Reactions of Enolate Anions:
Enolates + Electrophiles IV

Condensations and other Reactions

Acylation

Condensations (More)

Decarboxylation

Michael Addition

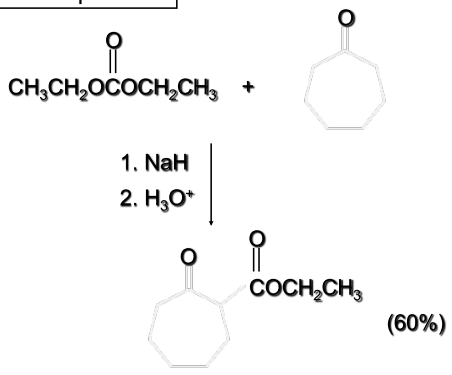
Lithium cuprates

Acylation of Ketones with Esters

Acylation of Ketones with Esters

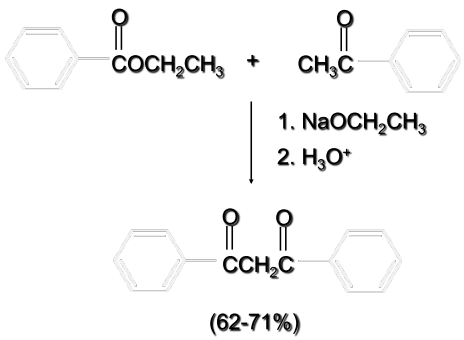
Esters that cannot form an enolate can be used to acylate ketone enolates.

Example



(60%)

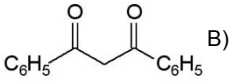
Example

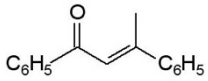


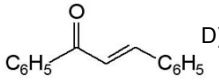
(62-71%)

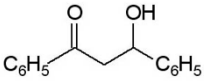
Question

What is the product formed in the condensation of ethyl benzoate with acetophenone?

A) 

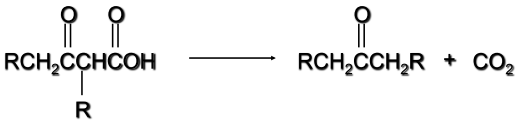
B) 

C) 

D) 

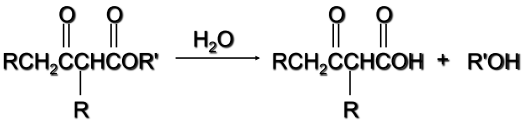
Ketone Synthesis via β-Keto Esters

Ketone Synthesis



β-Keto acids decarboxylate readily to give ketones.

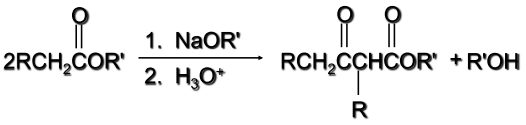
Ketone Synthesis



β-Keto acids decarboxylate readily to give ketones .

β-Keto acids are available by hydrolysis of β -keto esters.

Ketone Synthesis

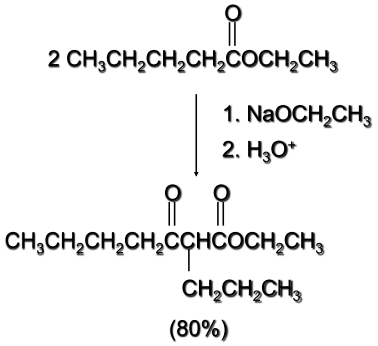


β-Keto acids decarboxylate readily to give ketones .

β-Keto acids are available by hydrolysis of β -keto esters.

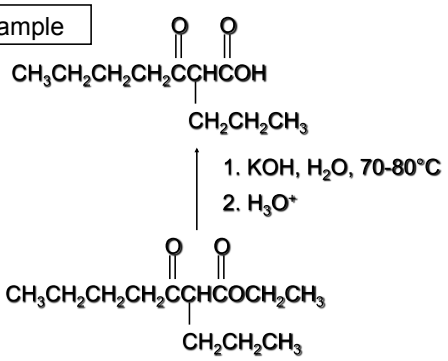
β-Keto esters can be prepared by the Claisen condensation.

Example

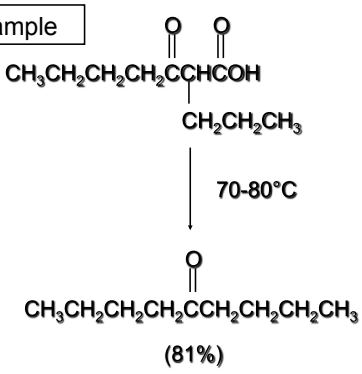


(80%)

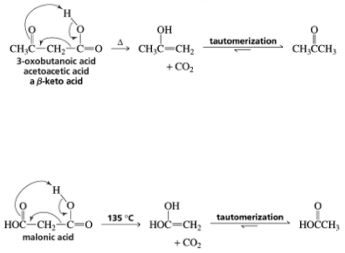
Example



Example

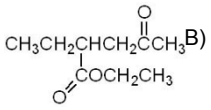


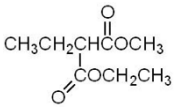
Decarboxylation of 3-Oxocarboxylic Acids

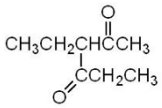


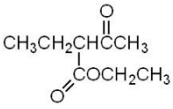
Question

Which compound will yield a ketone and CO_2 following saponification, acidification, and heat?

A) 

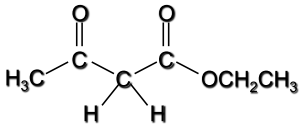
B) 

C) 

D) 

The Acetoacetic Ester Synthesis

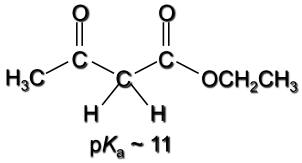
Acetoacetic Ester



Acetoacetic ester is another name for *ethyl acetoacetate*.

The "acetoacetic ester synthesis" uses acetoacetic ester as a reactant for the preparation of ketones.

Deprotonation of Ethyl Acetoacetate

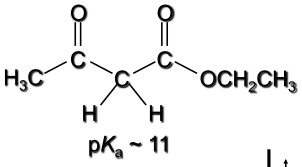


+ $CH_3CH_2O^-$

$pK_a \sim 11$

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

Deprotonation of Ethyl Acetoacetate

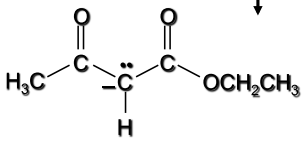


+ $CH_3CH_2O^-$

$pK_a \sim 11$

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

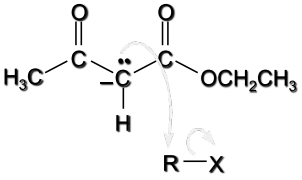
$K \sim 10^5$



+ CH_3CH_2OH

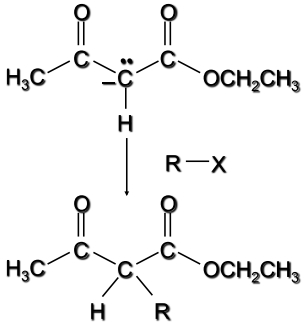
$pK_a \sim 16$

Alkylation of Ethyl Acetoacetate



The anion of ethyl acetoacetate can be alkylated using an alkyl halide (S_N2: primary and secondary alkyl halides work best; tertiary alkyl halides undergo elimination).

Alkylation of Ethyl Acetoacetate

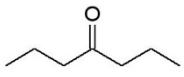


The anion of ethyl acetoacetate can be alkylated using an alkyl halide (S_N2: primary and secondary alkyl halides work best; tertiary alkyl halides undergo elimination).

Question

Treatment of methyl acetoacetate with $NaOCH_2CH_3$ followed by ethyl bromide will produce

A)



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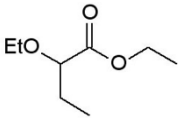
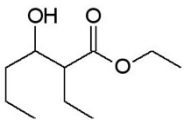
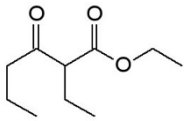


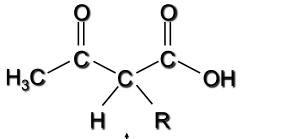
C)



D)

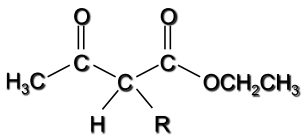


Conversion to Ketone



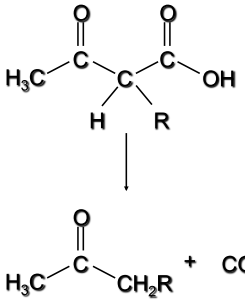
1. HO^-, H_2O
2. H^+

Saponification and acidification convert the alkylated derivative to the corresponding β-keto acid.



The β-keto acid then undergoes decarboxylation to form a ketone.

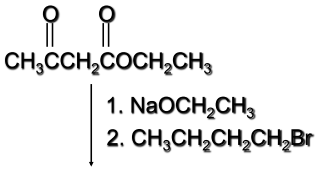
Conversion to Ketone



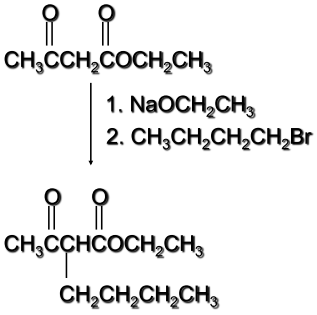
Saponification and acidification convert the alkylated derivative to the corresponding β -keto acid.

The β-keto acid then undergoes decarboxylation to form a ketone.

Example

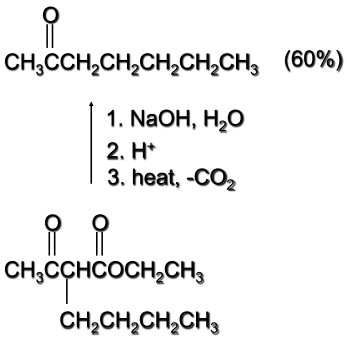


Example



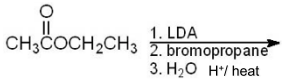
(70%)

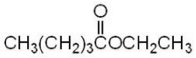
Example

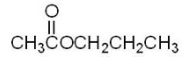


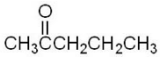
Question

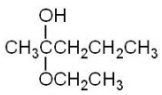
Identify the product of the reaction shown at the right.



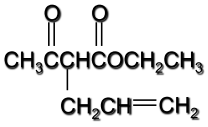
A) 

B) 

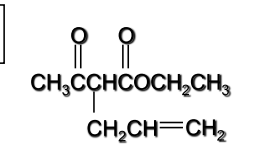
C) 

D) 

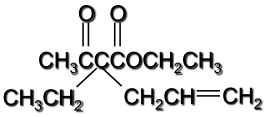
Example: Dialkylation



Example: Dialkylation

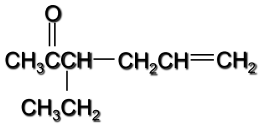


1. $NaOCH_2CH_3$
2. CH_3CH_2I

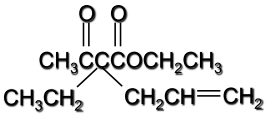


(75%)

Example: Dialkylation

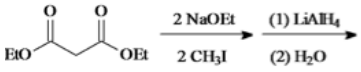


1. NaOH, H_2O
2. H^+
3. heat, $-CO_2$



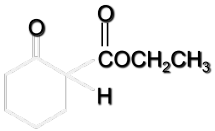
Question

What is the product of the following reactions?



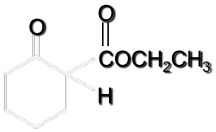
A. 2,2-dimethylpropanedioic acid
B. 2-methylpropanoic acid
C. 2-methyl-1-propanol
D. 2,2-dimethyl-1,3-propanediol

Another Example

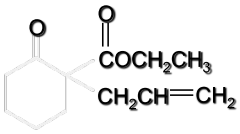


β-Keto esters other than ethyl acetoacetate may be used.

Another Example

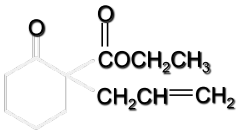


1. $NaOCH_2CH_3$
2. $H_2C{=}CHCH_2Br$

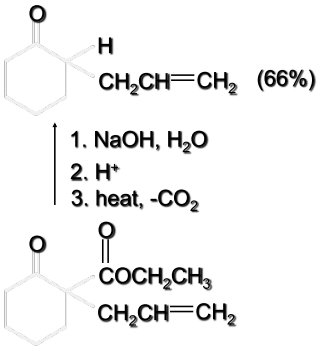


(89%)

Another Example

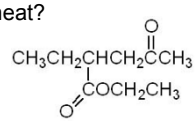


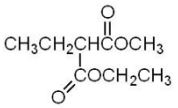
Another Example

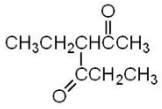


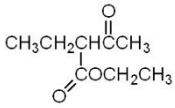
Question

Which compound will yield a ketone and CO_2 following saponification, acidification, and heat?

A) 

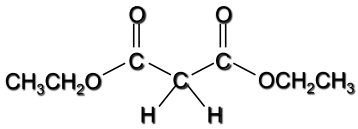
B) 

C) 

D) 

The Malonic Ester Synthesis

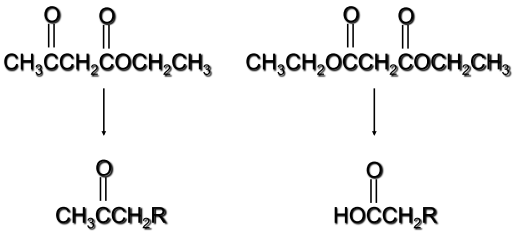
Malonic Ester



Malonic ester is another name for *diethyl malonate*.

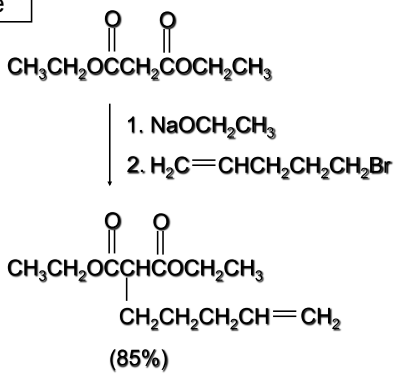
The "malonic ester synthesis" uses diethyl malonate as a reactant for the preparation of carboxylic acids.

An Analogy



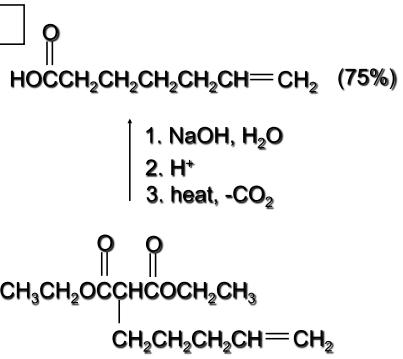
The same procedure by which ethyl acetoacetate is used to prepare ketones converts diethyl malonate to carboxylic acids.

Example

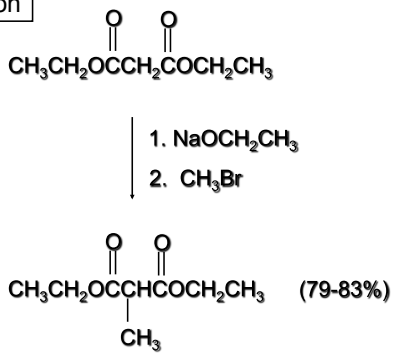


(85%)

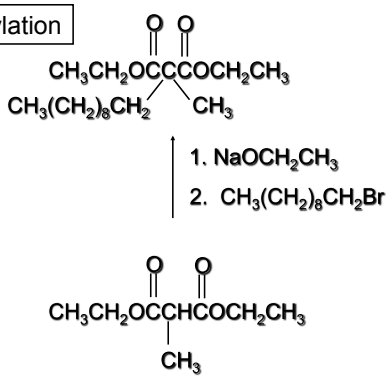
Example



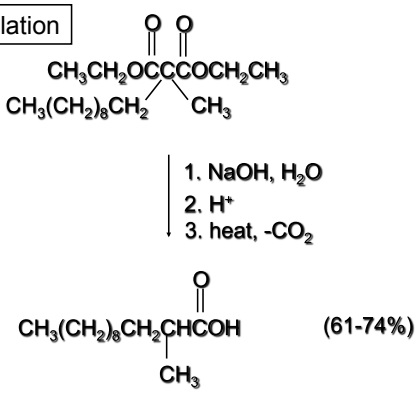
Dialkylation



Dialkylation



Dialkylation



Question

Which of the alkyl halides below would be the best choice for the synthesis of butanoic acid from diethyl malonate?

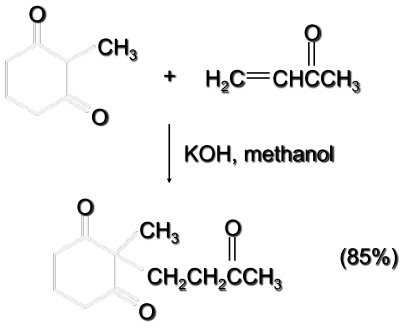
A) bromopropane
B) chloropropane
C) iodoethane
D) fluoroethane

Addition of Carbanions to α,β-Unsaturated Carbonyl Compounds: The Michael Reaction

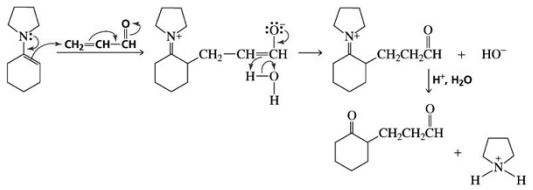
Michael Addition

Stabilized carbanions, such as those derived from β-diketones undergo conjugate addition to α,β-unsaturated ketones.

Example



The Stork Enamine Reaction



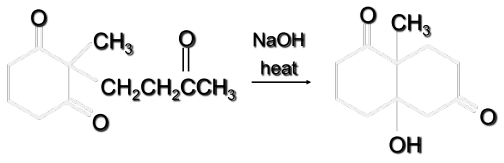
Enamines are used in place of enolates in Michael reactions

Michael Addition

The Michael reaction is a useful method for forming carbon-carbon bonds.

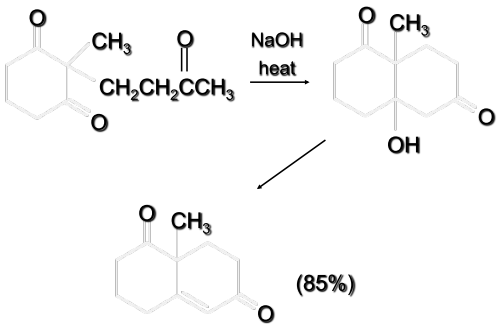
It is also useful in that the product of the reaction can undergo an intramolecular aldol condensation to form a six-membered ring. One such application is called the Robinson annulation.

Example



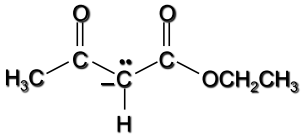
not isolated; dehydrates under reaction conditions

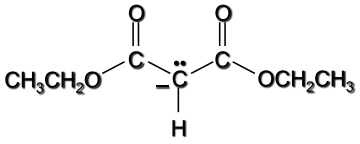
Example



Michael Additions of Stabilized Anions

Stabilized Anions



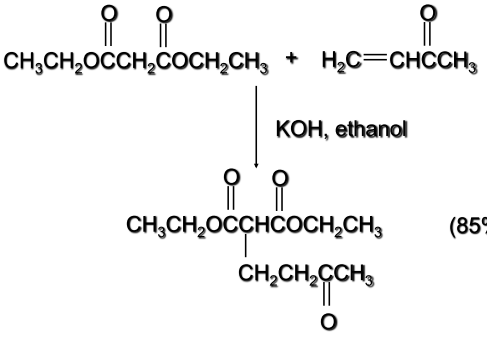


The anions derived by deprotonation of β-keto esters and diethyl malonate are weak bases.

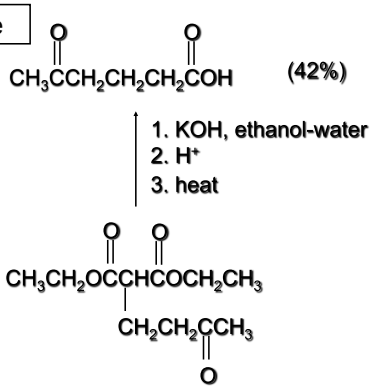
Weak bases react with α,β -unsaturated carbonyl compounds by conjugate addition.

Example

Example

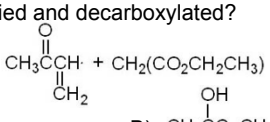


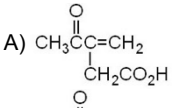
Example

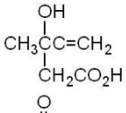


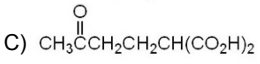
Question

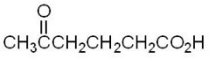
Which compound is isolated when the product of Michael addition of the compounds at the right is acidified and decarboxylated?



A) 

B) 

C) 



Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

1,2-addition (direct addition)

nucleophile attacks carbon of C=O

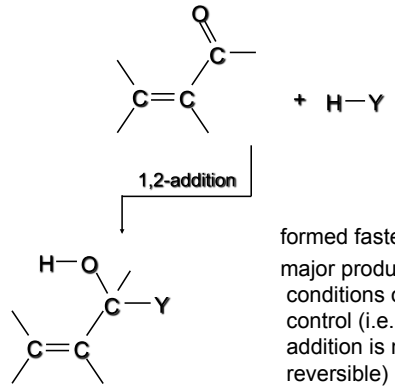
1,4-addition (conjugate addition)

nucleophile attacks β-carbon

Kinetic versus Thermodynamic Control

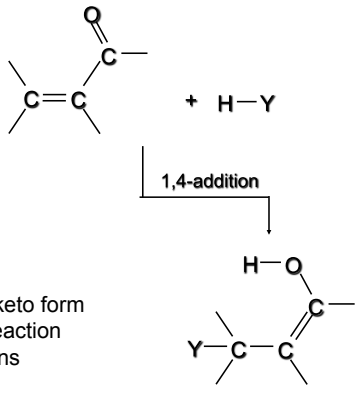
attack is faster at C=O

attack at β-carbon gives the more stable product



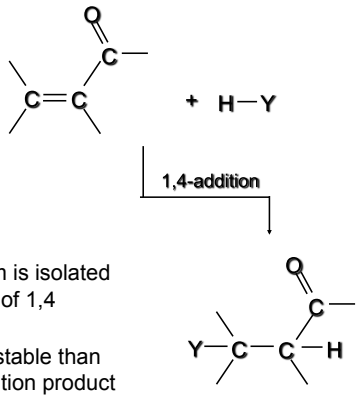
formed faster

major product under conditions of kinetic control (i.e. when addition is not readily reversible)



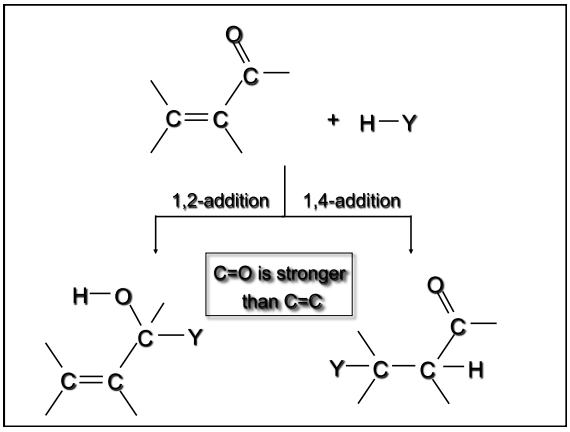
enol

goes to keto form under reaction conditions



keto form is isolated product of 1,4 -addition

is more stable than 1,2-addition product



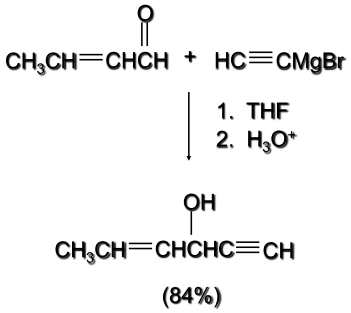
1,2-Addition

observed with *strongly* basic nucleophiles

- Grignard reagents
- $LiAlH_4$
- $NaBH_4$
- Sodium acetylide

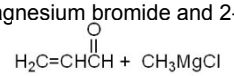
strongly basic nucleophiles add irreversibly

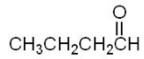
Example

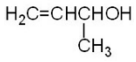


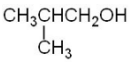
Question

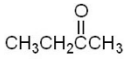
What is the product of the reaction between methylmagnesium bromide and 2-propenal?



A) 

B) 

C) 

D) 

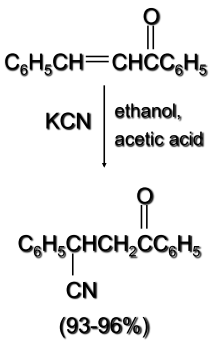
1,4-Addition

observed with *weakly* basic nucleophiles

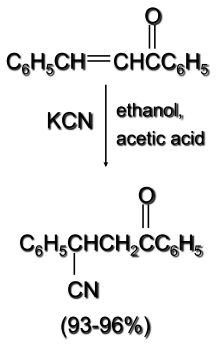
- cyanide ion (CN^-)
- thiolate ions (RS^-)
- ammonia and amines
- azide ion (N_3^-)

weakly basic nucleophiles add reversibly

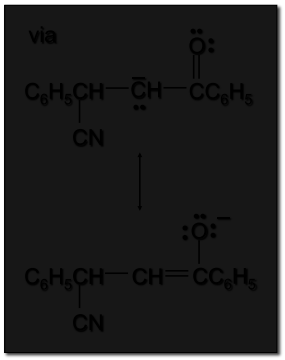
Example



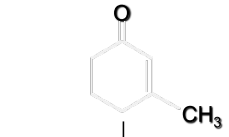
Example

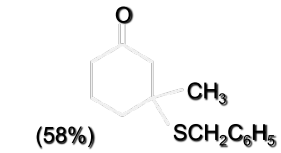


(93-96%)



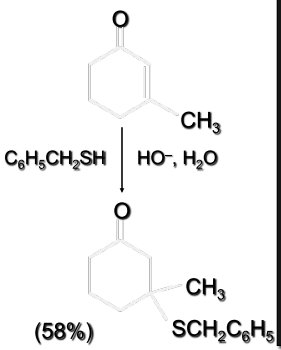
Example



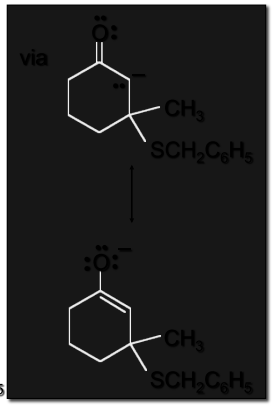


(58%)

Example



(58%)



Question

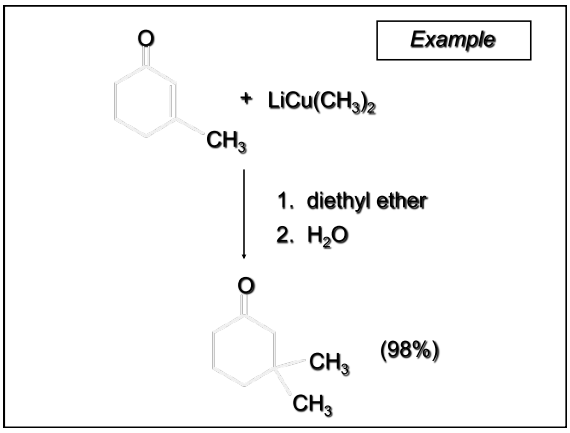
The reaction of an α,β-unsaturated ketone with NaCN occurs by conjugate addition. What is the product?

A) a cyanohydrin
B) an acyl cyanide
C) an α,β-unsaturated nitrile
D) a β-cyanoketone

Conjugate Addition of Organocopper Reagents to α,β-Unsaturated Carbonyl Compounds

Addition of Organocopper Reagents to α,β-Unsaturated Aldehydes and Ketones

The main use of organocopper reagents is to form carbon-carbon bonds by conjugate addition to α,β-unsaturated ketones.


Example
O
+ LiCu(CH3)2
CH3
1. diethyl ether
2. H2O
O
CH3
CH3
(98%)