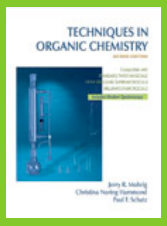
Chem 6B



INTERMEDIATE ORGANIC LAB

MICROSCALE TECHNIQUES IN ORGANIC SYNTHESIS

A guide for teaching assistants and students

Modus Operandi (1-4)

1. TA responsibilities.

General: For safety, TAs permit a maximum of eighteen students per section and require students to wear lab goggles and closed-toed-shoes. TAs also ensure that students finish their experiments in a timely fashion (4 hrs max!).

Instruction and score: In each experiment, TAs give a brief overview of the theory and procedure for the daily activities, give a quiz, grade the pre-lab, and in-lab parts, and assign a technique grade. After each experiment, TAs will request a photocopy of the entire experiment (pre-lab, in-lab and post-lab write-up) for grading. TAs should complete their grading within one week after receiving each lab report. During every experiment, TAs assign 2-3 low technique scores (50) and 2-3 outstanding technique scores (90) to students. TAs use an identical 6B grading spread sheet to track their grades.

Absence and make-up: TAs oversee all fourteen experiments, but **do not** have the authority to cancel class or permit a student to skip a lab. If a student cannot attend, students must inform the course instructor, who may provide a "permission" email. If space is available, TAs in other sections will contact the student to inform them of potential time to make-up the experiment. Make-up will be allowed up to 2 times. If a TA is sick, or must miss a lab, they will make arrangements to cover the sections and inform the instructor.

2. General procedures for students in each lab. Each class usually begins with a 5-10 minute quiz that emphasizes important aspects of the current experiment and specifics from the past lab. The TAs will give a 10-30 minute overview of the experiment, including the theory behind the practice; make notes in your notebook. While you are setting up your experiment, the TA will grade the "pre-lab" of your notebook in red ink, assigning a score with the date and their initials on the first page of the experiment. Before leaving lab, your TA will again initial the "in-lab" of your notebook to verify your experimental procedure and observations. You should work **independently** on **ALL** the experiments and write-ups.

Course Outline

Exp. 1 (esterification - ethyl laurate)

Exp. 2 (oxidation - cyclohexanone)

Exp. 3 (aldehyde olefination - stilbene)

Exp. 4 (hydroboration - octanol) NOT PERFORMED

Exp. 5 (Grignard 1,2-add. - triphenylmethanol)

Exp. 6 (Diels-Alder - cyclohexene)

Exp. 7 (Br_2, dehydrohalogenation - diphenylacetylene)

Exp. 8 (condensation - benzoin)

Exp. 9 (oxidation - benzil)

Exp. 10 (Aldol, Diels-Alder - hexaphenylbenzene)

Exp. 11 (amide acylation, Br_2 - 4-bromoacetanilide)

Exp. 12 (glucose acetylations - glucose penta-acetates)

Exp. 13 (diazonium coupling - methyl orange and red)

Exp. 14 (Friedel-Crafts - 2-(4-toluoyl)-benzoic acid)

Exp. 15 (Friedel-Crafts - 2-methylanthraquinone)

Instructor: Thomas Pettus

3. Lab Reports.

General: The laboratory notebook is a record of all work performed in the laboratory. It is a legal document that gives testimony of performed work. *It should be concise, written clearly and neatly, so as to allow a future experimentalist to reproduce the experiment.* Your ability to keep a good notebook can affect also your technique grades.

Notebook: Students should use a non-perforated notebook. Do *not use* a spiral/loose-leaf notebook, and *never remove* pages from your notebook. The notebook should begin with a **table of contents** (see page 3 marginal note), including the title of every experiment and the corresponding page number, listed in sequential order. All entries should be written **in ink**, whether done in advance of the experiment or while making observations. You should *never type* reports. All **pages** are to be numbered sequentially. The lab record (pre-, in- and post-labs) is written on only **right hand pages** of the notebook. This leaves the left-hand pages for notes and calculations.

Contents: Reports consist of three components. The pre-lab **(Part I)** is completed **before** coming to lab. During lab, TA lecture notes are then written into the notebook (left-side) and the actual in-lab procedure **(Part 2a)** is completed on the right-side. The post-lab experimental analysis **(Part 2b)** is completed after the experiment is done.
Part I will be initialed, dated and graded by the TA at the beginning of each experiment. Part I includes: A) a title, the date, your name, your perm number, and your TAs name; B) a purpose/objective; C) a reaction diagram or flow chart; D) table of reagents and products; and E) a brief intended procedure. Throughout the experiment, annotations and changes can be made to Part I and Part 2a on the left hand page in ink.
Part 2a is written during the lab. It is comprised of A) the actual experimental procedure and B) experimental observations. Before leaving lab you must get your TAs initials to verify you have composed an experimental procedure and have maintained experimental observations during lab.
Part 2b, the final post lab write-up, is written after lab. It includes A) your results, B) a discussion of your results, C) a conclusion, and D) references for any literature used. Any loose paper (spectra and quizzes) and TLC should be neatly taped into the notebook following to the appropriate lab.
Submission: ***<lab report for each lab>*** A photocopy of Part I and Part 2a/b including spectra are submitted to the TA for grading by Friday for the previous Monday and Tuesday labs and by Monday for the previous Wednesday, Thursday and Friday labs. *Your TA can reduce your notebook grade by 10% for each day it is late.* Experiments not submitted by the beginning of exam week will receive a score of zero.
<whole lab notebook> You are required to turn your notebook over to your TA at the end of the quarter. It will be used to assist the instructor in assigning your final letter grade. If students do not turn in a notebook, they should be prepared to lose at least 2/3 of a letter grade from their final letter grade. At the end of the course please write one page about the course, its strengths and weaknesses, as the last page of your notebook. Make suggestions about what you would you do to improve it.

Detail of notebook preparation:

---Pre-Lab [Part I]--- (30 pts) : need to be done before the beginning of lab

A. Title, date, name, student perm number and TA overseeing the experiment

B. Purpose/Objective

Give a brief introduction to the purpose of the experiment and the approach to be used. Demonstrate that you understand the objective and the key concepts of the experiment. **Do not copy directly from the laboratory manual.** Usually, one or two paragraphs will be adequate (less than 1/2 a page). Use only the **third person**, **present tense**, **passive voice** when writing the introduction.

(ex) Correct: Cyclohexanol is converted to cyclohexene using.....

Incorrect: In this experiment, I will be performing an acid catalyzed dehydration...

Example: Cyclohexene is prepared from purified cyclohexanol by acid catalyzed dehydration. Trace acid is neutralized with sodium carbonate and the product is salted out of the aqueous extract using brine. The organic layer is dried over magnesium sulfate as a drying reagent. Purified cyclohexene is obtained by simple distillation and it is characterized using IR and NMR spectroscopy by monitoring the loss of -OH and the gain of an alkene.

C. Reaction Diagram

Relevant balanced, and fully labeled, chemical equations should be included.

D. Table of Reagents and Products

Table of reagents needs to be **completed before Lab starts**. Include **all** physical data for **all** compounds Sigma Aldrich contains most of this data on their website (www.sigma.com)

Grading

Notebooks (100pts) [15%]
Part 1 (30pts)
Part 2a (20pts)
Part 2b (50pts)

Technique [5%]
(50, 70 or 90/100 pts)

Quizzes [20%]

Products (100 pts) [30%]
(0–100 pts)

Final [30%]

This class is curved. The average for each section of chem 6B is set to a [B-]. The instructor in charge assigns the final grades, not the TAs. After evaluating the notebooks and TA grade sheets, a decision is made in consultation with each TA.

E. Intended Procedure with Flow Chart

Demonstrate that you are prepared for lab by giving a brief description of what you actually intend to do in lab experimentally. A "game plan" or checklist, written in your own words, will save you time in lab. This can be written in paragraph form or as a bulleted list. Do not copy directly from the laboratory manual. The flow chart is helpful to understand the exact procedure of the lab. Beautiful drawing of the equipments is highly recommended.

(ex) Weigh lauric acid. Add to 3mL conical vial with stir bar. Add EtOH. Add AcCl. Reflux with water condenser and drying tube for 1 hr...

---In-Lab-[Part 2a]-- (20 pts)

A. Actual Procedure

This is an account of what really was done. Do not regurgitate the laboratory manual. Students need to write whole the procedure as exactly carried out. If the procedure has been modified, or changed in any way from the original way written in lab manual, note the changes here. Remember that the procedure section should be sufficiently detailed, such that another student would be able to repeat the whole experiment based on your report. Keep the following points in mind:

(i) Use the third person, the passive voice, and the **past** tense.

Correct: The solution was heated on a hot-plate for 30 minutes.
Incorrect: I heated the solution on a hot-plate for 30 minutes.
Incorrect: The solution is heated on a hot plate for 30 minutes.

(ii) Avoid the "recipe format".

Incorrect: Heat the solution on a hot-plate for 30 minutes.

(iii) Incorporate your **observations** into the procedure.

(ex) The solution was heated on a hot-plate for 30 minutes, during which time the color of the solution changed from red to green.

(iv) Should be written **concisely** written. Avoid unnecessary detail.

Correct: 20 mL of hydrochloric acid (3M) was added to the solution with constant stirring.
Incorrect: 20 mL of 22.5 °C hydrochloric acid (3M) was poured from a graduated cylinder into a 100-mL beaker containing the solution. During this process the solution in the beaker was stirred with a 15- cm long glass rod having a diameter of 5 mm.

B. Observations

Prepare a **simple flow chart** of the procedure, and record any observations alongside. This will show your **scientific engagement** and need to be considered as an important matter.

Correct: The reaction mixture turned green and a precipitate formed. The crude product, a yellow crystal, weight 15mg.

---Post-Lab-[Part 2b]-- (50 pts)

A. Results:

This is one of the most important section of your report. Wherever possible, tabulate your data, such as the melting/boiling point with its range, any IR and/or NMR spectra, and any other observations or measurements. Include all the spectra, which will be provided from your TA as standards, with your interpretations and peak assignments. Especially, show clearly how did you calculate the % yield.

B. Discussion

This section should be completely based on your results (measured or calculated values) and observations. Whatever the value you got is your data, and you need to consider the meaning of your data. You also need to show your understanding of the experimental mechanistic background. Often you need to site references where you can obtain the supporting information.

First, your discussion should state what you've made (draw the structure and name it) and what it appears like (was it as expected, compared to a standard or the literature, e.g. white shiny crystalline solid). Discuss the yield and purity of the product(s) you recovered/synthesized. Qualitatively assess the performance. A discussion should quote actual experimental values and not talk in vague terms.

Correct: The product obtained was found to be fairly pure, as it had a mp of 110-112° C, a mp range of only 2° C. This result was 3 degrees below the literature value of 115 °C for 'compound X'. This also shows that the product was not completely pure.

The next section of your discussion should include an interpretation of all available spectra online for starting material and product. A detailed analysis of changes observed in the spectra should be included. Also, students should include sources of error and loss. Try to think of at least two sources of each. Sources of error include theoretical sources, such as the reaction did not go to 100% completion, and practical sources, such as the instrument or glassware used was not calibrated. Sources of loss include theoretical sources, such as reaction byproduct formation, and practical sources, such as surface adhesion, loss on glassware, and mechanical transfer loss (a spill).

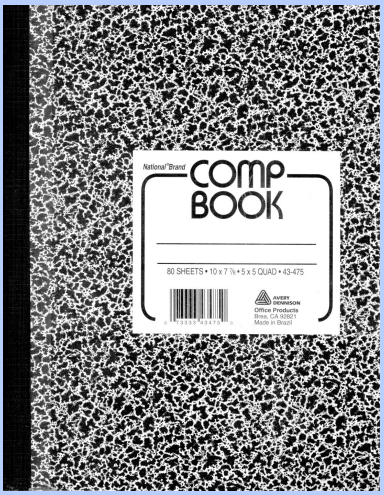
Finally, mention at least one way to improve the experiment.

C. Conclusion

Give your signature and a pledge that all of the observations and conclusion herein are your own and that you believe them to be correct. Then have another person witness your pledge with their signature.

D. References:

You should reference any literature used in your report, i.e. melting points, spectral data, etc. Use an acceptable scientific journal style/format for your references. Be consistent. Author name (surname, initials.), year published. Title, publisher name, publisher location, page numbers



ideal notebook 2 dollars at U-cen

Table of Contents Example

Chem 6B Lab
"STUDENT'S NAME" "PERM NUMBER"
"SECTION"
"TA'S NAME"

First Page (Table of Contents)

Experiment 1 (pages XX)
Fisher Esterification
Quiz 1 (0-100),
Prelab Score (0-30)
in-lab Score (0-20)
Post lab score (0-50)
Composite Notebook score (0-100)
Technique Score (50, 70 or 90)

Experiment 2 (pages XX)
Sodium Hypochlorite Oxidation of Cyclohexanol
Quiz 1 (0-100),
Prelab Score (0-30)
in-lab Score (0-20)
Post lab score (0-50)
Composite Notebook score (0-100)
Technique Score (50, 70 or 90)

continued....

etc., etc, etc.,

4. Technique Score. For each experiment technique scores will be assigned out of 100 pts; 3-4 low technique scores (50 pts) and 2-3 outstanding technique scores (90 pts) will be assigned to deserving students. The technique score can be very subjective. Your TA can give you a low score if you 1) are wearing inappropriate clothing, 2) have a messy area, 3) use incorrect disposal techniques, 4) are extremely inefficient in lab, 5) have an unorganized unkept notebook, 6) are not wearing your safety goggles, 7) are unprepared for lab. Failure to listen, learn, and comply will be reflected in your technique grade. Your TA can give you an outstanding score if you 1) clean up a dirty area, 2) ask good questions, 3) have a very neat, organized notebook, 4) are efficient during lab. TA's will strive to have everyone finish the lab course with an average technique score. Therefore, if you receive a low score, you should make use of opportunities (preferably in the same lab) to zero it out with a high score.

5. Product Score. Product scores will be assigned out of 0-100 pts for each experiment based on purity and product amount. Purity and product amount will be assessed separately, in relation to other students in the class, on a distribution of 0-50 pts and then the two scores are added together.

6. Grading. Grades are based on in class quizzes, notebooks, technique scores, and product scores. TAs will set the average grade of their section to a B-. TAs will entering **fifteen** notebook scores, **ten** quiz scores, **fifteen** product scores, and up to **fourteen** technique scores. All TAs use the same grading schemes and the same Excel® Chem 6B spread sheet. Students are to turn in their notebooks to their TA at the end of the quarter. The grade sheet is emailed to the instructor at the beginning of dead week. No reports or notebooks are accepted after the end of dead week. The TA brings his/her students' notebooks and meets with the instructor to discuss the final grade of each student.

7. Missing Lab. Missing lab is strongly discouraged. If you miss a lab for an excusable reason, you must contact the instructor (not the TA) within 24 hours to make arrangements for a make-up experiment in another TAs section. If excused, the instructor will contact other sections and the TA will contact you if they have space. TAs will not give unknown students entry without a permission email from the instructor. You must make-up the old experiment with minimal guidance from the new TA, who may be directing a different experiment. Because of waste disposal issues, if you do not make up the experiment within one week, you will receive "0's" for Part 1 and Part 2a/b. The new TA must initial and grade Part 1 of your notebook for the experiment that you are performing. The quiz in the other section does not count toward your grade. Your old TA will leave a blank for your missed quiz score. Be sure that your original TA enters scores for Part 1 of the make-up into their grade-book. You'll submit Part 2a/b to your original TA. However, even If you are allowed to make-up three or more labs, you will probably receive an F as a letter grade.

8. Rules for the Disposal of Reaction Wastes. Disposal of reaction wastes can effect your technique score! Dilute aqueous wastes containing only acids, bases, or salts (which have been neutralized!) may be disposed in sinks. Wet methanol, acetone and ethanol are considered aqueous waste. When mixed with dry organics, however, these solvents are considered organic waste. All organic wastes must be poured into the bottles provided. Please note that there will be separate bottles for halogenated and non-halogenated wastes. Bottles with specific labels for each experiment's waste will be available in the hood. Solids, such as drying agents, are placed in the plastic bags provided or in solid waste containers. TA's will independently dispose of your product vials after grading. Do not leave any unlabeled vials with chemicals in your drawer. At the end of the quarter, you must clear all chemicals out of your locker. When in doubt about how to dispose of something, ask your teaching assistant. Also, see the comments concerning waste given at the end of each experiment.

Post-Lab (examples)

Results: Label and title all attached flowcharts, spectra etc. The results section gives you an opportunity to discuss the significance of your results, to assess the validity of the method, to indicate possible reasons for a poor yield, and so on. Do not over-comment on IR spectra, just pick out and comment on the spectral peaks of importance. Show sample calculations. Remember there is a difference between % recovery yield calculations and % yield calculations. In the latter, you must determine limiting reagents and a theoretical yield.

Discussion: an example

A clear colorless liquid with a slight alcohol odor, corrected bp 196-201 °C, and refractive index of 1.5262 (at 20° C), was obtained from the reaction of...[also draw and name structure of product here]...

The yield of 1-phenylethanol was 13.2 g of clear, colorless liquid, and the % yield was 56%. The theoretical yield for the reaction was calculated to be 23.57 g, but this assumes that all the limiting reagent (acetophenone) reacted and that no byproducts formed (styrene). Thus, this is a fairly good yield for this reaction, which normally gives yields of product around 85% (ref: textbook pp. #). The product appears to be pure. According to the CRC Handbook the product should be a clear, colorless liquid, with a bp of 203 °C. The product obtained was clear and colorless with a (barometric pressure corrected) bp of 195-201 °C. The boiling point of the product was 2 C below the literature value, indicating some impurity and/or error, and boiled over a range of 6 °C, which definitely means some impurities are still present. The refractive index of the product was 0.0010 below the literature value of 1.5272, indicating again that some slight impurities are present. The infrared spectrum for the product shows good purity. All the signals for an aromatic/aliphatic alcohol were present; O-H stretch @ 3350 cm^{-1}, aromatic C-H stretch @ 3080 cm^{-1} and alkane C-H stretch @ 2850-2950 cm^{-1}, C=C stretching @ 1600, 1500 and 1450 cm^{-1} and C-O stretch for a alcohol @ 1077 cm^{-1}. No bands due to reasonable impurities were observed in the infrared spectrum. The HPLC chromatogram showed high purity, 99.54%, with only traces of acetophenone and styrene being present.

The boiling point of the product was 2 °C below the literature value, however an uncalibrated thermometer was used to take this reading. This may account for why the temperature reading was low, but does not explain why the product boiled over a range of 6 °C. The refractometer used in this experiment was uncalibrated. This is a practical source of error for the experiment. And might partly account for why the RI was 0.0010 below the literature value of 1.5272.

Perhaps, rinsing the flask more during transfers would have improved the overall yield.

Conclusion: an example

To the best of my knowledge all of the conclusion and observations herein are true [signed], [witnessed], dated.

9. Laboratory Safety. Laboratory safety can affect your technique score! Dealing with chemicals requires an alertness and awareness of the problems associated with the handling of volatile, flammable, corrosive and toxic materials. Many generations of organic chemists have learned how to do chemistry both safely and enjoyably. It is necessary to be always cautious, but not to the detriment of performing the experiments expeditiously. Learn to be aware of the safety requirements, but then to enjoy the experience of preparing materials and analyzing them as efficiently as possible.

Syringe disposal. Your TA will give you 1-2 capped needles during the experiments requiring syringes. Upon dispersal, 10-20 points will be subtracted from your quiz grade as an "insurance." When you return the needle, 20-30 points will be re-added to your quiz grade. TA's will put waste needles in the assigned disposal jars. **DO NOT PUT NEEDLES IN THE TRASH!! REPORT NEEDLES IN THE TRASH TO THE TA.**

Safety glasses. Safety glasses must be worn in the laboratory. You will not be admitted into the laboratory unless your eyes are and remain protected. Visitors must also wear safety glasses. Do not wear contact lenses in the laboratory. Organic fumes may harm them, and caustic reagents cannot be washed from the eye if contact lenses are worn.

Gloves. Gloves should be worn if you are handling corrosive materials. Surgical gloves will not protect you against strong acids, but they are available for your use at other times. Heavy rubber gloves are available for handling extremely corrosive materials. You may wish to purchase your own rubber gloves and keep them in your locker.

Shoes. Sandals or open shoes are forbidden in the laboratory. Clothing which leaves your legs exposed should not be worn, unless a laboratory coat or apron is worn as well.

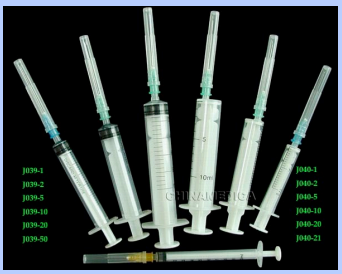
Hair. Your hair should be pulled and tied back from the face so that it cannot be caught in equipment or open flames.

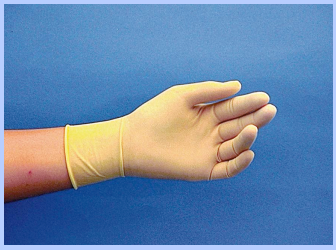
Glassware. Glassware is cleaned easiest after every use. Most organic materials are removed from glassware with acetone and water. Soap may not be necessary.

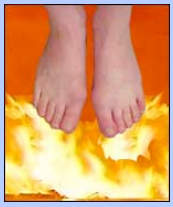
Heating. Heat is an ignition source. Only use heat in a working hood. Never heat a closed system! Keep flammable organic solvents away from flames and sources of heat. Ether has a very low flash point and may be ignited by a hot-plate.

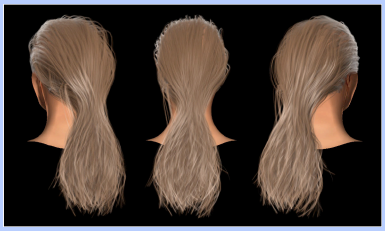
Cleanliness. Your locker and bench-top should always be ordered and neat. Do not store chemical or reagents in your locker, with the exception of labeled products and recrystallizations. The balance-area should be cleaned after every use. Clean up any spills immediately. Organic solvents often dissolve plastics and rubber items.

Accidents. Showers and eye washes are available. The eye wash fountains at the front of the lab are for flushing the eyes with water after an accident.









10. Laboratory Instruments

The IR: The Jasco FT-IR is a powerful, but easy to use instrument. First, you will need to acquire background scans by selecting "Background" from the Scan menu. Make sure that nothing is in the sample chamber when this is done. To run a sample, place the plate in the V-shaped sample holder that permanently resides within the FT-IR. Select "Sample Scan" from Scan menu. From the File menu, select "Plot". In the resulting window, select "Plot" once again. Click "Done" once plotting has begun.

Because of their expense and moisture sensitivity, the single crystal salt plates should be handled carefully by the edges. You will mostly use "the thin film technique" for your dry samples. To do this, set one salt plate flat on a clean surface (e.g. paper towel, kimwipe, etc.), put one small drop of "neat" (undiluted) sample on the plate, and one drop of methylene chloride to evenly disperse the sample. Let it dry on the plate. You can now run your sample. After recording your spectra, clean the salt plate with dichloromethane and kimwipes, touching the edges only. Put the plate back into the desiccator, or give it to the next student in line.

KBr pellets are obtained by using the metal hexagonal nut and tightening the bolts with a torque wrench to approximately 30-40 lbs/square inch. The most important part of the preparation of the pellet is to see that your dry sample is ground well (approximately 5 minutes grinding) and that about 10 times as much dry KBr is added to the mortar and mixed well. If everything is dry, when you carefully remove the screw on the die, you will see an almost transparent pellet that may be mounted by placing the die on the plastic cell holder.

The GC: Your TA will show you how to use the syringe, the recorder, and the gas chromatograph for the separation of your products during the elimination experiment.

Forward to the chem 6b student

Experimental techniques and instrumentation are the backbone of experimental organic chemistry. These experiments expose you to the fundamental techniques used by organic chemists. If you were to venture into a research corridor of the chemistry building, graduate students (your TAs) are taking melting points, performing distillations and extractions, using chromatography, and employing NMR and IR spectroscopy on a regular basis. Their apparatus may be more advanced, but the basic principles remain unchanged. Your TA serves as your well suited guide on this adventure. When you complete this course, we hope that you will further understand these principles. We hope to see you soon in Chem 6C or in one of our research labs soon. Have fun!

The Ft IR Spectrophotometer

The FT-IR is a powerful, but easy to use instrument. Please treat it with care and maintain the working area near the machine in a clean state. If any problems arise, please consult with any available TA before taking any action. However, the best plan of action is usually is to power down - wait 10 seconds - and restart both the computer and the spectral bench.

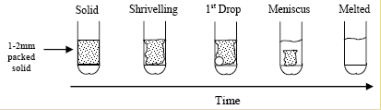
Spectra Manager II is the latest version of the Jasco innovative cross-spectroscopy software platform. The approach of having a single platform for data analysis is a unique and powerful way to manipulate and display data from any Jasco spectroscopy system. UV/VIS/NIR, Fluorescence, FT/IR, CD, ORD, LD, Raman, FT-Raman Polarimeters and other types of data files can be directly compared, processed, and printed together.

The Gas Chromatograph

The Series 400 Gow Mac gas chromatograph can be operated at temperatures from ambient to 300 °C. Temperature controls for injection ports, column oven, and detector are solid state proportioning type with direct dial setting. Platinum RTD temperature sensors ensure excellent reproducibility of oven temperatures. Temperature readout is displayed digitally with selector switches provided to set and read desired temperatures.

The Melting Point Apparatus

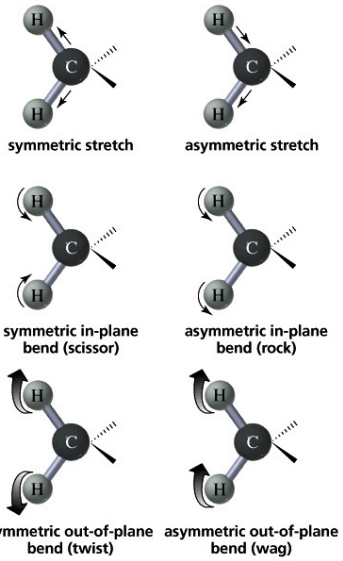
A block to accommodate the thermometer and up to three samples. Note that if only one sample is being investigated, the other two positions in the block must be occupied by empty tubes. If the approximate melting point of the sample is known, the apparatus may be heated rapidly to within 40 °C of the anticipated melting point. Rapid heating can be achieved by setting the fine control to its maximum setting, and adjusting the course temperature control to the appropriate position,Once the temperature of the block is within 40 °C of the anticipated melting point, the heating rate is adjusted using the "Fine Temperature Control" so that the temperature increases at a rate of not more than one to two degrees centigrade per minute. Do not be impatient! A higher rate of temperature increase will result in a melting point that is too high.

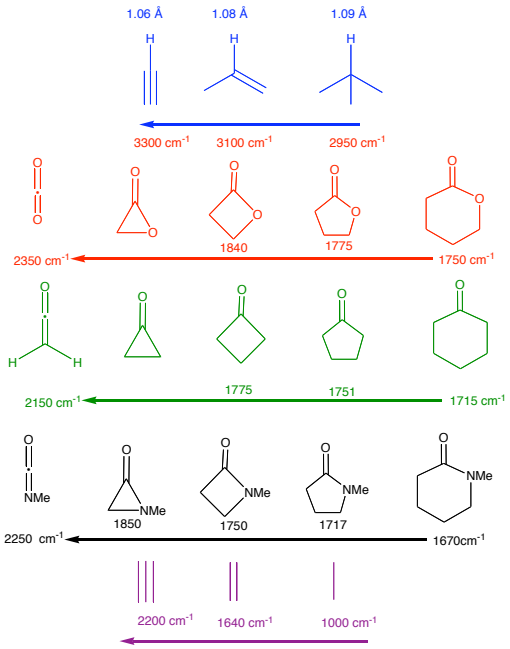


Review of spectroscopy

Infra Red.

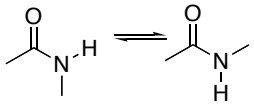
- IR is good for distinguishing functional groups.
- An infrared spectrum is obtained by passing infrared radiation through the sample.
- Wavenumber (υ) is another way to describe the frequency of electromagnetic radiation.
- High frequencies, large wavenumbers (υ), and short wavelengths are associated with high energy.
- The covalent bonds in molecules are constantly vibrating and each stretching and bending vibration of a bond occurs with a characteristic frequency.
- The greater the change in dipole moment, the more intense the absorption.
- Bonds in molecules lacking dipole moments will not be detected .
- The intensity of an absorption band depends on the # of bonds and therefore the strength of bond(s) responsible for the absorption .
- Bond order affects bond strength, so bond order affects the position of absorption bands.
- The approximate value can be calculated by Hooke's law.

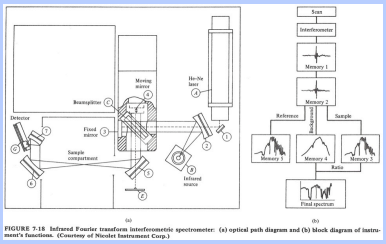


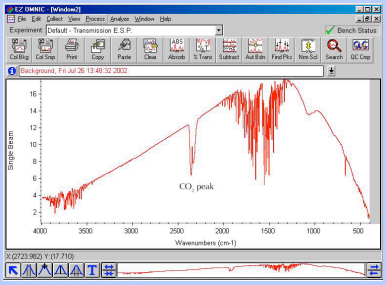


- The exact position of the absorption band depends on electron delocalization, the electronic effect of neighboring substituents,and hydrogen bonding.
- The predominant effect of the nitrogen of an amide is electron donation by resonance.
- The predominant effect of the oxygen of an ester is inductive electron withdrawal.
- The position and the breadth of the O–H absorption band depends on the concentration of the solution. It is easier to stretch an O–H bond if it is hydrogen bonded.
- The strength of a C–H bond depends on the hybridization of the carbon.
- Interference can be constructive or destructive and leads to overtones and Fermi resonances for ketones, anhydrides, and vinyl esters.
- Tells about functional groups by asymmetric bond motion. 1st order stretching frequencies are the easiest to understand by Hooke's law, IR confirms the presence of aldehydes, ketones, acids and their derivatives, alkenes, alkynes, aromatics, nitro, halides, amines, alcohols good for monitoring functional group inter-conversions (experiments 6-9).

- Alcohols and amines display strong broad O-H and N-H stretching bands in the region 3400-3100 cm.The bands are broadened due to hydrogen bonding and a sharp 'non-bonded' peak can often be seen at around 3400 cm. N–H's are usually sharper than O–H's because of less H-bonding. acyclic 2° amides may have two stretches.







B-H	C-H	N-H	O-H	F-H
2400	3000	3400	3600	4000
Al-H 1750	Si-H	P-H	S-H	Cl-H
	2150	2350	2570	2890
	Ge-H	As-H	Se-H	Br-H
	2070	2150	2300	2650

Table 13.4 Important IR Stretching Frequencies

Type of bond	Wavenumber (cm^{-1})	Intensity
C≡N	2260–2220	medium
C≡C	2260–2100	medium to weak
C=C	1680–1600	medium
C=N	1650–1550	medium
	~1600 and ~1500–1430	strong to weak
C=O	1780–1650	strong
C—O	1250–1050	strong
C—N	1230–1020	medium
O—H (alcohol)	3650–3200	strong, broad
O—H (carboxylic acid)	3300–2500	strong, very broad
N—H	3500–3300	medium, broad
C—H	3300–2700	medium

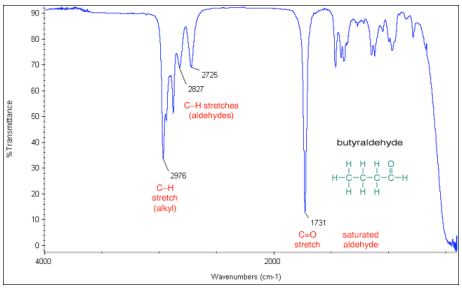
• Alkene and alkyne C-H bonds display sharp stretching absorptions in the region 3100-3000 cm. The bands are of medium intensity and are often obscured by other absorbances in the region (i.e., OH).

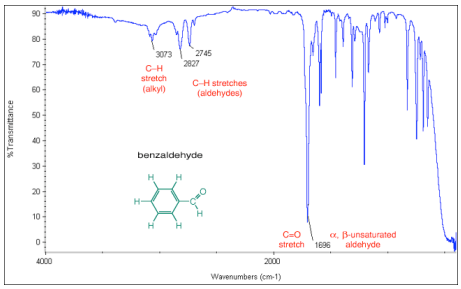
• Triple bond stretching absorptions occur in the region 2400-2200 cm. Absorptions from nitriles are generally of medium intensity and are clearly defined. Alkynes absorb weakly in this region unless they are highly asymmetric; symmetrical alkynes do not show absorption bands.

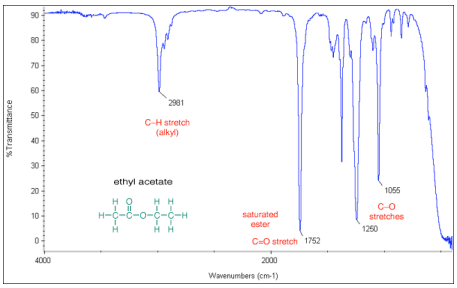
• Carbonyl stretching bands occur in the region 1800-1700 cm. The bands are generally very strong and broad. Carbonyl compounds which are more reactive in nucleophilic addition reactions (acyl halides, esters) are generally at higher wave number than simple ketones and aldehydes, and amides are the lowest, absorbing in the region 1700-1650 cm. More pi character leads to higher frequency.

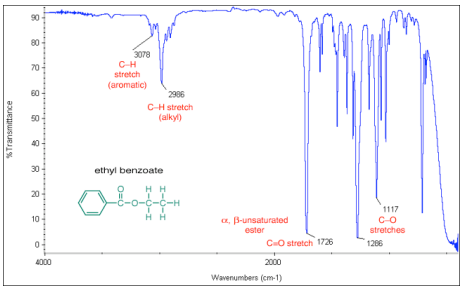
• Carbon-carbon double bond stretching occurs in the region around 1650-1600 cm. The bands are generally sharp and of medium intensity. Aromatic compounds will typically display a series of sharp bands in this region.

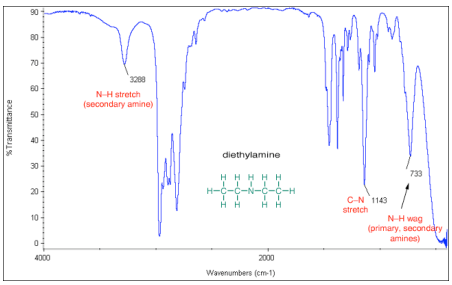
• Carbon-oxygen single bonds display stretching bands in the region 1200-1100 cm. The bands are generally strong and broad. You should note that many other functional groups have bands in this region which appear similar.

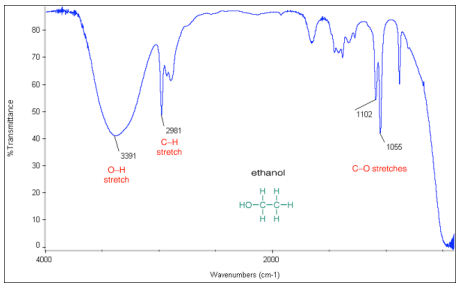


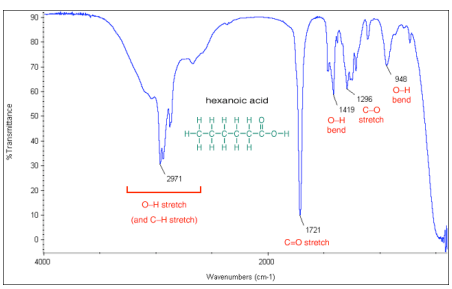


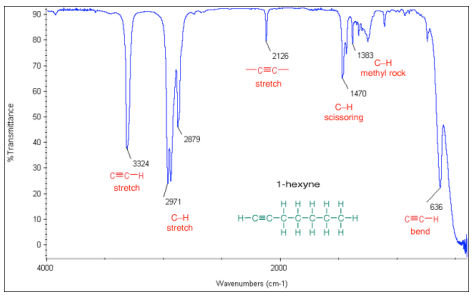


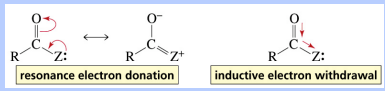












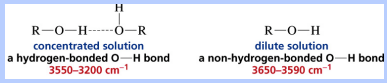
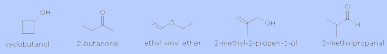
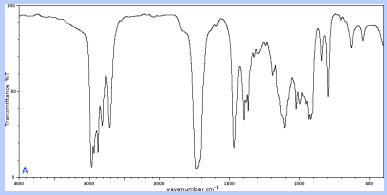
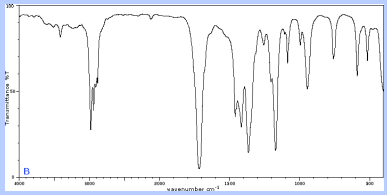


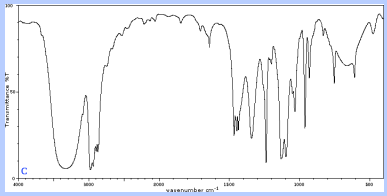
Table 13.5 IR Absorptions of Carbon–Hydrogen Bonds

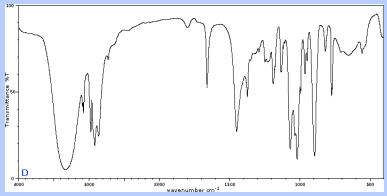
Carbon–Hydrogen Stretching Vibrations	Wavenumber (cm^{-1})
C≡C—H	~3300
C=C—H	3100–3020
C—C—H	2960–2850
O R—C—H	~2820 and ~2720
Carbon–Hydrogen Bending Vibrations	**Wavenumber (cm^{-1})**
CH_3- $-CH_2-$ $-CH-$	1450–1420
CH_3-	1385–1365
trans	980–960
cis	730–675
trisubstituted	840–800
terminal alkene	890
terminal alkene	990 and 910

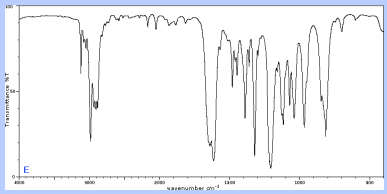












Mass Spec.

• Mass spec does not readily distinguish isomers but is good for distinguishing FGI and limited C—C connectivity and the FW and elemental composition.

• The peak with the highest m/z value represents the molecular ion ($M^{+\cdot}$).

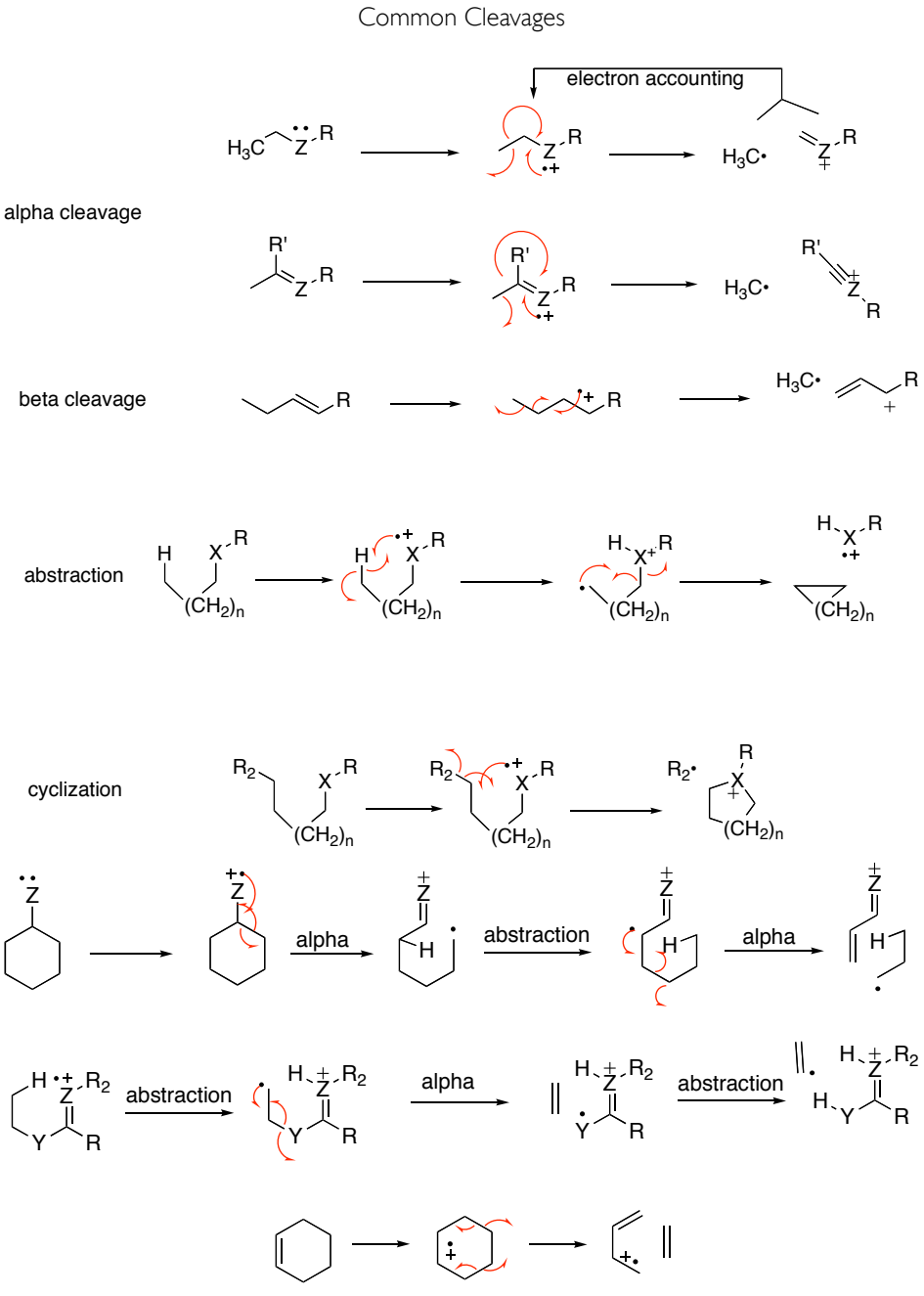
• Peaks with smaller m/z values are called fragment ion peaks and represent positively charged fragments of the molecule.

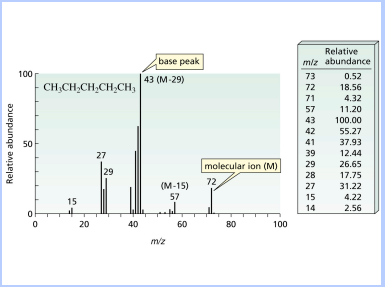
• Nominal molecular mass: the molecular mass to the nearest whole number. In calculating the molecular masses of molecular ions and fragments, the atom mass of a single isotope of an atom must be used.

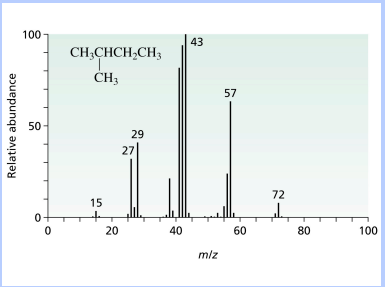
• Each m/z value is the nominal molecular mass of the fragment.

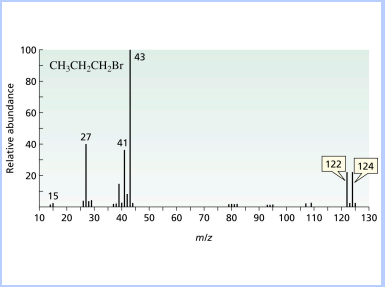
• The base peak is the peak with the greatest intensity due to its having the greatest abundance. Usually signifies the most facile cleavage, breaking weak bonds in preference to strong bonds.

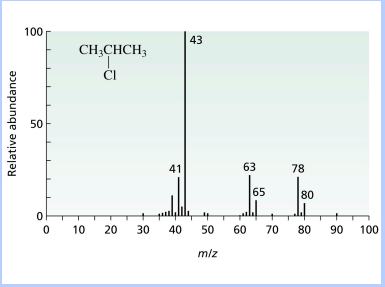
• Peaks that are attributable to isotopes can help identify the compound responsible for a mass spectrum.

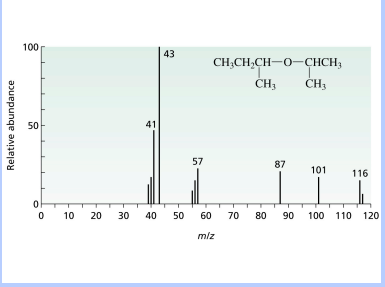


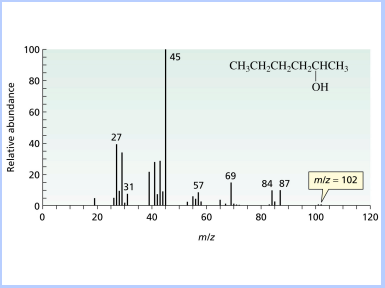




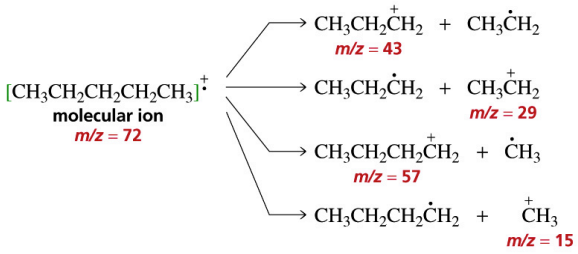






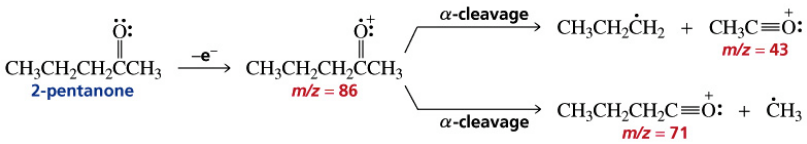


• Simple alkanes tend to undergo fragmentation by the initial loss of a methyl group to form a (M-15+) species. The carbocation then undergoes stepwise cleavage down the alkyl chain, expelling neutral two-carbon units (ethylene). Branched hydrocarbons form more stable secondary and tertiary carbocations, and these peaks will tend to dominate the mass spectrum.

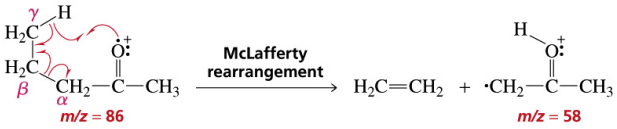


• The fragmentation of the aromatic nucleus is somewhat complex, generating a series of peaks having m/e = 77, 65, 63, etc. While these peaks are difficult to describe in simple terms, they do form a pattern (the "aromatic cluster") that becomes recognizable with experience. If the molecule contains a benzyl unit, the major cleavage will be to generate the benzyl carbocation, which rearranges to form the tropylium ion. Expulsion of acetylene (ethyne) from this generates a characteristic m/e = 65 peak.

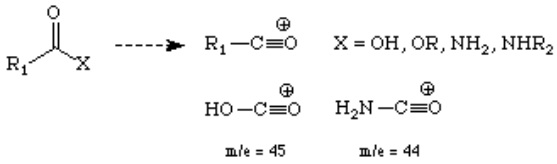
• The predominate cleavage in aldehydes and ketones is loss of one of the side-chains to generate the substituted oxonium ion. This is an extremely favorable cleavage and this ion often represents the base peak in the spectrum. The methyl derivative (CH3CO+) is commonly referred to as the "acylium ion".



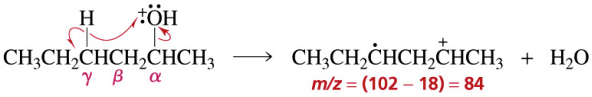
• Another common fragmentation observed in carbonyl compounds (and in nitriles, etc.) involves the expulsion of neutral ethene via a process known as the McLafferty rearrangement.

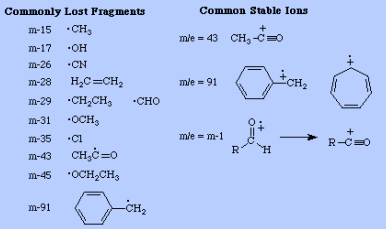


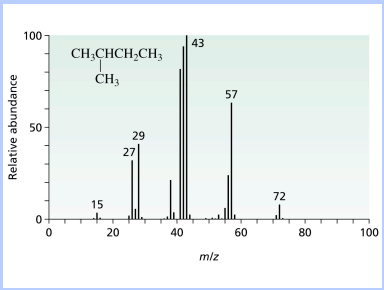
• The major cleavage observed for these esters, acids and amides involves loss of the "X" group, as shown below, to form the substituted oxonium ion. For carboxylic acids and unsubstituted amides, characteristic peaks at m/e = 45 are also often observed.

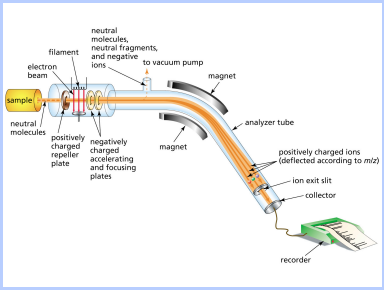


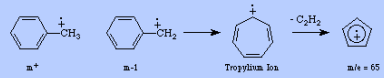
• In addition to losing a proton and hydroxy radical, alcohols tend to lose one of the -alkyl groups (or hydrogens) to form the oxonium ions shown below. For primary alcohols, this generates a peak at m/e = 31; secondary alcohols generate peaks with m/e = 45, 59, 73, etc., according to substitution.

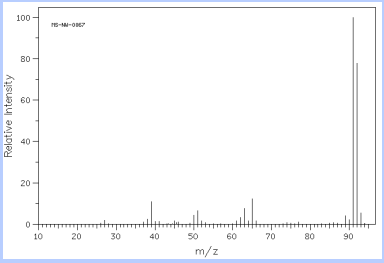




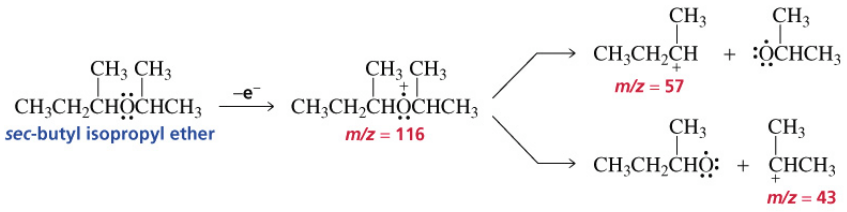




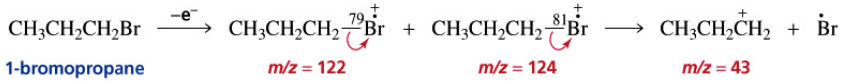




• Following the trend of alcohols, ethers will fragment, often by loss of an alkyl radical, to form a substituted oxonium ion, as shown below.



• Organic halides fragment with simple expulsion of the halogen, as shown below. The molecular ions of chlorine and bromine-containing compounds will show multiple peaks due to the fact that each of these exists as two isotopes in relatively high abundance. Thus for chlorine, the 35Cl/37Cl ratio is roughly 3:1 and for bromine, the 79Br/81Br ratio is 1:1. The molecular ion of a chlorine-containing compound will have two peaks, separated by two mass units, in the ratio 3:1, and a bromine-containing compound will have two peaks, again separated by two mass units, having approximately equal intensities.



NMR

• NMR is good for distinguishing C–C connectivity and total assignment.

• Then chemical shift tells about the immediate environment of the proton (electronegativity and anisotropy).

• The intensity of the signal is proportional to the number of protons; The area of a given peak (the integration) is directly proportional to the number of the responsible proton in the molecule. Integrations are given as simplest whole-number ratios.

• The coupling tells about the number of adjacent protons and their angle relative to the observed proton, but subject to magnetic equivalency.

• The greater the electron density, the greater this 'shielding' will be, hence nuclei which are in electron rich environments will undergo transition at a higher applied field (upfield) than nuclei in electron poor environments (downfield).

• The chemical shift of the hydroxyl hydrogen of an alcohol moves further downfield with increasing concentration, hydrogen bonding and acidity.

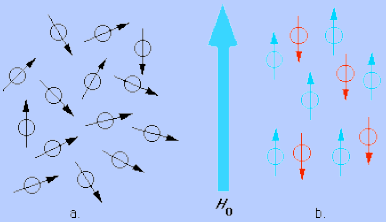
• Because of their favored hydrogen-bonded dimeric association, the hydroxyl proton of carboxylic acids displays a resonance signal significantly down-field of other functions.

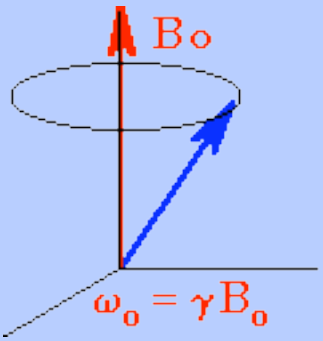
• The rapid OH exchange with the deuterium of heavy water can be used to assign hydroxyl proton resonance signals.

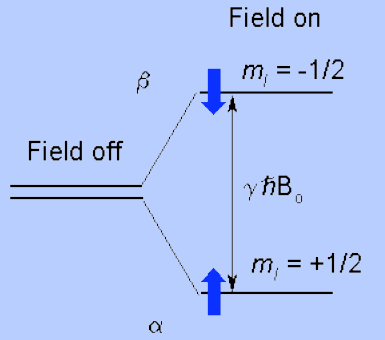
• Coupling constants are independent of the external magnetic field, and reflect the unique spin interaction characteristics of coupled sets of nuclei in a specific structure.

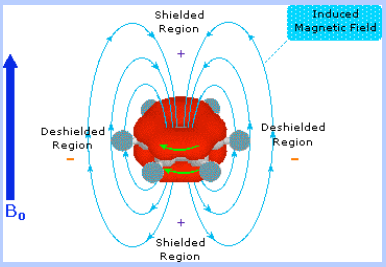
Experimentally, for the ^{1}H and ^{13}C NMR scale is anchored at zero by the NMR absorptions of the molecule tetramethylsilane ($(CH_3)_4Si$) for which the carbons and protons are more highly shielded than most common organic molecules.

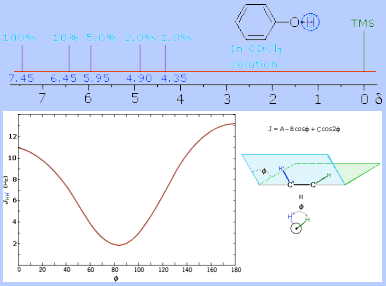
Pi-electrons are more polarizable than are sigma-bond electrons and a magnetic field induced pi-electron movements that perturb nearby nuclei. The pi-electrons associated with a benzene ring provide a striking example of this phenomenon. The electron cloud above and below the plane of the ring circulates in reaction to the external field so as to generate an opposing field at the center of the ring and a supporting field at the edge of the ring. This kind of spatial variation is called anisotropy, and it is common to non-spherical distributions of electrons, as well. Regions in which the induced field supports or adds to the external field are said to be deshielded, because a slightly weaker external field will bring about resonance for nuclei in such areas. However, regions in which the induced field opposes the external field are termed shielded because an increase in the applied field is needed for resonance. Shielded regions are designated by a plus sign, and de-shielded regions by a negative sign.





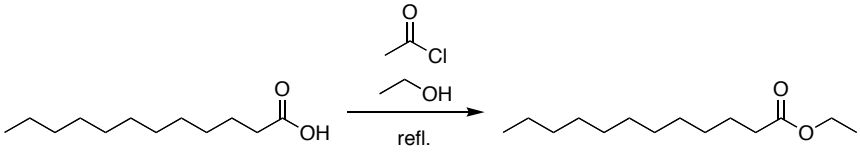






Experiment 1: Fisher esterification

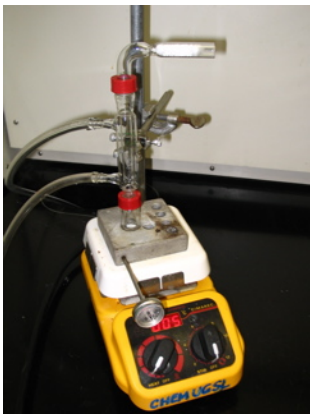
Theory & Background: Esters are widely found in nature and industry. In this experiment, lauric acid (dodecanoic acid) is converted to ethyl laurate. Lauric acid is representative of a class of molecules called fatty acids. These are long, straight-chain carboxylic acids (C_{12}-C_{40}) found as ester derivatives in oils, fats, and waxes. For example, a component of carnauba wax is $CH_3(CH_2)_{33}CO_2(CH_2)_{26}CH_3$. Carnauba wax is found in finer automobile waxes and is exuded by the leaves of the Brazilian wax palm tree. Animal fats are fatty acid esters of 1,2,3-propane-triol, also known as glycerol, and are often referred to as triglycerides. In this experiment, acetyl chloride and ethanol are combined to generate HCl. Acid facilitates the loss of water, which can give the long-chain acylium cation that is attacked by ethanol. In this lab, you will make HCl and cause the esterification of an acid. You will check the purity of your product using IR spectroscopy and a refractive index measurement.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	lauric acid	ethanol (absolute) no not the vodka	acetyl chloride corrosive	**Product** ethyl laurate
formula	$C_{12}H_{24}O_2$	C_2H_6O	C_2H_3ClO	$C_{14}H_{29}O_2$
equiv	1.0	solvent	1.0	
molecular weight				
density	-			
volume				
mass				
mmol.				
melting point				
boiling point				
(N)				

Glassware Set-up:

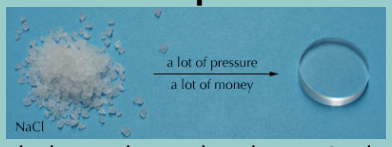


Procedure: Add lauric acid (100 mg, 1.0 equiv) to a clean and dry 5.0 mL vial equipped with a spin vane. Then sequentially add 200 proof Ethanol (2.0 mL) and acetyl chloride (1.0 equiv) with a syringe. Attach a water condenser with a $CaCl_2$ drying tube. Place the reaction on a stir plate and reflux (boil) the clear solution on an aluminum block for 30 minutes.

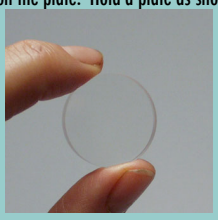
Work-Up: Reduce the heat to a gentle boil and carefully remove the water condenser. Allow the volume to reduce to ~0.5 mL, then cool the vial to room temperature by setting the vial on the benchtop, away from any heat sources. Add diethyl ether (2.0 mL) to the vial and begin stirring the solution. **Slowly** add 1M $NaHCO_3$ (1.0 mL) dropwise (this may vigorously bubble!). Stir the solution

Techniques

The IR and it salt plates



What happens when you place salt in water? It dissolves. What happens when you place your sweaty fingers on a salt plate? It dissolves the salt, leaving a fingerprint on the plate. Hold a plate as shown.



The thin film technique: Obtain a salt plate. Salt plates are stored in desiccators. Ideally, the plate was put away clean, although not all students are considerate enough to clean plates after use. If necessary, clean the plates with a small amount of methylene chloride. Ideally, the plates should be transparent, but quite foggy plates usually give acceptable spectra. Take a background spectra of the clean dry salt plate (4 scans). If your sample is a liquid, use a pipet to place a drop of your DRY unknown liquid on the center of salt plate. If your sample is a solid, use a spatula to place a few DRY crystals on the center of the plate. Add one drop of methylene chloride. Allow to dry, and then take your spectra, which will subtract the background. Print your spectra. Remove the plate from the IR, clean it with methylene chloride and place it in the desiccator or pass it on the the next waiting student. You can interpret directly onto the spectra, if you so choose and affix it to your notebook.

Refractive Index (N).

$N = \frac{c}{V}$ Defined as the relative speed at which light moves through a material with respect to its speed in a vacuum. The index of refraction, N, of transparent materials is defined through the equation shown above. c = $3X10^8$, which is the speed of light in a vacuum and V is the speed of light in some other medium. Since the speed of light is reduced when it propagates through transparent gasses, liquids and solids, the refractive index of these substances is always greater than 1.0. If the refractive index is 0.0010 below or above the literature value, it indicates that impurities are present.

Quiz ideas

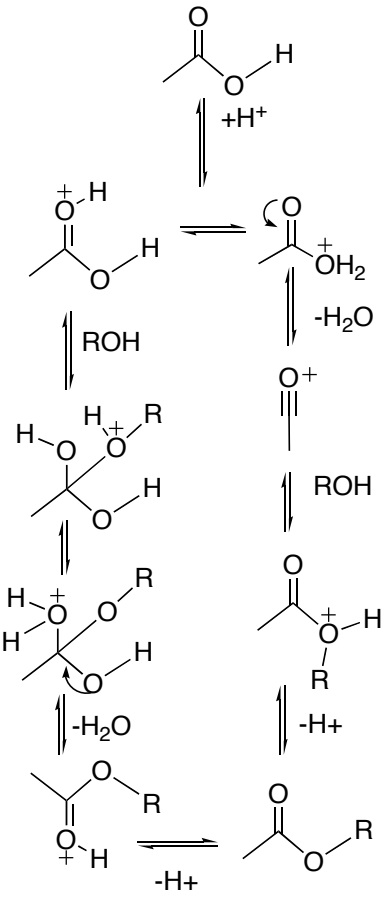
Give several questions on NMR, IR and MS.

until all bubbling has stopped, then stop stirring and allow the two phases to separate. Remove the bottom layer (1M $NaHCO_3$) with a pipet and place the aqueous extract in a clean and dry test tube. Again, add 1M $NaHCO_3$ (1.0 mL)to the vial containing the ether layer and stir briefly (~10 seconds). Discontinue stirring, allow the phases to separate, remove the bottom aqueous layer with a pipet, and place this aqueous extract in the test tube containing the first aqueous extract (you have now "washed" the organic layer 2x with 1M $NaHCO_3$ and "combined " the aqueous extracts!) Add ether (1.0 mL) to the test tube containing the aqueous extracts and agitate with a spatula briefly. Allow the phases to separate and this time, carefully remove the top organic layer with a pipet and combine this wash with the organic solution in the 5.0 mL vial (this step ensures complete recovery of all product). Add Brine (1.0 mL) to the vial containing the organic extracts and stir for 1 minute. Allow the phases to separate, remove the bottom aqueous layer with a pipet and combine this with the aqueous extracts in the test tube. Add enough sodium sulfate (~250 mg) to the 5.0 mL vial containing the organic extracts so that the sodium sulfate flows freely throughout the solution when agitated and does not clump up. Allow the solution to stand for 5 minutes.

Purification: A pipet plugged with a small wad of cotton is filled to 25% volume with a slurry of silica gel/CH_2Cl_2 and topped off with a 25% volume of Na_2SO_4 (now half full) and placed over a tared 25 mL Erlenmeyer flask (the TA should demonstrate how to set this up). The dried ethereal solution was passed through the column into the tared Erlenmeyer flask. The column contents were rinsed four times with 1.0 mL of CH_2Cl_2. After evaporation (< 0.1 mL remain) the residue was weighed and the % yield calculated.

Spectroscopy: An IR spectrum was obtained of the concentrated residue using the thin film technique. (Compare your experimental data (IR and refractive index) to actual data given for ethyl laurate. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook directly after the lab. Submit your entire sample in a tared vial to your TA and be sure that <u>your</u> IR is include in your notebook.)

Mechanisms:



Lecture ideas:
Push spectra concepts, lab techniques and calculations. Mechanisms and reactions are the focus of chem 109abc. Chem 6abc is for teaching spectroscopy and laboratory techniques. However, you can cover the mechanism and the role of the RC(O)Cl. Tell your students to place sand in a hole of the heating block and measure temperature of the block with the thermometer provided in their lab drawer. (TURKEY THERMOMETERS ARE FOR TURKEYS).

TAs:
Be sure that students have completed their entire table when scoring the pre-lab. Give the MC quiz on spectroscopy while contents are refluxing.

Score the products based on the IR. Watch-out for duplicate IR's (automatic zero for offending students). Be sure that students explain the MS and carbon and proton spectra when scoring their notebooks.

Reactions should always be monitored by TLC analysis at three different times, if possible.

Drops (size, amount and volume)
Through this manual volumes are often given in number of drops from a glass pipet. This is to speed the addition process and compensate for a lack o syringes. However, students should be aware that the size of a drop depends on the dropper tip and surface tension and density of the liquid. When bottles are changed, these figures may need to be re-calibrated. No pipet sharing or re-use unless so stated!!!!!

Natural Product Isolation
If you really wanted ethyl laurate, then you'd steam distill it from laurel leaves. Who knows how to steam distill?

Real Problems
Residual ethyl acetate can give a false positive for ester in IR spectra, Evaporate for awhile, use heat if necessary. Watch for acids in the IR (unreacted material) Mechanism: You should point out that acetyl chloride undergoes reaction with ethanol to form HCl and ethyl acetate. The anhydrous HCl acts as a catalyst for the esterification. It is also conceivable that a minute amount of the acetyl anhydride also forms.

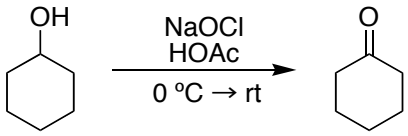
Calculating % yield:
First, you must calculate the **Theoretical Yield.** The theoretical yield is the maximum weight or quantity (in grams) of product that can be expected to be formed from a reaction. This number is also used to calculate the percentage yield (see below). The theoretical yield cannot be calculated until the limiting reagent for a reaction has been determined.

The **limiting reagen**t in a reaction is the reactant added to the reaction vessel in the fewest number of moles, after taking into account the stoichiometry of the reaction equation. To determine the limiting reagent, the first step is to write out the molecular/chemical formula and then calculate the molecular or formula weights for the reactants. The second step is to then calculate the # of moles of each reactant added to the reaction vessel. To calculate the number of millimoles of each reactant, divide the quantity of the reactant (mg) by the molecular or formula weight (mg/mmols). This procedure is made slightly more complicated with a weight percentage. (2% solution = 2 mg of compound A / in 100 mg of solvent B). The weight of the solvent B depends upon its density. The third step is to look at the stoichiometry of the reaction. Notice that in some cases 2 mmoles leads to 1 mmole. To take this fact into account, the moles of reactant are converted into equivalents). As you can see, a reaction table greatly speeds this process.

The percentage yield is one of the most important calculations to learn in organic chemistry. It is a measure of the efficiency of the reaction procedure, and is determined by dividing the isolated yield by the theoretical yield.

Experiment 2: Sodium hypochlorite oxidation of cyclohexanol

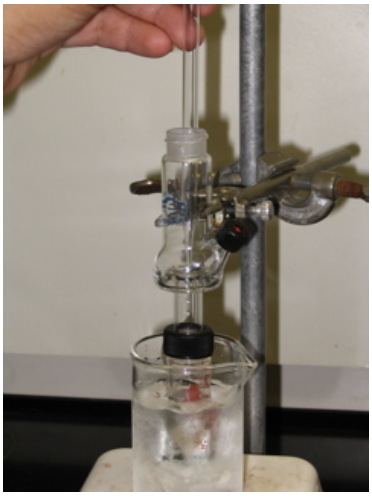
Theory & Background: The oxidation of alcohols to ketones or aldehydes is a common reaction. Have you ever wondered how oxy-clean removes stains? For many years, chromium-based reagents were used. In recent years, however, chromium reagents have been used less and less because of their toxicity. Consequently, a number of alternative oxidants have come into use. Sodium hypochlorite, bleach, is one such example. The weak [⁻O—Cl] bond, resulting in the formation of the non-toxic chloride ion [⁻Cl], is responsible for this reagent's ability to oxidize. This reaction will be monitored by a three lane TLC.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	cyclohexanol	acetic acid corrosive	sodium hypochlorite corrosive oxidant (12% active Cl^+)	**Product** cyclohexanone	**Work-up** aq. sodium bisulfite
formula	$C_6H_{12}O$	$C_2H_4O_2$	ClNaO	$C_6H_{10}O$	
equiv	1.0	4.5	4		
molecular weight					
density					
volume					
mass					
mmol.					
melting point					
boiling point					

Glassware Set-up:



Procedure: Add cyclohexanol (100 mg, 1.0 equiv) and acetic acid (4.5 equiv) to a 5.0 mL vial equipped with a spin vane. Attach a Hickman still and begin stirring as you chill the vial in a beaker containing ice water for 5 minutes. Add sodium hypochlorite solution (4.0 equiv) through the throat of the Hickman still head to the vial using a clean disposable pipet (don't lose compound on the sides of the still-head!). Remove the ice bath and stir for one hour at room temperature.

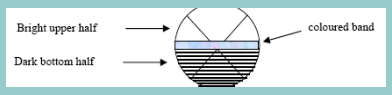
Work-Up: Add saturated sodium bisulfite (1.0 mL) and use KI starch paper to test for the presence of oxidants. If a positive test results (black starch paper), add more sodium bisulfite (1.0 mL). Once you obtain a negative test, add ether (1.0 mL) to the vial and stir briefly. Separate the layers and transfer the organic layer to a clean and dry test tube. Wash the aqueous layer two more times with ether (1.0 mL each time) and combine all the organic washes

Techniques

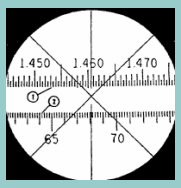
Refractive Index

Measuring the refractive index of a pure unknown liquid can often assist in its identification. The property arises from the fact that light travels at a different velocity in a liquid than it does in air.

1) Ensure that the refractometer is plugged into a main outlet. 2) Open the hinged prism and use a Pasteur pipette to apply a small drop of sample (i.e., cyclohexanol) to the lower (fixed) prism. Do not touch the prism with the pipette. 3) Close the prisms. A thin film of liquid will form between the surfaces of the two prisms. Turn on the instrument. 4) Look through the eyepiece and adjust the illuminator so that you obtain the best possible contrast between the light and dark halves of the visible field. Remember that certain organic liquids evaporate very quickly. 4) Set the borderline between the light and dark halves on the intersection of the two crosshairs. This is achieved by rotating the hand-wheel located on the right hand side of the instrument. 5) If the borderline between the light and dark areas of the visible field appears as a colored band chromatic abberation has occurred, and you must achromatize the borderline. Achromatization is achieved by rotating the compensator dial located just below the eyepiece.



8) Depress the contact switch (the same switch that you used to turn on the instrument) and read the refractive index of the sample from the top scale that will become visible through the eyepiece. 9) Open the hinged prism and gently clean the two surfaces with a soft tissue with acetone, ethanol or petroleum ether.



Quiz ideas

What is the molarity of a 40 wt% solution of NaOH?

Calculations of a table. (in class), including the mass of sodium hypochlorite!

Where does the water go into a reflux condenser (does not matter, highest point, lowest point).

If we formed 2.0 mmol of product Y (mw: 325) from 750 mg of starting material X (mw: 300), what is our percent yield?

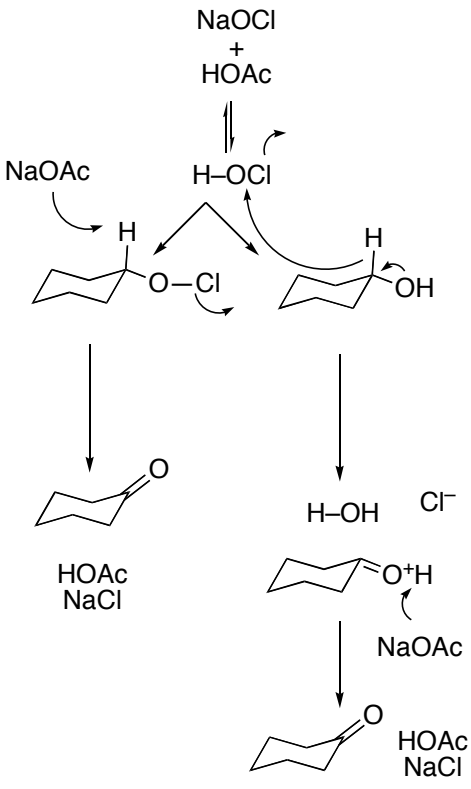
Give three likely MS peaks for ethyl laurate as well as the most significant IR and ^{1}H-NMR signals.

in the same test tube (the total volume in the test tube should now be ~3 mL). Next, wash the combined organic extracts with saturated $NaHCO_3$ (3 X 2.0 mL). ***Note:* One "wash" includes allowing two immiscible liquids to separate and removal of one of the immiscible liquids**. **Thus, extractions are often written as: "washed with XXX (3 X 2.0 mL)," which can be interpreted as washing a specific layer (organic or aqueous) 3 times with XXX using 2.0 mL each time**. Wash the organic layer with Brine (1 X 1.0 mL) and dry the organic extracts over sodium sulfate for 10 minutes.

Purification: A pipet plugged with a small wad of cotton is filled 1/2 full with a slurry of alumina/ether and topped with a small amount of anhydrous sodium sulfate is placed over a tared 25 mL Erlenmeyer flask. Pass the dried etheral solution through the column into the tared Erlenmeyer. The column contents are rinsed with ether (4 x 1.0 mL) into the same tared vial. After evaporation (< 0.1 mL of residue remains) the vial contents are weighed and the percent yield calculated.

Spectroscopy: An IR spectrum is obtained using the thin-film-technique. (Compare your experimental data (IR) to that of actual data given for cyclohexanone. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include all your analyzed spectra in your notebook. Submit your entire sample in a tared disposable vial to your TA along with its IR for grading.

Waste Disposal: Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is placed into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and then thrown into the sharps container. Loose solid wastes (silica, Na_2SO_4) are put into the solids waste container. All aqueous liquids (acetone, ethanol, water) are disposed in the sink after neutralization, or placed into the basic or acidic aqueous waste containers.



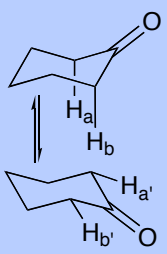
Mechanism: Both mechanisms use legitimate electron counting. However, it is best to think of oxidations as loss of hydride and reductions as addition of hydride.

Lecture ideas:
Keep pounding spectroscopy, but be sure to explain how the still works and how the column works. Discuss IR [ROH goes to RC(O)R]. Explain how magnesium sulfate works.

TAs:
Be sure that students have completed their entire table when scoring the pre-lab. Give quiz during the stirring.

Score the products based on the IR. Watch-out for duplicate IR's (automatic zero for the offending students). Be sure that students explain the MS and carbon and proton spectra when scoring their notebooks. Reactions should always be monitored by TLC analysis at three different times, if possible. Plates can be developed with 4:1 Hexanes:EtOAc and stained with I_2. The cyclohexanol has 1/2 the R_f of the cyclohexanone.

Chair-Chair Inter-conversions



Axial and equatorial protons are indistinguishable in the case of cyclohexanone because of rapid ring inter-conversions. If ring flips were slower than the NMR time scale, then the protons would have different chemical shifts with the axial protons would be further to the left.

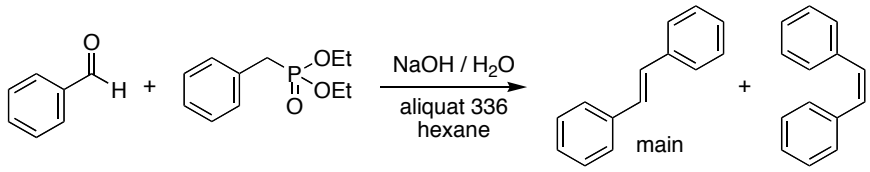
Drying an organic: Organic solvents that have been in previous contact with aqueous solutions are considered "wet" and need to be dried before they are distilled or evaporated. This is achieved by the addition of a brine solution (*sat.* $NaCl_{aq}$). The brine cause the bulk of the water to separate from the organic solvent, while also limiting the amount of organic solvent that can dissolve in the aqueous phase. Next, the final trace water can be bound by the addition of a suitable drying agent. The drying agent then can be removed form the organic by filtration or decantation. The over addition of a drying agent can significantly reduce your yield.

Converting mass (%) to Molarity (M)
The subsequent problem can be misleading. Mass % and mass-volume % are usually not the same. In the case of aqueous solutions mass percentage and mass-volume percentage are the same because the density of water means 1mL of water = 1g of water. However, organic chemist don't always use water as the solvent!
Question: what is M for a 40% NaOH aqueous solution?

40 mass % NaOH means
40g / 100 g of H_2O
because the density of H_2O equals
1000 mg/mL or 1g/mL
that is the same as saying
40000 mg of NaOH / 100 mL of H_2O or
400 mg of NaOH / 1 mL of H_2O
So now it is easy.
400 mg / (40 mg/mmol NaOH) equals
10 mmol/mL or 10 moles/liter or 10M
40% aqueous NaOH is 10M NaOH

Experiment 3: Horner-Wadsworth-Emmons addition of benzaldehyde, yielding stilbene

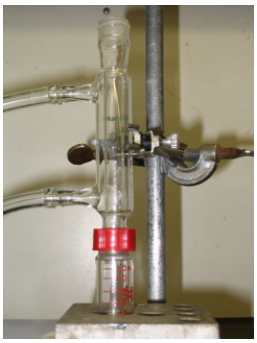
Theory & Background: Olefins are an important class of compounds in organic chemistry. They may be synthesized by several means, of which the Horner-Wadsworth-Emmons reaction is among the most convenient and mild. This is considered to be a modification of the original Wittig reaction, for which George Wittig received the chemistry Nobel prize in 1979. In this reaction, phase transfer catalysis occurs at the interface of the two liquids. The reagents themselves reside in different immiscible solvents. The phosphonate becomes deprotonated and undergoes reaction with benzaldehyde. The reaction should be monitored by a three lane TLC.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	benzaldehyde	diethyl benzylphosphonate	aliquat 336	sodium hydroxide caustic 40 wt% =10M	**Product** stilbene
formula	C_7H_6O	$C_{11}H_{17}O_3P$	$C_{25}H_{54}ClN$	HNaO	$C_{14}H_{12}$
equiv	1.0	1.1	0.2	15	
MW					
density					
volume					
mass					
mmol.					
melting point					
boiling point					
(N)					

Glassware Set-up:



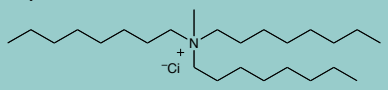
Procedure: Add benzaldehyde (100 mg, 1.0 equiv) to a 5.0 mL vial equipped with a spin vane. Then add Aliquat 336 (0.2 equiv), diethyl benzylphosphonate (1.1 equiv), hexanes (1.5 mL), and aqueous NaOH (15 equiv). Attach a water condenser to the vial, place on a stir plate with an aluminum block and stir as vigorously as possible. Heat to reflux until the reaction is complete by TLC analysis (~1 hour). (Be sure to draw pictures of your developed plates into your notebook)

Techniques

Phase Transfer Catalysis

There is a practical aspect of this reaction, aqueous sodium hydroxide, needed to generate the carbanion intermediate, is not miscible with the hexane solvent used to dissolve the phosphonate and benzaldehyde. In the absence of other additives then, carbanion generation would be expected to be very slow. The phase-transfer catalyst Aliquat 336, however, accelerates the reaction greatly, because it is soluble in both organic (long aliphatic side chains) and aqueous (charge) media. In the presence of sodium hydroxide, the chloride ion of Aliquat 336 can be exchanged for hydroxide. This material then diffuses into the hexane layer where it can deprotonate the phosphonate. Eventually the ammonium ion becomes the counter ion for diethylphosphate. This species then shuttles back into the aqueous phase where phosphate is exchanged for hydroxide to repeat the process.

Aliquat 336



Quiz ideas

Calculations of a table. (in class)
Where does O–H come in the IR?
Where does an unstrained ketone C=O come in the IR?
Where does the water go into a reflux condenser (does not matter, highest point, lowest point).
What is the multiplicity of each NMR signal for CH_3CH_2OH?
How does aliquot 336 assist the reaction?
Draw the ^{1}H-NMR spectra for ethyl acetate.
For experiment 2, what instrumental techniques can be used to follow the progress of the reaction? What would you see?

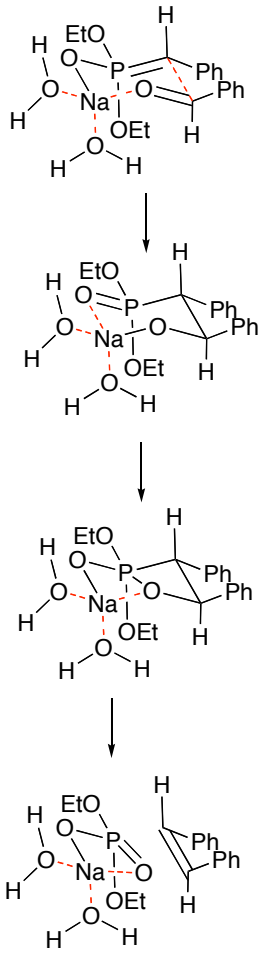
Work-Up: Remove the vial from the heat source and cool to room temperature. Start stirring the reaction mixture and add ether dropwise until all solids dissolve. Allow the layers to separate and transfer the bottom aqueous layer with a pipet to a clean test tube. Wash the organic layer with H_2O (2 X 1.0 mL) then brine (1 X 1.0 mL). Separate the layers and dry the organic layer over Na_2SO_4 (sodium sulfate). Filter the solution through a pipet containing a cotton plug (see picture on right bottom) into a tared 25mL Erlenmeyer flask and concentrated with heat.

Purification: The (E)-stilbene is recrystallized from a minimum amount of hot absolute ethanol. Slow evaporation afforded pure crystals. The solid residue is weighed and the % yield calculated.

Spectroscopy: A melting point and an IR are obtained. (Compare your experimental data (IR and melting point) to that of actual data given for (E)-stilbene. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Submit your entire sample in a tared vial to your TA along with a copy of your IR.)

Waste Disposal: Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is placed into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and then thrown into the sharps container. Loose solid wastes (silica, Na_2SO_4) are put into the solids waste container. All aqueous liquids (acetone, ethanol, water) are disposed in the sink after neutralization, or placed into the basic or acidic aqueous waste containers.

Mechanism:

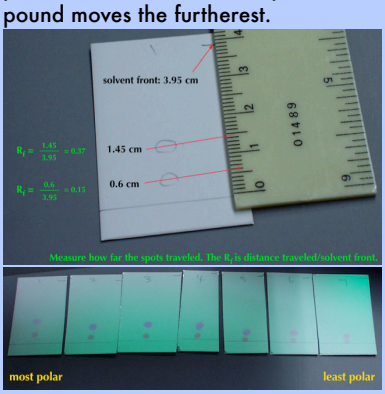


Lecture ideas:
Track the components in the two phases during the course of the reaction. Explain how phase transfer catalyst works. Keep hammering spectroscopy, techniques and calculations. Discuss conversion of wt% into molarity. Explain how to recrystallize and why it is important for purification and the use of a seed crystal.

TAs:
CHECKOUT THEIR NOTEBOOKS. Be sure that students have completed their entire table when scoring the pre-lab. Be sure they have interpretation of IR, MS and NMRs written on the spectra and these are in their notebooks. Give your quiz during the stirring. Reactions should always be monitored by TLC analysis at three different times, if possible.

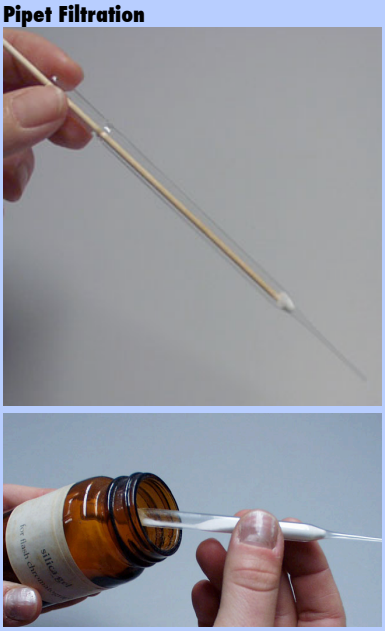
Score the products based on amount and purity (0-50)+(0-50). Check melting points if unsure of product quality when compared with the IR.

Thin Layer Chromatography
is a fast, convenient method that chemist use to analyze a composition of a mixture. Consider a reaction between two UV active substances that leads to two UV active products of different polarity. The products will adhere to polar silica with differing degrees and display different Rf values. However, an Rf is only meaningful if the solvent composition is reported. Polar solvents will carry compounds further than non-polar solvents. The least polar compound moves the furtherest.



If this hypothetical reaction is incomplete, then the starting materials will also be evident on the plate. Therefore, every TLC analysis should have a minimum of three lanes: one starting material, a mixture of the starting material and the reaction mixture ($T_{1/2}$), and the reaction mixture.

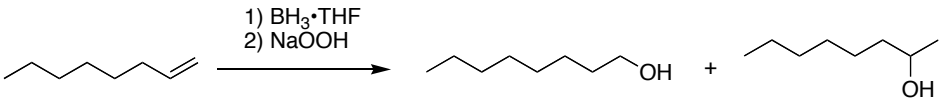
Pipet Filtration



The trick to a good filtration through a drying agent is a good brine work-up and separation. If the organic layer is wet the pipet will plug as the drying agent becomes its corresponding hydrate.

Experiment 4: Hydroboration-oxidation of an alkene

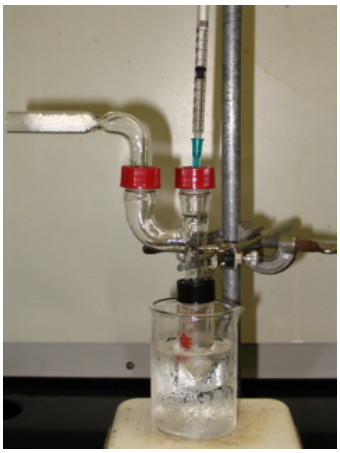
Theory & Background: The hydroboration-oxidation of alkenes to alcohols has long fascinated organic chemists because of its synthetic usefulness and interesting mechanism. H. C. Brown shared the 1979 Nobel prize for developing this and other boron reactions. The reaction of borane with an unsymmetric alkene can give two regioisomeric products: boron at the most substituted carbon (Markovnikov addition) or at the least substituted carbon (anti-Markovnikov addition). The latter is heavily favored, providing for a regioselective reaction. As long as a B-H bond remains, addition reactions to alkenes continue, eventually affording a trialkylborane. Each addition reaction is a four-centered, four-electron process that is extremely rapid. And, each sequential reaction is slightly more regioselective. A GC will be taken of the product mixture at the conclusion of the experiment to determine the ratio of components.



Please regenerate this table in your notebook filling in any of the blanks

Reagent Values	1-octene (98%) ignore the 2%	1M borane in THF a stock solution	HOOH 30% (w/w) active	3M sodium hydroxide 120g/l	octanol
formula	C_8H_{16}	NA	H_2O_2	NaOH	$C_8H_{18}O$
equiv	1.0	0.37 (1.1H- equiv)	2.2	0.67	1.0 expected
MW					
density					
volume					
mass					
mmol.					
boiling point					

Glassware Set-up:



Procedure 1: Add 1-octene (150 mg, 1.0 equiv) to a dry 5.0 mL conical vial equipped with a spin vane. Attach a Claisen adapter and a $CaCl_2$ drying tube. Then chill the vial in an ice water bath (0 °C) while stirring for 5 minutes. Now add 1M BH_3 in THF (0.37 equiv; 1.1 hydride equiv) with a plastic syringe and needle dropwise over 5 minutes. Remove the ice bath and stir for 30 more minutes. *Syringes for BH_3 additions may be shared.

Work-Up: Remove the Claisen adapter and drying tube. Add H_2O (5 drops) to the stirring solution slowly with a pipet to quench any unreacted borane.

Techniques

Syringe use reagent transfer in air sensitive systems

To help you preserve reagent quality, many Aldrich and Fluka air- and moisture-sensitive reagents are packaged under nitrogen or argon in crown-cap bottles, with a 6mm diameter hole in the crown-cap and a PTFE faced rubber liner under the crown-cap, for simple transfer of reagent using syringe or cannula techniques. When the syringe needle or cannula is withdrawn, the PTFE faced rubber liner reseals the bottle to prevent inflow of moist air which would react with the reagent. Syringe techniques have the disadvantage that a partial vacuum is created in the bottle by removal of reagent, this partial vacuum being sufficient to pull outside (moist) air through the pierced crown-cap liner. To overcome this disadvantage, you can provide a blanket of dry nitrogen or inert gas over the crown-cap, so that it is dry nitrogen or inert gas which replaces the reagent in the bottle, and contact of bottle contents with moist air is avoided. The following products will enable you to provide an effective blanket of dry nitrogen or inert gas over our crown-cap bottles.

Quiz ideas

Draw what happen in a biphasic reaction.

Give a list of compounds and ask, which could act as phase transfer catalyst.

Depict anticipated changes in the IR for propene going to 1-propanol.

Predict the MS, IR and ^1H NMR peaks for ethyl acetate and benzaldehyde.

How many available hydride(s) are in BH_3?

What is the molarity of a 20% by weight solution of hydrogen peroxide (mw = 34.14, d = 1.11 g/mL) in water?

What physical property traditionally dictates separation in gas chromatograpy?

What is the limiting reagent in this reaction (Exp 4)?

What instrumental techniques are well suited to distinguishing E from Z stilbene?

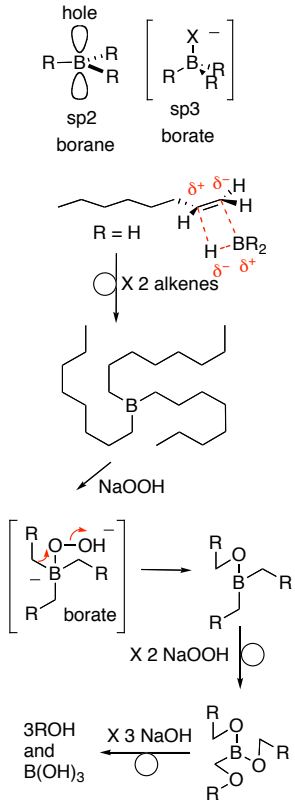
Procedure 2: Add 3M NaOH (0.67 equiv) and HOOH (2.2 equiv) to a separate 3.0 mL conical vial. This mixture is then slowly added in a dropwise fashion (1 drop / sec) with a pipet to the vial containing the trialkylborane while stirring. Stir for 15 minutes at room temperature

Work-Up: H_2O (1.0 mL) and ether (1.0 mL) are slowly added to the vial and stirred for 5 minutes. Stirring is ceased and the aqueous layer (bottom) is transferred to a clean test tube with a pipet. The aqueous layer is acidified with IM HCl (0.5 mL) and the aqueous layer is washed with ether (2 X 1.0 mL). The organic extracts are combined in the 5.0 mL vial containing the ethereal solution. The combined organic extracts are washed with water (3 X 1.0 mL) and brine (1 X 1.0 mL) and then dried over sodium sulfate. After pipet filtration (remember the cotton plug and small amount of Na_2SO_4) into a tared 25 mL Erlenmeyer containing a boiling stone, the solution is concentrated with heat and the percent yield can then be calculated.

Purification: If needed, dissolve the impure material in ether (2.0 mL) and pass through a pipet plugged with cotton and a small pad of silica gel. Rinse the pipet with additional ether (4 X 1.0 mL) and evaporate the solution.

Spectroscopy: The sample is analyzed by GC and the percent yield is calculated on the basis of the preceding crude product weight and the ratio of analytes as determined by GC. An IR (print two, one for your notebook and one for your TA) is obtained with a minimal sample. (Compare your experimental data (IR) to that for octanol. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectra provided by your TA. Include the analyzed spectra in your notebook. Submit your entire sample in a tared vial to your TA and an IR for grading.

Mechanism:



Waste Disposal: IMPORTANT - Syringes and their needles do NOT go in the trash. Return the needle in its capped form to the TA. Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is placed into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are first dumped into solid waste and then the glass is thrown into the sharps container. Loose solid wastes (silica, Na_2SO_4) are put into the solids waste container. All aqueous liquids (acetone, ethanol, water) are disposed in the sink after neutralization, or placed into the basic or acidic aqueous waste containers.

Lecture Suggestions:
Stress anhydrous conditions! Cover needle safety. Explain GC chromatography, and show how the data is to be reported. For example, "the product was analyzed by gas chromatography [4ft x ¼ in column, 20% DC-200 Chromosorb, 80-100 mesh, 100 °C, helium flow equal to 60 mL/mi. The observed retention times for 1-octene, 1-octanol, and 2-octanol were found to be x, y, and z minutes respectively. Give the crude yield of material the percent yield of each are computed to be X, Y, Z. Discuss the 30% HOOH.

TAs: Give your quiz during the stirring. Score the liquid products based amount and the IR. Use (N) if necessary. Reactions should always be monitored by TLC analysis at three different times, if possible.

Gas Chromatography Theory

Gas Chromatography, as the name implies, replaces the moving liquid phase of both column absorption chromatography and thin layer chromatography with a gaseous moving phase. Analytical scale GC involves the syringe injection of a small volume of liquid or gas (0.1 mL) through a rubber gasket (injection septum) into a stream of inert gas such as helium, which flows at a pre-adjusted rate. The injection port is maintained at a temperature high enough to vaporize the liquid which is then swept by the helium into a heated metal column (6' x 1/4") maintained at an appropriate temperature. The column is packed with various solid supports. The components of the sample mixture pass through the column at different velocities depending upon their relative gas-liquid phase partition coefficients. In general, non-polar substrates separate on the basis of boiling points while polar substrates separate more (but not exclusively) on the basis of polarity. After separation the components are analyzed by a detector such as a thermal conductivity cell. If the "run" has been standardized by adding a known amount of analyzed substance, then the area under a peak would proportional to the quantity of the substance present. **However, in experiment 4, the areas only provide the relative ratios of products.** Area = h (peak height at highest point) x w1/2h (peak width at 1/2 maximum height).

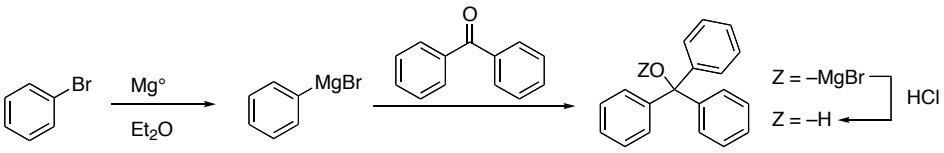
TA Notes

The borane solution is moisture sensitive, the glassware should be oven dried for 30 minutes. Put the intended vial in the oven before beginning your lecture or quiz (you will be using a plastic syringes). Monitor the needles given out and those returned. Students can share their borane syringe. H_2O_2 bleaches skin and clothes, it turns the KI paper black. Use a disposable pipets or tips to measure it.

The b.p. are 122 °C for 1-octene, 174 °C for 3-octanol, 181 °C for 2-octanol and 196 °C for 1-octanol. The order of the peaks on the GC should be the same on the chromatogram.

Experiment 5: Phenyl Grignard addition to benzophenone

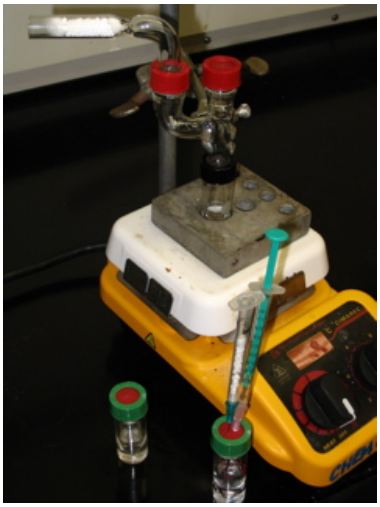
Theory & Background: Grignard reagents (RMgX), named for Victor Grignard, who won the Nobel prize for this discovery in 1921, are very useful reagents because of the nucleophilic character of the carbon bonded to magnesium atom. Grignard's breakthrough came with two discoveries—that an ether solvent was vital and that the reaction must be carried out under stringent anhydrous conditions. With such a nucleophilic carbon species, reactions occur with carbon electrophiles, such as carbonyl compounds, to form C-C bonds. In this experiment, triphenylmethanol is obtained from the reaction of phenylmagnesium bromide and benzophenone. Reaction progress should be monitored with three lane TLC analysis.



Please regenerate this table in your notebook filling in ALL of the blanks

Reagents Values	bromobenzene	magnesium	anhydrous ether	benzophenone	3N HCl	triphenylmethanol
formula						
equiv	1.5	2.0	solvent	1.0	10	
MW						
density						
volume						
mass						
mmol.						
melting point						
boiling point						

Glassware Set-up:



Procedure: Prepare a drying tube syringe from the body of a syringe by removing the plunger, affixing a needle, and packing with a cotton plug and dry $CaCl_2$. Add anhydrous ether (5.0 mL) to a capped and dry 5.0 mL conical vial **[A]** using the 1mL drying tube syringe. *Note*: The same syringe-needle ensemble can be used throughout this experiment. Add a stir bar and magnesium turnings (2.0 equiv) to a 10.0 mL round bottom flask **[B]** and flame dry this flask (have your TA help you). Attach a $CaCl_2$ drying tube ASAP to the flask as it cools. Once the flask has cooled, remove the drying tube and replace with a dry water condenser with a cap and septum. Now add bromobenzene (1.5 equiv) to a dry 3.0 mL tared conical vial **[C]** and Et_2O (2.0 mL) and seal with a cap and septum. Half of the ethereal solution of bromobenzene (1.0 mL) is withdrawn with a plastic syringe (don't forget to use your drying tube syringe before withdrawing the ethereal solution). The needle of this charged syringe is then pushed through the septum **[B]** of the reflux condenser. While stirring the magnesium vigorously, the first 1/4 of

Techniques

Low Temperature Reactions: In Chem 6B students usually perform reactions at 0 °C (ice/water), or heat their reaction (aluminum block). However, because of the reactivity of of organometallic reagents, most organometallic reactions are carried out at low temperature using a dewar (vacuum jacketed bath) and solid CO_2 added to the appropriate solvent.

LOW TEMPERATURE BATHS	
SYSTEM	°C
Ethylene glycol/CO_2	-15
o-Xylene/N_2	-29
Acetonitrile/CO_2	-42
Chloroform/CO_2	-61
Chloroform/N_2	-63
Ethanol/CO_2	-72
Acetone/CO_2	-77
Methanol/N_2	-98

Drying agents: Drying agents such as $CaCl_2$ readily hydrates. To ensure that you are using dry $CaCl_2$, you should obtain it directly from the oven. Other agents such as Na_2SO_4 and $MgSO_4$ are obtained from bottles marked as anhydrous. **DO NOT LEAVE THE TOP OFFF THESE DRYING AGENT CONTAINERS.**

Quiz ideas

Calculate the number of mg of methyl benzoate required to make 100 mg of triphenylmethanol given an excess PhMgBr.

How many signals in the ^{13}C-NMR for triphenyl carbinol?

How many hydrides in borane?

Why is an OH broad in the IR. When is it a sharp signal.

How would you determine the presence of an OH in an ^{1}H-NMR.

GC is most often used with molecules that have what trait?

What happens if you use a syringe with an o-ring with THF?

What happens when RMgBr is mixed with PhOH?

this solution (0.500 mL) is added. Bubbles are evident on the magnesium and the heterogeneous solution becomes brown and cloudy. If the solution does not turn brown or cloudy, add a crystal of iodine and stir until the violet color fades. The remaining ethereal solution (1.5 mL) is then slowly added over 5 minutes. Rinse the remainder of bromobenzene from the capped 3.0 mL vial **[C]** with anhydrous ether (0.5 mL) (taken from the 5.0 mL vial **[A]**; using the make shift drying tube as before) and add the rinse to the reaction flask **[B]**. Heat the reaction to a gentle reflux for 30 minutes.

While the reaction proceeds add benzophenone (105 mg, 1.0 equiv) to the now empty 3.0 mL vial **[C]** along with anhydrous ether (0.50 mL) from the 5.0 mL vial **[A]**. Cool the reaction mixture in flask **[B]** to room temperature. While stirring, the benzophenone solution prepared in vial **[C]** is cautiously added over one-minute to flask **[B]**. After addition is complete, rinse vial **[C]** with the ether (0.5 mL) from vial **[A]**. Add this solution to flask **[B]**. **The above detailed description should assist in preventing the exposure of reagents or solvent to moisture from humid air.** Stir for 15 minutes at room temperature.

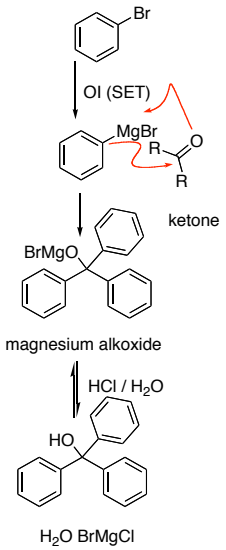
Work-Up: Remove the reflux condenser and while stirring, add 3N HCl (10 equiv) cautiously and stir until the solids dissolve (~10 minutes). Separate the layers, transfer the aqueous layer to a clean test tube, and wash the aqueous layer with ether (2 X 1.0mL), combine the organic extracts. Wash the organic extracts with saturated sodium bisulfite (2 X 1.0 mL) and brine (1 X 1.0 mL). Dry the ethereal solution over anhydrous sodium sulfate and then filter through a cotton plugged pipet into a 25 mL Erlenmeyer. A boiling stick is added and the solvent evaporated with heat.

Purification: High boiling, 60–80°C, pet ether (10 mL) is added until the solid has dissolved, and the solution is transfered to a beaker. The solution slowly evaporates in a bench drawer, uncovered, (2-4 days) to give uniform crystals.

Spectroscopy: The crystals are collected and weighed and the percent yield is calculated. A melting point and a IR are obtained. (Compare your experimental data (IR and melting point) to the actual data given for triphenylmethanol. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectra from your TA. Include the analyzed spectra in your notebook. Submit your entire sample in a tared vial to your TA for scoring.)

Waste Disposal: IMPORTANT - Syringes and their needles do NOT go in the trash. Return the needle in its capped form to the TA. Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is placed into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are first dumped into solid waste and then the glass is thrown into the sharps container. Loose solid wastes (silica, Na_2SO_4) are put into the solids waste container. All aqueous liquids (acetone, ethanol, water) are disposed in the sink after neutralization, or placed into the basic or acidic aqueous waste containers.

Mechanism:



Lecture Suggestions: Explain the set-up, the purpose of the three vials, their septa, and the homemade drying tube. Cover the purpose of scratching the magnesium and the use of iodine as reaction initiators. Explain that biphenyl is formed in small quantities by SET homo-coupling and how it is removed in two stages. Explain the incompatibility of Grignard reagents with a substrates containing acidic hydrogens. Show the reactions that occur when a Grignard reagent is added to an organic acid, or an alcohol.

TAs: Issue three syringes and needles (deduct tech points and return points when syringes are returned) Give your quiz during the stirring. Score products as usual (0-100). There should be a maximum of two duplicate scores. Reactions should always be monitored by TLC analysis at three different times, if possible.

Grignard Reaction Initiators

Why is the Grignard reaction tricky to initiate? The initial step requires electron transfer from the Mg surface to the alkyl halide leading to the formation of R•. This step is limited by diffusion control and the available surface area of active magnesium. However, magnesium turnings are generally covered with surface oxides, which preclude its ability to react with unreactive halides in the absence of initiators or mechanic pretreatment. In addition, adsorbed insulating layers and crystal lattice orientation can affect the heterogeneous reaction rates.

In general magnesium turnings are sufficiently prepared for reactive halides after removal of surface oxides and contaminations by hand with pestle and mortar by bending magnesium strips which cause the crystal lattice dislocations. Among the many usual methods of chemical activation, the addition of anhydrous cerium trichloride, iron trichloride, methyl iodide, iodine, and 1,2-dibromoethane are most common.

Here is a good trick. Scratch some magnesium turnings with a needle and immediately submerge the metal in anhydrous ether (Et_2O) and add one crystal of iodine.

TA Notes

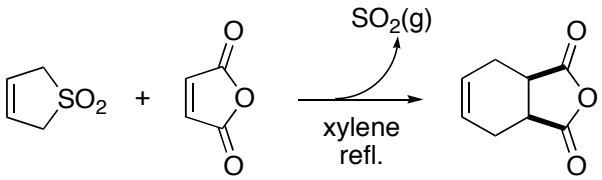
Put the vials and stir bars in the oven before your lecture and quiz. [NO PLASTIC ITEMS]. Scratching the metal with the syringe needle exposes fresh surface. The I+ in iodine is readily oxidized to I- exposing fresh surface. Don't use too much iodine and consume all of the magnesium (1 crystal) Starting over may be necessary.

The temperature of the drying oven may drop because it is opened so much. Keep it closed as much as possible. Students must not put a wet apparatus (needles or glassware) in the drying oven unless it is rinsed with acetone and air dried

Use the mL markings on the vials. Bromobenzene (bring your own) can be measured in the mL vial or added with a dry pipet. 7 drops is about 113 mg.

Experiment 6: [4+2] Cycloaddition of a masked butadiene

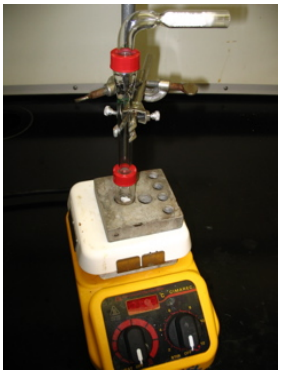
Theory & Background: Otto Paul Hermann Diels and Kurt Alder won the Nobel prize in 1950 for their discovery and development of cyclohexene synthesis using a [4+2] cycloaddition manifold. The resulting six-membered ring can be found in many natural products. The reaction proceeds with control of regiochemistry and stereochemistry and the required conditions are compatible with a large number of functional groups. Thus, the Diels-Alder reaction is frequently exploited. In this experiment, the dienophile, maleic anhydride, is coupled with 1,3-butadiene generated *in situ* by heat. A small amount of the resulting cyclohexene product is brominated. The reaction should be monitored by three using TLC analysis.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	3-sulfolene	maleic anhydride	xylenes	cis-1,2,3,6-Tetrahydrophthalic anhydride
formula			C_8H_{10}	
equiv	1.5	1.0	solvent	
MW				
density				
volume				
mass				
mmol.				
melting point				
boiling point				

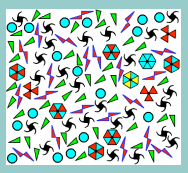
Glassware Set-up:



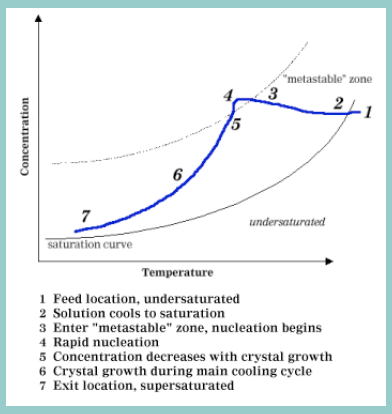
Procedure: Add maleic anhydride (90 mg, 1.0 equiv) to a clean 3.0 mL vial equipped with a spin vane. Then add 3-sulfolene (1.5 equiv) and xylenes (0.08 mL). Attach a reflux condenser and drying tube then heat to reflux for 15 minutes in a fume hood. Caution is taken because the sulfur dioxide formed during the reaction is very irritating to the eyes and mucous membranes.

Work-up: The reaction vessel is permitted to cool to the touch. Remove the condenser and drying tube then add hexanes (1.0 mL) or ligroin (high boiling petroleum ether). Amorphous crystals should form in an oil. Add just enough diethyl ether to solubilize the uncrystallized oil. Attach a reflux condenser and drying tube and reflux for one minute. Discontinue heating, remove the reflux condenser, drying tube, and allow the mixture to cool. The sides of the vial were scratched below liquid level with a glass stirring rod and crystals began to form. The crystals are quite large and may cling to the vial.

Techniques



Crystallization and recrystallization is a slow method of purification, but it can lead to extremely high purity. However, hydrates $X \bullet (H_2O)_n$ can pose a problem. In a nutshell, it is easier to pack similar things in tighter spaces than it is to pack dissimilar things. Crystallization begins in a supersaturated solution, which can be reached by lowering the temperature or evaporating a saturated solution.



Heating Reactions

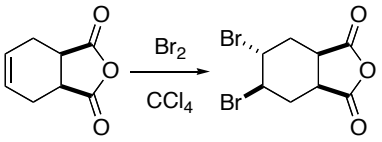
All heating devises work by the same principles. Among the concepts with which organic chemist must be familiar are thermal load and temperature endpoint over-run. While flask size and contents may vary, the heating sources usually does not. Thus, when heating a small item there exists a greater chances that that you will over-run the desired temperature and it will take a long time for the sample to return to the desired temperature. The trick is to heat SLOWLY!

Quiz ideas

Calculate the liters of gaseous SO_2 produced if 1000mg of 3-sulfolene is heated to 160° C [At STP 22.4 mL / mmol.]

What is the multiplicity, chemical shift and of vinyl protons Ha and Hb? in the product. Are they the same? Now consider Maleic anhydride. What is the coupling constant(s)?

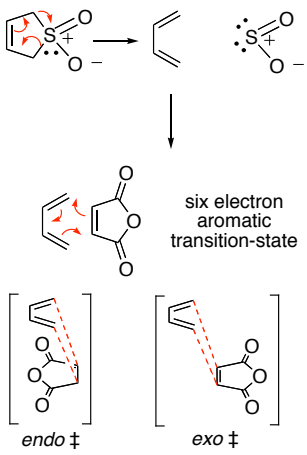
Purification: The mother liquor is carefully removed with a Pasteur pipet. The solids are given 1-2 minutes to dry and then scraped onto a sheet of filter paper. The capillary action of the paper draws out residual liquid, helping to further dry the crystals. The mass of the product is determined and the percent yield calculated. The presence of an alkene is then verified. To a solution of approximately 10 mg of product in a 3mL vial with carbon tetrachloride (0.5 mL), a 2% v/v bromine solution in carbon tetrachloride is added in a dropwise fashion from a plastic syringe without an o-ring. The amount of solution added for color to persist is recorded and used to determine the moles of alkene present in the 10 mg starting sample.



Spectroscopy: The melting point and IR spectra were taken for the initial cyclohexene product and compared with the melting point and IR spectra of the known Diels-Alder adduct. (Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectra from your TA. Include the labeled spectra in your notebook. Submit your entire sample in a tared vial to your TA for scoring.)

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 was put in a halogenated organic waste container. Non-halogenated organic waste was put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets were dumped into solid waste and then put into a sharps container. Free solid waste (silica, Na_2SO_4) was put into the solids waste container. All aqueous liquids (acetone, ethanol, water) was disposed of in the sink after neutralization or in the basic or acidic waste containers.

Mechanism:



Lecture Suggestions:
Explain the importance of s-cis vs. s-trans for the reaction. (What does the s- stand for?) Consider [4+2] transition states, normal vs. inverse demand from the perspective of the components. Cover regiochemistry, if you feel that you can explain it adequately; Most of these topics are ignored in 109abc.

TAs: Revisit NMR and discuss the electronegativity and carbonyl anisotropy. Show that ^{1}H signal for protons alpha to carbonyls and double bonds are in the 2-3.5 ppm range, while vinyls are in the 4.5-6.5 ppm range. (Bis-allylic 3.5-5.5 ppm) Revisit IR and carbonyl frequencies for anhydrides. Begin with anhydrides and work through the carbonyls to cyclohexanones. Then start with cyclohexanone and work to ketenes. Explain how the bromine solution can be used to quantitate the purity of the 10 mg (0.0658 mmols) of crystals. Calculate the molarity of a 2% v/v solution of Br_2 in CCl_4. Reactions should always be monitored by TLC analysis at three different times, if possible.

Typical Units

Mass % (g/g)
$$\left(\frac{grams\ solute \times 100}{grams\ solution}\right)$$

Mass-Volume % (g/mL)
$$\left(\frac{grams\ solute \times 100}{millilitres\ solution}\right)$$

Volume-Volume % (mL/mL)
$$\left(\frac{millilitres\ solute \times 100}{millilitres\ solution}\right)$$

Molarity (M, mol/L)
$$\left(\frac{moles\ solute}{litres\ solution}\right)$$

Molinity (mol/kg*)
$$\left(\frac{moles\ solute}{kilograms\ solution}\right)$$

Molality (m, mol/kg)
$$\left(\frac{moles\ solute}{kilograms\ solvent}\right)$$

Molar Fraction (chi, mol/mol)
$$\left(\frac{moles\ solute}{moles\ solution}\right)$$

Formal (F, mol/L)
$$\left(\frac{moles\ undissolved\ solute}{litres\ solution}\right)$$

Weight % is misleading. It is important to know both the denominator and the numerator.

TA Notes

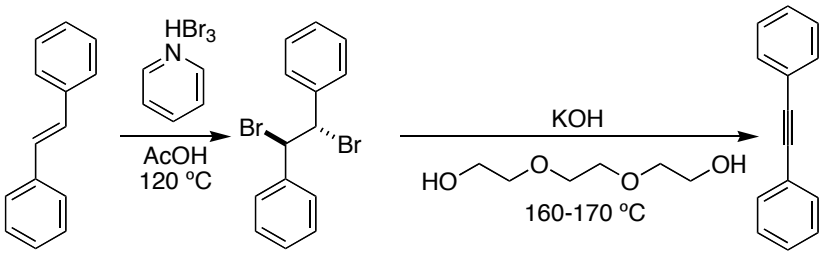
The 0.08 mL of xylenes can be measured as 4-drops from a pipet.

The 0.5 mL of toluene can be measured in the vial or as 25 drops from a pipet, while 0.3mL can be measured by the vial or 18 drops from the pipet.

Be sure to test the product for unsaturation and to take an IR and a m.p. Give your students copies of the NMRs and MS and ask them to analyze.

Experiment 7 Multi-Step (1) Synthesis of diphenylacetylene from stilbene

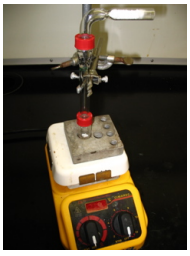
Theory & Background: Multi-step organic synthesis is extremely challenging. It is the process by which most pharmaceuticals are made. E. J. Corey won the 1990 Nobel prize for his development of the theory and methodology related to multi-step organic synthesis. By combining products from the next three experiments, you will build hexaphenylbenzene. Today is the first part of this process. You will begin by bis-brominating stilbene and then causing a bis-elimination to make diphenylacetylene. Reactions should always be monitored using a three lane TLC for analysis at three different times, if possible.



Please regenerate this table in your notebook filling in any of the blanks

Reagent Values	stilbene	pyridinium perbromide	dibromide	85% solid potassium hydroxide	acetylene
formula	$C_{14}H_{12}$	$C_5H_6Br_3N$	$C_{14}H_{12}Br_2$	KOH	$C_{14}H_{10}$
equiv	1.0	1.1			
			1.0	10.0	
MW					
mass					
mmol.					
melting point					
boiling point					

Glassware Set-up:



Procedure I: Add (E)-stilbene (200 mg, 1.0 equiv) and acetic acid (3.0 mL) to a clean 5.0 mL vial equipped with a spin vane. Attach a reflux condenser and drying tube and heat to reflux until a homogenous solution forms. Remove the drying tube and, while stirring, add pyridinium perbromide (400 mg) through the throat of the condenser in one portion. Wash residual solids into the vial with the minimal amount of acetic acid. Heat the mixture to reflux (120-130°C) for 5 minutes.

Work-Up I: Allow the reaction vessel to cool to the touch and then remove the condenser. Crystals should form. These are dislodged from the vial with a spatula and then collected by vacuum filtration using a Büchner funnel. Wash the crystal cake with cold *d.i.* water (2 X 2.0 mL) and with cold acetone (1 X 2.0 mL). The crystals are set aside to dry.

Techniques

Heating a reaction, cont.
Heating has solved many a problem for organic chemists. But, heating is not always the best remedy for a sluggish reaction, because products or reagents can decompose or unwanted side reactions can begin to predominate.

It is important to remember to never heat a closed system unless it is suitably protected. A sealed apparatus for this purpose are aptly named "**bomb reactors**" because of the possibility for a catastrophic explosion.

In general the rate of reaction doubles for every 10 °C rise in temperature.

Quiz ideas

What is a chemical test for the presence of an alkene?

Give a GC quiz for computing % yield.

Calculate the molarity of the starting material in acetic acid.

Why was sulfolene used in the preceding experiment rather than butadiene?

Describe the differences in the MS, IR and C and H NMR the differences between cyclohexenone and cyclohexanol.

What is the function of the KOH in experiment 7?

Purification I: none.

Procedure II: All of the remaining dibromide is transferred to a clean, tared pyrex (13X100mm) test tube. Add enough triethylene glycol to make a 0.6M solution. Add 85% potassium hydroxide (10.0 equiv) and heat the mixture for 6-10 minutes using an aluminum block pre-heated to 160-170 °C.

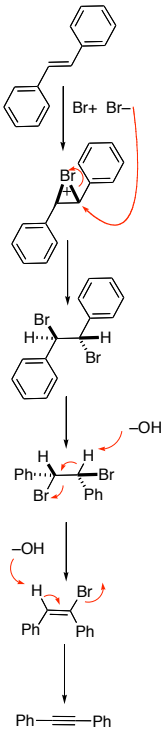
Work-Up II: The test tube is permitted to cool to the touch and 2 mL of *d.i.* water is added for each 1.0 mL of triethylene glycol. The product precipitates and is collected by vacuum filtration. The crystals are washed with cold 70% ethanol (1 mL X 2) and dried briefly.

Purification II: The product is recrystallized from warmed 95% ethanol (aim to make a 0.5M solution and then supersaturate the solution). If no crystals form, you can add water to the ethanol solution to precipitate, but this fine material is hard to collect by filtration. Large crystals can be collected by vacuum filtration.

Spectroscopy 1&2 The percent yield is calculated. A melting point and an IR are obtained. (Compare your experimental data (IR and melting point) to that of actual data given for diphenylacetylene. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Do not submit your product to the TA, you will use 150 mg of it in a future experiment. **If you failed to recover 150 mg, submit a request in writing to your TA for an exact amount of additional starting material so that you will have 150 mg at the beginning of the next experiment.**

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism:



Lecture Suggestions: Explain why this per-bromide is being used rather than the old stand-by (Br_2). Cover the mechanism of bromination. Discuss the importance of adjusting the table of reagents for procedure II based on the yields from procedure I. Cover what 85% KOH really means. Discuss making the 0.58 M glycol solution.

TAs: Please read the note at the right. This product scoring method applies to all of the multi-step experiments (experiments 7-10, 14-15). Please note that students can get a (0) for a product grade in these experiments. Reactions should always be monitored by TLC analysis at three different times, if possible.

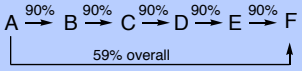
Retrosynthetic Analysis

benzaldehyde ⟸ hexaphenylbenzene

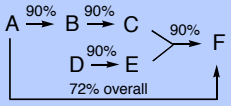
The arrow means built from. It points in the reverse direction from the conventional synthesis arrow.

Convergent verses linear synthesis

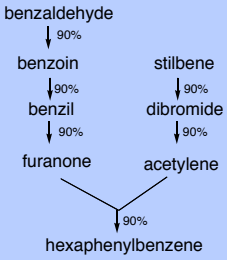
Consider a synthesis that involves 5 steps; each step occurs in 90% yield. The yields at each stage would be as follows (i.e. 90%x90% at stage 2, etc.). Thus the overall yield of product after 5 steps is 59%.



However we could also have run this sequence in a convergent manner and constructed F in a more efficient manner.



Compute the overall yield of hexaphenbenzene. What would the overall yield be if stillbene was converted to the dibromide in 25% yield?



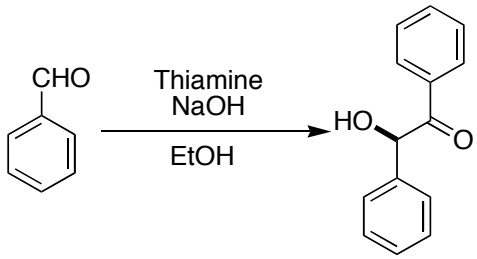
TA Notes

Computing a grade for the product for experiments 7-9. It works sort of like bowling. The product grade depends on how much starting the student request for the experiment where it is used. Use this formula to compute their score [100% - ((request/150)*100) = score]. Therefore, If a student request 150mg they get a product score of 0%. If they request nothing they get a product score of 100%.

At the end of this lab pass out a sheet of your student's names so they can indicate what they need for experiment 10. During free time in the next lab you weigh-out their requests for diphenyl acetylene and give it to them, scoring them appropriately

Experiment 8: Multi-Step (2) Umpolung synthesis of benzoin from benzaldehyde

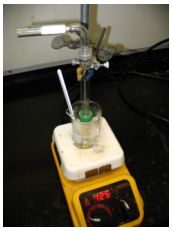
Theory & Background: Umpolung, or polarity reversal, is a fundamental biological and laboratory transformation. Vitamin B1 causes pyruvate to undergo decarboxylation. It is a surrogate of the polarity reversing reagent, thiamine, that you will use today. Every cell in the body requires vitamin B1 to perform this reaction, which generates adenosine triphosphate (ATP), the fuel the body runs on. In this experiment, you will use thiamine to turn benzaldehyde, an electrophile that undergoes reaction with the nucleophile phenyl magnesium bromide, into a nucleophile, whereupon benzaldehyde will add to itself to make benzoin. The purity of benzaldehyde for this reaction is critical. It must be free of benzoic acid. **Your TA has pre-distilled it for you**. Reactions should always be monitored by TLC analysis at three different times, if possible.



Please regenerate this table in your notebook filling in any of the blanks

Reagent Values	benzaldehyde	thiamine • HCl	95% EtOH	3M NaOH	benzoin
formula	C_7H_6O		C_2H_6O	NaOH	$C_{14}H_{12}O_2$
equiv	1.0	0.05	solvent	0.1	
MW					
den.					
vol.					
mass					
mmol.					
m.p.					
b.p.					

Glassware Set-up:



Procedure : Add thiamine hydrochloride (0.05 equiv) to a 5 mL conical vial with spin vane and then add D.I. water (0.2 mL). Then, add 95% ethanol (0.75 mL) and 3M sodium hydroxide (0.1 equiv) and stir. Then add **freshly distilled benzaldehyde** (417 mg, 1.0 equiv), then heat the reaction mixture to 60 °C for 1.5h hours. Do NOT let the temperature go above 65°C at any time during the experiment as this causes undesirable side reactions. The reaction can be monitored using TLC (3:1 hexanes:EtOAc) by developing the eluted plate in a iodine chamber or with iodine impregnated silica. *If no reaction is evident after 15 minutes, add another 0.05 equiv of thiamine.

Work-Up: Upon completion (TLC or 2h), cool the reaction mixture in an ice bath. If crystals do not appear, use a glass rod to scratch the inside surface of the test tube. If this fails to initiate crystallization, then add a few drops of water. The crystals are collected by

Techniques

The Seven Steps to Enlightened Distillation

1. Select the drying agent from which the substrate will be distilled.

2. Select the heat source (mantle, Bunsen burner, steam bath, water bath, or aluminum block).

3. Assemble the a clean, dry distillation apparatus from the bottom up. Place heat source. Clamp distillation flask. Set approximate height of receiving flask using a utility clamp. Place condenser into position and secure with joint clamps. Attach tubing to water inlet (lowest) and water outlet (highest) of the condenser. Adjust the height of thermometer (bulb below condenser). Inspect to ensure no joint is under stress, and that the system can be safely heated. (i.e., it is open to the air, nitrogen or vacuum, it is not a BOMB.)

4. Turn on the cold water supply to the condenser. Check for water leaks.

5. Add the drying agent and liquid to be distilled to the pot with boiling stones or a stir-bar.

6. Heat the liquid and collect the product in the receiving flask.

7. Allow the apparatus to cool and disassemble it. Clean all glassware parts thoroughly with acetone (discard in organic wastes) before washing with soapy water.

Quiz (8) ideas

IR questions on alcohols and ketones would be good.
Would diphenyl acetylene show a C%C stretch in the IR?
What about trans stilbene?
What does the German word Umpolüng mean? How does this apply to benzaldehyde?
Speculate on the shape of the OH peak of benzoin, if taken in a solution cell? What is its shape?
How might the presence of benzoic acid (a) affect the pH of the reaction and (b) affect the crystallization of benzoin at the end?

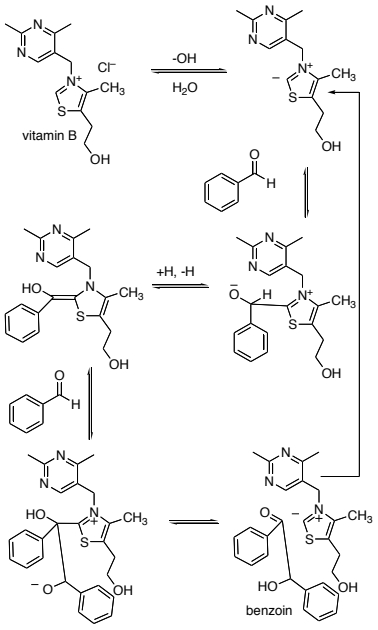
vacuum filtration with a Büchner funnel. Wash with an ice cold 1:1 mixture of ethanol and water. The washings should remove all of the yellow color and the final product should be colorless. The melting point of the pure product is 134-135° C. If the melting point of your product has a range greater than 4° or deviates much from the 134-135°C range, recrystallize the product from a minimum amount of 95% ethanol (7 mL/g of product). Use the clean dry, crystals for NMR, IR or other spectral analysis, as required.

Purification: none.

Spectroscopy: The percent yield is calculated. A melting point and IR is obtained. (Compare your experimental data (IR and melting point) to that of actual data given for diphenylacetylene. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Do not submit your product to the TA, you will use 200 mg of benzoin in a future experiment. **If you failed to recover 200 mg, submit a request to your TA for additional starting material so that you will have 200 mg at the beginning of the that experiment.)**

Waste Disposal: Any residual CH_2Cl_2 was put in a halogenated organic waste container. Non-halogenated organic waste was put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets were dumped into solid waste and then put into a sharps container. Free solid waste (silica, Na_2SO_4) was put into the solids waste container. All aqueous liquids (acetone, ethanol, water) was disposed of in the sink after neutralization or in the basic or acidic waste containers.

Mechanism:



TAs: Quite often, the biggest problem with this experiment is benzaldehyde contaminated with benzoic acid. This naturally happens as a bottle is exposed to air and ages after opening. (A bottle opened on Monday, may not work on Tuesday).

The second biggest problem is getting crystals, The crystallization procedure used here is referred to as solvent-pair crystallization. Here, benzoin has a low solubility in water, high in ethanol, so as the water content increases for an ethanol/water solution of benzoin, the benzoin (hopefully) begins to precipitate. Often, however, the resulting reaction mixture is an oil, i.e., a super-cooled liquid. Besides scratching the side of the glass of the container with the mixture, there are several other options that you may follow--sometimes a combination of the following are necessary. 1. Scratch the walls of the container with a glass stir rod. Don't bear down on the glass so much that you break the stir rod--shards of glass aren't the goal here. 2. Dip the stir rod into the mixture, let it air-dry until you see some small amount of crystalline or powdery solid on the stir rod. Now, place the container in ice water, and continue to scratch the walls of the container. 3. Try reducing the alcohol content of the mixture by letting it evaporate slowly from an uncovered container between lab periods or boiling away with the aid of some boiling chips. 4. Cool and add little more water. This causes more oil to form. Be sure you know which layer is the oil and which is the water. Take the oil, add just enough ethanol to re-dissolve the oil to give a homogeneous mixture, then try scratching, cooling, add a little more water until the solution just becomes a little cloudy, then let it stand uncovered. Chromatography is as always the last resort.

The Umpolüng Process

Any process by which the normal alternating donor and acceptor reactivity pattern of a chain, which is due to the presence of O or N heteroatoms, is reversed. Reactivity umpolung is most often achieved by temporary exchange of heteroatoms (N, O) by others, such as P, S and Se. The original meaning of the term has been extended to the reversal of any commonly accepted reactivity pattern. For example, reaction of R-C%C-X (X = halide) as a synthon for R-C%C^{+} (i.e. electrophilic acetylene) is an umpolung of the normal more common acetylide, R-C%C^{-} (i.e. nucleophilic) reactivity.

Vitamin B1 reverses the inherent polarity of an aldehyde.

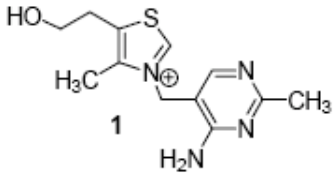


Figure 1. Thiamin, Vitamin B_1

TA Notes

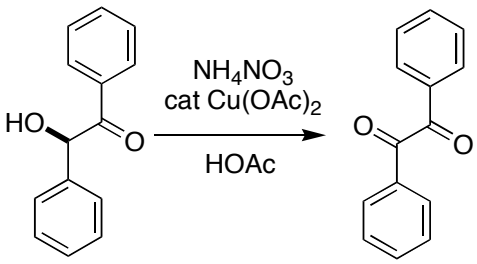
Notebooks should have a copy of the three TLC plates taken for at least three different times (30min, 60min, 90min) during the reaction. Check the UV and Stain with I_2/silica.

Explain the TLC method and how it is used to monitor a reaction and how silica on the plate slows down polar compounds.

Score the product grade as explained earlier.

Experiment 9: Multi-Step (3) Oxidation of benzoin to benzil

Theory & Background: This reaction uses a solution of ammonium nitrate, in the presence of a catalytic amount of copper (II) acetate, to oxidize benzoin to benzil. Reactions should always be monitored by TLC at three different times, if possible.



Please regenerate this table in your notebook filling in any of the blanks

Reagent Values	benzoin	0.15 M $Cu(OAc)_2$ in $HOAc/H_2O$	NH_4NO_3 Source of NO_3^-	benzil
formula	$C_{14}H_{12}O_2$			
equiv	1.0	0.12	1.5	
MW				
vol.				
mass				
mmol.				
m.p.				
b.p.				

Glassware Set-up:

Procedure: Preheat a hot plate and aluminum block to 150 °C. Add all the benzoin obtained from the previous lab (1.0 equiv) to a clean 5.0 mL conical vial, equipped with spin vane, then add 0.15 M copper acetate acetic acid solution (0.12 equiv) and ammonium nitrate (1.5 equiv). Attach a reflux condenser and place on the pre-heated aluminum block for 45 minutes.

Work-Up: Remove the reaction mixture from the heat source and allow to cool to room temperature. Remove the reflux condenser and add water (2.0 mL) and chill in an ice bath for 10 minutes. The yellow crystals are collected by vacuum filtration with a Büchner funnel and the filter cake is washed with H_2O (2 X 2 mL). After drawing air through the crystals for several minutes, further drying is accomplished by blotting the solid dry with filter paper. The filtrate is neutralized with 1M $NaHCO_3$, until slightly basic and flushed down the drain.

Purification: The benzil is slowly recrystallized from hot ethanol (7mL/g), collected, washed with ice cold ethanol, and air dried.

Techniques

De-gassing solvents: The best way to remove water and oxygen from a solvent is to distill it over an appropriate drying agent (such as sodium). This can sometimes be a lengthy (and dangerous) task. For small amounts, it is more efficient to de-gas the solvent by purging with an inert gas such as N_2 or Ar. 1) Place some activated molecular sieves in a hot round-bottomed flask, and purge with nitrogen until cooled to room temperature. Glass readily adsorbs moisture from the air, so it is important to thoroughly oven (or flame) dry all glassware. The sieves will act as a sponge to pick up water dissolved in the solvent. 2) When the flask has cooled, add the solvent and cap with a rubber septum. Secure the septum with copper wire. 3) Purge the solution by injecting a clean needle through the septum and placing it directly in the solvent. Vent the flask with another needle. You should see bubbles. 4) 15–20 minutes should be sufficient.

Another method of degassing a solution is **"freeze-pump-thaw."** The solution is cooled to -78 °C (dry ice), and then evacuated with vacuum as it is being frozen (using liquid nitrogen, for example), then vacuum is applied for several minutes. The cold bath is removed and the solvent is allowed to slowly warm, once it becomes a liquid, the vacuum is turned off. Repeat this procedure at least two more times.

Quiz ideas

Copper acetate is the oxidizing agent for oxidizing benzoin to benzil, and only 0.012 mmoles are used for 0.94 mmoles benzoin. How can this be possible?

How many nitrates are needed in this reaction?

What structural features make benzil yellow and benzoin white?

How and why does the color change occur when benzoin is oxidized to benzil?

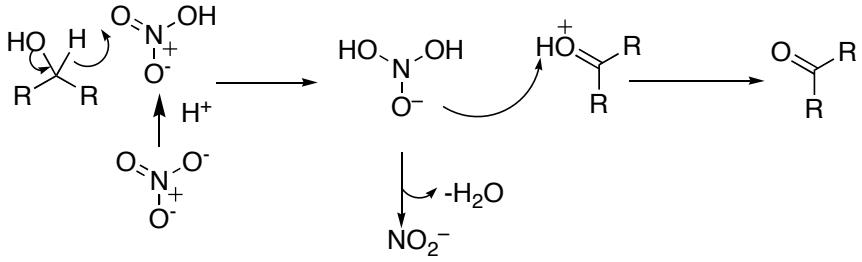
How much gas will be discharged at STP?

Test for the presence of unoxidized benzoin: Dissolve about 0.5 mg of crude or purified benzil in 0.5 mL of 95% ethanol or methanol, and add one drop of 10% sodium hydroxide. If benzoin is present, the solution soon acquires a purplish color. If no color develops in 2 to 3 minutes, it indicates that the sample is free from benzoin. For comparison, add a small amount of benzoin, observe the color that develops, and note if the contents are capped and shaken vigorously, the color momentarily disappears; when the solution is then let stand, the color reappears.

Spectroscopy: The percent yield is calculated. A melting point and IR are obtained. (Compare your experimental data (IR and melting point) to that of actual data given for benzil. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Do not submit your product to the TA, you will use 100 mg of benzoin in a future experiment. **If you failed to recover 100 mg, submit a request to your TA for additional starting material so that you will have 100 mg at the beginning of the next experiment.)**

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism: Cu^{+2} catalyzes this progress. Oxidations are best viewed as loss of hydride.



Lecture Suggestions:

TAs:

Techniques

Removing triphenyl phosphine oxide: If your product is stable and relatively-non polar, a good way of removing triphenylphosphine oxide (produced in Wittig, Mitsunobu, bromination, and other reactions) is to concentrate the reaction mixture to a smaller volume, suspend the residue in pentane (or hexane)/ether and filter over a silica plug. The compound can then be eluted with ether, leaving most of the phosphine oxide at the top of the column. Sometimes it is necessary to repeat this procedure 2-3 times to remove most of the phosphine oxide.

Removing copper salts: Quench the reaction with sat. aq. NH_4Cl, stir for a few hours until the solution becomes dark blue (indicates complexation). Separate and wash the organic layer (*sat. aq.* NH_4Cl X 3).

Removing water and other solvents: Often traces of a high boiling solvent or other impurity can be removed from a product or reaction mixture by concentration of a solution of the compounds from an appropriate solvent. This works because higher boiling solvents azeotrope with lower boiling solvents, forming an easy to remove binary distillate.

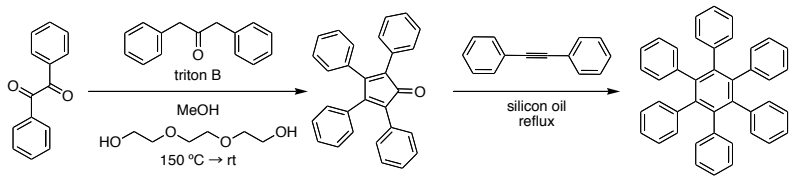
Removing pyridine: pyridine is easily

Quiz ideas (9)

How many mL of CO is produced from 100mg of TPCPD? What is triton B. What does triton B do? Why not use NaOH? How HO– is produced in the reaction? How much water? If you benzil is mixed with benzoin, what other signals would you see in the IR? Which aromatic carbon in the ^{13}C has the fewest hydrogens connected to it. Justify its height. Hand-out the IR, ^{1}H-NMR and ^{13}C-NMR spectra of benzaldehyde and have them assign the peaks. What is the chemical reaction of Br^{+} with $NaHSO_3$? In the previous lab, we oxidized benzoin to benzil using copper acetate and thiamine. What are three ways we could observe the progress of this reaction? Be specific. Do not simply name the method or technique, but describe how that technique would differentiate between the product and starting material.

Experiment 10: Multi-Step (4) Synthesis of hexaphenylbenzene from benzil

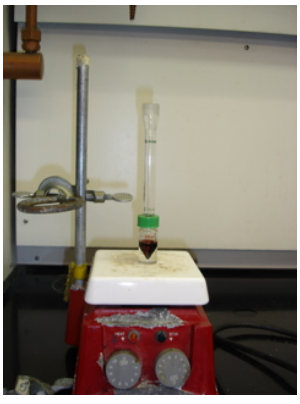
Theory & Background: The multi-step synthesis converges in this experiment as a bis-aldol condensation reaction is followed by a Diels-Alder [4+2] cycloaddition with diphenyl acetylene and concomitant loss of carbon monoxide. You will make a KBr pellet of the first intermediate and record it's IR. Reactions should always be monitored by TLC analysis at three different times, if possible.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	benzil	dibenzyl ketone	triton B 40 wt% in MeOH (1.79M)	$HO(CH_2CH_2O)_3H$	tetraphenyl cyclopenta-dienone	diphenyl acetylene	hexaphenyl benzene
formula							
equiv	1	1	0.37	solvent			
					1.0	2.0	
MW							
density							
volume							
mass							
mmol.							
mp							
bp							

Glassware Set-up:



Procedure 1: Preheat a hot plate and aluminum block to 150 °C. Add all the benzil obtained from the previous lab (1.0 equiv) and dibenzylketone (1.0 equiv) to a 3.0 mL vial equipped with a spin vane. Then add enough triethylene glycol to make a 1.0M solution based on the amount of benzil used and begin stirring. Attach an air condenser and heat the mixture until homogenous. Remove the heat source and while the solution is still stirring, add Triton B (0.37 equiv) through the condenser. Upon cooling purple crystals are formed.

Work-Up 1: While stirring at room temperature add methanol (1.3 mL /100 mg of benzil). Cool the vial in an ice bath, and the purple crystals are collected by vacuum filtration with a Büchner funnel. Wash the crystals with ice cold methanol until the filtrate is purple-pink, not brown. The crystals are collected and air dried. The filtrate is placed in an organic waste container. The percent yield of tetraphenylcyclopentanone is calculated.

Techniques

High Pressure Reactors
Hydrogenations are often run a high pressure. The apparatus below, a Parr Shaker, is for performing reactions at 10-100 psi.

Higher pressures 100-5000 psi are obtained using a Parr bomb.

Quiz (10) ideas

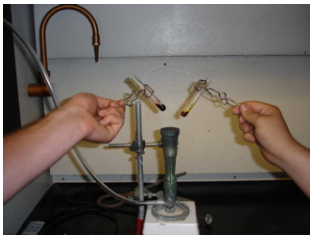
What is the molarity of a 10% by weight solution of hydrogen peroxide (mw = 34.14, d = 1.11 g/mL) in water?

Draw and label the ^1H NMR spectrum of 3-methoxy-pentane. Be sure to place peaks at appropriate chemical shifts in reference to one another, and illustrate multiplicity.

In total synthesis what aspect is the most critical in evaluating the efficiency of a route?

What is the function of the benzyltrimethylammonium hydroxide(Triton B)? Why is it better to use in this experiment than aqueous NaOH?

Purification: If the crystals are not well formed or if the melting point is low, then place the material in a reaction tube, add 0.6 mL of triethylene glycol, stir with a thermometer (You will need to use a mercury thermometer from one of the melting point apparati to do this. Please remember to put it back!), and raise the temperature to 220 °C to bring the solid into solution. Let it stand for crystallization (if initially pure material is recrystallized, the recovery is about 90%). Save 10 mg of these crystals for measuring a melting point and taking a KBr pellet IR. Run all of the remainder in the next reaction. If you need a supplement, ask your TA.



Procedure 2: Add tetraphenylcyclopentadienone (1.0 equiv) and diphenylacetylene (2.0 equiv) to a pyrex tube and silicone oil (2 mL). Care is taken to ensure that the components are completely **dry** before mixing (else, spattering could occur). The mixture is brought to a boil (250 °C) by rotating the pyrex test-tube over a micro-burner. A colored, homogeneous purple solution results after heating for 1-3 minutes. Heating is continued until the purple solution fades into a reddish brown mixture and no further lightening in color is observed.

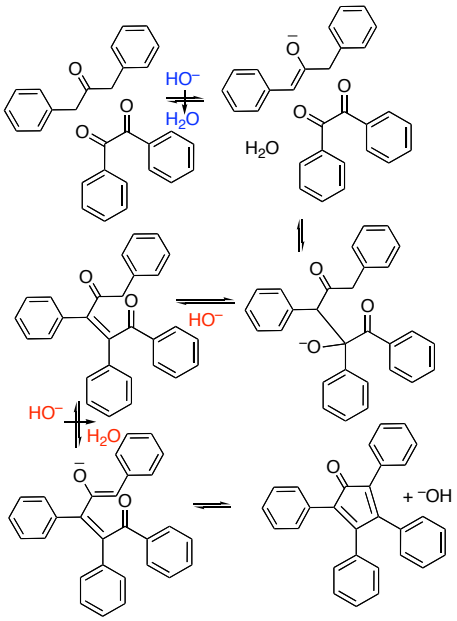
Work-Up 2: After cooling to room temperature, dilute the mixture with hexanes (6.0 mL). The crystals are collected by vacuum filtration with a Büchner funnel. Wash the filter cake with hexanes (2 X 1 mL) and cold toluene (2 X 1 mL). The filtrate is placed in an organic waste container. The cake is air dried for several minutes.

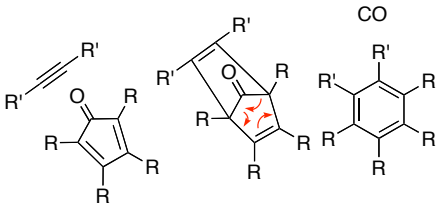
Purification: The crystals are further purified by recrystallization from a minimum amount of hot diphenyl ether (259°C).

Spectroscopy: The percent yield is calculated. The melting point of this last product is too high to measure. KBr pellet IR spectra are obtained for the two products. (Compare your experimental data (IR) to that given for tetraphenylcyclopentadienone and hexaphenylbenzene. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Submit your entire sample in a tared vial to your TA for scoring.

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism:





Lecture Suggestions: Cover an aldol condensation and a Diels-Alder reaction. Note however, that most 6B/109B students have only covered a simple [4+2] Diels-Alder reaction and have not yet seen an aldol reaction. You should not quiz on the mechanisms. Demonstrate a KBr pellet formation.

TAs: The final product is scored as usual

IR sampling techniques

Neat sample: A drop of sample is pressed between two halide salt crystals. A clean crystal window can be used as reference background.

Liquid cell: Liquid cells are available with either a fixed or an adjustable path length. This is one of the most economic techniques for liquid samples which requires a known path length, however, it is often difficult to clean out the cell and also leaking problem might occur. Cells should be filled carefully to avoid air bubbles.

Neat sample: Semi-solid of low melting materials may be heated and spread across the crystal window in a thin film with a spatula.

Cast films: Sample is dissolved in a suitable solvent. A drop of the prepared solution is then placed on the crystal window to allow the solvent to evaporate. A thin film of sample is left on the crystal for infrared measurement. Pressed films: Plastic materials can be pressed into thin films by using heated platens if decomposition, oxidation and degradation are not problems.

KBr pellets: Sample is ground thoroughly with KBr at approximately 1% to 3% by weight and pressed into a pellet with a thickness of about 1mm. A hand presser or a KBr die with a variety of sizes, ranging from 0.5mm to 13mm, are available to make pellets. Open beam air background is typically used for this technique.

Mull: Sample is ground and mixed with Nujol or Fluorolube. The mixture is then spread on the crystal window for measurement. Absorption bands of the oil will obscure some of the sample's features. Nujol has absorption bands at short wavelengths and Flourolube at longer wavelengths. Running the sample in both oils, separately, of course, will yield a complete spectral range of the sample. The spectrum of the pure sample may also be obtained by subtracting out the mulling material.

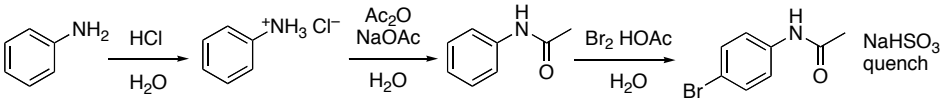
TA Notes

The same rules apply for benzil supplements. They need 100mg to run (That is all they get). If they have more, they should run all of it. Since a grade has already been given for the amount of the acetylene, you can supplement the amount without penalizing the student. TA grades final product as usual.

If the oil is wet when heated it will spatter.

Experiment 11: Acetanilide synthesis and aromatic bromination

Theory & Background: Bromination of aniline is an uncontrollable reaction. In this sequence, however, aniline is first acetylated. It thereby becomes less reactive. Bromination then proceeds in a regioselective manner. Reactions should always be monitored by TLC analysis at three different times, if possible.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	aniline	H_2O and HCl (12M)	Ac_2O	NaOAc • $3H_2O$	acetanilide	HOAc	7M Br_2 HOAc	4-Br-anilide
formula	$C_6H_5NH_2$							
equiv	1.0	1.1	1.5	1.1				
					1.0	1.2	1.1	
MW								
density								
volume								
mass								
mmol.								
melting point								
boiling point								

Glassware Set-up:

Procedure: Add aniline (102 mg, 1.0 equiv), then water (0.5 mL) and 12M HCL (0.1 mL) to a 13 x 100-mm test tube. Add several pellets of charcoal (~20 mg). If the solution does not become clear after swirling for 3-5 minutes, add additional charcoal and swirl until a clear solution is obtained. Filter the suspension through a cotton plugged pipet into a 3.0 mL conical vial containing a spin vane. Rinse the residue remaining in the test tube with water (0.5mL) and filter into the same 3.0 mL conical vial. Add sodium acetate-trihydrate (1.1 equiv) to the rinsed 13 x 100-mm test tube, followed by DI water (0.5 mL). This sodium acetate solution is set aside. Add acetic anhydride (1.5 equiv) to the 3.0 mL vial containing the aniline hydrochloride and then add the solution of sodium acetate. Stir for 15 minutes to ensure complete mixing of the reagents and reactant. Place the 3.0-mL via in an ice-water bath for 10 minutes to induce crystallization of product.

Work-Up: Isolate the product by vacuum filtration with a Büchner funnel. Rinse the 3.0-mL vial with water (0.5mL X 2). Allow the product to completely dry in the Büchner funnel before proceeding. The aqueous filtrate is disposed down the drain after dilution with water. The percent yield of acetanilide is calculated. About 10 mg of this material was saved for spectra and m.p. analysis.

Procedure 2: Add the acetanilide (1.0 equiv) obtained from Procedure 1 to a 5.0-mL vial, equipped with a clean spin vane. Add enough glacial acetic acid (~1.2 equiv) to dissolve the acetanilide while agitating. Because bromine is a powerful irritant and oxidant and displays a significant vapor pressure and extreme care should be exercised in the next step. Once the acetanilide is dissolved, add the 7M Bromine/HOAc solution (1.1 equiv)

Techniques

Quiz ideas

How does one evaluate a total synthesis?

Predict the IR of acetanilide? How many signals for the N–H.

Explain significant peaks in the Mass Spec.

How many signals in the 1H-NMR for 4-bromo-acetanilide?

Show what the MS would look like for the molecular ion.

What is the purpose of the NaHSO3 quench?

to the 5.0 mL vial and then cap the vial. Agitate the reaction mixture periodically. After 10 minutes, add water (1.5 mL) to the reaction mixture, followed by aqueous sodium bisulfite (1.0 mL) and allow the product to crystallize.

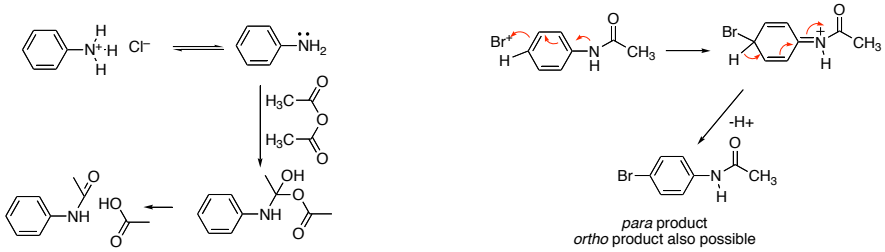
Work-Up: The crystals are collected by vacuum filtration using a Büchner funnel, washed with cold water (1mL X 3), and partially dried by drawing air through the crystals. The filtrates are flushed down the drain after dilution with water.

Purification: The crude 4-bromoacetanilide is recrystallized from 95% EtOH.

Spectroscopy: The percent yield is calculated. A melting point and IR spectrum is obtained for acetanilide and 4-bromoacetanilide. (Compare your experimental data (melting point and IR) to that of actual data given for acetanilide and 4-bromoacetanilide. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Submit your entire sample in a tared disposable vial to your TA.)

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism:

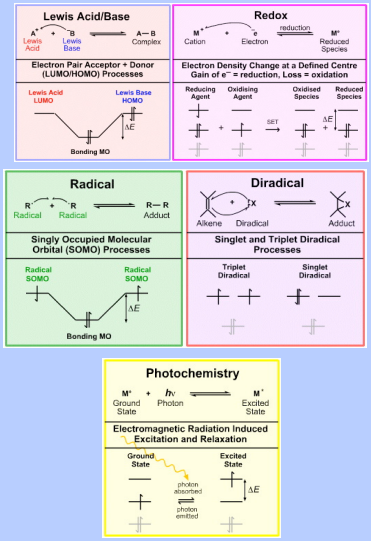


para product
ortho product also possible

Lecture Suggestions: Explain the importance of the peptide bond in nature. Explain why rotation is hindered and rotamers are the reason for the two different methyl singlets. Keep pounding spectroscopy (NMR, IR, MS).

The Five Mechanisms of O. Chem.

1) Lewis acid/base Chemistry, which involves LUMO/HOMO interactions.
2) Redox chemistry: Loss or gain of electrons from a defined centre and which may involve a cationic, anionic or SET process.
3) Radical chemistry, which involves SOMO interactions.
4) Diradical chemistry: singlet and triplet states.
5) Photochemistry, which involves excitation by photons and production of photons

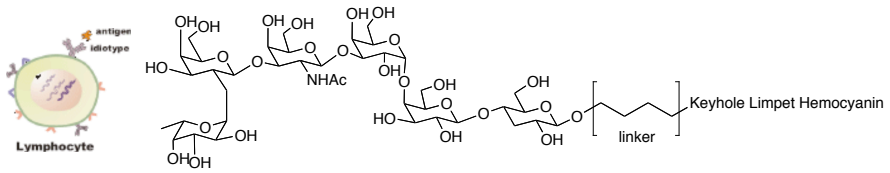


Single-electron transfer mechanism is often abbreviated at (SET). The mechanism is characterized by the transfer of a single electron between the species occurring on the reaction coordinate of one of the elementary steps. It is a key mechanism in redox processes

TA Notes

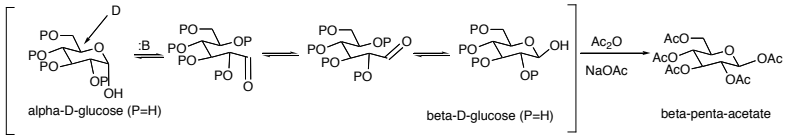
Experiment 12: Synthesis of α- and β- glucose penta-acetate

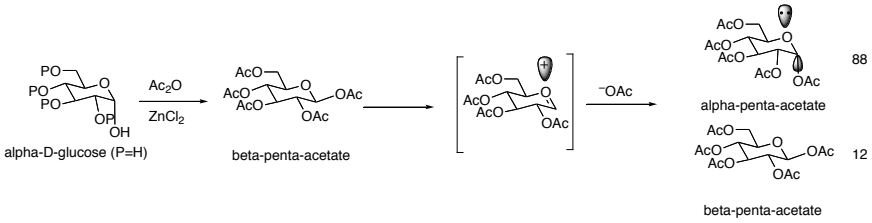
Theory & Background: Sugars and their anomers play import roles in cell recognition.



Globo-H is an idotype carbohydrate expressed on the surface of certain tumor cells. It is too small to be immunogenic so it is conjugated via a linker with a carrier protein that is visible to the immune system. "Shazam, you've got an anit-cancer vaccine"

Today you'll be working with glucose in two simultaneous experiments. Glucose exists in solution as an equilibrium between the α and β anomers of its pyranose hemi-acetal and its open form. However, the solid starting material provided by Aldrich exists exclusively as the α-anomers. When using sodium acetate and acetic anhydride, the less hindered, equatorial hydroxyl group of the β isomer undergoes reaction much much faster than the axial hydroxyl group of the α isomer. This results in the preferential formation of the β-glucose pentaacetate. What can you deduce about the difference in the rate of acylation for the α and β anomers verses the equilibrium constant between them? In the second experiment, you'll generate an oxonium ion. Because of the anomeric effect, it undergoes reaction to preferentially form the α anomer. You'll note the different NMR spectra. You will need to find a partner so that one sets a hot plate to 110 °C while the other set theirs to 95 ° C. You will share the hot plates, but you'll each run both experiments.





Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	glucose	acetic anhydride	sodium acetate	per-acetylated glucose
formula	$C_6H_{12}O_6$			$C_{16}H_{22}O_{11}$
equiv	1.0	15	2.0	
MW				
density				
volume				
mass				
mmol.				
melting point				
boiling point				

The anomers of both D-glucose pentaacetate and L-glucose pentaacetate have been found to display insulinotropic potential.

Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	glucose	acetic anhydride	zinc chloride	peracetylated glucose
formula	$C_6H_{12}O_6$			$C_{16}H_{22}O_{11}$
equiv	1.0	15	0.35	
MW				
density				
volume				
mass				
mmol.				
melting point				
boiling point				

Glassware Set-up:

Procedure 1: Preheat a hot plate to 110-120 °C. Add anhydrous glucose powder (100 mg, 1.0 equiv), anhydrous sodium acetate powder (2.0 equiv), and acetic anhydride (15 equiv) to a 5.0 mL vial, equipped with a spin vane. Attach an air condenser with drying tube to the vial. Heat and stir the mixture at 110-120°C for one hour.

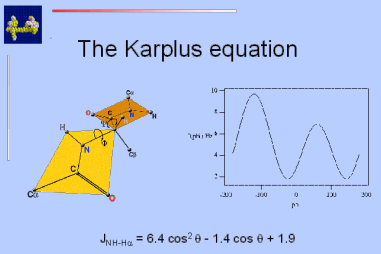
Work-Up 1: After heating for 1 hour, discontinue heating and allow the vial to cool to room temperature. Pour the reaction mixture onto ice (~5g) in a small beaker. An oil separates and solidifies after 30 minutes of stirring with a glass rod. The solids are collected by filtration using a Büchner funnel and washed with cold *d.i.* water (2 mL).

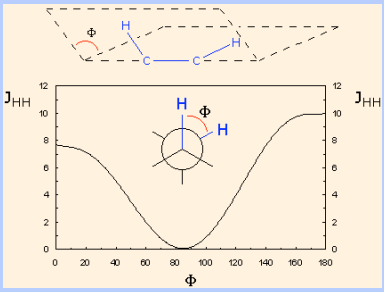
Purification 1: The solid is recrystallized from a minimum amount of hot 95% ethanol (1-2 times). The percent yield is calculated.

Procedure 2: Preheat the other hot plate (your partner's) to 95-100°C. Add anhydrous glucose powder (100mg, 1.0 equiv), zinc chloride (0.35 equiv), and acetic anhydride (15 equiv) to a 5.0 mL conical vial equipped with a spin vane . Attach an air condenser and drying tube to the vial. Heat the stirring mixture at 95-100°C for 1 hour.

Work-Up 2: After heating for 1 hour, discontinue heating and allow the vial to cool to room temperature. Pour the reaction mixture onto ice (~5g) in a small beaker. An oil separates and solidifies after 30 minutes of stirring with a glass rod. The solids are collected by filtration using a Büchner funnel and washed with cold *d.i.* water (2 mL).

The ^{1}H NMR spectra of the two peracetylated glucoses are similar of course, but key differences exist. The proton at C-1 called H-1 has the greatest chemical shift because it is on a C attached to two O's. The proton H-1 is at 5.7 ppm in the β isomer and at 6.3 ppm for the α isomer. Typically axial protons are at higher field (smaller chemical shift) than are the equatorial protons. Also notice that in the chair conformational structure of the β isomer that H-2 is anti to the H-1, and this geometry results in a doublet with splitting (coupling) of 9.0 Hz. In contrast the α isomer where the H-1 and H-2 are gauche to one another, has a splitting of only 3.5 Hz in accord with Karplus equation. These compounds were among those used in the early days of NMR to study these effects.





TA Notes

If there are not enough drying tubes then build one from a Claisen adapter.

Purification 2: The solid is recrystallized from a minimum amount of hot 95% ethanol (1-2 times). The percent yield is then calculated.

Spectroscopy 1&2: Melting point and IR spectra are obtained for both products. (Compare your experimental data (melting point and IR) to that of actual data given for both products. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Note the slight differences between the diastereomers particularly in vicinal coupling. Include the labeled spectra in your notebook. Submit your combined samples in a tared vial to your TA. Note the origins of the amounts.)

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Lecture Suggestions: First, re-examine NMR and discuss diastereotopic signals and coupling. Be sure to explain the Karplus rule ($\cos^{-1}$ of 90° = 0). Then explain the hemiacetal-aldehyde equilibrium. Next, discuss the anomeric effect. It is easiest to explain it as a means to prevent destabilization from electron-electron repulsion in the product.

Techniques

Quiz ideas

Excluding O–H denote the proton that would be the most shielded.

Other than a pyranose, are there other forms of glucose?

Explain the anomeric effect?

What governs a kinetic distribution of diastereomers?

What governs a thermodynamic distribution of diastereomers?

How do these topics apply to experiment 12?

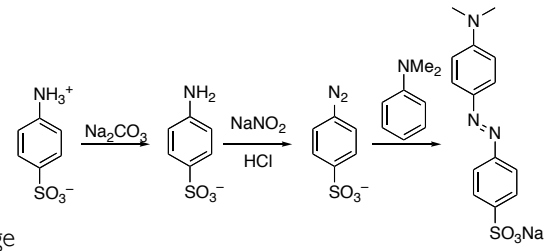
How might you monitor the reaction by IR?
What is the role of zinc chloride?

What does alpha and beta signify in general?

What does alpha and beta signify for carbohydrates?

Experiment 13: Synthesis of methyl red and orange via a diazonium coupling

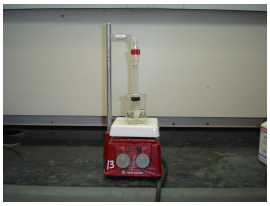
Theory & Background: Today you'll again be running two experiments in parallel. In the presence of nitrous acid, formed from sodium nitrite and hydrochloric acid, an aromatic amine is converted to an aryl diazonium ion ($Ar\text{-}N_2^+$). Close to 0 °C, the aryl diazonium ion is stable for hours. At higher temperature it loses N_2, forming a very reactive aryl cation. In these experiments, the respective diazonium ions undergo C–N bond formation with N,N-dimethylaniline. This forms azo-dyes, compounds that are used as acid-base indicators. Reactions as usual, should always be monitored by TLC analysis at different times, if possible.



orange

Please regenerate this table in your notebook filling in all of the blanks

Reagents Values	sulfanilic acid	0.24M Na_2CO_3	sodium nitrite	3M HCl	dimethyl aniline	acetic acid	3M sodium hydroxide	methyl orange
formula								
equiv	1.0	0.5	1.0	3.0	1.0	1.5	5.0	
MW								
den								
vol								
mass								
mmol.								
mp								
bp								



Procedure 1: Add sulfanilic acid (100mg, 1.0 equiv) to a 5.0 ml vial equipped with a spin-vane. Add 0.24 M sodium carbonate (0.5 equiv) and heat the vial until all solids dissolve. Cool the vial to room temperature, then place the vial in an ice water bath and add sodium nitrite (1.0 equiv). Stir for 5 minutes and then add 3M hydrochloric acid (3.0 equiv) to the vial. A slurry of the diazonium salt forms. In a separate 3.0 mL vial, add dimethylaniline (1.0 equiv) and acetic acid (1.5 equiv) and cool the vial to 0°C. Once cool, quickly transfer this ice cold solution with a pipet to the chilled diazonium salt. Rinse residual dimethylaniline from the vial with a few drops of water.

Work-Up 1: Stir for ~10 minutes and a paste should form. Slowly add 3 M NaOH (5.0 equiv). The mixture changes color to orange. While stirring, heat the vial in a beaker of boiling water until most of the solids dissolve. Upon cooling to 0°C, crystals form. These are collected by vacuum filtration. The filter cake is washed with saturated brine.

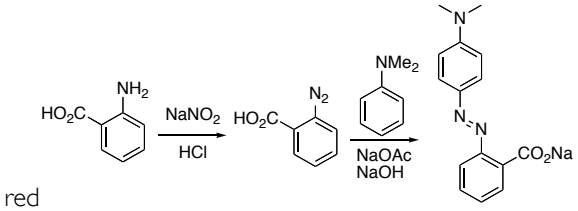
Purification 1: Recrystallization from water and calculation of the percent yield.

The products are both acid indicators, which are a weak acid or a weak base. The undissociated form of the indicator is a different color than the iogenic form of the indicator. An Indicator does not change color from pure acid to pure alkaline at specific hydrogen ion concentration, but rather, color change occurs over a range of hydrogen ion concentrations. This range is termed the color change interval. It is expressed as a pH range

Methyl orange

Methyl red in action. It has been used as an indicator for the bacteria Enterobacteriaceae.

The Enterobacteriaceae, Gram-negative bacilli, are the most frequently encountered bacteria isolated from clinical specimens. Widely dispersed in nature, the Enterobacteriaceae occupy a number of ecological niches including the intestinal tracts of humans and animals. Before the advent of antibiotics infectious diseases caused by the Enterobacteriaceae were well defined. Endotoxic shock is one of the potentially life-threatening consequences of infection by Gram-negative bacteria including the Enterobacteriaceae. Endotoxin is a lipopolysaccharide found in the outer membranes of Gram-negative bacteria. The lipid-A portion of the lipopolysaccharide molecule is primarily responsible for the bioactive properties of endotoxin. Endotoxin is highly antigenic and its structure is highly conserved in all strains of Gram-negative bacilli. Many bacteria use one of two alternative routes for reoxidizing NADH, which generate large quantities of acetic acid, lactic acid, and formic acid and lesser amounts of succinic acid, propionic acid, butyric acid, and butyl alcohol. In olden days, methyl red was used to screen surfaces for the presence of bacteria. Today, tests for detecting Gram-negative sepsis are based on the development of monoclonal antibodies specific for the conserved lipopolysaccharide molecule on the surface of the bacteria.



red

Please regenerate this table in your notebook filling in all of the blanks

Reagents Values	anthranilic acid	3M HCl	sodium nitrite	3M NaOAc	dimethyl aniline	3M NaOH	methyl red
formula							
equiv	1.0	4.0	1.0	2.0	1.5	0.5	
MW							
density							
volume							
mass							
mmol.							
mp or bp							

Procedure 2: Add anthranilic acid (80 mg, 1.0 equiv) to a 5.0 mL conical vial equipped with a spin vane. Next add 3M hydrochloric acid (4.0 equiv) and stir until homogeneous. Heat is applied if necessary to dissolve solids. Cool the vial in a small beaker of ice water for 5 minutes with stirring. Add sodium nitrite (1.0 equiv) to a 3.0 mL vial then dissolve in water (0.20 mL). Cool the sodium nitrite solution in ice water for 5 minutes and then add this to the solution of anthranilic acid via a pipet. Next add dimethylaniline (1.5 equiv) stir the contents for 15 minutes. Next, add 3M NaOAc (2.0 equiv) and continue stirring for 20 minutes. Allow the reaction to warm to room temperature and then add 3 M NaOH (0.5 equiv). Let the contents stand for 30 minutes to ensure thorough precipitation.

Work-Up 2: Methyl red is collected by filtration using a Büchner funnel. The reaction vial is rinsed with water. Wash the filter cake with 3M acetic acid (about 0.5mL) to remove excess dimethylaniline. Then wash the filter cake with a small amount of water.

Purification 2: In a fume hood, the product is recrystallized from methanol. Cool the solution to 0°C before filtering.

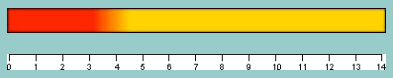
Spectroscopy 1&2 DO NOT TAKE MELTING POINTS. The percent yield is calculated. IR spectra are obtained for both products using KBr pellets. (Compare your experimental data (melting point and IR) to that of actual data given for methyl red and orange. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Note the differences in couplings for o-substitution verses p-substitution. Include the labeled spectra in your notebook. Submit both of your samples in separate tared vials to your TA.)

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism: Students should be able to propose one on their own.

Techniques

Methyl orange is an intensely colored compound used in dyeing and printing textiles. It is also known as C.I. Acid Orange 52, C.I. 13025, helianthine B, Orange III, Gold orange, and Tropaeolin D [1]. Chemists use methyl orange as an indicator in the titration of weak bases with strong acids. It changes from red (at pH 3.1) to orange-yellow (at pH 4.4).



TA Notes

Use a KBr pellet for the IR. These dyes stain the salt plate.

Do not take melting point.

Quiz (13) ideas

What might happen if aniline were used instead of dimethyl aniline?

In UV-Visible Spectroscopy, the presence of what lead to bathochromic shift.

What are some true concerning the absorption of light in UV-Visible spectroscopy?

What does Hyperchromic means?

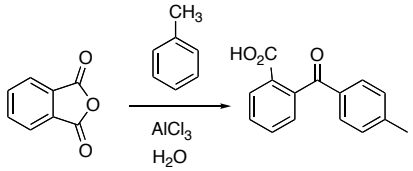
What does the absorption intensity reflect?

Explain how deprotonation affects the UV-Vis of these compounds.

Why would these compound's colors be different at differing pH?

Experiment 14: Synthesis of 2-(4-methylbenzoyl)benzoic acid

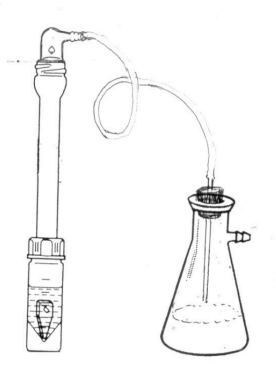
Theory & Background: Friedel-Crafts acylation involves the addition of a benzene ring at the carbonyl of an acyl chloride or an anhydride. This reaction has several advantages over Friedel-Crafts alkylation. Among these is the fact that the product is less reactive than the starting material, so multiple acylations do not occur. Also, there is little possibility for carbocation rearrangements in the side chain being added. Reactions, as usual, should be monitored by TLC analysis at different times, if possible.

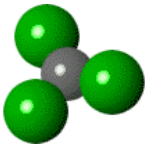


Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	phthalic anhydride	toluene	aluminum trichloride	solid water (ice)	2-(4-toluoyl)-benzoic acid
formula					
equiv	1	15	2.2		
MW					
density					
volume					
mass					
mmol.					
melting point					
boiling point					

Glassware Set-up:

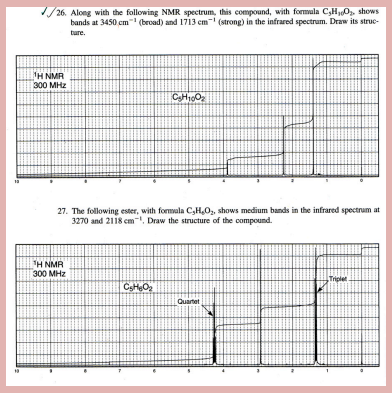




Procedure: Add phthalic anhydride (150 mg, 1.0 equiv) to a dry 5.0 mL vial equipped with a spin vane. Add toluene (15 equiv) then attach an air condenser to the vial. Cool the vial in an ice water bath. While vigorously stirring the solution, add three-full spatulas of **fresh** $AlCl_3$ (~300 mg, ~2.2 equiv) through the condenser directly into the vial. The contents should become olive-green. Assemble the gas bubbling apparatus, with toluene in the trap and replace the ice water bath with an aluminum block. Once the reaction has reached room temperature, stir and heat the contents to 90°C for 1 hour.

Techniques

Quiz (14) ideas



If we have 100mg of glucose (mw = 180.16) in 0.75mL of acetic anhydride (mw = 102, d = 1.08 g/mL), what is the molarity and weight percent of the solution?

What role does $AlCl_3$ play in this reaction?

Explain the C=O stretches in the IR for phthalic anhydride?

What is a fermi resonance?

Speculate on the shape of this RCO_2-H peak in the IR using solution cells.

Where do you think this signal will come in the ^{1}H-NMR?

Calculate the number of moles of hydrogen chloride liberated in the microscale synthesis of 2-benzoylbenzoic acid. If this gaseous acid were dissolved in water, hydrochloric acid would be formed. How many milliliters of concentrated hydrochloric acid would be formed in this reaction? The concentrated acid is 12 M in HCl.

Write a mechanism for the formation of 2-(4-methylbenzoyl)benzoic acid from toluene and phthalic anhydride using an aluminum chloride catalyst.

Work-up: Cool the vial to room temperature then place in an ice bath and remove the gas bubbler. Slowly add crushed ice chips through the condenser while vigorously stirring until the volume reaches ~3 mL. Continue stirring and carefully add concentrated HCl dropwise (1 drop/10 seconds) to the vial until all solids dissolve (this is very exothermic). Once the solids have completely dissolved, add ether (1.5 mL) to the stirring solution and allow to stir for 3 minutes. Remove the flask from the ice bath and discontinue stirring. Remove the aqueous layer (bottom layer) and place the aqueous extract in a test tube. Wash the organic layer once more with 3M HCl (1 X 1.0 mL) and combine the aqueous washes. Dry the ethereal solution over sodium sulfate and allow to stand for 10 minutes. After 10 minutes, filter the mixture through a cotton plugged pipet into dry clean 3.0 mL vial. Rinse the Na_2SO_4 with ether (1.0 mL X 2). A boiling chip is added and the combined solvent is evaporated with heat until the solution turns cloudy (super saturated).

Purification: Heating is discontinued and crystallization begins. It can be further induced with an ice-bath. The mono-hydrate product is placed in the oven at 100 °C for 1 hour or until the next class period. Note, if the oven is over 100 °C the product will decompose. It is essential that the dried product (no longer a hydrate) be re-crystallized before proceeding to the next experiment.

Spectroscopy: The percent yield is calculated. The melting point and IR spectrum are obtained. (Compare your experimental data (melting point and IR) to that of actual data given for the product. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. **Do not submit your product to the TA, you will use 100 mg of the product acid in a future experiment. If you failed to recover 100 mg, submit a request to your TA for additional starting material so that you will have 100 mg at the beginning of the that experiment.)**

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

Mechanism: Students should be able to propose one on their own. It is similar to the first lab. The first equivalent of $AlCl_3$ is bound to the acid, the other to the ketone carbonyl. On the addition of acid the aluminum complex decomposes.

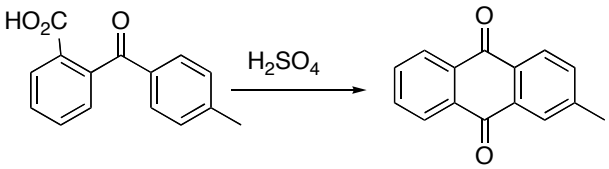
TA Notes

The stockroom should give each TA 5 grams of $AlCl_3$ in a parafilmed sealed bottle. TA's then eyeball the amount and add it to student's reactions. This is to prevent bottles from dying over the week of Chem 6b. Three heaping spatulas should prove satisfactory. TA's should dispose of any of the remaining $AlCl_3$ in their bottles.

Label the oven (don't raise temperature >100 °C)

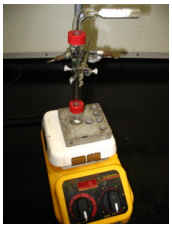
Experiment 15: Synthesis of 2-methylanthraquinone by Friedel-Crafts

Theory & Background: Anthraquinone, is a polycyclic, aromatic hydrocarbon containing two opposite carbonyl groups (C=O) at the 9,10 position. It is a yellow or light gray to gray-green crystal powder that is insoluble in water. In nature, it occurs in plants such as aloe, cascara sagrada, senna, and rhubarb. It is also found in fungi, lichens, and insects as a parent material for the coloring of yellow, orange, red, red-brown, or violet. It is commercially produced by several methods, including oxidation of anthracene with chromic acid, condensation of benzene and phthalic anhydride, followed by dehydration for cyclization, and diene Diels-Alder reaction. Anthraquinone is the most important quinone derivative of anthracene, as it is the parent substance of a large class of dyes and pigments. One of the oldest mordant dye, alizarin, is an anthraquinone derivative. Anthraquinone is a starting material for the production of coloring compounds, antioxidants, and polymerization inhibitors. Its derivatives are widely used as intermediates for dyes, pigments, photographic chemicals, and paints. Anthraquinone is used in paper industry as a catalyst to increase the pulp production yield and to improve the fiber strength through a reduction reaction of cellulose to carboxylic acid. Natural anthraquinones have cathartic properties. Anthraquinones derivatives are also used as drugs. Mitoxantrone, an anti-neoplastic (anti-cancer agent) is but one example.



Please regenerate this table in your notebook filling in any of the blanks

Reagents Values	2-(4-toluoyl)-benzoic acid	95% H_2SO_4	2-methylanthraquinone
formula			
equiv	1		
MW			
density			
volume			
mass			
mmol.			
melting point			



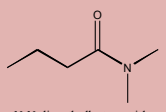
Procedure: Add the 2-(4-toluoyl)-benzoic acid (1.0 equiv) obtained from Experiment 14 to a 5.0 mL vial equipped with a spin vane. Begin stirring and add concentrated 18M sulfuric acid (1.0 mL). Attach an air condenser to the vial. Heat the vial to 100 °C for 1.0 hours.

Work-up: Discontinue heating and allow the vial to cool to room temperature. Next place the vial in an ice bath and add a small amount of ice through the throat of the condenser with stirring. Continue this process until crystallization stops or the vial volume reaches about 5 mL. If done slowly enough then the crystals will be large enough to collect by filtration and can be washed with 1.0 mL of concentrated ammonium hydroxide.

Techniques

Quiz ideas

Name three secondary reference sources that would be a good place to find the melting point of 2-methylanthraquinone.



N,N-dimethylbutyramide

Draw and label the ^{1}H NMR spectrum for this compound. Be sure to place peaks at appropriate chemical shifts in reference to one another, and illustrate multiplicity.

Describe the function of ammonium hydroxide in this experiment

Otherwise

Work-up #2: If crystallization does not occur, then proceed with this additional work-up procedure. Cautiously transfer the contents of the vial to a 25 mL Erlenmeyer containing solid NaOH (10 equiv) and agitate until all acid is completely quenched. A complete quench can be confirmed by the addition of Na_2CO_3; its addition should not emit any CO_2 gas if the solution is basic. The quinone can then be extracted with ether, dried over Na_2SO_4 and concentrated by evaporation.

Purification: Recrystallize the product from ethanol or toluene using Norit pellets for decolorization. Dry and determine the weight and melting point. If off, then the resulting anthraquinone can be further purified by sublimation in a 13 x 100 mm test tube as done in Chem 6a. The product should be light yellow in color after sublimation.

Spectroscopy: The percent yield is calculated. IR is obtained. Compare your experimental data (IR and melting point) to that of actual data given for 2-methylanthraquinone. Obtain and interpret an ^{1}H-NMR, MS and ^{13}C-NMR spectrum from your TA. Include the labeled spectra in your notebook. Submit your entire sample in a disposable tared vial to your TA for scoring.

Waste Disposal: IMPORTANT - Syringes do NOT go in the trash. Place syringes in the labeled sharps container! Any residual CH_2Cl_2 is put in a halogenated organic waste container. Non-halogenated organic waste is put into the non-halogenated waste container. Any silica or Na_2SO_4 loaded pipets are dumped into solid waste and the glass placed in a sharps container. Free solid waste (silica, Na_2SO_4) is put into the solids waste container. All aqueous liquids (acetone, ethanol, water) is flushed down the sink after neutralization.

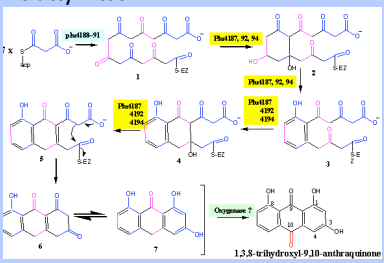
Mechanism: Students should be able to propose one on their own mechanism. It is similar to experiment-1.

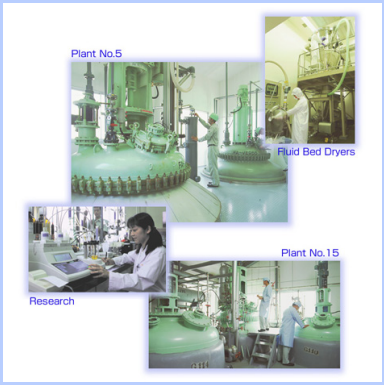
Note, that students are expected to take an exit practical exam which covers all aspects of Chem 6b in the next lab period.

Antraquinone is yellow or tan, water insoluble crystalline powder derived from phthalic anhydride used primarily in the textile and pulp industries.

- It decreases wood consumption
- Reduce hydrogen sulfide emissions
- Reduce chlorine bleach use
- Increase paper strength

The biosynthesis





TA Notes

Please contact the instructor to pick up the exit exam and administer it to your students during the lab period that would follows experiment 15.

Faculty and Staff affiliated with the organic laboratory program.

Armen Zakarian
Liming Zhang
R. Daniel Little
Bruce H. Lipshutz
Craig Hawker
Don Aue
Thomas R. R. Pettus
Javier Read de Alaniz
Elaine G. Merza

We enjoyed having you in Chem 6ab and hope to see you again in Chem 6c where we work on macroscale.

Notebook Submission

Turn your notebook(s) over to your TA before exam week begins for consideration by the instructor.

Chem and Biochem majors

Get to know your organic faculty and find a research job if you are interested.

The organic division strongly endorses the following course electives: Chem 124 (Spectroscopy), Chem 126 (Computational Methods), Chem 127 (Structure and Reactivity), Chem 128 (Organic Reaction Mechanism, Chem 129 (Synthetic Organic Reactions, Chem 199 (Undergraduate research). These courses can be taken in any particular order.

Notes from the Chem Club

The UCSB Student Affiliates of the American Chemical Society is a group that meets bi-monthly to discuss various topics in Chemistry and Biochemistry. Guest speakers often provide information about research, career opportunities and industry, and other aspects that encompass the field. The group also participates in other activities such as the ACS National Convention, National Chemistry Week Celebration, Outreach, and tours. A barbecue is also hosted at the end of the fall and spring quarters as are trips to the ACS meetings. For more information see:

http://www.chem.ucsb.edu/~chemclub/index.html

Check in & out procedures

Pick-up the inventory check list from the TA, which you initial along with your TA. Make sure your clean dry plastic bin contains all the equipment listed. If not, get TA approval and go to the storeroom to replace missing items. There should be no other items or chemicals in your bin when you check in & out. If your equipment is not clean, clean it!

3 Beakers (30, 50, 100 mL)
4- Erlenmeyer Flasks (2X25mL, 2X50 mL)
1 - Filter Flask (125 mL)
3 - Funnels (Büchner, plastic, 60 mL Separatory)
1 - Graduated Cylinder (10 mL)
5 - Pyrex Test Tubes (13 x 100 mm)
2 - Centrifuge Tubes (17 x 125 mm)
1 - Test Tube Brush
1 - Test Tube Clamp
1 - Filter Funnel Adapter
1 - Pasteur Pipet and Yellow Rubber Bulb
2 - Spatulas (micro, semi-micro)
1 - Stirring Rod
1 - Test Tube Rack (Plastic)
1 - Thermometer (150 °C)
1 - Watch Glass (65 mm)
2 - Wash Bottles (plastic)
15 - Vials, shell with plastic cap
4-Conical Vials (2 X 3mL, 1X5 mL)
1 - Claisen Adapter
2 - Condensers (air, water)
1 - Drying Tube
1 - Flask, 10 mL round-bottom
1 - Gas Delivery Tube
1 - Gas Collection Tube
1 - Hickman Distillation Still
1 - Magnetic Stir Bar
1 - Spin Vane Stir Bar
1 ft of polyethylene spaghetti tubing

The campus

The chemistry department

The organic division

The organic laboratory

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