Carbonyl Reactivity
Part I. Nucleophilic Acyl Substitution

OBJECTIVES

Name carboxylic acids (including acid derivatives such as acyl chlorides, anhydrides, esters, amides and nitriles)

Describe the preparation of carboxylic acids (and derivatives)

Provide mechanisms for nucleophilic substitutions at acyl carbons bearing a leaving group and discuss implications of leaving group ability

Name aldehydes and ketones.

Describe the carbonyl group and oxidation-reductions reactions associated with alcohols and carbonyl groups.

Describe addition reactions of aldehydes and ketones in which nucleophiles add to the electrophilic carbonyl.

Provide a rationale for the acidity of a-hydrogens

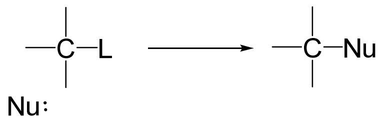
Illustrate the behavior of enols and enolates as nucleophiles in reactions with a variety of electrophiles

Describe the reactions of ester enolates (nucleophiles) with esters (electrophiles) to give b-keto esters *via* Claisen and crossed Claisen condensatiions.

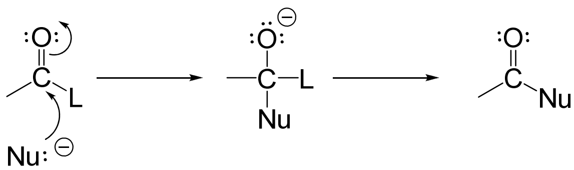
Describe the reactions of other active methyene compounds and the synthesis of acid derivatives.

Reactions of Carbonyl Compounds

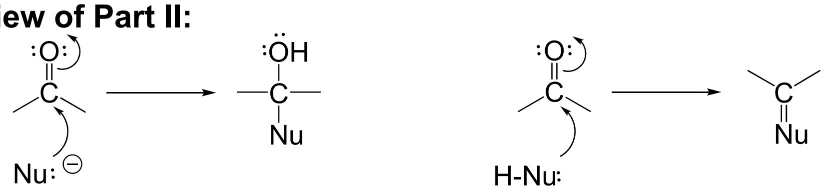
Review of nucleophilic substitution at *sp*³ carbons



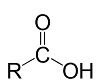
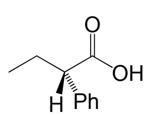
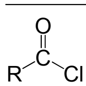
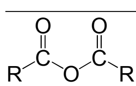
Preview of Part I:

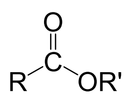
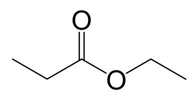
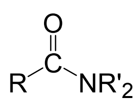
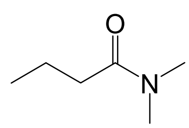


Preview of Part II:

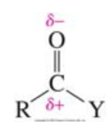


NOMENCLATURE OF ACYL COMPOUNDS

	general name		*example with R=CH_3*
 [RCOOH]	alkanoic acid		acetic acid
 [RCOCl]	alkan		acetyl chloride
 [$(RCO)_2O$]	alkan		acetic anhydride

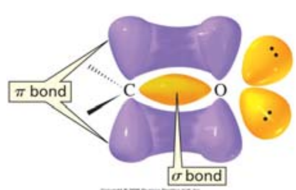
	alkan		alkyl acetate
	alkan		acetamide
R—C≡N	alkan		acetonitrile

Structures of Carboxylic Acids



Carbonyl carbon sp^2 hybridized

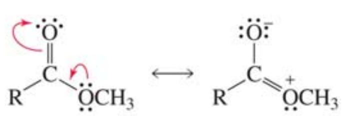
Carbonyl oxygen sp^2 hybridized



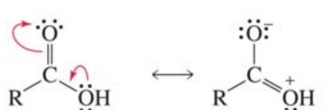
p orbitals overlap to form a π bond

2 lone pairs in sp^2 orbitals

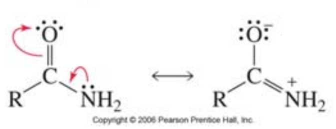
1. ester



2. carboxylic acid

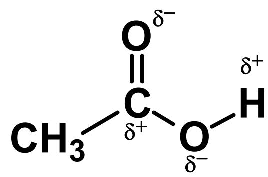


3. amide

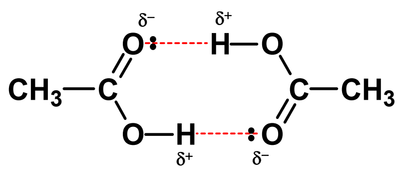


Physical Properties of Carboxylic Acids

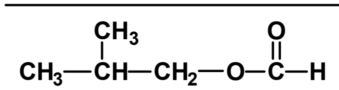
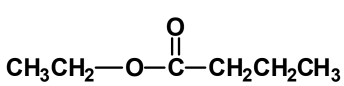
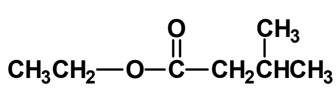
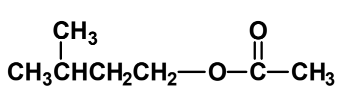
- Carboxylic acids are polar:



- Carboxylic acids can participate in hydrogen bonding:

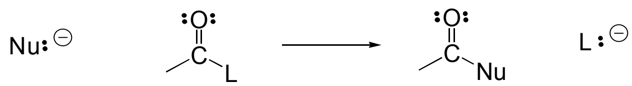


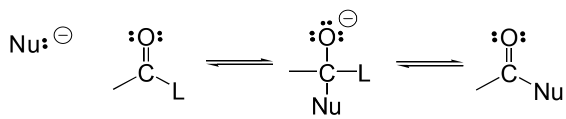
Naturally Occurring Carboxylic Acids and Derivatives

Compound	Name of ester		Flavor
	isobutyl formate		raspberry
	ethyl butanoate (ethyl butyrate)		pineapple
	ethyl 3-methylbutanoate (ethyl isovalerate)		apple
	isopentyl acetate (isoamyl acetate)		banana

NUCLEOPHILIC ADDITION - ELIMINATION AT THE ACYL CARBON

Overview

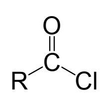


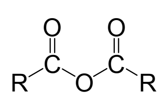


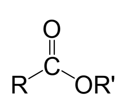
Leaving Group Ability

Relative Electrophilicity of Acid Derivatives

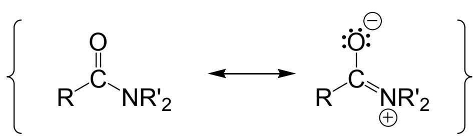
Most Reactive



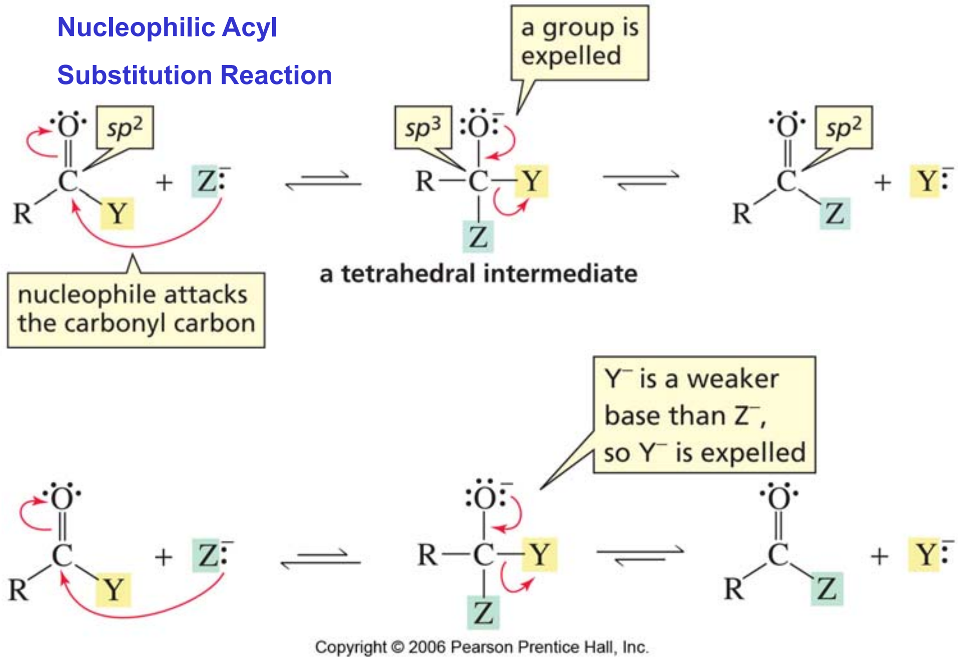




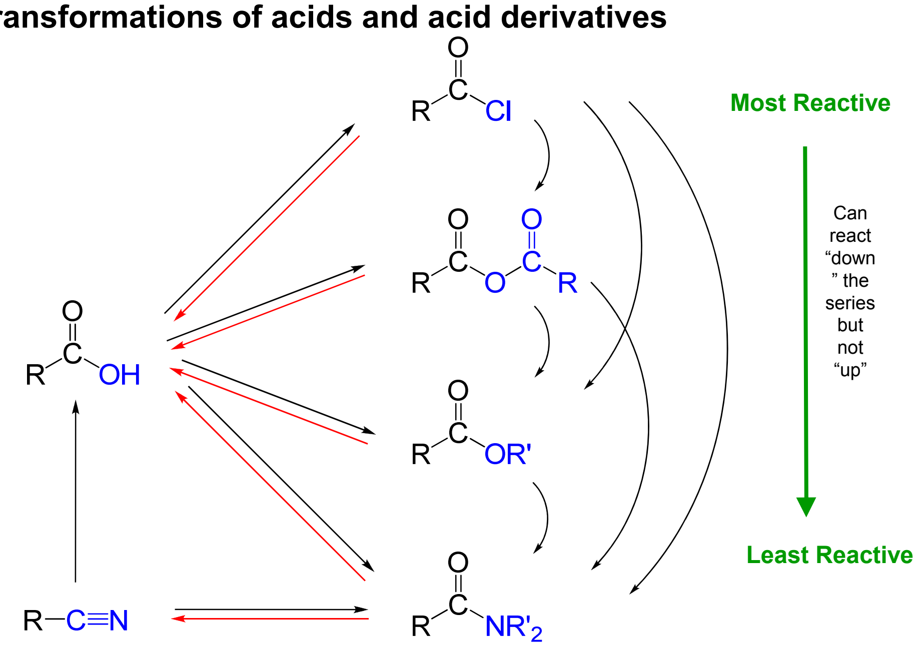
Least Reactive



Nucleophilic Acyl Substitution Reaction

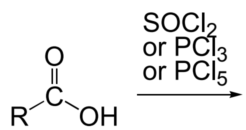


Transformations of acids and acid derivatives

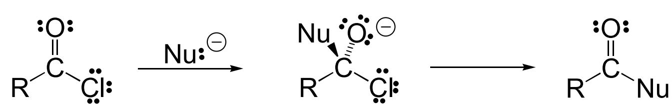


ACYL CHLORIDES

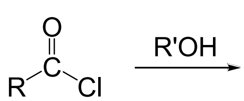
Formation of acyl chlorides from carboxylic acids
(and reverse reaction: hydrolysis)

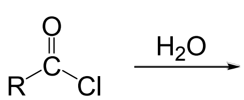


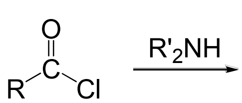
Nucleophilic displacement of chloride from acyl chlorides: General Mechanism



Reactions of acyl chlorides

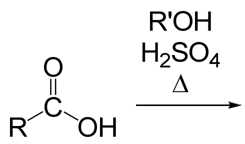


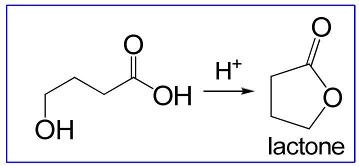




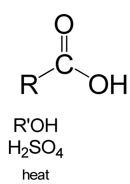
ESTERS

Acid catalyzed formation of esters from carboxylic acids





Mechanism – ESTER Formation (and reverse hydrolysis)



PAD PED

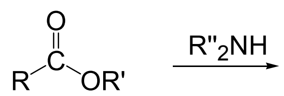
1. Protonation
2. Addition
3. Deprotonation

4. Protonation
5. Elimination
6. Deprotonation

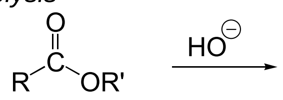
Note that all steps are reversible

Reactions of esters

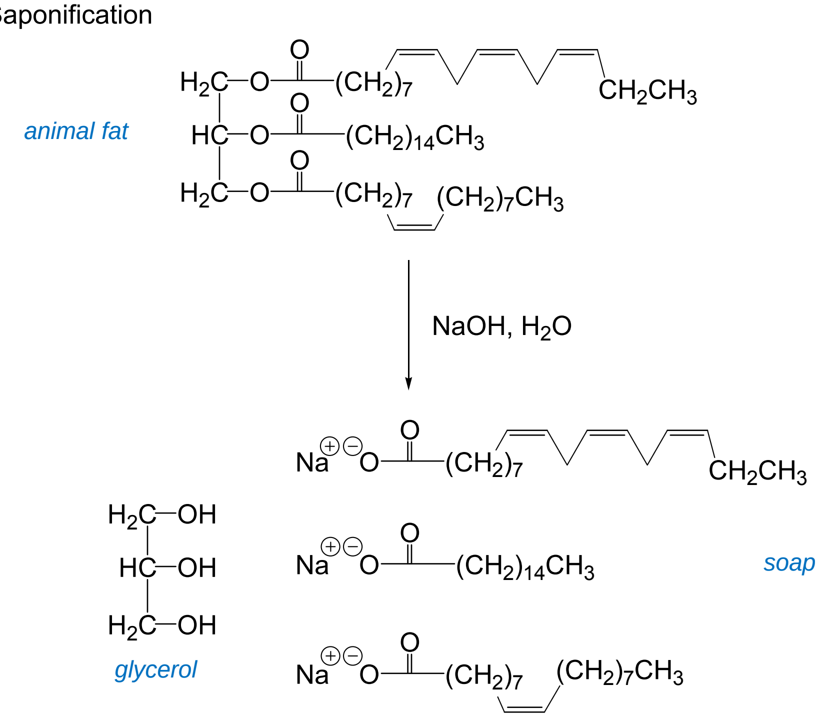
Amidation



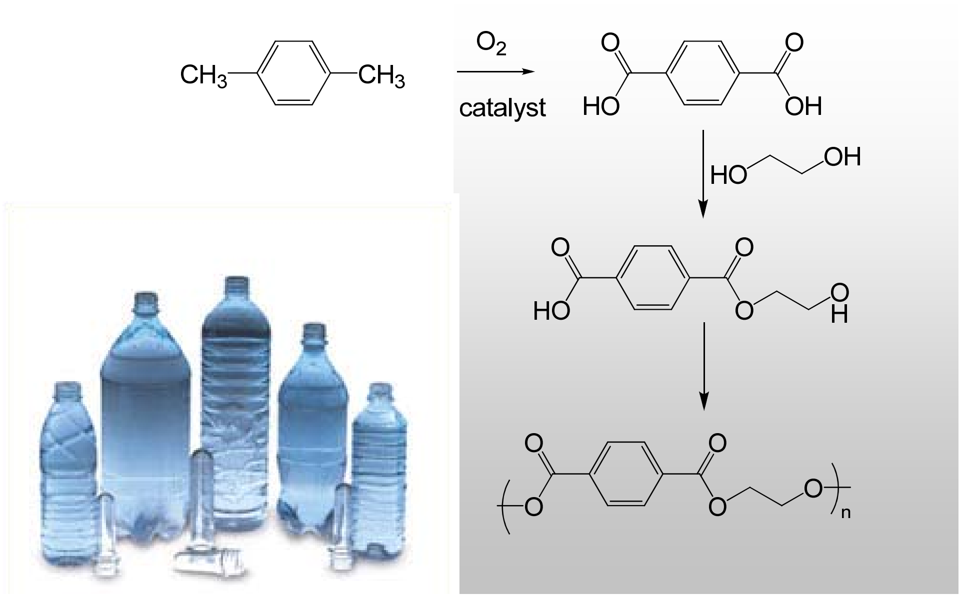
Hydrolysis



Saponification

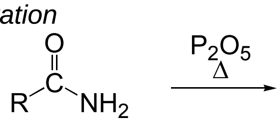


Oxidation of p-xylene to terephthalic acid
for production of polyester

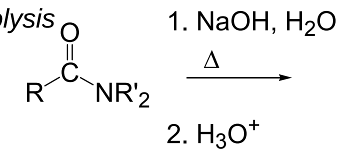


Reactions of amides

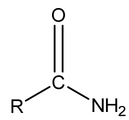
Dehydration



Hydrolysis



Amides are much stronger acids than amines. Why?



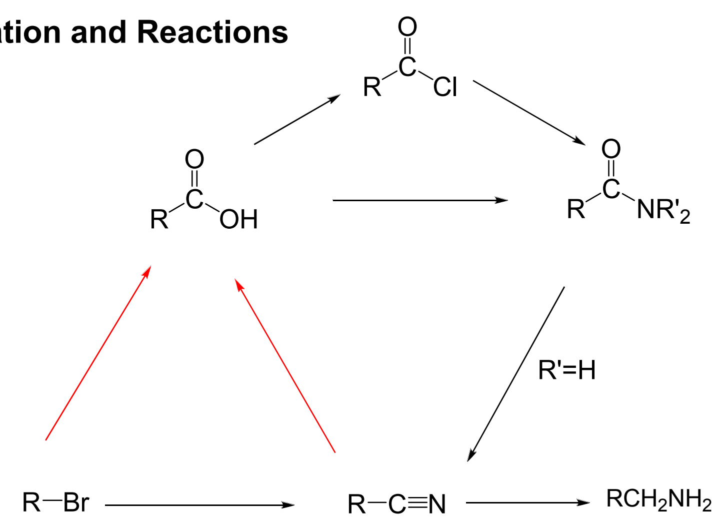
pKa about 15

R-NH_2

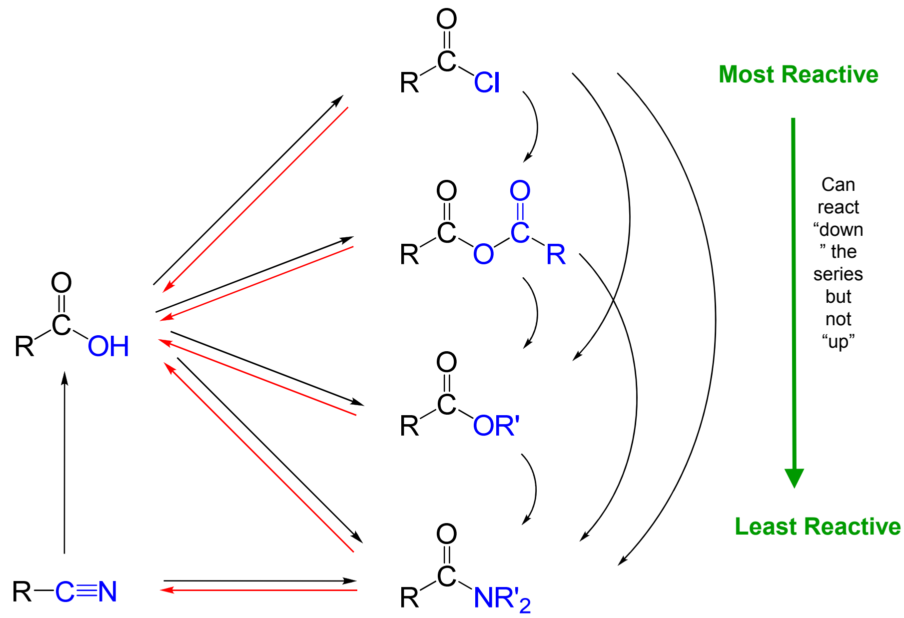
pKa about 35-40

NITRILES

Formation and Reactions

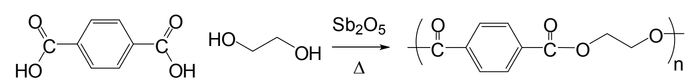


Transformations of acids and acid derivatives

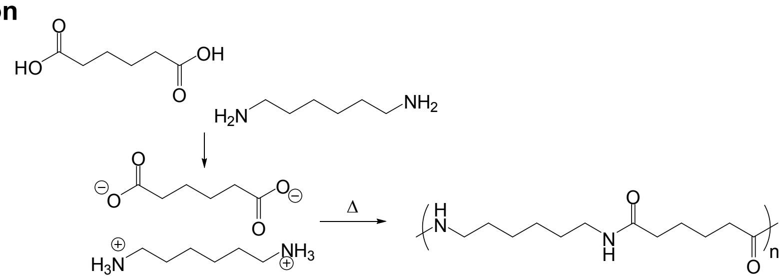


CONDENSATION POLYMERS

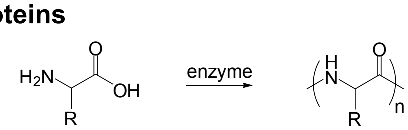
Polyester



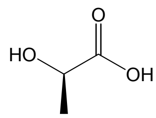
Nylon

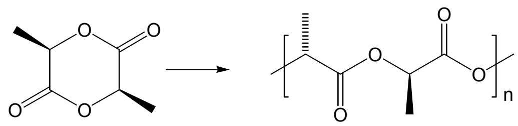


Proteins

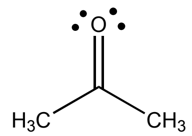


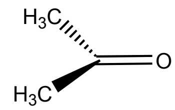
Poly(lactic Acid)

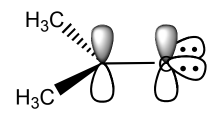




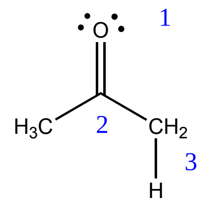
Carbonyl Reactivity
Part II. Reactions of Aldehydes and Ketones



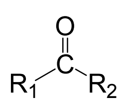


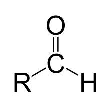


Reactive Sites



ALDEHYDES AND KETONES

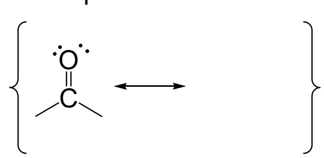




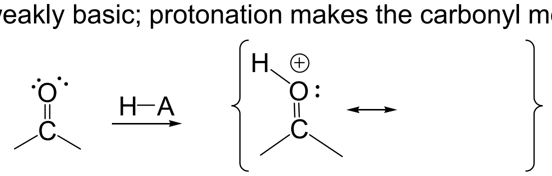
ketone, R_1 or R_2 = alkyl, aryl or alkenyl

aldehyde, R = H, alkyl, aryl or alkenyl

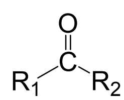
Carbonyls are electrophilic



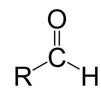
Carbonyls are weakly basic; protonation makes the carbonyl more electrophilic



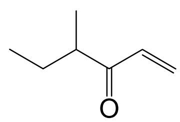
Nomenclature

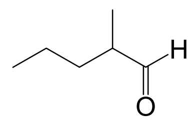


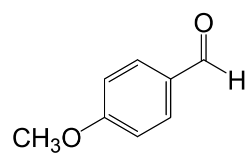
alkane ⟹ #-alkanone
or alkyl alkylketone



alkane ⟹ alkanal



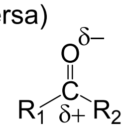


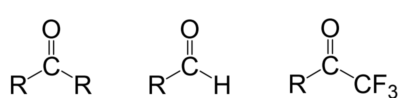


Relative reactivity of aldehydes and ketones

1. Inductive electronic factors

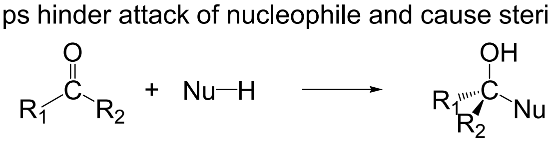
Electron donating groups decrease **electrophilicity** of carbonyl (and visa versa)





2. Steric factors

Bulky groups hinder attack of nucleophile and cause steric crowding in product

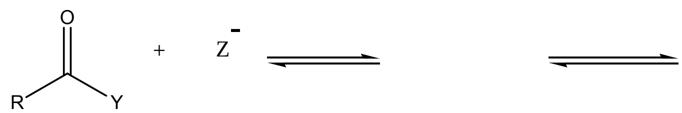


sp^2 120°   *sp*^{3} 109.5°

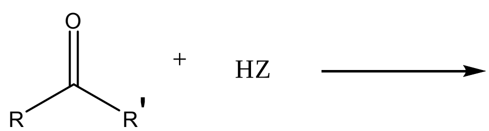
Chapter 13 slide 30

How Aldehydes and Ketones React

- **Nucleophilic Acyl Substitution (previous discussion)**



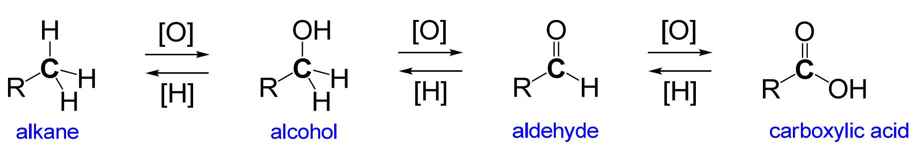
- **Nucleophilic Addition**



Oxidation-Reduction Reactions in Organic Chemistry

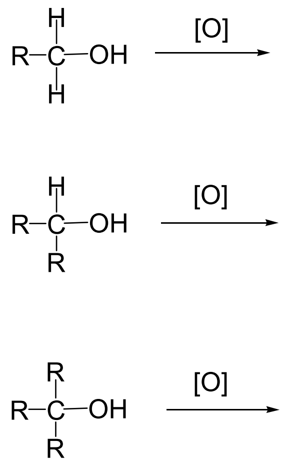
Reduction - adding electrons, more hydrogens, less oxygen
Oxidation - removing electrons, less hydrogens, more oxygen

[O] denotes oxidation   [H] denotes reduction

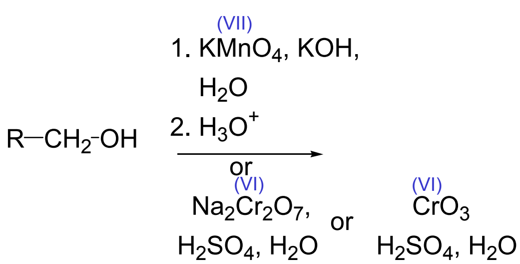


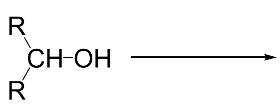
Lowest oxidation state → Highest oxidation state

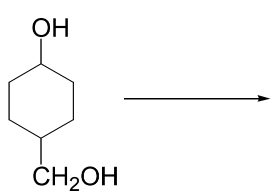
Oxidation of Alcohols (-1 → +1 → +3)



Strong Oxidants



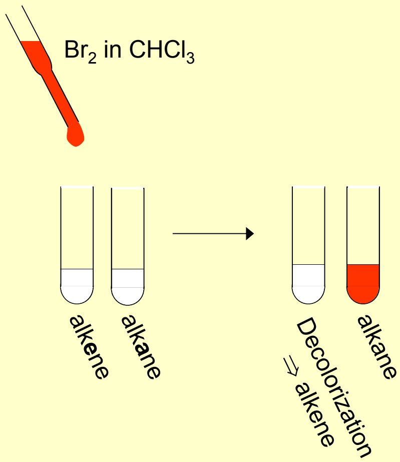




Chemical Tests for Functional Groups

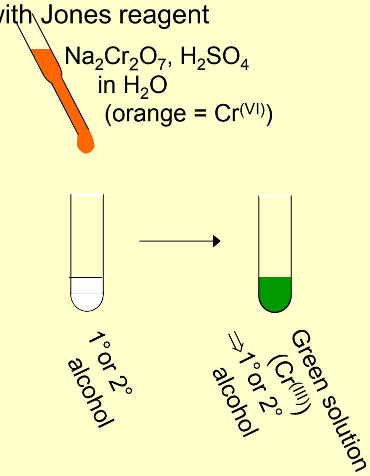
The molecular formula indicates one site of unsaturation. Is it a ring, or an alkene?

Alkenes decolorize bromine



Infrared spectroscopy indicates the presence of an alcohol (strong, broad absorption at 3500 cm^{-1}). But what type of alcohol is it?

1° and 2° alcohols give a positive test with Jones reagent



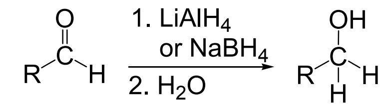
$$2Cr_2O_7^{2-} + 3C_2H_5OH + 16H^+$$

$$4Cr^{3+} + 3CH_3CO_2H + 11H_2O$$

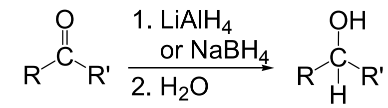
REDUCTION OF ALDEHYDES AND KETONES, ACIDS, ACID DERIVATIVES

Reduction (+3→+1→-1 with strong reducing agents: $LiAlH_4$ and $NaBH_4$

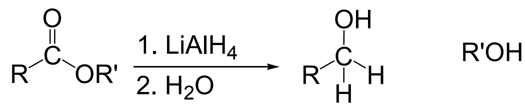
Aldehydes

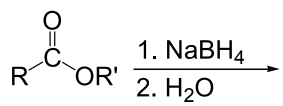


Ketones



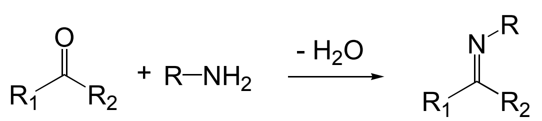
Esters and Acids





NITROGEN NUCLEOPHILES: ADDITION-ELIMINATION

Addition-elimination of 1º Amines



ketone or aldehyde

imine - *E* and *Z* isomers possible

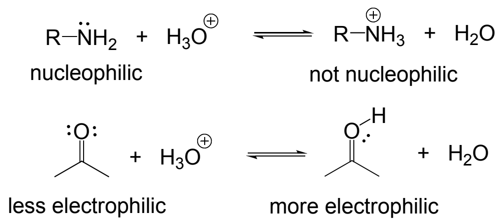
PAD PED

1. Protonation
2. Addition
3. Deprotonation

4. Protonation
5. Elimination
6. Deprotonation

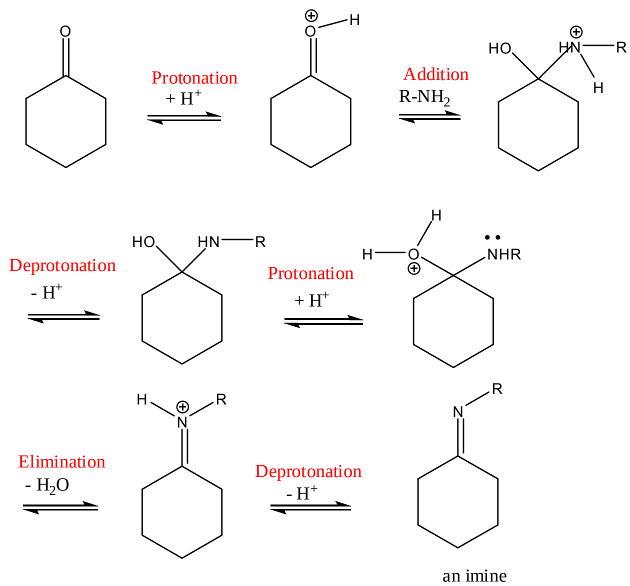
Mechanism

Acid or base catalyzed, but requires careful control of pH



Mechanism of imine formation

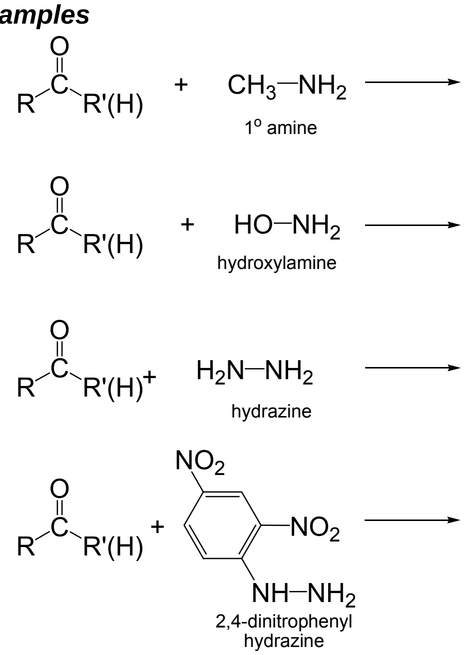
Acid or base catalyzed



PADPED

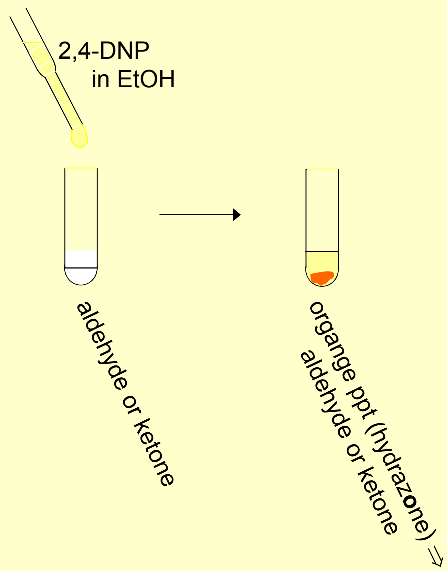
PAD PED

Examples

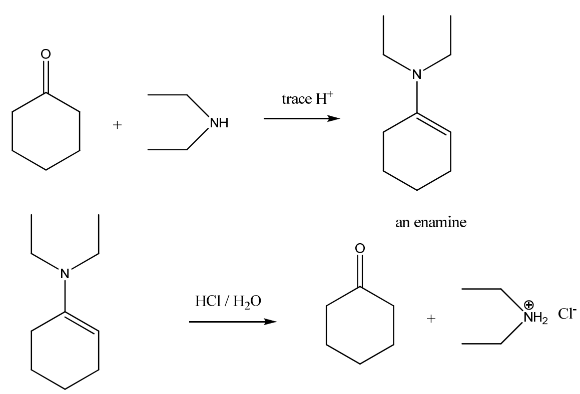


Chemical Tests for Functional Groups

Aldehydes and ketones give positive 2,4-DNP test

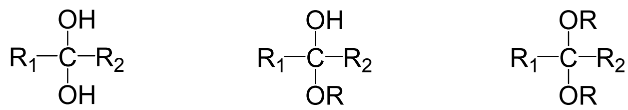


Addition of a Secondary Amine



OXYGEN NUCLEOPHILES:
ADDITION OF WATER AND ALCOHOLS

Structure

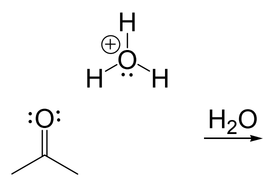


hydrate   hemiacetal   acetal

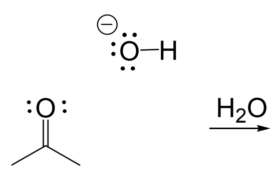
R_1 or R_2 = H or alkyl

Hydrates

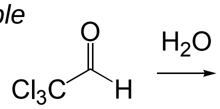
Mechanism of acid catalyzed reaction



Mechanism of base catalyzed reaction

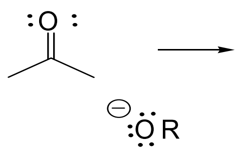


Example

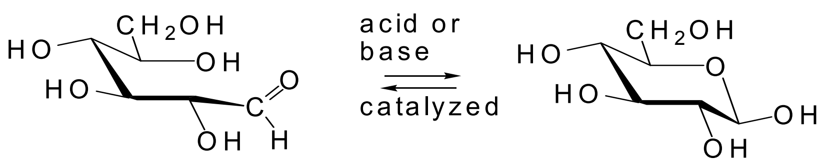


Hemiacetals

Formation: Base-catalyzed reaction [Draw the acid catalyzed reaction yourself]



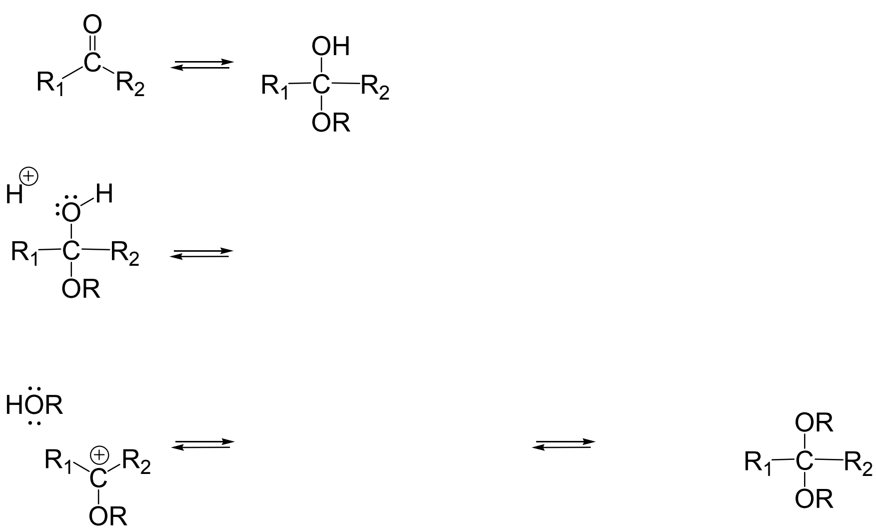
e.g. Glucose



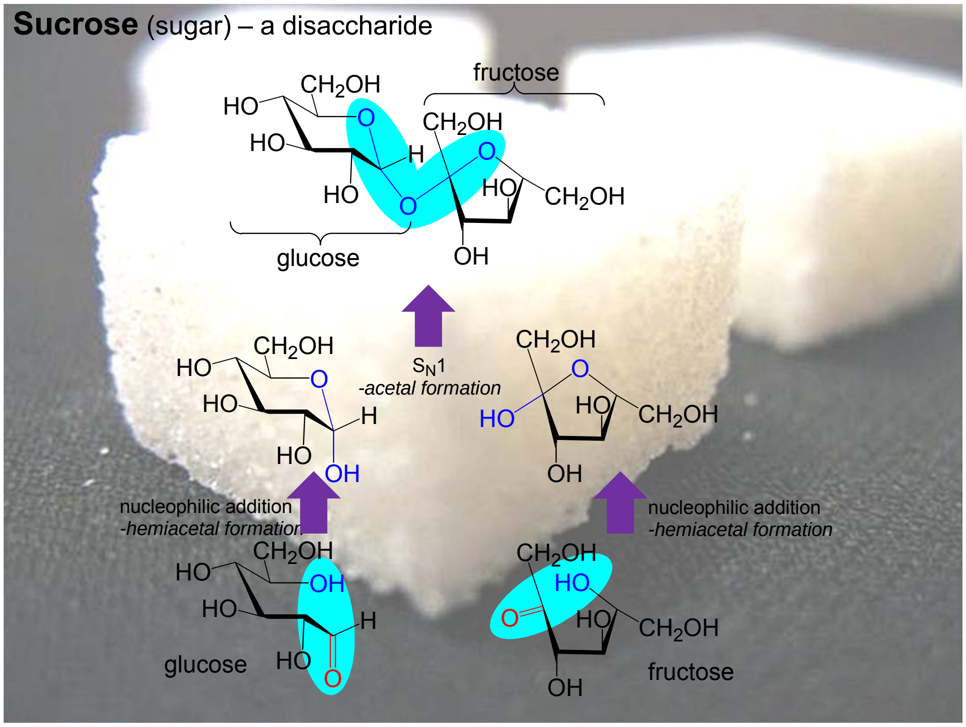
aldehyde form　　　　hemiacetal form

Acetals

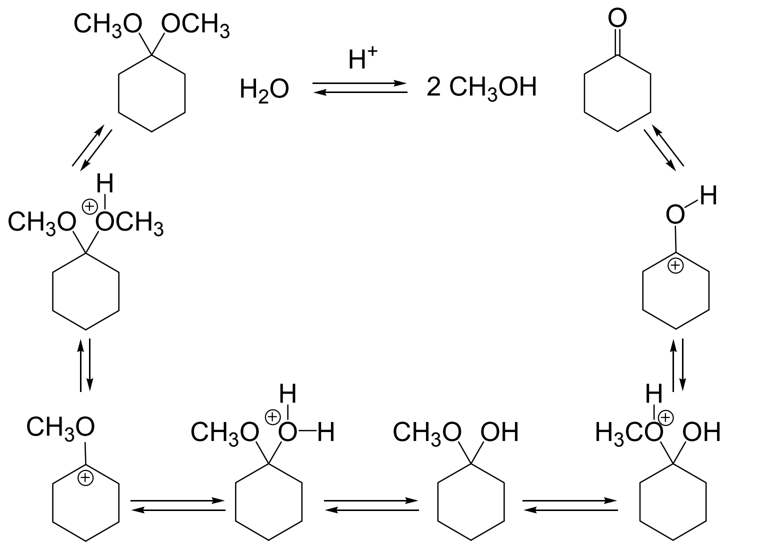
Formation: Only formed under <u>acidic</u> condition



All steps are reversible – must remove H_2O to drive reaction to completion.

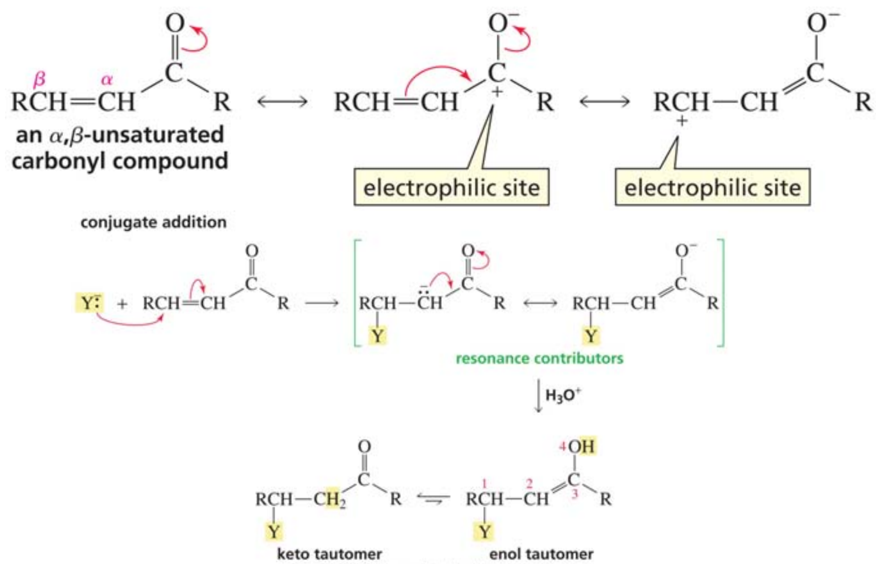


Hydrolysis of Acetals

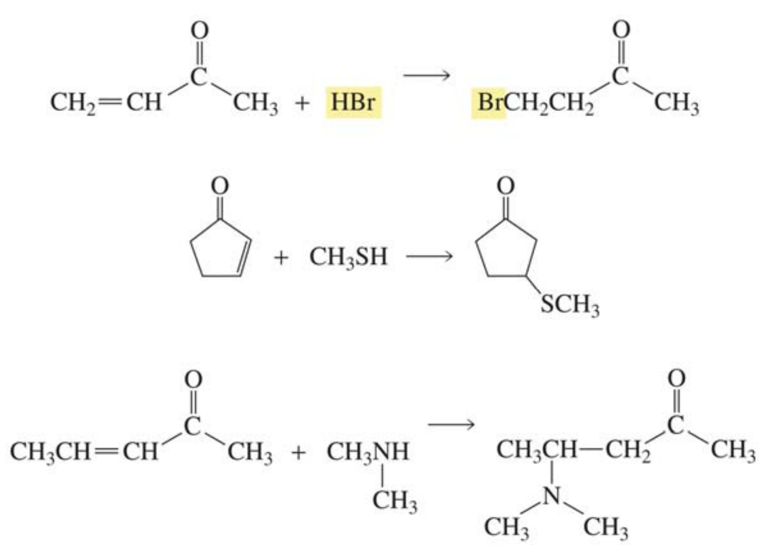


Principle of microscopic reversibility: Forward and back reactions take place via the same intermediates and transition states.

Nucleophilic Addition to α, β-Unsaturated Carbonyl Compounds

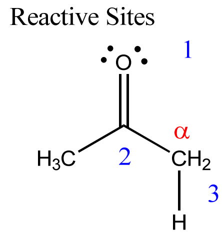


Examples: **Nucleophilic Addition to α, β-Unsaturated Carbonyl Compounds**



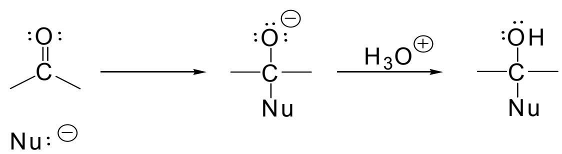
Carbonyl Reactivity

Part III: Reactions at the α-Carbon



INTRODUCTION: REVIEW OF THE ELECTROPHILICITY OF CARBONYLS

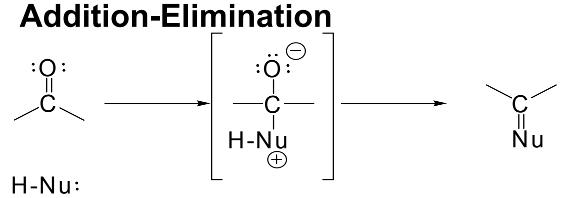
Addition



Nucleophile: Nu:⊖

- "R⊖" (from RMgBr or RLi)
- "H⊖" (from $LiAlH_4$)
- ⊖OH
- ⊖CN
- ⊖OR

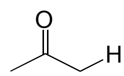
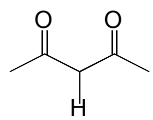
Addition-Elimination



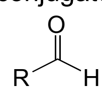
Nucleophile: H-Nu :

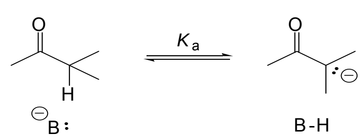
THE ACIDITY OF THE α-HYDROGENS OF CARBONYL COMPOUNDS: ENOLATE ANIONS

Protons α- to Carbonyl Groups are More Acidic Than Other Protons on Carbon (called "active" protons)

	pK_a		pK_a
	19.2	$H_3C{-}CH_3$	50
	9.0	$H_2C{=}CH_2$	44
		$HC{\equiv}CH$	25

Note: Protons attached to the carbonyl carbon of aldehydes are not particularly acidic, the conjugate base is not resonance stabilized.

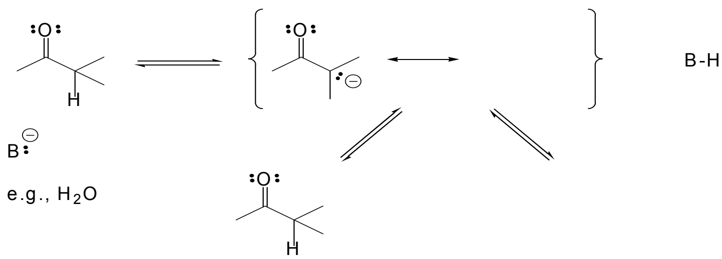




The negative charge of the conjugate base is <u>stabilized.</u> through <u>resonance</u>.

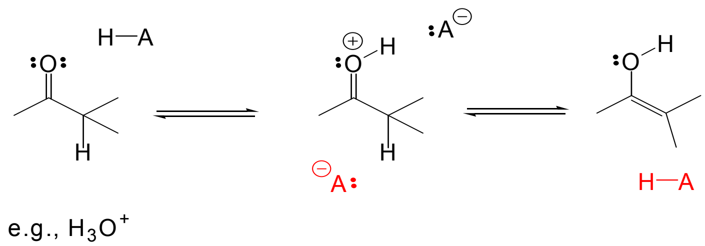
KETO AND ENOL TAUTOMERS

Base Catalyzed Tautomerization

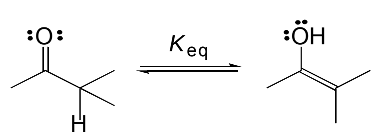


Keto and enol forms are in equilibrium. The interconversion process is called tautomerization or enolization .

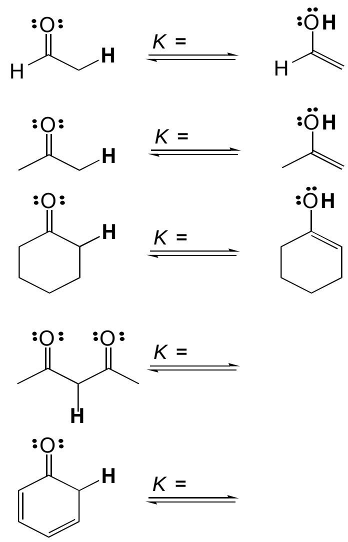
Acid Catalyzed Tautomerization



Keto and enol forms are in equilibrium. The keto form is *normally* more stable

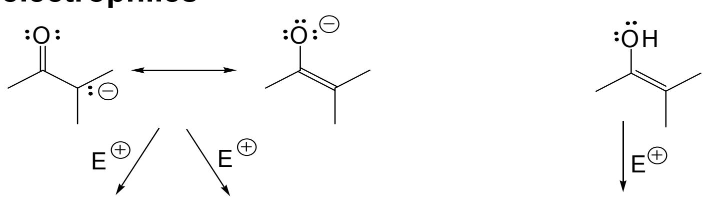


Keto and enol forms are in equilibrium. The keto form is *normally* more stable

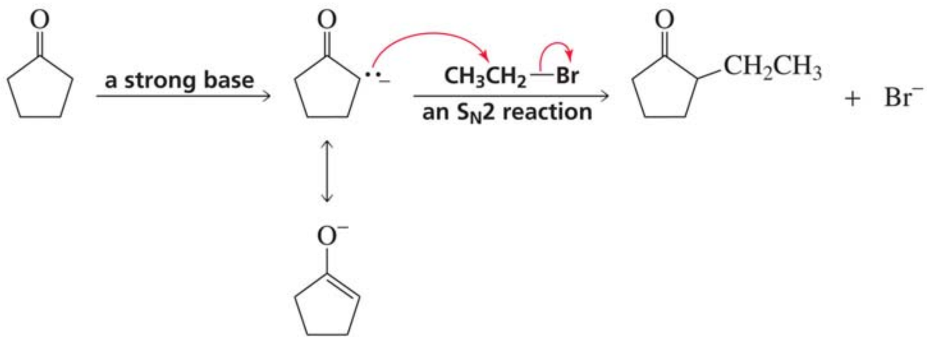


REACTIONS VIA ENOLS AND ENOLATE ANIONS

Preview: Enolates and Enols are nucleophilic and react with electrophiles



Alkylation of Enolate Ions

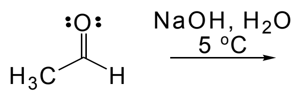


The S_N2 reaction works best with primary and secondary halides

Preview: Aldol Addition

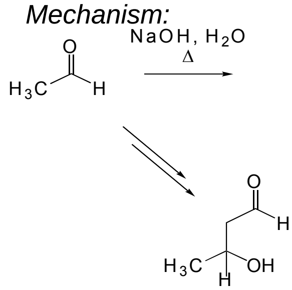
THE ALDOL REACTION: ADDITION OF ENOLATES TO ALDEHYDES & KETONES

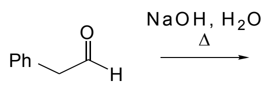
The aldol reaction: The reaction of an aldehyde with an aldehyde enolate



Heating causes dehydration to form α,β-unsaturated aldehyde, called an aldol condensation reaction.

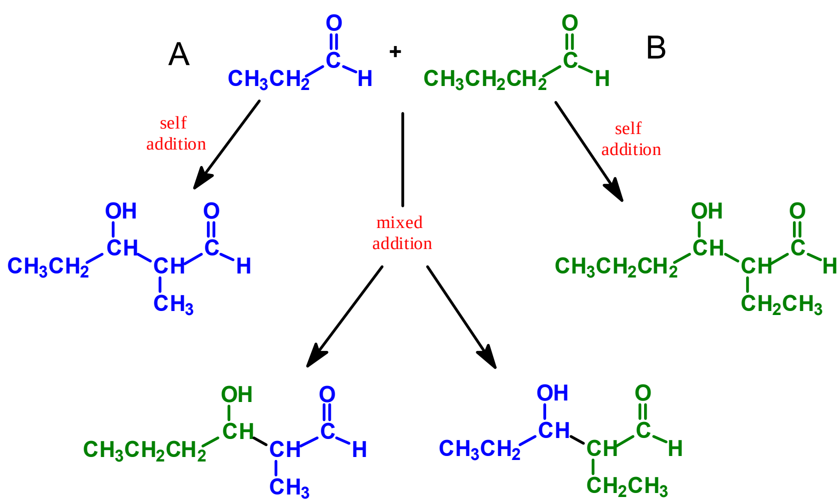
Mechanism:





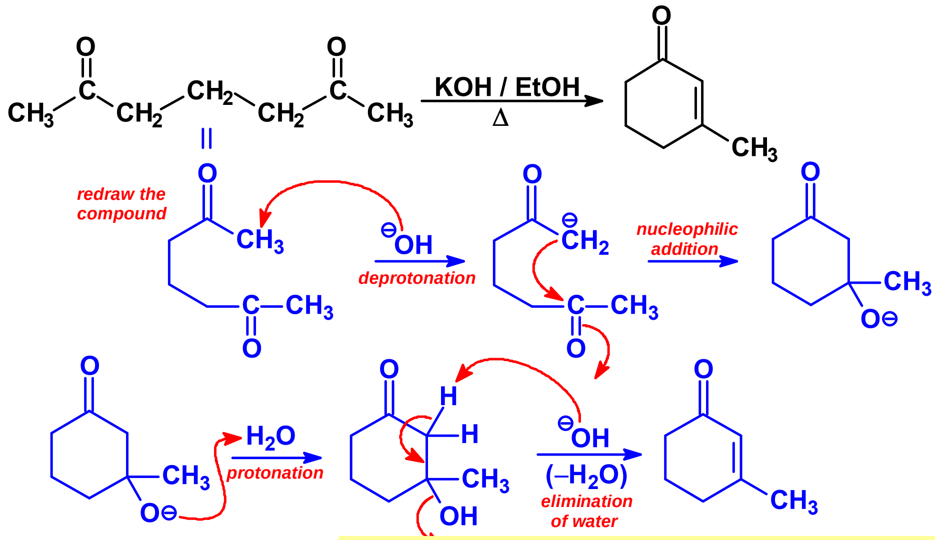
Limitations of the Aldol Addition

➢**Mixed aldol additions where both carbonyl compounds have α-hydrogens give mixtures of products.**



Mechanism for an internal Aldol condensation reaction:

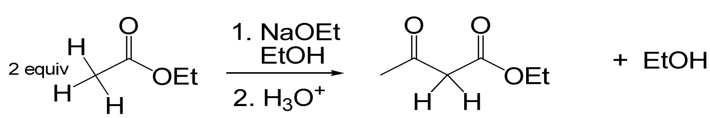
(an intramolecular reaction)

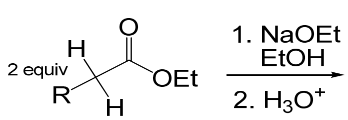


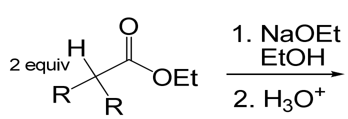
A poor LG, but …extended conjugation product is formed

THE CLAISEN CONDENSATION: THE SYNTHESIS OF β-KETO ESTERS

Overall reaction







Claisen Condensation

Mechanism: Driving force is the formation of a stable β-keto-enolate, which is protonated to the final product. <u>No reaction</u> if only one alpha hydrogen is present

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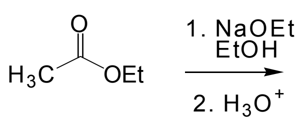
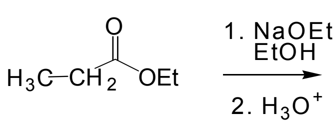
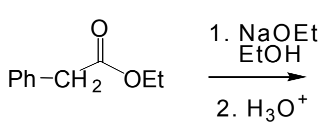
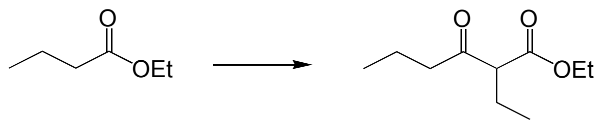
Examples

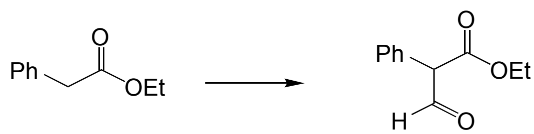






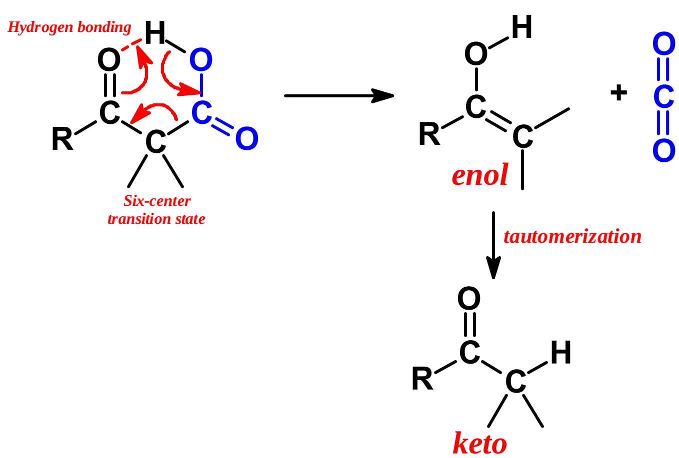
Problem – How would you achieve the following transformations?





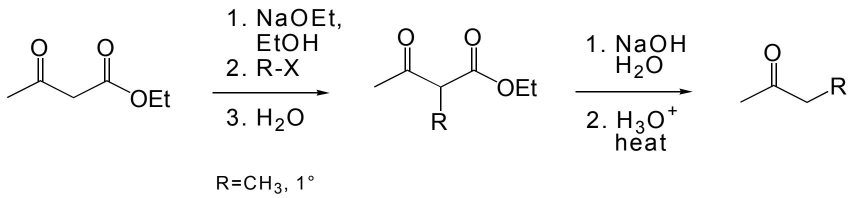
Mechanism of Decarboxylation

➢**3-Oxocarboxylic Acids or β-ketocarboxylic acids**



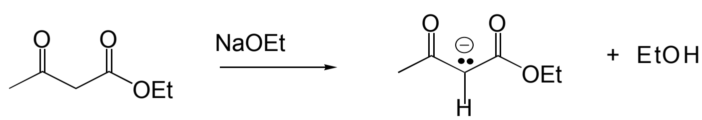
THE ACETOACETIC ESTER SYNTHESIS: SYNTHESIS OF METHYL KETONES

Overall reaction

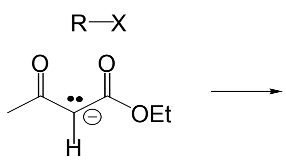


Mechanism

Deprotonation: Enolate formation

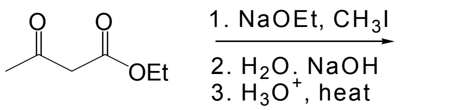


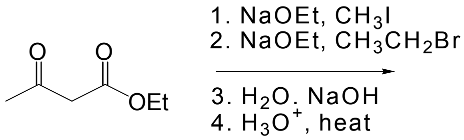
Alkylation

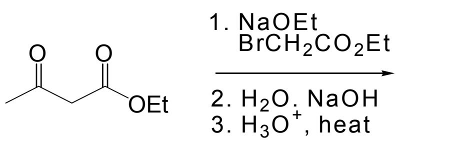


Followed by Ester hydrolysis and *decarboxylation*

Examples

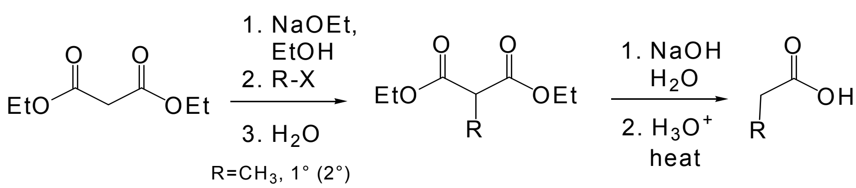






THE MALONIC ESTER SYNTHESIS: SYNTHESIS OF SUBSTITUTED ACETIC ACIDS

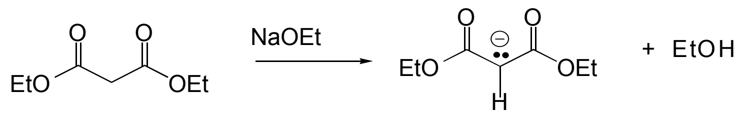
Overall reaction



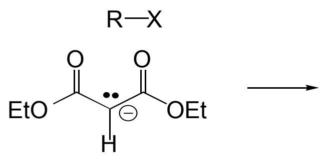
Mechanism next slide

Mechanism

Deprotonation: Enolate formation

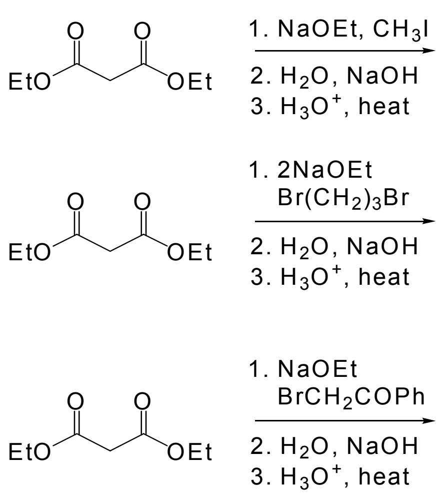


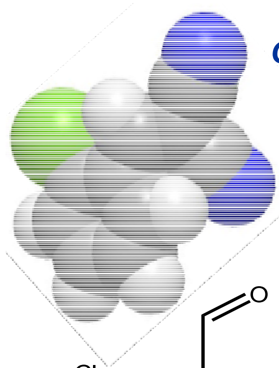
Alkylation



Followed by Ester hydrolysis and *decarboxylation*

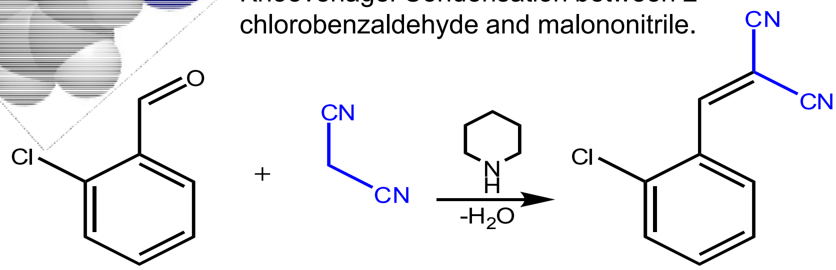
Examples



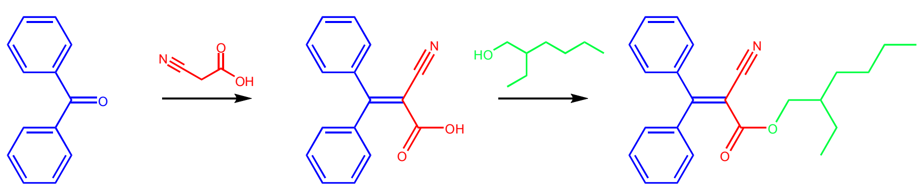


CS gas: *2-chlorobenzalmalononitrile*

Discovered by Ben Carson and Roger Staughton (hence the name CS gas), 2-chlorobenzalmalononitrile is prepared by a Knoevenagel Condensation between 2-chlorobenzaldehyde and malononitrile.



Octocrylene, 2-ethylhexyl-2-cyano-3,3-diphenyl-2-propenoate



Octocrylene is an ingredient used in cosmetics and sunscreen. The conjugated diphenyl cyanoacrylate absorbs UVB and UVA rays. The 2-ethylhexyl ester imparts hydrophobicity.

TOPICS ON EXAM

Types of Questions

- Predict the products obtained from given starting materials,
- Rationalize the outcome of a reaction (i.e., propose a mechanism, draw key intermediates)

Do the problems in the book; they are great examples of the types of problems on the exam!

Preparing for Exam

- Get up-to-date *NOW!*
- Work as many problems as possible. Do the problems first, then consult the solutions manual.
- Work in groups, discuss chemistry, teach and test each other.
- Do the "Learning Group Problem" at the end of the chapter.