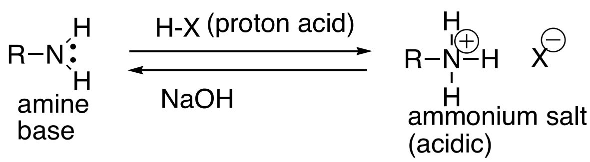
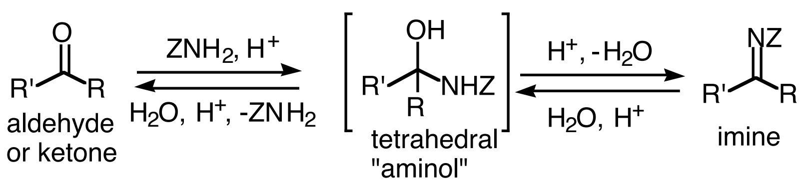
Reactions of Amines

1. **Reaction as a proton base** (Section 21.4)



- Mechanism: Required (protonation)
- Reverse Mechanism: Required (deprotonation)
- Amines are completely converted to ammonium salts by acids
- Ammonium salts are completely neutralized back to amines by bases
- Patterns in base strength: Reflect stabilization/destabilization factors for both the amine and the ammonium
    - N lone pair: $sp^3 > sp^2 > p$
    - For sp^3 nitrogens, 3º > 2º > 1º

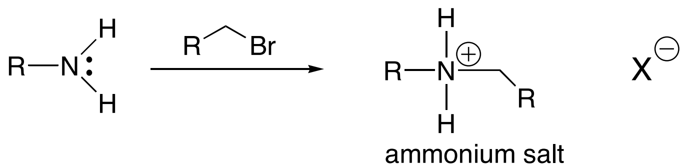
2. **Reaction with Ketones or Aldehydes** (Section 17.10)



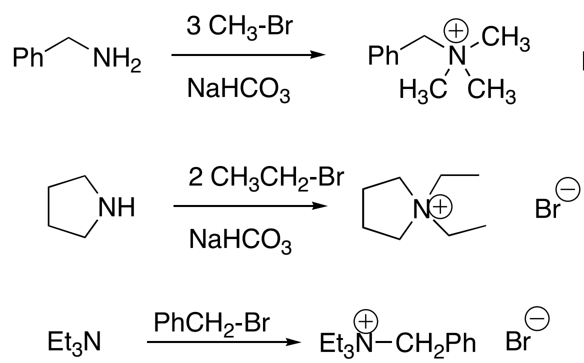
Notes:

- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2º, 3º amines can't do this

3. Alkylation of 1º Alkyl Halides **(Section 21.7,12)**

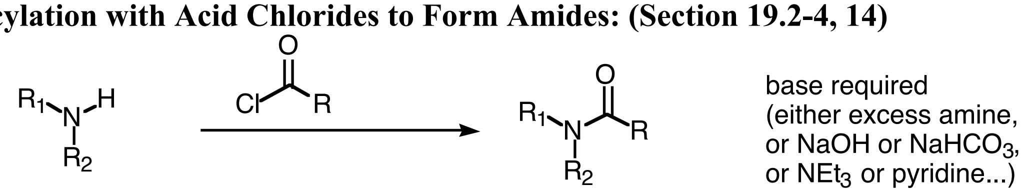


- **3a. Polyalkylation** is routine.
  - o With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
  - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



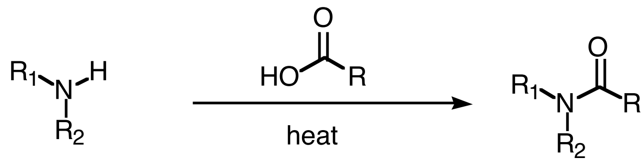
- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.

4. Acylation with Acid Chlorides to Form Amides: (Section 19.2-4, 14)



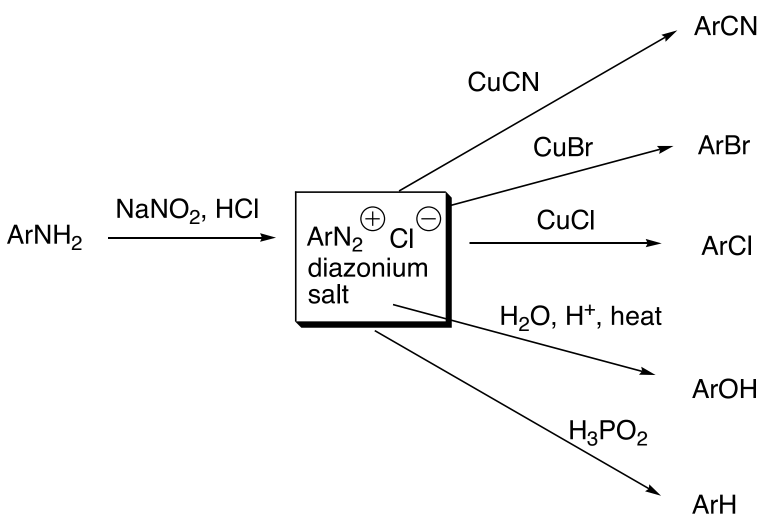
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

4b. **Acylation with Carboxylic Acids** to From Amides:



- Mechanism: Not Required
- Fairly high temperatures often required in human laboratory, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

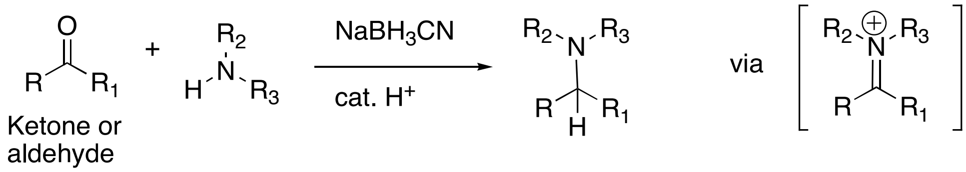
5. **Substitution for Aromatic Amines via the Diazonium Salts ("The Sandmeyer Reaction")** (Section 21.16-18)



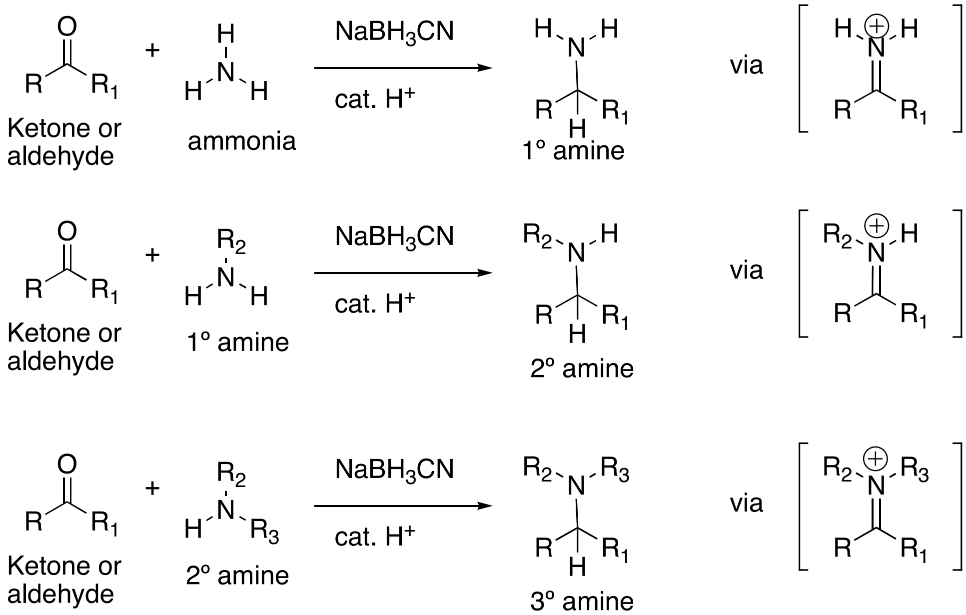
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

Synthesis of Amines

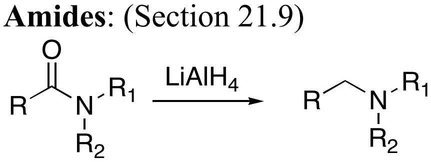
6. **From Aldehydes or Ketones: Reductive Amination** (Section 21.10)



- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - NH_3 → 1° RNH_2
  - 1° RNH_2 → 2° R_2NH
  - 2° R_2NH → 3° R_3N
  - 3° R_3N don't react

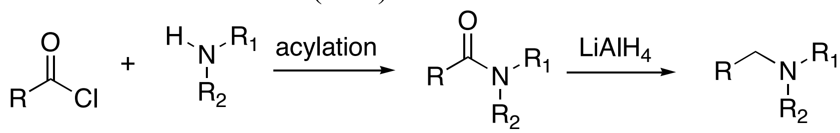


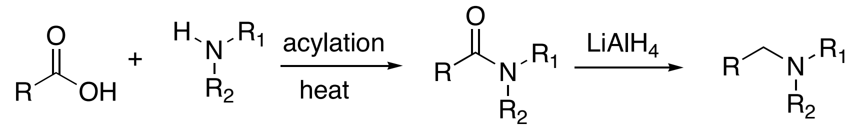
7. **Via Amides**: (Section 21.9)



- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - $RCONH_2$ → 1° RCH_2NH_2
  - $RCONHR$ → 2° RCH_2NHR
  - $RCONR_2$ → 3° RCH_2NR_2

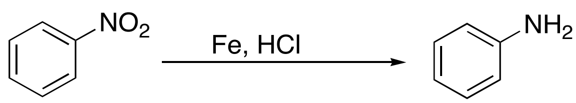
8. **From Amines via Amides**: (21.9)





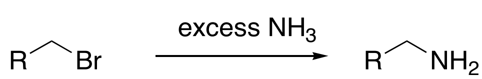
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 21.9)



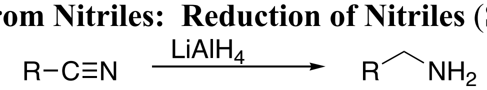
- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - o Pd/H_2, Ni/H_2, Pt/H_2,
  - o Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (21.7) (See reaction 3).



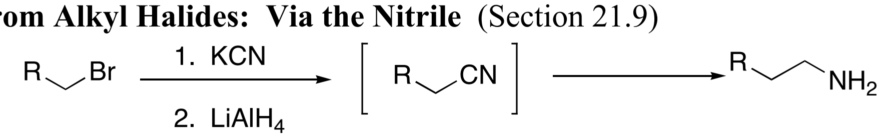
- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 21.9)



- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 21.9)



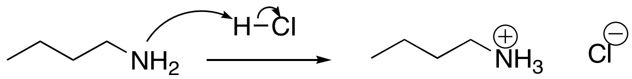
- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

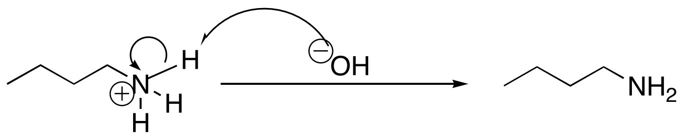
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	1. RCOCl (or RCO_2H, heat) 2. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	1. RNH_2 2. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1º $ArNH_2$	
6	#10	1º RCH_2Br	NH_3 (excess)	1º only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1º RCH_2Br (via nitrile)	1. KCN or NaCN 2. $LiAlH_4$	1º only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1º only, with CH_2 next to nitrogen	

Mechanisms

1. **Protonation**

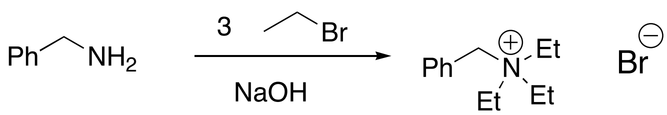


1.-**Reverse. Deprotonation**

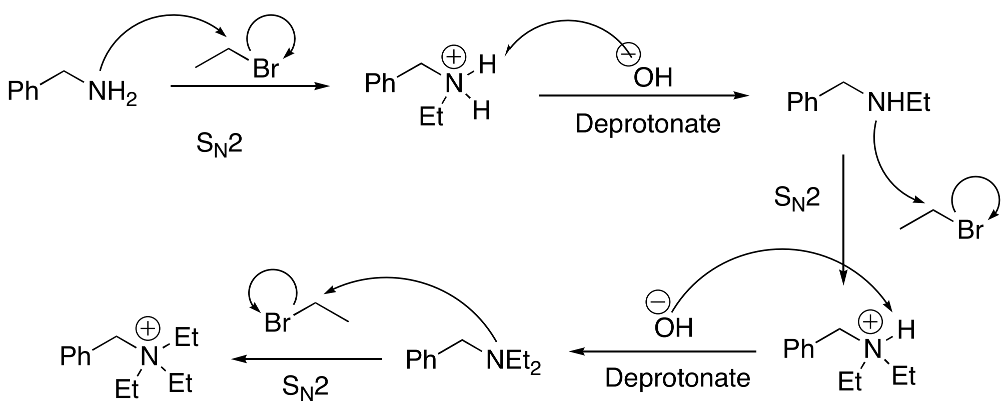


6. Polyalkylation

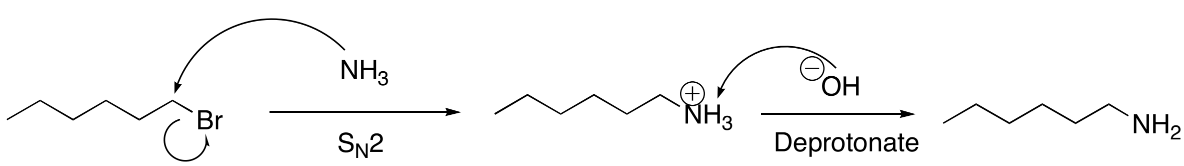
Ex:



Mech:

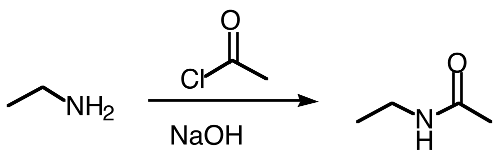


3b. Monoalkylation

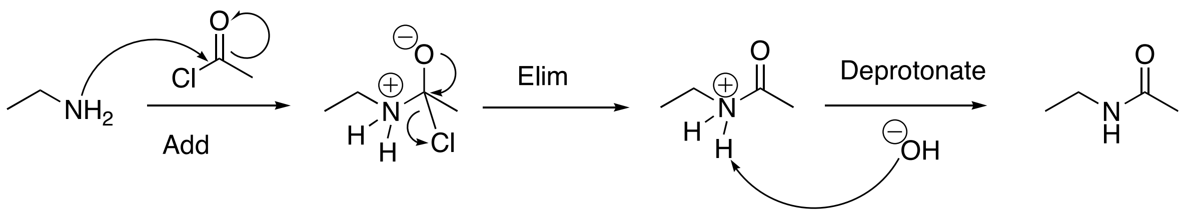


7. Acylation

Ex:



Mech: 3 steps: Addition-Elimination-Deprotonation

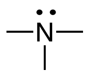
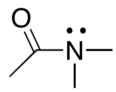
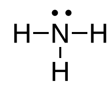


Chapter 21 Amines

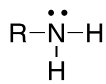
A. Miscellaneous

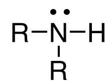
21.1 Intro, Terms

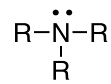
Amines versus Amides

 amine  amide  ammonia

1º, 2º, 3º classification: based on how many of the three nitrogen attachments are carbons:

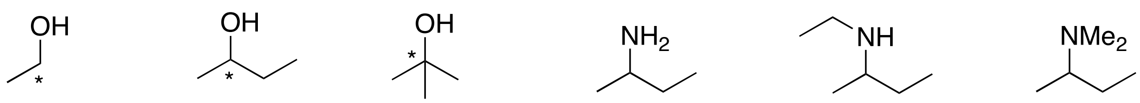

1° Amine


2° Amine

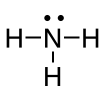
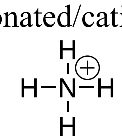

3° Amine

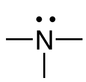
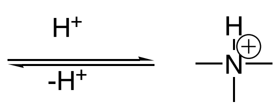
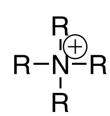
Note: 1º, 2º, 3º has a different sense than with alcohols.

1. In an alcohol, it's based on how many carbon groups are attached to the hydroxy-bearing carbon.
- The alcohol oxygen always has one carbon group.
2. But in amines, it's how many carbon groups are attached to the nitrogen itself.
- Because the nitrogen could have 0, 1, 2, or 3 carbon groups attached.



Amines versus Ammoniums: Neutral versus protonated/cationic

 ammonia  ammonium

 amine  ammonium  quaternary ammonium

<u>21.1 Formal **Amine Nomenclature**:</u> alkan-x-amine, N-alkylalkan-x-amine, etc.

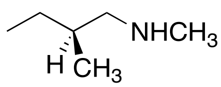
1. For core name, choose longest C-chain to which nitrogen is attached, and call it alkan-x-amine (including for alkan-1-amines)
   - Number from end nearer N
   - Be sure to specify with a number which **<u>carbon</u>** has the nitrogen
     - The nitrogen does ****not**** count as a number itself.
2. Substituents on the <u>nitrogen</u> (rather than on carbon) are designated as "N-"
   - Unlike substituents on a carbon, which are always designated by the carbon's number
   - The "N-" does not factor into alphabetizing. Ex: "N-ethyl" goes before "3-methyl"
3. NH_2 as a <u>Substituent: "Amino"</u>

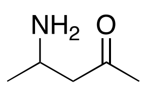
<u>Draw the structure or provide the name for the following.</u>

1. N-methyl-3-phenyloctan-2-amine

2. (Z)-pent-3-en-1-amine

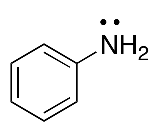
3. hexan-3-amine

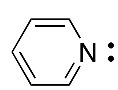
4. 

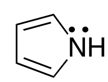
5. 

<u>Common Naming</u> (for simple amines): Alkylamine, dialkylamine, trialkylamine….

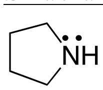
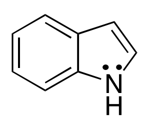
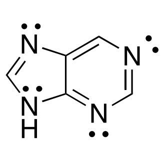
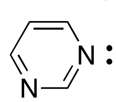
<u>Three Common Amine Names to Memorize (Review from Aromatics Chapter)</u>

Aniline 

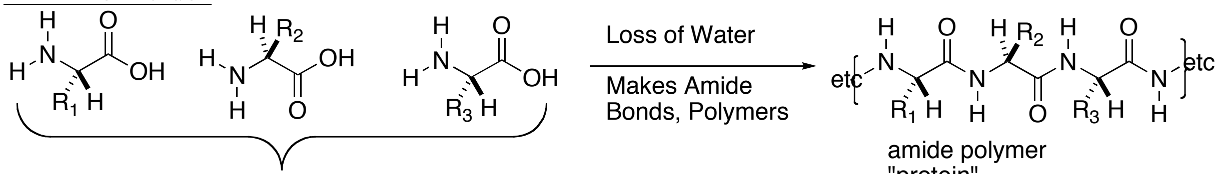
Pyridine 

Pyrrole 

<u>Some Other Famous Common Amine Names (No memory requirement)</u>

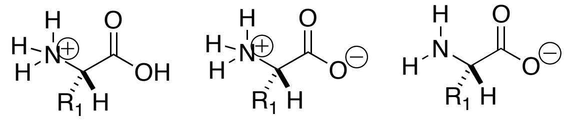
<u>Name</u>	<u>Structure</u>	<u>Name</u>	<u>Structure</u>	
Pyrrolidine		Indole		
Purine		Pyrimidine		RNA, DNA, ATP, and ADP are made from derivatives of Purine and Pyrimidine

"Amino Acids"



amide polymer
"protein"
"polypeptide"

-The major natural amino acids all have "S" configuration
-20 major natural amino acids
-Under neutral conditions, the amine actually deprotonates the acid to give not an "amino acid" but actually an "ammonium carboxylate"
-The side groups "R" can be acid, basic, hydrophilic, or hydrophobic.
-The sequence or R groups on thepolymer essentially spells out the biological activity of the protein.



acidic pH | neutral pH | basic pH

Test Keys:

1. Understand that amino acids are the building blocks for polymeric proteins, and that the biological information is specified by the identity and sequence of the side groups

2. Understand what form an "amino acid" exists in, depending on whether the conditions are acidic, neutral, or basic pH
   - Is the nitrogen neutral (base form) or protonated and cationic (acid form)?
   - Is the carboxylic acid anionic (base form) or protonated and neutral (acid form)?

   a. Acidic pH: both are in protonated acid forms — Overall Charge: POSITIVE
      - nitrogen is cationic and carboxylic acid is neutral

   b. Neutral pH: one in acid form, the other in base form — Overall Charge: NEUTRAL
      - One acidic H between the two of them
      - The amine is in its acid form (protonated, cationic); while the carboxylic acid is in its base form (deprotonated, anionic)
      - The amine is more basic than the carboxylate, the carboxylic acid more acidic than the ammonium cation. Acid base drives the equilibrium to the ammonium carboxylate form

   c. Basic pH: both are in deprotonated base form — Overall Charge: NEGATIVE
      - Nitrogen is neutral, carboxylic acid is anionic

21.2 Structure and Hybridization

1. **N <u>atoms</u>** are typically either sp^3 hybridized (normal) or sp^2 hybridized
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 in either of two cases:
        - N atom is itself double bonded
        - N atom is conjugated to a double bond

2. **<u>N lone pair</u>** is either:
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 when the N atom is itself double bonded
        - the p orbital is used to make the double bond
        - the lone pair is left in an sp^2 hybrid
    c. p when the N atom is conjugated to a double bond but is not itself double bonded
        - the lone pair sits in the p orbital so that it can overlap with the adjacent p orbital/π bond

<u>Practice</u>: For the nitrogens on page 10, identify the lone pair hybridization and bond angles.

Physical Properties (21.3)

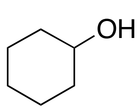
Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

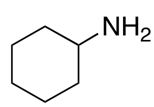
1. **Water Solubility**: All amines hydrogen-bond water → impacts solubility
   a. Because R_3N---HOH bond is stronger (due to amine lone-pair basicity) than ROH---HOH, amines tend to better H-bond water and are more soluble than oxygen analogs
   b. Based on basicity of substate (the acidity of water's hydrogen is common)

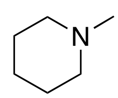
2. **Boiling Point:** 1° and 2° amines hydrogen bond themselves, but 3° amines don't
   a. Boiling point for similar mw amines: 1°, 2° amines > 3° amines
   b. amines generally have lower boiling points than analogous oxygen compounds
      - Boiling point for similar mw: RCO_2H > RCH_2OH > RCH_2NH_2
   c. for boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.

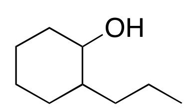
3. Amines stink! (ammoniums don't)

1. Boiling Points. Rank the following in terms of boiling point, 1 being highest, 4 being lowest.

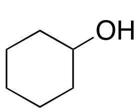


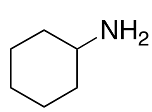


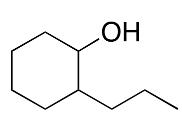


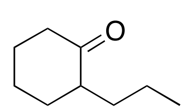


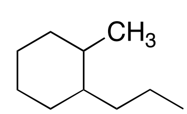
2. Water Solubility. Rank the following in terms of water solubility, 1 being most water soluble, 5 being least water soluble.







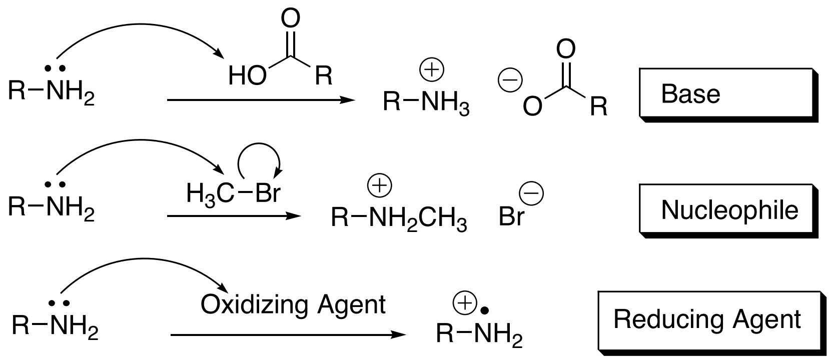




Keys:
1. H-bonding: Is there any at all?
2. How relatively strong is the H-bonding?
3. What impacts H-bonding strength?

What impact will extra carbons have?

B. Basicity of Amines: Reactivity of the Nitrogen Lone Pair



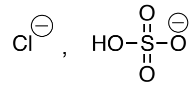
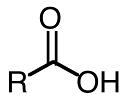
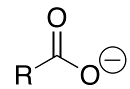
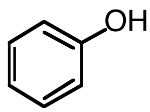
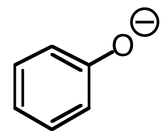
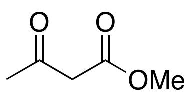
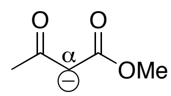
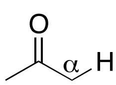
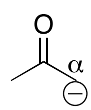
•The nitrogen lone pair dominates amine reactivity

•Trends in base strength, nucleophile strength, and redox strength follow similar patterns, based on lone pair stability/reactivity

Neutral amine bases are stronger than:
1. Neutral oxygens (water, alcohol, ketones…)
2. Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:
1. Anionic hydroxide or alkoxides
2. Anionic nitrogen or carbon bases

Acidity/Basicity Table 21.1: Neutral Acids and Anionic Bases

Class	Neutral Acid Structure	Ka	Acid Strength	Anion Base	Base Strength	Base Stability
Strong Acids	H-Cl, H_sSO_4	10^{2}				
Carboxylic Acid		10^{-5}				
Phenol		10^{-10}				
1,3-Dicarbonyl		10^{-12}				
Water	HOH	10^{-16}		$HO^{\ominus}$		
Alcohol	ROH	10^{-17}		$RO^{\ominus}$		
Ketones and Aldehydes		10^{-20}				
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		

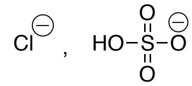
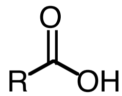
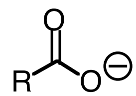
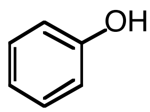
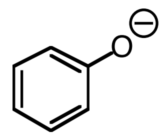
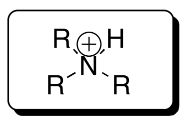
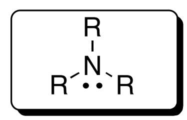
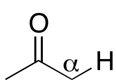
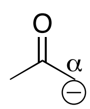
Quick Checklist of Acid/Base Factors

1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**

4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

- **When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.**
- **When a neutral acids are involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

Acidity/Basicity Table 21.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^{2}				**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^{0}		H_2O, HOR neutral		**H**umans
Carboxylic Acid		10^{-5}				**C**uz
Phenol		10^{-10}				**P**eople
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	$\mathbf{10^{-12}}$		 Neutral, but basic!		**A**gainst
Water	HOH	10^{-16}		$HO^{\ominus}$		**W**orking
Alcohol	ROH	10^{-17}		$RO^{\ominus}$		**A**re
Ketones and Aldehydes		10^{-20}				**K**ingdoms
Amine (N-H)	$(iPr)_2N\text{-}H$	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		**A**nimal
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		**A**ll

Notes to remember

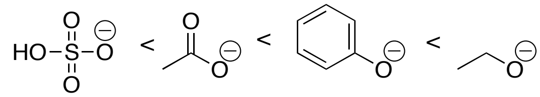
1. Average neutral amine a thousand billion times **more basic than a neutral oxygen** (**electronegativity** factor)
2. An average neutral amine is thousands of times **less basic than** non-resonance stabilized **hydroxide or alkoxide anions** (**charge** factor)
3. But average neutral amine **millions** of times **more basic** than highly resonance-stabilized **carboxylate anion** (**resonance** factor trumps charge factor in this case)
4. **Ammonium cations** are million of times **less acidic than** neutral **carboxylic acids**, but are **more acidic than neutral water/alcohol**!
5. Neutral amine can completely deprotonate carboxylic acids, but not water or alcohols.
6. Therefore hydroxide can deprotonate ammoniums, but carboxylates cannot.

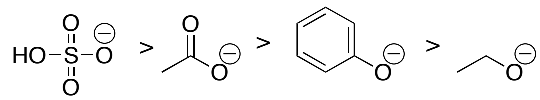
More Detailed Discussion of Acid/Base Patterns/Factors to remember

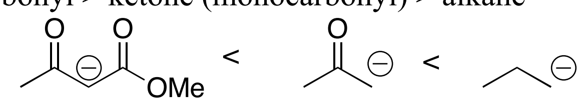
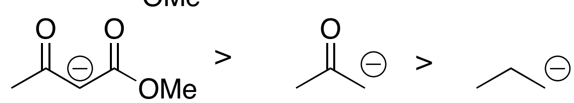
1. Charge
   - **All else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 21.2)**
   - Nonfactor on Table 21.1, since all of the "acids" have the same charge (neutral), and all of the "bases" have the same charge (anions)

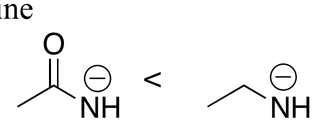
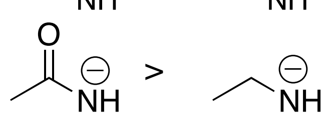
2. Electronegativity:
   - Acidity: H-C < H-N < H-O < H-X (halogen)
   - Basicity: $C^{\ominus} > N^{\ominus} > O^{\ominus} > X^{\ominus}$
   - Anion Stability: $C^{\ominus} < N^{\ominus} < O^{\ominus} < X^{\ominus}$

3. Resonance/Conjugation:
   - Oxygen Series:
     Acidity: sulfurice acid > carboxylic acid > phenol > alcohol

     Anion Basicity: 

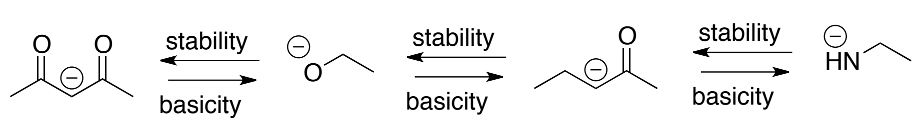
     Anion Stability: 

   - Carbon Series:
     - Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane
     - Anion Basicity: 
     - Anion Stability: 

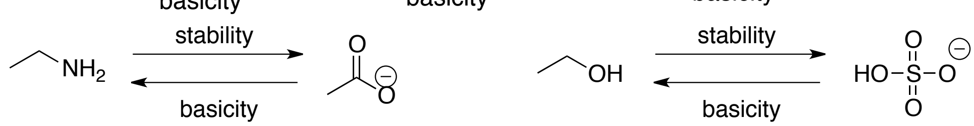
   - Nitrogen Series:
     - Acidity: amide > amine
     - Anion Basicity: 
     - Anion Stability: 

- Note: Resonance is often useful as a tiebreaker (oxyanion versus oxyanion, etc.)
- NOTE: Resonance can sometimes (not always) trump electronegativity or charge.

Electroneg.

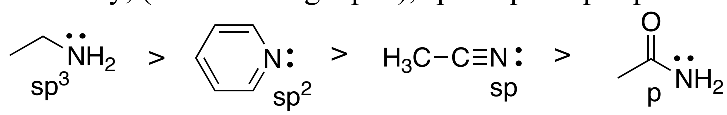


Charge

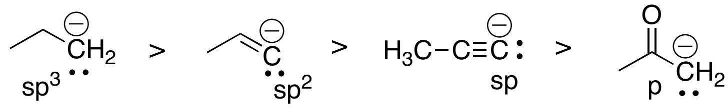


4. Hybridization:
   - For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$

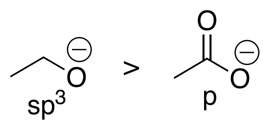
Neutral Nitrogen Series



Carbanion Series



Oxygen Anion Series



   - This means that for acidity, alkynes > alkenes > alkanes

5. Electron donating/electron withdrawing substituents:
   - Electron withdrawing substituents will stabilize negatively charged anions, but will destabilize positively charged cations.
     - This means a withdrawer will increase the acidity of a neutral acid because it will stabilize the resulting anion.
     - This means a withdrawer will decrease the basicity of a neutral base because it will destabilize the resulting cation
   - Electron donating substituents will stabilize positively charged cations, but will destabilize negatively charged anions.
     - This means a donor will increase the basicity of a neutral base because it will stabilize the resulting cation. The resulting cation will be less acidic.

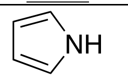
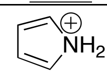
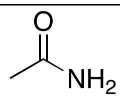
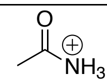
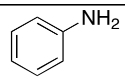
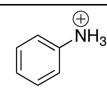
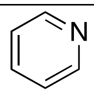
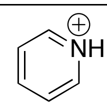
Basicity: $H-NH_2 < R-NH_2$ (ammonia, alkyl amine) Cation Acidity: $H-NH_3^+ > R-NH_3^+$ Cation Stability: $H-NH_3^+ < R-NH_3^+$

     - This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion

Acidity: $H-O-H > R-O-H$ (water, alcohol) Anion Basicity: $H-O^- < R-O^-$ Anion Stability: $H-O^- > R-O^-$

6. Ammonium Cations as Acids and Neutral Amines as Bases
   - Neutral amines are more basic than any neutral oxygen (electronegativity factor)
   - Neutral amines are less basic than most anionic oxygens, including alkoxides, hydroxides (charge factor)
   - However, neutral amines are more basic than highly resonance-stabilized carboxylate anions (in this case, resonance factor trumps the charge factor).

Table 21.3 Relative Basicity of Different Classes of Neutral Nitrogen Compounds.

Entry	Structure of Amine Base	Base Strenth	Lone Pair Hybrid		Impact On Base Strength	Structure of Ammonium Acid	K_a	Acid Strenth
1			P	Aromatic, Conjugated	Decrease		10^{1}	
2			P	Conjugated, Electron-Withdrawing Carbonyl	Decrease		10^{0}	
3			P	Conjugated	Decrease		10^{-4}	
4			sp^2				10^{-5}	
5	**NH_3**		**sp^3**	**Reference**		$\oplus NH_4$	$\mathbf{10^{-9.3}}$	
6	$EtNH_2$		sp^3	Alkyl Donor	Increase	$Et\overset{\oplus}{N}H_3$	$10^{-10.6}$	
7	Et_2NH		sp^3	Alkyl Donor	Increase	$Et_2\overset{\oplus}{N}H_2$	$10^{-10.8}$	
8	Et_3N		sp^3	Alkyl Donor	Increase	$Et_3\overset{\oplus}{N}H$	$10^{-11.0}$	

General Amine Basicity Patterns.

a. Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) > sp^2 (entry 4) > p (entries 1-3) (hybridization factor)

b. Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): 3º > 2º > 1º > NH_3 (electron donating group factor)

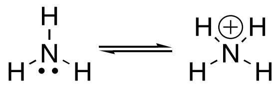
Note: patterns (a) and (b) essentially cover everything.

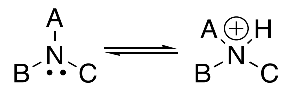
c. Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because or the electron-withdrawing group factor).

d. Conjugated nitrogens are in general less basic than isolated nitrogens (both hybridization and conjugation factors)

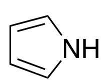
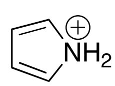
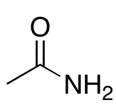
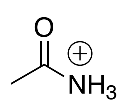
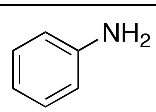
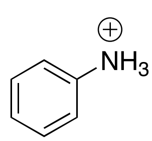
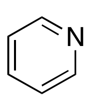
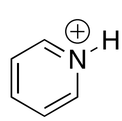
- Note: The **acidity of conjugate ammonium cations (conjugate acids relative to the amines) is directly and inversely related to the basicity of the neutral amines**.
- Key: remember patterns (a) and (b) above. That should help you solve relative basicity problems. If given ammoniums, draw the related conjugate neutral amines, rank them as bases, and realize that the strongest amine base relates to the weakest ammonium acid.
- You should be able to handle any ranking problems involving either amines as bases or their conjugate ammoniums as acids. This should include relative to non-nitrogen acids and bases.

Explanation for Basicity Pattern: Acidity/Basicity is an equilibrium measurement, and thus reflects both product stability and starting material stability.



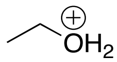
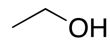


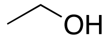
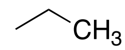
- Anything that **stabilizes the cation increases the basicity** of the nitrogen
- Anything that **destabilizes the cation decreases the basicity** of the nitrogen
- Anything that **stabilizes the amine decreases the basicity** of the nitrogen (especially if that stabilizing factor is sacrificed upon protonation)
- Anything that **destabilizes the amine** increases it's basicity
- When lone pair is p, that always reflects stabilizing conjugation and reduced basicity. This is the origin of both the p-hybridization factor and the resonance/conjugation factor.

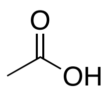
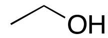
Entry	Base	Conjugate Cation	Substituent And it's Impact	Why: Which Side Is Stabilizied or Destabilized?
5	NH_3	NH_4^+	Reference	
6-8	Et_3N	Et_3NH^+	Alkyl Groups Increase Basicity	**Cation** side stabilized by alkyl groups (electron donors, cation stabilizers)
1			Being part of Aromatic ring Reduces Basicity	**Neutral** side is stabilized by aromaticity. (Aromaticity is lost following protonation.)
2			Acyl/Amide Conjugated To Carbonyl	**Neutral** side is stabilized by conjugation to the carbonyl. That conjugation is lost following protonation. Second, the **cation side is destabilized** by the strongly electron withdrawing carbonyl group.
3			Conjugated To Aromatic	**Neutral** side is stabilized by conjugation. (That conjugation is lost following protonation.)
5			Shorter, more stable lone pair	**Amine** side is stabilized by the sp^2 hybridization of the lone pair. An sp^2 lone pair is shorter than an sp^3 orbital. The shorter sp^2 orbital means the electrons are nearer and held more tightly by the nitrogen nucleus, and are thus more stable.

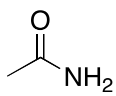
Choose the More Acidic for Each of the Following Pairs: Single Variable Problems

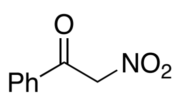
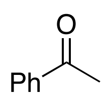
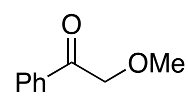
1. NH_3 $\oplus NH_4$

2.  

3.   

4.  

5.  

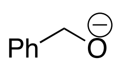
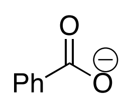
6.   

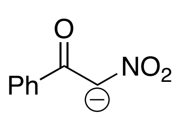
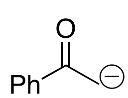
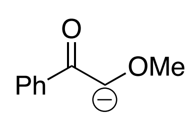
Choose the More **Basic** for Each of the Following Pairs (Single Variable)

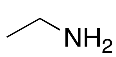
7. NH_3 $NaNH_2$

8. NaOH H_2O

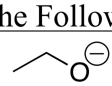
9. NH_3 H_2O

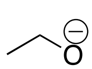
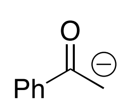
10.  

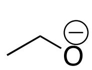
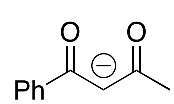
11.   

12.  NH_3 $O_2N{-}NH_2$

Choose the More **Basic** for Each of the Following (Multiple Variables, apples and oranges…)

13. NH_3 

14.  

15.  

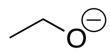
Choose the More Basic for Each of the Following Pairs

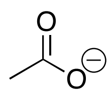
16. NH_3 $NaNH_2$

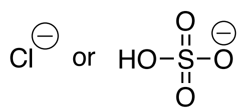
17. NH_3 NaOH

18. NH_3 H_2O

19. NH_3 CH_3OH

20. NH_3 

21. NH_3 

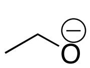
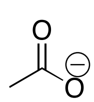
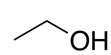
22. NH_3 

23. NH_3 CH_3MgBr

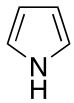
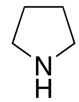
24. NH_3 CH_3NH_2

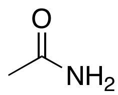
25. For the following sets of bases, rank them, 1 being the most basic.

a. CH_3MgBr CH_3NHNa CH_3NH_2 CH_3OH

b.   CH_3NH_2 

26. Amine Basicity. For the following pairs or sets of bases, rank them, 1 being the most basic.

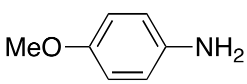
a.  

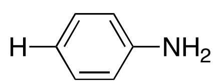
b.  

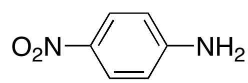
c. benzamide [PhC(O)NH_2] aniline ($PhNH_2$) pyridine triethylamine

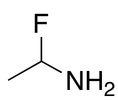
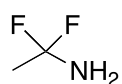
d. triethylamine ethylamine ammonia

e. dimethylamine methylamine aniline ($PhNH_2$)

f. 





g.   

h. triethylamine NaOH

i. methanol methylamine methane

j. CH_3MgBr CH_3NHNa CH_3ONa CH_3NH_2 CH_3CO_2Na CH_3OH

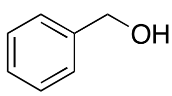
27. Rank the acidity of the following compounds, 1 being most acidic.

a. H_3O^+ $NH_4^+Cl^-$ water acetic acid (CH_3CO_2H) NH_3

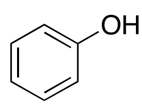
b. H_3O^+ acetic acid (CH_3CO_2H) $Me_3NH^+Cl^-$ ethanol

c. $NH_4^+Cl^-$ $Me_3NH^+Cl^-$ $PhNH_3^+Cl^-$

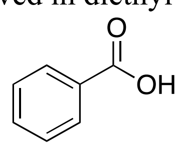
28. Suppose all of the molecules **A-D** are dissolved in diethyl ether.



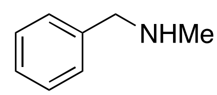
A



B



C



D

a. Which one or ones will extract (dissolve) into aqueous sodium hydroxide? (And why?)

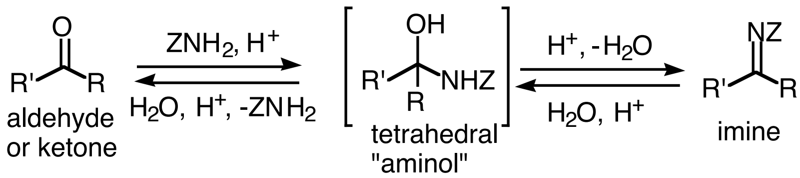
b. Which, if any, will extract into aqueous hydrochloric acid? (And why?)

c. Which, if any, will extract into neutral water? (Why or why not?)

d. Explain how you could use an extraction scheme to separate **D** from **A.**

<u>**C.**</u> <u>Reactions of Amines (other than as bases)</u>

2. Reaction with Ketones or Aldehydes (Section 17.10)



Notes:

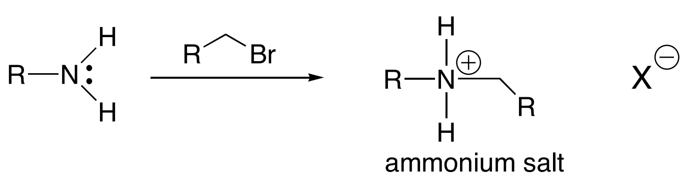
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2°, 3° amines can't do this

<u>Draw the Products of the following Amine reactions.</u>

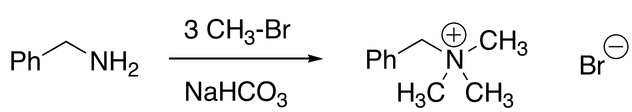
1. $PhNH_2$ $\xrightarrow{\text{4-phenyl-2-hexanone, } H^+}$

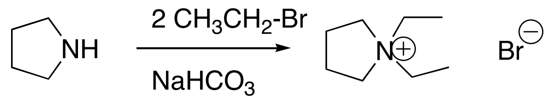
2. Cyclohexanone + H_2NNH_2 $\longrightarrow$

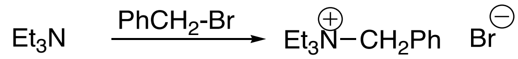
3. Alkylation of 1° Alkyl Halides (Section 21.7,12)



- <u>**3a. Polyalkylation**</u> is routine.
  - o With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
  - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.







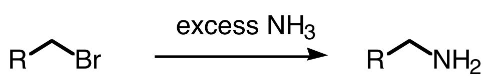
Notes

1. All amines are nucleophilic
   - 3° > 2° > 1° > NH_3
   - structural effects parallel basicity
2. Limited synthetic utility, due to frequent overalkylation
3. Due to S_N2 mechanism, limited to alkylation of 1° R-X

- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.

Synthetically Useful Alkylation Scenarios:

1. Exhaustive Alkylation to Intentionally produce quaternary ammonium salts
2. Reaction 10. **From 1° Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A)

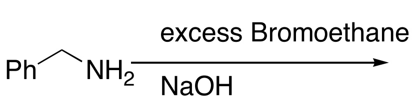


- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

3. Cyclization reactions in which a 5 or 6-membered ring can form.

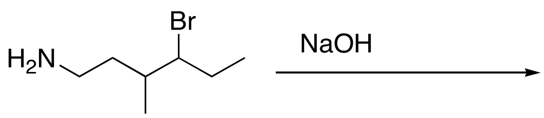
Draw the Products and mechanisms of the following Amine reactions.

1. Me_3N + $PhCH_2I$ ⟶

2. 

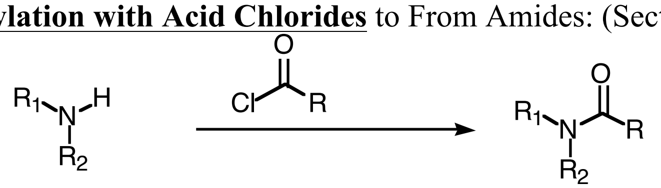
Draw the Products and mechanisms of the following Amine reactions.

1. $PhCH_2Br$ $\xrightarrow{\text{Excess } NH_3}$

2. 

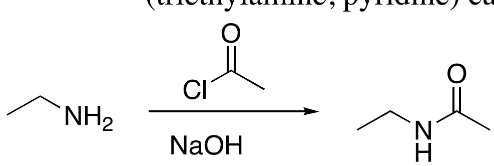
Why do you **not** get clean monoalkylation if you do a 1:1 mixture of RNH_2 and R-X?

4. Acylation with Acid Chlorides to From Amides: (Section 19.2-4, 14)

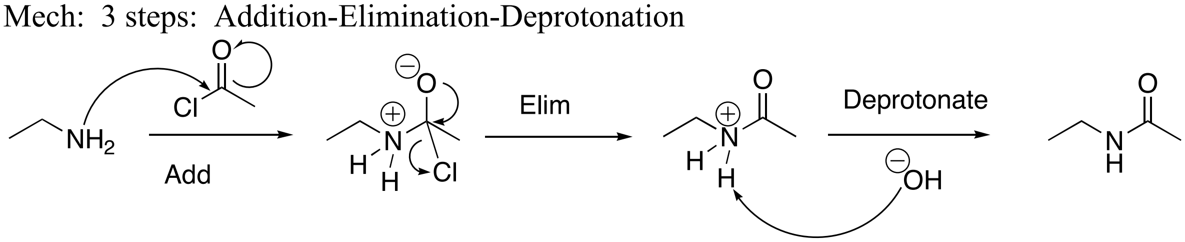


base required (either excess amine, or NaOH or $NaHCO_3$, or NEt_3 or pyridine...)

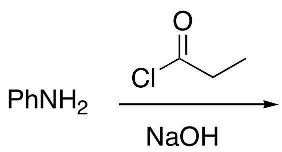
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

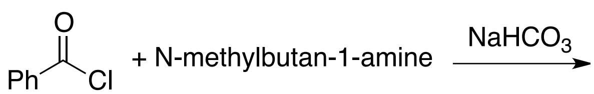


Mech: 3 steps: Addition-Elimination-Deprotonation

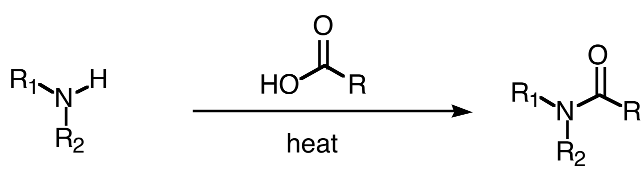


Draw the Products of the following Amine reactions, and the mechanism for the first one.

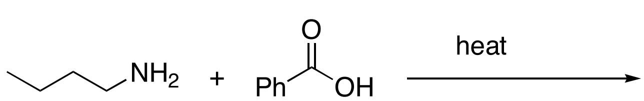
1. 

2. 

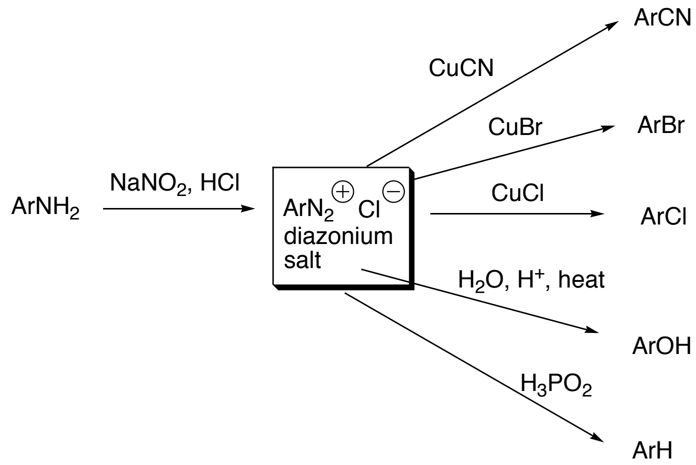
4b. **Acylation with Carboxylic Acids** to Form Amides:



- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

1. 

5. Substitution for Aromatic Amines via the Diazonium Salts ("The Sandmeyer Reaction") (Section 21.16-18)



- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

Lewis bases (lone pair electron donors) all function as:
1. Bases (give electrons to H^+)
2. Nucleophiles (give electrons to some other electrophile)
3. Reducing agents (give electrons to oxidizing agents)

Amines can be oxidized

$NaNO_2$/HCl is a strong oxidizing agent, converts RNH_2 to RN_2^+, and $ArNH_2$ to ArN_2^+
- "Diazonium salts"

RN_2^+ has the best leaving group known, because the leaving group is highly stable, neutral N_2 gas
1. Alkyl RN_2^+ are highly unstable, give cations, and usually give mixtures of E1, S_N1, and cation rearrangement product mixtures
2. Not much use synthetically
3. However, N_2 is such a great leaving group that even 1° carbocations can be formed/studied

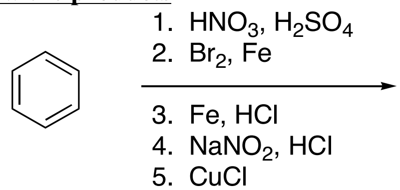
Reactivity: RN_2^+ > ROH_2^+ > ROTs > RI > RBr > RCl
Leaving group ability: N_2 > H_2O > TsO anion > Iodide anion > Bromide anion > Chloride anion

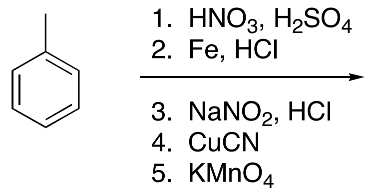
1. Unlike Alkyl diazoniums RN_2^+, aryl ArN_2^+ are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms

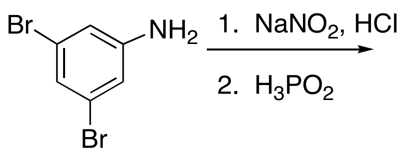
Synthetic Use:

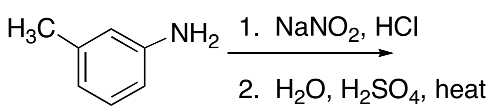
1. NO_2 (meta director) → NH_2 → N_2^+ → Cl, Br, OH, CN, H
2. Easy to get meta relationships, even when you end with things that are not meta directors

Draw the products

1. 

2. 

3. 

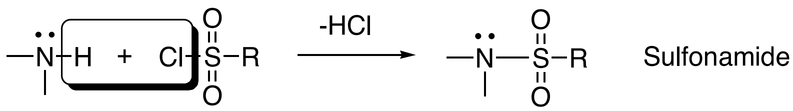
4. 

Design Synthesis

5. 

6. 

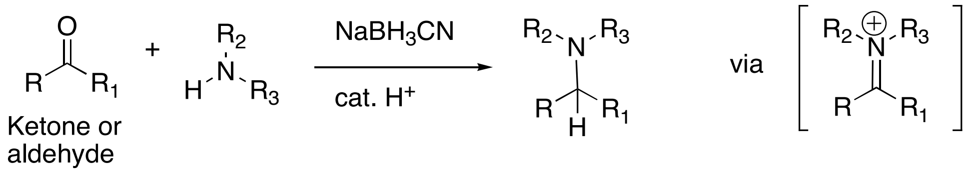
<u>Reaction with Sulfonyl Chlorides (Not tested)</u>



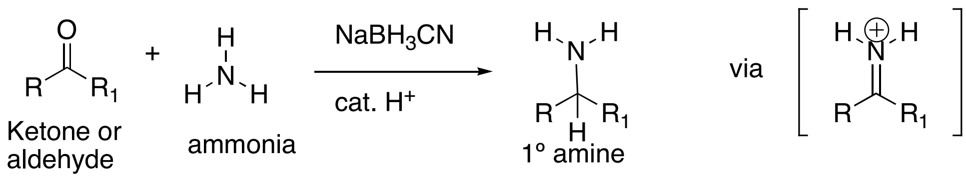
- Exactly as for amide formation
- Many antibiotic drugs: sulfonamides are so similar to amides that they occupy enzyme active sites → prevent bacterial growth

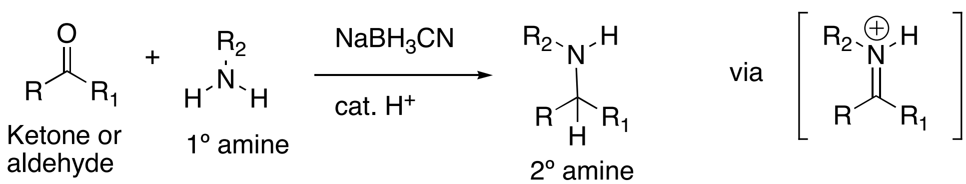
<u>**D.**</u> Synthesis of Amines

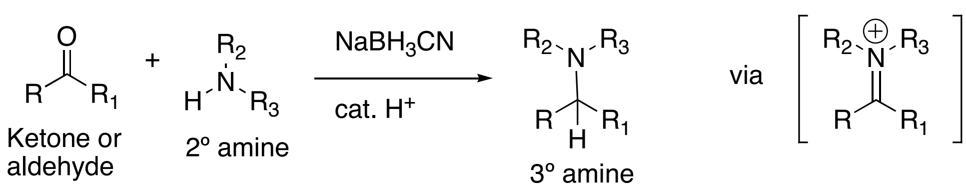
6. **From Aldehydes or Ketones: Reductive Amination** (Section 21.10)



- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - $NH_3 \rightarrow$ 1º RNH_2
  - 1º $RNH_2 \rightarrow$ 2º R_2NH
  - 2º $R_2NH \rightarrow$ 3º R_3N
  - 3º R_3N don't react

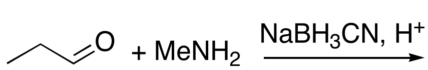


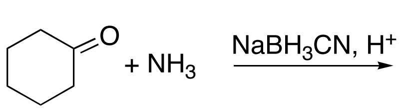


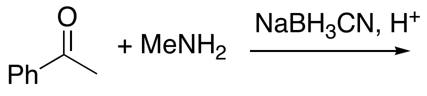


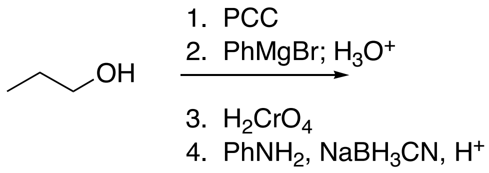
Note: book gives several other variants, but this is really the one universal method, and the one I'll use for my tests.

<u>Synthesis of Amines:</u> Draw the products for the following reactions.

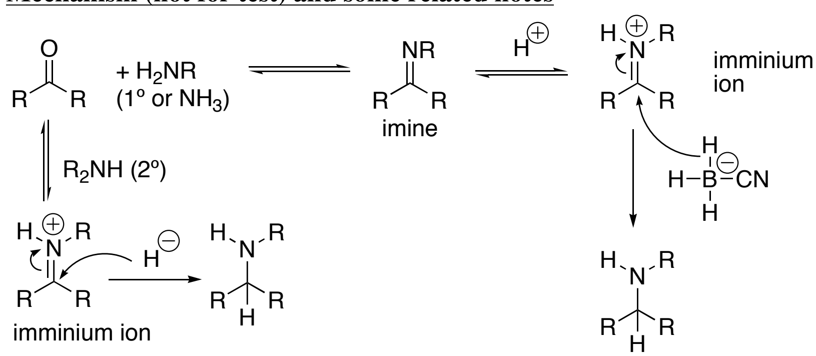
1. 

2. 

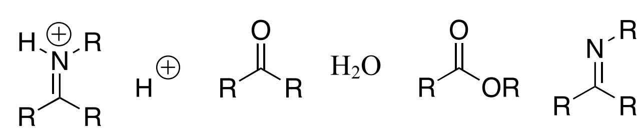
1. 

2. 

<u>Mechanism (not for test) and some related notes</u>



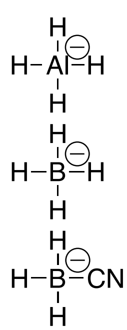
1. $NaBH_3CN$ functions as a hydride $H^{\ominus}$ source, similar to $NaBH_4$ and $LiAlH_4$
2. Formation of imminium cation is key
    - Highly electrophilic, much more so than neutral imine
3. $NaBH_3CN$ is a special, mild $H^{\ominus}$ source, much more stable and less reactive than $NaBH_4$ and $LiAlH_4$
    - So much so that it can coexist with acid (thus enabling imminium ion formation)
    - So much so that it does not reduce neutral ketones and aldehydes (thus allowing the aldehydes and ketones to sit around and equilibrate with imminium ion)

Hydride **<u>Stability</u>** Hydride **<u>Reactivity</u>** 

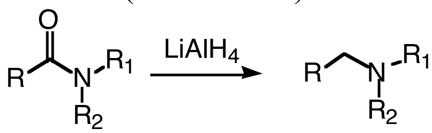
$LiAlH_4$

$NaBH_4$

$NaBH_3CN$

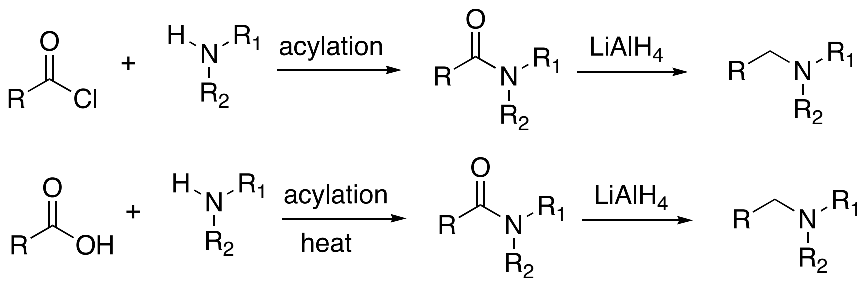


7. **Via Amides**: (Section 21.9)

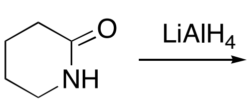


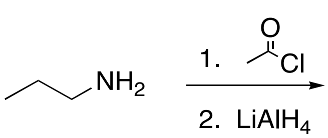
- No mechanism required for the reduction
- Access: 1º, 2º, or 3º Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1º, 2º, or 3º amines in this way:
  - $RCONH_2 \rightarrow$ 1º RCH_2NH_2
  - $RCONHR \rightarrow$ 2º RCH_2NHR
  - $RCONR_2 \rightarrow$ 3º RCH_2NR_2

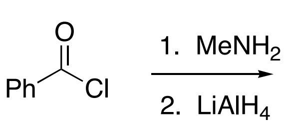
8. **From Amines via Amides**:



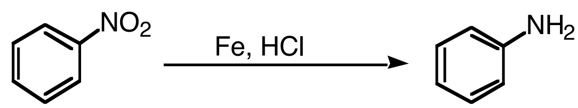
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

1. 

2. 

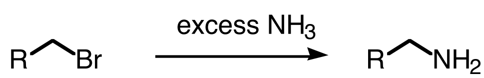
3. 

9. **Reduction of nitro compounds**: (section 21.9)



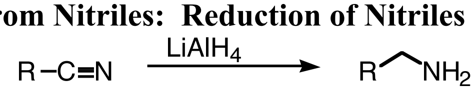
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H_2, Ni/H_2, Pt/H_2,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1° Alkyl Halides: Alkylation of Ammonia** (Section 21.7) (See reaction 3).



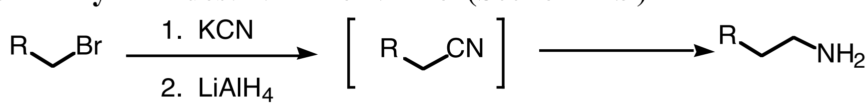
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 21.9)

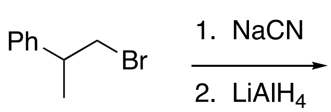


- Access: 1° amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 21.9)



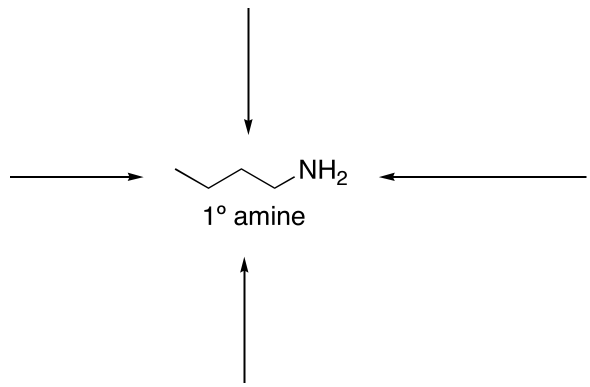
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!



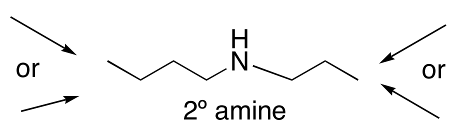
Summary of Amine Syntheses

Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	3. RCOCl (or RCO_2H, heat) 4. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	3. RNH_2 4. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1º $ArNH_2$	
6	#10	1º RCH_2Br	NH_3 (excess)	1º only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1º RCH_2Br (via nitrile)	3. 4. KCN 5. $LiAlH_4$	1º only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1º only, with CH_2 next to nitrogen	

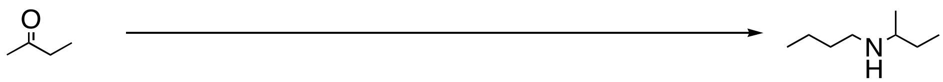
1. Come up with various pathways (4 good ones) to the following 1º amine:

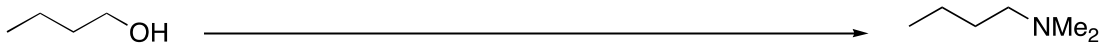


2. Come up with pathways (4 good ones) to the following 2º amine:

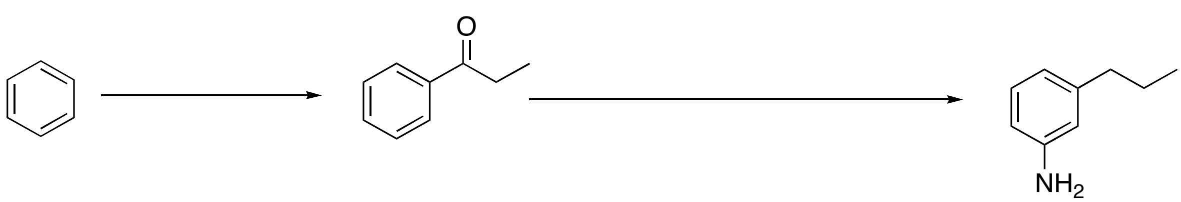


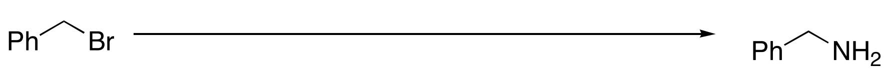
Provide Reagents for the following Transformations.

1. 

2. 

3. 

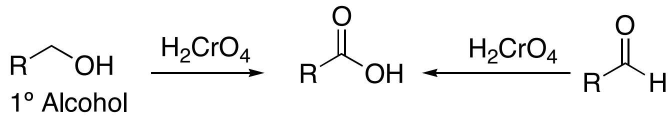
4. 

5. 

6. 

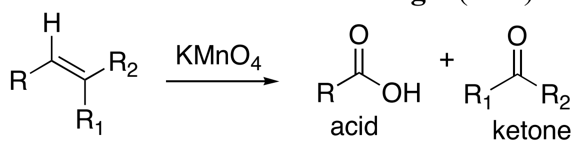
Synthesis of Carboxylic Acids

1. **From 1º Alcohols and Aldehydes: Oxidation** (Section 15.9)



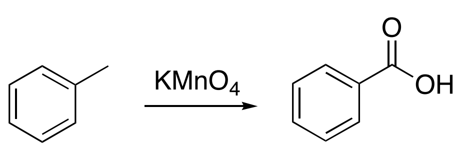
- No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage**: (6.20)



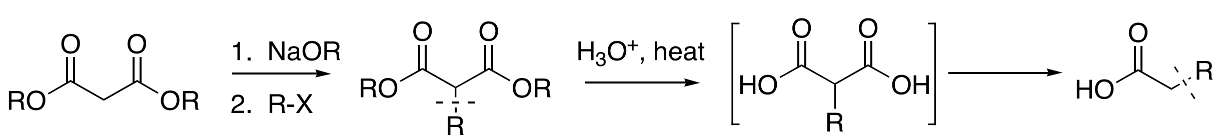
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH_2 would give an acid and carbonic acid (H_2CO_3), etc..

3. **From Aromatics**: **Oxidation of Alkylbenzenes** (11.12)



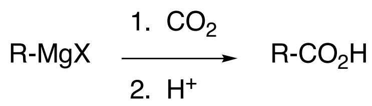
- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

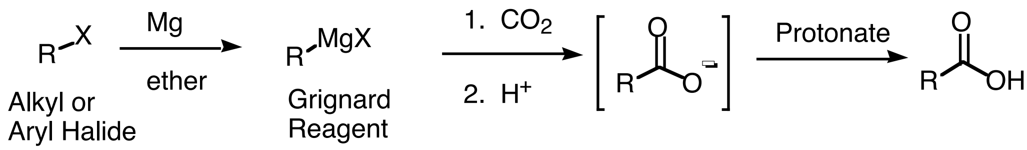
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 18.16)



- Mechanism: Deprotation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

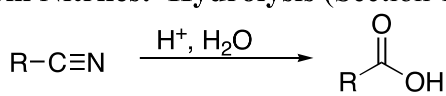
5. **From Grignard Reagents: Via Carboxylation**: (Section 18.11)





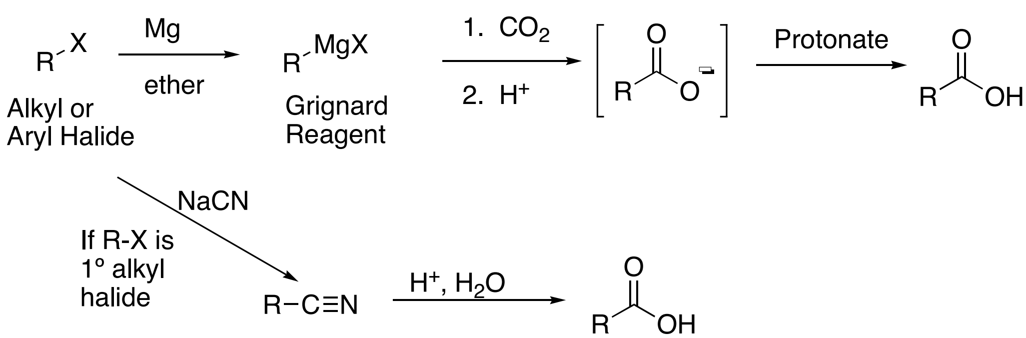
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 18.12)



- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**

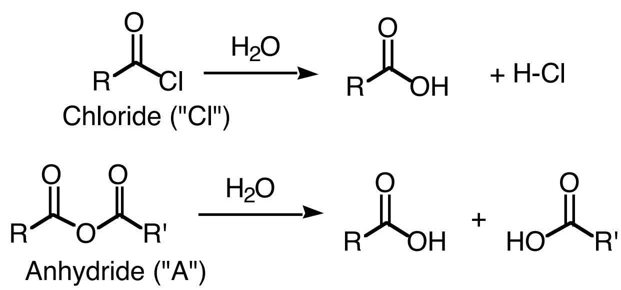


- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents

8. **From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis** (Ch 19)

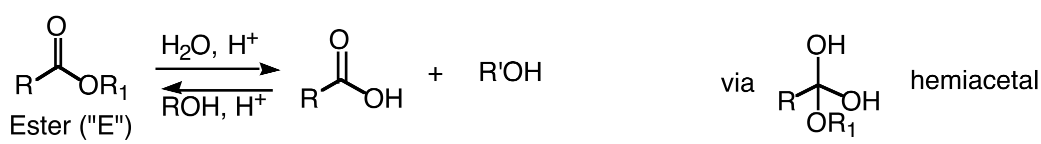
a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone

- **mechanism required: addition-elimination-deprotonation**



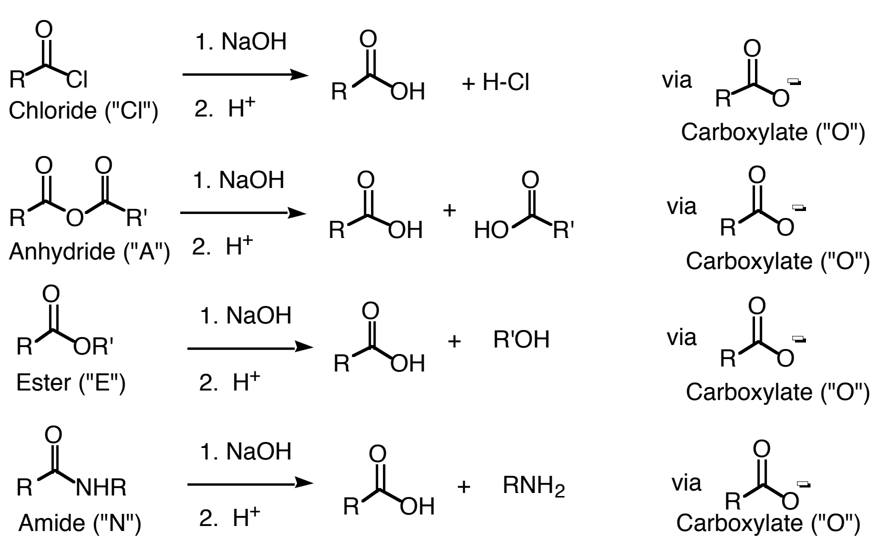
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester



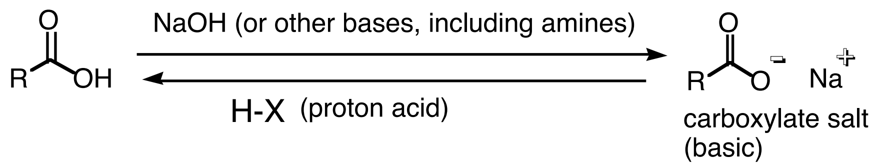
c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H^+ workup

- **mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation**
- Since the reaction with NaOH is always downhill, all of these reactions work



Reactions of Carboxylic Acids

9. **Reaction as a proton Acid** (Section 18.4-6)

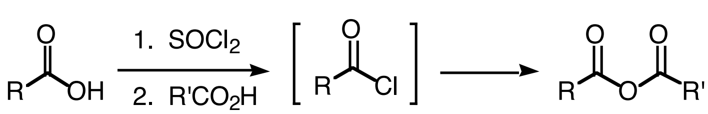


- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more stable than hydroxide or alkoxide anions, which is why the parents are carboxylic "acids"
- Carboxylic acids are more acidic than ammonium salts
- Patterns in acid strength: Reflect stabilization/destabilization factors on the carboxylate
    - Electron donors destabilize the carboxylate anion, so make the parent acid less acidic
    - Electron withdrawers stabilize the carboxylate anion, so make the parent acid more acidic

10. **Conversion to Acid Chlorides** (Section 12.7, 19.4)

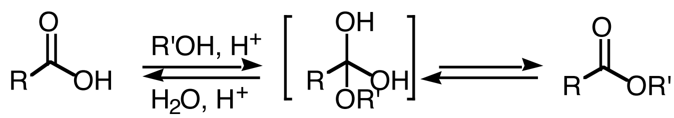
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides**



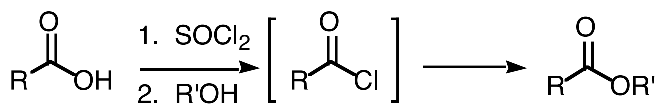
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction

12. **Direct Conversion to Esters** (18.13-15), 19.19



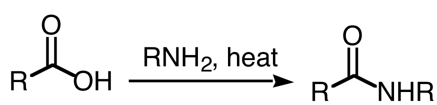
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a "lateral" reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b

13. **Indirect Conversion to Esters via Acid Chlorides** (Section 19.4)



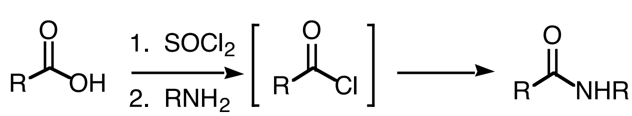
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.

14. **Direct Conversion to Amides**



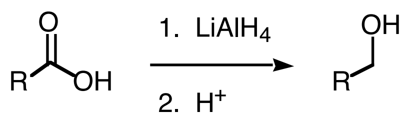
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.

15. **Indirect Conversion to Amides**



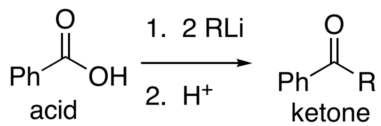
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

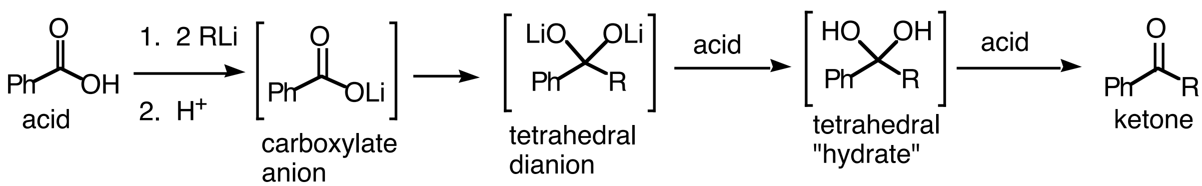
16. **Reduction to Primary Alcohol**



- **mechanism not required**

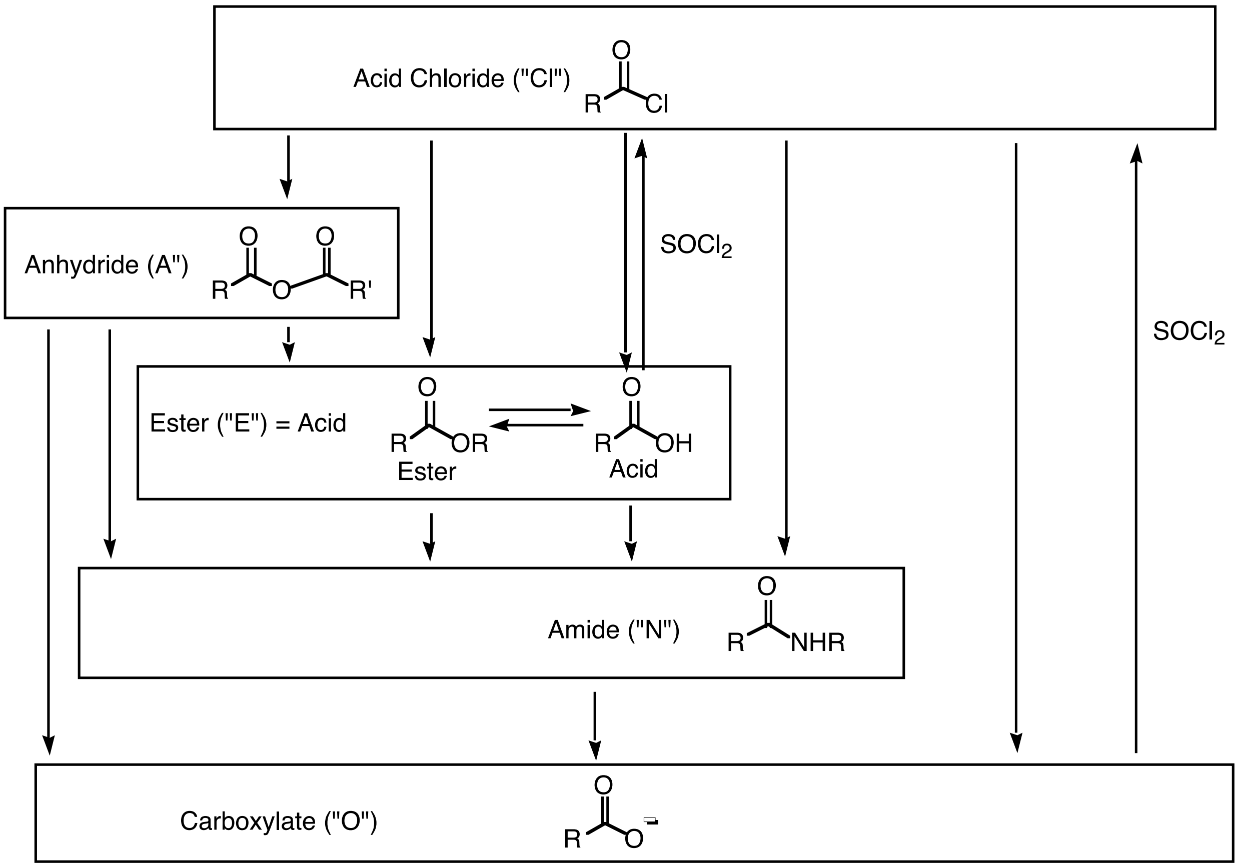
17. **Alkylation to Form Ketones** (Section)





- **mechanism not required**

18. **Interconversions of Acids and Acid Derivatives**

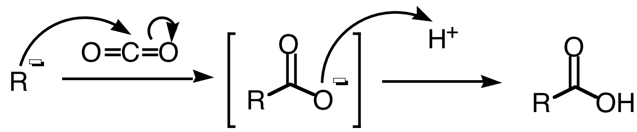


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with $SOCl_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

Mechanisms

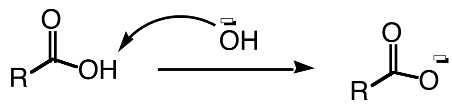
A. Miscellaneous

5. **From Grignard Reagents: Via Carboxylation**:



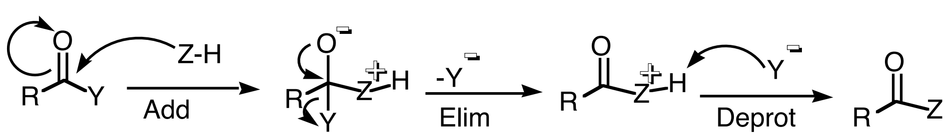
- exactly like any Grignard reaction

9. Reaction as a Proton Acid



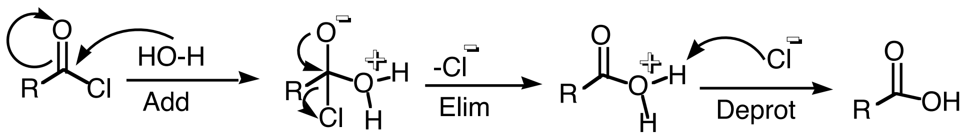
B. Any "Downhill" Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

General

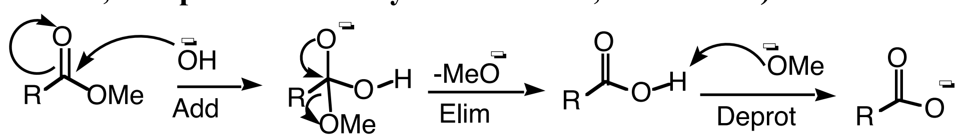


Examples

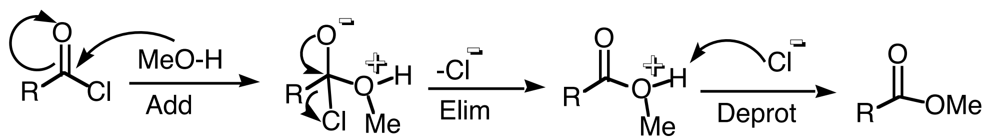
Reaction 8a



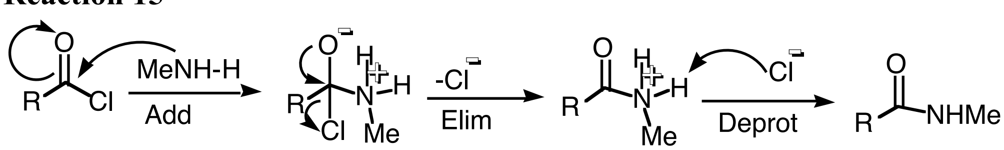
Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)



Reaction 13



Reaction 15

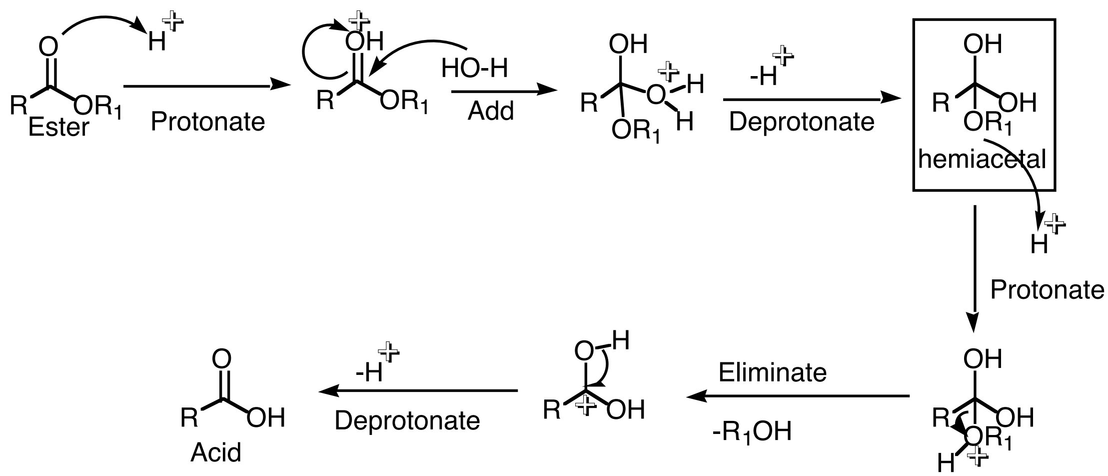


C. "Lateral" Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)

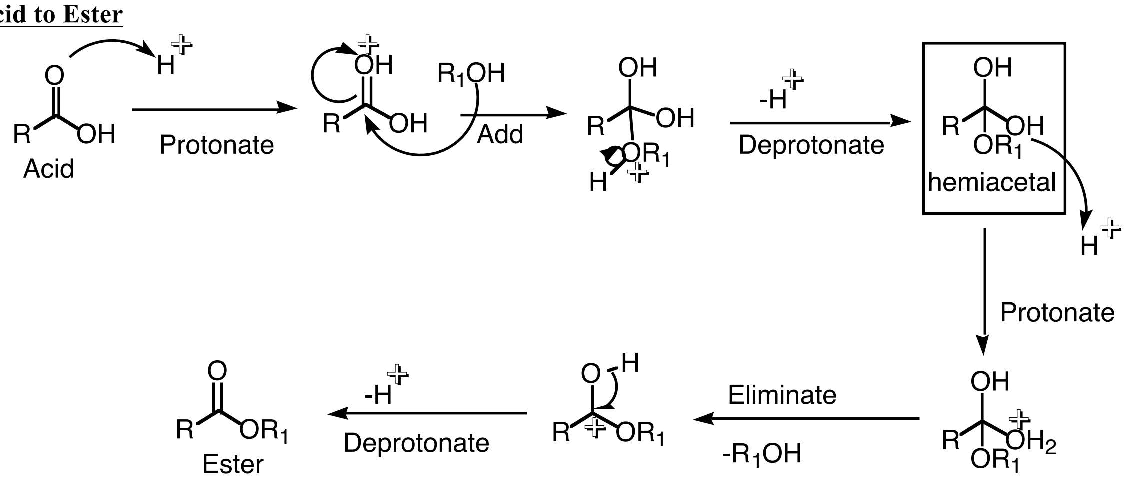
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

Examples

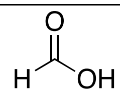
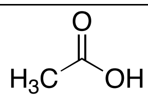
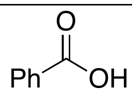
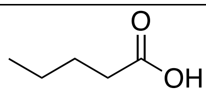
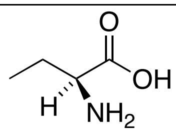
Reaction 8b: Ester to Acid



Reaction 12: Acid to Ester



Nomenclature (18.1) Formal: alkanoic acid (space in between)
-highest priority of any functional group

	Formal	Common
	Methanoic acid	Formic acid
	Ethanoic acid	Acetic acid
	Benzoic acid	Benzoic acid
	Pentanoic acid	
	(S)-2-aminobutanoic acid	

1. Nomenclature. Provide names or structures for the following.

   a. 3-phenylbutanoic acid

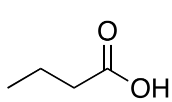
   b. 2,2-dichloropropanoic acid

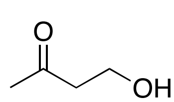
   c. 2-hydroxy-3-propanoyl-4-ethoxy-5-amino-6-oxoheptanoic acid

Physical Properties (Section 18.3)
Boiling Points: (weight being equal): acid > alcohol > 1,2º amines > non-H-bonders
- Acids boil about 20º higher than same-weight alcohols
- First four acids are completely water soluble

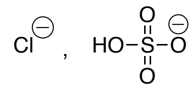
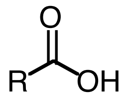
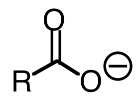
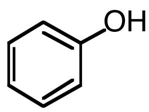
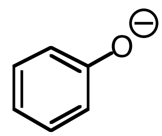
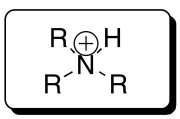
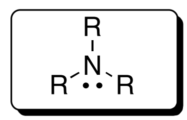
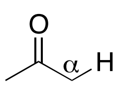
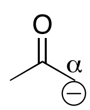
Water solubility (weight being equal): amines > acids ? ketones, alcohols, ethers >> alkanes
- Basicity is more important than acidity

2. Circle the one with higher boiling point, and square the one with the greater solubility in water.





Acidity/Basicity Table: With both Neutral and Cationic Acids and both Neutral and Anionic Bases (Section 18.4-7)

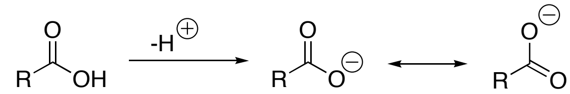
Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^{2}				**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^{0}		H_2O, HOR neutral		**H**umans
Carboxylic Acid		10^{-5}				**C**uz
Phenol		10^{-10}				**P**eople
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	**10^{-12}**		 Neutral, but basic!		**A**gainst
Water	HOH	10^{-16}		HO^-		**W**orking
Alcohol	ROH	10^{-17}		RO^-		**A**re
Ketones and Aldehydes		10^{-20}				**K**ingdoms
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^- Li^+$		**A**nimal
Alkane (C-H)	RCH_3	10^{-50}		RCH_2^-		**A**ll

Quick Checklist of Acid/Base Factors

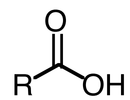
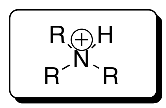
1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

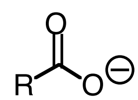
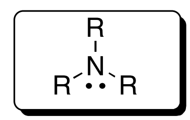
- **When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.**
- **When A neutral acid is involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

Acidity (18.4-6)



- Anion is stabilized by conjugation/resonance
- Charge dispersal
- Carboxylate is an anion, so is stabilized by electron withdrawing groups (increasing acidity) and destabilized by electron donating groups (decreasing acidity)

Carboxylic Acid		10^{-5}
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	$\mathbf{10^{-12}}$
Alcohol	ROH	10^{-17}


 Neutral, but basic!
$RO^{\ominus}$

- Acids are a million times more acidic than average ammoniums (despite charge)
- Acids are trillions more acidic than alcohols

Amino Acids:

- o Which way does the equilibrium lie?
- o Equilibrium always favors the weaker acid and weaker base?
- o What happens under acid conditions, and what happens under base conditions?

Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. acetic acid ethanol phenol

b. propanoic acid CH_3NH_3Cl $(CH_3)_3NHCl$

Substituent Effects (18.5)

- Withdrawers stabilize anions, increase acidity
- Donors destabilize anions, reduce acidity
- Opposite from the effect of donors and withdrawers on amines and ammoniums

1. Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. propanoc acid 3-Chloropropanoic acid 2-fluoropropanoic acid

b. benzoic acid p-methylbenzoic acid p-nitrobenzoic acid

2. For each of the following acid/base reactions, draw a circle around the weakest base, and draw an arrow to show whether the reaction would proceed from left to right, or from right to left.

a. 

b. Ph−OH + NaOH Ph−ONa + HOH

c. 

d. 

18.7 Carboxylate Salts

RCO_2H + NaOH → RCO_2Na + H_2O Produces weaker acid and base

- Easy to make
- Ionic → water soluble

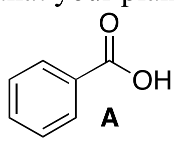
Acids are soluble in NaOH/water or $NaHCO_3/H_2O$

- Weak bases, react with HCl → RCO_2H
- Named: sodium alkanoate

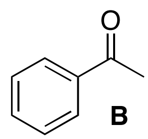
<u>Purification Schemes for Acids from other Organics Based on Acidity</u>

a. Dissolve acid and neutral organic in ether
b. Treat with NaOH/water
   - Neutral stays neutral, goes in ether layer
   - Acid is deprotonated to RCO_2Na, goes into water layer
c. Concentrate ether layer → pure neutral organic
d. Add HCl to aqueous layer, results in: RCO_2Na + HCl → RCO_2H
e. Neutral RCO_2H now has low solubility in water, so can be harvested by filtration (if solid) or by organic extraction

1. Design a solubility flow chart to separate benzoic acid ("**A**") from acetophenone PhC(O)CH_3 ("**B**"). Make sure that your plan enables you to isolate both **"A"** and "**B**".



A



B

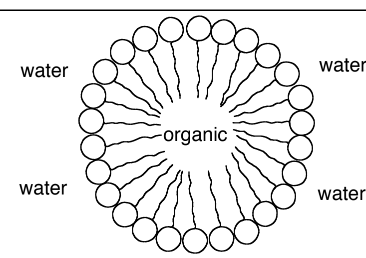
<u>Soaps (not for test)</u>

RCO_2Na with variable long alkyl chains

Ex: $C_{17}H_{35}CO_2^{\ominus}\ Na^{\oplus}$

Carboxylate head: hydrophilic → water soluble
Hydrocarbon tail: hydrophobic → can dissolve grease and organic materials

Form "micelles" in water

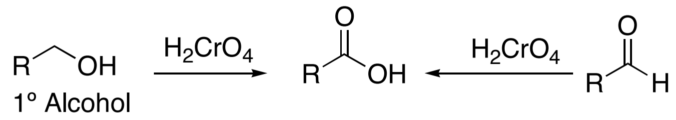
The hydrophobic hydrocarbon tails (strings) self-aggregate, while the ionic heads (circles) keep the microdroplet soluble in water. Organic materials can be dissolved inside the organic center, and carried through the water. Thus grease gets dissolved, and dirt protected by grease is freed.	

B. Synthesis of Carboxylic Acids

Synthesis of Carboxylic Acids

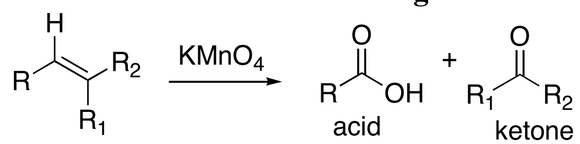
Review

1. **From 1º Alcohols and Aldehydes: Oxidation**



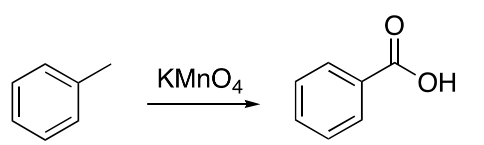
- No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage**:



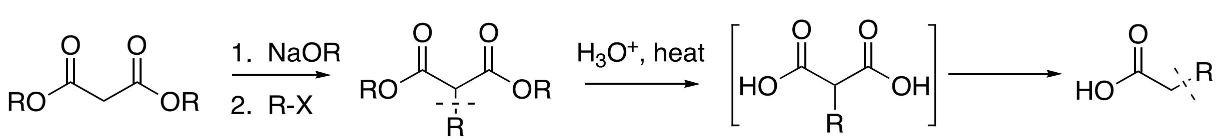
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH_2 would give an acid and carbonic acid (H_2CO_3), etc..

3. **From Aromatics**: **Oxidation of Alkylbenzenes**



- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

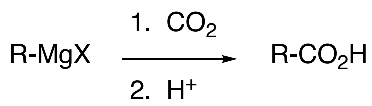
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**:

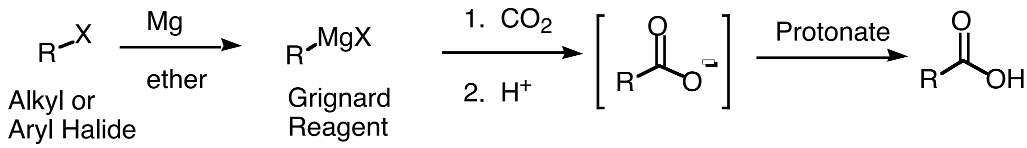


- Mechanism: Deprotation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

New Routes

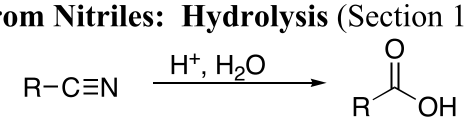
5. **From Grignard Reagents: Via Carboxylation**: (Section 18.11)





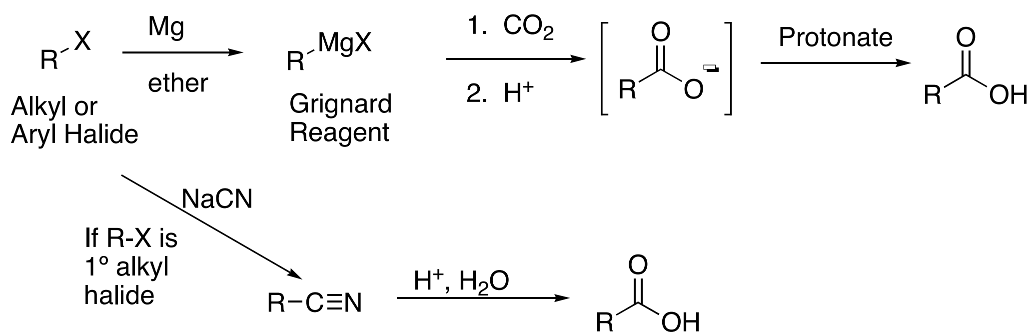
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 18.12)



- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**

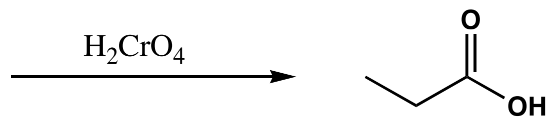


- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents

Problems

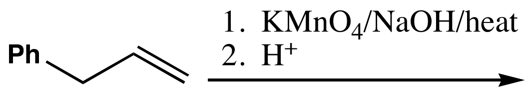
1. Preparation of Carboxylic Acids. Fill in the blanks for the following reactions.

a. (C_3H_8O)



b. Bromobenzene → 1. Mg; 2. epoxide; H_2O; 3. H_2CrO_4

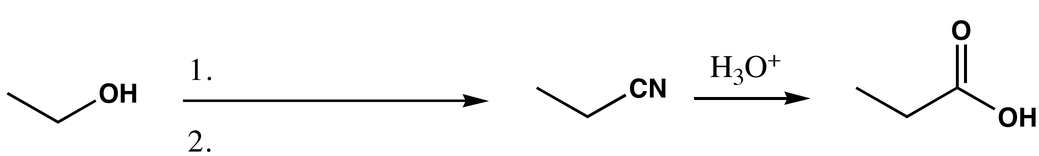
c.



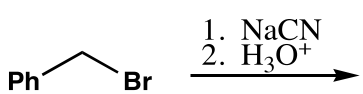
(+ carbonic acid)

d. Benzene → Br_2, $FeBr_3$ → Mg → 1. CO_2; 2. H^+ →

e.



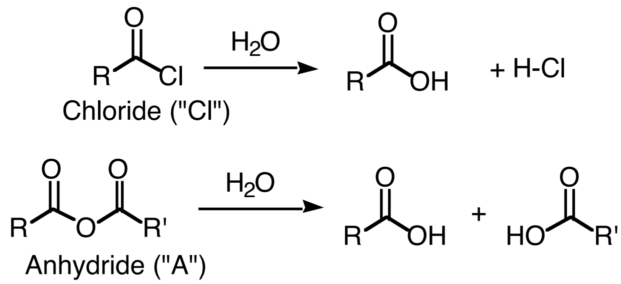
f.



8. **From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis**

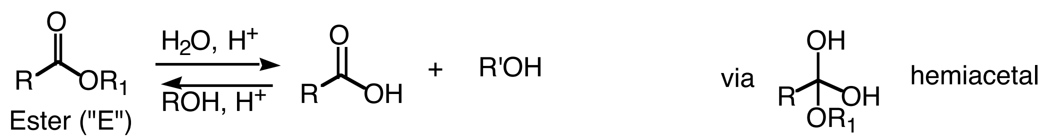
a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone

- **mechanism required: addition-elimination-deprotonation**



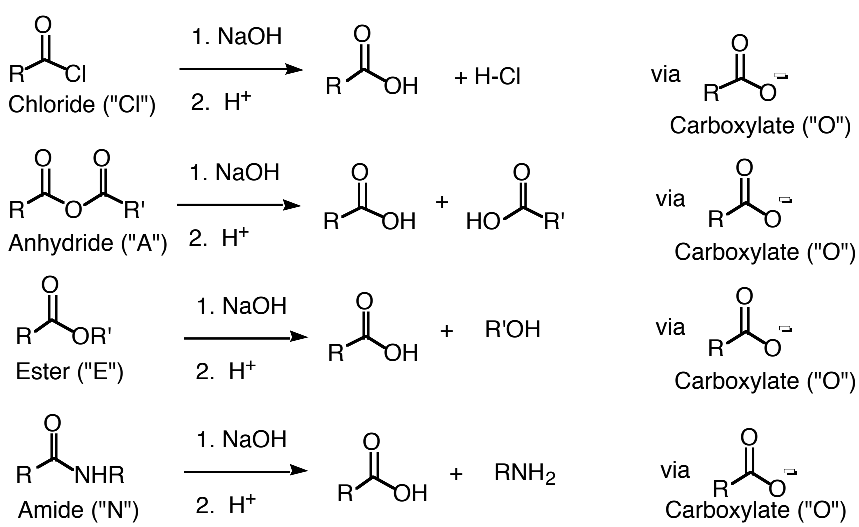
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester

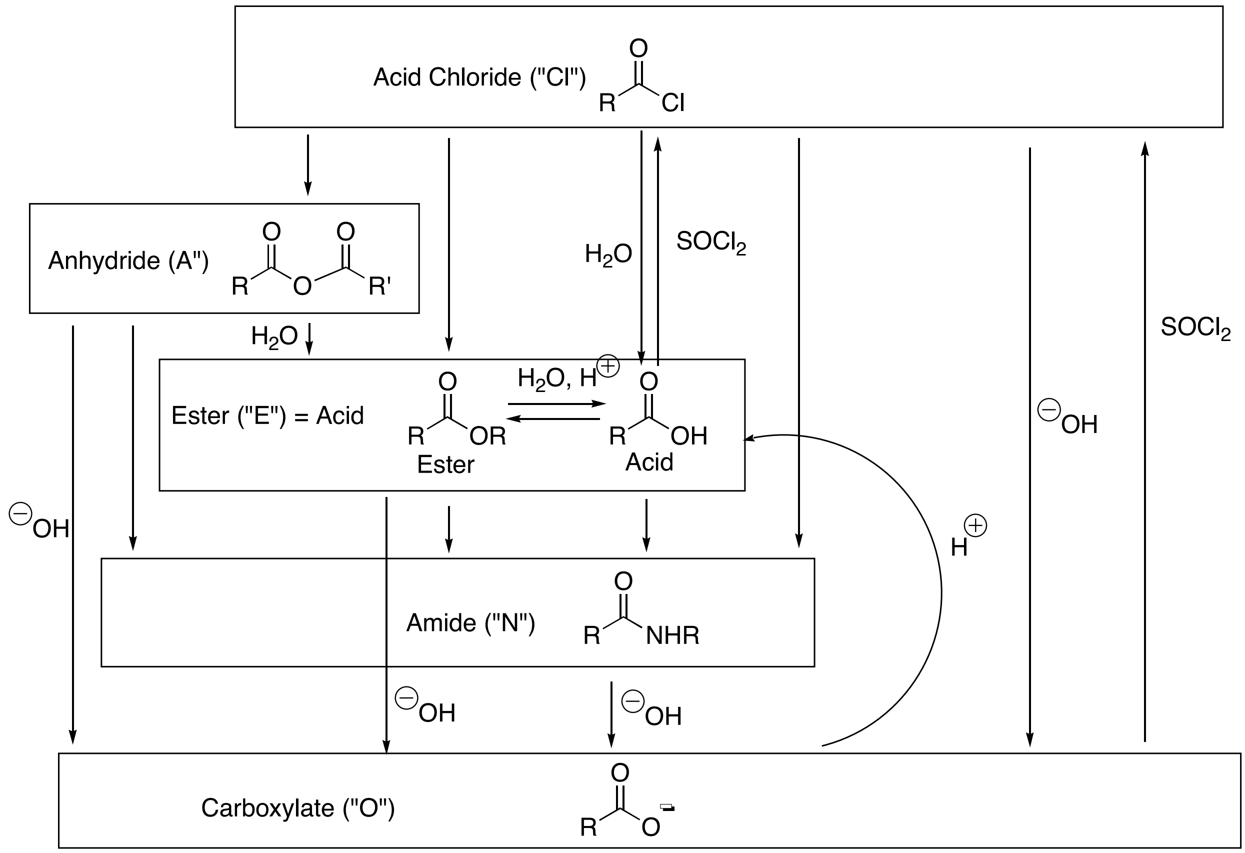


<u>c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H^+ workup</u>

- **mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation**
- Since the reaction with NaOH is always downhill, all of these reactions work



Interconversions and Reactivity of Acids and Acid Derivatives



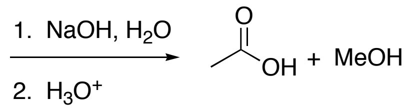
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires protonation or going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with $SOCl_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

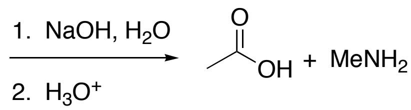
<u>"Cl-A-vE-N-O" applied to Hydrolysis</u>

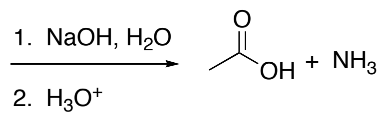
1. Chlorides and Anhydrides are "above" acids, so can be converted to acids by direct hydrolysis with neutral water
2. Esters are "lateral" to acids, so can be hydrolyzed to acids by acid-catalyzed hydrolysis
3. Chloride, anhydrides, esters, and amides can all be base-hydrolyzed (NaOH/water) to carboxylates.
   - Subsequent acid workup protonates the carboxylate and produces the acid
   - Base hydrolysis always works
4. For amides, basic hydrolysis is the only way to do it

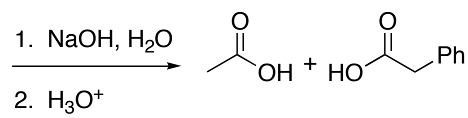
1. For the following problems, draw the starting materials that would give the indicated hydrolysis products.

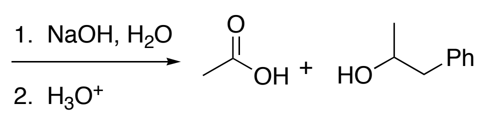
- Note: All of these are drawn as basic hydrolyses, but some could also be done using neutral water or acidic water. Mark which could proceed using neutral hydrolysis or acid-catalyzed hydrolysis in addition to via basic hydrolysis.







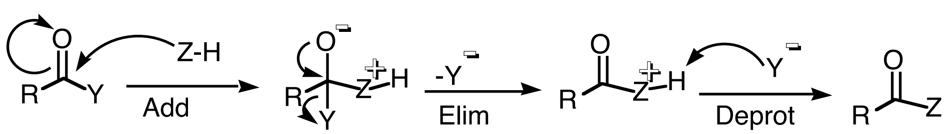




Mechanism: General Mechanism for Any "Downhill" Cl-A-vE-N-O Interconversions (19.3):

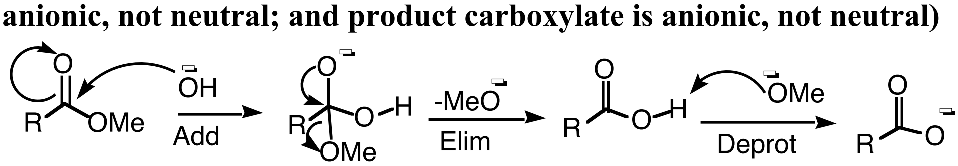
All Proceed by Addition-Elimination-Deprotonation

General



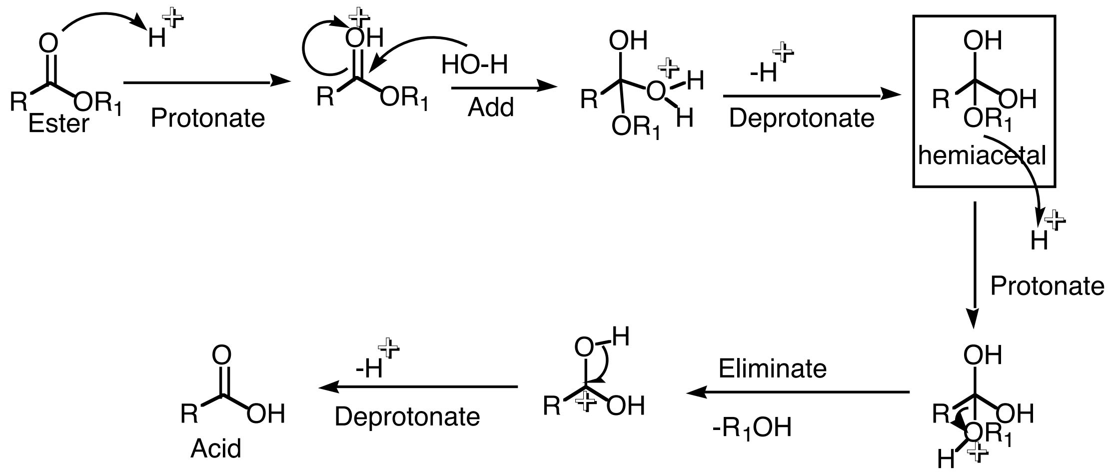
- note: there are variations on these, and this is somewhat simplistic. In many cases, the carbonyl will be pre-protonated or co-protonated to assist deprotonation, and will need to be deprotonated again later. I will settle for the simplified view shown.

<u>Base Case</u>, Using Anionic Hydroxide: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)

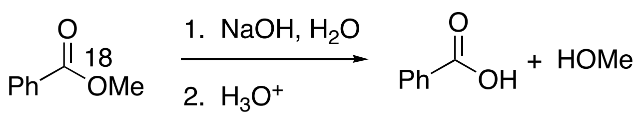


Acid-Catalyzed conversion from Ester to Acid (8b): (ACID WATER)

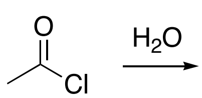
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

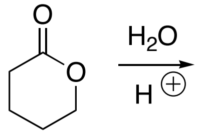


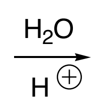
Draw the Mechanisms for the following Hydrolyses



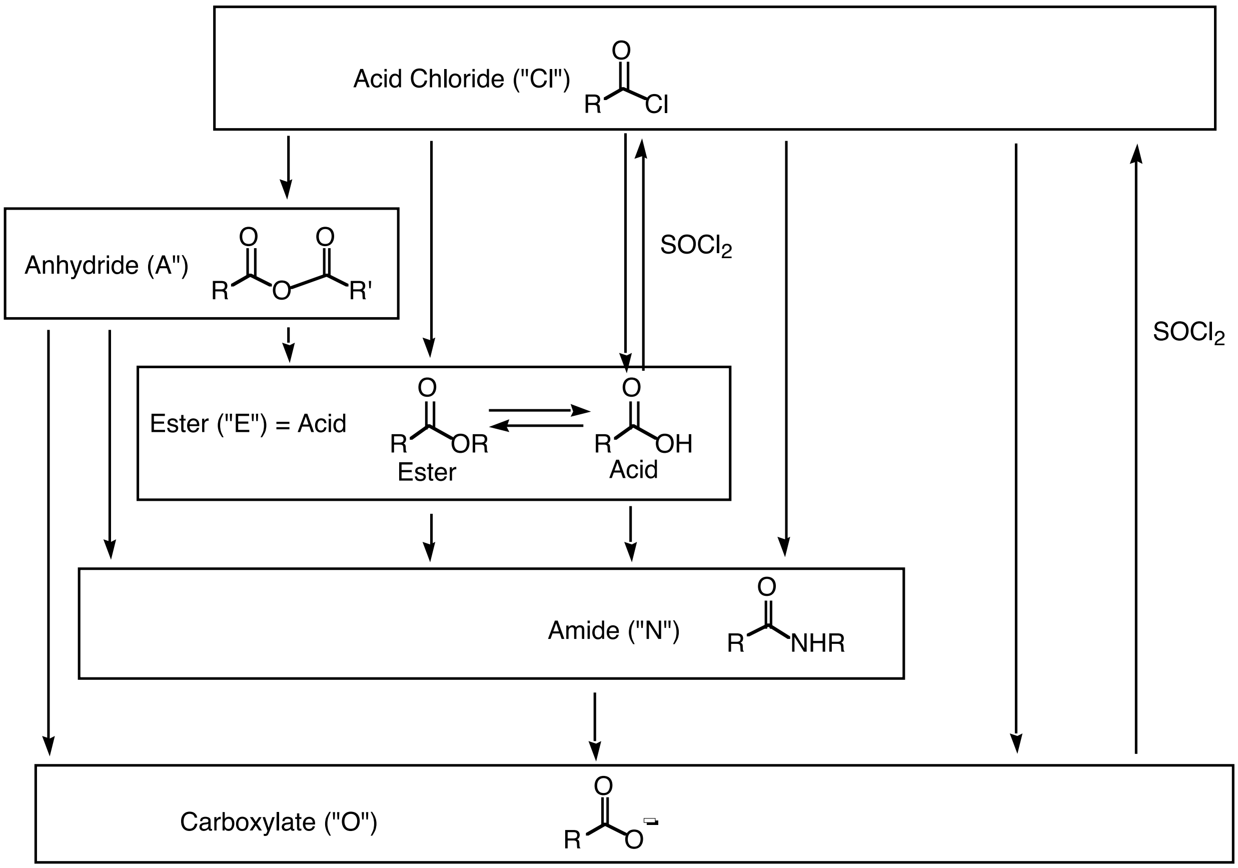
Where will the O^{18} label end up?







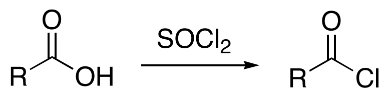
C. Reactions of Carboxylic Acids: Interconversions with Derivatives: Cl-A-vE-N-O

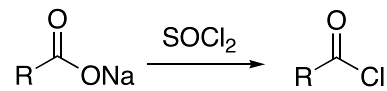


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with $SOCl_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

Acid Chlorides: Preparation and Uses

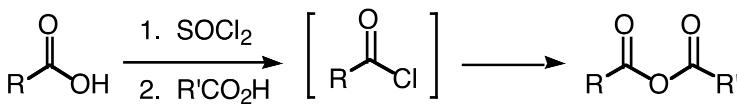
10. **Conversion of acids or Carboxylates to Acid Chlorides**





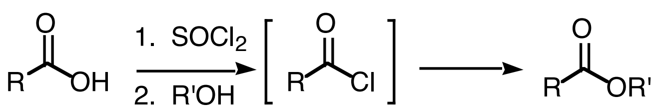
- Mechanism: Not Required
- Easy (but smelly) reaction.
    - Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides**



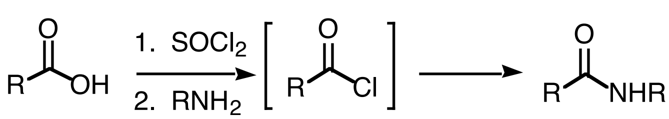
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction
- Base often present to absorb the HCl

13. **Indirect Conversion to Esters via Acid Chlorides**



- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.
- Base often present to absorb the HCl

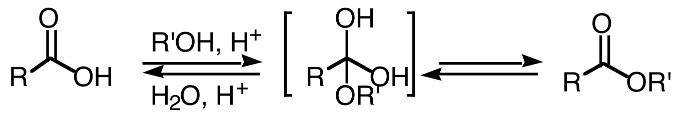
15. **Indirect Conversion to Amides**



- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory
- Base often present to absorb the HCl

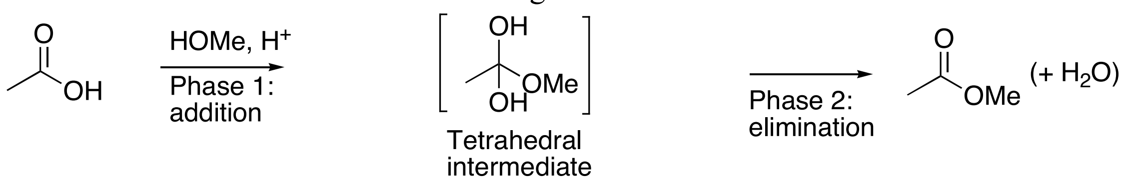
Condensation/Hydrolysis: Interconversions between Acids and Esters

12. **Direct Conversion to Esters**

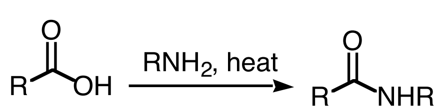


- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control.
  1. With excess water, you go to the acid.
  2. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a "lateral" reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b
- Under base conditions, the equilibrium always goes completely away from the ester and goes to the acid side
  1. The base deprotonates the carboxylic acid, so LeChatellier's principle says that the equilibrium keeps driving from ester towards acid to compensate

2. Draw the mechanism for the following reaction.



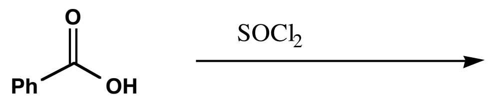
14. **Direct Conversion to Amides**

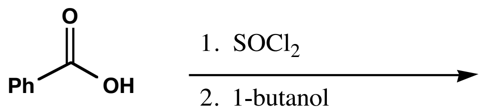


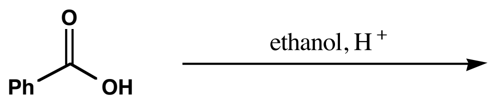
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.

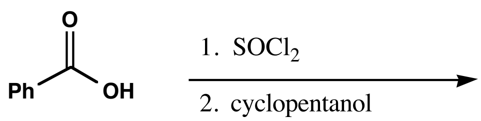
Problems

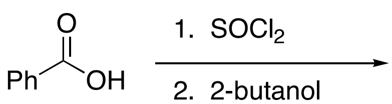
1. Synthesis of Acid derivatives. Draw the products for the following reactions.

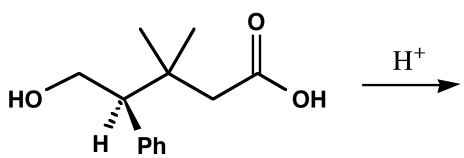
a.


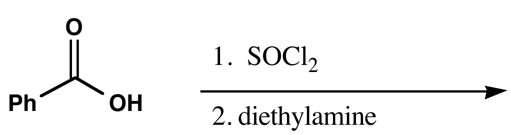
b.


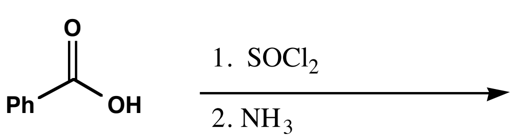
c.


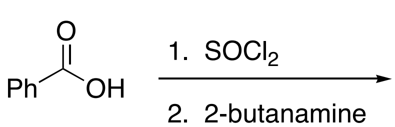
d.


e.


f.


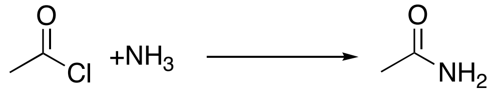
g.


h.


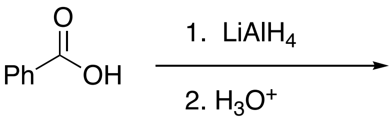
i.


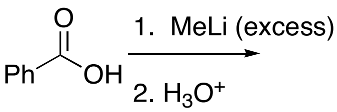
j.

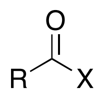

1. Draw the mechanism.

b. 

2. Draw the products for the following reactions.

a. 

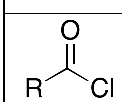
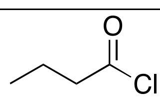
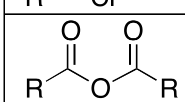
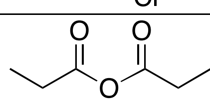
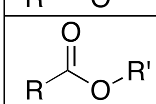
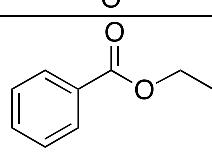
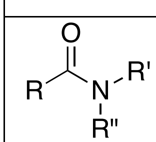
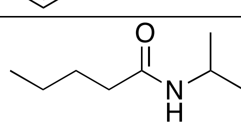
b. 

Ch. 19 Carboxylic Acid Derivatives: 

- Cl chloride
- A anhydride
- E ester
- N amide
- O: carboxylate

Structure, Names, Notes

- all are subject to hydrolysis
- All hydrolyze to acids (actually, to carboxylate anion) upon treatment with NaOH/H_2O
- Some (Cl and A) hydrolyze to acids under straight water treatment
- Esters hydrolyze to acids under acid catalysis

	General		Example	
	Alkanoyl chloride		Butanoyl chloride	• High reactivity • Named as if ionic
	Alkanoic Anhydride		Propanoic anhydride	
	Alkyl Alkanoate		Ethyl Benzoate	Named as if ionic
	Alkanamide		N-isopropyl pentanamide	

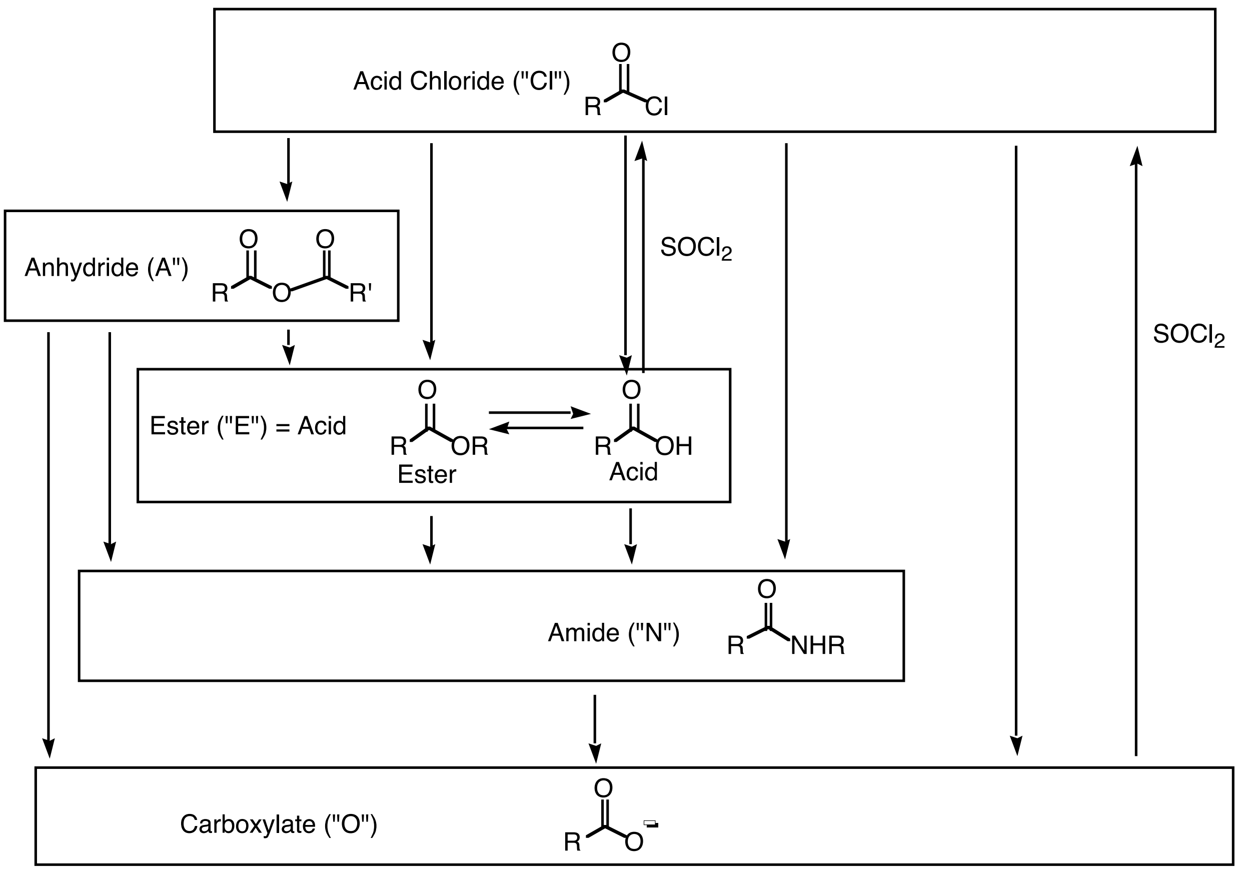
1. Draw the structures for the following esters.

a. propyl benzoate

b. methyl ethanoate

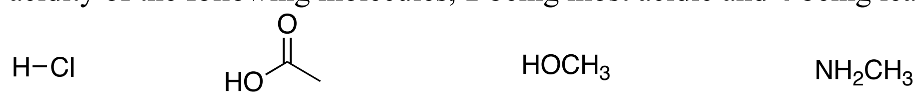
c. ethyl butanoate

Interconversion of Acid Derivatives: Cl-A-vE-N-O

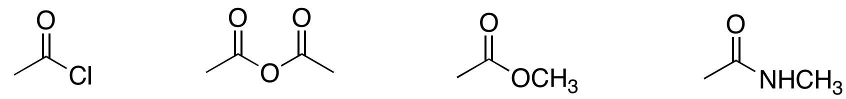


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with $SOCl_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

1. Rank the acidity of the following molecules, **1** being most acidic and **4** being least acidic.

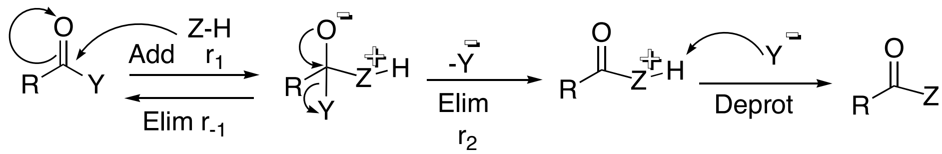


2. Rank the reactivity of the following toward hydrolysis. Do you see a similarity between your rankings for this question relative to your answers for previous question?



Notes:

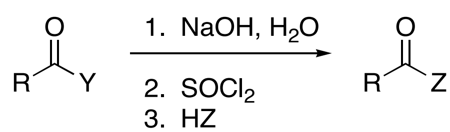
- Any "downhill" reaction can be done in one laboratory step
- Any "downhill" reaction involves a 3-step mechanism: addition-elimination-deprotonation



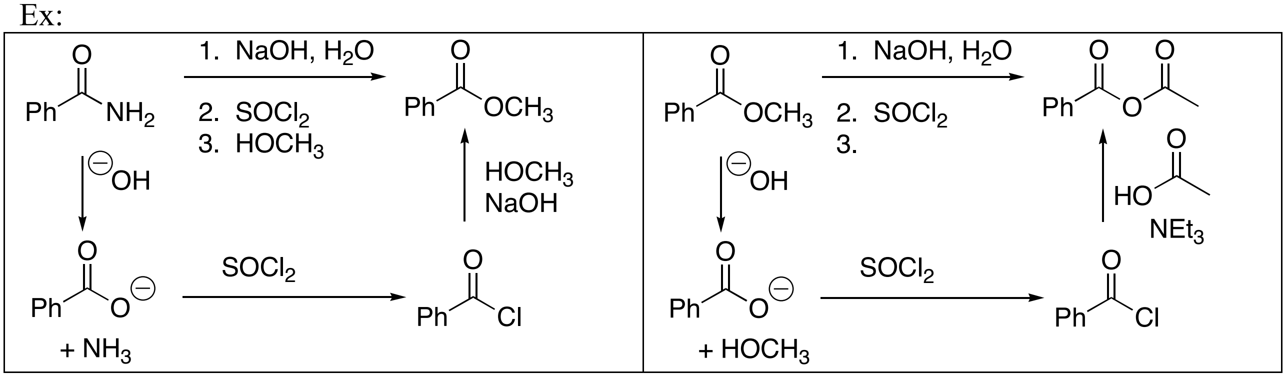
- The overall reactivity correlates the leaving ability of the Y ⊖ for two reasons
  1. This affects the kinetic r_2/r_{-1} partion. If r_2 is slow, the addition is simply reversible
  2. The same factors that make Y ⊖ a good leaving group also make the initial carbonyl more reactive toward addition (step 1, r_1).
  3. Thus good leaving groups have benefits at both r_1 and r_2

- Memory
  - Think anion stability
  - Cliff | Cl-A-vE-N-O |

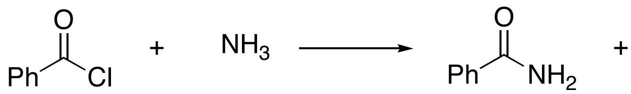
B. "Uphill" Reaction Sequences: 3-steps



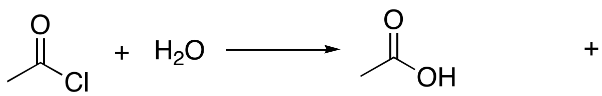
Ex:

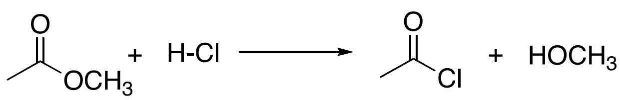


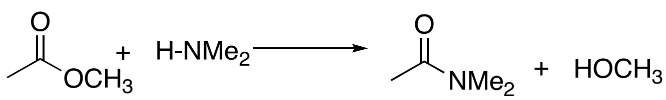
1. Which will proceed easily/directly? ("downhill"?) Add Appropriate Reactant(s) and Side Product. If it doesn't go directly, give indirect route.

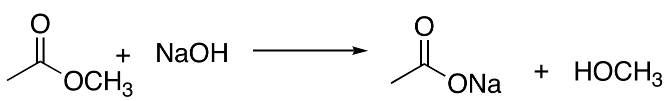
a. 

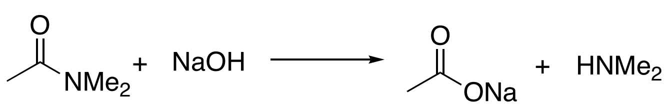
b. 

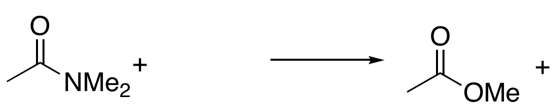
c. 

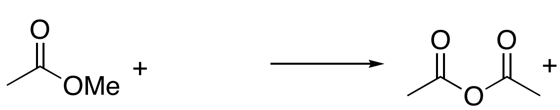
d. 

e. 

f. 

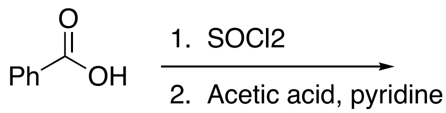
g. 

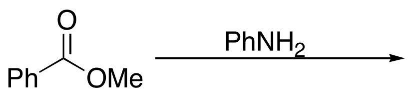
h. 

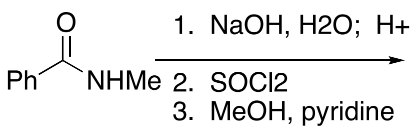
i. 

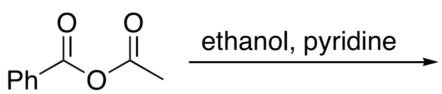
1. Provide products for the following transformations.

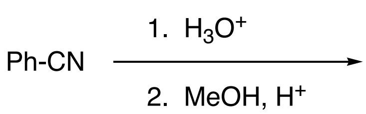
a. 

b. 

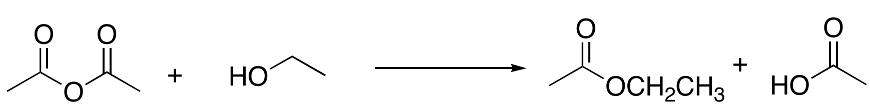
c. 

d. 

e. 

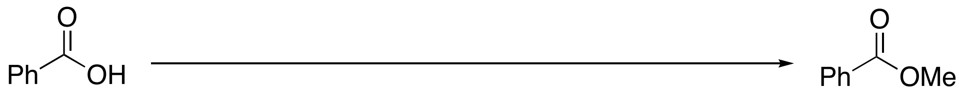
f. 

2. Draw the mechanism for the following reaction.



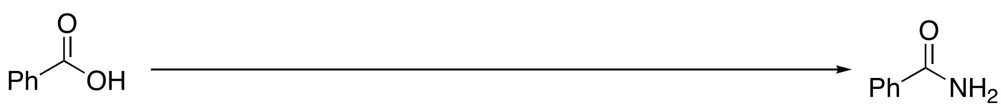
(3 steps)

1. Provide reagents for the following transformations.

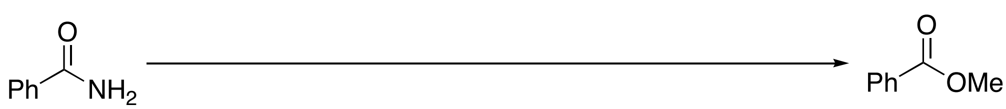
a.  (Method 1)

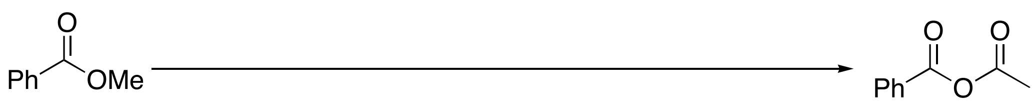
b.  (Method 2)

c.  (Method 1)

d.  (Method 2)

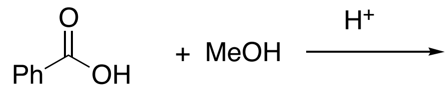
e. 

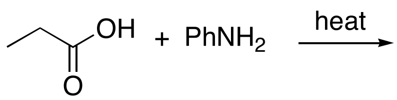
f. 

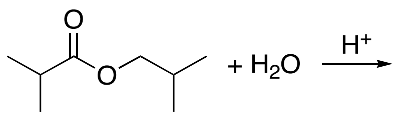
g. 

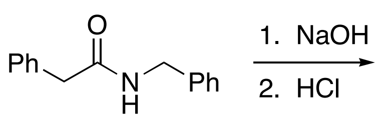
h. 

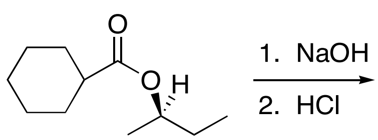
2. Provide products for the following condensation or hydrolysis transformations.

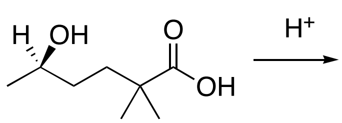
a. 

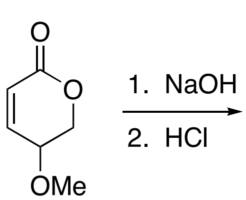
b. 

c. 

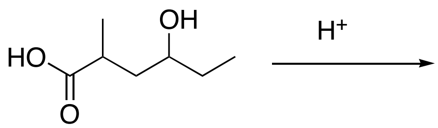
d. 

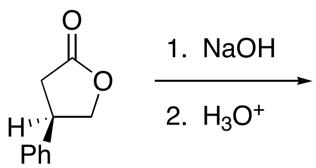
e. 

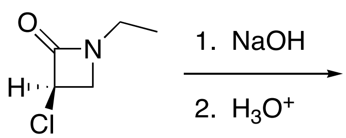
f. 

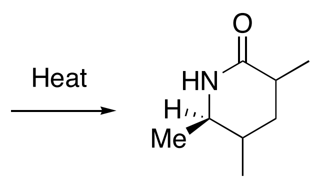
g. 

3. Cyclic Esters and Amides: Provide products or starting reactants for the following condensation or hydrolysis reactions involving cyclic esters or amides.

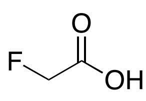
a. 

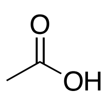
b. 

c. 

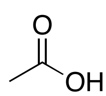
d. 

4. Rank the following as acids or bases.

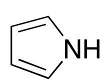
a. 



$CH_3NH_3^{\oplus}$ NH_3

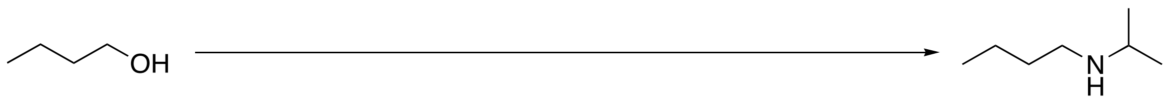
b. $(CH_3)_2NH_2^{\oplus}$ $PhNH_3^{\oplus}$ 

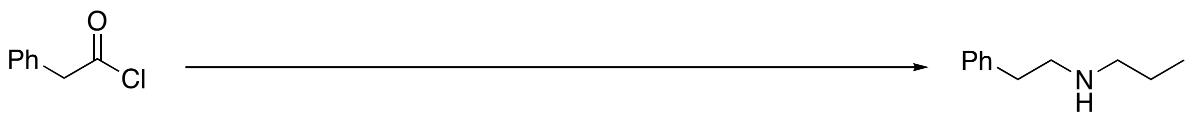
H_2O

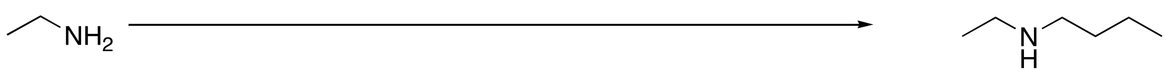
c. Et_3N $EtNH_2$ 

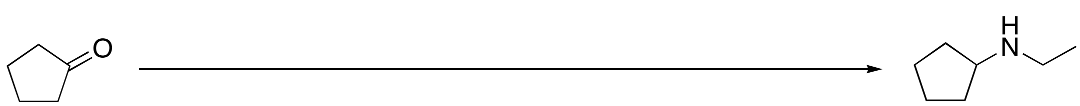
PhMgBr

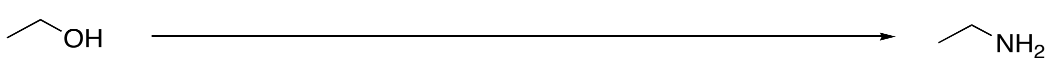
5. Provide reagents for the following transformations. There may be more than one solution.

a. 

b. 

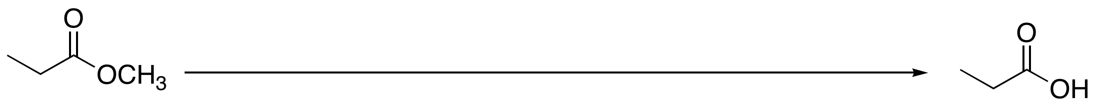
c. 

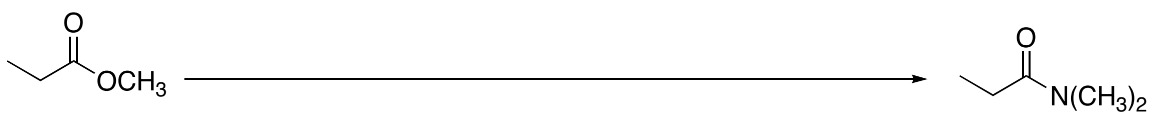
d. 

e. 

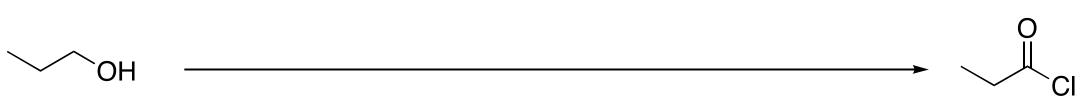
f. 

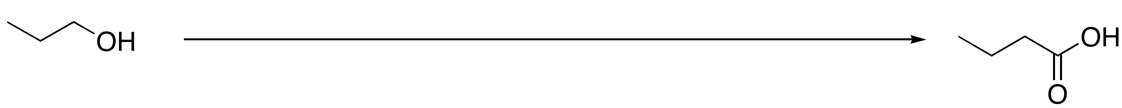
6. Provide reagents for the following transformations. There may be more than one solution.

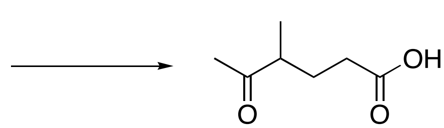
a. 

b. 

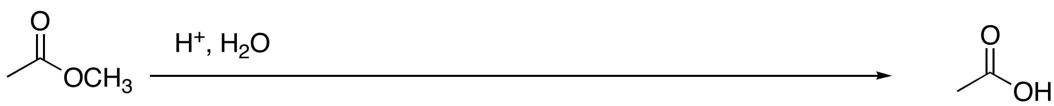
c. 

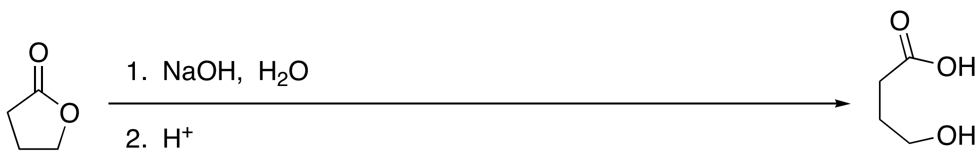
d. 

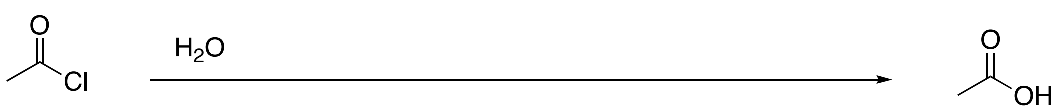
e. 

f. 

7. Provide mechanism for the following reactions.

a.


b.


c.


d. $CH_3NH_2 \xrightarrow{3\ CH_3Br,\ NaOH} (CH_3)_4N^{\oplus}\ Br^{\ominus}$