الجمهورية الجزائرية الديمقراطية الشعبية
Algerian Democratic and Popular Republic
Ministry Of Higher Education and Scientific Research

Institution: Ferhat ABBAS University – Setif 1

Faculty of Science

Department of Chemistry

Title of the master: Pharmaceutical Chemistry

MANUAL OF

Organic Chemistry Practical Works

Designated for 1st year Master Pharmaceutical Chemistry Students.

By

Dr. MESSASMA Zakia

Academic year: 2024–2025.

Table Of Contents

Avant Proposals

Introduction ..... ***Pg 1***

Manipulation **1 :** *Aldol Synthesis of Dibenzalacetone Report* ..... ***Pg 2***

Manipulation **2 :** *Synthesis and Characterization of Acetanilide from Aniline by Acetylation Reaction* ..... ***Pg 6***

Manipulation **3 :** *Synthesis and Characterization of 5- Nitro Salicylic Acid from Salicylic Acid by Nitration Reaction* ..... ***Pg 10***

Manipulation **4 :** *Synthesis and Characterization of Benzoic Acid from Benzyl Chloride by Oxidation Reaction* ..... ***Pg 12***

Manipulation **5 :** *Synthesis and Characterization of Benzoic Acid from Ethyl Benzoate by Hydrolysis Reaction*..... ***Pg 16***

Manipulation **6 :** *Synthesize Benzil from Benzoin by Oxidation Reaction* ..... ***Pg 19***

Manipulation **7 :** *Synthesis Of Cinnamic Acid From Benzaldehyde* ..... ***Pg 23***

Manipulation **8 :** *Synthesis of Schiff base ligand and its complexes* ..... ***Pg 25***

Manipulation **9 :** *Synthesis of a coumarin (7-hydroxy-4-methyl coumarin)* ..... ***Pg 30***

Manipulation **10 :** *Synthesis of Phenytoin* ..... ***Pg 32***

Avant Proposals

The goal of the practical organic chemistry assignments is to introduce students to the basic methods used in organic chemistry, such as distillation, recrystallization, and chromatography. These could be implemented in order to achieve :

- A chemical reaction
- Spectroscopic identification and characterization of synthesized products
- The use of experimental results to ascertain the mechanism or reactivity of chemical species
- Purification of the product by recrystallization
- Redaction of the results in the final accounts with strict scientific standards.

This polycopy of pratical work in organic chemistry is intended for first-year master's students in the pharmaceutical track of chemistry.

Introduction to the Organic Laboratory

The Organic Chemistry Laboratory is the most exciting part of the curriculum. It is the place where all of the abstract chemical concepts come to life. Although it is an exciting place it can also be one of the most dangerous environments that you have ever learned in. For that reason it is important to understand the nature of the organic compounds that you will encounter in the laboratory prior to implementing any lab experiment.

Calculations

A. Pre-Lab

1. Molecular Mass

The molecular mass gives us the total weight of the atoms in a compound it is important that students calculate the mass of the chemicals to aid in the theoretical and percent yield of the products.

2. Solubility

The amount of solute that can dissolve in a solvent is an important concept in the strength of solutions. Knowing the amount of solute and the right solvent will aid in the density an crystallization of compounds. One thing to remember is that "like dissolves like."

B. During

1. Density

Density is the ratio that compares the mass of an object to its volume. Density is a property that can be used to identify an unknown sample of matter.

Density = mass (g)/volume (ml)

2. Theoretical Yield

The theoretical yield of a product may be calculated from its molecular weight and the number of moles of the limiting reagent (the reactant that is short supply).

Theoretical Yield = (moles)(MW g/mol)

C. Post Lab

1. Percent Yield

The percent yield is the actual percent of the theoretical yield that you obtain from your calculations.

Percent yield = actual yield in g / theoretical yield in g

2. Specific Gravity

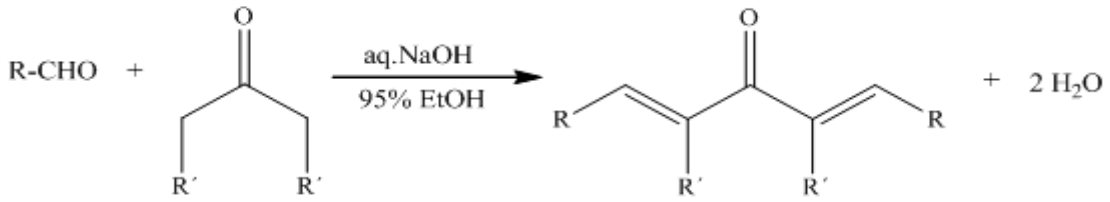
The specific gravity of a substance is the density of that substance compared to the density of water.

Specific Gravity= density of the substance/density of wate

Manipulation 1 : Aldol Synthesis of Dibenzalacetone Report [1,4-pentadien-3-one, 1,5-diphenyl-]

1. Introduction

Like the Grignard reaction, the Aldol Condensation is an extremely useful carbon-carbon bond forming reaction in organic chemistry. Under the reaction conditions in the experiment, two equivalents of aldehyde will react.



The aldol condensation is a reaction that is named based on the type of product formed when two aldehydes (or ketones), in the presence of dilute base, yields a molecule having both alcohol and aldehyde functional groups. An example of the type of base-catalyzed aldol condensation that you will perform is shown below.

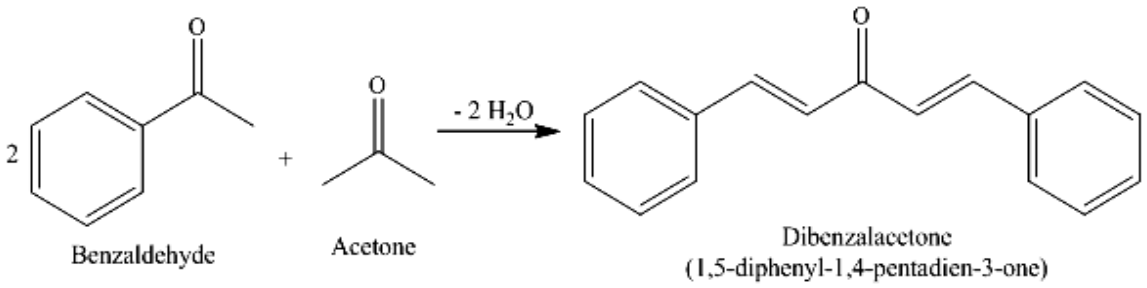


Diagram 1. Synthesis protocol of Dibenzalcetone.

These products are a ß-hydroxyaldehyde (or a ß-hydroxyketone). This reaction is used extensively in organic synthesis to form C-C bonds and make bigger molecules. In every case, the product results from the addition of one molecule of an aldehyde (or ketone) to a second molecule in such a way that the a-carbon of the first becomes attached to the carbonyl carbon of the second.

2. Principe

The base-catalyzed reaction of a ketone with an aldehyde is a mixed aldol condensation reaction, which is known as the Claisen-Schmidt reaction. Dibenzalacetone is prepared by the

condensation of acetone with two equivalents of benzaldehyde. The aldehyde carbonyl is more reactive that the ketone's and it reacts with the anion of the ketone which produces β-hydroxyketone, which easily undergoes base-catalyzed dehydration. This reaction can result in either monobenzalacetone or dibenzalacetone, depending on the relative quantities of the reactants. Dibenzalacetone is used in sunscreens and sunblock preparations because of its spectral properties. In this experiment, enough ethanol will be present as a solvent to readily dissolve the starting material which is benzaldehyde, as well as the intermediate benzalacetone. The benzalacetone onceit's formed, can easily react with another mole of benzaldehyde to produce dibenzalacetone.

3. Objective

The purpose of this experiment is to synthesize dibenzalacetone by aldol condensation from benzaldehyde and acetone. This experiment will further teach about the reaction of an aldehyde mixed with a ketone, which is called mixed aldol condensationn, which used extensively in organic synthesis to form C-C bonds and make bigger molecules.

4. Requirements Chemicals

As per specific quantity required

1. Benzaldehyde = 2.65 g
2. Acetone = 0.74 g
3. NaOH (40%) = 2.5 g
4. EtOH = 20 ml
5. Distilled water = 5 ml

5. Chemical Reaction

Benzaldehyde (C_6H_5CHO) and acetone $(CH_3)_2C=O$), the two substrates on which the reaction will be focused, are both unsymmetrical carbonyls. In the presence of dilute base, the carbonyl group of benzaldehyde does not readily undergo nucleophilic addition; however, the α-hydrogens of aldehydes are unusually acidic (pKa ≈ 16-20). This acidity is due to the resonance stabilization of an enol anion which can be formed by abstraction of the α-hydrogen by a base. Following the abstraction of the α-hydrogen of benzaldehyde by a molecule of sodium hydroxide to form the carbanion, the carbonyl group of a second molecule of benzaldehyde adds to the carbon of the carbanion. This aldol addition of an enol to a carbonyl is a powerful synthetic tool for forming carbon-carbon bonds. An aldol (first two reactions below) which is heated under acidic or basic conditions will dehydrate to give an α, β-unsaturated carbonyl compound (third reaction below). This final reaction is essentially the reverse of a Michael addition and provides another excellent method for forming carbon-carbon bonds. The overall reaction constitutes a convenient method for

the self-condensation of either of the carbonyl compounds and provides a useful route to several higher aldol or 'aldol-like' adducts. In the case of dibenzylideneacetone, while a crossed aldol could be attempted, steric hindrance of the adduct and/or the small Keq of each aldol often drive the reaction to the self-condensation of the more sterically accessible carbonyl compound.

6. Procedure

In a 100 ml two-necked flask equipped with a condenser, a dropping funnel and a magnetic bar, we put 2.65 g (2 mole) of benzaldehyde, 0.74 g (1 mole) of acetone, 24 mL of 40% NaOH, 20 mL of 95% ethanol, 4 mL of distilled water. We used the ethanol as a solvent to dissolve the sodium hydroxide. This solution was then added to a mixture of benzaldehyde and acetone. After the reaction was completed, filter the precipitate with a Buchner funnel and wash with iced water, check the washes with pH indicator paper (up to pH = 7). We dissolved the product in hot ethanol and allowed it to recrystallize by cooling.

An infrared and 1H NMR spectrums of the product is shown on the next page.

7. Questions

1. How would you modify the experiment in order to make benzalacetone, $PhCH=CHCOCH_3$ instead of dibenzalacetone PhCH=CHCOCH=CHPh.

2. What ingredients would you use if you wanted to make benzalacetophenone, PhCH=CHCOPh .

3. Calculate the quantities of matter and the theoretical mass.

4. Express the following yields as a function of the different masses.

- R1: yield of dry crude product.
- R2: recrystallization yield.
- R: overall yield.

5. Specify the role of ethanol.

6. Why must the temperature be maintained between 20 and 25°C.

7. Justify the use of ice water for washing the crude produc .

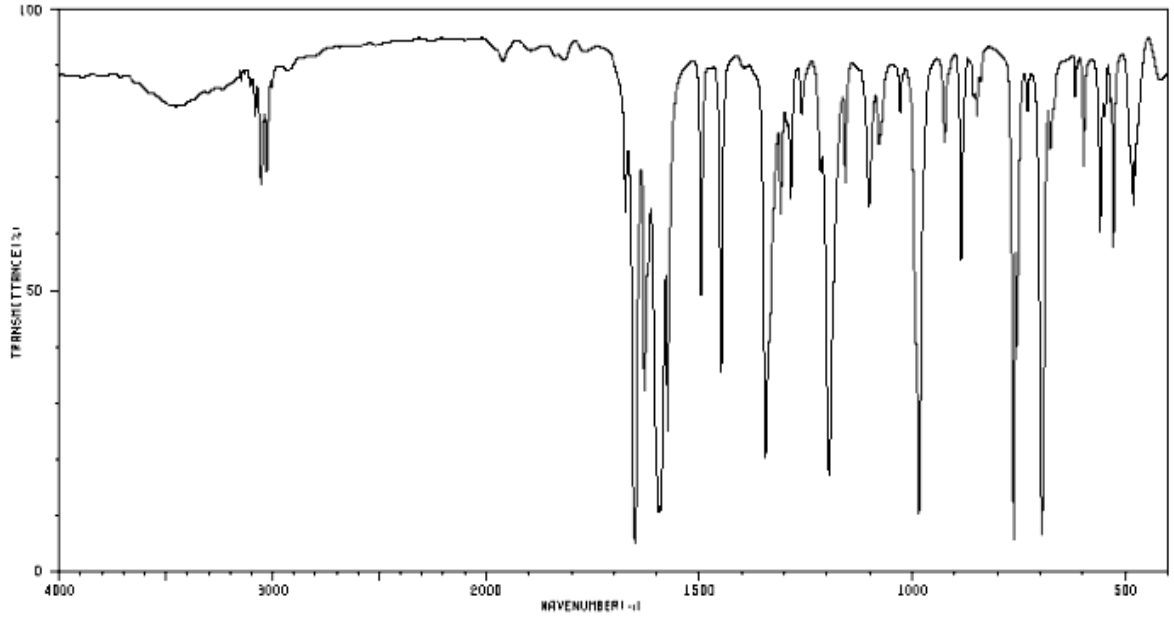
8. Justify the use of a mixture of solvents for recrystallization.

9. Comment on the TLC.

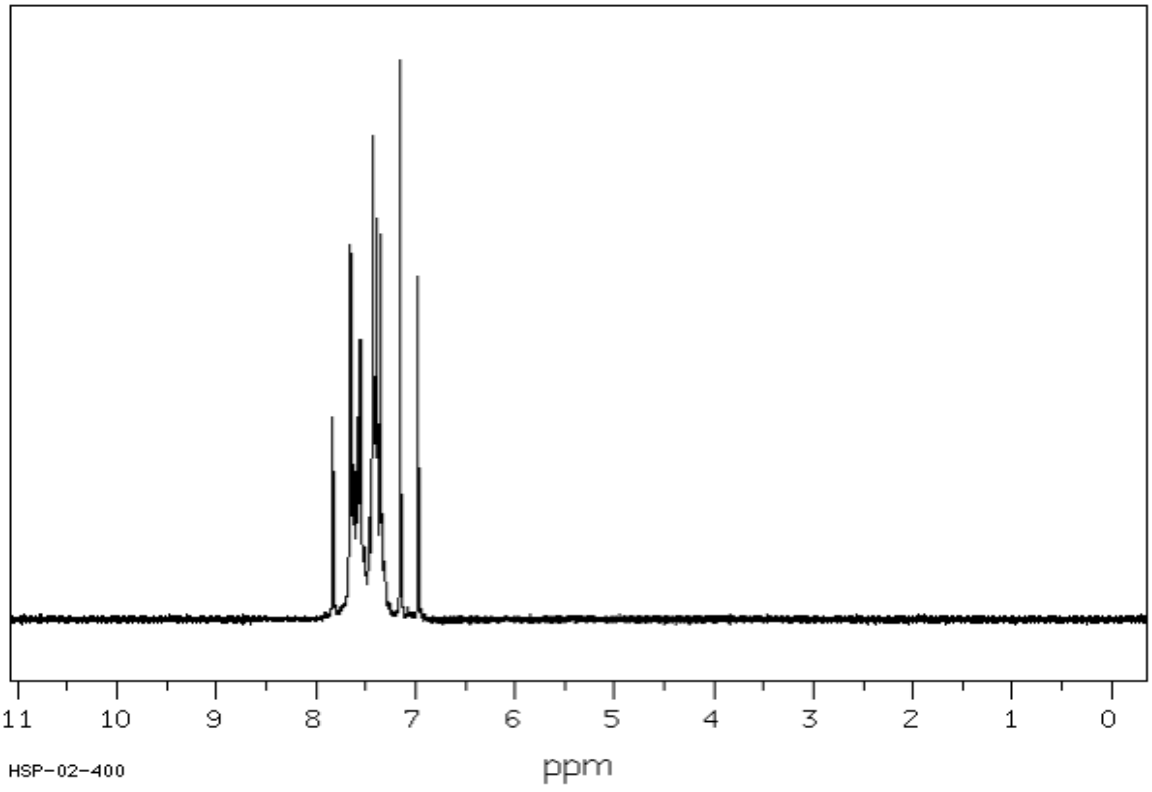
10. Identify the characteristic bands of dibenzilideneacetone in the spectrum IR given below.

11. Completely analyze the 1H NMR spectrum of dibenzilideneacetone.

IR spectrum of DBA



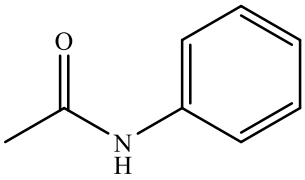
RMN-1H spectrum of DBA



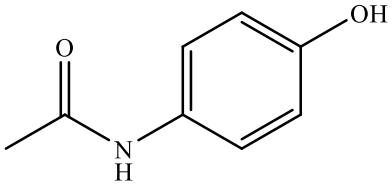
Manipulation 2 : Synthesis and Characterization of Acetanilide from Aniline by Acetylation Reaction

1. Introduction

Acetanilide is an analgesic, which was formally known as Antifebrin[1], and is structurally similar to acetaminophen (or Tylenol). However, unlike acetaminophen, acetanilide is toxic. Acetanilide is prepared from aniline using an acetylation reaction. Acetylation is often used to place an acetyl protecting group on primary or secondary amines to reduce their reactivity toward oxidizing agents or electrophiles. Acetamides are usually crystalline solids which can be a help in purification by recrystallization. The melting points can be used for characterization and identification of the corresponding compounds.



Acetanilide



Acetominophen (Tylenol)

2. Principe

Primary amines react with acid chlorides or anhydrides to form mono acetyl derivatives. Acetanilide is an organic chemical compound (meaning it›s composed of carbon and hydrogen mostly) that is classified as an amide in terms of its functional group. This means that it has the carbonyl group (carbon-oxygen double bond) bonded directly to a nitrogen atom. It also contains an aromatic ring, which is a ring composed of six carbon atoms and an alternating double-single-double-single bonding pattern all around the ring. Acetanilide is an analgesic, which was formally known as Antifebrin, and is structurally like acetaminophen (or Tylenol). However, unlike acetaminophen, acetanilide is toxic. Acetanilide is prepared from aniline using an acetylation reaction. Acetylation is often used to place an acetyl protecting group on primary or secondary amines to reduce their reactivity toward oxidizing agents or electrophiles. Acetamides are usually crystalline solids which can be a help in purification by recrystallization.

The melting points can be used for characterization and identification of the corresponding compounds.

3. Objective

The purpose of this experiment is to synthesize dibenzalacetone by aldol condensation from benzaldehyde and acetone. This experiment will further teach about the reaction of an aldehyde mixed with a ketone, which is called mixed aldol condensation.

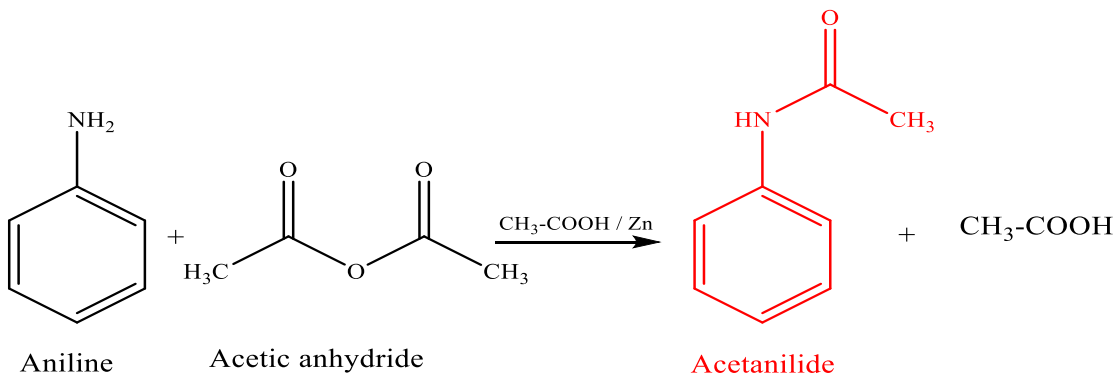
4. Requirements Chemicals

as per specific quantity required

1. Aniline = 10 ml
2. Glacial acetic acid = 10 ml
3. Acetic anhydride = 10 ml
4. Zinc dust = 15 ml
5. Distilled water = 100 ml

5. Chemical Reaction

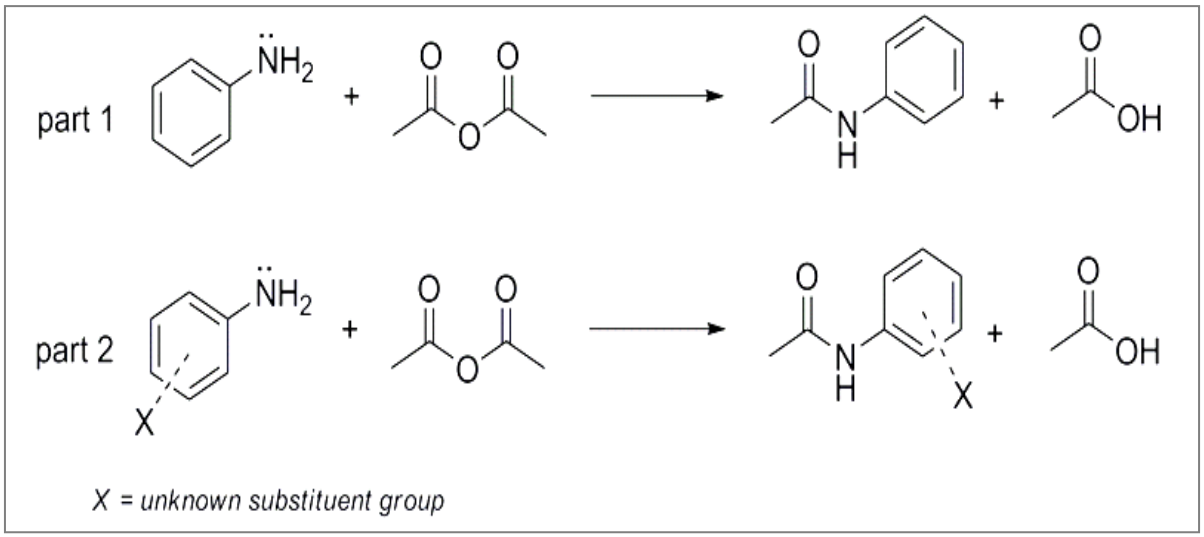
Acetanilide is prepared from aniline when it acylating with acetic anhydride in presence of glacial acetic acid and zinc dust. Aniline or phenylamine is a primary amine and basic in nature. Acetic anhydride as anhydride of acetic acid, act as a source of acyl group. Aniline reacts with acetic anhydride to form acetanilide by nucleophilic substitution reaction and the reaction is called acylation reaction. In this reaction aniline acts as a nucleophile and acyl (CH_3 CO-) group from acetic anhydride act as a electrophile. Hence the hydrogen atom of NH_2 group is replaced by the acyl group. Zinc is used to prevent the oxidation of aniline during the chemical reaction. Acetanilide is medicinally important, and it is used as febrifuge.



Other Names– N-phenyl acetamide, N-phenylethanamide, Acetanil.

Diagram 2. Synthesis protocol of Acetanilide.

Acetylation of aniline and unknown substituted anilines with acetic anhydride



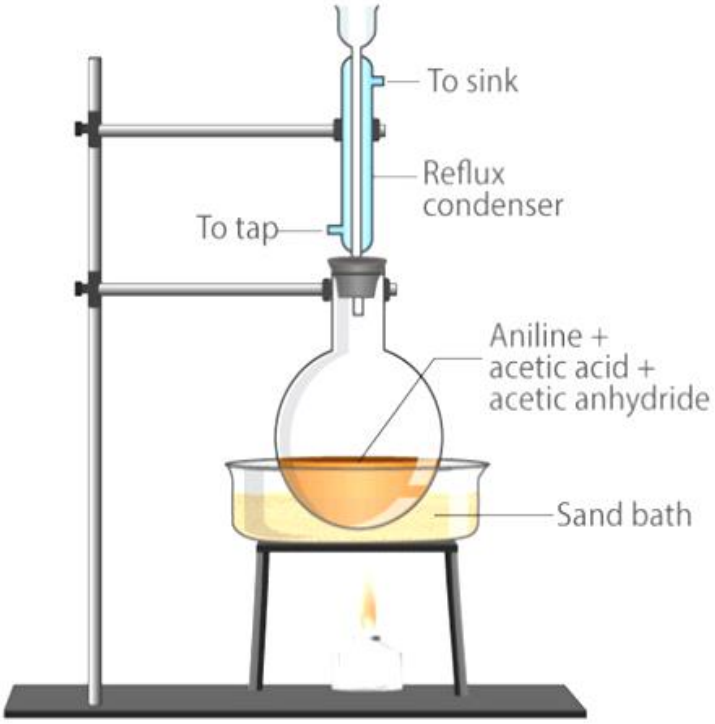
6. Procedure

Wash out all the apparatus with distilled water before starting the experiment.

Prepare a mixture of 10 ml of glacial acetic acid and 10 ml acetic anhydride in a beaker, place 10 ml ($10.^3$ gm) of aniline in a round bottom flask and carefully add 20 ml of acetic anhydride and glacial acetic acid mixture (equal volumes) and add a zinc dust. Set up the reflux condenser with the round bottom flask and heat the reaction mixture gently for about 15–20 minutes on oil bath. The reaction mixture quickly crystallize.

Pour the hot reaction mixture in a beaker containing ice cold water with constant stirring. And carefully stir the reaction mixture vigorously to hydrolyze excess of acetic anhydride.

The reaction mixture was recrystallized from about 60 ml mixture of one volume of acetic acid and two volumes of water. Crude product of acetanilide is precipitated, collect and filter of the colourless crystals at the suction pump, again wash thoroughly with water. Dried the crude product of acetanilide. After that recrystallization the crude product by using a 30 ml ethanol. Finally weigh the crude product and calculate the practical yield and obtained 12 gm and measure the melting point about 114^o C.



7. Questions

1. Describe in your own words what happens to aniline as concentrated hydrochloric acid is added.

2. Why is sodium acetate used ?

3. What if NaOH was used instead ?

4. Compare the behavior of the unknown substituted amine with aniline in the acetylation reaction. How did the 2 reactions differ?

5. What how might the structural differences in the unknown substituted amine cause it to react differently than aniline, which is un-substituted?

6. How does the Infrared spectrum of your unknown amine compare to that of aniline? How does the spectrum of your unknown acetamide product compare to that of acetanilide?

Manipulation 3 : Synthesis and Characterization of 4- Nitro Salicylic Acid from Salicylic Acid by Nitration Reaction

1. Introduction

Nitration are among the most common reactions carried out at industrial scale. Nitration on salicylic acid occurs by placing a nitro group on the aromatic ring system via an electrophilic aromatic substitution reaction. Here the calcium nitrate is used as the nitrating agent in the presence of acetic acid. Two groups -COOH and -OH in salicylic acid complement each other since they both direct the entering nitro group to the 5th position. The 5th position and the 3rd position are both electronically favored since the -COOH group is meta directing and -OH group is ortho para directing. The nitro group is attached at the 5th position, not at the 3rd position, due to steric effect. We can also use anhydrous nitric acid or concentrated and nitric acid and concentrated sulphuric acid as nitrating agent.

2. Objective

The purpose of this experiment is to synthesize a 5-Nitro Salicylic Acid from Salicylic Acid by Nitration Reaction .

3. Requirements Chemicals

1. Salicylic acid = 2 gm
2. Acetic acid = 10 ml
3. Calcium nitrate tetrahydrate = 3 gm

4. Chemical Reaction

The 4-nitrosalicylic acid is synthesized by nitration (generates the intermediate 2-Chloro-5-nitrobenzoic acid, and hydrolysis (generates the target product) of o-chlorobenzoic acid. The influences of the nitration of temperature, proportion of mixed acid and of the hydrolysis of temperature, reaction occurs.

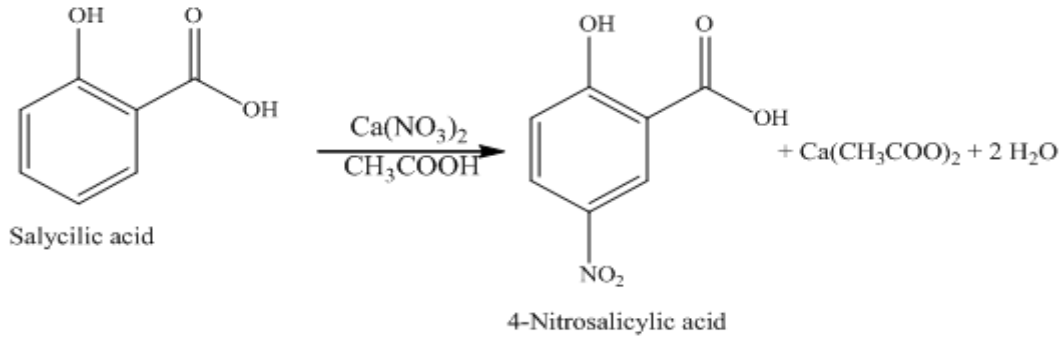


Diagram 3. Synthesis protocol 4-Nitrosalicylic acid.

5. Procedure

Place a 3 gm of calcium nitrate tetrahydrate is dissolved in a 10 ml of acetic acid in a 250 ml of conical flask by gently heating in a water bath, then 2gm of salicylic acid is added, and the reaction mixture is heated on boiling water bath (below 80 °C) for few minutes.

A dark red solution is formed. Then the dark red colour solution mixture is poured into 100 ml beaker containing 20ml ice water. A turbid dark red coloured solution is form which is kept in refrigerator and after 4–5 hours, yellow crystal of 5-Nitrosalicylic acid separate out.

Finally, yellow precipitate of 5-Nitro salicylic product is filtered at a suction pump wash with cold water and dried.

6. Questions

1. What is the limiting reactant in the nitration of salicylic acid

2. What type of reaction is the addition of salicylic acid to 5-Nitro salicylic acid

3. Why salicylic acid is used in the nitration of 5-Nitro salicylic acid

4. Identify what is the electrophile in this reaction

Manipulation 4 : Synthesis and Characterization of Benzoic Acid from Benzyl Chloride by Oxidation Reaction

1. Introduction

Benzoic acid is a white, solid, aromatic acid, used in a wide range of cosmetic products as a pH regulator, and in a wide range of cosmetic products.

In this reaction a side chain oxidation is performed. In order to achieve this benzyl chloride is mixed with sodium carbonate solution and is oxidized with potassium permanganate solution. The sodium salt of benzoic acid is formed, this is acidified with concentrated hydrochloric acid when benzoic acid crystallizes out.

2. Principle

In this reaction a side chain oxidation reaction is performed. If oxidation occurs an aromatic compound having an aliphatic side chain then, fission of the side chain occurs between the first and second carbon atom from the benzene ring and the first carbon atom thus becoming part of a carboxyl (-COOH) group. The oxidation process is carried out with a mixture of potassium permanganate and sodium carbonate in aqueous solution or dilute nitric acid. The reaction is quite slow if the side chain a simple alkyl group. The side chain containing chlorinated alkyl group is more susceptible to oxidation. Hence in comparison to toluene, benzyl chloride more rapidly oxidizes in the presence of an aqueous oxidizing agent. Here benzyl chloride is first hydrolyzed to benzyl alcohol and undergoes oxidation of a primary alcohol to the corresponding carboxylic acid. In order to achieve this benzyl chloride is mixed with sodium carbonate solution and is oxidized with potassium permanganate solution. The sodium salt of benzoic acid is formed, this is acidified with concentrated hydrochloric acid when benzoic acid crystallizes out.

3. Objective

The purpose of this experiment is to synthesize of Benzoic Acid from Benzyl Chloride by Oxidation Reaction.

4. Requirements Chemicals

1. Benzyl chloride = 5 mL (5.5 gm)
2. Sodium sulphite = 20 gm
3. Potassium permanganate = 10 gm
4. Anhydrous sodium carbonate = 5 gm
5. Con. Hydrochloric acid = 50 mL

5. Chemical Reaction

In this mechanism of reaction benzyl chloride is first hydrolyzed to benzyl alcohol in the presence of sodium carbonate in aqueous solution of nitric acid and undergoes oxidation of a primary alcohol to the corresponding carboxylic acid. In order to achieve this benzyl chloride is mixed with sodium carbonate solution and is oxidized with potassium permanganate solution. The sodium salt of benzoic acid is formed, this is acidified with concentrated hydrochloric acid when benzoic acid crystallizes out.

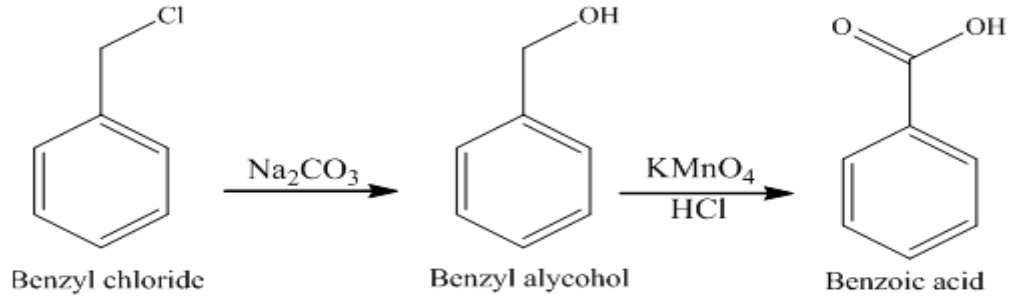


Diagram 4. Synthesis protocol of the Benzoic acid.

6. Procedure

5ml (5.5gm) of benzyl chloride is added to a solution of about 5 grams of anhydrous sodium carbonate dissolved in 100ml of distilled water in a round bottom flask. Then round bottom flask is fitted with a water reflux condenser. After that, added 10 grams of potassium permanganate in 80 ml of water in small quantities through the water condenser until a permanent pink colour persists even after continuous boiling. Then it is boiled gently for 1 to 1.5 hours to complete the reaction.

During the boiling time, the permanganate is slowly reduced, and manganese dioxide is separates as a dark brown precipitate. After the flask is cooled, and 50 ml of conc. hydrochloric acid is added cautiously until the mixture is strongly acidic, and all the benzoic acid precipitate is formed. Then added about 20 grams of sodium sulfite are added to this mixture slowly with shaking until the manganese dioxide is completely dissolved and only the white precipitate of benzoic acid is remains.

Reaction mixture is cooled, precipitated of benzoic acid is filtered and washed the suction pump. Crude product of benzoic acid is recrystallized from using of boiling water. Care should be taken while setting up the equipment's, the hydrochloric acid used in converting the sodium salt of benzoic acid is concentrated, so extreme care should be taken while handling

the chemicals and using them. Wear goggles, gloves and apron while performing the experiment.

An infrared and 1H NMR spectrums of the product is shown on the next page.

7. Questions

1. What is the limiting reactant in the oxidation of benzoyl chloride

2. What type of reaction is the addition of benzoyl chloride to benzoic acid

3. What do you think the purpose was to filter the hot product solution through the fluted filter paper

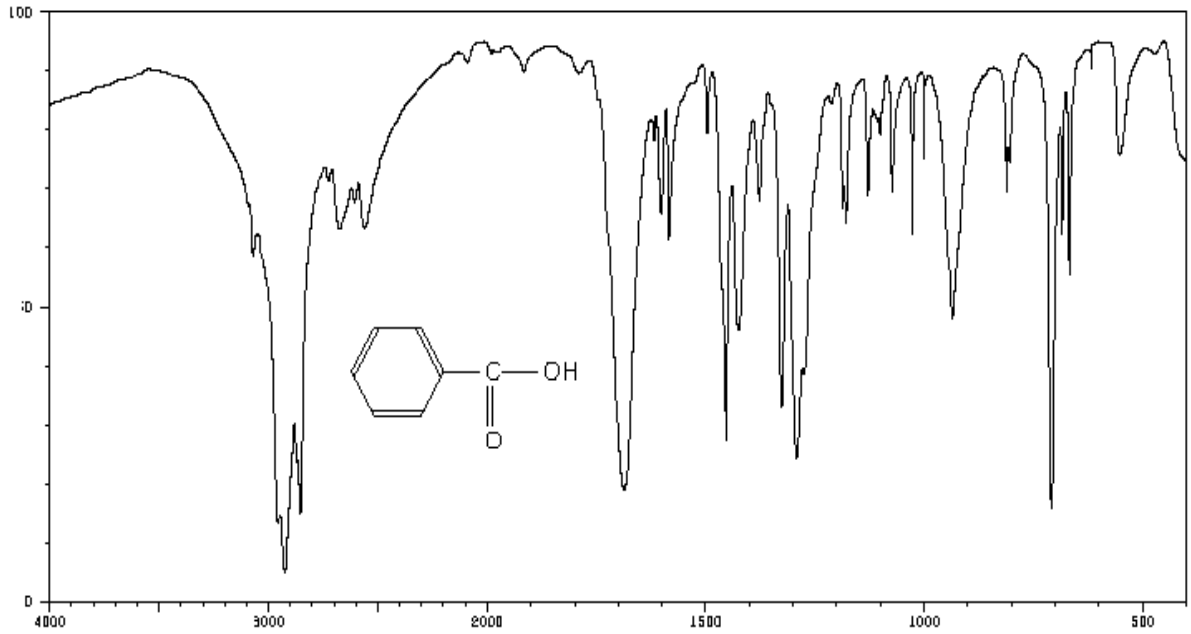
4. Write a good definition for what a catalyst is. Is the sodium hydroxide a catalyst in this experiment? Explain.

5. You could say that the reaction you have completed is "oxidation"

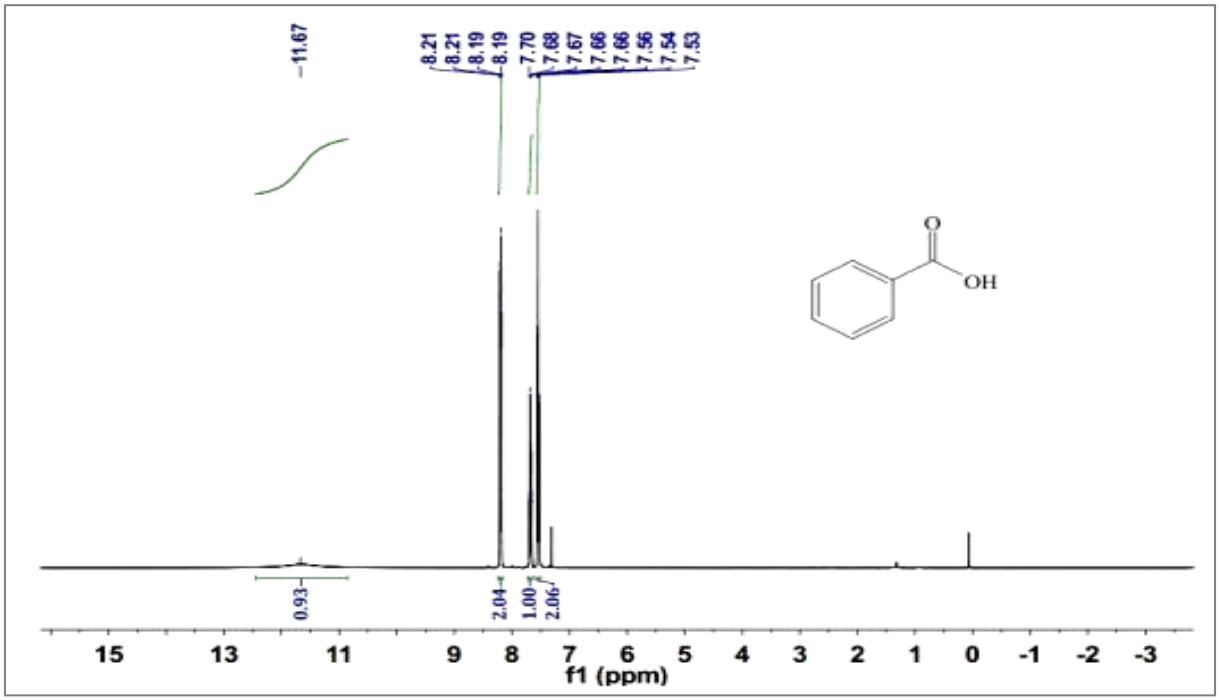
6. Identify the characteristic bands of Benzoic Acid in the spectrum IR given below.

7. Completely analyze the 1H NMR spectrum of Benzoic Acid.

IR spectrum of Benzoic Acid



RMN-1H spectrum of Benzoic Acid



Manipulation 5 : Synthesis and Characterization of Benzoic Acid from Ethyl Benzoate by Hydrolysis Reaction.

1. Introduction

Most benzoic acid produced today is synthetic. Its first industrial synthesis was the hydrolysis of benzotrichloride to calcium benzoate, followed by acidification. This method has been completely displaced by the air oxidation of toluene, which avoids the problem of product contamination with chlorinated by products.

Many processed foods contain benzoic acid or one of its salts as a preservative. The acid inhibits the growth of bacteria, molds, and yeasts; it works best when the food has an acidic pH value. Benzoic acid also is often found in topical antifungal preparations.

2. Principle

This process is called base hydrolysis (or saponification) of an ester and is used in this experiment to first obtain sodium benzoate solution, and then benzoic acid from ethyl benzoate. Ethyl benzoate belongs to a class of compounds called esters. Esters are hydrolyzed either by an acid or a base. Alkaline hydrolysis of ester is irreversible which is also called as saponification. Acid hydrolysis of ester is reversible reaction. Acid hydrolysis of ester is can occurs by more than one type of mechanism, the common mechanism is: Alkaline hydrolysis, which occurs through a nucleophilic acyl substitution. Here ethyl benzoate on hydrolysis with sodium hydroxide gives benzoic acid and ethyl alcohol, where OH ion of sodium hydroxide act as a nucleophile. When ethyl benzoate is shaken with water two liquid layers form. The upper layer is ethyl benzoate (less dense) and the lower layer is water. There is no clear indication of any reaction taking place. A more careful study shows that ethyl benzoate reacts very slowly with water and is hydrolyzed to give benzoic acid and ethanol, but the reaction does not go to completion. However, ethyl benzoate is found to react much faster with aqueous sodium hydroxide, the reaction going to completion, to give sodium benzoate (water soluble) and ethanol (miscible with water). The ethanol may be recovered by simple downward distillation from the reaction mixture and collected as a solution in water.

3. Objective

The purpose of this experiment is to synthesize of Benzoic Acid from Ethyl Benzoate by Hydrolysis Reaction.

4. Requirements Chemicals

1. Ethyl Benzoate = 2mL
2. 10% sodium Hydroxide solution = 100ml
3. Hydrochloric acid = Sufficient

5. Chemical Reaction

Ethyl benzoate is heated with aqueous sodium hydroxide. At the start of the reaction the flask contains two immiscible layers, a liquid layer of the water insoluble ethyl benzoate floating on the aqueous sodium hydroxide layer. reaction mixture to as the ethyl benzoate reacts, water soluble products are formed and the upper layer decreases in size until a homogeneous solution is obtained and the reaction is complete

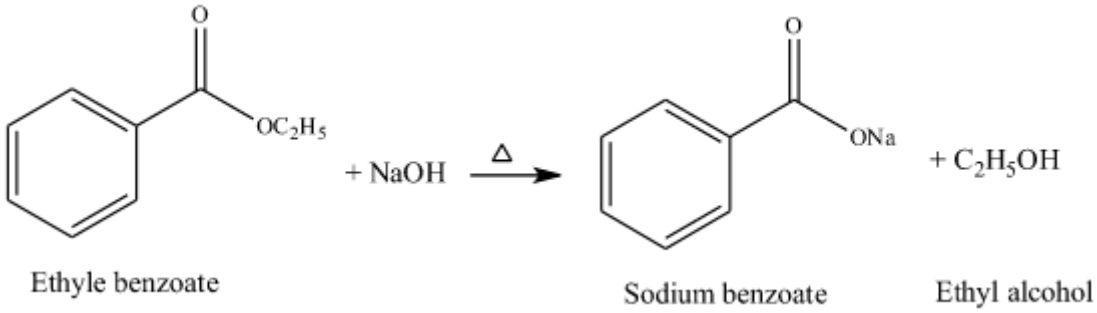


Diagram 5. Synthesis protocol of the Sodium benzoate.

6. Procedure

Properly clean the glassware and lightly grease the ground glass joints. Use only a small amount of the lubricant supplied (on the upper bench top) to grease the joints, then rotate them together to form a smooth seal. Excess grease may be wiped off with a towel.

Set up the apparatus with the condenser attached to the round bottom flask in the reflux position. Do not clamp too tightly or the glass may break. Never store glassware with the joints connected as they may "freeze" together. Then carefully detach the 100ml round-bottomed flask from the apparatus and dispense 2.0ml of ethyl benzoate into it. Then transfer 15ml (graduated cylinder) sodium hydroxide followed by 3 or 4 boiling granules to the ethyl benzoate in the flask and reattach it to the apparatus. After that, heat can be gently over a low flame so that the liquid refluxes for 30minutes at a temperature at 90–100°C.

Finally, reaction mixture in the flask should be shaken by using glass rod almost continuously to speed up the hydrolysis reaction.

7. Questions

1. What is the limiting reactant in the hydrolysis of ethyl benzoate

2. What type of reaction is the addition of Ethyl benzoate to benzoic acid

3. What do you think the purpose was to filter the hot product solution through the fluted filter paper?

4. Write a good definition for what a catalyst is. Is the sodium hydroxide a catalyst in this experiment? Explain.

5. You could say that the reaction you have completed is hydrolysis reaction

Manipulation 6 ; Synthesize Benzil from Benzoin by Oxidation Reaction

1. Introduction

Benzoin, which is a ketone, can be converted to benzil through nitration with nitric acid. This reaction involves the oxidation of the alcohol group to a ketone group, followed by the formation of a cyclic dimeric intermediate, which eventually forms benzil.

2.Principe

Alcohol group of benzoin is oxidized to ketone group forming benzil in the presence of concentrated nitric acid. Nitration of aromatic ring is not occurring as sulphuric acid is totally absent in the whole process.

3. Objective

The purpose of this experiment is to synthesize of Benzil from Benzoin by Oxidation Reaction

4. Requirements Chemicals

1. Benzoin = 4 g
2. Nitric Acid = 10 ml
3. Acetic Acid = 10 ml

5. Chemical Reaction

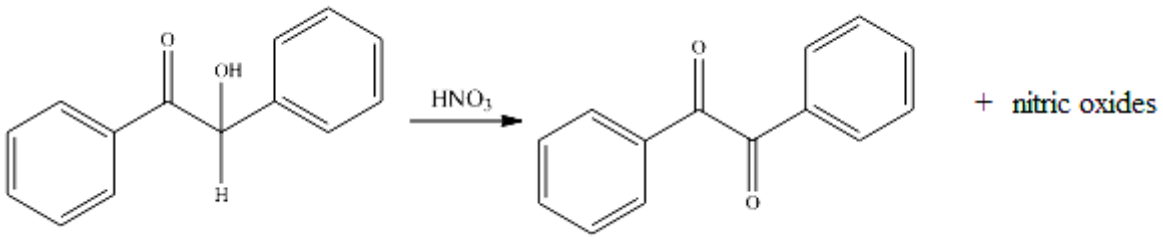


Diagram 6. Synthesis protocol of the Benzoin .

6. Procedure

Place 4 g. of crude benzoin and 10 ml, of concentrated nitric acid and 10 ml of acetic acid in a 100 ml. round-bottomed flask. Heat on a boiling water bath (in the fume cupboard) with occasional shaking until the evolution of oxides of nitrogen has ceased (about 1 hour). Pour the reaction mixture into 100 ml. of cold water contained in a beaker, stir well until the oil crystallizes completely as a yellow solid. Filter off the crude benzil at the pump, and wash it thoroughly with water to remove the fumes of nitric acid. Recrystallize from alcohol or methylated spirit (about 2-5 ml. per gram).

7. Questions

1. Report the yield and melting point of the product

2 . Express the following yields as a function of the different masses.

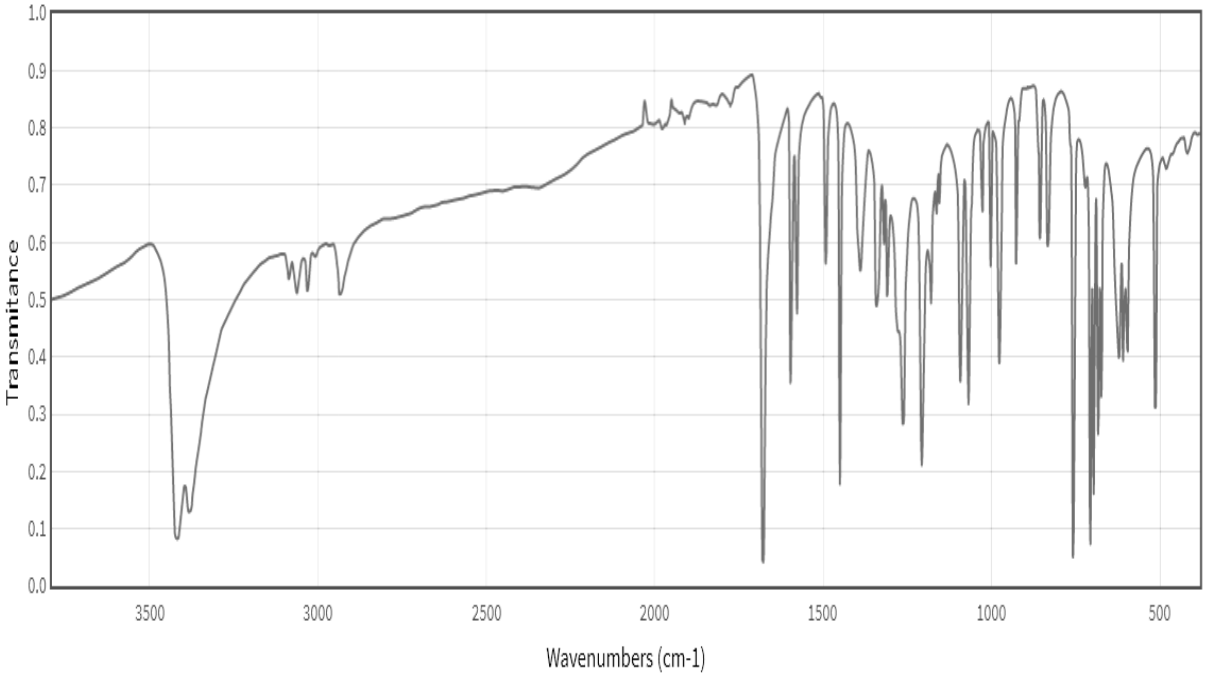
- R1: yield of dry crude product.
- R2: recrystallization yield.

3. Give the reaction mechanism

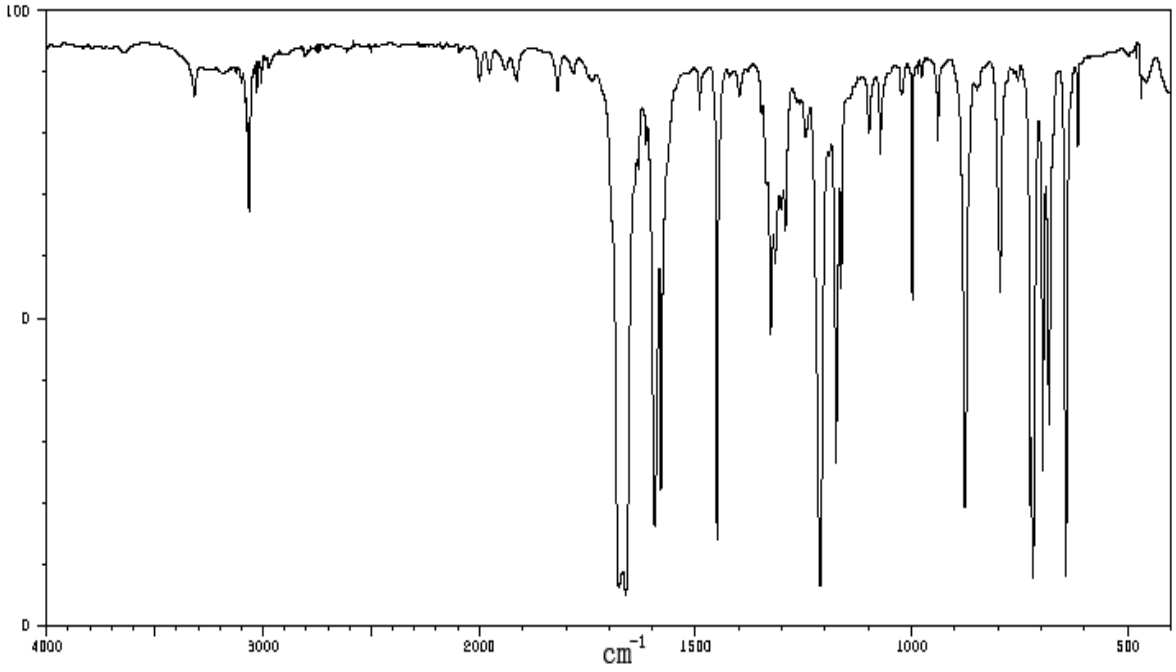
4. Identify the characteristic bands of Benzoin and Benzil in the spectrum IR given below and make the comparison.

5. Completely analyze the 1H NMR spectrum of Benzoin.

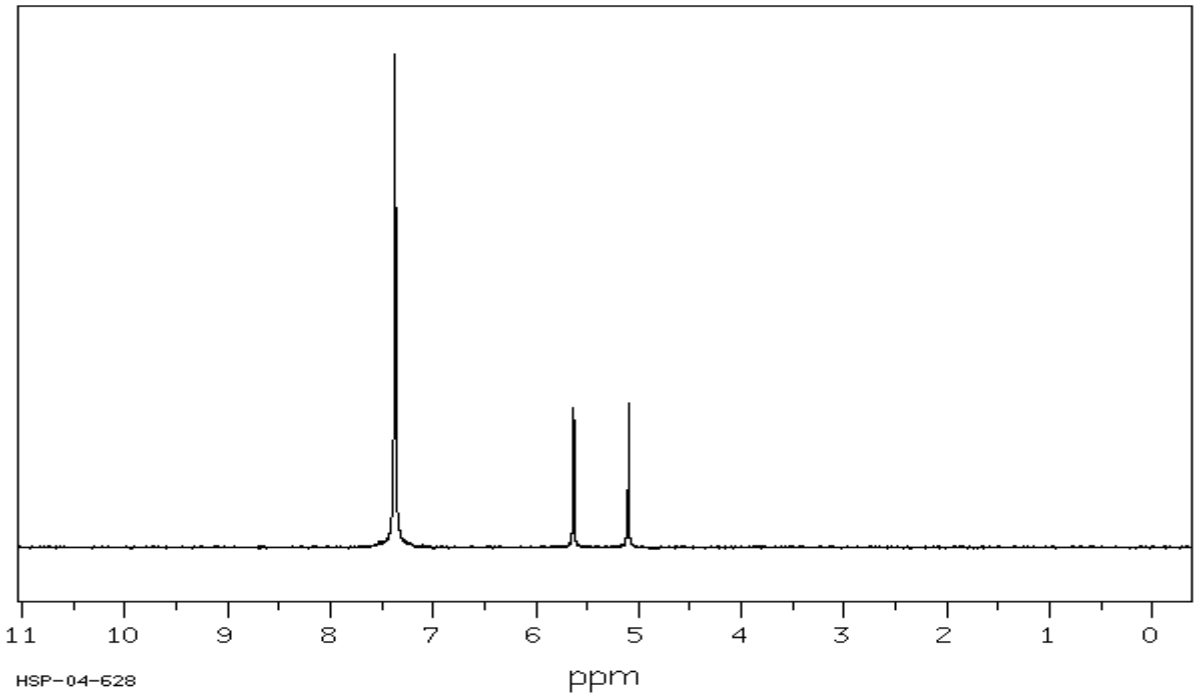
IR spectrum of Benzoin



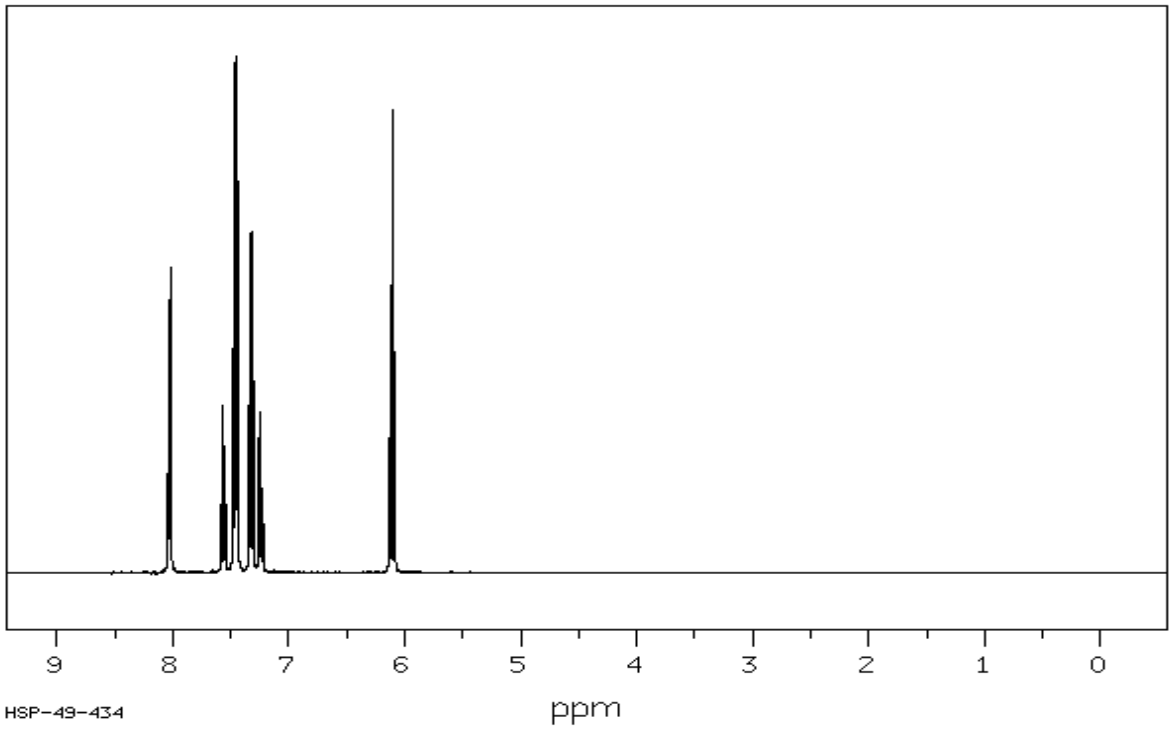
IR spectrum of Benzil



RMN-1H spectrum of Benzil



RMN-1H spectrum of Benzoin



Manipulation 7 : Synthesis Of Cinnamic Acid From Benzaldehyde

1. Introduction

Cinnamic acid is used in flavors, synthetic indigo, and certain pharmaceuticals. A major use is in the manufacturing of the methyl, ethyl, and benzyl esters for the perfume industry.

2. Objective

To synthesize trans-cinnamic acid from benzaldehyde and acetic anhydride by Perkin condensation reaction and find out percentage yield.

3. Principle

The formation of cinnamic acid from benzaldehyde undergoes perkin condensation. Perkin condensation is the condensation of an aromatic aldehyde with an acid anhydride in presence of sodium or potassium salt of the acid corresponding to the anhydride to yield an α,β-unsaturated acids. In this preparation benzaldehyde is reacted with acetic anhydride in presence of potassium acetate salt to yield cinnamic acid.

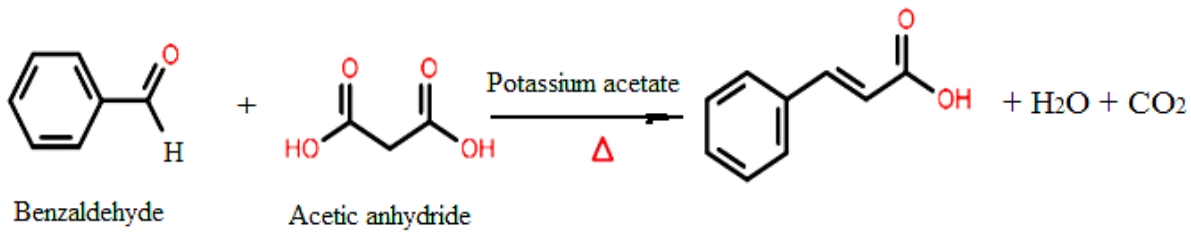


Diagram 7. Synthesis protocol of the Cinnamic acid.

4. Chemicals

1. Benzaldehyde = 1ml
2. Potassium acetate = 600 mg
3. Acetic anhydride = 1.4 ml
4. Na_2CO_3,
5. HCl
6. Water = 400 ml

5. Procedure

To a RBF add benzaldehyde 1 mL, potassium acetate 600 mg, and acetic anhydride 1.4 mL. A condenser was attached and the system was heated to reflux in a sand bath at 180° C for 1 hour. The reaction mixture was cooled, quenched with water (40 mL), made basic (pH 8-10) with saturated Na_2CO_3, transfer this aqueous solution to a separatory funnel and extract three

times with 10 mL of tert-butyl methyl ether (BME). The organic extracts will be discarded at the end of the experiment. Crude product was precipitated from the aqueous layer with 6 M HCl (pH=2), cooled in an ice bath, and then isolated as a white solid filtration. Recrystallize the sample. Determine the melting point of the product the melting point of pure cinnamic acid – 133° C.

6. Questions

1. Calculate the theoretical mass of Cinnamic acid expected.

2. Provide the mechanism of the reaction.

3. Calculate the yield of the reaction.

4. Provide the melting point of the recrystallized product.

Manipulation 8 : Synthesis of Schiff base ligand and its complexes

1. Introduction

Schiff base compounds and their metal complexes have been extensively investigated due to their wide range of applications including catalysts, medicine, crystal engineering, anti-corrosion agent. Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom; structural similarities with natural biological compounds and also due to presence of azomethine group(-N=CH-) which imports in elucidating the mechanism of transformation and racemization reaction biologically. Schiff bases having chelation with oxygen, nitrogen etc. donors and their complexes have been used as drugs and reported to possess a wide variety of biological activities against bacteria, fungi, and certain type of tumors and also, they have many biochemical, clinical and pharmacological properties. Imine or azomethine groups are present in various natural, naturally derived and nonnatural compounds. The imine group present in such compounds has been shown to be critical to their biological activities.

2.Principe

Aromatic amines generally condense with aldehydes or ketones to give imines (also called Schiff bases).

Our imine is prepared by condensing benzaldehyde with aniline, the mixture of aniline and anhydrous benzaldehyde gives a precipitate of N-phenyl phenylmethanimine, according to the following reaction.

3. Objective

Synthesis of an imine also called Schiff base and its complexes of metal transition.

4. Requirements Chemicals

1. Salicylaldehyde = 0.244 g
2. Ethylenediamine = 0.060 g
3. Ethanol = 30 ml
4. Ferric(III) chlorid
5. Manganese (II) chloride

5. Procedure

5.1. Synthése de ligand base de Schiff (type Salen)

A 50 ml volume balloon topped with a refrigerant containing 0.244 g (2 mmole) of Salicylaldehyde was dissolved in 5 ml of ethanol (EtOH) and stirred at room temperature. The

resulting solution was then added dropwise to 0.060 g (1 mmole) of 1,2-Ethylene diamine previously dissolved in 5 ml of ethanol. This mixture was stirred at 50 °C until it turned yellow. The crude reaction mixture is filtered, washed with small portions of cold ethanol, and then with diethyl ether. The purity of the ligand is checked by TLC using the same eluent as before. The resulting solid was dried under vacuum in the presence of $CaCl_2$.

The overall reaction scheme for the synthesis of the Schiff base is shown below :

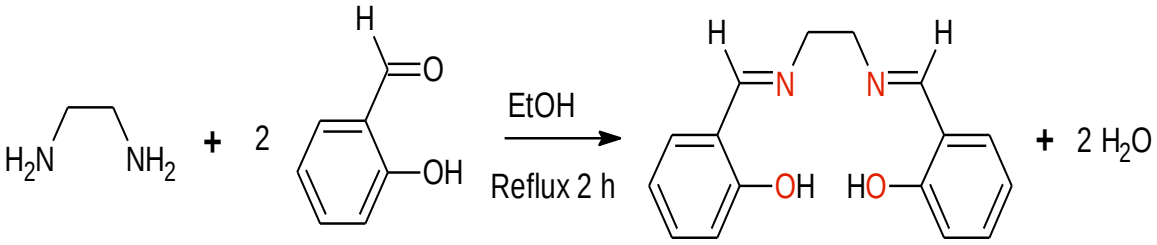


Diagram 8. Synthesis protocol of the Schiff base ligand .

5.2. Synthesis of the manganese III complex

A stoichiometric amount of manganese (II) chloride was added to a suspension of the ligand (100 mg) in ethanol and the suspension was refluxed. After 3 h, the solvent was concentrated and the brown solid was preciipitated with diethyl ether. The solid was vacuuum filtered and washed.

Considering that your complex precipitates directly in solution, estimate the environment around the metal knowing that the complex is in the oxidation state three.

5.3. Synthesis of the ferric III complex

A stoichiometric amount of ferric (II) chloride was added to a suspension of the ligand (200 mg) in ethanol and the suspension was refluxed. After 3 h, the solvent was concentrated and the black solid was preciipitated with diethyl ether. The solid was vacuuum filtered and washed.

The UV-Vis spectra and IR could also be carried out to characterize the ligand and tis complexes of manganese III and feriic II.

The overall reaction scheme for the synthesis of the complexes is shown below :

The overall reaction scheme for the synthesis of the Schiff base is shown below :

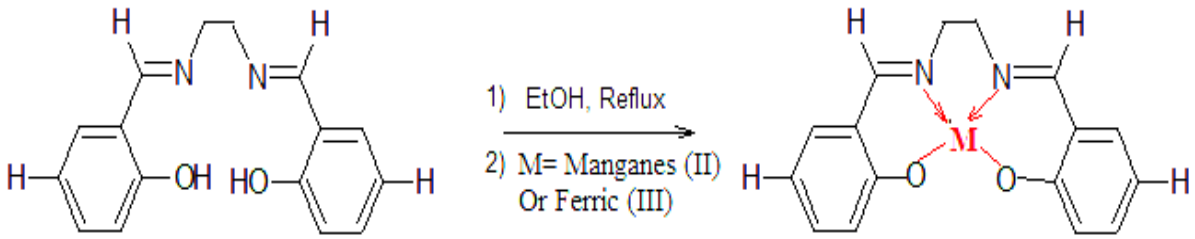


Diagram 9. Synthesis protocol of the complexes.

6. Questions

1. Calculate the syntheses yields of the Schiff base ligand and its two complexes.

2. What are the melting points of the obtained compounds.

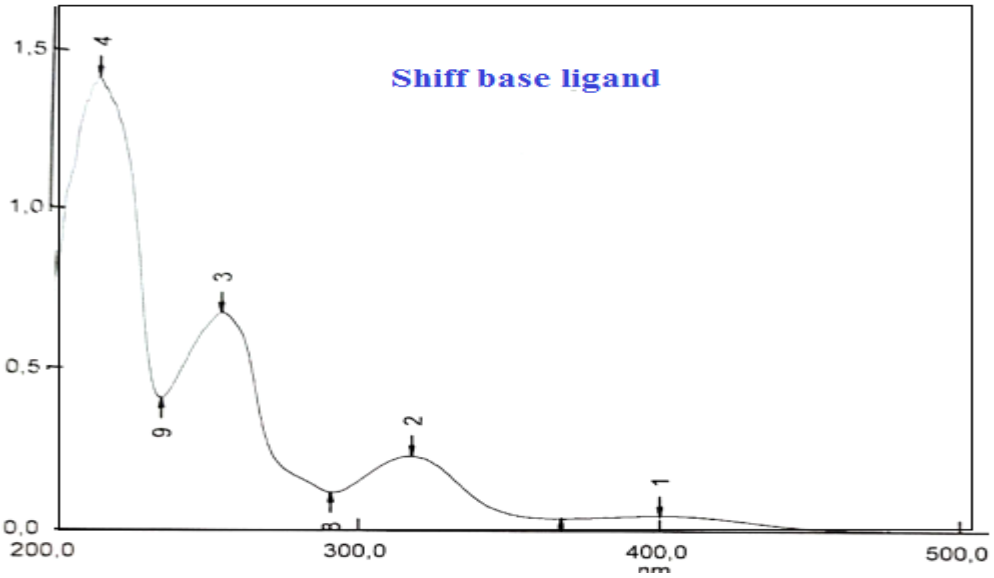
3. Interpret the IR and UV-Vis spectra of the ligand and its complexes and assign the observed absorption bands.

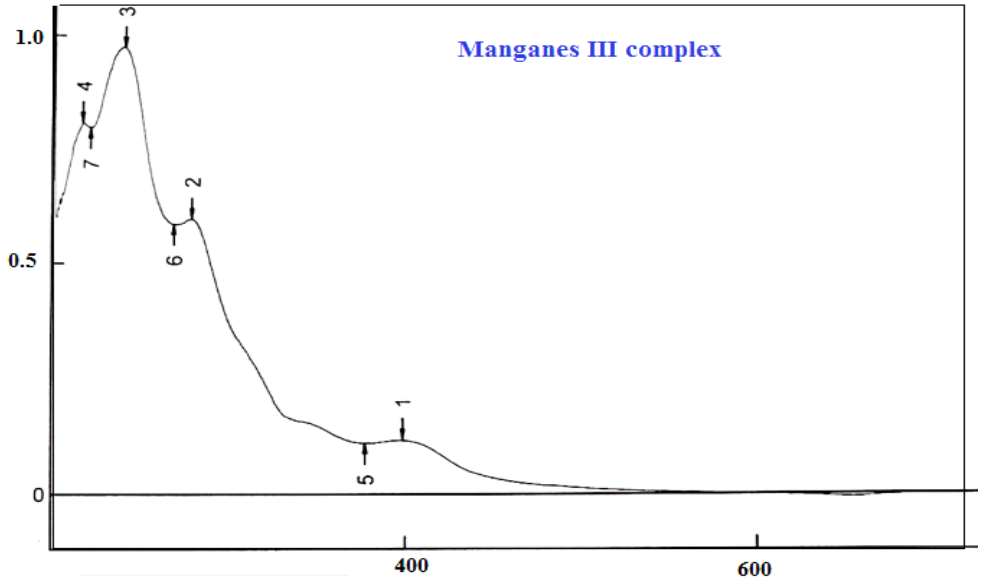
4. All the compounds you have synthesized were characterized by means of only 2 or 3 techniques. What other characterization methods seem feasible and suitable for the identification of these compounds? Justify your answers.

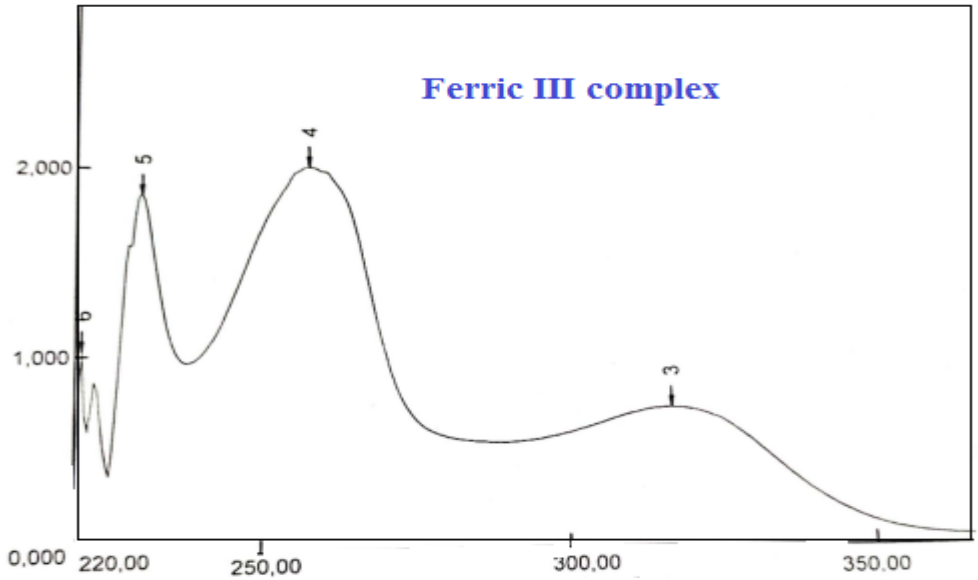
5. In your opinion, is it important to obtain complexes that possess a similar anion for these different complexes in view of future studies.

6. Describe the synthesis method of Jacobsen's catalyst. How does it introduce chirality into the ligand? What is the stereochemistry of the final product.

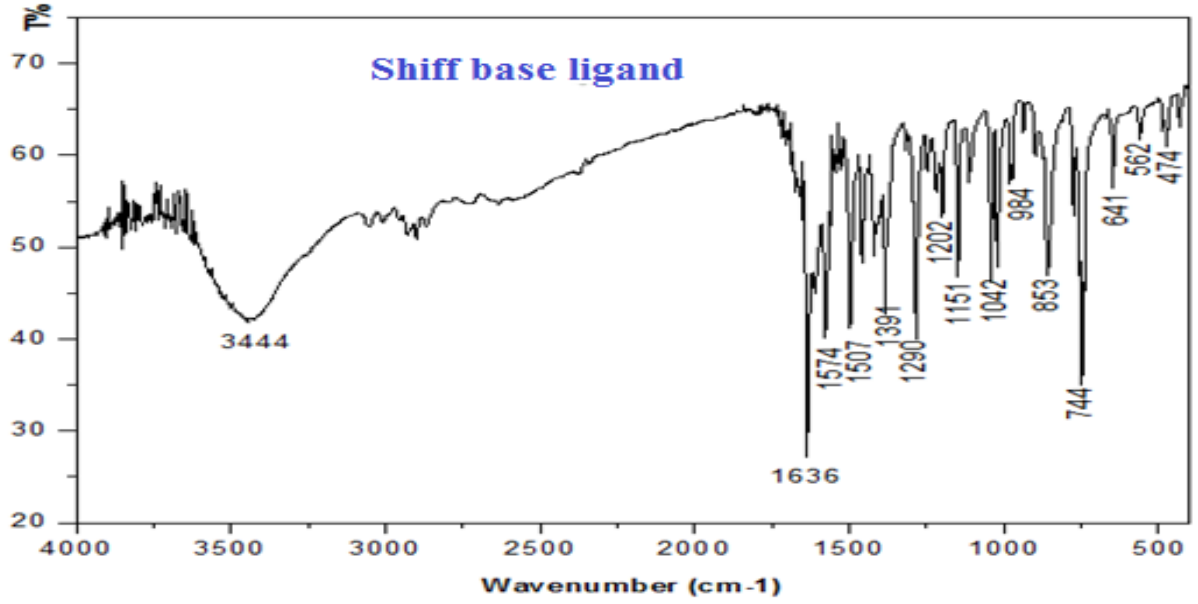
UV-Vis spectra

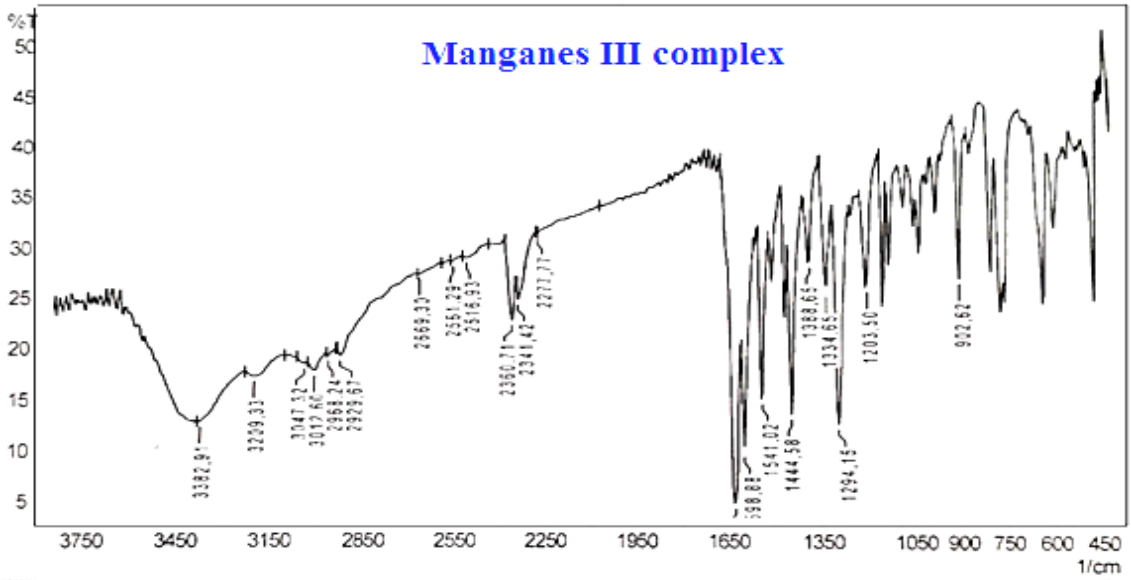


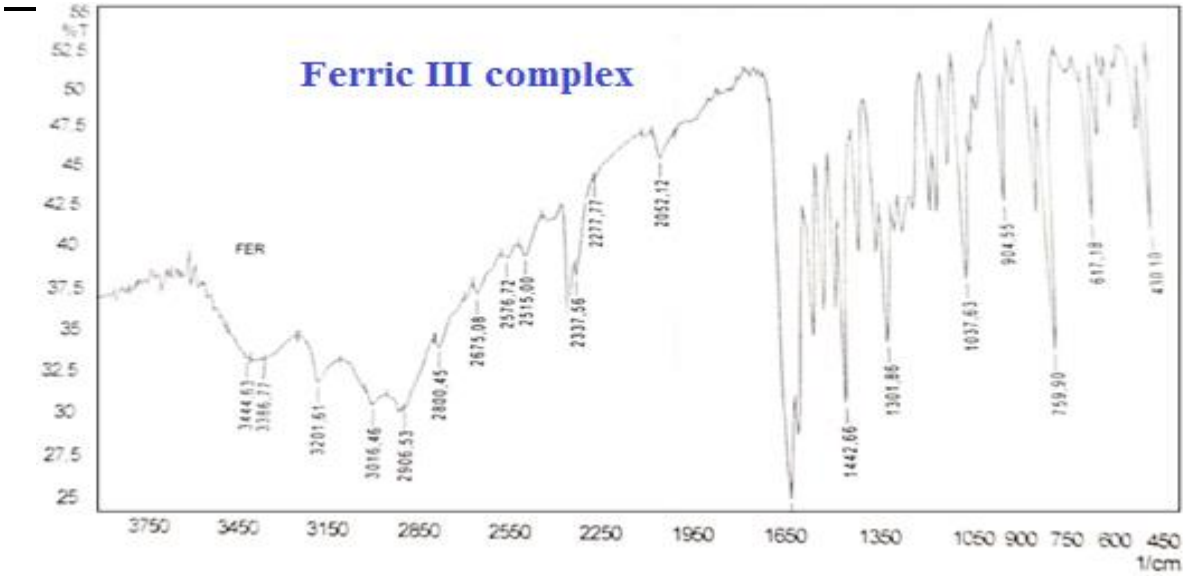




IR spectra


T%
Shiff base ligand
3444
1636
1574
1507
1391
1290
1202
1151
1042
984
853
744
641
562
474
Wavenumber (cm-1)


%T
Manganes III complex
1/cm


Ferric III complex
FER
1/cm

Manipulation 9 : Synthesis of a coumarin (7-hydroxy-4-methyl coumarin)

1. Introduction

Coumarins with one oxygen atom in their rings belong to the oxygen containing heterocycles, which are found in nature and synthetically produced. The association of β-pyrone rings with benzene leads to the formation of these phenolic. The name of coumarin originates from French word "Coumarou" for the *tonka bean*, because coumarin was first isolated from *tonka beans*. Although coumarins are found as secondary metabolites in many plants, such as *Dipteryx odorata*, *Anthoxanthum odoratum*, *Galium odoratum*

Coumarins have gained a reputation as a multifunctional scaffold because of their broad range of biological activities from being anti-oxidant, anti-inflammatory, anti-microbial, anti-fungal, anti-HIV, analgesic, anticancer, antiviral, anticoagulant, antituberculosis, insecticides, dyes, herbicides, and sensitizers.

2. Principle

The general synthesis of coumarins involves the interaction of a phenol with a β-ketoester in the presence of an acid condensing agent (Pechmann reaction). Concentrated sulfuric acid is generally used as the condensing agent for simple monohydric phenols and β-ketoesters, although phenol itself reacts better in the presence of aluminum chloride. It is believed that the mechanism of the reaction involves the initial formation of a β-hydroxy ester, which then cyclizes and dehydrates to give coumarin. Polyhydric phenols, particularly those with two hydroxyl groups oriented meta, react with great ease and sulfuric acid is used as the condensing agent with careful temperature control to ensure a good yield.

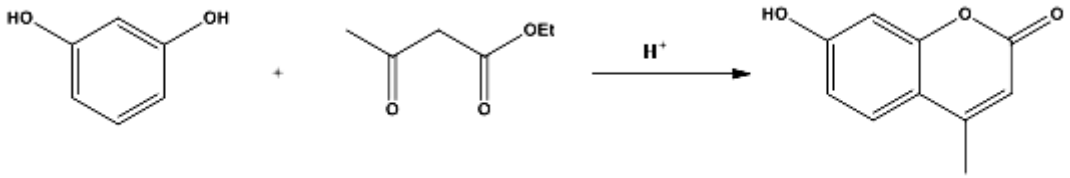


Diagram 10. Synthesis protocol of Coumarin.

3. Objective

To synthesize of a coumarin-type molecule : 3-acetyl-2H-1-benzopyran-2-one from salicylaldehyde and ethyl acetoacetate.

4. Requirements Chemicals

1. Conc. sulfuric acid
2. Resorcinol

3. Ethyl acetoacetate

4. Ice

5. Sodium hydroxide solution (5%)

6. Sulfuric acid (2 M)

7. Ethanol 95%

5. Procedure

Take 10 mL of concentrated sulfuric acid in a 250 mL round-bottom flask equipped with a thermometer, a mechanical stirrer, and a bromine bulb. Immerse the flask in an ice bath.

• When the temperature drops below 10 °C, add a solution of 1 g (9.1 mmol) of resorcinol in 1.34 g (1.30 mL, 10.3 mmol) of distilled ethyl acetoacetate dropwise and under stirring.

• Maintain the temperature below 10 °C using a salt-ice bath during the addition.

• Keep the mixture at room temperature for a few hours, then pour it into a mixture of 20 g of crushed ice under vigorous stirring and 30 mL of water.

• Collect the precipitate by vacuum filtration and wash it with three portions of 10 mL of cold water.

• Dissolve the solid in 15 mL of a 5% sodium hydroxide solution, filter, and add diluted sulfuric acid 2 M (about 5.5 mL) under vigorous stirring until the solution is acidic.

• Filter the crude 4-methyl-7-hydroxycoumarin by pump, wash with four portions of 10 mL of cold water, and dry at 100 °C. Recrystallize in 95% ethanol.

6. Questions

1. Draw and label the diagram of the assembly.

2. Name the reagents, research their physical characteristics.

3. Determine the yield of your reaction.

4. The literature gives a melting point of 185-186°C. Compare it to your result.

5. Propose a mechanism for this reaction.

6. The 1H NMR spectrum of 7-hydroxy-4-methylcoumarin, recorded at a frequency of 400 MHz is presented in the following table, complete it.

Nuclear magnetic resonance spectrum 1H of coumarin			
δ/ppm	integration	Appearance of the sigma	Attribution
9.50	1H	Very wide singulet	
7.59	1H	Doublet	
6.84	1H	Doublet of doublet	
6.72	1H	Doublet	
6.06	1H	Singulet	
2.41	3H	Singulet	

Manipulation 10 : Synthesis of Phenytoin

1. Introduction

Phenytoin or diphenylhydantoin is an active ingredient used in the treatment of epilepsy. With a structure related to barbiturates, hydantoins have important pharmacological properties. Thus, the first hydantoin marketed (1916), Nirvanol®, the trade name for 5-ethyl-5-phenylhydantoin, has strong structural similarities to phenobarbital (5-ethyl-5-phenylbarbituric acid), a well-known sedative. The synthesis of phenytoin from benzyl is known as Biltz synthesis, named after the German chemist Heinrich Biltz, and dates back to 1907. Lacking immediate application, its anticonvulsant properties were highlighted in 1937. Besides its action in the treatment of epilepsy seizures, phenytoin has antiarrhythmic properties but is also used against high blood pressure, psychoses, as an antidepressant, etc.

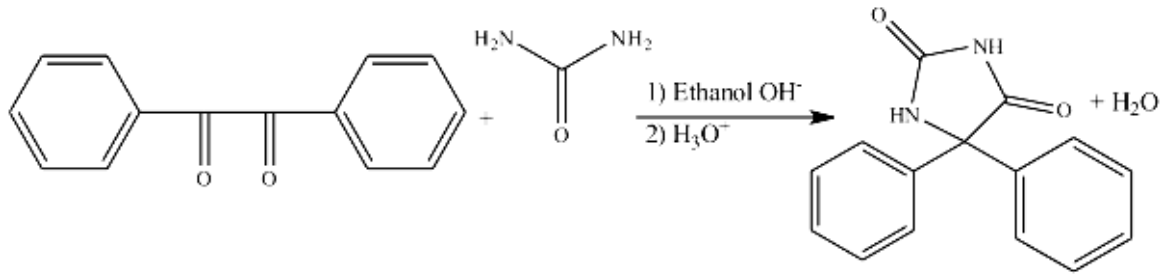


Diagram 11. Synthesis protocol of Phenytoin .

3. Objective

To synthesize of phenytoin from benzyl and urea.

4. Requirements Chemicals

1. benzil = 2g
2. urea = 0.96g
3. Ethanol = 50 ml
4. potassium hydroxide = 5 ml
5. Hydrochloric acid (a few drops)
6. Ice

5. Procedure

In a suitably equipped 200 mL balloon, dissolve 2.00 g of benzil and 0.96 g of urea in 50 mL of ethanol, then add 5 mL of a 10 $mol.L^{-1}$ aqueous potassium hydroxide solution. Heat under reflux for 2 hours. After cooling to room temperature, add 150 mL of ice-cold water while stirring, filter to remove the pale beige solid which is a by-product. Transfer the filtrate to a

400 mL beaker. Add to the filtrate, dropwise and while stirring, 6 $mol.L^{-1}$ hydrochloric acid until the precipitation of phenanthoin is complete. Finally, filter and wash the product with ice-cold water. Dry in the oven (80 °C) and recrystallize the remaining product in 95% ethanol by volume.

6. Questions

1. Calculate the theoretical mass of phenytoin expected.

2. Calculate the yield of crude product (R1), the yield of recrystallization (R2), as well as the yield of purified product (R2).

3. Name the reagents, research their physical characteristics.

4. The literature gives a melting point of 185-186°C. Compare it to your result.

5. Propose a mechanism for this reaction.

6. Recall the criteria required for a good recrystallization solvent.

References

1. Louis Fieser (1941). Manual for Experiments in Organic Chemistry, 2nd Ed, Harvard University, D. C. Heath and Company.

2. (2011, June), Laboratory Manual for Organic Chemistry I, Al-Akhawayn University, School of Science & Engineering

3. (2009, Fall), Chem 21: Nucleophilic Substitution, Amherst College, Department of Chemistry **https://www.amherst.edu/system/files/media/0931/Exp7.pdf.**

4. Elaine N., Melissa H., Jack R., (2015), Organic Chemistry with Vernier Lab book, Experiment 13: SN1: Synthesis of tert-Butyl Chloride, Vernier Lab Safety Instructions Disclaimer **http://www.vernier.com/products/books/chem-o/**

5. Cohnn J. B., "A class of organic chemistry" Nirav prakashn pvt. Ltd., page no. 295, 1918.

6. Mann F. J, Sunders B.C. "Practical of Organic Chemistry", Edition fourth, 2007, Dorling Kindersley (India) Pvt. Ltd., Delhi 2009, page no. 210 - 330.

7. Saluja M.P., "Pharmaceutical chemistry -II" Edition Second, 2019, Krishna's Educational Publishers Pvt. Ltd., Meerut, page no. 51-80.