The Cannizzaro Reaction
Synthesis of p-chlorobenzylalcohol and p-chlorobenzoic acd
Supplementary Material

This experiment is an interesting transformation since one can obtain two different compounds from a single reagent. The reaction is named after Stanislao Cannizzaro (1826-1910) who was an Italian chemist. He was first studying medicine, but soon turned to the study of organic chemistry. He discovered that aromatic aldehydes are decomposed by an alcoholic solution of potassium hydroxide into a mixture of the corresponding acid and alcohol. One typical example is the decomposition of benzaldehyde into benzoic acid and benzyl alcohol.[1] This reaction seems to be very popular among the different universities because of it character. It can done in macro- or microscale and can be found from many organic synthesis articles and books.

The Cannizzaro reaction is the disproportionation of an aldehyde to on equimolar mixture of primary alcohol and carboxylic acid. The first step in the mechanism is the nucleophilic attack of the hydroxide anion on the carbonyl group of the aldehyde to give a tetrahedral intermediate, which expels hydride ion as a leaving group and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic step and is thereby reduced. The detailed mechanism for the Cannizzaro reaction can be found from the books and article which are listed below.[1-4]

It is advisable to weight the *p*-chlorobenzaldehyde into a small beaker since it takes 5-10 minutes to be dissolved in methanol by stirring the mixture with a glass rod. The solution is then added to disstillation flask containing the 11 M potassium hydroxide solution. At this point of the experiment there is some precipitate (figure **SM 17.1.**2). While refluxing, the solid does not go completely into solution, starts to get stuck to the round bottom flask walls and occasional shaking is needed (Figure **SM 17.1.**3). After cooling the reaction mixture, students separate products by extracting mixture with dichloromethane. The newly formed alcohol will move to the organic layer while the carboxylic acid is left behind in the water layer in form of carboxylate. Students don't always realize which layer is the upper one and which layer the lower one (figure **SM 17.1.**4), and so they are advised to look to the dichloromethane density ($1{,}3266^{20}$g/cm^3).

The dichloromethane layers are washed with the saturated sodium bicarbonate solution in order to remove the acid residue (the students are usually challenged at this point to explain why this is done). After drying over anhydrous sodium sulfate, the dichloromethane layers are filtered to the distillation flask and the dichloromethane is evaporated in the rotary evaporator. The crude alcohol is purified by recrystallizing it using a solution of acetone in hexane (1:9) (usually 5-10 ml).

When acidifying the water layer with hydrochloric acid the mixture will warm up (figure **SM 17.1.**5). In order to avoid losses by dissolution of the carboxylic acid in the medium, the mixture should be cooled in an ice bath. About 20 mL of methanol are needed to perform the crystallization of the carboxylic acids.

This synthesis is one of the four syntheses for 2nd year Chemistry M. Sc. Students in the Technical university of Tampere who are doing their first organic chemistry laboratories. The experiment has been run by 60 students for two year, working individually in up 12 students per class. The reaction time mentioned in the experimental part is 1 h in order to fit the lab sessions into the planned schedule. Longer reaction times have not been tested. This experiment yields and melting points were measured by seven students and ranges of those are listed in the table below.

^{1}H NMR spectra of p-chlorobenzoic acid[5] and p-chlorobenzyl alcohol[6] in $CDCl_3$ can be found online in Sigma-Aldrich or Spectral Database for Organic Compounds websites.

Table SM 17.1.1 – Yields and melting points of the products

Product	Yield [%]	Melting point [°C]
p-chlorobenzyl alcohol	16-66	70-73
p-chlorobenzoic acid	31-56	239-243

If the students don't have time to be in the laboratory 7 hours at a time, it would be better to split the overall experiment in 3 sessions. The session 1 (3h) would consist of reaction and products isolation. During the next session (2h) the students can purify the crude products by recrystallizing and leave to dry overnight. During the last session (2h) they weight the products, determine the melting points and obtain IR and NMR spectra if it is possible.

Answers to the question in the experimental part

1. The mechanism for the reaction can be found from the literature mentioned below.[1-4]

2. The basis for separation of the compounds from the reaction mixture can be found from the background section of the main document

3. The reaction rate order for benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde in Cannizzaro reaction would be following: $MeO^- < H^- < Cl^- < NO_2^-$. The aromatic aldehydes may be divided into two classes: those that react faster than unsubstituted benzaldehyde and those that react more slowly. Those that go slower have electron donating substituents on the 4-position of the aromatic ring, whilst the electron withdrawing substituted benzaldehydes react faster due to their increased electrophilicity. See more details from the literature mentioned below.[2]
4. The melting points for the products can be found for example from the Handbook of Chemistry and Physics. In the edition 93th the melting point for the *p*-chlorobenzyl alcohol is 75°C and for the *p*-chlorobenzoic acid 243°C.

5. Interprepation of the main bands for the IR spectra can be found from the books dealing with principles of instrumental analysis. The IR spectra shown below (Figures **SM 17.1.**8 and **SM 17.1.**9) have been measured using the Fourier transform infrared spectrometer with attenuated total reflectance (diamond-ATR) and can differ from those where samples are powdered in KBr.

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Photos of the experiment

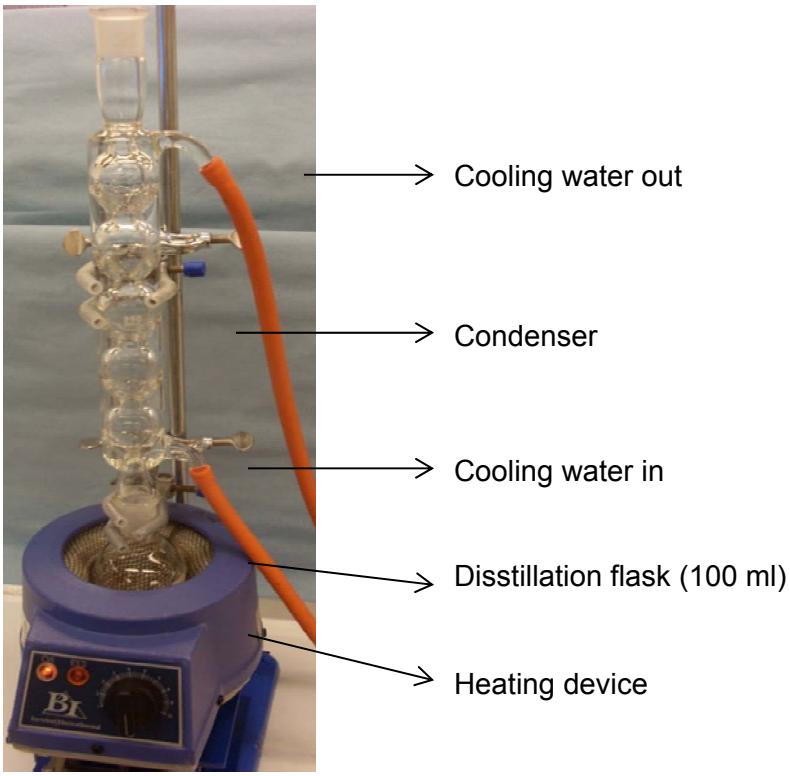

Figure SM 17.1.1 – The reaction setup. Used to reaction and recrystallizing.

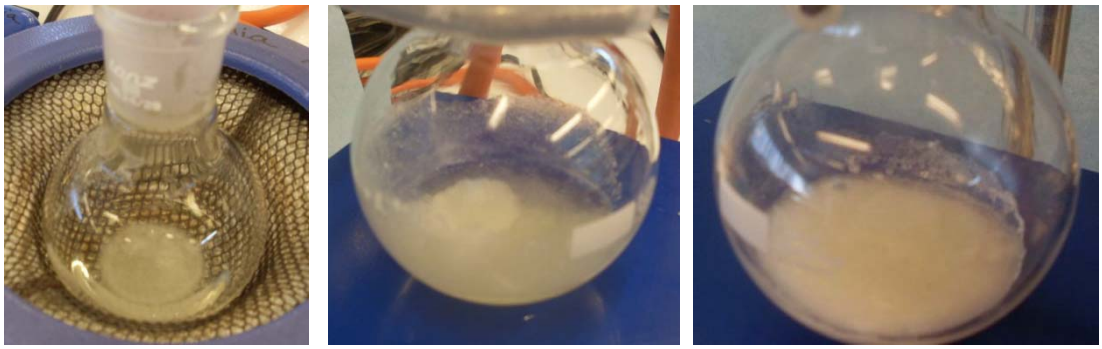

Figure SM 17.1.2 - Reaction mixture before refluxing, just after the heat is turned off and after the set up is cooled.

Figure SM 17.1.3 - Shaking off the precipitate from the walls of distillation flask.

Water layer

Dichloromethane layer

Figure SM 17.1.4 – Reaction mixture dissolved in water and after extraction with first 15 ml portion of dichloromethane.

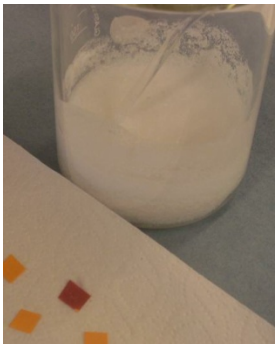

Figure SM 17.1.5 – The water layer after acidification with hydrochloric acid.

Figure SM 17.1.6 – The filtration instrumentation.

Figure SM 17.1.7 – The final products after recrystallization.

IR spectra of products

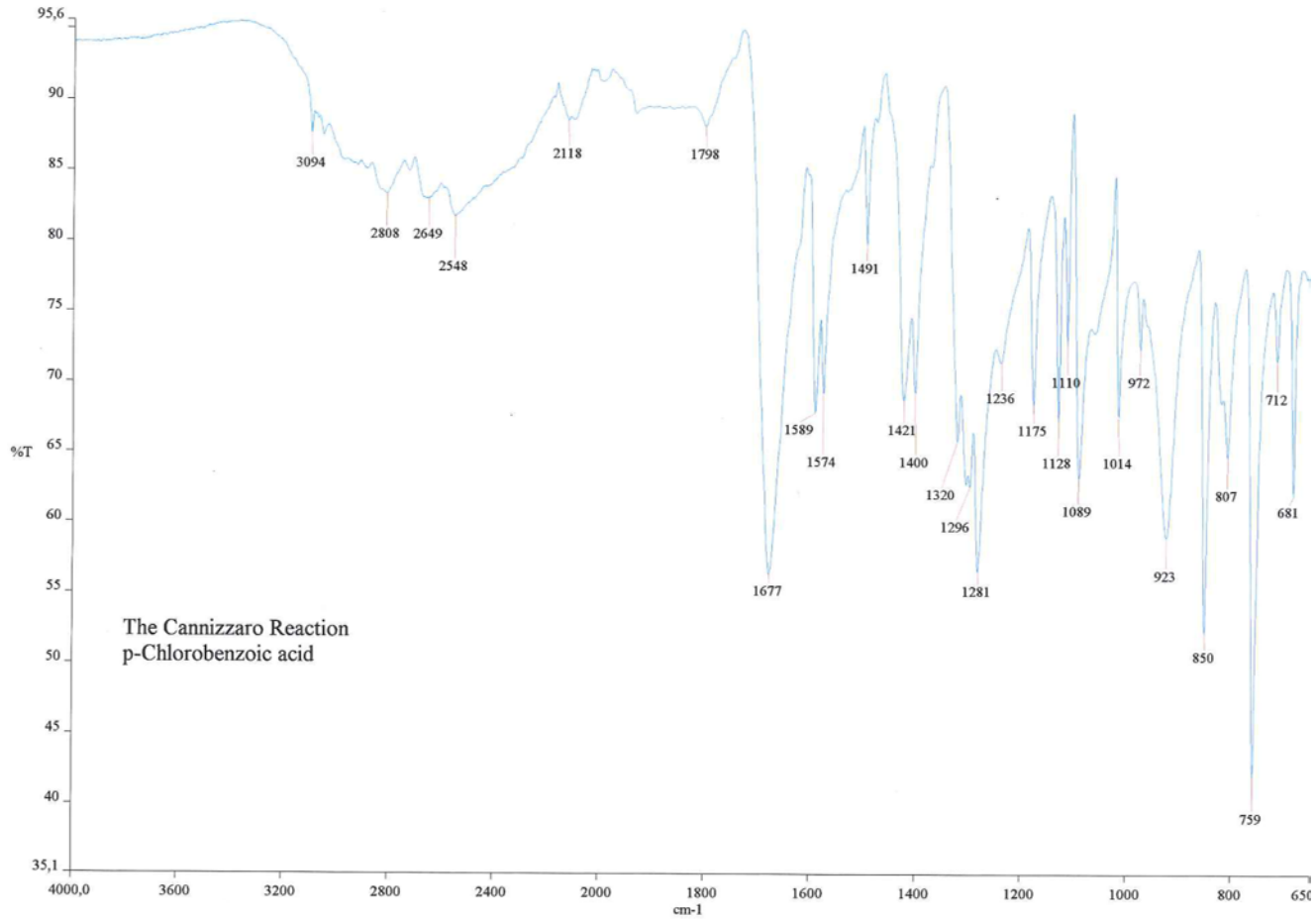

Figure SM 17.1.8 – IR spectra of *p*-chlorobenzoic acid

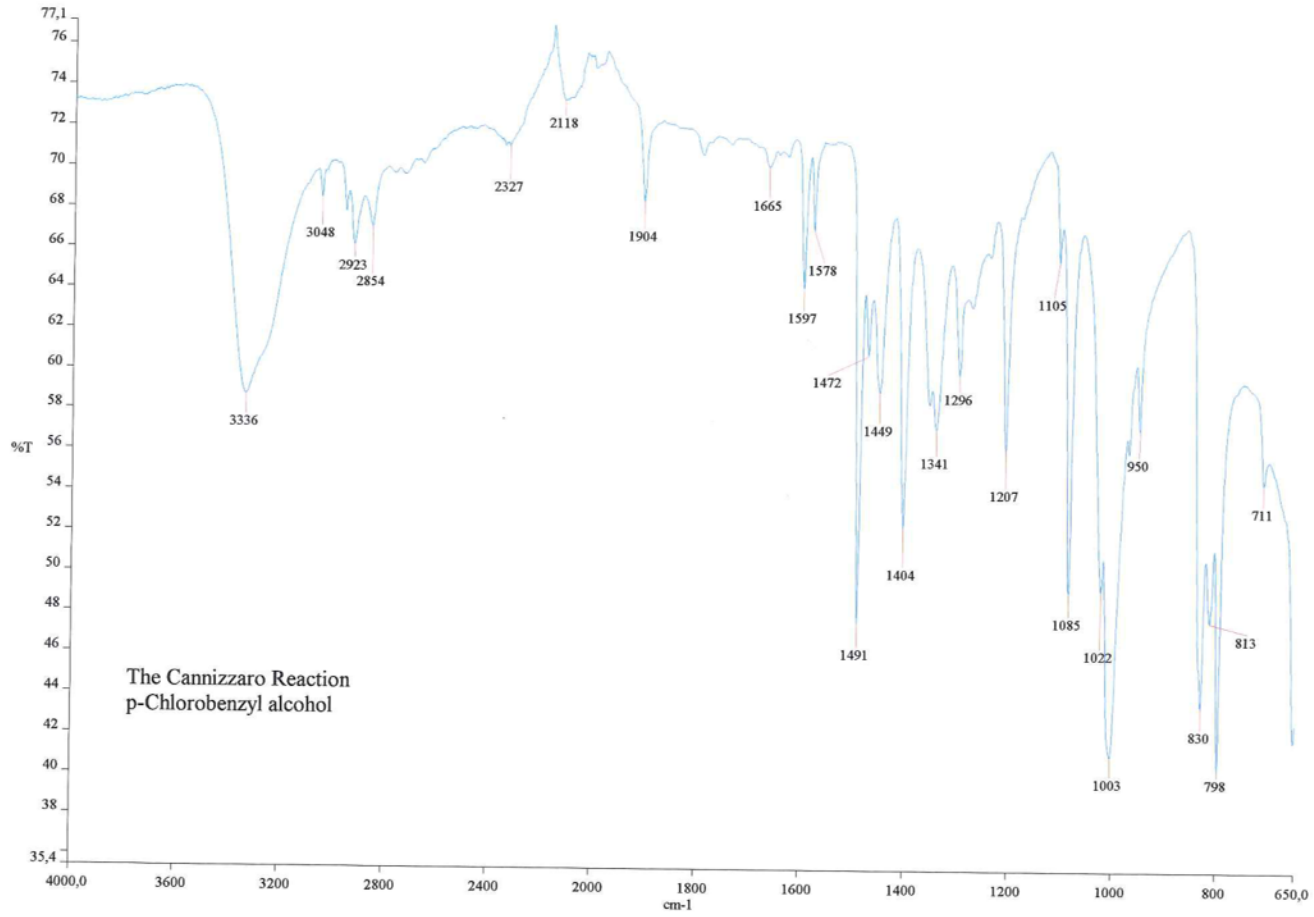

Figure SM 17.1.9 – IR spectra of p-chlorobenzyl alcohol

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[1] McMurry, J., *Organic Chemistry*, Thomson Learning, Inc., USA, 7th ed, 2008, 724-725

[2] Clayden, J., Greeves, N., Warren, S., Wothers, P., *Organic Chemistry*, Oxford University Press, UK, first published 2001, 2008, 1081-1084

[3] Swain, C. G., Powell, A. L., Sheppard, W. A. and Morgan, C. R., *J. Am. Chem. Soc*. 1979, **101(13)**, 3576

[4] Vogel, A. I., *A Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, London, 5th ed, 1989, 1028-1031

[5] http://www.sigmaaldrich.com/spectra/fnmr/FNMR001008.PDF ; http://sdbs.db.aist.go.jp (SDBS no. 1976) – accessed March 2015

[6] http://www.sigmaaldrich.com/spectra/fnmr/FNMR009685.PDF ; http://sdbs.db.aist.go.jp (SDBS no. 5668) – accessed March 2015

The Kemp Elimination in Water:

A Laboratory Experiment for Introductory Organic Chemistry

Supplementary Material

1. Material Provided to Students

    a. Pre-Lab Assignment

    b. Green Chemistry. An Introduction

2. Instructor Notes

    a. Description of the Experiment

    b. Answer key for Pre-Lab Questions

    c. Answer key for Post-lab Questions

    d. TA Notes

3. Representative ^{1}H NMR and IR Spectra

4. Summary of Student Results

5. CAS Registry Numbers

1a. Pre-Lab Assignment

The Kemp Elimination in Water:

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Note: The six questions found in the "Results interpretation and additional questions" section of the experiment document were modified from the pre- and post-lab assignments questions included here.

PRE-LAB ASSIGNMENT

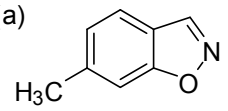
In this experiment, you will conduct an elimination reaction, using NaOH as base, to convert benzisoxazole to salicylonitrile. The product will be isolated and its melting point will be determined.

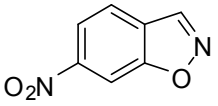
1. Given the following information, state whether the reaction will follow an E1 or E2 mechanism and explain how you arrived at your answer.

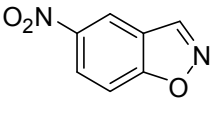
Experiment	Result
concentration of benzisoxazole doubled	reaction rate doubles
concentration of NaOH doubled	reaction rate doubles
concentration of both SM and NaOH doubled	reaction rate quadruples

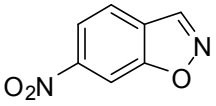
2. Draw an arrow-pushing mechanism for this transformation. Provide the structure of the intermediate indicated in the theory section of the experiment.
3. What is the melting point of salicylonitrile (a.k.a. *ortho*-cyanophenol or 2-hydroxybenzonitrile)? Provide an appropriate reference.

4. For each of the following pairs, indicate which would react faster in a Kemp elimination reaction and explain why.

(a)  **I**

 **II**

(b)  **I**

 **II**

5. Explain how IR spectroscopy could be used to confirm product formation. Refer to specific functional groups, provide characteristic IR band frequencies and indicate the type of vibration (i.e., stretching vs bending).
6. Look up and reference the MSDSs for benzisoxazole, salicylonitrile and ethyl acetate, and comment on the *human* toxicity of each.
7. Fill in the blanks in the following table (and bring a version of this table to the lab with you).

	MW (g/mol)	Density (g/mL)	Amount used (in g or mL)	#mmol	#equiv
benzisoxazole					
NaOH	[conc]:	*n/a*			
ethanol				*n/a*	*n/a*
water				*n/a*	*n/a*
salicylonitrile		*n/a*	*	*	*n/a*

***** theoretical, based on limiting reagent

8. The Kemp elimination has been employed for the development of artificial enzymes for what type of reaction?
9. For the liquid-liquid extraction carried out during the work-up, which layer will be on top – ethyl acetate or ethanol/water? Explain.
10. What is the purpose of adding $MgSO_4$ in this experiment?
11. Create a flow chart outlining the steps and separations followed in this experime

1b. Green Chemistry. An Introduction

In a typical introductory organic chemistry laboratory course, a variety of hazardous and potentially toxic chemicals and solvents are employed. As a result, extensive safety measures are enforced in an attempt to prevent or at least limit exposure to these chemicals, e.g., delivery and transfer of volatile solvents in a fume hood, use of safety goggles, laboratory coats and latex/nitrile gloves, disposal of waste materials in a common area, typically a fume hood. Another way to limit or prevent exposure to such chemicals is to develop experimental procedures that use and generate fewer and/or smaller amounts of hazardous and toxic chemicals and solvents or, better yet, eliminate their use and generation entirely. This is the primary goal of "green" chemistry.

WHAT IS "GREEN" CHEMISTRY?

Green chemistry is defined as the "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances."[1] The term was coined in the 1990s by Prof. Paul Anastas, an organic chemist at Yale University, who is known widely as the "Father of Green Chemistry," and who in 2009 was appointed Assistant Administrator for the United States Office of Research and Development (ORD) and Science Advisor to the Environmental Protection Agency (EPA). Green chemistry is not a separate and distinct subdiscipline of chemistry. It is an overriding strategy that permeates all fields of chemistry and aims to implement criteria for development of sustainable chemical processes. These criteria are summarized by the *Twelve Principles of Green Chemistry*.[2]

1. Prevention. It is better to prevent waste than to treat or clean up waste after it is formed.

2. **Atom Economy**. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Synthesis**. Whenever practicable, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.

5. **Safer Solvents and Auxiliaries**. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.

6. **Design for Energy Efficiency**. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**. Unnecessary derivatization (use of blocking groups, protection/deprotection, and temporary modification of physical/chemical processes)

should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-Time Analysis for Pollution Prevention**. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

As you read through experimental procedures, you should keep these Principles in mind and, for each experiment, you should attempt to identify which Principles are being applied and, more importantly, which ones are not.

GREEN CHEMISTRY METRICS

When organic chemists carry out a chemical reaction, the success of the reaction is typically expressed in terms of the percentage yield of the isolated product.

$$\text{percentage yield} = \frac{\text{actual \# moles of product isolated}}{\text{theoretical \# moles of product possible}} \text{ X } 100$$

A reaction providing a 95% yield of desired product would be deemed a success whereas a reaction yielding 10% of the theoretical yield would be considered unacceptable and would require optimization.

The problem with using percentage yield as an indicator of reaction success is that it does not provide information about the economics or environmental effects of a reaction. How much did it cost to synthesize the desired compound? How much waste was generated during the synthesis? If 100 mg of a compound, representing a 98% yield, has been isolated, the reaction should not be considered a success if it cost $100,000 to do so, or if 100 kg of waste was generated during the synthesis. To provide a better indication of economics and environmental impact of a given reaction, a number of *green chemistry metrics* have been developed. Some of the more commons ones are presented below.

Atom Economy (AE) assesses how efficient a chemical reaction is by considering what proportion of atoms from all reactants gets incorporated into the structure of the final product. In an ideal chemical reaction (100% AE), all atoms from the reactants are incorporated into the final product. Note that this calculation does not take into account reactant stoichiometry or % yield. It also ignores solvent.

$$\text{atom economy (AE)} = \frac{\text{molar mass of the desired product}}{\Sigma \text{ molar masses of all reactants}} \text{ X } 100$$

Reaction Mass Efficiency (RME) is a better assessment of reaction efficiency in that it does take stoichiometry and chemical yield into account but, again, solvent is ignored.

$$\text{reaction mass efficiency (RME)} = \frac{\text{isolated mass of the desired product}}{\Sigma \text{ masses (used) of all reactants}} \text{ X } 100$$

Environmental (E) factor is quite different from **AE** and **RME** in that it focuses on the amount of waste generated rather than the efficiency of product formation. In addition, it considers the entire process – reaction plus product isolation and purification – not just the reaction itself. Because it incorporates yield, stoichiometry and solvent usage, **E-factor** is an excellent green chemistry metric. Note that, unlike **AE** and **RME**, the smaller the **E-factor** is, the greener the process is.

$$\text{environmental (E) factor} = \frac{\text{mass of waste produced}}{\text{mass of desired product isolated}}$$

Cost is an important factor in evaluating chemical processes, especially when they are done on an industrial scale. In the pharmaceutical industry, for example, a synthetic route to a drug is not considered viable if it is cost prohibitive.

$$\text{cost} = \frac{\text{price of required amounts of chemicals used}}{\text{mass of desired product isolated}}$$

You may be asked to keep these green chemistry metrics in mind as you consider the greenness of experiments you will carry out in organic chemistry.

2a. Description of the Experiment

The experiment was successfully implemented in a 3 h second-semester organic chemistry lab with a lab coordinator and two teaching assistants for groups of

approximately 45 students. In this context, the experiment was successfully carried out by approximately 280 students.

Benzisoxazole is combined with ethanol and water, followed by the addition of 2M aqueous sodium hydroxide. The reaction mixture is stirred at room temperature for 10 minutes and then treated dropwise with concentrated HCl until the pH is near 1. The reaction mixture is extracted three times with ethyl acetate and the combined organic extracts were dried using $MgSO_4$, filtered, and concentrated to dryness. If time permits, the crude product can be recrystallized from water prior to melting point determination.

Discussion

The experimental procedure was adapted from the original report of Casey et al[3] and conducted on a 0.25-g scale. In order to reduce the use of toxic solvents, ethyl acetate was used for the extraction instead of dichloromethane. During the development of the experiment, an 85% yield of the crude product was obtained. The ^{1}H NMR spectrum of the crude product (see SI Section 3) showed that it was quite pure, so recrystallization was not necessary. The melting point of the crude product was 90-95 °C, as compared to the reported values of 92-96 °C.[4] When the experiment was carried out by approximately 280 students working in pairs, yields reported by the students were highly variable, with an average yield of 62% and a median of 64%. Approximately half of the student groups reported yields between 60 and 90%. The purity of the crude product could be improved by recrystallization; however, this was not carried out due to time constraints. The bottleneck of the experiment was the use of the rotary evaporators:

with large numbers of students and a limited number of rotary evaporators, students had to wait to concentrate their organic extracts.

The Kemp elimination is a variation of an E2 elimination, and therefore provides an opportunity for students to apply their understanding of mechanistic principles to a reaction that they have not seen in lecture. Students were given a pre-lab assignment (see SI Section 1a) that provided reaction rate data that allowed them to determine the mechanism. Students were also asked to draw a detailed arrow-pushing mechanism for the reaction and to predict substituent effects on reaction rate as part of their pre-lab assignment, which was submitted at the beginning of the laboratory experiment.

The experiment is amenable to characterization by tlc analysis or spectroscopic methods such as nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy. IR spectroscopy in particular offers a convenient method for characterization because the product of the reaction has functional groups that can be identified by their distinct IR absorption bands. Specifically, O-H and C≡N stretching bands are observed in the product, but are absent in the reactant (see SI Section 3).

In our laboratory, students were not asked to perform tlc analysis or obtain infrared spectra due to time constraints. However, in their pre-lab assignment they were asked to explain how IR spectroscopy could be used to confirm product formation. In the post-lab assignment they were provided with a representative IR spectrum of the product and asked to identify some of the key absorption bands. If desired, an even greater emphasis on spectroscopic techniques for structure elucidation in this experiment could

be easily achieved. Benzisoxazole and salicylonitrile are readily distinguished by ^{1}H NMR. Students could be asked to explain how starting material and product could be distinguished by ^{1}H NMR or they could be given ^{1}H NMR spectra for the starting material and product and asked to match each compound with its spectrum.

This experiment also features mild reaction conditions in a benign solvent system (ethanol-water), making it a relatively 'green' experiment. Substitution of the dichloromethane for the less toxic ethyl acetate for extraction made the experiment greener and less hazardous to students. As part of the post-lab assignment, students were asked to identify the green aspects of the experiment as well as the sources of waste, and to calculate the efficiency, atom economy, E-factor and cost of the reaction.[5]

2b. Answer Key for Pre-Lab Questions

The Kemp Elimination in Water:

A Laboratory Experiment for Introductory Organic Chemistry

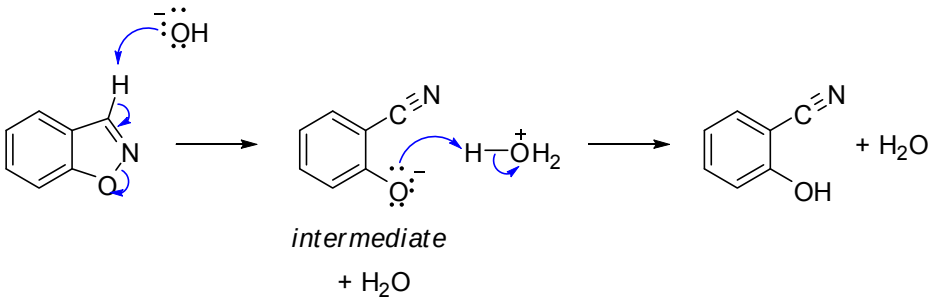
PRE-LAB ASSIGNMENT ANSWER KEY

1. Given the following information, state whether the reaction will follow an E1 or E2 mechanism and explain how you arrived at your answer.

Experiment	Result
concentration of benzisoxazole doubled	reaction rate doubles
concentration of NaOH doubled	reaction rate doubles
concentration of both SM and NaOH doubled	reaction rate quadruples

Answer: E2 because the rate depends on the concentration of both starting material and base

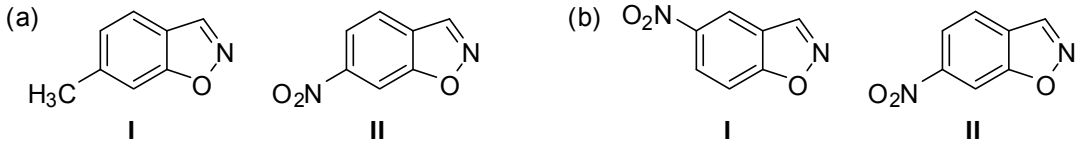
2. Draw an arrow-pushing mechanism for this transformation. Provide the structure of the intermediate indicated in the theory section of the experiment.



3. What is the melting point of salicylonitrile (a.k.a. *ortho*-cyanophenol)?

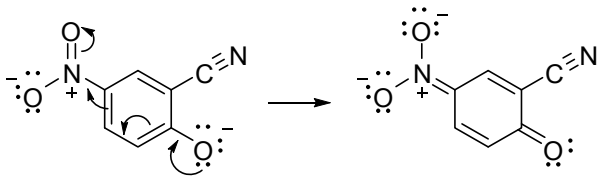
Answer: Anything close to 92-96 °C is acceptable.

4. For each of the following pairs, indicate which would react faster in a Kemp elimination reaction and explain why.



(a)II reacts faster than I because electron-withdrawing nitro group stabilizes (developing) negative charge on oxygen (CH_3 is e-donating and would destabilize it)

(b)I reacts faster than II because nitro group in I is able to stabilize negative charge on oxygen by resonance; nitro group in II can't do this.



5. Explain how IR spectroscopy could be used to confirm product formation. Refer to specific functional groups, provide characteristic IR band frequencies and indicate the type of vibration (i.e., stretching vs bending).

   Answer: OH group; stretching band; anything between 3200-3700 cm^{-1}

   CN group; stretching band; anything close to 2240-2280 cm^{-1}

6. Look up the MSDSs for benzisoxazole, salicylonitrile and ethyl acetate, and comment on the *human* toxicity of each.

   Answer:

   <u>benzisoxazole</u>: no data available; human toxicity not well-studied – student may mention possible irritation as indicated in experiment – ok

   <u>salicylonitrile</u>: essentially the same as for benzisoxazole

   <u>ethyl acetate</u>: may cause skin, eye, respiratory tract irritation, nausea/vomiting and CNS / behavior effects

7. Fill in the blanks in the following table (and bring a version of this table to the lab with you).

	MW (g/mol)	Density (g/mL)	Amount used (in g or mL)	#mmol	#equiv
benzisoxazole	119.04	*1.17*	0.25 g	2.10	1.0
NaOH	[conc]: 2M	*n/a*	7.5 mL	15.0	7.1
ethanol	46.04	0.789	1.5	*n/a*	*n/a*
water	18	1.0	1.5	*n/a*	*n/a*
salicylonitrile	119.04	*n/a*	* 0.25	* 2.10	*n/a*

* theoretical, based on limiting reagent

8. The Kemp elimination has been employed for the development of artificial enzymes for what type of reaction?

proton abstraction from carbon

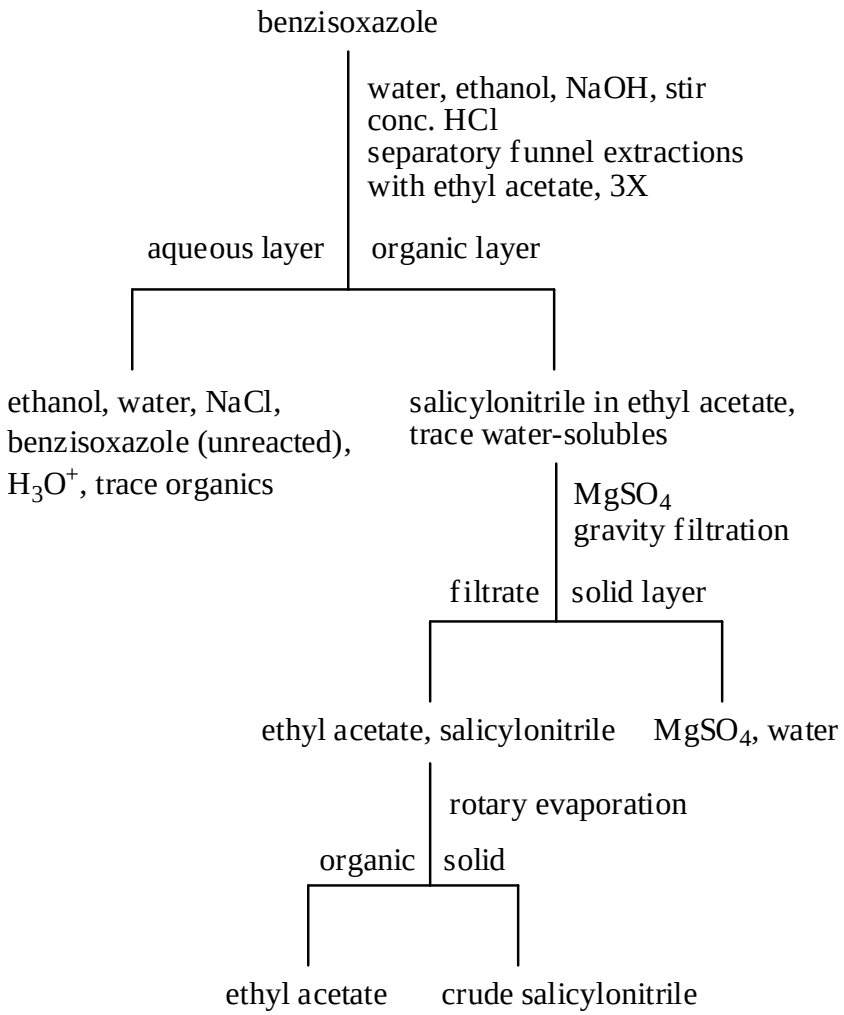
9. For the liquid-liquid extraction carried out in Part B, which layer will be on top – ethyl acetate or ethanol/water?

ethyl acetate as the density of ethyl acetate is 0.897 and the density of ethanol/water will be closer to 1.0

10. What is the purpose of adding $MgSO_4$ in step 4, part B of the experiment?

Magnesium sulfate is added to remove any traces of water from the ethyl acetate/product mixture.

11. Create a flow chart outlining the steps and separations followed in this experiment.



Total: 15pts

2c. Answer Key for Post-Lab Questions

The Kemp Elimination in Water:

A Laboratory Experiment for Introductory Organic Chemistry

POST-LAB ASSIGNMENT

1. What was green about this experiment?[6]

   Possible answers: (i) waste prevention (reaction) – only reaction byproducts are H_2O and NaCl (Green Chemistry Principle (GCP) #1); (ii) reasonably atom economical reaction (GCP#2); (iii) fairly innocuous reaction solvents (GCP#5); (iv) room temperature reaction (GCP#6); (v) no derivatizations (e.g., protections, deprotections) required (GCP#8)

2. What was not green?

   Possible answers: (i) waste generation (product isolation) – aqueous and organic wastes produced (GCP#1); (ii) use of ethyl acetate (GCP#5); (iii) no renewable feedstocks used (GCP#7); (iv) no catalysis – NaOH used stoichiometrically and in excess (GCP#9)

   Students shouldn't refer to GCPs 3 or 4 because there have been insufficient studies on human toxicity of reactants/reagents used or product formed.

3. How could the experiment be made greener?

   Possible answers: (i) ethyl acetate could be recycled (GCP#1); (ii) green chemistry metrics could be improved by reducing amount of NaOH used (GCP#1); (iii) reaction could be run in water only (but solubility might be an issue) (GCP#5)

4. Calculate the percentage yield for your product.

   [isolated mass of product/~0.25 g] x 100

5. Calculate the atom economy for the reaction.

   atom economy = [MW of product]/[MW of benzisoxazole + MW of NaOH] x 100

   = [119.04 g/mol]/[119.04 g/mol + 40.00 g/mol] x 100 = 75%

6. Calculate the reaction mass efficiency for the reaction.

   RME = [isolated mass desired product]/[mass benzisoxazole used + mass of NaOH used] x 100

   = [isolated mass desired product]/[~0.25 g + 0.6 g] x 100

7. Calculate the E-factor for the reaction. For simplification, 2M NaOH can be assumed to have a density of 1.0. Ignore the mass of concentrated HCl and $MgSO_4$ used since these were not determined accurately.

   E-factor = [mass of waste produced]/[mass of desired product isolated]

   = [mass of aqueous used + mass of ethanol used + mass ethyl acetate used]/[mass of desired product isolated]

   = [7.5 g + (1.5 mL)(0.789 g/mL) + (15 mL)(0.897 g/mL)]/[mass of desired product isolated

   = 22 g/mass of desired product

8. Calculate the cost/gram of product for the reaction given the following information: benzisoxazole ($19.42/g); ethanol ($15.28/L); ethyl acetate ($9.29/L) *Note: For this calculation, the cost of $MgSO_4$, HCl, NaOH and water may be ignored (all are dirt cheap!).* The product you synthesized can be purchased from the Sigma-Aldrich Chemical Company for $3.23/g. Is the reaction you performed cost effective? *Note: This question uses prices (Canadian $) that were in effect at the time of the experiment.*

   Cost = [price of required amounts of chemicals used]/[mass of desired product isolated]

   = [price benzisoxazole used + price ethanol used + price ethyl acetate used]/[mass of desired product isolated]

   = [(0.25 g)($19.42/g) + (1.5 mL)(1 L/1000 mL)($15.28/L) + (15 mL)(1 L/1000 mL) ($9.29/L)]/[mass of desired product isolated]

   = [$4.86 + $0.02 + $0.14]/ [mass of desired product isolated]

   = $5.02/[mass of desired product isolated]

   (0.5 pt – answers will vary)

   Note: actual amounts of chemicals used may vary

   Examples for quick checking of calculation:

   100% yld of product (0.25 g) → $20.08/g;

   80% yld of product (0.20 g) → $25.10/g;

   60% yld of product (0.15 g) → $33.47/g;

40% yld of product (0.10 g) → $50.20/g;

20% yld of product → (0.05 g) $100.40/g;

10% yld of product (0.025 g) → $200.80/g;

5% yld of product (0.125 g) → $401.60/g

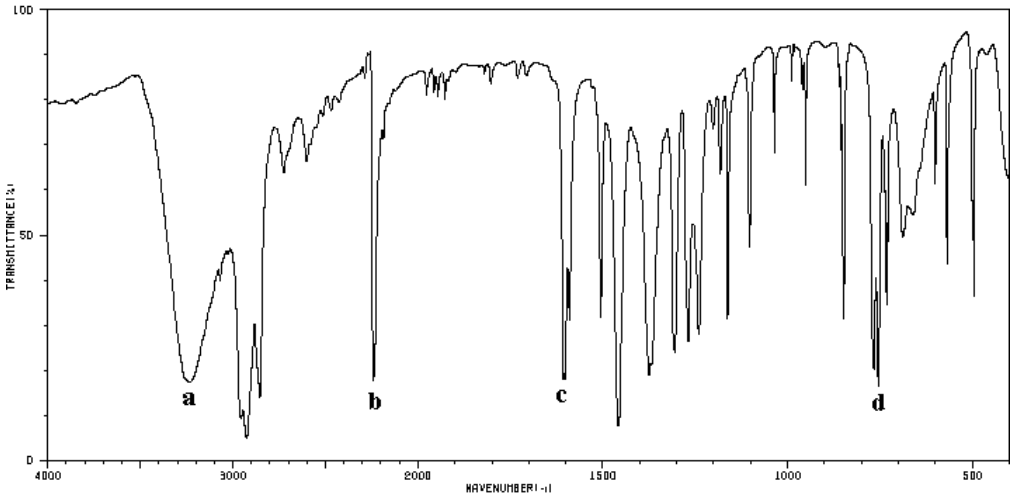
Even if 100% yield was attained, this reaction is <u>not</u> cost effective.

9. State the melting point range for your isolated product. Comment on the success (or lack thereof) of the experiment with reference to the percentage yield and the reported and observed melting point of your product.

   Melting point range (even if way off reported range of 92-96^{O}C)

   Statement on success (or lack thereof)

10. The following is the IR spectrum for salicylonitrile.[7] For bands a-d, indicate the functional group and vibration (stretch vs bend) responsible.



a – O-H stretch

b – C≡N stretch

c – C=C stretch

d – C-H bend (*ortho*-disubstituted benzene)

2d. TA Notes

Experiment A: Kemp Elimination in Water

The Lab

- monitor weighing of benzisoxazole which is a liquid; students should be able to transfer from bottle to Erlenmeyer flask using a disposable Pasteur pipette without a pipette bulb; same pipette should be used as much as possible to minimize loss; make sure they are not making a mess; make sure they are not taking too much time – 0.2-0.3 g is fine as long as they record and scale NaOH and ethanol/water accordingly
- monitor dispensing of ethanol, water and aq. NaOH to ensure syringes are not being mixed up
- monitor first few groups as they acidify the reaction mixture with HCl to see approximately how many drops are required to reach pH 1; will be useful for assisting other groups later
- monitor extractions; ethyl acetate should be dispensed in fume hood and transported to separatory funnel on bench; remind about frequent venting; question about which layer is which before mistakes are made
- monitor $MgSO_4$ dispensing; students tend to use way too much which results in product loss; as long as $MgSO_4$ is free flowing (not clumpy) when flask is swirled, they've added enough
- remind students to weigh the 25 mL round bottom flask before doing gravity filtration
- monitor rotovap use; assist as needed; it shouldn't take more than a few minutes to remove solvent; keep them moving!

Safety

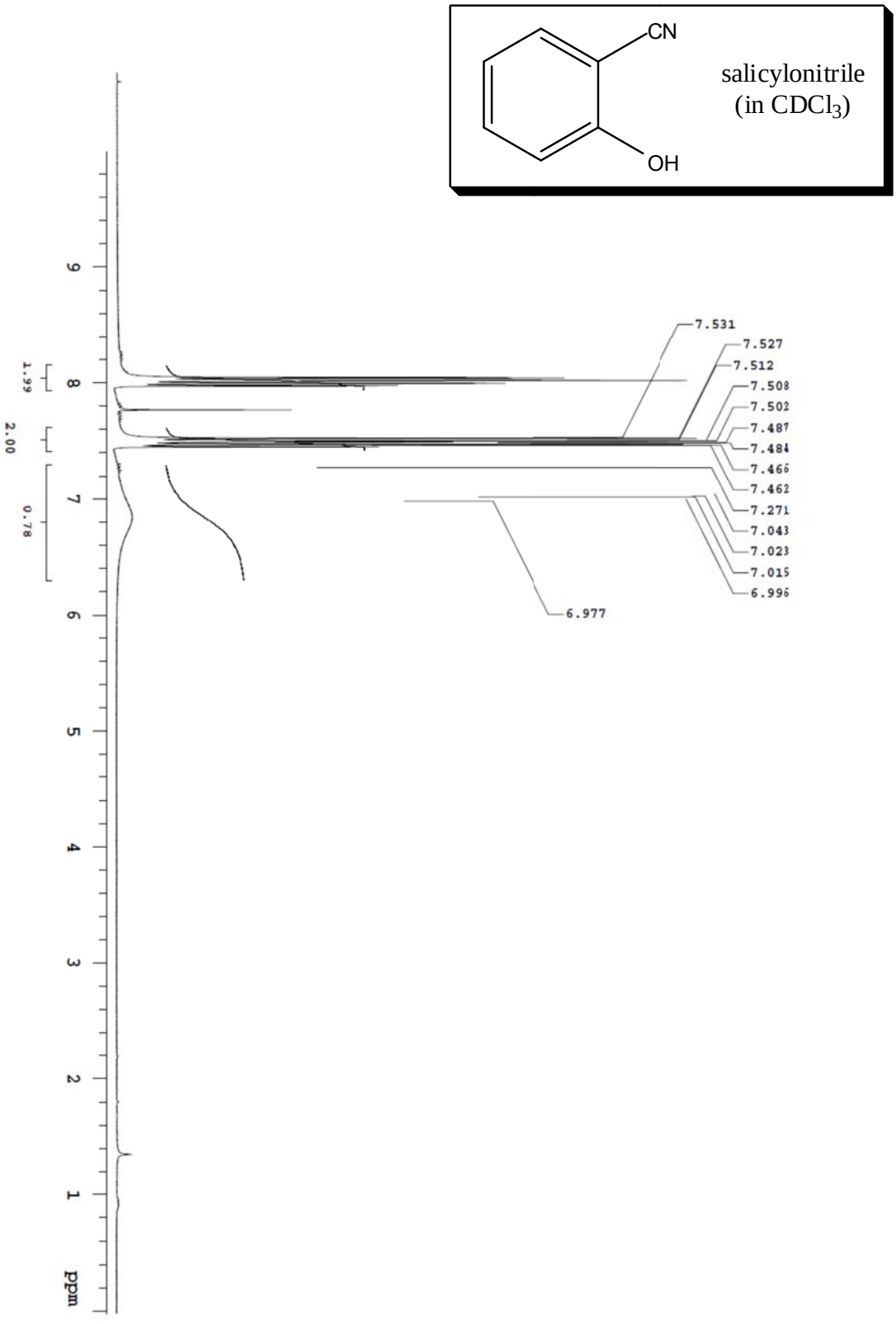
- benzisoxazole is a combustible liquid; no open flames (there shouldn't be anyway!); monitor for gloves and goggles while dispensing; might irritate skin and eyes; for skin exposure, wash with soap and water
- NaOH is corrosive and an irritant; gloves while dispensing; for contact with skin, rinse with plenty of water
- ethanol is a flammable liquid; no open flames; gloves while dispensing; don't dispense until needed
- HCl is corrosive and an irritant; gloves while dispensing; for contact with skin, rinse with plenty of water
- ethyl acetate is a flammable liquid; no open flames; irritant – gloves while dispensing and during extractions; do not dispense until needed; for skin contact, wash with soap and water
- salicylonitrile may be irritating to eyes, respiratory tract, and skin; lab coat, safety goggles, and gloves required while handling

Clean Up and Waste

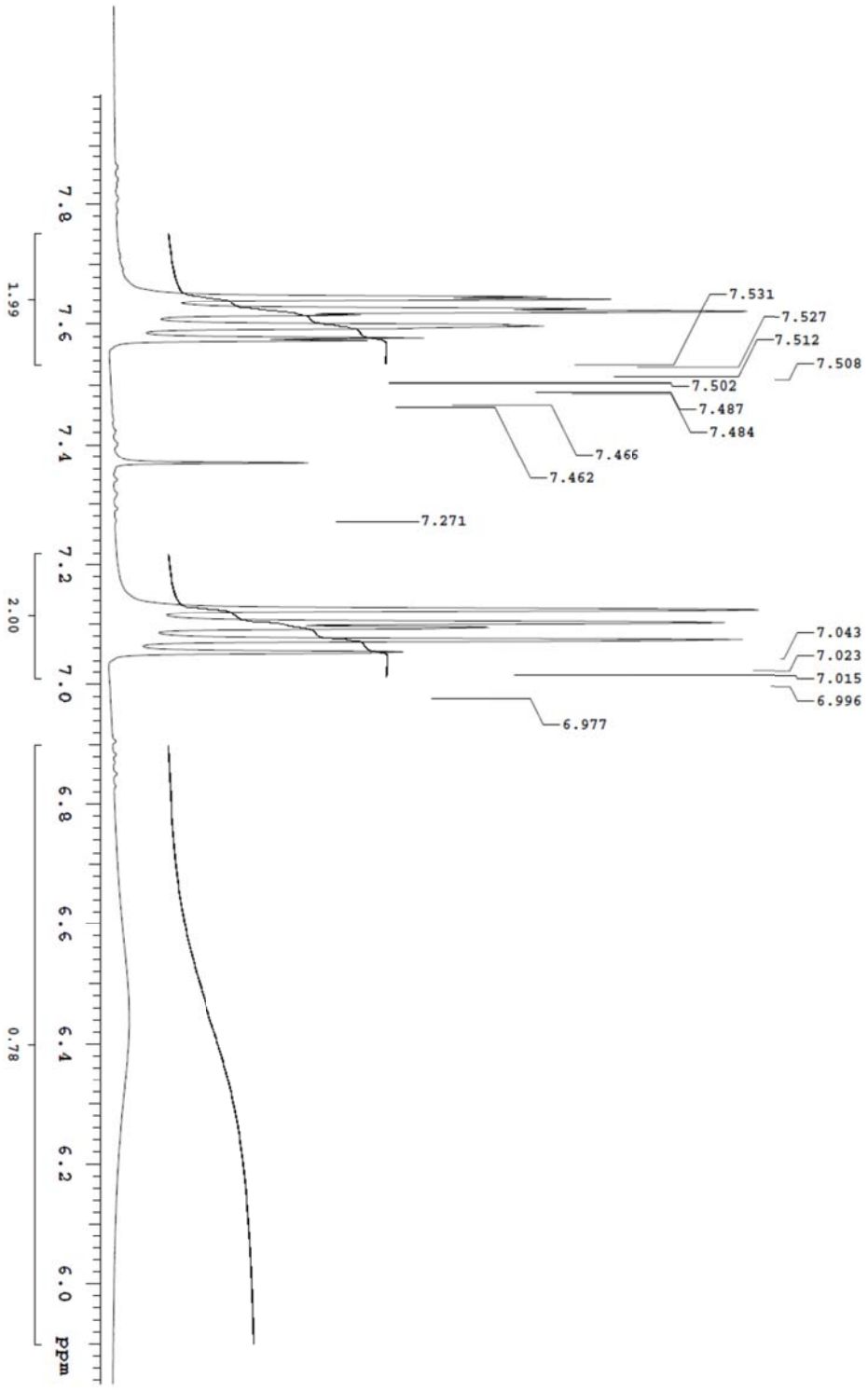
- don't let rotovap trap fill more than half-way; transfer ethyl acetate to organic waste container as needed
- transfer aqueous waste to appropriate waste container
- product, $MgSO_4$ and contaminated filter paper can be transferred to the appropriate waste containers
- all glassware should be rinsed with soap and water; round bottom flask with residual product may need to be rinsed with ethyl acetate prior to soap and water

3. Representative Spectroscopic Data

a.

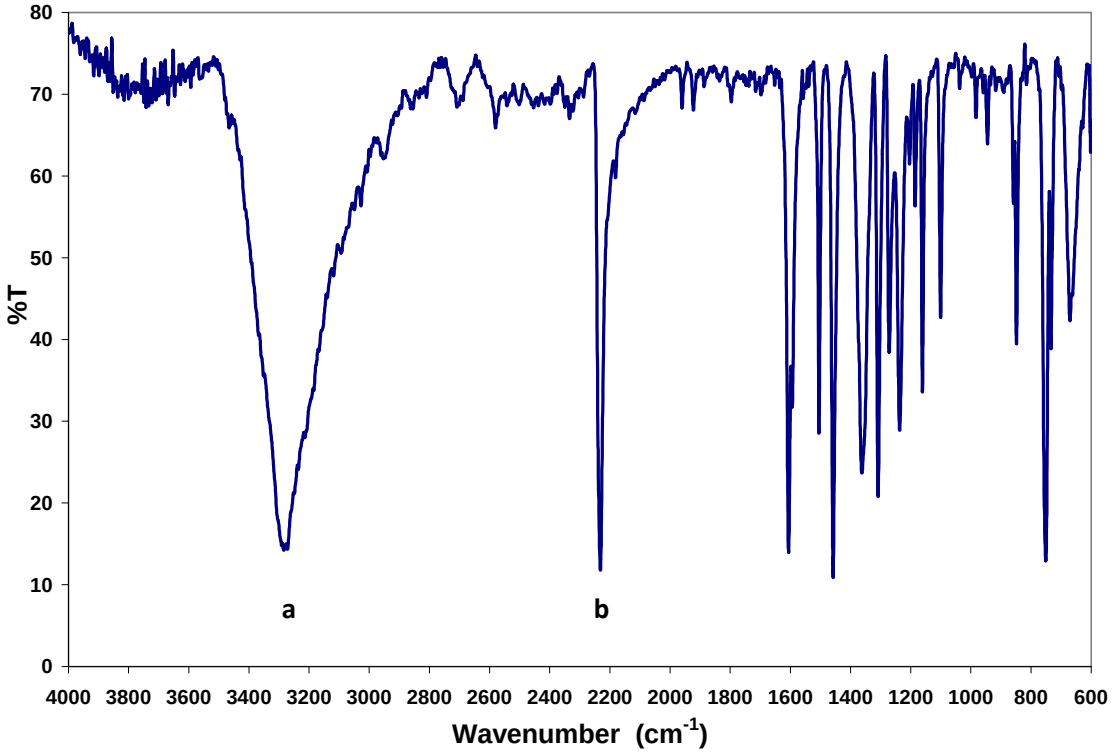


b.



Scheme SM 17.2.3.1. Representative ^{1}H NMR spectra for the crude product of the Kemp elimination obtained in $CDCl_3$ at 300 MHz.

c.

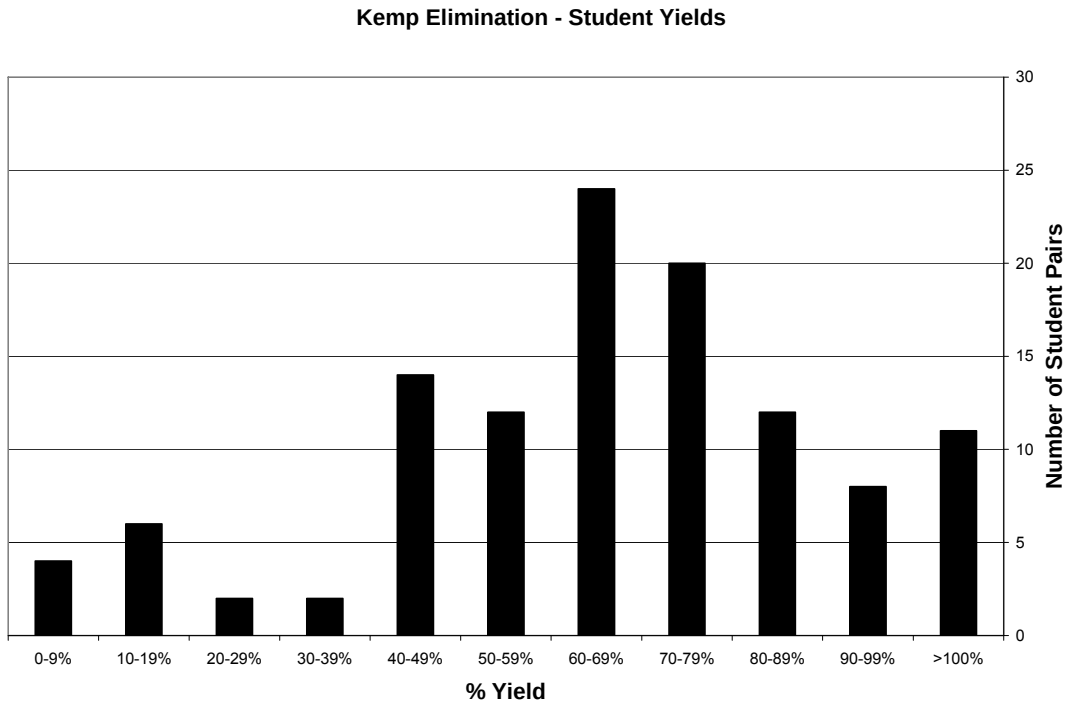


Scheme SM 17.2.3.2. Representative IR spectrum (KBr disc) of salicylonitrile, showing (a) OH stretching and (b) CN stretching bands.

4. Summary of Student Results

When the experiment was carried out by approximately 280 students working in pairs, yields reported by the students were highly variable, with an average yield of 62% and a

median of 64%. Approximately half of the student groups reported yields between 60 and 90%. A distribution of the reported yields is shown in **Scheme SM 17.2.**3.3.



Scheme SM 17.2.3.3. Distribution of Yields Reported by Student Groups

5. CAS Registry Numbers

- Benzisoxazole (C_7H_5NO): [271-95-4]
- Sodium Hydroxide (NaOH): [1310-73-2]
- Magnesium Sulfate ($MgSO_4$): [7487-88-9]
- Ethanol (C_2H_5OH): [64-17-5]
- Ethyl Acetate ($C_4H_8O_2$): [141-78-6]

Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*

[1]. (a) Anastas, P. T.; Warner, J. C. in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**; (b) Horvath, I.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2167; (c) Anastas, P. T.; Williamson, T. C. in *Green Chemistry: Designing Chemistry for the Environment*, American Chemical Series Books, Washington, DC, **1996**, pp. 1-20.

[2]. Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301-312.

[3] Casey, M. L.; Kemp, D. S.; Paul, K. G.; Cox, D. D. *J. Org. Chem.* **1973**, *38*, 2294-2301.

[4] Petridou-Fischer, J.; Papadopoulos, E. P. *J. Hetercyclic. Chem.* **1983**, *20*, 1159-67.

[5] Lapkin, A.; Constable, D. (**2008**) *Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes*; Wiley: Ames (Iowa, pp. 69-199)

[6] For Questions 1-3, GCP refers to the 12 Principles of Green Chemistry. See Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301-312.

[7] Spectral Database for Organic Compounds: http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi.

Synthesis of Veratronitrile

Supplementary Material

This work was introduced in the 1980's 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 could study the reactivity of the carbonyl group and analyze the different synthetic routes for this compound available in literature[1-2]. The main purpose of this work is illustrating an indirect conversion of an aromatic aldehyde into nitrile by dehydration of the correspondent oxime. In addition, the experiment exposes the student cohort to a wide range of laboratory skills. The experimental procedure is very easy although time management problems can arise due to the use of a CO_2 gas cylinder by several students at the same time.

Additional notes on the preparation of veratraldoxime:

Reaction set up for veratraldoxime is shown in figure **SM 17.3.1**. 12 hours to aldoxime precipitation.

SM 17.3.1 – Reaction set up for veratraldoxime

It takes about 15 to 30 minutes to saturate the solution with CO_2 that acts as anti-solvent inducing crystallization[3]. Session 2 can be avoided if students carry out the vacuum filtration before next session. This compound is obtained in 70-80 % yield (96%[4]). Melting points are between 90 and 94ºC with a melting point range never superior to 1ºC (94-95ºC[5]).

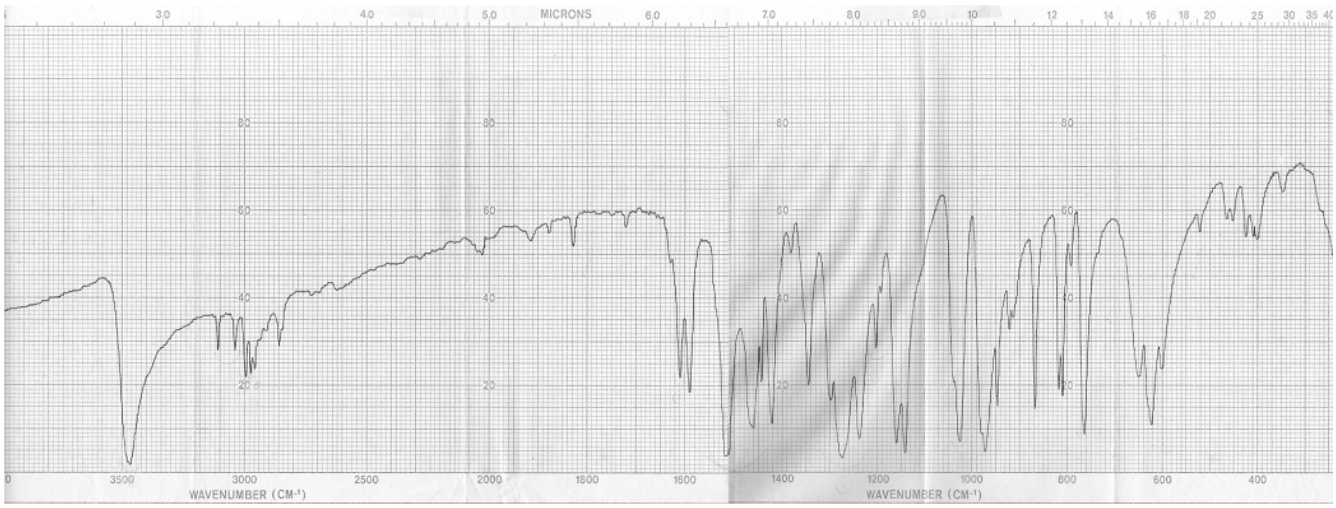
Additional notes on the preparation of veratronitrile:

The dehydration of the oxime must be performed with freshly distilled acetic anhydride. In the original experimental procedure, a flame was used to initiate the reaction and maintain the reflux, it was found later that a water bath can be used instead (Figure **SM 17.3.2**). The final product has a yellowish color (unlike described in literature) but it becomes colorless when washed with water until the filtrate presents neutral pH. Yield is 70-80% (73.5%[4]). The melting point is between 66 and 67ºC, with a melting point range never higher than 2ºC (67.8ºC[6]).

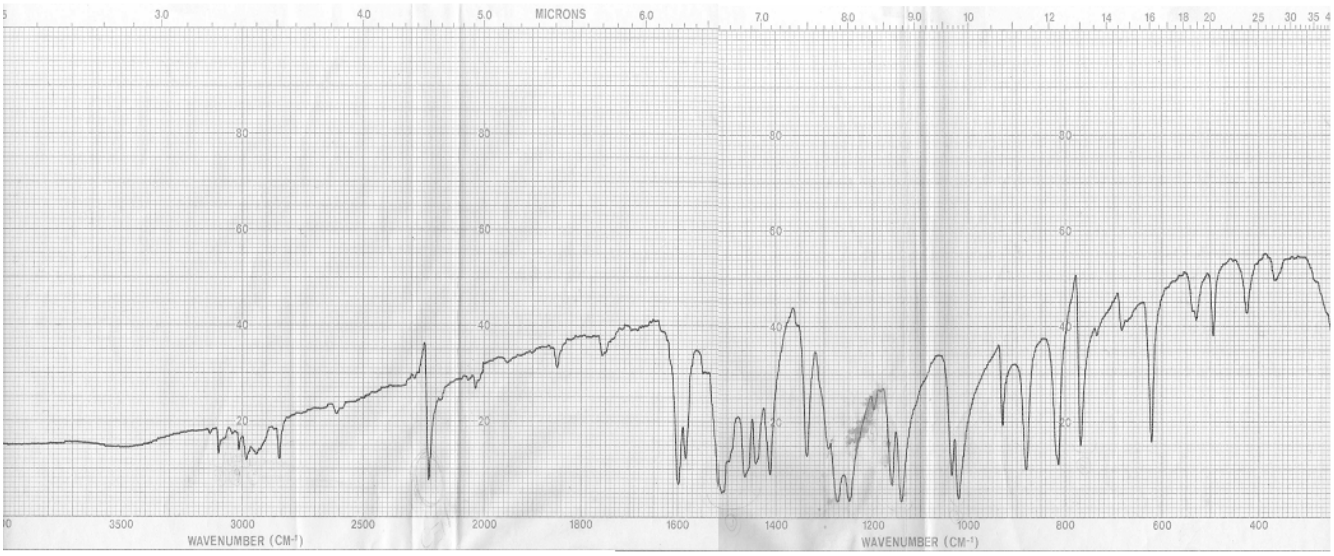
SM 17.3.2 – Reaction set up for veratronitrile

IR spectra:

Students easily identify a strong band due to O-H group at 3480 cm^{-1} and a C=N absorption band at 1620 cm^{-1} for veratraldoxime (Figure **SM 17.3.3**). The typical C≡N absorption band and at 2230 cm^{-1} is easily observed for veratronitrile (Figure **SM 17.3.4**). The IR spectrum of veratronitrile is also available on SDBS[7] under number 13075.



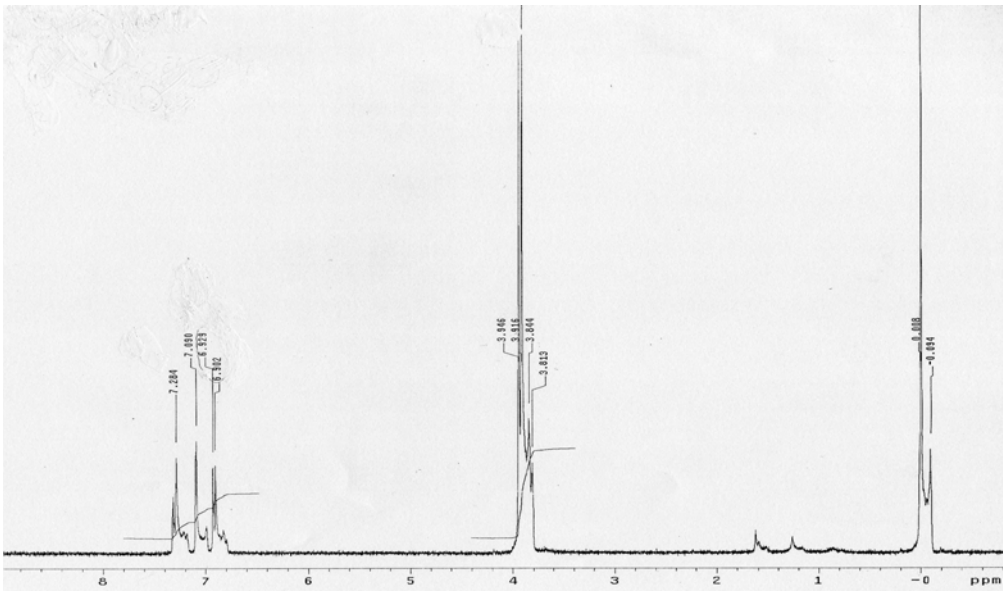
SM 17.3.3: IR (KBr) of veratraldoxime



SM 17.3.4: IR (KBr) of veratronitrile

NMR spectra:

Veratraldoxime ^{1}H NMR spectrum was not recorded but it can be found in literature[8]. Veratronitrile ^{1}H NMR spectrum (Figure **SM 17.3.5**) was obtained with student's samples and present some impurities and low resolution; nevertheless students easily identify the two singlets corresponding to strongly deshielded CH_3 protons.



SM 17.3.5: ^{1}H RMN ($CDCl_3$) of veratronitrile

^{1}H and ^{13}C NMR spectra for veratronitrile are available on SDBS[7] under number 13075.

[1] S. N. Karmarkar, S. L. Kelkar, M. S. Wadia, *Synthesis Comm.*, 1985, 510.
[2] A. Arques, P. Molina, A. Soler, *Synthesis Comm.*, 1980, 703.
[3] F. M. Kerton, *Alternative Solvents for Green Chemistry*, RSC Publishing, 2009, 191.
[4] A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, 5th ed. 1989, 1084.
[5] *Dictionary of Organic Compounds*, Chapman and Hall, 5th ed., 2, 2043.
[6] *Handbook of Chemistry and Physics*, CRC Press, 1st Student ed., C-546.
[7] http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi, accessed in Oct 2015.
[8] K. Ramanjaneyulu, P. S. Rao, T. Rambabu, K. Jayarao, C. B. T. S. Devi, B. V. Rao, *Der Pharma Chemica*, 2012, **4**, 473.

Synthesis of Levulinic Acid from Sucrose

João P. Telo[a]

Supplementary Material

This experiment was performed in our laboratory for several years with students from the graduation in Chemistry and Chemical Engineering. The work was done by only one group per year (all the groups had different experiments), but it can be adapted to a lab session with up to 5 groups. The procedure used here is essentially that from Organic Synthesis (ref. 5) with some modifications. Evaporation of the aqueous filtrate overnight in a steam bath, as suggested in the original work, seemed unpractical and was replaced by rotary evaporation. The result is a viscous solution that, in our hands, never crystallized. Extraction with ethyl ether is not very efficient, and the viscous residue should be well shaken with the ether. The use of a soxhlet continuous extraction would be ideal, but the absence of a solid prevented its use. The boiling point of pure Levulinic Acid at a given pressure can be obtained by the formula $\log P = - 3888/T_{eb} + 10.3815$, where P is the pressure in mmHg and T_{eb} the boiling point in K.[1] Note the use of common logarithms (base 10). Early fractions of the distillation consist mainly in water and some by-products of the reaction.

Figure SM 17.4.1 Example of the reaction apparatus for the fractional vacuum distillation.

The average yield is in the range 11%-17%, somewhat lower than the one reported in reference 5 (21%-22%) The melting point of the pure product is mp=37º C, but, as is usual for low-melting point substances, is very affected by impurities. Some samples obtained never crystallized, while others showed melting points close to the one of the pure product. The refraction index of the pure product is n_D=1.4396, and the ones obtained by the students are in the rage 1.4326-1.4390.

Spectroscopic data:

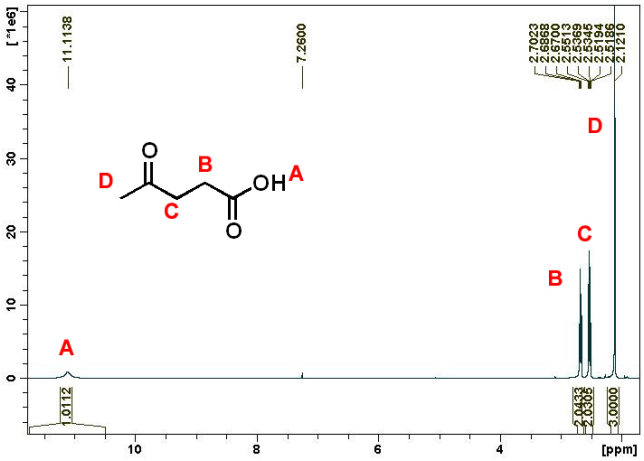


Figure SM 17.4.2 - ^{1}H RMN spectrum ($CDCl_3$) of Levulinic acid (400 MHz)

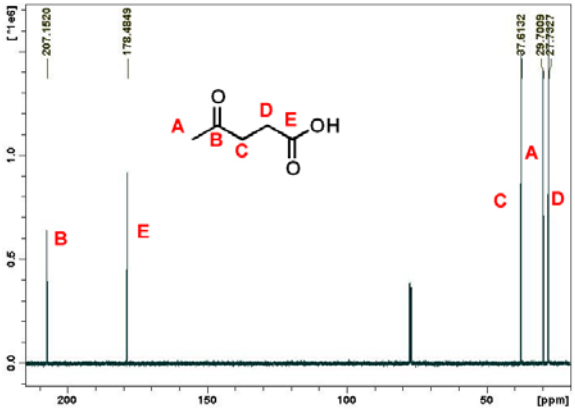


Figura SM 17.4.3 - ^{13}C RMN spectrum ($CDCl_3$) of Levulinic acid. (400 MHz)

[1] R. Weast, CRC Handbook of Chemistry and Physics, 1st Student Ed. **1988** Florida.

Synthesis of 1-(4-bromophenyl)-1H-pyrrole by Clausson-Kaas reaction

Supplementary Material

1. Experiment notes

2. Mechanism for the synthesis of 1-(4-bromophenyl)-1-H-pyrrole by Clausson-Kaas synthesis

3. Figures

3.1 Photo for the apparatus used in session 1

3.2 Photo of the TLC plate with the reagents and the product

3.3 ^{1}H NMR spectrum of the product

1. Experiment notes

The aim of this work is the synthesis of 1-(4-bromophenyl)-1-H-pyrrole using simple experimental techniques and commercially available reagents. The synthesis of these compounds involves the classical Clauson-Kass pyrrole synthesis.[1]

This experiment was previously developed in the research group of the author and was performed later by students of the 3rd year of the undergraduate Chemistry degree course at the University of Minho. Therefore, this experiment is appropriate for undergraduate Chemistry students who have previously acquired some skills with the experimental techniques involved ~~used~~ as well some knowledge regarding the theoretical concepts presented (synthesis, reactivity and spectroscopic data interpretation).

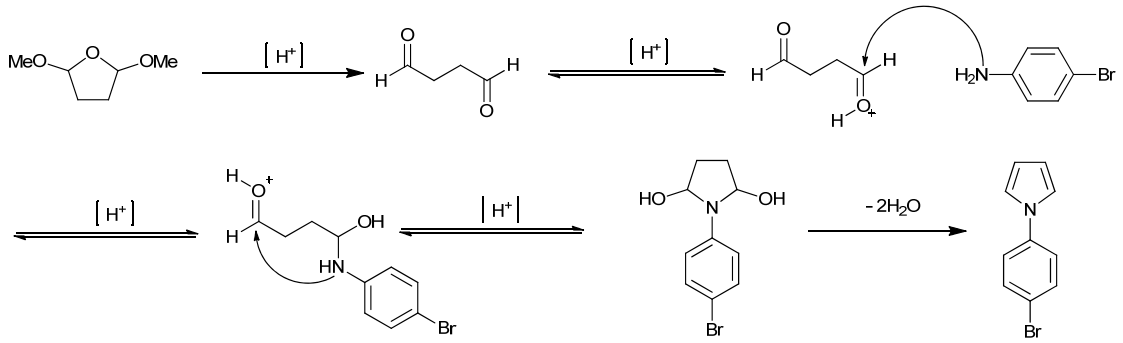
Laboratory sessions 1 and 2: Synthesis and purification of 1-(4-bromophenyl)-1H-pyrrole

The crude 1-(4-bromophenyl)-1H-pyrrole obtained in session 1 is purified by precipitation from dichloromethane/hexane. The crude product obtained after evaporation of the solvent should be dissolved in the smallest possible amount portion of dichloromethane followed by addition of hexane in order to precipitate. The pure pyrrole derivative was isolated in 93% yield, as a beige solid[2] (m.p. 96-97 ºC).

The range of yields obtained earlier by students of the 3rd year of the degree course in Chemistry of University of Minho was 82-87%.

2. Mechanism

The preparation of the pyrrole derivative occurs by the Clausson-Kaas synthesis which converts the primary amino group into a pyrrole group and involves the acid-catalyzed, cyclization between an aromatic (or primary aliphatic) amine and 2,5-dimethoxy-tetrahydrofuran.[3] Scheme SM 17.5.1 shows a proposal for the plausible mechanism where the acid conditions allows the hydrolysis of the tetrahydrofuran ring and posterior cyclization with the amine group to form the pyrrole ring.



Scheme SM 17.5.1. Proposed mechanism of Clausson-Kaas pyrrole synthesis.

References

[1] N. E. N. Clauson-Kaas, *Acta Chem. Scand.*, 1953, **6**, 867.

[2] M. C. R. Castro, M. Belsley, A. M. C. Fonseca M. M. M. Raposo, *Tetrahedron*, 2012, **68**, 8147.

[3] L. Kurti, B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, S. Diego, USA, 2005, p 328.

3. Figures

3.1 Photo for the apparatus used in session 1

Figure SM 17.5.1. Photo of the apparatus used in laboratory session 1.

3.2 Photos of the TLC plate with the reagents and the product

A= 2,5-dimethoxytetradihydrofuran; R_f=0.32

B=4-bromoaniline; R_f=0.60

C=1-(4-bromophenyl)-1*H*-pyrrole; R_f=0.88

Figure SM 17.5.2. Photo of the TLC plate with the acetal (A) and the aniline (B) precursors and the pure pyrrole product (C) obtained after precipitation. Left: before elution and right after elution (eluent: dichloromethane: petroleum ether 40-60; 1:1) laboratory session 2.

3.3 ^{1}H, NMR spectrum of the product

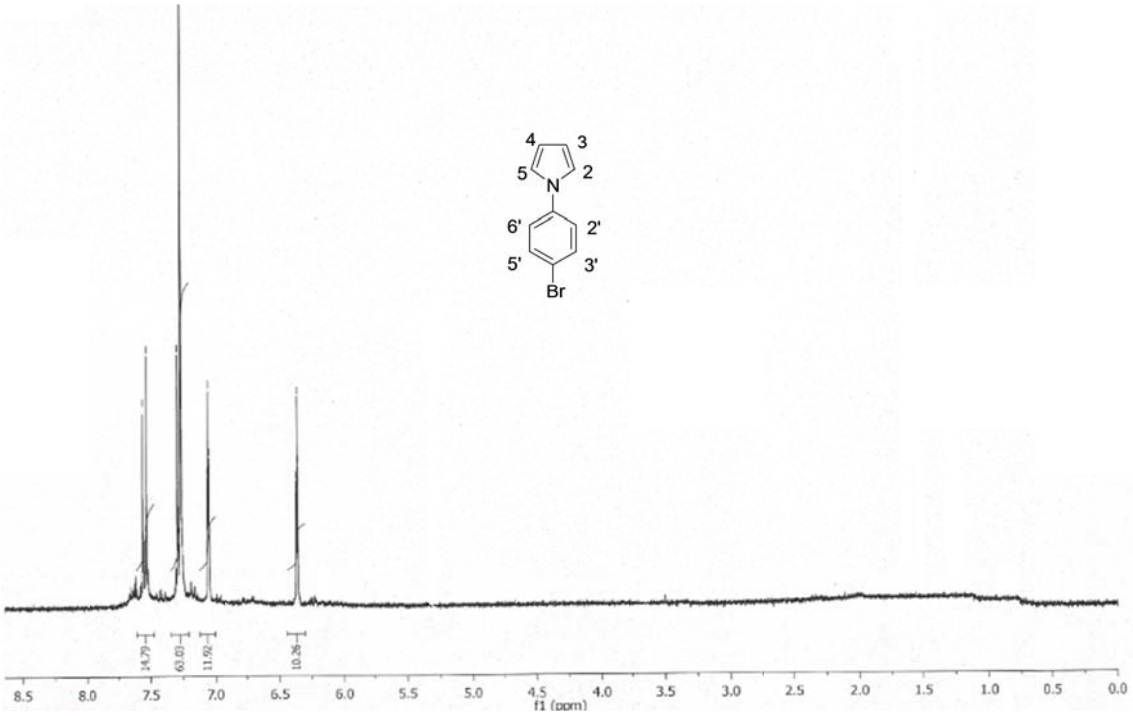


Figure SM 17.5.3. ^{1}H NMR spectrum of 1-(4-bromophenyl)-1H-pyrrole in $CDCl_3$ obtained using a Bruker Avance III spectrometer operating at 400 MHz at 25 ºC.

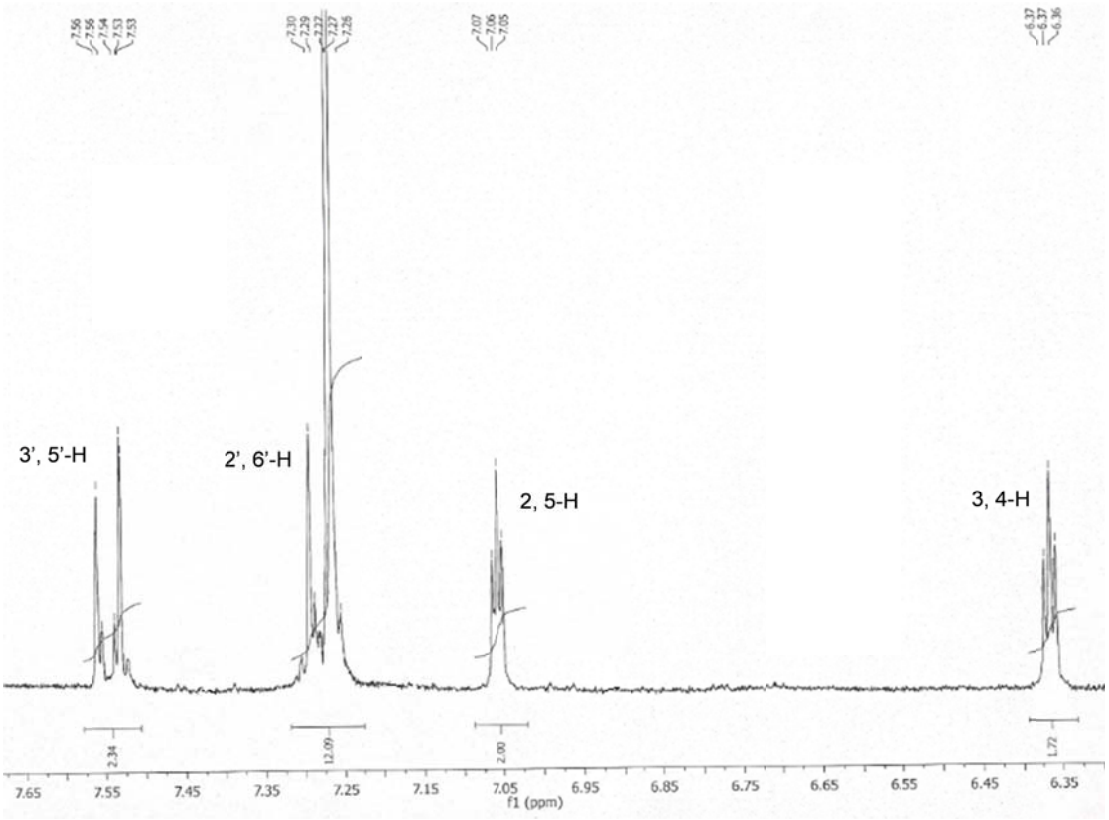


Figure SM 17.5.4. Expansion of the aromatic zone of the ^{1}H NMR spectrum of 1-(4-bromophenyl)-1H-pyrrole in $CDCl_3$.

Synthesis of the manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin

Supplementary Material

Experimental notes

Notes 1

Figures

Figure SM 17.6.1 – Structure of manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin [Mn(TDCPP)Cl] 2
Figure SM 17.6.2 - Reaction apparatus 2
Figure SM 17.6.3 - Monitoring the reaction progress by TLC after one hour (right). A new red spot of the manganese(III) complex can be observed at the base, in contrast with the brown spot (left control) of the free-base porphyrin in the top of the TLC plate, using CH_2Cl_2 as eluent. 3
Figure SM 17.6.4 – Typical UV-Vis spectra of 5,10,15,20-tetrakis(2,6-dichlorophenyl) porphyrin (above) and manganese(III) complex of 5,10,15,20-tetrakis (2,6-dichlorophenyl)porphyrin (below). 4

Notes:

In this work, which is planned for two sessions of 3 hours, students (in groups of two) will synthesise the manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin [Mn(TDCPP)Cl]. The manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin (Figure SM 17.6.1) will be synthesised by a methodology consisting in the reaction of the 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin with manganese(II) chloride in dimethylformamide (DMF) and pyridine at 153 °C (Figure SM 17.6.2).

The reaction can be followed by thin layer chromatography (TLC). At the end of the reaction, a new red spot of manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin can be observed at the base, in contrast with the brown spot of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin at the top of the TLC plate, using CH_2Cl_2 as eluent (Figure SM 17.6.3).

The reaction can also be monitored by UV-Vis spectrophotometry. By comparison of the UV-Vis spectrum of the free-base porphyrin (Figure SM 17.6.4), the manganese(III) complex shows a Soret band shift to a higher wavelength (λ_{max}= 478 nm) and the disappearance of two Q bands of the free-base macrocycle, that confirms the presence of the manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin. The transition band of manganese at λ_{max} = 371 nm can also be observed (Figure SM 17.6.4).

The reaction normally takes two hours to be complete.

The DMF and the pyridine are removed in the rotary evaporator and the residue is dissolved in dichloromethane and washed with an aqueous saturated sodium chloride solution to ensure that the chloride is the counter anion.

The metalloporphyrin complex is crystallized in a mixture of dichloromethane and hexane.

This experiment is intended for a fifth semester organic-inorganic-analytical-physical chemistry laboratory of the BSc Chemistry course. Normally, students who enrol in this laboratory have already attended two semesters of organic chemistry, one semester of a practical organic chemistry course, one semester of inorganic chemistry and one semester of a practical inorganic chemistry course.

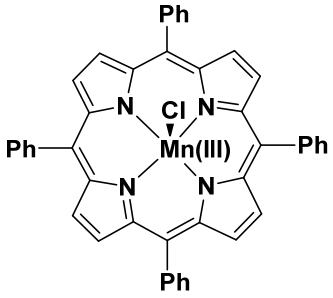


Figure SM 17.6.**1 –** Structure of manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin [Mn(TDCPP)Cl] (Ph = 2,6-diclorophenyl).

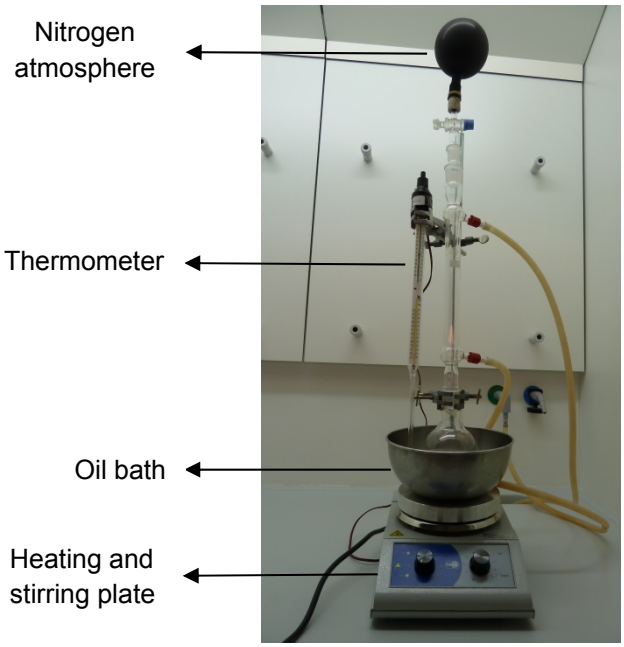


Figure SM 17.6.**2 -** Reaction apparatus.

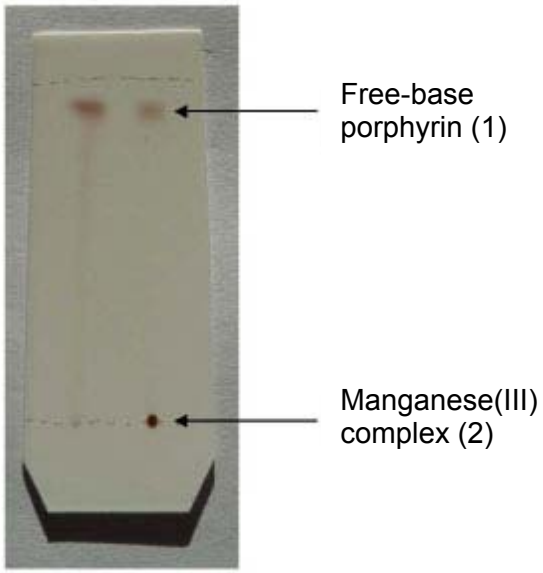


Figure SM 17.6.**3** - Monitoring the reaction progress by TLC after one hour (right). A new red spot of the manganese(III) complex can be observed at the base, in contrast with the brown spot (left control) of the free-base porphyrin in the top of the TLC plate, using CH_2Cl_2 as eluent.

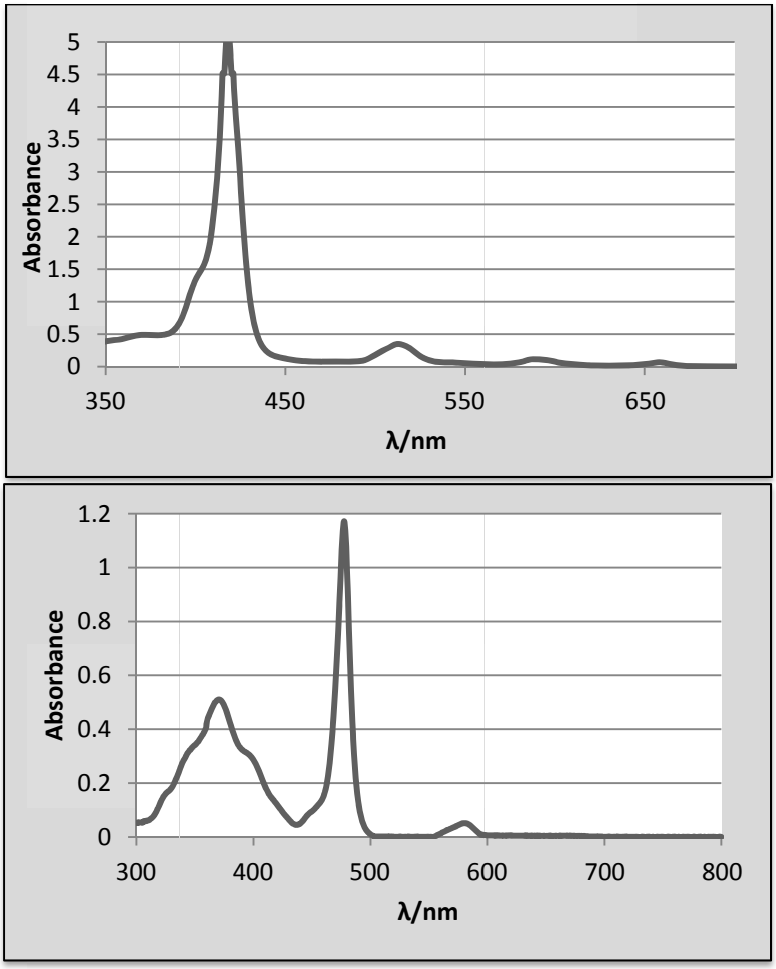


Figure SM 17.6.**4** – Typical UV-Vis spectra of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin (above) and manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin (below).

Synthesis of 1,3-Dithienylbenzo[c]thiophene

Supplementary Material

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Experiment Notes 2

Synthesis of S,S-Di(pyridin-2-yl)benzene-1,2-bis(carbothioate) (1) 3

Synthesis of 1,2-Phenylenebis(thiophen-2-yl-methanone) (2) 4

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^{1}H NMR spectrum for 1,3-Dithienylbenzo[z]thiophene (**3**) 11

Expansion of the ^{1}H NMR spectrum for 1,3-Dithienylbenzo[z]thiophene (**3**) 12

^{13}C NMR spectrum for 1,3-Dithienylbenzo[z]thiophene (**3**) 13

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Experiment Notes

This goal of this experiment is the synthesis of 1,3-Dithienylbenzo[c]thiophene starting from phthaloyl dichloride. The experiment procedure is presented in a succession of steps that will make it easier for a student to understand the overall synthetic route. Focus on the importance of leaving groups in addition/substitution reactions, namely in those involving Grignard reagents, are showed in Steps 1 and 2. In these steps, students are requested to explain the reactivity of acyl chlorides *vs.* thioesters in the formation of the *ortho*-diketone (**2**) (*vide infra* – ***The importance of the leaving group***). S-Heterocyclization, by the use of Lawesson's reagent is the ultimate goal of this experiment.

This procedure is suitable for students with previous laboratory experience in organic chemistry that feel comfortable with unitary operations. Previous know-how on working under inert atmosphere is needed to execute this experiment and to ensure high yields. One MSc. Student and one PhD. student assessed the reproducibility of all the reported experiments in the *Faculdade de Ciências*, *Universidade de Lisboa*. The experiment yields and NMR spectra were measured by students and ranges are listed in the **Table SM 17.7.1**.

Table SM 17.7.1 – Yield range of each synthetic step.

Product	Yield Range (%)
S,S-Di(pyridin-2-yl)benzene-1,2-bis(carbothioate) (**1**)	63 - 80
1,2-Phenylenebis(thiophen-2-yl-methanone) (**2**)	46 - 60
1,3-Dithienylbenzo[z]thiophene (**3**)	30 - 55

These reactions can be conducted at higher scale by doubling the amount of reactants and solvents and increasing the reflux time of the Grignard reaction and the S-heterocyclization reaction for an additional to 2 hours, each.

THF and triethylamine should be previously dried under standard conditions.[12] For more details, please *vide infra* the extended individual notes for each synthetic step. NMR spectra were obtained in a 400 MHz Brucker Avance spectrometer using $(CD_3)_2CO$ as solvent.

Notes for the synthesis of S,S-Di(pyridin-2-yl)benzene-1,2-bis(carbothioate) (1)

The reaction should be conducted in a very well ventilated fume hood since the use of hydrochloric acid and phthaloyl dichloride can be harmful. Freshly dried THF as reaction solvent is preferable because phthaloyl dichloride, as any acyl chloride, can hydrolyse in the presence of water leading to a significant decrease in the reaction yield. This step can be by-passed if a new anhydrous reagent bottle is available and can be opened for the experiment.

The addition of the phthaloyl dichloride solution to the 2-mercaptopyridine solution results in the formation of a huge amount of precipitate, and the use of a big magnetic stir in the reaction flask is of crucial importance. The quenching of the reaction with hydrochloric acid solution has to be done ***immediately*** after the addition of the 2-mercaptopyridine solution and with vigorous stirring, to prevent the formation of the thermodynamically favoured lactone. Authors recommend that only one student perform this operation in case they work in pairs or in groups, as showed in **Figure SM 17.7.1.**

Figure SM 17.7.1 – Student performing the addition of the phthaloyl dichloride solution to the 2-mercaptopyridine solution, followed by immediate quenching with hydrochloric acid.

Extraction of the product can be performed either using dichloromethane or chloroform. The authors recommend the use of chloroform since lower volumes are needed and the extraction is more efficient, leading to higher yields. After the extraction, the product can be precipitated by dissolving the resulting solid in the minimum amount of dichloromethane and adding twice the amount of diethyl ether. Full precipitation should occur within 30 minutes if dichloromethane is used. Chloroform lead to slightly higher precipitation times. If a fairly good amount of product is not precipitated in the first 15/20 minutes, forcing the precipitation by slowly stirring the flask can be helpful. The precipitation step can be avoided if a good product (white crystalline powder) is obtained after solvent removal in the rotatory evaporator. In this case, washing the resulting solid twice with diethyl ether is sufficient.

Once crystalized and properly dried, the product should be kept under nitrogen atmosphere since it quickly hydrolyses in the presence of moisture. The hydrolysis of the product is easily observed by an yellowish/greenish coloration on the white solid. Purification can be performed by re-dissolving the product in dichloromethane and washing the organic phase with sodium hydroxide followed by water, and recrystallization with the solvents indicated in the experimental procedure.

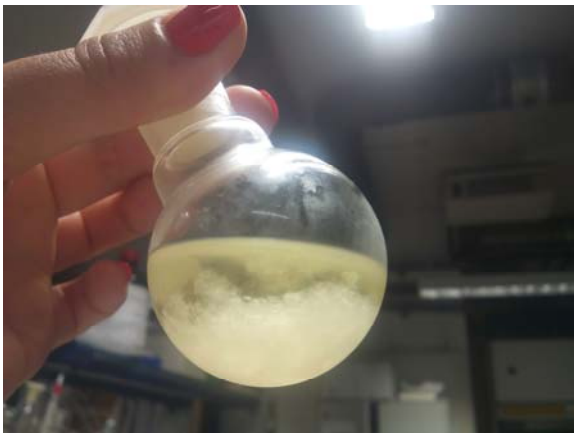


Figure SM 17.7.2 – Aspect of product (**1**) after crystallization.

Notes for synthesis of 1,2-Phenylenebis(thiophen-2-yl-methanone) (2)

This Grignard synthesis is preferably performed with standard *Schlenk* techniques. However, the use of properly dried glassware, purged with nitrogen can be sufficient for an overall good yield of this reaction. Nonetheless, the use of freshly dried and degassed THF is mandatory. Degassing of THF can be done either by bubbling nitrogen gas or by performing three to five vacuum/nitrogen cycles in a vacuum line.

The addition of 2-bromotiophene to the suspension of magnesium should be done at room temperature and not under reflux conditions. This reaction is exothermic and a gentle heating of the solution if observed in the first 30 minutes. Afterwards, heating is necessary for completion. The reaction can be monitored by observing the dissolution of the magnesium. If a small amount of metallic magnesium is still present by the end of the reflux time, students can add 15 mL of dried THF followed by 2-3 drops of 2-bromothiophene. The solution should be refluxed again for additional 20-30 minutes until full dissolution is obtained. However, it is often observed that after the reflux time a minimal amount of magnesium persists and presents a dark opaque blackish colour (**Figure SM 17.7.3**). In this case reaction should be considered as terminated. Filtration of these impurities is not necessary since it will not affect further reactions.

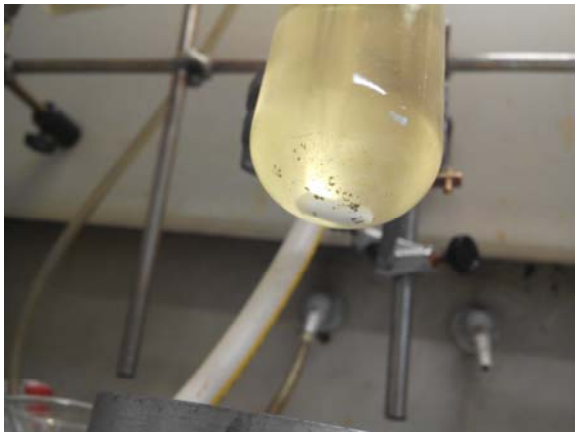


Figure SM 17.7.3 – Unreacted magnesium turnings.

The transfer of the Grignard reagent solution to the flask containing S,S-Di(pyridin-2-yl)benzene-1,2-bis(carbothioate) should be done in the absence of moisture under nitrogen atmosphere. If a cannula is not available, a well-dried glass syringe can be used to transfer small portions at a time (**Figure SM 17.7.4**). Stirring of the final solution at low temperature is also mandatory, especially in the first minutes of reaction. Afterwards, the reaction can be continued at room temperature under stirring.

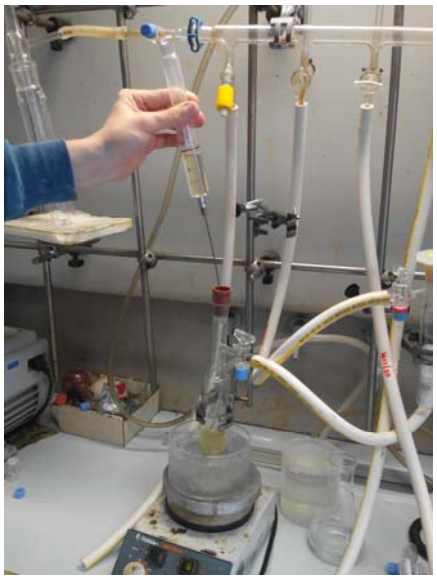


Figure SM 17.7.4 – Addition *via* serynge of the Grignard reagent solution to the cooled Schlenk containing the S,S-Di(pyridin-2-yl)benzene-1,2-bis(carbothioate) solution.

Figure SM 17.7.5 – Aspect of product (**2**) after crystallization and the removal of the supernatant.

Notes for the synthesis of 1,3-Dithienylbenzo[*z*]thiophene (3)

The structure of the Lawesson's reagent is depicted in **Figure SM 17.7.6**.

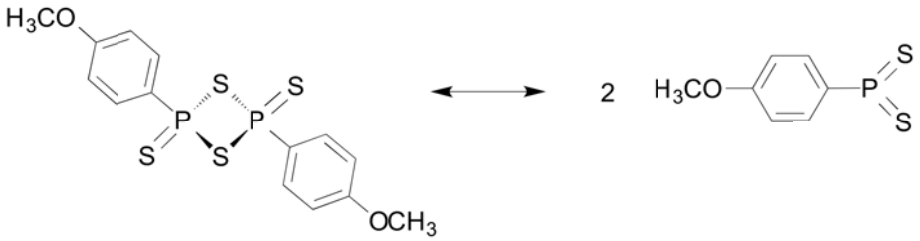


Figure SM 17.7.6 – Generally accepted structures for the labile equilibrium of Lawesson's reagent:

Reactions involving this reagent have a very strong odour derived from formation of the H_2S gas. As such, every manipulation should be performed in a **very well ventilated fume hood**. After completion of the reaction and evaporation of the dichloromethane (while the reaction mixture is being heated in ethanol), it is advisable to clean the rotatory evaporator by evaporation of a flask containing water followed by acetone. This will avoid strong odours

to remain on the apparatus. Also, the ethanol evaporation should be performed carefully since it can lead to some dragging of the product to the collecting vessel on the rotatory evaporator. Adding a small amount of silica gel will prevent this from happening. Even so, **care needs to be taken** when the flask is close to dryness to prevent the very thin powder to be dragged to the evaporator condenser.

Students are advised to perform the chromatography in a large column using only hexane or light petroleum spirit as eluent. Any addition of a second, more polar eluent will result in an unsuccessful separation. Crystallization from ethanol is also possible after the chromatography step but typically this is not necessary. The product is an orange crystalline solid that sometimes appears with a lightly brownish/green coloration. It is extremely fluorescent in solution and should be stored in the dark.

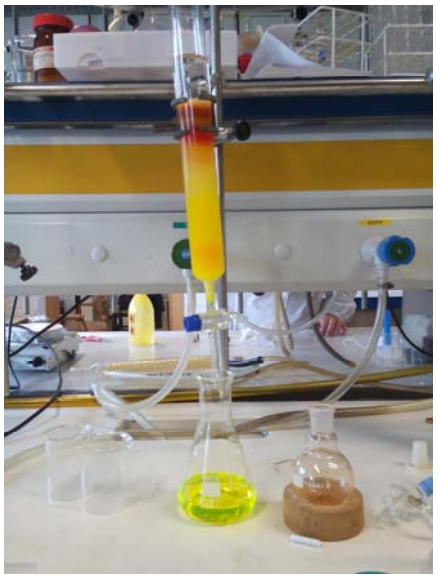


Figure SM 17.7.7 – Column Chromatography of step 3.

Other notes:

At this point, some remarks about the overall reactions should be made.

- The importance of the leaving group:

The bottleneck step in the synthesis of the benzo[c]thiophene skeleton is the preparation of the *ortho*-diketone (**2**) that will further be used in the S-heterocyclization reaction. The importance of the leaving group in the synthesis of compound (**2**) is very well documented (see ref. 3).

The Grignard reaction cannot be initiated with phtaloyl dichloride since the presence of the highly reactive acyl chlorides lead to the main formation of a side product (3,3-Dithienylisobenzofuran-1(3*H*)-one) resulting from intramolecular re-cyclization reactions, being the desired *ortho*-diketone obtained below a 10% yield, as showed in **Figure SM 17.7.8**. S-(2-pyridinyl)thioesthers in their turn are less reactive than acyl chlorides and were shown to be adequate in the synthesis of *ortho*-diketones by Grignard reactions. It was hypothesized that the high reactivity of S-(2-pyridinyl)thioesthers toward Grignard reagents was due to the formation of a six-membered intermediate (**Figure SM 17.7.9**) that prevented the above mentioned intramolecular re-cyclization reactions to occur, hence resulting in high yield reactions.

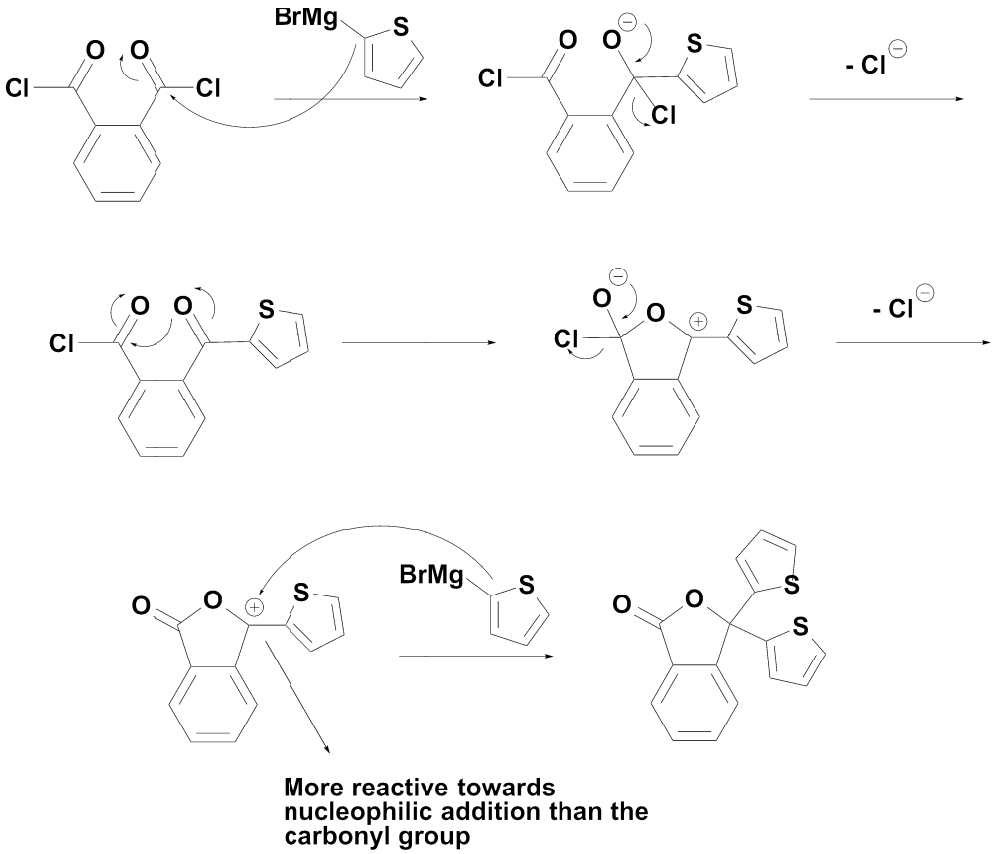


Figure SM 17.7.8 – Formation of 3,3-Dithienylisobenzofuran-1(3*H*)-one.

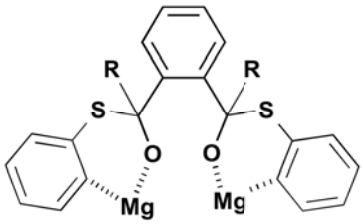
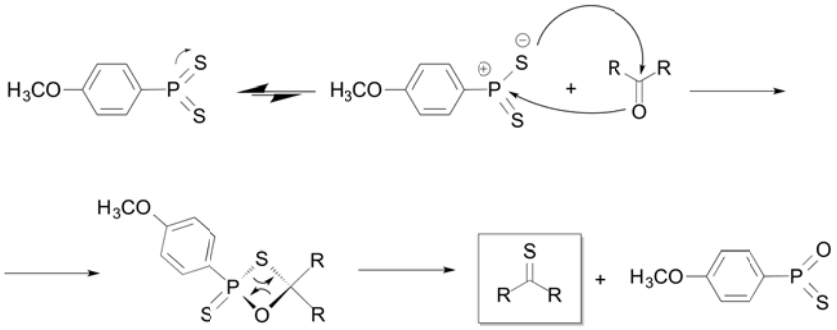


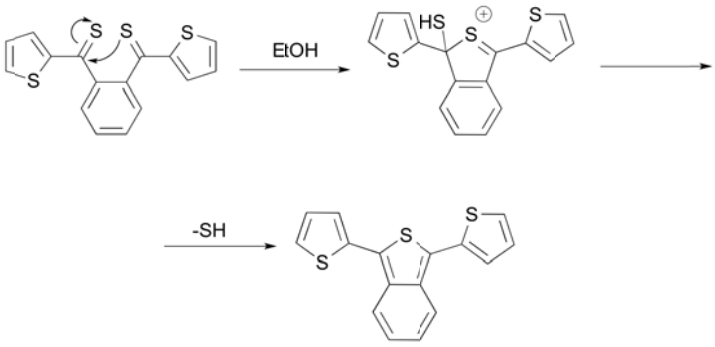
Figure SM 17.7.9 – Structure of the hypothesized six-membered intermediate formed during the Grignarg reaction involving S-(2-pyridinyl)thioesters.

- Thionation Reaction Mechanism:

It is generally accepted that in solution the Lawesson's reagent is in equilibrium with its dimeric structure, as showed in **Figure SM 17.7.6**. The reaction of this ylide with carbonyl containing compounds in a nucleophilic addition to the sp^2 carbon of the carbonyl group affords a four-membered thiaoxaphosphetane intermediate, which resembles the intermediate formed in the mechanism of the Wittig reaction. Ring cleavage of this intermediate by a concerted mechanism affords the desired thioketone:



In the case of the present diketone (compound **2**), the thionation is followed by enolization, with the consequent intramolecular cyclization, to afford the desired 1,3-dithienylbenzo[c]thiophene:



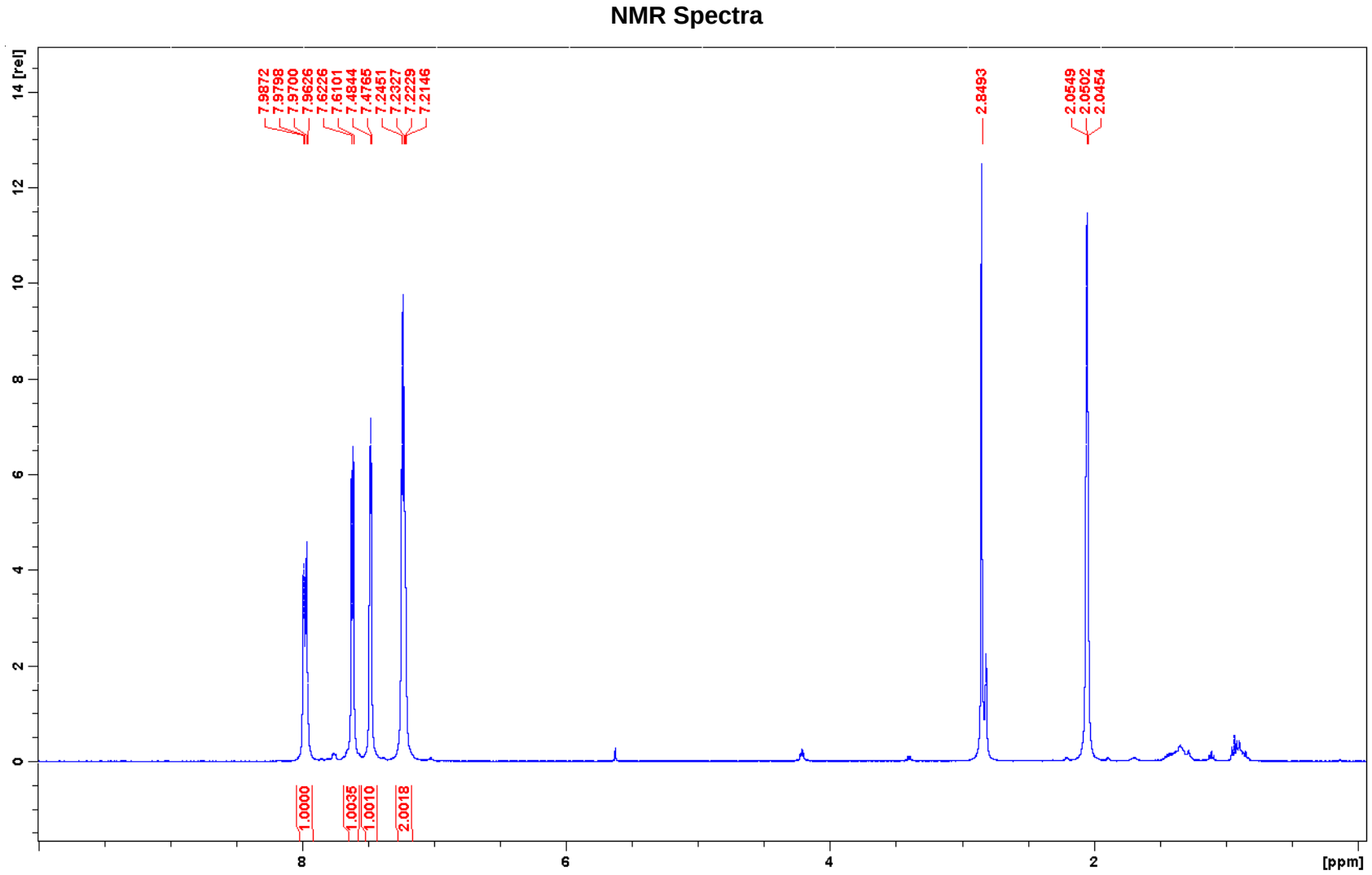


Figure SM 17.7.9 – ^{1}H NMR spectrum in $(CD_3)_2CO$ of 1,3-Dithienyl-Benzo[c]thiophene.

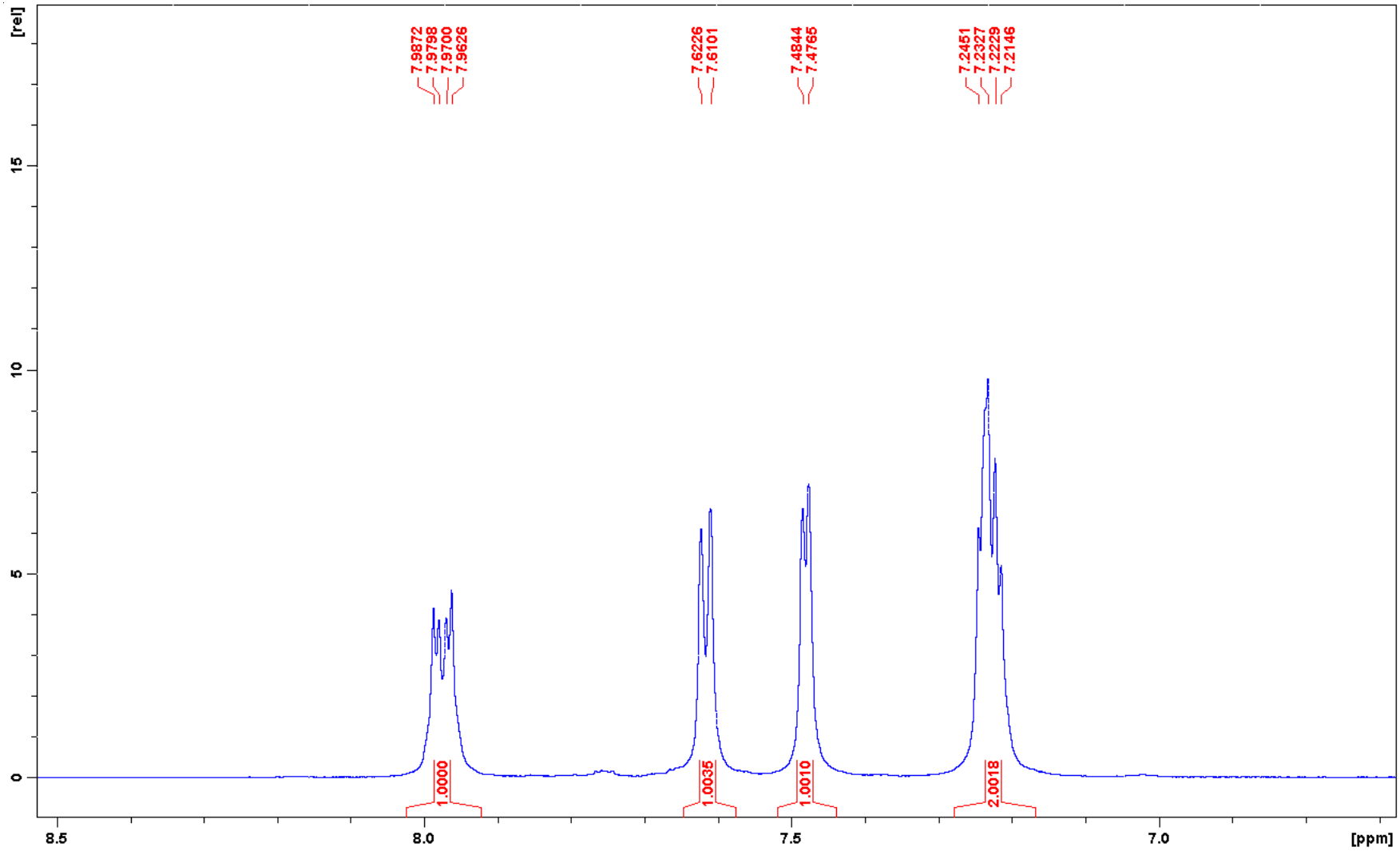


Figure SM 17.7.10 – Expansion of the ^{1}H NMR spectrum in $(CD_3)_2CO$ of 1,3-Dithienyl-Benzo[c]thiophene.

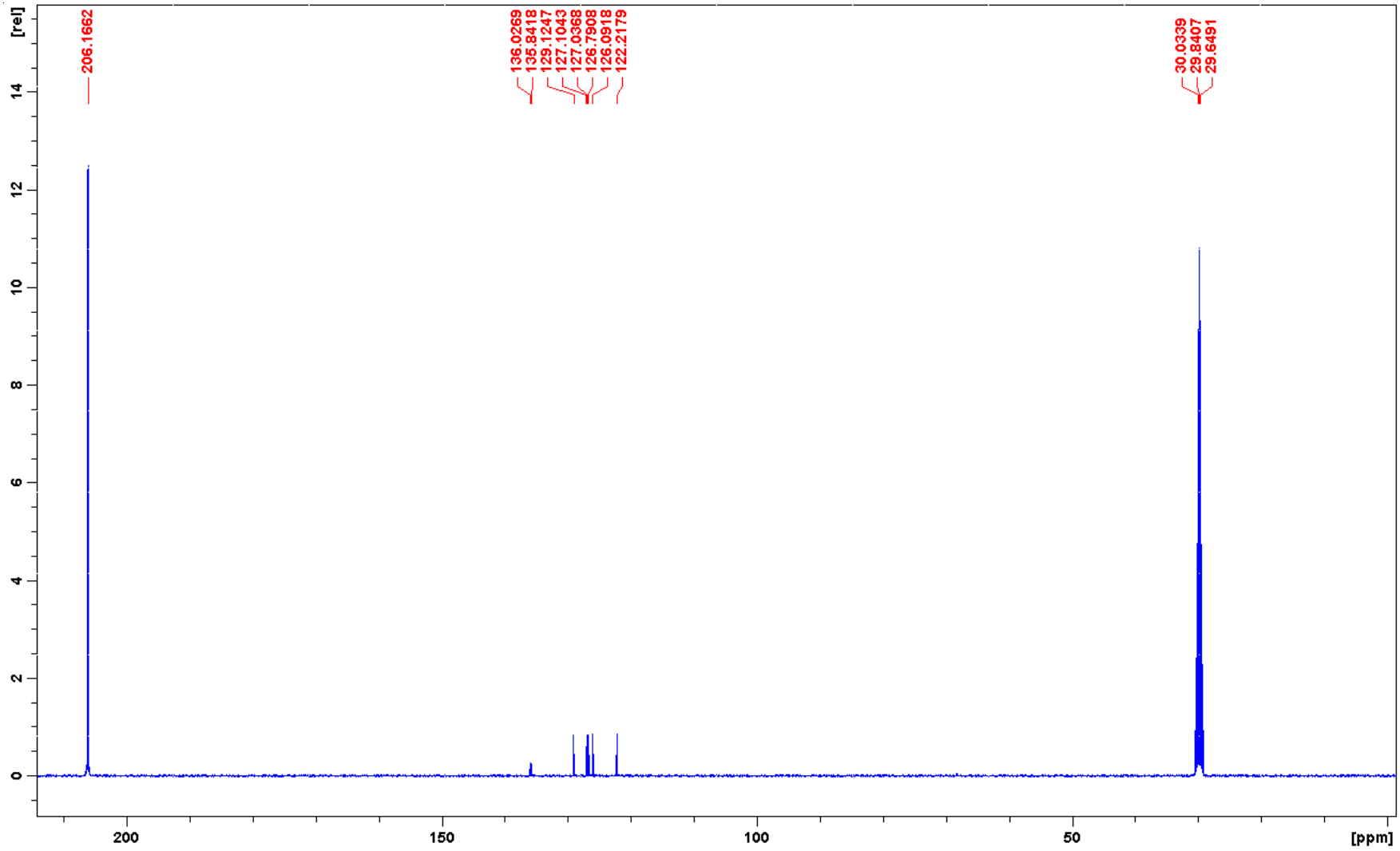


Figure SM 17.7.11 – ^{13}C NMR spectrum in $(CD_3)_2CO$ of 1,3-Dithienyl-Benzo[c]thiophene.

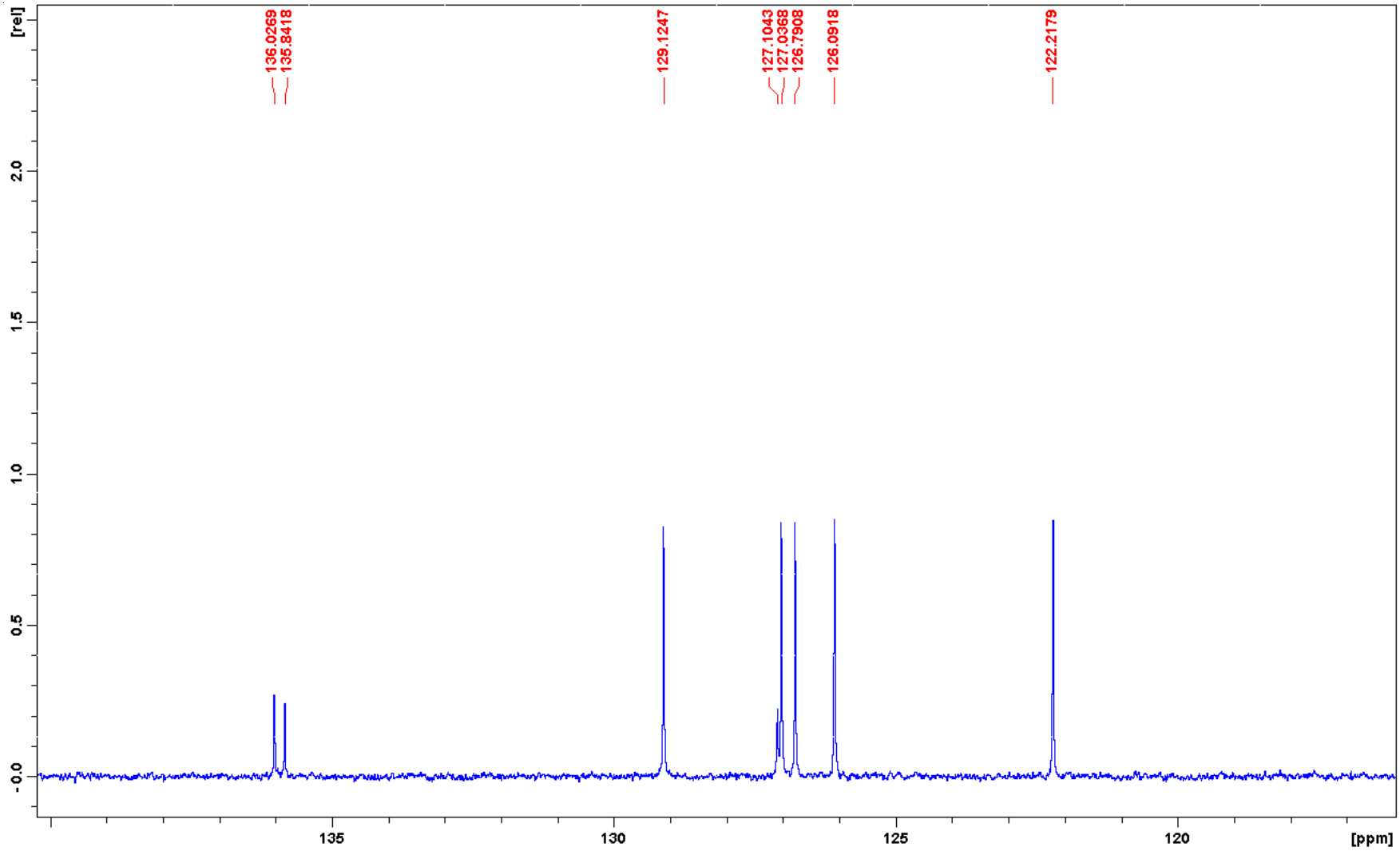


Figure SM 17.7.12 – Expansion of the ^{13}C NMR spectrum in $(CD_3)_2CO$ of 1,3-Dithienyl-Benzo[c]thiophene.

Synthesis of 1-propyl-2-(thiophen-2-yl)-1*H*-pyrrole
Supplementary Material

1. Experiment notes

2. Mechanisms

2.1. Mechanism for the formation of a thienylpyrrole from a secondary γ–keto amide

2.2. Mechanism for the formation of a 5-*N*,*N*-dialkylamino-2,2´-bithiophene from a tertiary γ–keto amide

3. Figures

3.1 Photos for the apparatus used in session 3

3.2 Photos for the apparatus used in laboratory sessions 4 and 5

3.3 Photo of the TLC plate with the reagent and product for laboratory session 5

3.4 ^{1}H, ^{13}C NMR, IR and UV-visible spectra of the products

1. Experiment notes

The aim of this experiment is the synthesis of a thienylpyrrole derivative involving several synthetic transformations, namely: i) synthesis of a secondary γ-ketoamide by direct amidation of the 4-oxo-(2'-thienyl) butanoic acid in the presence of DCC/HOBt coupling reagents[1-3]; ii) thionation of carbonyl groups using Lawesson´s reagent (LR)[4] (Scheme SM 17.8.1.), followed by cyclization of the 4-thioxo derivative through a nucleophilic intramolecular attack yielding the thienylpyrrole heterocyclic system.[5]

Scheme SM 17.8.1. Structure and mechanism of dissociation of Lawesson reagent.

The preparation of 1-propyl-2-(thiophen-2-yl)-1*H*-pyrrole through the thionation reaction of 4-oxo-*N*-propyl-4-(thiophen-2-yl)butanamide followed by cyclisation in the presence of Lawesson reagent will allow a critical analysis of the different reactivities of secondary γ-keto amides (*e.g.* 4-oxo-*N*-propyl-4-(thiophen-2-yl)butanamide) compared to tertiary γ-keto amides (*e.g.* 1-(piperidin-1-yl)-4-(thiophen-2-yl)butane-1,4-dione). In the case of secondary γ-keto amides the product of intramolecular cyclisation is a thienylpyrrole while tertiary γ-

keto amides gave a 5-*N,N*-dialkylamino-2,2´-bithiophene derivative as reaction product.[5-8] (see also experiment 5.2.10)

Other methods of synthesis of thienylpyrroles might be discussed with a view of giving a broad approach to this subject.[9]

The students should interpret the ^{1}H NMR, ^{13} NMR and IR spectroscopic data of all synthesized products in order to identify the compounds obtained as well to check their purity. Additionally the characterization of the compounds through the usual spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR) is extremely interesting and could be used in order to compare the spectra of the precursors with the spectra of the final products in order to confirm the functional group transformations.[10]

The students will use several experimental techniques such as heating at reflux, liquid-liquid extraction, gravity and vacuum filtration, recrystallization, evaporation of organic solvents with a rotary evaporator, thin layer chromatography (TLC), column chromatography and melting point.[11]

This experiment was previously developed in the research group of the author and was performed later by eight students of the 4th year of the undergraduate Chemistry degree course at the University of Minho as well as by four Erasmus students from the undergraduate Chemistry degree course at the University of Metz, France. In both cases they worked in groups of two members. This experiment is appropriate for undergraduate Chemistry who have previously acquired some skills with the experimental techniques involved used as well some knowledge regarding the theoretical concepts presented (synthesis, reactivity and spectroscopic data interpretation).

Synthesis of 4-oxo-*N*-propyl-4-(thiophen-2-yl)butanamide

In session 1 the 4-oxo-4-(thiophen-2-yl)butanoic acid (synthesised in experiment 132) is used as precursor for the synthesis of 4-oxo-*N*-propyl-4-(thiophen-2-yl)butanamide. However, this compound is also commercially available.

The synthesis of amide through the direct amidation method using DCC/HOBt coupling agents leads to a mixture of compounds constituted by the title compound and some residual DCU. The presence of DCU in the mixture is confirmed by ^{1}H NMR and the purification of the amide (session 2) will be carried out inducing the precipitation of the DCU by dissolving the reaction mixture in acetone using a water bath, followed by cooling of the solution at 0-4 ^{o}C (refrigerator).

The mechanism of amidation in the presence of DCC is well known[1-3] (see also experiment 132).

The range of yields obtained earlier by students of the 4th year of the degree course in Chemistry of University of Minho as well as by Erasmus students was 73-80%.

4-Oxo-N-propyl-4-(thiophen-2-yl)butanamide:[7] colourless solid (80%). Mp: 96.2-97.6 ^{o}C (EtOH). ^{1}H NMR (acetone-d_6) δ 0.92 (t, 3H, J=7.2 Hz, NHCH$_2$CH$_2$*CH$_3$*), 1.52 (m, 2H, NHCH$_2$*CH$_2$*CH$_3$), 2.61 (t, 2H, J=7.8 Hz, CO*CH$_2$*), 3.10 (t, 2H, J=7.2 Hz,NH*CH$_2$*CH$_2$CH$_3$), 3.38 (t, 2H, J=7.8 Hz, CO*CH$_2$*), 7.10 (large s, 1H, NH), 7.22-7.25 (m, 1H, 4´-H) 7.90 (dd, 1H, J=5.1 and 1.2 Hz, 5´-H), 7.95 (dd, 1H, J=3.7 and 1.2 Hz, 3´-H).^{13}C NMR ($CDCl_3$) δ 11.3, 22.8, 30.3, 34.6, 41.3, 128.2, 132.2, 133.7, 143.6, 171.7, 192.1. IR (liquid film) v 3311 (NH), 3029, 1661 (C=O), 1645 (C=O), 1552, 1523, 1420,1397, 1248, 1179, 1063, 983, 954, 910, 851, 717 cm^{-1}.

Synthesis of 1-propyl-2-(thiophen-2-yl)-1*H*-pyrrole

In session 4 the heating of the reaction mixture should be made at gentle reflux and only during 30 minutes (check the conversion of the amide by TLC). Prolonged heating of the reaction mixture may lead to decomposition ~~products~~ of the Lawesson reagent.

In the purification of the 1-propyl-2-(thiophen-2-yl)-1*H*-pyrrole by gravimetry column chromatography (session 5) the reaction mixture should be dissolved in the minimum amount of chloroform in order to avoid the rapid elution of the product [R_F=0.51, petroleum ether (40-60 ^{o}C)/diethyl ether (5:5)], together with the impurities.

A plausible mechanism[5,8] for the formation of five membered heterocycles, (pyrroles and/or bithiophenes) from secondary amides in the presence of LR, involves an initial thionation of the amides to the corresponding 4-thioxo thioamides followed by further changes shown in Schemes SM 17.8.2 and SM 17.8.3. In the case of secondary amides a subsequent intramolecular nucleophilic attack of thioamide N-atom to thiocarbonyl group leads to cyclized product, which, after elimination of H_2S, suffers desulfurization of thioxo group to 1-(alkyl)aryl-2-(2´-thienyl)pyrroles (Scheme SM 17.8.2). On the other hand, the imidothiol form of 4-thioxo tertiary thioamides undergoes a ring closure to give 5-*N,N*-dialkylamino-2,2´-bithiophenes (Scheme SM 17.8.2). More information can be found in reference 5 where Nisho proposed a similar mechanism for the formation of pyrroles and thiophenes from diphenyl-4-oxobutanamides.

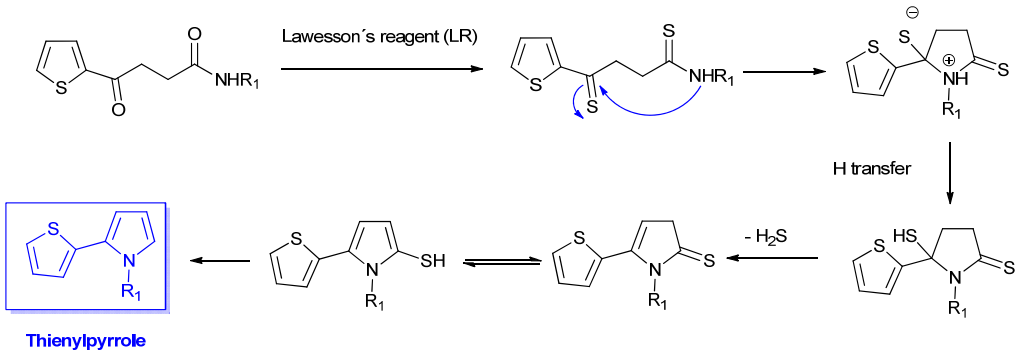
The range of yields obtained earlier by students of the 4th year of the degree course in Chemistry of University of Minho as well as by Erasmus students was 35-47%.

1-Propyl-2-(thiophen-2-yl)-1H-pyrrole:[7] orange oil (47%). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.2 Hz, $CH_2CH_2CH_3$), 1.65-1.68 (m, 2H, $CH_2CH_2CH_3$), 3.97 (t, 2H, J=7.2 Hz, $CH_2CH_2CH_3$), 6.17-6.22 (m, 1H, 4-H), 6.31 (dd, 1H, J=3.6 and 1.8 Hz, 3-H), 6.76-6.88 (m, 1H, 5-H) 7.01 (dd, 1H, J=3.6 and 1.2 Hz, 3´-H), 7.06-7.09 (m, 1H, 4´-H), 7.29 (dd, 1H, J=5.1 and 1.2 Hz, 5´-H). ^{13}C NMR ($CDCl_3$) δ 11.2, 24.7, 49.0, 107.7, 110.2, 122.7, 124.7, 125.3, 126.3, 127.2, 135.0. IR (liquid film) v 3102, 2964, 2932, 2874, 1508, 1470, 1430, 1383, 1345, 1299, 1234, 1201, 1108, 1070, 941, 896, 844, 783, 711, 613 cm^{-1}. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 291 (1803), 226 (2054).

Note: All the ^{1}H and ^{13}C NMR spectra presented in this experiment were obtained by MsC and/or PhD researchers of the author's group.

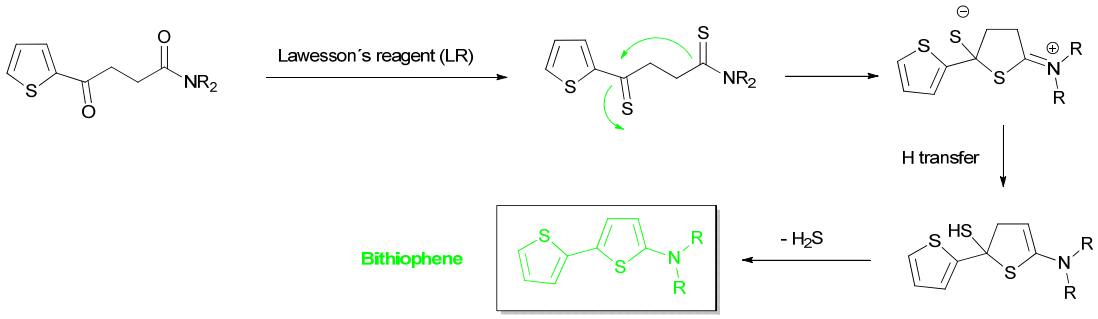
2. Mechanisms

2.1. Mechanism for the formation of a thienylpyrrole from a secondary γ–keto amide



Scheme SM 17.8.2. Mechanism for the formation of a thienylpyrrole from a secondary γ–keto amide by reaction with Lawesson reagent.

2.2. Mechanism for the formation of a bithiophene from a tertiary γ–keto amide



Scheme SM 17.8.3. Mechanism for the formation of a 5-*N,N*-dialkylamino-2,2´-bithiophene from a tertiary γ–keto amide by reaction with Lawesson reagent.

3. Figures

3.1 Photos for the apparatus used in laboratory session 3.

Figure SM 17.8.1 Left - Photo for the apparatus for heating at reflux (recrystallization); centre and right- photos of the vacuum filtration of the recrystallized solid.

Figure SM 17.8.2 Left - Sample loaded into the sealed capillary; Right- Photo of the apparatus for the determination of the melting point.

3.2 Photos for the apparatus used in laboratory sessions 4 and 5.

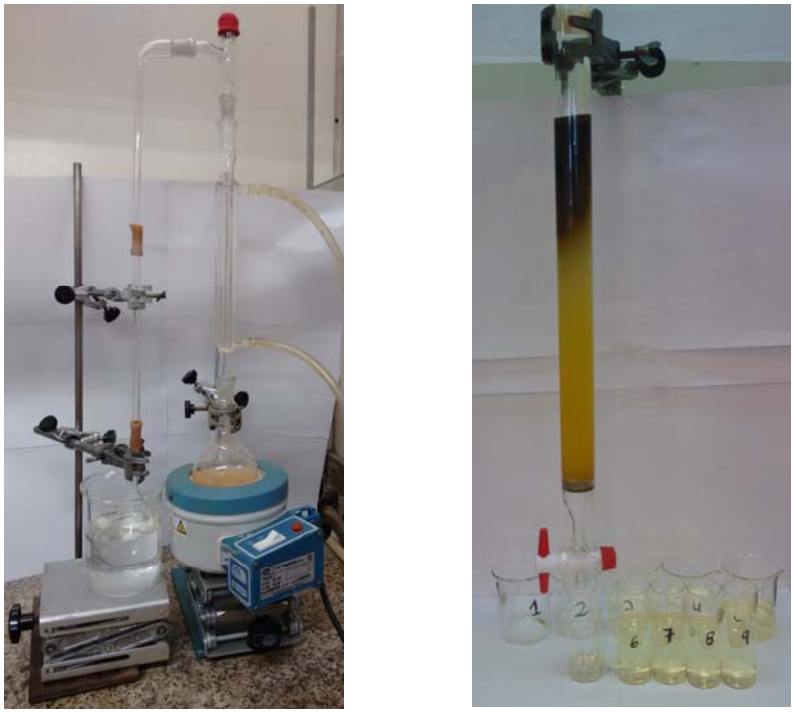


Figure SM 17.8.3 Left - Photo of the apparatus for heating at reflux with a H_2S trap (laboratory session 4); Right- Photo of the apparatus for purification of the product by column chromatography (laboratory session 5).

3.3 Photo of the TLC plate with the reagent and product for laboratory session 5.

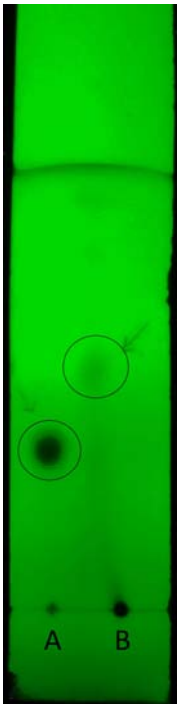


Figure SM 17.8.4. Photo of the TLC plate with the amide precursor (A) and the thienylpyrrole product (B) obtained after column chromatography (eluent: petroleum ether (40-60 ^{O}C)/: diethyl ether; 5:5), laboratory session 5.

References

[1] C. A. G. N. Montalbetti and V. Falque, *Tetrahedron* 2005, **61**, 10852.

[2] (a) M. Bodansky, "Peptide Chemistry: A Pratical Textbook"; Springer: New York, 1988. (b) *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*"; A. J. Pearson, W. R. Roush Eds., John Wiley and Sons: Chichester, 2000, p. 133.

[3] (a) M. Bodansky, *J. Protein Chem.*, 1989, **8**, 461. (b) *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*"; A. J. Pearson, W. R. Roush Eds., John Wiley and Sons: Chichester, 2000, p. 220.

[4] (a) M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061. (b) R. A. Cherkasov, G. A. Kutyrev and A. N. Pudovick, *Tetrahedron*, 1985, **41**, 2567. (c) T. Ozturk, E. Ertas and O. Mert, *Chem Rev*. 2007, **107**, 5210.

[5] T. Nisho, T. *Helv. Chim. Acta*, 1998, **81**, 1207.

[6] M. M. M. Raposo, A. M. B. A. Sampaio and G. Kirsch, *Synthesis*, 2005, **2**, 199.

[7] M. M. M. Raposo, A. M. B. A. Sampaio, A. M. C. Fonseca and G. Kirsch, *Tetrahedron*, 2006, 62, 3493.

[8] M. M. M. Raposo, In: *Targets in Heterocyclic Systems*: *Chemistry and Properties*, "Recent developments in the chemistry of 2-thienylpyrroles: synthesis, reactivity and applications", O. A. Attanasi and D. Spinelli, Eds; Italian Society of Chemistry, 2007, Vol. 11, 122-154.

[9] (a) G. P. Bean, Pyrroles In *The Chemistry of Heterocyclic Compounds*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, Part 1; p. 105. (b) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans.*, *1*, 1999, **1**, 2849. (c) V. F. Ferreira, M. C. B. V. de Souza, A. C. Cunha, L. O. R. Pereira, M. L. G. Ferreira, *Org. Prep. Proced. Int.*, 2001, **33**, 411.

[10] (a) R. M. Silverstein, F. X. Webster and D. J. Kiemle, "Spectrometric Identification of Organic Compounds", 7th Edition, John Wiley and Sons: New York, 2005. (b) E. Pretsch, P. Buhlmann and C. Affolter, "Structure Determination of Organic Compounds" 3rd Edition, Springer-Verlag: Berlin, 2000.

[11] W.-L.F. Armarego and D. D. Perrin, "Purification of laboratory chemicals", 4th Ed.; Butterworth Heinemann, Oxford, 2000.

3.4 ^{1}H, ^{13}C NMR, IR and UV-visible spectra of the products

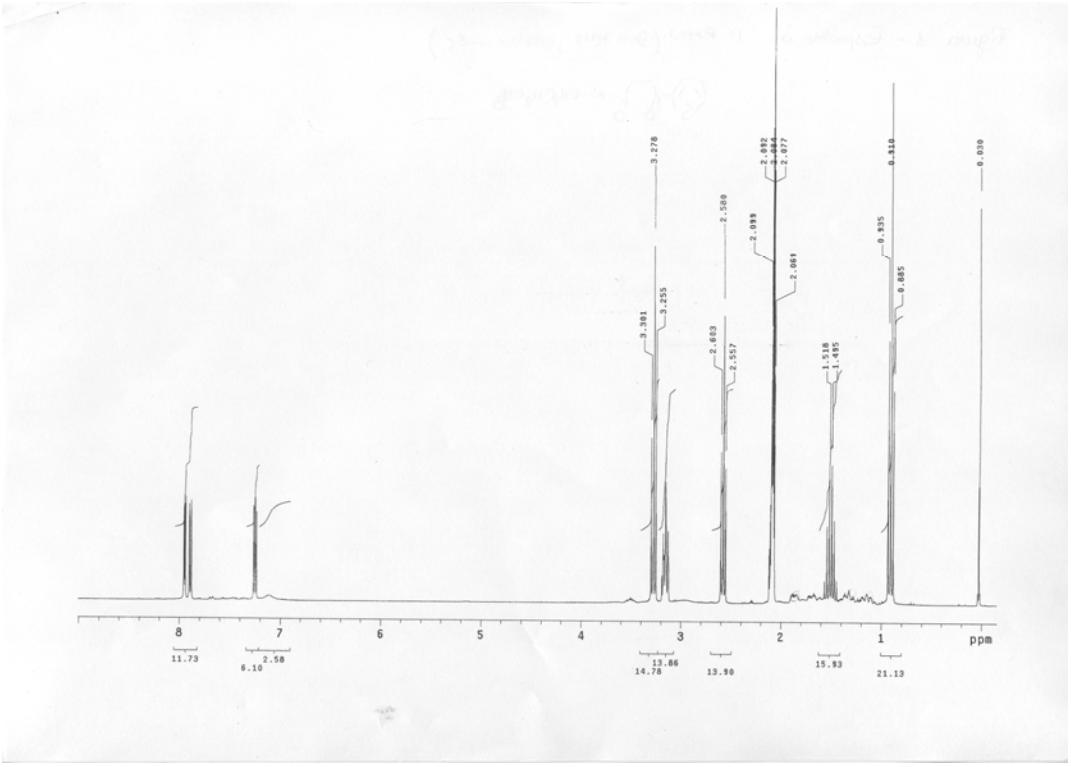


Figure SM 17.8.5. ^{1}H NMR Spectrum of 4-oxo-*N*-propyl-4-(thiophen-2-yl)butanamide in acetone-d_6 obtained using a Varian Unity Plus spectrometer operating at 300 MHz at 25 ^{o}C.

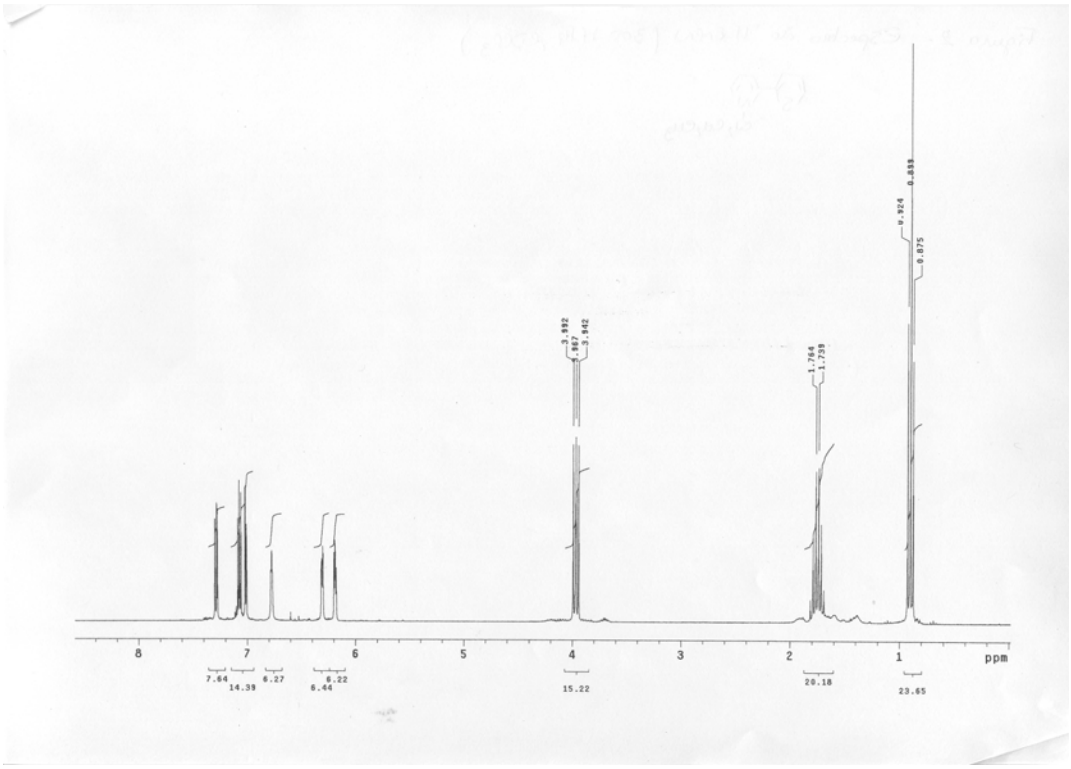


Figure SM 17.8.6. ^{1}H NMR Spectrum of 1-propyl-2-(thiophen-2-yl)-1H-pyrrole in $CDCl_3$ obtained using a Varian Unity Plus spectrometer operating at 300 MHz at 25 ^{o}C.

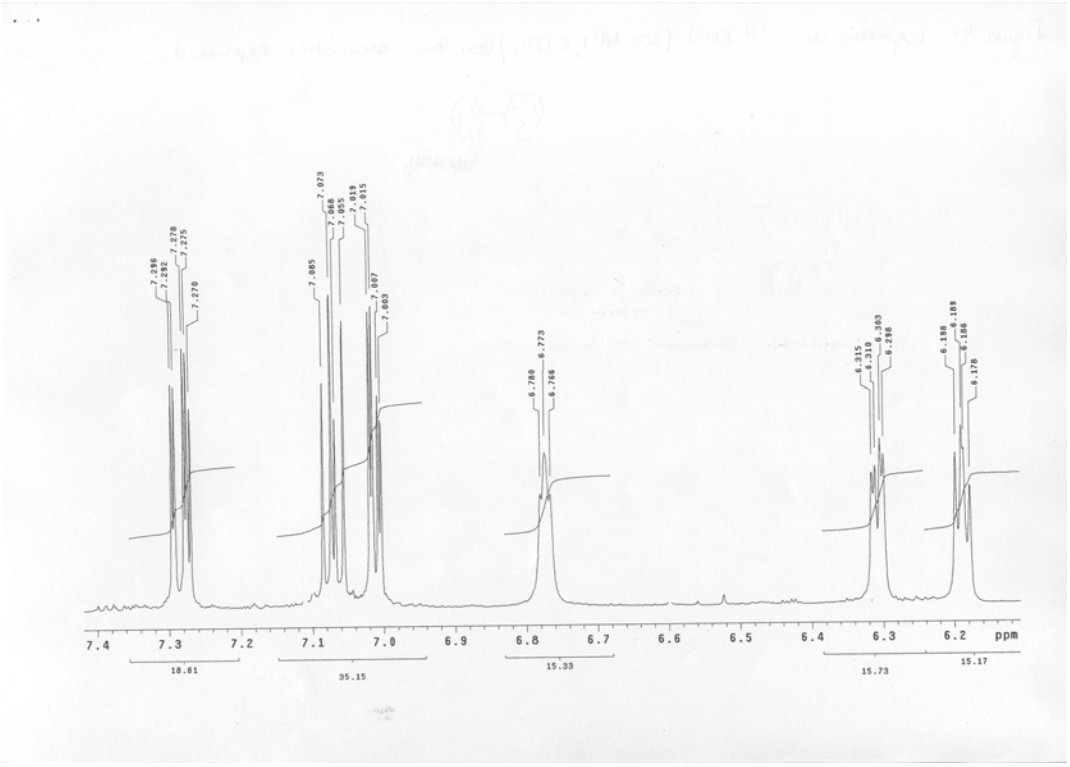


Figure SM 17.8.7. ^{1}H NMR Spectrum with expanded aromatic zone of 1-propyl-2-(thiophen-2-yl)-1H-pyrrole in $CDCl_3$ obtained using a Varian Unity Plus spectrometer operating at 300 MHz at 25 ^{o}C.

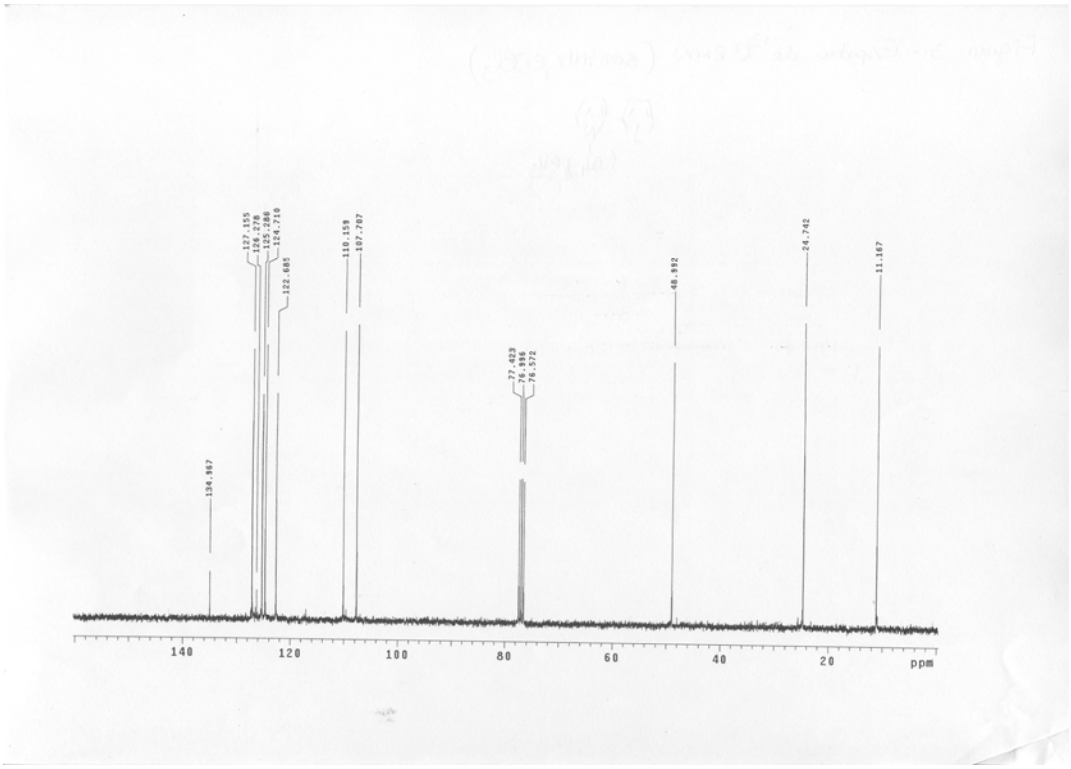


Figure SM 17.8.8. ^{13}C NMR Spectrum of 1-propyl-2-(thiophen-2-yl)-1H-pyrrole in $CDCl_3$ obtained using a Varian Unity Plus spectrometer operating at 75.4 MHz at 25 ^{o}C.

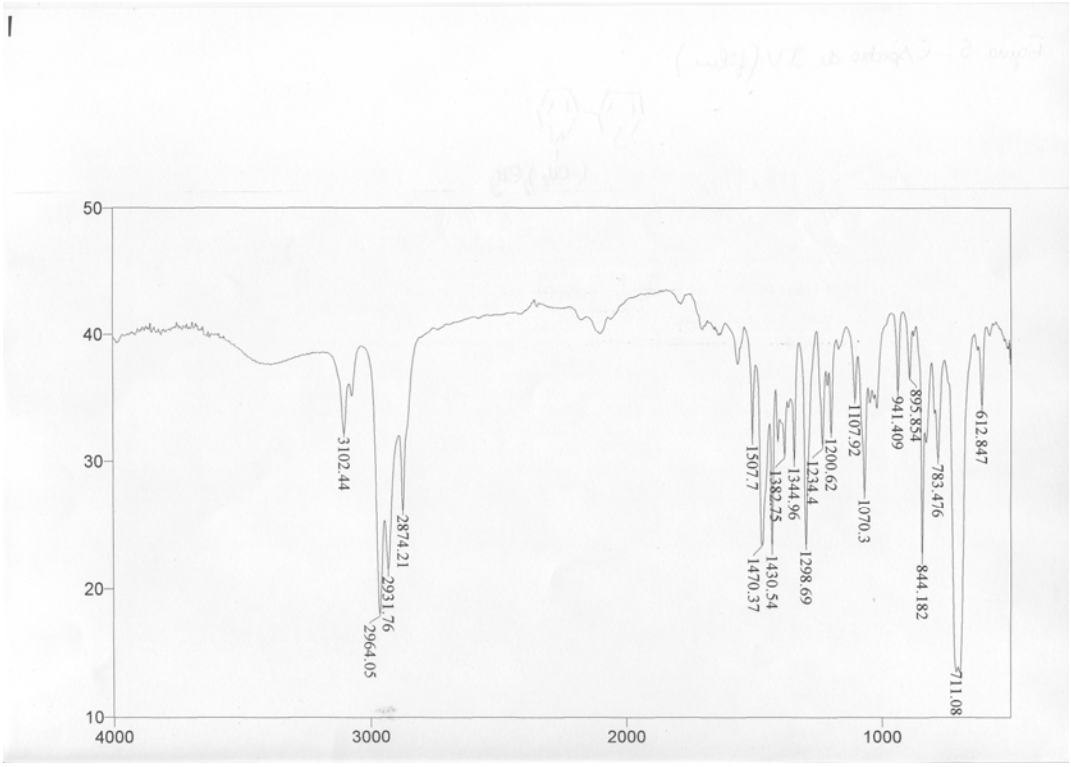


Figure SM 17.8.9. IR Spectrum of 1-propyl-2-(thiophen-2-yl)-1H-pyrrole in liquid film obtained using a Perkin Elmer FTIR-1600 spectrophotometer.

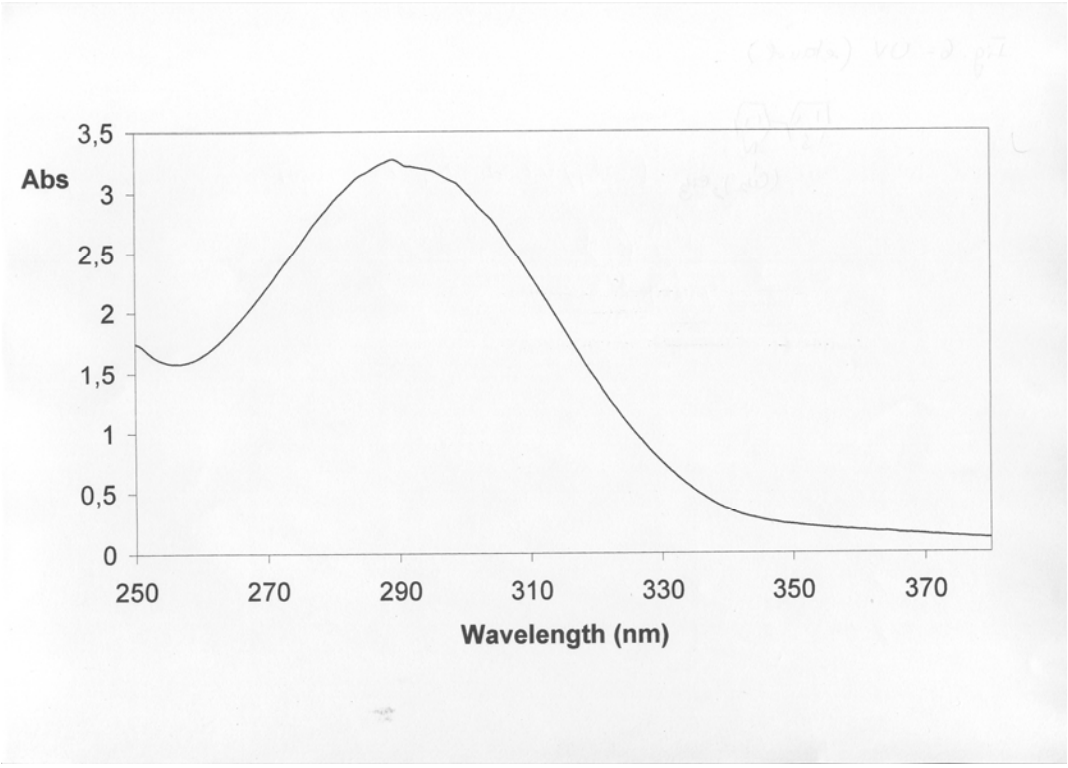


Figure SM 17.8.10. UV-visible spectrum of 1-propyl-2-(thiophen-2-yl)-1H-pyrrole in ethanol obtained using a Shimadzu UV/2501PC spectrometer at 25ºC.

Rhodium Carbene C-H insertion in Water and Catalyst Reuse

Supplementary Material

This experiment was firstly developed in a research environment and later executed by a group of two chemistry undergraduate students at Instituto Superior Técnico, as part of a research project in a laboratorial course of the 4th year of master studies. The yield obtained by the group of students is indicated below for each step. This experiment allows to exploring several topics of organic chemistry, including sustainable chemistry and should be given only to advanced level students as many of the topics covered are advanced and need proper studies.

Instructor notes for the experiment

Step I – Preparation of *p*-toluenesulfonyl azide

- High temperatures in the evaporation of solvents are undesirable. *p*-Toluenesulfonyl azide is extremely reactive and can explode when heated at higher temperatures (heating until 50 ºC was the maximum temperature reached by us). Such azide has been prepared more than 60 times by several researchers of the group in up to 5 g without any explosion. However, special care should be taken.
- After solvent evaporation the residue looks like an emulsion which becomes clear after overnight under vacuum and solid after overnight in the freezer.

Step II – Synthesis of *N*-Benzyl-*N*-*tert*-butyl-α-ethoxycarbonyl-acetamide

- Addition and handling of ethyl malonyl chloride should be done very carefully due to its toxicity and high reactivity.
- The triethylamine hydrochloride salt formed along the reaction does not go completely into solution. Hence, vigorous stirring should be used during and after the addition of the acid chloride to the reaction mixture.

- Purification besides usual work-up of reaction mixture is needed to obtain the product pure enough for the next step. In order to avoid a time consuming column chromatography, the residue can be filtered through a sintered glass funnel with silica and using a low polarity eluent (Et_2O/Hexane 4:1). This allows the removal of the remaining triethylamine hydrochloride salt.
- It is important to use anhydrous diethyl ether as reaction solvent as water will compete with the malonyl chloride for formation of the carboxylic acid. In this experiment the ethyl ether used was allowed to stand over $CaCl_2$ at room temperature overnight prior to use and the use of a calcium chloride tube was enough to avoid decomposition of the malonyl chloride by moisture.

Step III – Preparation of N-Benzyl-N-tert-butyl-α-ethoxycarbonyl-α-diazoacetamide

- The same batch of diethyl ether dried overnight over $CaCl_2$ was used in this step. The suspension of sodium hydride in ethyl ether should be kept in an ice bath and putted at reflux only after it reached room temperature. It is recommended that the preparation and execution of this experiment to be done in a well ventilated fume hood.
- The use of diethyl ether under reflux can be avoided by allowing the reaction to proceed at room temperature for longer times (it takes 2 hours to achieve approximately 40% conversion) nevertheless this procedure was chosen due to time constraints.
- One of the byproducts of this step is the *p*-toluenesulfonylamide which is removed by the aqueous work-up. If this procedure proves to be inefficient, the diazo compound can be recrystallized in diethyl ether and hexane. The purity of the diazo compound obtained after reaction work-up can be determined by TLC (*p*-toluenesulfonylamide R_f=0.60, silica, diethyl ether/hexane 1:4)
- The quaternary carbon bearing the diazo function is usually not observed by ^{13}C NMR spectrum, even after prolonged acquisition times.

Step IV – Cyclization of *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonyl-*α*-diazoacetamide in water and reuse of the catalytic system

- The described procedure does not require any major concerns related to the stability of the compounds to moisture or specific safety warnings.
- No water circulation is needed in the condenser as water will not reflux. Nevertheless, the use of condenser allows avoiding solvent loss during the heating process.
- Due to the small scale of the reaction and the intention of reuse the catalytic system, the extraction process should be made by using a Pasteur pipet to get the organic layers in a very gently way, so that water removal is minimum.
- The filtration through neutral alumina has two main goals. It epimerizes the *cis*-β-lactam to its *trans*-diastereomer, and removes catalyst traces that can be present in the residue.
- We strongly recommend the catalyst reuse process is strongly recommended. Nevertheless, the experiment can be adapted to be given to students without this last step. If so, 3 laboratory sessions should be enough to perform the experiment. The second run of the catalyst can be performed later, as the aqueous solution of dirhodium (II) tetraacetate can be stored in a fridge or even in the bench and reuse after some days.
- If the catalyst reuse step is left out of the procedure, water can be removed in a rotary evaporator and the extraction procedure is not needed. In such case, different diastereoselectivity of the crude lactam should be expected as the heating needed and change of concentration of the reaction mixture can induce epimerization of the α-carbonyl position towards the more stable *trans* diastereomer.

Step V – Reuse of the catalytic system and determination of reactions diastereoselectivity

- Several spectra of the synthesized β-lactam can be found below. Figures SM 17.9.5-8 refers to the described catalyst reuse process. However, the characterization of the isolated *trans*-lactam was performed during our optimization conditions (Figure SM 17.9.9-12).

Spectral Characterization of the synthesized compounds

Step I – *p*-Toluenesulfonyl azide

Obtained by students in 71% yield (3.91 mg). (R_f 0.28 silica, diethyl ether/hexane 1:9).

Step II - *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonylacetamide

Obtained by students in 93% yield (630 mg). R_f 0.55 (Et_2O:Hexane 4:1); ^{1}H NMR δ 7.38-7.34 (2H, t, 7.4 Hz, Ph), 7.28-7.21 (3H, m, Ph), 4.58 (2H, s, NCH_2Ph), 4.19-4.14 (2H, q, 7.1 Hz, OCH_2CH$_3$), 3.36 (2H, s, OCCH$_2$CO), 1.44 (9H, s, NC(CH_3)$_3$), 1.29-1.24 (3H, m, OCH$_2$CH_3); ^{13}C NMR δ 168.1 (*C*O), 167.7 (*C*O), 138.6 (Ph), 128.9 (Ph), 127.2 (Ph), 125.4 (Ph), 61.2 (O*C*H$_2$CH$_3$), 58.3 (N*C*(CH$_3$)$_3$) 49.1 (N*C*H$_2$Ph), 43.9 (COCH_2CO), 28.5 (NC(*C*H$_3$)$_3$), 14.0 (OCH$_2$*C*H$_3$) ppm.

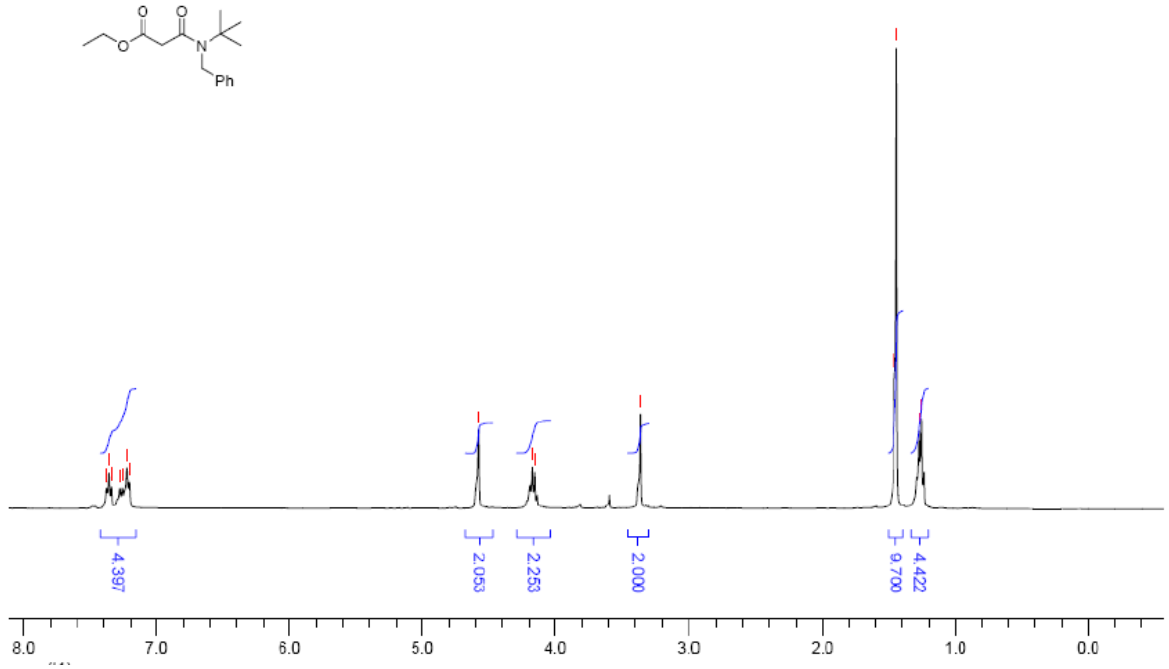


Figure SM 17.9.**1**. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonylacetamide

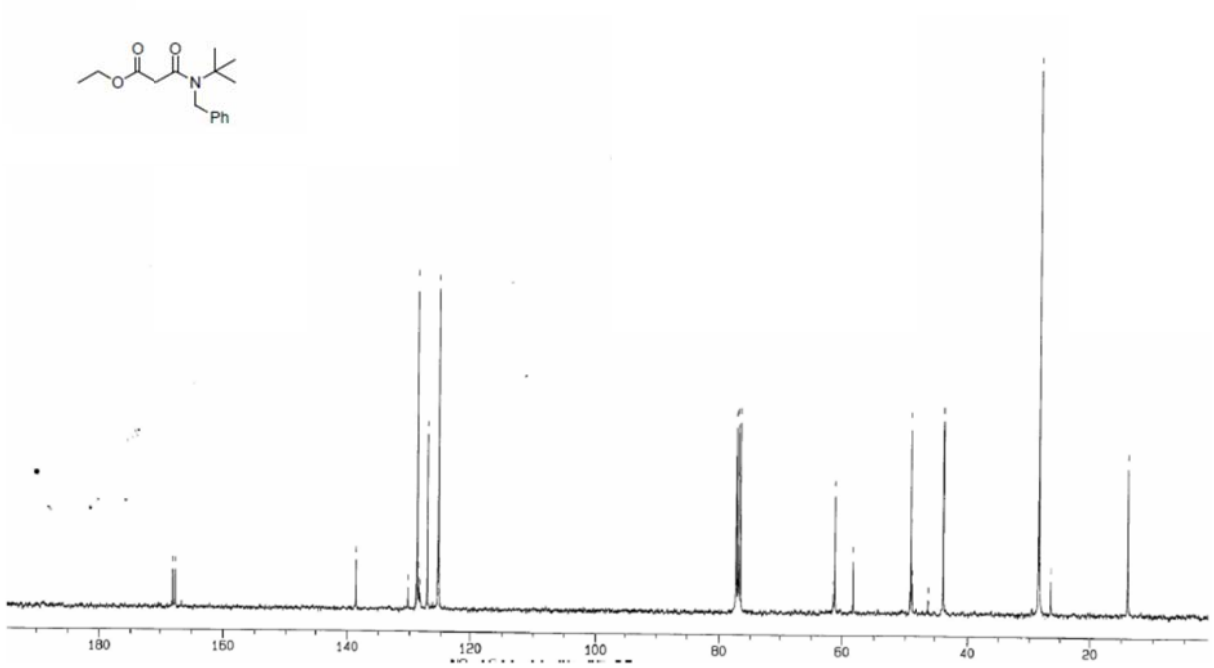


Figure SM 17.9.**2**. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-Benzyl-*N-tert*-butyl-*α*-ethoxycarbonylacetamide

Step III – *N*-Benzyl-*N-tert*-butyl-*α*-ethoxycarbonyl-*α*-diazoacetamide

Obtained by students in 86 % Yield (474 mg), yellow oil. R_f 0.67 (ethyl acetate/hexane 1:4). ^{1}H NMR δ 7.35-7.19 (5H, m, Ph), 4.61 (2H, s, NCH_2Ph), 4.25-4.20 (2H, q, 7.1 Hz, OCH_2CH$_3$), 1.38 (9H, s, NC(CH_3)$_3$), 1.26-1.30 (3H, t, 7.1 Hz, OCH$_2$CH_3) ppm, ^{13}C NMR δ 163.3 (*C*O), 162.5 (*C*O), 139.6 (Ph), 128.6 (Ph), 127.3 (Ph), 126.8 (Ph), 61.2 (O*C*H$_2$CH$_3$), 58.9 (N*C*(CH$_3$)$_3$) 51.6 (N*C*H$_2$Ph), 28.8 (NC(*C*H$_3$)$_3$), 14.4 (OCH$_2$*C*H$_3$) ppm. IR (film): ν_{max}=3064, 3058 (aromatic C-H), 2962, 2925, 2854 (aliphatic C-H), 2125 (N=N), 1712 (C=O), 1631 (C=O), 1454, 1385, 1288, 1198, 1169, 1093, 1027, 964 cm^{-1}.

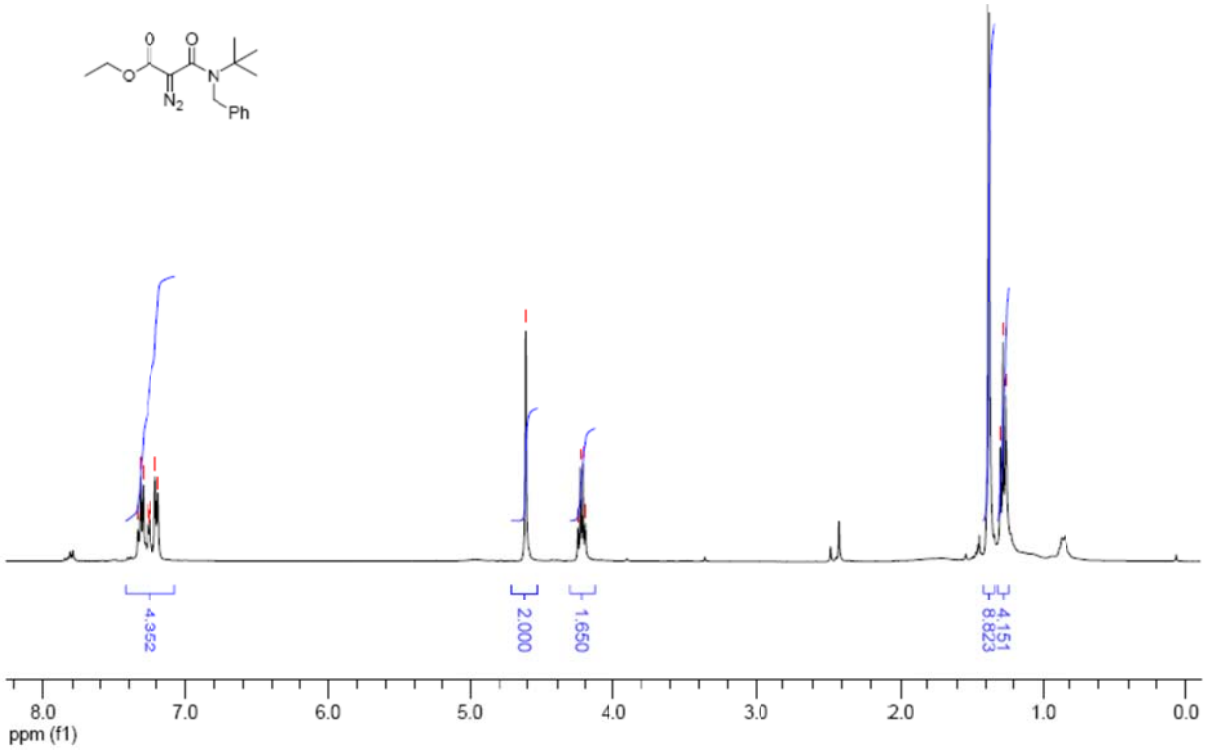


Figure SM 17.9.**3**. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonyl-*α*-diazoacetamide

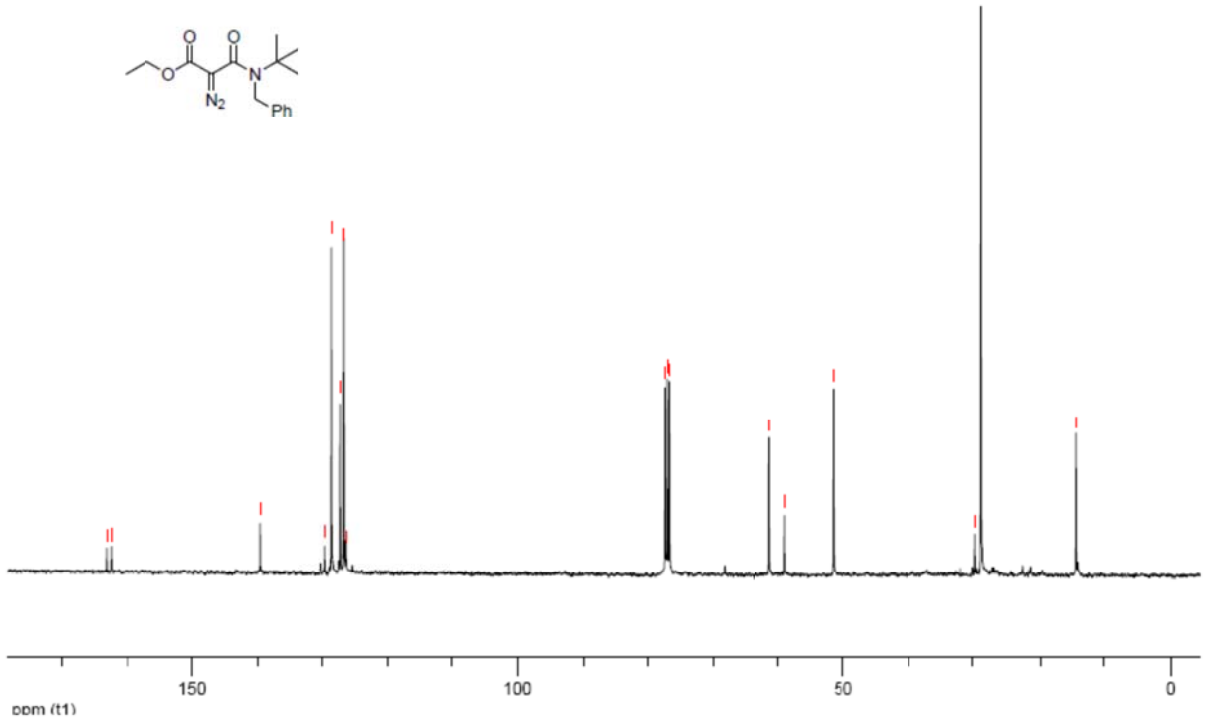


Figure SM 17.9.**4**. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonyl-*α*-diazoacetamide

Step IV – Cyclization of *N*-Benzyl-*N*-*tert*-butyl-*α*-ethoxycarbonyl-*α*-diazoacetamide in water and reuse of the catalytic system

In the ^1H NMR spectrum of the crude reaction mixture a diastereomeric ratio of 1:0.3 *cis*/*trans* (using the integration of the signals at 4.90 and 4.82 ppm for the major and minor diastereomer respectively) is observe.

^1H NMR δ 7.36-7.24 (10H, m, Ph), 4.90 (1H, d, 6.3 Hz, COC*H*CO *cis* diastereomer), 4.82 (1H, d, 1.9 Hz, NC*H*Ph *trans* diastereomer), 4.22-4.18 (3H, m, overlapped signals of NC*H*Ph of the *cis* diastereomer, and OCH_2CH$_3$ of the *trans* diastereomer), 3.75-3.69 (2H, q, 7.1 Hz, OCH_2CH$_3$ *cis* diastereomer), 3.66 (1H, d, 2.0 Hz, OCC*H*CO *trans* diastereomer), 1.28-1.24 (21H, m, overlapped signals of NC(CH_3)$_3$ *cis* and *trans* diastereomers and OCH$_2$CH_3 *trans* diastereomer), 0.82-0.78 (3H, t, 7.1 Hz, OCH$_2$CH_3 *cis* diastereomer). The NMR spectra of *cis* diastereomer was described elsewhere[1].

Results obtained by the students for the cyclisation step:

Run	Reaction Diastereoselectivity (*cis*/*trans* ratio of β-lactam in the reaction crude mixture)	Isolated Yield (%)	*cis*/*trans* ratio of isolated β-lactam
1	1:0.30	78	only *trans* β-lactam
2	1:0.43	70	only *trans* β-lactam

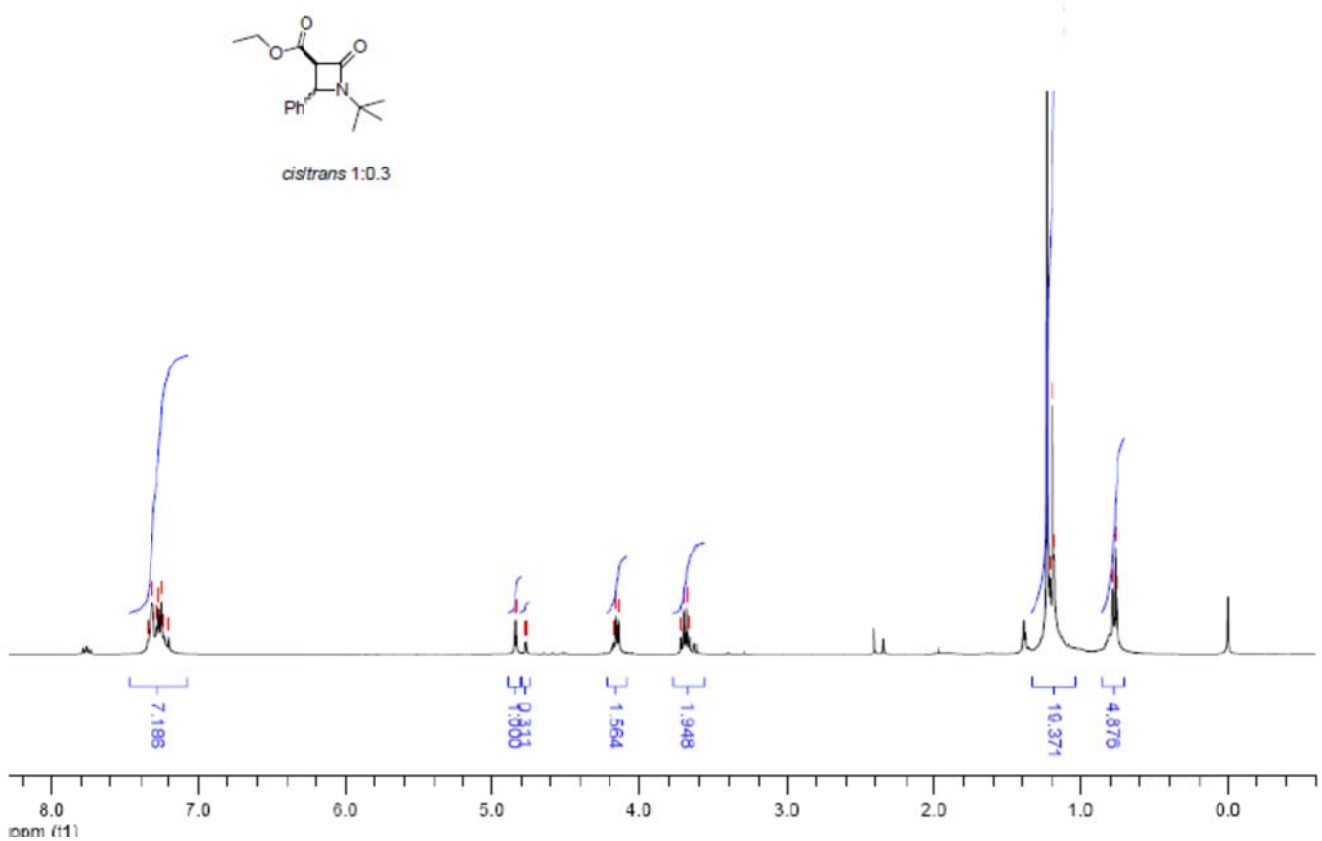


Figure SM 17.9.**5**. ^{1}H NMR (400 MHz, $CDCl_3$) of unpurified *N*-Benzyl-*N*-*tert*-butyl-*3*-ethoxycarbonyl-4-phenyl-β-lactam obtained by students in the first run (mixture of diastereomers prior to epimerization in alumina)

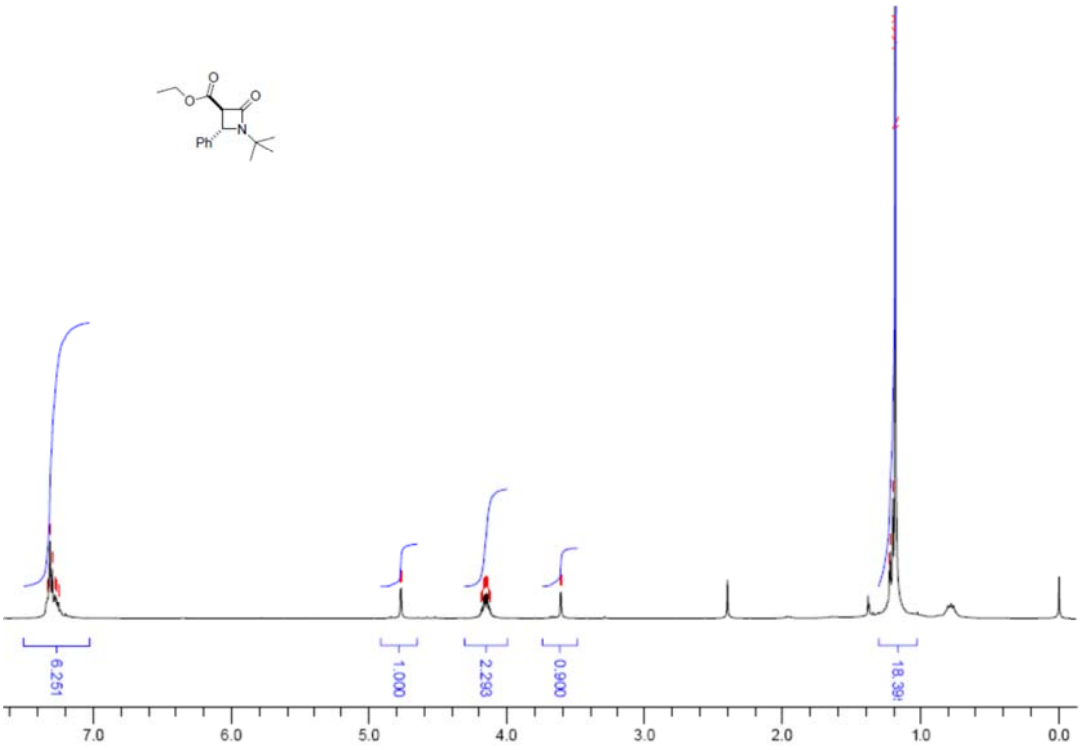


Figure SM 17.9.**6**. ^{1}H NMR (400 MHz, $CDCl_3$) of purified *N*-Benzyl-*N*-*tert*-butyl-3-ethoxycarbonyl-4-phenyl-β-lactam obtained by students in the first run (only *trans* diastereomer after epimerization in alumina)

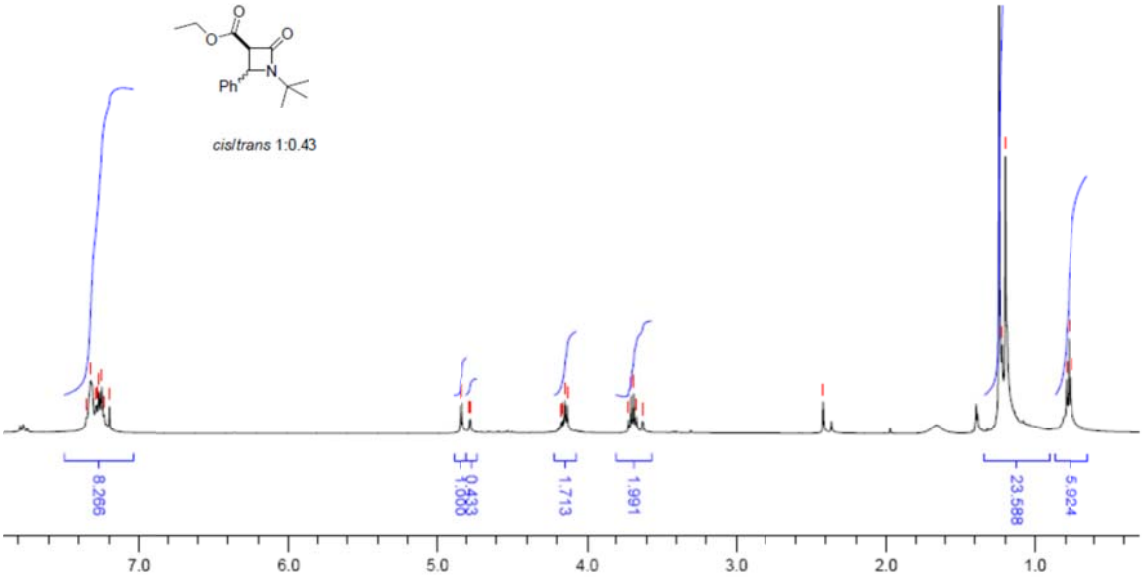


Figure SM 17.9.**7**. ^{1}H NMR (400 MHz, $CDCl_3$) of unpurified *N*-Benzyl-*N*-*tert*-butyl-*3*-ethoxycarbonyl-4-phenyl-β-lactam obtained by students in the second run (mixture of diastereomers before epimerization in alumina)

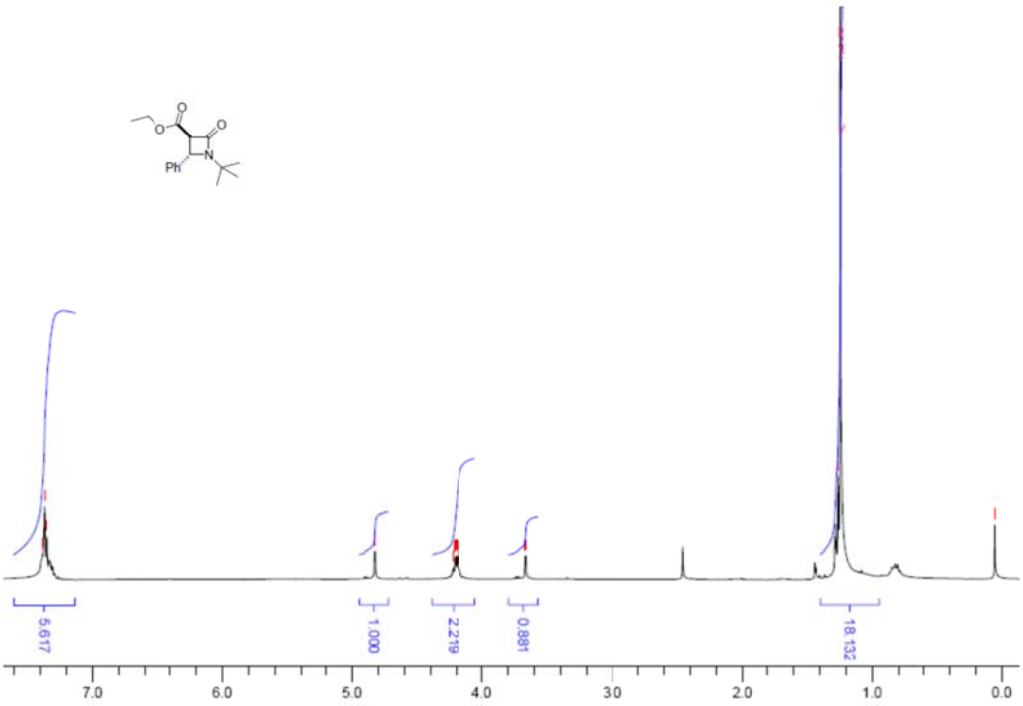


Figure SM 17.9.**8**. ^{1}H NMR (400 MHz, $CDCl_3$) of purified *N*-Benzyl-*N*-*tert*-butyl-*3*-ethoxycarbonyl-4-phenyl-β-lactam obtained by students in the second run (only *trans* diastereomer after epimerization in alumina)

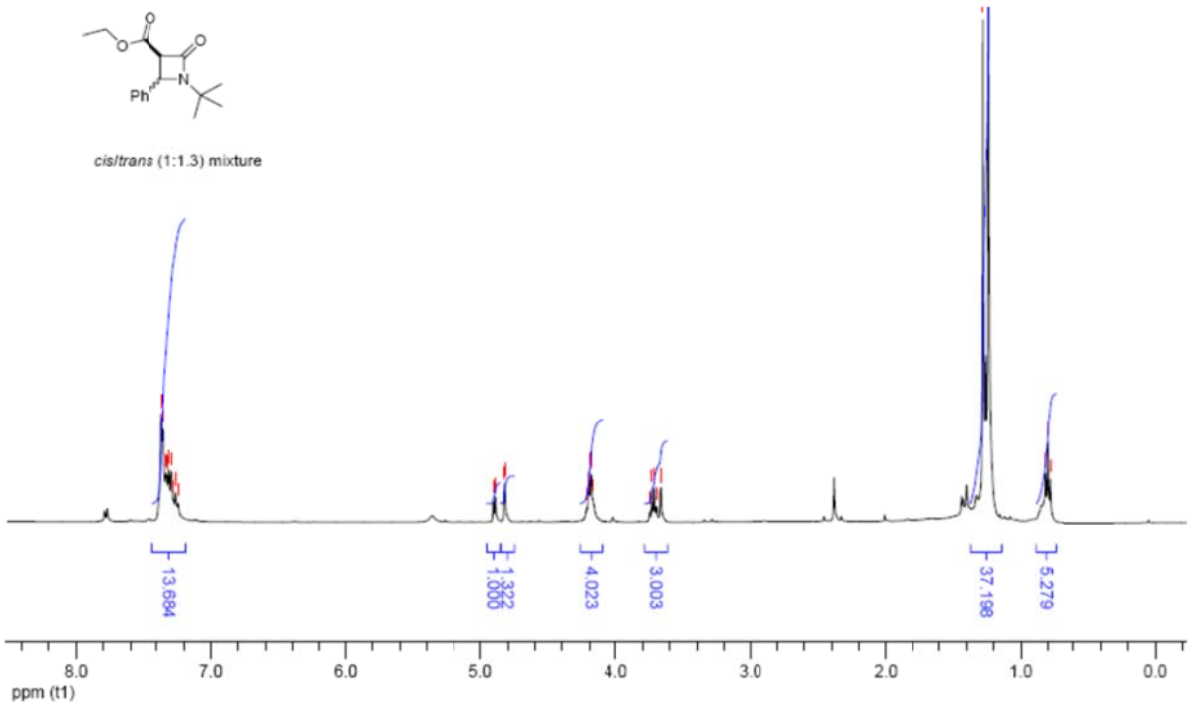


Figure SM 17.9.**9**. ^{1}H NMR (400 MHz, $CDCl_3$) of reaction mixture of diazo acetamide cyclisation after evaporation of water (spectrum obtained during experiment development)

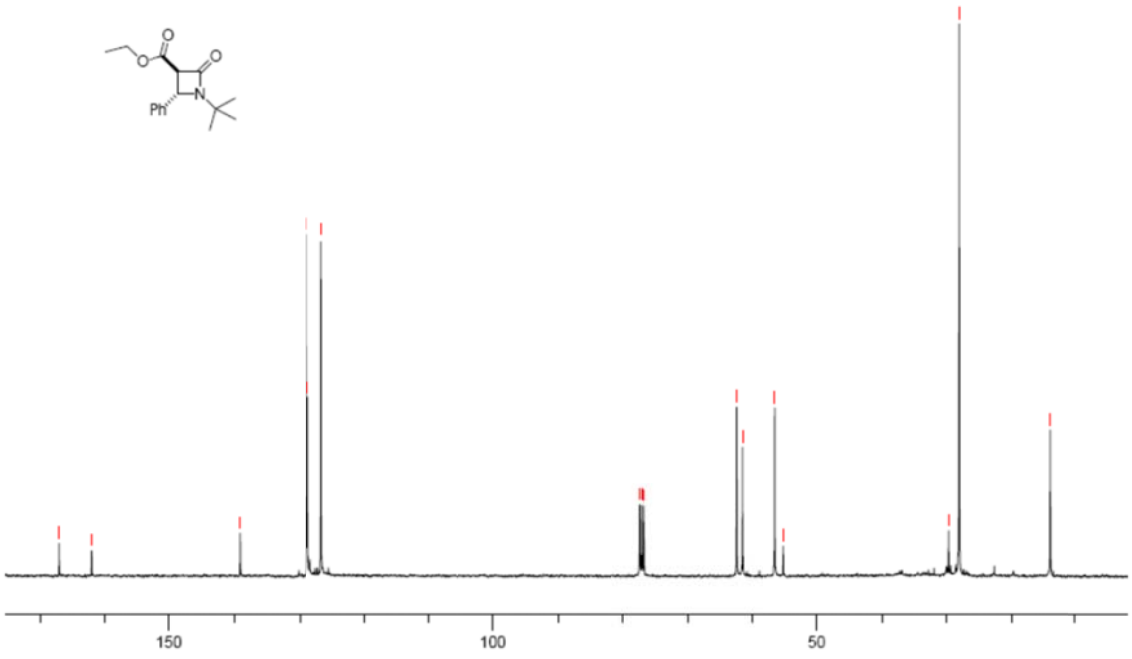


Figure SM 17.9.**10**. ^{13}C NMR (100 MHz, $CDCl_3$) of pure *trans*-*N*-Benzyl-*N*-*tert*-butyl-3-ethoxycarbonyl-4-phenyl-β-lactam

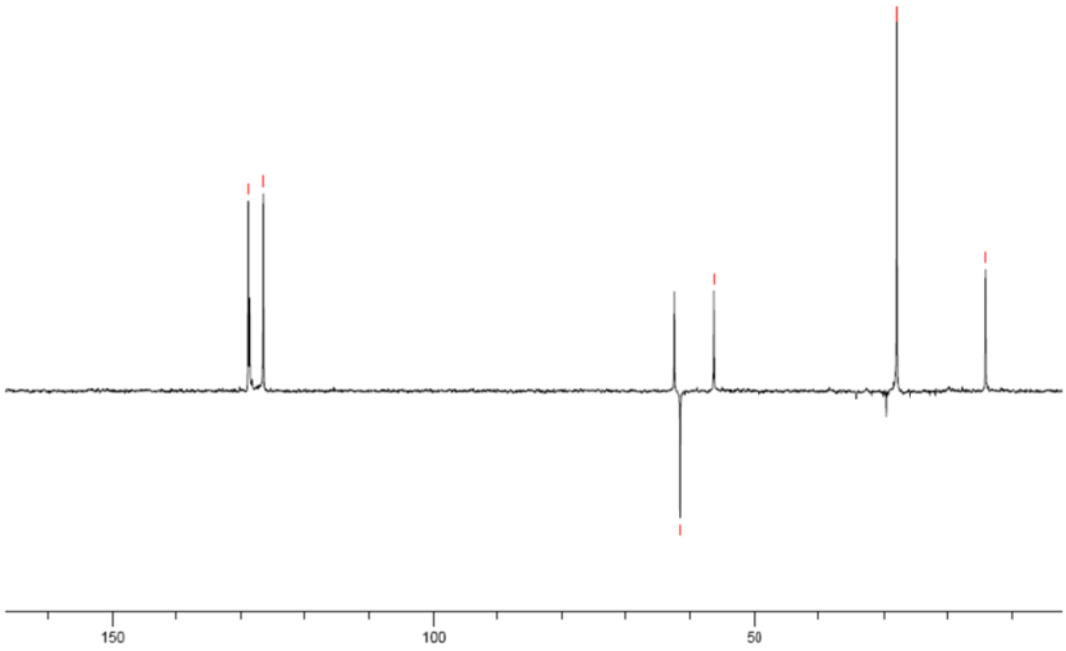


Figure SM 17.9.**11**. DEPT NMR (100 MHz, $CDCl_3$) of pure *trans*-*N*-Benzyl-*N*-*tert*-butyl-*3*-ethoxycarbonyl-4-phenyl-β-lactam

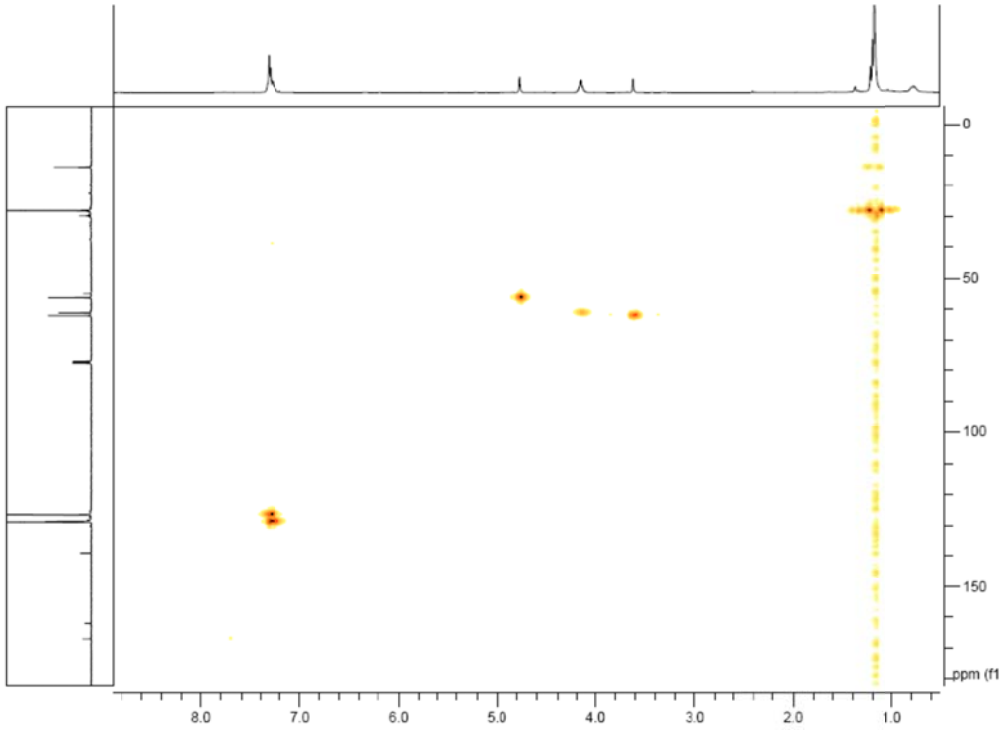


Figure SM 17.9.**12**. HMQC NMR ($CDCl_3$) of pure *trans*-*N*-Benzyl-*N*-*tert*-butyl-*3*-ethoxycarbonyl-4-phenyl-β-lactam

Auxiliary material to answer additional questions

Q1: Due to simplicity of this transformation the reader is instructed to consult any organic chemistry textbook for the mechanism discussion. HCl is used to protonate the excess triethylamine and remove the triethylammonium salt and $NaHCO_3$ is used to remove traces of the carboxylic acid formed from reaction of ethyl malonyl chloride with water.

Q2: A mechanism proposal for the Regitz diazo transfer can be found in the literature.[2] Several other reagents have been developed for this transformation.[3] Open access material for a fruitful discussion can also be found.[4]

Q3: The reader is encouraged to consult some comprehensive reviews on this topic.[5]

Q4: Considering that the hydrogen proton at C-3 in the β-lactam is placed in the α-position to two carbonyls it becomes labile enough to allow the epimerization of the tertiary carbon. The purification with neutral alumina induces the epimerisation of lactam towards the more stable *trans* diastereomer.

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[1] Choi, M. K. W.; Yu, W. Y.; Che, C. M.; *Org. Lett.* **2005**, *7*, 1081.

[2] a) Regitz, M.; *Angew. Chem. Intern. Ed. Engl.*, **1967***, 6*, 733.b) Regitz diazo synthesis, In *Name Reactions*; Springer Berlin Heidelberg, **2006**; pp. 489-491

[3] a) Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J.; *Synthesis*, **2011**, 2549. b) Kitamura, M.; Kato, S.; Yano, M.; Tashiro, N.; Shiratake, Y.;Sando, M.; Okauchi, T.; *Org. Biomol. Chem.*, **2014**, *12*, 4397.

[4] Organic Chemistry Portal, accessed in January 2015, http://www.organic-chemistry.org/synthesis/C2N/diazoesters.shtm

[5] a) Li, C.-J.; Chen, L.; *Chem. Soc. Rev.*, **2006**, *35*, 68; b) Lindström, U. M.; *Chem. Rev.,* **2002***, 102,* 2751.

Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*

Determination of the C-C Bond Strength of Substituted Cyclopropanes and Cyclobutanes Using Bomb Calorimetry

Supplementary Material

Steffanie H. Liskey, Alan R. Esker, and J. M. Tanko

Department of Chemistry, Virginia Tech, Blacksburg, VA 24061

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Determination of C-C Bond Strength of Substituted Cyclopropanes and Cyclobutanes Using Bomb Calorimetry

Steffanie H. Liskey, Alan R. Esker, and J. M. Tanko

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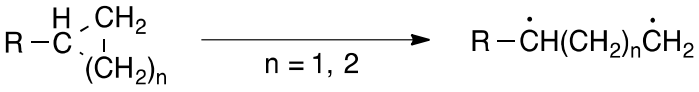
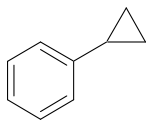
Purpose: To estimate the strength (bond dissociation energy, BDE) of the C_1-C_2 bond of substituted cyclopropanes and cyclobutanes, approximated as $\Delta_r\bar{H}^o$ for Eq. 1.



(**1**)

The specific compounds to be examined (experimentally) will be selected from one of the following: Phenylcyclopropane (**1**), cyclopropyl phenyl ketone (**2**), and cyclobutyl phenyl ketone (**3**). The C-C bond strength of these (and other) compounds will also be examined computationally with molecular orbital theory to calculate the pertinent heats of formation.



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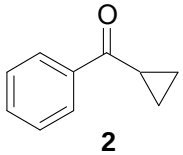

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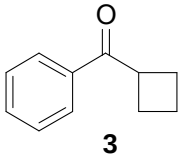

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Semiempirical Molecular Orbital (MO) Theory:

Examine how well semiempirical MO calculations are able to predict C-C bond strengths. Using heats of formation obtained from AM1 (Austin Model 1),[1] calculate $\Delta_r\bar{H}^o$ for hydrogenation of ethane, cyclopropane, ethylbenzene, phenylcyclopropane, cyclopropyl phenyl ketone, and cyclobutyl phenyl ketone in analogy to Eq. 3 in the main text (*i.e.*, R_1-R_2 + H_2 → R_1-H + R_2-H). Higher levels of theory such as density functional theory may also be used.[2-5] Using the BDE's provided in Table 17.10.1 of the main text, calculate the predicted C-C BDE of each of these compounds. How do the calculated values compare to the experimental values? Are the observed trends reasonable? Note: $\Delta_f\bar{H}^o_{H_2(g)}$ = 0 (element in its standard state).

Calculations

1. Heat Capacity of the Calorimeter

The heat capacity of the calorimeter at constant volume (C_v) is determined by measuring the energy released by combustion of a standard compound, such as benzoic acid (BA). Applying the first law of thermodynamics (U_{total} = q + w, where U is the internal energy, q is heat and w is work), one can write an equation to calculate the heat capacity. For a process that is at constant volume, no expansion occurs and work is equal to zero. Hence:

$$\Delta U_{total} = q_v \qquad (\mathbf{2})$$

where we add a subscripted v to q to remind us that the process is at constant volume. For the combustion of a substance, the energy released is:

$$q_v = m\Delta_c \overline{U} \qquad (\mathbf{3})$$

where m is the mass of the sample (g) and $\Delta_c \overline{U}$ is the specific internal energy of combustion (kJ/g) of the material. For benzoic acid, the specific internal energy of combustion is $\Delta_c \overline{U}_{BA}$ = -26.41 kJ/g.

Because one ignites the wire as a means to combust the sample, the value for ΔU_{total} must take into account the energy emitted by combustion of both the sample and the wire. Utilizing equation 3 for each of the components that contribute to the total energy, one can derive the final equation, by which one calculates the heat capacity of the calorimeter:

$$C_v = -(m_{BA}\Delta_c \overline{U}_{BA} + l_w \Delta_c \overline{U}_w)/\Delta T \qquad (\mathbf{4})$$

where m_{BA} and $\Delta_C U_{BA}$ represent the mass and specific internal energy of combustion of benzoic acid, respectively. l_w represents the length of wire that is consumed during combustion, and the energy released by the wire per unit length is represented by $\Delta_c \overline{U}_w$. Finally, ΔT is the observed change in temperature. The Parr Company provides a nichrome wire for use with their bomb calorimeter. The internal energy of combustion of the wire per unit length is $\Delta_c \overline{U}_w$ = -9.6 J/cm.[6]

By definition, the heat capacity of the calorimeter is:

$$C_v = (\partial U_{total}/\partial T)_v \approx (\Delta U_{total}/\Delta T)_v \quad (\mathbf{5})$$

Making the appropriate substitutions leads to:

$$C_v = -[(-26.41kJ/g) \cdot m_{BA} + (-9.6 \times 10^{-3} kJ/cm) \cdot (L_o - L)]/\Delta T \quad (\mathbf{6})$$

where m_{BA} is the mass of benzoic acid in grams, L_o and L are the initial and final lengths of the nichrome wire in cm, and ΔT is the observed temperature change in degrees Celcius (or Kelvin).

2. Heat of Combustion Calculation

Having determined the heat capacity of the calorimeter, the heats of combustion of the compounds of interest can be calculated. A modified version of equation 5 is used to calculate the internal energy released by the combustion of any compound (cpd):

$$\Delta_c U_{cpd} = -C_v \Delta T - l_w \Delta_c \overline{U}_w = -C_v \Delta T + (9.6 \times 10^{-3} kJ/cm) \cdot (L_o - L) \quad (\mathbf{7})$$

and if the moles of compound are known (n_{cpd}), the molar internal energy of combustion is:

$$\Delta_c \overline{U}_{cpd} = \Delta_c U_{cpd}/n_{cpd} \quad (\mathbf{8})$$

As the enthalpy is defined as $\overline{H} = \overline{U} + p\overline{V}$, one may write $\Delta\overline{H} = \Delta\overline{U} + \Delta(p\overline{V})$. Assuming ideal gas behavior and isothermal conditions, the enthalpy of combustion is:

$$\Delta_c \overline{H}_{cpd} = \Delta_c \overline{U}_{cpd} + RT\Delta\nu \quad (\mathbf{9})$$

where R is the gas constant, T is the initial temperature expressed in Kelvin, and $\Delta\upsilon$ is defined as:

$$\Delta\nu = \sum_{j=1}^{k} \nu_{j,gaseous\ products} - \sum_{j=1}^{l} \nu_{j,gaseous\ reactants} \quad (\mathbf{10})$$

were the υ_j are the stoichiometric coefficients (positive numbers) of the k different gaseous products and l different gaseous reactants in the balanced chemical equation. Note: Oxygen and carbon

dioxide are the only gases used, or produced for a room temperature reaction assuming complete combustion and a compound composed of only carbon, hydrogen and oxygen.

One final correction is needed. The experiment was conducted at high pressure in the calorimeter, not standard conditions (*i.e.*, 1 bar pressure). While this situation is of little concern for liquids and solids, a correction is required for gases.

Using naphthalene ($C_{10}H_8$) as an example, the combustion under "standard" conditions is outlined in Eq. 11:

$$C_{10}H_8\ (s) + 12\ O_2\ (g, 1\ atm) \rightarrow 10\ CO_2\ (g, 1\ atm) + 4\ H_2O\ (l) \qquad \Delta_c\overline{H}^o \qquad (\mathbf{11})$$

Of course, the combustion was not performed at 1 atm pressure, but rather at high pressure, P:

$$C_{10}H_8\ (s) + 12\ O_2\ (g, P) \rightarrow 10\ CO_2\ (g) + 4\ H_2O\ (l) \qquad . \ \Delta_c\overline{H} \qquad (\mathbf{12})$$

Noting that enthalpy is a function of T and P, it is possible to define the Euler relationship:

$$\left(\frac{\partial\overline{H}}{\partial P}\right)_T\left(\frac{\partial P}{\partial T}\right)_{\overline{H}}\left(\frac{\partial T}{\partial\overline{H}}\right)_P = -1 \qquad (\mathbf{13})$$

or

$$\left(\frac{\partial\overline{H}}{\partial P}\right)_T = -\left(\frac{\partial T}{\partial P}\right)_{\overline{H}}\left(\frac{\partial\overline{H}}{\partial T}\right)_P = -\mu_{JT}\overline{C}_p \qquad (\mathbf{14})$$

where $\bar{C}_p$ is the molar isobaric heat capacity and μ_{JT} is the Joule-Thomson coefficient. By integrating Eq. 14 from the initial pressure P_i to the final pressure P_f,

$$\Delta\overline{H}_{corr} = \int_{H_i}^{H_f} d\overline{H} = -\int_{P_i}^{P_f} \mu_{JT}\overline{C}_p \ dP = -\mu_{JT}\overline{C}_p(P_f - P_i) \qquad (\mathbf{15})$$

one obtains the change in enthalpy associated with a change in pressure by assuming that $\bar{C}_p$ and μ_{JT} are pressure independent. For a reactive system, Eq. 15 leads to:

$$\Delta\overline{H}_{corr} = -\left[\sum_{j=1}^{k}\int_{Pi}^{Pf} \upsilon_{j,\,\text{products}}\mu_{\text{JT, j}}\overline{C}_{p,j}dP - \sum_{i=1}^{l}\int_{Pi}^{Pf} \upsilon_{j,reac\,tan\,ts}\mu_{JT,j}\overline{C}_{p,j}dP\right] \quad (\mathbf{16})$$

The application of Eq. 16 to the complete combustion of sample containing carbon, hydrogen, and oxygen yields:

$$\Delta_c\overline{H}_{corr} = -\left[\nu_{CO_2}\mu_{JT,CO_2(g)}\bar{C}_{p,CO_2(g)}(p_f - p_i) - \nu_{O_2}\mu_{JT,O_2(g)}\bar{C}_{p,O_2(g)}(p_f - p_i)\right] \quad (\mathbf{17})$$

where P_i = P and P_f = 1 bar, the standard state.

The molar heat capacity and Joule-Thomson coefficients of O_2 and CO_2 are: CO_2 ($\bar{C}_p$ = 37.14 J mol^{-1} K^{-1}, μ_{JT} = 1.115 K bar^{-1}) and O_2 ($\bar{C}_p$ = 29.72 J mol^{-1} K^{-1}, μ_{JT} =0.314 K bar^{-1}).

Thus,

$$\Delta_c\overline{H}^o = \Delta_c\overline{H} + \Delta_c\overline{H}_{corr} \quad (\mathbf{18})$$

For the naphthalene example at P_i = P:

$$\Delta_c\overline{H}^o = \Delta_c\overline{H} - \begin{bmatrix} 10\,(1.115\,\text{K bar}^{-1})(37.14\,\text{J mol}^{-1}\,\text{K}^{-1}) \\ -12\,(0.314\,\text{K bar}^{-1})\,(29.72\,\text{J mol}^{-1}\,\text{K}^{-1}) \end{bmatrix}(1\,\text{bar} - \text{P}) \quad (\mathbf{19})$$

3. Calculation of the Heat of Formation

The next step is to convert the enthalpy of combustion into an enthalpy of formation. This task is accomplished by means of a thermochemical cycle, illustrated below using naphthalene as an example. By definition, the enthalpy of formation of naphthalene is the enthalpy of the following reaction:

10 C (s, graphite) + 4 H_2 (g) → $C_{10}H_8$ (s), $\Delta_r\overline{H}^o = \Delta_f\overline{H}^o_{C_{10}H_8(s)}$

This overall reaction can also be achieved by adding three reactions pertaining to the combustion of graphite, hydrogen, and naphthalene depicted below:

10 x [C (s, graphite) + O_2 (g) → CO_2 (g), $\Delta_r\overline{H}^o = \Delta_c\overline{H}^o_{C(s,graphite)}$]

4 x [H_2 (g) + ½ O_2 (g) → H_2O (l), $\Delta_r\overline{H}^o = \Delta_c\overline{H}^o_{H_2(g)}$]

10 CO_2 (g) + 4 H_2O (l) → $C_{10}H_8$ (s) + 12 O_2 (g), $\Delta_r\overline{H}^o = -\Delta_c\overline{H}^o_{C_{10}H_8(s)}$

Because enthalpy is a state function, it follows that:

$$\Delta_f\overline{H}^o_{\mathrm{C_{10}H_8\ (s)}} = -\Delta_c\overline{H}^o_{\mathrm{C_{10}H_8\ (g)}} + 10\ \Delta_c\overline{H}^o_{\mathrm{C\ (s,\ graphite)}} + 4\ \Delta_c\overline{H}^o_{H_2(g)} \qquad (\mathbf{20})$$

In fact, by similar reasoning, it can be shown that for any organic compound whose molecular formula is $C_mH_nO_p$, the heat of formation can be related to the heats of combustion by the relationship:

$$\Delta_f\overline{H}^o_{C_mH_nO_p} = -\Delta_c\overline{H}^o_{C_mH_nO_p} + m\Delta_c\overline{H}^o_{\mathrm{C\ (s,\ graphite)}} + \left(\frac{n}{2}\right)\Delta_c\overline{H}^{\mathrm{o}}_{\mathrm{H_2\ (g)}} \qquad (\mathbf{21})$$

or plugging in the heats of combustion of graphite and hydrogen:

$$\Delta_f\overline{H}^o_{C_mH_nO_p} = -\left[\Delta_c\overline{H}^o_{C_mH_nO_p} + 393.51m + 142.92n\right]\ \ in\ kJ/mol \qquad (\mathbf{22})$$

References

1. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P., *Am1: A new general purpose quantum mechanical molecular model*, *J. Am. Chem. Soc.* **1985,** *107*, 3902 - 3909.

2. Becke, A. D., *Density-functional thermochemistry. Iii. The role of exact exchange*, *J. Chem. Phys.* **1993,** *98* (7), 5648 - 5651.

3. Hariharan, P. C.; Pople, J. A., *Chem. Phys. Lett* **1972,** *66*, 217.

4. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A., *Ab initio molecular orbital theory*. Wiley: New York, 1986.

5. Lee, C.; Yang, W.; Parr, R. G., *Development of colle-salvetti correlation-energy formula into a functional of electron density*, *Phys. Rev. B.* **1988,** *37* (2), 785 -789.

Instructor Notes

A. Materials

Benzoic acid (65-85-0): For calibration of the calorimeters. Available from Parr Instrument Company as a 1 gram pellet and from the National Institute of Standards & Technology (NIST SRM 350b.)

One (or more if desired) of the following pairs of compounds, all available from Aldrich Chemical Company:

a) Cyclopropylbenzene (CA: 873-49-4) and n-propylbenzene (CA: 103-65-1)

b) Cyclopropyl phenyl ketone (CA: 3481-02-5) and butyrophenone (CA: 495-40-9)

c) Cyclobutyl phenyl ketone (CA: 5407-98-7) and valerophenone (CA: 1009-14-9)

B. Equipment/Procedures

A bomb calorimeter such as the Parr 1341 oxygen bomb calorimeter. Detailed instructions for use of the calorimeter are available from the manufacturer online at http://www.parrinst.com/. Note: To access some features of this website, you may need to register (free of charge). These instructions also provide detailed instructions for measuring ΔT (the temperature change resulting from combustion of the sample), and for converting the observed ΔT values into heats of combustion. (The procedure outlined in the student handout describes how to convert ΔT into a heat of combustion and heat of formation; students are referred to the Parr manual or their physical chemistry laboratory text for the determination of ΔT. Texts such as such those authored by Garland, et al. and Halpern have nice sections on bomb calorimetry. We have used both these texts in our physical chemistry lab course, and with the text and handout in hand, students have more than enough information regarding the use and calibration of the equipment and calculations leading to the final heat of formation).

C. Tips for success

- Temperature measurement is critical in these experiments. An error of $\pm$ 0.01 ^{o}C translates into about a 20 kJ/mol (5 kcal/mol) error in the derived heat of formation. Since students must first combust a sample a benzoic acid to determine the heat capacity of the calorimeter, then

combust two separate organic compounds to determine their $\Delta_f \overline{H}^o$ values, and then use these $\Delta_f \overline{H}^o$ values to determine the C-C BDE of interest, these errors add up quickly.

- Because a small amount of material (<1 gram) is combusted, careful weighing is also important. A 0.001 g error in weighing will affect the final heat of formation by nearly 8 kJ/mol (2 kcal/mol).

- The calculations for this lab are fairly detailed, and students typically did not perform them correctly on their first attempt. The consequence was that although they had reasonable data, errors in calculations led to final BDEs which were ridiculously off (*i.e.*, prohibitively high, or negative). A solution to this problem was to provide students with a prelab exercise which requires them to perform the basic calculations required for this experiment in advance: a) Calibration of the calorimeter, b) determination of a heat of formation, and c) computation of a C-C bond strength. A copy of the exercise and a key are appended.

- Round off errors can also add up quickly when doing the fairly long series of calculations. Students should be advised to avoid truncating significant figures during the series of calculations, and wait until reporting the final derived heats of formation and BDEs before they consider significant figures.

- Sample volatility of cyclopropylbenzene and n-propylbenzene can be a problem, because the calorimeter is typically purged several times with oxygen (to remove nitrogen which can undergo combustion and thus affect the results). In most cases, this is not a problem if the students are careful (*i.e.*, during the purge sequence, depressurize the calorimeter *slowly*.) Volatility is much less of a problem with the carbonyl compounds because of a) increased molecular weight, and b) the presence of a polar functional group.

- One solution attempted to address the volatility problem associated with cyclopropylbenzene and *n*-propylbenzene involved the use of combustible gel capsules, which are available from Parr. In our experience, this “solution” only made matters worse. The heat output (which had to be determined via combustion of the capsules) from these capsules proved to be too variable, likely attributable to variations during production. In addition, a separate titration is suggested to correct for the nitrogen and sulfur content of the capsules.

D. General Comments

Our laboratory course has been running this experiment for over ten years. Results from the Spring 2004 semester (*ca*. 80 – 100 students) are summarized in Table **SM 17.10.**2. Also included in Table **SM 17.10.**2 are literature (where available or calculable) and calculated values for the C-C bonds of interest obtained by various levels of molecular orbital calculations. The major source of scatter in the students' reported BDE's, approaching ± 40 kJ/mol for cyclobutyl- and cyclopropyl phenyl ketone, is undoubtedly related to uncertainty in the measurement of temperature. At the scale of this experiment, ΔT is typically on the order of 2 – 3 degrees. An error of ± 0.01 °C translates to ca. ± 20 kJ/mol in the derived heat of formation, and these errors propagate in the final calculation of the C-C BDE. For cyclopropylbenzene/*n*-propylbenzene, there is even more scatter in the data, mainly attributable to the volatility of these compounds. Use of a combustible gel capsule to eliminate evaporative loss did not significantly improve the results.

Table SM 17.10.2. C_1-C_2 bond strengths obtained experimentally and by molecular orbital calculations

compound	BDE (C_1-C_2, kJ/mol)				
	experiment[a]	molecular orbital calculations			literature
		AM1	PM3	DFT[b]	
CH_3CH_3	---	444	410	360	380[c]
c-C_3H_6	---	230	240	210	260[d]
c-C_4H_8	---	280	300	220	260[e]
$C_6H_5CH_2CH_3$	---	360	340	300	330[c]
C_6H_5-*c*-C_3H_5	220 ± 75	170	180	160	230[f]
Bz-*c*-C_3H_5	230 ± 30	190	210	200	
Bz-*c*-C_4H_7	260 ± 30	240	270	200	
$BzCH_2CH_3$	---	390	370	330	

[a]Reported ± one standard deviation. [b]B3LYP/6-31G* (References 12 - 15, main text). [c]Reference 4, main text. [d]Reference 3, main text. [e]Reference 5, main text. [f]Calculated from heats of formation based upon Eqs. X.3 and X.4, main text.

Overall, this experiment works very well for most students. The derived C-C BDE's are in the range expected. By examining a broader range of compounds, the results from MO theory provide the basis for further discussion, *e.g.*, comparision of theory vs. experiment and the "chemical explanation" for observed trends in the data.

Learning Outcomes

This experiment demonstrates basic principles of thermodynamics and bomb calorimetry, as well as providing an introduction to the use of molecular modeling to obtain data for systems which compliment the experimental work and cannot easily be studied in the lab. The experiment illustrates how basic thermodynamic data such as a heat of formation can be used in the context of a thermochemical cycle to obtain a fundamental physical property such as bond strength. The diversity of the compounds examined allows students to probe the effect of structure (conjugation and ring strain) on bond strength. As part of their laboratory report, students are also asked to extend this method to other systems. For example, the strength of the C_2-C_3 bond in cyclopropylbenzene can be estimated by studying this compound in conjunction with isopropylbenzene.

Prelab Quiz (Take-Home) on Bomb Calorimetry

Note: This exercise must be completed and turned in on the day you first use the calorimeter.

1. 1.027 g of benzoic acid is placed in calorimeter #1, and a nichrome wire fuse 10.0 cm in length is attached. After ignition, the observed temperature increase is 2.65 ^{o}C; 4.2 cm of the fuse wire remains. Calculate the heat capacity (C) of calorimeter #1.

2. Using calorimeter #2, whose heat capacity was previously determined to be 10.50 kJ/K, a 0.7110 g sample of *n*-propylbenzene was placed in the calorimeter, a 9.8 cm fuse wire was connected, and (after purging with oxygen), the pressure was brought to 29.9 bar. Combustion resulted in a temperature increase of 2.68 ^{o}C. After combustion, 3.2 cm of the fuse wire remained. Calculate the standard heat of combustion and heat of formation of *n*-propylbenzene.

3. The AM1-calculated heats of formation of cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, butyrophenone, and valerophenone are 14.77, -2.78, -24.74, and -34.54 kcal/mol, respectively. Estimate the C_1-C_2 bond strength of phenyl cyclopropyl ketone in kJ/mol. Note 1 kcal/mol = 4.184 kJ/mol

KEY

1)

$$C_v = \frac{-\left[-(26.41\,\frac{\text{kJ}}{\text{g}})(1.027\text{ g}) - 9.6\text{x}10^{-3}\,\frac{\text{kJ}}{\text{cm}}(10.0-4.2)\text{ cm}\right]}{2.65\text{ K}}$$

$$= 10.2561\text{ kJ/K (10.3 kJ/K)}$$

2)

$$\Delta\overline{U} = \frac{(-10.50\,\frac{kJ}{K})(2.68\,K) + 9.6x10^{-3}\,\frac{kJ}{cm}(9.8-3.2)\,cm}{\left(0.7110\,g \Big/ 120.20\,\frac{g}{mol}\right)}$$

$$= -4746.57\,kJ/mol$$

$C_6H_5CH_2CH_2CH_3$ (l) + 12 O_2 (g) → 9 CO_2 (g) + 6 H_2O (l)

$\Delta\upsilon = 9 - 12 = -3$

$$\Delta_c\overline{H} = \Delta\overline{U} + \Delta\upsilon RT$$

$$= -4746.57\,\frac{kJ}{mol} + (-3)\left(\frac{8.314x10^{-3}\,kJ}{molK}\right)(298\,K)$$

$$= -4754.00\,kJ/mol$$

$$\Delta\overline{H}_{corr} = -\left[\left((1.115\,\frac{K}{bar}((37.14\,\frac{J}{molK})(9) - (0.314\,\frac{K}{bar})(29.72\,\frac{J}{molK})(12)\right)\right](1-29.9)\,bar$$

$$= +7534.7\,J/mol$$

$$= +7.54\,kJ/mol$$

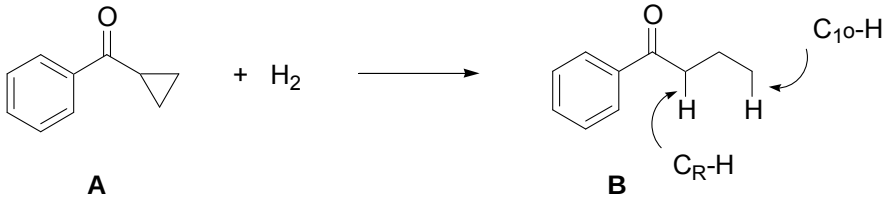
$$\therefore \Delta_c\overline{H}^o = -4754.00\,kJ/mol + 7.54\,kJ/mol$$

$$= -4746.46\,kJ/mol (-4750\,kJ/mol)$$

$$\Delta_f\overline{H}^o = -\big(-4746.67 + 9(395.51) + 12(142.92)\big)\,kJ/mol$$

$$= -527.95\,kJ/mol (-528\,kJ/mol)$$

3)



A **B**

$$\Delta_f H_B^o - \Delta_f H_A^o = BDE(C-C) + BDE(H-H) - BDE(C_R - H) - BDE(C_{1^o} - H)$$

$$\begin{aligned} BDE(C-C) &= \Delta_f H_B^o - \Delta_f H_A^o - BDE(H_2) + BDE(C_R - H) + BDE(C_{1^o} - H) \\ &= \left[(-24.74) - (14.77) - 104.2) + (92.2) + (100.8)\right] \ kcal/mol \\ &= 49.3 \ kcal/mol \\ &(= 206 kJ/mol) \end{aligned}$$