Supplemental Material

Title: A Discovery-Based Friedel-Crafts Acylation Experiment: Student-Designed Experimental Prodedure

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Lab Documentation

1. General Comments for Instructors

This experiment is an example of a simple electrophilic aromatic substitution reaction suitable for secondsemester organic chemistry students. The experiment itself can be completed in a three hour laboratory period. The discussion of synthesis and the development of a student-designed procedure and work up as outlined below takes about one hour. This discussion lends itself to a small class, but if the procedure were provided, the unknown identification and molecular modeling portion of the experiment could be done with larger classes. Furthermore, spectral data for the product could be provided if it is too cumbersome to allow large numbers of students access to the NMR instrument. The NMR peaks are extremely well-resolved for all of the products, so the experimental data is easy to interpret, even on 60 MHz instruments.

This experiment works well with mini-scale glassware, such as Kontes® threaded kitware. If the scale is increased ten fold, macro-scale glassware can be used and the product can be distilled. The boiling point of the distillate can be used to support the spectroscopic identification of the product. While the boiling points of the starting materials and products are sufficiently different that residual starting material, if any, can be separated from the product, the boiling points of the ortho isomers of the products are not sufficiently different from the para isomers for the ortho isomer (if any) to be separated by distillation. In our hands, the reaction proceeds to give the para isomer quite cleanly. To the detection limit of our ¹H-NMR, the ortho isomer is not observable. Occasionally the reaction will not proceed to completion. Using the extractive work-up, the starting material and product are inseparable. In these cases, students integrate their ¹H-NMR spectrum to calculate the percent of each component.

On the mini-scale, the reflux condenser is precautionary. We have never observed boiling of the reaction mixture when the aromatic starting material is added. On the macro-scale, boiling can occur. Each student group will need a round-bottomed flask, magnetic stir bar and stir plate, Claisen head, and reflux condenser. On the mini-scale, students will also need a syringe for addition and a septum or cap assembly for the vertical arm of the Claisen head. On the macro-scale, a separatory funnel or addition funnel equipped with a ground glass joint should be attached to the vertical arm of the Claisen head. In each case, students should be reminded to attach the reflux condenser to the curved arm of the Claisen head. Alternatively, a two or three-necked round-bottomed flask could be used. We have found that the easiest way to supply the aromatic starting material is to provide one vial for each group with the unknown pre-measured into it. Students make a solution directly in this vial and add it to the reaction mixture using a syringe. The residue is used for TLC. Other necessary materials are reagent grade methylene chloride, concentrated HCl, saturated NaHCO₃, and anhydrous MgSO₄.

The molecular modeling portion of the experiment runs quickly at the semi-empirical level (AM1) using Spartan'02 for Windows.¹ Ab initio calculations can take up to 60 minutes, depending on the speed of the computer. Satisfactory data can be obtained using simple molecular mechanics energy minimization.

2. Safety and Hazards

Students should wear safety goggles and gloves for this experiment. Methylene chloride is a suspected human carcinogen and an irritant; students must work in an efficient fume hood for the entire experiment. Acetyl chloride is corrosive. Students should minimize contact with the vapors and liquid by quickly measuring out the required amount. Aluminum chloride is water sensitive, liberating HCl upon contact with water. Be sure to warn students to keep reagent bottles tightly capped and to efficiently weigh out only the amount necessary. Also, students should be instructed to wash their glassware the week before the lab is conducted. Students should also be instructed on proper syringe addition technique. Spattering may occur when the reaction mixture is poured into ice/HCl on macro-scale.

3. Discussion Outline/Procedure Design Problem

This discovery-based discussion serves to introduce the students to the fundamentals of experimental design, while simultaneously reviewing the first semester material, especially solubility, extraction, and TLC. A more extensive review that includes spectroscopy could be incorporated at the same time. Another goal of the discussion is to get the students to understand the purpose of each experimental step. As a result of this exercise, our students are quite capable of and confident in designing their own procedure for a number of experiments later in the semester. For these reasons, this portion of the lab is pedagogically the most important. It takes some preparation on the part of the instructor and a willingness to be patient, ask leading questions, and frame the discussion. At first the students might show some frustration, because up to this point, detailed procedures have been provided. They are usually surprised that so many variables must be considered to execute a fairly simple synthetic reaction. At the conclusion of the exercise, when a complete (or nearly complete) procedure is developed, they see the connections between each of the variables and are also able to state why each step is done.

We begin the discussion with the overall reaction scheme, using one of the possible unknowns or benzene itself as an example. The instructor then asks a leading question about what variables must be considered when no procedure is available. The goal is to get the students to generate the following list: scale, stoichiometery, solvent, reaction conditions, reaction time, work up (isolation and purification of the product), analysis of the product, safety, and waste disposal. They usually need some help to generate the complete list, so leading questions are used to help them generate more ideas as necessary. At this point, they are not experienced enough to decide which solvent to use for the reaction, so they need to be told that this reaction is typically done in an inert solvent such as methylene chloride. It works best for the instructor to then lead the students through a discussion of the overall scale of the reaction, given their particular glassware kit, followed by reaction stoichiometry (i.e. are any reactants used in excess?). We do this in an interactive way, also using leading questions. Then, once the overall scale is established, the remaining tasks are divided among student groups as shown.

 The approximate volumes are known, so a group is assigned to discuss how one would actually set up such a reaction, including required glassware. This group will need some help with describing how to prevent boiling (they do not know to consider this) and how to add the reagents.

2) A group is assigned to figure out how one would determine whether the reaction is complete.

3) A group is assigned to figure out how to isolate the product at the conclusion of the reaction. If they need help, ask them to figure out what is present in the reaction mixture at the conclusion of the reaction and to consider relative solubility.

4) A group is assigned to discuss analysis of the product.

5) A group is assigned to do stoichiometry calculations and to address safety and waste disposal.

Once the discussion time is complete, students reconvene in the larger group to develop a complete procedure from beginning to end. Each group presents the summary of their discussion and takes questions. The presentations are given in the order above so that the procedural steps are listed in the same order as they will be carried out in the lab. The instructor continues to ask leading questions as necessary and to add additional information to ensure that all students are following the discussion and that the procedure is going to be safe. Issues that are covered are listed below. The numbered list corresponds to the numbers above.

1) The glassware required is discussed, as is cooling and warming. We also discuss how reactants will be added. This leads to a brief discussion of adding solids vs. adding liquids and whether to add portionwise or all at once.

2) Students are expected to predict that the TLC R_f of the product is lower than the starting material and that when the starting material spot is gone, the reaction is complete. This lends itself to a review of factors affecting TLC R_f .

3) Students are expected to predict that the inorganic products are water soluble and can be removed from the desired organic products by extraction. A good review of solubility and extraction is provided. Students are also expected to be able to generate an outline of the extraction procedure.

4) Students are expected to decide to use ¹H-NMR spectroscopic analysis to determine the identity of their product. They should also be able to list characteristic IR bands for the product. We allow then to use their text as a reference. This lends itself to a brief spectroscopy review.

5) Students should be able to complete the stoichiometry calculations with no difficulty. Web-based MSDS references can be consulted to address safety. The instructor needs to ensure that all students are aware of the necessary safety precautions. We cover waste disposal in the first semester, so this group is expected to know to separate halogenated solvents and to discard aqueous solutions down the drain while water is running.

At the conclusion of the discussion, students should execute the consensus procedure developed by the class (the instructor should check for safety) or be given a copy of the procedure below. The end result of the student discussion might not be a completely polished procedure that lists every experimental detail, but the goals are accomplished in getting them to think about what is actually happening in each step and to consider a large number of variables. Also, by the end of the discussion, students are aware that most procedures do not have every experimental detail worked out in advance. The procedure below is a consensus procedure from a class discussion, written up as a formal handout with complete description of the details. It could be used as a handout if the experiment was done without the student procedure design.

If time is limited, students can still benefit from a discovery-based exercise by designing the work up procedure using the following assignment as a guideline. This discussion takes 15-20 minutes, so it could be used as a pre-lab exercise for a three hour period. Enough time would remain in the period to complete the experimental work as long as students can access spectrometers at alternate times. This exercise works best if the students are permitted to work in a small group. The instructor can circulate among the groups and ask leading questions or give hints as necessary. Once the procedure is proposed and checked for safety, students can execute their own procedure or be given a copy of the workup procedure.

Procedure Design Assignment (for Work Up Only)

With your group, decide how to purify the product by extraction. Consider the following:

- a) the solubility of your product (you do not need to look it up; your instincts are correct; remember like dissolves like)
 - b) the solvent the reaction mixture is currently in
 - c) the fact that the reaction mixture is quite acidic and the ketones are somewhat acid-sensitive over time
 - d) you need to have pure, dry product to analyze.

3. Student Handout (with experimental procedure)

If the students design the procedure, this handout is modified to include only the introductory material, the safety instructions, and modeling exercise. If the students design the work up, that portion is removed from the handout and replaced with this or a similar sentence, "The reaction was worked up and the product analyzed by TLC and IR and NMR spectroscopy."

FRIEDEL-CRAFTS ACYLATION OF AN UNKNOWN AROMATIC COMPOUND

GOALS:

- 1. Work with water-sensitive reagents.
- 2. Design synthetic procedure and purification/work-up procedure.
- 3. Use IR and NMR to assign the identity of an unknown.
- 4. Use molecular modeling to explain product distribution.

INTRODUCTION

Aromatic systems undergo substitution reactions by an electrophilic pathway. That is, the nucleophilic pi electrons of the aromatic ring attack strong electrophiles. An intermediate carbocation is formed that rapidly loses H^+ to reform the aromatic system. The overall result is the substitution of an aromatic hydrogen with the electrophile. In the case of Friedel-Crafts acylation, the electrophile is an acylium ion, formed by the reaction of an acid chloride with aluminum chloride. A general mechanism is shown below.

Step 1. Formation of the electrophile



Step 2. Attack by the aromatic ring



Step 3. Regain aromaticity



FIGURE. Friedel-Crafts acylation of benzene.

In this experiment, you will be given a sample of an unknown aromatic compound. You will conduct the reaction and determine the identity of the product (and therefore the starting material) by IR and NMR spectroscopy. The possible starting materials are toluene, ethylbenzene, and methoxybenzene (anisole).

SAFETY AND HAZARDS

Please wear gloves for this experiment. Aluminum hloride is water sensitive, an irritant, and corrosive. It will react with the moisture on your skin to liberate HCl. Handle it with care, weigh out only what is necessary, and work quickly. Acetyl chloride is also corrosive. Be sure to keep it in the hood. Keep all reagent bottles tightly capped. Discard aqueous waste down the drain with lots of water. Collect organic waste into the appropriate waste containers. Handle syringes with care. Cap and dispose of used needles in the biohazard container.

PROCEDURE AND NOTES

The procedure is written in the simple past tense as you would see in a journal article.

Mini-Scale

Anhydrous aluminum chloride (5.5 mmol, 1.1 equiv.) and 1.5 mL of methylene chloride were placed into a 10 mL round bottomed flask equipped with a stir bar. A Claisen head, septum, cap, and reflux condenser were attached and the stirred mixture was cooled in an ice/water bath. Acetyl chloride (5.5 mmol, 1.1 equiv) and 1.0 mL of methylene chloride were combined in a conical vial. The clear, colorless solution was added to the reaction flask dropwise using a syringe over 5 - 10 minutes with stirring. The aromatic compound (5.0 mmol, 1.0 equiv) was dissolved in 1.0 mL of methylene chloride. This solution was added to the cooled reaction mixture dropwise over 5 minutes using the same syringe. After addition was complete, the cooling bath was removed and the reaction mixture was poured carefully, with swirling, into 5 g of ice combined with 1.5 mL of concentrated HCl. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted with 5-10 mL of methylene chloride. The combined organic layers were extracted with two portions of saturated sodium bicarbonate and dried over anhydrous MgSO₄. The drying agent was removed by gravity filtration into an

appropriately sized round bottomed flask. The methylene chloride was removed by rotary evaporation. The product was weighed and analyzed by infrared and NMR spectroscopy and TLC (ethyl acetate:hexane :: 1:4) in comparison with the proposed starting material.

Macro-Scale

Anhydrous aluminum chloride (0.055 mol, 1.1 equiv.) and 15 mL of methylene chloride were placed into a 100 mL round bottomed flask equipped with a stir bar, Claisen head, addition funnel, and reflux condenser. The mixture was cooled to 0°C in an ice/water bath. Acetyl chloride (0.055 mol, 1.1 equiv.) as a solution in 10 mL of methylene chloride was added to the mixture dropwise over 10 min using the addition funnel. After the addition was complete, the unknown aromatic compound (0.050 mol) was added in the same manner, also as a solution in 10 mL of methylene chloride. The addition rate was adjusted so the solution did not boil excessively. After addition was complete, the ice bath was removed and the reaction was allowed to come to room temperature. After stirring for an additional 15 minutes at room temperature, the reaction mixture was poured carefully and slowly, with stirring, into about 25 g of ice and 15 mL of concentrated HCl in a beaker. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted with 20 mL of methylene chloride. The combined organic layers were extracted with two portions of saturated sodium bicarbonate and dried over anhydrous MgSO₄. The drying agent was removed by gravity filtration into an appropriately sized round bottomed flask. The methylene chloride was removed by rotary evaporation (or simple distillation if rotovaps are not available). Once the methylene chloride was removed, the flask was set up for simple distillation and insulated with aluminum foil or glass wool. The mixture was distilled, raising the setting on the variac as necessary. If residual starting material was present, it distilled around 150°C, while each of the products has a boiling point greater than 200°C. The product was weighed and analyzed by infrared and NMR spectroscopy and TLC (ethyl acetate:hexane :: 1:4) in comparison with the proposed starting material.

Notes

1. Do not wash your glassware just before doing this experiment. Your glassware must be clean and dry. Do not wash your syringe (addition funnel) between adding the acetyl chloride and the aromatic compound.

2. Weigh out the aluminum chloride quickly and keep the container tightly capped.

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3. Obtain the IR spectrum as a thin film for liquids or as a solution in CHCl₃ for oils. Put the analysis in your notebook. Obtain an NMR spectrum in the normal way in CDCl₃. Also put the analysis of the NMR spectrum in your notebook. Obtain an accurate integration of your NMR spectrum. If you suspect that your product is contaminated with starting material, carefully integrate the starting material peaks separately so you can calculate an approximate percent of each.

4. Once you have proposed an identity for your product, calculate a percent yield.

5. Obtain literature NMR and IR spectra for your product and for the ortho isomer. Do you see any evidence in either your experimental NMR or IR spectrum that your product contains the ortho product?

Molecular Modeling

Use Spartan02¹ to construct a molecular model of the product you made. Click on the minimize icon on the toolbar to perform a quick minimization. Make a note of the energy value on the bar at the bottom right of the screen. This is a molecular mechanics strain energy in kcal/mol. Set up calculations at the semi-empirical AM1 level by clicking on Calculations in the Setup menu. Be sure Equilibrium Geometry and Ground state are selected (these are the defaults.) Submit your calculation. Once the calculation is complete, select Output from the Display menu. Print out the results, noting the energy of the compound. This is a heat of formation, in kcal/mol. Now construct a model of the ortho isomer. Perform the same calculations on it and print the results. Record both minimized energies with units. Does this explain the ortho-para isomer distribution in the Friedel-Crafts acylation reaction? Why or why not? Are the results from the molecular mechanics strain energy and the AM-1 heat of formation consistent? Print out your models in tube or ball and stick form from the View screen.

Reference

1. Spartan'02, Wavefunction, Inc., Irvine, CA.

4. CAS Registry Numbers for all Chemicals

acetyl chloride	75-36-5
aluminum chloride	7446-70-0

anisole	100-66-3
chloroform	67-66-3
chloroform-d	865-49-6
dichloromethane (methylene chloride)	75-09-2
ethyl acetate	141-78-6
4'-ethylacetophenone	937-30-4
ethyl benzene	100-41-4
hexane	110-54-3
hydrochloric acid	7647-01-0
magnesium sulfate	7487-88-9
4'-methylacetophenone	100-06-1
sodium hydrogencarbonate	144-55-8
toluene	108-88-3