



Hashemite University
Faculty of Pharmaceutical Sciences



Department of Pharmaceutical Chemistry

Practical Medicinal chemistry Manual

(131703425)

للاب الحيد بسنال عنا (١٠) تجارب
(٨) من المختبر
drug design (٥)
drug discovery

استخراج من مصدر طبيعي: م.و. نبات
(biological source)

Synthesis

drug design

Student Name:

Student number:

عن طريق

الكمبيوتر
بنشوف

اذا ممكن
يكون له

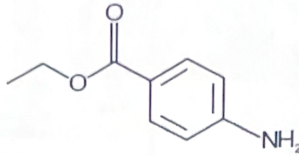
biological
activity

Edited by:
Farah Hudaib

2023/2024

Cycle 1

Multistep Synthesis of Benzocaine



Target Product

- Benzocaine is a local anesthetic from the ester family.
- The drug benzocaine is used in multiple forms including lotion, gel, liquid, lozenges, and sprays as a topical pain reliever.
- When Benzocaine is applied in any form, it temporarily numbs or blocks the nerve endings by inhibiting the voltage dependent Na channels on the neuron membrane, which leads to decrease in the amount of pain.

① Acetylation :- $\text{amine group} + \text{acetyl group} \rightarrow \text{amide}$
(amidation) $\text{amine} \rightarrow \text{amide}$
$$\text{N} - \overset{\text{O}}{\parallel}{\text{C}}$$

N-acetyl toluidine

② oxidation

③ Acid hydrolysis

④ esterification

General scheme of synthesis

acetic
anhydride



Part 4: Synthesis of Benzocaine

benzocaine:
(acetotoluidine = acetyl toluidine)

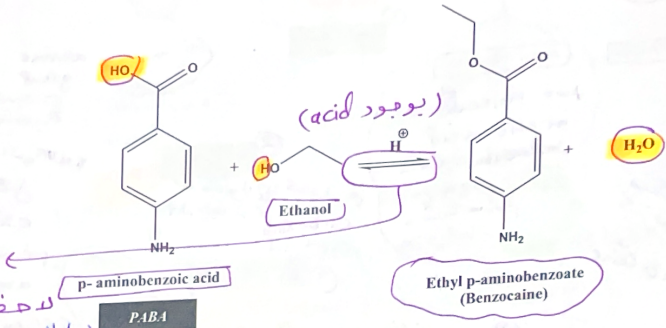
من الالب فقط 21 نستغل
هائي الخطوة لانه ار
PABA مركب متوافر بكثرة

You will see the mechanism only for the forth steps.

Experiment 1

Multistep Synthesis of Benzocaine

Part 4: Benzocaine synthesis



لحظوا انه التفاعل (reversible) ، ما بوقف

لا reaction الا لنموذج

لا equilibrium بين

product reactant

- Benzocaine is synthesized through the Fischer esterification of p-aminobenzoic acid (PABA) and ethanol, using sulfuric acid as a catalyst.

- PABA: is amphoteric that has weak acidic and weak basic properties.

→ To push the reaction forward

عشان اخلي التفاعل

يعيش باتجاه Benzocaine

H₂O (products)

لازم إما ازايه من ال

reactants (excess)

واحد من ال products (مجرد ما يتكون

عشان أمثل محفزة التفاعل

5 Assignment

5.1 Find a commercial synthesis pathway of PABA.

ال products

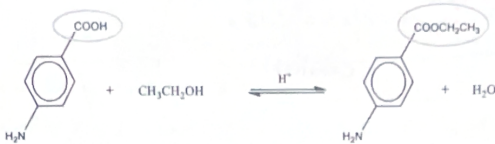
- reversible → يعني راجع يضل جزء من

ال reactant موجود ما يتفاعل

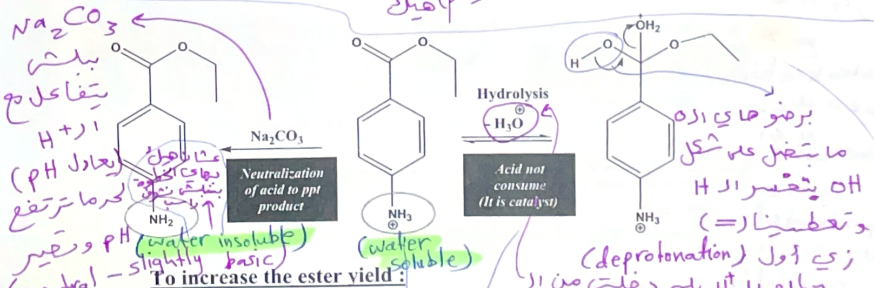
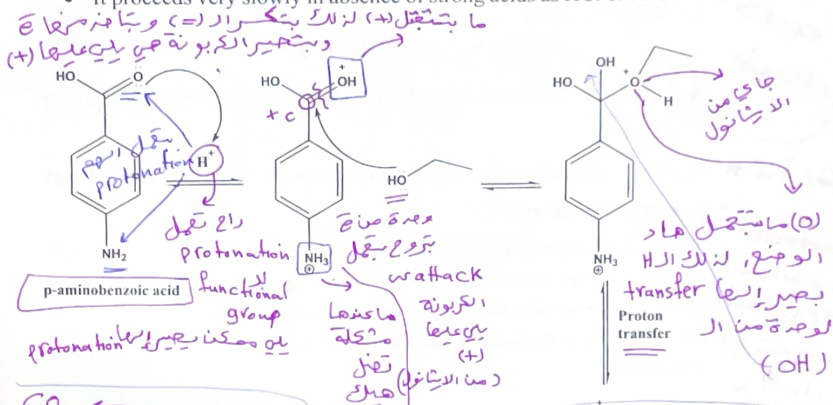
و جزء يتحول إلى product

$\text{H}^+ + \text{Na}_2\text{CO}_3 \leftarrow \text{بعض ايفاً } \text{Co}_2 \text{ (gas)}$
 Na_2CO_3 لو مطينا منه زياده عادي، مارح تزيه H^+ يعني
 8

Mechanism



- This reaction is called **Fischer esterification reaction**: a type of condensation reaction (both way reaction- limited yield)
- It is acid catalyzed (it not consume in the reaction). Catalyst يكون كيش يطرح
- It proceeds very slowly in absence of strong acids as HCl or H_2SO_4 .



To increase the ester yield:

- Use excess from the reactants
 - Remove water from reaction mixture as it is formed
- benzocaine
 لانه لساتنا بـ acidic، لانه sulfuric acid
 reaction طلع زي صاهو، لانه حسان نتا
 من الـ proton يبي على الـ NH_3^+ بضعيف
 neutralizing agent

لانه او ethand + sulfuric acid مع الحرارة راح يتبخرو
 لدرنا نرفعهم مرة ثانية وينخل هاد اسي عن طريق
 reflux condenser عبارة عن tube بدقل من باردة ما يصير تبخر
 بدقل هاد ال Condenser ويجو عني سطح باردة يتكاثفوا
 لل reactants
 Procedure
 اول ش لانه acid Conc لازم نضيقه شوي شوي
 وبعنا تدره راح يصير عنا production of heat وينزلو

تانية على مرة Round Bottom Flask
 كافيه لدرنا
 تتفكك مع ال
 1.32 g of PABA
 وبعنا كمان excess of ethanol

- In a 100 ml round-bottomed flask place 1.32 g of PABA, 10 ml of ethanol, and 1 ml of sulfuric acid (add cautiously) / Add a couple of boiling chips* then attach a reflux condenser and heat under reflux for 1 hour.
- Cool the solution to room temperature, neutralize with 10% sodium carbonate (foaming), and extract* with two 10-ml portions of dichloromethane (DCM) [use separatory funnel in extraction]. Then dry the combined organic layers over anhydrous magnesium sulfate [drying agent].⁽¹⁾
- Remove the dichloromethane by distillation using a steam bath as a heat source.

* اذا افكره من
 Condenser انه ما تقصر
 reactants
 من التبخر
 من الحرارة

- Then recrystallize the residue from methanol-water [Mixed solvent recrystallization*].⁽²⁾
 - Add 3-4 gm of anhydrous magnesium sulfate, swirl the mixture for about 5 minutes, and then remove it by gravity filtration.
 - Add 5 ml portions of methanol (with heating) until all the amount is dissolved, then add water drop wise until the solution becomes turbid, after that cool it in an ice bath to complete crystallization.

* مع
 neutralization
 راح تدا حقة

	Weight (gm)	M.P
Benzocaine		

انه ال BenzoCaine
 لانه كل protonated
 راح يصير له precipitation

- Brain storming Question
 - Discuss the reason behind doing extraction in DCM, and define the component for each layer.
 - Discuss the reason behind adding drying agent for the organic layer.
- مبتلاقوا لهم شرح يا اخو الما يقول
 Refer to appendix V: Boiling chips
 *Refer to appendix III: Recrystallization-Mixed solvent recrystallization.
 *Refer to appendix VII: Extraction.

بعنا بنخل
 Collection عن طريق
 funnel vacuum filtration
 ممكن نعمل recrystallization
 crystalline
 من كثر char أو من كثر crystalline

← procedure (تابع) 8 - مكيانف خطوة 2 +
خطوة 3 مارج نعلم

بالخبر

حسا من حال عملت neutralization وما صار عندي
precipitation ممكن نضيف في أو PCM ونخام
separation باستخدام separatory funnel لانه Benzocaine
من water soluble راج يروح الي organic layer

← بعد ال vacuum filtration اذا كانت ال powder
من crystalline ممكن نعمل recrystallization مع ال
methanol-water ، بناخذ ال powder بنو بجا ب 5 ml
(ethanol or methanol)

لما نتا به انه زاب تماما بنضيف عليه
drops of water عيينه راجل ، اسب مرة
تانية ، راج يكون هاد الراسب بار crystalline form
ونبرج نعمله filtration مرة تانية ونجوه
ال powder الي على ال filter paper

Sara Jammam



Artery Academy
