

## Thiamine Catalyzed Benzoin Condensation

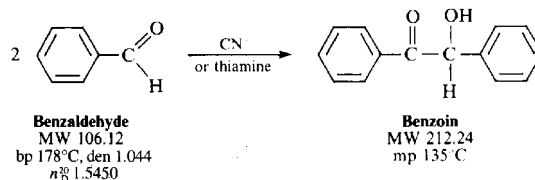
Adapted by Jon Landis and R. Minard (Penn State Univ.) FROM K. L. Williamson, *Macroscale and Microscale Organic Experiments*, 2nd Ed. 1994, Houghton Mifflin, Boston. Revised 2/22/02

### Prelaboratory Exercise:

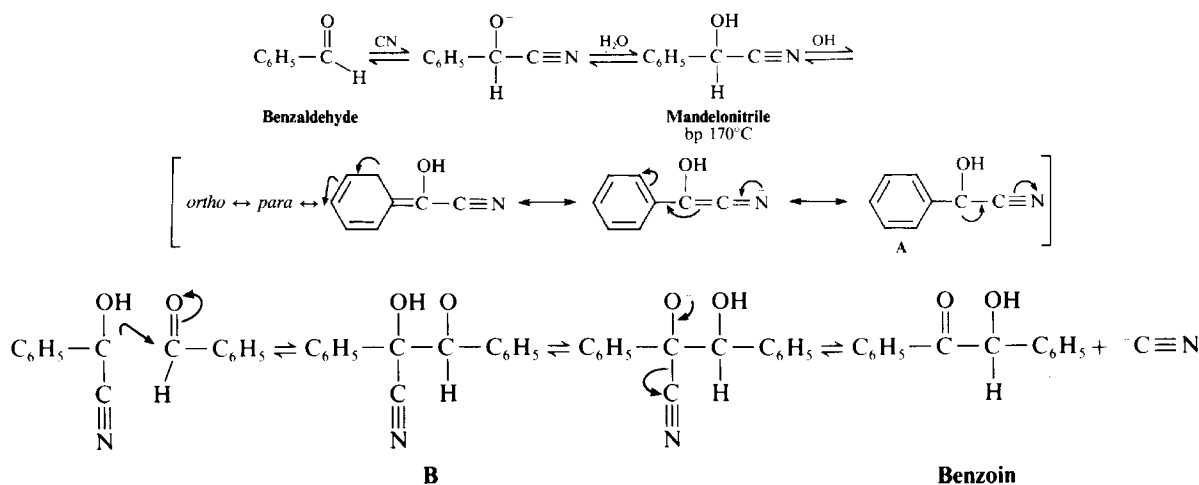
A student performing this experiment retrieves the bottle of benzaldehyde from the reagent shelf and notices a white precipitate in the bottle. What is this solid? How is it formed? Will its presence effect the experimental results?

### Introduction

The reaction of two moles of benzaldehyde to form a new carbon-carbon bond is known as the *benzoin condensation*. It is catalyzed by two rather different catalysts, cyanide ion and the vitamin thiamine, which on close examination are seen to function in exactly the same way.



Consider first the cyanide ion-catalyzed reaction. The cyanide ion attacks the carbonyl carbon to form a stable cyanohydrin, mandelonitrile, a liquid of boiling point 170°C that under the basic conditions of the reaction loses a proton to give a resonance-stabilized carbanion (A). This carbanion attacks another molecule of benzaldehyde to give B, which undergoes a proton transfer and loses cyanide to give benzoin. Evidence for this mechanism lies in the failure of 4-nitrobenzaldehyde to undergo the reaction, because the nitro group reduces the nucleophilicity of the anion in A. On the other hand, a strong electron donating group in the 4-position of the phenyl ring makes the loss of the proton from the cyanohydrin very difficult, and thus 4-dimethylaminobenzaldehyde also does not undergo the benzoin condensation with itself.

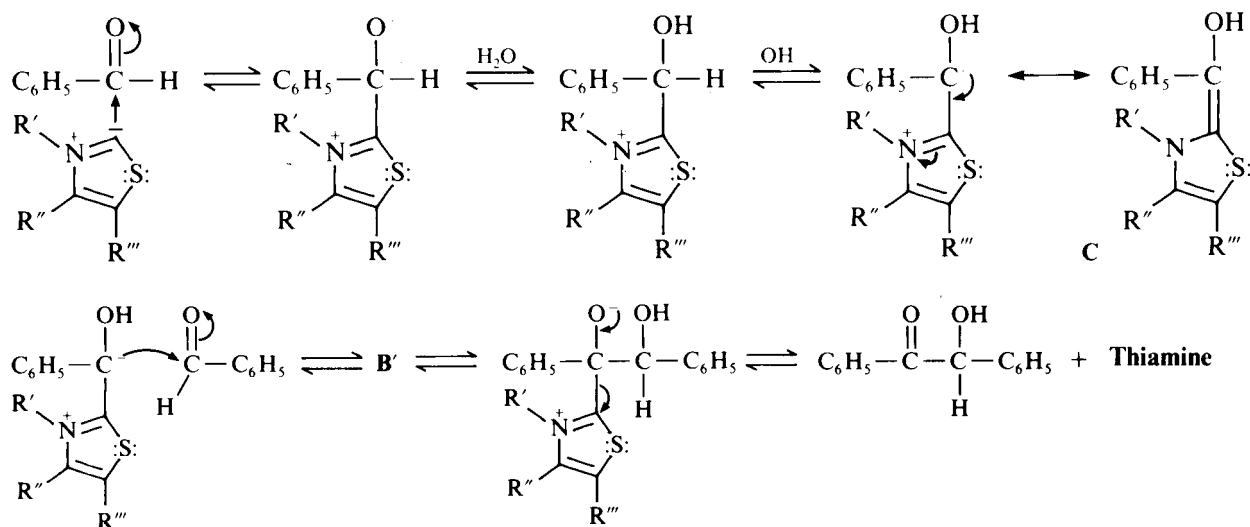
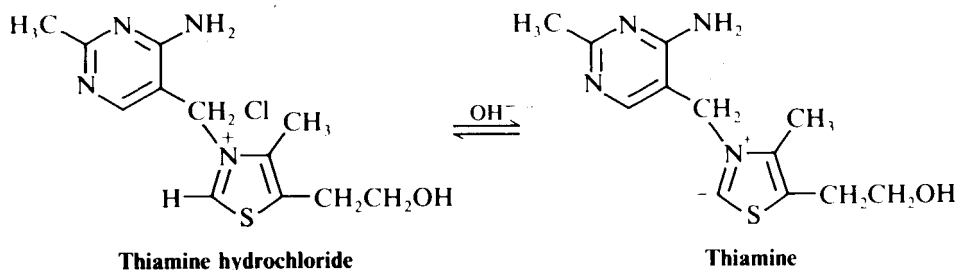


A number of biochemical reactions bear a close resemblance to the benzoin condensation but are not, obviously, catalyzed by the highly toxic cyanide ion. Some 30 years ago Breslow proposed that vitamin B<sub>1</sub>, thiamine hydrochloride, in the form of the coenzyme thiamine pyrophosphate, can function in a manner completely analogous to cyanide ion in promoting reactions such as the benzoin condensation. In the scheme below, the resonance-stabilized conjugate base of the thiazolium ion, thiamine, and the resonance-stabilized carbanion (C) that it forms, are again the keys to the reaction. Like the cyanide ion, the thiazolium ion has just the right balance of nucleophilicity, ability to stabilize the intermediate anion, and good leaving group qualities.

The importance of thiamine is evident in that it is a vitamin, an essential substance that must be provided in the diet to prevent beriberi, a nervous system disease.

In the reactions that follow, cyanide ion functions as a fast and efficient catalyst, although in large quantities it is highly toxic. The amount of potassium cyanide used in the present experiment (15 mg) is about eight times less than the average fatal dose, a difference that underlines the advantage of carrying out organic experiments on a microscale.

The thiamine-catalyzed reaction is much slower, but the catalyst is edible.



There are two versions of the synthetic procedure given below. You may try either one of them; both have given good results. If one doesn't work, you can try the other version. You are encouraged to read through both and make proper preparations in your PreLab for each version.

#### Synthesis Version A:

##### Condensation Reaction:

Obtain a sample of fresh pure benzaldehyde prepacked in a shorty vial from the hooded shelf. In a 20-mL vial place a 1/2-inch teflon-coated stir bar, add 0.13 g of thiamine hydrochloride, and dissolve it in 0.4 mL of water. Add 1.5 mL of 95% ethanol and 0.25 mL of 3M sodium hydroxide and stir. Add 0.75 mL of pure benzaldehyde and stir and heat the reaction mixture to 60°C for 1 to 2 hours by clamping it in a 100-mL beaker of water heated gently in your heating mantle with a magnetic stirrer underneath. Do NOT let the temperature go above 65°C at any time during the experiment as this causes undesirable side-reactions. Cap and set the vial in your locker until the next lab period to work-up the reaction.

##### Isolation and Purification:

Cool the reaction mixture in an ice bath. If crystals do not appear, use a glass rod to scratch the inside surface of the vial. If this fails to initiate crystallization, allow to the reaction to evaporate slowly from the open vial in your locker until the next lab period. Use suction filtration with a Hirsh funnel to collect the product and wash with an ice cold 1:1 mixture of ethanol and water. The washings should remove all of the yellow color and the final product should be colorless. The melting point of the pure product is 134-135°C. If the melting point of your product has a range greater than 4° or deviates much from the 134-135°C range, recrystallize the product from 95% ethanol (7 mL/g of product). Use the clean dry, crystals for NMR, IR or other spectral analysis, as required.

#### Synthesis Version B:

##### Condensation Reaction:

Obtain a sample of fresh pure benzaldehyde prepacked in a shorty vial from the hooded shelf or the stockroom. Obtain two Vitamin B-1 tablets and grind them up thoroughly using a mortar and pestle, obtainable from the stockroom. In a 20-mL vial place a 1/2-inch teflon-coated stir bar, add the powdered Vitamin B-1 (active ingredient is thiamine hydrochloride), and add 0.4 mL of water. Add 1.5 mL of 95% ethanol and 0.25 mL of 3M sodium hydroxide and stir. Add 0.75 mL of pure benzaldehyde and stir and heat the reaction mixture to 60°C for 1 to 2 hours by clamping it in a 100-mL beaker of water heated gently in your heating mantle with a magnetic stirrer underneath. Do NOT let the temperature go above 65°C at any time during the experiment as this causes undesirable side-reactions. Cap and set the vial in your locker until the next lab

period to work-up the reaction.

#### **Isolation and Purification:**

Let the reaction mixture cool to room temperature and decant the mixture into one or two test tubes, leaving as much of the tablet binder in the vial as possible. Pipet filter to remove sediments. Cool the reaction mixture in an ice bath. If crystals do not appear, use a glass rod to scratch the inside surface of the flask. If this fails to initiate crystallization, allow the reaction to evaporate slowly from the open vial in your locker until the next lab period. Use suction filtration with a Hirsch funnel to collect the product and wash with an ice cold 1:1 mixture of ethanol and water. The washings should remove all of the yellow color and the final product should be colorless. The melting point of the pure product is 134-135° C. If the melting point of your product has a range greater than 4° or deviates much from the 134-135°C range, recrystallize the product from a minimum amount of 95% ethanol (7 mL/g of product). Use the clean dry, crystals for NMR, IR or other spectral analysis, as required.

#### **Troubleshooting the Benzoin Condensation Reaction**

Quite often, the biggest problem with this experiment is trying to get the product to crystallize. The crystallization procedure used here is referred to as solvent-pair crystallization. Here, benzoin has a low solubility in water, high in ethanol, so as the water content increases for an ethanol/water solution of benzoin, the benzoin (hopefully) begins to precipitate. Often, however, the resulting reaction mixture is an oil, i.e., a supercooled liquid. Besides scratching the side of the glass of the container with the mixture, there are several other options that you may follow--sometimes a combination of the following are necessary.

1. Scratch the walls of the container with a glass stir rod. Don't bear down on the glass so much that you break the stir rod--shards of glass aren't the goal here.
2. Dip the stir rod into the mixture, let it air-dry until you see some small amount of crystalline or powdery solid on the stir rod. Now, place the container in ice water, and continue to scratch the walls of the container.
3. Try reducing the alcohol content of the mixture by letting it evaporate slowly from an uncovered container between lab periods or boiling away with the aid of some boiling chips.
4. Cool and add little more water, dropwise. This causes more oil to form. Be sure you know which layer is the oil and which is the watery layer. Take the oil, add just enough ethanol to redissolve the oil to give a homogeneous mixture, then try scratching, cooling, add a little more water until the solution just becomes a little cloudy, then let it stand uncovered.
6. Although the details have not been worked out, you should be able to easily separate the benzoin from the unreacted starting materials by column chromatography, as you did in the column chromatography experiment. However, less alumina should be used, as benzoin, an alcohol, will be retained strongly by the alumina.

**Cleaning Up:** The filtrate can be diluted with water and washed down the drain.

**Final Report:** Present the spectroscopic and chemical evidence, give the structure of the final product(s).

Answer these questions at the end of your report:

1. Predict whether the benzoin condensation would work with 4-tolualdehyde, 4-trifluoromethylbenzaldehyde, and 4-N-ethylaminobenzaldehyde. Draw the structure of any products that are formed.
2. Draw the complete structure of thiamine hydrochloride and use an arrow pushing mechanism to show its acid-base reaction with hydroxide ion.
3. How might the presence of benzoic acid (a) affect the pH of the reaction and (b) affect the crystallization of benzoin at the end?

# Synthetic Experiment PreLab Grading Sheet

Name(s): \_\_\_\_\_

TA: \_\_\_\_\_

Date: \_\_\_\_\_

## PreLab For Exp't # 12

### Thiamine Catalyzed Benzoin Condensation

	Possible Points	Missed Points
Date, Name, Desk #, Experiment # & Title(abbreviated after 1 <sup>st</sup> pg), Section & TA Name	4	
Summary (Choose ONE of the methods and discuss)	8	
Goals	8	
Reactions, structures, conditions, diagrams	14	
Completeness of Chemical Data Table(s)	14	
Chromatographic Behavior Comparison	16	
Spectral Features Comparison	12	
Work-up - Explanation of the product isolation and purification process	12	
PreLab Questions	12	
<b>TOTAL FOR PRELAB</b>	<b>100</b>	

Date Handed in: \_\_\_\_\_

General Comments:

**Total Points:** \_\_\_\_\_

# Synthetic Experiment Final Report Grading Sheet

Name: \_\_\_\_\_

TA: \_\_\_\_\_

Date: \_\_\_\_\_

## Final Report For Exp't # 12

### Thiamine Catalyzed Benzoin Condensation

	Possible Points	Missed Points
Name, Date, Experiment Title (abbreviated after 1st page) and every page numbered	4	
<i>OBSERVATIONS and DATA</i> - Overall organization, readability, completeness	8	
Data: Weighing data, molecular weights, moles, density, volumes, $R_f$ 's. Product analysis conditions i.e. weight of sample and KBr for IR; solvent and field strength for NMR; ionization mode for MS; solvent and wavelength range for UV/Vis,	12	
Yield: Show % yield calculations with limiting reagent clearly stated. Purity: Record melting points, color, or other indicators of purity.	12	
<i>RESULTS AND DISCUSSION</i> - Overall organization, readability, completeness	8	
Results; Achievement of goals	16	
Product Analysis Data: Quality and Interpretation – Structure(s) drawn on each Spectrum or Chromatogram Interpret all major MS or IR peaks. Discuss all UV/Vis $\lambda_{\max}$ in terms of conjugation. Explain how spectra confirm product identity <i>See Lab Guide Chapter 3, Section 3.4 for guidelines in annotating spectra and Ch 11 for help with interpretation.</i>	24	
POSTLAB QUESTIONS	16	
TOTAL POINTS	100	

Date Handed in: \_\_\_\_\_

General Comments:

**Total Points:** \_\_\_\_\_