SEPARATION OF ACIDIC AND NEUTRAL SUBSTANCES

OBJECTIVES

1. To separate a two-component mixture into the individual components by acid-base extraction.

2. To identify the separated compounds and their purity by melting point determination.

BACKGROUND

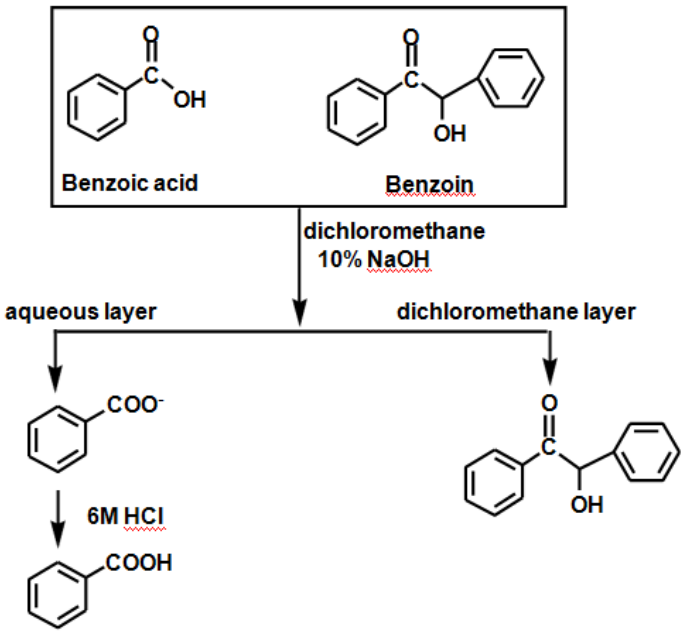
Separation is a routine method commonly used in organic chemistry to separate a certain material from the others during the work-up of the organic chemical reactions and the isolation of the compounds from crude natural product extracts. The common methods for separating and purifying organic liquids and solids are distillation and recrystallization, respectively. However, another useful technique for this purpose is an extraction. Liquid- liquid extraction is one of the most common methods for removing an organic compound from a mixture. In some extractions, the distribution of a compound between two immiscible solvents simply occurs because of its different solubility in the two solvents. However, it is sometimes necessary to alter a compound chemically to change its distribution between the two different solvents which is most commonly done through an acid-base reaction.

In this experiment, a mixture comprised of benzoic acid and benzoin will be separated into the individual components using acid-base extraction. The identification of the extracted components and their purity will be determined by their melting points.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flasks
2. Erlenmeyer flasks
3. Pasteur pipettes
4. Filtering flask
5. Suction glass funnel
6. Receiver distilling still
7. Capillary tubes
8. Ice-water bath
9. Hot plate and heat dissipation block



PROCEDURE

PART I: Separation of benzoic acid and benzoin

1. Place benzoic acid and benzoin 300 mg each into 10-mL conical bottom flask, Flask No.1, containing 5 mL of dichloromethane. Swirl the mixture gently until all the solid has dissolved.
2. Add 3 mL of 10% NaOH and stir the mixture using a Pasteur pipette method.
3. Allow the mixture to separate completely into two distinct layers. Remove the lower dichloromethane layer, using a Pasteur pipette method. Transfer it into another conical bottom flask, Flask No.2.
4. Repeat the extraction of the upper aqueous layer in Flask No.1 with 3 mL of dichloromethane. Combine the lower dichloromethane layer in Flask No.2 and save it for a later step.

PART II: Recovery of benzoic acid

1. Add small amount of 6M HCl dropwise to Flask No.1, swirl the mixture and check until it is just acidic with litmus paper.
2. Further add a few drops of 6M HCl until no more formation of white precipitate, the product A, can be observed when a drop of 6M HCl reaches the solution. Place Flask No.1 in the ice-water bath for 5 minutes.
3. Collect the product A by suction filtration.
4. Weigh the product A and keep a small amount for its melting point determination.

5. Transfer the product A into a 10-mL conical bottom flask, add 3 mL of distilled water, boil and often swirl the mixture until a clear solution is obtained.
6. If there is an impurity which does not dissolve in hot water, filter it off using a Pasteur filter-tip pipette method.
7. Transfer the hot solution in the pipette into another flask. Rinse the pipette with a tiny amount of hot water into the receiving flask. Allow the solution to cool down. Then place the flask in an ice-water bath.
8. After crystallization is complete, collect the crystals by suction filtration as described in step 7. Wash the crystal A with a tiny amount of water and continue suction to air-dry.
9. Weigh the crystals of product A and calculate its percent recovery. Determine its melting point before and after crystallization and A mixed with benzoic acid (1:1) and A mixed with benzoin (1:1).

PART III: Recovery of benzoin

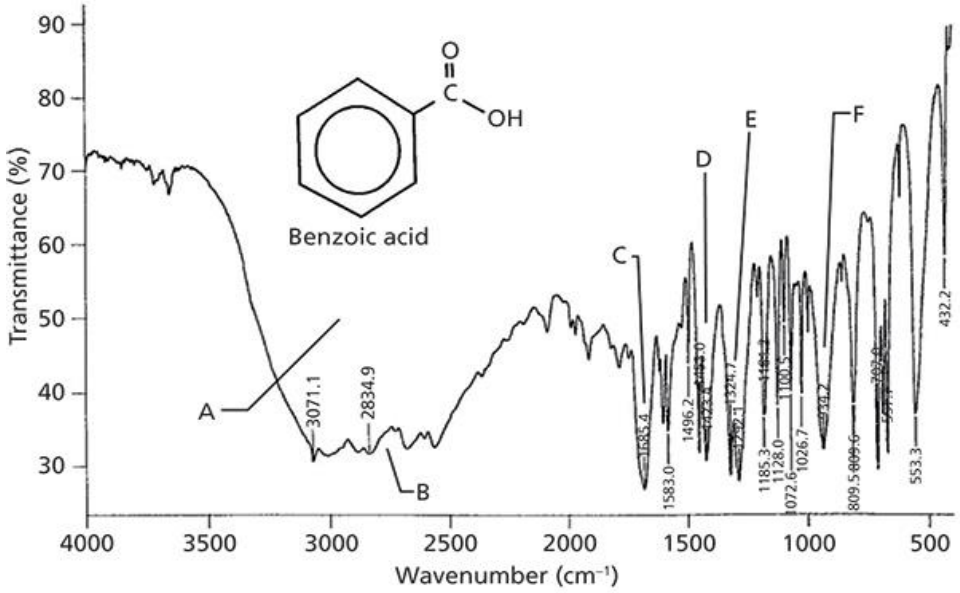
1. From the dichloromethane layer in Flask No.2 in step 4, wash it with 2 mL of 10% NaOH by stirring the mixture using a Pasteur pipette method as described in step 2.
2. Allow the mixture to separate completely into two distinct layers. Remove the lower dichloromethane layer, using a Pasteur pipette method as described in step 3. Transfer it into another conical bottom flask, Flask No.3.
3. Repeat the extraction of the upper aqueous layer in Flask No.2 with 3 mL of dichloromethane. Combine the lower dichloromethane layer in Flask No.3.
4. Add a tiny amount of anh.Na_2SO_4, and swirl the solution. Keep adding until some of it swirls freely, and then set aside when the solution no longer cloudy.
5. Filter the solution using a Pasteur filter-tip pipette method as described in step 10.
6. Transfer the solution in the pipette into another conical bottom flask. Connect the flask with a receiver distilling still and condenser. Distil off the dichloromethane to obtain the solid, the product B, at the bottom of the flask.
7. Weigh the product B and keep a small amount for its melting point determination.
8. Transfer the product B into a 5-mL conical bottom flask, add 3 mL of ethanol, boil gently and often swirl the mixture until clear solution is obtained.
9. If there is an impurity which does not dissolve in hot ethanol, filter it off using a Pasteur filter-tip pipette method as described in step 10.
10. Transfer the hot solution in the pipette into another flask. Rinse the pipette with a tiny amount of ethanol into the receiving flask. Allow the solution to cool down. Then place the flask in an ice-water bath.
11. After crystallization is complete, collect the crystals by suction filtration as described in step 7. Wash the crystals B with a small amount of the solvent, ethanol:water at 1:1, and continue suction to air-dry.

12. Weigh the crystals of product B and calculate its percent recovery. Determine its melting point before and after crystallization, and B mixed with benzoic acid (1:1), and B mixed with benzoin (1:1).

CLEANUP

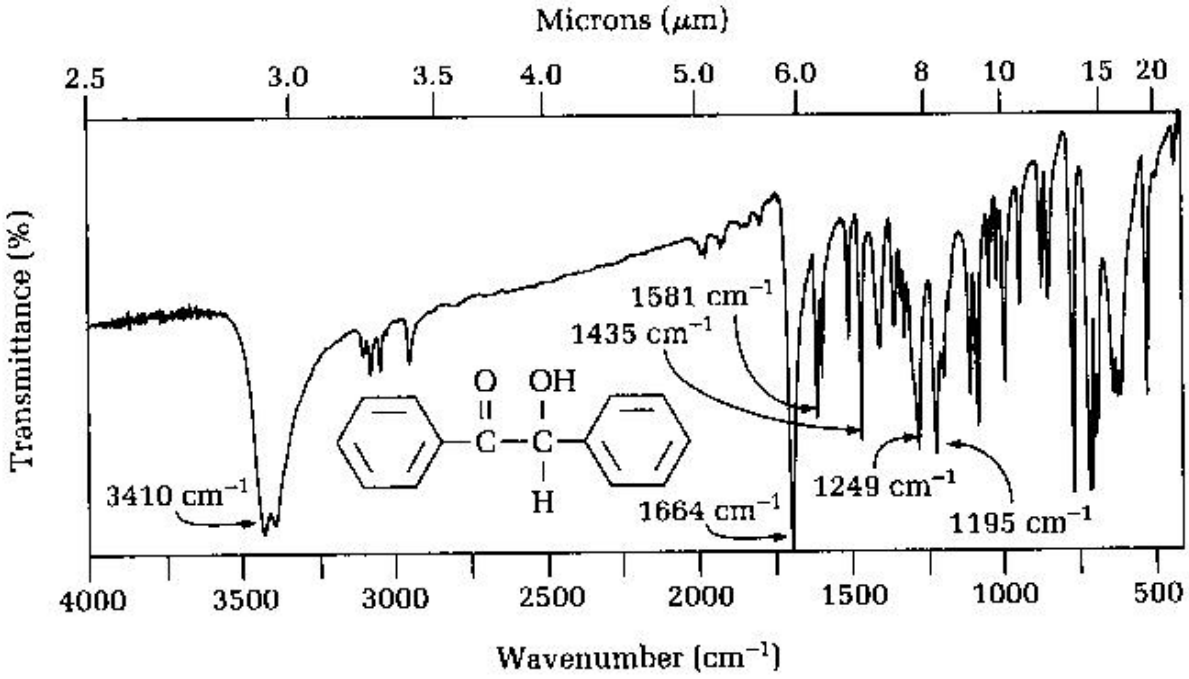
1. Pour dichloromethane waste into a chlorinated hydrocarbon waste container.
2. Pour ethanol waste into an organic waste container.
3. Use sodium carbonate to neutralize the acid solvent and use acetic acid to neutralize the base solvent before flushing them down the drain with copious amount of water.

IR Spectra for Benzoic Acid



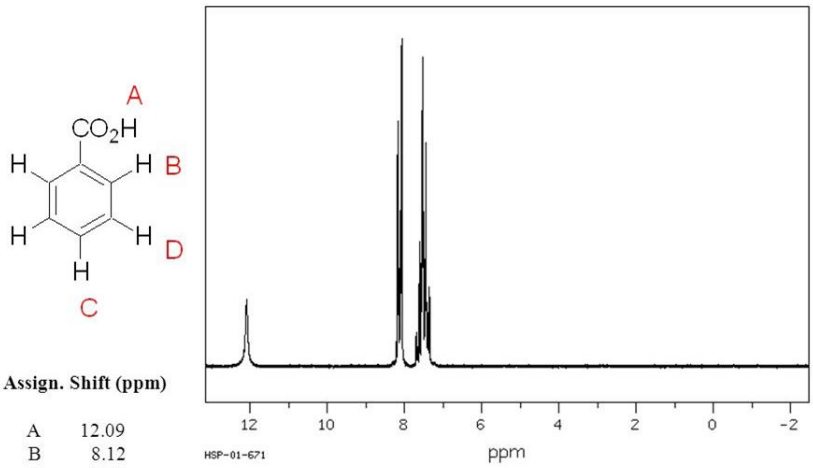
A	3500-2500	O-H stretch
B	2800-2500	Overtone and combination bands
C	1685	C=O stretch
E	1292	C-O stretch
F	934	Out-of-plane O-H bend

IR Spectra for Benzoin



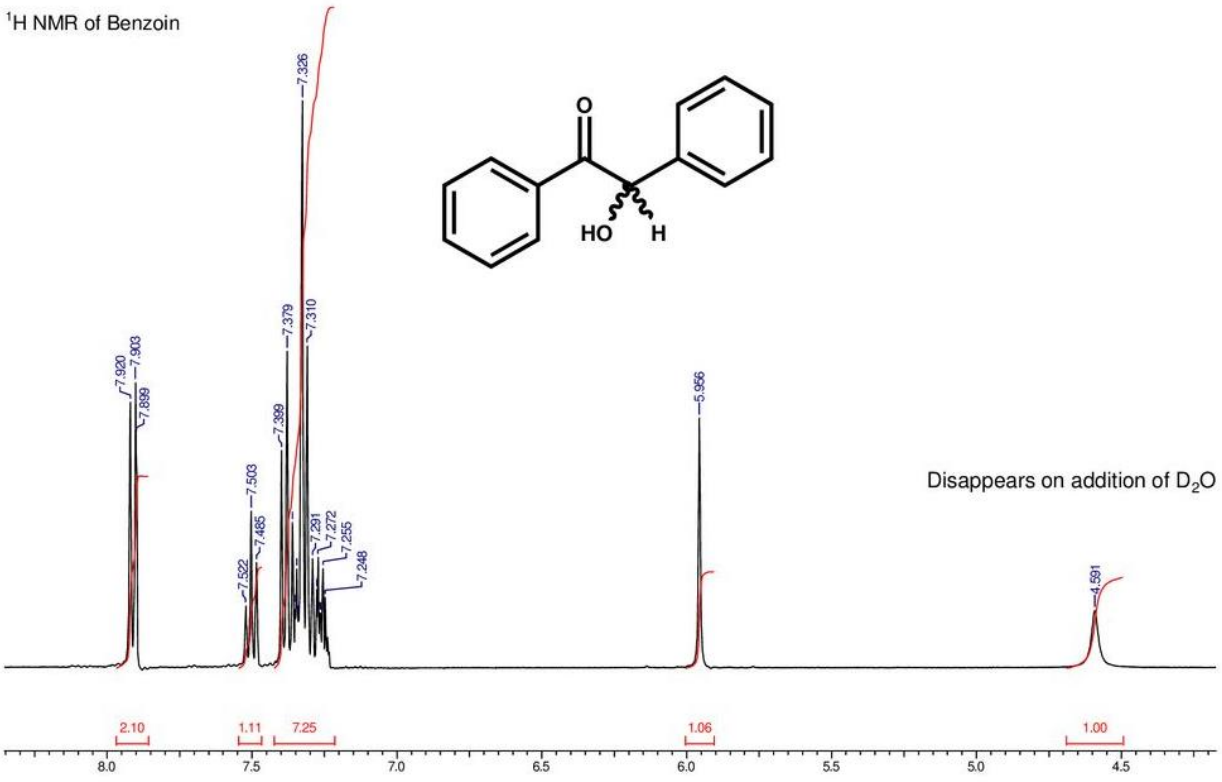
NMR Spectra for Benzoic Acid

Benzoic acid ($C_7H_6O_2$) 89.56 MHz ($CDCl_3$)



Assign.	Shift (ppm)
A	12.09
B	8.12
C	7.62
D	7.45

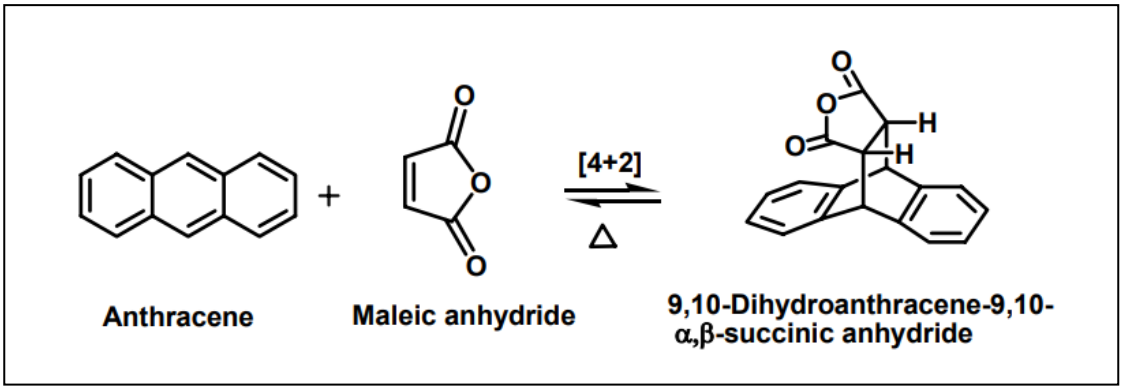
NMR Spectra for Benzoin



QUESTIONS FOR VIVA VOCE

1. What is the principle in benzoic acid and benzoin separation?
2. After adding 10% NaOH into a mixture of benzoic acid and benzoin in dichloromethane, which ones are in the upper and lower layers?
3. During the filtration of crystals B, why it is necessary to wash the crystals with a mixture of ethanol and water? Can it be washed by either ethanol or water, why?
4. Do you think the solvents used in crystallization of benzoic acid and benzoin are suitable? If not, how it can be improved?
5. Do you know which extracted compound is benzoic acid and benzoin? Explain.
6. How much is the difference in the melting points of pure and impure compounds?
7. In determining the melting point of a substance, what precautions do you take in order to have an accurate result?
8. Discuss about quantity and purity of the crystallized benzoic acid and benzoin.
9. Draw an extraction flow chart of the mixture of ethyl *p*-aminobenzoate (*p*-NH_2-C_6H_4-$COOC_2H_5$), benzophenone (C_6H_5-CO-C_6H_5) and benzoic acid.

DIELS-ALDER REACTION

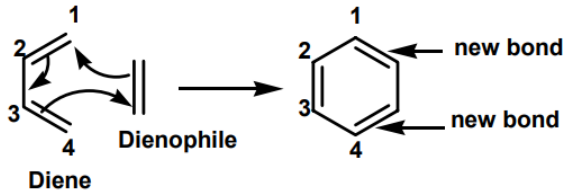


OBJECTIVES

1. To synthesize 9,10-dihydroanthracene-9,10-α,β- succinic anhydride by Diels-Alder reaction.
2. To practice the experimental techniques on reflux, recrystallization, melting point determination and thin-layer chromatography.

BACKGROUND

The Diels-Alder reaction combines a diene (a molecule with two alternating double bonds) and a dienophile (an alkene) to make rings. The three double bonds in the two starting materials are converted into two new single bonds and one new double bond leading to the formation of a six-membered ring.



When the diene contains an electron donating group or the dienophile contains an electron- withdrawing group, the reaction will work well. Therefore this reaction is very useful for the preparation of a wide variety of six-membered ring compounds.

In this experiment, the reaction between anthracene and maleic anhydride will be carried out by refluxing at temperature 185-190^{0}C. The product will be purified by crystallization and identified by thin-layer chromatography.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flask
2. Condenser
3. Filtering flask
4. Filtering glass funnel
5. TLC plates
6. Three-way pipette rubber bulb
7. Hot plate and heat dissipation block

Chemicals: Anthracene ($C_{14}H_{10}$); maleic anhydride ($C_4H_2O_3$); xylene (CH_3-C_6H_4-CH_3); hexane (C_6H_{14}); ethyl acetate ($CH_3CO_2CH_2CH_3$); calcium chloride (anh.$CaCl_2$).

PROCEDURE

PART I: Reaction of anthracene and maleic anhydride

1. Place 100 mg (0.5 mmol) of anthracene, 50 mg (0.5 mmol) of maleic anhydride and 1 mL of xylene in a 5-mL conical bottom flask. Add a boiling stone in the flask.

2. Equip the flask with a water-cooled condenser and heat the mixture to gentle reflux at 185-190 ºC for 30 minutes.

3. Allow the mixture to cool down at room temperature and then cool in an ice-water bath for 10 minutes.

4. Filter the precipitate by suction filtration.

5. Wash with 0.5 mL of cool xylene and 1.0 mL of cool hexane.

6. Transfer the precipitate into another 5-mL conical bottom flask. Recrystallize the precipitate in 1 mL of ethyl acetate.

7. After crystallization is complete, collect the crystals by suction filtration as described in step 4.

8. Weigh the crystals and calculate its percent recovery. Determine its melting point.

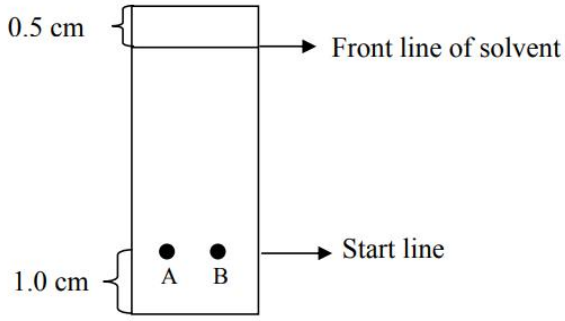
PART II: Thin-layer chromatography

1. Prepare 1 TLC plate (2x7 cm dimension).

2. Obtain a TLC chamber and place solvent, a mixture (by volume) of 2% ethyl acetate in hexane to 0.5 cm height. Place a piece of filter paper around the inside surface of the container and extend into the solvent.

3. Using clean capillary tubes, carefully spot two sample solutions at two pencil marks as shown below.

4. When the spots are dry, place the TLC plates in the developing chamber. Then gently close the chamber.



A: 9,10-Dihydroanthracene-9,10-α,β-succinic anhydride
B: Anthracene

5. When the solvent has moved to the front line, remove the plate. Lay it on a clean surface in a fume hood or well ventilated area and allow the solvent to evaporate until the plates appear dry.

6. Then view the plate under UV light and immediately draw a light pencil line around each spot.

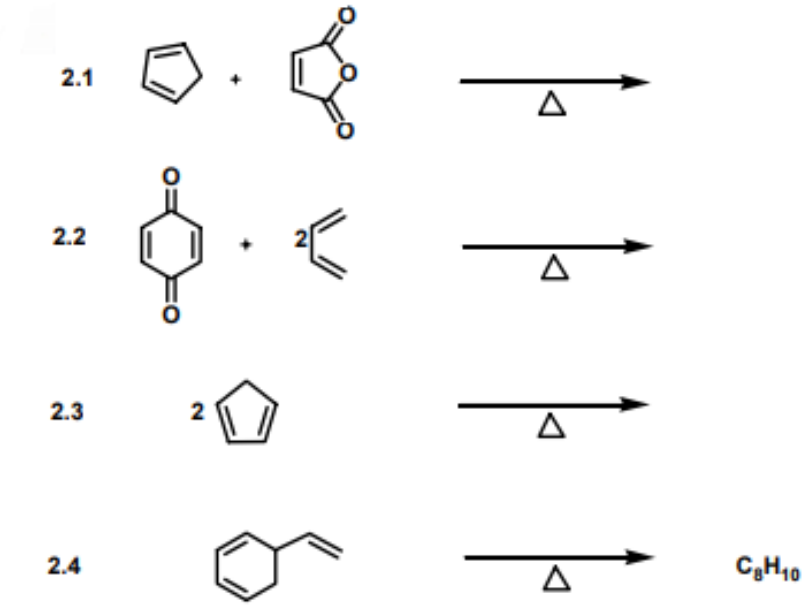
7. Measure all the distances traveled by the compounds and solvent. Calculate the retention factor (R_f) for the component.

CLEANUP

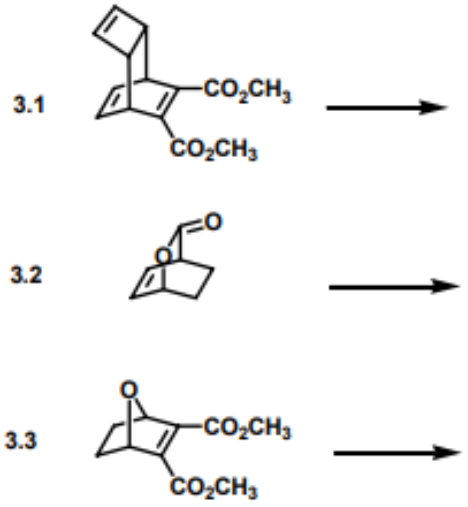
1. Pour xylene, hexane and ethyl acetate into the hydrocarbon waste container.

QUESTIONS FOR VIVA VOCE

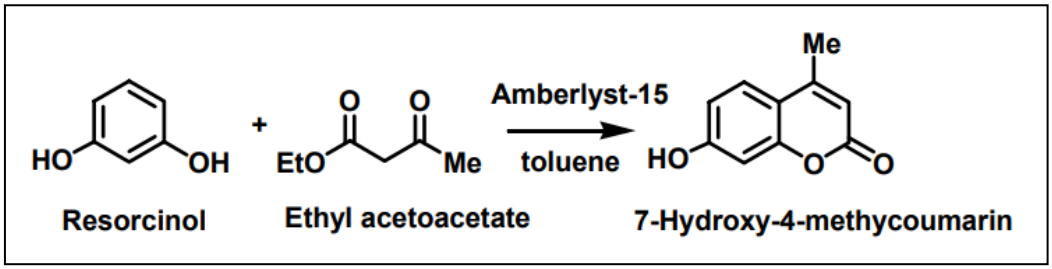
1. In this experiment the solvent used is xylene. Can other solvents such as toluene or ethyl acetate be used in this experiment? Explain.
2. Show product structures in the following reactions:



3. Show products in the following reverse Diels-Alder reactions:



SYNTHESIS OF COUMARIN USING A RESIN AS CATALYST



OBJECTIVES

1. To synthesize 7-hydroxy-4-methyl coumarin from resorcinol and ethylacetoacetate with Pechmann reaction using amberlyst-15.
2. To practice the organic experimental technique on reflux, crystallization.

BACKGROUND

Coumarin is an important group of organic compounds that are used as additives to food, cosmetics, optical brightening agents, and dispersed fluorescent and laser dyes. Some coumarin derivatives occur naturally in seeds, roots, and leaves of many plants. Coumarins can also be synthesized by many methods such as the Claisen rearrangement, Perkin reaction, Pechmann reaction and Knoevenagel condensation. In this experiment, coumarin will be synthesized by Pechmann reaction from resorcinol and ethyl acetoacetate using Amberlyst-15 as a catalyst.

REQUIREMENTS

Apparatus and materials:

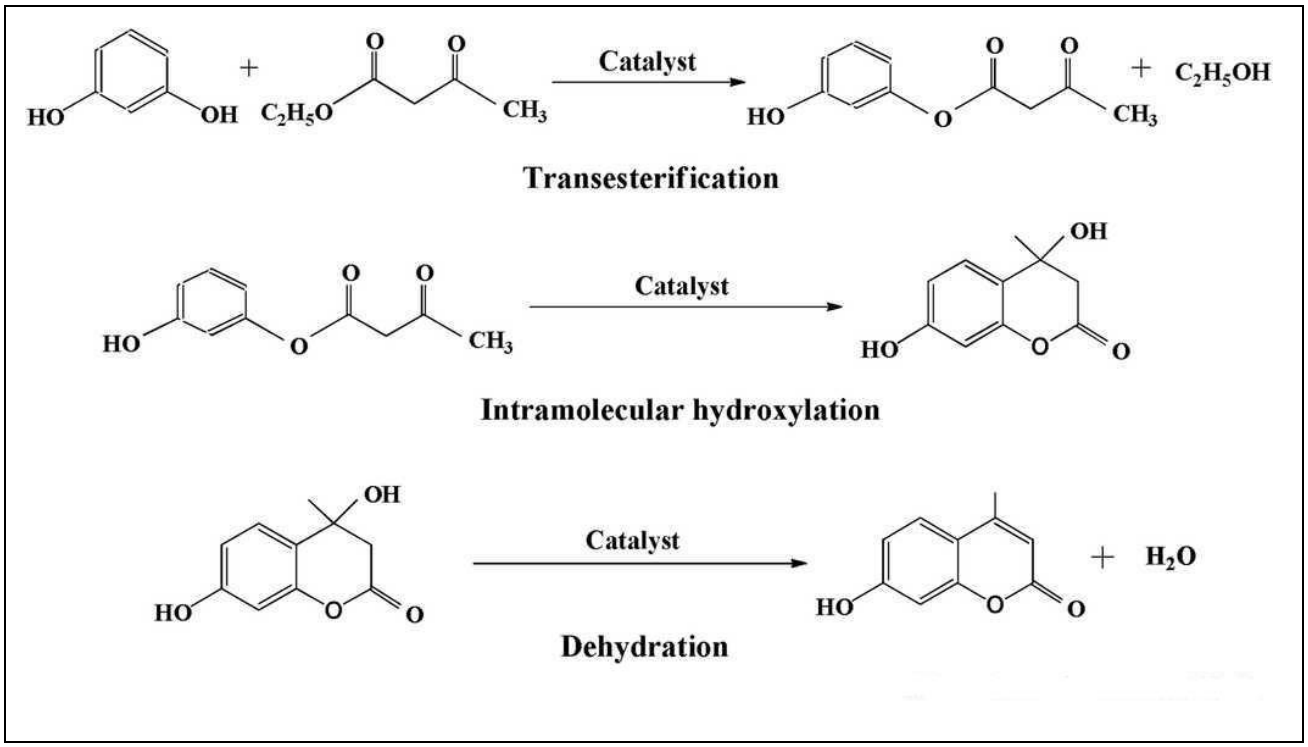
1. Conical bottom flasks
2. Erlenmeyer flasks
3. Hot plate and heat dissipation block
4. Condenser
5. Pasteur pipette
6. Receiver distilling still
7. Filtering flask
8. Suction glass funnel
9. Amberlyst-15
10. Boiling stone

Chemicals: Resorcinol (*m*-HOC_6H_4OH); ethyl acetoacetate ($CH_3COCH_2COO\ CH_2CH_3$); toluene (C_6H_5-CH_3); methanol (CH_3OH).

PROCEDURE

1. Place 220 g (2.0 mmol) of resorcinol, 0.25 mL or 260 mg (2.0 mmol) of ethyl acetoacetate, 3 mL of toluene and 200 mg of Amberlyst-15 in 5-mL conical bottom flask. Equip the flask with a receiver distilling still connected to a water-cooled condenser and fill the trough with toluene.
2. Add a boiling stone and heat the mixture at reflux with azeotropic removal of water for 45 minutes.
3. Remove the apparatus system from the heat and allow the mixture to cool down.
4. Add 4 mL of warm methanol to dissolve the product.
5. Remove Amberlyst-15 in the solution using a Pasteur filter-tip pipette method.
6. Transfer the solution into a 10-mL conical bottom flask. Connect it with a receiver distilling still and a water-cool condenser. Distil off the methanol.
7. Crystallize the product from methanol/water in a 25-mL Erlenmeyer flask.
8. Collect the crystal by suction filtration.
9. Weigh the crystals of product and calculate its percent recovery. Determine its melting point.

MECHANISM

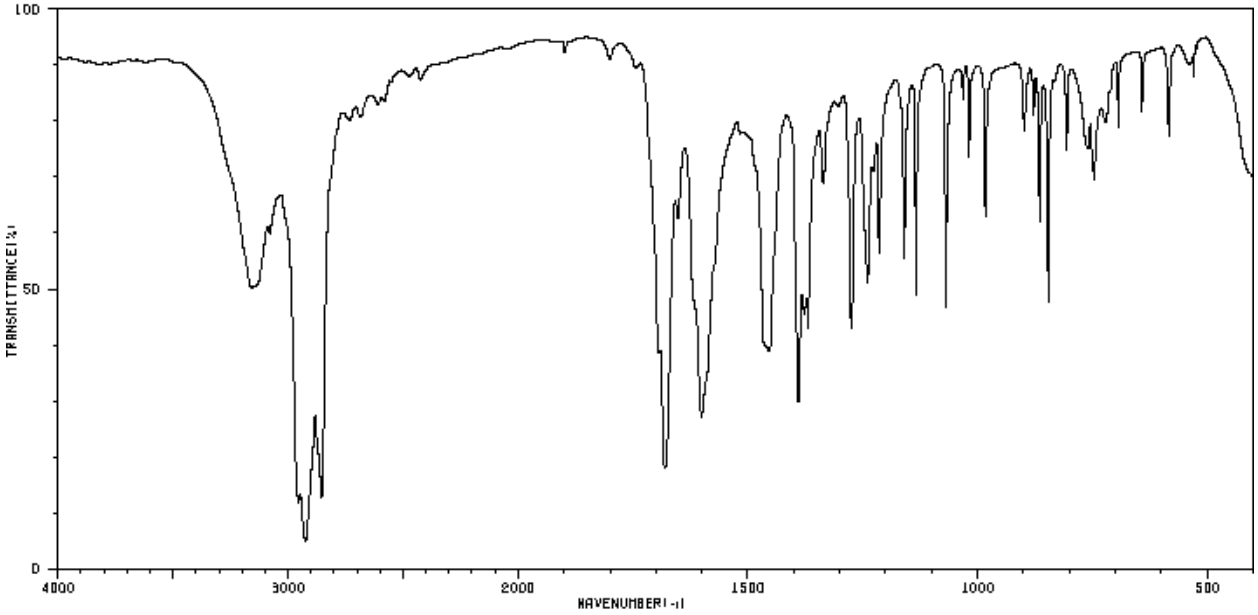


IR Spectra for 7 - Hydroxy - 4 - Methyl Coumarin

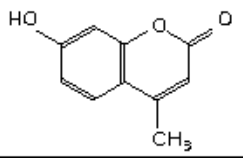
HIT-NO=3347	SCORE= ( )	SDBS-NO=6626	IR-NIDA-15673 : NUJOL MULL

7-HYDROXY-4-METHYLCOUMARIN

$C_{10}H_8O_3$



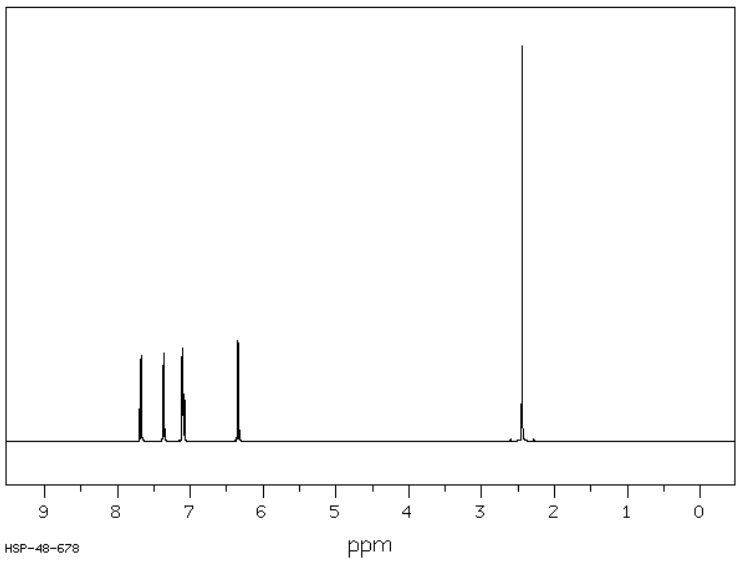
3167	47	1694	37	1463	37	1228	68	899	74
3144	49	1680	17	1390	28	1214	53	865	60
3077	57	1652	60	1377	43	1160	59	846	46
2954	11	1601	26	1369	41	1134	47	806	72
2924	4	1588	34	1336	66	1069	44	761	72
2854	12	1463	38	1275	41	1019	70	747	66
2731	77	1458	37	1240	49	983	60	684	74

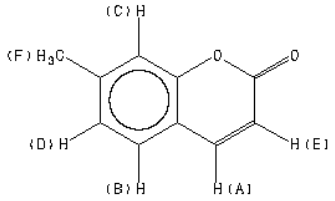


NMR Spectra for 7 - Hydroxy - 4 - Methyl Coumarin

399.65 MHz

0.041 g : 0.5 ml $CDCl_3$





标记氢	化学位移(ppm)
A	7.678
B	7.364
C	7.110
D	7.090
E	6.342
F	2.444

Hz	ppm	Int.
3073.61	7.691	207
3064.09	7.667	216
2947.39	7.375	193
2939.58	7.356	223
2841.92	7.112	236
2837.77	7.101	151
2829.83	7.081	119
2539.55	6.355	255
2530.03	6.331	250
976.81	2.445	1000

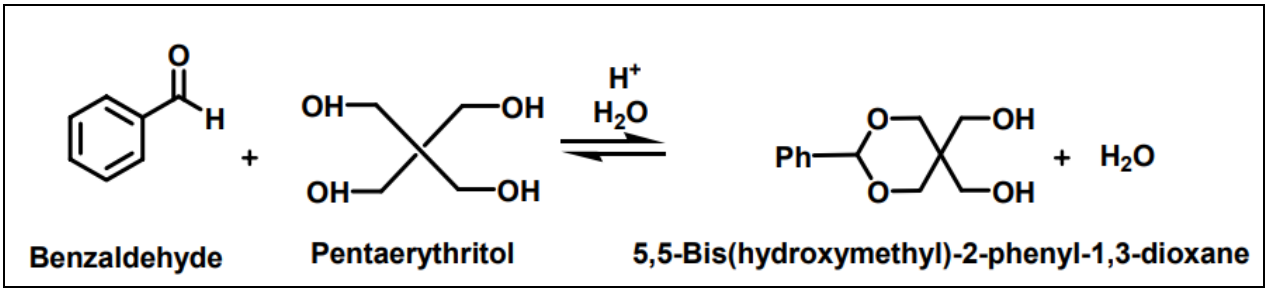
CLEANUP

1. Dispose of Amberlyst-15 in the appropriate wasted container.
2. Pour the remaining methanol in the organic waste container.
3. Pour the mixture of toluene and water waste into the chlorinated hydrocarbon wasted container.

QUESTIONS FOR VIVA VOCE

1. What was the purpose of adding toluene?
2. If *m*-N,N-dimethylaminophenol reacts with ethyl acetoacetate, what product will be obtained? Draw the structure.
3. Draw the mechanism of the reaction in question 2.

SYNTHESIS OF CYCLIC ACETAL

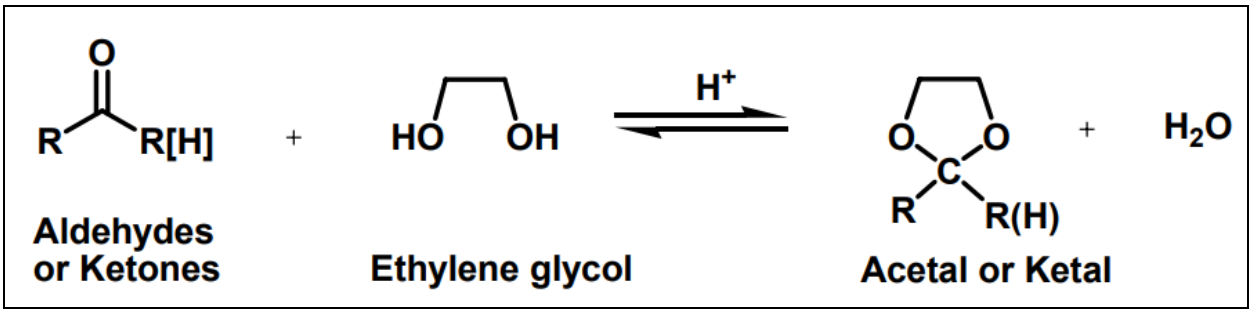


OBJECTIVES

1. To synthesize cyclic acetal from benzaldehyde and pentaerythritol in acid condition
2. To purify the product by crystallization.

BACKGROUND

Aldehydes and ketones react with alcohols in acid condition to give acetals and ketals. Cyclic acetals or ketals are more stable towards hydrolysis than acyclic ones. Cyclic acetals or ketals are readily formed by the reaction of two molecules, an aldehyde or a ketone and a diol. The reaction produces two products, the acetal or ketal and water.



It is an equilibrium reaction. The equilibrium is shifted towards the acetal or ketal by using an excess of the alcohol and/or removing water as it forms. Acetal or ketal can be readily converted back to the aldehyde or ketone, respectively, by heating with aqueous acid. Therefore, the formation of acetal or ketal can be used as protecting groups for aldehydes or ketones.

In this experiment, the cyclic acetal, 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane will be synthesized by dehydration reaction between benzaldehyde and pentaerythritol in aqueous acid.

REQUIREMENTS

Apparatus and materials:

1. Round bottom flask
2. Hot plate and heat dissipation block
3. Pasteur pipette
4. Three-way pipette rubber bulb
5. Receiver distilling still
6. Filtering flask
7. Suction glass funnel

Chemicals: Pentaerythritol ($C(CH_2OH)_4$); benzaldehyde (C_6H_5-CHO); hydrochloric acid (conc.HCl); toluene (C_6H_5-CH_3).

PROCEDURE

1. Place 1 g (7.34 mmol) of pentaerythritol and 10 mL of water into 25-mL conical bottom flask.
2. Heat the mixture gently in the heat dissipation block on a hot plate, at 35^0C. Stir with a glass rod until the solid has dissolved.
3. Add 2 drops of conc.HCl and 0.75 mL (7.34 mmol) of benzaldehyde, heat at 35 ^{0}C and occasionally stir the mixture for 1 hour using a Pasteur pipette method.
4. Collect the product by suction filtration.
5. Wash it with cold water. Continue suction for a few minutes to air-dry.
6. Recrystallize the product from toluene. Collect the crystals by suction filtration as described in step 4. Wash the crystals with a small amount of toluene and continue suction to air-dry.
7. Weigh the product and calculate its percent recovery. Determine its melting point (reported melting point is 135^0C).

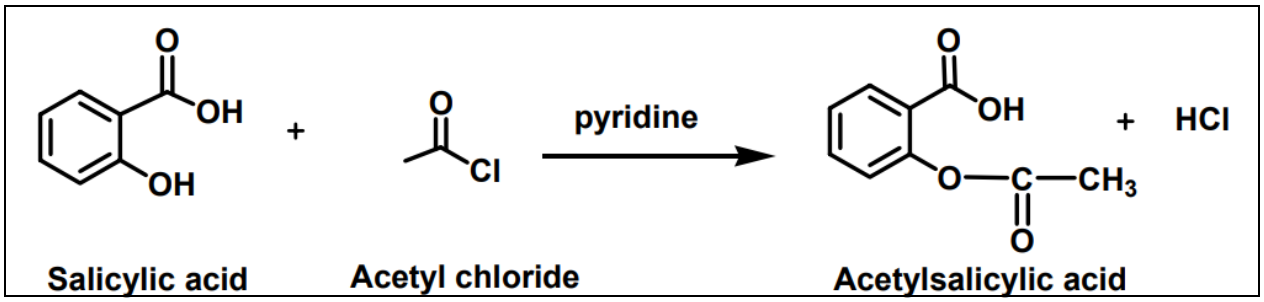
CLEANUP

1. Dispose of the remaining precipitate in the appropriate waste container.
2. Pour waste toluene in the hydrocarbon waste container.

QUESTIONS FOR VIVA VOCE

1. The synthesis of cyclic acetal is a reversible reaction. If water is removed from the reaction, more products will be obtained. Why can, however, water be used as the solvent in this experiment?
2. In this experiment, monobenzal is formed as the only product. When the temperature is increased, dibenzal will be obtained. Explain why?

SYNTHESIS OF ASPIRIN



OBJECTIVES

1. To synthesize aspirin from salicylic acid and acetyl chloride with esterification reaction by using pyridine.
2. To purify the product by recrystallization.

BACKGROUND

Aspirin is the trade name for acetylsalicylic acid. Salicylic acid derivatives have been used as remedies for reducing fever and relieving aches and pains since ancient times. They are found naturally in many plants including white willow and wintergreen. Aspirin can be produced in a one step reaction by reacting salicylic acid with acetyl chloride or acetic anhydride and sulfuric acid as a catalyst. The exothermic reaction will cause the temperature increase to 70-80 ºC. When the reaction is complete and cooled down, the acetylsalicylic acid crystallizes out.

In this experiment, acetylsalicylic acid will be synthesized and identified by melting point determination.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flasks
2. Pasteur pipette
3. Filtering flask
4. Filtering glass funnel
5. Glass rod
6. Three way pipette rubber bulb.

Chemicals: Salicylic acid (*o*-HO-C_6H_4-COOH); pyridine (C_5H_5N); acetyl chloride (CH_3COCl); ethanol (CH_3CH_2OH); ferric chloride (1% $FeCl_3$).

PROCEDURE

1. Place 275 mg (2 mmol) of salicylic acid in a 10-mL conical bottom flask**.** Place the flask in an ice-water bath.
2. Add 0.1 mL of pyridine, just enough to dissolve salicylic acid. Add 0.2 mL (2.80 mmol) of acetyl chloride to the reaction.
3. Leave it in the ice-water bath for 15 minutes. Add 5 mL of cold water to the reaction mixture. Stir the mixture using a glass rod.
4. Collect the product by suction filtration.
5. Crude aspirin crystals are purified by recrystallization with methanol/water.
6. After crystallization is complete, collect the crystals by suction filtration as described in step 4. Wash the crystal with a minute amount of cold water and continue suction to air-dry.
7. Weigh the crystals of product and calculate its percent recovery.
8. Test for its purity with 1% $FeCl_3$ and determine its melting point.

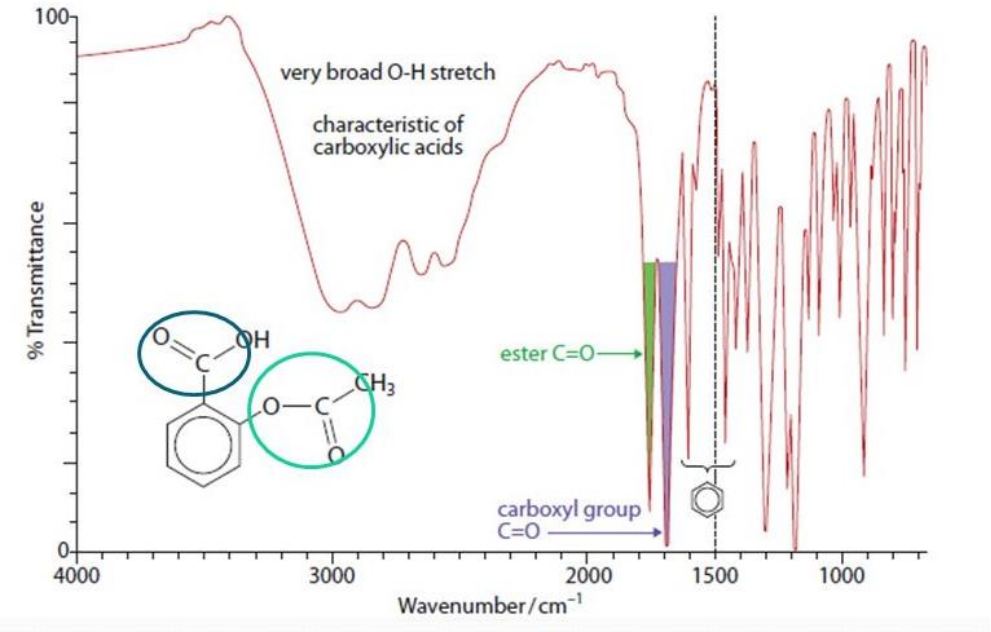
CLEANUP

1. Pour waste solutions from filtration down the drain with copious amount of water.
2. Dispose of an excess salicylic acid or aspirin in the proper waste containers.

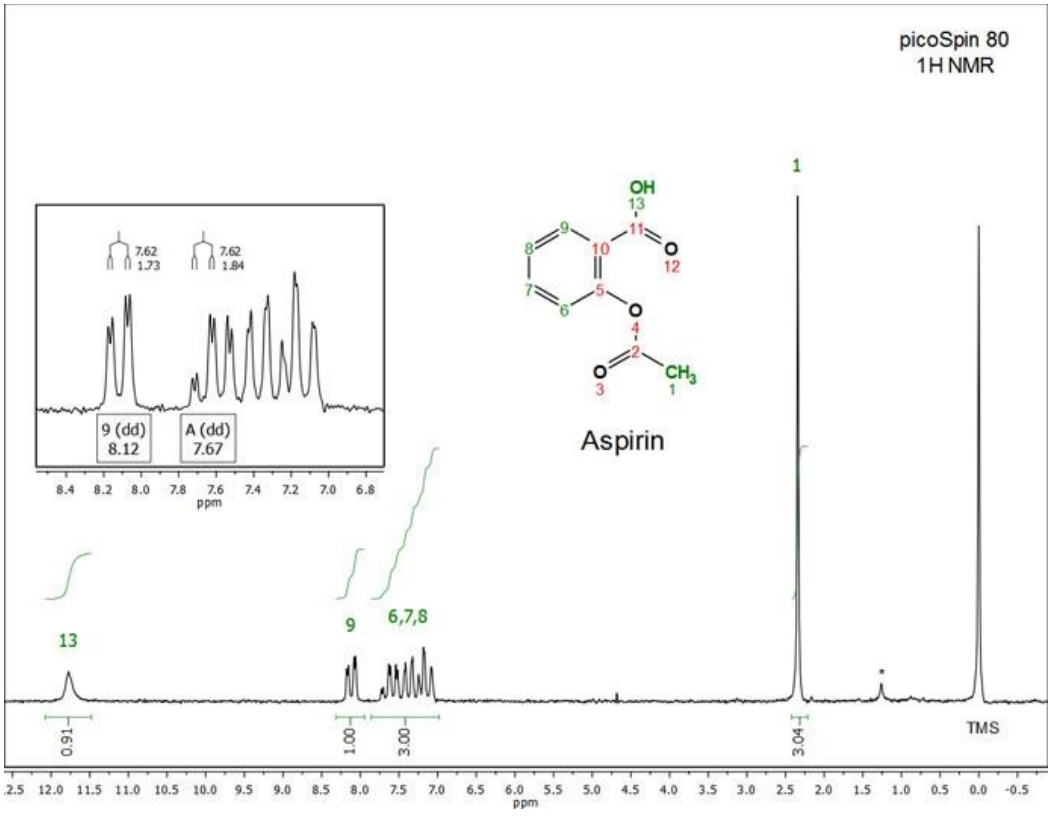
QUESTIONS FOR VIVA VOCE

1. Explain the role of pyridine in the experiment and write a balanced chemical equation for the reaction.
2. Why does aspirin have an odour like acetic acid when it is stored or kept for a long time? Write a chemical equation to explain this phenomenon. If this aspirin is tested with 1% $FeCl_3$, what will be the result?
3. Among salicylic acid, acetylsalicylic acid and methyl salicylate, which one will react with 1% $FeCl_3$?

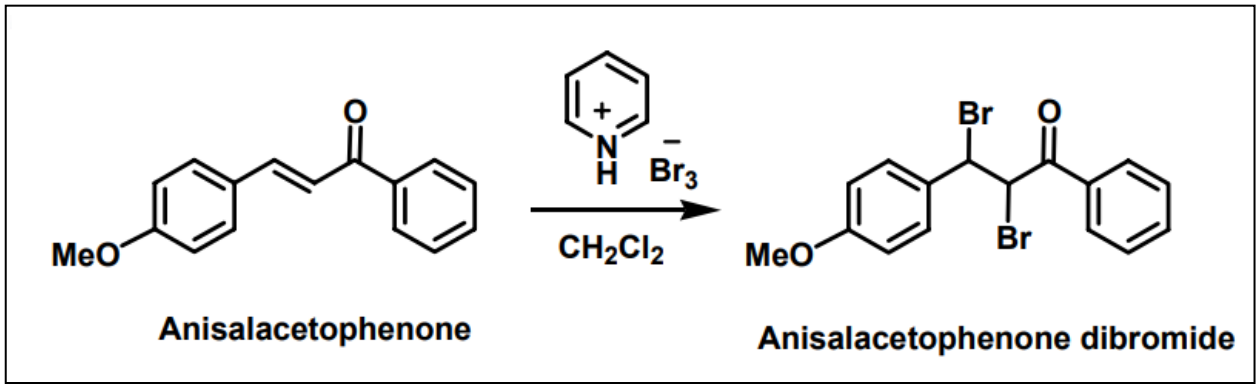
IR Spectra of Aspirin



NMR Spectra of Aspirin



A SAFER AND RAPID BROMINATION OF ALKENES

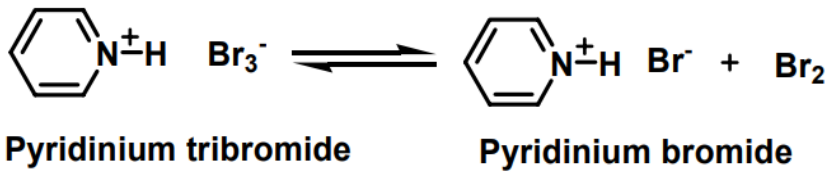


OBJECTIVES

1. To synthesize anisalacetophenone dibromide by stereospecific bromination with pyridinium bromide perbromide.
2. To purify the product by recrystallization.

BACKGROUND

Addition reactions are the most common reactions of alkenes. For example, the halogenation of an alkene, in which halogen adds across the double bond, will give a vicinal dihalide. The alkyl halides are then capable of undergoing a variety of further chemical reactions. However, the typical reagent used in bromination of an alkene is bromine in a chlorinated solvent. Besides the suspected carcinogenic solvent, the elemental bromine is highly corrosive, causing severe burns upon contact with the skin and inhalation. An alternative brominating reagent is pyridinium tribromide which exists in rapid equilibrium with pyridinium hydrobromide and bromine. It will gradually release bromine into the reaction mixture. Therefore it is a safer brominating reagent and easier to handle than liquid bromine.



In this experiment, anisalacetophenone will be firstly prepared by Aldol condensation reaction between anisaldehyde and acetophenone in base condition. Then bromination of anisalacetophenone using pyridinium tribromide, a comparatively safe and convenient source of bromine, will be carried out. The product will be characterized by measuring its melting point.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flask
2. Erlenmeyer flask
3. Test tube
4. Receiver distilling still
5. Condenser
6. Hot plate and heat dissipation block
7. Filtering flask
8. Ice-water bath
9. Suction glass funnel

Chemicals: Anisaldehyde (*p*-CH_3CO-C_6H_4-CHO); acetophenone (C_6H_5-$COCH_3$); pyridinium tribromide ($C_5H_5NH^+$ Br_3^-); sodium hydroxide (NaOH); dichloromethane (CH_2Cl_2); hexane (C_6H_{12}); ethanol (CH_3CH_2OH).

PROCEDURE

PART I: Preparation of anisalacetophenone

1. Place 544 mg (4 mmol) of anisaldehyde and 480 mg (4 mmol) of acetophenone in a 10-mL conical bottom flask.
2. Dissolve a minute amount of NaOH with 1 mL of ethanol in a test tube and add in the mixture.
3. Stir until it appears as yellow slurry and stir for another 5 minutes. Place the flask in an ice-water bath for 5 minutes.
4. Collect the precipitated product by suction filtration
5. Wash the product with a tiny amount of ice-cold ethanol.
6. Crystallize the product from ethanol. Collect it by suction filtration as described in step 4 and continue suction to air-dry.

7. Measure its mass. Calculate the percent yield and determine its melting point.

PART II: Preparation of anisalacetophenone dibromide

1. Dissolve 238 mg (1 mmol) of anisalacetophenone with 5 mL of dichloromethane in a 10-mL conical bottom flask.
2. Gently add 336 mg (1.05 mmol) of pyridinium tribromide. Swirl the mixture gently until all the solid has dissolved.
3. Connect the flask with a receiver distilling still and a water-cooled condenser. Distil off the solvent.
4. Add 5 mL of distilled water and stir the mixture using a Pasteur pipette method.
5. Collect the precipitated product by suction filtration as described in step 4.
6. Crystallize the product from mixed solvent of dichloromethane and hexane (1:1) in a 25-mL Erlenmeyer flask.
7. After crystallization is complete, collect the crystals by suction filtration as described in step 4. Wash the crystal with a minute amount of cool mixed solvent and continue suction to air-dry.
8. Weigh the crystals of product and calculate its percent recovery. Determine its melting point.

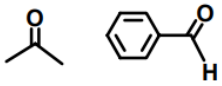
CLEANUP

1. After filtration of ethanol, any remaining sodium hydroxide can be neutralized by acid and flush them down the drain with copious amount of water.
2. Pour any remaining mixed solution of dichloromethane in chlorinated hydrocarbon waste container.
3. Do not use acetone to rinse glassware containing residual bromine (to prevent the formation of bromoacetone, a severe lachrymator). Add solid sodium thiosulfate to all test solutions to destroy residual bromine, then neutralize and filter them. Flush the filtrate down the drain with copious amount of water and place the filter paper in the container for halogenated organic compounds.

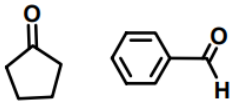
QUESTIONS FOR VIVA VOCE

1. What are the product structures obtained from the addition of bromine to cinnamic acid by using Br_2/Et_2O reagent? Show the stereochemistry of this compound.
2. What is the product structure when the reagent is changed to Br_2/H_2O-EtOH solution?
3. Predict the products for the Aldol condensation reactions of the following two

compounds?

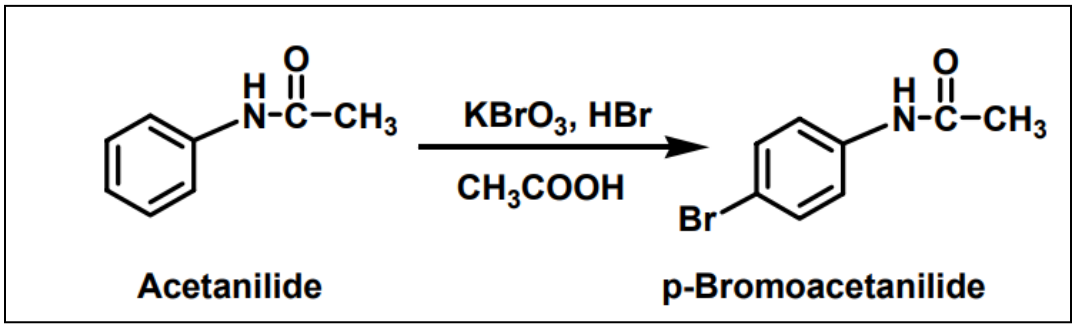
a) 

b) 

c) 

4. List the chiral center and stereoisomer of anisalacetophenone dibromide compound?

BROMINATION OF ACETANILIDE



OBJECTIVE

To brominate an activated aromatic compound and isolate the solid product.

BACKGROUND

Bromination of aniline *via* an electrophilic aromatic substitution usually gives only tribromoaniline. This is because the electron-donating amino group of aniline greatly activates the ring toward electrophiles. Acetylating the amino group of aniline moderates the activating effect of the non-bonded pair of electrons on the nitrogen atom which is delocalized by both the carbonyl group and the phenyl ring. The acetamido group is *ortho*- and *para-directing*, but the steric bulk of this substituent hinders the attack at the 2- position. Therefore the selective monobromination of acetanilide to give *para*- bromoacetanilide is strongly favored under mild condition such as bromine in acetic acid. However the elemental bromine is highly corrosive, causing severe burns upon contact with the skin and inhalation. An alternative brominating reagent is bromine generating *in situ* from the oxidation of bromide ion with potassium bromate, according to the following equation:

$$6H^+ + 5Br^- + BrO_3^- \longrightarrow 3Br_2 + 3H_2O$$

The amount of bromine generated is determined by the amount of potassium bromate used. Potassium bromate is a granular solid that can be measured easily and accurately.

In this experiment, bromination of acetanilide will be carried out using hydrobromic acid and potassium bromate.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flasks
2. Pasteur pipette
3. Beaker
4. Magnetic stirrer
5. Receiver distilling still
6. Filtering flask
7. Suction glass funnel

Chemicals: Acetanilide (C_6H_5-$NHCOCH_3$); potassium bromate ($KBrO_3$); hydrobromic acid (48% HBr); glacial acetic acid (CH_3COOH); sodium bisulfate (10% $NaHSO_3$); ethanol (CH_3CH_2OH).

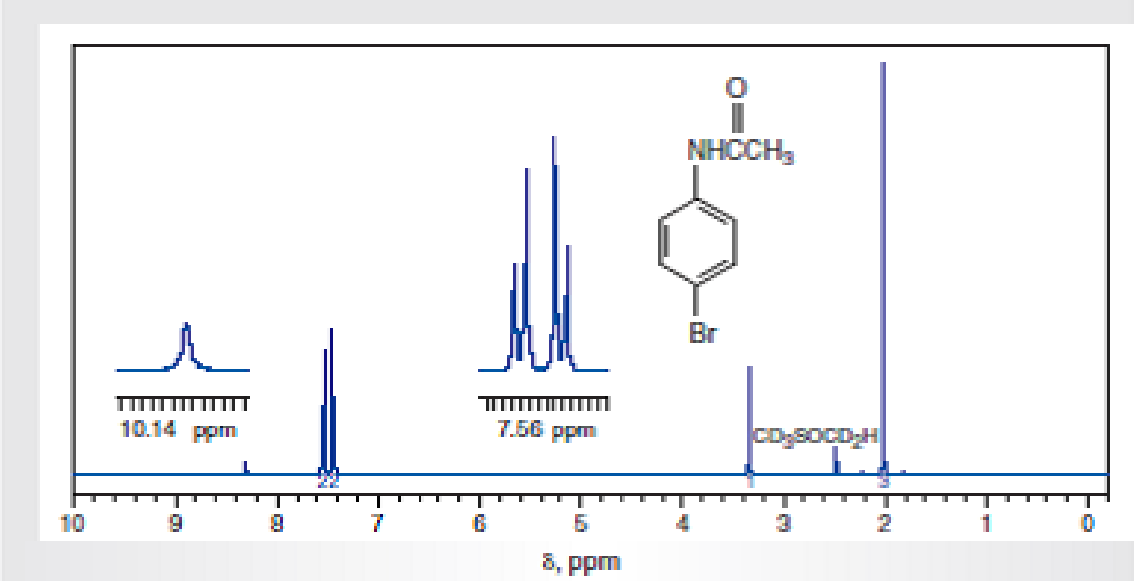
PROCEDURE

1. Weigh 200 mg (1.5 mmol) of acetanilide, 85 mg (0.5 mmol) of potassium bromate in 10-mL conical bottom flask and 2 mL of glacial acetic acid to the flask and swirl the mixture until all the solid has dissolved.
2. Add 0.3 mL of 48% HBr and often stir the mixture at room temperature for a 30 minute period of reaction time using a Pasteur pipette method.
3. Pour the mixture into a 100-mL beaker containing 25 mL of water and stir the mixture rapidly for 15 minutes.
4. Collect the solid product on by suction filtration.
5. Wash the precipitate with several drops of 10% $NaHSO_3$ and water to remove any residual bromine.
6. Recrystallize the crude product from ethanol.
7. After crystallization is complete, collect the crystals by suction filtration as described in step 4. Wash the product with cold ethanol and continue suction to air- dry.
8. Weigh the product and calculate its percent recovery. Determine its melting point.

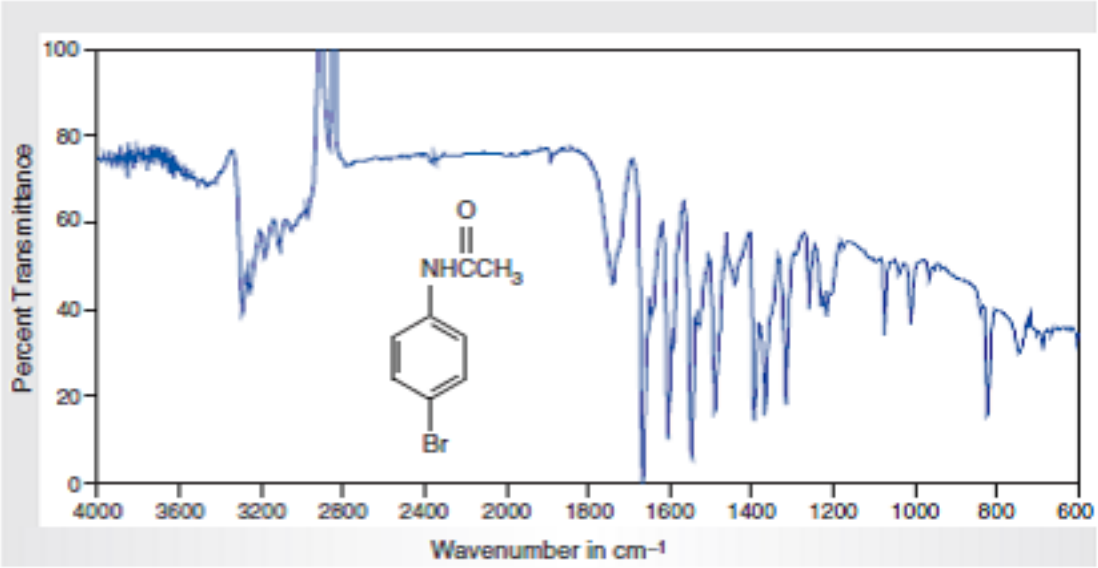
CLEANUP

Treat the filtrate with 10% $NaHSO_3$ to destroy the left over HBr before pouring it into the appropriate waste container.

NMR Spectra of 4 - Bromo acetanilide



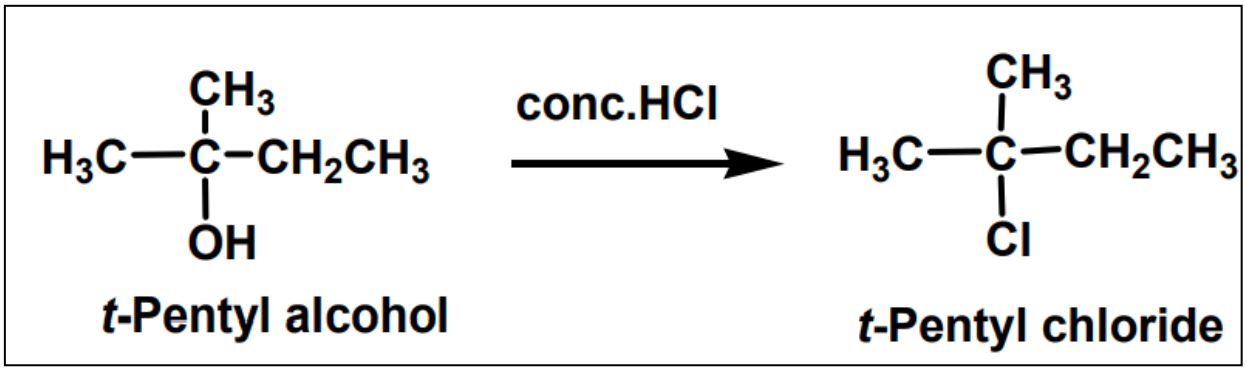
IR Spectra of 4 - Bromo acetanilide



QUESTIONS FOR VIVA VOCE

1. Why is an acetamido group less reactive toward electrophilic aromatic substitution at *o*- and *p*-positions than an amino group? Explain by using resonance structures.
2. Write the mechanism of the bromination reaction of acetanilide.
3. What is the purpose of adding 10% $NaHSO_3$ to the solution? Write the equation of this reaction.

SYNTHESIS OF *t*-PENTYL CHLORIDE BY UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION



OBJECTIVE

To convert *tert*-pentyl alcohol to *tert*-pentyl chloride using an S_N1 reaction with HCl.

BACKGROUND

Alkyl halides can be prepared from alcohols by reacting them with a hydrogen halide, HX (X=Cl, Br, or I). The mechanisms of acid-catalyzed substitution of alcohols can be unimolecular nucleophilic substitution (S_N1) or bimolecular nucleophilic substitution (S_N2). Secondary alcohols react with hydrogen halides by both S_N1 and S_N2 mechanisms, primary alcohols by S_N2 and tertiary alcohols by S_N1.

In this experiment, *t*-pentyl chloride will be synthesized from *t*-pentyl chloride through an S_N1 nucleophilic substitution. The tertiary alcohol (*t*-pentyl alcohol) will be treated with strong hydrogen halide (HCl) to initially form the oxonium ion. The oxonium ion then reacts to form a stable tertiary carbocation. The chloride ion from HCl, reacts with the carbocation in the final step of the reaction to give the tertiary chloride as the product of the reaction.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flasks
2. Erlenmeyer flasks
3. Condenser
4. Receiver distilling still

5. Hot plate and heat dissipation block
6. Pasteur pipette
7. Capillary tubes

Chemicals: *t*-Pentyl alcohol ($CH_3CH_2(CH_3)_2$-C-OH); hydrochloric acid (HCl); sodium hydrogen carbonate (5% $NaHCO_3$); sodium sulfate (anh.Na_2SO_4); silver nitrate (0.1M $AgNO_3$ in 95% ethanol).

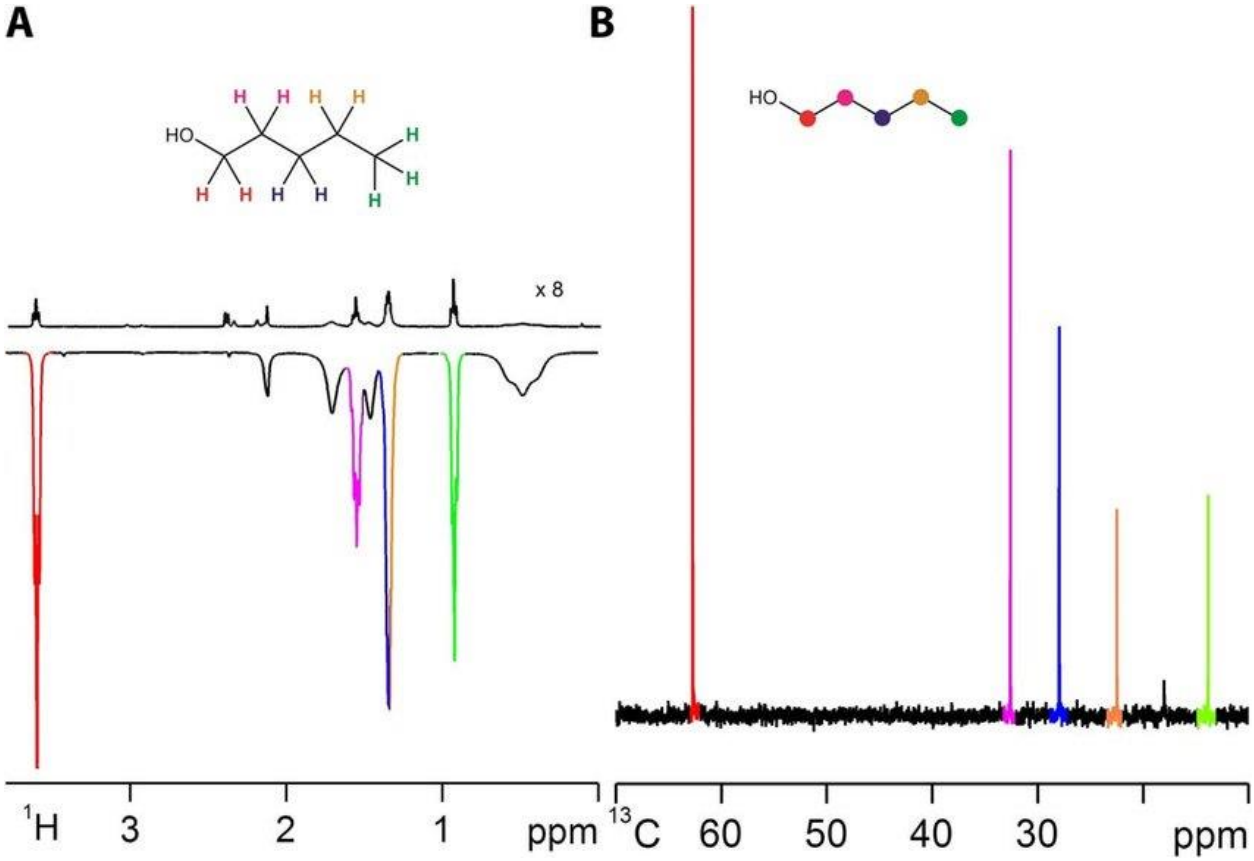
PROCEDURE

1. Place 1.0 mL (9.27 mmol) of *t*-pentyl alcohol into 5-mL conical bottom flask, Flask No.1.
2. Cautiously add 2.5 mL of conc.HCl (30 mmol). Stir the mixture using a Pasteur pipette method.
3. Allow the mixture to separate completely into two distinct layers. Remove the lower aqueous layer, using a Pasteur pipette method.
4. Leave the upper *t*-pentyl chloride in Flask No.1 and keep the lower aqueous in an Erlenmeyer flask for disposal.
5. Wash the *t*-pentyl chloride layer in Flask No.1, by first stirring as described in step 2 and then separation as described in step 3, sequentially with 1 mL of cold water, 1 mL of satd.NaCl, 1 mL of 5% $NaHCO_3$ and 1 mL of satd.NaCl.
6. Transfer the upper *t*-pentyl chloride into another conical bottom flask, Flask No.2 and keep all lower aqueous layers in another Erlenmeyer flask for disposal.
7. Add a minute amount of anh.Na_2SO_4 in Flask No.2 and swirl the solution. Keep adding until some of it swirls freely, and then set aside when the solution is no longer cloudy.
8. Filter the solution using a Pasteur filter-tip pipette method.
9. Transfer the solution in the pipette into another conical bottom flask, Flask No.3. Connect the flask with a receiver distilling still and a water-cooled condenser. Distil the solvent off at 84-86ºC to obtain the solid in the flask.
10. Weigh the product and keep a small amount for its melting point determination.
11. Test for alkyl halide with $AgNO_3$: Place a few drops of the product in a small test tube. Add 2 drops of 0.1M $AgNO_3$ test solution and mix.
12. The appearance of a white precipitate indicates that a reaction has taken place between the alkyl halide and silver nitrate.

CLEANUP

1. Carefully dilute the aqueous layer with water and then neutralize it with sodium carbonate.
2. Combine the solution with other aqueous washes (water, $NaHCO_3$) and flush them down the drain with copious amount of water.
3. Pour the contents of the test reaction in the halogenated waste.

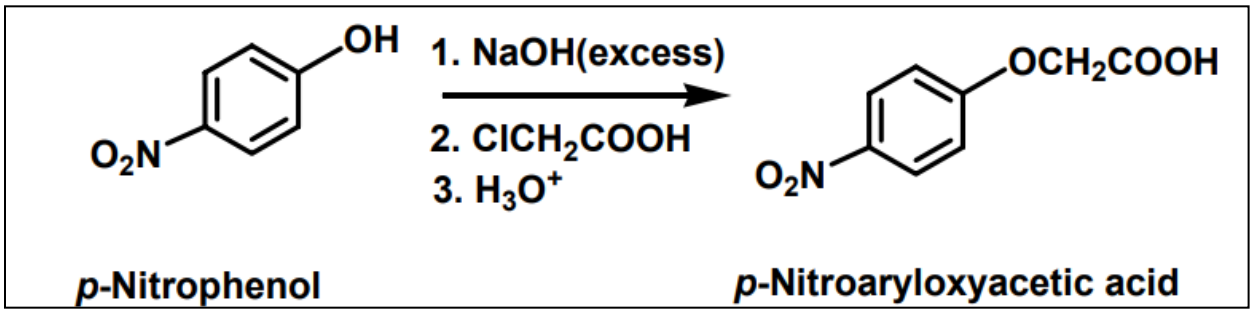
NMR Spectra of t - Pentyl alcohol



QUESTIONS FOR VIVA VOCE

1. Why is the *t*-pentyl chloride phase the upper layer?
2. $NaHCO_3$ solution was used to wash the crude *t*-pentyl chloride,
   - What was the purpose of this wash? Give equations.
   - Why is it undesirable to wash the crude halide with aqueous NaOH?
3. How was the unreacted *t*-pentyl alcohol removed in this experiment?
4. Explain why some 2-methyl-l-butene can be formed in this experiment.

SYNTHESIS OF ARYLOXYACETIC ACID BY BIMOLECULAR NUCLEOPHILIC SUBSTITUTION

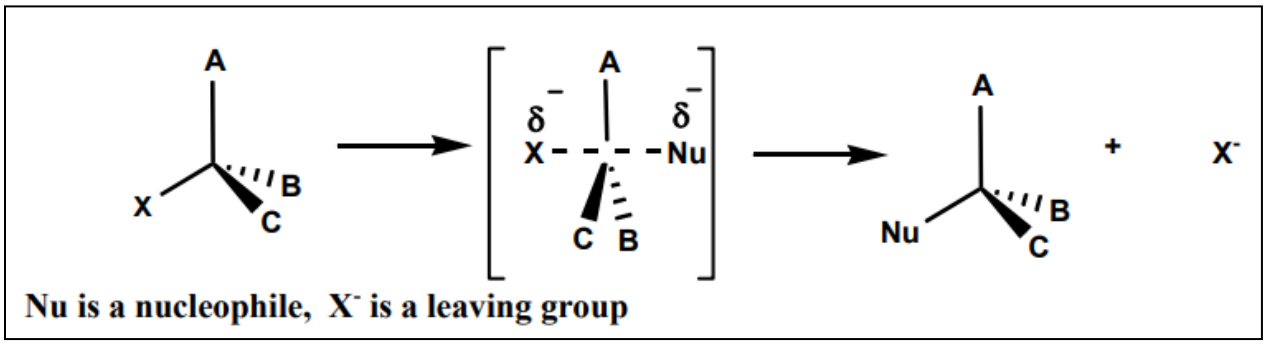


OBJECTIVES

1. To synthesize *p*-nitroaryloxyacetic acid from *p*-nitrophenol with bimolecular nucleophilic substitution.
2. To practice reflux, extraction, thin-layer chromatography and recrystallization.

BACKGROUND

Nucleophilic substitution reactions are an important class of reactions which allow the displacement of one functional group or substituent on an sp^3-hybridized carbon atom with another. There are two kinds of nucleophilic substitutions, unimolecular nucleophilic substitution (S_N1) and bimolecular nucleophilic substitution (S_N2). S_N2 reactions occur as a concerted process. As the nucleophile approaches the carbon atom and bond forming begins, bond breaking between the carbon atom and the leaving group occurs simultaneously as shown below. The S_N2 reaction thus proceeds with inversion (reversal of the configuration).



In this experiment, *p*-nitroaryloxyacetic acid will be synthesized from the S_N2 reaction of *p*-nitrophenol, a nucleophile, and chloroacetic acid which has chlorine as a leaving group.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flask with stopper
2. Hot plate and heat dissipation block
3. Filtering glass funnel
4. Filtering flask
5. Pasteur pipette
6. Thin-layer chromatography plates
7. Boiling stone
8. TLC chamber

Chemicals: *p*-Nitrophenol (*p*-NO_2-C_6H_4-OH); sodium hydroxide (6M NaOH); chloroacetic acid (50% $ClCH_2COOH$); hydrochloric acid (6M HCl); dichloromethane (CH_2Cl_2); sodium carbonate (5% Na_2CO_3); sodium sulfate (anh.Na_2SO_4); ethyl acetate ($CH_3COOCH_2CH_3$); hexane (C_6H_{14}).

PROCEDURE

PART I: Synthesis of aryloxyacetic acid

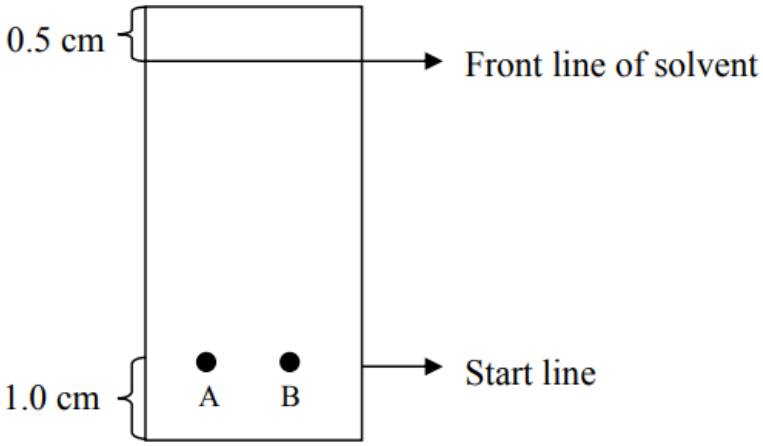
1. Place 400 mg (2.87 mmol) of *p*-nitrophenol and 2 mL of 6M NaOH in 10-mL conical bottom flask, Flask No.1, and immediately swirl the mixture until all solid has dissolved.
2. Slowly add 1 mL (5.20 mmol) of chloroacetic acid and a boiling stone to the flask.
3. Equip the flask with a water-cooled condenser. Heat the solution to reflux at 90-100ºC for 1.5 hour.
4. Allow the mixture to cool down. Add 4 mL of water and swirl to mix well. Add 6 M HCl to the solution until it is just acidic with litmus paper.
5. Add 1 mL of dichloromethane and stir the mixture using a Pasteur pipette method.
6. Allow the mixture to separate completely into two distinct layers. Remove the lower dichloromethane layer, using the Pasteur pipette method.
7. Transfer it into another conical bottom flask, Flask No.2.
8. Extract the upper aqueous layer in Flask No.1 with another 1 mL of dichloromethane by stirring as described in step 5. Remove the lower dichloromethane layer as described in step 6. Combine the dichloromethane layer in Flask No.2.
9. Wash the dichloromethane layer in Flask No.2 with 2 mL of water and then 2 mL of 5%Na_2CO_3 using the Pasteur pipette method as described in steps 5 and 6.
10. Transfer the upper solution in the pipette into another conical bottom flask. Add

6M HCl to the solution until it is just acidic with litmus paper. Add 0.5 mL more to ensure complete precipitation of the product.

11. Collect the product by suction filtration.
12. Wash the product with cool water. Continue suction to air-dry.

PART II: Thin-layer chromatography

1. Prepare 1 TLC plate (2x7 cm dimension).
2. Obtain a TLC chamber and place solvent, 70% ethyl acetate in hexane to 0.5 cm height. Place a piece of filter paper around the inside surface of the container and extend into the solvent.
3. Using clean capillary tubes, carefully spot two samples at two pencil marks as shown below.
4. When the spots are dry, place the TLC plate in the developing chamber. Then gently close the chamber.



A: *p*-Nitroaryloxyacetic
B: *p*-Nitrophenol

1. When the solvent has moved to the front line, remove the plate. Lay it on a clean surface in a fume hood or well ventilated area and allow the solvent to evaporate until the plate appears dry.
2. Visualize the plate under UV light and immediately draw a light pencil line around each spot.
3. Measure all the distances traveled by the compounds and solvent. Calculate the retention factor (R_f) for each compound.

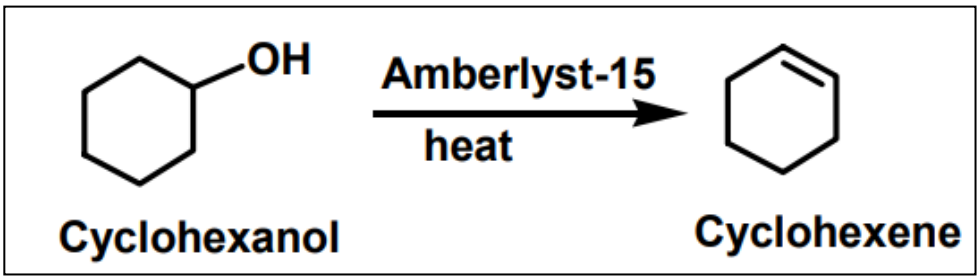
CLEANUP

1. Carefully dilute all solvents with water and flush them down the drain with copious amount of water.
2. Pour the mixture of ethyl acetate and hexane to the organic waste container.
3. Pour the waste dichloromethane to the halogenated hydrocarbon waste container.

QUESTIONS FOR VIVA VOCE

1. If *p*-nitrophenol is unavailable, can any other phenol be used in this reaction and which type of substitutions will make this reaction work well?
2. What is the purpose for the first acidification of the solutions with 6M HCl in this experiment?
3. Why is 5% Na_2CO_3, needed? Write the equation of this reaction.

DEHYDRATION OF ALCOHOL
USING A CATION EXCHANGE RESIN CATALYST



OBJECTIVES

1. To synthesize cyclohexene by dehydration of cyclohexanol using Amberlyst-15.
2. To practice distillation with the receiver distilling still and testing for unsaturation.

BACKGROUND

The most common methods for introducing unsaturation into the organic compounds, to prepare alkenes, are dehydration and dehydrohalogenation. This type of reactions is known as an elimination reaction. Dehydration reaction is readily accomplished by heating the alcohol in the presence of an acid catalyst such as sulfuric acid or phosphoric acid. It has recently been reported that a cation exchange resin can be used as a successful catalyst replacing those mineral acids which are corrosive.

In this experiment, dehydration of cyclohexanol will be carried out using Amberlyst-15, a cation exchange resin, as a catalyst. The product will be tested for the presence of unsaturation by reacting with bromine in carbon tetrachloride and potassium permanganate solution.

REQUIREMENTS

Apparatus and materials:

1. Conical bottom flasks
2. Receiver distilling still
3. Condenser
4. Pasteur pipette
5. Thermometer
6. Hot plate and heat dissipation block

7. Boiling stone
8. Amberlyst-15

Chemicals: Cyclohexanol (C_6H_{11}-OH); sodium chloride (satd.NaCl); sodium sulfate (anh.Na_2SO_4); bromine in carbon tetrachloride (1%Br_2/CCl_4); potassium permanganate (5% $KMnO_4$).

PROCEDURE

1. Place 2g (10 mmol) of cyclohexanol in a 5-mL conical bottom flask, Flask No.1. Add 0.20 g of the ion exchange resin (Amberlyst 15) and a boiling stone to the flask.
2. Connect the flask to a receiver distilling still fitted with a water-cooled condenser. Gradually heat the mixture until the product begins to distil.
3. When the distillation is finished, transfer the crude product from the trough of the receiver distilling still by using a Pasteur pipette to another 5-mL conical bottom flask, Flask No.2.
4. Rinse the inside of the receiver distilling still with 1 mL of satd.NaCl solution and add this solution to Flask No.2.
5. Stir the mixture using a Pasteur pipette method.
6. Allow the mixture to separate completely into two distinct layers. Remove the lower aqueous layer, using a Pasteur pipette method.
7. Transfer it into another conical bottom flask, Flask No.3.
8. Add a minute amount of anh.Na_2SO_4, and swirl the solution. Keep adding until some of it swirls freely, and then set aside when the solution is no longer cloudy.
9. Filter the solution using a Pasteur filter-tip pipette method.
10. While the product is drying, clean and dry the receiver distilling still.
11. Add a boiling stone into Flask No.3. Assemble the apparatus for simple distillation
12. Distil the product. Collect the fraction that boils between 82 and 85^oC. Weigh and calculate percent yield.
13. Test the product for unsaturation by adding it dropwise into two test tubes containing a few drops of 1% Br_2/CH_2Cl_2 and 5% $KMnO_4$ separately. Shake well after each addition and observe the change in color of both reagent solutions. Record the results.

CLEANUP

1. Place Amberlyst-15 in an appropriate waste container.
2. Aqueous solutions should be diluted and poured down the drain with copious amount of water.
3. Pour the unsaturated testing solution into the appropriate waste container.
4. Add water to dissolve sodium sulfate until solid disappear and flush them down the drain with copious amount of water.

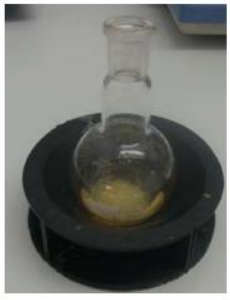
QUESTIONS FOR VIVA VOCE

1. Write the equation showed the dehydration reaction from tertiary amyl alcohol by using Amberlyst-15 as a catalyst.
2. From Q1, what is the major product? Write the mechanism.
3. From Q1, is the reaction faster or slower than the dehydration of cyclohexanol? Explain.

Benzilic Acid Rearrangement

Experimental notes

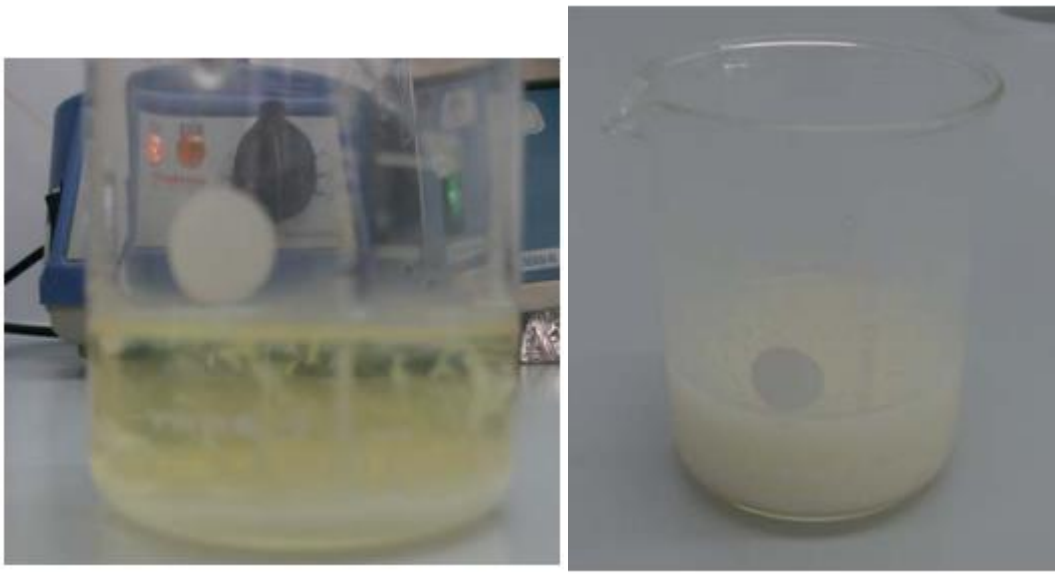
This experiment aims at the preparation of 2-hydroxy-2-phenylbenzylic acid from benzil through a molecular rearrangement in basic medium. The experiment is very simple and adequate for 1st year chemistry students. The reaction is performed in a water/ethanol solution where the yellowish solid benzil reagent is soluble and thus the initial solution is slightly yellow. As the solution is heated under reflux the solution acquires a violet/blue colouration that becomes dark orange after heating for 20 min. The reaction is not complete but further heating does not lead to an increased yield. The carboxylate salt present in the reaction mixture does not precipitate by simply putting the flask in an ice bath. It is necessary to scratch the flask to initiate the crystals formation. The crystals thus obtained are yellowish and very soluble in water. The addition of the H2SO4 solution leads to the immediate formation of the 2-hydroxy-2-phenylbenzilic acid that precipitates as white crystals. By the end of the H_2SO_4 addition all the aqueous solution becomes white. We chose to use a 2M solution of H_2SO_4 but either a more diluted solution or other strong acids, like HCl, can be used. The final product is isolated by filtration and washed with cold ethanol to remove traces of benzil. The recrystalization can be done with water (around 50 mL). The final product, 2-hydroxy-2- phenylbenzilic acid, is a white solid and the TLC and 1 H NMR analysis confirm its purity. This experiment is very reproducible and the 2-hydroxy-2-phenylbenzilic acid can be isolated in one session of 2h, however, the measurement of the weight and melting point of the product can only be made after drying overnight in an oven. The yields vary between 32-64% and the melting point of product is 148-150 ºC (lit 150-152 ºC) .



Initial yellowish solution of benzil

Reaction apparatus and the initial violet solution obtained after starting the heating

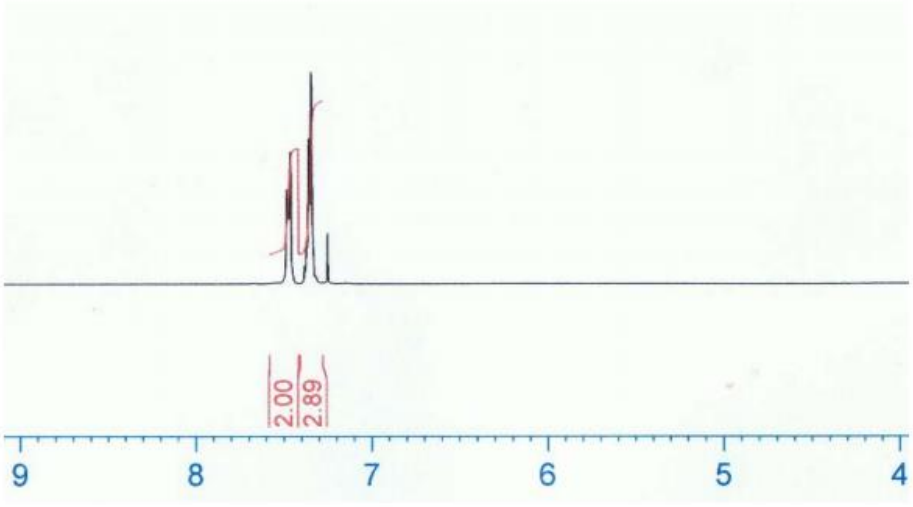
Reaction mixture after heating for 20 min



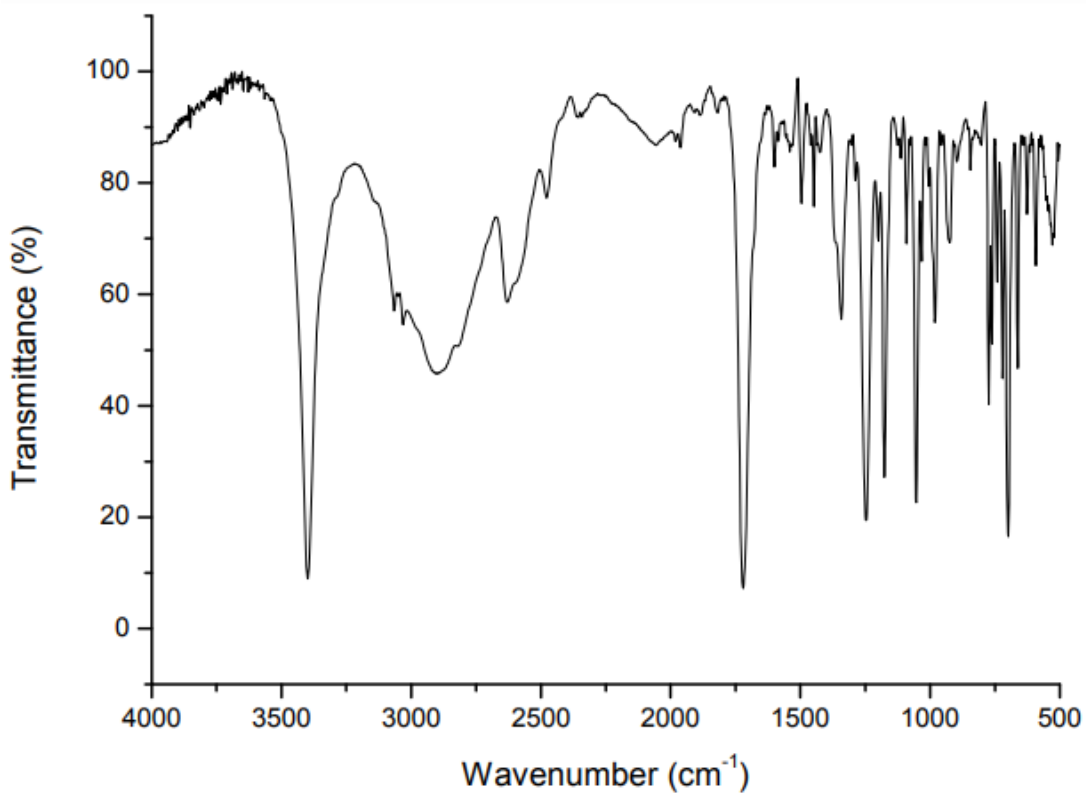
Addition of H_2SO_4 to the carboxylate aqueous solution and formation of the final product

TLC plate. 80% diethyl ether/petroleum ether. a) Benzil b) Product

^{1}H NMR and IR Spectra



^{1} H NMR spectrum (400 MHz, $CDCl_3$) of the 2-hydroxy-2-phenylbenzilic acid.



IR spectra of the 2-hydroxy-2- phenylbenzilic acid

Preparation of Phenyl Acetate and its Conversion to 4-Hydroxyacetophenone

Experiment Notes

Step 1: Preparation of phenyl acetate:

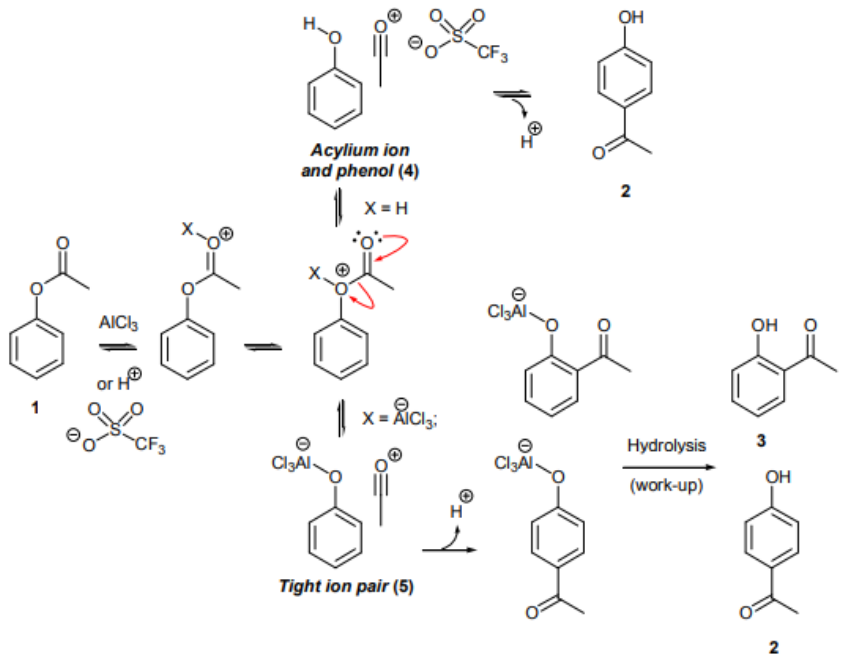
This reaction is rapid and from an experimental perspective, relatively straightforward. Phenol readily dissolves in an excess of basic solution to generate the phenoxide ion. Because this is moderately exothermic we have found that, as directed, cooling the solution by adding ice-chilled water is beneficial. The subsequent reaction with acetic anhydride is practically instantaneous and despite a moderate excess of hydroxide the final yield of phenyl acetate is high. The work-up procedure is also standard and the inclusion of a saturated sodium bicarbonate wash is solely a precaution in case incorrect amounts of reagents have been added and acetic acid is present following the reaction. If the amounts are correctly measured, as directed, no carbon dioxide evolution is observed. Following drying (anhydrous MgSO4 or Na2SO4), filtration and solvent removal under reduced pressure the phenyl acetate can be reliably distilled using a small, standard distillation apparatus, either at atmospheric pressure (b.pt. approx. 190 °C/760 mmHg),1 or under reduced pressure (b.pt. approx. 95 °C/20 mm Hg). Reasonable to good (50-80%) yields of a colourless mobile liquid are produced. This part of the experiment has been run successfully for several years in our second year undergraduate laboratories (30-60 students per class). Historically, the reaction, the work-up and the distillation was performed on the bench in the open laboratory, however, more recently the whole experiment has been relocated to fume cupboards. The mechanism of this reaction helps teaching/understanding of pKa values of alcohols and the resonance of the phenoxide anion, in addition to presenting nucleophilic acyl substitution and the chemistry of the carbonyl group more generally.

- ✓ Phenol: MWt.: 94.11 gmol-1: Causes burns/corrosive, toxic (R = 23/24/25; 68); Avoid contact with skin, wear suitable protective equipment.
- ✓ 4 M NaOH solution: Causes burns/corrosive (R = 35); Avoid contact with skin, wear suitable protective equipment.
- ✓ Acetic anhydride: MWt.: 102.09 gmol-1; d = 1.08 gmL-1: Causes burns (R = 22); flammable (R = 10); harmful (R 20/22); Avoid contact, wear suitable protective equipment.

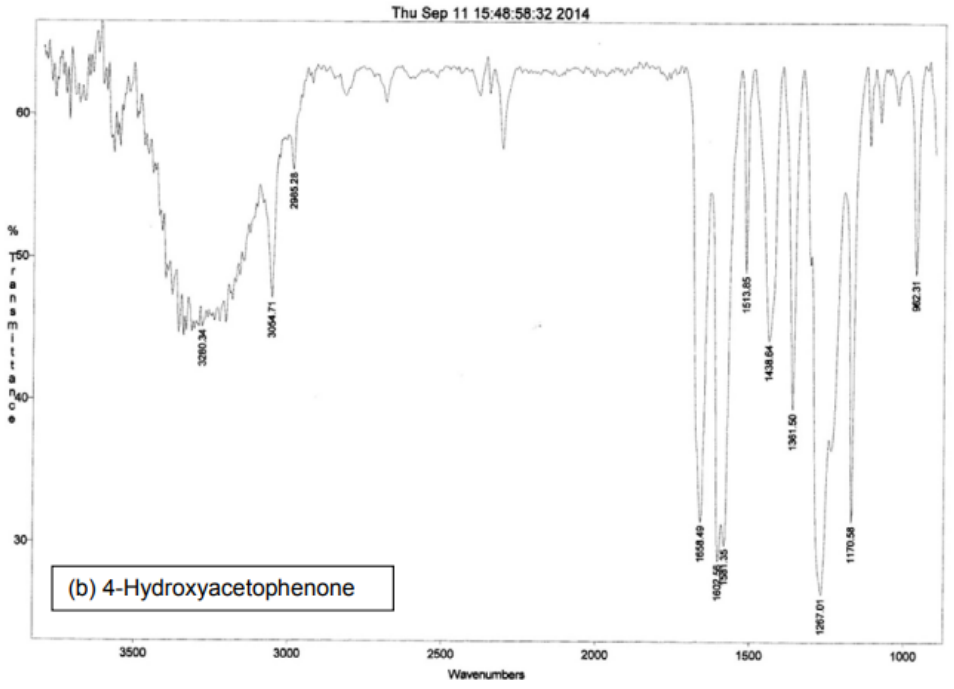
- ✓ Phenyl acetate MWt.: 136.15 gmol-1; d = 1.073 gmL-1; Harmful if swallowed (R = 22); Wear suitable protective equipment. Approx. b.pt. 190 °C/760 mm Hg; 95 °C/20 mm Hg.
- ✓ Dichloromethane: Limited evidence of a carcinogenic effect (R = 40).
- ✓ Sodium hydrogen carbonate solution: Liberates CO_2 on acidification.

Step 2: Fries rearrangement: Conversion of phenyl acetate to 4- hydroxyacetophenone:

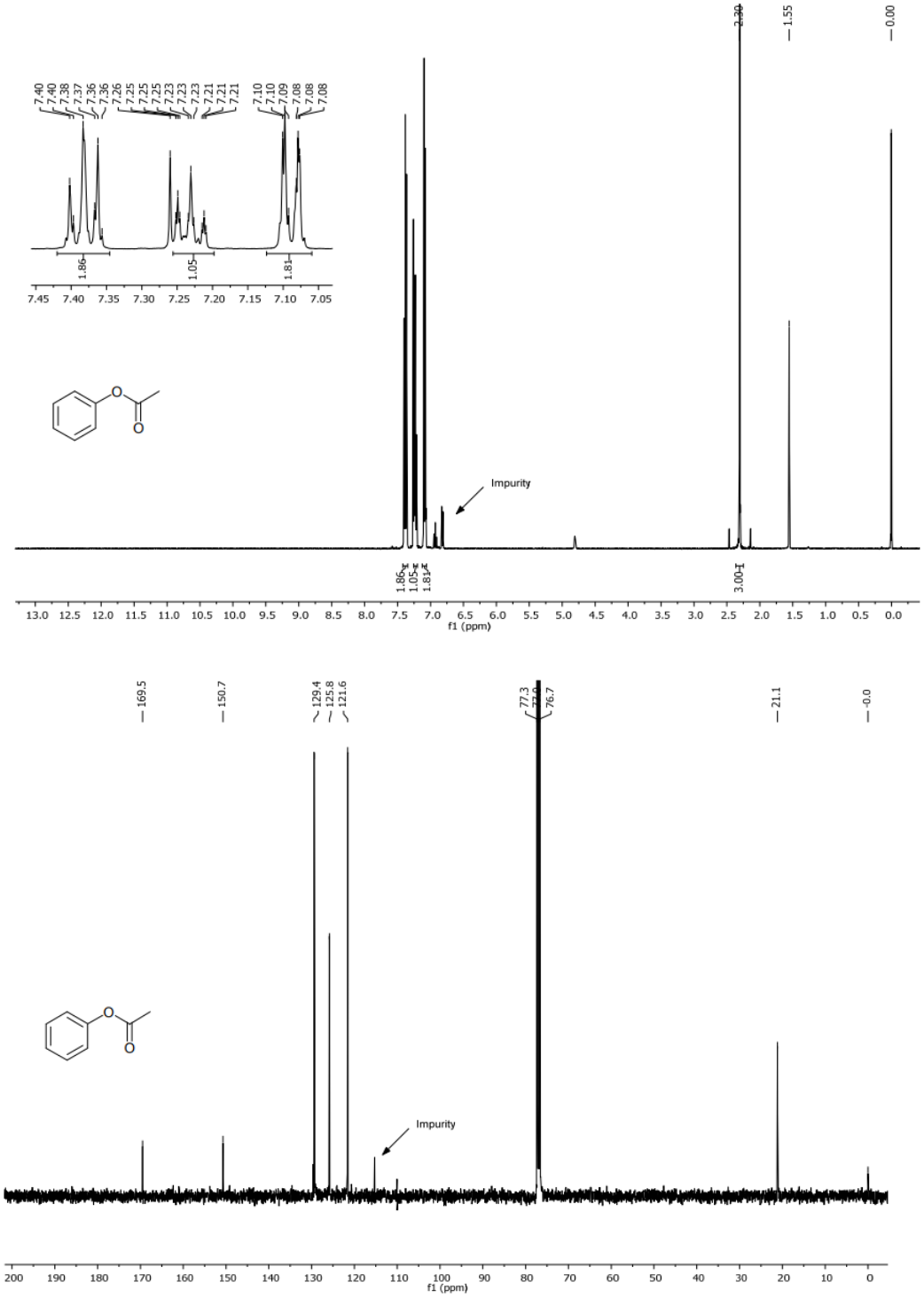
In a fume cupboard, trifluoromethane sulfonic acid is transferred by syringe to a clean dry round bottom flask (RBF) equipped with a stirrer bar. The flask was cooled externally with an ice-water bath for 5 to 10 minutes before the appropriate amount of phenyl acetate was added in a dropwise fashion with another syringe. Under the conditions outlined, this reaction is fast and proceeds reliably to completion. In addition, only the para-isomer (4- isomer) is detected. This is in contrast to alternative methods using Lewis acids, such as AlCl3, and using less polar media, in which typically significant amounts of the 2-isomer are encountered (see for example Figure SM 14.2.6).3 The literature,2 used as a guide for this experiment, reports a general procedure using 0.28 mmol of the acetate with 3 mL of trifluoromethane sulfonic acid. We have found that one can significantly increase the relative ratio of phenyl acetate to trifluoromethane sulfonic acid to the 0.34 mmol to 0.5 mL level reported in this experiment. However, we have found that attempts to increase the concentration leads to formation of side-products that are difficult to remove by recrystallization (see Figure SM 14.2.3). Replacement of trifluoromethane sulfonic acid with alternative Brønsted acids, such as trifluoroacetic acid, proved unsatisfactory. Please note trifluoromethane sulfonic acid is very corrosive so care and careful supervision should be taken introducing the trifluoromethane sulfonic acid to both the reaction vessel and the final solution of the reaction product to the separating funnel. These operations should only be performed in a fume cupboard. We found that the best way to perform the work-up was, in the fume cupboard, to transfer the contents of the reaction flask to ice-chilled water in a beaker using a Pasteur pipette. Once this has been performed the contents of the RBF and the pipette may be safely washed out with dichloromethane and added to the same beaker. Following a standard extraction process it is recommended to discard this initial aqueous layer (containing trifluoromethane sulfonic acid) in a separate receptacle for disposal. Replacement of trifluoromethane sulfonic acid with alternative Brønsted acids, such as trifluoroacetic acid, proved unsatisfactory.



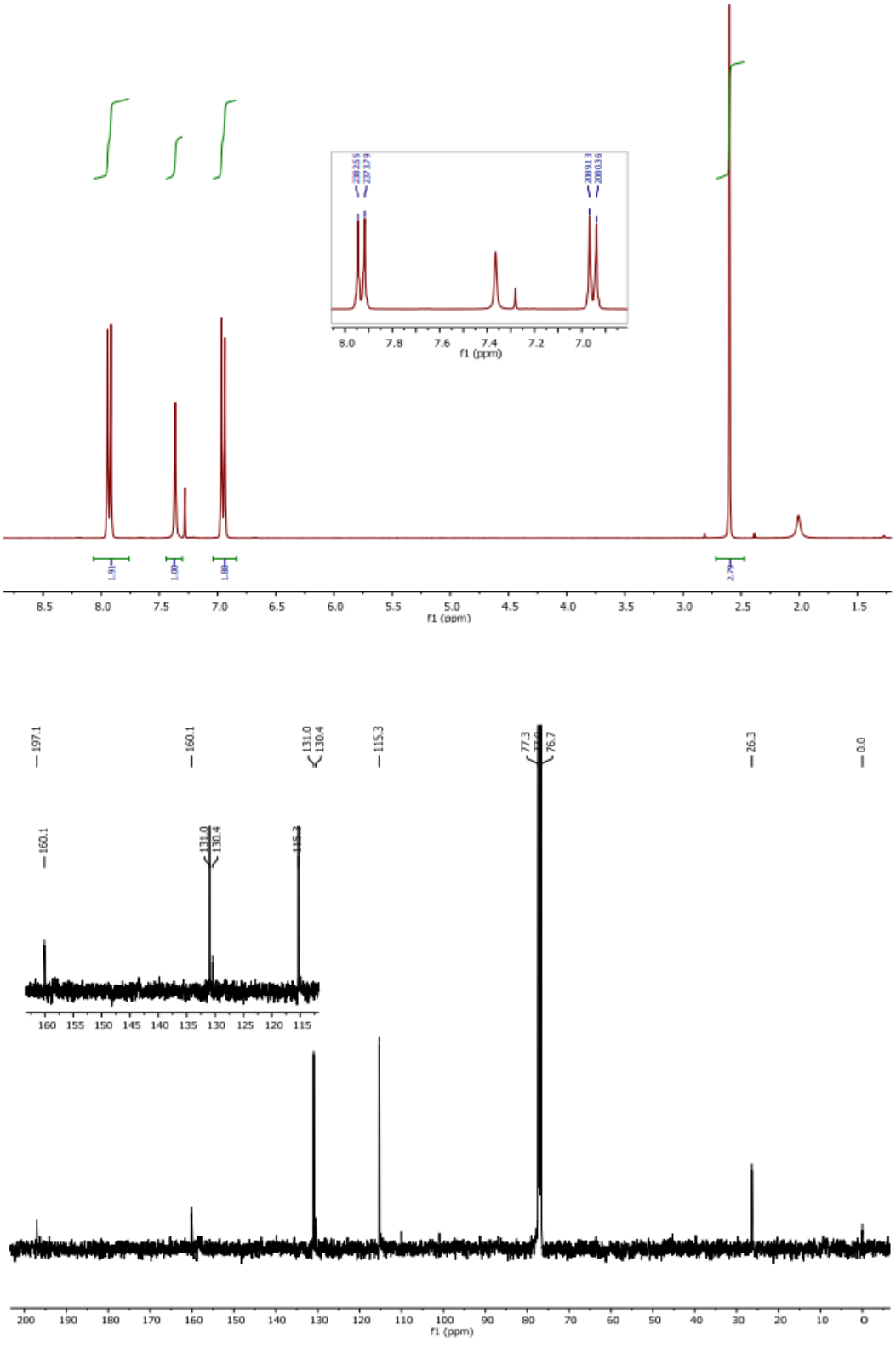
Mechanistic pathways for the Fries rearrangement under Lewis, or Brønsted acid mediated reaction conditions.



Infrared spectra of 4- hydroxyacetophenone



^{1}H NMR (400 MHz, CDCl3) and 13C NMR (100 MHz, CDCl3) spectra for phenyl acetate.

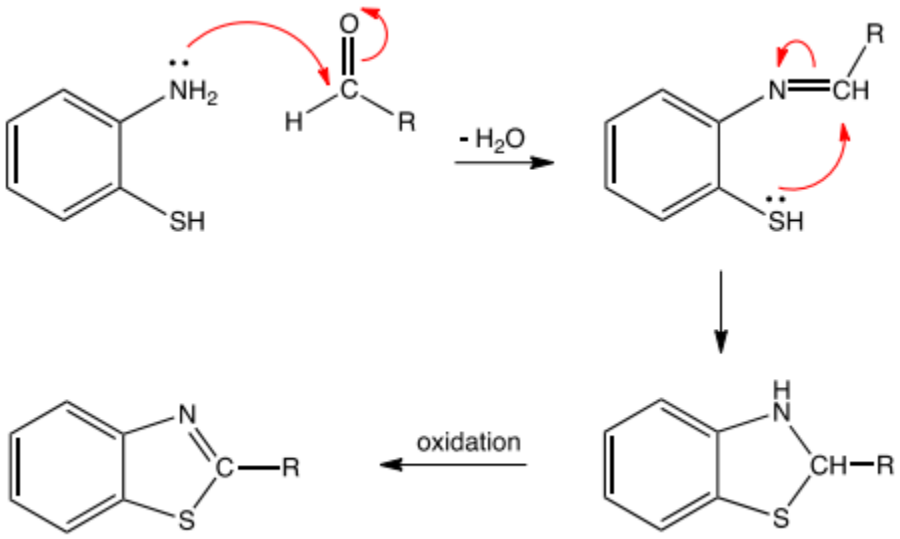


^{1}H NMR (400 MHz, CDCl3) and ^{13}C NMR (100 MHz, CDCl3) spectra for 4-hydroxyacetophenone {note: depending on concentration the phenol OH peak (@7.36 ppm in the spectrum below) differs in terms of chemical shift}

Synthesis of 2-(5’-phenylthien-2’-yl)benzothiazole

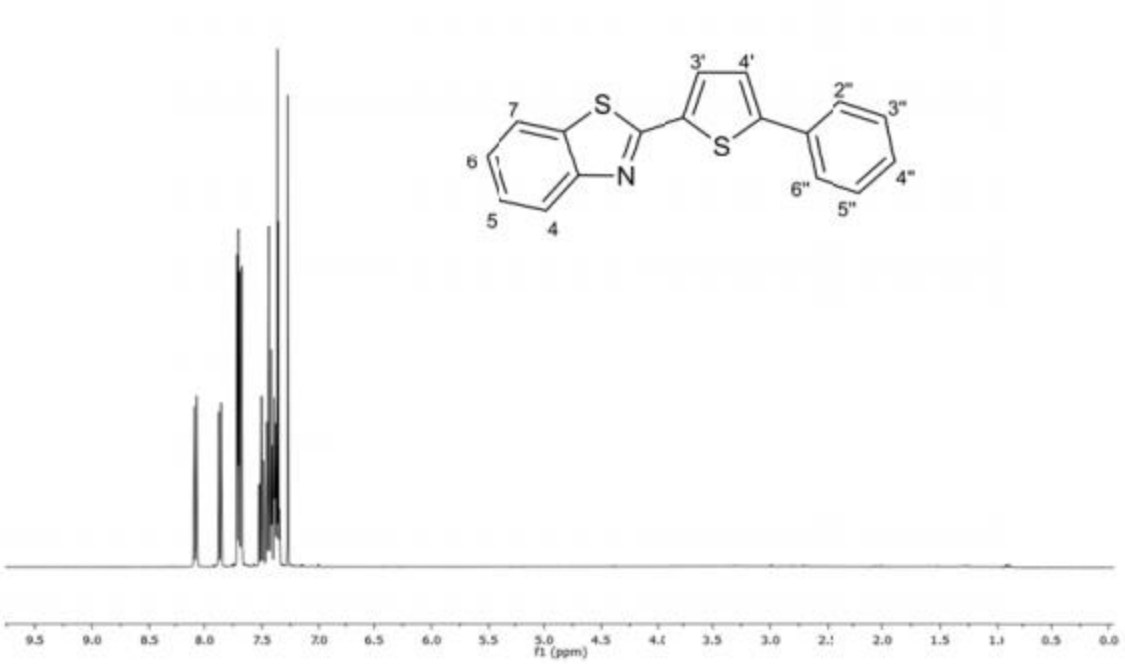
Experiment notes

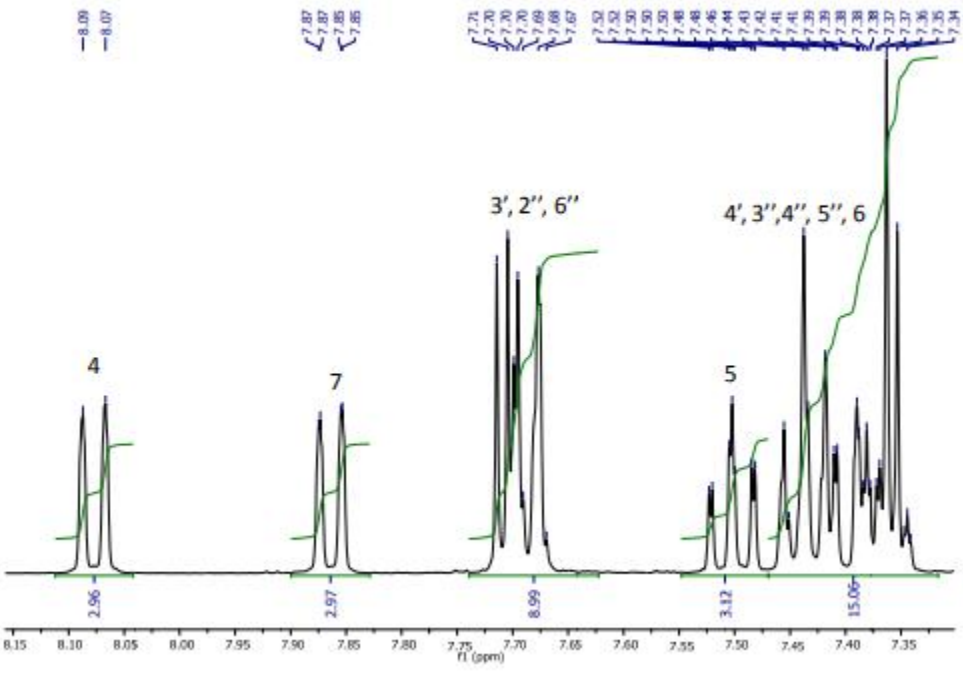
This experiment involves simple experimental techniques and commercially available reagents, and it is expected that the students possess previously acquired practical skills (in terms of isolation and purification techniques) and theoretical background (synthesis, reactivity and spectroscopic data interpretation). Therefore, this experiment may be appropriate for last year project in Chemistry degree or as the practical component of chemistry subjects at Master level. The purpose of this experiment is the synthesis of 2-(5'-phenylthien-2'-yl) benzothiazole from the condensation of an aldehyde with 2-aminobenzenethiol. The reaction is initiated by the formation of the corresponding imine, by nucleophilic attack of the nitrogen to the carbon of the carbonyl group, that cyclises spontaneously, yielding the intermediate benzothiazoline, which is oxidised to the benzothiazole.



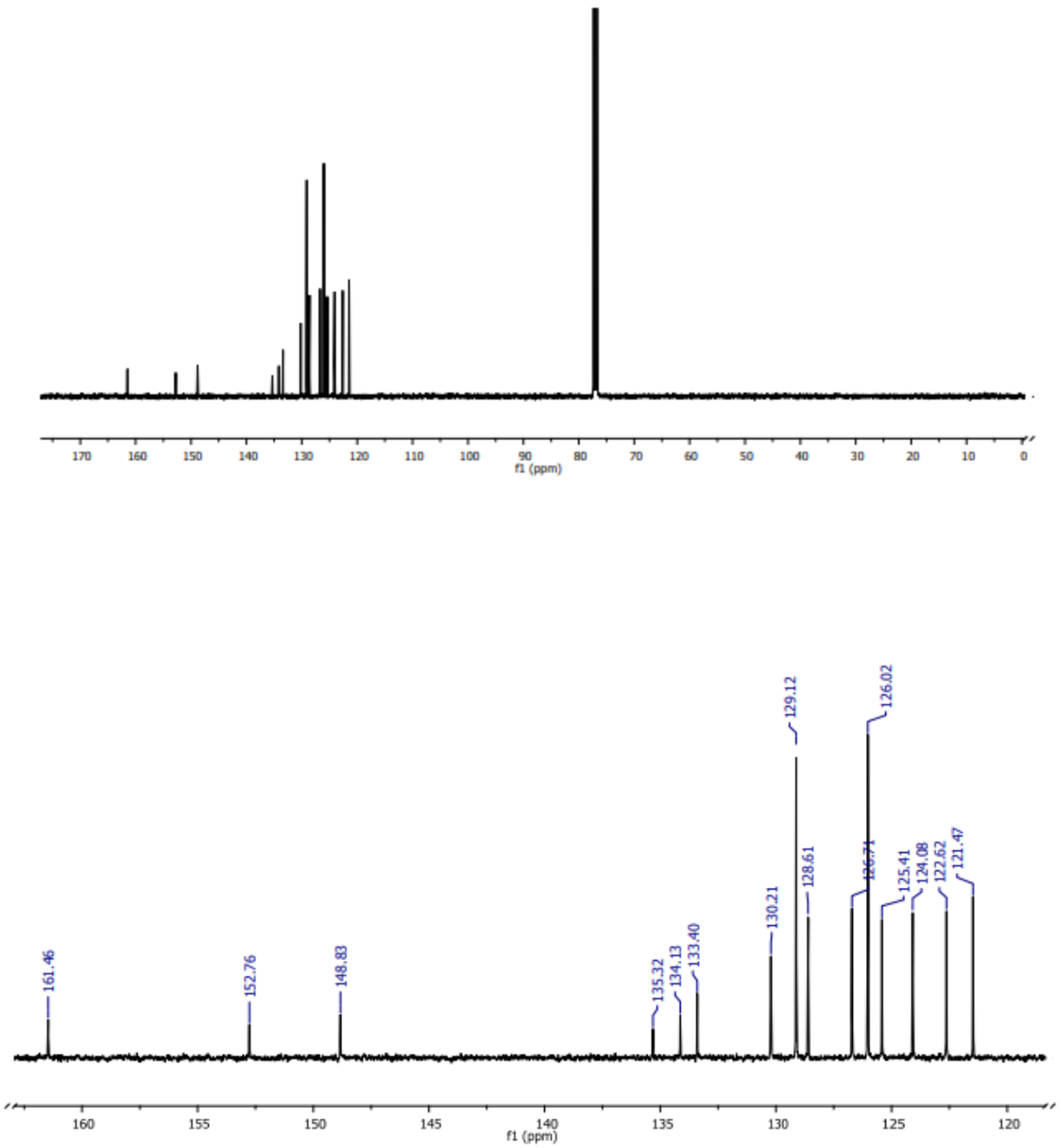
Mechanism of the intramolecular oxidative cyclization.

The use of DMSO as reaction solvent avoids the use of an oxidizing agent as DMSO promotes the conversion of the intermediate benzothiazoline to benzothiazole due to its oxidant character. Also, DMSO has a high boiling point and conducting the reaction at high temperature favours the formation of the desired product in shorter reaction time and elimination of water as the reaction by-product. Samples dissolved in DMSO cannot be as easily recovered compared to other solvents, as it is very difficult to remove all traces of DMSO by conventional rotary evaporation. In this experiment, liquid liquid extraction is used to fully recover the product: the reaction mixture is diluted with water (some precipitation of the product may occur) and extracted with ethyl acetate (the precipitate dissolves in ethyl acetate). The column chromatography on silica gel can be carried out with petroleum ether 40- 60, as described, or with hexanes. Using the present reaction conditions, 2-(5'-phenylthien-2'-yl) benzothiazole was prepared in 90% yield with m.p. 149.5-150.8 ºC.1 In these conditions, in various repetitions carried out by third year Chemistry students, the product was obtained in 88-93% yield as a off-white solid. This synthetic method has been applied in the preparation of other functionalized thienylaryl, (oligo)thienyl, and thienylpyrrolyl benzothiazoles, from the corresponding aldehydes and 2- aminobenzenethiol, in good yields by third year Chemistry students.2 The yield for the various derivatives was influenced by the electronic character of the substituents at the heterocyclic ring bearing the aldehyde and was higher for the derivatives with electron-withdrawing groups, as expected from the mechanism. As for the influence of substituent groups on the 2-aminobenzenethiol, it was confirmed that electrondonating groups at suitable positions resulted in higher yields, due to an increase of electron density at the nitrogen atom of the amino group, thus increasing its nucleophilicity. The title benzothiazole could be synthesised by using other reagents mentioned in the background section of this experiment, for example from 2-aminobenzenethiol and an adequate carboxylic acid, acyl chloride or nitrile, instead of the aldehyde.





^{1}H NMR spectrum of 2-(5'-phenylthien-2'- yl) benzothiazole in $CDCl_3$.



^{13}C NMR spectrum of 2-(5'-phenylthien-2'-yl) benzothiazole in $CDCl_3$.

Selective C-acylation of 3-methyl-1-phenyl-pyrazol-5-one

Synthesis of 4-aroyl-3-methyl-1-phenyl-pyrazol-5-ones

This particular laboratory experiment meets the goals of providing students with practical experience in regioselective acylation of heterocyclic compounds and acquiring skills in interpreting 1D and 2D NMR spectra. 3-Methyl-1-phenyl-pyrazol-5-on is chosen as starting material due to a combination of its low prize and the broad applicability of C-acylated compounds as extractants in separation science. Several 4-substituted aroyl chlorides are selected as acylating agents as the corresponding acylpyrazolones are displayed great complexation and extraction ability towards metal ions.

The protocol is appropriate for student's exercises due to several practical features: Fast conversion – all synthetic work can be performed in less than 5 h. Simple manipulation – do not need special precautions. No tedious work-up – simple recrystallization and filtration. Applicable to other heterocyclic systems possessing tautomeric C-OH/C=O group; for instance isoxazolones. The experiment is suitable for second/third year undergraduate students and can be achieved individually or in couples. If necessary to shorten the students' class room, the experiment can be performed in 3-3.5 h and to filter the crude product on next day.

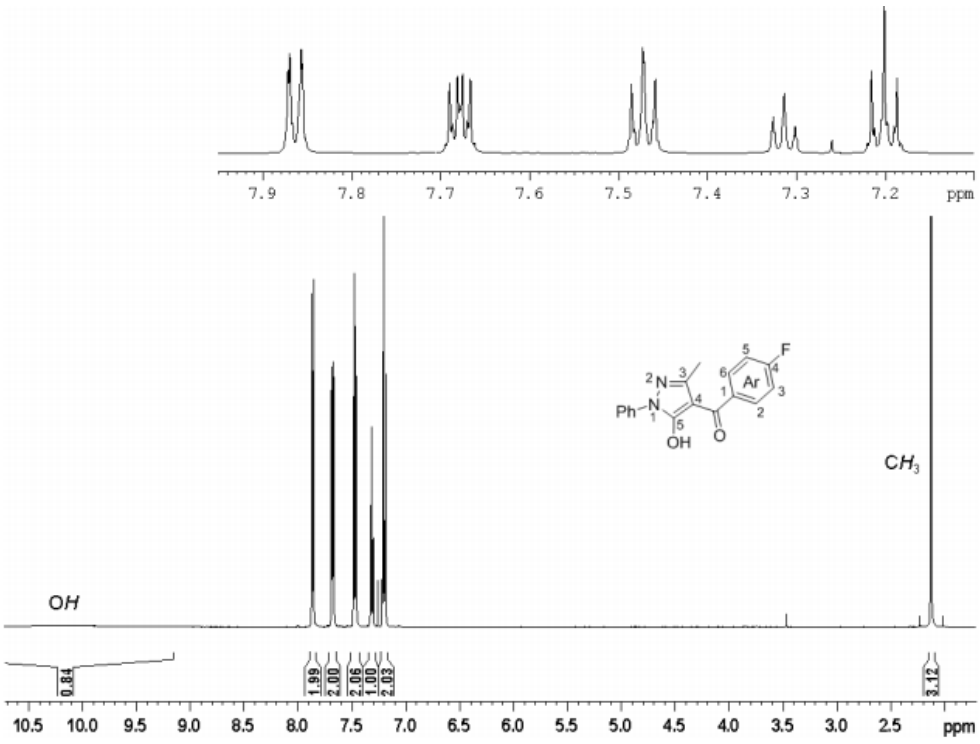
To achieve the C-acylation selectively and effectively, several experimental issues have to be taken into account: Note 1. It is important to protect the reaction mixture from moisture to avoid acyl chloride hydrolysis. Use anhydrous dioxane; water content below 0.05 %. Note 2. Grind pyrazolone with pestle in a mortar before addition of 1,4-dioxane to accelerate the dissolution. Note 3. It is important to dissolve fully the starting pyrazolone before addition of calcium hydroxide; Note 4. Use calcium hydroxide in 2 equivalents to trap the liberated hydrogen chloride and keep the reaction media basic. Note 5. It is necessary to use high turbulence magnetic stir bar to afford the efficient complex formation because calcium hydroxide forms very heavy residue, which cannot be stirred with common bars. Note 6. It is crucial to form calcium complex before the addition of acylating agent! If the latter is added to free pyrazolone, the corresponding O-acylated compound is the only or main reaction product. Note 7. Follow the complex formation by TLC on basic alumina; the complex is not stable enough to

be monitored by TLC on silica gel. Note 8. The addition of acyl chloride to the mixture can generate heat. Be very careful and add the reagent drop-wise under cooling. Note 9. Observe the colour of the reaction mixture. It changes from yellow to orange; Note 10. Stir vigorously during the addition of the reaction mixture to hydrochloric acid in order to avoid lumps formation. The latter hindered the decomposition of the complex and can result in a decrease of the product yield. If the lumps are formed, they have to be grinded. Note 11. Keep the acidic mixture at room temperature at least 1.5 h before filtration to achieve complete complex decomposition. Note 12. Wash carefully the residue to dissolve fully $CaCl_2$ and eventually traces of $Ca(OH)_2$. Note 13. Wash further with small portions of ethanol to eliminate the dark brown coloured impurities.

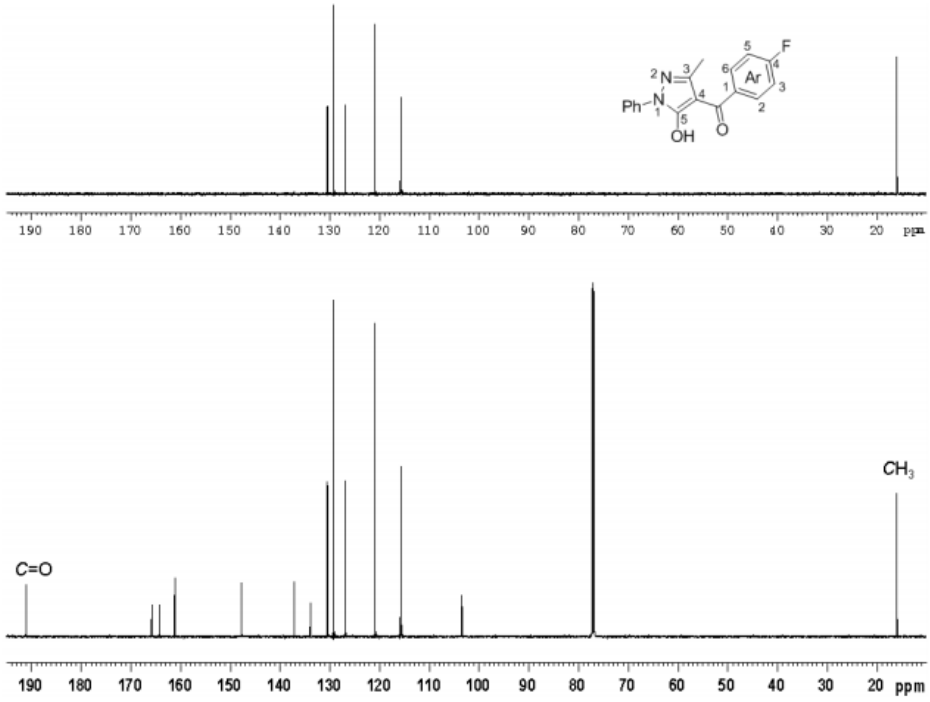
Several acyl derivatives are obtained, namely 4-(4-methylbenzoyl)-, 4-(4-fluorobenzoyl)-, 4-(4- phenylbenzoyl)-, and 4-(4-trifluoromethylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one. All experiments are performed at least 6 times by the teachers. The synthesis of 4-(4-methylbenzoyl)-3- methyl-1-phenyl-1H-pyrazol-5-one, the cheapest example, is reproduced 4 times by eight second-year undergraduate students working in couples. All reaction parameters are the same except the duration of the acylation step, which is dependent on the substituent in aroyl chloride, and solvents used for recrystallization.

As seen, the last reagent is not appropriate for students' laboratories due to its high price and the relatively long reaction time necessary to achieve full conversion. Nevertheless, the prolongation of the reaction does not influence the reaction yield and so, the acylation can be carried out overnight if necessary to obtain 4-(4-trifluoromethylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one. The pure products, shown on Figure SM 2.2.1.5, are analysed by TLC on silica gel and melting points. The mobile phase was varied and was found that 5 % methanol in dichloromethane (5 % MeOH/DCM) lead to best separation.

It is very important for second year undergraduate students to acquire basic knowledge in the interpretation of NMR spectra and in the application of the method for structure determination. At the end of these exercises they are able to analyze the spectra of the crude products, which is much more complicated than the analyses of pure compounds.



[1]H spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.



[13]C (down) and DEPT (up) spectra of 3-methyl-4-(4-fluorobenzoyl)-1-phenylpyrazol-5-one.

Synthesis of paracetamol by acetylation

Supplementary Material

The object of the present experiment is to synthesize an aromatic amide by addition-elimination reaction with acetic anhydride. This organic experiment is done in our laboratory for more than 20 years (approximately 200 students per year) without any difficulty or problem and has the advantage to introduce students to the medicinal chemistry field. As a matter of fact this is normally their first synthesis of a pharmaceutical active ingredient which always generates great motivation and expectation. In addition, it can also be adequate to introduce the topic of paracetamol (acetaminophen) toxicity, as an acute overdosage is relatively common and may cause severe liver damage, although it is an analgesic widely used to treat mild to moderate pain, and often found in familial pharmacies.

Synthesis and crystallization

As a pre-lab assignment, students should make a table showing the physical properties (molecular formula, molecular mass, purity grade of the reagents, m.p., b.p., solubility, and theoretical and used mass in grams and moles) of 4-aminophenol, acetic anhydride (etanoic anhydride) and paracetamol. This table must have a footnote with the corresponding bibliography sources.

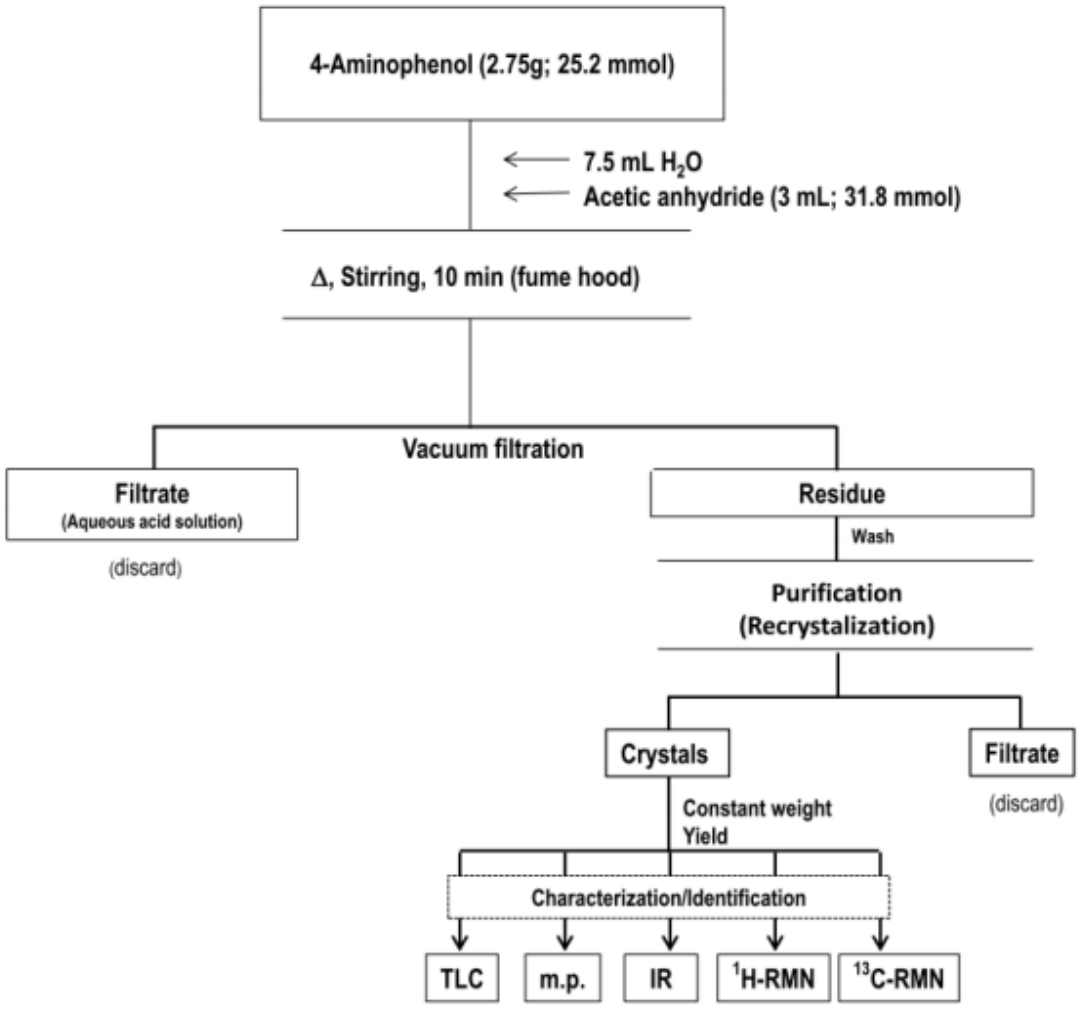
The reaction is done in an Erlenmeyer flask but, if possible, it can take place in a round-bottom flask with a reflux condenser. If not, and for security reasons, students must previously fix the Erlenmeyer with a clamp holder to a universal support or hold it with a wood clamp. In this last situation, the reaction can be done without magnetic stirring. To reduce class time, water baths should be provided already near boiling. It should be noted that extending the time of the reaction may lead to the formation of the diacetylated derivative of 4-aminophenol. Note that acetic anhydride should be added to the aqueous suspension of paracetamol. After completion of the synthesis, the crude solution often appears slight yellow or pinkish. A good filtration and washing with cold water is mandatory as it is the quantitative recovery of the product. During the hot dissolution of paracetamol for crystallization the solution can also be coloured and the use of activated charcoal does not greatly improve the situation. However, slow crystallization and a

careful wash of the crystals allow obtaining pearly crystals and ensure a good melting point. In addition, 4-aminophenol can also be crystallized before synthesis takes place.

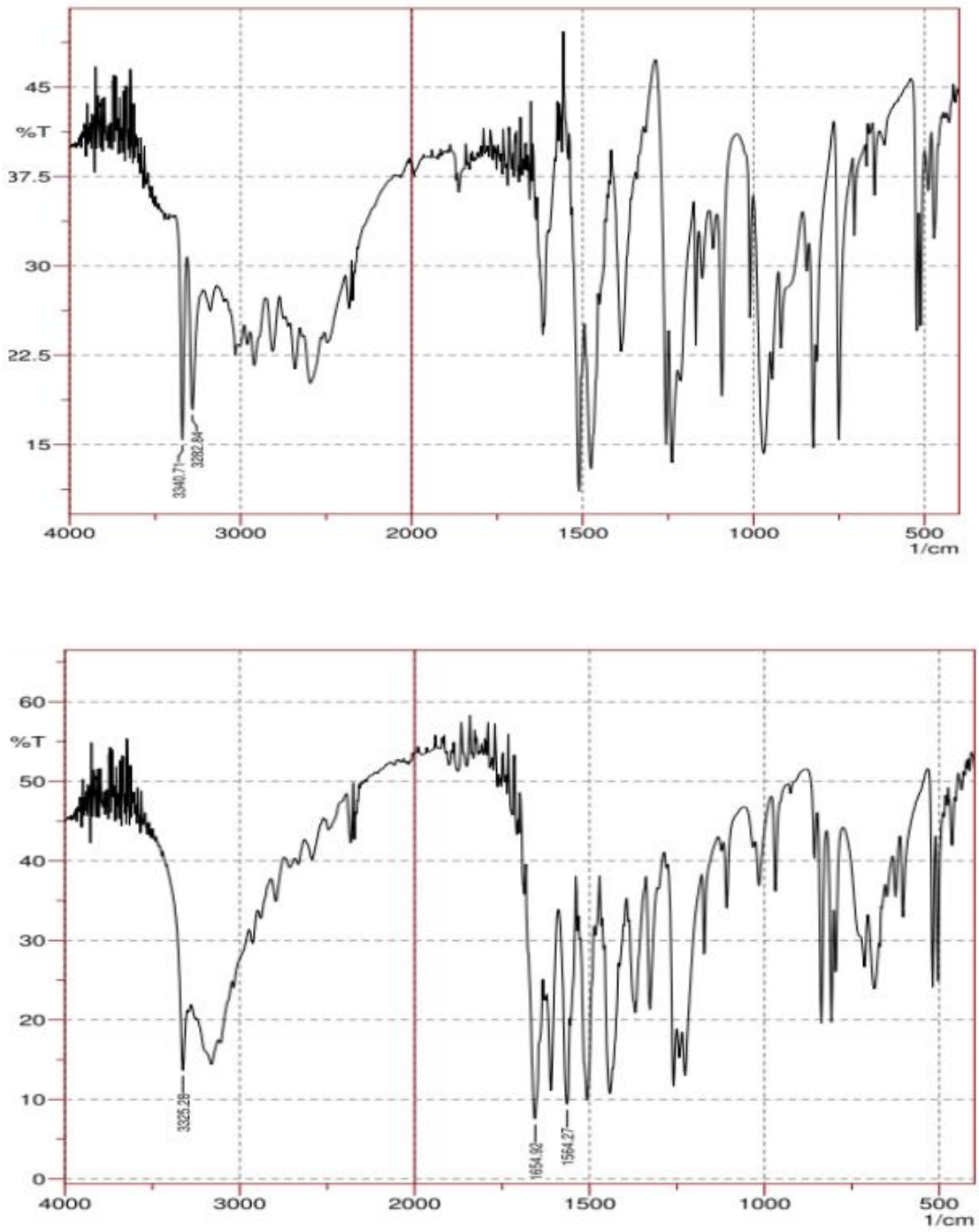
Crystallization of paracetamol occurs easily when the solution cools. Nevertheless, if crystallization doesn't occur or occurs with difficulty, it may be induced with a glass rod by gently rubbing the inside surface of the crystallization vessel. With this option, crystallization is almost immediate but very small crystals are formed. After cooling to room temperature, the crystallization vessel is placed in an ice bath for some minutes. As the washing of the crystals is carried out with water, they will be placed in an oven with appropriate temperature and/or stored in the desiccator until constant weight. As a rule, and for the objectives pursued, we consider constant weight a difference of less than 5 mg between two weightings with intermediate drying. The yields range from 35% to 70%. If necessary, class time can be reduced by performing crystallization (and crystals wash) with hexane (or petroleum ether). This will decrease the product drying time to constant weight. In this situation, attention should be drawn to the fact that it is more difficult to perform the crystallization by first year students as the volatile solvent will evaporate during the operation. But, if this is the option, students should be encouraged to think about what to do for the solvent elimination which must be collected in a conveniently labelled non-halogenated organic solvent container for posterior treatment and recovery.

If paracetamol m.p. is unsatisfactory (169-170.5 ºC),5 it may be speculated if the reaction was complete or if the diacetylated derivative was formed. To purify a product containing the diacetylated derivative, dissolve the crystals in 10% NaOH, v/v (cold dilute alkali will not hydrolyze the amide bond of acetyl but only the ester) and reprecipitate with 10% HCl (v/v).6 The IR spectra (KBr pellet) were collected on an IR Affinity-1 Shimadzu spectrophotometer. The IR spectrum of 4-aminophenol shows the two N-H amine bands at 3340 and 3282 cm-1, emerging from the broadband of the phenolic OH. On the other hand, the IR spectrum of paracetamol shows the N-H amide band near 3325 cm-1 although it is on top of the broad band of phenolic O-H that is at its right. Other important informative bands are the appearance of the amide carbonyl band at 1654 cm-1 and N-H band at 1564 cm-1. The 1 H-NMR spectrum of paracetamol shows signals with chemical shifts in agreement with the proposed structure and with the literature data. In the aromatic region, the four signals are indicative of a 1,4-substituted aromatic ring with two different substituents: two upfielded =9.14 ppm), and two downfielded

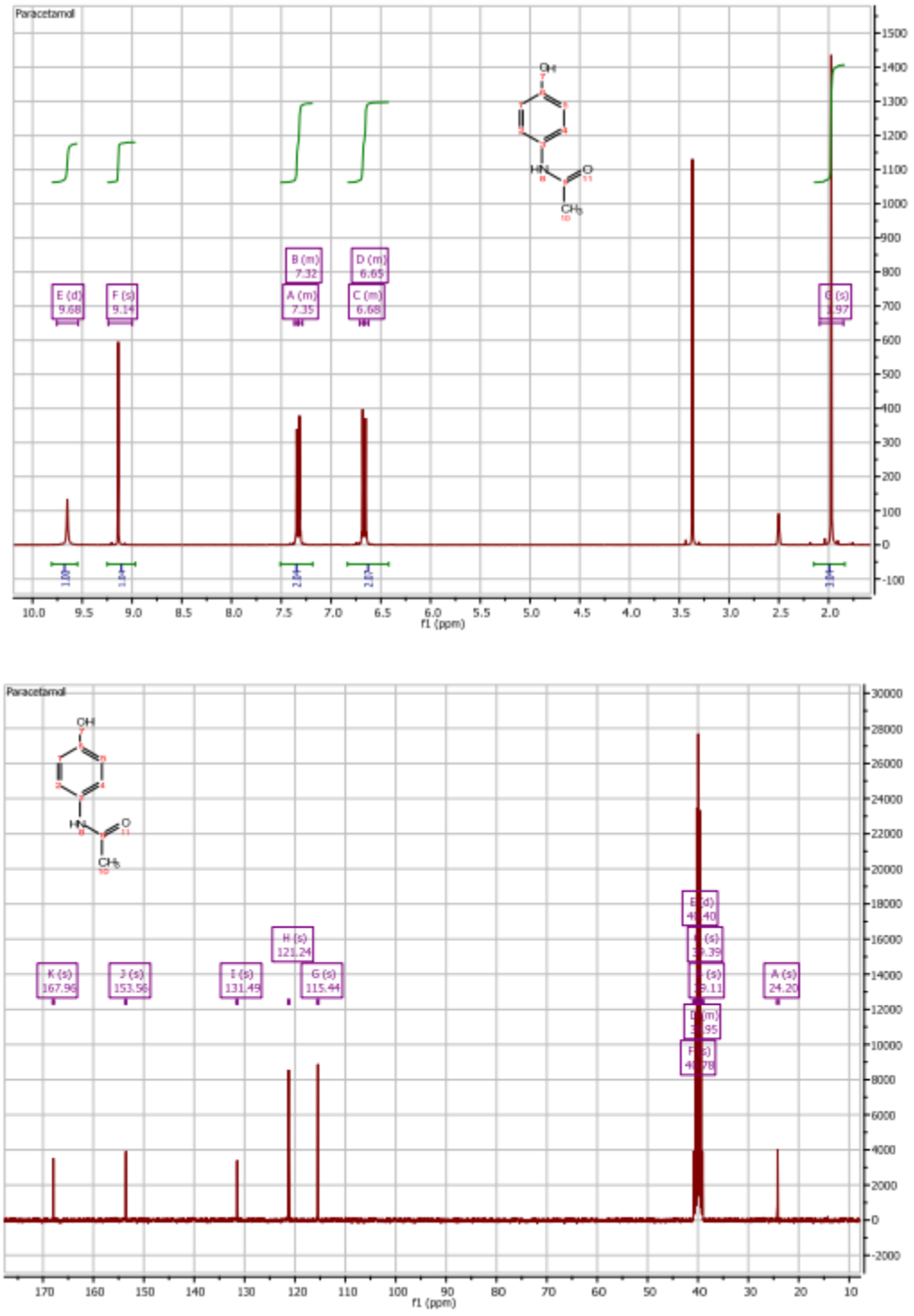
ortho-coupled doublets ofδ=9.68 ppm) and OH (δsinglets of the NH (=6.68 ppm. The observation of a large singlet, integrating forδ=7.35 and δthe aromatic protons at =3.4δ=1.97 ppm, corresponds to the methyl protons. DMSO (δthree protons at =2.5 ppm) can also be observed in the spectra provided.δppm) and water contamination (13C-NMR spectrum of paracetamol reveals four signals in the aromatic region: one C-OH at 153.56 ppm, one C-NH at 131.49 ppm and two pairs of equivalent C-H (121.24 and 115.44 ppm). A deshielded carbonyl carbon at 167.96 ppm, and the methyl carbon at 24.20 ppm are also observed.



Flowchart for the synthesis, purification and characterization of paracetamol.



Infrared spectra of a) 4-aminophenol and b) paracetamol (KBr pellet).



a) [1] H-NMR spectrum (300 MHz) and b) [13]C-NMR spectrum (75 MHz) of paracetamol dissolved in DMSO d6 (≈40.00 ppm).

Synthesis of 7-methoxy-4-oxo-N-phenyl-4H-chromene-2- carboxamide

Supplementary Material

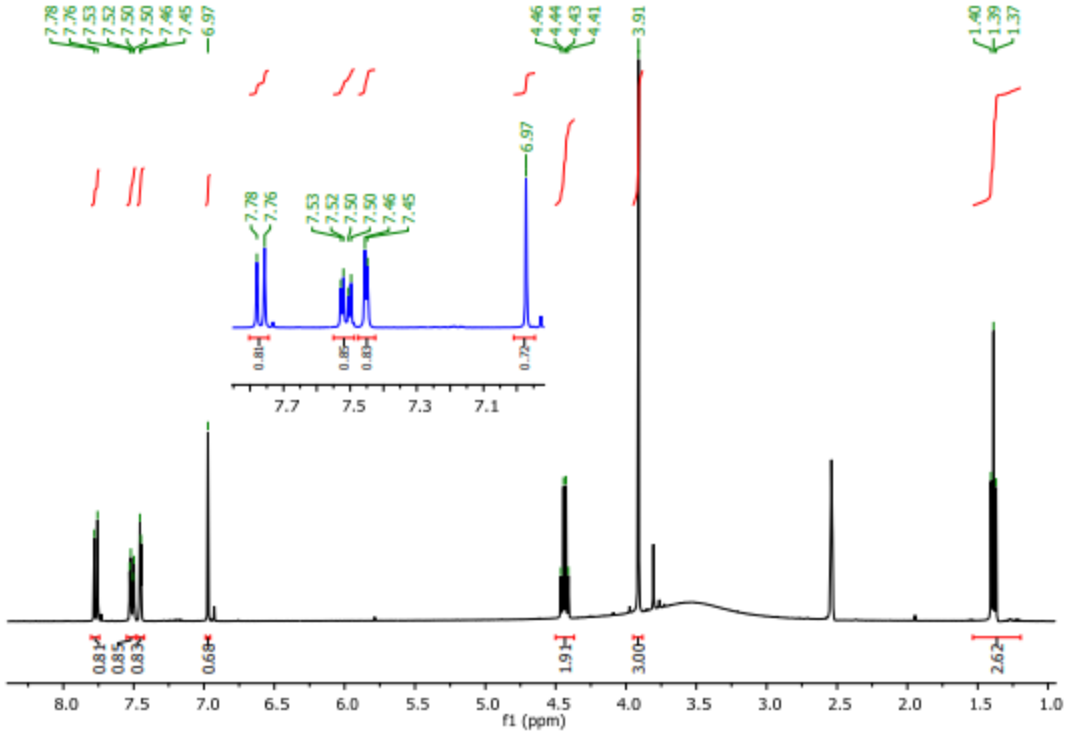
The chromone scaffold has been elected as a privileged structure for drug discovery programs due to its noteworthy pharmacological activities. The chemical decoration of the heterocyclic framework allows the obtention of a diversity of chemical libraries namely those enclosing chromone carboxamide derivatives. Herein we report a three-step synthetic procedure to obtain one chromone carboxamide derivative of the library. In general, the experiment was easy to perform and the purification processes easy to undertake.

Considering that the proposed experiment correspond to a three step procedure, it is advised to start the first stage with an appropriate amount of the starting material acetophenone (2 g). The yields of step 1 (formation of the chromone ester) and step 2 (formation of the chromone carboxylic acid) are 70-80% and 80-90%, respectively. In the amidation reaction a moderate yield (around 60-75%) is always obtained. The purification by flash column chromatography allows removing the by-products formed along the reaction. All the NMR spectra should be performed in DMSO-d6, except for the chromone ester (2) as the product is not soluble enough.

Structural analysis- key notes

Step 1: Synthesis of ethyl 7-methoxy-4-oxo-4H-chromene-2-carboxylate

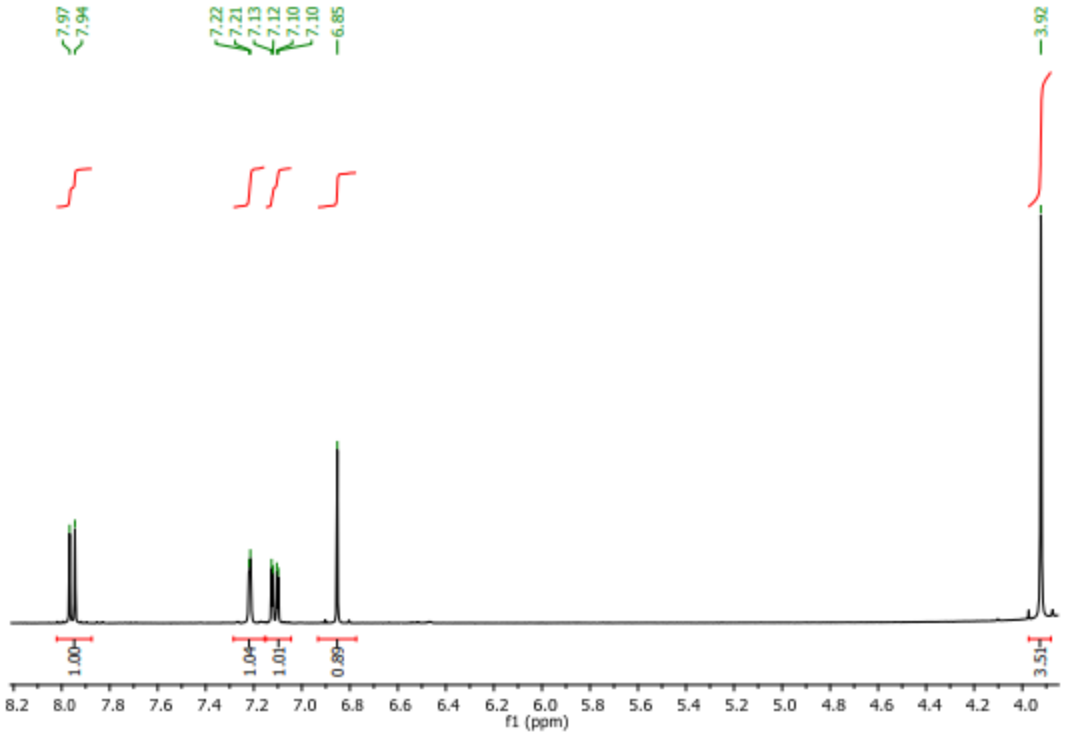
^{1}H NMR allow to identify the compound, namely by noticing the multiplicity vs integration data of CH2 (quartet-2H) and of CH3 protons (triplet-3H) of the ester function that are identified around δ4.46 and δ1.43 ppm, respectively. Furthermore, the aromatic protons of the benzopyrone ring (δ = 8.09 – 6.99 ppm), the hydrogen of the pyrone ring (singlet-1H) and the methoxyl function (singlet-3H) are well recognized in the spectra.



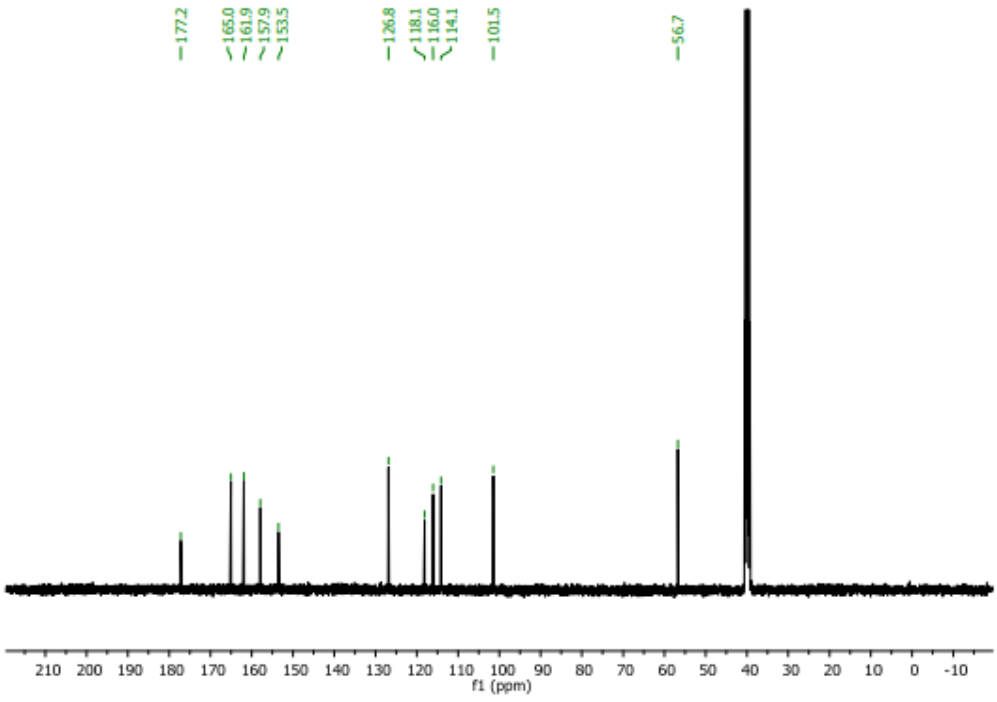
^{1}H NMR of ethyl 7-methoxy-4-oxo-4H-chromene-2-carboxylate (400 MHz, $CDCl_3$)

Step 2: Synthesis of 7-methoxy-4-oxo-4H-chromene-2-carboxylic acid

The hydrolysis reaction yield is almost quantitative (100%), as expected for a complete reaction. Since the 1 H NMR signal for the proton of the carboxylic group is usually not observed due to proton exchange with the solvent, the presence of the function is confirmed in 13C NMR spectra. The signal of the carbonyl moiety appears at a predictable chemical shift (COOH at δ = 161.89 ppm). Moreover, it is detected in the both spectra the disappearance of the signals corresponding to the ethyl moiety of the ester function.



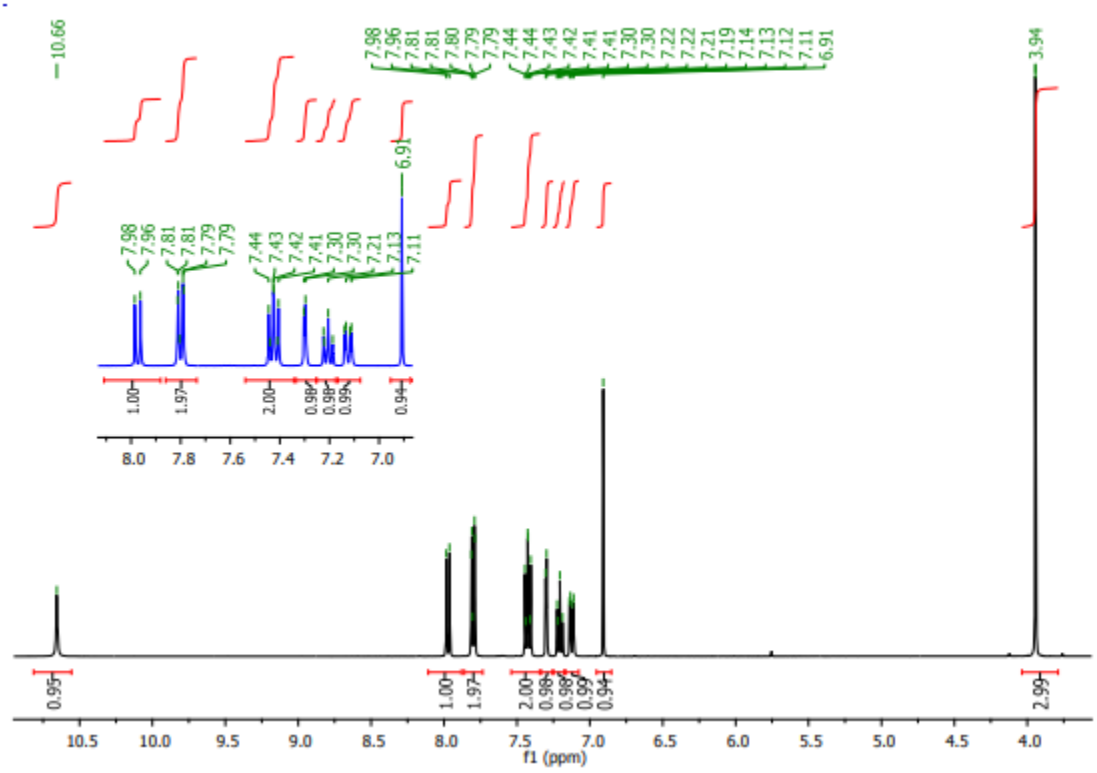
[1]H NMR of 7-methoxy-4-oxo-4H-chromene-2-carboxylic acid (400 MHz, DMSO-d6)



[13]C NMR of 7-methoxy-4-oxo-N-phenyl-4H-chromene-2- carboxamide (101 MHz, DMSO-d6)

Step 3: Synthesis of 7-methoxy-4-oxo-N-phenyl-4H-chromene-2-carboxamide

The chromone carboxylic acid was activated with the coupling agent PyBOP and then the ester intermediate (for more details see reference 13 of the protocol) will react with the amine (aniline). The purification by flash column chromatography (eluent: dichloromethane/methanol 90:10 (v/v))) will remove the by-products. A recrystallization process with dichloromethane/n-hexane is strongly advised. In 1 H NMR the signal corresponding to the proton of the amide group (CONH) appears at δ = 10.66 ppm.



^{1}H NMR of 7-methoxy-4-oxo-N-phenyl-4H-chromene-2- carboxamide (400 MHz, DMSO)

References

1. A. Gaspar, M. J.Matos, J. Garrido, E.Uriarte, F. Borges, Chem. Rev., 2014, 114 (9), 4960- 4992.

2. A. Gaspar, T. Silva, M. Yanez, D. Vina, F. Orallo, F. Ortuso, E. Uriarte, S. Alcaro, F. Borges, J. Med. Chem., 2011, 54, 5165-5173.

3. A. Gaspar, J. Reis, S. Kachler, S. Paoletta, E. Uriarte, K.N. Klotz, S. Moro, F. Borges, Biochem. Pharmacol., 2012, 84, 21-29.

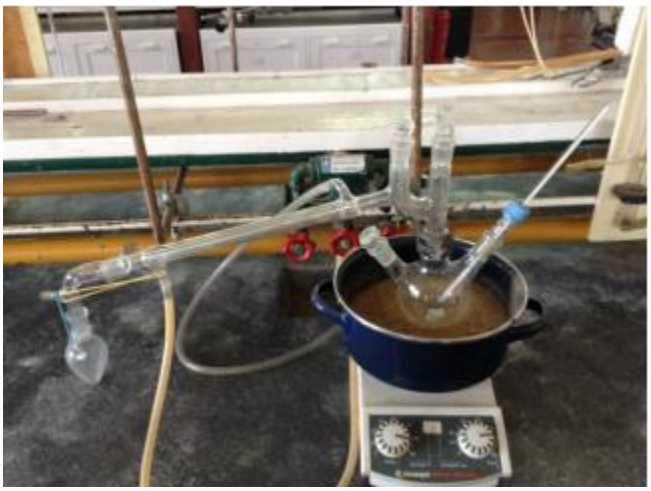
4. W. R. Dolphin, Writing Lab Reports and Scientific Papers; McGraw-Hill: New York, 1997. http://www.mhhe.com/biosci/ genbio/maderinquiry/writing.html

5. J. Reis, A. Gaspar, F. Borges, L. Rebelo Gomes, J. Nicolson Low, J. Mol. Struct., 2014, 1056, 31-37.

Synthesis of 2,3-diphenylindenone

Supplementary Material

This experiment was performed by several groups of graduate students in the Advanced Organic Chemistry Lab. The experimental procedures are essentially those of R. Weiss and T.J. Clark with some modifications. In the first synthesis the phthalic anhydride used should be pure and free from phthalic acid. If necessary, it can be purified by sublimation. Sodium acetate should be molten by heating in a porcelain cap. Note that at the beginning of the heating the hydrated salt dissolves in the crystallization water, becomes solid again and then melts. Benzalphtalide is obtained with an average yield of 72 % (mp=100-101º C).



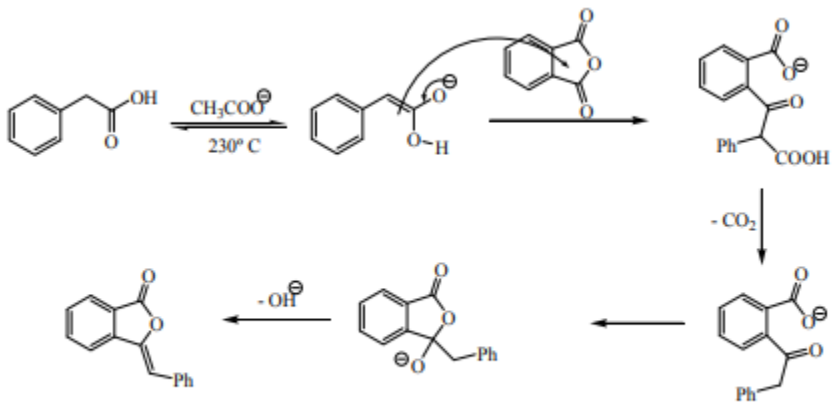
Reaction apparatus for the preparation of Benzalphthalide

The second synthesis is too long to be performed in a 4 hour lab class. It should be interrupted after the addition of the 6M H2SO4 solution, but not before, because the decomposition of the excess of Grignard reagent leads to undesirable by products like phenol and benzoic acid.

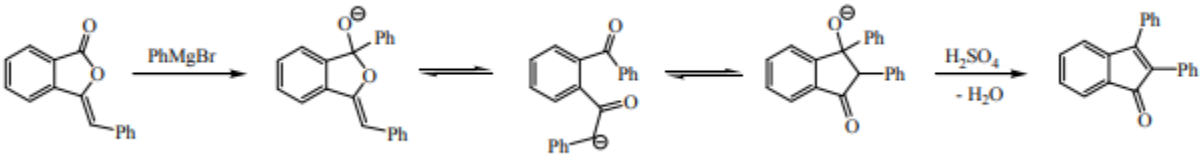
Reaction apparatus for the preparation of 2,3-diphenylindenone

2,3-Diphenylindenone is obtained with an average yield of 90 % (mp=150.5-152ºC).2 Beautiful red prismatic crystals are obtained from the slow evaporation of the recrystallization solution.

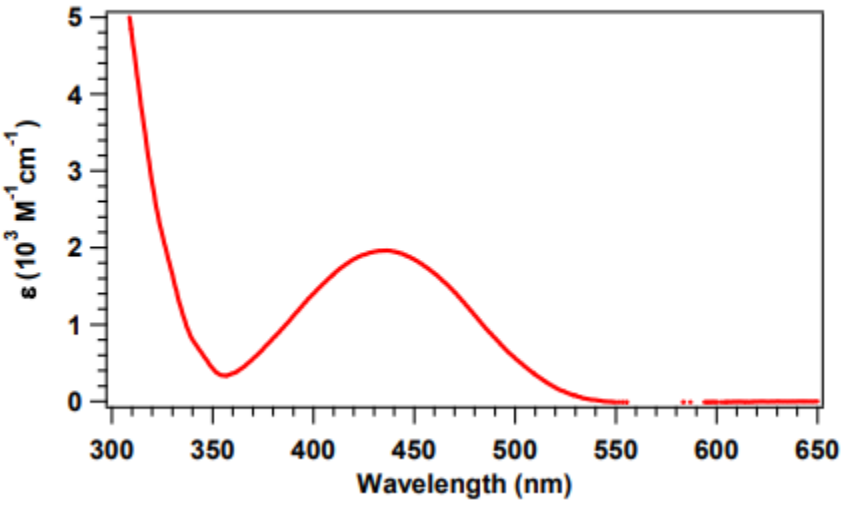
Prismatic crystals of 2,3-diphenylindenone



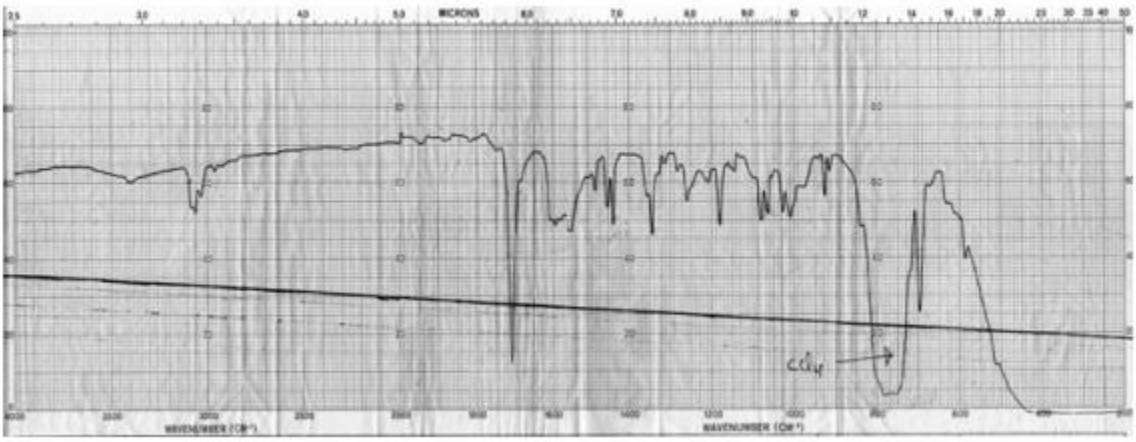
Proposed mechanism for the formation of Benzalphthalide



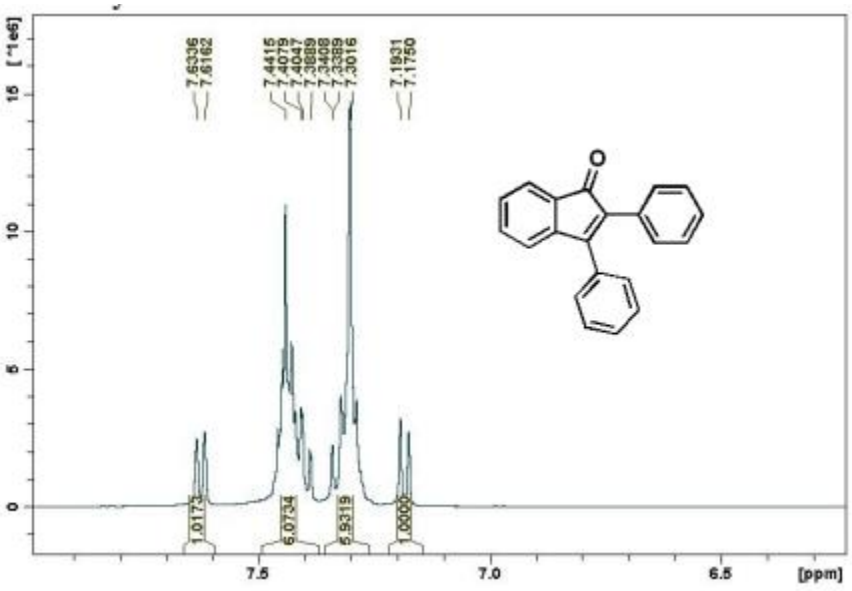
Proposed mechanism for the formation of 2,3-diphenylindenone



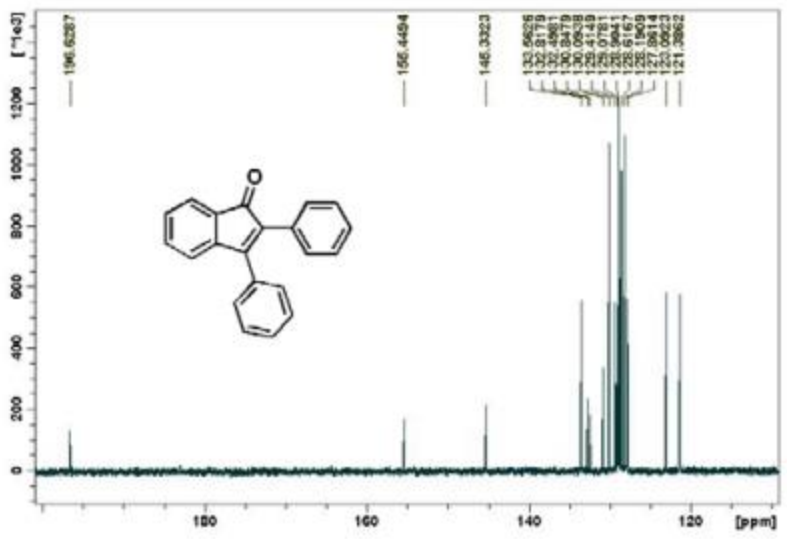
UV-Vis spectrum of 2,3-dihenylindenone in toluene.



IR spectrum of 2,3-dihenylindenone in CCl_4



^{1}H NMR (400 MHz) spectrum of 2,3-diphenylindenone in $CDCl_3$



^{13}C RMN (400 MHz) spectrum ($CDCl_3$) of 2,3-diphenylindenone.

Synthesis of Dimedone

Supplementary Material

The synthesis of dimedone was introduced first in 2003 to 2nd year undergraduate students of intermediate organic chemistry as a short project involving bibliographic research and experimental work (three groups of two students). They have the opportunity to study several carbonyl group transformations as Michael Addition and Claisen Condensation widely used in organic synthesis as well tautomerism where an enol is formed by proton transfer. Once dimedone forms crystalline derivatives with aldehydes, it is used to aldehydes identification, so if desired, students can perform this reaction in classroom.

Additional notes on the preparation of dimedone:

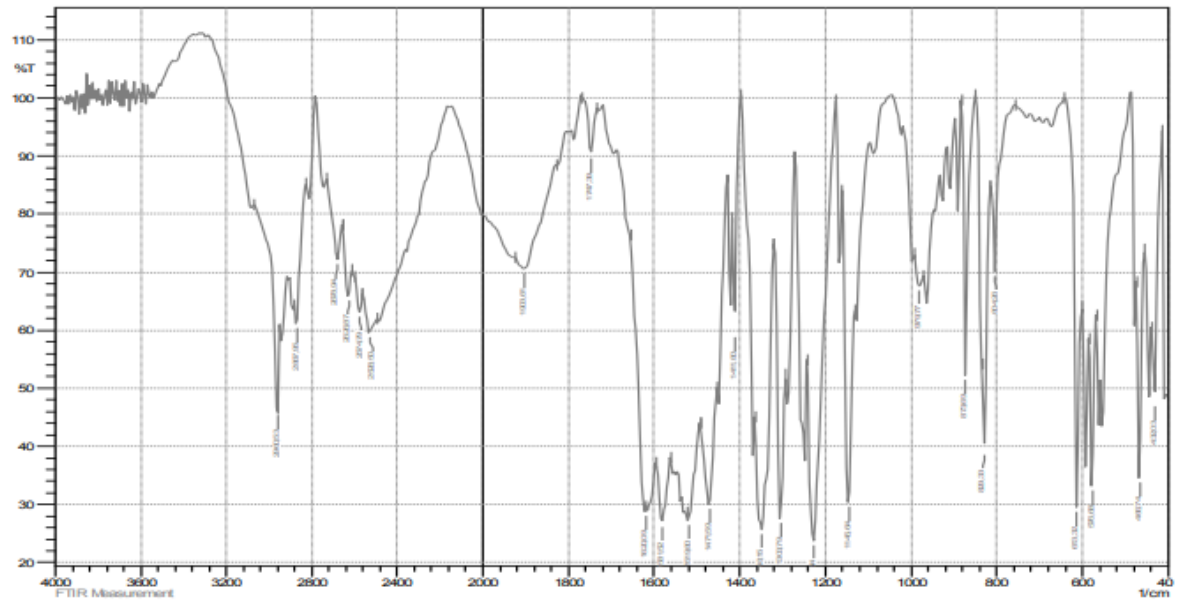
This synthesis is usually made in two sessions of c.a. 3 hours each. The first one includes the dissolution of sodium metal in absolute ethanol (which takes some time to complete), two 45-minute periods with refluxing, and dropwise addition of several reactants. Distillation is usually left for the second session.

Reaction set-up apparatus for dimedone

Rotary evaporator for distillation of ethanol-water mixture

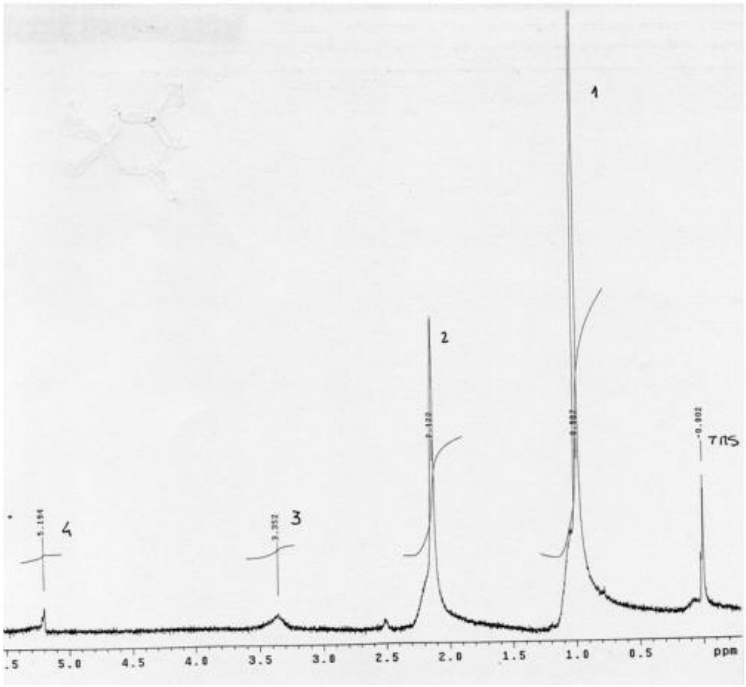
On the liquid-liquid extraction step, students must be warned to preserve the aqueous layer instead of the organic one. The final vacuum filtration should be performed only when the product is completely crystallized, which may take anything from 1 to 24 hours. If possible, it is advisable to leave the mixture to precipitate overnight. The yield of dimedone is 20-25%, much lower than the 70% reported in literature . The low yield low could be related to ineffective liquid-liquid extraction and recrystallization. According to this reference, the yield also depends on the purity of mesityl oxide, which should be distilled prior to its use. In this experiment, mesityl oxide purchased from Aldrich was used without further purification. Experimental melting point is 148-150ºC (148-149ºC1 and 148- 150ºC).

The students can realize that enolic form does not show the usual absorption of conjugated ketones. A broad band can be observed at 2800-2400 cm-1 and near 1600 cm-1 due to enol form.



IR (KBr) of dimedone

They can easily identify the broad signal at 3.35 ppm OH proton and the signal at 5.19 ppm relative to the proton of sp2 carbon atom.



1 H NMR ($CDCl_3$) of dimedone

References

1. A. I. Vogel, Vogel's Textbook of Practical Organic Chemistry, Longman Scientific and Technical, 5th ed. 1989, 1259.

2. R. L. Shriner, H. R. Todd, Org.Synth. Coll., 1943, 2, 200.

3. The Merck Index., 11th ed., 1989, 511.

4. http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi accessed in Oct 2015.

5. Clayden, Greeves, Warren and Wothers, Organic Chemistry, Oxford, 2001, 524.

6. The Aldrich library of NMR spectra, 2nd ed., 1, 1983, 391.

Bromination of Cinnamic acid

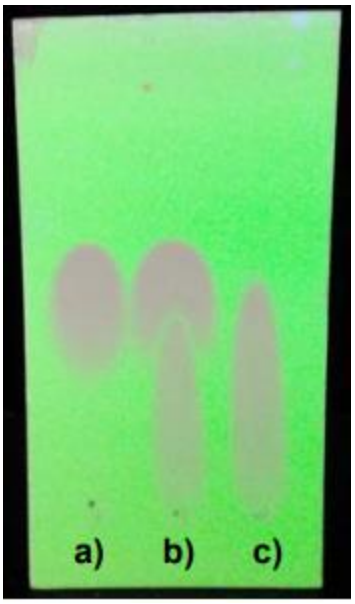
Supplementary Material

Experimental notes

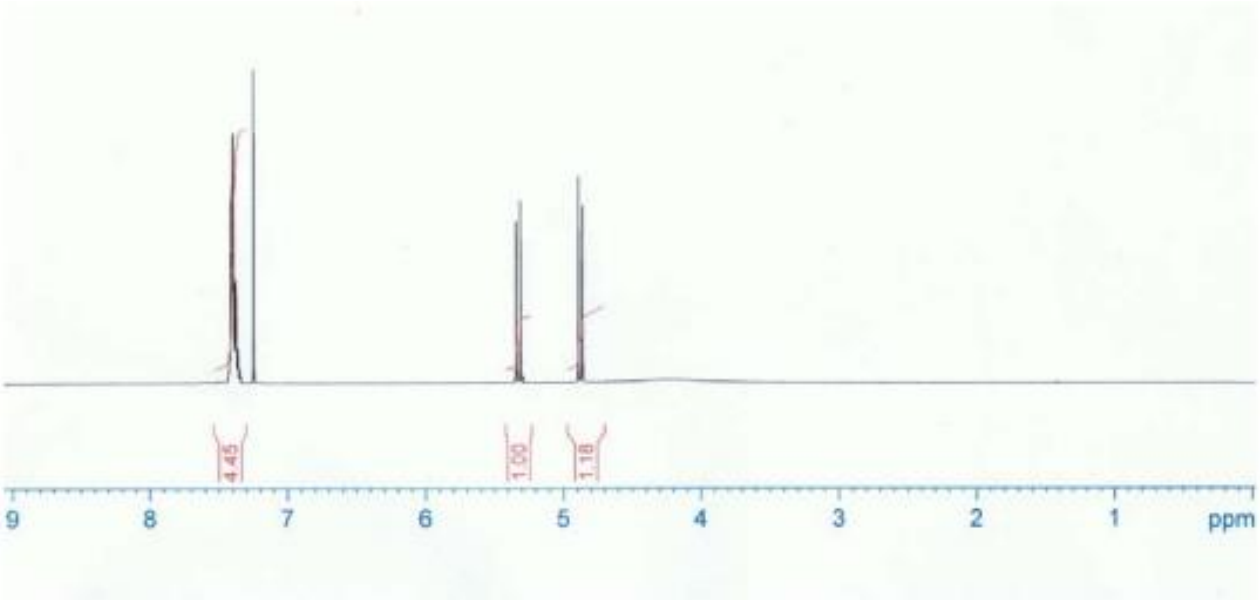
This experiment aims at the preparation of the 2,3-dibromo-3-phenylpropanoic acid from cinnamic acid by bromine addition. The cinnamic acid is soluble in dichloromethane at room temperature and thus before the bromine addition the reaction vessel holds a colourless solution. The bromine solution is intensively red coloured and since the addition reaction is relatively fast at this temperature, the reaction evolution can be followed by the progressively disappearance of the red colour. The addition can be done in 30 min. As the reaction proceeds, the product starts to precipitate and by the end of the bromine addition there is a significant amount of the product although usually the reaction mixture is still slightly coloured. 0.1-0.2 mL of cyclohexene are sufficient to remove all bromine traces and since the product of this reaction, 1,2-dibromocyclohexane, is soluble in CH_2Cl_2 it doesn't disturb the isolation of the desired product. Pay attention that cyclohexene stinks with a smell that resemble the additives present in the butane bottles which alert us to a gas leak. The product isolation by filtration is simple and, as the dicloromethane is quite volatile, the product can be quickly air dried and the melting point determined in the same experimental session. As the cinnamic acid is soluble in cold CH_2Cl_2 the washing of the final product is essential to assure a good purity. TLC and ^{1}H NMR analysis confirm the purity of final product, without any cinnamic acid contamination, and thus it is not necessary to make any recrystallization. The measurement of the melting point allows determining the addition mode of the bromine to the double bond. The values obtained confirm the erythro configuration of the product resulting from an anti addition. This experiment is very reproducible and was performed with students of the first year of the Chemistry degree. One session of 2 h is enough to perform the entire experiment which can also be conducted in a lower scale. The yields vary between 80-93% and the melting point of product is 206-208 ºC (lit 202-204 ºC, Mayo, D., W., Pike, R., M., Forbes, D., C. Micro scale organic laboratory: with multistep and multiscale synthesis, 5nd edition, Wiley Custom Services, chapter 7, pp 486).

The cinnamic acid solubilization in CH_2Cl_2 **Reaction apparatus before the Br_2 addition**

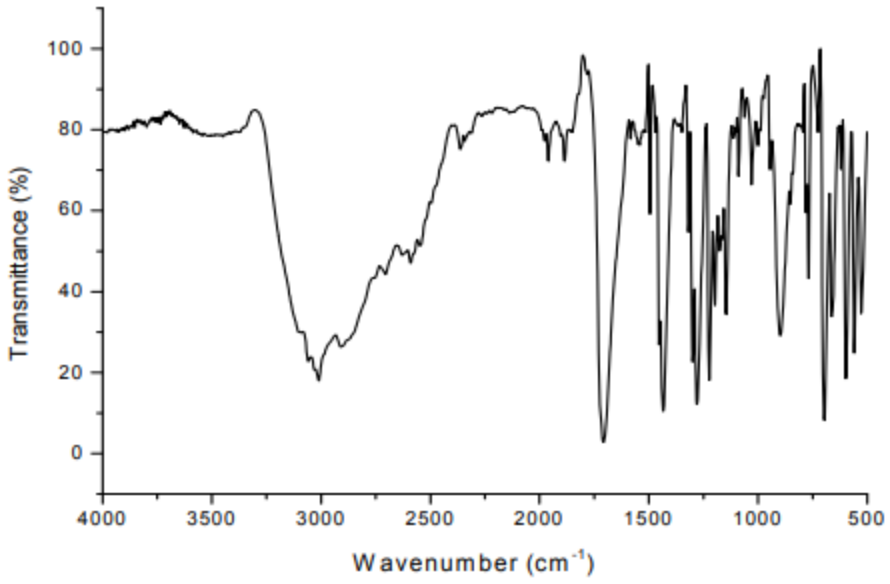
Reaction apparatus after the Br_2 addition.



TLC plate. 60% diethyl ether/petroleum ether. a) cinnamic acid b) cinnamic acid and product c) Product



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the reaction product



IR spectra of 2,3-dibromo-3-phenylpropanoic acid

Synthesis of methyl triphenylmethyl ether

Supplementary Material

The synthesis of triphenylmethanol (first step) has been performed since the 1980s to illustrate a Grignard reaction. Since 2001 the second step of this synthesis was introduced as a classroom experiment. The experimental procedure for the preparation of the ether is simple and a good example of a SN1 reaction, thus appropriate for first-year undergraduate students since the mechanisms of the reactions involved are taught during the first semester of Organic Chemistry. An important feature of this synthesis is the extraordinary stabilization of the carbocation, which can be observed by students during the experiment. Also, the product cannot undergo E1 elimination due to the absence of β-protons and no side products are formed. On the other hand, the synthesis of the alcohol involves a Grignard reaction performed under anhydrous conditions and is suitable for second-year undergraduate students.

Additional notes on the preparation of triphenylmethanol:

Great care is required to ensure water-free conditions once Grignard reagent reacts as a strong base with water or alcohols. All glassware must be dried thoroughly in the oven and removed only to assemble the reaction apparatus. The mechanical stirrer can be replaced by a vigorous magnetic one.

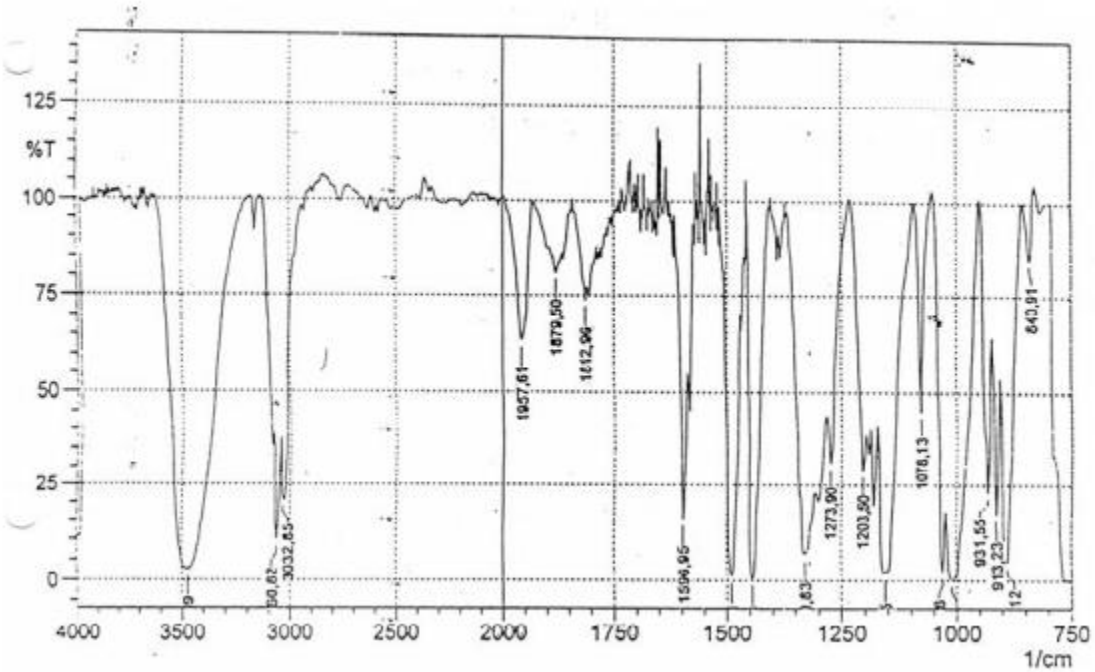
Reaction set apparatus for triphenylmethanol

All adjustments needed to guarantee an effective stirring must be performed upon complete assembly, without any reactant or solvent inside the flask. Only then students can measure the chemicals and introduce them immediately into the reaction flask. The reaction initiates once bromobenzene is added, but sometimes some gentle warming is required. In general there is no need to add a crystal of iodine. If ethyl benzoate is used instead of benzophenone, two molar equivalents of Grignard reagent are required to produce the alcohol. The reaction mixture using the ester has a different color and consistence. There are two side products formed in this reaction: Biphenyl (Ph-Ph) and benzene that can be separated using a steam distillation apparatus (Photo of steam distillation apparatus taken for another experiment; the residue contained in the flask does not correspond to reaction mixture).

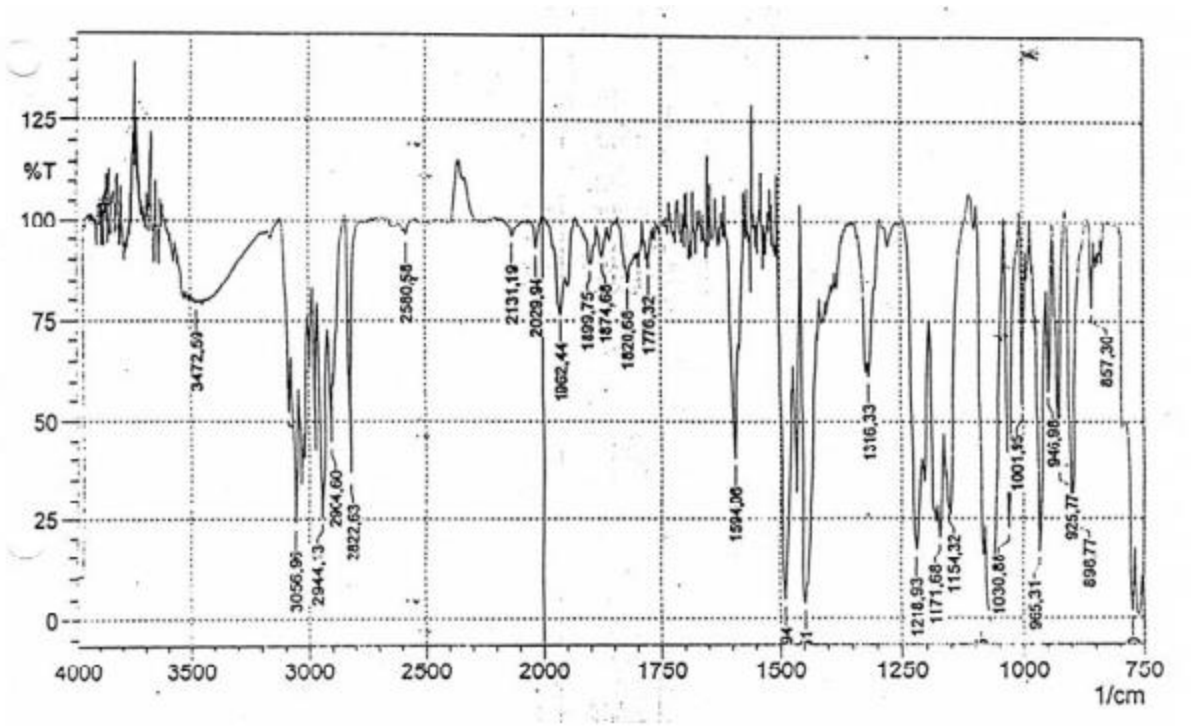
Steam distillation apparatus

The average yield is 30-35% and it is highly affected by any residual humidity present in the apparatus and the chemicals used. The TLC plate should contain samples of both crude and recrystallized product, benzophenone and the mother liquor from recrystallization. The products and benzophenone should be dissolved in dichloromethane. Since the compounds are colorless, a UV light is required to reveal the spots on the plate. The impurity corresponding to benzophenone can be easily identified by comparing the Rf. TLC eluted with dichloromethane/petroleum ether (40-60) (1:1) where R= recrystallized triphenylmethanol, NR=crude triphenylmethanol (not recrystallized), AM=mother liquor from recrystallization and BF=benzophenone. Melting points are between 135 and 145ºC for the crude product and between 156 and 163ºC for the recrystallized product (164.2ºC).

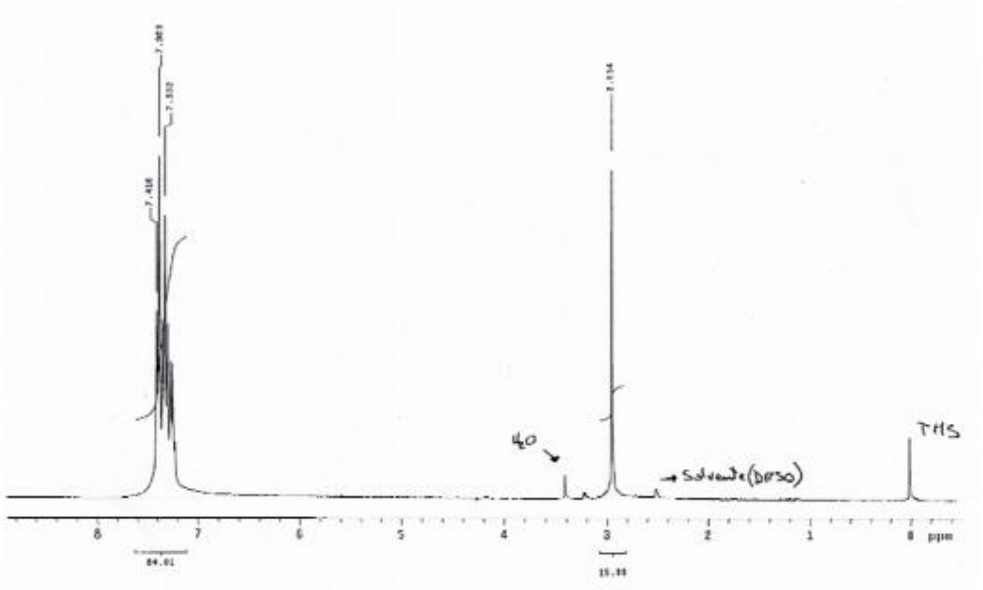
Students easily identify in a broad absorption near 3472 cm-1 in the IR spectrum due to the OH group. The same absorption can be detected for methyl triphenylmethyl ether due to insufficient drying of the product.



IR (KBr) of triphenylmethanol



IR (KBr) of methyl triphenylmethyl ether



^{1}H NMR (DMSO-d6) of methyl triphenylmethyl ether

References

1. Handbook of Chemistry and Physics, CRC Press,1st Student Ed., C-534.

2. http://www.sigmaaldrich.com/catalog/product/aldrich/69493?lang=pt&region=PT, accessed in May 2015.

3. http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_search.cgi, accessed in May 2015.

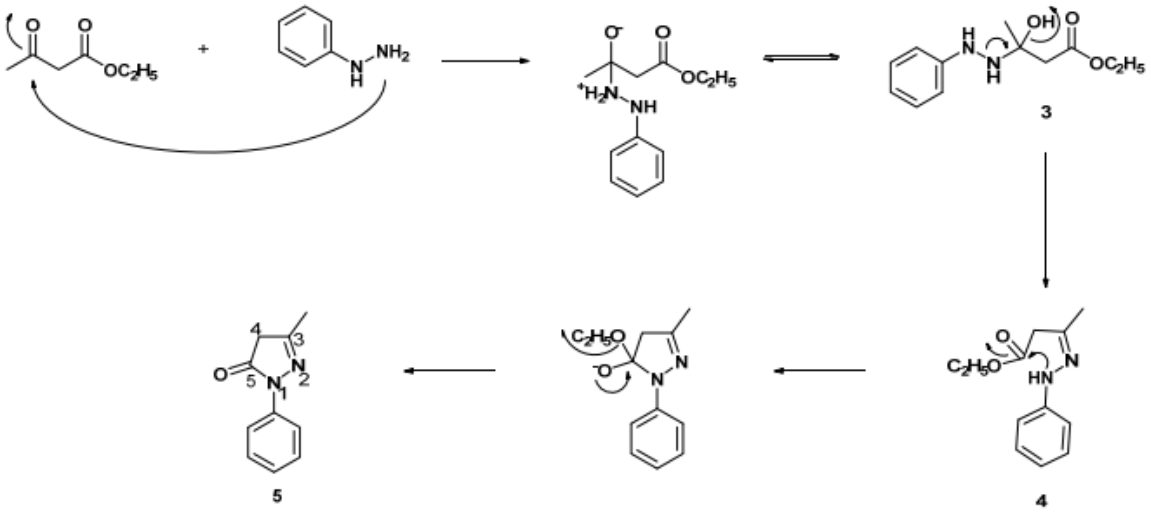
4. L. F. Fieser, K. L. Williamson, Organic Experiments, Houghton Mifflin Company, 8th Ed., 1998, 324.

Knorr Pyrazole Synthesis of Edaravone

Supplementary Material

Experiment notes

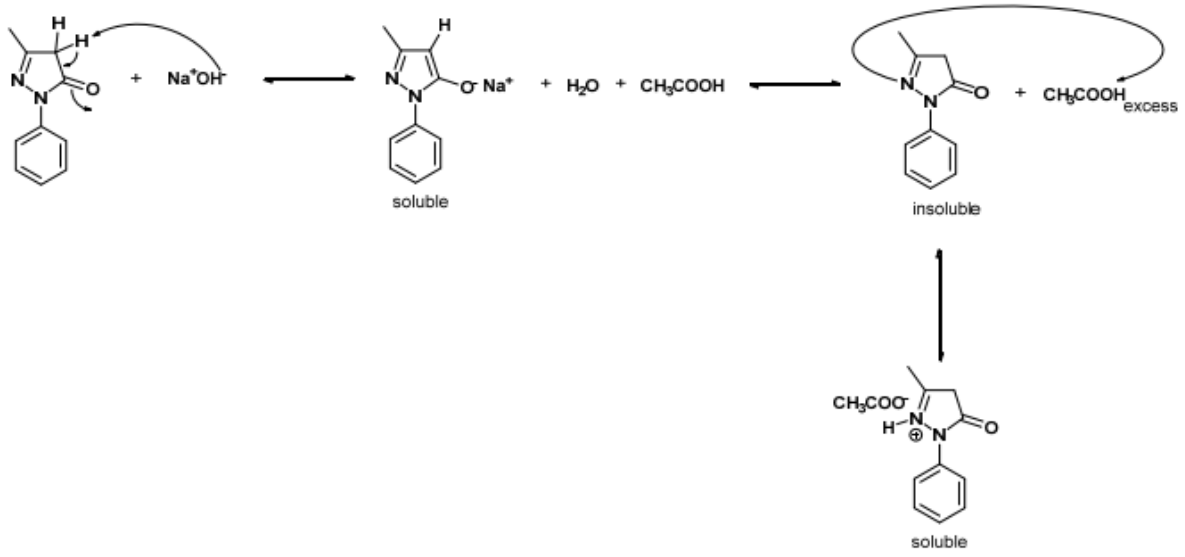
The objective of this experimental work is to introduce the students to the synthesis of heterocycles using the Knorr pyrazole reaction. The experimental work is easy to perform and at the same time is an excellent example for teaching students about the concepts of regioselectivity and tautomerism. Solubility of edaravone in acidic and basic solutions could be discussed with reference to its tautomeric forms. Mechanism of the reaction Mechanistically, reaction proceeds through the carbinolamine 3, and hydrazone 4, which cyclizes intramolecularly, to give edaravone 5. The regioselectivity of the reaction is governed by the higher reactivity towards nucleophiles of the ketone moiety over ester, and the more nucleophilic and least hindered nitrogen atom of hydrazine.



Mechanism for the formation of edaravone

Acidity of edaravone The methylene hydrogen atoms of edaravone are slightly acidic due to the resonance of the corresponding conjugate base, which exists in the enolate form. Basicity of edaravone The imine like N-2 nitrogen atom is basic and can be protonated in acid aqueous solutions. In contrast, the amide like N-1 nitrogen atom is non-basic.

Solubility tests Solubility tests confirm the amphoteric character of edaravone and the chemical reactions illustrate the acidic and basic properties of the compound.



Acidic and basic reactions of edaravone

Addition of both reagents into the round bottom flask is slightly exothermic and the students will see the formation of some drops of water (derived from imine formation) in the walls of the reaction flask.

Reaction mixture. The mixing of both reagents is slightly exothermic

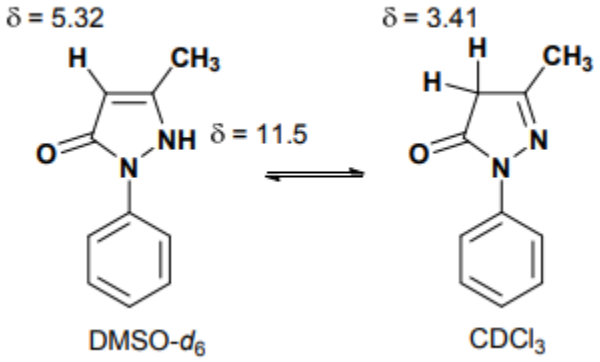
The heating must be done carefully; the round bottom flask must stay away from the bottom and the walls of the mantle, to avoid overheating. Otherwise it is possible to see projections of the reaction mixture into the walls of the flask during the heating process. The principal concern in the experiment is related with precipitation of the product with diethyl ether. The addition of the ether must be done after cooling the syrup, with caution and the mixture must be stirred vigorously, while maintained in the ice bath. Addition of a small volume of the solvent (2 mL) and in small portions is also important for good practice. If the total volume (8 mL) of diethyl ether is added at once it will be very difficult to induce the precipitation of the product, as it will separate as oil.

Mixing the first portion of diethyl ether

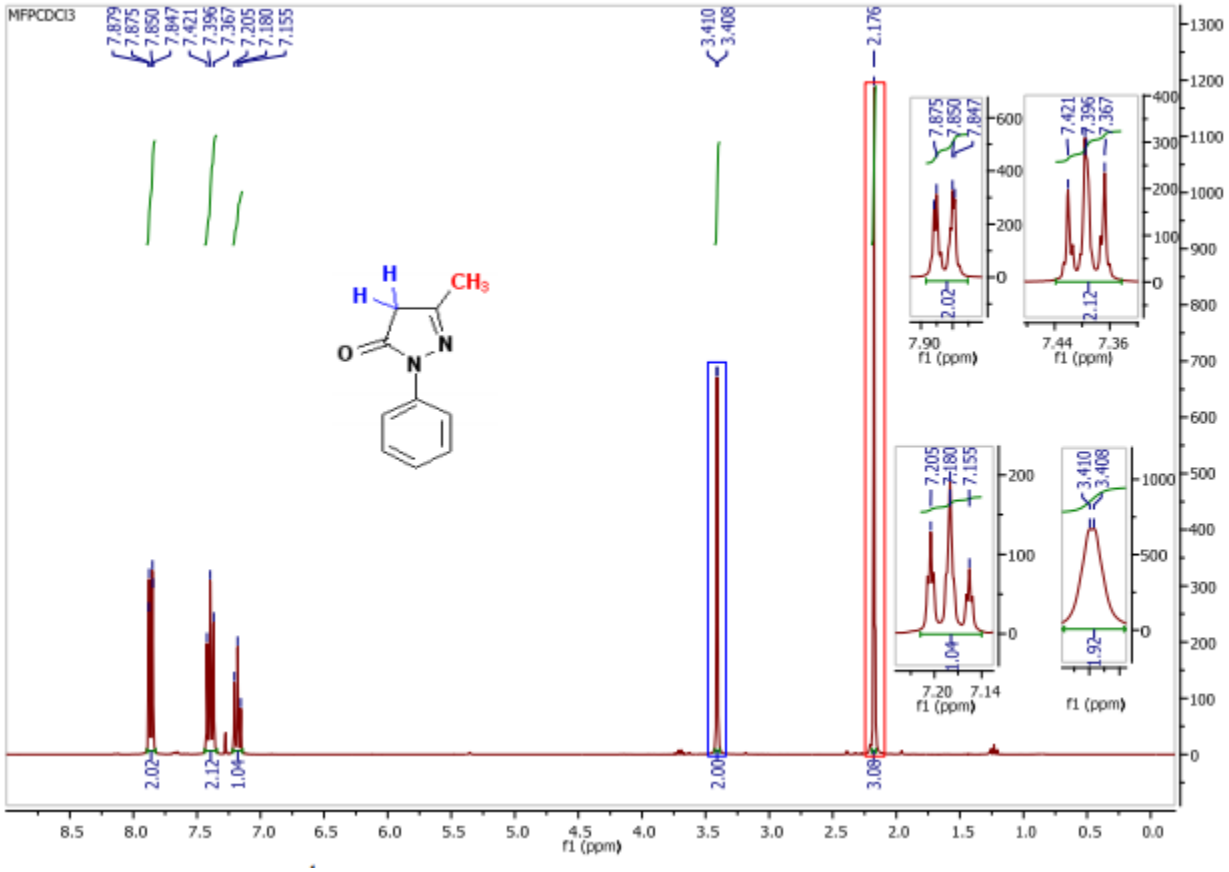
Recrystallized edaravone

Care should be taken during recrystallization. Addition of an excess of the solvent results in low yields as the product solubilizes quite well in ethanol 95%.Solubility tests should be first exemplified by the instructor, in order to show students how to estimate the correct amount of compound necessary to perform the tests and to determine the amount of basic and acidic solutions for neutralization and precipitation of the product.

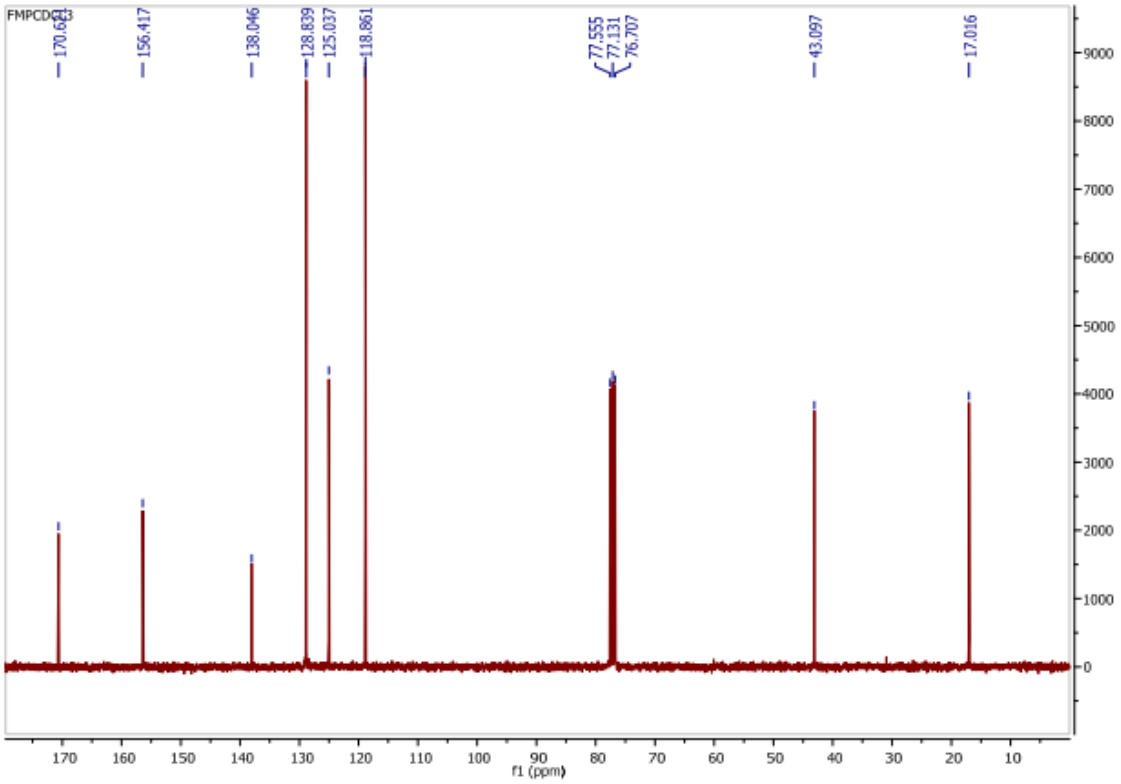
Edaravone was analysed by ^{1}H NMR in $CDCl_3$ and DMSO-d6. Spectra were acquired on a 300 MHz Bruker spectrometer and reported in parts per million (δ) referenced against a residual solvent peak. In general the students obtained pure products, but in some spectra is possible to identify residual peaks from reagents. Performing the analysis in $CDCl_3$ and DMSO permits the identification of the signals corresponding to the enol form of edaravone.



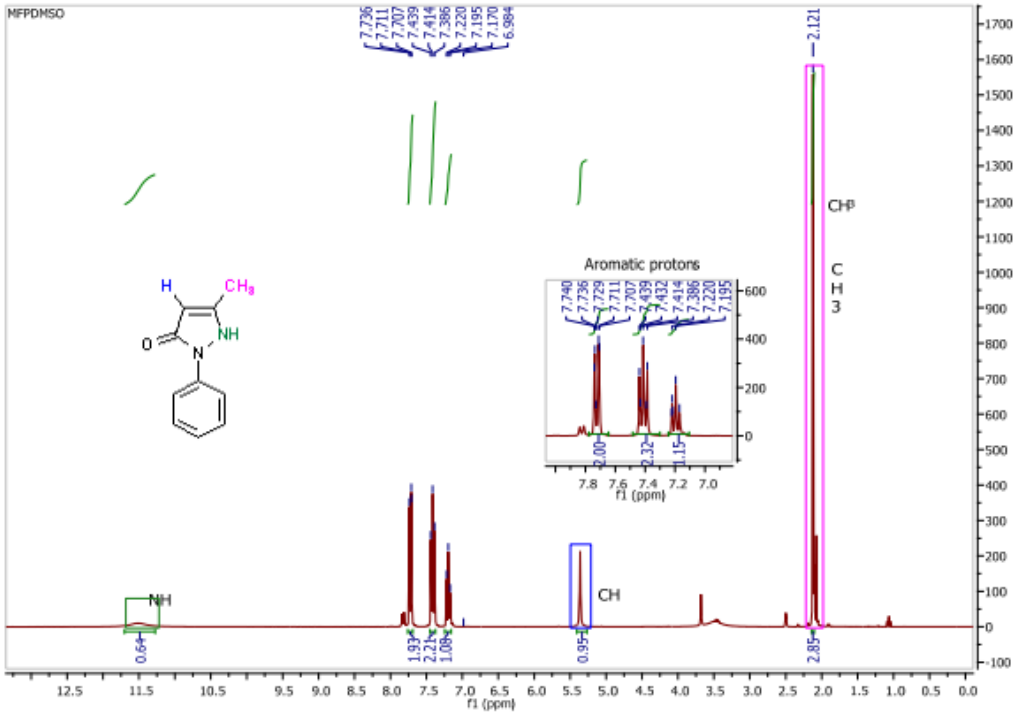
Two major tautomeric forms of edaravone in DMSO-d^6 and $CDCl_3$



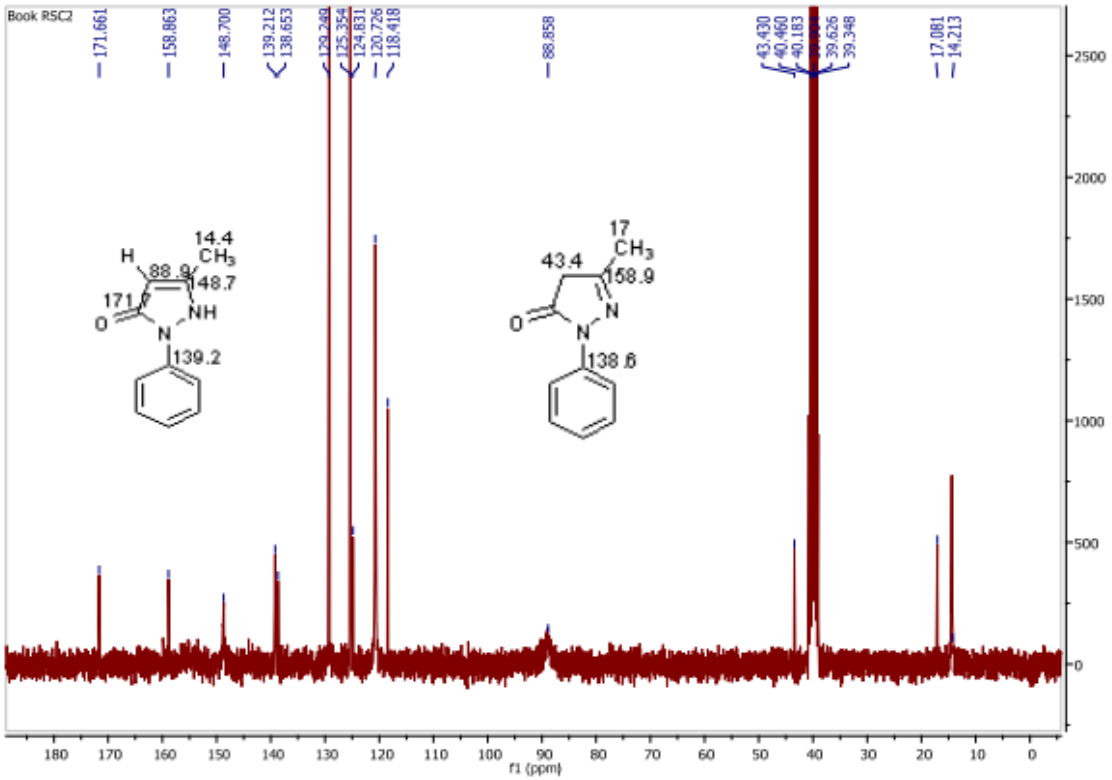
^{1}H NMR of 3-methyl-1-phenyl-5-pyrazolone in $CDCl_3$



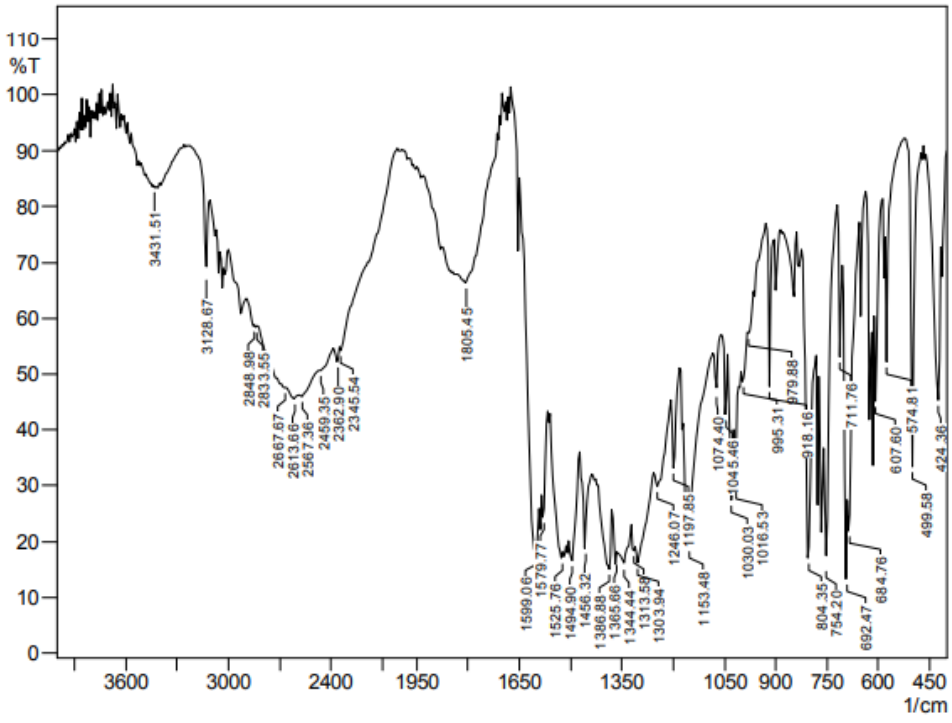
^{13}C NMR of 3-methyl-1-phenyl-5-pyrazolone in $CDCl_3$



^{1}H NMR of 3-methyl-1-phenyl-5-pyrazolone in DMSO



^{13}C NMR of 3-methyl-1-phenyl-5-pyrazolone in DMSO



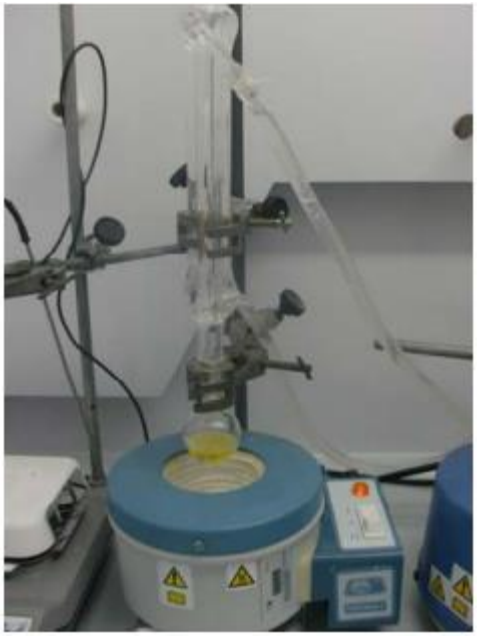
IR spectra of 3-methyl-1-phenyl-5-pyrazolone (KBr)

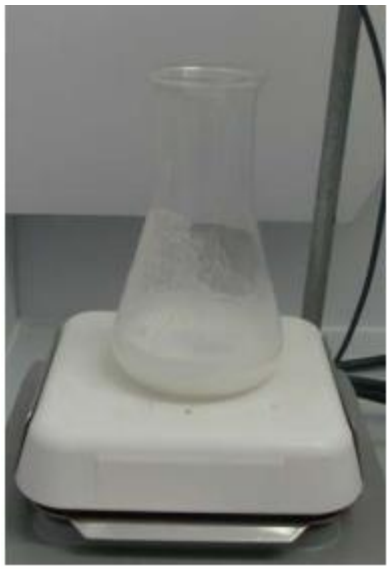
Synthesis of coumarin-3-carboxylic acid

Supplementary Material

Experimental notes

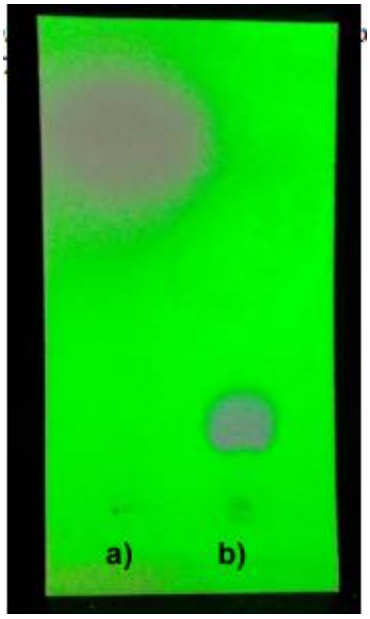
This experiment aims at the preparation of coumarin-3-carboxylic acid, in two steps, through the Knoevenagel condensation of salicylaldehyde with diethyl malonate followed by basic hydrolysis. The experiment requires two 2h sessions but the products are easily isolated by filtration after precipitation. This experiment is very reproducible and easy to perform but due to the concepts involved, the experiment is more adequate to 2nd year chemistry students. The initial solution is yellow and after one hour at reflux there is still a small amount of the salicylaldehyde, which can be easily detected by TLC. Increasing the reaction time does not lead to higher yields. The residual salicylaldehyde does not interfere with the isolation of the coumarin ester as the addition of cold water to the reaction mixture leads to the immediately formation of white crystals of the coumarin ester while the salicylaldehyde rests in solution. It is thus important to wash the crystals to assure its purity. The yields of this first step vary between 82-83% and the melting points, 88-92ºC, are similar to those reported in the literature (92-95ºC, Bhat, M. A., Siddiqui, N., Khan, S. A. (2008) Synthesis of novel 3-(4-acetyl-5H/methyl-5-substituted phenyl-4,5- dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-ones as potential anticonvulsant agents. Acta Poloniae Pharmaceutica Drug Research, Vol. 65 No. 2 page. 235-239) The second step is a classic basic hydrolysis. The initial reaction mixture is opaque, due to low solubility of the coumarin ester in the water/ethanol mixture, but as the mixture is heated under reflux it progressively becomes transparent. After 30 min the reaction is complete and upon acid addition there is the instantly formation of white crystals of the coumarin acid. It is not necessary to recrystallize the product as it appears pure by TLC and NMR. The measurement of the weight and melting point of the product can only be made after drying the product overnight in a oven The yields of the second step vary between 80-88% and the melting points, 190-192ºC are similar to those reported in the literature (189-192ºC, Karami, B., Farahi, M. and Khodabakhshi, S. (2012), Rapid Synthesis of Novel and Known Coumarin-3-carboxylic Acids Using Stannous Chloride Dihydrate under Solvent-Free Conditions. Helvetica Chimica Acta, Vol. 95 pp 455–460). The global yield is thus between 70-81%.





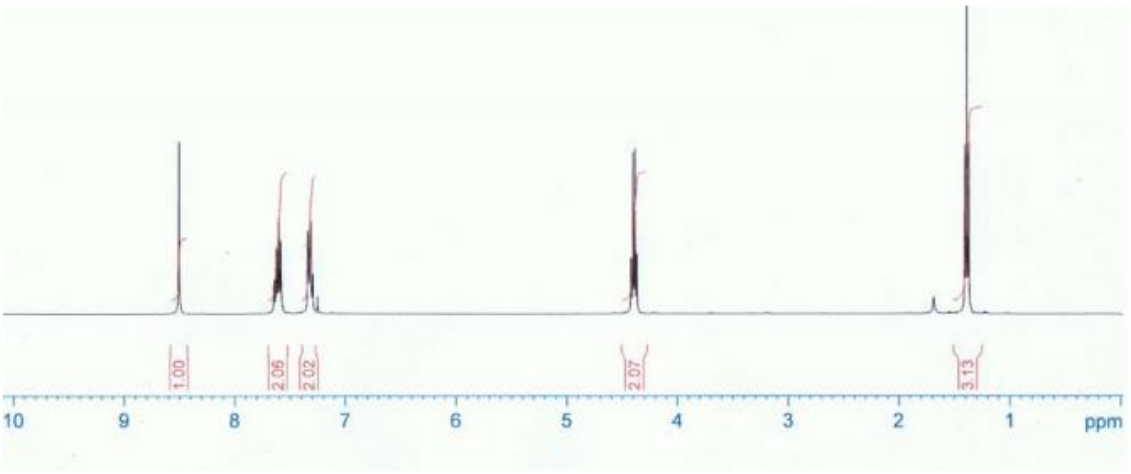
a) Reaction apparatus with the initial yellowish solution

b) Addition of HCl to the basic aqueous solution and formation of the final product

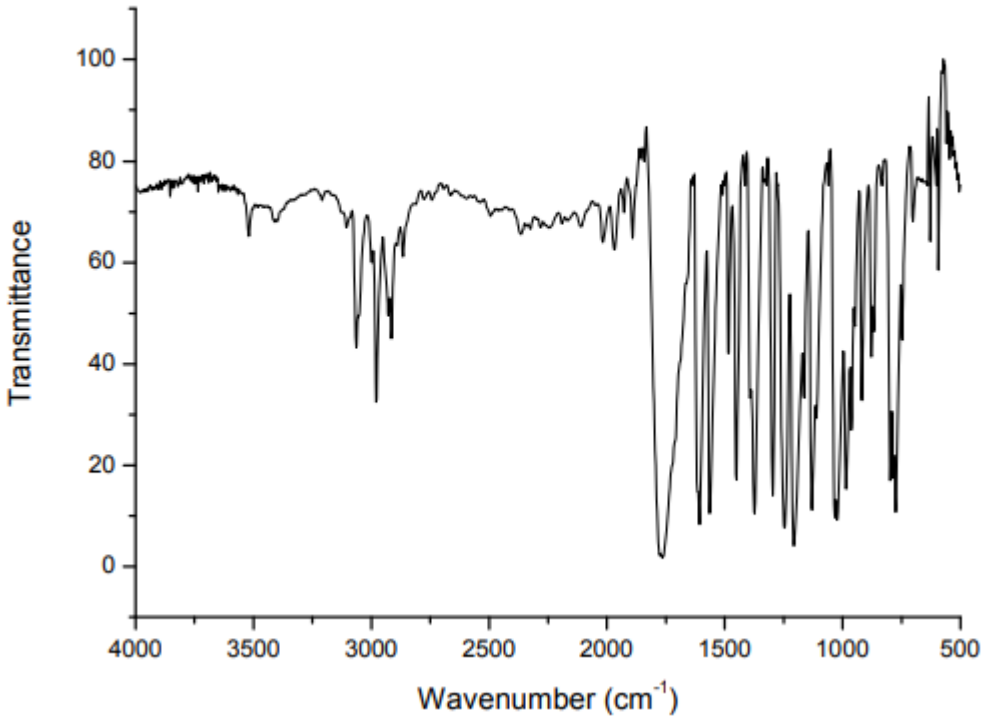


1. 60% diethyl ether/petroleum ether. a) Salicylaldehyde b) Product (coumarin ester)

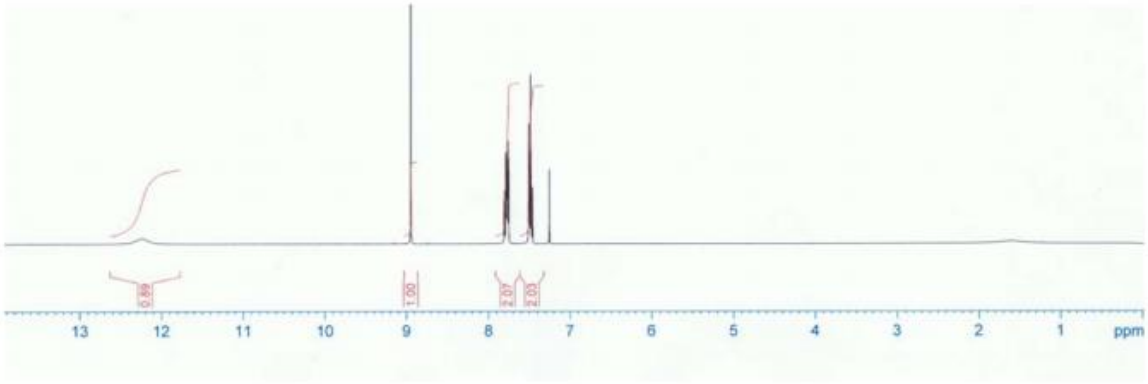
2. 80% diethyl ether/petroleum ether. a) Coumarin ester b) Product (coumarin-3-carboxylic acid)



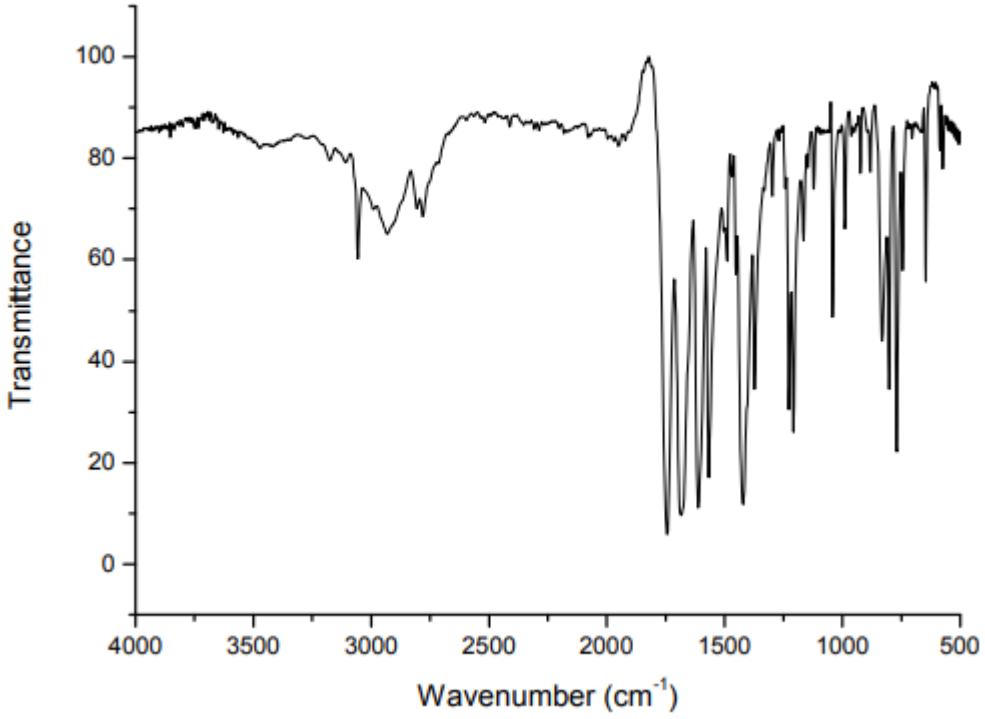
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the coumarin ester



IR spectra of the coumarin ester



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the coumarin-3-carboxylic acid



IR spectra of the coumarin-3-carboxylic acid

Preparation of chalcone and its further Robinson annulation with ethyl acetoacetate

Supplementary Material

Notes for the Claisen-Schmidt condensation:

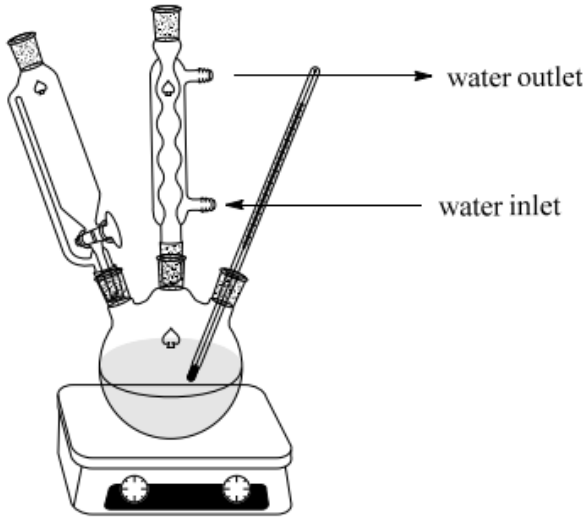
Although not absolutely necessary for this reaction, the students are usually instructed to use a threenecked round bottomed flask equipped also with a condenser. This will avoid any problems arising from an accidental fast addition of benzaldehyde. The typical reaction apparatus used by the students. Benzaldehyde is usually added for 5-10 min, as the fast addition of this reactant has shown to have a detrimental effect in the reaction yield. The occurrence of a Cannizzaro reaction might be on the basis of the lower yield, but this aspect was never confirmed by the authors. The students are usually instructed to follow the reaction by TLC, using Hexane 9/1 AcOEt as eluent. Acetophenone and the chalcone have similar Rf's and so the reaction is followed by checking the consumption of benzaldehyde, using UV lamp (254 nm). Nevertheless, when developing the TLC plates with Cerium Molybdate benzophenone is not visible whilst the product develops into a yellow/greenish color. A standard of the previously prepared chalcone is usually provided to the students for the sake of comparison. Students are instructed to prepare much diluted samples of starting materials as spots usually get spread in the TLC. Other combinations of eluents for the TLC were unsuccessfully tested (Toluene/AcOEt; CH_2Cl_2/$CHCl_3$; CH_2Cl_2/Hexane; Et_2O/Hexane).

The reaction takes 2-3 hours to reach completion and usually results in a very thick mixture containing the precipitated chalcone. In some instances the product does not precipitate and two layers are visible in the reaction flask, even though the benzaldehyde has been completely consumed. In such cases the reaction is stirred in an ice bath for some minutes to induce precipitation of the chalcone, or a minimum amount of cold water can be added. In order to keep the schedule, the reaction mixture can be kept overnight in the fridge and the filtration done in session 2. The recrystallization of the chalcone should be done at 50 ºC, since its melting point is only 55-57 °C. The amount of ethanol needed for the recrystallization is 5 mL/g of crude chalcone. The dissolution of the chalcone in ethanol has been performed aided by a water bath at 50 ºC. The recrystallization of the compound is performed by cooling the mixture at room

temperature to get the first crystals and then moved to the fridge (4 °C) for about 20 min. The beaker walls have been scratched with a glass rod to induce crystallization when needed.

Notes for the Robinson Annulation:

The use of different amounts of barium hydroxide and different reaction temperatures allow the preparation and isolation of the intermediaries of this reaction, as described by Delaude.1 In order to show the students the presence of such intermediaries, samples of the 1,5-diketone and the hydroxy ketone have been prepared beforehand according to the procedure developed by Delaude,1 and given to the students for them to prepare TLC standards for comparison. TLC's of the reaction mixture are performed by diluting the reaction mixture in ethanol and eluting twice with AcOEt 15/85 Hexane. Observation of the spots can be achieved either with a UV lamp (254 nm) or by developing with KMnO4 solution followed by heating. After 1h it is possible to observe 4 spots in the reaction mixture, corresponding to the starting chalcone, the 1,5-diketone, the hydroxy ketone and the cyclic enone. After overnight reaction traces of chalcone are still visible, nevertheless the reaction can be quenched as the desired product is obtained pure after crystallization. It is important to keep vigorous reflux (around 90 °C), as longer reaction times are needed for gentle refluxes due to the low solubility of the barium hydroxide in ethanol. After overnight reflux, it is important to efficiently cool the reaction mixture and to use very cold water in the dilution step. If not, a yellow gum will form and clog the surface of the sintered glass funnel, making the filtration to take long time and decreasing the purification yield. Enough ethanol just to dissolve the crude enone lumps is used in the recrystallization. During the dissolution of the product in boiling ethanol the mixture becomes milky and care should be taken in order to avoid the use of excess ethanol (25-40 mL of ethanol have been used).



Reaction apparatus used for the aldol condensation

Tips to answer the questions

1. This question intends to make the student think about the different electrophilicity of the aldehyde and the ketone. It is expected the student to identify the formation of the aldol selfcondensation of acetophenone as the main possible side product of this reaction.

2. Performing crystallizations at a higher temperature than the melting point is detrimental to yield of the process, as the compound can decompose. In this case the melting point of the product is 55-57 ºC.

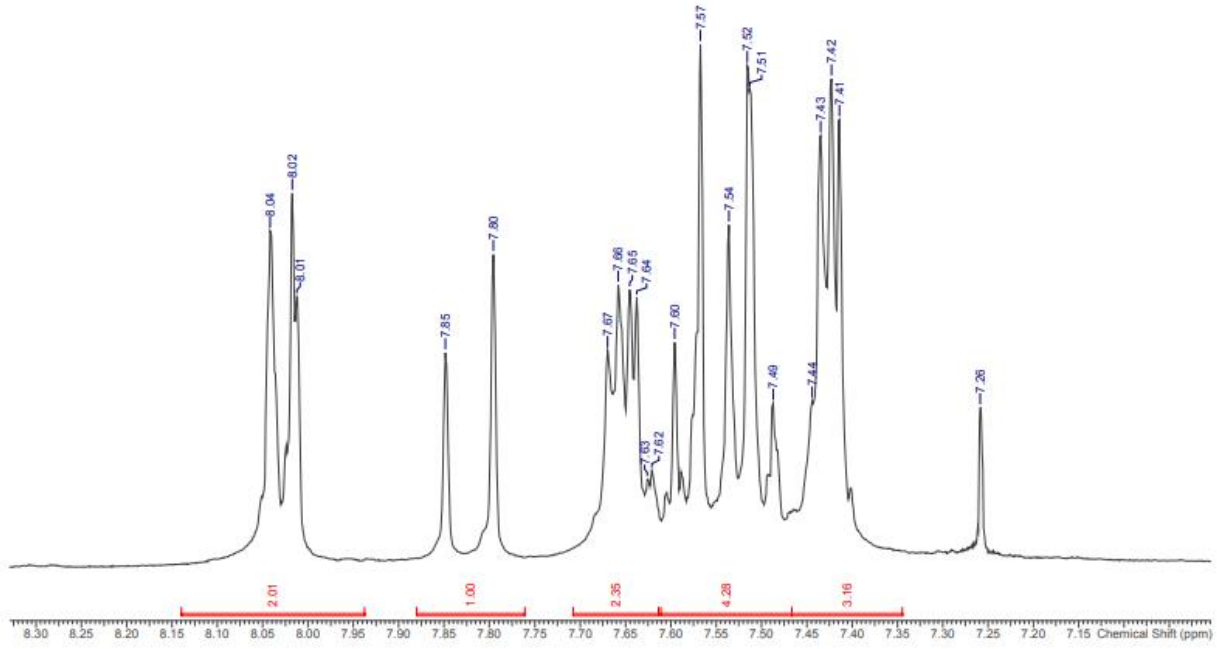
3. The analysis of the 1 H NMR of the prepared chalcone clearly shows a duplet at 7.82 ppm. The large coupling constant of that duplet (J = 15.5 Hz) and the absence of any other visible duplet indicate the exclusive formation of the E-alkene. The student should be instructed to think on the possibility of the Z-alkene to form and equilibrate to the E-alkene because of thermodynamic control.

4. The students should be able to easily identify the spots on the TLC below the desired product, even if the instructor does not provide intermediary samples for comparison.

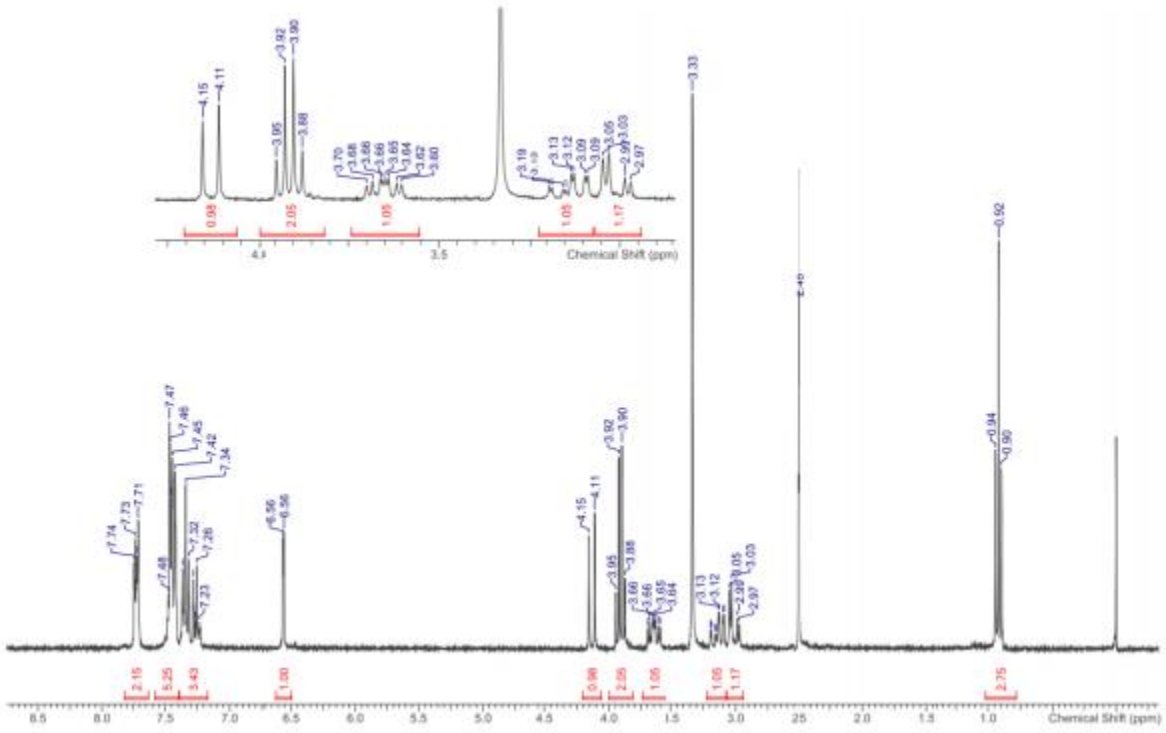
5. It is intended that the students think about the amount of catalyst used, as well as the need for higher temperatures in order to trigger the dehydration of the tertiary alcohol.

6. The atom economy of the Robinson annulation reaction studied in this experiment is 95 %, as only water is produced as a side-product. However, due to the difficulty in the precipitation of the reaction product, the experimental atom economy has been determined by the students to be only 34 % - (1.53 g average obtained product) / (3.38 g total mass of reactants).

Spectra of the Robinson annulation product in CDCl3 can be found in the literature,6 as well as the exhaustive structural characterization in DMSO-d6. 1 The use of DMSO as deuterated solvent is advised if the instructor is planning to go deep into the structural analysis of the compound. In CDCl3, the benzylic proton and the vicinal α-carbonyl proton resonate at the same frequency and so cannot be distinguished.



300 MHz ^{1}H NMR ($CDCl_3$) of chalcone



300 MHz ^{1}H NMR (DMSO-d_6) of Robinson annulation product

References

1. L. Delaude, J. Grandjean and A. F. Noels, J. Chem. Educ., 2006, 83, 1225.

2. J. Clayden, N. Greeves and S. G. Warren, Organic chemistry, 2nd edn., Oxford University Press, Oxford ; New York, 2012, pp. 679-680.

3. Compound 12 in T. Yamakawa, H. Kinoshita and K. Miura, J. Organomet. Chem., 2013, 724, 129-134.

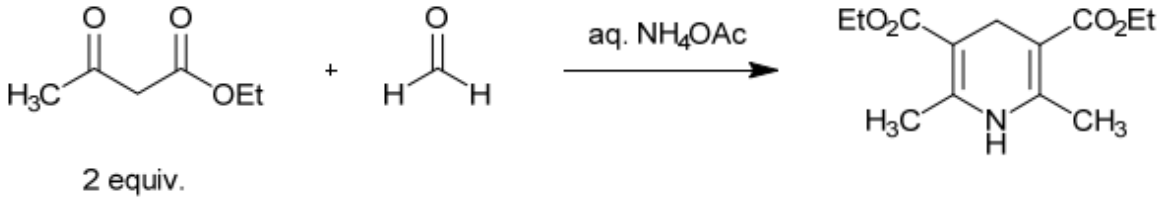
4. SDBSWeb : http://sdbs.riodb.aist.go.jp (National Institute of Advanced Industrial Science and Technology), August 2014

5. Compound 16a in N. A. Shakil, M. K. Singh, M. Sathiyendiran, J. Kumar and J. C. Padaria, Eur. J. Med. Chem., 2013, 59, 120-131.

Hantzsch synthesis of nifedipine

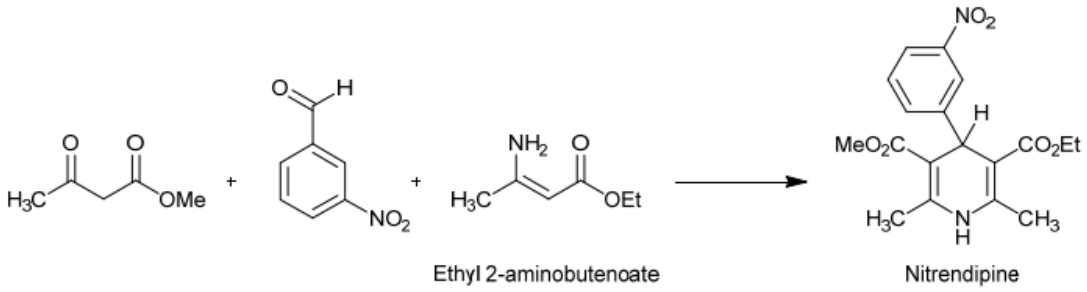
Supplementary Material

The standard Hantzsch dihydropyridine synthesis experiment used in teaching labs usually employs ethyl acetoacetate, formaldehyde and an ammonium salt. Urotropine is sometimes used in lieu of aqueous formaldehyde.



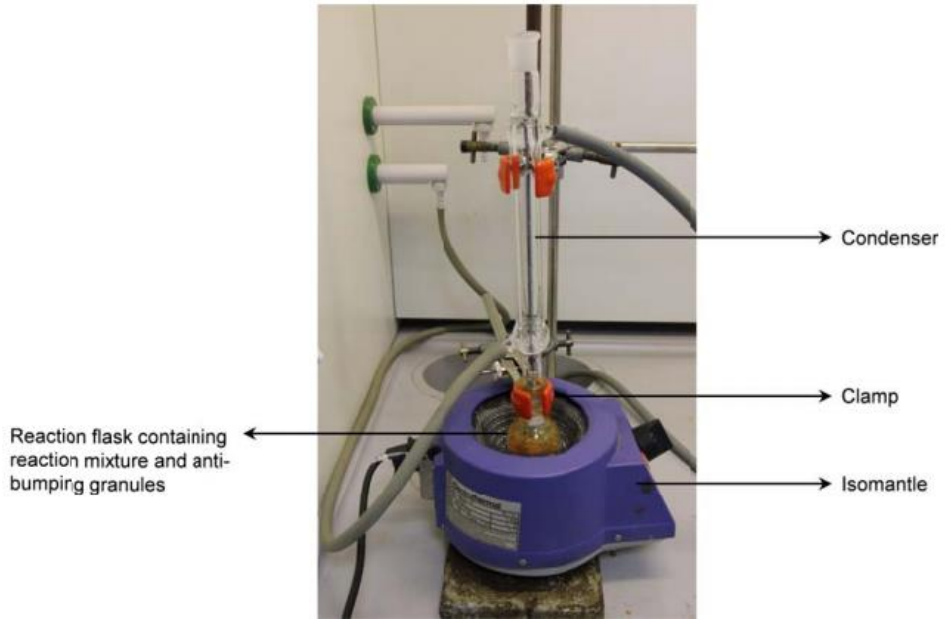
Commonly used example of a Hantzsch dihydropyridine synthesis

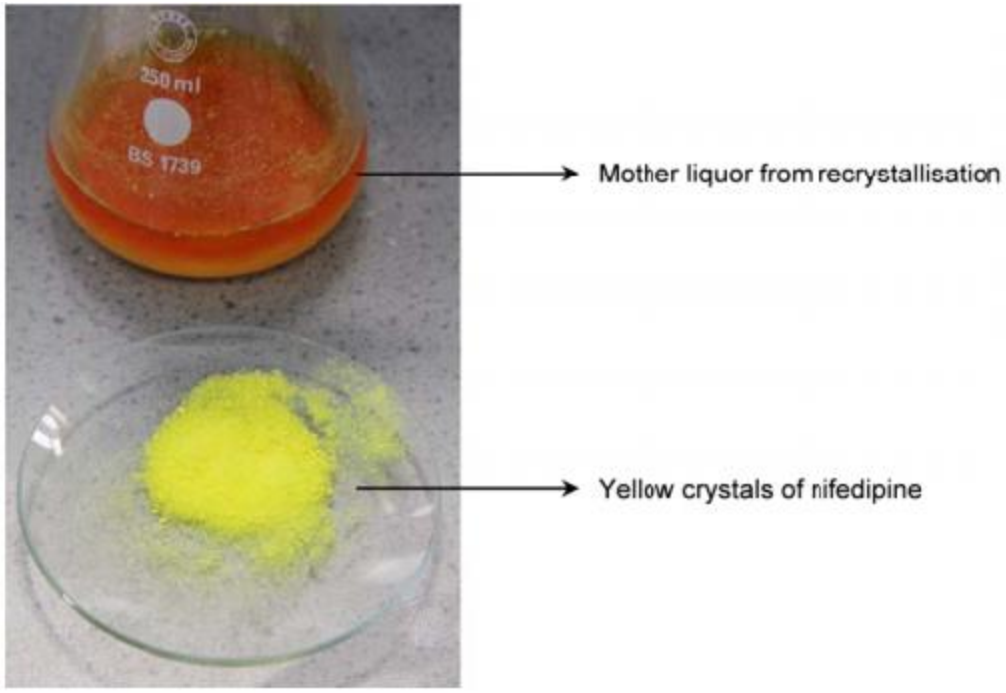
In this experiment students carry out a Hantzsch synthesis to make nifedipine, an anti-hypertensive drug, in a single step from methyl acetoacetate, ammonia and an aromatic aldehyde (orthonitrobenzaldehyde). Unlike acetylsalicylic acid and paracetamol which can also be prepared in a single step, nifedipine has a more complex heterocyclic structure and its preparation involves a multicomponent reaction. The experiment illustrates the importance of heterocyclic chemistry, particularly to students specialising in pharmaceutical chemistry. Nifedipine was introduced as an antihypertensive drug in the 1980s. Second-generation drugs of the nifedipine type are no longer symmetrical and they possess different ester groups. Nitrendipine, for example, is made by a variant of the Hantzsch synthesis using equal amounts of an aldehyde, methyl acetoacetate and ethyl 2-aminobutenoate. Its synthesis requires no further -βsource of ammonia. Ethyl 2-aminobutenoate is a stable enamine that is readily obtained from the ketoester and ammonia.



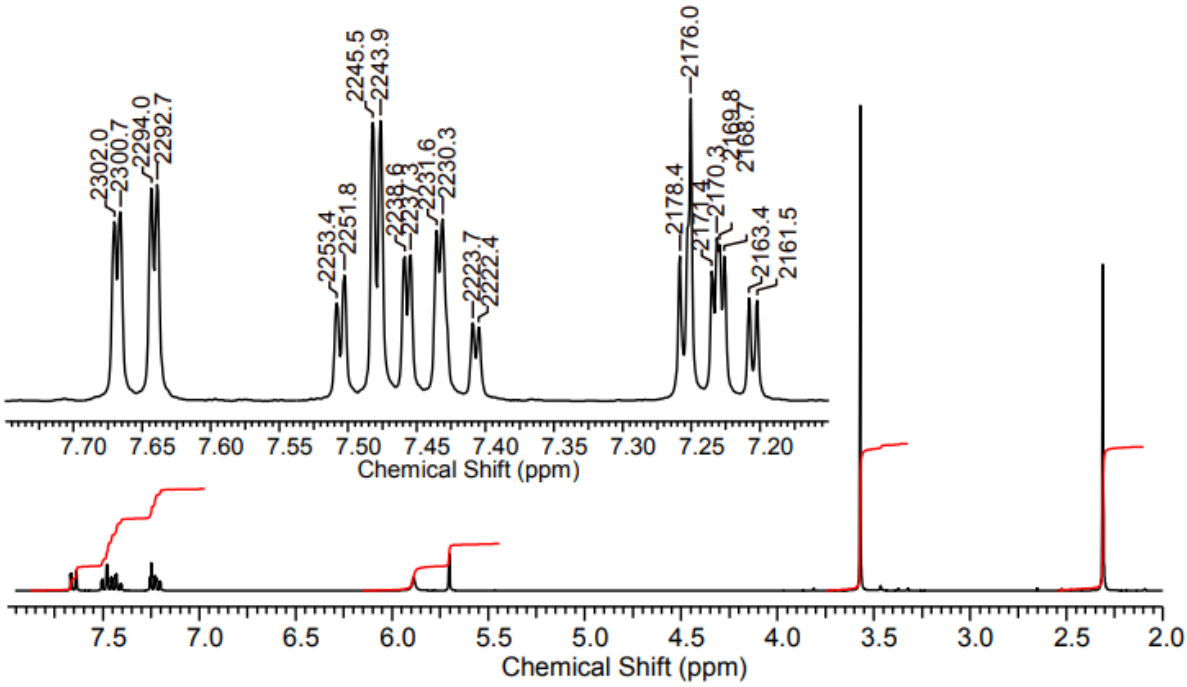
Preparation of nitrendipine

The procedure for the Hantzsch synthesis of nifedipine has been adapted from a patent publication. Students have encountered few problems with this experiment over the years, although yields can vary between 25 and 60%, which reflect mostly a student's recrystallisation skills. The limiting reagent is the aldehyde (theoretical yield of nifedipine = 15.0 mmol or 5.19 g). At Heriot-Watt University Chemistry students have a series of lectures on heterocyclic chemistry during the course of Year 3. They also carry out the synthesis of several heterocycles of which the Hantzsch dihydropyridine synthesis is an example. Only students specialising in pharmaceutical chemistry are asked to make nifedipine since the experiment complements their specialist lecture course. The scale of the experiment produces a sufficient amount of nifedipine that recrystallisation provides no problems. M.p.: 169-171 °C (yellow crystalline solid).

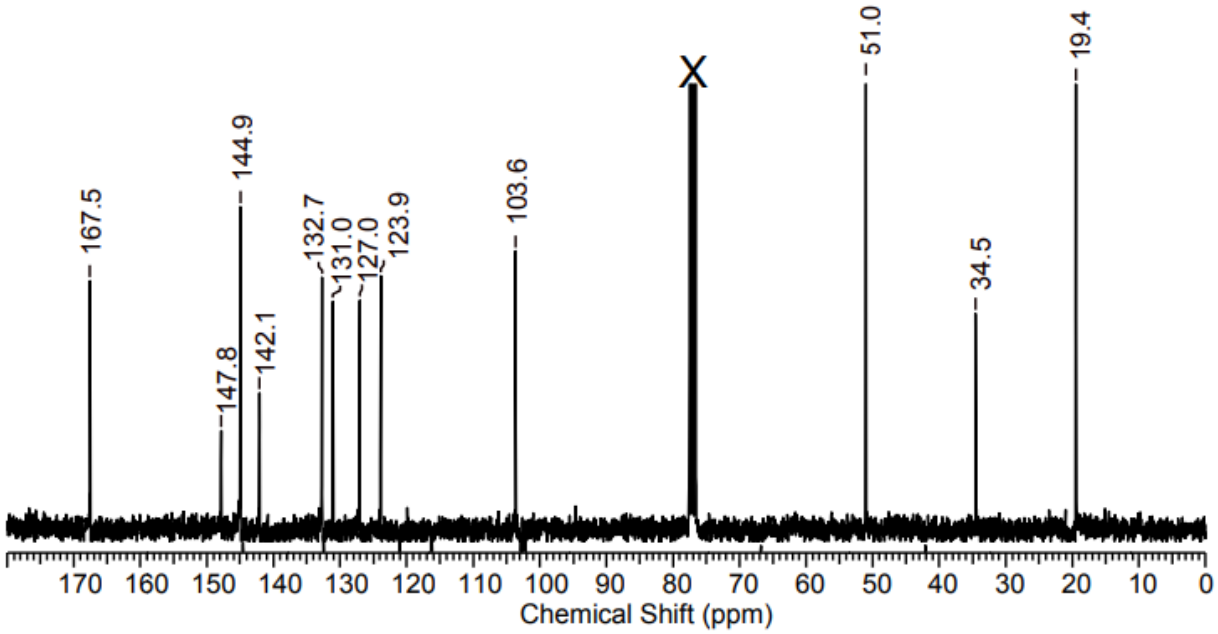




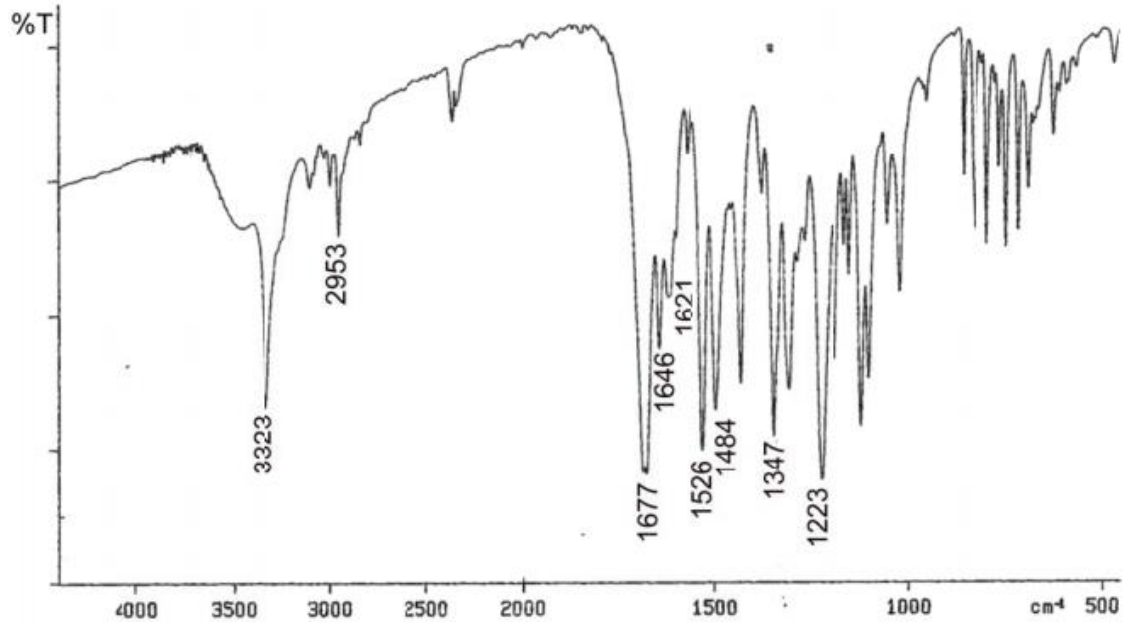
Nifedipine after recrystallization and filtration



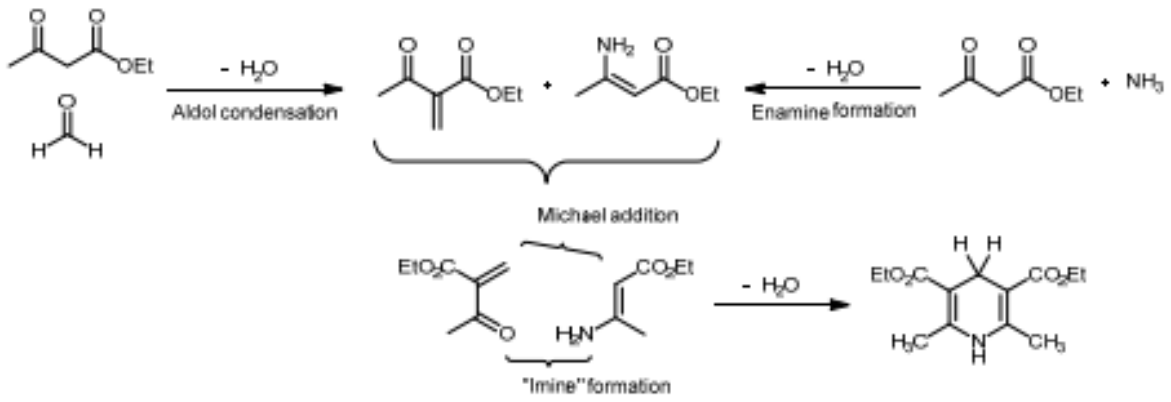
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the recrystallised nifedipine.



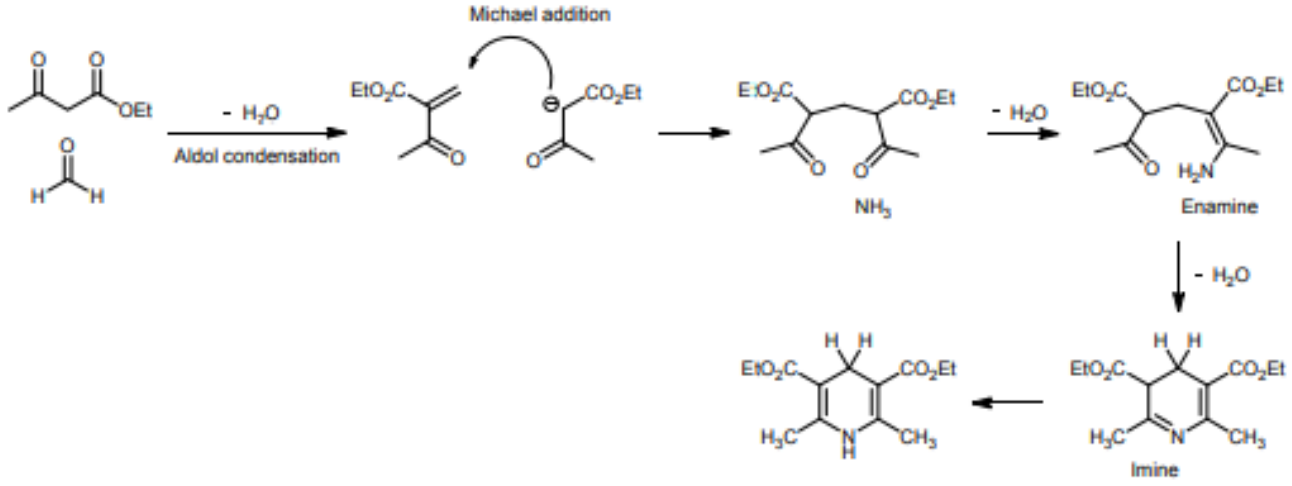
^{13}C NMR spectrum (300 MHz, $CDCl_3$) of the recrystallised nifedipine.



IR spectra of the recrystallised nifedipine



Outline mechanism for the formation of nifedipine.



Alternative outline mechanism for the formation of nifedipine.

References

1. L. L. W. Cheung, S. A. Styler and A. P. Dicks, J. Chem. Educ., 2010, 87, 628-630.

2. B. E. Norcross, G. Clement and M. Weinstein, J. Chem. Educ., 1969, 46, 694-695.

3. U. Eisner and J. Kuthan, Chem. Rev. 1972, 72, 1-42.

4. K. M. Bucholtz, J. D. Hugdahl, A. M. Kiefer, K. M. Kiefer and A. M. S. Maria, Chem. Educator, 2012, 17, 125- 127.

5. J. A. Joule and K. Mills, Heterocyclic Chemistry, 4th ed., Blackwell Publishing, Oxford, 2000, 104-105.

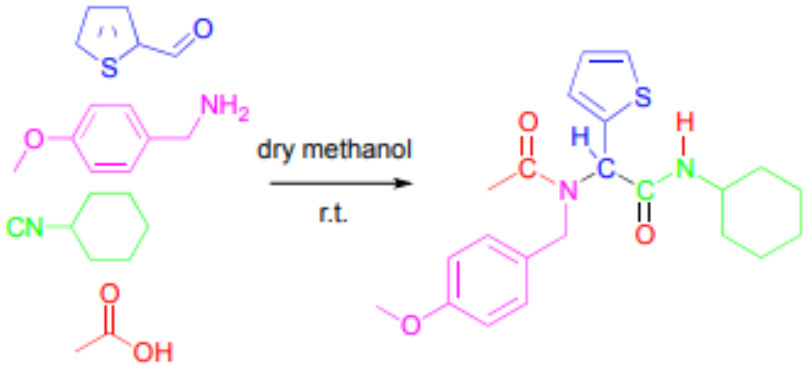
A Ugi multicomponent reaction in the synthesis of N-cyclohexyl-2- (N-(4-methoxybenzyl)acetamido)-2-(thien-2'-yl)acetamide

Supplementary Material

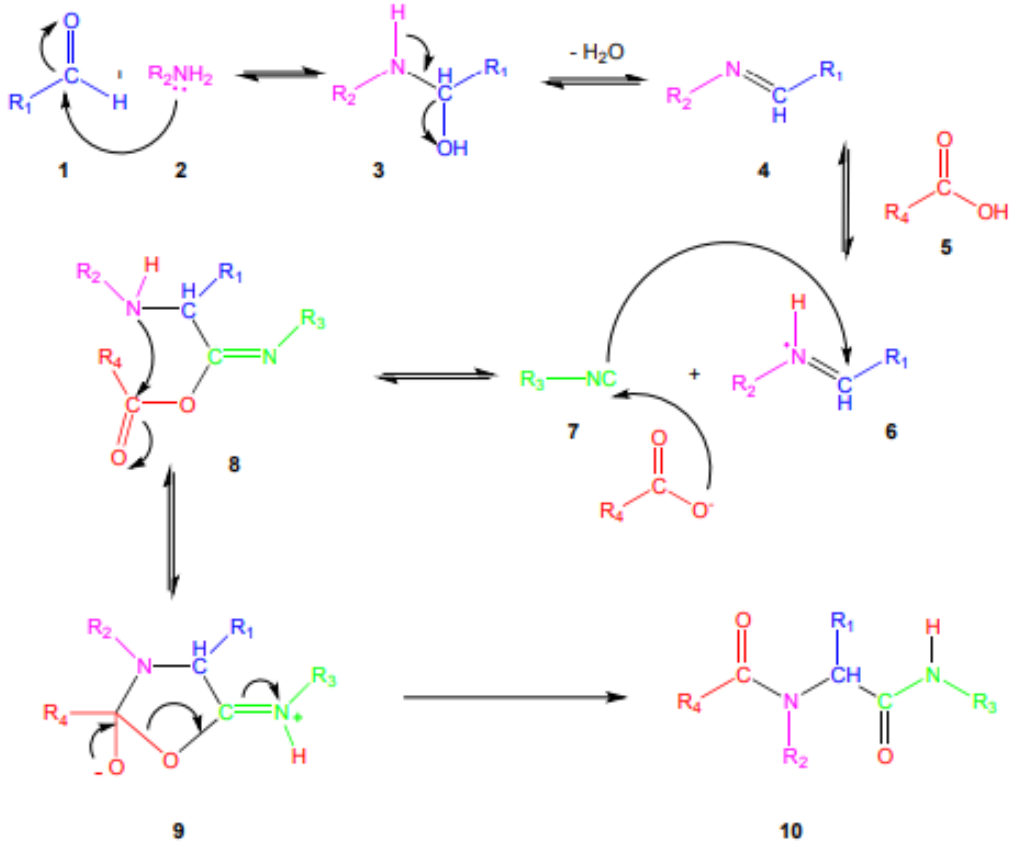
Experiment notes

This experiment involves simple experimental techniques and commercially available reagents, and it is expected that the students possess previously acquired practical skills (in terms of isolation and purification techniques) and theoretical background (synthesis, reactivity and spectroscopic data interpretation). Therefore, this experiment may be appropriate for last year project in Chemistry degree or as the practical component of advanced chemistry subjects at Master level. The synthesis of the title compound is achieved by a four-component condensation reaction, the Ugi reaction, by reacting an amine, a carbonyl compound, an acid and an isocyanide. The Ugi reaction is based on a previous three-component reaction proposed earlier by Passerini, which involved the reaction of a carboxylic acid, a carbonyl compound and an -acyloxycarboxamides. Since the carbonyl group of aldehydes and α isocyanide to yield ketones is isoelectronic with the imino group, Ugi decided to add an extra reagent (the -αamine) thus developing a novel four-component reaction that produces acylamidocarboxamides. The final product is obtained by combination of all reagents with the loss of a water molecule. In the present experiment, thiophene-2-carboxaldehyde, 4-methoxybenzylamine, acetic acid and cyclohexylisocyanide are reacted in order to obtain the corresponding N-cyclohexyl-2- (N-(4-methoxybenzyl)acetamido)-2-(thien-2'-yl)acetamide. In the present experiment conditions, in various repetitions carried out by third year Chemistry students and first year Chemistry MSc students, the product was obtained in 30-40% yield as orange oil.

As for the mechanism, the reaction is initiated by nucleophilic substitution of the amine 2 with the aldehyde 1, via hydroxylamine 3, yielding the imine 4. Protonation of the imine nitrogen by carboxylic acid 5 increases the electrophilic character of the C=N bond in the resulting imminium cation 6. This species undergoes nucleophilic attack by the isocyanide 7, followed by the nucleophilic attack of the carboxylate anion, resulting in intermediate 8. -acylaminoamide 9 with an O- to Nacyl transfer to yield the final product 10. All the steps are in α Finally a rearrangement occurs through intermediate equilibrium except for the last acyl transfer which is irreversible.



Preparation of N-cyclohexyl-2-(N-(4-methoxybenzyl)acetamido)-2- (thien-2'-yl)acetamide by a Ugi reaction.



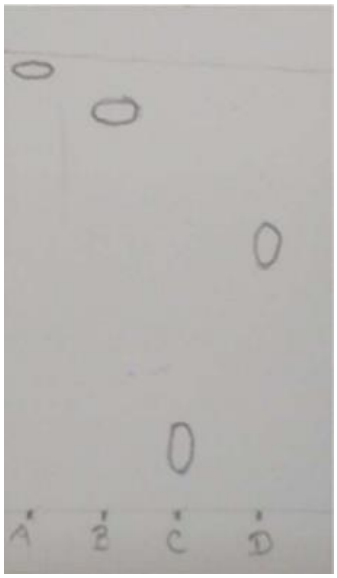
Mechanism of the Ugi reaction.

Although the condensation of the four reagents can be done at the same time, it is advantageous to form the imine prior to the addition of the other components, to increase the final yield. The Passerini reaction may occur as a side reaction in certain conditions (use of nonpolar solvents, bulky reagents). This experiment has been replicated with other aldehydes (a series of 5-phenylthiophene-2- carboxaldehyde bearing different substituents of different electronic character at the phenyl ring) and other commercial isocyanides (liquid or solid) and the procedure and results were reproducible. The isocyanide used in this experiment was chosen for being a liquid, which minimizes the risks associated with the handling of this smelly reagent.

a) Reaction setup for the Ugi reaction

b) Reaction mixture filtration setup after the Ugi reaction.

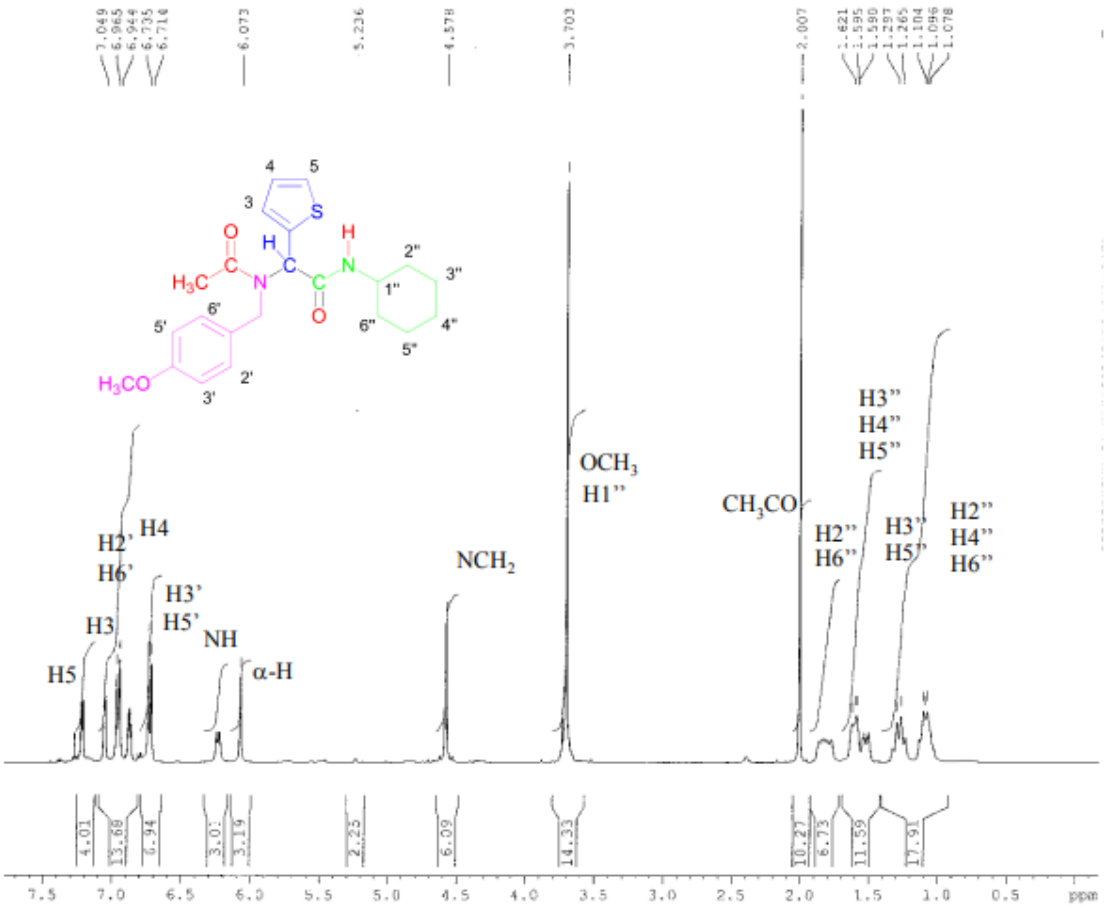
Column chromatography purification of the evaporated crude residue.



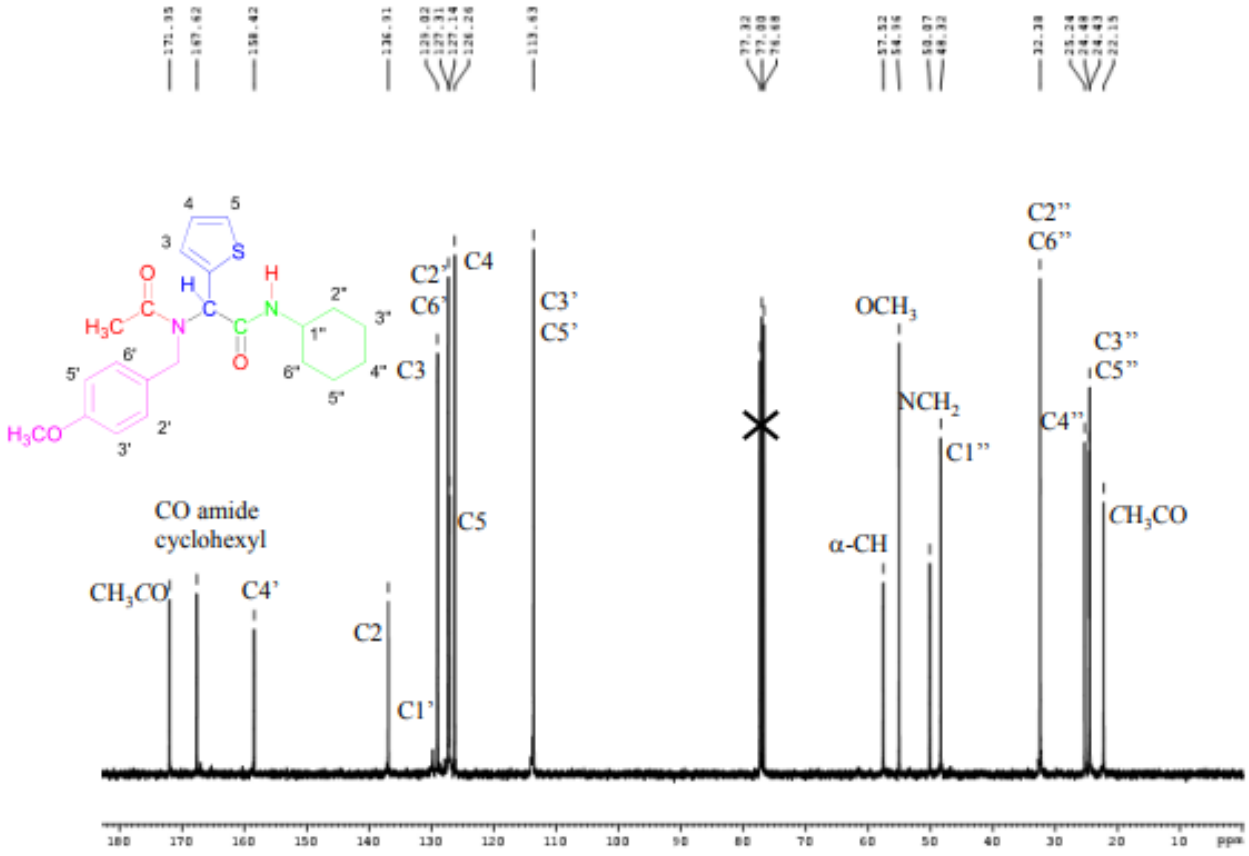
A – isocyanide
B – aldehyde
C – amine
D – product

Retention factors, R_f

A – isocyanide	$R_f = 0.96$
B – aldehyde	$R_f = 0.87$
C – amine	$R_f = 0.14$
D – product	$R_f = 0.62$



^{1}H NMR spectrum of the product in $CDCl_3$ obtained in a Bruker Avance III spectrometer operating at 400 MHz at 25ºC.



^{13}C NMR spectrum of the product in $CDCl_3$ obtained in a Bruker Avance III spectrometer operating at 100 MHz at 25ºC.