ACTIVE METHYLENE Compounds

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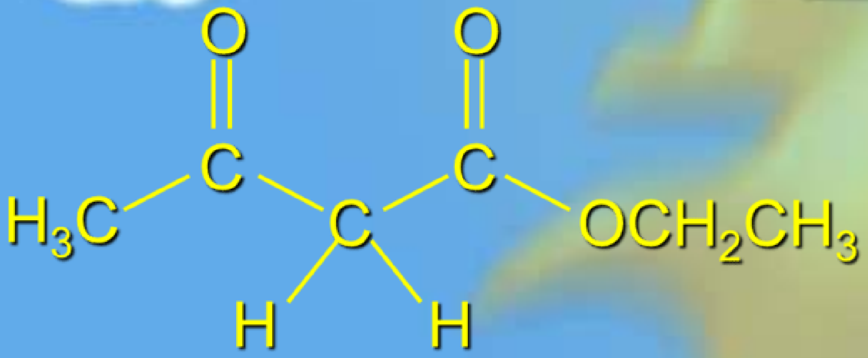
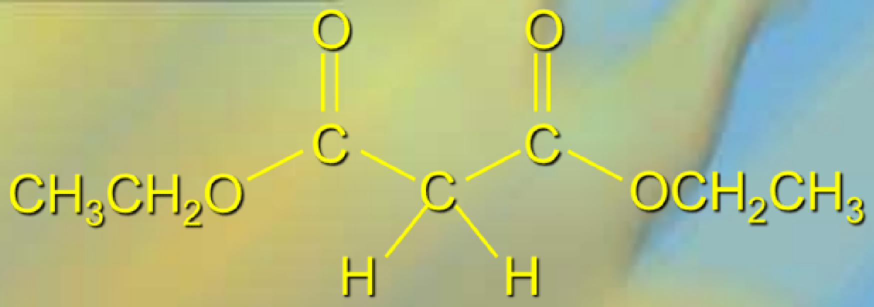
ACTIVE METHYLENE COMPOUNDS

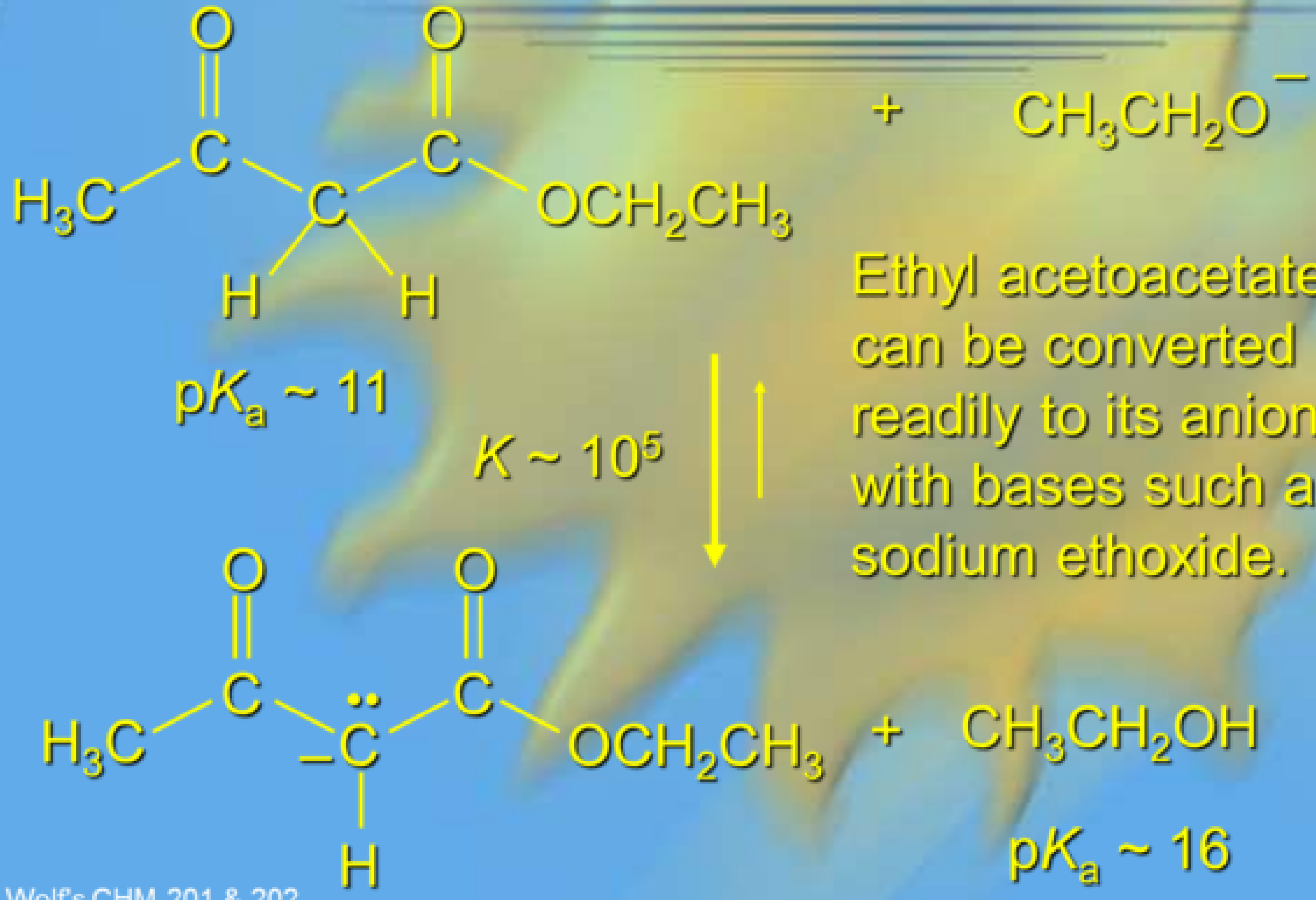




- *Acetoacetic ester* is another name for *ethyl acetoacetate.*
- The "acetoacetic ester synthesis" uses acetoacetic ester as a reactant for the preparation of ketones.

Malonic ester is another name for diethyl malonate.
The "malonic ester synthesis" uses diethyl malonate as a reactant for the preparation of carboxylic acids.

APPLICATION OF ETHYL ACETOACETATE

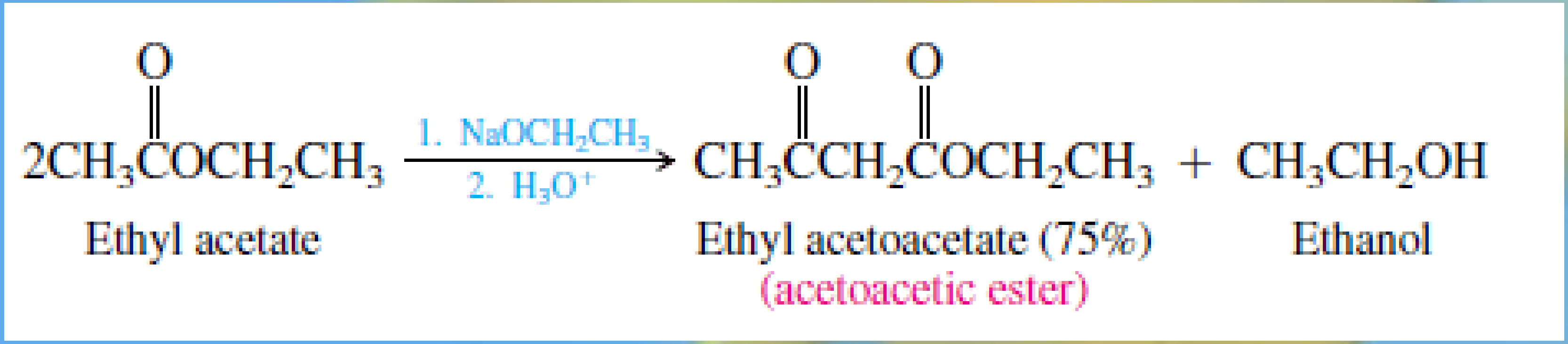


Ethyl acetoacetate can be converted readily to its anion with bases such as sodium ethoxide.

SYNTHESIS OF ETHYL ACETOACETATE

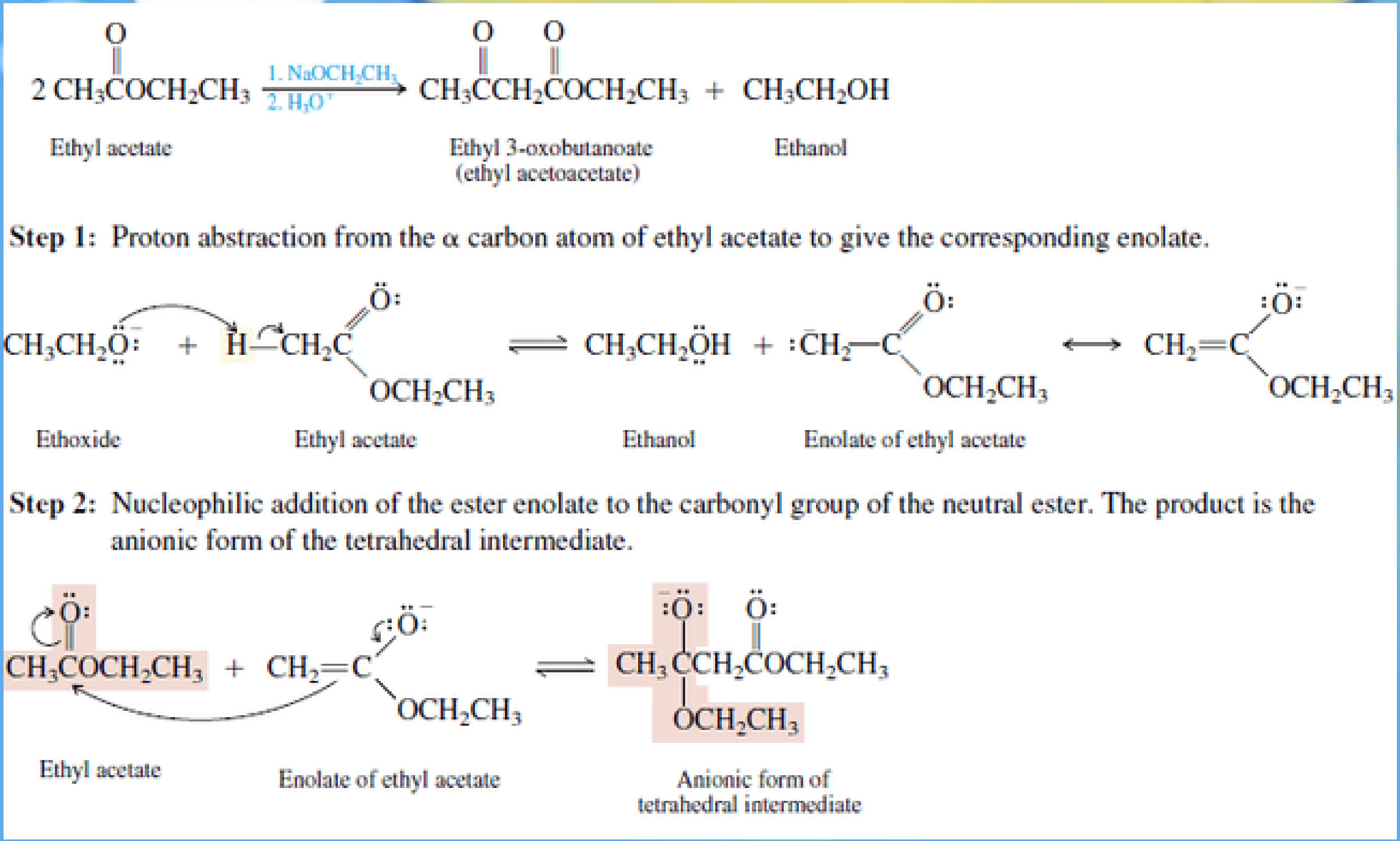
THE CLAISEN CONDENSATION

On treatment with alkoxide bases, esters undergo self-condensation to give a β-keto ester and an alcohol.



$$2CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$$

OVERALL REACTION:



$$2\ CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2OH$$

Ethyl acetate

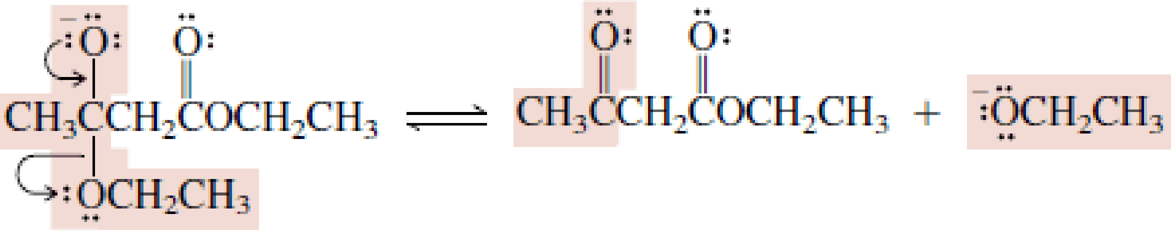
Ethyl 3-oxobutanoate
(ethyl acetoacetate)

Ethanol

Step 1: Proton abstraction from the α carbon atom of ethyl acetate to give the corresponding enolate.

Step 2: Nucleophilic addition of the ester enolate to the carbonyl group of the neutral ester. The product is the anionic form of the tetrahedral intermediate.

Step 3: Dissociation of the tetrahedral intermediate.



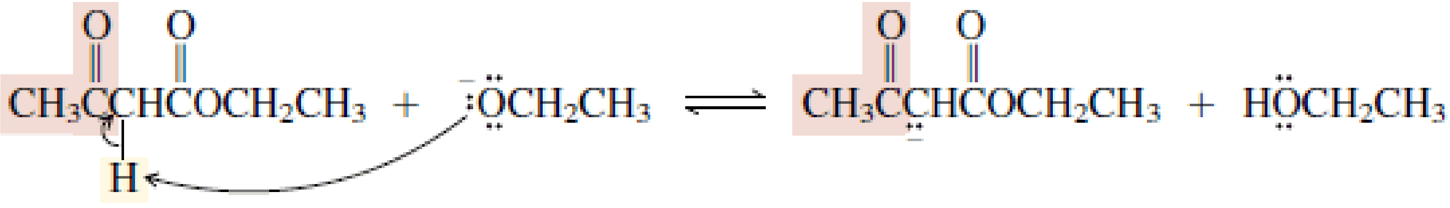
$$CH_3\underset{OCH_2CH_3}{\overset{O^-}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + {}^-OCH_2CH_3$$

Anionic form of tetrahedral intermediate

Ethyl 3-oxobutanoate

Ethoxide ion

Step 4: Deprotonation of the β-keto ester product.



$$CH_3\overset{O}{\overset{\|}{C}}\underset{H}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + {}^-OCH_2CH_3 \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\overset{-}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + HOCH_2CH_3$$

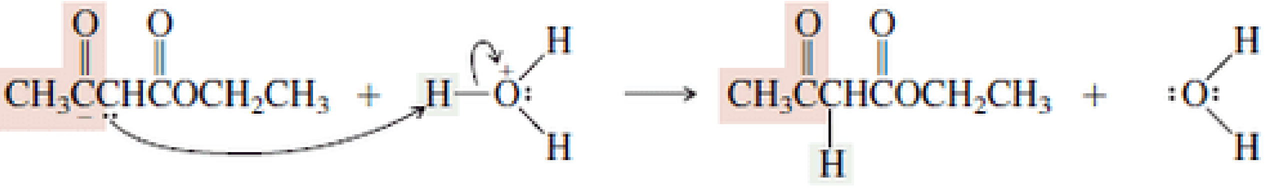
Ethyl 3-oxobutanoate (stronger acid)

Ethoxide ion (stronger base)

Conjugate base of ethyl 3-oxobutanoate (weaker base)

Ethanol (weaker acid)

Step 5: Acidification of the reaction mixture. This is performed in a separate synthetic operation to give the product in its neutral form for eventual isolation.



$$CH_3\overset{O}{\overset{\|}{C}}\overset{-}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + H-\overset{+}{O}H_2 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}\underset{H}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + H_2O$$

Conjugate base of ethyl 3-oxobutanoate (stronger base)

Hydronium ion (stronger acid)

Ethyl 3-oxobutanoate (weaker acid)

Water (weaker base)

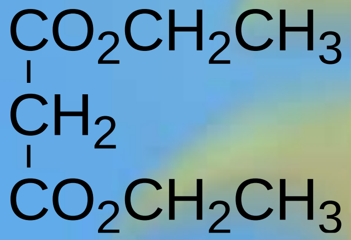
SYNTHESIS OF DIETHYL MALONATE

$$\begin{tikzcd}
Cl{-}CH_2{}^{\cdot}COOH \arrow[r, "Na_2CO_3"] & Cl{-}CH_2{}^{\cdot}CONa \arrow[r, "NaCN"] & NC{-}CH_2{}^{\cdot}CONa \arrow[d, "H^+"] \\
C_2H_5OOC{-}CH_2{}^{\cdot}COOC_2H_5 & & HOOC{-}CH_2{}^{\cdot}CONa \arrow[ll, "C_2H_5OH/H_2SO_4", "Heat"']
\end{tikzcd}$$

Diethyl malonate

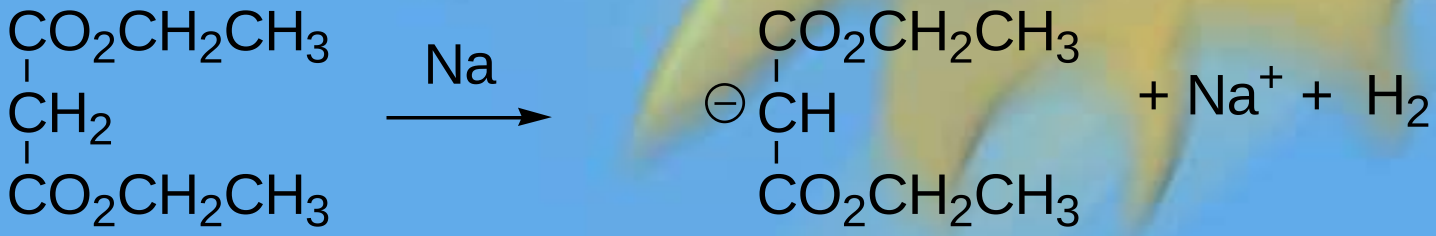
APPLICATION OF DIETHYL MALONATE

1.Diethyl malonate has acidic alpha-hydrogens



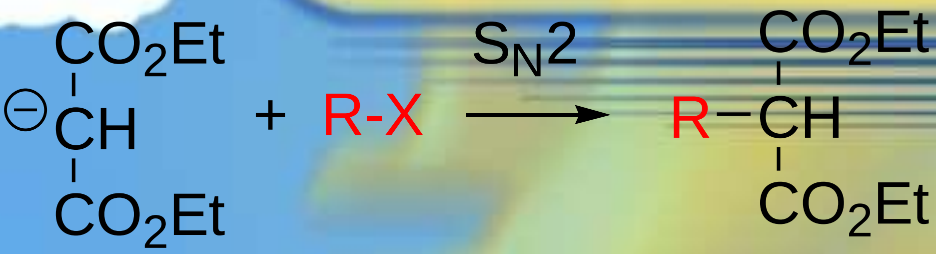
$$\begin{array}{l} \mathrm{CO_2CH_2CH_3} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{CO_2CH_2CH_3} \end{array}$$

2.When reacted with sodium metal, the ester is converted into its conjugate base (an enolate anion)



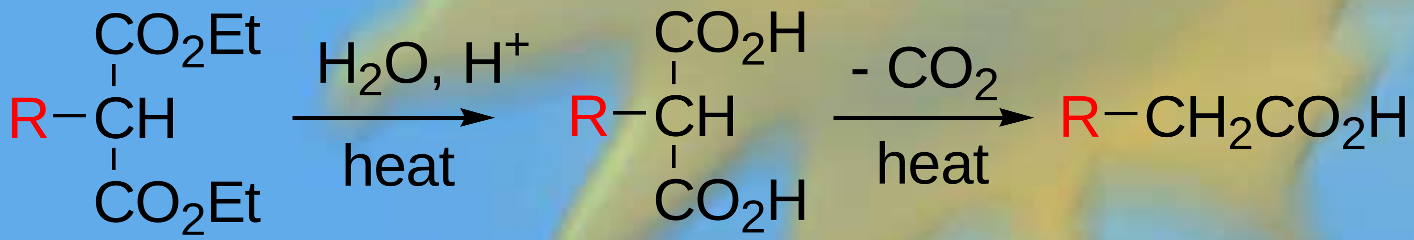
$$\begin{array}{l} \mathrm{CO_2CH_2CH_3} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{CO_2CH_2CH_3} \end{array} \xrightarrow{\mathrm{Na}} \begin{array}{l} \mathrm{CO_2CH_2CH_3} \\ | \\ \ominus\,\mathrm{CH} \\ | \\ \mathrm{CO_2CH_2CH_3} \end{array} + \mathrm{Na^+} + \mathrm{H_2}$$

3. The enolate can be used as the nucleophile in an S_N2 reaction with a 1° or CH_3 alkyl halide.



$$\overset{\ominus}{C}H(CO_2Et)_2 + R\text{-}X \xrightarrow{S_N2} R-CH(CO_2Et)_2$$

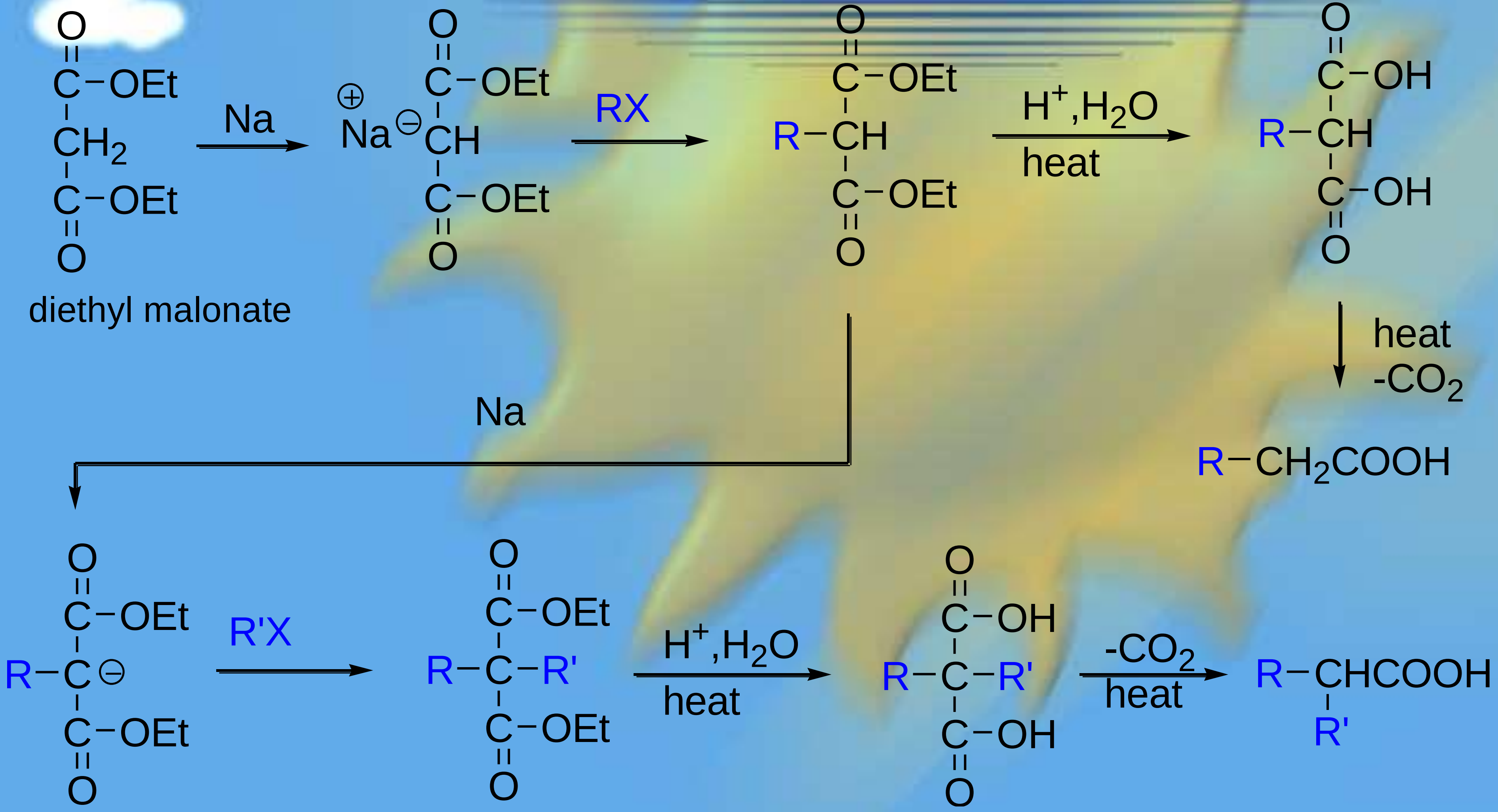
4. Upon hydrolysis, the substituted malonic acid will decarboxylate when heated.



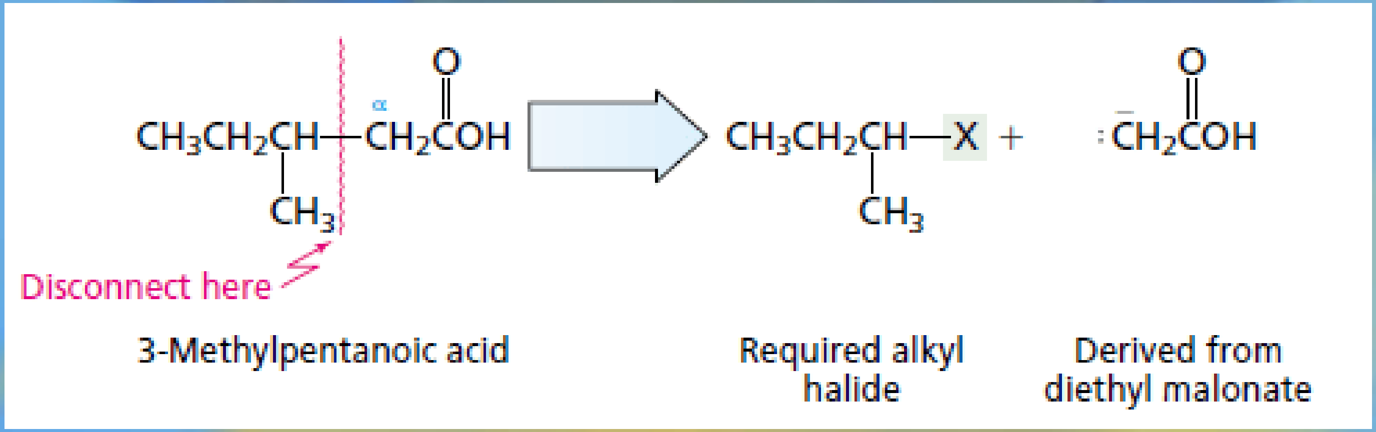
$$R-CH(CO_2Et)_2 \xrightarrow[\text{heat}]{H_2O,\ H^+} R-CH(CO_2H)_2 \xrightarrow[\text{heat}]{-\ CO_2} R-CH_2CO_2H$$

5. Product is a carboxylic acid derived from acetic acid.

SYNTHESIS OF CARBOXYLIC ACIDS FROM DIETHYL MALONATE



SYNTHESIS OF 3-Methylpentanoic acid FROM DIETHYL MALONATE

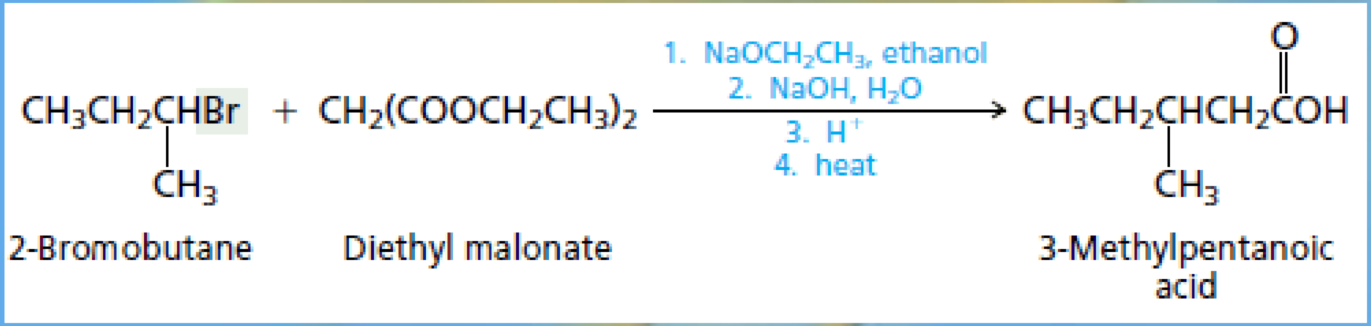


$$CH_3CH_2\underset{\displaystyle CH_3}{CH}-\overset{\alpha}{C}H_2\overset{\displaystyle O}{\overset{\|}{C}}OH \Rightarrow CH_3CH_2\underset{\displaystyle CH_3}{CH}-X + {}^{-}\!:CH_2\overset{\displaystyle O}{\overset{\|}{C}}OH$$

3-Methylpentanoic acid

Required alkyl halide

Derived from diethyl malonate



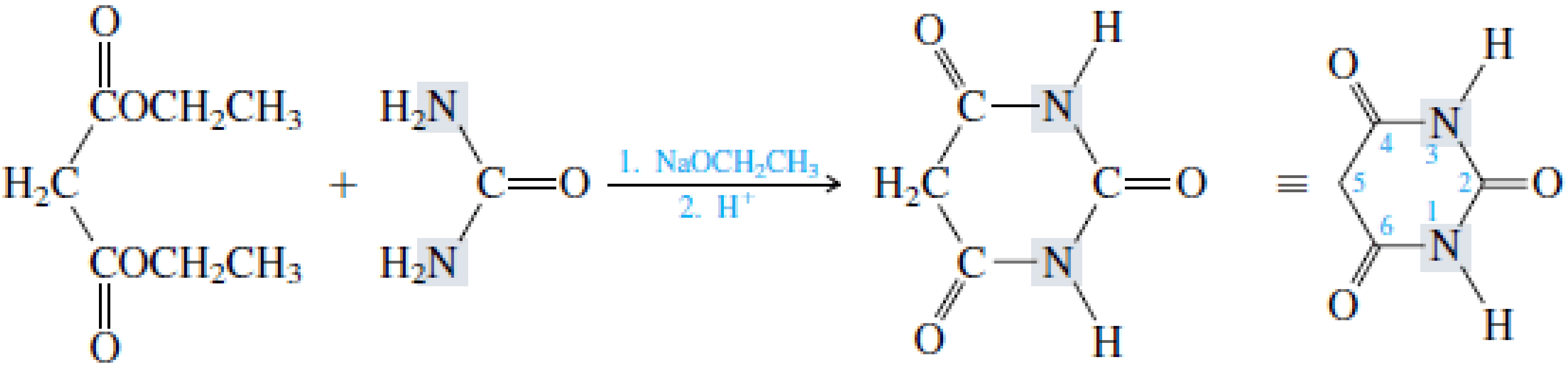
$$CH_3CH_2\underset{\displaystyle CH_3}{CH}Br + CH_2(COOCH_2CH_3)_2 \xrightarrow[\text{3. } H^+ \text{ 4. heat}]{\text{1. } NaOCH_2CH_3\text{, ethanol 2. } NaOH\text{, } H_2O} CH_3CH_2\underset{\displaystyle CH_3}{CH}CH_2\overset{\displaystyle O}{\overset{\|}{C}}OH$$

2-Bromobutane

Diethyl malonate

3-Methylpentanoic acid

SYNTHESIS OF BARBITURIC acid FROM DIETHYL MALONATE

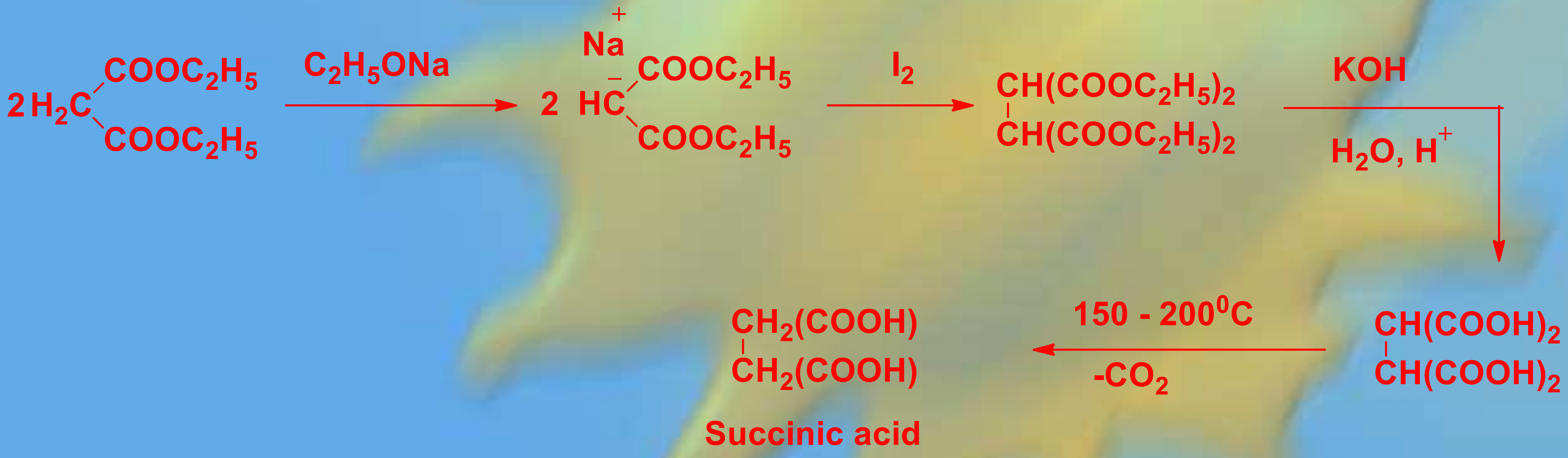


Diethyl malonate

Urea

Barbituric acid (72–78%)

SYNTHESIS OF Succinic acid FROM DIETHYL MALONATE

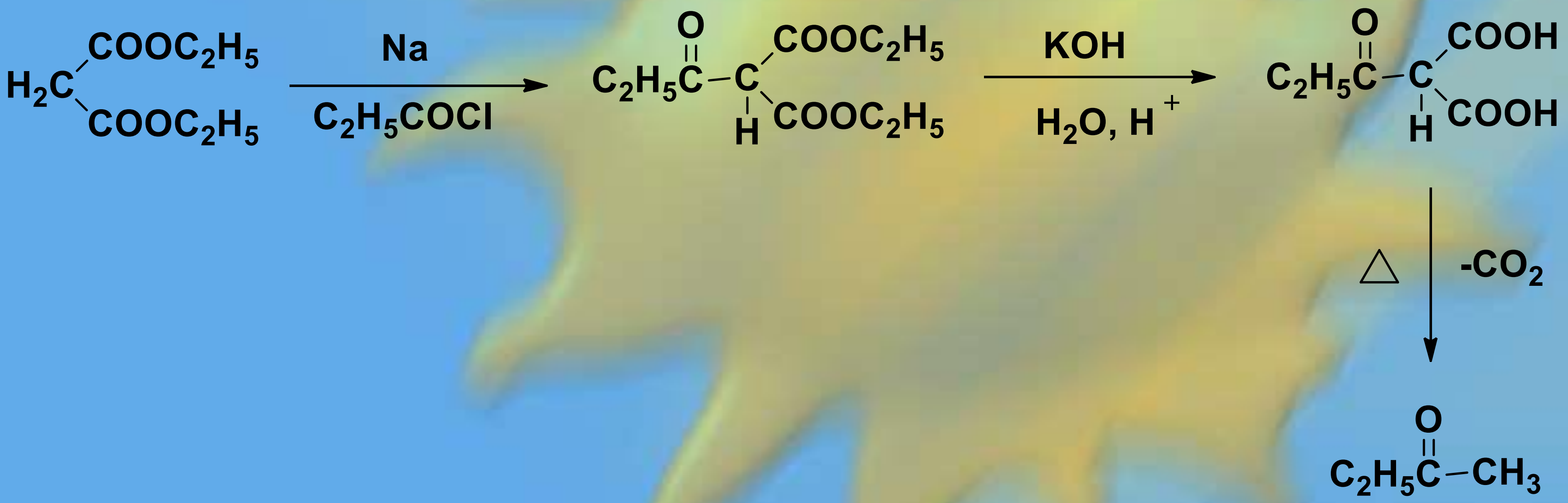


$2\,H_2C(COOC_2H_5)_2 \xrightarrow{C_2H_5ONa} 2\,\overset{+}{Na}\,\overset{-}{H}C(COOC_2H_5)_2 \xrightarrow{I_2} \begin{matrix} CH(COOC_2H_5)_2 \\ | \\ CH(COOC_2H_5)_2 \end{matrix}$

$\xrightarrow[H_2O,\ H^+]{KOH} \begin{matrix} CH(COOH)_2 \\ | \\ CH(COOH)_2 \end{matrix} \xrightarrow[-CO_2]{150 - 200^0C} \begin{matrix} CH_2(COOH) \\ | \\ CH_2(COOH) \end{matrix}$

Succinic acid

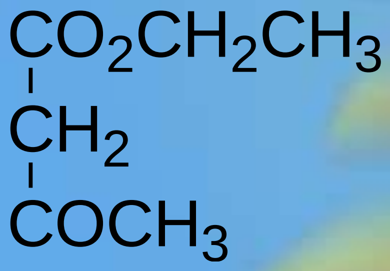
SYNTHESIS OF BuTANONE FROM DIETHYL MALONATE



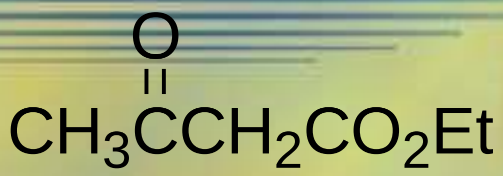
Butanone

APPLICATION OF ETHYL ACETOTATE

1. Ethyl acetoacetate has acidic alpha-hydrogens.



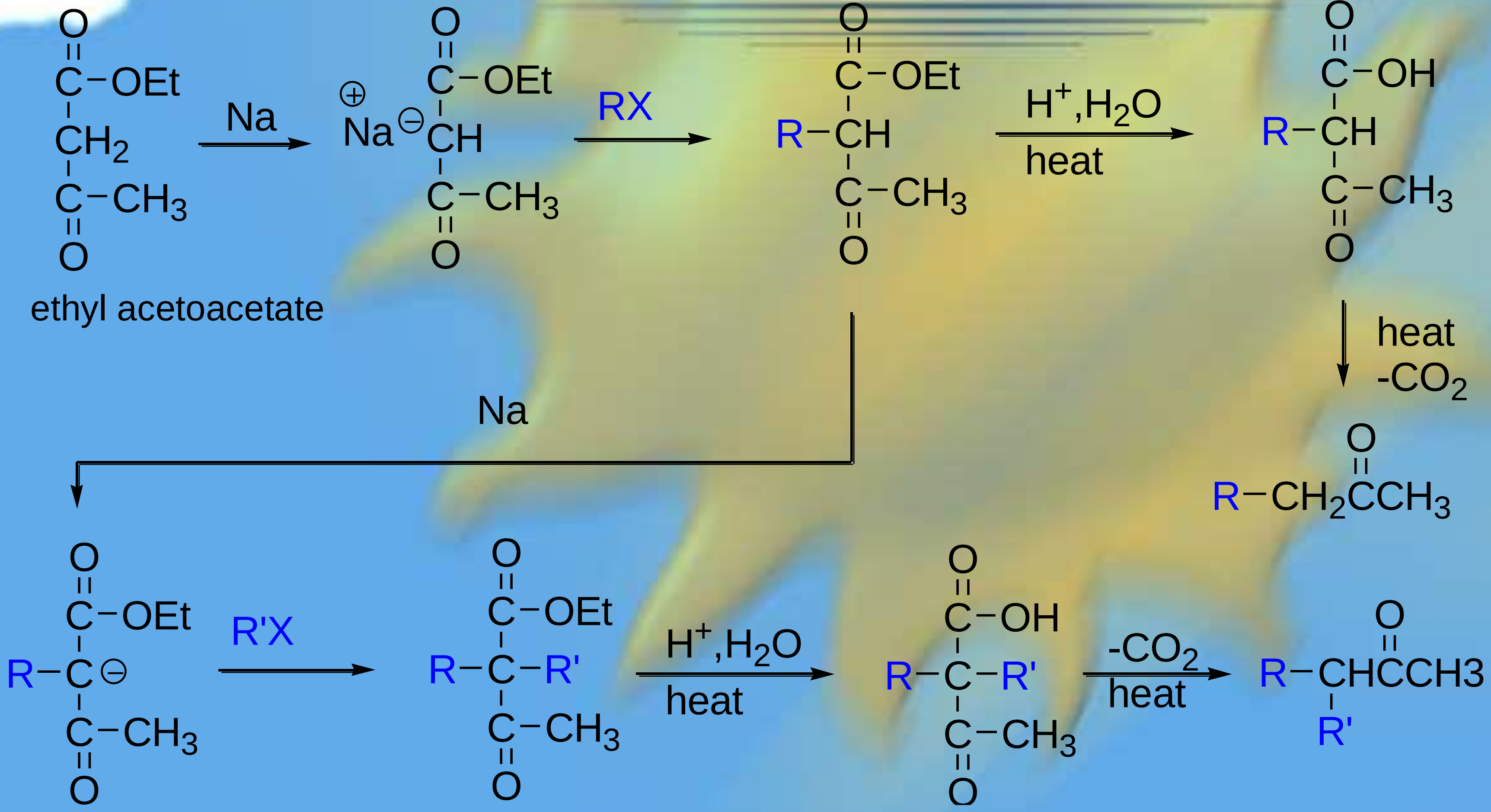
$$\begin{array}{l} CO_2CH_2CH_3 \\ | \\ CH_2 \\ | \\ COCH_3 \end{array}$$



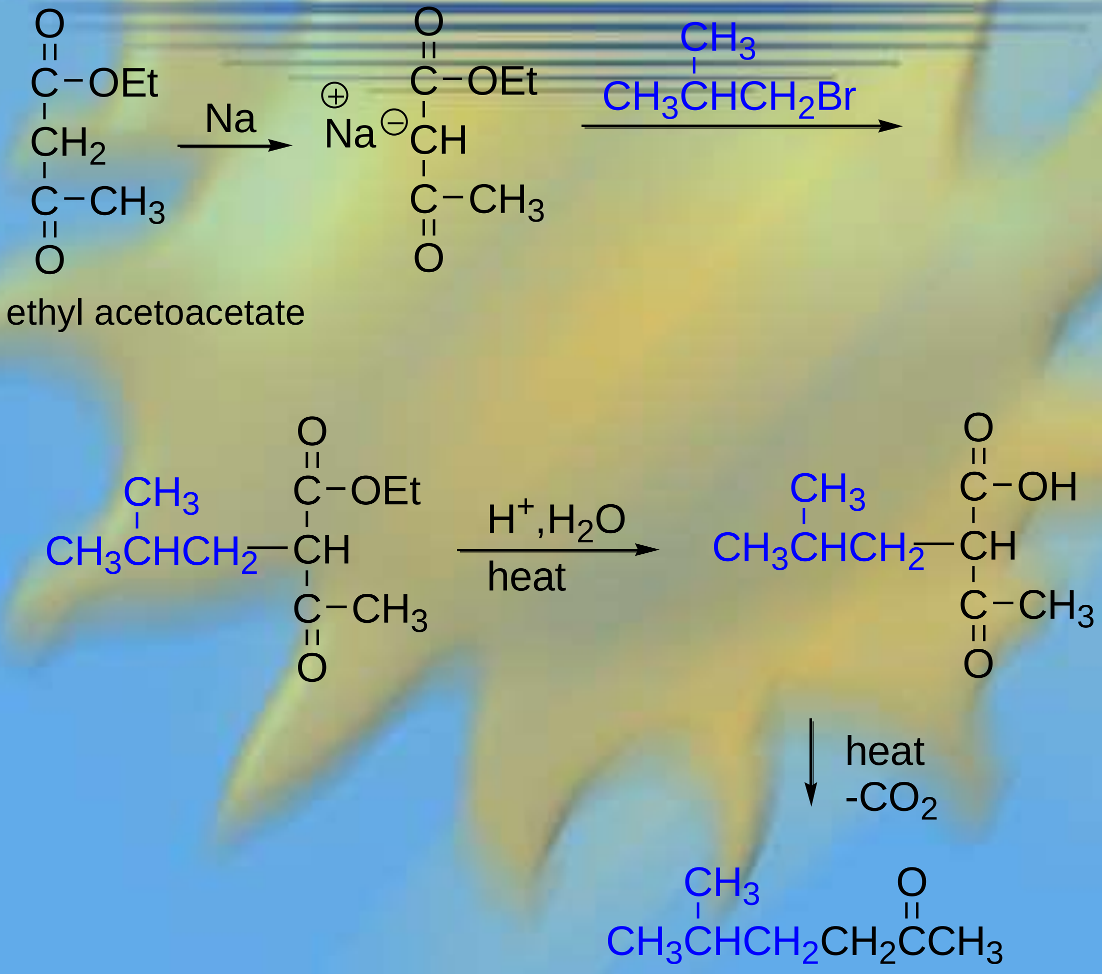
$$CH_3\overset{\overset{O}{\|}}{C}CH_2CO_2Et$$

1. When reacted with sodium metal, the ester is converted into its conjugate base (an enolate anion).
2. The enolate can be used as the nucleophile in an S_N2 reaction with a 1^o or CH_3 alkyl halide.
3. Upon hydrolysis, the substituted acetoacetic acid will decarboxylate when heated.
4. Product is a ketone derived from acetone.

SYNTHESIS OF KeTONE FROM ethyl acetoacetate



SYNTHESIS OF 5-Methyl-2-hexanone FROM ETHYL ACETOACETATE

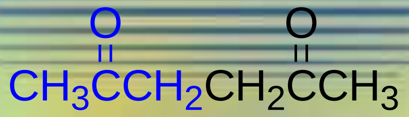


ethyl acetoacetate

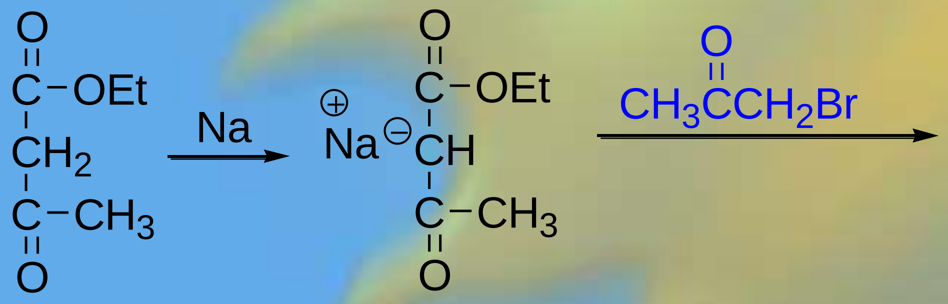
$$CH_3COCH_2COOEt \xrightarrow{Na} Na^{\oplus}\,{}^{\ominus}CH(COCH_3)COOEt \xrightarrow{(CH_3)_2CHCH_2Br} (CH_3)_2CHCH_2CH(COCH_3)COOEt \xrightarrow[\text{heat}]{H^+,H_2O} (CH_3)_2CHCH_2CH(COCH_3)COOH \xrightarrow[-CO_2]{\text{heat}} (CH_3)_2CHCH_2CH_2COCH_3$$

SYNTHESIS OF 2,5-hexadione FROM ETHYL ACETOACETATE

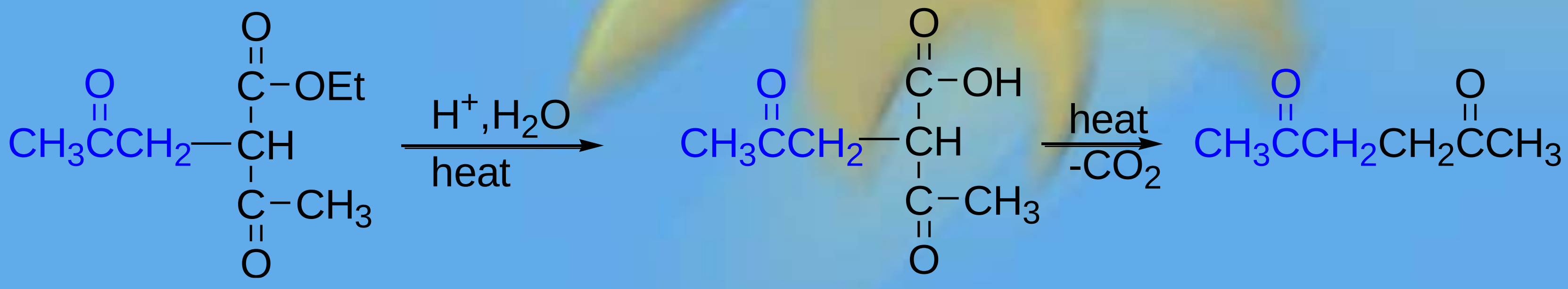
Synthesis of 2,5-hexanedione



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$$

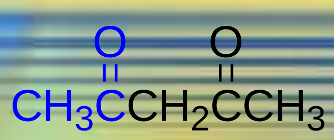


ethyl acetoacetate

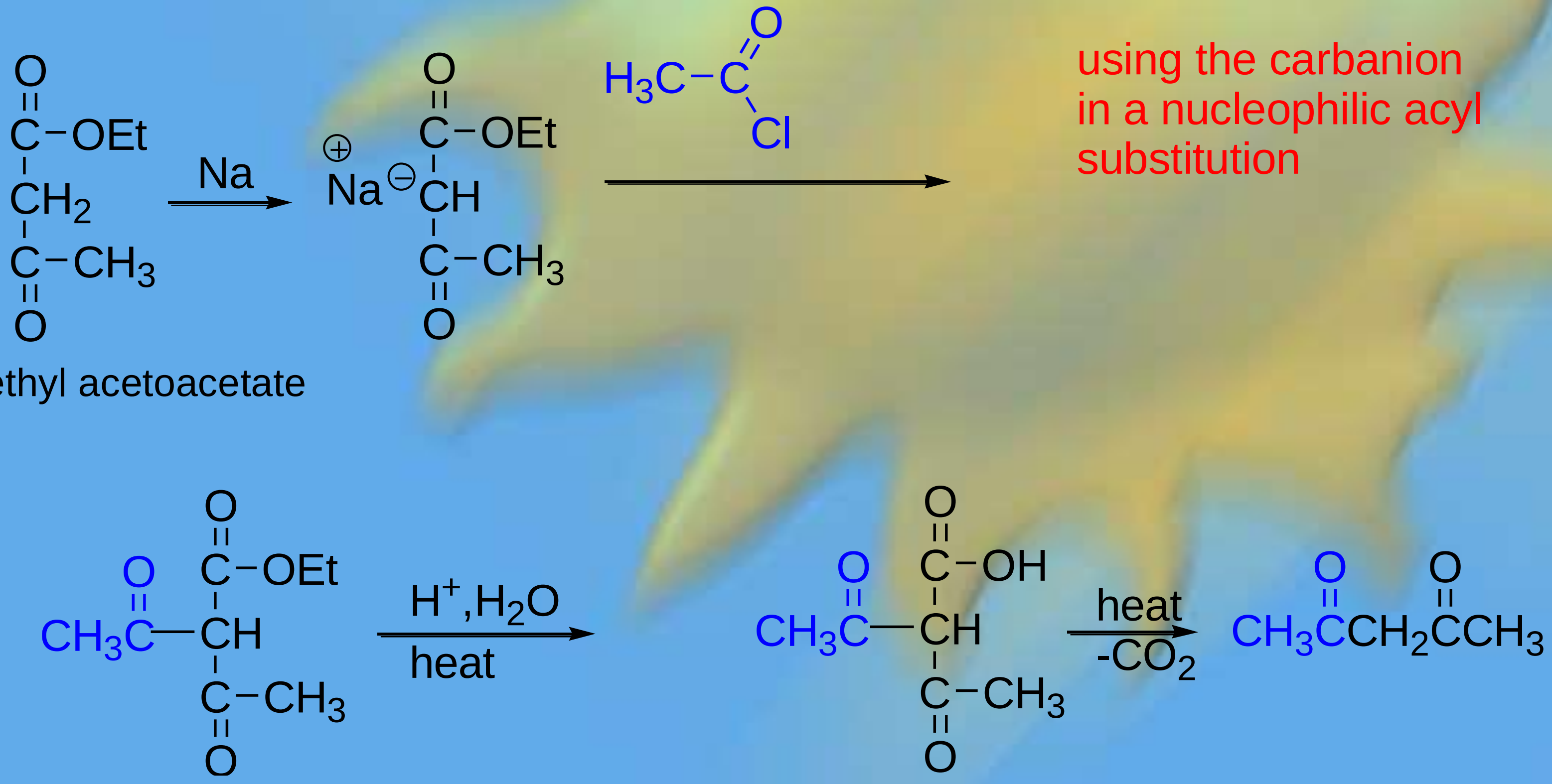


SYNTHESIS OF 2,4-pentadione FROM ETHYL ACETOACETATE

Synthesis of 2,4-pentanedione



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



ethyl acetoacetate

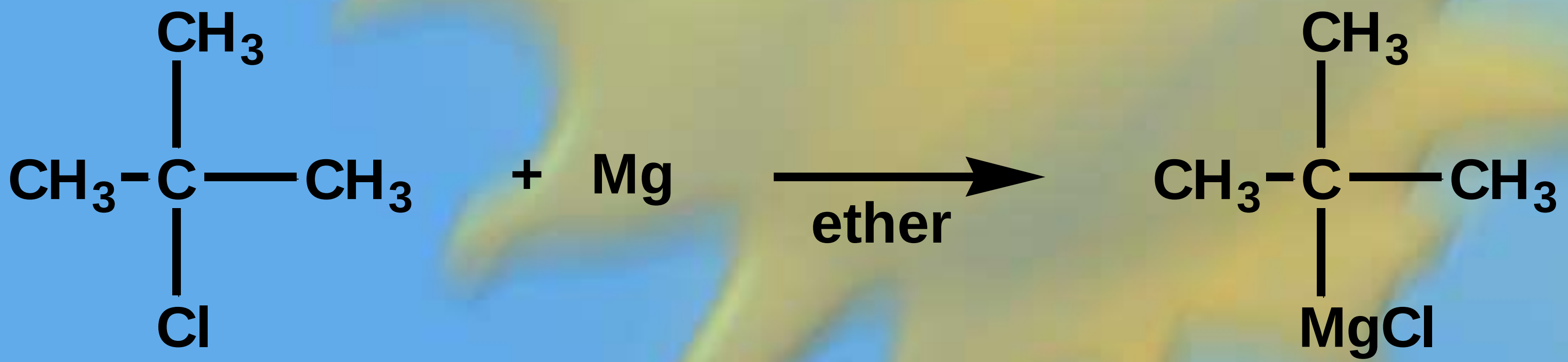
using the carbanion in a nucleophilic acyl substitution

GRIGNARD REAGENTS

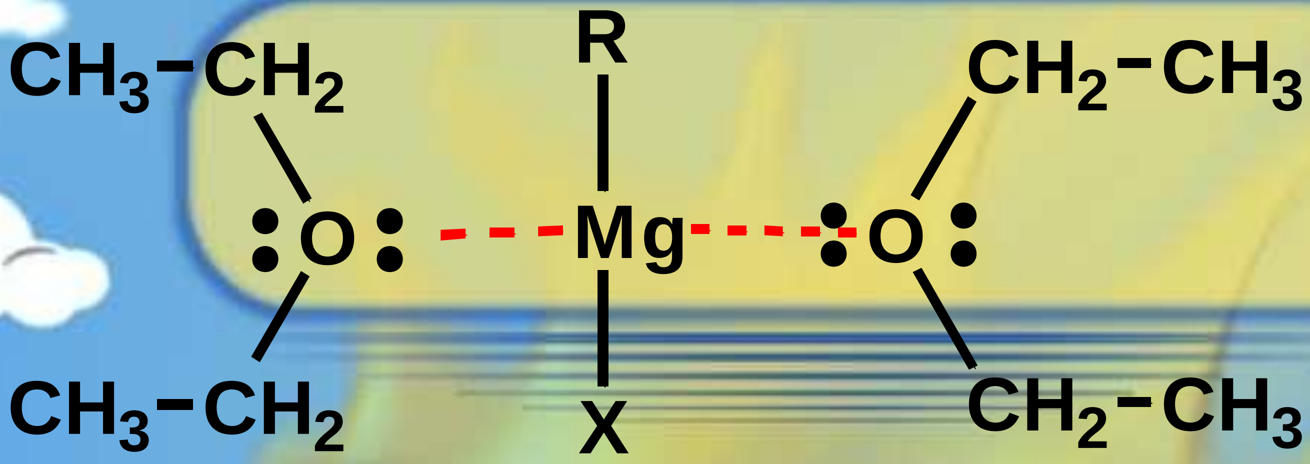
Preparation

$$R - X \quad + \quad Mg \xrightarrow{\text{ether}} R - MgX$$

R = 1°, 2°, 3°, aryl



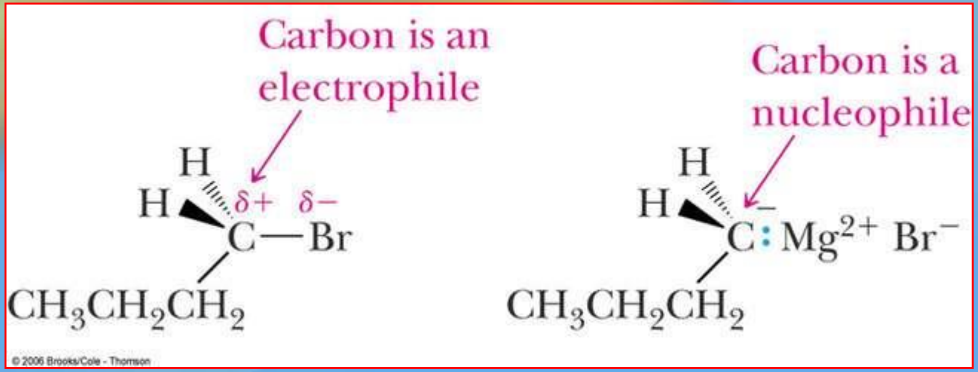
$$\begin{array}{c} CH_3 \\ | \\ CH_3 - C - CH_3 \\ | \\ Cl \end{array} \quad + \quad Mg \xrightarrow[\text{ether}]{} \begin{array}{c} CH_3 \\ | \\ CH_3 - C - CH_3 \\ | \\ MgCl \end{array}$$



Owing to the electronegativity difference between the metal and carbon, the carbon-metal bond has a great deal of *partial ionic character.* The bonds are *polar covalent* in nature.

This means that we can write:

$$\overset{\delta-}{\mathrm{R}}\text{——}\overset{\delta+}{\mathrm{MgX}}$$



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- The Alkyl portion of the Grignard reagent behaves as if it had the characteristics of a Carbanion – the carbon atom bears a formal negative charge
- The Magnesium portion bears the positive charge.
- Grignard Reagent, thus, acts as a Strong Base and is a strong Nucleophile that acts as a Lewis Base donating an Electron pair to a positively charged Electrophile
- Especially useful in Nucleophilic Addition reactions of the Carbonyl group, which has electrophilic character where the positive charge of the carbonyl carbon atom is attractive to the Grignard Nucleophile

Grignard reagents react with:

formaldehyde to give primary alcohols

aldehydes to give secondary alcohols

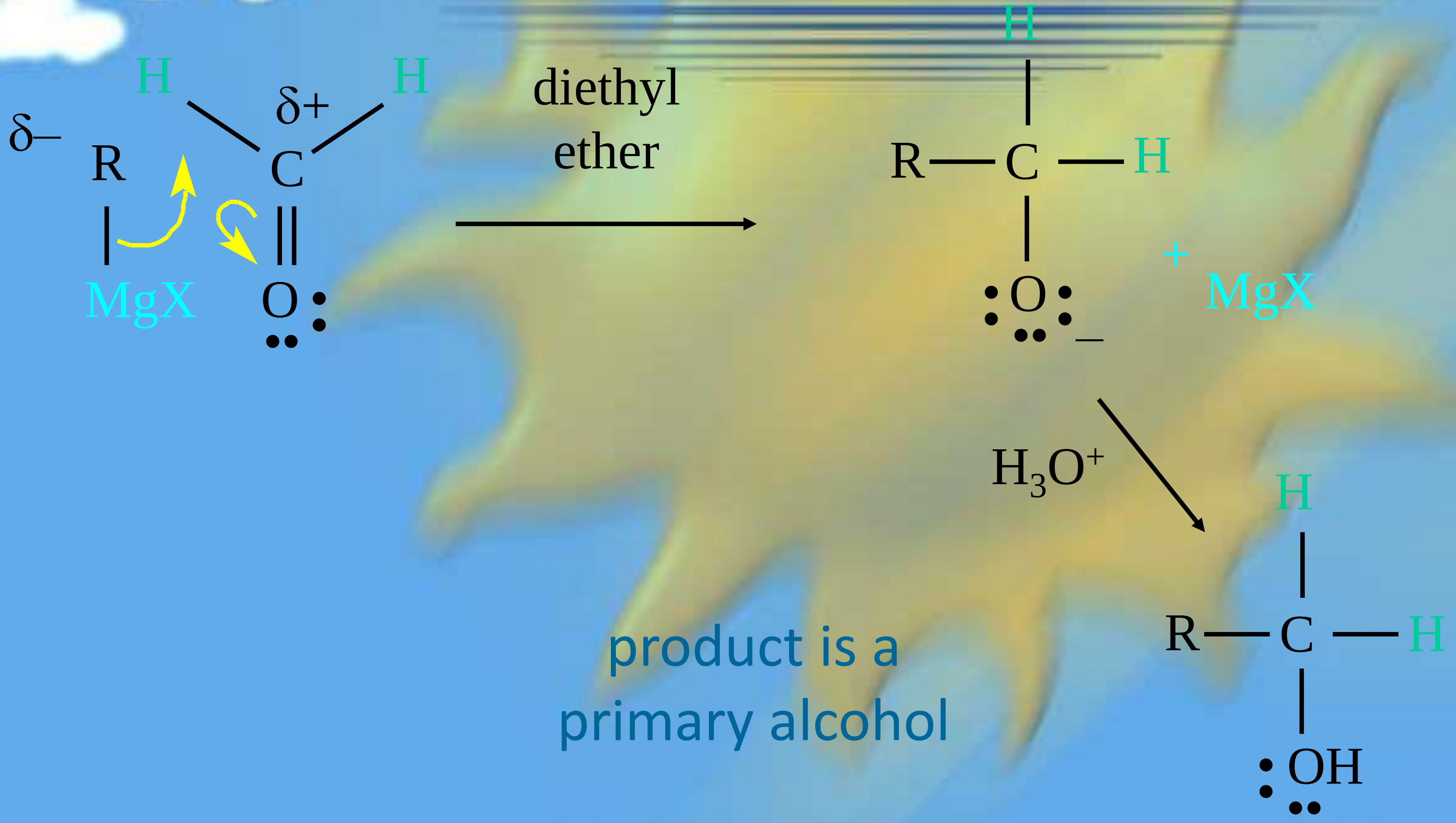
ketones to give tertiary alcohols

esters to give tertiary alcohols

CO_2 to give carboxlic acids

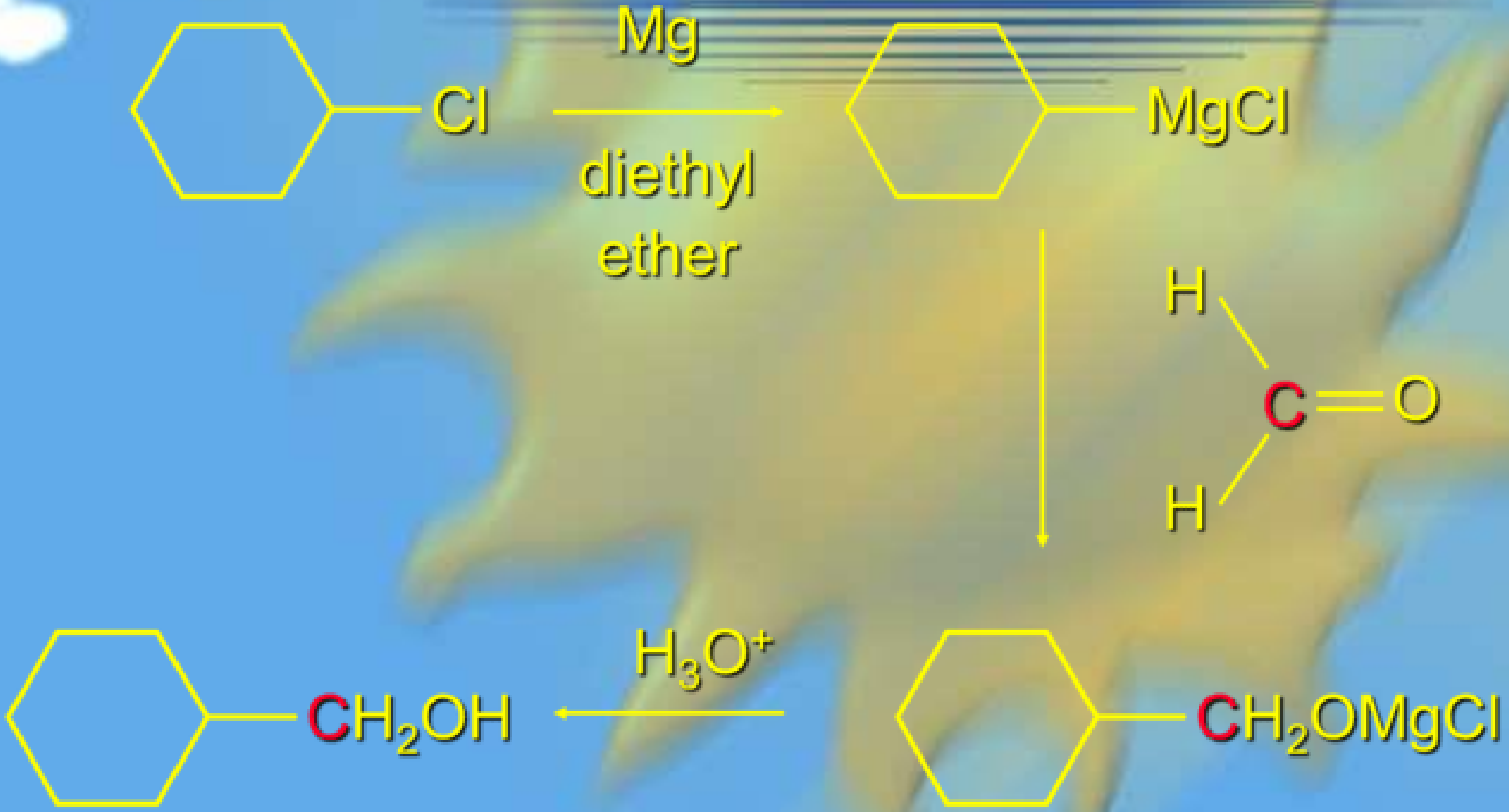
water to give alkane

Grignard reagents react with formaldehyde



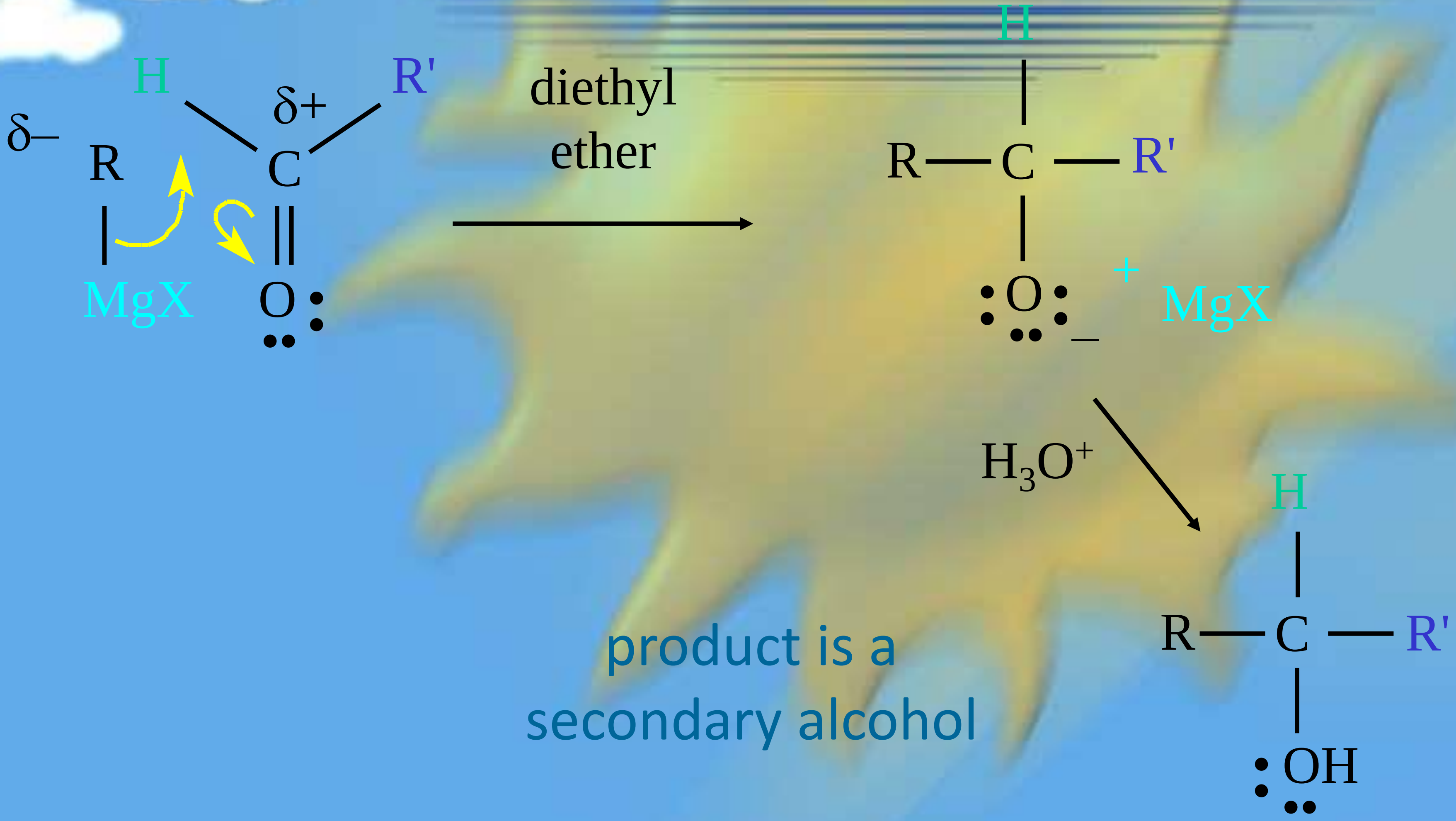
product is a primary alcohol

Example



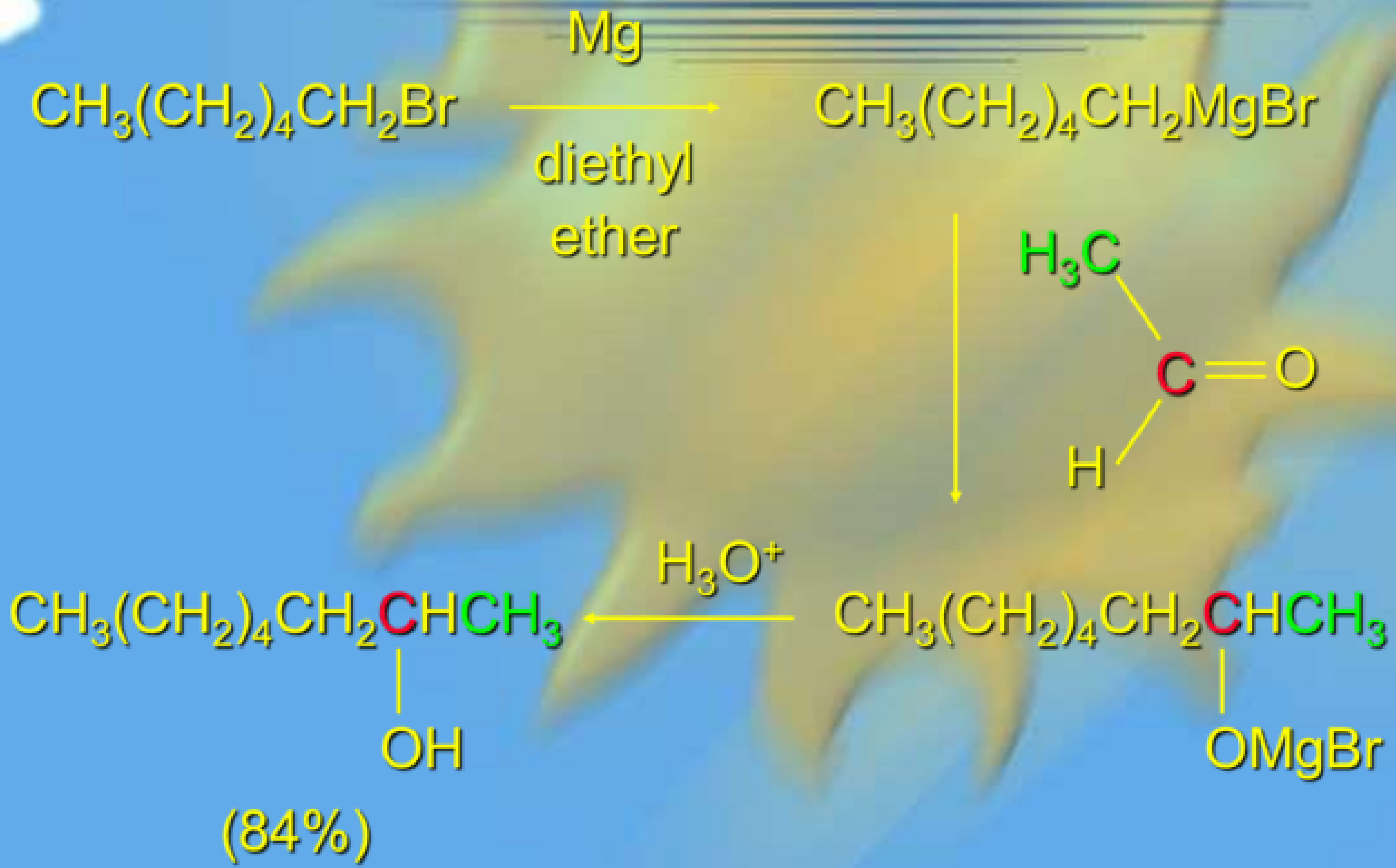
(64-69%)

Grignard reagents react with aldehydes



product is a secondary alcohol

Example



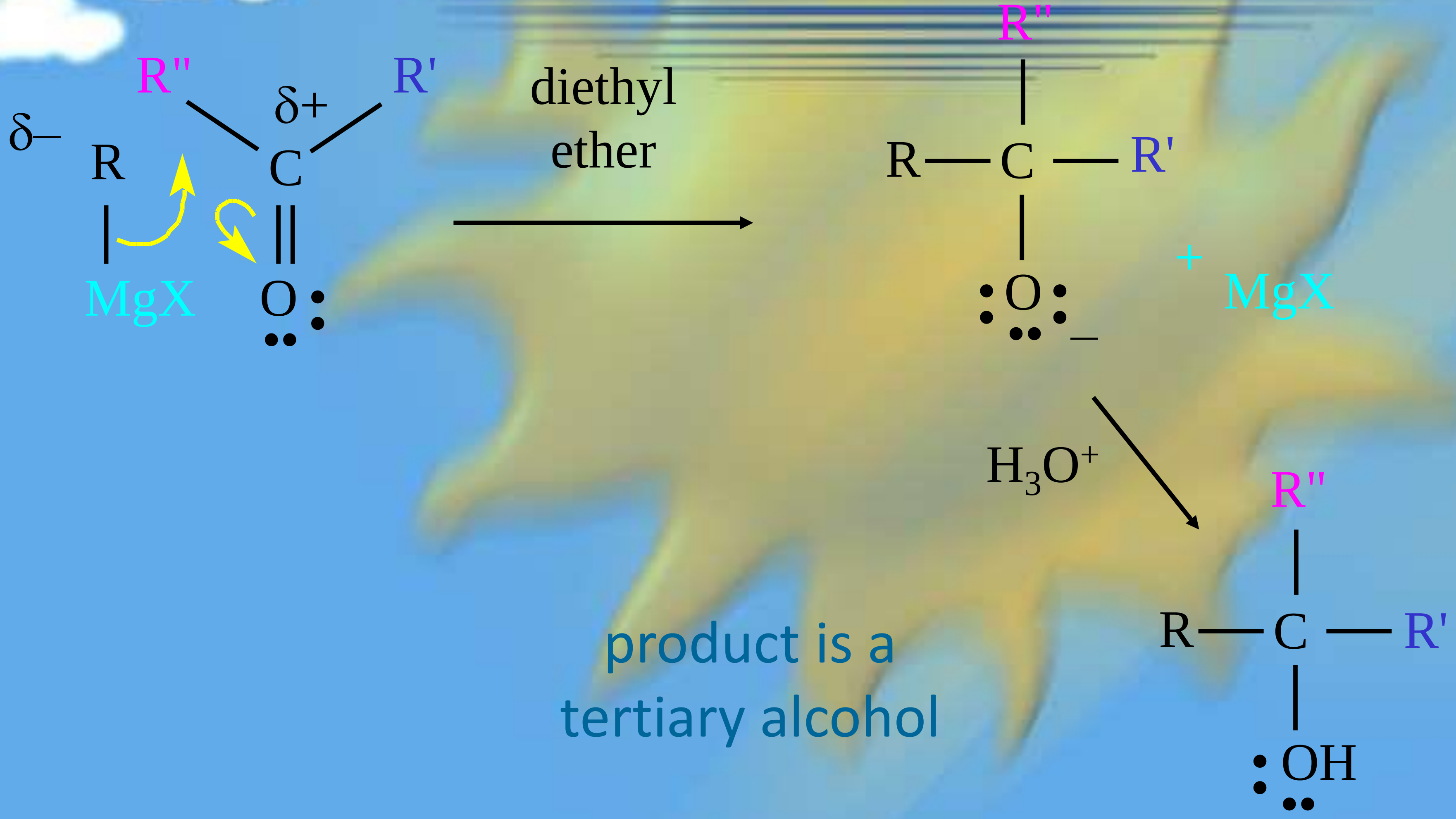
$$CH_3(CH_2)_4CH_2Br \xrightarrow[\text{diethyl ether}]{Mg} CH_3(CH_2)_4CH_2MgBr$$

$$CH_3(CH_2)_4CH_2MgBr + H_3C{-}CH{=}O \longrightarrow CH_3(CH_2)_4CH_2\underset{\displaystyle OMgBr}{\underset{|}{C}}HCH_3$$

$$CH_3(CH_2)_4CH_2\underset{\displaystyle OMgBr}{\underset{|}{C}}HCH_3 \xrightarrow{H_3O^+} CH_3(CH_2)_4CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

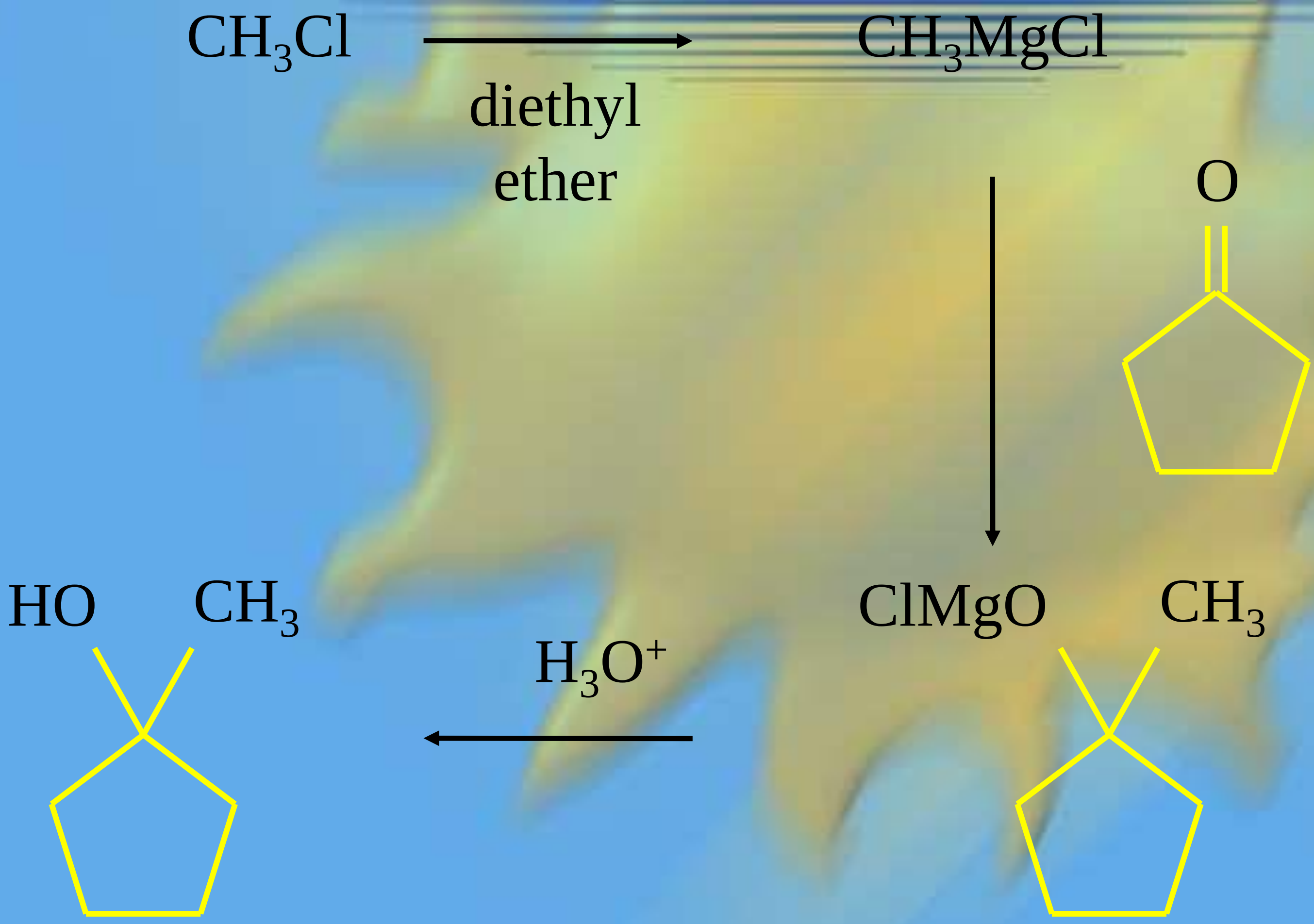
(84%)

Grignard reagents react with ketones



product is a tertiary alcohol

Example



$CH_3Cl \xrightarrow[\text{diethyl ether}]{} CH_3MgCl$

O

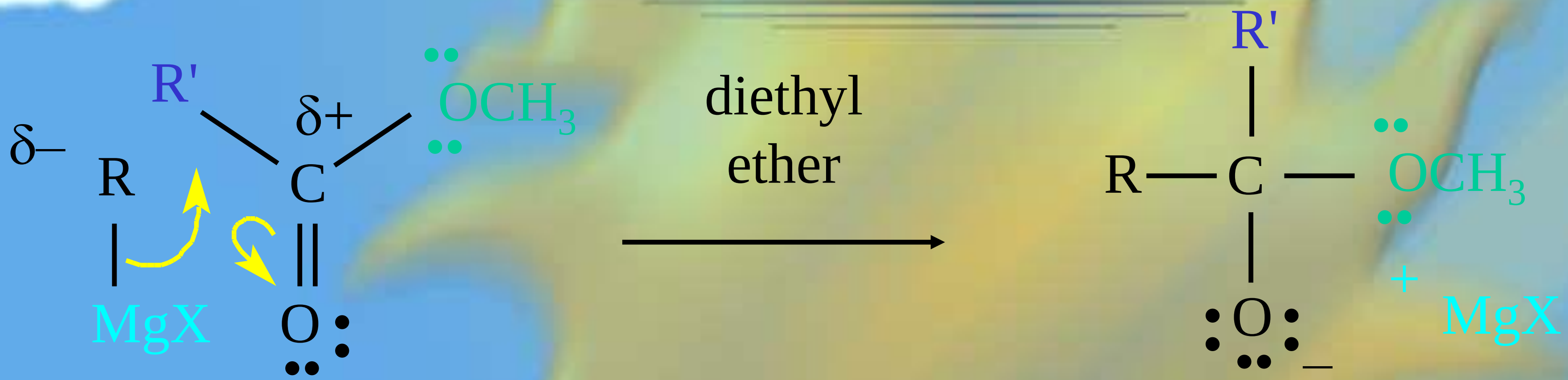
ClMgO CH$_3$

H_3O^+

HO CH$_3$

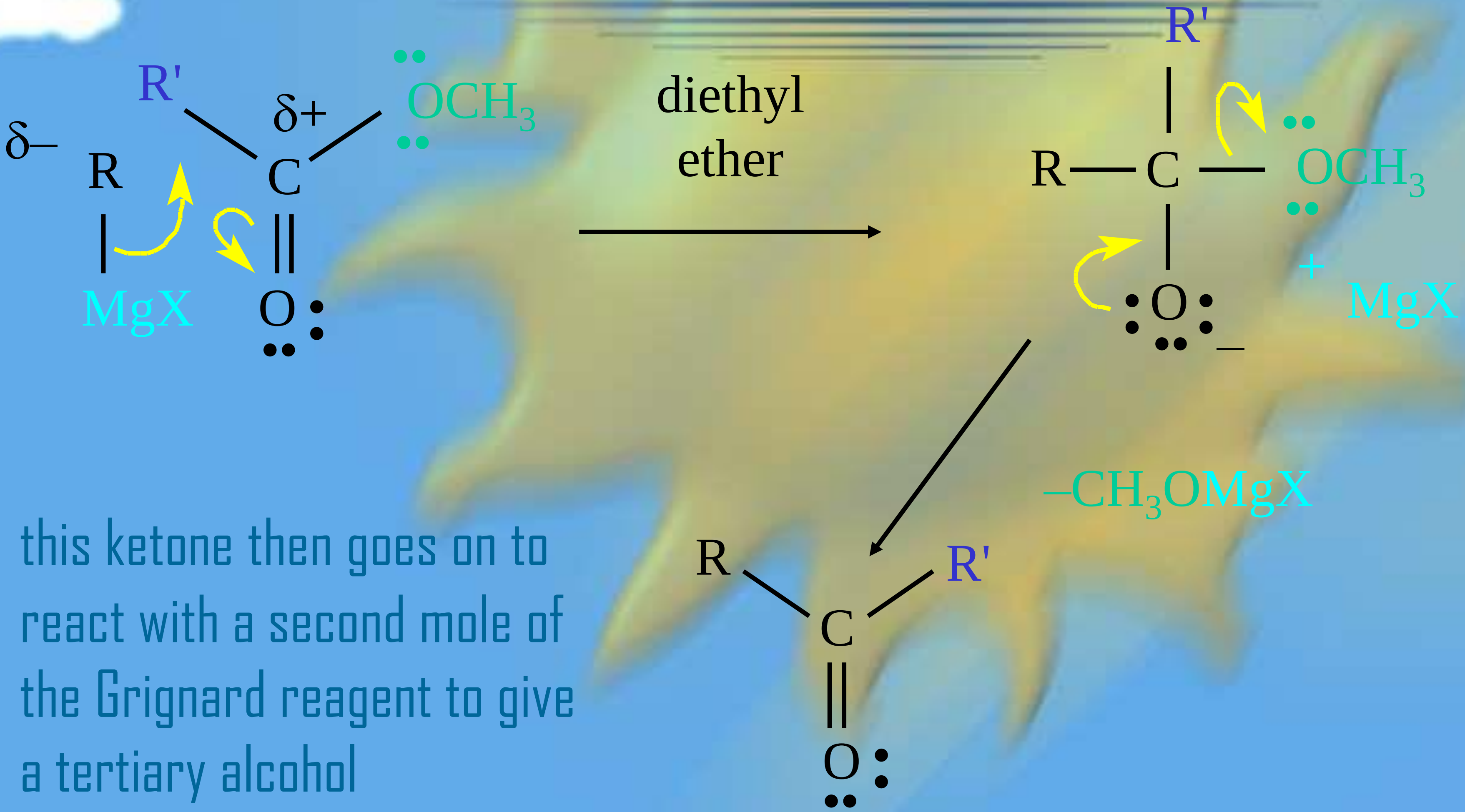
(62%)

Grignard reagents react with esters



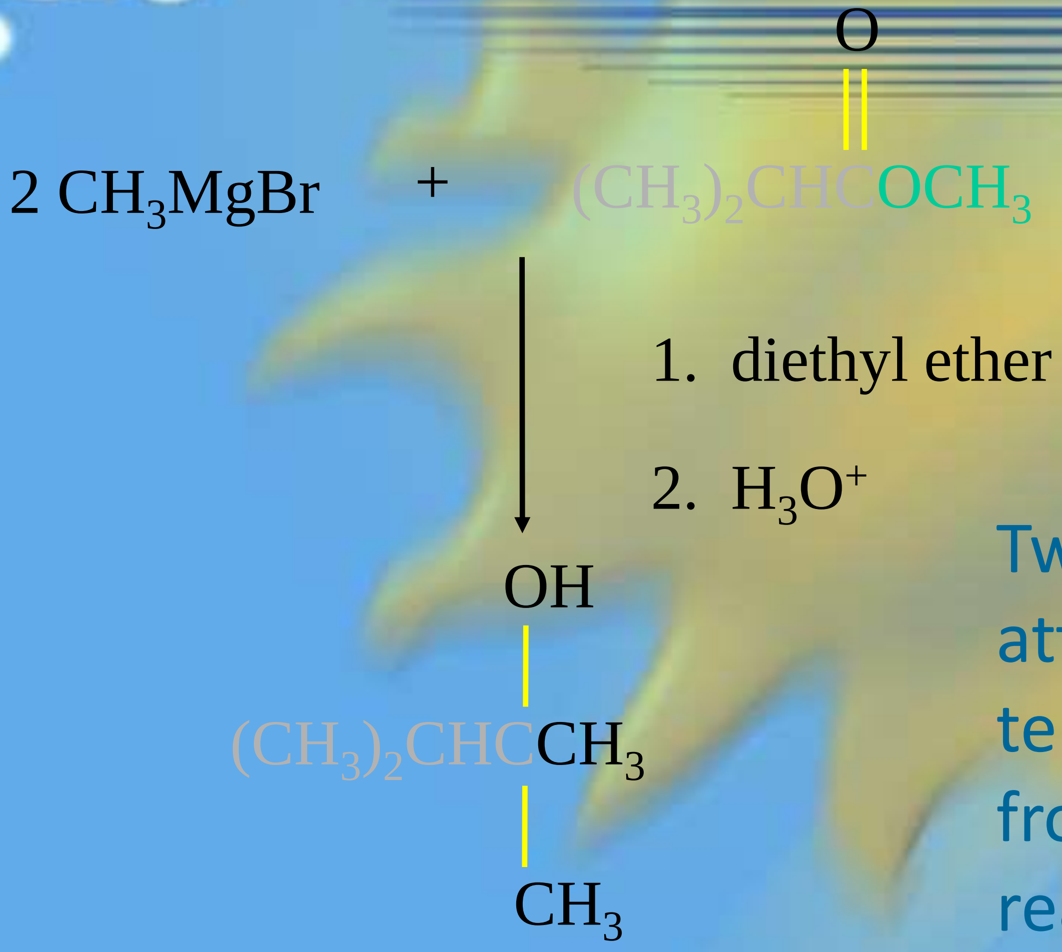
but species formed is unstable and dissociates under the reaction conditions to form a ketone

Grignard reagents react with esters



this ketone then goes on to react with a second mole of the Grignard reagent to give a tertiary alcohol

Example

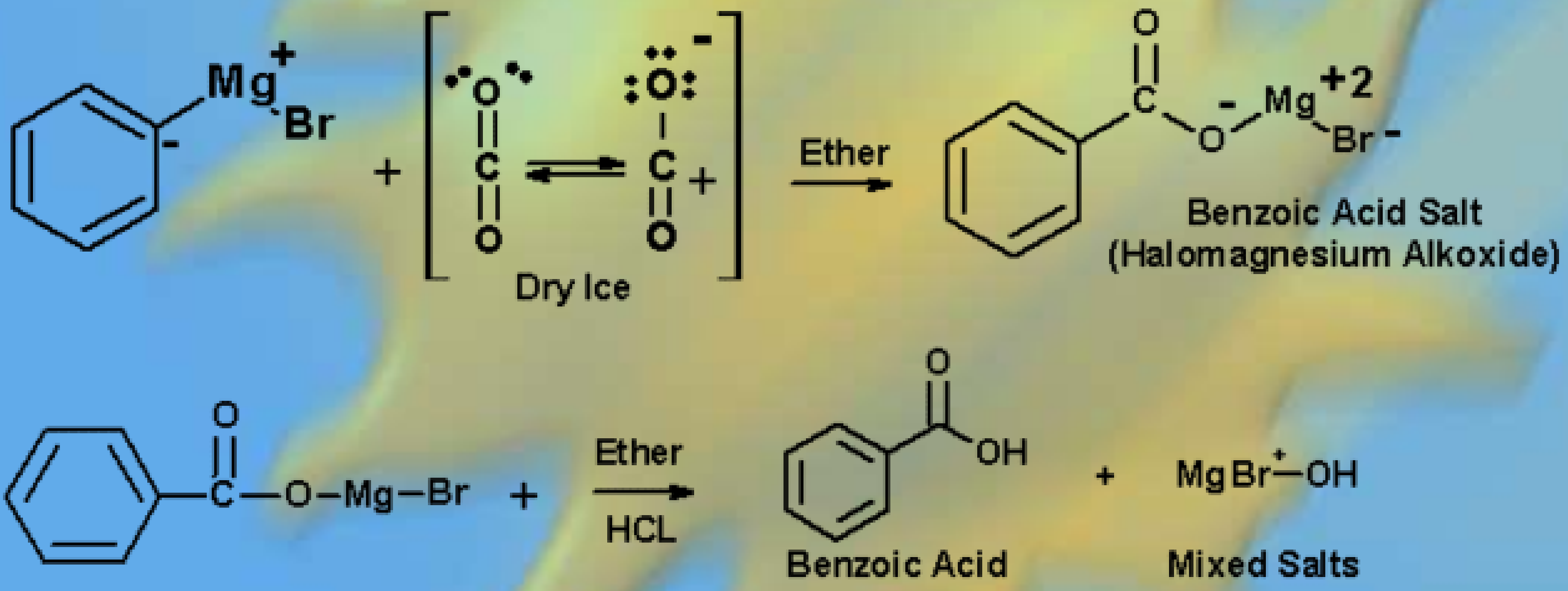


$$2\,CH_3MgBr + (CH_3)_2CH\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[\text{2. } H_3O^+]{\text{1. diethyl ether}} (CH_3)_2CH\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3$$

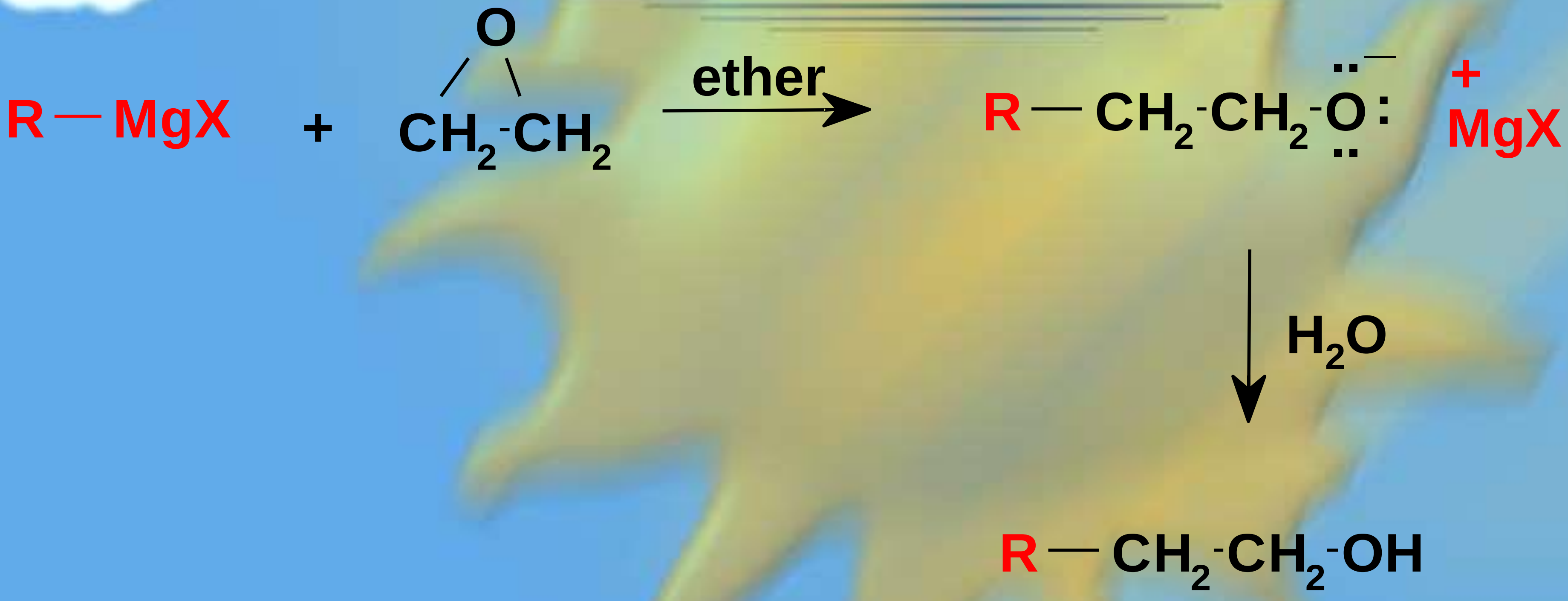
(73%)

Two of the groups attached to the tertiary carbon come from the Grignard reagent

Grignard reagents react With carbon dioxide



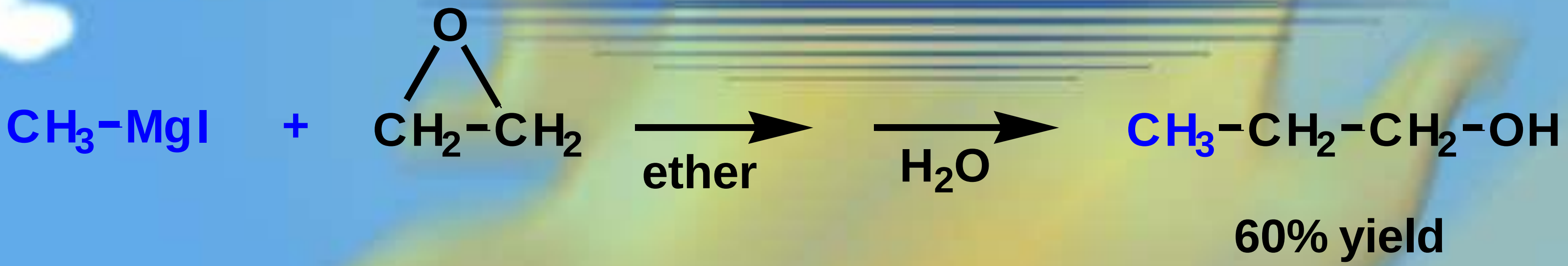
Grignard reagents react With epoxides



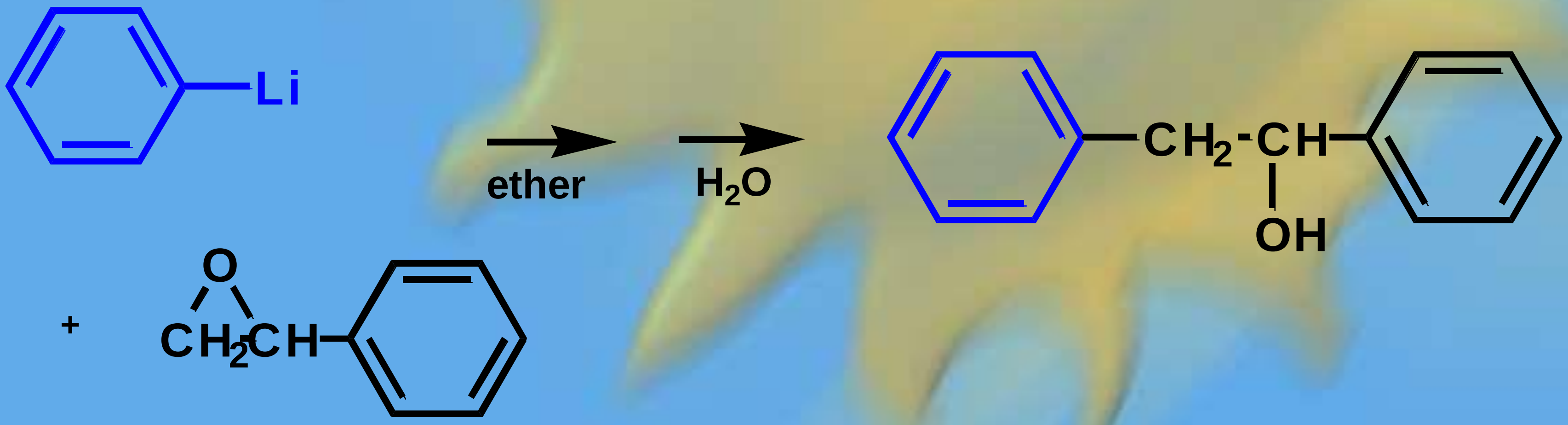
$$\text{R}-\text{MgX} + \overset{\text{O}}{\text{CH}_2\text{-CH}_2} \xrightarrow{\text{ether}} \text{R}-\text{CH}_2\text{-CH}_2\text{-}\ddot{\underset{..}{\text{O}}}\text{:}^{-}\ \overset{+}{\text{MgX}}$$

$$\xrightarrow{\text{H}_2\text{O}} \text{R}-\text{CH}_2\text{-CH}_2\text{-OH}$$

Example



60% yield



Grignard reagents react With water

$$RMgX + H_2O \rightarrow RH + Mg(OH)X$$

$$CH_3CH_2CH_2\text{-}Br + Mg \rightarrow CH_3CH_2CH_2\text{-}MgBr$$

n-propyl bromide — *n*-propyl magnesium bromide

$$CH_3CH_2CH_2\text{-}MgBr + H_2O \rightarrow CH_3CH_2CH_3 + Mg(OH)Br$$

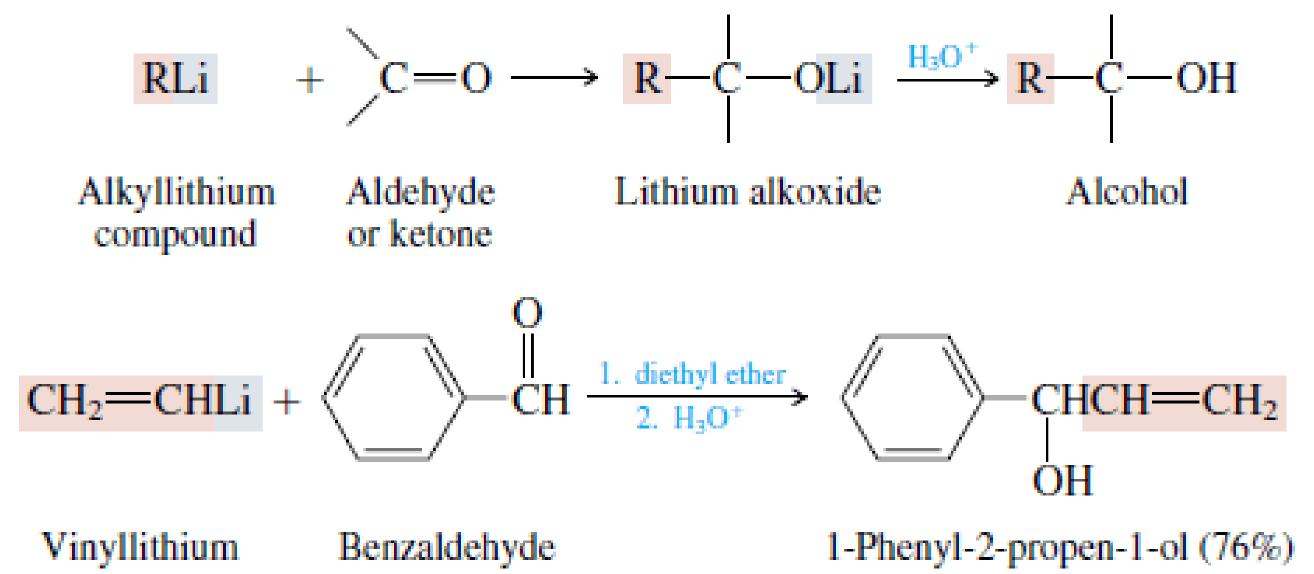
propane

ORGANOLITHIUM

$2\ Li + R-X \longrightarrow R-Li + LiX$

R = 1°, 2°, 3°, aryl

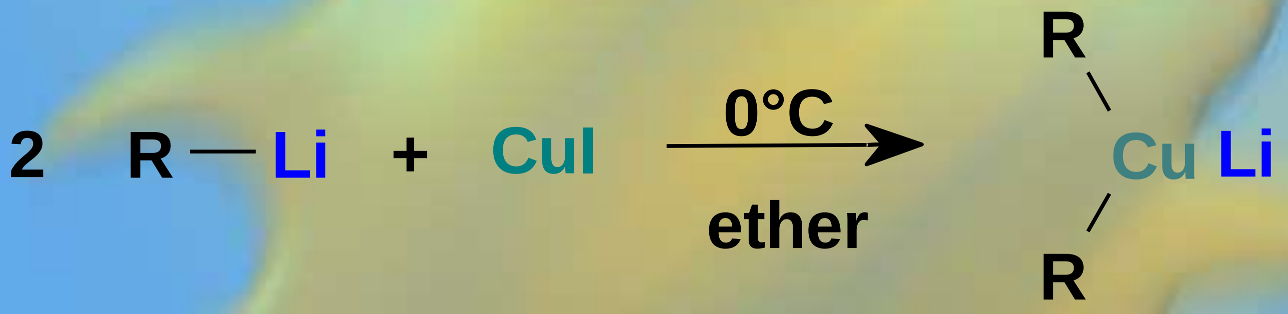
X = I > Br > Cl



Organocuprates

Lithium Dialkylcuprates

$$R-X \xrightarrow{Li} R-Li$$



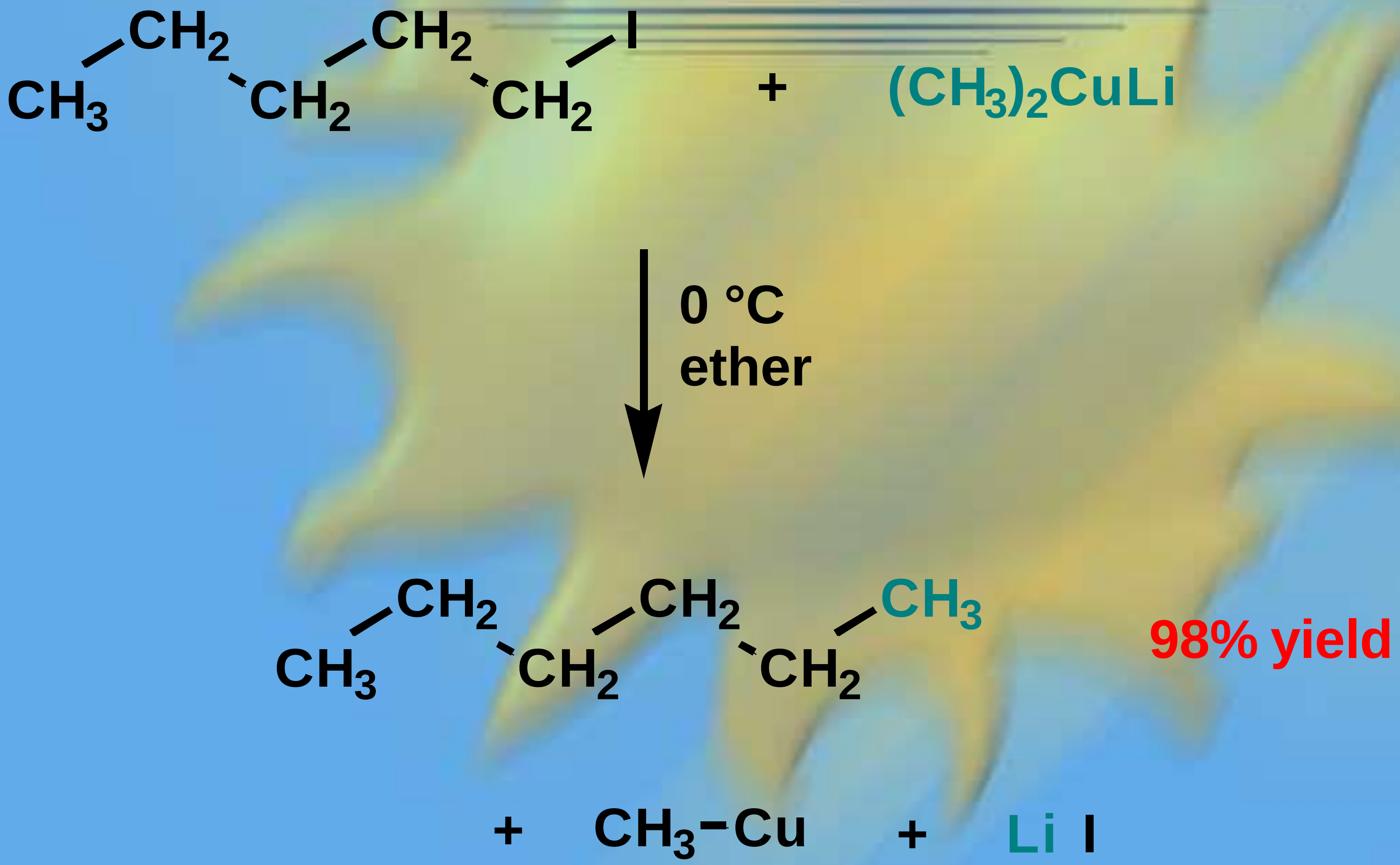
$$2\ R-Li + CuI \xrightarrow[\text{ether}]{0°C} R_2Cu\,Li$$

a lithium dialkylcuprate

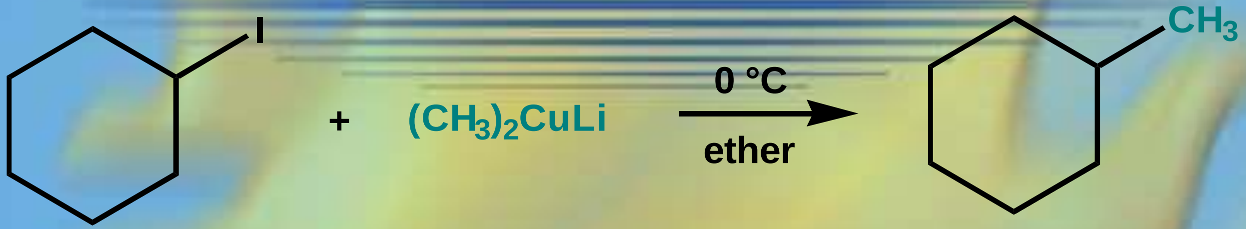
$$R-X + R_2CuLi \xrightarrow[\text{ether}]{0\ °C} R-R + R-Cu + Li\,X$$

X = Cl, Br, I

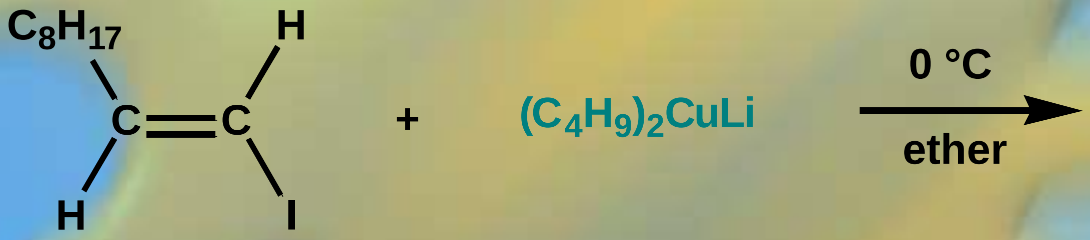
Example


CH3 CH2 CH2 CH2 CH2 I
+
(CH3)2CuLi
0 °C
ether
CH3 CH2 CH2 CH2 CH2 CH3
98% yield
+ CH3−Cu + Li I

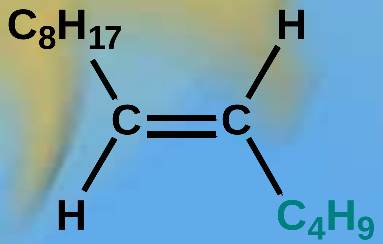
Example



75% yield



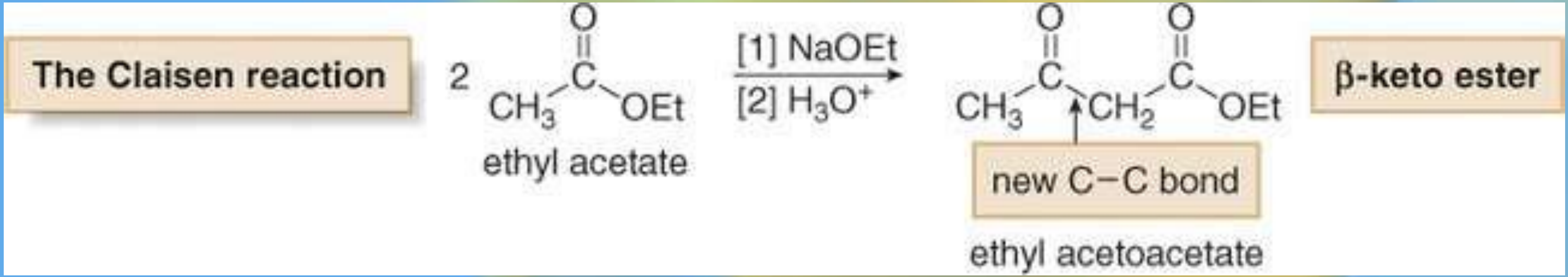
(*E*)-1-Iodo-1-decene

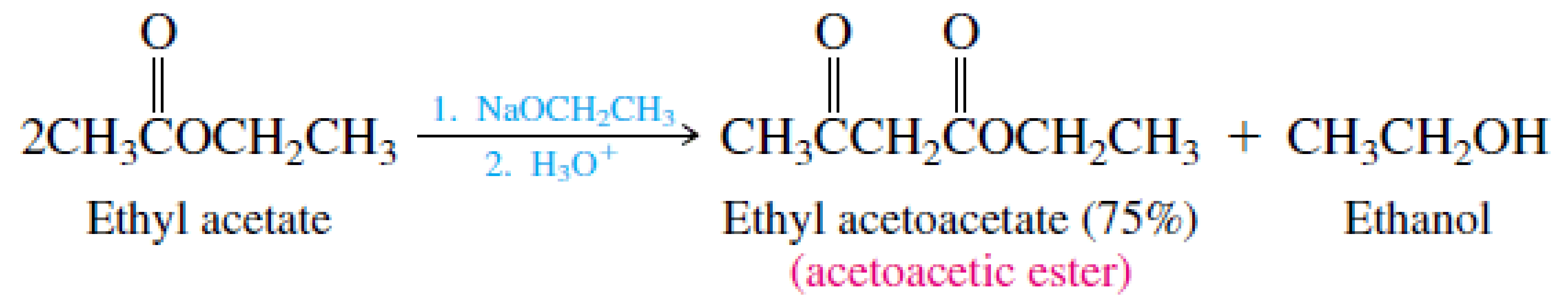


(*E*)-5-Tetradecene

Claisen Condensation

- In the Claisen reaction, two molecules of an ester react with each other in the presence of an alkoxide base to form a β-keto ester.

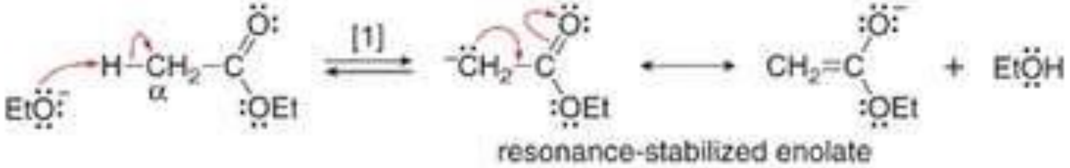




$$2CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2OH$$

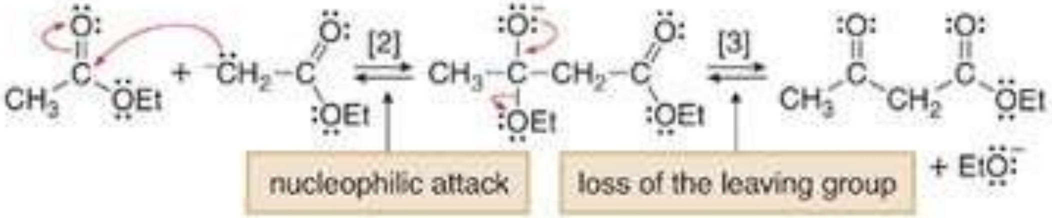
Mechanism 24.4 The Claisen Reaction

Step [1] Formation of a nucleophilic enolate



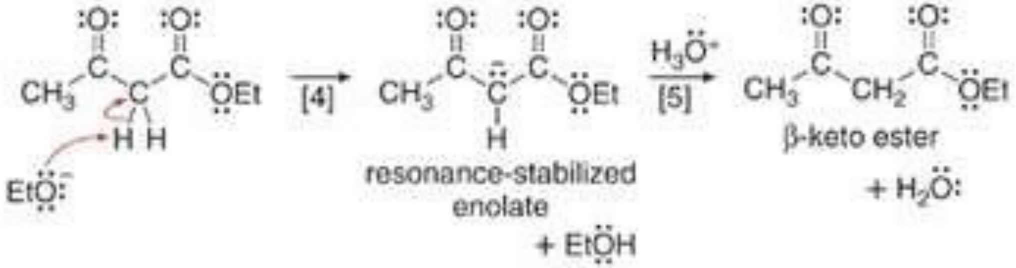
- In Step [1], the base removes a proton from the α carbon to form a **resonance-stabilized enolate.**

Steps [2]–[3] Nucleophilic addition and loss of the leaving group



- In Step [2], the nucleophilic enolate attacks the electrophilic carbonyl carbon of another molecule of ester, forming a new carbon–carbon bond. **This joins the α carbon of one ester to the carbonyl carbon of a second ester.**
- Elimination of the leaving group, EtO⁻, forms a β-keto ester in Step [3]. Steps [1]–[3] are reversible equilibria.

Steps [4]–[5] Deprotonation and protonation



- Because the β-keto ester formed in Step [3] has especially acidic protons between its two carbonyl groups, a proton is removed under the basic reaction conditions to form an enolate (Step [4]). **The formation of this resonance-stabilized enolate drives the equilibrium in the Claisen reaction.**
- Protonation of this enolate with strong acid re-forms the neutral β-keto ester to complete the reaction.