A Discovery-Based Friedel–Crafts Acylation Experiment: Student-Designed Experimental Procedure

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Friedel–Crafts acylation reactions are relatively common in the literature and are used widely in research and industrial processes *(1)*. This important carbon–carbon bond forming reaction dates from before 1900, yet to this day its broad scope makes it an efficient method for modifying a variety of aromatic and heteroaromatic rings *(2)*. One of the simplest Friedel–Crafts procedures involves adding an acetyl group to an aromatic ring with acetyl chloride in the presence of a stoichiometric amount of anhydrous aluminum chloride (Figure 1). This reaction is appealing for an undergraduate lab because the acylium ion electrophile does not rearrange and multiple additions are not observed. The para-substituted acetophenone derivatives produced are simple to analyze by infrared and ^{1}H-NMR spectroscopy. Good to excellent yields are obtained for a variety of aromatic rings, as long they are at least as reactive as benzene itself.

In 1964, Casanova remarked that organic chemistry textbooks thoroughly discuss electrophilic aromatic substitution (EAS) because this series of reactions is an excellent example of an internally consistent body of information *(3)*. Such is still the case and most instructors spend significant classroom time on these transformations. However, the EAS experiments in many organic laboratory texts *(4)* are not so compelling: most are cookbook procedures, describe the kinetics of the reaction, or involve multiple starting materials in an attempt to have students learn directive effects by experimentation.

EAS laboratory exercises have been well-represented in this *Journal (5),* but we have designed a discovery-based experiment that is used as a first exercise in synthetic design after students have learned the fundamental techniques of purification and analysis (including spectroscopic) of organic compounds. While the actual synthetic procedure is based roughly on the experiment described by Schatz *(6),* we have made significant modifications in the pedagogical goals of the exercise and in what the students are required to do to complete the lab. The most important innovation and educational benefit of the lab exercise described in this article is the student-designed procedure. Additionally, students carry out spectroscopic analysis of the product and use molecular modeling to explain the product distribution. Thus, this experiment integrates a number of concepts into one laboratory exercise. The reaction itself is flexible in scale, complete in 30 minutes, and requires no specialized equipment.

General Experimental Procedure

Anhydrous aluminum chloride is suspended in methylene chloride in a round-bottomed flask equipped for reflux with addition. A solution of acetyl chloride in methylene chloride is added to the flask using a syringe, followed by a solution of the aromatic starting material in methylene chloride, also by syringe. After stirring for 15 minutes at room temperature, the suspension is poured into ice combined with concentrated HCl. The work up is completed using a simple extractive procedure. Rotary evaporation yields the product as a viscous oil.

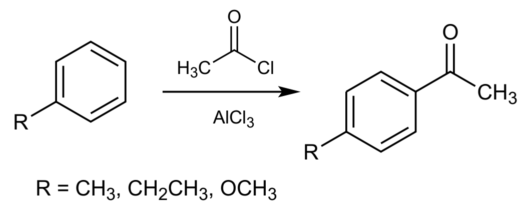

Figure 1. Friedel–Crafts acylation of substituted benzenes.

Hazards

Methylene chloride is toxic, an irritant, and a suspected human carcinogen. Aluminum chloride is corrosive and moisture sensitive. Acetyl chloride is corrosive. Students should be instructed to wash and dry their glassware the week before the experiment is done. The reaction and workup should be conducted in a fume hood and reagent bottles should be kept tightly capped. Students should wear gloves and eye protection for the entire experiment.

Results and Discussion

Discovery-Based Procedure Design

Discovery-based exercises usually begin with an open-ended question and often involve pooling of data or systematic alterations in procedure *(7)*. We are interested in using the discovery process to improve the problem-solving skills of our students; consequently, we strive to minimize the "cookbook" approach to lab work. The ability to design an experiment is one of the most important skills a budding scientist can develop; therefore, we place this exercise at the beginning of the second semester of organic lab to introduce students to the practical and theoretical parameters that must be considered when designing a synthetic procedure *de novo*. The discovery-based discussion leads to a student-designed procedure for the Friedel–Crafts acylation reaction. It also serves to review and integrate the techniques covered individually in the first semester of organic lab and to prepare the students for the multistep syntheses they will face later in the semester.

We begin the discussion with the reaction itself, providing the goal of the synthesis and the starting materials. An open-ended question directed to the whole class is then posed about what variables must be considered when no procedure is given. Students suggest a variety of answers, but invariably fall short of considering all of the parameters necessary to design a safe, complete procedure. At this point, the instructor guides the discussion by asking leading questions to get students to propose additional ideas. Our goal is for students to generate the following list of experimental variables common to nearly all synthetic procedures: scale, stoichiometry, solvent, reaction conditions, reaction time, workup (isolation and purification of the product), analysis of the product, safety, and waste disposal.

Once the list is complete, the instructor discusses stoichiometry and the scale of the reaction that is compatible with the students' glassware kit. After breaking the students into groups, remaining components of the list are assigned to each group. For example, a group asked to think about reaction time devises a method for ascertaining when the reaction is complete and predicts the results of the method (in this case, the students are expected to predict that the TLC R_f of the product is lower than the starting material and when the starting material spot disappears, the reaction is complete.) Following a time for discussion, the class reconvenes and each group presents their conclusions and takes questions from the class. The instructor (or a student recorder) takes notes. This large group exchange of ideas allows the class to come to consensus about what should be done to accomplish the reaction. To conclude the exercise, the instructor summarizes the discussion. We actually do the experimental work the week following the discussion, so the instructor reviews the notes, checks for safety, and then provides the class-designed procedure to the students either electronically or as a handout prior to the next class meeting. This discovery-based procedure design takes approximately one hour in a discussion format.

Experimental Results

Students are provided with an unknown aromatic starting material that could be toluene, ethylbenzene, or anisole. Other substituted aromatics could be used for the synthesis, but the molecular modeling portion of the experiment requires the theoretical possibility of obtaining ortho–para mixtures. Most student groups achieve a 50–85% yield of pure para-substituted product in less than 30 minutes reaction time. A simple extractive workup avoids time-consuming distillation steps.

Students then analyze the acetophenone products by IR and ^{1}H-NMR spectroscopy. The IR spectra show intense conjugated carbonyl and para-substitution bands. The ^{1}H-NMR spectra are first-order and well-resolved, even on low-field instruments. Students are readily able to identify their product and hence the unknown starting material based on the ^{1}H-NMR spectrum. While using an unknown starting material has little real-life application, it serves the following purposes: (i) shows a general procedure can be developed for a series of structurally related compounds; (ii) provides a somewhat more challenging spectroscopy problem than simply checking off peaks of a known compound; and (iii) provides an added item of interest for the students.

Molecular Modeling

Finally, we use molecular modeling to help explain that one reason for the lack of observable ortho product is the greater thermodynamic stability of the para isomer. Using Spartan 02 *(8),* students perform semi-empirical calculations (AM1) on their product and the ortho isomer. The resulting data are shown in Table 1. Molecular mechanics (MMFF) also provides values for the strain energy of the isomeric compounds that allow students to draw the same conclusion.

Table 1. Calculated Energy of Reaction Products

Compound	ΔH_f/ (kcal mol^{-1})[a]	Strain Energy/ (kcal mol^{-1})[b]
p-methylacetophenone	−22.85	37.26
o-methylacetophenone	−20.81	41.89
p-ethylacetophenone	−28.57	36.89
o-ethylacetophenone	−25.92	42.46
p-methoxyacetophenone	−53.63	38.44
o-methoxyacetophenone	−47.43	46.05

[a]Data from semi-empirical (AM1) calculations.

[b]Data from molecular mechanics (MMFF).

Summary

The discovery-based procedure design process used in this lab not only affords the students the unique experience of designing and conducting a reaction in a similar way to what one would do in a research lab, but also encourages them to think about each procedural step and its purpose. Therefore, students begin to appreciate the large number of variables for which one must account in the design of any synthesis. These goals are accomplished in the context of a relatively straightforward Friedel–Crafts acylation reaction. Also, placing this lab as the first experiment in the second semester curriculum has the pedagogical benefit of reviewing and integrating first semester material in an interesting and challenging new context. The spectroscopic analysis and modeling complete the exercise nicely and provide very good quality data. Our students respond favorably to this experience and are able to design procedures for other experiments in the second semester of organic chemistry lab as a result of beginning the semester with this Friedel–Crafts acylation experiment.

[W]Supplemental Material

Instructor notes and class discussion guidelines, results of student-designed procedure (as a formal handout), molecular modeling instructions, and the CAS numbers of all compounds are available in this issue of *JCE Online*.

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