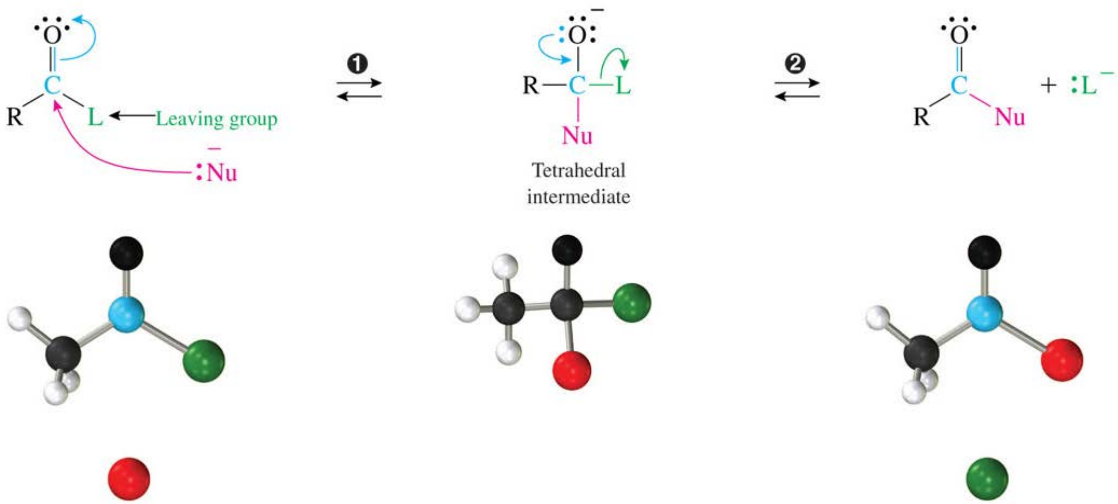
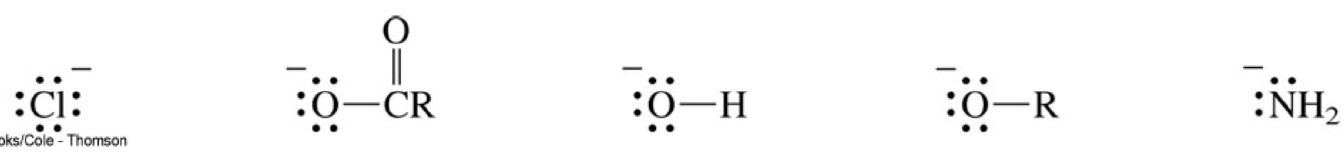
Chapter 19
Substitution at the Carbonyl Group

Substitution at Carbonyl Group

- Nucleophilic addition: RDS
- Tetrahedral mechanism: SP3-hybridized intermediate



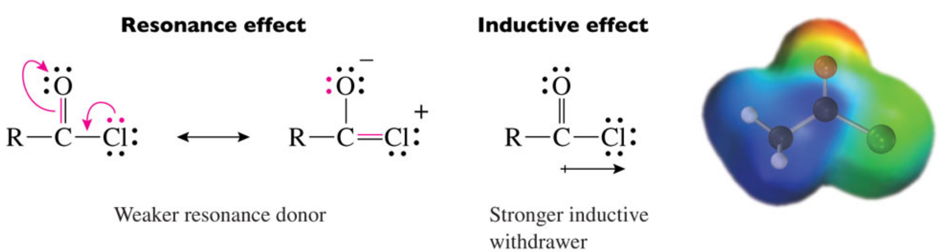
Leaving group

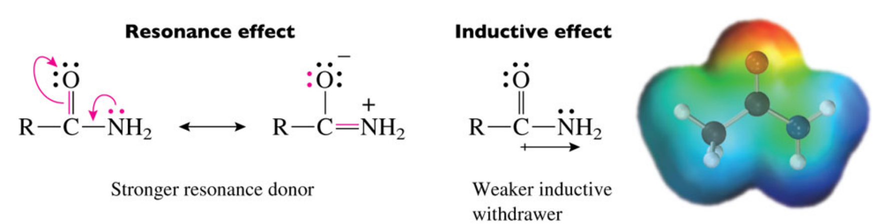


Too basic to act as leaving groups in the S_N2 reaction

Reactivity

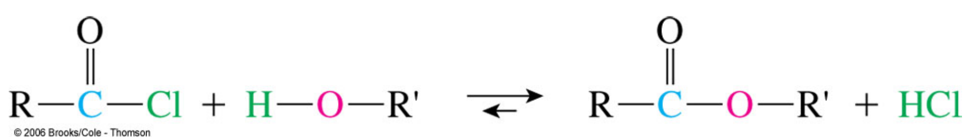
- Steric effects: slowed by steric hindrance
- Inductive effects
  - EWG → mole electrophilic carbonyl → increase the rate
  - EDG → decrease the rate
- Resonance effects
  - Resonance : electron-donating group → decrease the rate
- Effect of LG
  - Weaker bases: products are favored at equilibrium





Reactivity Scale for Carbonyl Compounds

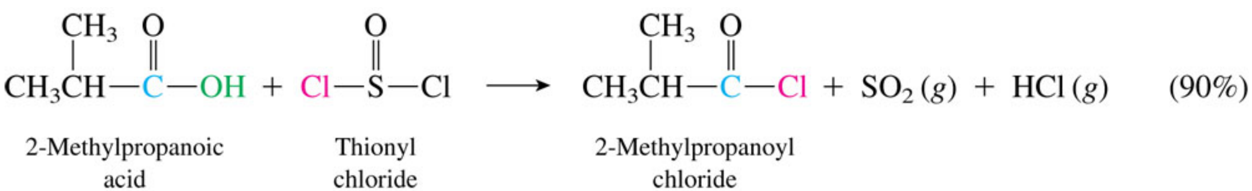
Compound		Structure	Leaving Group	Comment	
Most reactive compound	Acyl chloride	$R-C(=O)-Cl$	Cl^-		Less favored at equilibrium
	Anhydride	$R-C(=O)-O-C(=O)-R$	$^-O-C(=O)-R$		
	Aldehyde	$R-C(=O)-H$		First step only	
Increasing reaction rate	Ketone	$R-C(=O)-R'$		First step only	Increasing equilibrium constant
	Ester	$R-C(=O)-O-R'$	$^-O-R'$	Esters and acids are very similar in both rate and equilibrium position	
	Acid	$R-C(=O)-O-H$	^-O-H		
	Amide	$R-C(=O)-NH_2$	$^-NH_2$		
Least reactive compound	Carboxylate anion	$R-C(=O)-O^-$	O^{2-}	Poor leaving group; seldom leaves	More favored at equilibrium

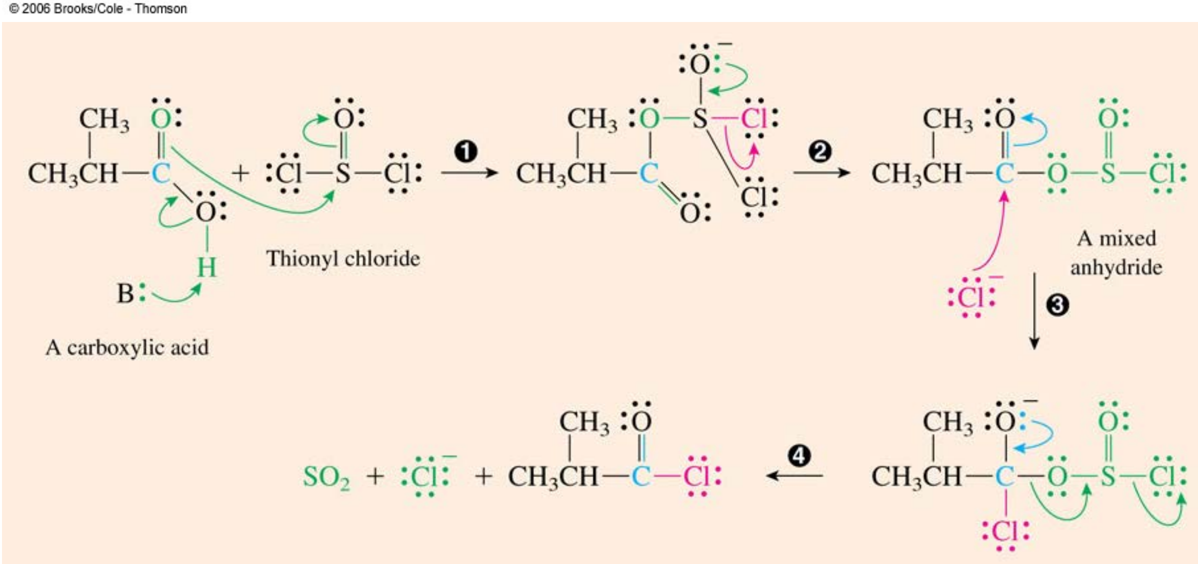


Lower on the reactivity scale

Preparation of Acyl Chlorides

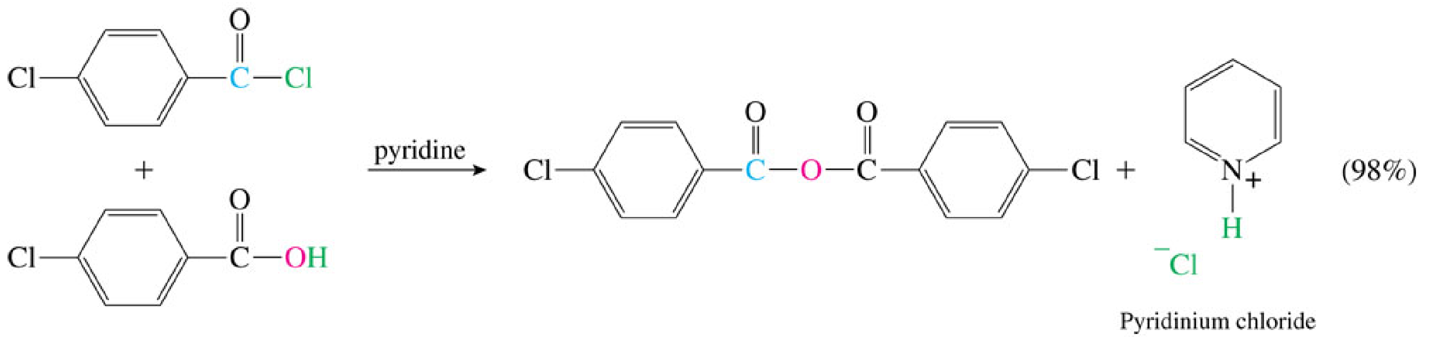
- Acyl (acid) chlorides: RCO-Cl (chloride)
  - Most reactive: to prep other derivatives
  - $SOCl_2$, PCl_3, PCl_5



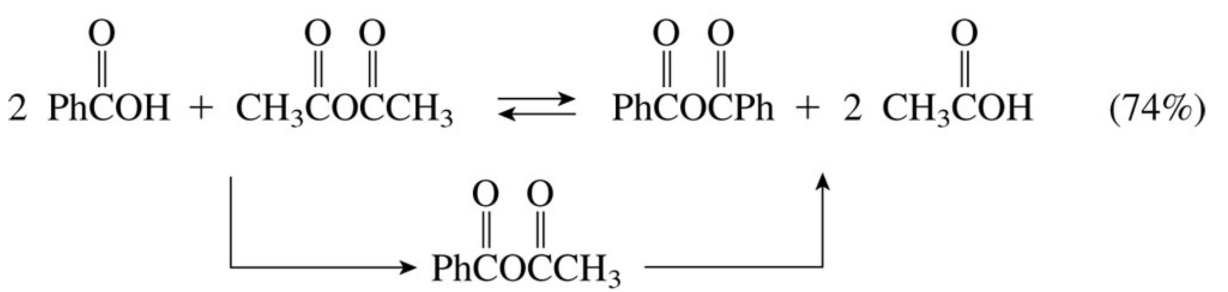


Preparation of Anhydrides

- From acyl chlorides: with a base

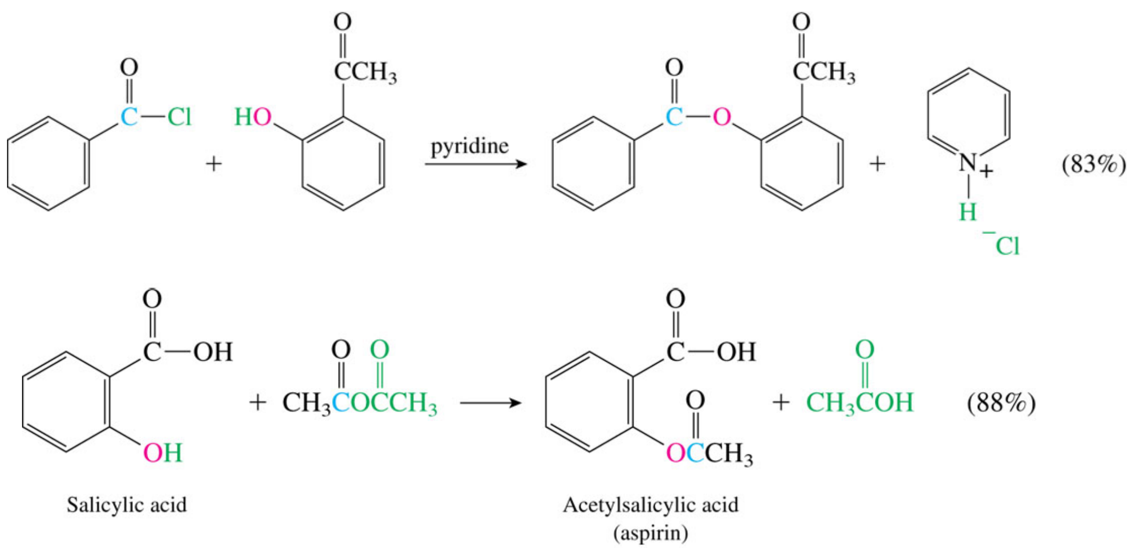


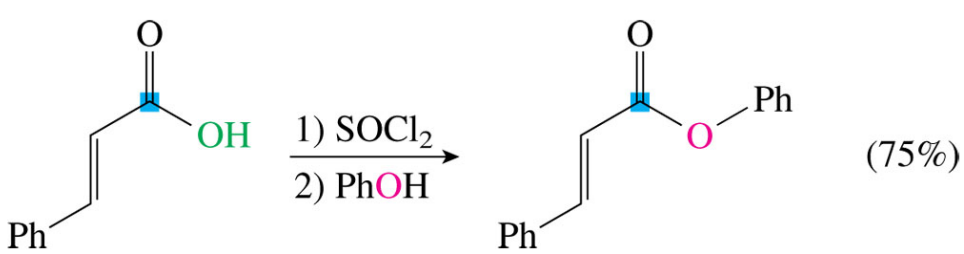
- Carboxylic acid with other anhydride : Mixed ahnydride
  - Removal of acetic acid by distillation



Preparation of Esters

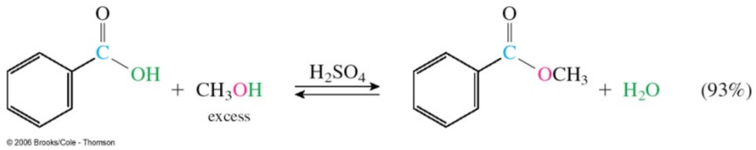
- Alcohol with either acyl chloride or anhydride

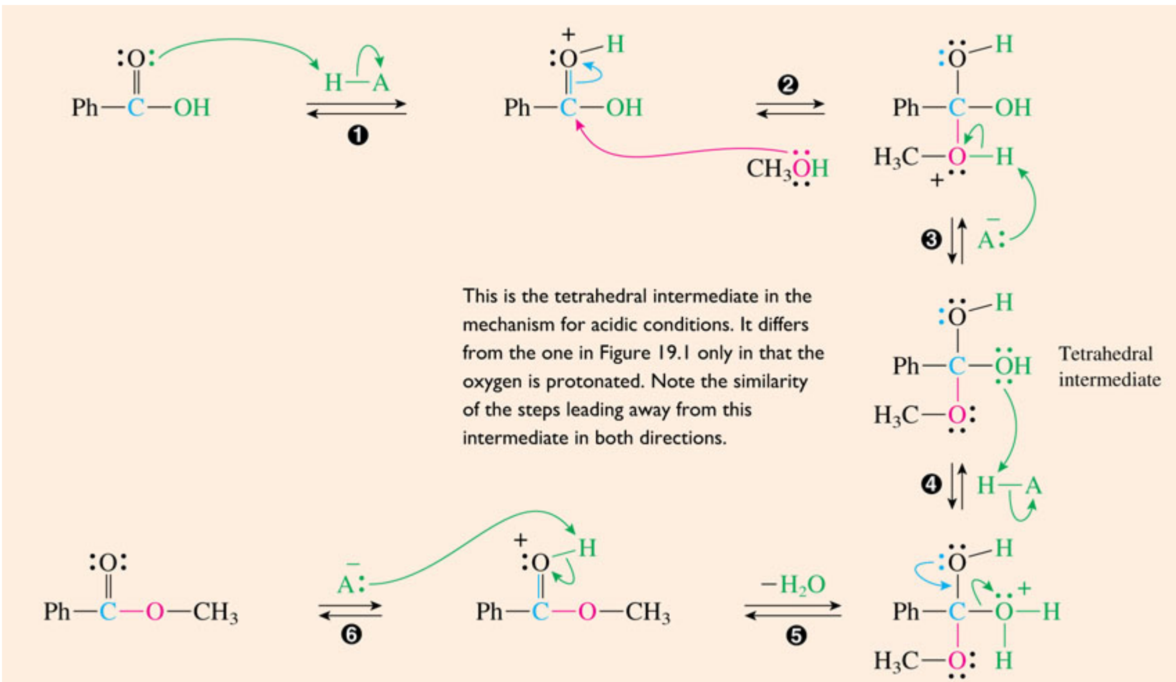




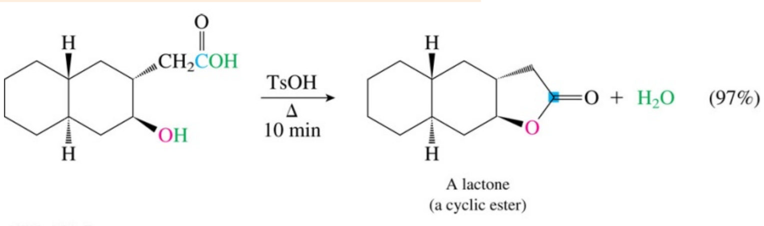
Preparation of Esters

- Fischer esterification: acids & alcohol
  - mechanism: acid catalyst/equilibrium





  - lactones: cyclic esters

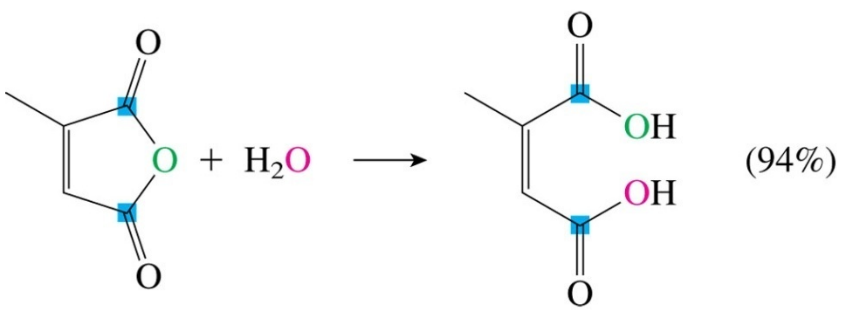


Preparation of Carboxylic Acids

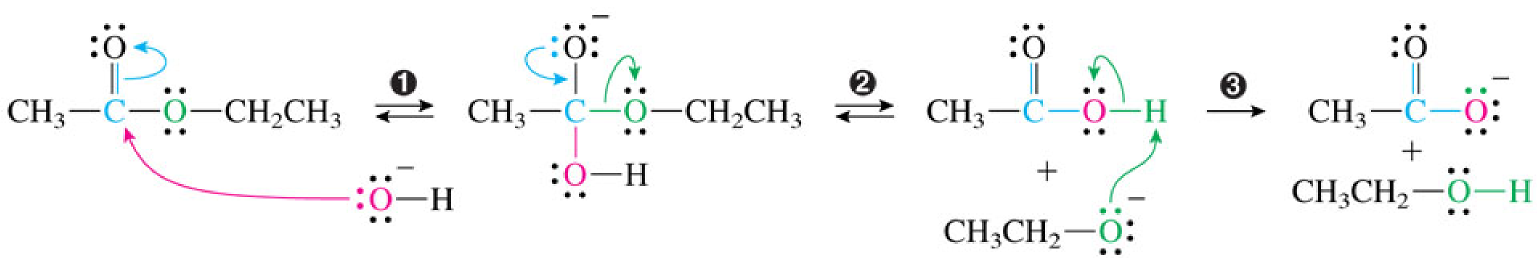
- Hydrolysis of acid derivatives: RCOY $\rightarrow$ RCO_2H
  - Acyl chlorides & Anhydrides: reactive
  - Esters: acid / base (saponification),
  - Amides: needs harsh conditions for hydrolysis
  - Nitriles: amide intermediate
  - $R\text{-}CO_2H \rightarrow R\text{-}CH_2CO_2H$

Preparation of Carboxylic Acids

- Acyl chlorides & anhydrides hydrolysis

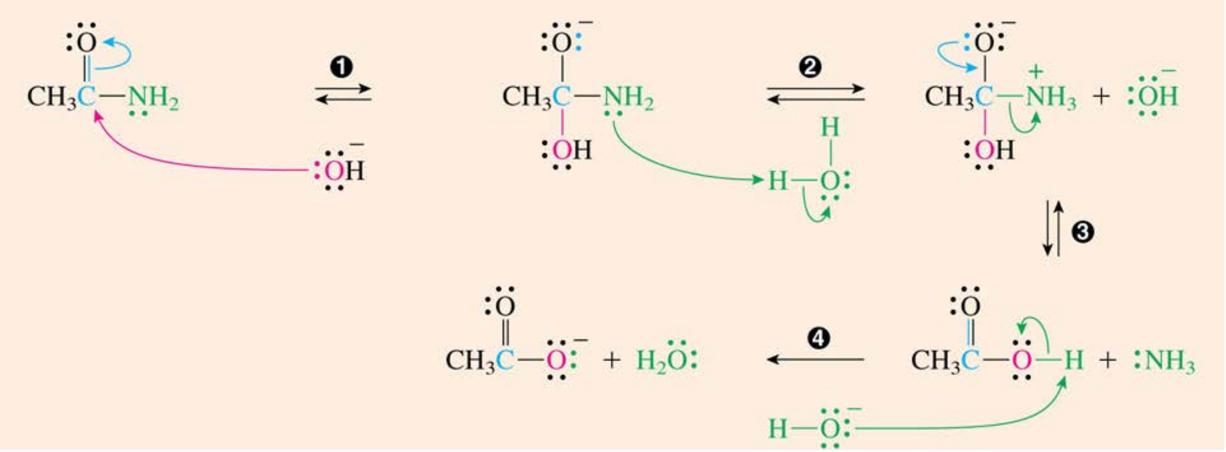


- Ester
  - Acidic conditions: reverse of Fischer esterification
  - Basic condiions : Saponification (비누화)



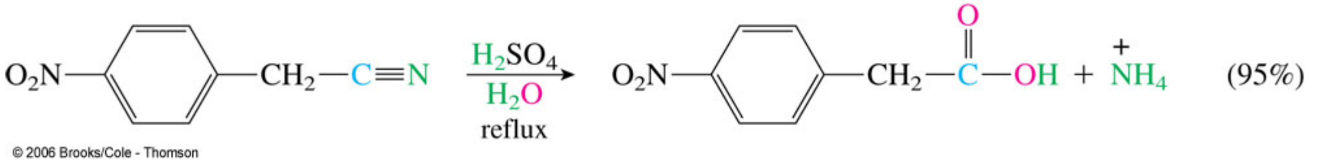
Preparation of Carboxylic Acids

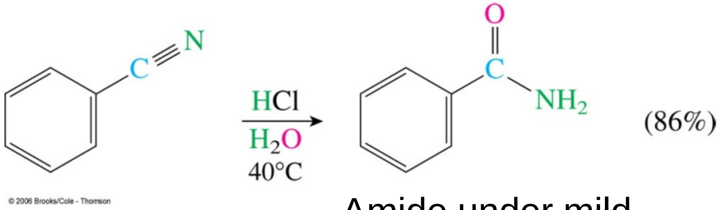
- Amide Hydrolysis
  - Less reactive than esters: vigorous heating in aueous acid or base
  - Acidic conditions: similar to the reverse of the Fischer esterification
  - Basic conditions: protonation of NH_2- before leaving

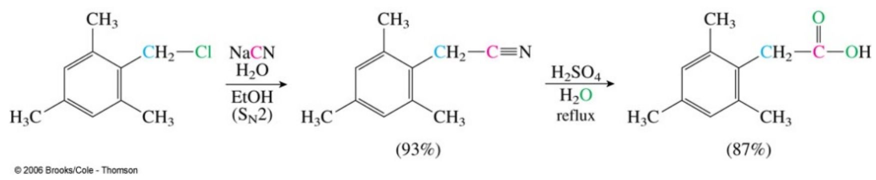


Preparation of Carboxylic Acids

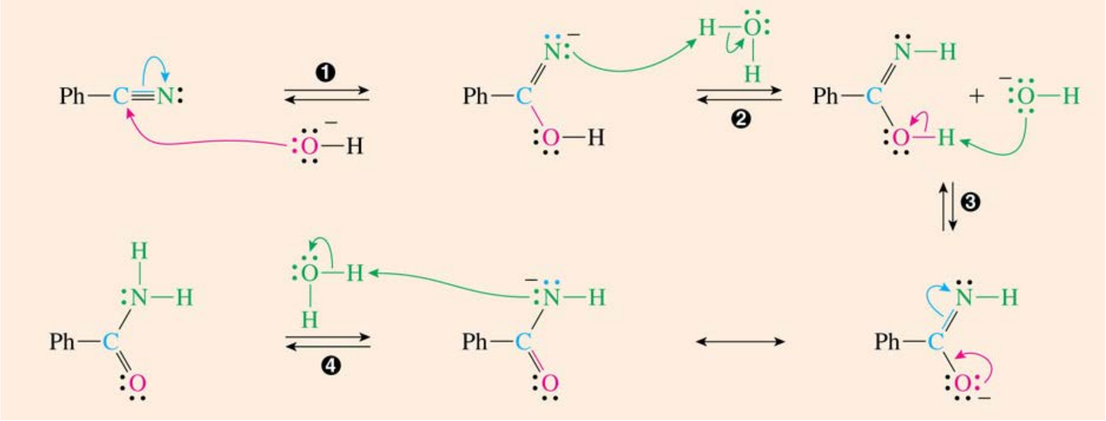
- Nitrile Hydrolysis
  - Amide intermediate





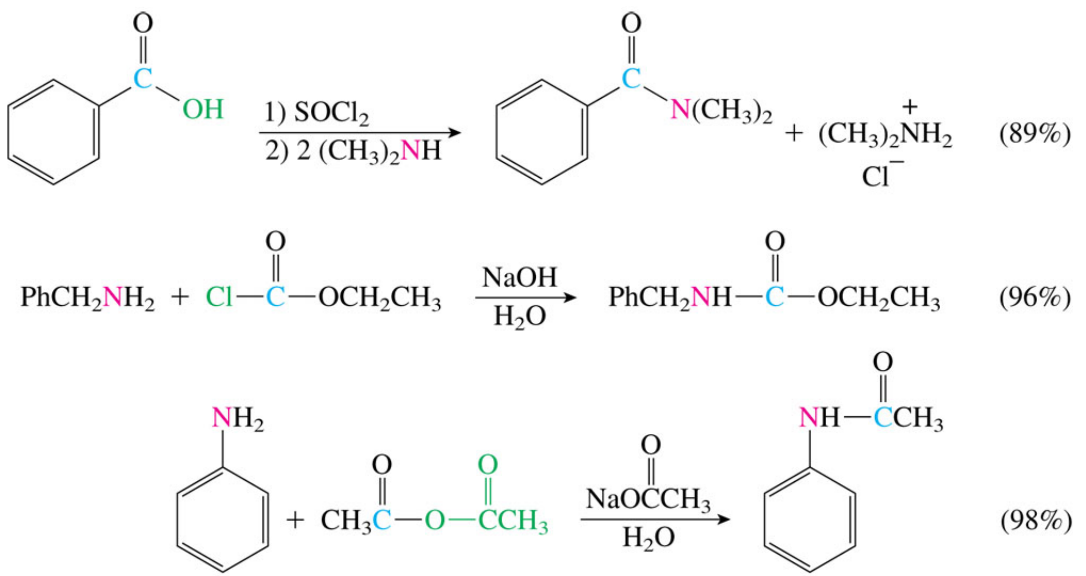


Amide under mild conditions

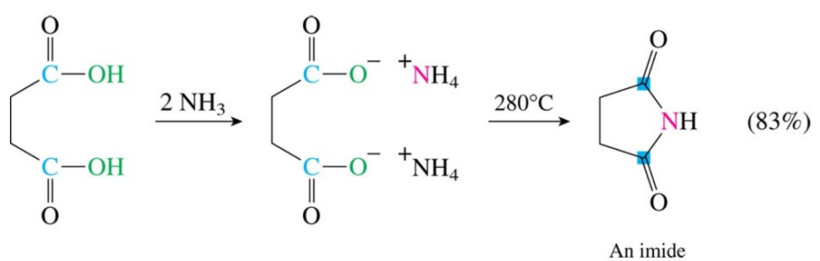


Preparation of Amides

- Acyl chloride/ anhydride with ammonia or amine

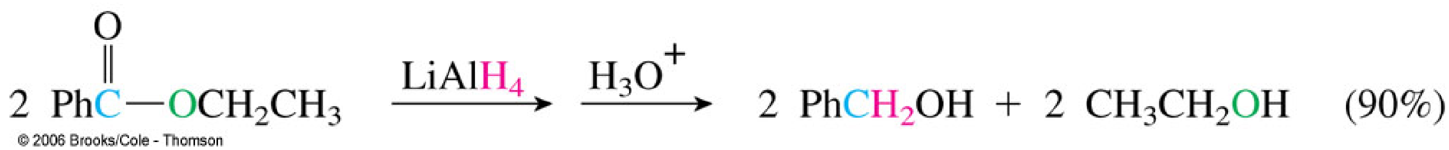


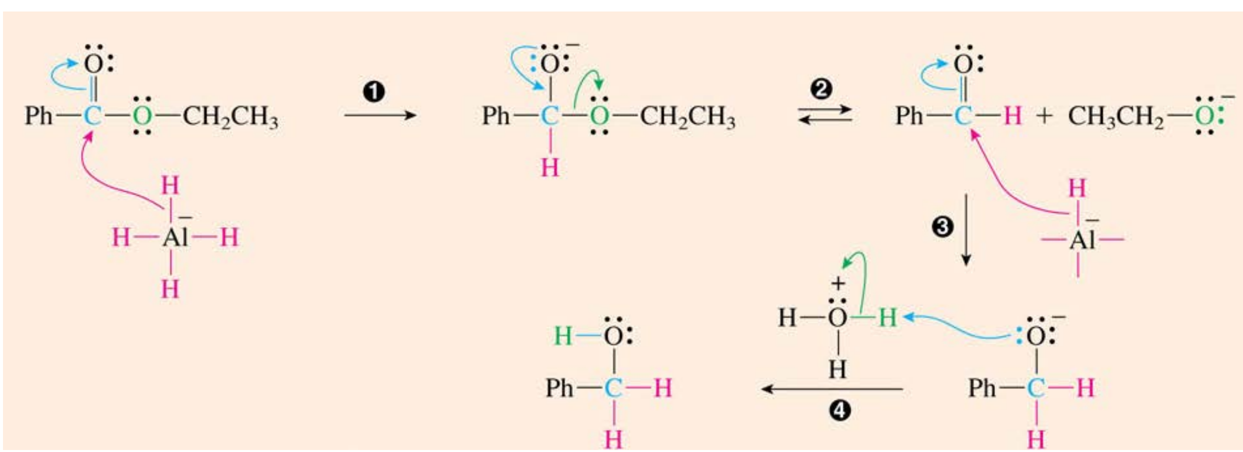
- Carboxylic acid with amine: lactams / imides



Reaction with Hydride Nucleophiles : Ester → Alcohol

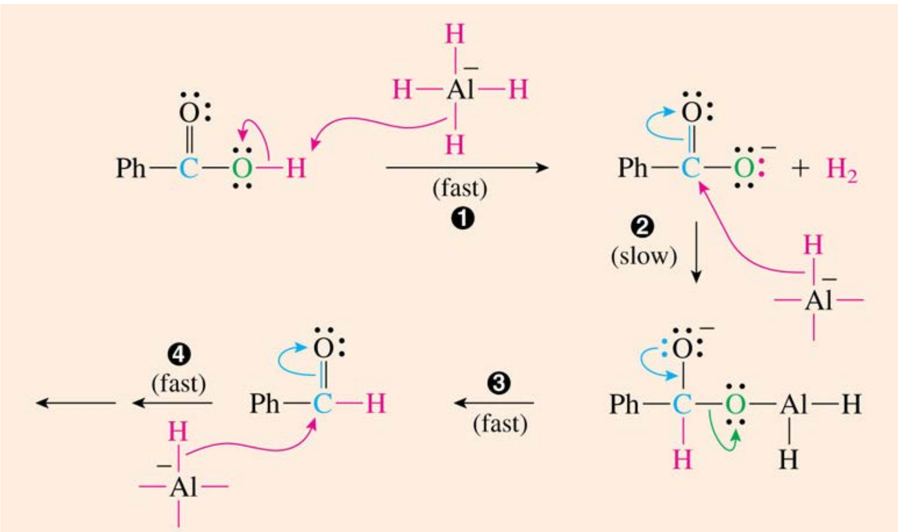
- Carboxylic acid derivatives with hydride →alcohol
  - From Ester
  - From Acyl chlorides and Anhydrides (less convenient to work with)

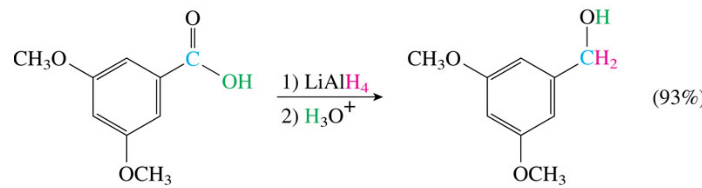


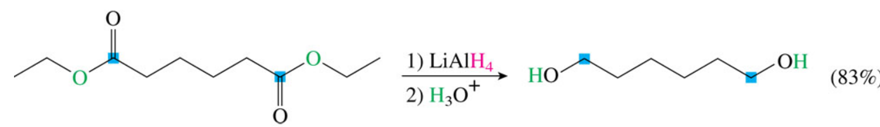


Reaction with Hydride Nucleophiles : Carboxylic acid → Alcohol

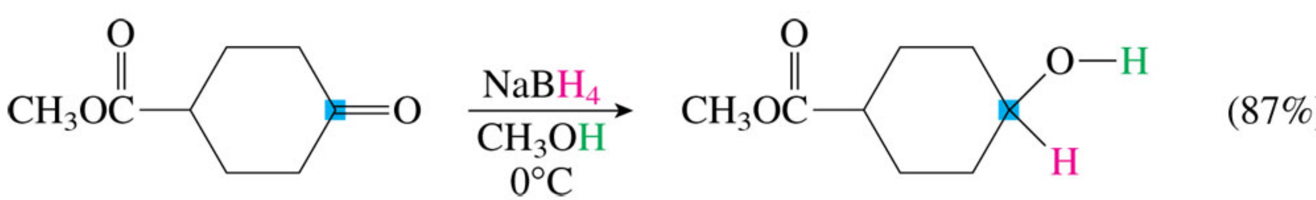
- From caboxylic acid





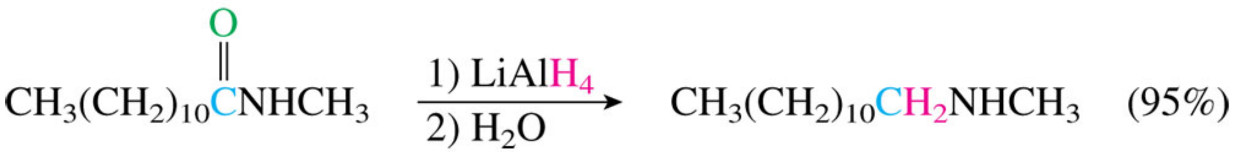


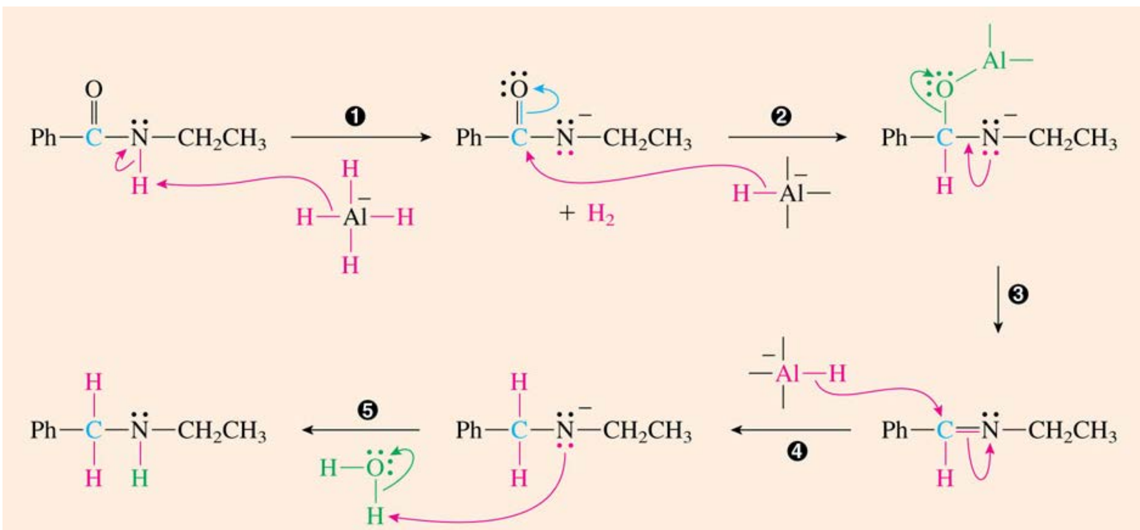
- $NaBH_4$ is less reactive (more selective) than $LiAlH_4$
  - Reduction of aldehyde or ketone w/out reducing ester



Reaction with Hydride Nucleophiles : Amide → Amine

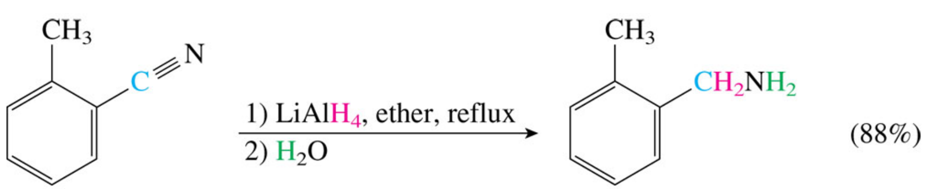
- Reduction of Amides with $LiAlH_4$ → Amine





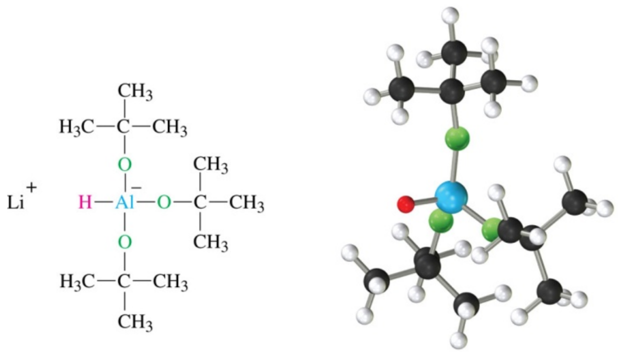
O: weak base, better leaving group than N

- Reduction of nitriles with $LiAlH_4$ → 1° Amine

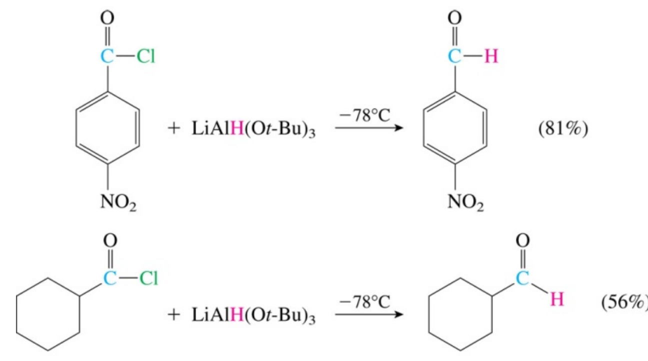


Reduction of Acid Derivatives to Aldehydes

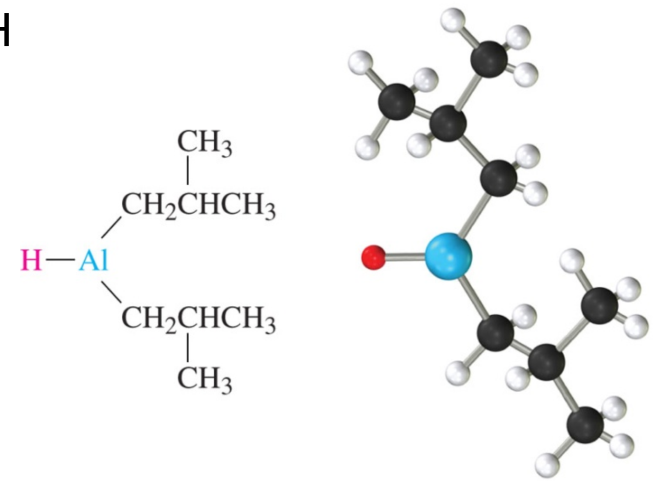
- Lithium tri-t-butoxyaluminum hydride: $LiAlH(Ot\text{-}Bu)_3$



Lithium tri-*t*-butoxyaluminum hydride [$LiAlH(Ot\text{-}Bu)_3$]
(reduces an acyl chloride but not an aldehyde)



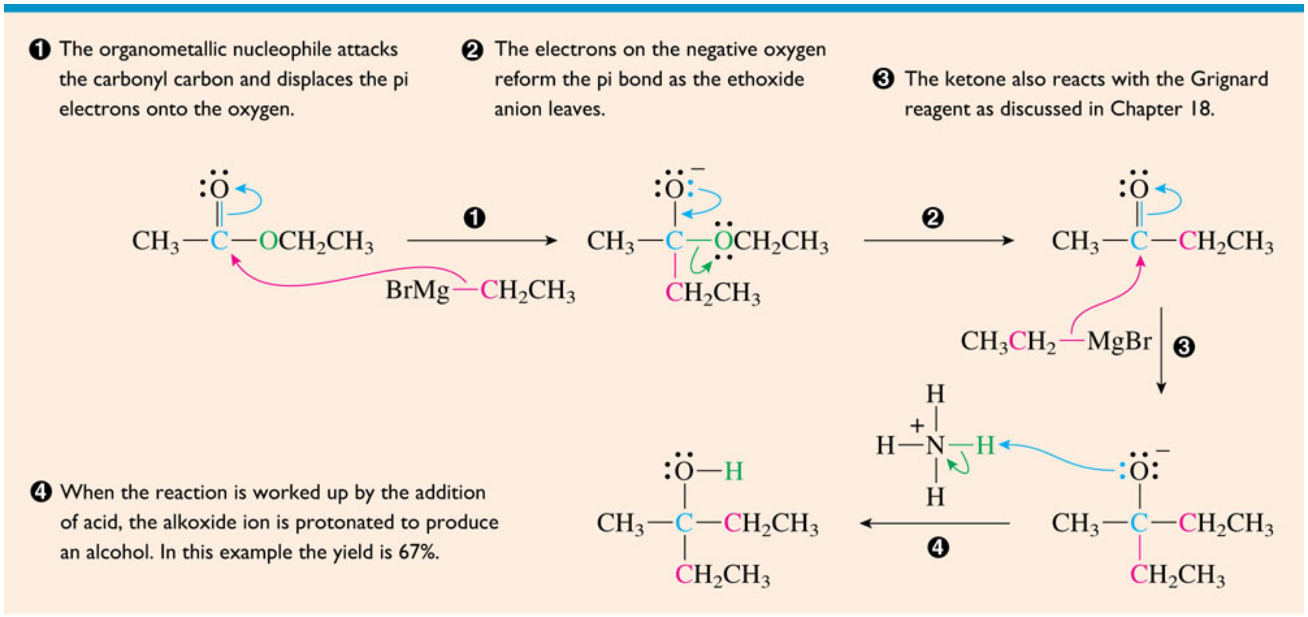
- Diisobutylaluminum hydride: $i\text{-}Bu_2AlH$



Diisobutylaluminum hydride
(DIBALH or $i\text{-}Bu_2AlH$)

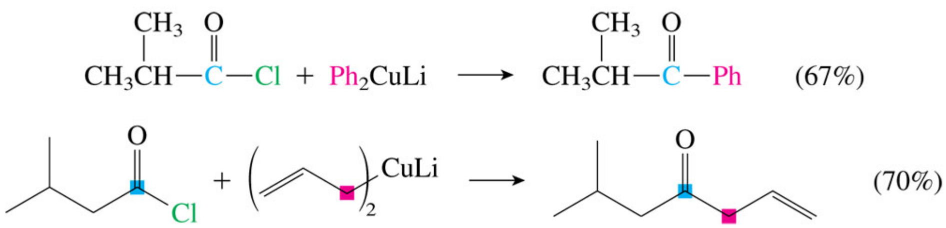
Reactions with Organometallic Nucleophiles

- Ester → Ketone → Alcohol

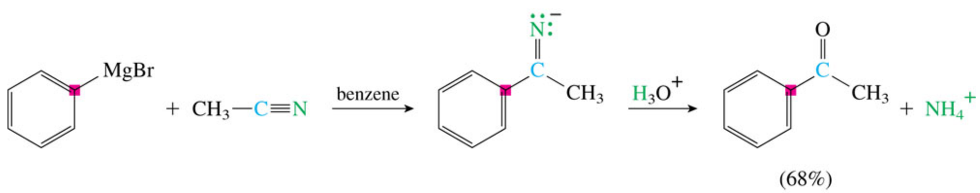


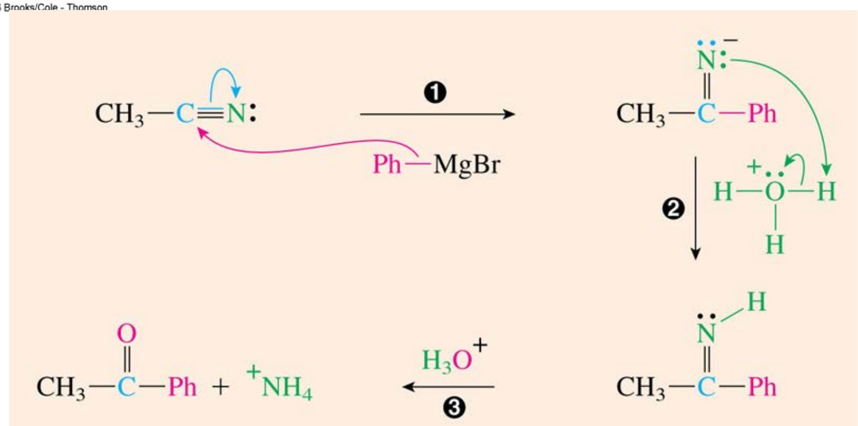
Preparation of Ketones

- Acyl chloride with lithium diorganocuprate reagent



- Nitrile with a Grignard reagent

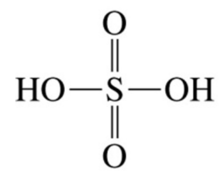




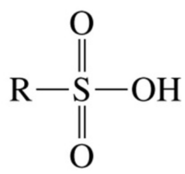
Too weak electrophile to react with the Grignard reagent

Derivatives of Sulfur

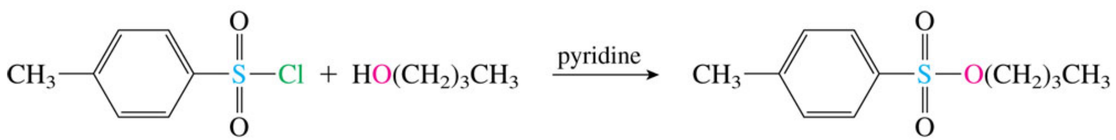
- Sulfonic acid
  - One OH group of sulfuric acid → R
  - Stronger acid than carboxylic acids, but similar behavior



Sulfuric acid

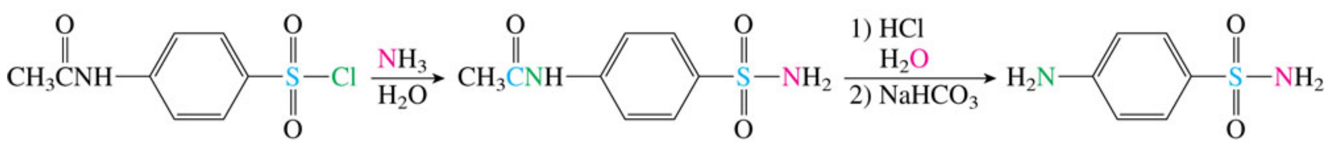


A sulfonic acid

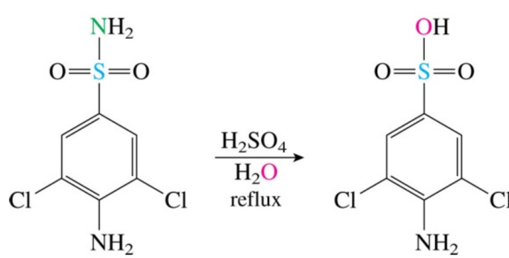


p-Toluenesulfonyl chloride

(90%)
A toluenesulfonate ester



p-Aminobenzenesulfonamide
(sulfanilamide)

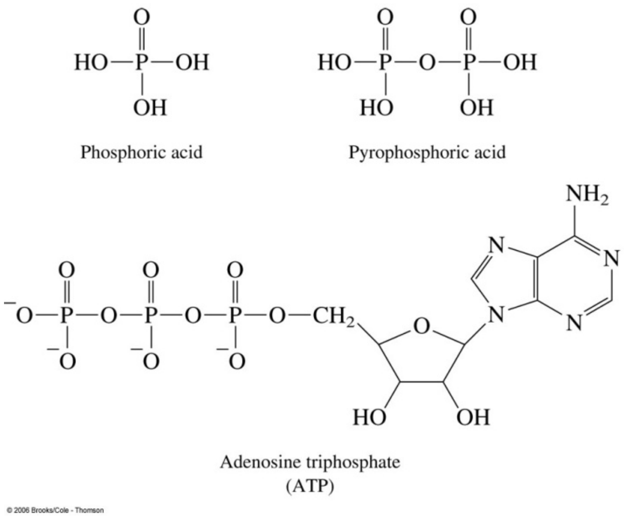


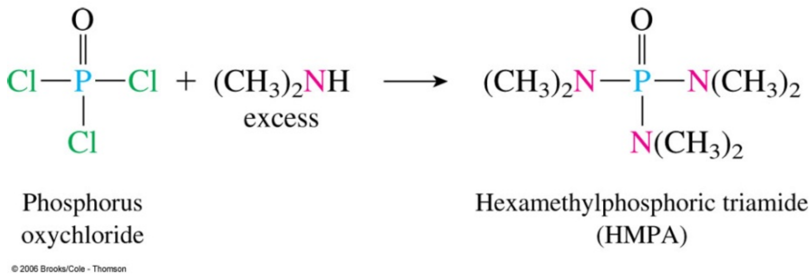
(80%)

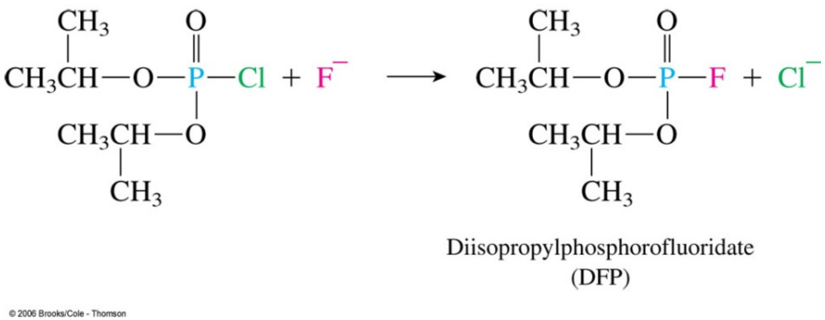
Less reactive for hydrolysis

Derivatives of Phosphorus Acids

- Pyrophosphoric acid



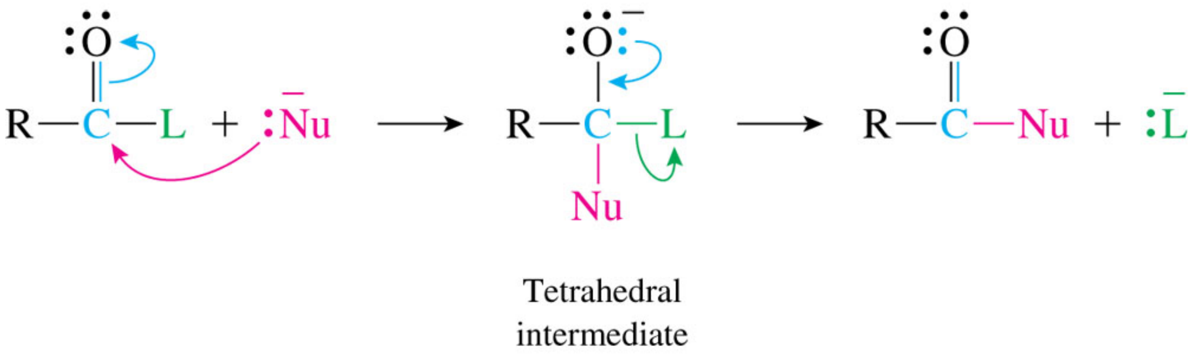


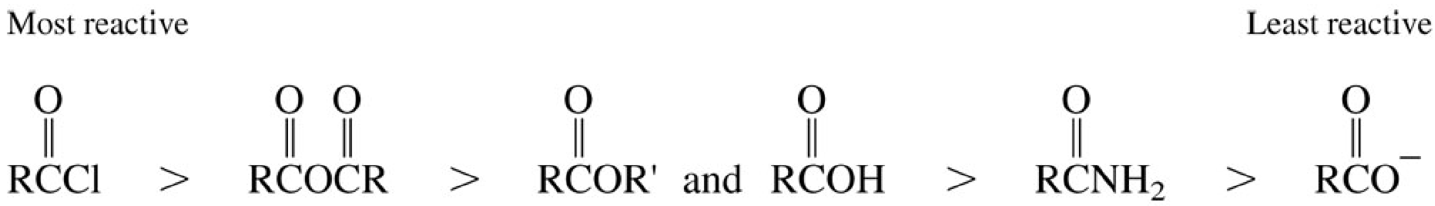


❖ Sulfur & Phosphorus Analogues

- sulfonic acid: RSO_2-OH
  - RSO_2-Cl (sulfonyl chloride), RSO_2-OR' (sulfonate), RSO_2-NR'R" (sulfonamide): 📖 728~729
- phosphoric acid: $(O)P(OH)_3$; 📖 729
  - $(O)P$-Cl_3 (phosphoryl chloride), $(HO)_2P(O)$-O-$(O)P(HO)_2$ (pyrophosphoric acid), $(O)P$-$(OR)_3$' (triphosphate), $(O)P$-$(NR_2)_3$' (phosphoric triamide)
  - nerve gases & pesticides: 📖 838 - 839 Elaboration

Summary





Practice & Report **:** **Problem 29, 37, 39, 42, 50, 57, 58**