

Montogue

Quiz CH207

Organic Chemistry

Carboxylic Acids and their Derivatives

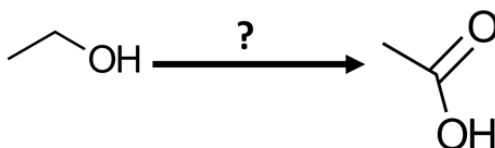
Lucas Monteiro Nogueira

►► PROBLEMS

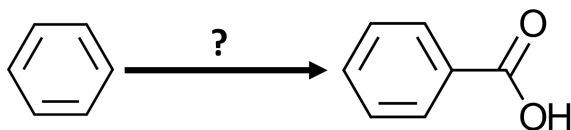
► Problem 1

Let's begin by reviewing some reactions that may be used to prepare carboxylic acids. Identify the reagents you would use to perform the following transformations.

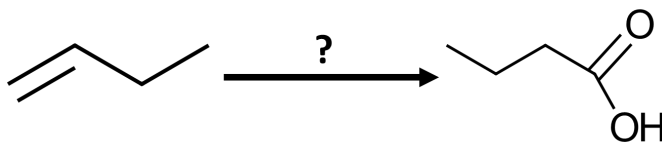
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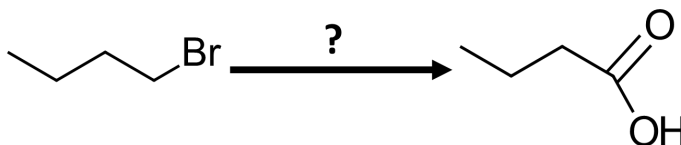
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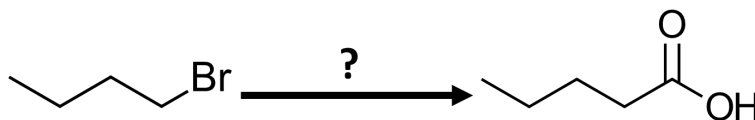
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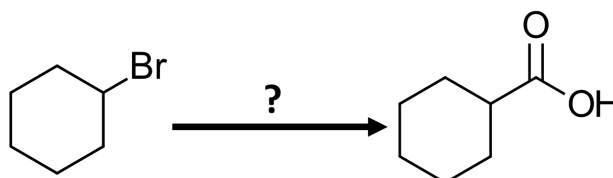
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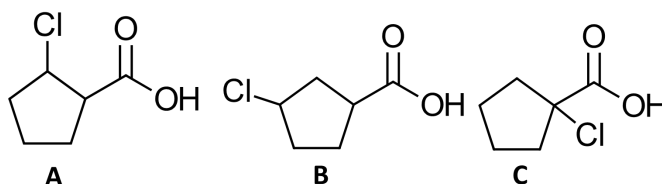


1.6.



► Problem 2

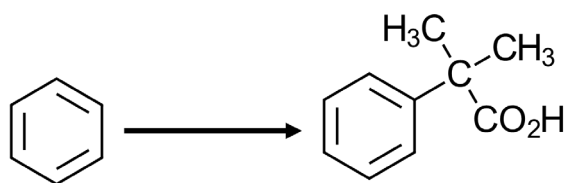
Rank the three following acids in order of increasing acidity.



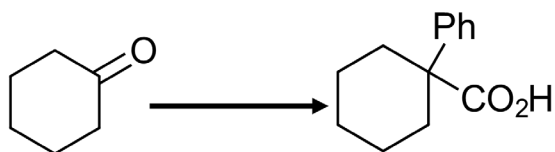
► **Problem 3** (McMurry, 2008, w/ permission)

How would you carry out the following transformations? More than one step is required in each case.

3.1.

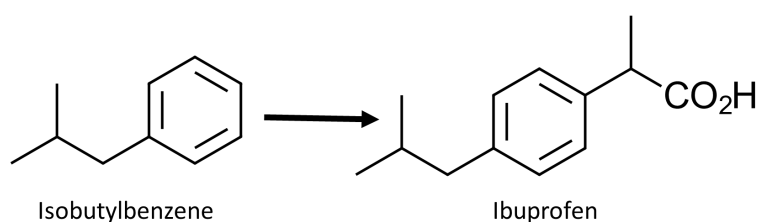


3.2.



► **Problem 4** (McMurry, 2008, w/ permission)

Show how you might prepare the anti-inflammatory agent ibuprofen starting with isobutylbenzene. More than one step is needed.



► **Problem 5** (McMurry, 2008, w/ permission)

Using ^{13}C as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?

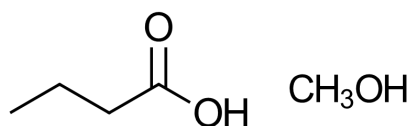
5.1. $\text{CH}_3\text{CH}_2^{13}\text{CO}_2\text{H}$

5.2. $\text{CH}_3^{13}\text{CH}_2\text{CO}_2\text{H}$

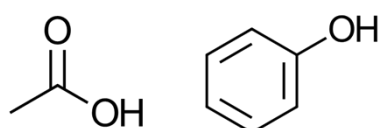
► **Problem 6**

Draw and name the esterification products of the following acid/alcohol pairs.

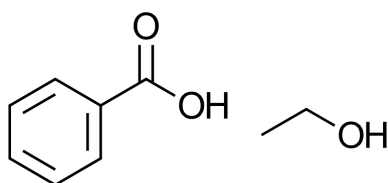
6.1.



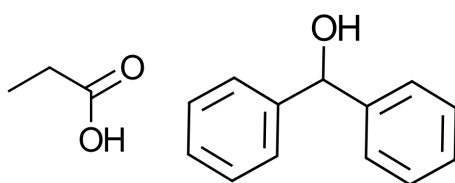
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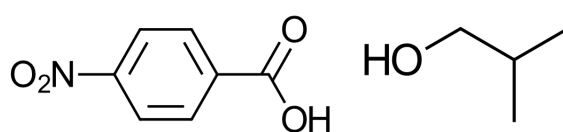
6.3.



6.4.



6.5.



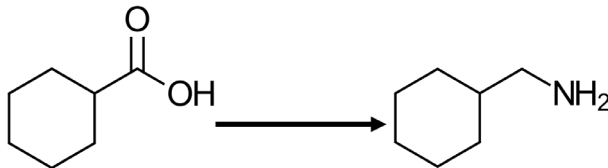
► **Problem 7**

Let's study reactions involving carboxylic acid derivatives. Identify reagents that will accomplish each of the following transformations.

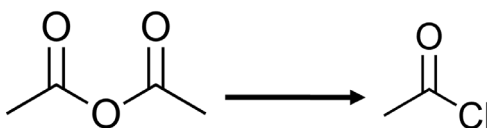
7.1.



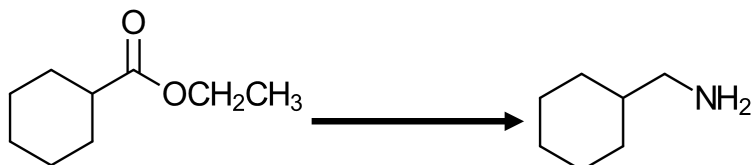
7.2.



7.3.



7.4.



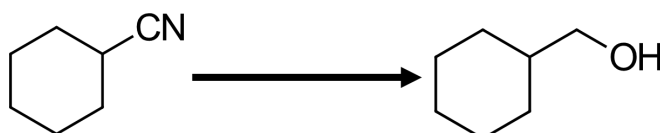
7.5.



7.6.



7.7.

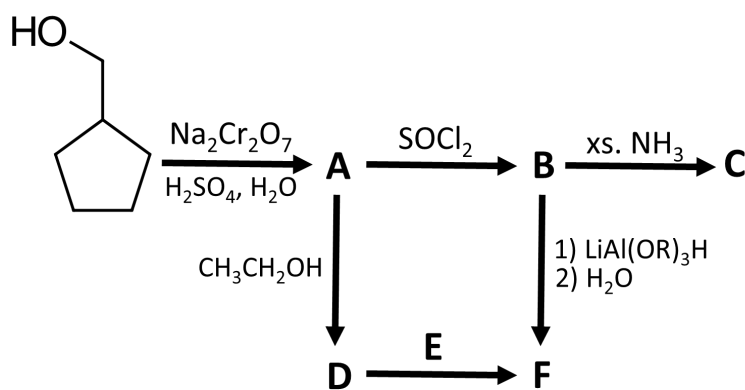


7.8.



► **Problem 8** (Klein, 2017)

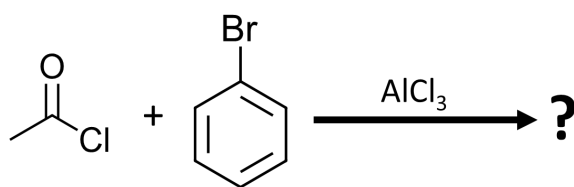
Determine the structures of compounds A through F. Compound E is a reagent.



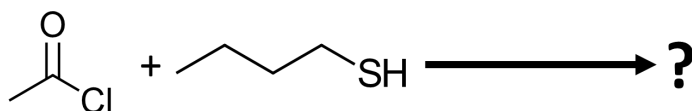
► **Problem 9** (Carey, 2008, w/ permission)

Write a structural formula for the principal organic product or products of each of the following reactions.

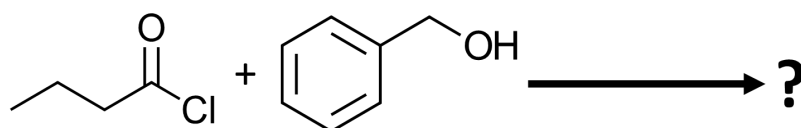
9.1.



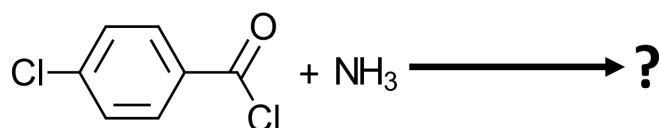
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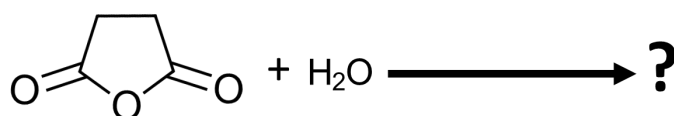
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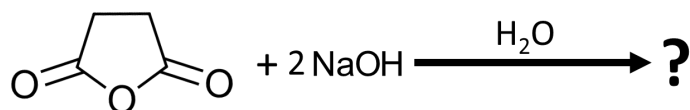
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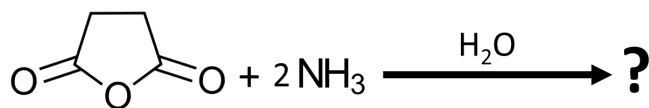
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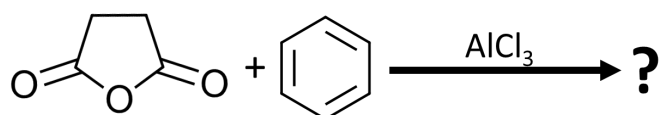
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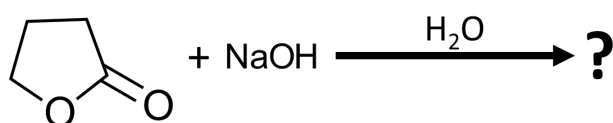
9.7.



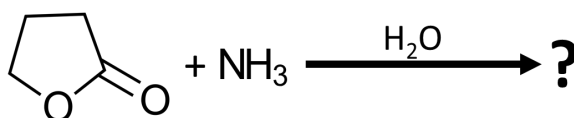
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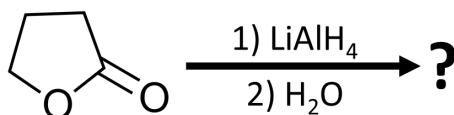
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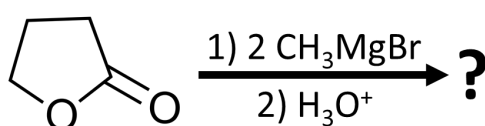
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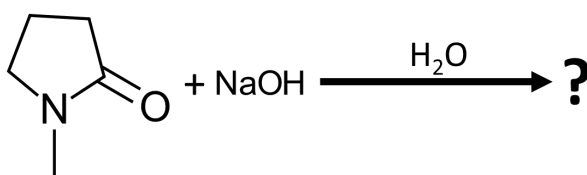
9.11.



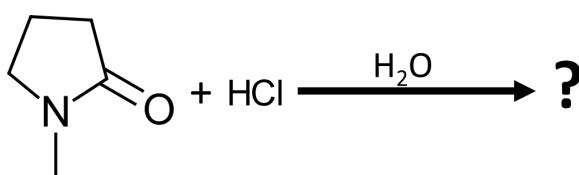
9.12.



9.13.



9.14.



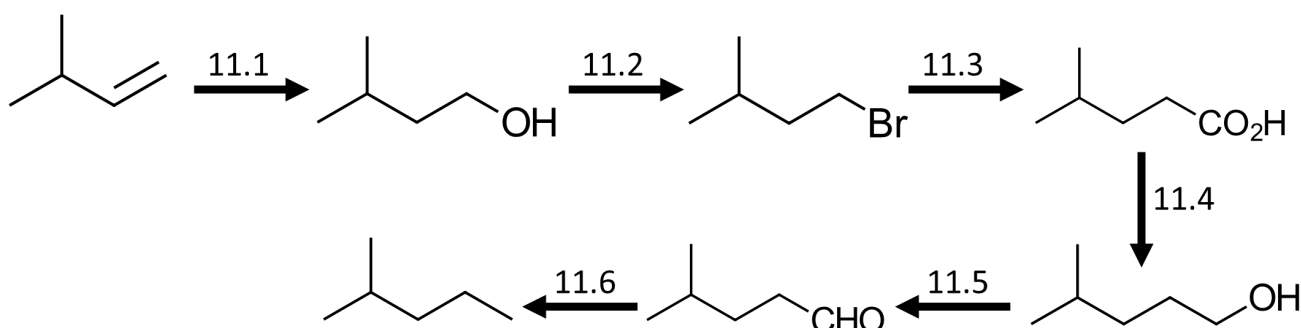
► **Problem 10** (Carey, 2008, w/ permission)

Using toluene, sodium cyanide, and carbon dioxide as the only sources of carbon atoms, along with any necessary inorganic reagents, show how you would prepare each of the following.

- 10.1. Benzoyl chloride
- 10.2. Benzoic anhydride
- 10.3. Benzyl benzoate
- 10.4. Benzamide
- 10.5. Benzonitrile
- 10.6. Benzyl cyanide
- 10.7. Phenylacetic acid
- 10.8. *p*-Nitrobenzoyl chloride
- 10.9. *m*-Nitrobenzoyl chloride

► **Problem 11** (Modified from McMurry, 2008)

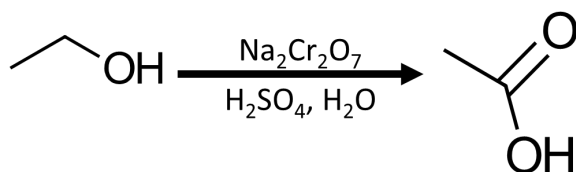
Identify the missing reagents in the following scheme.



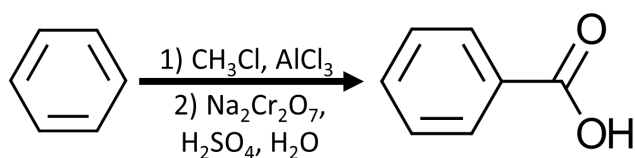
►► **SOLUTIONS**

P.1 → **Solution**

1.1: Ethanol can be converted to acetic acid by oxidation with chromic acid.

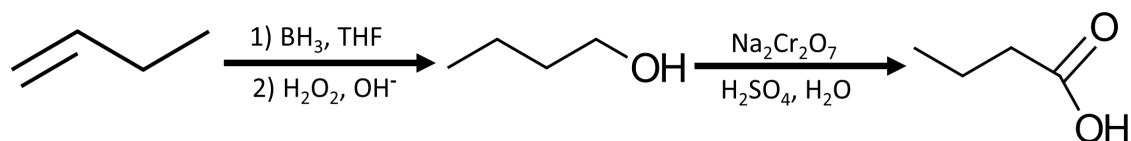


1.2: The conversion of benzene to benzoic acid requires the installation of a carbon atom on the skeleton of the starting material. One approach to attain this transformation is to install a methyl group using a Friedel-Crafts alkylation (CH_3Cl , AlCl_3), followed by an oxidation of the methyl group under strongly oxidizing conditions.

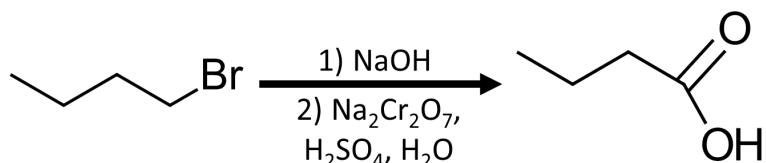


Klein notes that there are other acceptable solutions. One alternative pathway is to brominate benzene and treat the resulting bromobenzene with magnesium, yielding phenyl magnesium bromide. This Grignard reagent can then be treated with CO_2 , followed by acid workup, to yield benzoic acid.

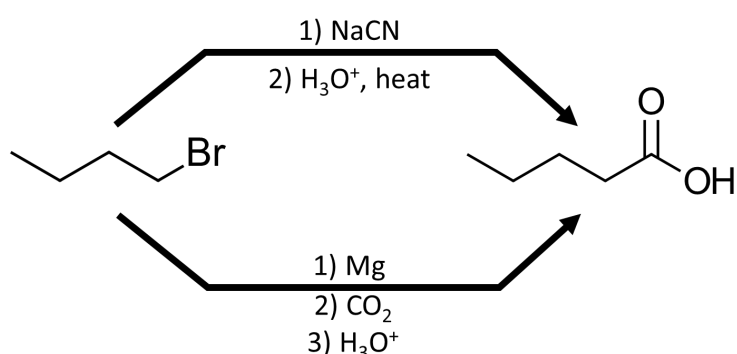
1.3: We begin by hydroxylating 1-butene via hydroboration/oxidation. Then, we oxidize the ensuing alcohol with chromic acid.



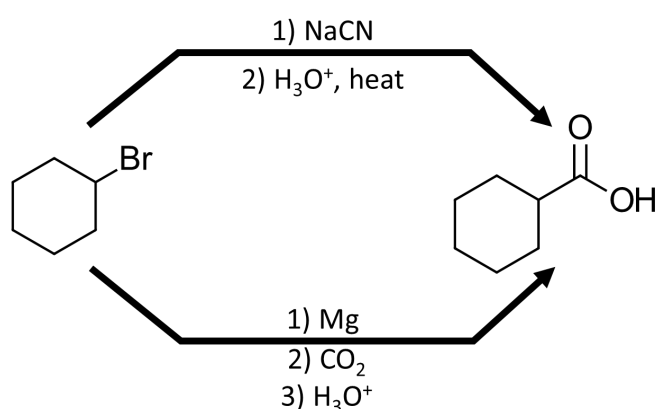
1.4: We need to convert bromobutane to butanoic acid. To achieve this transformation, we first substitute the bromine group of the starting material with a hydroxyl group by reacting it with NaOH under $\text{S}_{\text{N}}2$ conditions. Next, we oxidize the ensuing alcohol with chromic acid.



1.5: The starting material (1-bromobutane) has four carbon atoms, whereas pentanoic acid has five. One way to introduce a fifth carbon atom in the starting material is to perform a $\text{S}_{\text{N}}2$ substitution with sodium cyanide (NaCN), yielding valeronitrile. Hydrolysis of this nitrile (H_3O^+ , heat) gives the desired carboxylic acid. An alternate approach is to convert the starting alkyl halide to the corresponding Grignard reagent with magnesium, followed by reaction with CO_2 to produce a carboxylate. Protonation with aqueous acid completes the synthesis.



1.6: 1-Bromocyclohexane can be converted to cyclohexane carboxylic acid by either of the same pathways suggested in the previous problem.

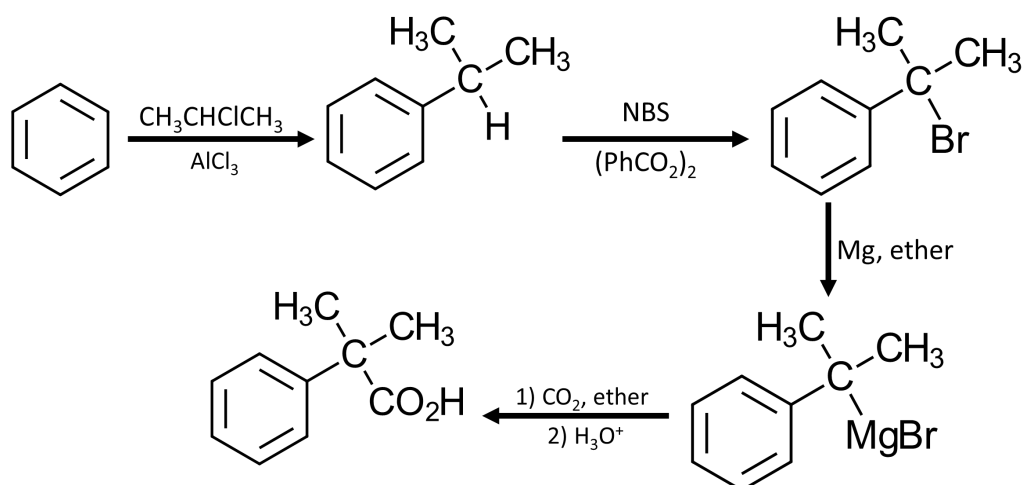


P.2 → Solution

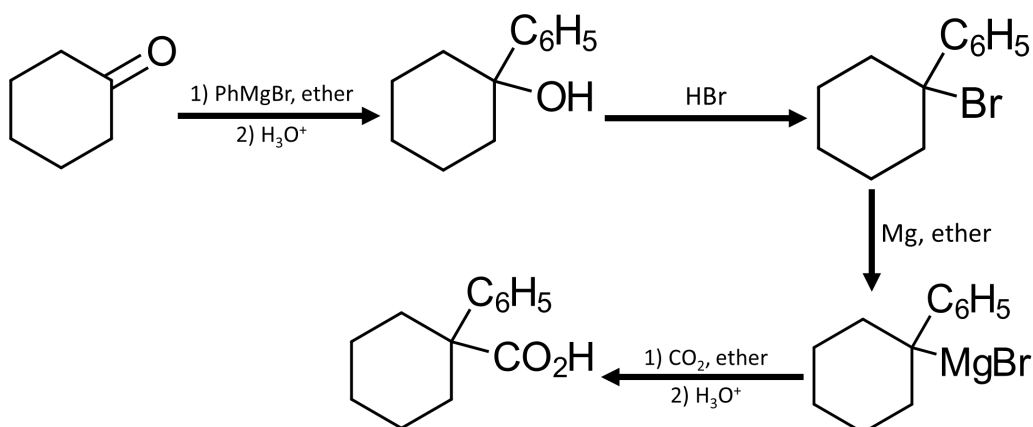
The acidity of these compounds is associated to the electron-withdrawing chlorine group to the carboxylic acid group. The closer the chlorine atom is to the carboxylic acid, the more it stabilizes the anionic charge on the conjugate base. Accordingly, the strongest acid in the series has the chlorine atom *alpha* to the carboxylic acid, followed by the isomer with the chlorine atom on a *beta* position, and then the isomer with a chlorine atom on a *gamma* position. Accordingly, the correct order, from least acid to most acid, is **B < A < C**.

P.3 → Solution

3.1: We begin by alkylating the benzene ring with a propyl group. Next, we perform an allylic bromination of the propyl group. Reaction with magnesium in ether converts the ensuing molecule to an organometallic compound. Finally, reaction with carbon dioxide followed by an acid workup introduces a carboxylic acid on the molecule. McMurry notes that other routes are possible. The present pathway was chosen because it has relatively few steps and because the Grignard reagent can be prepared without competing reactions. Nitrile hydrolysis is not a possible route here because the halide precursor is tertiary and does not undergo S_N2 substitution.

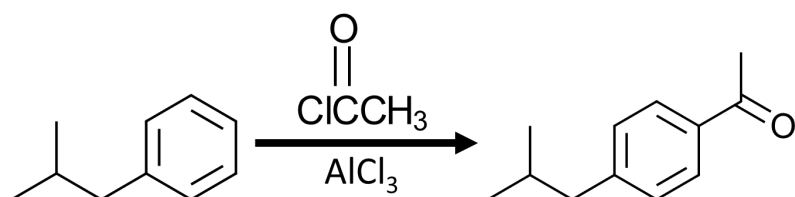


3.2: Reaction of cyclohexanone with phenylmagnesium bromide introduces an aromatic ring and an alcohol group on the molecule. Reaction with HBr replaces the hydroxyl group with a bromine group. The ensuing molecule can be treated with magnesium in ether to yield an organometallic compound. Finally, a Grignard reaction with carbon dioxide followed by an acid workup introduces a carboxylic acid on the molecule. McMurry notes that, as in the previous problem, nitrile hydrolysis is not a viable route to the compound in question.

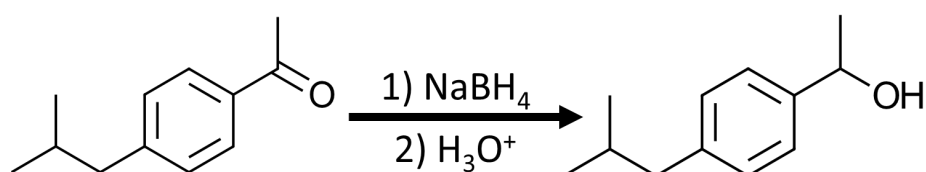


P.4 → Solution

We begin by acylating isobutylbenzene with acetyl chloride.



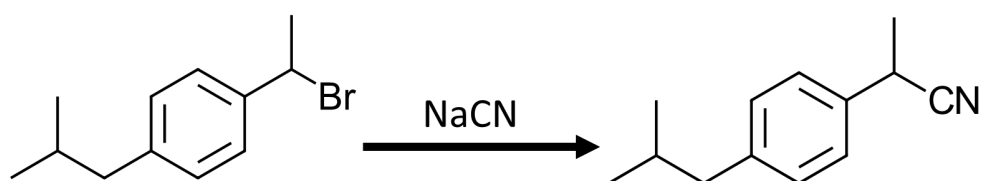
Next, we convert the carbonyl group to an alcohol by addition of hydride.



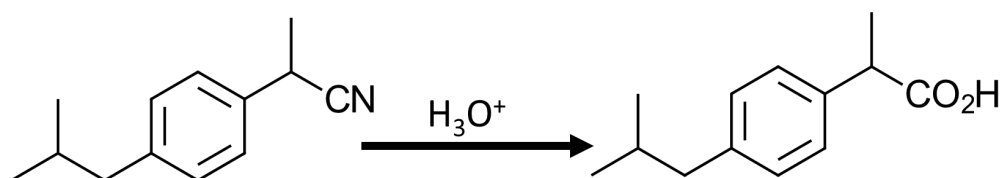
Next, we substitute the ensuing hydroxyl group with Br by reacting the alcohol with phosphorus tribromide.



Next, we perform a S_N2 substitution by reacting the product above with sodium cyanide.

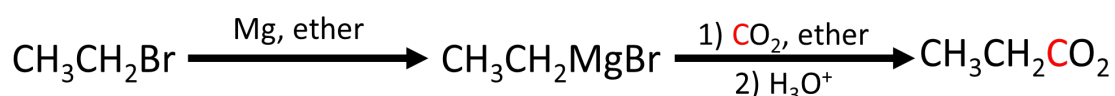


Finally, we hydrolyze the ensuing nitrile to yield ibuprofen.

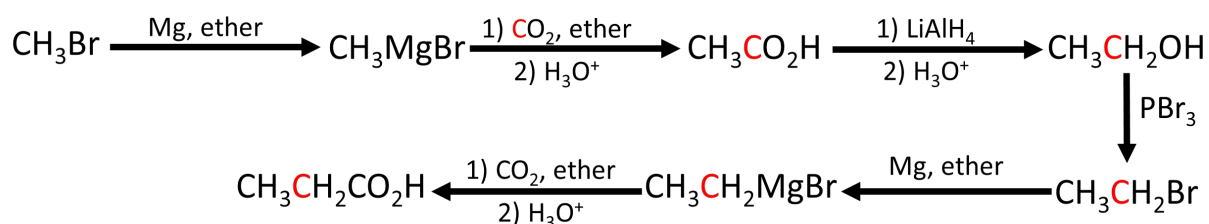


P.5 → Solution

5.1: Begin with bromoethane, which contains two carbons. The third carbon, which is labeled, comes from $^{13}\text{CO}_2$; this carbon is highlighted in red below.

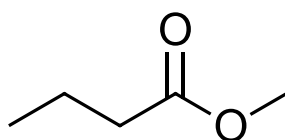


5.2: Begin with bromomethane, which contains one carbon. The second carbon, which is labeled, comes from $^{13}\text{CO}_2$; this carbon is highlighted in red below. The third carbon comes from unlabeled CO_2 and is attached to the carbon chain in a second Grignard reaction.

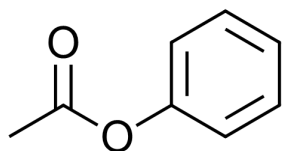


P.6 → Solution

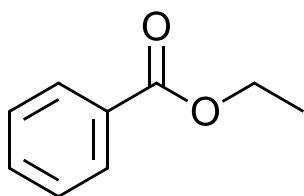
6.1: The acid is butanoic acid and the alcohol is methanol. The esterification product of these two compounds is methyl butyrate.



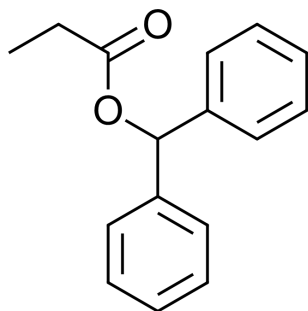
6.2: The acid is acetic (ethanoic) acid and the alcohol is phenol. The esterification product of these two compounds is phenyl acetate.



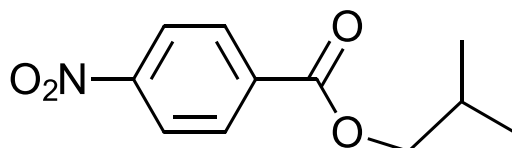
6.3: The acid is benzoic acid and the alcohol is ethanol. The esterification product of these two compounds is ethyl benzoate.



6.4: The acid is propanoic acid and the alcohol is diphenylmethanol. The esterification product of these two compounds is benzhydryl propionate.

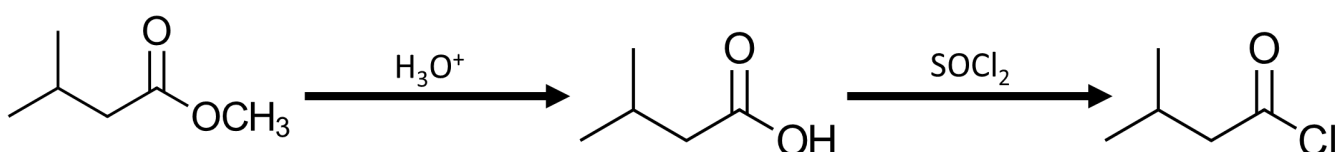


6.5: The acid is *p*-nitrobenzoic acid and the alcohol is isobutanol. The esterification product of these two compounds is isobutyl *p*-nitrobenzoate.

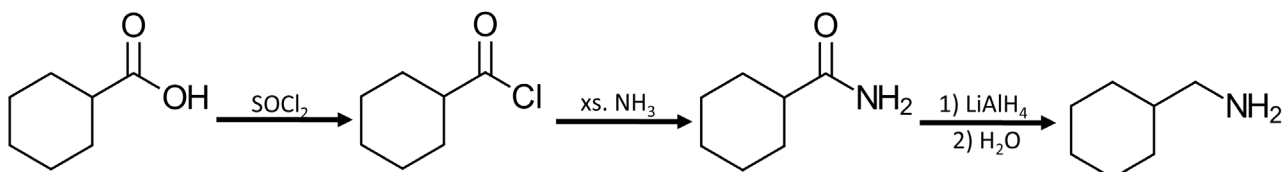


P.7 → **Solution**

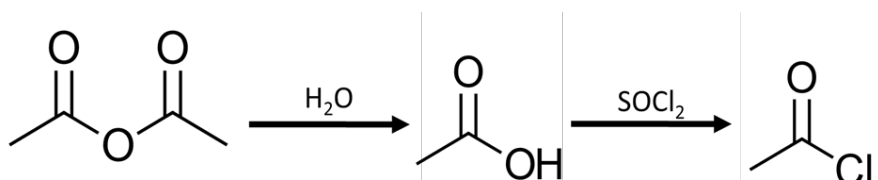
7.1: The starting material is an ester (methyl 3-methylbutyrate) and the desired molecule is an acid chloride (isovaleryl chloride). The ester can be converted to a carboxylic acid by acid hydrolysis; then, treatment with thionyl chloride yields the acid chloride.



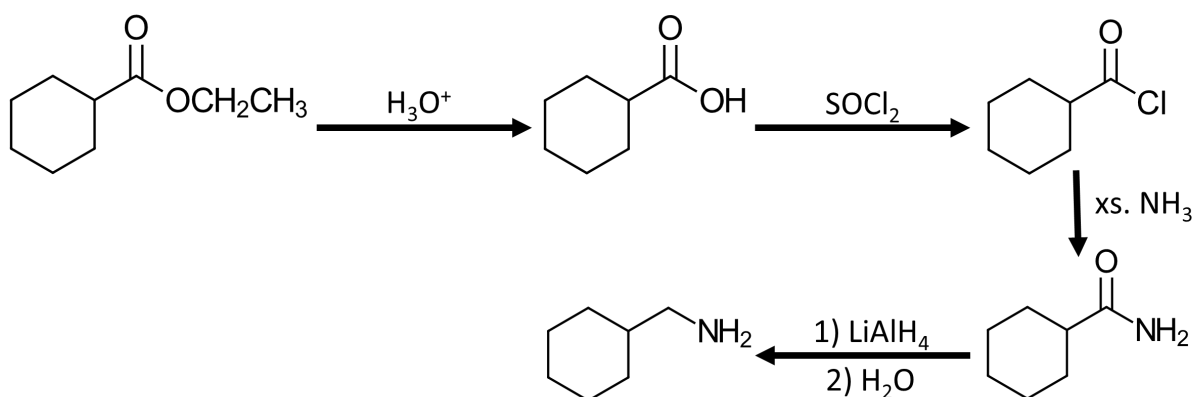
7.2: The starting material is a carboxylic acid (cyclohexanecarboxylic acid) and the desired molecule is an amine ((cyclohexylmethyl)amine). Upon treatment with thionyl chloride, a carboxylic acid is converted to the corresponding acid chloride. Treatment of the acid chloride with excess ammonia produces an amide. Finally, reduction of the amide with LiAlH_4 followed by protonation with water yields the desired primary amine.



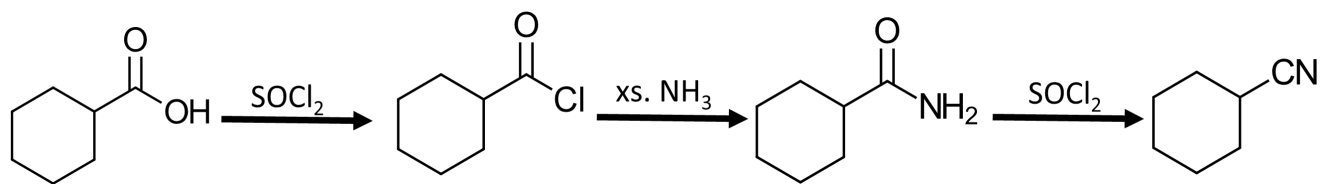
7.3: The starting material is an acid anhydride (acetic anhydride) and the desired molecule is an acid chloride (acetyl chloride). Hydrolysis of acetic anhydride produces acetic acid; then, treatment with thionyl chloride yields the acid chloride.



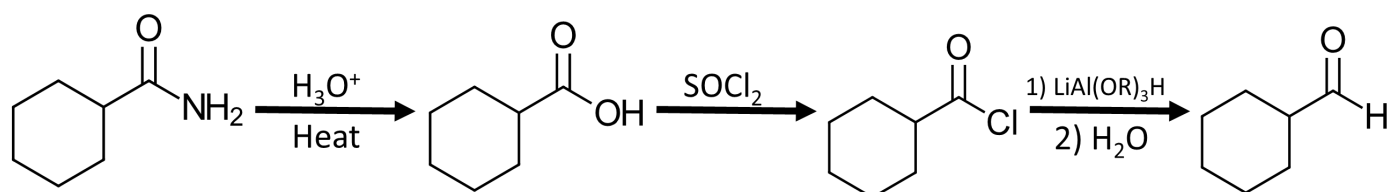
7.4: The starting material is an ester (ethyl cyclohexanecarboxylate) and the desired molecule is an amine ((cyclohexylmethyl)amine). We begin by hydrolyzing the ester to a carboxylic acid. The resulting acid is converted to an acid chloride by treatment with SOCl_2 . Reaction of this acid chloride with excess ammonia gives rise to an amide. Finally, reduction of the amide with LiAlH_4 followed by water workup yields the desired primary amine.



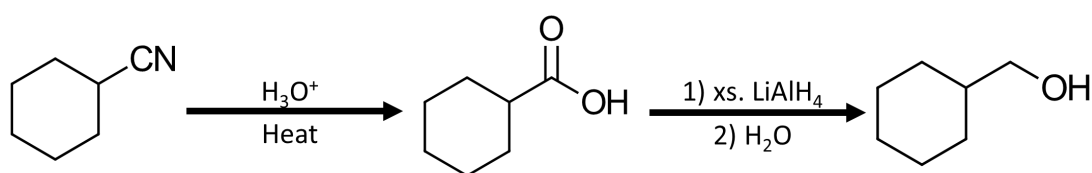
7.5: The starting material is a carboxylic acid (cyclohexanecarboxylic acid) and the desired molecule is a nitrile (cyclohexanecarbonitrile). We begin by converting the acid to an acid chloride by dint of a reaction with thionyl chloride. Reaction of the acid chloride with excess ammonia yields an amide. Finally, the ensuing amide can be dehydrated with SOCl_2 to yield the desired nitrile.



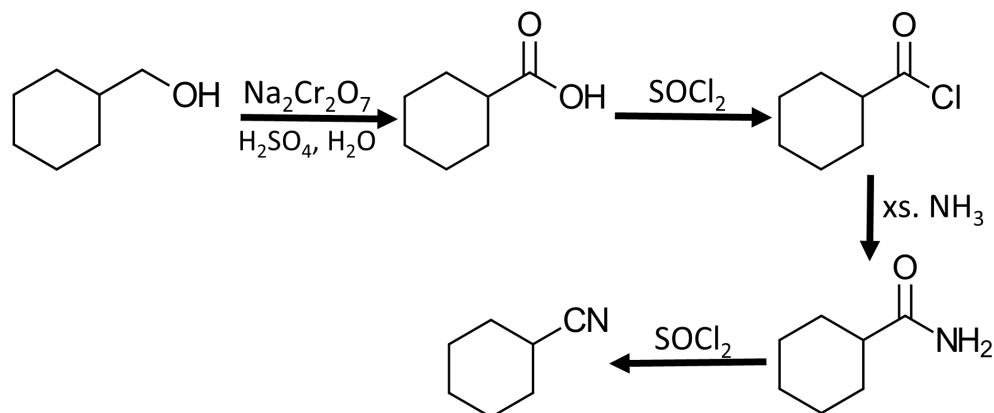
7.6: The starting material is an amide (cyclohexanecarboxamide) and the desired molecule is an aldehyde (cyclohexanecarbaldehyde). We begin by hydrolyzing the amide to a carboxylic acid. Treatment of the ensuing acid with thionyl chloride produces an acid chloride. Finally, reaction with a sterically hindered lithium trialkoxy aluminium hydride reagent followed by water workup produces the desired aldehyde.



7.7: The starting material is a nitrile (cyclohexanecarbonitrile) and the desired molecule is an alcohol (cyclohexylmethanol). The ester can be converted to a carboxylic acid by acid hydrolysis; then, reduction with LiAlH_4 followed by water workup yields the desired alcohol.



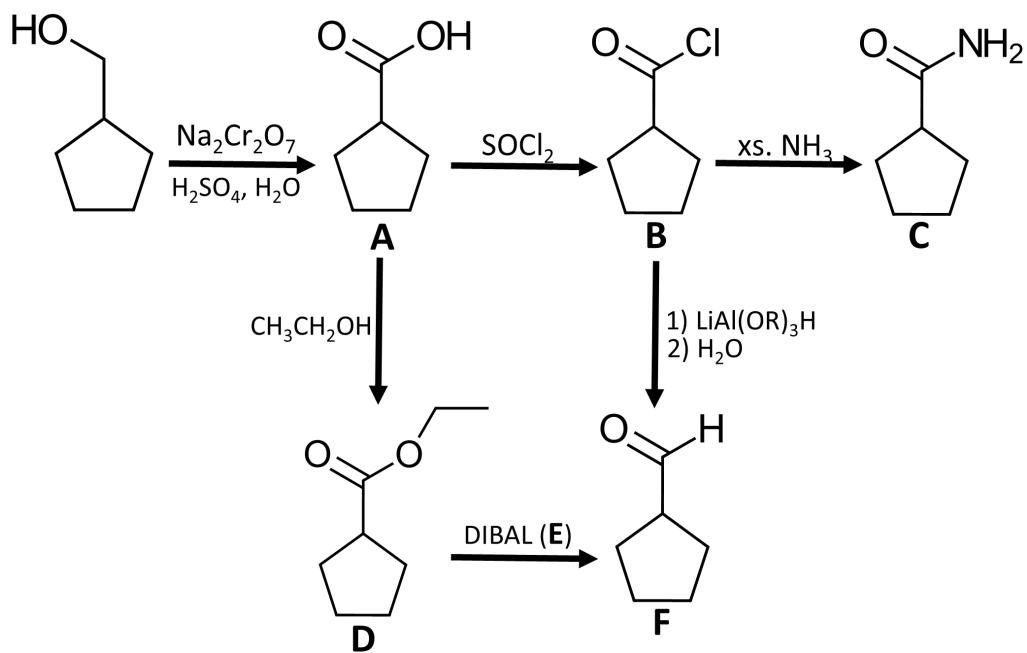
7.8: This is an inverted version of the transformation addressed in the previous problem. We begin by converting cyclohexylmethanol to a carboxylic acid via treatment with chromic acid. Next, we react the acid with thionyl chloride to create an acid chloride. Reaction of this chloride with ammonia produces an amide. Finally, treating the amide with SOCl_2 produces the desired nitrile.



P.8 → Solution

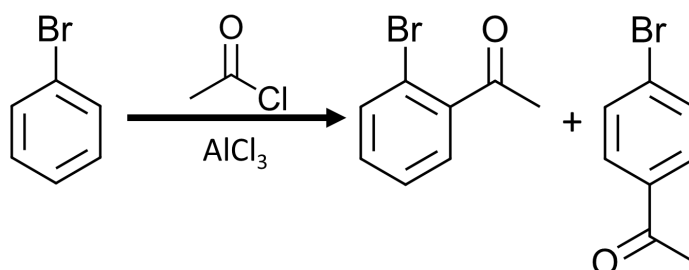
The starting material is cyclopentylmethanol. In the first reaction, this alcohol is oxidized with chromic acid to yield cyclopentanecarboxylic acid, which is compound A. Upon treatment with thionyl chloride, this acid becomes cyclopentanecarbonyl chloride, which is compound B. Reaction of this acid chloride with ammonia produces cyclopentanecarboxamide, which is compound C.

The acid obtained in the first reaction can undergo esterification with ethanol to yield ethyl cyclopentanecarboxylate, which is compound D. Treatment of this ester with some reagent E should yield a compound F. From the diagram, we know that F is also the product of treatment of cyclopentanecarbonyl chloride (compound B) with a sterically hindered lithium trialkoxy aluminium hydride reagent, followed by water workup. This type of reaction is used to convert acid chlorides to aldehydes; accordingly, compound F can only be cyclopentanecarbaldehyde. Reagent E is diisobutylaluminum chloride (DIBAL), which can be used to convert esters to aldehydes.

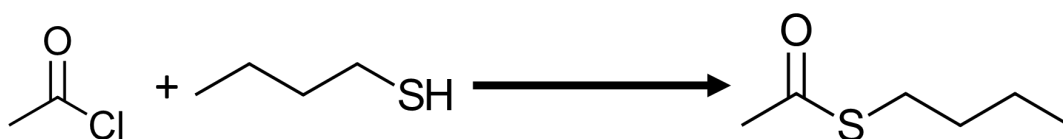


P.9 → **Solution**

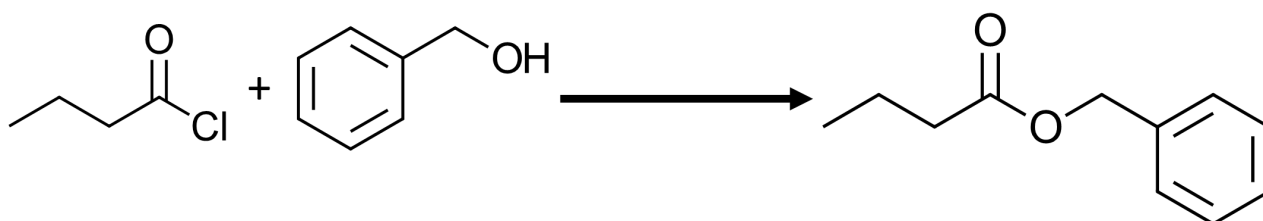
9.1: Although this reaction involves an acid chloride, the process in question is actually a Friedel-Crafts acylation, which is usually addressed in the electrophilic aromatic substitution chapters of organic chemistry textbooks. These reactions are the subject of Quiz CH205 – *Electrophilic Aromatic Substitution*. Recall that bromine is an *ortho-para* director; thus, acylation of bromobenzene should yield a mixture of *o*-bromoacetophenone and *p*-bromoacetophenone.



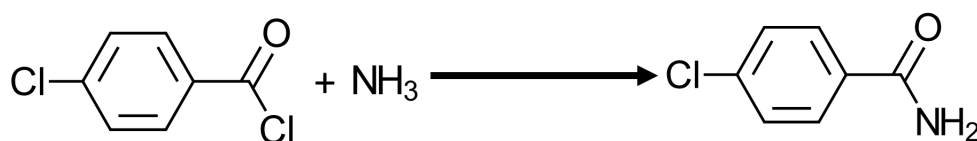
9.2: Acid chlorides react with thiols to give thioesters. The product in this case is *S*-butyl ethanethioate.



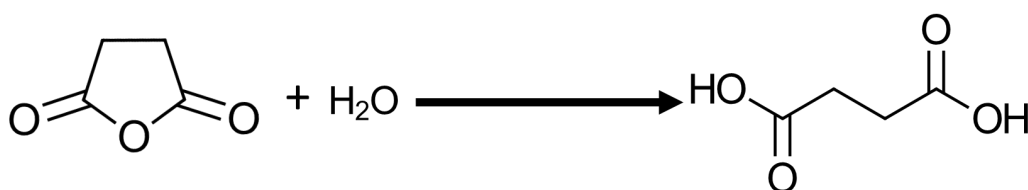
9.3: Acid chlorides convert alcohols to esters. The product in this case is benzyl butyrate.



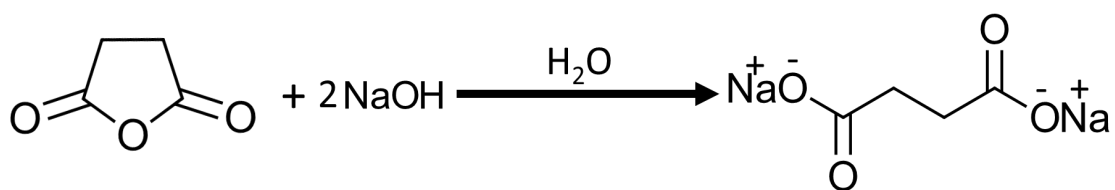
9.4: Acid chlorides react with ammonia to yield amides. The product in this case is *p*-chlorobenzamide.



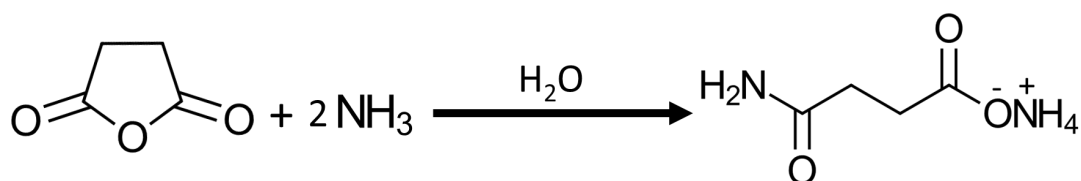
9.5: The starting material is a cyclic anhydride (succinic anhydride). Acid anhydrides react with water to yield two carboxylic acid functions. When the anhydride is cyclic, a dicarboxylic acid results. The product in this case is succinic acid.



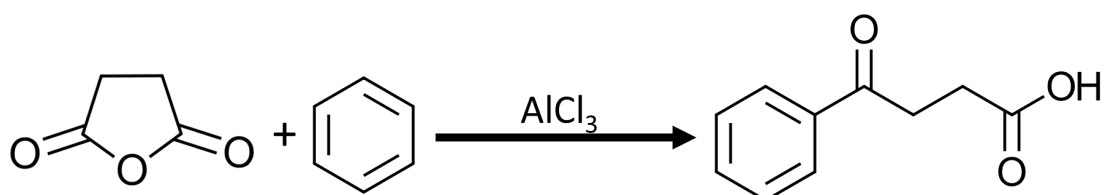
9.6: In aqueous sodium hydroxide the anhydride undergoes saponification and is converted to the disodium salt of the diacid. The product in this case is sodium succinate.



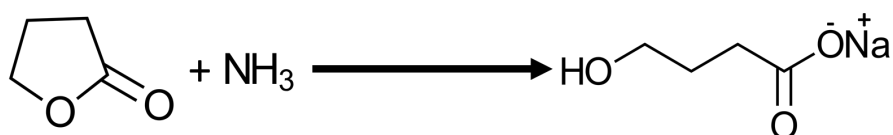
9.7: One of the carbonyl groups of the cyclic anhydride is converted to an amide function on reaction with ammonia. The other, the one that would become a carboxylic acid group, is converted to an ammonium carboxylate salt. The product in this case is ammonium succinate.



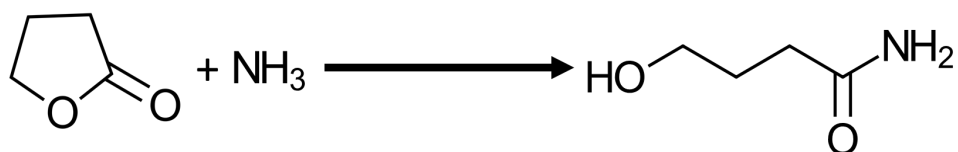
9.8: This is a Friedel-Crafts acylation reaction; like acid chlorides, some acid anhydrides can also be used as acylation agents. The product in this case is 3-benzoylpropionic acid.



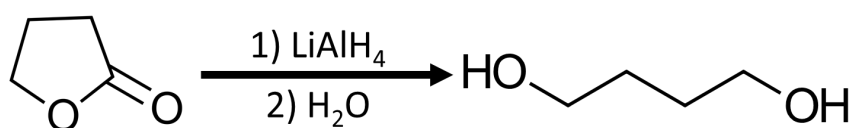
9.9: This cyclic ester, a lactone, undergoes saponification with sodium hydroxide to yield an alcohol and a carboxylate salt. The resulting salt is sodium 4-hydroxybutanoate.



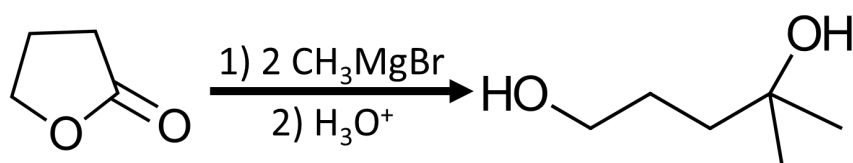
9.10: The cyclic ester reacts with ammonia to give an amide and an alcohol. The resulting amide is 4-hydroxybutyramide.



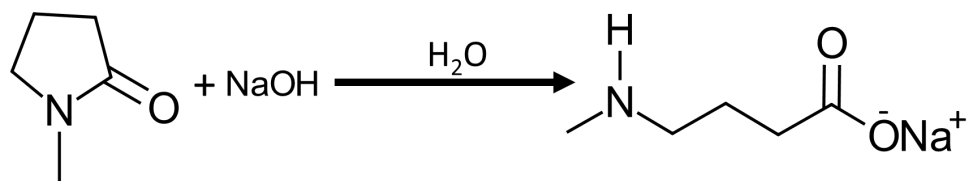
9.11: Lithium aluminum hydride reduces esters to two alcohols; the one derived from the acyl group is a primary alcohol. Reduction of a cyclic ester gives a diol. The product in this case is 1,4-butanediol.



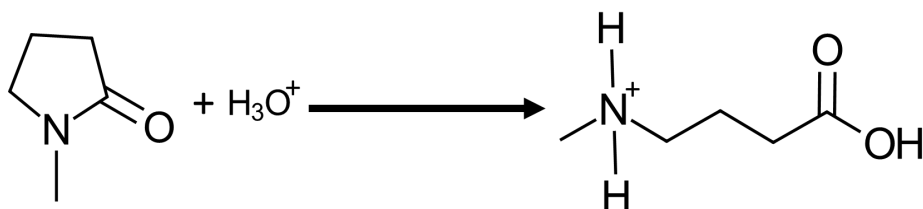
9.12: Grignard reagents react with esters to give primary alcohols. The product in this case is 4-methyl-1,4-pentanediol.



9.13: This cyclic amide, a lactam, is hydrolyzed in aqueous base to yield an amine and a carboxylate salt. The resulting organic salt in this case is 4-(methylamino)butanoate.

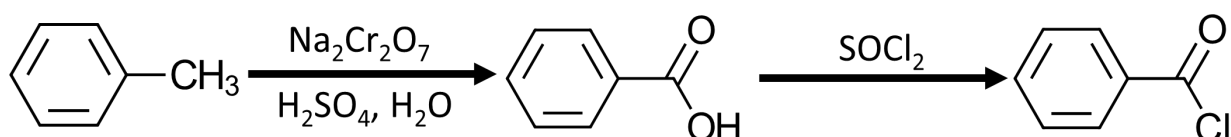


9.14: In acid solution, amides yield carboxylic acids and ammonium salts. The product in this case is 4-(methylammonio)butanoic acid.

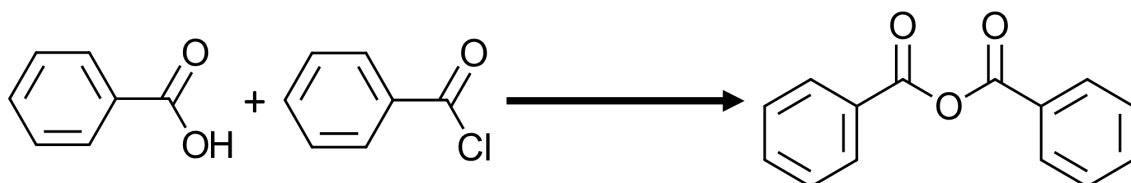


P.10 → **Solution**

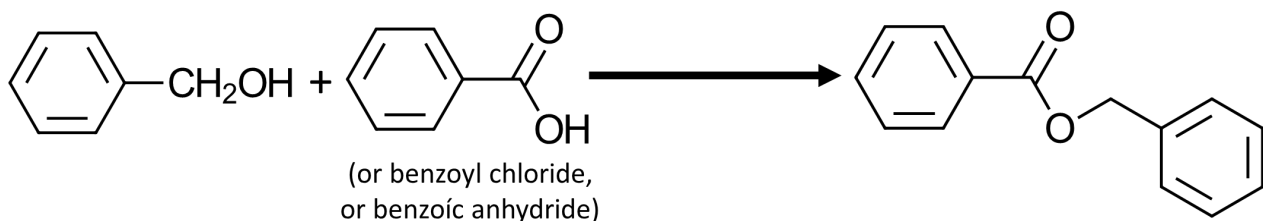
10.1: Benzoyl chloride is made from benzoic acid. Oxidize toluene to benzoic acid, and then treat with thionyl chloride.



10.2: Benzoic anhydride can be produced by reacting benzoic acid with benzoyl chloride. As mentioned in Problem 10.1, the former can be produced by oxidizing toluene, while the latter can be obtained by treating benzoic acid with thionyl chloride.

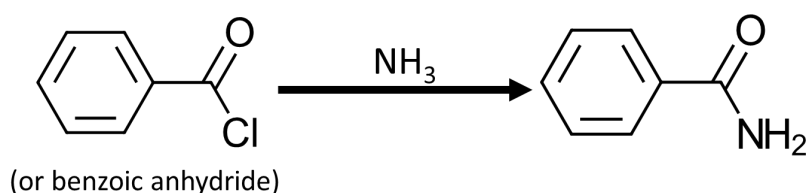


10.3: Benzoic acid, benzoyl chloride, and benzoic anhydride have been prepared in previous parts of this problem. Carey notes that any of these can be converted to benzyl benzoate by reaction with benzyl alcohol. The issue, then, becomes how to synthesize benzyl alcohol from toluene. This can be done by first brominating the methyl group by means of NBS or photohalogenation, followed by a nucleophilic substitution.

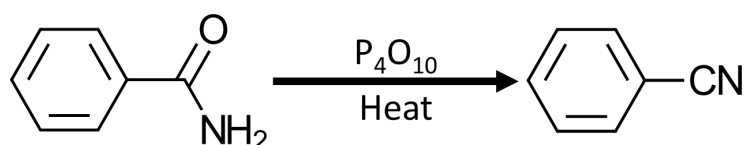


The product of this process is then reacted with benzoic acid, benzoyl chloride, or benzoic anhydride.

10.4: Benzamide is prepared by reacting excess ammonia with either benzoyl chloride, as produced in Problem 10.1, or benzoic anhydride, as produced in Problem 10.2.

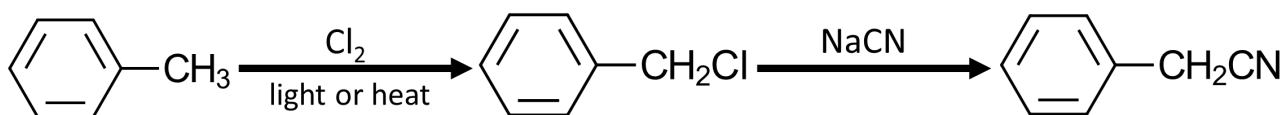


10.5: Benzonitrile can be obtained by dehydrating benzamide, which in turn is produced by reacting benzoyl chloride or benzoic anhydride with excess ammonia, as mentioned in the previous problem.

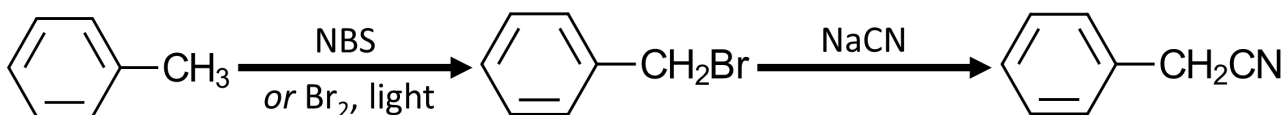


10.6: Benzyl cyanide is the product of nucleophilic substitution by cyanide ion on benzyl bromide or benzyl chloride. The benzyl halides are

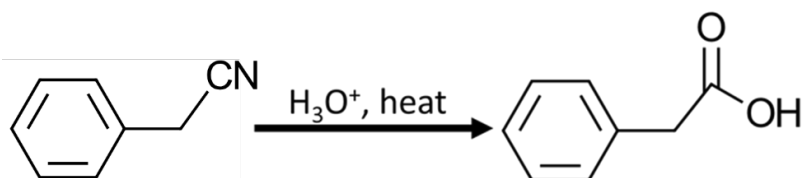
prepared by free-radical halogenation of the toluene side chain. That is, we may use the pathway below,



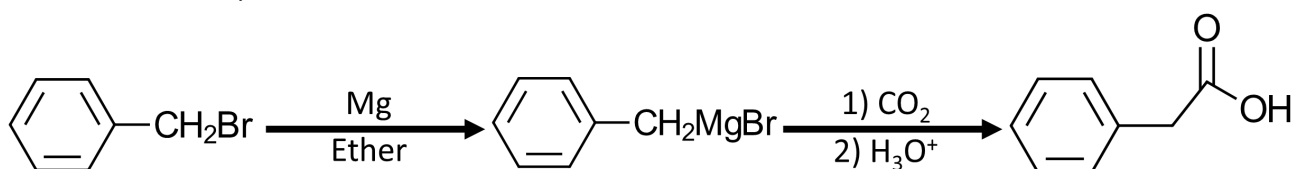
or this one,



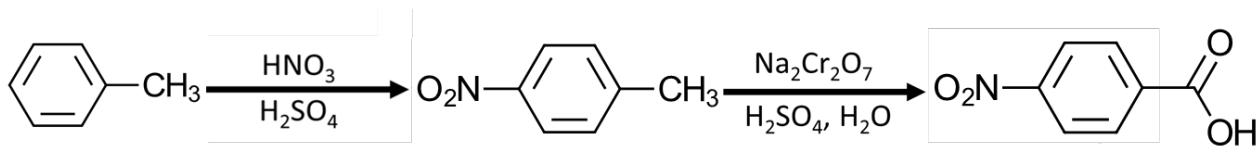
10.7: As mentioned in Problem 10.6, benzyl cyanide can be produced by halogenating toluene and subsequently treating it with NaCN. We can then hydrolyze benzyl cyanide to produce phenylacetic acid.



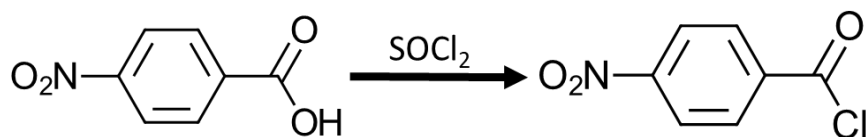
Alternatively, the Grignard reagent derived from benzyl bromide may be carboxylated.



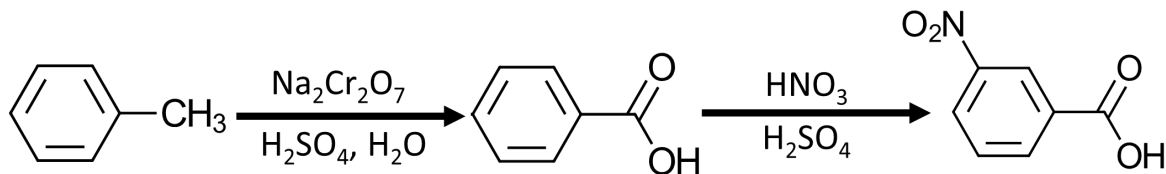
10.8: The first goal is to synthesize *p*-nitrobenzoic acid because this may be readily converted to the desired acyl chloride. First convert toluene to *p*-nitrotoluene; then oxidize. Nitration must precede oxidation of the side chain in order to achieve the desired *para* orientation.



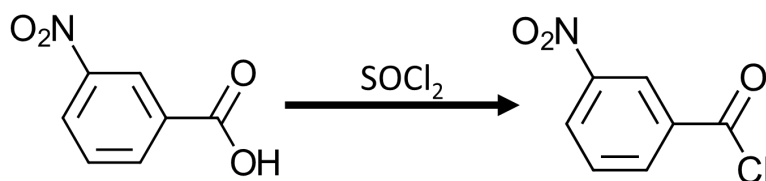
Treating *p*-nitrobenzoic acid with thionyl chloride yields the acid chloride we are looking for.



10.9: To make sure that the nitro group is incorporated in the *meta* position of the aromatic ring, we begin by oxidizing toluene to benzoic acid and only then do we nitrate the substrate. The carboxylic acid group is *meta* directing and should ensure that the nitro group is incorporated in the desired position.

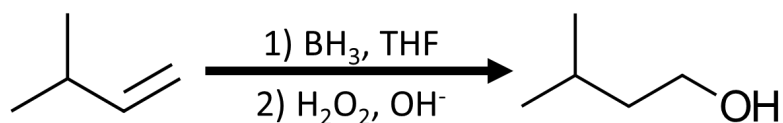


Treating *m*-nitrobenzoic acid with thionyl chloride yields the acid chloride we are looking for.

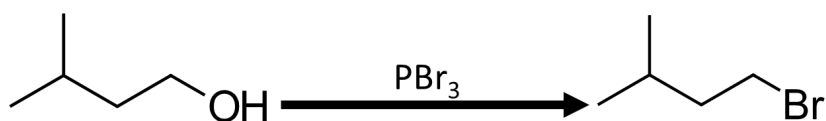


P.11 → Solution

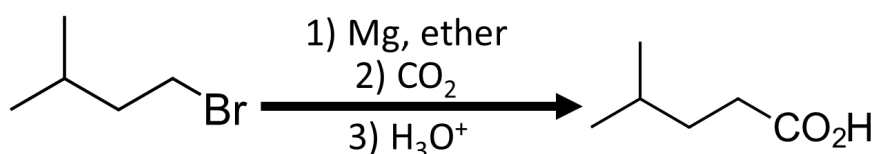
11.1: Process 11.1 is the hydroxylation of an alkene, with the hydroxyl group being added to the less substituted carbon. Such a transformation can be accomplished by hydroboration/oxidation.



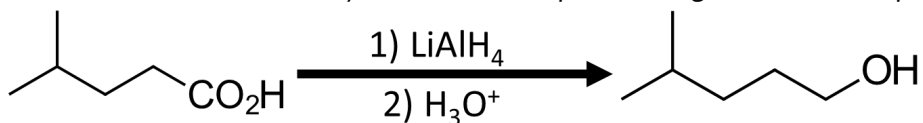
11.2: Process 11.2 is the substitution of the hydroxyl group obtained in the previous problem with a bromine group. Such a transformation can be achieved by treating the alcohol with phosphorus tribromide.



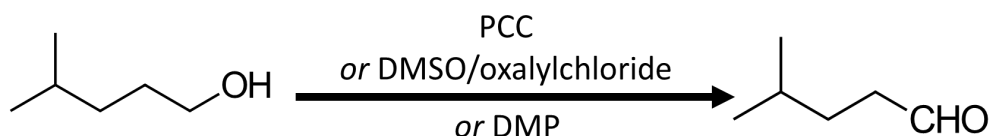
11.3: Process 11.3 is the substitution of the bromine group obtained in the previous problem with a carboxylic acid group. Such a transformation can be achieved if we first convert the haloalkane to a Grignard reagent by treating it with magnesium in ether, then carboxylate the organometallic compound with CO_2 , and lastly perform an aqueous workup. Another way to establish this transformation is to perform a nucleophilic substitution with NaCN and then hydrolyze the resulting nitrile in an acid medium.



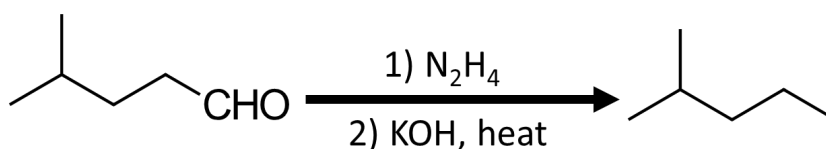
11.4: Process 11.4 is the reduction of the carboxylic acid obtained in the previous problem to an alcohol. This transformation can be attained by reacting the acid with lithium aluminum hydride and then performing an acid workup.



11.5: Process 11.5 is the oxidation of the hydroxyl group obtained in the previous problem to a carbonyl group. A number of reagent preparations can be used to oxidize alcohols to aldehydes, including pyridinium chlorochromate (PCC), DMSO/oxalyl chloride, and Dess-Martin periodinane (DMP).



11.6: Process 11.6 is the conversion of the aldehyde obtained in the previous problem to an alkane. One way to deoxygenate an aldehyde is to use Wolff-Kishner reduction, in which the substrate is treated with hydrazine and then reacted with a strong base such as KOH at high temperature.



►► 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.



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