ORGANIC CHEMISTRY for STEM MAJORS

Part 3 of 3

Workbook designed to accompany Organic Chemistry by David Klein, 4th ed

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19: ALDEHYDES AND KETONES

MAIN IDEA

Due to difference in electronegativity, the carbon atom of a carbonyl group is partially-positive. This makes it susceptible to nucleophilic attack, similar to what is observed in a nucleophilic substitution reaction (S_N1 and S_N2). When the carbonyl group of an aldehyde or ketone is attacked by a nucleophile, there is no appropriate leaving group to allow for a nucleophilic substitution to occur. Instead of losing a leaving group, the carbonyl carbon pushes away its pi electrons, converting the carbon-oxygen double bond to a single bond and creating a lone pair of electrons on the oxygen. This reaction, called nucleophilic addition, ultimately results in the addition of new substituents to both the carbon and oxygen atoms of the carbonyl group.

OBJECTIVES

- ☐ Learn how to name aldehydes and ketones
- ☐ Understand nucleophilic addition under acidic and basic conditions
- ☐ Learn how to synthesize aldehydes and ketones
- ☐ Learn how to convert aldehydes and ketones to hydrates, acetals, imines, enamines, and alcohols

SKILLS TO MASTER

- ☐ Name aldehydes and ketones using IUPAC rules
- ☐ Draw the mechanism of a nucleophilic substitution reaction under acidic or basic conditions
- ☐ Identify the correct reagents needed to perform the following conversions:
    - ☐ Primary alcohols, alkenes, and alkynes to aldehydes
    - ☐ Secondary alcohols, alkenes, and alkynes to ketones
    - ☐ Aldehyde to hydrate under acidic or basic conditions
    - ☐ Aldehyde to ketone to acetal, imine, or enamine
    - ☐ Aldehyde or ketone to alcohol via reduction
    - ☐ Aldehyde or ketone to alcohol via Grignard reaction

☐ Predict the products of the hydrolysis of an acetal, hemiacetal, imine, or enamine

☐ Identify the correct reagents needed to form a Wittig reagent and use it to synthesize a desired alkene

TERMINOLOGY

☐ Acetal

☐ Cyanohydrin

☐ Enamine

☐ Hemiacetal

☐ Hydrate

☐ Imine

☐ Nitrile

☐ Nucleophilic addition

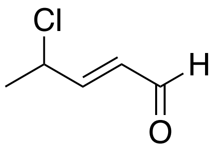
☐ Ylide

1: NAMING ALDEHYDES AND KETONES

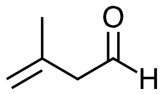
1. To name an aldehyde by IUPAC rules:

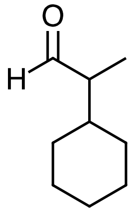
   - Find the longest carbon chain containing the carbonyl (C=O) group
   - Number the carbon chain so the carbonyl group is carbon #1
   - Follow all IUPAC rules regarding stereochemistry and substituents
   - Replace the “-e” ending of the parent chain with “-al”
   - The location of the aldehyde group is always carbon #1 and therefore it is never included in the IUPAC name

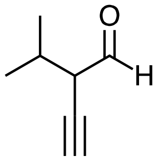
Look at the example to the right, and then provide names for the remaining aldehydes.



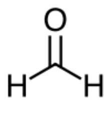
trans-4-chloropent-2-enal

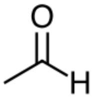


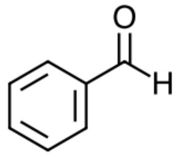




2. Several aldehydes are known by common names. Memorize the common names of these aldehydes.



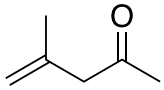




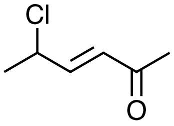
3. To name a ketone by IUPAC rules:

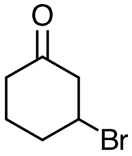
- Find the longest carbon chain containing the carbonyl (C=O) group
- Number the carbon chain so the carbonyl group gets the lowest possible number
- Follow all IUPAC rules regarding stereochemistry and substituents
- Replace the “-e” ending of the parent chain with “-one”

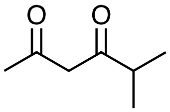
Look at the example to the right, and then provide names for the remaining ketones.



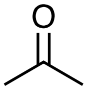
4-methylpent-4-en-2-one

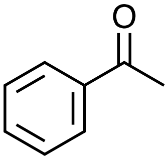


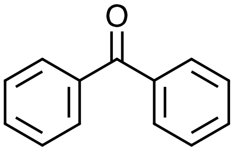




4. Several ketones are known by common names. Memorize the common names of these ketones.







2: INTRODUCTION TO NUCLEOPHILIC ADDITION REACTIONS

1. Aldehydes and ketone are good electrophiles and subject to nucleophilic attack at the carbonyl carbon. Does this mean the carbonyl carbon carries a positive or negative formal/partial charge?

2. Use resonance to explain the formal/partial charge on the carbonyl carbon of an aldehyde or ketone. Use acetone as your example.

3. Use electronegativity to explain the formal charge on the carbonyl carbon of an aldehyde or ketone. Use acetone as your example.

4. In general, aldehydes are more reactive than ketones. Propose two explanations for this trend:

   1:

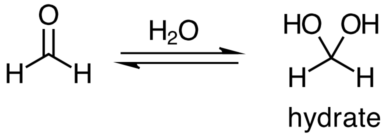
   2:

Nucleophilic addition to a carbonyl carbon can take place in either acidic or basic conditions.

5. Propose a generic mechanism for nucleophilic addition in basic conditions. Use acetone as your example. Attack the carbonyl carbon with $^{-}$Nuc (notation for a generic nucleophile). Follow up with water. Your product will be an alcohol.

6. Propose a generic mechanism for nucleophilic addition in acidic conditions. Use acetone as your example. Protonate with H_3O^+ and then attack the carbonyl carbon with Nuc (notation for any generic nucleophile without a formal charge). Your product will be an alcohol.

3: OXYGEN NUCLEOPHILES

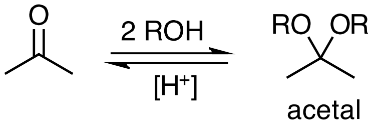


Formation of a hydrate

This reaction only works with formaldehyde

1. Propose a mechanism under basic conditions. What is a reasonable nucleophile for this reaction?

2. Propose a mechanism under acidic conditions. Use H_3O^+ as your acid.



Formation of an acetal

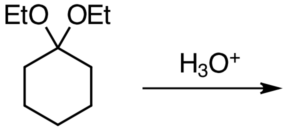
This reaction only occurs under acidic conditions

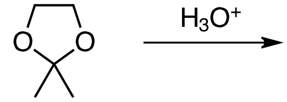
3. Propose a mechanism under acidic conditions. Use H^+ as the acid and ROH as the alcohol.

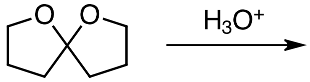
Hydrolysis of an acetal

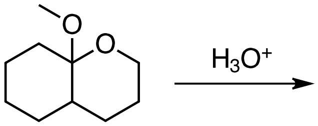
Acetals can be converted back to aldehydes or ketones

4. Draw the products of the following hydrolysis reactions.



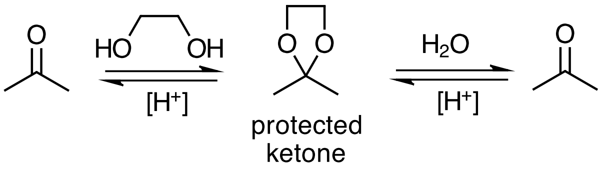






Acetals as Protecting Groups

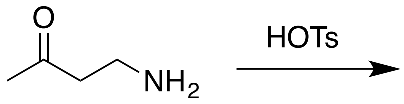
This can be used to prevent aldehydes or ketones from undergoing an unwanted reaction.

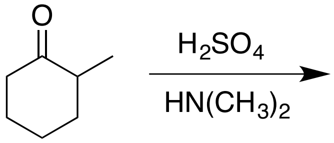


5. Show how to perform the following conversion using an acetal as a protecting group (step 1) and a Grignard reaction / acetal hydrolysis (step 2). *Carboxylic acids and esters cannot be converted to acetals, even though they have a carbonyl group.*

4: NITROGEN NUCLEOPHILES

Draw the mechanism for the following reactions.

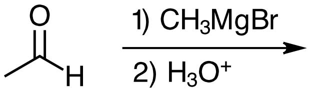




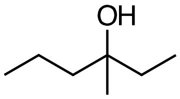
5: CARBON NUCLEOPHILES

Grignard Reaction

1. Predict the product of the following reactions.

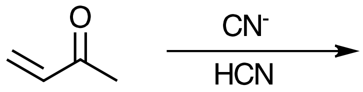


2. Show how to form the following alcohol via a Grignard reaction.

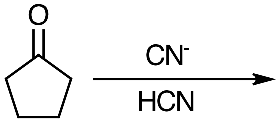


Formation of a Cyanohydrin

3. Draw the mechanism for the following reaction.

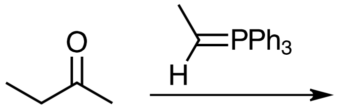


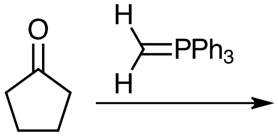
4. Predict the product of the following reaction.

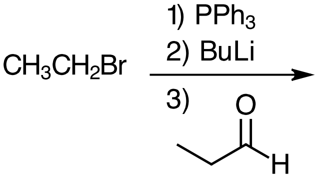


Wittig Reaction

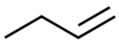
5. Predict the products of the following reactions. Pay attention to stereochemistry of the double bond.

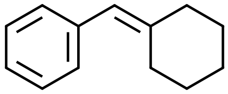






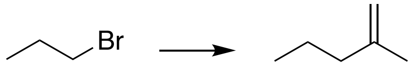
6. Show how to form the following molecules using a Wittig reaction, starting from an alkyl halide.

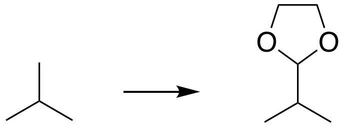


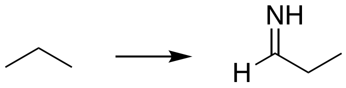


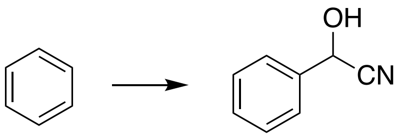
6: SYNTHESIS STRATEGIES

Show how to perform each of the following conversions.









20: CARBOXYLIC ACIDS AND THEIR DERIVATIVES

MAIN IDEA

Carboxylic acids are susceptible to nucleophilic attack at the carbonyl carbon. When a nucleophile attacks a carboxylic acid, the hydroxyl group of the carboxylic acid is capable of acting as a leaving group. This allows for nucleophilic substitution to occur at the carbonyl carbon. The resulting molecule is often referred to as a *carboxylic acid derivative*. This type of reaction, called nucleophilic acyl substitution, has a mechanism similar to that of both nucleophilic addition as well as S_N2.

OBJECTIVES

- ☐ Learn how to name carboxylic acids
- ☐ Understand nucleophilic acyl substitution
- ☐ Learn how to synthesize carboxylic acids
- ☐ Learn how to convert between carboxylic acids and their derivatives

SKILLS TO MASTER

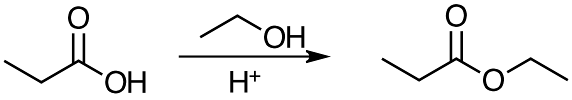
- ☐ Name carboxylic acids using IUPAC rules
- ☐ Identify the correct reagents needed to perform the following conversions:
    - ☐ Alkyne, alcohol, alkylated benzene, acid halide, ester, and nitrile to carboxylic acid
    - ☐ Carboxylic acid, acid chloride, anhydride, and ester to primary alcohol
    - ☐ Acid chloride, anhydride, and ester to aldehyde
    - ☐ Amide and nitrile to amine
    - ☐ Carboxylic acid to acid halide
    - ☐ Carboxylic acid, acid halide, and anhydride to ester
    - ☐ Acid halide to anhydride
    - ☐ Acid halide, anhydride, and ester to amide
    - ☐ Amide and nitrile to carboxylic acid
    - ☐ Amide to nitrile
- ☐ Identify the correct reagents needed to form a carboxylic acid using a Grignard reaction

TERMINOLOGY

- ☐ Alcoholysis
- ☐ Aminolysis
- ☐ Dialkyl cuprate
- ☐ Fischer esterification
- ☐ Hydrolysis
- ☐ Nucleophilic acyl substitution
- ☐ Saponification

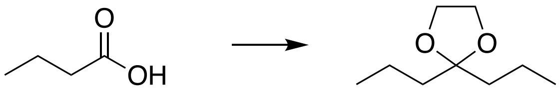
7: PREPARATION OF ESTERS

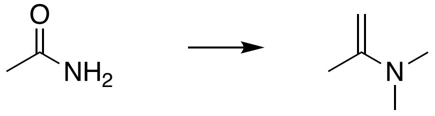
Propose a mechanism for the following Fischer esterification reaction.

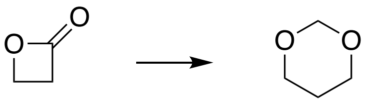


8: SYNTHESIS STRATEGIES

Show how to perform each of the following conversions.







21: ALPHA CARBON CHEMISTRY: ENOLS AND ENOLATES

MAIN IDEA

Carbon atoms attached directly to carbonyl carbons are referred to as *alpha* carbon atoms. Alpha carbon atoms are easily deprotonated to form *enolate* ions, which are stabilized via resonance from the adjacent carbonyl group. Even though they are stabilized by resonance, enolate ions are reactive and undergo interesting reactions that resemble nucleophilic addition, nucleophilic substition, and 1,4-addition reactions of conjugated dienes. Many of the reactions of enolate ions are used to create bonds between carbon atoms and therefore are useful for lengthening carbon chains or creating cyclic molecules.

OBJECTIVES

- ☐ Understand the reactivity of alpha carbon atoms
- ☐ Learn how to halogenate and alkylate alpha carbon atoms
- ☐ Learn the reactions that to use enolate ions to create new carbon-carbon bonds

SKILLS TO MASTER

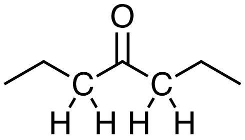
- ☐ Draw the structures of enolates formed from the deprotonation of aldehydes and ketones
- ☐ Identify the correct reagents needed to perform the following reactions:
    - ☐ Alpha halogenation of ketones, aldehydes, and carboxlylic acids
    - ☐ Alpha alkylation of ketones and aldehydes
- ☐ Identify the correct reagents and draw the mechanisms for the following reactions:
    - ☐ Aldol addition and condensation
    - ☐ Claisen condensation
    - ☐ Malonic ester synthesis
    - ☐ Acetoacetic ester synthesis
    - ☐ Michael addition
    - ☐ Stork enamine synthesis

TERMINOLOGY

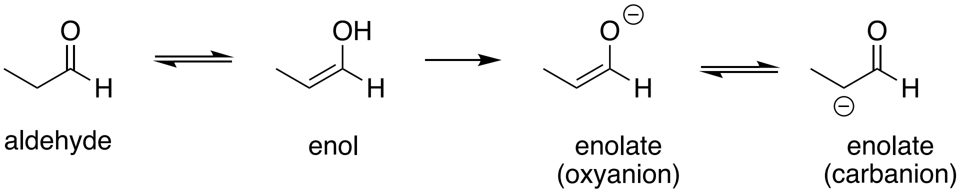
- Acetoacetic ester
- Aldol
- Alpha-beta unsaturated carbonyl compound
- Alpha carbon
- Alpha hydrogen
- Enolate
- Kinetic control
- Intramolecular reaction
- Malonic ester
- Thermo control

9: INTRODUCTION TO ALPHA CARBON CHEMISTRY

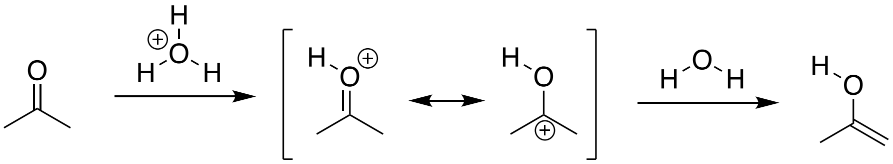
Alpha carbons are those bonded directly to a carbonyl carbon. Alpha hydrogen are bonded directly to an alpha carbon. In the molecule to the right, the alpha carbon and hydrogen are represented by their atomic symbols.



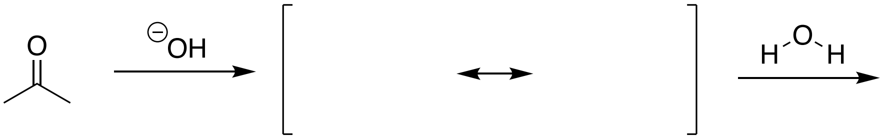
Alpha hydrogen are acidic and can be easily removed. This forms an enolate ion. The relationship between aldehydes (or ketones), eons, and enolate ions is shown below:



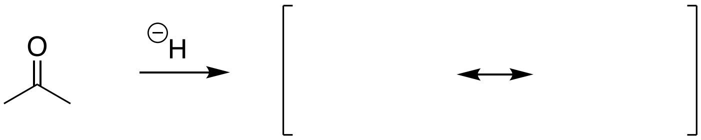
1. Fill in the curved arrows to show the mechanism for the acid-catalyzed conversion of a carbonyl compound (acetone) to an enol (not enolate)



2. Propose a mechanism for the base-catalyzed conversion of a carbonyl compound (acetone) to an enol (not enolate).

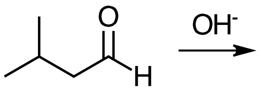


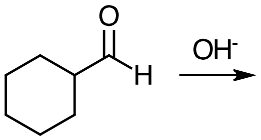
3. Propose a mechanism for the formation of an enolate (not enol). Notice that this reaction stops with the resonance structures. Of the two resonance structures, identify which is the most reactive (least stable).



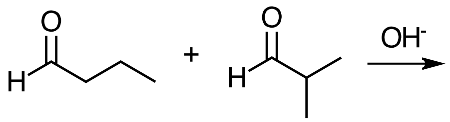
10: ALDOL REACTIONS

Draw the mechanisms for the following aldol addition reactions. If possible, continue the reaction by drawing the mechanism for condensation.

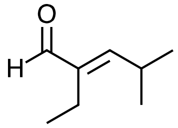


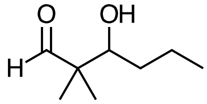


Draw all possible products for the following crossed aldol reaction. When possible, the reaction should go through condensation.

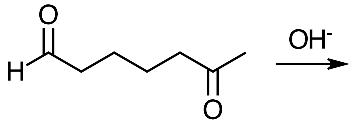


Show how to synthesize the following compounds by a directed aldol reaction.



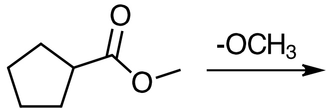


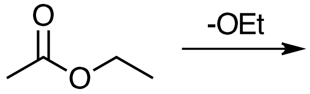
Draw all possible products of the following intramolecular aldol reaction. When possible, the reaction should go through condensation.



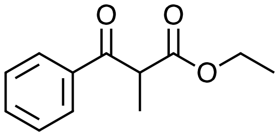
11: CLAISEN CONDENSATION

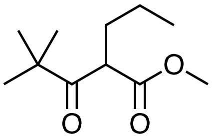
Draw the mechanism for each of the following Claisen reactions.



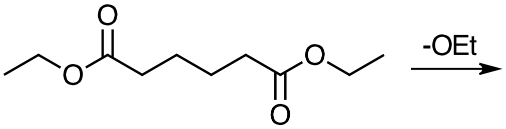


What esters can be used other than make the following molecules in a Claisen reaction?





Draw the product(s) of the following Dieckmann reaction.



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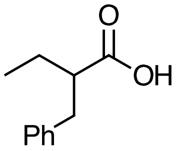
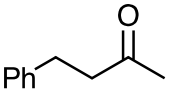
12: ALKYLATION OF THE ALPHA POSITION

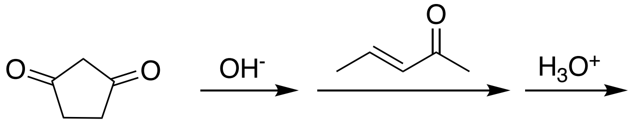
Show how to make the following molecules via a malonic or acetoacetic ester synthesis.



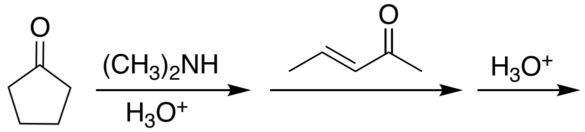


13: CONJUGATE ADDITION REACTIONS

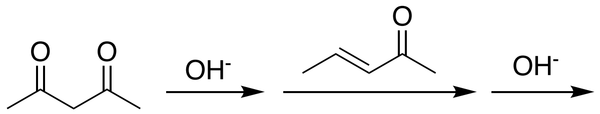
Draw the mechanism for the following Michael reaction.



Draw the mechanism for the following Stork enamine reaction.



Draw the mechanism for the following Robinson annulation reaction.



Summarize and differentiate these three reactions in terms of their reactants / reagents and the mechanism / product.

1)

2)

3)

22: AMINES

MAIN IDEA

Amines are molecules that contain a nitrogen atom in a bonding pattern that cannot be classified as a nitrile or amide. They typically contain a nitrogen atom with two or more bonds to hydrogen or carbon. Due to the lone pair of electrons on the nitrogen, amines are easily protonated and are therefore classified as bases. In this chapter, we will review reactions that can be used to synthesize amines, or increase the number of alkyl groups attached to the nitrogen of an amine. We will also learn how to convert amines to alkenes.

OBJECTIVES

- ☐ Understand the stereochemistry of amines
- ☐ Understand what dictates the relative boiling points of amines
- ☐ Learn how to synthesize amines from alkyl halides, carboxylic acids, aldehydes, or ketones
- ☐ Learn how to convert amines to alkenes, benzene, or derivatives of benzene

SKILLS TO MASTER

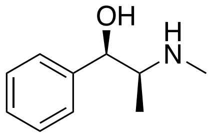
- ☐ Explain why chiral amines are not classified as (*R*) or (*S*)
- ☐ Rank amines in order of increasing boiling point
- ☐ Identify the correct reagents needed to perform the following reactions:
    - ☐ Alkyl halide, carboxylic acid, aldehyde, or ketone to amine
    - ☐ Amine to alkene
    - ☐ Aniline to aryldiazonium
    - ☐ Aryldiazonium to benzene, halogenated benzene, phenol, or benzoic acid

TERMINOLOGY

- ☐ Aryldiazonium
- ☐ Azide

14: REDUCTIVE AMINATION

Show two ways to prepare ephedrine by reductive amination.



Show how to prepare the following amine by reductive amination.