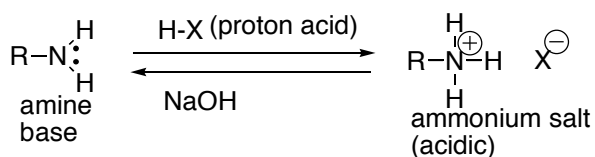
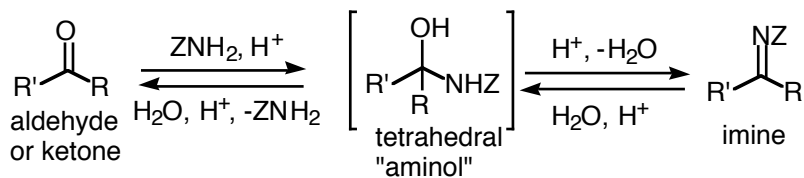


## Reactions of Amines

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

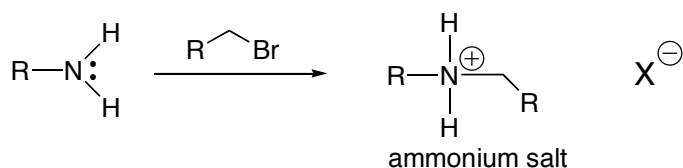
- Mechanism: Required (protonation)
- Reverse Mechanism: Required (deprotonation)
- Amines are completely converted to ammonium salts by acids
- Ammonium salts are completely neutralized back to amines by bases
- Patterns in base strength: Reflect stabilization/destabilization factors for both the amine 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)

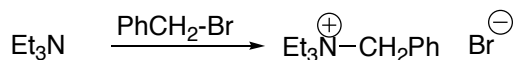
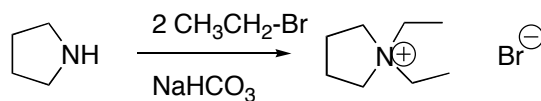
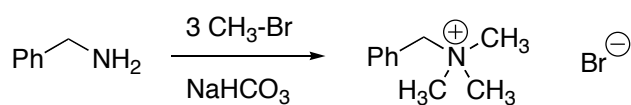
Notes:

- “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  $\rightarrow$   $2^\circ$ ,  $3^\circ$  amines can’t do this

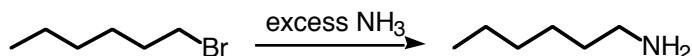
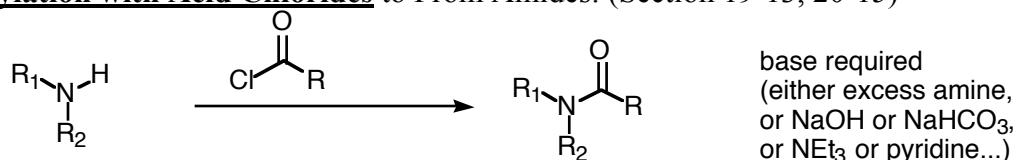
## 1. Alkylation of 1° Alkyl Halides (Section 19-12, 19-21A)



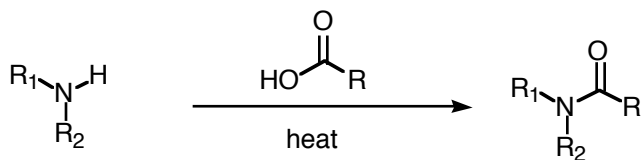
- **3a. Polyalkylation** is routine.
  - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below).
  - Mechanism required for polyalkylations. The mechanism involves repetitive sequential S<sub>N</sub>2 alkylation-deprotonations.



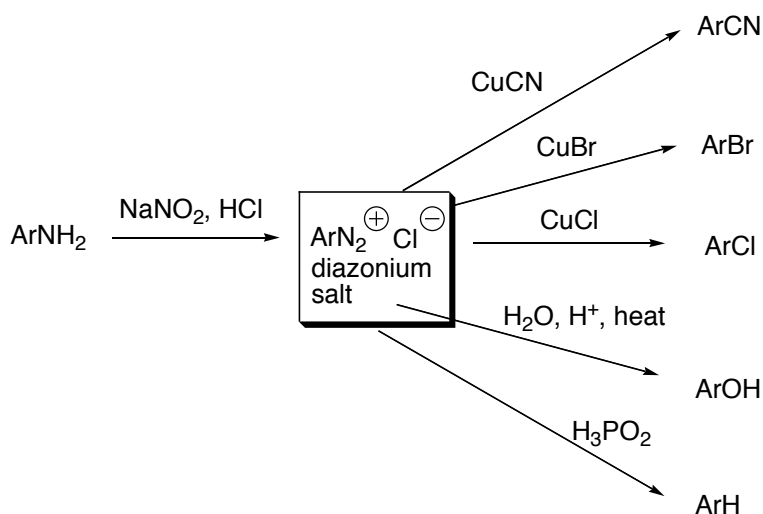
- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S<sub>N</sub>2, followed by deprotonation by the excess amine.

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 NH<sub>3</sub> 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<sub>3</sub> can be used.

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

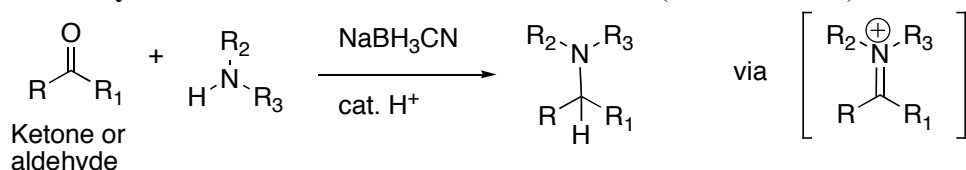
- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid  $\rightarrow$  amide is routine, and is facilitated by complex enzyme mechanisms

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

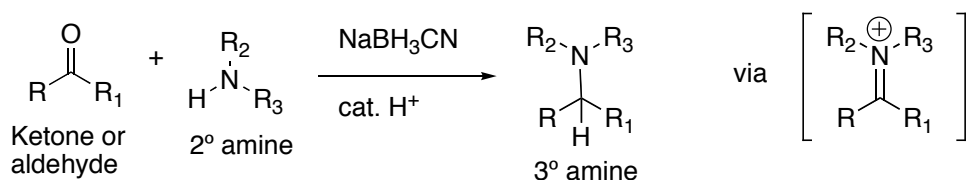
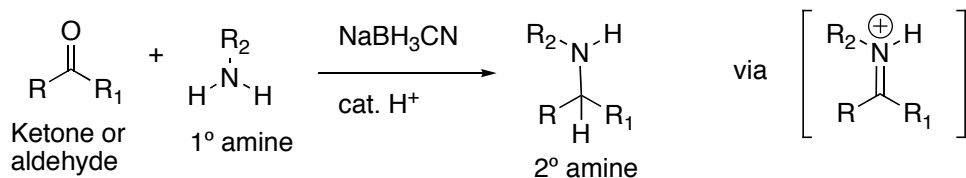
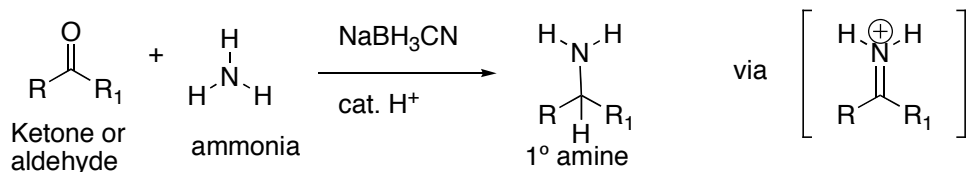
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces  $\text{N}_2$ , a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta 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

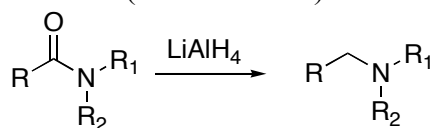
## 6. From Aldehydes or Ketones: Reductive Amination (Section 19-19)



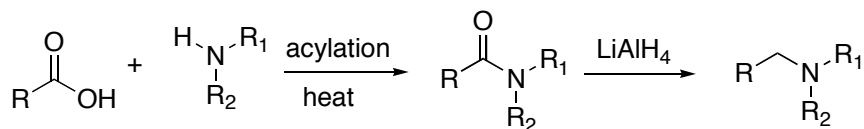
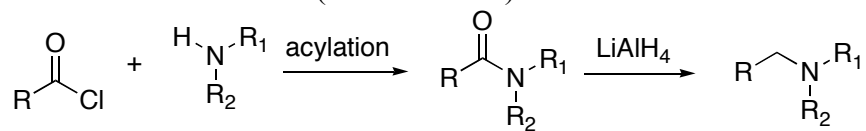
- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R<sub>2</sub> and/or R<sub>3</sub> can be either a carbon or a hydrogen. Thus:
  - NH<sub>3</sub> → 1° RNH<sub>2</sub>
  - 1° RNH<sub>2</sub> → 2° R<sub>2</sub>NH
  - 2° R<sub>2</sub>NH → 3° R<sub>3</sub>N
  - 3° R<sub>3</sub>N don't react



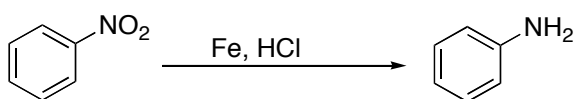
## 7. Via Amides: (Section 19-20)



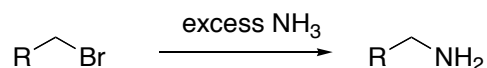
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R<sub>1</sub> and R<sub>2</sub> can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - RCONH<sub>2</sub> → 1° RCH<sub>2</sub>NH<sub>2</sub>
  - RCONHR → 2° RCH<sub>2</sub>NHR
  - RCONR<sub>2</sub> → 3° RCH<sub>2</sub>NR<sub>2</sub>

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

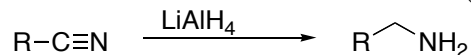
- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

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

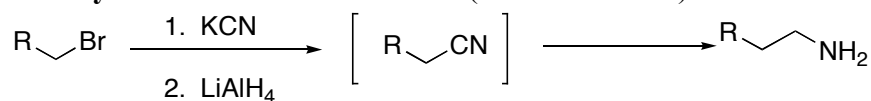
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H<sub>2</sub>, Ni/H<sub>2</sub>, Pt/H<sub>2</sub>,
  - Fe/HCl, Zn/HCl, Sn/HCl

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 NH<sub>3</sub> prevents polysubstitution.

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

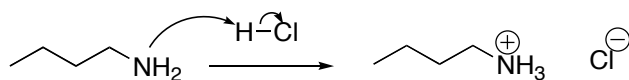
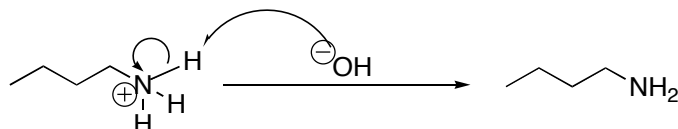
- Access: 1° amines
- Mechanism not required.

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

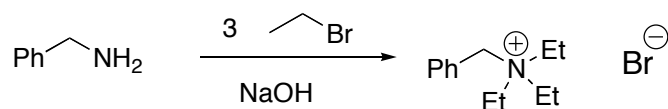
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!

**Summary of Amine Syntheses**

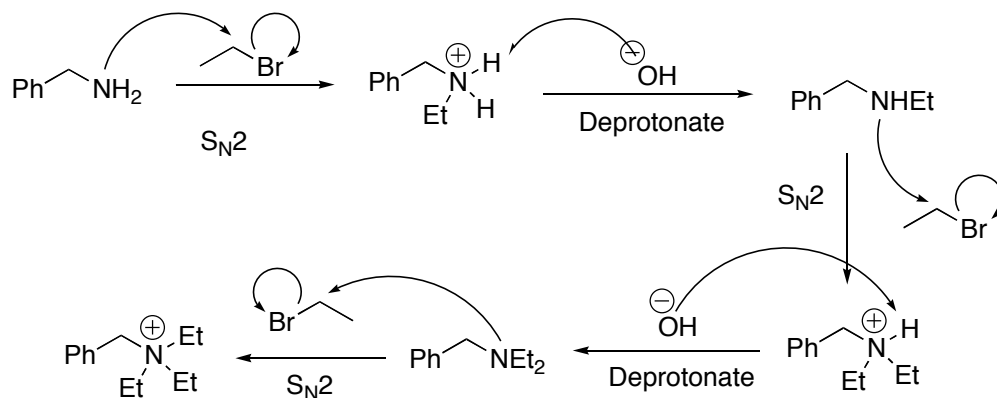
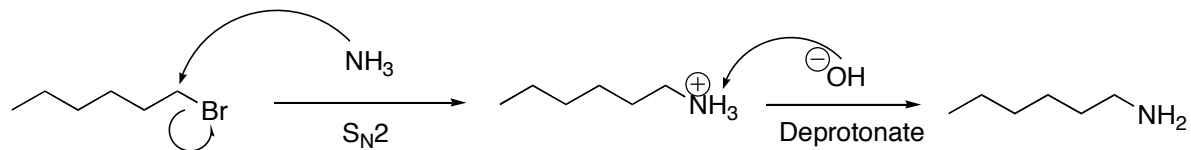
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	$R_2NH$ , $H^+$ $NaBH_3CN$ ,	1°, 2°, or 3° Amines	
2	#7, #8	Amides	$LiAlH_4$	1°, 2°, or 3° Amines	
3	#7, #8	Amines (via Amide)	1. $RCOCl$ (or $RCO_2H$ , heat) 2. $LiAlH_4$	1° $ArNH_2$	
4	#7, #8	Acid Chlorides 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:

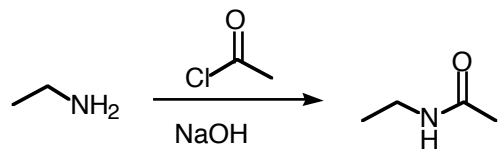


Mech:

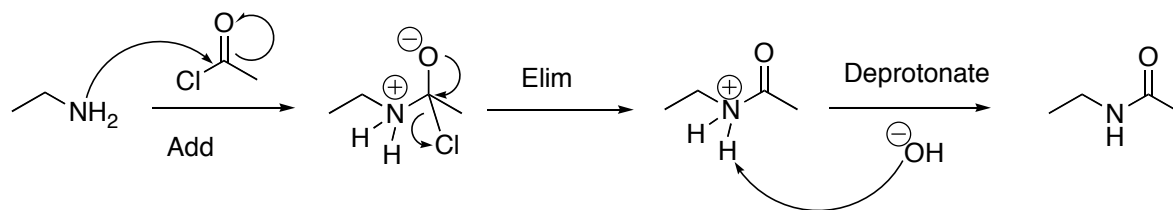
**3b. Monoalkylation**

#### 4. Acylation

Ex:



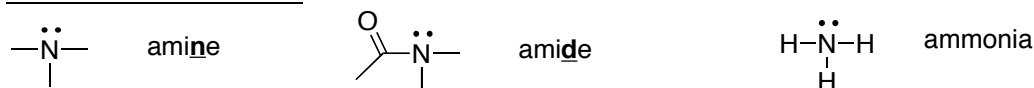
Mech: 3 steps: Addition-Elimination-Deprotonation



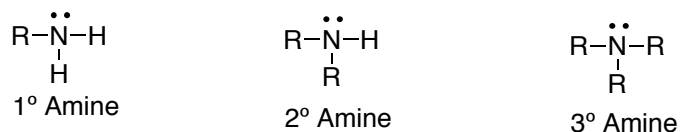
## Chapter 19 Amines

## A. Miscellaneous

## 19.1 Intro, Terms

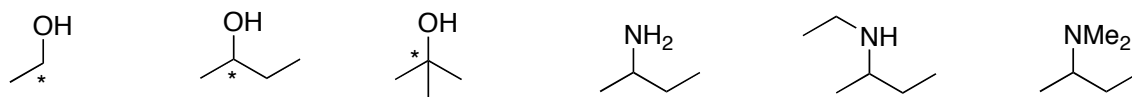
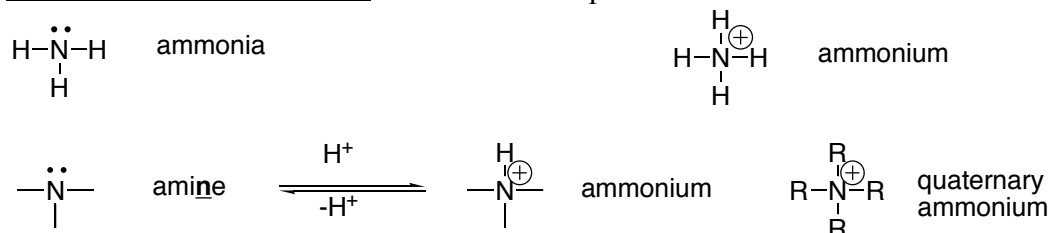
Amines versus Amides

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.

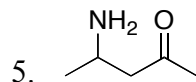
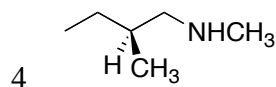
Amines versus Ammoniums: Neutral versus protonated/cationic

**19.2 Formal Amine Nomenclature:** X-alkanamine, N-alkyl-X-alkanamine, etc.

- For core name, choose longest C-chain to which nitrogen is attached, and call it X-alkanamine
  - 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-alkyl"
  - The position of substituents on a carbon are always designated by the carbon's number
  - this is the first time we've had a substituent on something other than carbon, so it's location is designated by "N-" rather than by a number
- NH<sub>2</sub> as a Substituent: "Amino"

Draw the structure or provide the name for the following.

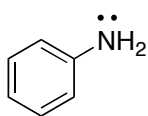
- N-methyl-3-phenyl-2-octanamine
- Z-3-penten-1-amine
- 3-hexanamine



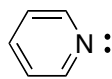
Common Naming (for simple amines): Alkylamine, dialkylamine, trialkylamine....

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

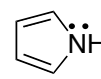
Aniline



Pyridine



Pyrrole

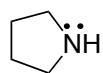


Some Other Famous Common Amine Names (No memory requirement)

Name

Structure

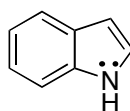
Pyrrolidine



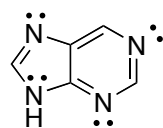
Name

Structure

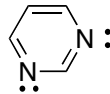
Pyridine



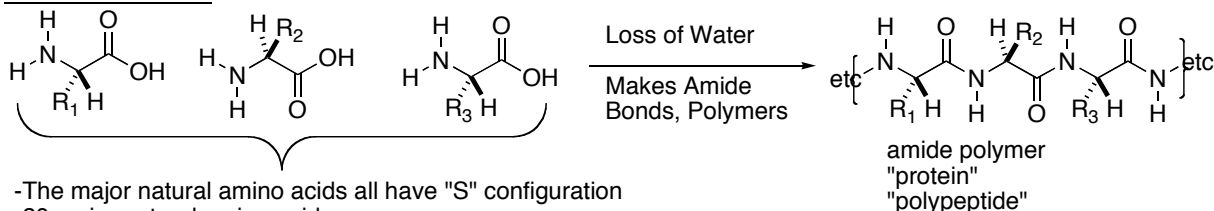
Purine



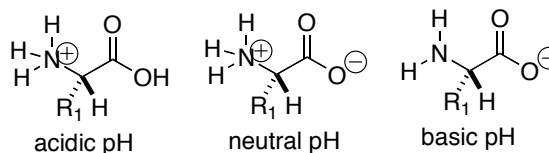
Pyrimidine



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

## 19.3 Structure and Hybridization

- N atoms** are typically either  $sp^3$  hybridized (normal) or  $sp^2$  hybridized
  - $sp^3$  is the default (when no double bonds/conjugation require a p orbital)
  - $sp^2$  in either of two cases:
    - N atom is itself double bonded
    - N atom is conjugated to a double bond
- N lone pair** is either:
  - $sp^3$  is the default (when no double bonds/conjugation require a p orbital)
  - $sp^2$  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
  - 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/ $\pi$  bond

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

## 19.4 Physical Properties

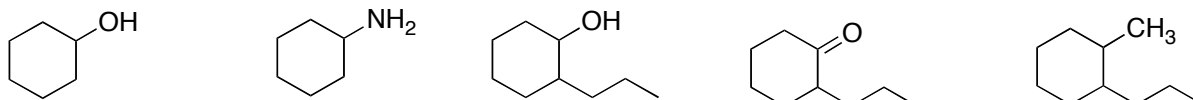
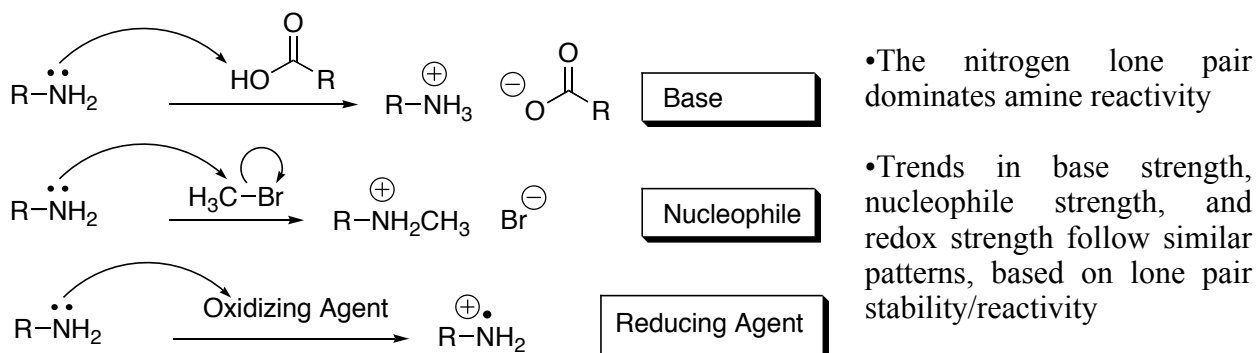
Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

- Water Solubility:** All amines hydrogen-bond water  $\rightarrow$  impacts solubility
  - 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
  - Based on basicity (the acidity of water's hydrogen is common)
- Boiling Point:** 1° and 2° amines hydrogen bond themselves, but 3° amines don't
  - Boiling point for similar mw amines: 1°, 2° amines > 3° amines
  - amines generally have lower boiling points than analogous oxygen compounds
    - Boiling point for similar mw:  $RCO_2H > RCH_2OH > RCH_2NH_2$
  - 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.
- Amines stink! (ammoniums don't)

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



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

**B. Basicity of Amines: Reactivity of the Nitrogen Lone Pair (19.5,6)**

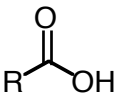
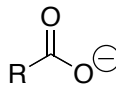
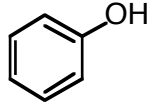
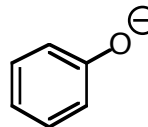
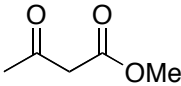
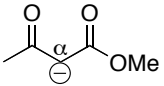
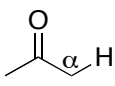
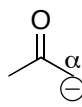
Neutral amine bases are stronger than:

- Neutral oxygens (water, alcohol, ketones...)
- Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:

- Anionic hydroxide or alkoxides
- Anionic nitrogen or carbon bases

**Acidity/Basicity Table 19.1: Neutral Acids and Anionic Bases**

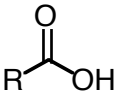
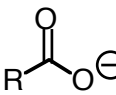
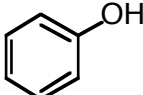
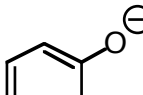
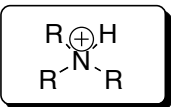
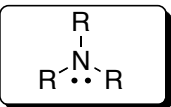
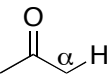

<u>Class</u>	<u>Neutral Acid Structure</u>	<u>K<sub>a</sub></u>	<u>Acid Strength</u>	<u>Anion Base</u>	<u>Base Strength</u>
Strong Acids	H-Cl, H <sub>2</sub> SO <sub>4</sub>	10 <sup>2</sup>		Cl <sup>⊖</sup> , HO-SO <sub>3</sub> <sup>⊖</sup>	
Carboxylic Acid		10 <sup>-5</sup>			
Phenol		10 <sup>-10</sup>			
1,3-Dicarbonyl		10 <sup>-12</sup>			
Water	HOH	10 <sup>-16</sup>		HO <sup>⊖</sup>	
Alcohol	ROH	10 <sup>-17</sup>		RO <sup>⊖</sup>	
Ketones and Aldehydes		10 <sup>-20</sup>			
Amine (N-H)	(iPr) <sub>2</sub> N-H	10 <sup>-33</sup>		(iPr) <sub>2</sub> N <sup>⊖</sup> Li <sup>⊕</sup>	
Alkane (C-H)	RCH <sub>3</sub>	10 <sup>-50</sup>		RCH <sub>2</sub> <sup>⊖</sup>	

Quick Checklist of Acid/Base Factors

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

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

**Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases**

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

- Nonfactor on Table 19.1, since all of the “acids” have the same charge (neutral)
- In Table 19.1, all of the “bases” have the same charge (anion, single negative charge)
- **Normally, all else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 19.2)**

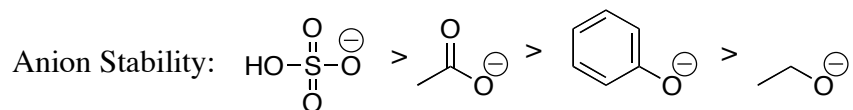
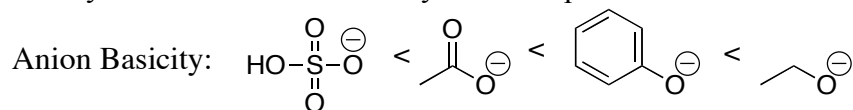
## 2. Electronegativity:

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

## 3. Resonance/Conjugation:

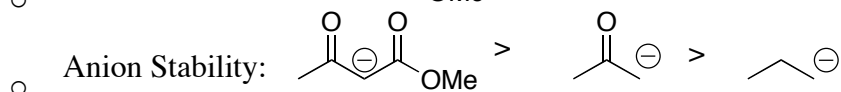
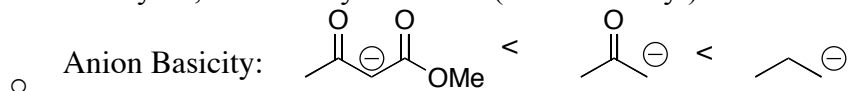
- Oxygen Series:

Acidity: sulfuric acid > carboxylic acid > phenol > alcohol



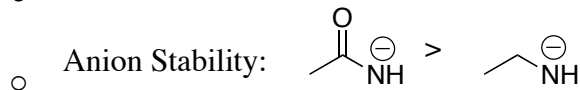
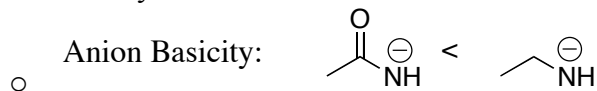
- Carbon Series:

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



- Nitrogen Series:

○ Acidity: amide > amine

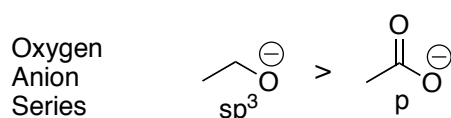
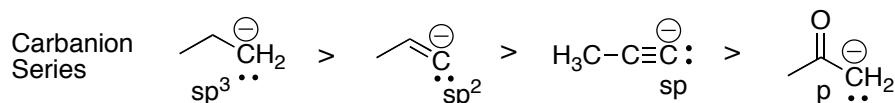
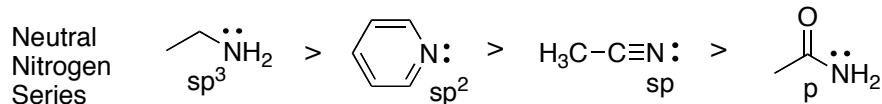


- Note: Resonance is often useful as a tiebreaker (for example, molecules in which both have O-H bonds and both have equal charge, so that neither the charge factor nor the electronegativity factor could predict acidity/basicity)
- NOTE: Resonance can sometimes (not always) trump electronegativity or even charge.
  - Example of resonance versus electronegativity: a C-H with carbonyl resonance (ketone/enolate case) is more acidic than an N-H with no resonance help but less acidic than an O-H with no resonance help. A C-H with two carbonyl resonances (a 1,3-dicarbonyl case) is more acidic than even an O-H that has no resonance help.

- Example of resonance versus charge: A carboxylate anion, with serious resonance stabilization, ends up being so stabilized that it is even less basic than a neutral, uncharged amine! A hydrogen sulfate anion from sulfuric acid is less basic than not only neutral amines but also neutral oxygen (water, etc.)

## 4. Hybridization:

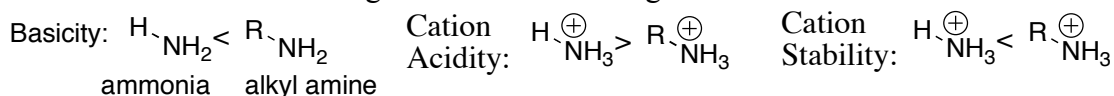
- For lone-pair basicity, (all else being equal),  $sp^3 > sp^2 > sp > p$



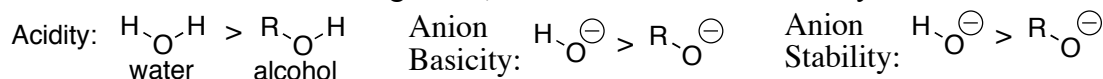
- This means that for acidity, alkynes > alkenes > alkanes

## 5. Electron donating/electron withdrawing substituents:

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



- 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	$NH_3$		$sp^3$	<b>Reference</b>		$\oplus NH_4$	$10^{-9.3}$	
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.**

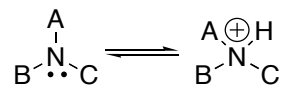
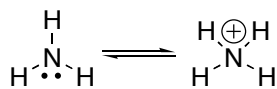
- Relative basicity correlates Lone pair hybridization:  $sp^3$  (entries 5-8) >  $sp^2$  (entry 4) > p (entries 1-3) (hybridization factor)
- Within the  $sp^3$  amines, increasing alkyl substitution increases basicity (entries 5-8):  $3^\circ > 2^\circ > 1^\circ > NH_3$  (electron donating group factor)

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

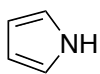
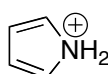
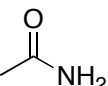
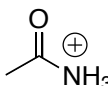
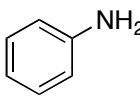
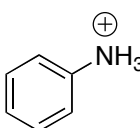

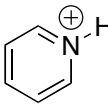
- Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because of the electron-withdrawing group factor).
- Conjugated nitrogens are in general less basic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

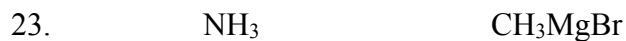
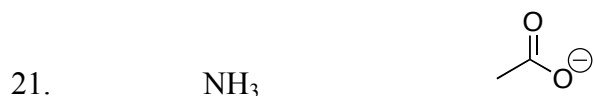
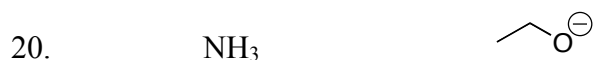
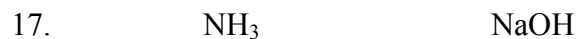


- Anything that **stabilizes the cation increases the basicity** of the nitrogen
- Anything that **destabilizes the cation decreases the basicity** of the nitrogen
- Anything that **stabilizes the amine decreases the basicity** of the nitrogen (especially if that stabilizing factor is sacrificed upon 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.

<u>Entry</u>	<u>Base</u>	<u>Conjugate Cation</u>	<u>Substituent And it's Impact</u>	<u>Why: Which Side Is Stabilized or Destabilized?</u>
5	NH <sub>3</sub>	NH <sub>4</sub> <sup>+</sup>	Reference	
6-8	Et <sub>3</sub> N	Et <sub>3</sub> NH <sup>+</sup>	Alkyl Groups Increase Basicity	<b>Cation</b> side stabilized by alkyl groups (electron donors, cation stabilizers)
1			Being part of Aromatic ring Reduces Basicity	<b>Neutral</b> side is stabilized by aromaticity. (Aromaticity is lost following protonation.)
2			Acyl/Amide Conjugated To Carbonyl	<b>Neutral</b> side is stabilized by conjugation to the carbonyl. That conjugation is lost following protonation. Second, the <b>cation side is destabilized</b> by the strongly electron withdrawing carbonyl group.
3			Conjugated To Aromatic	<b>Neutral</b> side is stabilized by conjugation. (That conjugation is lost following protonation.)
5			Aromatic. Part of Aromatic Ring	<b>Amine</b> side is stabilized by the sp <sup>2</sup> hybridization of the lone pair. An sp <sup>2</sup> lone pair is shorter than an sp <sup>3</sup> orbital. The shorter sp <sup>2</sup> orbital means the electrons are nearer and held more tightly by the nitrogen nucleus, and are thus more stable.



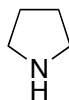
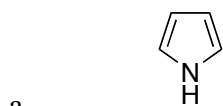
Choose the More Basic for Each of the Following Pairs



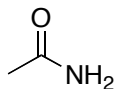
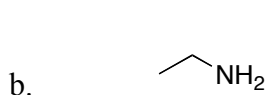
25. For the following sets of bases, rank them, 1 being the most basic.



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



a.



b.

c. benzamide [ $\text{PhC(O)NH}_2$ ]aniline ( $\text{PhNH}_2$ )

pyridine

triethylamine

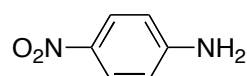
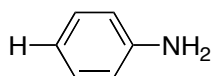
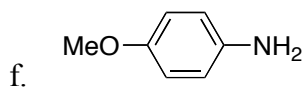
d. triethylamine

ethylamine

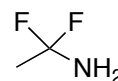
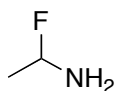
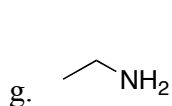
ammonia

e. dimethylamine

methylamine

aniline ( $\text{PhNH}_2$ )

f.



g.

h. triethylamine

NaOH

i. methanol

methylamine

methane

j.  $\text{CH}_3\text{MgBr}$  $\text{CH}_3\text{NHNa}$  $\text{CH}_3\text{ONa}$  $\text{CH}_3\text{NH}_2$  $\text{CH}_3\text{CO}_2\text{Na}$  $\text{CH}_3\text{OH}$

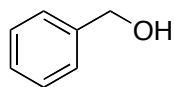
27. Rank the acidity of the following compounds, 1 being most acidic.

a.  $\text{H}_3\text{O}^+$        $\text{NH}_4^+\text{Cl}^-$       water      acetic acid ( $\text{CH}_3\text{CO}_2\text{H}$ )       $\text{NH}_3$

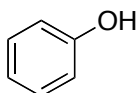
b.  $\text{H}_3\text{O}^+$       acetic acid ( $\text{CH}_3\text{CO}_2\text{H}$ )       $\text{Me}_3\text{NH}^+\text{Cl}^-$       ethanol

c.  $\text{NH}_4^+\text{Cl}^-$        $\text{Me}_3\text{NH}^+\text{Cl}^-$        $\text{PhNH}_3^+\text{Cl}^-$

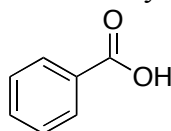
28. Suppose all of the molecules **A-D** are dissolved in diethyl ether.



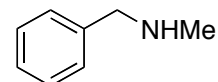
**A**



**B**

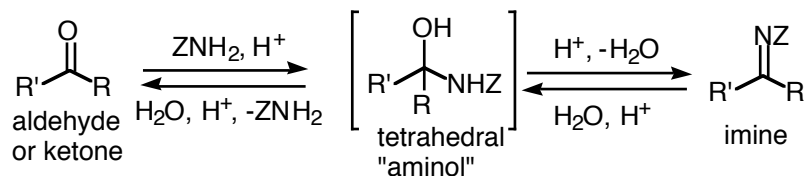


**C**



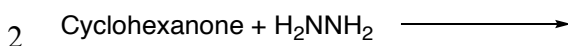
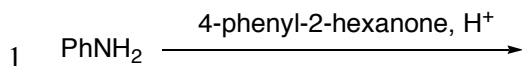
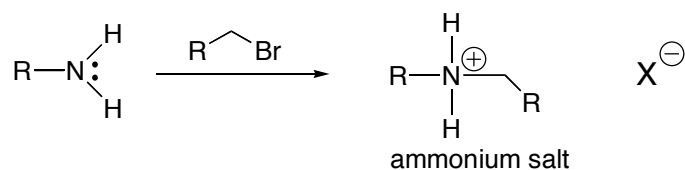
**D**

- 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)

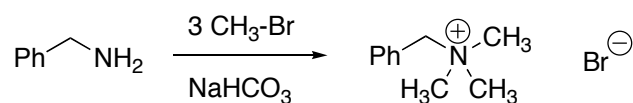
Notes:

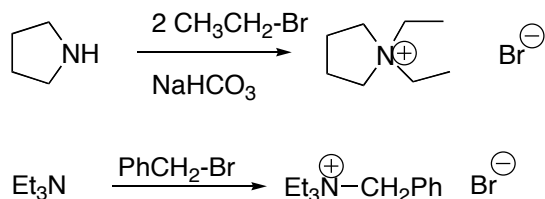
- “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The “aminol” can’t be isolated, it’s only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must 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)

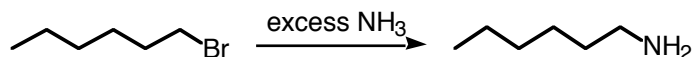
- **3a. Polyalkylation** is routine.

- 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<sub>N</sub>2 alkylation-deprotonations.

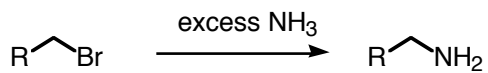


Notes

- 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  $1^\circ \text{R-X}$
- 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.

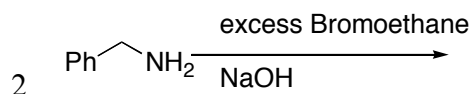
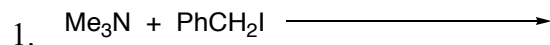
Synthetically Useful Alkylation Scenarios:

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

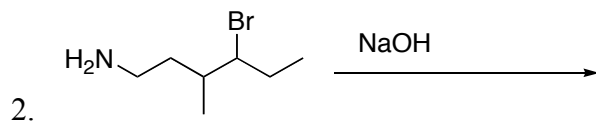
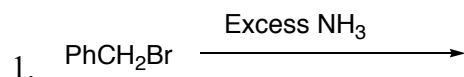


- Access:  $1^\circ$  Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess  $\text{NH}_3$  prevents polysubstitution.

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

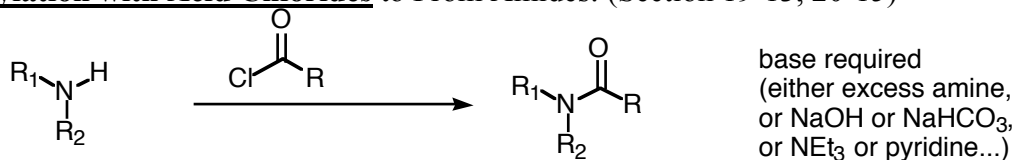
Draw the Products and mechanisms of the following Amine reactions.

Draw the Products and mechanisms of the following Amine reactions.

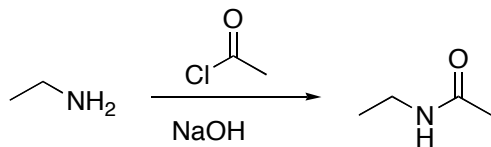


Why do you **not** get clean monoalkylation if you do a 1:1 mixture of  $\text{RNH}_2$  and  $\text{R-X}$ ?

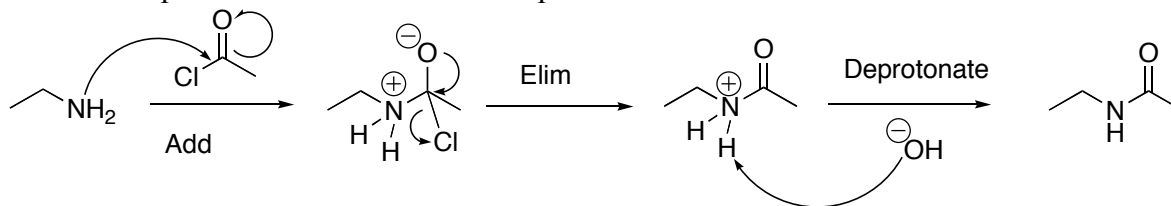
4. **Acylation with Acid Chlorides** to Form Amides: (Section 19-13, 20-15)



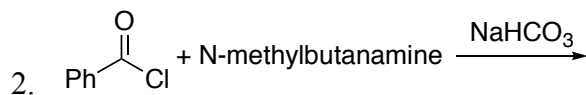
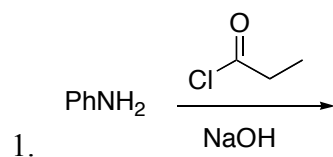
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But  $1^\circ$ ,  $2^\circ$ , or  $\text{NH}_3$  all react well.
- But  $3^\circ$  amines can't work.
- Some base is required for the deprotonation step and to absorb the  $\text{HCl}$ . For cheap amines, excess amine can simply be used. Alternatively, amines with no  $\text{H}$ 's (triethylamine, pyridine) can be used. Or else  $\text{NaOH}$  or  $\text{NaHCO}_3$  can be used.



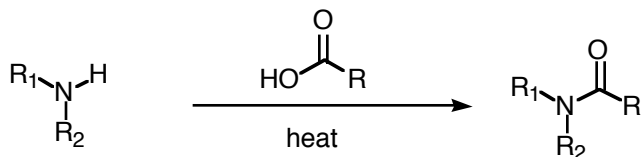
Mech: 3 steps: Addition-Elimination-Deprotonation



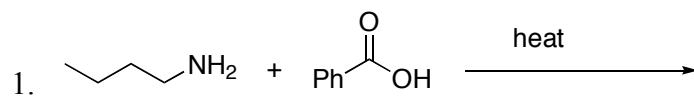
Draw the Products of the following Amine reactions, and the mechanism for the first one.



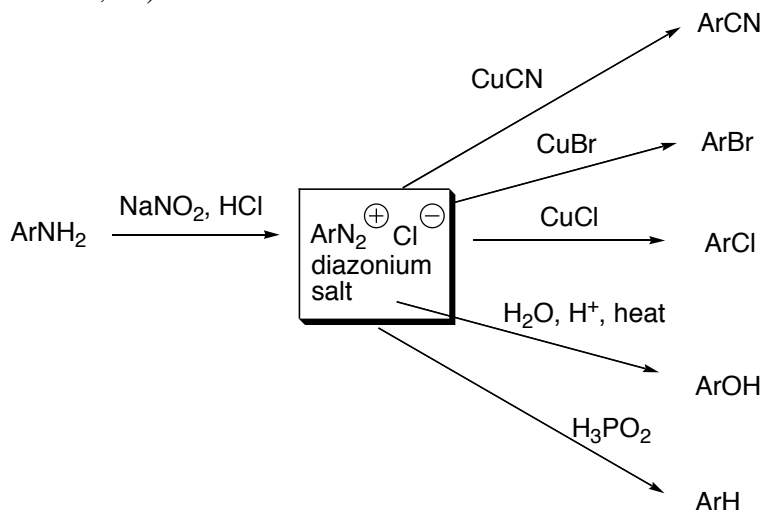
4b. **Acylation with Carboxylic Acids** to Form Amides: (Section 20-12)



- 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  $\text{N}_2$ , 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  $\text{H}^+$ )
2. Nucleophiles (give electrons to some other electrophile)
3. Reducing agents (give electrons to oxidizing agents)

Amines can be oxidized

$\text{NaNO}_2/\text{HCl}$  is a strong oxidizing agent, converts  $\text{RNH}_2$  to  $\text{RN}_2^+$ , and  $\text{ArNH}_2$  to  $\text{ArN}_2^+$

- “Diazonium salts”

$\text{RN}_2^+$  has the best leaving group known, because the leaving group is highly stable, neutral  $\text{N}_2$  gas

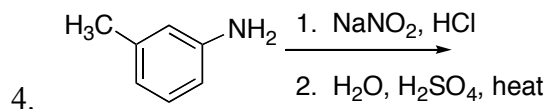
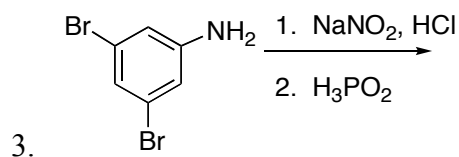
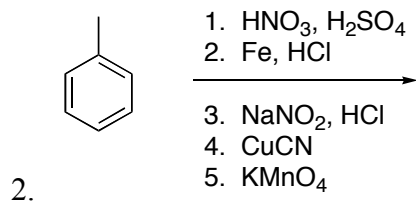
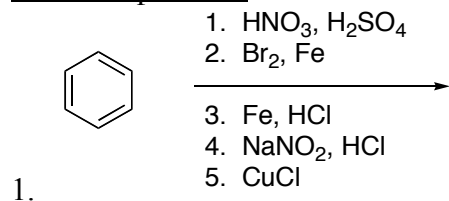
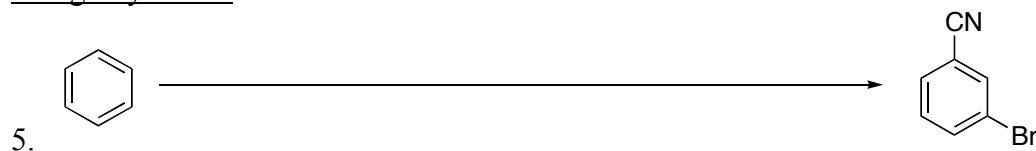
1. Alkyl  $\text{RN}_2^+$  are highly unstable, give cations, and usually give mixtures of  $\text{E1}$ ,  $\text{S}_{\text{N}}1$ , and cation rearrangement product mixtures
2. Not much use synthetically
3. However,  $\text{N}_2$  is such a great leaving group that even  $1^\circ$  carbocations can be formed/studied

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

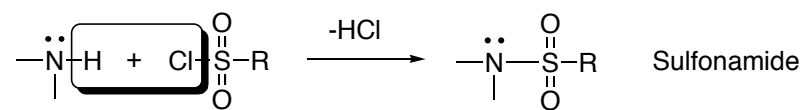
1. Unlike Alkyl diazoniums  $\text{RN}_2^+$ , aryl  $\text{ArN}_2^+$  are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms

Synthetic Use:

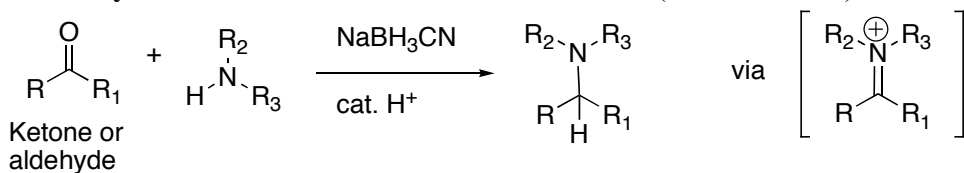
1.  $\text{NO}_2$  (meta director)  $\rightarrow \text{NH}_2 \rightarrow \text{N}_2^+ \rightarrow \text{Cl, Br, OH, CN, H}$
2. Easy to get meta relationships, even when you end with things that are not meta directors

Draw the productsDesign Synthesis

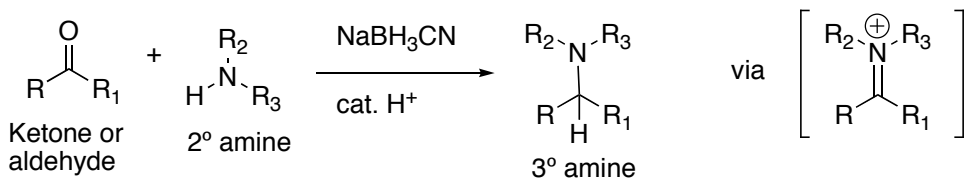
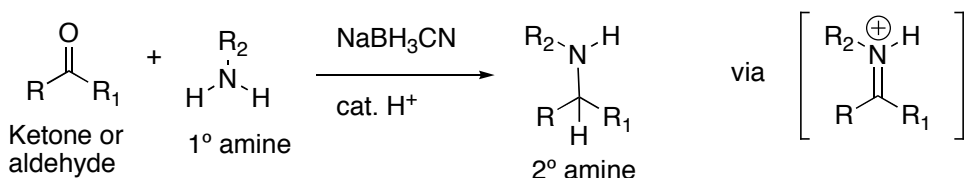
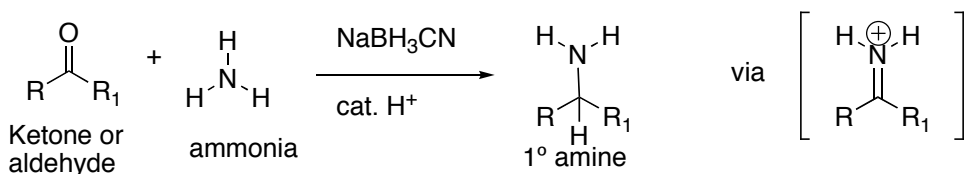
## 19.14 Reaction with Sulfonyl Chlorides (Not tested)



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

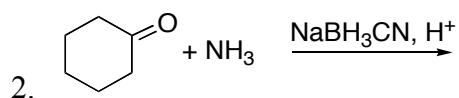
**D. Synthesis of Amines****6. From Aldehydes or Ketones: Reductive Amination (Section 19-19)**

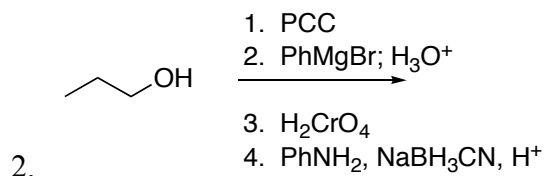
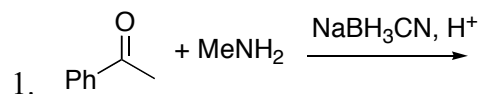
- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R<sub>2</sub> and/or R<sub>3</sub> can be either a carbon or a hydrogen. Thus:
  - NH<sub>3</sub> → 1° RNH<sub>2</sub>
  - 1° RNH<sub>2</sub> → 2° R<sub>2</sub>NH
  - 2° R<sub>2</sub>NH → 3° R<sub>3</sub>N
  - 3° R<sub>3</sub>N don't react



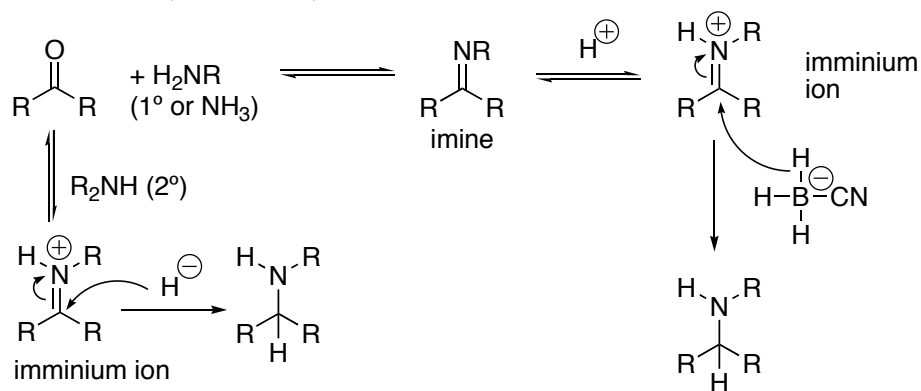
Note: book gives several other variants, but this is really the one universal method, and the one I'll use for my tests.

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

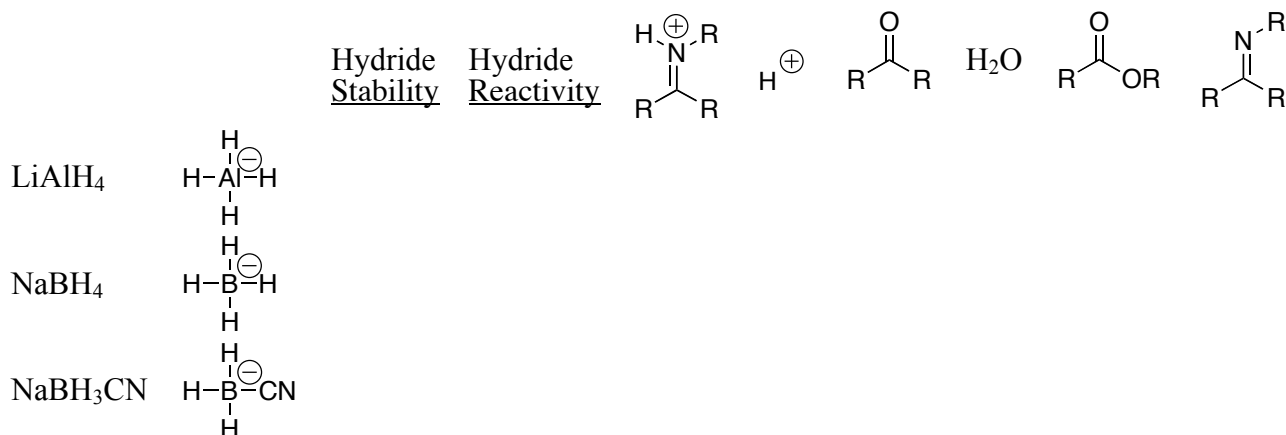


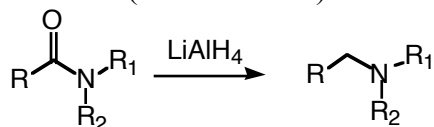


Mechanism (not for test) and some related notes

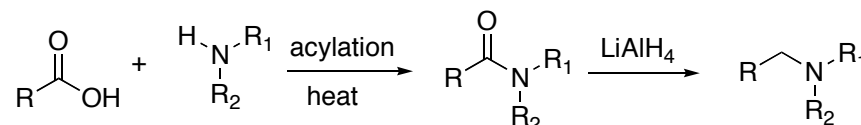
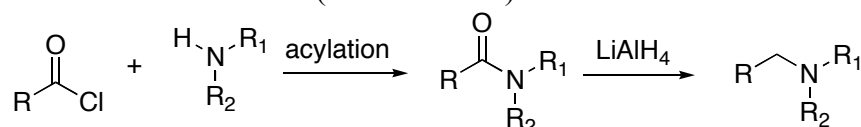


- $\text{NaBH}_3\text{CN}$  functions as a hydride  $\text{H}^\ominus$  source, similar to  $\text{NaBH}_4$  and  $\text{LiAlH}_4$
- Formation of iminium cation is key
  - Highly electrophilic, much more so than neutral imine
- $\text{NaBH}_3\text{CN}$  is a special, mild  $\text{H}^\ominus$  source, much more stable and less reactive than  $\text{NaBH}_4$  and  $\text{LiAlH}_4$ 
  - 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)

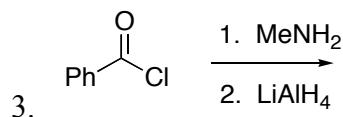
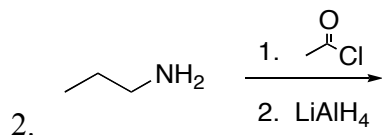
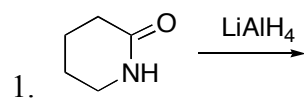


7. **Via Amides:** (Section 19-20)

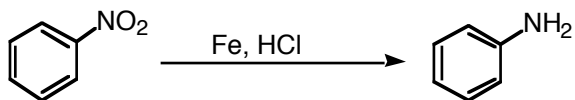
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R<sub>1</sub> and R<sub>2</sub> can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - RCONH<sub>2</sub> → 1° RCH<sub>2</sub>NH<sub>2</sub>
  - RCONHR → 2° RCH<sub>2</sub>NHR
  - RCONR<sub>2</sub> → 3° RCH<sub>2</sub>NR<sub>2</sub>

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.

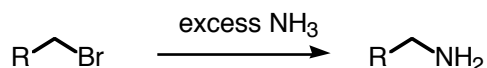


## 9. Reduction of nitro compounds: (section 19-21C)



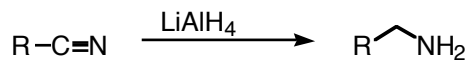
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H<sub>2</sub>, Ni/H<sub>2</sub>, Pt/H<sub>2</sub>,
  - Fe/HCl, Zn/HCl, Sn/HCl

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



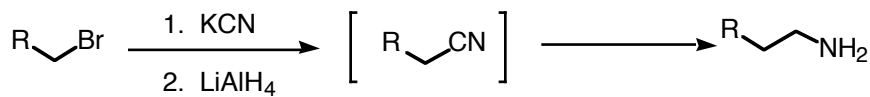
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH<sub>3</sub> prevents polysubstitution.

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

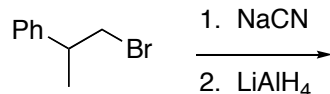


- Access: 1° amines
- Mechanism not required.

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



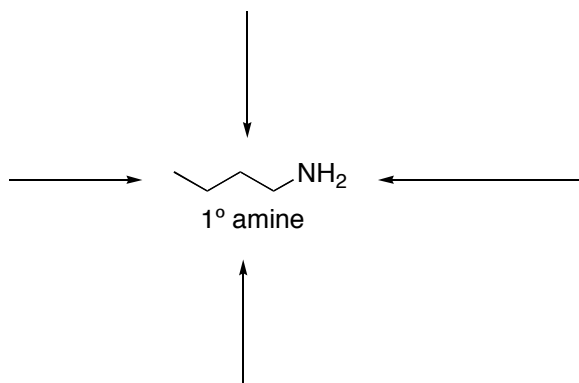
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!



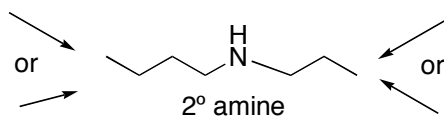
**Summary of Amine Syntheses**

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.

