31/03/2026 Prof. Olomola's Par

Organic Reactions & Synthesis

Introduction

Organic synthesis is the process of building organic molecule 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 recrystalization, preparative thin layer chromatog column chromatography, radial chromatography, high performance liquid chromatography etc

iv) Identification using chemical test and more convenently instrumentation techniques such as IR, UV, NMR, MS and X-ray crystallography

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

diasteroselectivity and enantioselectivity)
Furthermore, the experimental ease of ~~a~~ transformation an 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 price in chemistry introduced and promoted the concept of retrosynthetic analysis wherby 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 (⟶): It means "react to give".

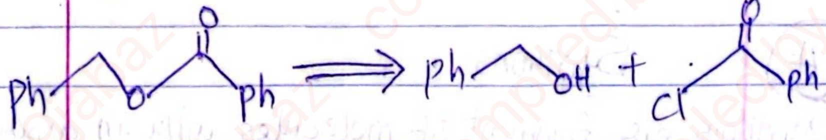
(b) delocalization arrow (⟷) means that the two different structures are the same or there are two different ways to draw a delocalized structures

(c) Equilibrium arrow (⇌): Meaning the two structures are intercoverting

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

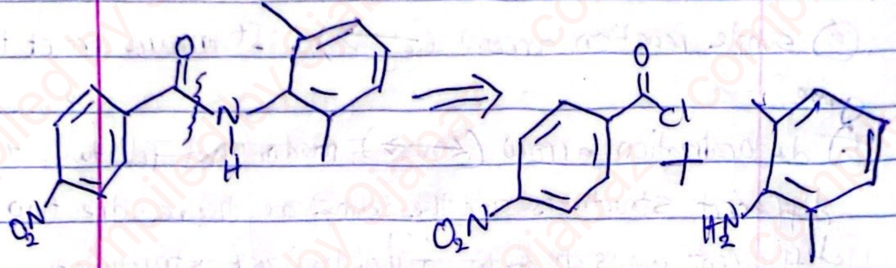
$$Z \Longrightarrow x + y$$

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

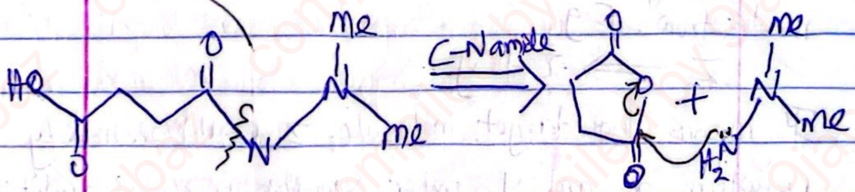


(3) Disconnection: Mentally breaking a molecule into its component parts is known as disconnection and it is normal to indicate the site of the disconnection

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



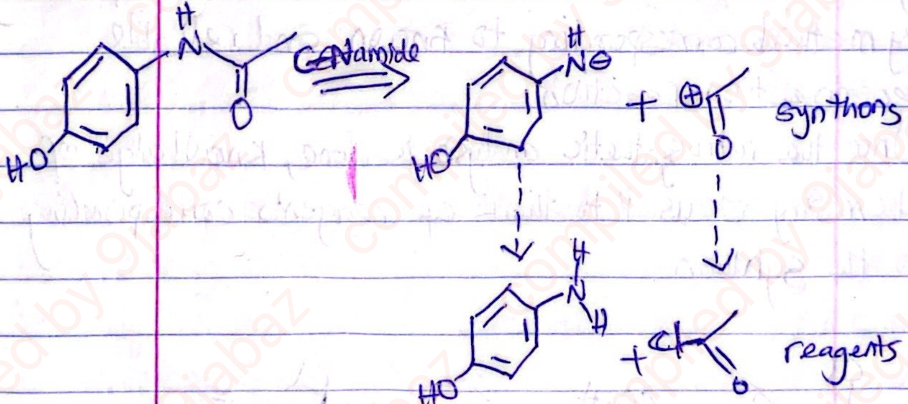
④ Synthons

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

By disconneting 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 ⇒ Synthons ·····> Synthetic equivalent or reagents



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(5.) Synthetic Design

It involves two distinct steps;

(I) retrosynthetic anaylsis

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

retrosynthetic analysis;

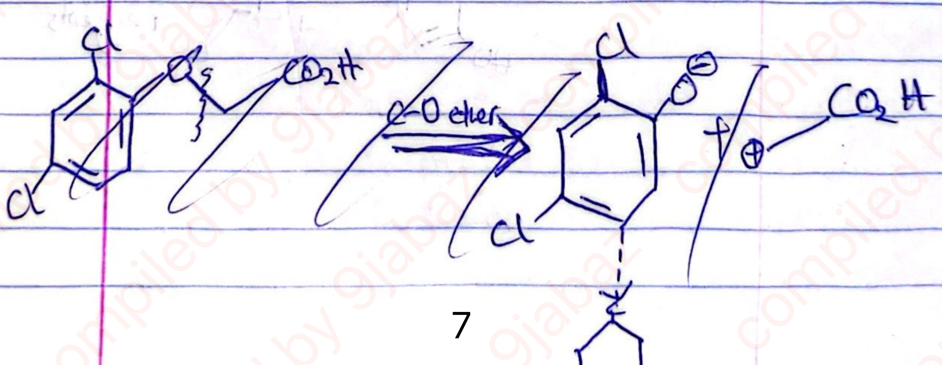
$$TM \Rightarrow A + B \Rightarrow C$$

forward sythesis

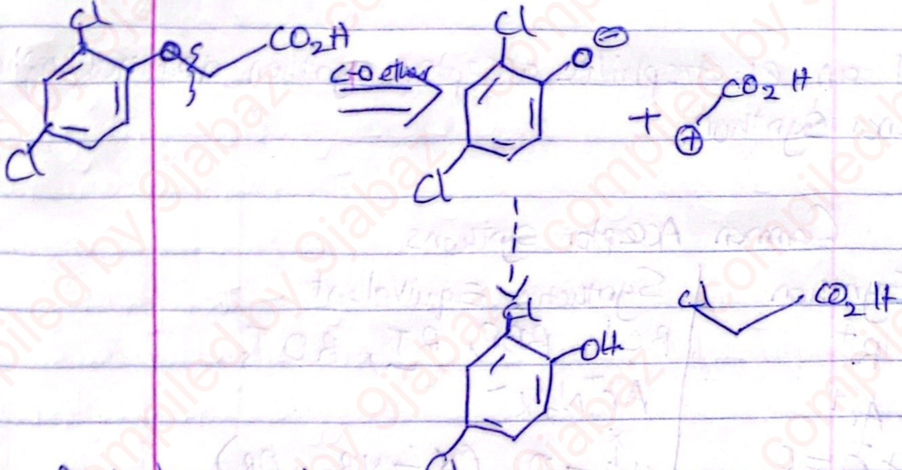
$$C \longrightarrow A + B \longrightarrow TM$$

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

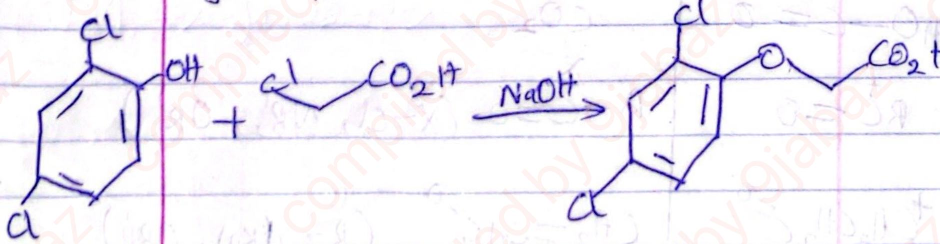
Once the retrosynthetic analysis is done, knowlledge of chemistry is used to think of reagents corresponding to the synthon



retrosynthetic analysis;



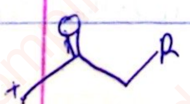
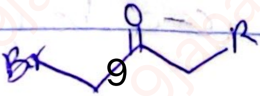
forward synthesis;



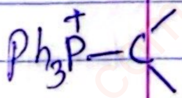
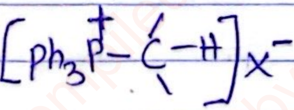
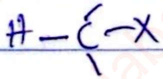
Chemical bonds can be cleaved heterolytically; homolytically or through concerted transformation Heterolytic retrosynthetic disconnection of a C–C bond in a molecule breaks the target molecule into an acceptor synthon (a carbocation) and a donor synthon (carbonanion).

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^+	RCl, RBr, RI, ROTs
Ar^+	$Ar^+N_2X^-$
$H\overset{+}{C}=O$	$H\overset{X}{C}=O$ ($X = NR_2$, OR)
$HO-\overset{+}{C}=O$	CO_2
$R\overset{+}{C}=O$	$R-\overset{X}{C}=O$ ($X = Cl$, NR'_2, OR')
$^+CH_2CH_2C(=O)R$	$CH_2=CHC(=O)R$ (R = alkyl, OR')
$^+CH_2-CH_2C\equiv N$	$CH_2=CHC\equiv N$
$^+CH_2OH$	HCHO
$R_2\overset{+}{C}-OH$	$R_2C=O$
	
	

Common Donor Synthons

Synthon	Derived reagent	Synthetic Equivalent
R^-	$RMgX$, RLi, R_2CuLi	RX
^-CN	$NaC\equiv N$	HCN
$RC\equiv C^-$	$RC\equiv CMgX$, $RC\equiv CLi$	$RC\equiv CH$
		
		

Choosing a Disconnection

The hardest ~~part~~ task 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 sumarized important guidelines for choosing disconnections of bond.

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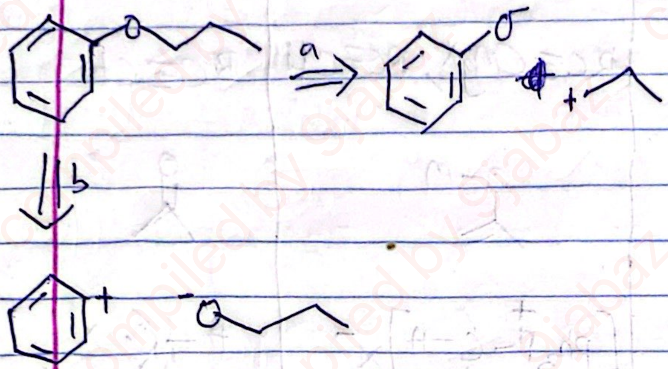
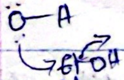
1) Disconnection of bond should be carried out only if the ~~disconnected~~ resultant fragment can be reconnected by known and reliable reaction.



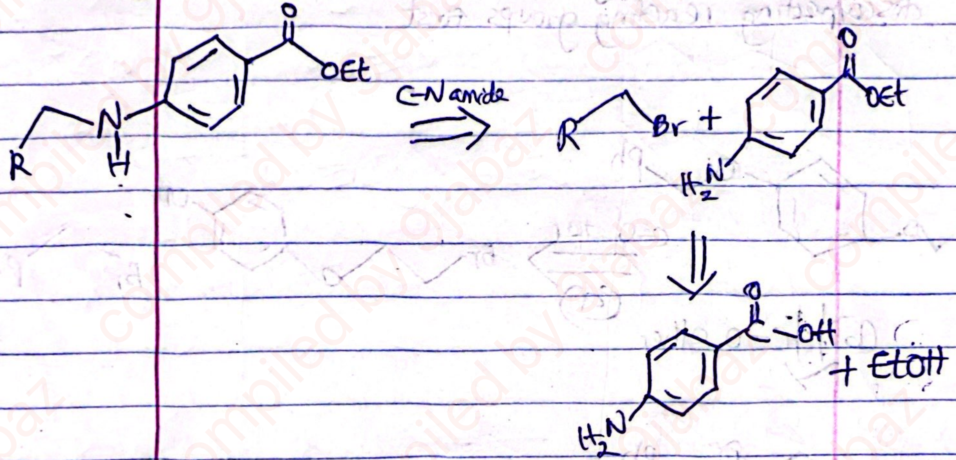
Disconnection of the aryl side of the oxygen atom is a bad choice because there is no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.

(2) Aim for the fewest number of disconnection. ~~having~~ Adding large fragment in a single reaction is more productive than adding several small fragments sequentially

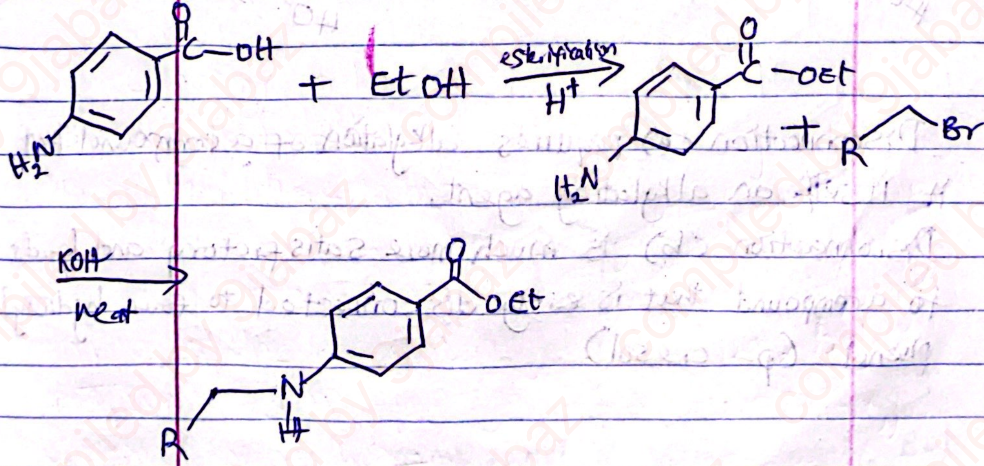
(3) For compounds consisting of two parts joined by a hetero atom disconnects next to the hetero atom. This guideline works for esters, amides, ethers, amines,



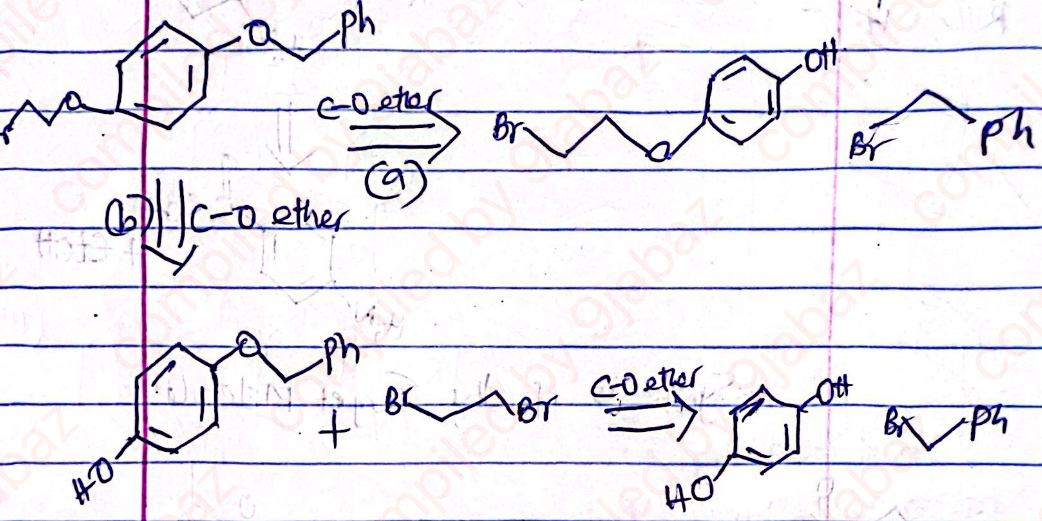
acetals and sulphides, because this compounds are often made by a substitution reaction.



Synthesis of the Target Molecule



④ consider alternative disconnection and choose ~~routes~~ route that avoid chemoselectively problems. This often means disconnecting reacting groups first



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

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

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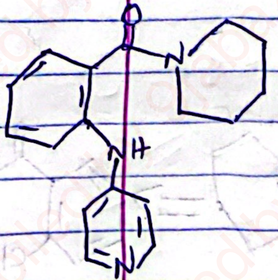
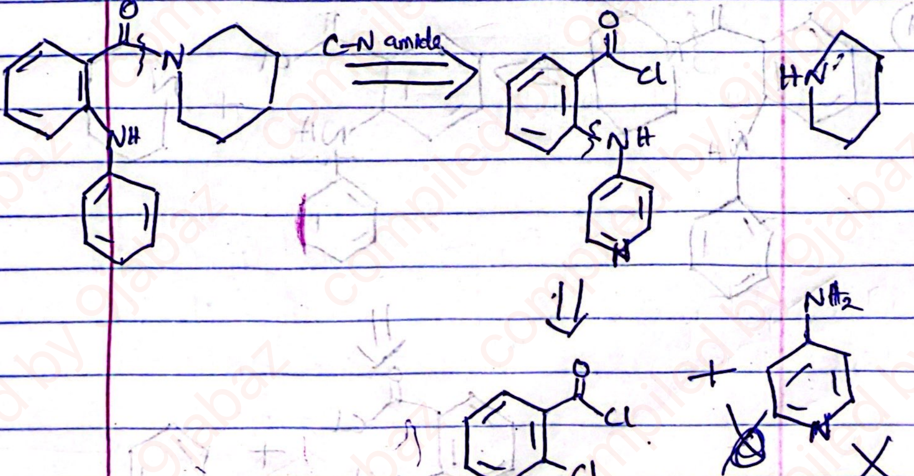
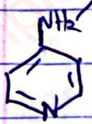
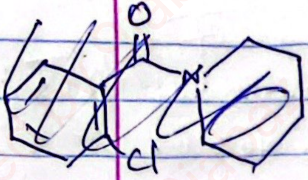


using the disconnection approach, outline a synthesis for the target molecule above;

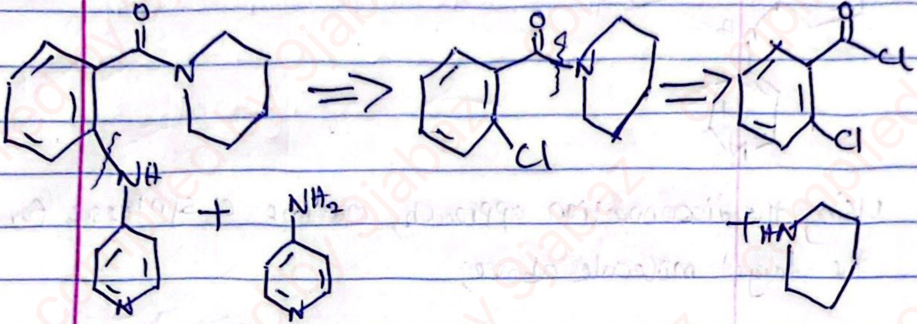


This method will not work because the  will attack the carbonyl group, not the second C–Cl. But If OH is used (for the second C–Cl) instead of Cl, it would have worked

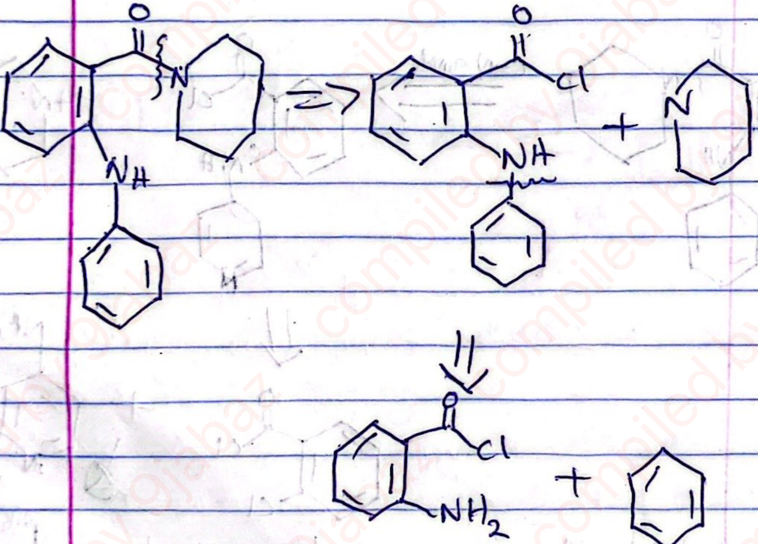
(i)



(1)



(ii)



Write the Synthesis

R-X

~~F~~unctional Group Inter Conversion

- (i) haloalkane → alcohol

  haloalkane → nitrile

synthesis involve either formation of new bond or functional group interconversion (no. of C-atom does'nt change).

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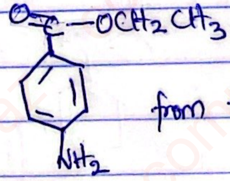
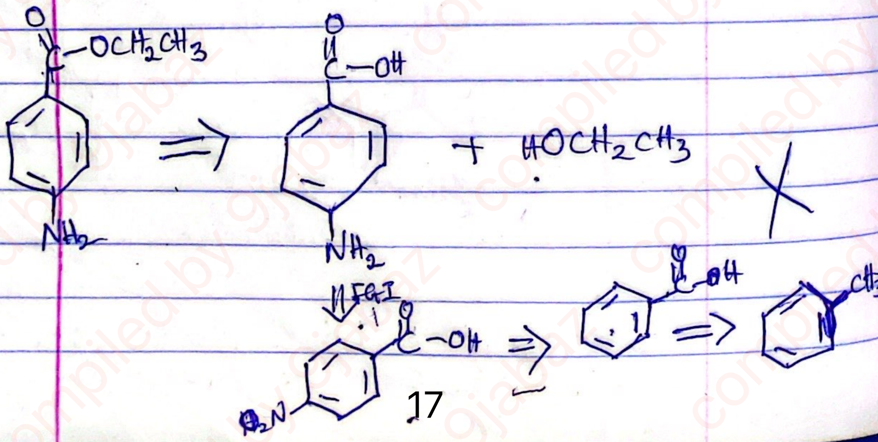
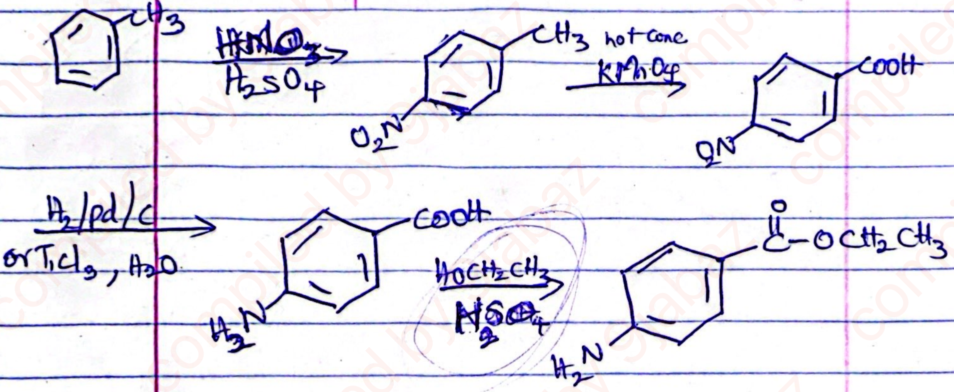
Using the disconnection approach write the synthesis for the compound below



from toluene



Synthesis



Retrosynthesis

10/04/26 Prof. Aderogba's part

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

$Na_2SO_4 + KNO_3 \longrightarrow K_2SO_4 + NaNO_3$

$2Na^+ + SO_4^{2-} + K^+ NO_3^- \rightarrow 2K^+ SO_4^{2-} + Na^+ + NO_3^-$

Inorganic reactions are instantaneous, because they exists in ion

The reactions of inorganic compounds are reactions of ions usually such reactions are instantaneous because the ions are already present in the reaction medium

$CH_3COOH + C_2H_2OH \rightleftharpoons CH_3COOC_2H_5 + H_2O$

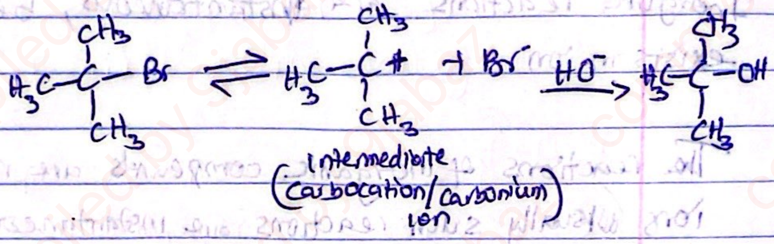
On the other hand, reactions of the organic compounds are molecular in nature, because the consitutent atoms of molecules of organic compounds are firmly bonded by covalent bonds. In this case, for a compound to undergo chemical reactions, It is essential that existing bonds must be broken and new bonds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

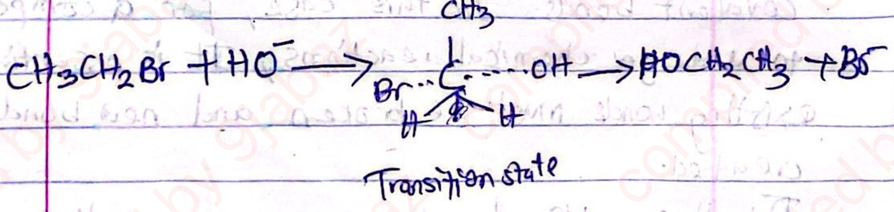
SN1



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

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

(ii) SN2



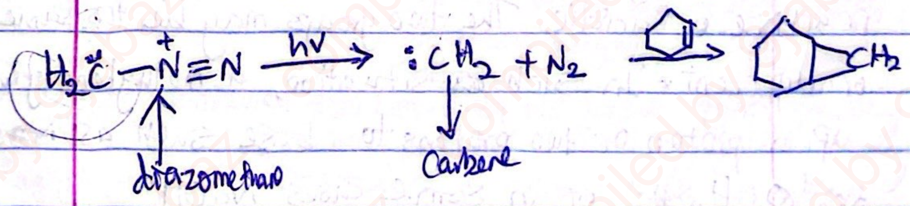
Alternatively, both processes may occur simultaneously giving synchronous or concerted step. This reaction results in the formation of transition state which may or may not be isolable.

Alkylation Reactions

It is the transfer of an alkyl group from one molecule to anoter. 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

$\cdot CH_3 + \cdot CH_3 \longrightarrow CH_3CH_3$



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 reaction 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 reaction will always have the same number of carbon as the starting material

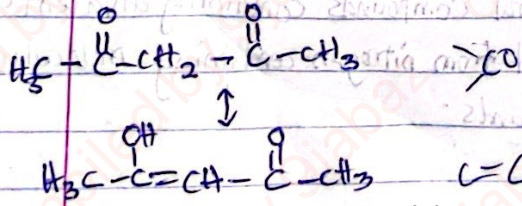
Specific Reactions

Reactive methylene Compounds $(X_1 - \overset{\alpha\text{-hydrogen}}{\overset{\uparrow}{C}}H_2 - X_2)$

When a methylene ~~compound~~ group is present between two strongly electron attracting group such as carbonyl, $-C\equiv N$, $-COOR'$, $-CHO$, $CONR'_2$, 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 situation, a methylene gives up a proton or two protons to a base such as $Na^+ \ominus OCH_2CH_3$ or in some cases NaOH

Reactive methylene e.g acetylacetone



$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$ $>CO$

$\updownarrow$

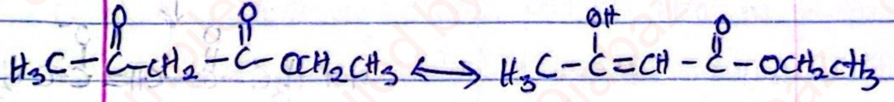
$H_3C-\overset{OH}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH_3$ $C=C$, OH

enol

on enol

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

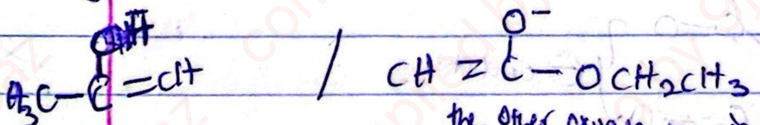
If the compound is unsymmetrical, only one form is present predominantly and the migration of H-atom depends upon the inductive effect of the alkyl group or other group present in either side of the $-CH_2-$



$$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_2CH_3 \longleftrightarrow H_3C-\overset{OH}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$$

ethyl acetoacetate

enol only one form



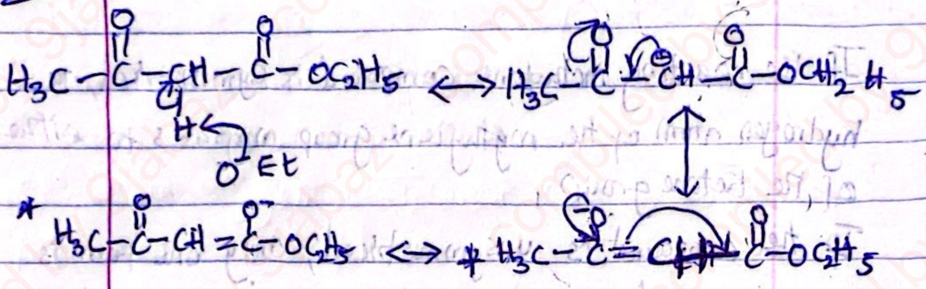
$$H_3C-\overset{OH}{\overset{|}{C}}=CH \quad / \quad CH=\overset{O^-}{\overset{|}{C}}-OCH_2CH_3$$

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 of (abstraction of proton) may take place from both keton 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

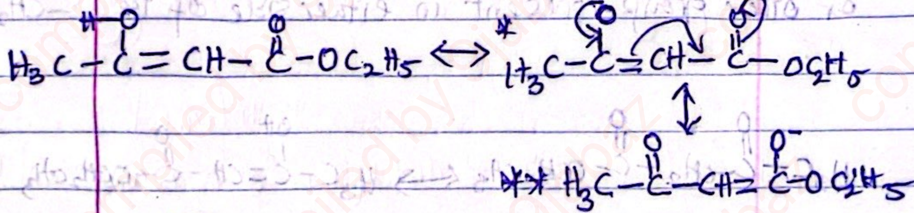


$$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \leftrightarrow H_3C-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-OCH_2H_5$$

$$H_3C-\overset{O}{\overset{\|}{C}}-CH=\overset{O^-}{C}-OC_2H_5 \leftrightarrow H_3C-\overset{\ominus O}{C}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

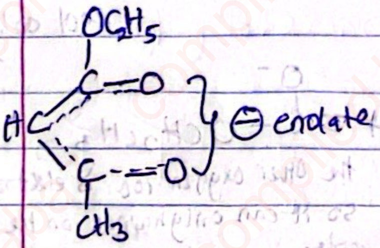
$EtONa \rightarrow EtO^- + Na^+$

Enol



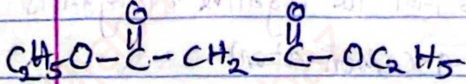
$$H_3C-\overset{H-O}{C}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5 \leftrightarrow H_3C-\overset{\ominus O}{C}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

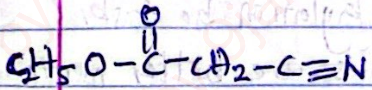
$$H_3C-\overset{O}{\overset{\|}{C}}-CH=\overset{O^-}{C}-OC_2H_5$$

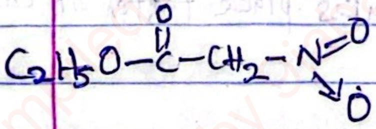


18th April, 2026

Some other examples with reactive methylene groups

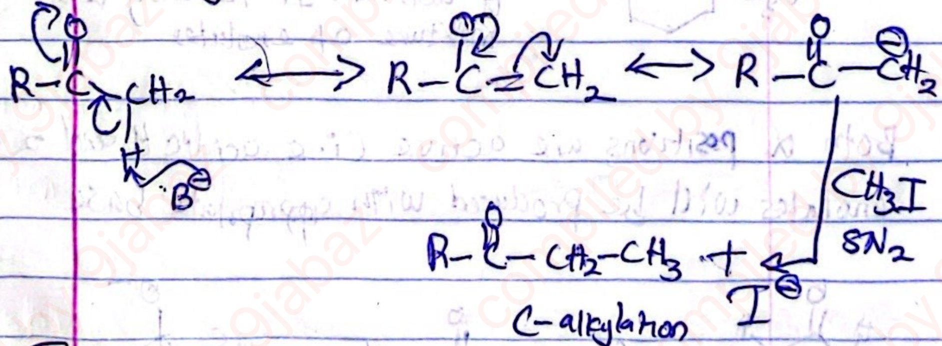
① 
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$ diethyl malonate

② 
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-C\equiv N$ ethyl cyanoacetate

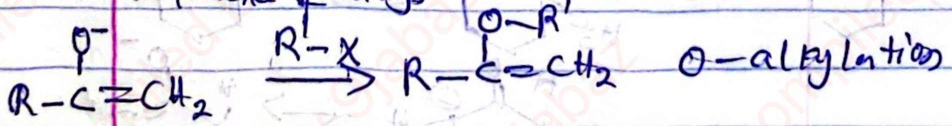
③ 
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-N(=O)\rightarrow \dot{O}$ ethyl nitro acetate

NaNH₂ been a stronger base can be used to perform reaction with reactive methylene groups with just one electron withdrawing groups

Alkylation Of Enolate



In the presence of alkyl



The enolate acts as a nucleophile. The resonance formulation of enolate anions shows that the negative charged is shared between an oxygen and a carbon atom

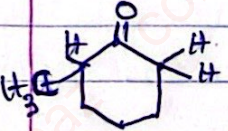
At which atom would the alkylation be faster?

It turns out that most enolates are better nucleophile at carbon. So, alkylation takes place faster at carbon than oxygen

Limitation

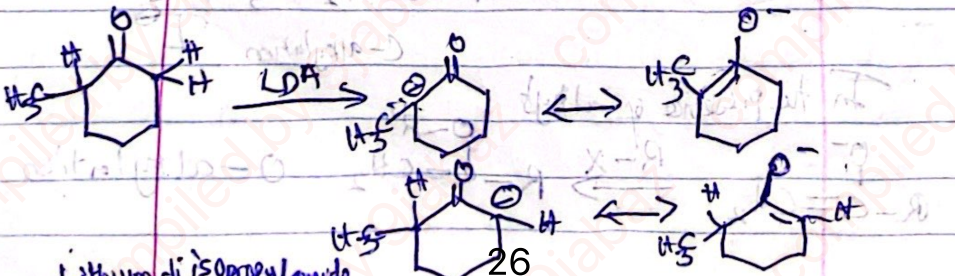
① We cannot a 3° alkyl halide due to steric hindrance

② ~~[illegible]~~ 2-methyl cyclohexanone



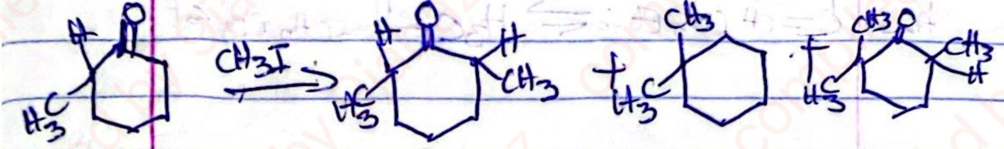
This compound has its α_1- and ~~[illegible]~~ α_2 H active. It thereby leads to mixture of enolates

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



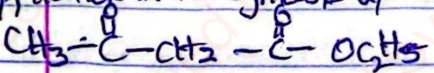
Lithium diisopropylamide

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



Important Examples

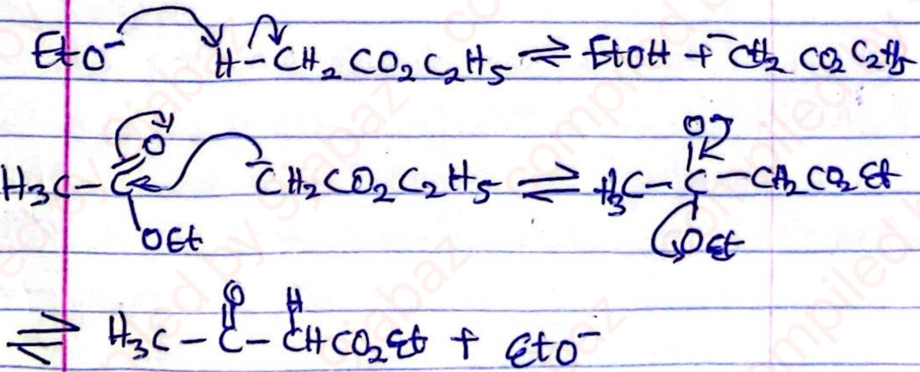
① Application in the synthesis of ethylacetoacetate



$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$

Ethylacetoacetate is the ethylesters of acetoacetic acid $CH_3\overset{O}{\overset{\|}{C}}-CH_2-COOH$. It is prepared by condensation of 2 molecules ethyl acetate in the presence of a base NaOEt. This is an example of Claisen condensation reaction

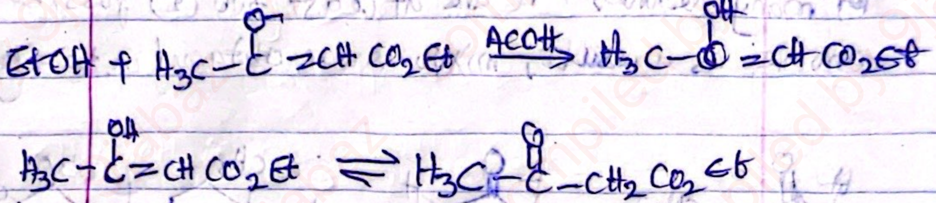
$EtONa \rightarrow EtO^- \; Na^+$



$$EtO^- \quad H-CH_2CO_2C_2H_5 \rightleftharpoons EtOH + {}^-CH_2CO_2C_2H_5$$

$$H_3C-\underset{OEt}{\overset{O}{\overset{\|}{C}}} \quad {}^-CH_2CO_2C_2H_5 \rightleftharpoons H_3C-\underset{OEt}{\overset{O^-}{C}}-CH_2CO_2Et$$

$$\rightleftharpoons H_3C-\overset{O}{\overset{\|}{C}}-\overset{H}{CH}CO_2Et + EtO^-$$



$$EtOH + H_3C-\overset{O^-}{C}=CH\,CO_2Et \xrightarrow{AcOH} H_3C-\overset{OH}{C}=CH\,CO_2Et$$

$$H_3C-\overset{OH}{C}=CH\,CO_2Et \rightleftharpoons H_3C-\overset{O}{\overset{\|}{C}}-CH_2\,CO_2Et$$

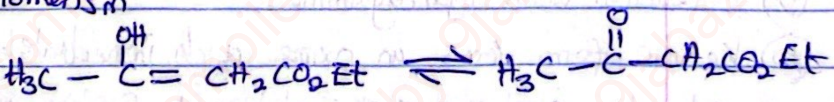
Properties of Ethylacetoacetate (physical

Properties of Ethyl 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 exhibit keto-enol tautomerism



$$H_3C-\overset{OH}{C}=CH_2CO_2Et \rightleftharpoons H_3C-\overset{O}{\overset{\|}{C}}-CH_2CO_2Et$$

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

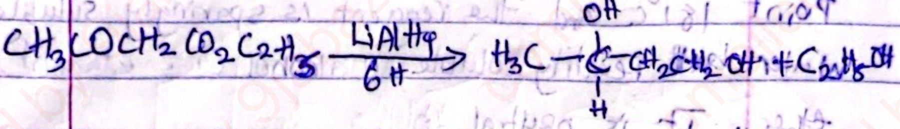
Reduction

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

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

$$CH_3COCH_2CO_2C_2H_5 + 2H \rightarrow CH_3CHOHCH_2CO_2C_2H_5$$

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



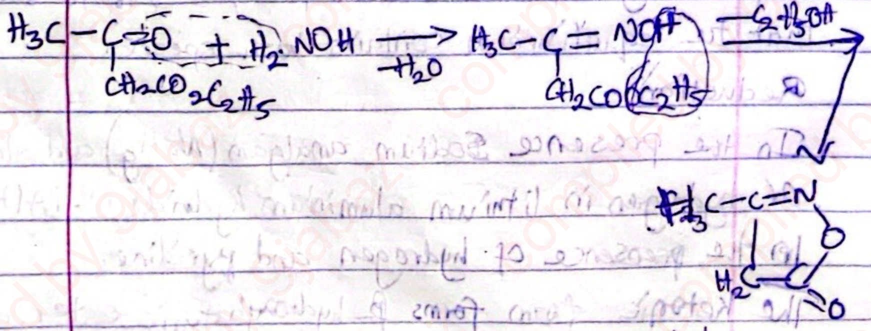
$$CH_3COCH_2CO_2C_2H_5 \xrightarrow[6H]{LiAlH_4} H_3C-\overset{OH}{\underset{H}{C}}-CH_2CH_2OH + C_2H_5OH$$

1, 3-butanediol

① Common reaction: Test for carbonyl

② Reaction with hydroxyamine

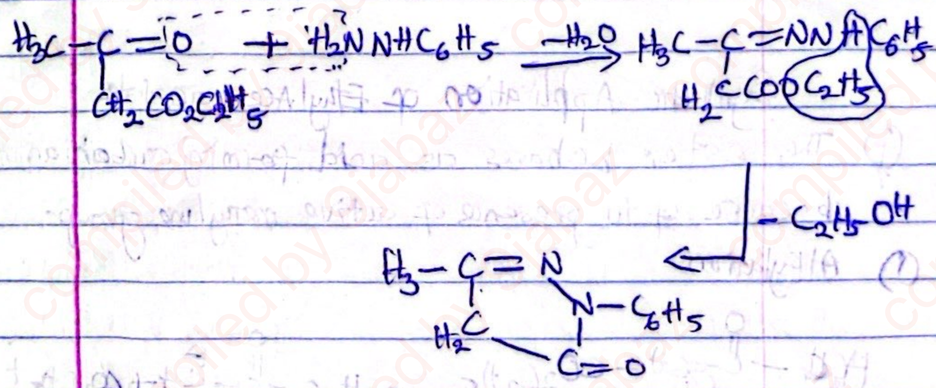
③ Ketonic form forms an oxime which immediately uses a molecule of alcohol (ethanol) and forms methyl isoxazolone.



methyl isoxalone

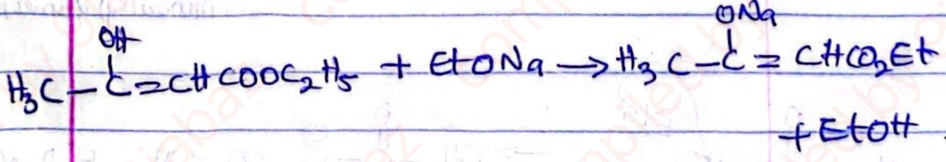
⑤ Reaction with Phenylhydrazine

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



Reactions Involving the Enolate form

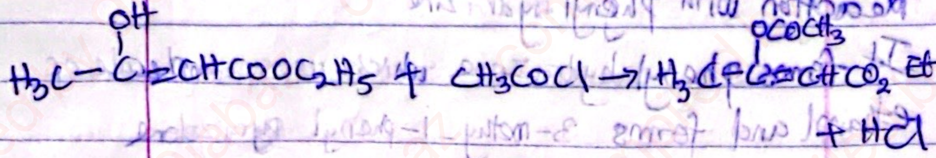
① Reaction with Na, or NaOEt to form sodio derivative of the reagent



$$H_3C-\overset{OH}{C}=CHCOOC_2H_5 + EtONa \rightarrow H_3C-\overset{ONa}{C}=CHCO_2Et + EtOH$$

② Acetylation reaction

It happens in the presence of acetyl chloride

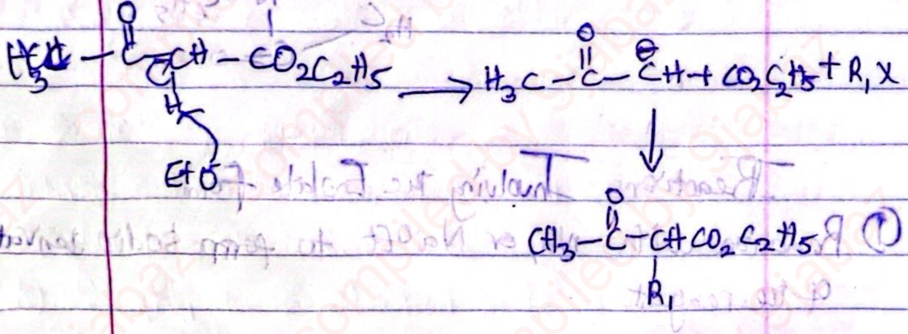


$H_3C-C(OH)=CHCOOC_2H_5 + CH_3COCl \rightarrow H_3C-C(OCOCH_3)=CHCO_2Et + HCl$

Synthetic Application of Ethyl Aceto acetate

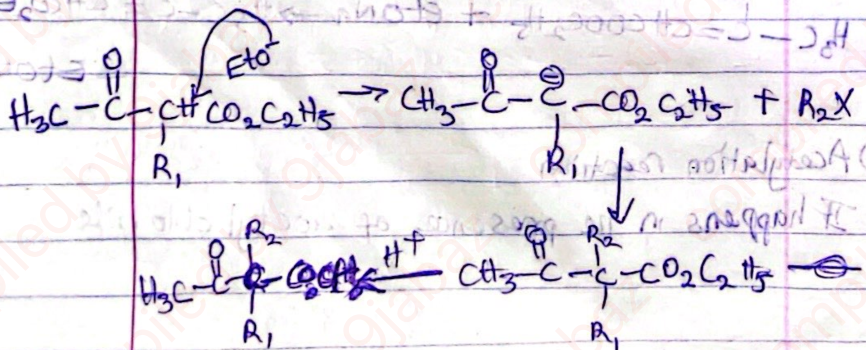
(1) The ester behaves as acid forming carbanion because of the presence of active methylene group.

(i) Alkylation



$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-CO_2C_2H_5 \xrightarrow{EtO^-} H_3C-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-CO_2C_2H_5 + R_1X \rightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH(R_1)CO_2C_2H_5$

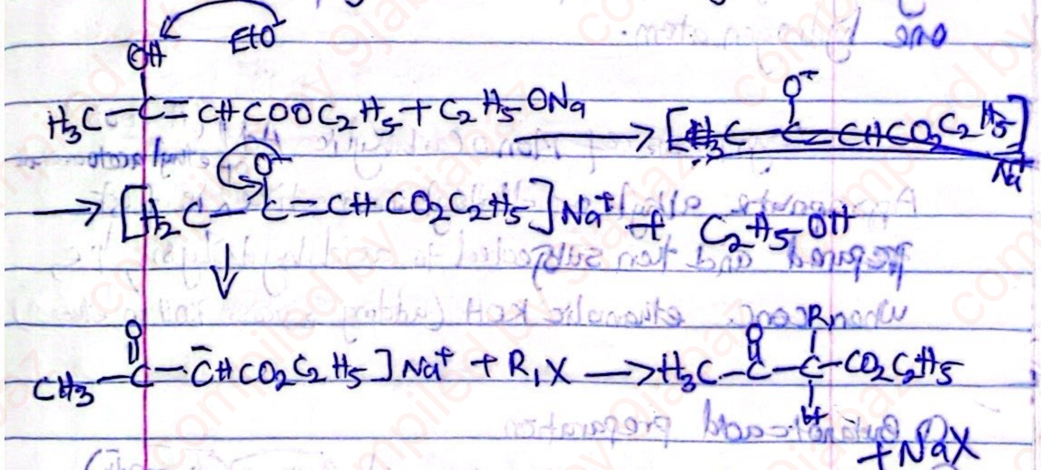
monoalkyl derivative



$H_3C-\overset{O}{\overset{\|}{C}}-CH(R_1)CO_2C_2H_5 \xrightarrow{EtO^-} CH_3-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}(R_1)-CO_2C_2H_5 + R_2X \rightarrow CH_3-\overset{O}{\overset{\|}{C}}-C(R_1)(R_2)-CO_2C_2H_5 \xrightarrow{H^+} H_3C-\overset{O}{\overset{\|}{C}}-C(R_1)(R_2)-COOH$

The carbanion is resonance stabilized and can undergo nucleophilic substitution reaction.

① mono and dialkyl derivative can be obtained as given [illegible]

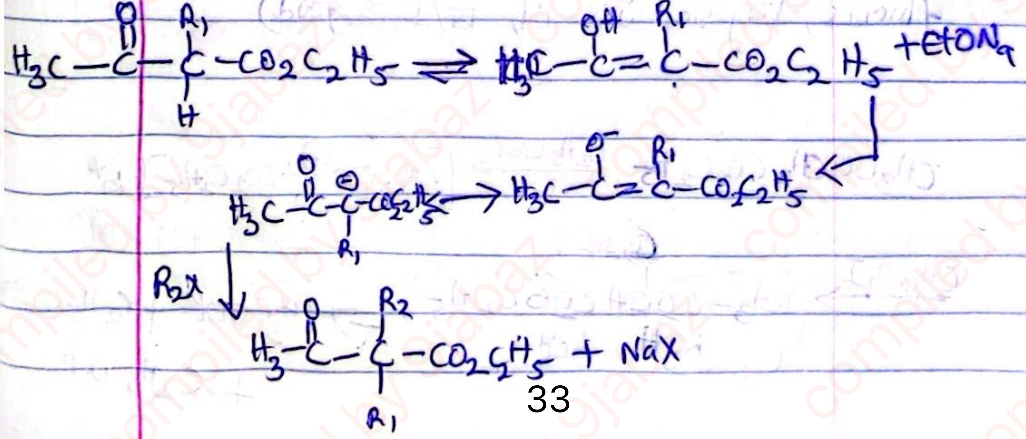


$$H_3C-\overset{OH}{C}=CHCOOC_2H_5 + C_2H_5ONa \longrightarrow \cancel{[H_3C-\overset{O^-}{C}=CHCO_2C_2H_5]Na^+}$$

$$\longrightarrow [H_3C-\overset{O^-}{C}=CHCO_2C_2H_5]Na^+ + C_2H_5OH$$

$$CH_3-\overset{O}{\overset{\|}{C}}-\bar{C}HCO_2C_2H_5]Na^+ + R_1X \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{R_1}{C}}-CO_2C_2H_5 + NaX$$

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



$$H_3C-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{R_1}{C}}-CO_2C_2H_5 \rightleftharpoons H_3C-\overset{OH}{C}=\overset{R_1}{C}-CO_2C_2H_5 + EtONa$$

$$\longrightarrow H_3C-\overset{O^-}{C}=\overset{R_1}{C}-CO_2C_2H_5$$

$$H_3C-\overset{O}{\overset{\|}{C}}-\underset{R_1}{\overset{\ominus}{C}}-CO_2C_2H_5 \xrightarrow{R_2X} H_3C-\overset{O}{\overset{\|}{C}}-\underset{R_1}{\overset{R_2}{C}}-CO_2C_2H_5 + NaX$$

Both alkyl group cannot be simultaneosly introduced with one single step because the hydrogen can only be displaced by ~~hydrogen~~ NaOEt from the enolic form which contains one hydrogen atom.

Synthesis of Monocarboxylic Acid (R-COOH)

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

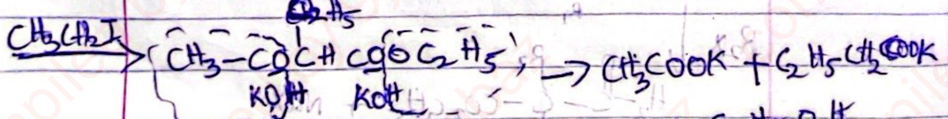
(i) Butanoic acid preparation

ⓐ Write out the formular of the acid ($CH_3CH_2CH_2COOH$)

ⓑ Identify acetic acid nucleus

ⓒ The alkyl group attached to the acetic acid nucleus is introduced $\underbrace{CH_3CH_2}$ CH_2COOH (almost impossible with fluorine, very slow with Cl, Br/I is good)

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3CO\overset{\ominus}{C}HCO_2C_2H_5]Na^+$$



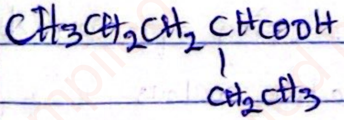
$$\xrightarrow{CH_3CH_2I} CH_3-\underset{KOH}{CO}\overset{C_2H_5}{CH}\underset{KOH}{CO}OC_2H_5 \longrightarrow CH_3COOK + C_2H_5CH_2COOK$$

$$+ C_2H_5OH$$

$C_2H_5CH_2COOH \xrightarrow{H^+} CH_3CH_2CH_2COOH$

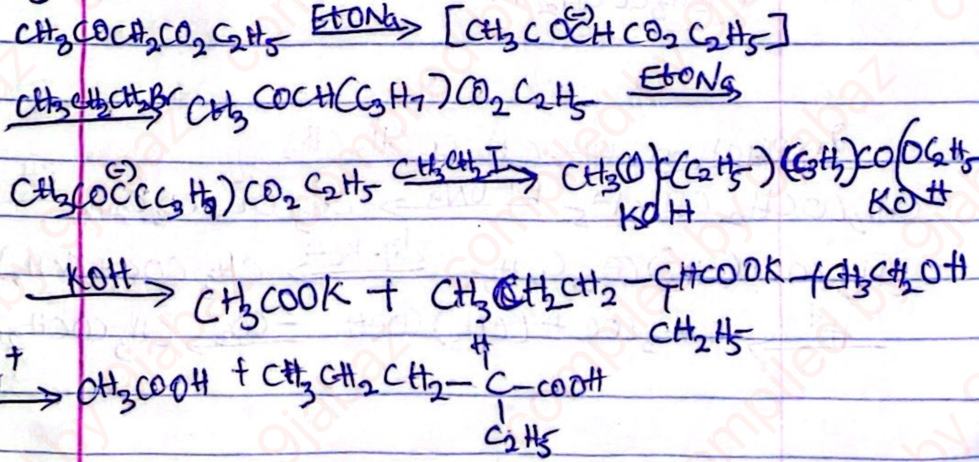
24/04/26

2-ethylpentanoic acid synthesis
Ethyl propyl acetic acid



$$\underset{\displaystyle CH_2CH_3}{CH_3CH_2CH_2\,\overset{|}{C}HCOOH}$$

Synthesis



$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{EtONa} [CH_3CO\overset{(-)}{C}HCO_2C_2H_5]$$

$$\xrightarrow{CH_3CH_2CH_2Br} CH_3COCH(C_3H_7)CO_2C_2H_5 \xrightarrow{EtONa}$$

$$CH_3CO\overset{(-)}{C}(C_3H_7)CO_2C_2H_5 \xrightarrow{CH_3CH_2I} CH_3CO\,C(C_2H_5)(C_3H_7)CO\,OC_2H_5$$

KOH KOH

$$\xrightarrow{KOH} CH_3COOK + CH_3CH_2CH_2-\underset{\displaystyle CH_2H_5}{\overset{|}{C}HCOOK} + CH_3CH_2OH$$

$$\xrightarrow{H^+} CH_3COOH + CH_3CH_2CH_2-\underset{\displaystyle C_2H_5}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-COOH$$

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

Synthesis of Keton

Ketone can be synthesized via $\overline{\text{ethyl}}$acetoacetate provided it contains the group, CH_3CO-

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

acetone nucleus

$$\boxed{CH_3COCH_2}R$$

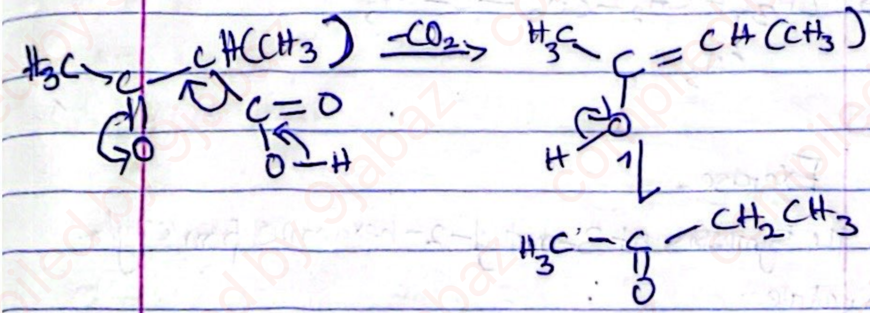
Preparation of $CH_3COCH_2CH_3$

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{EtONa} CH_3CO\overset{(-)}{C}HCO_2C_2H_5 \xrightarrow{CH_3Br}$$

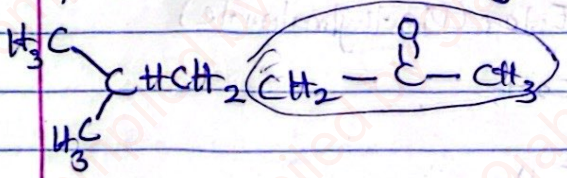
$$CH_3COCH(CH_3)CO_2C_2H_5 \xrightarrow{dil.\ KOH} CH_3COCH(CH_3)COOK$$

$$\xrightarrow{H^+} CH_3COCH(CH_3)COOH \xrightarrow{-CO_2} CH_3COCH_2CH_3$$

Mechanism of Decarboxylation



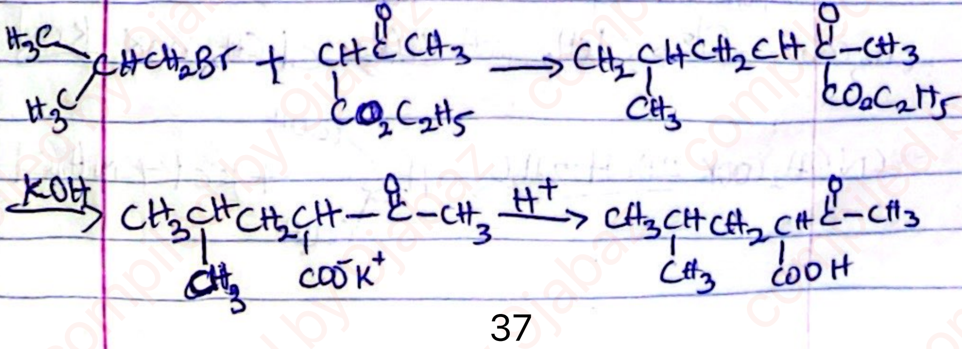
Preparation of 5-methyl-2-hexenone



$CH_3COCH_2CO_2C_2H_5$

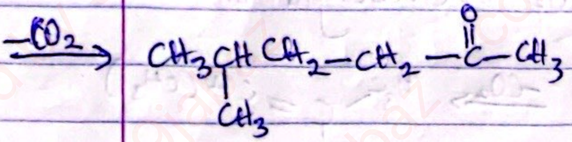
In order to prepare the ketone above by ethylacetate synthesis, isobutylbromide must be made use of

$CH_3COCH_2CO_2C_2H_5 \xrightarrow{EtONa} CH_3CO\overset{-}{C}HCO_2C_2H_5$



$$(H_3C)_2CHCH_2Br + \underset{CO_2C_2H_5}{CH}\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow CH_2\underset{CH_3}{CH}CH_2\underset{CO_2C_2H_5}{CH}\overset{O}{\overset{\|}{C}}-CH_3$$

$$\xrightarrow{KOH} CH_3\underset{CH_3}{CH}CH_2\underset{COO^-K^+}{CH}-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{H^+} CH_3\underset{CH_3}{CH}CH_2\underset{COOH}{CH}\overset{O}{\overset{\|}{C}}-CH_3$$

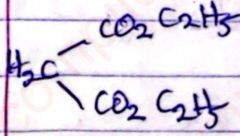


$$\xrightarrow{-CO_2} CH_3\underset{\underset{CH_3}{|}}{C}H\,CH_2-CH_2-\overset{\overset{O}{\|}}{C}-CH_3$$

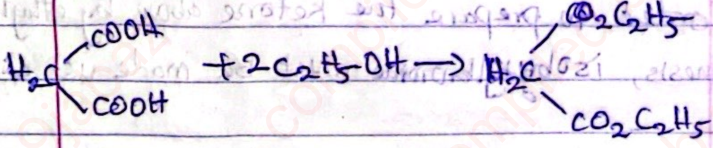
Exercise

Outline the synthesis of 3-methyl-2-hexanone from ethyle acetoacetate

Malonic Ester (Dimethylmalonate)

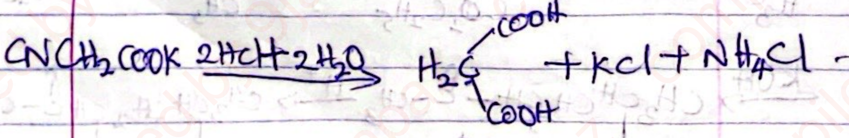


It is prepared from malonic acid



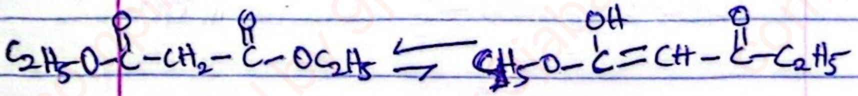
Preparation of Malonic Acid

$CH_3COOH \xrightarrow{Cl_2} ClCH_2COOH \xrightarrow{K_2CO_3} ClCH_2COOK \xrightarrow{KCN}$



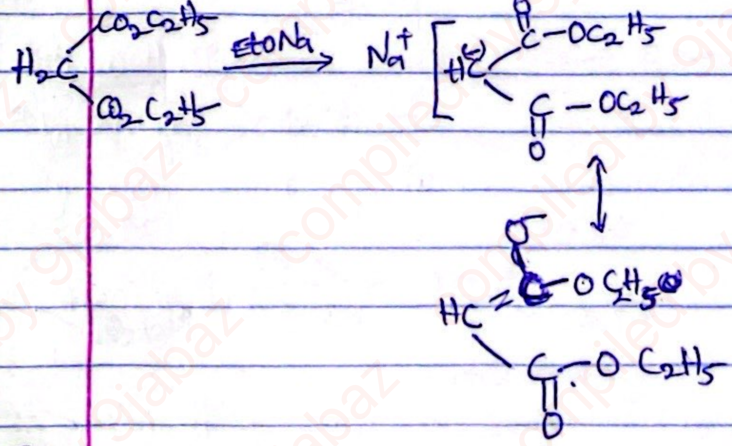
$$CNCH_2COOK \xrightarrow{2HCl + 2H_2O} H_2C(COOH)_2 + KCl + NH_4Cl$$

In presence of 2 carbonyl groups, one each on either side of methylene group except 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



$$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \rightleftharpoons C_2H_5O-\overset{OH}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-C_2H_5$$

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



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

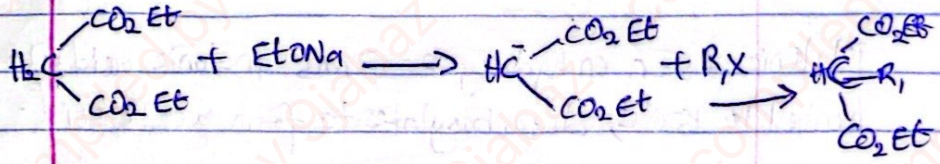
25th April, 2026

KOH in ethanol attack carbonyl

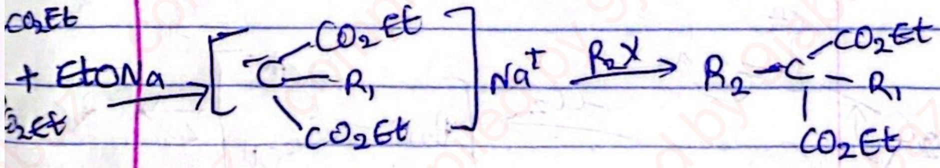
KOH dilute attack carbonyl ester

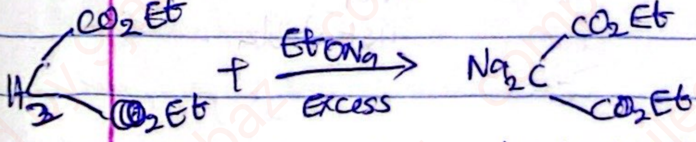
Example of nucleophilic substitution reaction

(i) Reaction with alkyl halide (alkylation)



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

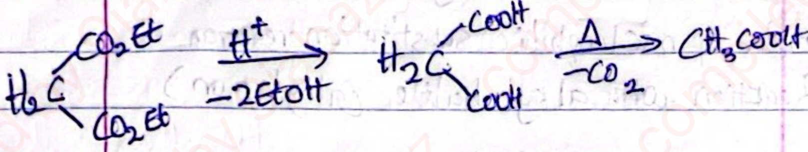




disodiodiethyl malonate

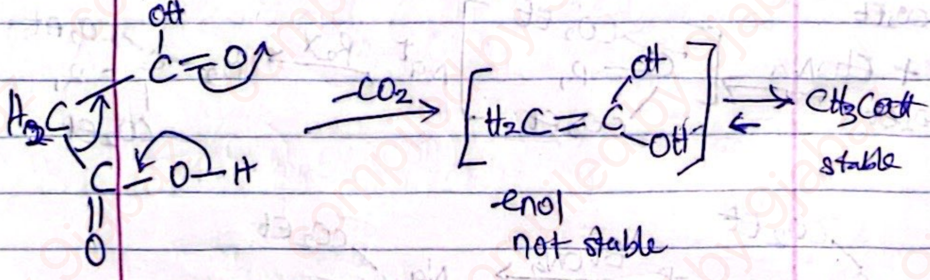
Synthetic Application

Synthesis of Monocarboxylic acid



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

Mechanism of Decarboxylation

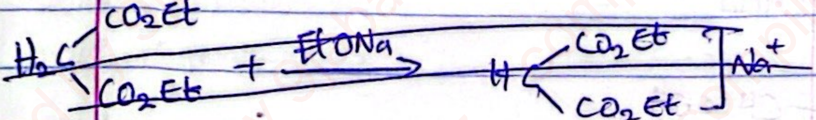


Using this method, we can prepare higher ~~Carboxylic acid~~ fatty acids as follows;

(i) Write out the structural formular of the acid required

(ii) Identify acetic acid nucleus from the structural formular of the acid required.

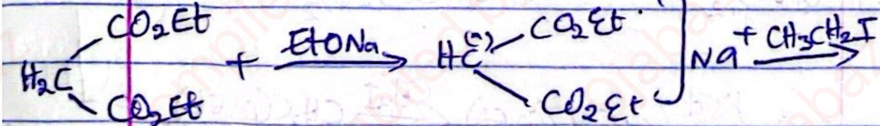
ii) Prepare Sodio malonic, and treate it with an approxiate alkyl halide followed by acid hydrolysis.



$$H_2C\begin{cases}CO_2Et\\CO_2Et\end{cases} + \xrightarrow{EtONa} \left[H\overset{}{C}\begin{cases}CO_2Et\\CO_2Et\end{cases}\right]Na^+$$

Synthesis of Butanic Acid

(1) $CH_3CH_2\boxed{CH_2COOH}$



$$H_2C\begin{cases}CO_2Et\\CO_2Et\end{cases} + \xrightarrow{EtONa} \left[H\overset{(-)}{C}\begin{cases}CO_2Et\\CO_2Et\end{cases}\right]Na^+ \xrightarrow{CH_3CH_2I}$$

$$C_2H_5CH(CO_2Et)_2 \xrightarrow[-2EtOH]{KOH} C_2H_5CH(COOK)_2$$

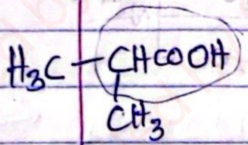
Ethyl malonic ester

$$\xrightarrow{H^+} C_2H_5CH(COOH)_2 \xrightarrow[\substack{150-200°c\\-CO_2}]{\Delta} C_2H_5CH_2COOH$$

) 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. Dialkyl ester form obtained when ~~you~~ refluxed with

KOH and acidified HCl to form dialkyl malonic acid, which decarboxylate on heating and forms dialkyl acid



$H_3C-CH(CH_3)COOH$

dimethyl acetic acid.

$$H_2C(CO_2Et)_2 \xrightarrow{EtONa} \overset{+}{Na}\,\overset{\ominus}{C}H(CO_2Et)_2 \xrightarrow{CH_3I} CH_3CH(CO_2Et)_2$$

$$\xrightarrow{EtONa} CH_3\overset{\ominus}{C}(CO_2Et)_2 \xrightarrow{CH_3I} (CH_3)_2C(CO_2Et)_2 \xrightarrow{KOH} (CH_3)_2C(COOK)_2$$

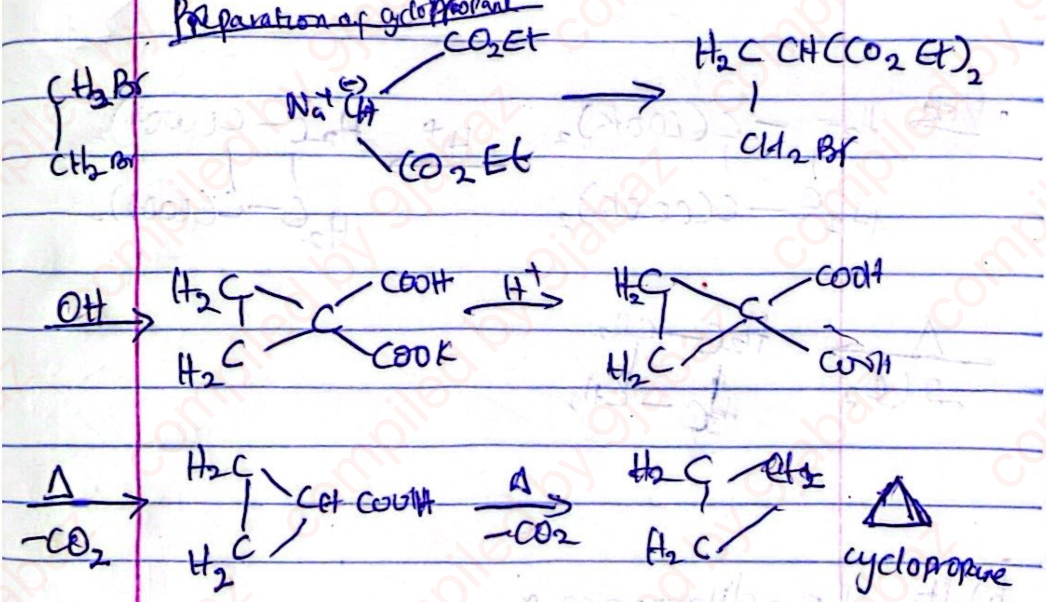
$$\xrightarrow{H^+} (CH_3)_2C(COOH)_2 \xrightarrow[150^\circ-200^\circ C]{\Delta} (CH_3)_2CHCOOH$$

This reaction indicates where two alkyl groups are the same, the dialkyl derivatives is obtained in one operation by taking 2 moles of NaOEt per mole of diethylmalonate and ~~And trough mixture dilution~~ treat the mixture with excess alkyl halide

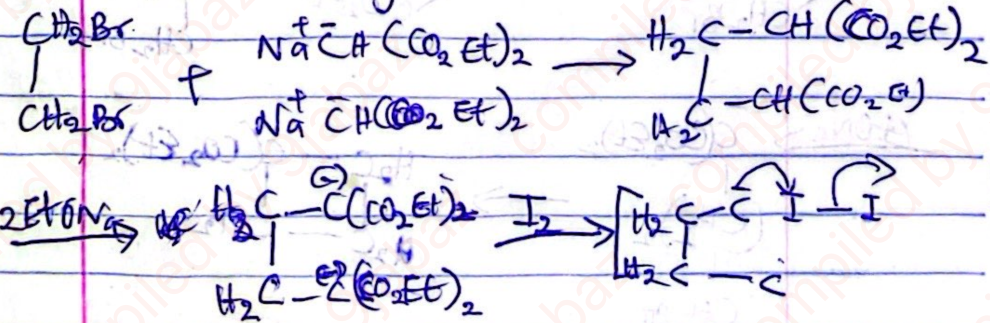
(8) Synthesis of Cyclic Compounds

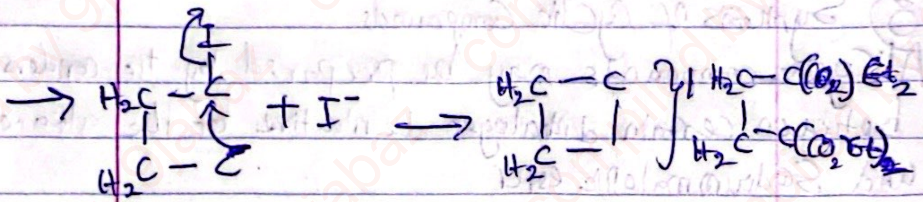
Alicyclic compounds may be prepared by the condensation between certain dihalogen derivative of the alkane and Sodiummalonic ester

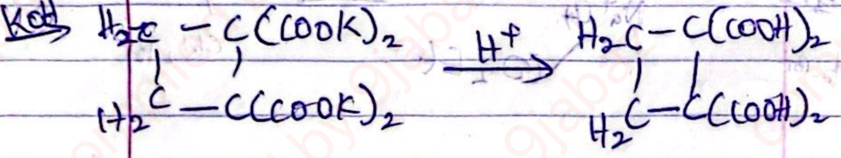
Preparation of cyclopropane

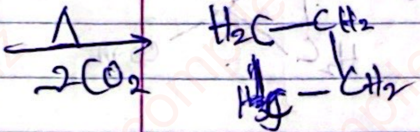


Preparation of cyclobutane

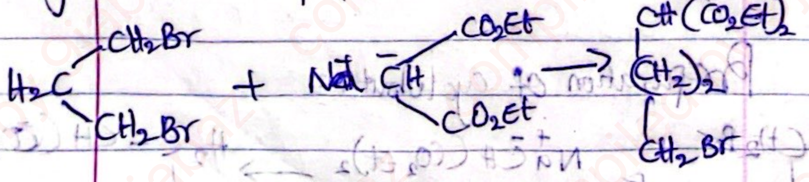


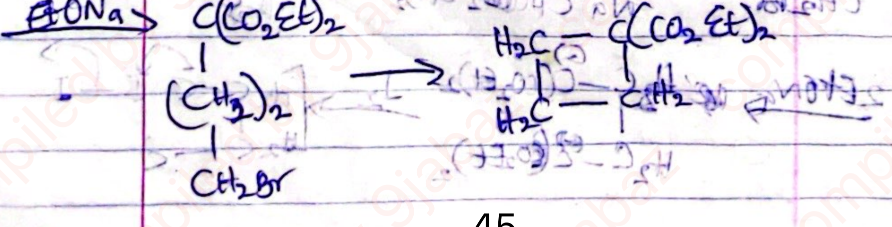


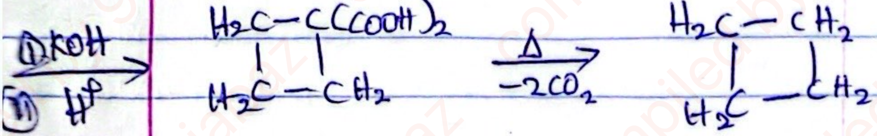




h) Using 1,3-dibromopropane







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