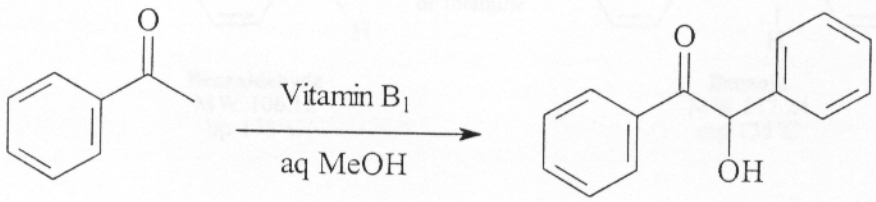
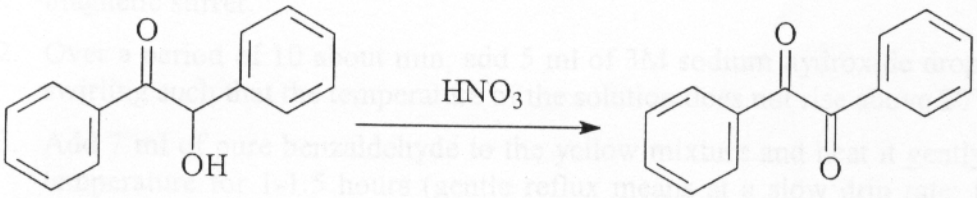
Synthetic Route of Benzylic Acid



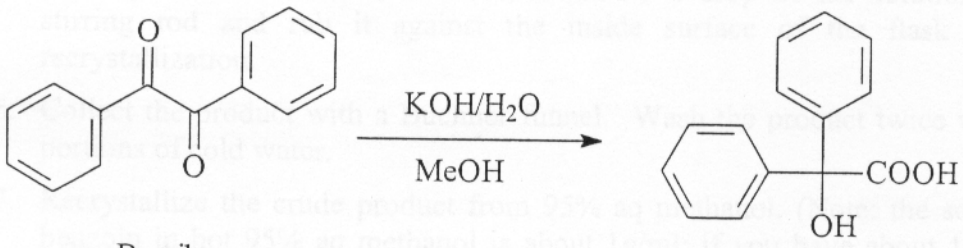
Benzaldehyde

Benzoin



Benzoin

Benzil

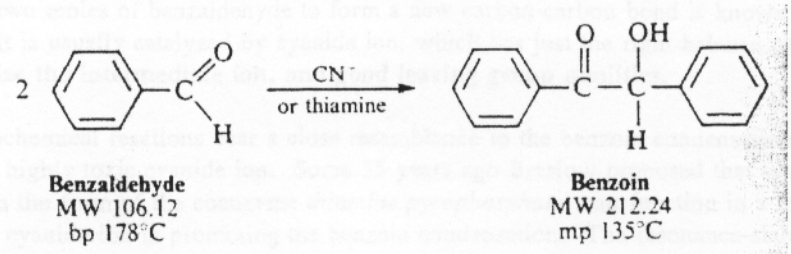


Benzil

Benzylic Acid

Experiment 2-6

Experiment 2 The Benzoin Condensation: Thiamine Catalyzed



Benzaldehyde
MW 106.12
bp 178°C

Benzoin
MW 212.24
mp 135°C

1. Dissolve 2.6 g of thiamine hydrochloride in 8 ml of water contained in a 250-ml round bottom flask equipped with a magnetic stir bar and a condenser for reflux. Add 20 ml of 95% ethanol and cool the solution in an ice bath. Turn on the magnetic stirrer.
2. Over a period of 10 about min, add 5 ml of 3M sodium hydroxide dropwise with swirling such that the temperature of the solution does not rise above 20°C.
3. Add 7 ml of pure benzaldehyde to the yellow mixture and heat it gently at reflux temperature for 1-1.5 hours (gentle reflux means at a slow drip rate; i.e., just a few drops per minute).
4. Cool the reaction mixture to room temperature and then in an ice bath.
5. If recrystallization does not occur, withdraw a drop of the solution with the stirring rod and rub it against the inside surface of the flask to induce recrystallization.
6. Collect the product with a Buchner funnel. Wash the product twice with 50 ml portions of cold water.
7. Recrystallize the crude product from 95% aq methanol. (Note: the solubility of benzoin in hot 95% aq methanol is about 1g/ml; if you have about 1g of crude product, use 10ml of aq MeOH; about 2g, use 20 ml of aq MeOH, and so forth.)
8. Collect the product with a Buchner funnel. Transfer the product to dry paper and allow it is air dry for 10 to 15 min.
9. Determine the melting point of the product. Calculate the percent yield of the product.

Answer the following questions in your notebook. (The reaction mechanism is shown in the next three pages)

1. What is the structure of the thiazole ring?
2. How many steps are there in the reaction mechanism?
3. What is the name of each reaction mechanism step?
4. What is the structure of the Enamine (Deprotonated "Catalyst" Adduct)

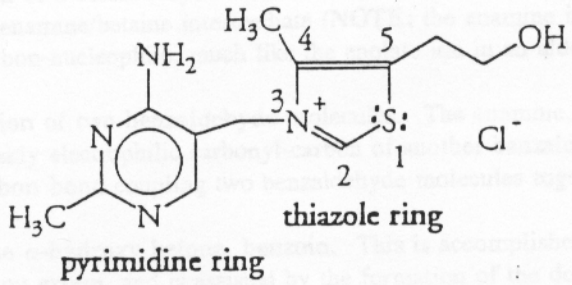
INTRODUCTION

1. The reaction of two moles of benzaldehyde to form a new carbon-carbon bond is known as the benzoin condensation. It is usually catalyzed by cyanide ion, which has just the right balance of **nucleophilicity, ability to stabilize the intermediate ion, and good leaving group qualities.**

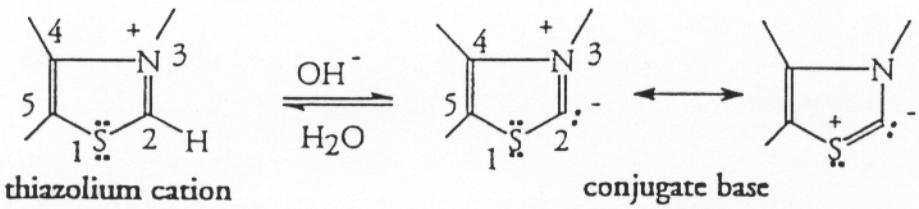
2. A number of biochemical reactions bear a close resemblance to the benzoin condensation but are not, obviously, catalyzed by the highly toxic cyanide ion. Some 35 years ago Breslow proposed that vitamin B1, *thiamine hydrochloride*, in the form of the coenzyme *thiamine pyrophosphate*, can function in a manner completely analogous to the cyanide ion in promoting the benzoin condensation. The resonance-stabilized conjugate base of the thiazolium ion (**thiamine-ylide**), and the resonance-stabilized carbanion (**the enamine/betaine**) are the keys to the reaction.

SOME GENERAL CONSIDERATIONS CONCERNING THE REACTION

1. First of all, we will look at the structure of vitamin B1 (thiamine hydrochloride)



2. Next, we will look at the acidity of the thiazolium cation. **Basically, it is understandable in terms of the activating (electron-withdrawing) effect of the adjacent positive charge on nitrogen and the resonance interaction with the neighboring sulfur atom**



3. Lastly, we will define some terms whose understanding is basic to understanding the reaction mechanism of the vitamin B1 catalyzed benzoin-condensation.

   a. **Catalyst:** A catalyst is a substance that speeds up a reaction; that is, it increases the rate at which the product is formed. It does so by allowing reactants and products to be interconverted by a new pathway in which the rate-determining step has an **activation energy** lower than the reaction would have in the absence of the catalyst. In other words, the catalyst lowers the **activation energy barrier.** Also during the course of the reaction, the **concentration** of the catalyst remains essentially **unchanged.**

b. **Vitamin B1** is a good catalyst for the benzoin condensation reaction because: (i) **it is a good nucleophile**; that is, in the presence of strong base, it forms a high concentration of its **ylide**; and (ii) **it is a good leaving group**; that is its **ylide** is stable.

c. **The ylide of vitamin B1 is especially stable** because: the carbanion carbon (the C2 carbon of the thiazole ring) is stabilized by the adjacent positive charge on nitrogen and a strong resonance interaction with the neighboring **sulfur atom**

d. An **Ylide** is a dipolar compound with **adjacent** plus and minus charges.

e. A **Betaine** is a dipolar compound with **non-adjacent** plus and minus charges

REACTION MECHANISM FOR THE VITAMIN B_1-CATALYZED BENZOIN CONDENSATION

Step one: generation of the thiamine-ylide. Because its pKa value is relatively high (ca 10), a strongly basic solution is required to generate an adequate concentration - once formed, however, it can function as a **good** nucleophile.

Step two: generation of the enamine/betaine. The ylide, functioning as a strong nucleophile, attacks the weakly electrophilic carbonyl-carbon of a benzaldehyde molecule - the resultant adduct is sufficiently acidic to be transformed into its conjugate base: the enamine/betaine intermediate (**NOTE:** the enamine is a resonance-stabilized **carbanion,** so it can function as a strong carbon-nucleophile, much like the enolate ion in an aldol condensation reaction).

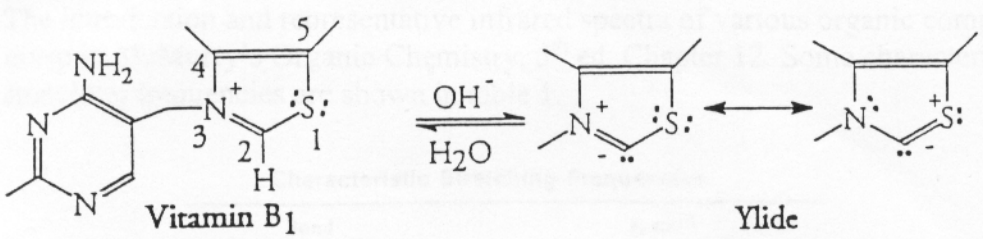
Step three: coupling reaction of two benzaldehyde molecules. The enamine, functioning as a strong carbon nucleophile, attacks the weakly electrophilic carbonyl-carbon of another benzaldehyde molecule (**NOTE:** the adduct contains a **new carbon-carbon** bond coupling two benzaldehyde molecules together).

Step four: liberation of the α-hydroxy ketone, benzoin. This is accomplished by the **expulsion** of the **ylide catalyst** functioning as a **good leaving group**, and is assisted by the formation of the double bond in the reformed carbonyl group.

Overall, then, vitamin B1 is an effective catalyst for the benzoin condensation: because its conjugate base - **thiamine ylide** - has just the right balance of **nucleophilicity, ability to stabilize the intermediate enamine/betaine, and good leaving group qualities.**

 EXPERIMENT #2 - THE BENZOIN CONDENSATION (Aldehyde Coupling)

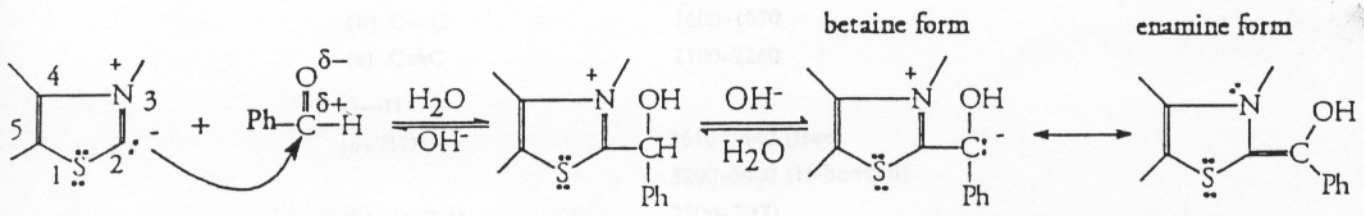
Mechanism, step one: generation of "YLIDE" catalyst from vitamin B1



Vitamin B_1 Ylide

NOTE: in the resonance-stabilized conjugate base of the thiazolium ion, the thiamine ylide, the carbanion carbon at C2 is conjugated with the neighboring sulfur atom

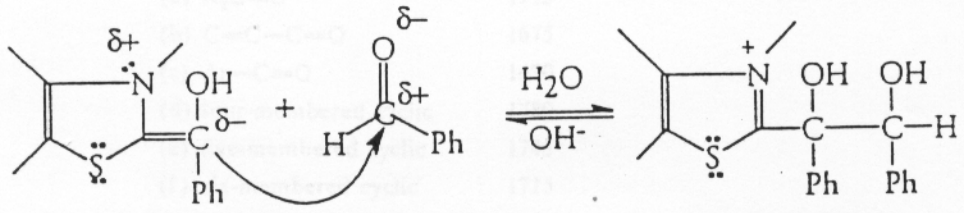
Mechanism, step two: generation of **ENAMINE** nucleophile



YLIDE benzaldehyde ADDUCT ENAMINE-BETAINE FORM

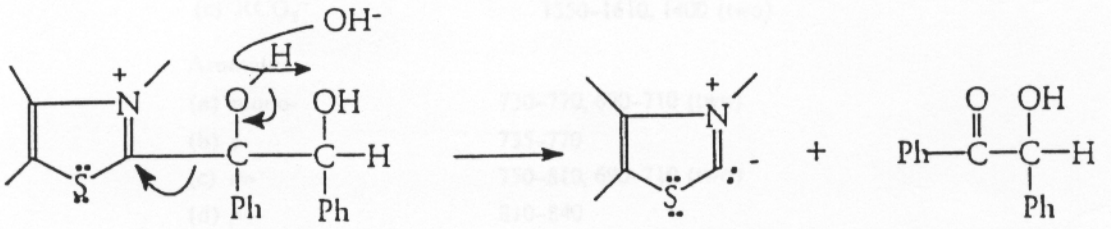
NOTE: an enamine is a resonance-stabilized carbanion so it can function much like the enolate-ion

Mechanism, step three: coupling reaction of two benzaldehyde molecules



carbon nucleophile carbon electrophile benzaldehyde adduct

Mechanism, step four: expulsion of the **THIAMINE-YLIDE catalyst** from the benzaldehyde adduct



benzaldehyde adduct ylide catalyst benzoin product

NOTE: expulsion of the thiamine-ylide catalyst is assisted by the formation of the stable carbonyl group as well as by the stability of the thiamine-ylide

Experiment 3: Characterization of Benzoin by FT-IR

The introduction and representative infrared spectra of various organic compounds are given in McMurry's Organic Chemistry, 5th ed. Chapter 12. Some characteristic stretching frequencies are shown in table 1.

Characteristic Stretching Frequencies

Bond	$\tilde{\nu}$, cm^{-1}
C—H	
(a) C_{sp^3}—H	2800–3000
(b) C_{sp^2}—H	3000–3100
(c) C_{sp}—H	3300
C—C	
(c) C—C	1150–1250
(b) C=C	1600–1670
(c) C≡C	2100–2260
O—H	
(a) ROH	3610–3640 (free)
	3200–3400 (H-bonded)
(b) RCO_2H	2500–3000
Aldehydes	
(a) RCHO	1725
(b) C=CCHO	1685
(c) ArCHO	1700
Ketones	
(a) R_2C=O	1715
(b) C=C—C=O	1675
(c) Ar—C=O	1690
(d) four-membered cyclic	1780
(e) five-membered cyclic	1745
(f) six-membered cyclic	1715
Carboxylic acids	
(a) RCOOH	1760 (monomer)
	1710 (dimer)
(b) C=C—COOH	1720 (monomer)
	1690 (dimer)
(c) RCO_2^-	1550–1610, 1400 (two)
Aromatic	
(a) mono-	730–770, 690–710 (two)
(b) *o*-	735–770
(c) *m*-	750–810, 690–710 (two)
(d) *p*-	810–840

Report: Peak Pick – Benzaldehyde Infrared Spectrum

Peak Pick (cm^{-1})	Functional Group

Report: Peak Pick – Benzoin Infrared Sepctrum

Peak Pick (cm^{-1})	Functional Group