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Prof. Olomola's Part

31/03/2026

Prof. Domola's part

Organic Reactions & Synthesis

Introduction

Organic synthesis is the process of building organic molecules from simple precursors. It typically involves,

- (i) Carrying out a reaction following an exact or slight modified procedure from a scientific paper. This usually involves stirring, addition of reagent and in some cases, temperature control.
- ii) Work up procedure such as, quenching, solvent extraction, adsorption of impurities, neutralization, removal of solvents and so on.
- iii) Purification using techniques such as recrystallization, preparative thin layer chromatography, column chromatography, radial chromatography, high performance liquid chromatography etc.
- iv) Identification using chemical test and more conveniently instrumentation techniques such as IR, UV, NMR, MS and X-ray crystallography.

The overriding concern in a synthesis is the yield, including the inherent concept of simplicity (fewest possible steps) and selectivity (chemoselectivity, regioselectivity).

diastereoselectivity and enantioselectivity)

Furthermore, the experimental ease of the transformation and whether they are environmentally acceptable must be considered.

01/04/26

Retrosynthetic Analysis

The synthesis of any molecule involves careful planning and strategy. E. J. Corey the winner of the 1990 Nobel prize in chemistry introduced and promoted the concept of retrosynthetic analysis whereby a molecule is disconnected leading to logical precursors.

Today retrosynthetic analysis plays an integral and indispensable role in research.

Synthetic planning starts with the product which is fixed and unchangeable (called the target molecule) and walks backwards towards the starting material.

This process is called retrosynthesis (backward synthesis) and the art of planning the synthesis of target molecule is called retrosynthetic analysis.

Definitions

(1) Target molecule (TM): It is the molecule to be synthesized

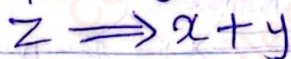
(2) Arrow:

(a) simple reaction arrow ($\longrightarrow$): It means "react to give"

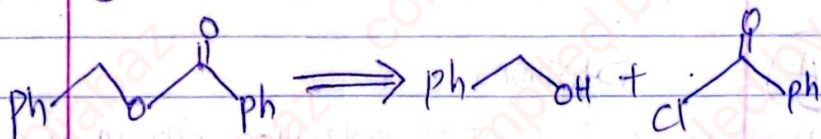
(b) delocalization arrow ($\longleftrightarrow$) means that the two different structures are the same or there are two different ways to draw a delocalized structures

(c) Equilibrium arrow ($\rightleftharpoons$): Meaning the two structures are interconverting

(d) retrosynthesis arrow ($\Rightarrow$): It means "could be made from". E.g

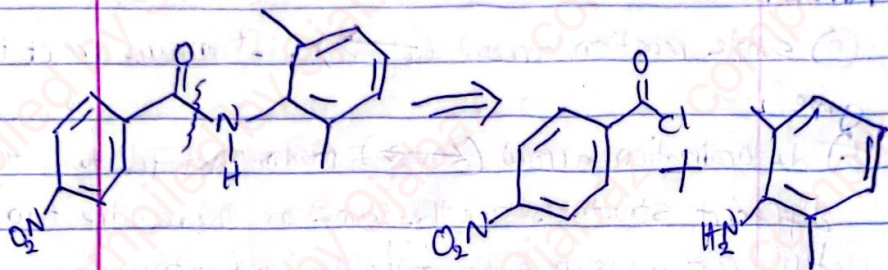


It means that target molecule Z could be made by reacting X and Y under specific reaction condition

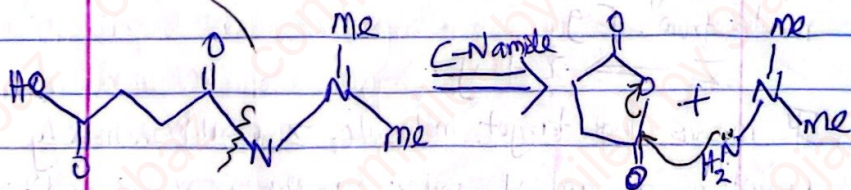


(3) Disconnection: Mentally breaking a molecule into its component parts is known as disconnection and it is normal to indicate the site of the disconnection

with a wiggly line. Disconnection is an imaginary bond cleavage corresponding to the reverse of a real reaction.



Note: Disconnection must correspond to known reliable reaction



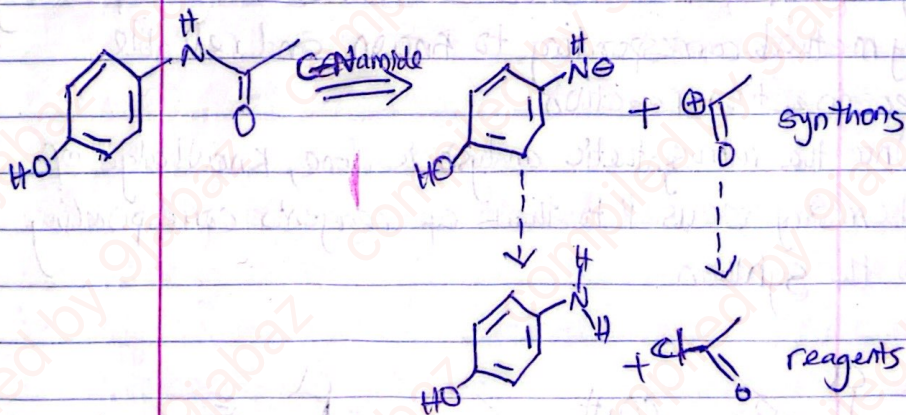
④ Synthons

Synthons are fragment of molecules with an associated polarity (represented by a + or -) which stands for reagent used in the forward synthesis. They are not themselves reagent, though they made occasionally turn out to be intermediate along the reaction pathway.

By disconnecting bonds to synthons rather than actual reagent, the polarity of the bond forming reaction can be indicated without having to specify details of the reagent.

Simply put - Synthons are idealized fragment resulting from a disconnection. Synthons need to be replaced by reagent in a suggested synthesis.

TM $\Rightarrow$ Synthons $\dots\dots$ Synthetic equivalent
or
reagents



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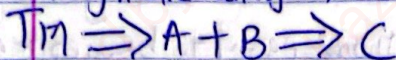
(5) Synthetic Design

It involves two distinct steps;

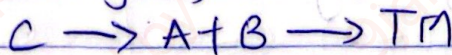
(1) retrosynthetic analysis

(2) Subsequent translation of the analysis into a forward reaction synthesis

retrosynthetic analysis;

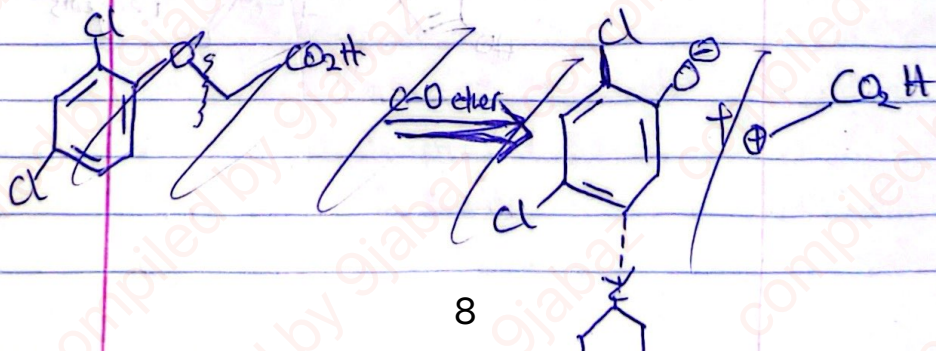


forward synthesis

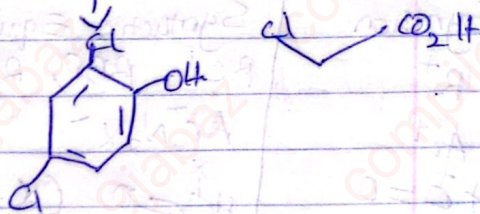
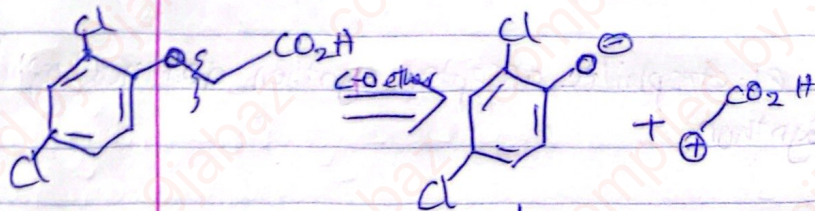


In the analysis, the chemist recognizes the functional groups in a molecule and disconnects them proximally by methods corresponding to known, and reliable reconnection reactions.

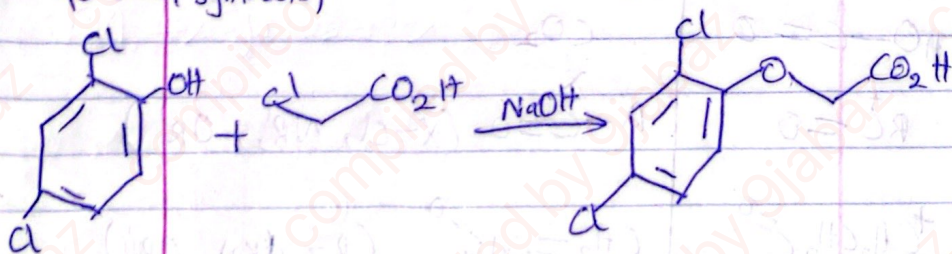
Once the retrosynthetic analysis is done, knowledge of chemistry is used to think of reagents corresponding to the synthesis.



retrosynthetic analysis;



forward synthesis;

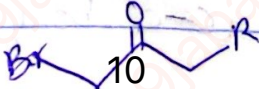


Chemical bonds can be cleaved heterolytically; homolytically or through concerted transformation. Heterolytic retrosynthetic disconnection of a C-C bond in a molecule breaks the target molecule into an acceptor synthon (a carbocation) and a donor synthon (carbanion).

In a formal sense, the reverse reaction, i.e. the formation of a C-C bond, then involves the union

of an electrophilic acceptor synthon and nucleophilic donor synthon

Common Acceptor synthons

Synthon	Synthetic Equivalent
R^+	$RL, RBr, RI, ROTs$
Ar^+	$Ar^+N_2X^-$
$H-C^+=O$	$H-C^+=O \quad (X=NR_2, OR)$
$HO-C^+=O$	CO_2
$R-C^+=O$	$R-C^+=O \quad (X=Cl, NR'_2, OR')$
$^+CH_2CH_2C(=O)R$	$CH_2=CHC(=O)R \quad (R=alkyl, OR')$
$^+CH_2-CH_2C\equiv N$	$CH_2=CHC\equiv N$
$^+CH_2OH$	$HCHO$
R_2C^+-OH	$R_2C=O$
$^+CH_2OH$	
$^+CH_2C(=O)R$	

Common Donor Synthons

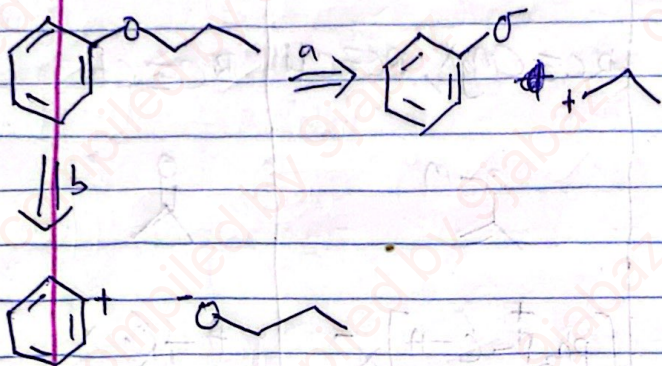
Synthon	Derived reagent	Synthetic Equivalent
R^-	$RMgX, RLi, R_2CuLi$	'RX
^-CN	$NaC\equiv N$	HCN
$RC\equiv C^-$	$RC\equiv CMgX, RC\equiv CLi$	$RC\equiv CH$
		
$Ph_3P^+ - C^-$	$[Ph_3P^+ - C^- - H]X^-$	$H - C - X$

Choosing a Disconnection

The hardest ~~task~~ ^{part} in designing a retrosynthetic analysis is spotting where to make the disconnection(s). The overall aim of retrosynthetic analysis is to get back to starting materials that are available from chemical suppliers and to do this as efficiently as possible. Below are summarized important guidelines for choosing disconnections of bond.

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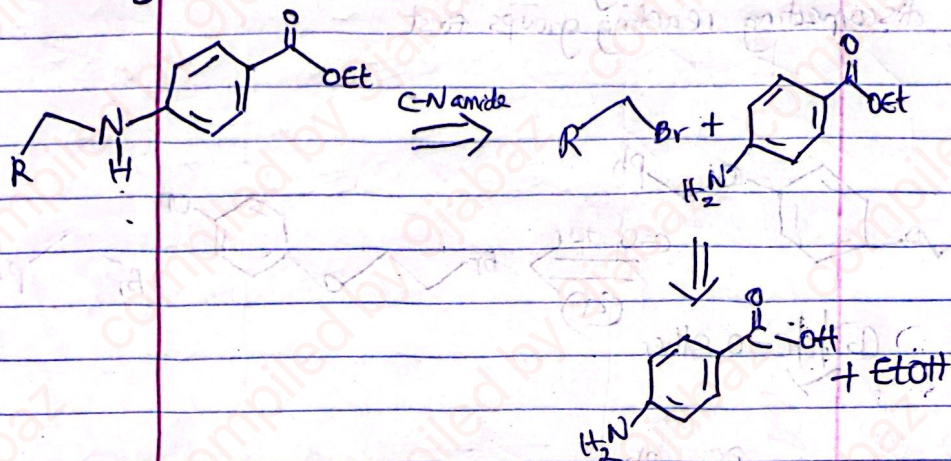
- 1) Disconnection of bond should be carried out only if the resultant fragment can be reconnected by known and reliable reaction.



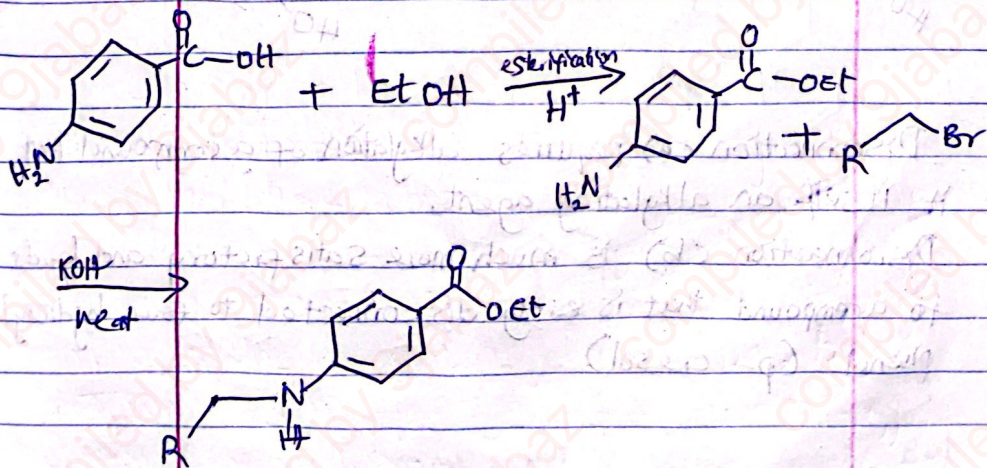
Disconnection of the aryl side of the oxygen atom is a bad choice because there is no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.

- ② Aim for the fewest number of disconnection. Adding large fragment in a single reaction is more productive than adding several small fragments sequentially.
- ③ For compounds consisting of two parts joined by a hetero atom disconnects next to the hetero atom. This guideline works for esters, amides, ethers, amines,

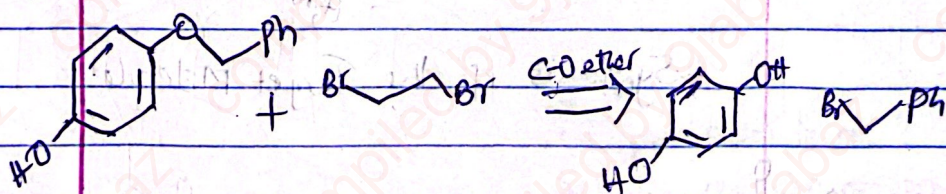
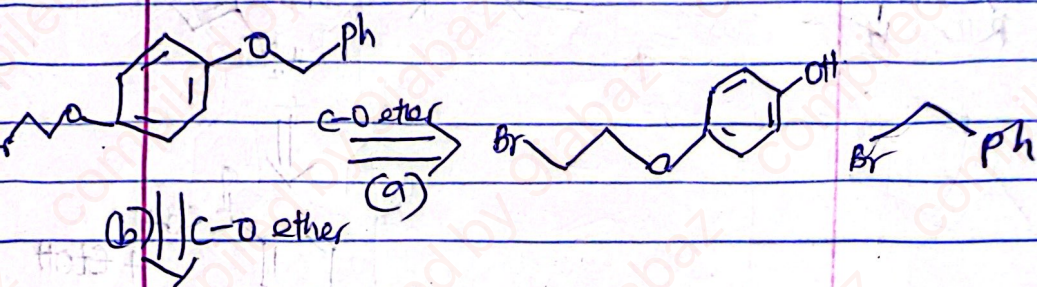
acetals and sulphides, because these compounds are often made by a substitution reaction.



Synthesis of the Target Molecule



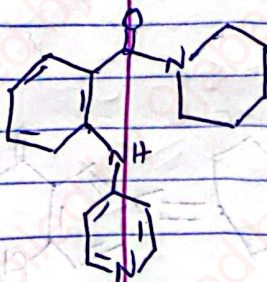
- (4) Consider alternative disconnection and choose ^{route} ~~fast~~ that avoid chemoselectivity problems. This often means disconnecting reacting groups first



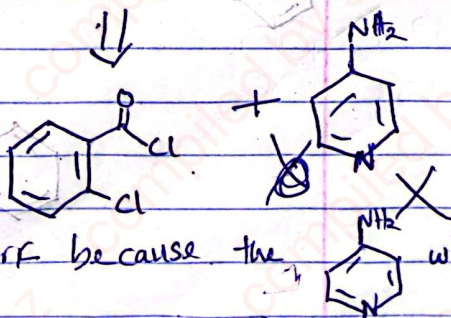
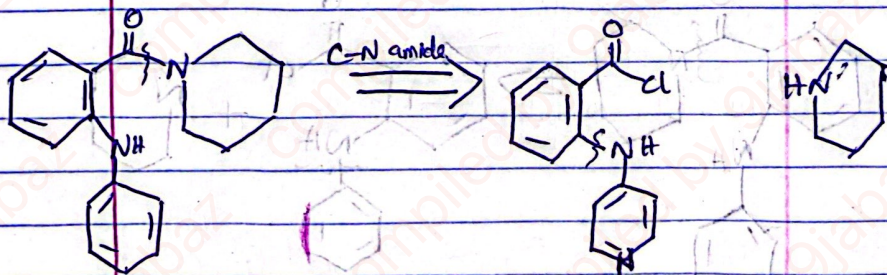
Disconnection (a) requires alkylation of a compound that is itself an alkylating agent.

Disconnection (b) is much more satisfactory and leads to a compound that is easily disconnected to four hydroxyphenol (p-cresol)

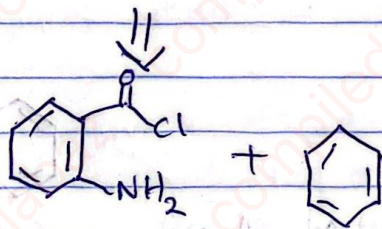
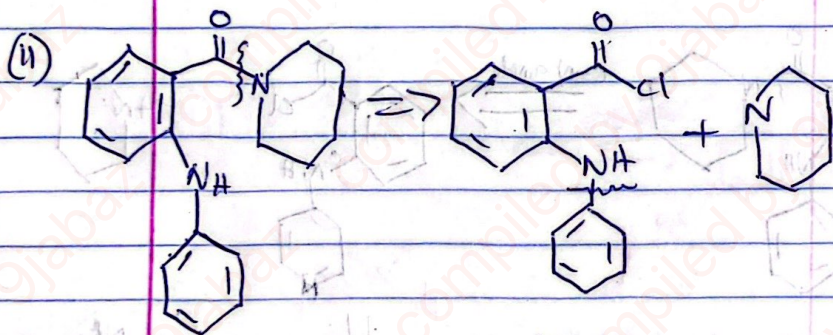
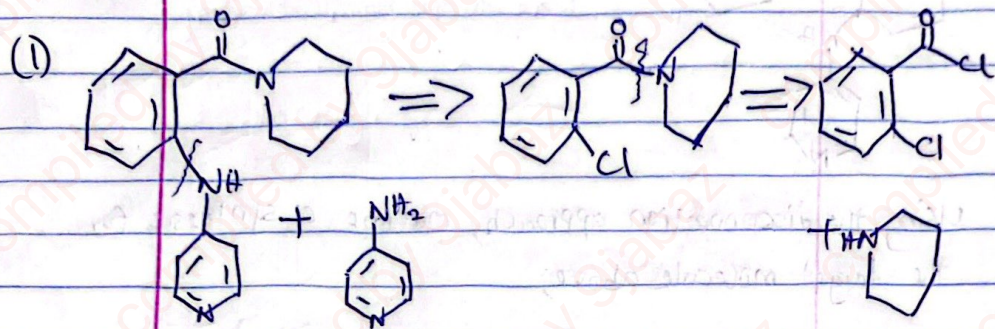
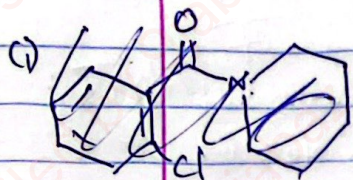
09/04/26



Using the disconnection approach, outline a synthesis for the target molecule above;



This method will not work because the ~~pyridine~~ will attack the carbonyl group, not the second C-Cl. But if OH is used (for the second C-Cl) instead of Cl, it would have worked.



Write the Synthesis

benzene $\rightarrow$ acetophenone (1)

alcohol $\rightarrow$ methylol

benzene $\rightarrow$ nitrobenzene $\rightarrow$ nitrobenzene
nitrobenzene $\rightarrow$ nitrobenzene $\rightarrow$ nitrobenzene
(1) (1) (1)

Functional Group Interconversion

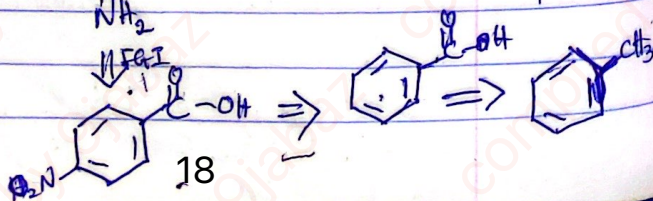
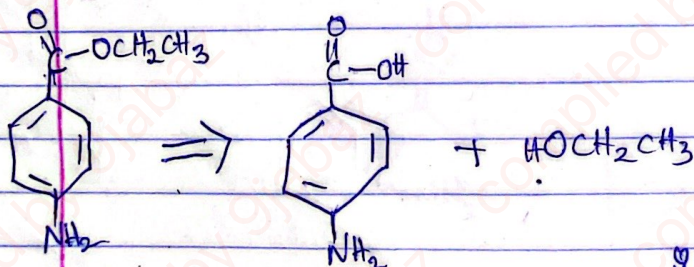
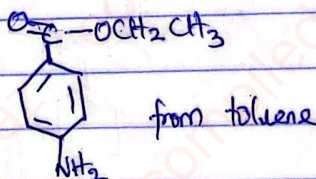
R-X

- (i) haloalkane $\rightarrow$ alcohol
- haloalkane $\rightarrow$ nitrile

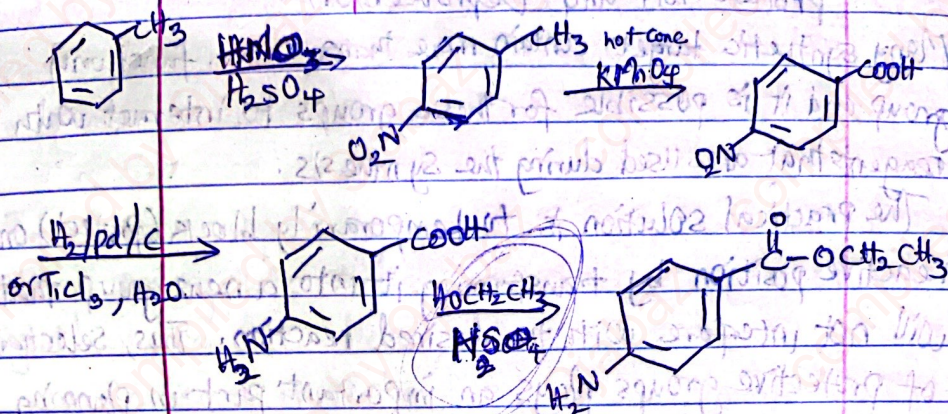
Syntheses involve either formation of new bond or functional group interconversion (no. of C-atom does not change).

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Using the disconnection approach, write the synthesis for the compound below

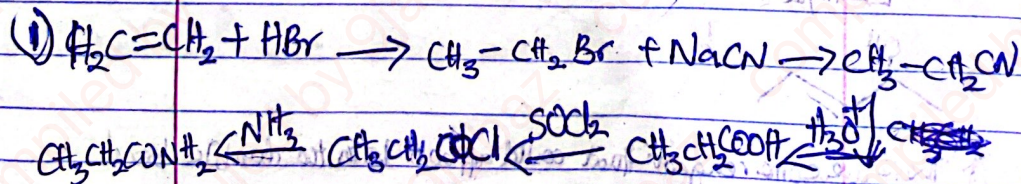
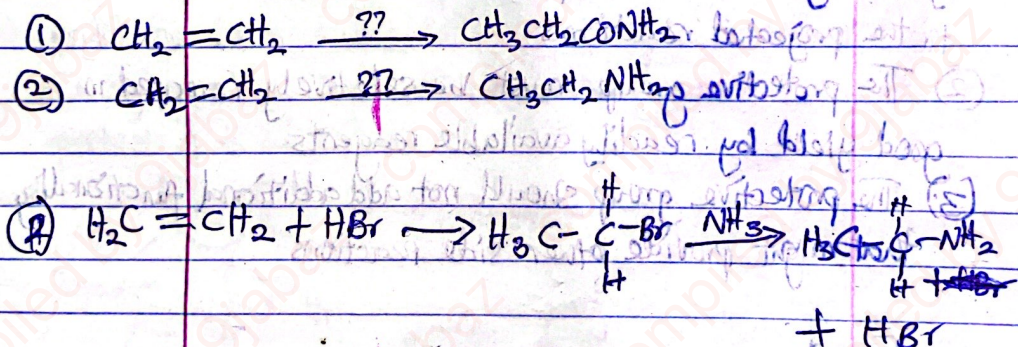


Synthesis



Retrosynthesis

21/05/26



26/05/26

Protection and Deprotection

Many synthetic target contain more than one functional group and it is possible for these groups to interact with reagents that are used during the synthesis.

The practical solution is to temporarily block (protect) one reactive position by transforming it into a new group that will not interfere with the desired reaction. Thus, selection of protective groups plays an important part in planning a synthesis.

A protective group must fulfill a number of requirements

- (1) The protective group reagent must react selectively in good yield to give a desired protected substrate that is stable to the projected reactions.
- (2) The protective group must be selectively removed in good yield by readily available reagents.
- (3) The protective group should not add additional functionality that might provide other side reactions.

Example



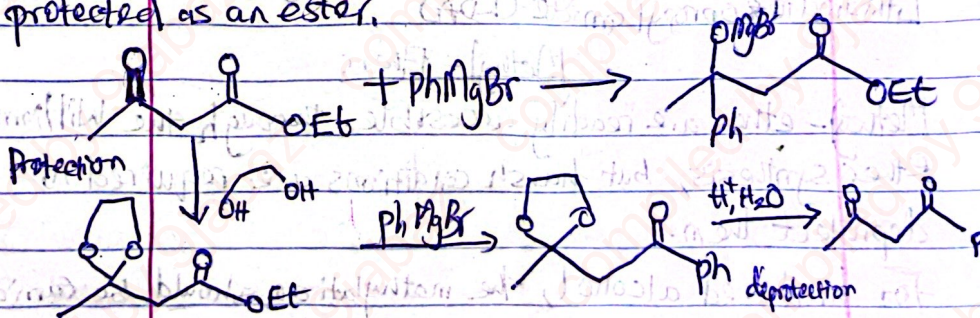
* There are some reagents that could affect both the double bond

and the $-OH$ functional group. For this not to happen, we could decide to protect one of the groups. This is not a desired step because when we protect, we still have to deprotect.

Introduction of a protecting group adds at least two additional steps to a synthetic scheme with possible effect of reduced yield and extra cost. Hence, all efforts should be made to keep the use of protecting group to a minimum. Effectively planning the order for insertion of each functional group can actually minimize the use of protecting groups and where possible this option should be used.

Most important functional groups which cause reactivity problems are alcohols, ketones, aldehyde and amines.

Carboxylic acid group can give some concern as this is often protected as an ester.



Alcohol Protection

The interfering part of the alcohol group is always the acidic proton. The most important protective group for alcohol are ethers and mixed acetals. The proper choice of protecting group is critical if chemoselectivity is desired. Reactivity of alcohol is $1^\circ > 2^\circ > 3^\circ$.

The stability of ethers and mixed acetals as protecting groups for alcohol varies from very stable methyl-ether to the highly acid labiles. However, all ethers are stable to basic reaction conditions. Hence, ether of mixed acetal protecting group, specifically to tolerate Grignard reagent (R^MgX), RLi , nucleophilic reducing reagent such as $LiAlH_4$, $NaBH_4$, oxidizing agents such as PCC (pyridium chlorochromate), MnO_2 (manganese (IV) oxide), Wittig reagent and strong bases such as Lithium diisopropyl amide (LDA).

Methyl-Ethers

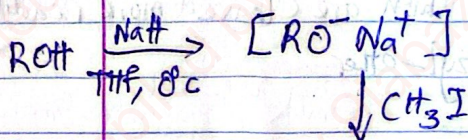
Methyl-ether are readily accessible through the Williamson-ether synthesis, but harsh conditions are required to deprotect them.

For hindered alcohol, the methylation should be carried out in the presence of KOH and DMSO (dimethylsulphoxide). The reagent for cleaving methyl-ethers include;

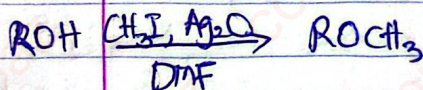
(i) Conc HI (ii) Me_3SiI (trimethylsilyliodide) in DCM

(iii) BBr_3 in DCM

BBr_3 is especially effective for cleaving PhOCH_3 i.e. Phenylmethyl ether



Methylation of 2° -OH groups in sugars with methyl iodide and silver oxide (Ag_2O) is often the method of choice.

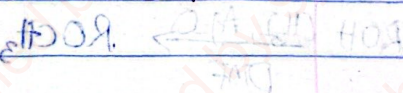
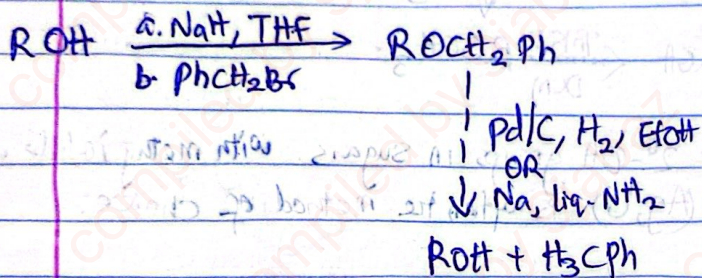


Benzyl - Ethers

Benzyl ethers are quite stable under both acidic and basic conditions and towards a wide range of oxidizing and reducing reagents. Hence, they are frequently used in organic synthesis as protecting groups.

Note: $n\text{-BuLi}$ may deprotect a benzylic hydrogen especially in the presence of tetramethylethylenediamine (TMEDA)

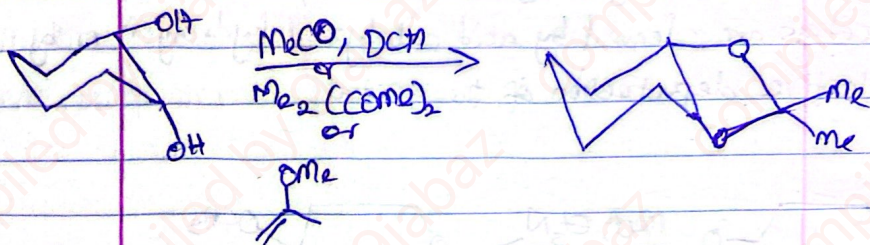
Catalytic hydrogenolysis offers the mildest method for deprotecting benzyl-ether. Hydrogenolysis of 2° and 3° benzyl ethers may be sluggish. Protection of alcohols using benzyl (oxy) methyl chloride produces the corresponding benzyloxymethyl-ether which are cleaved more readily than the corresponding benzyl-ether



Benzyl - Ether

3/06/26

Only vicinal cis-OH group of cyclic 1,2-diol readily form acetal



Aqueous HCl , acetic acid or para-toluene sulfonic acid can be used to cleave the Acetal

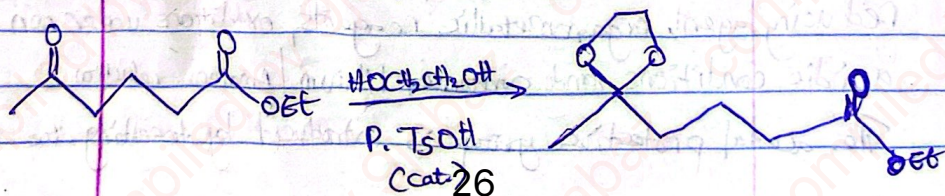
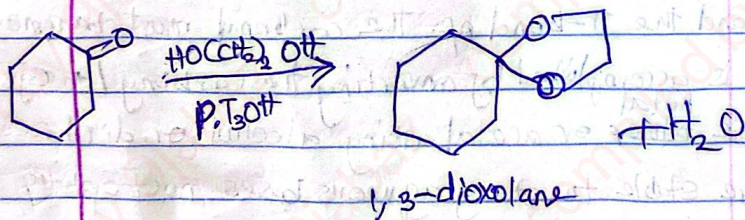
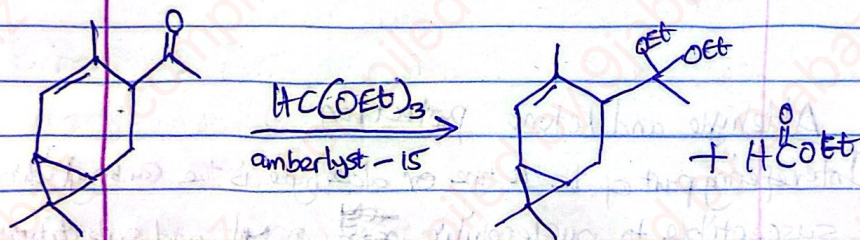
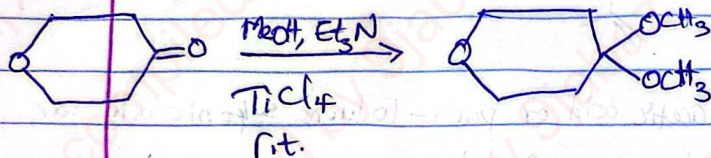
Aldehyde and ketone protection

Interfering part of the ketone or aldehyde is the carbonyl which is susceptible to nucleophilic ~~and~~ ^{acyl} and substitution reaction. To prevent these reactions, the electrophilic carbon and the π -bond of the carbonyl must be removed and this is accomplished by converting the carbonyl to cyclic ^{ketal} or acyclic ~~ether~~ or acetal using alcohol or diol reactants. Acetals are stable to strong aqueous bases, nucleophilic reducing agents, organometallic reagents, oxidations under non acidic conditions and sodium or lithium / ammonia reduction.

The acetal protective group is introduced by treating the

Carbonyl compound with an alcohol or orthoester in the presence of a Lewis acid catalyst, dry HCl or H_2SO_4 .

Acetals are cleaved by acid catalyzed hydrolysis or by a selective deprotection of the acetal



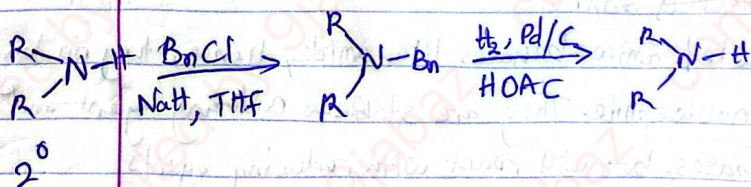
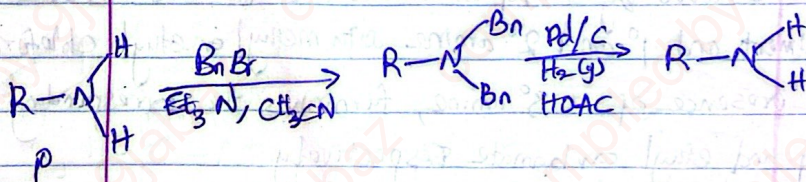
Amine Protection

The interfering portion of amine is the basic and nucleophilic lone pair of electron on nitrogen which is susceptible to alkylation, basicity and oxidation reaction. The common method of amine group protection involves conversion of primary and secondary amine to a 3° amine (usually benzyl or trialkyl(silyl)) (conversion to an amide (or a carbamate) and conversion to a sulphonamide.

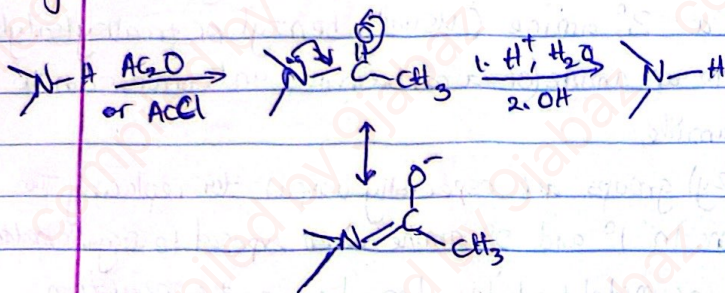
N-Benzyl groups are especially useful for replacing the NH protons in 1° and 2° amine when exposed to organometallic reagents or metal hydride depending on the reaction conditions, 1° can form mono and/or dibenzylated products.

Hydrogenolysis of benzylamine with ~~path~~ Pd catalyst in the presence of an acid regenerates the amine.

Note: benzyl amines are generally not cleaved by Lewis acid.



Acylation of 1° and 2° amine with acetic anhydride or acid chlorides gives the corresponding amides in which the basicity of the nitrogen is reduced making them less susceptible to attack by electrophilic reagents.

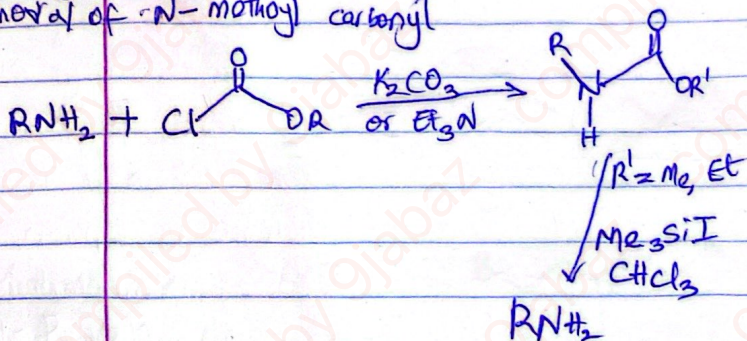


Benzamides are formed by the reaction of amines with benzoyl chloride in pyridine or trimethylamine, the group is stable from pH 1 to 14, nucleophile, organometallic (except organolithium reagent), catalytic hydrogenation and oxidation. It is cleaved by strong acids such as 6N HCl or HBr . Treatment of 1° and 2° amine with methyl or ethyl chloroformate in the presence of a 3° amine, furnishes the corresponding methyl and ethyl carbamate respectively.

~~Protected amine~~

The protected amine behaves like amide, hence, they no longer act as nucleophile. They are stable to oxidizing agent and aqueous bases, but will react with reducing agents.

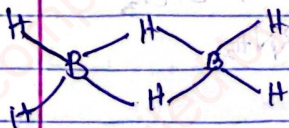
Trimethylsilyl iodide is often the reagent of choice for the removal of *N*-methoxy carbonyl



Hydroboration

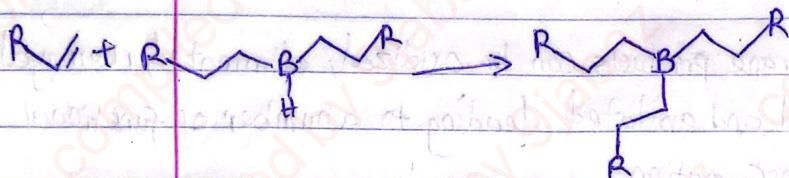
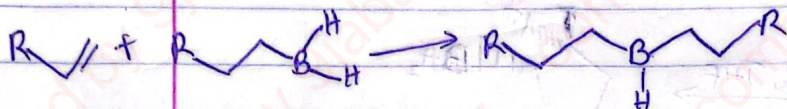
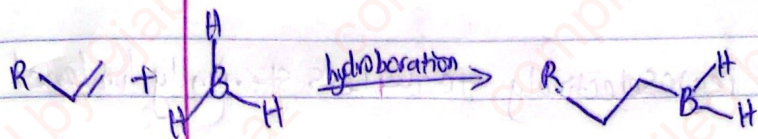
Boron has only nine electrons in its second shell, and so typically forms three conventional two centre two electron bonds with other atoms in a planar structure leaving a vacant sp orbital.

Borane exists as mixture of B_2H_6 (a dimer with hydrogen bridges) and the monomer BH_3 .



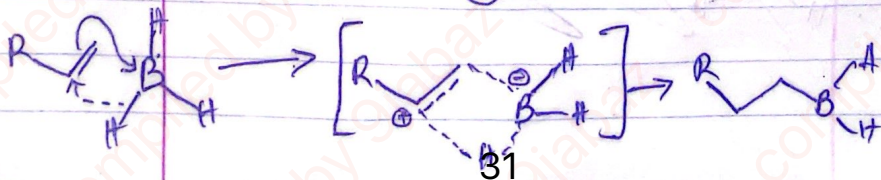
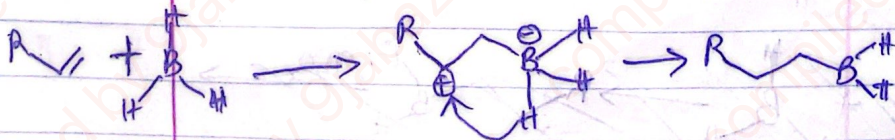
A vacant orbital is able to accept a lone pair of electron from a Lewis base to give a neutral species or can combine with a nucleophile to form a negatively charged tetrahedral anion.

Brown (Nobel prize recipient 1979) discovered that diborane (B_2H_6) reacts with alkenes in ether solvent to form trialkyl borane. Alkene reaction with borane, described as hydroboration is an overall addition of borane across the double bond. Unlike most electrophilic additions to alkenes that occur in a stepwise manner via charged intermediates. This addition is concerted so that both new bonds are formed more or less at the same time, the result is an alkyl borane in which one of the hydrogen atoms has been replaced by an alkyl group.

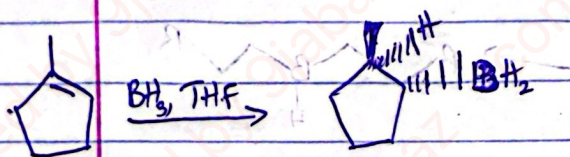


Hydroboration is a syn addition across the alkene. As the addition of the empty p-orbital to the less substituted alkene is occurring, a hydrogen atom from the boron adds with its pair of electrons to its carbon atom.

The two steps are concerted but the formation of the Carbon-Boron bond goes ahead of the Carbon-Hydrogen bond so that boron and carbon are partially charged in the first centered transition state.



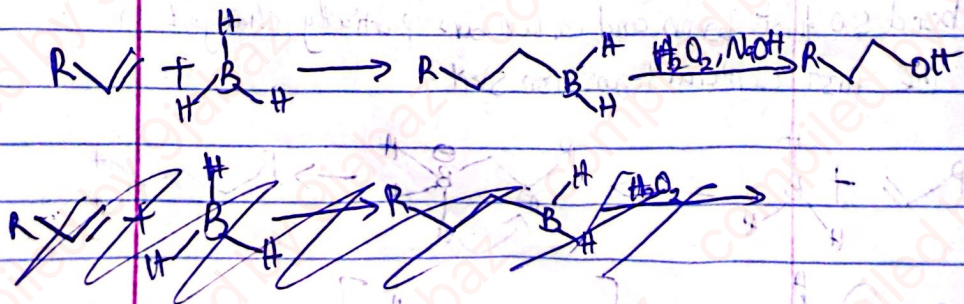
Boranes have regioselectivity to the less sterically hindered position

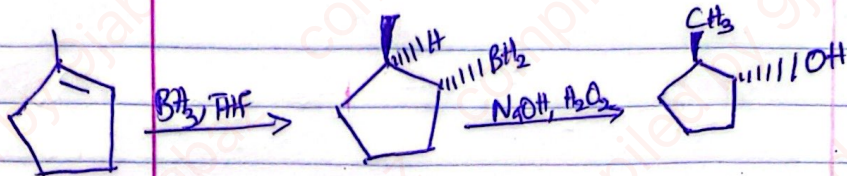


Organoborane products can be oxidized, eliminated, rearranged, protonated and anilated leading to a number of functional group transformation

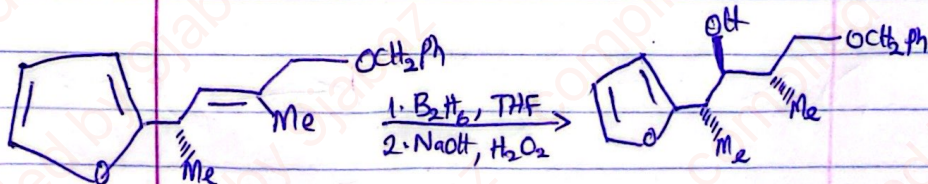
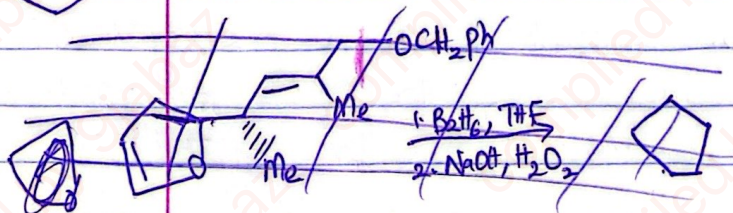
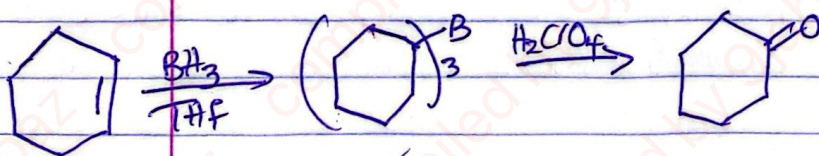
① Oxidation of Borane to Alcohol

Perhaps, the most utilized transformation of hydroboration is the oxidation of alkyl boranes to alcohol, accomplished by basic hydrogen peroxide

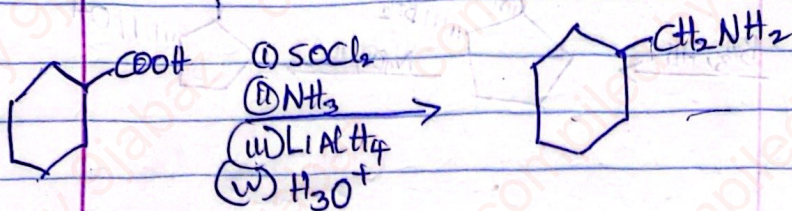




② Oxidation of Boranes to aldehydes and ketone
 While 1° or 2° alcohols produced from hydroboration followed by oxidation and the further oxidized to carbonyl compounds. The organoborane can be directly oxidized to corresponding carbonyl compounds by treatment with chromic acid.

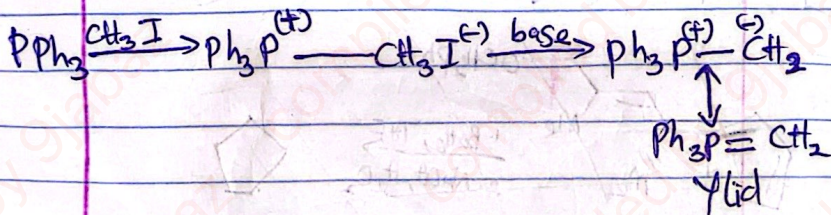


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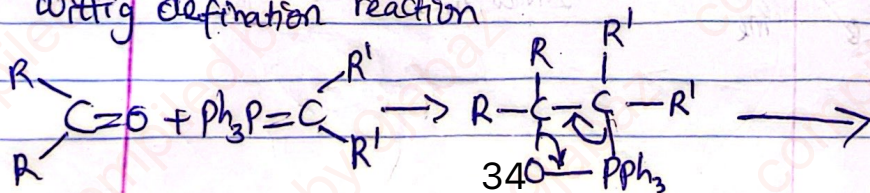


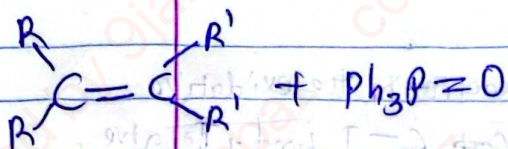
Wittig Reaction

Ylides are compound in which a carbon anionic carbon is adjacent to an atom bearing a five centre. The reactivity of phosphorus. Ylid was first exploited by Wittig who found that phosphonium salt were generated by an S_N2 reaction of a trialkyl-phosphine with an alkyl halide. The phosphonium salt reacts with a strong base such as *N*-butyllithium (*n*-BuLi).



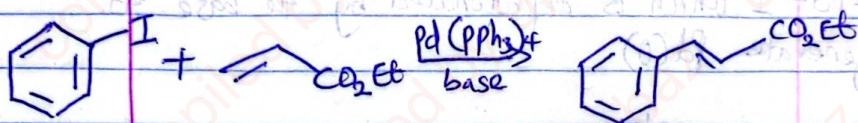
Wittig discovered that phosphorus Ylid reacts with aldehydes and ketones to form an alkene. This reaction is called Wittig deoxygenation reaction





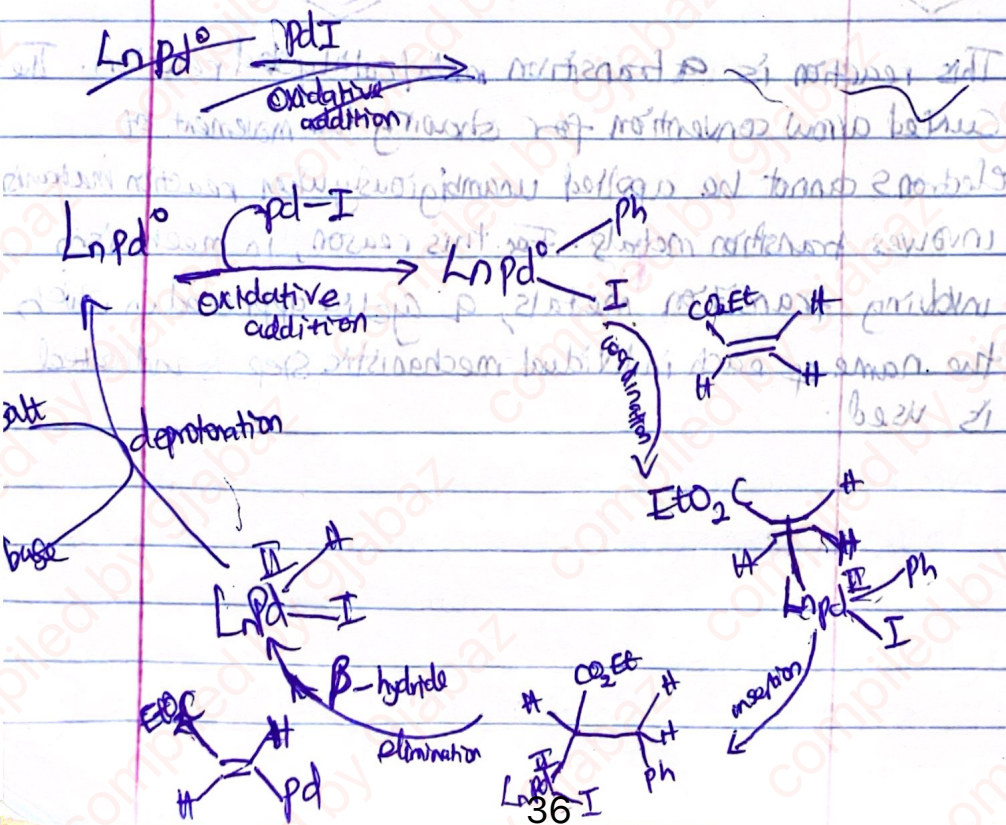
Heck Reaction

This is the chemical reaction of an unsaturated halides or triflate with an alkene in the presence of a base and a palladium catalyst to form a more substituted alkene. The Heck reaction can be carried out intra or intermolecularly.



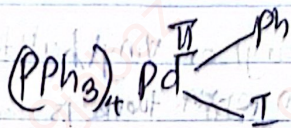
This reaction is a transition metal catalyzed reaction. The curved arrow convention for showing the movement of electrons cannot be applied unambiguously when reaction mechanism involves transition metals. For this reason, in mechanism involving transition metals, a cyclic approach in which the name of each individual mechanistic step is indicated is used.

The first step of the Heck reaction is the oxidative reaction of $Pd(0)$ to the $C-I$ bond, to give $Pd(II)-Ph$. The $Pd(II)-Ph$ complex then coordinates to the alkene and this is followed by an insertion of the alkene into the $Pd(II)-Ph$ bond giving a new $C-C$ bond. A β -hydride elimination then gives the product and $H-Pd-I$ which is deprotonated by the base to regenerate $Pd(0)$.

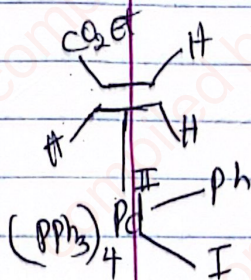


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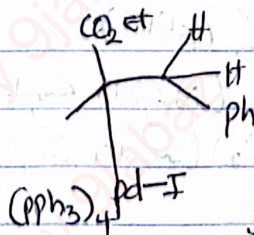
① Oxidative addition



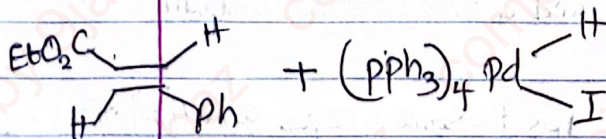
② Coordination



③ Insertion



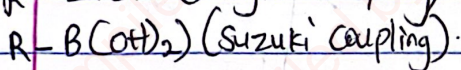
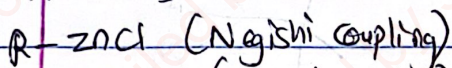
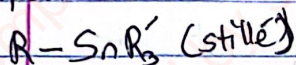
④ β -hydride elimination (regenerates double bond)



⑤ Deprotonation

Other coupling reactions include Negishi, Stille, Suzuki, Sonogashira, and Ullmann reactions.

In these reactions, an aryl or vinyl halide or ~~pseudo-alkyl~~ pseudo halide (a system in which there is good leaving group e.g. triplate) undergoes a palladium catalyzed Substitution reaction with a nucleophilic alkyl metal compound such as

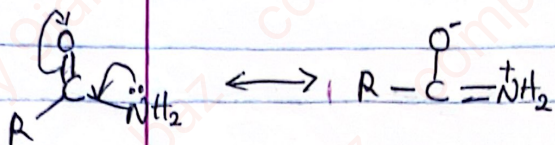


In the Sonogashira coupling, terminal alkynes are coupled with alkyl halides, in the presence of a base, a palladium catalyst and a sub catalytic amount of $Cu(I)$ iodide.

The Heck reaction has the same scope and limitations as palladium catalyzed carbonylation. $Pd(II)$ complexes are often added to the reaction mixture and are reduced in-situ before the catalytic cycle can proceed.

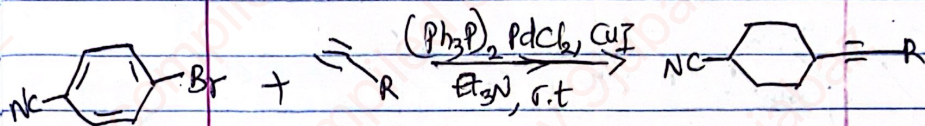
Primarily, trans alkenes are obtained due to conformational preferences in the 'rotamer' (rotational isomers of each other) form which β -hydride elimination takes place.

* Asymmetric synthesis is the synthesis of molecules that have chiral centers.

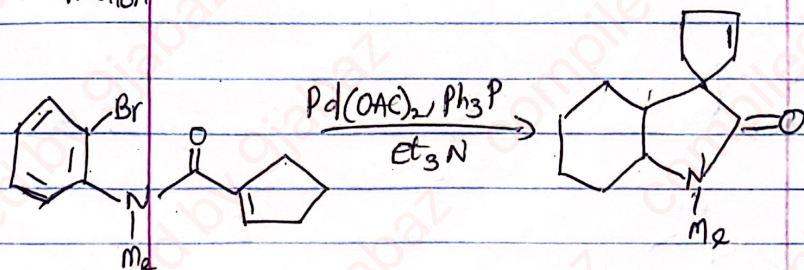
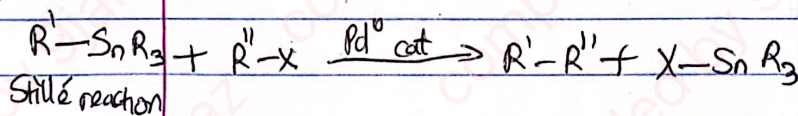


Sometimes, the β hydride elimination takes place away from the new C-C bond, and in such cases, a new stereocenter is formed.

If the starting material is prochiral, the reaction can be made asymmetric by the use of chiral ligands



Sonogashira reaction



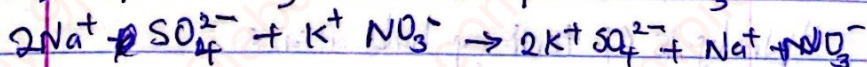
* Draw a reasonable mechanism for the above reaction

Prof. Aderogba's Part

10/04/26

Prof. Aderogba's part

Transformations of Compounds/molecules into different forms occurs through chemical reactions. for examples



Inorganic reactions are instantaneous, because they exists in ion

The reactions of inorganic compounds are reactions of ions. Usually such reactions are instantaneous ~~because~~ ^{because} the ions are already present in the reaction medium.



On the other hand, reactions of the organic compounds are molecular in nature, because the constituent atoms of molecules of organic compounds are firmly bonded by covalent bonds. In this case, for a compound to undergo chemical reactions, it is essential that existing bonds must be broken and new bonds created.

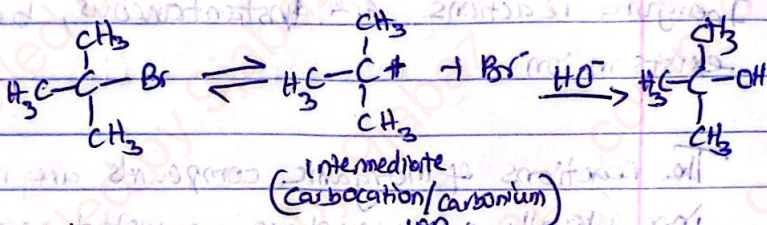
~~At times~~, Usually, the sequence and timing of this bond breaking and making processes are important.

in the study of organic reactions.

Examples

(i) hydrolysis of tertiary halo alkane

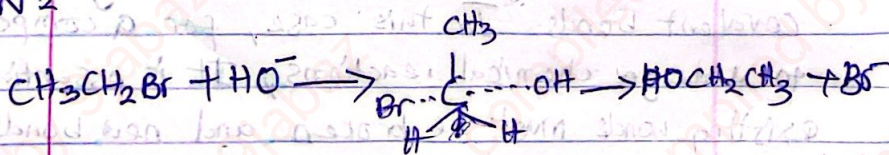
S_N1



When we have a carbocation that is stable, that it can be isolated, we called it isolable

Bond breaking may precede bond formation or vice versa resulting in a stepwise reaction and formation of compound known as intermediate which may or may not be ~~isolable~~ isolable

(ii) S_N2



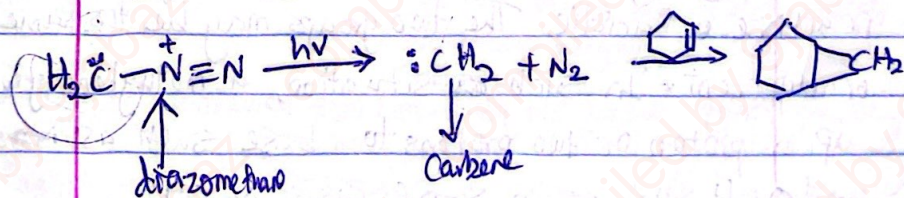
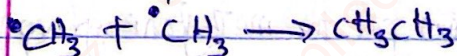
Transition state

Alternatively, both processes may occur simultaneously giving synchronous or concerted step. This reaction results in the formation of transition state which may or may not be isolable.

Alkylation Reactions

It is the transfer of an alkyl group from one molecule to another. The alkyl group may be transferred as an alkyl carbocation, ~~the alkyl group may be transferred~~ a free radical, carbene ~~or~~ their equivalent.

For example, termination reaction of halogenation of methane



Carbenes are neutral compounds containing divalent carbon and are often formed from nitrogen containing molecules called diazo compounds.

This reaction forms new C-C bond (and the two reactions formed are important in the synthesis of organic compound).

Without such reactions, we could not convert molecules with small carbon skeleton to larger ones. The product of the reaction will always have the same number of carbon as the starting material.

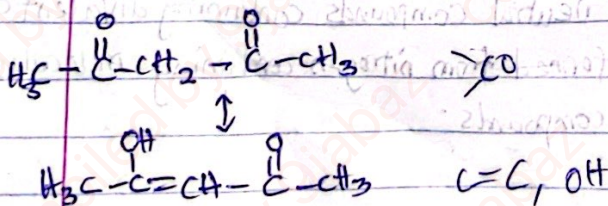
Specific Reactions

Reactive methylene compounds ($X_1 - \overset{\alpha\text{-hydrogen}}{\text{CH}_2} - X_2$)

When a methylene ~~compound~~ ^{group} is present between two strongly electron attracting group such as carbonyl, $-C \equiv N$, $-\text{COOR}$, $-\text{CHO}$, CONR_2 , NO_2 etc.

The hydrogen atom for the methylene group becomes reactive or acidic. The two groups may be the same or different. In such a situation, a methylene gives up a proton or two protons to a base such as ~~meth~~ $\text{Ag}^+ \text{OCH}_2\text{CH}_3$ or in some cases NaOH .

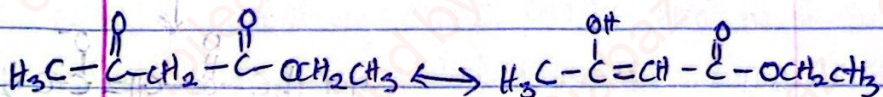
Reactive methylene e.g. acetyl acetone



enol

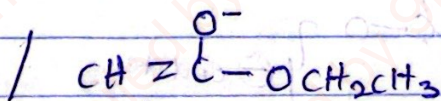
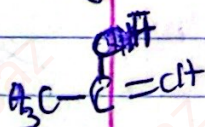
If the reacting methylene compound is symmetrical, the hydrogen atom of the methylene group migrates to either of the ketone group

If the compound is unsymmetrical, only one form is present predominantly and the migration of H-atom depends upon the inductive effect of the alkyl group or other group present in either side of the $-CH_2-$



ethyl acetoacetate

enol only one form

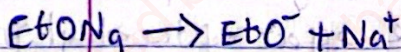
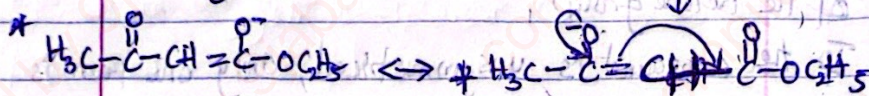
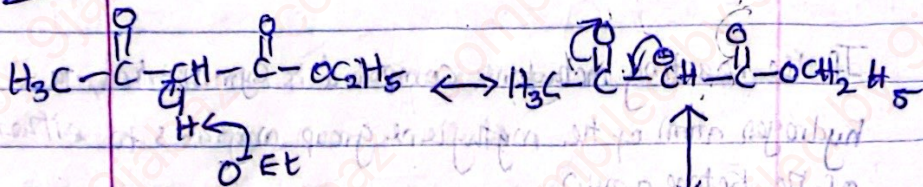


the other oxygen too, is electronegative, so it can only happen on the other side.

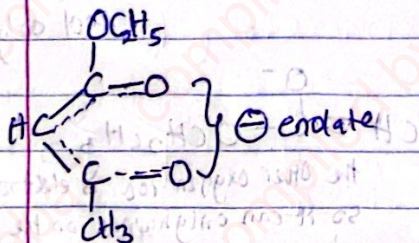
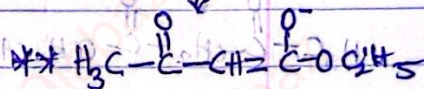
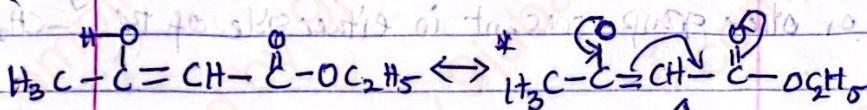
* Proton can be abstracted from both enol and ketone form, are the products obtained from both same or not?

When a molecule containing a active methylene group reacts with a strong base, the proton removal (abstraction of proton) may take place from both ketone and enol form. The resultant enolate form (a carbanion stabilized by an adjacent carbonyl group) obtained by resonance stabilization is the same in both cases.

Ketone

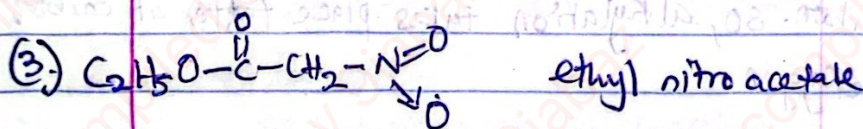
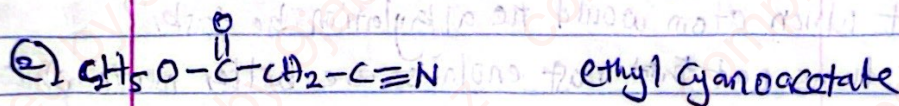
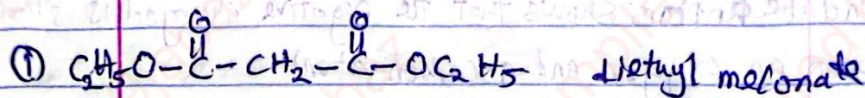


Enol



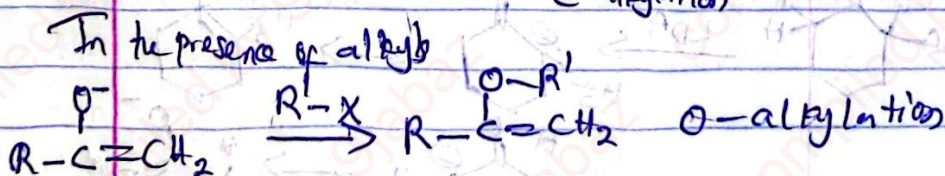
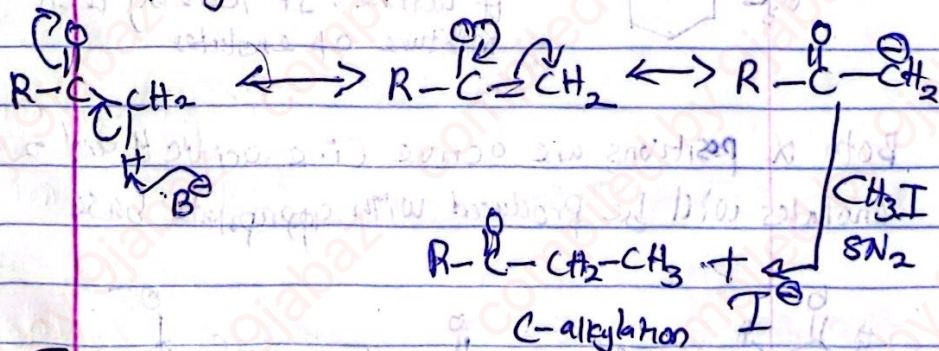
18th April, 2026

Some other examples with reactive methylene groups



NaNH_2 been a stronger base can be used to perform reaction with reactive methylene groups with just one electron withdrawing groups

Alkylation of Enolate



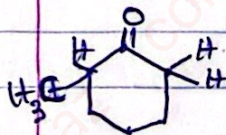
The enolate acts as a nucleophile. The resonance formulation of enolate anions shows that the negative charge is shared between an oxygen and a carbon atom. $\text{H}_2\text{C}=\text{C}(\text{O}^-)\text{R} \leftrightarrow \text{H}_2\text{C}^--\text{C}(\text{O})\text{R}$ (1)

At which atom would the alkylation be faster?

It turns out that most enolates are better nucleophiles at carbon. So, alkylation takes place faster at carbon than oxygen. $\text{H}_2\text{C}=\text{C}(\text{O}^-)\text{R} \leftrightarrow \text{H}_2\text{C}^--\text{C}(\text{O})\text{R}$ (2)

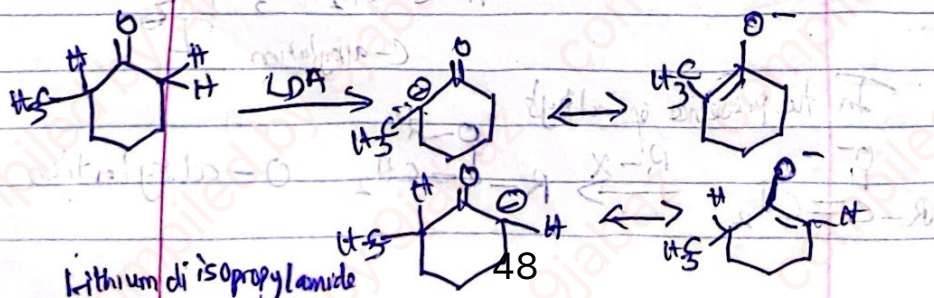
Limitation

- (1) It cannot alkylate a 3° allyl halide due to steric hindrance.
- (2) 2-methylcyclohexanone



This compound has its α_1 and α_2 H active. It thereby leads to a mixture of enolates.

Both α positions are active (i.e. acidic H) and 2 enolates will be produced with appropriate base.

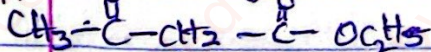


For many ketones, there are at least two (2) possible enolate as a result, mixtures are obtained in the alkylation

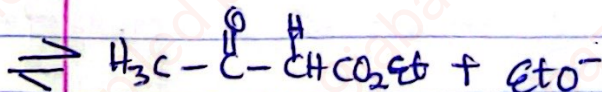
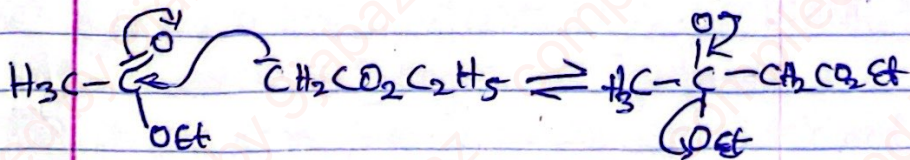
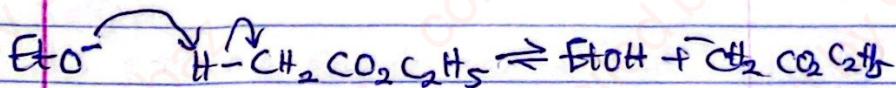
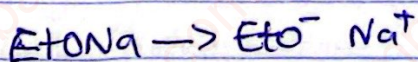


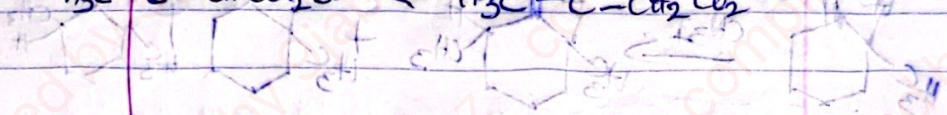
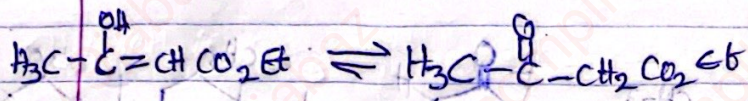
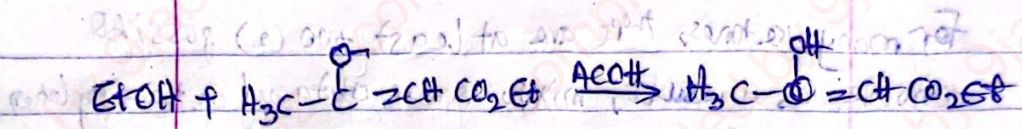
Important Examples

① Application in the synthesis of ethylacetoacetate



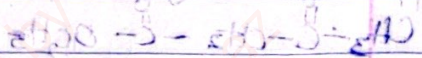
Ethylacetoacetate is the ethylesters of acetoacetic acid $\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{COOH}$. It is prepared by condensation of 2 molecules ethylacetate in the presence of a base NaOEt . This is an example of Claisen condensation reaction





Properties of Ethylacetoacetate (Physical)

① Ethylacetoacetate is a colorless liquid.



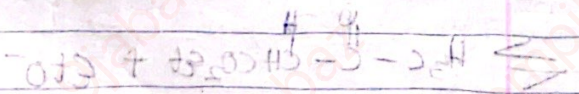
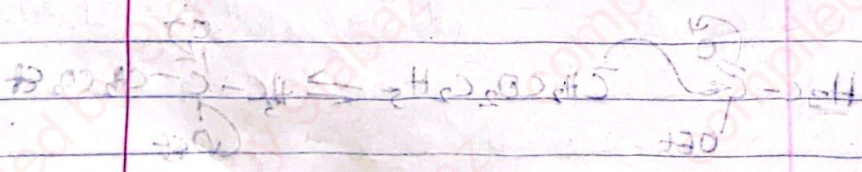
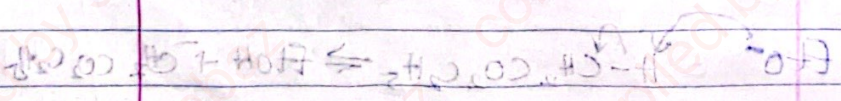
② Ethylacetoacetate is the simplest of acetoacetic acid.

③ Ethylacetoacetate is a weak acid. It is prepared by condensation of

a molecule of ethyl acetate in the presence of a base.

Reaction: This is an example of Claisen condensation.

Reaction



Properties of ~~Triethyl~~ Acetoacetate — P

It is a colourless, pleasant smelling liquid, with boiling point 181°C and the reagent is sparingly soluble in water ~~but~~ readily soluble in alcohol (i.e. ethanol) and ether. It is neutral.

Chem

- ① It behaves as a ketone and as an alcohol, (because of the presence of OH) — because it exhibits keto-enol tautomerism

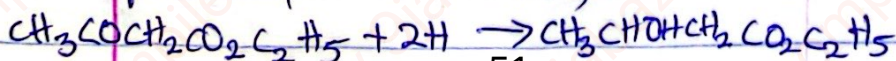


The equilibrium mixture contains both forms but the percentage of the enolic form, 7.5% to show that the equilibrium contains both species.

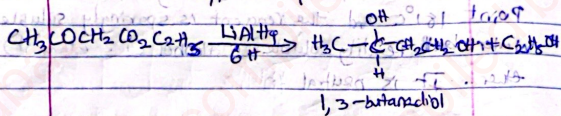
Reduction

In the presence Sodium amalgam (NaHg) and alcohol or hydrogen in lithium aluminium hydride (LiAlH_4) in the presence of hydrogen and pyridine.

The ketonic form forms β -hydroxybutyric ester and the equations of the reaction;



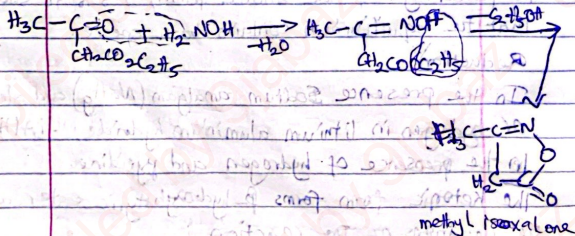
We can also carry this reaction in the absence of pyridine, and we obtain a different product



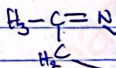
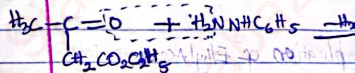
① Common reaction - Test for Carbonyl

② Reaction with Hydroxylamine

③ Ketone form forms an oxime which immediately loses a molecule of alcohol (ethanol) and forms methyl isoxazalone.

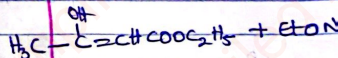


④ Reaction with phenylhydrazine
It forms phenyl hydrazone which uses ethanol and forms 3-methyl-1-phenyl



Reactions Involving the Ester

① Reaction with Na, or NaOH + of the reagent

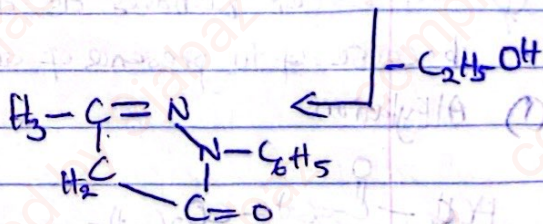
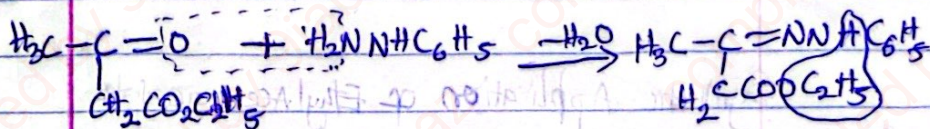


② Acetylation reaction

It happens in the presence

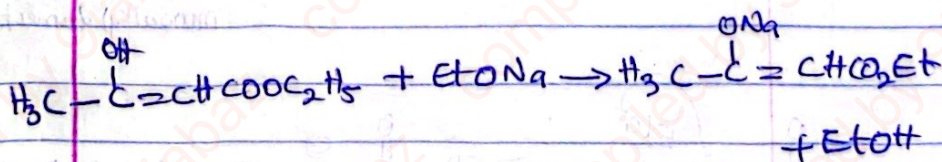
⑤ Reaction with phenyl hydrazine

It forms phenyl hydrazone which uses a molecule of ethanol and forms 3-methyl-1-phenyl pyrazolone



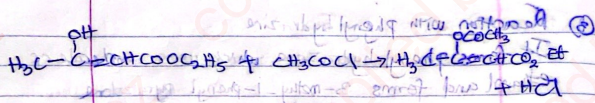
Reactions Involving the Enolate form

① Reaction with Na , or NaOEt to form sodium derivative of the reagent



② Acetylation reaction

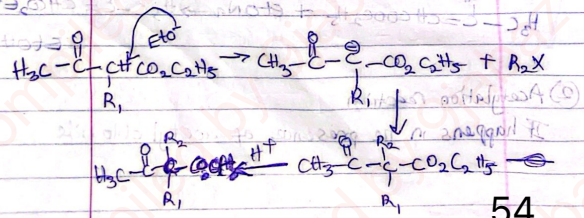
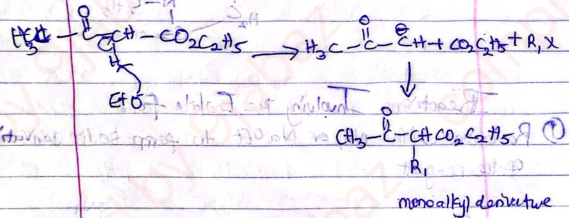
It happens in the presence of acetyl chloride



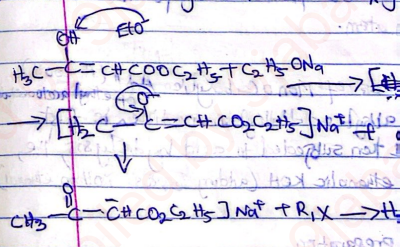
Synthetic Application of Ethyl Acetoacetate

- ① The ester behaves as acid forming carbanion H_3C because of the presence of active methylene group.

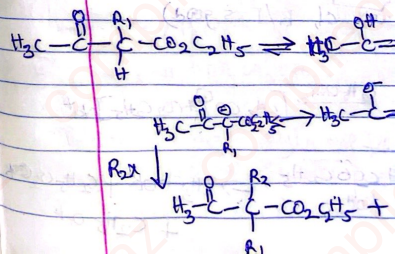
① Alkylation



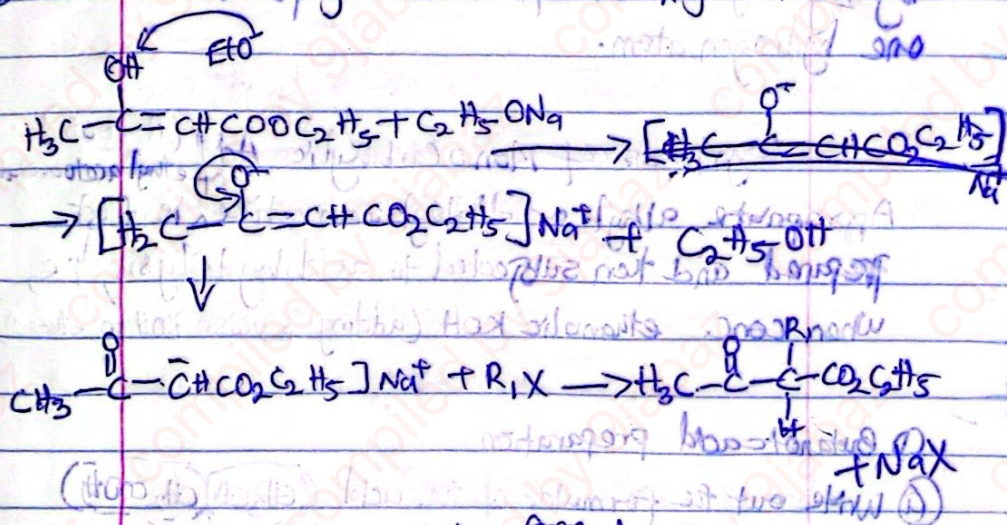
The carbanion is resonance stabilized and can undergo nucleophilic substitution reaction. obtain ① mono and dialkyl derivative can be g



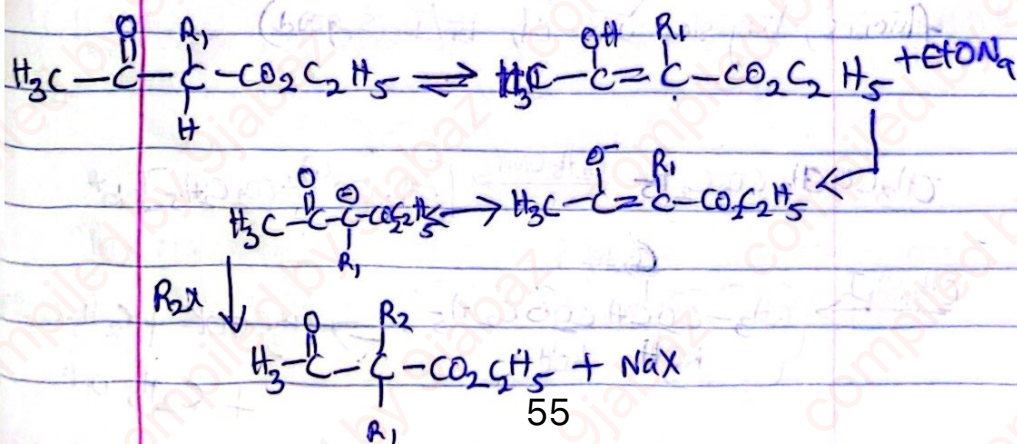
For the reaction to proceed, to form the monoalkyl derivative must be in equilibrium.



The carbanion is resonance stabilized and can undergo nucleophilic substitution reaction. obtained as
 ① mono and dialkyl derivative can be given below



For the reaction to proceed, to form dialkyl derivative, the monoalkyl derivative must be converted to the enol form.



Both alkyl group cannot be simultaneously introduced into one single step because the hydrogen can only be displaced by hydrogen NaOEt from the endic form which contains one hydrogen atom.

Synthesis of Monocarboxylic Acid ($R-COOH$)

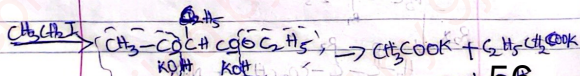
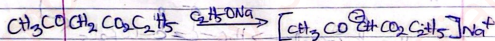
Appropriate alkyl or dialkyl derivative is first prepared and then subjected to acid hydrolysis, i.e., when conc. ethanolic KOH (adding excess KOH in ethanol)

Butanoic acid preparation

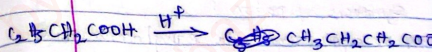
- Write out the formulae of the acid ($CH_3CH_2CH_2COOH$)
- Identify acetic acid nucleus
- The alkyl group attached to the acetic acid nucleus is introduced

$CH_3CH_2CH_2COOH$ (almost impossible with

fluorine, very slow with Cl, Br/I is good)

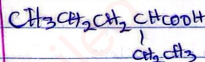


+ C_2H_5 56

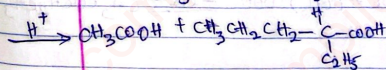
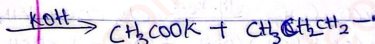
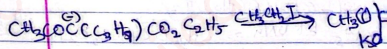
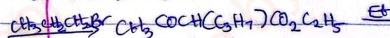
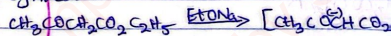


2-ethylpentanoic acid

2-ethylpentanoic acid synthesis
Ethyl propyl acetic acid



Synthesis

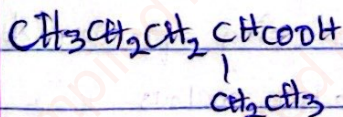


Introduce the larger alkyl group before methyl addition (because of steric

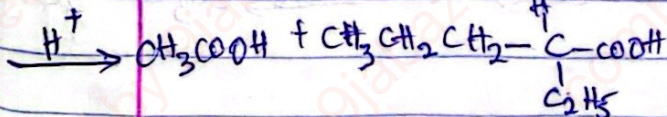
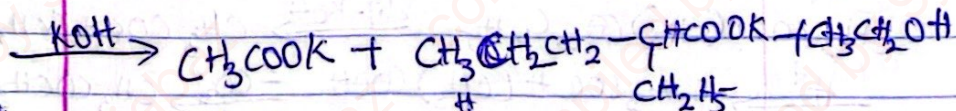
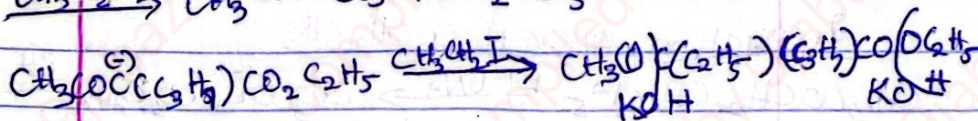
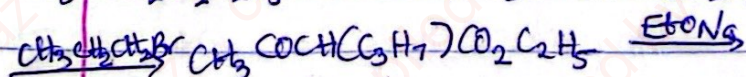
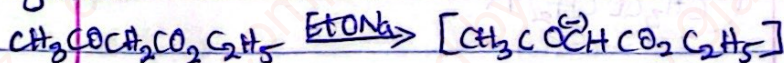


24/04/26

2-ethylpentanoic acid synthesis
Ethyl propyl acetic acid



Synthesis



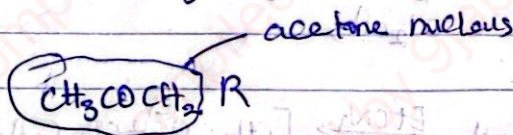
Introduce the larger alkyl group before the smaller one in dialkyl addition (because of steric hindrance)

Synthesis of ketone

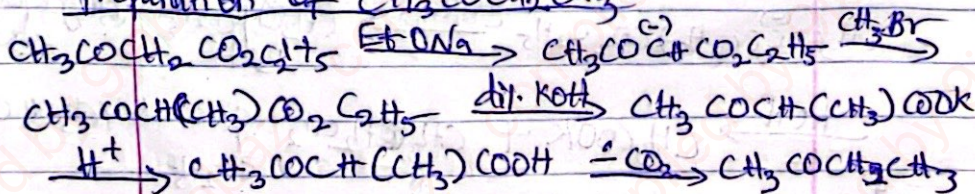
Ketone can be synthesized via ethyl acetoacetate provided it contains the group, $\text{CH}_3\text{CO}-$

Steps

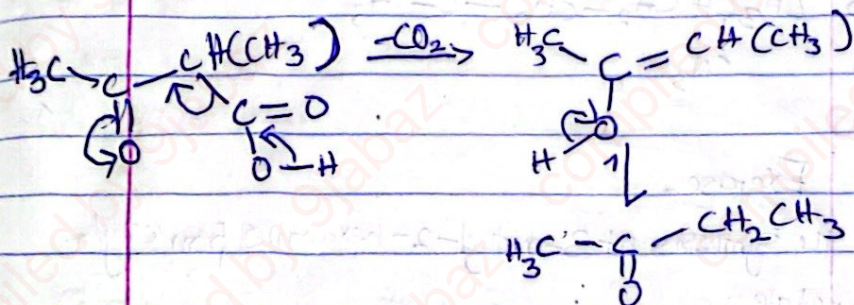
- (1) Write out the formula of the ketone
- (2) Within the formula of the ketone, identify the acetone nucleus.
- (3) Alkyl group attached to the nucleus (acetone needed) is/are introduced to the ester one at a time
- (4) Carry out ketonic hydrolysis using aqueous or dilute KOH



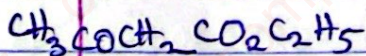
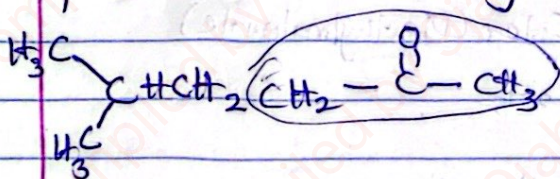
Preparation of $\text{CH}_3\text{COCH}_2\text{CH}_3$



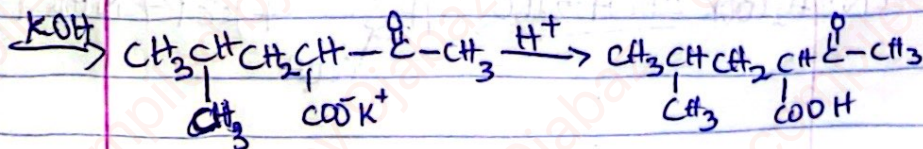
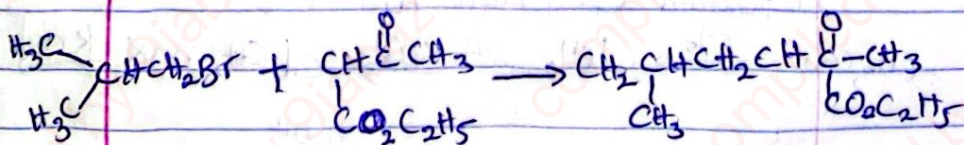
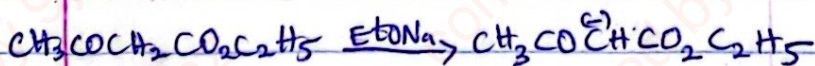
Mechanism of Decarboxylation

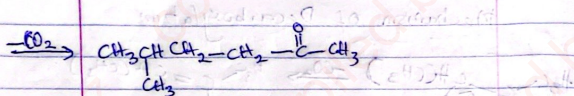


Preparation of 5-methyl-2-hexenone



In order to prepare the ketone above by ethyl acetate synthesis, isobutylbromide must be made use of

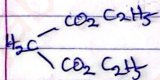




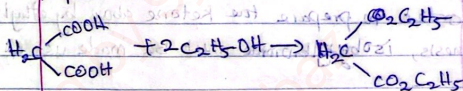
Exercise

Outline the synthesis of 3-methyl-2-hexanone from ethyl acetate

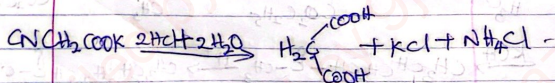
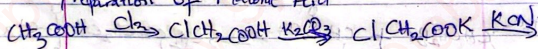
Malonic Ester (Dimethylmalonate)



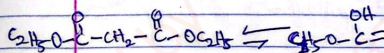
It is prepared from malonic acid



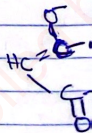
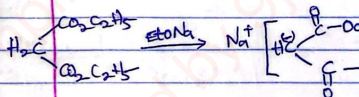
Preparation of Malonic Acid



In presence of 2 carbonyl groups, on side of methylene group exerts negative effect. The effect added to the form stabilized anion and makes the H more active. The compound exists in the following form but contains a minute quantity of enol mixture

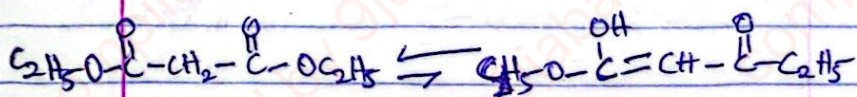


malonic ester can also exhibit o-a

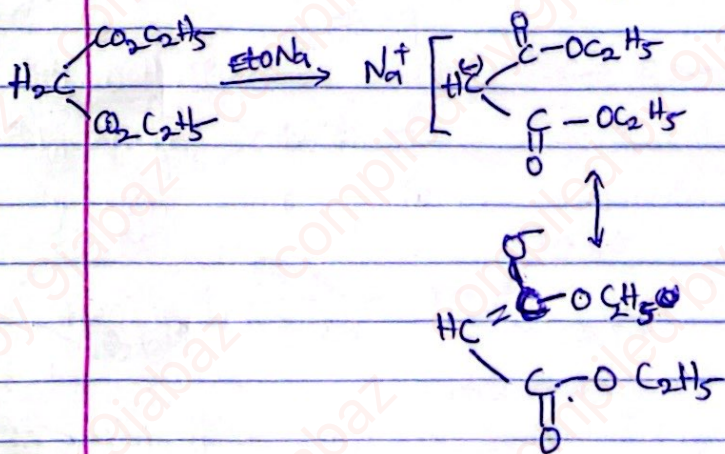


The anion acts as a nucleophile in nucleophilic substitution reactions

In presence of 2 carbonyl groups, one each on either side of methylene group ~~exert~~ negative inductive effect. The effect added to the formation of resonance stabilized anion and makes the H of the methylene group acidic. The compound exists in the following keto-enol form but contains a minute quantity of enol form in the equilibrium mixture



malonic ester can also exhibit O-alkylation & C-alkylation



The anion acts as a nucleophile and can participate in nucleophilic substitution reaction

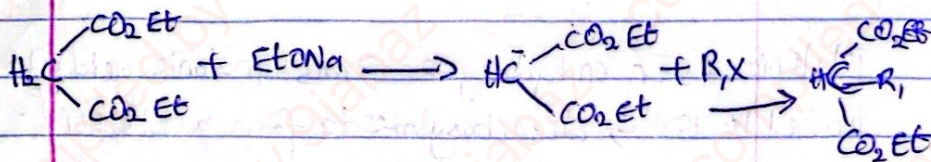
25th April, 2026

KOH on ethand attack carbonyl

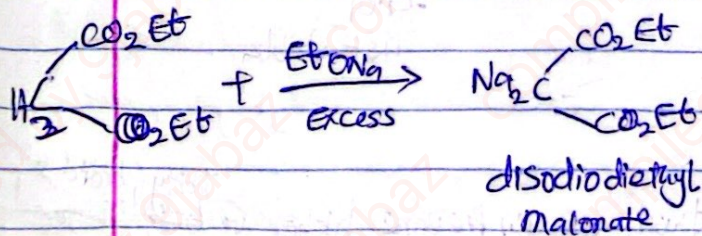
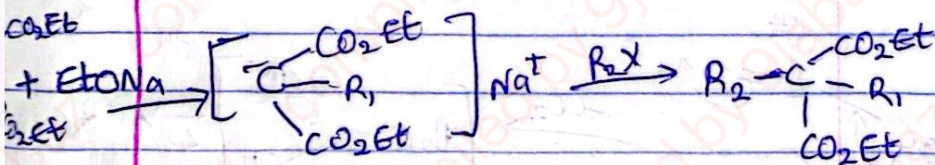
KOH dilute attack carbonyl ester

Example of nucleophilic substitution reaction

(i) Reaction with alkyl halide (alkylation)

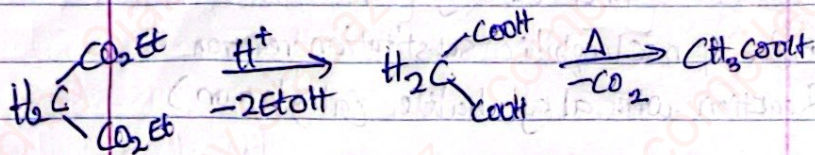


Mono alkyl ester contains an active hydrogen and can undergo further nucleophilic substitution forming dialkyl ester.



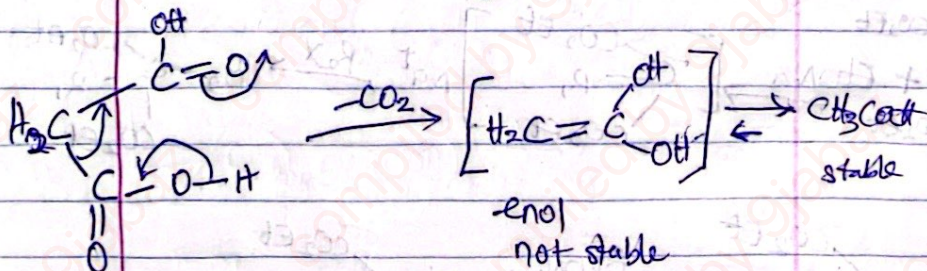
Synthetic Application

Synthesis of Monocarboxylic acid



Malonic ester on hydrolysis forms malonic acid when heated to 150°C , decarboxylates to form acetic acid.

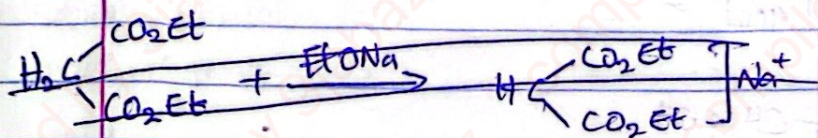
Mechanism of Decarboxylation



Using this method, we can prepare higher ~~carboxylic acid~~ ^{fatty acids} as follows;

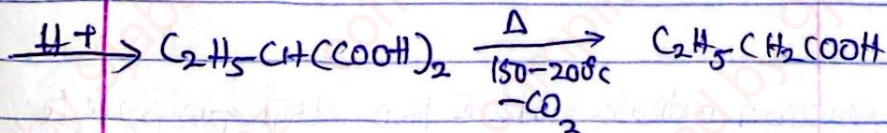
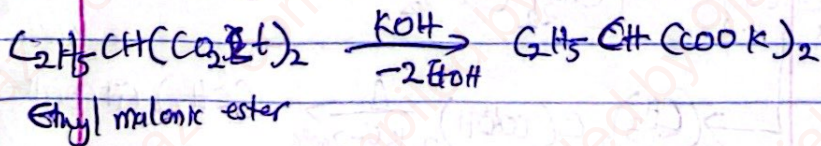
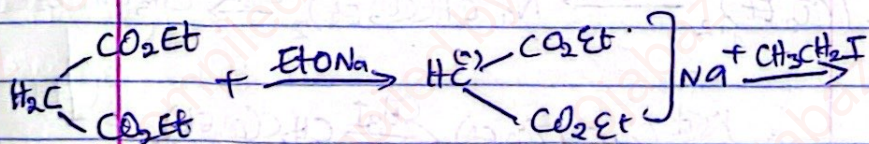
- (i) Write out the structural formula of the acid required
- (ii) Identify acetic acid nucleus from the structural formula of the acid required.

i) Prepare sodium malonic, and treat it with an appropriate alkyl halide followed by ~~ethyl~~ acid hydrolysis.



Synthesis of Butanoic Acid

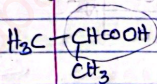
i) $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$



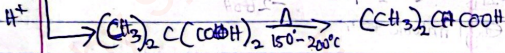
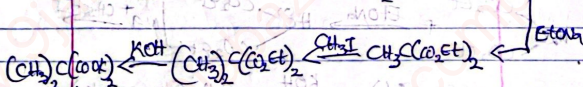
ii) Synthesis of α -branched

Substituted fatty acids can be prepared by first converting mono alkyl malonic ester to dialkyl malonic acid by treatment with NaOEt , then alkyl halide. Alkyl ester form obtained when ~~you~~ refluxed with

Kott and acidified HCl to form dialkyl malonate (11)
acid which decarboxylate on heating and forms
dialkyl acid



dimethyl acetic
acid.

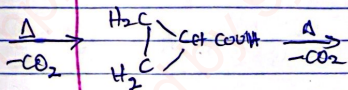
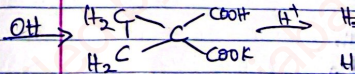
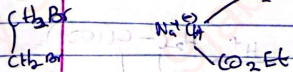


This reaction indicates where two alkyl groups are the same, the dialkyl derivative is obtained in one operation by taking 2 moles of NaOH, 1 mole of diethyl malonate and 1 mole of alkyl halide. For unsymmetrical dialkyl derivatives, the mixture with excess alkyl halide.

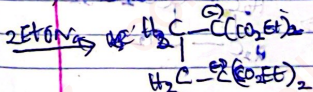
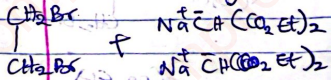
18) Synthesis of Cyclic Compounds

⑧ Synthesis of Cyclic Compounds
Alicyclic compounds may be prepared between certain dihalogen derivatives and Sodium malonic ester

Preparation of glycerol
CO₂Et



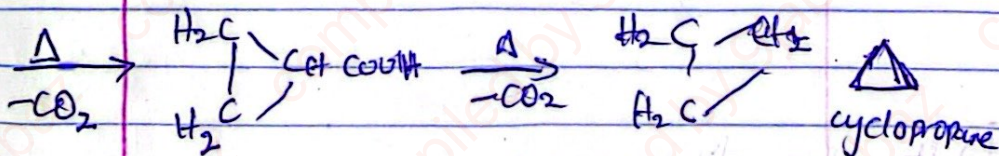
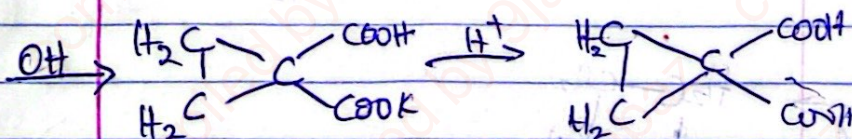
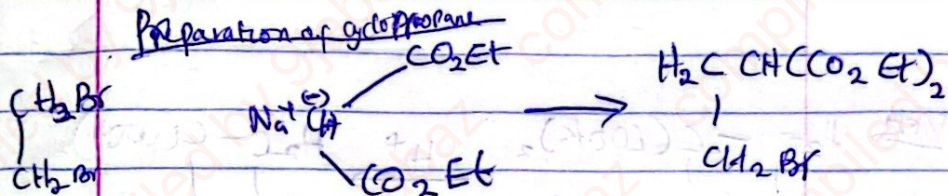
Preparation of cyclobutane



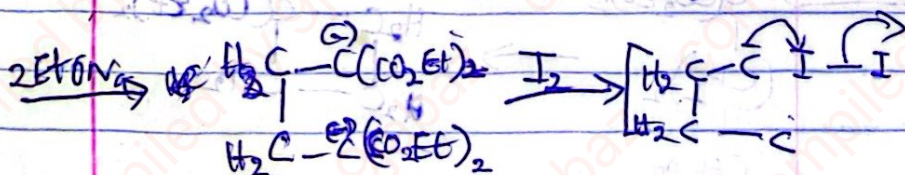
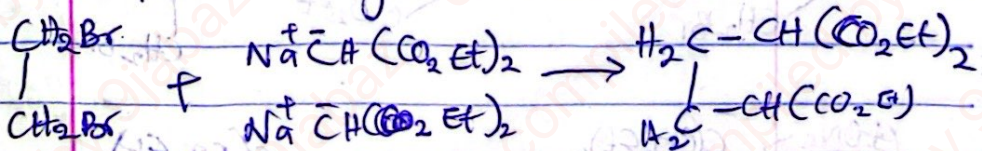
③ Synthesis of Cyclic Compounds

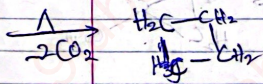
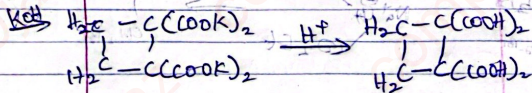
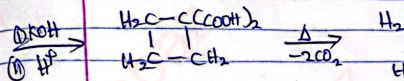
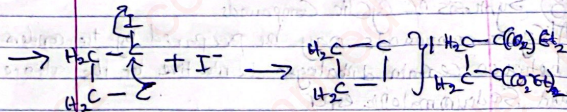
Alcyclic compounds may be prepared by the condensation between certain dihalogen derivative of the alkane and Sodium malonic ester

Preparation of cyclopropane

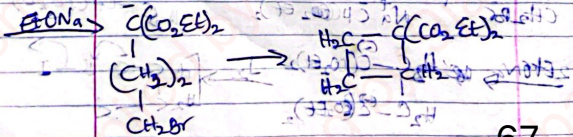
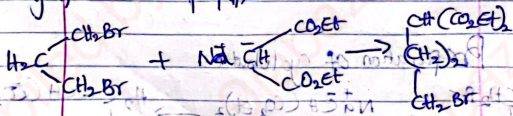


Preparation of cyclobutane

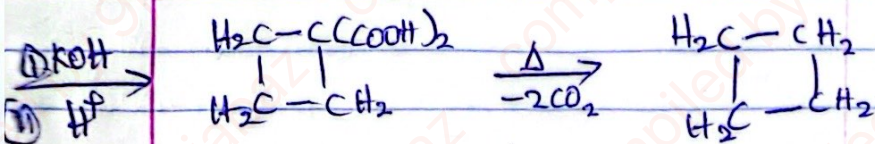




b) Using 1,3-dibromopropane



By using appropriate dihalogen derivative under suitable conditions, it is possible to synthesize compounds containing 3-7 carbon atoms.



By using appropriate dihalogen derivative of the alkane under suitable conditions, it is possible to prepare rings containing 3-7 carbon atoms.

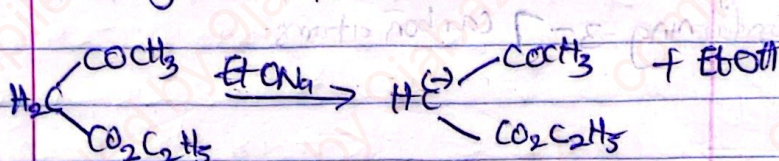
Alcyclic compounds

Preparation of Cyclohexane (from ethylacetoacetate)



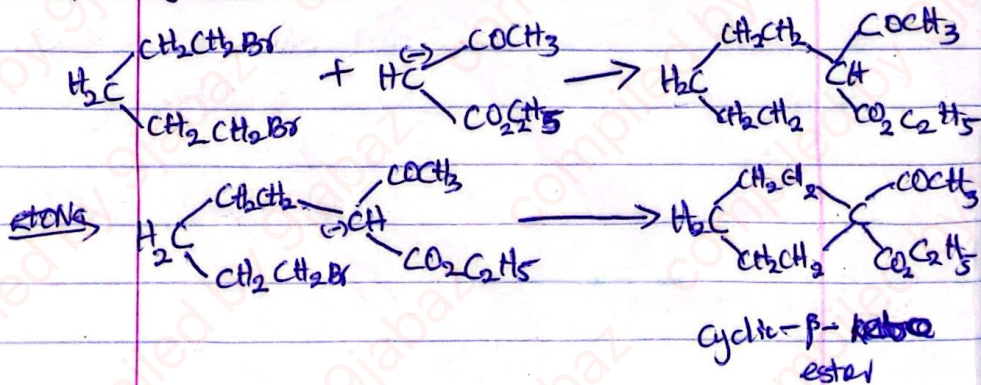
① formation of enolate ion

Ethylacetoacetate reacts with a strong base, i.e. $\text{Na}^+ \text{O}^- \text{C}_2\text{H}_5$ in ethanol. The base selectively deprotonates the acidic methylene to form a stable enolate ion



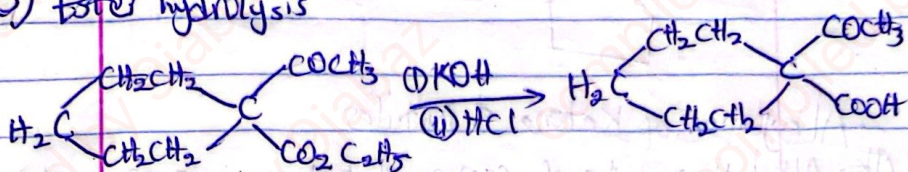
② Alkylation

Treat the enolate ion with 1,5-dibromopentane or 1,5-dibromooctane in this case. Intramolecular displacement of the bromides results in the formation of the cyclic β -keto ester



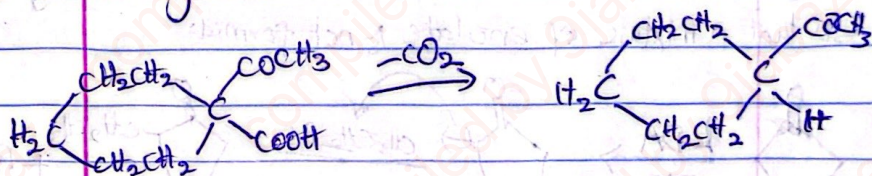
~~Treat the~~

③ Ester hydrolysis



Reflux the cyclic ester with dilute acid, this hydrolyses the ester group to carboxylic group creating a cyclic β -keto acid

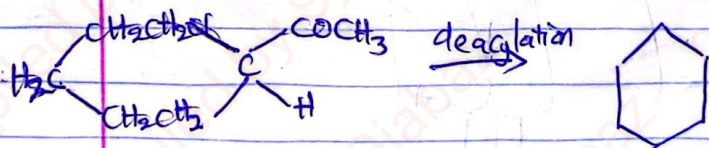
④ Decarboxylation



Heat the resulting β -keto acid, this promotes loss of CO_2 leaving behind an alicyclic methyl ketone

Acetoacetic acid or ethyl acetoacetate method can

prepare 3, 5, 6 & 7 carbon ring, except 4, because
4 will lead to formation of tetrahydropyran



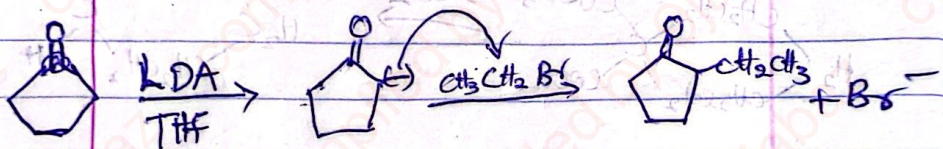
4 - ~~Carbonyl~~ rings will lead to tetrahydrofuran



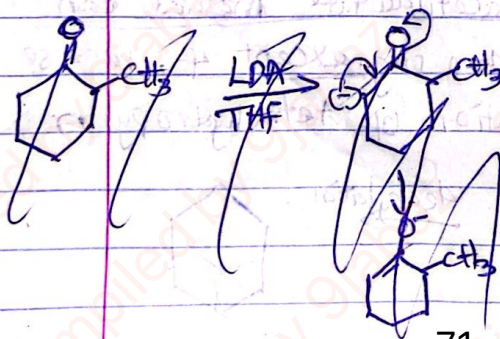
Alkylation of Ketone & Nitriles

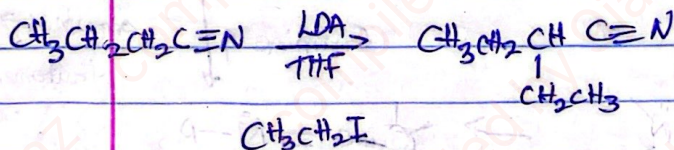
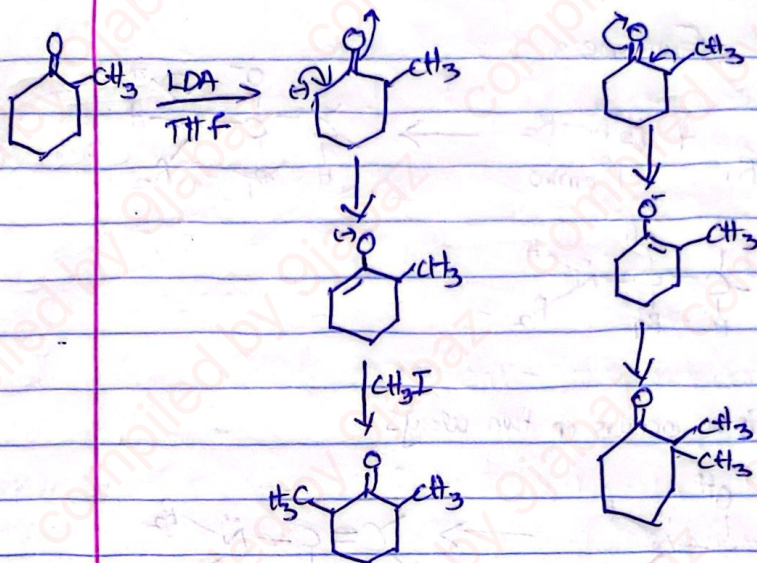
~~Alkylation~~ Alkylation of the α -carbon of ketone gives us another way to form a new C-C bond. The alkylation is carried out by removing a carbon from the α -carbon with a strong base such as LDA (lithium diisopropyl amide) $\text{LiN}[(\text{CH}(\text{CH}_3)_2)_2]$ or NaNH_2 (sodium amide)

This procedure works best with ketone that are symmetrical so that a mixture of enolate is not formed.



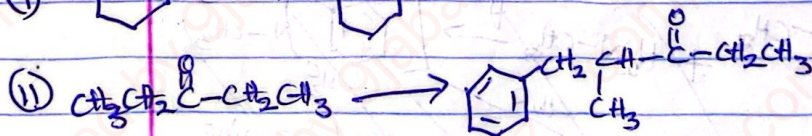
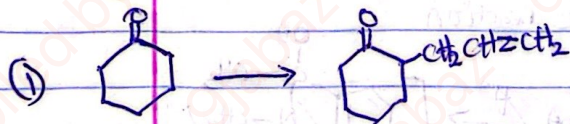
But if the ketone is unsymmetrical



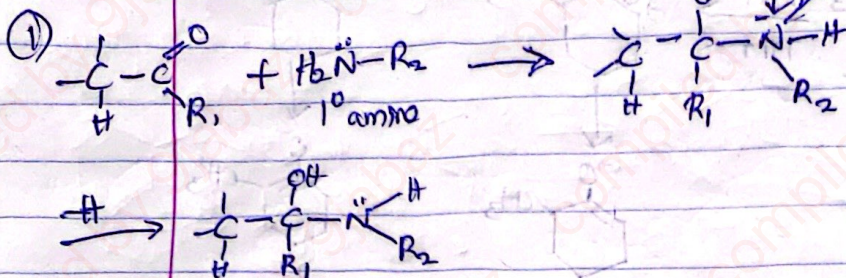


Exercise

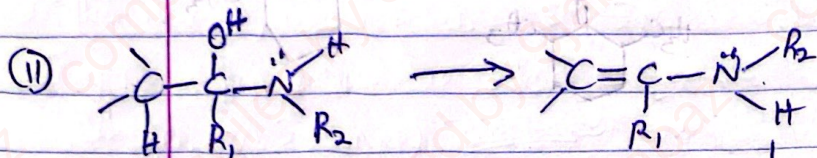
How could each of the following compound be prepared from the given starting material.



Enamines

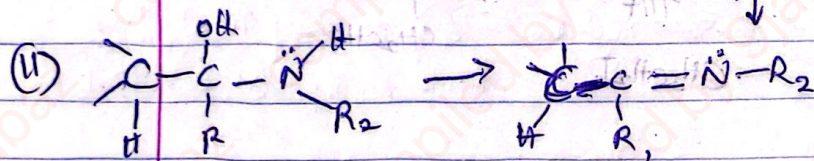


Dehydration occurs in two ways



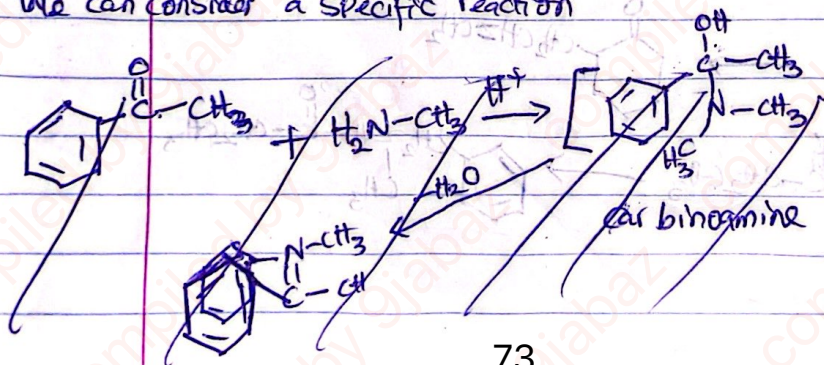
Enamine $\downarrow$

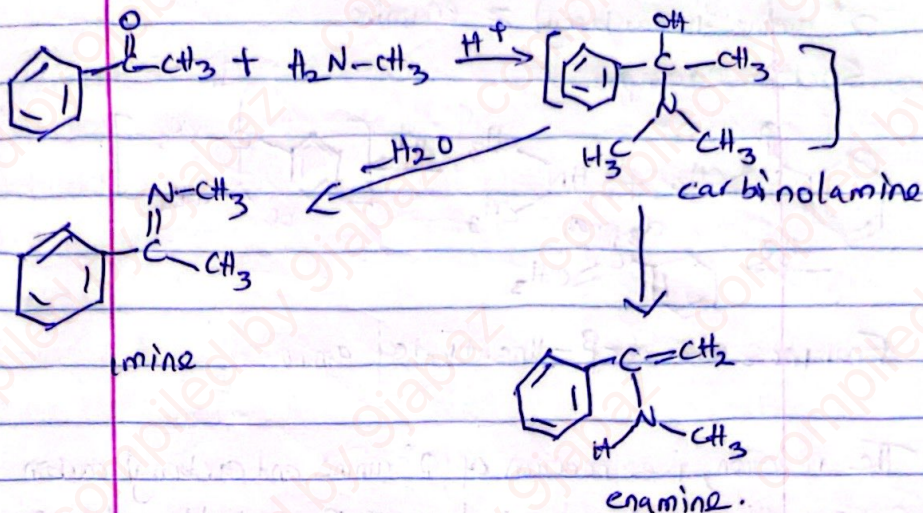
enamines $\rightarrow$ imine
tautomerism



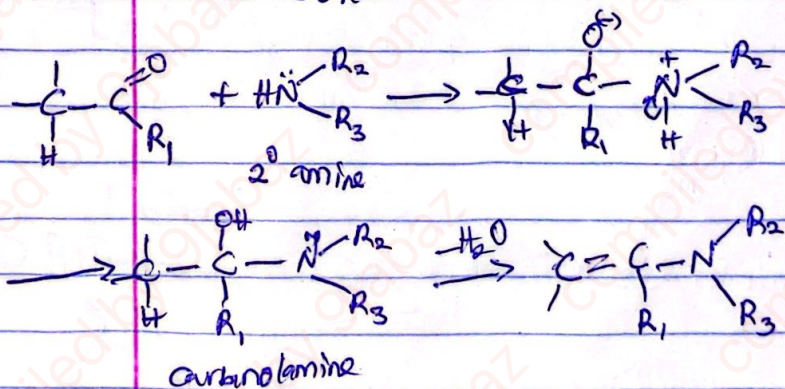
imine

We can consider a specific reaction



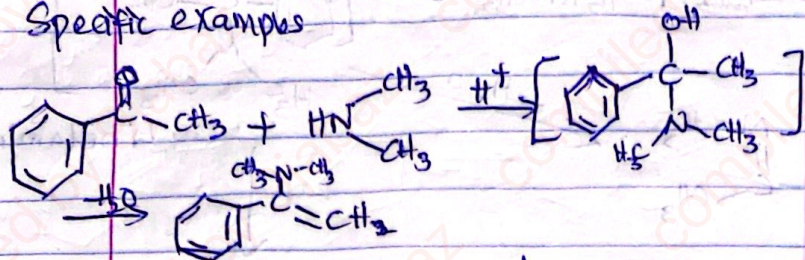


In this case, the reaction of 1° amine, carbonyl compound, ketone and aldehyde, enamine-ketone tautomerism is possible and the equilibrium lies on the imine side, because C=N bond is most stable than the C=C bond.



2° amine + carbonyl = enamine

Specific examples



Enamines are α - β -unsaturated amine

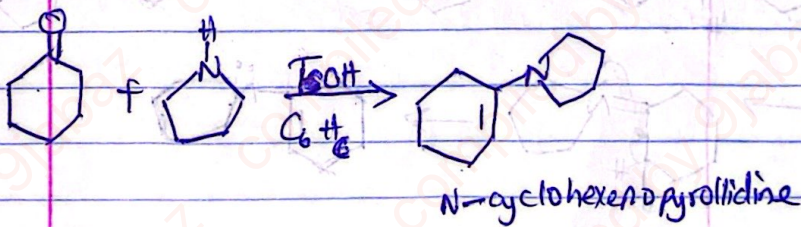
* The reaction, i.e. reaction of 2° amine and carbonyl carbon cannot form amine due to lack of second H-atom on Nitrogen on 2° amine, ~~Thus~~ So we have an alkene, this special alkene is called enamine. The word is derived from ~~the~~ -ene used from the suffix alkene and the word amine from amine alkene + amine.

Enamine are referred to α - β -unsaturated amine and their most common methods of Preparation is their reaction between a carbonyl compound which contains at least one α -H and 2° amine.

Note

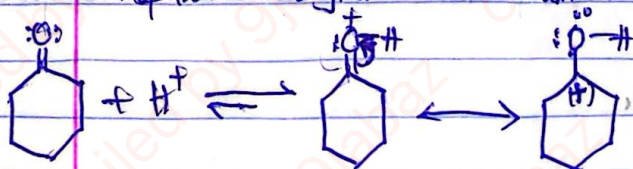
- ① Enamine derived/obtained from ketones are more stable than those obtained from aldehyde.
- ② Enamine derived from acyclic 2° amine are less stable than those from cyclic 2° amines. Example of cyclic 2° amines are pyrrolidine and piperidine.

Reaction between cyclohexanone and pyrrolidine

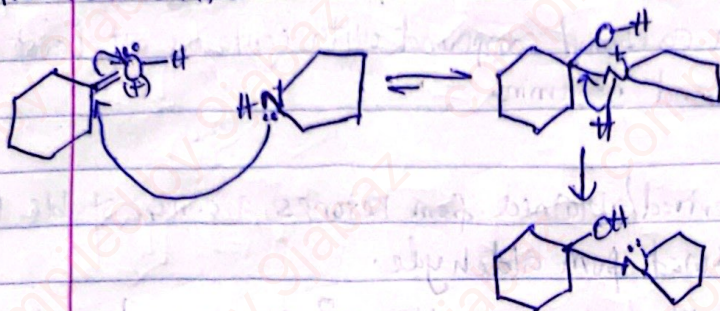


Mechanism (Cyclohexanone)

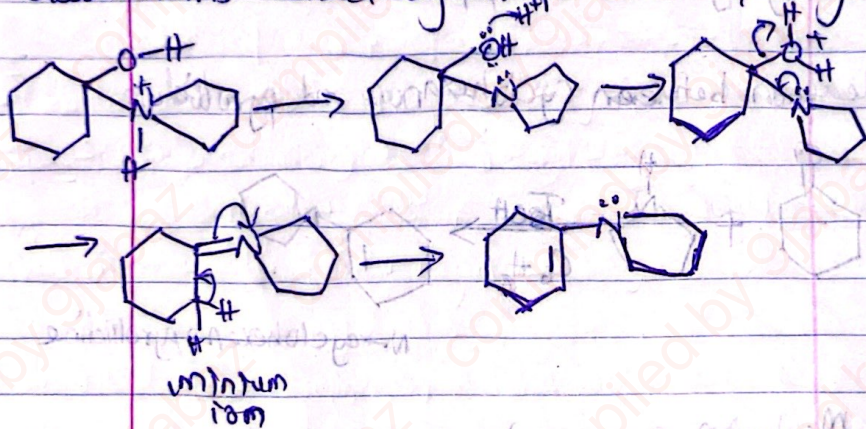
① Protonation of the Carbonyl in acidic medium



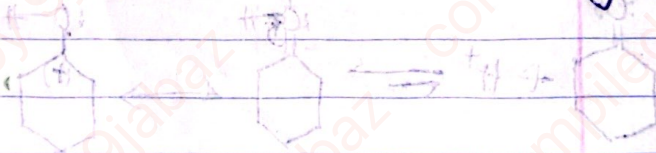
2) Pyrrolidine undergoes nucleophilic addition to carbonyl to give a carbinamine

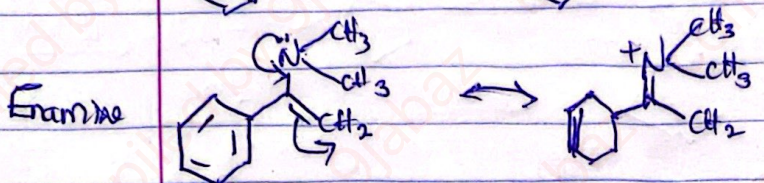
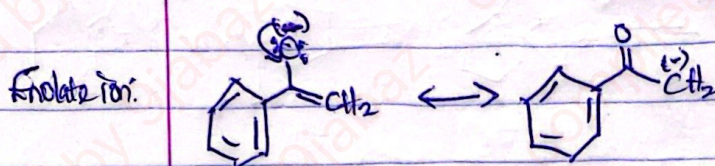
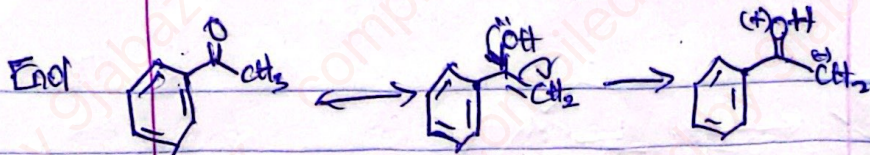


3) The carbinamine dissociates by loss of water. This dissociation is assisted by lone pair donation of Nitrogen.



* The iminium ion is deprotonated in the direction to give a $C=C$





Enamines are closely related to enols and enolate ion, Ketone exists in solution in equilibrium with the enol tautomerism

- Enolate ion exists as a resonance hybrid in which the $-ve$ charge resides primarily on the carbonyl oxygen of $\alpha-C^-$
- Charge delocalization occurs in enamine in which the α -Carbon bears the formal negative charge

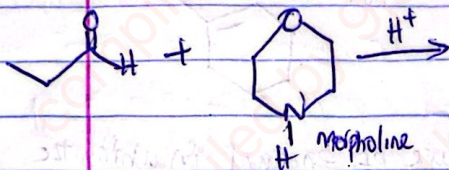
In all of these compounds, a lone pair of electrons is conjugated in π -systems of the $C=C$ bond. These interaction leads nucleophilic character to the α -carbon atom in each case.

However, there are significant difference between these types of nucleophilic reagents

① N is a better electron pair donor than oxygen, as a result, an enamine is more nucleophilic than phenol.

② Enamines being neutral molecules are however less nucleophilic than enolates which are anions.

Exercise: Draw the structure of the enamine that can be formed in these reactions.



② Write the structure of the carbocation intermediate and the enamine product formed in the reaction of each of the following

(a) propanal + diethylamine

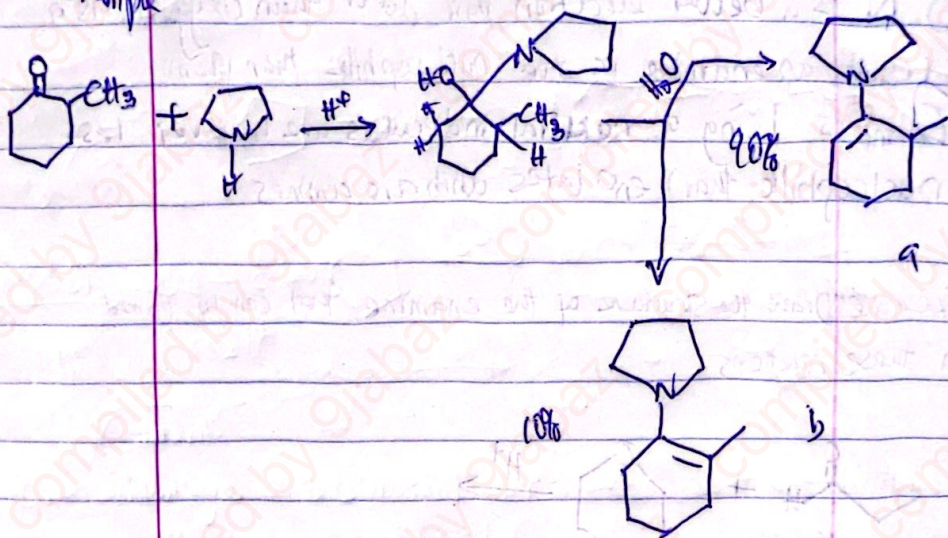
(b) acetone + piperidine



Two enamine can be formed in an unsymmetrical ketone which can react two side from the carbonyl.

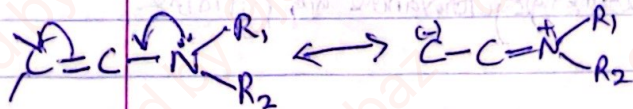
Eg reaction of 2-methylcyclohexanone and pyridine

Example



The reaction produces a mixture of enamine in which the less substituted isomer will dominate, this is because an enamine is stabilized by the interaction of the alkene π system. Steric interaction of the methyl group on the cyclohexyl group and the methylene group of pyrrolidine ring reduces the extent of the conjugation in the more substituted case.

Alkylation of Enamine



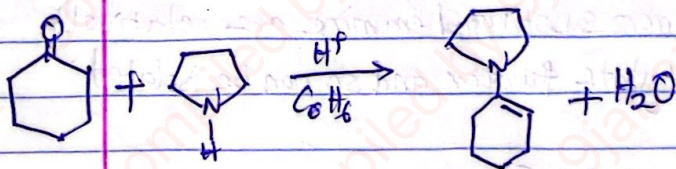
The enamine can be alkylated at the nucleophilic carbon

by reactive alkyl halides. The product of alkylation is an iminium ion which is readily hydrolyzed to regenerate the carbonyl group.

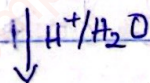
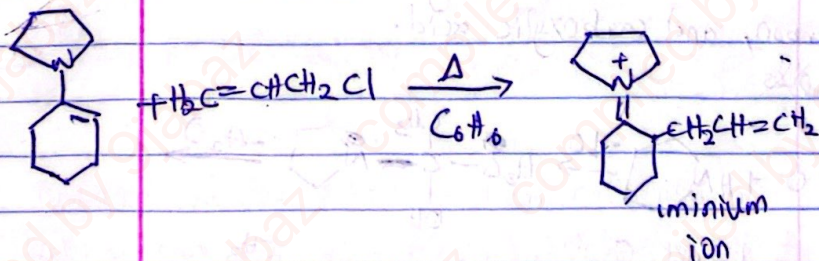
The following are examples of reactive alkyl halides;

1°-alkyl and benzylic halide, α -halo ether and α -halo nitrile, acyl chloride, α - β -unsaturated nitriles

Best yield are obtained with reactive halides like benzyl and allyl halides to halo ester and halo ketone



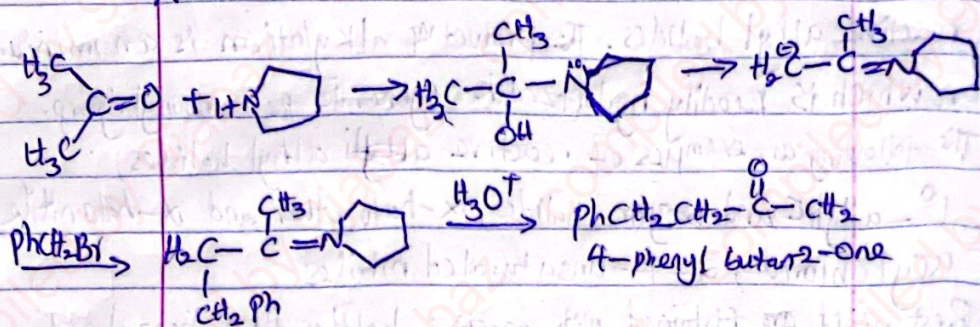
N-cyclohexenopyrrolidine



2-allylcyclohexanone

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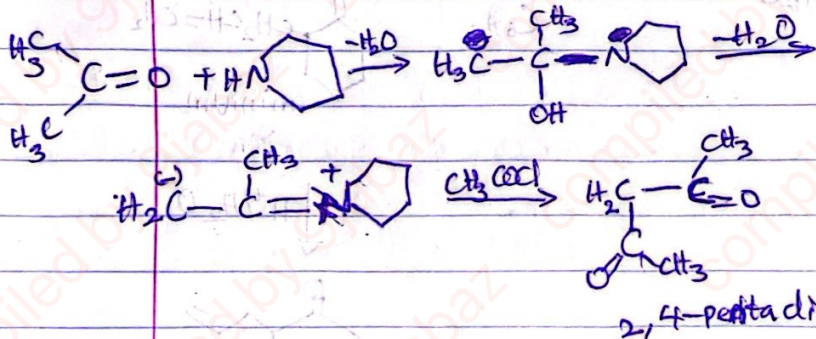
Comment:

One advantage of this method over that of direct action the ketone is that mono substituted enamine are relatively difficult to alkylate further and so can be isolated.

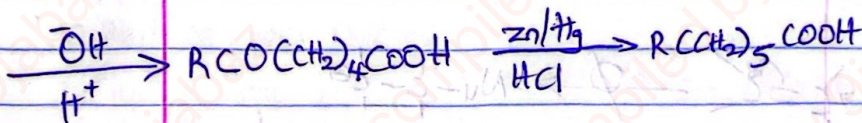
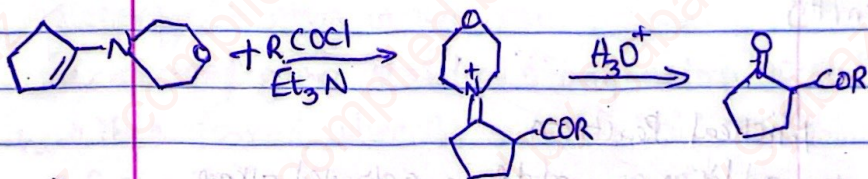
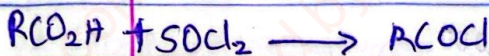
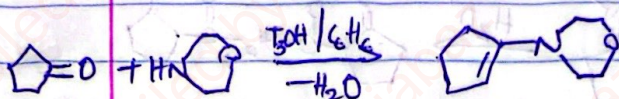
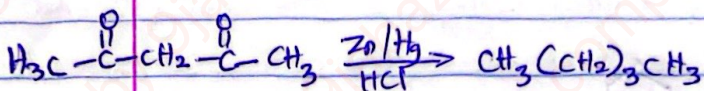
Acetylation Of Enamines

This particular reaction can give substituted ketone, hydrocarbon, and carboxylic acid.

Examples

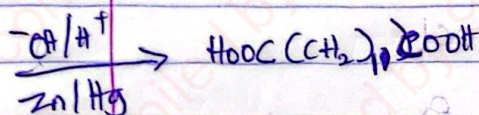
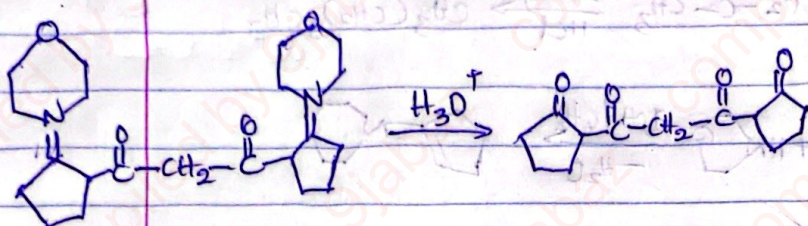


Penta-2,4-dione can be reduced with Zn amalgam Zn/Hg and HCl to get the hydrocarbon



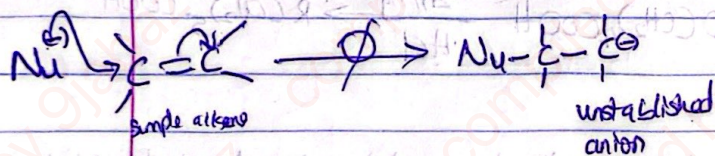
Comment: In this way it is possible to extend the chain of a monocarboxylic acid by 5-carbon at a go, if cyclohexenone^{enamine} is used, the chain can be extended by six carbon atoms at a go.

COOH

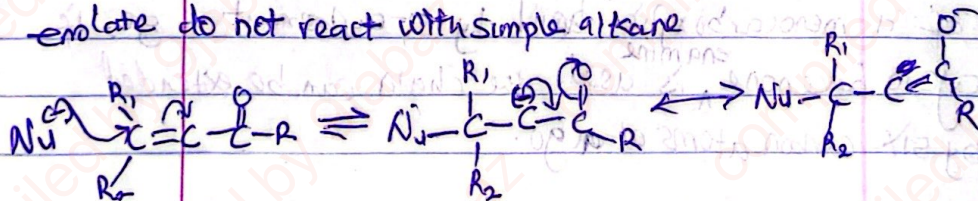


Michael Reaction

It is the addition of enolate to activated alkene



enolate do not react with simple alkene

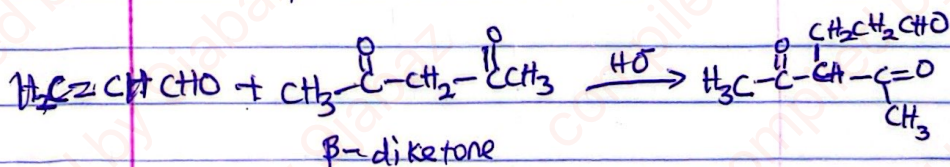


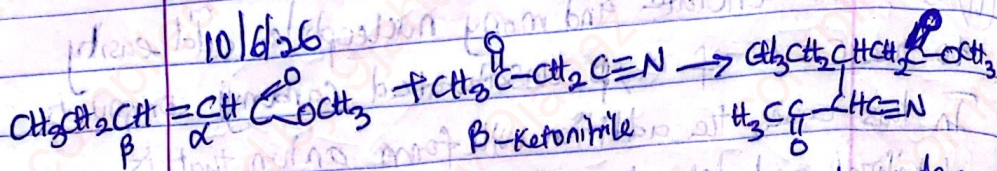
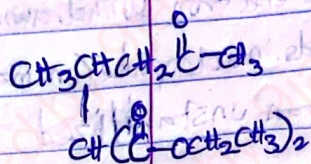
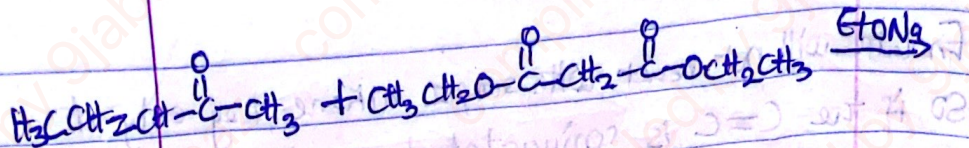
Enolate will not react with simple alkene they only do so if the $C=C$ is conjugated to an electron withdrawing group. $C=C$ are unreactive towards nucleophile (enamine) because the addition ~~with~~^{require} formation of an unstabilized anion.

(ii) ~~C=C~~ The enolate and many nucleophiles ^{reacts or} add easily to the $C=C$ of α, β unsaturated carbonyl compounds. In this case, the addition will form an anion that is stabilized and delocalization of the charge unto the electronegative atom in this case, oxygen.

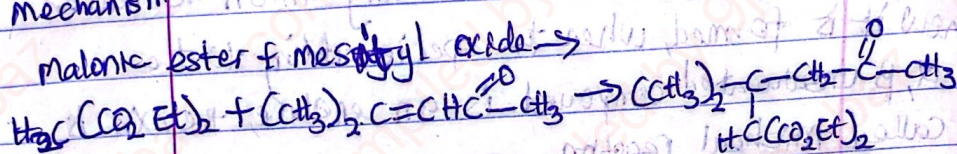
The carbonyl group stabilizes any anion no matter how it is formed, when the species adding to the α, β unsaturated compound is an enolate, the rxn is called Michael reaction.

The enolate that works best in Michael reaction are β -diketone, β -diesters, β -ketoesters and β -ketonitriles, ~~this react~~



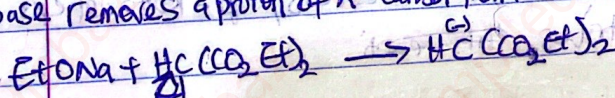


A wide variety of α - β -unsaturated carbonyl compounds undergo Michael reactions. All these reactions take place by the same mechanism.

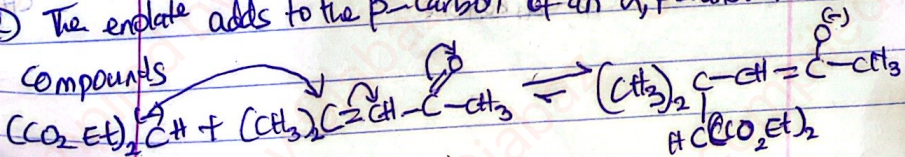


Mechanism

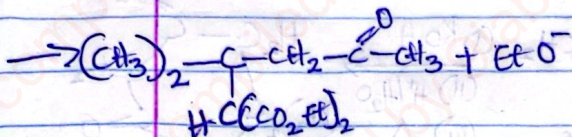
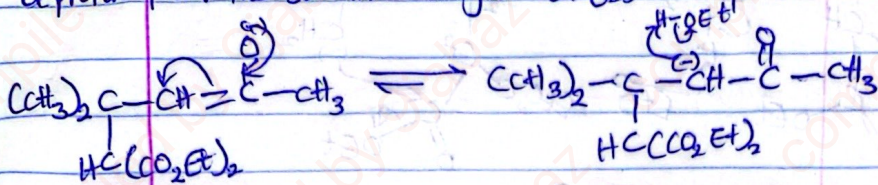
(1) A base removes a proton of α -carbon from the nucleophile



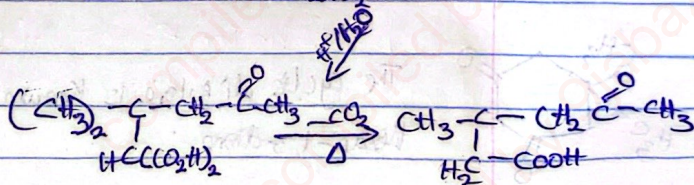
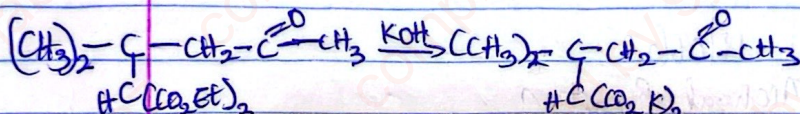
(2) The enolate adds to the β -carbon of an α , β -unsaturated carbonyl compounds



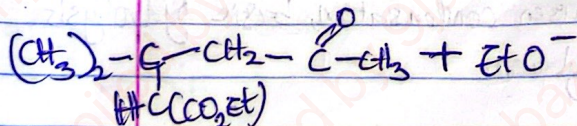
③ The intermediate formed in the nucleophilic addition step abstracts a proton from the solvent ^{ethanol} to give the observed product

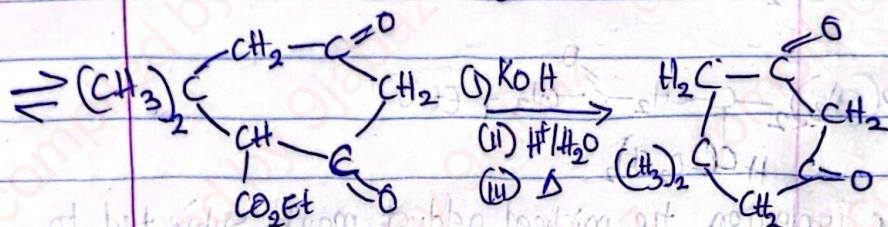
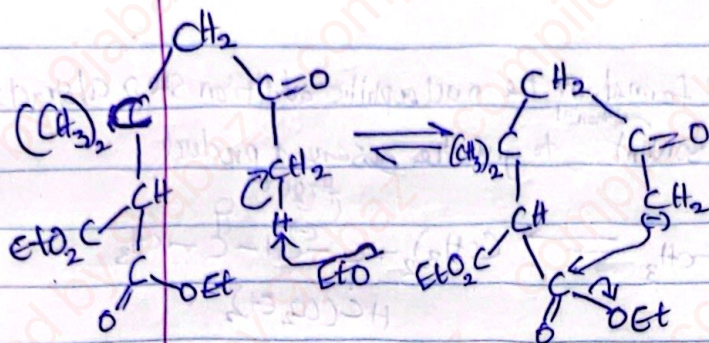


After isolation, the michael adduct may be subjected to ester hydrolysis and decarboxylation to give 5-ketone acid

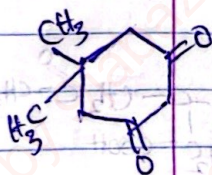


The complication is the formation of side reactions and formation of by-product known as Dimedon





11/06/26 Michael Reaction

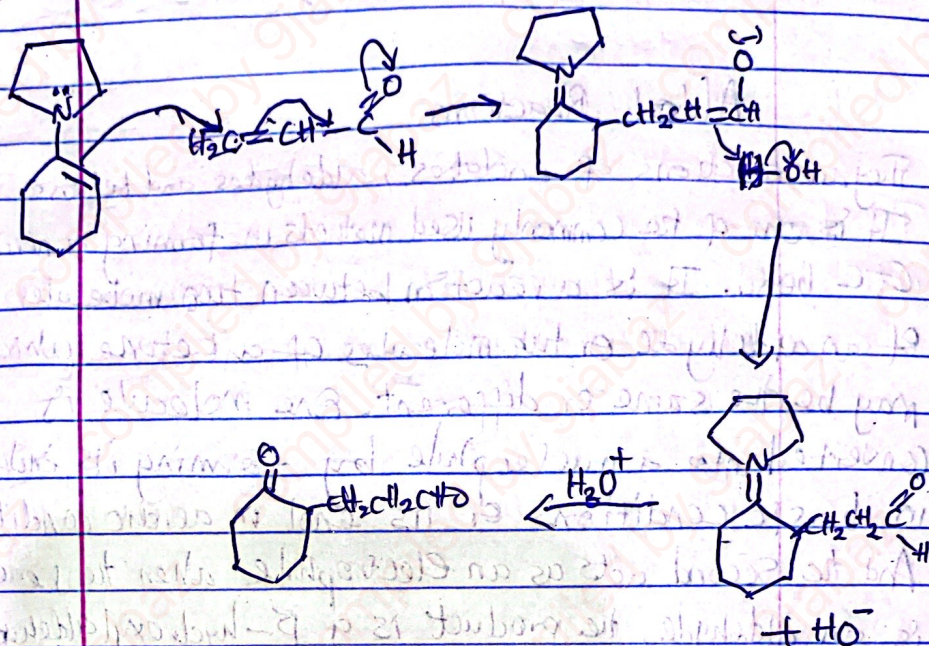


The cyclic diketone is known as 5,5-dimethylcyclohexan-1,3-dione.

The molecule is formed as a by product reaction of diethyl malonate and methyl acetate through a Michael addition reaction followed by intramolecular Claisen condensation, basic hydrolysis and finally decarboxylation.

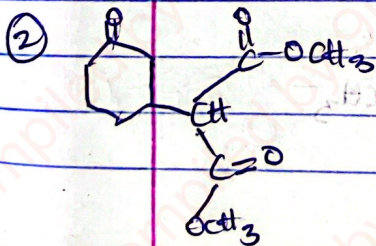
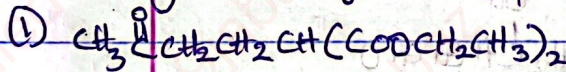
Stork - Enamine Reaction

Enamine can be used in place of enolate in Michael reaction, when an enamine is used as a nucleophile, the reaction is called a Stork-enamine reaction.

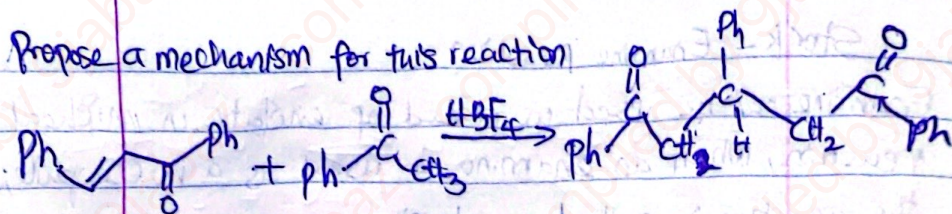


Exercise

What reagent would you use to prepare the following compounds:



Propose a mechanism for this reaction

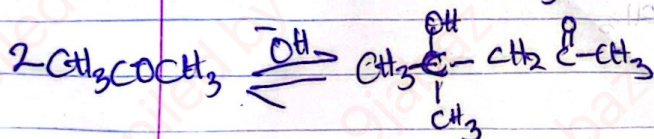
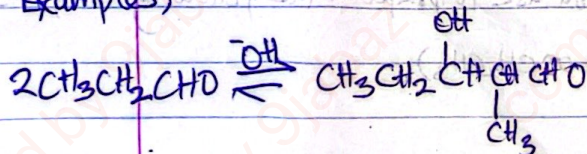


Aldol Reactions

They are reactions of enolates, aldehydes and ketone

It is one of the commonly used methods in forming a new C-C bond. It is a reaction between two molecules of an aldehyde or two molecules of a ketone which may be the same or different. One molecule is converted into a nucleophile by forming its enolate in basic conditions or its enol in acidic conditions. And the second acts as an electrophile when the reactant is an aldehyde, the product is a β -hydroxyaldehyde, ketone gives β -hydroxy ketone

Examples;



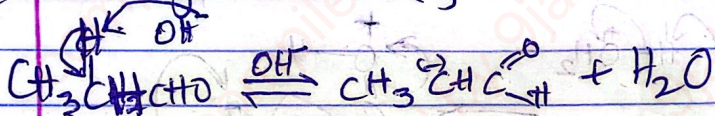
The resulting equilibrium lies to the right for many aldehydes and to the left for most ketone.

β -hydroxy aldehyde is called an aldol because it contains both an aldehyde and alcohol function.

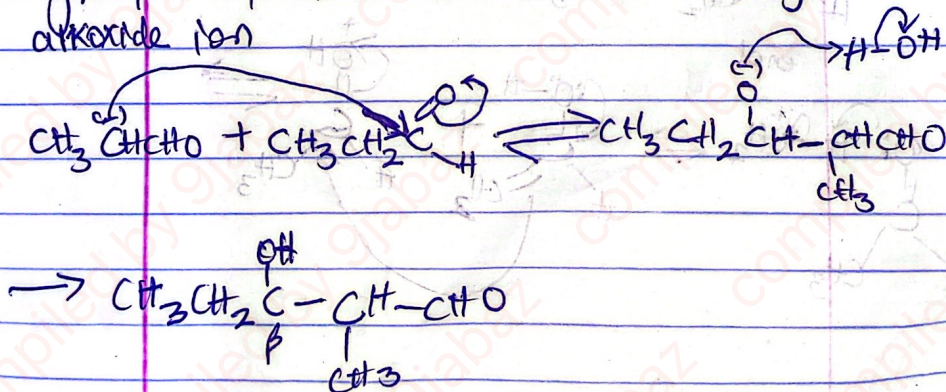
-al from aldehyde, -ol from alcohol. This C-C ~~bonding~~ bond forming reaction is called aldol addition.

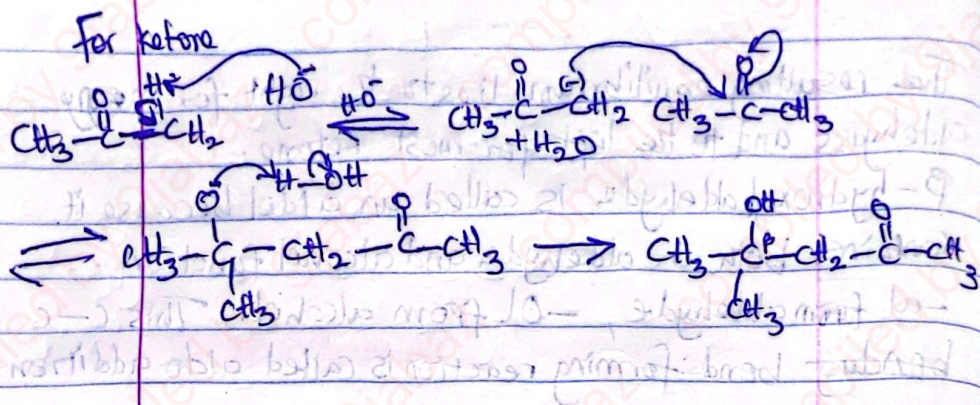
Mechanism of the Reaction

- (1) Enolate is formed by deprotonation of α -carbon (either aldehyde or ketone).

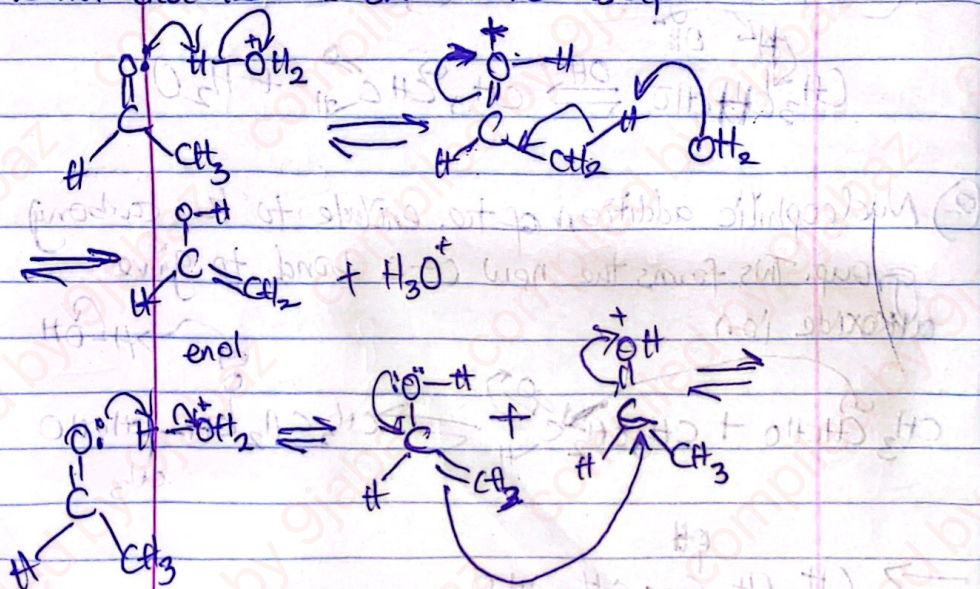


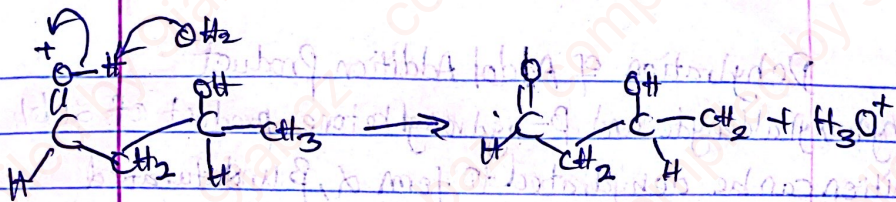
- (2) Nucleophilic addition of the enolate to the carbonyl group. This forms the new C-C bond to give alkoxide ion





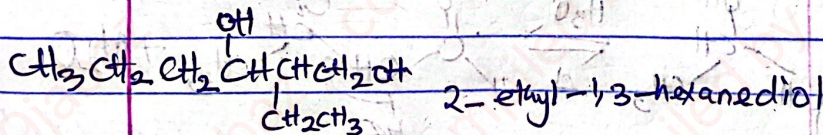
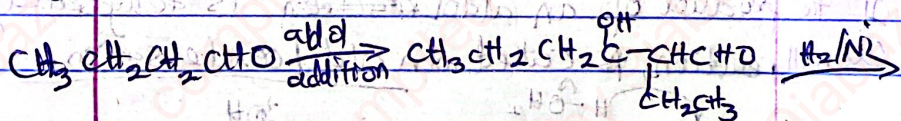
This base catalyzed reaction has a ~~acid~~ catalyzed counterpart, the catalyst is H_3O^+ and the active ingredient is not enolate ion but the enol itself.



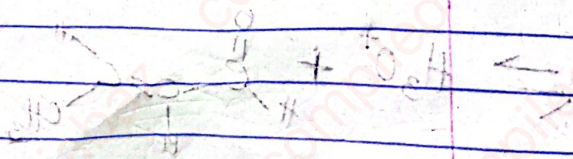


The acid and base catalyzed aldol reaction gives the same product. Aldol contains functional groups capable of further transformation.

They provide access to a host of useful materials



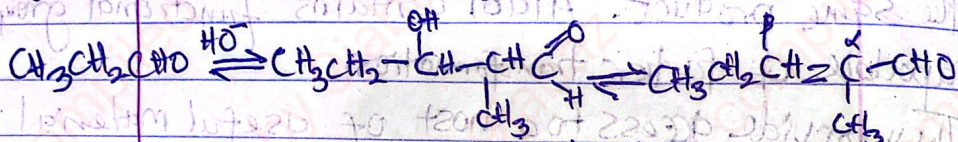
The molecule is an insect repellent



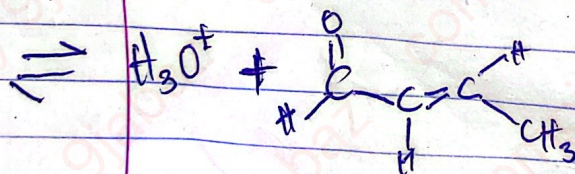
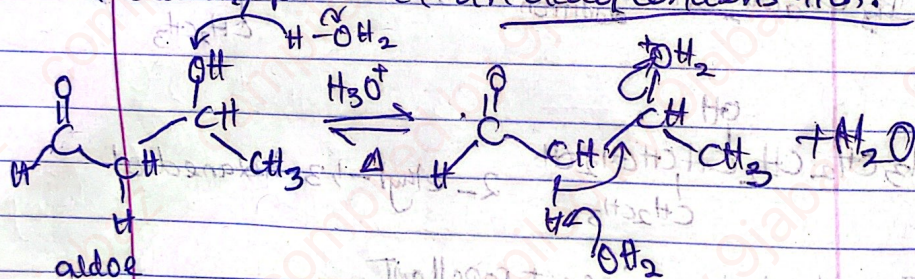
Dehydration of Aldol Addition Product

β -hydroxyaldehyde and β -hydroxy ketone, product of aldol addition can be dehydrated to form α, β unsaturated aldehyde and ketone.

Conjugation of the double bond formed with a carbonyl group increases the stability of the product.



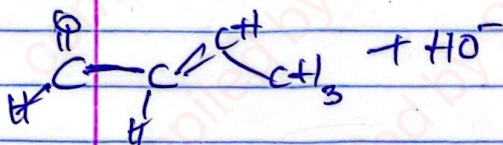
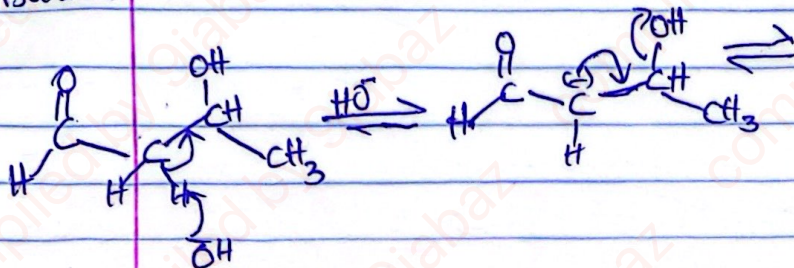
If the product of an aldol ~~addition~~ reaction is dehydrated, the overall reaction is called an aldol condensation.



Comment:

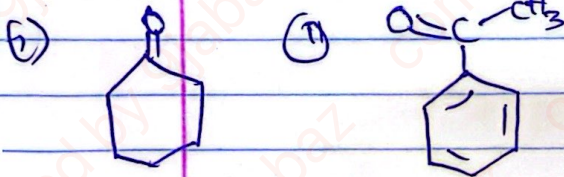
β -hydroxyaldehyde and β -hydroxy ketone can also be dehydrated under basic condition. Under basic condition, dehydration is difficult because OH^- is a poor leaving group.

group, as a result β -hydroxyl compound can also be isolated.



Exercise

What are the products of aldol condensation of the compounds,

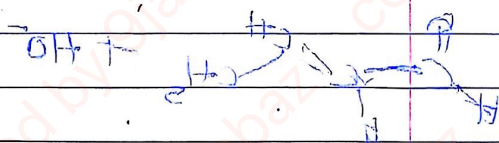
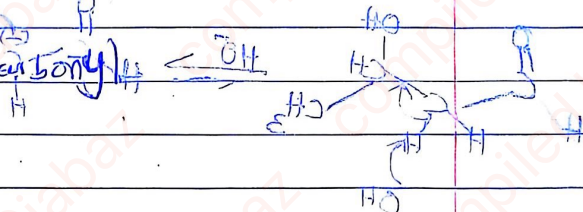


n/06/26

Alko addition: This takes place in both acidic and basic medium. This reaction have 2 steps.

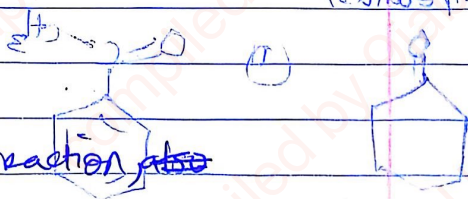
(1) Generate enolate

(i) Enolate attack carbonyl

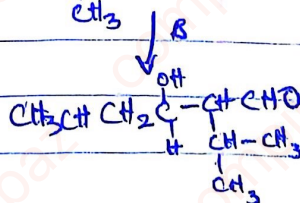
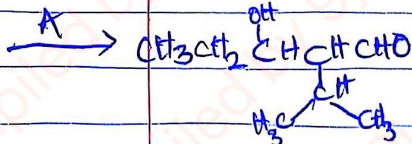
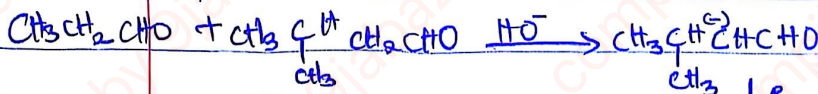


Exercise

Write the products of the following reaction (2 marks)



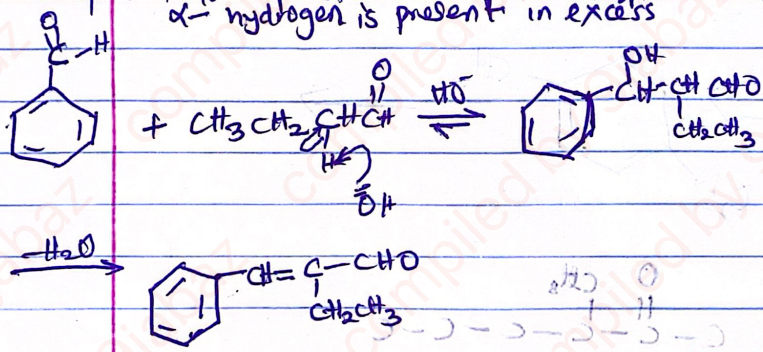
During the course of this reaction also



The four products have similar physical properties making them difficult to separate. Aldol addition that gives four products is not synthetically useful.

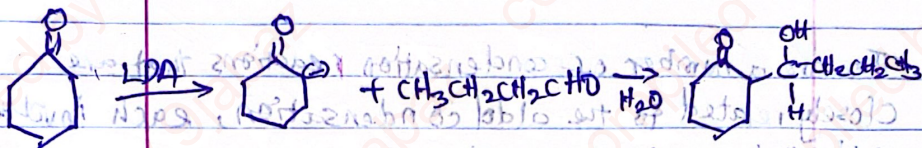
Mixed Aldol condensation can be effective only if we limit the number of reaction possibilities. Under certain conditions, a mixed aldol can lead primarily to one product.

If one of the carbonyl does not have α -hydrogen, it can not form an enolate. A greater amount of one of the two products is formed, ~~if the~~ the compound without α -hydrogen is present in excess.

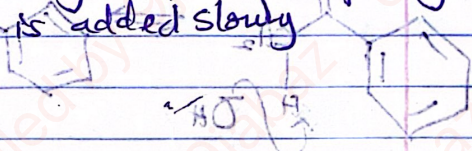


~~Under certain conditions~~

If both carbonyl compound

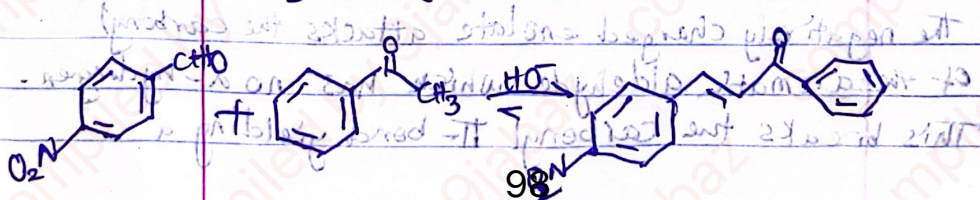
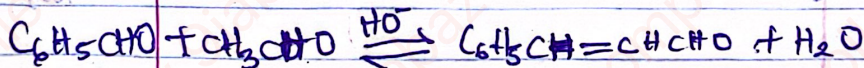


If both carbonyl compounds have α -hydrogen, primarily one aldo can be used if LDA is used to remove the α proton that creates the enolate. Under this condition, enolate of the first carbonyl is formed completely and the second carbonyl is added slowly.



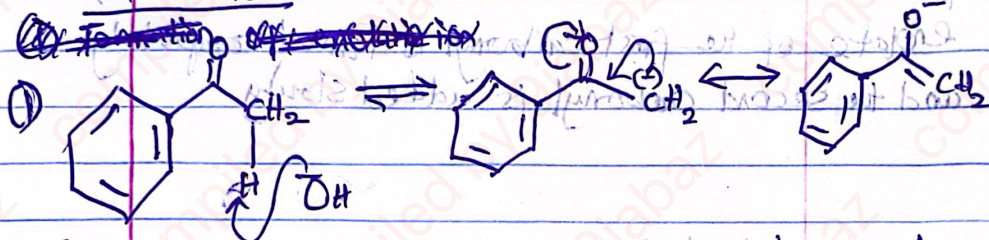
25/06/26
Claisen-Schmidt Reaction

It is condensation between aromatic aldehyde that has α -hydrogen and an aldehyde or ketone in the presence of dilute alkaline to form an α, β unsaturated aldehyde and ketone. It is a form of mixed aldol reaction.

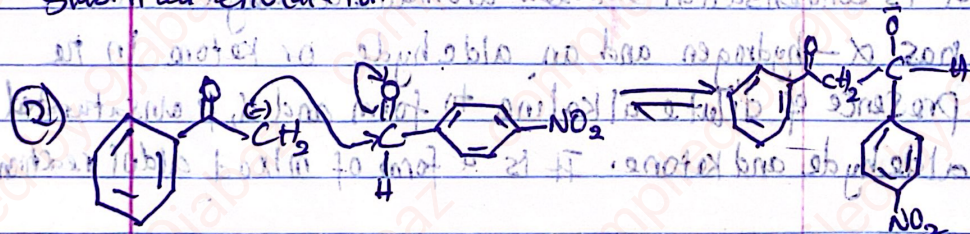


There are a number of condensation reactions that are closely related to the aldol condensation, each involves attack by carbanion on a carbonyl group. The main differences on each reaction is the carbanion and the base used for the abstraction of proton.

Mechanism

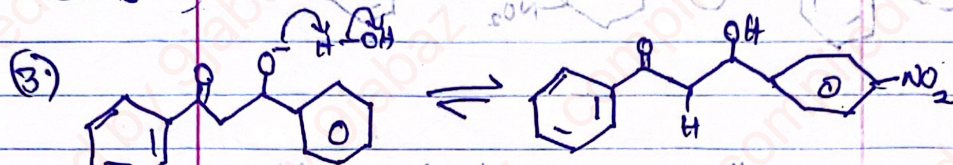


Deprotonation of enolate formation: The base abstracts an acidic α -hydrogen from the enolizable carbonyl compound (aldehyde or ketone) and form a resonance stabilized enolate ion.

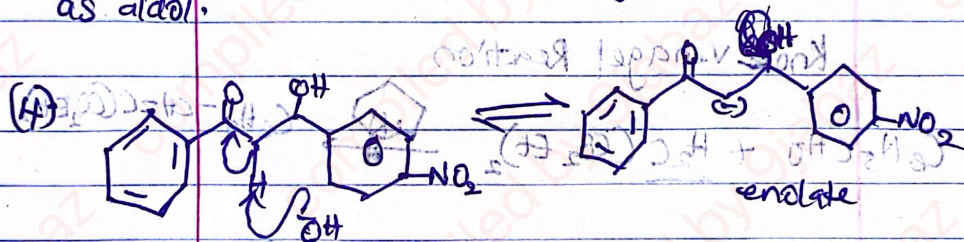


The negatively charged enolate attacks the carbonyl of the aromatic aldehyde which has no α -hydrogen. This breaks the carbonyl π -bond yielding a

~~tetrahedral alkoxide~~ tetrahedral alkoxide

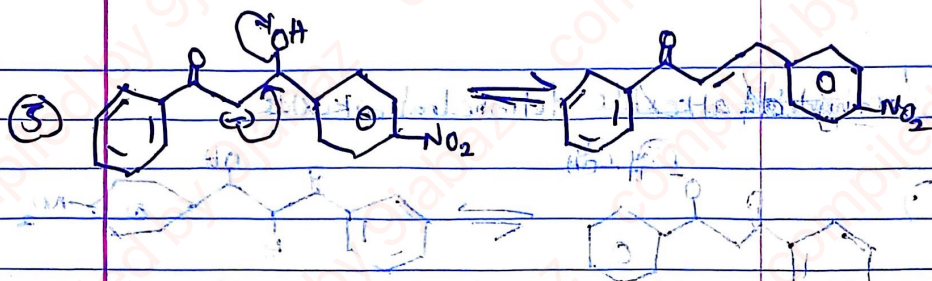


The alkoxide intermediate is protonated by water (H₂O) to form ~~the~~ β -hydroxyl carbonyl also known as aldol.



Under the basic conditions, α -hydrogen from the β -hydroxyl intermediate is removed by OH^- to form a new enolate

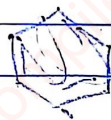
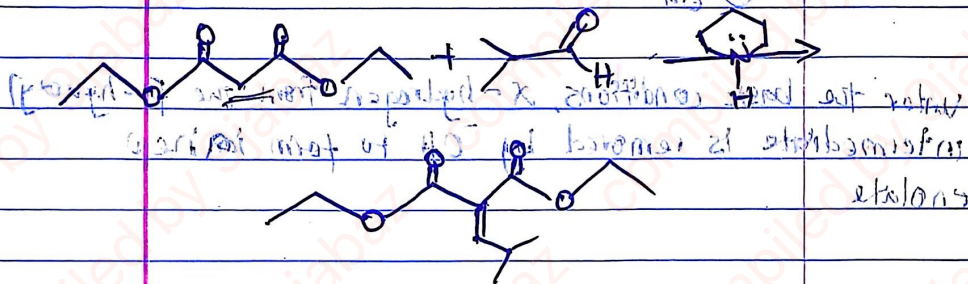
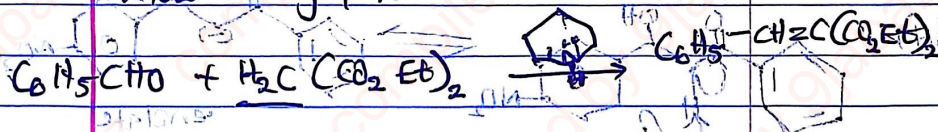


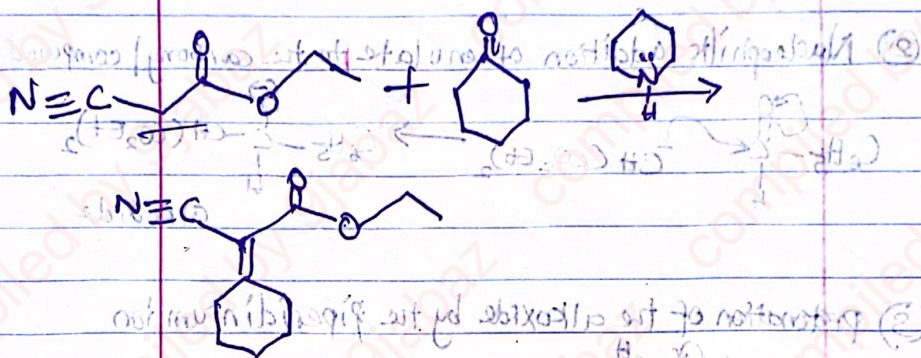


The enolate collapses expelling the hydroxyl ion and forming a highly stable conjugated α, β -unsaturated carbonyl compound.

Hand-drawn chemical reaction mechanism showing the conversion of a 1-nitro-2-phenylcyclohexanone derivative to a conjugated enone. The mechanism involves deprotonation at the alpha position to form an enolate, followed by the loss of a hydroxyl group to form a double bond, and finally the loss of a nitro group to form a conjugated system.

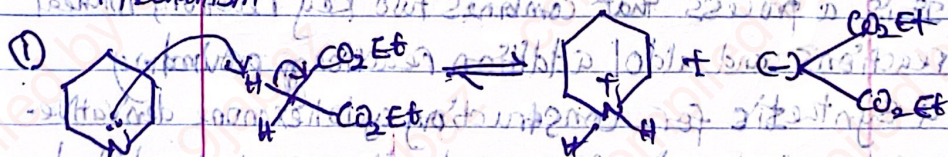
Knorr Venagel Reaction





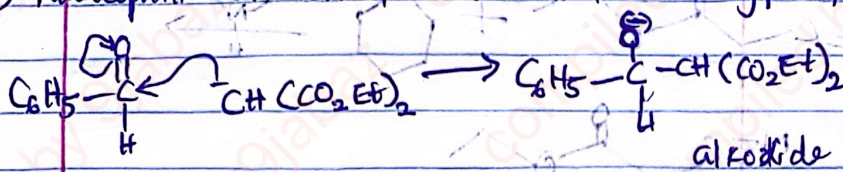
It is a reaction between dicarbonyl compound with acidic $-\text{CH}_2-$ group from either malonate, acetoacetic ester or reductive methylene compounds and aldehyde or ketone in the presence of a weak base e.g. pyrrolidine or piperidine to give an α, β condensation product which upon hydrolysis and heating gives the respective α, β -unsaturated acid.

Mechanism

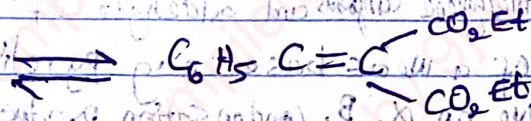
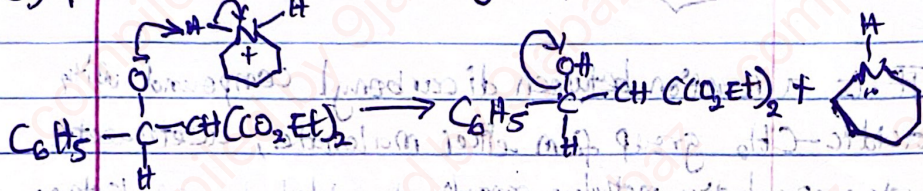


Enolate formation, i.e. proton abstraction by the base.

(2) Nucleophilic addition of enolate to the carbonyl compound.



(3) Protonation of the alkoxide by the piperidinium ion

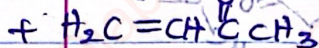


~~It combines two~~

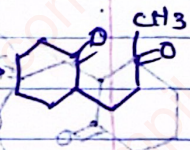
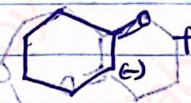
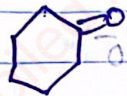
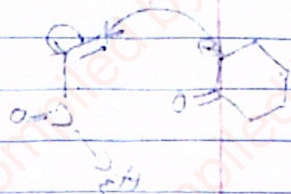
Robinson Annulation Reaction

It is a process that combines two key reactions: Michael reactions and aldol addition reactions, providing a synthetic for constructing cyclohexenone derivative. A ketone ~~is treated~~ is treated with methyl vinyl ketone in a base catalyzed reaction to give the new 6 membered ring.

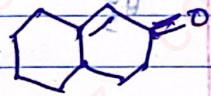
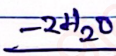
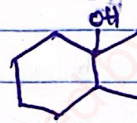
Example



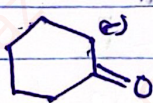
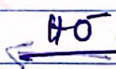
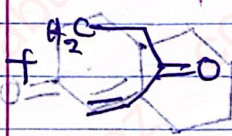
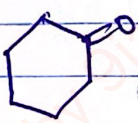
activated alkene

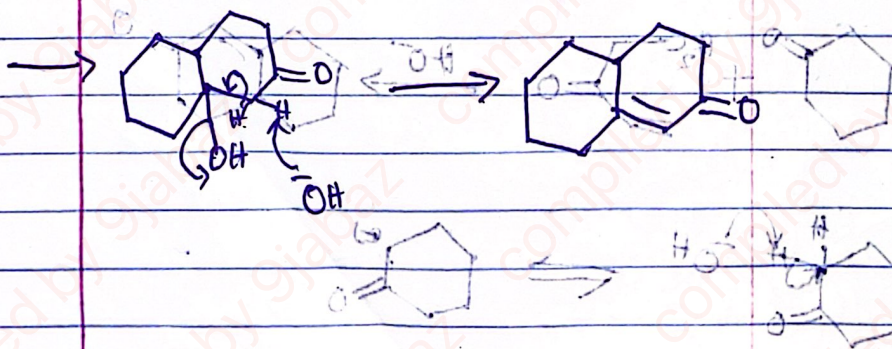
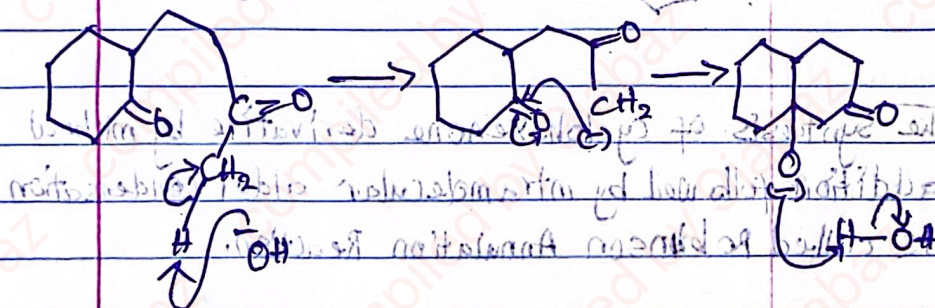
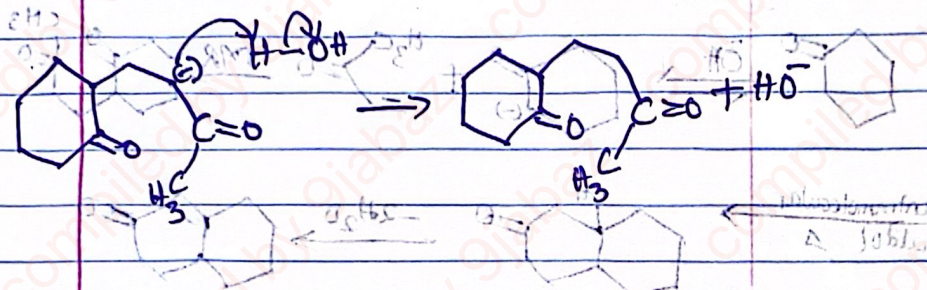
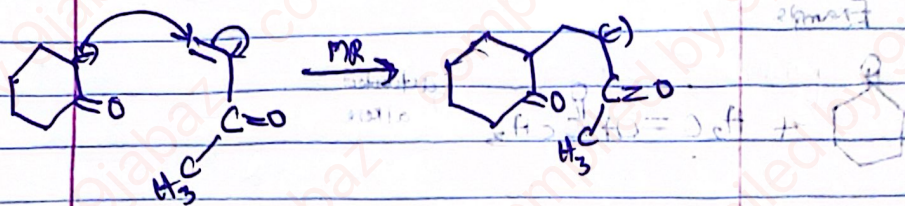


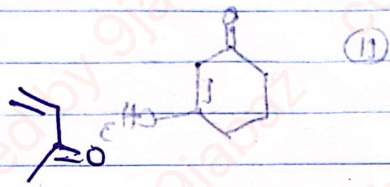
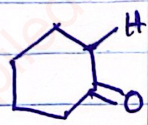
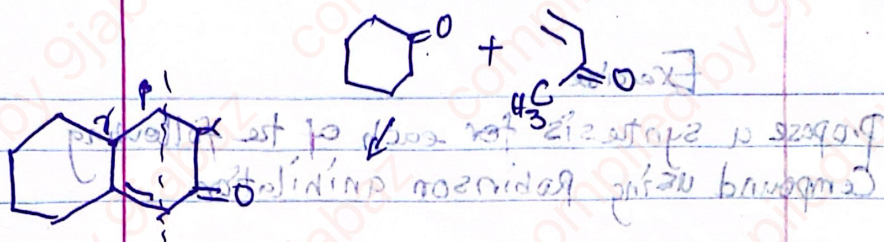
intramolecular aldol Δ



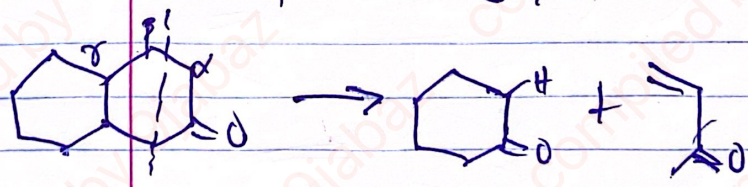
The synthesis of cyclohexenone derivative by michael addition followed by intramolecular aldol condensation is called Robinson Annulation Reaction.





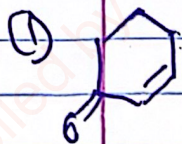


Robinson annulation product shows that the ketone group from the cyclohexenone comes from α , β unsaturated carbonyl and the double bond results from attack of the enolate of the α , β - unsaturated compound on the carbonyl group of the other reaction. We can arrive at the appropriate reactant for Robinson annulation by cutting through the double bond and between β , γ carbon on the other side of the carbonyl, for example

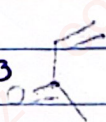
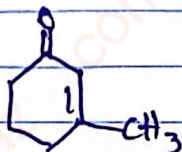


Exercise

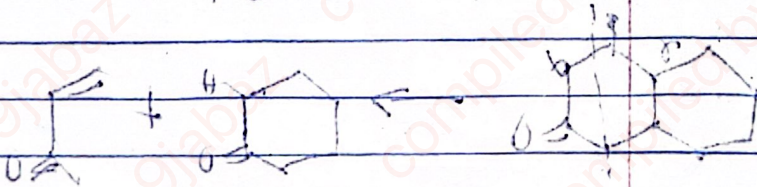
Propose a synthesis for each of the following Compound using Robinson annihilation



(II)

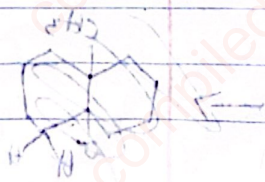
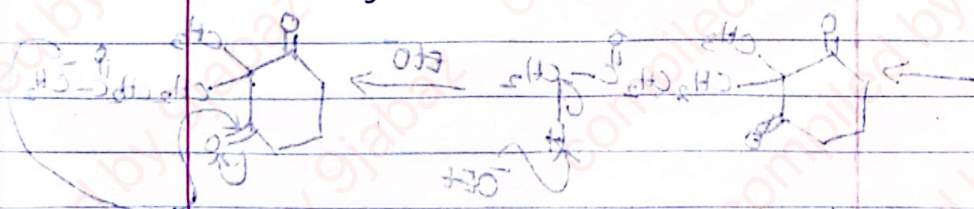
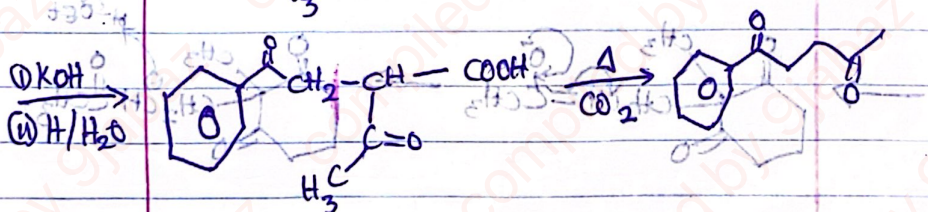
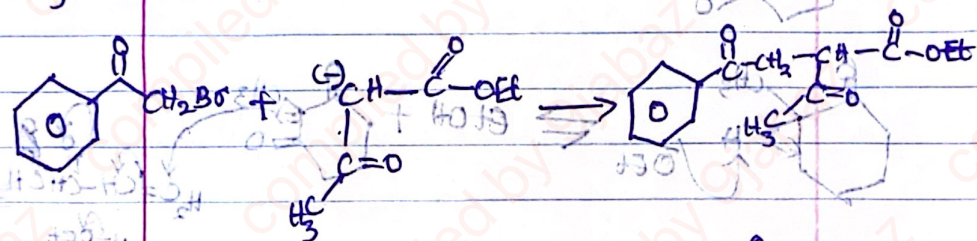
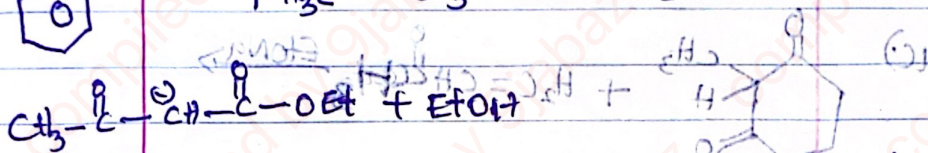
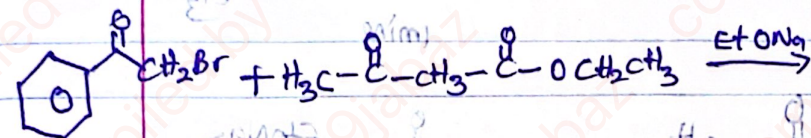
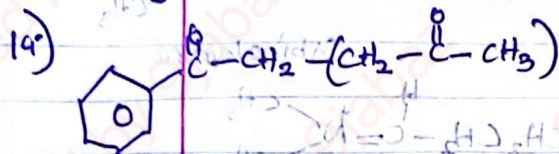


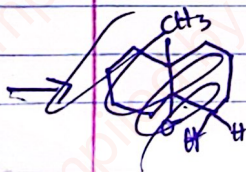
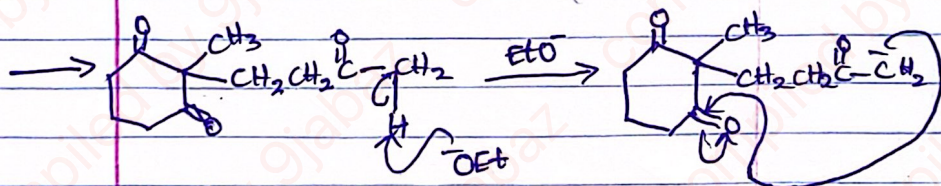
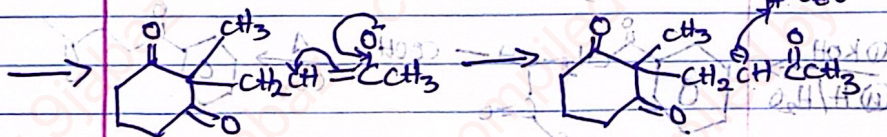
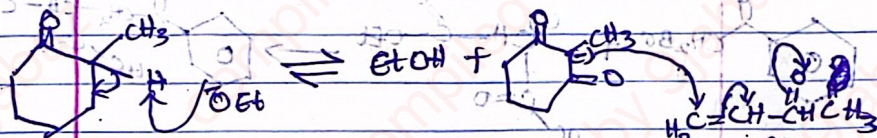
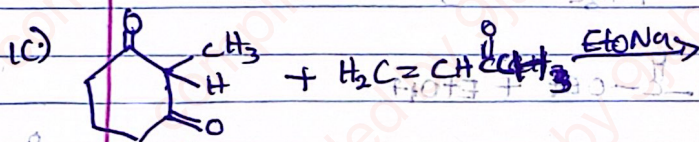
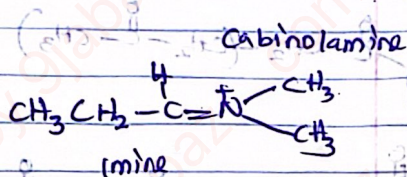
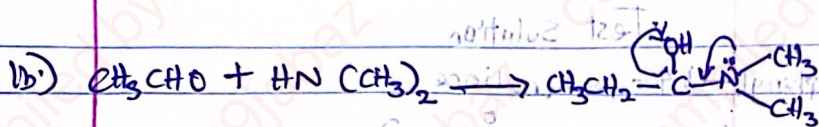
Robinson annihilation is a sequence of reactions that converts a ketone with an α,β -unsaturated ketone into a β -keto ester. The reaction involves the formation of an enolate, followed by Michael addition to an α,β -unsaturated ketone, and subsequent dehydration to form the β -keto ester. This reaction is useful for the synthesis of complex molecules, particularly in the synthesis of steroids and other natural products.

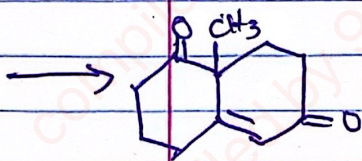
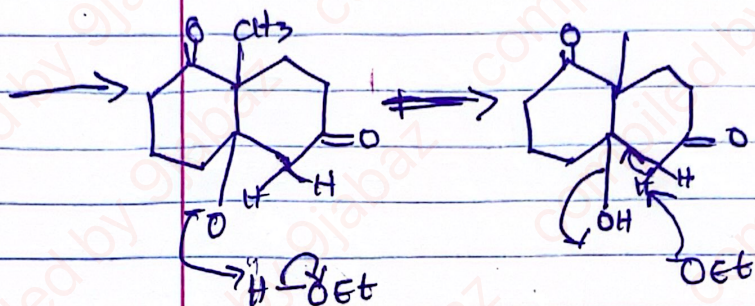


Test solution

(1-phenyl)-1,4-pentanedione $(C_{11}H_{14} + 2H_2O_2) \quad (d)$









OBAFEMI AWOLOWO UNIVERSITY, ILE-IFE
CHM 408 - Organic Reactions and Synthesis

Mid-semester Exam

ATTEMPT ALL QUESTIONS

Time: 50 minutes

- 1a. Show how you could prepare 1-phenyl-1,4-pentanedione from ethyl acetoacetate and any necessary organic and inorganic reagents
- 1b. Write the structures of the cabinolamine and iminium ion formed in the reaction of propanal and dimethyl amine
- 1c. Consider this Micheal reaction,

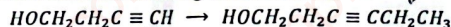


outline the mechanism of the reactions leading to the formation of the intramolecular addition condensation product (P)

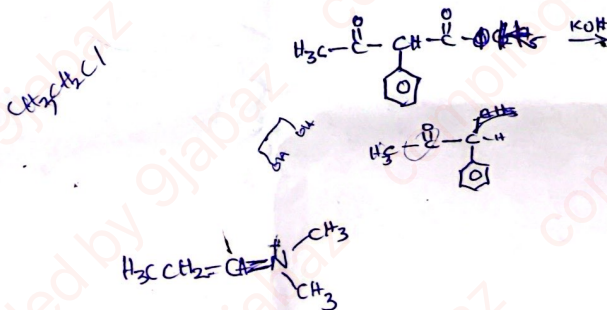
2. a. Using the disconnection approach, outline a synthesis of *p*-aminobenzoic acid starting from benzene. Indicate all reagents and experimental conditions.
- b. For the synthetic sequence shown below, propose suitable reagents and reaction conditions for Steps 1–3. Briefly state the type of reaction occurring in each step.



- c. Show how you would effect the following transformation:

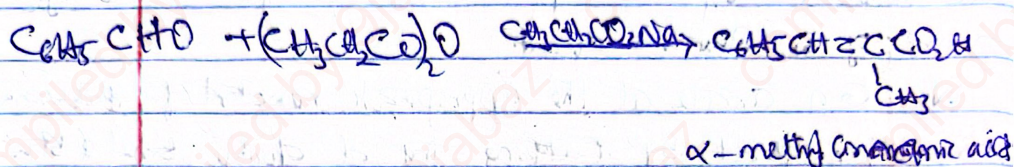
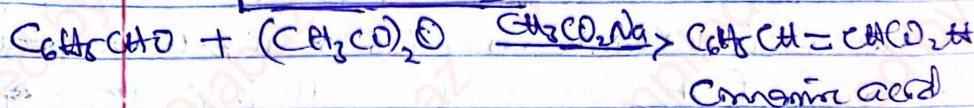


Give all reagents and reaction conditions required.



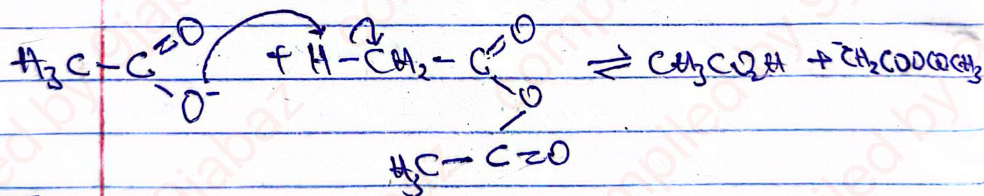
expt 12

Perkin Reaction

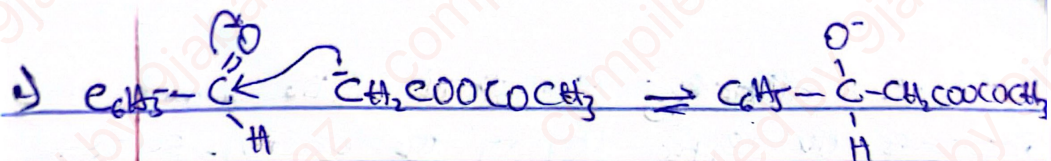


When an aromatic aldehyde is heated with the anhydride of an aliphatic acid containing two α -hydrogen in the presence of its sodium salt which acts as a catalyst, condensation takes place to form an α,β -unsaturated aromatic acid.

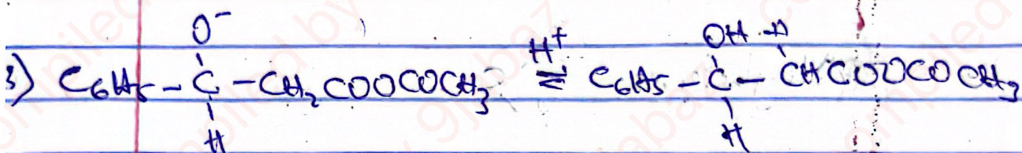
Mechanism



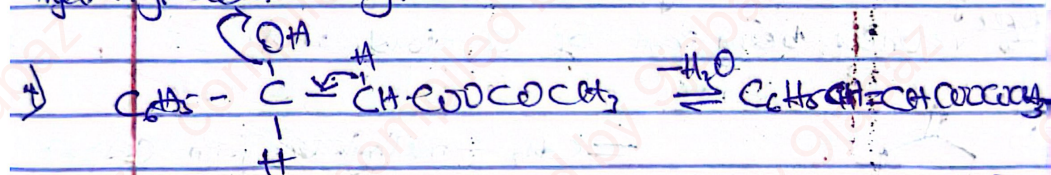
The acetate anion obtained from the sodium acts as a basic catalyst and abstracts an α -hydrogen from the aliphatic anhydride.



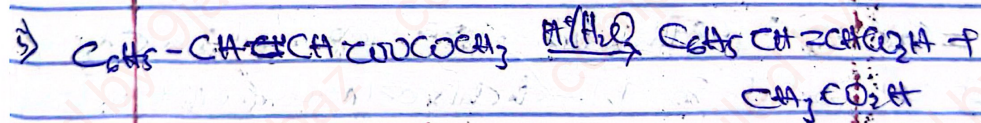
The Carbanion adds to the carbonyl of the aromatic aldehyde to form alkoxide.



Protonation of the alkoxide intermediate gives/produces hydroxy acid anhydride.

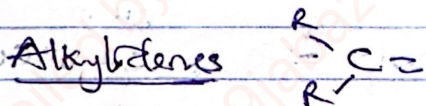


Elimination of water molecules gives α,β -unsaturated mixed anhydride.

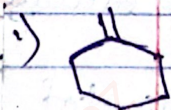


Hydrolysis of the anhydride forms trans cinnamic acid.

Electron attracting substituent on the aromatic ring increase the efficiency of the reaction. For example p-nitrobenzaldehyde gives 82% yield of p-nitrobenzoic acid.



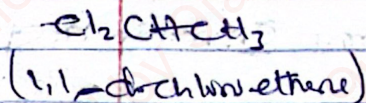
These are divalent groups formed from alkenes by removal of 2-H atoms from the same carbon atoms. The free valences being part of a double bond.



methylene cyclohexane

$=CH_2$ — methylene, from $CH_2=CH_2$ which forms methylene cyclohexane

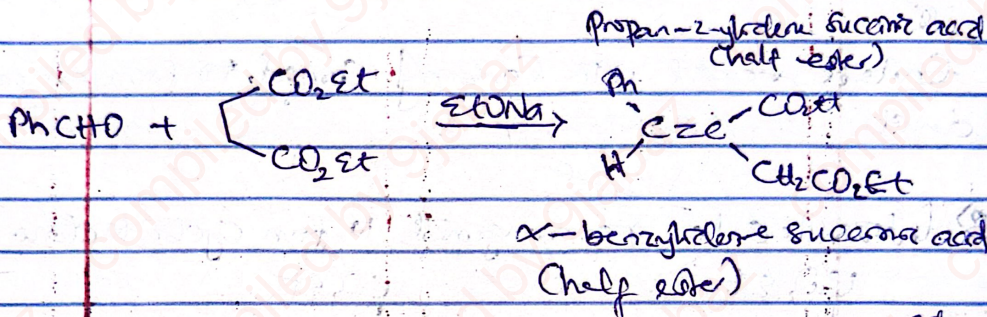
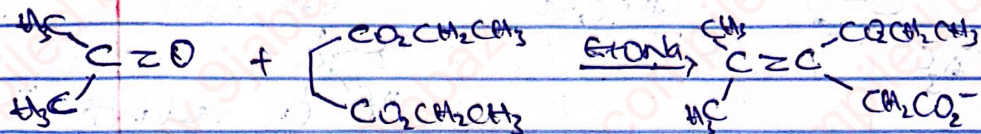
2) $=CHCH_3$ — ethylene, which is formed from $CH_3CH=CH_2$. It is found in 1,1-dichloroethene (ethylene dichloride)



3) $=CH-C_6H_5$: benzylidene formed from toluene.



Stobbe Reaction



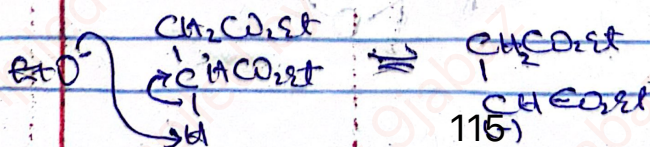
Stobbe reaction is a base-catalysed (NaOEt, NaOH) condensation of aldehyde or ketone with succinic acid ester (e.g. diethyl succinate), it yields alkylidene succinic acid half ester.

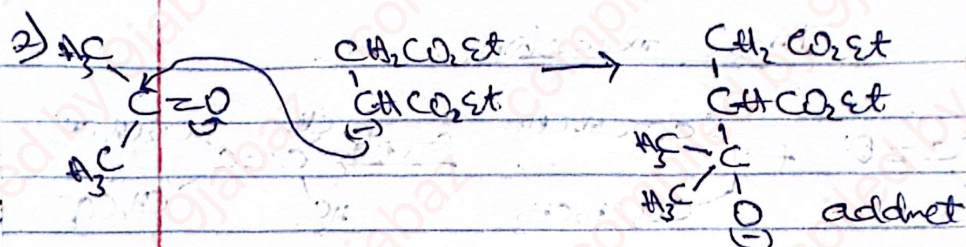
A pathway leading to this product involves a cyclic β -lactone intermediate.

Mechanism

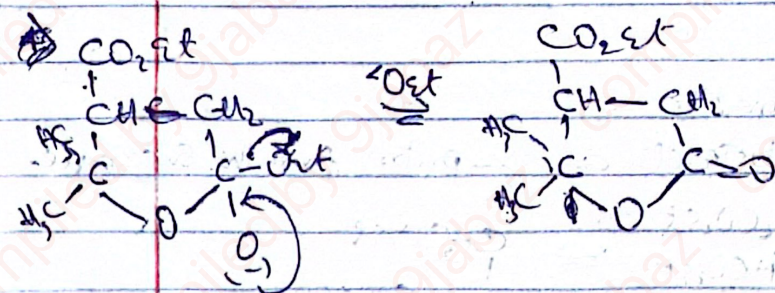
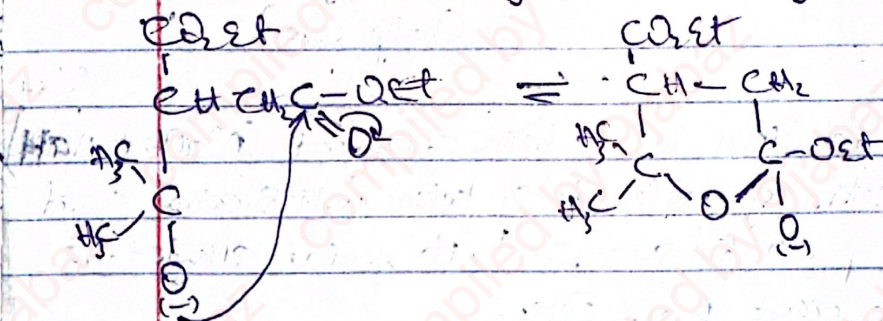
Enolate formation

A base abstracts an α -proton from the succinate.

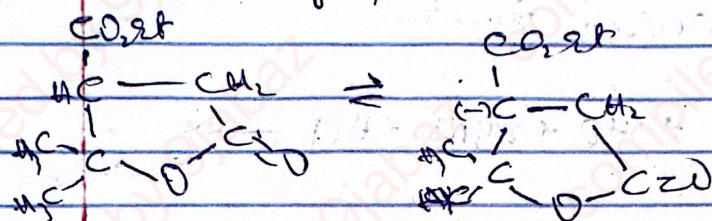




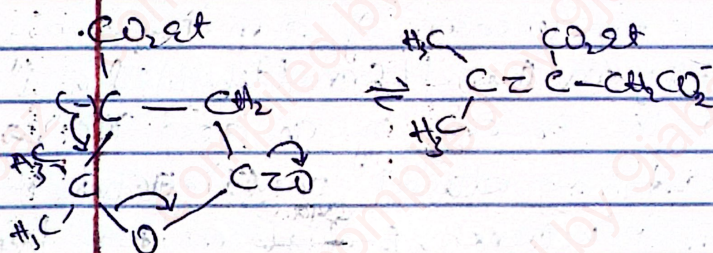
3) Intramolecular rearrangement to form cyclic lactone.



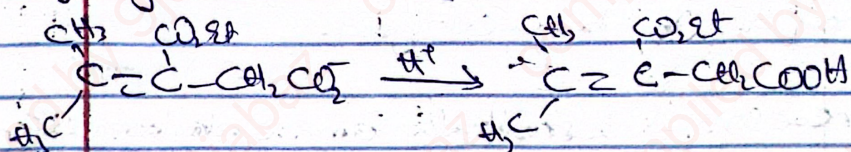
c) Abstraction of proton



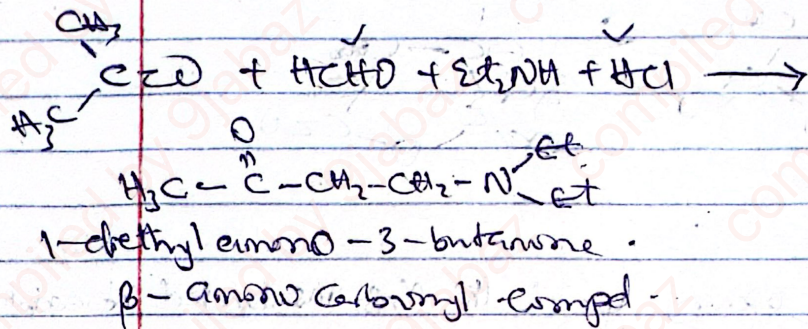
d) The ring opening yield the α,β -unsaturated intermediate



e) ~~hydrolysis~~ Protonation yield succinic acid half ester



Mannich Reaction



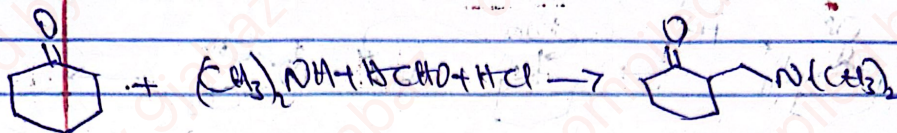
This reaction is condensation of a mixture of an aldehyde (usually formaldehyde) & a 1, 2°-amino in the presence of an acid, HCl, and a compound containing atleast one (1)-active H-atom e.g. (ketone, β -ketoster, β -~~hydroxy~~^{amino} ketone, α -amino ketone).

The final product is a β -amino carbonyl compound also known as Mannich base.

This reaction is usually carried out in acid solution but may also be base-catalysed.

The reaction is essentially amino alkylation of an acidic proton next to a carbonyl group.

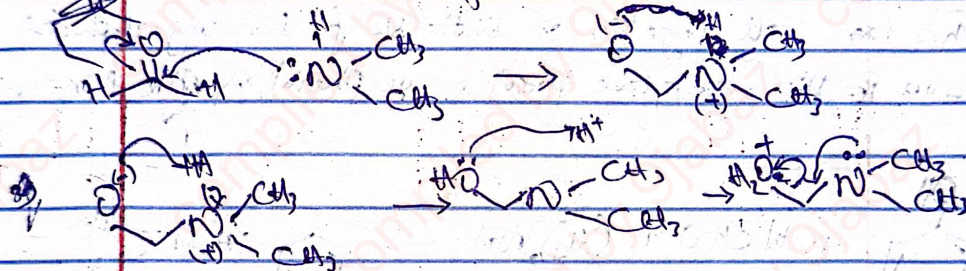
Reaction



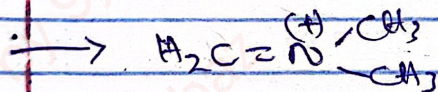
2-(dimethylamino)cyclohexanone

Mechanism

1. Immonium ion formation

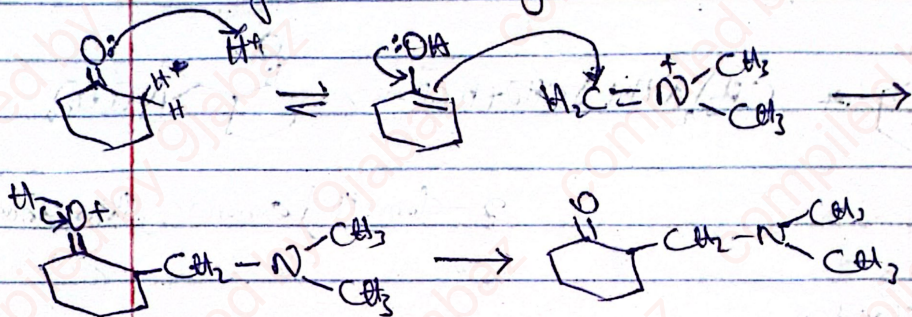


Protonation of oxygen on the hydroxyl; the next step is acidic medium.



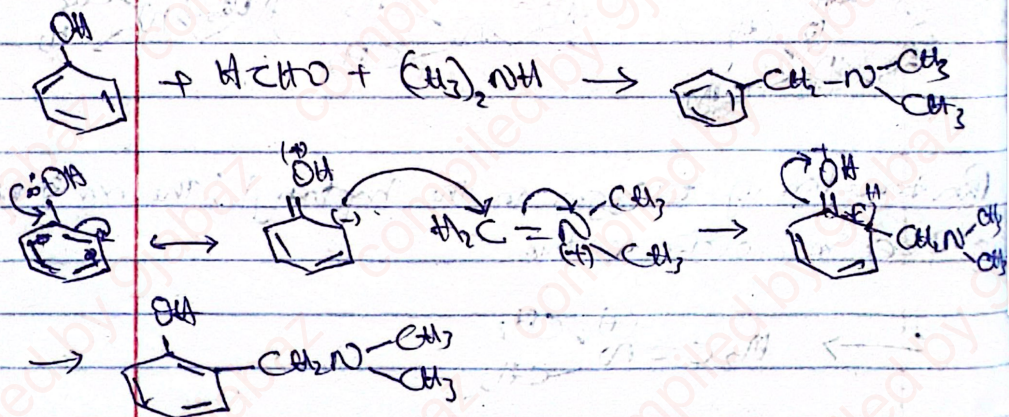
The amine reacts with the formaldehyde to form a reactive immonium ion intermediate.

2) Protonation of the Carbonyl, ~~then~~ ^{to} form ~~reactive~~ ^{retro-syn}

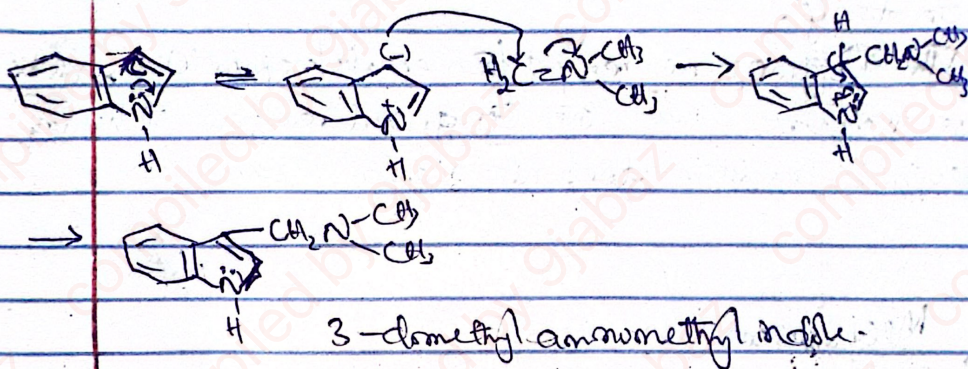
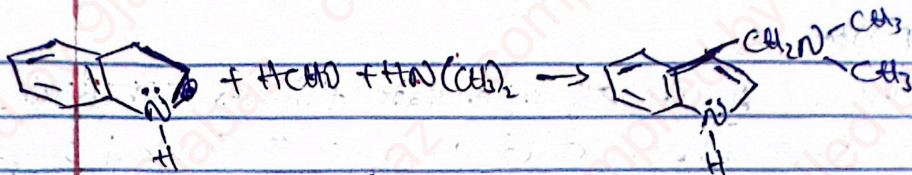


Answer -

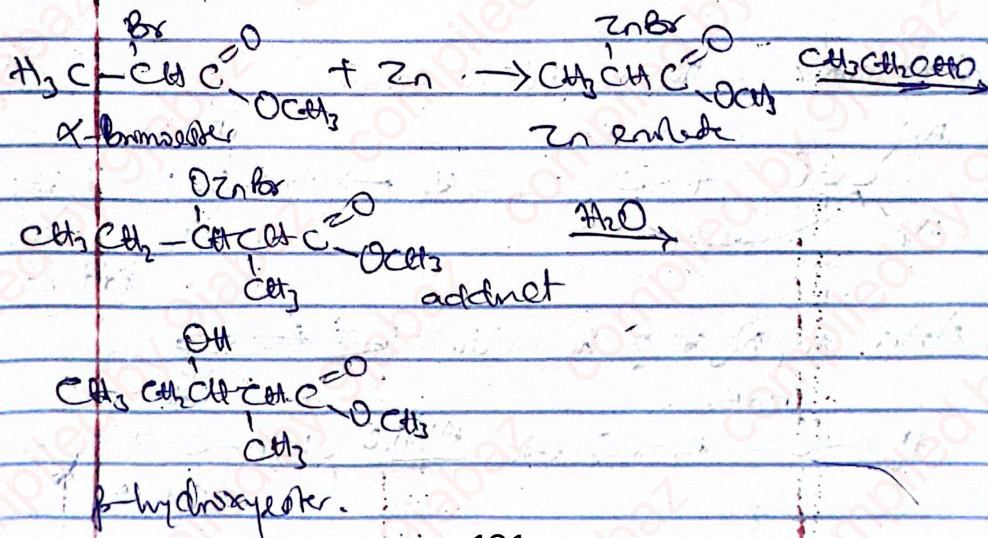
This reaction all together is suitable for bonding aliphatic carbons to the reactive position of phenol, pyridine & indole.



2-dimethylaminomethyl phenol



Reformatsky Reaction

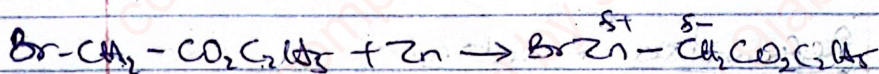


Note

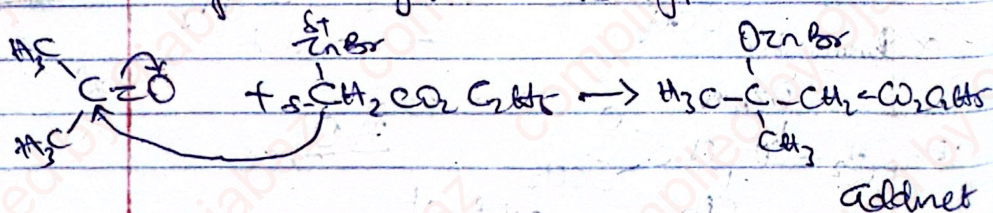
- 1) The use of Zn allows enolate formation without using any base which would condense the Carbonyl compound on itself.
- 2) The Organozinc reagent / Zn enolate / reproductively enolate is less reactive than Grignard reagent & hence nucleophilic addition does not occur.

Mechanism

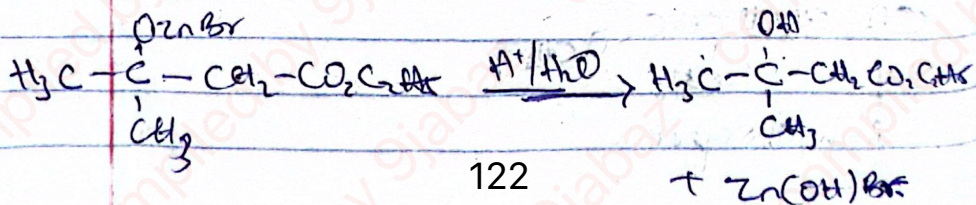
- 1) Formation of Organozinc comp. reagent -



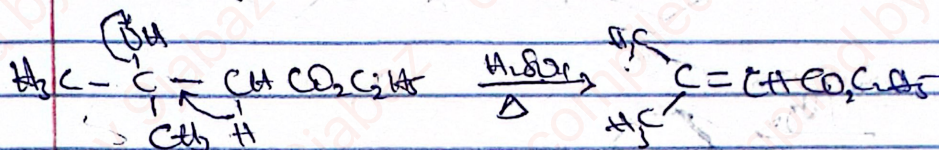
- 2) Addition of the reagent to carbonyl



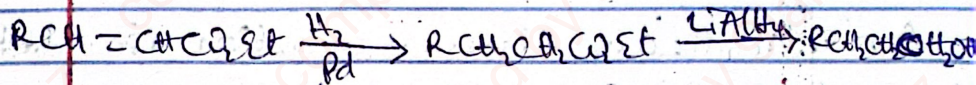
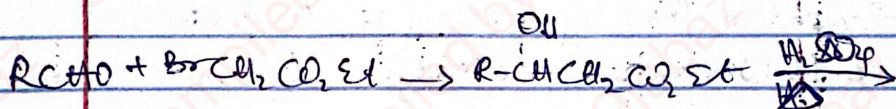
- 3) Acid hydrolysis of the adduct ~~to the formic acid~~



a) Elimination of H_2O

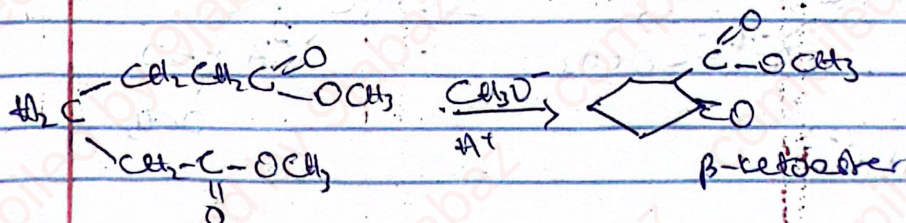


Two β - are given as this reaction
We can apply this reaction

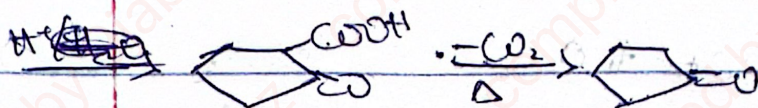


Bretmann Condensation Reaction:

(1,6-dicarbonyl — 5-membered ring)
(1,7-dicarbonyl — 6-membered ring)



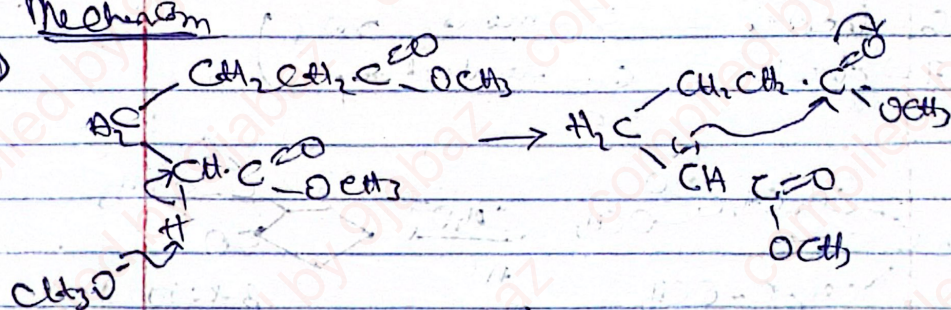
in presence of base

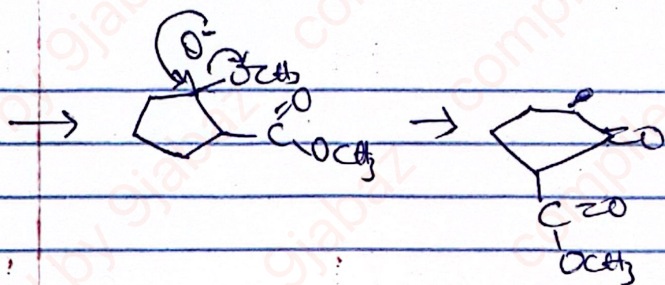


Addition of a (strong) base to diester of C₆ & C₆ causes the diester to undergo an intramolecular Claisen condensation thereby forming a 5 & 6-membered ring β-ketoester respectively.

An intramolecular Claisen condensation using diester is called Dieckmann condensation reaction.

Mechanism





Derivatives of shorter chain carboxylic acid do not undergo Dieckmann reaction because of the strain which would result in the small ring formed.