A S_N1 Reaction: Synthesis of *tert*-Butyl Chloride

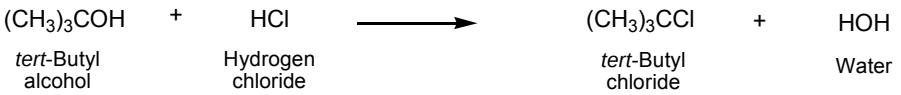
Supplementary Material

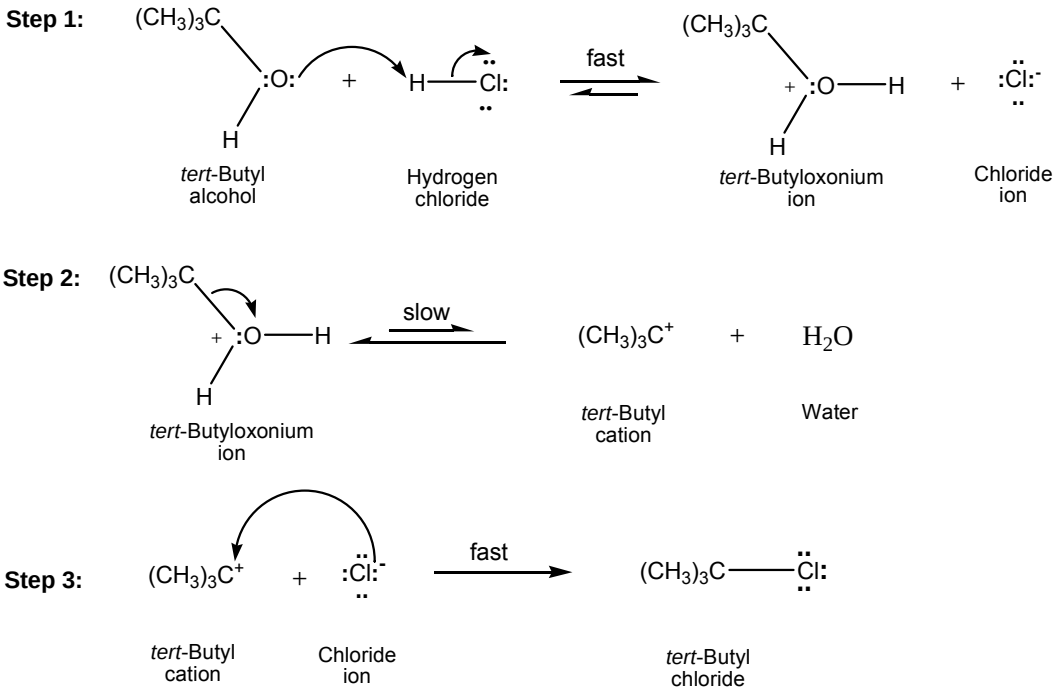
Experiment Notes:

This lab experiment proposes the synthesis of an alkyl halide by reacting the corresponding alcohol with a hydrogen halide in an easy and inexpensive S_N1 reaction.[1,2] tert-Butanol reacts readily with HCl and forms the corresponding *tert*-butyl chloride at room temperature. S_N1 mechanisms are unimolecular because its slow step is unimolecular. The reaction proposed involves an initial step where the *tert*-butyloxonium ion is formed by protonation. This ion then dissociates to a second intermediate a carbocation - an ion that contains a positively charged carbon. Since only one species, *tert*-butyloxonium ion, undergoes a chemical change in this step, the step is unimolecular. This is the rate-controlling step. The carbocation (*tert*-butylcation) being strongly electrophilic then reacts with the nucleophile chloride ion in a fast step originating the *tert*-butyl chloride final product – Scheme SM 2.1.1.1.[3] Since the nucleophile is not involved in the rate–determining step of the process a strong nucleophile is not important in this process.

More stable carbocations are formed faster than the less stable ones. That stability is conferred by hyperconjugation - electron delocalization via orbital overlap. Therefore the S_N1 mechanism is generally accepted to be correct for the reaction of tertiary and secondary alcohols with hydrogen halides but not for methyl and primary alcohols as methyl and primary carbocations are too unstable to be reasonably involved. Instead methyl and primary alcohols will suffer an initial protonation and then react slowly by a bimolecular S_N2 mechanism. Therefore if the same conditions were applied to *n*-butanol just small amount, if any, of 1-chlorobutane would be obtained.

The overall reaction





Scheme SM 2.1.1.1 – Mechanism for the formation of *tert*-Butyl Chloride from *tert*-Butyl Alcohol and Hydrogen Chloride

The importance of S_N1 experimental conditions will be emphasised to the students with this experiment. While conducting the reaction, the use of vigorous magnetic stirring in an uncapped Erlenmeyer is important to promote a close contact among the reactants. To avoid any reaction mixture spilling it is advisable to adjust an air condenser to the clamped jointware Erlenmeyer during the reaction course. Alternatively, the reaction can be carried out in a 250 mL separatory funnel, shaking for about 10 minutes with the appropriate cautions: slow swirling until all the gas is extruded from the medium and

frequently opening of the funnel stopper to release internal pressure, followed by a more vigorous shaking. Care must be taken in this operation to avoid over-pressure inside the stopper separatory funnel. The reaction mixture is then transferred from the Erlenmeyer to the separatory funnel, and the discharge of the different acid and alkaline aqueous phases should be done with care.

The reaction mixture treatment includes an initial neutralization with CO_2 formation, and care must be taken to avoid over-pressure inside the separatory funnel; an initial slow swirling until most of the gas liberates followed of a slow shaking with pressure equilibration followed by a more vigorous shaking and subsequent phase separation.

After the reaction mixture treatment, the organic phase must be dried with enough anhydrous sodium sulphate, which must be added in small portions with careful swirling, to avoid the excess of that agent. The dried solution is then filtrated by gravity to a round bottom distillation flask. Care should be taken to hold the funnel over the round bottom flask such that the air leaves as the filtrate flows to the flask in order to avoid over-pressure in the distillation flask.

Before the simple distillation, make sure that the round bottom flask, with the appropriate boiling stones or magnetic stirrer, is properly fixed with a clamp inside the heating mantle or in a water / oil bath over a heating plate, not touching the heating equipment to avoid over-heating during the distillation. All the glass jointware should be properly adjusted avoiding any vapour leakage, and the condenser must be properly fixed. After everything set up – figure SM 2.1.1.1 - make sure the temperature can be easily registered and the graduated cylinder to recover the product has the weight registered. Then the distillation operation must start. Since the product fraction has a boiling temperature between 48 and 52 ºC, a very slow heat increase is advisable and the recover equipment should be kept in an ice bath. After product recovery the distillation heating should be turned off and let to cool down before disconnecting the distillation equipment. The recover joint glass graduated cylinder with the distilled

product must be capped before taken from the ice bath, out-cleaned not to be wet and then weighted. The distillation operation should be done in a fume cupboard.

With the obtained volume and weight of the product, the reaction yield must be calculated, making note of the limiting reagent in this specific reaction.

This organic chemistry experiment has been performed by Pharmaceutical Sciences degree students (1st year) for more than 20 years in the Organic Chemistry laboratory of Pharmacy Faculty – *Universidade de Lisboa*, Portugal.

Typical yields vary between 40% and 65%. Vigorous shaking/stirring is an important factor to obtain good yields.

If students are already familiar with infrared, *tert*-butanol and *tert*-butyl chloride infrared spectra can be obtained in order to confirm the disappearance of the alcohol band around 3300 cm^{-1} in the alkyl halide product. For that, it is important that the final product will be properly dried. IR for *tert*-butanol (A) and *tert*-butyl chloride (B) with a laser IRAffinity-1 Shimadzu apparatus are included in figures 2.1.1.2. These spectra are also available on-line from different sources.[4]

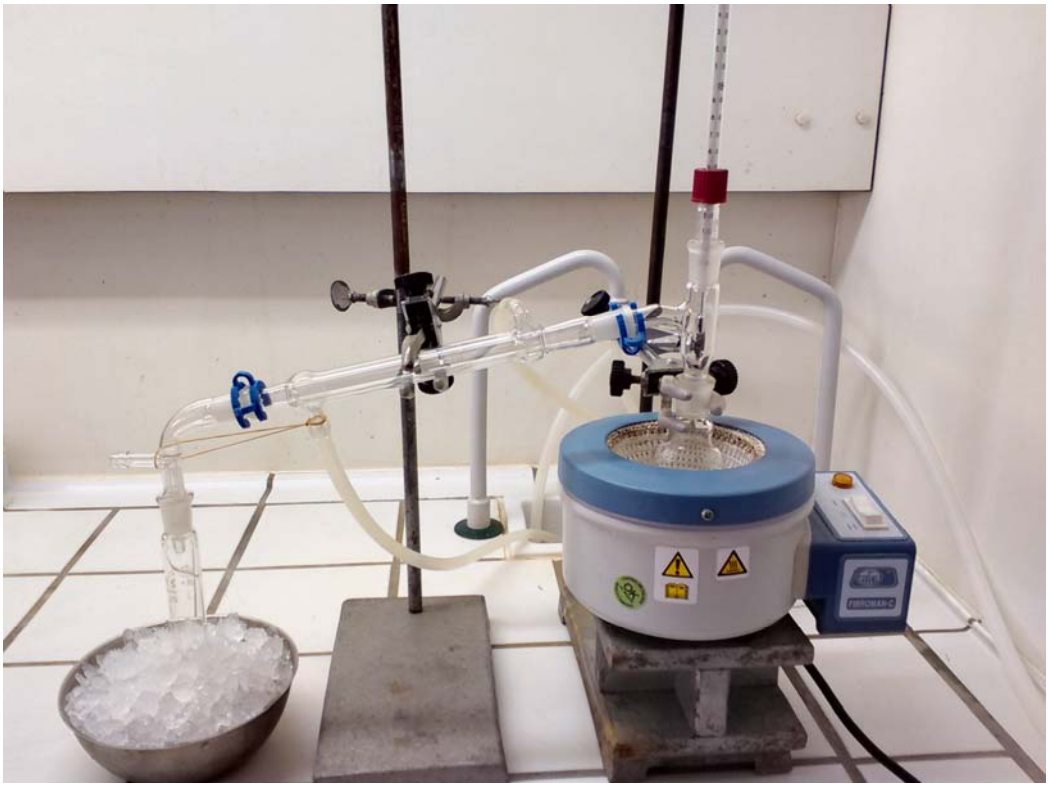
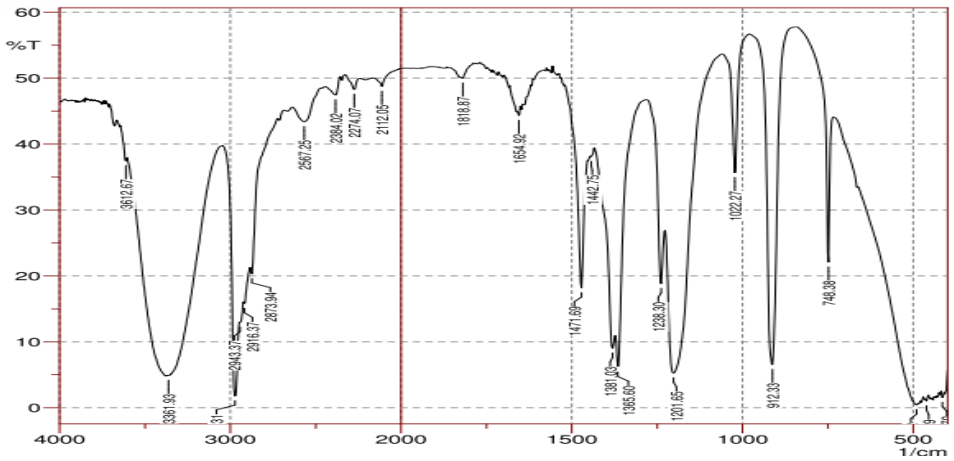


Figure SM 2.1.1.1. *tert*-Butyl chloride distillation set up.

tert-Butanol (A)



tert-Butylcloride (B)

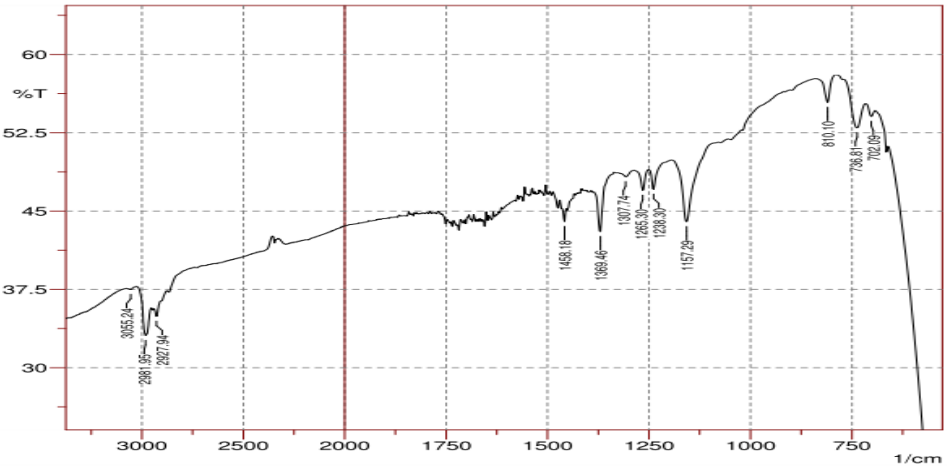


Figure SM 2.1.1.2. Infrared spectra obtained by Pharmaceutical Sciences students, Lisbon University, Portugal with a laser IRAffinity-1 Shimadzu apparatus: (A) *tert*-butanol (C-OH ≈ 3361.93 cm^{-1}) (B) *tert*-butylcloride.

References:

[1] K.P.C., Vollhardt, N.E. Schore, *Organic Chemistry: Structure and Function*, Freeman and Company, New York. 6th Ed, 2010
[2] J. Clayden, N. Greeves, S. Warren,*Organic Chemistry*, Oxford University Press Inc., New York, 2nd Ed., 2012.
[4]. F.A.Carey, R.M.Giuliano,*Organic Chemistry,* McGraw-Hill, New York, 8th Ed, 2011.
[3] Examples of IR spectra websites (accessed at 27 March 2017): a) chemicalbook.com; b) chem.uiuc.edu; c) webbook.nist.gov

Optimizing the Reaction Conditions for the Synthesis of tert-pentyl Chloride

Supplementary Material

Substitution reactions of tertiary alcohols are introduced early in the organic chemistry sequences, and the preparation of 2-methyl-2-chlorobutane is a classic experiment.[1,2] Variations of this experiment have been published to produce a solid product.[3] Furthermore, there are laboratory experiments based on substitution reactions that are discovery in nature, particular on the role of structure of the alcohol (primary, secondary, tertiary) and the nature of the nucleophile (Cl^- or Br^-)[4]. Instead of focusing on these factors, these experiments are focused toward the optimization of reaction conditions to obtain the highest possible yield.

This experiment has been performed twice in our approximately 200 person standard introductory organic chemistry laboratory which is taught primarily by undergraduate teaching assistants in five sections of 40-50 students. This course is the first organic laboratory for these students and for some students is there first university science laboratory. This experiment is used near the end of the first semester of organic instruction. The lab periods for this course are five hours long. This particular experiment does not take five hours to complete. In addition to the 5 hours of laboratory time, there is 1 hour of lecture time per week. For the second implementation the prelab information had been moved to an online format to allow more time for class discussion of the results.

Pre-laboratory Preparation

As this experiment was performed late in the semester, it was expected that students would have a general grasp of organic laboratory techniques, and this experiment was designed to allow students to apply these techniques. Below is the pre-laboratory assignment that students were expected to complete, followed by the answers.

- Write the title, draw the reaction scheme and create and fill in the table. Your table should be set up for the scenario that you will be doing based on your drawer number.
- Your table should include tert-pentyl alcohol (volume, mass, mmoles, density, equivalents and boiling point) and concentrated HCl (volume, mmoles, equivalents)

	Volume (mL)	Mass (g)	mmoles	Density	Equiv	Boiling Point/Properties
tert-pentyl alcohol	6.0	4.8	55	0.805	1.0	Bp:102°
Concentrated	4.5	[redacted]	55	1.2	1.0	Extremely

HCl		[redacted]				Corrosive
Concentrated HCl	13		163	1.2	3.0	Extremely Corrosive

- You should also look up and include in your notebook the boiling point and density for tert-pentyl chloride*. The density is 0.866 g/mL and the boiling point is 85-86°*
- Answer the following questions
  - What is an appropriately sized round bottom flask? *A 25 mL round bottom if they are using 1 equivalent and a 50 mL round bottom if they are using 3 equivalents*
  - Which layer is your desired organic layer? *The product, which completely forms the organic layers is less dense, and therefore will be the top layer*
  - Why is venting very important in the purification process? *When the HCl reacts with the $NaHCO_3$ it produces CO_2 gas, which much be released from the separatory funnel to prevent a buildup of pressure*?
  - What is the purpose of the brine? *To begin to "pre-dry" the alcohol before the addition of powdered drying agent, although this effect is controversial.*

We found that the calculation of the volume of the concentrated hydrochloric acid from the weight percent and density was quite difficult for students. It is important to verify that students are using the stated number of equivalents.

Solvent Free Conditions and Use of Brine

This experiment was run solvent-less to avoid the waste associated with using a solvent and to avoid the difficulty of separating an organic solvent from the product, which boils at 85-86°C. This does lead to some intrinsic loss of yield. The compound is only sparingly soluble in water, but the solvent-less extraction will lead to a small amount of product loss. In order to reduce this product loss, we add a saturated $NaHCO_3$ directly to the reaction mixture rather than first washing with water. If students are not careful, this does increase the likelihood of generating excessive pressure in the separatory funnel.

In our procedure students washed with saturated sodium bicarbonate followed by brine. While it has been reported that brine is not generally effective at pre-drying organic layers,[5] many universities online organic techniques manuals still state that brine can be used to remove some water from the organic layer before treatment with solid drying agents.[6] In our class we teach students that there is controversy in the organic chemistry community over the use of brine as a drying agent. We choose to use brine in this procedure because the brine will reduce the amount of product lost into the

aqueous phase compared to pure water. Therefore, we use this experiment to introduce the use of brine. We use solid $CaCl_2$ pellets to dry the solution and decant the product of the $CaCl_2$. When we have attempted to use a cotton plug for removing the $CaCl_2$ the students have used excessive amounts of cotton and lost significant amount of product.

Characterization of products

We characterized the product of the reaction only by boiling point. This will lead to some variability in the reported purity. The products could easily be characterized by NMR or GC to better determine the purity of the products.

Discussion of Student Results: Kinetic vsThermodynamic (Equilibrium) Effects

The results of two classes of student compiled data are remarkably consistent, and are shown in Table 1. The only difference between the two years was in the effect of the $CaCl_2$. The difference between 1.0 equiv of HCl and the 3.0 equiv of HCl clearly illustrates the importance of excess reagent in increasing the yield. Without excess reagent, there is a significant amount of unreacted alcohol. While some of this alcohol may need to be purified away by distillation, it is also much more water soluble than the chloride and much of it is removed in the bicarbonate wash. The effect of excess Cl- in the form of $CaCl_2$ is less clear as the results differed between the two years. The $CaCl_2$ may also serve to remove water from the reaction rather than provide a source of Cl^-. The reflux condition was designed to illustrate the difference between failing to allow enough time to reach equilibrium (slow kinetics) and the equilibrium itself not favoring product enough for complete conversion. In this reaction it actually appears that refluxing the reaction reduces the yield. One of the difficulties in this reaction is that it is an equilibrium, and the reverse reaction to reform the alcohol will occur when the chloride is treated with aqueous bicarbonate. As long as this step is carried out quickly, the reaction should not reach the new equilibrium position. However, if the solution is warm when it is exposed to the bicarbonate the reverse reaction will occur more quickly.

Table SM 2.1.2.1: Average class results

Scenario	Year 1 # student	Year 1 Avg Percent yield	Year 2 # students	Year 2 Avg Percent Yield
1 equiv conc HCl	55	21%	54	19%
3 equiv conc HCl	59	49%	51	49%

3 equiv conc HCl+ reflux	49	43%	48	41%
3 equiv conc HCl + $CaCl_2$	48	54%	49	45%

Continuation of the Experiment: Special Projects

At the end of the semester, the students are given the opportunity to propose an extension or variation of one of the experiments they completed. Some examples of student experiments are:

$CaCl_2$ vs $MgSO_4$ in the synthesis of tertpentyl chloride: Source of Cl^- ion or drying agent

Excess HCl: Would 5 equivalents be better?

Refluxing the reaction with $CaCl_2$: Would this make a difference?

How important is the drying agent and brine wash? Will yield and purity go down if these steps are eliminated?

How does time spent shaking with sodium bicarbonate affect the yield of the tert-pentyl chloride?

Plotting the equivalents vs the yield…what does the slope and intercept look like?

Will a fractional distillation work better to separate out tert-pentyl alcohol than a simple distillation?

How will cooling the reaction between tert-pentyl alcohol and HCl affect the yield and purity?

Will NaCl has the same affect as $CaCl_2$ or was the drying affect of $CaCl_2$ important?

How would phosphoric acid and NaCl compare to HCl for synthesis of tert-pentyl alcohol?

How will 1 equiv of HCl + $CaCl_2$ affect the yield and purity of tert pentyl chloride?

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[1] Landgreve, *Organic Laboratory Microscale and Standard Scale Experments,* Brooks/Cole Publishing Company, Pacific *Grove, CA, 4th Edition, 1993, pp. 395-397.*

[2] Palleros, Daniel R. Experimental Organic Chemistry, John Wiley and Sons, Hoboken, NJ, 2000, pp. 284-285

[3] C.E. Wagner and P. A. Marshall, *J. Chem. Ed*., 2010, **87**, 81-83.

[4] Warren, H. W.; Newton, T. A. *J. Chem. Ed.* 1980**, 57***,* 747.

[5] Ellern, James B. *J. Org. Chem*. 1982, **47**, 35690-3570

[6] http://orgchem.colorado.edu/Technique/Procedures/Drying/Drying.html, http://www.columbia.edu/cu/chemistry/ugrad/hssp/EXP_3.html, http://chem.chem.rochester.edu/~nvd/pages/tips.php?page=drying_methods, http://ocw.mit.edu/courses/chemistry/5-301-chemistry-laboratory-techniques-january-iap-2012/labs/MIT5_301IAP12_Work_Handout.pdf

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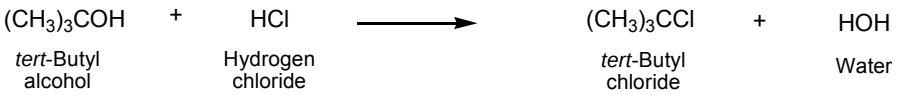

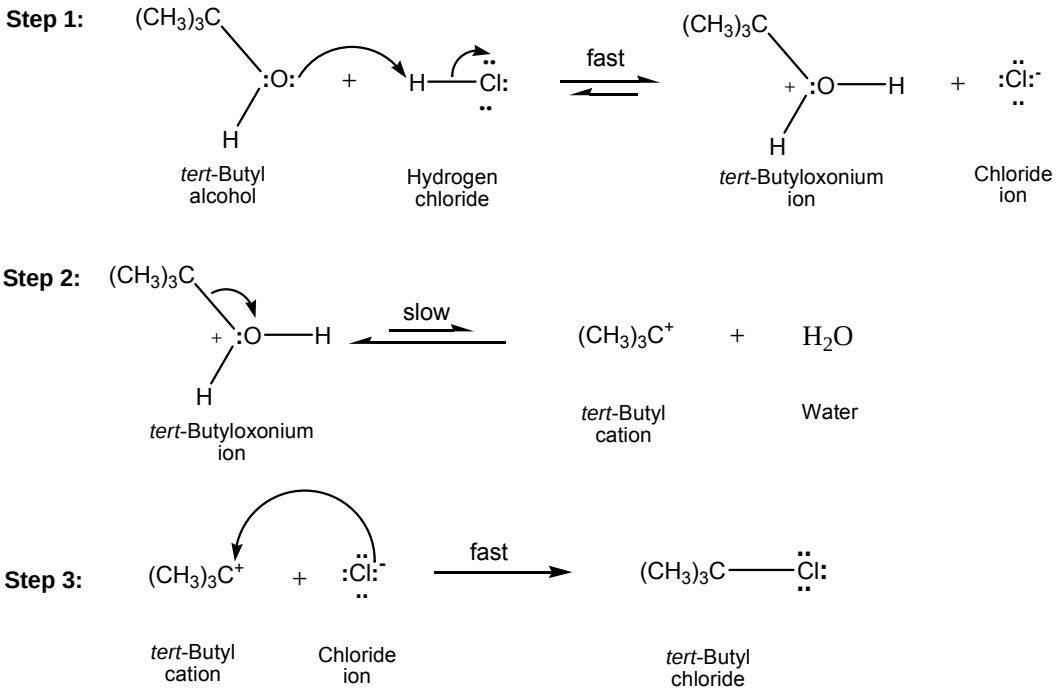

Scheme SM 2.1.1.1 – Mechanism for the formation of *tert*-Butyl Chloride from *tert*-Butyl Alcohol and Hydrogen Chloride

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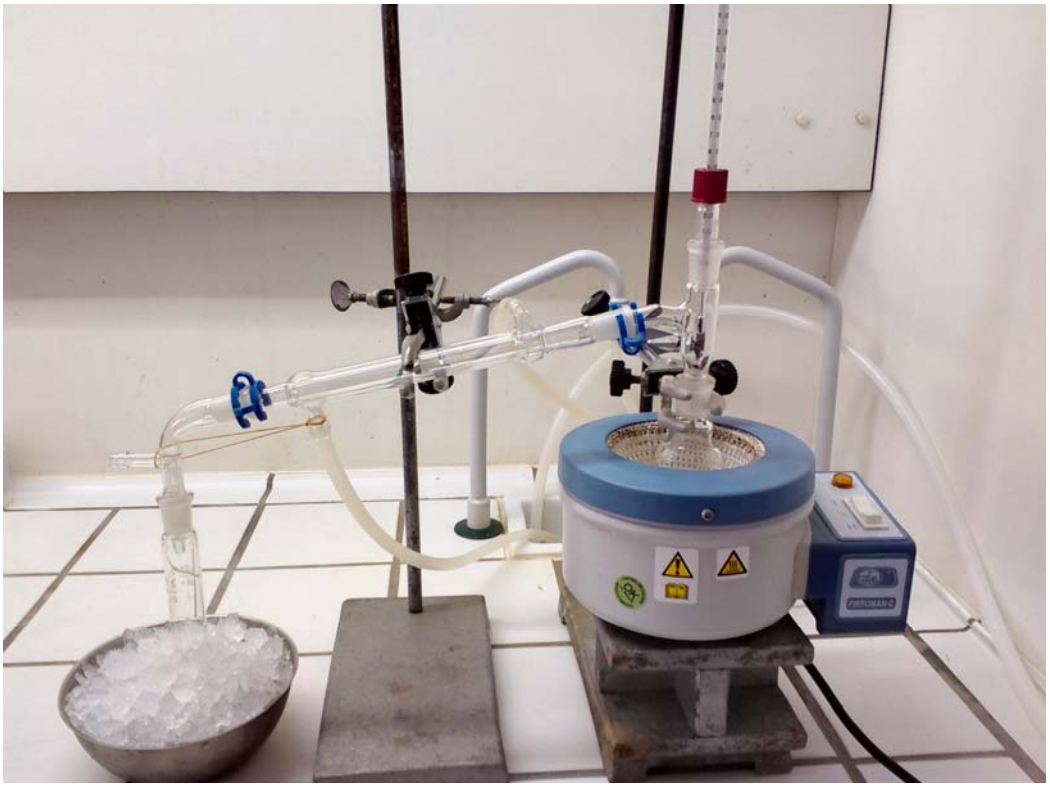
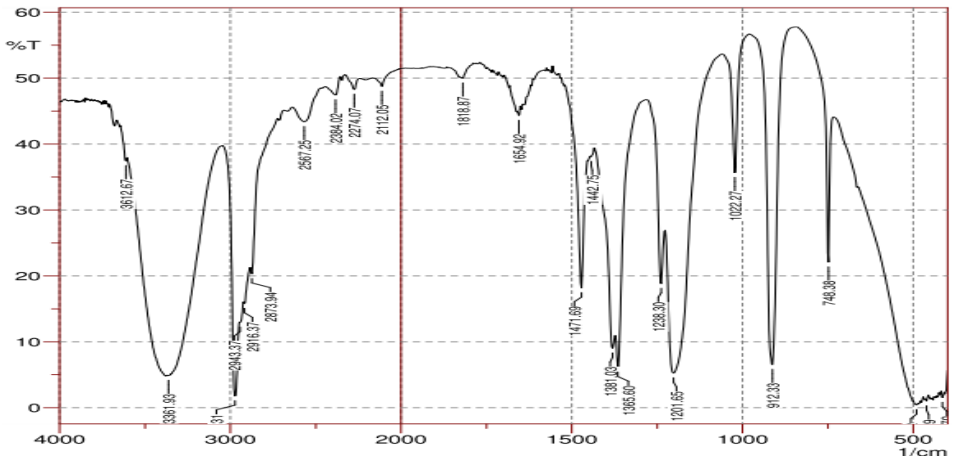


Figure SM 2.1.1.1. *tert*-Butyl chloride distillation set up.

tert-Butanol (A)



tert-Butylcloride (B)

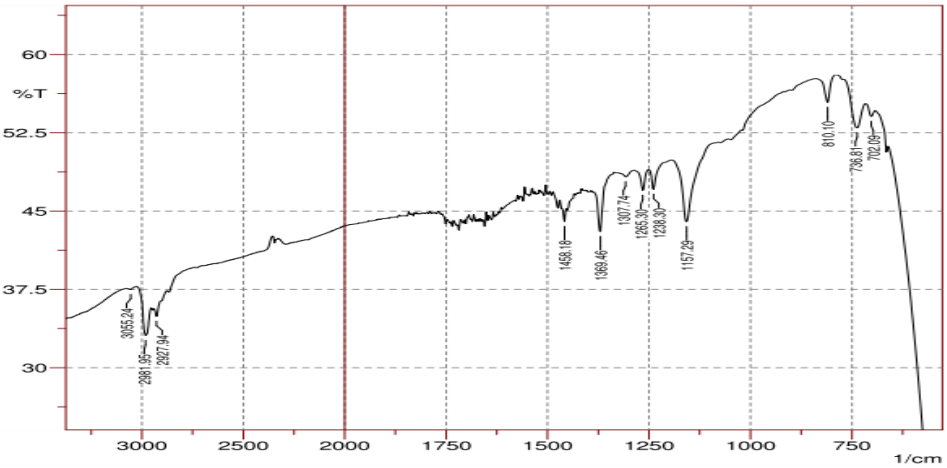


Figure SM 2.1.1.2. Infrared spectra obtained by Pharmaceutical Sciences students, Lisbon University, Portugal with a laser IRAffinity-1 Shimadzu apparatus: (A) *tert*-butanol (C-OH ≈ 3361.93 cm^{-1}) (B) *tert*-butylcloride.

References:

[1] K.P.C., Vollhardt, N.E. Schore, *Organic Chemistry: Structure and Function*, Freeman and Company, New York. 6th Ed, 2010
[2] J. Clayden, N. Greeves, S. Warren,*Organic Chemistry*, Oxford University Press Inc., New York, 2nd Ed., 2012.
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[3] Examples of IR spectra websites (accessed at 27 March 2017): a) chemicalbook.com; b) chem.uiuc.edu; c) webbook.nist.gov

Counterion Effects in the Nucleophilic Substitution Reaction of the Acetate Ion with Alkyl Bromides in the Synthesis of Esters: STUDENT MANUAL

Adapted from *Journal of Chemical Education,* 2009, **86** (11), 1315.

Pre Laboratory assignment:

1. Find the ionic radius for each of these ions:
    a. Br^-
    b. Cs^+
    c. Na^+
    d. K^+
    e. Li^+

2. Define each of the following concepts and show at least one example. You must cite the reference(s) used:
    a. Hard and Soft Acids and Bases principle (HSAB)
    b. Hard acid
    c. Hard base
    d. Soft acid
    e. Soft base
    f. S_N2 reaction and mechanism
    g. S_N1 reaction and mechanism
    h. Polarizability

3. Review the following laboratory techniques:
    a. Extraction
    b. Thin layer chromatography (TLC)
    c. Gas chromatography (GC)

4. Read the Chapter on acids and bases in Daley's book. It may be downloaded free of charge from the website: http://www.ochem4free.info. You must have the Adobe Reader installed on your computer to download it. Other sources of information regarding the HSAB theory are welcomed.

5. Find the boiling points for all the alkyl bromides used on this experiment, as well as the boiling points of the following esters
    a. benzyl acetate
    b. isoamyl acetate
    c. *n*-octyl acetate

Introduction

Have you ever wondered why food seems flavorless when you have a cold? Although we are able to detect only five flavors (sweet, sour, bitter, salty, and umami), there is a wide array of tastes associated with foods. All foods contain volatile compounds, which enter the nose to generate a unique flavor (Taste plus aroma) pattern for each food.[1] The human nose can detect the smallest of molecular changes, even stereochemical differences of molecules. Figure SM 2.1.4.1 2.1.4.1 shows a schematic representation of how flavor, released from food, is perceived by our mouth and nose. When food enters the mouth, the non-volatile compounds in the liquid phase (saliva), are exposed to the tongue (step 2) and sensed by the taste buds (step 3). Simultaneously, all volatile compounds enter the air phase (step 4), and transferred to the olfactory receptors by the tidal air, for the perception of the characteristic aroma.

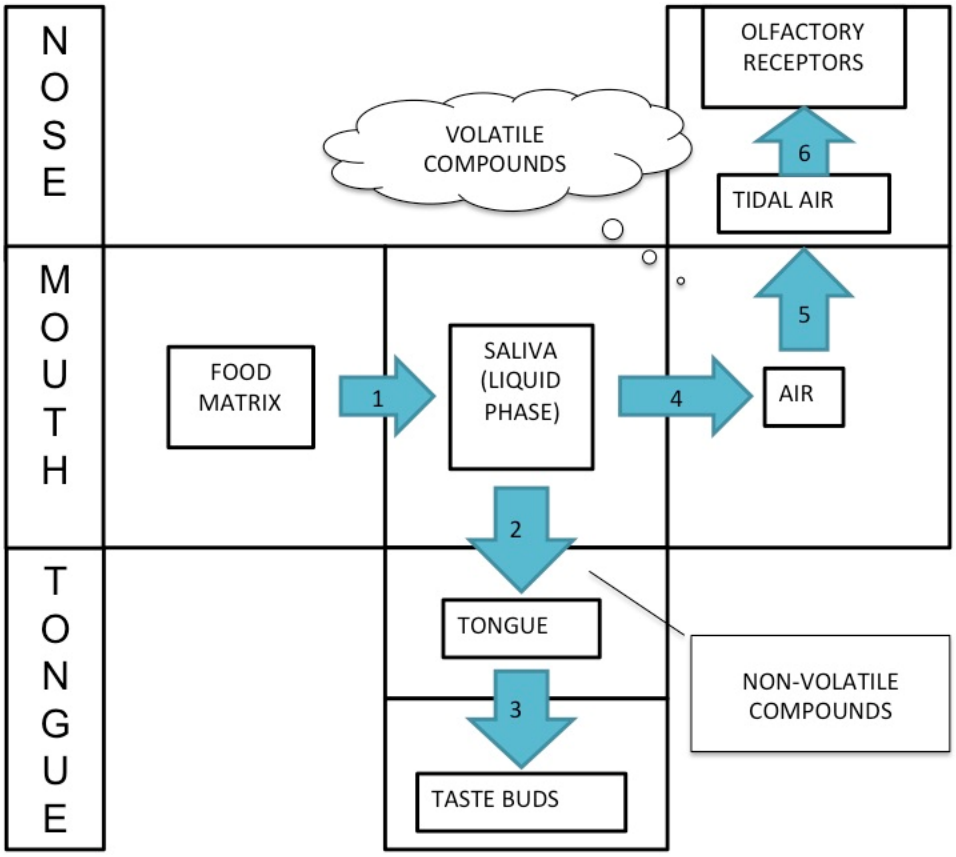
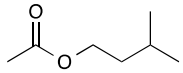
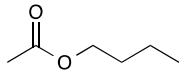
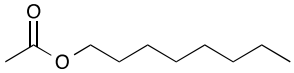
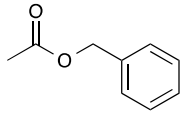
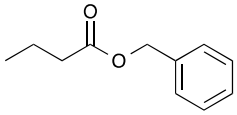
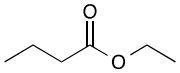


Figure SM 2.1.4.1: Flavor perception by the nose and mouth
Taylor, A. J., *Compr. Rev. Food Sci. F.,* 2002, **1,** 45.

Volatile esters, both naturally occurring or artificially synthesized, are used as food flavorings. Some examples of such volatile esters are shown in Table SM 2.1.4.1.

Table SM 2.1.4.1: Names, structures, and fruit and flower aromas of some common natural esters[a]

Ester name	Structure	Aroma
Isoamyl acetate		Bananas
n-butyl acetate		Pears
n-octyl acetate		Oranges
benzyl acetate		Peaches
benzyl butyrate		Flowers[b]
ethyl butyrate		Pineapples

[a]Eskew, R.J., *J. Chem. Educ.,* 1951*,* **18**, 326.
[b]Jasmine with a fruity character reminiscent of rose and apricot.

A variety of synthetic methods are available to prepare esters; this experiment focuses on nucleophilic substitution reactions, either S_N1 or S_N2. The carboxylate anion acts as the nucleophile, while the alkyl halide serves as substrate. Such nucleophilic substitution reactions may also be considered as acid-base reactions, in which the base (the nucleophile) reacts with the acid (the electrophile) to form the product. Pearson's principle of Hard and Soft Acids and Bases (HSAB) is quite helpful to predict the outcome of acid-base reactions as described above.

The HSAB principle classifies acids and bases as hard or soft according to their polarizability. A cation with a high positive, non-polarizable charge is considered a hard acid: whereas one with a polarizable charge is a soft acid. Bases are defined

accordingly. Table SM 2.4.1.2 provides some examples of hard, soft, and borderline acids and bases. Soft bases are generally good nucleophiles, while hard ones are usually strong bases. The HSAB principle states that *a hard acid reacts preferably with a hard base, whereas a soft acid favors a soft base.* Consequently, we may predict the reactivity of acid-base encounters in terms of the hard-hard, soft-soft and hard-soft combinations. The same concept can be applied to nucleophile-electrophile interactions in nucleophilic substitutions, by considering the degree of softness or hardness of the nucleophile and its counterion, as well as of the electrophile, i.e., the substrate and its leaving group.

Table SM 2.4.1.2: Examples of hard, soft, and borderline acids and bases classified according to Pearson's HSAB principle[a]

Acids	***Type***	***Bases***
H^+, Li^+, H_3C^+, Na^+, K^+, Mg^{2+}, Al^{3+}, BR_3, R_3C^+, Fe^{2+}	***Hard***	H_2O, HO^-, F^-, Cl^-, RCO_2^-, CO_3^{2-}
	Borderline*	R^-, $C_6H_5NH_2$
Cs^+, Cu^+, Ag^+, Br_2, BH_3	***Soft***	Br^-, I^-, H^-, RS^-, NC^-
****Species which cannot be definitively placed in one category***		

[a]Daley, R.F.; Daley, S.J.; *Organic Chemistry*, pp. 209–242, http://www.ochem4free.info. Accessed November 2014

Figure SM 2.4.1.2 shows the computed MMFF structures of the metal acetates in the gas phase, which exhibit the degree of association between the acetate ions and the metal. According to the HSAB principle, the carboxylate anion is a hard base, so it prefers to be associated with hard acids: the harder the acid, the stronger the association. As an exercise, arrange the counterions shown in the figure SM 2.4.1.2 in decreasing order of hardness and predict how strong or weak the interaction with the acetate ion is.

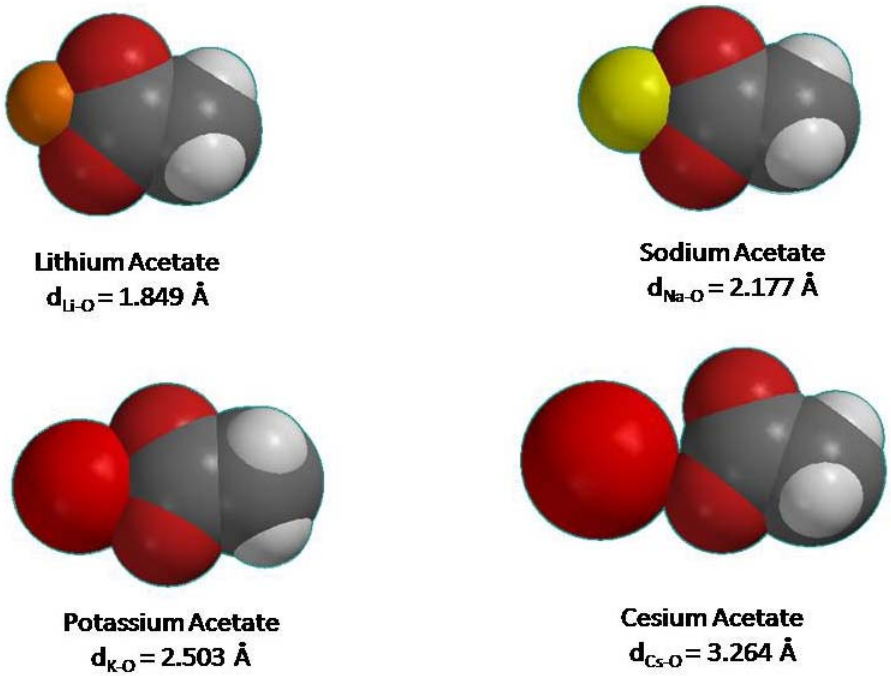


Figure SM 2.4.1.2: Merck Molecular Mechanics Force Field (MMFF) of the metal acetates. (Calculated using Spartan '06)

In this experiment (Figure SM 2.4.1.3) you will synthesize one of three ester flavorings, namely isoamyl acetate (bananas), *n*-octyl acetate (oranges) or benzyl acetate (peaches) by carrying out the nucleophilic substitution of alkyl bromides by the respective metal acetates, for which different metal counterions will be: lithium, sodium, cesium or potassium. From the composite results of the class, you will learn about the effect of the metal counterion and the alkyl bromide structure in nucleophilic substitution reactions and rationalize the results in terms of HSAB principle.

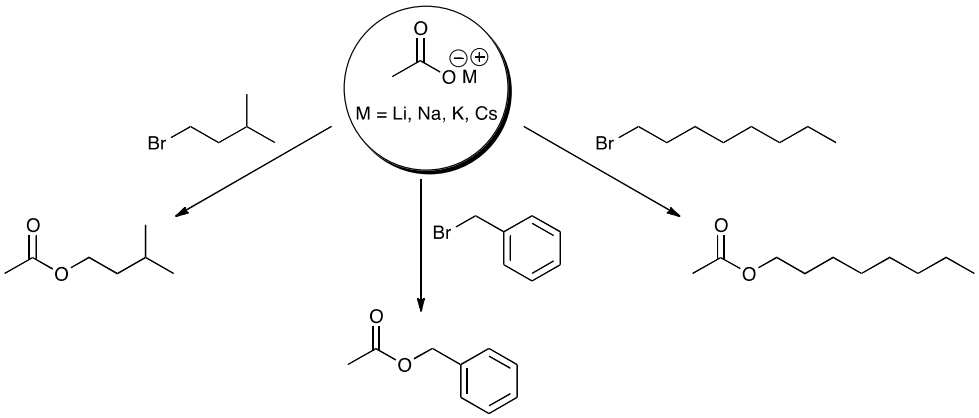


Figure SM 2.4.1.3: Esters to be synthesized by the nucleophilic substitution reaction of alkyl bromides with metal acetates

Safety

<u>Always consult the MSDS before performing any experiment</u>. The alkyl bromides used herein are irritant and flammable liquids, and should be handled with care. Benzyl bromide and acetic acid are corrosive, combustible, and lachrymatory substances, which should be used in a well-ventilated hood. The solid acetates are hygroscopic and may cause irritation if absorbed through the skin or inhaled. Hexane, ethyl acetate, and especially ether, are flammable liquids, which are very harmful if inhaled or absorbed through the skin. Iodine is eye and skin irritant and harmful if inhaled or swallowed, and should be handled with care. Use protective equipment at all times!

Objectives

Upon completion of this experiment, the student is expected to have learned how to:

- Synthesize esters by the nucleophilic substitution reaction.
- Rationalize S_N2 / S_N1 mechanisms in terms of the HSAB principle.
- Apply previously learned separation techniques such as chromatography and extraction.

- analyze and interpret gas chromatographic and mass spectrometric data.

Materials

Capillary tubes
Chromatographic paper
Clamps
Filter paper
Heating mantle
Magnetic stirrer
Pipettes
Reflux condenser
50 mL round bottom flask
Separatory funnel
TLC plates – alumina coated

Reagents

Acetic acid, glacial
Benzyl bromide
Cesium acetate
Ethyl acetate
Ethyl ether
Hexane
Isoamyl bromide
iondine
Lithium acetate
Magnesium sulfate
n-octyl bromide
Potassium acetate
Sodium acetate
Sodium bicarbonate
Sodium chloride

Experimental Procedure

This experiment will be performed individually or in pairs. The instructor will assign a specific metal acetate and an alkyl bromide substrate according to those shown in Figure SM 2.1.4.3. ***Consult the MSDS before carrying out the experiment.***

Add 18 mmol of the assigned metal acetate to a 50 mL round-bottom flask supplied with a magnetic stirring bar, along with 8 mL of acetic acid (*metal acetates are hygroscopic,*

so work quickly, taking care of not to leave any reagents uncovered; also, acetic acid is a lachrymator substance, use it in a well-ventilated hood). Wait for partial dissolution of the acetate (*some acetates take longer to dissolve, but will dissolve completely upon heating the reaction with the reflux; note how fast or how slow your acetate dissolves*) then add 12 mmol of the alkyl bromide (*alkyl bromides are irritating substances, some are lachrymators, do not inhale the vapors)*. Quickly connect the reflux condenser (Figure SM 2.1.4.4), and gently heat under a gentle reflux for 60–90 min. Observe the reaction progress and note any changes. Is there a precipitate formed? What is it? How long did it take to form?

After the allotted reflux time, let the reaction mixture cool to room temperature, then add 20 mL of a saturated aqueous solution of sodium bicarbonate to neutralize the acetic acid. (How can you tell if you added enough?) At this point you should be able to detect the aroma of the ester product by gently ventilating the vapors of the reaction mixture towards you with your hand. ***Do not place your nose directly above the reaction flask.*** The reaction mixture is extracted with diethyl ether (2 x 10 mL) as solvent. Dry the combined organic extracts over $MgSO_4$, remove the drying agent by filtration and evaporate the solvent by mildly heating with a warm water bath (approximately 45 ºC). Be aware that your ester product is also volatile. Weigh your product and run a TLC on alumina plates with a 9:1 hexane: ethyl acetate solvent mixture as eluent. Since both the product and the starting material are colorless, they may be visualized in an iodine chamber (or UV lamp in the case of benzyl acetate). Was the reaction finished? How can you tell? Calculate the yield of the crude product, and subsequently the actual product yield by using the purity determined in GC chromatogram (see below)

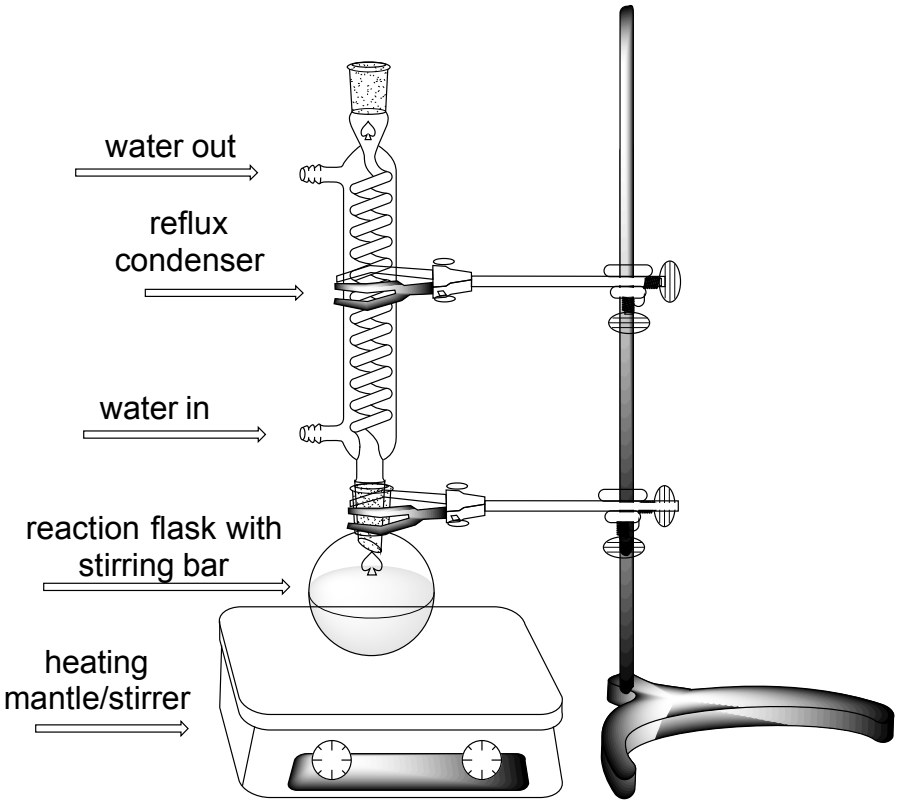


Figure SM 2.1.4.4: Apparatus for running the reaction under reflux

Example: to determine percent yield by GC analysis

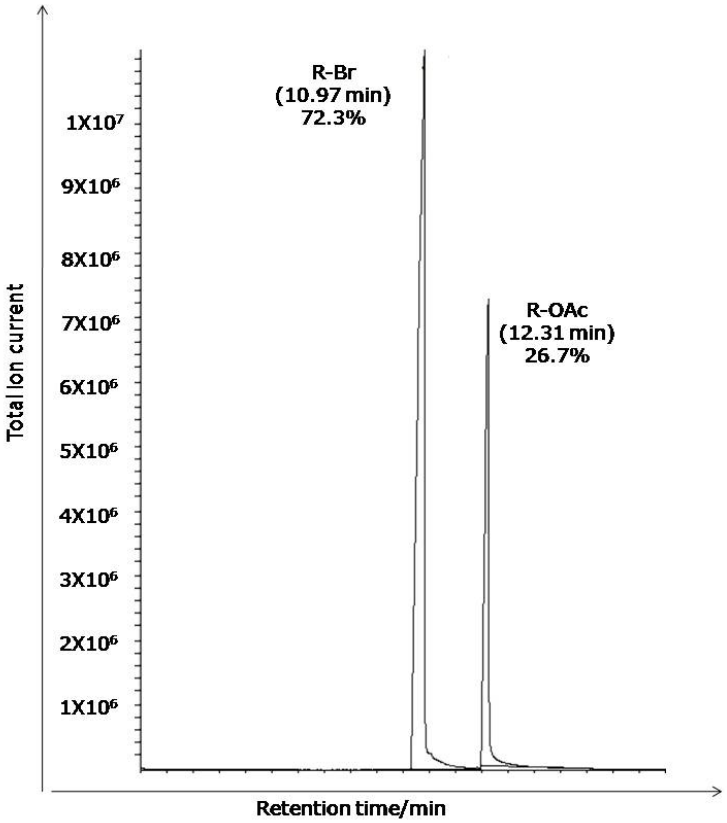
There are different methods to determine the yield by GC analysis. The one provided is simple, but the students should feel free to use any other method.

i. *Determine the yield of crude product*.

Example: You obtained 1.866 g of *n*-octyl acetate in the reaction of sodium acetate with octyl bromide for which the theoretical yield is 2.116 g.

Crude product yield = (1.866/2.116) x 100 = **88.2 %**

ii. *Obtain a gas chromatogram of your sample.*



iii. Multiply your crude product yield by the area percent indicated underneath your chromatogram. Identify correctly which peak is your ester product and which is your starting material.

In this example, the first peak corresponds to *n*-octyl bromide, whilst the second belongs to *n*-octyl acetate.

Peak #	***RT(min)***	***Rel. Area[(a)]***
***n*-octyl bromide**	10.97	0.723
***n*-octyl acetate**	12.31	0.267

(a) relative area obtained from the chromatogram

GC yield = [crude product yield (%) x rel. area]

= 88.2 % x 0.267 = 23.5%

Discussion questions

1. Complete the following table for each of the esters synthesized in class.

Reaction equation				
Alkyl halide used				
Acetate counterion	Cesium	Sodium	Potassium	Lithium
Was precipitate present?				
GC yield (%)				

2. For each reaction, identify the nucleophile, the counterion, the substrate, and the leaving group. Classify each as a hard or soft acid or base. Feel free to consult literature for your conclusions.
3. Is there a relationship between the ionic radius and the hardness of an ion? Briefly explain.
4. According to your experimental results:
    a. How do your TLC results match with those of the gas chromatography?
    b. Which metal counterion promotes the most efficient reaction?
    c. Which metal counterion promotes the least efficient reaction?
5. Is there a relationship between the formation of precipitate and reaction efficiency?
6. Explain the effect of the metal counterion in an S_N reaction in terms of the HSAB principle.
7. Discuss what mechanism is preferred for each of the alkyl bromides used; justify your answer.

Counterion Effects in the Nucleophilic Substitution Reaction of the Acetate Ion with Alkyl Bromides in the Synthesis of Esters: NOTES TO INSTRUCTORS

- ✓ This experiment is scheduled as the last experiment in the first semester of the Organic Chemistry laboratory. It reinforces separation techniques learned by the student, such as extraction and chromatography.
- ✓ This experiment is most likely the student's first exposure to the HSAB principle, as it is not usually covered in the most commonly used organic chemistry textbooks. Therefore, a detailed pre-laboratory assignment is provided, so that the student is better prepared for an in-depth discussion.
- ✓ Although this experiment may be performed in one four-hour laboratory period, it is recommended to use two periods. During the first period the students learn the theoretical aspects of the experiment, as well as conduct the experiment. In the second period, the student will run the GC analysis, determine the yield of their experiment and discuss the results with the rest of the class.
- ✓ When assembling the equipment, care must be taken to add all the reagents while in a well-ventilated hood. Acetate salts must be added immediately after weighing due to their hygroscopic nature. The alkyl bromide should be the last reagent to be added. The student does not need to wait until the metal salt ions dissolved to start heating the reaction; the metal salt will dissolve on heating. The exception is cesium acetate, which dissolves fast on its own. The reason for this solubility behavior is the degree of association (see Figure SM 2.1.4.3 in the student manual) between the acetate and the metal ions: the weaker the association, the faster the salt dissolves.
- ✓ See the MSDS for the hazards associated with the used reagents. Care must be taken to provide just enough heat for a gentle reflux; DO NOT OVERHEAT.

- ✓ The students have to wait 60–90 min for the reaction to be completed, which allows time to elaborate on the HSAB principle to clarify any doubts they may still have about this concept.
- ✓ For convenience and necessity, the HSAB principle was briefly presented in this manual, but the student should consult more elaborate treatments to become familiar with this important concept in chemistry.

The Hard and Soft Acid Base Principle (HSAB)

Pearson introduced the HSAB principle in 1963, in which he empirically classified *acids* and *bases* as *hard* (non-polarizable) or *soft* (polarizable) according to their mutual reactivity. A *hard acid* is defined as a small acceptor entity with a high positive charge and preferably no unshared electrons pairs in its valence shell and has, therefore, a low polarizability and high electronegativity. A *soft acid*, in contrast, is a large acceptor entity with a low positive charge that bears unshared electrons pairs and has, thus, a high polarizability and low electronegativity. Analogously, a *hard base* is a small donor species with a high negative charge, and not easily polarized, whereas a *soft base* is a large, negatively charged, highly polarizable molecule. Some species cannot be definitively placed into one of these two categories and are considered borderline. Examples of hard, soft, and borderline cases are shown in Table SM 2.1.4.2 (see student's manual above.) The HSAB principle states that *hard acids* prefer to combine with *hard bases*, whereas *soft acids* favor *soft bases*. This principle applies generally to acid-base reactions in chemistry, but also to the encounter of electrophiles with nucleophiles, the case of particular interest in organic chemistry. In summary, the HSAB principle allows to predict intuitively the efficacy of a specific reaction in terms of the *hardness* or *softness* of the reactants. In the present experiment we apply it for the first time in an introductory organic chemistry course.

- ✓ Students should note when a precipitate starts to form in the reaction. Cesium bromide will start to precipitate within 5–10 min from the beginning of reflux, potassium bromide will precipitate within 15–20 minutes, sodium bromide will take longer, and lithium bromide will not precipitate at all. This is because of the hard nature of the lithium and sodium ions, which do not associate well with the bromide ion, a borderline soft base. The cesium ion is a soft acid and, therefore, it associates well with the bromide ion and quickly forms the salt.
- ✓ About 20 mL of $NaHCO_3$ are needed to neutralize the acetic acid. The pH of the workup may be monitored by litmus paper.
- ✓ In most cases, the only substitution reaction to be completed are those with cesium acetate, therefore, all other crude products should show starting material in the TLC.
- ✓ The instructor has the option of instructing the students in the use of the GC/MS method to interpret more quantitatively the results.
- ✓ Molecular modeling may be effectively introduced to explain the association of the acetate ion with the different metal ions; suggested programs are Spartan, CAChe, and Chem3D.

Answers to the pre-laboratory assignment

1. Ionic radii

    a. Br^- = 1.96 Å

    b. Cs^+ = 1.65 Å

    c. Na^+ = 0.98 Å

    d. K^+ = 1.33 Å

    e. Li^+ = 0.75 Å

2. Concept definitions:

    a. *HSAB* is the theory developed by Ralph Pearson that classifies acids and bases according to their polarizability. Hard acids prefer to react with hard bases and soft acids with soft bases; unfavorable associations are soft /hard and hard/soft encounters.

    b. *Hard acids* are electron acceptors have a high positive charge in view of their electronegativity, are devoid of unpaired electrons in their valence shell, and possess a low polarizability; typical elements are located in the upper left corner of the periodic table.

    c. *Soft acids* are also electron acceptors with a lower positive charge density, less electronegative and higher polarizability; typical elements are found in the lower left corner of the periodic table.

    d. *Hard bases* are electron pair donors that are negatively charged or possess a poorly polarizable lone pair.

    e. *Soft bases* are excellent electron pair donors with a high negative charge low electronegativity and easily polarized.

    f. S_N2 reaction is a **N**ucleophilic **b**imolecular **s**ubstitution.

    g. S_N1 reaction is a **N**ucleophilic **u**nimolecular **s**ubstitution

h. *Polarizability* is the relative tendency of a charge distribution, like the electron cloud of an atom or molecule, to be distorted from its normal shape by an external electric field, which may be caused by the presence of a nearby ion or dipole.

3. http://www.ochem4free.info. You must have the Adobe Acrobat Reader installed in your computer to download the chapters. This book may be used on any subject of organic chemistry. The webpage includes a section where it converts the information found in other commonly used books.
4. Boiling points of products:
    a. Benzyl acetate = 206 ºC
    b. Isoamyl acetate = 142 ºC
    c. *n*-octyl acetate = 205 ºC
5. Data for the reagents used in the experiment:

Table SM 2.1.4.3: Stoichiometric amounts, densities, and volumes of the reagents used in the experiment

Reagent	Amount (mmol)	Weight (g)	Density (g/mL)	Volume (mL)
Isoamyl bromide	12	1.89	1.208	1.6
n-Octyl bromide	12	2.31	1.11	2.1
Benzyl bromide	12	2.05	1.44	1.5
Lithium acetate	18	1.19	---	---
Sodium acetate	18	1.48	---	---
Potassium acetate	18	1.77	---	---
Cesium acetate	18	3.46	---	**---**

Answers to the discussion questions:

1. Complete the following table for each of the esters synthesized in class. Approximately 100 students performed this experiment yearly and has been part of the curriculum for the last eight years. The following are students' representative results of their results (±15% except for Lithium ± 5%)

Ester product	*Isoamyl acetate (banana flavor)*			
Substrate	Isoamyl bromide (1-bromo-3-methylbutane)			
Metal Counterion	Cesium	Potassium	Sodium	Lithium
Precipitation	Yes	Yes	No	No
GC yield (%)	76	58	21	8

Ester product	*n-octyl acetate (orange flavor)*			
Substrate	*n*-octyl bromide			
Metal Counterion	Cesium	Potassium	Sodium	Lithium
Precipitation	Yes	Yes	No	No
GC yield (%)	78	40	22	13

Ester product	*Formation of benzyl acetate (peach flavor)*			
Substrate	benzyl bromide			
Metal Counterion	Cesium	Potassium	Sodium	Lithium
Precipitation	Yes	Yes	Yes	No
GC yield (%)	75	76	84	>95

2. For each reaction, identify the nucleophile, the metal counterion, the substrate (electrophile), and the leaving group. Classify each as a hard or soft acid or base. Feel free to consult literature for your conclusions.

Nucleophile – acetate (hard base) Acetate counterions – Lithium (hard acid)

Sodium (hard acid)

Potassium (hard acid)

Cesium (soft acid)

Substrate-substitution side (hard acid)

Leaving group – bromide ion (borderline base)

3. Does the hardness of metal counterion depends on the ionic radius? Briefly explain.

As the ionic radius increases with atomic number (*Z*), the ion posses more electrons, becomes more polarizable and, thus, its softness augments.

4. According to the experimental results:
    a. How do your observations on the TLC results match those of the gas chromatography?

The TLC shows the presence of starting material (incomplete substitution) except for cesium acetate, for which the reaction has been completed during the assigned time. The GC chromatographs for isoamyl and n-octyl acetates match the TLC results, but for benzyl acetate only a small amount of starting material is detected.

b. Which metal counterion reacts most?

The cesium ion reacts most, because it is less associated with the nucleophile (acetate).

b. Which metal counterion reacts least?

Lithium ion reacts least, because it more strongly associated with the nucleophile.

5. Is there any dependence between precipitate formation and reaction yield?

Yes! More precipitate is formed in the more efficient reaction. This can be explained by Le Chatelier's principle.

6. Explain the effect of the metal counterion in an S_N2 reaction in terms of the HSAB principle.

The HSAB principle states that hard acids react with hard bases and soft acids react with soft bases. If the nucleophile (acetate ion) is a hard base, the association with a soft counterion is weaker, which favors reaction.

7. Discuss what mechanism is preferred in each of the alkyl bromides used; justify your answer.

The data displayed above and in Table SM 2.1.4.4 exhibit some definitive trends that reflect the strong interplay between the *bromide-ion leaving group* in the substrate and the *acetate-ion nucleophile* in the metal salt as a function of the *metal ion*, namely Cs^+, K^+, Na^+, and Li^+. For example, the ester yields of the substrates isoamyl and *n*-octyl bromides follow the regular order $Cs^+ > K^+ > Na^+ > Li^+$, with cesium acetate (CsOAc) the highest and lithium acetate (LiOAc) the lowest. These two alkyl bromides are typical S_N2 substrates, excellent prototypes to illustrate the efficacy of Pearson's HSAB principle. The bromo substituent at the reaction center is a weak electron-attracting group, which imparts a low electrophilic character to the Br-substituted carbon atom; thus, this carbon center is a relatively *soft* acid (electrophile) in want of a *soft* base (nucleophile) for best interaction. The attacking acetate ion, however, is a relatively *hard* base (nucleophile), whose reactivity is modulated by the accompanying metal counterion, for which the degree of softness follows the order $Cs^+ > K^+ > Na^+ > Li^+$. The acetate nucleophile is a *softer* base – therefore a better nucleophile – when combined with Cs as a counterion than with Li. The cesium acetate salt (the combination of the *soft* Cs^+ metal counterion with the *hard* acetate nucleophile) is more dissociated in solution than lithium acetate salt (the combination of the *hard* Li^+ counterion with the *hard* acetate nucleophile). The

more dissociated the salt, the softer a base the acetate ion will be and more reactive towards the S_N2-type alkyl bromide substrate (softer acid). The expected reactivity would be CsOAc best and LiOAc worst, as revealed by the observed yields in Table SM 2.1.4.4.

For the benzyl bromide substrate, the yields follow the order $Cs^+ < K^+ < Na^+ < Li^+$, namely LiOAc is now the best and CsOAc the worst. Benzyl bromide may behave either as S_N2 or S_N1 substrate, for which the role of the metal counterion is more complex to rationalize definitively. What also should be kept in mind is the fact that the variation in the yields, taken as reactivity criterion, is much less pronounced for the benzyl than for the isoamyl and *n*-octyl bromides (see Table SM 2.1.4.4) and, thus, more difficult to interpret mechanistically. The important point, however, is that for a reaction following the S_N1 mechanism, the role of the metal counterion differs from a reaction subject to the S_N2 mechanism. Consequently, the reactivity pattern changes, because the carbocation (a harder acid) instead of the intact alkyl halide substrate (a softer acid) is attacked by the nucleophile in the S_N1 reaction. For the benzyl bromide substrate, which may readily form a stabilized carbocation in an ionizing medium like acetic acid, the acetate ion is a harder base when combined with Li than with Cs. According to the HSAB principle, the reactivity of the acetate nucleophile towards benzyl bromide will then be given by the greater hardness of the metal counterion, i.e., $Li^+ > Na^+ > K^+ > Cs^+$, as observed in Table SM 2.1.4.4.

Table SM 2.1.4.4: Yield of ester product as a function of metal counterion in the nucleophilic substitution reaction of alkyl bromides with metal acetates

	Yield (%)[a]			
Acetate product	Cesium	Potassium	*Sodium*	Lithium
Isoamyl	76	58	21	8
n-Octyl	78	40	22	13
Benzyl	76	76	84	> 95

[a] The yields were obtained by multiplying the gravimetric yields of the crude product by the relative areas (uncorrected) under the GC peaks; the gravimetric yields were

determined by weighing the isolated, crude product, error limits about 5% of the stated values.

Table SM 2.1.4.5: CAS registry numbers for reagents used

Reagent (Purity)	***CAS No.***	***Safety hazards***
Benzyl bromide Reagent grade, 98%	100-39-0	Flammable, irritant, corrosive, lachrymatory, mutagenic
n-Octyl bromide, 99%	111-83-1	Flammable, Irritant
Isoamyl bromide	107-82-4	Flammable, irritant
Cesium acetate (99.9%)	3396-11-0	Irritant, hygroscopic
Lithium acetate, (99.99%)	546-89-4	Irritant, hygroscopic, may cause dizziness and affects the central nervous system; when inhaled.
Potassium acetate, ACS Reagent (99.0%)	127-08-2	Irritant, hygroscopic
Sodium acetate, ACS Reagent (99.0%)	127-09-3	Irritant, hygroscopic
Acetic acid (glacial)	64-19-7	Flammable, corrosive, lachrymatory; may cause burns, attacks the mucous membranes and respiratory tract.
Diethyl ether	60-29-7	Flammable liquid and vapor, irritant, harmful on ingestion, inhalation, and may cause coma; may cause allergy and is harmful to eyes, skin and the respiratory system.
Ethyl acetate	141-78-6	Flammable liquid and vapor**.** Irritating to skin and eyes. Breathing vapors may

		cause drowsiness and dizziness.
Hexane	110-54-3	Flammable. Irritant. Harmful on ingestion, inhalation and irritating to skin and eyes. Dangerous for the environment.
sodium bicarbonate	144-55-8	High concentrations of dust may cause coughing and sneezing. Ingestion of extremely large oral doses may cause gastrointestinal disturbances.
iodine	7553-56-2	Corrosive, causes eye and skin irritation and burns, and may cause allergic skin reaction

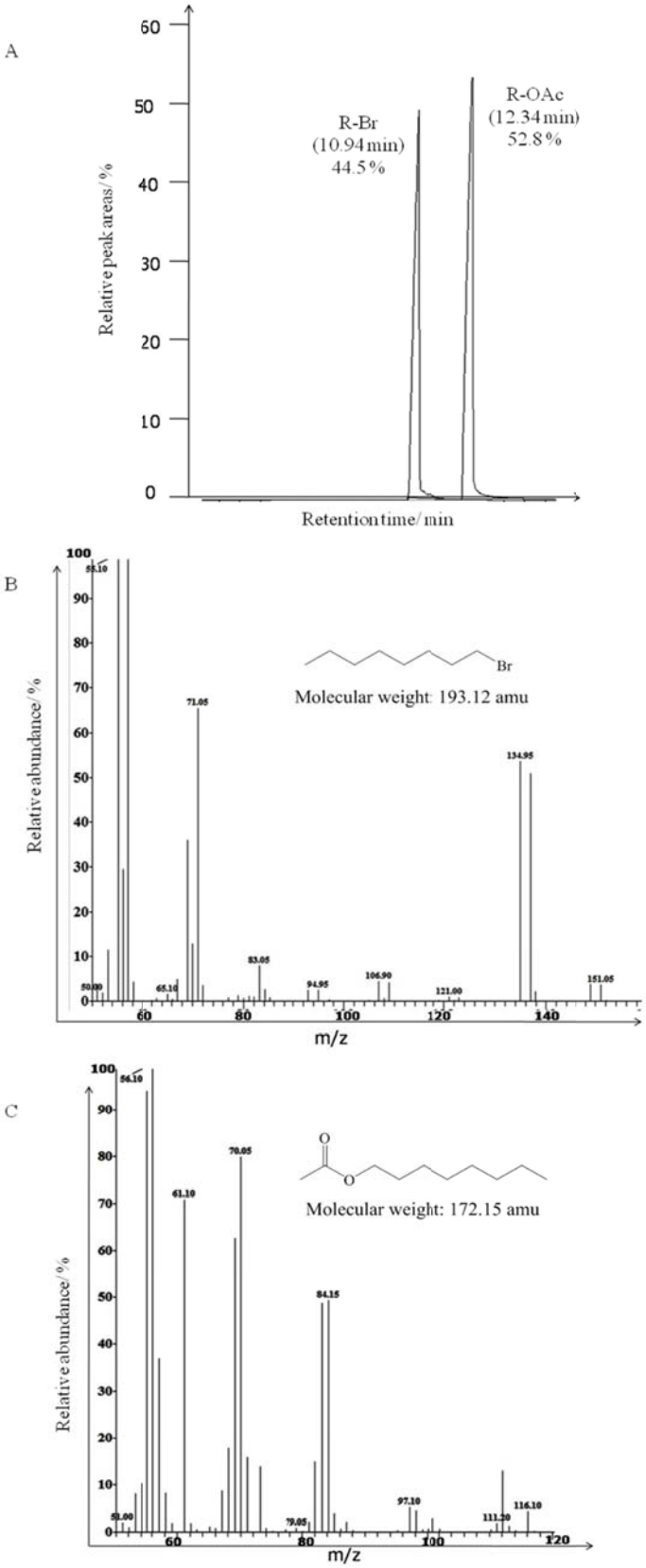


Figure SM 2.1.4.5: The chromatogram of the crude product mixture for the reaction of *n*-octyl bromide with potassium acetate is given in panel **A**, in which the retention times (min) and the uncorrected relative peak areas (%) are listed in parenthesis for the peaks; the relative peak areas (%) were determined for each component from the total ion current of the mass-selective detector. The mass spectra of the two GC components are shown in the panels **B** and **C**, identified respectively as *n*-octyl bromide (10.94 min, 193.12 amu) and *n*-octyl acetate (12.34 min, 172.26 amu)

Mass spectra data were acquired using a GC-MS (Hewlett-Packard 5972 MS Chem-Station; Hewlett-Packard, Palo Alto, CA, USA) at 70 eV equipped with a 30 m x 0.25 mm special performance capillary column (HP-5MS) of polymethylsiloxane cross-linked with 5% phenyl methylpolysiloxane.

- [a] A helium mobile phase flow rate was 2 mL/min, the acquisition method started at 50 °C and finished at 290 °C programmed at a temperature rate of 7 °C /min.

1. Chaudari, N.; Roper, S.D. *J. Cell Biol*. 2010, **190 (3)**, 285.

N-Alkylation of Pyrazole Reaction in Ionic Liquid

- The objective of this experiment is the preparation of 1-butyl-3,5-dimethyl-1*H*-pyrazole from 1*H*-pyrazole and 1-bromobutane, using an ionic liquid (IL).
- The items necessary to accomplish this reaction are shown in **Figure SM 2.1.5.1**.
- The time required for the class session was determined to be 4 h, which includes some time for discussion.
- At the beginning of the reaction, the color of the reaction mixture is totally white (**Figure SM 2.1.5.2a**). It is possible to follow the reaction by direct visual observation, in which the appearance of an orange color indicates that the product is being formed (**Figure SM 2.1.5.2b**). Vigorous stirring must be maintained throughout the process, because this enables better interaction between the reactants.
- The product isolation process also needs vigorous stirring to enable solubilization of the product formed in the diethyl ether. The [BMIM][BF_4] (**Scheme SM 2.1.5.1**) used as the reaction solvent eliminates the need for organic solvent, because it acts more effectively in the active complex and increases the reaction rate.

- After the isolation step, the solvent is evaporated and an orange oil is formed in the flask (**Figure SM 2.1.5.3**).
- This experiment was based on a paper developed by Frizzo et al.[1] In this work the authors obtained a 62 % yield in a reaction time of 4 h. The synthesis using acetonitrile instead of IL was also accomplished; however, the use of the IL showed an improvement in both the reaction time (from 16 h in CH_3CN) and yield (50 % yield in CH_3CN). It is important to mention that in the absence of an inorganic base, the product yield also decreases (33 % yield at 16 h of reaction time).[1]
- When the experiment was conducted by an undergraduate student, the product was obtained at a 72 % yield in 2 h of reaction time, showing that the reaction can be accomplished in a shorter reaction time (**Table SM 2.1.5.1**). A pre-requisite for the students is to have done a basic organic chemistry course.
- The physical properties of the compounds used in this experiment are presented in **Table SM 2.1.5.2**.
- This experiment will allow the student to understand the nucleophilic substitution mechanism (S_N2) via nitrogen attack of the pyrazole molecule (**Scheme SM 2.1.5.2**). Initially, the KOH removes the hydrogen bonded to the *N* of the *NH*-pyrazole, resulting in the negatively charged pyrazole ring being used as a nucleophile for the S_N2 reaction. The electron pair from the *n*-orbital of the nucleophile (HOMO) attack the σ^*-orbital of the C-Br bond (LUMO). The reaction is considered to be second order, because both the nucleophile and electrophile participate in the transition state. As the pyrazole ring is added, bromide will be eliminated (**Scheme SM 2.1.5.2**). The IL should act to stabilize the partial charges formed during the transition state. Therefore, when the transition state energy decreases, it leads to lower activation free energy ($\Delta G^{\circ\ddagger}$) and, as a consequence, an increase in the reaction rate occurs. This IL behavior can be more effective than the stabilization provided by conventional

organic molecular solvents. On the other hand, when the reaction is performed in the absence of a base, the reaction yield decreases considerably, due to the *NH* of the *NH*-pyrazole being a weaker nucleophile than the negatively-charged *N*.

- The ^{1}H NMR technique can be used to follow the reaction's conversion of reactants to the final product. The signals of the CH_2 (H8; δ = 3.94) of a side alkyl chain directly bonded to the N of the N-butyl pyrazole (product) and the CH_2 (H1; δ = 3.42) directly bonded to the Br of the 1-bromobutane (reactant) can be used for this purpose. A conversion of around 64 % is observed in 15 min of reaction time. When submitted to 1 h of reaction, the conversion increases to approximately 92 %. This technique can also be used to characterize the product at the end of the reaction. **Figures SM 2.1.5.4** and **SM 2.1.5.5** demonstrate the ^{1}H and ^{13}C-NMR spectra of the product, respectively. In the ^{1}H-NMR spectrum, it is possible to observe the signal multiplicities of the butyl chain connected to the pyrazole ring. The signal expansion of H6 and H7 reveals two signals related to two methyl groups connected to the pyrazole ring of the product. This indicates that the methyl groups have different coupling constants with the H4. The same behavior is noted in the signal expansion of H6 and H7 (methyl groups) of *NH*-pyrazole (reactant) — see **Figure SM 2.1.5.6**. Furthermore, the ^{1}H-NMR spectra of the product can be compared with **Figures SM 2.1.5.6** and **SM 2.1.5.7**, which demonstrate the ^{1}H-NMR of the reactants *NH*-pyrazole and 1-bromobutane, respectively.
- The thermal analysis, presented in **Figure SM 2.1.5.8**, provides the decomposition temperature (T_d) (around 102.28 °C) of the final product. The T_d value indicates that the reaction temperature (80 °C) should be controlled to avoid product decomposition occurring during the reaction time. This information allowed us to conclude that the low yield observed in this reaction may be due to the low temperature at which this product starts its

decomposition process (~ 35 °C). Another reason for the decrease in the reaction yield may be the inefficient extraction, which must be done in accordance with the experimental data (extraction with diethyl ether 5 or 6 times).

Table SM 2.1.5.1. Experiments conducted in a round-bottom flask coupled to a condenser, using 3,5-dimethyl-1H-pyrazole and butylbromide as starting materials, KOH (2.4 mmol) as the base, and IL (2.0 mmol) as the reaction medium.

	Entry	Base	Solvent	Temperature (°C)	Reaction time (h)	Isolated yield (%)[a]
Frizzo et al.[1]	1	KOH	[BMIM][BF_4]	80	4	62
	2	-	[BMIM][BF_4]	80	4	33
	3	KOH	Acetonitrile	80	16	50
Undergraduate student	4	KOH	[BMIM][BF_4]	80	2	72

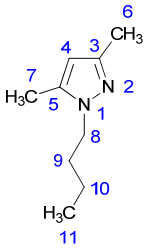
[a] The compound was extracted by washing the reaction mixture with diethyl ether (more than 5 times).

Table SM 2.1.5.2. Physical properties of chemical compounds used in the experiment.

Compound	Chemical formula	Molecular mass ($g \cdot mol^{-1}$)	Density ($g \cdot cm^{-3}$)[a]	Melting point (°C)	Boiling point (°C)	Refractive index
1	$C_5H_8N_2$	96.13	-	105–108	218	-
2	C_4H_9Br	137.02	1.276	-112	100–104	1.439
[BMIM][BF_4]	$C_8H_{15}BF_4N_2$	226.02	1.21	-	-	1.520
Potassium hydroxide	KOH	56.11	-	361	-	-
Sodium sulfate	Na_2SO_4	142.04	2.68	884	-	-
Diethyl ether	$C_4H_{10}O$	74.12	0.706	− 116	35	1.353
3	$C_6H_{16}N_2$	152.24	-	-	93-96[c]	1.462

[a] At 25 °C
[b] Decomposition temperature (T_d): 102°C - see **Figure SM 2.1.5.8.**
[c] At 11 torr.

Characterization Data

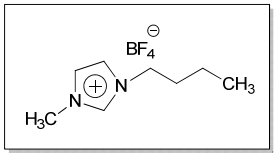


1-butyl-3,5-dimethyl-1*H*-pyrazole. Aspect: orange oil. ^{1}H NMR ($CDCl_3$, 600MHz): δ, 0.93 (t, 3H, ^{3}J = 7.36 Hz, H11), 1.33 (sex, 2H, ^{3}J = 7.33 Hz, H10), 1.76 (qui, 2H, H9), 2.21 (s, 6H, H6,H7), 3.93 (t, 2H, ^{3}J = 7.38 Hz, H8), 5.76 (s, 1H, H4). ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ, 11.0 (C7), 13.4 (C6), 13.7 (C11), 19.9 (C10), 32.5 (C9), 48.4 (C8), 104.6 (C4), 138.4 (C3), 147.1 (C5). m/z (%)= 152 [M^+] (27), 109 [M-MeCN]$^+$ (100), 91 [M-Bu]$^+$ (77), 68 [M-Bu-2Me]$^+$ (36).

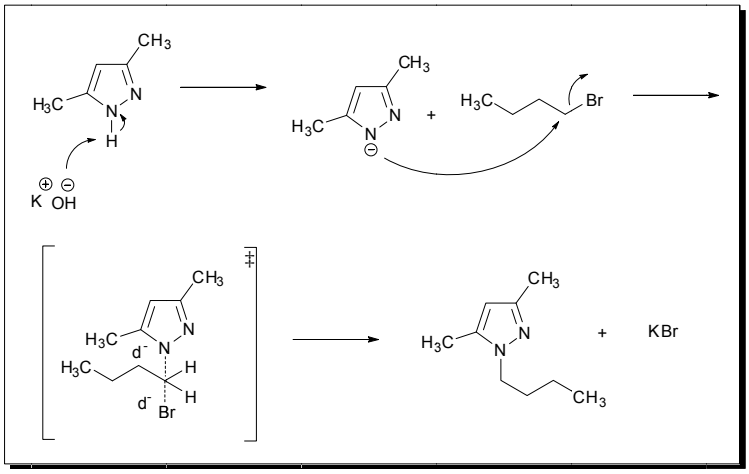
How to prepare an NMR sample for analysis

1. Place 0.020 g (20 mg) of the obtained product (M3) into an NMR tube.
2. Add 600 µL of $CDCl_3$ (containing TMS as an internal reference) to the NMR tube.
3. Acquire the ^{1}H NMR and ^{13}C NMR spectra.

Schemes



Scheme SM 2.1.5.1. Molecular structure of 1-Butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]).



Scheme SM 2.1.5.2. reaction mechanism for the nucleophilic substitution reaction for obtaining 1-butyl-3,5-dimethyl-1*H*-pyrazole

Figures

Photos of the experiment

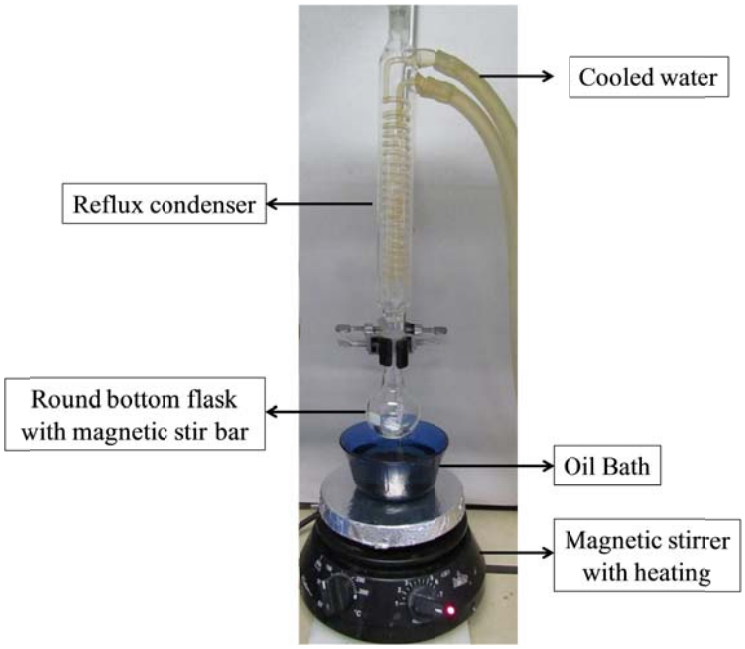


Figure SM 2.1.5.1. Reflux system for the reaction.

(a) (b)

Figure SM 2.1.5.2. Comparison between aspects of: a) the reactants; and (b) the final product.

(a) (b) (c)

Figure SM 2.1.5.3. Images of: (a) the reaction mixture during the extraction step; (b) the isolated product in diethyl ether; and (c) the pure product after concentration of the solvent under reduced pressure.

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

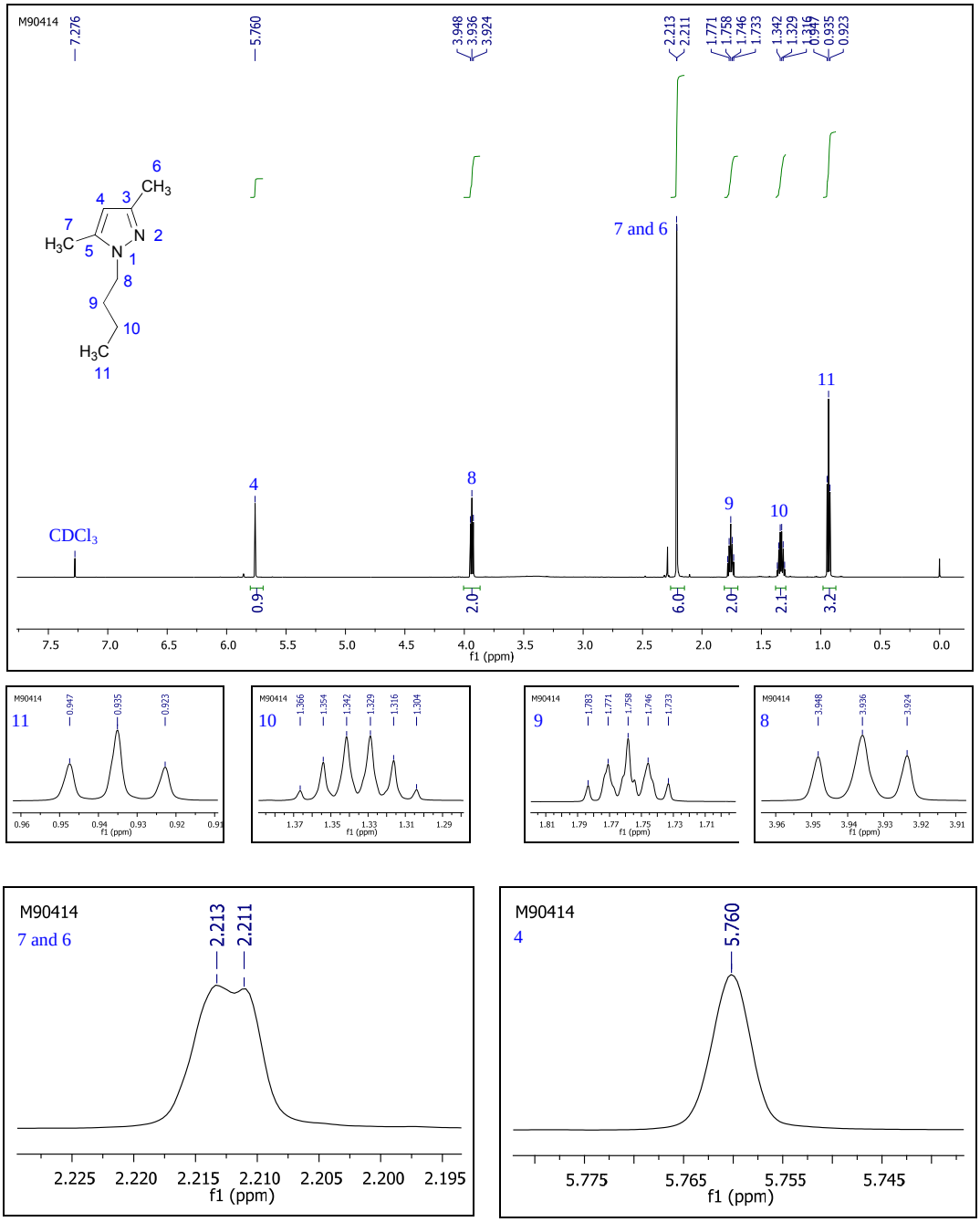


Figure SM 2.1.5.4. ^{1}H NMR spectrum (600 MHz, $CDCl_3$, 25 °C) of 1-butyl-3,5-dimethyl-1*H*-pyrazole.

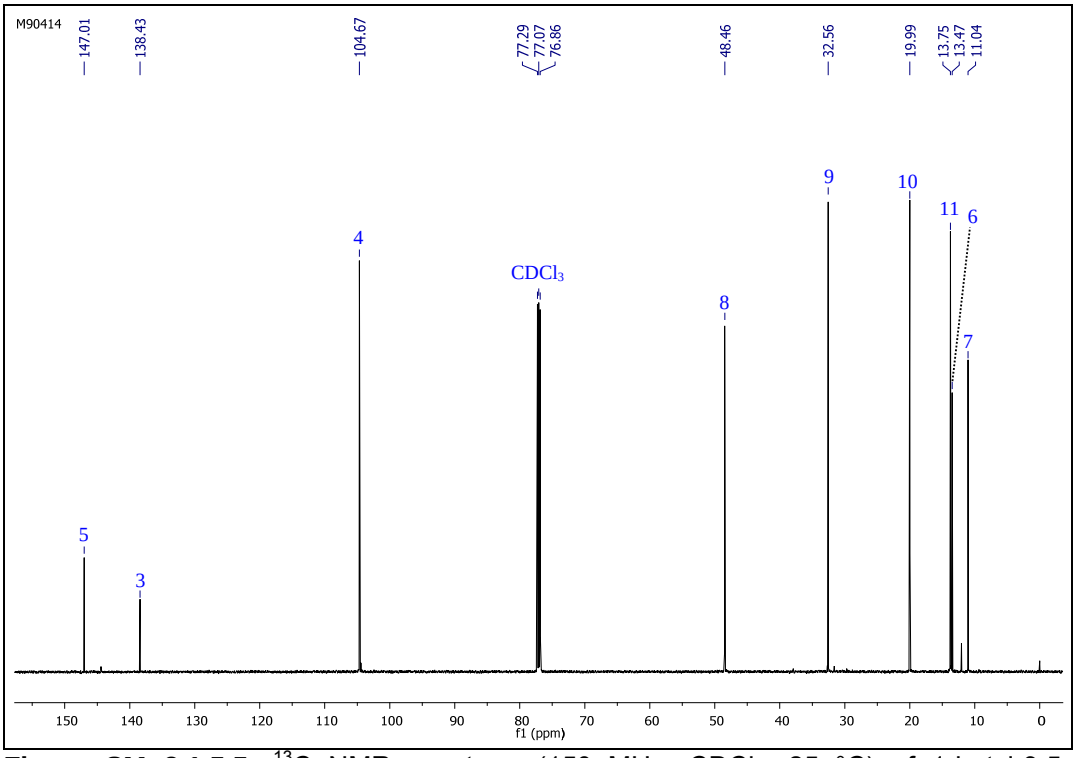


Figure SM 2.1.5.5. ^{13}C NMR spectrum (150 MHz, $CDCl_3$, 25 °C) of 1-butyl-3,5-dimethyl-1*H*-pyrazole.

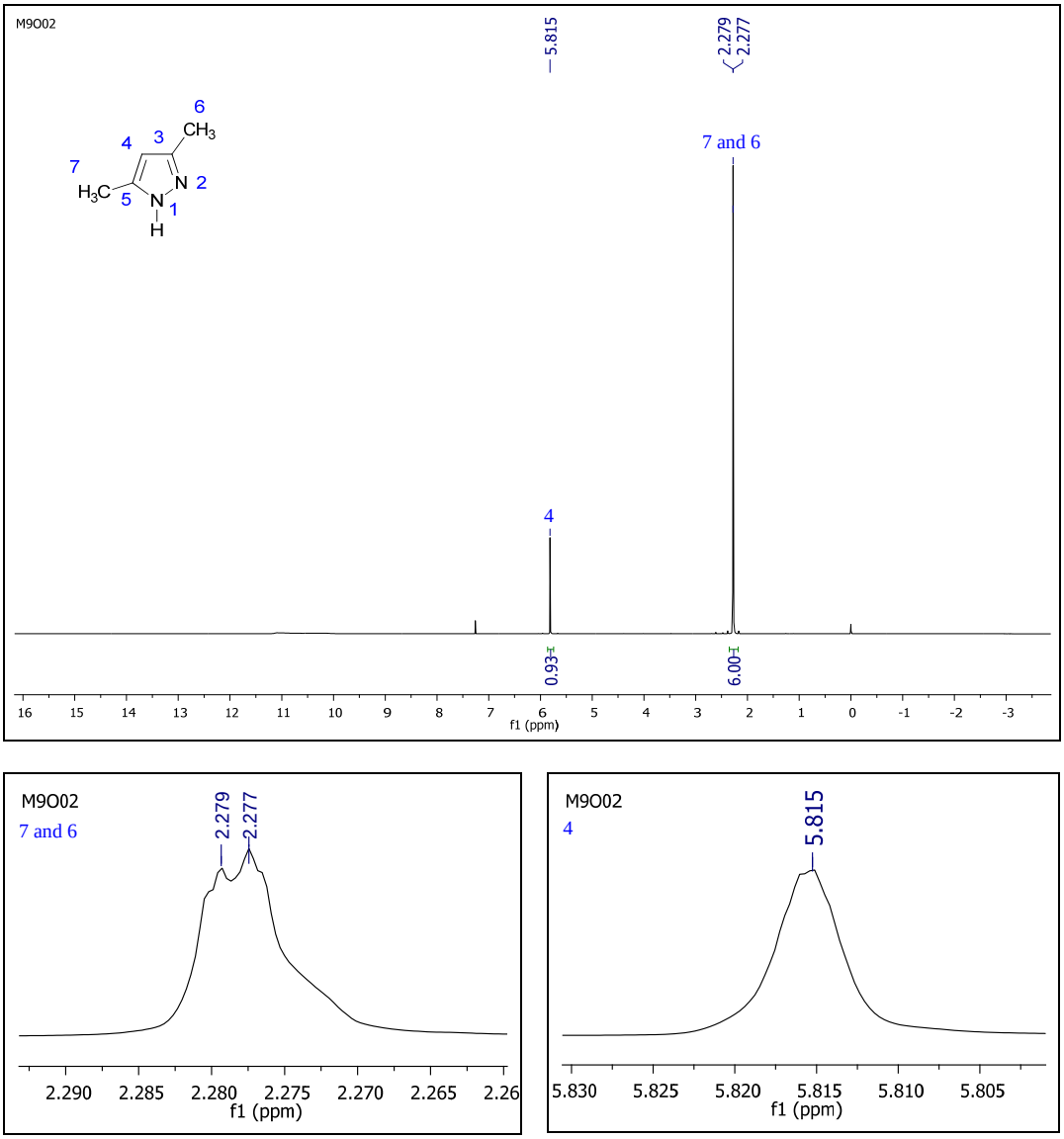


Figure SM 2.1.5.6. ^{1}H NMR spectrum (600 MHz, $CDCl_3$, 25 °C) of 3,5-dimethyl-1*H*-pyrazole.

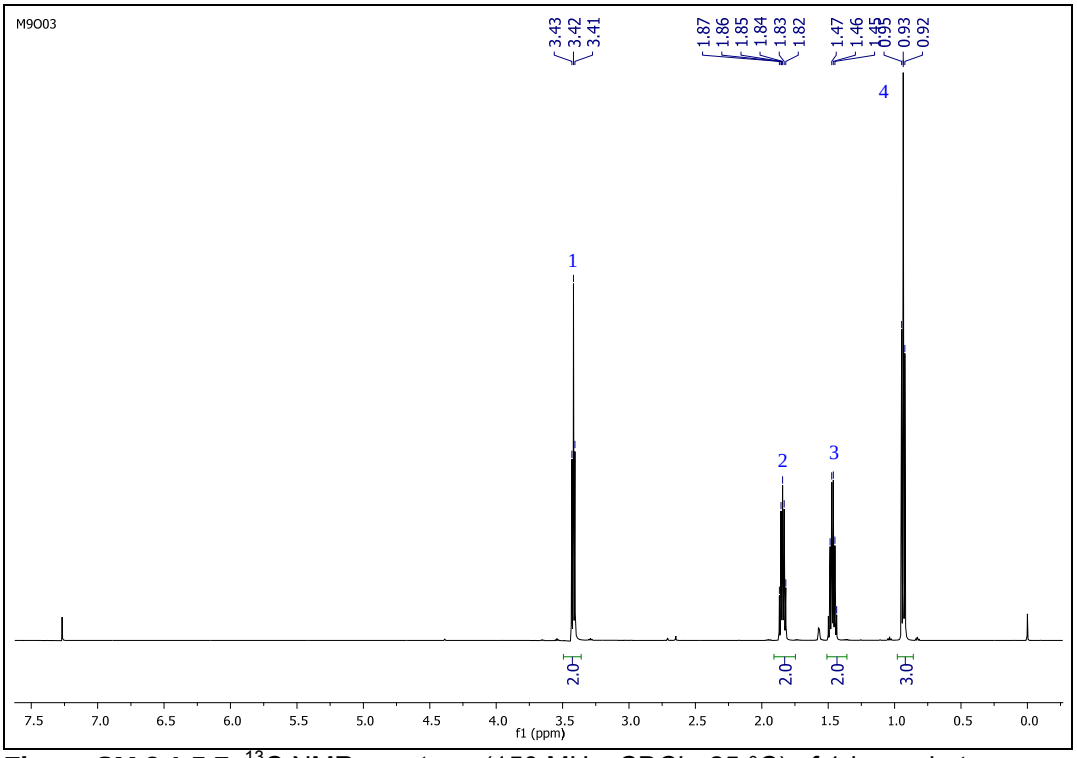


Figure SM 2.1.5.7. ^{13}C NMR spectrum (150 MHz, $CDCl_3$, 25 °C) of 1-bromobutane.

Thermal analysis

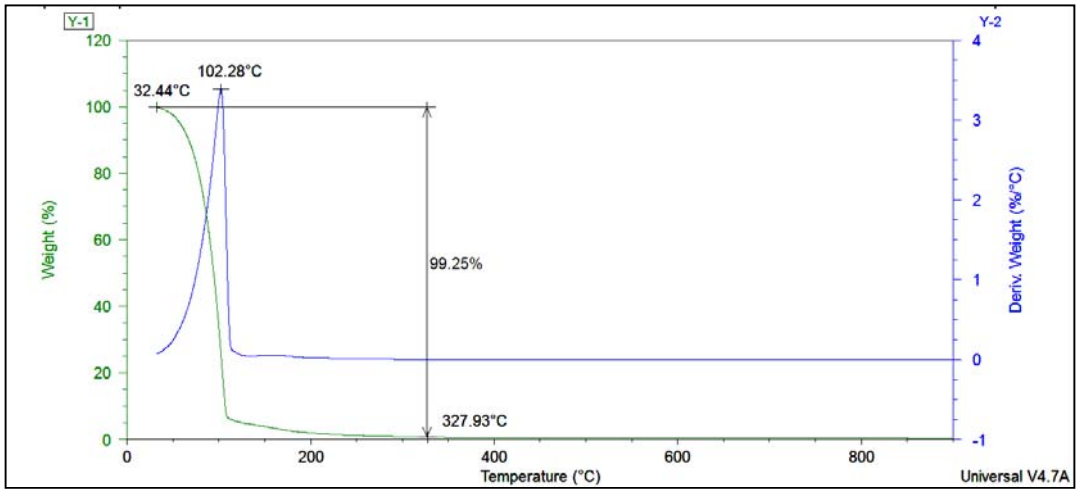


Figure SM 2.1.5.8. Thermogravimetric analysis (TGA) of the 1-butyl-3,5-dimethyl-1*H*-pyrazole.

[1] C. P. Frizzo, D. N. Moreira, E. M. Guarda, G. F. Fiss, M. R. B. Marzari, N. Zanatta, H. G. Bonacorso, M. A. P. Martins. *Catal.Commun*. 2009, ***10***, 1153.

Conversion of alcohols to alkyl chlorides using cyanuric chloride

Supplementary Material

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Table of Contents

1. Results

This experiment describes an easy and robust synthesis of alkyl chlorides from alcohols. This experiment was reproduced by students of Chemistry and Pharmaceutical Sciences degrees (around 15 students) during the second Practical Organic Chemistry course. Chemistry students used 1-phenyl ethanol as starting material and Pharmaceutical sciences students used geraniol.

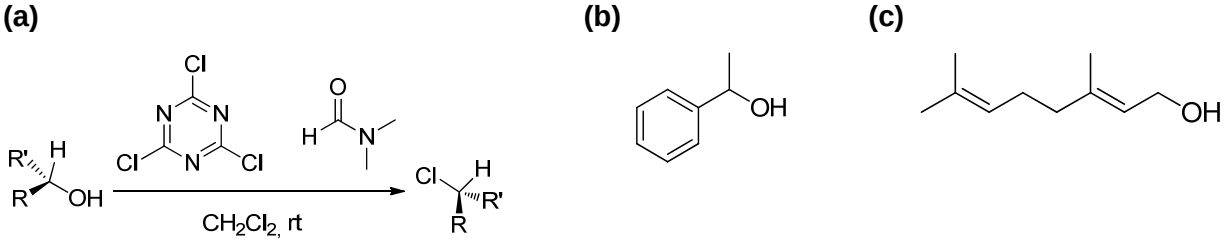


Figure SM 2.1.6.1. (a) Conversion of alcohols to alkyl chloride mediated by cyanuric chloride and DMF, and structures of (b) 1-phenyl-ethanol and (c) geraniol.

The first step of this experiment is the preparation of the reactive intermediate with DMF and cyanuric chloride which generates a sticky white foam that requires a big magnetic stirrer to maintain a continuous stirring.

A total conversion of the alcohol to the corresponding chloride was usually obtained by the students (confirmed by TLC) without need of chromatographic separation, using simple filtration of the crude trough a short pad of silica and celite as purification step. The isolated yields obtained by the students were in the range of 58-65%. To achieve a better purity of the product some key actions have to be taken into account:

- is fundamental to use the smallest amount possible of dichloromethane to avoid contamination with the secondary product cyanuric acid during the filtration process,
- a small diameter *Buchner* filter with bigger length should be used to allow the use of higher height of silica (4 cm).

The purity of the obtained compounds was accessed by both TLC and NMR.

By comparing the ^{1}H NMR of the starting material (commercial sample) and the obtained product we can identify the success of the experiment due to a notorious deviation of the protons connected to the reactive carbon (carbon attached to the hydroxyl group). The IR spectra also give important information about the reaction, the absorption band at 3500 cm^{-1} corresponding to an O-H stretch almost disappeared in the alkyl chloride IR spectra.

2. Notes for the Instructor

2.1. What is the mechanism of the reaction? Does the reaction work with tertiary alcohols?

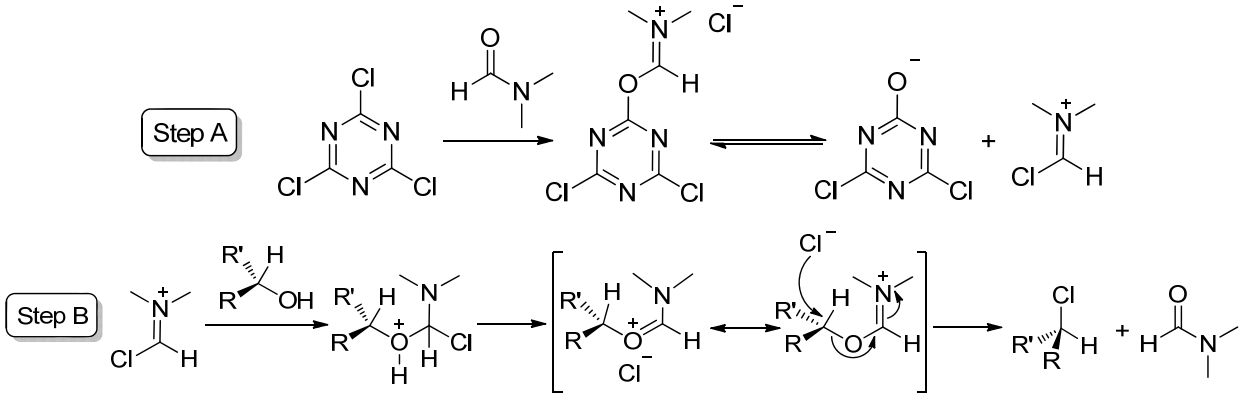


Figure SM 2.1.6.2. SN_2 Mechanism of conversion of alcohols to alkyl chloride mediated by cyanuric chloride and DMF.

The mechanism of the reaction regards a bimolecular nucleophilic substitution (SN_2). This type of mechanism does not occur with tertiary substrates, however, the substitution of the tertiary alcohol can occur by a unimolecular mechanism (SN_1) with formation of a carbocation resulting in a mixture of stereoisomers.

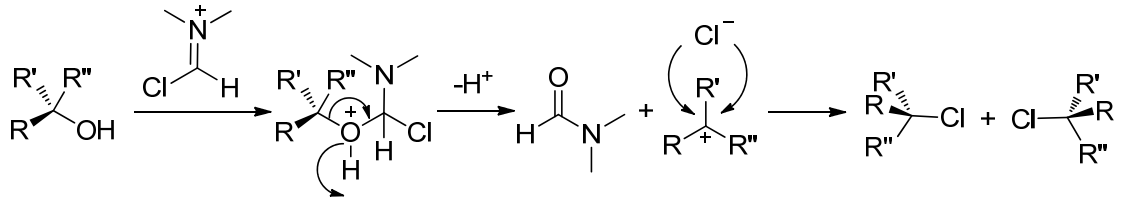


Figure SM 2.1.6.3: SN_1 Mechanism of conversion of tertiary alcohols to alkyl.

2.2. What do you expect to obtain from (-)-menthol?

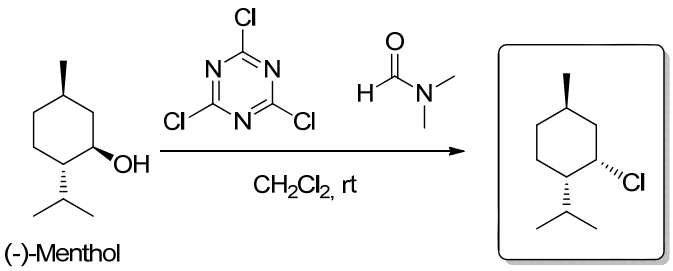


Figure SM 2.1.6.4: Reaction using (-)-Menthol.

2.3. Why does this reaction should be carried out under anhydrous conditions?

Cyanuric chloride and the intermediate formed from the reaction with DMF are both sensitive to water and/or moisture, and so anhydrous conditions should be used.

2.4. Does the reaction work with a catalytic amount or without DMF?

No, from the reaction mechanism is clear that one equivalent of DMF will form one equivalent of the reactive intermediate that will produce one equivalent of the desired product. So, at least one equivalent of DMF is needed to perform this reaction.

2.5. How do you prepare the bromide derivative from the used substrate?

The bromide derivative can be obtained using cyanuric bromide instead cyanuric chloride.

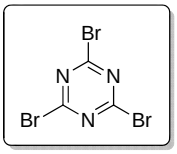
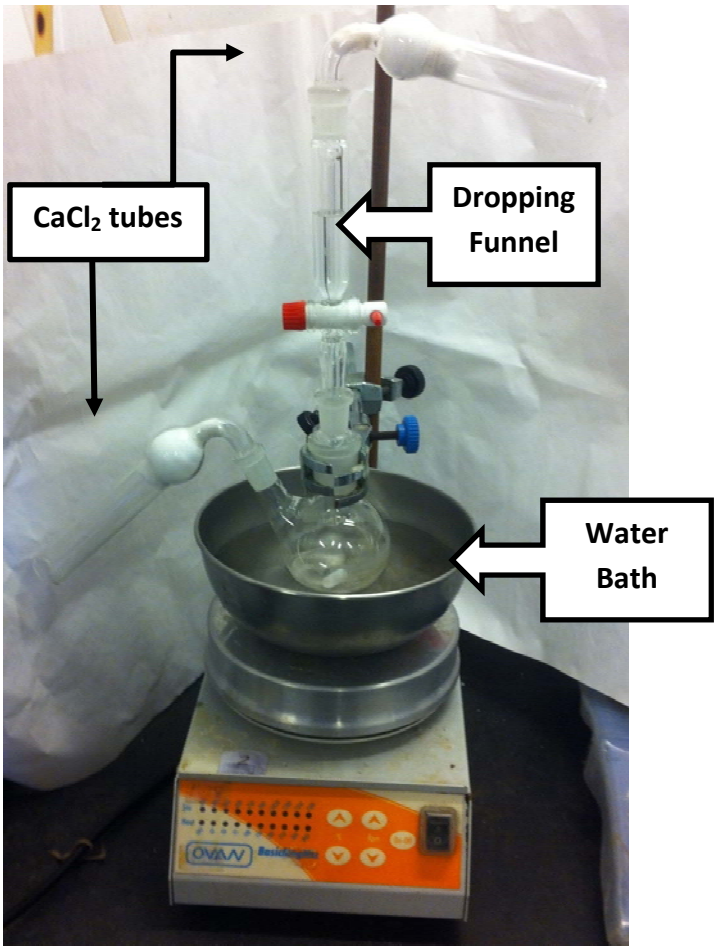
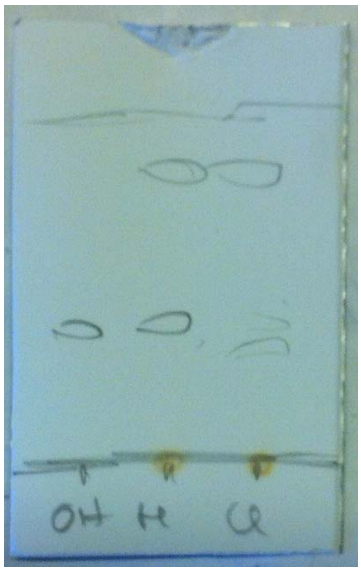


Figure SM 2.1.6.5: Cyanuric bromide

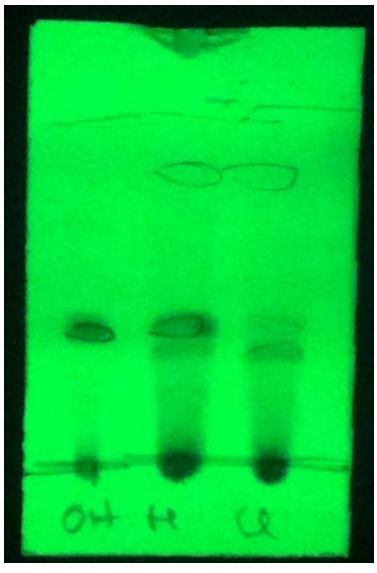
3. Experiment's Photos



(a)



(b)



(c)

Figure SM 2.1.6.6: (a) Reaction set-up, TLC of OH-Geraniol, M-mixture of starting material and product, Cl- product of the reaction of geraniol (b) under visible light and (c) under 254 nm.

4. Compounds Characterization

4.1. Geranyl Chloride

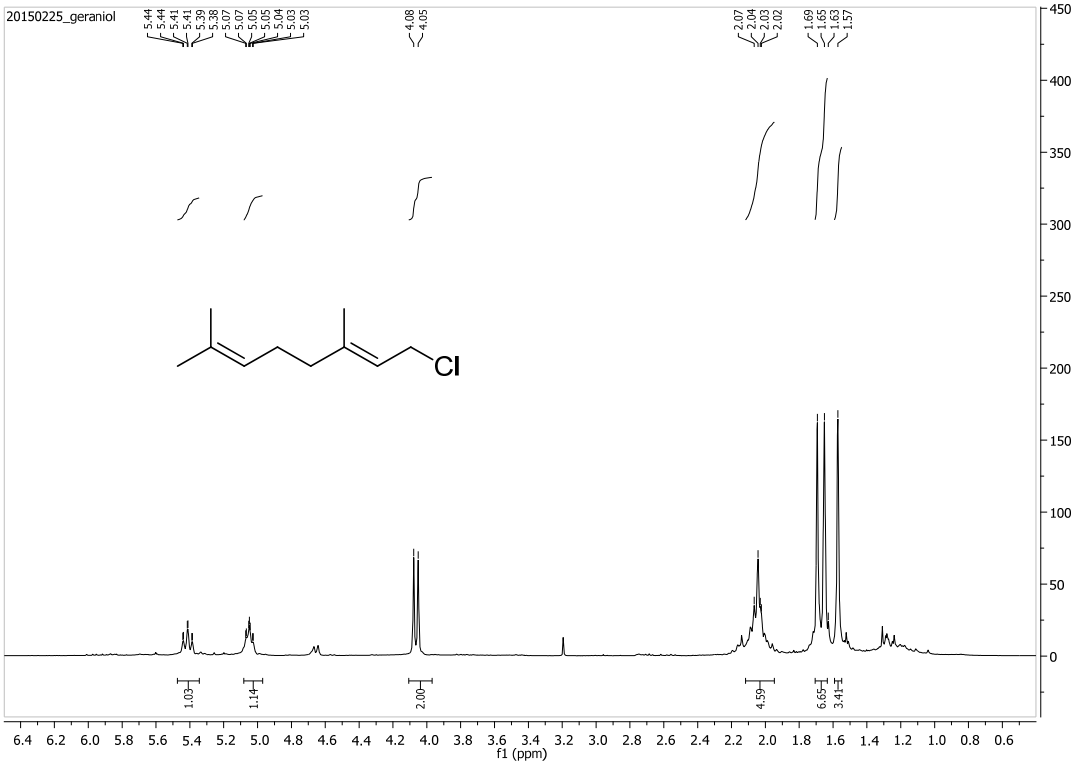


Figure SM 2.1.6.7. ^{1}H NMR ($CDCl_3$) spectra of geranyl chloride obtained from geraniol.

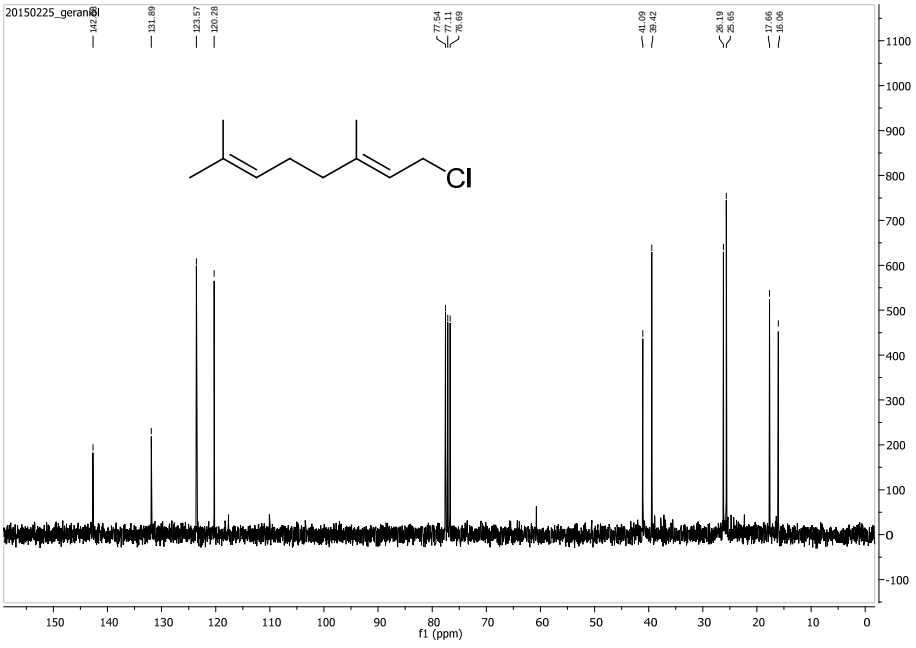


Figure SM 2.1.6.8. ^{13}C NMR ($CDCl_3$) spectra of geranyl chloride obtained from geraniol.

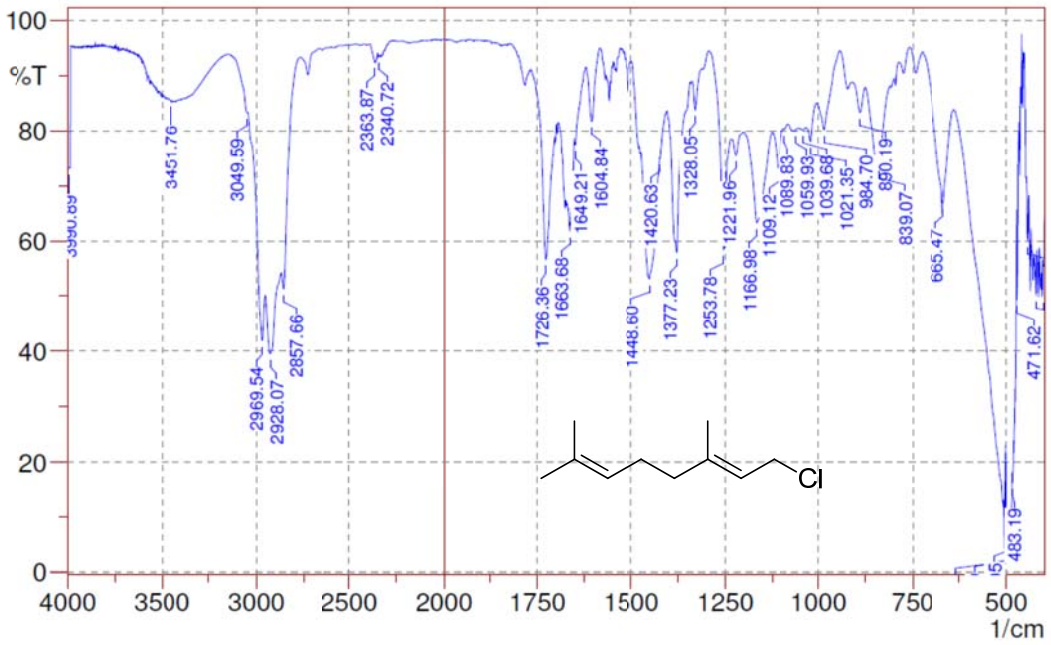


Figure SM 2.1.6.9. IR spectra of geranyl chloride obtained from geraniol.

4.2. Geraniol

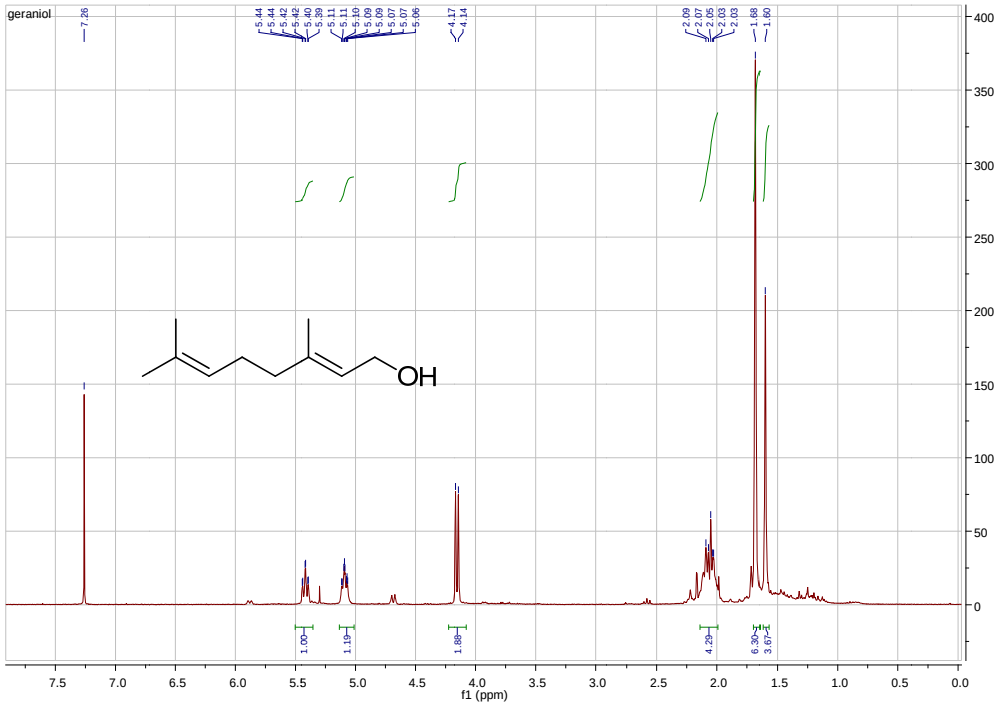


Figure SM 2.1.6.10. ^{1}H NMR ($CDCl_3$) spectra of commercial sample of geraniol.

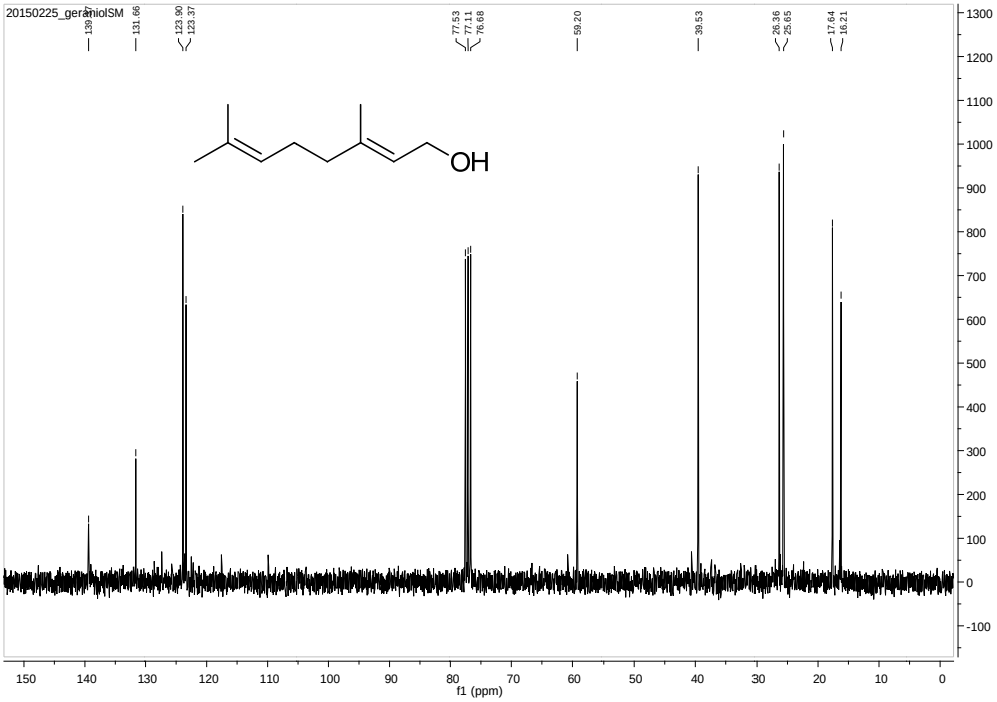


Figure SM 2.1.6.11. ^{13}C NMR ($CDCl_3$) spectra of commercial sample of geraniol.

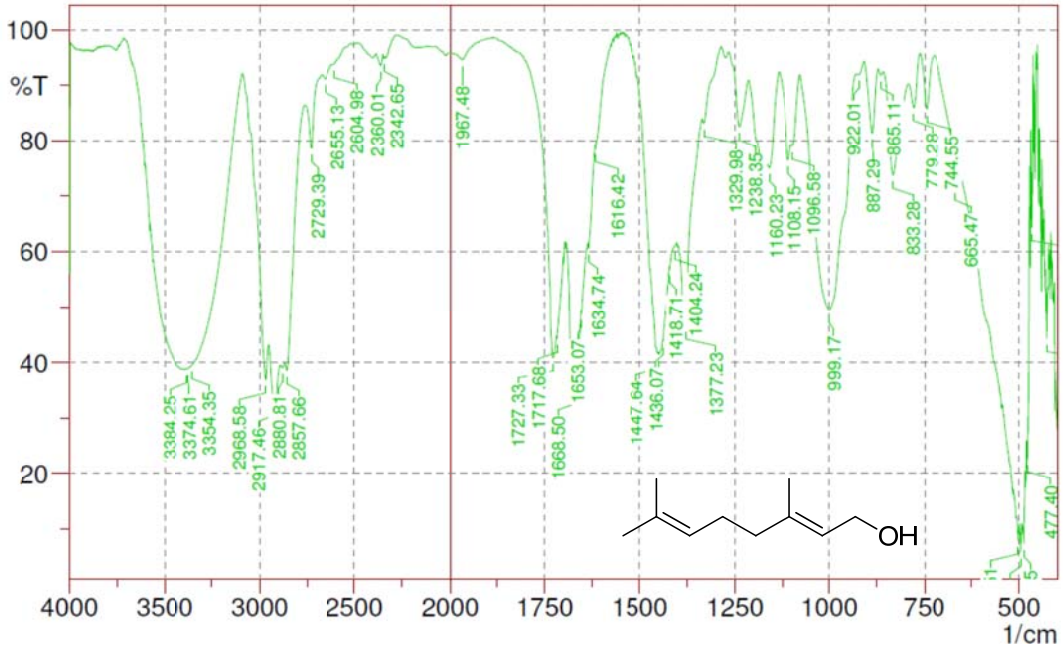


Figure SM 2.1.6.12. IR spectra of commercial sample of geraniol.

4.3. 1-phenyl ethanol and 1-phenyl ethyl chloride

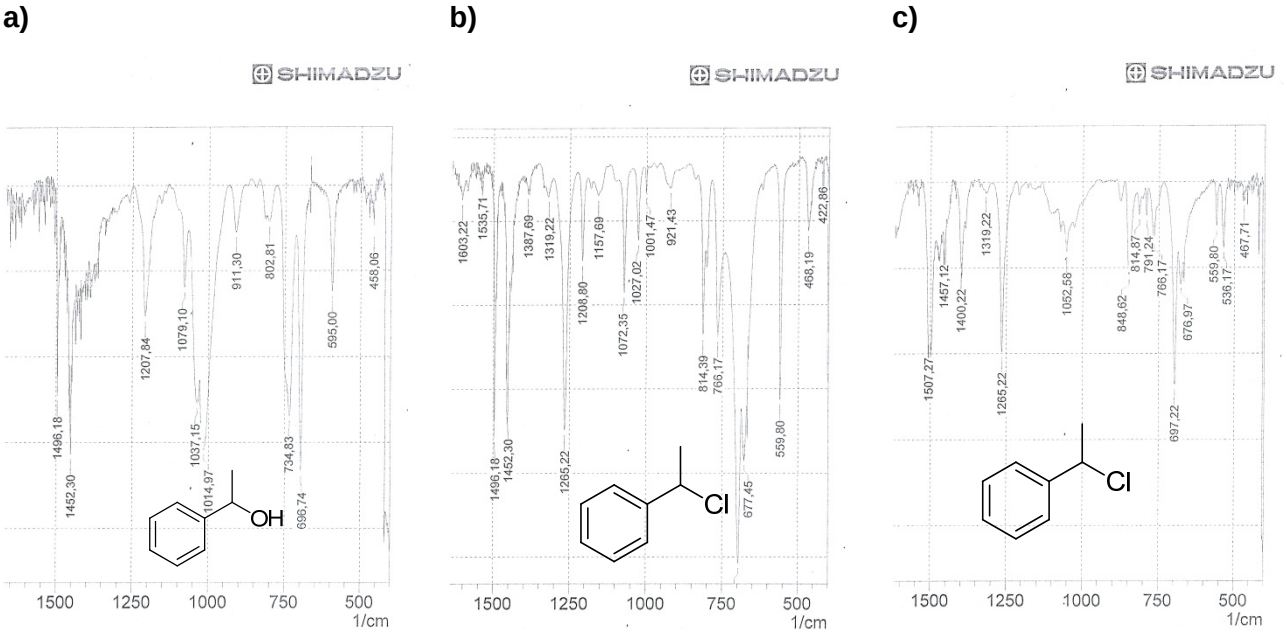


Figure SM 2.1.6.13. IR Spectra (film) commercial sample of (a) 1-phenyl ethanol, (b) 1-phenyl ethanol and (c) obtained product from 1-phenyl ethanol.

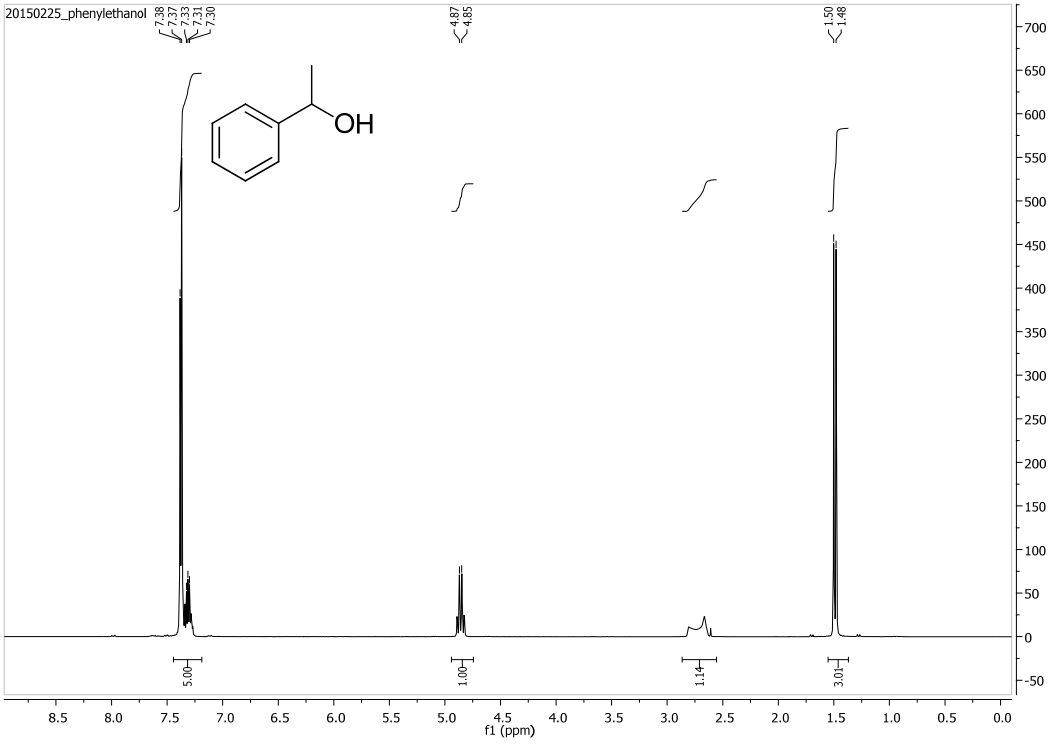


Figure SM 2.1.6.14. ^{1}H NMR ($CDCl_3$) spectra of commercial sample of 1-phenyl ethanol.

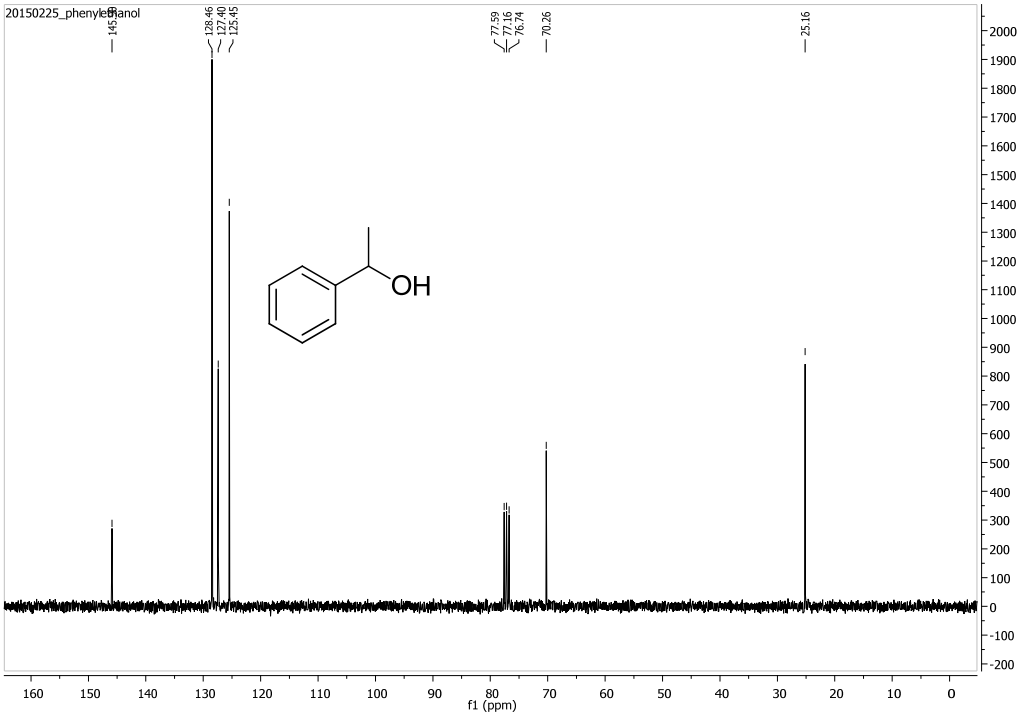
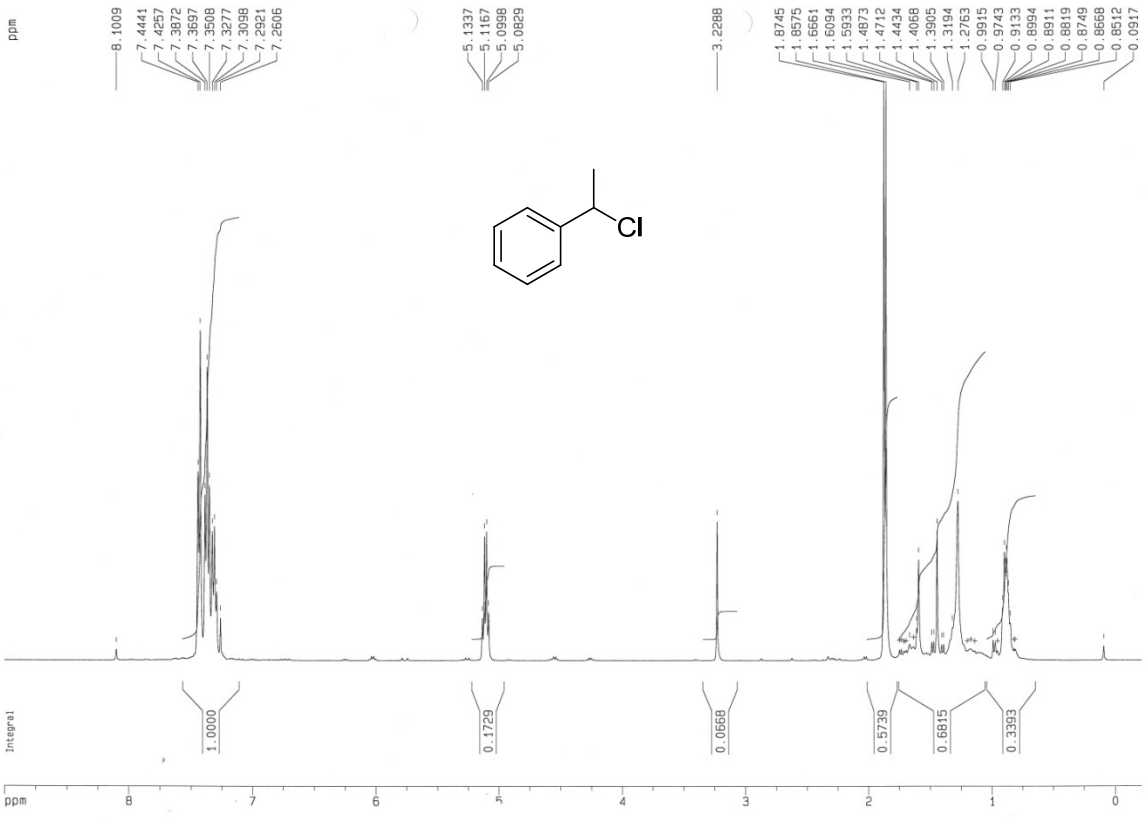


Figure SM 2.1.6.15. ^{13}C NMR ($CDCl_3$) spectra of commercial sample of 1-phenyl ethanol.



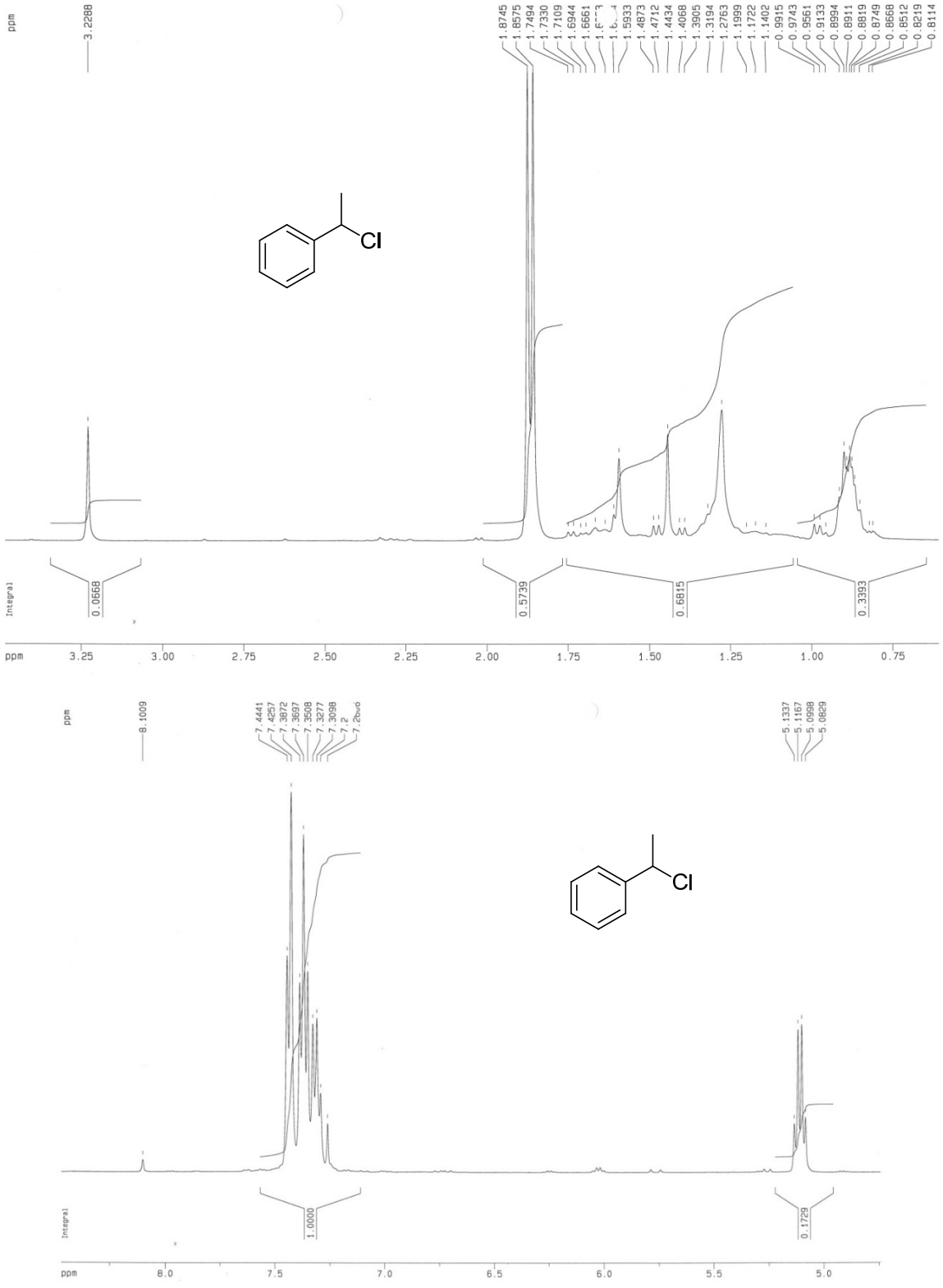


Figure SM 2.1.6.16. ^{1}H NMR ($CDCl_3$) spectra of 1-phenyl-ethyl chloride obtained from 1-phenyl ethanol.

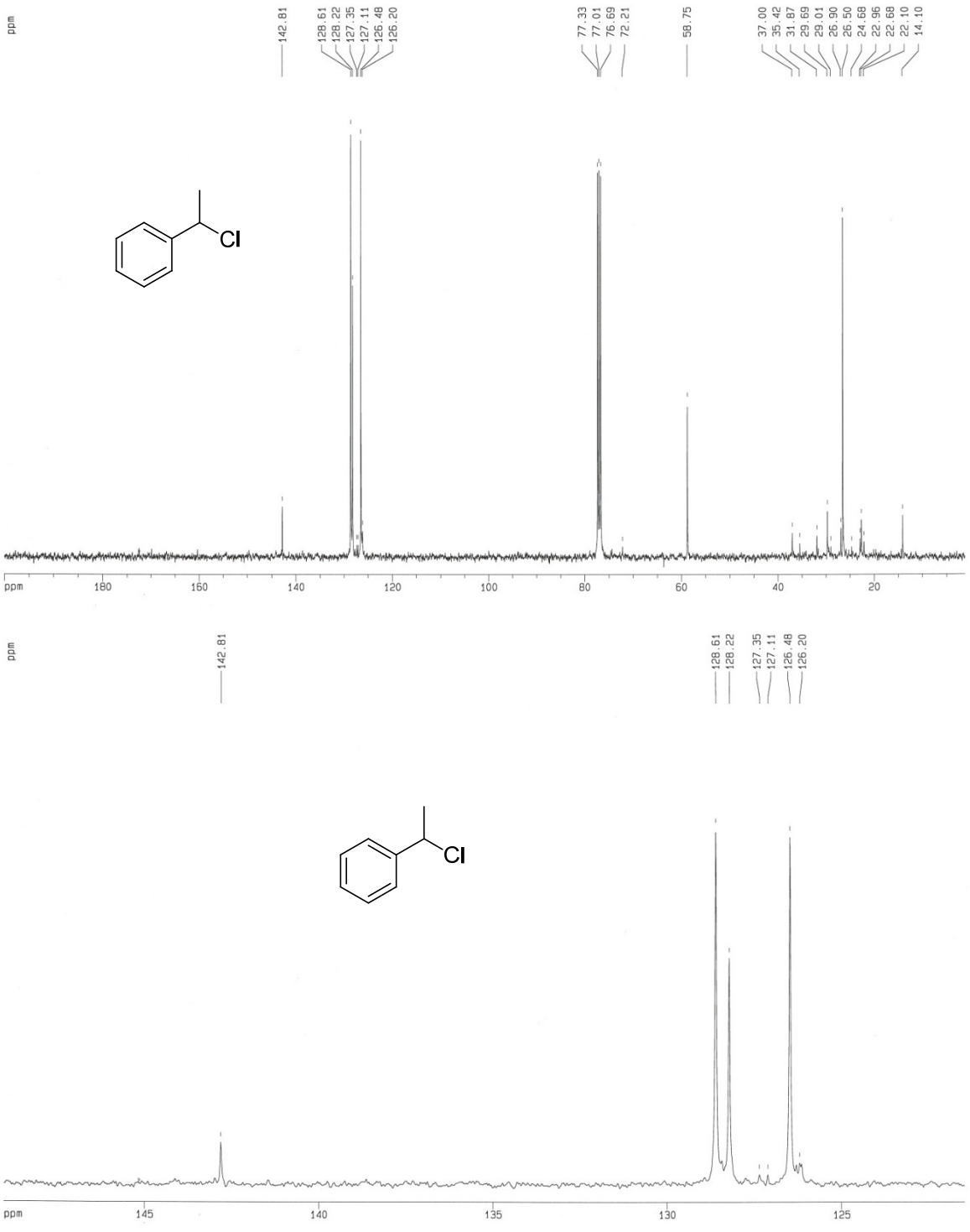


Figure SM 2.1.6.17. ^{13}C NMR ($CDCl_3$) spectra of 1-phenyl-ethyl chloride obtained from 1-phenyl ethanol.

Synthesis of phenacetin

Supplementary Material

Experimental notes

This experiment aims at the preparation of phenacetin from *p*-aminophenol in two steps. The first one is an acetylation and the second an alkylation with ethyl iodide in basic medium. Although simple, each step require one laboratory session since the reactions are not very fast. The experiment is adequate to 2nd year chemistry students. It can be used in an intermediate organic synthesis course or in medicinal organic chemistry. Since a fume hood is necessary the number of students/class depends on the lab configuration. This experiments has been performed in classes of 10 students.

The acetylation using acetic anhydride is performed in water at 100ºC for 20 min but it is not complete as confirmed by TLC (*p*-aminophenol in not soluble in common solvents; ethanol is adequate to prepare a dilute solution of this reagent). Increasing the reaction time did not improve the yield. However the product, paracetamol, precipitates easily from the reaction mixture in a pure form as white crystals. The yields vary between 61 to 62% and the melting point of product is 169-172 ºC (lit. 168-172 ºC).

For the second step it is necessary to prepare a solution of sodium ethoxide from ethanol and metallic sodium. This can be done at room temperature, but since the reaction is quite slow it is better to heat the mixture at reflux for 10 min to ensure the complete consumption of the sodium.

The addition of ethyl iodide leads to the formation of phenacetin. It is necessary to heat the solution for 1 hour. A TLC analysis confirms that the reaction is complete. Upon cooling the solution the phenacetin starts to precipitate, but to ensure a complete precipitation it is better to add some water to the reaction mixture and place it in an ice bath. Phenacetin, *N*-(4-ethoxyphenyl)acetamide, is a white solid and the TLC and ^{1}H NMR analysis confirm its purity. The yields of the second step vary between 75 to 80% and the melting point of product is 131-134ºC (lit. 134ºC d, Storey, R., A., Ymen, I. Solid State Characterization of Pharmaceuticals, 1nd edition, Wiley-Blackwell, 2011). The overall yield was 46-50%. A possible side product of this reaction would be ethene formed by a competitive elimination reaction.

Both compounds were obtained in a pure form. However, paracetamol can be recrystallized from water (10 mL) and phenacetin from a mixture of ethanol (10mL)/water (15 mL).

Photos of experiment

Figure SM 2.1.7.1. Reaction apparatus for the acetylation reaction

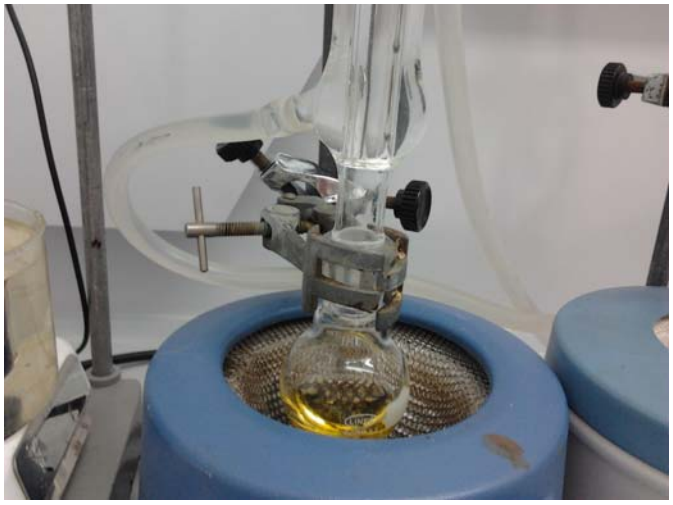


Figure SM 2.1.7.2. Reaction apparatus for the alkylation reaction

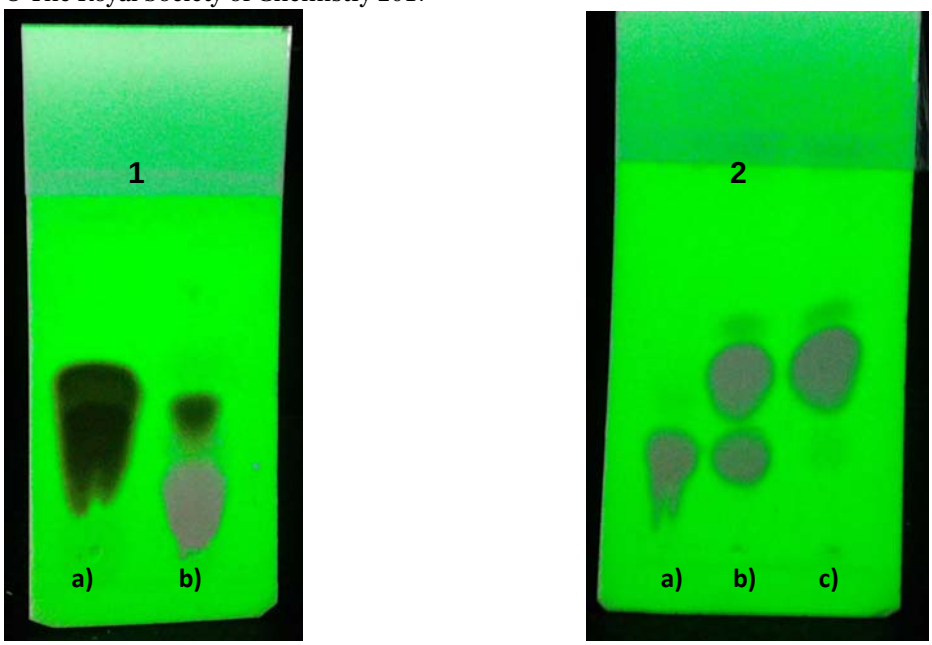


Figure SM 2.1.7.3. TLC for the acetylation and alkylation reaction using 80% ethyl ether/petroleum ether as eluent. **1** a) p-aminophenol b) reaction mixture; **2** a) paracetamol b) paracetamol + reaction mixture c) reaction mixture

^{1}H NMR and IR Spectra

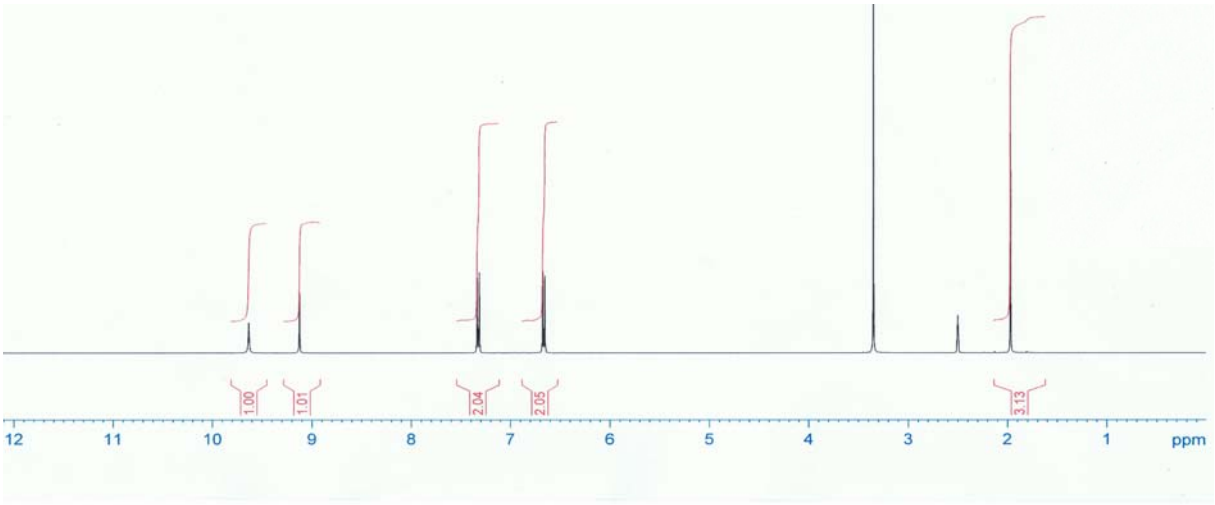


Figure SM 2.1.7.4. ^{1}H NMR spectrum (400 MHz, DMSO) of paracetamol

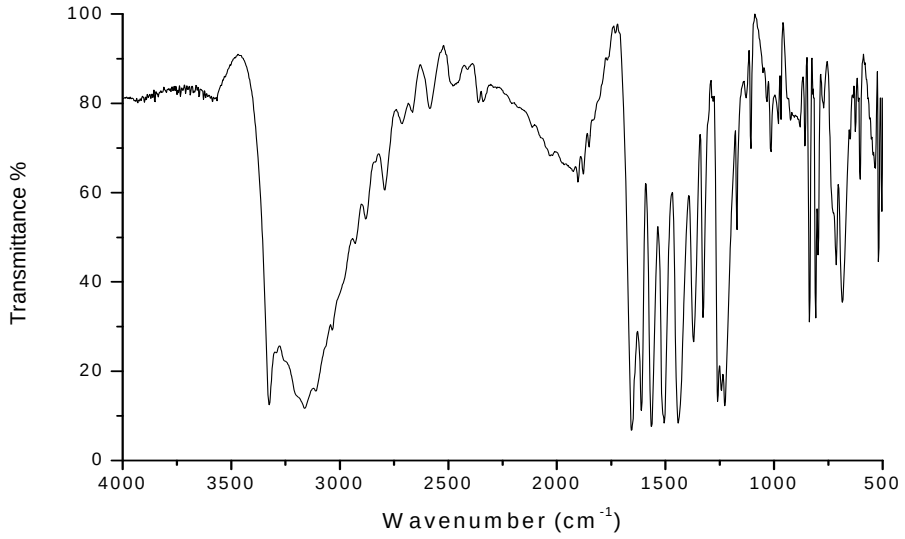


Figure SM 2.1.7.5. IR spectrum of paracetamol

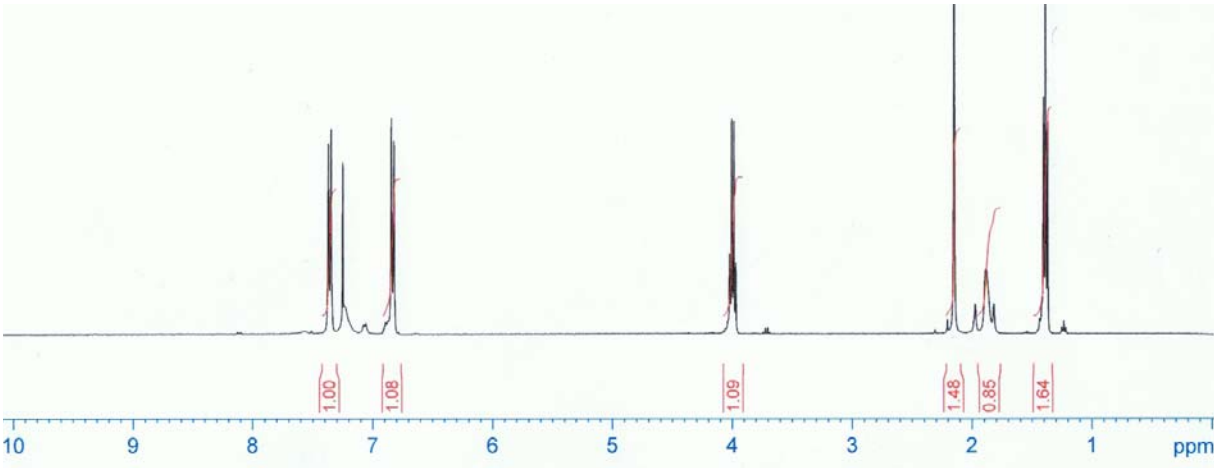


Figure SM 2.1.7.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of phenacetin.

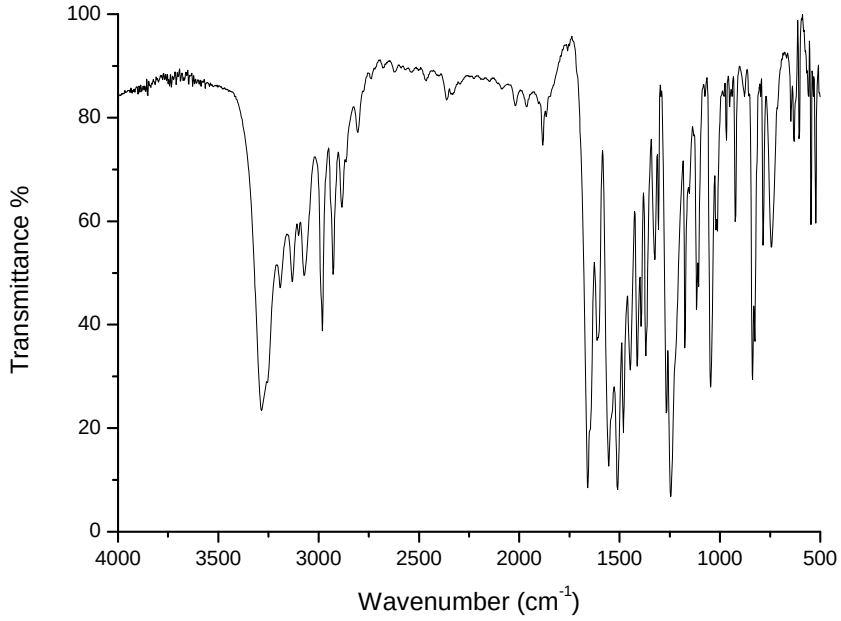


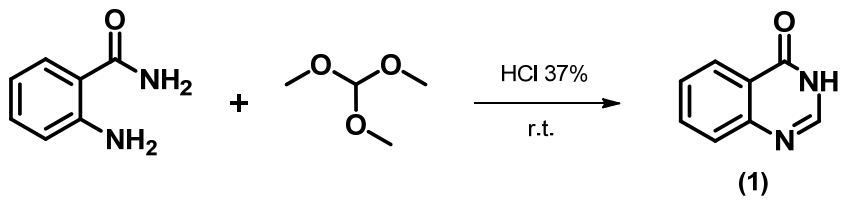
Figure SM 2.1.7.7. IR spectrum of phenacetin.

One-step synthesis of 4(3*H*)-quinazolinones: an important heterocyclic scaffold in Medicinal Chemistry

Supplementary Material

4(3*H*)-Quinazolinone and its derivatives constitute an important class of fused heterocycles that are found in more than 100 naturally occurring alkaloids[1] and several marketed drugs. From a synthetic point of view, the first 4(3*H*)-quinazolinone compound was obtained as early as 1869 from anthranilic acid and cyanogen.[2] Since then, due to their pharmacological importance, several synthetic routes and strategies have been reported for the generation of highly functionalized 4(3*H*)-quinazolinones.[3]

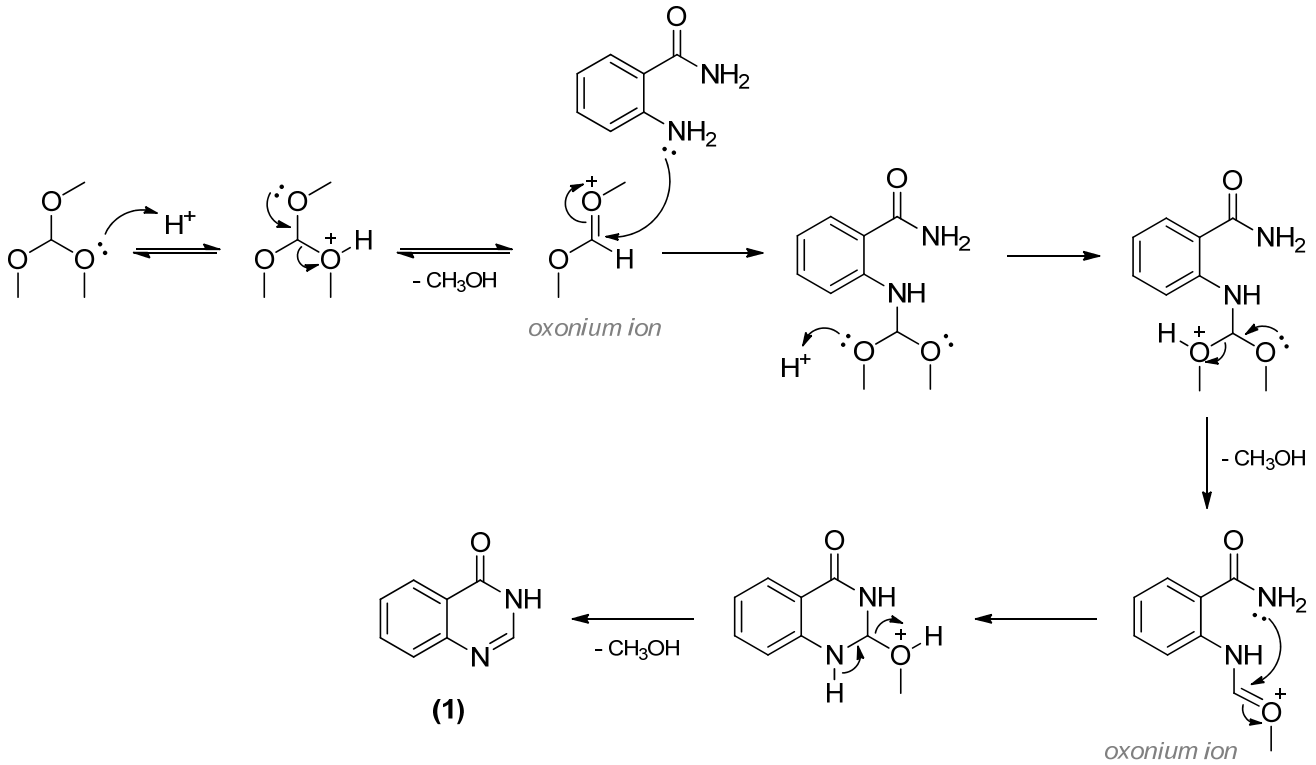
The main goal of this experiment is to demonstrate the use of organic synthesis to achieve a relevant heterocyclic core structure in Medicinal Chemistry, starting from readily available starting materials. The synthesis involves a one-pot heterocyclisation of 2-aminobenzamide with trimethyl orthoformate using acid catalysis. This synthetic methodology was also successfully applied in our lab using 4- and 5-substituted *o*-aminobenzamides,[4] although the reaction times may be longer depending on the position and electronic properties of the substituents. Additionally, the pure product is easily isolated from the reaction mixture using liquid-liquid extractions, avoiding the use of expensive purification techniques and equipment. It should be highlighted that this operationally simple methodology is very attractive from a pedagogical point of view, especially if we consider that the synthetic strategy proposed will afford a reasonably complex fused heterocyclic core structure.



(1)

Scheme SM 2.1.8.1

Moreover, students should be able to rationalise the reaction mechanism through the formation of oxonium ions as the electrophilic species (Scheme SM 2.1.8.2) and understand the relevance of the acid catalysis.



Scheme SM 2.1.8.2

Table SM 2.1.8.1 summarises the reaction conditions screened and results obtained. As exemplified, the reaction was performed with: (i) different amounts of limiting reagent (50 to 200 mg scale of 2-aminobenzamide); (ii) different reaction times and (iii) with or without inert atmosphere. The reproducibility of the experiment was assessed by its repetitive execution by two undergraduate students, a M.Sc. student, a research fellow and a postdoc researcher at the laboratory of Medicinal Chemistry, Faculty of Pharmacy – University of Lisbon. The yield of the reaction is in the range of 60-90%. Higher yields where observed when the experiment was performed by more experienced researchers.

Table SM 2.1.8.1 - Experiments conducted in a round bottom flask starting from 2-aminobenzamide (limiting reagent) and trimethyl orthoformate in acidic medium at room temperature.

Entry	Limiting Reagent (mg)	Reaction time (min)	Isolated Yield (%)	Melting Point (ºC)
1[a]	50	90	70	214-218
2[a]	50	60	88	207-211
3[a]	50	60	63	208-212
4[a]	50	60	73	210-213
5[a]	50	60	87	214-217
6	50	30	93	210-213
7	100	30	83	208-212
8	200	30	79	209-212

[a] Experiments performed under inert atmosphere.

General Notes / Troubleshooting Information:

- To the addition of trimethyl orthoformate is recommended the use of glass material, either a microsyringe or a pipette.

- The addition of hydrochloric acid should be done dropwise and at 0 ºC (ice bath). During this step the formation of a white precipitate is observed (Figure SM 2.1.8.1)**.**

- The reaction should be completed at the end of 30 min. To analyse it by TLC, students should be instructed to use a Pasteur pipette to transfer a small drop of the reaction mixture to an eppendorf with 0.5 mL of MeOH and spot a TLC plate with the reaction mixture and the limiting starting material (Figure SM 2.1.8.2). TLC eluent can be either EtOAc (100%) or EtOAc:Hex (9:1).

- After the reaction reaches completion, the mixture is diluted with water and the pH is adjust to 6 with NaOH 5M. If the pH rises above 6, it should be readjusted with HCl 3M.

- The precipitate (impurity) present at pH 6 must be filtered-off from the aqueous reaction mixture and it is recommended the use of a vacuum filtration apparatus equipped with a sintered glass Büchner funnel (grade 3 or 4). We were unable to characterise the impurity formed.

- The product can be extracted from the aqueous mixture either with EtOAc or CH_2Cl_2. Although the first one is less toxic the second has a much lower boiling point, being easier to properly dry the product.

- The pure product is obtained as a white solid that can be dry in a vacuum pump or, if time is very limited, in a pre-heated oven at 80 ºC.

- If additional purification is required, the product can be recrystallized from 5-10 mL of near-boiling EtOAc. If it doesn't precipitate after cooling down to room temperature, a small amount of hexane can be added to the mixture.

- The NMR spectra should be performed in DMSO-d_6 since is difficult to observe the NH peak in $CDCl_3$.

Photos of the experiment:

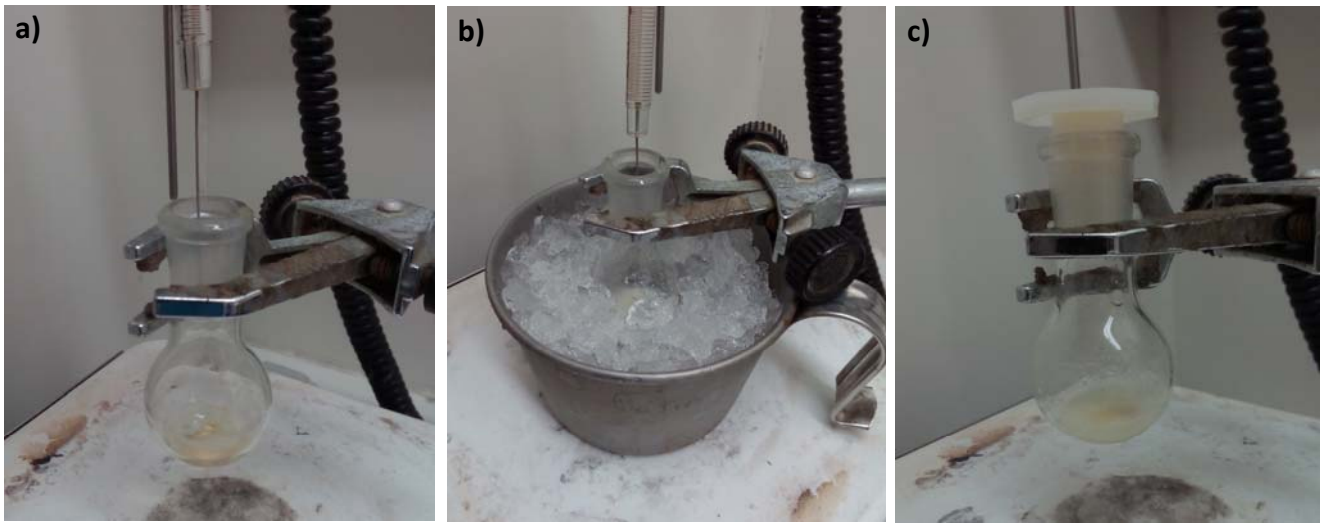


Figure SM 2.1.8.1 – Illustrative photos of the reaction: a) addition of trimethyl orthoformate; b) dropwise addition of HCl at 0 ºC; and c) reaction at t = 30 min.

a) **b)**

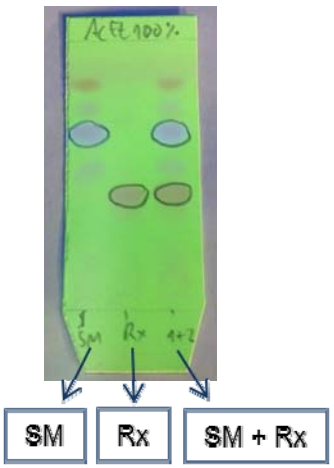


Figure SM 2.1.8.2 – a) Example of a TLC when reaction reaches completion, visualized by UV light (254 nm), and b) product (white solid) drying in a vacuum pump.

NMR spectra:

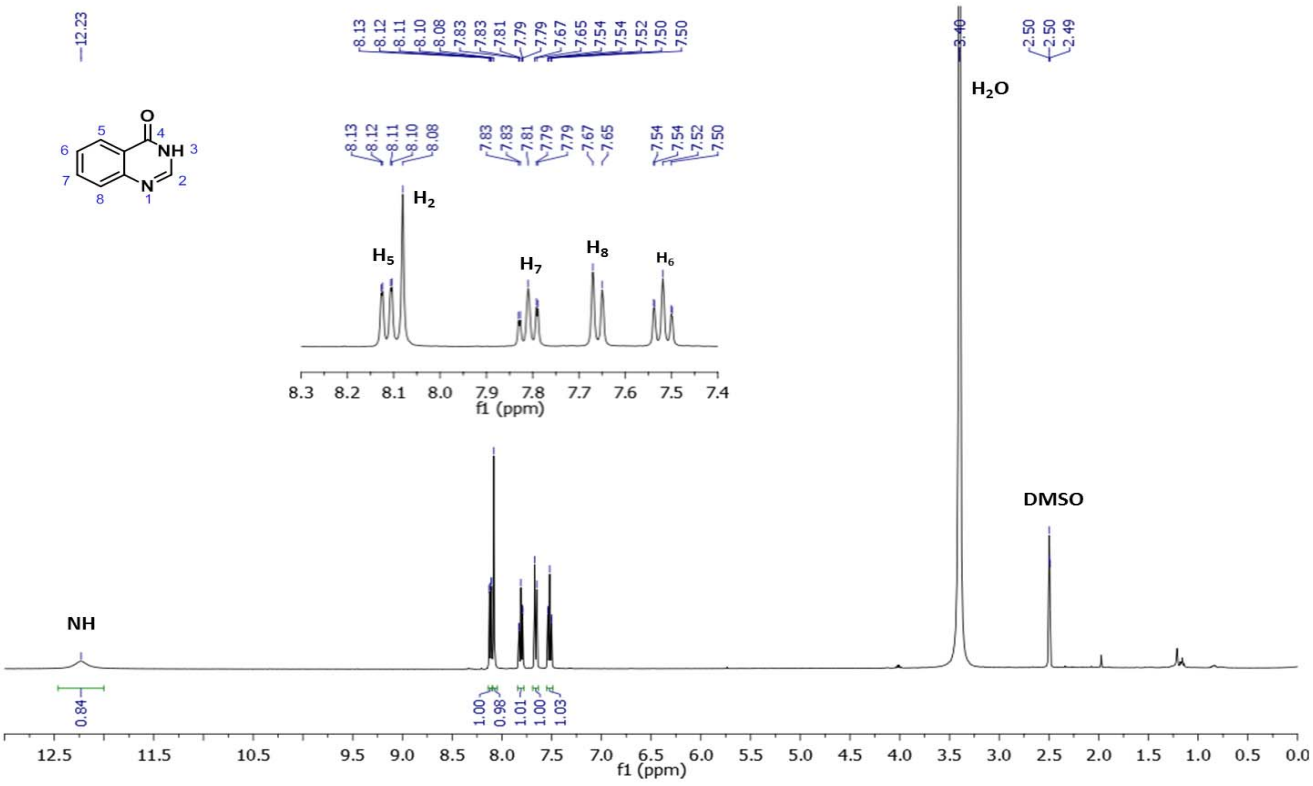


Figure SM 2.1.8.3 – ^{1}H spectrum of 4(3*H*)-quinazolinone (400 MHz, DMSO) and peak assignment.

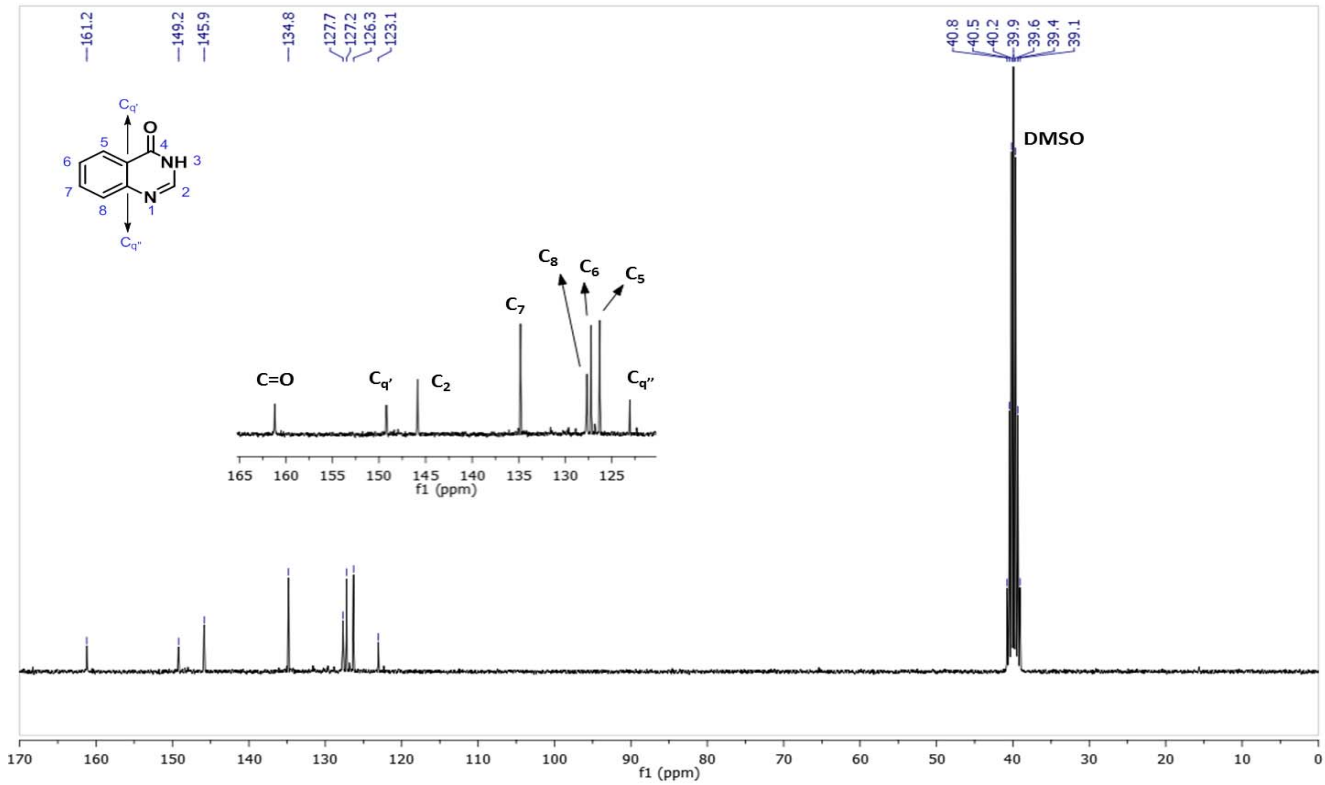


Figure SM 2.1.8.4 – ^{13}C spectrum of 4(3*H*)-quinazolinone (300 MHz, $CDCl_3$) and peak assignment.

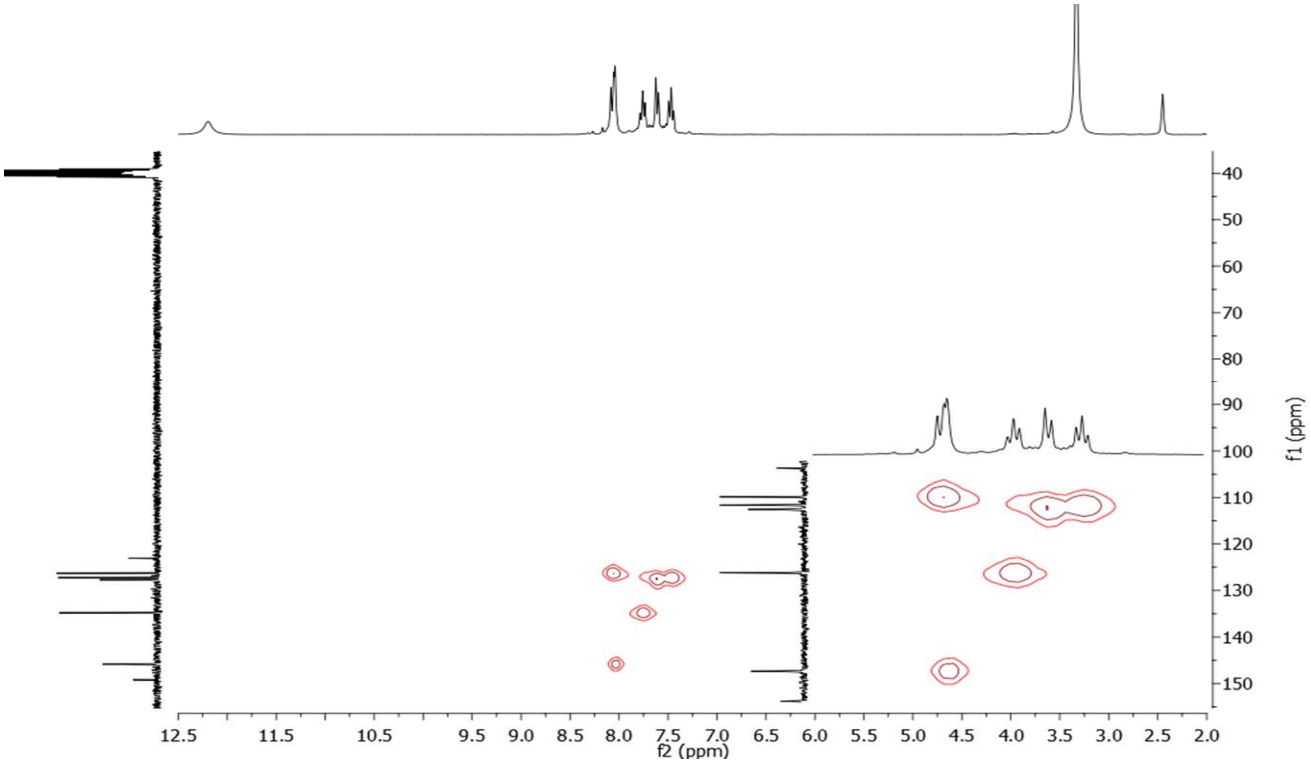


Figure SM 2.1.8.5 – HMQC spectrum of 4(3*H*)-quinazolinone (300 MHz, $CDCl_3$).

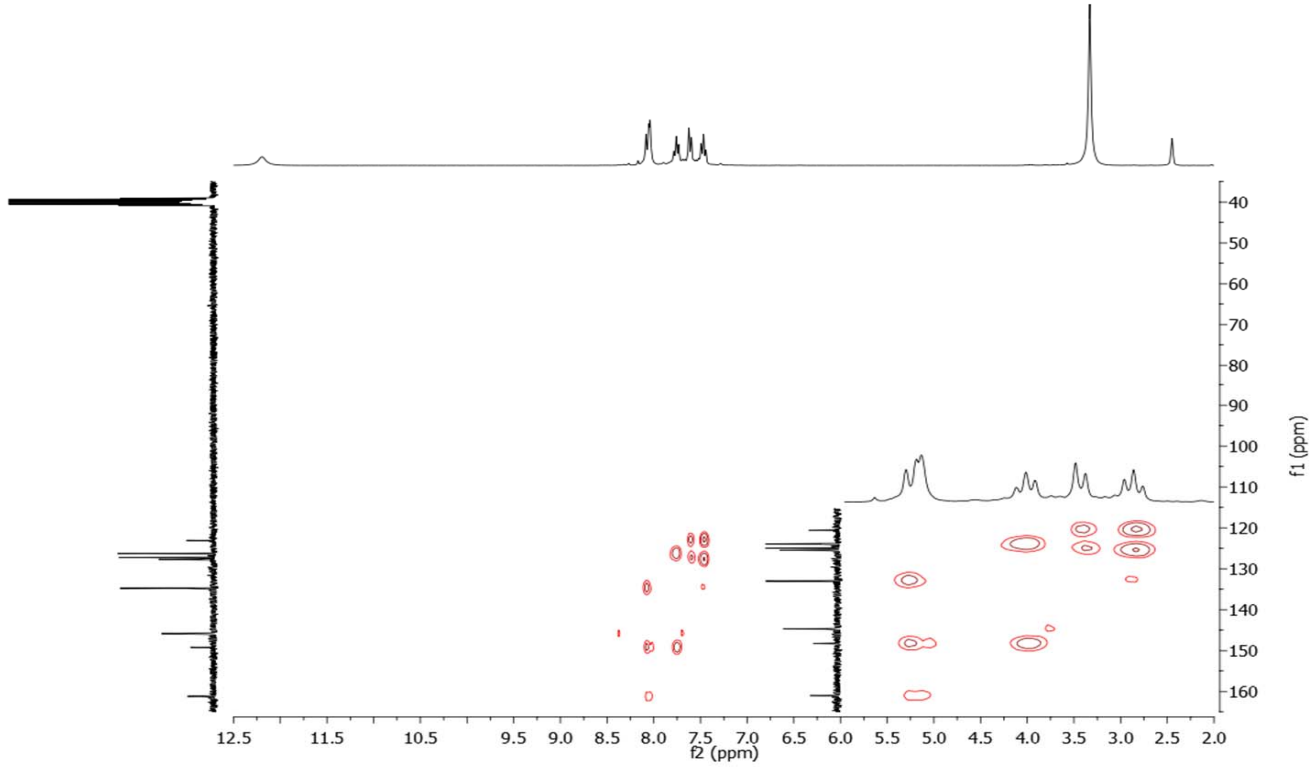


Figure SM 2.1.8.6 – HMBC spectrum of 4(3*H*)-quinazolinone (300 MHz, $CDCl_3$).

[1] S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.

[2] The first report of a 4(3*H*)-quinazolinone compound: P. Griess, *J. Prakt. Chem.*, 1869, 369.

[3] Recent advances in 4(3*H*)-quinazolinone synthesis have been revised in: a) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; and b) L. He, H. Q. Li, J. B. Chen and X. F. Wu, *RSC Adv.*, 2014, **4**, 12065.

[4] *O*-aminobenzamide tested: 2-amino-4-chlorobenzamide; 2-amino-5-chlorobenzamide; 2-amino-5-bromobenzamide; 2-amino-4-metoxibenzamide; 2-amino-5-metoxibenzamide; 2-amino-5-nitrobenzamide.

Controlled monoalkylation of the structurally rigid bicyclic system isomannide

Supplementary Material

This experiment aims the regioselective allylation of the one hydroxyl group of the bicyclic carbon system isomannide. This mono allylation to yield an allyl ether derivative is possible due to the steric hindrance of the other hydroxyl group in the rigid cyclic structure.

The students should identify the two hydroxyl groups on the isomannide rigid structure and recognize the steric hindrance imposed by the first allyl substituent on the hydroxyl group of the mono alkylated compound. This fact avoids the S_N2 replacement of the bromine in allyl bromide by the free hydroxyl group. However If the reaction time and concentration of allyl bromide are increased the double allylation can proceed and the corresponding isommanide diether allylic is obtained as by product.

Four groups of two students of the 1st year Bioorganic Chemistry M. Sc. from Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa did the experiment during ordinary classes affording the results and yields after chromatographic purification for (3*R*,3a*R*,6*R*,6a*R*)-6-(allyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (**1**) and (3*R*,3a*R*,6*R*,6a*R*)-6-propoxyhexahydrofuro[3,2-b]furan-3-ol (**2**) presented in the following table.

Groups (two students)	Yield (% product **1**)	Yield (%product **2**)	Global yield
1	33%	57%	19%
2	15%	64%	10%
3	22%	84%	19%
4	38%	54%	21%

In this experiment the students can use the IR and ^{1}H NMR spectroscopies to describe the purified products of both reactions.

Phase transfer catalysts facilitate the contact of the water soluble isomannide, in aqueous phase to allyl bromide solubilized in dichloromethane, in organic phase. Phase transfer catalysts are known to accelerate reaction rates and minimize solvent waste, since the reactions tend to be heterogenous. Allyl bromide is soluble in organic phase and the reaction take place in the interphase. The syn addition of hydrogen to the double bound is achieved in the presence of the insoluble metal catalyst, palladium in the form Pd-C. Different catalysts[1] can be used in the hydrogenation reaction.

In the presence of a metal catalyst, the H-H bond in H_2 cleaves and each hydrogen atom attaches to the metal catalyst surface, forming metal-hydrogen bonds. The metal catalyst also absorbs the alkene onto its surface. A hydrogen atom is then transferred to the alkene, forming a new C-H bond. A second hydrogen atom is transferred forming another C-H bond. At this point, two hydrogens have added to the carbons across the double bond. Because of the physical arrangement of the alkene and the hydrogens on a flat metal catalyst surface, the two hydrogens must add to the same face of the double bond.

Both reactions are followed by TLC (experimental procedure). The reactions are stopped when the starting materials are absent from the corresponding chromatogram. At this time the reaction mixtures are worked-up.

Infra-Red spectra

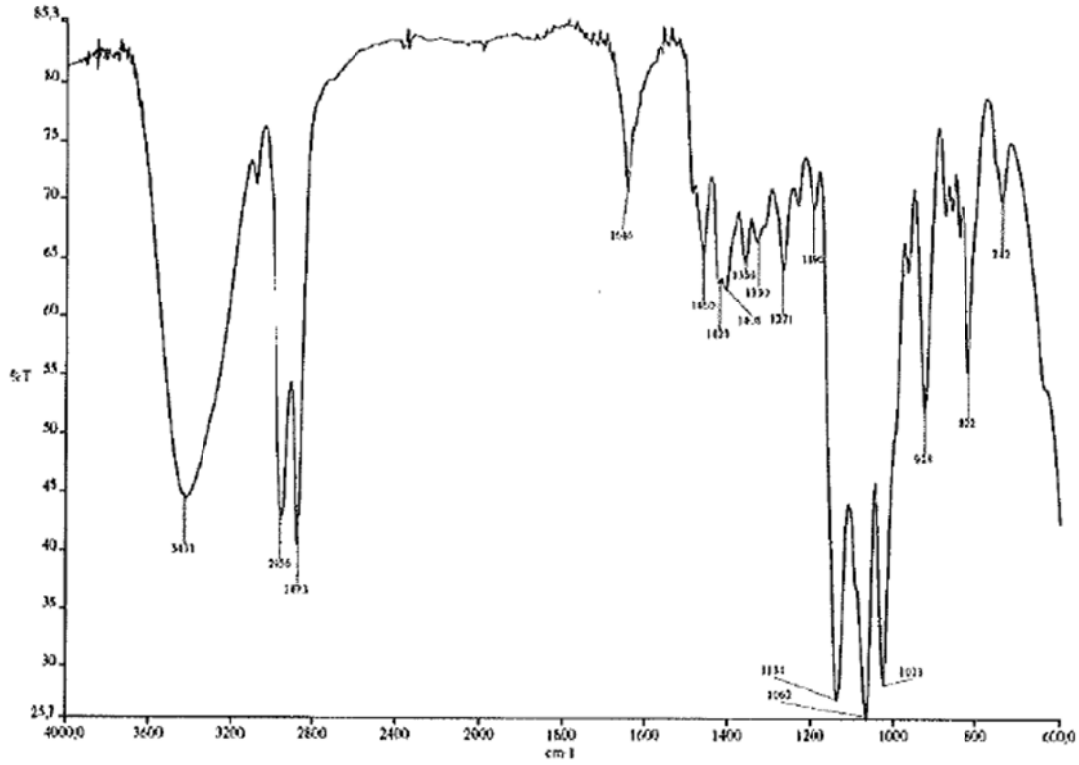


Figure SM 2.1.9.1 – IR spectrum of (3*R*,3a*R*,6*R*,6a*R*)-6-propoxyhexahydrofuro[3,2-b]furan-3-ol (film NaCl)

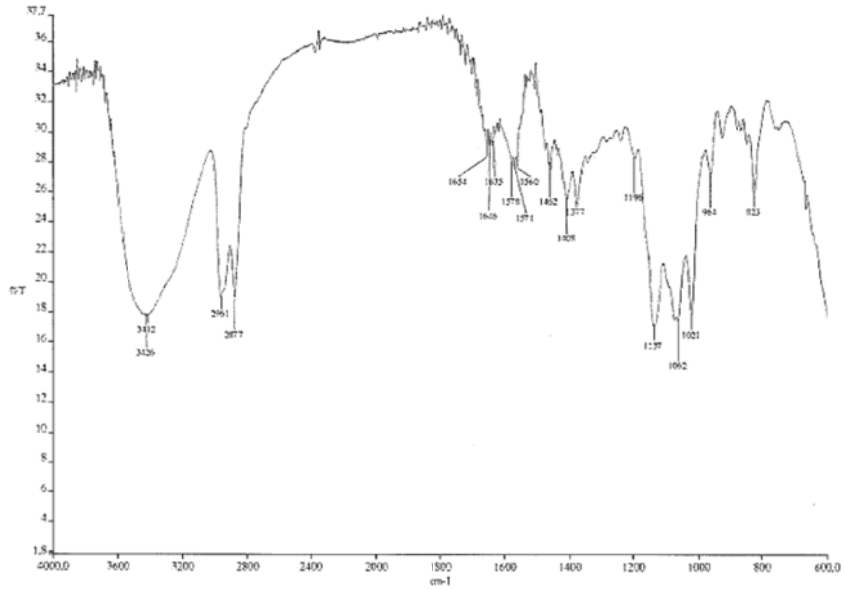


Figure SM 2.1.9.2 – IR spectrum of (3*R*,3a*R*,6*R*,6a*R*)-6-(allyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (film NaCl).

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

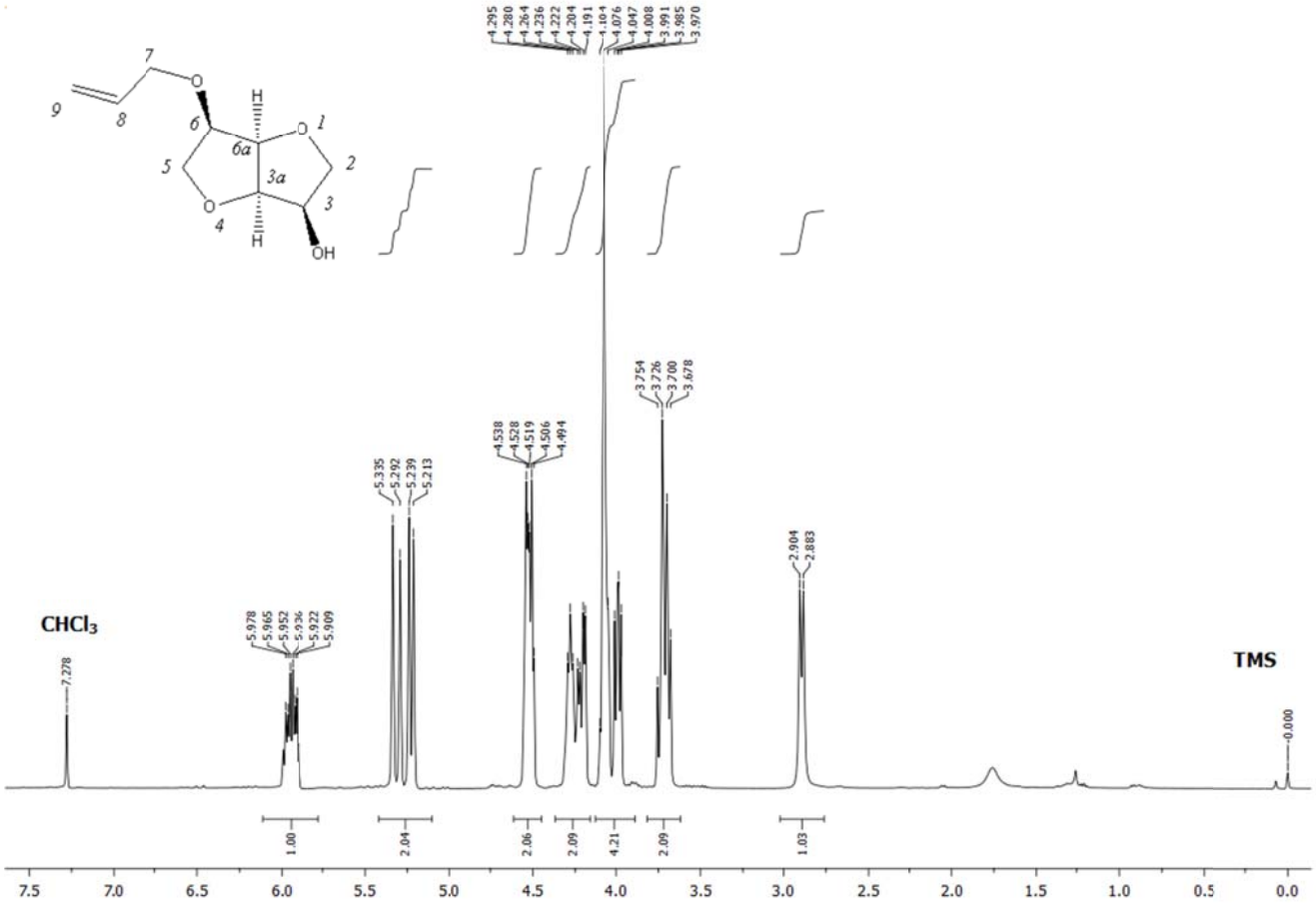


Figure SM 2.1.9.3 – ^{1}H NMR spectrum (400MHz, $CDCl_3$) of (3*R*,3a*R*,6*R*,6a*R*)-6-(allyloxy)hexahydrofuro[3,2-*b*]furan-3-ol with tetramethylsilane as internal standard.

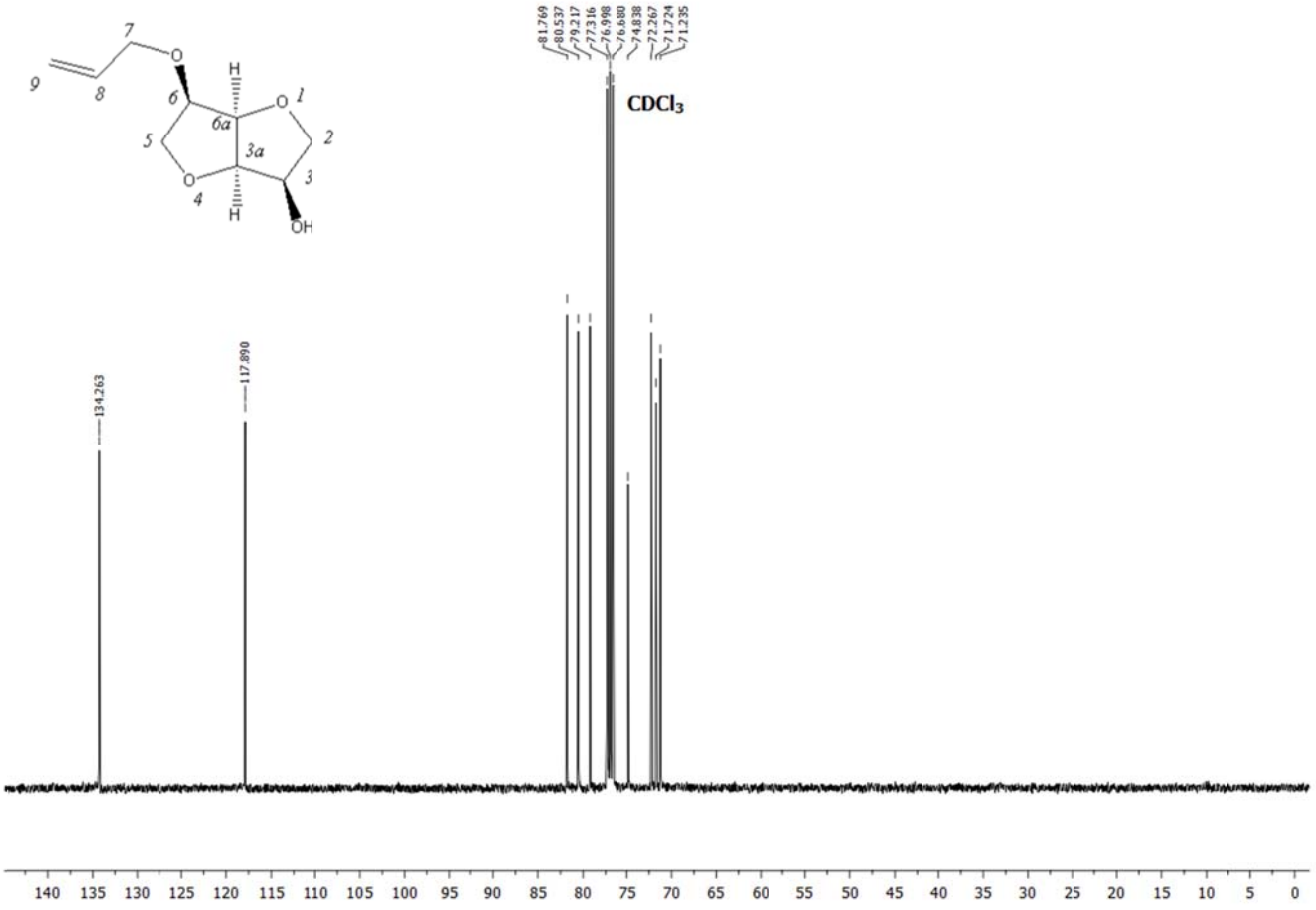


Figure SM 2.1.9.4 – ^{13}C NMR spectrum (100MHz, $CDCl_3$) of (3*R*,3a*R*,6*R*,6a*R*)-6-(allyloxy)hexahydrofuro[3,2-*b*]furan-3-ol.

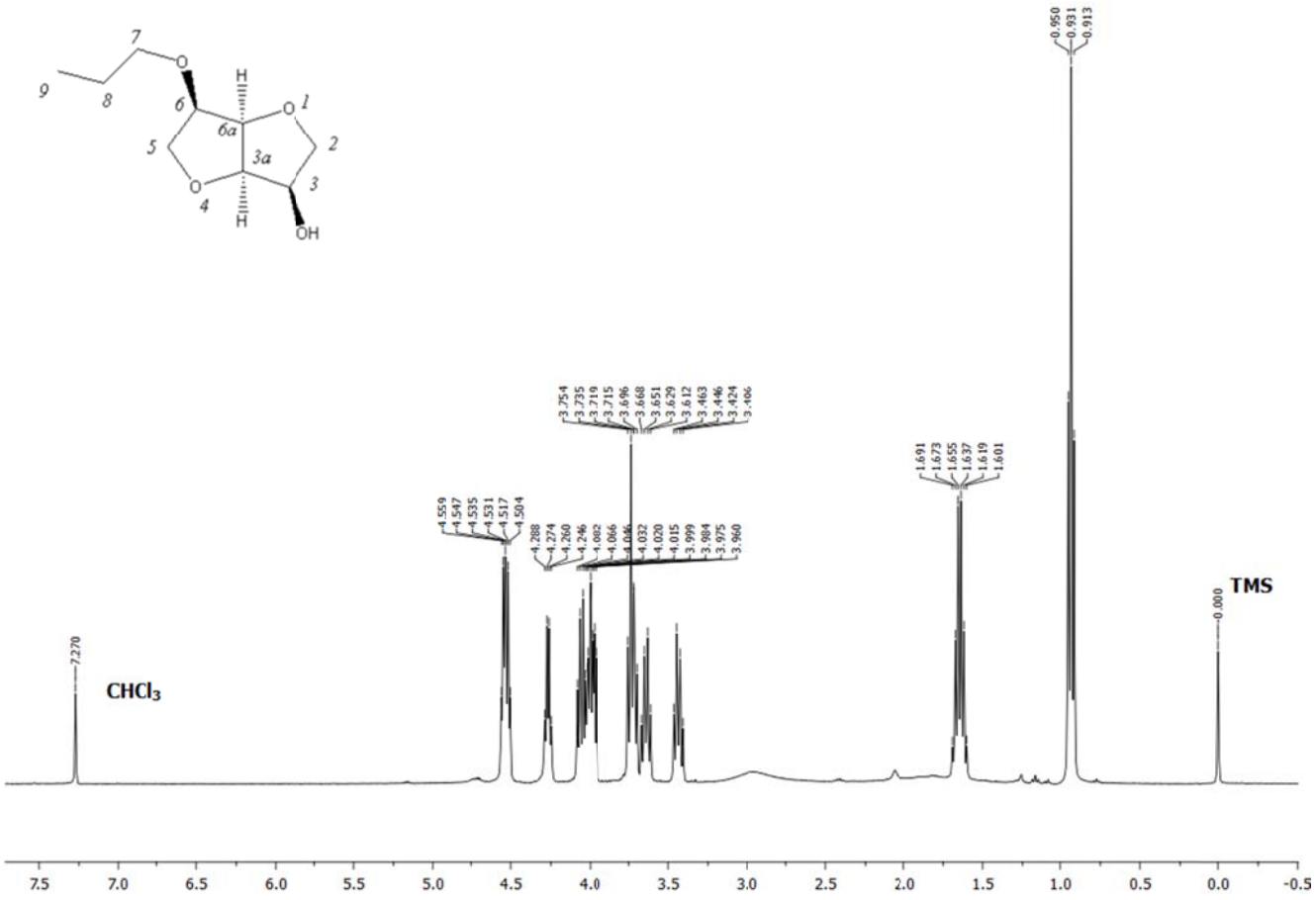


Figure SM 2.1.9.5 – ^{1}H NMR spectrum (400MHz, $CDCl_3$) of (3*R*,3a*R*,6*R*,6a*R*)-6-propoxyhexahydrofuro[3,2-*b*]furan-3-ol with tetramethylsilane as internal standard.

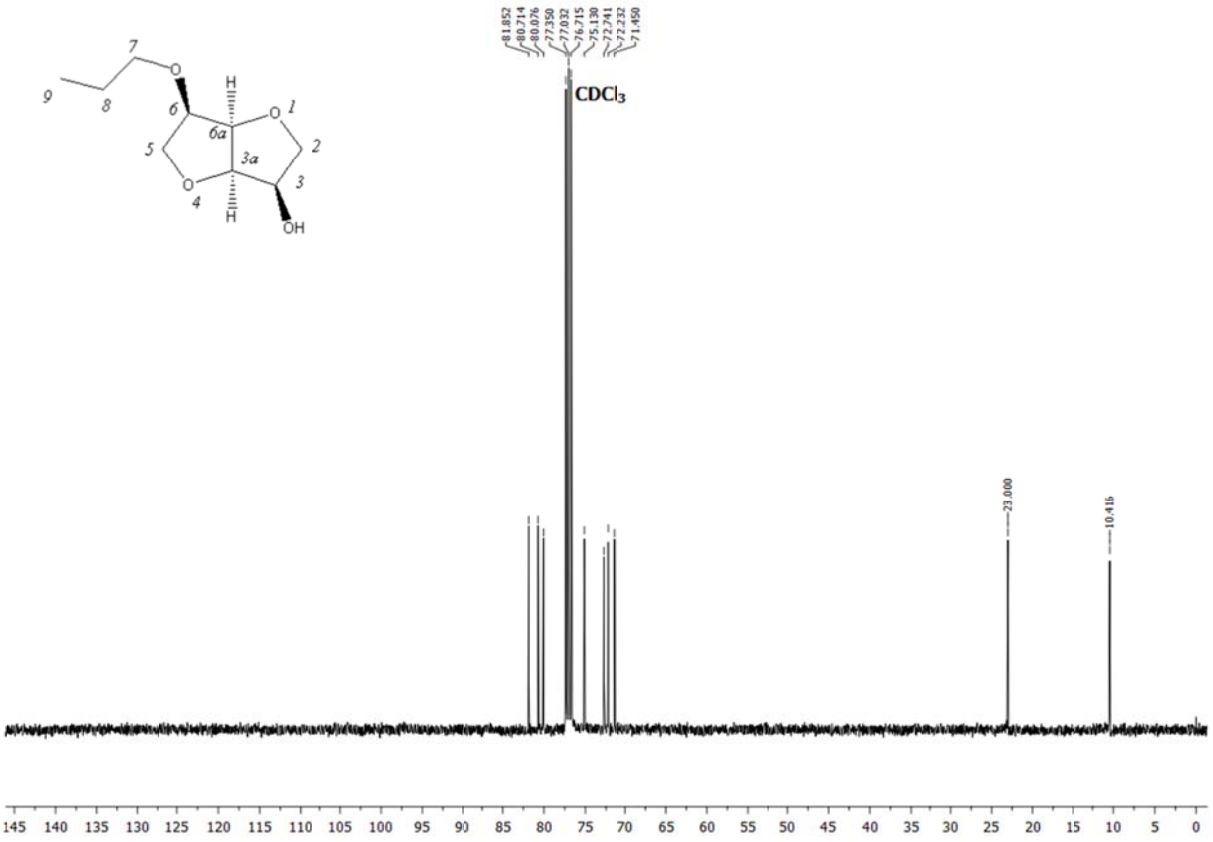


Figure SM 2.1.9.6 – ^{13}C NMR spectrum (100MHz, $CDCl_3$) of (3*R*,3a*R*,6*R*,6a*R*)-6-propoxyhexahydrofuro[3,2-*b*]furan-3-ol.

1. D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621-6686.

Regioselective *N*-alkylation of adenine by nucleophilic substitution

Supplementary Material

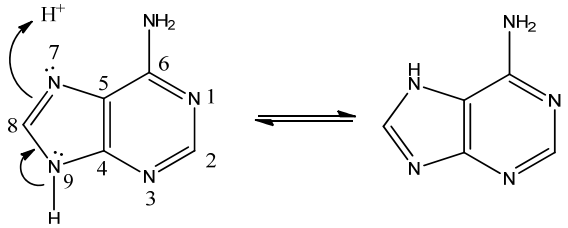
After some reaction conditions optimization, the product was obtained in 0.23-0.24 g (= 49-50 %) as a white powder. The alkylation of the adenine was followed by TLC (Figure 1) and ^{1}H NMR (Figure SM 2.1.10.4) and was completed in 16 h. This experiment was reproduced by a master student of pharmaceutical science (obtained yield of 50%).

The optimization of this experiment in order to become feasible and in the teaching laboratory was performed by changing some experimental conditions such as temperature, bromide equivalents and also by improving the purification method. The literature only provides synthetic conditions for the derivatization of adenine with mono-halogens[1] and our strategy of using a di-bromide allows to obtain a modified adenine that is suitable for further linkage to platforms such as polymers or other molecules. We first started using 2 equivalents of 1,3-dibromopropane relatively to adenine. The insolubility of potassium carbonate, K_2CO_3, in DMF does not allow to understand if adenine was completely solubilized in the quantity of solvent used. At the end of the reaction we filter the precipitate and analyze by TLC the content of the solid and the solution and observed that both had the same composition. So we decided to evaporate DMF after completion of the reaction instead of filter to obtain a higher yield. The evaporation could be performed faster and efficiently by using a piece of paper between the round-bottom flask and the adapter that will be used in the rotary evaporator and use 100 mbar of pressure (Figure SM 2.1.10.2). This procedure avoids the condensation of the DMF in the rotary conducting glass tube of the rotary evaporator because a small stream of air helps to drag the solvent through the rotary. First we tried to wash the solid with acetone, filter and then concentrate the solution and further wash the solid with MeOH to obtain the product with a 16% of yield. Another strategy was to extract the product with brine solution and CH_2Cl_2 and we observed the formation of a precipitate in the organic layer that complicated the extraction. We collected the organic layers and to avoid losing product we dissolved the precipitate with acetone before filtration. By proceeding with the purification by chromatographic column and the final product was obtained in a yield of 27%. Once this is not satisfying, before adopting a new strategy we started to test the solubility of the product in several solvents and only became soluble in CH_2Cl_2/MeOH 10:1 solution, DMF and DMSO. The subsequent strategy was to increase the temperature of the reaction to 50 ˚C but we observed the degradation of the product after its formation and more secondary products were formed. In addition, we increased the equivalents of 1,3-dibromopropane relatively to the adenine. We used 3 mole equivalents of bromide and for the purification we first evaporated the solvent, washed the solid with a solution of CH_2Cl_2/MeOH 10:1, filter and concentrate and then proceed with chromatographic column

to obtain the product with a 35% yield. With this result we increased to 5 mole equivalents of bromide and used the same purification procedure obtaining a 50% of yield. For these two last reactions, comparatively to the one using 2 equivalents of bromide, we observed by TLC that the spot that appeared in the base that most probably could be the adenine dimer is less intense, which is in accordance with the expected. The purification of the product proceeded by chromatographic column and it was necessary to first start only with CH_2Cl_2 as eluent to eliminate the excess of 1,3-dibromopropane and then change to CH_2Cl_2/MeOH 10:0.5. The final product is only soluble in a solution of CH_2Cl_2/MeOH 10:0.5 and in DMF and DMSO. Adenine is mostly soluble in polar solvents such as water, DMF and DMSO. The introduction of an apolar alkyl chain in the purine decreased the polarity of the compound making it also soluble in a CH_2Cl_2/MeOH mixture.

By ^{1}H NMR it is possible to confirm the successful alkylation of the adenine once the peak related with the N-9 disappears (Figure SM 2.1.10.4) when compared with the initial adenine (Figure SM 2.1.10.3). Also, three new peaks appear at 2-4.5 ppm relative to the protons of the alkyl chain. The initial 1,3-dibromide has only two peaks in the ^{1}H NMR but after the reaction with adenine, the protons of the carbon that bounds to the nitrogen originate a new signal.

The NOESY is one of the most useful tools to confirm which of the nitrogen atoms was bounded to the alkyl chain. By ^{1}H NMR (Figure SM 2.1.10.3) we confirm that the alkylation did not occurred in the –NH_2 group. Adenine could rapidly be interconverted in another tautomer as scheme 1 shows and this could lead to a wrong attribution of the final compound. Additionally, the confirmation that the alkylation occurred in the N-9 instead of N-7 is given in the NOESY spectrum where we do not observe correlation between the protons of the alkyl chain and the protons of the primary amine (Figure SM 2.1.10.5).



Scheme SM 2.1.10.1. One possible interconversion of adenine.

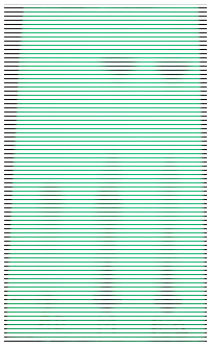


Figure SM 2.1.10.1. TLC for the reaction of adenine alkylation after 16 h (right) and comparison with adenine (left). In the middle is the application of the two samples, left and right.

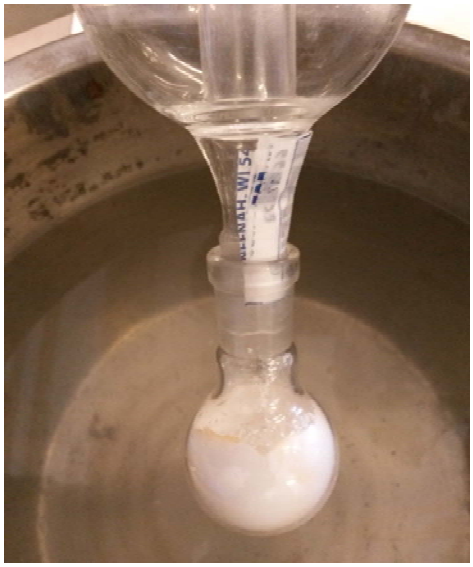


Figure SM 2.1.10.2. Strategy for the evaporation of DMF in the rotavapor.

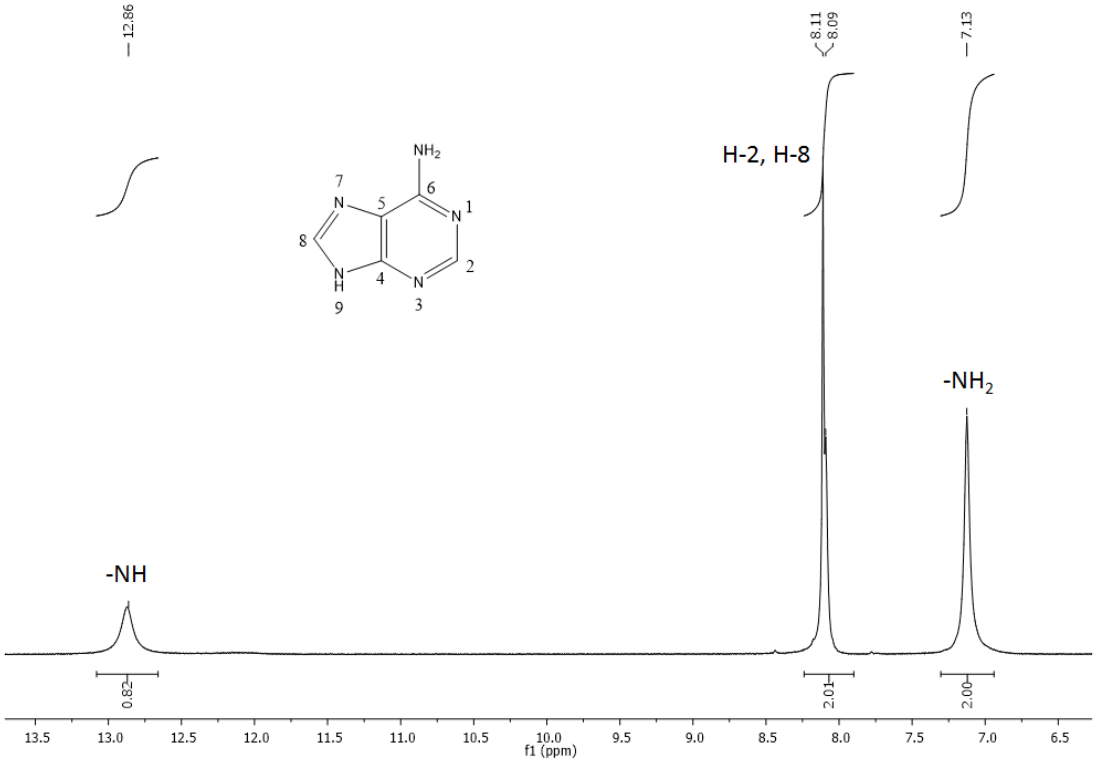


Figure SM 2.1.10.3. ^{1}H NMR (DMSO-d_6) spectrum of commercial adenine.

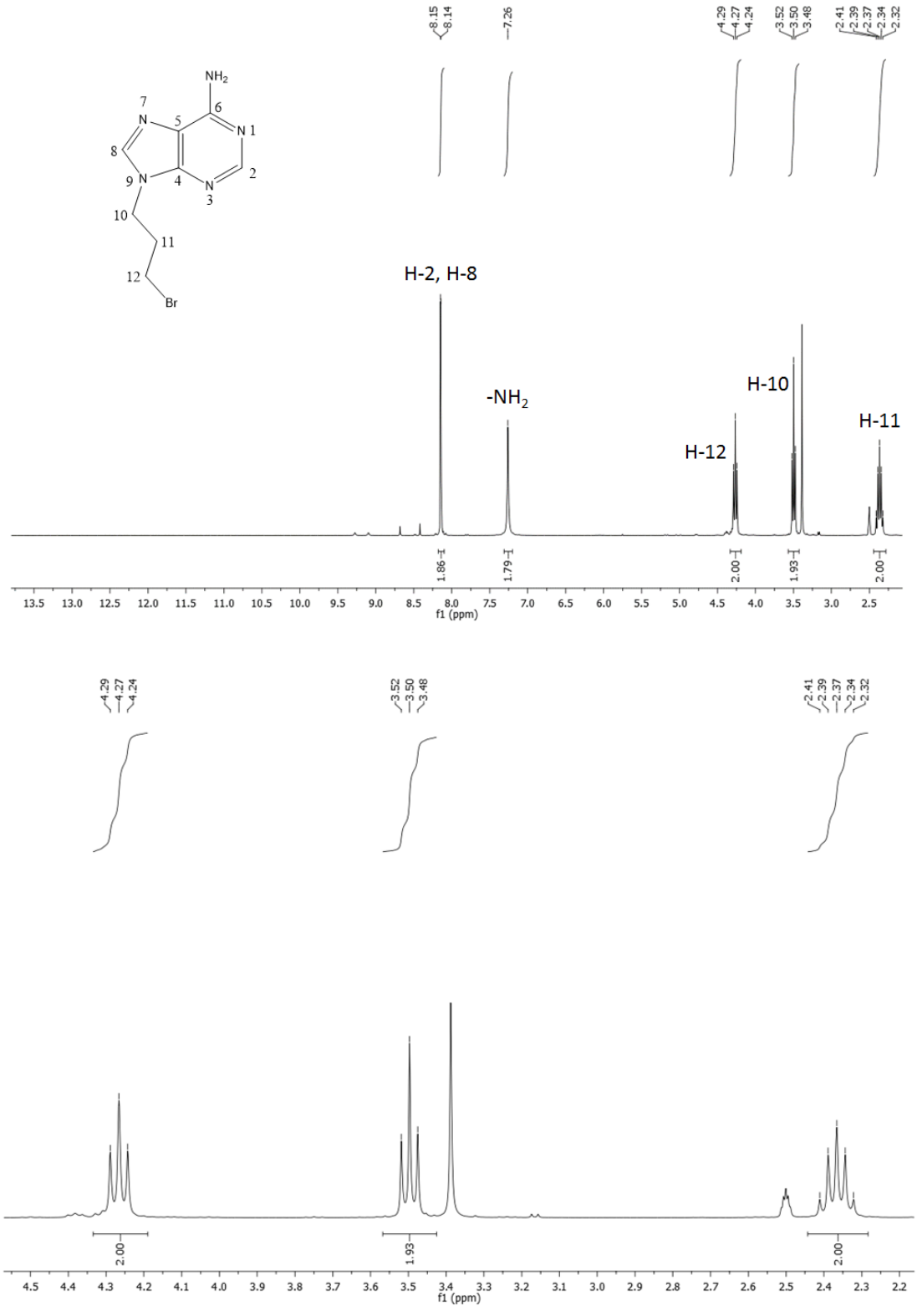
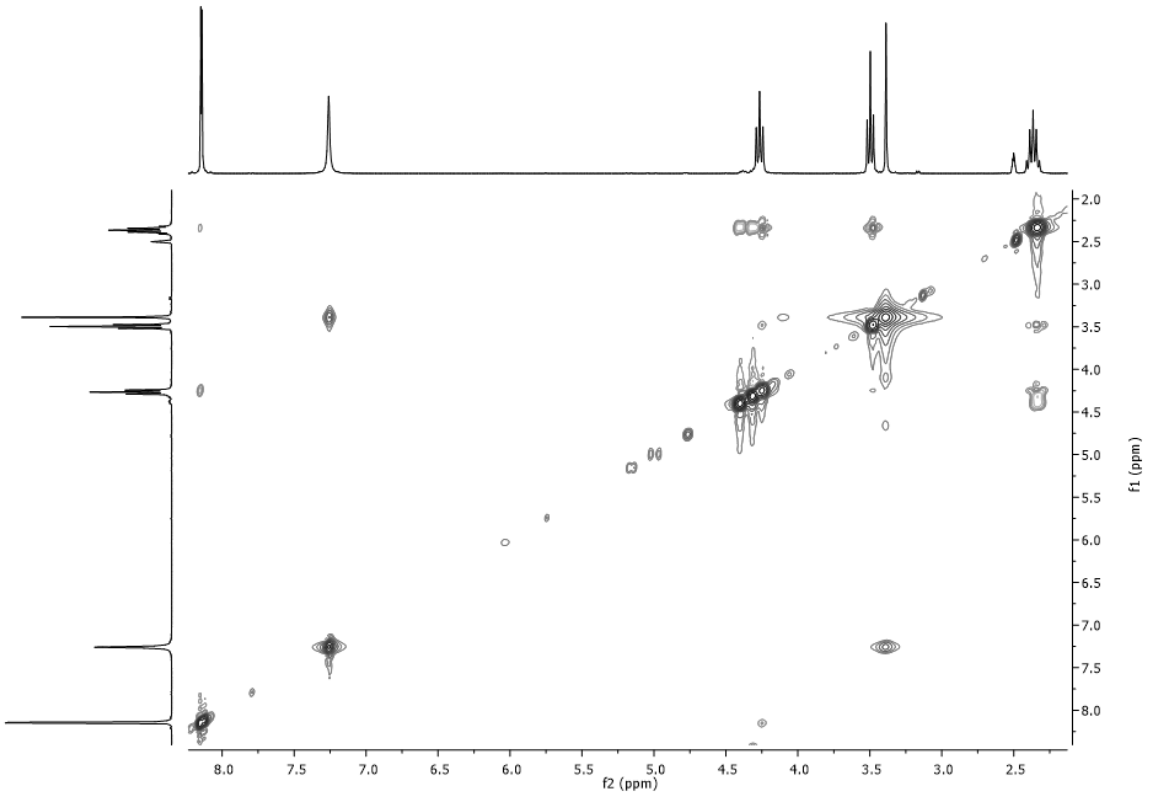


Figure SM 2.1.10.4. ^{1}H NMR (DMSO-d_6) spectra of the product obtained from adenine alkylation.



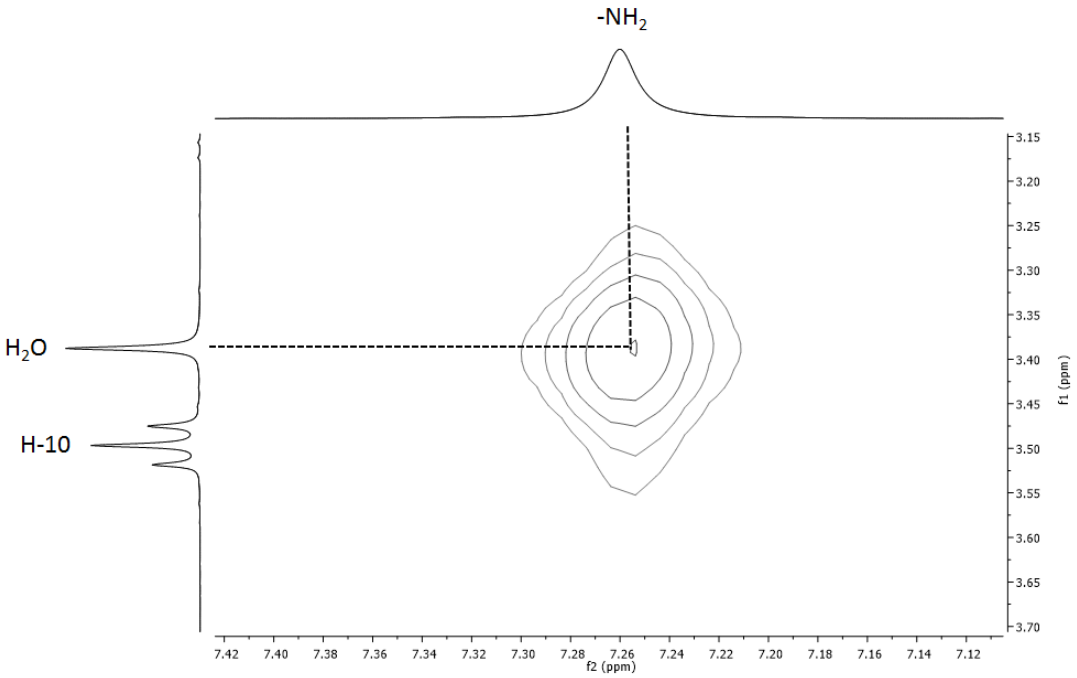


Figure SM 2.1.10.5. NOESY NMR (DMSO-d_6) spectra of the product obtained from adenine alkylation

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[1] a) Kumaresh Ghosh, Tanushree Sen; *Beilstein J. Org. Chem.* 2010, 6, 44; b) S. G. Srivatsan, Masood Parvez, Sandeep Verma; *Chem. Eur. J.* 2002, 8, 22, 5184.

Gabriel synthesis of *n*-octylamine under phase transfer catalysis: the first step

Supplementary Material

Additional background/discussion to be optionally delivered to the student

The choice of the solvent is crucial, as in all S_N2 reactions.

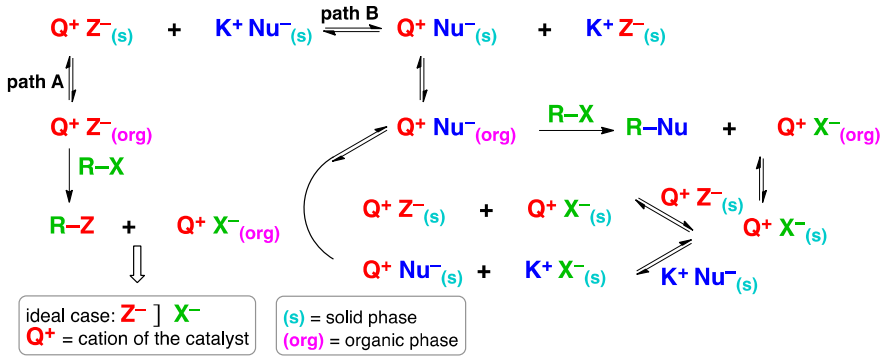
- ✓ Protic solvents are able to efficiently solvate both the anion and the cation. Contrary to what happens in S_N1 reactions, the beneficial solvating effect is higher for the reagents than for the transition state. Even if these solvents better solubilize the reagents the activation energy increases and therefore the reactions become slower.
- ✓ Dipolar aprotic solvents, such as *N*,*N*-dimethylformamide, can be used instead, because they are able to efficiently solvate only the cation, thus leaving the naked anion free to react. However, also with these solvents, the reaction times could be too long for a students experiment. Moreover, these solvents cannot be easily evaporated under reduced pressure and thus an extractive work up must be performed with care in order to completely remove them from the organic extracts.

An efficient alternative is represented by phase-transfer catalysis. The catalysts employed are typically ammonium or phosphonium salts where the cation is soluble either in water or in an organic solvent, even if of low polarity. This property makes them suitable for either liquid-liquid or solid-liquid transfer, as illustrated in Scheme SM 2.1.11.1.

Scheme SM 2.1.11.1. Liquid-liquid and solid-liquid phase-transfer catalysis.

In the reaction described in this experiment the solid-liquid catalysis is used and the mechanism can be summarized as reported in Scheme SM 2.1.11.2. The catalyst may migrate from the solid phase to the solution and use its counterion as nucleophile (**path A**), affording R–Z. This is not a problem when X = Z, because the same product as the reacting halide is obtained. If the catalyst with same counterion as the leaving group is not available, a good solution is to use a non nucleophilic

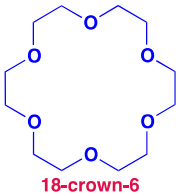
counterion (as HSO_4^-). If **path B** is followed the catalyst may exchange its counterion with the nucleophile through an equilibrium reaction. This path is more favorable, because of the large excess of the nucleophile with respect to the catalyst.



Scheme SM 2.1.11.2. Catalytic cycle.

Part of the nucleophile can go into the organic phase where the reaction occurs, releasing the catalyst with a different counterion. The latter can return to the solid phase, giving the two equilibrium reactions depicted in Scheme SM 2.1.11.2. When the nucleophile replaces X^- or Z^-, the reactive species is regenerated and the catalytic cycle can start again. A similar process occurs if the liquid-liquid catalysis is employed, with the difference that the catalytic cycle starts with the catalyst in the aqueous phase.

Finally, also crown ethers may be used as catalysts. They are able to form a complex selectively with a specific cation, leaving the anion unsolvated and naked. The structure of 18-crown-6, which selectively coordinates potassium is reported in Scheme SM 2.1.11.3. This ether is however quite expensive, about six times more expensive than the employed phosphonium salts (comparison based on cost/mols). Its employment must therefore be limited to very specific cases where other activations failed.



Scheme SM 2.1.11.3. An example of crown ether.

Note to the instructor

General

This experiment has been given for several years to students of the second year of bachelor course in Chemistry. Typically classes of 25-32 students were hosted at a time in the laboratory.

The second year bachelor students in Chemistry had already attended a complete course of Organic Chemistry during the first year.

For these experiments, students typically work in pair. This is particularly useful during the chromatography. Actually, while one student collects the fractions, the other one spots the TLC plates.

In our lab we use flat-bottomed flasks in order to heat them directly with a stirring hot plate. However, if other heating means are used (e.g. sand baths, oil baths), round-bottomed flasks are equally suitable.

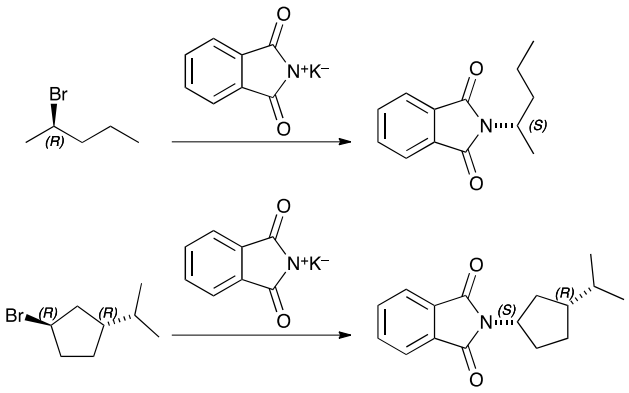
The use of a Büchner funnel for the filtration is not recommended in this step, because the filtration is more difficult: the solution is too viscous and the filtration becomes slow. In addition, often part of the salts passes into the receiving flask with this crude.

Typical yields are between 70 and 95% and the melting point is 45-47 °C.

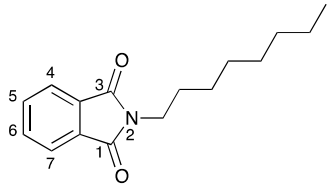
The R_f of *N*-octylphthalimide and of the potassium phtalimide conjugate acid are 0.54 and 0.23 respectively, using petroleum ether/diethyl ether 7:3 as eluent. The spots can be detected with the UV lamp.

Hints to answer questions

- ✓ Why does the phase transfer catalyst improve the reaction rate? It transfers the phthalimide anion into toluene as an unsolvated, more reactive, nucleophile. The cation is quite encoumbered and therefore the interaction with the reacting anion is only weak, which enhances its nucleophilicity.
- ✓ Which is the composition of the filtered solid? KBr and the unreacted excess of potassium phthalimide.
- ✓ Calculate the overall yield. In addition, using your TLC, calculate the R_f for both *N*-octylphthalimide and phthalimide. Why is the R_f of *N*-octylphthalimide greater than the one of phthalimide? *N*-octylphthalimide is less polar because of the presence the long hydrocarbon chain which prevents also hydrogen bonding with silica gel through the NH group.
- ✓ Why is KOH a base strong enough for transforming phthalimide into the conjugated base? pK_a of phthalimide is 8.3, which renders this species much more acidic than water (pK_a 15.7), the conjugate acid of hydroxide.
- ✓ In your opinion is it possible to use $KHCO_3$ or KNH_2 to obtain potassium phthalimide? $KHCO_3$ is unsuitable because pK_a of H_2CO_3 is 6.35. KNH_2 is suitable because pK_a of NH_3 is ≈ 35.
- ✓ Which product do you expect to isolate performing the same reaction on: a) (*R*)-2-bromopentane; b) (1*R*,3*R*)-1-bromo-3-isopropylcyclopentane? Consider also the stereochemical issues.



^{1}H-NMR SPECTRUM OF *N*-OCTYLPHTHALIMIDE



The ^{1}H-NMR spectrum of a sample prepared by the students was recorded on a 300 MHz spectrometer in $CDCl_3$, with tetramethyl silane as internal standard.

Interpretation: 0.87 (3 H, t, J = 6.8 Hz, C*H*$_3$); 1.20-1.40 (10 H, m, C*H*$_2$); 1.67 (2 H, broad quintuplet, J = 7.3 Hz, NCH$_2$C*H*$_2$); 3.67 (2 H, t, J = 7.2 Hz, NC*H*$_2$CH$_2$); 7.69-7.72 (2 H, m, H-5 and H-6); 7.83-7.86 (2 H, m, H-4 and H-7).

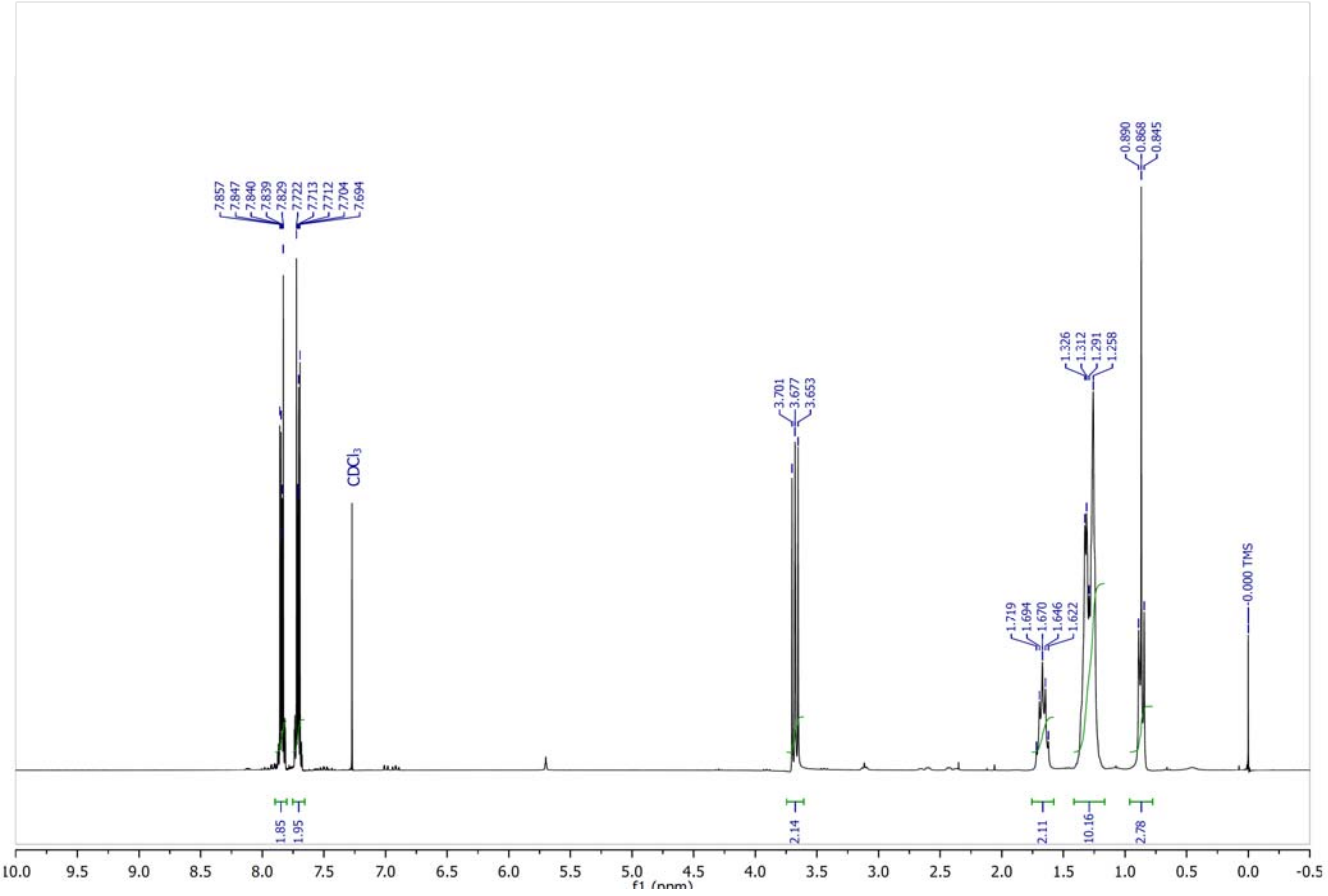


Figure SM 2.1.11.1 ^{1}H NMR, $CDCl_3$ (300 MHz) of product

PICTURES

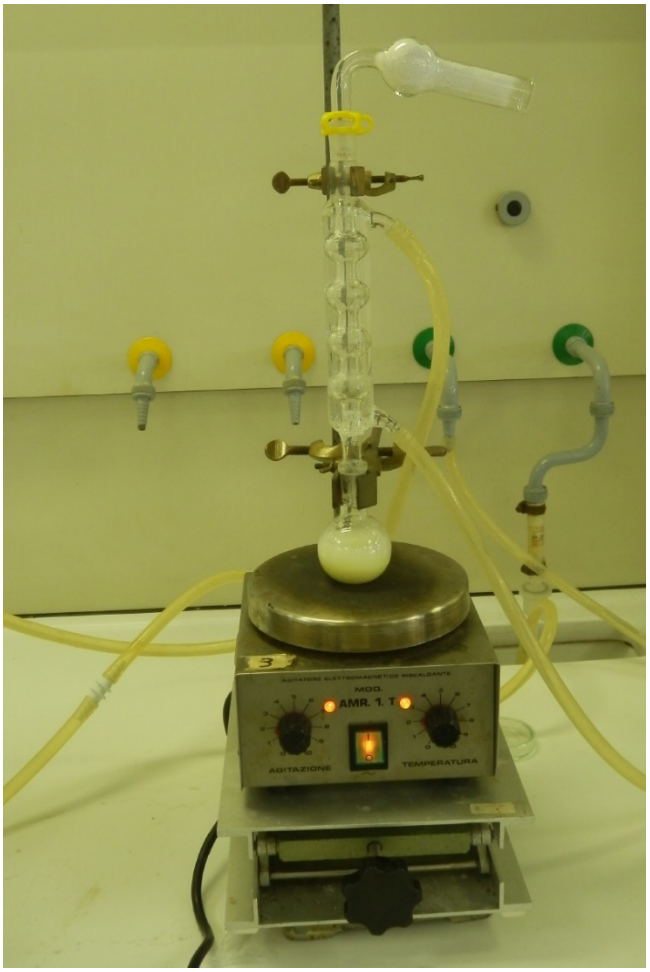


Figure SM 2.1.11.2 Glassware assembly for heating at reflux

Figure SM 2.1.11.3 Column chromatography

Figure SM 2.1.11.4 The final product after chromatography

Preparation of Diethyl 2,3-O-isopropylidene-L-tartrate

Supplementary Material

The purpose of this experiment is to introduce an undergraduate student to a classical set-up of an organic chemistry laboratory, namely a reaction under reflux employing a Dean-Stark apparatus (Figure SM 2.1.12.1).[1] In addition, the context of the synthesis introduces also a typical protection strategy of 1,2-diols *en route* to an important chiral enantiopure molecule, (-)-TADDOL (*cf.* exp. 4.2.1.5).[2]

The duration of 3h for the reflux is generally enough for reaction completion (Figure SM 2.1.12.2). If necessary, the reaction can also be conducted for longer periods (~12h) without any prejudice on the outcome. The change of color from transparent to dark yellow during the heating process is a good sign that the reaction is evolving as expected (Figure SM 2.1.12.3). The yields calculated based on the crude reaction mixtures obtained are generally good to excellent (82-99% yield, 3rd year undergraduate students), where the losses are in most of the cases attributed to the extraction process (Figure SM 2.1.12.4).

The reaction scale was designed in order to challenge the experimentalist to train the manipulation of chemicals in a reasonable small scale. This will be an invaluable skill when working on real research problems later on. Nevertheless, if necessary, this protocol can also be employed in gram-scale, with similar results.

L-(+)-Diethyl tartrate is a viscous oil. It is more practical to weight it on a balance using a pipette, rather than using a syringe. It is not necessary to conduct the reaction under an inert atmosphere.

The reaction can be performed without a Dean-Stark apparatus, only by heating the reaction mixture to the reflux of toluene. The yields of crude materials thus obtained are virtually identical to the previous ones. In this case, one observes only a slightly more important amount of the corresponding

transesterification product, where the MeOH liberated displaces an ethoxy group of the expected diethyl 2,3-O-isopropylidene-L-tartrate.[3] Regardless, this is of no consequence for the next step (*cf.* exp. 4.2.1.5), as the addition of phenylmagnesium bromide will produce exactly the same compound, (-)-TADDOL.

Regarding the experiment with a Dean-Stark apparatus, one can observe only small differences from experiment to experiment on the relative amount of the transesterified compound formed when compared to the expected diethyl 2,3-O-isopropylidene-L-tartrate.

The reaction has an approximate duration of 3h for completion. This session has a duration established of 5h to allow the students to have enough time to carefully set up the experiment, perform the work-up procedure and concentrate the combined organic phases from the extraction procedure.

Photo Gallery:

Figure SM 2.1.12.1: Reaction set-up

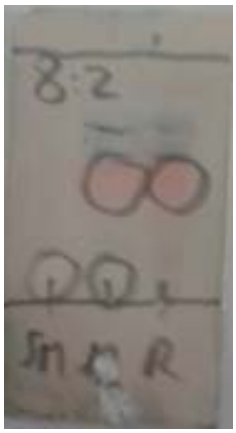


Figure SM 2.1.12.2: TLC at the end of 3h period
Left: SM, starting Material; Middle: M, mixture (SM + R); Right: R, reaction; Eluent: 8:2 Hexanes:AcOEt
Stain solution: 4-anisaldehyde

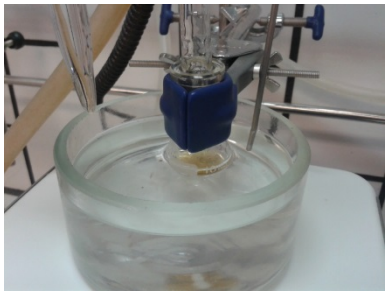


Figure SM 2.1.12.3: Closer look at the reaction mixture.
The reaction color changes from transparent to dark yellow upon heating

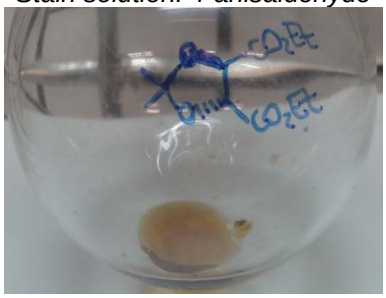


Figure SM 2.1.12.4: Crude reaction mixture after work-up and concentration under reduced pressure

Elements for answering the proposed questions:

1) What is the mechanism of the reaction performed?

Main product:

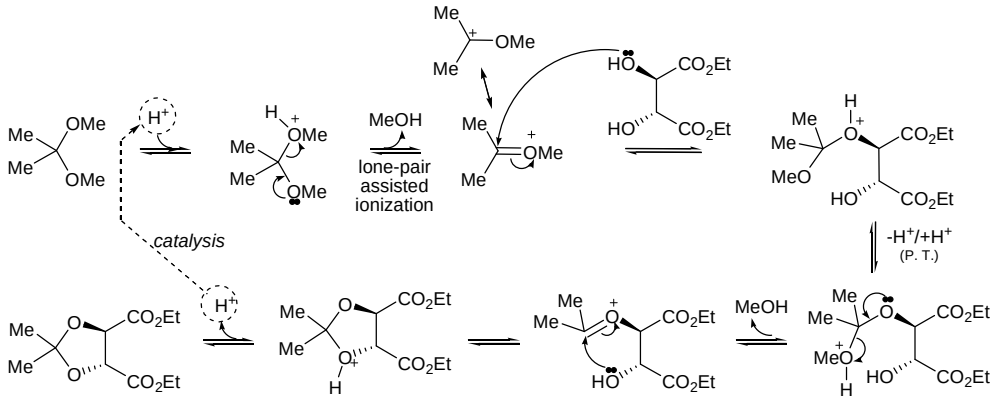


Figure SM 2.1.12.5: Reaction mechanism for transketalization

Transesterified product:

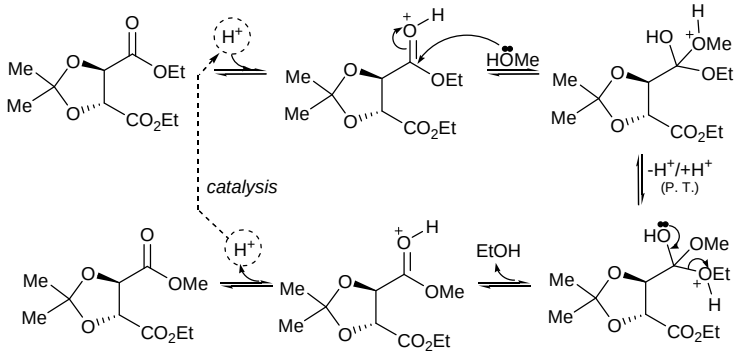


Figure SM 2.1.12.6 Reaction mechanism for transesterification

2) What is the importance of adding a saturated solution of $NaHCO_3$ at the end of the reaction?

It neutralizes the acid catalyst employed in the reaction. Ketals are stable under basic conditions, but unstable under acidic conditions.

3) Interpret the ^{1}H NMR of the crude reaction mixture obtained. What does the singlet at 3.8 ppm suggest? Is the presence of this second product a problem that hampers the use of the crude reaction mixture in the next step, without any purification?

It suggests that a methoxy group (MeO) was incorporated in the final compound. A closer inspection of other minor ^{1}H and ^{13}C NMR signals reveals the presence of a transesterification product (see attribution of NMR, Figure SM 2.1.12.7 and Figure SM 2.1.12.8), where one of the ethoxy groups (EtO) of Diethyl 2,3-O-isopropylidene-L-tartrate has been replaced by a methoxy group. The transesterified product does not hamper the next reaction, because this next step consists of a double Grignard addition to each ester group. Therefore, the same addition product is obtained starting from any of these two diesters.

^{1}H NMR (500MHz, $CDCl_3$)

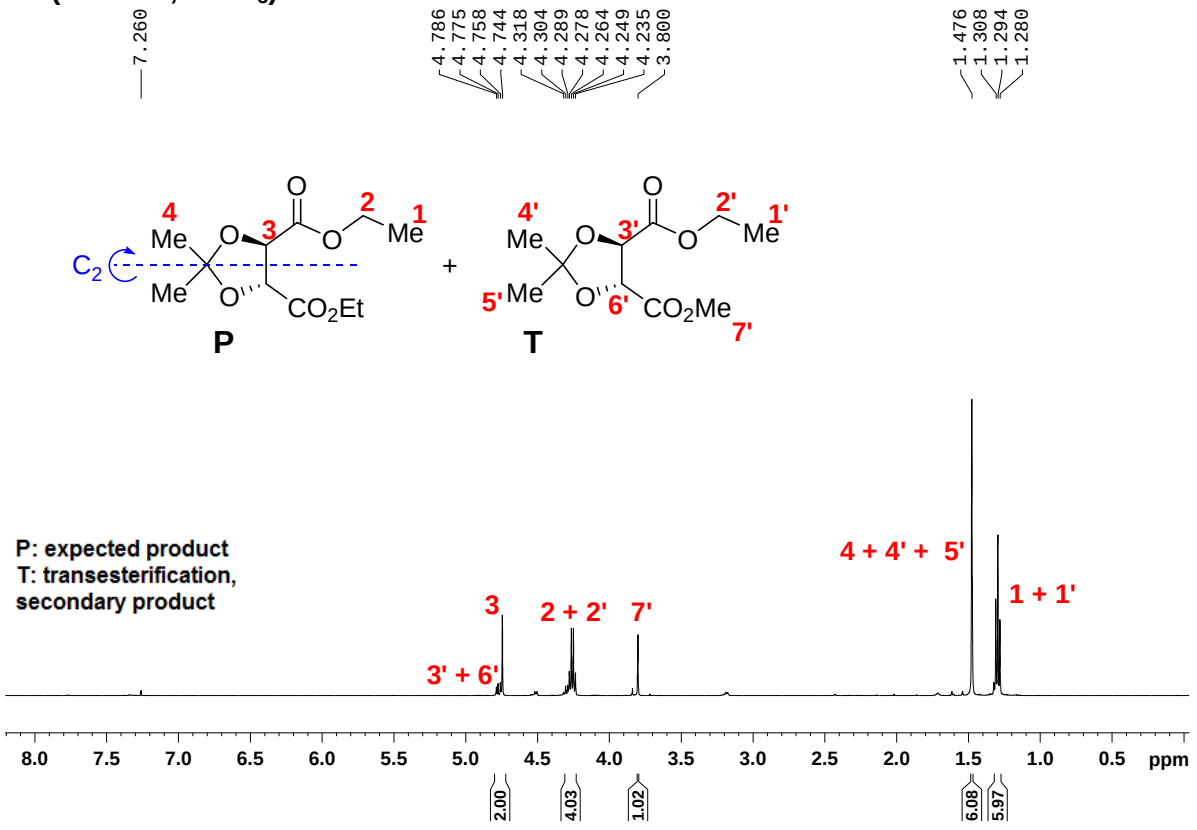
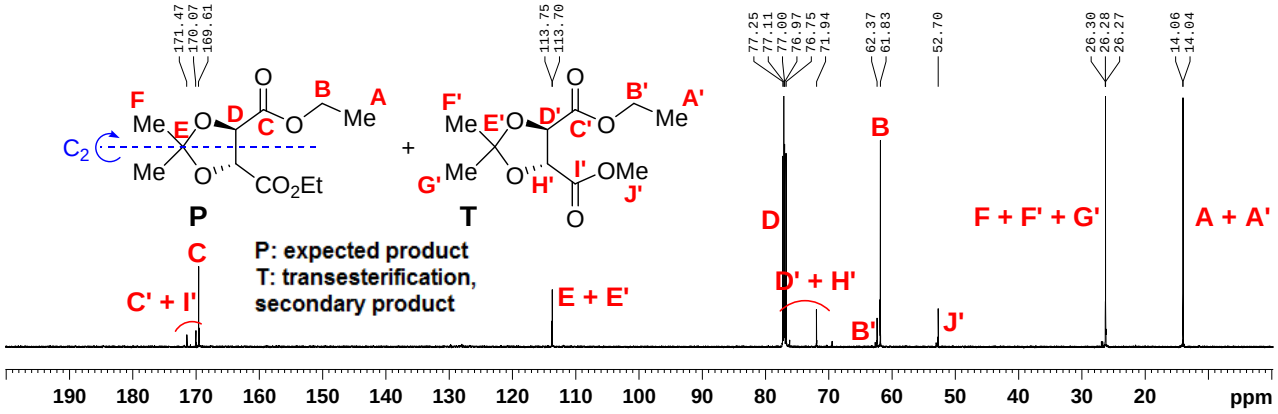


Figure SM 2.1.12.7: ^{1}H NMR of the crude reaction mixture for the synthesis of Diethyl 2,3-O-isopropylidene-L-tartrate.

^{13}C NMR (500MHz, $CDCl_3$)



DEPT-135 NMR (125MHz, $CDCl_3$)

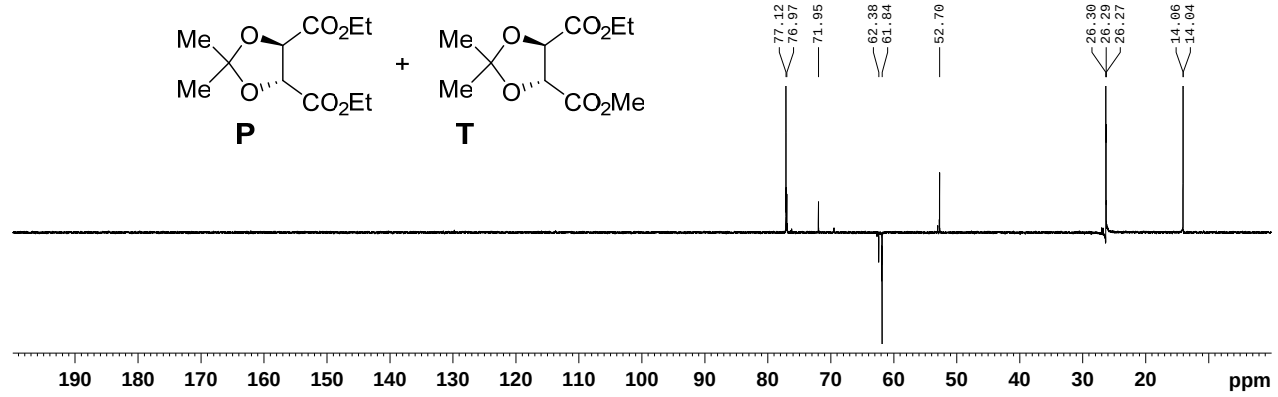


Figure SM 2.1.12.8: ^{13}C NMR and DEPT-135 NMR of the crude reaction mixture for the synthesis of Diethyl 2,3-O-isopropylidene-L-tartrate.

4) The same protected diester could be aimed if we had employed acetone instead of 2,2-dimethoxy propane under the very same reaction conditions. Explain why the transketalization procedure employed here is a better option.

The transketalization procedure using 2,2-dimethoxy propane is an entropically favoured process, while the ketalization employing acetone is not a especially favoured transformation

(As a consequence, transketalization procedures generally require milder conditions than ketalizations from ketones). Indeed, in both transformations one starts with two molecules, but when using 2,2-dimethoxy propane, one produces 2 molecules of methanol and the final ketal (3 molecules in total, Figure SM 2.1.12.9), *while when using acetone, one produces a molecule of water and the final ketal (2 molecules in total*, Figure SM 2.1.12.10).[4]

Using 2,2-dimethoxy propane:

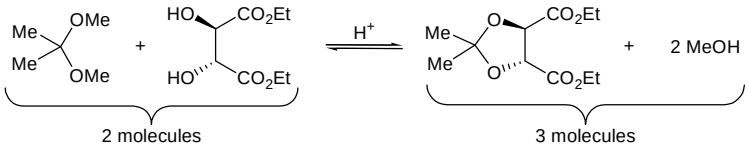


Figure SM 2.1.12.9: The transketalization process employing 2,2-dimethoxy propane.

Using acetone:

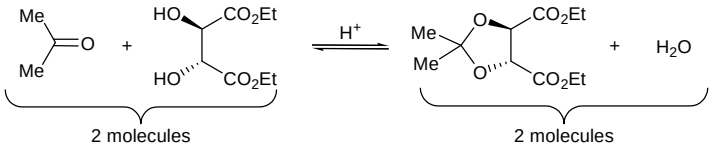
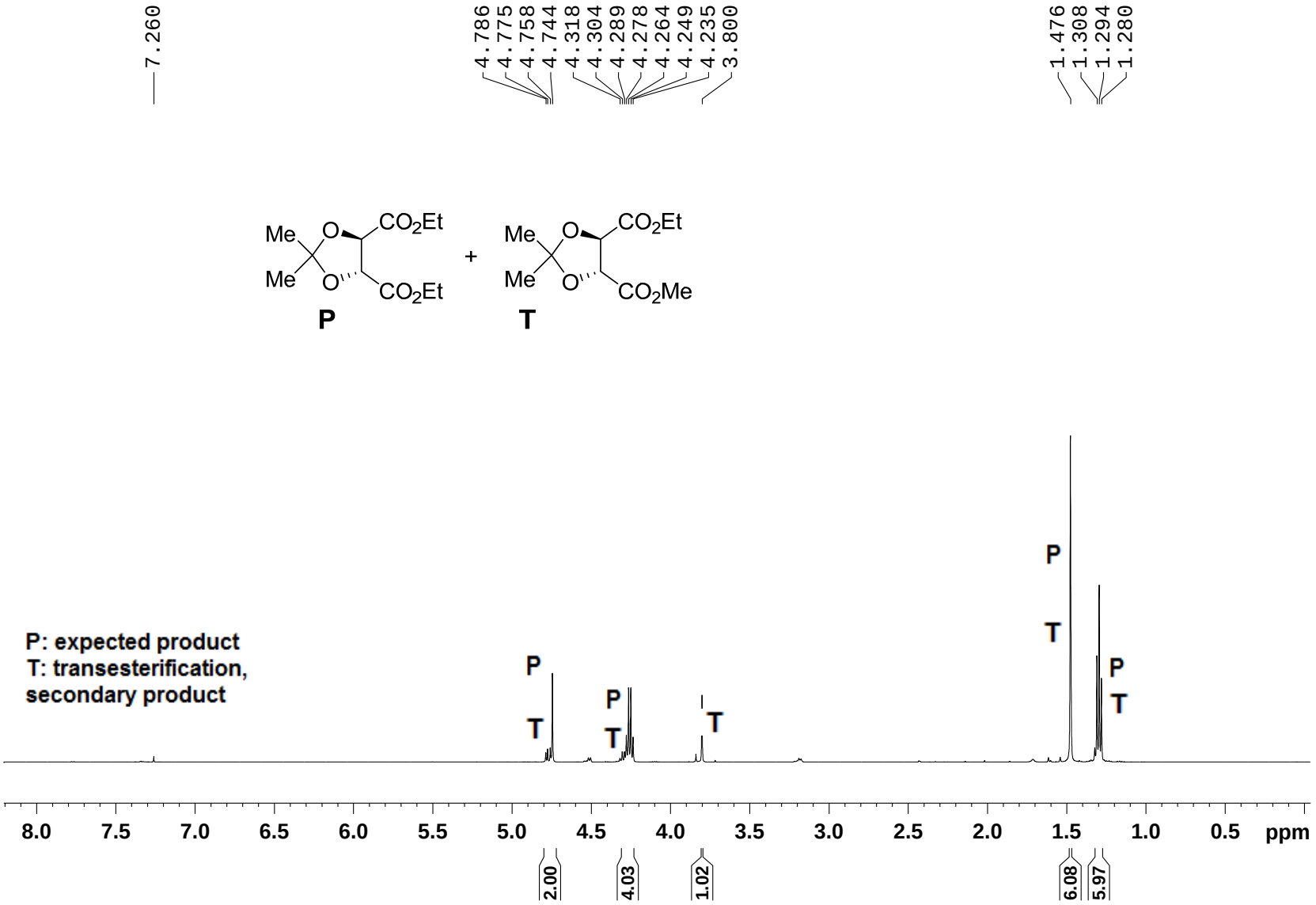


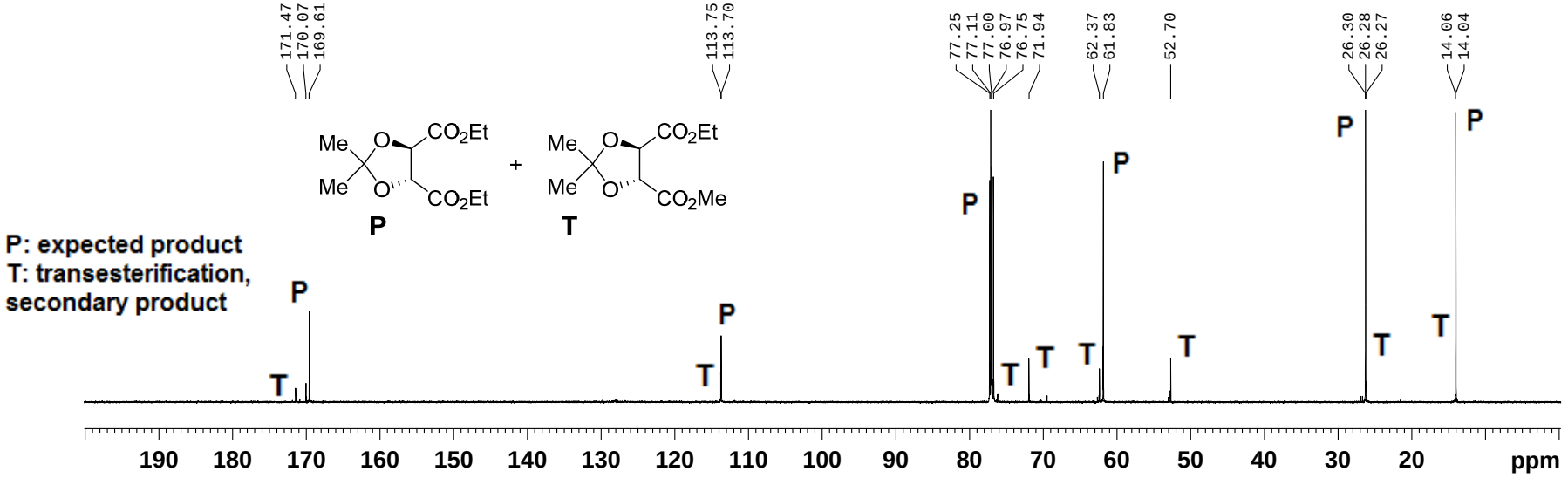
Figure SM 2.1.12.10: The ketalization process employing acetone.

NMR spectra:

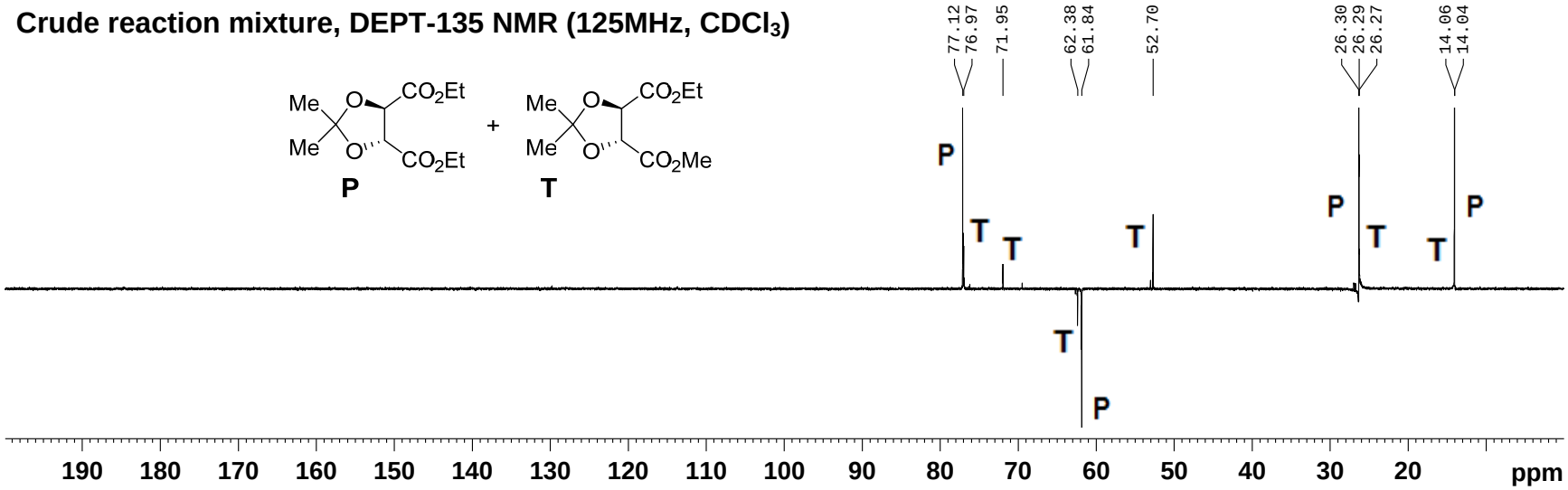
Crude reaction mixture, ^{1}H NMR (500MHz, $CDCl_3$)



Crude reaction mixture, ^{13}C NMR (500MHz, $CDCl_3$)



Crude reaction mixture, DEPT-135 NMR (125MHz, $CDCl_3$)



References:

[1] For an historical account on the development of this glassware, visit: http://www.rsc.org/chemistryworld/Issues/2010/June/DeanStarkApparatus.asp
[2] D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem. Int. Ed.* 2001, **40**, 92.
[3] a) M. Carmack, C. J. Kelley, *J. Org. Chem.* 1968, **33**, 2171. b) R. A. Fernandes, *Eur. J. Org. Chem.* 2007, **30**, 5064.
[4] For a complementary reading on this topic, see: J. Clayden, N. Greeves, S. Warren, *Organic Chemistry.* Oxford University Press, New York, 2nd *ed.*, 2012, chapter 12, 246-248.

Redox-neutral synthesis of a cyclic *N,O*-acetal from salicylaldehyde and 1,2,3,4-tetrahydroisoquinoline.

Supplementary Material

Experiment Notes

Figures

Our experimental procedure is designed to show undergraduate students the kind of interesting transformations they can effect in a laboratory setting using only simple starting materials and basic laboratory techniques. To successfully complete this reaction the students do not require advanced knowledge of organic chemistry, however an intermediate level of experience will be helpful to better appreciate the reaction fundamentals and principles behind the techniques involved (e.g. ^{1}H NMR spectroscopy, column chromatography).

This reaction can be run successfully in air. 3 Å or 4 Å powdered molecular sieves that have been activated at high temperatures (300 °C for 2 h) are preferable, although possible alternatives include replacing the molecular sieves with drying agents such as anhydrous magnesium sulfate or sodium sulfate. Without any drying agent to absorb water from the solution, the reaction progression slows significantly and product yields are low. Technical grade toluene is adequate for this reaction.

A slight excess of the 1,2,3,4-tetrahydroisoquinoline (1.3 equiv.) is necessary to suppress by-product formation under elevated temperatures. Only one equivalent of acetic acid is required to accelerate the reaction, although up to 1.3 equiv is tolerated without detrimental effect on the yield.

As the reaction proceeds, students should be able to observe several distinct color changes caused by the formation and disappearance of reactive intermediates: from colorless to bright yellow/orange followed by the color fading slightly. Extended heating of the reaction at 80 °C or above for more than 1 hour will lead to the formation of by-products and possible decomposition. If the reaction is stopped between 30 min and 1 hour it should still be possible to obtain moderate quantities of clean product.

To properly remove the molecular sieves, students should transfer the Celite powder to a fritted funnel and compress it to form a solid plug approximately 1 cm thick. When pouring the reaction solution onto the Celite, care should be taken so as not to disturb the integrity of the plug – a pipette is most suited to this. If Celite is not available in your laboratory, students can use filter paper instead to remove the molecular sieves from the reaction mixture.

When separating the organic and aqueous layers, keep in mind that the toluene/dichloromethane organic phase will sit above the aqueous layer and be bright orange in color. As a high-boiling point solvent, toluene is difficult to remove on the rotatory evaporator after the work-up. Students should set the temperature of their water bath to 50 °C and use low pressure settings for at least 5 minutes to ensure that all the solvent has been removed.

As the column chromatography progresses, the product appears as a bright yellow band in the silica gel, which is very easy for students to track by eye and collect. The product elutes as a colorless liquid.

Under vacuum conditions on the rotatory evaporator, the pure product should appear in the round bottom flask as a yellow oil that solidifies on standing to form a cream-colored solid. An advanced student should be able to obtain 70-90 % yield of the cyclic *N,O*-acetal product without impurities visible in the spectrum. This *N,O*-acetal is bench stable for several days.

This reaction procedure was tested by several undergraduate students at Rutgers, The State University of New Jersey (USA), the results of which are summarised in **Table SM 2.1.13.1**. Yields are

reported as the isolated product after aqueous work-up and column chromatography purification. Student A was a 1st year Chemistry B.Sc. undergraduate with no prior university-level laboratory experience. Student B was a 3rd year chemistry B.Sc. undergraduates who had taken intermediate practical organic chemistry courses.

Entry	Product Yield
Student A	34%
Student B	81%

Table SM 2.1.13.1. Results obtained from undergraduate students.

Answers to the Additional Questions for students

2. All the aromatic protons are found between approximately 6.5 and 7.5 ppm in the ^{1}H NMR spectra. See **Figure SM 2.1.13.8** for detailed assignments of alkyl protons. The reason that two protons on the same carbon have different chemical shifts is because there are two different chemical environments above and below the plane of the fused ring system. Therefore, even though two protons are located on the same carbon, they are in different chemical environments and will be deshielded to different extents.

3. The appearance of the bright yellow color indicates that the azomethine ylide intermediate is being formed. Its disappearance during the course of the reaction indicates that this intermediate is being converted to the desired product.

4. Acetic acid acts as a proton shuttle during the reaction. It speeds up the proton transfer steps by donating a proton to the intermediates. The acetate anion can then also accept a proton back from the intermediate.

5. Intermediate 2 and Intermediate 4 in the reaction mechanism both have a negative charge on their heteroatom (in case of the *N,O*-acetals, on oxygen). The more electronegative the hetereoatom then the tighter this negative charge will be held on the heteroatom and the slower the subsequent step of nucleophilic attack in the reaction will be. The order of decreasing electronegativity is oxygen>nitrogen>sulfur, so the order of increasing reactivity and nucleophilic strength for this series will be oxygen<nitrogen<sulfur.

Mechanism of the *N,O*-acetal formation reaction (handout for students)

Although this reaction involves very simple reagents and functional groups that you should be familiar with, the mechanism itself involves several unusual intermediates and not the typical iminium ions that you might expect. Three different types of zwitterions are involved, the most important of which is an azomethine ylide. When we developed this reaction, our group carried out several experimental and computational studies to determine the precise reaction mechanism, the results of which are summarised in **Figure SM 2.1.13.1**.

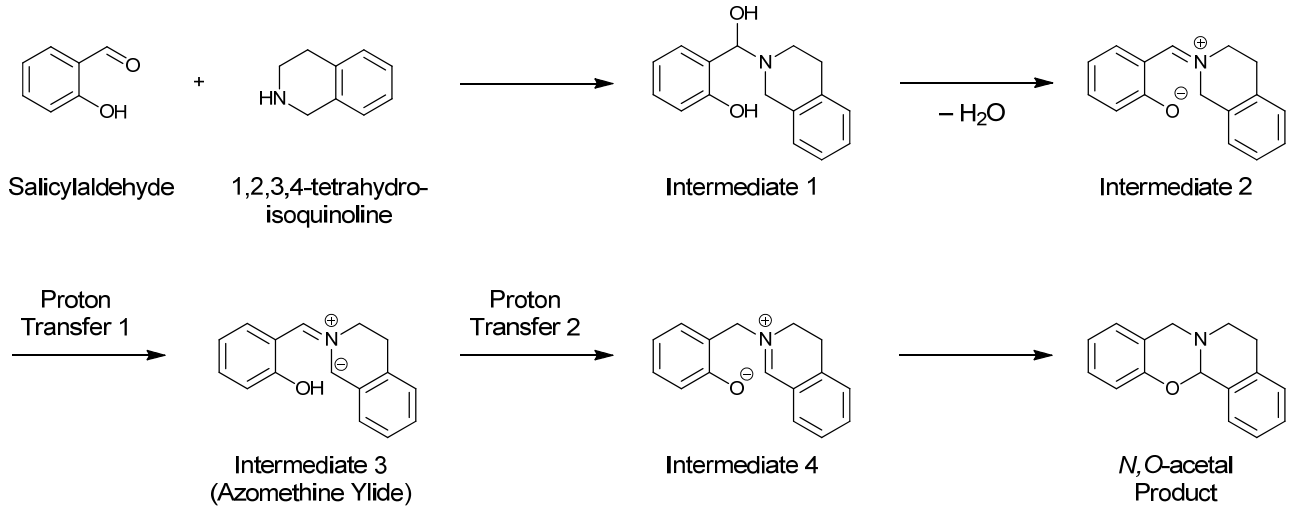


Figure SM 2.1.13.1 – Reaction mechanism scheme.

First, the amine adds to the aldehyde to give Intermediate 1 (note that, like the final product, this is an *N*,*O*-acetal). Loss of water then results in the first zwitterion (Intermediate 2). Two intramolecular proton transfer steps follow before, finally, ring-closure occurs to give the *N,O*-acetal product.

The intermediate species are brightly-coloured, and you should be able to see evidence of them when you are monitoring the reaction.

References

1. An overview of similar azomethine ylide intermediate reactions we have developed in our research group: D. Seidel. *Acc. Chem. Res.*, 2015, **48**, 317.

2. Our original report on the synthesis of *N,O*-acetals and determination of the mechanism: M. T. Richers, M. Breugst, A. Y. Platonova, A. Dieckmann, K. N. Houk, D. Seidel, *J. Am. Chem. Soc.* 2014, **136**, 6123.

Adaptation of reaction for intermediate level chemists

To adapt this reaction for intermediate level chemists or a shorter laboratory session, replace the silica column chromatography step with immediate ^{1}H NMR analysis of the worked-up crude product. The reaction is clean enough that students should obtain an ^{1}H NMR spectra with the desired product as the major component.

Photos of Experiment

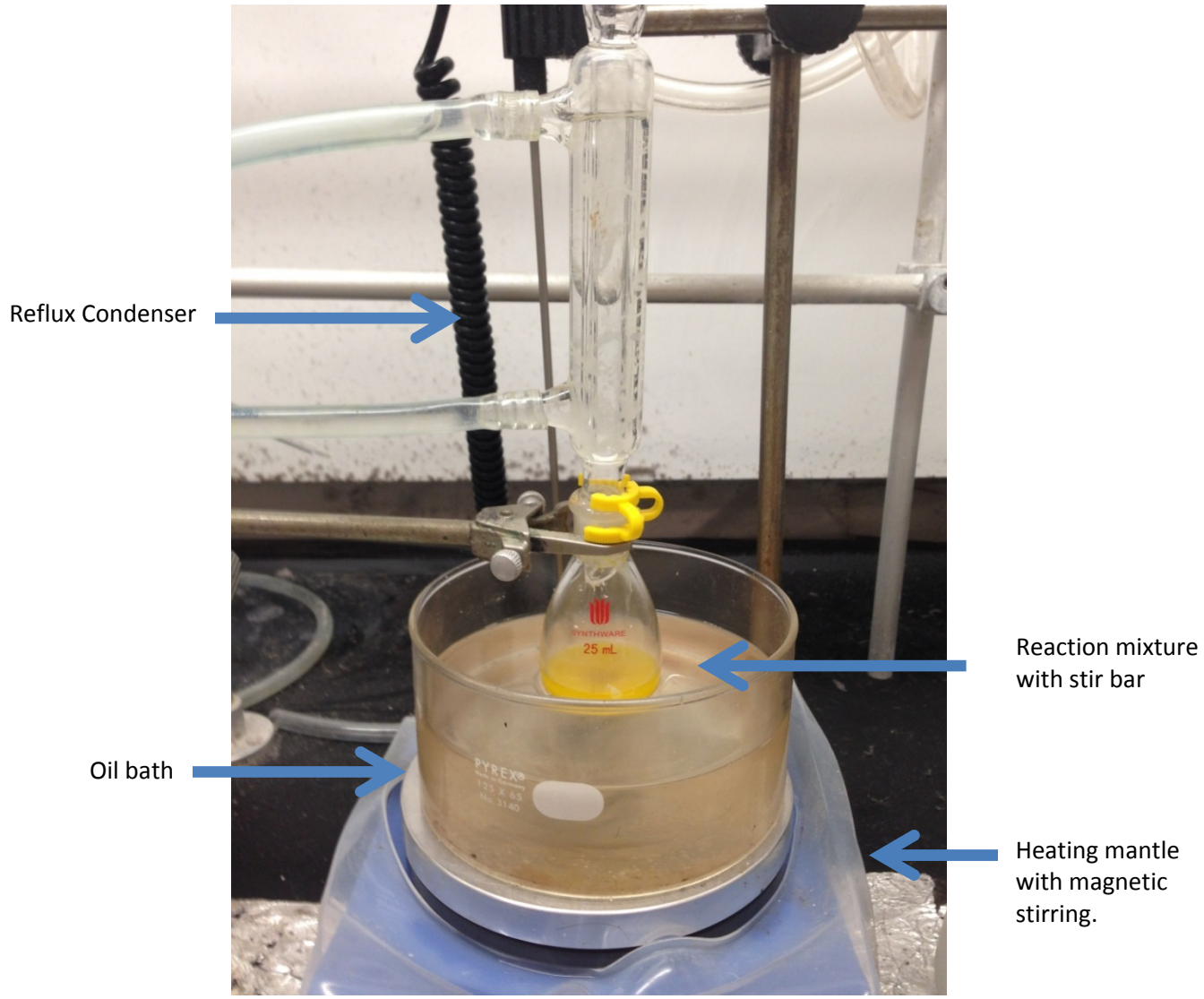


Figure SM 2.1.13.2 - Set-up of reaction heating apparatus.

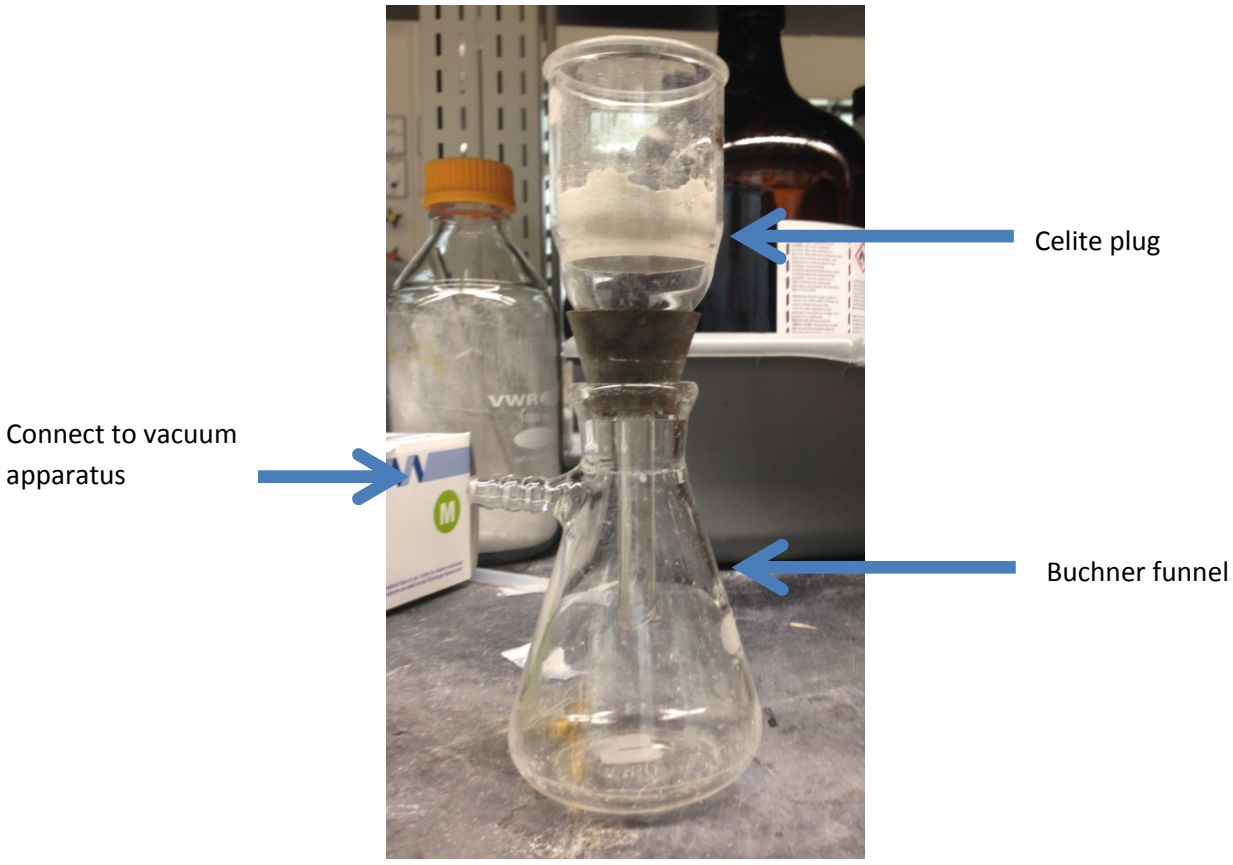


Figure SM 2.1.13.3 - Set-up for Celite plug filtration

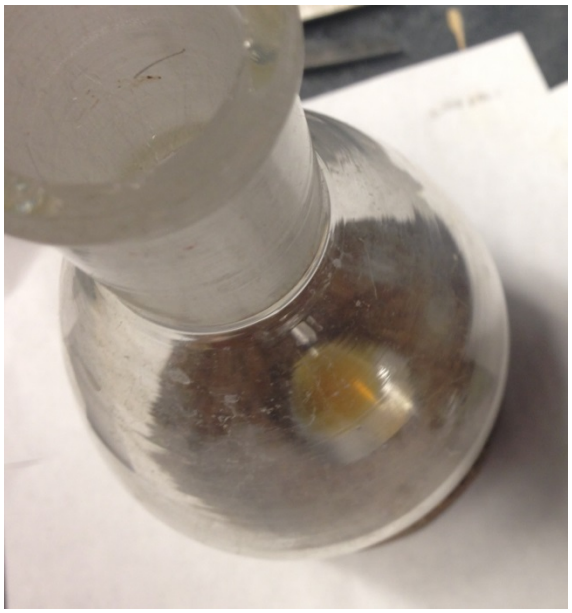


Figure SM 2.1.13.4 - Crude product isolated after work-up

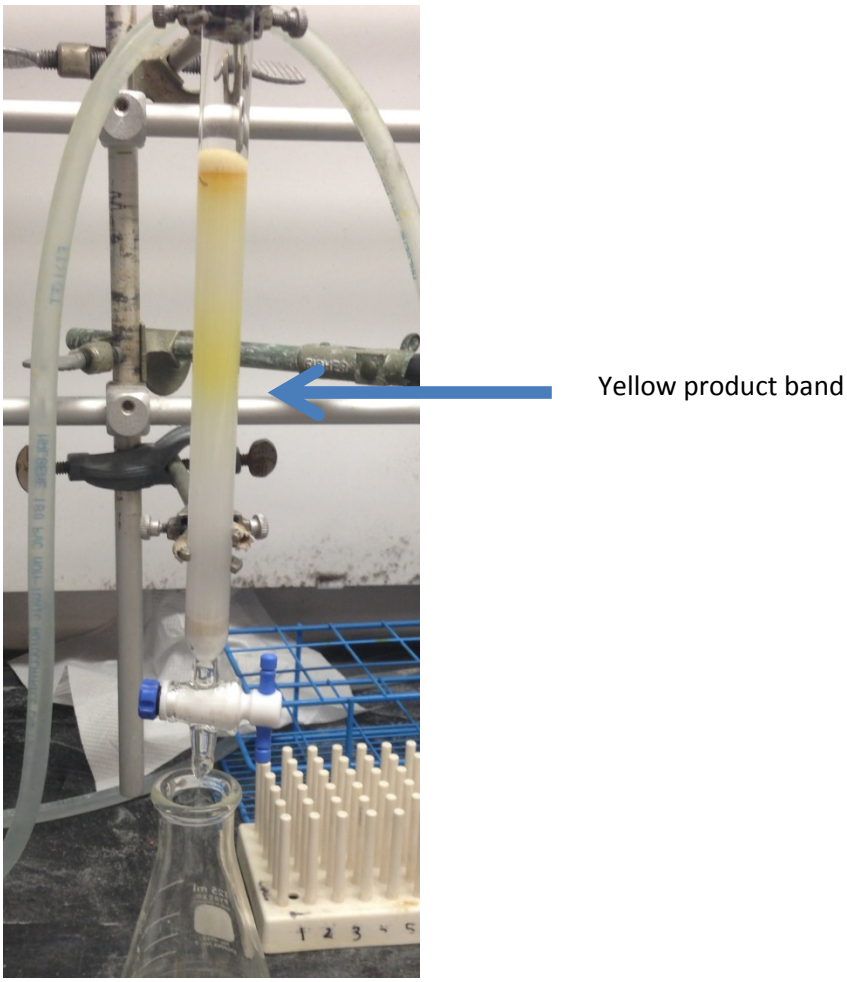


Figure SM2.1.13.5. - Column chromatography of reaction mixture, with *N*,*O*-acetal product visible as the yellow band

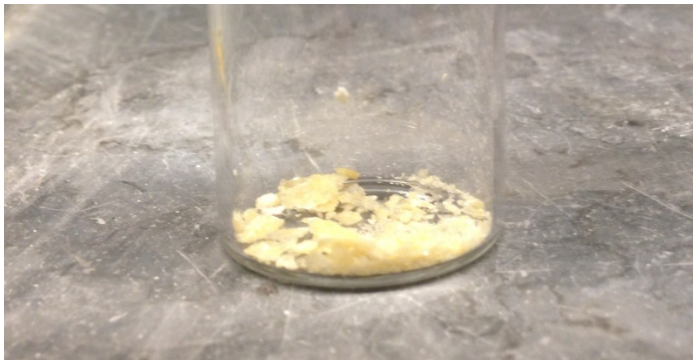


Figure SM 2.1.13.6 - Isolated pure *N*,*O* acetal product.

^{1}H NMR Reference Spectra

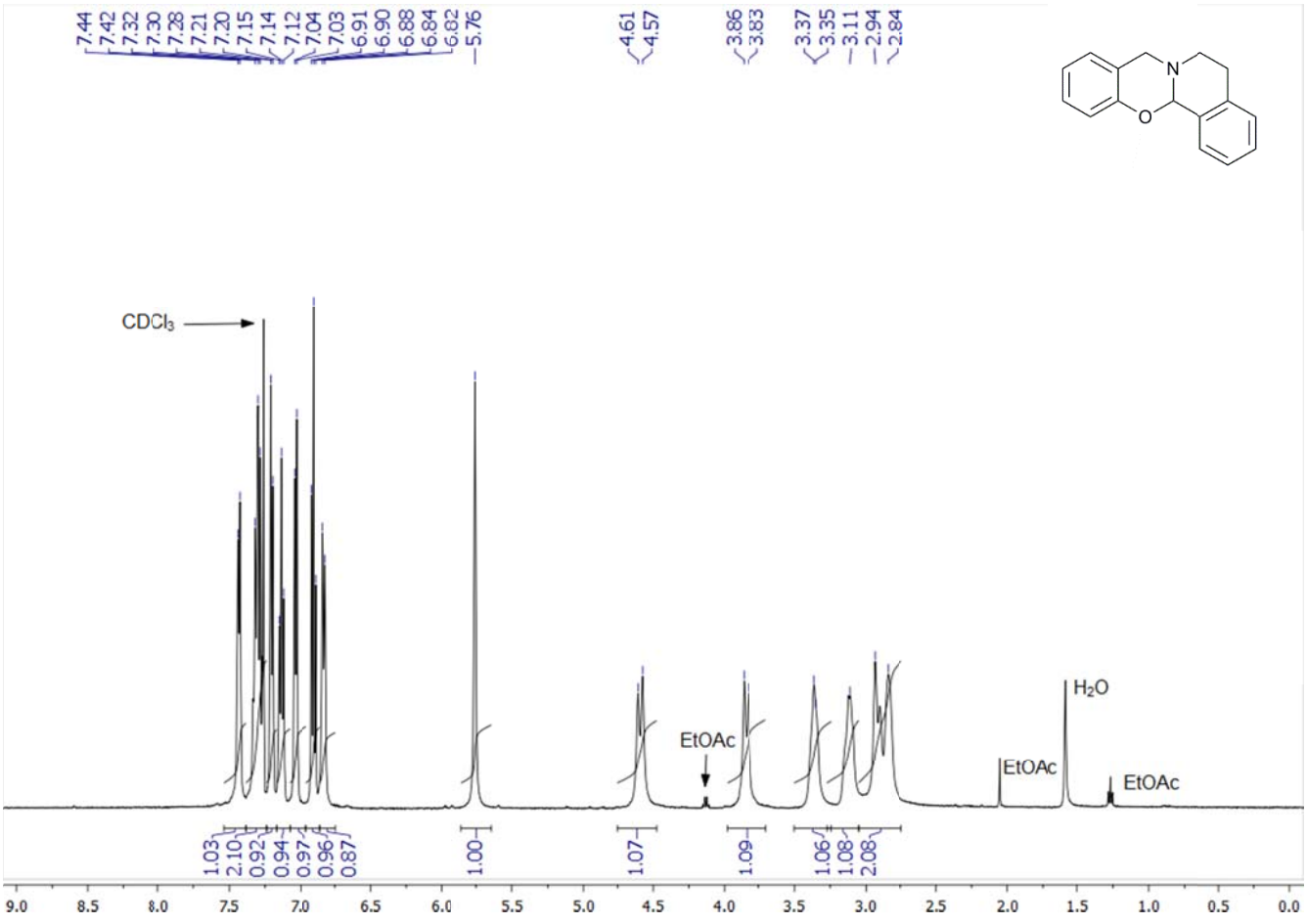


Figure SM 2.1.13.7 - ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the pure *N*,*O*-acetal product after silica column chromatography.

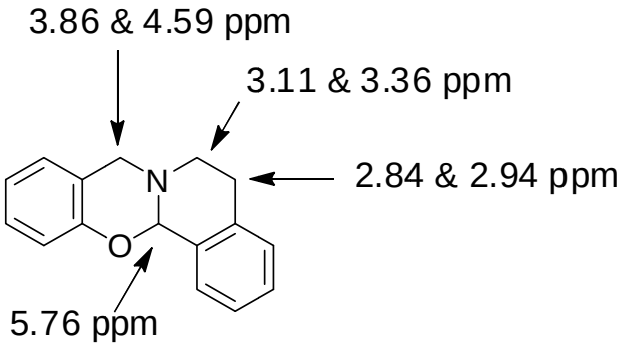


Figure SM 2.1.13.8 - ^{1}H NMR product peak assignments based upon **Figure SM 2.1.13.7.**

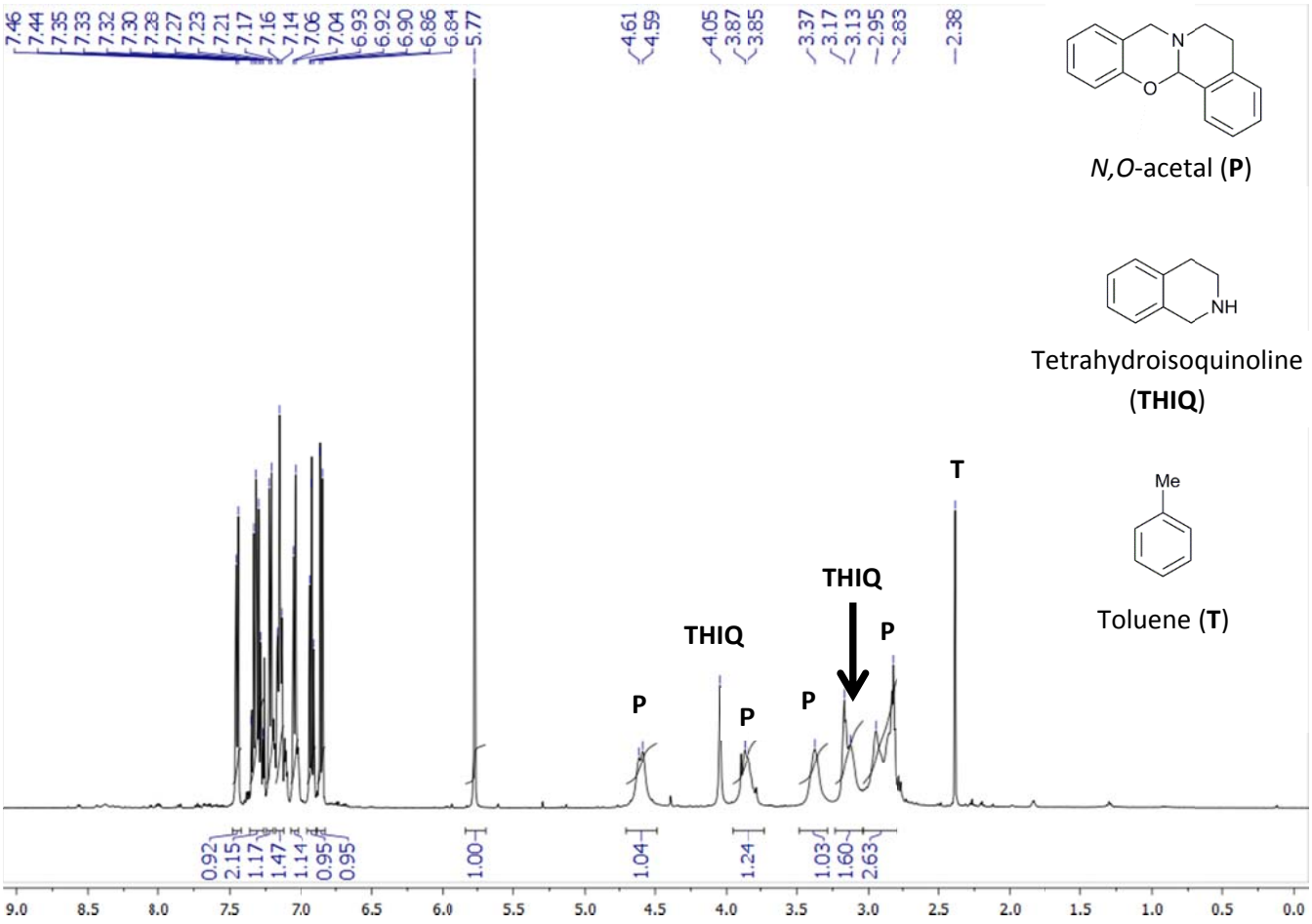


Figure SM 2.1.13.9 - ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the crude *N*,*O*-acetal product after aqueous work-up and rotatory evaporation.