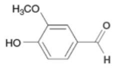
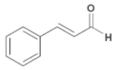
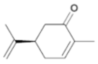
Aldehydes and Ketones

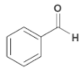
Nucleophilic Addition
to the
Carbonyl Group

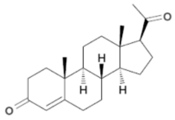
Ketones and Aldehydes

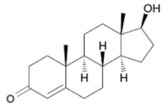

Vanillin


Cinnamaldehyde

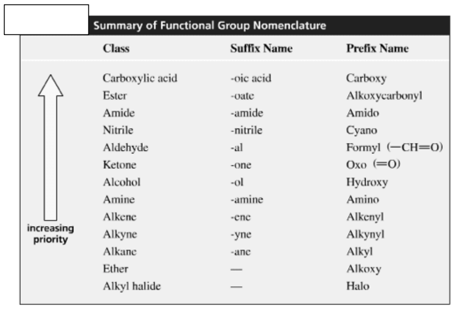

(R)-Carvone


Benzaldehyde


Progesterone


Testosterone

Nomenclature



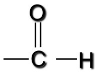
Summary of Functional Group Nomenclature

Class	Suffix Name	Prefix Name
Carboxylic acid	-oic acid	Carboxy
Ester	-oate	Alkoxycarbonyl
Amide	-amide	Amido
Nitrile	-nitrile	Cyano
Aldehyde	-al	Formyl (—CH═O)
Ketone	-one	Oxo (═O)
Alcohol	-ol	Hydroxy
Amine	-amine	Amino
Alkene	-ene	Alkenyl
Alkyne	-yne	Alkynyl
Alkane	-ane	Alkyl
Ether	—	Alkoxy
Alkyl halide	—	Halo

increasing priority

IUPAC Nomenclature of Aldehydes

when named as a substituent



$$-\overset{\displaystyle O}{\overset{\|}{C}}-H$$

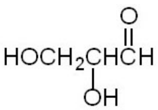
when named as a suffix

formyl group

carbaldehyde or carboxaldehyde

Question

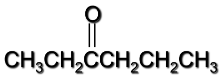
- What is the correct IUPAC name of the aldehyde at the right?



$$HOCH_2\underset{\displaystyle OH}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}H$$

- A) 2,3-dihydroxypropanol
- B) 1,2-dihydroxypropanal
- C) 2,3-dihydroxypropanal
- D) 2,3-propanediol-1-aldehyde

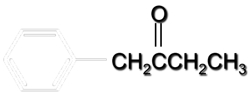
Functional Class IUPAC Nomenclature of Ketones



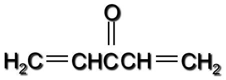
$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3$

3-hexanone
or hexan-3-one

or
ethyl propyl ketone



benzyl ethyl ketone

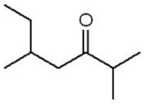


$H_2C{=}CH\overset{\overset{O}{\|}}{C}CH{=}CH_2$

divinyl ketone

Question

- What is the IUPAC name for the ketone shown below?



- A) 5-ethyl-2-methyl-3-hexanone
- B) 2,5-dimethyl-3-heptanone
- C) 3,6-dimethyl-5-heptanone
- D) 2-ethyl-5-methyl-5-hexanone

Question

- A compound ($C_7H_{14}O$) has a strong peak in its IR spectrum at 1710 cm^{-1}. Its ^{1}H-NMR spectrum consists of 3 singlets in the ratio 9:3:2 at δ1.0, δ2.1, and δ2.3, respectively.

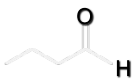
  Identify this compound.

- A) 3-heptanone
- B) 2,2-dimethyl-3-pentanone
- C) 4,4-dimethyl-2-pentanone
- D) 2,4-dimethyl-3-pentanone

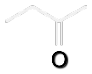
The Carbonyl Group
Structure, Bonding

Carbonyl Group of a Ketone is More Stable than that of an Aldehyde

heat of combustion



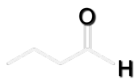
2475 kJ/mol



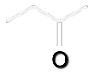
2442 kJ/mol

Alkyl groups stabilize carbonyl groups the same way they stabilize carbon-carbon double bonds, carbocations, and free radicals.

Spread is Greater for Aldehydes and Ketones than for Alkenes



2475 kJ/mol



2442 kJ/mol

Heats of combustion of C_4H_8 isomeric alkenes

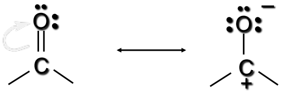
$CH_3CH_2CH{=}CH_2$
2717 kJ/mol

***cis*-$CH_3CH{=}CHCH_3$**
2710 kJ/mol

***trans*-$CH_3CH{=}CHCH_3$**
2707 kJ/mol

$(CH_3)_2C{=}CH_2$
2700 kJ/mol

Resonance Description of Carbonyl Group



Nucleophiles attack carbon; electrophiles attack oxygen.

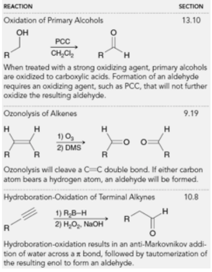
Synthesis
Aldehydes & Ketones

Synthesis of Aldehydes and Ketones

A number of reactions already studied provide efficient synthetic routes to aldehydes and ketones.

from alkenes
  ozonolysis
from alkynes
  hydration (via enol)
from arenes
  Friedel-Crafts acylation
from alcohols
  oxidation

Aldehyde and Ketone Syntheses

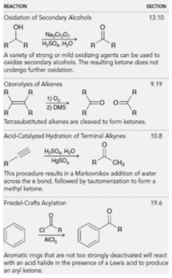


REACTION	SECTION
Oxidation of Primary Alcohols	13.10
Ozonolysis of Alkenes	9.19
Hydroboration-Oxidation of Terminal Alkynes	10.8

When treated with a strong oxidizing agent, primary alcohols are oxidized to carboxylic acids. Formation of an aldehyde requires an oxidizing agent, such as PCC, that will not further oxidize the resulting aldehyde.

Ozonolysis will cleave a C═C double bond. If either carbon atom bears a hydrogen atom, an aldehyde will be formed.

Hydroboration-oxidation results in an anti-Markovnikov addition of water across a π bond, followed by tautomerization of the resulting enol to form an aldehyde.



REACTION	SECTION
Oxidation of Secondary Alcohols	13.10
Ozonolysis of Alkenes	9.19
Acid-Catalyzed Hydration of Terminal Alkynes	10.8
Friedel-Crafts Acylation	19.6

A variety of strong or mild oxidizing agents can be used to oxidize secondary alcohols. The resulting ketone does not undergo further oxidation.

Tetrasubstituted alkenes are cleaved to form ketones.

This procedure results in a Markovnikov addition of water across the π bond, followed by tautomerization to form a methyl ketone.

Aromatic rings that are not too strongly deactivated will react with an acid halide in the presence of a Lewis acid to produce an aryl ketone.

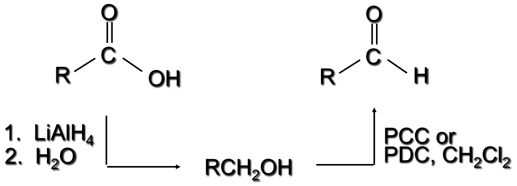
Question

- What combination of reagents will transform 1-butyne into 2-butanone?

- A) 1. O_3 2. H_2O, Zn
- B) $K_2Cr_2O_7$, H_2SO_4
- C) H_2SO_4, $HgSO_4$
- D) OsO_4 (cat), $(CH_3)_3COOH$, $(CH_3)_3OH$, HO^-

Reduction & Oxidation

aldehydes from carboxylic acids



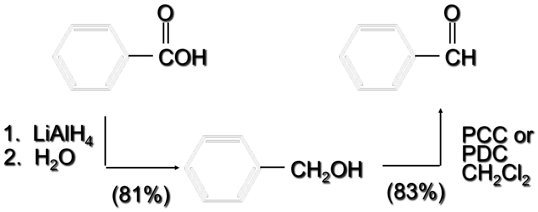
1. $LiAlH_4$
2. H_2O

RCH_2OH

PCC or
PDC, CH_2Cl_2

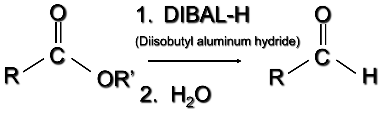
Example

Benzaldehyde from benzoic acid



Reduction

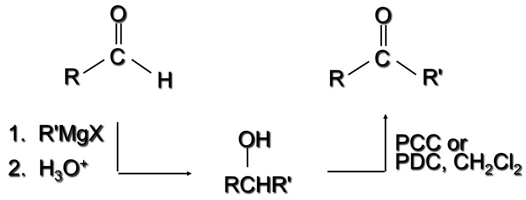
aldehydes from carboxylic acid esters



or from nitriles R-CN with DIBAL-H

Grignard & Oxidation

Ketones from aldehydes



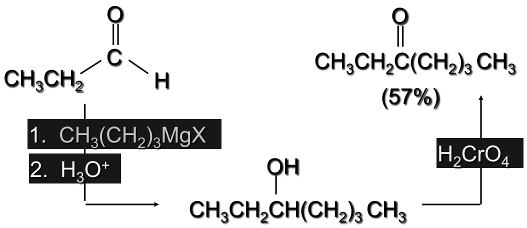
Question

- Which combination of reagents will produce 2-hexanone as the major organic product?

- A) 2-hexanol + PCC in CH_2Cl_2
- B) 1-hexene + H_2O, H_2SO_4, $HgSO_4$
- C) pentanal + methylmagnesium bromide followed by H_3O^+
- D) All of the above (a-c) will produce 2-hexanone as the major product.

Example

3-heptanone from propanal



Question

- An alcohol with a molecular formula $C_7H_{16}O$ was treated with chromic acid. The product produced 4 signals in its ^{13}C-NMR spectrum: one at 210 ppm and 3 others below 50 ppm. Identify the ketone.
- A) 4-heptanone
- B) 2,4-dimethyl-3-pentanone
- C) 4,4-dimethyl-2-pentanone
- D) 5-methyl-3-hexanone

Reactions of Aldehydes and Ketones

Reactions of Aldehydes and Ketones

Reduction of C=O to CH_2

Clemmensen reduction

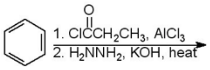
Wolff-Kishner reduction

Reduction of C=O to CHOH

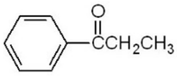
Addition of Grignard and organolithium reagents

Question

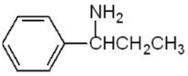
- Which compound will be isolated from the synthetic sequence shown below?



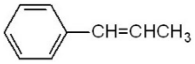
- A)



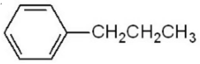
B)



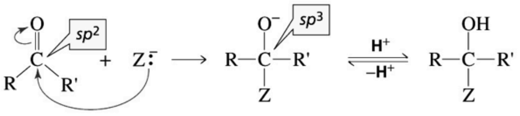
- C)



D)



Aldehydes and ketones react with nucleophiles to form addition products: nucleophile addition reactions

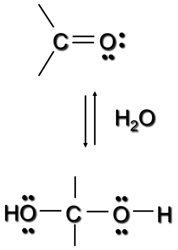


Question

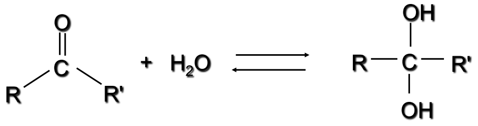
- When a nucleophile encounters a ketone, the site of attack is
- A) the carbon atom of the cabonyl.
- B) the oxygen atom of the carbonyl.
- C) both the carbon and oxygen atoms, with equal probability.
- D) No attack occurs--ketones do not react with nucleophiles.

Hydration of Aldehydes and Ketones

Hydration of Aldehydes and Ketones



Substituent Effects on Hydration Equilibria



compared to H

electronic: reactants	alkyl groups stabilize
steric: product	alkyl groups crowd

Equilibrium Constants and Relative Rates of Hydration

C=O	hydrate	*K*	%	Relative rate
CH_2=O	$CH_2(OH)_2$	2300	>99.9	2200
CH_3CH=O	$CH_3CH(OH)_2$	1.0	50	1.0
$(CH_3)_3CCH$=O	$(CH_3)_3CCH(OH)_2$	0.2	17	0.09
$(CH_3)_2C$=O	$(CH_3)_2C(OH)_2$	0.0014	0.14	0.0018

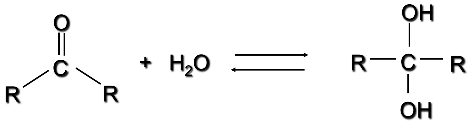
Equilibrium Can Favor a Hydrate

(But not very often)

Only when the carbonyl group is destabilized

- alkyl groups stabilize C=O
- electron-withdrawing groups destabilize C=O

Substituent Effects on Hydration Equilibria

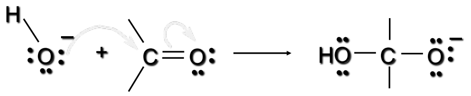


← R = CH_3: K = 0.0014

R = CF_3: K = 22,000 →

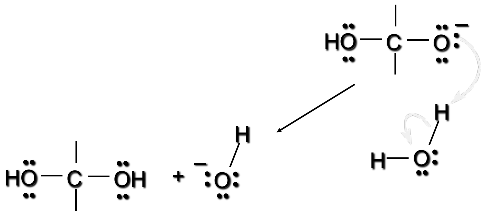
Mechanism of Hydration (base)

Step 1:



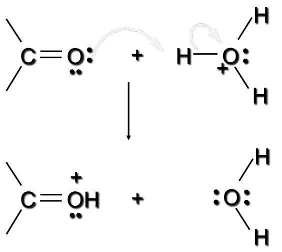
Mechanism of Hydration (base)

Step 2:



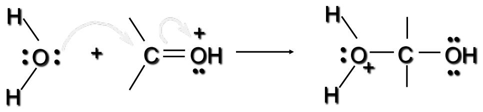
Mechanism of Hydration (acid)

Step 1:



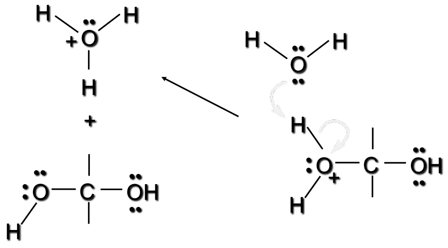
Mechanism of Hydration (acid)

Step 2:



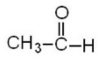
Mechanism of Hydration (acid)

Step 3:



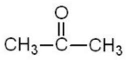
Question

- Which one of the compounds below has the fastest hydration rate?
- A)



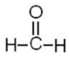
$CH_3-\overset{\overset{O}{\|}}{C}-H$

B)



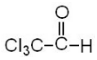
$CH_3-\overset{\overset{O}{\|}}{C}-CH_3$

- C)



$H-\overset{\overset{O}{\|}}{C}-H$

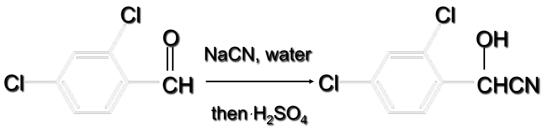
D)



$Cl_3C-\overset{\overset{O}{\|}}{C}-H$

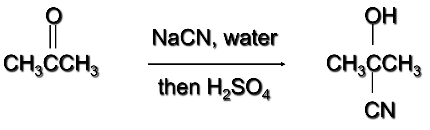
Cyanohydrin Formation

Example



2,4-Dichlorobenzaldehyde
cyanohydrin (100%)

Example



$$CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[\text{then } H_2SO_4]{\text{NaCN, water}} CH_3\underset{CN}{\overset{OH}{C}}CH_3$$

(77-78%)

Acetone cyanohydrin is used in the synthesis of methacrylonitrile

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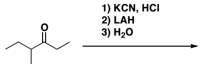
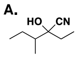
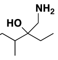
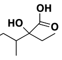
Question

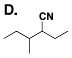
What is the product of the following reaction?



A.


B.


C.


D.


Acetal Formation

Some reactions of aldehydes and ketones progress beyond the nucleophilic addition stage

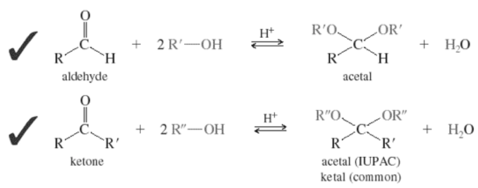
Acetal formation

Imine formation

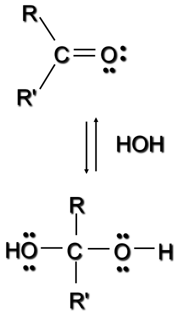
Enamine formation

Compounds related to imines

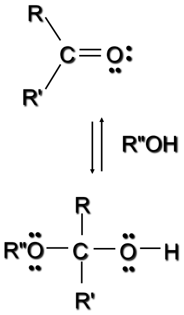
The Wittig reaction



Recall Hydration of Aldehydes and Ketones

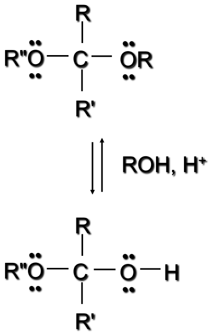


Alcohols Under Analogous Reaction with Aldehydes and Ketones



Product is called a *hemiacetal*.

Hemiacetal reacts further in acid to yield an acetal



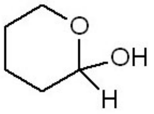
Product is called an *acetal*.

Product is called a *hemiacetal*.

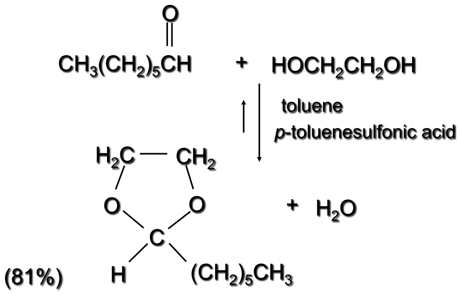
Question

- The structure shown at the right would be best classified as a(n)

- A) acetal.
- B) hemiacetal.
- C) hydrate.
- D) cyanohydrin.



Diols Form Cyclic Acetals

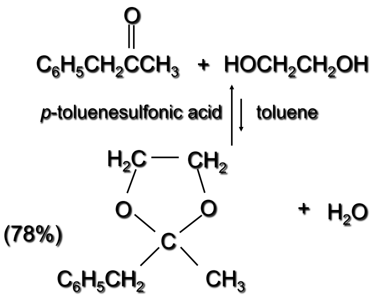


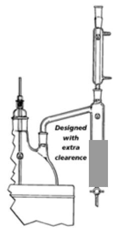
In general:

Position of equilibrium is usually unfavorable for acetal formation from ketones.

But:
Cyclic acetals can be prepared from ketones.

Example

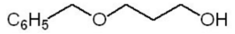




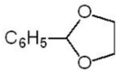
Question

What is the product of the reaction between benzaldehyde and 1,3-propanediol?

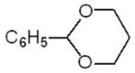
- A)



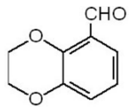
B)



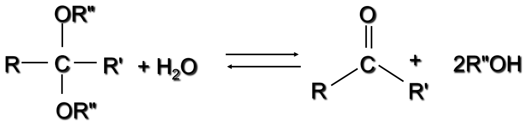
- C)



D)



Hydrolysis of Acetals



$$R-\overset{OR''}{\underset{OR''}{C}}-R' + H_2O \rightleftharpoons R-\overset{O}{\overset{\|}{C}}-R' + 2R''OH$$

mechanism:

reverse of acetal formation;
hemiacetal is intermediate

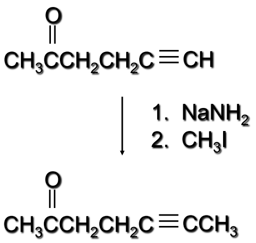
application:

aldehydes and ketones can be "protected" as acetals.

Acetals as Protecting Groups

Example

The conversion shown cannot be carried out directly...



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2C\equiv CH \xrightarrow[2.\ CH_3I]{1.\ NaNH_2} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2C\equiv CCH_3$$

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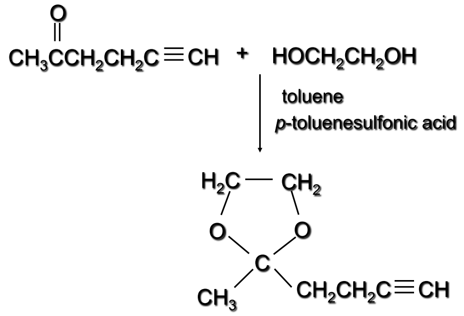
because the carbonyl group and the carbanion are incompatible functional groups.

CH_3 [redacted] CH_2CH_2 [redacted]

Strategy

1) protect C=O
2) alkylate
3) restore C=O

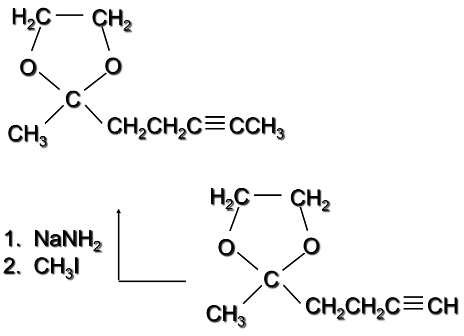
Example: Protect



$CH_3C(=O)CH_2CH_2C{\equiv}CH$ + $HOCH_2CH_2OH$

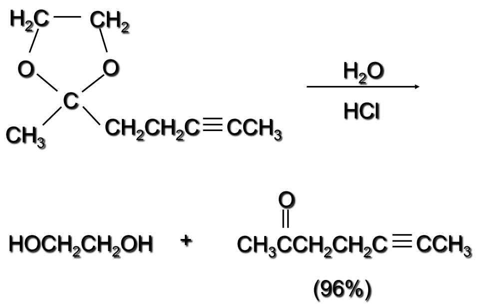
toluene
p-toluenesulfonic acid

Example: Alkylate



1. NaNH$_2$
2. CH$_3$I

Example: Deprotect



H_2O

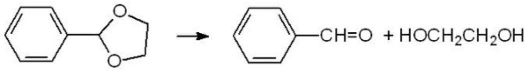
HCl

$HOCH_2CH_2OH$ + $CH_3C(=O)CH_2CH_2C{\equiv}CCH_3$

(96%)

Question

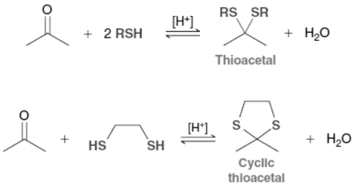
- What reagent and/or reaction conditions would you choose to bring about the following conversion?



- A) 1. $LiAlH_4$; 2. H_2O
- B) H_2O, H_2SO_4, heat
- C) H_2O, NaOH, heat
- D) PCC, CH_2Cl_2

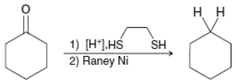
Sulfur Nucleophiles

- Under acidic conditions, thiols react nearly the same as alcohols. Examples:



Alternative to Wolff-Kishner

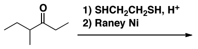
- Conversion of a ketone into an alkane:



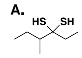
1. A thioacetal is formed via an acid catalyzed nucleophilic addition mechanism.
2. Raney Ni transfers H_2 molecules to the thioacetal converting it into an alkane.

Question

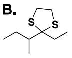
What is the product of the following reaction?



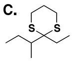
A.



B.



C.



D.