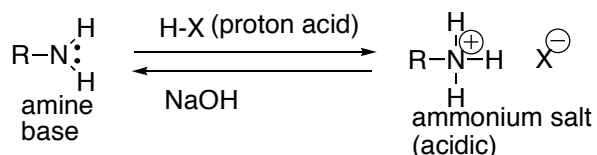


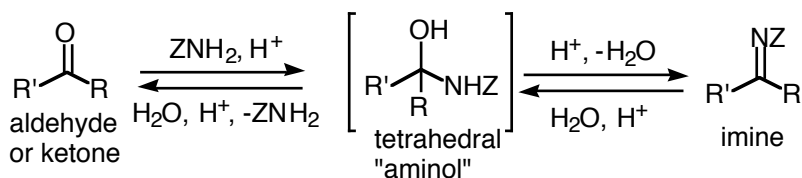
Reactions of Amines

1. Reaction as a proton base (Section 19-5 and 19-6)



- 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, $3^\circ > 2^\circ > 1^\circ$

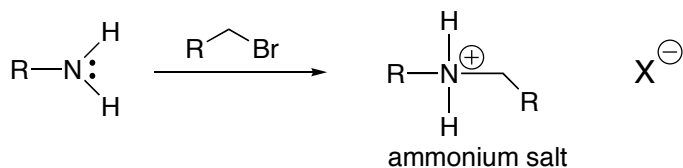
2. Reaction with Ketones or Aldehydes (Section 18-16,17 and 19-10)



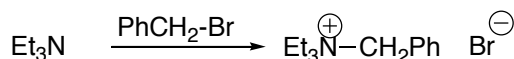
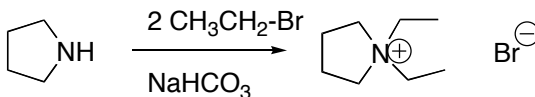
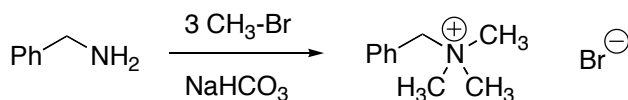
Notes:

- “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 \rightarrow 2° , 3° amines can’t do this

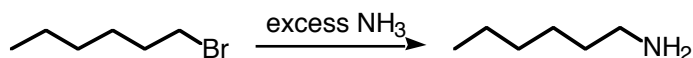
1. Alkylation of 1° Alkyl Halides (Section 19-12, 19-21A)



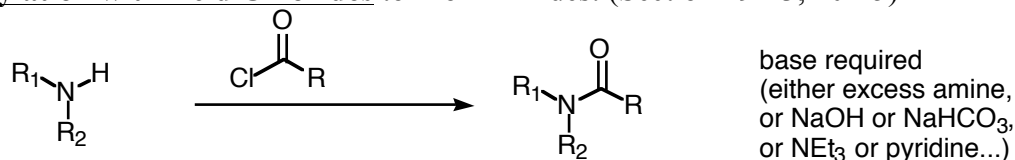
- **3a. Polyalkylation** is routine.
 - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below).
 - Mechanism required for polyalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



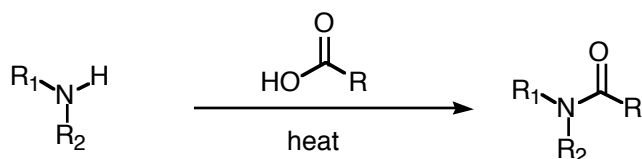
- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
 - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.



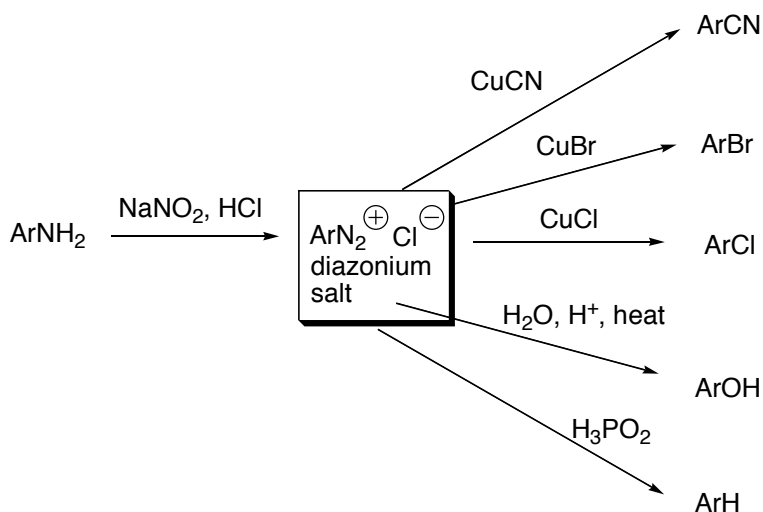
2. Acylation with Acid Chlorides to Form Amides: (Section 19-13, 20-15)



- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1°, 2°, or NH₃ all react well.
- But 3° 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 NaHCO₃ can be used.

4b. **Acylation with Carboxylic Acids** to Form Amides: (Section 20-12)

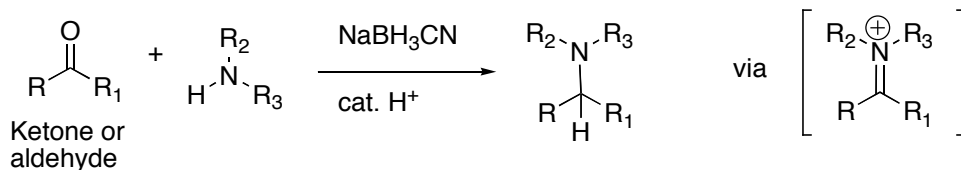
- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid \rightarrow amide is routine, and is facilitated by complex enzyme mechanisms

3. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)

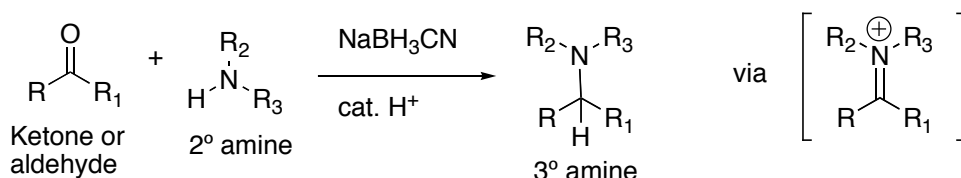
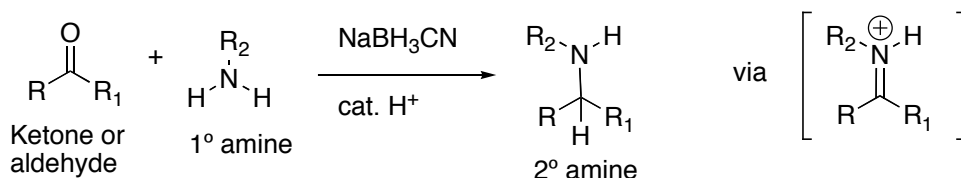
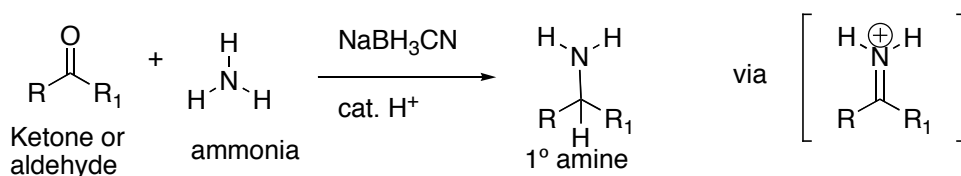
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2 , a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). 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

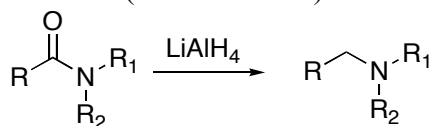
6. From Aldehydes or Ketones: Reductive Amination (Section 19-19)



- 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 R₂ and/or R₃ can be either a carbon or a hydrogen. Thus:
 - NH₃ → 1° RNH₂
 - 1° RNH₂ → 2° R₂NH
 - 2° R₂NH → 3° R₃N
 - 3° R₃N don't react

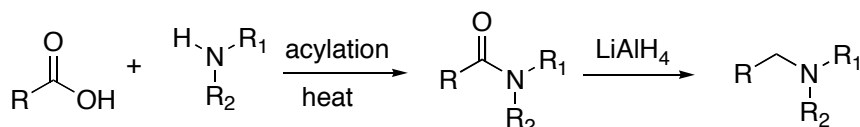
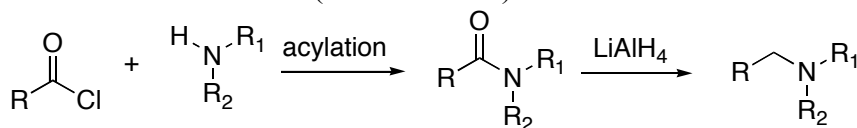


7. Via Amides: (Section 19-20)



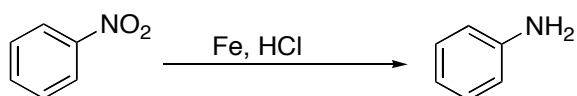
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R₁ and R₂ can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
 - RCONH₂ → 1° RCH₂NH₂
 - RCONHR → 2° RCH₂NHR
 - RCONR₂ → 3° RCH₂NR₂

8. From Amines via Amides: (Section 19-20)



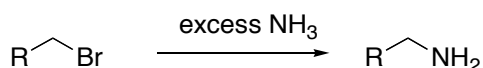
- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. Reduction of nitro compounds: (section 19-21C)



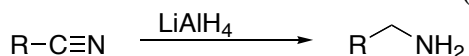
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
 - Pd/H₂, Ni/H₂, Pt/H₂,
 - Fe/HCl, Zn/HCl, Sn/HCl

10. From 1° Alkyl Halides: Alkylation of Ammonia (Section 19-12, 19-21A) (See reaction 3).



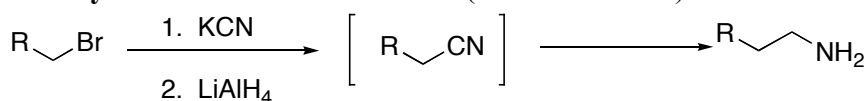
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH₃ prevents polysubstitution.

11. From Nitriles: Reduction of Nitriles (Section 19-21B)



- Access: 1° amines
- Mechanism not required.

12. From Alkyl Halides: Via the Nitrile (Section 19-21B)



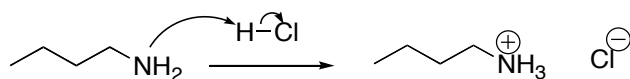
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

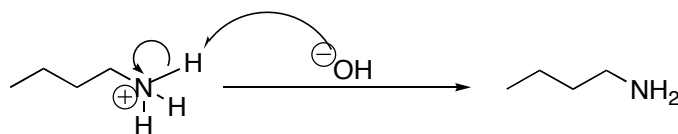
| Route | Reaction Number | Source/ Precursor | Reagent | Available Amines | Comments |
|-------|-----------------|---|--|--|--|
| 1 | #6 | Aldehydes or Ketones | R_2NH , H^+ $NaBH_3CN$, | 1°, 2°, or 3° Amines | |
| 2 | #7, #8 | Amides | $LiAlH_4$ | 1°, 2°, or 3° Amines | |
| 3 | #7, #8 | Amines (via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

Mechanisms

1. Protonation

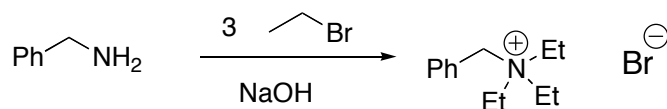


1.-Reverse. Deprotonation

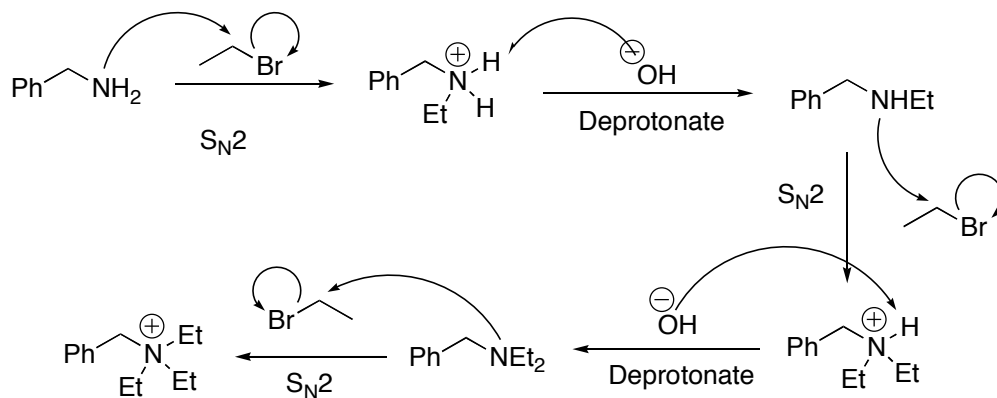


3. Polyalkylation

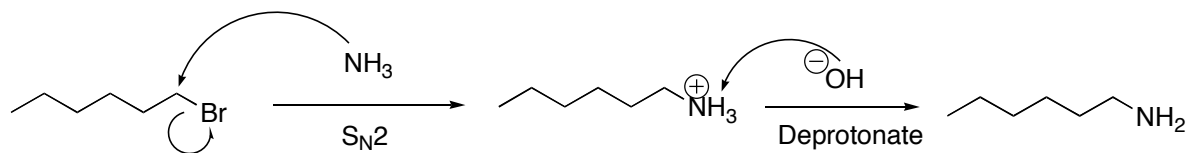
Ex:



Mech:

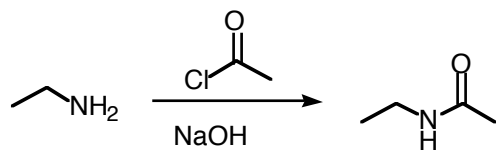


3b. Monoalkylation

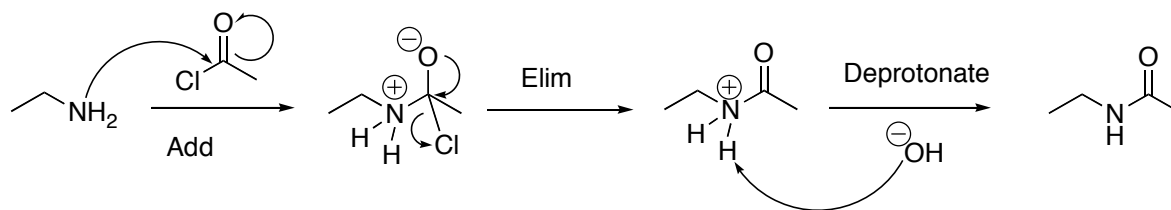


4. Acylation

Ex:



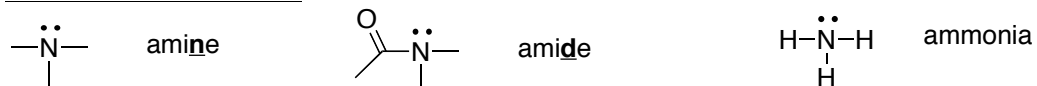
Mech: 3 steps: Addition-Elimination-Deprotonation



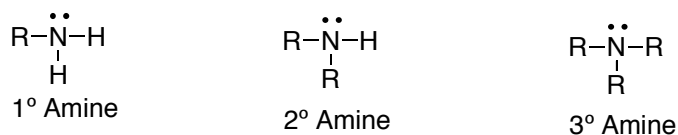
Chapter 19 Amines

A. Miscellaneous

19.1 Intro, Terms

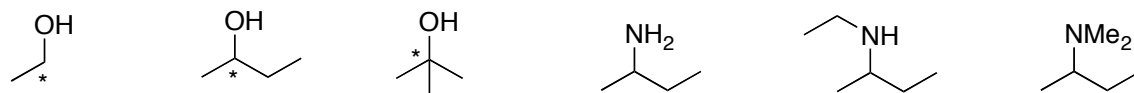
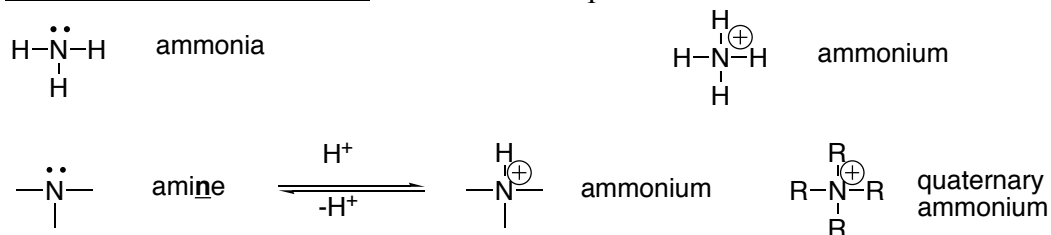
Amines versus Amides

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



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

- 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.
- 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

19.2 Formal Amine Nomenclature: alkan-x-amine, N-alkylalkan-x-amine, etc.

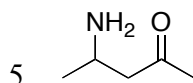
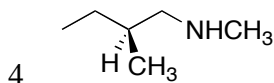
- For core name, choose longest C-chain to which nitrogen is attached, and call it alkan-x-amine (including for alkan-1-amines)
 - Number from end nearer N
 - Be sure to specify with a number which **carbon** has the nitrogen
 - The nitrogen does ****not**** count as a number itself.
- Substituents on the nitrogen (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”
- NH₂ as a Substituent: “Amino”

Draw the structure or provide the name for the following.

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

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

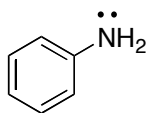
3. hexan-3-amine



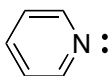
Common Naming (for simple amines): Alkylamine, dialkylamine, trialkylamine....

Three Common Amine Names to Memorize (Review from Aromatics Chapter)

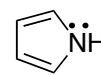
Aniline



Pyridine



Pyrrole



Some Other Famous Common Amine Names (No memory requirement)

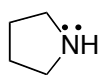
Name

Structure

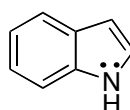
Name

Structure

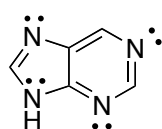
Pyrrolidine



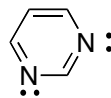
Indole



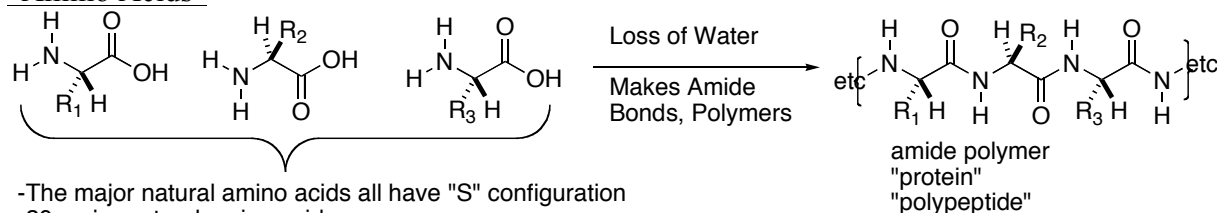
Purine



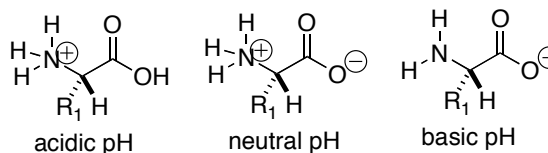
Pyrimidine



RNA, DNA, ATP, and ADP are made from derivatives of Purine and Pyrimidine

“Amino Acids”

- 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 the polymer essentially spells out the biological activity of the protein.

Test Keys:

- 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
- 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)?
 - Acidic** pH: both are in protonated acid forms **Overall Charge: POSITIVE**
 - nitrogen is cationic and carboxylic acid is neutral
 - 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
 - Basic** pH: both are in deprotonated base form **Overall Charge: NEGATIVE**
 - Nitrogen is neutral, carboxylic acid is anionic

Structure and Hybridization

1. **N atoms** 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. **N lone pair** 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

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

19.3 Physical Properties

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

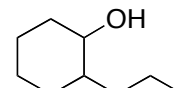
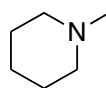
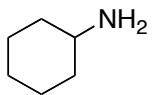
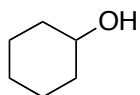
1. **Water Solubility:** All amines hydrogen-bond water → impacts solubility
 - a. Because $R_3N\cdots HOH$ bond is stronger (due to amine lone-pair basicity) than $ROH\cdots HOH$, amines tend to better H-bond water and are more soluble than oxygen analogs
 - b. Based on basicity of substrate (the acidity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

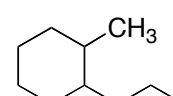
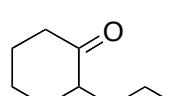
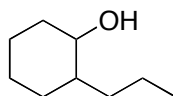
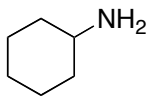
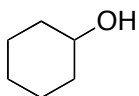
- Boiling point for similar mw: $RCO_2H > RCH_2OH > RCH_2NH_2$
 - c. for boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.

3. Amines stink! (ammoniums don't)

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

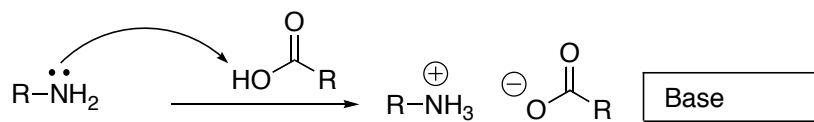


2. **Water Solubility.** Rank the following in terms of water solubility, 1 being most water soluble, 5 being least water soluble.

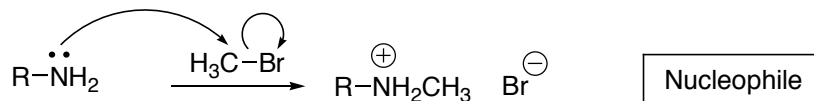


Keys:

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 (19.5,6)

•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 19.1: Neutral Acids and Anionic Bases

| Class | Neutral Acid Structure | K _a | Acid Strength | Anion Base | Base Strength | Base Stability |
|-----------------------|--------------------------------------|-------------------|---------------|---|---------------|----------------|
| Strong Acids | H-Cl, H ₂ SO ₄ | 10 ² | | Cl [⊖] , HO-S(=O) ₂ -O [⊖] | | |
| Carboxylic Acid | | 10 ⁻⁵ | | | | |
| Phenol | | 10 ⁻¹⁰ | | | | |
| 1,3-Dicarbonyl | | 10 ⁻¹² | | | | |
| Water | HOH | 10 ⁻¹⁶ | | HO [⊖] | | |
| Alcohol | ROH | 10 ⁻¹⁷ | | RO [⊖] | | |
| Ketones and Aldehydes | | 10 ⁻²⁰ | | | | |
| Amine (N-H) | (iPr) ₂ N-H | 10 ⁻³³ | | (iPr) ₂ N [⊖] Li [⊕] | | |
| Alkane (C-H) | RCH ₃ | 10 ⁻⁵⁰ | | RCH ₂ [⊖] | | |

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 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 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

| Class | Structure | K _a | Acid Strength | Base | Base Strength | |
|-------------------------------|--|-------------------|---------------|--|---------------|------------------------------|
| Strong Acids | H-Cl, H ₂ SO ₄ | 10 ² | | Cl^{\ominus} , $\text{HO}-\text{S}(=\text{O})_2-\text{O}^{\ominus}$ | | <u>S</u> mell <u>A</u> wful! |
| Hydronium | H ₃ O ⁺ , ROH ⁺ cationic | 10 ⁰ | | H ₂ O, HOR neutral | | <u>H</u> umans |
| Carboxylic Acid | | 10 ⁻⁵ | | | | <u>C</u> uz |
| Phenol | | 10 ⁻¹⁰ | | | | <u>P</u> eople |
| Ammonium Ion (Charged) | Charged, but only weakly acidic! | 10 ⁻¹² | | Neutral, but basic! | | <u>A</u> gainst |
| Water | HOH | 10 ⁻¹⁶ | | HO [⊖] | | <u>W</u> orking |
| Alcohol | ROH | 10 ⁻¹⁷ | | RO [⊖] | | <u>A</u> re |
| Ketones and Aldehydes | | 10 ⁻²⁰ | | | | <u>K</u> ingdoms |
| Amine (N-H) | (iPr) ₂ N-H | 10 ⁻³³ | | (iPr) ₂ N [⊖] Li [⊕] | | <u>A</u> nimal |
| Alkane (C-H) | RCH ₃ | 10 ⁻⁵⁰ | | RCH ₂ [⊖] | | <u>A</u> 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 19.2)**

- Nonfactor on Table 19.1, since all of the “acids” have the same charge (neutral), and all of the “bases” have the same charge (anions)

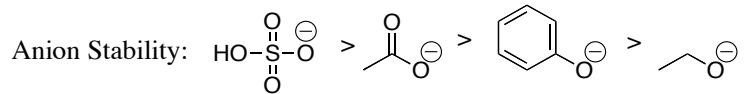
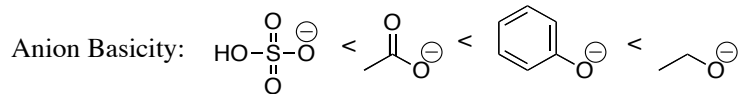
2. Electronegativity:

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

3. Resonance/Conjugation:

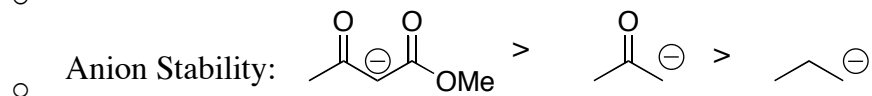
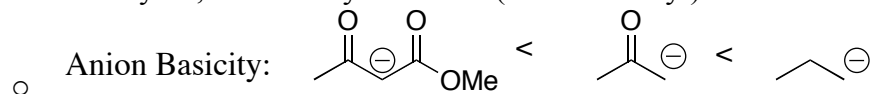
- Oxygen Series:

Acidity: sulfuric acid > carboxylic acid > phenol > alcohol



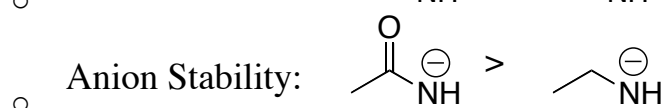
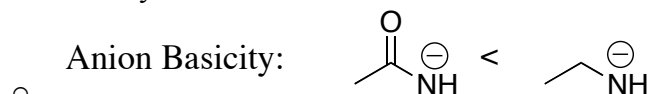
- Carbon Series:

○ Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane



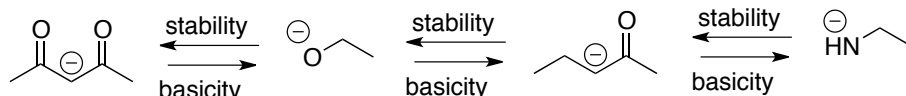
- Nitrogen Series:

○ Acidity: amide > amine



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

Electroneg.

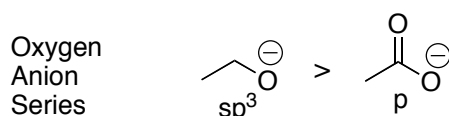
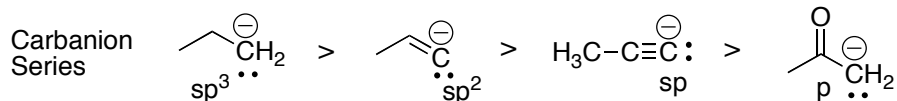
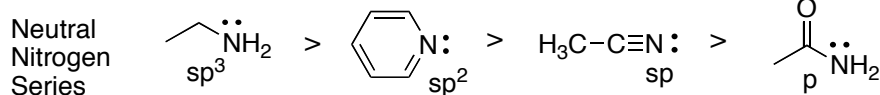


Charge



4. Hybridization:

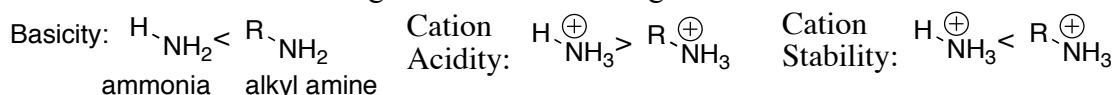
- For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$



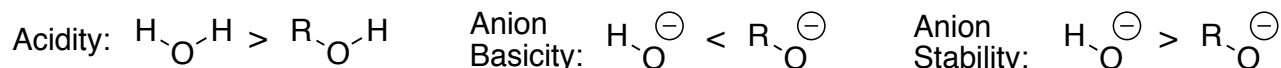
- This means that for acidity, alkyne > alkenes > alkanes

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.





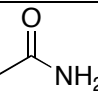
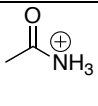


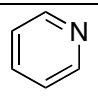
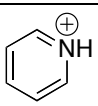
- This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion



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 9.3 Relative Basicity of Different Classes of Neutral Nitrogen Compounds.

| Entry | Structure of Amine Base | Base Strength | Lone Pair Hybrid | | Impact On Base Strength | Structure of Ammonium Acid | K_a | Acid Strength |
|-------|---|---------------|------------------|---|-------------------------|---|--------------|---------------|
| 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 | | $\oplus NH_4$ | $10^{-9.3}$ | |
| 6 | $EtNH_2$ | | sp^3 | Alkyl Donor | Increase | $\oplus EtNH_3$ | $10^{-10.6}$ | |
| 7 | Et_2NH | | sp^3 | Alkyl Donor | Increase | $\oplus Et_2NH_2$ | $10^{-10.8}$ | |
| 8 | Et_3N | | sp^3 | Alkyl Donor | Increase | $\oplus Et_3NH$ | $10^{-11.0}$ | |

General Amine Basicity Patterns.

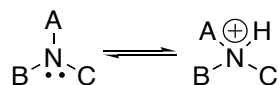
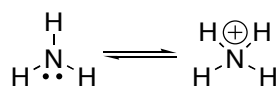
- Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) > sp^2 (entry 4) > p (entries 1-3) (hybridization factor)
- Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): $3^\circ > 2^\circ > 1^\circ > NH_3$ (electron donating group factor)

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


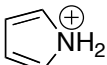
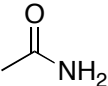
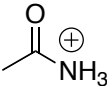
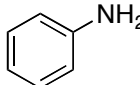
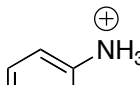

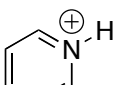
- Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because of the electron-withdrawing group factor).
- Conjugated nitrogens are in general less basic 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 its 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 Stabilized or Destabilized? |
|-------|---|---|--|---|
| 5 | NH ₃ | NH ₄ ⁺ | Reference | |
| 6-8 | Et ₃ N | Et ₃ NH ⁺ | 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 $\oplus\text{NH}_4$
- 2.
- 3.
- 4.
- 5.
- 6.

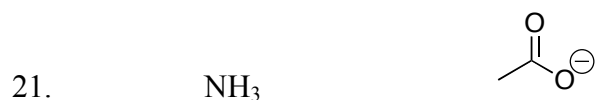
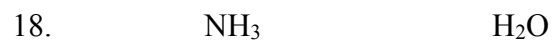
Choose the More **Basic** for Each of the Following Pairs (Single Variable)

7. NH_3 NaNH_2
8. NaOH H_2O
9. NH_3 H_2O
- 10.
- 11.
12. NH_3 $\text{O}_2\text{N}-\text{NH}_2$

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

13. NH_3
- 14.
- 15.

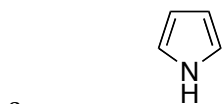
Choose the More Basic for Each of the Following Pairs



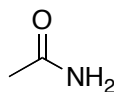
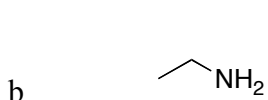
25. For the following sets of bases, rank them, 1 being the most basic.



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

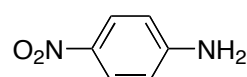
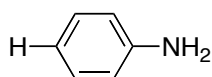
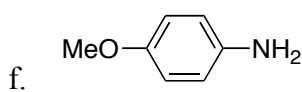
d. triethylamine

ethylamine

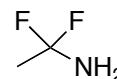
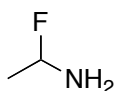
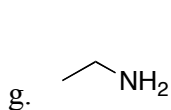
ammonia

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 $\text{CH}_3\text{CO}_2\text{Na}$ CH_3OH

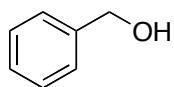
27. Rank the acidity of the following compounds, 1 being most acidic.

a. H_3O^+ NH_4^+Cl^- water acetic acid ($\text{CH}_3\text{CO}_2\text{H}$) NH_3

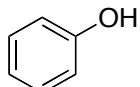
b. H_3O^+ acetic acid ($\text{CH}_3\text{CO}_2\text{H}$) $\text{Me}_3\text{NH}^+\text{Cl}^-$ ethanol

c. NH_4^+Cl^- $\text{Me}_3\text{NH}^+\text{Cl}^-$ $\text{PhNH}_3^+\text{Cl}^-$

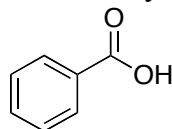
28. Suppose all of the molecules **A-D** are dissolved in diethyl ether.



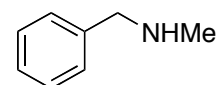
A



B



C

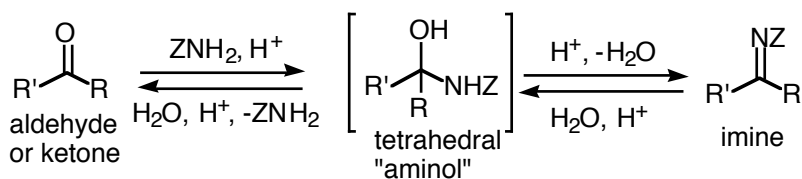


D

- Which one or ones will extract (dissolve) into aqueous sodium hydroxide? (And why?)
- Which, if any, will extract into aqueous hydrochloric acid? (And why?)
- Which, if any, will extract into neutral water? (Why or why not?)
- Explain how you could use an extraction scheme to separate **D** from **A**.

C. Reactions of Amines (other than as bases)

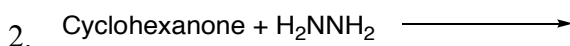
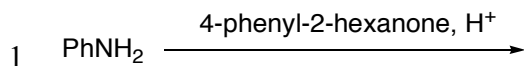
2. Reaction with Ketones or Aldehydes (Section 19.10)



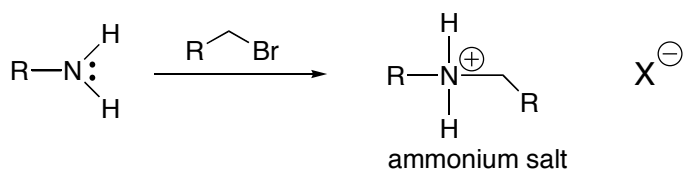
Notes:

- “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

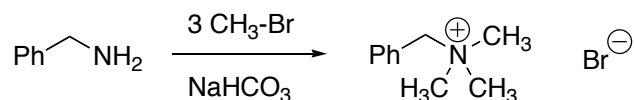
Draw the Products of the following Amine reactions.

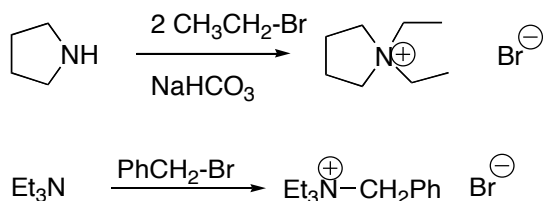


3. Alkylation of 1° Alkyl Halides (Section 19.12)

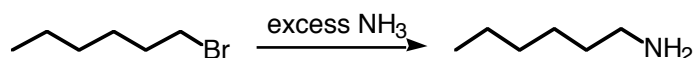


- **3a. Polyalkylation** is routine.
 - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H’s on nitrogen, examples below).
 - Mechanism required for polyalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.

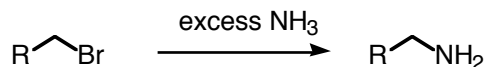


Notes

- All amines are nucleophilic
 - $3^\circ > 2^\circ > 1^\circ > \text{NH}_3$
 - structural effects parallel basicity
 - Limited synthetic utility, due to frequent overalkylation
 - Due to $\text{S}_{\text{N}}2$ 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 $\text{S}_{\text{N}}2$, followed by deprotonation by the excess amine.

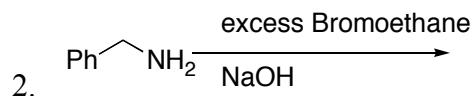
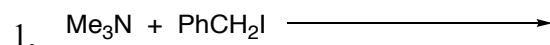
Synthetically Useful Alkylation Scenarios:

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

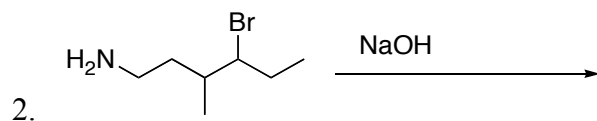
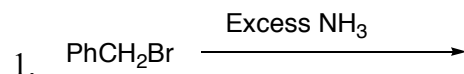


- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

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

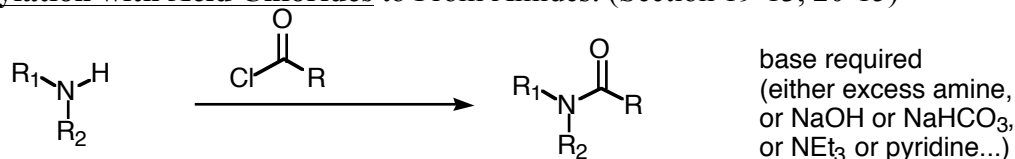
Draw the Products and mechanisms of the following Amine reactions.

Draw the Products and mechanisms of the following Amine reactions.

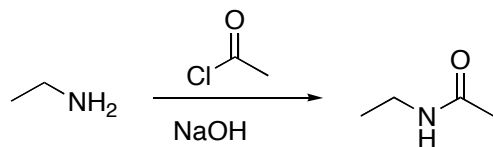


Why do you **not** get clean monoalkylation if you do a 1:1 mixture of RNH_2 and R-X ?

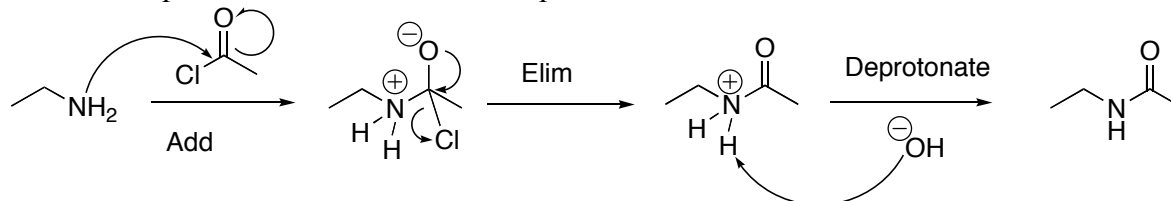
4. Acylation with Acid Chlorides to Form Amides: (Section 19-13, 20-15)



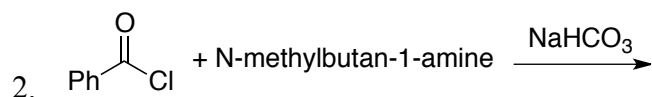
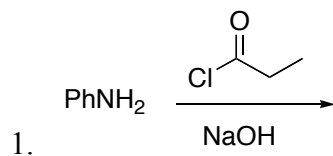
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1°, 2°, or NH_3 all react well.
- But 3° amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively,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



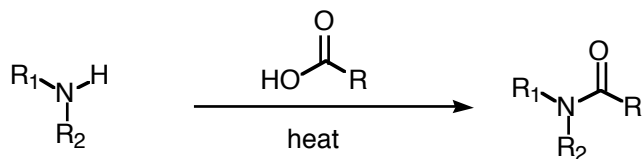
Mech: 3 steps: Addition-Elimination-Deprotonation



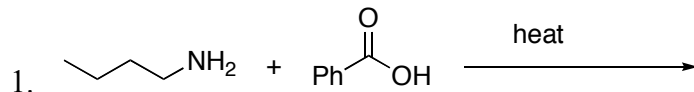
Draw the Products of the following Amine reactions, and the mechanism for the first one.



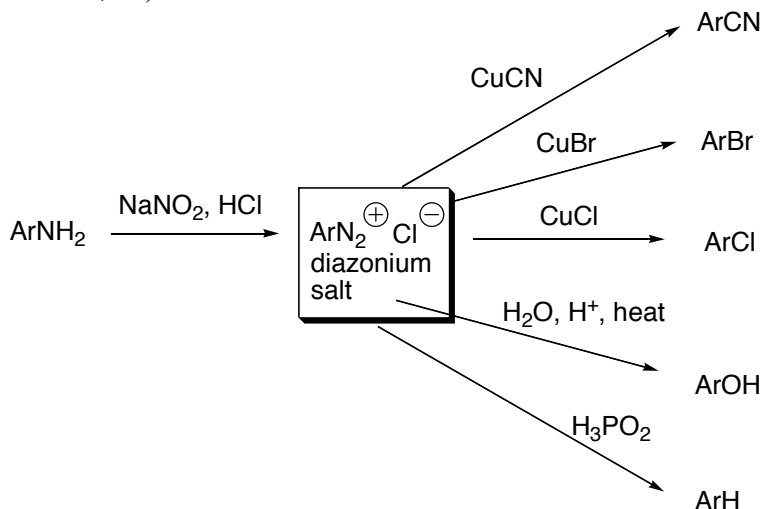
4b. Acylation with Carboxylic Acids to Form Amides: (Section 20-12)



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



5. Substitution for Aromatic Amines via the Diazonium Salts (“The Sandmeyer Reaction”) (Section 19-17, 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

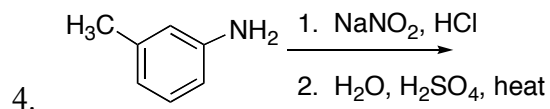
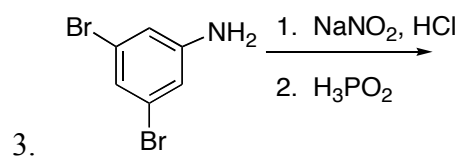
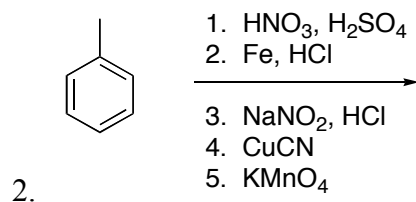
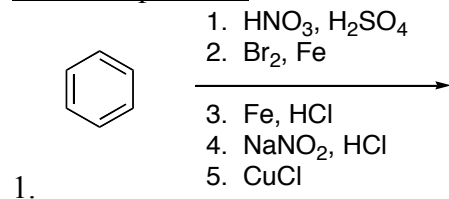
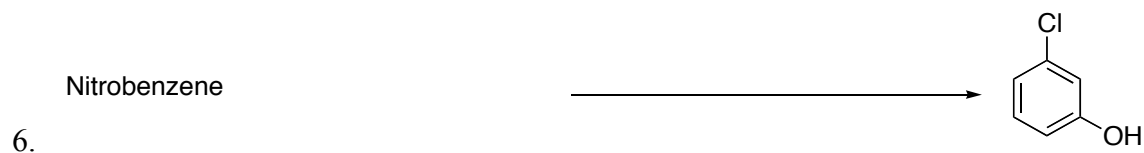
1. Alkyl RN_2^+ are highly unstable, give cations, and usually give mixtures of E1 , $\text{S}_{\text{N}}1$, and cation rearrangement product mixtures
2. Not much use synthetically
3. However, N_2 is such a great leaving group that even 1° carbocations can be formed/studied

| |
|--|
| Reactivity: $\text{RN}_2^+ > \text{ROH}_2^+ > \text{ROTs} > \text{RI} > \text{RBr} > \text{RCl}$ Leaving group ability: $\text{N}_2 > \text{H}_2\text{O} > \text{TsO anion} > \text{Iodide anion} > \text{Bromide anion} > \text{Chloride anion}$ |
|--|

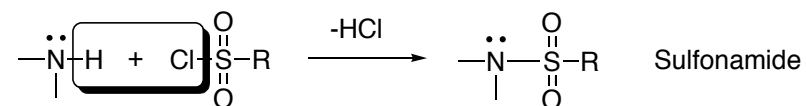
1. Unlike Alkyl diazoniums RN_2^+ , aryl ArN_2^+ are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms

Synthetic Use:

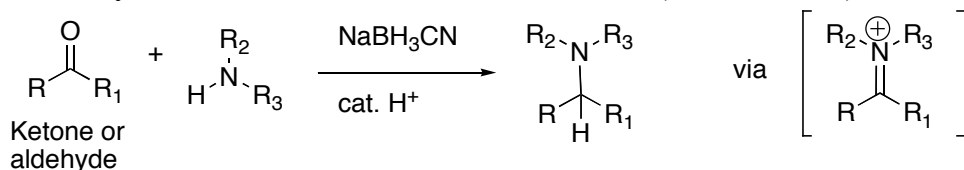
1. NO_2 (meta director) \rightarrow $\text{NH}_2 \rightarrow \text{N}_2^+ \rightarrow \text{Cl, Br, OH, CN, H}$
2. Easy to get meta relationships, even when you end with things that are not meta directors

Draw the productsDesign Synthesis

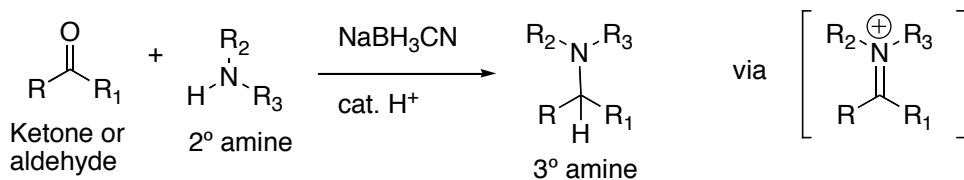
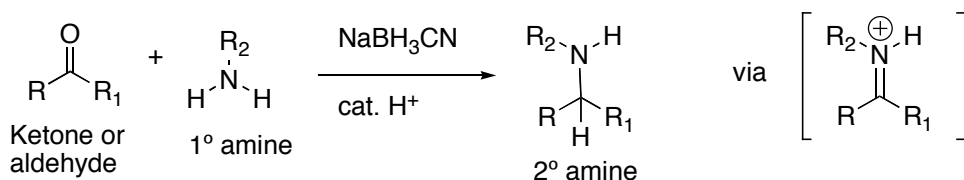
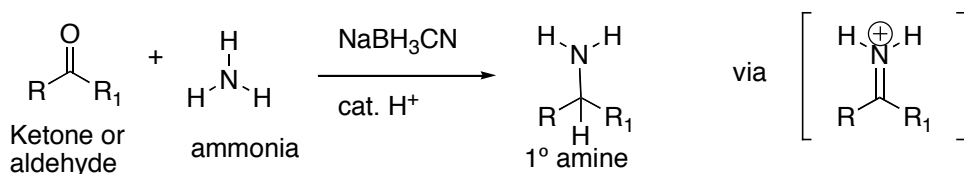
19.14 Reaction with Sulfonyl Chlorides (Not tested)



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

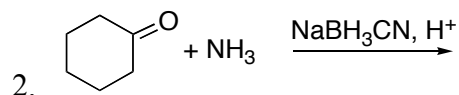
D. Synthesis of Amines**6. From Aldehydes or Ketones: Reductive Amination (Section 19-19)**

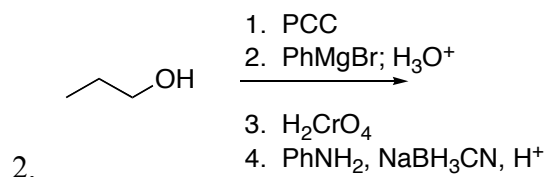
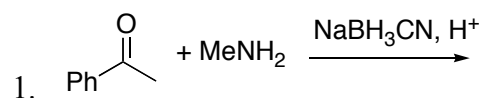
- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R₂ and/or R₃ can be either a carbon or a hydrogen. Thus:
 - NH₃ → 1° RNH₂
 - 1° RNH₂ → 2° R₂NH
 - 2° R₂NH → 3° R₃N
 - 3° R₃N don't react



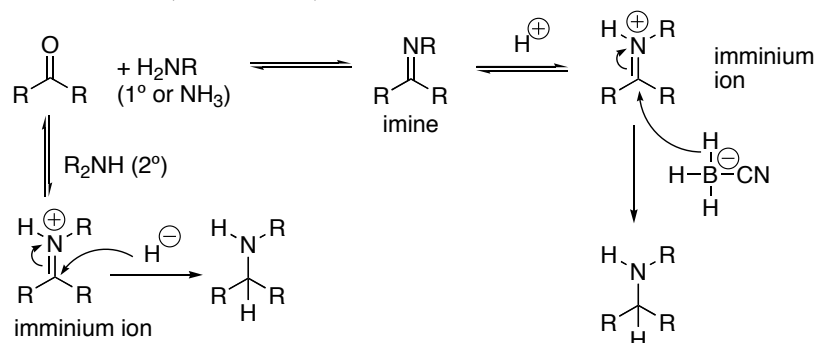
Note: book gives several other variants, but this is really the one universal method, and the one I'll use for my tests.

Synthesis of Amines: Draw the products for the following reactions.

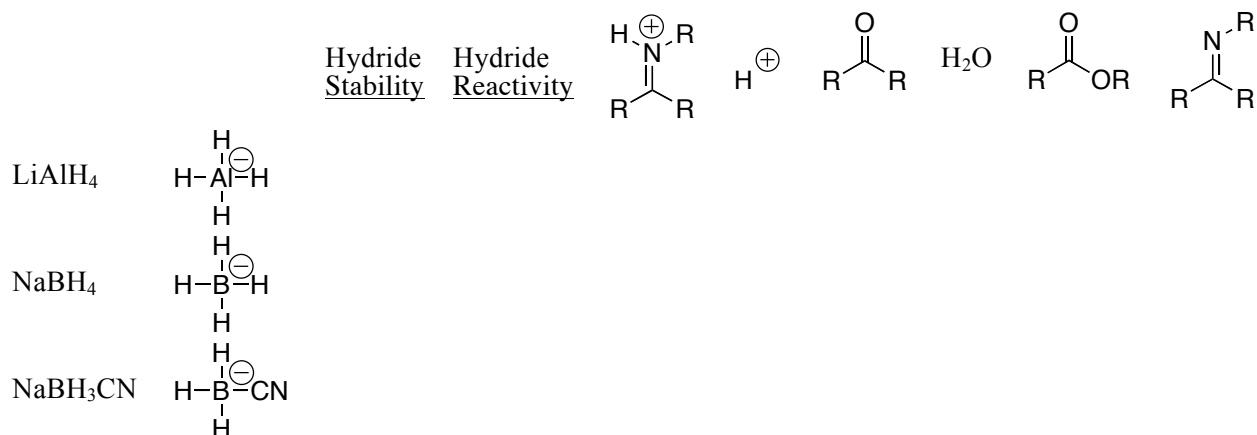


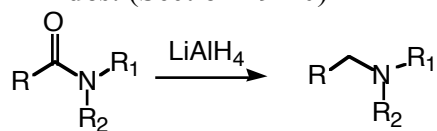


Mechanism (not for test) and some related notes

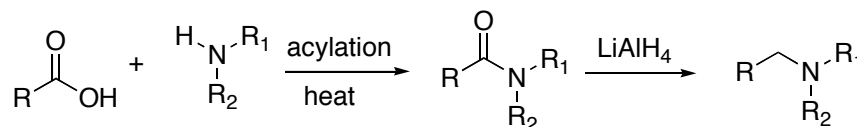
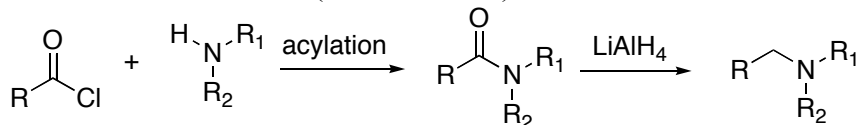


1. NaBH_3CN functions as a hydride H^\ominus source, similar to NaBH_4 and LiAlH_4
2. Formation of iminium cation is key
 - Highly electrophilic, much more so than neutral imine
3. NaBH_3CN is a special, mild H^\ominus source, much more stable and less reactive than NaBH_4 and LiAlH_4
 - So much so that it can coexist with acid (thus enabling iminium 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 iminium ion)

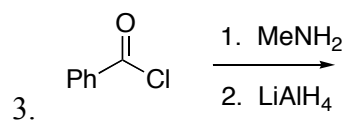
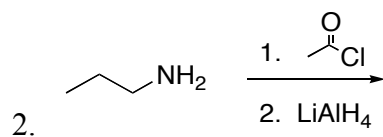
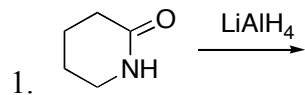


7. **Via Amides:** (Section 19-20)

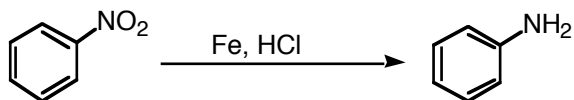
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R₁ and R₂ can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
 - RCONH₂ → 1° RCH₂NH₂
 - RCONHR → 2° RCH₂NHR
 - RCONR₂ → 3° RCH₂NR₂

8. **From Amines via Amides:** (Section 19-20)

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

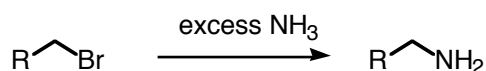


9. Reduction of nitro compounds: (section 19-21C)



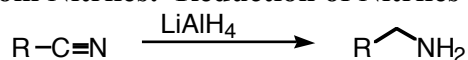
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
 - Pd/H₂, Ni/H₂, Pt/H₂,
 - Fe/HCl, Zn/HCl, Sn/HCl

10. From 1° Alkyl Halides: Alkylation of Ammonia (Section 19-12, 19-21A) (See reaction 3).



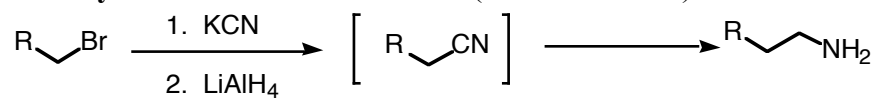
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH₃ prevents polysubstitution.

11. From Nitriles: Reduction of Nitriles (Section 19-21B)

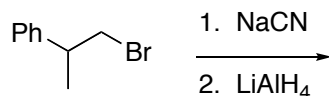


- Access: 1° amines
- Mechanism not required.

12. From Alkyl Halides: Via the Nitrile (Section 19-21B)



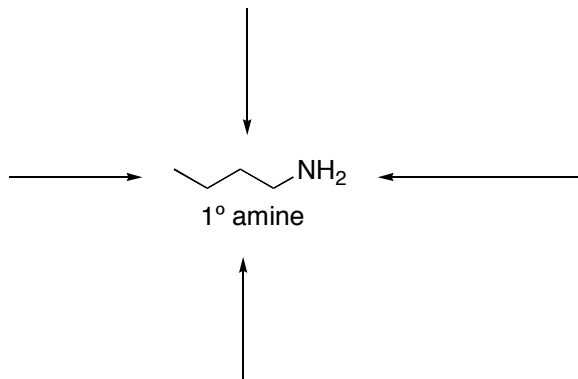
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!



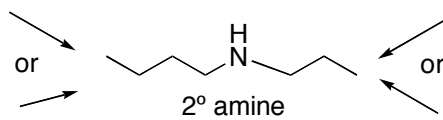
Summary of Amine Syntheses

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

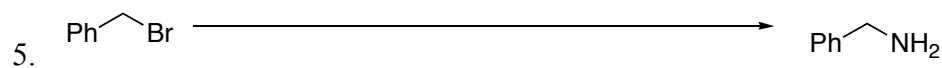
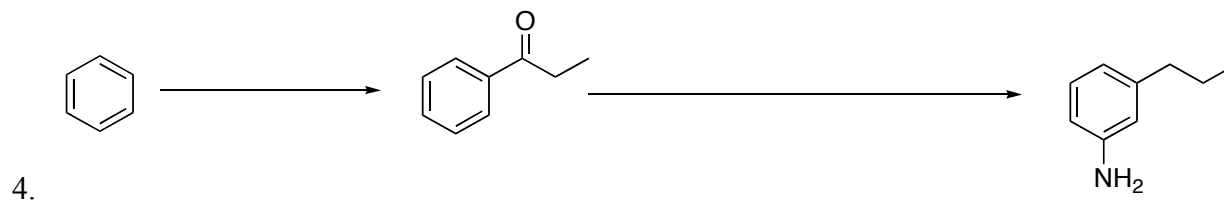
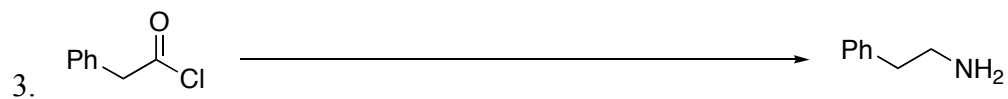
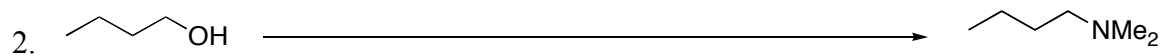
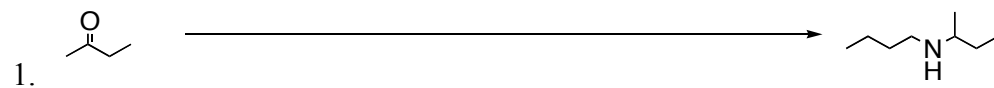
1. Come up with various pathways (4 good ones) to the following 1° amine:



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

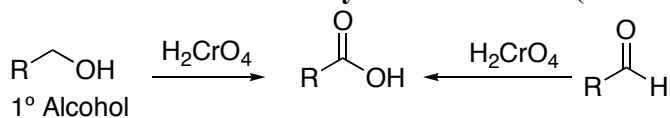


Provide Reagents for the following Transformations.



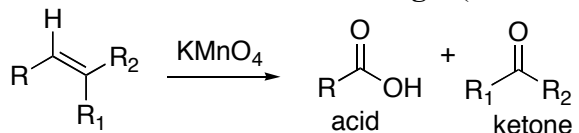
Synthesis of Carboxylic Acids

1. From 1° Alcohols and Aldehydes: Oxidation (Section 11-2B and 18-20)



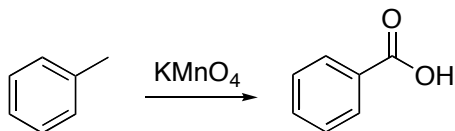
- No mechanism required for the reaction

2. From Alkenes: Oxidative Cleavage: (Section 8-15A and 9-10)



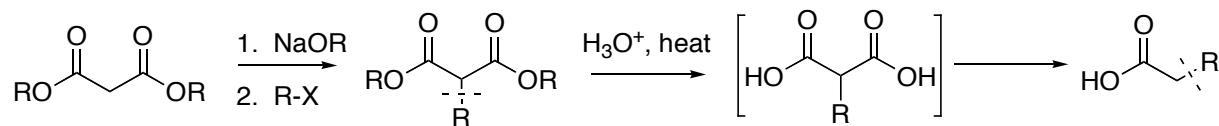
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH₂ would give an acid and carbonic acid (H₂CO₃), etc..

3. From Aromatics: Oxidation of Alkylbenzenes (Section 17-14A)



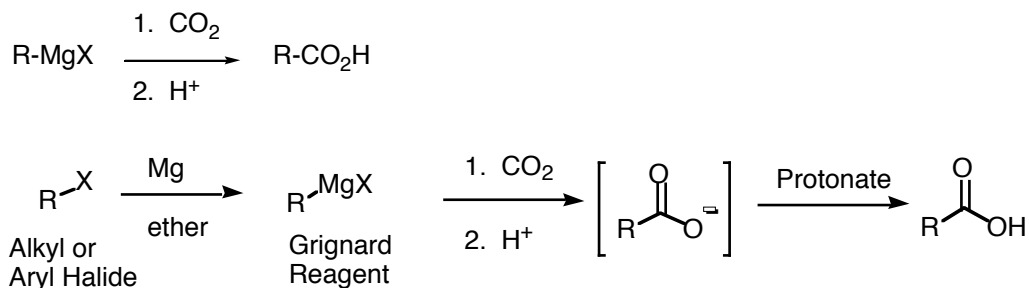
- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

4. From 1,3-Diesters: Via Hydrolysis/Decarboxylation: (Chapter 22)



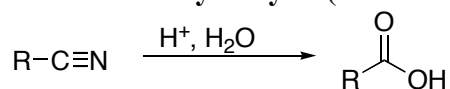
- Mechanism: Deprotonation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

5. From Grignard Reagents: Via Carboxylation: (Section 20-8B)



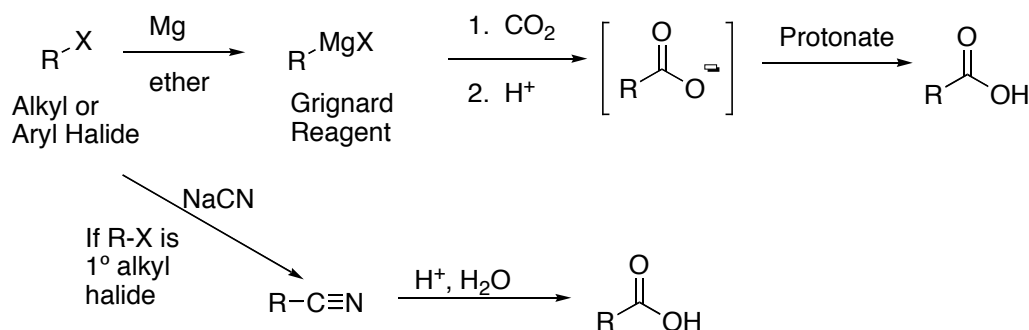
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1°, 2°, or 3°
- Mechanism required. (From Grignard on.)

6. From Nitriles: Hydrolysis (Section 20-8C)



- Mechanism not required.

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

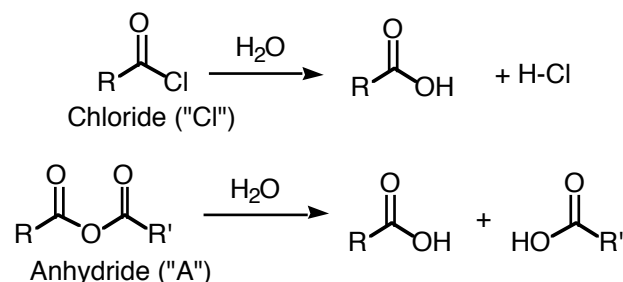


- Formation/Hydrolysis of Nitriles Requires a 1° Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1° alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive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

8. From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis (Section 20-8C)

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

- mechanism required: addition-elimination-deprotonation

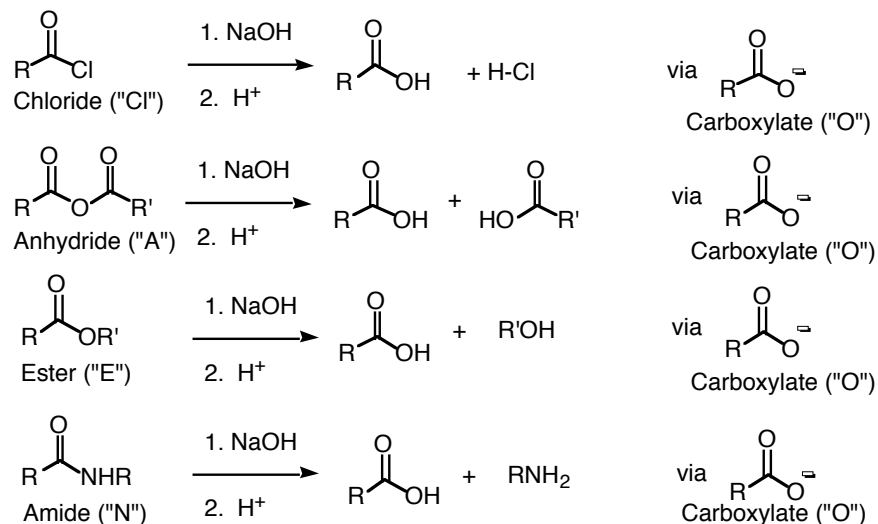


b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- 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

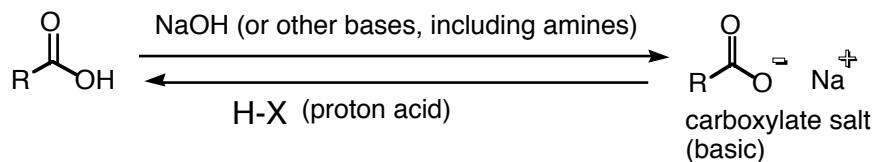
c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H⁺ workup

- 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 20-4, 20-5)



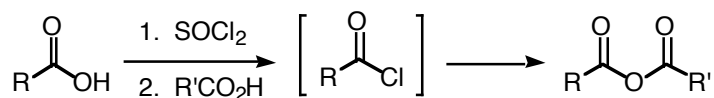
- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonance stabilization makes carboxylates much more 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 20-11, 21-5)



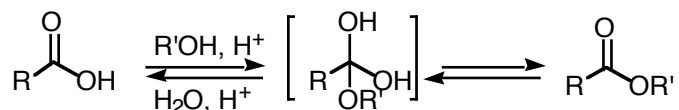
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO₂ are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. Indirect Conversion to Anhydrides



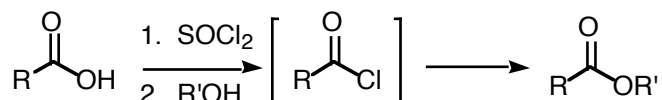
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a “downhill” reaction energetically.
- Conversion of the acid to the anhydride directly would be an “uphill” reaction

12. Direct Conversion to Esters (Sections 20-10-12, 21-5)



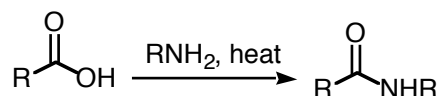
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium 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 (Sections 20-10-12, 21-5)



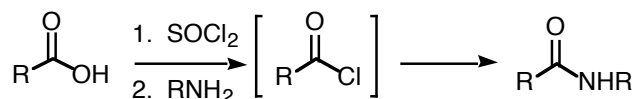
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a “downhill” reaction energetically.

14. Direct Conversion to Amides



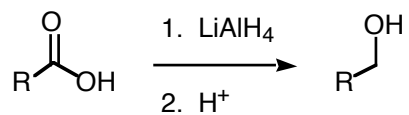
- **mechanism not required**
- This is a “downhill” reaction energetically, but is complicated and retarded by acid-base reactions. Normally the “indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

15. Indirect Conversion to Amides



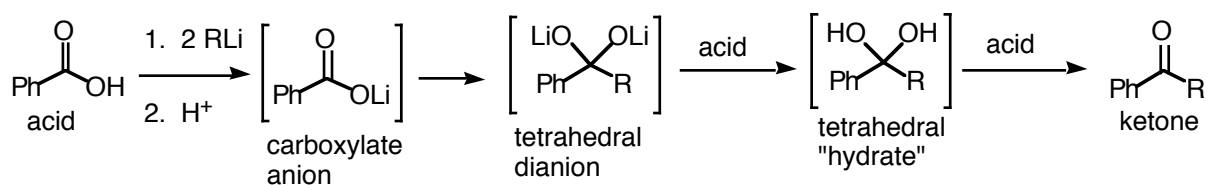
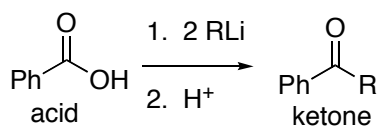
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

16. Reduction to Primary Alcohol (Sections 10-11, 20-14)



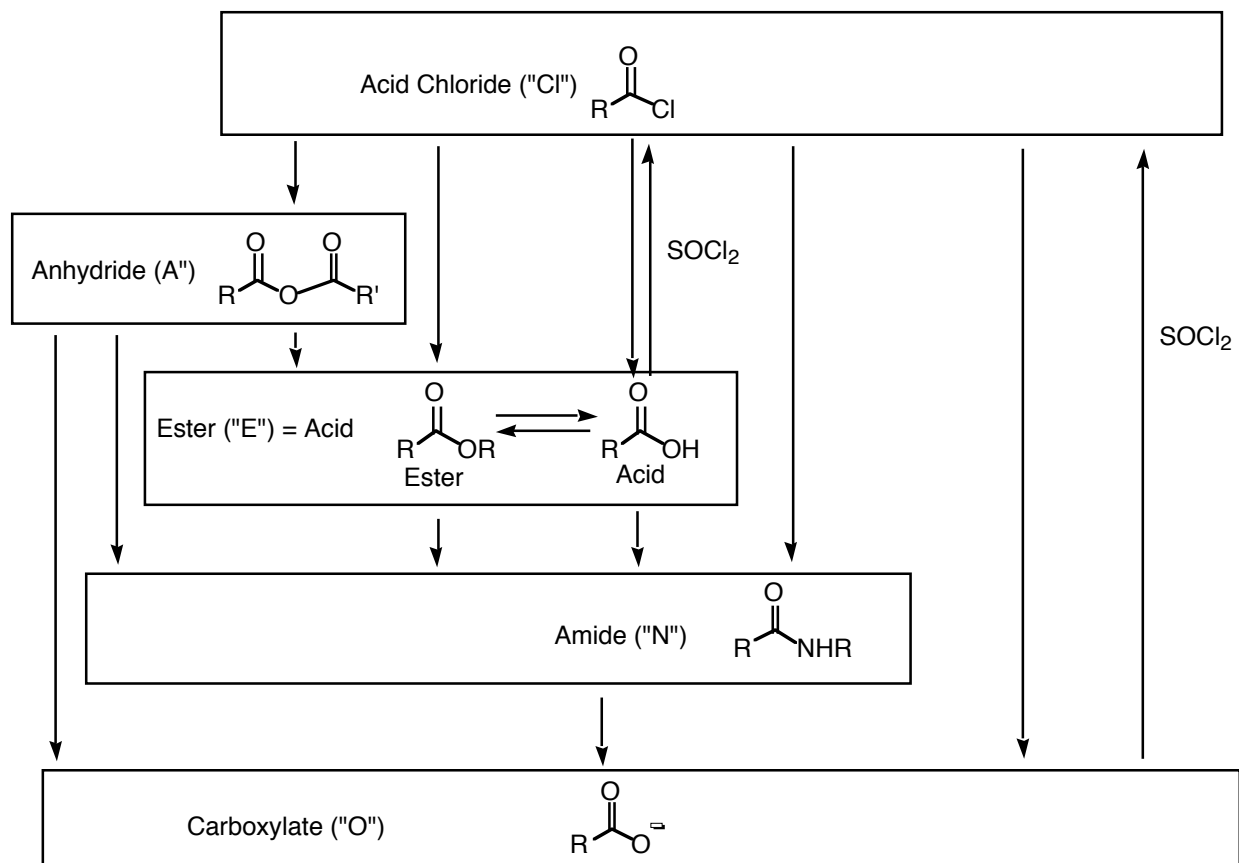
- mechanism not required

17. Alkylation to Form Ketones (Section 18-19, 20-15)

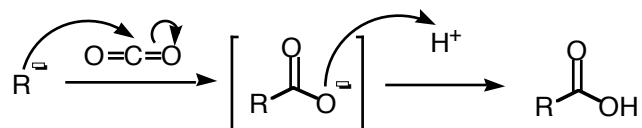


- mechanism not required

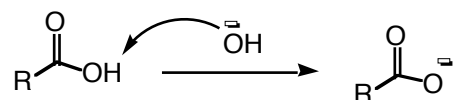
18. Interconversions of Acids and Acid Derivatives (Section 21-5 and many others)



- "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)

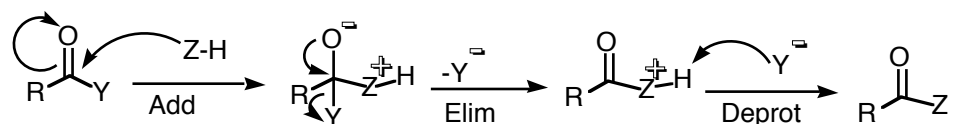
Mechanisms**A. Miscellaneous****5. From Grignard Reagents: Via Carboxylation:**

- exactly like any Grignard reaction

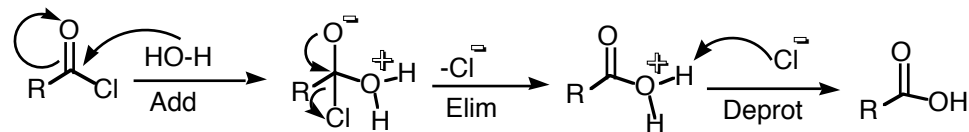
9. Reaction as a Proton Acid

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

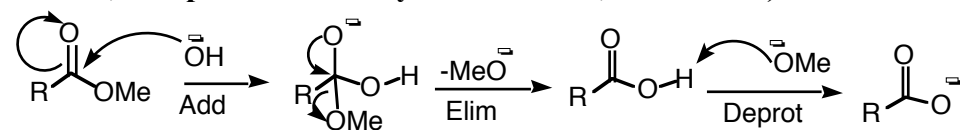
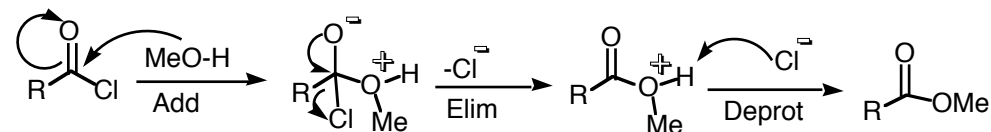
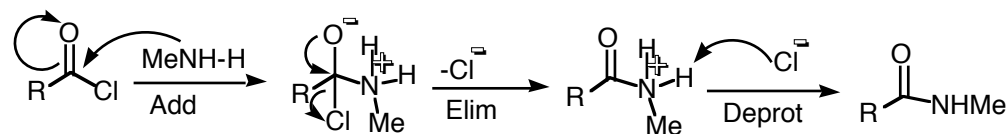
General



Examples

Reaction 8a

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

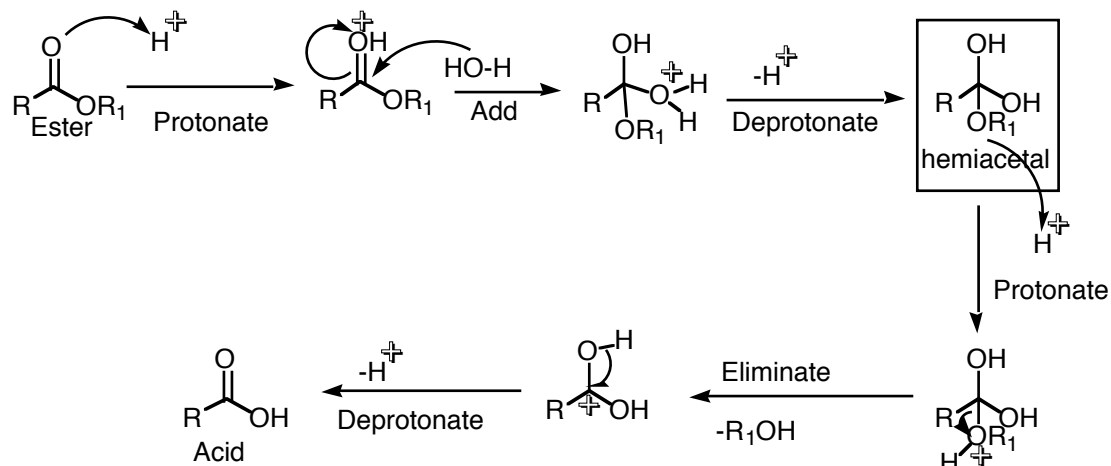
**Reaction 13****Reaction 15**

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

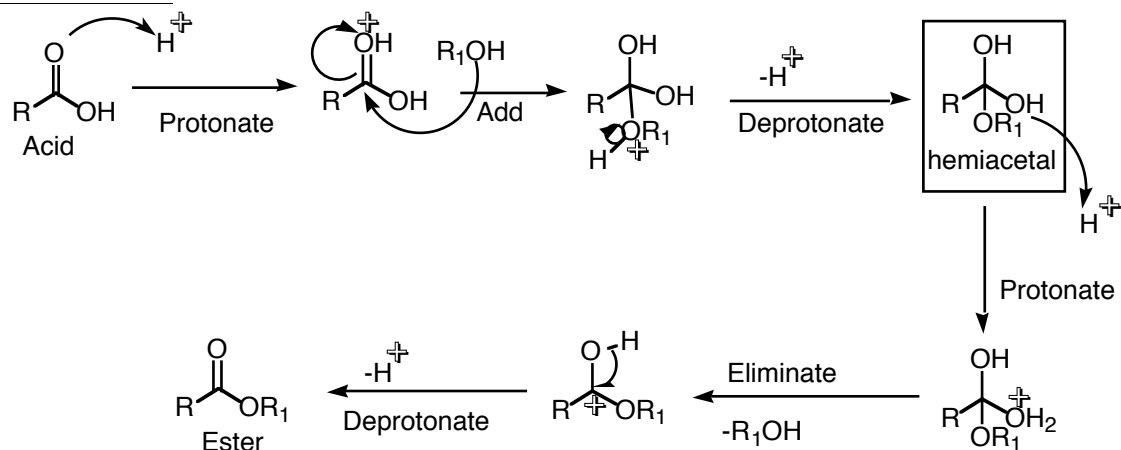
- **General Mechanism:** protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)

Examples

Reaction 8b: Ester to Acid

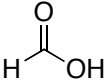
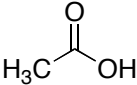
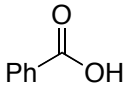
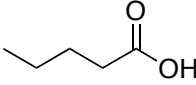
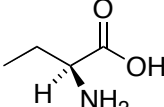


Reaction 12: Acid to Ester



Nomenclature (20.2) Formal: alkanoic acid (space in between)

-highest priority of any functional group

| | <u>Formal</u> | <u>Common</u> |
|---|--------------------------|---------------|
|  | 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 > 1,2° amines > non-H-bonders

- Acids boil about 20° higher than same-weight alcohols
- First four acids are completely water soluble

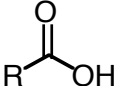
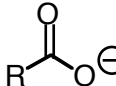
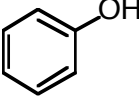
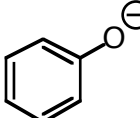
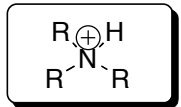
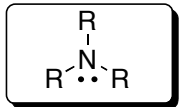
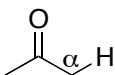

Water solubility (weight being equal): amines > acids ? ketones, alcohols, ethers >> alkanes

- Basicity is more important than acidity

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

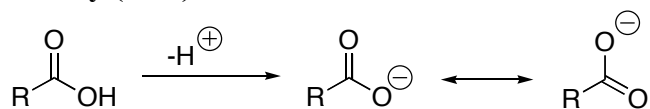


Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases (Section 20-4)

| Class | Structure | K _a | Acid Strength | Base | Base Strength | |
|-------------------------------|---|-------------------|---------------|---|---------------|------------------------------|
| Strong Acids | H-Cl, H ₂ SO ₄ | 10 ² | | Cl [⊖] , HO-S(=O) ₂ -O [⊖] | | <u>S</u> mell <u>A</u> wful! |
| Hydronium | H ₃ O ⁺ , ROH ⁺ cationic | 10 ⁰ | | H ₂ O, HOR neutral | | <u>H</u> umans |
| Carboxylic Acid |  | 10 ⁻⁵ | |  | | <u>C</u> uz |
| Phenol |  | 10 ⁻¹⁰ | |  | | <u>P</u> eople |
| Ammonium Ion (Charged) |  Charged, but only weakly acidic! | 10 ⁻¹² | |  Neutral, but basic! | | <u>A</u> gainst |
| Water | HOH | 10 ⁻¹⁶ | | HO [⊖] | | <u>W</u> orking |
| Alcohol | ROH | 10 ⁻¹⁷ | | RO [⊖] | | <u>A</u> re |
| Ketones and Aldehydes |  | 10 ⁻²⁰ | |  | | <u>K</u> ingdoms |
| Amine (N-H) | (iPr) ₂ N-H | 10 ⁻³³ | | (iPr) ₂ N [⊖] Li [⊕] | | <u>A</u> nimal |
| Alkane (C-H) | RCH ₃ | 10 ⁻⁵⁰ | | RCH ₂ [⊖] | | <u>A</u> 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 (20-4)

- 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! | 10^{-12} | Neutral, but basic! |
| Alcohol | ROH | 10^{-17} | |

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

Amino Acids:

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



38. 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 $\text{CH}_3\text{NH}_3\text{Cl}$ $(\text{CH}_3)_3\text{NHCl}$

20.5 Carboxylate Salts



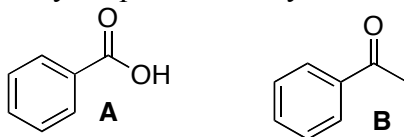
- Easy to make
- Ionic \rightarrow water soluble

Acids are soluble in NaOH/water or NaHCO₃/H₂O

- Weak bases, react with HCl \rightarrow RCO₂H
- Named: sodium alkanoate

Purification Schemes for Acids from other Organics Based on Acidity

- Dissolve acid and neutral organic in ether
 - Treat with NaOH/water
 - Neutral stays neutral, goes in ether layer
 - Acid is deprotonated to RCO₂Na, goes into water layer
 - Concentrate ether layer \rightarrow pure neutral organic
 - Add HCl to aqueous layer, results in: $\text{RCO}_2\text{Na} + \text{HCl} \rightarrow \text{RCO}_2\text{H}$
 - Neutral RCO₂H now has low solubility in water, so can be harvested by filtration (if solid) or by organic extraction
- Design a solubility flow chart to separate benzoic acid ("A") from acetophenone PhC(O)CH₃ ("B"). Make sure that your plan enables you to isolate both "A" and "B".

**Soaps (not for test)**

RCO₂Na with variable long alkyl chains

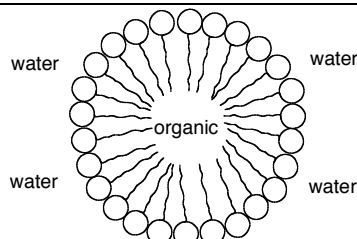
Ex: C₁₇H₃₅CO₂[⊖] Na[⊕]

Carboxylate head: hydrophilic \rightarrow water soluble

Hydrocarbon tail: hydrophobic \rightarrow can dissolve grease and organic materials

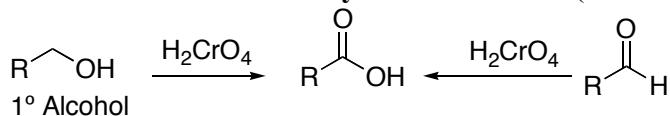
Form "micelles" in water

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.

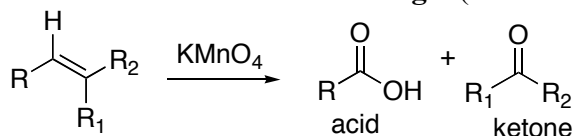


B. Synthesis of Carboxylic Acids**Synthesis of Carboxylic Acids**

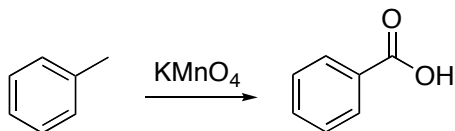
Review (20.8)

1. From 1° Alcohols and Aldehydes: Oxidation (Section 11-2B and 18-20)

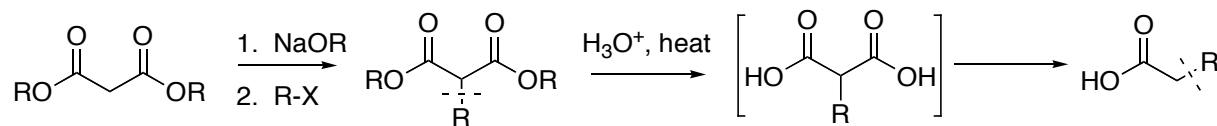
- No mechanism required for the reaction

2. From Alkenes: Oxidative Cleavage: (Section 8-15A and 9-10)

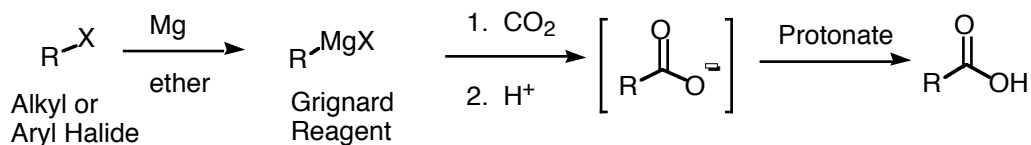
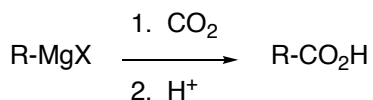
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH₂ would give an acid and carbonic acid (H₂CO₃), etc..

3. From Aromatics: Oxidation of Alkylbenzenes (Section 17-14A)

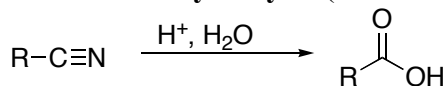
- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

4. From 1,3-Diesters: Via Hydrolysis/Decarboxylation: (Chapter 22)

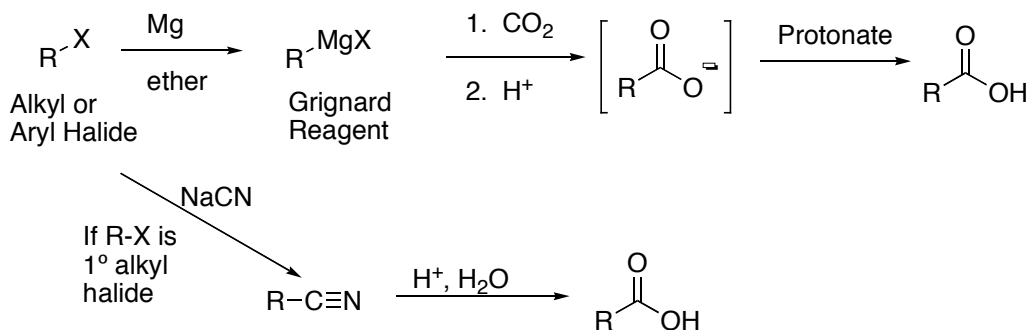
- Mechanism: Deprotonation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

New Routes5. **From Grignard Reagents: Via Carboxylation:** (Section 20-8B)

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

6. **From Nitriles: Hydrolysis** (Section 20-8C)

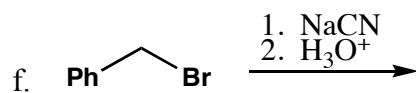
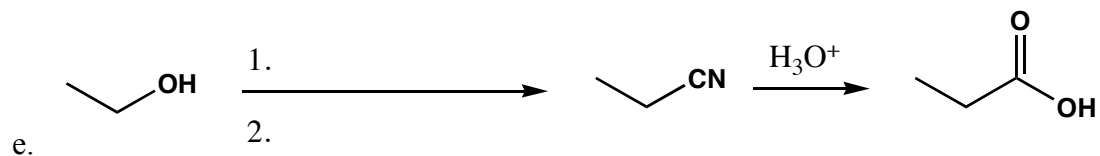
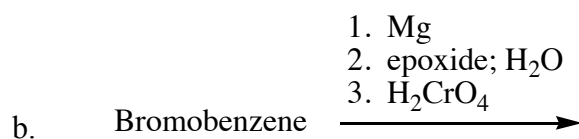
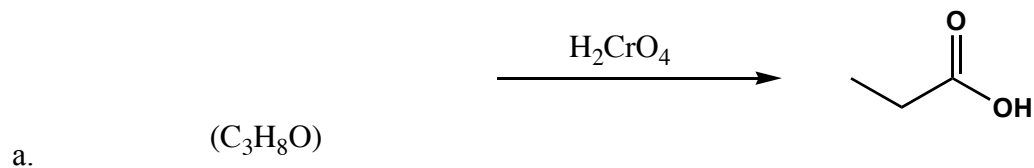
- Mechanism not required.

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

Problems

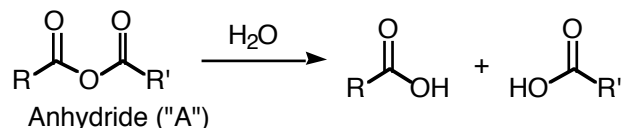
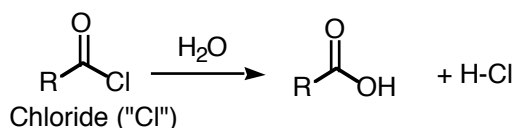
1. Preparation of Carboxylic Acids. Fill in the blanks for the following reactions.



8. From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis (Section 20-8C)

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

- mechanism required: addition-elimination-deprotonation

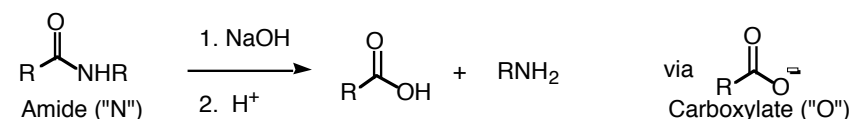
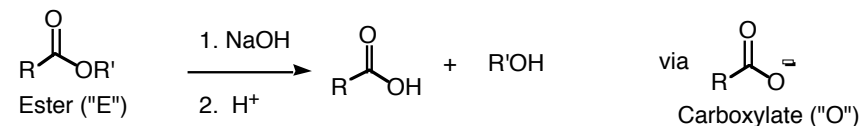
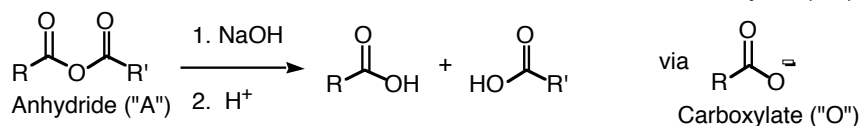
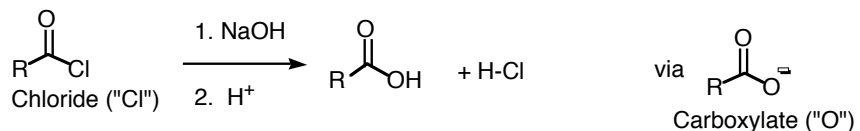


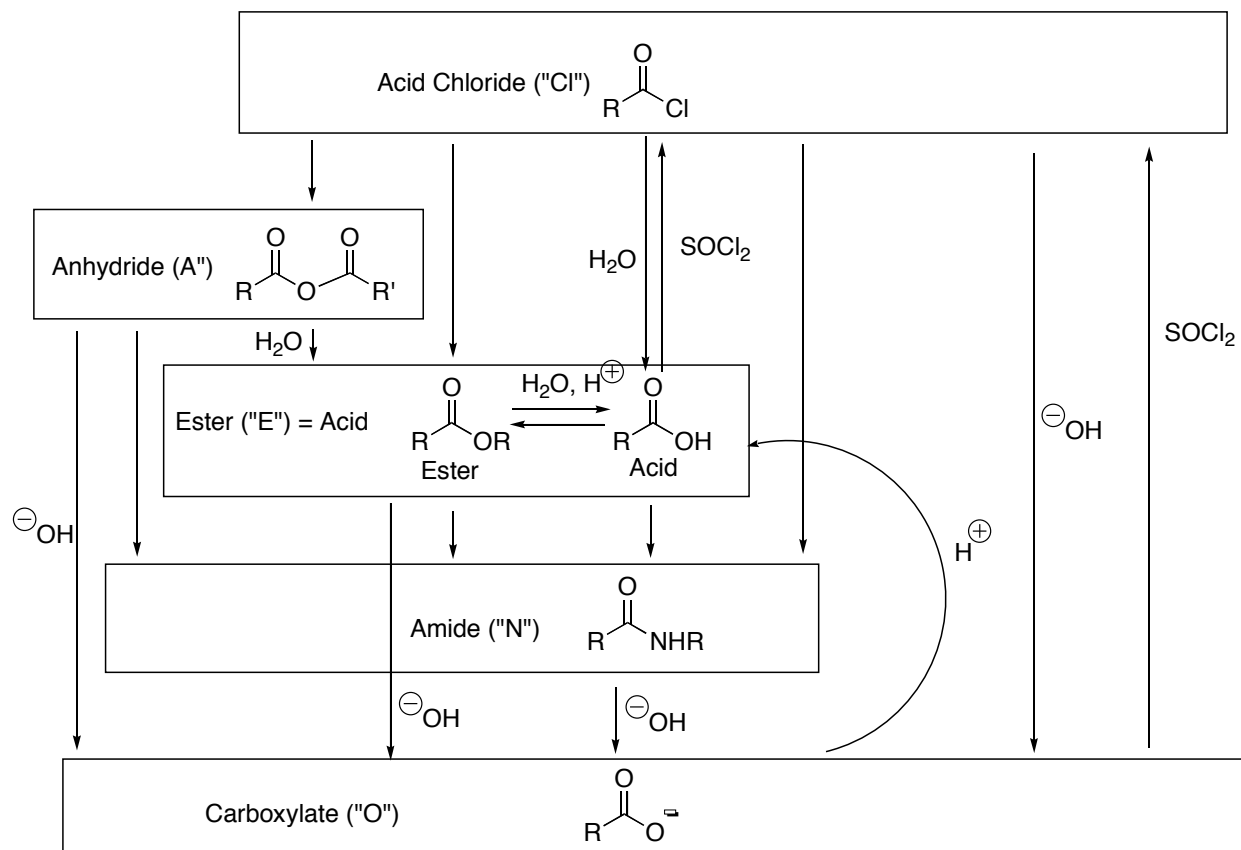
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- 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



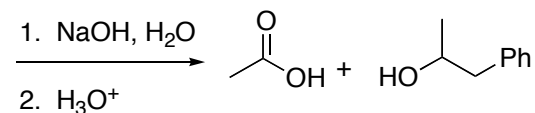
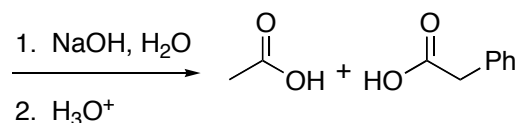
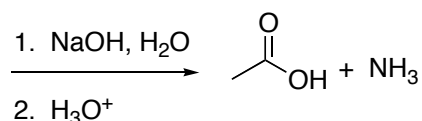
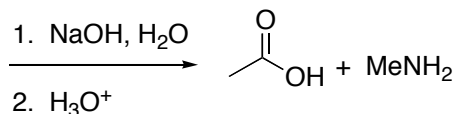
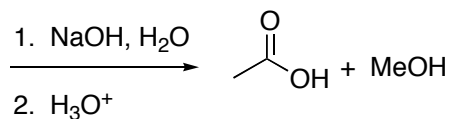
Interconversions and Reactivity of Acids and Acid Derivatives (Section 21-5 and others)

- "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)

"Cl-A-vE-N-O" applied to Hydrolysis

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

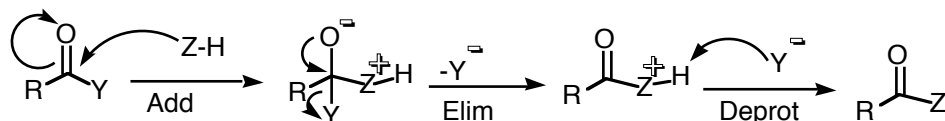
1. For the following problems, draw the starting materials that would give the indicated hydrolysis products.
- Note: All of these are drawn as basic hydrolyses, but some could also be done using neutral water or acidic water. Mark which could proceed using neutral hydrolysis or acid-catalyzed hydrolysis in addition to via basic hydrolysis.



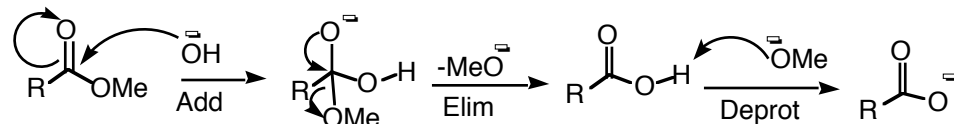
Mechanism: General Mechanism for Any “Downhill” Cl-A-vE-N-O Interconversions (8a, 8c, 11, 13, 15, 18):

All Proceed by Addition-Elimination-Deprotonation

General

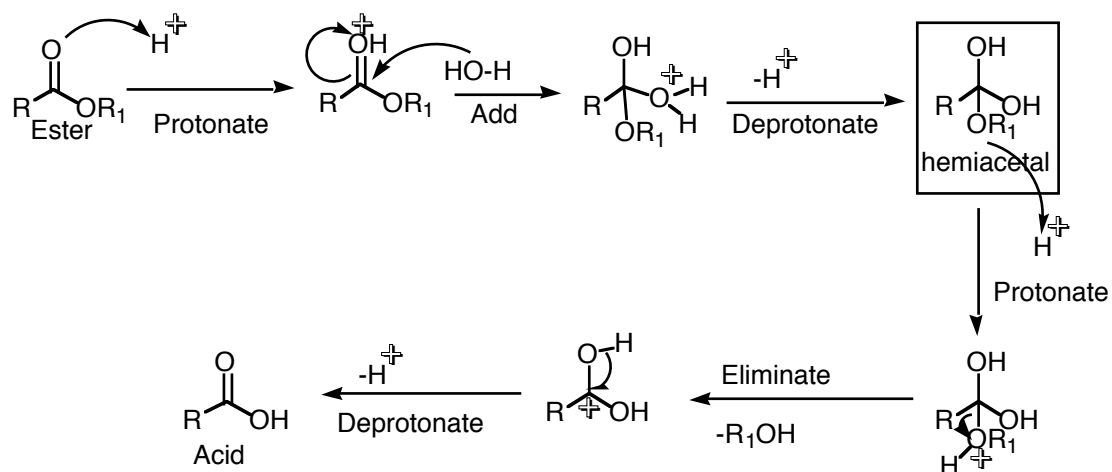
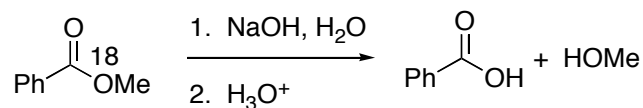
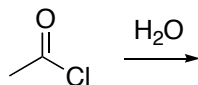


Base Case, Using Anionic Hydroxide: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)



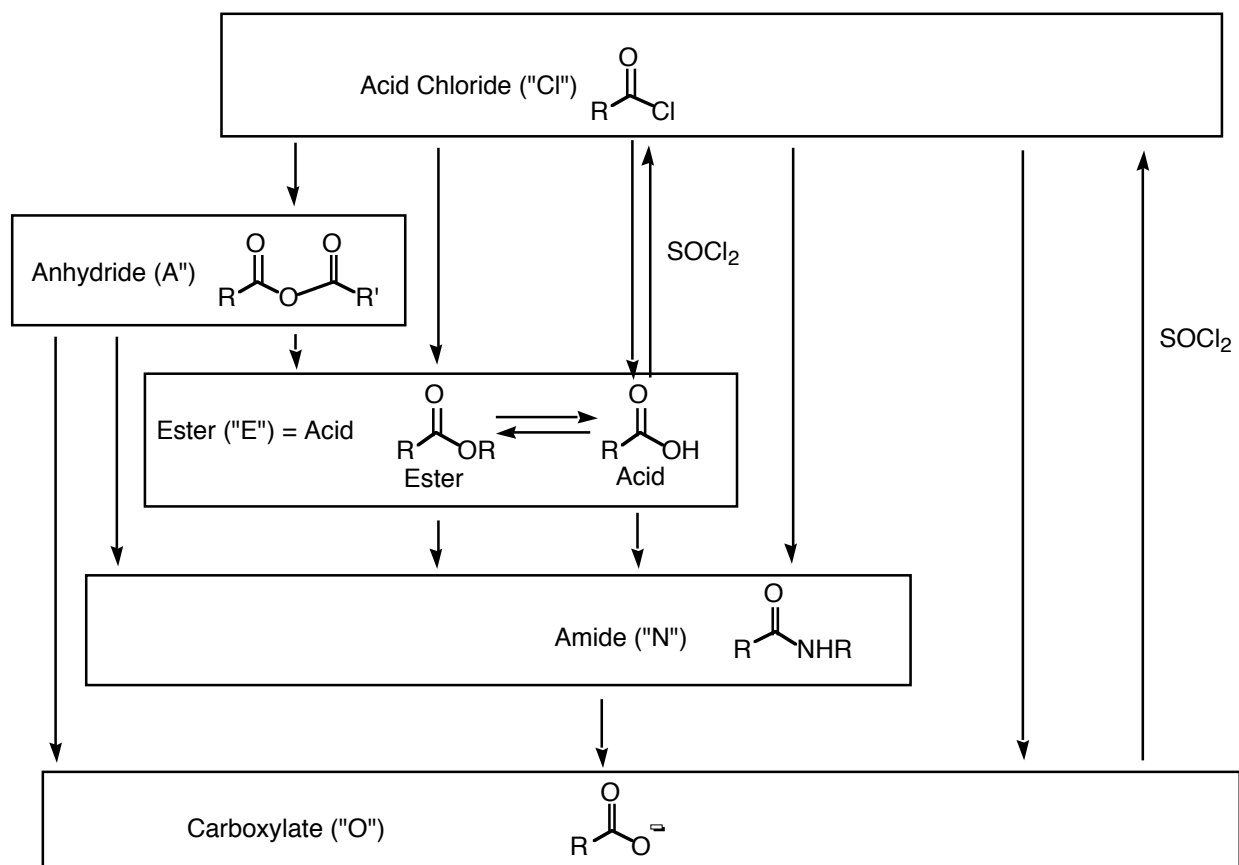
Acid-Catalyzed conversion from Ester to Acid (8b): (ACID WATER)

- **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 O¹⁸ label end up?

C. Reactions of Carboxylic Acids

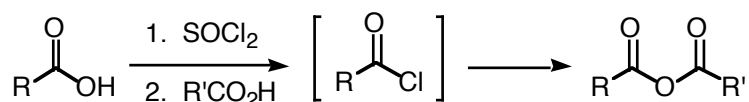
20.9, 21.5 Interconversions with Derivatives: Cl-A-vE-N-O



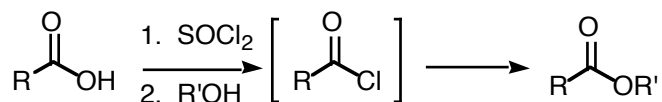
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl₂ 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 (Sections 20.11 and 21.5)**10. Conversion of acids or Carboxylates to Acid Chlorides**

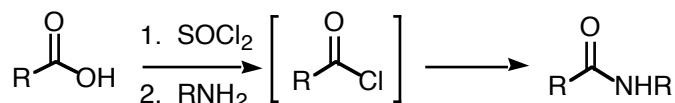
- Mechanism: Not Required
- Easy (but smelly) reaction.
 - Side products HCl and SO₂ are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. Indirect Conversion to Anhydrides

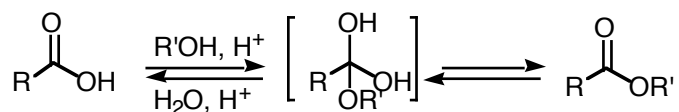
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a “downhill” reaction energetically.
- Conversion of the acid to the anhydride directly would be an “uphill” reaction
- Base often present to absorb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

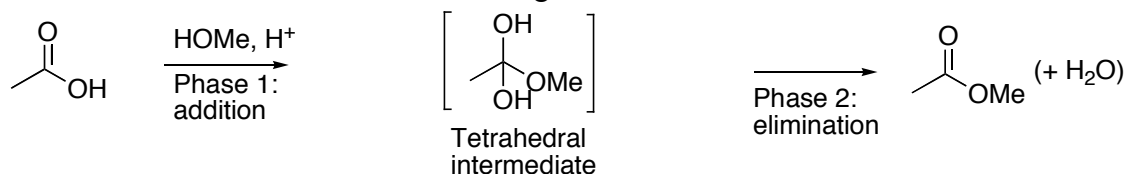
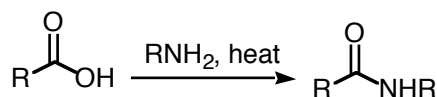
15. Indirect Conversion to Amides

- 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 (20.10, 13, 21.7)12. **Direct Conversion to Esters** (Sections 20-10-12, 21-5)

- **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

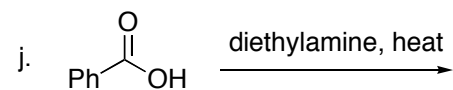
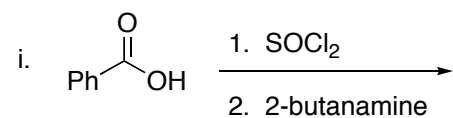
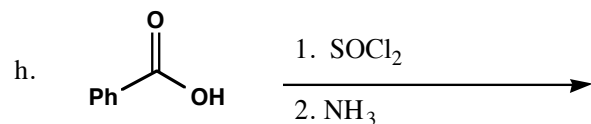
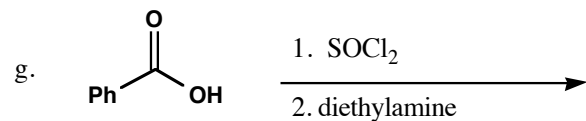
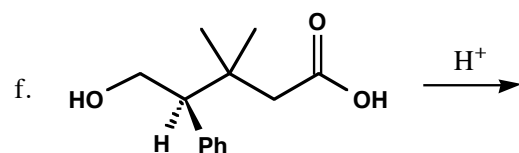
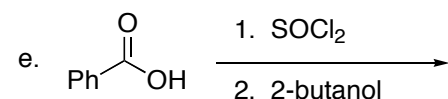
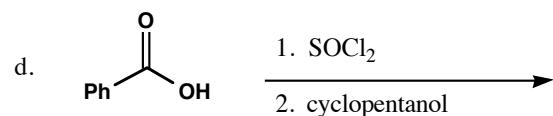
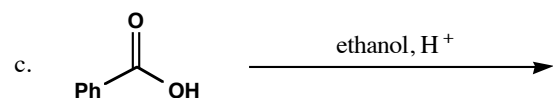
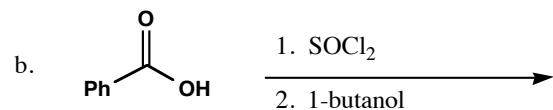
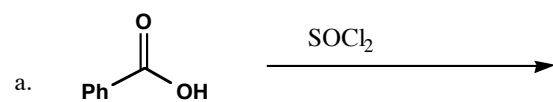
2. Draw the mechanism for the following reaction.

14. **Direct Conversion to Amides** (Sections 20-11, 20-13, 21-5)

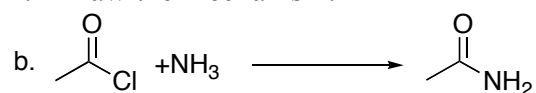
- **mechanism not required**
- This is a “downhill” reaction energetically, but is complicated and retarded by acid-base reactions. Normally the “indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

Problems

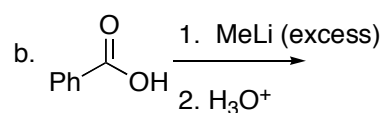
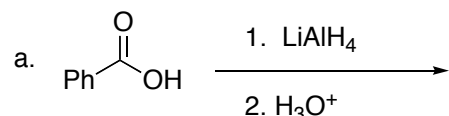
1. Synthesis of Acid derivatives. Draw the products for the following reactions.



1. Draw the mechanism.



2. Draw the products for the following reactions.



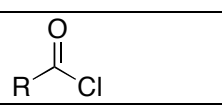
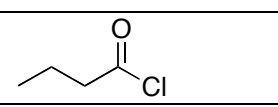
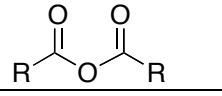
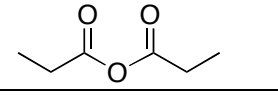
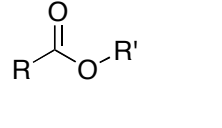
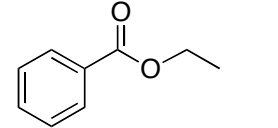
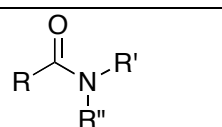
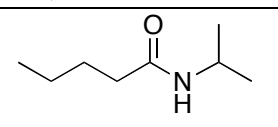
Ch. 21 Carboxylic Acid Derivatives:



- 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/H₂O
- Some (Cl and A) hydrolyze to acids under straight water treatment
- Esters hydrolyze to acids under acid catalysis

| | General | | Example | |
|---|--------------------|---|-------------------------|--|
|  | Alkanoyl chloride |  | Butanoyl chloride | <ul style="list-style-type: none"> • High reactivity • Named as if ionic |
|  | Alkanoyl Anhydride |  | Propanoic anhydride | |
|  | Alkyl Alkanoate |  | Ethyl Benzoate | Named as if ionic |
|  | Alkanamide |  | N-isopropyl pentanamide | |

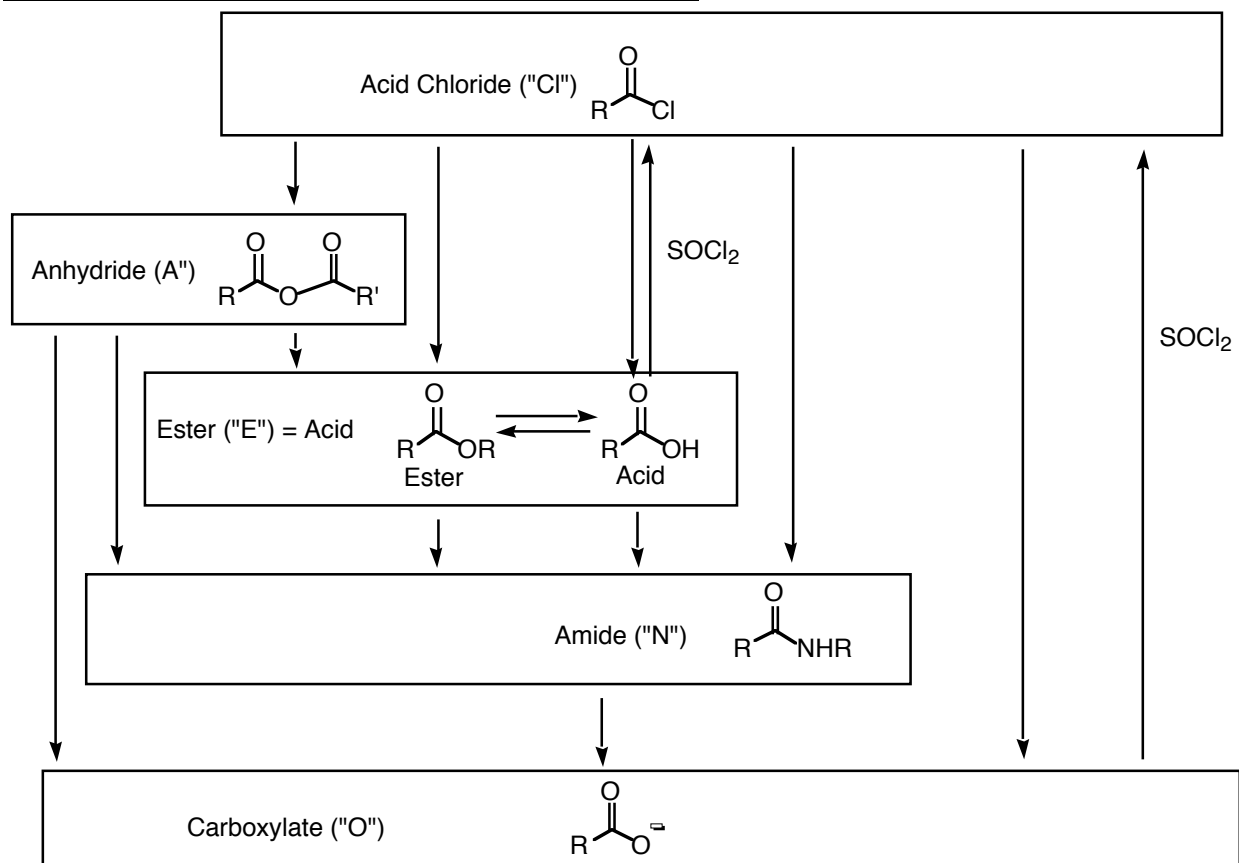
1. Draw the structures for the following esters.

a. propyl benzoate

b. methyl ethanoate

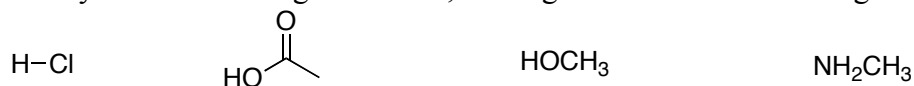
c. ethyl butanoate

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

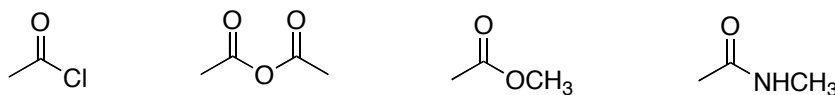


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going 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)

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

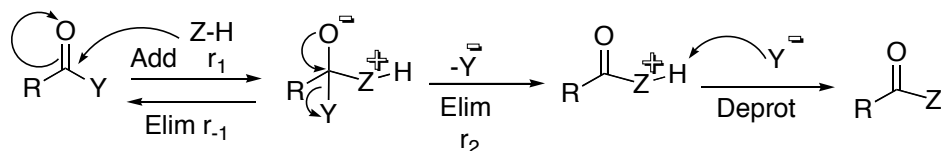


3. Rank the reactivity of the following toward hydrolysis. Do you see a similarity between your rankings for this question relative to your answers for previous question?



Notes:

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

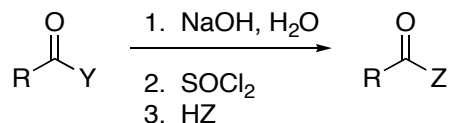


- The overall reactivity correlates the leaving ability of the Y^- for two reasons
 1. This affects the kinetic r_2/r_{-1} portion. If r_2 is slow, the addition is simply reversible
 2. The same factors that make Y^- a good leaving group also make the initial carbonyl more reactive toward addition (step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

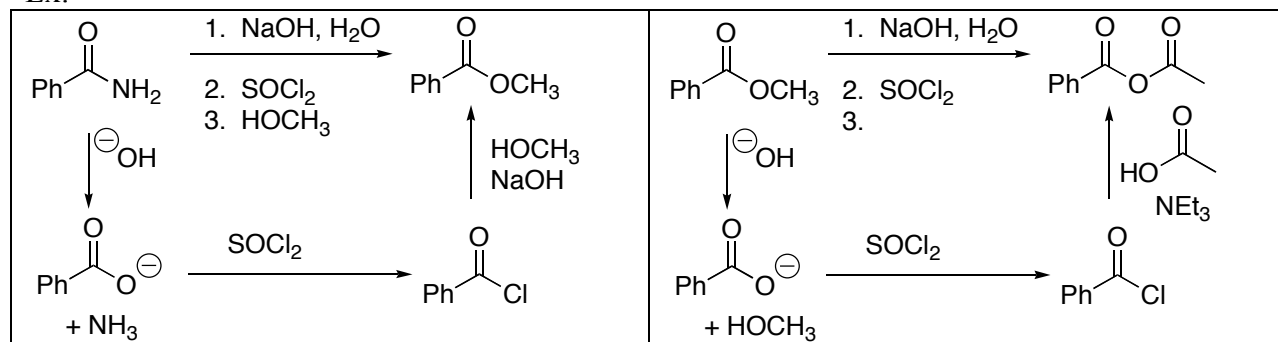
• Memory

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

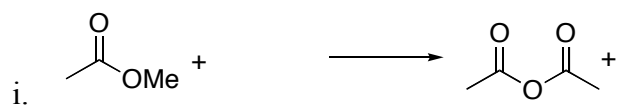
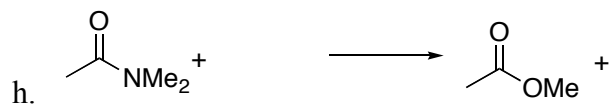
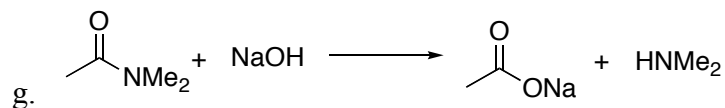
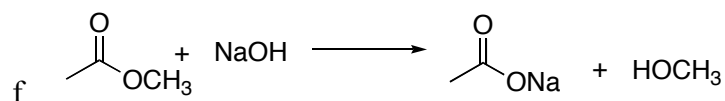
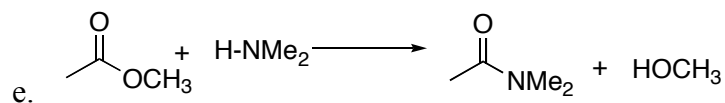
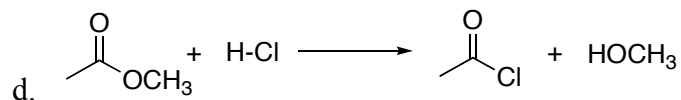
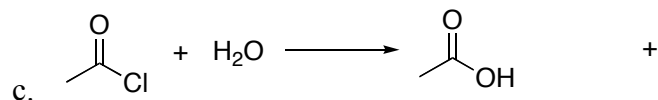
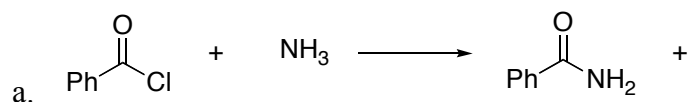
B. “Uphill” Reaction Sequences: 3-steps



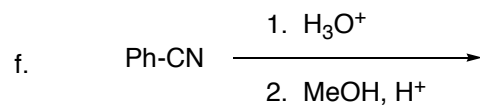
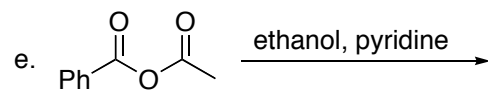
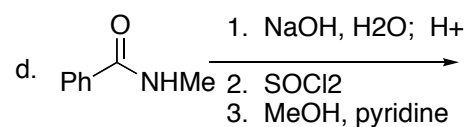
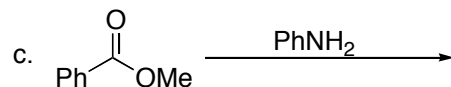
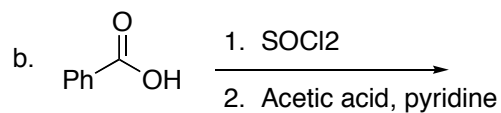
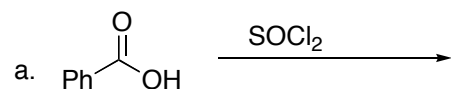
Ex:



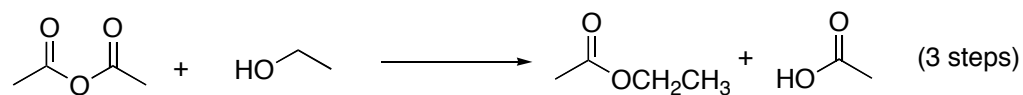
1. Which will proceed easily/directly? (“downhill”?) Add Appropriate Reactant(s) and Side Product. If it doesn’t go directly, give indirect route.



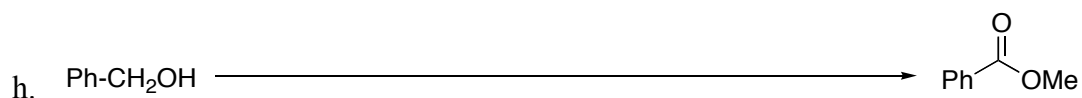
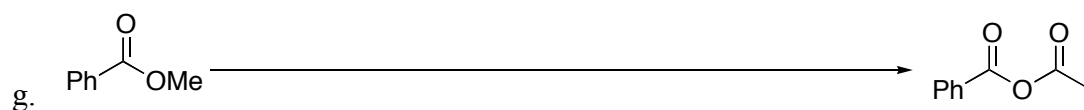
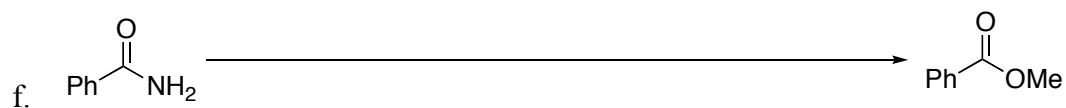
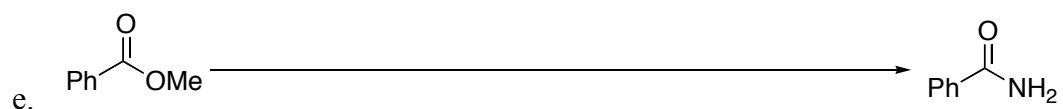
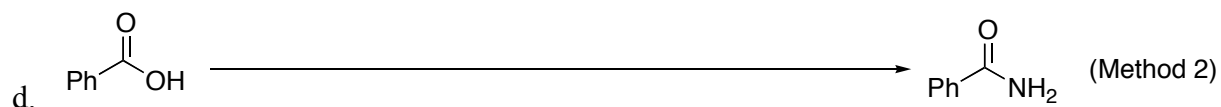
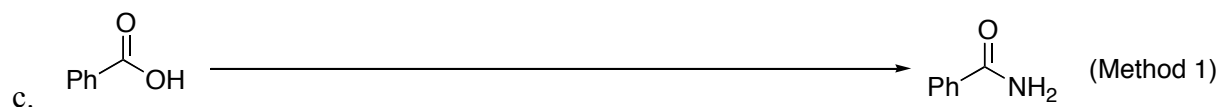
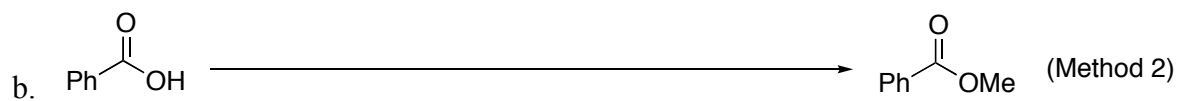
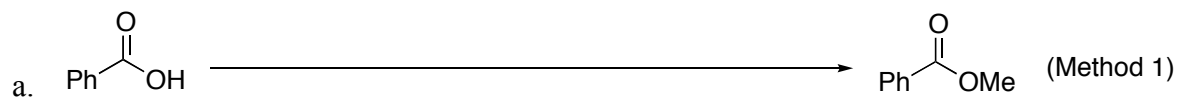
1. Provide products for the following transformations.



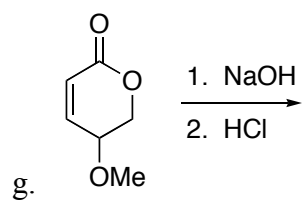
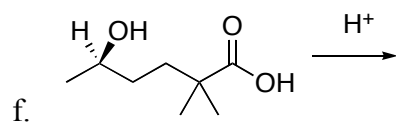
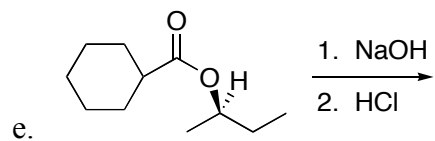
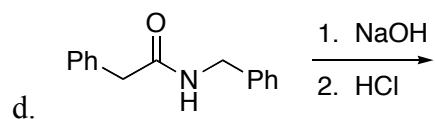
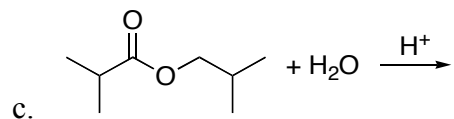
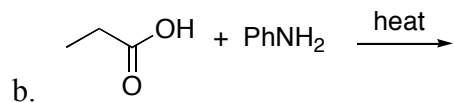
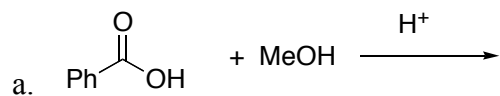
2. Draw the mechanism for the following reaction.



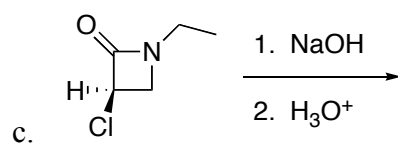
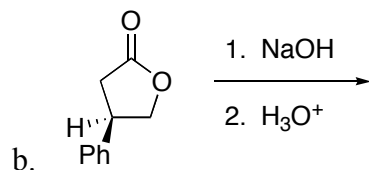
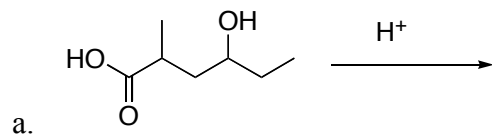
1. Provide reagents for the following transformations.



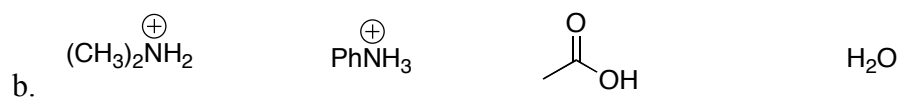
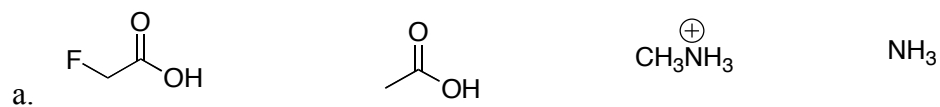
2. Provide products for the following condensation or hydrolysis transformations.



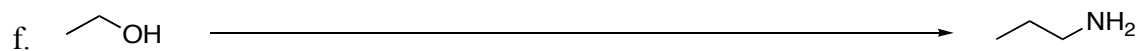
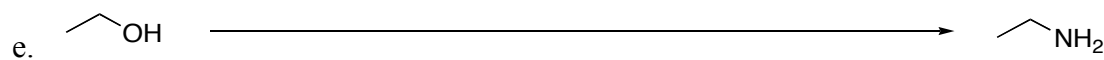
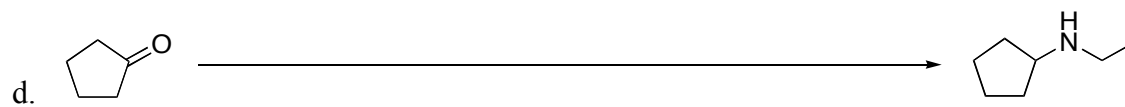
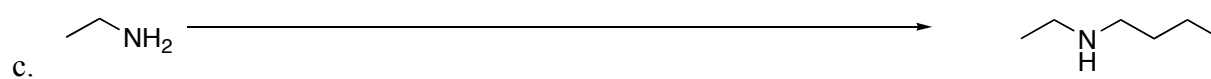
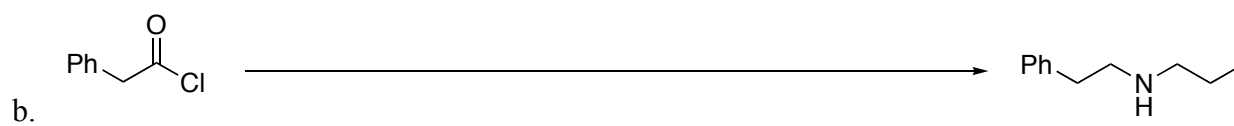
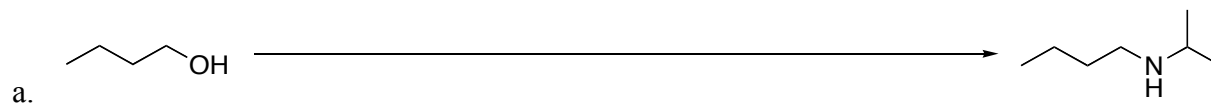
3. Cyclic Esters and Amides: Provide products or starting reactants for the following condensation or hydrolysis reactions involving cyclic esters or amides.



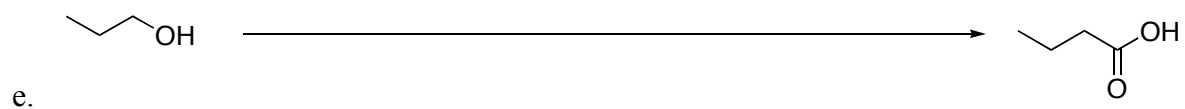
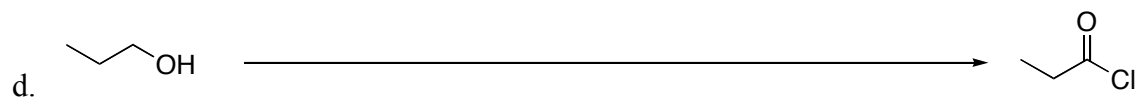
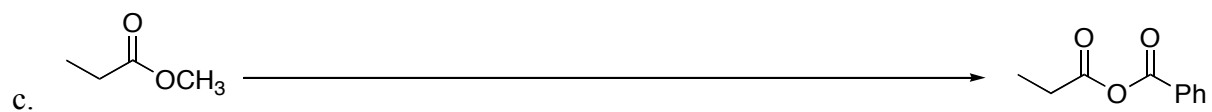
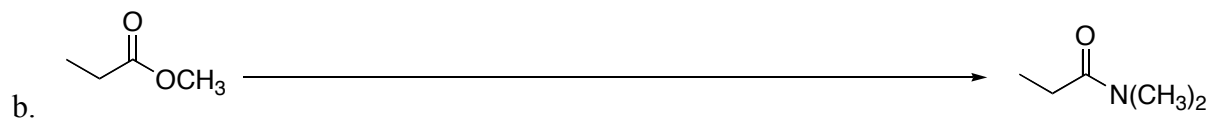
4. Rank the following as acids or bases.



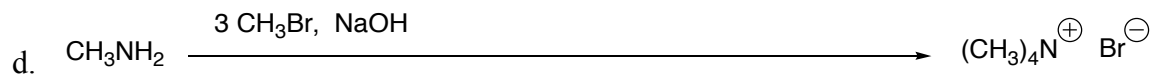
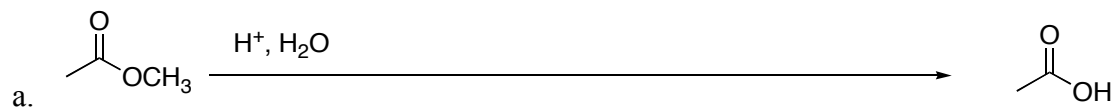
5. Provide reagents for the following transformations. There may be more than one solution.



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



7. Provide mechanism for the following reactions.

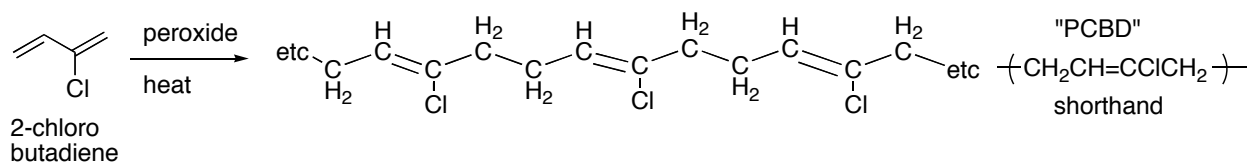
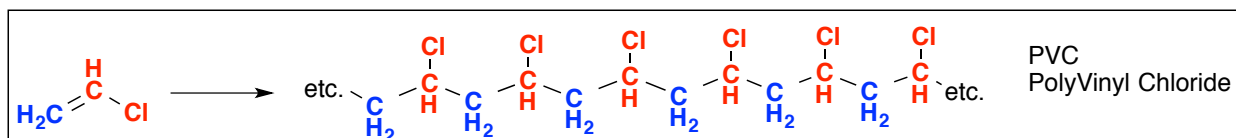
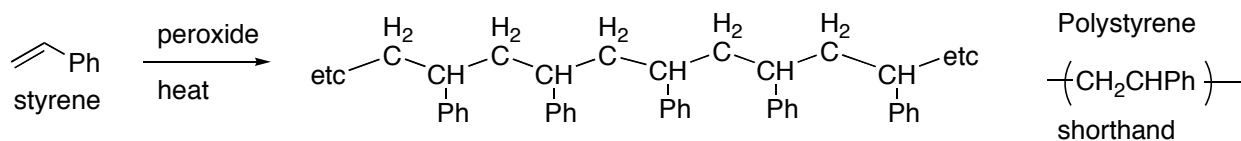


Polymers: Very large molecule composed of small repeating units (monomers) (8-16, ch26)

Two major classes of polymers:

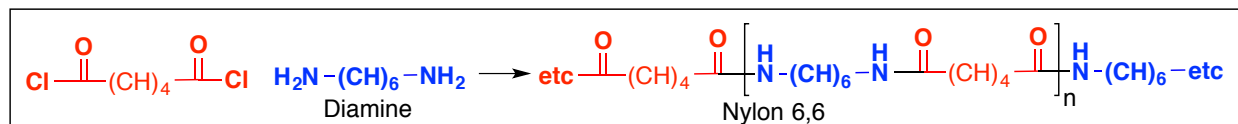
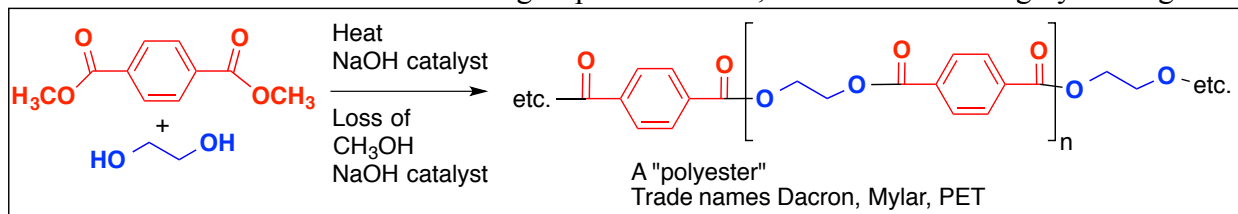
1. Addition polymers, made from alkenes and conjugated dienes:

- All of the atoms in the original monomers are present in the polymers.
- Additions can proceed via any of radical, cationic, anionic, or transition-metal mediated mechanism



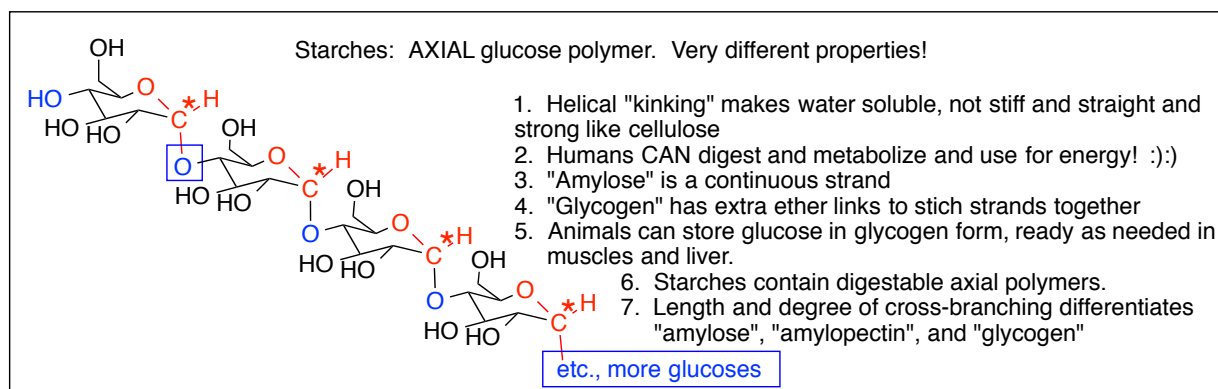
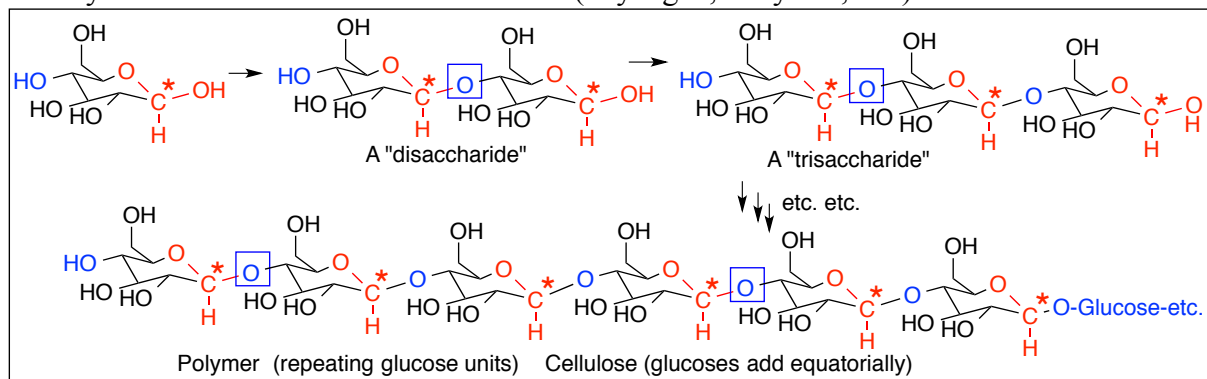
2. Condensation polymers,

- Amides or Esters links connect units
- Typically amines or alcohols reacting with carboxylic acids or ClAvENO variants
- Polymerization is accompanied by extrusion of water if an acid is the precursor for the ester or amide
- HCl, RCO_2H , or ROH may be produced if using RCOCl , anhydride, or an ester
- Each unit needs a functional group at either end, so as to be able lengthy chain growth

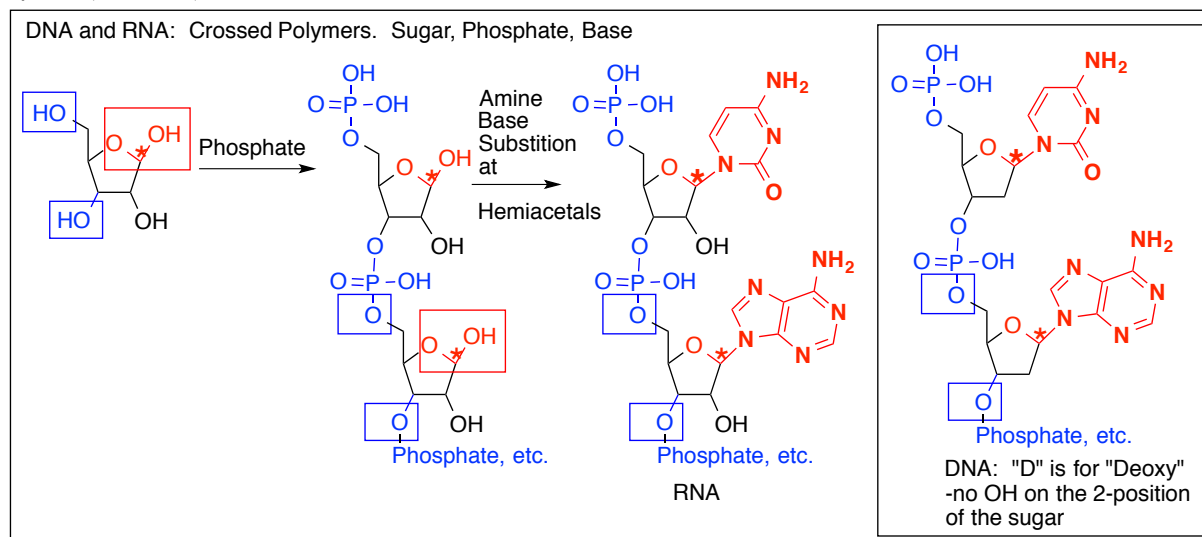


Major BioPolymers (All are Condensation Polymers)

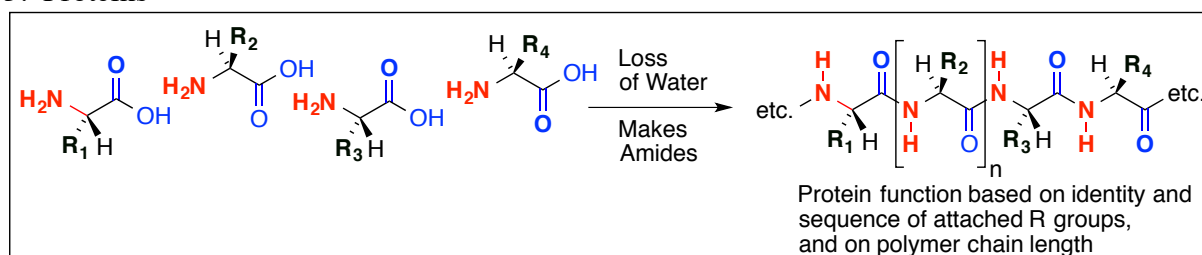
1. Polysaccharides: Cellulose and Starches (Glycogen, Amylose, etc.)



2. DNA + RNA



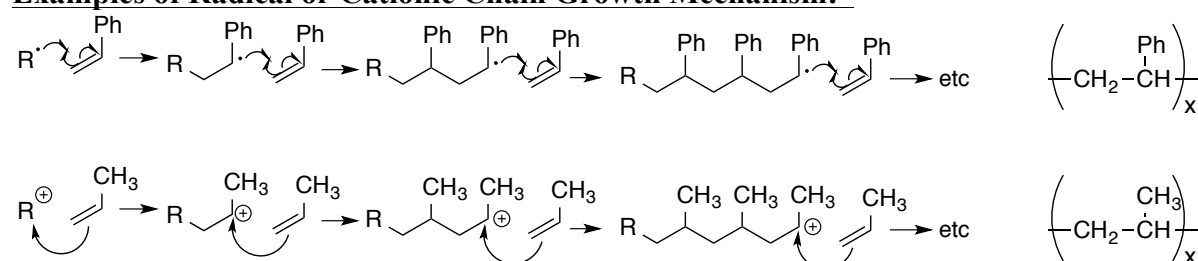
3. Proteins



Addition Polymers from Alkenes and Conjugated Dienes

- Alkenes are common monomers for many common polymers
- Rubbers, plastics, piping, and all kinds of varying materials.
- Routinely named after the alkene, usually using its common name
 - Polyethylene, polypropylene, polystyrene, polyisobutylene, polyvinyl chloride (PVC)
- Addition polymerization: chain-growth by having monomer alkenes add onto the reactive end of a growing polymer
- Reactive end is usually a cation, radical, anion, or organometallic
- Something highly reactive
- Initiation: Getting it started by creation of a high reactive intermediate
- Termination: Some process to depopulate the cation or radical or whatever.

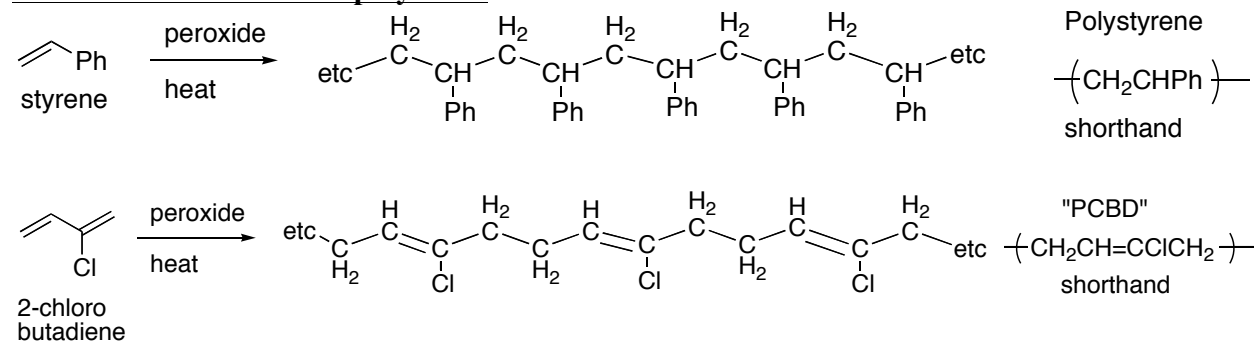
Examples of Radical or Cationic Chain Growth Mechanism:



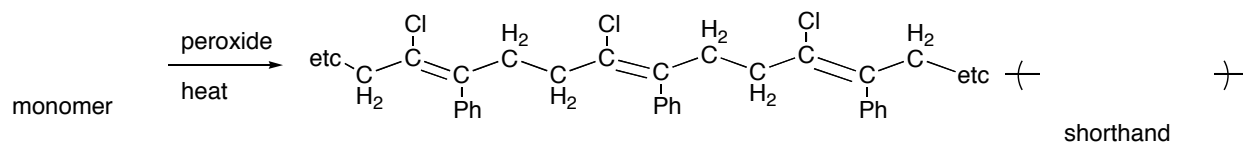
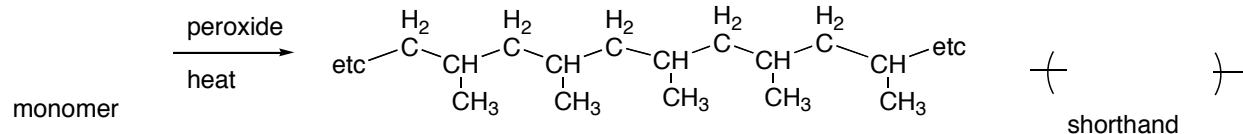
Addition Polymers

- No change in atoms, you simply add all the atoms in the reactants together to make long polymer strings.
- The repeat unit in the polymer must have the same atoms as the monomer.
- Precursors: Alkenes or Conjugated Dienes
- Polymer has one fewer double bond than monomer: monoalkene \rightarrow none; diene \rightarrow one.
- For a conjugated diene, the two middle carbons end up double-bonded in the polymer
- Initiation/recognition: Usually radical/peroxides. Sometimes acid or Lewis acid catalyzed.
- Skills: Given monomer, draw polymer
- Skills: Given polymer, recognize monomer.
- Skills: Use and understand shorthand

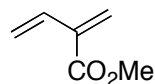
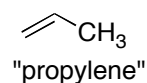
Ex: Mono-ene and diene polymers



Problems: Draw the monomer and the shorthand version of polymer

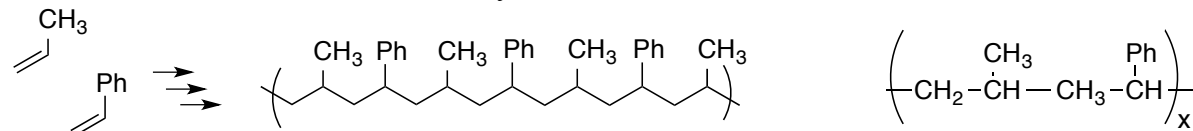


Draw the polymer from the following monomer, both shorthand and longstretch



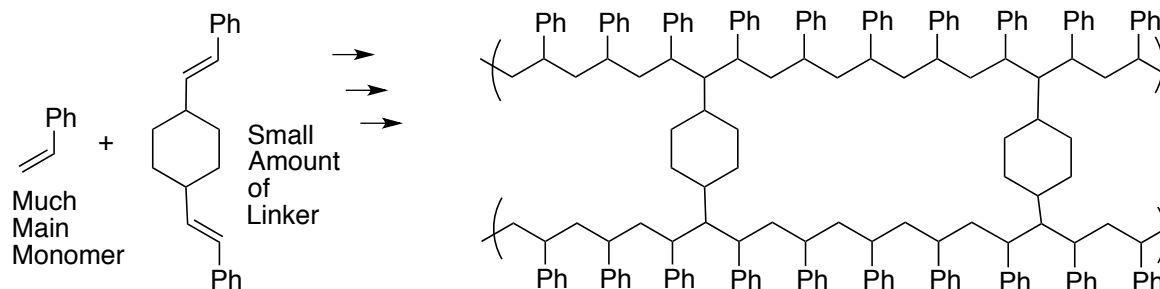
Mixed Polymers: When two different alkenes are used.

- Some will alternate consistently, others will be kind of random



Cross-linked Polymers: When two chains are linked together

- Use some variably small concentration of a molecule with two alkenes (or dienes) and some kind of tether/spacer
- Cross-linked chains are stronger and less flexible
- The ratio of main monomer to cross-linker dictates the frequency of ties.



Polymers and Physical Properties:

- Beyond scope here
- But lots of ways to manipulate length and degree of crosslinking
- Many laboratory ways to adjust practical factors such as strength and flexibility,