Montogue

Quiz CH209

Organic Chemistry

Amines

Lucas Monteiro Nogueira

PROBLEMS

Problem 1 (McMurry, 2008, w/ permission)

The benzylammonium ion ($C_6H_5CH_2NH_3^+$) has pK_a = 9.33, and the propylammonium ion has pK_a = 10.71. which is the stronger base, benzylamine or propylamine?

Problem 2 (Vollhardt and Shore, 2014)

In which direction do you expect the following equilibria to lie?

2.1. $CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + OH^-$

2.2. $CH_3NH_2 + (CH_3)_3NH^+ \rightleftharpoons CH_3NH_3^+ + (CH_3)_3N$

Problem 3 (Vollhardt and Schore, 2014)

How would you expect the following classes of compounds to compare with simple primary amines as bases and acids?

3.1. Carboxylic amides (for example, CH_3CONH_2).

3.2. Imides (for example, $CH_3CONHCOCH_3$)

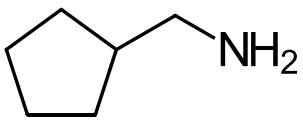
3.3. Enamines (for example, $CH_2{=}CHN(CH_3)_2$)

3.4. Benzenamines (for example, aniline)

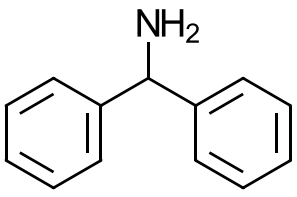
Problem 4

Using a Gabriel synthesis, show how you would make each of the following compounds.

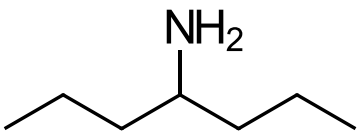
4.1.



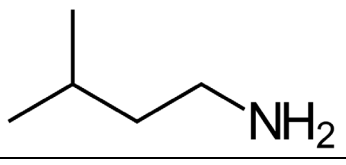
4.2.



4.3.



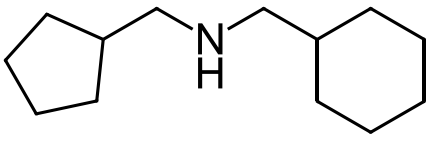
4.4.



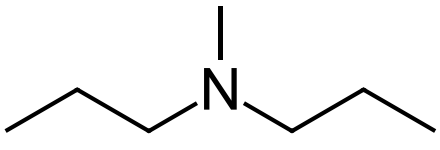
Problem 5 (Klein, 2017)

Show two different ways of preparing each of the following compounds by reductive amination.

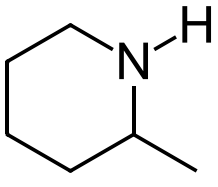
5.1.



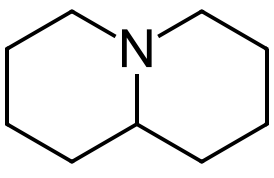
5.2.

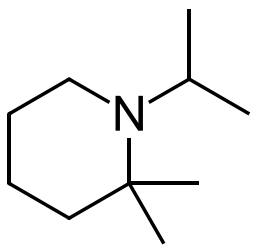
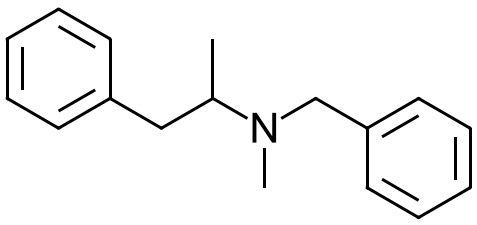


5.3.



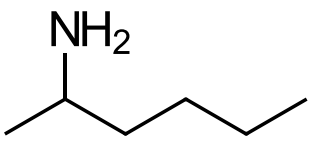
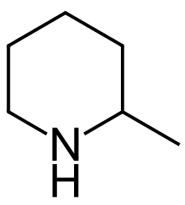
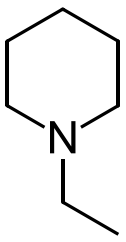
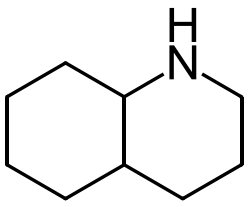
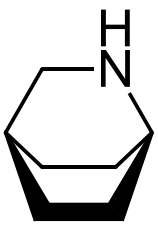
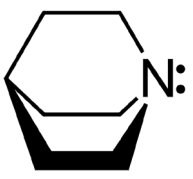
5.4.



5.5.	5.6.
	

▶ Problem 6 (Wade and Simek, 2016)

Predict the major products formed when the following amines undergo exhaustive methylation, treatment with Ag_2O, and heating.

6.1.	6.2.
	
6.3.	**6.4.**
	
6.5.	**6.6.**
	

▶ Problem 7 (Carey, 2008)

7.1. Give the structure and provide an acceptable name for all the isomers of molecular formula C_7H_9N that contain a benzene ring.

7.2. Which one of these isomers is the strongest base?

7.3. Which, if any, of these isomers yield an *N*-nitroso amine on treatment with sodium nitrite and hydrochloric acid?

7.4. Which, if any, of these isomers undergo nitrosation of their benzene ring on treatment with sodium nitrite and hydrochloric acid?

▶ Problem 8 (McMurry, 2008, w/ permission)

How would you prepare the following compounds from benzene, using a **diazonium replacement reaction** in your scheme?

8.1. *p*-Bromobenzoic acid
8.2. *m*-Bromobenzoic acid
8.3. *m*-Bromochlorobenzene
8.4. *p*-Methylbenzoic acid
8.5. 1,2,4-Tribromobenzene

▶ Problem 9 (McMurry, 2008, w/ permission)

Problem 9.1: How would you prepare aniline from each of the following materials?
9.1.1. Benzene
9.1.2. Benzamide
9.1.3. Toluene

Problem 9.2: Let's reverse Problem 9.1.
9.2.1. How would you convert aniline back to benzene?
9.2.2. How would you convert aniline back to benzamide?
9.2.3. How would you convert aniline back to toluene?

Problem 9.3: How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene?

▶ Problem 10

Give the structures of the major organic products you would expect from reaction of *m*-toluidine (*m*-methylaniline) with the following reagents.

10.1. Br_2 (1 equivalent)
10.2. CH_3I (excess)
10.3. CH_3COCl in pyridine
10.4. The product of 10.3, then HSO_3Cl

▶ Problem 11

Show the products from reaction of *p*-bromoaniline with the following reagents.

11.1. CH_3I (excess)
11.2. HCl
11.3. HNO_2, H_2SO_4
11.4. CH_3COCl in pyridine
11.5. CH_3MgBr
11.6. Product of 11.3 with CuCl, HCl
11.7. Product of 11.4 with CH_3CH_2Cl, $AlCl_3$

▶ Problem 12

How would you prepare the following substances from 1-butanol?

12.1. Butylamine
12.2. Dibutylamine
12.3. Propylamine
12.4. Pentylamine
12.5. *N*,*N*-Dimethylbutylamine
12.6. Propene

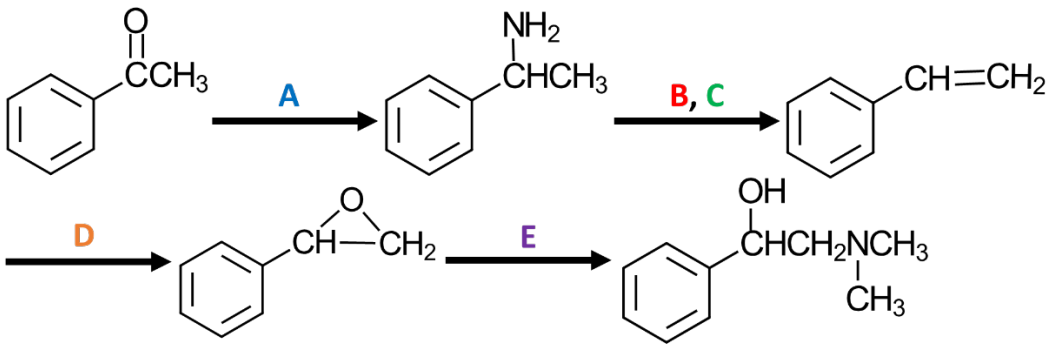
▶ Problem 13

How would you prepare the following substances from pentanoic acid?

13.1. Pentanamide
13.2. Butylamine
13.3. Pentylamine
13.4. Hexanenitrile
13.5. Hexylamine

▶ Problem 14 (McMurry, 2008, w/ permission)

Fill in the reagents **A** – **E** in the following scheme.



SOLUTIONS

P.1 ➡ *Solution*

Recall that the product of a base's dissociation constant, K_b, and that of its conjugate acid, K_a, equals 10^{-14}. Applying the operator $pX = -\log_{10} X$, we have $pK_a + pK_b = 14$, or $pK_b = 14 - pK_a$. Benzylammonium ion is the conjugate acid of benzylamine and has $pK_a = 9.33$; accordingly, the pK_b of benzylamine is 14 – 9.33 = 4.67. Similarly, the pK_b of propylamine is 14 – 10.71 = 3.29. The lower the pK_b, the greater the dissociation constant of the base. Since propylamine has a lower pK_b than benzylamine, we surmise that propylamine is a stronger base than benzylamine.

P.2 ➡ *Solution*

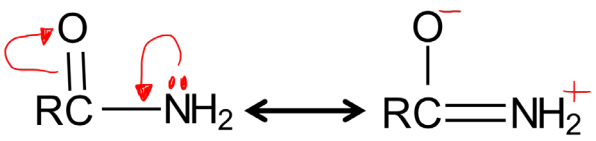
2.1: This equilibrium should be displaced to the left, because methylamine is a weaker base than OH^-, and H_2O is a weaker acid than $CH_3NH_3^+$.

2.2: This equilibrium should be displaced to the right, because methylamine is a stronger base than trimethylamine. As noted by Vollhardt and Schore, the electron-donating character of alkyl groups would, in principle, make trimethylamine a stronger base than methylamine; however, increasing

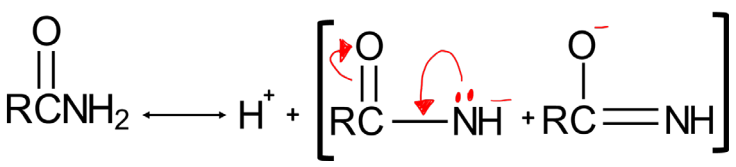
the number of alkyl groups on the amine nitrogen increases unfavorable steric disruption of the solvent shell. At the same time, it decreases the number of hydrogens attached to the nitrogen capable of entering into favorable hydrogen bonds. In conjunction, these two effects imply that tertiary alkylamines make for weaker bases than primary alkylamines.

P.3 ➡ *Solution*

3.1: Carboxylic amides tend to be weaker bases than simple primary amines because the lone pair on N is "tied up" by resonance, as shown.

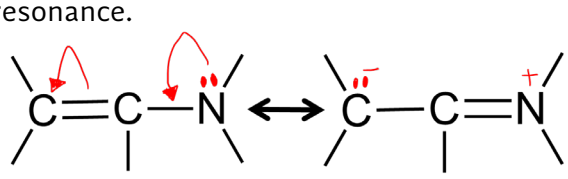


Amides are generally stronger acids than amines because the conjugate base is stabilized by both the inductive effect of the carbonyl group and by resonance.



3.2: Like carboxylic amides, imides make for weaker bases and stronger acids than primary amines, but to a greater extent (due to the presence of two carbonyl groups).

3.3: Compared to primary amines, enamines are somewhat weaker bases because of resonance.

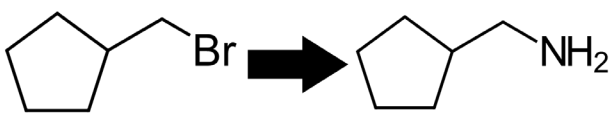


Further, enamines are not acidic, because there are no hydrogens linked to the nitrogen atom.

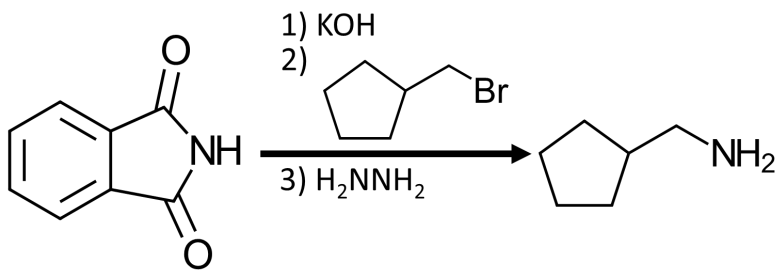
3.4: Benzenamides tend to be weaker bases and stronger acids, for the same reasons given in 3.1 for carboxamides.

P.4 ➡ *Solution*

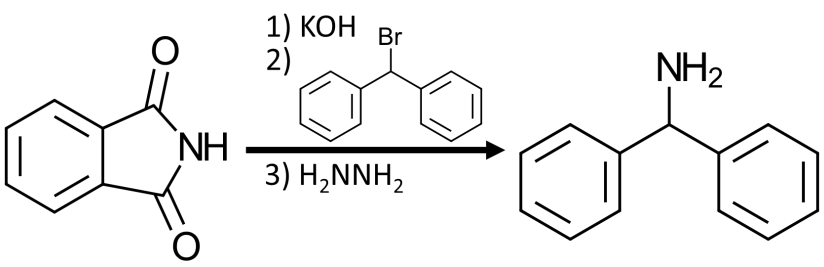
4.1: We begin by identifying an alkyl halide that can serve as a precursor. 1-(Bromomethyl)cyclopentane is a viable choice in this case.



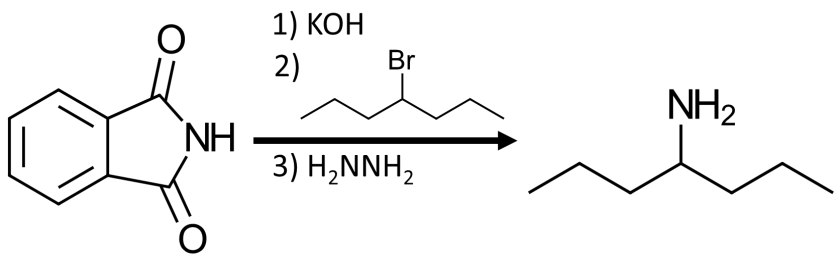
In the Gabriel synthesis, phthalamide is the starting material, and three steps are required. In the first step, phthalamide is deprotonated by hydroxide to give potassium phthalamide, which can serve as a nucleophile and attack the alkyl halide above in a S_N2 process. Subsequent treatment with hydrazine (or aqueous acid) releases the desired amine.



4.2: This problem follows the same logic as Problem 4.1; bromodiphenylmethane can serve as a precursor.

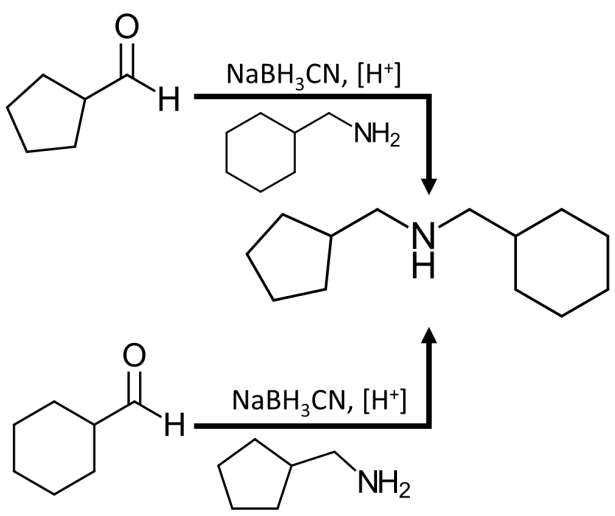


4.3: 4-Bromoheptane is a viable precursor in this case.

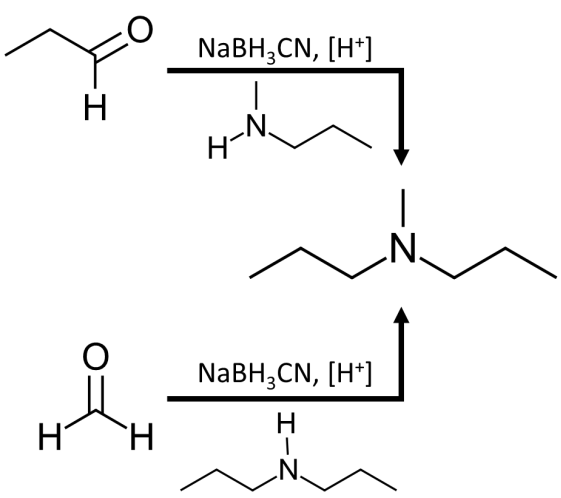


P.5 ➡ *Solution*

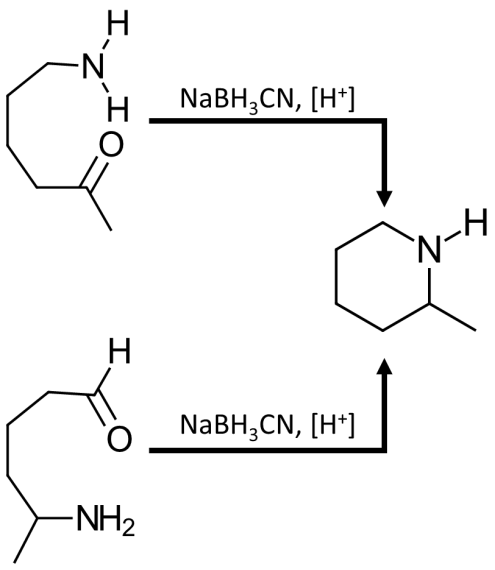
5.1: The compound has two C—N bonds. Each of these bonds can be made via reductive amination, giving two possible synthetic routes, as shown. Sodium cyanoborohydride is the reducing agent of choice.



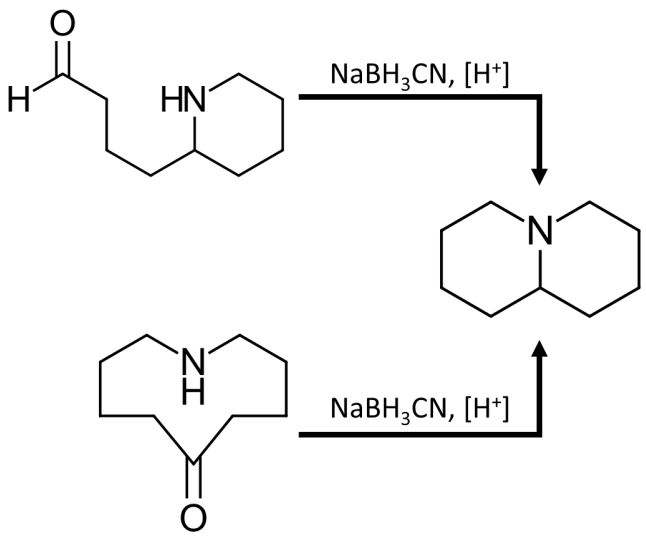
5.2: The compound has three C—N bonds. Each of these bonds can be made via reductive amination. However, two of them are identical (because of symmetry), giving two possible synthetic routes, as shown.



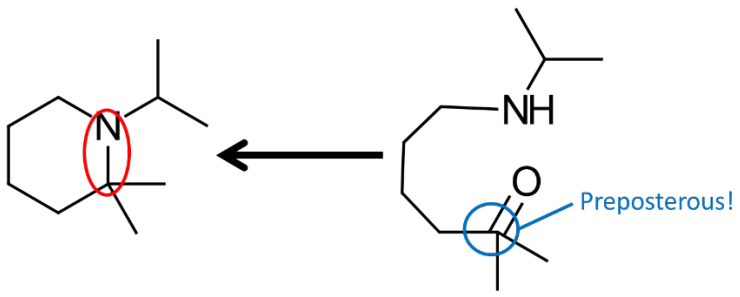
5.3: The compound has two C—N bonds. Each of these bonds can be made via reductive amination, giving two possible synthetic routes, as shown.



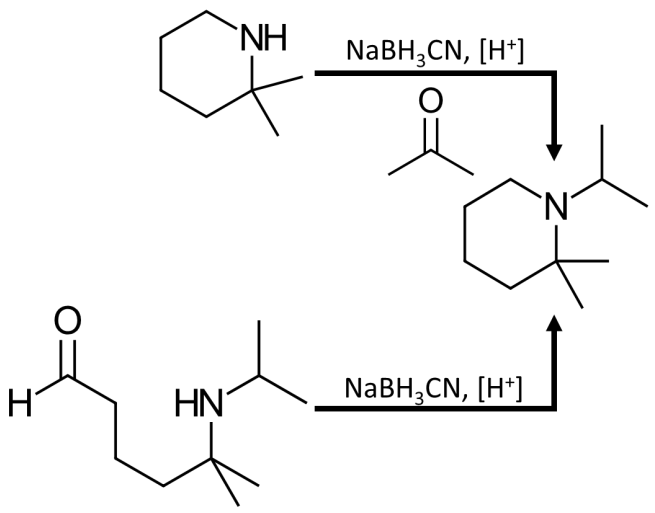
5.4: The compound has three C—N bonds. Each of these bonds can be made via reductive amination. However, two of them are identical (because of symmetry), giving two possible synthetic routes, as shown.



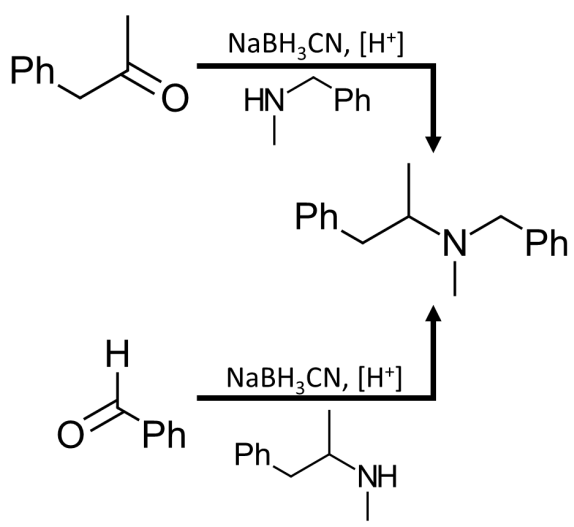
5.5: The compound has three C—N bonds. Two of these bonds can be made via reductive amination, but the bond highlighted in red below cannot be made by this process because the starting material would have a pentavalent carbon atom.



The other two bonds can be made by dint of reductive amination, using one of the two following synthetic routes.

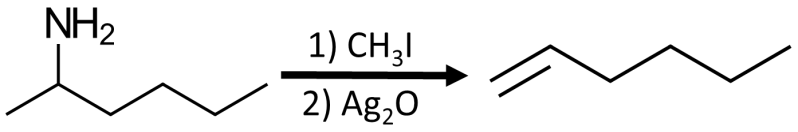


5.6: The compound has three C—N bonds. Each of these bonds can be made by reductive amination, leading to three possible synthetic routes. Two possible routes are shown here; the third begins with formaldehyde.

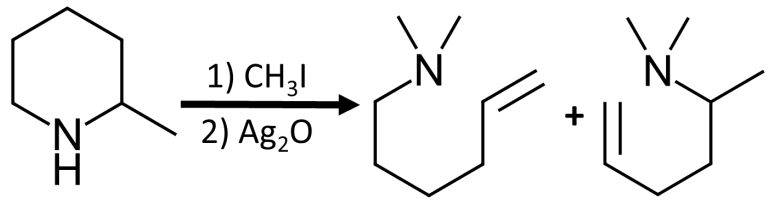


P.6 ➡ *Solution*

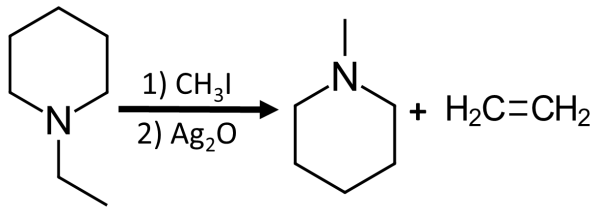
6.1: Hexan-2-amine undergoes Hofmann elimination to yield two alkenes. The less substituted alkene, 1-hexene, is favored.



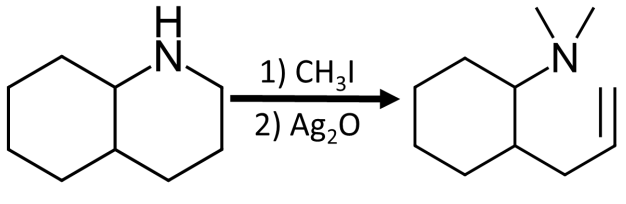
6.2: This molecule, 2-methylpiperidine, undergoes Hofmann elimination to yield two major products.



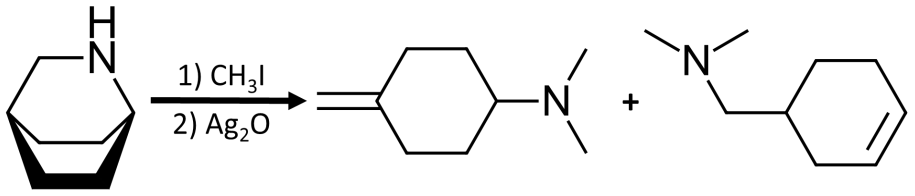
6.3: This molecule, *N*-ethylpiperidine, undergoes Hofmann elimination to yield a tertiary amine with a methyl group as one of its substituents and ethylene.



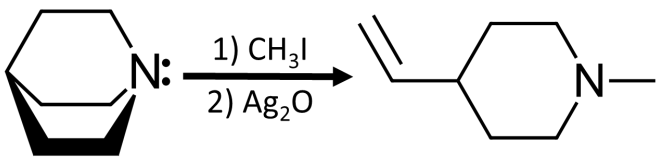
6.4: Upon being subjected to Hofmann elimination, this molecule (perhydroquinoline) yields the following unsaturated amine.



6.5: Upon being subjected to Hofmann elimination, this molecule becomes one of the following monocyclic, unsaturated amines.

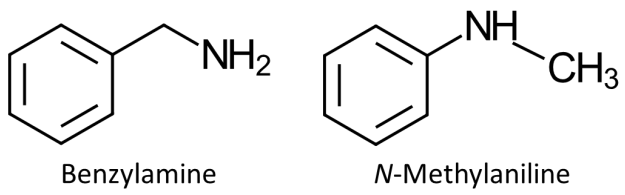


6.6: Hofmann elimination of this molecule is similar to that of Problem 6.5, but only one major product is formed.

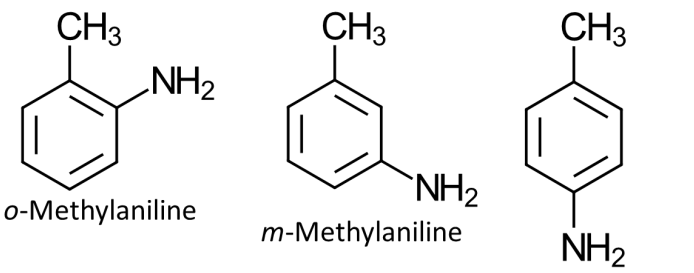


P.7 ➡ *Solution*

7.1: There are five isomers of C_7H_9N that contain a benzene ring, as shown.



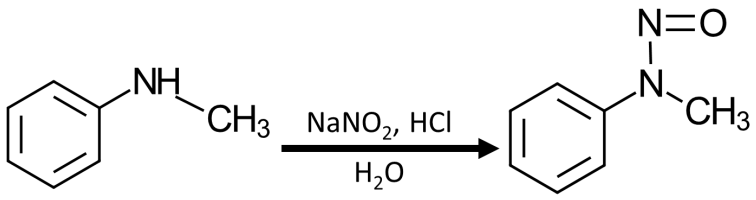
Benzylamine *N*-Methylaniline



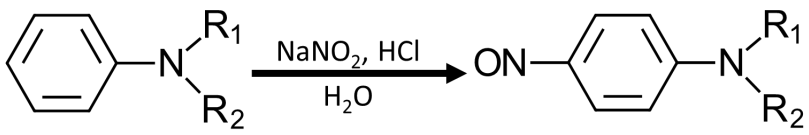
o-Methylaniline *m*-Methylaniline *p*-Methylaniline

7.2: Benzylamine is the strongest base because its amine group is bonded to an sp^3-hybridized carbon. Benzylamine is a typical alkylamine, with aa K_b of 2×10^{-5}. All the other isomers are aryl amines, with K_b values in the 10^{-10} range.

7.3: The formation of *N*-nitrosoamines on reaction with sodium nitrite and hydrochloric acid is a characteristic reaction of secondary amines. The only C_7H_9N isomer in this problem that is a secondary amine is *N*-methylaniline.



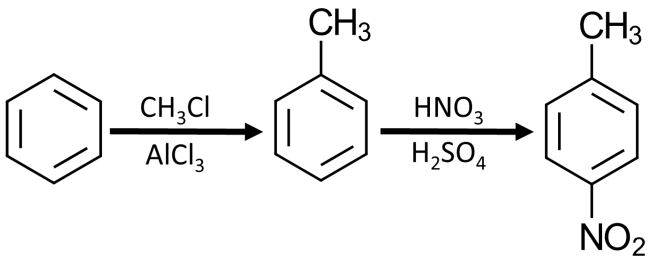
7.4: Ring nitrosation is a characteristic reaction of tertiary arylamines.



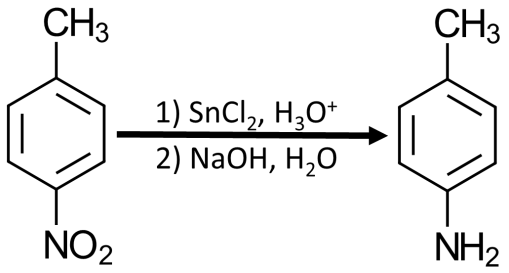
None of the C_7H_9N isomers in this problem is a tertiary amine; hence, none will undergo ring nitrosation.

P.8 ➡ *Solution*

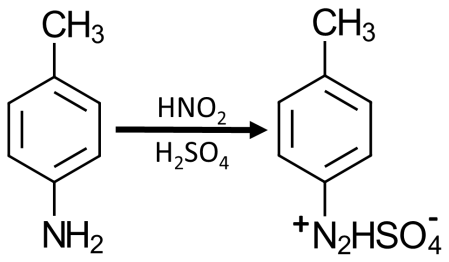
8.1: We begin by performing two electrophilic aromatic reactions in succession, namely (1) a Friedel-Crafts methylation and (2) a nitration.



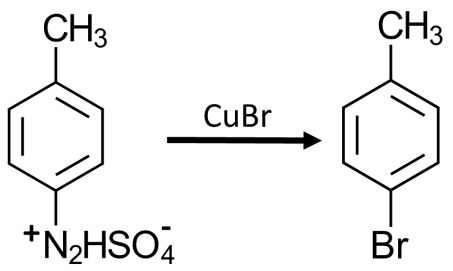
The next step is to reduce the nitro group to an amine group.



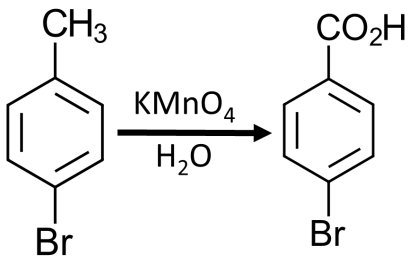
At this point, we perform a diazotization reaction to produce an arenediazonium salt.



Next, a nucleophilic substitution should introduce a bromine group in the molecule.

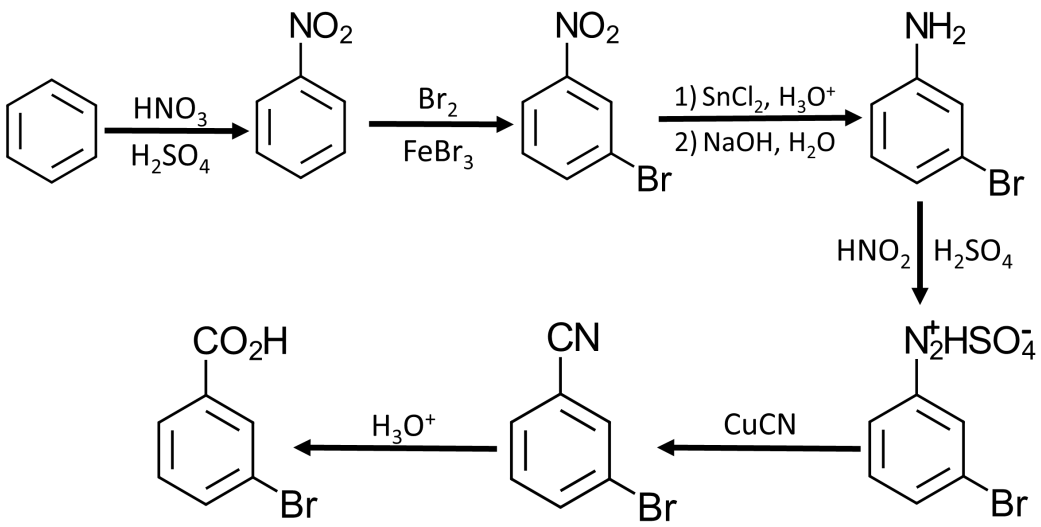


Lastly, the methyl group can be oxidized to a carboxylic acid group.

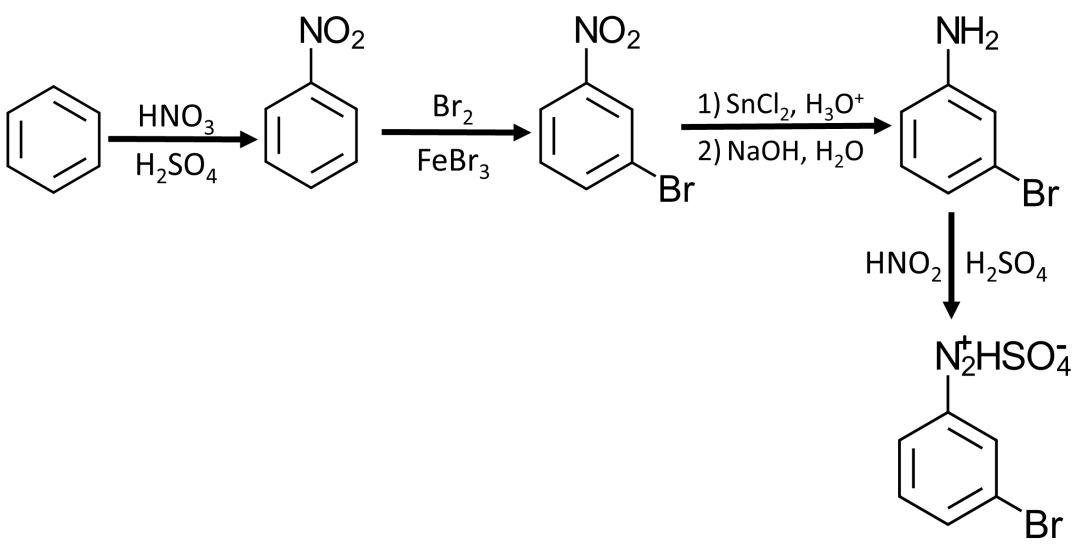


McMurry observes that this is definitely *not* the simplest way to achieve *p*-bromobenzoic acid; the simplest route would be Friedel-Crafts alkylation → bromination → oxidation.

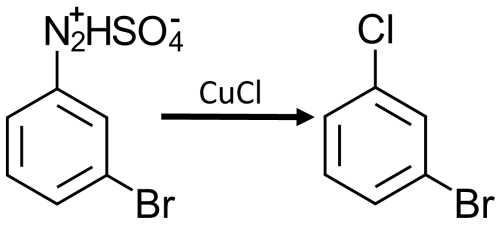
8.2: In this case, we begin with nitration, followed by bromination, diazotization, treatment with CuCN, and, finally, hydrolysis of the nitrile.



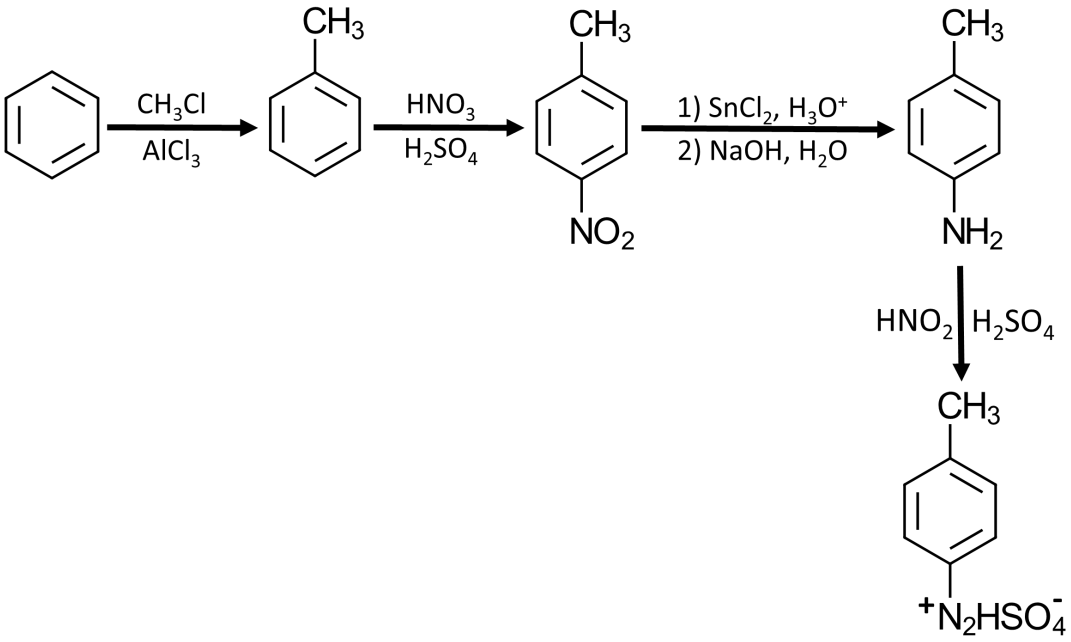
8.3: We proceed as we did in the previous problem up to the point where the arenediazonium salt is formed.



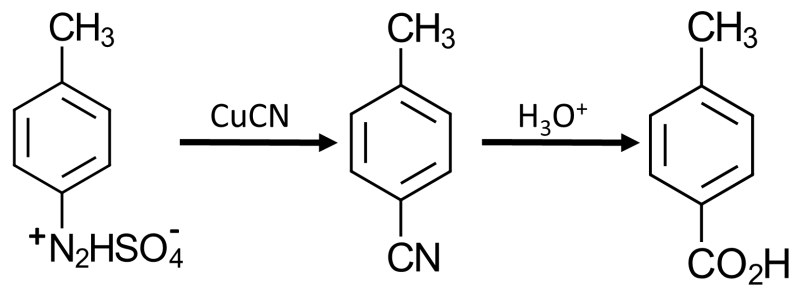
Here, we react the salt with CuCl, yielding *m*-bromochlorobenzene.



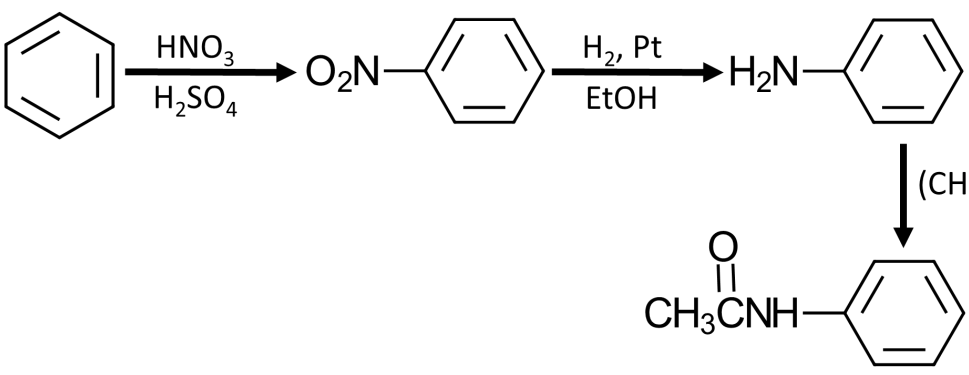
8.4: We proceed as we did on Problem 8.1 up to the point where the arenediazonium salt is formed; the synthetic route in question is repeated in the next page.



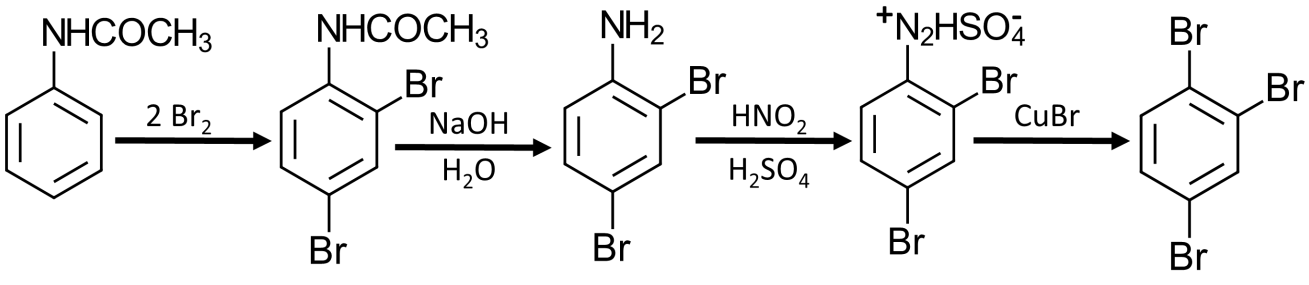
Here, we react the salt with CuCN, yielding a nitrile. Finally, hydrolysis of the nitrile produces *p*-methylbenzoic acid.



8.5: Beginning with benzene, we perform a few predictable steps to form an amide group.

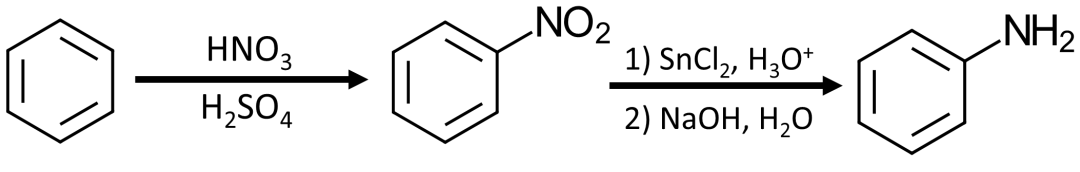


Next, we brominate the aromatic ring, hydrolyze the amide, react with HNO_2 to form a salt, and ultimately substitute the diazonium group with bromine, yielding 1,2,4-tribromobenzene.

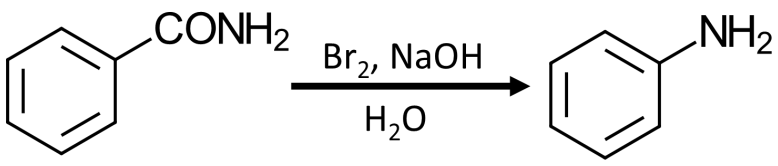


P.9 ➡ *Solution*

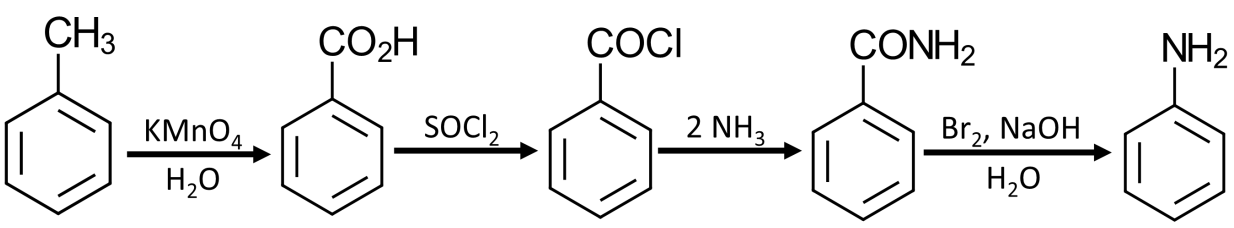
9.1.1: We begin by nitrating the aromatic ring. Then, reduction of the nitro group with stannous chloride leads to aniline.



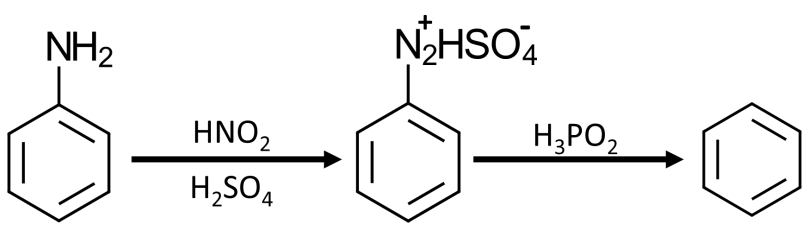
9.1.2: Use of the Hofmann-bromamine reaction efficiently converts benzamide to aniline.



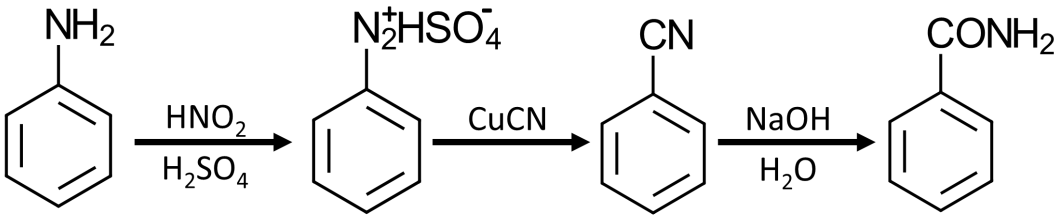
9.1.3: We begin by oxidizing the methyl group to a carboxylic acid group. Then, treatment with thionyl chloride converts benzoic acid to the corresponding acid chloride. Next, reaction with ammonia converts the acid chloride to benzamide. Finally, application of the Hofmann-bromamide reaction yields aniline.



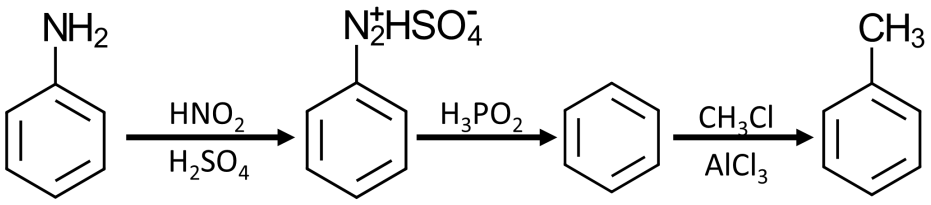
9.2.1: We begin by performing a diazotization reaction. Afterwards, treatment with H_3PO_2 suppresses the diazonio group, and benzene is formed.



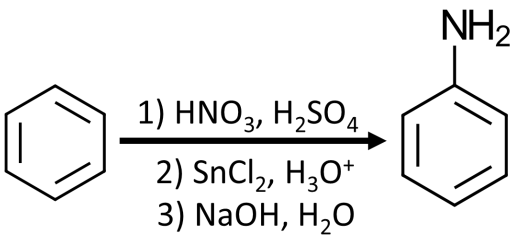
9.2.2: As was done in Problem 9.2.1, we first form an arenediazonium salt. The second step is a substitution reaction with copper cyanide. Lastly, an aqueous treatment with base yields benzamide.



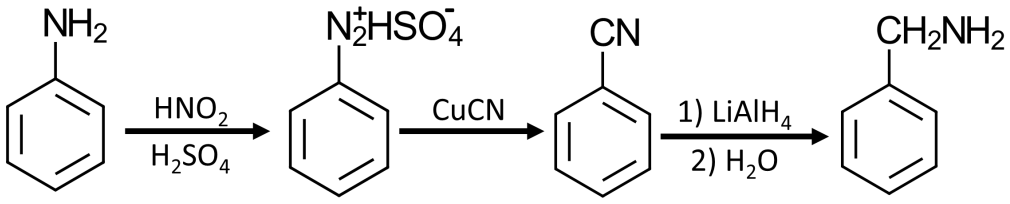
9.2.3: We synthesize benzene as we did in Problem 9.2.1. Friedel-Crafts alkylation yields toluene.



9.3: The first step is to synthesize aniline from benzene; this synthetic route was presented in Problem 9.1.1 and consists of nitrating the benzene ring and then reducing the nitro group.

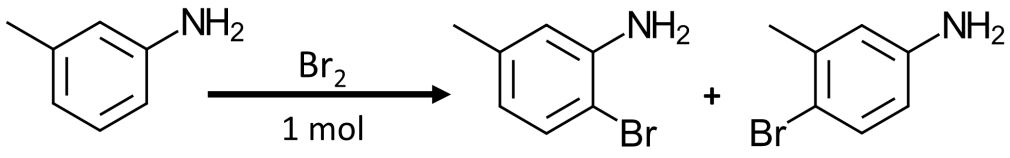


Next, treatment with HNO_2 yields an arenediazonIum salt. Reaction of this salt with CuCN replaces the diazonio group with a cyano group. Lastly, reduction of the nitrile gives benzylamine.

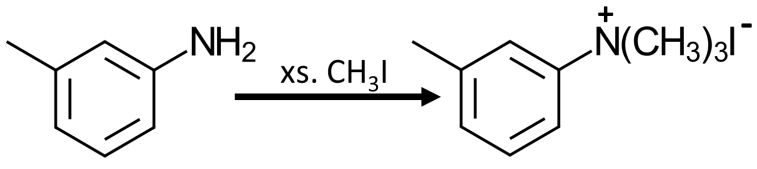


P.10 ➡ *Solution*

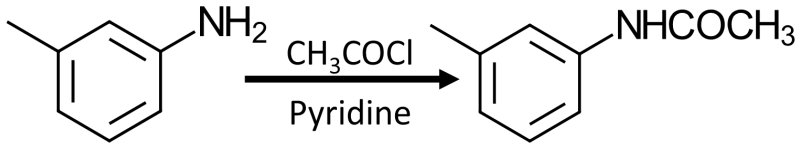
10.1: Methyl and amine groups are activating, *ortho-para* directing groups. Reaction of *m*-toluidine with one equivalent of bromine should install a Br atom on the *ortho* position relatively to the amine group (*para* with reference to the methyl group) or *para* relatively to the amine group (*ortho* with reference to the methyl group).



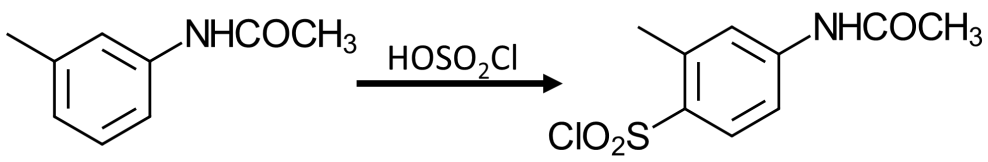
10.2: When treated with excess methyl iodide, the amino group of *m*-toluidine undergoes exhaustive alkylation to give a quaternary ammonium salt.



10.3: Toluidine is a strong nucleophile. When treated with an acid chloride, the amino group undergoes acylation. Pyridine functions as an acid sponge to neutralize the HCl that is produced as a byproduct of the reaction.

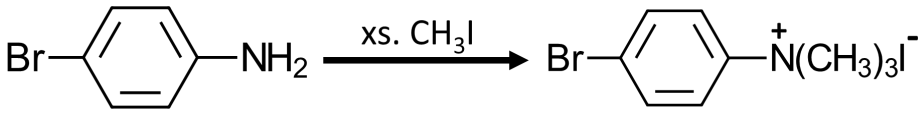


10.4: This is a chlorosulfonation reaction. The amide group, which is a moderate activator, directs the reaction to the *para* position of the aromatic ring.

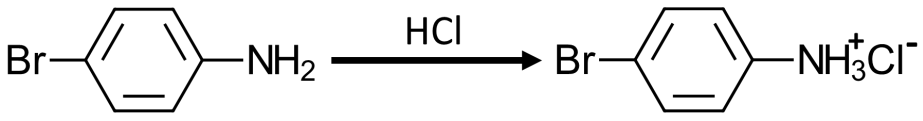


P.11 ➡ *Solution*

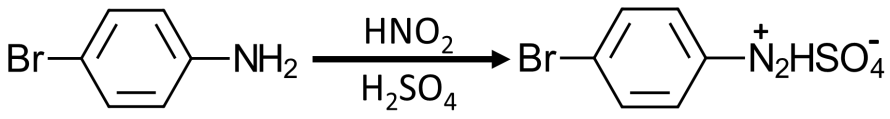
11.1: As in Problem 10.2, reaction of *p*-bromoaniline with excess methyl iodide produces a quaternary ammonium salt.



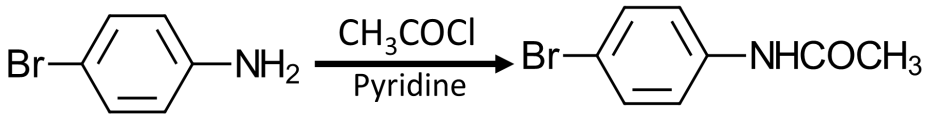
11.2: The amine group, a base, is neutralized by hydrochloric acid to yield an organic salt.



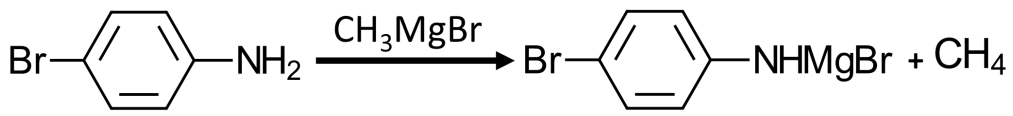
11.3: Treatment of an aromatic amine with nitrous acid produces an arenediazonIum salt.



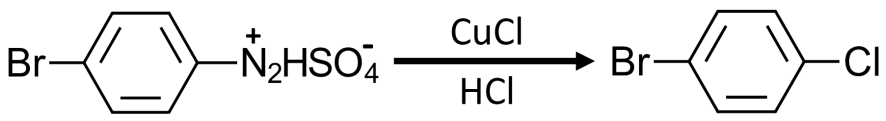
11.4: Similarly to Problem 10.3, reaction of *p*-bromoaniline with an acid chloride leads to acylation of the amine group.



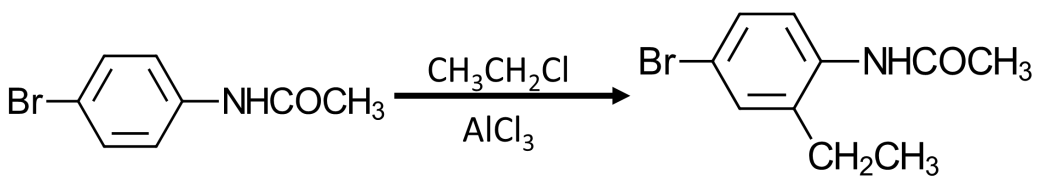
11.5: Reaction of *p*-bromoaniline with methylmagnesium bromide leads to the formation of a Grignard reagent and methane.



11.6: Reaction of CuCl with an arenediazonium salt leads to a substitution reaction, replacing the diazonio group with chlorine.

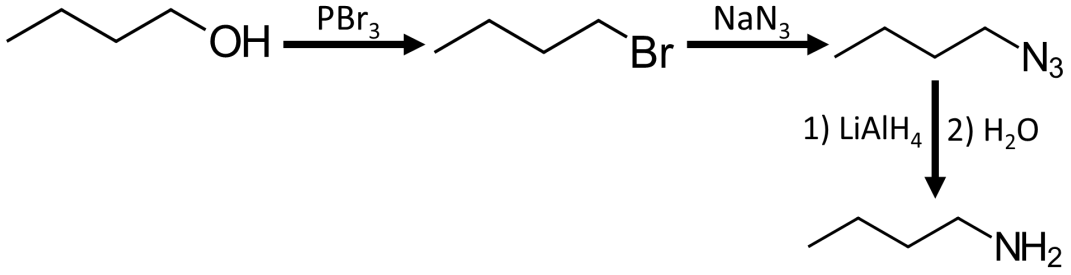


11.7: This is a Friedel-Crafts alkyation. The amide group formed in Problem 11.4 is a moderate activator and directs the reaction to the *ortho* and *para* positions; the *para* position is already occupied, leaving us with the following *ortho* product.

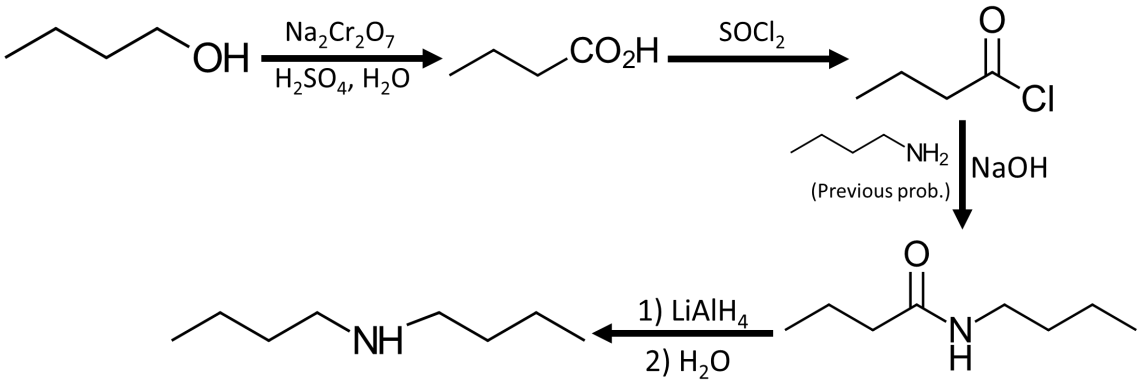


P.12 ➡ *Solution*

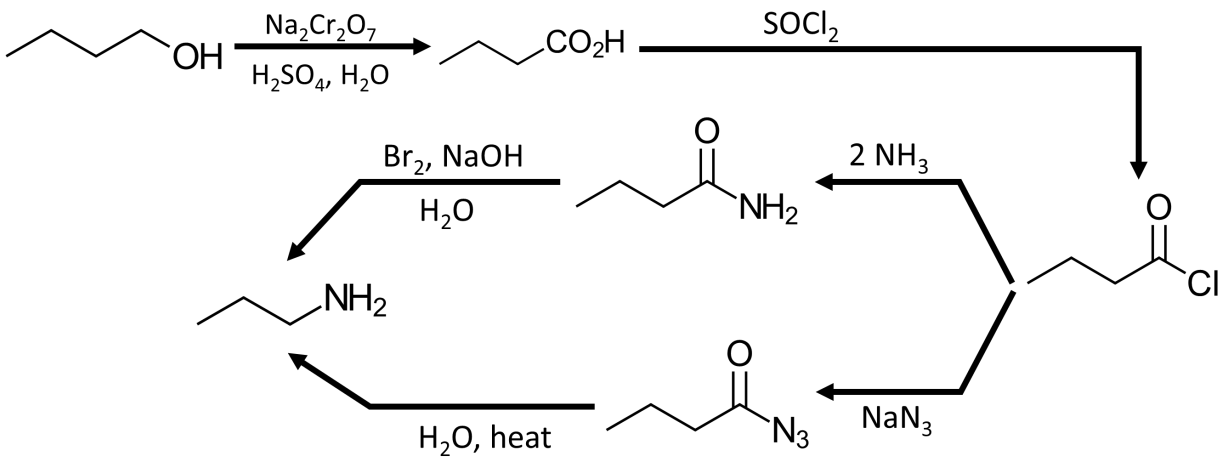
12.1: We begin by reacting the initial alcohol with phosphorus tribromide, thereby substituting the hydroxyl group with a bromine group. Then, we react the ensuing alkyl halide with NaN_3, which converts the alkyl halide to an alkyl azide. Lastly, we react the azide with lithium aluminum hydride followed by aqueous workup, reducing it to butylamine.



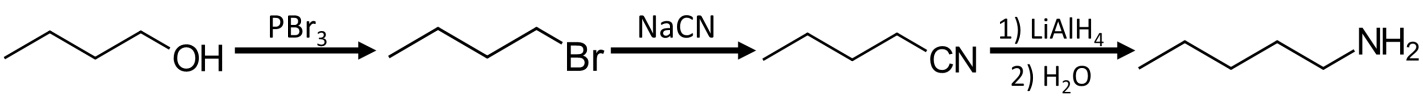
12.2: We begin by oxidizing butanol to butanoic acid. Then, reaction with thionyl chloride yields an acid chloride. Next, reaction of the ensuing acid chloride with butylamine – which can also be synthesized from butanol, as shown in the previous problem – leads to the formation of an amide. Finally, reduction of the amide yields dibutylamine.



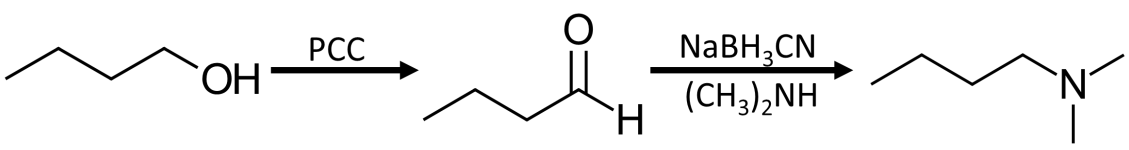
12.3: The first step is to convert the alcohol to an acid chloride; this can be done by oxidizing the alcohol and then treating the ensuing acid with thionyl chloride. At this point, we can proceed in two ways. The first option is to treat the acid chloride with excess ammonia, then perform a Hofmann-bromamide reaction to yield the desired primary amine. The second option is to treat the acid chloride with NaN_3, giving an acyl azide, then heat this product to induce a Curtius rearrangement, which yields the desired primary amine.



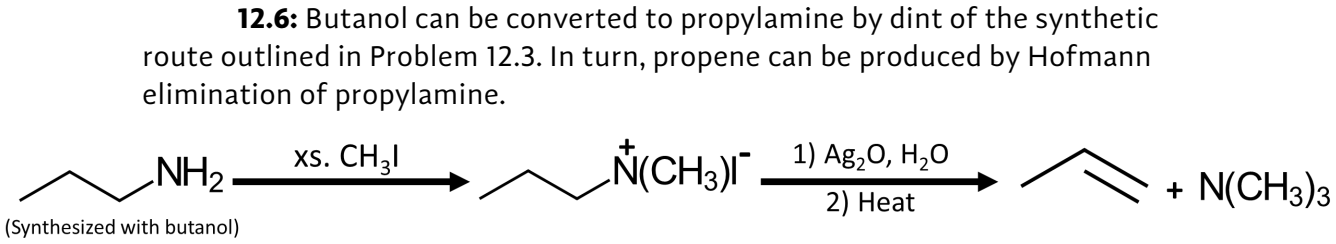
12.4: Butanol has four carbons, whereas pentylamine has five; thus, one additional carbon must be introduced somewhere in the synthetic route. The easiest way to obtain this carbon is to install a cyano group in the molecule. Reduction of the ensuing nitrile yields pentylamine.



12.5: The first step is to oxidize butanol to butyraldehyde; this can be done by treating the alcohol with pyridinium chlorochromate (PCC), DMSO/oxalyl chloride, or Dess-Martin periodinane (DMP). Reductive amination of butanal with dimethylamine yields the desired product.

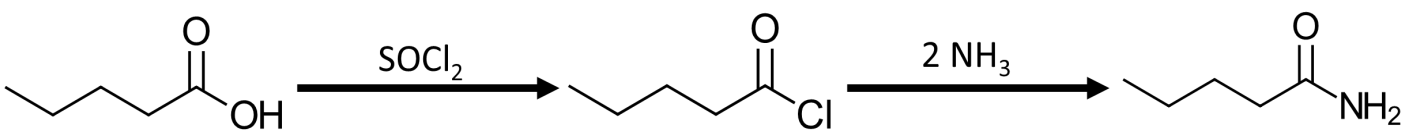


12.6: Butanol can be converted to propylamine by dint of the synthetic route outlined in Problem 12.3. In turn, propene can be produced by Hofmann elimination of propylamine.

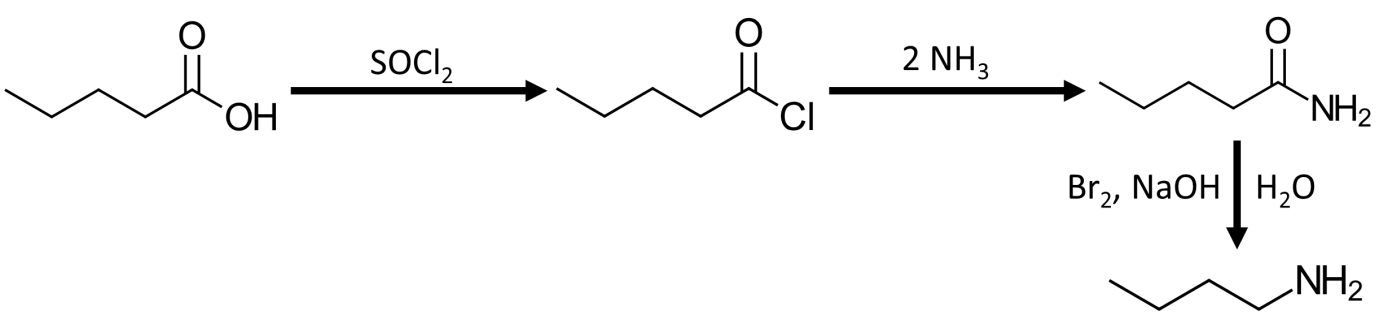


P.13 ➡ *Solution*

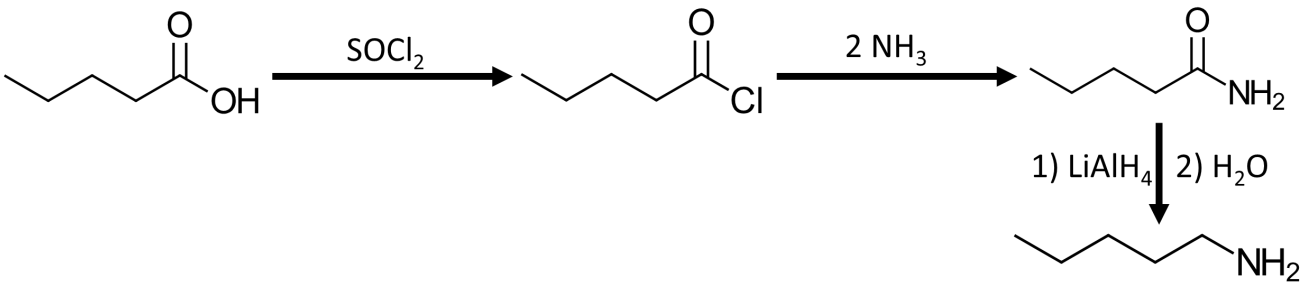
13.1: Treatment of pentanoic acid with $SOCl_2$ yields an acid chloride. Then, reaction of the acid chloride with excess ammonia gives pentanamide.



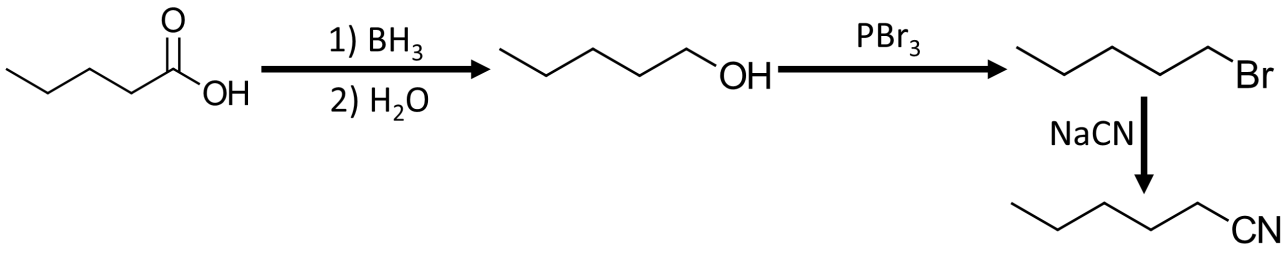
13.2: We synthesize pentanamide as we did in Problem 13.1. Then, a Hofmann-bromamide reaction converts the amide to the corresponding primary amine with one less carbon.



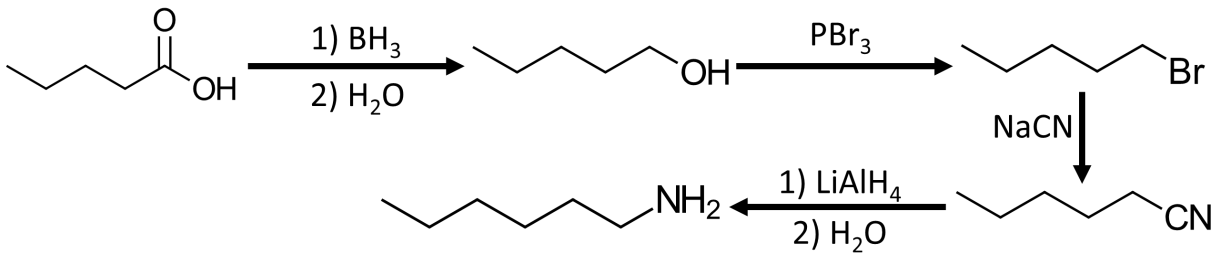
13.3: Again, we synthesize pentanamide as we did in Problem 13.1. Then, reduction of this amide with lithium aluminum hydride yields the desired amine.



13.4: Treatment of pentanoic acid with borane followed by an acid workup yields 1-pentanol. Then, reaction of the ensuing alcohol with phosphorus tribromide substitutes the hydroxyl group with a bromine group. Lastly, treatment of the alkyl halide with NaCN replaces the Br atom with a cyano group, and hexanenitrile is formed.

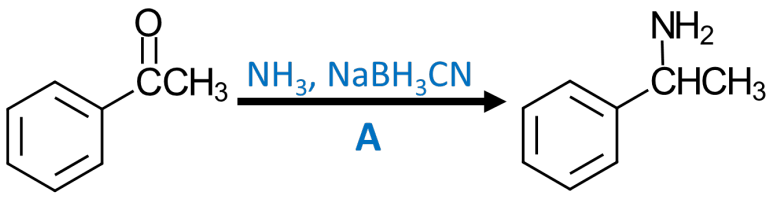


13.5: We proceed as we did in Problem 13.4 to synthesize hexanenitrile. Then, treatment with lithium aluminum hydride followed by an acid workup yields the amine in question.

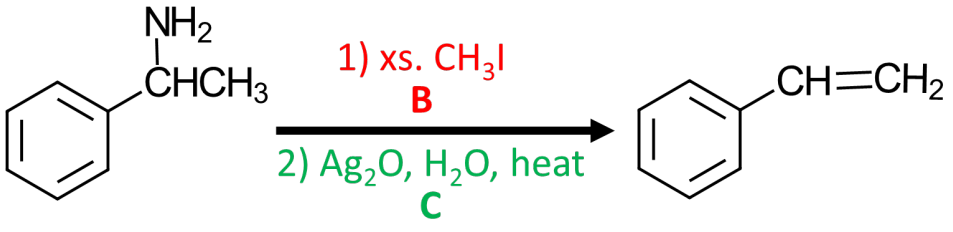


P.14 ➡ *Solution*

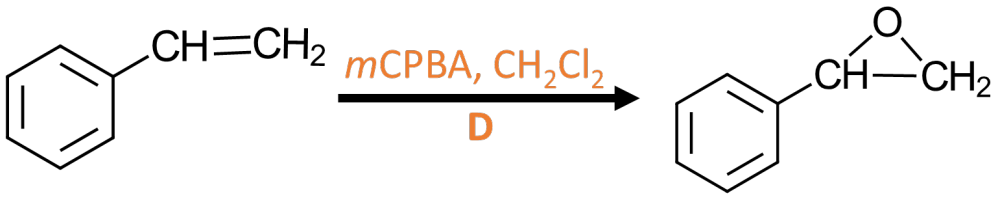
In the first reaction, the starting ketone is converted to a primary amine. this transformation can be achieved by reductive amination, treating a mixture of ketone and ammonia with $NaBH_3CN$; these are reagents A.



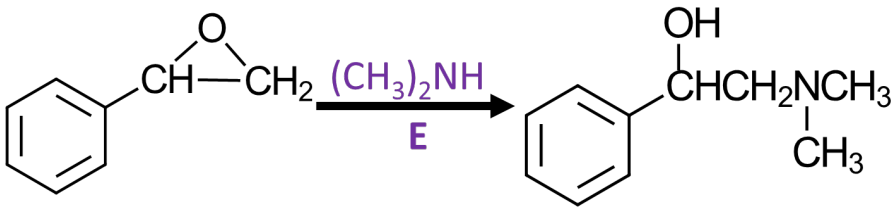
With the application of reagents B and C, the amine group is eliminated and the molecule is converted to an alkene; a Hofmann elimination has occurred. Accordingly, reagent B is excess methyl iodide and reagent C is a combination of silver oxide, water and heat.



Reagent D converts the alkene to an epoxide. Alkenes can be epoxidated by reaction with peroxycarboxylic acids. One common preparation used to achieve this conversion is *meta*-chloroperoxybenzoic acid in CH_2Cl_2; these are reagents D.



The final reaction is an S_N2 ring opening of the epoxide by nucleophilic substitution of the amine at the primary carbon; dimethylamine is reagent E.



REFERENCES

- CAREY, F. (2008). *Organic Chemistry*. 7th edition. New York: McGraw-Hill.
- KLEIN, D. (2017). *Organic Chemistry*. 3rd edition. Hoboken: John Wiley and Sons.
- MCMURRY, J. (2008). *Organic Chemistry.* 7th edition. Belmont: Thomson.
- VOLLHARDT, P. and SCHORE, N. (2014). *Organic Chemistry: Structure and Function.* 7th edition. New York: W.H. Freeman.
- WADE, L. and SIMEK, J. (2016). *Organic Chemistry.* 9th edition. Upper Saddle River: Pearson.

Got any questions related to this quiz? We can help!
Send a message to contact@montogue.com and we'll
answer your question as soon as possible.