SANTA CLARA UNIVERSITY **SUMMER TERM 2019**
ORGANIC CHEMISTRY III **CHEMISTRY 33L**

LABORATORY SYLLABUS

INSTRUCTORS

Raymond Gipson, Ph.D.; Beatrice Ruhland, Ph.D.

TIMES

- Monday/Wednesday: 8:00-12:30 p.m.
- Monday/Wednesday: 4:30-9:00 p.m.
- Tuesday/Thursday: 8:00-12:30 p.m.
- Tuesday/Thursday: 4:30-9:00 p.m.

Laboratories begin on **Monday, July 29th** and are held in DS 126

MATERIALS

1. Course syllabus (available on Canvas, Chem33 lab course page or on google sites https://sites.google.com/a/scu.edu/organic-chemistry-laboratory/, and from Copy Craft Printing, 341 Lafayette St.)
2. *Laboratory Techniques in Organic Chemistry* by Mohrig, Alberg, Hofmeister, Schatz and Hammond, 4th Edition
3. Bound laboratory notebook embossed with "Santa Clara University", Scientific Notebook Company (available from the bookstore); **you may use the same notebook as you purchased for Chem32L**
4. Safety splash goggles
5. Laboratory coat (available from the bookstore)

LABORATORY GUIDELINES

1. The laboratory in Daly Science 100 were modernized and redesigned in 1994, with safety as the primary concern. The main improvement in these laboratories was increasing the number of hoods so that each student has a workstation in a hood, two students per hood. This significant enhancement in safety protects everyone because many organic compounds are volatile and using a hood minimizes your exposure to fumes. Therefore, **virtually 100% of your chemical work should be performed in a fume hood**.
2. To do organic chemistry safely, you should treat all chemicals with respect; **gloves should be worn** unless otherwise directed by the instructor.
3. Because we are limited in space for each laboratory section, you may only attend your assigned laboratory time. To be granted an exception for special circumstances, you must request permission from both your regular laboratory instructor and the instructor for the laboratory you wish to attend. An e-mail to both instructors is the easiest method to achieve this; **if you do not make a formal request to both instructors, you will not be admitted to another laboratory section**.
4. Care of the organic laboratory is important because over 200 students share this room each term, so we must regularly maintain this facility. It is important that you **clean your work area at the end of each laboratory period** as well as help with keeping the balances, instrument room, and other general use areas clean. Please **inform the instructor of any spills and make sure you clean up the spill completely**.

ACADEMIC INTEGRITY

You are expected to maintain the highest standards of academic integrity in both the lecture and laboratory components of this course. In the context of the laboratory, you may help each other understand and complete various procedures. However, **all work recorded in your notebook must be your own**. Giving or receiving unauthorized aid in any form can result in course failure. Please see your laboratory instructor if you need clarification on what constitutes unauthorized aid in your laboratory work. More information about the SCU policy on academic integrity can be found at:http://www.scu.edu/studentlife/resources/policies.cfm. or p.14 of the Student Handbook. An excellent resource is the Academic Integrity Brochure (http://www.scu.edu/studentlife/resources/upload/Academic-Integrity-brochure-2014.pdf)

In your laboratory notebook, you will be asked to sign an academic integrity pledge before submitting your work for grading. The pledge reads: "I am committed to being a person of integrity. I pledge, as a member of the Santa Clara University community, to abide by and uphold the standards of academic integrity contained in the Student Conduct Code."

FORMAT

There are six groups of experiments this quarter. **Your goal is to complete one from each of these groups. You may carry out the experiments in any order you like**. If you have time and motivation, you may do more than six experiments, but we would much rather see six experiments well done than seven done poorly. **You must successfully complete the laboratory course to pass the lecture course.** Your laboratory grade is based upon the quality of your work, your effort, your attendance, the difficulty of the experiments you choose, and your lab notebook. Your laboratory grade is based upon the quality of your work, your effort, your attendance and your lab notebook.

At least one of your six experiments must be a multistep synthesis—one that includes a minimum of two separate steps. To count as a multistep synthesis, the product of one step must be isolated and characterized before being used for a subsequent step. Characterization includes a comparison of the compound's bp or mp with literature values, an IR spectrum, and a test of purity such as TLC or GC analysis.

Some experiments are easy, and others are difficult. You are encouraged to choose a balanced mixture of experiments. Avoid doing all the easy ones or all the hard ones. Remember that you will usually have to be working on more than one experiment at any one time. You must carefully analyze the procedures of the experiments you choose before coming to lab in order to use the available time effectively. Planning ahead is especially important this quarter because many of the experiments involve long waiting periods while reactions occur. Other experiments or compound characterization should be carried out during these waiting times.

Given the organization of this laboratory and the freedom you have in choosing experiments, it is imperative that all chemicals be returned to the proper location after you use them. As part of check-out of the lab each day, you will be required to demonstrate that you have complied with this laboratory requirement.

SAFETY

It is important to read *carefully* the safety section (1) in the laboratory textbook (Chapter 1, pages 1 to 21) and (2) on the back of your laboratory equipment check-in card before signing it. Critical points are highlighted below.

1. Safety goggles and a lab coat must be worn in the laboratory at all times!
2. To prevent exposure of others to chemicals, do not wear your lab coat or gloves outside of Daly Science 126.
3. Required apparel for working in a teaching or research laboratory in the Department of Chemistry & Biochemistry at SCU:

   a. Laboratory coat.
   b. Long pants.
   c. Closed-toe shoes, ideally with a non-permeable upper component covering the foot.

   Failure to meet these requirements will result in a student having to leave the laboratory until such time as any deficiencies have been addressed.
4. Use of cell phones, radios, iPods, and the like is not permitted in the laboratory.
5. Most organic solvents are flammable and should never be heated with an open flame. Hot plates or heating mantles are available for this purpose. **Never use an open flame in the organic laboratory.** Some solvents such as diethyl ether, t-butyl methyl ether, and methanol have flash points so low that they can be ignited by the surface of a hot plate.
6. Be sure to handle organic chemicals carefully as many are toxic if absorbed through the skin or inhaled. **Gloves must be worn for all experiments.** Disposable gloves are provided in the laboratory. Change gloves when necessary. To avoid chemical contamination of the chemistry building, do not used gloved hands to handle objects outside the laboratory.
7. **You should perform all chemical work at the fume hoods.** The fume hood is designed to limit your exposure to noxious or toxic vapors. It also protects you in the event that a chemical reaction gets out of control.
   a. Volatile substances must be measured only in the fume hoods.
   b. Never allow your head to cross the plane of the fume while dismantling apparatus or any other time (do not put your head inside the fume hood).
   c. Do not prop your laboratory notebook or any other books/papers inside the fume hood.
   d. Keep the sash lowered so that arrows are aligned.
   e. Lower the sash immediately if there is a splatter or fire.
8. Exercise the following precautions when heating materials:
   a. Make sure that a boiling stone or stir bar is contained in all liquids before heating.
   b. Never heat a closed (sealed) container.
   c. Never place your face over material that is being heated.
9. Neatness in carrying out laboratory work is related to safety. It is important that each student help keep the laboratory clean and organized. Allow enough time for cleanup when planning your laboratory activities.
10. Under no circumstances will you be allowed to conduct experiments that have not been assigned for you to do.
11. Do not deviate from the procedure without first getting the modification cleared through the instructor. Even if you think there is a typo in the guided procedure, check first.
12. In case of an **evacuation**, proceed to the Saint Claire Garden.
13. Always treat **unfamiliar chemicals** as if they are dangerous.
   a. Never use a chemical from an unlabeled container.
   b. Never substitute a chemical in an experiment without the instructor's permission.
14. Report all accidents and spills to the instructor.
15. Use water to immediately wash off all chemicals that are accidently spilled on your skin.
16. Know the locations of the safety showers, eyewash stations and fire extinguishers.

WASTE DISPOSAL

One of the most important practices in lab is the proper disposal of chemical wastes. The only substance allowed to go down the drain is uncontaminated water. The general rule is that **nothing should be poured into any sink or placed in the garbage cans**. There are containers in the lab for the various kinds of waste materials generated: aqueous waste, basic aqueous waste, acidic aqueous waste, solid organic waste, organic solvent waste (non-halogenated), halogenated organic waste, and contaminated glass. Be absolutely positive that you are putting the proper materials in the containers. Useful directions for waste disposal are provided with each experimental procedure, and there is a handout that specifies where to put the waste you generate as a result of performing experiments. Remember that anything with **WATER** in it is an aqueous waste and must go in one of the containers so labeled. It is also extremely important that you enter into the appropriate logbook the identity and

amount of each substance added to each container. **If you are unsure of which container to use, ask one of the lab instructors**.

- **All chemicals must be placed in the appropriate waste container.** There is a list posted in the laboratory to aid you in determining the appropriate container for the wastes generated for each experiment. If you are unsure about any waste, ask your laboratory instructor.
- Disposing of chemicals in the wrong containers is potentially dangerous.
- You are required to enter the identity and amount of the waste in the logbook.

USE OF THE ROTARY EVAPORATOR

A rotary evaporator (also called a "rotavap") is a specialized distillation apparatus used to remove solvents from reaction mixtures and can remove large volumes of solvent very quickly. A typical rotary evaporator has a water bath that is heated, and the solvent is trapped by a condenser and collected for disposal. Most rotovaps use “house” vacuum or a special vacuum pump that lowers the boiling point of the solvent and increases the rate of solvent removal.

You will be trained to use the rotovap this quarter, and we will use this method instead of the typical evaporation steps, such as boiling off the solvent on a hotplate or simple distillation that we used in CHEM 31 and 32. The procedure for this valuable, new technique is discussed in your laboratory text on pp. 171-173.

NOTEBOOK

The guidelines are derived from those drawn up by the chemistry faculty for all lab courses. Please look at them carefully before making entries in your notebook. Remember that in addition to the specifics below, the goal of the notebook is for another person to be able to repeat your lab work precisely as you did it.

Data, conclusions and results for all experimental work should be included in the notebook. A running commentary of the experimental procedure should also be included with all observations made during the experiment. The term “running commentary” is used to highlight that you should write what you are doing as you do it; you should not record what the textbook or supplement tells you to do, but instead what you actually did and saw. Examples of appropriate styles for lab notes are available in Section 3.1 of the textbook (pages 33 to 35).

1. The notebook must be bound with at least 100 pages and pages that are consecutively numbered.
2. Pages must never be torn out or otherwise removed from the notebook.
3. The notebook should have a title page identifying you, the course name and number, and the lab instructor. The same notebook may be used for Chem 31, 32, and 33.
4. Reserve space at the beginning of the notebook for a Table of Contents. Entries in the Table of Contents should be identified by title and page numbers for all pages containing information relevant to that title.
5. Use a ballpoint pen for all entries in the notebook.
6. Any given page in your notebook should only include data for a single experiment. As a result, organize your notebook entries based on the experiment to which they correspond, not the date on which they were performed.
7. If an experiment involves running a chemical reaction, the structures of the reactants and products should be illustrated at the **beginning** of the notebook entry for this experiment. A table of the reactants, amounts used, and their physical constants should also precede your written procedure (see an example on p. 6 in the yield calculation section).

8. Each page in the notebook should be dated using an unambiguous notation like 15 October 2013. If a page includes work done for the same experiment on different days, date each entry separately.
9. If you need to continue an experiment onto another page, write the continuing page on the bottom of the initial page (cont'd on page xxx) and the page from which you are continuing at the top of the new one (cont'd from page xxx).
10. Cross out sections of pages you choose not to fill out. Do not leave blank spaces to be filled in later.
11. Graphs and spectral charts should be attached to notebook pages using glue or tape. **Each should be completely labeled.**
12. All entries should be legible and contain sufficient detail. For example: use proper names for instruments and glassware: "10-ml Erlenmeyer flask" rather than just "flask"; indicate the specific concentration of reagents used: "6 M" or "0.1 M" rather than just "dilute"; indicate how precisely reagents were measured: graduated cylinder versus pipette; record the sequence in which chemicals were mixed and the method and length of time for heating and/or stirring; note whether a heating mantle or hot plate was used; completely record all observations like color changes, precipitates, gas evolution, etc.; display any calculations in full detail for ease of verification.
13. Draw a single line through mistakes. Erasing and over-writing are not acceptable methods for error correction.
14. At the end of each lab period sign and date your notebook and have the instructor sign it also.

You should answer the questions at the end of each experiment in your notebook as well.

SCHEDULE

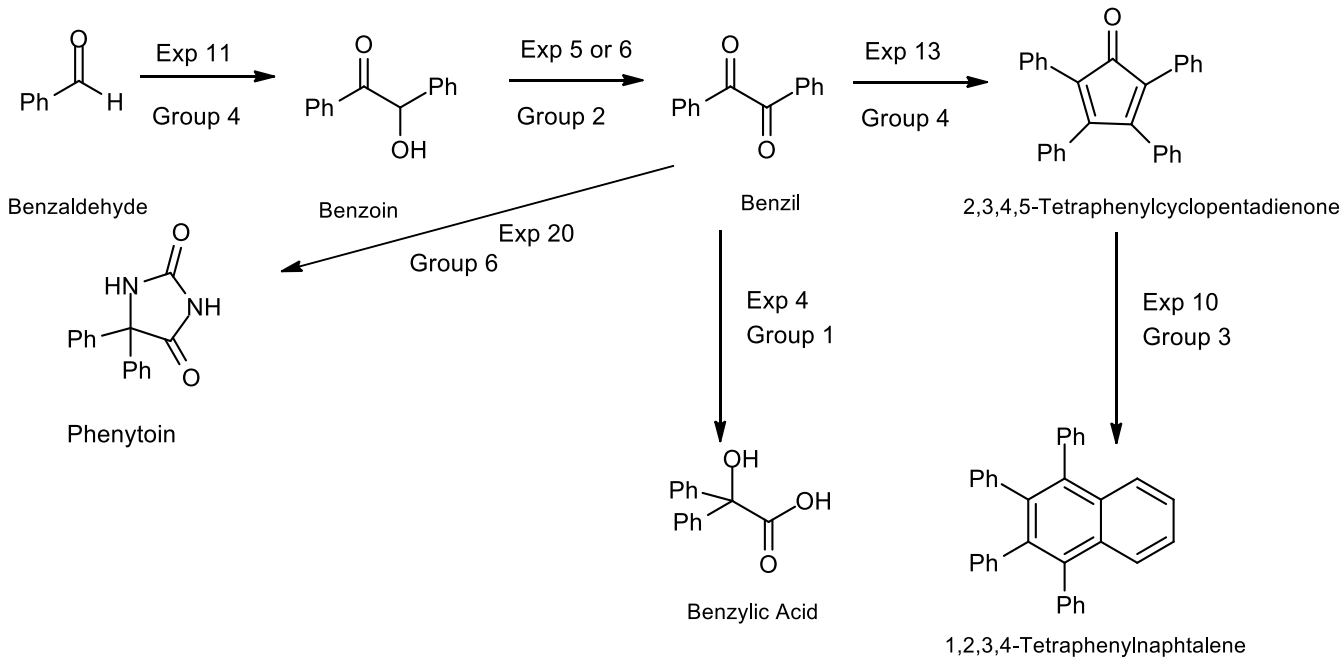
Lab will start the first week of the term. Because we are limited in space for each laboratory section, you may only attend your assigned laboratory time. To be granted an exception for special circumstances, you must request permission *both from your regular laboratory instructor and from the laboratory instructor for the laboratory you wish to attend*. An e-mail to both instructors is the easiest method to achieve this; if you do not make a formal request to both instructors, you will not be admitted to another laboratory section. **The notebooks will be due at the end of your last laboratory period and you must check out of laboratory on your last regularly scheduled laboratory day.**

GRADES

No specific laboratory grades will be assigned, but each student's work will be evaluated against an absolute standard; for many students the laboratory will not change the grade earned in lecture but for borderline cases, or instances of exceptional performance, the laboratory may affect the grade. **Please note that a grade cannot be issued for CHEM 33 unless you have completed the laboratory and turned in a notebook, so be sure to turn in your notebook on time to your laboratory instructor.**

EXPERIMENTS

There are six categories of experiments. You are to choose one experiment from each group. If you have the time and interest to do more than six experiments, you are free to choose any of the experiments listed in the syllabus. You can find supplemental spectra on the Chem33L course pages. **You are free to choose experiments in any order you like, but remember that *at least one of your six experiments must include a procedure that requires at least two steps.*** The individual steps in this multistep experiment may include experiments from two of the six categories. Examples of multistep syntheses are included in the scheme below. You may start anywhere in this scheme.



Some experiments are easy and others are difficult. Each of the experiments is ranked according to its difficulty. "0" means an average experiment, "-" means easier than average, and "+" means more difficult. You should choose a balanced mixture of experiments, avoid either doing all easy ones or all hard ones.

DATA, EXPERIMENTAL RESULTS, AND EXERCISES

You may recall from last term that complete characterization of compounds includes appropriate tests for identity and purity. Identity is typically determined using spectroscopic methods, which usually includes taking ^{1}H NMR and IR spectra of the compound. In practice, all the organic students cannot run ^{1}H NMR spectra given the time and technical expertise required, but you should acquire and interpret the IR spectrum for all the compounds you prepare. In some cases, you will have to interpret NMR spectra which you can find on the Chem33L course page.

Melting points for solids and boiling points for liquids (measured during distillation) should be compared to literature values to determine if the compound was prepared successfully. Remember that the mp or bp will only correspond to literature values if the compound is pure and these values are measured accurately. Purity should be determined by TLC for solids and GC for liquids. High-boiling liquids can be analyzed by TLC as well. For synthesis experiments, you should calculate the percent yield of your product to evaluate the efficiency of your procedures. Consult with your laboratory instructor if you have any questions concerning the characterization of your products or other data to be included for each experiment.

The following tests need to be conducted for most of the compounds prepared or isolated in the laboratory this term. Although some experiments entail additional analyses, the tests below for purity and identity are general guidelines to follow.

Purity of a solid:

1. TLC: Report the R_f and compound identity of each spot on the TLC. Ideally, R_f for the product should be about 0.5. Report developing solvent system, visualization method (UV usually), and attach or draw the TLC plate in your notebook.

2. MP: A sharp mp (2–3 ^{o}C melting range) usually indicates that the sample is pure. Comparison to literature value is required for indication of purity (and identity, see below). If the rate of heating for obtaining the mp is too rapid, the mp range will always be large, resulting in a mp that will be lower than literature values.

Purity of a Liquid:

1. GC: Report retention times for all peaks and provide the identity of the compound responsible for the major peak and that of any other peaks that you can. Determine the percentage of product in your sample. High-boiling liquids (bp >170 ^{o}C) should be analyzed by TLC, given the temperature limits of our GCs.
2. BP: Report bp of fractions from distillation containing the final product. Comparison to literature value is required for indication of purity (and identity, see below). A small-scale bp determination can be done in required cases; see your instructor for details.

Identity:

Determined using spectroscopic means, such as ^{1}H NMR and IR spectroscopy. We have ready access to IR spectrometers in the laboratory, so an IR spectrum should be collected for most compounds prepared in the laboratory. ^{1}H NMR spectra and ^{13}C NMR spectra are available for interpretation on the Chem 32L web pages for some compounds. If you do produce a sample of very high quality, please submit it to your laboratory instructor in a labeled vial and show your purity data to your laboratory instructor.

1. IR: Report the frequency of all the major (or largest) IR peaks and which functional group is indicated by that peak. Comparison to a literature spectrum of the compound is required to confirm identity. List the major peaks that are consistent with the literature spectrum if the IR spectrum indicates that the desired compound was prepared. A table is a useful method of presenting this data with the following headings:

IR Data

Frequency (cm^{-1})	Functional Group

2. ^{1}H NMR: The chemical shift (in ppm), coupling (*e.g.,* singlet, doublet, triplet, etc.), integration should be reported for all peaks. Each peak should then be correlated to a proton or group of protons in the compound. A table with the following headings should be used:

^{1}H NMR Data

Chemical Shift (ppm)	Coupling	Integration	proton(s)

Yield:

1. Percentage Yield for Synthesis Experiments:

You need to calculate the percent yield of your product to evaluate the efficiency of your procedures. Because most experiments in a sophomore organic course should work most of the time, a good yield of a pure compound is expected. Low yield of the correct compound is most commonly attributed to the quality of the reagents or mistakes in the procedure. Note these sources of possible error as you conduct the experiment, and document them in your results and discussion section. Recall that an accurate percent yield calculation requires that you determine the number of moles of the limiting reactant and use that number for the maximum moles of your product. Dividing the actual moles of the product by the maximum moles possible and multiplying by 100 gives the percent yield. You can also convert the maximum number of moles to the theortical yield in grams

and then divide the grams of the product isolated by the theoretical yield mutlplied by 100 to determine the percent yield. Again a table for these calculations is used with the following headings:

Reactant/product names	MW (g/mol)	Density (for liquids) (g/ml)	Quantity Used (g or mL)	Moles Used (mmol)	Theoretical Yield (g)

Examples of calculations of % yield are provided in the laboratory textbook, pp. 35-36.

2. Weight Percent for Isolation Experiments:

For the isolation experiments, report a weight percent recovered. The weight percent is calculated by dividing the weight of the compound isolated by weight of the material from which the compound was extracted from.

EXPERIMENT LIST WITH REQUIRED ANALYSES

GROUP 1: CARBOXYLIC ACID DERIVATIVES

Difficulty	Exp. #	Title	Required Analysis
(0)	1	Amide Preparation of Using Chloroformate-Mixed Anhydride Activation	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(0)	2	Peptide Synthesis: Preparation of a Protected Dipeptide via EDC Coupling	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	3	Formation of an Acid Hydrazide: Preparation of Luminol and Chemiluminescence	% yield, TLC, interpret ^{1}H NMR spectrum
(0)	4	Benzylic Acid Synthesis	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum

GROUP 2: OXIDATION AND REDUCTION

(0)	5	Oxidation of Benzoin: Preparation of Benzil	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(0)	6	Green Chemistry-Bleach Oxidations	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(0)	7	Reductive Amination-Acylation Process	% yield, mp, TLC, IR spectrum

GROUP 3: ADDITION REACTIONS

(0)	8	Suzuki Coupling	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(0)	9	Diels-Alder Reaction in Water	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(0)	10	Preparation of 1,2,3,4-Tetraphenylnaphthalene	% yield, mp, TLC, IR spectrum

GROUP 4: CONDENSATION REACTIONS

(+)	11	Synthesis of Benzoin	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	12	Aldol Condensation – Select Your Own Nucleophilic and Electrophilic Components	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectra (if available)
(+)	13	Aldol Condensation: Preparation of 2,3,4,5-Tetra phenylcyclopentadienone	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum

GROUP 5: ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

(+)	14	Nitration of Methyl Benzoate	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	15	Friedel-Crafts Alkylation	% yield, mp, TLC, IR spectrum
(+)	16	Pechman Condensation for Coumarin Synthesis	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum

GROUP 6: CHALLENGE EXPERIMENTS

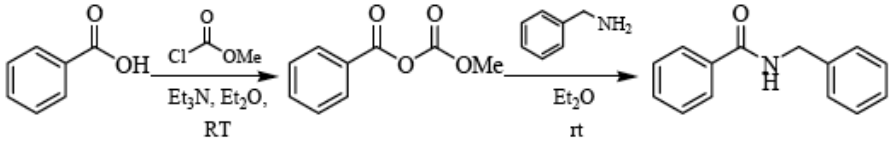
The Challenge Experiment procedures are open-ended experiments that will challenge you to work more independently than is typical for sophomore organic experiments. **Discuss your chosen experiment one week in advance with your instructor so that you understand the specific details of the procedure**.

(+)	17	Acetanilide via Beckman Rearrangement	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	18	Synthesis and Polymerization of Caprolactam	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	19	Synthesis of Methyl Diantilis	% yield, TLC, IR spectrum
(+)	20	Synthesis of Phenytoin	% yield, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	21	Knoevenagel Condensation: Preparation of 1,1-Dicyanoalkenes from Aldehydes	% yield, mp, TLC, IR spectrum, interpret ^{1}H NMR spectrum
(+)	22	Esterification Reactions of Vanillin: and NMR Structure Proof Challenge	% yield, mp, TLC, IR spectrum, interpret ^{1}H and ^{13}C NMR spectrum

GROUP 1: CARBOXYLIC ACID DERIVATIVES

EXPERIMENT 1 -- PREPARATION OF *N*-BENZYL BENZAMIDE USING CHLOROFORMATE-MIXED ANHYDRIDE ACTIVATION

In qualitative organic analysis the preparation of a derivative of an identified organic compound is required for confirmation of its identity. For carboxylic acids the most common derivatives are amides and acetanilides. These derivatives are prepared through acid chlorides by treatment of the carboxylic acid with phosphorus pentachloride or thionyl chloride, both of which are highly toxic. Thus, an alternative method for preparation of a solid derivative of carboxylic acids avoiding these toxic chemicals is highly desirable. The *N*-benzyl benzamide can be a good alternative, and it can be prepared in a greener way. The reaction scheme you will use is shown below.



EXPERIMENTAL PROCEDURE

Weigh about 2.46 mmol of benzoic acid (MW = 122.1 g/mol) and place it in a 25 ml Erlenmeyer flask. Clamp the flask, add 12 ml of ethyl acetate and 0.4 ml of triethylamine and stir the mixture vigorously. At room temperature add dropwise 2.58 mmol of methyl chloroformate (MW = 94.50 g/mol; d = 1.22 g/mL). You will have to ask your instructor for a 1.0 mL syringe and needle to dispense this reagent. After 10 minutes of stirring, filter the mixture through a Hirsch funnel and wash the precipitate with ethyl acetate (3 ml). Place the **filtrate** in a clean 25 ml Erlenmeyer flask and treat it with 2.75 mmol (1.12 equiv) of benzylamine (MW = 107.15 g/mol; d = 0.981 g/ml). Stopper the flask with a cork and stir the mixture for 15 minutes at room temperature. Once the reaction is complete, transfer the solution into a 25 mL round bottom flask and evaporate the ethyl acetate on the rotavapor. Add some crushed ice to the viscous residue (about 3 g) and stir it with a glass rod until you obtain a white solid Filter the solid through a Hirsch funnel and let it air dry for five minutes. If you obtained a solid after evaporating the ethyl acetate on the rotavapor you can directly move to the recrystallization step. Weigh your crude product and recrystallize it from a 2:1 hexane/ethyl acetate mixture. Weigh the recrystallized product and calculate its percentage yield. Determine the melting point range of your recrystallized product (lit. mp: 104-106 °C). Obtain an IR spectrum of your recrystallized product and perform a TLC analysis. Interpret the ^{1}H NMR of *N*-benzyl benzamide that is posted online. Refer to the Table on pages 9&10 for a complete list of all required analysis.

Questions

1. What is the role of triethylamine in the first step of this synthesis?
2. Could you have made *N*-benzyl benzamide directly by reacting benzoic acid with benzyl amine? Briefly explain.
3. Using curved arrows, write a complete mechanism for the reaction you performed.

EXPERIMENT 2 -- PEPTIDE SYNTHESIS: PREPARATION OF α-PROTECTED DIPEPTIDE VIA EDC COUPLING

Amino acids are multifunctional molecules that are the building blocks from which all peptides (oligomers of amino acids) and proteins (polymers of amino acids) are constructed. Using the 20 common, naturally occurring amino acids, an enormous array of peptides and proteins can be constructed. Because amino acids have (at a minimum) both an amino group and a carboxylic acid group, it can be a challenge to design reaction conditions in which only one functional group from one molecule reacts with only one functional group from another molecule.

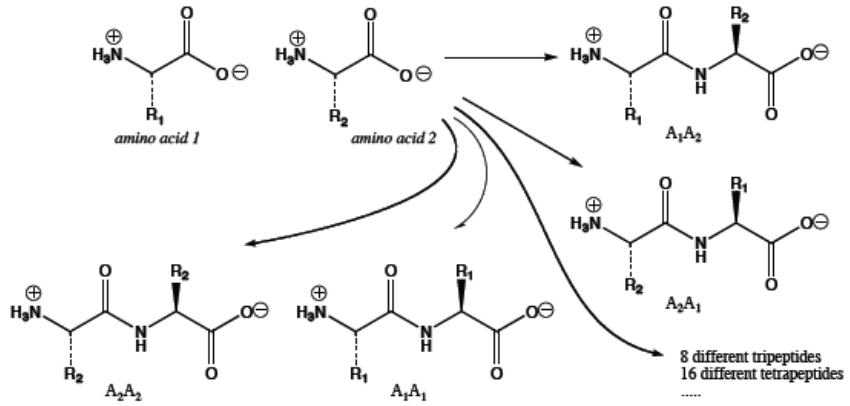


Figure 1. Random coupling of amino acids can result in a mixture of products.

The common solution to this problem is to use *protecting* groups to block the reactivity of certain functional groups. As a result, it is possible to make amino acids in which only the acid group is available to react and to make amino acids in which only the amino group is available to react. Under these conditions, only one dipeptide product will result.

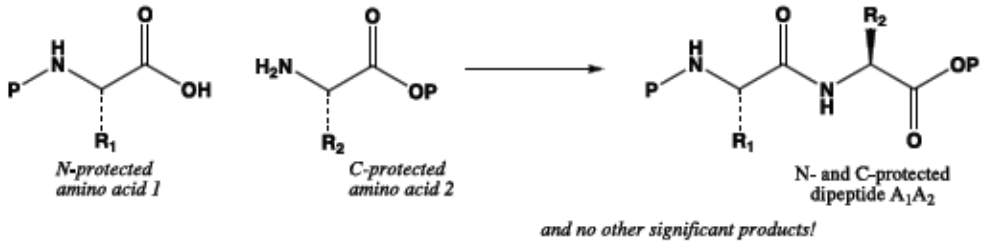
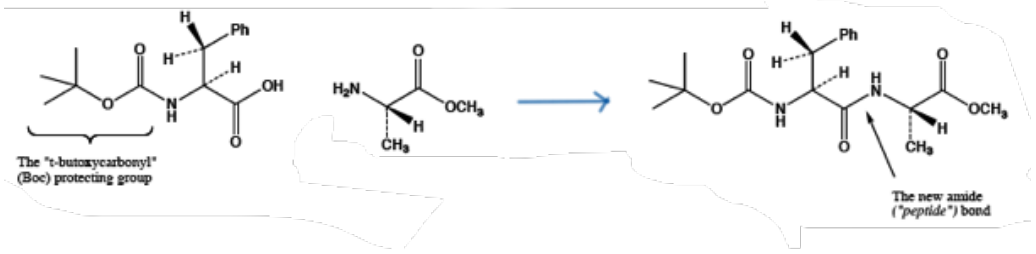


Figure 2. Coupling of protected amino acids result in one major product.

In this experiment you will use two different amino acids: one that is N-protected (so the amino group does not react) and one that is C-protected (so the carboxylate does not react). Accordingly, only one dipeptide can result. In principle (and in practice), one end can then be deprotected and the chain can then be elongated with a third amino acid, then a fourth, and so on. A number of important synthetic peptides are prepared in the laboratory by this stepwise approach. We will be using a simple methyl ester as a way to block the reactivity of one carboxylic acid group, and we will use a “Boc” protecting group to block the amino group on the other amino acid.



We will use a carbodiimide coupling agent to bring about the formation of an amide (or “peptide”) bond that links these two amino acids. The carbodiimide functional group contains an N=C=N linkage, and these functional groups are unusual in that they preferentially react with carboxylate nucleophiles rather than amine nucleophiles. The resulting adduct is an *active ester*. The active ester is electrophilic and reacts with another nucleophile in a classical addition-elimination manner, and if that nucleophile is the amino group of the C-protected amino acid, the desired dipeptide product is formed. If the nucleophile happens to be the carboxylate group of another molecule of N-protected amino acid, then an anhydride is formed. Anhydrides are highly reactive species, and when this anhydride reacts with the amino group of the C-protected amino acid, the desired dipeptide is also formed.

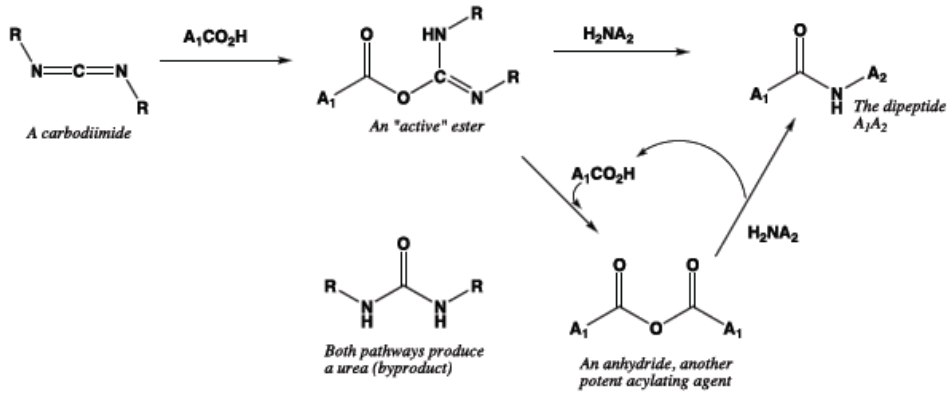


Figure 3. The carbodiimide-mediated coupling of an N-protected amino acid (A_1CO_2H) and a C-protected amino acid (H_2NA_2) to produce an N- and C-protected dipeptide A_1A_2.

We will be using a specific carbodiimide reagent known as EDC (1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide). The major advantage of this reagent over other carbodiimides is that the urea byproduct is water-soluble and can be easily removed from the product mixture after the reaction. We will also use HOBt (*N*-hydroxybenzotriazole), which helps to suppress racemization of the active ester, and DMAP (*N*,*N*-dimethylaminopyridine) as a base.

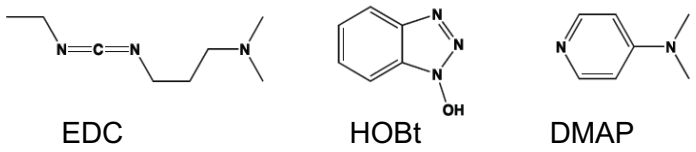


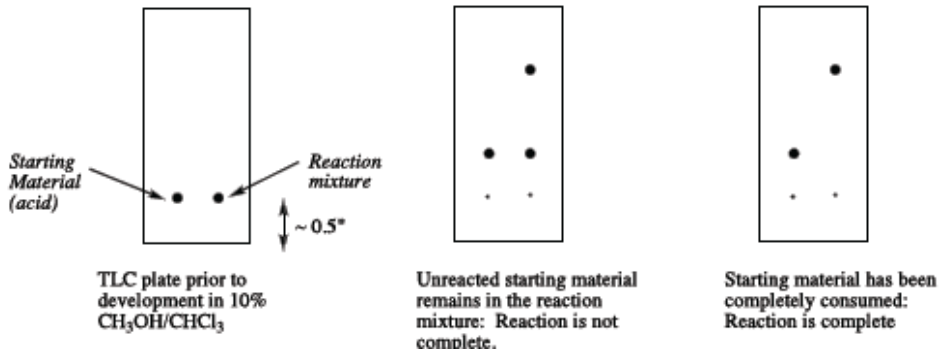
Figure 4. The carbodiimide coupling reagent EDC, the additive HOBt, and DMAP.

EXPERIMENTAL PROCEDURE

Coupling reaction

You will be preparing a solution that contains both amino acids, cooling it, and then adding the coupling agent EDC. Please note that the AlaOMe is supplied as the hydrochloride salt (AlaOMe•HCl), so the molecular weight includes one equivalent of HCl. Carefully weigh 0.942 mmol (1eq) of BocPhe (MW = 265.3 g/mol), 1.036 mmol (1.1 eq) of AlaOMe•HCl (MW = 139.6 g/mol), 1.036 mmol (1.1 eq) of HOBt (153.1 g/mol), 1.036 mmol (1.1 eq) of DMAP (122.17 g/mol) and add to a 10 ml round bottom flask. Then add 2.5 ml of CH_2Cl_2 along the sides of the flask to wash off any residue that is stuck to the sides, add a magnetic stir bar, and cap the flask. DO NOT add EDC at this step. Set up an ice bath over a stir plate and cool and stir the reaction mixture. While the mixture is cooling, weigh 1.978 mmol (2.1 eq) of EDC (155.2 g/mol) by using a capped vial, and by dispensing the reagent in the hood. After the mixture of amino acids and HOBt in CH_2Cl_2 has cooled, add the EDC, recap, and continue to stir the mixture.

Monitor the progress of the reaction every 20 minutes by TLC using 10% methanol in chloroform (1 ml of methanol mixed with 9 ml of chloroform) as the developing solvent. To perform the TLC, use a Pasteur pipet to remove a small sample of the reaction mixture and put it in a labeled vial. Dilute that sample with a small amount (~0/5 ml) of CH_2Cl_2. To compare to starting materials, dissolve a small amount of the "Acid" used for the reaction in CH_2Cl_2 in another labeled vial. Then carefully make two spots on your TLC plate using separate capillary tubes for each mixture: one of the "Acid", one of the reaction mixture. When no spot is present in the reaction mixture where the "Acid" spot lies, the reaction is complete. Repeat every 20 minutes until the reaction is complete, making sure to use clean pipets, vials, and capillary tubes for each trial.



Work-up and purification

At this stage, the product is in a mixture that contains a number of other compounds that we are not interested in. Removal of undesired compounds in the mixture is accomplished (in part) in a *workup* process, in which different byproducts and left over starting materials will be washed out of the organic solution that contains the product. For the workup, first dilute with ~10 mL of CH_2Cl_2 and divide up the mixture equally into 2 centrifuge tubes. Then add ~5 mL of 1M HCl to each centrifuge tube and shake while intermittently venting. The solution will form two layers, and dichloromethane, like other halogenated organic solvents, is denser than water and falls to the bottom. Remove the aqueous layer (top layer) and place it in a beaker labeled "acid waste". Add ~5 mL of 5% aqueous $NaHCO_3$ to each centrifuge tube, gently shake and vent, and allow the mixture to separate into two layers. Remove the aqueous layer and place it in a beaker labeled "basic waste". Save the organic layer (again, CH_2Cl_2 is the lower layer). Repeat the above step with ~5 mL of distilled water, keeping the organic layer. Repeat the above step with ~5 mL of brine (a concentrated NaCl solution), keeping the organic layer. Set a funnel into an Erlenmeyer flask and line the funnel with a filtration paper. Then add some sodium sulfate (Na_2SO_4) over the filter paper and drain the organic layer through the sodium sulfate into the flask. Dribble some additional CH_2Cl_2 over the sodium sulfate to wash down any extra product that may be stuck to the sodium sulfate. Add product to a pre-weighed round bottom flask and evaporate the CH_2Cl_2. A white solid should be left in the round bottom flask. Recrystallize the crude product from a 3:1 Hexane:Ethyl Acetate mixture. Weigh the pure product and determine its percent yield. Obtain an IR spectrum and check the purity of the product by TLC. Refer to the Table on pages 9&10 for a complete list of all required analysis.

QUESTIONS

1. Using curved arrows, write a complete mechanism for the formation of the peptide from the starting amino acids.
2. Draw the structure of the peptide you would obtain by using Boc-Ala and Phe-OMe as the starting amino acids and keeping all the other reagents the same.

EXPERIMENT 3 -- SYNTHESIS OF LUMINOL

OVERVIEW

In this experiment you will synthesize the compound Luminol (Fig. 1). The synthesis involves generating the hydrazide of 3-Nitrophthalic Acid, followed by reduction of the nitro (-NO_2) group to an amine (-NH_2) (Scheme 1). Then you will examine the chemiluminescence exhibited by this compound.

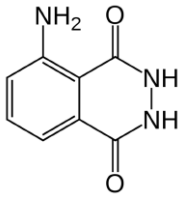
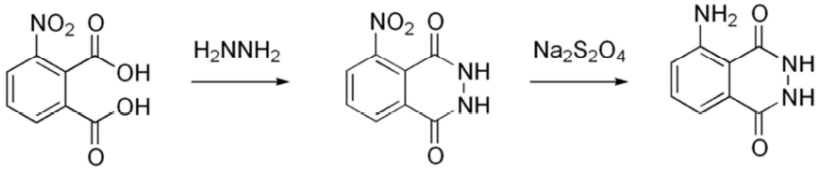


Figure 1. Luminol

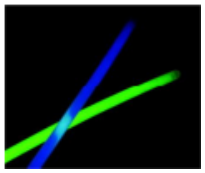


Scheme 1. Synthesis of luminol.

INTRODUCTION TO LUMINESCENCE

Molecular luminescence occurs when a transition from an electronically excited state to a more relaxed state results in the emission of a photon. In the case of fluorescence and phosphorescence, the excited molecular state is the result of the molecule having absorbed a photon.

Chemiluminescence occurs when a molecule is left in an electronically excited state as a result of a chemical reaction. This is the type of luminescence is exhibited by commercially available glowsticks.

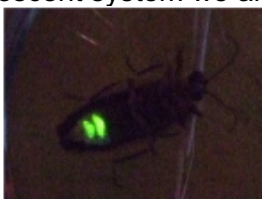


Glowsticks (http://en.wikipedia.org/wiki/Chemiluminescence

Bioluminescence, chemiluminescence occuring biologically, has been known for some time. It was first discovered in a Mediterranean clam by Dubois:[1]

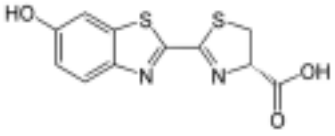
> *The first significant studies of a bioluminescent organism were by the French physiologist Raphael Dubois in 1887. He studied the mollusk Pholas dactylis, a bioluminescent clam indigenous to the Mediterranean Sea. Dubois found that a cold-water extract of the clam was able to emit light for several minutes following the extraction. When the light emission ceased, it could be restored, he found, by a material extracted from the clam by hot water. A hot-water extract of the clam alone did not produce the luminescence. Reasoning carefully, Dubois concluded that there was an enzyme in the cold-water extract that was destroyed in hot water. The luminescent compound, however, could be extracted without destruction in either hot or cold water. He called the luminescent material* ***luciferin****, and the enzyme that induced it to emit light,* ***luciferase****,; both names were derived from Lucifer, a Latin name meaning "bearer of light." Today the luminescent materials from all organisms are called luciferins, and the associated enzymes are called luciferases.*

A bioluminescent system we are all probably familiar with is that of the firefly.



Firefly Luminescence: http://en.wikipedia.org/wiki/Firefly

The firefly luciferin requires O_2, Mg^{2+}, and ATP, in addition to Luciferase, for activity. It is thought reaction bringing about luminescence occurs in two steps. First, Luciferin is adenlyated by ATP, releasing Pyrophosphate (PP).



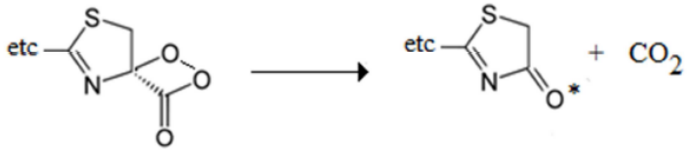
Luciferin + ATP → Luciferyl Adenylate + PP

The adenylate is then oxidized by the O_2, resulting in the production of a cyclic endoperoxide intermediate; an unfavorable reaction that requires "priming" by the ATP. The endoperoxide decarboxylates, resulting in electronically excited Decarboxyketoluciferin, which then chemilumineses.

Luciferyl Adenylate + O_2 → Decarboxyketoluciferin* + AMP + CO_2

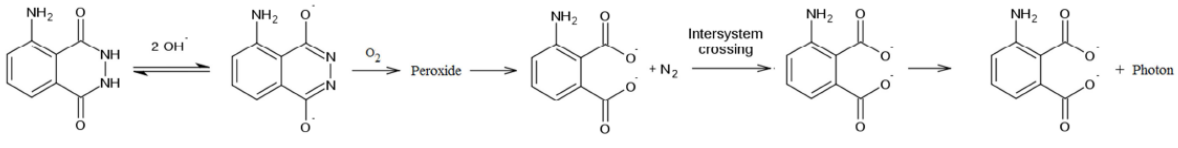
Decarboxyketoluciferin* → Decarboxyketoluciferin + photon

It is the decomposition of the endoperoxide that Molecular Orbital Theory predicts will result in an excited carbonyl group,that then leads to chemiluminescence.



Endoperoxidase

In our case, we will produce the synthetic chemiluminescent compound Luminol. When oxidized by an oxidizing agent such as O_2 in a basic solution, Luminol forms an unstable peroxide. This peroxide decomposes to an electronically excited dianion that then chemiluminesces.



Although first synthesized in 1902, it was not until recently that Luminol found commercial importance. Currently it is used to detect trace blood samples at crime scenes.

EXPERIMENTAL PROCEDURE

Safety notes

- The entire synthetic procedure should be carried out in the fume hood.
- Hydrazine is extremely toxic. Do not spill this on your skin.

- Foaming sulfur dioxide is liberated during the reduction step. This gas is toxic.

Synthesis of luminol

Combine 1.42 mmol of 3-Nitrophthalic Acid (MW = 211.1 g/mol) and 0.6 ml of 10% hydrazine solution in a 5 ml conical vial. Add a spin vane to the vial and immerse it in a sand bath. Secure the vial with a small clamp. Heat the mixture until the solid dissolves. Add 0.8 ml of triethylene glycol. Insert a thermometer into the solution and secure it with a small clamp. Boil the solution to remove the water, and then bring the temperature to 210-220 °C. You may have to wrap some aluminum foil around the vial if the temperature doesn't go over 200 °C. Maintain the temperature for 3-4 minutes. Turn off the heat and allow the mixture to cool to 100 °C. In the meantime, bring about 10 ml of water to boiling and then slowly add 4.0 ml of your hot water to the reaction mixture. Cool the conical vial in an ice bath while stirring the mixture with a glass rod. 3-Nitrophthalhydrazide should form. Vacuum filter this compound and use it without further purification. Transfer the moist compound to the conical vial. Add slowly 1.30 ml of 10% Sodium Hydroxide and swirl the mixture until the hydrazide dissolves. Add slowly 3.81 mmol of sodium dithionite ($Na_2S_2O_4$; MW = 174.1 g/mol) and 1-2 ml of water. Heat the mixture to boiling. Stir and maintain boiling for 5 minutes. Cool the mixture. Add 0.50 ml of Glacial Acetic Acid and swirl the mixture during cooling.The resulting solution should be acidic to litmus. Collect the light yellow precipitated luminol by vacuum filtration using a Hirsch funnel. Weigh your product and determine the percent yield. The product may be used without drying for the chemiluminesence experiment. Refer to the Table on pages 9&10 for a complete list of all required analysis.

Chemiluminescence

Add a layer of potassium hydroxide pellets to the bottom of a 10 ml Erlenmeyer flask. Add a small amount of dimethylsulfoxide, enough to cover the pellets. **In a darkened area,** add 0.04-0.06 g of luminol to the flask. Stopper the flask and shake it vigorously to mix air into the solution. Note what happens.

QUESTIONS

1. Write the complete mechanism for the formation of the hydrazide from 3-Nitrophthalic Acid.
2. Write an alternate resonance structure for the dianion that results from placing Luminol in a basic solution.

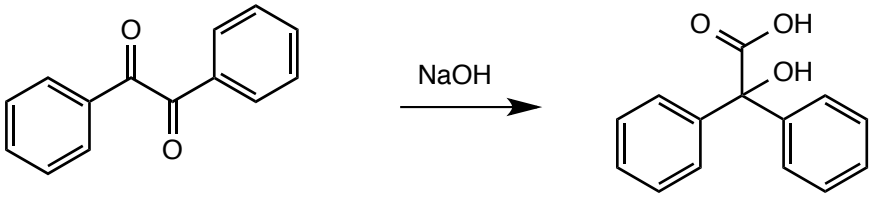
REFERENCES

1. *Introduction to Organic Laboratory Techniques* Donald L. Pavia, Gary M. Lampman and George S. Kriz

EXPERIMENT 4 -- BENZILIC ACID SYNTHESIS

OVERVIEW

You will synthesize benzilic acid from benzil using a solvent-free, solid state method shown below. This procedure is "greener" than the conventional procedures that use organic solvents.



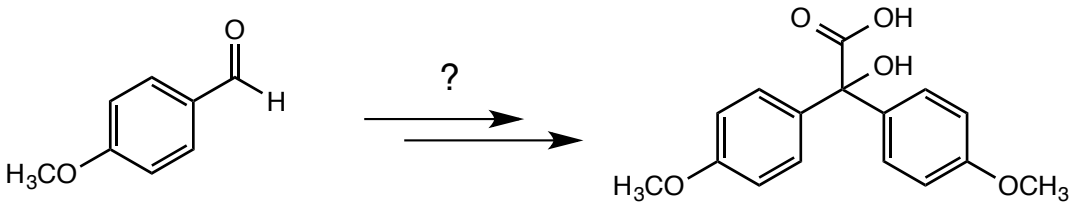
benzil benzilic acid

EXPERIMENTAL PROCEDURE

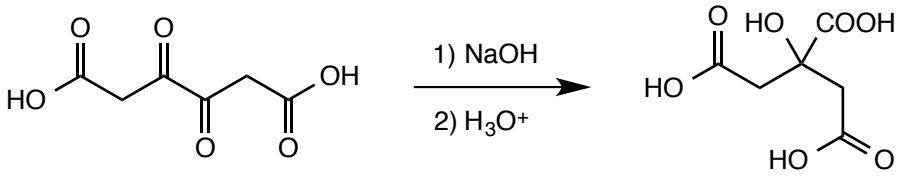
Place benzil (0.952 mmol; MW = 210.2 g/mol) and solid NaOH (5 mmol; MW = 39.99 g/mol) in a dry mortar. With the help of a pestle, thoroughly grind them together to make an easy flowing powder. Place this material in a dry 5 mL conical vial fitted with an air condenser and a drying tube containing a piece of cotton at its mouth. Heat the mixture in a hot boiling water-bath for 20 min. Cool it to room temperature and dissolve it in 15 mL of water. (If you have any unreacted benzil, remove it simply by filtration.) Acidify the aqueous solution with conc. HCl while cooling in ice. Filter the precipitated benzilic acid, wash it with cold water, and recrystallize it from hot water. Weigh the recrystallized product and calculate the percent yield. Measure its melting point, which is reported to be 149-151 °C. Obtain an IR spectrum and analyze the product by TLC. Refer to the Table on pages 9&10 for a complete list of all required analysis.

QUESTIONS:

1. Show how you might prepare the following analog of benzilic acid starting from 4-methoxybenzaldehyde.



2. Draw a detailed mechanism for the following transformation.



REFERENCES

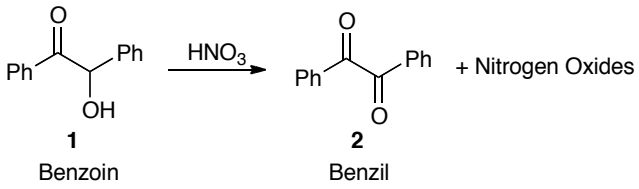
K. Tanaka and F. Toda, *Chem. Rev.,* **2000***, 100,* 1045.

GROUP 2: OXIDATIONS AND REDUCTIONS

EXPERIMENT 5: PREPARATION OF BENZIL

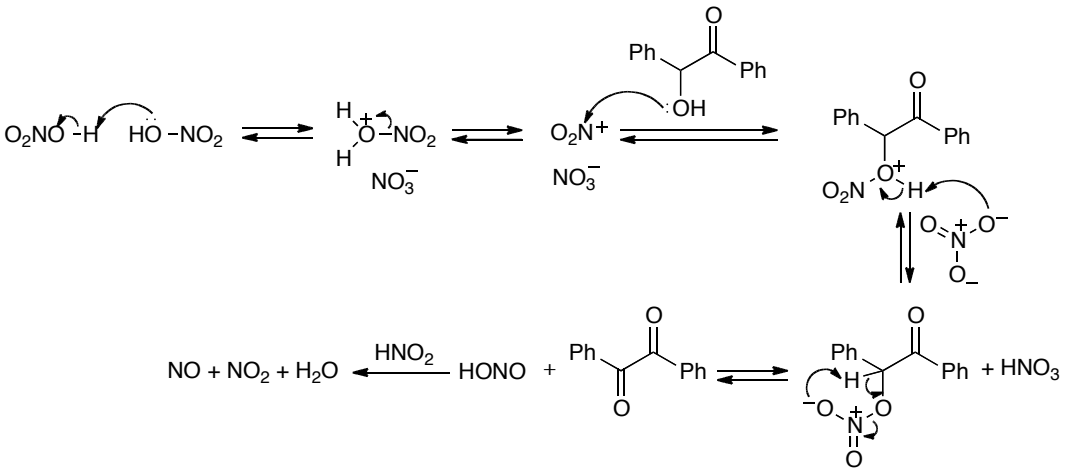
INTRODUCTION

This procedure involves the oxidation of the alcohol of benzoin (**1**) to a ketone to produce benzil (**2**). A number of oxidizing agents can be used to accomplish this transformation; nitric acid will be used in this case. You probably think of nitric acid as a very strong inorganic acid, i.e. a powerful proton-transfer agent, rather than as an oxidant, but it serves the latter function as well.



1 Benzoin **2** Benzil

The possible mechanistic sequence by which oxidation occurs is outlined in general terms below. Note the formation of oxides of nitrogen by decomposition of the nitrous acid, HNO_2, that is formed in the oxidation.



EXPERIMENTAL PROCEDURE

Safety notes

- Concentrated nitric acid causes severe chemical burns. Do not allow it to come into contact with your skin. Wash any affected area immediately with water and then with 5% sodium bicarbonate. Wear latex gloves when transferring this reagent.

Oxidation to form benzil

Place 2.00 mmol of benzoin (MW = 212.2 g/mol) in a 4 mL conical vial equipped with a spinvane. (Note: if you are doing this as a multi-step and do not have 2.00 mmol of benzoin, supplement with the benzil we have on the shelf. Add 1.5 ml of *concentrated* nitric acid (63.01 g/mol; 70% aqueous solution; d = 1.51 g/mL) and attach the air condenser to the vial and a drying tube (do not add any cotton or drying reagent to the drying tube). Clamp the apparatus in a water bath (half-filled 100 mL beaker) and heat the water bath at about 70 °C for 75 min. Direct the drying tube away from you towards the back of the hood. Note that heating above this temperature may result in formation of undesired by-products and should be avoided. Remove the heating source and transfer the hot mixture to a beaker containing 4 ml of ice-cold water, using a short stem piper. Rinse the vial and spinvane with a little water, adding the rinses to the beaker. Cool the beaker in an ice-water bath until crystallization occurs. If the product oils out rather than crystallizing, scratch at the air/water interface with a glass rod

to induce crystallization. Isolate the crude product by vacuum filtration through a Hirsch funnel. Wash the filter cake well with 4–5 ml of cold water to remove any residual nitric acid from it. Continue to draw air through the filter cake in order to dry the product. Measure the weight of the solid obtained.

Purification of benzil

Transfer the crude product to an Erlenmeyer flask and recrystallize the product in 95% Ethanol. You will need about 5 ml of solvent per 0.5 g of product, so be certain the Erlenmeyer flask is of appropriate size. Use care in effecting dissolution by ensuring that the solid does not melt as a result of the heating but rather dissolves in the solvent. Frequent swirling of the flask will minimize the possibility of melting occurring, and you will obtain better crystalline product if a bit more than the minimum amount of solvent needed for complete dissolution is used. Once the solid has dissolved, remove the flask from the hot plate and allow the solution to cool slowly. Once the flask is a room temperature, crystallization will occur. In case you do not see any crystals forming scratch the bottom of the flask with a glassrod. Complete the crystallization by placing the flask in an ice-water bath and collect the benzil by vacuum filtration through a Hirsch funnel. Rinse the flask with a total of about 1 ml of ice-cold 95% ethanol to complete transfer of the purified product to the funnel. As before, continue to draw air through the filter cake for about 5 minutes in order to partially dry the benzil. Transfer the filter cake to a small beaker and air-dry the solid. Weigh the product and calculate the yield. Measure the melting point, which is reported to be 94–95 °C. Obtain an IR spectrum and analyze the purity of the product by TLC. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

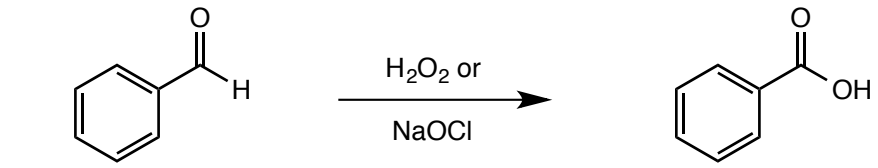
Questions

1. How many peaks would be expected in the ^{13}C NMR spectrum of benzoin?
2. How many peaks would be expected in the ^{13}C NMR spectrum of benzil?
3. What is the color of the benzil you isolated, and how does its mp compare to that reported in the literature?

EXPERIMENT 6: OXIDATION OF ORGANIC COMPOUNDS USING GREEN CHEMISTRY

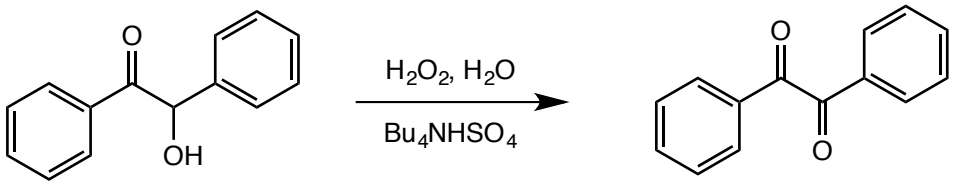
OVERVIEW

Green Chemistry endeavors to use new reagents or familiar reagents that are less toxic in order to be more environmentally friendly. In this experiment, Chlorox (which does present some hazards) will be used in place of the more commonly used, but also more toxic, dichromate reagents. The three reactions you will perform are given below.



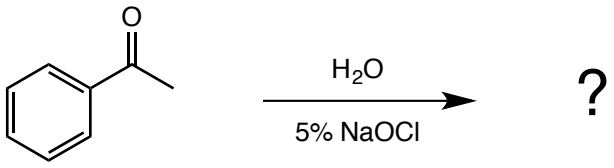
benzaldehyde
(MW 106.1, bp 178 °C)

benzoic acid
(MW 122.1, mp 121-122 °C)



benzoin
(MW 212.3)

benzil
(MW 210.2)



acetophenone

INTRODUCTION

Green chemistry is a new aspect of chemistry in which environmentally friendly reagents are used in place of more hazardous traditional reagents. A great deal of research is currently being done in this area and major successes have been achieved.

However, one difficulty with green chemistry is finding reagents that perform as well as the traditional reagents. Consider a simple reaction such as the oxidation of benzaldehyde to benzoic acid. Traditional dichromate reagents perform this oxidation very efficiently, but the chromium waste is a significant environmental problem. Because of the general ease of oxidation of aldehydes, it was thought that simple household oxidants might be used instead but still perform as efficiently.

In this experiment, you will use household reagents not only to oxidize benzaldehyde but also to oxidize benzoin and acetophenone. Note that the oxidation of benzoin can be part of a multi-step synthesis if you use benzoin you made in Experiment 11. The oxidation of acetophenone is an interesting open-ended experiment, and you will have to determine the identity of the product.

Chlorox, a mild oxidant, is a dilute solution of sodium hypochlorite (NaOCl). Chlorox should never be mixed with ammonia solutions or ammoniated cleansers because a reaction that releases deadly chlorine gas occurs.

EXPERIMENTAL PROCEDURE

Safety notes

- The entire synthetic procedure should be carried out in the fume hood.
- Although the oxidants are household chemicals, you still need to be careful handling them. If you get any on your hands, you will not feel it immediately, but white patches will soon appear: use gloves and treat with caution.

Oxidation of Benzaldehyde

Place benzaldehyde (9.0 mmol) and glacial acetic acid (0.50 ml) in a 50 ml Erlenmeyer flask with a magnetic stir bar, and gently heat on a stirrer-hotplate. To the reaction mixture add household bleach (15 ml) in approximately 2.5 ml portions over a 2-3 min period. After addition is complete, heat the reaction to approximately 80-90 °C (with stirring) for 45 minutes. **Do not allow the solution to boil.** Remove the flask from the stirrer-hotplate, allow it to cool to room temperature, and then place it in an ice bath. Filter off the product using a Buchner funnel, and rinse out the reaction flask and wash the product with ice-cold water. Allow the solid to dry. Analyze your product by TLC, determine the melting point and the percent yield of the benzoic acid produced. Refer to the Table on pages 9&10 for a complete list of all required analysis.

QUESTIONS

1. How many peaks would be expected in the ^{13}C NMR spectrum of benzoic acid?
2. Discuss the relative success of this reaction based on your percent yield and the melting point range of your product.

Oxidation of Benzoin to Benzil

Place benzoin (4.5 mmol), tetrabutylammonium hydrogen sulfate (0.30 mmol), ethyl acetate (15 ml), and household bleach (15 ml) in a 125 ml Erlenmeyer flask equipped with a magnetic stirrer bar. (Note: if you are doing this as a multi-step and do not have 4.5 mmol of benzoin, use the amount you have and adjust the other reagent amounts accordingly.) Stir well the mixture for 30 minutes. Check by TLC that all the benzoin was converted to product using 3:1 Hexane:Ethyl Acetate as eluent. If there is unreacted benzoin, let the reaction stir for 30 more minutes and perform another TLC. If the reaction is complete, remove the stir bar and remove the lower aqueous layer, using a Pasteur pipette. Extract the organic layer first with 10 ml of saturated sodium chloride and then with 10 ml of water. Dry the organic layer over anhydrous sodium sulfate. Decant or gravity filter to remove the solid drying agent and then evaporate the organic solvent using a rotavapor. Purify the product by recrystallization as described on page 20 under “Purification of Benzil”. Determine the melting point and the percent yield of the purified benzil product. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. How many peaks would be expected in the ^{13}C NMR spectrum of benzoin?

2. How many peaks would be expected in the ^{13}C NMR spectrum of benzil?

3. What is the color of the benzil you isolated, and how does its mp compare to that reported in the literature?

Oxidation of Acetophenone[1]

Place bleach (5% NaOCl, 7.0 ml) and a magnetic stirring bar in a 10 ml round-bottom flask. Begin stirring, and add acetophenone (1.7 mmol) in one portion. (Use a 1 ml syringe to measure the acetophenone). Continue stirring for 60 min, during which time the solution will turn from yellow to colorless. Add 0.2 g of sodium sulfite to destroy any residual oxidant. Transfer the reaction mixture equally into two 10 mL centrifuge tubes and add 2 ml of ethyl acetate to each. Cap the centrifuge tubes, shake the mixtures and wait for the layers to separate. Using a glass pipet, remove the bottom aqueous layer from each tube and place it in a 25 ml Erlenmeyer flask. The top ethyl acetate layer can be discarded in the appropriate waste container. Washing with ethyl acetate removes any unreacted acetophenone plus other side products produced in the reaction.

Cool the aqueous layer in an ice bath. While swirling the flask, add dilute sulfuric acid (3 M) dropwise until the solution is acidic to pH paper. A thick, white precipitate should form. Isolate the solid by vacuum filtration using your Hirsch funnel. Recrystallize your product from water. After drying the solid, determine its melting point and obtain its IR spectrum. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. Determine the structure of the product. Once you have determined the structure, calculate the yield of its formation.

2. Formulate a mechanism for the formation of this product. Were there any other products formed in this reaction other than the product you isolated?

REFERENCES

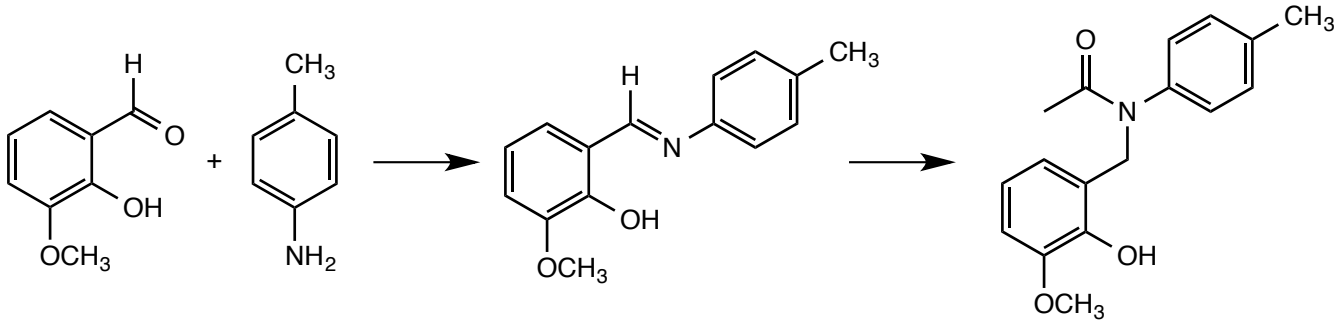
1. Adapted from Perkins, R. *J. Chem. Educ.*, **1984**, *61*, 551.

EXPERIMENT 7 -- REDUCTIVE AMINATION-ACYLATION PROCESS: TANDEM REACTIONS IN SYNTHESIS

INTRODUCTION

Reductive amination is a procedure in which an aldehyde or ketone reacts with ammonia or an amine to form an imine, which is then reduced to give a new amine. Commonly it is performed in a one-pot procedure where all the components -- carbonyl compound, starting amine, and reducing agent -- are present simultaneously. Hydrogen over nickel or a weakened hydride donor ($NaBH_3CN$, $NaBH(OAc)_3$) is often used to reduce the imine because these reagents effectively reduce imines but are slow to reduce the corresponding carbonyl compounds.

In this experiment you will react ortho-vanillin (**1**) with para-toluidine (**2**) to generate the imine **3**. The reaction occurs between the two solids in a solvent free reaction. The imine is subsequently reduced with sodium borohydride to the amine, followed by acetylation to afford the amide derivative **4** as a solid.



1 **2** **3** **4**

EXPERIMENTAL PROCEDURE

Safety notes

- Organic amines are considered potential carcinogens. Handle with caution.

Synthesis of 2-methoxy-6-(*p*-tolyliminomethyl)phenol (3): Imine formation

Place ortho-vanillin (2.5 mmol) in a 125 ml erlenmeyer flask. Using a capped vial to avoid excess exposure outside the hood, accurately weigh an equivalent molar amount of para-toluidine (2.5 mmol), and add this amine to the flask. Observe this mixture for a few minutes and record what is happening. Using a heavy glass-stirring rod, mix and grind the solids until they become a homogeneous dry powder.

Synthesis of *N*-(2-hydroxy-3-methoxybenzyl)-p-methylaniline: Reduction of the Imine

Add about 8 ml of 95% ethanol and a stir bar to the flask containing your imine product, and stir the mixture to partially dissolve the imine. Weigh out approximately 0.05 grams of sodium borohydride and slowly add this to the Erlenmeyer flask in small increments with continued stirring. Record all observations and explain what is occurring in the reaction by drawing a reaction scheme.

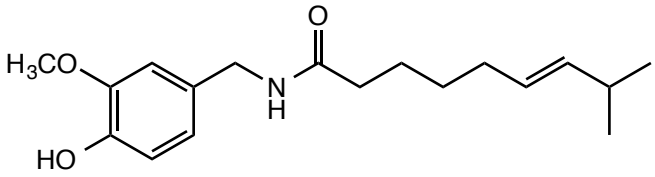
Synthesis of *N*-(2-hydroxy-3-methoxybenzyl)-N-*p*-tolylacetamide (4): Acetylation of the Amine

Add 1 ml of acetic acid to the amine to destroy the excess borohydride and to neutralize the phenoxide ion. Add 1 ml of acetic anhydride and a boiling chip and warm the solution on a stirring hot plate for 5-10 minutes. Discontinue heating, but continue stirring the solution fairly rapidly while slowly adding 38 ml of water. The addition of water should leach out the alcohol and acetic acid and cause the amide product to precipitate. Cool the mixture in an ice bath and collect the solid. Allow the solid to air-dry for

10 minutes and recrystallize it from a 9:1 Ethyl acetate/Ethanol mixture. Obtain an IR spectrum and a melting point for your purified solid (lit. melting point 127- 128^{o}C), and calculate the percent yield. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. The amine was not isolated in this reaction sequence. Briefly describe a procedure that would allow you to isolate the amine as a solid product. Predict how the IR spectrum of the amine would differ from the IR spectrum of the amide.
2. In the reduction of the imine to the amine, the imine appears to slowly dissolve in the solution. Explain what is happening. Explain why the amide product precipitates out of solution as water is added to the ethanolic solution.
3. The structure of capsaicin, the pungent ingredient in red pepper or capsicum annuum, is shown below. Suggest a multi-step synthetic scheme analogous to the sequence used in this experiment to prepare capsaicin.



capsaicin

REFERENCES

1. Adapted from Touchette, K. M. *J. Chem. Educ.*, **2006**, *83*, 929.

GROUP 3: ADDITION REACTIONS

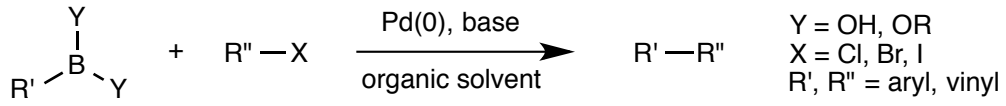
EXPERIMENT 8 -- SUZUKI COUPLING

OVERVIEW

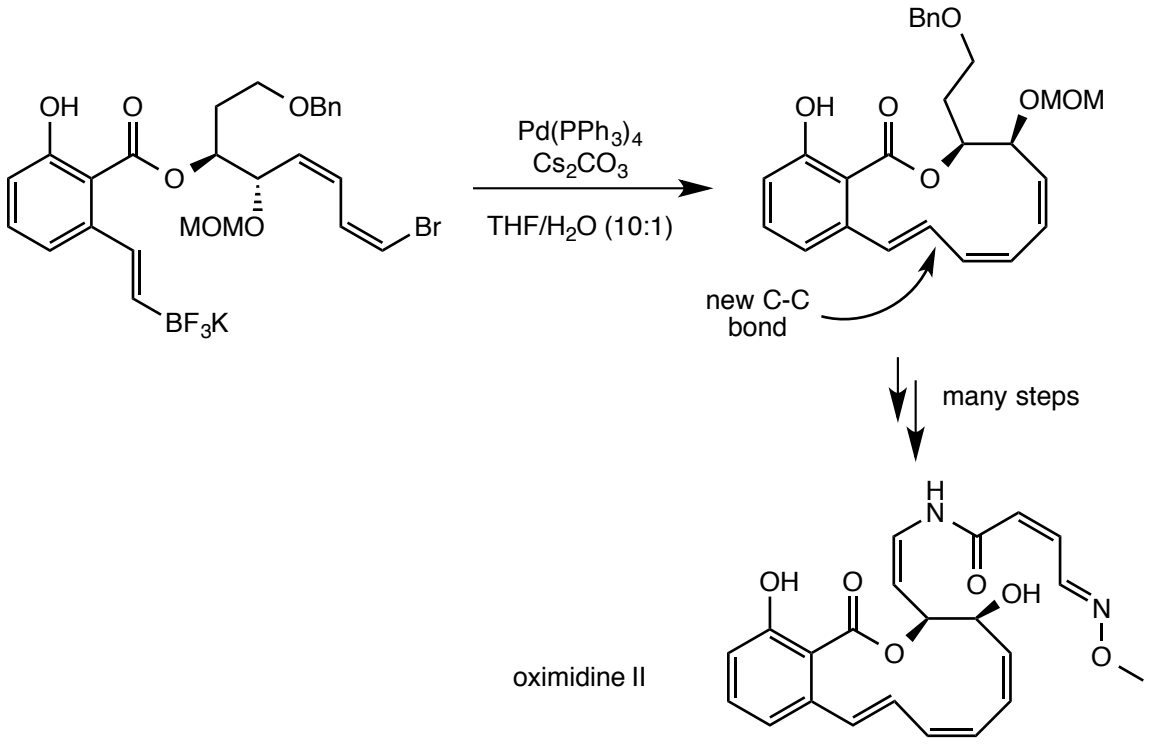
In this experiment you will synthesize 4-phenylphenol (4-hydroxybiphenyl) by a Suzuki reaction. You will analyze the ^{1}H NMR, ^{13}C NMR, and IR spectra of the product. This experiment continues the theme of green chemistry by its use of water as the solvent and because it is highly "atom economical".

INTRODUCTION

The Suzuki reaction is a very popular, mild approach for synthesis of carbon-carbon sigma bonds. This approach generally involves reaction of a boronic acid or ester with an aryl or vinyl halide under basic conditions in the presence of a palladium (0) catalyst acording to the generic reaction equation below.[1]



Many fundamental transformations involved in the synthesis of pharmaceutically significant compounds are achieved by Suzuki reactions.[2] A recent example is in the preparation of Oximidine II, a substance that exhibits selective cytotoxicity for oncogene transformed cells.[3] (An oncogene is a gene that causes the transformation of normal cells into cancerous tumor cells). The key step in the synthesis of Oximidine II is an intramolecular Suzuki reaction between a vinyl bromide and a potassium trifluoroborate salt (see below). This example illustrates that Suzuki reactions are often undertaken in an organic solvent with water as a co-solvent. An inorganic base (such as sodium, potassium or cesium carbonate) is also commonly used. An educational example of this reaction type has been published.[4]



An active area in synthetic research is developing “green chemistry”, i.e. employing reaction conditions that are less harmful to the environment than previous approaches. Environmentally, using pure water as a solvent is highly preferable to the use of organic solvents. Most organometallic reactions (e.g.

Grignard reactions) cannot be performed in aqueous conditions, but the Suzuki coupling has the potential for pure water to be used as the solvent for a key C-C bond forming reaction. Because creating new carbon-carbon □igma-bonds forms the basis of organic synthesis, adapting such reactions to more environmentally friendly solvents is an important development.[5]

The reaction you perform in this experiment is an example of the "greening" of an industrially important synthetic method (Fig. 1). Phenylboronic acid is coupled with 4-iodophenol in the presence of 10% palladium on carbon and potassium carbonate.[6] These conditions afford a biaryl product (4-phenylphenol) of the type currently marketed as non-steroidal anti-inflammatory drugs (NSAIDs) (Fig. 2).

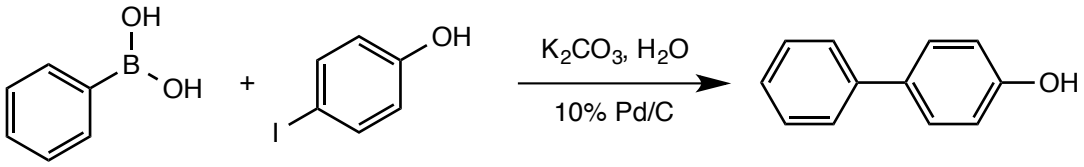


Figure 1. Aqueous Suzuki Synthesis Of 4-Phenylphenol

Diflunisal Felbinac

Figure 2. Two Biaryl Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

EXPERIMENTAL PROCEDURE

Safety notes

- Potassium carbonate is irritating to the eyes, respiratory system and skin.
- Phenylboronic acid and 4-iodophenol are skin irritants and harmful if inhaled.
- 10% Palladium on carbon is harmful if swallowed.
- Methanol is highly flammable and toxic if swallowed.
- Hydrochloric acid causes burns and is irritating to the respiratory system.

Suzuki coupling

Compound	MW	mp (°C)
phenylboronic acid	121.93	216-219
4-iodophenol	220.01	92-94
potassium carbonate	138.21	891

1. Place the following in a 50-ml round-bottomed flask: phenylboronic acid (1.0 mmol), potassium carbonate (3.0 mmol), 4-iodophenol (1.0 mmol) and water (10 ml). Add a magnetic stir bar.
2. Weigh ~ 3 mg of 10% palladium on carbon in a vial and add water (~ 1 ml) to it to create a suspension. Transfer the suspension to the reaction mixture.

3. Heat the mixture vigorously under reflux (water condenser) for 30 minutes, using a sand bath as the heat source and **maintaining rapid stirring**. Some solid may precipitate.
4. Remove the flask from the sand bath and allow cooling to room temperature.
5. Add aqueous HCl (2 M) to the mixture until acidic to litmus paper. Collect the crude solid (still containing catalyst) by vacuum filtration (Hirsch funnel) and wash with water (10 ml).
6. Dissolve the collected solid in ~10 ml methanol (25-ml Erlenmeyer flask), and remove the Pd/C by gravity filtration (collect the filtrate in a 50-ml Erlenmeyer flask).
7. Add ~10 ml distilled water to the crude product dissolved in methanol, which should cause solid to precipitate. Heat until the entire product has gone into solution (adding 1 – 2 ml portions of methanol if necessary). Once complete dissolution has occurred, allow the solution to cool slowly to room temperature and then cool in an ice-bath.
8. Collect the recrystallized product by vacuum filtration (Hirsch funnel) and dry very thoroughly (can be left until the following laboratory period). Remove the solid from the funnel, weigh and calculate the percentage yield. Take appropriate physical measurements (mp, IR, NMR spectra) to ascertain the purity of your compound, comparing with literature data where possible. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. Write a detailed catalytic cycle illustrating formation of 4-phenylphenol. Your cycle should include the steps of oxidative addition, transmetallation, reductive elimination and regeneration of Pd (0), and a rationale for the quantity of base used.
2. Calculate the atom economy of the reaction (see reference 7). How might the atom economy be improved by changing the structure of one of the starting materials? Can you predict any drawbacks to doing this?
3. Analyze and interpret the provided NMR spectra. Analyze and compare your IR spectrum with the one provided.
4. Outline of the benefits of performing the Suzuki reaction under aqueous conditions (compare and contrast this reaction with the approach in reference 4 and original reports of the Suzuki reaction). Why is it important to develop reactions that use water as the solvent?

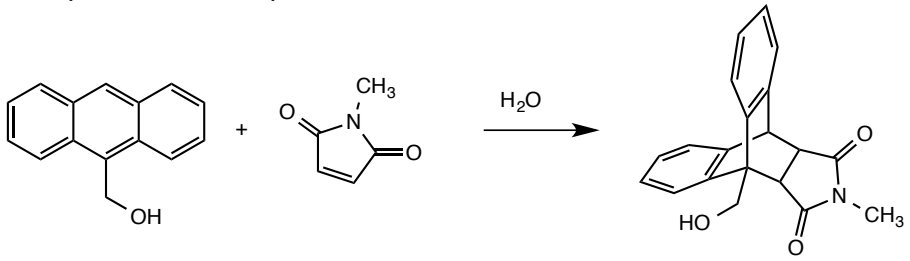
REFERENCES

1. Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457-2483.
2. Franzén, R.; Xu, Y. *Can. J. Chem.*, **2005**, *83*, 266-272.
3. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.*, **2004**, 126, 10313-10318.
4. Callam, C. S.; Lowary, T. L. *J. Chem. Educ.*, **2001**, 78, 947-948.
5. Li, C-J. *Chem. Rev.*, **2005**, *105*, 3095-3165.
6. (a) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.*, **2002**, *67*, 2721-2722. (b) Kuznetsov, A. G.; Korolev, D. N.; Bumagin, N. A. *Russ. Chem. Bull., Int. Ed.*, **2003**, *52*, 1882-1883.
7. Trost, B. M. *Science*, **1991**, *254*, 1471-1477.

EXPERIMENT 9 -- DIELS-ALDER REACTION IN WATER[1]

INTRODUCTION

Diels Alder reactions are very important carbon-carbon bond forming reactions. The mechanisms and reaction rates of these reactions have been studied a great deal, and very interesting work found that the rates could be accelerated by virtue of the hydrophobic effect when the reactions are run with water as the solvent.[2-5] Using those studies and related work[6,7] as a model, you will perform a Diels-Alder reaction in water with anthracene-9-methanol and *N*-methylmaleimide (see below). This reaction demonstrates that a greener solvent might be used not only because it is more environmentally benign but also because it improves other aspects of the reaction.



EXPERIMENTAL PROCEDURE

Safety notes

- *N*-methylmaleimide is corrosive and should be handled with care.

Diels-Alder reaction

1. Place anthracene-9-methanol (0.65 mmol) and 50ml water in a 100 ml in a round-bottom flask equipped with a stir bar. Add *N*-methylmaleimide (1.95 mmol) to the reaction flask, and fit the flask with a water-cooled condenser.
2. Heat the reaction to reflux using a sand bath, and let the reaction reflux for 1 hour with stirring.
3. Verify that all the anthracene-9-methanol has fully reacted by performing a TLC of the reaction mixture using 1:1 ethyl acetate: hexanes as the developing solvent. Take a capillary tube, dip it in the reaction mixture and spot it on a small TLC plate against a solution of the starting material, anthracene-9-methanol. Make sure the water spotted on the TLC plate evaporates completely before developing the plate.
4. When the TLC analysis shows that the reaction is complete, remove the flask from the heat, and let cool to room temperature. Chill the flask in ice and then collect the yellow solid by vacuum filtration.
5. Recrystallize the product from 95% Ethanol. After drying the crystals, obtain a melting point and IR spectrum and calculate the percentage yield. The product should be an off-white solid with a melting point of 237-239 ºC. Refer to Table on pages 9&10 for a complete list of all the required analysis.

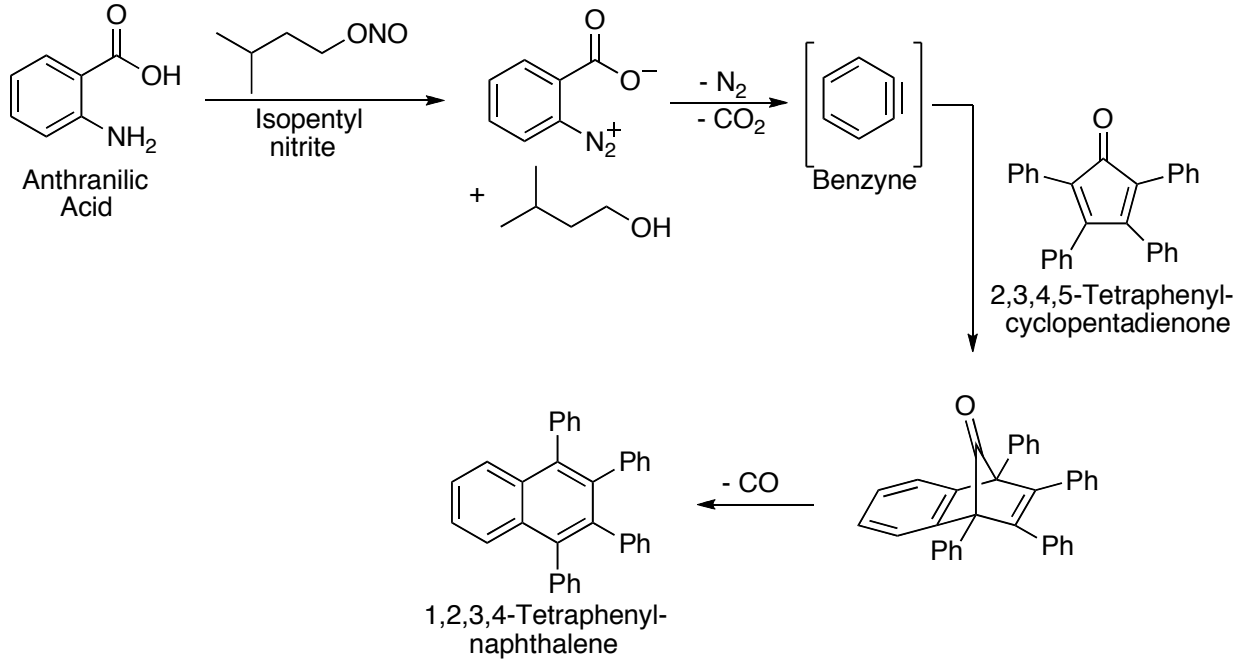
References

1. Adapted from McKenzie, L. C.; Huffman, L. M.; Hutchison, J. E.; Rogers, C. E.; Goodwin, T. E.; Gary O. Spessard, G. O. *J. Chem. Educ.*, **2009**, *86*, 488. DOI: 10.1021/ed086p488
2. Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817.
3. Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340-1.
4. Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923-4.
5. Breslow, R.; Groves, K.; Mayer, M. U. *Pure and Applied Chemistry* **1998**, *70*, 1933-1938.
6. Meyers, K. E.; Kumar, K. *J. Am. Chem. Soc.* **2000**, *122*, 12025-12026.
7. Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901-1904.

Experiment 10 -- Preparation of 1,2,3,4-Tetraphenylnaphthalene

INTRODUCTION

This experiment involves synthesis of 1,2,3,4-tetraphenylnaphthalene from benzyne and 2,3,4,5-tetraphenylcyclopentadienone. The overall transformation in this one-pot reaction is astonishing and complex. Benzyne is a highly strained and therefore very unstable derivative of benzene that contains a carbon-carbon "triple bond". To make benzyne, the amino group of anthranilic acid is "diazotized", i.e. converted into the diazonium group, N_2^+, which is an excellent leaving group. Decarboxylation fosters the loss of N_2. The resulting highly distorted triple bond that results is an excellent dienophile and reacts rapidly with 2,3,4,5-tetraphenylcyclopentadienone in a Diels-Alder cycloaddition. This product is unstable and spontaneously undergoes another pericyclic reaction, known as a cheletropic reaction, in which carbon monoxide is lost to form another aromatic ring.



EXPERIMENTAL PROCEDURE

Safety notes

- 1,2-dimethoxyethane (also known as ethylene glycol dimethyl ether and as glyme) may cause reproductive disorders and should only be used in a hood.
- Isopentyl nitrite is a powerful heart stimulant; take care not to breathe it.
- A small quantity of carbon monoxide is produced in the reaction, but as long as the reaction is kept appropriately in the hood, any CO generated should be of no concern.

Reaction sequence

Place 2,3,4,5-tetraphenylcyclopentadienone (0.24 mmol) in a 5-ml conical vial. Then add anthranilic acid (0.30 mmol) and 1,2-dimethoxyethane (1.2 ml). Insert a magnetic spinvane (point down!) and attach a water-jacketed condenser to the vial.

Working at the hood, transfer isopentyl nitrite (0.40 mmol, also called isoamyl nitrite), which is stored in the refrigerator, to a clean 3-ml conical vial. Do this transfer by volume using a pipetman so that everything remains in the hood when not capped. Immediately cap both the reagent bottle and the vial, and return the reagent bottle to the refrigerator. Add 1,2-dimethoxyethane (0.50 ml) to the conical vial containing the isopentyl nitrite. Cap it and set it aside.

Heat the solution of 2,3,4,5-tetraphenylcyclopentadienone and anthranilic acid with good stirring using an aluminum block at about 140 °C. When the solution boils, add the isopentyl nitrite solution directly to

the reaction mixture through the top of the condenser with a Pasteur pipet over a period of about 30 seconds. Be sure that the pipet is inserted far enough into the condenser so that its contents can be added to the boiling mixture without touching the walls of the condenser. Rinse the 3-ml conical vial with a few drops of 1,2-dimethoxyethane and add this rinse directly to the reaction mixture. Continue boiling the mixture until the deep purple color of the starting material is replaced by a yellow-orange color. This color change usually occurs in less than 10 min. If it has not happened within 15 min, add a drop of isopentyl nitrite as before and boil the mixture for another 15 min.

Workup

After the color has changed, allow the reaction mixture to cool to room temperature. Prepare a solution of 5 ml of water and 2 ml of methanol in an appropriately sized beaker. Using a Pasteur pipet, transfer the cooled reaction mixture to the beaker. Stir the mixture well to break up the precipitate that forms. Isolate the solid via vacuum filtration. Use about 10 ml of cold methanol to aid in the transfer of any solid remaining in the beaker and to wash the solids in the funnel. If the filtration is slow because of formation of solid plugs, add a small amount of ice-cold methanol. (Why should the methanol be cold for these steps?) Additional product may precipitate from the mother liquor in the filter flask. If so, transfer the mother liquor to an Erlenmeyer flask, reassemble the filtration apparatus with a fresh piece of filter paper, and then filter and wash the solids that formed in the mother liquor. Do not dispose of the mother liquor! Combine all crops of crude product and determine their total weight.

Purification

Place the crude product in a 25-ml Erlenmeyer flask. Add a minimum amount of boiling 2-propanol (isopropyl alcohol) until the solid dissolves. If it does not all dissolve, break up any lumps with a spatula. Approximately 12 ml of the solvent will probably be required. After dissolution is complete, place the flask in an ice-water bath to start recrystallization. After the flask has cooled, if necessary, scratch the inside of the flask with a glass rod at the interface between air and the solution to facilitate crystallization. Continue cooling the mixture for at least 30 min, and then collect the solid by vacuum filtration. Wash the filter cake with a small amount of *cold* 2-propanol. Dry the solid thoroughly.

Weigh the product and calculate the % yield. Determine its mp, then remove the capillary from the heat source and let the melt resolidify. Repeat your measurement of the mp on the same sample. Be aware that the product can exist in two different crystalline forms, each of which has a unique mp. One of them melts at 196–199 °C and the other at 203–204 °C. Obtain the IR spectrum of your product. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. Write the structure of 1,2-dimethoxyethane and state whether there are any centers of chirality in it.
2. Why was the use of *cold* 2-propanol specified for washing the filter cake containing the product?
3. What change, if any, did you observe upon measuring the mp of your product a second time?
4. Using standard curved arrow notation, write a mechanism for each step of the reaction.
5. How many peaks would you expect to observe in the ^{13}C NMR spectrum of 1,2,3,4-tetraphenylnaphthalene?
6. How many peaks would you expect to observe in the DEPT spectrum of 1,2,3,4-tetraphenylnaphthalene?

REFERENCES

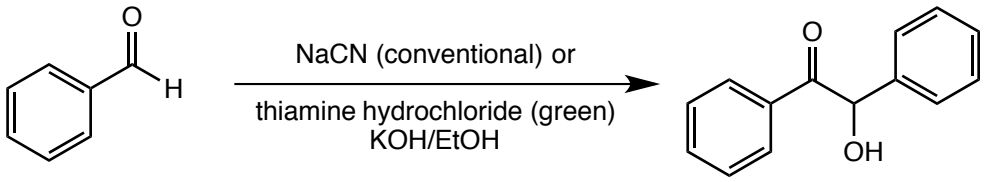
1. Dougherty, C. M.; Baumgarten, R. L.; Sweeney, A.; Concepcion, E. *J. Chem. Educ.* **1977**, *54*, 643.
2. Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599–1606.

GROUP 4: CONDENSATION REACTIONS

EXPERIMENT 11 -- SYNTHESIS OF BENZOIN

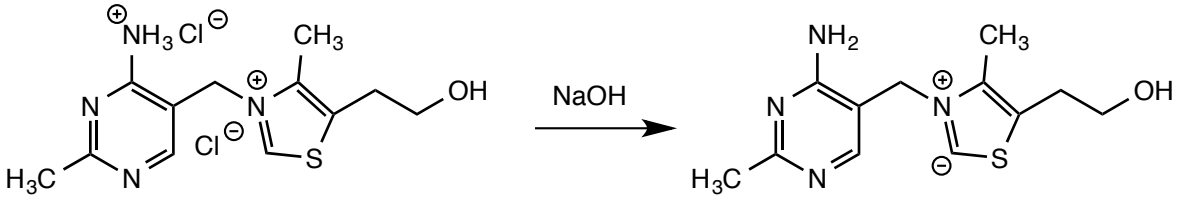
INTRODUCTION

This reaction is a classic -- the "condensation" of two molecules of an aldehyde to form an alpha-hydroxy ketone in a process known as the benzoin condensation, named for the version you will run (Scheme 1). The reaction requires a catalyst and is often performed with cyanide ion. However, cyanide is toxic and an environmental hazard. Instead, you will use thiamine as a catalyst. Thiamine is used by our bodies to perform similar processes, which speaks to its relative environmental friendliness. The initial stage of the reaction is converting the thiamine hydrochloride to its catalytically active ylide form (Scheme 2). This ylide then catalyzes the condensation of two molecules of benzaldehyde to form benzoin.



benzaldehyde benzoin

Scheme 1. The benzoin condensation.



thiamine hydrochloride catalytic thiamine ylide

Scheme 2. Thiamine hydrochloride and its treatment with base.

Because thiamine is heat-sensitive and may decompose if heated too vigorously, you will run the reaction at room temperature for 24 hours or more. The benzaldehyde used is easily oxidized to benzoic acid, so it is important to use a freshly distilled or newly opened bottle. The concentration of reactants and temperatures of solutions are critical to obtaining a good yield, so procedures must be followed carefully. For instance, too much water will force benzaldehyde out of solution, which prevents an efficient reaction, but too little water prevents the thiamine hydrochloride from dissolving.

EXPERIMENTAL PROCEDURE

Safety notes

- The 8% solution of NaOH is extremely caustic. handle with care.
- Isopentyl nitrite is a powerful heart stimulant; take care not to breathe it.

Condensation reaction

Place 0.90 ml of 8% (wt/v) aqueous NaOH in a small test tube and cool in an ice bath. In a 25 ml Erlenmeyer flask dissolve the thiamine hydrochloride (0.90 mmol) in water (0.45 ml). Add 3.0 ml of 95% ethanol to the thiamine and swirl the solution until it is homogeneous. Cool the solution for several minutes in an ice bath. While keeping both flasks in the ice bath, add the 0.90 ml of previously cooled sodium hydroxide solution dropwise (over 3-5 minutes) to the thiamine solution with swirling so that the solution stays below room temp. Remove the 25 ml flask from the ice bath and add the benzaldehyde (9.0 mmol) in one portion using a mechanical pipet, swirling the flask so that the benzaldehyde mixes with the yellow, aqueous, basic layer. The solution should become homogeneous. If the mixture does not become a homogeneous solution (e.g. if two layers are obvious), place the flask in a warm water bath at approximately 50 °C until the solution clears but no longer than 10 minutes. You can use hot water from the faucets at the front of the lab. The mixture should become homogeneous in the water bath, but it may not stay homogeneous once it cools. Seal the flask with a cork and Parafilm and place it in your drawer until the next lab period.

In the next period, if crystals have formed, filter them using vacuum filtration, wash them free of mother liquor with 2-3 ml of a cold 2:1 mixture of water and 95% ethanol, and air dry them for 10 min. If crystals have not formed, initiate crystallization by scratching the inside of the flask with a glass stirring rod and leave it in an ice bath for 15-20 min until crystals form.

Weigh your crystals to determine your crude yield. Recrystallize the crude benzoin from hot 95% ethanol (about 8 ml per gram), making sure to break up any chunks. You should not have to filter the hot solution. Let the solution cool down to room temperature to allow the crystals to form. Complete the crystallization by cooling the solution in an ice bath. Vacuum filter the crystals, wash them with a minimum of a cold 2:1 mixture water and 95% ethanol mixture, and air dry them for 15 min or leave them drying in you locker until the next lab period. Obtain the mp and IR spectrum of the recrystallized benzoin, and analyze its purity by TLC. Interpret the ^{1}H NMR spectrum of benzoin that is posted. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. What are the main peaks in your IR spectrum that prove that your product is benzoin?
2. Draw a mechanism for the cyanide-catalyzed conversion of benzaldehyde to benzoin.
3. What modifications in the reaction conditions would be necessary if an enzyme were used to catalyze the reaction?

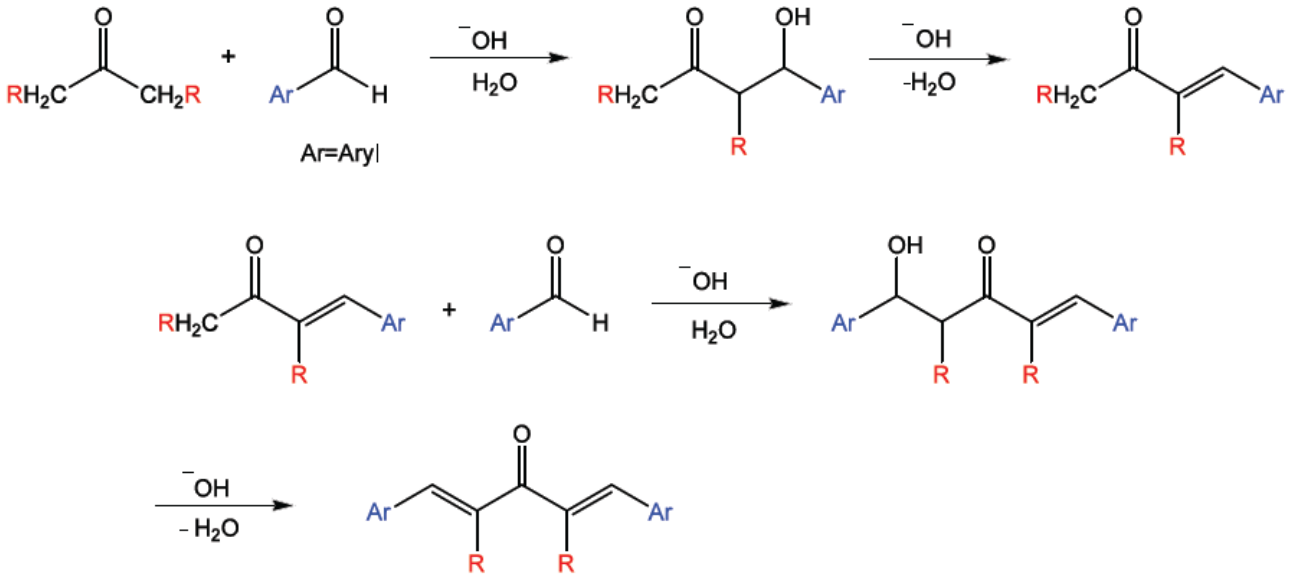
REFERENCES

1. Lampman, P. D. L. ; Chriz, G. M. *Introduction to organic lab technique;* College Publishing, New York,**1982**.

EXPERIMENT 12 -- ALDOL CONDENSATIONS

INTRODUCTION

Condensations are important reactions in organic synthesis because they are excellent methods for making new carbon-carbon bonds. Aldol condensations can be catalyzed by acid or base, with basic catalysis being more common. In many cases the initial condensation is followed by dehydration to form a conjugated enone, as in the example below.



In this example, the condensation begins by deprotonation of the ketone (pKa ≈ 20), followed by attack of the resulting enolate ion on the aldehyde carbonyl, and protonation. The initial condensation product can be deprotonated again, and this enolate ion then expels hydroxide to form the CC π-bond (an "E1cB" reaction; cB = conjugate base). This dehydration step is especially facile in cases where the new double bond becomes part of an extended conjugated π-system. Mixed (or "crossed") aldol condensations — those between two different carbonyl compounds — can often lead to mixtures of products. However, reactions between ketones with only one type of α-H and aldehydes without α-Hs are especially clean because only one enolate can form and addition to the aldehyde carbonyl is much more favorable than addition to the ketone carbonyl.

OVERVIEW

In this experiment you will carry out an aldol condensation of the type illustrated above, isolate and purify the product, and establish its structure by NMR. Although you will know the possible starting aldehydes and ketones, you will not know precisely which you are using. As a result, you will need to establish your product's structure from the spectral data alone rather than simply comparing your data with known data.

You will pick a ketone (A, B, or C) and an aldehyde (1, 2, or 3) from the bottles in the lab. The possibilities are given in the following lists.

Ketones	**Aldehydes**
cyclopentanone	benzaldehyde
cyclohexanone	*trans*-cinnamaldehyde
cycloheptanone	

EXPERIMENTAL PROCEDURE

Safety notes

- The compounds are all flammable and irritants. Avoid breathing their vapors.

Aldol condensation

In a 25 mL round bottom flask equipped with a magnetic stirring bar, add about **0.30 g** of aldehyde (record exact amount) and 5 ml of 95% ethanol. Begin stirring to form a solution and add about **0.30 g** of ketone (record exact amount). Cool the flask in an ice bath and add 4 ml of 2 M aqueous NaOH dropwise while stirring the mixture. Leave the mixture in the ice bath for 5 more min and then continue stirring it for 15 min at room temperature or until precipitation of solid has stopped. If no precipitate has formed by this time, try heating the solution for a few minutes on the heating block at 40-50 ^{o}C and then allowing it to cool, by placing the round bottom flask in a cold water bath. Collect the precipitate by vacuum filtration and rinse it with 10 mL of ethanol and with 7 mL of a 4% acetic acid solution in ethanol. If your product doesn't precipitate, extract it with ethyl acetate, wash the ethyl acetate solution with a little 5% aq HCl, dry it with sodium sulfate, and remove the solvent using a rotavapor. Recrystallize the product from a Hexane/Ethyl Acetate mixture Dry it thoroughly and analyze it.

Compound characterization

You will then need to prepare a sample of your product for NMR analysis. It is important that your sample be free of residual solvents. Air drying for a week will usually be sufficient, but you can also consider using treatment under vacuum with the help of your instructor. To make your NMR sample, take about 30 mg and place it in an NMR tube. Add about 0.5 ml of $CDCl_3$ (note: **deuterated** chloroform, not regular) to dissolve your campound. Cap, label clearly, and give to your instructor for NMR analysis. The NMR tube MUST be clearly labeled with your name, section, and instructor. Tubes not properly labeled will be lost. When you receive your spectra back, interpret them as completely as possible. The interpretation may be tough for some of the condensation products, but do the best you can, and at a minimum try to determine which combination of aldehyde and ketone you must have used. Once you have determined the starting materials you used, calculate the percent yield for your synthesis. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

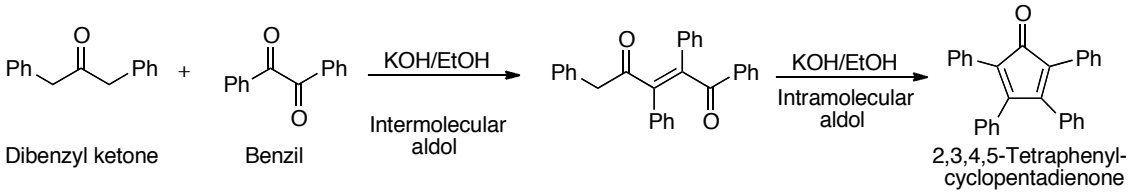
REFERENCES

Based on Hathaway, B. A. *J. Chem. Educ.* **1987**, *64*, 367.

EXPERIMENT 13 -- PREPARATION OF 2,3,4,5-TETRAPHENYLCYCLOPENTADIENONE

OVERVIEW

In this experiment, 2,3,4,5-tetraphenylcyclopentadienone will be synthesized from dibenzyl ketone and benzil. The synthesis involves a double-aldol reaction: the first aldol is *intermolecular*, and the second is *intramolecular*. You will recall that an aldol reaction involves an aldehyde or ketone and an enolate of a second aldehyde or ketone. Under these reaction conditions, the α-hydroxyketone that results is readily dehydrated to form an α,β-unsaturated ketone.



EXPERIMENTAL PROCEDURE

Safety notes

- The KOH solution is caustic. Be careful to avoid any contact with skin.

Synthesis and purification

To a 5-ml conical vial, add 0.71 mmol of dibenzyl ketone (1,3-diphenyl-2-propanone or 1,3-diphenylacetone). Weigh the compound in the hood and leave the vial capped when handling the compound outside of the hood. Then add 0.71 mmol of benzil, and 1.2 ml of *absolute* ethanol (*Ethyl Alcohol Absolute* or 200 proof ethanol). Be sure to record the exact weights in your lab notebook. Add a magnetic spinvane (point down!) to the vial and attach a water-cooled condenser to the vial.

Set the conical vial in the aluminum block, clamp it and heat the mixture on a hot plate to 80 °C. Continue heating until the solids dissolve. If all of the solids are not dissolving, make sure the vial is in good contact with the aluminum block. Raise the temperature of the hot plate until the mixture is just below its boiling point. Measure out 0.2 ml of 9.1% ethanolic potassium hydroxide with a pipetman and add it to a 2 mL conical vial. Using a Pasteur pipet, carefully add the 0.2 ml of 9.1% ethanolic potassium hydroxide to your reaction mixture through the condenser. Once the KOH has been added, increase the temperature until the mixture is boiling gently and continue this for 15 minutes. You should see a color change with the solution turning black. Caution: *foaming may occur!* Be certain to note any changes you observe in your lab notebook.

Remove the vial from the heating block, allow the reaction mixture to cool to room temperature, and then place the vial in an ice-water bath for 5 min to complete crystallization. Collect the crystalline product in a Hirsch funnel using standard vacuum filtration apparatus. Hold the spinvane with forceps and scrape as many crystals off of it as possible into the Hirsch funnel. Use three 0.5-ml portions of *ice-cold* 95% ethanol to aid in the transfer of crystals from the vial and spinvane and to wash them. (Note: This ethanol is of a different purity than you used originally as the solvent.) Dry the product thoroughly. Weigh the product and calculate the % yield based on the moles of the *limiting reagent* used. Determine the mp of the crude product. Its literature value is 218–220 ˚C. If necessary, the product can be recrystallized from a 1:1 mixture of toluene:95% ethanol. You will need approximately 1 ml of this mixture for every 0.05 g of product. Obtain an IR spectrum of the product and analyze the product by TLC to evaluate its purity. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

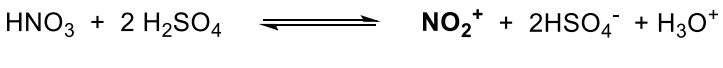
1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for this reaction.
2. What are some of the possible by-products in the reaction?
3. Given the possible by-products, why does one get primarily 2,3,4,5-tetraphenylcyclopentadienone? In other words, why does the enolate of dibenzyl ketone preferentially attack benzil and not another molecule of dibenzyl ketone?
4. How many peaks would be expected in the ^{13}C spectrum of 2,3,4,5-tetraphenylcyclopentadienone? How many peaks would be expected in its DEPT spectra?

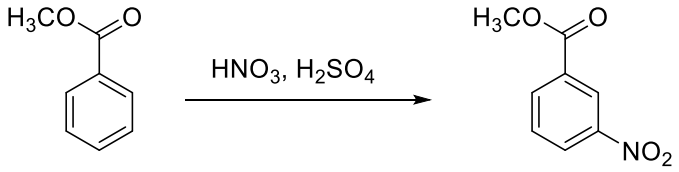
GROUP 5: Electrophilic Aromatic Substitution Reactions

EXPERIMENT 14 -- AROMATIC NITRATION REACTION

OVERVIEW

This experiment will introduce you to one of the important electrophilic aromatic substitution reactions, nitration. Reaction of the substituted aromatic ring shown below will lead to nitration at the carbon meta to the substituent.





Methyl benzoate

Methyl 3-nitrobenzoate

EXPERIMENTAL PROCEDURE

Safety notes

- Concentrated nitric acid and concentrated sulfuric acid are highly corrosive. Use great care in handling these reagents. If any of the acid mixture gets on the skin, it must be immediately washed with large amounts of cold water.

Synthesis and purification

Carefully combine 0.4 ml concentrated sulfuric acid and 0.4 ml concentrated nitric acid in a conical vial and place it in an ice bath. To a *separate* 5-ml conical vial, add a spin vane, 6.6 mmol methyl benzoate and 1.2 ml concentrated sulfuric acid. Gently stir to mix the components of this viscous mixture while cooling it in an ice bath. Using a glass Pasteur pipette add the sulfuric-nitric acid mixture to the stirring methyl benzoate solution one drop at a time. Upon complete addition of the acid mixture, remove the reaction from the ice bath, allow it to warm up to room temperature, cap it and let it stand for 15 minutes.

Note that this reaction often shows a delayed start. It is important to be patient. If the mixture is heated higher or longer than directed, an uncontrolled reaction may ensue; di- and trisubstitution of the ring could lead to explosive products. If brown fumes start to form, the reaction may be proceeding too quickly and should be moderated.

After 15 minutes at room temperature, pour the mixture into a small beaker that contains approximately 5 g of ice. Your product should crystallize. Isolate the solid by filtration using a Hirsch funnel and wash out the conical vial with ice-cold water to transfer all of the solid to the Hirsch funnel. Then wash the product with 0.25 ml of ice-cold water.

Recrystallize the product from methanol. After recrystallization, record the weight of the product, calculate the percentage yield, and determine the mp of the purified product. Obtain an IR spectrum and TLC of the pure product. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

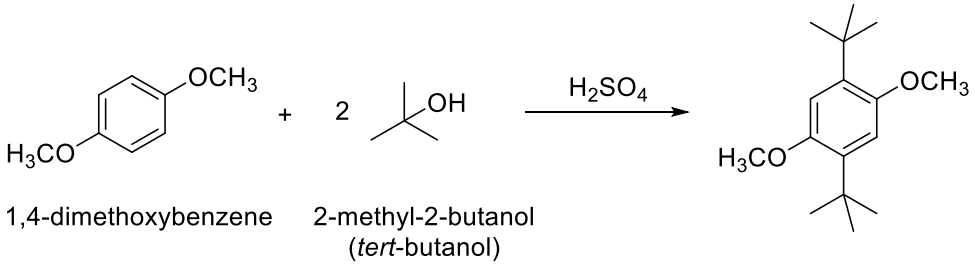
QUESTIONS

1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for this reaction.
2. What are some of the possible by-products in the reaction?
3. Why does one get primarily mono-nitrated product?
4. How would the reaction outcome be different if you used anisole (Ph-OCH_3) as a reactant instead of methyl benzoate?

EXPERIMENT 15 -- FRIEDEL-CRAFTS ALKYLATION REACTION

OVERVIEW

This experiment will introduce you to one of the important electrophilic aromatic substitution reactions, Friedel-Crafts alkylation. Reaction of the substituted aromatic ring shown below will lead to di-alkylation. The experiment uses concentrated sulfuric acid to generate an unstable carbocation from an alcohol.



1,4-dimethoxybenzene 2-methyl-2-butanol (*tert*-butanol)

1,4-di-t-butyl-2,5-dimethoxybenzene

EXPERIMENTAL PROCEDURE

Safety notes

- Concentrated sulfuric acid is highly corrosive. Use great care in handling it. If any of the acid mixture gets on the skin, it must be immediately washed with large amounts of cold water.

Synthesis and purification

Place 1,4-dimethoxybenzene (2.2 mmol) and 1 ml of acetic acid in a 25 ml round-bottom flask. Add a magnetic stir bar, and stir with gentle warming if needed to dissolve the solid. Add 0.5 ml of *t*-butanol to this flask and cool the entire mixture in an ice-water bath with continued stirring. With the mixture stirring, carefully add 1 ml concentrated sulfuric acid dropwise via a **Pasteur** pipette. A solid product may be visible at this point, but in order to complete the reaction, remove the reaction vessel from the ice bath, place a cork on the round bottom flask and allow it to warm to room temperature, Stir it for another 30 minutes at room temperature. After this time, turn off the stirring and cool the reaction flask again in an ice-water bath in order to induce complete crystallization. After 10 minutes, add 5 ml of water **dropwise** to the mixture in the reaction vessel, stirring after the addition of each drop. Isolate the solid by filtration using a Hirsch funnel. Wash out the reaction flask with ice-cold water to transfer all solid to the funnel. Wash the crystals in the Hirsch funnel with a small volume of ice-cold methanol.

Recrystallize the product from methanol. After recrystallization, record the product mass, calculate the percentage yield, and determine the mp of the purified product (lit. melting point is 104-105^{o}C). Obtain an IR spectrum and TLC of the pure product. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

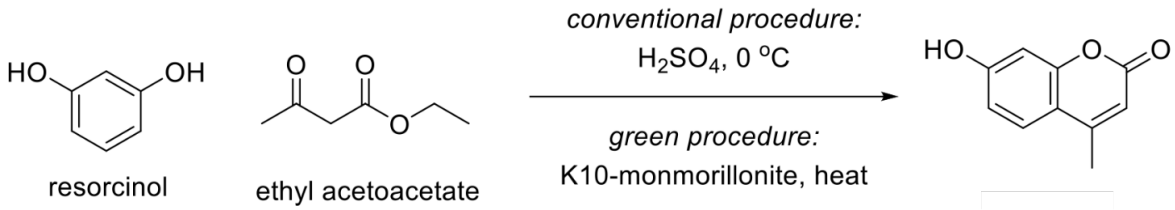
Questions

1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for this reaction.
2. There are three main difficulties that typically arise in Friedel-Crafts alkylation reactions: the initial reactivity of the ring with a carbocation electrophile, the possibility of carbocation rearrangements, and further activation of the ring by adding alkyl groups. How does the choice of reactants in this reaction address each of these difficulties? What other isomers would be possible? Why do only two t-butyl groups add to the ring?

EXPERIMENT 16 -- PECHMANN CONDENSATION FOR COUMARIN SYNTHESIS

OVERVIEW

This experiment will introduce you to the Pechmann condensation reaction, shown below. The product of this reaction is coumarin, a fragrant molecule produced by many plants. Coumarin is used in perfumes and as a precursor to some pharmaceutical ingredients. Traditionally, the Pechmann reaction of resorcinol with ethyl acetoacetate is catalyzed by strong acid. However, you will use a green procedure that employs a solid material (a clay) to catalyze this transformation; this new procedure eliminates the need for a reaction solvent and the use of the corrosive strong acid. Moreover, the catalytic material can be reused.



resorcinol ethyl acetoacetate 4-methyl-7-hydroxy-coumarin

EXPERIMENTAL PROCEDURE

Combine resorcinol (5 mmol) and ethylacetoacetate (5.2 mmol) in a 25-ml round bottom flask, and swirl the mixture gently. Add K10-montmorillonite catalyst (0.75 g), and stir the reaction mixture thoroughly with a glass rod until it looks like a paste. Place the reaction flask in a sand bath and heat at 80 °C gently for 2 h. Cool the reaction to room temperature, then add 10 ml ethyl acetate to the reaction flask. Transfer the slurry mixture into a centrifuge tube. Use a few ml of additional ethyl acetate to wash any remaining catalyst into the jar. Use 2 centrifuge tubes if necessary. Cap the centrifuge tube, then shake vigorously to extract the product from the clay into the ethyl acetate solution. (CAUTION: this step will build up pressure; vent the centrifuge tube by loosening the cap *carefully*.) Filter the mixture through your Hirsch funnel to remove the clay solid. Wash the clay twice more with 2 ml of ethyl acetate. Save the FILTRATE liquid, and transfer it to a clean, tared round bottom flask. Use a rotovap to evaporate the ethyl acetate solvent from your product.
Weigh the product and calculate the % yield based on the moles of the *limiting reagent* used. Determine the mp of the crude product (its literature value is 188-190 °C), and analyze the product by TLC to evaluate its purity. Obtain an IR spectrum of the product. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

Questions

1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for this reaction. *Hint*: it starts by a trans-esterification reaction. This mechanism is tough, but do your best and see your instructor if you need more help.
2. Why do you need two electron donating groups on the aromatic ring in this reaction?

REFERENCES

Greener approach to undergraduate chemistry experiments, ACS publications, **2002**, p 25.

GROUP 6: CHALLENGE EXPERIMENTS

GENERAL INFORMATION

All of the experimental procedures performed in the organic laboratory thus far have included the complete experimental details: the types and sizes of glassware, reaction times, volumes of solvents used for crystallizations, and the quality of chemicals are just a few of the details provided in typical undergraduate laboratory experiments. However, in common practice in the research laboratory the researcher must interpret and modify any published procedure. One must adjust amounts for the scale required and use her experience in conducting reactions to adapt a literature procedure for her own research objectives. The beginning student needs more procedural details in order to develop the skill and experience demanded of work in the organic laboratory, but after two quarters of work, you are now equipped with sufficient "common practice" experience to adapt procedures from the literature. Journal articles, because they are written for researchers in the field and to save journal space, present much less experimental detail, and the laboratory worker is expected to know standard procedures and methods.

Brief procedures, similar to what might be found in journals, of six experiments have been reproduced here. None of these contains the level of detail provided previously in this course, yet each represents a precise synthetic method. You must examine the chosen procedure and determine the specific equipment, glassware, reagents, and reaction times that will be employed and conduct the experiment safely and accurately.

It is essential to be thoroughly familiar with the nature of the reactants and products before conducting the experiment. The following points must be considered:

1. The physical states (liquid? solid? gas?) of all reactants and products.
2. The toxicity of reagents.
3. The type and size of glassware and the set up to be employed. Should an Erlenmeyer flask or a round-bottomed flask be used in a particular step? Should an air condenser or a water condenser be used? What size?
4. Preparing solutions. How is a 10% sodium bicarbonate solution prepared? A 2.4 *M* hydrochloric acid solution? Any solution needed in an experiment must be made by the experimenter if it is not available in the lab.
5. Measuring liquid reactants. If a mass is given, what is the corresponding number of milliliters? How should the liquid be measured: graduated cylinder, pipetman, or by weight? With which accuracy?
6. At what temperature should the reaction be run? How is the temperature of the reaction measured? Which heating source should be used? Sand bath or aluminum block?
7. Total time involved in the procedure. Can it be completed in one laboratory period? How will the reaction be monitored to determine whether it is complete?
8. Isolating product(s). Is the method of isolation obvious from the procedure? If not, what is an appropriate isolation of the product from the procedure
9. Purification. How will the product be purified? If by recrystallization, what amount and type of solvent should be used? How can these be determined if they are not specified?
10. Characterization. How will the product be characterized and its purity confirmed?

These questions must be addressed in advance of the day the experiment will be conducted. **A written, detailed analysis of the procedure should be submitted to the lab instructor before you do the experiment.** Discuss the details of your experimental plan with your instructor when you submit your experimental plan so that adjustments to your approach can be made prior to beginning the experiment.

These elements should be part of your written, preliminary analysis:

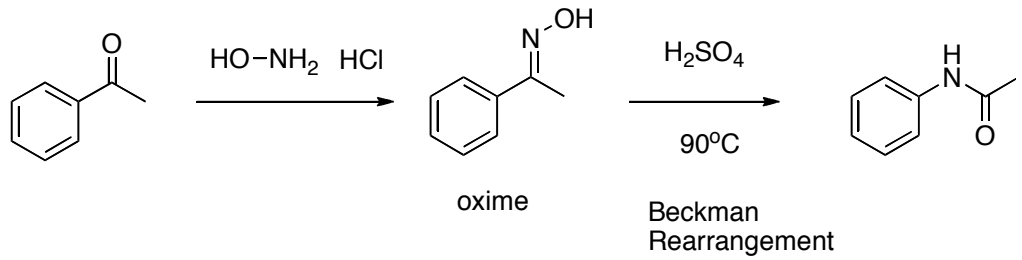
1. An equation for the reaction(s).
2. A summary of the materials needed for the experiment and their associated data. A convenient way to portray this information is to use a table that includes the following data for each substance: name/structure of the compound, molecular formula, molecular weight, number of moles to be used in the reaction, and its relative stoichiometry (with the limiting reagent generally being set as 100 mol%).
3. An outline of how you will measure the quantities of each reagent required and the equipment you will need to make the measurement. The equipment includes what vessels you will use to measure and store chemical in prior to adding the compounds to the reaction mixture. You should consider and note any special precautions that should be taken when working with or measuring the chemicals for your procedure and also discuss these issues with your instructor.
4. The quantities of solvents used and methods for the preparation of any necessary solutions.
5. How you will purify the product. If a distillation will be used, you should find the boiling point of the product. If recrystallization will be used, solubility information will be useful in deciding the solvent to be used. Some of this information may be found in an Aldrich catalog or on the Aldrich web site (www.sigmaaldrich.com).
6. What glassware will be appropriate for conducting the reaction, workup, and purification.

When you have done the reaction and a pure product is obtained, you should calculate the percent yield, obtain an infrared spectrum, and test its purity (TLC or GC). If you prepare a solid, determine the melting point for comparison to literature values. If distillation is used to purify the product, determine the boiling point during distillation by noting the temperature of the vapor while you collect individual fractions. In special cases, a ^{1}H NMR spectra will be obtained on a sample of your compound, especially if you are the first to do the experiment and you produce high-quality material. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

SAFETY REMINDERS

- All chemical compounds should be considered to be hazardous and therefore always be handled in the hood with gloves at all times.
- For weighing of compounds, you should discuss how to do this safely with your instructor to avoid having open containers outside of a hood.
- Although specific hazard warnings are not included in most literature procedures (unless the compound has unusually high toxicity or is explosive), when conducting the procedures below, you should always use the same precautions as if the compounds you are working with were highly toxic: work so that you do not come in contact with the compounds or their vapors.

EXPERIMENT 17 -- SYNTHESIS OF ACETANILIDE FROM ACETOPHENONE: THE BECKMAN REARRANGEMENT[1]



oxime

Beckman Rearrangement

EXPERIMENTAL PROCEDURE

Preparation of Oxime

Acetophenone (12.8 mmol), hydroxylamine hydrochloride (19.2 mmol), and sodium acetate (15.1 mmol) were added to an Erlenmeyer flask containing 10 ml of water. The mixture was stirred until the solids dissolved. Sufficient 95% ethanol was added with stirring to dissolve the acetophenone Approximately 1-3 ml of ethanol was required. The solution was heated on a steam bath for 40 minutes, then cooled in an ice bath. After crystals formed, the flask remained in the ice bath for 30 min. The solid oxime was collected by vacuum filtration and recrystallized from water.

Scale the rearrangement procedure below to the amount of acetophenone oxime you have available from the first part of the experiment.

Beckmann Rearrangement

Concentrated sulfuric acid (1 ml) in a 50-ml round-bottom flask was heated on a steam bath until the temperature of the acid was at least 90 °C. Acetophenone oxime (7.4 mmol) was added in small portions with stirring and heating. A vigorous reaction was observed after each addition, and care was taken that one portion reacted before adding the next small portion of the oxime. After all the oxime had been added, the mixture was heated an additional 15 min. The reaction mixture was added to approximately 25 g of crushed ice. When the ice had melted, the precipitate was isolated by vacuum filtration, and the crude product was recrystallized from water. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for each of these reactions.

REFERENCES

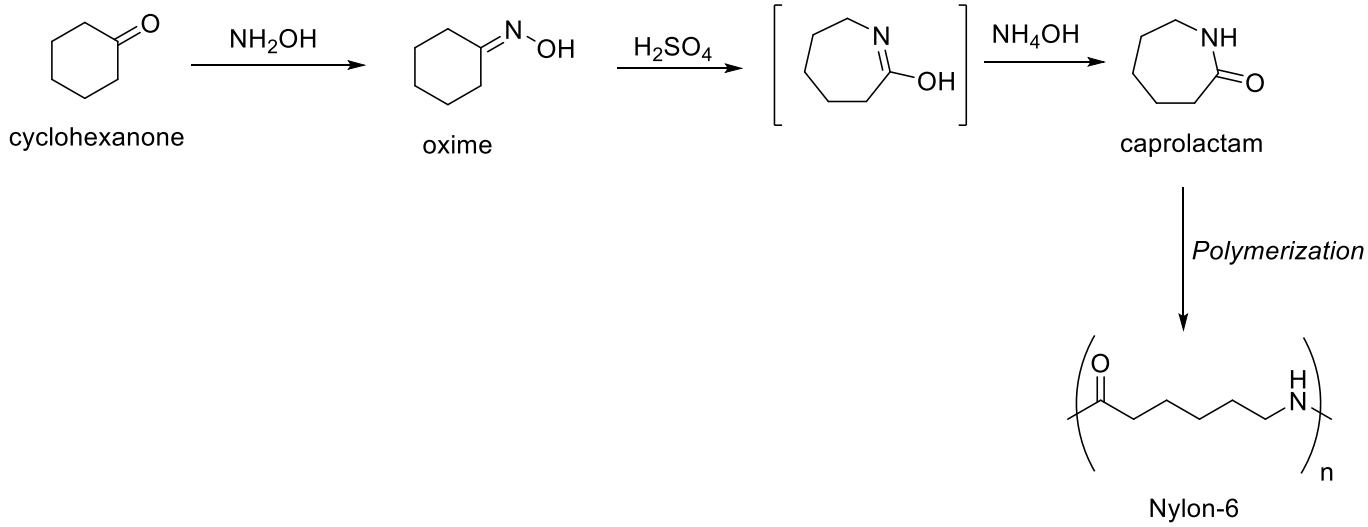
1. G. K. Helmkamp and H. W. Johnson, Jr., Selective Experiments in Organic Chemistry, Freeman, San Francisco, 1964, p. 93.

EXPERIMENT 18 -- SYNTHESIS AND POLYMERIZATION OF CAPROLACTAM: A MULTISTEP SYNTHESIS

INTRODUCTION

The synthesis of caprolactam is important industrially because it is the starting material in the synthesis of Nylon-6. Nylons are a class of synthetic polymers made up of millions of identical repeat units. Nylon was first used in 1938 as toothbrush bristles, but toothbrushes were quickly followed up in 1940 by the use that almost everyone knows today – stockings or pantyhose. Today, Nylon is still used as clothing but it has found industrial uses in the manufacture of combat uniforms, tires, and luggage.

The synthesis of caprolactam is a two-step reaction, starting from cyclohexanone. The cyclohexanone is converted into an oxime by reaction with hydroxylamine. The caprolactam is produced when the oxime undergoes a Beckman rearrangement.



EXPERIMENTAL PROCEDURE

Preparation of cyclohexanone oxime

In a 125 ml Erlenmeyer flask, 0.35 g of hydroxylamine hydrochloride and 0.5 g of sodium acetate trihydrate were dissolved in 1.5 ml of water. The solution was stirred and warmed to 35-40 °C with a hot plate. In 4 roughly equal portions, 0.35 g cyclohexanone was added, and a solid precipitated. After all the cyclohexanone was added, the flask was stoppered and shaken vigorously until the oxime completely precipitated as a fine white powder. Large lumps were removed by further shaking. The flask was cooled to room temperature and the solid was collected by vacuum filtration, washed with a small amount of water, and allowed to air dry.

Scale the next reaction according to the amount of oxime that you have from the first reaction.

Synthesis of caprolactam

In a 25 ml beaker, 0.5 g of cyclohexanone oxime and 1 ml of 80% sulfuric acid were combined to form a thin layer on the bottom of the beaker. This mixture was heated on a hot plate **with the hood sash closed as far as possible** until large amounts of (relatively nasty) vapors were given off, indicating that the reaction was taking place.

The flask was cooled to room temperature in a crushed ice/NaCl bath (3:1). When the temperature of the reaction mixture went down to 5 °C, 20% ammonium hydroxide solution was added slowly and carefully with stirring until the reaction mixture became basic. Care was taken to maintain the temperature below 20 °C at all times to minimize hydrolysis of the caprolactam. If a solid precipitated

out, 2.5 ml of water was added and the mixture was stirred. If the solid persisted, it was filtered out and rinsed with water. The reaction mixture was sometimes observed to be biphasic at this point.

The aqueous mixture was extracted twice with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The brownish solid was recrystallized from petroleum ether. Refer to the Table on pages 9&10 for all the required analysis of your product.

The polymerization reaction is optional. See your instructor before beginning this procedure. If you do this part, scale the amounts according to the amount of caprolactam you made.

Polymerization

In a 13 x 100 mm disposable test tube, caprolactam (1 g), Polyethylene Glycol of molecular weight 6000-7500 daltons (0.060 g), and N-acetylcaprolactam (1 drop) were mixed. The mixture was melted by heating the tube in a sand bath. As soon as the mixture melted, the tube was removed from the bath and a spatula tip (approximately 20 mg) of gray (not white) sodium hydride was added. The NaH was stirred into the melt with a pipette; it is important that all of the NaH contact the mixture to ensure uniform initiation. The clear solution was heated rapidly to 200–230 °C in the sand bath until reflux was just starting, as evidenced by continuous but not violent bubbling. Rapid polymerization was indicated by an increase in viscosity of the mixture. If polymerization did not occur after several minutes, the mixture was cooled to just above the melting point and reinitiated with NaH. When the solution was so viscous that it barely flowed, it was removed from heat. A wooden stick or pipette was used to pull to draw fibers from the melt. The remaining mixture was allowed to cool and the remaining polymer plug was removed from the test tube. Refer to Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

1. Using curved arrows to symbolize the flow of electrons, write out the complete mechanism for each of these reactions.
2. In the synthesis of cyclohexanone oxime, a large amount of sodium acetate was added. What was the purpose of this? Would sodium chloride work?
3. What is the other product of the Beckmann rearrangement reaction step? Hint not all the reagents end up in the final product. Where do they go?

REFERENCES

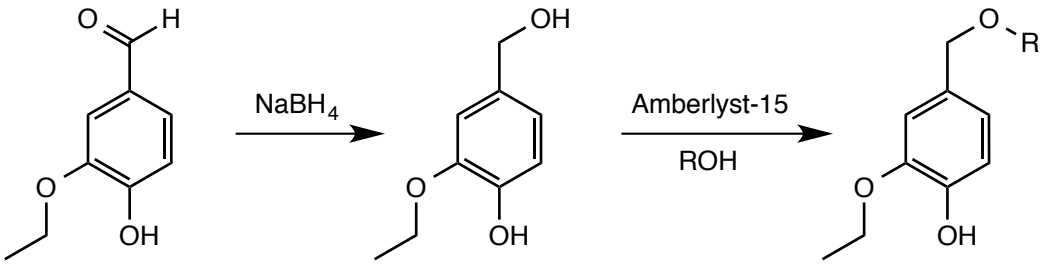
1. http://people.clarkson.edu/~ochem/Spring01/CM244/caprolactam.html, Yuzhuo Li, Department of Chemistry, Clarkson University
2. http://library.thinkquest.org/C004179/nylon.htm, Accessed January 3, 2007

EXPERIMENT 19 -- SYNTHESIS OF A COMMERCIAL FRAGRANCE: METHYL DIANTILIS AND HOMOLOGUES

INTRODUCTION

Perfumes and scents are big business. International Flavors and Fragrances (IFF) is a multinational company specializing in the development of flavors for corporations such as McDonald's and fragrances for many perfumes. In 2005, sales for IFF exceeded 2 BILLION dollars. One of the more popular scents is vanilla. Many different derivatives of vanilla have been developed, each with its own character. One derivative, Methyl Diantilis®, is an elegant, spicy-sweet ingredient with an olfactive note similar to that of isoeugenol, but with an additional powdery scent reminiscent of carnation, *Dianthus caryophyllus*. This compound has been synthesized and marketed by the company Givaudan.

In this experiment you will be synthesizing Methyl Diantilis and a homologue. Below is the synthesis of Methyl Diantilis, **3,** where R = methyl (CH_3). For your homologue, R will be ethyl, propyl, or isopropyl.



1 **2** **3** R = CH_3

EXPERIMENTAL PROCEDURE

Sodium Borohydride Reduction of 3-Ethoxy-4-hydroxybenzaldehyde (1)

Dissolve 2.4 mmol of 3-ethoxy-4-hydroxybenzaldehyde in 2.5 ml of 1.0 M NaOH in a 10 ml Erlenmeyer flask with a magnetic stir bar. Cool the flask in a ice-water bath, and then add, in small portions, 2 mmol of $NaBH_4$ over five minutes while stirring the mixture. Remove the ice-water bath and allow the reaction to stir at room temperature for thirty minutes. Take out a small sample from your reaction mixture using a pipet and analyze it by TLC to verify that the reduction of the aldehyde went to completion. If some aldehyde remains, add a small amount of $NaBH_4$ to the reaction mixture and let it react for 10 more minutes at room temperature, Once the reaction is complete, cool the reaction flask in the ice water bath, and slowly add 2.5 M HCl (**Add the hydrochloric acid solution SLOWLY; there is a lot of foaming. Caution: Hydrogen gas evolution!).** Check the pH of the reaction mixture once the gas evolution begins to be less pronounced, somewhere around 1.5-2 ml. Keep adding the hydrochloric acid until the reaction mixture is acidic. Let the flask sit in the ice-water bath for an additional five minutes, then vacuum filter the precipitate, washing with cold water (4 x 2.5 ml). Allow the solid to dry with the vacuum on for at least fifteen minutes; water is hard to get rid of. This material should be pure enough for characterization and for the next reaction.

Etherification of 3-Ethoxy-4-hydroxybenzyl Alcohol (2)

Transfer 0.25 g (0.23-0.27 g; record exact weight) of "wet" Amberlyst® 15 (Aldrich) into a 10 ml round bottom flask. Wash the "wet" Amberlyst® 15 three times with 2.5 ml portions of methanol. Carefully decant the methanol from the resin. Add 4 ml of methanol, and then add 1.5 mmol of 3-ethoxy-4-hydroxybenzyl alcohol in small portions with vigorous stirring. Remove a few drops of the reaction mixture for TLC analysis, place a condenser on the reaction flask, and then heat the mixture to reflux for fifteen minutes. Check the reaction by TLC (1:1 hexane:ethyl acetate) and continue heating until the reaction is complete. Allow the reaction mixture to cool to RT and then filter the reaction mixture directly into a small beaker, washing out the reaction flask two times with 1 mL of methanol. Gently remove the solvent on the rotary evaporator. **Do not overheat** your compound or it may decompose! You can

purify the compound by dissolving the crude product in hot hexanes (10 ml for R = $-CH_3$; $-CH_2CH_3$; 20 ml for R = $-CH_2CH_2CH_3$; $-CH(CH_3)_2$), filtering, and removing the solvent from the filtrate using the rotary evaporator. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

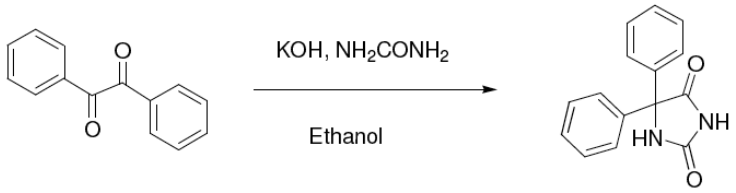
REFERENCES

1. 1. IFF 2005 Annual Report, http://www.iff.com/internet.nsf/0/38C7BE1C7DB473A28525713E00596C28/$File/IFF%20Annual%20Report-10K.pdf.
2. http://www.bojensen.net/EssentialOilsEng/EssentialOils30/EssentialOils30.htm, Accessed January 3, 2007.
3. "Creative Sensory Advantage – Givaudan", http://www.givaudan.com/givcomweb/StaticFiles/GivaudanExtranet/Publications/fin_present/2003/alpine_summit_030125.pdf.
4. Miles, W. H; Connell, K. B *J. Chem. Educ.*, **2006**, *83,* 285.

EXPERIMENT 20 -- SYNTHESIS OF 5,5-DIPHENYLHYDANTOIN (PHENYTOIN)

INTRODUCTION

Phenytoin has been widely prescribed for the control of epilepsy since its introduction as a pharmaceutical agent during 1950's, and although superseded by a number of newer drugs, it remains in use today in this role. The main structural challenge for the synthesis of this compound is the construction of the hydantoin ring. This hydantoin ring can be formed in a one-pot procedure starting from benzil. The procedure for this reaction is a base catalysed addition of urea to benzil that is an interesting example of a benzilic acid re-arrangement where the phenyl groups undergoes a 1,2-migration during formation of the hydantoin ring (Scheme 1).



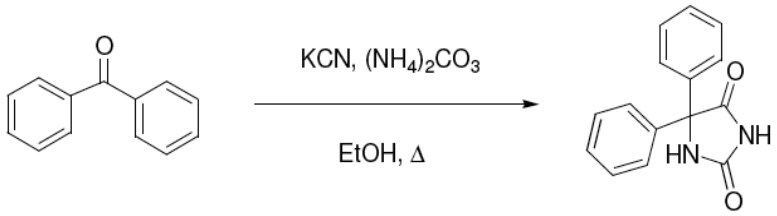
Scheme 1. Synthesis of phenytoin from benzyl

EXPERIMENTAL PROCEDURE

Benzil (2.5 mmol), potassium hydroxide (4.5 mmol) and urea (3.3 mmol) were dissolved in 200 Proof Ethyl alcohol (10 ml) and heated gently to reflux on a sand bath until TLC analysis (4:1 hexane:ethyl acetate) indicated complete consumption of starting material. The reaction mixture was then poured onto an ice/water mixture (25 ml), and the solution was filtered to remove the solid which is 4,5-diphenyl-4,5-dihydroxy-2-imidazolone. The filtrate was slowly acidified by the dropwise addition of concentrated hydrochloric acid to precipitate the product as a white solid, which was removed by filtration, washed with water, and dried to give the crude product. The product was recrystallized from 95 % ethanol. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

QUESTIONS

The most common method for the synthesis of phenytoin analogues is the Bergs synthesis, which has been used to prepare a large number of analogues for pharmacological screening studies (Scheme 2).



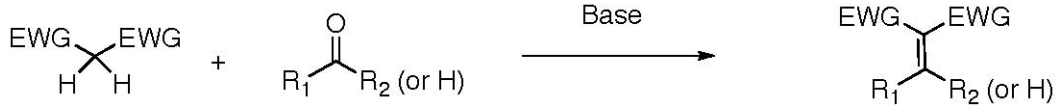
Scheme 2. Bergs synthesis of phenytoin

1. Why do we not use this method?
2. Draw a detailed mechanism for this reaction.

EXPERIMENT 21 -- PREPARATION OF 1,1-DICYANOALKENES FROM ALDEHYDES

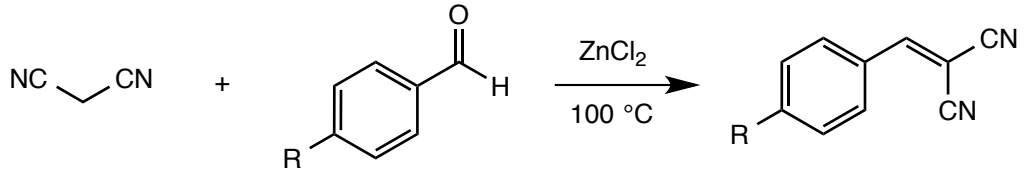
OVERVIEW

In this experiment you will conduct a "green" version of the Knoevenagel Condensation (KC). The KC is a variation of the Aldol condensation where an acidic CH_2-group does a nucleophilic addition to an aldehyde or ketone followed by a dehydration reaction to yield an alkene.[1,2] Generally, the two groups flanking the methylene group are electron-withdrawing groups like carbonyls (think of stabilized enolates), so the normal product of a KC is an α,β-unsaturated carbonyl compound.



Scheme 1. Generic Knoevenagel condensation reaction.

Traditional conditions involve organic solvents. However, solvent-free (and therefore greener) conditions were reported to be successful in 1991 using zinc chloride as a catalyst.[3] You will perform a solvent-free KC using malononitrile (**1**) and one of the following aldehydes: benzaldehyde (**2a)**, 4-methoxybenzaldehyde (**2b**), or 4-nitrobenzaldehyde (**2c**). The general synthesis is given in Scheme 2.



1 **2a** R=H **3a-c**
2b R=OCH_3
2c R=NO_2

Scheme 2. Knoevenagel condensation of malononitrile with substituted benzaldehydes

The synthesis of your Knoevenagel product is not the only goal of this experiment. You will also examine the resonance effects of electron donating and withdrawing groups in conjugated systems. The resonance effect can be seen by how the R group affects the chemical shift of carbons in "distant" parts of the molecule. Here we will compare the chemical shifts for the carbons α to the nitriles.

EXPERIMENTAL PROCEDURE

Knoevenagel condensation

Place a 250-ml beaker containing about 200 ml of water on the hot plate and bring the water to a gentle boil. Place a clean, dry 10-cm test tube in a 25 ml Erlenmeyer flask. Add (by pipet if a liquid) 3.0 mmol of your chosen aromatic aldehyde directly to the bottom of the test tube. (Avoid getting liquid on the wall.) Then add 3.15 mmol of the dinitrile by dropper directly to the bottom of the test tube. Then add about 40 mg (record the exact mass) of $ZnCl_2$ to the test tube.

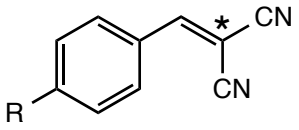
Insert a glass rod and clamp the test tube in the boiling water bath. Stir the mixture often with the rod over a period of 10 min. Note any changes in color or physical state of the reaction mixture. Remove the tube from the bath and stir the mixture with the rod as it solidifies. Add 5 ml of 1% aqueous ethanol, pulverize the solid as well as possible, then cool the tube in an ice-water bath for about 10 min. Collect the solid on a Hirsch funnel and rinse the tube and rod four times with a dropper-full of cold 1% aqueous ethanol.

Recrystallize the crude product by dissolving the solid in the minimum amount of hot acetone. You may need to filter the warm solution through a cotton plug if there are undissolved solids, rinsing the funnel with some acetone. Concentrate the solution by boiling to <1 ml (or until precipitation occurs from the boiling solution), then add about 2 ml of methanol. Allow the product to crystallize at room temperature.

Cool the flask in an ice-water bath for 10 min, and then collect the crystals using vacuum filtration and a clean Hirsch funnel, rinsing the solid with a small amount of cold methanol. Spread the crystals on a small piece of paper and allow to air-dry overnight. For reference, the literature melting points for the products are: **3a**, 88 °C; **3b**, 119 °C; **3c**, 163 °C. Refer to the Table on pages 9&10 for a complete list of all the required analysis.

Spectral interpretation

As we learn as part of the benzene chemistry this quarter, the three variations in R groups for the possible aldehydes represent a electron-neutral substituent (H), an electron-donating substituent (OCH_3), and an electron-withdrawing substituent (NO_2). We can see direct evidence for these designations and how they translate their properties via resonance in the ^{13}C NMR spectra of the products. Specifically, we can chart the chemical shifts of the carbon that is α to the nitriles. That carbon is starred in the picture below. This carbon is a useful indicator both because it experiences large chemical shift changes and because it appears in a portion of the spectrum distinct from all the other carbons -- in the 70-90 ppm range.



Using the available spectra, make a table of the chemical shift of this carbon by substituent. Explain the trend that you find. Rationalize this trend using simple NMR knowledge in combination with drawing key resonance structures for each of the products.

QUESTIONS

1. Using curved arrows to symbolize the flow of electrons, write a reasonable stepwise mechanism that accounts for the formation of your product. (Remember that $ZnCl_2$ is a Lewis acid.)
2. We normally expect sp^2 carbons of alkenes to have chemical shifts above 100 ppm. Briefly explain why that is not the case for the α carbon of your product.

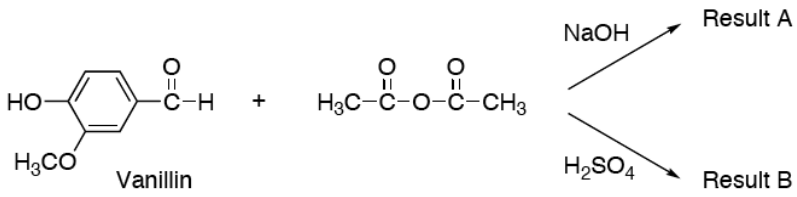
REFERENCES

1. "The Knoevenagel Condensation," Jones, G. Chapter 2, *Organic Reactions*, **1967**, *15,* Chapter 2, John Wiley & Sons, Inc., New York.
2. Jones, Jr., M *Organic Chemistry*, 4th edition, W. W. Norton and Company, New York, 2010, pp. 965–974.
3. Rao, P. S.; Venkataratnam, R. V. *Tetrahedron Lett.,* **1991**, *32*, 5821–5822.

EXPERIMENT 22 -- ESTERIFICATION REACTIONS OF VANILLIN: THE USE OF NMR TO SOLVE A STRUCTURE PROOF PROBLEM

INTRODUCTION

The reaction of vanillin with acetic anhydride in the presence of base is an example of the esterification of a phenol. The product is a white solid and can be characterized easily by its IR and NMR spectra.



When vanillin is reacted with acetic anhydride in the presence of acid, however, the product that is isolated has a different melting point and different spectra. Your job is to identify the products formed in each of these two reactions and to propose mechanisms that will explain why the reaction proceeds differently under acidic and basic conditions.

EXPERIMENTAL PROCEDURE

Reaction of vanillin and acetic anhydride in the presence of base

Dissolve 2 mmol of vanillin in 5 ml of 10% sodium hydroxide in an Erlenmeyer flask. Add 6 g crushed ice, and 10 mmol of acetic anhydride. Stopper the flask with a cork and stir the solution over a 20 minutes period. A cloudy, milky-white precipitate will form immediately upon adding the acetic anhydride. Vacuum filter the precipitate, and wash the solid with three 1-ml portions of ice-cold water.

Recrystalllize the product by adding warm 50% EtOH in water and letting the solution cool slowly. In this case **it is critical that the solution containing the product is not heated directly**. (Literature melting point value = 78-79°C).

Reaction of vanillin and acetic anhydride in the presence of acid

Dissolve vanillin (2 mmol) in acetic anhydride (21 mmol). With the mixture stirring, add one drop of 4.5 M sulfuric acid to the reaction mixture. Stopper the flask, and stir at room temperature for one hour. During this period, the solution will turn purple or purple-orange in color. At the end of the reaction period, cool the flask in an ice-water bath for 3-4 minutes. Add a mixture of 4 ml cold water and 3 g ice to the flask. Stopper the flask and shake vigorously. Continue to cool and shake the flask to induce crystallization, adding more ice to the flask if necessary. Vacuum filter the product, and wash the solid with 3x1 ml portions of ice-cold water. Recrystallize the solid from 95% ethanol. (Literature melting point value = 90-91°C). Refer to the Table on pages 9&10 for a complete list of all the required analysis.

Product identification and comparative analysis:

Refer to the Table on pages 9&10 for a complete list of all required analysis.

Compare the two sets of spectra obtained for the acid and base promoted reactions. Using the spectra, identify the structures of the compound formed in each reaction. Outline mechanistic pathways to account for the formation of both products isolated in the experiment.

1. Draw a mechanism for the formation of your proposed structure for the acid-catalyzed reaction of vanillin and acetic anhydride.
2. How did you distinguish the “acid” product from the expected esterification product observed in the base-catalyzed reaction using spectroscopy?