Solvent-Free Aldol Condensation Reactions: Synthesis of Chalcone Derivatives

Supplementary Material

Experiment Notes

Figures

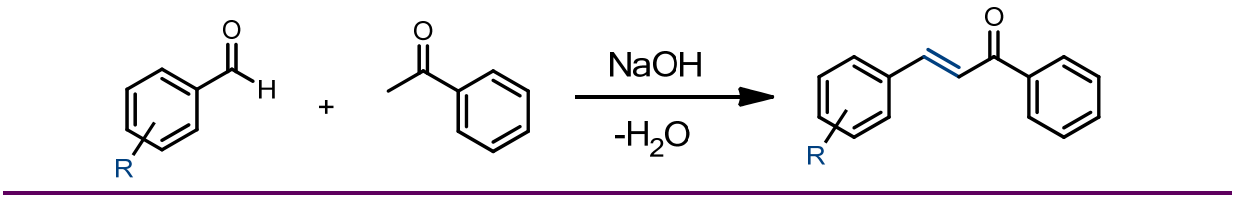
Instructor Notes

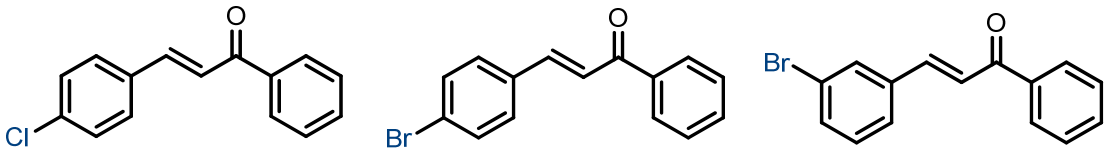
This inquiry-based laboratory features one of the most powerful carbon-carbon bond forming reactions in organic chemistry while highlighting several green and sustainable principles. At the beginning of the experiment, each student obtains an “unknown” benzaldehyde derivative (4-chlorobenzaldehyde, 4-bromobenzaldehyde, or 3-bromobenzaldehyde) to use in the solvent-free aldol condensation. The procedure involves grinding acetophenone with one equivalent of sodium hydroxide and benzaldehyde derivative for ten minutes using a mortar and pestle. Each chalcone is then isolated by suction filtration after washing with water. Although the crude chalcone is often found to have sufficient purity for product characterization, recrystallization is performed with 95% ethanol to remove trace impurities. Once students isolate their product, they use a variety of techniques (melting point determination, thin-layer chromatography (TLC), NMR and IR spectroscopy) in order to determine the identity of their chalcone. This simple experiment is ideal for intermediate organic chemistry students as it is easily and consistently executed in high yield, incorporates problem solving and highlights green chemistry principles as the synthesis minimizes waste production (no reaction solvent) and proceeds with high atom economy.

This experiment was designed for CHM 249 (Organic Chemistry) at the Department of Chemistry at the University of Toronto. The undergraduate program in the Department of

Chemistry includes a first year twelve week introductory course in organic chemistry. In second year, degree students continue with CHM 249 (enrollment of approximately 60-80 students), which takes place over a twelve week semester. This specialist course introduces students to numerous organic transformations with an emphasis on mechanistic theory and synthetic applications. The course also incorporates eleven weeks of laboratory work (4.5 h each week) which provides students with valuable hands-on experience.

This experiment was developed with two undergraduate students who tested the reproducibility of the experiment prior to its introduction into CHM 249 where it was performed by an additional 129 students over two years. After implementing this new laboratory, positive feedback was received from students who enjoyed learning about solvent-free reactions and carrying out the grinding technique. The results can be found in Scheme SM 4.2.2.1.1.





	4-chlorochalcone	4-bromochalcone	3-bromochalcone
Recrystallized Yield (%)[c]:	68-83[a]	56-65[a]	59-65[b]
Melting Point (°C):	113-117	117-119	83-85

[a] Average of 50-55 total trials. [b] Average of 30-35 total trials. [c] Crude yields are often near quantitative. It is suspected that the yields drop significantly during the recrystallization due to student error.

Scheme SM 4.2.2.1.1 – Chalcone synthesis results

Experimental Tips

As the experiment requires students to use 5 mmol of benzaldehyde derivatives of varying molecular weight, it is recommended that samples are provided in vials to maintain benzaldehyde anonymity. It is recommended that the vials be labelled

"unknown A", "unknown B", and "unknown C" corresponding to 4-chlorobenzaldehyde, 4-bromobenzaldehyde, and 3-bromobenzaldehyde, respectively.

- At room temperature, 4-chlorobenzaldehyde and 4-bromobenzaldehyde are both white solids while 3-bromobenzaldehyde is a colorless liquid (mp 20 °C). It is recommended that all sample vials are kept in a chemical refrigerator prior to the experiment and stored on ice during the experiment in order to maintain benzaldehyde anonymity, as all derivatives are white solids at reduced temperatures.
- Although the melting points of 4-bromochalcone (117-119 °C) is similar to 4-chlorochalcone (113-117 °C), students rarely confuse the two since the products are of sufficient purity to obtain accurate melting point data.

Optional Modifications

This experiment was designed for a 2-3 hour laboratory session where students perform one chalcone synthesis and a variety of characterization techniques. However, there are several procedural modifications that can be employed to cater to your unique teaching laboratory:

Experiment Simplification:

- Instructors may choose to disclose the identity of the benzaldehyde derivatives
- TLC analysis can be a time consuming technique for students with limited experience, and as such, can be omitted from the experiment.
- Students can analyze the purity and structure of their unique chalcone by collecting IR and ^{1}H NMR spectra independently, but these methods may be time consuming and costly. Alternatively, the spectra (one or both) can be provided directly to students for post-laboratory analysis. For example, students may collect an IR spectrum of their chalcone product while the ^{1}H NMR can be provided in the laboratory manual.

Experiment Extension:

- Students may perform two or three chalcone syntheses if time permits. Alternatively, students can work in groups of three where each student performs a unique chalcone synthesis. After each student isolates pure product, they can share the material with each partner for independent analysis. This method allows each student to gain experience with one chalcone synthesis but enhances the inquiry-based learning component of the experiment as they are required to characterize all three chalcones.

Experimental Photos

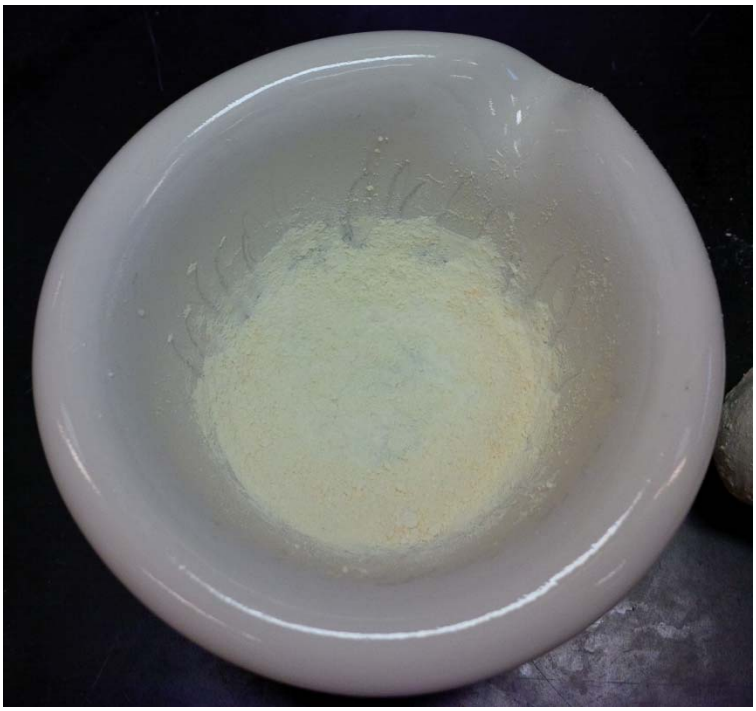


Figure SM 4.2.2.1.1 – Reaction mixture after grinding for 10 minutes.

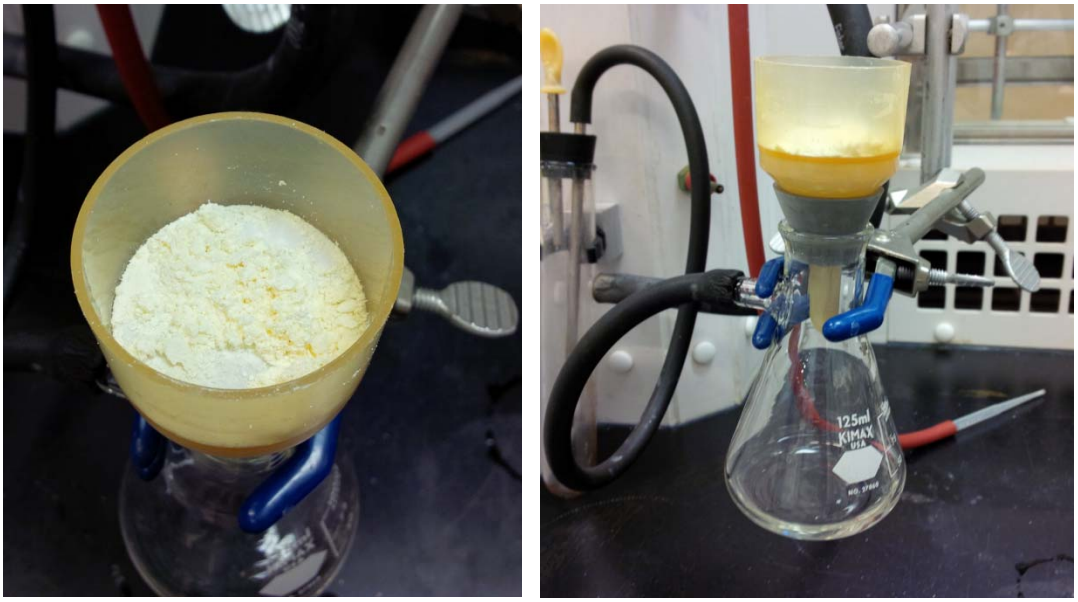


Figure SM 4.2.2.1.2 – Collection of the crude solid by suction filtration on a Büchner funnel.

Figure SM 4.2.2.1.3 – Pure chalcone products after recrystallization (all pale yellow crystals).

^{1}H NMR Spectra

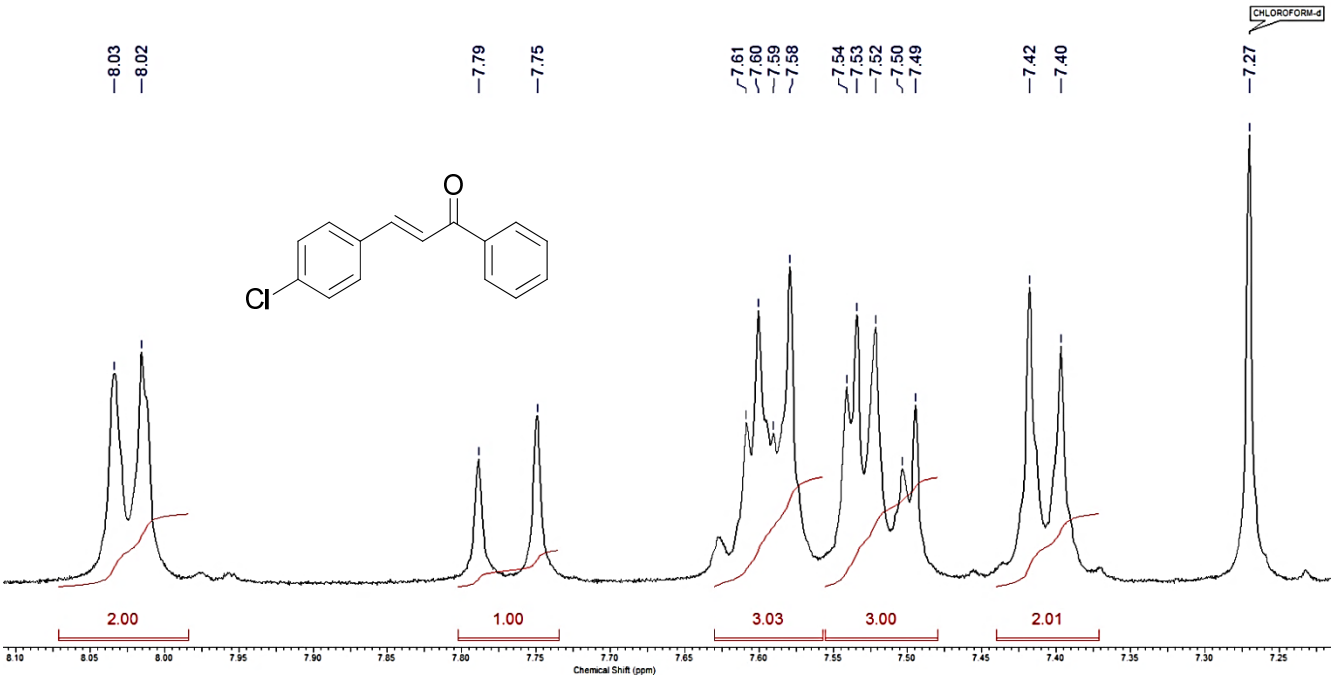


Figure SM 4.2.2.1.4: ^{1}H NMR spectrum of *trans*-4-chlorochalcone ($CDCl_3$, 400 MHz)

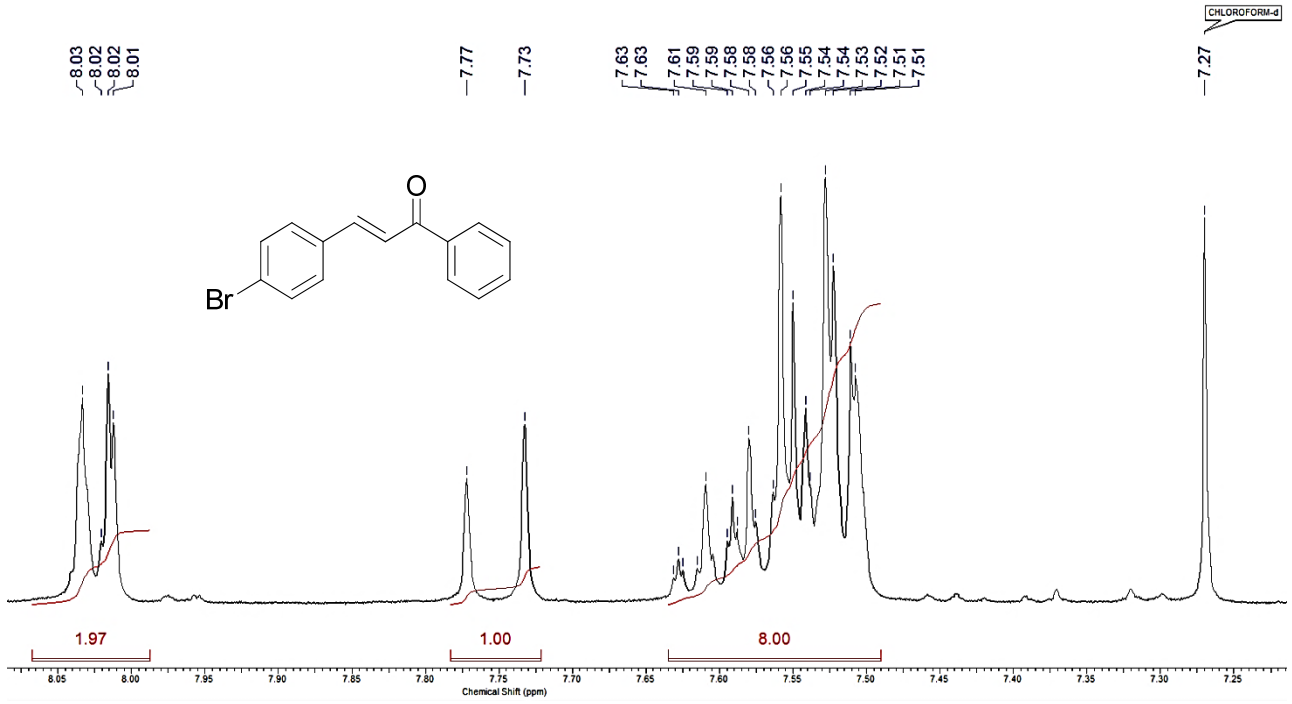


Figure SM 4.2.2.1.5: ^{1}H NMR spectrum of *trans*-4-bromochalcone ($CDCl_3$, 400 MHz)

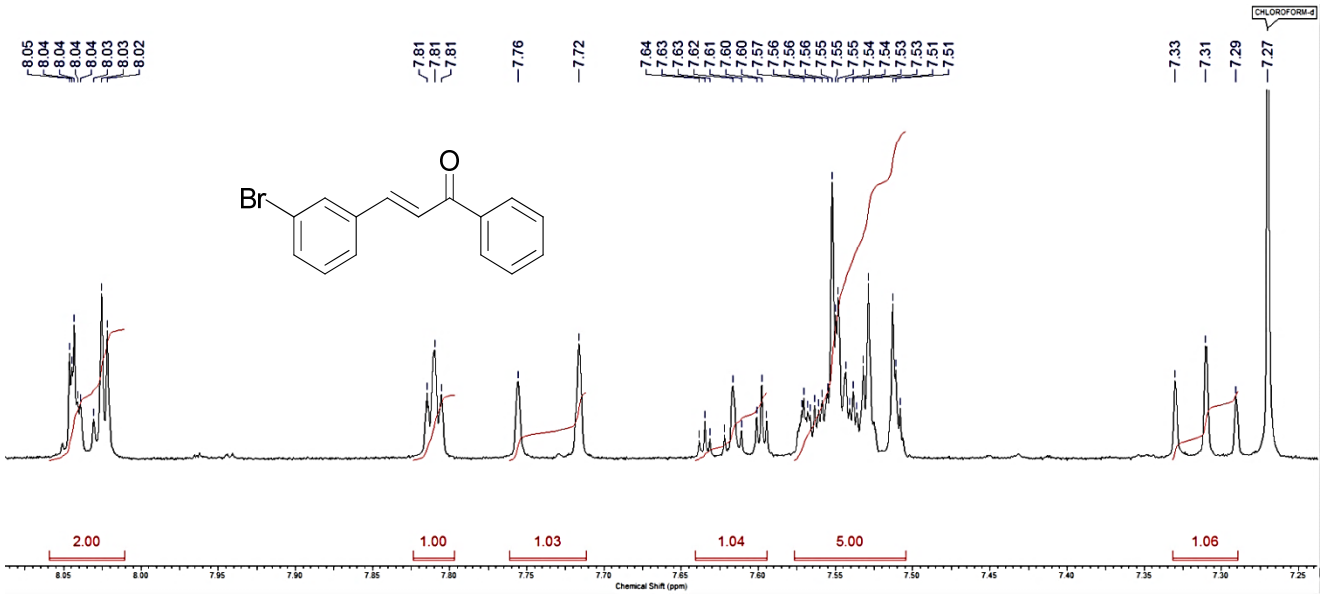


Figure SM 4.2.2.1.6: ^{1}H NMR spectrum of *trans*-3-bromochalcone ($CDCl_3$, 400 MHz)

IR Spectra

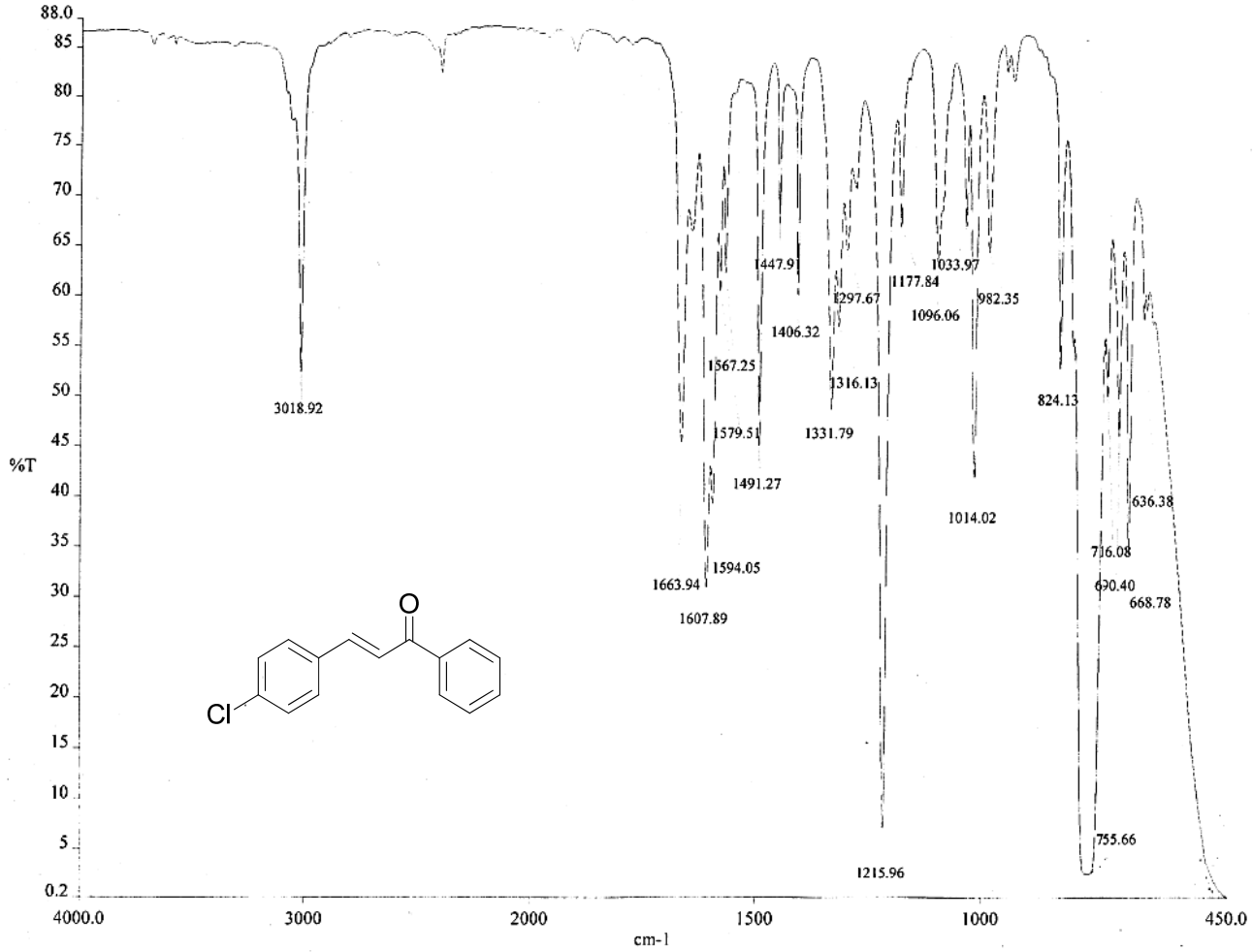


Figure SM 4.2.2.1.7: IR spectrum of *trans*-4-chlorochalcone ($CHCl_3$ solution)

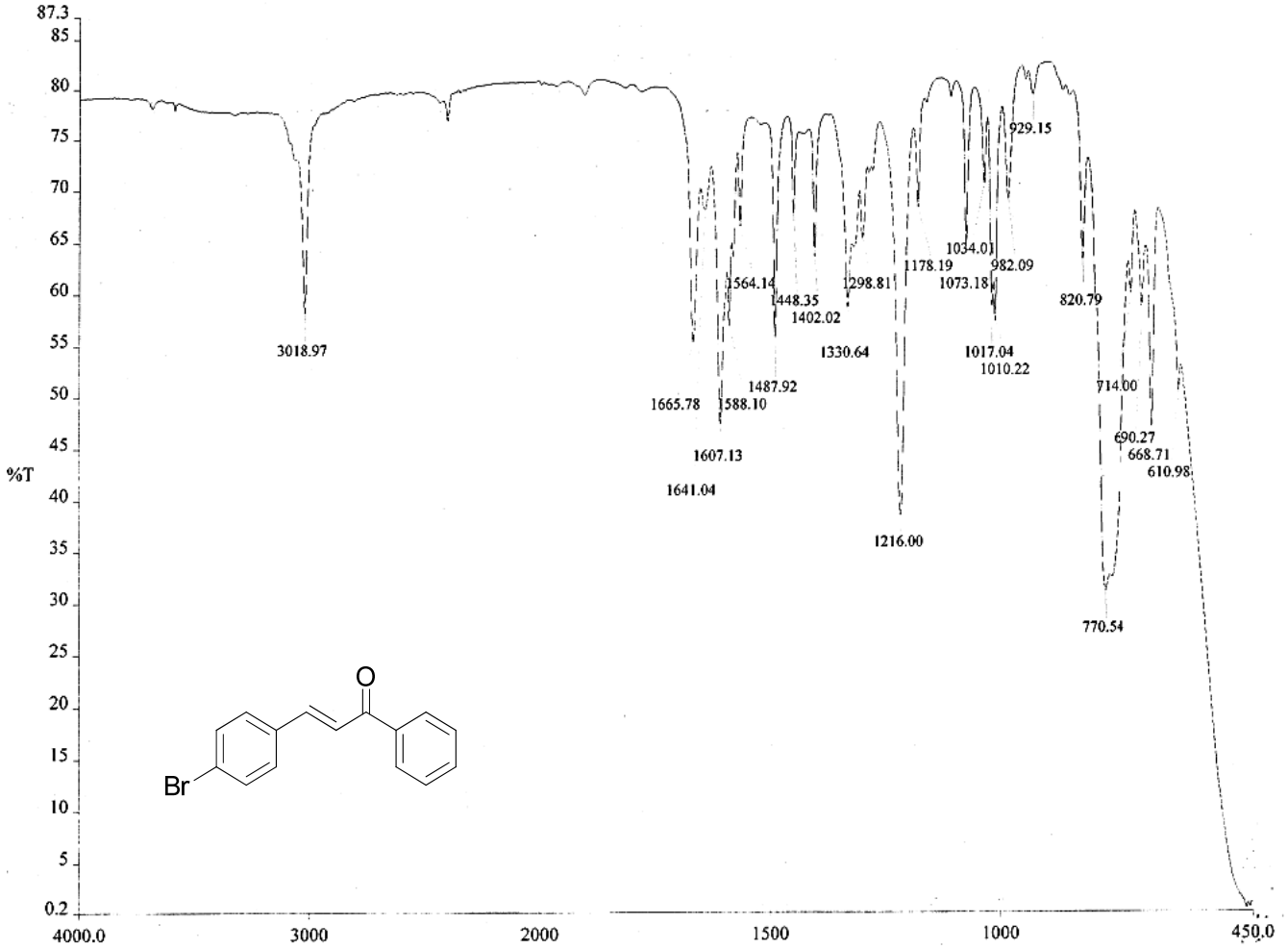


Figure SM 4.2.2.1.8: IR spectrum of *trans*-4-bromochalcone ($CHCl_3$ solution)

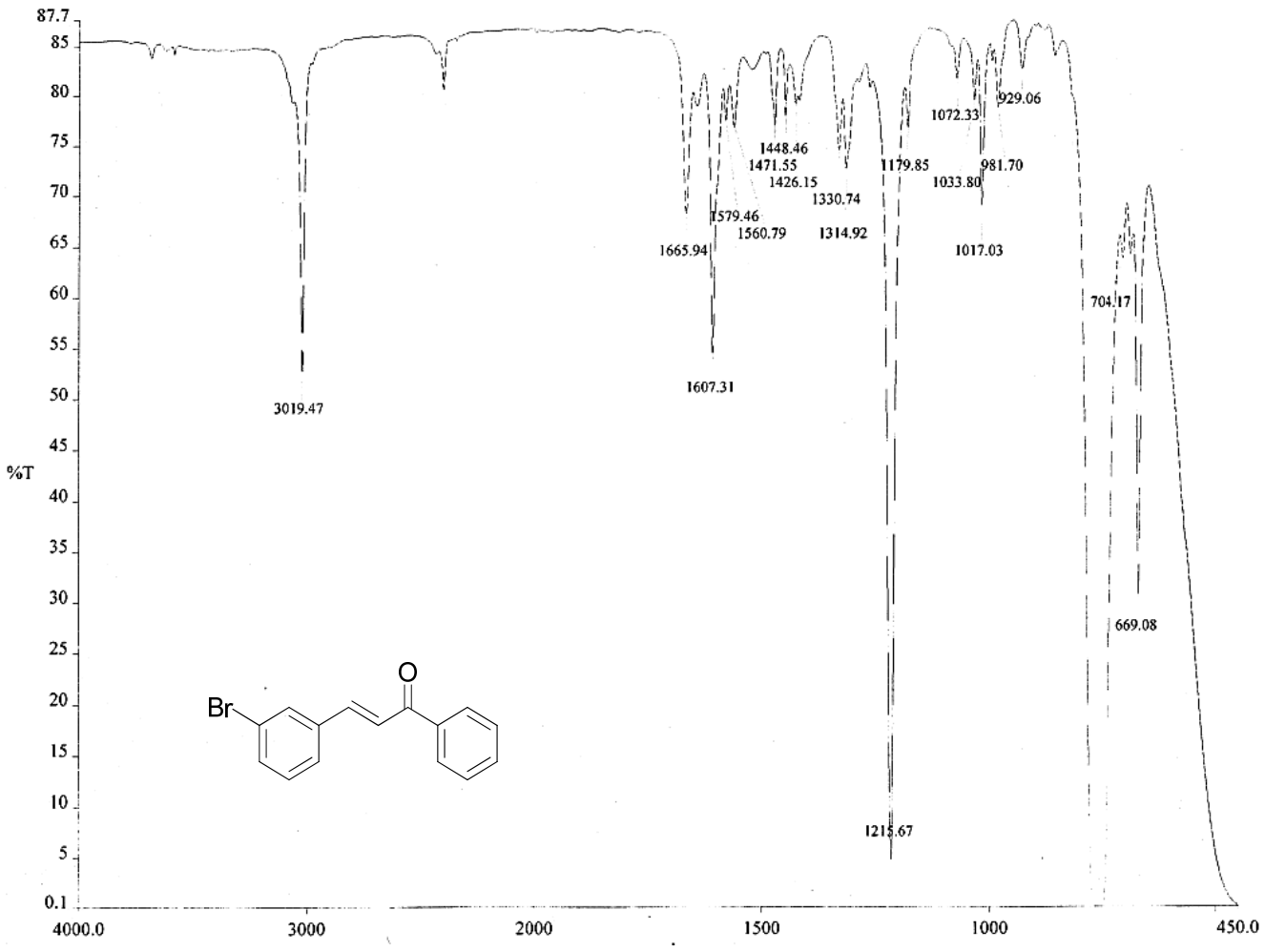


Figure SM 4.2.2.1.9: IR spectrum of *trans*-3-bromochalcone ($CHCl_3$ solution)

Thin-Layer Chromatography (TLC) Analysis

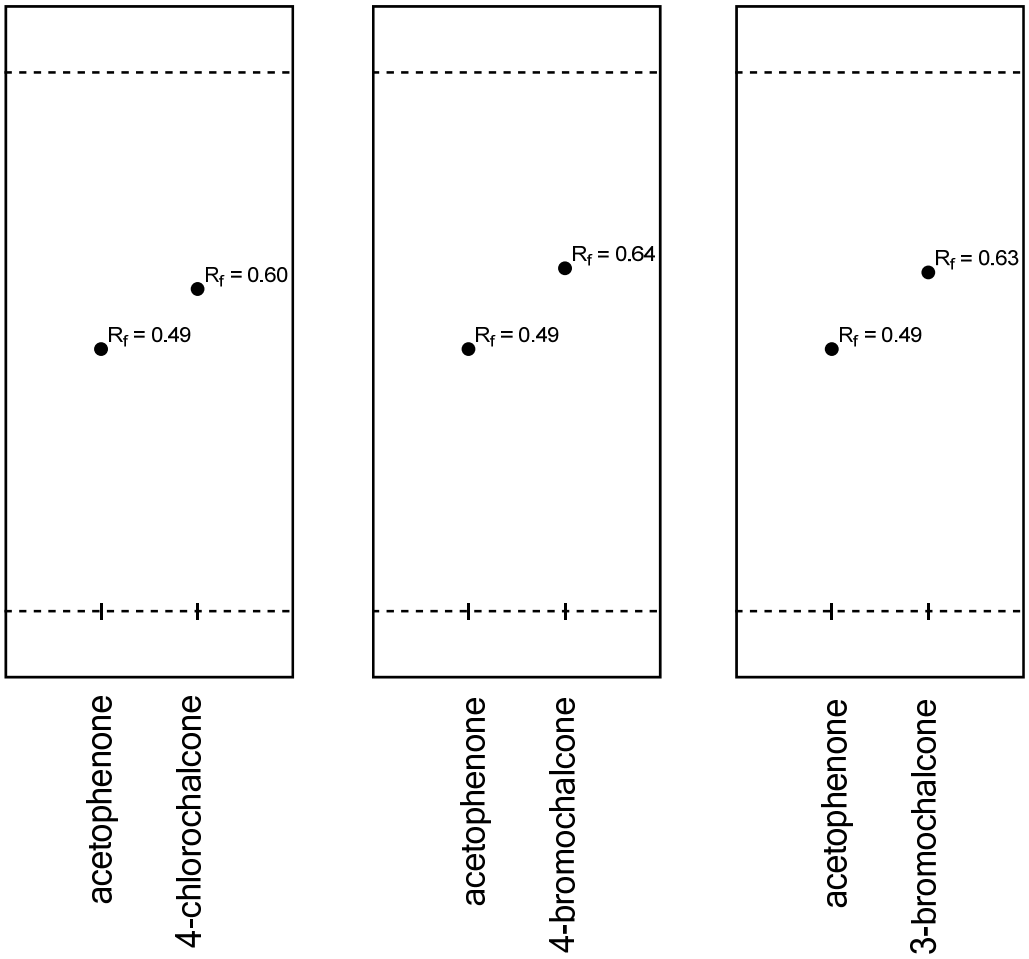


Figure SM 4.2.2.1.10: Chalcone TLC analysis. Each chalcone was run alongside acetophenone using a 3:1 hexanes/ethyl acetate solvent system.

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Synthesis of (*E*)-chalcones [(*E*)-1,3-diarylprop-2-en-1-ones]

Supplementary Material

In this work, which is planned for 1 session or 2 sessions 3 hours each, students (individually or in groups of two) will synthesize (*E*)-chalcone derivatives by the reaction of acetophenones with benzaldehydes. This experimental work illustrates the aldol condensation reaction.

The desired product is obtained directly by filtration or can be used to illustrate chromatographic techniques (in a second session).

The amount of solvent (methanol or THF) necessary should be adjusted because with some substitution pattern after the base addition a precipitate is produced; in these cases more solvent should be added to allow a proper stirring.

The benzaldehydes should be added with the reaction container immersed in an ice bath.

The (*E*)-chalcone derivatives show different colours depending of the substituent present in the aromatic rings (R= H, white, R= OH yellow, if R^1=NO_2 derivatives are more orange). This experiment was performed by nearly 500 students and the yields and melting points are an average of the students' results.

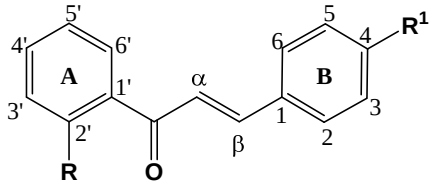


Figure SM 4.2.2.2.1 - (*E*)-chalcone structure

Table of Results: Reaction Yield and Melting Point of some (*E*)-chalcones

Entry	Substituent R	Substituent R^1	Yield of the crude (%)	Melting point (°C)
1*	H	H	65-75	56-57
2	OH	H	75-85	87-89
3	OH	OCH_3	70-85	89-90
4	OH	NO_2	70-85	153-154

*The unsubstituted derivative is presented to help students and/or instructors in the NMR analysis

Typically the TLC R_f of acetophenone and chalcone using mixtures of hexane/ethyl acetate are very different. If the eluent used is 80-20% (hexane/ethyl acetate) chalcone will have an R_f of approximately

0.5 (see Fig. SMX.2.). 2'-Hydroxychalcone spot is usually yellow and can be seen by human eye whereas acetophenone can be seen using an UV lamp and TLC plates of Silica gel 60 F_{254}.

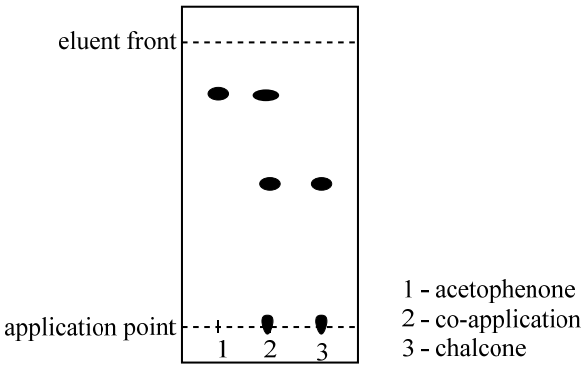


Figure SM 4.2.2.2.2 – Typical TLC plate after elution

The most important aspects in the ^{1}H NMR analyses are the presence of AB spin systems due to the vinylic protons H-α and H-β. It is also interesting to highlight the coupling constant value (J ~ 16 Hz) characteristic of an (*E*)-configuration. The presence of a 2'-hydroxyl group is essential to the intramolecular cyclization of 2'-hydroxychalcones and gives a very distinct singlet in the ^{1}H NMR spectra (δ 12-13 ppm); its presence in the chalcone A ring also gives a very interesting inequivalence of the aromatic protons that allow students to study important aspects such as multiplicity and long range coupling constants and also the shielding effect of the hydroxy group. Finally we also present examples of the presence, in the B ring, of electron withdrawing (nitro) and electron donating (OCH_3) groups, which allow studying the effects on chemical shifts. In the ^{13}C NMR spectra the signal due to the carbonyl group carbon (C-1) is also characteristic of these compounds (δ 190-195 ppm). The deshielding effect of the carbonyl group in the proton and carbon resonances of the A and B rings and also in the β–position of the α,β-unsaturated system can also be explored in the ^{1}H and ^{13}C NMR spectra of these compounds. In the following figures are given, as examples, the ^{1}H and ^{13}C NMR spectra of (*E*)-chalcone, (*E*)-2'-hydroxychalcone, (*E*)-2'-hydroxy-4-methoxychalcone and (*E*)-2'-hydroxy-4-nitrochalcone.

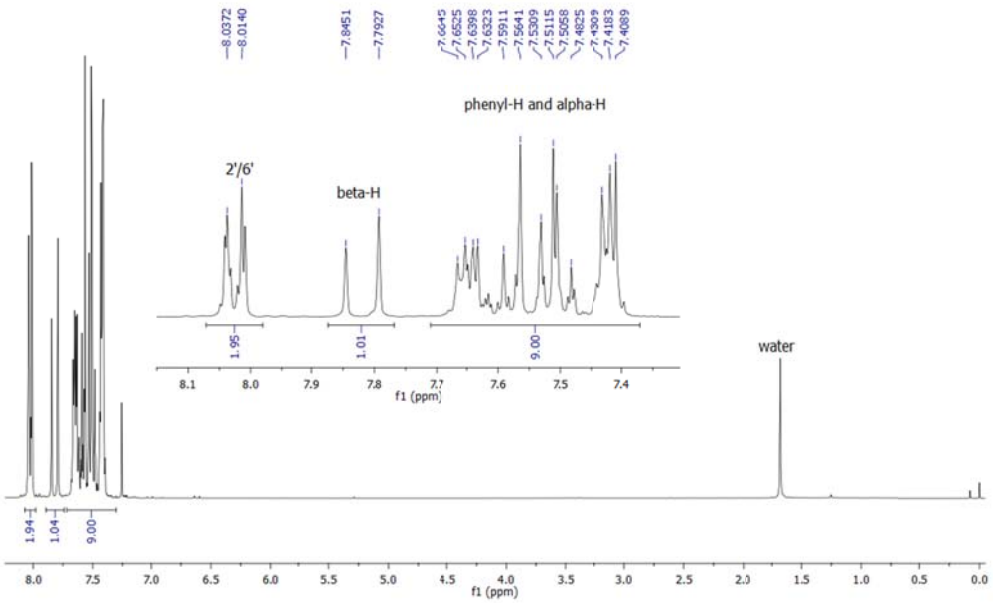


Figure SM 4.2.2.2.3 - ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the (*E*)-chalcone.

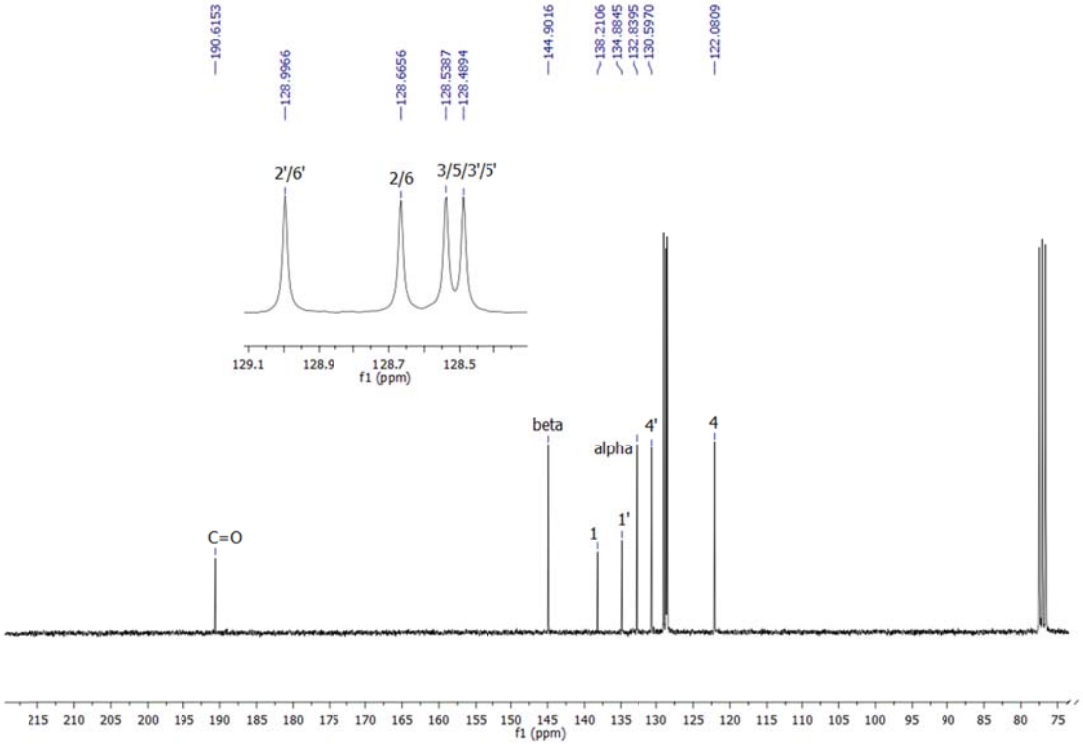


Figure SM 4.2.2.2.4 - ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the (*E*)-chalcone

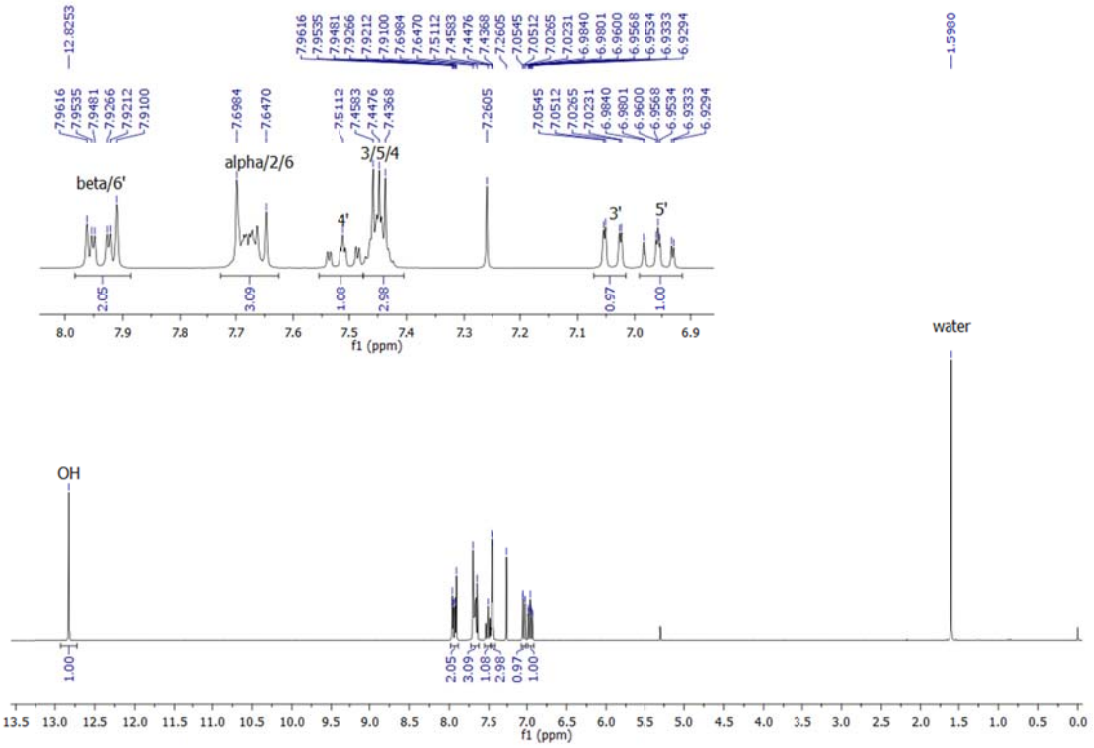


Figure SM 4.2.2.2.5 - ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the (*E*)-2'-hydroxychalcone.

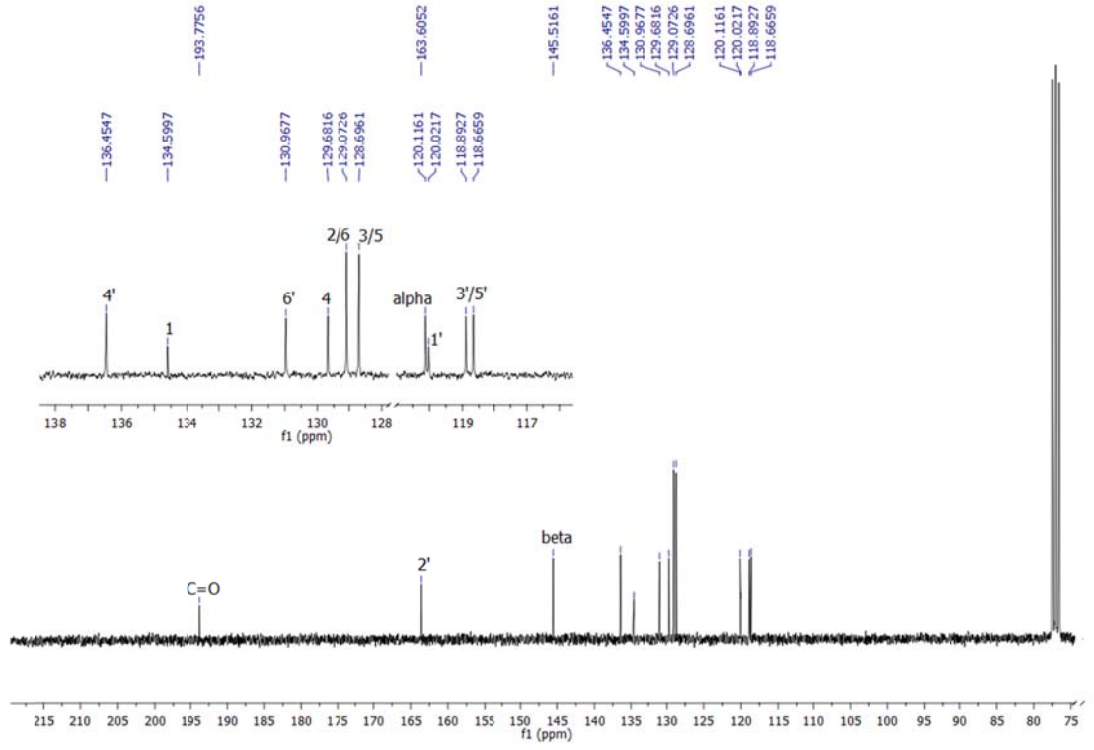


Figure SM 4.2.2.2.6 - ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the (*E*)-2'-hydroxychalcone.

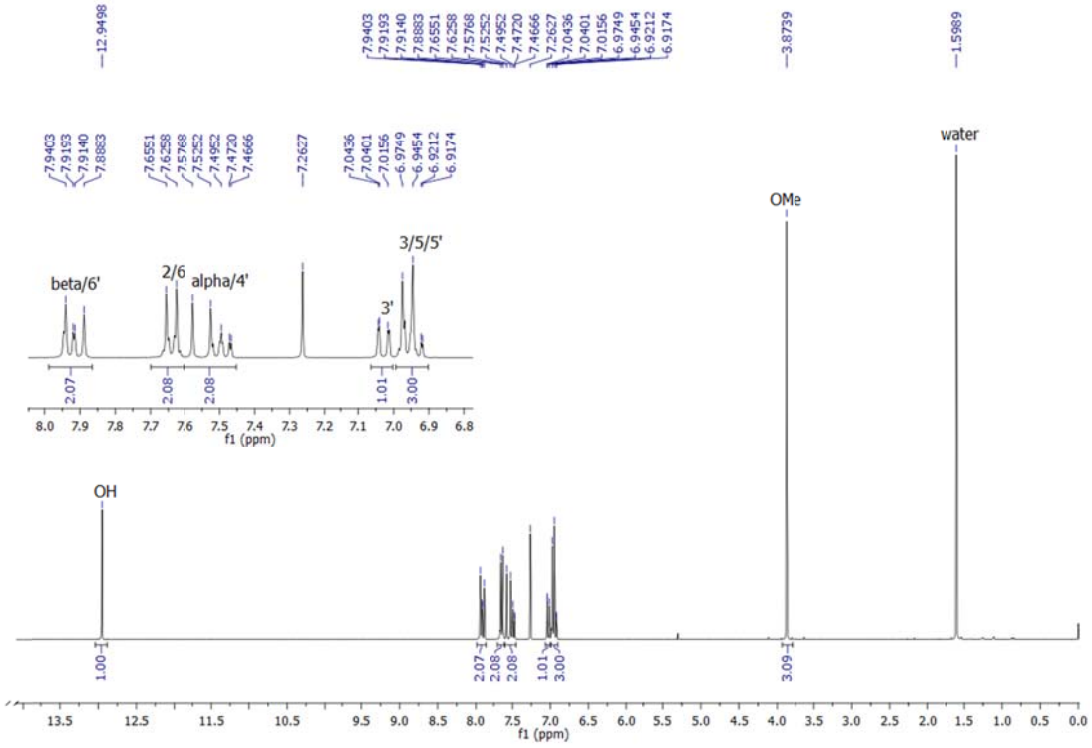


Figure SM 4.2.2.2.7 - ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the (*E*)-2'-hydroxy-4-methoxychalcone.

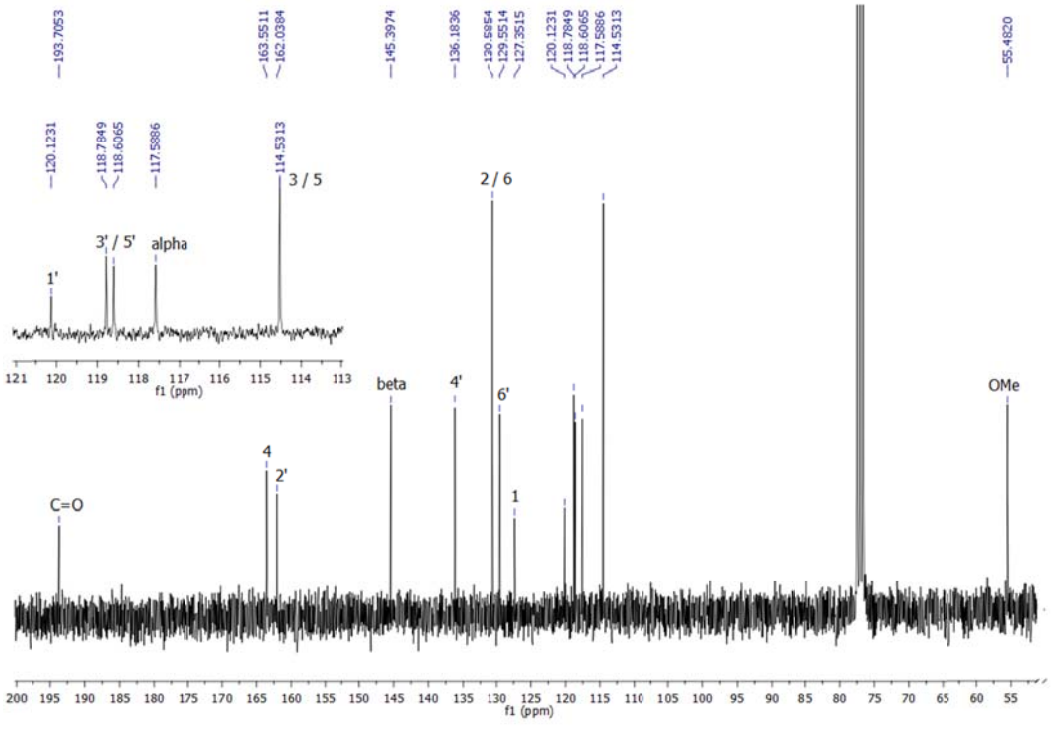


Figure SM 4.2.2.2.8 - ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the (*E*)-2'-hydroxy-4-methoxychalcone.

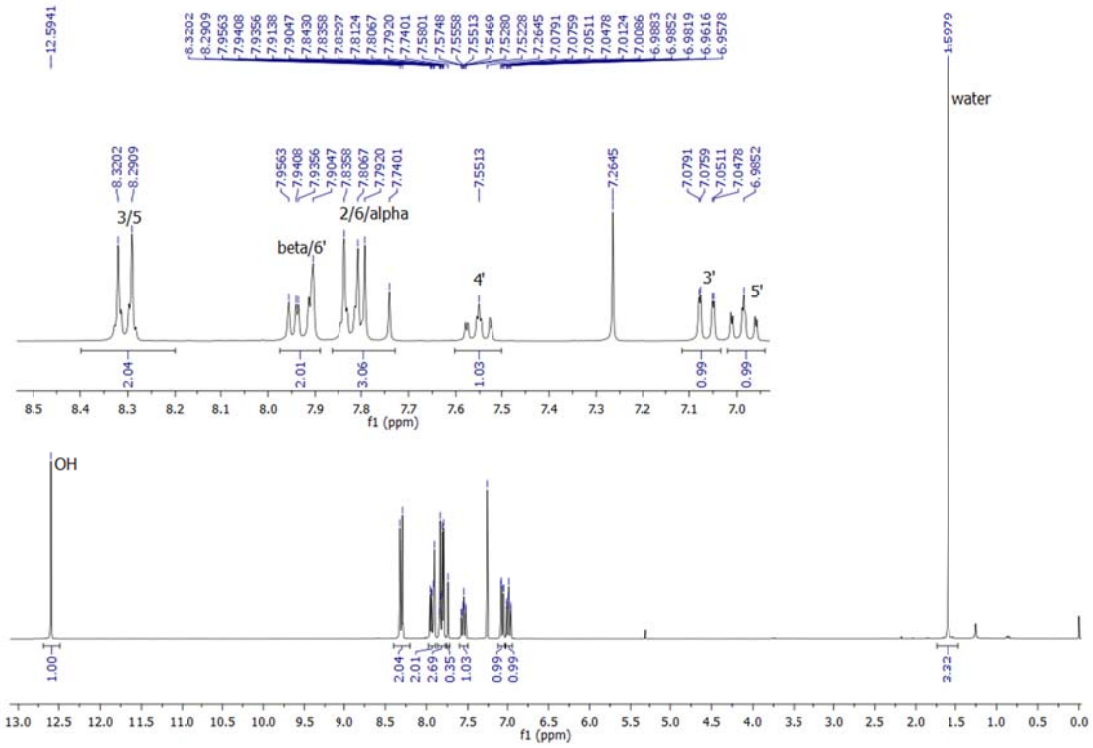


Figure SM 4.2.2.2.9 - ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the (*E*)-2'-hydroxy-4-nitrochalcone.

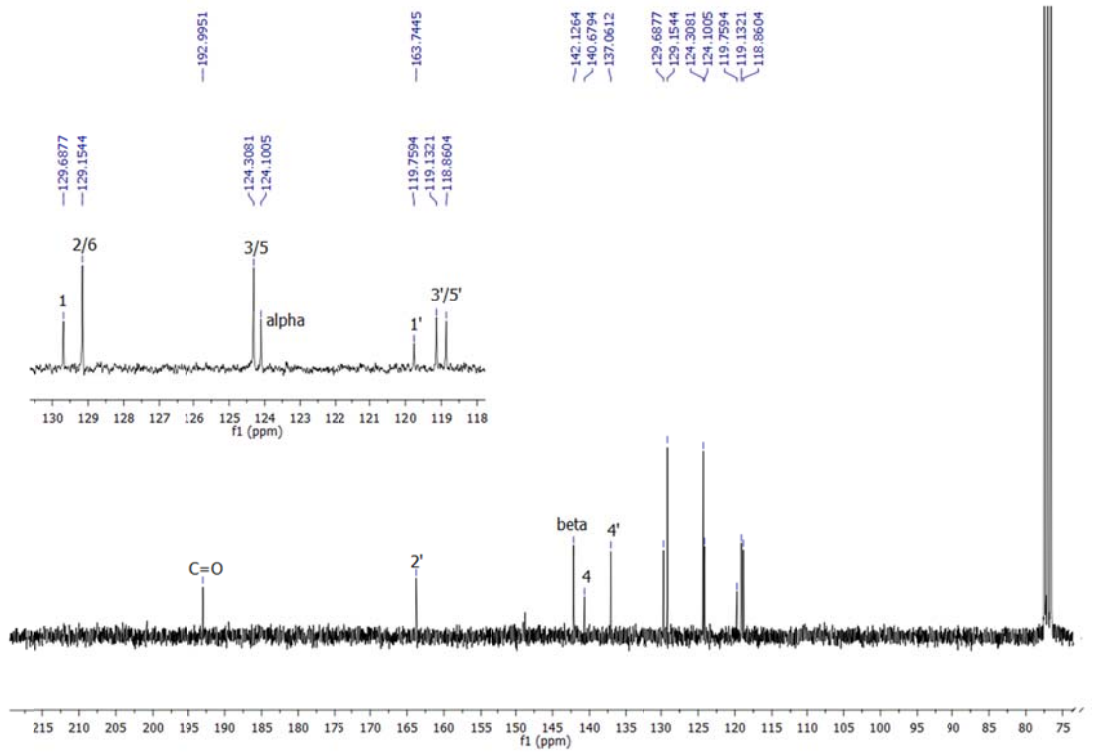


Figure SM 4.2.2.2.10 - ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the (*E*)-2'-hydroxy-4-nitrochalcone.

Experimental procedure for microwave synthesis:

1. In a fume hood add to a two-necked flask, equipped with a magnetic stirring bar, fiber-optic temperature control and reflux condenser (**Figure SM 4.2.2.2.11**) was charged with 0.2 mL of the desired acetophenone and 10 mL of dried THF.
2. Put the round bottom flask in an ice bath placed on a stirring plate and slowly add 2 equiv. of sodium hydride.
3. Put the two-necked flask in Ethos SYNTH microwave (Milestone Inc.) (**Figure SM 4.2.2.2.11**) and irradiate at constant power of 400 W for 15 minutes.
4. After this period pour the reaction mixture into a vessel containing ice (~ 20 g) and add hydrochloric acid to adjust pH to ~ 2.
5. The formed solid is filtered using a vacuum filtration apparatus.

Figure SM 4.2.2.2.11 - Reaction setup apparatus.

A free-solvent approach for chalcone synthesis *via* aldol reaction

Supplementary Material

This experiment aims the synthesis of the chalcone (*E*)-1-(4'-chlorophenyl)-3-phenyl-2-propen-1-one, prepared by a Claisen-Schmidt aldol condensation between an aldehyde lacking an α-hydrogen (benzaldehyde) and a ketone (4´-chloroacetophenone) in the presence of solid NaOH.

Therefore, 0.5 mL (5.0 mmol., 1 eq.) of benzaldehyde, 0.65 mL (5.0 mmol., 1 eq.) of 4´-chloroacetophenone and a pellet of NaOH (weighing approximately 0.2 g, 5.0 mmol., 1 eq.) were added into a porcelain mortar (8 cm diameter). After few seconds of grinding with the aid of a pestle, the reaction mixture became a yellow paste. The mixture was grinded for a period of 20-30 minutes until totally solidified when a beige solid powder became (Figure SM 4.2.2.3.1).

At the end of grinding, 10 mL of distilled water was added to the mortar (to facilitate the product isolation by filtration) and further well mixed with the product so obtained using the pestle and a spatula to remove the solid from mortar´s wall. The resulting solid was collected by vacuum filtration on a Büchner funnel. The mortar and pestle were washed with more 10 mL of distilled water, in order to remove remained solid therein. This solid was added to the same filter and all of product on the filter was washed with distilled water (10 mL). The solid so obtained was recrystallized from ethanol, collected by vacuum filtration on a Büchner funnel and the crystals so collected were allowed to dry in an oven. Once dried, the product was weighed and their melting point determined. The structure of the obtained compound was elucidated by m.p., IR (KBr), EIMS and NMR spectroscopy (solutions were made in DMSO-d_6 and spectra obtained using a 600 MHz instrument). Table SM 4.2.2.3.1 describes the average values of yield, m.p. and IR spectrum of pure chalcone. The ^{1}H NMR, ^{13}C NMR and EIMS spectra of the recrystallized chalcone are shown in Figures SM 4.2.2.3:2 to XM X.5. The doublets of the alkene hydrogens, typical of chalcones, arise at 7.78 and 7.95 ppm. Students can concluded that chalcone is trans by measuring the large coupling constant (15,6 Hz) of the alkene hydrogens. The reproducibility of this experiment was assessed by its repetitive execution, namely by 2nd year Biochemistry students from University of Trás-os-Montes e Alto Douro, in each year.

Table SM 4.2.2.3.1 – Yield, m.p. and IR spectrum of recrystallized chalcone.

Yield (%)	90-95
m.p. (ºC)	97-98
IR (KBr, υ_{max}, cm^{-1}	1662, 1603, 1483, 1444, 1335, 1210, 1092, 1025, 1008, 975, 825, 757, 683

Photos of the experiment

a b c

Figure SM 4.2.2.3.1 – Reaction mixture: a) paste at the beginning of the grinding; b) using the spatula to remove the solid from mortar´s wall; c) beige solid obtained after complete grinding.

^{1}H, ^{13}C NMR and EIMS spectra

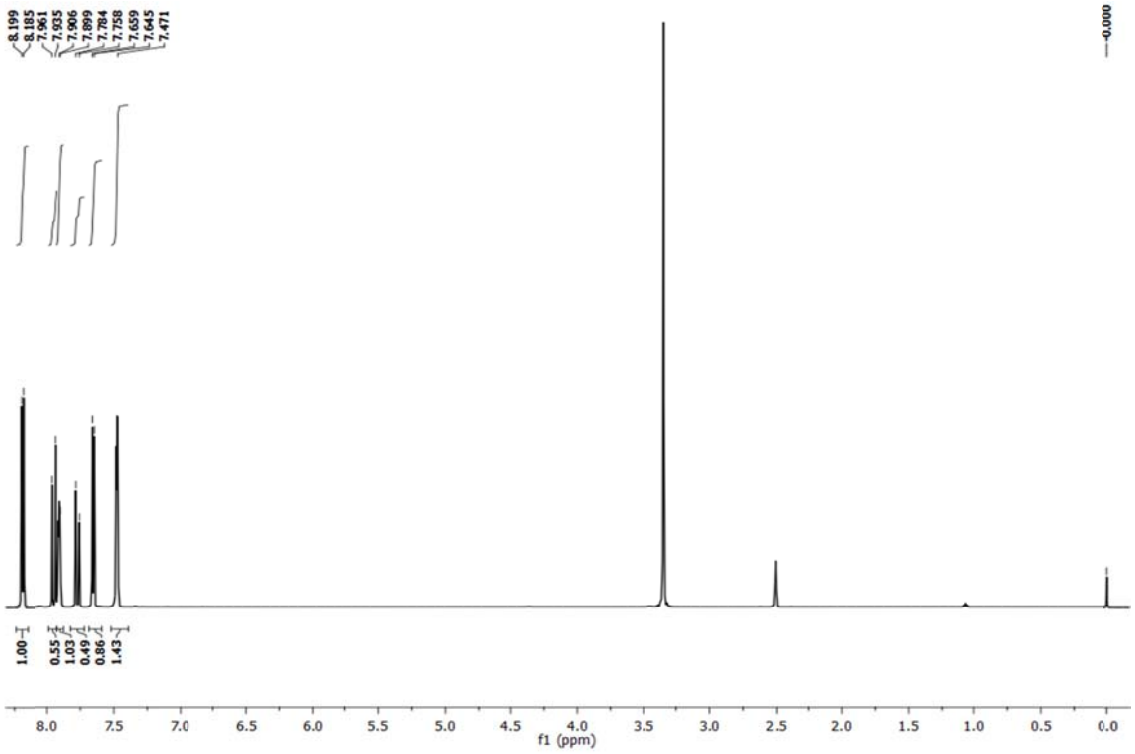


Figure SM 4.2.2.3.2 – ^{1}H NMR spectrum (600 MHz, DMSO-d_6) of recrystallized chalcone.

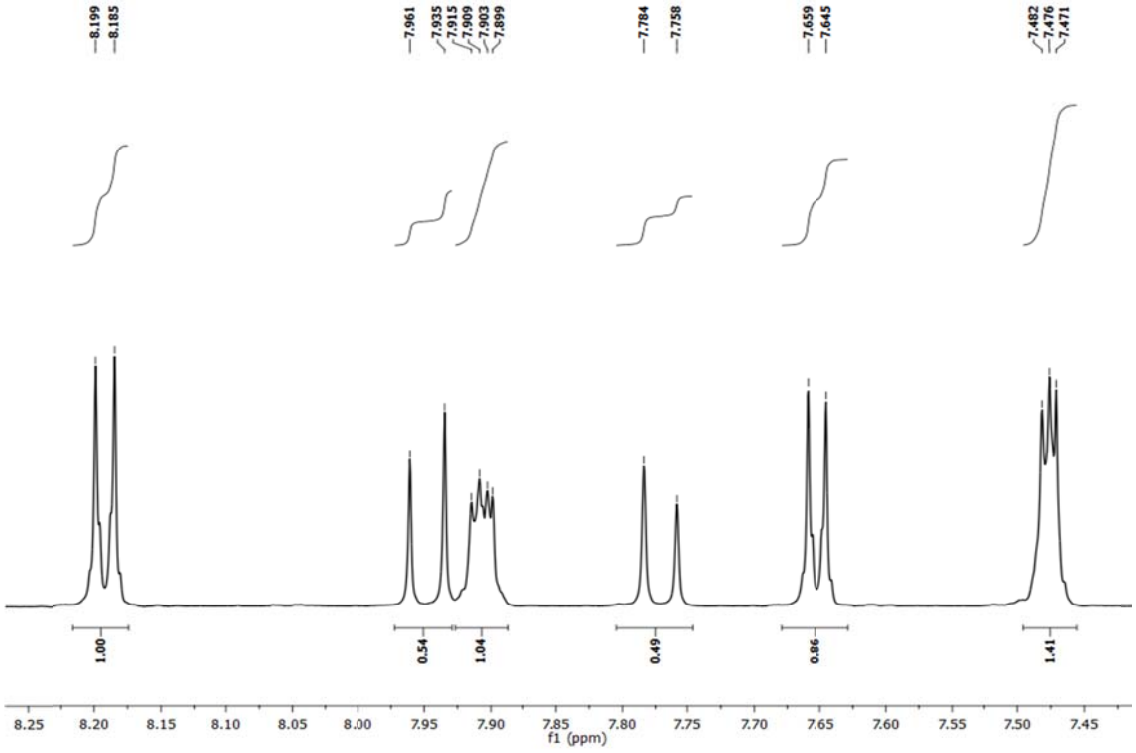


Figure SM 4.2.2.3.3 – ^{1}H NMR spectrum detail showing the chalcone peaks

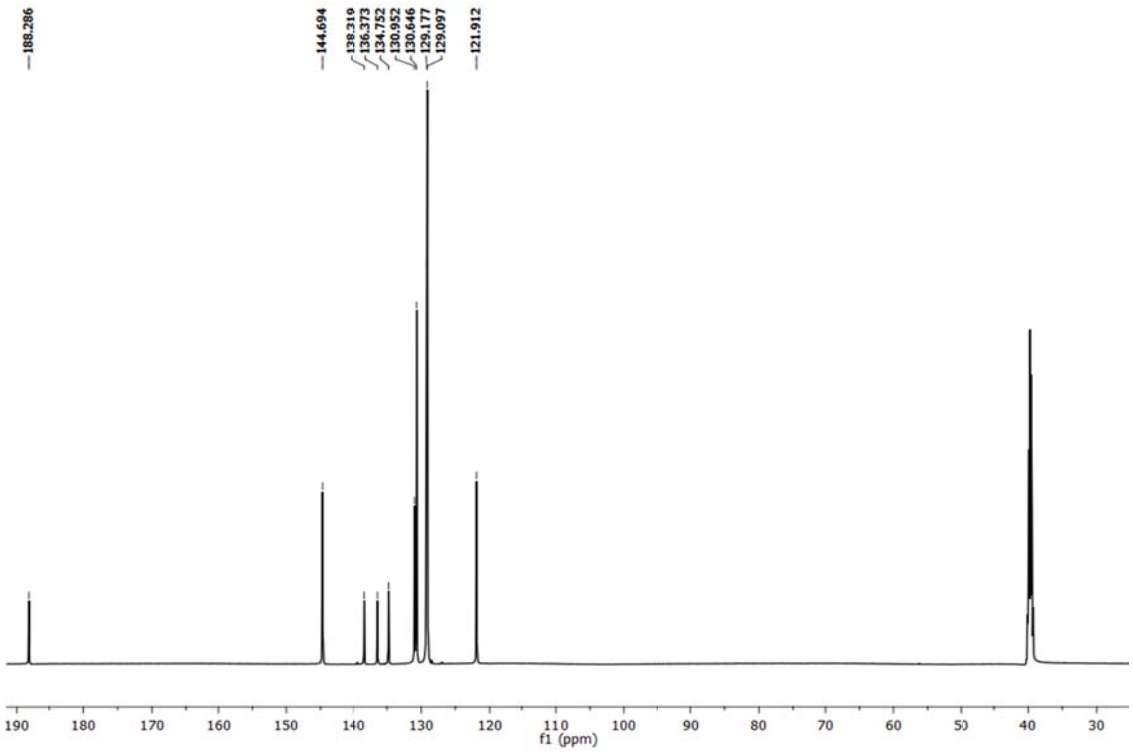


Figure SM 4.2.2.3.4 – ^{13}C NMR spectrum (600 MHz, DMSO-d_6) of recrystallized chalcone.

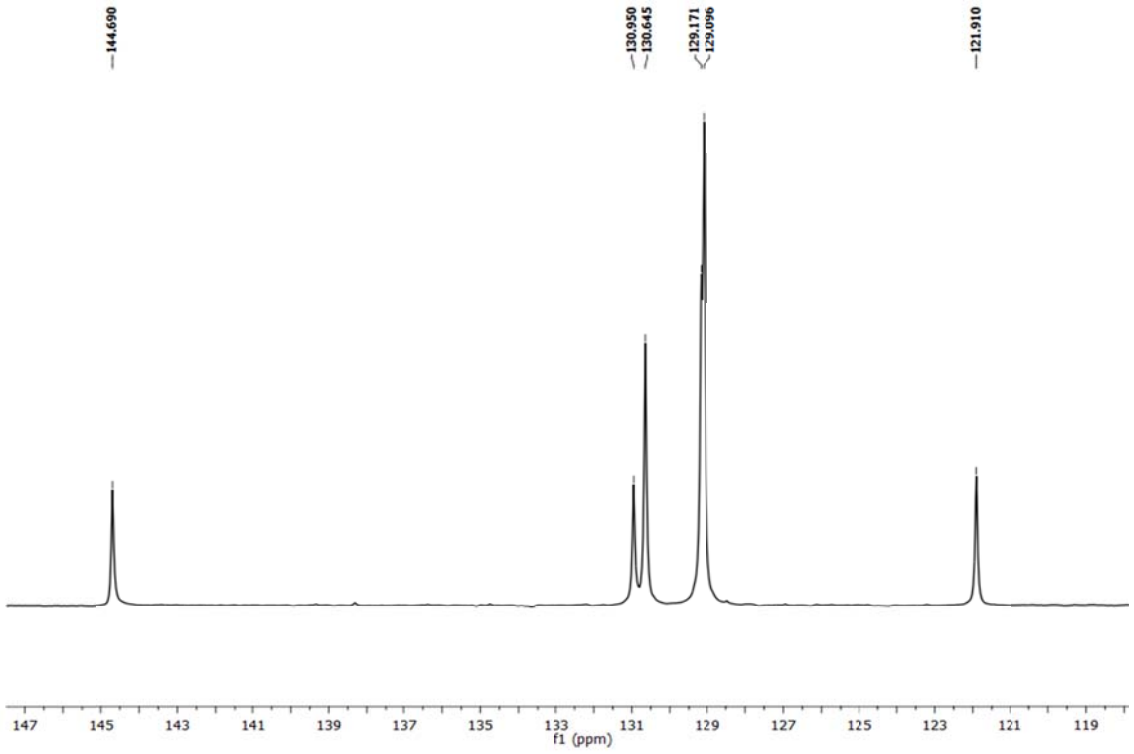


Figure SM 4.2.2.3.5– DEPT 135 NMR spectrum (600 MHz, DMSO-d_6) of recrystallized chalcone

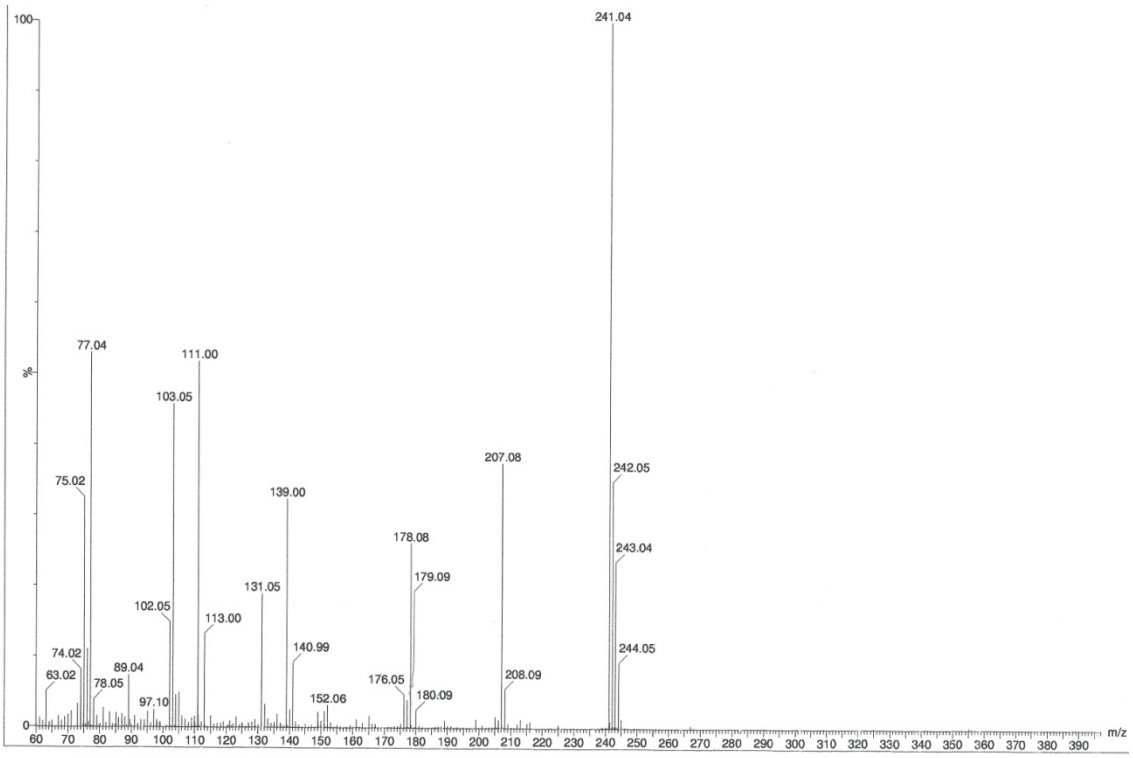
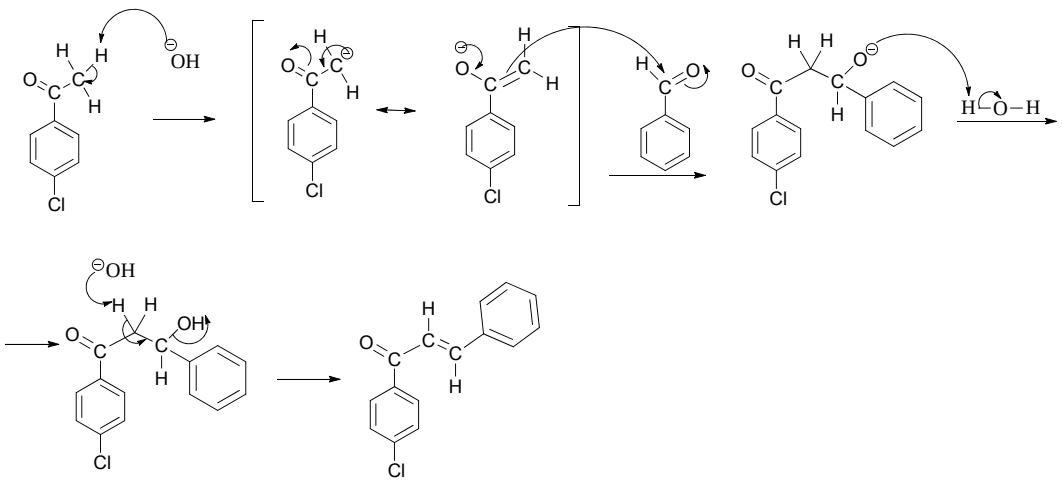


Figure SM 4.2.2.3.6 – EIMS (EI-TOF) spectrum of recrystallized chalcone.

Proposed mechanism for chalcone synthesis



Scheme SM 4.2.2.3.1 - Proposed mechanism for chalcone synthesis

Preparation of dibenzylideneacetone

Supplementary Material

Experimental notes

Figures

Experimental notes

Background topics

This experiment aims to illustrate the reactivity of carbonyl compounds at both carbonyl and α carbon atoms. An insight at tautomeric equilibrium (formation of enol/enolates) and nucleophilic addition to the carbonyl group should be emphasized. The Claisen-Schmidt reaction, a cross aldol condensation, is particularly adequate to illustrate these important features of the carbonyl Chemistry.

The experiment is appropriate to medium level students, who are encouraged to rationalise the mechanism of the reaction and some experimental details through the answers to a set of additional questions. It was realized by more than 150 students of the Faculty of Sciences and Technology, Universidade Nova de Lisboa (in classes of 22 students/ class, 11 groups of two), who accepted very well the work and enjoyed its execution.

Two main aspects are very important and should be understood and explained by the students: (1) the occurrence of a spontaneous dehydration reaction in a basic medium (E_{1cB} mechanism), after the aldol formation by addition of the ketone enolate to the aldehyde carbonyl, and (b) the reason of the yellow colour of the final product (extended conjugation of the π system and absorption in the Visible).

Suggest the students to write the reaction mechanism: formation of the ketone enolate, nucleophilic addition to the C=O bond of the aldehyde, dehydration of the aldol. Ask about the molar ratio ketone/aldehyde (1:2 favours double condensation; ketone in excess favours mono-condensation). IUPAC name for dibenzylideneacetone is 1,5-diphenylpenta-1,4-dien-3-one.

Experimental details

Experimentally the work is very simple, with low difficulty and hazard levels.

Ethanol is the only organic solvent used, at room temperature for the synthesis and at boiling point to the recrystallization. About 80-90 mL of ethanol will be needed for recrystallization.

An interesting suggestion can be made to the students: to keep a small amount of the crude product (before purification by recrystallization) and to dry it. Then, when measuring the melting point of a

sample of the purified product, also determine the melting point of a sample of the crude product. Both experimental values should be compared and discussed. Ask the students about the reasons of (eventual) differences, also including the value reported in the literature.
Some experimental results obtained by the students in the laboratory are presented in Table 4.2.2.4.1.

Table 4.2.2.4.1. Typical experimental results obtained in the Laboratory

Yield of crude product	Not significant. The crude product contains a large amount of water and some unreacted benzaldehyde, even after air drying.
Melting point of crude product	94-101ºC
Yield of recrystallized product (average)	4,1 g (55%); lower: c.a 40%; higher: c.a 70%
Melting point of purified product	104-106ºC

The preparation of samples for spectral analysis is also very important.
Students should be familiarized with the technique of preparing a solid transparent disk for IR spectroscopy, by using a small amount of a dried sample of the compound and KBr and the adequate material.
For ^{1}H-NMR spectroscopy test the solubility of dibenzylideneacetone in acetone, chloroform or carbon tetrachloride (or other solvents). After making the choice (in terms of availability, cost, toxicity…) use the chosen solvent in the corresponding fully deuterated form. $CDCl_3$ is a good choice.

Figures

Photos of the experiment

Figure 4.2.2.4.1. Chemicals

Figure 4.2.2.4.2. Set up of experimental apparatus

Figure 4.2.2.4.3. Starting the product formation

Figure 4.2.2.4.4. End of reaction

Figure 4.2.2.4.5. Recovery of crude product

Figure 4.2.2.4.6. Air drying of crude product

Figure 4.2.2.4.7. Hot filtration after recrystallization

Figure 4.2.2.4.8. Starting crystal formation

Figure 4.2.2.4.9. Collecting crystals by suction filtration

Figure 4.2.2.4. 10. Crystals of purified product

Spectra

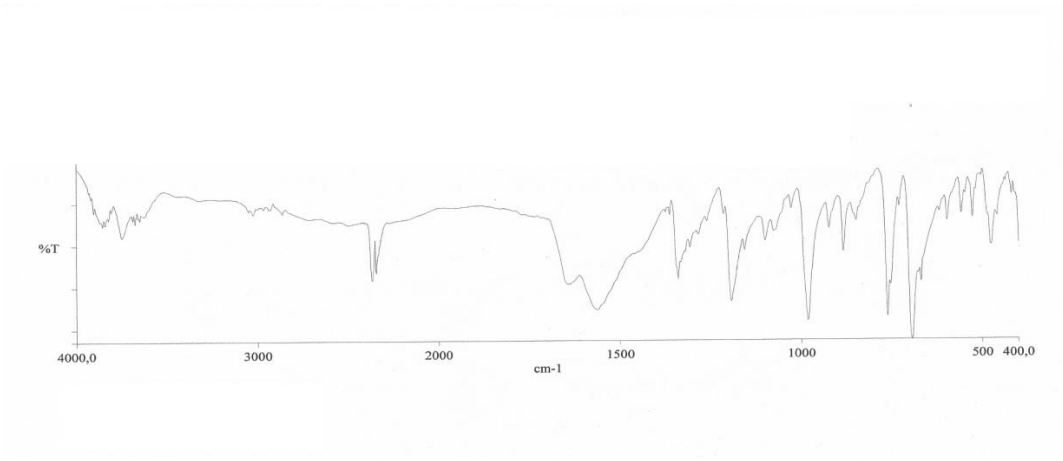


Figure 4.2.2.4.11. IR spectrum of dibenzylideneacetone (in KBr disk)

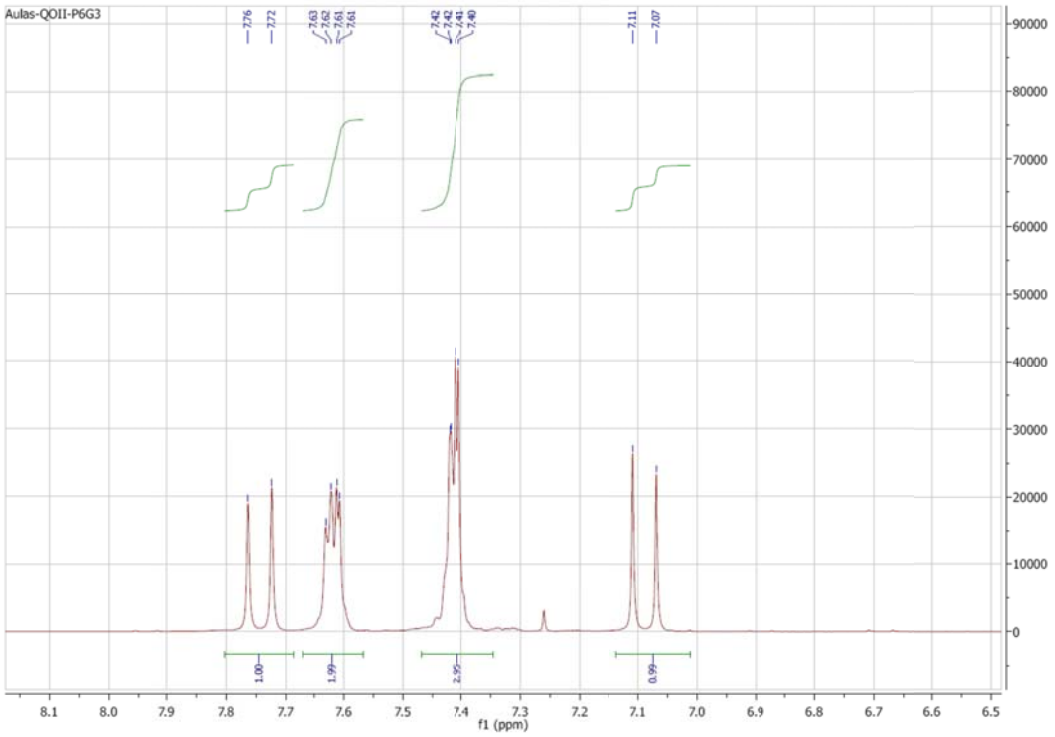


Figure 4.2.2.4.12. ^{1}H-NMR spectrum of dibenzylideneacetone (in $CDCl_3$)

L-proline Catalyzed Aldol Reaction of 4-Nitrobenzaldehyde with Acetone

Supplementary Material

Figures

The main purpose of this experiment is to illustrate the utility of *L*-proline as the catalysis in the preparation of chiral compounds. The experimental simplicity of this kind of reactions lies in mild reaction conditions without the requirement of pre-formation or isolation of unstable enamines, or preactivation of carbonyl compounds. It also can draw the student's attention and interest to the application of commercially available, non-toxic, natural amino acid as catalysts in asymmetric synthesis and the origin of chirality in nature.

In order to accurately determining the yield and enantioselectivity of reaction product，running flash column chromatography is necessary in the product purification process. Based on the TLC analysis, the size of column, the quantity of silica gel and the polarity of eluent are the three carefully-decided crucial factors for the fast and economical chromatography isolation.

Students need to have learned advanced organic chemistry, in which the concepts of chirality, asymmetric synthesis and enamine formation were taught. The students should have acquired the basic knowledge of instrumental analysis and be skilled enough in order to perform the reaction at a micro-scale and handle the work-up process as here planned.

Additional notes on the preparation of(4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone:

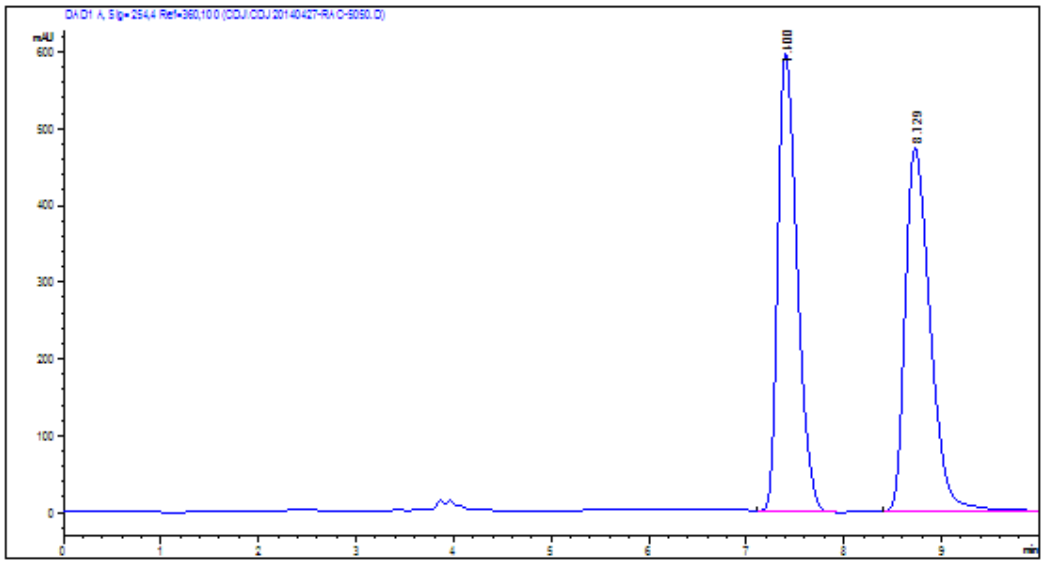
This procedure was successfully implemented at the described scale.

The product yields obtained by the students are about 53~74%, and the values of ee are about 62~69%.

Using ethyl acetate/petroleum ether = 1/3 as the eluting solvent, the R_f value of the product is about 0.2-0.3.

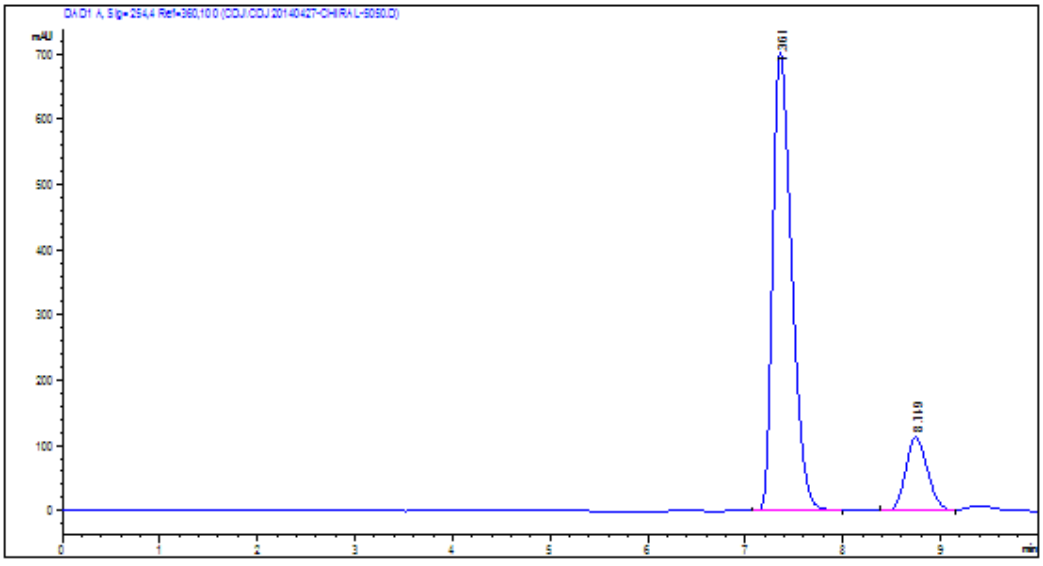
We recommend the column with the diameter about 20 mm and the length about 200 mm. The column will fill to about 100 mm with the amount of silica being used.

The ee of product was determined by chiral HPLC analysis (Daicel Chiralpak AS-H, isopropanol/hexane = 50/50, 1.0 mL/min, λ = 254 nm, t_R (major) = 7.4 min, t_R (minor) = 8.7 min.). Authentic racemic standard for the HPLC analysis was synthesized using pyrrolidine as a catalyst.



#	Time	Area	Height	Width	Symmetry	Area%
1	7.4	8125.5	569.2	0.213	0.635	49.259
2	8.729	8370	472.5	0.2747	0.617	50.741

Figure 4.2.2.5.1- HPLC analysis of racemic product catalyzed by pyrrolidine.



#	Time	Area	Height	Width	Symmetry	Area%
1	7.361	9488.8	703.7	0.2093	0.624	84.319
2	8.749	1764.7	112.7	0.2447	0.811	15.681

Figure 4.2.2.5.2- HPLC analysis of chiral product catalyzed by *L*-proline.

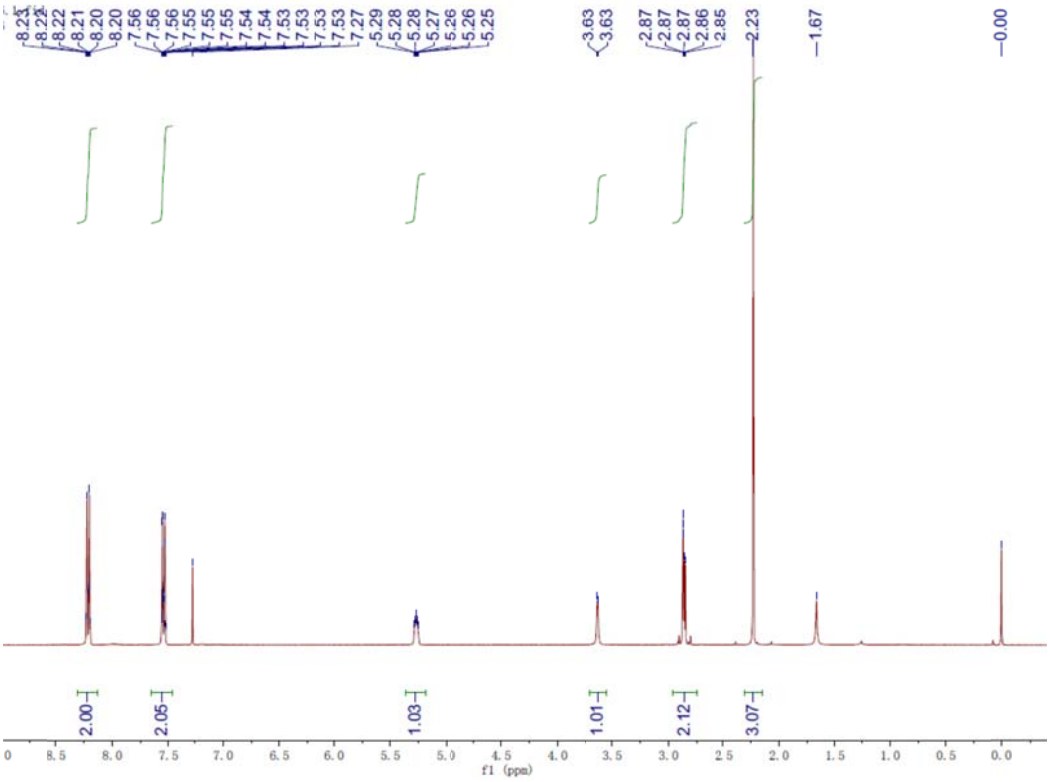


Figure 4.2.2.5.3 - ^{1}H NMR spectrum (400MHz, $CDCl_3$) of (4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone.

Preparation of a *β*-nitrostyrene derivative by the Henry reaction: comparison of a conventional and a microwave-assisted method

Supplementary Material

In the experiment proposed herein the advantages of using microwave-assisted organic synthesis methods (MAOs) in the preparation of *β*-nitrostyrene derivatives are explored. Comparing with the conventional synthesis of *β*-nitrostyrene derivatives, it requires shorter heating times and relative smaller amounts of the nitroalkane reactant. The use of more resource-efficient, greener and economical synthetic routes is undeniably a trend in modern organic chemistry laboratories. Additionally, the use of MAOs has been reported to increase product yields and ease of work-up and purification compared to conventional "heating and stirr" methods.[1, 2]

Students' laboratorial sessions

The experiments were designed for chemistry-based curricula, namely medicinal chemistry courses, and are best suited for students that have organic chemistry (theoretical and practical) foundations. This same experiment was tested in a first year master chemistry course including over 25 students. The suggested experiments were easy to perform and produced clear and obvious results which directed the students in a more applied and real organic chemistry lesson.

The average success of students in the integrated experience was quite satisfactory (>90%). Students obtained adequate amount of compound to complete the hands-on experience of structural characterisation. No extraordinary difficulties in the work-up step and acquisition of NMR spectra have been detected. However, in the interpretation of NMR data, some drawbacks have been noticed; students were advised to use molecular model kits to assist in the visualization process. Furthermore, a theoretical class for data discussion is strongly recommended. A lab report was written according standard guidelines.

Notes:

- Students must read the details of the experiments and prepare a procedure flow chart to be followed in the class;
- Students must previously explore microwave-assisted synthesis features;
- Students must check the identity and purity of each product by TLC, NMR (^{1}H and ^{13}C) and melting point determination;

- Students must be familiar with *β*-nitrostyrene derivatives structural features;
- Students must review NMR spectroscopic concepts.

Additional notes on the preparation of *β*-nitrostyrene derivatives

In the so called **conventional method** (Figure SM 4.2.2.6.1a), the first 6 hours of reaction must be performed prior to the actual lab session by the instructor or the student, since the required heating time is about 7 hours or even more. The average yields fluctuate from 90 to 95%, depending on the reaction time and experience of the operator. In the work-up step the progress of the reaction can be monitored by TLC, using petroleum ether/diethyl ether 50:50 (v/v), as eluent; a small difference between the R_f of the aldehyde and the corresponding *β*-nitrostyrene derivative is observed, being the *β*-nitrostyrene spot easily observed due to its strong yellow colour (R_f nitrostyrene > R_f benzaldehyde). Before the extraction step it is important to evaporate (*ca.* half of the initial volume) some of the nitroalkane to prevent distribution of nitrostyrene between the two layers (organic and aqueous).

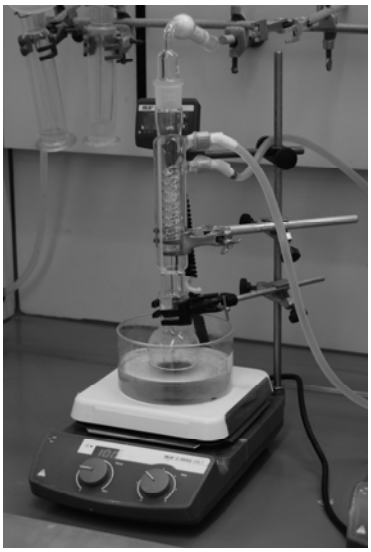
a)  **b)** 

Figure SM 4.2.2.6.1. Henry's reaction setup: **a)** Conventional method and **b)** Microwave-assisted apparatus.

In **microwave-assisted method** (Figure SM 4.2.2.6.1b) the reaction time may vary according to the apparatus used, mainly due to fluctuations on temperature/pressure control. This experiment was performed and fully optimised using a Biotage Initiator 2.5 Microwave oven. TLC was used to monitor the progress of the reaction. At various time

intervals during the reaction, mixture samples were taken and subjected to TLC analysis. The average yields also fluctuate from 90 to 95%, depending on reaction conditions and operator skills.

Although the yields obtained for the two methods are very similar, the students will have the opportunity to observe the simplification of the technique as well the significant reduction of preparation time of a simple organic compound, recurring to microwave-assisted organic synthesis approach. The melting point evaluation could be compared with the literature values to assess compound purity.[3]

Herein is proposed the study of a specific *β*-nitrostyrene derivative (4-hydroxy-3-methoxybenzaldehyde), however it was already tested the same method, with equally satisfactory results, for the preparation of other *β*-nitrostyrene and *β*-methyl-*β*-nitrostyrene derivatives, starting for a wide variety of substituted benzaldehydes.

β-nitrostyrene derivatives preparation: the chemistry behind and beyond

The synthetic route proposed in this work involves a Henry reaction type condensation between the carbonyl compound (benzaldehyde) and the nitroalkane in basic conditions. The basic catalyst deprotonates the nitroalkane in the α-Carbon to the strong electron withdrawing group (NO_2) and the resulting resonance-stabilised anionic intermediate then attacks the carbonyl compound. This step yields a *β*-nitroalcohol, which, after heat-promoted dehydration, forms the intended *β*-nitrostyrene derivative. The proposed mechanism for the Henry reaction is depicted in Figure SM 4.2.2.6.2.

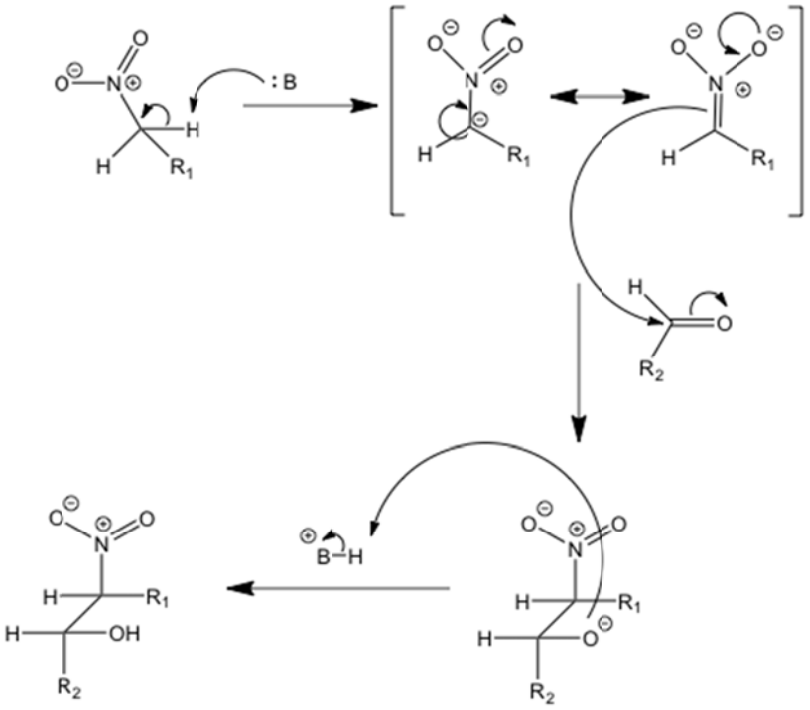


Figure SM 4.2.2.6.2. Proposed mechanism for the first step of the Henry reaction to obtain the *β*-nitroalcohol.

The intermediate is difficult to isolate, especially when aromatic aldehydes are used.[4] The nitroaldolic condensation is a classic synthetic reaction that implies the formation of a carbon-carbon bond. This reaction occurs easily in the presence of basic catalysts of organic or inorganic nature, as primary and tertiary amines, alkaline metal hydroxides, carbonates and alkoxides, among others.[4, 5] Ammonium acetate and buffer solution of ammonium acetate in acetic acid are the most common catalysts used in the Henry reaction setup[6]. Unwanted parallel pathways can occur along with the aldolic condensation, as the *Cannizzaro* reaction, or polymerization can occur simultaneously to the formation of the nitroalkenes.[7] These parallel reactions can be minimized, or even avoided, with the use of the proper catalyst.[8]

The Henry reaction proceeds in a non-aqueous environment mainly because nitrostyrenes are highly insoluble in water. The final compounds are usually very coloured, from light yellow to intense orange, due to the existence of a pronounced

electronic delocalization through the double bond and the aromatic ring (highly conjugated system). The *β*-nitrostyrene derivatives show a predominance of the *E* isomer (trans) as could be inferred by the analysis of the coupling constants of the vinylic protons (Figure SM 4.2.2.6.3) in the ^{1}H NMR spectrum.[9] The aromatic substitution pattern of the compounds could also be concluded by the NMR analysis.

The ^{1}H, ^{13}C and DEPT spectra are depicted in Figures SM 4.2.2.6.3, SM 4.2.2.6.4, SM 4.2.2.6.5, and SM 4.2.2.6.6.

Structural analysis

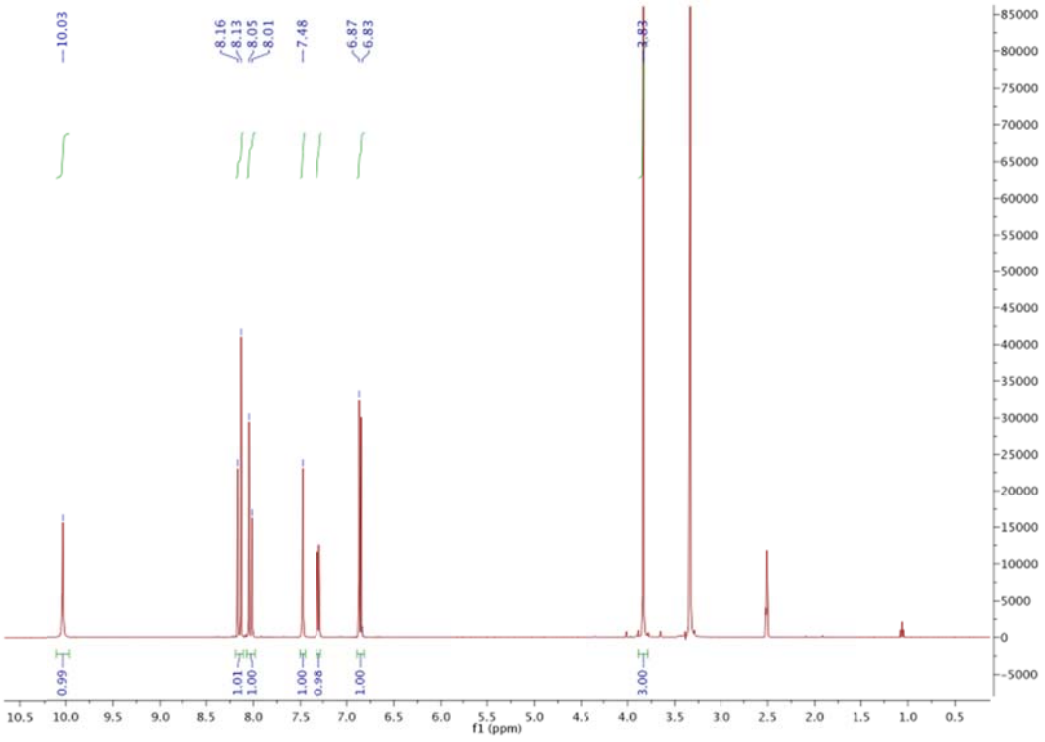


Figure SM 4.2.2.6.3. ^{1}H NMR spectrum (400 MHz, DMSO) of 4-hydroxy-3-methoxy-*β*-nitrostyrene.

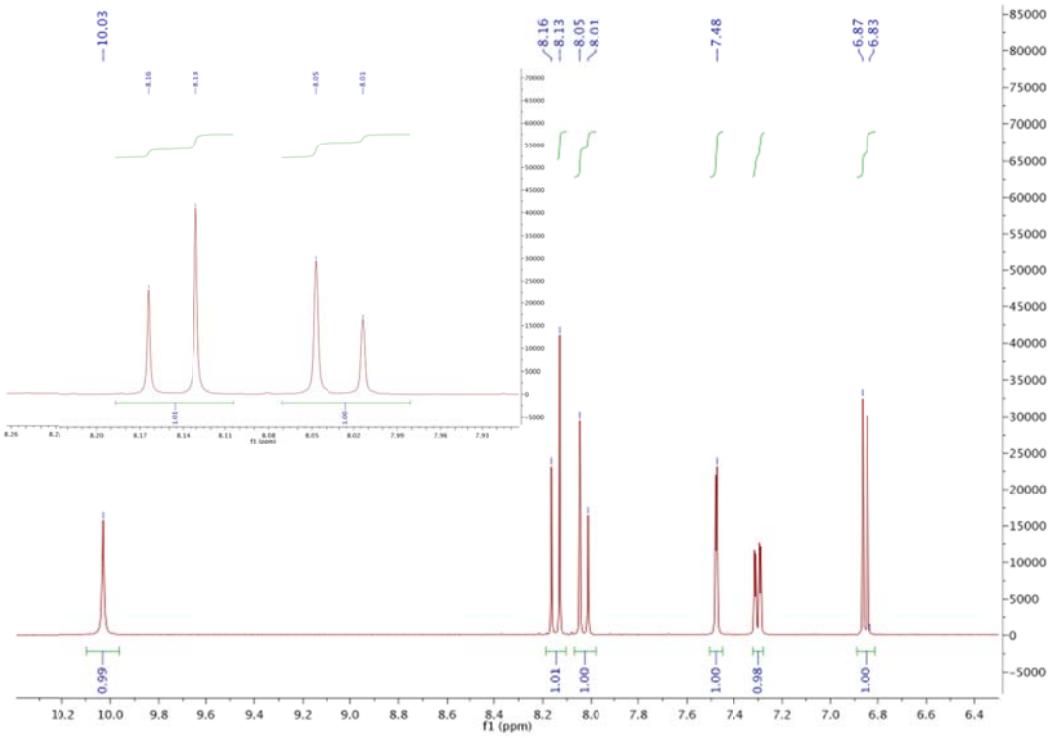


Figure SM 4.2.2.6.4. Expansion of ^{1}H NMR spectrum (400 MHz, DMSO) of 4-hydroxy-3-methoxy-*β*-nitrostyrene.

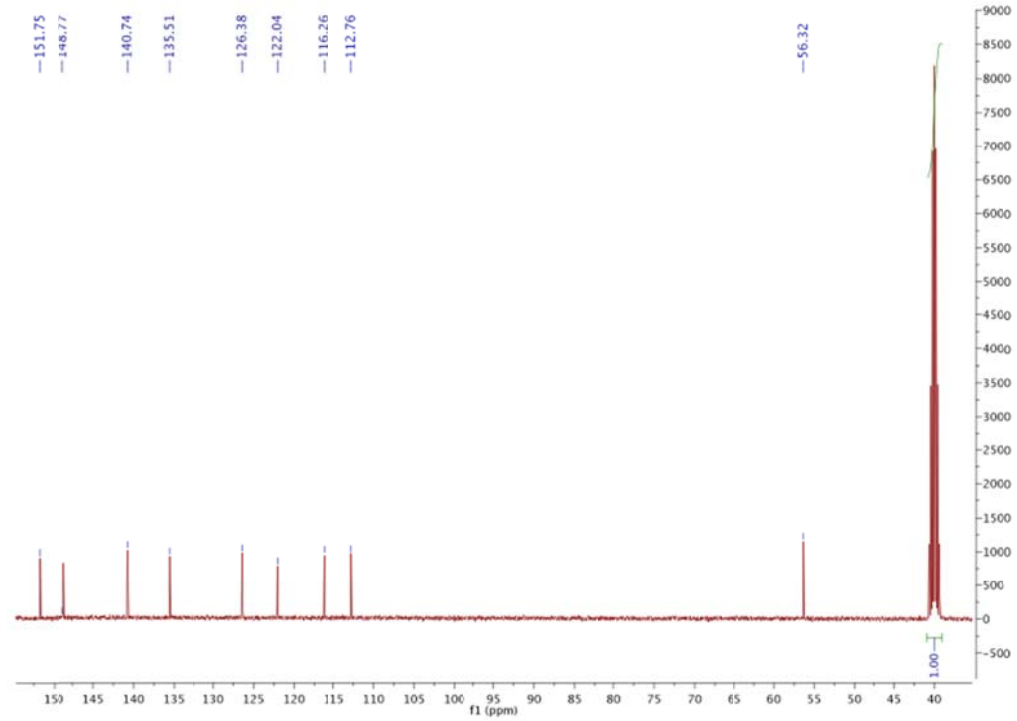


Figure SM 4.2.2.6.5. ^{13}C NMR spectrum (100 MHz, DMSO) of 4-hydroxy-3-methoxy-*β*-nitrostyrene.

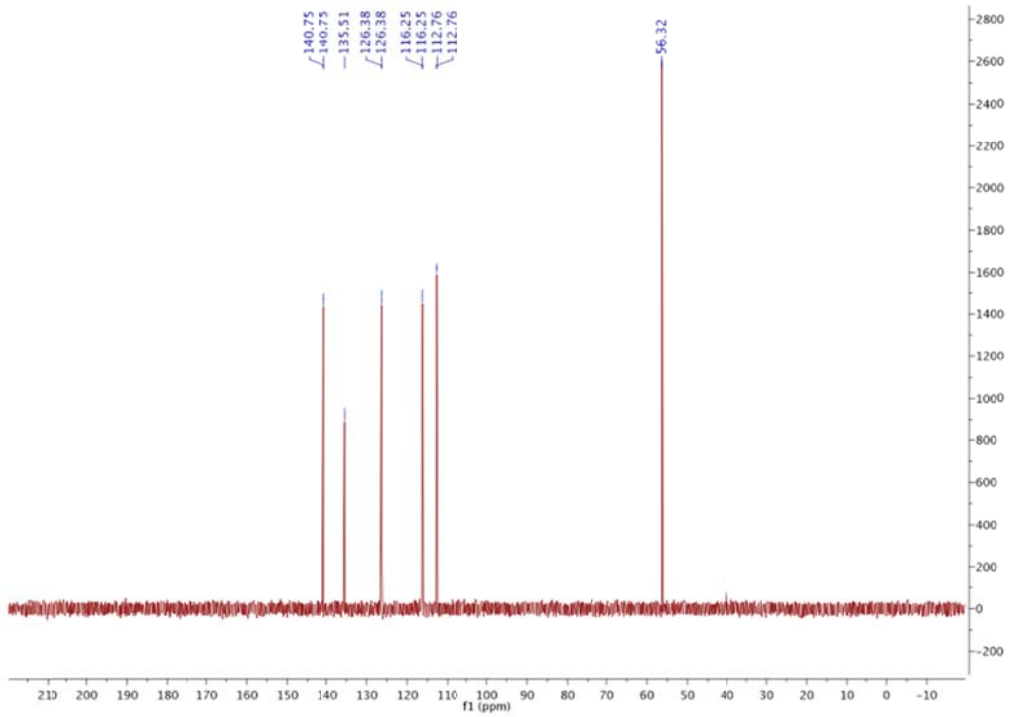


Figure SM 4.2.2.6.6. DEPT-135 spectrum (100 MHz, DMSO) of 4-hydroxy-3-methoxy-*β*-nitrostyrene.

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Additional Reading

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D. L. Pavia, G. M. Lampman, G. S. Kriz, J. A. Vyvyan, *Introduction to Spectroscopy*, Belmount, 8th ed., 2008.

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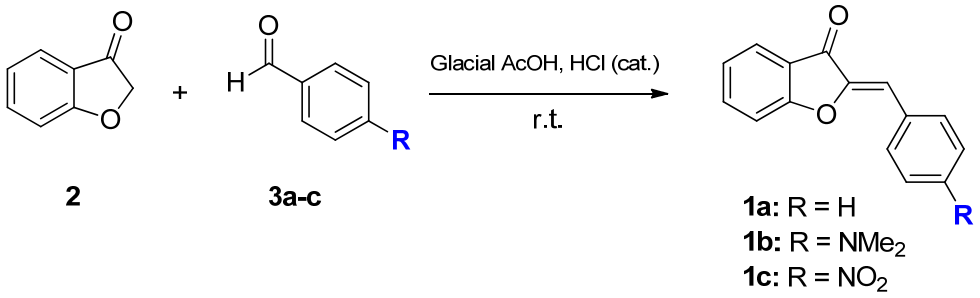
Synthesis of Aurone derivatives through acid-catalysed aldol condensation

Supplementary Material

Aurones are minor tricyclic flavonoids, structurally isomers of flavones, which have been studied not only for their physiological properties and effects on Nature, but also for their therapeutic potential. From the synthetic approaches towards aurones, the aldol condensation between benzofuran-3(2*H*)-one and benzaldehydes is one of the most popular due to its compatibility with a wide range of substituents.

This experiment aims at the preparation of a small library of aurone derivatives (**1a-c**) through a simple acid-catalysed aldol condensation (more specifically, a Claisen-Schmidt condensation), starting from cheap and readily available starting materials. Additionally, the product is quickly precipitated from the reaction medium and the pure product is easily isolated by filtration, avoiding the use of expensive purification techniques and equipment. Since no organic solvent is used either in the reaction or purification step, this synthetic methodology is attractive from a sustainable point of view and emphasis can be given to this aspect, as well as, to the therapeutic potential of the synthetized compounds.

The experiment was designed to be performed in a 100 mg scale of benzofuran-3(2*H*)-one (**2**) and using three different benzaldehydes (**3a-c**, Scheme SM 4.2.2.7.1).[1] It encompasses a 15-45 minute reaction (depending on the benzaldehyde used), elementary techniques such as precipitation, filtration, and product characterization by melting point and NMR. The procedure is operationally simple and can be performed by any undergraduate student following organic chemistry courses where the concepts of nucleophilic addition to the carbonyl group and NMR spectroscopy are discussed.



Scheme SM 4.2.2.7.1

The reproducibility of the experiment was assessed by its repetitive execution namely by:

1) six undergraduate students attending the laboratory classes of the Organic Chemistry I course (first year of the Integrated Master of Pharmaceutical Sciences Degree, FFUL); and
2) three graduate students (i.e. one Master student and two PhD candidates) with different backgrounds (Biochemistry, Pharmaceutical Sciences, Chemistry) and different levels of experience in organic chemistry lab work.

Table SM 4.2.2.7.1 summarizes the conditions used and results obtained using the three different benzaldehydes, with yields in the range of: 45–59% (**1a**), 50–73% (**1b**) and 62–95% (**1c**).

Table SM 4.2.2.7.1 - Experiments conducted in a round bottom flask starting from benzofuran-3(2*H*)-one and different benzaldehydes at r.t.

Entry	R	Reaction time (min)	Product	Isolated Yield (%)	Melting Point (ºC)
1[a]	H	30	**1a**, yellow solid	45-51	110-113
2[b]	H	30	**1a**, yellow solid	59	113-114
3[a]	NMe_2	40	**1b**, orange solid	50-62	174-176
4[c]	NMe_2	40	**1b**, orange solid	69-73	178-180
5[a]	NO_2	15	**1c**, yellow solid	80-85	N.D.
6[d]	NO_2	15	**1c**, yellow solid	62	216-220
7[b]	NO_2	15	**1c**, yellow solid	95	222-225

[a] Experiments performed individually by two undergraduate students; [b] experiments performed by PhD candidate 1; [c] two runs of the same experiment performed by PhD candidate 2; [d] experiment performed by a M.Sc. student.

General Notes / Troubleshooting Information:

- The aspect of the reaction mixture varies depending on the benzaldehyde used. If R = H, the mixture maintains the yellow colour during the course of the reaction; if R = NMe_2 the colour changes from yellow to dark orange; and if R = NO_2 a precipitate is formed during the reaction (Figure SM 4.2.2.7.1).

- Since the reaction solvent is acetic acid it is recommended the following procedure to monitor the progression of the reaction. TLC preparation: at 15-min time intervals, use a Pasteur pipette to transfer a drop of the reaction mixture to an eppendorf with 0.5 mL distilled H_2O. Add approximately an equal volume of EtOAc and shake the solution. After phase separation spot a TLC plate with the organic phase and the limiting starting material (Figure SM 4.2.2.7.2). Compound **1a**: R_f = 0.69 (Hex/EtOAc, 7:3)[2]; compound **1b** and **1c**: R_f = 0.33 and 0.40, respectively (Hex/EtOAc, 8:2).

- In order to avoid loss, product precipitation and wash should be done with cold distilled water. Since the product is filtered-off from an aqueous solution it is advice to use a porcelain Büchner funnel and filter paper Whatman No.1.

Photos of the experiment:

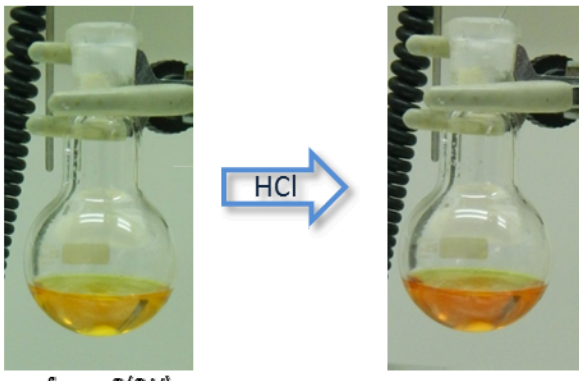


Figure SM 4.2.2.7.1 – Illustrative photos of the reaction with different benzaldehydes (R = NMe_2 and NO_2) at t = 0 min.

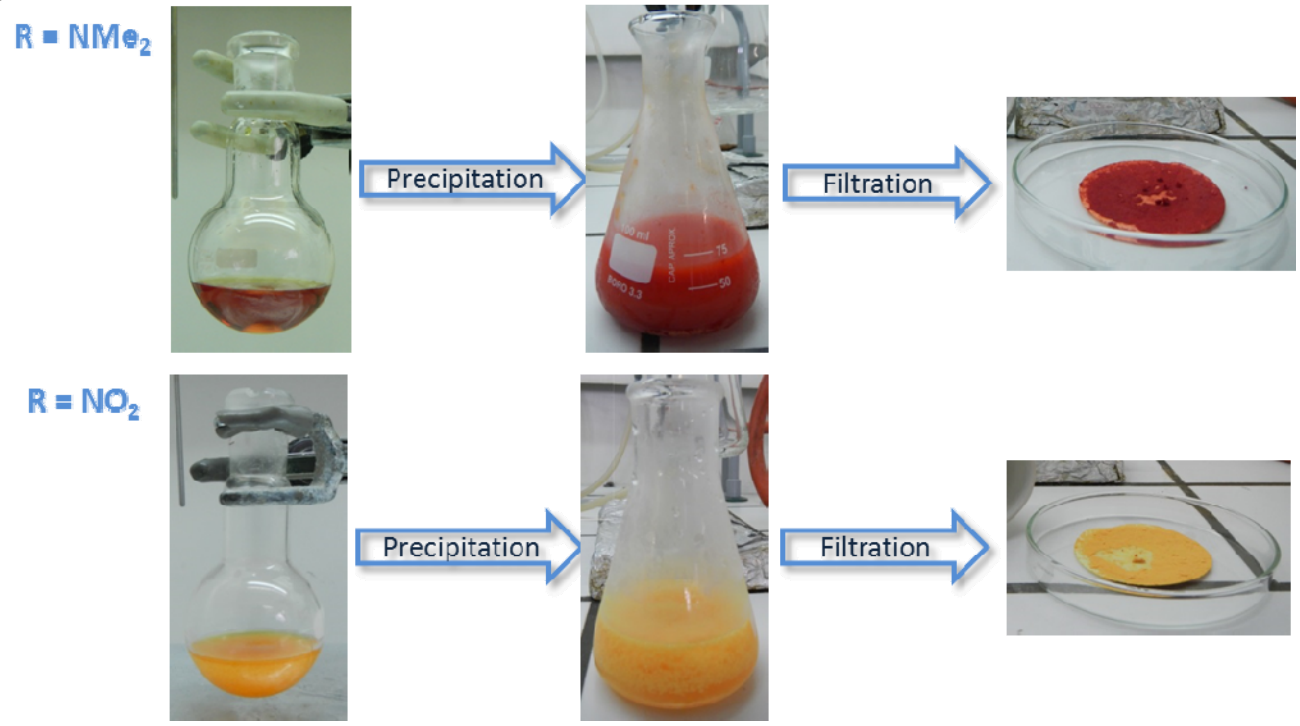


Figure SM 4.2.2.7.2 – Illustrative photos of the reaction with different benzaldehydes (R = NMe_2 and NO_2) at completion and subsequent product isolation.

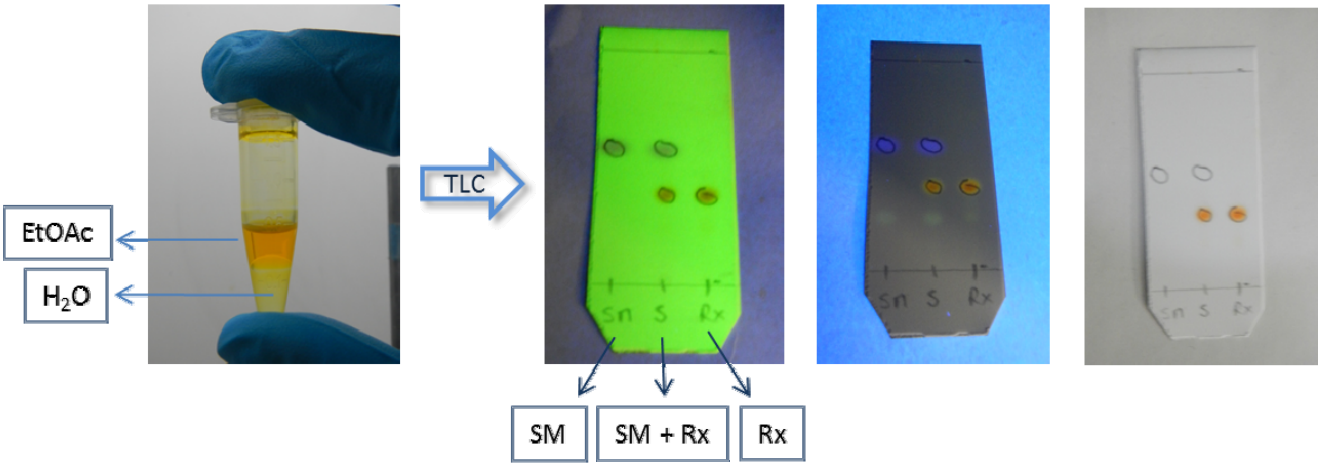


Figure SM 4.2.2.7.3 – TLC preparation for compound **1b** and visualization at 254 nm, 366 nm, and without UV light, respectively.

^{1}H and ^{13}C NMR spectra:

The stereochemistry of the carbon-carbon double bond in aurones **1a-c** was assigned as having the (*Z*)-configuration based on the ^{1}H and ^{13}C chemical shifts for the exocyclic double bond. The ^{1}H NMR data obtained reveal that the chemical shifts for the β-hydrogen atoms for aurones **1a-c** range from 6.80 to 6.95 ppm, which is consistent with reported values for both (*Z*)-aurones (ca. 6.70 ppm) and (*E*)-aurones (ca. 7.10 ppm), making the attribution ambiguous. However, the ^{13}C NMR spectra were much more conclusive, revealing that the chemical shift for the exocyclic carbon range from 109 to 115 ppm, in line with the values reported for (*Z*)-aurones, the thermodynamically more stable isomer. In contrast, the ^{13}C chemical shifts for the exocyclic carbon in (*E*)-aurones are usually observed at significantly higher frequency (ca.120-130 ppm).[3]

The ^{13}C NMR spectrum for compound **1a** is reported in reference 4.

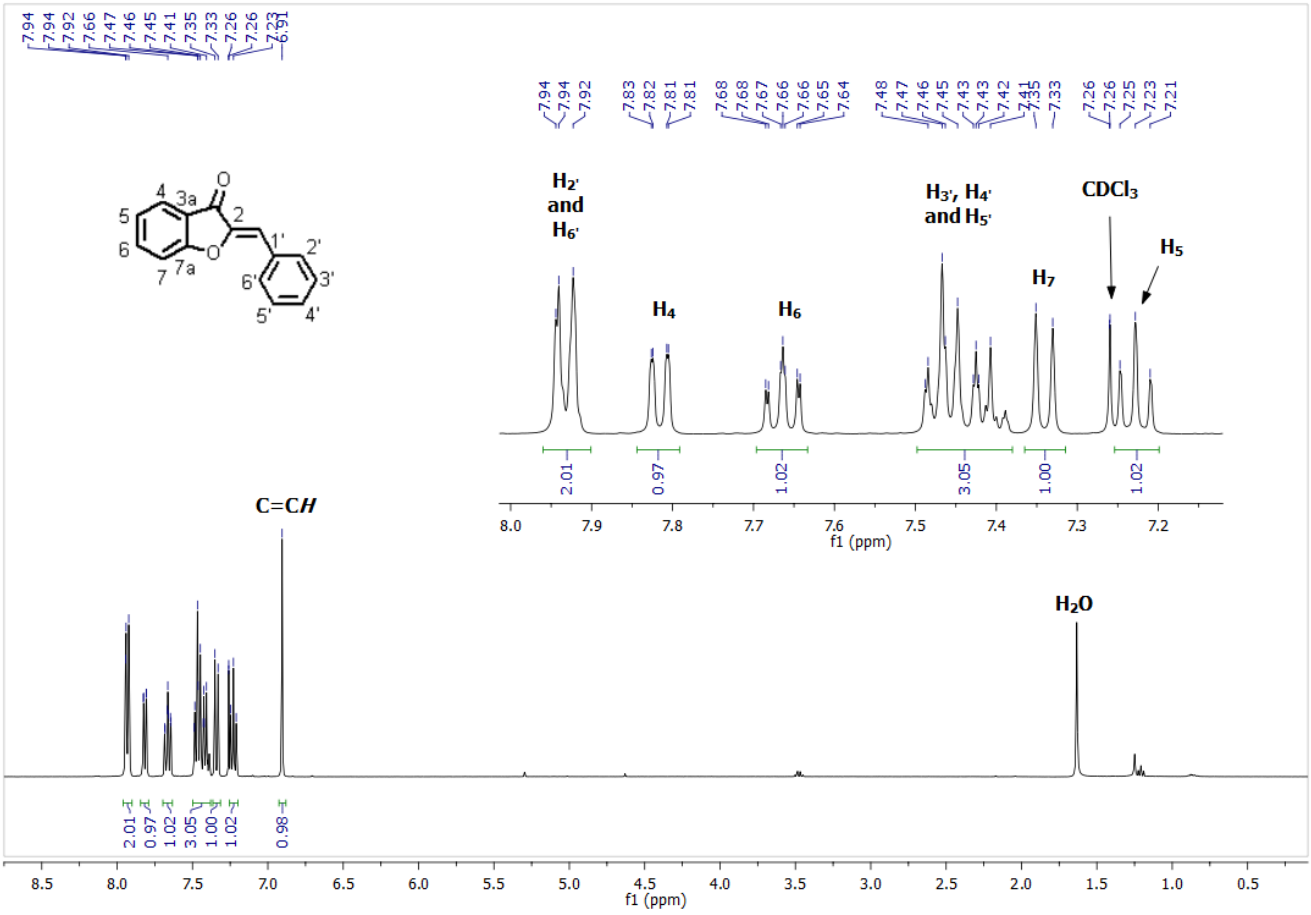


Figure SM 4.2.2.7.4 – ^{1}H spectrum of compound **1a** (400 MHz, $CDCl_3$) and peak assignment.

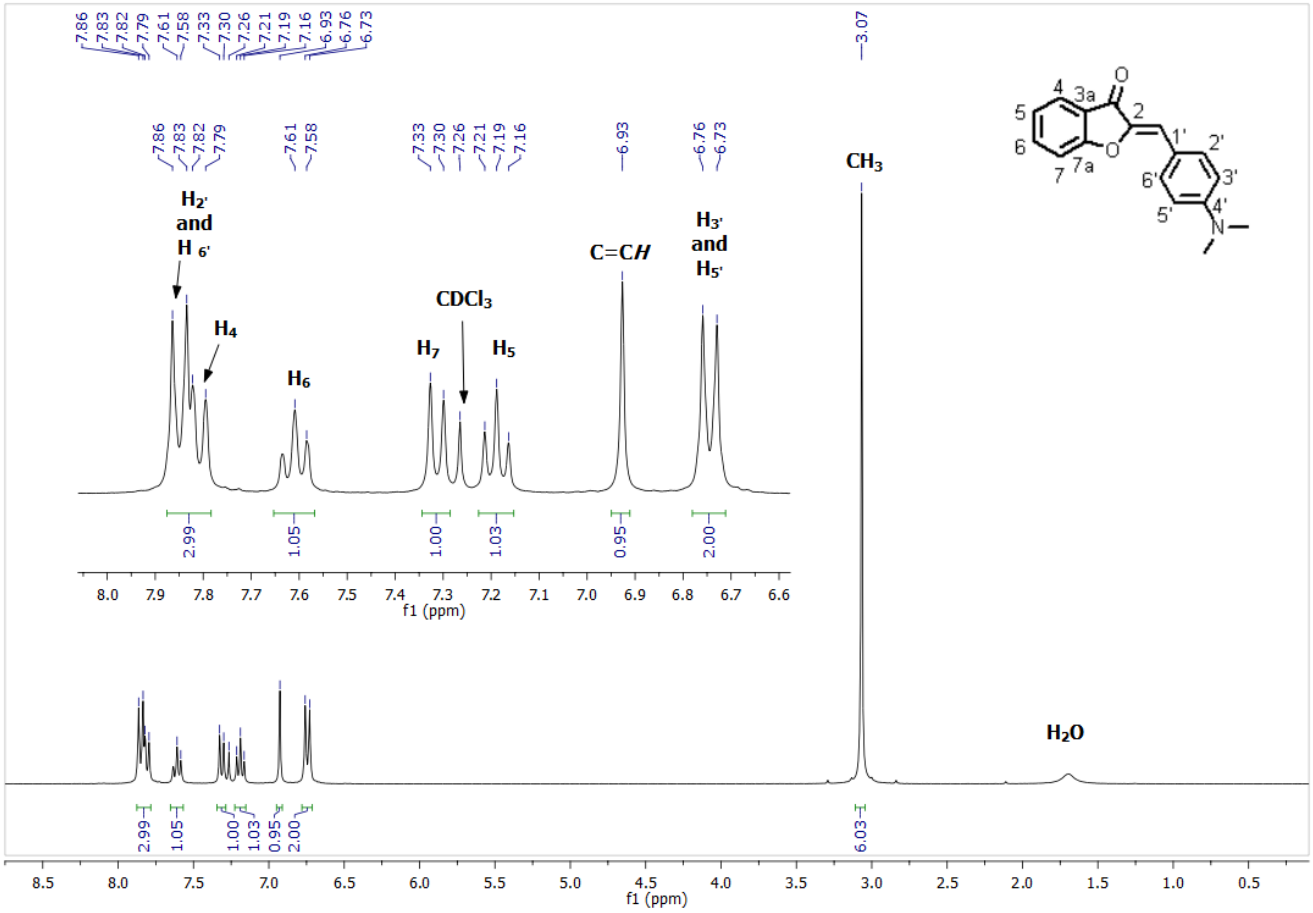


Figure SM 4.2.2.7.5 – ^{1}H spectrum of compound **1b** (300 MHz, $CDCl_3$) and peak assignment.

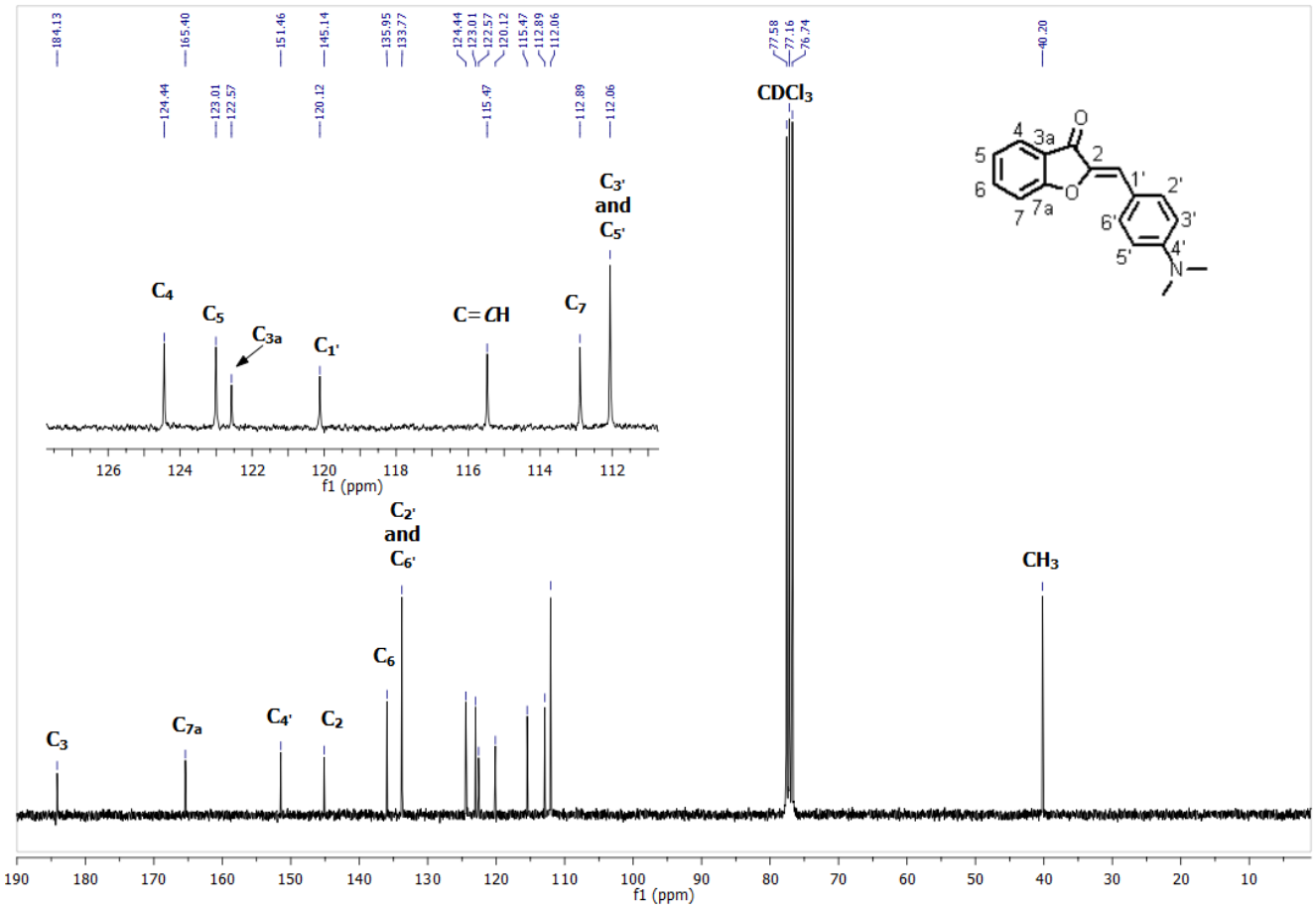


Figure SM 4.2.2.7.6 – ^{13}C NMR spectrum of compound **1b** (300 MHz, $CDCl_3$) and peak assignment.

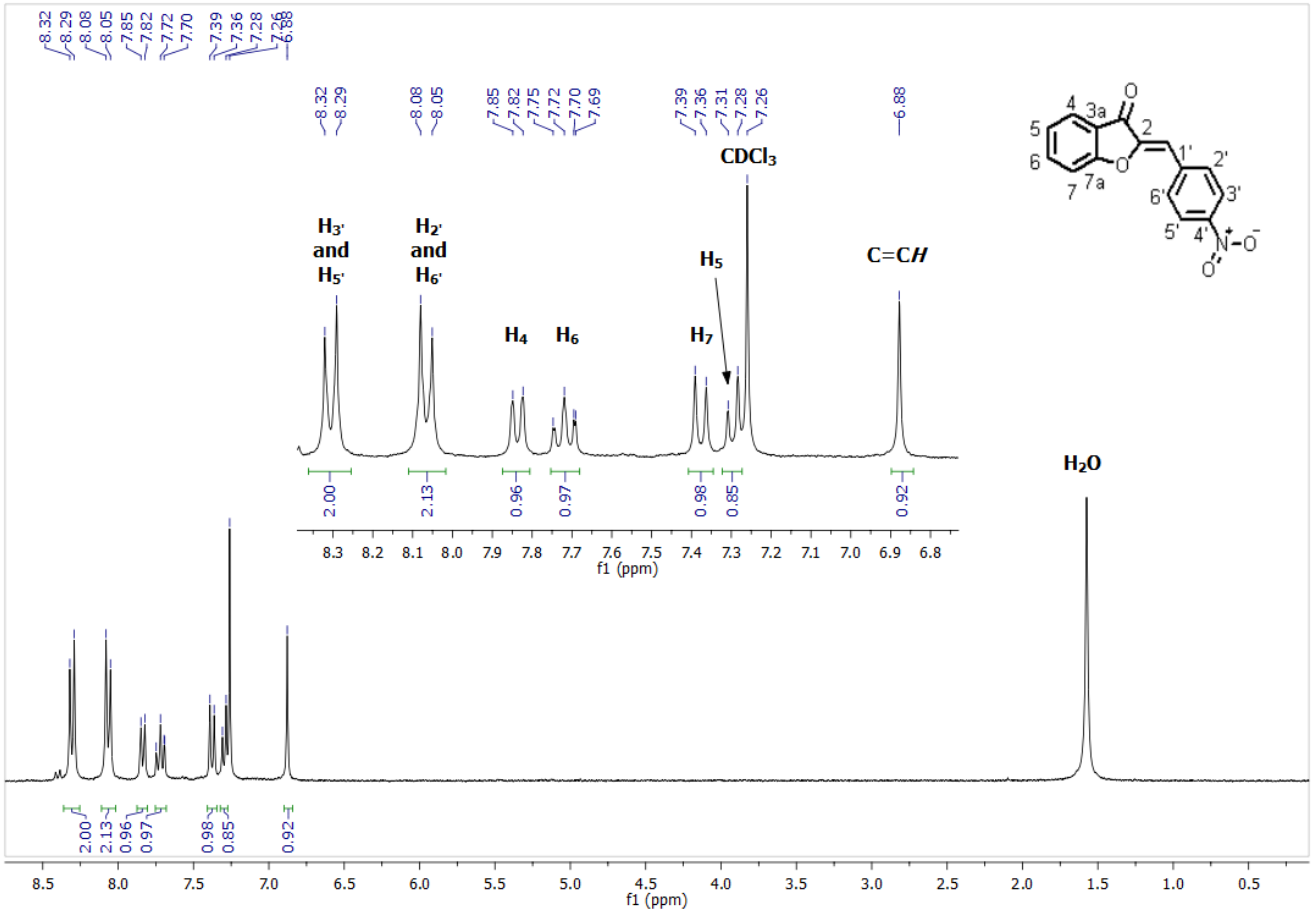


Figure SM 4.2.2.7.7 – ^{1}H NMR spectrum of compound **1c** (300 MHz, $CDCl_3$) and peak assignment.

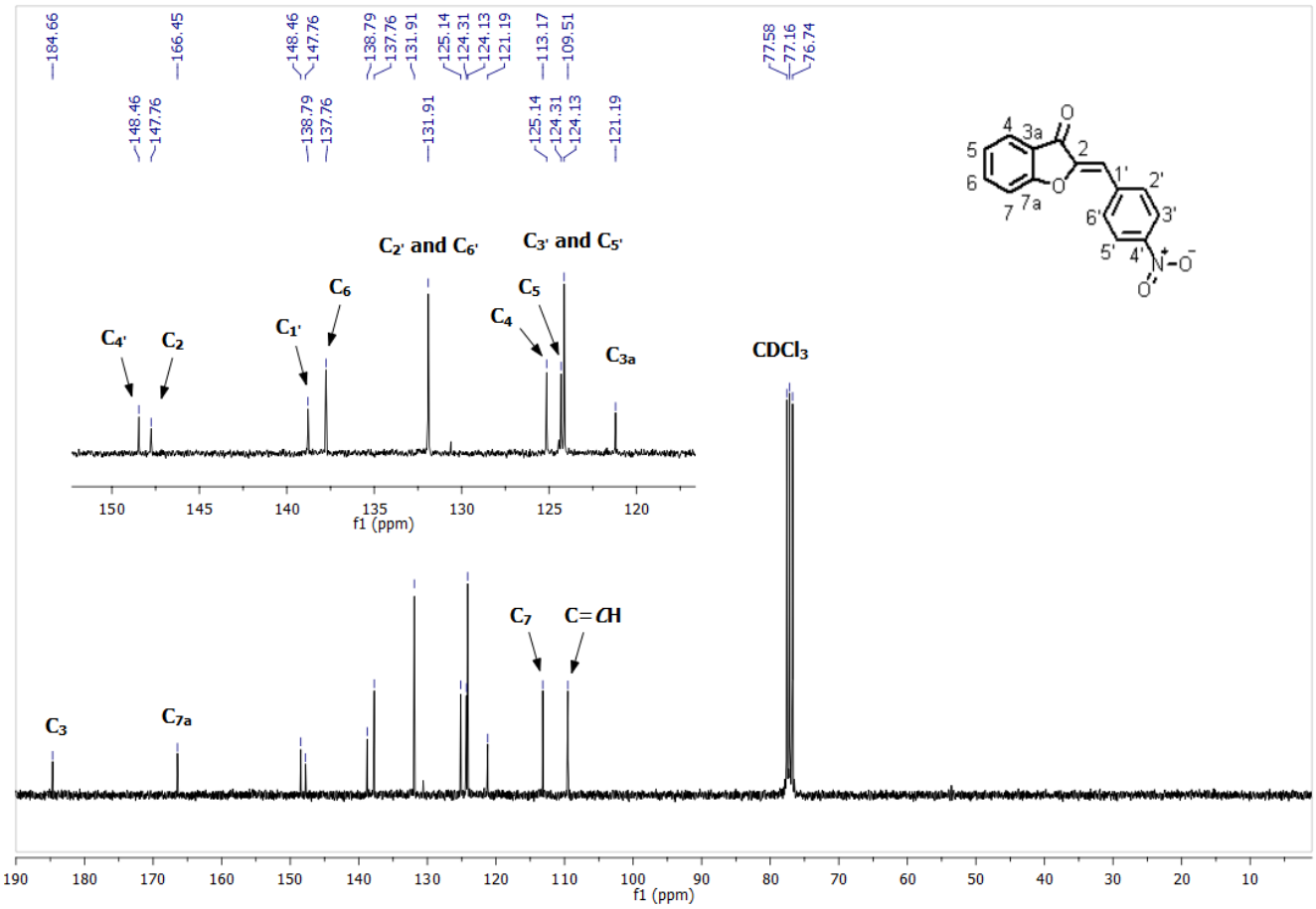


Figure SM 4.2.2.7.8 – ^{13}C NMR spectrum of compound **1c** (300 MHz, $CDCl_3$) and peak assignment.

[1] The execution of the experiment at a larger scale or using other substituted benzaldehydes might require increased reaction times.

[2] The R_f between the starting material and compound **1a** is similar but they spot differently at 366 nm.

[3] A. Pelter, R. S. Ward and T. I. Gray, *J. Chem. Soc.-Perkin Trans. 1*, 1976, 2475.

[4] M. P. Carrasco, A. S. Newton, L. Goncalves, A. Gois, M. Machado, J. Gut, F. Nogueira, T. Hanscheid, R. C. Guedes, D. dos Santos, P. J. Rosenthal and R. Moreira, *Eur. J. Med. Chem.*, 2014, **80**, 523.

Synthesis of pyrazole heterocycles

Supplementary Material

Thomas A. Logothetis

Experiment notes

The TLC monitoring for both reactions involves a mini-work-up, *i.e.* the partitioning of an aliquot of the reaction mixture between water and diethyl ether, and utilising the organic layer for TLC analysis.

Reaction 1: Synthesis of 2-(4-chlorobenzylidene)quinuclidin-3-one

This reaction affords the aldol condensation product in a high yield only if the following parameters are taken into consideration by a skilled student; lower yields should be expected if the specifications are not meticulously adhered to. In our year 2 laboratory class this reaction is also used to discuss in depth aspects that normally do not feature high in lectures, *i.e.* surface area and particles sizes' influence on reaction kinetics; TLC monitoring and visualisation techniques and their physicochemical basis; and different techniques of heating and temperature controlling.

The sodium hydroxide used in this reaction should have a reasonably large surface area, *i.e.* a small particle size: Pellets or flakes will not work well whereas small pearls or freshly ground NaOH work well. However, the weighing needs to be reasonably fast due to the hygroscopic nature of the base.

This reaction demands precise temperature control, best via internal measurement, although careful monitoring of the external heating works sufficiently well. Ideally, the temperature is kept in the given range (externally: 60-65 °C) to achieve a reasonably fast reaction, but not higher than 65 °C as this will lead to a diminished yield. This would be apparent in a darkening reaction mixture, due to side-

product formation. Reactions starting from 4-chloro- or 4-bromobenzaldehyde are particularly sensitive to excess temperatures, whereas 4-fluoro- and 4-methylbenzaldehyde are slightly more tolerant.

TLC monitoring indicates that the reaction takes circa 60 min of heating. The visualisation of the limiting reagent is difficult as it neither oxidises nor shows up under UV irradiation. While a stock solution of pure 3-quinuclidinone hydrochloride only produces barely visible whiteish spots at the baseline, the reaction mixture is alkaline and the 3-quinuclidinone travels up slightly from the baseline and can be oxidised with a permanganate dip and subsequent heating of the TLC plate, producing spots that are easier to notice.

The product easily crystallises and this is exploited in the isolation and purification step.

*Reaction 2: Synthesis of 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine*

This reaction is straightforward and takes around 45-60 minutes of heating. Again the product forms a solid easily. The only precaution necessary is related to the handling of hydrazine hydrate, which should only be done in a well ventilated fume cupboard. It readily forms a hydrazone with acetone in an exothermic reaction, which is exploited in decontamination and cleaning procedures.

The TLC monitoring uses two eluents which differ strongly in polarity, which reflects the polarity differences of the starting material and the product. Removing a sample from the reaction mixture is achieved by briefly lifting the reflux condenser and using a Pasteur pipette. **Note:** The reaction is not carried out under reflux conditions but some hydrazine hydrate will collect at the bottom of the reflux condenser. This should be rinsed with acetone during clean-up.

Optional features

The described sequence of two reactions can be complemented by two more steps, namely the *Boc*-protection of the secondary amine in the piperidine ring followed by a bromination of the pyrazole ring

as described in the chapter "*Selective Boc-protection and bromination of pyrazoles*" to afford a versatile scaffold.

Another feature of the synthesis of a pyrazole heterocycle is that the starting aldehyde can be easily modified to afford a potentially large library of products. Although this script only describes the synthesis starting from 4-chlorobenzaldehyde, three more *para*-substituted benzaldehydes have been tested and used in practicals (see tabulation of experimental results below) employing the same conditions. Theoretically, *ortho* and *meta*-substituted as well as disubstituted benzaldehydes should be possible starting materials, although these options have not been tested.

Experimental results

The following tables summarise the results achieved with second year undergraduate students averaged over several years. Starting materials are *para*-substituted benzaldehydes, *i.e.* 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, and 4-methylbenzaldehyde (4-tolylaldehyde). The colour of the crystalline products from reaction 1 is yellow (intensive yellow for the chloro and bromo derivatives), the powdery solids produced in reaction 2 are all pale yellow.

Typical melting points and yields for products of reaction 1 (aldol condensation):

Residue	mp [°C]	Recrystallisation solvent	Yield [%]
R = Cl	112-114	ethanol	80-85
R = Br	119-121	ethanol	80-85
R = F	118-120	ethanol	75-80
R = Me	110-112	ethanol	70-75

Table SM 4.2.2.8.1: Data for 2-(4-chlorobenzylidene)quinuclidin-3-one

Typical melting points and yields for products of reaction 2 (pyrazole formation):

Residue	mp [°C]	Recrystallisation solvent(s)	Yield [%]
R = Cl	174-175	ethanol	65-70
R = Br	184-186	ethanol	65-70
R = F	178-180	ethanol	60-65
R = Me	128-130	ethanol	60-65

Table SM 4.2.2.8.2: Data for 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine

The ethanol recrystallisation also works with a mixed solvent system using ethanol and water.

Photos of the products

Figure SM 4.2.2.8.1: Aldol condensation product (left) and pyrazole heterocycle (right)

Typical TLC plates for both reactions

Reaction 1 (aldol condensation):

The limiting reagent, 3-quinuclidinone hydrochloride (Q), is not visible under UV light. When using a

coloured stain like potassium permanganate it produces a faint white spot due to the lack of penetration of the reagent into the spotted material. The aldehyde (SM) is clearly visible under UV irradiation and the spot can be oxidised. Sometimes the aldehyde is contaminated with a little of its corresponding acid, depending on quality and age of this starting material. If it is spotted from a concentrated solution, the acid spot becomes visible under UV light only. Depending on the concentration of the reaction mixture (R) in the solution from which it is spotted, the now deprotonated 3-quinuclidinone and (oxidation only) and an intermediate can be observed.

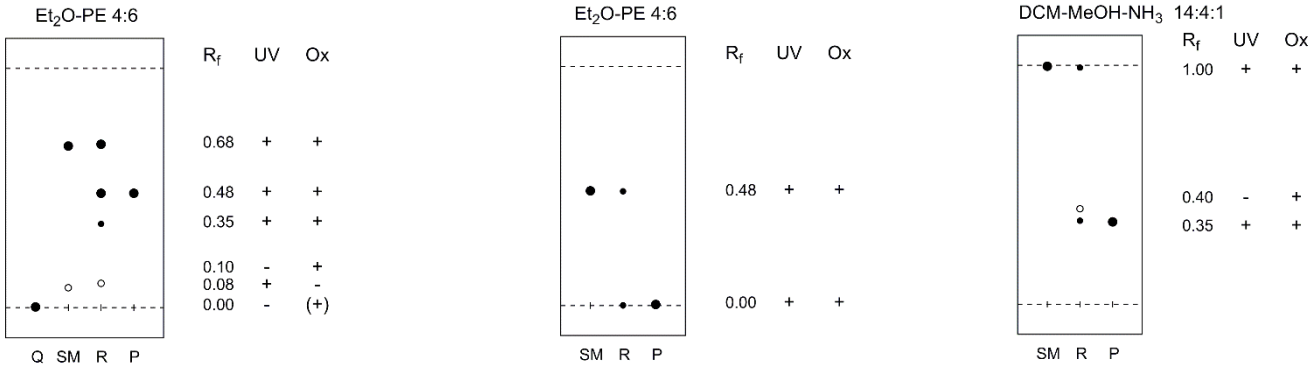


Figure SM 4.2.2.8.2: Exemplary observations on TLC plates when monitoring reaction 1 (left) and reaction 2 (middle & right)

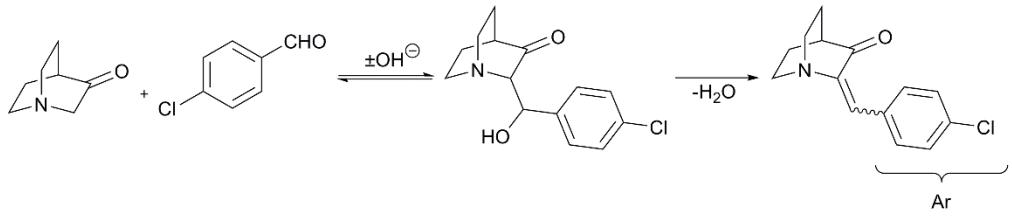
Reaction 2 (pyrazole formation):

Due to the strongly different polarity of the starting material (SM) and the product (P) it is advised to use two different eluents to follow the reaction (R). In the more polar eluent ethylene glycol sometimes becomes visible under oxidative staining.

Mechanistic details

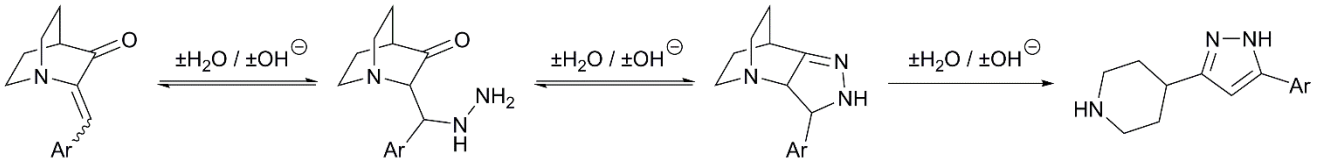
The two mechanisms are briefly summarised below. The base used in the aldol condensation would first abstract the ammonium proton followed by a proton from the CH_2 group next to the carbonyl; the bridgehead proton next to the carbonyl cannot be abstracted as the lone pair would occupy a sp^3 orbital lobe that cannot overlap with the carbonyl π-system/orbital set (Bredt's rule). The pK_a values would be similar to ammonium, acetone and alkane (pK_a ~9, ~20, ~40).

Step 1 is an aldol formation with subsequent elimination of water, in total a typical aldol condensation:



Scheme SM 4.2.2.8.1: Steps of reaction 1

The decontamination of hydrazine exploits its fast and exothermic reaction with acetone to form the corresponding hydrazone, which is less toxic and not a reported carcinogen. Discussion of this topic during a lab class can lead to the second mechanism, which consists of a Michael addition followed by an intramolecular hydrazone formation, and finally an aromatisation with opening of the bicyclic system to afford a piperidine and pyrazole ring.



Scheme SM 4.2.2.8.2: Steps of reaction 2

Spectra

The spectra depicted here illustrate the chloro-derivatives only. Only spectra asked to obtain are exhibited here. Spectra not showing here have been found to be less useful in the context of this practical. NMR spectra stemming from the fluoro-derivatives would exhibit additional coupling between ^{1}H and ^{19}F nuclei as well as between ^{13}C and ^{19}F nuclei. Mass spectra of the bromo-derivatives would present – like the described chlorine containing products – a typical isotope pattern. In infrared spectra the ν(C-X) can be seen depending on the resolution and spectral width of the spectrometer in the region 1030 – 1100 cm^{-1}. The ν(C-H) are visible between 2850 – 3000 cm^{-1} and the ν(C=O) absorbs around 1710 cm^{-1}.

The mass spectrum below shows two peaks found for $[M+H]^+$ with the 3:1 isotope pattern with 2 amu difference typical for Cl_1 as evidenced by the detected mass (column 1) and relative abundance in % (column3).

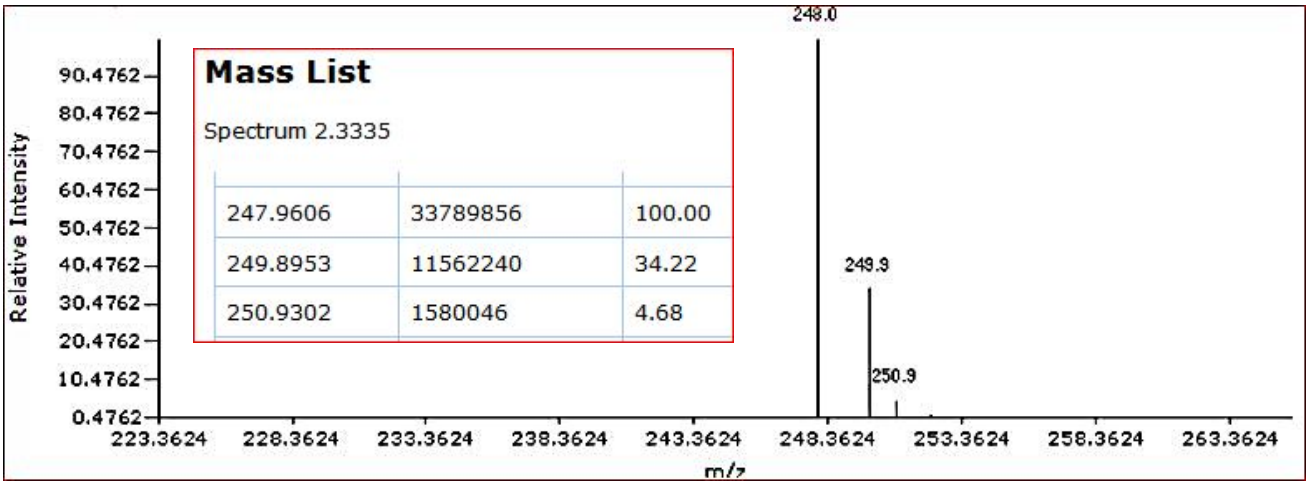


Figure SM 4.2.2.8.3: ES+ (MeCN) of 2-(4-chlorobenzylidene)quinuclidin-3-one

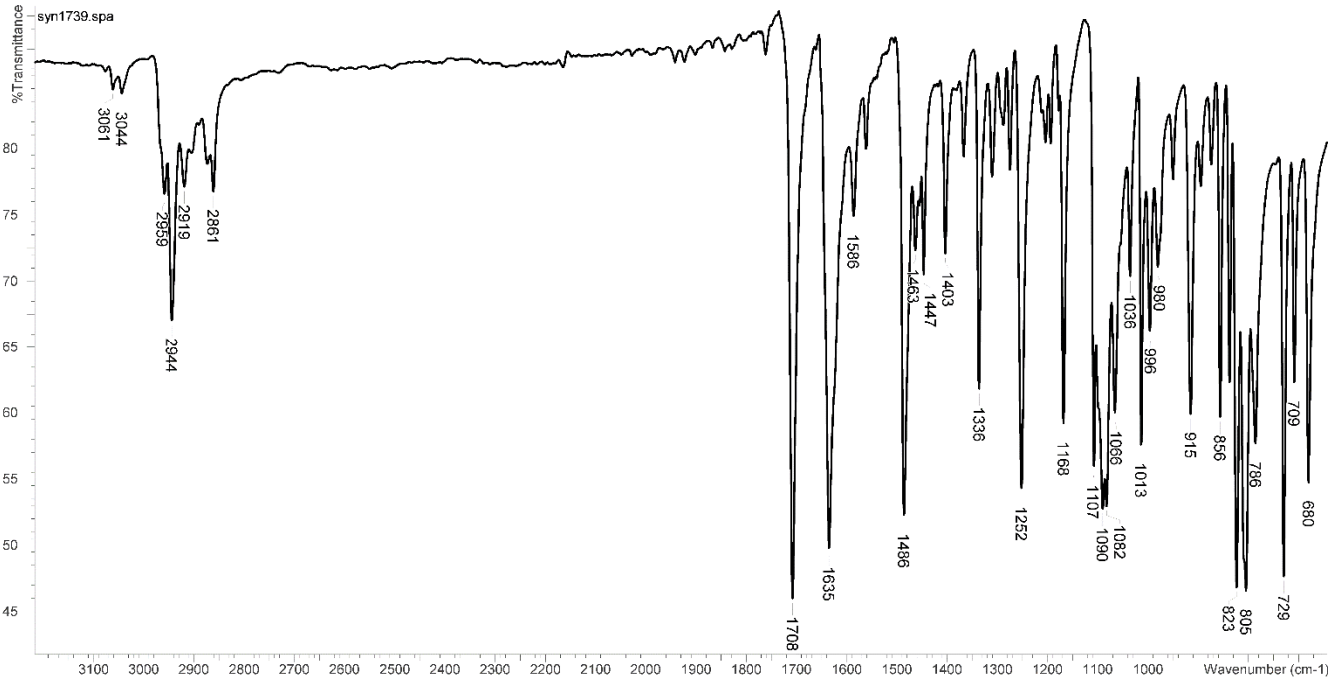
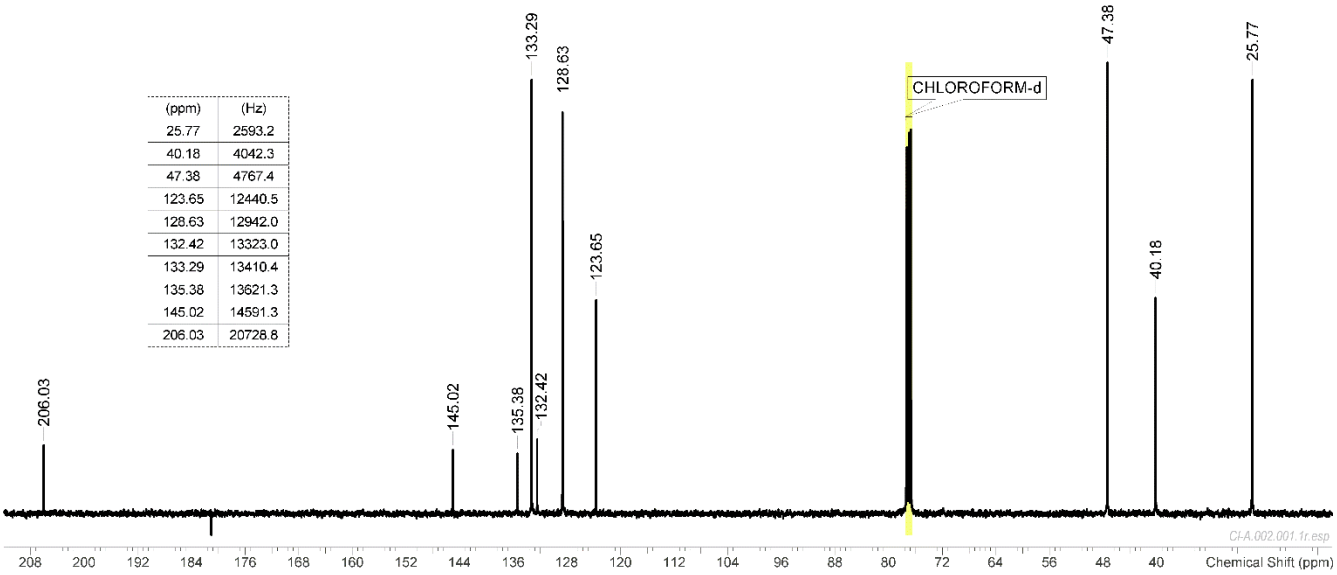
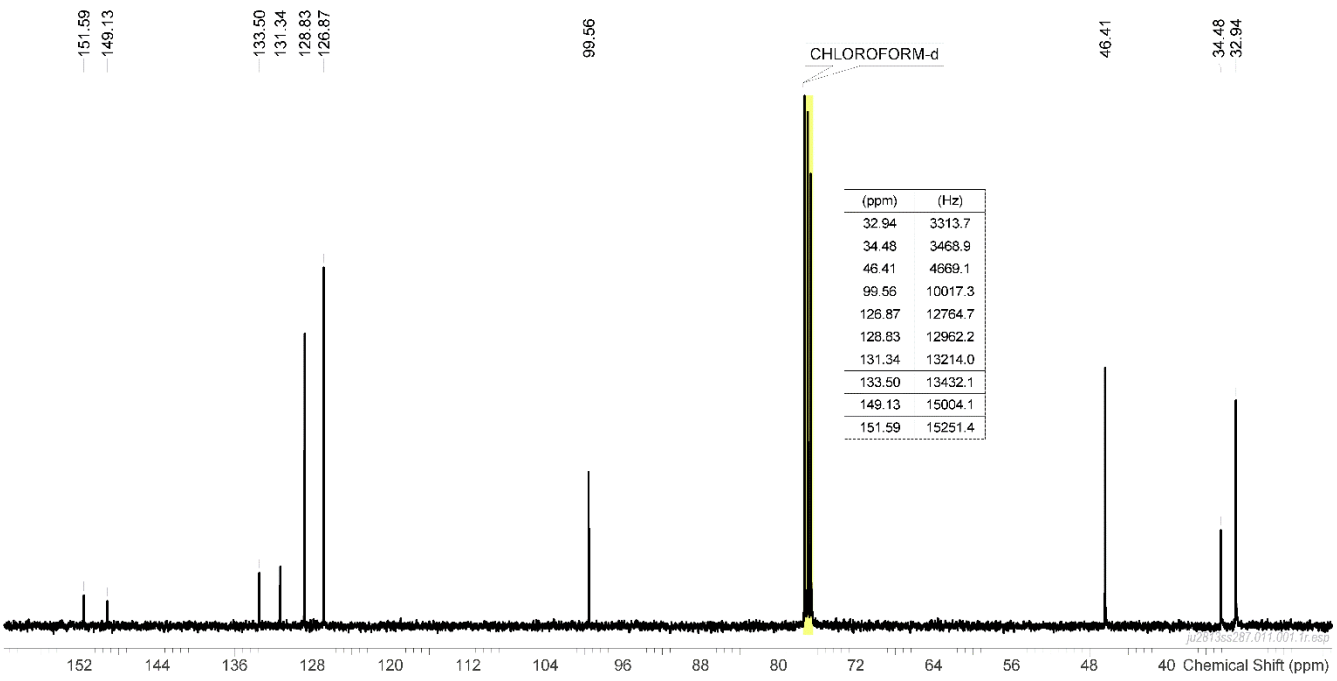


Figure SM 4.2.2.8.4: IR (ATR) of 2-(4-chlorobenzylidene)quinuclidin-3-one



(ppm)	(Hz)
25.77	2593.2
40.18	4042.3
47.38	4767.4
123.65	12440.5
128.63	12942.0
132.42	13323.0
133.29	13410.4
135.38	13621.3
145.02	14591.3
206.03	20728.8

Figure SM 4.2.2.8.5: ^{13}C NMR (100 MHz, $CDCl_3$) of 2-(4-chlorobenzylidene)quinuclidin-3-one



(ppm)	(Hz)
32.94	3313.7
34.48	3468.9
46.41	4669.1
99.56	10017.3
126.87	12764.7
128.83	12962.2
131.34	13214.0
133.50	13432.1
149.13	15004.1
151.59	15251.4

Figure SM 4.2.2.8.6: ^{13}C NMR (100 MHz, $CDCl_3$) of 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.67 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 6.35 (s, 1H), 3.19 (dt, *J* = 12.2, 3.1 Hz, 2H), 2.81 (tt, *J* = 12.1, 3.9 Hz, 1H), 2.74 (td, *J* = 12.2, 2.5 Hz, 2H), 1.97 (d, br, *J* = 12.5 Hz, 2H), 1.71 (qd, *J* = 12.7, 3.6 Hz, 2H).

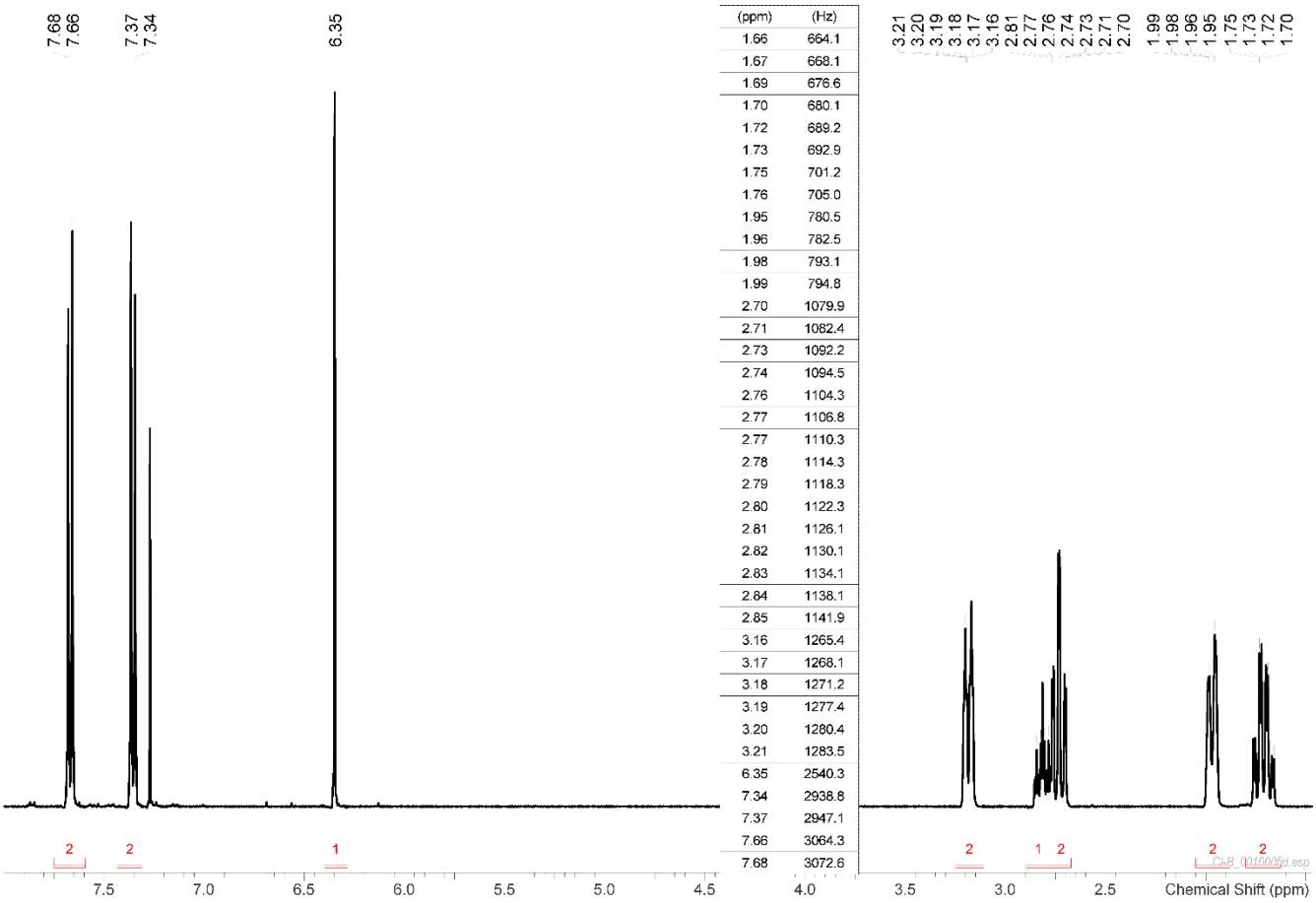


Figure SM 4.2.2.8.7: ^{1}H NMR (400 MHz, $CDCl_3$) of 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine

The conformational analysis of the piperidine ring of the final product is based on analysing coupling patterns and constants ($^{2,3}J_{HH}$) and relating the information to the torsion angle via the Karplus curve. Data are listed together with the spectrum and from the large triplet coupling constant in the *tt* it can be derived that the C*H* in the piperidine ring has an equatorial substituent (the pyrazole residue), *i.e* that the hydrogen atom occupies the axial position.

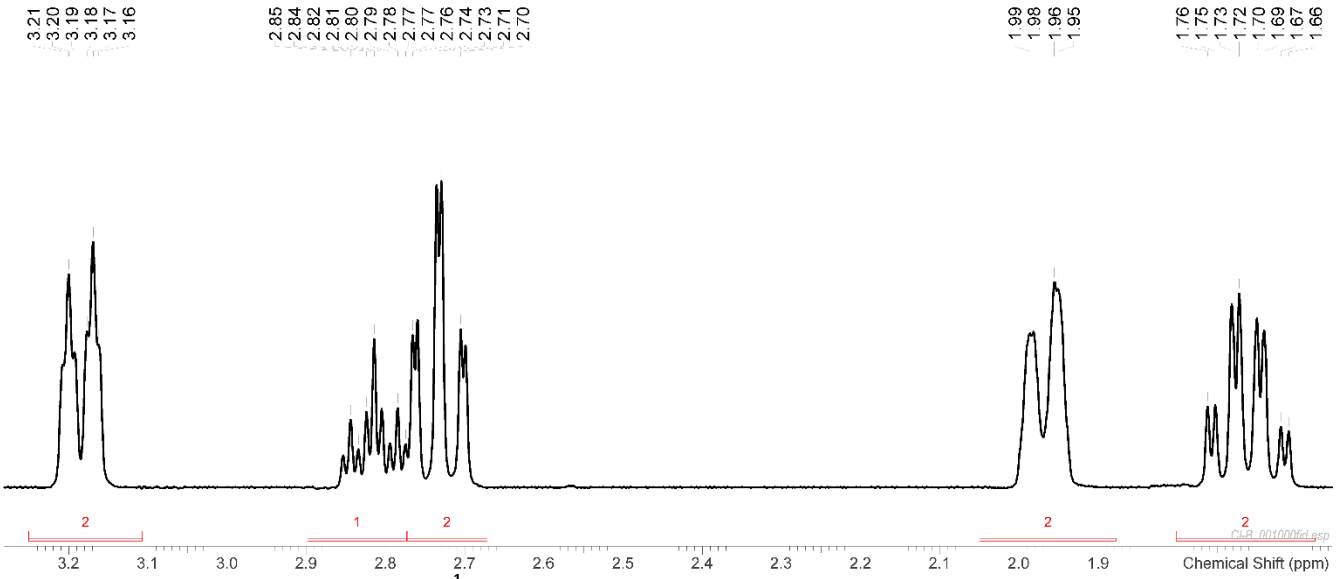


Figure SM 4.2.2.8.8: Expansion of ^{1}H NMR (400 MHz, $CDCl_3$) of 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine

A green approach to 3-carbonylchromones

Ana Bornadiego, Jesús Díaz, Ana G. Neo, Carlos F. Marcos*

Supplementary Material

Notes for the instructor

The experiment was designed for an intermediate level organic chemistry course. However, as the experimental protocols are simple and reliable, it could also be suitable for introductory courses. Protocol was comfortably performed in a three-hour session with groups of 8-10 students organized in teams of 2. However, as microwave irradiation times are very short, it can be easily adapted to larger groups only slightly increasing the length of the lab session, even if only one microwave reactor is available. Both reactions give reasonably pure products and can be used with any further purification processes. Student's typical yields range from 70-90% (average 80%) for the first step, and 15-60% (average 32%) for the second step.

The experiment was performed as part of the teaching laboratory sessions corresponding to a course of Organic Chemistry included in the first year of the BSc in Biochemistry. The students can easily perform the experimental procedure, though they have some difficulties understanding the mechanisms involved in the reactions. This problem can be satisfactorily solved scheduling a pre-lab seminar and a pre-lab assignment in which emphasis on both mechanistic and environmental aspects of the reactions was made.

Liquid reagents were measured using micropipettes with disposable tips.

Anhydrous pyridine should be used to guarantee consistent high yields of the chromone. Optimally, pyridine can be distilled immediately before the addition. Recently distilled pyridine stored under nitrogen over KOH is also a good option.

Liquid-liquid extraction of the crude of the chromone synthesis can be performed using a separation funnel, as explained in the experiment description, or, alternatively, in the same reaction vial with the help of a Pasteur pipette. In the latter case, 4-6 washings with $CuSO_4$ solution (c.a. 2 mL) are necessary.

Figure SM 4.2.2.9.1. Different phases of the experiment. (**A**) Reaction mixture of the enaminone synthesis after microwave irradiation. (**B**) Filtration of the enaminone after crystallisation in toluene. (**C**) Reaction mixture of the chromone synthesis before microwave irradiation.

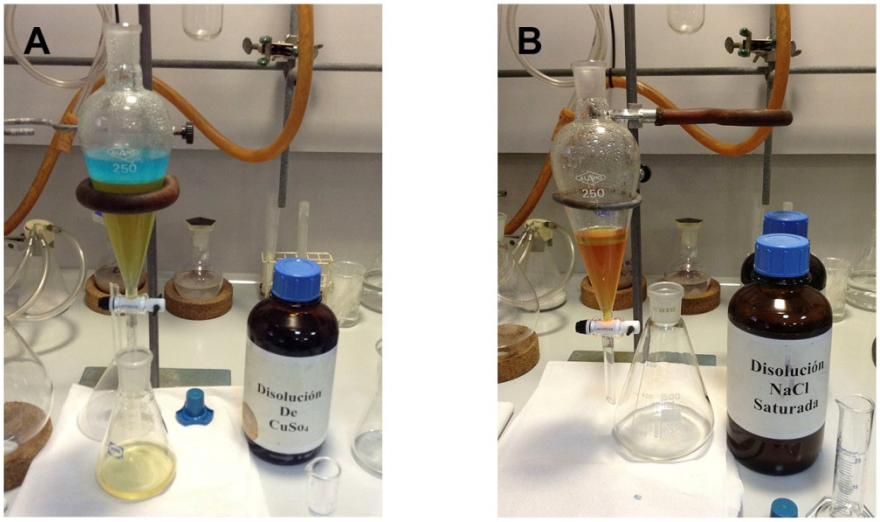


Figure SM 4.2.2.9.2. Synthesis of the chromone: Liquid-liquid partition of the reaction crude with copper sulphate (**A**) and brine (**B**).

Mechanism of the reactions

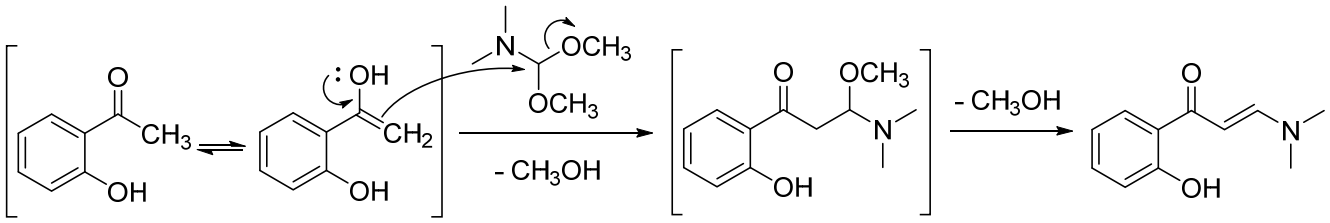


Figure SM 4.2.2.9.3. Mechanism for the synthesis of the enaminone intermediate.

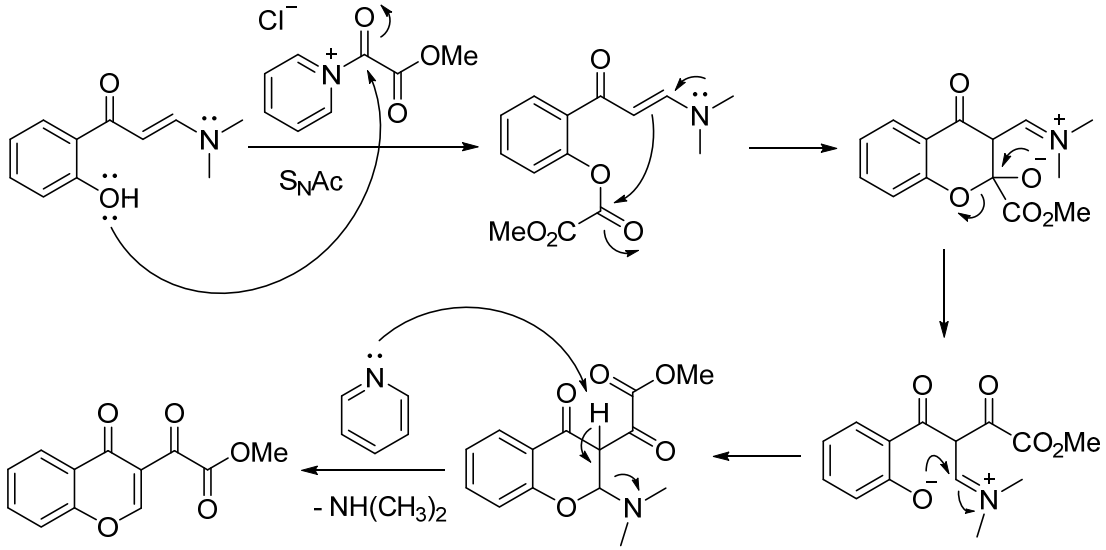
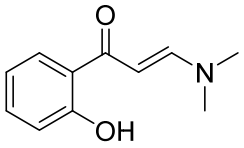


Figure SM 4.2.2.9.4. Mechanism for the synthesis of the chromone.

Spectroscopic data and spectra



(*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one.

Orange solid; mp: 133-137 ºC.

IR (cm^{-1}): 2920, 1628, 1548.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.94 (s, 1H, OH), 7.89 (d, *J* = 12.1 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.81 (t, *J* = 8.1 Hz, 1H), 5.79 (d, *J* = 12,1 Hz, 1H), 3.18 (s, 3H), 2.96 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.7 (C), 163.2 (C), 154.9 (CH), 134.1 (CH), 128.4 (CH), 120.5 (C), 118.4 (CH), 118.2 (CH), 90.3 (CH), 45.6 (CH_3), 37.6 (CH_3) ppm.

MS (CI) m/z (%) 220 ($M+29$, 79), 193 (M^+, 92), 191 (100), 190 (35), 147 (90), 98 (100).

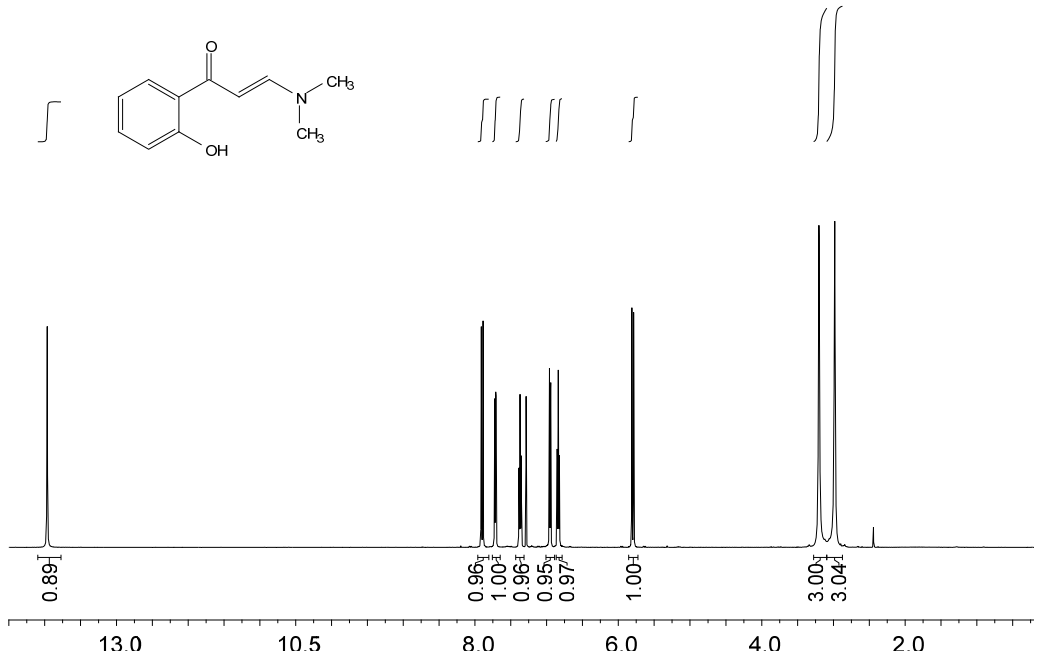


Figure SM 4.2.2.9.3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the enaminone.

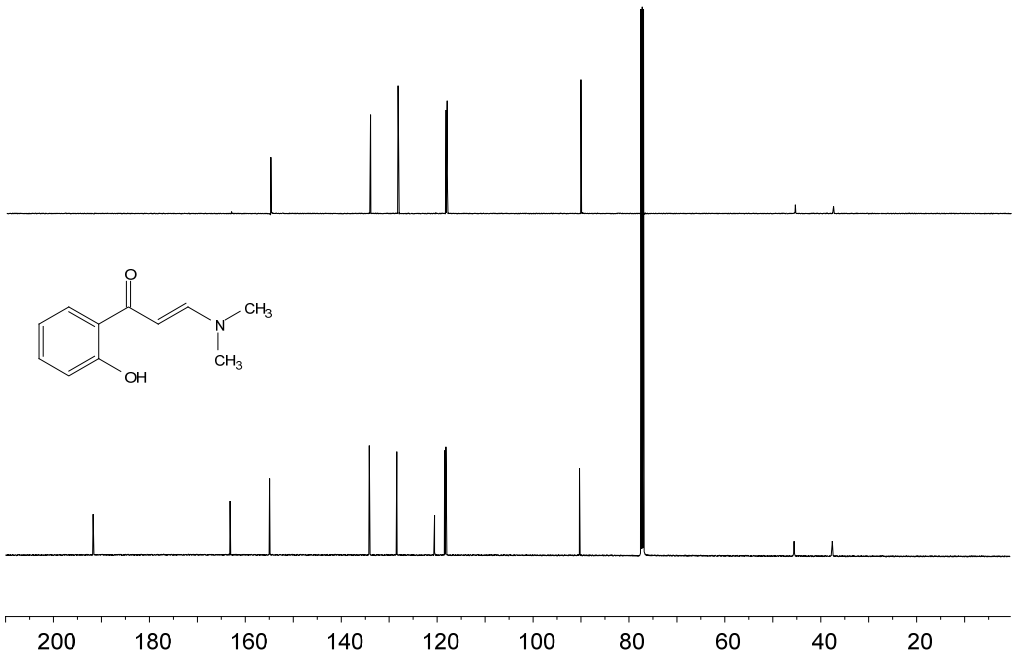
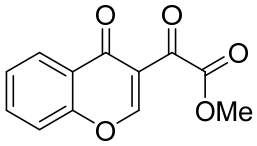


Figure SM 4.2.2.9.4. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the enaminone.



Methyl 2-oxo-2-(4-oxo-4*H*-chromen-3-yl)acetate

Bright brown solid; mp: 131-135 ºC.

IR (cm^{-1}) 3063, 2955, 1731, 1694, 1649.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.5, 1H), 4.00 (s, 3H), ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7 (C), 174.8 (C), 164.4 (C), 162.4 (CH), 156.3 (C), 135.2 (CH), 127.1 (CH) 126.5 (CH), 124.9 (C), 120.1 (C), 118.8 (CH), 53.2 (CH_3) ppm.

MS (CI) m/z (%) 261 (M+29, 22), 234 (M+2, 85), 233 (M+1, 98), 232 (M^+, 99), 217 (69), 121 (22).

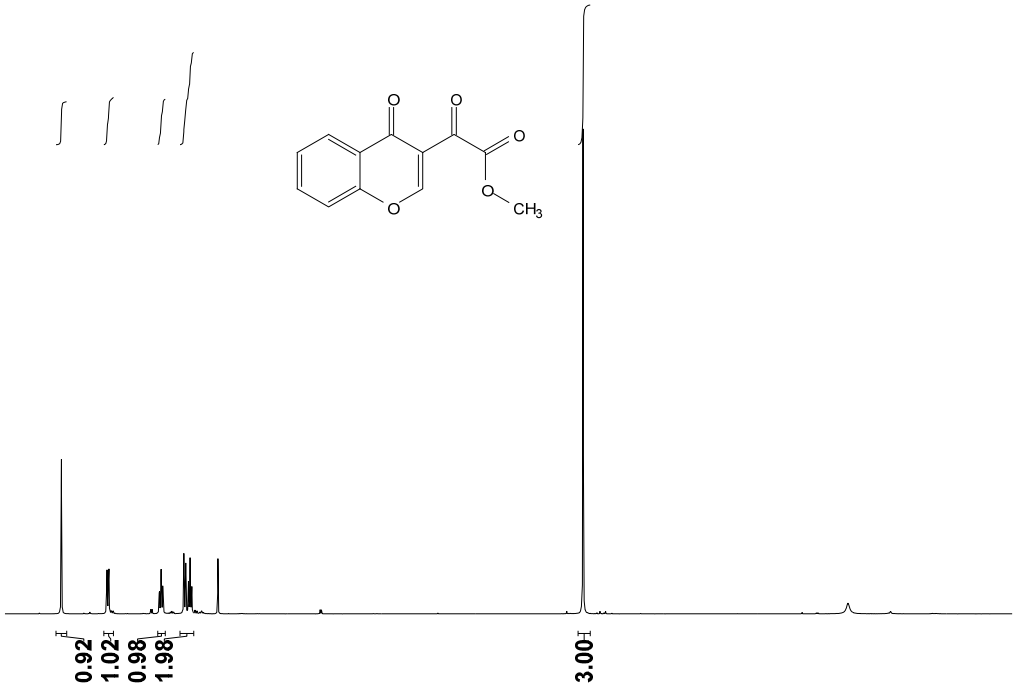


Figure SM 4.2.2.9.5. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the chromone.

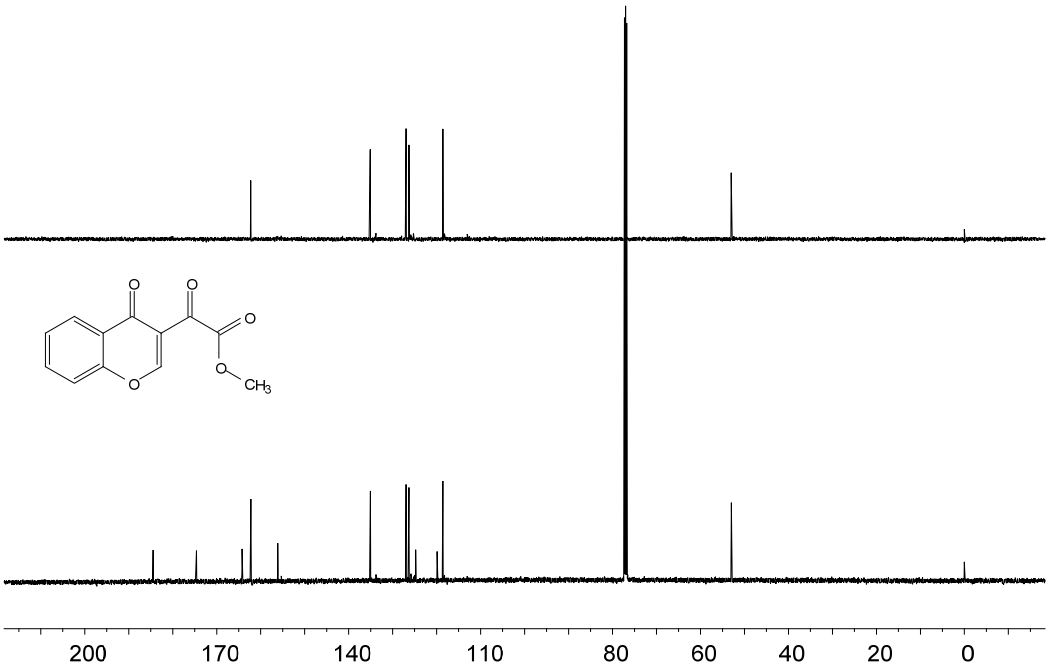


Figure SM 4.2.2.9.6. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the chromone.

Synthesis of indigo and dyeing process

Supplementary Material

The main purpose of this experiment is the preparation of indigo, a product that students are in contact daily. It also aims to draw the student's attention to enolate anions, Aldol-type reactions and redox chemistry involved on dyeing process. This experiment was tested by students of intermediate organic chemistry because the reaction mechanism of indigo formation is complex[1-4] (Baeyer-Drewson reaction). On the other hand, this demonstration is also appropriate for high school level students, due to its simple and fast procedure. When acetone, sodium hydroxide and 2-nitrobenzaldehyde are mixed, the reaction begins with an enolate ion attack to at the carbonyl group of 2-nitrobenzaldehyde to form a hydroxy ketone. The reaction continues in a series of condensations, tautomerizations and dehydratations to give indigo within a matter of seconds. Indigo is not soluble in water (vat dye), so the students have the opportunity of learn about dyeing processes involving oxidation and reduction reactions. An alternative method in two steps, but not tested in the classroom, can be performed starting from 2-nitrobenzaldehyde with addition of nitromethane and base catalyst, followed by reduction with sodium hydrosulfite[5].

Additional notes on the preparation of indigo

More precipitated product is obtained if the filtration is made in the next day of the lab session. Student yields are usually 65-75%. The melting point found in the literature is 390-392ºC and sublimes without decomposition to form copper-red prisms[6]. This mark is too high to be recorded at classroom. The NMR spectra performed in acetone and DMSO-d_6, did not show any signals due to insolubility of this dye.

Figure SM 4.2.2.10.1 – Indigo after precipitation and vacuum filtration

Additional notes on dying of cotton[7]

If substantial amounts of blue-purple solid remain, the solution should be decanted before cotton immersion.

Figure SM 4.2.2.10.2 – Piece of cotton after dyeing process

IR spectra:

Students easily identify N-H stretching band between 3250 and 3400 cm^{-1} and the strong absorption C=O stretching band (1600-1640 cm-1). IR spectrum of indigo is also available in SDBS (nº 21446)[8].

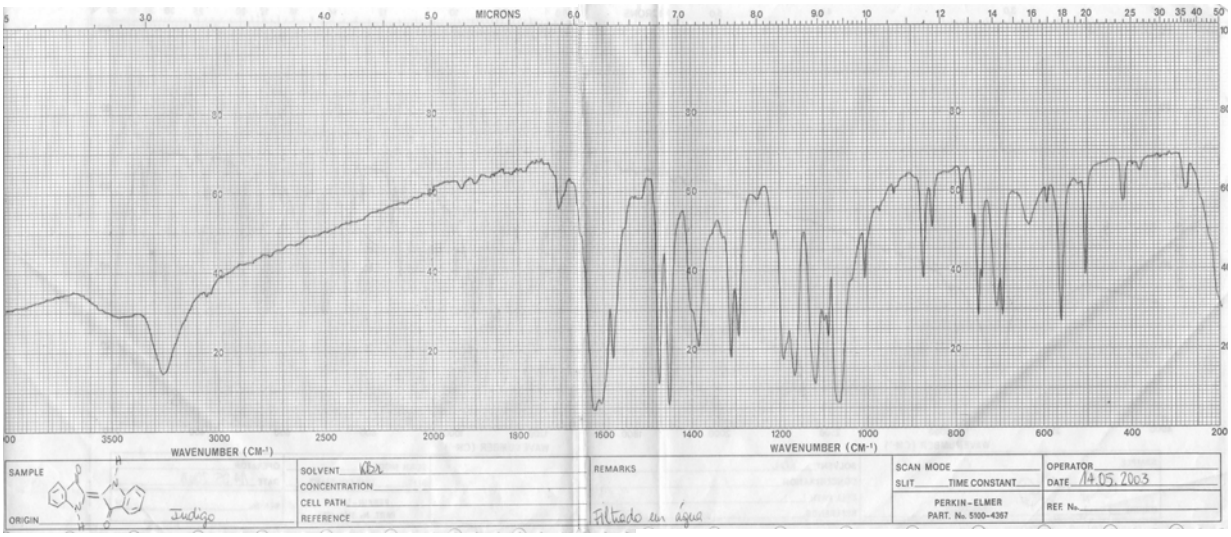


Figure SM 4.2.2.10.3 - IR (KBr) of indigo

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