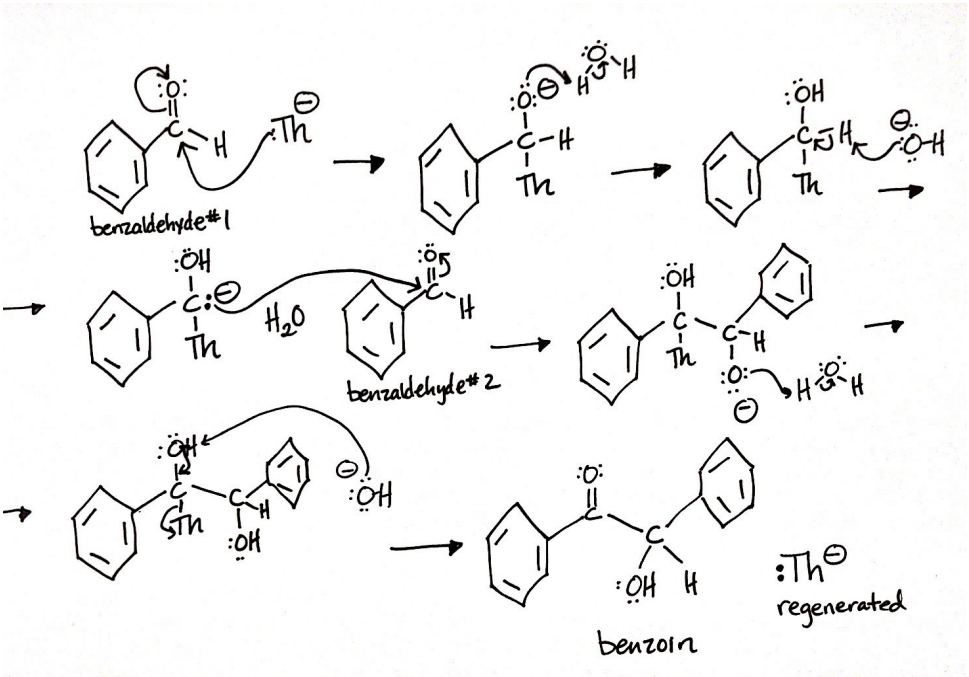
12BL Experiment 12 (4 days): Multistep Synthesis of Benzilic Acid

Safety: Proper lab goggles/glasses must be worn (even over prescription glasses). Wear Gloves! Concentrated nitric acid is highly corrosive and causes severe burns if spilled onto your skin. Nitrogen dioxide fumes are highly toxic and can damage the lungs due to inflammation. Do not breathe NO_2 fumes, and perform Stage 2 in the hood! As always, ask where organic waste containers are located in the lab.

Background: Multistep reactions are necessary to synthesize complex organic molecules. At this stage of your second semester organic chemistry lab course, you should be confident and adept at handling multiple steps. You are responsible for obtaining adequate yields of pure compounds in order to move on to each next step in the synthesis. It is imperative that you take your time as any mishaps will require you to start over. Your goal is to successfully covert Benzaldehyde to Benzilic Acid following what we will nickname the "B^4 pathway":
Benzaldehyde → Benzoin → Benzil → Benzilic Acid

Stage 1: Condensation

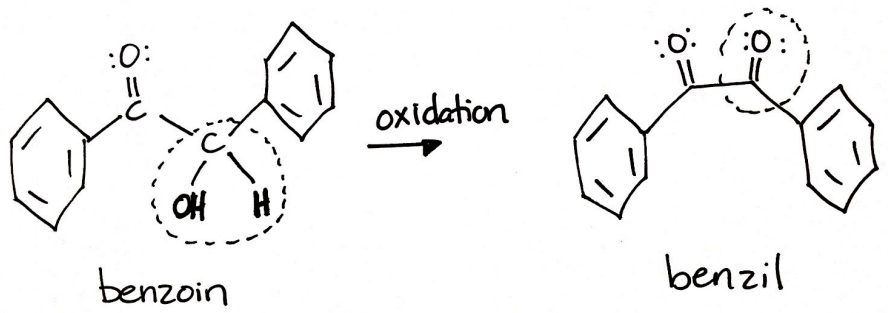
2 Benzaldehyde --(Thiamine)→ Benzoin
Benzaldehyde will be condensed, using Thiamine, a coenzyme catalyst, to produce benzoin, an α-hydroxyketone . Thiamine, otherwise known as Vitamin B1, is a coenzyme universally present in all living organisms. It functions as a coenzyme, a biological molecule that assists in enzymatic reactions. In most cases, coenzymes are directly involved in the biochemical reaction that the enzyme catalyzes since they usually bind the substrate (reactant) for the reaction. Without the coenzyme, no reaction will take place.



Stage 2: Oxidation

Benzoin --(HNO_3)→ Benzil

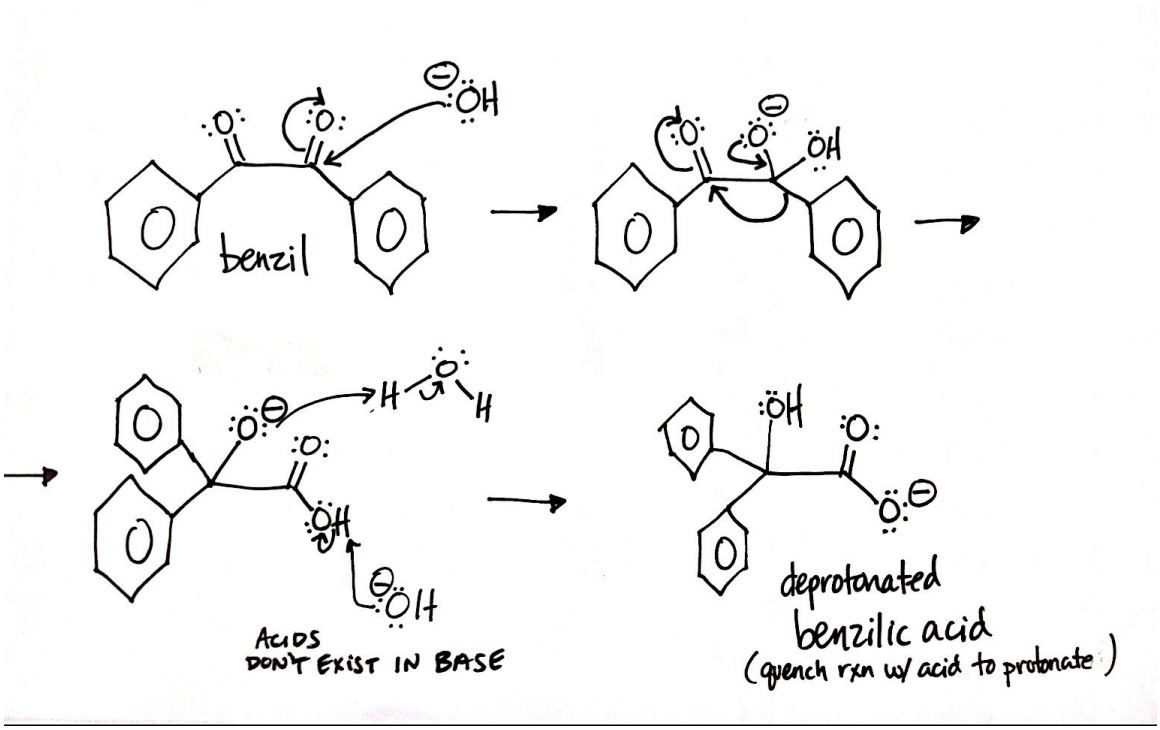
Benzoin, prepared in Stage 1, will be oxidized to form Benzil, an α-diketone.



Stage 3: Rearrangement

Benzil → Benzilic Acid

Benzilic acid will be prepared by causing a rearrangement of the α-diketone benzil. The driving force for the reaction is provided by the formation of a stable carboxylate salt (potassium benzilate). Once this salt is produced, acidification yields benzilic acid.



Objective: To successfully synthesize pure Benzilic Acid through a Multi-step Synthesis. To gain experience with multi-step synthetic pathways.

Procedure:

Stage 1

1. Add 1.30 g of thiamine hydrochloride to a dry 50 mL round bottom flask. Dissolve the solid in 4.0 mL of water by swirling.

2. Add 15 mL of 95% ethanol and cool the solution for a few minutes in an ice bath.

3. Very carefully and slowly, add 2.5 mL of 3 M NaOH drop by drop and mix by swirling, *making certain that the temperature of the solution never rises above 20˚C.*

4. To the yellow solution, add 7.5 mL of pure benzaldehyde, carefully attach a condenser for **air reflux** (no water connected to condenser). *Heat the mixture at 60˚C for about **1.5 hour** on a water bath.* **Caution: The temperature of this reaction cannot go above 65˚C. Constant monitoring of temperature is crucial & must be maintained between 60-65˚C.**

5. Cool the reaction mixture in an ice bath. If immediate crystallization does not occur, withdraw a drop of the solution on a stirring rod and let it dry to produce a solid; then, rub it against the inside surface of the flask to induce crystallization. Collect the product by vacuum filtration and wash it (rinse it) with a 1:1 mixture of 95% ethanol and water.

6. Recrystallize the crude product using hot 95% ethanol. Once your pure product has been obtained, dry it thoroughly before continuing on (if time is limited, dry overnight and continue on day 2 of experiment). Ethanol used in crystallization should be placed in the organic non-halogenated waste container.

7. Weigh your purified product & record its mass. Typical yield should be about 4-6 grams and the product should be colorless. If your yield is extremely low, you need to repeat this experiment as you will not have enough substrate for stage 2 and so on.

8. Take the melting point range of the pure product and record the IR spectrum.

Stage 2

1. Place 2.0 g of benzoin (prepared in Stage 1) into a round-bottom flask with 10.0 mL of concentrated nitric acid. Add a stirring bar and attach a condenser for reflux to the top of the flask.

2. Set up a reflux **<u>in the hood</u>** to vent NO_2 produced during the reaction. **Use a hot plate for heating.** (Remember, "water in" at the bottom and "water out" at the top of the condenser).

*Hood Space is "First Come, First Serve". You will have to wait patiently for additional space to open up.

3. With stirring, heat the reaction mixture. Begin timing the reaction when NO_2 fumes (red-brownish colored gas) are visible above the reaction mixture and gas bubbles are present on the stir bar. Reflux for at least 30 minutes, or until no more NO_2 gas is apparent. *Do not stop the reaction until the reaction is complete:* it should turn bright yellow color with a visible layer of product on top of the aqueous solution.

4. Stop the reaction by carefully removing the hot plate, and letting the reaction mixture cool for about 5 minutes.

5. Add about 75 mL of cold water to the reaction mixture, cool to room temperature, and swirl for a minute or two to coagulate the precipitated product.

6. Collect and wash the yellow solid using vacuum filtration. Continue drawing air through the crystals on the funnel by suction for about 5 minutes to assist in drying the crystals. Cleaning up: The aqueous filtrate (containing HNO_3) should be neutralized with sodium carbonate, diluted with water, and flushed down the drain.

7. Recrystallize the crude product using hot 95% ethanol. Once your pure product has been obtained, dry it thoroughly before continuing on (if time is limited, dry overnight and continue on next day of experiment). Ethanol used in crystallization should be placed in the organic non-halogenated waste container.

8. Take the melting point range of the pure product and record the IR spectrum.

Stage 3

1. Add 1.5 g of benzil and 5.0 mL of 95% ethanol to a 50-mL round-bottom flask.

2. Place a stirring bar in the flask and attach a reflux condenser. (Remember, "water in" at the bottom and "water out" at the top of the condenser). Heat the mixture with stirring until the benzil is dissolved. Add drop by drop 4.0 mL of an aqueous potassium hydroxide solution downward through the condenser into the flask.

3. Gently reflux the mixture for 15 minutes with stirring. After the mixture has dissolved and heated for a few minutes, the mixture will turn blue-black in color. As the reaction proceeds, the reaction product will turn brown and the solid may, or

may not, be completely dissolved. At the end of the reaction, remove the flask and let it cool.

4. When the apparatus is cool enough to handle, remove the condenser and transfer the contents, including any solids, into a 150-mL beaker.

5. Allow the mixture to cool to room temperature (do not rush!). When the mixture is cooled, continue the cooling in an ice-water bath for an additional 15 minutes, when crystallization should be complete. Crystallization is complete when it appears that virtually the entire mixture is solidified.

6. Collect the crystals using vacuum filtration and wash the crystals throughly with three 7-mL portions of ice cold 95% ethanol. The solvent should remove most of the color from the crystals. Ethanol used in crystallization should be placed in the organic non-halogenated waste container.

7. Leave the product in your locker to dry until the next class period.

8. Transfer the solid, which is mostly the potassium benzilate salt, to a 125-mL Erlenmeyer flask containing 15mL of hot water.

9. Stir the mixture until all solid has dissolved or until it appears that the remaining solid will not dissolve. If solid still remains in the flask, filter the mixture through a Hirsch funnel to remove any particulate material. (If all solid dissolved, then filtration is not required.)

10. With stirring, add dropwise 7.5 mL of 1 M HCl to the solution of potassium benzilate. The pH should be about 2; if it is higher than this add a few more drops of acid and check the pH again.

11. Allow the mixture to cool to room temperature and then complete the cooling in an ice bath. Let the solid form in the ice bath *for at least 30 min, up to about 60 min.* If solid has not formed after an hour, you can store your sample until the next lab period to crystallize.

12. Collect the benzilic acid by vacuum filtration. Wash the crystals with 15-20 mL of water to remove any salts. Dry the product thoroughly.

13. Take the melting point range of the pure product and record the IR spectrum.

http://www.sayhellotochemistry.com/Site/Chem-106_files/Multistep%20Synthesis.pdf

12BL Prelab Experiment 12: Multistep Synthesis of Benzilic Acid

1. Give the structure of Thiamine.

2. Research and give an example of how Thiamine is used in the human body. Be clear and specific. Document your source.

3. Draw structures for the following and give **<u>ALL</u> IR bonds with wavenumbers** that you would see for each: (be clear; ALL means every unique bond that appears in IR!)

A. Benzaldehyde

B. Benzoin

C. Benzil

D. Benzilic Acid

4. Label ALL functional groups each contains: (ex: ketone, alkene, aromatic, etc…)

A. Benzaldehyde

B. Benzoin

C. Benzil

D. Benzilic Acid

5. For each pair below, give a Qualitative Chemical Test that could be used to distinguish between them (no litmus/pH paper)

*Clearly label the test, the functional group being tested, and what observations you would expect. (EX: $NaHCO_3$ test – carboxylic acids – gas evolution; this is good review for you!)

A. Benzaldehyde & Benzoin

B. Benzoin & Benzil

C. Benzil & Benzilic Acid

12BL Postlab Experiment 12: Multistep Synthesis of Benzilic Acid

Data

Take the Melting Point Range of the following:

Benzaldehyde (your initial reactant)_____˚C

Benzoin (pure recrystallized)_____˚C

Benzil (pure recrystallized)_____˚C

Benzilic Acid (pure recrystallized)_____˚C

Attach all IRs. Each IR should be completely labeled with all bonds & wavenumbers involved & each IR should have the molecule's NAME & STRUCTURE.

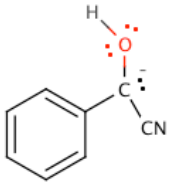
Questions

1. Explain specifically using structures & a detailed explanation why the conversion of 2 Benzaldehyde → Benzoin is a Condensation.

2. Explain specifically using structures & a detailed explanation why the conversion of Benzoin → Benzil is an Oxidation.

3. Draw the Complete Mechanism for the conversion of 2 Benzaldehyde → Benzoin using the nucleophilic catalyst, cyanide, $^{-}$CN. You should know how to draw the Lewis structure of $^{-}$CN to show in your mechanism! (Note: we used Thiamine, abbreviated Th^{-}, in the lab.)

*Hint: The following intermediate structure is formed during your mechanism so make sure you have it! Also, make sure you regenerate the catalyst at the end.



4. Draw the Complete Mechanisms for Condensation, Oxidation, & Rearrangement if your starting reactant was Acetaldehyde instead of Benzaldehyde.