

Organic Chemistry II

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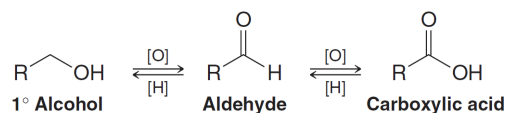
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1 Aldehydes and Ketones

1.1 Physical Properties

- Aldehydes and ketones are polar and thus have higher boiling points than similar hydrocarbons and are generally soluble in water
- Aldehydes and ketones do not have hydrogen bonding between molecules, so they have lower boiling points than corresponding alcohols
- The order of oxidation states is given as follows:

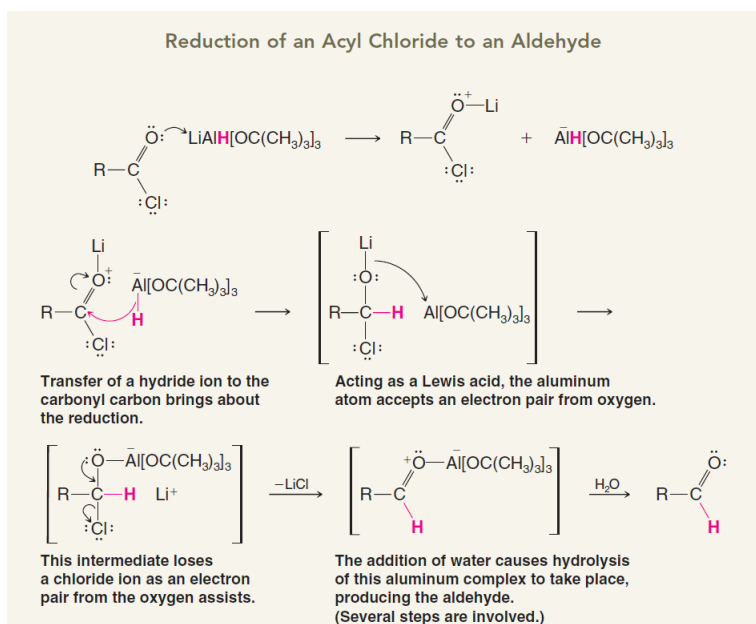


1.2 Synthesis of Aldehydes

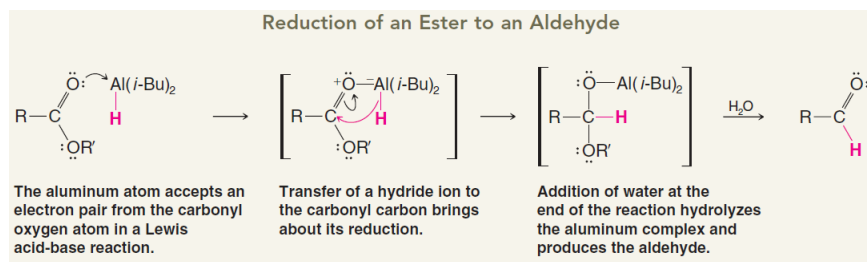
1.2.1 Reduction and Oxidation¹

- To convert 1° alcohols to aldehydes via oxidation, PCC in CH₂Cl₂ can be used
- Ozonolysis - through the use of O₃, CH₂Cl₂ and then Me₂S - can produce aldehydes (or ketones) from alkenes
- Since LAH is such a strong reducing agent, it cannot convert a carboxylic acid to an aldehyde since it, instead, converts it to a 1° alcohol
- LiAlH(O-t-Bu)₃ or DIBAL-H in hexane can be used as a less reactive reducing agent (note: H₂O is used afterwards)
 - LiAlH(O-t-Bu)₃ in Et₂O and then water can convert an acyl chloride (RC=OCl) to an aldehyde
 - DIBAL-H in hexane and then water can convert an ester (RCO₂R') or nitrile (RCN) to an aldehyde
- Carboxylic acids can be converted to acyl chlorides by using SOCl₂

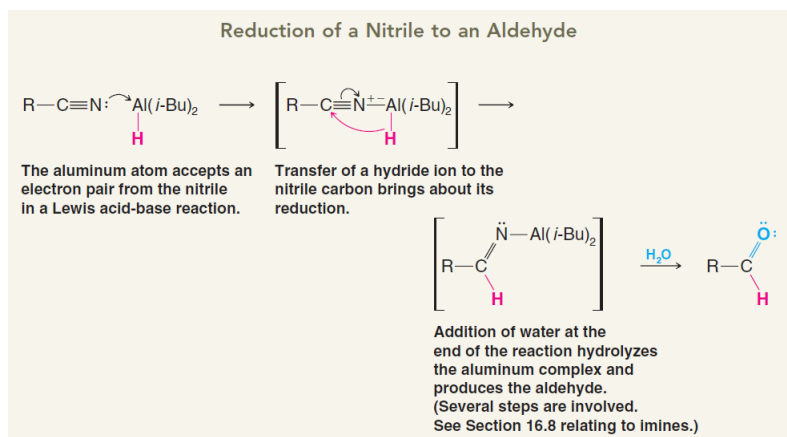
1.2.2 Mechanisms for Aldehyde Synthesis



¹Page 734 of the textbook has an error. The first graphic shows a 1° alcohol converting to an “aldehyde,” but the aldehyde is actually a carboxylic acid. The OH group should actually just be a hydrogen atom.

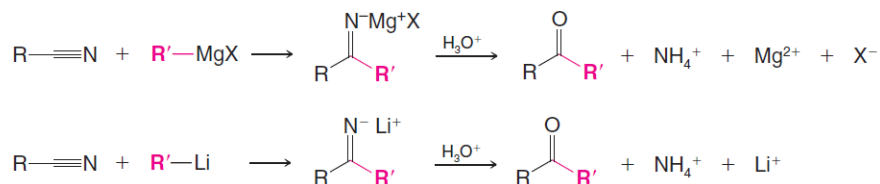


- For the ester reduction, if it's a cyclic ester, the product would be an aldehyde that also has an alcohol hydroxy group (instead of the OR group being entirely replaced by H)

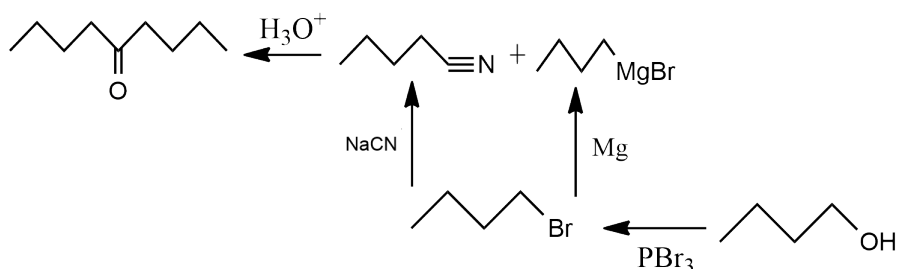


1.3 Synthesis of Ketones

- The use of H_2CrO_4 or PCC in CH_2Cl_2 will convert a 2° alcohol to a ketone
- Grignard reagents or organolithium reagents can convert a nitrile to a ketone. Examples are shown below:



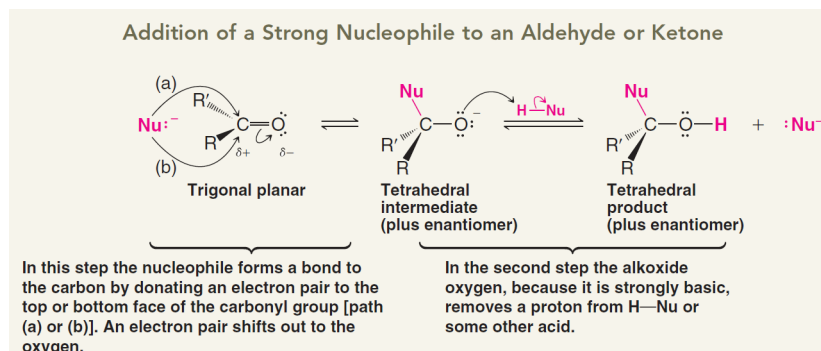
1.4 Synthesis of Ketone Example



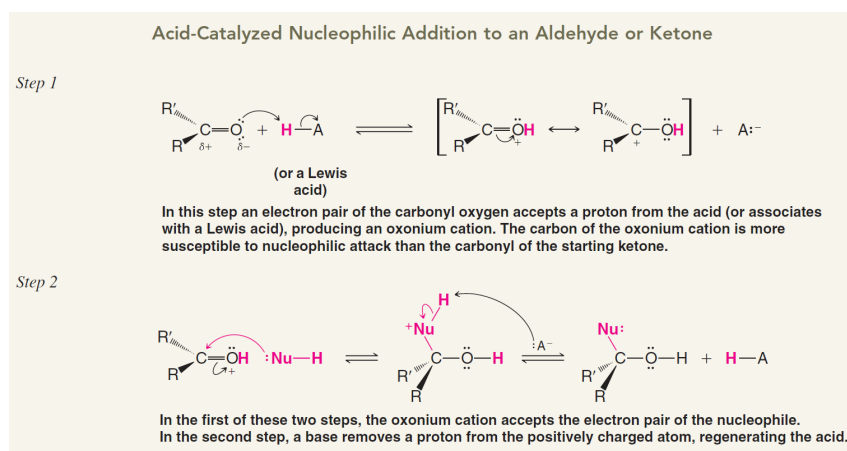
- Note that PBr_3 replaces an OH with a Br and does not have rearrangements
 - It is useful for creating alkyl bromides, which can then make grignard reagents
- The creation of nitriles via this method is useful to make aldehydes using DIBAL-H

1.5 Nucleophilic Addition to the Carbon-Oxygen Double Bond

- When the reagent is a strong nucleophile, addition takes place as follows without stereospecificity:



- When an acid catalyst is present and the nucleophile is weak, addition takes place as follows²:

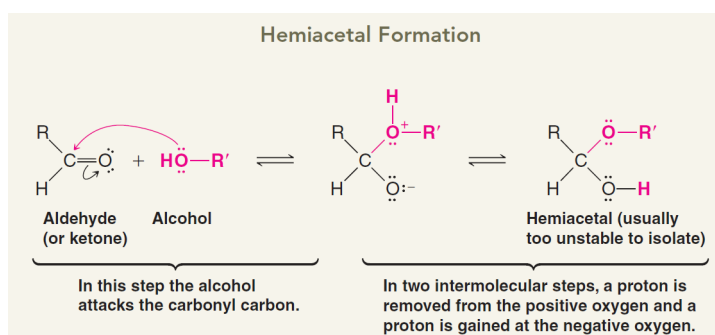


- Aldehydes are more reactive than ketones in nucleophilic additions
 - Aldehydes have less steric hindrance at the carbonyl carbon
 - Aldehydes have a larger dipole moment on the carbonyl carbon

1.6 The Addition of Alcohols: Hemiacetals and Acetals

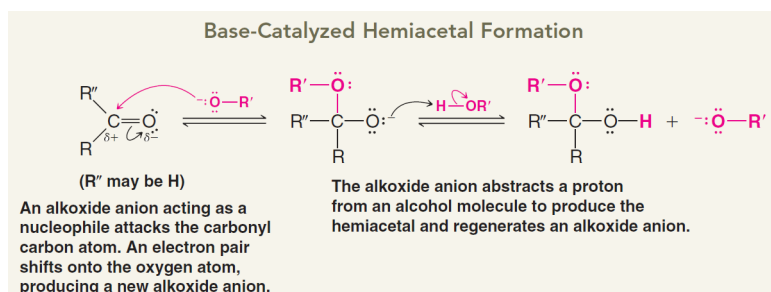
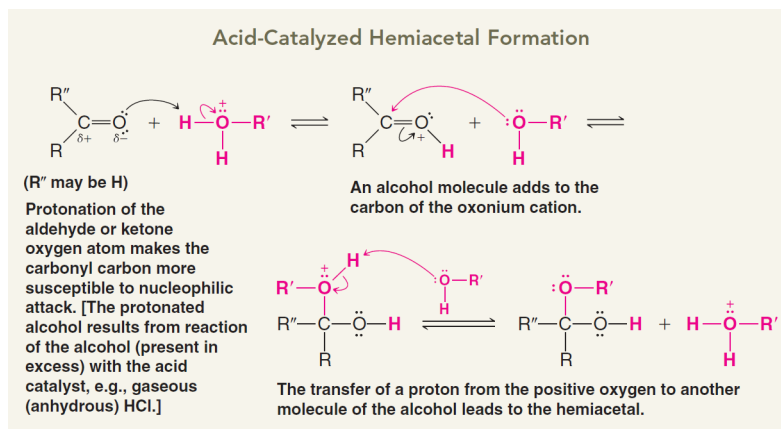
1.6.1 Hemiacetals

- A hemiacetal is a molecule with an OH and an OR group attached to the same carbon
- Alcohols can react with aldehydes or ketones to form hemiacetals:



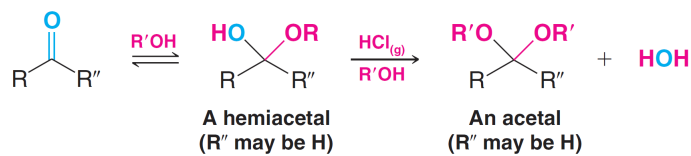
²The protonated carbonyl compound is called an oxonium cation and is highly reactive toward nucleophilic attack

- Hemiacetal formation is catalyzed by acids and bases:

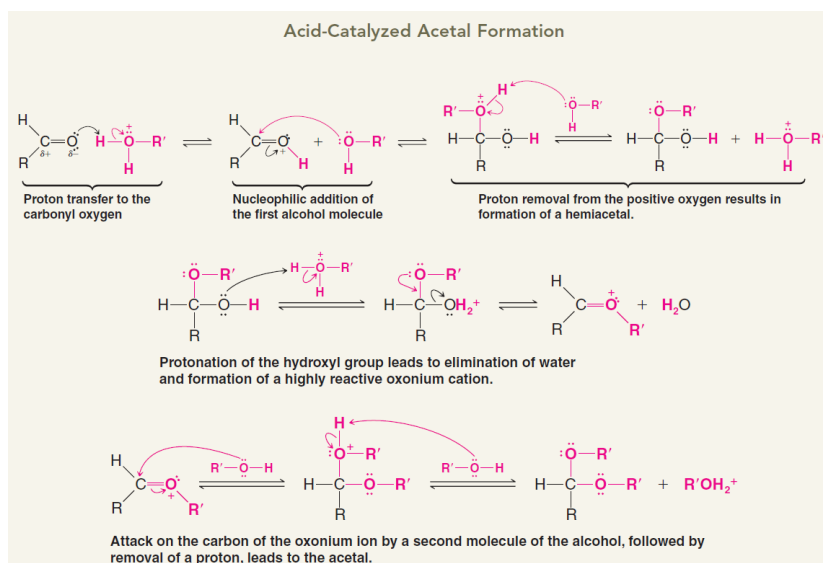


1.6.2 Acetals

- An acetal has two OR groups attached to the same carbon
- Treating a ketone or aldehyde in an alcohol solution with some gaseous HCl will form an acetal
 - Adding water to this acetal will shift the equilibrium left and form the aldehyde

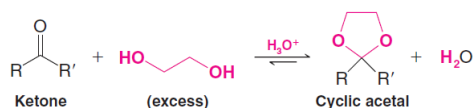


- An aldehyde or ketone can be converted to an acetal via acid-catalyzed formation of the hemiacetal and then acid-catalyzed elimination of water. This is followed by addition of the alcohol and loss of a proton
 - All steps are reversible. Be able to draw the mechanism of making an aldehyde from the acetal



1.6.3 Cyclic Acetals

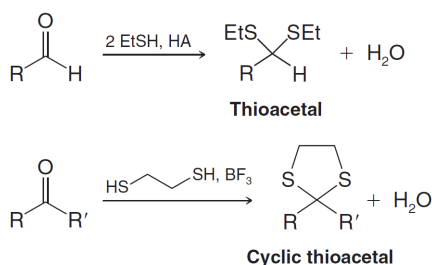
- A cyclic acetal can be formed when a ketone or aldehyde is treated with excess 1,2-diol and a trace of acid (be able to write the mechanism)
 - This reaction can be reversed by treating the acetal with water and acid (H_3O^+)



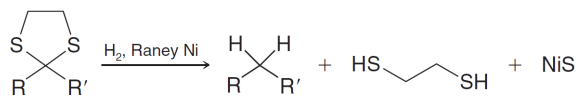
- Acetals are stable in basic solutions (nonreactive)
- Acetals can act as protecting groups for aldehydes and ketones in basic solutions due to their stability
 - For instance, to protect a carbonyl group, one can add a cyclic acetal in HCl. Then one can perform the desired reaction without worrying about the carbonyl group. Finally, to remove the cyclic acetal and restore the carbonyl group, use $\text{H}_3\text{O}^+/\text{H}_2\text{O}$

1.6.4 Thioacetals

- An aldehyde or ketone can react with a thiol (R-SH) in HA to form a thioacetal
- Additionally, an aldehyde or ketone can react with a di-thiol (HS-R-SH) with BF_3 to form a cyclic thioacetal



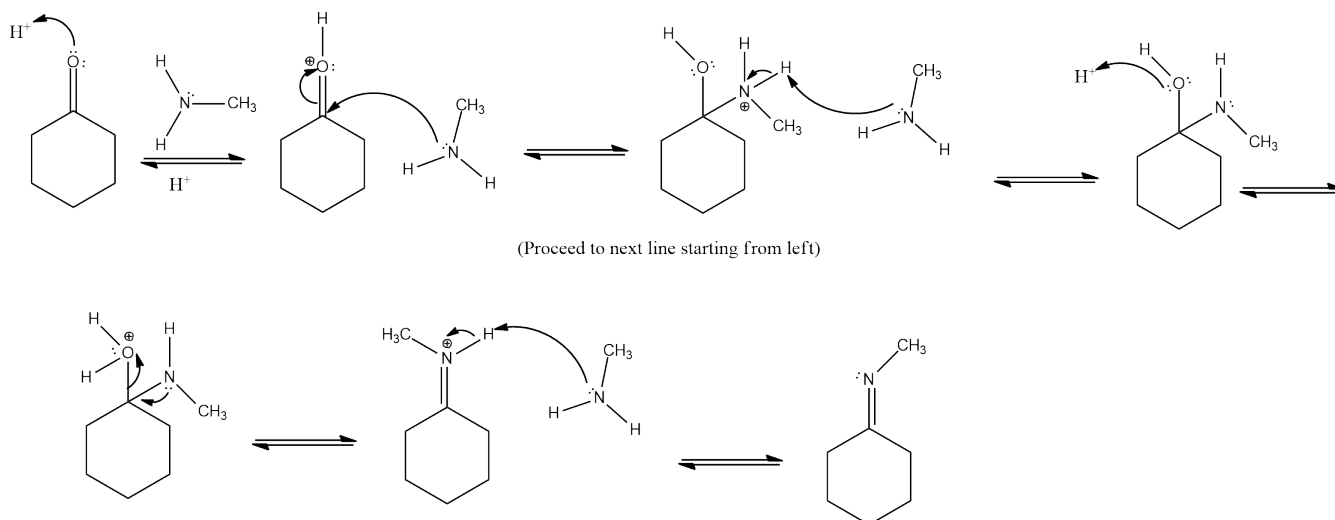
- H_2 and Raney nickel can convert a thioacetal or cyclic thioacetal to yield hydrocarbons



1.7 The Addition of Primary and Secondary Amines

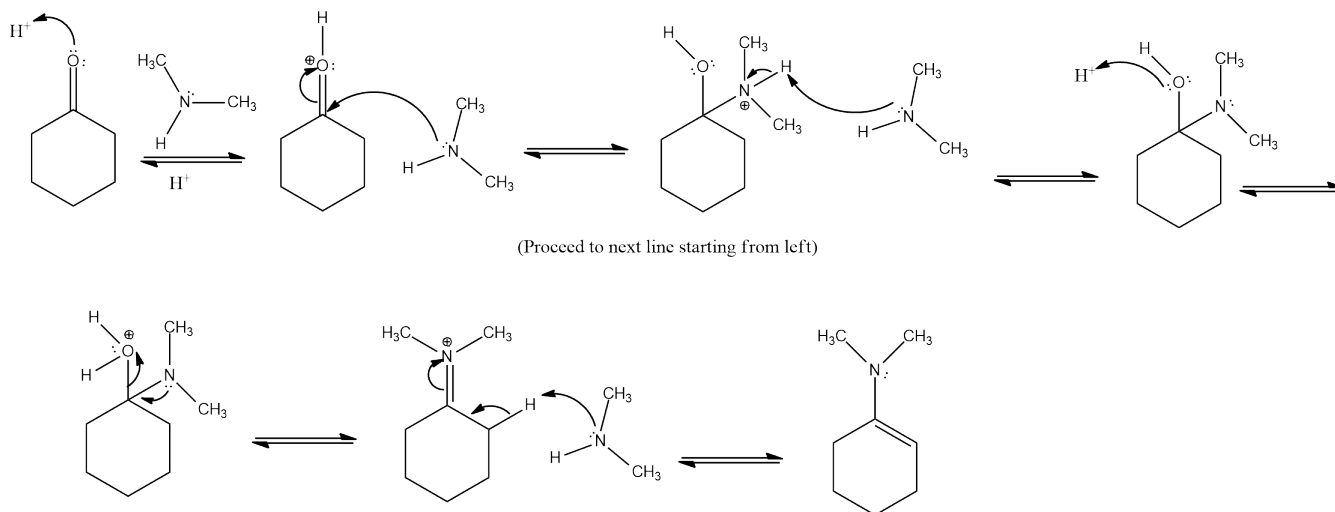
- Imines have a carbon-nitrogen double bond
- An aldehyde or ketone can react with a primary amine to form an imine³

Imine Formation



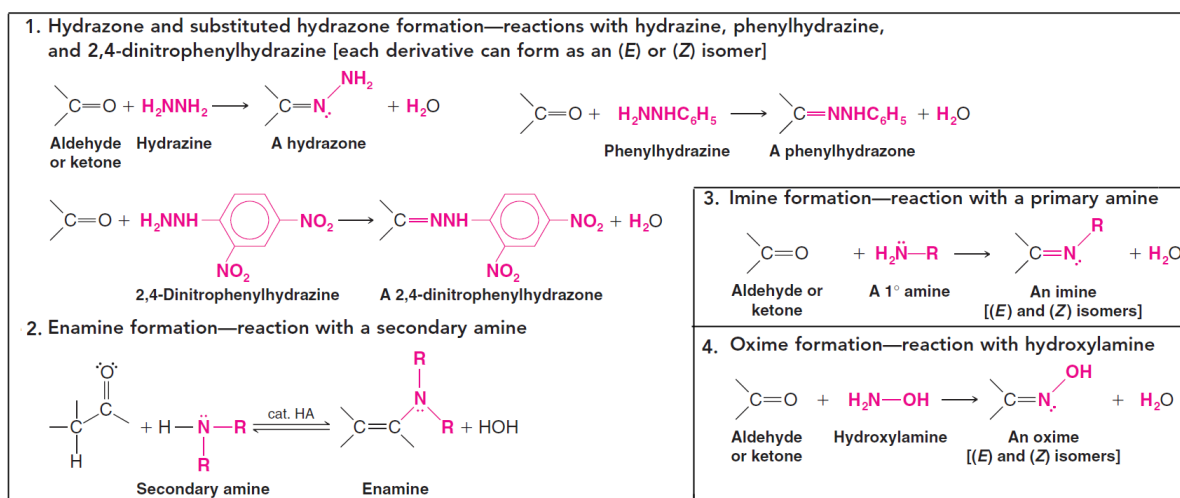
- Enamines are alkeneamines and thus have an amino group joined to a carbon-carbon double bond
- An aldehyde or ketone can react with a secondary amine under acid catalysis to form an enamine

Enamine Formation



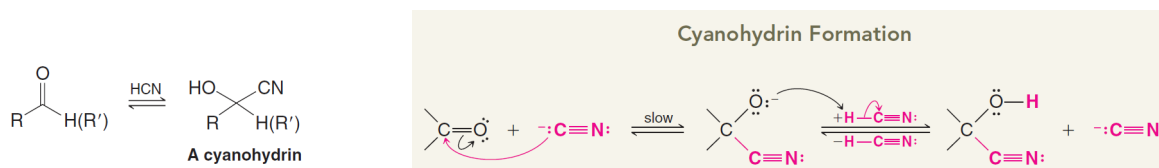
³Note that this mechanism is different than what the textbook provides

- The following graphic summarizes these two reactions as well as oxime and hydrazone formation:

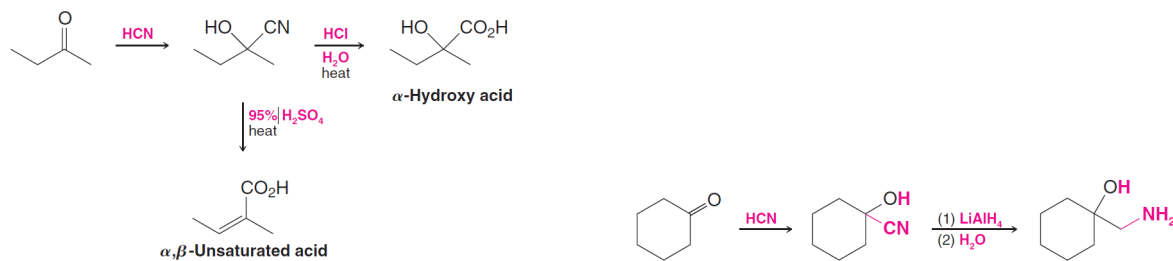


1.8 The Addition of Hydrogen Cyanide: Cyanohydrins

- A cyanohydrin has an OH and CN group attached to the same carbon
- Reacting an aldehyde or ketone with HCN will form a cyanohydrin

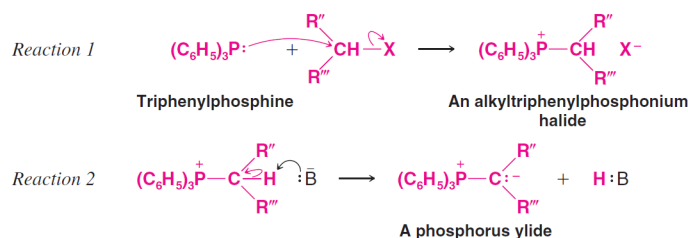


- See graphics below for a preview of nitrile reactions that will be discussed in the future

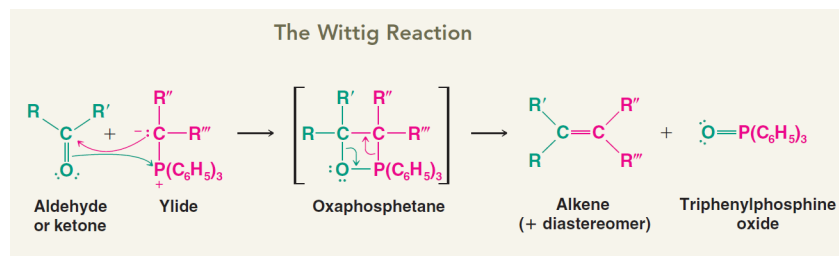


1.9 The Addition of Ylides: The Wittig Reaction

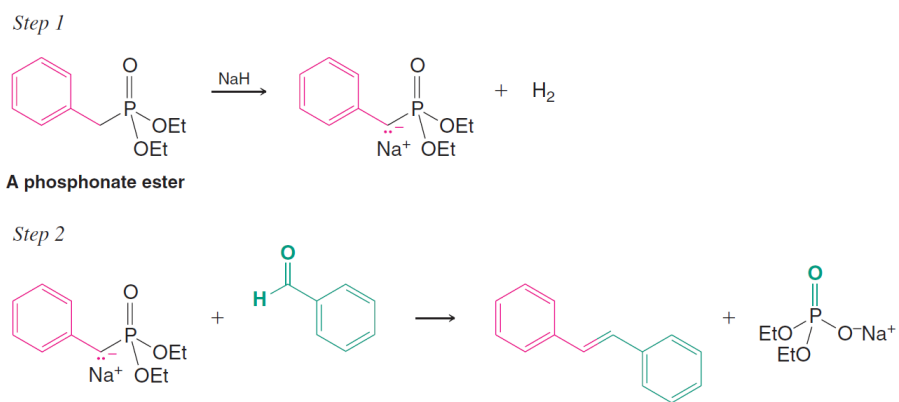
- An ylide is a molecule with no net charge but which has a negative carbon atom adjacent to a positive heteroatom. It can be formed as follows (a useful base is C₆H₅Li),



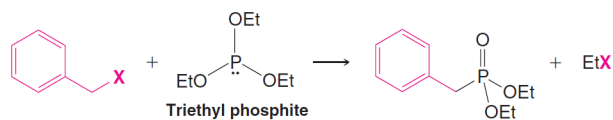
- Aldehydes and ketones react with phosphorous ylides to yield alkenes - The Wittig Reaction



- To prepare the ylide, one can begin with a primary or secondary alkyl halide
 - Reacting the 1° or 2° alkyl halide with $\text{:P}(\text{C}_6\text{H}_5)_3$ will cause the halide to be replaced by $\text{P}^+(\text{C}_6\text{H}_5)_3$
 - Using RLi will take off the hydrogen of the attached carbon of the alkane and give it a -1 charge due to the new electron pair
- The Horner-Wadsworth-Emmons reaction is a variation of the Wittig reaction and involves the use of a phosphonate ester to make an (*E*)-alkene. Example shown below:



- To prepare the phosphonate ester, $(\text{RO})_3\text{P}$ can be reacted with an appropriate halide. Example shown below:



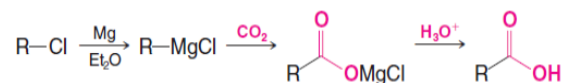
1.10 Oxidation of Aldehydes

- The use of KMnO_4 with OH^- or Ag_2O with OH^- can oxidize an aldehyde to a carboxylic acid when followed by H_3O^+

2 Carboxylic Acids and Their Derivatives

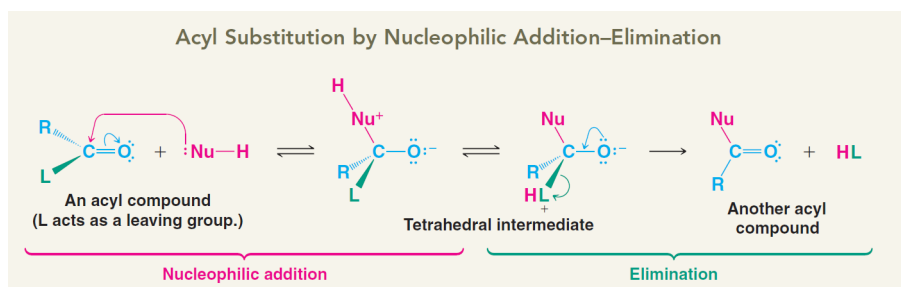
2.1 Preparation of Carboxylic Acids

- Ozonolysis via O_3 and then H_2O_2 workup yields carboxylic acids from alkenes
- H_2CrO_4 can oxidize a 1° alcohol or aldehyde to a carboxylic acid
- Using CO_2 and then acidification with H_3O^+ can convert a grignard reagent to a carboxylic acid



2.2 Acyl Substitution: Nucleophilic Addition-Elimination at the Acyl Carbon

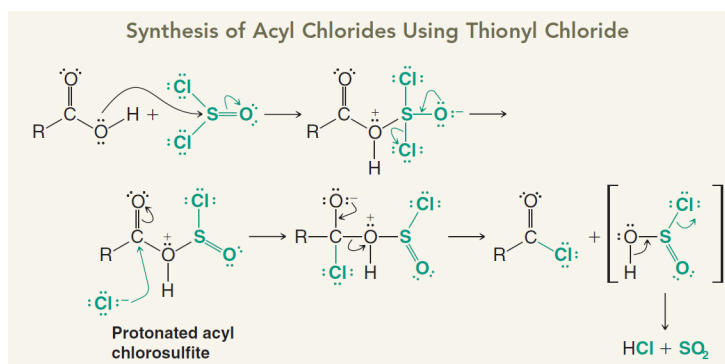
- An acyl substitution can occur as follows but always requires a leaving group at the carbonyl carbon:



- The order of relative reactivity of acyl compounds goes as follows: acyl chloride > acid anhydride > ester > amide

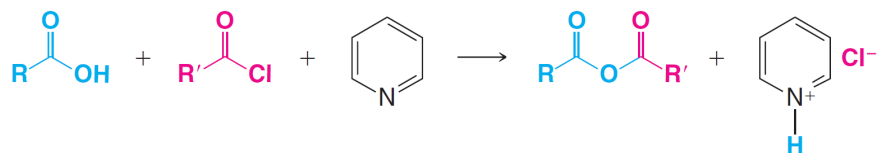
2.3 Acyl Chlorides

- The use of $SOCl_2$, PCl_3 , or PCl_5 will yield an acyl chloride from a carboxylic acid:

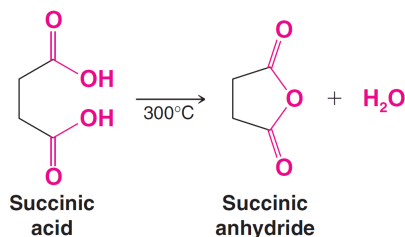


2.4 Carboxylic Acid Anhydrides

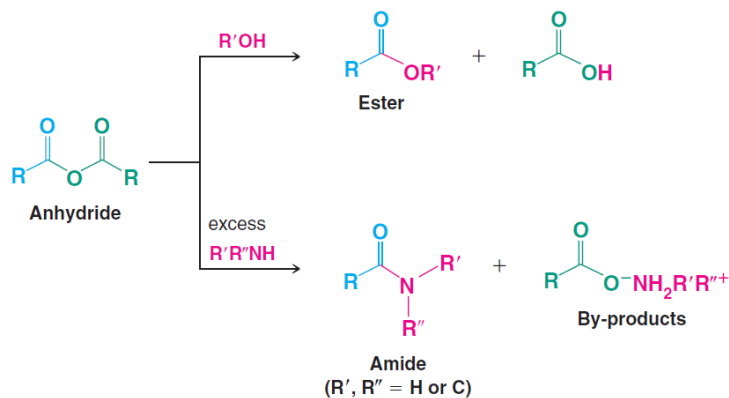
- Carboxylic acids react with acyl chlorides in pyridine to form carboxylic acid anhydrides
 - This is also applicable for sodium salts of carboxylic acids



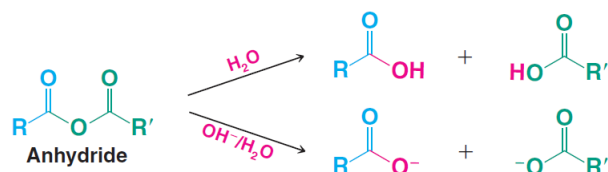
- Cyclic anhydrides (five- or six-membered ring) can be prepared from heating a dicarboxylic acid. An example is,



- Carboxylic acid anhydrides can form esters or amides



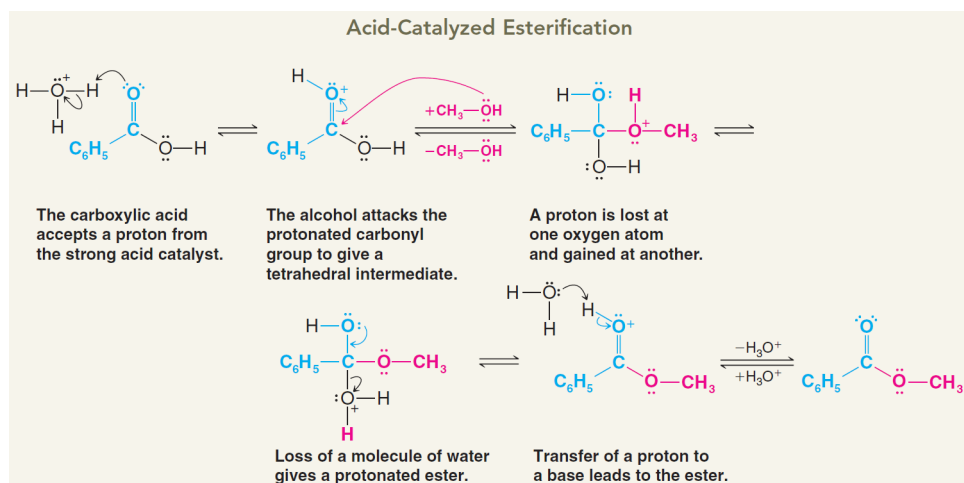
- Carboxylic acid anhydrides can undergo hydrolysis



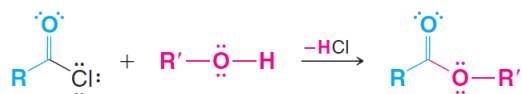
2.5 Esters

2.5.1 Esterification

- Carboxylic acids react with alcohols to form esters through esterification
 - Fischer esterifications are acid-catalyzed



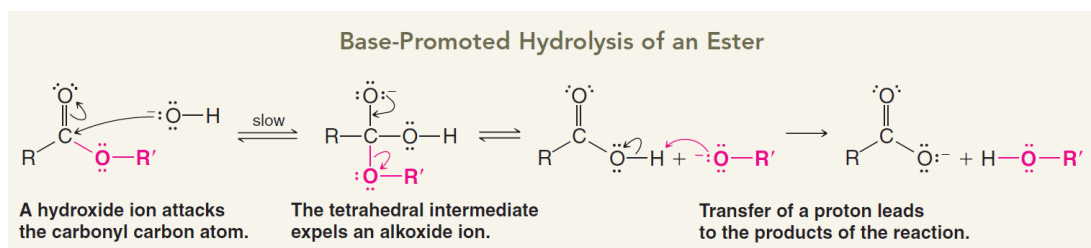
- An acyl chloride can be reacted with an alcohol in pyridine to form an ester



- Carboxylic acid anhydrides react with alcohols to form esters in the absence of an acid catalyst
- Cyclic anhydrides react with an alcohol to form compounds that are both esters and carboxylic acids

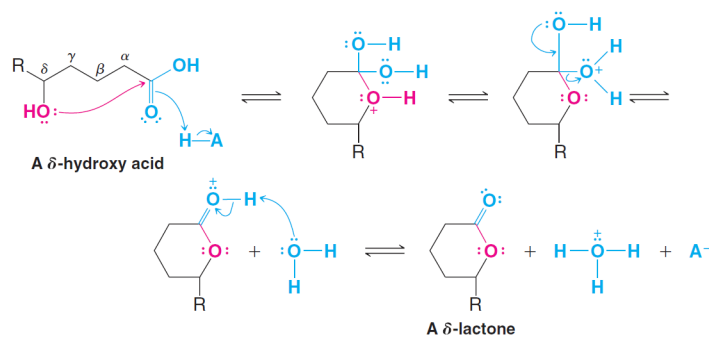
2.5.2 Saponification

- One can reflux an ester with a strong base such as NaOH in water to produce an alcohol and carboxylate salt

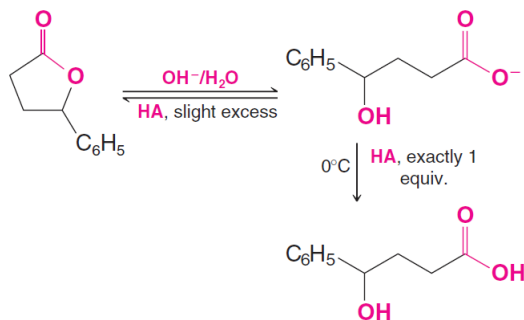


2.5.3 Lactones

- Carboxylic acids with a γ or δ (3rd or 4th adjacent) carbon can undergo intramolecular esterification to form cyclic esters - lactones
- The forward reaction is:



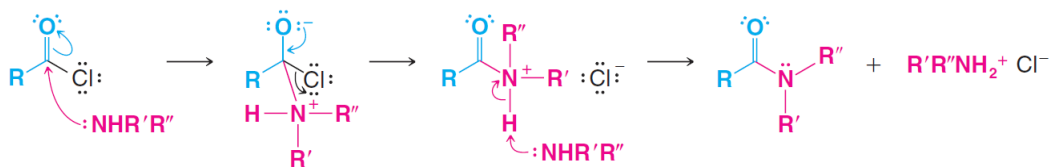
- The reverse process is:



2.6 Amides

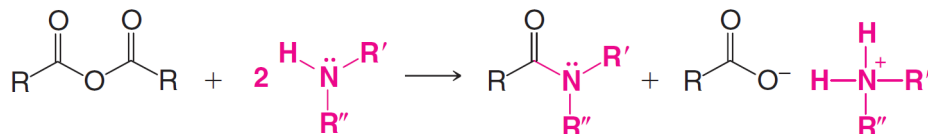
2.6.1 Amides from Acyl Chlorides

- A 1° amine, 2° amine, or ammonia can react with an acyl chloride to form an amide

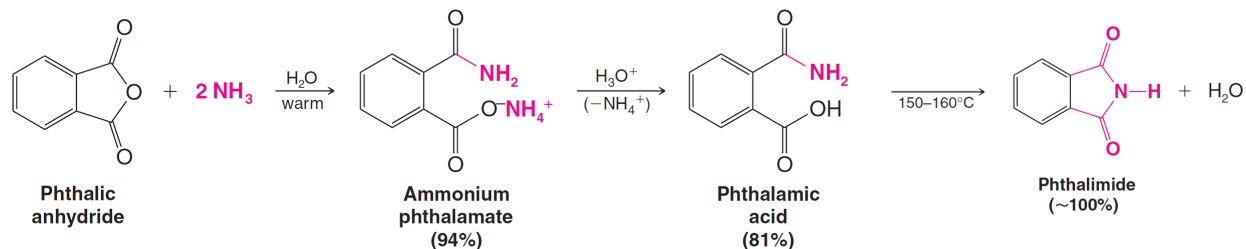


2.6.2 Amides from Carboxylic Anhydrides

- A 1° amine, 2° amine, or ammonia can react with an acid anhydride to form an amide



- Cyclic anhydrides react too; however, it yields a compound that is an imide when heated

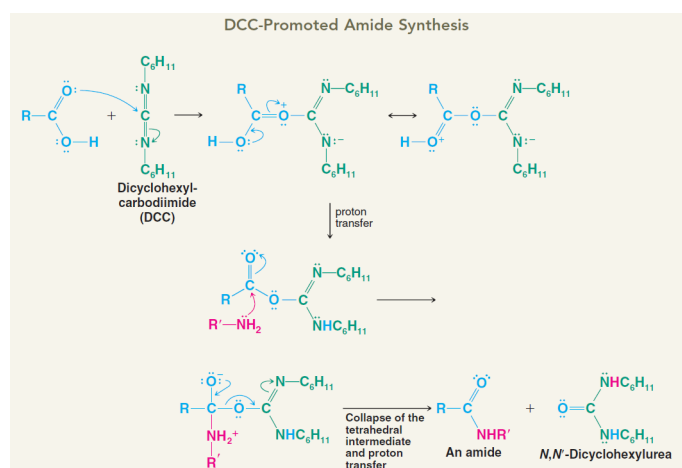


2.6.3 Amides from Esters

- A 1° amine, 2° amine, or ammonia can react with an ester to form an amide

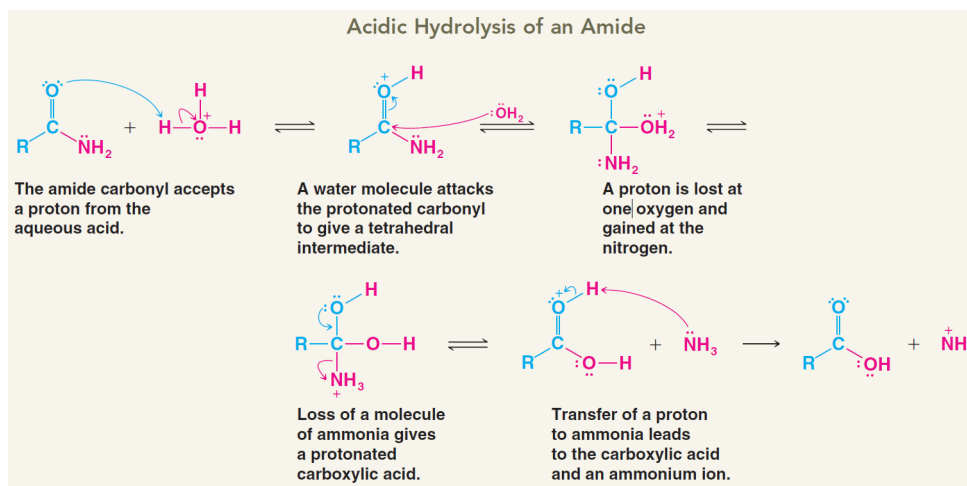
2.6.4 Amides from Carboxylic Acids and Ammonium Carboxylates

- Carboxylic acids can be reacted with DCC to form an amide

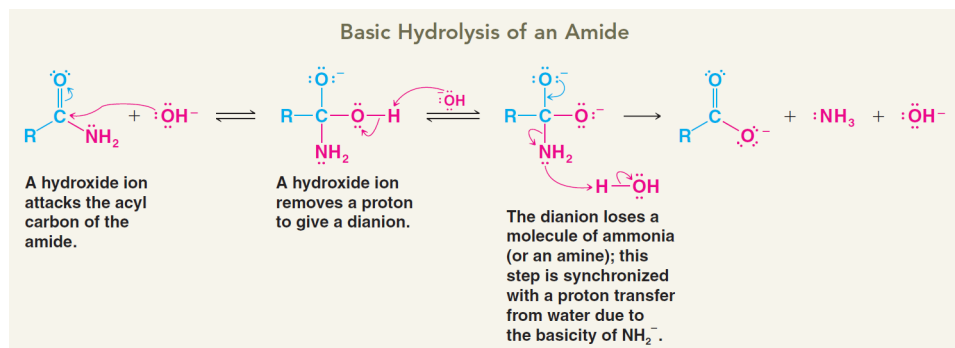


2.6.5 Hydrolysis of Amides

- Amides hydrolyze under heated aqueous acid to form a carboxylic acid



- Amides hydrolyze under heated aqueous base to form a carboxylate anion

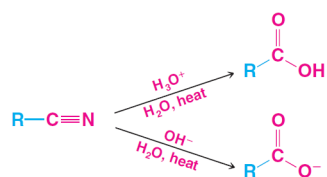


2.6.6 Nitriles from the Dehydration of Amides

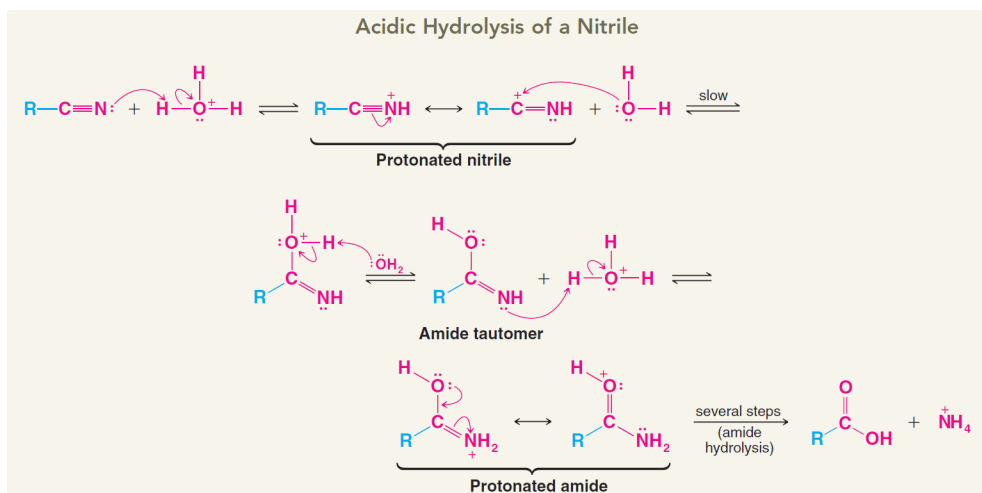
- Amides react with P_4O_{10} or $(\text{CH}_3\text{CO}_2)_2\text{O}$ to form nitriles

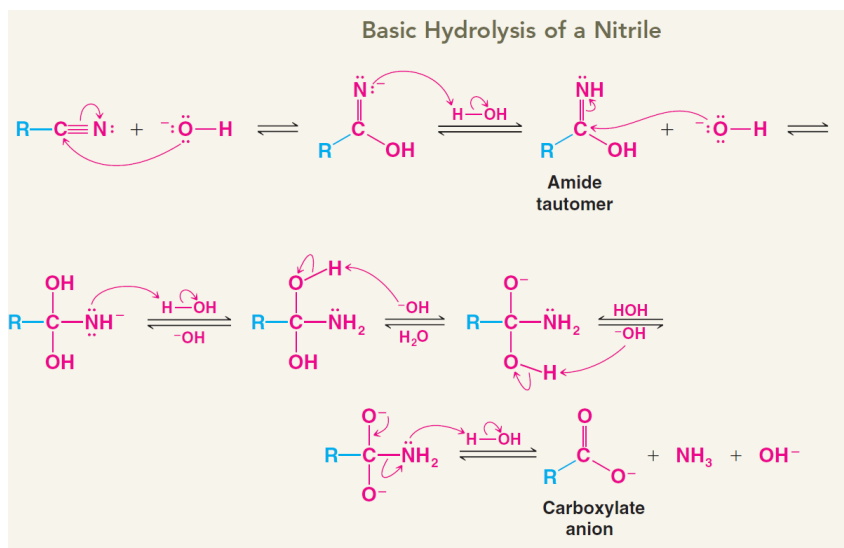
2.6.7 Hydrolysis of Nitriles

- Nitrile hydrolysis yields a carboxylic acid or carboxylate anion



- The mechanisms are shown below:



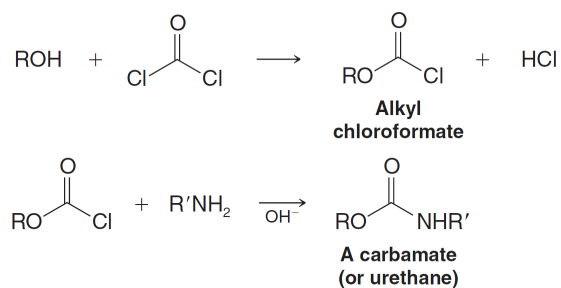


2.6.8 Lactams

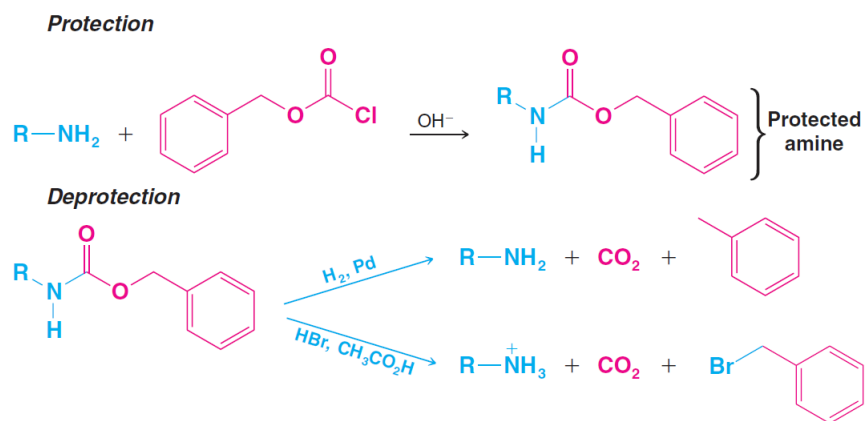
- γ and δ amino acids spontaneously form γ and δ cyclic amides - lactams

2.7 Derivatives of Carbonic Acid

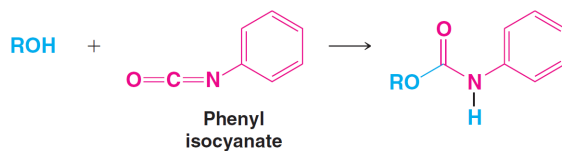
- Reacting a carbonyl dichloride with an alcohol leads to an alkyl chloroformate
 - These alkyl chloroformates can react with ammonia or amines to form carbamates (urethanes)



- Benzyl chloroformate can be used to create a protecting group, and it can be removed by $\text{H}_2/\text{Pd-C}$ or HBr in $\text{CH}_3\text{CO}_2\text{H}$



- Reaction of an alcohol with an isocyanate ($R-N=C=O$) will yield a carbamate



2.8 Decarboxylation of Carboxylic Acids

- Decarboxylation is when a carboxylic acid loses CO_2
- Carboxylic acids that have a carbonyl group one carbon removed from the carboxylic acid group decarboxylate readily when heated
 - This occurs because the transition state is a six-membered cyclic molecule
 - Resonance-stabilization also permits this process
- 1,3-dicarboxylic acids decarboxylate readily when heated as well
- Carboxyl radicals decarboxylate readily by losing CO_2 and forming an alkyl radical

3 Enols and Enolates

3.1 Enolate Anions

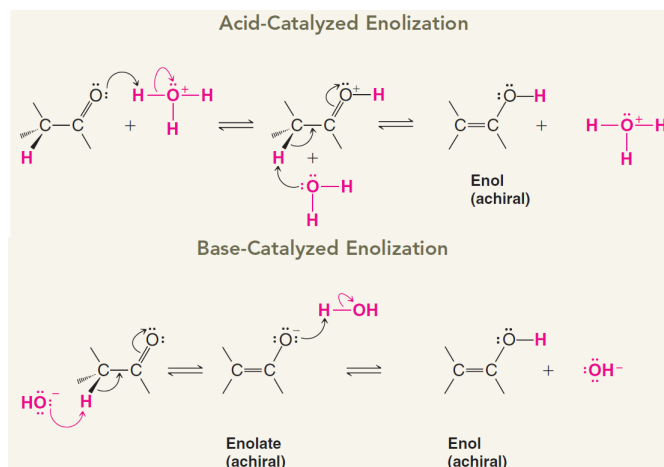
- An enolate is the anion produced when a carbonyl compound loses an α proton
 - Resonance stabilization of an enolate makes the hydrogen more acidic than usual
- If an enolate accepts a proton to form the original carbonyl compound, the keto form, or it can accept it at the oxygen, which is the enol form

3.2 Keto and Enol Tautomers

- Interconvertible keto and enol forms are called tautomers (the process of interconversion is known as tautomerization)
- Simple monocarbonyl compounds exist mostly in the keto form
- A β -dicarbonyl compound has enol with a greater stability due to resonance stabilization

3.3 Reactions via Enols and Enolates

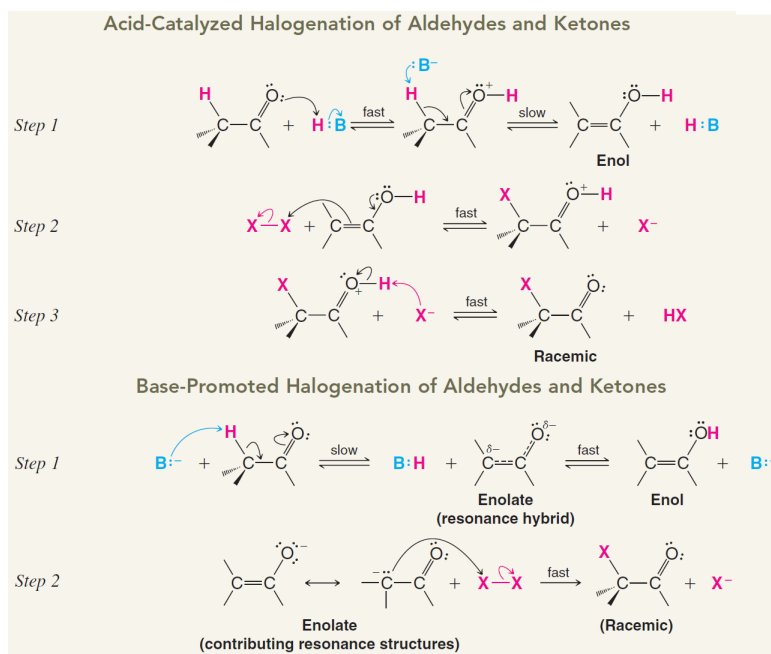
3.3.1 Racemization



- Diastereomers that differ in configuration at only one of multiple chirality centers are known as epimers

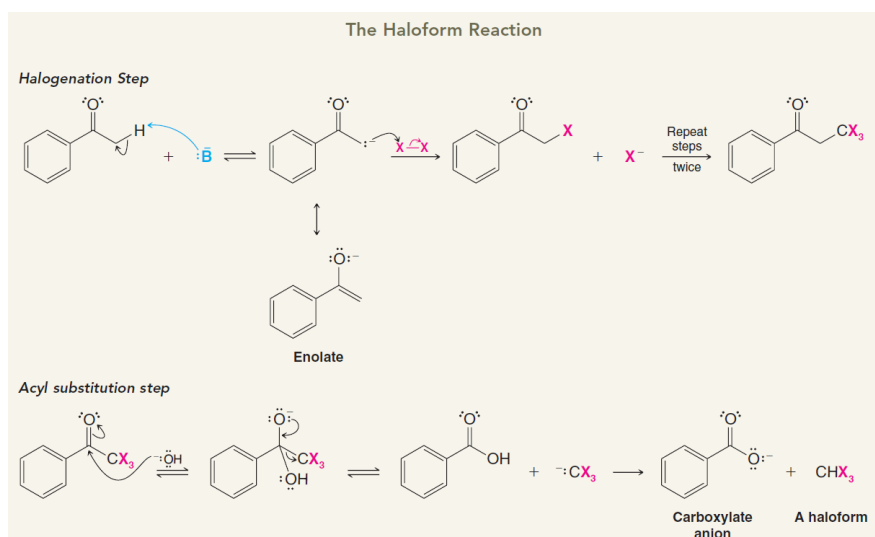
3.3.2 Halogenation at the α Carbon

- Carbonyl compounds that have an α hydrogen can undergo halogen substitution at the α carbon in acid or base



3.3.3 The Haloform Reaction

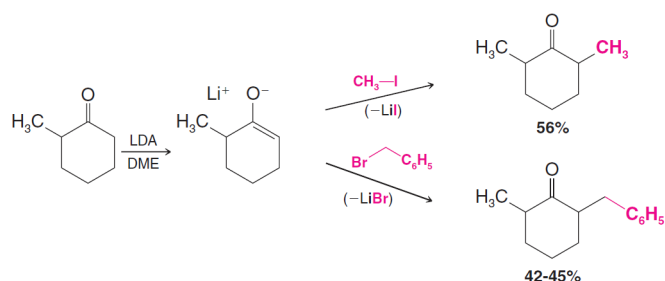
- Multiple halogenations occur when methyl ketones react with halogens in excess base
- The haloform reaction converts methyl ketones to carboxylic acids



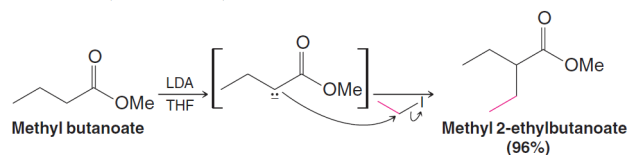
3.4 Lithium Enolates

- A strong base like LDA can convert a carbonyl compound to an enolate

- The more highly substituted enolate is the more stable one and predominates under conditions where interconversion may occur
 - Use of hydroxide or an alkoxide will form this
 - This enolate is known as the thermodynamic enolate
- The enolate formed from removal of the least sterically hindered α hydrogen forms under conditions that do not favor equilibrium among possible enolates
 - Use of LDA in THF or DME will form this
 - This enolate is known as the kinetic enolate
- Enolates can be alkylated when a primary alkyl halide is used:

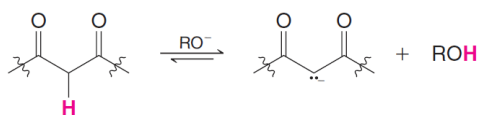


- Esters can be directly alkylated using LDA in THF or DME and then a primary halide:



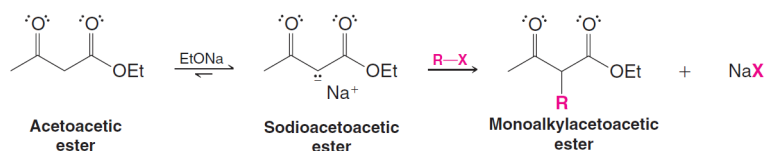
3.5 Enolates of β -Dicarbonyl Compounds

- An RO^- base can form an enolate from a β -dicarbonyl compound

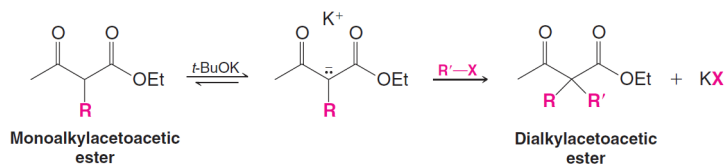


3.6 Synthesis of Methyl Ketones: The Acetoacetic Ester Synthesis

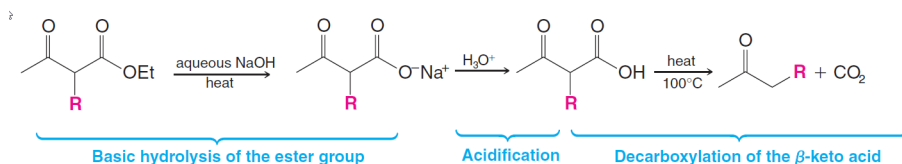
- An example of acetoacetic ester synthesis is shown below,



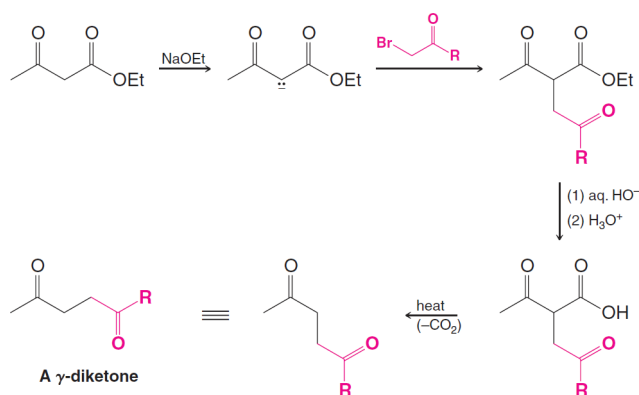
- An example of dialkylation is shown below (*t*-BuOK is used),



- To synthesize a monosubstituted methyl ketone, one alkylation is performed. Then, the ester is hydrolyzed with a strong base. Finally, acidification and heating yields decarboxylation



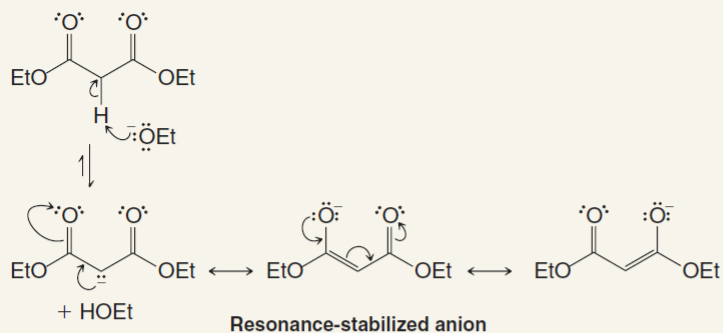
- Anions from acetoacetic esters undergo acylations when treated with acyl chlorides or acid anhydrides. Example shown below,



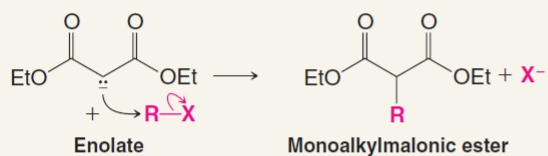
3.7 Synthesis of Substituted Acetic Acids: The Malonic Ester Synthesis

The Malonic Ester Synthesis of Substituted Acetic Acids

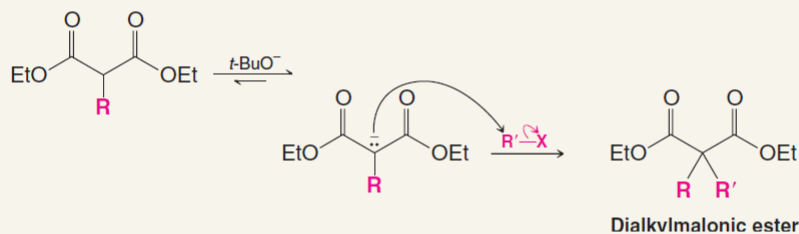
Step 1 Diethyl malonate, the starting compound, forms a relatively stable enolate:



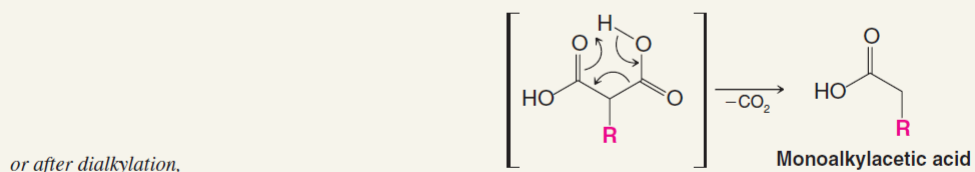
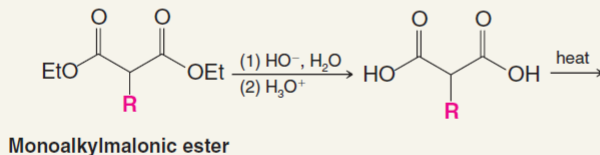
Step 2 This enolate can be alkylated in an S_N2 reaction,



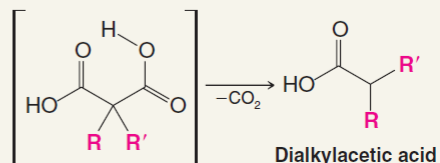
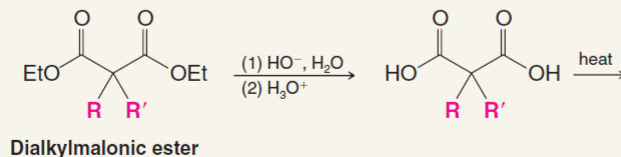
and the product can be alkylated again if our synthesis requires it:



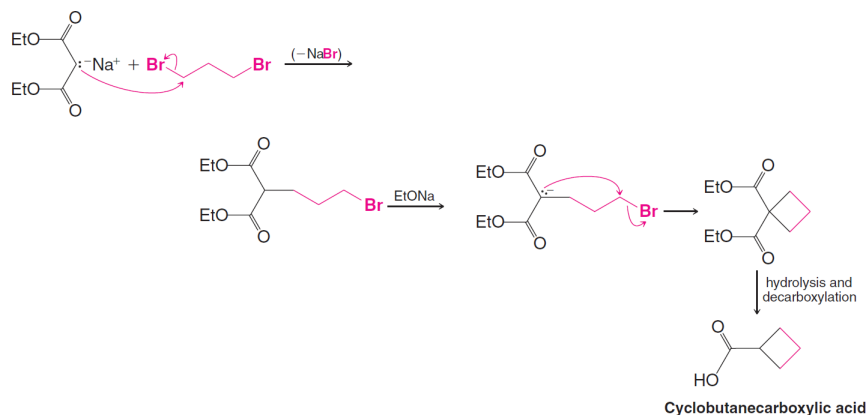
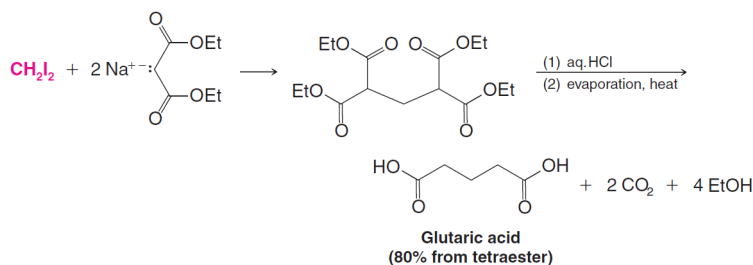
Step 3 The mono- or dialkylmalonic ester can then be hydrolyzed to a mono- or dialkylmalonic acid, and substituted malonic acids decarboxylate readily. Decarboxylation gives a mono- or disubstituted acetic acid:



or after dialkylation,



- Dihaloalkanes can be used for a variation on the Malonic Ester Synthesis. Two instances are shown below,

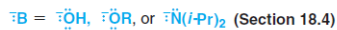
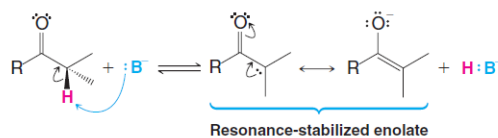


3.8 Further Reactions

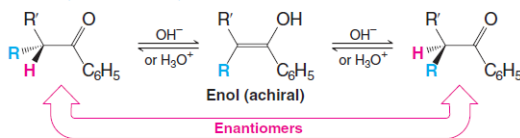
- Active hydrogen compounds have two electron-withdrawing groups attached to the same carbon atom
- The Stork Enamine reaction converts an aldehyde/ketone and 2° amine into an enamine

3.9 Summary of Enolate Chemistry

1. Formation of an Enolate (Section 18.1)

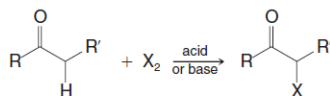


2. Racemization (Section 18.3A)

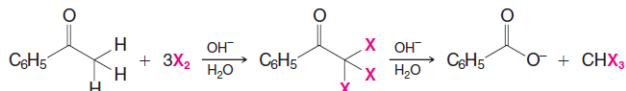


3. Halogenation of Aldehydes and Ketones (Sections 18.3B and 18.3C)

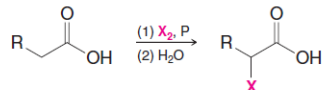
General Reaction



Specific Example—Haloform Reaction

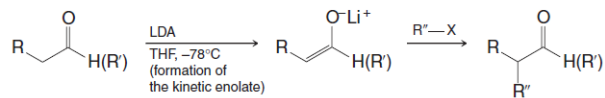


4. Halogenation of Carboxylic Acids: The HVZ Reaction (Section 18.3D)

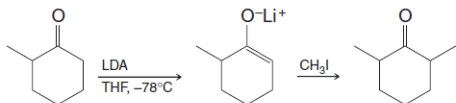


5. Direct Alkylation via Lithium Enolates (Section 18.4)

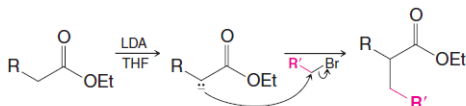
General Reaction



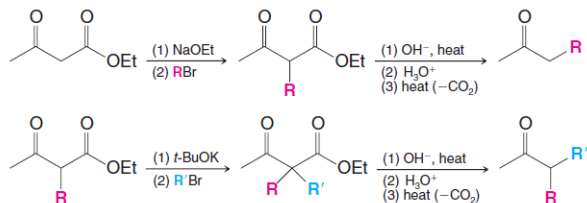
Specific Example



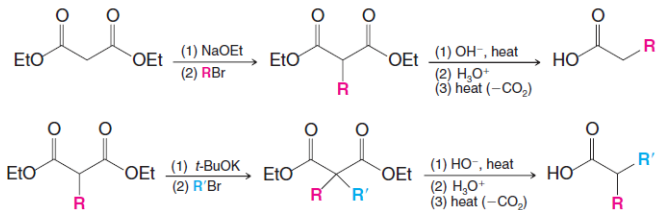
6. Direct Alkylation of Esters (Section 18.4C)



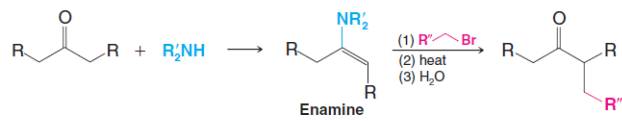
7. Acetoacetic Ester Synthesis (Section 18.6)



8. Malonic Ester Synthesis (Section 18.7)



9. Stork Enamine Reaction (Section 18.9)



4 Condensation and Conjugate Addition