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CHEMISTRY 365 SYLLABUS**Spring 2019****Organic Chemistry Laboratory II**

Classroom: Langseth 307 Dr. Craig P. Jasperse web: http://www.mnstate.edu/jasperse/ Office: Hagen 407J Telephone: 477-2230 e-mail: jasperse@mnstate.edu	Office Hours: M/W/F 9-10:30, 1:00-2:00, Mon 9-10:30, 1:00-2:00 Tues 10:30-12:00, 1:00-2:00 Wed 9-10:30, 1:00-2:00 Thurs: None Fri 9-10:30, 1:00-2:00
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Required Text and Materials:

Room: Langseth 307 (lab)

1) Safety Goggles

2) Lab Manual (print from website, see <http://web.mnstate.edu/jasperse/Chem365/Chem365.html>)

*note: Avoid printing this from university computers/printers using Firefox.

Lab Schedule: SL307	Thursday, 9-11:50	Thursday, 1:30-4:20
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Date	
Jan 17	Cyalume: Chemiluminescence
Jan 24	Grignard Reaction, Part 1
Jan 31	Grignard Reaction, Part 2
Feb 7	Alcohol to Ester; Catalysis; Distillation; NMR
Feb 14	HPLC: High Pressure Liquid Chromatography
Feb 21	Alcohol Unknown (NMR)/Synthesis of Aspirin
Feb 28	Wittig Reaction
Mar 7	No Lab. Spring Break.
Mar 14	Aldehydes and Ketones Unknown/Derivative
Mar 21	Dibenzalacetone by Aldol Condensation
Mar 28	Multistep Synthesis Module Week One
Apr 4	Multistep Synthesis Module Week Two
Apr 11	Multistep Synthesis Module Week Three
Apr 18	No Lab. Easter Break
Apr 25	Amine Unknowns
May 2	Carboxylic Acid Unknown and Titration Catchup, Cleanup, Checkout

Grading Policy:

1. **Attendance:** Laboratory attendance is important! In the event of an absence, you will receive zero points for that experiment. Attending a different session for a given week may be possible upon arrangement.
2. **Individual Lab Scores:** Most experiment will require completion of a lab report, perhaps answers to some questions, and often identification of unknowns. Some of the grade will be based on quality of results, for example successful identification of an unknown, or high yield, or high product purity. Unless notified otherwise lab reports should be completed by the following lab period. For lab reports in which you are required to answer some questions, these will count into the lab report scores.
3. **Write Your Own Lab Report.** While some experiments may be done with a partner, you should keep your own observations and write your report individually, unless told otherwise.
4. Instructor's **evaluation of your laboratory technique and understanding:** This can contribute up to 20% of the total grade. Expect this to be more a grade-lowering factor than a grade-elevating factor.

Tentatively letter grades will be assigned as follows. There will be some + and – grades.

A/A-	(≥90%)
B-/B/B+	(≥80%)
C-/C/C+	(≥70%)
D-/D/D+	(≥60%)

Safety Notes: Noncompliance may result in dismissal from lab and a zero for the week!

1. Wear safety goggles in the organic laboratory.
2. Dispose of chemical wastes in appropriate containers.
3. The impact of the chemicals used in some of these experiments on unborn babies is not fully known. If you are pregnant or become so, I advise you to drop organic chemistry laboratory.

Course Description

CHEM 365 Organic Chemistry Laboratory II (1 credit)

Purification, synthesis, and identification of organic compounds, and the study of organic reactions.

Prerequisite: Chem 355

Student Learning Outcomes/Course Objectives

Students should master the laboratory techniques required for various synthetic reactions, and for the characterization, identification, and purification of various organic compounds. The ability to identify unknowns, including via use of spectroscopy, is an important outcome goal.

Academic Honesty

Cheating will not be tolerated and will be reported to the Dean of your College and the Vice President for Academic Affairs. It may also be reported to the Student Conduct Committee for further disciplinary action. For a full description of the MSUM Academic Honesty Policy, please see the Student Handbook. (<http://www.mnstate.edu/sthandbook/POLICY/index.htm>)

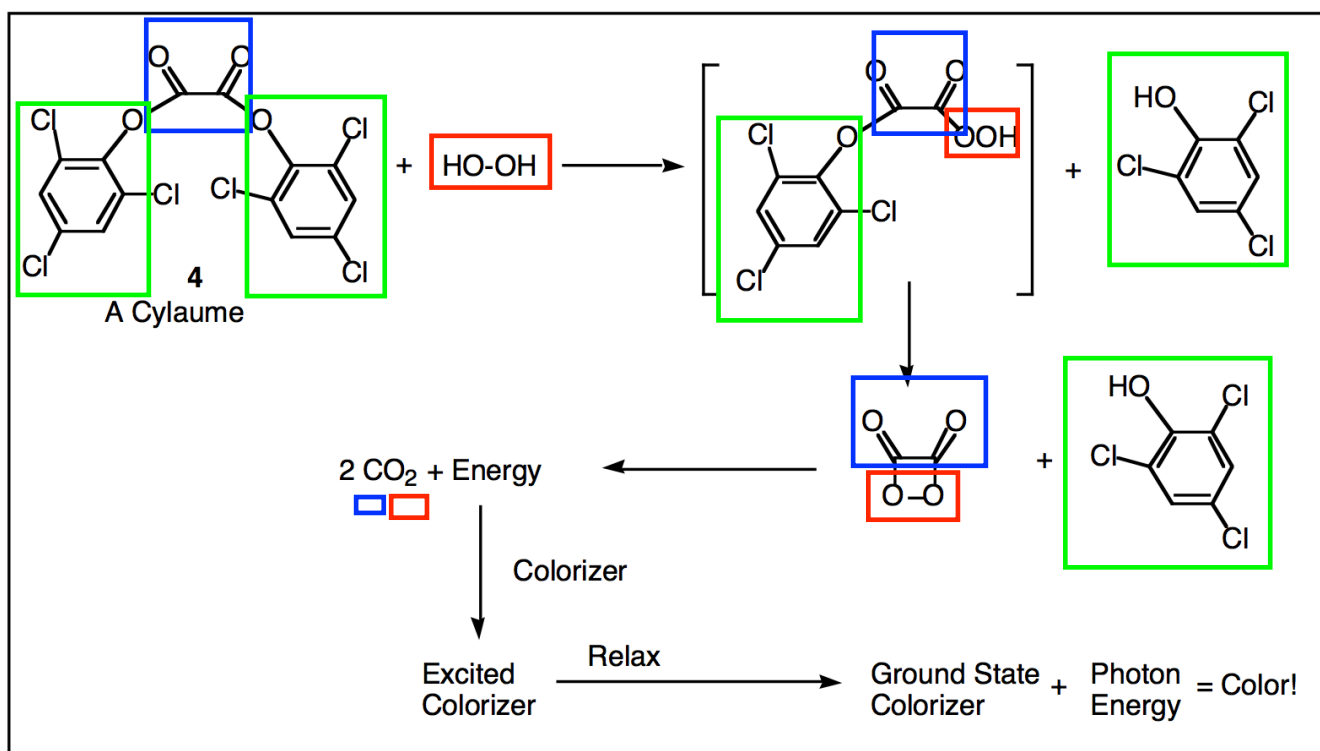
Accessibility: MSUM is committed to providing equitable access to learning opportunities for all. Students with disabilities who believe they may need an accommodation in this class are encouraged to contact the Disability Resource Center (DRC), Coordinator of Disability Services at (218) 477-4318 (Voice) or 1-800-627-3529 (MRS/TTY), CMU 114 to schedule an appointment for an intake. Additional information is available on the [DRC website](http://www.mnstate.edu/disability/): <http://www.mnstate.edu/disability/>

Chemiluminescence: Synthesis of Cyalume and Making it Glow

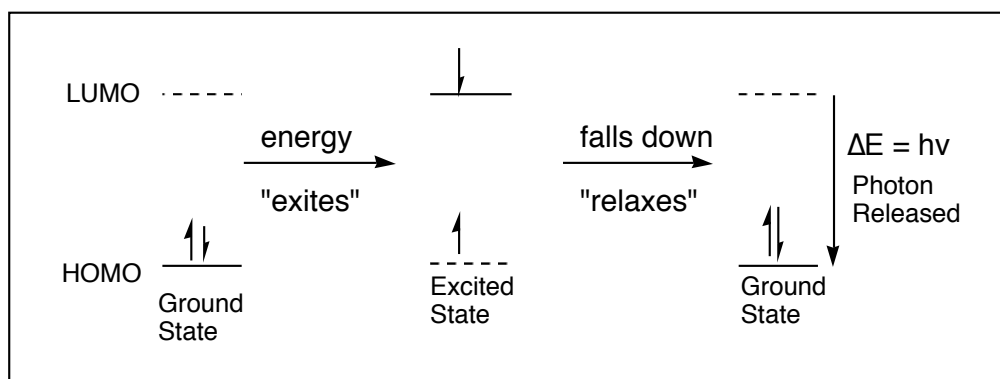
Intro *Chemiluminescence* is the process whereby light is produced by a chemical reaction. The flashes of the male firefly in quest of a mate is an example of natural chemiluminescence. In this experiment we will make Cyalume, the chemical used in “light sticks.” A light stick contains a solution of cyalume containing a trace catalytic amount of a colorizing agent (catalyst). Inside is a sealed vial of aqueous hydrogen peroxide. When you bend the light stick, the hydrogen peroxide vial breaks, the hydrogen peroxide reacts with the cyalume (those are the two stoichiometric reactants), and energy is released. This energy is absorbed/released by the catalytic colorizing agent, resulting in the bright glow of varying color; the same stoichiometric reactants can be used, but when different colorizing catalysts are included, different colors result. Cyalume is an invention of the American Cyanamide Company. In today’s experiment, we will make some cyalume, then make up two glow solutions: one will use a commercial colorizer, and the other will use a home-made colorizer that you will synthesize later this semester. (We’ll use material that students from previous year made.)

Nature of the Energy Release and Glow Formation

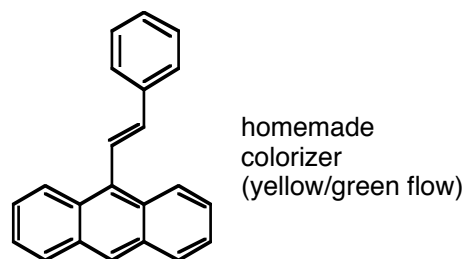
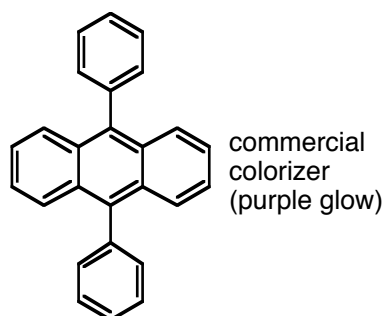
The chemistry that forms the color glow in a light stick is shown below. A cyalume is a symmetric diester, such as **4**. It reacts with hydrogen peroxide (red oxygens) by oxygen exchange. Trichlorophenol (green) is released as each of the two red oxygens of hydrogen peroxide connect to the two blue carbonyl groups. The 4-membered ring “squarate” diester, including the two carbonyls from the original cyalume and the two oxygens from hydrogen peroxide, is unstable due to ring-strain, and fragments to give two molecules of carbon dioxide and energy.



The energy released during the fragmentation “excites” a colorizing molecule that must be present. In other words, an electron in the colorizer gets “excited” from its ground state to an excited state. When it subsequently relaxes back to the ground state, a photon of energy is released. If the energy gap ΔE between the excited state and the ground state is in the visible region of the electromagnetic spectrum, then visible photons of distinctive color are released. This is what causes the bright colors. Since different colorizers have different ΔE , they release photons of different colors.

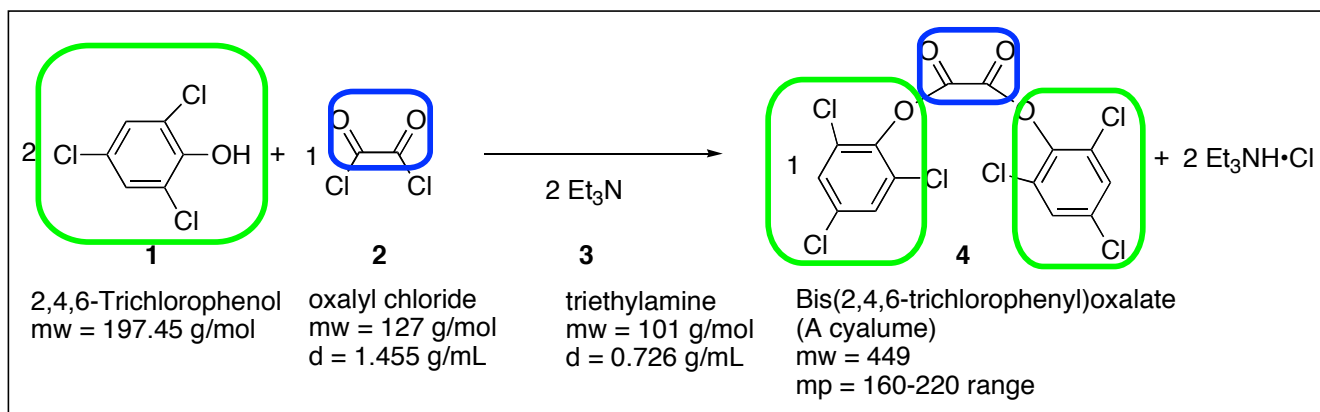


Several things to note about the excitation/relaxation process: 1) The energy gap between the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) determines the photon frequency and the color of the photon released. 2) For most organics, the HOMO-LUMO gap is not in the visible frequency. 3) To have a HOMO-LUMO gap that's in the visible spectrum, extensive conjugation is required. The examples shown below, which are the colorizers we will use, are representative. 4) Only a catalytic amount of colorizer is required. Excitation and relaxation regenerates the original molecule in its ground state, ready to repeat the process.



Cyalume Synthesis Overview

The synthetic reaction is shown below. Oxalyl chloride **2** (the blue reactant) is a symmetric acid chloride that is highly electrophilic and is very reactive because of the chloride leaving group. One oxalyl chloride reacts with two molecules of phenol **1** (green chemical) to give the diester **4**, which is a cyalume. (Not all cyalumes have the same 2,4,6-trichloro substitution pattern on the arene rings.) Triethylamine is an amine base which serves to absorb the two HCl's that get produced during formation of the diester.



Part I: Cyalume Synthesis Procedure

1. Work with partner
2. Use a 25-mL round-bottomed flask containing a medium-sized stir bar (not the really small “flea” stir-bars, use the next larger one...)
3. Add about 0.790 g of trichlorophenol. (Record to three significant figures.)
4. Add 6 mL of toluene (solvent, bp = 111°C). (This is solvent, so need not measure precisely.) (Record observations).
5. Add 0.56 mL of triethylamine by syringe, and swirl. (Bring the solution to the dispensing hood, with both partners to watch. Record observations).
6. Bring to other hood where instructor will inject 0.200 mL of oxalyl chloride. Swirl. The oxalyl chloride is a smelly lachrymator (makes you cry), and needs to be measured with a special syringe in the hood. (Both partners come. Record observations.)
7. After swirling your mixture, attach a reflux condenser, and reflux the mixture gently while stirring for 15 minutes on a hot plate/stir plate to complete the reaction. Note: With no heat, the reaction is too slow. But with excess heat, decomposition can occur. You’d like to have it hot enough so that your toluene can barely boil, but you don’t want to go to extremes and have it boiling super-crazy.
 - Set the hot plate heat setting to 6.
 - Since the hot plate doesn’t make very good contact with the flask, that’s why the hot plate needs to be set that high. Make sure it’s actually contacting the flask.
 - During the fifteen minutes of heating, you could calculate your moles of each of the three reactants, identify which is limiting, and calculate your theoretical yield. You can also write up much of your report.
8. Cool the mixture well, eventually in ice, and collect the solid (both cyalume and triethylamine hydrochloride salt) with a small Buchner funnel and vacuum.
 - Use a bent/curved spatula to try to help drag/scrape as much as possible of your solid material out of the round-bottomed flask.
9. Use about 5 mL of hexane to rinse the flask and rinse the solids in the Buchner funnel. Pour the liquid into the organic waste bottle.
10. Make sure the solid is pretty dry before the next step.
11. Transfer the solid into a beaker, and add 10-12 mL of water. Stir the solution well with a spatula, trying to break up the solid chunks if necessary.
 - Purpose: The triethylamine hydrochloride, being ionic, should dissolve into the water. The cyalume, being organic, should remain insoluble.
12. Filter using a small Buchner funnel.
13. Rinse with an additional 5-10 mL of water.
14. Transfer the cyalume solid into your smallest beaker. Add 2 mL of toluene.
15. Heat on a hot-plate until the toluene achieves a gentle boil. (Hot-plate setting of maybe 4?) Maintain a gentle boil for 2-4 minutes (record observations, for example whether there are brown particles left, or whether it all dissolves...), then remove from the heat and let the solution cool, eventually to ice-cold.
 - Heating a solid that doesn’t dissolve completely is called “**digestion**”. So long as the crystal has some solubility in the solvent, digestion still allows back-and-forth between solid phase and solution, and can frequently still allow impurities to be released to the solvent. In the current case, if you use more toluene in order to get a true recrystallization, sometimes it’s hard to initiate crystal growth, and the loss of product to solvent is frequently very severe.
16. Filter on a Hirsch funnel (smallest ceramic filtration unit). (You’ll need to “mold” your 42.5mm filter paper.)
17. Rinse with 2-4 mL of hexane (one or two pipets worth..).
18. Vacuum thoroughly. (10 minutes should be good.)
19. Take mass. (Do this today, don’t need to wait.)
20. Take out sample for melting point. (Can wait if you wish, but you can do this today if you want.)

Part II: The Chemiluminescent Reaction

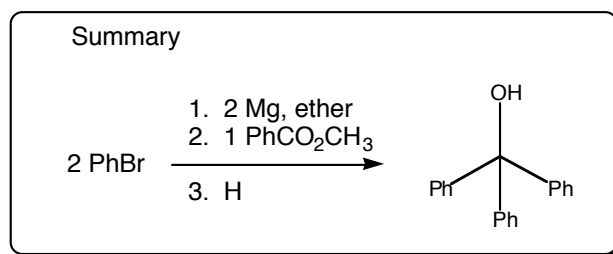
1. The instructor will distributed two vials to each pair of students. Each will have about 3 mg of colorizer, one with the commercial colorizer and the other with the home-made colorizer.
2. Add 0.1g (or more) of cyalume to each vial.
 - 0.1 grams should be enough to get a good glow
 - Excess can be donated to Dr. Jasperse's cyalume jar in the acetone/waste hood
 - I can use your student-prepared cyalume for school demonstrations
 - If you have a good yield, you could also put in >0.1g of cyalume into each of your vials. Probably the reaction will glow longer if you put in more cyalume fuel.
3. Add 5 mL of diethyl phthalate (organic solvent, bp > 298°C) into each of the two vials.
4. Warm the vials on a hot plate. (The heating is not essential. But the initial glow will be more dramatic if the temperature is hot, resulting in faster reaction.) Don't heat too much; you need to be able to carry the vials. Suggestion: hot-plate setting of 3.5, for five minutes.
5. Bring your vials, with their caps, to the dark room. (Room across the hall.) Both partners come.
6. The instructor will then inject 0.35 mL of 30% hydrogen peroxide/water.
7. Screw the covers back on, shake, and observe the pretty lights!
8. Each partner can take one of the vials home. Show them off to your roommates to show that chemistry is fun! (Woo hoo.) Watch to see how long you can still see them glow. Some students have glow for 2 days or even longer..
9. Eventually it's best to bring the vials back and pour the material out in the waste bottle in the hood. However, if you do drain the liquid in the sink or toilet, that's acceptable also.

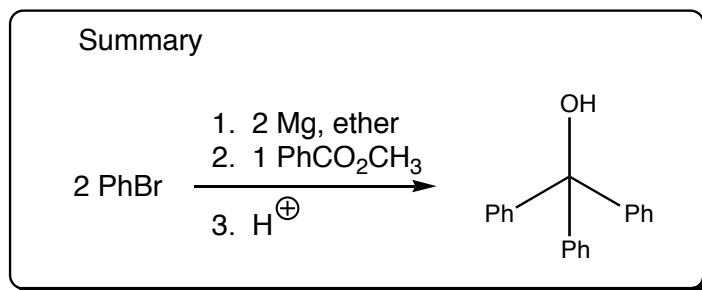
Lab Report

- Write up a standard synthesis lab report for Part I. (Review to make sure you know what the standard synthesis style lab report should look like. Ask instructor if in doubt.)
 - Hand-written work should be OK.
 - Make sure your first page shows the reaction; lists the chemicals used (actual measured amounts); shows the mole calculations for the trichlorophenol, the oxaly chloride, and the triethylamine; shows the work unit conversions involved in the mole calculations; identifies which reactant is limiting; and shows the theoretical yield in grams.
 - Normally the procedure can start on a second page.
 - The data/results should come following the procedure, and should include mp, mass yield, and percent yield.
 - No assigned post-lab questions.
- You don't need to write anything up for Part II. That's just for fun!
-

Standard Synthesis Laboratory Report Format (example): The following layout is standard for a “synthesis reaction” report. Provide the parts and information in the sequence specified.

- Title = Reaction Summary
For an organic reaction, there is no point in having a Worded Title: The chemical reaction is the best title summary of what you did!
- Listing of all Chemicals Used
 - This should include all chemicals used, including solvents.
 - For each chemical, you should include the actual quantity used and measured. For example, with the methyl benzoate you measured a volume by syringe, rather than by weighing on a balance. So you should list the volume you actually used rather than just the weight.
 - For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, you must include more than just the quantity of chemical used. You should also include a conversion from what you measured into the number of moles used.
 - In some cases, there may be considerable roundoff (you needn't keep precise record of the quantity of solvent that was used, for example, or of sodium sulfate drying agent...)
 - If a person was later to repeat your experiment, they should be able to look at this list and know all the chemicals they'd need to have on hand and in what quantities, in order to complete the experiment.
- Calculation of Theoretical Yield
 - Specify which chemical is the limiting reactant
 - Given moles of limiting reactant, calculate theoretical moles of product
 - Given moles of product, calculate theoretical grams of product.
 - Note: Why do this so early in report?
 - First, because it fits in near your mole calculations above.
 - Second, if calculated in advance. as with most research, you know which chemical is limiting and thus must be measured most carefully, but you also know which are in excess and thus need not be measured with equal precision.
 - Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or problematic.
- Writeup of Actual Procedure.
 - For this particular experiment, the “procedure” section will be by far the biggest portion of your report.
 - This should be a concise but detailed description of things, including:
 - What you actually did (even if not recommended or not from recipe)
 - All observations should be included. These include all observed changes, such as:
 - Changes in **color**
 - Changes in **solubility** (formation of precipitate or cloudiness...)
 - Changes in **temperature** (like, reaction became hot...)
 - Formation of **bubbles**
 - Time and temperature details:
 - Whenever you heat something or cool something, the procedure should specify
 - Specify times. Whether you boiled for 5 minutes or 5 hours matters!
 - Writing details: As a record of what actually happened, the report must be written in **past tense**, not **command tense**. (Rather than “Add this”, should read “I added this”, or “I dropped that...”)
 - Use of personal pronouns is accepted in this class. You may use “I” or “we” to simplify writing.
- Product Analysis
 - Any GC, NMR, mp, bp, or TLC information. For this report, mp information must be included. What's required depends on the actual experiment and what data was obtained.
 - Final yield and percent yield information.
- Discussion/Summary. Need not be long, but any conclusions or excuses would go here...
- Answers to any assigned Questions





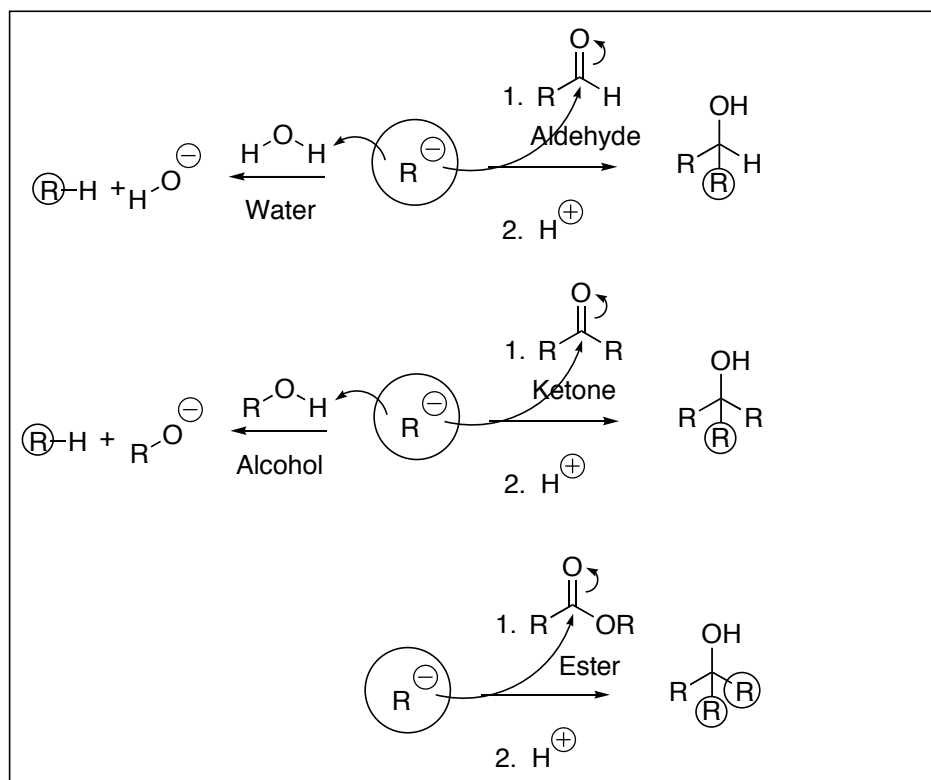
I. Background In 1912 Victor Grignard received the Nobel prize in chemistry for his work on the reaction that bears his name, a carbon-carbon bond-forming reaction by which almost any alcohol may be formed from appropriate alkyl halides and carbonyl compounds. The Grignard reagent RMgBr is easily formed by redox reaction of an alkyl halide with magnesium metal in anhydrous diethyl ether solvent.



The Grignard reagent **can be viewed as an ionic species consisting of carbanion R^-** , with a Mg^{2+} counterion and an additional Br^- counterion. **The carbanion R^- is very reactive, and functions both as an extremely strong base and an extremely strong nucleophile.**

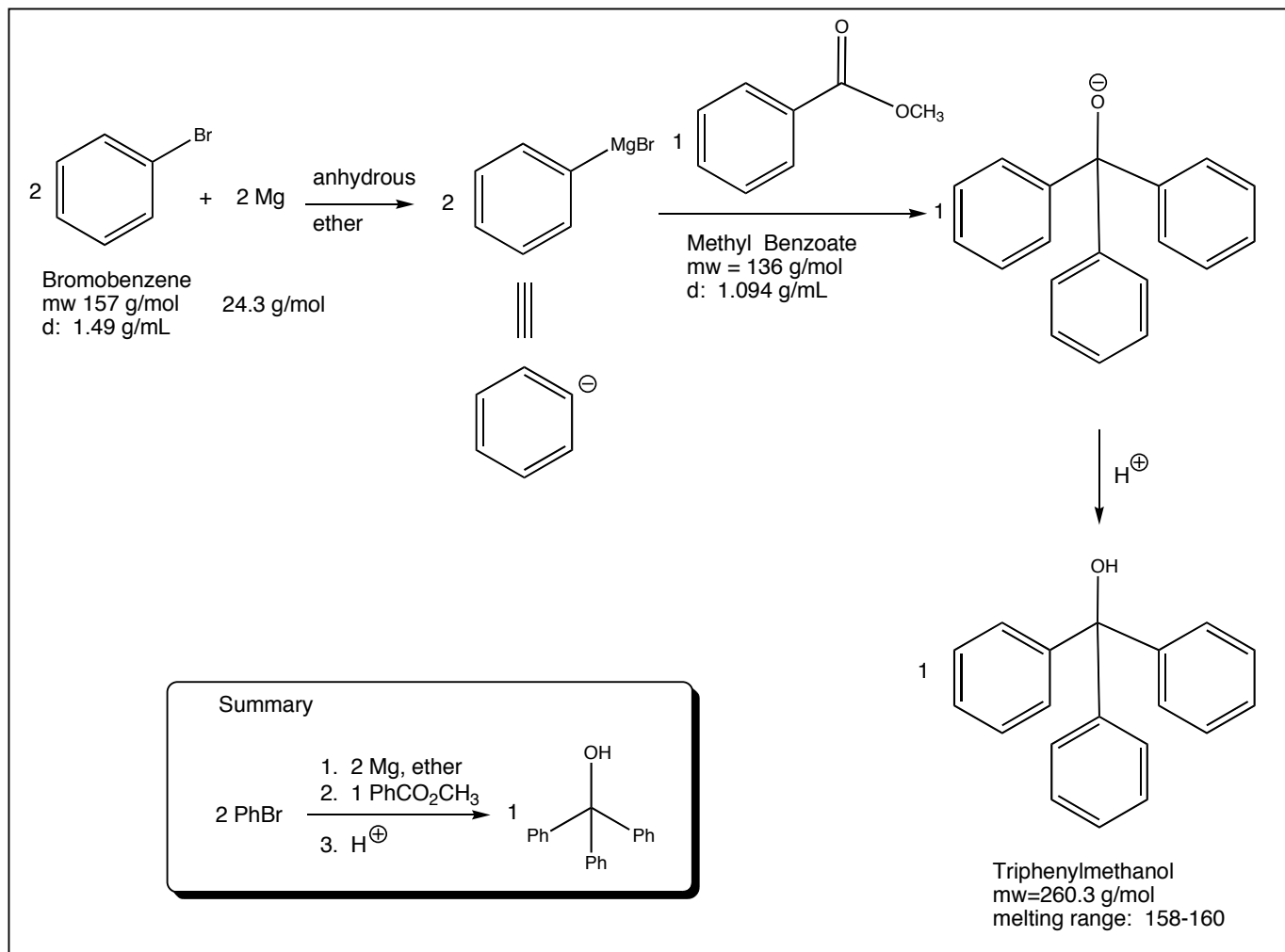
Some of its reactions are shown below.

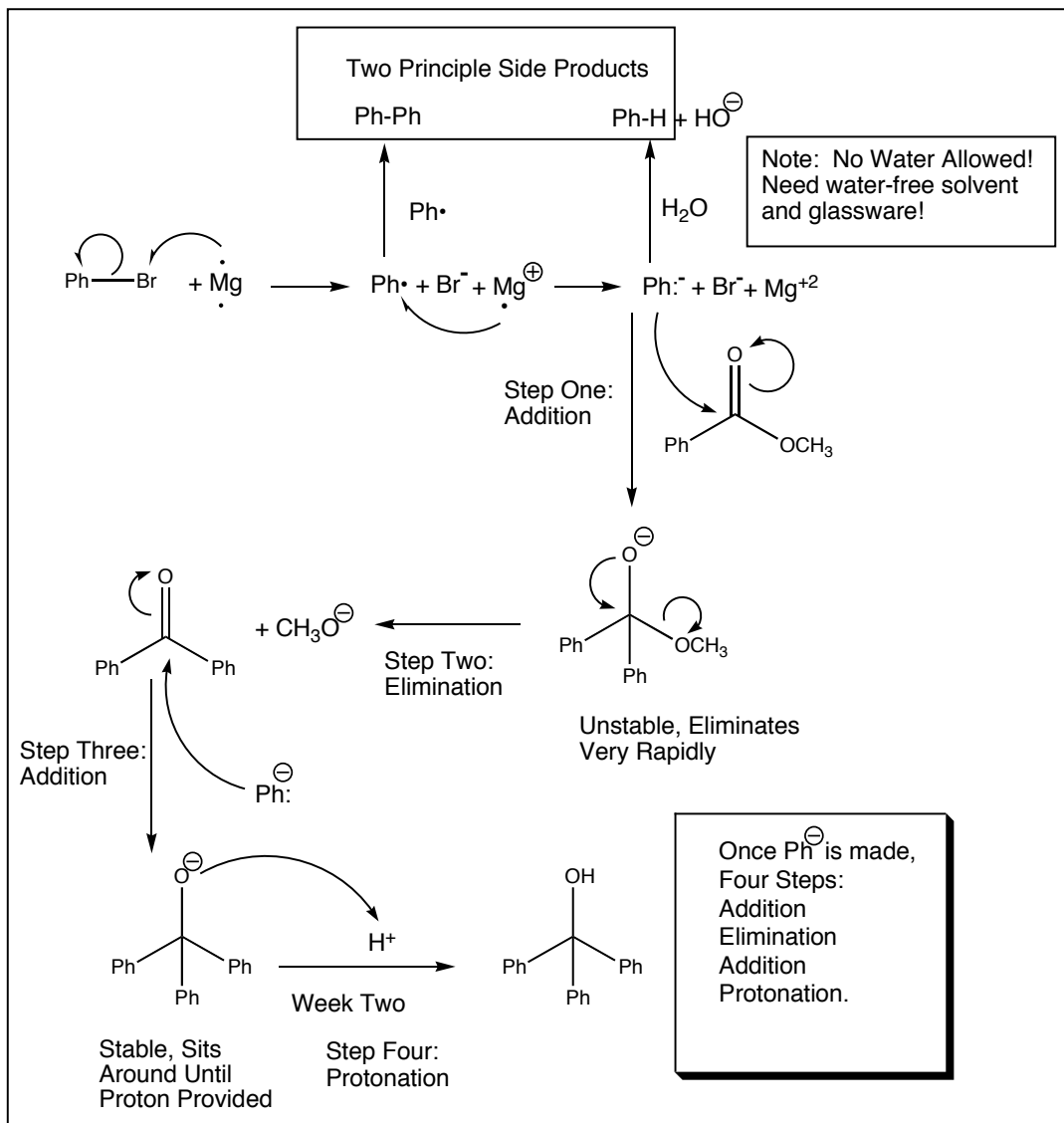
- **It reacts as a strong base with water or alcohols.**
 - Conversion from less stable R^- to more stable HO^- or RO^- is favorable.
- **It reacts as a strong nucleophile with carbonyl groups aldehydes, ketones, and esters.**
 - Conversion from less stable R^- to more stable RO^- is favorable, followed by protonation to give alcohols ROH .



II. Overview of Our Experiment

Our experiment is shown below. During week one we will generate the Grignard reagent (step one) and react it with the ester (step two). During the second week we will neutralize the alkoxide (step three), isolate the alcohol, purify the alcohol by recrystallization, and do product analysis.





The overall mechanism is illustrated above. The carbanion is generated by electron transfer from magnesium metal. The reactive carbanion then attacks electrophilic carbonyl to give an anionic intermediate (step one). This unstable intermediate rapidly eliminates a methoxide anion (step two). The resulting ketone is attacked again (step three). The resulting anion waits patiently until next laboratory period, at which time acid will be added to protonate the anion (step four).

Byproducts and Potential Problems There are two main byproducts and three problems.

- The first side product is biphenyl, Ph-Ph**, which is formed in competition with the Grignard reagent PhMgBr. Following initial electron transfer, the phenyl radical Ph• can either accept another electron leading to the desired carbanion, or combine with another phenyl radical to make biphenyl.
- The second side product is benzene (Ph-H), resulting from protonation of the carbanion.** The carbanion is supremely basic, so if there is any water in the solvent or in the glassware, or if moist air is allowed to enter the reaction mixture, some of the carbanion will be protonated. **Great care is thus required to ensure “dry”, water-free conditions.**
- The third problem is getting the magnesium to actually do the electron transfers!** Pure magnesium is an active metal, so active that any magnesium that has been exposed to air is inevitably coated with a film of magnesium oxide on its surface. This oxide film blocks the bromobenzene from actually contacting active magnesium, and thus prevents the requisite electron transfer. **For a Grignard reaction to work, it is necessary that fresh active magnesium be exposed.** Otherwise no electron transfer from magnesium to bromobenzene can take place, no carbanion can be formed, and no reaction proceeds. We will use two techniques, iodine activation and physical crushing, to activate our magnesium.
- The fourth problem is unreacted starting material.** (Could be the Ph-Br, the Mg, and/or the ester).

III. Procedure: Week One

Note: All equipment and reagents must be dry!

Phase 1: Preparing the Grignard Reagent

1. Dig out the following pieces of glassware: (Instructor will have a demo-display set up).
 - a. 250-mL round-bottomed flask
 - b. "Claisen" two-branched connecting adapter (piece #9 in your kit)
 - c. reflux condenser (piece #12 in your kit)
 - d. separatory funnel with stopper
 - e. drying tube packed with calcium chloride
2. Clamp the 250-mL round-bottomed flask to a vertical rod. Use a clamp with metal grips. (Rubber clamps will melt and stink when subjected to Bunsen-burner flame!) Don't add other glassware yet.
3. Light your Bunsen burner and pass the flame over the flask until there is no more steam visible on the surface of the glass.
4. As soon as the steam is gone from the flask, add the Claisen adapter to the flask and flame dry it as well. (Note: do NOT add the stir-bar until after step 16.)
5. As soon as the steam is gone from both the flask and the adapter, add the reflux condenser to the flask, and flame dry briefly, as best you can. (Do not flame-dry the separatory funnel or drying tube.)
6. While everything is still hot, attach the drying tube into the top of the reflux condenser, add the separatory funnel with its stopper on into the other arm of the Claisen adapter.
 - **At this point, the interior should be entirely closed from wet air getting in. The separatory funnel blocks out one side, and any air coming in through the column must pass through the drying tube.**
7. Weigh out about 2 grams of magnesium metal. (Record weight to at least 3 significant figures.)
8. When the glassware is cool enough to handle, add tubing to the condenser so that you can run a slow stream of tap water through the condenser. Reassemble the array as quickly as possible.
9. When the glassware is cool enough to handle, lift out the condenser and pour in the magnesium, perhaps using folded weighing paper or weighing boat, then replace the condenser as soon as possible.
10. Pour 40 mL of ether into the separatory funnel and put stopper back on.
11. Measure out 9.0 mL of bromobenzene in a graduated cylinder, and add it to the separatory funnel.
12. If he hasn't already done so, ask the instructor to add one small chip of iodine into the separatory funnel.
13. Drain the bromobenzene/ether/iodine solution into the round-bottomed flask.
 - **The iodine serves two functions.**
 - a. **Indicator.** The color will disappear when the magnesium is activated. Until the color goes away, the magnesium won't be able to react with the bromobenzene.
 - b. **Activator.** Iodine is sometimes able to chemically "clean" the surface of the magnesium so that fresh, active magnesium is exposed so that it can do redox chemistry with bromobenzene. However, it doesn't often work!
 - **Make a mental picture of how much magnesium you have to begin with, so you can remember later on for comparison.**
14. Put a jack with a stir-plate underneath your flask. If the redox chemistry of the Grignard reaction initiates, the iodine color will go away, the solution will begin to get hot, there will be some bubbling, and things may become slightly cloudy.
15. If there is no indication of reaction after 1-2 minutes, beg the instructor to come over to crush some magnesium. Note: If yours starts without need for crushing, specifically note this in your write-up.
16. With a medium stir bar ready but not in the flask, ask the instructor to come over and use a glass rod to try to crush some of the pieces of magnesium firmly against the bottom of the flask. This will expose fresh, active magnesium that should be able to initiate the redox chemistry and the formation of the Grignard reagent. Trying to crush very very hard magnesium pieces inside a glass flask is dangerous, though; it's easily possible to punch a hole in the glass. So if somebody is going to poke a hole in your flask, let it be the instructor so he can take the blame! **ADD A MEDIUM STIR BAR AS SOON AS THE MAGNESIUM IS CRUSHED.**

- The reaction should be so exothermic that it will be self-boiling for some time. Note the position of the "reflux ring". Within 10 minutes, the boiling will probably moderate. Turn the hot-plate heat setting to 5 in order to maintain a good rate of boiling.
- Maintain boiling for one hour.
 - Note: notice how the reflux condenser works. The bottom flask can be boiling hot (which facilitates maximum reaction rate), but the condenser enables you to liquify and recycle all of the boiling solvent.**
 - Keep good procedural and observational notes of everything that you see and do!**

Phase 2: Things to do during the Grignard Hour...

Once the reaction is clearly going, prepare for Phase 3, in which you will add the methyl benzoate ester electrophile to the carbanion that you are making. And do the calculations that you will eventually need to include in your report.

- Calculate what volume (in mL) it will take to add 5.0 grams of liquid methyl benzoate (density = 1.094 g/mL).
- Calculate the number of **moles** used for magnesium, bromobenzene, and methyl benzoate.
- Calculate the **overall theoretical yield** (in grams) for your final product of next week, triphenylmethanol (mw = 260 g/mol).
 - To do this, you must **first identify** which of the three reactants (Mg, PhBr, or PhCO₂CH₃) is the **limiting reactant**
 - To do this, you must factor in the overall stoichiometry, which is not all 1:1:1:1. (Given your calculated moles of Mg, how many moles of Ph₃COH could you make? Given your calculated moles of PhBr, how many moles of Ph₃COH could you make? Given your calculated moles of PhCO₂CH₃, how many moles of Ph₃COH could you make?)
 - In calculating theoretical yield for a multistep reaction, theoretically every step will be perfect. (We know otherwise, but we're talking theoretical yield here...) Thus you don't need to calculate or measure quantities for any intermediates. Your limiting reactant and theoretical yield should consider only original reactants and final product, all things which are easily quantified.
- After the Grignard solution has reacted for one hour, check to see how much magnesium is left. Any qualitative estimate of about how much is left? (None? 10%? 50%?)
 - What implications might this have on your possible yield? Is it necessary for all of your magnesium to have reacted completely in order to get 100% yield? Or could you get 100% yield even if some of your magnesium remains unreacted?

Phase 3: Reacting the Grignard Reagent with the Methyl Benzoate

- The following two steps can be done in advance, during the last ten minutes of your reaction....
- Add 15 mL of ether to your separatory funnel. (Stopcock closed).
 - Add 5.0 grams of methyl benzoate to your separatory funnel by syringe. (Remember, you calculated this volume in Phase 2...) (Return syringe to the hood! ☺)
 - After the hour is up, let the reaction cool down so that it's not much hotter than room temperature. (Add some ice to a metal pail. Applying an ice bath in the metal pail for one minute might help cool.)
 - While magnetic-stirring, and with the solution in the flask not much hotter than room temperature, drain the ester/ether solution into the round-bottomed flask, slowly so that the reaction doesn't overheat too much. If things start to boil too hard, pause/slow the addition and/or apply the cold bath.
 - Record your observations!
 - After everything is added, keep stirring for an additional 20 minutes, during which time the exotherm and boiling should subside. If the reaction is still hot after 20 minutes, cool it with the ice bath.
 - Remove all the glassware from the top of the round-bottomed flask, and stuff in a rubber stopper.
 - Note: it is essential that the solution isn't hot when you do this. If it is, then when it cools it will create a vacuum and suck the stopper in...)
 - Note: it is essential that the vigorous exothermic reaction is done before you stopper the flask. Otherwise if stirring or further reaction generates enough heat, it will cause the ether to boil and blow the stopper off!
 - Using your round-bottomed flask holder, stash the round-bottomed flask with the chemicals and the stopper into a secure spot in your drawer, and wait till next lab to finish!

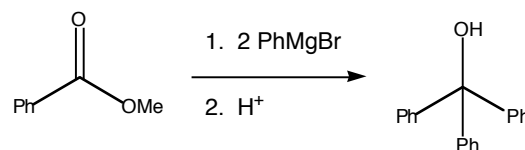
IV. Procedure: Week Two

1. Record your observations for what your mixture looks like at this point.
2. Remove the stopper, and add about 30 mL of ether, 40 grams of ice, and 50mL of 2M sulfuric acid
 - The acid will react exothermically with both the anion and unreacted magnesium. The ice is there simply to absorb the heat.
3. Swirl, and use a microspatula to break up the big chunks and to free up the stir-bar. Then use magnetic stirring to try to help dissolve things.
4. In the process, three things should happen:
 - The anion should be protonated, giving the neutral organic alcohol product. This should partition into the organic ether layer.
 - Magnesium salts should be ionic, so they should partition into the aqueous layer.
 - Unreacted leftover magnesium metal will react with the acid to give molecular hydrogen. That's what causes the bubbling. ($1 \text{ Mg} + 2 \text{ H}^+ \rightarrow \text{Mg}^{2+} + \text{H}_2 \text{ gas}$)
5. Pour the mixture into your separatory funnel. (The magnesium doesn't need to be totally dissolved...)
 - Note: pour as much of your solution in as can fit. The water layer will settle to the bottom. Drain off some water layer to make more space, so that you can add the rest of your original mixture.
6. Pour an additional 10 mL of sulfuric acid and 30 mL of ether into your flask, swirl to try to dissolve up anything left on the walls, and pour into the separatory funnel. (These need not be measured, just pour some in approximately.)
7. Drain off the bottom aqueous layer into a beaker.
8. Add another 20 mL of sulfuric acid into the separatory funnel, shake it up, and drain off the aqueous layer again. Pour the combined aqueous layers into the aqueous waste bottle in the hood.
9. Prepare a sample of the "crude" solution for GC-MS analysis. Take out one pipet from your organic phase and place it into a GC-MS vial (should be at least 0.3mL deep) and submit to the GC-MS queue.
10. Drain the organic layer from the separatory funnel into a 250-mL Erlenmeyer flask.
 - You will see some solid product on various surfaces after this. Wherever ether with product went, the ether will evaporate and leave product behind. You can recover this product with additional ether rinse. Fortunately, the theoretical yield is so high that small amounts of lost product don't add up to much.
11. Add about 5 grams of sodium sulfate to "dry" the ether layer. Add additional scoops if there is no dry granular sodium sulfate left, and is instead all clumped up (indicating that there may be too much water for the sodium sulfate to handle).
12. Plug your long-stem funnel with a little glass wool
13. Pour the ether solution through the glass-wool-plugged funnel into a different 250-mL Erlenmeyer flask.
 - The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask.
 - Rinse your original flask and the sodium sulfate with an additional portion of ether.
 - At this point, your solution should be free of water and of magnesium salts. Other than the ether solvent itself, you should have nothing but the desired product and organic contaminants.
14. Make a TLC plate with five pencil marks for five tracks ready:
 - a. Authentic biphenyl
 - b. Authentic methyl benzoate
 - c. Crude mixture
 - d. Purified mixture
 - e. Post-crystallization solvent
15. Take a capillary droplet from your mixture, and put it on the "crude mixture" spot C. (Some capillaries should be on the end bench across from the liquid-dispensing hood). Take droplets from the authentic biphenyl and methyl benzoate bottles in the hood and apply them as well, to spots A and B. Save the plate until you've finished purifying the product, at which point you'll be able to apply your last spots D and E.

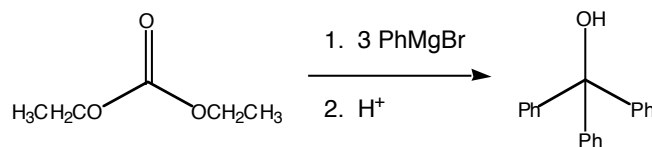
16. Add 25 mL of “ligroin” solvent (all hydrocarbons, mostly hexanes, but not pure) to your ether solution. The product is more soluble in ether than in hydrocarbons, so you are essentially adding some “bad solvent” to facilitate a mixed solvent recrystallization.
17. Add a boiling stick to your organic solution
18. Now heat your solution on a hot plate. A power setting around 5 might be a good starting guess?
19. Boil the solution down to 20-25 mL or so, then add another 20 mL ligroin and again boil down to around 25 mL. (Crystals may start to form before this, depending on your yield. But if you stop boiling as soon as the first crystals form, you’ll still have too much solvent and will get a low yield.)
20. Remove the boiling stick, remove from heat and put a beaker or watch-glass over the top to prevent evaporation, and let cool slowly to grow your crystals, first to room temperature and then to 0°C.
 - Note: You need to have some solvent left for the impurities to swim in! If it looks like your solvent is less than 25 mL, add additional ligroin and swirl.
21. After the mixture has cooled, prepare a sample of the “mother liquor” (the liquid above the crystals) for GC-MS analysis. Take out one pipet from your solvent phase and place it into a GC-MS vial (should be at least 0.3mL deep), dilute with a comparable volume of ether and submit to the GC-MS queue following step 22.
22. Use a capillary to take a droplet from your GC-vial of “mother liquor” solution, and put it on the tlc plate in the “post-crystallization solvent” spot E.
23. Filter your crystals with your medium Buchner funnel (using vacuum as usual).
24. Rinse with 15 mL of cold ligroin.
25. Make a solution of the “pure” product by transferring a spatula tip of your crystals (needn’t be very dry) to a GC vial, maybe half of the bottom should be covered, and add some ether. Then take a capillary and put a droplet of this “purified” solution (it doesn’t need to be dissolved) onto your tlc plate in the “purified” spot D.
 - The solid probably won’t dissolve completely, just take from the solution phase.
26. Submit your “pure” to the GC-MS queue.
 - Upon completion, comparing the GC of the purified crystals to the “crude” and “mother liquor” GC’s that you took earlier will let you see how much your purity improved as a result of the crystallization process; how some product remained dissolved in the “mother liquor”; and how impurities predominantly remained in the “mother liquor”.
 - Based on retention times and comparison to the GC-with-labelled-peaks the instructor gave you, you should be able to identify whether you had biphenyl or methyl benzoate in your crude mix.
 - The GC’s will need to be attached in your lab report, and what conclusions or observations can be made from them will need to be discussed in your lab report.
27. Run the tlc in designated solvent (10% ethyl acetate/hexane), and analyze by UV and the “dip” solution.
 - Mark down the results, with the following questions in mind:
 - Is biphenyl present in the crude mix (lane C)? In the purified material (lane D)?
 - Is methyl benzoate present in the crude mix (lane C)? In the purified material (lane D)?
 - Any other side products in the crude (lane C)?
 - Did recrystallization purify the material (lane D versus lane C)?
 - Did most impurities in crude lane C end up in the crystal (lane D) or the solvent (lane E)?
28. Take a melting range on your final product. (Should melt above 150°, so heat accordingly)
29. Get your final mass.
30. Lab Report: Write a “standard synthesis-style” lab report. A summary of what a standard synthesis-style lab report should look like is described in more detail a few pages after this. This must include calculations, observations, results, and analysis, in addition to answers to the assigned post-lab questions.
 - The assigned post-lab questions are on the following page. You can perhaps answer some or all of them on the page, or else answer some or all of them on attached sheet(s) of paper.
 - This two-week lab and two-week lab report will count for 20 rather than 10 points.
 - For this report (and this report only!), you may submit a “team” report with your partner, if you wish. If so, each student should attach answers to the post-lab questions. Many of you may find it easier to just write your own individual lab report. So team versus individual, whichever you prefer!

Assigned Questions, Grignard Lab

1. Draw a detailed, step-by-step mechanism for the reaction you actually did: (on attached sheet?)



2. Triphenylmethanol can also be prepared by the reaction of PhMgBr with diethylcarbonate ($\text{CH}_3\text{CH}_2\text{O}$)₂C=O, followed by H^+ workup. Draw a detailed, step-by-step mechanism for the following reaction: (on attached sheet?)

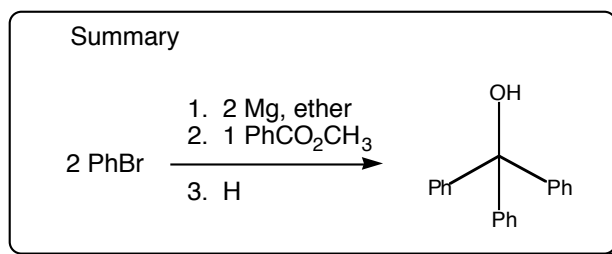


3. If you hadn't bothered to flame-dry your glassware or used a drying tube, what byproduct would have formed?
4. If the methyl benzoate you used had been wet (contained water), what byproduct would have formed? (Note: the answer for this problem may or may not be the same as for previous problem.)
5. Your yield was considerably less than 100%. Discuss where you think things might have come up short. You may wish to differentiate reaction things (reasons or evidence that you didn't have complete chemical conversion) versus isolation things (reasons or evidence that you didn't isolate all of the product that was actually made chemically). (It's possible that your TLC may support or disprove some possible explanations.)
6. Given the quantities of chemicals used in this recipe, one could conceivably have gotten a 100% chemical yield without having completely reacted all of the magnesium, or without having completely reacted all of the bromobenzene. But it would not have been possible to get 100% chemical yield if the methyl benzoate didn't react completely. Explain.

Standard Synthesis Laboratory Report Format: The following layout is standard for a “synthesis reaction” report. Provide the parts and information in the sequence specified.

1. Title = Reaction Summary

For an organic reaction, there is no point in having a Worded Title: The chemical reaction is the best title summary of what you did!



2. Listing of all Chemicals Used

- This should include all chemicals used, including solvents.
- For each chemical, you should include the actual quantity used and measured. For example, with the methyl benzoate you measured a volume by syringe, rather than by weighing on a balance. So you should list the volume you actually used rather than just the weight.
- For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, you must include more than just the quantity of chemical used. You should also include a conversion from what you measured into the number of moles used.
- In some cases, there may be considerable roundoff (you needn't keep precise record of the quantity of solvent that was used, for example, or of sodium sulfate drying agent...)
- If a person was later to repeat your experiment, they should be able to look at this list and know all the chemicals they'd need to have on hand and in what quantities, in order to complete the experiment.

3. Calculation of Theoretical Yield

- Specify which chemical is the limiting reactant
- Given moles of limiting reactant, calculate theoretical moles of product
- Given moles of product, calculate theoretical grams of product.
- Note: Why do this so early in report?
 - First, because it fits in near your mole calculations above.
 - Second, if calculated in advance, as with most research, you know which chemical is limiting and thus must be measured most carefully, but you also know which are in excess and thus need not be measured with equal precision.
 - Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or problematic.

4. Writeup of Actual Procedure.

- For this particular experiment, the “procedure” section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
 - What you actually did (even if not recommended or not from recipe)
 - All observations should be included. These include all observed changes, such as:
 - i. Changes in **color**
 - ii. Changes in **solubility** (formation of precipitate or cloudiness...)
 - iii. Changes in **temperature** (like, reaction became hot...)
 - iv. Formation of **bubbles**
 - Time and temperature details:
 - v. Whenever you heat something or cool something, the procedure should specify
 - vi. Specify times. Whether you boiled for 5 minutes or 5 hours matters!
- Writing details: As a record of what actually happened, the report must be written in **past tense**, not **command tense**. (Rather than “Add this”, should read “I added this”, or “I dropped that...”)
- Use of personal pronouns is accepted in this class. You may use “I” or “we” to simplify writing.

5. Product Analysis

- Any NMR, mp, bp, gc/ms, TLC information. For this report: Crude vs recrystallized mp; crude vs recrystallized GC/MS, and TLC information.
- Crude and Final yield and percent yield information.

6. Discussion/Summary. This will need to be significant for the Grignard lab. What do GC and TLC data indicate about purity prior to recrystallization? After? Was the crude material pure? Was all of the methyl benzoate converted to product? Was biphenyl formed as a side product? Were there additional side products? Did the recrystallization clean things up well? Was some of the product lost to the recrystallization solvent? Why did your yield decrease from crude to recrystallized, and what are key reasons why you didn't get 100% yield? (These are just some suggested ideas to deal with.)

7. Answers to any assigned Questions

Basic GC-MS Operation Compressed Draft 3 For Chem 355 Organic Unknowns Lab

Note: The following assumes that the hydrogen and compressed air gases have been turned on; that the machine has been warmed up; that the gc/ms program has been opened; that an appropriate “method” and “sequence” has been selected; and that Jasperse will shut things down.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared and started a “sequence” (“Chem355 Unknowns..”, or “Nitration” or “Grignard..” or “Esters” for example), but you are trying to add your sample to the lineup.

1. **If you’re first in line, get Jasperse to come and help.**
 - **Add your sample to the back of the line in the autosampler.**
 - Do NOT leave any open holes (unless the sample belonging in that hole is being sampled.)
 - Filling a “sample-is-in-the-injector-tray” hole will cause a system freeze. When the machine tries to put the injection sample back, it will have no place to go.
 - **Open “edit sequence” by clicking the “edit” icon on the yellow panel low on the computer screen.**
 - This will open a spreadsheet that you can edit.
 - Add your names in the “sample” box that goes with your vial number.
 - **Click OK.** Note: if you don’t click “OK”, the machine will freeze at the end of the current run. NEVER leave the spreadsheet page open unless somebody behind you is going to close it.

Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.

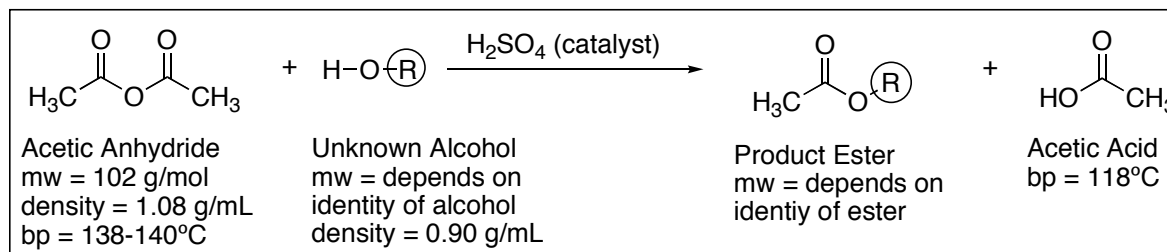
- Note: data analysis can be done while acquisition is ongoing.
- Note: this assumes that the “**gcms data analysis**” software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says “Enhanced data analysis-ADEFAULT-RTE.M..”, or “Grignards”, or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)

1. **Open a data file using the left mouse button to double click.**
 - Your data file should be within the folder Organic Lab within the Data folder.
 - Data file will have the names “Vial-1” or “Vial-2”, so **remember which vial was yours.**
2. **Printing GC Graph, % report, and retention times: Click Method>Run Method**
 - Repeat as many times as needed to provide prints for each student in your group.
3. **Printing Mass Specs: Click the 2nd Hammer icon.**
 - Click the 2nd hammer icon as many times as needed to provide prints for each student in group.
 - Note: You don’t need to wait for a print to finish before clicking the hammer again. If you’ve got 5 partners, just click the hammer five times and the prints will come out one by one....

Library Matching: With a data file open (as described in #3 above):

4. **Right mouse double-click on a peak in the top window** to get its individual mass spectrum to appear in the lower window.
5. **Right mouse double-click on the mass spectrum to get a library search results**
 - Note: the library searches aren’t perfect and don’t always find the very best structure match

ALCOHOL TO ESTER
Acid-Catalyzed Esterification of an Unknown Alcohol



Summary: You will be given an unknown alcohol, you will convert it to an ester, and you will identify both the original alcohol and the derived ester using boiling point and H-NMR.

Some Learning Goals:

1. Observe the dramatic impact of acid catalysis
2. Understand the construction of esters
3. Review the distillation process
4. Use NMR combined with boiling point to identify the product ester

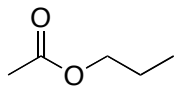
Procedure: NMR of reactant: Prepare a proton NMR on your starting alcohol by injecting about 0.07 mL into an NMR tube, followed by about 0.8 mL of CDCl₃. Submit to the NMR queue. (Instructor: experiment used is "Proton 8".)

Reaction: To a 50-mL round-bottomed flask, add your tiniest stir bar. Take to hood area. Add 7.5 mL of acetic anhydride via syringe, and directly add 5.0 mL of an unknown alcohol via syringe. (Measure as precisely as possible. Notice that nothing happens.) Back in hood, attach a Claisen adapter to the flask. Place a thermometer adapter with a thermometer in the main arm of the Claisen adapter so that the thermometer point is immersed in the liquid (but not so deep that it interferes with the stir bar.) Place a reflux condenser in the side arm of the Claisen adapter. Note that no exotherm or reaction has occurred. Then remove the Claisen adapter and add two drops of concentrated sulfuric acid (may be strong exotherm). Rapidly plug the Claisen adapter (with thermometer and condenser) back into the flask, and magnetically stir the solution while checking the thermometer to see if the temperature jumps. After the internal temperature has reached its maximum, wait an additional 3 minutes before beginning workup.

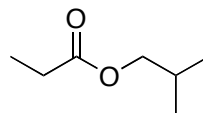
Workup: Pour the mixture into a separatory funnel, and use a 25-mL ether rinse to aid the transfer. Add some solid ice (around 15-20g). Extract the acids and unreacted acetic anhydride by adding 20-mL of NaOH solution. Be sure to shake things up vigorously, let settle, and then drain the lower aqueous layer into a beaker. Add a little more ice, another 20-mL of NaOH, shake, settle, and again drain the aqueous layer into the same beaker. Repeat this process a 3rd time. Pour the organic layer into an Erlenmeyer flask and rinse the separatory funnel with an additional 5mL of ether. Dry the ether solution over anhydrous sodium sulfate, then filter the solution (use a long-stemmed funnel with a little glass wool) into a clean, dry, 50- or 100-mL round-bottomed flask. Add a tiny stir bar.

Distillation: Have two 125-mL Erlenmeyer flasks (**A** and **B**) ready, with **B** pre-weighed. Distill (simple distillation) the ether and then the product. The ether will boil off at relatively low temperature (<95°) and should be collected in flask **A**. After the temperature has surpassed 100° allow 5 more drops, then switch to flask **B** to collect the ester. (The 5 drops rinse off ether still in the condenser). For samples C,D,E some glass-wool insulation will be needed, get instructor. Record the "plateau" temperature at which most of your ester boils off. Remove the heat/jack/hot-plate as soon as high-boiling ester stops dripping steadily. (Don't boil dry; heat too long causes insoluble black material to "burn" onto the flask.)

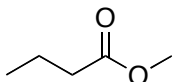
Analysis: Weigh your product ester in flask **B**. Prepare and submit a GC-MS for **B** by adding one drop and diluting with a pipet of ether. Prepare and submit an NMR for **B** by filling the skinny end of a long pipet to about 1-2cm, shoot that into your tube, rest the pipet inside the NMR tube, and then use 0.8 mL of CDCl₃ to dilute/rinse through the pipet directly into the NMR tube. Between the bp information about the product ester and the NMR information about the alcohol and/or product ester, determine the structure of both the product ester and the starting alcohol.

Ester Candidates

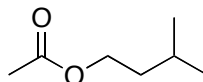
Propyl Acetate, 100-105° ± 10°



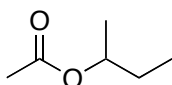
Isobutyl Propionate, 132-147°



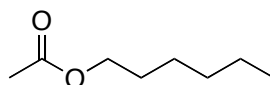
Methyl Butyrate, 100-105° ± 10°



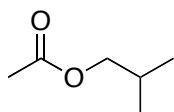
Isopentyl Acetate, 132-147°



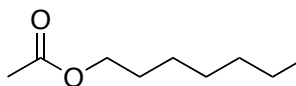
s-Butyl Acetate, 112-120°



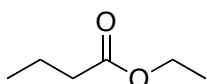
Hexyl Acetate, 167-177°



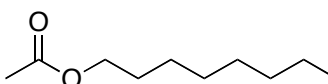
Isobutyl Acetate, 114-120°



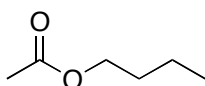
Heptyl Acetate, 187-197°



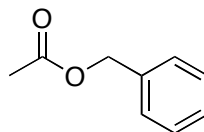
Ethyl Butyrate, 117-125°



Octyl Acetate, 202-220°



Butyl Acetate, 114-126°



Benzyl Acetate, 202-220°

Lab Report: This week, we'll skip the usual procedure writeup. Instead, report or attach:

1. Mass yield of collection **B**.
2. Boiling range of ester
3. H-NMR spectra of starting alcohol.
 - See <http://web.mnstate.edu/jasperse/Chem365/H-NMR%20Interp%20Short.doc.pdf> for some interpretation tips.
4. H-NMR spectra of product ester(s). (Instructor will use this to help assess product purity)
5. GC chromatogram of your distilled product. Graph/% Report only, not mass spec.
6. **Identity of the ester you made**. Key clues are the boiling point, the NMR(s), and the identity of the acetic anhydride reactant.
7. Identity of the alcohol you began with. (Based on your product ester and/or your NMR.)
8. Calculate the % yield [Note: this depends on your alcohol and ester structures and on their molecular weights.] Assume each starting alcohol had a density of 0.90 g/mL for your volume-mass-mole calculation. (This is not exactly true, but close enough, and simplifies.)
 - tip: To determine the theoretical, yield, you'll need to figure out the molecular weight of both your alcohol and your product ester in order to do mass/mole interconversions.

Student Name:

1. Alcohol Letter:

2. Ester Identity: (picture, don't need name) mw of Ester:

3. Alcohol Identity: (picture, don't need name) mw of Alcohol:

4. GC Retention time for Ester:

5. GC purity for Ester:

(Note: the GC ignores low-boiling components, so the purity level shown does not consider contamination by ether, acetic anhydride, or acetic acid.)

6. Boiling Range of Ester:

7. Mass Yield of Ester:

8. Theoretical yield: (**show your work**)

9. % Yield:

10. Attach your NMR's, for both starting alcohol and product ester collection **B**, or else write the name of the partner to whose report they are attached:

11. Instructor only: does the product ester NMR show good purity?

Basic GC-MS Operation Compressed Draft 3 For Chem 365 Organic Unknowns Lab

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Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.

- Note: data analysis can be done while acquisition is ongoing.
 - Note: this assumes that the "**gems data analysis**" software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says "Enhanced data analysis-ADEFAULT-RTE.M...", or "Grignards", or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)
6. **Open a data file using the left mouse button to double click.**
 - Your data file should be within the folder Organic Lab within the Data folder.
 - Data file will have the names "Vial-1" or "Vial-2", so **remember which vial was yours.**
 7. **Printing GC Graph, % report, and retention times: Click Method>Run Method**
 - Repeat as many times as needed to provide prints for each student in your group.
 8. **Printing Mass Specs: Click the 2nd Hammer icon.**
 - Click the 2nd hammer icon as many times as needed to **provide prints for each student in group.**
 - Note: You don't need to wait for a print to finish before clicking the hammer again. If you've got 5 partners, just click the hammer five times and the prints will come out one by one....

Library Matching: With a data file open (as described in #3 above):

9. **Right mouse double-click on a peak in the top window** to get its individual mass spectrum to appear in the lower window.

10. Right mouse double-click on the mass spectrum to get a library search results

Note: the library searches aren't perfect and don't always find the very best structure match.

User's Guide to NMR: General

- For help, see Dr. Jasperse, Hagen 407J, phone 477-2230

Draft 10/28/15

1. Add sample to a Spinner/Turbine

2. **Adjust depth** by placing the turbine into the golden depth finder

3. Load sample/turbine into autosampler.

- Press the round white **Access Request Button** on the panel below the sample trays/doors
- **Wait until "status" light turns to a solid yellow, and the message panel reads "door unlocked"**

4. Opening Program on Computer: Usually already open, and usually to correct "operator"

- If not open: Operator: Should be your class or research group Password: none.
- To switch operator, click **Logout** from submit mode and select the correct operator

5. "Submit" vs "Spectrometer" modes: New Study/Submit Queue to submit; Spectrometer to print/view

- Click "**New Study**" button (lower left) to jump from Spectrometer to Submit mode
- Click "**Cancel**" button (lower left) to exit Submit queue and go to Spectrometer:

6. Experiment Selection (from within Submit mode). Usually preselected for organic labs.

- If not already in New Sample/submit queue mode, push **New Study** button on lower left
- **Proton8** is the normal H-NMR experiment, under the "UserStudies" folder
- For some classes/operators, **Proton8** has been set to open by default, since most NMR's are regular H-NMR's
- Add experiments as needed from the Experiment Selector.
- To **edit or delete**: **right click** on experiment and select "Open Experiment" or "Delete Experiment"

7. 3 Step Submission (assuming the experiment already specified, and still/already in Submit mode).

- Fill Sample Name** (for both computer filing and printout recognition)
 - Click Sample Spot**: Click on the button showing your sample site. (Remember/record! ☺)
 - Submit**: clicking the **red Submit** button on the lower left side.
- **Note**: Can repeat this 3-step sequence for new samples/new students, if running same experiment
 - **Comment box**: (can add comments for the paper printout). (Control C to cut and Control K to paste)
- Other submission options** of possible use for advanced labs, research, or offsite Concordia users:
Solvent; **Autoplot** (offsite Concordia users should turn this off); **Email**; **Email Address** (offsite Concordia users should set this correctly!☺); **Lock**: (with non-deuterated solvent run unlocked),
Shim (with non-deuterated solvent run 1H PFG); **Tune**

8. Opening Completed Samples for Printing and Processing. ("Spectrometer Mode" required)




- Must be in "Spectrometer" mode, not "Submit" mode.
 - If in submit mode, "Submit" button will display (lower left). Click "**Cancel**" to exit Submit mode.
 - In "Spectrometer" mode, must **have "Zones" map displayed** (96 sample nodes show). Click on little circle icon (🔍) to the upper left of the spectra-display panel, if zones map not already open.
- Right click on sample number**
 - Click "Show Study"
 - Click on file folder name located on the left**
 - Then **double click on spectrum** you want to view to load it into the spectra-display viewscreen.
 - Process > **Auto Plot or Print**. See next page for more detailed printing and processing instructions.
 - Re-click the little circle icon (🔍) to get back to zone map in order to open other files
 - To return to "Submission" mode in order to run more samples, click "New study"

9. Logout: Click "**Logout**" button underneath spectrum-display from Submit Mode. _____


10. Plotting (when wanting non-automatic plots)

- Must be in the process mode. (Highlight "Process" beneath the spectrum display)
- a. Click "Auto Plot" or "Print" button, way on lower right corner of page.
- b. Re-click if you want to print additional copies for the other students
 - Note to offline Concordia users: this "plot" command will print to MSUM NMR-room printer. ☺
 - For advanced labs or research groups, additional plot preferences are available in the process mode by clicking "Plot (Beneath spectrum display, 2nd from bottom underneath "Start")

11. Horizontal Expansions

- With spectrum displayed on screen, use a panel of display icons on the far right.
- a. Click on the magnifying glass icon (6th icon down, )
- b. Move your cursor to the left end of the zone you want to expand, then **hold down left mouse button** and slide it to the other end of the zone you want to expand.
 - To return to the full display, you can either click on the 3rd icon () or the 5th icon ()
 - If the lines aren't tall enough, type "vsadj" (vertical scale adjust) on the command line.

12. Manual Integration: Defining Integrals Yourself (see #13 to also give nice integral numbers)

- With spectrum displayed, **must be in the process mode** ("Process" beneath the spectrum display)
- a. Choose "Integration" (Beneath spectrum display towards left, 2nd underneath "Start")
- b. Hit "Clear Integrals" button (slightly further to the right and lower down from previous button)
- c. Hit "Interactive Resets" button (immediately above the "clear integrals" button) and define
 1. Move cursor beyond the left end of the signal you want to integrate.
 2. **Left-mouse click-and-release**
 3. Move the cursor to the right of the signal, and again click-and-release. Everything between the two "clicks" will be integrated.
 4. Repeat this for each area you want to integrate.
- d. Click very top cursor icon () to the right of the display screen to regain normal cursor function

13. Setting Nice Integral Numbers (While already in integration mode following steps a-d above)

- a. Click cursor on one of your integral regions
- b. Click "Normalize Area to" "Single Peak" below "Set Integral Area" panel underneath the display
- c. Set "integral area" to some nice whole number (1, 2, or 3, depending on your molecule)
- d. Click the "set integral value" button
 - If it says "cursor is outside of integral region", then reset the cursor on an integral of choice, and re-click the "set integral value" button again.
 - Click "Auto Plot" (lower right) in order to print.


14. Other Processing Options for Advanced Users/Research Groups/2D-NMR

- | | | |
|---------------------|---------------------|--|
| 1. Peak Picking | 4. Insets | 6. Absolute Concentration Integration |
| 2. Vsadj | 5. Arraying spectra | 7. 2D NMR processing, including varying the signal intensity |
| 3. wp=2p sp=2p plot | | |

15. Opening Spectra From the Data Folders

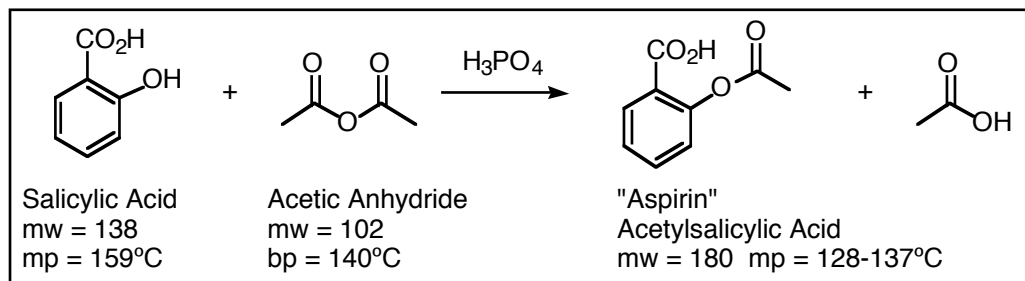
- Click on the Folder icon and find your class or research professor's folder
- Double-click on the folder with your name.
- Double click on the experiment file
- To get the Folder icon to go back up a step, click on the Folder icon again, then click ONCE only on the little icon that shows an arrow up

16. Getting the last sample out and replacing with a Lock Sample (if auto-eject isn't turned on)

- a. In "Spectrometer" mode, display "zones" map ()
- b. Right click on sample 48 => select "Sample in Magnet" (3rd choice from the bottom) => OK.
 - **Logout:** Click "Logout" button underneath spectrum-display

Alcohol Unknowns and Aspirin

Part 1: Microscale Synthesis of Aspirin



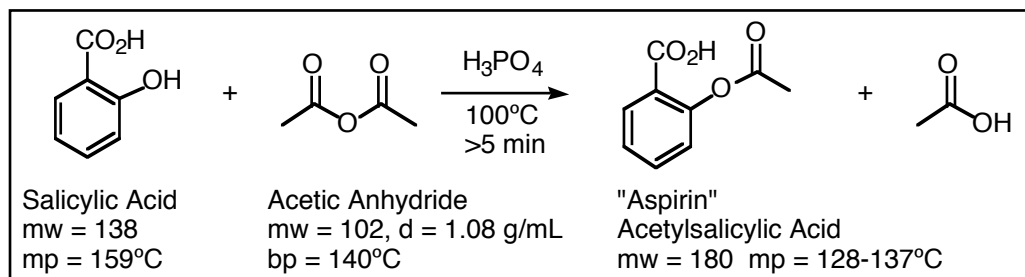
Intro Aspirin is among the most versatile drugs known to medicine, and is among the oldest (the first known use of an aspirin-like preparation can be traced to ancient Greece...). The starting material salicylic acid is cheap (~\$50/kg), because it is available by carboxylation of phenol with carbon dioxide. The esterification that we will do today is the same process that is used industrially for commercial aspirin synthesis.

Aspirin is found in more than 100 common medications. It is usually used for one of four reasons: as an analgesic (painkiller), as an antipyretic (fever reducer), as an anti-inflammatory agent, or as an anti-clotting agent. It is a premier drug for reducing fever. As an anti-inflammatory, it has become the most widely effective treatment for arthritis. Patients suffering from arthritis must take so much aspirin (sometimes several grams a day) that gastric problems may result. For this reason aspirin is often combined with a buffering agent. The ability of aspirin to diminish inflammation occurs because aspirin transfers its acetyl group onto an enzyme; conversion of the enzyme from its amine form to amide form inhibits the synthesis of certain prostaglandins that enhance inflammation.

If aspirin were a new invention, the FDA would place hurdles in the path of its approval. It has an effect on platelets, which play a vital role in blood clotting. In newborn babies and their mothers, this reduction in clotting can lead to bleeding problems. However, this same reduction in clotting has been turned to great advantage. Heart specialists urge potential stroke victims to take aspirin regularly to inhibit clotting in their arteries, and it has been shown that one-half tablet per day will help prevent heart attacks in healthy men. Adult diabetics are routinely advised to take regular aspirin as a preventative measure against heart attacks.

Although aspirin once made up >90% of the commercial pain-killer market, it now faces stiff competition from other analgesics (acetaminophen [Tylenol], ibuprofen [Advil], and naproxen [Aleve]...)

The aspirin you make today is exactly the same chemically as a commercial aspirin except for two things: yours has not met FDA purity standards, and yours is also "undiluted". Commercial aspirin is held together by a binder which makes up most of the mass. Medicines are never the pure chemical. When you take a tablet or a capsule or a liquid dose or an injection of a medicine, the active ingredient usually comprises only a small fraction of the mass. Most of the "stuff" is binder (for a tablet) or solvent. While most aspirins are the same (other than "baby aspirin", for many others medicines the dosage of active ingredient varies (children's Tylenol versus adult...))



Procedure

1. Work with partner if you want.
2. Fill a 50-mL beaker with hot water, and begin heating on a hot plate. (Hot plate setting of ~5?). The goal is to get the water hot enough to approach a gentle boil.
3. Weigh out 0.138 g of salicylic acid (1.0 mmol) and add it to a small test tube
4. Add one small drop of 85% phosphoric acid
5. Add 0.30 mL of acetic anhydride by syringe. This is present in excess, and can be used in part to rinse down any salicylic acid that was stuck on the walls of the tube.
6. Swirl the reactants thoroughly; then heat the mixture in a beaker of boiling water for ≥ 5 minutes.
7. Remove the test tube from the heat.
8. Add about 1 pipet of water, carefully (a few drops) at first then faster, and allow the tube to cool slowly to room temperature.
9. Cool in ice-water bath.
10. If crystallization of the product does not occur during the cooling process, try swirling and poking with a boiling stick, and/or add an ice chip and poke some more with the boiling stick. If this still doesn't promote crystal formation, add a second pipet of cold water and poke some more with the boiling stick.
11. Vacuum-filter using a small Hirsch funnel, into which is molded a water-dampened (to make it limp and flexible) filter paper. (The size that is fitted and would lay perfectly flat on your smaller Buchner funnel).
12. Rinse the tube and the funnel with a pipet of ice-cold water.
13. Rinse with a second pipet of ice-cold water.
14. Let the crystals dry before getting the yield and taking a melting point. (Water doesn't evaporate/dry very fast, so you'd probably like it to be vacuuming for at least 15 minutes, or longer if you're busy with other work anyway.)

15. Lab report on the aspirin. Report the:

- mass recovered,
- calculate the % yield, and
- report the melting range.
 - Note: The melting range is typically rather broad for aspirin because of the carboxylic acid which hydrogen-bonds to the ester.
 - No procedure writeup required.
 - The data can be reported either on the bottom or on the back-side of your alcohol-unknown sheet.

Part 2: Analysis of an unknown alcohol.

- A list of alcohol candidates with their boiling points is listed two pages after this.
- Conduct classification tests shown below to try to determine the following:
 - Is alcohol “big” or “little”? (solubility test)
 - Is alcohol “dense” (aromatic) or “non-dense” (alkyl alcohol)? (solubility test)
 - Is alcohol 1°, 2°, or 3°? (NMR, Chromic Acid test, Lucas test)
- Use NMR to identify your specific alcohol
- Use micro-boiling point (hard!) to try to shorten your list of candidates

Classification Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut. Useful, but don't depend on it too much?!)
 - Add 15 drops of water to a small test tube, and then add 2 drops of alcohol. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
 - Interpretation:
 - a. **Big alcohols:** Alcohols with >6 carbons definitely **won't be soluble**.
 - b. **Small alcohols:** Alcohols with <3 carbons definitely **will be soluble**.
 - c. **Borderline:** Alcohols with 3-6 carbons may be borderline, and **could go either way**.
 - d. An insoluble alcohol that **sinks** is an alcohol that has an aromatic ring present
 - e. An insoluble alcohols that **floats** is probably an alkyl alcohol, although some aromatics are also floaters.

Practical Interpretation: Insoluble doesn't prove ≥ 6 carbons; it only proves ≥ 3 carbons. And soluble doesn't prove ≤ 3 carbons; it only proves ≤ 6 carbons.

- If you think you're **borderline**, then adding more water should enable full dissolving. Or adding more drops of alcohol should confirm incomplete solubility
2. Chromic Acid test (Jones Oxidation): positive for 1° or 2° alcohols (or amines)
 - Add 15 drops of acetone, 1 drop of alcohol, and then 1 drop of Jones reagent
 - A positive test is color change from orange → green/brown/ugly within 5 seconds. The reaction is normally accompanied by formation of a precipitate
 - Interpretation: indicates the presence of a 1° or 2° alcohol (or an amine)
 - Note: The test involves oxidation to a carbonyl product. If the alcohol doesn't have a hydrogen on the hydroxyl-bearing carbon, no oxidation is possible. Thus tertiary alcohols don't react, but both primary and secondary do.
 3. Lucas Test (ZnCl₂/conc. HCl): positive for 3° or 2° alcohols, or for allylic/benzylic 1°
 - Add 30 drops of Lucas reagent to small test tube, then add 3-4 drops of alcohol, stir really vigorously with a boiling stick, and let settle.
 - **Tertiary alcohols or allylic/benzylic alcohols** react pretty **quickly** to give **two layers**
 - **Secondary alcohols** react within **<5 minutes** to give a **cloudy solution or two layers**
 - **Primary alcohols that are neither benzylic or allylic dissolve**. Primary alcohols that are allylic/benzylic react, because they can make carbocations very well.
 - **Interpretation: if the mixture remains homogeneous** after several minutes, you know you have a non-allylic/non-benzylic **primary** alcohol.
 - Note: The test involves the S_N1 conversion of alcohols (acid-water soluble) to alkyl chlorides, which are insoluble.

NMR Run proton; decoupled carbon; and 2D H-C NMR.

- Add sample by drawing up about 1 inch of your unknown into the skinny part of a long-stemmed pipet, then place the pipet into an NMR tube.
- Add 0.8-mL of CDCl_3 solvent (volumes not critical) **directly through the same pipet into the NMR tube** to rinse the sample into the NMR tube.
- Cap and shake the sample and take it to the NMR room (SL 305), get it loaded, and submit into the queue. (This will involve both correctly placing it into the autosample, and entering/submitting info on the computer.) The experiment is probably called “H_C_HC” and is under the “355-365” folder. The instructor will presumably have this all ready and queued up.
- Upon completion, do expansions as appropriate to both H-NMR (to clarify splitting) and the 2D HC-NMR. Manual integrations on the H-NMR may often help. Zooming and adjusting the scaling on the 2D H-C NMR could also help. If available, consulting from instructor may help.
- The 2D H-C NMR is invaluable for identifying each carbon. Consult with instructor.
- Several challenges may complicate interpretation of the H-NMR:
 1. In **longish alkyl** groups, several alkyl CH_2 groups will often overlap. In 1-octanol, for example, CH_2 's 3-7 will probably all make a big superimposed lump that integrates for around 10H.
 2. For secondary alcohols, CH_2 groups adjacent to the OH-bearing-carbon often show the 2 H's as non-equivalent; one H is cis, the other H is trans to the OH. Due to this cis/trans nonequivalence, the two H's may end up with possibly different chemical shifts and much-complicated splittings.
 3. The OH hydrogen can come almost anywhere, and may superimposes on other alkyl H's.
 4. The OH hydrogen is often/usually (but not always) a lumpy shape.
 5. Often the OH doesn't split at all with the C-H hydrogens, but sometimes it does to variable extent.
 6. On the carbon to which the OH is attached, the hydrogens are sometimes broadened or deformed by the OH hydrogen. So splitting can be complex. Consult with instructor.
 7. Aromatic H's commonly overlap into one big 5H lump.

Micro-Boiling Points in the Melting Point Apparatus

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. A "bell" is a narrow piece of glass tubing, narrow enough to fit inside a melting point tube. A bell must have its upper end closed off, and should be at least the length of a fingernail.

Make six "bells" by glass melting/stretching/sealing/breaking (we'll make extras for later.) Bring a 50-mL Erlenmeyer with 6 regular empty melting-point tubes (into which the bells will be placed) to the bell-making station. The instructor will train you how to make the bells. (Scary and fun!)

Prepare two boiling point samples, one a control containing **1-propanol** with a known boiling point of $\sim 90\text{-}95^\circ\text{C}$; the **second** with your **actual unknown** alcohol. Bring your unknown alcohol and your tubes-with-bells to the loading area (on center table). For each tube, use a syringe to add about 5 μL of either the propanol or unknown sample; try to tap or drop such that the liquid settles to the bottom.

Run the two samples side-by-side (propanol in one tube, unknown in the other.) **Carefully note the original liquid levels at the start.** (Noticing that it drops later is key clue that boiling has occurred.)

When a liquid is heated, **pre-boiling bubbling** will usually occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the **real boiling point** is reached, more **rapid bubbling often takes place, but not always; in many cases, though, you won't see nice bubbles. What will always reliably happen**, though, is that at or somewhat beyond the boiling point, the **liquid level will drop, as liquid vaporizes and goes up the tube. This liquid-level-drop is a more reliable indicator, since it happens whether or not bubbling occurs.** Keep heating somewhat beyond the point where you think boiling has occurred, because you may not be experienced enough to distinguish "pre-boiling" bubbles from real boiling bubbles.

These **boiling points** will **not** be **very accurate**, especially for an inexperienced user. Don't trust them to be accurate better than to **about 10 degrees**. While the observed boiling points are imprecise, they still greatly shorten the list of candidates. The instructor will have a list of boiling points; **check with instructor** to confirm whether you're boiling point is within 10° and is close enough, or whether you need to re-run the micro-boiling point.

Alcohol Candidates

<u>bp</u>	<u>Alcohol</u>
65	Methanol
78	Ethanol (anhydrous)
82	2-propanol (isopropanol)
83	t-butyl alcohol (2-methyl-2-propanol)
97	1-propanol (propyl alcohol)
98	2-butanol (sec-butyl alcohol)
102	2-methyl-2-butanol
108	2-methyl-1-propanol (isobutyl alcohol)
115	3-pentanol
118	1-butanol
119	2-pentanol
129	3-methyl-1-butanol
132	4-methyl-2-pentanol
137	1-pentanol
140	cyclopentanol
140	2-hexanol
157	1-hexanol
160	cyclohexanol
176	1-heptanol
178	2-octanol
185	2-ethyl-1-hexanol
195	1-octanol
204	benzyl alcohol (phenyl methanol)
204	1-phenylethanol (sec-phenethyl alcohol)

Unknown Report Sheet

Unknown Number or Letter:

Your Name

Draw your unknown's Structure:

Data Summary

1. Boiling points: measured bp _____ listed bp _____

2. Chemical Tests _____ Result and probable meaning _____

a. Water solubility

If insoluble, did it sink or float?

b. Jones Reagent (Chromic Acid)

c. Lucas Reagent

3. Attach copies of all three of your NMR spectra, with interpretation details (see below).

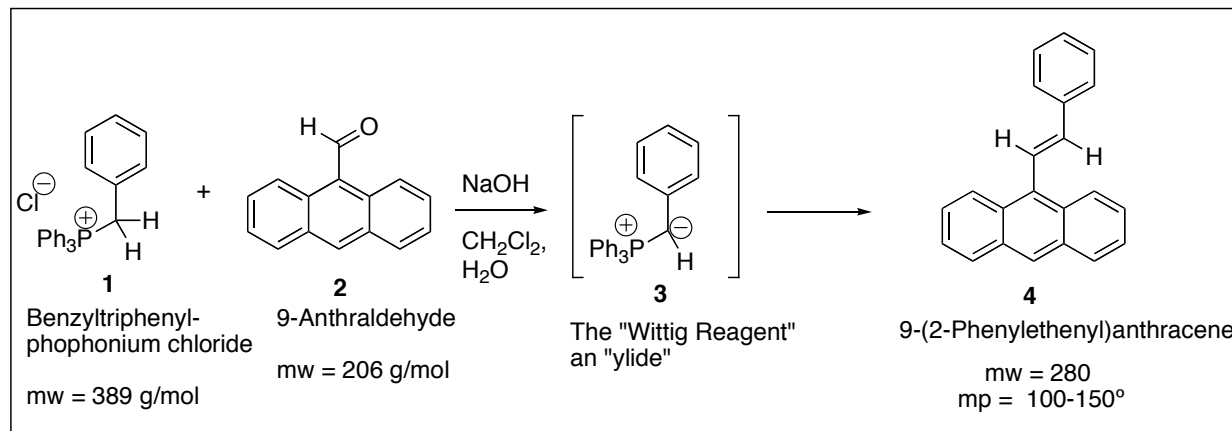
4. **On the H-NMR spectrum, create a 4-column STANDARD SUMMARY REPORT of your ACTUAL H-NMR data, detailing chemical shifts, integrations, and splittings, and source.** Chemical shifts need to be specified to at least the nearest 0.1 ppm. Draw the structure of your molecule, with **identifiers** by each carbon (typically a, b, c... or 1, 2, 3...). Then on your standard summary table include a "source" column in which you show which hydrogens (CH₂-1 or CH₂-b, or CH₃-6 or CH₃-a, or whatever) are responsible for each signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic. The OH may also induce weird splitting, as may cis/trans issues in 2° alcohols. In many cases, some overlapping may occur. Consult with instructor if you have questions!

5. **On the carbon spectrum, draw the structure of your molecule, again with identifiers by each carbon (typically a, b, c... or 1,2,3).** Then **next to each line in the carbon spectrum, write the letter a, b, or c etc. which is responsible.** Using your H-C 2-dimensional NMR will be very helpful for figuring out which carbon is which in the 0-50 zone.

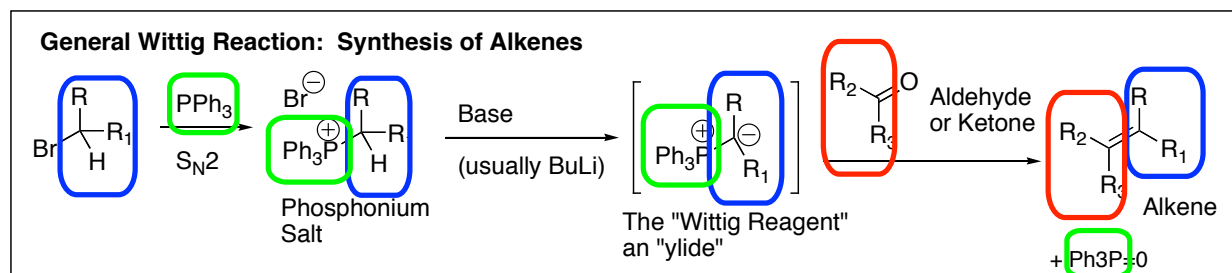
6. Comments (if any).

7. **Remember to attach your aspirin data, (including showing calculations), or write on this sheet somewhere (or on the backside).**

The Wittig Reaction: Synthesis of Alkenes

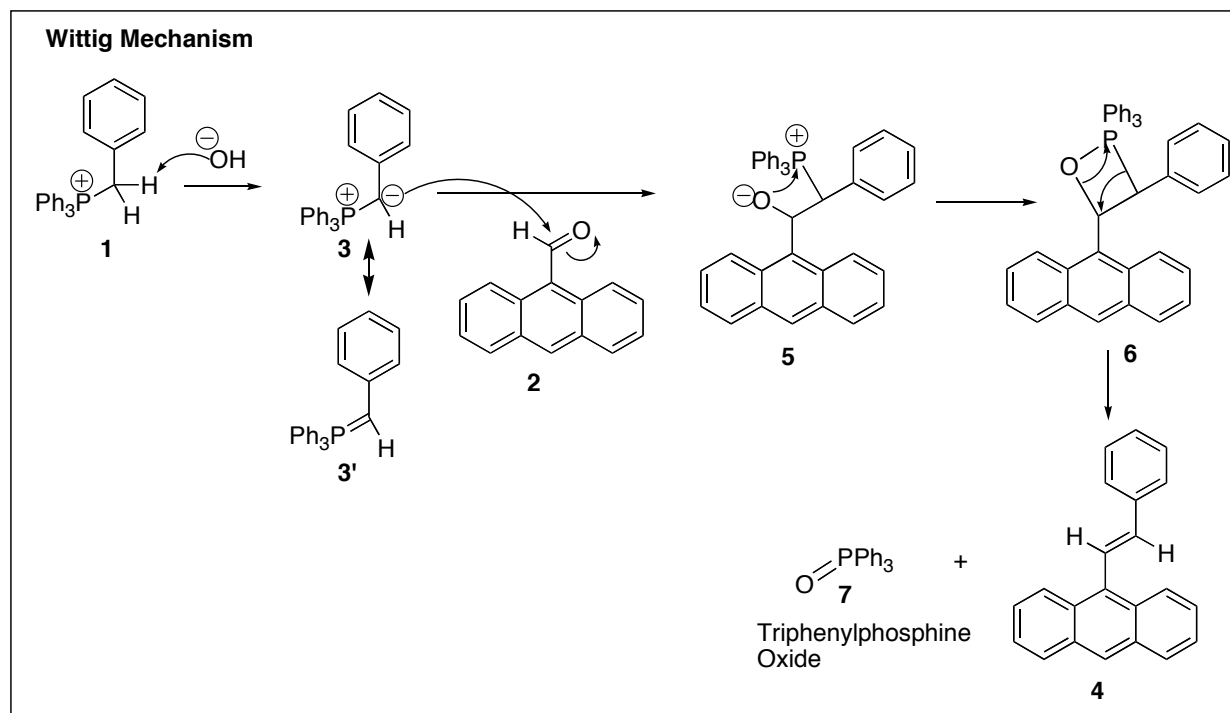


Intro The “Wittig Reaction” is one of the premier methods for the synthesis of alkenes. It uses a carbonyl compound as an electrophile, which is attacked by a “phosphorus ylide” (the “Wittig reagent”.) While many other routes to alkenes can proceed via elimination reactions (E1 or E2 reactions from alcohols or alkyl halides, for example), in elimination reactions the carbon skeleton is already pre-assembled. In the Wittig reaction, however, two smaller carbon units are conjoined to make the alkene double bond. Thus molecules of increasing size and complexity can be quickly assembled. In addition, there is no ambiguity regarding the site of the double bond. (In contrast to elimination reactions, which often give mixtures of “more substituted” and “less substituted” structural isomers.) The Wittig reaction is nicely complementary to the aldol condensation, in which carbonyl compounds are attacked not by a phosphorus ylide but by an enolate. Aldol condensations always result in “enones”, alkenes with a carbonyl attached. Wittig reactions are more general in that the product carbonyl does not need to have an attached carbonyl. The alkene product **4** that you make today is the one that was used a few weeks ago as the colorizer for the chemiluminescence experiment (it gave the green solution.)



Mechanism

The general mechanism of the Wittig reaction is shown above. The phosphonium ion is deprotonated by base. The positively charged phosphorus atom is a strong electron-withdrawing group, which activates the neighboring carbon atom as a weak acid. For many phosphonium ions, a very strong base (commonly butyl lithium) is required in order to do the deprotonation. The use of such strong base requires moisture-free conditions such as were required for doing the Grignard reaction. In today’s experiment, however, very concentrated sodium hydroxide is



strong enough to do the deprotonation. This is because the carbanion **3** that is produced is stabilized not only by the positive phosphorus, but also by conjugation with the benzene ring. Notice that carbanion **3** has a resonance structure, **3'**, in which it is unnecessary to draw any formal charges. Either resonance structure is reasonable; **3'** has the advantage that it involves no formal charge, and has a double bond to carbon in exactly the same place where the final alkene C=C double bond ends. But **3'** has the disadvantage that it doesn't illustrate why the carbon should be so nucleophilic. In addition, it involves a phosphorus with five bonds. Resonance structure **3** is useful in that it shows why the carbon should be so nucleophilic, and also is consistent with the popular octet rule.

Once the carbanion/ylide **3** is formed, it is strongly nucleophilic, and attacks carbonyls just like other strong nucleophiles (for example, Grignard reagents...), producing an alkoxide **5**. Alkoxide **5** rapidly closes onto the phosphorus to form the 4-membered ring **6**, which is not very stable. The "betaine" **6**, with its 4-membered ring, rapidly fragments to give the desired alkene **4** and triphenylphosphine oxide **7** as a side product.

Wittig Reactions and the Phosphine Oxide Side Product 7: This side product is non-trivial to remove. It's too "organic" to wash out into a water layer, and it's too heavy to boil away. In today's experiment, we will remove it based on its polarity and H-bonding ability, in contrast to the non-polar alkene **4**. This separation will be accomplished by recrystallization from a somewhat polar hydrogen-bonding alcohol solvent, but it needs to be done carefully to selectively remove phosphine oxide **7** without losing too much of alkene **4**.

The Diagnostic Color Changes of Wittig Reactions: One interesting aspect of Wittig reactions that is not well illustrated today is that normally the carbanion/ylides **3** are colored, often intensely so. (Many are a deep, blood red or sometimes grape-juice purple). The product alkene and phosphine oxides are normally not colored, as is normally true of the phosphonium salt and the carbonyl electrophile. Thus you can often monitor Wittig reactions by color: formation of color shows you've made the ylide; disappearance of the color shows that the ylide has reacted and gone on to final products. While you will see some meaningful color changes today, they won't be as intense or diagnostic, for a couple of reasons. 1) In today's case, the extended conjugation of both the starting anthraldehyde **2** and the product alkene **4** make both of them colored. So whereas normally there is no color at the beginning or the end, only during the ylide middle, today the colors of both the starting aldehyde and the product alkene partially mask the color of the ylide. 2) In today's case, the conjugation of the ylide carbanion with the benzene

weakens the color of the ylide. It's not nearly as intense or red as for a non-conjugated ylide. Still, you will be able to see some changes in color as the reaction proceeds. One additional factor to consider is whether the phosphonium salt or the carbonyl is the limiting reactant. If the carbonyl is in surplus, all of the ylide (and its color) should get consumed. But if the carbonyl is limiting, even after it is fully reacted there may be some residual ylide (and its color) that survives.

The Unusual Solvent Combination for Today: Most reactions are conducted in a homogeneous solution, where everything is dissolved and can move around such that reactants can collide. This is difficult to accomplish, however, when you have both strongly hydrophobic reactants (the aldehyde in today's experiment) and strongly hydrophilic reactants (sodium hydroxide). The phosphonium salt is also ionic, and thus also has problems dissolving in organic solvent. Rather than having a homogeneous solvent system that can get these extremely opposite chemicals all into the same solution, today's solvent system will be a mixture of water and dichloromethane. These two are not cosoluble, and will give two separate layers. Thus the ionic hydroxide and the phosphonium salt can go into the water, and the aldehyde and the product alkene can go into the dichloromethane. When the ylide forms, it has no overall charge, and thus can switch phase from the water to the organic phase. (This is called a "Phase Transfer" reaction.) **Note: Phase transfer can only take place at the interface between the two phases. In order to maximize contact between the two phases, it is very important that the mixture be well stirred to provide lots of small droplets and lots of surface area for organic/water contact.**

Wittig Reaction Procedure

1. May work with partner, or may work alone.
2. Place a small (smallest possible) stirring bar in a large test-tube.
3. Set the test-tube into a 125-mL Erlenmeyer so that you can stand it on a stir-plate. (Or clamp.)
4. Weigh out ~0.300 g of 9-anthraldehyde **2** and add this to the test tube. (Record exact mass)
5. Add three pipets of dichloromethane and stir. (Squeeze the bulb, draw up what you get, ~1mL)
 - Note: does the aldehyde dissolve?
 - What color is the solution?
6. Weigh out 0.480 g of benzyltriphenylphosphonium chloride **1** and place it into the test tube.
7. Add 1 pipet of water, using this to try to rinse down any phosphonium salt that's stuck on the sides
 - Note: does the salt dissolve?
 - What color is the salt?
 - Is the solution warm to the touch at this point?
8. Stir the mixture vigorously, and then add 0.65 mL of 50% sodium hydroxide solution by syringe.
 - Note: Is the solution warm to the touch at this point?
 - What colors are the layers?
 - Which layer is on top, the aqueous or the organic layer?
9. Stir the solution vigorously for 10 minutes.
10. Workup: Dilute with 5 mL of dichloromethane and 12 mL of water, and pour the mixture into the separatory funnel. Add 20 more mL of water to the separatory funnel
11. Rinse the test tube with another 3 mL of dichloromethane and 12 mL of water and pour this also into the separatory funnel. Shake it up vigorously, and then allow time to settle.
 - Which layer is on top, the aqueous or the organic layer?
12. Pour the organic layer into a 125-mL Erlenmeyer. (Adding a long-stemmed funnel may help.)
13. Add an additional 8-mL of dichloromethane to the separatory funnel, and shake vigorously again. (Any yellow color is product, so where yellow is, more CH₂Cl₂ rinse might be good...)
14. Pour the organic layer into the same 125-mL Erlenmeyer that has the other dichloromethane.
15. "Dry" the organic solution with sodium sulfate.
16. At this point or sooner, get a 400-mL beaker ~1/3 filled with hot water in it, and warm on hot plate. Maybe target ~55° water bath; with the hot-plate around 5, maybe?)
17. Filter the organic solution into a separate ground-glass-neck 125-mL Erlenmeyer, using a long-stemmed funnel lightly-plugged with glass wool to filter off the sodium sulfate.
18. Rinse the original Erlenmeyer and the funnel (anything yellow) with additional dichloromethane.

19. Add a boiling stick to your organic solution, and then place the Erlenmeyer into the warm-water bath to boil off the dichloromethane. (Be thorough.... Once it's boiled down some, you can turn up the hot plate to a higher temperature to facilitate a faster boil-off. No point in wasting lots of time boiling the solvent off if we can do it faster. But, we don't it to go crazy and go boiling over the top, either.)
 - Note: How do you know when to quit? If you know what your theoretical yield is, it will help you realize approximately how much stuff you should expect to have left once the solvent is removed...
20. Once the solvent is pretty much gone, remove from hot bath, add a vacuum adaptor, turn on vacuum, and continue under vacuum for 2 minutes to remove any last traces of CH_2Cl_2 .
21. Remove your Erlenmeyer from the hot water bath.
 - Does anything crystallize?
 - At this point you have at least two things present: the desired alkene **4** and the undesired phosphine oxide side product **7**. If you also have some CH_2Cl_2 solvent that hasn't quite all boiled away, that will reduce your eventual yield and prevent crystallization.
 - Place your material into an ice bath, and scratch it with a boiling stick. If it crystallizes, that confirms that you've done an adequate job of boiling off your dichloromethane. If it doesn't crystallize, you should probably boil some more off. (Jasperse has a quick way.)
 - If you don't get rid of your dichloromethane adequately, leftover dichloromethane will keep product dissolved at the end of the recrystallization process, and your yield will be compromised.
22. Purify your alkene by recrystallizing from 1-propanol solvent. (The water bath can now be boiling hot, so turn up your hot-plate setting to ~5.) The concept here is that the triphenylphosphine oxide is more soluble in the propanol than is the alkene product, because the phosphine oxide can use its oxygen to hydrogen-bond to the solvent, whereas the alkene has no hydrogen-bonding capability.
 - Do you remember the logic and procedure for a recrystallization? If not, try to review!
 - A good starting guess may be about 6 mL.
 - This recrystallization can be done right in the same 125-mL Erlenmeyer flask.
23. After Buchner funnel filtration, rinse with a very small amount (2-4 mL?) of ice-cold propanol. We don't want to add water and make the solvent much "worse" for fear that water will knock the triphenylphosphine oxide out of solution and contaminate the product.
24. Let things dry thoroughly before getting your yield and mp. (Vacuum for at least 10 minutes.) Once you have your mass, also calculate your % yield. (Don't expect a very high yield. The solvent good enough to host all of the triphenylphosphine oxide also hosted much product.)

Lab Report: Standard synthesis style lab report. Be sure to include detailed observations on some of the things that happened. For product, include yield, mp, and % yield.

Questions: None assigned.

Carbonyl Unknowns

Overview:

You will receive a carbonyl compound as an unknown. It can be either an aldehyde or a ketone, and may or may not contain an aromatic ring. Your job will be to identify your carbonyl compound. Several pieces of information will be useful:

- NMR information on the starting material. (H, C-decoupled, and 2D HC-NMR)
- Water solubility tests (big or small? Aromatic or not?)
- Boiling point of starting material (try at least once)
- The melting point of the derivative (required)

Classifying Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut. Use, but don't depend on it too much?!)
 - Add 15 drops of water to a small test tube, and then add 2 drops of sample. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
 - Interpretation: **Insoluble proves ≥ 3 carbons. Soluble proves ≤ 6 carbons.**
 - a. **Small:** Carbonyls with <4 carbons always **dissolve**
 - b. **Big:** Carbonyls with >6 carbons **never dissolve**
 - c. **Borderline:** Carbonyls with **4-6 C's, borderline, may dissolve or may not.** Sometimes adding some more water will dissolve, if doesn't initially.
 - d. An **insoluble carbonyl that sinks** has an **aromatic** ring present for sure
 - e. An **insoluble carbonyl that floats is probably nonaromatic**, although some aromatics are also floaters.
2. Summary of chemical tests related to carbonyls, (we'll only do 2,4-DNP), but which you should know to answer post-lab questions
 - 2,4-dinitrophenylhydrazine (**DNP**) test: positive for **aldehydes or ketones**.
 - **Tollens'** test: Positive for **Aldehydes**, not for Ketones. Similar to Schiff's test, but more famous (good) but more expensive (bad) (Note: we'll tell by H-NMR. Shift at ~ 9 - 10 ppm proves aldehyde.)
 - **Iodoform** Test: Positive for **Methyl Ketones** (CH_3COR). (This is also pretty easy to see by H-NMR, since you get a 3H singlet in the 2's.)
 - **$\text{Br}_2/\text{CH}_2\text{Cl}_2$** test: Positive for **Alkenes** (to distinguish $\text{C}=\text{C}$ from $\text{C}=\text{O}$ double bonds)
3. **NMR: Prepare a sample** by drawing up about 1 inch of your unknown into the skinny part of a long-stemmed pipet, then place the pipet into an NMR tube. Add 0.8 mL of CDCl_3 directly through the pipet to rinse the sample into the NMR tube. Cap it, shake it, and set it into the NMR queue and run the experiment called "H_C_HC" in the 355-365 folder.
 - **Aldehydes** are easily distinguished from ketones by H-NMR. The aldehyde hydrogen, which is attached to the carbonyl carbon, **shows up in the 9-10.5ppm chemical shift area**. Ketones will show no such signal in that area.
 - **Aromatic hydrogens ortho to a carbonyl are typically pushed downfield, toward 8 ppm.** This is because a carbonyl group is a strong electron withdrawer, so it makes the ortho carbons more electron poor, which "deshields" the ortho hydrogens.

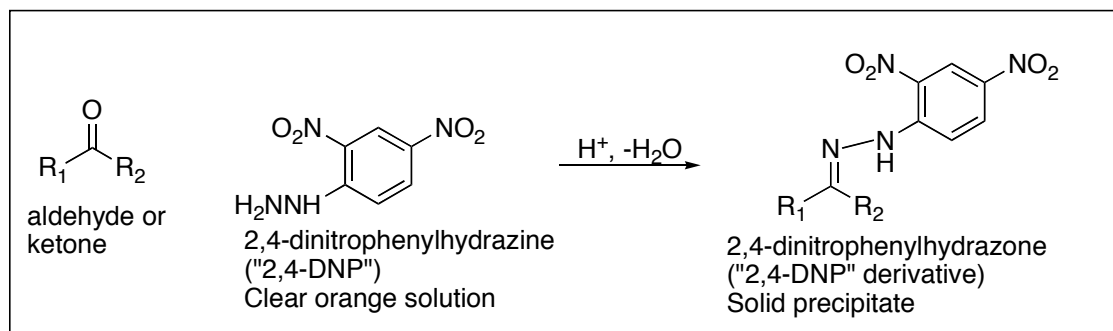
Derivative: Making a 2,4-DNP Derivative of Your Aldehyde or Ketone

Put 4 pipets of 2,4-DNP solution into a large test tube, add a stirring bar, begin very strong stirring, and add 30 drops of your unknown to the well-stirred solution. After 2 minutes, cool, add 2 pipets of cold water, stir, filter, wash with cold water, and wash with a small amount (three pipets) of cold ethanol. Vacuum for a while (5 minutes is probably plenty), and if possible prepare a crude mp sample. (Melt it later, not now. You may need a metal wire “ramrod” to push sticky material to the bottom of a tube. If it’s too sticky to get in, don’t worry about it.)

Recrystallize (or “digest”) from absolute ethanol, using a 125-mL Erlenmeyer. Make a starting guess of 4 mL ethanol; then once the mixture reaches boiling, improvise/adjust appropriately depending on what you see. Prewarm some water in a half-filled 400-mL beaker. (Hot-plate ~6? Would like the bath to be ~80-90°.) If you also **prepare some hot ethanol**, that may make it faster/easier to make rapid adjustments to your solvent. (If you add cold ethanol or water, the response is complicated by the change in temperature.)

In some cases, it takes a lot of ethanol to get the crystals dissolved. The amount of ethanol required will vary from one unknown to another; saturated alkyl ones usually dissolve easily, the longer the alkyl chains the easier. Aromatic aldehydes/ketones are often much harder to dissolve and require a lot of ethanol, or else simply will never dissolve completely. If you have added 50 mL of ethanol to your boiling solution and the solid has still not dissolved completely, then just boil for another five minutes and then take it off from the heat and allow cooling to proceed. In this case (“digestion”), simply boiling the mixture for a while enables the impurities to get free, even if not all of the crystal is completely dissolved at any one time.

Disposal: Into DNP waste container.

**Chemical Derivatives: General Considerations/Purpose**

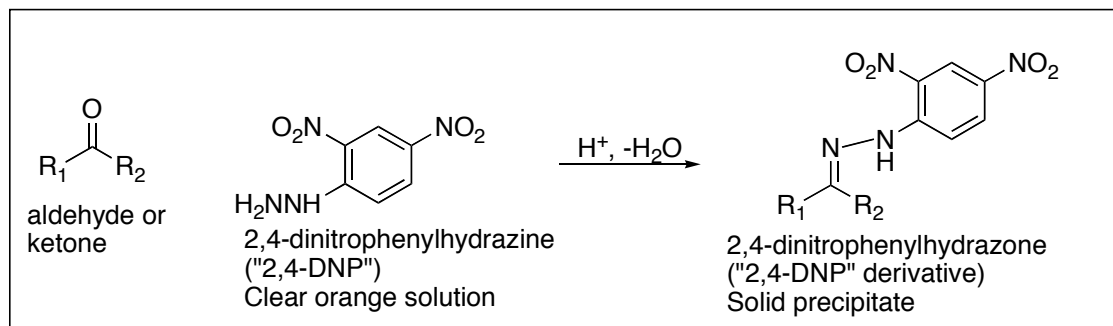
A classic way to help identify a material is to convert it into a crystalline derivative. This is particularly valuable if the initial chemical is a liquid or is impure. We’ve seen that although melting points are easy to measure, boiling points are not. **By converting a liquid (or impure) sample (for which a meaningful, precise bp/mp is not easy to obtain) into a pure crystalline solid for which a precise mp can be obtained, we can get useful melting points.**

Unfortunately the usefulness of a solid’s melting point is **dependent on having very pure solids**. Your product must be purified well and dried well if it’s melting range is expected to have any accuracy. Thus your success in making and using solid derivatives for identification purposes will hinge on your purification skills.

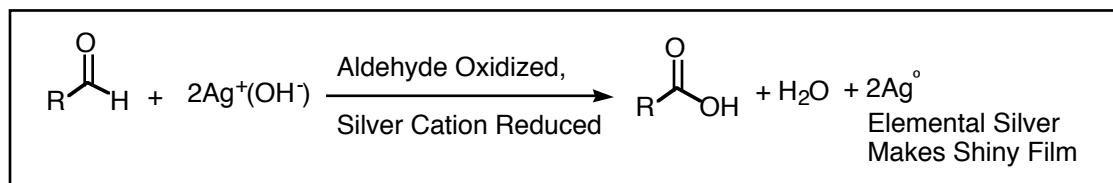
Lists of derivatives with their characteristic melting points are widely available. These are useful even if the melting point or boiling point of the starting material is available. Often several candidates may fit into the mp/bp of the starting unknown. But by having both a value for the starting material as well as the derivative, resolution is often possible.

SOME CHEMICAL TESTS TO KNOW

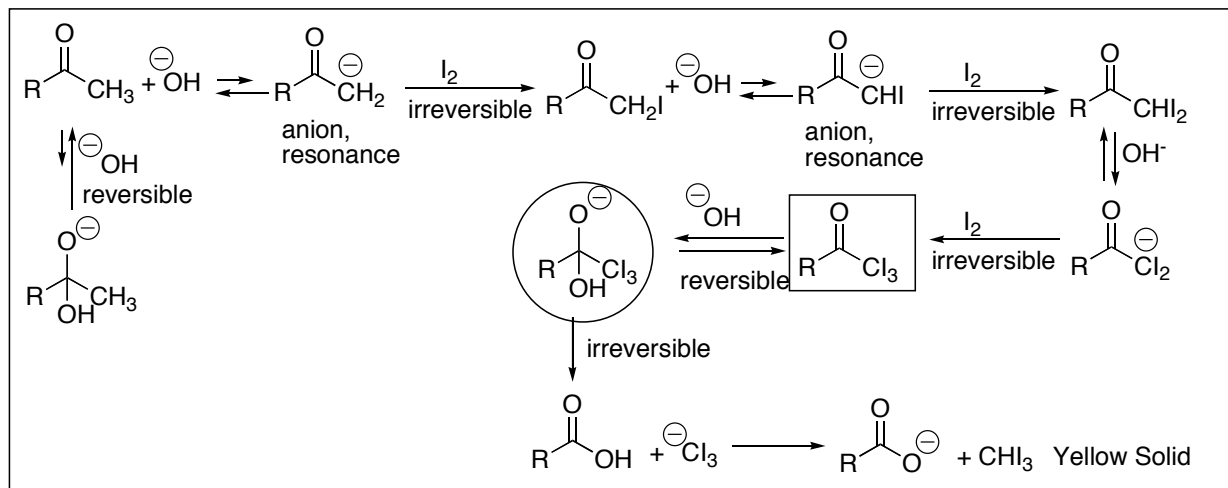
2,4-Dinitrophenylhydrazine (“DNP”) Test: Specific for Aldehydes or Ketones (but not esters, acids, or amides)



The “DNP” test is positive for both aldehydes and ketones, but not for alkenes or esters/acids/amides. This is representative of how $\text{H}_2\text{N-Z}$ reagents react with aldehydes or ketones to eliminate water and make “imines”, with a $\text{C}=\text{N-Z}$ bond. In the chemical test, the DNP reagent is soluble; if a derivative forms, it precipitates from solution. So the formation of a precipitate is what you watch for. The DNP-derivatives tend to be highly crystalline because of the extended conjugation; from the carbonyl carbon through the two nitrogens through the ring through the two nitro attachments, all the atoms are flat and sp^2 . The color of the precipitate is often informative; saturated carbonyl compounds tend to give yellow derivatives, while unsaturated aldehydes or ketones tend to give red or orange derivatives. The experiment is excellent as a chemical test, when you don’t know if you have an aldehyde or ketone. But it is also excellent as a way to make a solid derivative which can be purified by recrystallization and whose melting point can be taken. The melting points of many DNP derivatives are known and listed.

Tollens Test: Specific for Aldehydes. Positive for Aldehydes Only.

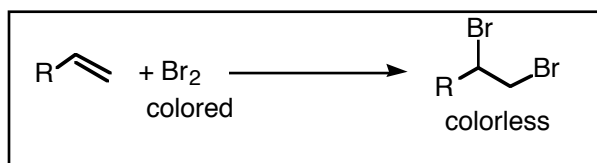
A classic alternative to the Schiff’s test for aldehydes is the Tollens Test. Tollens reagent is a soluble AgOH solution. [Actually $\text{Ag}(\text{NH}_3)_2\text{OH}$]. When mixed with an aldehyde, the aldehyde carbon is oxidized to a carboxylic acid, and the $\text{Ag}(\text{I})$ cation is reduced to elemental $\text{Ag}(0)$. The elemental silver films out on the surface of the test tube in which the test is conducted, and a “silver mirror” can be observed. This reaction has historic importance. For centuries during the middle ages this was the process used to make mirrors. (These silver mirrors were less clear than modern mirrors). This silver coating process was also used to apply a silver coating to any object. We will not use this test in lab because the Schiff’s test is cheaper and easier. Test tubes used for Tollens’ test must be thrown away, and the silver reagent is somewhat expensive.

Iodoform Test: Specific for Methyl Ketones (CH₃COR)

Methyl ketones can be distinguished from other ketones by the iodoform test. The methyl ketone is treated with iodine in an NaOH/water solution. Methyl ketones produce a yellow solid called “iodoform”, other ketones or aldehydes do not. The mechanism is shown below, and is somewhat complex. Deprotonation of the methyl ketone hydrogen gives a resonance-stabilized anion, which attacks iodine. Once the first iodine is installed, the remaining methyl hydrogens become even more acidic and get deprotonated followed by iodination in rapid sequence to generate the tri-iodo RCOCl₃ species (in box). Hydroxide routinely adds to carbonyls, but normally this addition is reversible, non-productive, and insignificant. However, hydroxide addition to the RCOCl₃ is productive; in this case, the anion (in circle) can eliminate the ⁻Cl₃ anion. This is a decent leaving group because the three electron-withdrawing iodo groups stabilize the anion. This elimination is also irreversible, so by LeChatelier’s principle all of the chemicals drain off through this pathway. Following elimination, the ⁻Cl₃ anion picks up a proton to make iodoform, CHI₃, which is a yellow crystalline solid. The formation of this yellow solid is a “positive” test; if no yellow solid forms, the test is “negative”. Ketones other than methyl ketones are unable to get to the RCOCl₃ species (in box), are unable to undergo the fragmentation that the circled anion undergoes, and are unable to make the solid iodoform.

Br₂ Test: Specific for Alkenes (Not Ketones or Aldehydes)

Bromine is a routine test for alkenes. (Although a mono-substituted alkene is shown in the picture, di-, tri- and tetra-substituted alkenes also react with bromine.) Bromine adds to alkenes but not to carbonyl compounds (or to ordinary arenes). The nature of the test is to add a few drops of bromine, which is strongly colored, to an excess of an organic sample. If the color disappears, it means the bromine reacted and therefore that the organic unknown contains an alkene. If the color persists, it means the bromine did not react, and therefore that no alkene is present in the organic unknown.



Aldehyde/Ketone Candidates

<u>Bp of Starting Carbonyl</u>	<u>Unknown</u>	<u>mp of 2,4-DNP Derivative</u>
48	propanal	148
56	acetone	126
63	2-methylpropanal	187(183)
75	butanal	123
80	2-butanone	117
91	3-methylbutanal	123
92	2-methylbutanal	120
100	2-pentanone	143
102	3-pentanone	156
103	pentanal	107(98)
115	4-methyl-2-pentanone	95
128	5-hexen-2-one	108
129	4-methyl-3-penten-2-one	205
131	cyclopentanone	146
131	hexanal	104(107)
145	4-heptanone	75
145	5-methyl-2-hexanone	95
146	2-heptanone	63-68 *
147	3-heptanone	81
153	heptanal	108
156	cyclohexanone	162
169	3-methylcyclohexanone	155
173	2-octanone	58
179	benzaldehyde (PhCHO)	237
200	o-methylbenzaldehyde	194
204	p-methylbenzaldehyde	234
202	ethanoylbenzene	244
216	1-phenyl-2-propanone	156
217	(2-methylpropanoyl)benzene	163
218	propanoylbenzene	191-198 *
226	p-methylacetophenone	258
232	butanoylbenzene	191
235	4-phenyl-2-butanone	127
248	p-methoxybenzaldehyde	253

Name:

Lab Report Requirements: No procedure or yield information required. Fill out the unknown report sheet. Attach your NMRs. (Must take at least one of H-NMR or C-NMR, or both.) Answer the following questions.

Questions:

1. What is the purpose of making derivatives of liquid unknowns?
2. Using a chemical test or tests, how could you distinguish between 3-pentanone and pentanal?
3. Using a chemical test or tests, how could you distinguish between 3-pentanone and 2-pentanone?
4. Using a chemical test or tests, how could you distinguish between 3-pentanone and 4-penten-1-ol?
5. Draw a possible structure for a molecule C_5H_8O that gives a positive tollens' test and does not react with Br_2/CH_2Cl_2 ?
6. Draw the structure of a compound C_5H_8O that reacts with 2,4-dinitrophenylhydrazine, decolorizes bromine in dichloromethane, but does not give a positive iodoform test.
7. Draw two structural isomers for $C_5H_{10}O$ that would both give positive iodoform tests?
8. Draw a possible structure for C_4H_8O that would not give a positive dinitrophenylhydrazone test?

Unknown Report Sheet-Carbonyls Name

Your unknown Letter/Number:

Draw the structure for your unknown:

1. Solubility Tests on Starting Material

Solubility in Water: _____ If Insoluble, Does it Float or Sink?

Conclusion:

2. Boiling point:

3. Derivative: observed mp literature mp (see p41)

Crude (if possible):

Recrystallized

4. H-NMR (attach, with assignments/interpretation.)

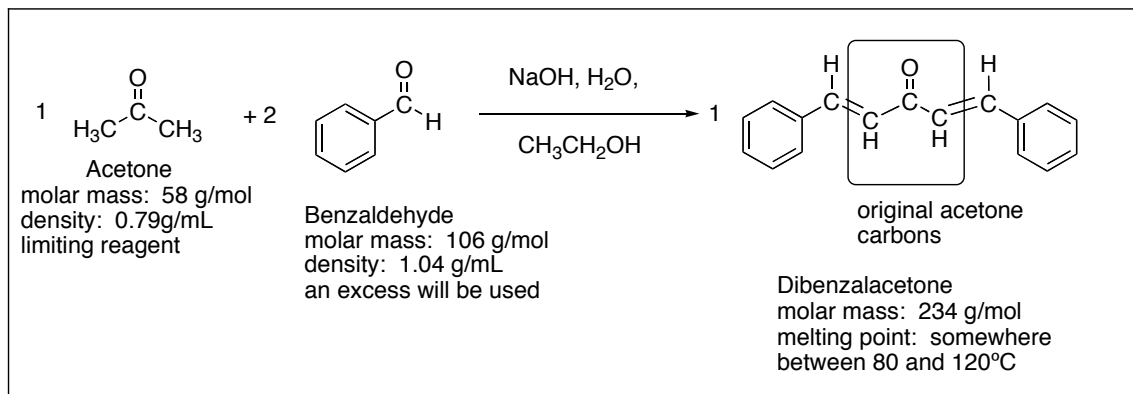
- **On the proton spectrum, create a STANDARD 4-column SUMMARY REPORT of your ACTUAL H-NMR data, detailing chemical shifts, integrations, and splittings, and "source".**
- Chemical shifts need to be specified to at least the nearest 0.1 ppm
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Then on your standard summary table add a "source" column in which you explain which hydrogens (a, b, or c, etc...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.

5. C-NMR (attach, with assignments/interpretation)

- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Draw letters next to carbon lines that can be assigned.
 - The C-H 2D NMR will help you to be able to assign all of your lines.)

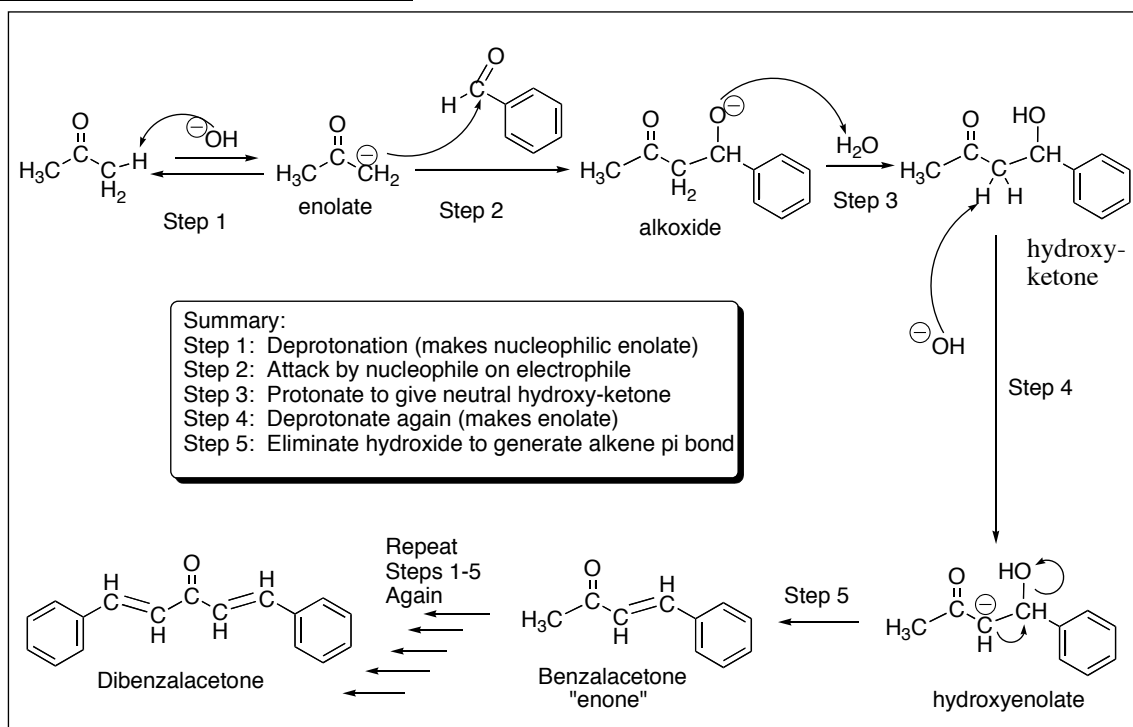
6. Comments, difficulties, complaints, etc.

ALDOL SYNTHESIS of DIBENZALACETONE, AN ORGANIC (SCREEN



Overview: The reaction of an aldehyde with a ketone employing sodium hydroxide as the base is an example of a mixed aldol condensation reaction. You will do a double mixed-aldol condensation reaction between acetone and benzaldehyde. Acetone has α -hydrogens (on both sides) and thus can be deprotonated to give a nucleophilic enolate anion. The aldehyde carbonyl is much more electrophilic than that of a ketone, and therefore reacts rapidly with the enolate. The alkoxide produced is protonated by solvent, giving a β -hydroxyketone, which undergoes base-catalyzed dehydration. The elimination process is particularly fast in this case because the alkene is stabilized by conjugation to not only the carbonyl but also the benzene. In today's experiment you will use excess benzaldehyde, such that the aldol condensation can occur on both sides of the ketone.

Mechanism for Aldol Condensation



Procedure:Calculations

1. Calculate the volume required to produce 0.0125 mol of acetone.
 2. Calculate the volume of 2.2 “equivalents” of benzaldehyde. (In other words, 2.2 times as many moles of benzaldehyde as of acetone.) Note: the equation involves a simple 2:1 stoichiometry.
- By using an actual 2.2:1 ratio, it ensures that the benzaldehyde is surplus and that the acetone is limiting. This is helpful for several reasons:
 - a. **Aldehyde oxidation.** Aldehydes are often impure, because oxidation to carboxylic acid is fairly facile. By using 2.2 equivalents of benzaldehyde, then even if 10% of the benzaldehyde is corrupt we ensure that we still have enough to fully react with the acetone.
 - b. **Reaction Time.** By having an excess of benzaldehyde, it makes it easier for the reaction to go to completion. Otherwise late in the reaction there isn't much benzaldehyde left to react, so the reaction slows down a lot. By intentionally putting in some extra, it maintains at least a minimal concentration of electrophilic benzaldehyde till the very end, such that getting 100% conversion of isn't so hard and doesn't take so long.
 - c. **Ease of Product Purification: Disubstitution versus monosubstitution.** Enabling complete conversion greatly simplifies purification. If complete conversion does not occur, either because benzaldehyde runs out or because insufficient time is used, the desired “disubstitution” product “dibenzalacetone”, in which two benzaldehydes have been incorporated, is contaminated by “benzalacetone”, the “monosubstitution” product in which only one benzaldehyde has been incorporated. Since the mono- and disubstituted products aren't that different, it's not that easy to remove the undesired side-product from the main desired product. But if you just make sure the reaction goes all the way to the desired product, then you don't need to worry about it!

Doing the Reaction:

1. Use a 125-mL Erlenmeyer flask with a magnetic stirring bar.
2. Add 50 mL of the NaOH-Ethanol-Water solution mixture. (This was premixed for you.)
3. Place the solution on the magnetic stirrer and adjust the stirring dial to get a nice, even stirring action.
4. To this add the calculated amount of benzaldehyde by syringe
5. Add the calculated amount of acetone by syringe, last. (The acetone should go in last, after the benzaldehyde electrophile is already available. If the acetone goes in first, it could do aldol condensation on itself, in which enolate anions just attack neutral acetone carbonyls. Ketone carbonyls aren't competitive with aldehyde carbonyls as electrophiles, but if there are no aldehydes available, ketones are better than nothing!)
6. Watch the solution carefully, with a watch, at the beginning of the reaction, so that you can keep good observational records.
 - How long does it take for the solution to turn yellow? Given that all the reactants are colorless, what does the yellow color mean?
 - How long does it take for the solution to become cloudy, and for solid to then accumulate?
7. Let the solution stir for 30 minutes. (Calculate, write report, do theoretical yield, etc.)
8. Add 20 mL of water, and then filter the mixture
9. Pour the filtrate into the waste container.
10. Wash the crystals three times with 50-mL of water each time.
 - The product is so organic that it has essentially no solubility in water. Water washes are no threat to your yield.
 - The initial product is contaminated by sodium hydroxide. The extensive water washes removes all traces of sodium hydroxide.
11. If the crystals are still pretty wet, press them drier by pressing a filter paper on top to absorb water.

12. Weigh the crude product, and remove a small crystal for a crude melting point that you can run later. Note: your yield may be $\gg 100\%$, due to residual water. That's OK, you're going to recrystallize again anyway.
13. Prepare a hot water bath (400-mL beaker, hot-plate ~ 5). Having somebody in your hood (or adjacent) heat some ethanol, in case one of you needs it, is advisable, too.
14. Purify the bulk of your crystals by recrystallizing from ethanol, using a 125-mL Erlenmeyer inside your hot-water bath. A reasonable starting guess is to add ~ 4 mL ethanol/gram product, and heat it up. Improve if needed once hot, depending on what you see. (You can add more hot ethanol to increase solubility, or hot water to reduce solubility.) Note: The product has a low melting point, so it's easy to think you've dissolved it when actually you've only melted it. Note: the water bath provides even heating and avoids overheating on the hot-plate surface.
15. After cooling, rinse the crystals with an appropriate rinse solvent. (What might that be?)
16. Dry thoroughly.
17. Take yield and mp, and calculate the % yield.

Lab Report:

Standard synthesis lab report. Yield, % yield, and mp's of crude and recrystallized products.

Questions:

1. How would you modify the experiment in order to make benzalacetone, $\text{PhCH}=\text{CHCOCH}_3$, instead of dibenzalacetone $\text{PhCH}=\text{CHCOCH}=\text{CHPh}$?
2. What ingredients would you use if you wanted to make benzalacetophenone, $\text{PhCH}=\text{CHCOPh}$?

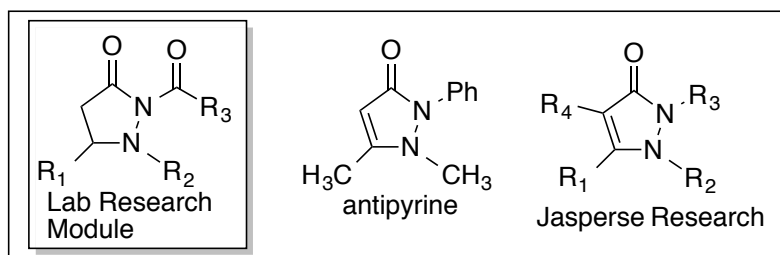
Miscellaneous Notes

- Does the benzaldehyde smell familiar? It's found in almond, almond paste, and is familiar from cherries and vanilla. Lots of cookies and bars have this smell.
- Acetone has many uses, including as a paint and varnish remover; as a fingernail polish remover, and as a solvent in many varnishes, rubber cements, lacquers, etc. It is also a natural metabolic byproduct found in the body in limited quantity. Elevated quantities are symptomatic of metabolic disorders, such as uncontrolled diabetes.
- Q: The formation of the yellow color shows that a new chemical is forming, very quickly. The formation of the cloudiness and the insoluble solid also indicates that something is forming that wasn't present at first. Actually, the yellow color and the solid are one and the same. But how come the solid doesn't appear instantly, as fast as the yellow color?
- A: This is the result of solubility chemistry. The solvent has the ability to dissolve a limited quantity of the product. Product is forming continuously, right from the start; but it takes a minute or so until there is enough product formed to hit the solubility-saturation threshold. Any further product exceeds the solvent's ability to hold it, and thus comes out as insoluble solid. At first this insoluble stuff looks to the eye as if it is just milky cloudiness. But soon enough it looks like solid crystalline material.

Chem 365 Lab Manual Part II

Multistep synthesis of an Acyl Pyrazolidinone**Introduction**

We will begin a multi-step semi-research sequence in which we make a library of different “acyl pyrazolidinones” (see left-most “Lab Research Module” structure). The project will illustrate a variety of fundamental organic reactions and fundamental procedures. The acyl pyrazolidinones are of interest as medicinal candidates, as well as for use in further synthetic reactions. (The Jasperse research group is involved in making and bio-screening a diverse library of analogs for “antipyrene”, a lead/best but very imperfect drug candidate for treating pulmonary fibrosis.)

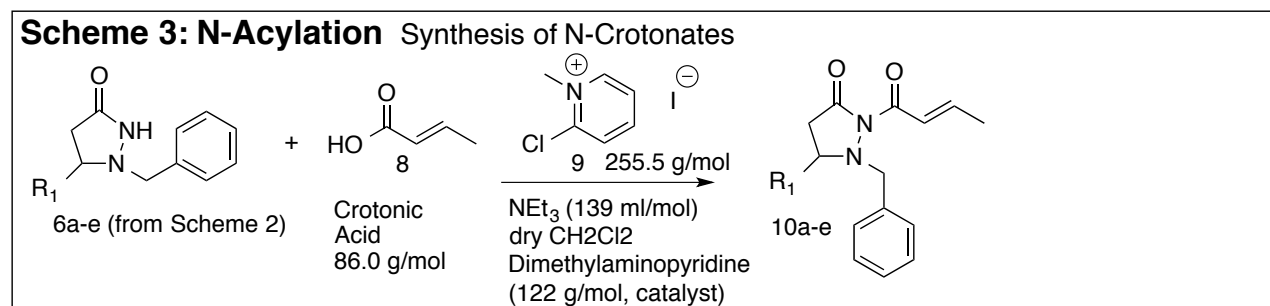
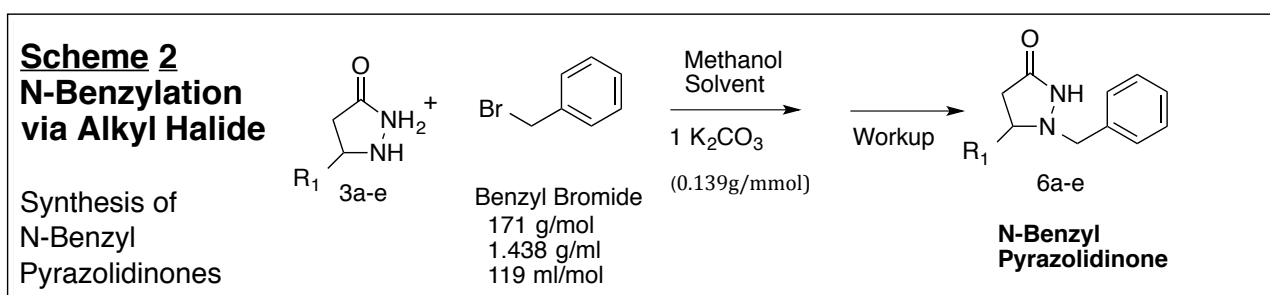
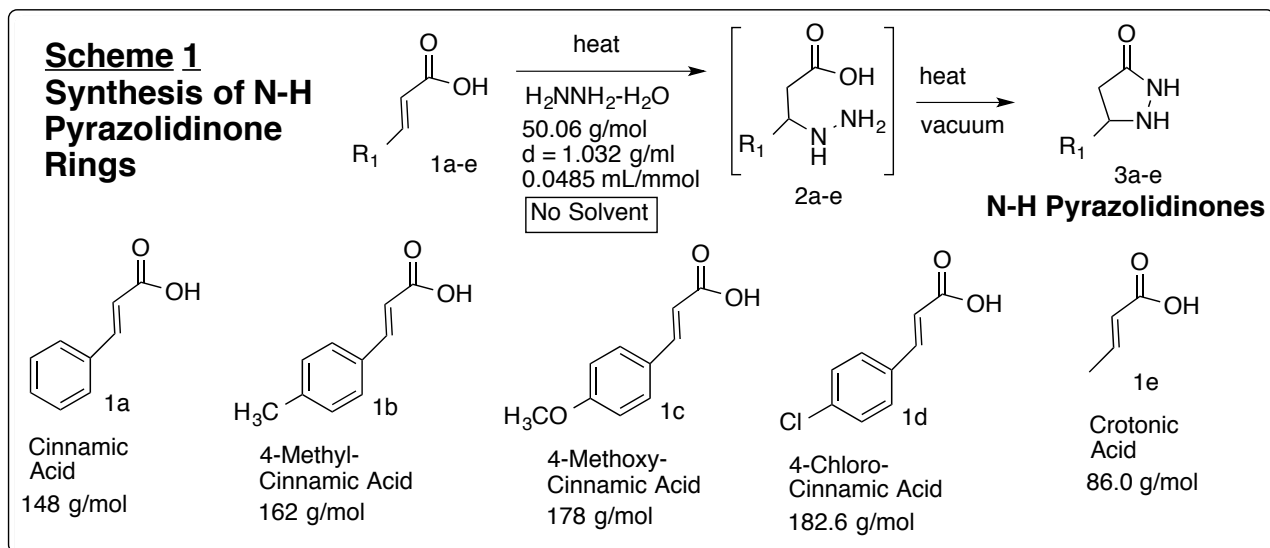


As shown in the “Lab Research Module” picture, there are three different variable R groups in the acyl pyrazolidinones. We will use five different R_1 groups; one, two, or three different R_2 groups; and for this year we’ll use a single R_3 group. But imagine if we used five of each group; we could then produce a library of up to $5 \times 5 \times 5 = 125$ different products! This kind of modular preparation of chemical libraries is routine in industry and medicinal chemistry. Subsequent biological testing can provide insights into the relationships between structure and activity. (Which parts of the molecule matter? Where does getting bigger or smaller help? Etc.)

In the first stage, pyrazolidinone rings will be assembled with just one of the substituents attached, R_1 , which is bound to the C5-carbon. (See Scheme 1, next page). In the pyrazolidinone ring numbering, the two nitrogens are #1 and #2, the carbonyl carbon is #3, etc.). An unsaturated acid will be treated with excess hydrazine hydrate. The nitrogen will initially add nucleophilically to the alkene, in a mechanism that can be viewed as involving either an enol or an enolate intermediate. This reaction is done in the absence of any solvent other than the hydrazine hydrate itself. Following addition, the product **2** undergoes loss of water and cyclic amide formation under high-temperature and vacuum, again with no solvent. The vacuum is important because it helps to distill off the water, whose hydrogen-bonding otherwise inhibits the ring closure. The pyrazolidinone rings **3** are often thick and gummy. The product (**3**) following the vacuum heating will need to be evaluated by NMR and GC-MS. Unfortunately getting rid of the excess hydrazine is hard, and it doesn’t display under either our NMR or GC conditions.

A second substituent (R_2) will be attached to N1, using Scheme 2. The bottom N1-nitrogen will effectively exchange a hydrogen for a new carbon substituent, CH_2Ph (which is called a “benzyl” group). This alkylation involves an S_N2 reaction, with the N1-nitrogen acting as nucleophile despite being neutral. The potassium carbonate serves to remove the proton after the nitrogen has become four-bonded with a formal plus charge. The risk in the S_N2 mechanism is that the nitrogen can perhaps alkylate twice, leading to a quaternary ammonium salt. Because of the S_N2 mechanism, the alkyl halide electrophile must be an S_N2 -eligible alkyl halide.

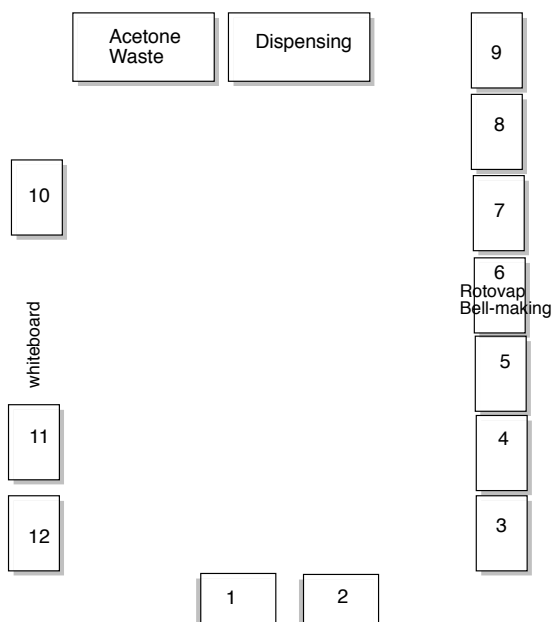
It is noteworthy that the two nitrogens in pyrazolidinones **3** behave very differently. The bottom nitrogen is sp^3 -hybridized and is basic/nucleophilic, essentially like an “amine” nitrogen. The top nitrogen is sp^2 -hybridized and is non-basic/non-nucleophilic because it is essentially an “amide” nitrogen, and is stabilized by conjugation to the carbonyl. Thus, as is typical when there are two functional groups of unequal reactivity, reaction proceeds selectively on the more reactive one.

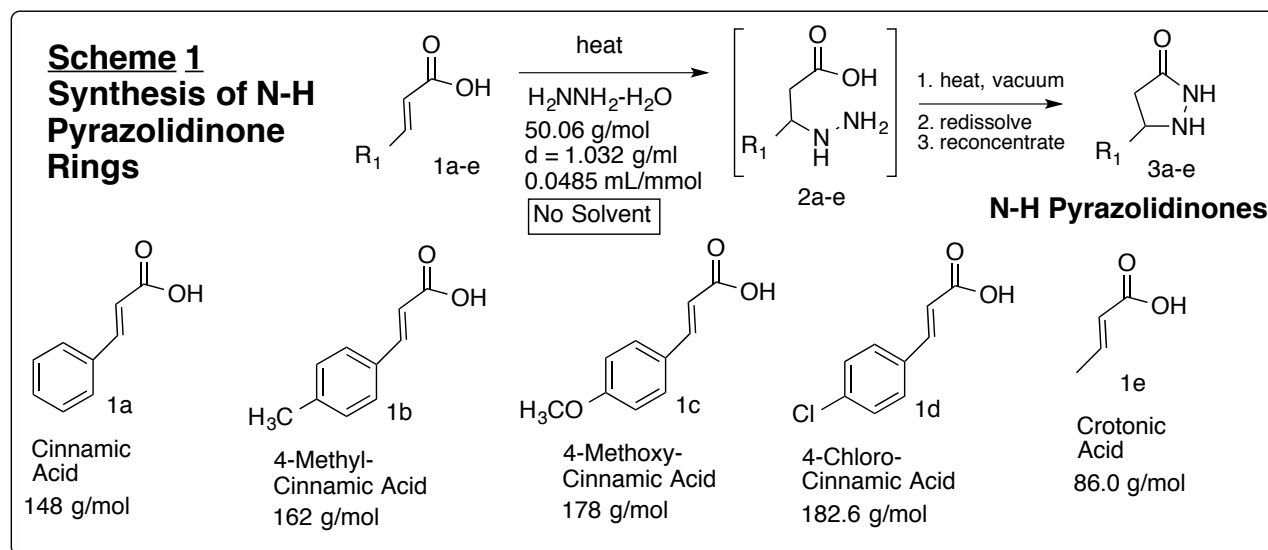


The last stage (Scheme 3) will involve acylation of the top amide nitrogen. The procedure has been invented and developed by MSUM students (most notably Amie Nowacki and Kris Brandvold). A water molecule effectively needs to be eliminated (H from the amide nitrogen in structure **6**, OH from the carboxylic acid **8**). The water oxygen gets absorbed by “Mukayama’s Reagent” **9**, and the two H’s end up getting absorbed by basic triethylamine. Dimethylaminopyridine functions as an essential catalyst. Since the function of **9** is to absorb water, the solvent needs to be dry, so that Mukayama’s agent acts on reactants **6** and **10** rather than getting destroyed by water in the solvent. This reaction takes several hours at least. So it will be desirable to start it at the end of the second lab period, and worked up during the third week. The risks in this reaction are various. First, if things are wet, it’s a problem. Second, if there are other NH or OH bonds present in residual contaminants, they will also be able to react to give new contaminants. The reaction should really work with any carboxylic acid, so if a student wanted to try something other than crotonic acid **8**, it should be possible.

Overall Format and Initial Assignments: You can work with a partner but don't need to. Each hood has a number above the top of it; see the lab map below. Assignments are based on which hood you are working in.

Hoods	Initial Reactant + Week 1	Week Two	Week Three	Chemical ID's
1 + 2	cinnamic acid 1a Execute Scheme 1. Product = 3a	Setup and execute Scheme 2 Workup and purify Product = 6a Begin Scheme 3.	Workup and Purify Product = 10a (Scheme 3)	1a, 2a, 3a, 5a, 6a, 10a
3 + 4	4-chlorocinnamic acid 1d Execute Scheme 1. Product = 3d	Setup and execute Scheme 2 Workup and purify Product = 6d Begin Scheme 3.	Workup and Purify Product = 10d (Scheme 3)	1d, 2d, 3d, 5d, 6d, 10d
5 + 7	crotonic acid 1e Execute Scheme 1. Product = 3e	Setup and execute Scheme 2 Workup and purify Product = 6e Begin Scheme 3.	Workup and Purify Product = 10e (Scheme 3)	1e, 2e, 3e, 5e, 6e, 10e
8, 9, 10	methylcinnamic acid 1b Execute Scheme 1. Product = 3b	Setup and execute Scheme 2 Workup and purify Product = 6b Begin Scheme 3.	Workup and Purify Product = 10b (Scheme 3)	1b, 2b, 3b, 5b, 6b, 10b
11, 12	methoxycinnamic acid 1c Product = 3c	Setup and execute Scheme 2 Workup and purify Product = 6c Begin Scheme 3.	Workup and Purify Product = 10c (Scheme 3)	1c, 2c, 3c, 5c, 6c, 10c





Scheme 1 Procedure: Formation of Pyrazolidinone Ring Using Hydrazine

Part A. Heating/Hydrazine Addition Phase

- Put your hot-plate/stirrer on a jack, and turn your hot-plate heater to a setting of 8, so that by the time everything else is assembled the hot plate is good and hot.
- Get a 125-mL ground-glass jointed Erlenmeyer, and add a long stir-bar. **Weigh the combination and record the mass.**
 - You'll need this mass both this week and in ensuing weeks, so record it somewhere where you'll be able to find the information next week.
- Add 20.0 mmol (0.0200 mol) of whichever alkene acid **1a-1e** is assigned to you.
 - Calculate how much mass it will take for your particular alkene acid **1a-1e**
 - Use a weighing boat.
 - Add through a powder funnel into your Erlenmeyer flask. (Record actual mass difference.)
- Add 50 mmol (0.050 mol) of liquid hydrazine hydrate via syringe.
 - Hydrazine hydrate: 0.0485 mL/mmol
- Attach a reflux condenser to your flask, with a gentle water flow.
- Set the securely clamped flask with the condenser directly on the pre-heated hot plate (heat = 8) and stir for 60 minutes at spinner = 3.
 - Make sure that the flask is not tipped and doesn't have any air-space between the hot-plate and the flask.
 - You need ideal, direct contact for the heat to do its work in the time given. If you leave space in between, or have a tipped flask without good thermal contact, the reaction might not complete correctly.
 - Within several minutes your solid should melt/dissolve, and boiling should proceed.
- During the 60 minutes, plan ahead. During the 60 minutes, prepare the following:
 - Find your vacuum adapter, and plug it into the vacuum hose. This is about 1 inch long, with a ground-glass joint on one end and a 90-degree curve. The ground-glass end will plug into a reflux condenser, the tapered end into your vacuum hose.
 - Familiarize yourself with your vacuum: With your vacuum attached to the vacuum hose, put your thumb over the end, and turn the vacuum counterclockwise to get an idea of how far you have to turn it before any vacuum actually starts to work. Then turn the vacuum back off.
 - A spike on the valve will typically need to be turned more than one quarter of a revolution, and sometimes considerably more, before the vacuum engages.

- o You'll want to know this so that when you really need to apply the vacuum, you'll be able to get near the point where the vacuum engages, and then open it VERY cautiously and slightly at first.
 - c. Ensure that the vacuum is turned all the way off (to the right). IF SOMEBODY HAS THEIR VACUUM OPEN TO THE AIR, THAT AIR LEAK WILL COMPROMISE EVERYBODY'S VACUUM AND NOBODY WILL GET THE LOW PRESSURE THEY NEED for the next procedure. Don't let your hood's vacuum ruin everybody's experiment!
 - d. Get a glove for your left hand, so you can handle the hot glassware;
 - e. Draw the structure for the pyrazolidinone **3** that you should end up making, given the starting material **1a-1e** that you used. Will yours be **3a**, **3b**, **3c**, **3d**, or **3e**? What will it look like? What will it weigh, to the nearest whole number?
 - The structure of your starting reactant dictates what the R1 group will be in your product **3**.
 - Calculate what the molar mass of your product **3** should be, given its structure. (To the nearest whole number. You can round off the atomic masses: C=12, N=14, O=16, H=1)
 - f. Calculate what the theoretical yield for your **3** should be, given the 20.0 mmol scale.
 - g. Look ahead to both subsequent stages of Scheme 1, but also to Scheme 2, which you will do today and will start shortly after you complete Scheme 1....
 - h. Get an empty NMR tube and stand it inside an empty Erlenmeyer, with a red cap;
 - i. Get a long-stemmed pipet, with a pipet bulb to be used with NMR tube;
8. After the 60 minutes of heating is complete, a) slide the hot plate out from under your flask, b) **reduce the hot-plate setting to 5**, c) turn off your reflux condenser water, and d) detach the hose from the water source and redirect it into the drain so that most of the water in the condenser can drain out.
9. Let your solution (and the hot-plate) cool for at least **5 minutes** before starting Scheme 1 Part B.

Scheme 1 Part B: Heat/Vacuum/Ring-Closure/Amide Formation Phase

10. After the 5-minutes, attach the vacuum adapter to your reflux condenser, and then slide your hot plate back under the reaction flask. The hot plate should be set at 5 for heat and 3 for stirring.
- If you didn't turn your hot plate down to 5 earlier, do so now and wait five minutes.
11. Crack the vacuum open, really, really carefully and gently at first (so that it doesn't cause everything to erupt and boil/foam over). As soon as the vacuum is engaged but the bubbling isn't too wild, open the vacuum until it's wide open as soon as possible (two full revolutions will more than suffice). If the mixture splatters/bubbles a lot, it may help to lower the plate slightly.
12. Stir/heat/vacuum for **twelve minutes**, then a) **turn off the vacuum**, b) slide the hot plate out from under the flask, c) turn your condenser water back on, and d) detach the vacuum adaptor from your reflux condenser.
- Excess vacuum heating may result in some decomposition, so avoid excess time.
 - Notice that the volume should decrease and the solution should get thicker as the water and excess hydrazine boil off with the assistance of the vacuum.
 - The hot vacuum is intended to do several things:
 - a. Facilitate/complete ring closure (**2** → **3**).
 - b. Distill away water
 - c. Vacuum/distill away much of the extra hydrazine. Leftover hydrazine causes a problematic side-product in the Scheme 2 reaction, so we want to remove it.
 - d. Unfortunately this process will still leave a problematic amount of hydrazine behind, which is why we'll do parts C and D.
 - **NOTE: If you forget to turn your vacuum off, it will ruin things for everybody else!**

Scheme 1 Part C: Redissolve the mixture in methanol


13. Slowly/carefully add 10 mL of methanol (for **3a**, **3b**, or **3e**) or 20 mL of methanol (for **3c** or **3d**) down through the reflux condenser onto your mixture.
 - Pour it down one side of the condenser. Your product in the flask is very hot, enough so that the methanol will immediately boil on contact. So don't pour in all 10 mL fast down the middle or the boiling vapor will shoot out the top and carry liquid with it! Do it carefully by pouring down one side of the condenser slowly.
 - The 4-methoxy and 4-chloro compounds **3c** and **3d** are less soluble than the others, so need more methanol to get them relatively dissolved.
14. Reapply the hot plate/stir plate, with heat still at 5 and stirring still at 3. If the stir bar stirs freely and all of your material dissolves right away, proceed with Part D.
 - If not, heat/stir until you get a homogeneous solution. Turning the stirrer to 6 might help.
 - If the stir bar isn't coming free even after several minutes, you may wish to detach the condenser and poke the stir-bar free with a spatula
 - For **3c** and **3d**, if most of the material is dissolved and the stir-bar is stirring, it's OK if there are a few undissolved particles.

Scheme 1 Part D: Reconcentration of the Methanol Solution

- **Purpose note:** Reconcentrating the methanol solution will help to remove much of the hydrazine that was not removed during the vacuum heating of Part B. This will prevent/limit problems and side-products in Scheme 2.
15. Reattach the vacuum adaptor to the reflux condenser.
 16. Turn the water flow to the condenser off, and detach the water-hose from the water source, quickly redirecting it into the sink/drain, so that most of the water in the condenser will drain out.
 17. **Hard, ask Jasperse if he's available:** Very cautiously/slowly open the vacuum.
 1. If you open too quickly the hot methanol will boil like crazy and all get sucked up the condenser and into the vacuum hose. So you need to be super careful.
 2. If the instructor is available, call him over to do this step.
 3. Crack open the vacuum as aggressively as you can get away without causing the mixture to foam over.
 4. If the mixture splatters/bubbles a lot, it may help to slightly lower the hot plate so the flask is not fully in contact with the hot surface, in order to reduce the bubbling/foaming. Gradual return of the hot plate until it's in full contact with the flask can sometimes help to moderate the foaming.
 18. Once the vacuum is wide open and the hot plate is actually touching the flask, heat/vacuum for 15 minutes (hot plate at 5, stirrer at 3).
 - It's possible that some of the material will foam up during this process; but don't stop. That will normally return to liquid form in time.
 19. After 15 minutes, a) slide the hot plate out from under your reaction mixture, b) **turn the vacuum off**, and c) detach the vacuum adapter.
 - **NOTE: If you forget to turn your vacuum off, it will ruin things for everybody else because their vacuum won't work if yours is left open to the air.**
 - Pulling the vacuum adapter is easier if you grasp the hot flask with a GLOVED hand
 - Be prepared to rapidly/immediately continue with the next step while the solution is still hot and melted.

Scheme 1 Part E: Product Analysis. NMR, GC/MS, and yield. And Deciding whether You Need to Heat and Vacuum Further.

- Hopefully everything has gone reasonably well. However, this isn't certain; perhaps the ring closure and water/hydrazine removal is not sufficiently complete, in which case you'll need to do some more vacuuming. (And in which case the yield will be too high, and the NMR will be contaminated.)
 - We don't want to do additional heat/vacuum time unless absolutely necessary, though, because doing so can cause some decomposition of your product.
 - So, in order to decide whether you're done, or whether you need to do more heating/vacuuming, you need a quick way to assess the situation. Both the NMR and/or the % yield can tell us. (See some of the following steps.) If the yield significantly exceeds 100%, that represents trouble. And if the NMR shows a lot more peaks than would be expected from the target, that also represents trouble.
20. **Immediately**, while the material is still in a hot melted form, dip a long-stemmed pipet into the hot residue and draw up about a quarter-inch (1 cm) sample (finger-nail length) of your hot mixture into the skinny tip of your pipet
 - Consult the instructor if he's available. You'll do this again in the next two weeks.
 - Sample should be small, both to give sharpest NMR and to minimize yield loss.
 21. Put your pipet with that small sample into an NMR tube. The material will probably harden (perhaps except for **3e**.)
 22. Put a septum into the top of your reaction flask to keep air out.
 - Air can cause some oxidation and decomposition of your product, particularly when it's hot.
 23. Add 1.2 mL of CDCl₃ into the same pipet that has the sample in it and is in the NMR tube, and attach a pipet bulb to the pipet.
 - The sample will have probably hardened/frozen and will probably prevent the solvent from running out the bottom.
 24. Take the NMR tube with the pipet inside it to the heat gun station. Use the heat gun to apply heat directly on the spot where the sample is hardened until the sample softens and the CDCl₃ is able to rinse through the pipet into the NMR tube.
 - Consult Dr. Jasperse for help with this if he's available.
 - Use your pipet bulb to flush solvent back and forth to help to dissolve any sample that is still stuck at the end of your pipet.
 25. Using the same long-stemmed pipet, draw out what solution it can reach and transfer it into a GC-MS vial.
 - There will still be enough solution for the NMR.
 - Basically the same solution will feed both NMR and GC-MS analyses
 26. Submit the NMR sample to the NMR queue.
 - Students will be using the NMR both for submitting, but also for processing (printing extra copies, doing horizontal expansions, etc.) So you may need to be able to work your way between "submit" and "spectrometer" modes.
 - If not in submit mode, click "New Study" to get into submit mode. The correct experiment should automatically load when you do so, if the software is working right.
 27. Submit your GC-MS sample to the GC-MS queue.
 - This will probably take a while to run.
 28. Take your flask to the balance and measure the mass.
 - Subtract the original mass of the flask and stir bar in order to determine the mass of product.
 29. If you have the NMR, or you have the mass and use that to calculate the % yield, those will provide the information needed to determine whether or not you're good, or need more vacuum.

30. **Make 3 extra copies of your NMR and put them in your drawer.** You'll need to have one as part of your lab report for Scheme 1, but you'll need to have another copy for comparison to derivative NMR's in Scheme 2, and you'll need one for inclusion in your final overall report following Week 3.
- Today's product **3** will be Scheme 2's reactant. As you go through Scheme 2, you'll want to be able to compare your NMR for product **6** to the NMR of the reactant **3** that you started with. After Scheme 3, you'll want to be able to compare/contrast NMR's of **3** to **6** to **10**.
 - NMR: If in submit mode, click "**Cancel**" to exit Submit mode in order to enter the spectrometer/processing mode for doing additional prints or horizontal expansions.
 - In "Spectrometer" mode, must have "Zones" map displayed (96 sample nodes show). Click on little circle icon () to the upper left of the spectra-display panel, if zones map not already open.
31. NMR labeling/reporting: In all of your reports, refer to this NMR as NMR-3a-e.
- (Well, don't actually refer to it as "a-e". If you're working with the "a" series, then yours should be NMR-3a. If you're the "b" series, then yours should be NMR-3b, etc.! ☺)
 - On the main NMR, rotate it 90° to the left, and write the label in the upper right-hand corner.
32. Calculate the percent yield of your Scheme 1 reaction (**1** → **3**)
- **If your yield exceeds 100%, it probably means your heat/vacuum process had problems. See instructor, in that case.**
33. Calculate how many mmol of product you have.
- Given your yield in grams, you could convert the grams into mmol if you knew the molar mass of your product. But the molar masses will be different for each of **3a**, **3b**, **3c**, **3d**, and **3e**. So you need to have drawn out your actual specific structure, and added up its molecular weight.
 - Hopefully you already had time to do all these drawings and calculations during the 30 minutes of heating earlier.
34. **Record the structure, molecular weight, mass in grams, and calculated number of millimoles on a sheet of paper and save it in your drawer. (Perhaps on an NMR you're saving?) You'll want all of that information next week, because your product 3 today will be your starting reactant next week, and your yield and stoichiometry calculations then will require that you know how many grams and millimoles you're starting with then.**
35. GC-MS labeling/reporting: In all of your reports, refer to this week's GC as GC-3a-e.
- (Don't actually refer to it as "a-e". If you're working with the "a" series, then yours should be GC-3a. If you're working with the "b" series, then yours should be GC-3b, etc.. ☺)
 - Write that label on the upper right-hand corner of every GC-MS sheet.
 - **Print two extra copies and leave in your drawer.**
36. Note: for analyzing/understanding/interpreting and reporting on your NMR and GC-MS data, see the section in the manual dedicated to that. The instructor also has a movie available from the Chem 365 website discussing the NMR details, and how to understand, report, and analyze these in your lab report.
37. Put a septum or stopper into your flask and store it for use next week. Once again, you'll need to know the mass of your flask/stir-bar next week; the mass of sample in your flask (it's next week's starting material); the molar mass; and the number of millimoles you'll be starting with.

NMR and GC-MS Data in the Research Module.

1. How to notate the spectra.	3. How to understand the Data.
2. How to report the data.	4. How to use your Mass Spectra for your main GC peak(s).

How to notate the spectra and refer to them in the reports.

Each NMR and each GC/MS will need to have a clear label that corresponds to the identity of the chemical. If the chemical is **3c**, then the NMR for that sample should be labeled as **NMR-3c**, and the GC/MS should be labeled as **GC/MS-3c**.

A labeling system like this is invaluable for synthesis reports. You can refer to **NMR-3c** in your procedure and in your data analysis sections, and you can label your actual NMR printouts (or GC-MS printouts) with the same labels.

These labels should be written on the upper right-hand corner of each spectra, relative to how a spectrum will be stapled into an actual report. Just as a page number is normally shown in the upper right-hand corner where it's easy to see as you page through a book, so too should spectra be labeled where it's easy to find the labels.

You MUST also draw the actual structure of your product on both your NMRs and your GC/MS's. (If you do several horizontal expansions, you don't need to redraw it on each page. But you should on the front page. And you should draw the label **3a-e** on every page.)

When discussing NMR's or GC/MS's in the reports, always do so by label. (For example, "GC-MS 3c was taken", or "as shown in NMR-3C, the product was very pure....")

NMR Analysis/Interpretation, General Considerations,

1. An **abbreviated summary report** process will be useful and required. Draw the structure and label the different carbons. Then make a table with the chemical shifts for the actual non-aromatic C-H's, and by each one write the letter of the carbon to which it is attached. This will demonstrate that you have analyzed and understand your spectrum.

- Also include integration.
- But you do not need to analyze/report the splitting (although you may do so.)
- Which signal is from the β -H, and which signals are from the α -H's?
- Which signals are the methyls or methoxy signals in **3b, 3c, and 3e**?
- Does your product look pretty pure? If so, there should be a fairly limited number of non-aromatic signal sets.

2. **Does your NMR confirm that your heat-vacuum completed ring-closure, and removed water and hydrazine?** If your heat-vacuum concentration of product **3** was successful, you should NOT see a big broad lump that appears in the non-aromatic region. If you do have a big lump, that probably reflects residual water and/or hydrazine. Does it look like the hydrazine/water is gone?

3. **Chirality, H-non-equivalency, and chemical shift:** In your NMR, the β -carbon will be chiral. When you have a chiral carbon, it makes the two α -hydrogens (on the CH₂ group next to the carbonyl) unequal to each other. One α -H is cis and the other is trans to your β -H, so they are not in the same chemical environment. These unequal α -hydrogens usually (not always) come at different chemical shifts. (Depending on which **3** you made.)

4. **Chirality, H-non-equivalency, and splitting:** The non-equivalence of the two α -hydrogens also complicates the splitting. They now are split by each other, as well as by the neighboring β -H. Plus the splitting magnitudes are different because of the differing distances. (The "other" α -H is closer than the β -H, so they don't usually provide equivalent magnetic splitting, and don't usually provide a nice triplet.) In practice, each of the two α -hydrogens will usually appear as a four-line "doublet of doublets", and the two α -hydrogens should normally combine to show eight lines. The β -H will typically also look like a 4-line "doublet of doublets", unless

further split by the methyl group in **3e**. (In one of the **3**'s, the two α -hydrogens have almost exactly the same chemical shift and could look like just a simple doublet that integrates for 2H, in which case the β -H may look like a simple triplet.)

- N-H hydrogens**, like OH hydrogens, are typically broad and unpredictable. In many cases you won't be able to see them at all. Don't look for them or try to assign them
- For your reports, account for all the hydrogens connected to sp^3 carbons. You don't need to discuss/present N-H hydrogens or aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)
- Signature signals**: All of the samples will have the interesting α - and β -hydrogens. But there will be other signature peaks for other situations:
 - the para methoxy methyl in **3c**;
 - the para methyl group in **3b**;
 - the methyl doublet in the **3e**.
 - 3a** and **3d** won't have any non-aromatic C-H's other than the three on C- α and C- β .
- Nitrogen impact on chemical shift**: The impact of a nitrogen attachment on chemical shifts is similar to the impact of an oxygen attachment. In other words it has an addition factor of about +2. This will impact the chemical shift for hydrogen on the β -carbon (β relative to the carbonyl).
- Chemical shift logic**:
 - For the α -hydrogens in each of **3a-3e**, they are next to a carbonyl. So we'd expect them to come in the 2's. They are also β to nitrogen and perhaps also an aromatic, which further pushes them a bit downfield. So typically they should fall in the high 2's or perhaps slip into the low 3's.
 - For the β -hydrogen in **3a-3d**, the β -carbon has both a nitrogen (+2) and an aromatic (+1) attached, so normally we'd anticipate the β -hydrogen to show up in the 4's. For the β -hydrogen in **3e**, the β -carbon has a nitrogen (+2), so we'd anticipate the β -hydrogen to show up in the 3's.
- Impurities/contamination**: Real products often are accompanied by many impurities. The present of impurities, can complicate NMR interpretation. Recognizing which signals come from the desired product and which do not is significant. And qualitatively recognizing whether a spectrum is relatively clean or is pretty contaminated is important.
 - Remember that there should be a logical integration ratio for the main H's in your actual product **3**
 - Often there will be a variable amount of smaller signals in the baseline resulting from contaminants, side products, and product-decomposition. The less, the better.
 - In the cases of **3b** and **3c**, if you see "extra" methyl groups, those might result from side products or from starting reactants **1b** and **1c** that never reacted at all. Again, the less the better.
- Comparison to Other NMR's**: It may be very interesting to look at how your NMR looks compared to how NMR's of other students look.
 - How different is yours from different versions of **3**?
 - If you compare yours to somebody else who made the same version of **3**, how clean is yours compared to theirs?

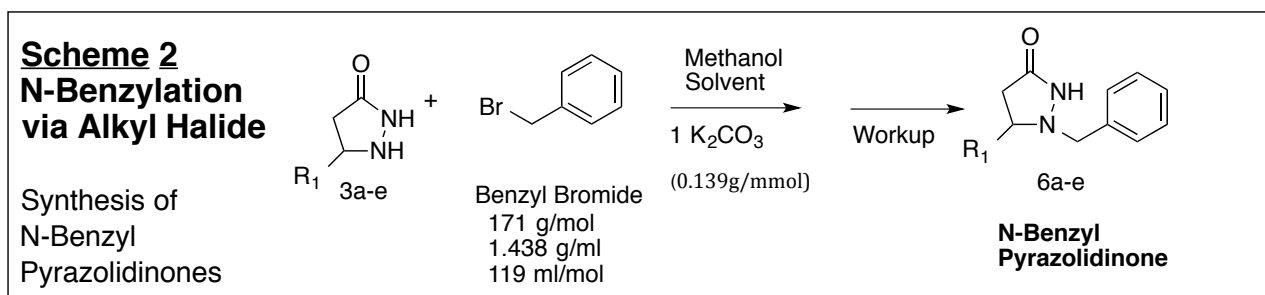
GC-MS Analysis/Interpretation

- Clearly label each page of each GC/MS printout with the appropriate GC/MS-**3a-e** label in the upper right corner.
- Draw the structure for your specific product on each GC-MS sheet, and write the molecular weight underneath the picture. (No "R" groups; write the specific structures.)

14. **Retention time?** What is the retention time for your **3**?
 - Bigger structures will have longer retention times. Next week, your product **6** should have a longer retention time than this week's **3**. Likewise this week heavier versions of **3** should have longer retention times than smaller versions.
15. **Purity:** How pure is your **3** by GC?
 - Many contaminants will NOT appear, since they come off fast during the solvent delay. So your purity reading will be deceptively high. NMR, which shows everything, is qualitatively more representative.
16. **Mass Spec and Molecular Ion:** For your major product **3**, check in the mass-spec whether there is a molecular ion peak that matches the molecular weight for your product.
17. **Lab report:** In your lab report, make sure that you have not only attached the labeled GC-MS information, but that you also discuss/present the retention time and purity in your data/results/discussion section.

Scheme 1/Week 1 Lab Report:

1. Write a standard synthesis style lab report for your Scheme 1 reaction (**1** → **3**).
2. Make sure that all structures are drawn explicitly.
 - As always for a synthesis style report, you'll want to draw out the reactants and the products. In this case, be sure you draw the **actual** reactant and product in your reaction.
 - None of your pictures should have an "R1": you should illustrate each structure with your actual R1 group drawn, whether that's methyl or phenyl or 4-methoxyphenyl or whatever.
3. Show all calculations. (Including any mole ⇒ mass for reactants, or mass ⇒ mole for products)
4. Include procedural details and observations as usual.
5. Calculate mass yields, and percent yields, etc., for product **3**.
6. Include your NMR-**3** (**3a** or **3b** or **3c** or **3d** or **3e**, as your case may be).
 - This must be clearly labeled.
 - Be sure to draw your structure, and then provide an abbreviated summary report. This should include a listing of chemical shifts for **non-aromatic C-H hydrogens**, integrations for them, and a matchup-assignment between signals and hydrogens in the molecule.
 - **Note: you do not need to include aromatic H's, N-H's, or impurities/solvents/contaminants in the abbreviated NMR summary report.** There are so many overlapping aromatic H's that they are not really interpretively useful.
7. By putting definite labels on your NMR (for example, **NMR-3b...**), you will be able to easily refer to that that NMR in your report. (For example, "NMR-3b was submitted at this point." Or "NMR-3b shows considerable product, but it is clearly not clean. There is extensive solvent visible...".)
8. Include your GC-MS-**3**, and **print and attach mass spectra**.
9. Include a results/data/discussion/analysis section. The analysis/discussion section needs to address what the yield information told you, and what the NMR and GC-MS data tells you about both the success and the efficiency of your reaction, and the purity of your product **3**.
10. The results/data/discussion/analysis section should summarize what the mass/yield/NMR/GC-MS data is, and what conclusions can be drawn from them. Just attaching the NMR's and GC-MS's without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic C-H hydrogens in your NMR? What is your GC-retention time? Between the NMR and the GC, did it look like the product **3** was formed successfully, and does it look reasonably clean? Or is it obviously significantly contaminated?
11. Note: Keep two extra copies of your NMR and your GC-MS's. Pyrazolidinone **3** functions as the product in week one report, but it is the reactant in the week two report. So when writing up and analyzing Scheme 2, you'll need information about mass, molecular weight, structure, and mmol of your reactant **3**. You'll also need to have NMR and GC for **3** so that you'll be able to compare your product **6** to reactant **3** and tell whether the reaction really worked. You'll also want copies of **3** for your Final Report after week 3.



Scheme 2 Part A: Redissolve in Methanol

- Turn hot plate to 5.
- To the flask with your product 3 from Scheme 1, attach a condenser with gentle water flow.
- Add 15 mL of methanol for **3a**, **3b**, **3d**, or **3e**. Add 35 mL of methanol for **3c**.
 - More methanol is needed for 4-methoxy compound **3c** because it is less soluble.
- Heat the mixture on the hot plate with the stirrer at 5 until the material dissolves and becomes completely homogeneous.
 - If the stir bar isn't coming free even after several minutes, detach the condenser and try to poke the stir-bar free with a spatula
 - Make sure that there aren't big chunks or blobs of undissolved material on the outside. Everything needs to be dissolved or else in as small of particles as possible.
 - While you are heating/dissolving/waiting, calculate the amounts and find the potassium carbonate and benzyl bromide that will be used in the next steps.
- Once your material is largely dissolved, reduce the hot plate setting to 4.

Scheme 2 Part B: Addition and reaction of Benzyl Bromide

- Add K₂CO₃:** Add 20 mmol of potassium carbonate powder (K₂CO₃, 0.139g/mmol) through a powder funnel. (It's a white solid, and will be next to one of the balances.)
 - You'll need to detach the reflux condenser while you do this. If your benzyl bromide is ready, you can immediately add that too. If not, reapply the reflux condenser until benzyl bromide time.
 - Because the potassium carbonate is ionic, it won't dissolve in the methanol.
 - The function of the potassium carbonate is to deprotonate the proton that is originally on the nitrogen, but that gets replaced by the benzyl group
- Calculate 0.85 equivalents of benzyl bromide.** Calculate how many mL of benzyl bromide (119 mL/mol) you need to add 0.85 mmol benzyl bromide per each mmol of 3. In other words, if you have 20.0 mmol of **3**, how many mL of benzyl bromide will it take to add 17.0 mmol?
 - Calculation: Benzyl bromide 0.119 mL/mmol.
 - You need to know how many mmol of reactant **3** you are working with. To do that, you need to know your structure, your molar mass, and your actual number of grams that you began with today. You should have recorded and saved all of this information at the end of Scheme 1.
 - The reason we're using less than an equal amount of benzyl bromide is because excess benzyl bromide leads to side products. Probably at least 10-15% (if not more) of your mass of reactant **3** is probably junk or side products or unreacted alkene **1** or something.
- Carefully/slowly add the 0.85 equivalents of benzyl bromide** (119 mL/mol) by syringe. (It's a smelly liquid in the hood. You can temporarily carry the entire bottle over to your hood, so long as you return it as soon as you've finished adding it. ☺)
 - In order to add it, first detach the reflux condenser so that you can drip the benzyl bromide straight into the reaction flask. Reattach the reflux condenser as soon as addition is done.

- There may be some initial foaming; add slowly enough so that it doesn't foam up uncontrollably and foam over the flask.
 - Replace the reflux condenser as soon as all the benzyl bromide has been added
 - Benzyl bromide smells bad and is a lachrymator. Avoid getting it on your hands or spilling any. The benzyl bromide should be returned to the main dispensing hood as soon as you are done adding it to your reaction.
9. Let the benzyl bromide reaction continue for **15 minutes**, with stirring (setting 3) and heat (setting 4). After the 15 minutes remove the hot plate.

Scheme 2 Part C: Workup Using Separatory Funnel and Chromatography

10. Add 20 mL of dichloromethane.
11. Add 30 mL of water and stir cautiously, then vigorously, for 30 seconds.
- Hopefully the two layers will be relatively homogeneous, with most of the solids dissolved either in the organic or aqueous phase. For methoxy substrate **6c**, that may not be so true...
12. Pour the mixture into a separatory funnel.
13. Rinse the original reaction flask with an additional 10 mL dichloromethane and add to the separatory funnel.
14. After the separatory funnel layers have settled, drain off the dichloromethane phase (lower layer, presumably) into a 250-mL Erlenmeyer (not the ground glass one).
15. Then add another 15mL of dichloromethane into the separatory funnel, shake, let settle, and again drain off the lower dichloromethane layer into the same Erlenmeyer with the first extract
- The liquid left in the separatory funnel should be aqueous, with nothing we want. But you may want to save it for a while, just in case your layers got mixed up by mistake! You probably don't want to go back and start over from Scheme 1 again!
16. Take a drop of water from the aqueous phase (can use a pipet or a boiling stick or something) and add it to a piece of pH paper. Record the approximate pH in your lab report.
- Hopefully the pH is somewhere in the 4-10 range. Let Dr. Jasperse know if it isn't.
17. Add 50 mL of ether to the same Erlenmeyer that already has the dichloromethane extracts.
18. Preweigh a 250-mL groundglass Erlenmeyer with a clean long stir bar already inside.
19. Find your fritted filter funnel (the unit that has a 6-inch column, a white filter disk, a ground-glass joint on the bottom, and a vacuum vent.) Attach this to the 250-mL Erlenmeyer flask with stir-bar.
20. Add 15 grams of silica gel (approximately) to the fritted filter funnel.
21. Add 20 grams of sodium sulfate to the fritted funnel, on top of the silica gel layer.
22. Filter your organic solution. Pour your organic solution directly onto the sodium sulfate/silica filter. Carefully open the vacuum so that it pulls the solution through the filter pack into the Erlenmeyer without causing excessive foaming or getting material sucked back up into the tube.
23. Water and highly polar side products will hopefully be retained on the polar silica column, while the desired product will hopefully wash through. (Side products that will hopefully be retained might include any double-alkylation side product; any residual hydrazine-derived side products; any unreacted pyrazolidinone **3** that may not have been converted in Scheme 2; and original carboxylic acid **1** that may not have been converted in Scheme 1.)
24. Pour 25-mL of a 2:1 ether/dichloromethane mixture in a graduated cylinder, and add 3 mL of methanol to that. Rinse this through your filter column. (For **6e**, do an additional 25-mL rinse.)
- This should ensure that all/most of the desired product comes through, so that your yield can be reasonable. Hopefully without also washing off many of the polar side products that we want to stay on the silica.
 - Substrate **3e** binds more tightly to the silica than **3a-d**, so some extra rinsing may help to boost the yield

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Scheme 2 Part D: Concentration

25. To your 250-mL flask with the long stir bar and the organic solution, attach a reflux condenser, at first with water running through it, with a vacuum adaptor connected to a vacuum hose.
26. While stirring and with no heat turned on, very cautiously/slowly open the vacuum. Things will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
 - Within about 2-5 minutes you should be able to get the vacuum fully opened. (This may depend on how much solvent is in your 250-mL ground-glass Erlenmeyer.)
 - Notice the condensation (and perhaps ice) that forms on the outside of the flask.
 - This is a manifestation of how endothermic the vaporization process is.
27. Once the vacuum is wide open, turn the condenser water off, detach the hose from the water source and quickly direct it into the drain so that most of the water runs out. Turn the hotplate heat to 5 and vacuum for 25 minutes while stirring rapidly (set the stirrer to 6.)
 - Try to wipe off the frost from the walls as early as possible, this will make the solvent boiloff more efficient.
 - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
 - In many cases, foaming may be a problem. The material may foam up like cotton candy or taffy. This occurs when a limited amount of solvent is still present, but the mixture has gotten so thick that the solvent can't easily escape from its "shell" of non-volatile material. So when solvent molecules inside are vaporizing, but they can't escape easily, the volume puffs up as with cotton candy. With continued heating, though, usually any entrapped solvent does escape, and the material collapses back to a thick paste.
28. During the 25 minutes, do some calculations if you haven't before.
 - Draw out the structure of what your product **6** should be.
 - Given the structure, calculate what the molar mass of **6** should be, to the nearest whole number.
 - For atoms C, N, O, and H, you can just use their whole number masses in all calculations (in other words, C is 12, N is 14, O is 16, and H is 1. You don't need to use more detailed mass values than that, for example just use 1 rather than 1.0079 for H.)
 - For Cl, use 35.5, because that doesn't round off to a whole number so nicely as H/C/N/O.
 - Given the molar mass of your product, and given the mass and mmol of the reactant **3** that you started with, calculate what your theoretical yield in grams should be for product **6**.
 - The molar mass will also be needed for preparing your next reaction (Scheme 3).
29. After the vacuum-heating has completed, turn off your vacuum first, then turn off the heat, remove the flask from the heat, and detach the vacuum hose.
30. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. A glove to grip the hot flask may help. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as it cools. Attach a septum to block air from your hot sample as soon as possible.
31. Add 1.2-mL of CDCl₃ into the pipet, then take the NMR tube with the pipet inside it over to the heat gun. With or without the instructor's assistance try to heat and melt your product so that the solvent can flow into the NMR tube.
32. Reach the long pipet in, and transfer the top quarter of NMR solution into a GC-MS vial. Submit this sample into the GC-MS queue. This should be labeled as "GC-**6x**" and referred to as "GC-**6x**" in your report. (Well, not really **GC-6x**, it should be **6a** or **6b** or **6c** etc., depending on which chemical you're really working with.)

33. Submit the NMR to the NMR queue for purity analysis.
- Students will be using the NMR both for submitting, but also for processing (printing extra copies, doing horizontal expansions, etc.) So you may need to be able to work your way between “submit” and “spectrometer” modes.
 - If not in submit mode, click “New Study” to get into submit mode. The correct experiment should automatically load when you do so, if the software is working right.
 - Each partner will want two copies of the NMR printouts. One for inclusion in your Week 2 lab report, but the second both for comparison purposes when you complete Scheme 3, and also to include in your final data report.
34. Measure and record the mass of the flask. Given the original mass of the flask and stir bar, determine the yield of product in grams.
- Record this on an extra sheet; save in your drawer. You’ll need this data for Scheme 3.
35. Calculate the percent yield for Scheme 2, based on the number of millimoles of benzyl bromide you began with. Since we used 0.85 equivalents of benzyl bromide, that functions as the limiting reactant for Scheme 2.
- This is a record of the Scheme 2 process.
 - Note: Yields will probably be modest, especially for **6e**. But we’ve gone through a lot of processes, there have been a lot of competing side reactions that cut into actual yield, plus probably some of our desired material was lost to solvents or silica while trying to remove side products.
36. Given the structure of your product and the molar mass that you calculated earlier, determine the number of mmol of product **6** that you made.
- Record this on an extra sheet; save in your drawer. You’ll need this for calculations involved in Scheme 3.
37. Also, just for interest, calculate the overall percent yield from the beginning, based on the number of grams/mmol that you ended with, for the **overall 1 → 3 → 6** operations thus far.
- From the 20 mmol of **1** that we started with, what percentage of that is now at **6**?
 - Context: For a 3-operation sequence, if each step is 80% (good), you’d end up 51% overall.

38. Critical Note: Start the next reaction as described in Scheme 3 before week two is done.

- Before week two is completed, it is urgent that you get the final reaction started, see Scheme 3.
- This reaction takes at least several hours after it is begun, so you don’t want to be trying to both start and finish it during the same lab period. Plus it requires time-consuming workup.
- So it is essential that it gets set up before the third lab period.
- If you don’t get it started during the second lab period, you will want to/need to come in sometime at least a day before the final lab period to get it started.

Scheme 2 Part F: NMR and GC-MS.

- Checking your NMR prior to starting Scheme 3 is wise.
- Each NMR and each GC/MS will again need to have a clear label that corresponds to the identity of the chemical.
- You **MUST** again draw actual structures of your product on both NMRs and GC/MS's.
- When discussing NMR's or GC/MS's in the reports, always do so by label. (For example, "GC-MS-6c was taken", or "as shown in NMR-6C, the product was very pure....")

NMR Analysis/Interpretation. Concepts and expectations are similar to the Scheme 1 report.

39. An **abbreviated summary report** process will again be required. Draw the structure and label the different carbons. Then make a table with the chemical shifts for the actual **non-aromatic C-H's**, and by each one write the letter of the carbon to which it is attached. This will demonstrate that you have analyzed and understand your spectrum.

- **Also include integration.**
- But you do not need to analyze/report the splitting (although you may do so.)
- Which signal is from the β -H, which are from the α -H's, and which are the benzyl H's?
- Which signals are the methyls or methoxy signals in **6b**, **6c**, and **6e**?
- Does your product look reasonably pure?

40. **Does your NMR confirm that the reaction, and the solvent-removal basically worked?**

- Does it look like your starting reactant **3** is still present, or gone?
- Does it look like there is significant amount of solvent left? (Dichloromethane leaves a singlet at about 5.3 ppm.)

41. **Chirality, H-non-equivalency, and chemical shift:** The chirality of the β -carbon not only makes the two β -H's non-equivalent, but also makes the two hydrogens on the newly attached CH₂ carbon nonequivalent. The two benzyl hydrogens should each appear as two doublets.

42. **Chirality, H-non-equivalency, and splitting:** As in product **3**, the non-equivalence of the two α -hydrogens, and now the two benzyl hydrogens, complicates their splitting.

- Each of the two α -hydrogens will usually appear as a four-line "doublet of doublets".
- The β -H will typically also look like a 4-line "doublet of doublets", unless further split by the methyl group in **6e**.

- **The two benzyl H's are each split by each other, so each should look like a doublet.**
- **The appearance of these two new doublets is very diagnostic for product **6** formation!**

43. For your reports, **account for all and only the hydrogens connected to sp³ carbons.** You don't need to discuss/present N-H hydrogens or aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)

44. **Signature signals:** All of the samples will have the interesting α - and β -hydrogens, and the benzyl hydrogens (5 hydrogens combined). But there will be other additional signature methyl peaks for **6c**; **6b**; and **6e**.

45. **Chemical shift logic:**

- The α -hydrogens, being next to a carbonyl, but being also β to nitrogen and perhaps also an aromatic, should fall in the high 2's or perhaps the low 3's.
- The β -hydrogen in **6a-6d** should show up around the low 4's. For the β -hydrogen in **6e**, we'd anticipate the β -hydrogen to show up in the 3's.

- For the benzyl hydrogens, they are on a carbon that has both a nitrogen (+2) and a benzene (+1) attached, so we'd expect them to come around the low 4's or high 3's as well.

46. **Impurities/contamination:** Recognizing which signals come from the desired product and which do not is again significant.

- Remember that there should be a logical integration ratio for the main H's in product **6**

47. **Comparison to Other NMR's:** It may be very interesting to look at how your NMR **6** looks compared to how other NMR's look.

- How different is your **6** from the **3** that you began with in Scheme 2?
- How different is your **6** compared to classmates who made different versions of **6**?
- How clean is your NMR compared to that of classmates who made the same version of **6**?

48. **GC-MS:** Clearly label each page of each GC/MS printout.

49. Draw the structure and molecular weight for your specific product on each GC-MS sheet.

18. **Retention time?** What is the retention time for your **6**? How much longer is it than **3**?

19. **Purity:** How pure is your **6** by GC?

20. **Mass Spec and Molecular Ion:** For your major product **3**, check in the mass-spec whether there is a molecular ion peak that matches the molecular weight for your product.

21. **Mass Spec and Fragmentation:** The weakest break-point is at the N-benzyl bond. You should be able to see a benzyl fragment ($\text{PhCH}_2^+ = 99$) and a fragment that it molecular weight - 99. Do you see both of those fragments?

22. **Lab report:** In your lab report, make sure that you have not only attached the labeled GC-MS information, but that you also discuss/present the retention time and purity.

Scheme 2/Week 2 Lab Report:

1. Write a standard synthesis style lab report for your Scheme 1 reaction (**3** → **6**).

2. Make sure that all structures are drawn explicitly.

- As always for a synthesis style report, you'll want to draw out the reactants and the products. In this case, be sure you draw your **actual** reactant **3** and product in your reaction.
- None of your pictures should have an "R1": you should illustrate each structure with your actual R1 group drawn, whether that's methyl or phenyl or 4-methoxyphenyl or whatever.

3. Show all calculations. (Including any mole ⇒ mass for reactants or products)

4. When listing your chemicals/reactants and showing gram → mol calculations, make sure that you include your main reactant **3**!

5. Include procedural details and observations as usual.

6. Calculate mass yields, and percent yields, etc., for product **6**.

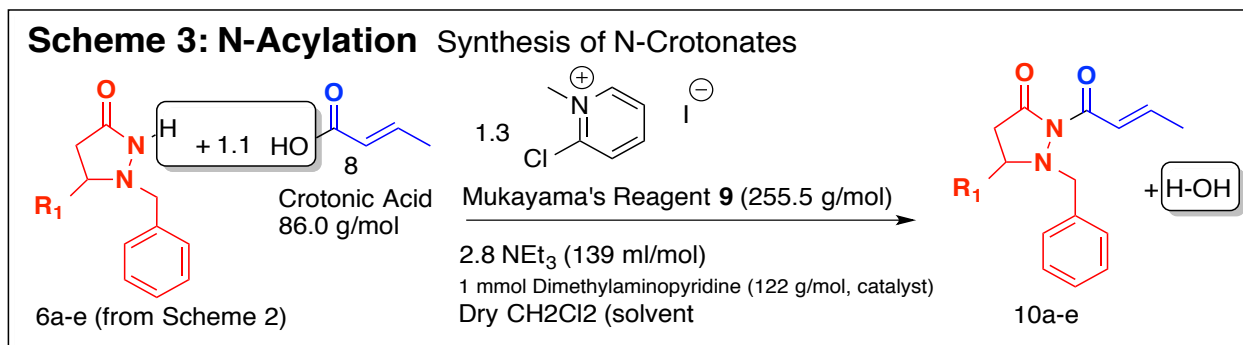
7. Include your **NMR-6** and **GC-MS-6**, with clear labels, structures drawn, **and the abbreviated summary report** for non-aromatic C-H hydrogens for **NMR-6**.

8. Print and attach mass spectra for **GC-MS-6**.

9. Include a results/data/discussion/analysis section. The analysis/discussion section needs to address what the yield information told you, and what the NMR and GC-MS data tells you about both the success and the efficiency of your reaction, and the purity of your product **6**.

10. The results/data/discussion/analysis section should summarize what the mass/yield/NMR/GC-MS data is, and what conclusions can be drawn from them. Just attaching the NMR's and GC-MS's without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic C-H hydrogens in your NMR? What is your GC-retention time? Between the NMR and the GC, did it look like the react **3** was successfully converted to product **6**, and does your product **6** look reasonably clean? Or is it obviously significantly contaminated? Was the yield respectable, or terrible?

11. Note: Keep extra copies of your NMR and your GC-MS's. Pyrazolidinone **6** functions as the product in week two report, but it is the reactant in the Scheme 3/Week 3 report. So when writing up and analyzing Scheme 3, you'll need information about mass, molecular weight, structure, and mmol of your reactant **6**. You'll also need to have NMR and GC for **6** so that you'll be able to compare your product **10** to reactant **6** and tell whether the reaction really worked. You'll also want copies of **6** for your Final Report after week 3.



Scheme 3 Procedure: N-Acylation of N-Benzyl Pyrazolidinone (6a-e) Using Crotonic Acid (8) and Mukayama's Reagent (9)

- Start new Scheme 3 lab report here

Scheme 3, Part 1: Starting the Reaction for N-Acylation, 6 → 10

- Determine the number of mmol of pyrazolidinone **6** that you have in your Erlenmeyer.
 - You should have calculated your mass yield, as well as the molar mass and the number of mmol for your version of **6**, at the end of Scheme 2.
 - Note: Your substrate **6** might be somewhat contaminated, so you may not actually have as many mmol of **6** as you calculated based on mass alone.
- Add 25 mL of dry anhydrous CH₂Cl₂ and stir. (The correct bottle will have “molecular sieves” pellets to sponge up any water, and the label should say “Anhydrous” or “dry”.)
 - Add a rubber septum to exclude air (and the water that it's in the air), if you aren't ready to continue with following steps very quickly.
 - Hopefully the sample will dissolve on it's own within a few minutes. If not, you may wish to add a reflux condenser and heat the mixture (hot plate 5) until it dissolves. If you did heat it to facilitate dissolving, then turn the hot plate off as soon as things are dissolved, and take the flask away from the hot plate to cool for 5 minutes.
- Add 1.1 equivalents of solid crotonic acid **8** (86.0 g/mol). (Based on how many mmol of pyrazolidinone **6** you have.) (The crotonic acid should be by one of the balances.)
 - In other words, if you have 10 mmol of **6**, add 11 mmol of **8**.
- Then add 1 mmol of dimethylaminopyridine (122.2 g/mol). This is a catalyst, so the exact amount isn't crucial, and we're using a lot less of this than of the other reactants.
- Weigh out and add 1.3 equivalents of 2-chloro-1-methylpyridinium iodide (Mukayama's Reagent, **9**, 255.6 g/mol).
 - Immediately reclose the bottle from which you took reagent **9**, since it is moisture sensitive. If you leave it uncovered, it will go bad and subsequent users will have problems.
 - Mukayama's reagent functions to stimulate and absorb loss of H-OH from reactants **6** and **8**.
 - The “excess” is to absorb any trace water on the glassware, from the air, or in the solvent.
- Record all of your observations. (Is the mixture homogeneous or heterogeneous, etc.)
- Syringe in 2.8 equivalents of triethylamine (139 mL/mol).
 - This will get the reaction started.
- Record observations. Does anything happen? Exotherm or anything? Color change? Solubility changes?
- Add a septum into your flask, and poke a syringe needle through it to serve as a pressure vent.
- THIS IS AN IDEAL PLACE TO STOP AT THE END OF WEEK TWO. LET THINGS STIR FOR 5 MINUTES, MAKE SURE THERE IS A SEPTUM TO YOUR FLASK WITH A SYRINGE NEEDLE POKING IN TO SERVE AS A PRESSURE VENT, AND STASH IT IN YOUR DRAWER TILL NEXT WEEK.**
 - Emergency Note: If you don't get this far during week two, be sure that you come in and get the reaction set up at least a day before your lab period.

Scheme 3, Part Two: Workup/Isolation of Product 10 (Week Three Begins Here)

11. Add 50 mL of aqueous NH_4Cl /water solution (already prepared, in the hood).
12. Get about 45 mL of ether (possible labeled as ether “ether” or “diethyl ether”)
13. Pour about half of the ether and about half of the NH_4Cl /water into your reaction flask. Stir the mixture for a minute.
14. Pour the contents of your reaction flask into a separatory funnel.
15. Add the rest of the ether and NH_4Cl /water into your Erlenmeyer, rinse them around, and then add that to your separatory funnel.
 - The purpose of the NH_4Cl /water wash is to convert the neutral triethylamine into ionic triethylamine-hydrochloride, which will extract into the aqueous layer.
16. Shake cautiously, with venting, then allow the mixture to settle.
 - The organic layer will probably be more strongly colored
 - The top layer will normally be the organic layer, but if you aren't sure, add some extra water to see which layer gets bigger.
 - If the layers separate poorly, consult the instructor and we can improvise.
17. Prepare a clean 250-mL Erlenmeyer flask with a ground-glass joint, with a long stir bar inside, and with the mass of the combination recorded.
 - This could be the same flask/stirrer you did the Scheme 3 reaction in, and whose mass you have previously recorded. If so, clean it by rinsing/brushing with water, then with acetone.
18. Find a fritted filter column (the one with the 6-inch column above a white fritted filter, with a ground-glass joint on the bottom, and with a vacuum connector on the side.)
19. Weigh out 20 g of silica, pour it into the filter funnel, and attach the filter funnel into the 250-mL Erlenmeyer.
 - This is a lot more silica than was used in Scheme 2. When the dry silica is poured into your fritted filter column, it should fill about half of the space from the frit to the top of the column. If not, consult instructor. If the pile is too short, contaminants will get through.
 - The silica layer is meant to absorb some polar, sticky byproduct from the Mukayama Reagent **9**, and also any triethylamine hydrochloride that did not get removed by the separatory funnel treatment. We are doing a crude but rapid “flash chromatography” to try to partially purify your product **10**.
20. Weigh out 30 g of sodium sulfate, and pour this on top of the silica bed.
 - The sodium sulfate will function to absorb water.
21. Assuming the top layer in the separatory funnel is the organic phase, carefully drain out the lower aqueous layer into a beaker.
 - If you can't tell which layer is which, and if your sep funnel has space, add in either an extra 20 mL of brine and/or an extra 20mL of ether to try to help clarify.
22. Carefully drain the organic solution onto the filter column, evenly so that the surface of the column doesn't get all pitted. (Pitting may compromise the effective length/function.)
 - If you scissor-cut a piece of filter paper to kind of lay on top of the sodium sulfate, that can help to protect against pitting. Probably not needed.
23. Carefully/gradually open up the vacuum so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
24. Pour the aqueous phase back into the separatory funnel.
25. Add an additional 25 mL of 2/1 ether/dichloromethane, and shake it up briefly. The organic layer will probably again be the top layer.
26. Pour off the aqueous layer back into the same beaker (this will get thrown away)
27. Drain the organic phase through the filter column. Purpose: this extra rinse of the filter column should remove more of the desired product otherwise still absorbed on the silica.

- Waste handling: all of the solid silica and sodium sulfate in your filter column should go into a solid-waste container in the hood. Bulk may NOT go into the sink or garbage. (Trace amounts stuck on wall may.)

28. **Concentrate this solution.** Attach a reflux condenser with no water flow, and with a vacuum adaptor on top. While stirring and with no heat turned on, slowly/carefully open the vacuum. Things will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
- Within about 2 minutes you should be able to get the vacuum fully opened.
 - Notice the condensation (and perhaps ice) that forms on the outside of the flask.
29. Once you've been able to safely open the vacuum fully, turn the hot plate on at a setting of 5, and heat/boil/vacuum the mixture while continuing to stir (setting 6) for 20 minutes.
- Try to wipe off the frost from the walls as early as possible.
 - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
 - In some cases, the material will foam up like cotton candy or taffy. With continued heating, though, usually the entrapped solvent does escape, and the material collapses back to a thick paste.
30. After the vacuum-heating, turn off your vacuum first, then turn off the heat, remove the flask from the heat, detach the vacuum hose, and remove the condenser.
31. **NMR-Sample Preparation:** Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as soon as it cools.
32. Add 1.0 mL of CDCl_3 as solvent to your NMR sample.
- We won't run a GC on this one. The product is so big that it doesn't vaporize well.
33. Submit your NMR-10 to the NMR queue.
34. **Mass/Yield:** Weigh your flask, so that you can determine mass, millimoles, and percent yield.
- It is well possible that your mass recovery will exceed your theoretical yield. That would be impossible if the material was all and only desired product 10. But there were a lot of side products, and solvents, to try to remove in a short purification sequence. If the yield exceeds 100%, perhaps by a lot, that's evidence that the purification/distillation was imperfect. (Perhaps badly so....)
35. **Yield Analysis:** Calculate the % yield for both the final step (Scheme 3), but also for the overall process. (If every step of the synthesis had worked perfectly, you'd end up with 17 mmol of product. So 17 mmol is your theoretical number of moles overall.)

Scheme 3 Part Three: Cleaning Up and Pooling Products into the Collection Jars

1. Add 10 mL of dichloromethane to your flask, and try to dissolve up all of your product with that.
 - If that doesn't succeed, try heating the mixture on a hot plate for a few minutes to facilitate solubility, and/or perhaps add an additional 10mL of dichloromethane.
 2. Once the product is dissolved, simply pour the solution into the appropriately labeled collection jar.
 - Make sure you're putting your stuff into the correct jar
- | |
|---|
| <ol style="list-style-type: none">3. IF POSSIBLE, AND IF YOU'VE GOTTEN AN NMR FOR YOUR PRODUCT, SHOW IT TO THE INSTRUCTOR BEFORE PUTTING YOUR PRODUCT INTO THE COLLECTION JAR. IF YOUR STUFF IS JUNK FOR SOME REASON, WE DON'T WANT IT TO BE CONTAMINATING THE GOOD PRODUCT CONTRIBUTED BY OTHER STUDENTS. ☺4. BE SURE THAT YOU'RE PUTTING YOUR PRODUCT INTO THE CORRECT CONTAINER. WE DON'T WANT ANY 10a GOING INTO THE 10b CONTAINER, ETC. |
|---|

NMR Analysis/Interpretation. Concepts and expectations are similar to the Scheme 1 report.

1. An **abbreviated summary report** process will again be required. Draw the structure and label the different carbons. Then make a table with the chemical shifts for the actual **non-aromatic, non-alkenyl C-H's**, and by each one write the letter of the carbon to which it is attached. This will demonstrate that you have analyzed and understand your spectrum.
 - **Also include integration.**
 - But you do not need to analyze/report the splitting (although you may do so.)
 - Which signal is from the β -H, which from the α -H's, which are the benzyl H's, and which the crotonate methyl?
 - Which signals are the methyls or methoxy signals in **3b**, **3c**, and **3e**?
 - Does your product look reasonably pure?
2. **Does your NMR confirm that the reaction, and the solvent-removal basically worked?**
 - Does it look like your starting reactant **6** is still present, or gone?
 - Does it look like there is significant amount of solvent left? (Dichloromethane leaves a singlet at about 5.3 ppm.)
3. **The Crotonate Methyl Doublet:** If the reaction worked and you attached the new crotonate portion, that should introduce a new methyl group into your NMR that was not present in **6**. Because the new CH_3 group is attached to an alkene, and there is one H on the neighboring alkene, **the new methyl group should be a 3H doublet. It's allylic, but it's chemical shift will typically be around 1.9 ppm (just underneath 2).**
 - The present of the methyl doublet is the clearest signature for formation of product **10**
 - Ideally there will be one pretty clean doublet around 1.9. Extra doublets in that area reflect impurities. (Other contaminants may also have been "crotonated".)
4. **Chirality, H-non-equivalency, and chemical shift:** The chirality of the β -carbon makes the two β -H's and the two hydrogens on the benzyl carbon nonequivalent.
5. **Chirality, H-non-equivalency, and splitting:**
 - Each of the two α -hydrogens will usually appear as a four-line "doublet of doublets".
 - The β -H will typically also look like a 4-line "doublet of doublets", unless further split by the methyl group in **3e**.
 - The two benzyl H's are each split by each other, so each should look like a doublet.
6. For some of the samples **10**, you will see some **surprising changes in the splitting for the α - and β -hydrogens**. In some 5-membered rings, hydrogens which are trans to each other don't actually split. So it's possible that your β -hydrogen will be a doublet rather than a doublet-of-doublets, because it's split by the cis α -hydrogen but not by the trans α -hydrogen. Likewise it may be that one of the α -hydrogens will be 4-line doublet-of-doublets (the cis α -hydrogen, which is split by the β -hydrogen and the other α -hydrogen.) But the other α -hydrogen might be a simple doublet, split only by the other α -hydrogen but not by the β -hydrogen.
7. For your reports, **account for all and only the hydrogens connected to sp^3 carbons**. You don't need to discuss/present N-H hydrogens **or alkenyl hydrogens** or aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)
8. **Signature signals:** As mentioned above, inclusion of a new allylic methyl doublet around 1.9 ppm is diagnostic of product formation. All of the samples **10** will also have the interesting α - and β -hydrogens, and the benzyl hydrogens (5 hydrogens combined, in addition do the 3H crotonate methyl.) But there will be other additional signature methyl peaks for **6c**; **6b**; and **6e**.
9. **Signal Movement:** Notice that the α - and β -hydrogens, and the benzylic hydrogens have moved again. The chemical environment may be similar to in previous structures **3** and **6**, but the environments are not identical, so the chemicals shifts move to varying extent.
10. **Chemical shift logic:**

- The α -hydrogens, being next to a carbonyl, but being also β to nitrogen and perhaps also an aromatic, should fall in the high 2's or perhaps the low 3's.
- The β -hydrogen in **3a-3d** should show up around the low 4's. For the β -hydrogen in **3e**, we'd anticipate the β -hydrogen to show up in the 3's.
- For the benzyl hydrogens, they are on a carbon that has both a nitrogen (+2) and a benzene (+1) attached, so we'd expect them to come around the low 4's or high 3's as well.

- The crotonate methyl doublet is allylic, so you might expect it in the 2's. In reality, it is likely to "overlap" into the 1.8-2.0ppm region.

11. **The two alkene hydrogens** should actually appear probably in the high 6's, or perhaps even overlapping with the aromatic signals in the 7's. The electronic impact of the strongly electron-withdrawing carbonyl group on the alkene has a strong deshielding impact. You can ignore these in your simplified summary report.
12. **Impurities/contamination:** Recognizing which signals come from the desired product and which do not is again significant.
 - Remember that there should be a logical integration ratio for the main H's in product **10**
 - Between carry-over contaminants, the dimethylaminopyridine, the large excess of triethylamine, and the excess of Mukayama's reagent, there were a lot of other chemicals in your Scheme 3 mixture. It won't be surprising if the cleanup procedure didn't remove all of them. So your mix could be fairly contaminated at this point.
13. **Likely contaminants:**
 - a. Unconverted starting material **6**.
 - b. Residual solvents that didn't all boil off.
 - a. Dichloromethane gives a singlet at around 5.28 ppm.
 - b. Ether gives a quartet in the 3's and a triplet in the low 1's.
 - c. Triethylamine, which gives a triplet in the low 1's and a quartet in the upper 2's.
 - c. Carry-over contaminants that were already in reactant **6**. (Garbage in, garbage out).
 - d. Material from the Mukayama reagent **9**. The intent is that the silica will have retained all of that, but maybe not entirely?
14. **Comparison to Other NMR's:** It may be very interesting to look at how your NMR **6** looks compared to how other NMR's look.

- How different is your **10** from the **6** that you began with in Scheme 3?

- How different is your **10** compared to classmates who made different versions of **10**?
- How clean is your NMR compared to that of classmates who made the same version of **10**?

15. **GC-MS: NOT REQUIRED.** None for product **10**. Some of the larger versions are getting so big so that it's hard to vaporize them, as needed for gas chromatography. And for some the injector needs to be so hot in order to vaporize them that they partially decompose under such hot temperatures, in which case the purity-measurement becomes confusing or misleading.

Scheme 3/Week 3 Lab Report + Overall Project Data Summary:

- For this week, I want both a synthesis-style lab report for Scheme 3, AND a summary report and collection of all of your NMR's/GC's.
1. Write a standard synthesis style lab report for your Scheme 3 reaction (6 → 10);
 2. Make sure that all structures are drawn explicitly.
 - As always for a synthesis style report, you'll want to draw out the reactants and the products. In this case, be sure you draw your **actual** reactant **6** and product in your reaction.
 - None of your pictures should have an "R1": you should illustrate each structure with your actual R1 group drawn, whether that's methyl or phenyl or 4-methoxyphenyl or whatever.
 3. Show all calculations. (Including any mole ⇒ mass for reactants or products)
 4. When listing your chemicals/reactants and showing gram → mol calculations, make sure that you include your main reactant **6**!
 5. Include procedural details.
 6. For this report, you can skip the observations, just to keep the report shorter and since you've written up enough of these by now.
 7. Calculate mass yields, and percent yields, etc., for product **10**.
 8. Include your **NMR-10**, with clear labels, structures drawn, **and the abbreviated summary report** for non-aromatic and non-alkenyl C-H hydrogens for **NMR-10**. But assuming you hand in both your Scheme 3 report and your Data-Summary report at the same time, you could just include the NMR with the data-summary packet.
 9. Include a results/data/discussion/analysis section. The analysis/discussion section needs to address what the yield information told you, and what the NMR data tells you about both the success and the efficiency of your reaction, and the purity of your product **10**.
 - The results/data/discussion/analysis section should summarize what the mass/yield/NMR data is, and what conclusions can be drawn from them. Just attaching the NMR without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic, non-alkenyl C-H hydrogens in your NMR? Does the NMR show that all of reactant **6** reacted, or is there still some reactant **6** left showing up in your NMR? Can you see how your carryover hydrogens, hydrogens that were already in reactant **6** and are still in product **10**, all have variably changed chemical shifts? (The α- and β-hydrogens and the benzylic hydrogens). Does your product **10** look reasonably clean, or is it obviously significantly contaminated? Does it look cleaner or more contaminated than the reactant **6**? If it's less clean, is it much more contaminated, or only modestly more so? Was the yield respectable, or terrible?

Overall Project Data Summary:

1. Fill out the overall project data sheet on the following page.
2. Attach copies of all NMR's and GC-MS's.

Final Report Data Sheet.**1. Which Series Did You Make? (a,b,c,d,e..)** _____**2. GC Results Table:**

Substrate ID (ex 3a or 3b...)	Retention Time	Product Purity	Did the molecular ion show in the mass spec?	Retention Times and %'s for 3 Largest Impurities (if you have 3...)
3				
6				

- the molecular ion is the “molecular weight” ion, basically the unbroken molecule

3. Mass and % Yields Results Table:

Substrate ID	Molar Mass	Yield in grams	Yield in mmol	% yield
3				
6				
10				

4. NMR Results Table.

- Unless the header indicates otherwise, enter the chemical shifts.
- Some of the boxes will be blank, depending on the structure. For example, products **3** don't have any benzyl hydrogens yet. And only the “e” family has a methyl group attached to the β -carbon.

Substrate ID	β -H	α -H's (list both)	Benzyl H's (list both)	Methyl Doublet (in “e” series)	4-Methyl Singlet (in “b” series)	4-methoxy Singlet (in “c” series)	Crotonate Methyl group (only in product 10)
3			-None				None
6							None
10							

5. Draw Structures for your Three Substrates: (may do on back if you want more space)**3****6****10****6. Attach labeled NMR's and GC-MS's for products 3, 6, and 10. Include standard summary reports on the NMR's (unexpanded page only).**

Amine Unknowns

Overview:

You will receive an amine as an unknown. Your job will be to both identify your compound and prepare a derivative. Several pieces of information will be useful:

- Water solubility tests (big or small? Aromatic or not?)
- Solubility in acid-water. (Many basic amines ionize and dissolve in acid-water.)
- Boiling point or melting point of starting material.
- The melting point of the derivative.
- H-NMR information on the starting material.

Classifying Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut.)

- Add 15 drops of water to a small test tube, and then add 2 drops or a spatula tip of sample. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
- **Interpretation:**
 - a. **Small:** Amines with <6 carbons always dissolve.
 - b. **Big:** Amines with >10 carbons have $\leq 5\%$ solubility (never dissolve)
 - c. **Borderline:** Amines with 6-9 C's may or may not dissolve.
 - a. Amines are more soluble than alcohols; no 7-carbon alcohols would dissolve.
 - b. Water solubility depends on basicity. Amines in which the nitrogen lone pair is sp^3 hybridized tend to dissolve much better than if the lone-pair is p.
 - c. For basic sp^3 -hybridized amines, the solution may take on a cloudy look when they dissolve. This is due to the basicity and the formation of ammonium hydroxide.

2. HCl/Water Solubility Test

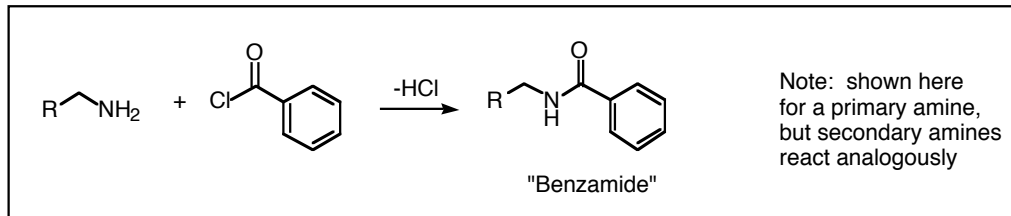
- Same procedure as above, except use a large test tube, use acid-water (HCl-solution in dispensing hood), add a stir-bar, and use 25 drops of acid-water instead of 15. Use magnetic stirring.
- Interpretation: Most amines with normal basicity will be protonated and become soluble. If you had a sample that didn't dissolve in water, but does dissolve easily in acid-water, it is likely to be an amine. Caution: solid amines sometimes take a while to ionize and dissolve, and amines in which the nitrogen is conjugated and has the nitrogen lone-pair in a p orbital may be relatively nonbasic and may not dissolve.

3. Amines Smell Variably Rancid. Liquids with sp^3 lone pairs smell worse than solids (less volatile).

4. Many Amines are Solids

5. NMR:

- Splitting: The N-H hydrogens in an amine experience hydrogen bonding. So like alcohol hydrogens, they tend to be a little broad and normally don't participate in splitting.
- NH or NH₂ signals can integrate for 1H or 2H, and typically show in the 1-3 ppm range.
- Chemical shift: hydrogens on a nitrogen-bearing carbon are not moved as far as when the carbon is oxygenated, but more than when it's allylic. Typically the additivity factor is about 1.5 ppm, and for a typical CH₂ group connected to an amine nitrogen, the CH₂ group would show up around 2.7 ppm.
- On an aniline (ArNH₂), the hydrogens ortho to the nitrogen are typically pushed upfield, into the 6 ppm window. This is because an amino group is a strong electron donor, so it makes the ortho carbons more electron rich and "shields" the ortho hydrogen, pushing them upfield.

Derivatives: Benzamide Derivatives

1. Place a small stir-bar and 2 mL of aqueous sodium hydroxide solution into a large test tube.
2. Add the amine, about 15 drops if it's a liquid, about 0.20 g if it's a solid.
3. Stir the solution vigorously, and add about 15 drops of benzoyl chloride.
4. Stir vigorously for 5 minutes.
5. Then acidify with aqueous HCl (this helps the amide to crystallize), while continuing to stir vigorously. (Use pH paper to confirm that the pH is lower than 7. This can be done by touching a boiling stick into the mixture, then touching it onto a strip of pH-paper. An acidic solution should turn the paper red.) There is no risk in making it too acidic.
6. Cool on ice for one minute.
7. Filter the lumpy product through a Buchner funnel, using vacuum. **Pulverize/crush any chunks.**
 - If material is chunky, transfer to a small weighing boat. Place a second empty boat on top, and then grind down on the top boat to crush/grind/pulverize the solid material between the two boats. Then return the material to your Buchner funnel.
 - Chunks/blocks are a problem because contaminants (either amine or benzoyl chloride derivatives) may be entrapped and may not have any exposure/contact with the subsequent acid-water or base-water rinses that are intended to ionize and extract those impurities.
8. Wash repeatedly: with 3 x 10 mL of cold water, then 2 x 10 mL of HCl/water (to wash off unreacted amine), then 2 x 10 mL of NaOH/water (to wash off unreacted benzoyl chloride), then wash again with 10 mL of HCl/water (to make sure there is no ionic PhCO_2Na present).
9. **Recrystallize**, perhaps adding ethanol or water as necessary. A suggested starting point is 3mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders (read):
 - Use a small Erlenmeyer (25 or 50-mL), not a beaker, to reduce solvent evaporation.
 - Make all your adjustment decisions while the solution is boiling hot.
 - Heating your Erlenmeyer in a hot-water beaker (150-mL) is convenient, to provide more even heating and to avoid overheating on the hot-plate surface.
 - You and your hood partner should also warm up some ethanol in case you need to add some
 - Other than when you're just starting, don't add cold solvents.
 - During cooling, cover flask to avoid evaporation of the hot solvent.
 - If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
 - If after chilling you seem to have no solvent, add some cold ethanol. You need solvent for the impurities to have a place to swim!
 - Your rinse solvent should be similar to what you think your actual solvent blend is. But avoid water if possible so that your crystals will dry better.

Micro-Boiling Points in the Melting Point Apparatus (if you have a liquid unknown)

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. Add about 7 μL of liquid via syringe and tapping. Pre-boiling bubbling will often occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the boiling point is reached, the liquid level should begin to drop (slowly at first, more rapidly the more "above" the boiling point you are.) Sometimes more rapid bubbling often takes place, but not always. Keep heating somewhat beyond the point

where you think boiling has occurred, because you may not be experienced enough to distinguish “pre-boiling” bubbles from real boiling bubbles. And in some cases, you’ll never see bubbles. Even so, at or somewhat beyond the boiling point, vaporization should accelerate such that the liquid level will drop. Watch for this.

These boiling points will not be very accurate, especially for an inexperienced user. Don't trust them to be accurate better than to about 10 degrees. While the observed boiling points are imprecise, they still greatly shorten the list of candidates.

Amine Candidates

Bp of Starting Amines (Liquids)	Unknown	mp of Benzamide Derivative
48	Propylamine	84
55	Diethylamine	42
78	Butylamine	42
159	Dibutylamine (Bu ₂ NH)	oil
182-185	Benzylamine (PhCH ₂ NH ₂)	105
184	Aniline	163
185	PhCH(CH ₃)NH ₂	120
196	N-Methylaniline (PhNHCH ₃)	63
200	2-Methylaniline	144
204	3-Methylaniline	125
208	2-Chloroaniline	99
210	2-Ethylaniline	147
216	2,6-Dimethylaniline	168
218	2,4-Dimethylaniline	192
218	2,5-Dimethylaniline	140
225	2-Methoxyaniline	60
230	3-Chloroaniline	120

Mp of Starting Amines (Solids)	Unknown	mp of Benzamide Derivative
35-38	PhCH ₂ NHPh	107
41-48	4-methylaniline	158
49-51	2,5-dichloroaniline	120
52-55	Diphenylamine (Ph ₂ NH)	180
57-60	4-methoxyaniline	158
57-60	2-aminopyridine	165
58-66	4-bromoaniline	204
71-73	2-Nitroaniline	110
112-114	3-nitroaniline	157
115-116	4-methyl-2-nitroaniline	148
138-140	2-methoxy-4-Nitroaniline	149
148-149	4-Nitroaniline	199

Note: amines are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown No. _____ Name _____

1. Physical Examination of Starting Material

a) Physical State _____ b) Color _____ c) Odor _____

2. Solubility Tests on Starting Material

Solubility in Water: _____ If Insoluble, Does it Float or Sink?

Solubility in HCl/Water: _____

3. Boiling point or melting point for starting material:

“Literature” value:
(list, previous page)

4. Recrystallized Derivative

observed mp

literature mp

5. H-NMR (attach, with assignments/interpretation.)

- **On the proton spectrum, create a standard 4-column summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings, and “source” hydrogens.**
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Then on your standard summary table include a column in which you explain which “source” hydrogens (a, b, or c, etc...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.
- **Aromatic H's:** Do analyze aromatic H's for solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

6. What is My Actual Unknown? (Letter, Structure and Drawing of structure)

7. Comments, difficulties, complaints, etc..

CARBOXYLIC ACID UNKNOWN

A. Solubility Tests: Water, NaHCO₃, and NaOH

Test the solubility of your acid first in neutral water, in NaOH/H₂O, and in NaHCO₃. For each test, add 15 drops of aqueous solution to a small test tube, and then add 2 drops of sample if it is a liquid, or a little spatula quantity if you have a solid. If you do have a solid, double your NaOH/H₂O and NaHCO₃ to 30 drops. Swirl/mix well. Use of small stir bar helps.

- Water Test: Only acids with small numbers of carbons should be soluble.
- NaOH/H₂O: Carboxylic acids are ionized by NaOH, and the resulting sodium carboxylates are usually soluble (with some exceptions, if there are too many carbons present...).
 - Note: Solubility of solid acids is often quite slow, because the hydroxide may only be able to “attack” the acid at the surface. Trying this test in a large test tube with a stir-bar is sometimes helpful. But be sure to check after five or ten minutes have passed, not just initially. Also, sometimes it helps if you double your NaOH/H₂O beyond 30 drops, because if you put in more acid than you realized, and the hydroxide runs out, you won’t get full dissolving.
- NaHCO₃/H₂O: An acid-base reaction should lead to solution, but the other unique thing is that acid-base protonation of bicarbonate may lead to CO₂ bubbles. If the solubility is poor the bubbles are small and slow, but even with a solid you can often see little bubbles forming. As with the NaOH/H₂O, solubility is often quite slow; often benefits from a larger portion of NaHCO₃/H₂O; and often benefits from stirring with a stir bar.
 - Note: If you see the bubbles, it’s a firm proof of acid. But the failure to see bubbles isn’t proof to the contrary, that you don’t have an acid. Sometimes the bubbles are too small, or too slow, or you just can’t see them for whatever reason.

B. Melting Point/Boiling Point

If your carboxylic acid is a solid, take its melting point. If it is a liquid, take its micro-boiling point.

C. Titration/Neutralization Equivalence → Molecular Weight Determination

Weigh, as accurately as possible, around 200 mg (0.200g) of your acid into a 125 mL Erlenmeyer flask. Use the balance nearest the acetone-hood. (You want 3-4 significant figures after the decimal for this, so the other balances are unacceptable.) Pre-tare the flask, then add sample directly into the flask and record the mass to avoid inaccuracy. (Adding to a boat, recording, and then pouring into Erlenmeyer will introduce error.) Whether you have 200 mg or 220 or 180 doesn't matter, so long as you know exactly what your original mass is. Dissolve your material in around 25 mL of ethanol. [Logic: It is vital that the solution be homogeneous, so you need ethanol to keep it dissolved. But the indicator needs water to work right.] Add 2 drops of phenolphthalein indicator solution. Titrate the solution with _____ M NaOH. (Copy the concentration down from the bottle!)

Summary of titration logic: Molecular weight (or "formula weight", FW) is the ratio of mass per mole. Having weighed your acid, you know the mass very precisely; but how do you know how many moles? By titrating against the precisely standardized base! From the precisely known volume of base and the molarity of the base, you can determine the # of moles of base used. Since the mole/mole stoichiometry is 1 mole of base per 1 mole of acid, the # of moles of base tells the # of moles of acid. Knowing mass of acid and moles of acid, the ratio gives you the formula weight.

Note: Do your titration once, and check the molecular weight value with me. If you get within 5 g/mol, I'll tell you and you won't need to repeat. If you don't get within 5 g/mol, then you'll need to do it again. (Normally several repeats for reproducibility would be in order.)

Molecular weight calculations like this are not perfectly reliable (even if you calculate right!). In general an error of up to five grams/mole is acceptable. Logical reasons for errors are shown below:

- Reason 1: If you don't see the color change right away and "overshoot" the amount of NaOH added, you will have added more moles of NaOH than necessary. The calculation assumes that the number of moles of acid is exactly the same as the number of moles of NaOH added; but if you overshoot the NaOH, this won't actually be true. Your moles of acid will actually be slightly less than the number of moles of base. So when you are dividing mass of acid by moles of acid, you will have a slightly exaggerated number for the denominator. This will result in an underestimation of the grams/mole ratio, and will underestimate the actual molecular weight.
- Reason 2: Not all of the acids are perfectly pure. For example, if the solid sample is only 95% pure, this will cause an error in the calculation! Since acids are somewhat hydrophilic, it's not uncommon for acids to be somewhat wet and to give somewhat exaggerated molecular weight numbers.

•
Example of Molecular Weight Calculation:

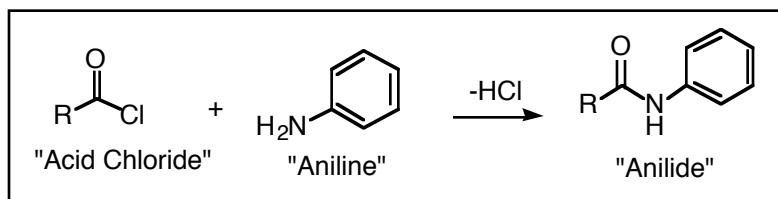
Measured data:

- Weight of acid: 0.2015 g
- Molarity of NaOH: 0.1005 M
- Volume of NaOH to reach the titration end-point: 14.50 mL

Mathematical Calculation of Molecular Weight:

- Moles of NaOH = $(14.50\text{mL})\left(\frac{1\text{L}}{1000\text{mL}}\right)\left(\frac{.1005\text{mol}}{1\text{L}}\right) = 0.001457 \text{ mol NaOH}$
- Moles of acid = moles of base = 0.001457 mol acid
- Molecular weight of acid = $\frac{0.2015\text{g}}{0.001457\text{mol}} = 138.3 \text{ g/mol}$

D. Anilide Derivative



Place 10 drops (or 0.10 grams, if it's a solid) of the acid chloride into a large test tube. Add a stir bar, and add 1 pipet of ether. To this solution add 20 drops of aniline, dropwise (may spatter if you add it all at once) and stir for 5 minutes if it's not already solid. The primary precipitate that forms is the aniline hydrochloride salt. If your reaction is so exothermic that the ether boils away and you end up with an unstirrable solid, then add another pipet of ether. After the five minutes is up, add 2 pipets of aqueous NaOH, and continue stirring for an additional five minutes. If some precipitate remains it is the derivative itself. Use a long pipet to remove the aqueous layer from the bottom of the test tube. (Any unreacted acid chloride should be removed by the basic water.) Then add 2 pipets of aqueous HCl, and stir vigorously. Use a long pipet to remove the aqueous layer. (The aniline should be removed in the process.) Cool your solution in an ice-bath.

If you have a significant amount of precipitate at this point, it is the desired derivative. Filter directly over a Hirsch funnel. Rinse with some HCl/water and then some water to get your crude derivative. If you don't have a significant amount of precipitate, skip down to the instructions in bold.

Recrystallize the crude derivative from ethanol. Ideal volumes will vary depending on your unknown, but a suggested starting point is 2mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders:

- Use a small Erlenmeyer, not a beaker, to reduce solvent evaporation.
- Make all your adjustment decisions while the solution is boiling hot.
- Heating your Erlenmeyer in a hot-water beaker is convenient, to provide more even heating than if you just stand it on a hot plate, and to avoid overheating on the hot-plate surface.
- You and your hood partner should also warm up some ethanol in case you need to add some
- Other than when you're just starting, never add cold solvents.
- During cooling, cover the flask to avoid evaporation of the hot solvent.
- Supersaturation is quite common. If you think you're at 50% water, probably stop and cool and see whether crystals will form.
- If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
- Your rinse solvent should be very similar to what you think your actual solvent blend is.

If following the acid wash you do not have a precipitate (or don't have very much precipitate), then much/all of the derivative is dissolved in the ether. Add a boiling stick and heat your test-tube to boil off the ether, either with a heat gun or in a hot-water bath. place it in an ice-bath. (Maybe consult with the instructor for fast help.) The residue will probably then crystallize. If not, try to add an ice chip and scrape it with a rough stick. Whether it actually crystallized or not, just recrystallize right in the large test tube. Start with around 1 mL of water. Heat it up in a hot water bath, and add as much hot ethanol as it takes to just barely get the product to just barely dissolve. Cool slowly, and perhaps stimulate crystal formation with an ice chip if necessary. Then harvest your crystals. Your wash solvent should probably be at least 50% water.

E. NMR ^1H will be useful. Don't bother with a ^{13}C NMR, since solubility will probably be too low to get anything worthwhile. The OH hydrogen is often very broad, due to H-bonding, sometimes so broad that you won't see it at all.

- Aromatic hydrogens ortho to a carbonyl are typically pushed downfield, toward 8 ppm. This is because a carbonyl group is a strong electron withdrawer, so it makes the ortho carbons more electron poor, which "deshields" the ortho hydrogens.
- A carboxylic acid hydrogen will normally be invisible, so don't look for it. They are so broadened by hydrogen-bonding that they often just blend into the baseline. Even if you could see them, they appear down at 11-14 ppm, which is off-scale from our plots.
- Some solid carboxylic acids will have low solubility in CDCl_3 . If your sample is not completely soluble, you can run it anyway. But sometimes when there isn't that much sample dissolved, background lines from components in the CDCl_3 solvent can be misinterpreted for real sample lines. The two most common candidates are a line at 0.00 ppm (tetramethylsilane) and a singlet at 7.26 (CHCl_3). These two components are always present when you use CDCl_3 solvent, but their height in a printed spectrum looks much taller relative to other signals if the real sample is very dilute versus if the real sample is more concentrated.

Carboxylic Acid Candidates

Liquid Acid Unknowns	bp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Ethanoic Acid	118	60	47
Propanoic Acid	141	74	103
Butanoic Acid	162	88	95
Pentanoic Acid	185	102	63
2,2-Dichloroethanoic Acid	194	129	118
Hexanoic Acid	202	116	95
Octanoic Acid	237	140	57

Solid Acid Unknowns	mp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Decanoic Acid	31-32	164	70
Bromoethanoic Acid	47-49	139	131
3-Phenylpropanoic Acid	47-49	150	92-98
2,2,2-Trichloroethanoic Acid	54-58	163.4	97
2-Chloroethanoic Acid	61-62	94.5	137
2-Butenoic Acid ($\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$)	71-73	86	118
2-Phenylethanoic Acid	76-79	136	118
3-Methylbenzoic Acid	108-110	136	126
Benzoic Acid	122-123	122	163
2-Benzoylbenzoic Acid ($\text{PhCOC}_6\text{H}_4\text{CO}_2\text{H}$)	127-128	226	195
Cinnamic Acid ($\text{PhCH}=\text{CHCO}_2\text{H}$)	133-135	148	153
2-Chlorobenzoic Acid	138-142	156.5	118
3-Nitrobenzoic Acid	140-142	167	155
2,2-Diphenylethanoic Acid	147-149	212	180
2-Bromobenzoic Acid	150	201	141
2,2-Dimethylpropanoic Acid	163-164	102	127
3,4-Dimethoxybenzoic Acid	179-182	182	154
4-Methylbenzoic Acid	180-182	136	145
4-Methoxybenzoic Acid	182-185	152	169-171
3-Hydroxybenzoic Acid	201-203	138	157
3,5-Dinitrobenzoic Acid	203-206	212	234
4-Nitrobenzoic Acid	239-241	167	211-217

- Note: Carboxylic acids are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown Report Sheet- Carboxylic Acid

Unknown No. _____ Name _____

1. Physical Examination of Starting Material

a) Physical State _____ b) Color _____

2. Solubility Tests on Starting Material

Solvent:	Water	If Insoluble in Water, Does it Float or Sink?	Aq NaOH	Aq NaHCO
Solubility:	_____	_____	_____	_____

3. Melting point or boiling point for starting material: _____ List value: _____

4. What is the approximate molecular weight (mw) of my sample, based on my titration?

_____ g/mol. (Attach a separate sheet that details your weights, calculation!)
 *Beware of ridiculous significant figures.

5. Derivative

	<u>observed mp</u>	<u>literature mp</u>
Crude (optional)		
Recrystallized		

6. H-NMR (attach, with assignments/interpretation. Do analyze aromatic H's)

- **On the proton spectrum, create a standard 4-column summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings, and "source".**
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Then on your standard summary table add a "source" column in which you explain which hydrogens (a, b, or c, etc...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.
- Do analyze aromatic H's for solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

7. What is My Actual Unknown? (Letter and Draw Structure)

8. Comments, difficulties, complaints, etc..

User's Guide to NMR: General

- For help, see Dr. Jasperse, Hagen 407J, phone 477-2230

Draft 10/28/15

1. Add sample to a Spinner/Turbine**2. Adjust depth by placing the turbine into the golden depth finder****3. Load sample/turbine into autosampler.**

- Press the round white **Access Request Button** on the panel below the sample trays/doors
- **Wait until "status" light turns to a solid yellow, and the message panel reads "door unlocked"**

4. Opening Program on Computer: Usually already open, and usually to correct "operator"

- If not open: Operator: Should be your class or research group Password: none.
- To switch operator, click **Logout** from submit mode and select the correct operator

5. "Submit" vs "Spectrometer" modes: New Study/Submit Queue to submit; Spectrometer to print/view

- Click "**New Study**" button (lower left) to jump from Spectrometer to Submit mode
- Click "**Cancel**" button (lower left) to exit Submit queue and go to Spectrometer:

6. Experiment Selection (from within Submit mode). Usually preselected for organic labs.

- If not already in New Sample/submit queue mode, push **New Study** button on lower left
- **Proton8** is the normal H-NMR experiment, under the "UserStudies" folder
- For some classes/operators, **Proton8** has been set to open by default, since most NMR's are regular H-NMR's
- Add experiments as needed from the Experiment Selector.
- To **edit or delete**: **right click** on experiment and select "Open Experiment" or "Delete Experiment"

7. 3 Step Submission (assuming the experiment already specified, and still/already in Submit mode).

- Fill Sample Name** (for both computer filing and printout recognition)
 - Click Sample Spot**: Click on the button showing your sample site. (Remember/record! ☺)
 - Submit**: clicking the **red Submit** button on the lower left side.
- **Note**: Can repeat this 3-step sequence for new samples/new students, if running same experiment

- **Comment box**: (can add comments for the paper printout). (Control C to cut and Control K to paste)
- Other submission options** of possible use for advanced labs, research, or offsite Concordia users:
Solvent; **Autoplot** (offsite Concordia users should turn this off); **Email**; **Email Address** (offsite Concordia users should set this correctly!☺); **Lock**: (with non-deuterated solvent run unlocked), **Shim** (with non-deuterated solvent run 1H PFG); **Tune**

8. Opening Completed Samples for Printing and Processing. ("Spectrometer Mode" required)




- Must be in "Spectrometer" mode, not "Submit" mode.
 - If in submit mode, "Submit" button will display (lower left). Click "**Cancel**" to exit Submit mode.
 - In "Spectrometer" mode, must **have "Zones" map displayed** (96 sample nodes show). Click on little circle icon (🔍) to the upper left of the spectra-display panel, if zones map not already open.
- Right click on sample number**
 - Click "Show Study"
 - Click on file folder name located on the left**
 - Then **double click on spectrum** you want to view to load it into the spectra-display viewscreen.
 - Process > **Auto Plot or Print**. See next page for more detailed printing and processing instructions.
- Re-click the little circle icon (🔍) to get back to zone map in order to open other files
 - To return to "Submission" mode in order to run more samples, click "New study"

9. Logout: Click "Logout**" button underneath spectrum-display from Submit Mode.**


10. Plotting (when wanting non-automatic plots)

- Must be in the process mode. (Highlight "Process" beneath the spectrum display)
- a. Click "Auto Plot" or "Print" button, way on lower right corner of page.
- b. Re-click if you want to print additional copies for the other students
 - Note to offline Concordia users: this "plot" command will print to MSUM NMR-room printer. ☺
 - For advanced labs or research groups, additional plot preferences are available in the process mode by clicking "Plot" (Beneath spectrum display, 2nd from bottom underneath "Start")

11. Horizontal Expansions

- With spectrum displayed on screen, use a panel of display icons on the far right.
- a. Click on the magnifying glass icon (6th icon down, )
- b. Move your cursor to the left end of the zone you want to expand, then **hold down left mouse button** and slide it to the other end of the zone you want to expand.
 - To return to the full display, you can either click on the 3rd icon () or the 5th icon ()
 - If the lines aren't tall enough, type "vsadj" (vertical scale adjust) on the command line.

12. Manual Integration: Defining Integrals Yourself (see #13 to also give nice integral numbers)

- With spectrum displayed, **must be in the process mode** ("Process" beneath the spectrum display)
- a. Choose "Integration" (Beneath spectrum display towards left, 2nd underneath "Start")
- b. Hit "Clear Integrals" button (slightly further to the right and lower down from previous button)
- c. Hit "Interactive Resets" button (immediately above the "clear integrals" button) and define
 5. Move cursor beyond the left end of the signal you want to integrate.
 6. Left-mouse click-and-release
 7. Move the cursor to the right of the signal, and again click-and-release. Everything between the two "clicks" will be integrated.
 8. Repeat this for each area you want to integrate.
- d. Click very top cursor icon () to the right of the display screen to regain normal cursor function

13. Setting Nice Integral Numbers (While already in integration mode following steps a-d above)

- a. Click cursor on one of your integral regions
- b. Click "Normalize Area to" "Single Peak" below "Set Integral Area" panel underneath the display
- c. Set "integral area" to some nice whole number (1, 2, or 3, depending on your molecule)
- d. Click the "set integral value" button
 - If it says "cursor is outside of integral region", then reset the cursor on an integral of choice, and re-click the "set integral value" button again.
 - Click "Auto Plot" (lower right) in order to print.


14. Other Processing Options for Advanced Users/Research Groups/2D-NMR

- | | | |
|---------------------|---------------------|--|
| 1. Peak Picking | 4. Insets | 6. Absolute Concentration Integration |
| 2. Vsadj | 5. Arraying spectra | 7. 2D NMR processing, including varying the signal intensity |
| 3. wp=2p sp=2p plot | | |

15. Opening Spectra From the Data Folders

- Click on the Folder icon and find your class or research professor's folder
- Double-click on the folder with your name.
- Double click on the experiment file
- To get the Folder icon to go back up a step, click on the Folder icon again, then click ONCE only on the little icon that shows an arrow up

16. Getting the last sample out and replacing with a Lock Sample (if auto-eject isn't turned on)

- a. In "Spectrometer" mode, display "zones" map ()
- b. Right click on sample 48 => select "Sample in Magnet" (3rd choice from the bottom) => OK.

17. Logout: Click "Logout" button underneath spectrum-display

Summary of ¹H-NMR Interpretation

I. Number of Signal Sets

II. "Chemical Shifts" of the Signal Sets

9's (9.0-10.0)	<u>Aldehyde</u> sp ² hybridized C-H's
7's (6.5-8.4)	<u>Aromatic</u> sp ² hybridized C-H's
5's (4.8-6.8)	<u>Alkene</u> sp ² hybridized C-H's
3's (2.8-4.5)	Oxygenated or Halogenated sp ³ hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp ³ -carbons are routinely present for the following functional groups that contain oxygen single bonds: a. alcohols , b. ethers , or c. esters
2's (1.8-2.8)	<u>Allylic</u> sp ³ hybridized C-H's (sp ³ hybridized C-H's that has a double bond attached to the sp ³ hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present: d. carbonyls , (ketones, esters, aldehydes, acids, amides) e. alkenes , or f. aromatics
1's (0.7-2.0)	sp ³ hybridized C-H's, with no attached Functional Groups g. Note: Many molecules with non-functional alkyl portions will give a lot of signal in this area.
0-12 (anywhere!)	<u>Alcohol/Acid</u> O-H hydrogens (N-H hydrogens likewise) h. alcohols , i. carboxylic acids

1. Check each of the zones. Each one gives you a yes or no answer about the presence of absence of the featured group.
2. End-Check: Check that the functional groups indicated by your chemical shift information match with the structure you believe you actually have! If not, structure needs correction!
3. The regions are somewhat approximate, and have some spillover.
4. For multi-functional complex molecules, there are more complex ways for a C-H to come in some of the above window. For example, an sp³-hybridized C-H with two attached oxygens can come in the 5's, or an sp³-hybridized C-H that is doubly allylic can come in the 3's. In other words, the impact of functional groups is roughly additive.

III. Integration These **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)

IV. Splitting

- **N-1 Rule:** **N lines** ⇒ **N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
 - The N-1 Rule is useful when working from spectrum to actual structure
- **N+1 Rule:** **N neighbor H's** ⇒ **N+1 lines**
 - The N+1 Rule is useful when working from structure to actual spectrum

Note: OH hydrogens don't participate in splitting (normally)

Summary of C13-NMR Interpretation

- Count how many lines** you have. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons can at times cause the number of lines to be less than the number of carbons in your structure.)
 - Each "unique" carbon gives a separate line.
 - Symmetry duplicates give the same line.
 - If there are more carbons in your formula than there are lines in your spectrum, it means you have symmetry.
- Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.

220-160	C=O carbonyl carbons, sp ² hybridized
160-100	C alkene or aromatic carbons, sp ² hybridized
100-50	C-O oxygen-bearing carbons, single bonds only, sp ³ hybridized
50-0	C alkyl carbons, no oxygens attached, sp ³ hybridized

- Use DEPT and/or Coupled C13 NMR to Differentiate C, CH, CH₂, and CH₃ carbons.**

<u>Type of C</u>	<u>Name</u>	<u>DEPT-135</u>	<u>Coupled C13</u>
CH ₃	Methyl	Up	Quartern (q)
CH ₂	Methylene	Down	Triplet (t)
CH	Methane	Up	Doublet (d)
C (no attached hydrogens)	Quaternary	Absent	Singlet (s)

- Aromatics, Symmetry, and C-13 Signals.** Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry)
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry)
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry)

- Signal Height/Size**
 - Carbons without any attached H's are short. This is common for carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached) and for substituted carbons in a benzene ring.
 - Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

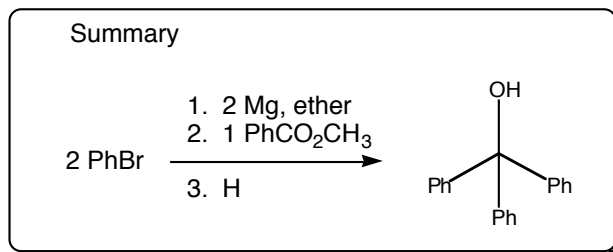
Standard Synthesis Laboratory Report Format: The following layout is standard for a “synthesis reaction” report. Provide the parts and information in the sequence specified.

1. Title = Reaction Summary

For an organic reaction, there is no point in having a Worded Title: The chemical reaction is the best title summary of what you did!

2. Listing of all Chemicals Used

- This should include all chemicals used, including solvents.
- For each chemical, you should include the actual quantity used and measured. For example, with the methyl benzoate you measured a volume by syringe, rather than by weighing on a balance. So you should list the volume you actually used rather than just the weight.
- For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, you must include more than just the quantity of chemical used. You should also include a conversion from what you measured into the number of moles used.
- In some cases, there may be considerable roundoff (you needn't keep precise record of the quantity of solvent that was used, for example, or of sodium sulfate drying agent...)
- If a person was later to repeat your experiment, they should be able to look at this list and know all the chemicals they'd need to have on hand and in what quantities, in order to complete the experiment.



3. Calculation of Theoretical Yield

- Specify which chemical is the limiting reactant
- Given moles of limiting reactant, calculate theoretical moles of product
- Given moles of product, calculate theoretical grams of product.
- Note: Why do this so early in report?
 - First, because it fits in near your mole calculations above.
 - Second, if calculated in advance. as with most research, you know which chemical is limiting and thus must be measured most carefully, but you also know which are in excess and thus need not be measured with equal precision.
 - Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or problematic.

4. Writeup of Actual Procedure.

- For this particular experiment, the “procedure” section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
 - What you actually did (even if not recommended or not from recipe)
 - All observations should be included. These include all observed changes, such as:
 - Changes in **color**
 - Changes in **solubility** (formation of precipitate or cloudiness...)
 - Changes in **temperature** (like, reaction became hot...)
 - Formation of **bubbles**
 - Time and temperature details:
 - Whenever you heat something or cool something, the procedure should specify
 - Specify times. Whether you boiled for 5 minutes or 5 hours matters!
- Writing details: As a record of what actually happened, the report must be written in **past tense**, not **command tense**. (Rather than “Add this”, should read “I added this”, or “I dropped that...”)
- Use of personal pronouns is accepted in this class. You may use “I” or “we” to simplify writing.

5. Product Analysis

- Any NMR, mp, bp, TLC information. For this report, mp and TLC information must be included.
- Final yield and percent yield information.

6. Discussion/Summary. Need not be long, but any conclusions or excuses would go here...

7. Answers to any assigned Questions

Basic GC-MS Operation Compressed Draft 3 For Chem 355 Organic Unknowns Lab

Note: The following assumes that the hydrogen and compressed air gases have been turned on; that the machine has been warmed up; that the gc/ms program has been opened; that an appropriate “method” and “sequence” has been selected; and that Jasperse will shut things down.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared and started a “sequence” (“Chem355 Unknowns..”, or “Nitration” or “Grignard..” or “Esters” for example), but you are trying to add your sample to the lineup.

3. If you’re first in line, get Jasperse to come and help.

- **Add your sample to the back of the line in the autosampler.**
 - Do NOT leave any open holes (unless the sample belonging in that hole is being sampled.)
 - Filling a “sample-is-in-the-injector-tray” hole will cause a system freeze. When the machine tries to put the injection sample back, it will have no place to go.
- **Open “edit sequence” by clicking the “edit” icon on the yellow panel low on the computer screen.**
 - This will open a spreadsheet that you can edit.
 - Add your names in the “sample” box that goes with your vial number.
 - **Click OK.** Note: if you don’t click “OK”, the machine will freeze at the end of the current run. NEVER leave the spreadsheet page open unless somebody behind you is going to close it.

Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.

- Note: data analysis can be done while acquisition is ongoing.
- Note: this assumes that the “**gcms data analysis**” software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says “Enhanced data analysis-ADEFAULT-RTE.M..”, or “Grignards”, or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)

11. Open a data file using the left mouse button to double click.

- Your data file should be within the folder Organic Lab within the Data folder.
- Data file will have the names “Vial-1” or “Vial-2”, so **remember which vial was yours.**

12. Printing GC Graph, % report, and retention times: Click Method>Run Method

- Repeat as many times as needed to provide prints for each student in your group.

13. Printing Mass Specs: Click the 2nd Hammer icon.

- Click the 2nd hammer icon as many times as needed to provide prints for each student in group.
- Note: You don’t need to wait for a print to finish before clicking the hammer again. If you’ve got 5 partners, just click the hammer five times and the prints will come out one by one....

Library Matching: With a data file open (as described in #3 above):**14. Right mouse double-click on a peak in the top window to get its individual mass spectrum to appear in the lower window.****15. Right mouse double-click on the mass spectrum to get a library search results**

- Note: the library searches aren’t perfect and don’t always find the very best structure match

