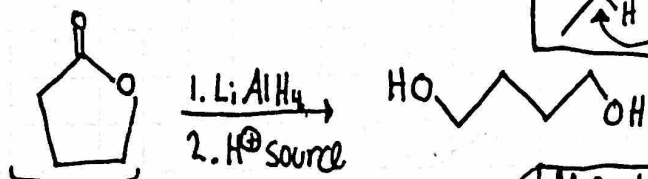
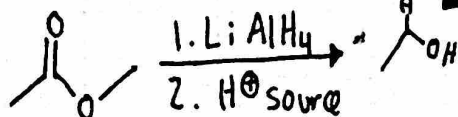
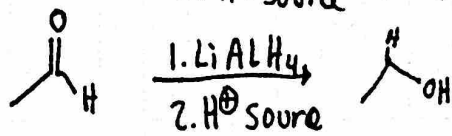
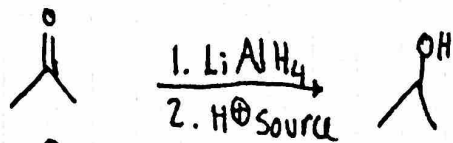
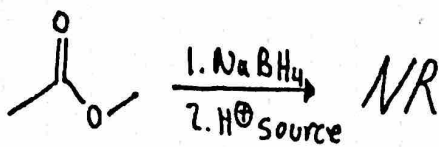
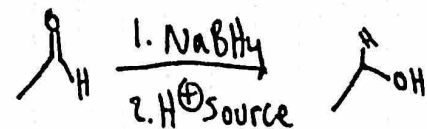
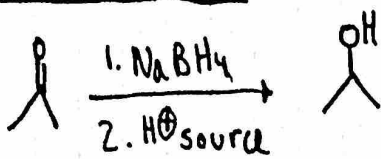
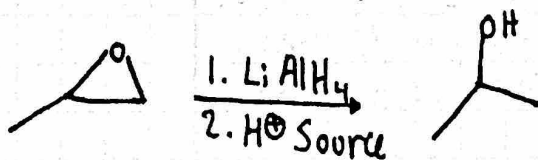
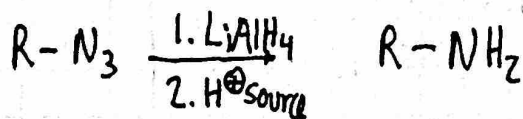
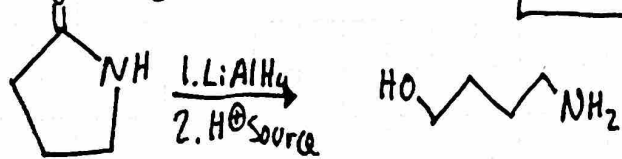




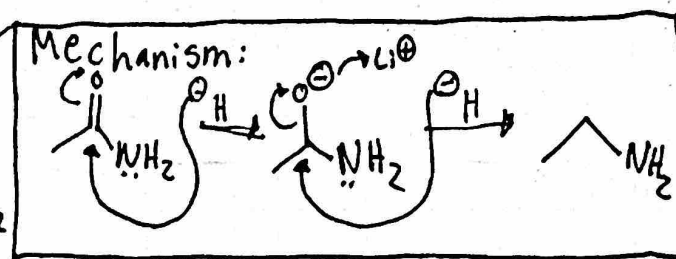
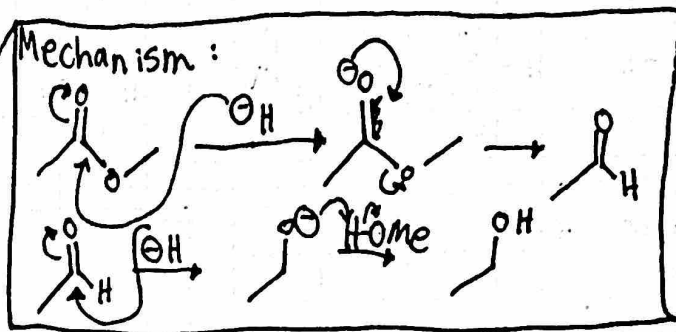
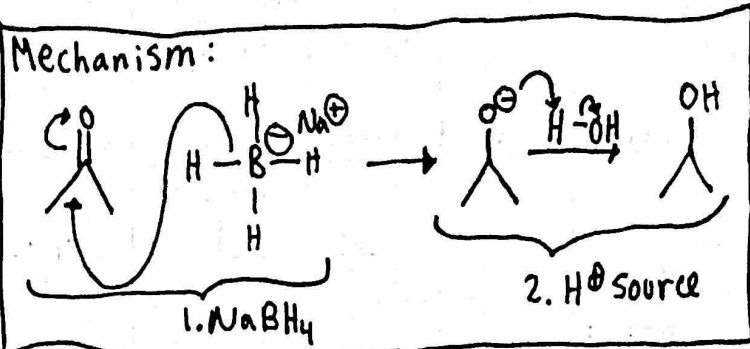
Reductions:



2 Lactone



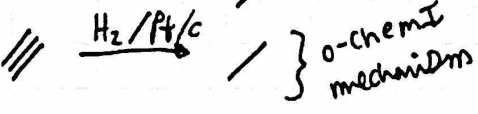
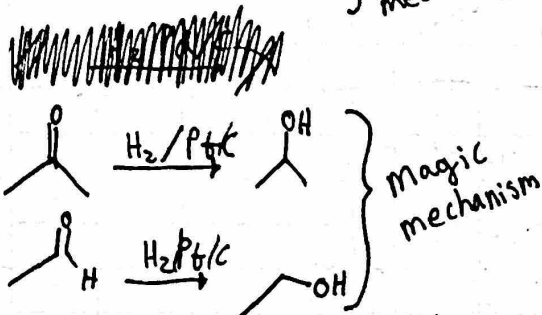
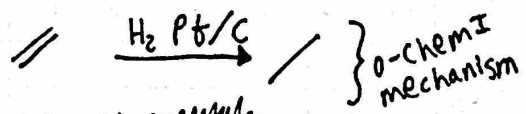
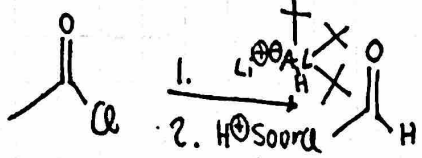
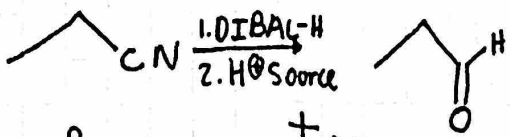
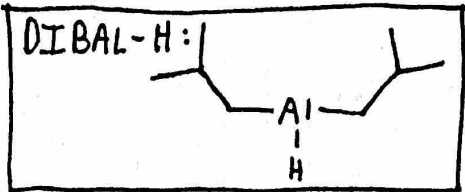
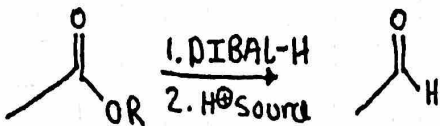
H<sup>+</sup> source:  
H<sub>3</sub>O<sup>+</sup>  
H<sub>2</sub>O / D<sub>2</sub>O  
R-OH



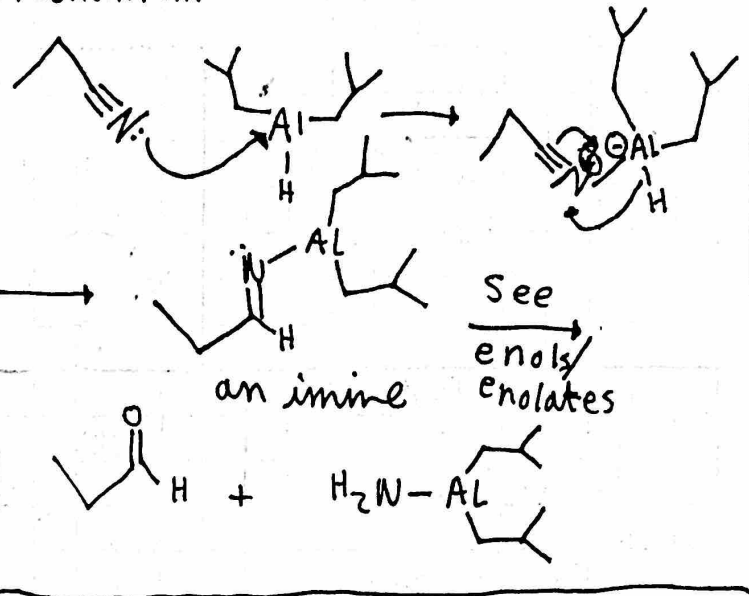
Reactivity of Carbonyls

Aldehydes	<chem>RCHO</chem>	} NaBH <sub>4</sub>
Ketones	<chem>RC(=O)R</chem>	
-----		
Acyl Chlorides	<chem>RCOCl</chem>	} LiAlH <sub>4</sub>
Esters	<chem>RCOOR</chem>	
Amides	<chem>RC(=O)NH2</chem>	
Carboxylic Acids	<chem>RCOOH</chem>	

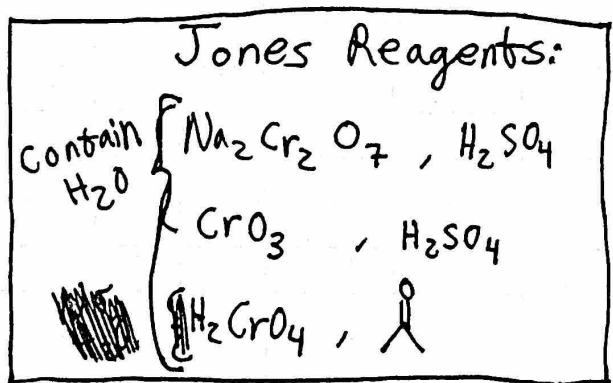
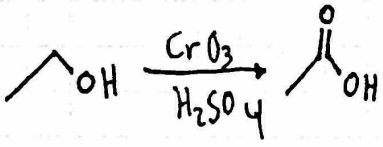
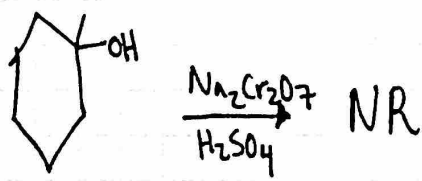
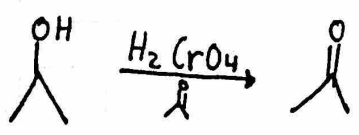
Reductions (continued):



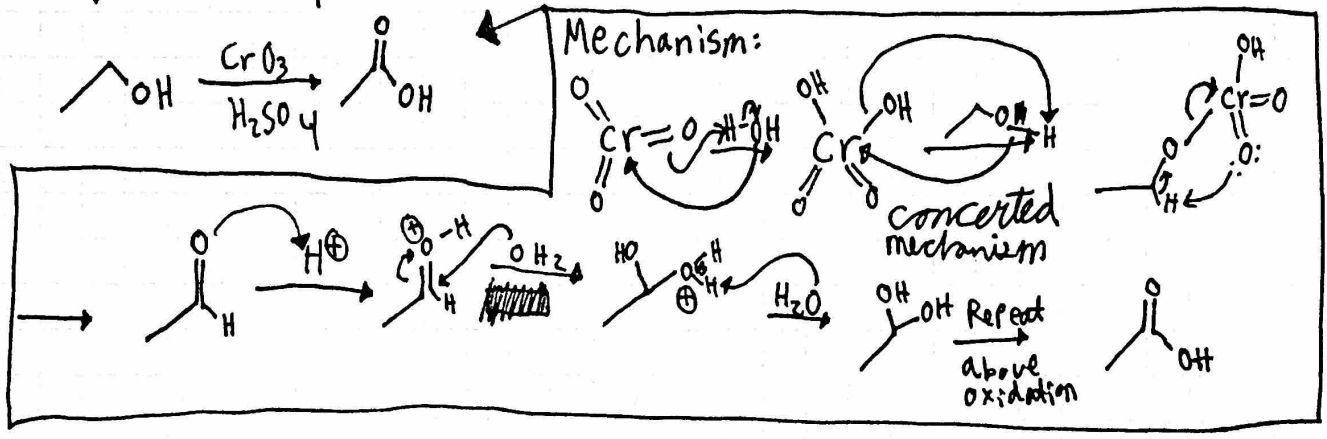
Mechanism:



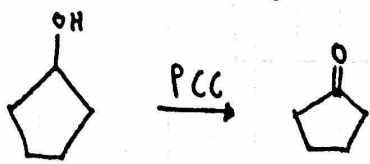
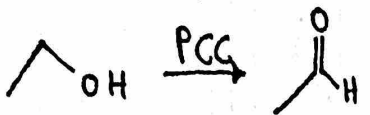
oxidations:




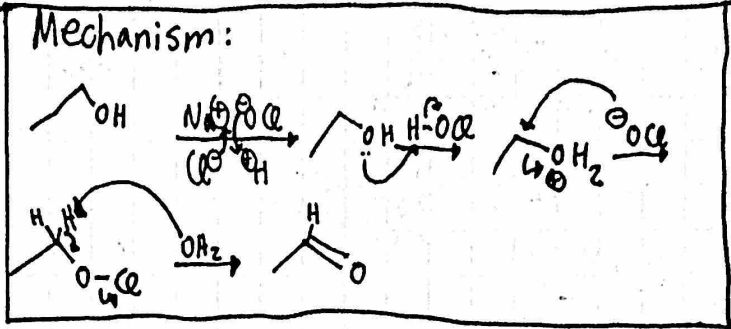
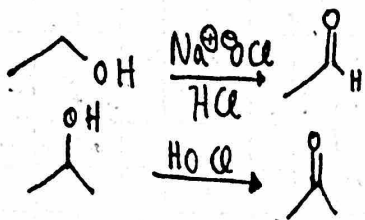
Mechanism:



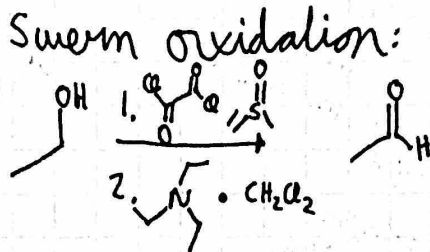
# 4 Oxidations (Continued):



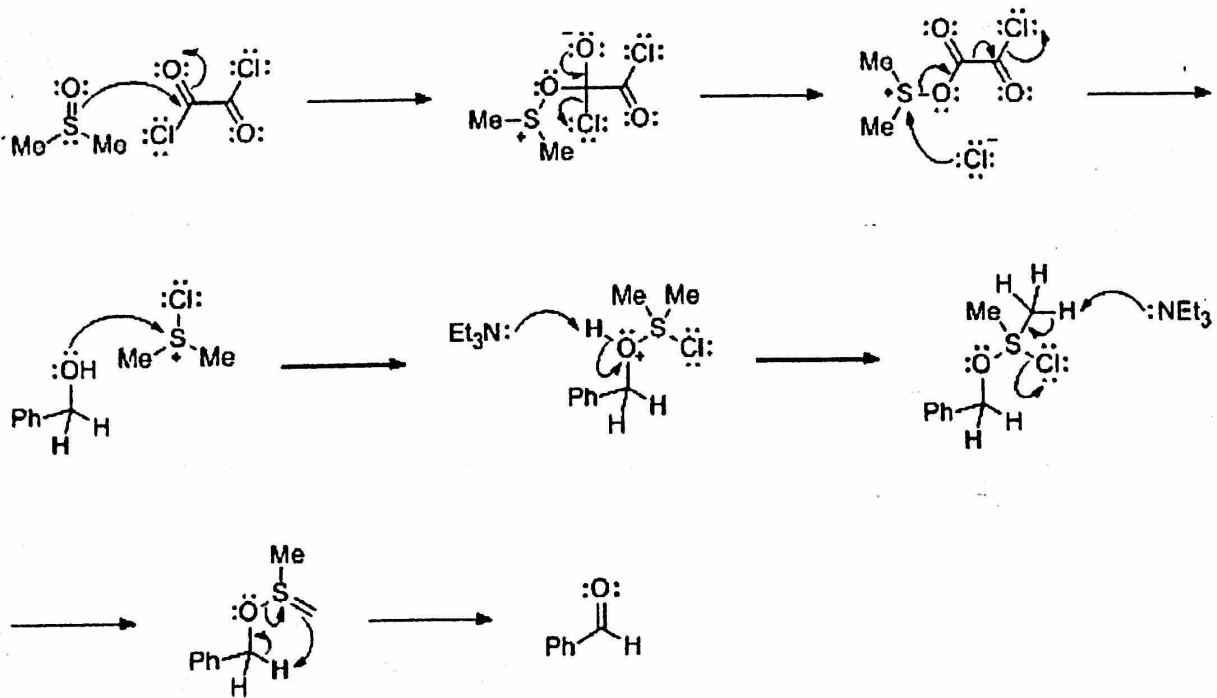
PCC:  
 $CrO_3, HCl,$    
 Anhydrous!



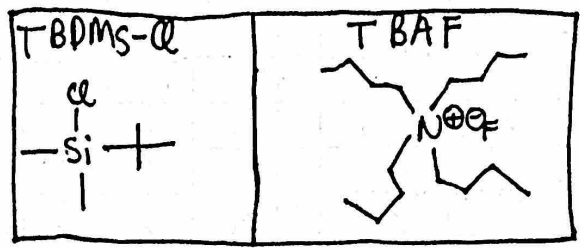
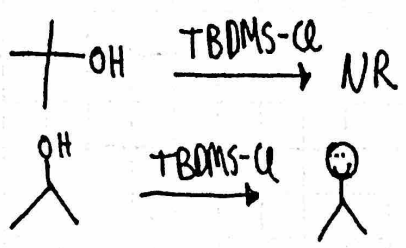
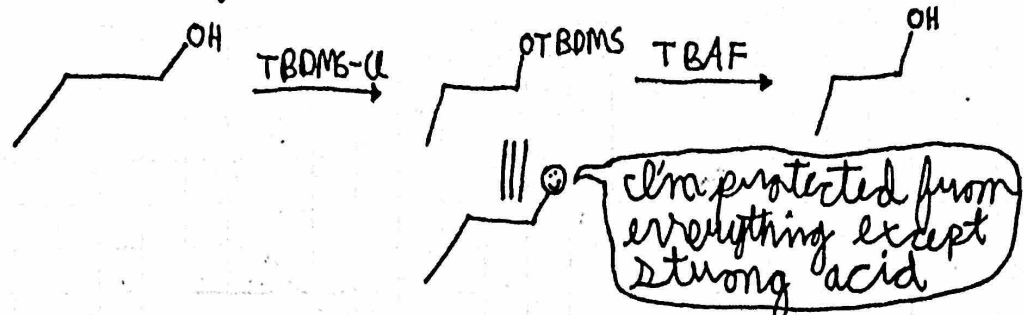
Other oxidizers:  
 strong {  $KMnO_4, \Delta, OH^-$   
 $KMnO_4, cold, ^-OH$   
 $OsO_4$   
 $O_3 / ZnHOAc$   
 weak { Swern



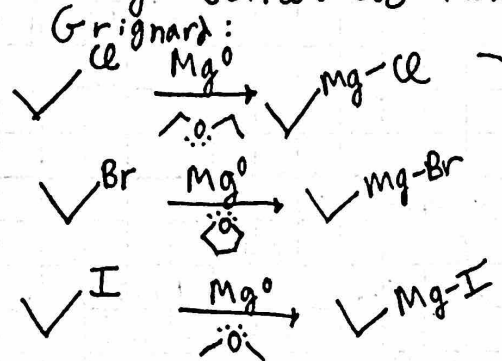
## Mechanism



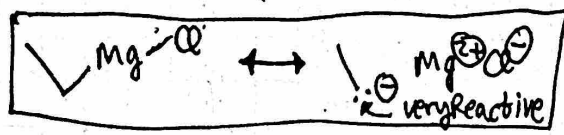
Protecting an Alcohol:



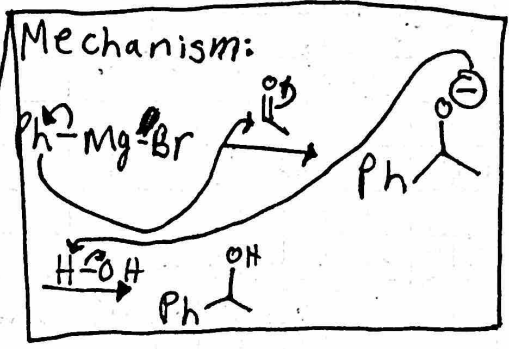
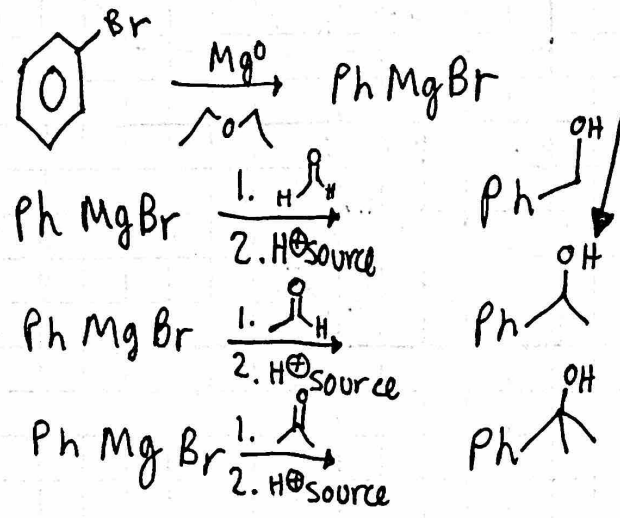
Organometallic Reactions:



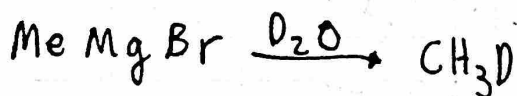
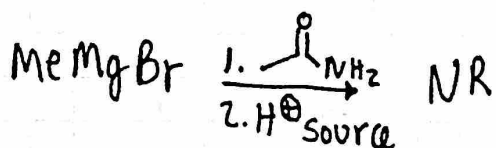
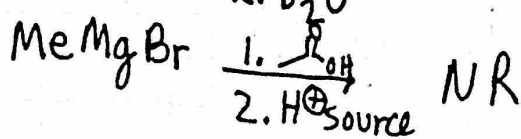
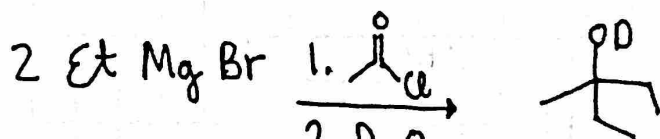
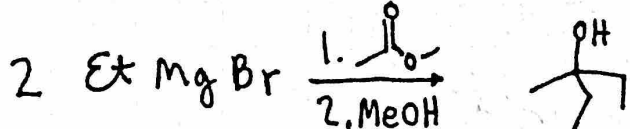
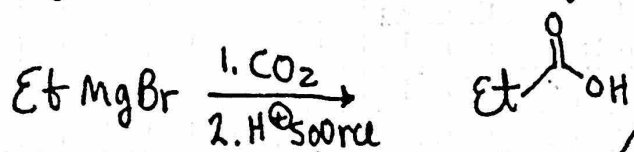
Grignard reagents formed by radical mechanism.



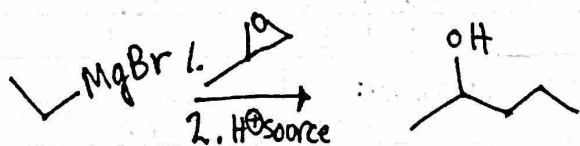
Bromine preferred.



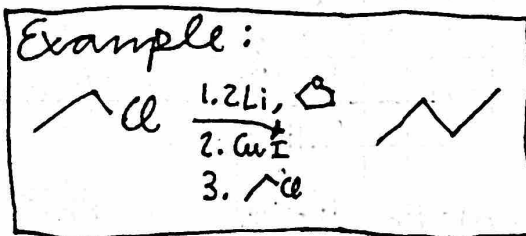
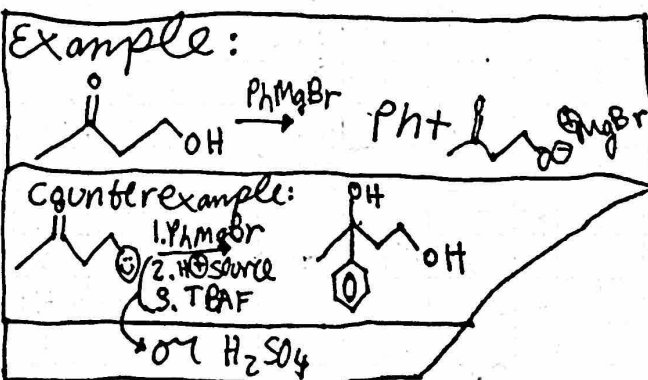
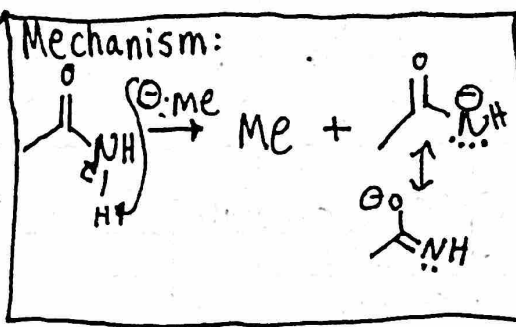
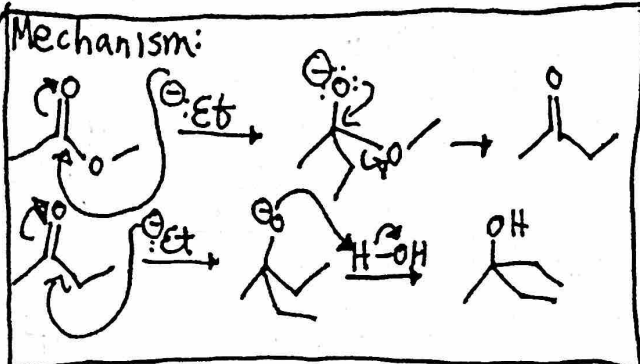
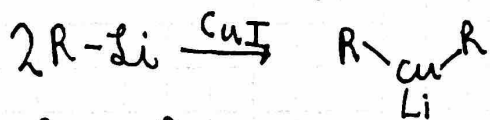
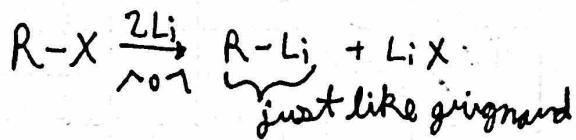
## 6 Organometallic Reactions/Grignard (Continued)



No loose protons near strong bases like Grignard



Gilman Reagents:



# Conjugated Systems ~~and Alkyl Alkyls~~:

For  $e^-$  to delocalize the system must be planar

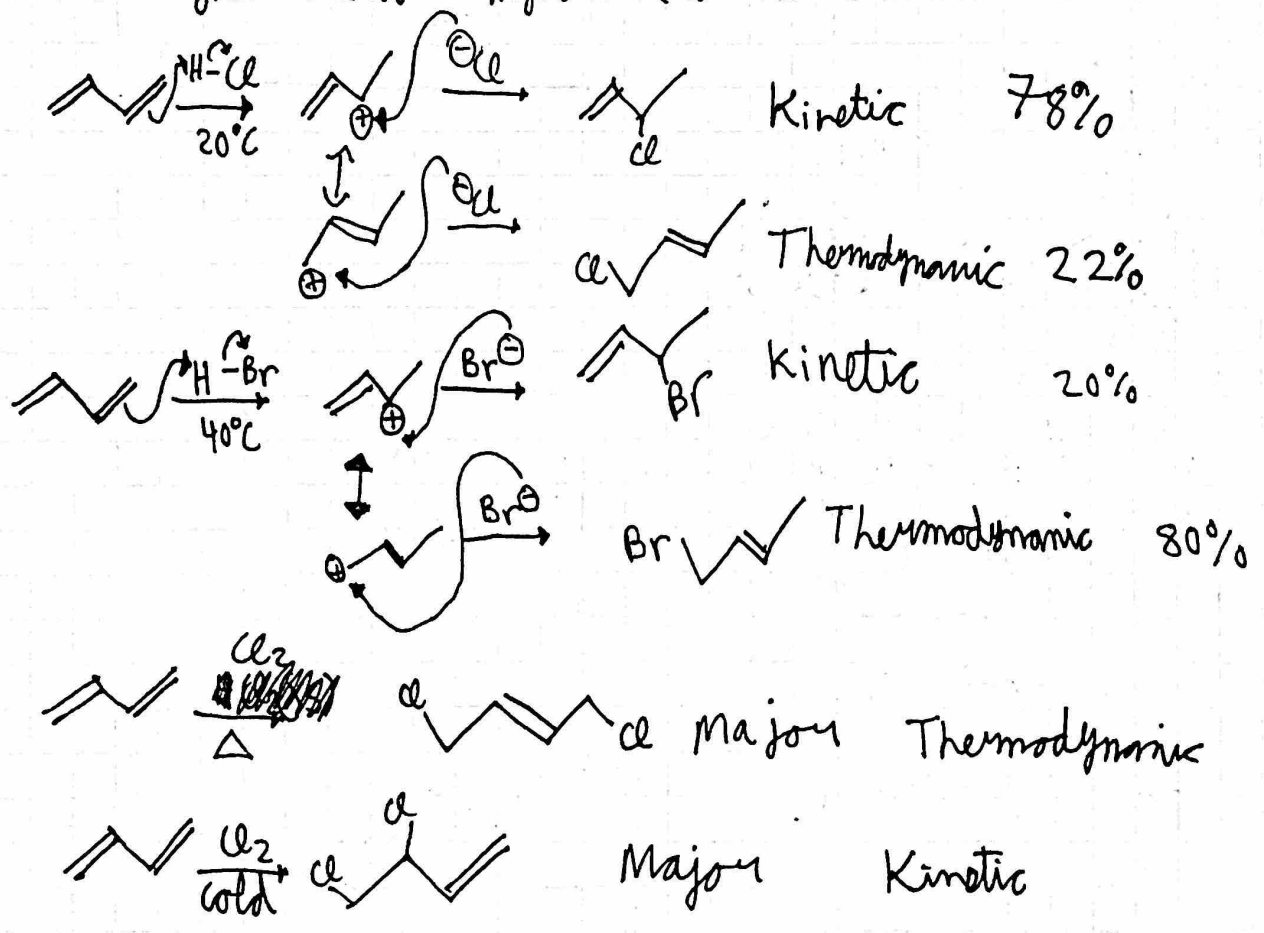
More conjugation  $\rightarrow$  can be visible  
 $\rightarrow$  Lower HOMO LUMO  
 $\rightarrow$  Longer wavelength absorbed/emitted

Nonconjugated  $< 200\text{nm}$

Conjugated  $> 200\text{nm}$  (Visible 400-800nm)

Kinetic Product : Lower  $E_a$ , higher  $E$

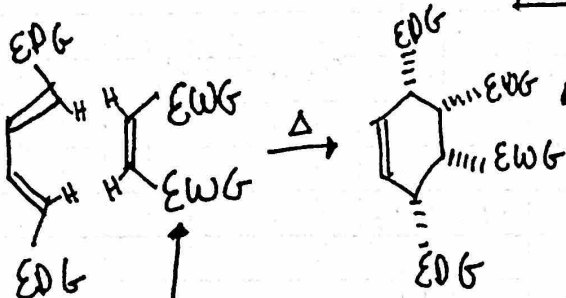
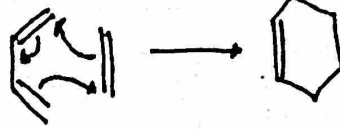
Thermodynamic Product : Higher  $E_a$ , Lower  $E$



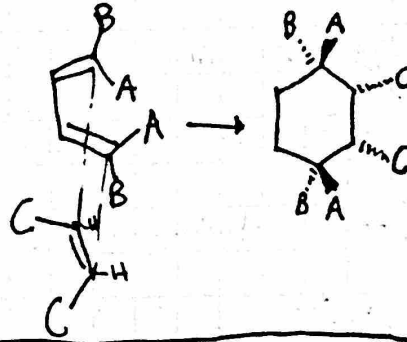
# Diels Alder Reaction:



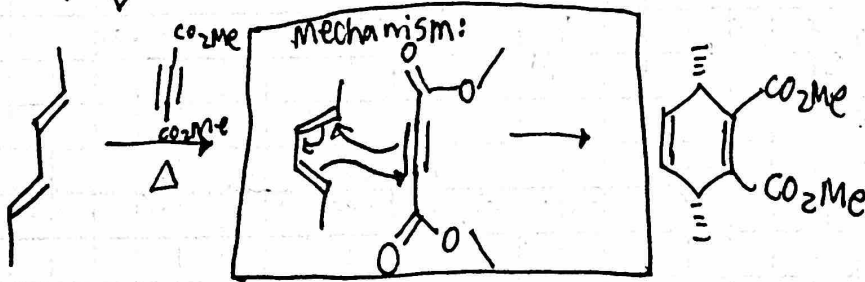
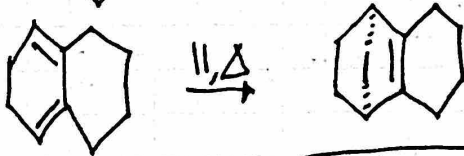
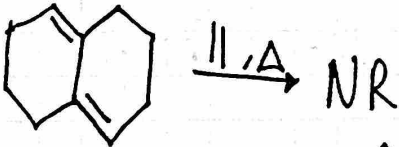
Mechanism:



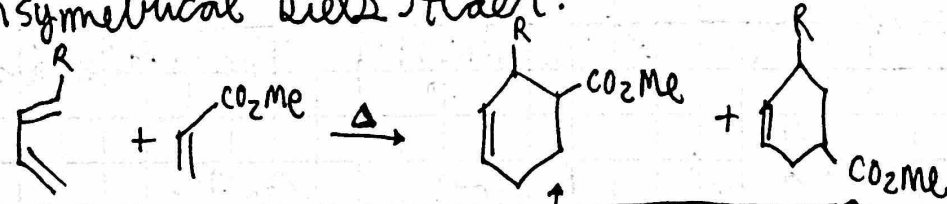
Stereochemistry:  
A result of the endo rule:



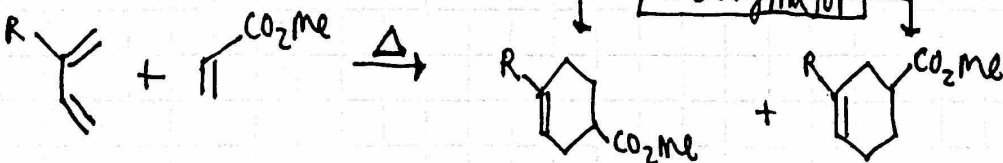
these substituents help



## Unsymmetrical Diels Alder:

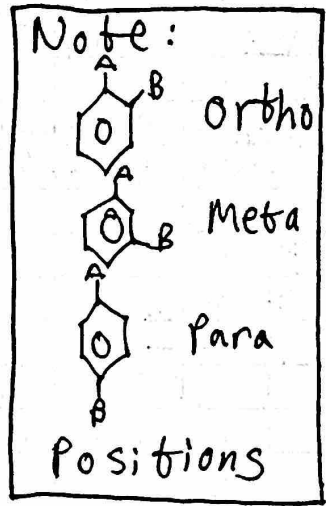
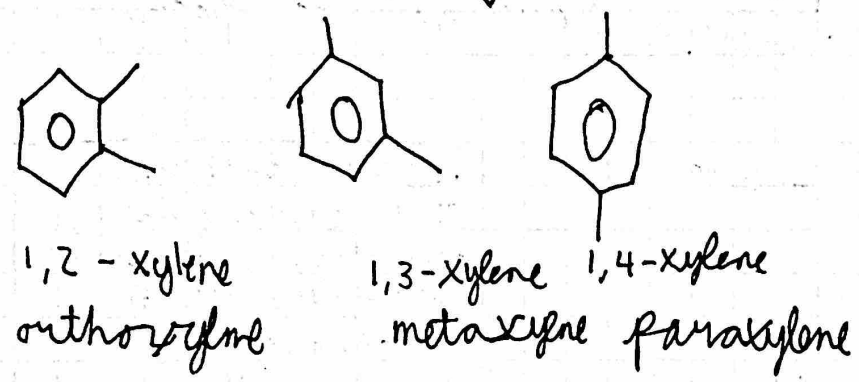
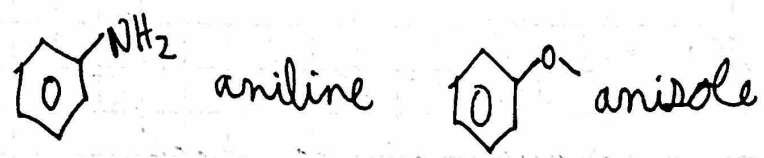
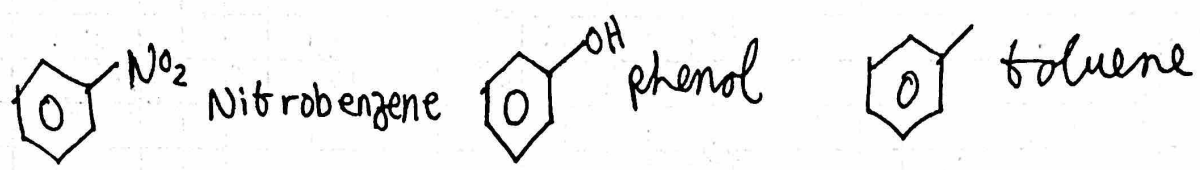
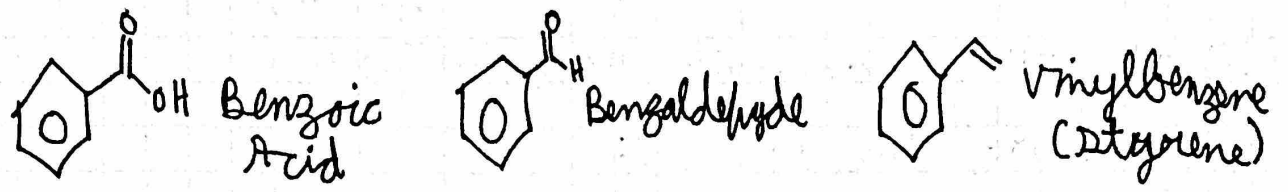
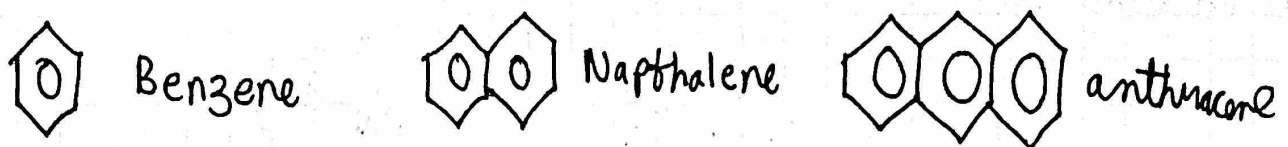


one is usually vastly major





# Benzene, Substituted benzene and Aromatic Compounds



**Annulene:** A cyclic hydrocarbon with alternating double bonds

**Aromatic:** Extra-stable Annulenes

1. on annulene
2. P orbitals all around
3. planar
4.  $4n+2 \pi e^-$  : aromatic  
 $4n \pi e^-$  : anti-aromatic  
 ↓  
 diradical :  
 ↳ paramagnetic  
 ↳ diamagnetic

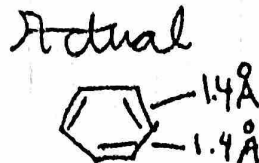
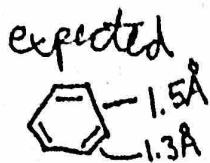


→ An issue for rings larger than 10

Aromatics are extra stable (low energy)

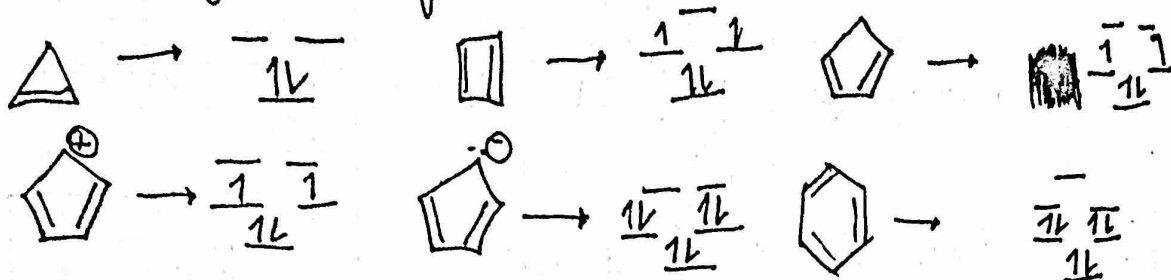
Bond lengths:

Benzene:



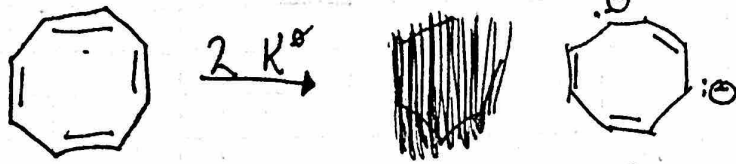
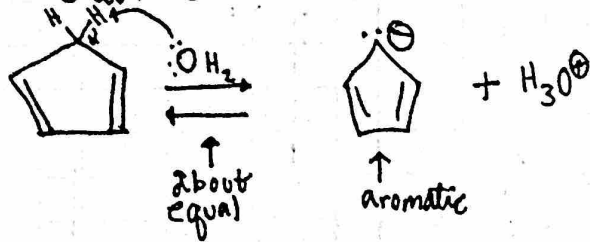
M.O. theory of conjugated cyclic systems:

The Polygon Rule for  $\pi e^-$ :



Turn one corner Down, draw a line for each orbital at each corner.

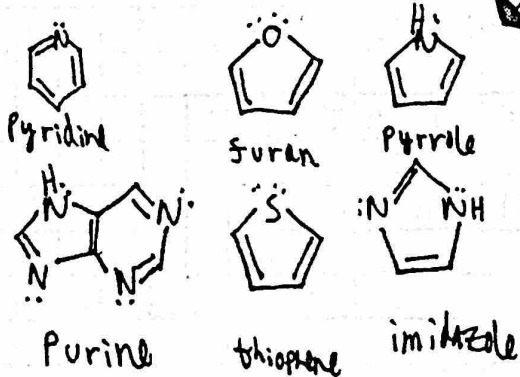
Fill in  $e^-$ .



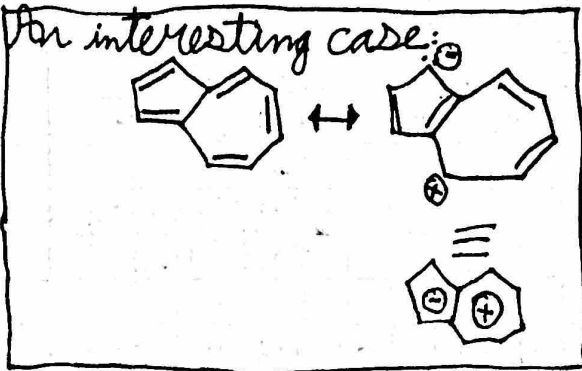
Acid Base Properties of conjugated cycles:

- if losing  $H^+$  will make it aromatic it is ~ acidic
- if losing  $H^+$  will break aromaticity it is NOT acidic
- if gaining  $H^+$  will retain aromaticity it is ~ basic
- if gaining  $H^+$  will break aromaticity it is NOT basic

Heteroaromatics:



Practica Problems: which  $e^-$  pairs are basic?





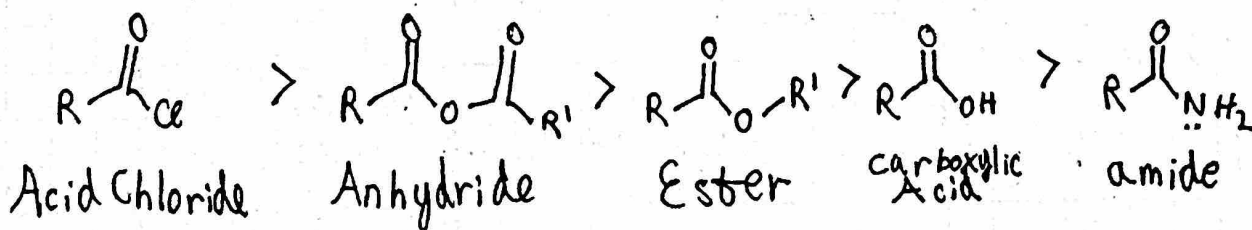
# TABLE OF Substituents

Electron Donating Groups		Electron Withdrawing Groups	
Ortho	Para	Directors	Meta Directors
Activators		Deactivators	
Strong	Weak	Weak	Strong
Non Bonding e <sup>-</sup> -OH -N(R)(H) <sub>2</sub>	Alkyl Groups Ethers Ph-OR Amides Ph-N <sub>H</sub> COCH <sub>3</sub> Esters Ph-OCOCH <sub>3</sub>	Halogens	Carbonyls (except aldehydes) -SO <sub>3</sub> H -CN -CF <sub>3</sub> -NO <sub>2</sub> Ph-Z <sup>+</sup> -Block

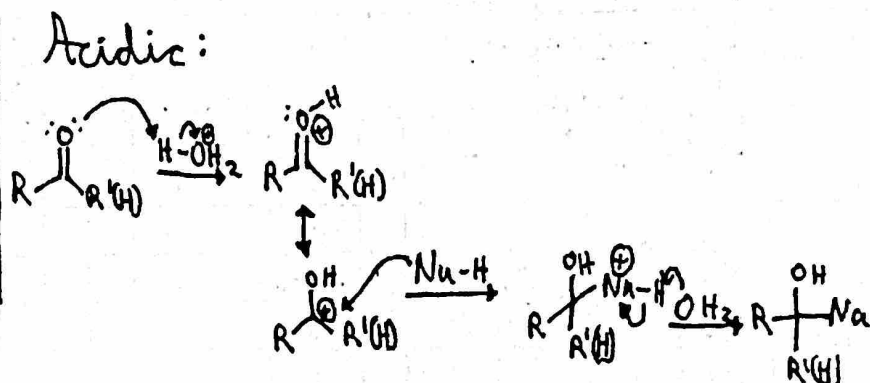
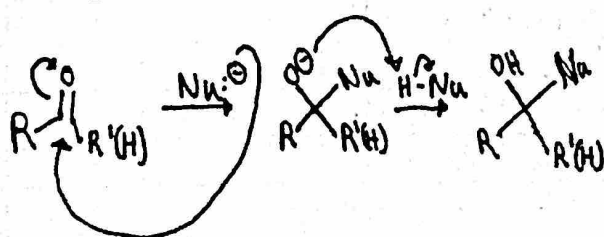
## Reactions of Carbonyls: Ketones and Aldehydes

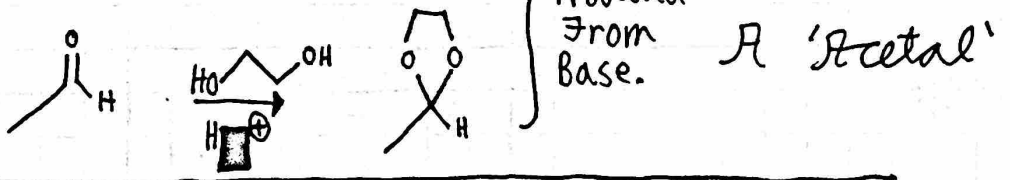
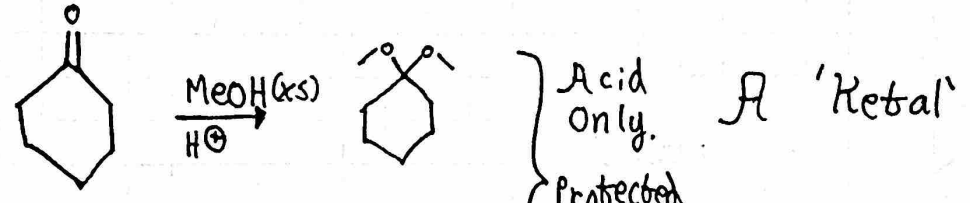
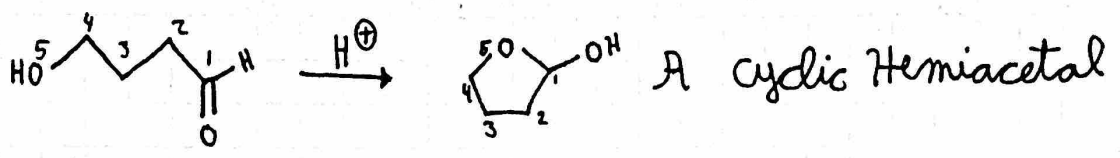
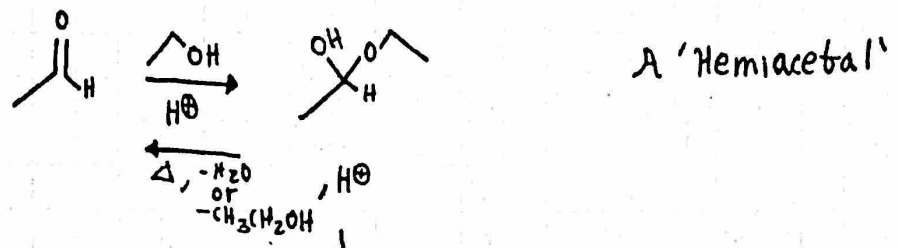
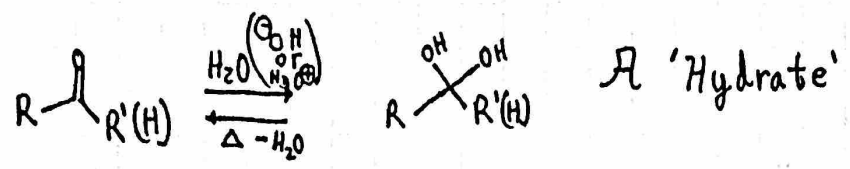
$R-\overset{\overset{O}{\parallel}}{C}-H$  is more reactive to Nu<sup>⊖</sup> than  $R-\overset{\overset{O}{\parallel}}{C}-R'$   
 draw dipoles

### Reactivity of Carboxylic Acid Derivatives:



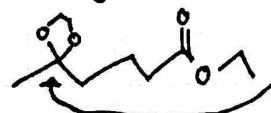
### Addition Mechanism:

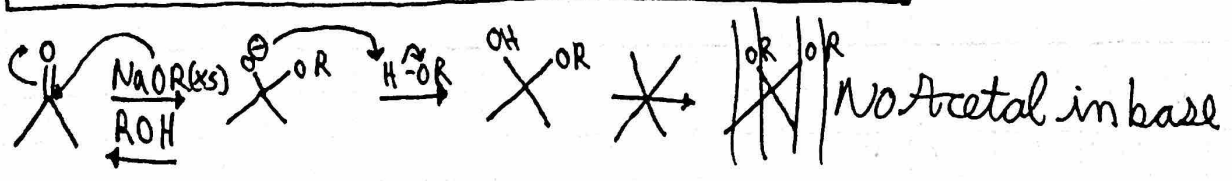




Sample Question:

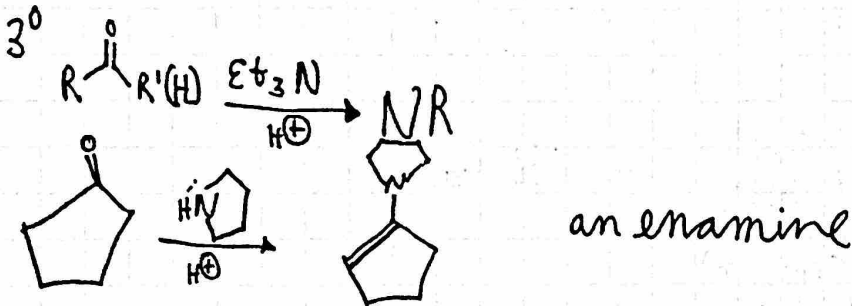
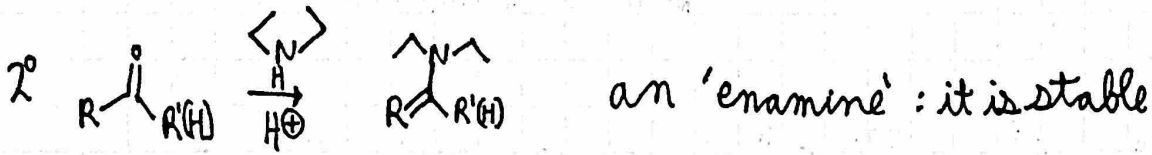
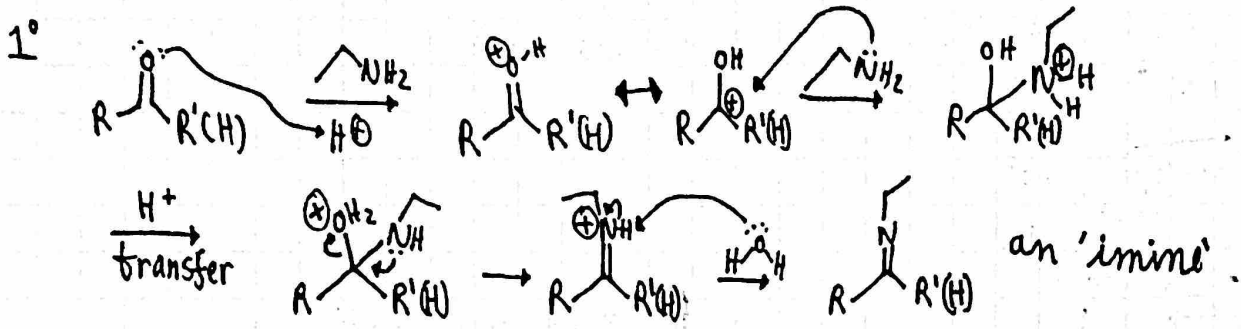
$$CH_3CO(CH_2)_4COCH_3 \xrightarrow[2. LAH]{1. HOCH_2CH_2OH, H_2SO_4(conc.)} CH_3CO(CH_2)_4COH$$

Intermediate:  Protected from base

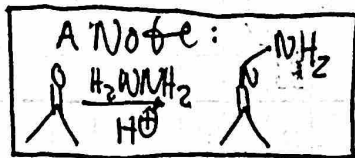


Imines:

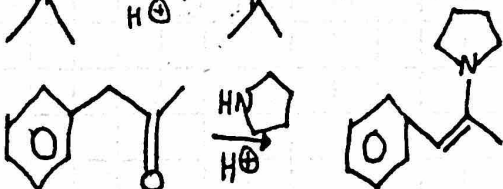
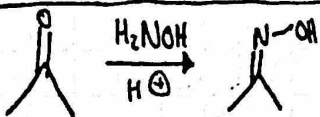
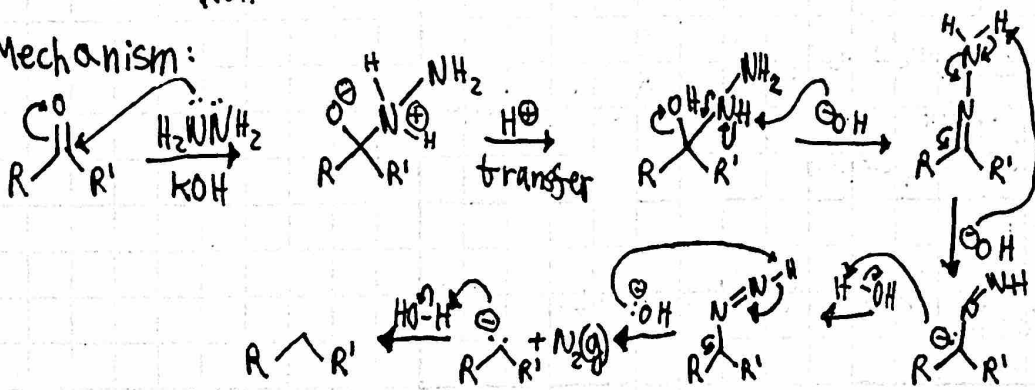
pH 4-5 : formation pH 'acidic'



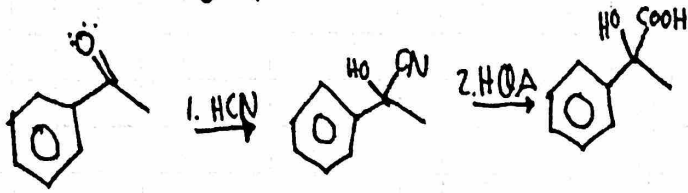
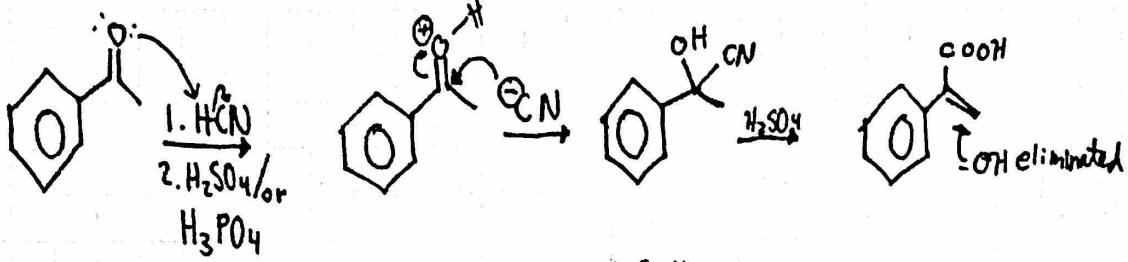
Wolff - Kishner:



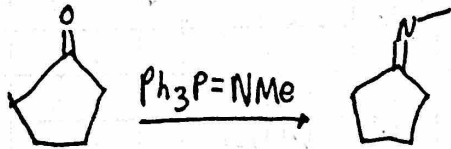
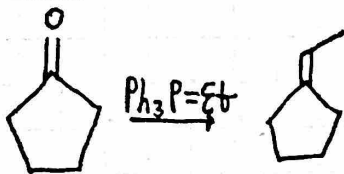
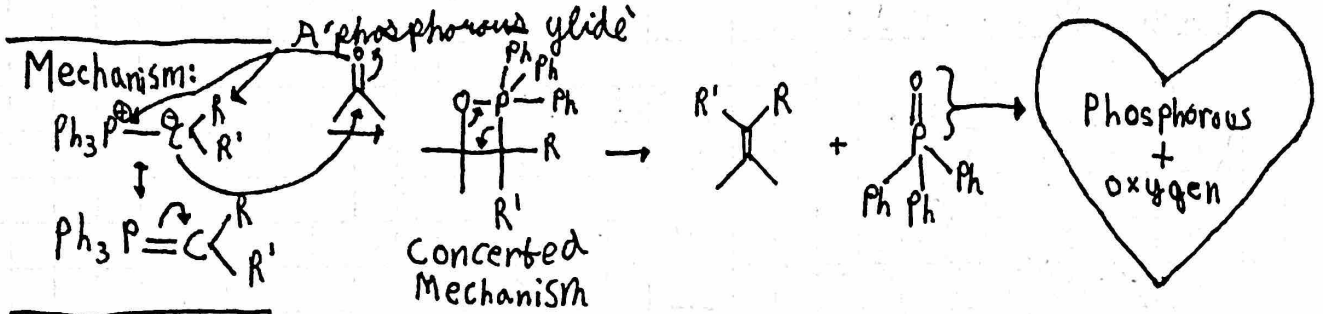
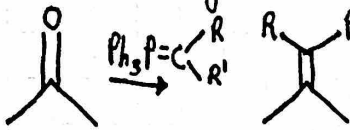
Mechanism:



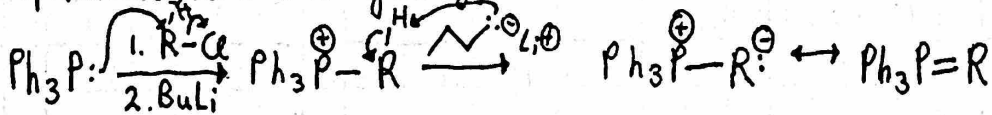
more substituted Alkene



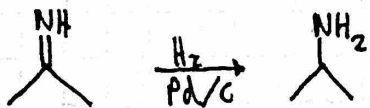
The Wittig reaction:



Preparation of the Wittig Reagent:



Miscellaneous Reactions:

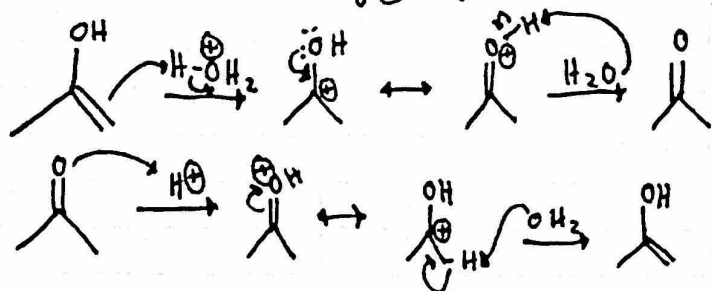


16

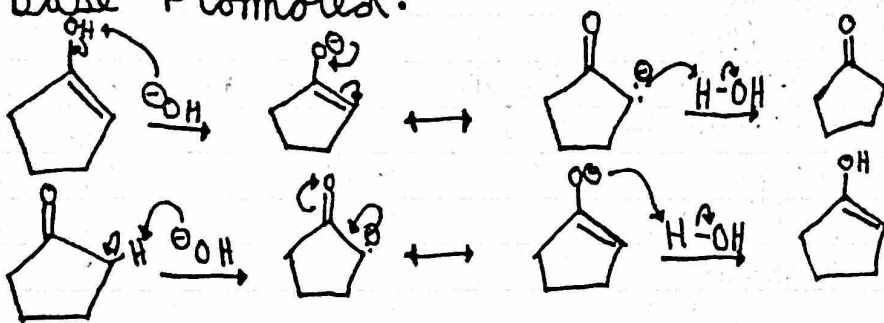
Enols:



Acid Catalyzed:



Base Promoted:



$pK_a$ 's:

- CC(=O)C 20
- CC(=O)C 17
- CC(=O)O 16
- CC(=O)CC 45
- CC(=O)CC(=O)C 9
- CC(=O)C([N+](=O)[O-])[N+](=O)[O-] 3.6
- CC(=O)COCC 23

a significant equilibrium exists

Issues & Concerns:

CC1CCCC1  $\xrightarrow{H^+ / OH^-}$  Racemized

CC(=O)C  $\xrightarrow{OH^-}$  CC(O)=C

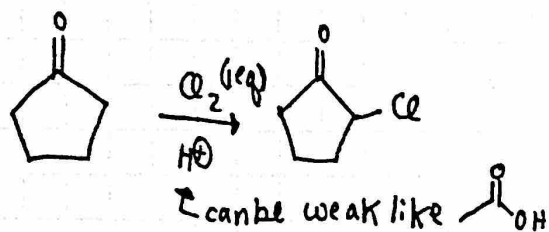
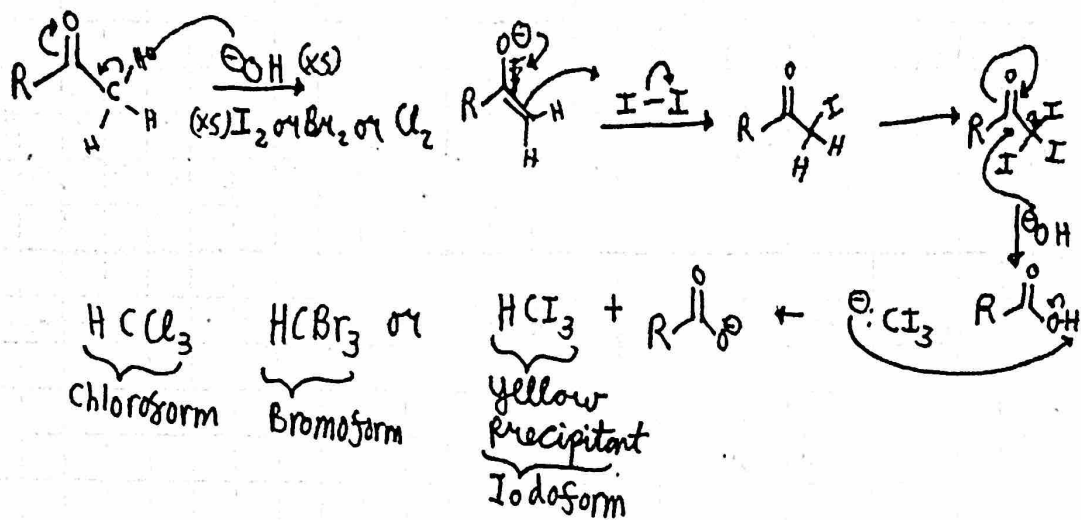
Stronger bases work too:

CC1CCCC1  $\xrightarrow{LDA}$  CC1=CCCC1 + CC(=O)C

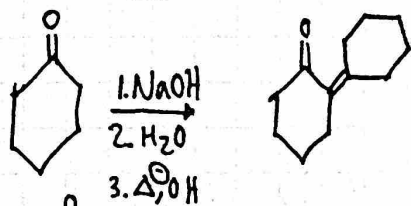
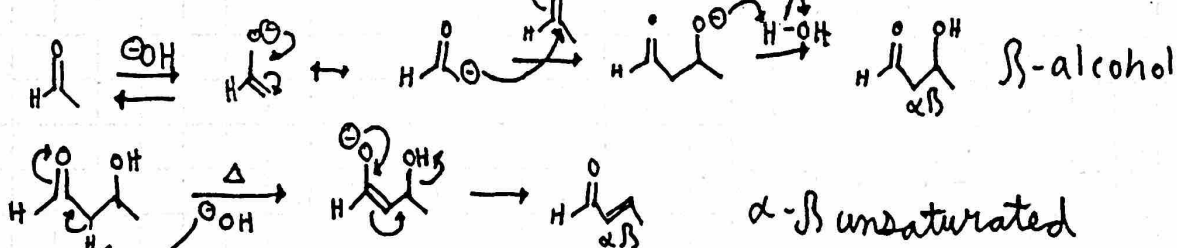
$pK_a 20$                        $pK_a 36$



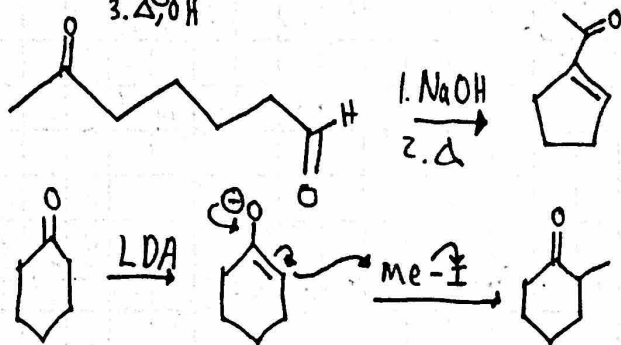
### The Haloform Test:



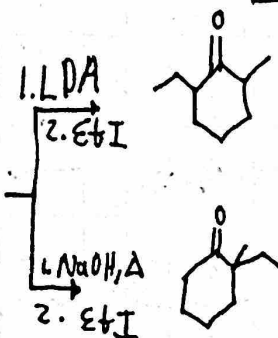
### Aldol Reaction: Aldehydes and Ketones



In more advanced classes Aldol Reactions are reversible.

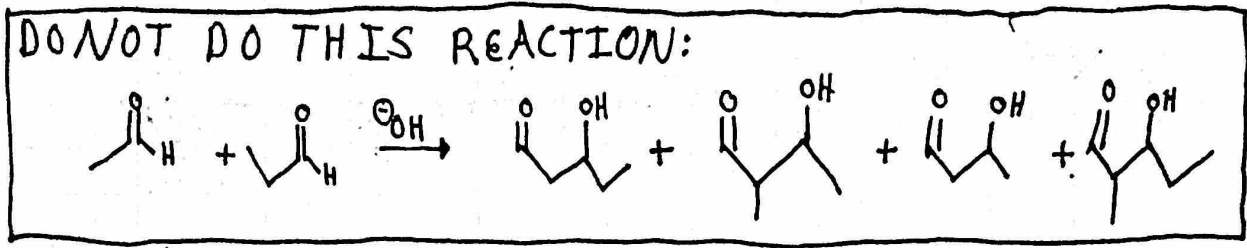


LDA: Less Substituted  
NaOH: More Substituted

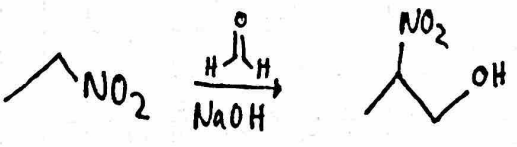
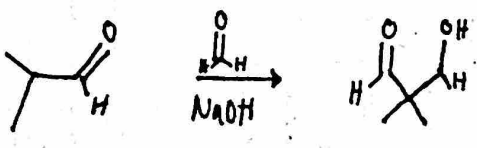
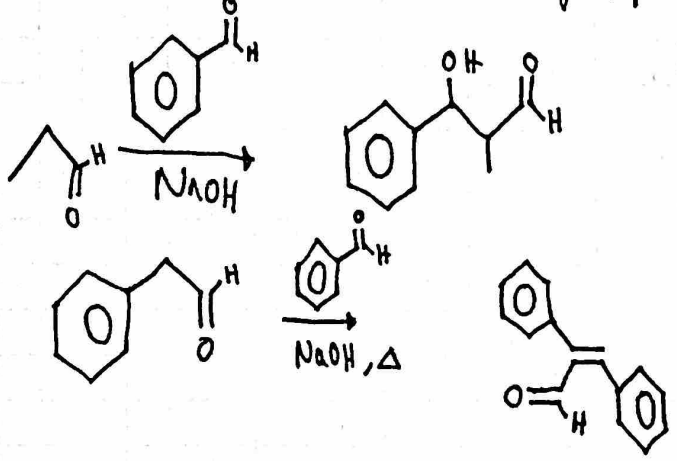


sterics.

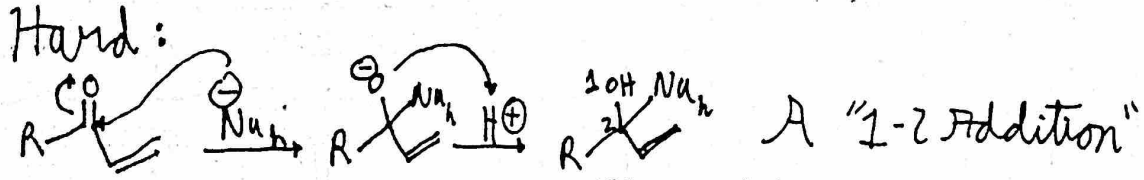
18 Aldol Reaction (Continued): Crossed Aldol



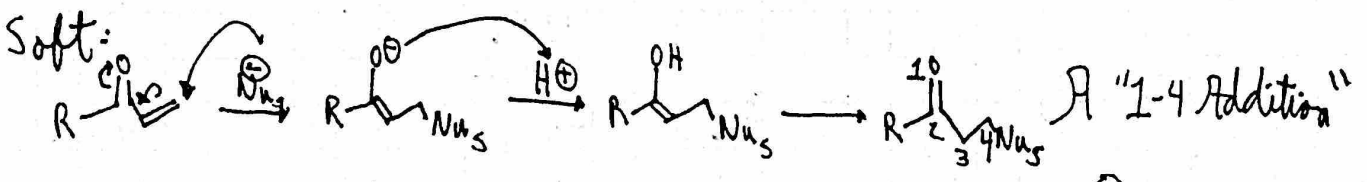
Can be limited to a single product if one has no  $\alpha$ -protons.



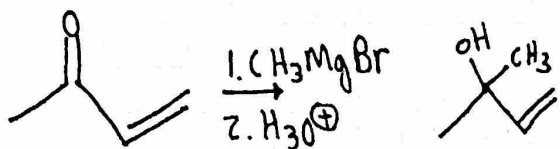
Where Nucleophiles Attack:



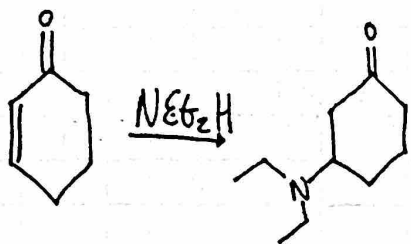
Nucleophiles: Hydrides, ~~Grignards~~ Grignards



Nucleophiles: 1° Amines, Gilman's, CN (generally), S-R



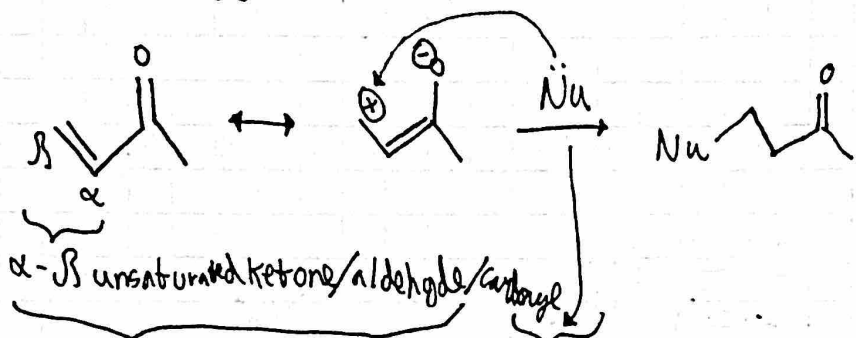
1,2-Addition



1,4-Addition

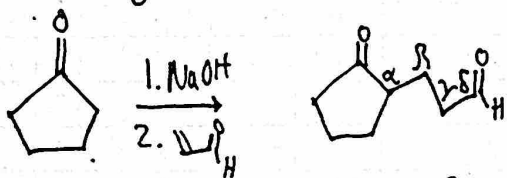
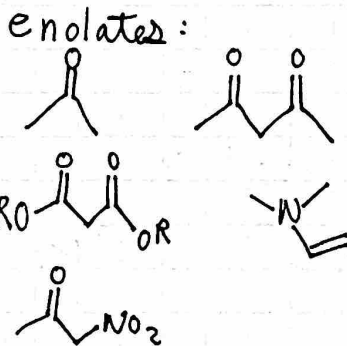
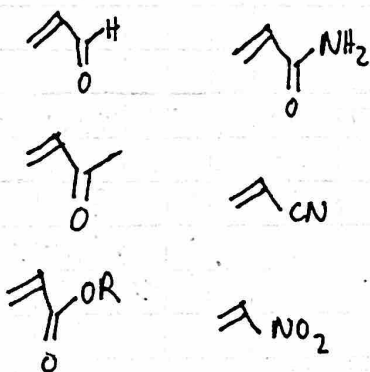
Note: if pH 4-5: imine

The Michael Reaction:

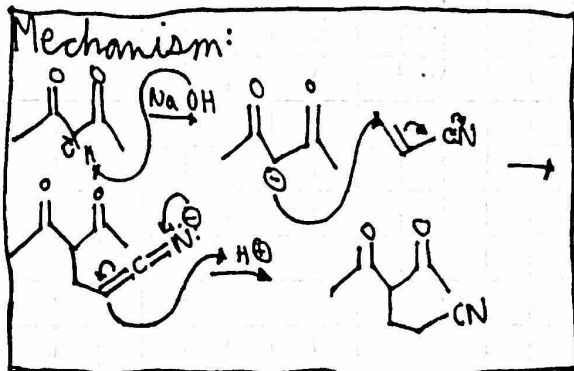
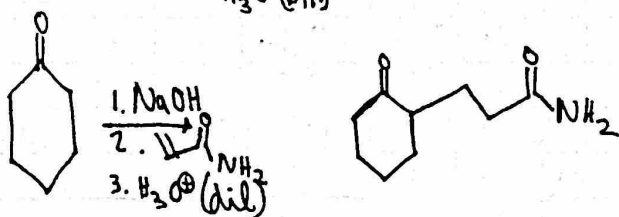
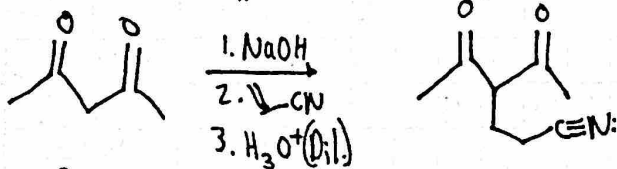


Michael Acceptors:

Michael Donors:

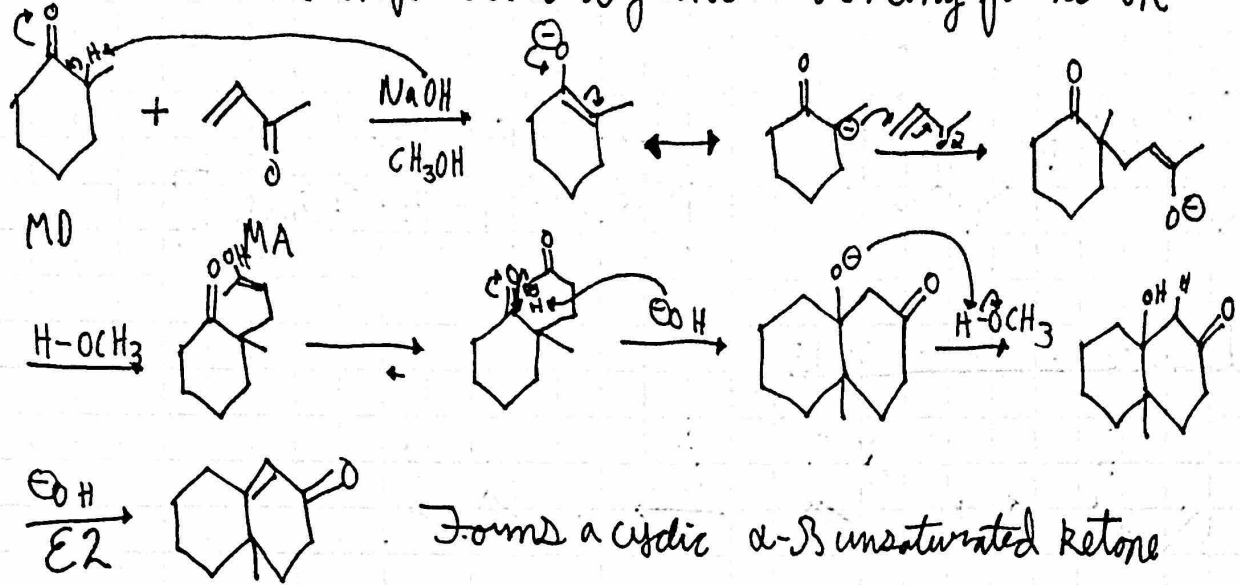


$\delta$ -addition

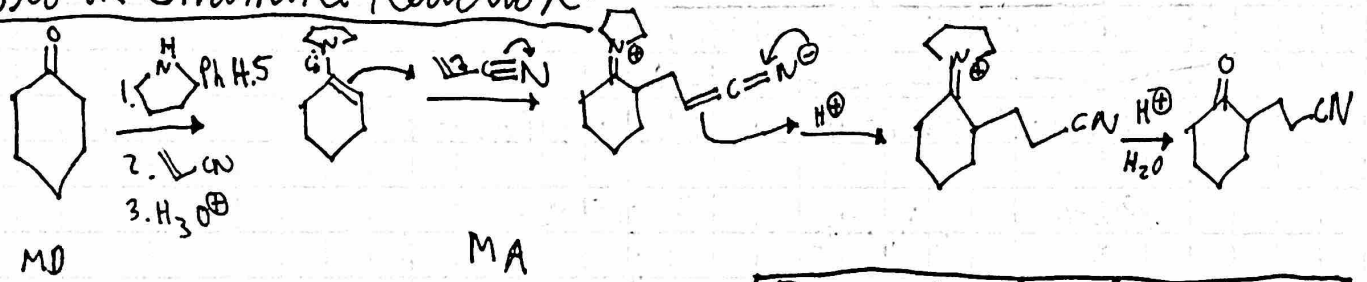


The Robinson Annulation:

A Michael reaction followed by an Aldol ring formation

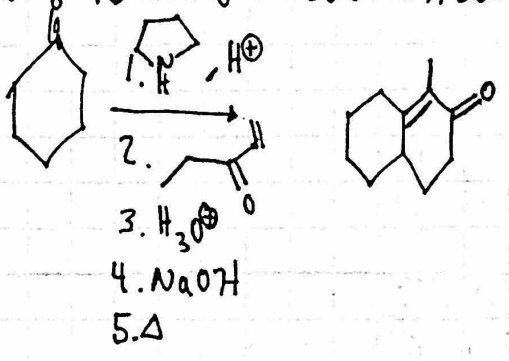


Stork Enamine Reaction:



Acidic Michael Addition

Stork Robinson Annulation:

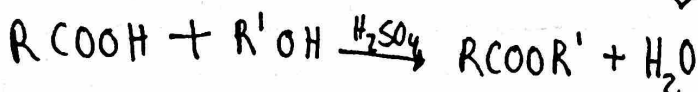
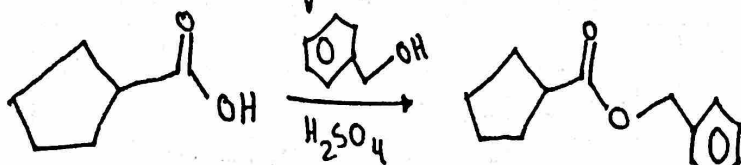


An interlude:  
Relative acidities:

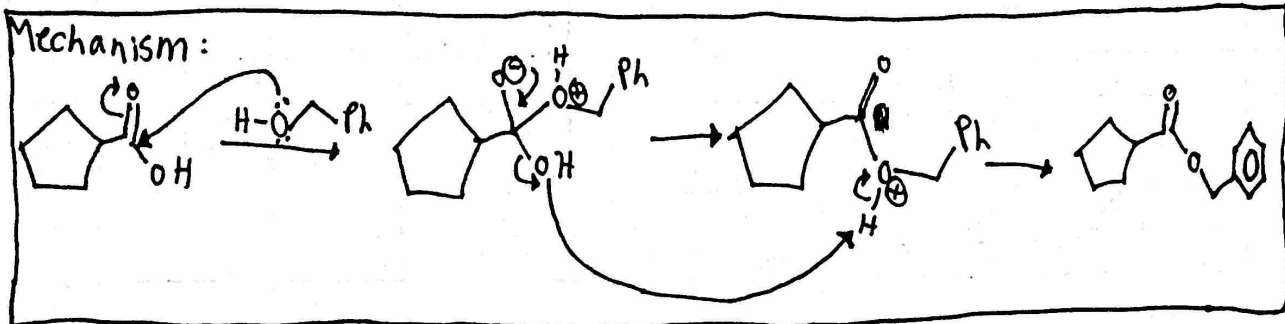
Strong	weak	strongest	<del>moderate</del> weak
pKa 5	16	< 5	25.5
moderate	weak	strong	
pKa 9	16		
Weak	moderate	weak	
pKa 2.5	13	16	

# Reactions of Carboxylic Acid Derivatives:

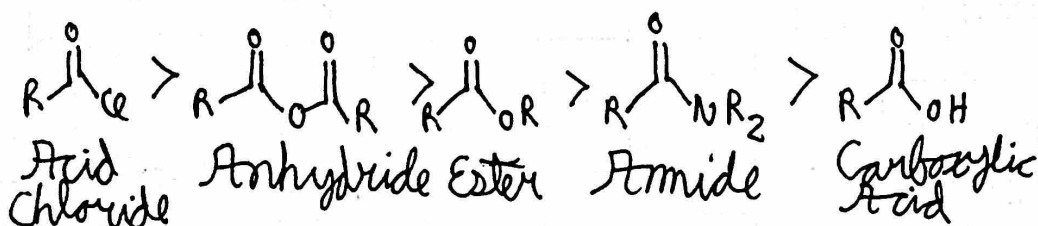
## Fischer Esterification:



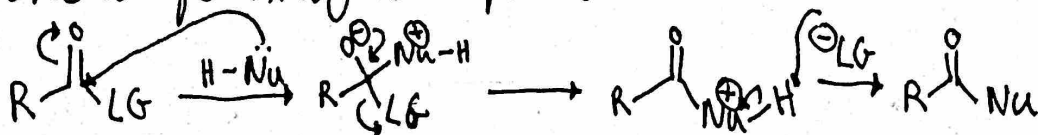
Mechanism:



## Relative Carbonyl Reactivity: (nucleophilic substitution)

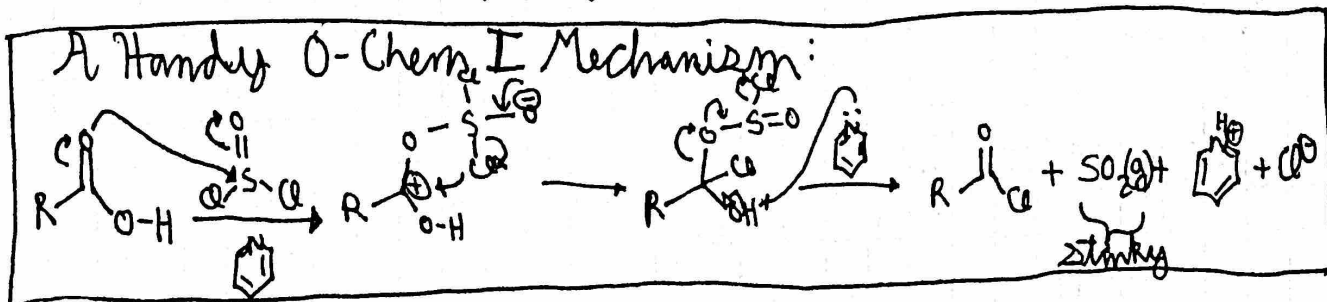


General form of nucleophilic substitution:

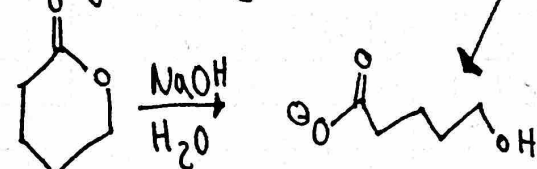
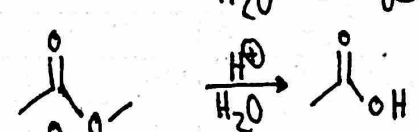
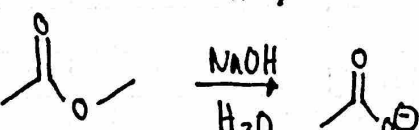
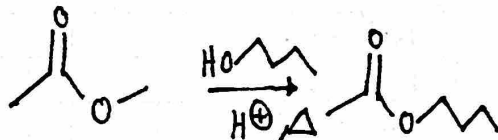
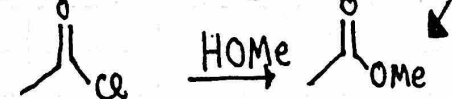
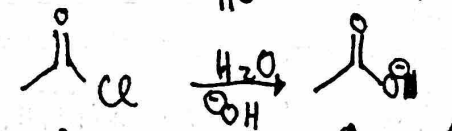
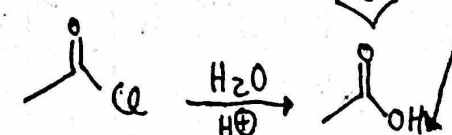
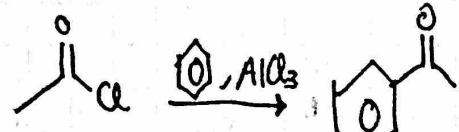
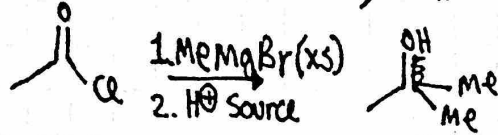
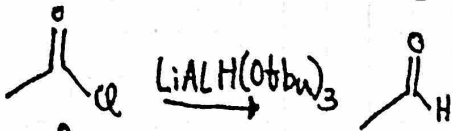
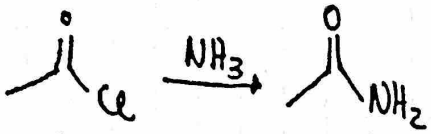


This reaction works when the substitution of LG with Nu forms a less reactive Carbonyl.  
 "The better nucleophile gets the  $\delta^+$ "

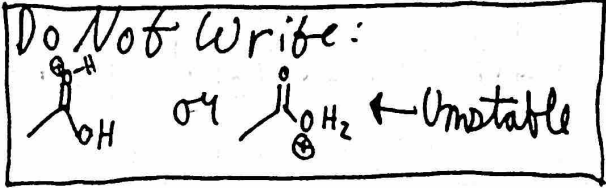
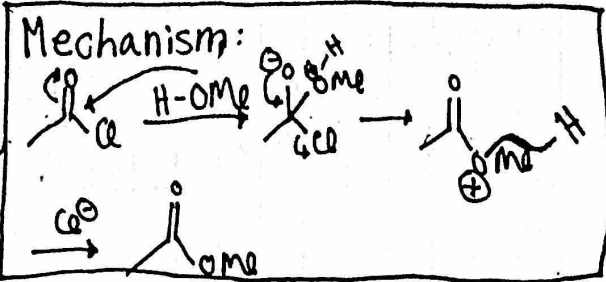
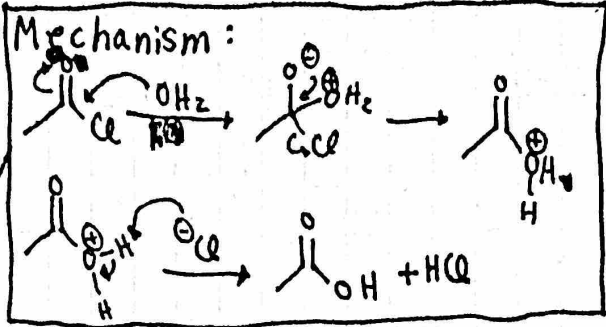
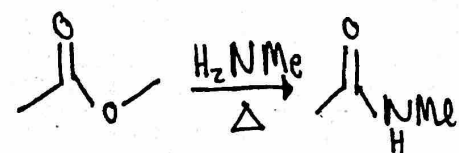
## A Handy O-Chem I Mechanism:



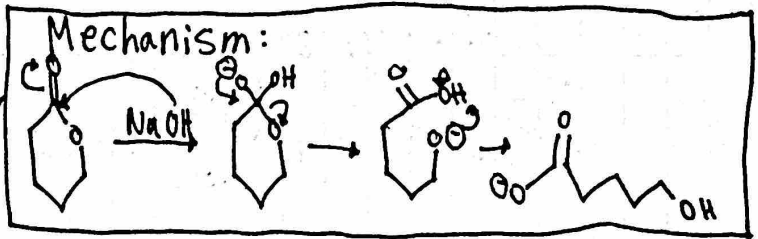
Reactions:

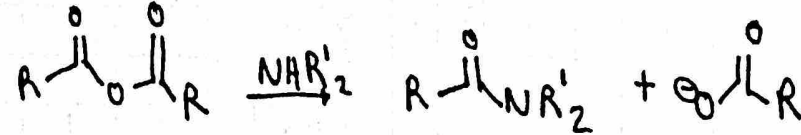
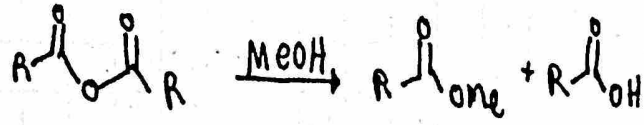
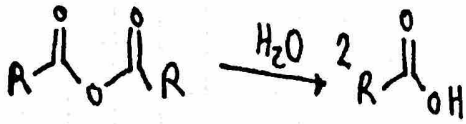


A lactone

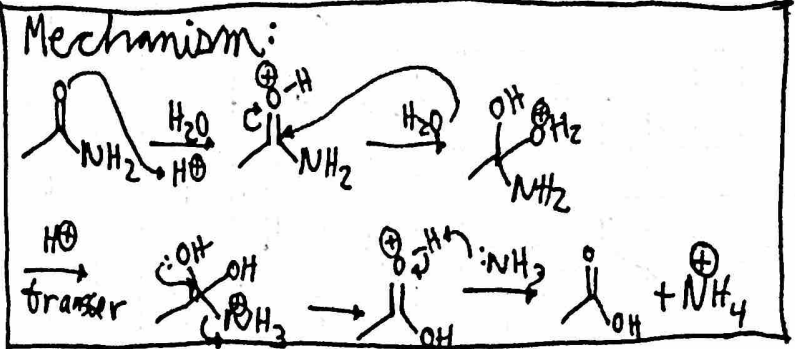
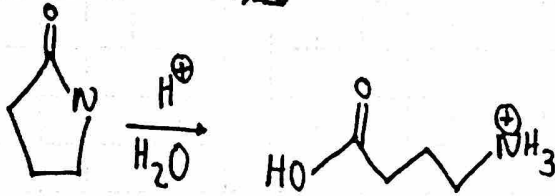
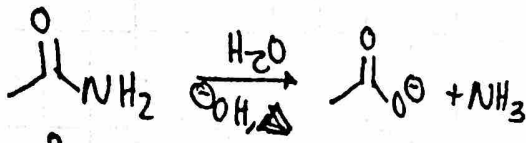
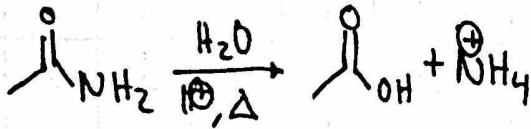


Higher BP added, Lower boils off

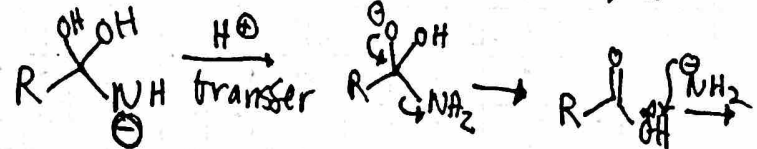
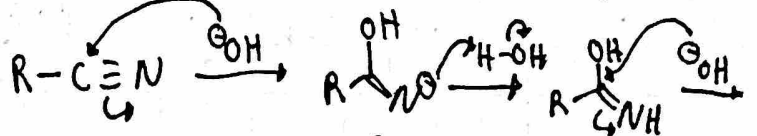
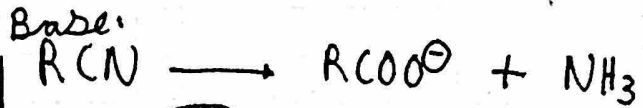
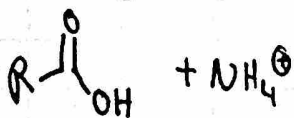
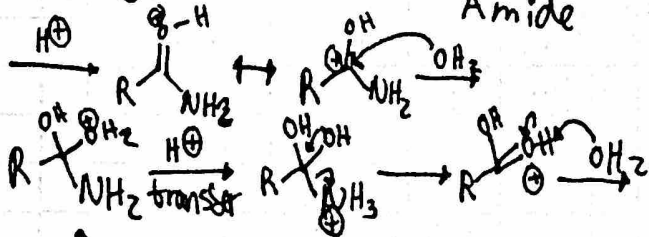
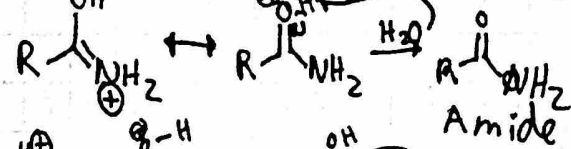
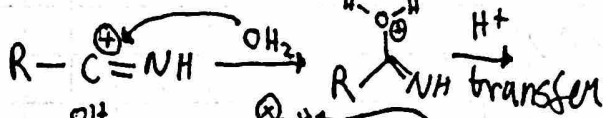
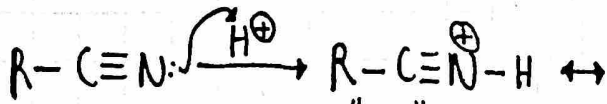
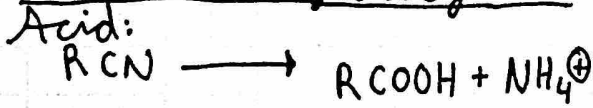




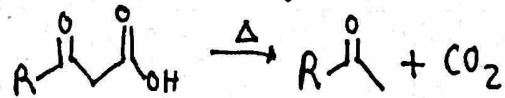
} if not symmetric a mixture of products is generated



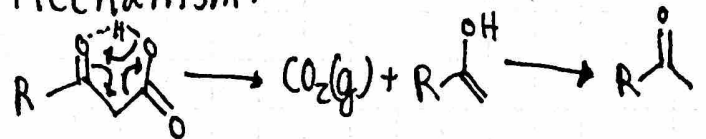
Nitrile Hydrolysis:



Decarboxylation of  $\beta$ -ketoacids:

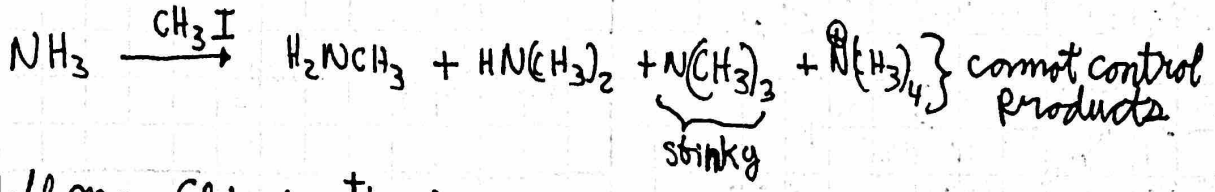
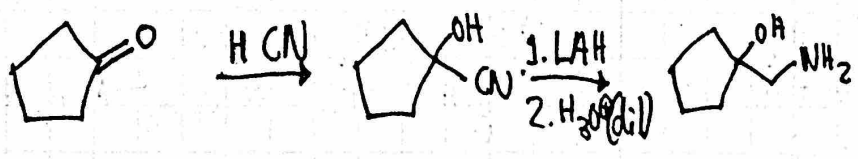
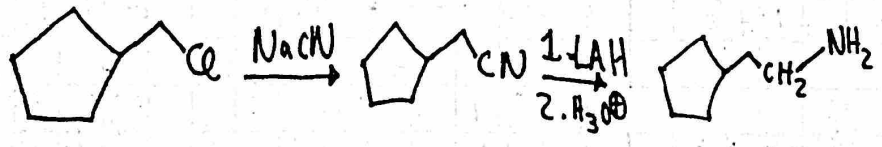
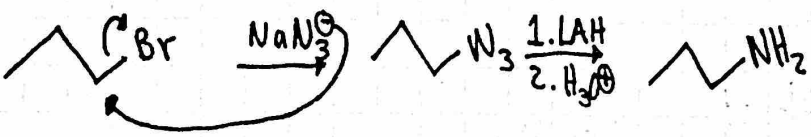
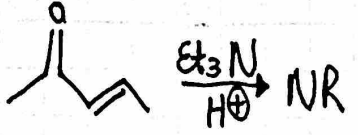
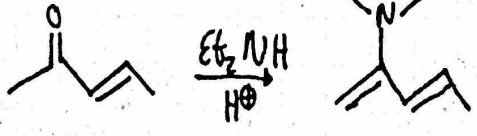
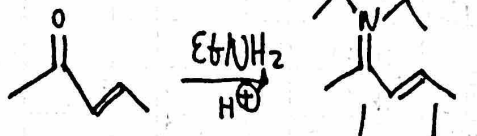
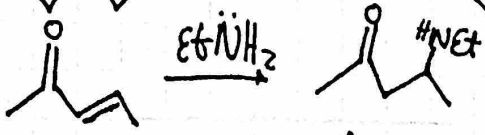
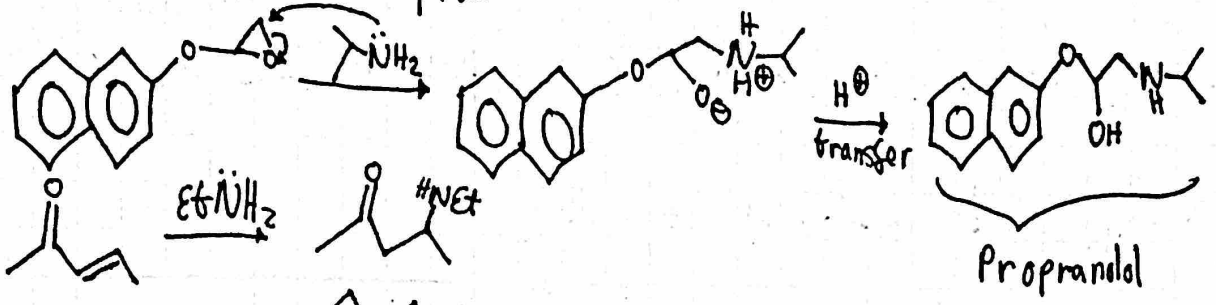


Mechanism:

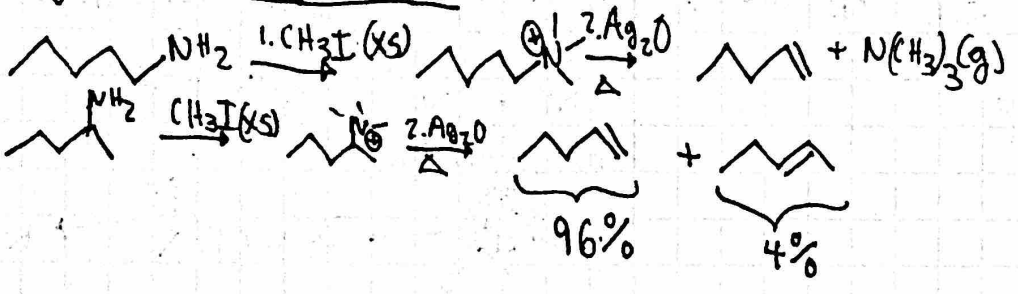


Amines:

amines are nucleophiles

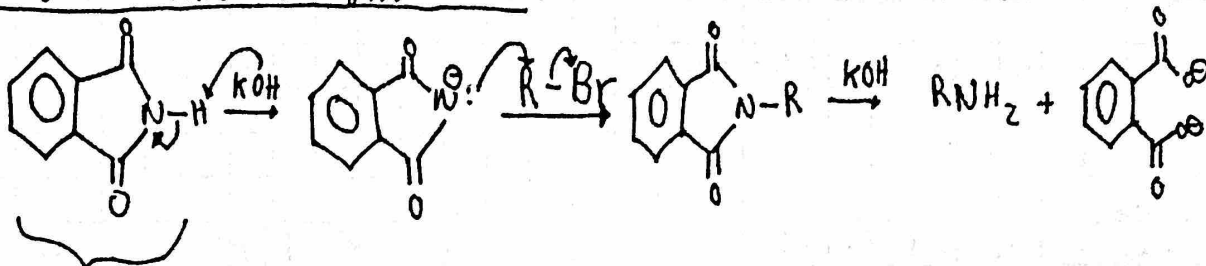


Hoffman Elimination:



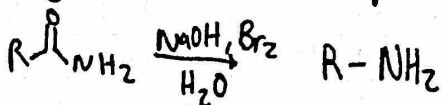


Gabriel Amine Synthesis:

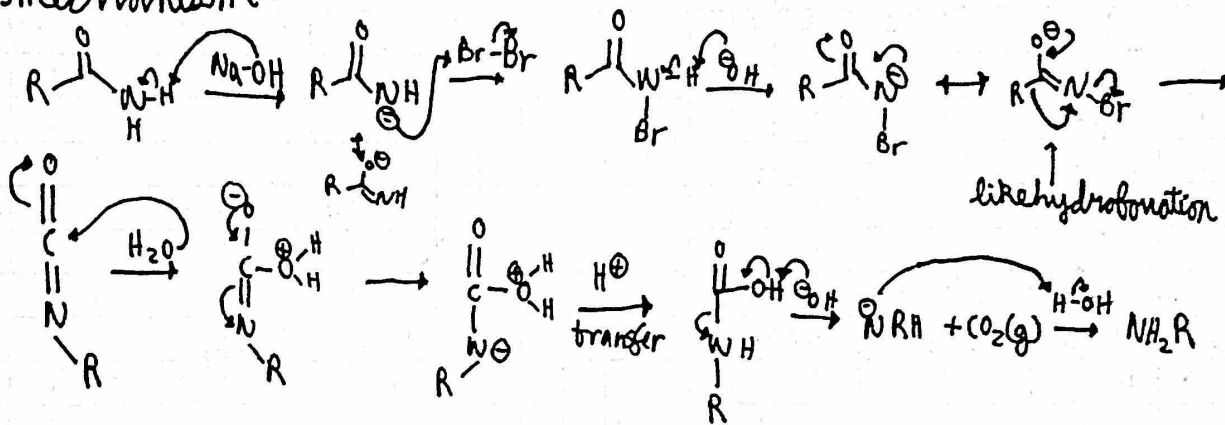


Phthalimide

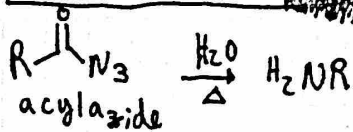
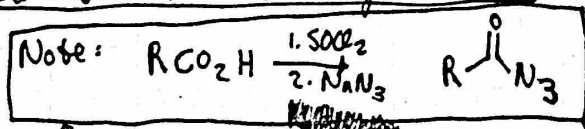
Hofmann Rearrangement:



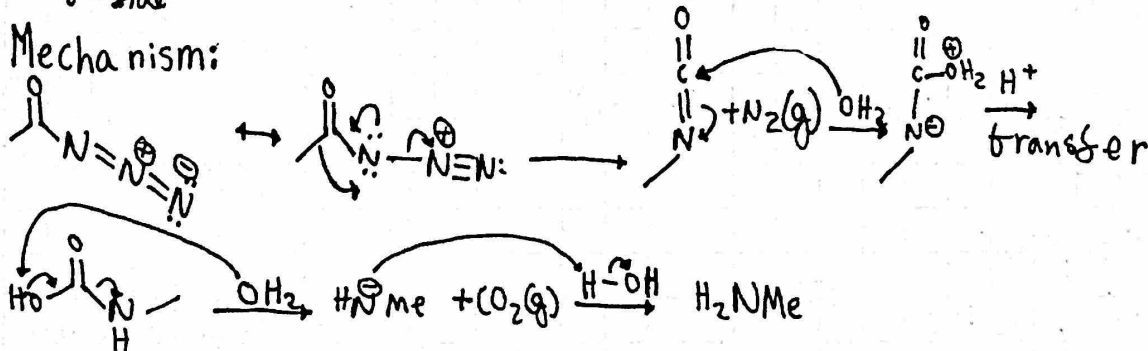
Mechanism:



Curtius Rearrangement:



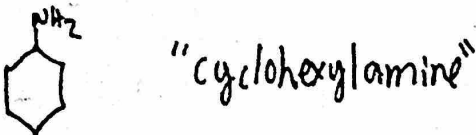
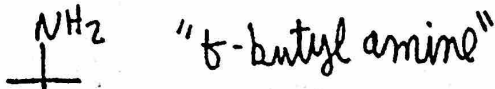
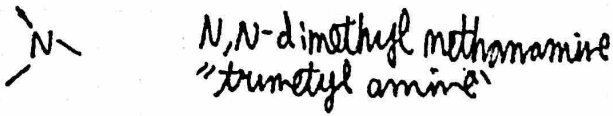
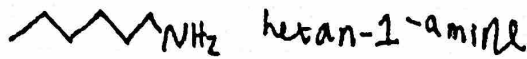
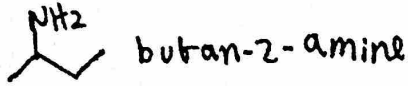
Mechanism:



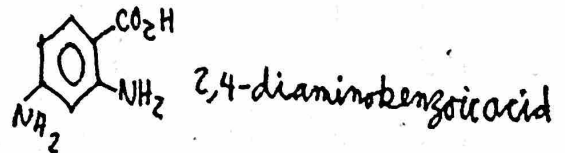
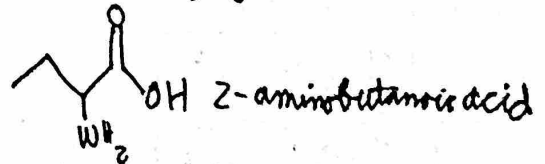
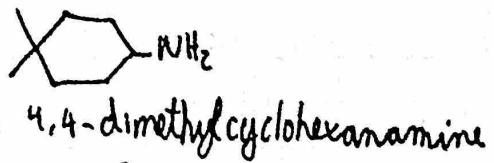
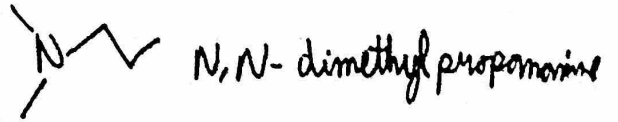
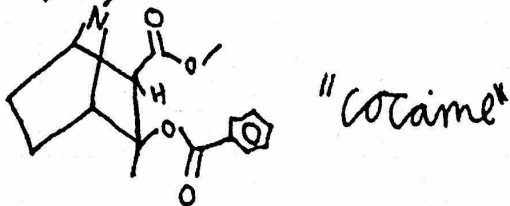
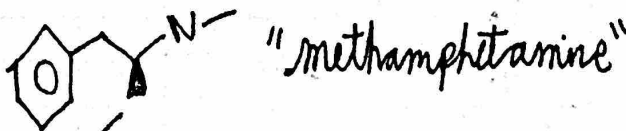
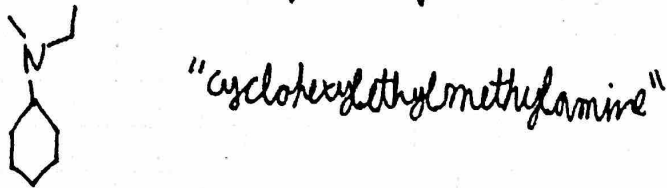
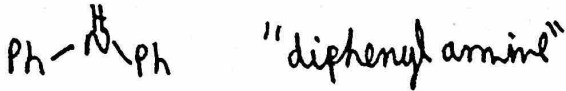
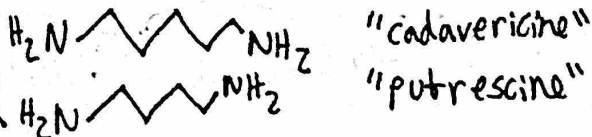
Nomenclature of Amines:

Common names more frequently used than IUPAC

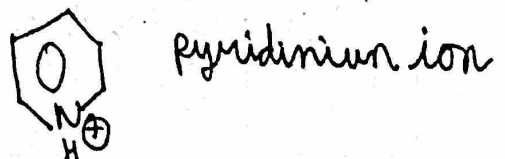
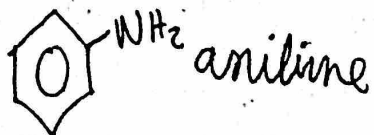
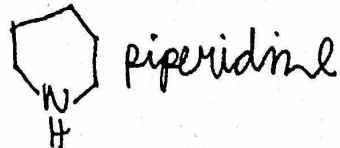
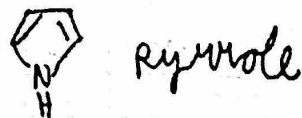
alkane  $\rightarrow$  alkanamine



very good nucleophiles

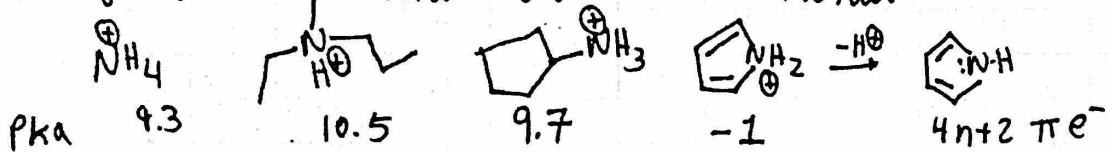


N-heterocyclics:

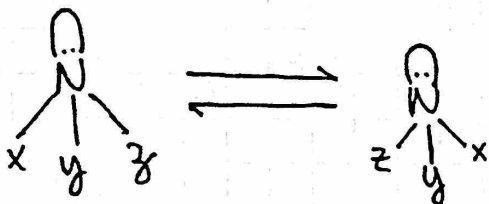


### Basicity of amines:

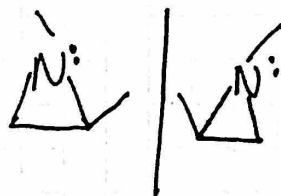
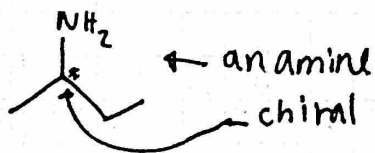
alkylated amines are more basic than ammonia



### Chirality of amines:

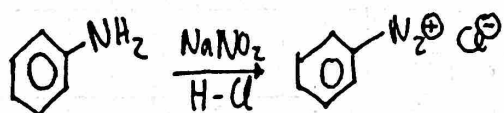


$e^-$  quantum tunnel → does not retain chirality



aziridine: chiral, ring sterically inhibits quantum tunneling

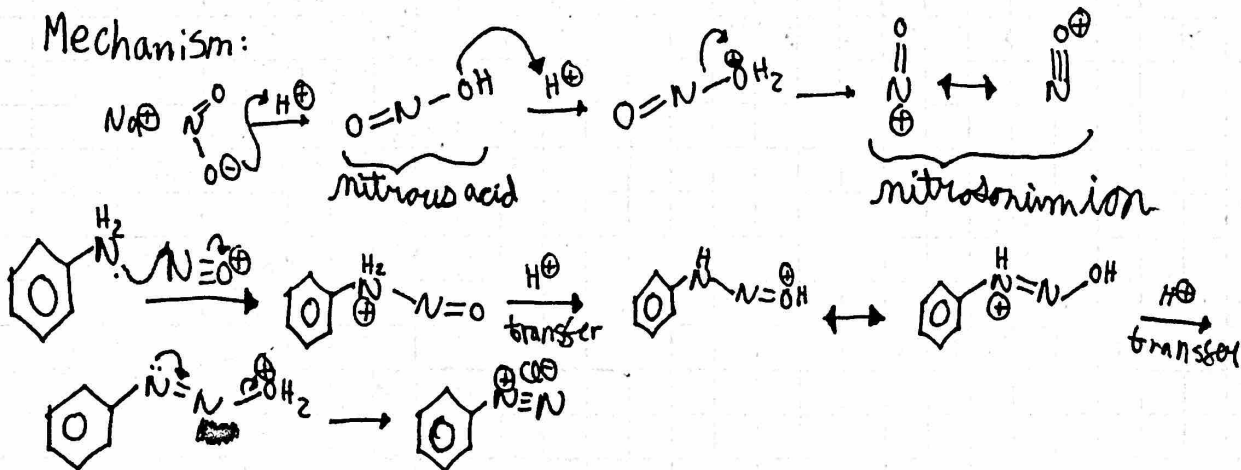
### Sandmeyer Reaction:

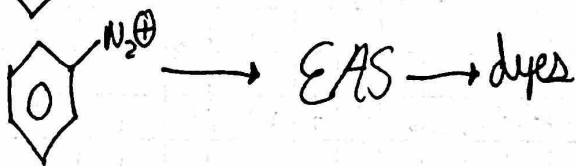
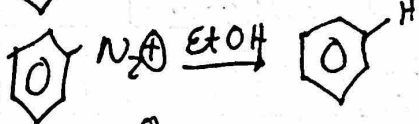
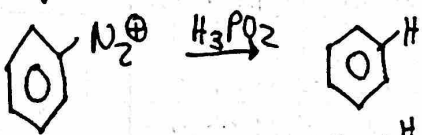
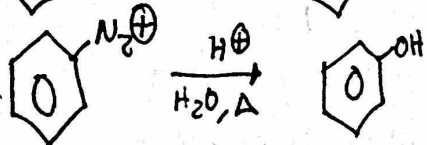
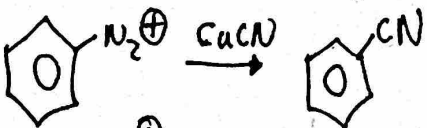
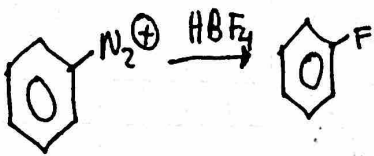
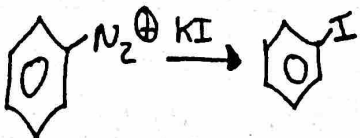
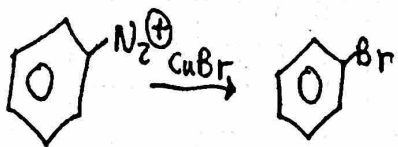
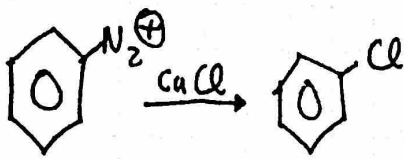


Note difference between:  
 sodium nitrite  $\text{NaNO}_2$  & sodium nitrate  $\text{NaNO}_3$

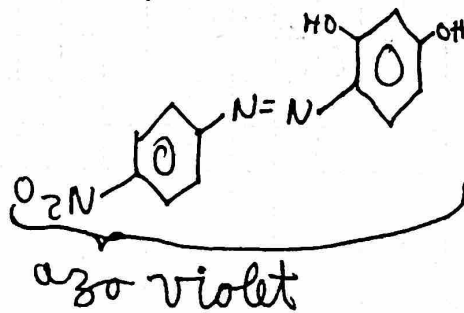
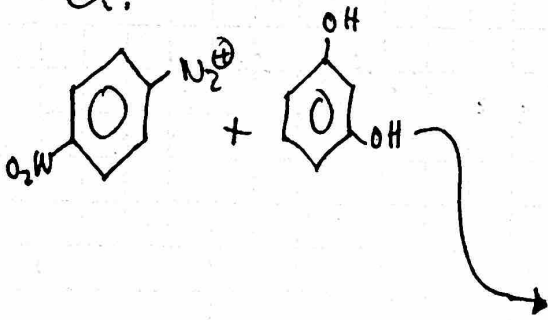
diazonium ion

Mechanism:





ex.



### Nucleophilic Aromatic Substitution

1.  $S_NAr$

O=[N+]([O-])c1ccc(cc1)[N+]#N  $\xrightarrow{NaOH}$  Oc1ccc(O)cc1

EWG LG EWG EWG

2+ EWG

Fc1ccc(cc1)[N+]#N  $\xrightarrow{NaOH}$  NR ; No resonance stability

lots of resonance

Fc1ccc(cc1)[N+]#N  $\xrightarrow{OH^-}$  [O-]c1ccc(cc1)[N+]#N  $\rightarrow$  Oc1ccc(O)cc1

2.

Oc1ccc(O)cc1  $\xrightarrow[2. H_3O^+, \text{High Pressure}]{1. NaOH}$  Oc1ccc(O)cc1

c1ccc(cc1)[N+]#N  $\xrightarrow[NH_3]{NaNH_2}$  Nc1ccc(cc1)[N+]#N + Nc1ccccc1

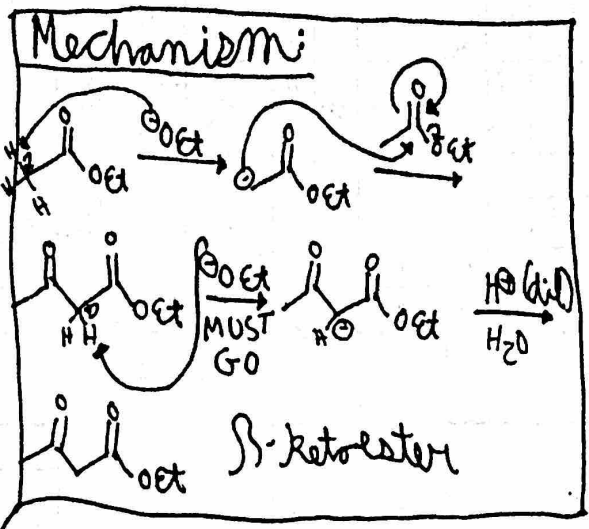
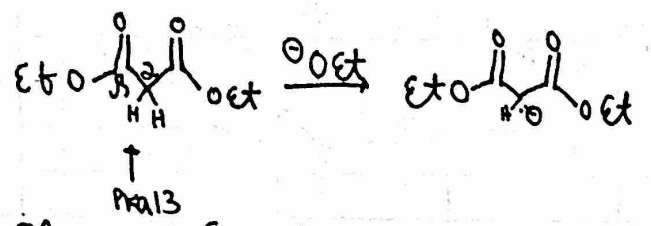
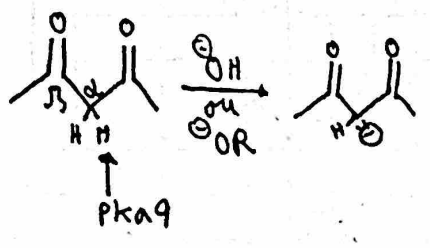
50 : 50

benzyne intermediate

3.

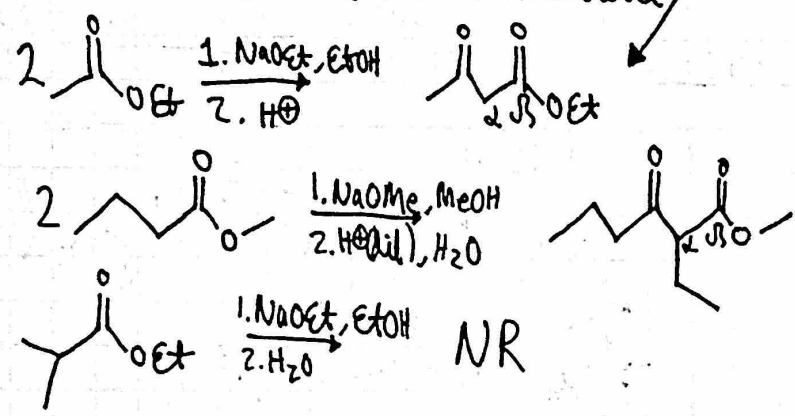
O=[N+]([O-])c1ccc(cc1)[N+]#N  $\rightarrow$  [O+]c1ccc(cc1)[N+]#N  $\xrightarrow{Na}$  [O+]c1ccc(cc1)Nu

# β-Carbonyl Reactions:

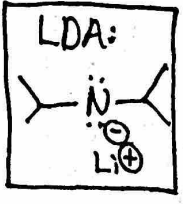
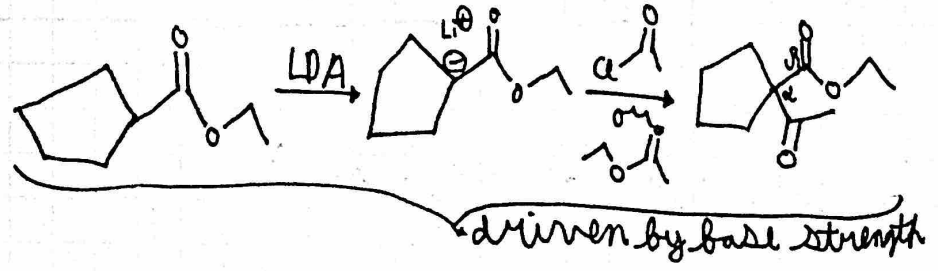


## Claisen Condensation:

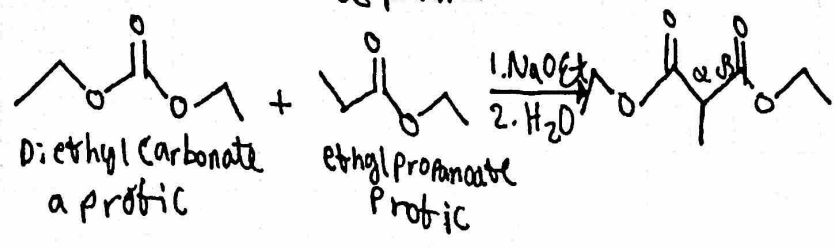
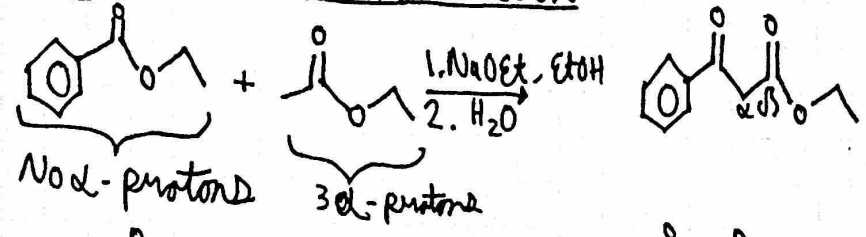
driven by stable intermediate



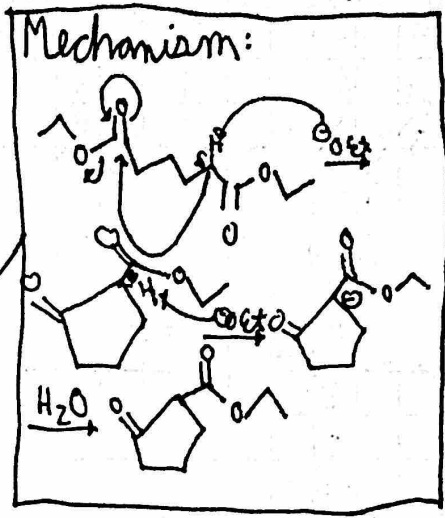
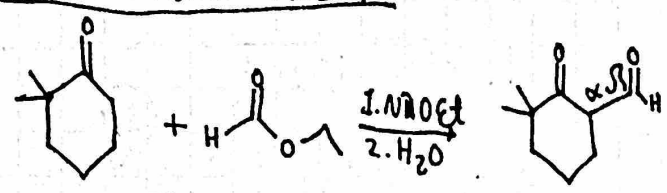
Note:  
Claisen cannot take place with alkoxide ion if only 1 proton is available. The necessary intermediate cannot occur. If LDA is used the reaction will proceed.



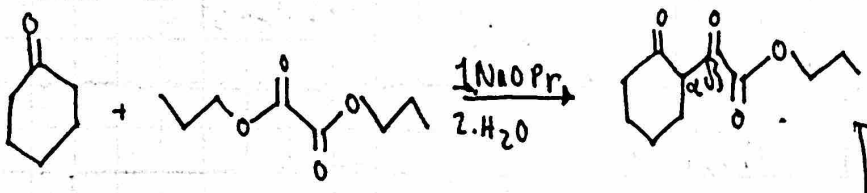
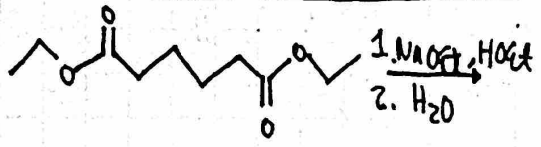
## Crossed Claisen Reaction:



Mixed Aldol-Claisen:

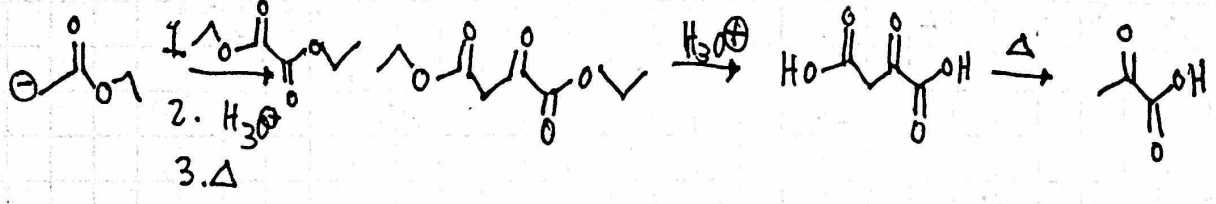
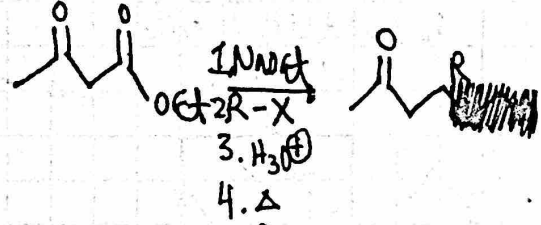
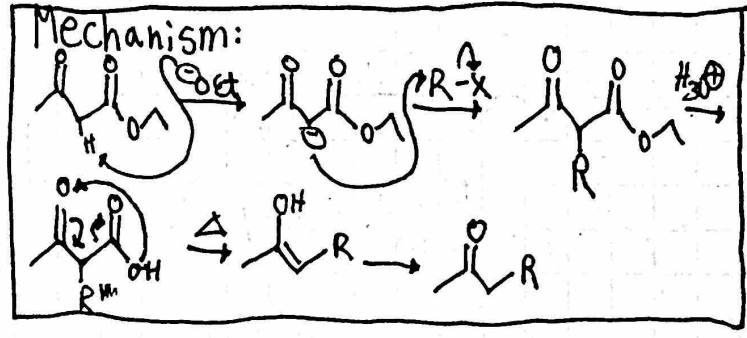
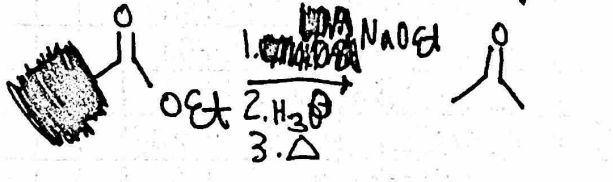


Dieckmann Condensation (intermolecular Claisen):

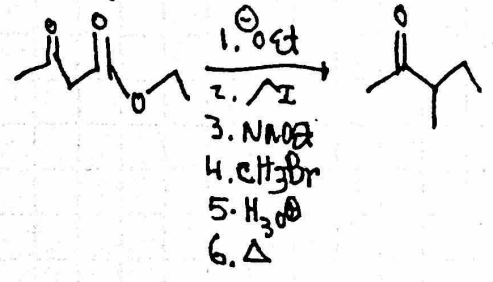


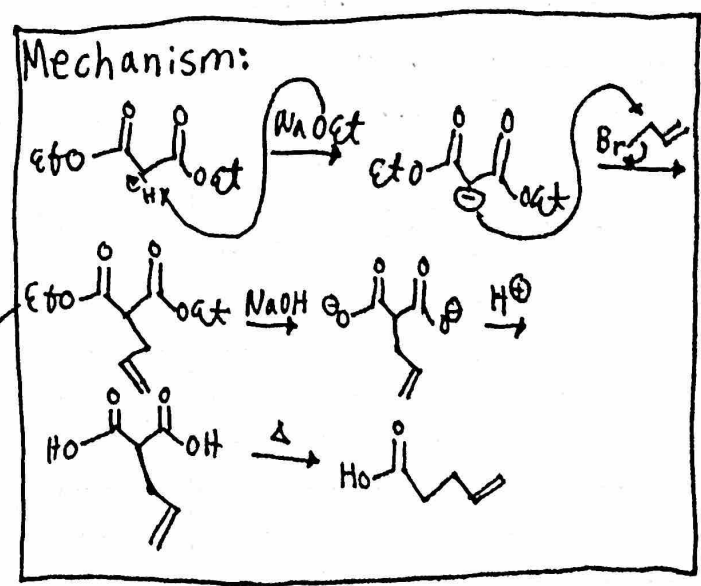
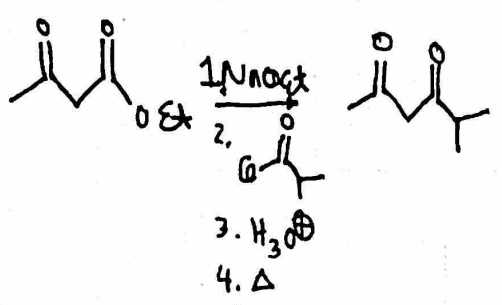
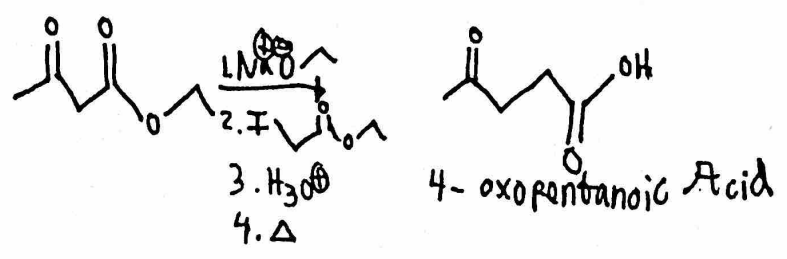
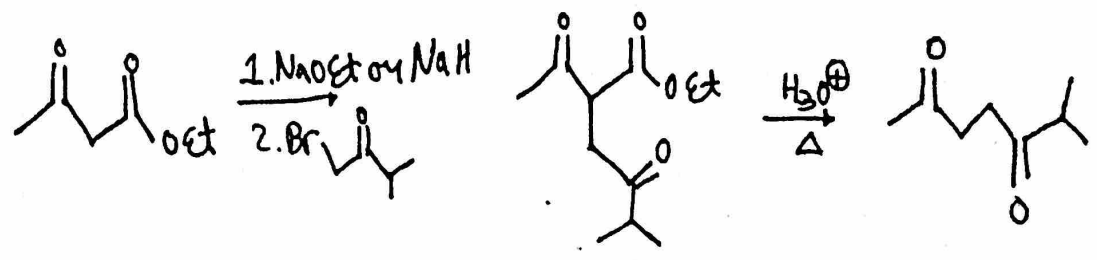
Note: Less substituted Carbanions are more stable

Acetoacetic Ester Synthesis:

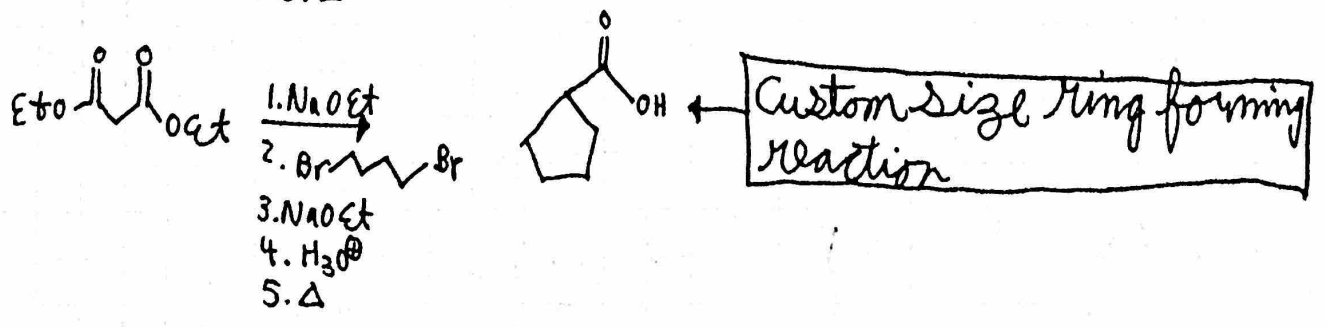
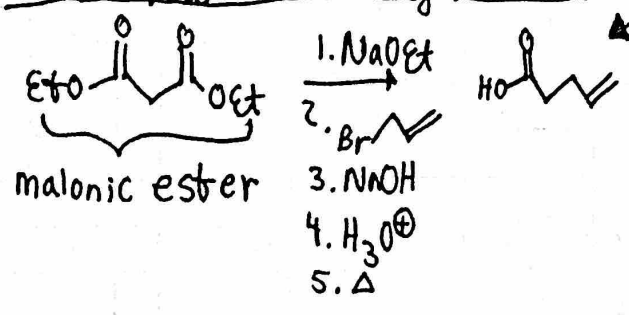


Methyl ketones:

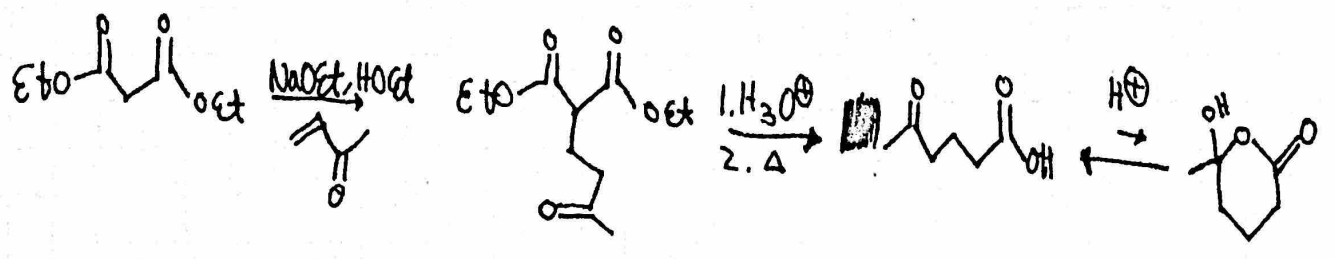


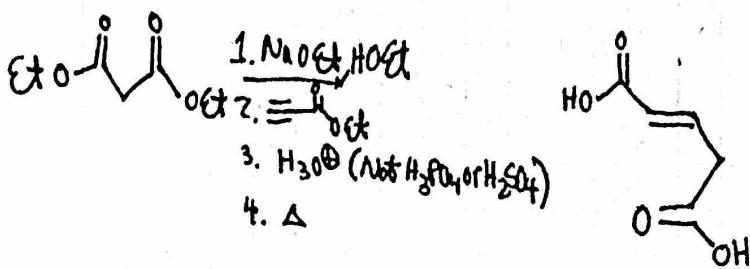


Malonic Ester Synthesis:



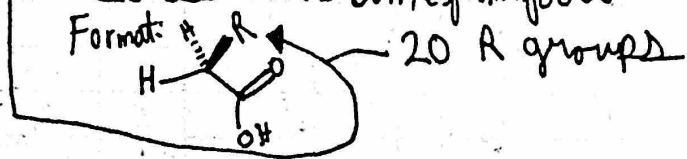
Michael Version of M E S:





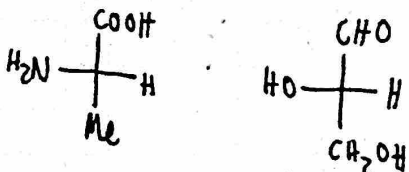
Amino Acids:

20 standard, many rare amino acids.  
 ↳ 10 essential come from food



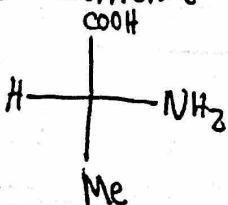
A rare amino acid:  
C[C@H](O)C(=O)O forms ether in plants

All L-amino acids: (All s except cysteine)



← Fischer Projections

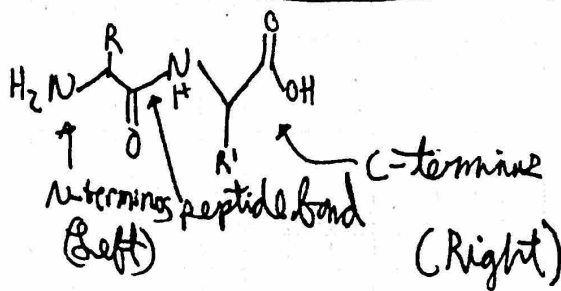
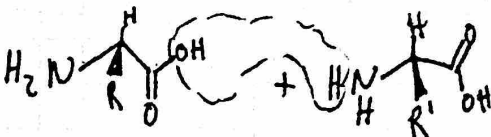
L-alanine L-glyceraldehyde



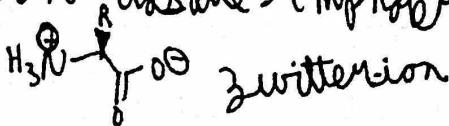
D-alanine (unnatural)

Peptides:	
Mono-	1
di-	2
tri-	3
oligo-	4-15
Poly-	16+
Protein	6000-40,000,000 amu

constituents → 5000 amu

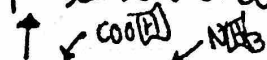


Amino acids are Amphoteric:



What is protonated depends on pH

PI is isoelectric point (no charge = 0)



$\frac{pK_{a1} + pK_{a2}}{2}$       or if diacid group is

acidic or basic replace opposite in formula.

Misc. Data:

- all are soluble in water
- extra polar
- MP > 200°C
- Less acidic than COOH
- Less basic than NH<sub>2</sub>