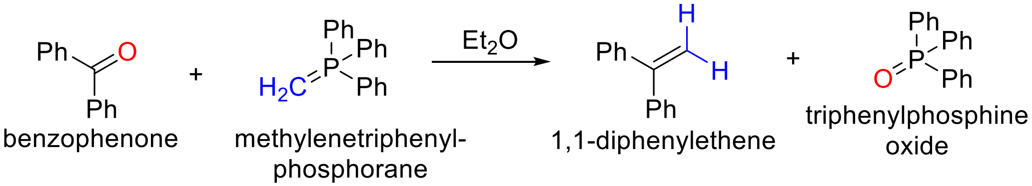
is more stable than



(two EWG on the same ring in 1,4-position)

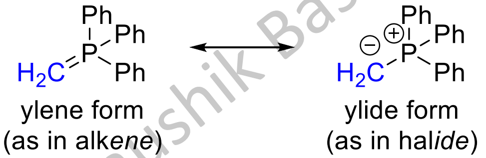
Chemistry of Carbonyl: Wittig reaction:

The formation of carbon-carbon double bonds (olefins) from carbonyl compounds and phosphoranes (phosphorous ylides) is known as the Wittig reaction.



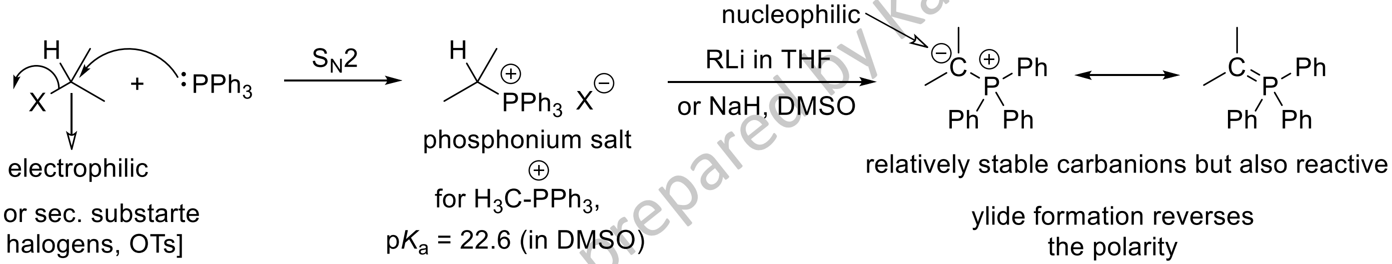
Ylides: Compounds in which an anionic site Y^- (originally on carbon, but now including other atoms) is attached directly to a heteroatom X^+ (usually nitrogen, phosphorus or sulfur) carrying a formal positive charge. They are thus 1,2-dipolar species of the type $R_mX^+–Y^-R_n$.

Two forms for ylides are possible when Y is a third row element, like P:



Triphenylphosphonium methylide
aka phosphonium ylide,
aka Wittig reagent

Preparation of phosphonium ylides:

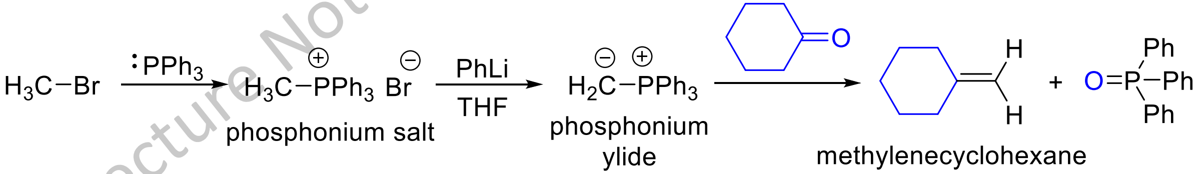


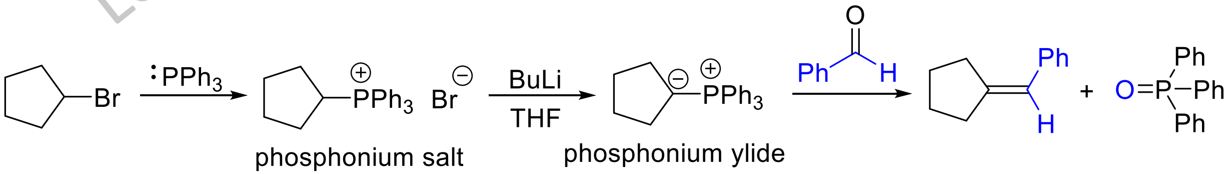
stabilization :

i) close proximity of opposite charges,

ii) p_π(C)-d_π(P) backbonding

Examples:

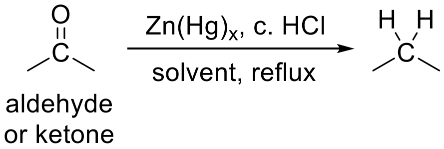




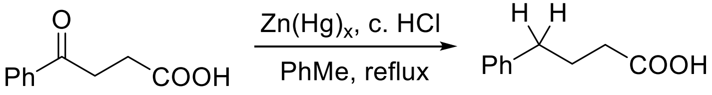
Chemistry of Carbonyl: Clemmensen and Wolff-Kischner reduction:

Reduction of C=O group: Deoxygenation - converting carbonyl to methylene

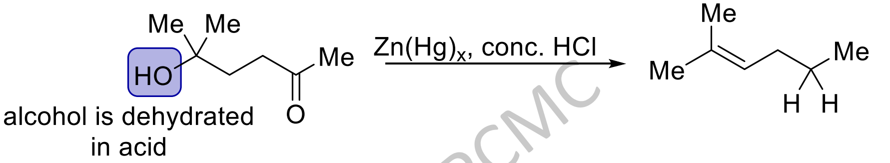
Method-1: Clemmensen reduction:



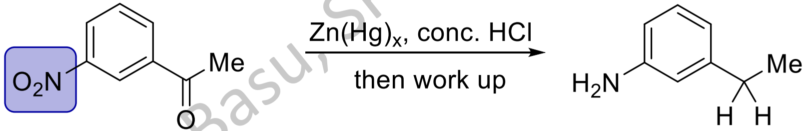
Examples:



Limitation: Cannot be used for acid-sensitive substrates:



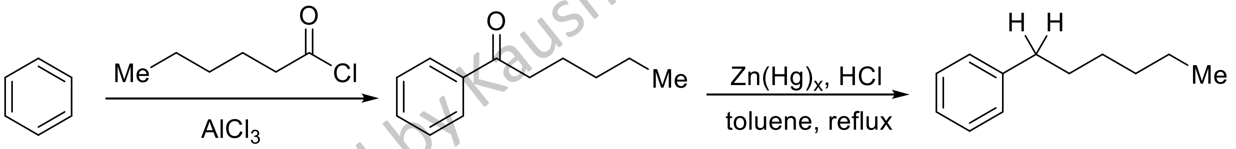
alcohol is dehydrated in acid



NO_2 gets reduced in Zn/HCl

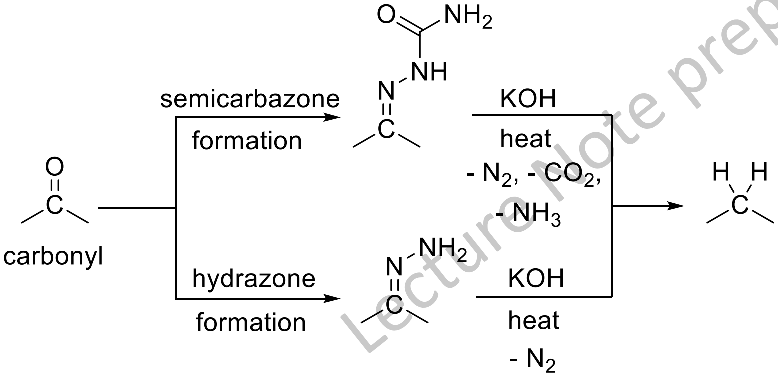
Synthetic utility:

Accessing alkylbenzene derivatives *via* Fridel-Crafts acylation-reduction sequence:

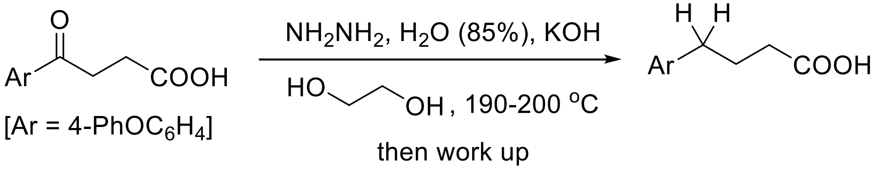


(direct prep. problematic due to polyalkylation)

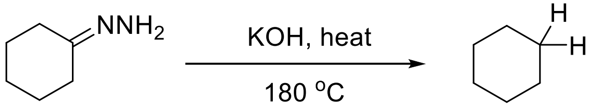
Method-2: Wolff-Kischner reduction:

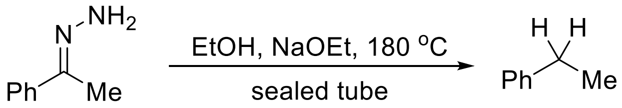


Modification: using a high-boiling solvent:



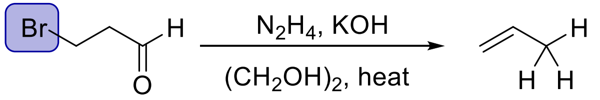
Examples:





Limitation: Cannot be used for base-sensitive substrates:

1. Aldehydes, ketones bearing α-H are prone to enolisation - can lead to epimerization.
2. Organohalides with β-H are prone to elimination



3. Esters, lactones, amides are normally hydrolysed.