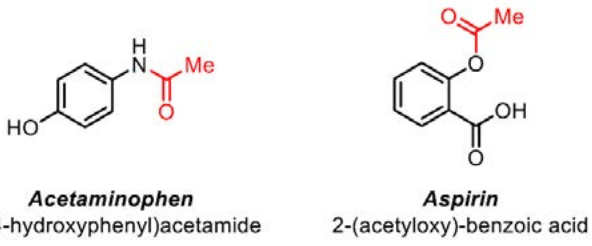
Syntheses of Acetaminophen and Aspirin

Introduction

Ethanoylation, a process better known as acetylation, is the introduction of an acetyl group (–$COCH_3$) onto a compound. The acetyl group is commonly encountered in organic synthesis, whether functioning as a (temporary) protecting group or present in a synthetic target (**Figure 1**).



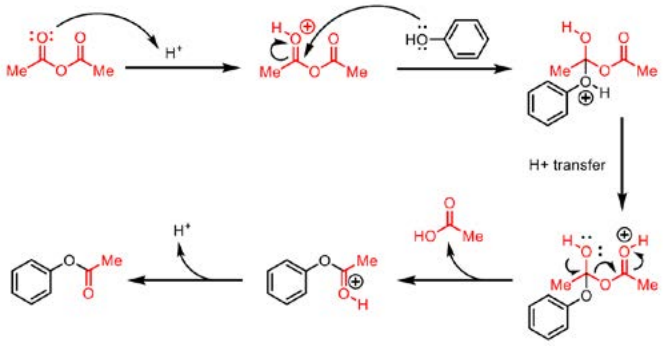
Acetaminophen
N-(4-hydroxyphenyl)acetamide

Aspirin
2-(acetyloxy)-benzoic acid

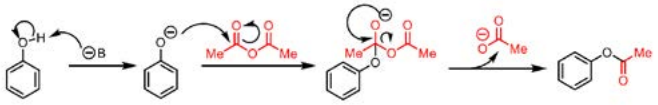
Figure 1: Acetylated (highlighted in red) pharmaceuticals

Acetylation can proceed through both acid- and base-catalyzed pathways. In acid-catalyzed acetylation, protonation of an acetic anhydride carbonyl activates the carbonyl's α-carbon for nucleophilic attack. Upon nucleophilic attack, subsequent tetrahedral intermediate formation, and a proton transfer, acetic acid is eliminated, furnishing the acetylated product (**Scheme 1**).

In base-catalyzed acetylation, a non-nucleophilic base deprotonates the atom to undergo acetylation, activating it for nucleophilic attack on acetic anhydride. Similar to acid-catalyzed acetylation, the acetylated product is furnished upon nucleophilic attack, tetrahedral intermediate formation, and elimination of acetate anion (**Scheme 2**).



Scheme 1: Acid-catalyzed acetylation of phenol with acetic anhydride



Scheme 2: Base-catalyzed acetylation of phenol with acetic anhydride

Through the microwave-assisted syntheses of acetaminophen and aspirin (outlined below), the principles of acetylation will be explored.

Materials and Methods

Reagents

Acetic anhydride, 4-aminophenol, deionized water, and 2-hydroxybenzoic acid.

Synthesis of Acetaminophen

Part I: Complete Reagent Table

Reagent	MW (g/mol)	Density (g/mL)	Equivalents	Amount (mmol)	Amount
4-aminophenol		---			0.30 g
acetic anhydride					0.27 mL
deionized water			---	---	5.0 mL

Part II: Procedure

1. Program a one-step "Dynamic" method. Method parameters include: (maximum) Temperature = 110 °C, (maximum) Power = 300 W, (maximum) Pressure = 300 psi, Hold Time = 60 sec, PowerMax = Off, and Stirring = High.
2. Charge a 10-mL vessel, equipped with stir bar, with 4-aminophenol (0.30 g). Add deionized water (5.00 mL), washing any particulates on vessel walls into solution, then acetic anhydride (0.27 mL).
3. Seal the vessel with a Teflon® -lined silicone cap and placed in the Discover SP™ microwave cavity.
4. Upon method completion, transfer the solution to a small flask.
5. Place the flask in an ice bath and scratch the bottom of the flask with a glass stirring rod. Allow the solution to cool for at least 15 minutes upon precipitate formation.
6. Isolate the product via vacuum filtration, washing with ice-cold deionized water.
7. Allowing the crystalline precipitate to thoroughly dry over vacuum prior to recording the product yield (in the table below).
8. Perform melting point analysis (literature: 169–172 °C).
9. Perform IR and/or NMR analysis, if available.

Part III: Complete Product Table

Product	MW (g/mol)	Yield (g)	Theoretical Yield (mmol)	Theoretical Yield (g)	% Yield
N-(4-hydroxyphenyl) acetamide					

Synthesis of Aspirin

Part I: Complete Reagent Table

Reagent	MW (g/mol)	Density (g/mL)	Equivalents	Amount (mmol)	Amount
2-hydroxybenzoic acid		---			0.50 g
acetic anhydride					1.0 mL

Part II: Procedure

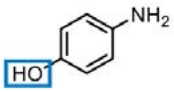
1. Program a two-step "Dynamic" method. Step 1 method parameters include: (maximum) Temperature = 110 °C, (maximum) Power = 300 W, (maximum) Pressure = 300 psi, Hold Time = 60 sec, PowerMax = Off, and Stirring = High. Step 2 method parameters include: (maximum) Temperature = 130 °C, (maximum) Power = 200 W, (maximum) Pressure = 300 psi, Hold Time = 60 sec, PowerMax = Off, and Stirring = High.
2. Charge a 10-mL vessel, equipped with stir bar, with 2-hydroxybenzoic acid (0.50 g) and acetic anhydride (1.0 mL).
3. Seal the vessel with a Teflon-lined silicone cap and placed in the Discover SP microwave cavity.
4. Upon method completion, transfer the solution to a small flask and dilute with ice-cold deionized water (2.0 mL).
5. Place the flask in an ice bath and scratch the bottom of the flask with a glass stirring rod. Allow the solution to cool for at least 15 minutes upon precipitate formation.
6. Isolate the product via vacuum filtration, washing with ice-cold deionized water.
7. Recrystallize the product from hot deionized water. If necessary, add a few drops of ethanol to assist with dissolution
8. Isolate the recrystallized product via vacuum filtration, allowing the crystalline precipitate to thoroughly dry over vacuum prior to recording the product yield (in the table below).
9. Perform melting point analysis (literature: 134–136 °C).
10. Perform IR and/or NMR analysis, if available.

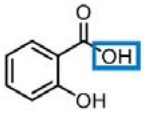
Part III: Complete Product Table

Product	MW (g/mol)	Yield (g)	Theoretical Yield (mmol)	Theoretical Yield (g)	% Yield
2-acetoxybenzoic acid					

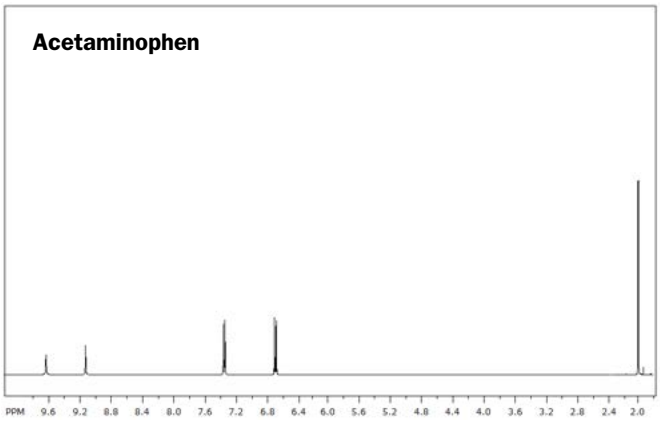
Discussion Questions

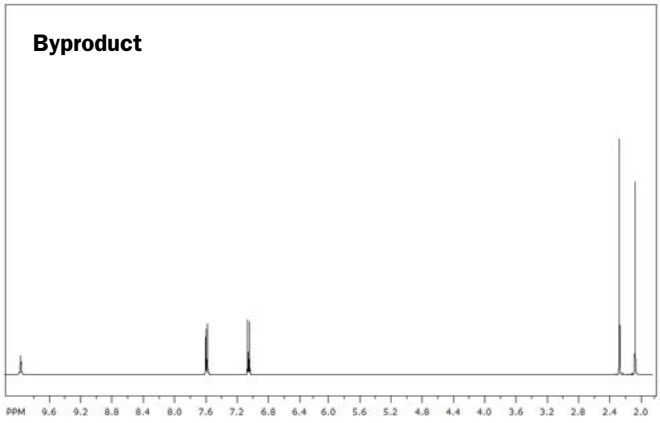
1. Draw the microwave reaction schemes for the synthesis of acetaminophen and aspirin.
2. Explain why acetylation does NOT take place at the positions indicated.



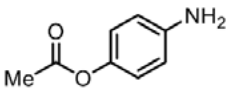


3. The following ^{1}H NMR spectra respectively depict acetaminophen and an undesired byproduct. What is the byproduct and how did it form?





4. How would you prevent the formation of the byproduct, discussed in Question 3?
5. Water is not used in the acetylation of 2-(acetyloxy)-benzoic acid. Why?
6. How would you make the compound below?



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