11

Amines and Related Nitrogen Compounds

Chapter Summary

Amines are organic derivatives of ammonia. They may be **primary**, **secondary**, or **tertiary**, depending on whether one, two, or three organic groups are attached to the nitrogen. The nitrogen is sp^3-hybridized and pyramidal, nearly tetrahedral.

The **amino group** is $-NH_2$. Amines are named according to the Chemical Abstracts (CA) system by adding the suffix *-amine* to the names of the alkyl groups attached to the nitrogen. Amines can also be named using the IUPAC system in which the amino group is named as a substituent. Aromatic amines are named as derivatives of aniline or of the aromatic ring system.

Primary and secondary amines form intermolecular N–H···N bonds. Their boiling points are higher than those of alkanes but lower than those of alcohols with comparable molecular weights. Lower members of the series are water-soluble because of N···H–O bonding.

Amines can be prepared by S_N2 alkylation of ammonia or 1^o and 2^o amines. Aromatic amines are made by reduction of the corresponding nitro compounds. Amides, nitriles, and imines can also be reduced to amines.

Amines are weak bases. Alkylamines and ammonia are of comparable basicity, but aromatic amines are much weaker as a result of delocalization of the unshared electron pair on nitrogen to the *ortho* and *para* carbons of the aromatic ring. **Amides** are much weaker bases than amines because of delocalization of the unshared electron pair on nitrogen to the adjacent carbonyl oxygen. Amides are stronger Brønsted acids than amines because of the partial positive charge on the amide nitrogen and resonance in the **amidate anion**.

Amines react with strong acids to form **amine salts**. The pK_as of amine salts are related to the base strength of the corresponding amines. Alkylammonium salts have pK_as of 9–10 while arylammonium salts have pK_as of 4–5. The fact that these salts are usually water-soluble can be exploited in separating amines from neutral or acidic contaminants. Chiral amines can be used to resolve enantiomeric acids, through the formation of diastereomeric salts.

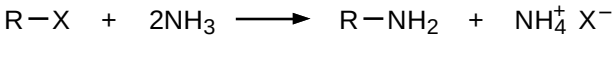
Primary and secondary amines react with acid derivatives to form amides. Amides made commercially this way include **acetanilide** and ***N,N*-diethyl-*m*-toluamide** (the insect repellent Off®).

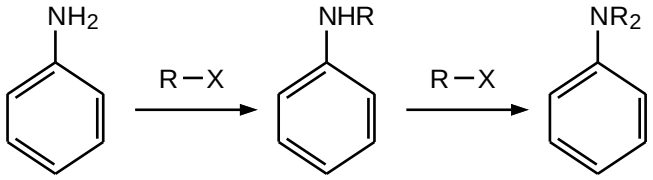
Tertiary amines react with alkyl halides to form **quaternary ammonium salts**. An example of this type of salt with important biological properties is **choline** (2-hydroxyethyltrimethylammonium ion).

Primary aromatic amines react with nitrous acid to give **aryldiazonium ions**, ArN_2^+, which are useful intermediates in synthesis of aromatic compounds. The process by which they are formed is called **diazotization**. The nitrogen in these ions can readily be replaced by various nucleophiles (OH, Cl, Br, I, CN). Diazonium ions couple with reactive aromatics, such as amines or phenols, to form **azo compounds**, which are useful as dyes.

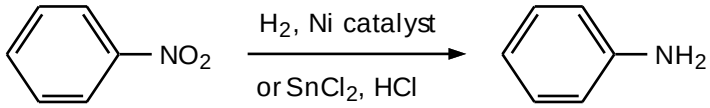
Reaction Summary

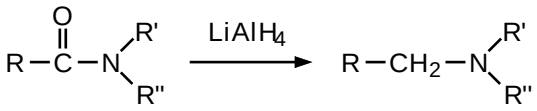
Alkylation of Ammonia and Amines

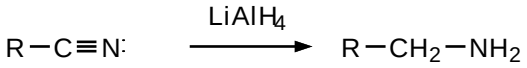


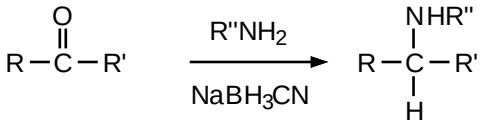


Reduction Routes to Amines

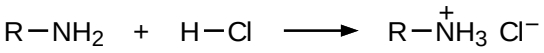




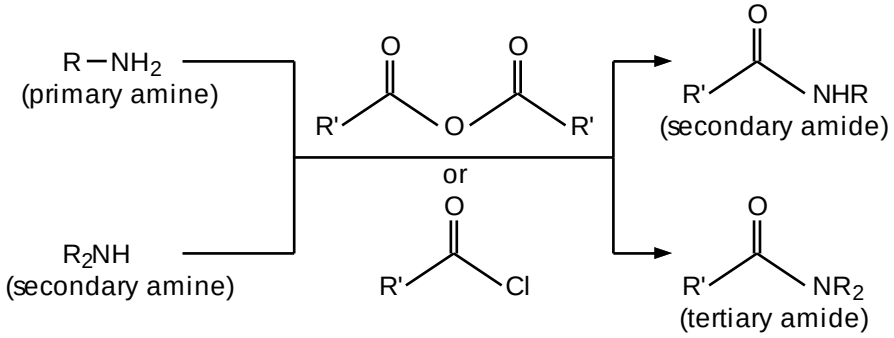




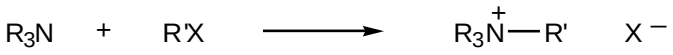
Amine Basicity



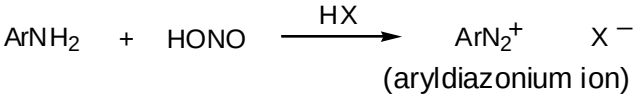
Acylation of Primary and Secondary Amines

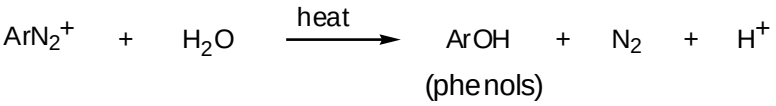


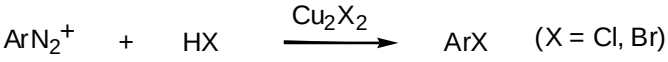
Quaternary Ammonium Salts

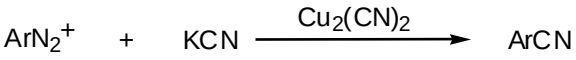


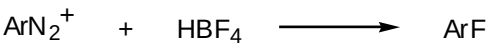
Aryldiazonium Salts

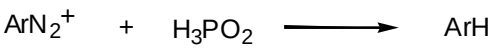




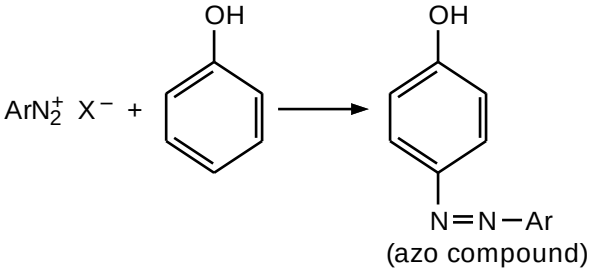






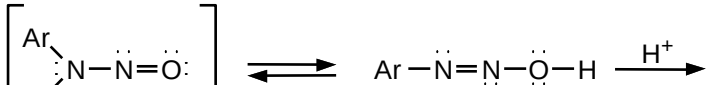


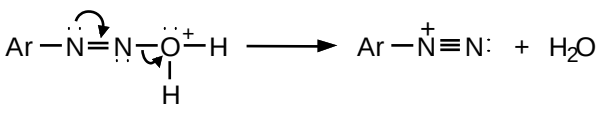
Diazo Coupling



Mechanism Summary

Diazotization





Learning Objectives

1. Know the meaning of: primary, secondary, and tertiary amine, amino group, aniline, amine salt, quaternary ammonium salt.

2. Know the meaning of: nitrous acid, diazonium ion, diazotization, azo coupling.

3. Given the structure of an amine, identify it as primary, secondary, or tertiary.

4. Given the structure of an amine, name it. Also, given the name of an amine, write its structural formula.

5. Explain the effect of hydrogen bonding on the boiling points of amines and their solubility in water.

6. Write an equation for the reaction between ammonia or an amine of any class and an alkyl halide.

7. Write an equation for the preparation of a given aromatic amine from the corresponding nitro compound.

8. Write an equation for the preparation of a given amine of the type RCH_2NH_2 or $ArCH_2NH_2$ by reduction of the appropriate nitrile.

9. Write an equation for the preparation of a secondary amine from a ketone, primary amine, and sodium cyanoborohydride.

10. Write an equation for the dissociation of an amine in water.

11. Write an expression for K_a of any amine salt.

12. Draw the important contributors to the resonance hybrid for an aromatic amine.

13. Given the structures of several amines, rank them in order of relative basicity.

14. Account for the difference in basicity between an aliphatic and an aromatic amine.

15. Write an equation for the reaction of a given amine of any class with a strong acid. Also, write an equation for the reaction of an amine salt with a strong base.

16. Account for the basicity and acidity difference between amines and amides.

17. Explain, with the aid of equations, how you can separate an amine from a mixture containing neutral and/or acidic compounds.

18. Explain how chiral amines can be used to resolve a mixture of enantiomeric acids.

19. Write an equation for the reaction of a given primary or secondary amine with an acid anhydride or acyl halide.

20. Write the steps in the mechanism for acylation of a primary or secondary amine.

21. Write an equation for the diazotization of a given primary aromatic amine.

22. Write the equations for the reaction of an aromatic diazonium salt with: aqueous base; HX + Cu_2X_2 (X = Cl, Br); KCN + $Cu_2(CN)_2$; HBF_4; and H_3PO_2.

23. Write an equation for the coupling of an aromatic diazonium salt with a phenol or aromatic amine.

ANSWERS TO PROBLEMS

Problems Within the Chapter

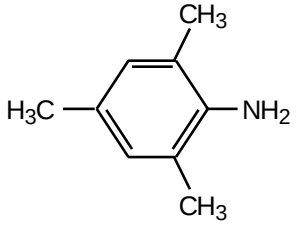
11.1 a. primary b. secondary c. primary d. tertiary

11.2 *N,N*-dimethyl-3-pentanamine

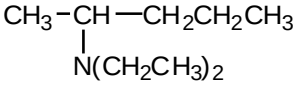
11.3 a. *t*-butylamine or 2-methyl-2-propanamine
b. 2-aminoethanol c. *p*-nitroaniline

11.4 a. $(CH_3CH_2CH_2)_2NH$ b. $CH_3CH_2CH(NH_2)CH_2CH_2CH_3$

c.

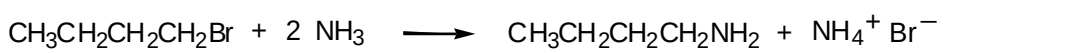


d.

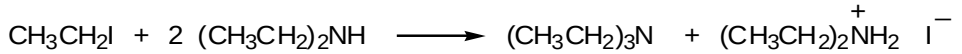


11.5 Trimethylamine has no hydrogens on the nitrogen: $(CH_3)_3N$. Thus, intermolecular hydrogen bonding is not possible. In contrast, intermolecular hydrogen bonding is possible for $CH_3CH_2CH_2NH_2$ and this raises its boiling point considerably above that of its tertiary isomer.

11.6 a.



b.



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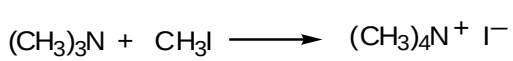

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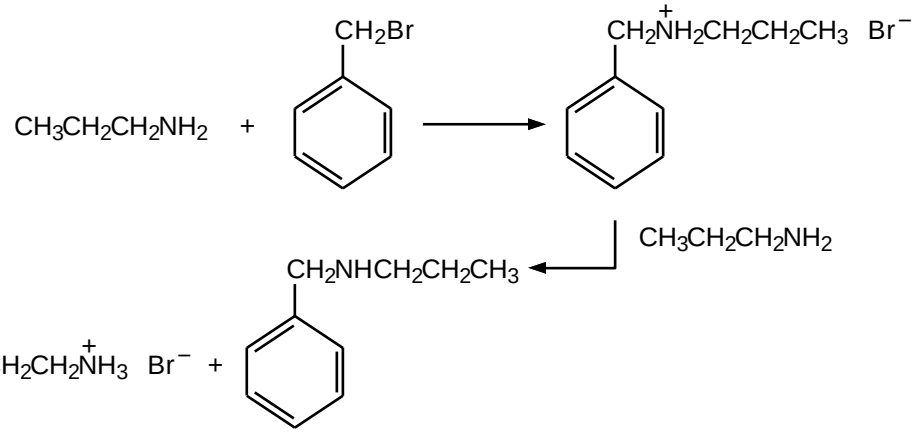
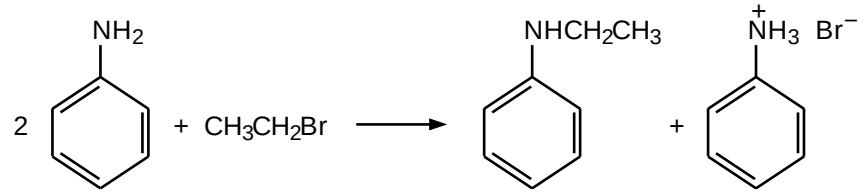
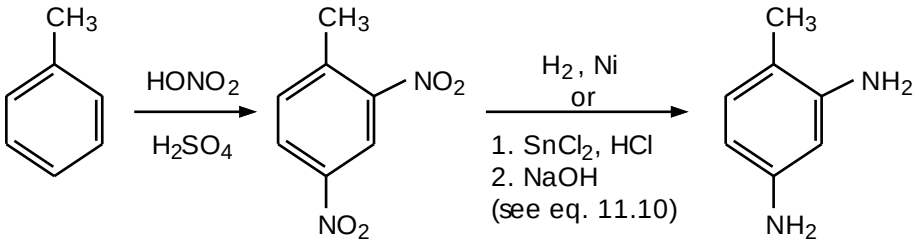


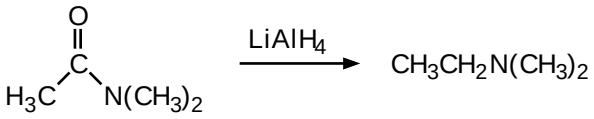
11.7



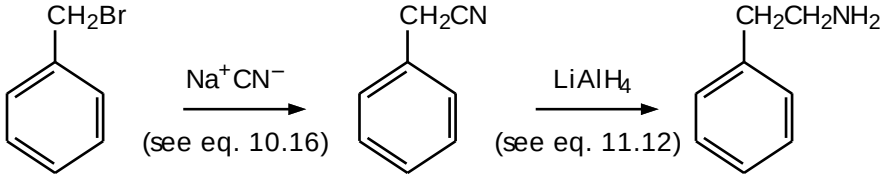
11.8 Nitration of toluene twice gives mainly the 2,4-dinitro product. Reduction of the nitro groups completes the synthesis. The NaOH converts the amine hydrochloride salt to the free amine.



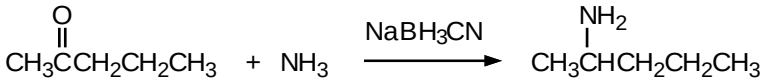
11.9 See eq. 11.11



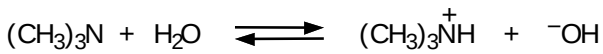
11.10 See eq. 11.12



11.11 See eq. 11.13



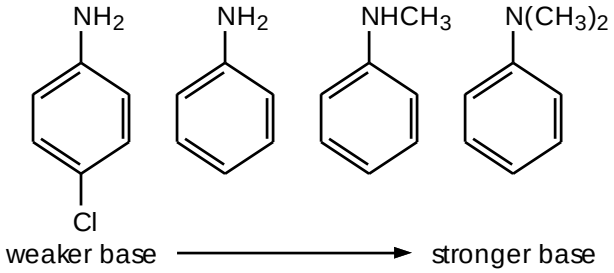
11.12 See eq. 11.14



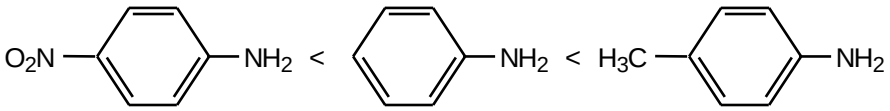
11.13 $ClCH_2CH_2NH_2$ is a weaker base than $CH_3CH_2NH_2$. The chlorine substituent is electron-withdrawing compared to hydrogen and will destabilize the protonated ammonium ion because of the repulsion between the positive charge on nitrogen and the partial positive charge on C-2 due to the C–Cl bond moment:

Ethylamine is therefore easier to protonate (more basic) than 2-chloroethylamine.

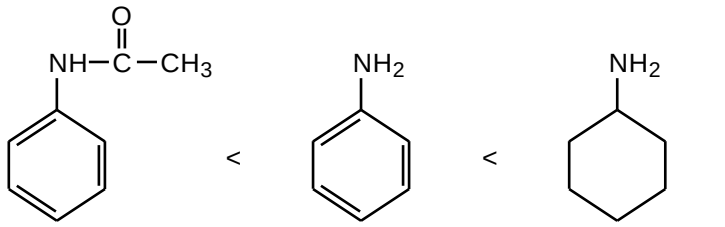
11.14 Alkyl groups are electron-donating and stabilize the positively charged ammonium ion relative to the amine. Therefore, *N,N*-dimethylaniline is a stronger base than *N*-methylaniline, which is a stronger base than aniline. The electron-withdrawing chlorine in *p*-chloroaniline destabilizes the positively charged ammonium ion. Therefore *p*-chloroaniline is a weaker base than aniline:



11.15 The order of the substituents by increasing electron-donating ability is $–NO_2 < –H < –CH_3$. Therefore, the basicities will increase in that order:



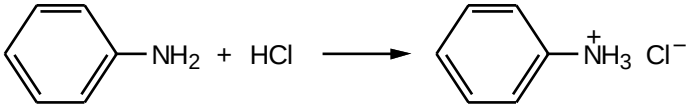
11.16 Amides are less basic than amines, and aromatic amines are less basic than aliphatic amines. Therefore, the order is:



acetanilide aniline cyclohexylamine

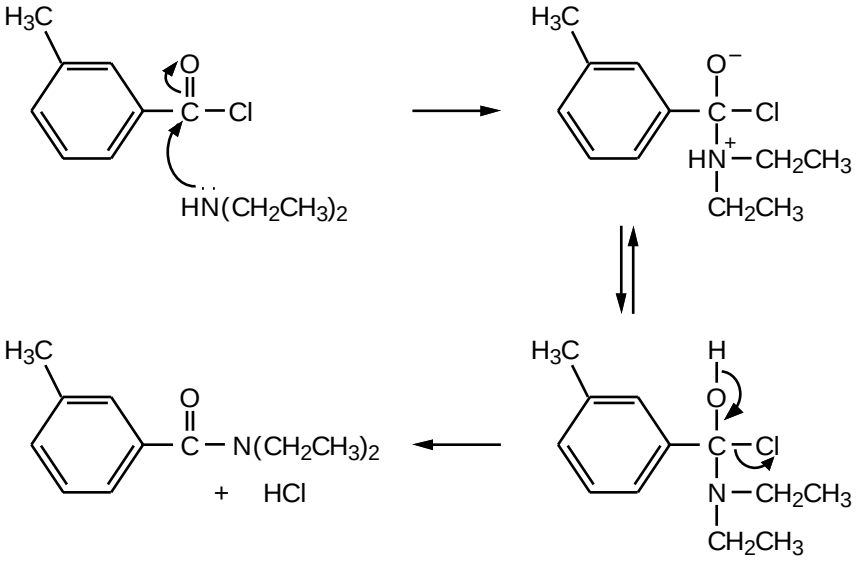
The acidity increases in the reverse direction.

11.17



anilinium chloride

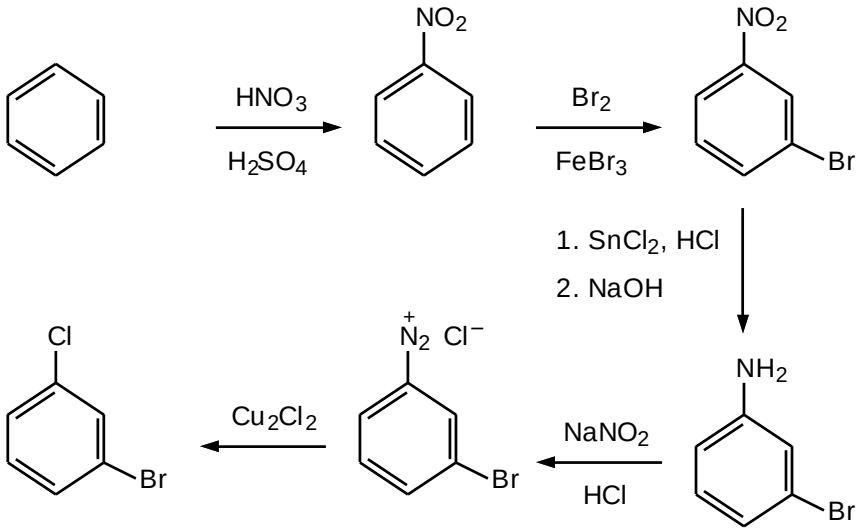
11.18



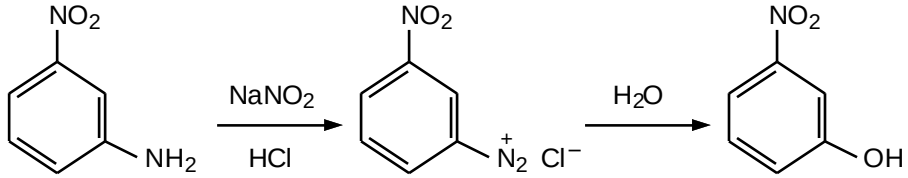
The sodium hydroxide reacts with the HCl to form sodium chloride and water. Otherwise, the HCl would protonate the diethylamine and prevent it from functioning as a nucleophile.

11.19 a. $CH_3CONHCH_2CH_3$ b. $CH_3CON(CH_2CH_3)_2$

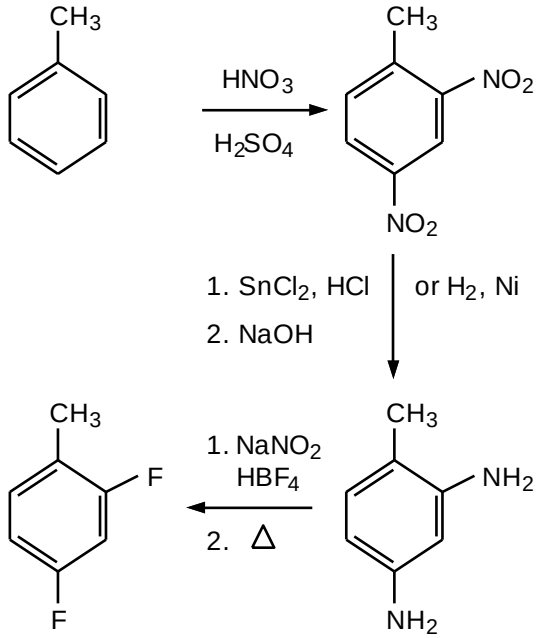
11.20 a. Use the *meta*-directing nitro group to establish the proper relationship between the two substituents:



b. Convert the amino group to a hydroxyl group.

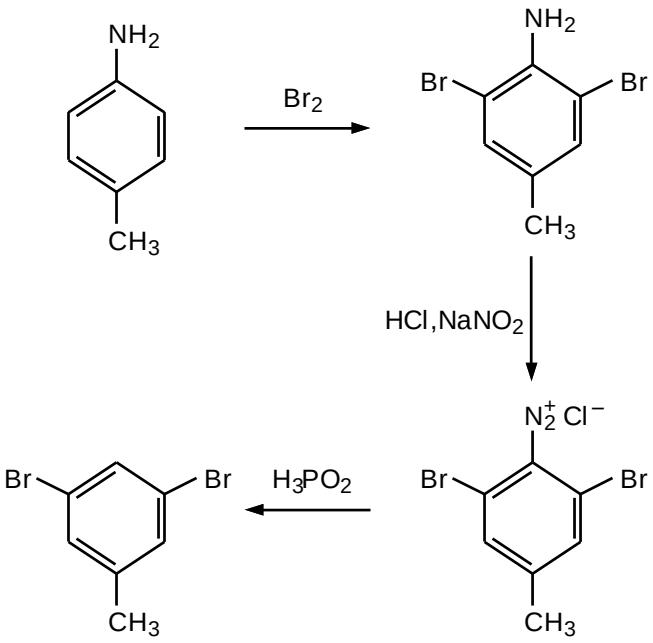


c. Introduce the fluoro groups as follows:

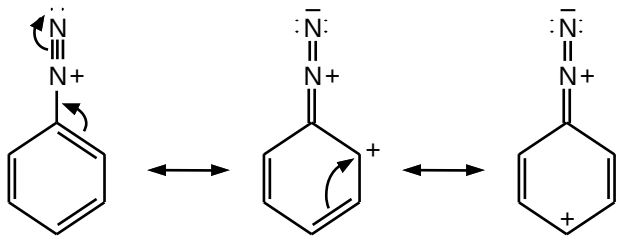


The use of HBF_4 in place of HCl gives an intermediate diazonium tetrafluoroborate.

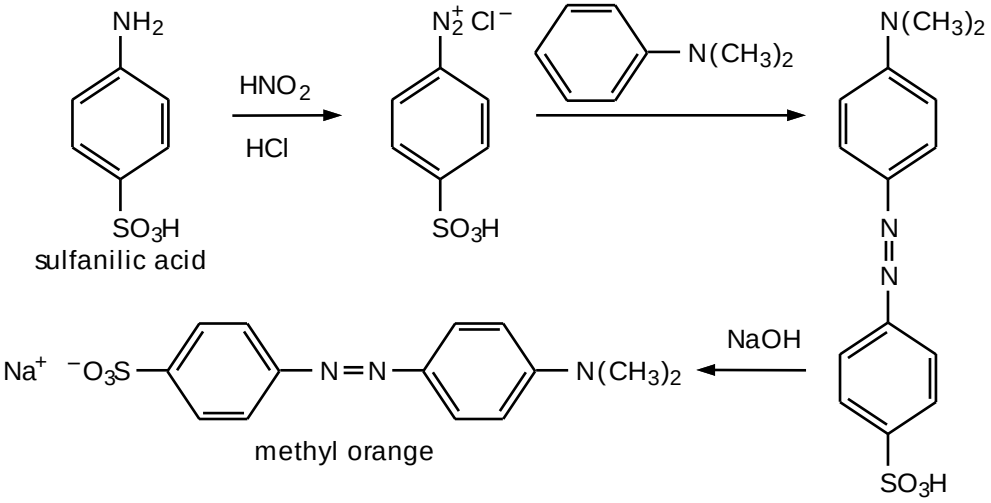
d. Use the amino group to introduce the bromines and then replace the amino group by a hydrogen.



11.21



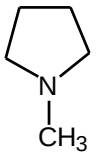
11.22

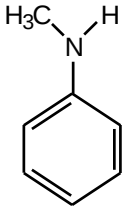


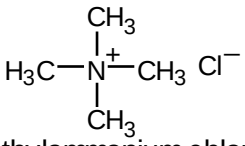
ADDITIONAL PROBLEMS

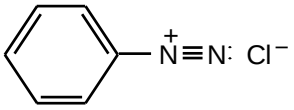
11.23 Many correct answers are possible, but only one example is given in each case.

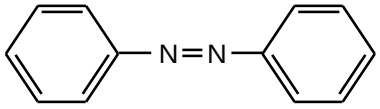
a. CH_3NH_2
methylamine

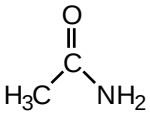
b. 
N-methylpyrrolidine

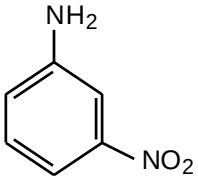
c. 
N-methylaniline

d. 
tetramethylammonium chloride

e. 

f. 
azobenzene

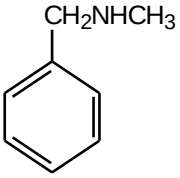
g. 
acetamide

11.24 a. 

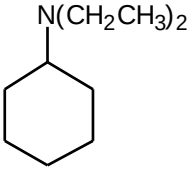
b. $CH_3CHCH_2CH_3$ (NH_2 on the second carbon)

c. $CH_3CHCH_2CH_2CH_3$ (NH_2 on the second carbon)

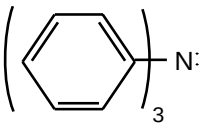
d. $CH_3CH_2CH_2N(CH_3)_2$

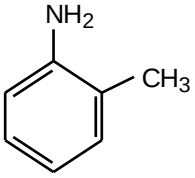
e. 

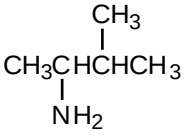
f. $H_2NCH_2-CH_2-CH_2NH_2$

g. 

h. $(CH_3CH_2)_4\overset{+}{N}\ Br^-$

i. 

j. 

k. 

l. $CH_3CH_2CHCH_2CH_2CH_3$ ($N(CH_3)_2$ on the second carbon)

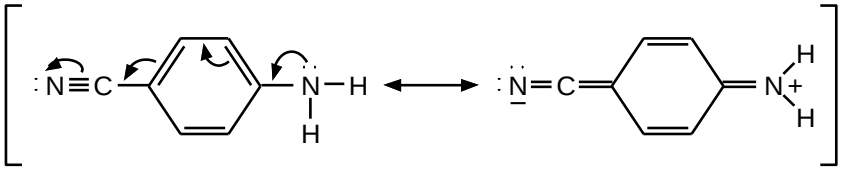
11.25 a. *p*-chloroaniline

b. methylpropylamine (or *N*-methylpropanamine)
c. diethylmethylamine
d. tetramethylammonium chloride
e. 3-amino-2-butanol
f. 2-aminocyclohexanone
g. *p*-chlorobenzenediazonium chloride
h. *N*-methyl-*p*-methoxyaniline
i. *trans*-1,3-diaminocyclobutane
j. 1,6-diaminohexane

11.26

$CH_3CH_2CH_2CH_2NH_2$	*n*-butylamine or 1-butanamine (primary)
$CH_3CH_2CH(NH_2)CH_3$	2-butylamine or 2-butanamine (primary)
$(CH_3)_2CHCH_2NH_2$	2-methylpropanamine (primary)
$(CH_3)_3CNH_2$	2-methyl-2-propanamine or *t*-butylamine (primary)
$CH_3CH_2CH_2NHCH_3$	*N*-methylpropanamine (secondary)
$(CH_3)_2CHNHCH_3$	*N*-methyl-2-propanamine (secondary)
$(CH_3CH_2)_2NH$	diethylamine or *N*-ethylethanamine (secondary)
$(CH_3)_2NCH_2CH_3$	ethyldimethylamine or *N,N*-dimethylethanamine (tertiary)

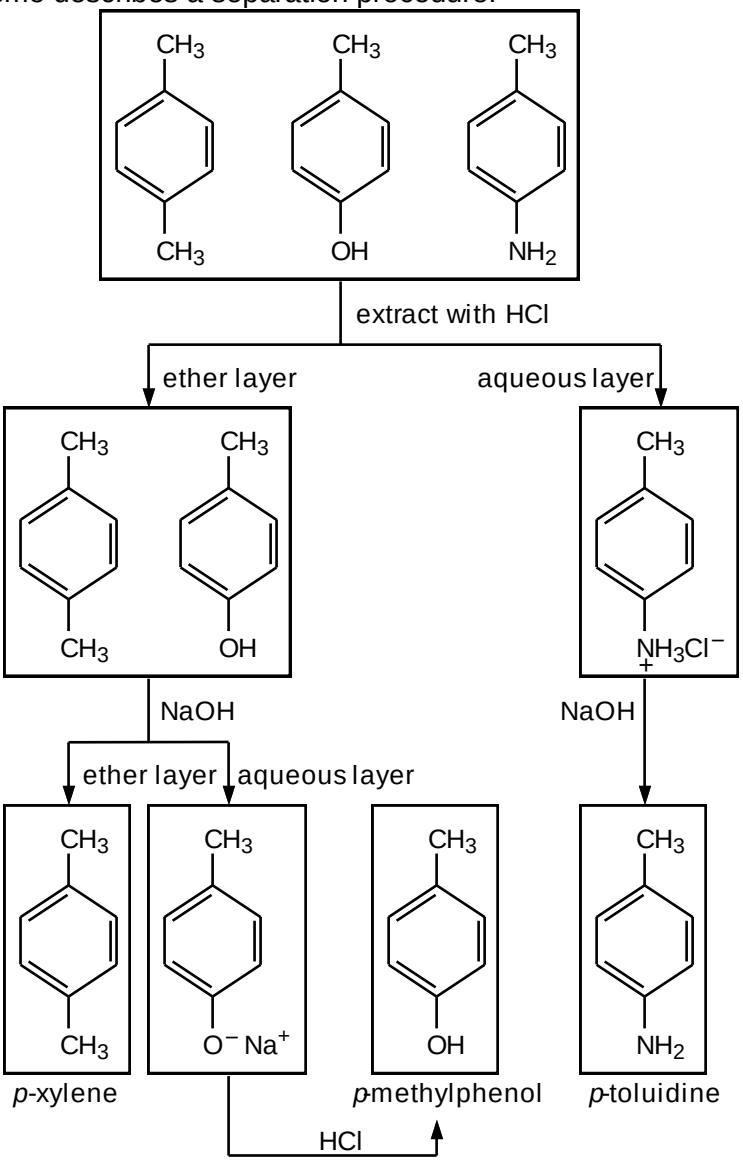
11.27 a. Aniline is the stronger base. The *p*-cyano group is electron-withdrawing and therefore decreases the basicity of aniline. Note that the possibilities for delocalization of the unshared electron pair are greater in *p*-cyanoaniline than in aniline.



Resonance stabilizes the free base relative to its protonated form, and the effect is greater with *p*-cyanoaniline than with aniline.

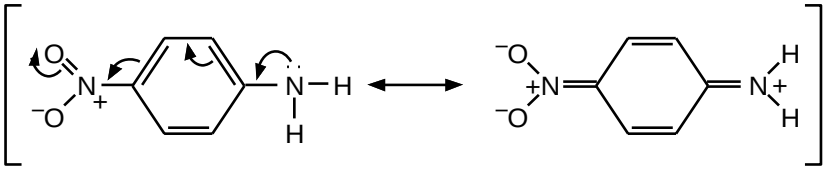
b. The possibilities for delocalization of an electron pair are greater in diphenylamine than in aniline (two phenyl groups versus one phenyl group). Thus, aniline is the stronger base.

11.28 The mixture is first dissolved in an inert, low-boiling solvent such as ether. The following scheme describes a separation procedure:



To recover the *p*-xylene, the ether is evaporated and the *p*-xylene distilled. In the case of *p*-toluidine and *p*-methylphenol, once the product is liberated from the corresponding salt, it is extracted from the water by ether. The ether is then evaporated and the desired product is distilled. The order of extraction—acid first, then base—can be reversed.

11.29 The unshared electron pair on the amino group can be delocalized not only to the *ortho* and *para* carbons of the ring as with aniline (see Sec.11.6), but also to the oxygen of the nitro group.

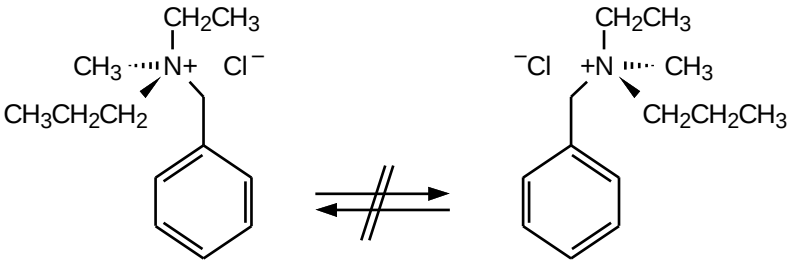


11.30 The boiling point order is

pentane < methyl propyl ether < 1-aminobutane < 1-butanol

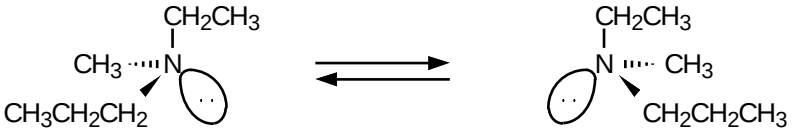
O–H···O bonds are stronger than N–H···N bonds, which explains the order of the last two compounds. No hydrogen bonding is possible in the first two compounds, but C–O bonds are polar, giving the ether a higher boiling point than the alkane. The actual boiling points are pentane, 36°C; methyl propyl ether, 39°C; 1-aminobutane, 78°C; and 1-butanol, 118°C.

11.31 The *R* and *S* enantiomers of ammonium salt **A** can interconvert only by processes that involve breaking a carbon–nitrogen bond. This does not occur easily, and thus, the enantiomers can be separated by formation of diastereomeric salts.

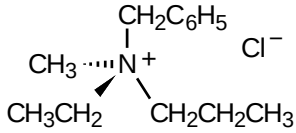


(*R*)-**A** (*S*)-**A**

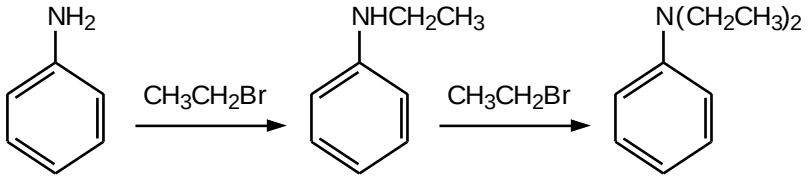
The enantiomers of amine **B** can easily interconvert by "inversion" of the nitrogen lone pair (see eq. 11.1) and thus cannot be separated.



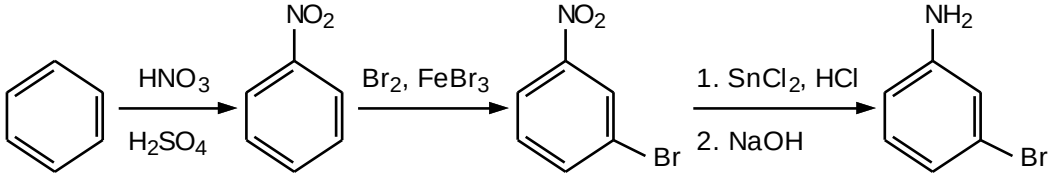
11.32 The priority order is $CH_2C_6H_5 > CH_2CH_2CH_3 > CH_2CH_3 > CH_3$



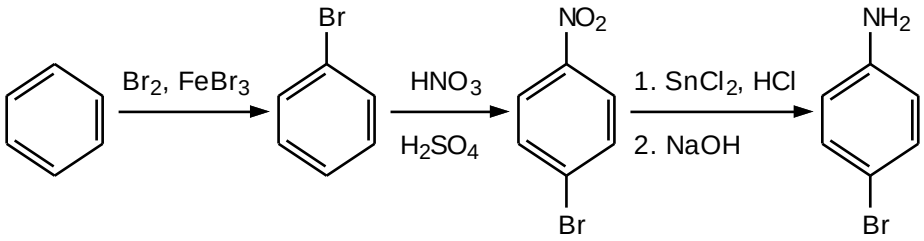
11.33 a. Alkylate aniline twice with ethyl bromide or ethyl iodide.



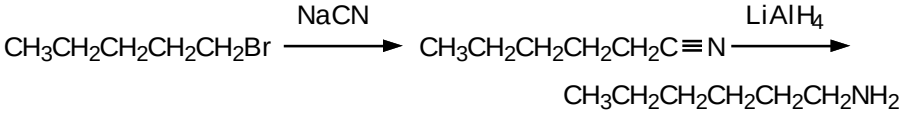
b. First nitrate, then brominate, to obtain the *meta* orientation.



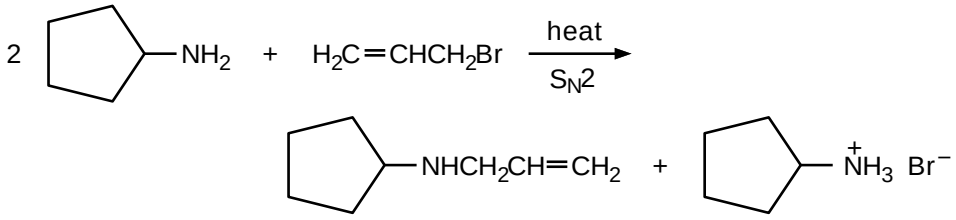
c. The reverse of the sequence in part b gives mainly *para* orientation.



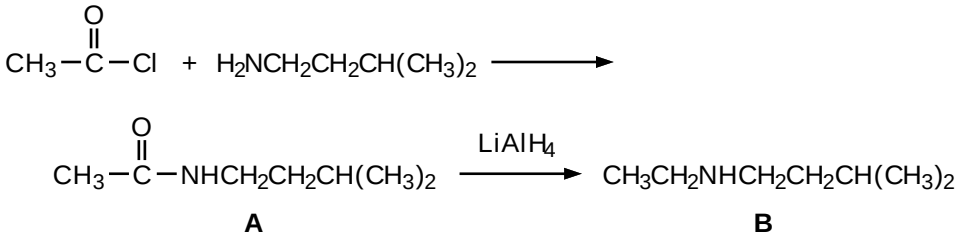
d. Displace the bromide and then reduce the nitrile.



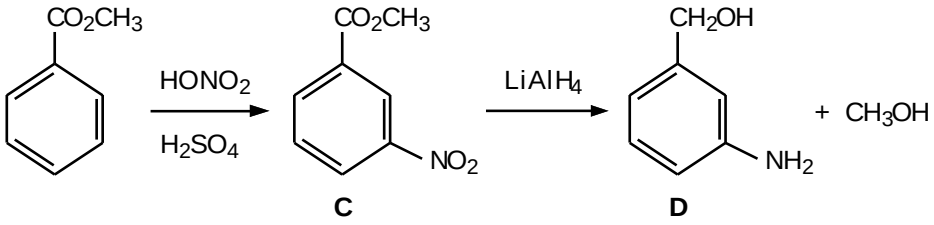
11.34 a.



b.

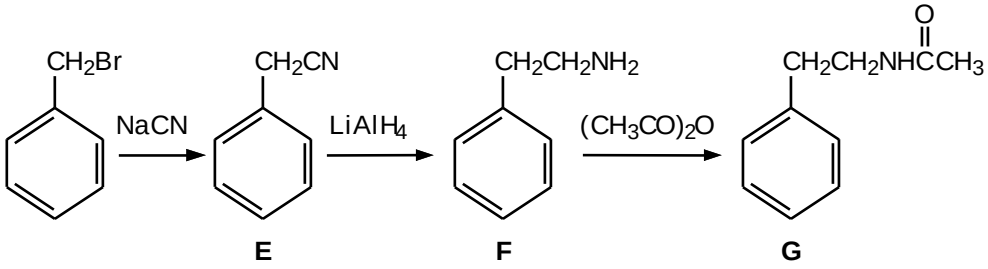


c.

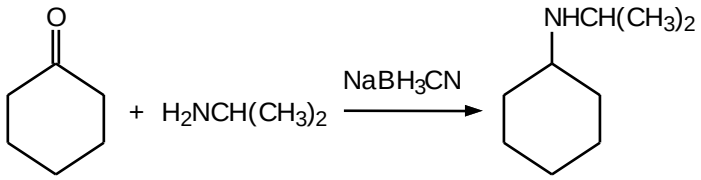


In the first step, the ester group is *meta*-directing. In the second step, both the nitro group and the ester group are reduced when excess $LiAlH_4$ is used.

d.

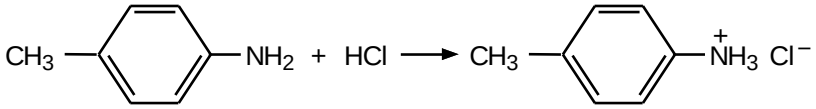


e.



H

11.35 a. Compare with eq. 11.18.



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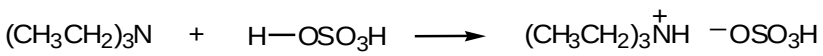
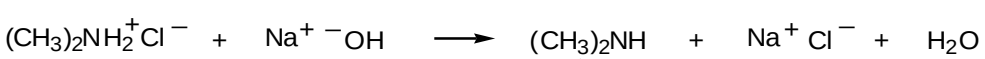
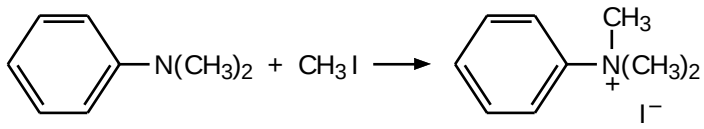


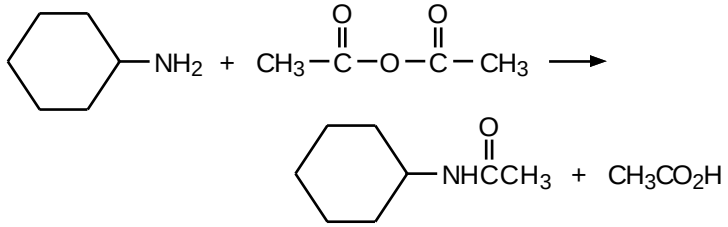
c.



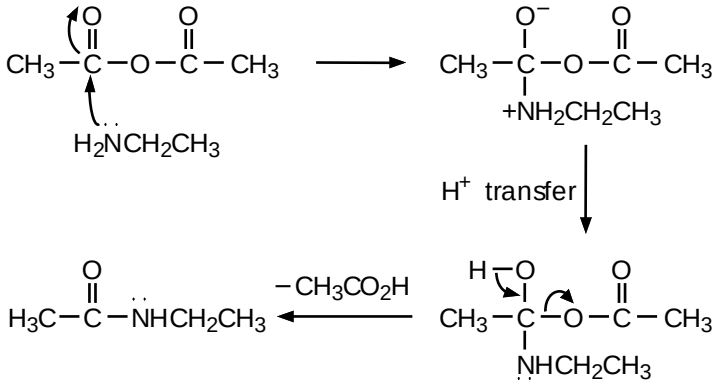
d.



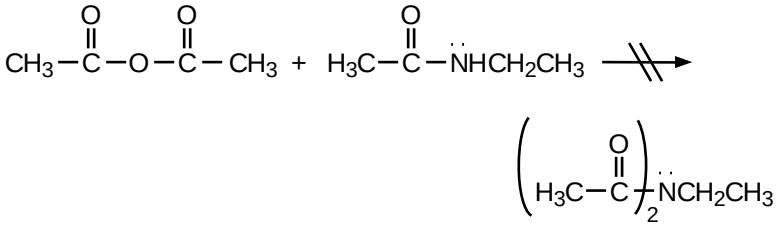
e.



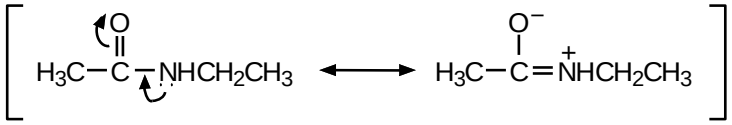
11.36 The reaction begins with nucleophilic attack by the amine on the carbonyl group of the anhydride.



Even though the resulting amide has an unshared electron pair on nitrogen, it does not react with a second mole of acetic anhydride to become diacylated:



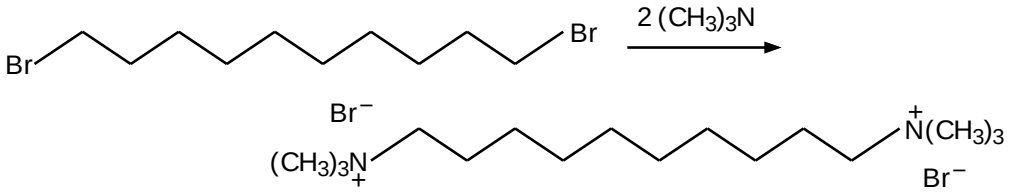
The reason is that amides are poor nucleophiles because the unshared electron pair on the nitrogen is delocalized through resonance:



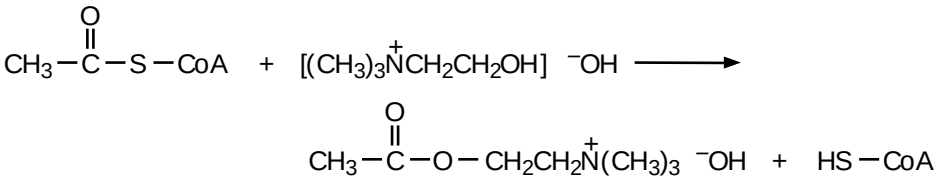
The amide is ineffective with respect to nucleophilic attack on the carbonyl group of acetic anhydride.

11.37 Each of these alkaloids have 4 stereogenic centers.

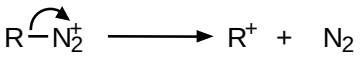
11.38 Use eq. 11.26 as a guide.



11.39



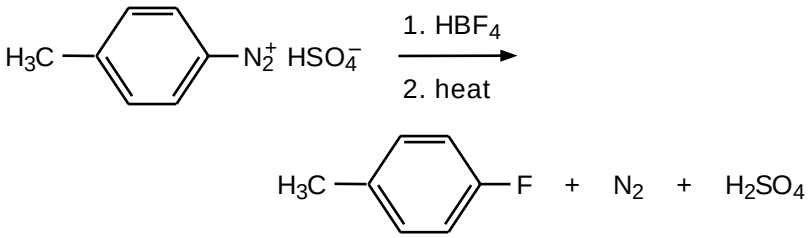
11.40 Alkyl diazonium salts can lose nitrogen to give 1°, 2°, or 3° carbocations, depending on the nature of the alkyl group.



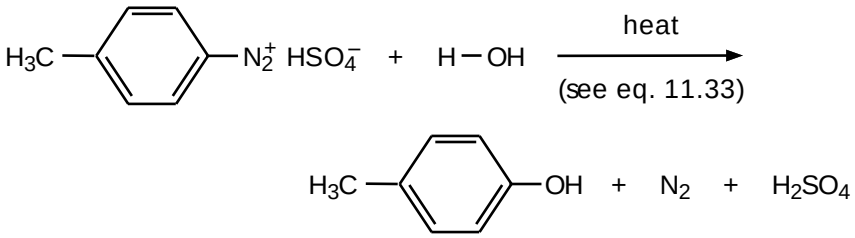
Aryl cations are less stable than 1°, 2°, or 3° carbocations, so aryl diazonium salts are more stable than alkyl diazonium salts.

11.41 These equations illustrate the reactions in Secs. 11.12 and 11.13.

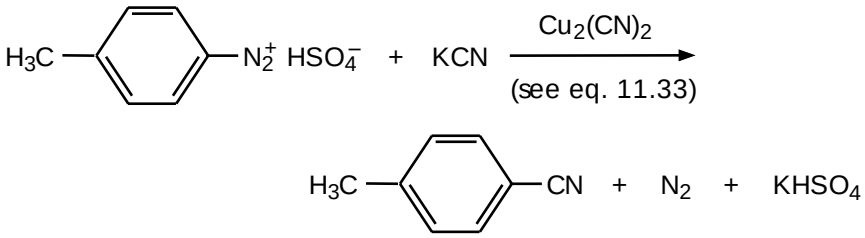
a.



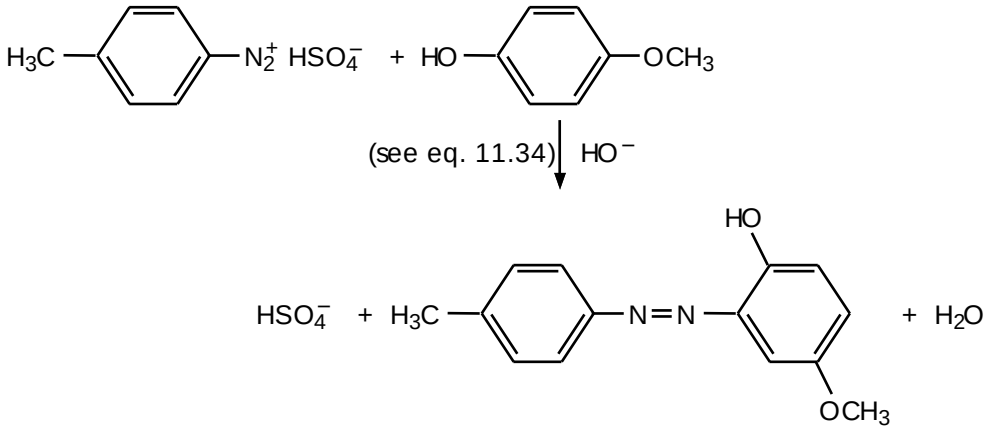
b.



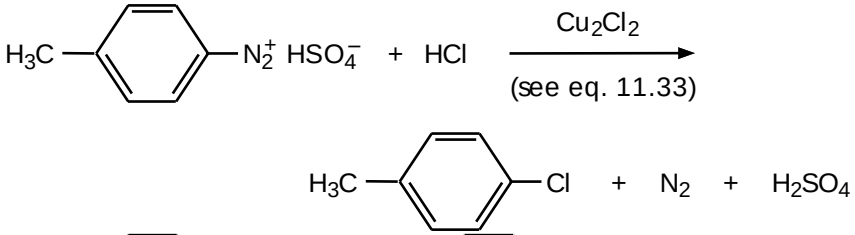
c.



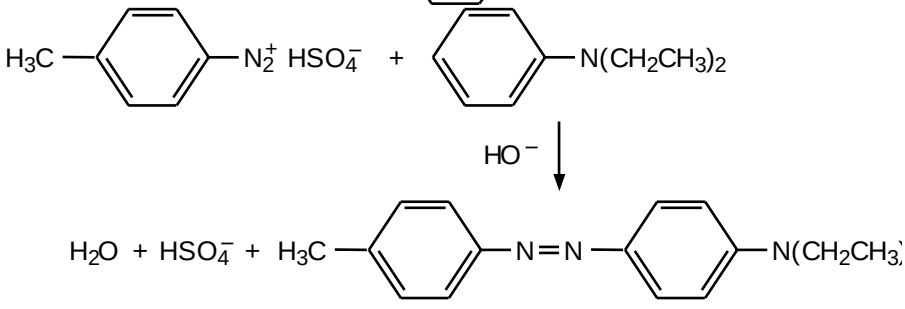
d. Since *para* coupling is blocked by the methyl substituent, *ortho* coupling occurs:



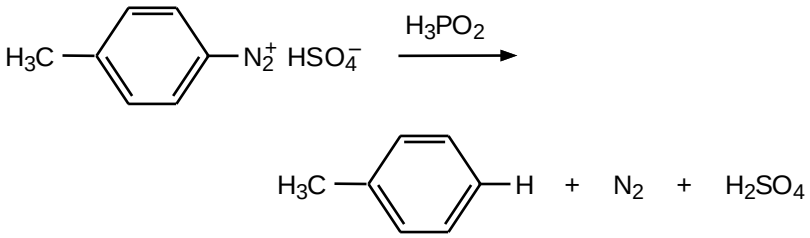
e



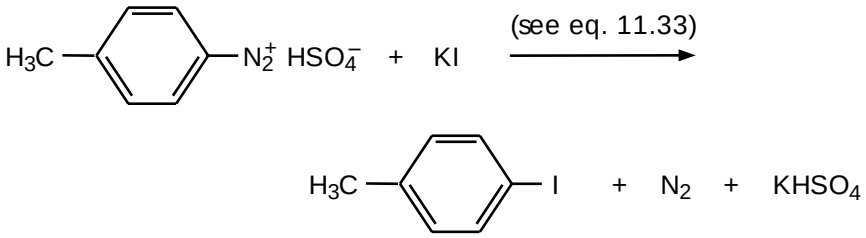
f.



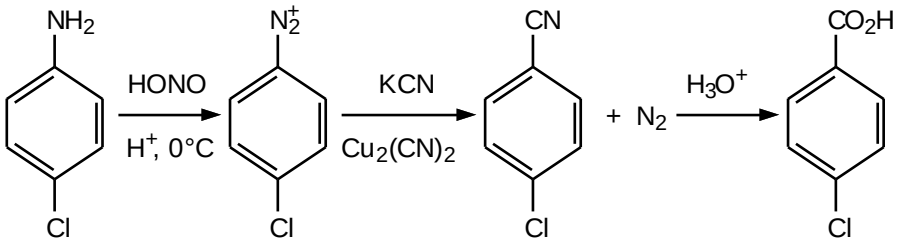
g.



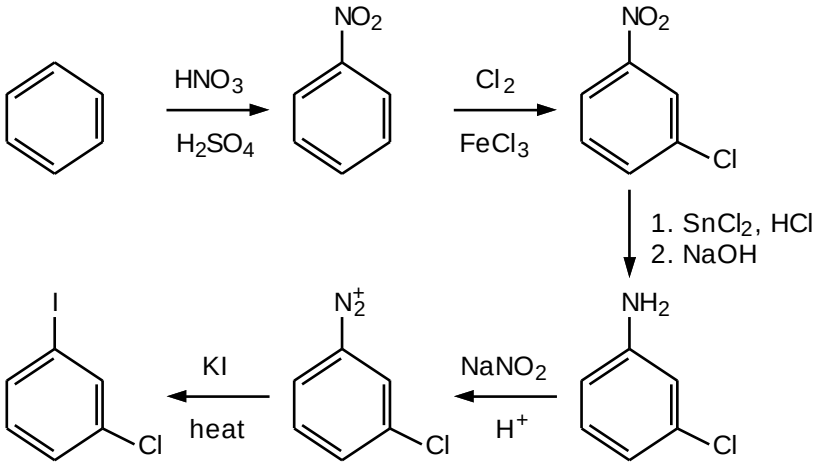
h.



11.42 a.

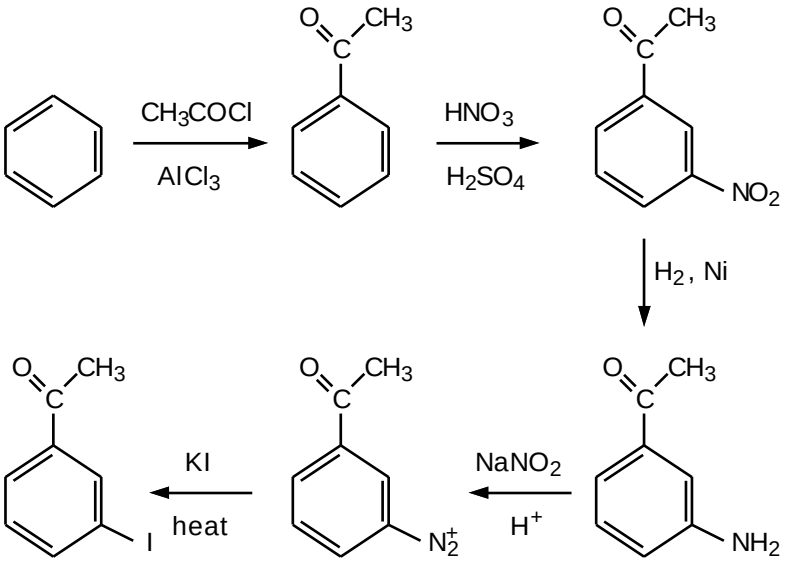


b.

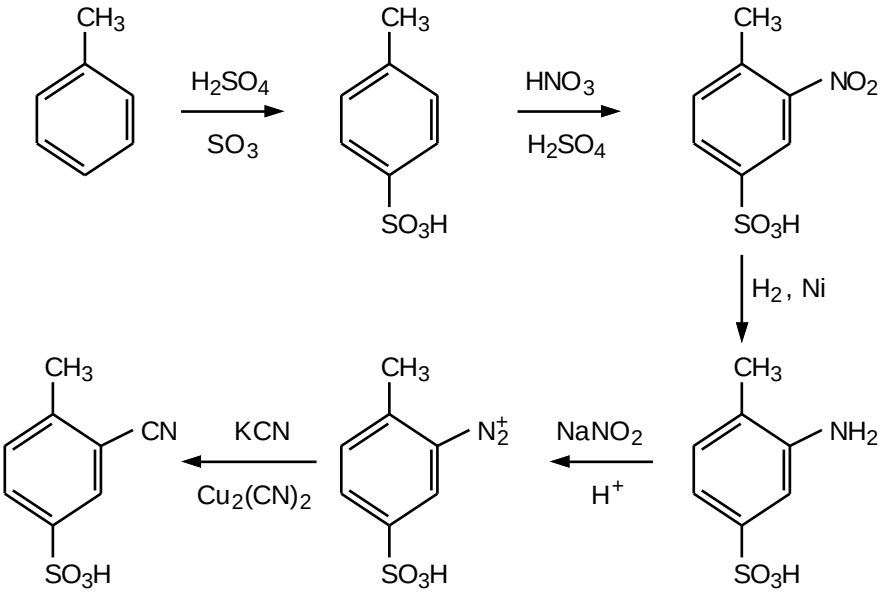


Note that the order of each step in the sequence is important. The benzene must be nitrated first and then chlorinated to attain *meta* orientation. Chlorination of iodobenzene would not give *meta* product, so this indirect route must be used.

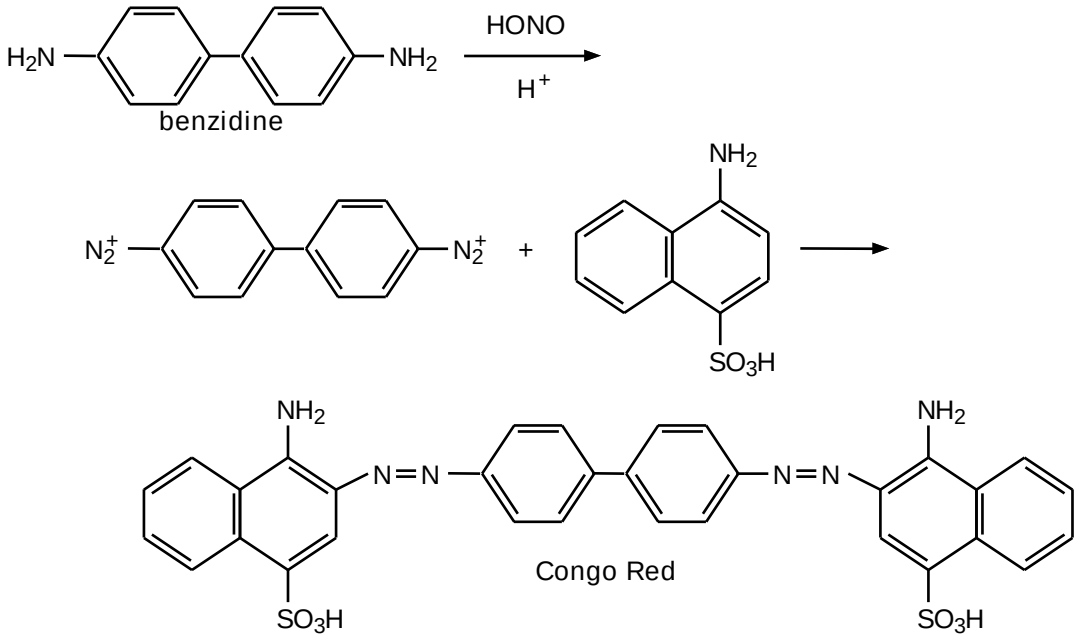
c.



d.



11.43 Benzidine can be diazotized at each amino group. It can then couple with two equivalents of the aminosulfonic acid. Coupling occurs *ortho* to the amino group since the *para* position is blocked by the sulfonic acid group.



11.44