Ch 24 Amines

Description of Amines
- An amine is a compound with a nitrogen atom that
  has single bonds to carbon and hydrogen atoms.
- An uncharged nitrogen atom normally has three bonds and a lone pair.
- The lone pair on N makes amines both basic and nucleophilic.

Naming Amines
- Amines are categorized according to the number of alkyl substituents on the N.
  RNH_2 is 1°, R_2NH is 2°, and R_3N is 3°, and R_4N^{+1} is 4° (quaternary).
- Simple 1° amines are typically named as alkylamine,
  such as propylamine and cyclohexylamine.
- Amines with two or three identical alkyl groups can be similarly named,
  such as diethylamine and triethylamine.
- The N can also be named as an amino substituent on a parent molecule, such as with
  2-aminopropanoic acid (alanine), where the acid has a higher naming priority than the N.
- Two or three N groups can be named with diamine and triamine suffixes,
  such as 1,3-propanediamine.
- Unsymmetrical amines can be named with largest group as the alkylamine
  parent which has N-substituents, such as N,N-dimethylbutylamine.
- Numerous common names exist for aromatic rings, such as aniline ($C_6H_5NH_2$),
  and heterocyclic rings, such as pyridine (C_5H_5N).

Structure and Bonding
- Normally, the N is sp^3 with a tetrahedral e^{-1} pair arrangement.
- Since, N has one lone pair, the geometry is trigonal pyramidal.
- If N has three different substituents, such as N-methyl-N-ethylpropaneamine,
  then the molecule is chiral because the lone pair functions as the fourth group.
  The lone pair has the lowest priority: #4.
- Chiral amines do not show optical activity because they are self-racemizing.
  This happens because the N can rapidly rehybridize to planar sp^2,
  and then revert to sp^3 with the lone pair on the opposite side.
  This inverts the configuration, so that the R and S exist in equal proportions.
- Alkylamines with four or fewer C's are generally water-soluble.
  This is due to H-bonding between the N and the H's of water,
  as well as between the O and the H's attached to N.
- Amines also stink like dead fish.
 As a result, 1,5-pentanediamine has a suitable common name: cadaverine.

Basicity
- N's lone pair can be donated like a nucleophile (Lewis base),
  and can accept a proton (Bronsted base).
- Amines are typically weak bases with pKb ~ 5.
- The basicity of an amine is more often measured by the pKa of its cationic conjugate.
  The sum of the pKa and pKb for a pair of conjugates is 14.
  For instance, ammonia has pKb = 4.74, while ammonium has pKa = 9.26.
- A more basic amine would have a less acidic conjugate, which has a higher pKa.
  For instance, methylamine is more basic than ammonia, and its conjugate methylammonium
  has pKa = 10.64 (Compare the pKa's: 10.64 > 9.26).
- Alkylamine conjugates typically have pKa's between 10 and 12.
- Aromatic amines are much less basic due to the e^{-1} withdrawing effect of the rings.
  So, aniline's conjugate has pKa = 4.63.
- Aromatic heterocycles are also much less basic than alkylamines as well.
  If the lone pair is sp^2, such as with pyridine (conjugate pKa = 5.25), it is closer
  to the N nucleus than an sp^3 orbital, which makes it much less available.
  If the lone pair is a p orbital that is part of the aromatic Π system, it really is not
  available at all. As a result, pyrrole's conjugate has pKa = 0.4 and it is nonbasic.
- Amides ($RCONH_2$) are nonbasic. The lone pair is not available
  because it is stabilized by a resonance that is similar to that of enolates.
  The resonance allows amides to donate an H^{+1} instead,
  so that amides are marginally acidic (pKa = 22).
- Amines are typically soluble in acidic (aqueous) solution, because
  they are converted into their conjugate cations (HR_3N^{+1}) by acids.
  This is a convenient way to extract amines from an organic mixture.

$$R_3N_{(org)} + H_3O^{+1}{}_{(aq)} \rightarrow HR_3N^{+1}{}_{(aq)} + H_2O_{(liq)}$$

Basicity of Substituted Aromatic Amines
- An e^{-1} withdrawing substituent (deactivator) on the aromatic ring will stabilize N's lone pair.
  This makes the lone pair less available and decreases basicity.
  So, p-nitroaniline has pKa = 1.00 and is much less basic than aniline (pKa = 4.63).
- An e^{-1} donating substituent (activator) on the aromatic ring will destabilize N's lone pair.
  This makes the lone pair more available and increases basicity.
 So, p-methoxyaniline has pKa = 5.34 and is more basic than aniline.

Preparation by Reduction
- Reduction of nitriles and amides with $LiAlH_4$ was covered in chapters 20 and 21.
- Aromatic nitro compounds can be reduced as well, using tin (II) chloride in aqueous acid, followed by aqueous base. This is a very useful way to create aromatic amines, because it is not usually possible to place NH_2 directly on an aromatic ring.
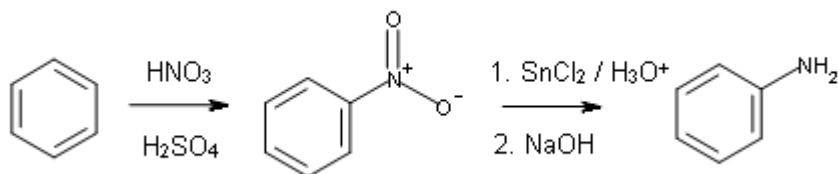

Preparation with S_N2 Reactions
- Ammonia (and other amines) can be used as a Nu in an S_N2 reaction with a 1° alkyl halide (RCH_2X).
- Although the initial reaction creates a 1° amine (RCH_2NH_2), the amine products can also react with the alkyl halide. So, the 1° amine can be converted to 2° ($RCH_2)_2NH$, the 2° can be converted to 3° ($RCH_2)_3N$, and the 3° can be converted to 4° ($RCH_2)_4N^{+1}$. So, the end result is a mixture of amines.
- This works as a synthesis method with simple amines where the mixtures can be separated by distillation.
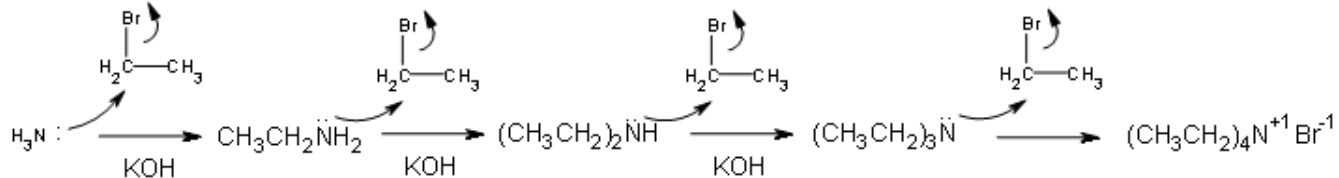

Azide Synthesis of Amines
- The azide ion (N_3^{-1}) can react as a Nu in an S_N2 reaction with a 1° alkyl halide (RCH_2X). The S_N2 product is a 1° alkyl azide (RCH_2N_3). This azide can be reduced to an amine (RCH_2NH_2) with $LiAlH_4$ in ether, followed by H_2O.
- The alkyl azide is not a Nu, so further alkylation does not happen as it does with ammonia and amines. So, the product is not a mixture.
- However, azides are explosive and must be handled carefully.
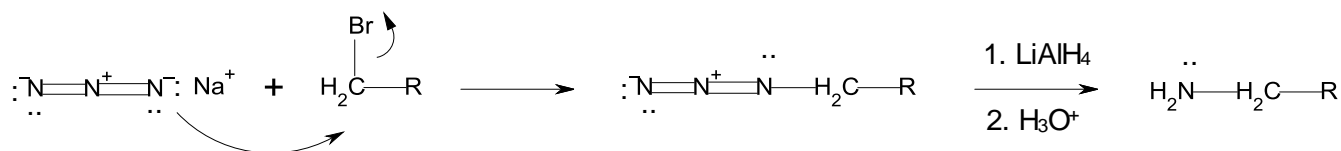
The Gabriel Amine Synthesis
- Uses phthalimide, where the N is bonded between two carbonyl C's.
  The two carbonyls provide more resonance than in amides.
  The increased resonance will further stabilize a negative charge.
  So, the N can be deprotonated (pKa = 8.3) by NaOH (in ethanol) or by $CO_3^{-2}{}_{(aq)}$.
- The deprotonated anionic N acts as a Nu in an S_N2 reaction with a 1° alkyl halide
  (dissolved in DMF) to create an N-alkylated imide. The N-alkyl phthalimide can be
  hydrolyzed with $NaOH_{(aq)}$ to create the 1° amine along with the phthalate anion.


phthalimide

phthalate anion
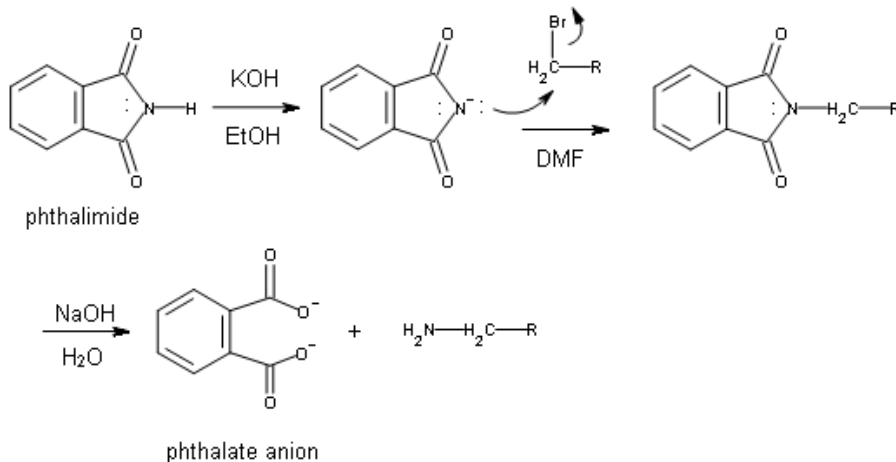
Preparation by Reductive Amination
- Essentially, this process creates an imine (or enamine) from an aldehyde or ketone using
  ammonia (or a 1° or 2° amine), then reduces the imine (or enamine) to an amine.
- See chapter 19 notes for the mechanism of imine and enamine formation.
- The carbonyl C=O is converted to $C=NH_2$ by ammonia,
  C=NHR by a 1° amine, and $C=C-NR_2$ (enamine) by a 2° amine.
- The C=N Π bond is then hydrogenated. This is accomplished
  in the laboratory with $NaBH_4$ or related borohydrides, such as
  sodium triacetoxyborohydride ($NaBH(OAc)_3$).
- Industrially, the hydrogenation is accomplished with H_2/Ni at 90 atm and 70 ^{o}C.
- Biologically, the hydrogenation occurs with reduced nicotinamide adenine dinucleotide
 (NADH) as the reducing agent, where NADH is converted to the oxidized form (NAD^{+1}).

1-phenylpropanone   1-phenyl-2-propanimine   amphetamine
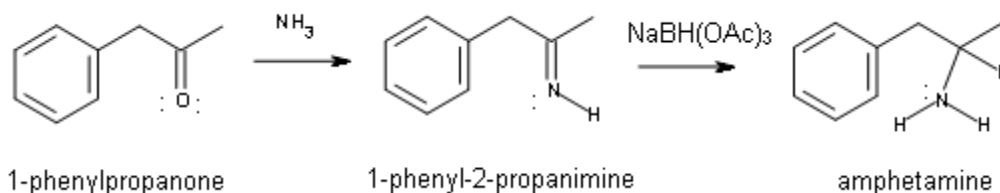
Preparation by Hofmann Rearrangement
- Mixes an amide ($RCONH_2$) with NaOH, Br_2 (or Cl_2), and H_2O
  to create a 1° amine that has one less C than the amide.
  Overall, the amide's carbonyl C=O is expelled.
- Initially, the base removes an H from the N to create an anion.
  The anion is a Nu which removes Br^{+1} from Br_2, creating an N-brominated amide and Br^{-1}.
- The other H is removed from the N to create a resonance-stabilized anion.
  The resonance-stabilized anion then rearranges while expelling the bromide.
  The alkyl group on the carbonyl moves to the N to create an isocyanate (R-N=C=O).
- H_2O adds across the N=C double bond to create a carbamic acid (RNHCOOH).
  Finally, the carbamic acid essentially expels CO_2 to create the amine.

amide   N-bromoamide

isocyanate   carbamic acid 1° amine
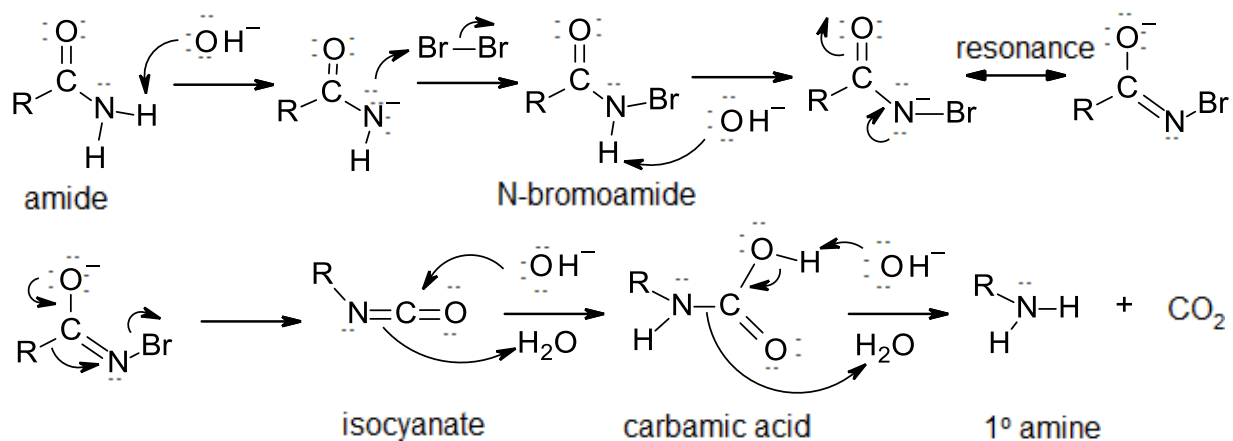
Preparation by Curtius Rearrangement
- Similar to the Hofmann Rearrangement, but uses
  an acyl azide ($RCON_3$) rather than an amide.
- The acyl azide is created from an acid chloride and sodium azide (NaN_3).
  The acyl azide then rearranges when heated.
- The alkyl group on the carbonyl moves to the N to create an isocyanate (R-N=C=O).
  H_2O adds across the N=C double bond to create a carbamic acid (RNHCOOH).
 The carbamic acid essentially expels CO_2 to create the amine.

acid chloride

acyl azide   isocyanate   carbamic acid 1° amine
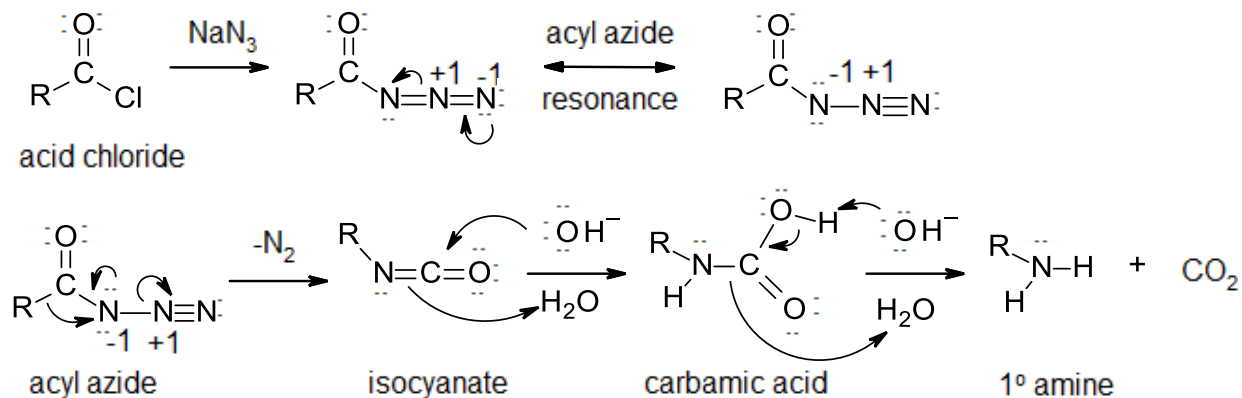
Hofmann Elimination
- Converts 4° ammonium cations into alkenes using a non-Zaitsev E2 reaction.
- Excess CH_3I is used to convert 1° and 2° amines into 4° $RN(CH_3)_3^{+1}I^{-1}$ by S_N2.
- The 4° cation is then heated with aqueous Ag_2O (a base), which creates $OH^{-1}_{(aq)}$.
  The OH^{-1} removes an H^{+1} from the least hindered C than is next to the C with the N.
  The e^{-1} pair from the C-H bond creates the alkene Π bond, while $N(CH_3)_3$ is the LG.
- The 4° cation's reaction is E2, although it creates the least-substituted alkene possible.
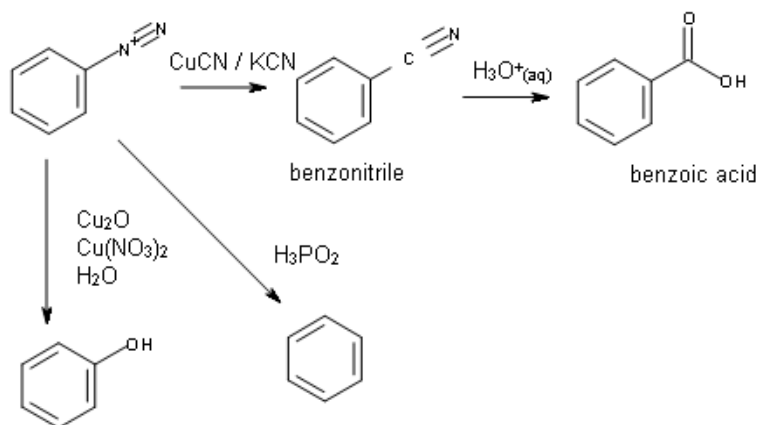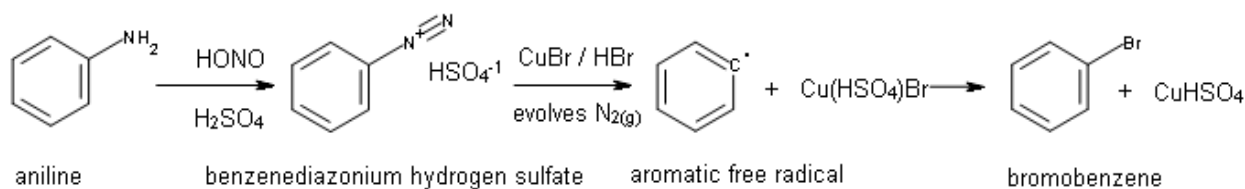 The non-Zaitsev product results from the steric hindrance of the ammonium group.

2-methyl-3-pentanamine   E2   4-methyl-2-pentene (non-Zaitsev product)
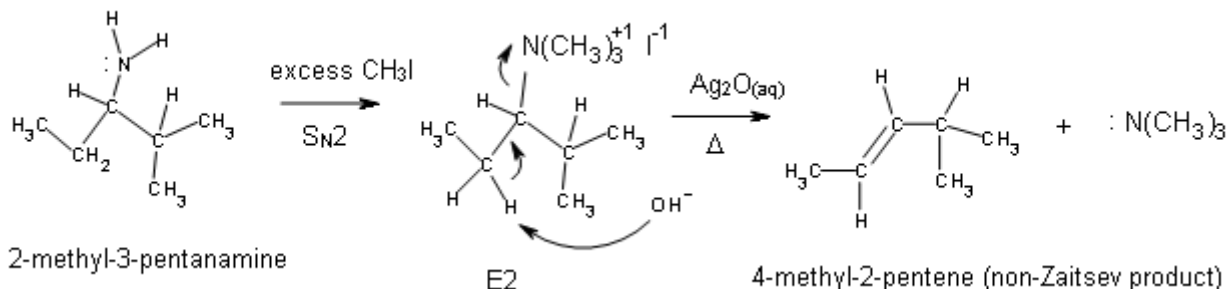
E+ Aromatic Substitution
- Aniline and other aromatic amines are strongly activated rings that
  polysubstitute when E+'s are added in halogenation reactions.
  The result is that three substituents are added, one at each ortho position
  and one at para, to create a 2,4,6-trihalogenated aniline.
- Also, Friedel-Crafts reactions do not work on rings with basic N substituents.
- Polysubstitution can be prevented if the amine group is less activating.
  Also, Friedel-Crafts reactions can be performed by making the N group less basic.
  These can both be accomplished by adding acetic anhydride, $(CH_3CO)_2O$,
  which replaces an H on the N with an acetyl group (CH_3CO).
- The N-acetylated aniline will add only one halogen, and
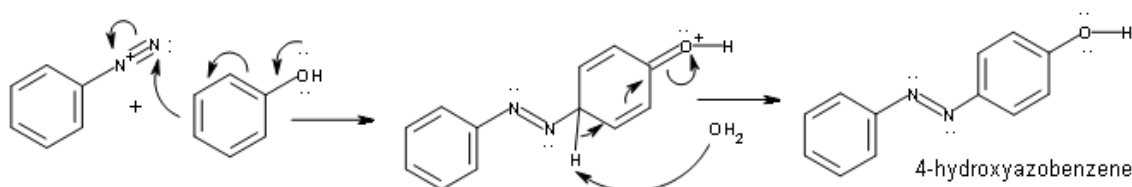 will also work normally in Friedel-Crafts reactions.

aniline   N-phenylacetamide   4-aminoacetophenone
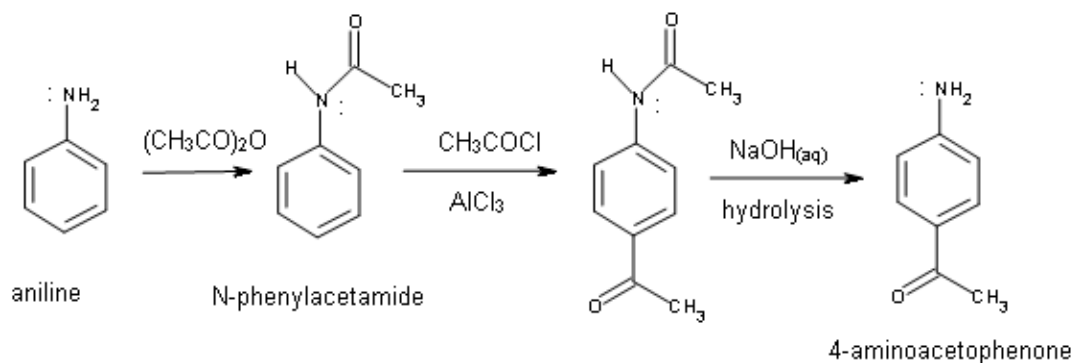
Sandmeyer Reactions
- Converts an aromatic amine to a diazonium salt (Ar−N$^+$≡N: Cl$^-$)
  using nitrous acid (HONO) with H_2SO_4.
- The diazo group can then be replaced with many other groups by a radical reaction.
- Ar−N$^+$≡N: can be converted to Ar−Br using CuBr along with HBr.
  CuCl with HCl works similarly. Ar−I can be created using only NaI.
- Ar−N$^+$≡N: can be converted to Ar−C≡N: using a combination of CuCN and KCN.
  Also, Ar−C≡N: can be hydrolyzed to Ar−COOH with H_3O^{+1} or OH^{-1}.
- Ar−N$^+$≡N: can be converted to a phenol (Ar-OH)
  using a combination of Cu_2O, $Cu(NO_3)_2$ and H_2O.
  This is a very useful way to create a phenol in the laboratory.
- The diazo group can be removed with hypophosphorous acid (H_3PO_2),
  which converts Ar−N$^+$≡N: into Ar−H.

aniline   benzenediazonium hydrogen sulfate   aromatic free radical   bromobenzene

benzonitrile   benzoic acid

Diazonium Coupling
- Uses a diazonium cation, but adds an activated aromatic ring
  to the outer N, instead of replacing the diazo group.
- Essentially, Ar−N$^+$≡N: becomes Ar−N=N−Ar', where the activating
  group (OH or NH_2) on the second ring (Ar') is para to the N=N group.
- The reaction is E+ aromatic substitution on the activated ring,
  where Ar−N$^+$≡N: is the E+.

4-hydroxyazobenzene

Creation of Aromatic Amine and Diazonium Ion

Nitrobenzene

Aniline

$H_2SO_4 + HONO \longrightarrow HSO_4\text{-}1 + H_2ONO^{+1} \longrightarrow H_2O + {}^{+1}:N{=}\ddot{O}:$ (nitroso ion)

Diazonium Salt