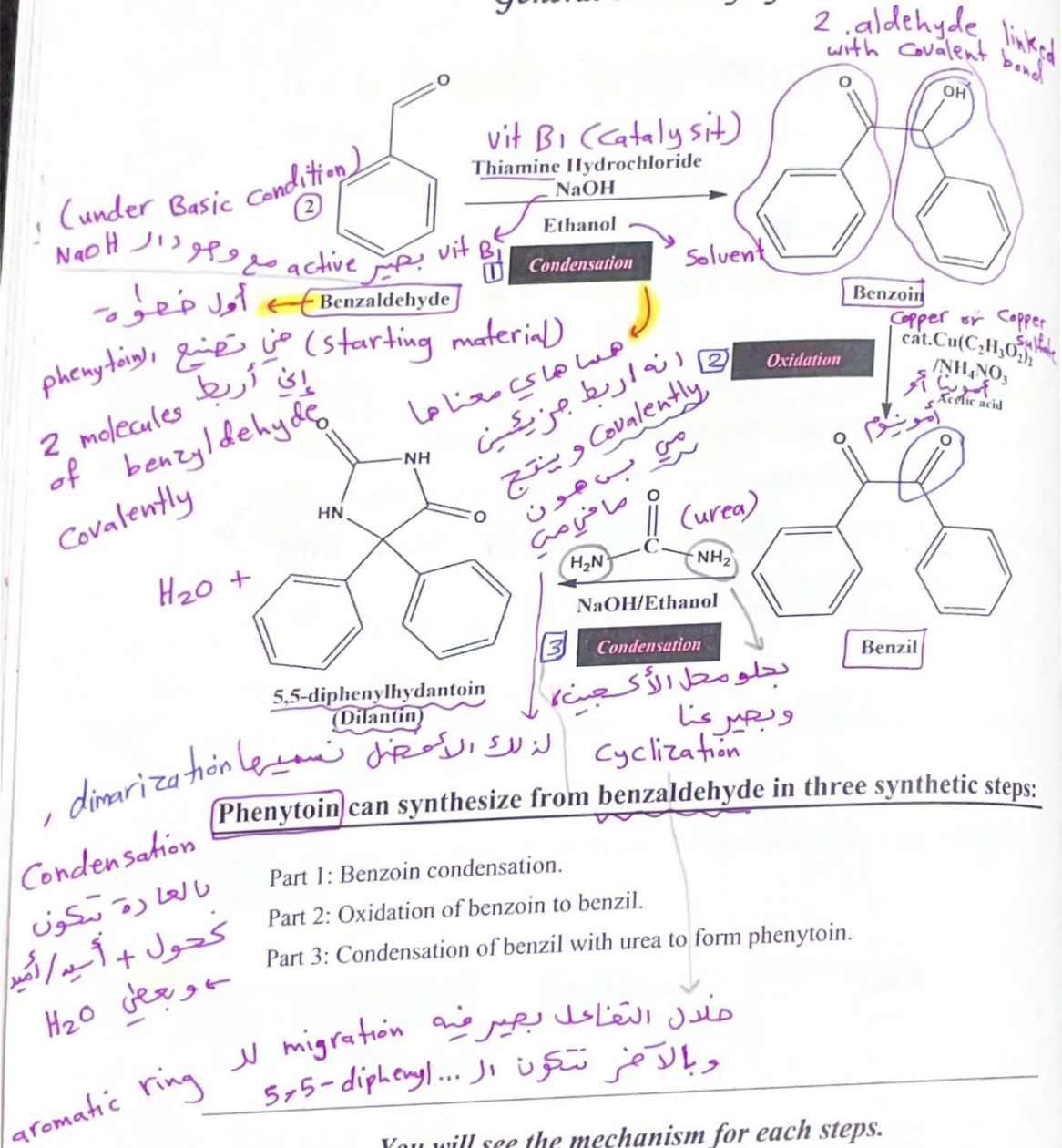


Cycle 2

Multistep synthesis of Phenytoin

- Phenytoin, sold under the brand name Dilantin among others.
- It is an anti-seizure medication.
- It is useful for the prevention of tonic-clonic seizures and partial seizures.
- Phenytoin blocks the spread of seizure activity in the brain by causing voltage dependent block of the voltage gated Na channels.
- It may also be used for certain heart arrhythmias or neuropathic pain.
- It doesn't have sedative hypnotic activity *or very little*
- It can be taken intravenously or by mouth

General scheme of synthesis



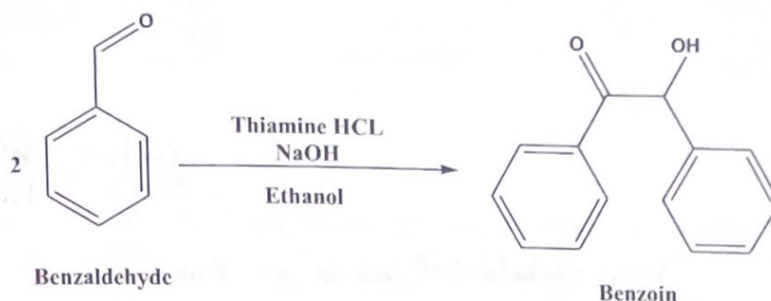
You will see the mechanism for each steps.

Try to enjoy it

Experiment 2

Multistep synthesis of Phenytoin

Part1: Benzoin Condensation



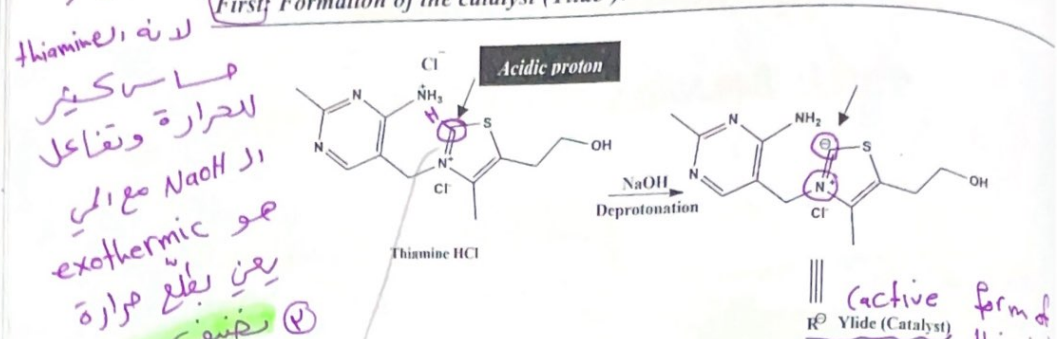
- Benzoin is produced by dimerization of 2 molecules of benzaldehyde, The benzoin condensation[§] is in fact a dimerization and not a condensation because a small molecule like water is not released in this reaction
- This reaction doesn't occur spontaneously. It needs a **catalyst** to render the aldehydic carbon acidic so that it can be deprotonated and function as a nucleophile to attack the second benzaldehyde carbon.
- Cyanide* [$K^+C \equiv N^-$] can use as a catalytic reagent use at 75°C (give faster rate) but they are extremely poisonous.
- **Thiamine** (contains a thiazole unit) is the catalyst was used here at Room temp, (give very slow rate).

-
- Thiamine (Vit B1) is non-toxic (edible) material
 - Thiamine is heat sensitive and may decompose if heated vigorously
 - Instead of running the reaction at elevated temperature. We will allow it to proceed closer to room temperature for at least 24 hours
-

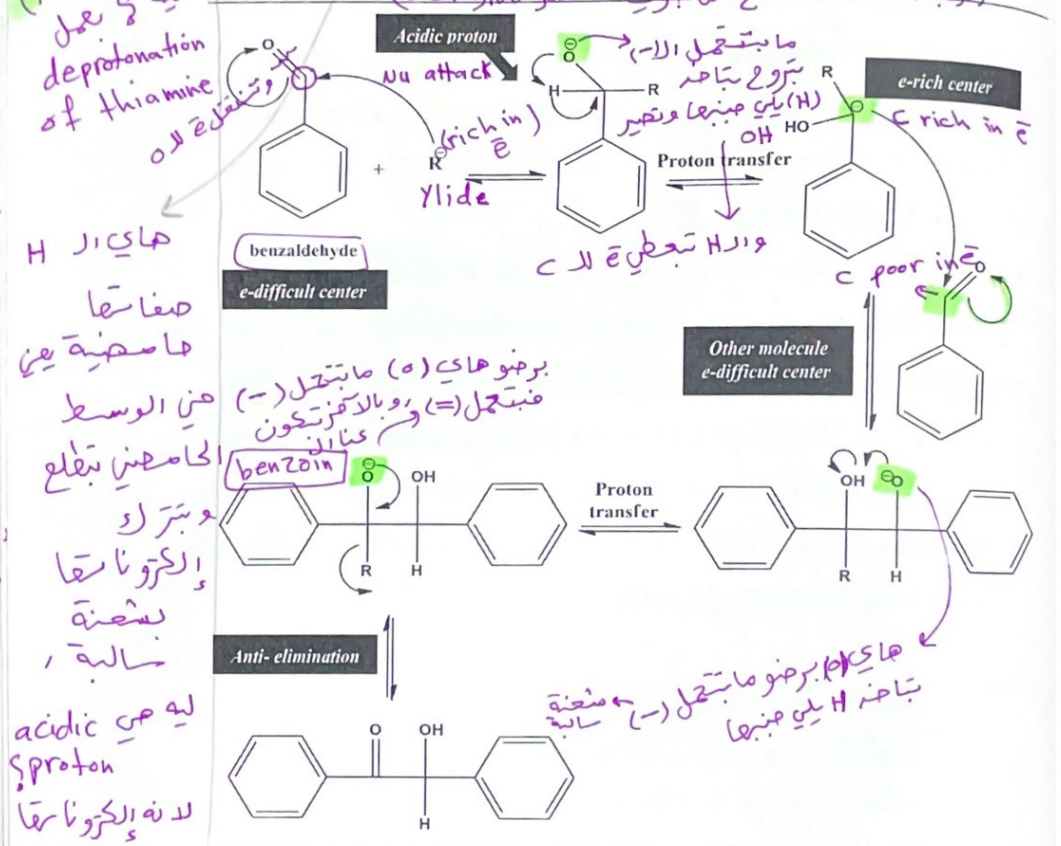
[§] **Condensation reaction:** a reaction in which two molecules combine to form a larger molecule, producing a small molecule such as H₂O as a by-product.

*Refer to appendix VIII: Benzoin condensation using cyanide.

أول خطوة في هائي التجربة هو تحضير ال active form of the catalyst (thiamine) → ylide
 ① يذوب ال thiamine (water soluble vit B₁)
 Mechanism في ابي ⑤ بنحلة من Ice Bath
 First Formation of the catalyst (Ylide*):



Second: The condensation reaction start with umpolung[†] to the carbonyl center of benzaldehyde: (ارتباط thiamine مع اول جزي من ال benzaldehyde)



*Ylide: is a species with opposite formal charges on adjacent atoms (both on same bond, no distance between them like in zwitter ion).
 zwitter ion: a molecule or ion having separate positively and negatively charged groups.
 معنا هائي المركبة كان ال (في تحول ال -)
 (Umpolung or polarity inversion) in organic chemistry: is the chemical modification of a functional group with the aim of the reversal of polarity of that group. This modification allows secondary reactions of this functional group that would otherwise not be possible.

بالتجربة الجاي بنعمل على ال benzoin وبفعل
 له oxidation بواسطة اوم مشتقات ال Copper
 مريتكون عنا benzyl

Procedure

1. In a stoppered E. Flask, prepare a solution of 1.04 g of thiamine hydrochloride in 3 ml of water⁴.
2. When all the thiamine hydrochloride has dissolved, add 8 ml of 95% ethanol with mixing.
3. Cool the solution for a few minutes in an ice bath [because thiamine is heat sensitive].
4. Very carefully and slowly add 3 ml of 10% NaOH with mixing "making sure that the temperature of the solution never rises above 20 C" [because NaOH with water exothermic].
5. Add to the mixture 7 ml of pure Benzaldehyde with mixing.
6. Stopper the flask and allow it to stand at room temp at least overnight (longer period do no harm). At the end of the reaction period, the benzoin should have separated as fine crystals.
7. Cool the reaction mixture in an ice bath to complete the crystallization.
8. Collect the product by vacuum filtration and wash them thoroughly with two 7 ml portions of cold 50% ethanol and several portions of water⁵ [color change from yellow to white].
9. Drain well and leave your product to dry (no need for recrystallization*).

	Weight (gm)	M.P
Benzoin		

لما تركنا
 على البنسيت
 ما صار غنا
 التفاعل
 لكن ما
 حركناه
 بال magnetic
 stirrer
 تكون
 fine line
 crystals

3 Brain storming Question

- 3.1 Discuss the chirality of the product, does it optically active? Explain your answer.

⁴ Water is required in this reaction BUT in specific amount:

- Too much water will force benzaldehyde out of the solution preventing an efficient reaction.
- Too little water prevents thiamine-HCl from dissolving.

* Re-crystallization is done using 95% ethanol.

⁵ Ethanol to remove excess benzaldehyde and water to get rid of thiamine.

* ملاحظة ٤ - لما أضفنا NaOH على الـ thiamine (كان clear ومار لونه أصفر، (تغير لونه) ليصبح
بسبب تحرر الـ R^-

← من الرسمة تأت الـ ylide تكون عندي
سُحبة سالبة كأنه عملت Conjugation (عقرة في
الحركة)، دائماً الـ Conjugation يعطي لون، فظهر
اللون الأصفر معناها انه الـ ylide الـ (R^-) تكون
← تحرر البروتون وعل عندي بدالة $(-)$ ومارت
الـ $(-)$ مع الـ aromaticity بدورو، مار معنا امتصاص
للطيف الكهرومغناطيسي (الطيف الضوئي)
وماديين أطياف اللون

يعطي لون $\rightarrow \text{Conjugation}$

Exp (3)

* توضح الخطوات العملية -

Dimerization of two molecules of
benzyl dehyde using catalysit (thiamine)
vit B1

① بنوزن 1.04 من ال Vitamine B1 ونخطه في E-flask

② نضيف حوالي 3 mL من الماء ثم نفوق thiamine
(water soluble) بنوزن كامل بنصف بعدها 8 mL
ethanol (solvent)

③ إذا صفتنا أكثر من 3 mL من الماء يمكن التفاعل
مع Benzyl dehyde (لأنه organic) طابعا

④ نضع ال E-flask في بار stopper ونفعل shaking

⑤ نخطه في ال ICE Bath من 5 min - 10 min (cooling)

(لأنه ال vit B1 حساس للحرارة ممكن يتكسر
من اكرارة العالية وبعض side product طابعا)

⑤ يجرى Ice bath بنصف حوالي 3 mL of 10% Sodium hydroxide solution (NaOH) في graduated cylinder

← Carefully and slowly NaOH مع الامتصاص exothermic (بمطهرارة) ، لاحظ التغير في Reaction

بعد الاضافة انه اكرارة لا تتجاوز 20°C ← يتحول اللون الى الاصفر

⑥ بنصف حوالي 7 mL من benzyldehyde ينسكرها ويخل Shaking ، يغيرنا turbidity (دليل على بداية حدوث التفاعل بين benzyldehyde

thiamine hydrochloride ← الاصل يخلو على البنش at least over night لكن لانه يجب نقله الى خطه عن magnetic stirrer

حتى تتكون عناء crystals يخل بعد filtration

⑦ بعد م بلست تتكون عندي ال crystals (بعد م تركناه فترة) بقطه بار Ice Bath مكان نقله crystallization (ينفصل ال benzoin على شكل solid form crystalline بعد التبريد بتكون عندي crystals أكثر)

⑧ vacuum filtration

⑨ فن عنا 50% ethanol / water solution بنقل فيه ال solid

المتكون (بأقل كمية ممكنة) , water : صبان

يخلصنا من ال

excess thiamine

ethanol : صبان يخلصنا

من ال excess

benzyl aldehyde

← solid لازم يطوع لونه أبيض + crystalline (benzoin)

Sara Jammain



Artery Academy
