Experiments for CEM 355 US18

Melting Point Experiment
Pre-Lab: OP1-6 (pp.586-599), OP33 (pp.737), Appendices I-VII (pp.833-872), Introduction and Safety (pp.1-30)

We have provided purified samples of naphthalene (80.2° C), benzoic acid (122.24° C), and salicylic acid (158.3° C) for the calibration of SMP30 melting point apparatus. Although there are many ways to obtain melting points we will only describe the one which you will be using in CEM 355. By following these steps, a good melting range may be obtained.
1) Obtain a melting point capillary tube. **These have one end sealed.**
2) Tamp the open end of the tube into a small pile of the compound whose melting point you plan to measure.
3) By tapping the closed end gently on a book, the compound will be forced to the bottom of the tube. Only 0.5 mm of compound are needed.
4) Find an unused melting point apparatus SMP30, and write down the instrument ID–number as they each have individual numbers (1-40). You should remember to always use the same melting point apparatus in future. Read the instrument instruction and take melting points for naphthalene, benzoic acid, and salicylic acid. Assuming a melting point of 0.0 for ice, draw a precise graph of your observed values (X-axis) vs the literature values (Y-axis) for naphthalene (80.2° C), benzoic acid (122.24° C), and salicylic acid (158.3° C). You should also write up a concise directions for using the SMP30 melting point apparatus as part of your lab report.

Post Lab:
1. Why might the melting point of a compound vary from its known literature value? What causes this change?
2. How might the heating rate effect the observed melting point? Why?
3. How much sample is ideal for a melting point determination? What might happen if too much sample is used?
4. What is the optimal method for determining melting point using the SMP-30s?

A. Distillation

Pre-Lab: OP7-12 (pp.602-621), OP30 (pp.710-719), OP31 (pp.719), OP32 (pp.727), OP34 (pp.744-747), OP37 (pp.758-768), Knowledge of OP 1-10 is also assumed.

This exercise is intended to develop your skills in and understanding of the technique of distillation. Each portion should be performed in such a manner that the best separation is achieved.

First distillation. Distill approximately 50 mL of equimolar acetone/ethanol through a simple distillation apparatus. Clamp the **NECKS** of the 100 mL round bottom distilling flask and the vacuum adapter. These are the best two places to clamp in view of the cost of this apparatus! See Fig. E6 on pp. 714 of textbook. Grease is not required provided the apparatus is disassembled promptly at the end of the distillation. Heat is to be provided by heating mantle supported by an iron ring positioned to allow rapid removal if the rate of distillation becomes excessive. Using a 100 mL graduated cylinder as a receiver allows the collection of continuous temperature (ordinate) vs. volume (abscissa) data.

When your apparatus is complete, have your instructor check it. Then introduce the equimolar solution and a large stir bar by removing the thermometer and thermometer adapter. Use a short-stemmed funnel to direct the liquid to the boiling flask. Finally, replace the thermometer, turn on the water gently, and start heating.

The most commonly asked question at this point is "What is the correct setting?" The answer is "It depends." The amount, heat capacity, boiling point, and heat of vaporization of the liquid, the size of the flask, the initial temperature, the electrical characteristics of each of the controllers and heating mantles, and the rate of boiling all affect the "right" setting. The settings must be determined by experiment and adjusted as conditions warrant it. Think of the controller as an accelerator pedal. Use a high setting when first starting, then reduce the setting as bubbles begin to form. The best separation will occur if condensate forms at the rate of one drop every 1-2 seconds. If you "over-accelerate" and the rate of distillation exceeds this, turn off the controller and lower the mantle for a few minutes to allow the excess heat in the mantle to dissipate.

Collect a small sample of the distillate in a clean and dry vial before 10 mL have been collected. This sample is to be analyzed the **same day** on a gas chromatograph. Stopper the vial securely if a G.C. is not immediately available.

Take frequent readings of boiling point vs. total volume collected. The data is to be recorded directly into your notebook. **Prepare a plot of the data simultaneously**, using enough points to permit drawing a smooth curve. An ordinate (vertical) scale of 40-90° C should be adequate. Holding the notebook sideways will allow more room for a 50 mL abscissa. **The completed graph is to be submitted before leaving.**

Continue distilling the mixture until about 5 mL of the liquid is left in the distilling flask. Heating a flask to dryness frequently bakes on a residue which can be removed only with extreme measures. Sometimes, if a cold drop of refluxing liquid falls into a hot dry flask, the thermal shock will crack the glass. Also, hydroperoxides, such as those commonly formed by ethers, become explosive when heated to dryness.

Return all distillation liquids, including any still-pot residues and the remaining G.C. sample to the Hazardous Waste Container. Storing flammable solvents in lockers creates an unnecessary fire hazard. As the only compounds put in the glassware were low boiling solvents, drain any excess into the Hazardous Waste Container and let the residual solvent evaporate until your next lab period.

Submit an empty, labelled large vial. This will be used to issue the limiting reagent for the cyclohexene synthesis. **PUT EVERYTHING AWAY AND LOCK UP!**

Second distillation. Repeat the same distillation, with one variation. Insert a Claisen adapter with an unpacked Liebig column (the "fat condenser") in the side opening between the distilling flask and the stillhead. Clamp the stillhead also, since this apparatus is quite tall, but be sure that all joints are closed. Stopper the center opening after introducing 50 mL of the equimolar solution and a pair of boiling chips.

Collect the same types of data as last time, both G.C. and boiling point vs. volume of distillate. Can you determine the volume ratio of the mixture better this time, based on your temperature/volume graphs? Clean up procedure is also the same. Remember to return the flammable liquids.

Third distillation. Repeat the same distillation a third time, but with a packed column in place of the unpacked column. The column should be **loosely packed** with shredded copper foil. Be careful not to break the support "nibs" near the bottom of the Liebig condenser. Packing too tightly will probably result in a flooded column and a poor separation, or cause the distillation to take much longer.

Fourth distillation. Microscale distillation using a spinning band in a Hickman-Hinkle still.

a) Check out a Hickman-Hinkle apparatus and a Teflon spinning band from the stockroom. Assemble a Hickman-Hinkle distillation apparatus as shown below. Use a 5 mL conical vial for distilling flask. Add 2.0 mL of the acetone-ethanol mixture to the 5.0 mL conical vial and distill until the well of the Hickman-Hinkle condenser is full. Allow the system to cool down and draw 0.5 mL from the side arm of the Hickman-Hinkle and collect the data from the GC as before.

b) Place a fresh 2.0 mL portion of ethanol-acetone mixture and a Teflon spinning band in the 5 mL conical vial, assemble the Hickman-Hinkle apparatus, and repeat the above experiment. Compare the results of part a and b.

Data analysis. For the case where the initial acetone/ethanol mixture is equimolar, the Fenske equation (p. 74, 713) may be rewritten as:

$$n = \frac{\mathrm{Log}(Z_{ac}/Z_{et})}{\mathrm{Log}\alpha}$$

Derive this expression from the Fenske equation. Examine your volume-temperature plots and decide where you should have changed receivers if you wanted to collect "pure" acetone and "pure" ethanol separately. Although the first distillation is called a "simple" distillation, considerable fractionation occurs in the region between the liquid surface and the side-arm. Your TA will demonstrate the use of a syringe to collect a small sample of the vapor just above the boiling equimolar mixture. This sample will be used to determine the relative volatility, α, of the equimolar mixture. Your TA will also demonstrate the use of the G.C. with "authentic" equimolar acetone/ethanol to collect data for calculating response factor. Use the TA data to calculate α, then calculate n for your distillations. Xerox copies of these data will be distributed. The final report, due the fourth day, should include the number of theoretical plates in each of your distillations and any appropriate conclusions.

Post Lab:
1. Calculate 'n' for each distillation using the Fenske equation.
2. Which distillation gives the purest product? Why? What data supports this?
3. Does the data support or vary from theory? What does this suggest?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? (Think in terms of experimental steps, i.e., set up, heating parameters, etc.)

B. Synthesis of Cyclohexene

Pre-Lab: OP18 (pp.635-645), OP24 (pp.678-680), OP25 (pp.680-685), OP32 (pp.727-737), OP34 (pp.744-748), OP35 (pp.748-752)

You will be issued a 20 mL sample of cyclohexanol (d=0.963). Slowly distill a mixture of the cyclohexanol and 10 mL 85% H_3PO_4 through an unpacked fractionating column. Cool the 50 mL R.B. receiver in a beaker of ice water to reduce loss of product. The cyclohexene (83°) and water boil well below cyclohexanol (161°). When the rate of product formation drops, the still pot residue turns amber, and white fumes appear, stop the heating immediately. Cool the still pot briefly, add 20 mL of xylene through the Claisen adapter and resume heating until the temperature approaches 130° C. Caution: Hot xylene will dissolve polyethylene; don't use a plastic stopper.

Working in a hood, wash the product (OP 18, 24) with an equal volume of saturated aqueous sodium chloride, remove water from the separated upper layer with sufficient anhydrous sodium sulfate (OP 25), and fractionally distill (packed column) the cyclohexene from the xylene. A trace of water (cloudiness) may be removed with some more sodium sulfate. Record the boiling point range and yield of your product.

All distillation residues--from both distillations--go to the Hazardous Waste Container. The saturated salt water from the extraction may go down the drain. The sodium sulfate and filter paper should be wrapped in a paper towel and placed in the Hazardous Solid Waste Container. Submit the product in a properly labelled, well-sealed vial.

If you take 2 days to complete this exercise, seal your product securely. A sound cork which has been softened in the cork roller makes an excellent seal. The 19/22 plastic stoppers are ok for short term storage. Glass stoppers tend to get stuck. Plastic wrap (e.g., Glad or Saran) is very porous to organic molecules.

Post Lab:
1. What role does xylenes play in this distillation? What kind of distillation is this considered?
2. What steps did you take to maximize your yield and purity?
3. How can you determine your yield while minimizing loss of product?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

Solids Module

Thorough understanding of the basic operations (OP 1-12) is assumed for this set of units. The individual units may

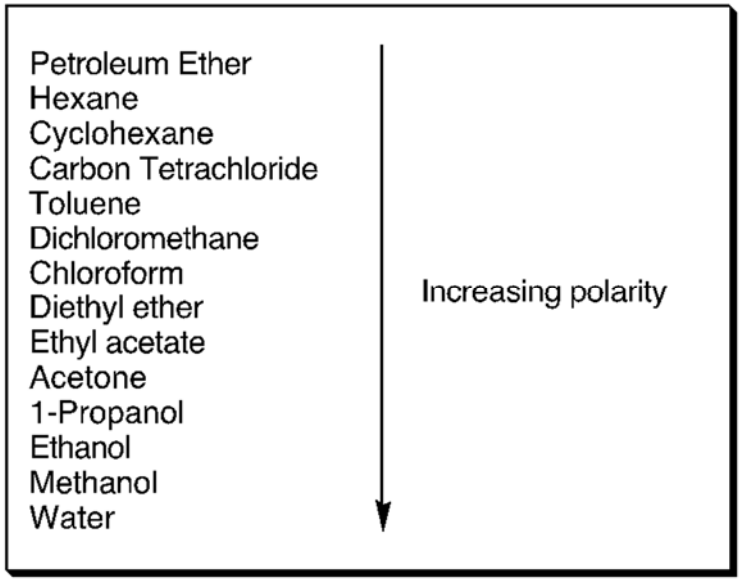
be done in any order, as long as the recrystallization unknown is done last.

A. Thin Layer Chromatography

Pre-Lab: OP22 (pp.665-673)

Chromatography is a method of separation of compounds based on the principle of phase distribution. There are several different kinds of chromatography: thin layer, column, gas, paper, and liquid chromatography are among the most common types used in organic chemistry. All methods of chromatography involve the partitioning of a substance between a stationary phase and a mobile phase. In paper chromatography the paper itself serves as the stationary phase and the eluting solvent as the mobile phase. In thin layer chromatography the stationary phase is the silica gel layer, the plate only serving as a support, while again the eluting solvent functions as a mobile phase.

The stationary phase absorbs compounds by molecular interactions between functional groups on the stationary phase and the analyte compound. The commonly used stationary phases are polar. Thus, in most forms of chromatography polar compounds are held more strongly by the stationary phase. Therefore, in order to elute increasingly polar compounds a mobile phase of greater polarity is needed. This property defines an *eluotropic* series. It begins with nonpolar solvents and proceeds gradually to the most polar organic solvent, methanol and finally water. The ability of a solvent to elute a given substance from a stationary phase depends on that solvent's eluting power and thus its polarity.



When a drop of ink is analyzed by paper chromatography, the different components of the ink are adsorbed with different strengths by the stationary phase. A component that is more soluble in the mobile phase (less polar, weakly absorbed by the stationary phase) will travel farther, in the same amount of time, as a component that is less soluble (more polar, strongly absorbed by the stationary phase) in the mobile phase. This can be quantified by measuring the retention factor or R_f, for a compound. The R_f can be calculated by dividing the distance the compound of interest traveled by the distance the solvent front traveled.

$$R_f = \frac{\text{Distance traveled by compound X}}{\text{Distance traveled by the solvent fron}}$$

Fig. 1 shows a developed TLC plate. Note that the compounds on the developed plate are not all perfect circles. To measure the R_f of a spot, measure the distance traveled from the origin to the **front** of the spot. Measure the solvent front distance immediately after removing the TLC plate from the developing chamber, solvent evaporate quickly! If the solvent

front travels 10 cm and compound one traveled 8 cm, what is the R_f of compound one? Using the formula above: 8/10 = 0.8, so 0.8 is the R_f of compound one in the solvent system used. The same compound is likely to have different R_f values in different solvents.

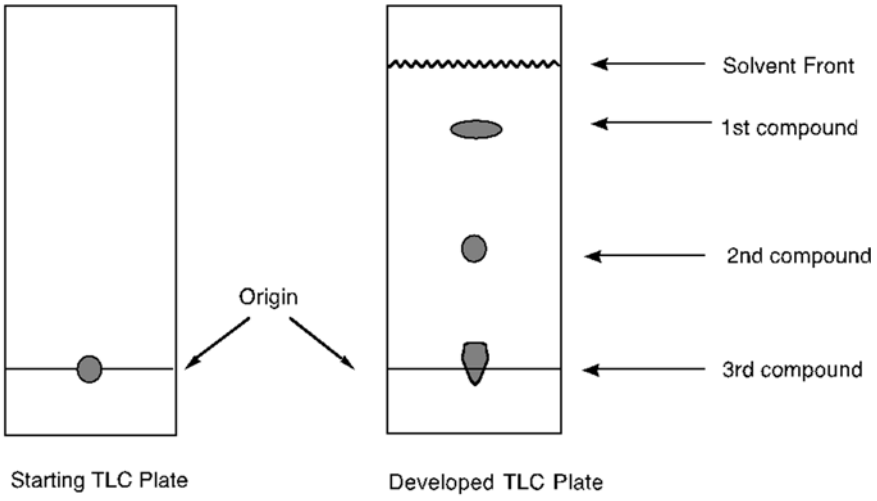


Fig. 1 Sample TLC Plate

As most organic compounds are white or colorless, detecting the position of each compound after a chromatogram has been run involves one more step: development. Often the desired compounds can be made detectable by exposure to a chemical reagent. Iodine is often used as it reacts with many different functional groups to produce colored, and thus visible compounds. By placing the TLC plate in a chamber with a few iodine crystals the analyte will become visible. Another method involves using TLC plates that contain a UV-active dye. When the finished chromatogram is viewed under a UV light, the spots of compounds block the dye and show up as dark spots. Careful marking of the spots' positions under the UV lamp gives a permanent record.

I. Preparation of Thin Layer Chromatography (TLC) Plates TLC plates are available commercially and are sold in a ready-to-use form. The TLC plates used in this experiment are manufactured by Whatman Co. and have a flexible plastic backing which are coated with silica gel and a fluorescent indicator. This allows one to view the compound(s) on the TLC plate when it is exposed to UV-light at 254 nm.

Prepare several pairs of capillary micropipettes while the plates are drying. Make sure no one is using ether anywhere in the lab before you light up. Hold the middle of an open-ended capillary tube in the hottest part of a micro burner flame until a one-inch portion of the tube is very soft. Remove the tube from the flame, wait one second and then pull the ends apart rapidly. A flexible 10-20 cm piece of capillary should have formed. Discard the center portion, but keep about 3-4 cm of the fine capillary attached to the "handle" ends. If the flow is too slow, some of the fine capillary can be broken off. The most common causes of failure are not heating the glass enough or pulling apart while still heating. It usually takes several tries until the techniques are mastered. Remember to put the scraps, failures, and used capillaries in the BROKEN GLASSWARE bucket.

In this experiment, each student is given a two or three component unknown mixture from the list below:

Benzophenone
Biphenyl
Triphenylmethanol
Salicylic acid
Methyl benzoate

The objective of the experiment is to identify the unknown correctly using the TLC technique.

Spotting technique - Dissolve about 10 mg of the unknown mixture in 0.5 ml of a volatile solvent such as acetone or methylene chloride.

Using a micropipette, apply a spot of your unknown mixture about 1 cm from the bottom of a TLC plate. Check

under a UV-light to make sure that you have enough compound on the TLC plate. The size of the spot should not exceed 2-mm in diameter (this size: "O"). Allow the spot to dry completely (2-5 minutes depending on the solvent used to dissolve the mixture). The developing chamber is made by lining the inner side walls of an absolutely dry beaker (150, 250, or 400 ml) with a strip of paper towel, adding 0.5 cm of developing solvent and covering with a water glass. The paper helps to saturate the chamber with the solvent vapor which in turn reduces the amount of evaporation from the TLC plate and gives better separation. Give the chamber about 10 minutes to equilibrate before placing TLC plate. Several plates can be developed in one chamber. Careful not to add too much solvent into the developing chamber because the spots on the TLC plate must not be immersed in the solvent of the chamber. Why?

By trial and error, find a solvent system to separate the three components from each other. Please note that the most polar spot must be risen above the origin in order for the results to be meaningful. Why? What solvent system would be appropriate? Answer: it depends on the mixture. Most people start with a solvent system and based on the result obtained, either increase or decrease the polarity of solvent until the components of the mixture are separated. For instance, if one starts with a 10% ethyl acetate: 90% hexanes as the solvent system and the spot is still at the origin, then he/she must increase the polarity of his/her solvent by changing the concentration of ethyl acetate to 20% and so on until the components of the mixture are separated.

The identification of the unknown components is best achieved by spotting the known compounds (prepared by dissolving 10 mg in 0.5 ml of a volatile solvent) along with your unknown mixture on the same plate (Fig. 2). You need to leave enough space between the spots so that they do not come in contact with each other.

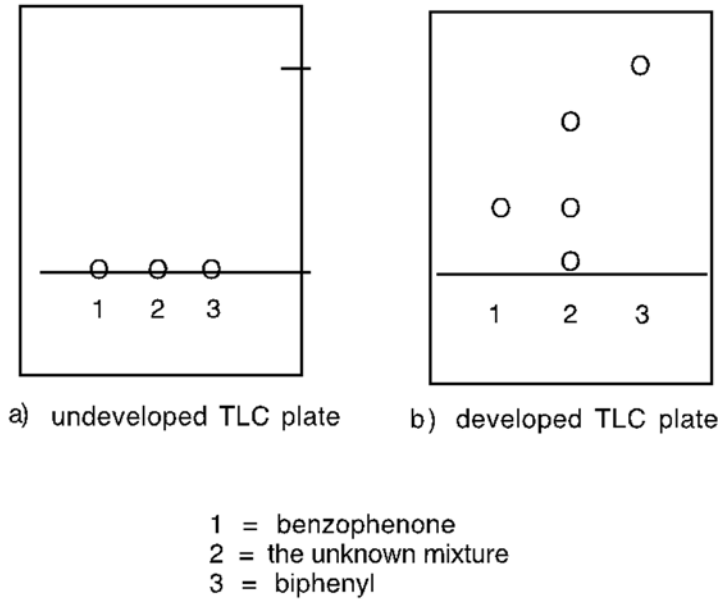


Fig. 2. Developed TLC plate of unknown mixture with reference standards.

After eluting a TLC plate in the developing chamber, look at it under a UV-light and carefully circle each of the spots with a pencil and determine the R_f value for each. The spots with the similar R_f value are the same compound. For instance, in Fig. **2**, the unknown mixture contains benzophenone since the middle spot on plate "b" has a matching R_f value with that of benzophenone. Furthermore, the analysis of plate "b" indicates that the unknown mixture does not include any biphenyl. Therefore, additional plates should be spotted with the remaining compound until "a match" has been identified for the remaining spots.

Three points of this experiment will be based on the correct identification of your unknown. In your lab report, you should include a diagram of the TLC plates. Make sure to write down your unknown number which is the last four digits of your student I.D. and clearly specify each of the components.

Example: Unknown No: 5291
Unknown Components:
Benzophenol triphenylmethanol

Post Lab:

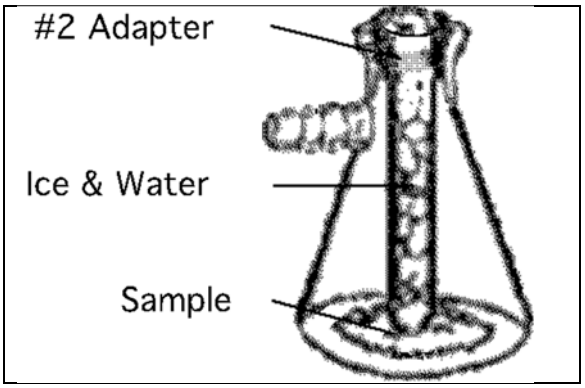
1. If your compound does not travel far by TLC in dichloromethane, what solvent should you try next to get good development?
2. What will happen if your solvent in the solvent chamber is above your origin and spots?
3. How might TLC be useful in ways other than identifying an unknown compound when comparing with standards?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

B. Column Chromatography

Pre-Lab: OP16 (pp.629-634), OP21 (pp.656-665), OP26 (pp.685-690), OP28 (pp.692-707), OP29 (pp.707-710)

This unit requires a single three-hour time block. Obtain a clean and dry chromatography column by presenting your MSU student ID at the stockroom window. Any cloudiness on the column is due to traces of alumina powder and will not interfere with the separation. Water will totally destroy the separation. Fill the column to the base of the bulb with 10 percent ethyl acetate/ 90 percent hexanes mixture after setting your column as instructed by your TA. Then add in order, a 1/4-inch layer of sand, slurry mixture of 15 g of powdered freshly baked alumina and the 10% ethyl acetate/ 90% hexanes mixture (the eluent), and finally another thin layer of sand. Pour the slurry **slowly** through a glass funnel to prevent blocking the column. Once the alumina is packed down, add another 1/4 inch of sand on top of the alumina. The level of eluent must never go b e l o w the upper sand layer as this would "shock" the column and would ruin your separation. Drain the excess 10 % ethyl acetate to the top of the upper sand layer. This clean solvent mixture may be used to start the elution of your sample mixture (fluorine/fluorenone).

Dissolve 0.25 gm of your fluorene/fluorenone mixture in the **minimum amount of 10 % ethyl acetate** and carefully, transfer the solution to the top of the upper sand layer with a long Pasteur pipette. Once the sample is transferred and drained into the sand, add the eluting solvent in small portions with the pipette until the sample is embedded in the alumina layer. Continue adding solvents so that the column doesn't go dry at any time. Collect at least 3 mL (or smaller) aliquots of eluent mixture until the yellow spot (fluorenone) gets closer to the lower sand level.



Complete the elution with 10 % ethyl acetate mixture, until no more yellow product is obtained. The volatile solvents are to be removed by distillation on a steam bath or via a rotary evaporator. Do not evaporate the ethyl acetate mixture into the laboratory atmosphere. They are toxic. Remember that the products melt below 100° and may also sublime; don't leave the flasks on the steam longer than necessary. Redissolve those aliquots that contain appreciable amounts of the first (white, fluorene) product and transfer the solutions to a 10 mL pear shaped flask with a pipette. Again carefully remove the solvent over steam and under a hood. The next step involves using glassware under vacuum. Be sure that there are no cracks in any of the glassware, and take care that you do not bang it while it is being evacuated. Evacuated glassware may implode, showering you with glass fragments. All occupants of the lab must have eye protection on while this operation is in progress. Assemble a microscale sublimation adapter (right). Place the microscale sublimation adapter into the 10 mL pear shaped flask containing the solids to be sublimed. Adjust the condenser tube about 2-3 mm above the solids inside the pear shaped flask. Clamp the assembly above the rings of a steam bath and draw a strong vacuum for about one minute to remove the last traces of solvent. Remember to use a trap (p. 630) to prevent water being drawn back into the product. Once the last traces of solvent have been removed, pack the condenser tube with ice/water and start heating the filter flask. Replenish the ice as needed, pipetting out the excess water.

When the sublimation is completed, carefully disconnect the vacuum hose from the side arm before turning off the aspirator. Carefully remove the sublimation adapter and scrape the pure solid into a tared vial. Determine the recovery and melting point.

Recrystallize your second solid residues (yellow, fluorenone) in a 4-inch test tube from ethanol/water. (OP 28) Small amounts of crystals are best separated by centrifuging and removing the mother liquor with a pipette. Dry the pure material, and determine this melting point also.

Drain any remaining liquid from the column, and working in the hood, blow the solid out into the Hazardous Solid

Waste Container with compressed air. Aim carefully or clean up the mess afterwards. Wash the column with water and a buret brush. Please return it as soon as possible so that the stockroom personnel can get it ready for the next section.

Post Lab:

1. What steps can you take as you prepare your column to ensure a good separation of your sample?
2. When performing column chromatography on a new/unknown mixture of compounds, what should you do first to ensure you can get a good separation?
3. How do you determine an appropriate recrystallization solvent?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

C. Extraction

Pre-Lab: OP18 (pp.635-645), OP25 (pp.678-680)

CAUTION: You will be working with many **HIGHLY FLAMMABLE** liquids. **NO FLAMES** (e.g. Bunsen burners) are allowed anywhere in the lab.

I. Introduction. Both components of this extraction mixture are solids. This simplifies isolation and purification of the separated components. **Save and label all solutions** until you have isolated both solids. Extractions tend to be messy and smelly. **Work in a hood**. Do not oven dry the samples.

II. Separation of the Organic Acid. Weigh out 2.0 ± 0.2 gm of the solid extraction mixture and thoroughly pulverize the solid on a piece of smooth weighing paper. Combine the powdered solid, 30 mL of diethyl ether (a.k.a. ether - HIGHLY FLAMMABLE), and 30 mL of 0.25 M sodium carbonate in a 200 or 250 mL Erlenmeyer flask. Vigorous swirling should dissolve the solid. An occasional boiling chip may be encountered, since the mixture is made from recycled student products.

Assemble a separatory funnel by lightly greasing the glass tumbler or by properly tightening the nut on the Teflon stopcock. See your TA for assembly details. Support the funnel with an iron ring and close the stopcock. Decant the double solution prepared above into the funnel. Any insoluble matter should be left in the flask. Rinse the flask clean with water and discard any residue. Allow the two layers to settle, then drain the denser aqueous base layer (but not any remaining emulsion) into a **400 mL beaker**.

Extract the ether layer with another 10 mL of 0.25 M sodium carbonate solution. Shake the mixture thoroughly as described in the text. Allow the layers to separate and drain the aqueous layer into the 400 mL beaker. Keep the emulsion layer with the ether. The beaker now holds all of the organic acid, in solution as its conjugate salt, RCO_2^-, Na^+. Drain the ether layer containing the neutral compound into an Erlenmeyer flask, add some sodium sulfate and stopper it.

III. Isolation of the Organic Acid. If the carbonate layer is cloudy, filter it into a 250 mL Erlenmeyer flask through a pea-sized ball of loose cotton in a glass funnel to remove these trace impurities. The impurities are coarse enough to be trapped by the cotton. Acidify the clarified sodium carbonate solution of the organic acid with 10 mL of 2M H_2SO_4. Add the acid slowly and with swirling, as the mixture will evolve much CO_2. Before you come to lab, calculate the theoretical volume of CO_2 which will be generated. The solution should now turn blue litmus pink. If the solution is not yet acidic, add a little more acid, mix well, and retest with litmus paper.

Organic acids precipitated this way form very fine particles and filter only very slowly. Don't bother trying to collect the solid at this point. Instead it is easier to extract the organic acid back into ether. Question: Why is the organic acid ether soluble/water insoluble while in the presence of sodium carbonate it is water soluble/ether insoluble?

Extract the acidified water layer with 30 mL of ether. (Your recovery will be improved if you pour the acidified layer into the separatory funnel and then use this ether to rinse any residue in the beaker into the separatory funnel.) Drain the water back into the beaker and save the 30 mL of ether in an appropriately sized Erlenmeyer flask. Repeat the extraction of the water, this time with another 10 mL of ether. Discard the water layer and add the 10 mL of ether to the 30 mL. This combined ether layer now has all of the organic acid. Do NOT combine these ether extractions with the neutral extract of step II.

IV. Purification of the Organic Acid. Dry this ether layer by adding just enough sodium sulfate to combine with all the remaining water. Clean up a bit while the sodium sulfate absorbs any water dissolved in the ether. (Ether can dissolve 1.2% water at 20° C.) Filter the dried ether solution into your 100 mL distilling flask. Assemble a still (diagram) and remove the

ether by heating with a steam bath. Heat with only the minimum amount of steam or it will boil over. When no more ether distills, remove the distillation apparatus and reposition the condenser for refluxing. *If the residue forms a solid lump*, break it up carefully with a glass rod, add a small amount of ethanol and reheat. To recrystallize, dissolve the solid in the minimum amount of ethanol while heating. Add DI water dropwise until a slight cloudiness appears, and then add just enough ethanol to make the solution clear again.

Pour the hot saturated solution into a warm Erlenmeyer flask, stopper and allow to cool slowly. Scratching may be needed to start crystal growth. Check with your instructor. Once crystallization has started, the process should be completed by clamping the flask in an ice bath. You might also let this stand until the next lab period. This crystallization is slow! Plan on icing for at least 15 minutes. Collect the "free acid" by suction filtration (Hirsch). Use the clear filtrate (mother liquor) to rinse any remaining solids into the funnel. Dry and package the product in a vial. The filtrate goes into the Hazardous Waste Container.

V. Isolation of the Neutral Compound.

Examine the Erlenmeyer containing the ether solution of the neutral compound saved in step 2. This drying agent has also eliminated the dirty emulsion by absorbing all the water in it along with any remaining solid particles. Note any changes in the appearance of both the granular solid and the solution as you swirl the mixture. Assemble a distillation apparatus, remove the stopper, and filter (gravity) the dried solution into your 50 mL distilling flask. Remember to attach the thin-walled water hoses to the condenser **before** assembling the apparatus. The used sodium sulfate may be discarded. Add 1 or 2 boiling chips, re-stopper the Claisen adapter, turn on the condenser water and heat solution with steam until boiling virtually ceases. Collect this ether in your 250 mL round bottom flask also. The distilled ether goes into the Hazardous Waste Container. The neutral compound will be a yellow oil at this point.

Dismantle the distillation setup and heat briefly with the stillhead removed to eliminate the last few drops of ether. Failure to remove all of the ether interferes with the crystallization steps. Mount the condenser directly on this same flask for refluxing. Add 10 mL of methanol to the colored, oily distillation residue and bring the mixture to a boil. Continue heating and add water slowly until a trace of permanent cloudiness is present. It may require up to 5 mL. Add just enough methanol dropwise to remove the cloudiness. Cloudiness here may also be caused by residual ether. If boiling is erratic add one more boiling chip. Pour the hot solution into a clean, dry, and warm 50 mL Erlenmeyer flask and set the solution aside to crystallize as you did last time. After 10 minutes of slow cooling, the flask may be clamped in ice water to complete the crystallization.

Collect the crystalline neutral compound by suction filtration (Hirsch). Use an empty filter flask, since this solution should be kept separate from the ethyl acetate-cyclohexane of Part IV. The filtrate goes into the Hazardous Waste Container. Submit the solid "Neutral Compound" in a properly labelled vial.

VI. Determine the melting points: the recrystallized acid, the recrystallized neutral compound and the starting mixture. All three can be done at the same time - there are three holes.

Post Lab:

1. How does the extraction performed in this experiment enable a separation of two organic liquids?
2. How can you determine which layer is the aqueous and which is the organic in an extraction?
3. Theoretically, how could you determine how many extractions you need to do to achieve a good separation?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

D. Recrystallization OP 28 (p 792)

Pre-Lab: OP15 (pp.626-629), OP16 (pp.629-634), OP28 (pp.692-707)

You will be given approximately 2 gm of a contaminated solid which can be recrystallized from water, ethanol/water, or ethanol. You will need to evaluate these solvents both while hot and while cold. The only colored contaminants are red or pink. Some unknowns are a pale yellow or tan. Purify the solid and determine the melting point. You may recrystallize the sample as often as time and ambition permit. Your grade will depend upon the appearance of the purified product in a vial and on your reported melting point of the sample in the vial. In order to reduce the amount of chemical fumes in the laboratory air, all crystallization solutions are to be prepared in round-bottom flasks with reflux condensers. Hot filtrations will be done by gravity with preheated apparatus to prevent crystallization in the funnel.

Your report should include the amounts and disposal method of the mother liquors. Do the amounts discarded balance the amounts taken from stock? Can you explain any discrepancies? This product is graded on both your reported melting point and the crystalline appearance of the product.

Post Lab:

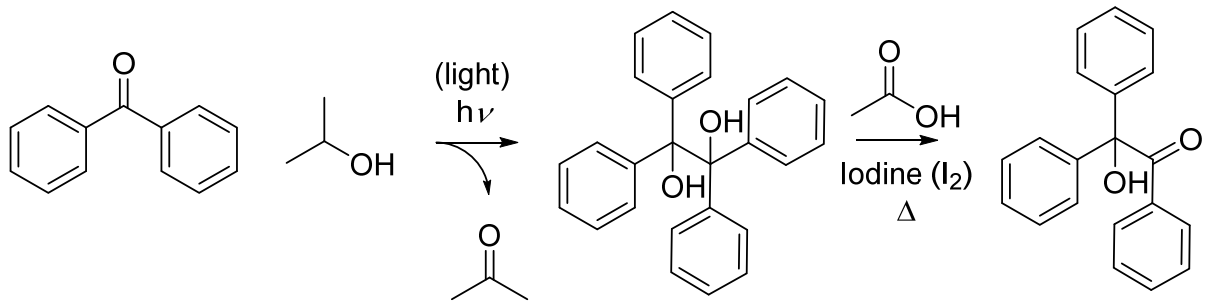
1. What steps did you take to determine an appropriate recrystallization solvent or solvent pair?
2. How do you determine how much solvent is required to recrystallize your sample? If you have more sample, will you need to use more solvent?
3. Once you have obtained crystals, how should you decide which solvent to use to rinse your crystals?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

Synthesis Module

I. Synthesis of Benzopinacolone

Pre-Lab: OP26 (pp.685-690), OP39 (pp.773-802)

In this reaction benzophenone goes through a photochemical dimerization/reduction to form benzopinacolone in the presence of isopropyl alcohol.



Benzophenone **Isopropanol** **Acetone** **Benzopinacol** **Benzopinacolone**

A. Preparation of benzopinacol

Add 2.0 gm benzophenone and 10 mL 2-propanol in an 8-inch test tube and heat over a steam bath until a homogeneous solution is obtained. Label your test tube with your name and section number, add two drops of glacial acetic acid, place a cork on the test tube, and submit it to your TA for irradiation in a photochemical reactor. After the irradiation is completed and the mixture is cooled to room temperature, filter the crystals (benzopinacol) suspended in the solution, dry them thoroughly, and take the melting point of it.

B. Preparation of Benzopinacolone, Pinacol Rearrangement

In a 50-mL round bottom flask, add 1.0 gm of benzopinacol, 6 mL acetic acid, and one small crystal of iodine and reflux for 15 minutes using a heating mantle or thermowell. Cool the reaction vessel to room temperature, add 6 mL of ethanol, and chill the flask in an ice bath for 5 minutes. Collect the benzopinacolone crystals by suction filtration and rinse the crystals with small amount of cold ethanol and determine its percent yield and melting point. Make a KBr pellet of each of benzopinacol and benzopinacolone and obtain an IR spectrum of them. Compare the IR spectrum of benzopinacol with that of benzopinacolone. You should carefully assign the IR-peaks to the appropriate stretching/bending vibrations.

You should turn in the IR spectra and a sample of benzopinacol and benzopinacolone in labeled vials to your TA.

Post Lab:

1. This experiment is analyzed using IR spectroscopy. Discuss the spectra you obtained, identifying all relevant peaks. How do the spectra of the starting material and product differ?
2. Draw out and discuss the mechanism of benzopinacolone formation from benzopinacol, labeling the intermediates A, B, C, etc.
3. The pinacol rearrangement is well known in organic chemistry. Explain the driving force for this rearrangement.

Consider using a reaction coordinate diagram to compare the relative energies of the intermediates you identified above.

4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

II. Microscale Grignard Reaction Experiment

Pre-Lab: OP11 (pp.619-621), OP12 (pp.621-623), OP39 (pp.773-802)

Background and Discussion

The Grignard reaction was one of the first organometallic reactions discovered and is still one of the most useful synthetically. By reacting an organohalide (usually a bromide) with magnesium in ethereal solvent, carbon becomes a nucleophile—and the starting point for many efficient syntheses. Grignard reagents are the starting points for many syntheses of alkanes, primary, secondary, and tertiary alcohols, alkenes, and carboxylic acids.

The formation of Grignard reagents are extremely sensitive to moisture, therefore it is imperative that all apparatus and glassware used for their preparation be as dry as possible. Phenyl magnesium bromide is one of the easier Grignard reagents to prepare. As bromobenzene is relatively inexpensive phenyl magnesium bromide may be used economically in excess. Also, competing coupling reactions, to form biphenyl are not a major concern.

Triphenylmethanol is synthesized by reacting phenyl magnesium bromide with an ester of benzoic acid (Fig. 3). The particular ester (Me or Et most common) does not affect the final product, as the alcohol group is lost during the reaction. As ester consumes two equivalents of Grignard reagent, and the stoichiometry of the reaction is:

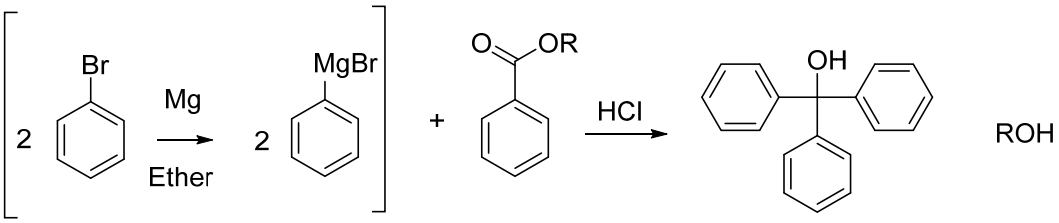
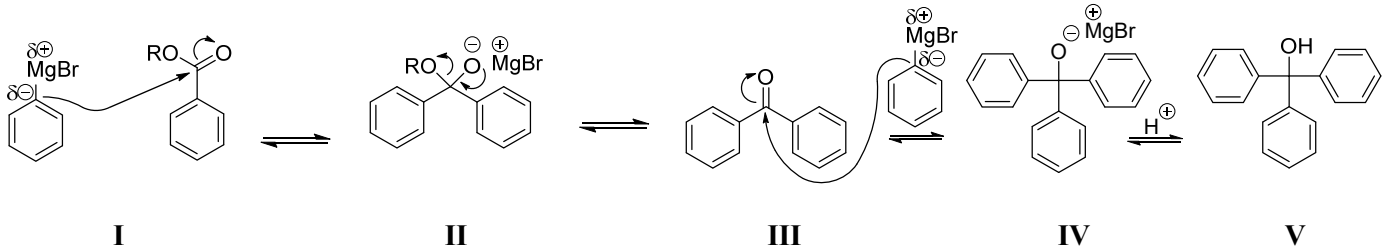


Fig. 3. Grignard Synthesis of Triphenylmethanol

The initial reaction, between the magnesium and the alkyl halide to form the Grignard reagent, takes place via a radical mechanism. The presence of free radicals leads to the generation of biphenyl as a byproduct. The Grignard reagent reacts with remaining unreacted alkyl halide to give the dimer. Byproduct formation is increased by an increase in concentration of the starting alkyl halide solution.

The second step in the Grignard reaction is much simpler mechanistically (Fig. 4). The electropositive magnesium adjacent to the carbon, causes the carbon to behave as a carbanion and thus, behave as a nucleophile. The Grignard nucleophile attacks the ester carbonyl with a resulting loss of alkoxide, II. This generates an intermediate ketone, III that is generally not isolable. Instead, a second Grignard nucleophile attacks the newly formed ketone carbonyl and generates the final alkoxide, IV. The free alcohol is generated after acidic workup, to give the final product, triphenylmethanol, V.



I **II** **III** **IV** **V**

Fig. 4. Mechanism of Grignard Reaction

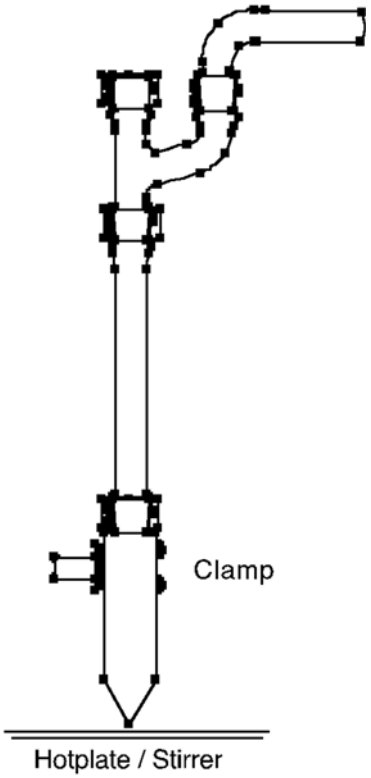


Fig. 5. Grignard experimental setup

Caution: Preparation of the Grignard reagent, its addition to an ester and acid hydrolysis to the final product are all highly exothermic reactions. Mix the reagents slowly and be prepared with a water-ice bath to moderate any over-exuberant reaction. Ether fumes will ignite if they touch any surface over 200° C (auto ignition temperature). No flames will be permitted anywhere in the lab. Measure out the required amounts of ether as needed in the hood. Do not leave open beakers or bottles of ether on your bench top.

Experimental

All glassware used in a Grignard reaction must be scrupulously dried. Dry the following glassware in an oven at 110° C for at least 30 minutes: drying tube, Claisen Adapter, 8 mL conical vial, 5 mL conical vial, distilling column (air condenser), and a magnetic spinvane.

Assemble the oven dried apparatus as shown in Fig. 5. Weigh 53 mg (2.2 mmol) magnesium turnings (Mg, Grignard grade). Remove the air condenser assembly and quickly add the turnings to the 8 mL conical vial. Immediately add

2.0 mL of anhydrous ether and 260 μL (2.5 mmol) bromobenzene to the vial. Support the bottom of the vial with a cork stopper and press firmly on the Mg turnings with a clean, dry glass stirring rod repeatedly to expose fresh metal to induce the reaction. When the reaction starts, the solution will turn cloudy, then amber and boil spontaneously. Check with your instructor if you cannot get your reaction to start. Add a spinvane to the reaction vial, replace the air condenser assembly, and tighten the cap seal. Adjust the reaction vial on a hotplate stirrer and begin rapid stirring. Most of the Mg will be gone and the solution will appear dark amber after 10 minutes. Heat slowly to reflux (hotplate setting approximately at 1.5) for an additional 10 minutes. Then cool the reaction mixture via an ice bath for 5 minutes.

Dissolve 0.125 mL of methylbenzoate in 1.0 mL anhydrous ether in a 5 mL conical vial. Draw the methyl benzoate solution into a clean dry syringe. Place the syringe containing methyl benzoate solution in the septum of the cap of the Claisen adapter and add the solution dropwise over 1-2 minutes. Vigorous stirring of the reaction vial contents is essential. Stir at room temperature for 15 minutes and then warm to reflux for an additional 15 minutes.

Cool the reaction vessel to room temperature and add 1 mL of dilute HCl. All solids should dissolve; if not, add 0.5 mL more dilute HCl. Stir the reaction mixture for 3-4 minutes.

Insert a small piece of cotton inside the tip of a short stem pipette using a long piece of a stainless steel wire.

Remove the spinvane and pipette the aqueous layer into a four inch test tube (ether is less dense than water). Wash the ether (still in the reaction vial) with two 1 mL aliquots of water.

Prepare a short column of magnesium sulfate or sodium sulfate to affect drying as follows: 1) place a wad of cotton in a Pasteur pipette; 2) add 5 mm of sand; 3) add 2 cm of $MgSO_4$; 4) add 5 mm of sand. Clamp the Pasteur pipette upright and pass the ether layer through the drying agent into a 25 mL Erlenmeyer flask. Rinse the reaction vial with two 1-2 mL aliquots of ether and pass these through the pipette containing $MgSO_4$ in order to make the transfer quantitative.

Add a boiling chip to the ether solution and remove ether by distillation. When the ether is almost gone, slowly add 2-3 mL of hexanes to the flask and allow the mixture to cool gradually to room temperature. Solids should appear before cooling in an ice bath. Filter the solids using your small Hirsch funnel. Weigh the dried crystals and take a melting point prior to recrystallization from hot ethanol and take the melting point. In some cases, the vacuum in the filter flask may cause additional solid to separate from the liquid due to evaporation of solvents, both ethanol and residual ether in this case. If this happens, pure product from this residue may be isolated by warming the filtrate to dissolve all precipitated solids, pouring the solution into the original Erlenmeyer flask, and heating to boiling over steam. But do **not** remove a large amount of solvent. If excess ethanol is removed, the solid which forms will be heavily contaminated with a biphenyl, formed by the reaction of aryl Grignard with hot aryl halide. Cool, collect and rinse the product as before. As before, do NOT wash with water. This second crop frequently needs to be recrystallized again from fresh ethanol. Take heart, second recrystallizations proceed much more easily. Check the melting point to decide. Pour all of the used ethanol into the Hazardous Waste Container.

Spread the product (both crops) on an 8 x 11 sheet of paper to dry. Determine the melting point (and range) of your purified product. If the range is greater than 3° C, either the sample is impure or wet, or the melting point was improperly done. Correct any flaws, and repeat the melting point. Place the dry product in a properly labeled plastic bag. See page 1b of this handout for label details. Be sure to seal the bag completely.

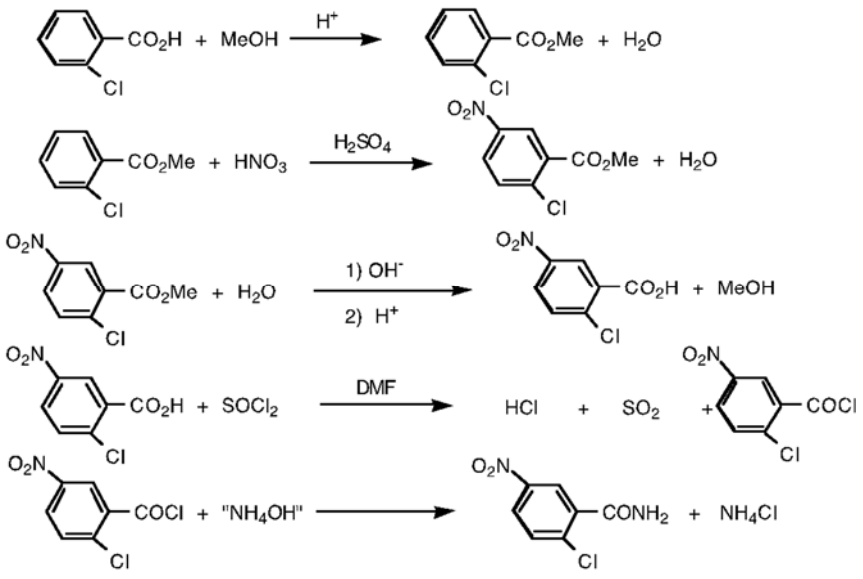
Post Lab:

1. Why were efforts made to exclude water from this reaction? Draw the mechanism of what would occur if water was present.
2. Are you convinced that you synthesized the correct product? How does the data support your conclusion? What other analysis could be performed to gain more confidence?
3. Why is the order of addition important in this reaction?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

III. Multistep Synthesis: Preparation of 2-Chloro-5-Nitrobenzamide

Pre-Lab: OP 18 (pp.635-645), OP28 (pp.692-707), OP 30 (pp.710-719), OP39 (pp.773-802), OP40a (pp.802-815)

The conversion of 2-chlorobenzoic acid into 2-chloro-5-nitrobenzamide is a multistep reaction sequence.



In multistep syntheses, the overall yield is calculated by multiplying the fractional yields of the individual steps. In this 5 step synthesis, the overall yield will be under 60% even if each individual step produced 90% of theoretical yield. You are encouraged to plan your work so that the minimum number of transfers are made and that they are as quantitative as possible. You have been issued a 10 g sample of 2-chlorobenzoic acid which you will convert — by modifying the procedures — into 2-chloro-5- nitrobenzamide. Yes, you will have to do plenty of arithmetic! Convert all of your 2-chlorobenzoic acid sample into the amide, making the appropriate adjustments of amounts at each step. You will need to make "cost-effective" judgments at points where you may repeat a step with isolated by-products. **CAUTION:** This involves the use of concentrated nitric and sulfuric acids.
Work carefully, rinse all apparatus immediately, and wipe up spills promptly. **First aid treatment** of acid spills on flesh is immediate, continued rinsing with water. First aid for acids on clothing consists of immediate removal followed by generous rinsing. Let your lab instructor know promptly in either case.

1. Methyl 2-chlorobenzoate. Introduce the entire 10.0 gm sample of 2-chlorobenzoic acid into a 250 mL round bottom flask. Add 25 mL of methanol to the solid and then carefully pipette 3 mL of concentrated sulfuric acid slowly **down the inside wall of the flask**. Swirl to mix, attach a condenser and reflux over steam for one hour. Plan on doing something useful in the lab for the one hour reflux interval. The solution may also sit overnight. Cool the reaction mixture with an ice-water bath and then pour it into 50 mL of water. Immediately extract the mixture with three 20 mL portions of ether. Discard the water layer (drain) which contains the bulk of the methanol and the sulfuric acid. Confirm the identity of the water layer before you discard it - second samples of 2-chlorobenzoic acid will not be issued. Wash the organic layer again with water followed by a 25 mL wash with 5% sodium bicarbonate. Acidify the separated bicarbonate layer to precipitate any unreacted 2-chlorobenzoic acid. Repeat the bicarbonate washings until no more 2-chlorobenzoic acid precipitates on acidification. Any 2-chlorobenzoic acid may be recovered and recycled at your discretion. Dry the solution with sodium sulfate and remove the ether by distillation using steam as the heat source. **CAUTION:** *Ether vapors would ignite if they come in contact with a surface exceeding 200° C.*

2. Methyl 2-chloro-5-nitrobenzoate. **The following procedure is written for 0.05 moles of methyl benzoate. You should adjust the reagent amounts to match your molar yield of methyl 2-chlorobenzoate.** Transfer the corrosive acid mixtures with great care. The presence of water will hinder this reaction. Use only dry glassware. Do the nitration in a hood. Thoroughly cool 15 mL of concentrated sulfuric acid (18 M) in a 250 mL-Erlenmeyer flask (not a beaker) with an ice bath. Add 6.8 gm of methyl 2-chlorobenzoate to the 250 mL-Erlenmeyer flask, swirl to mix, and continue cooling the solution in the ice bath.

Prepare a second cold solution by combining 5 mL of concentrated nitric acid (15.7 M) and 6 mL sulfuric acid. Transfer the nitric acid solution to the methyl 2-chlorobenzoate solution dropwise with a Pasteur pipette. Keep the pipette upright; if the acid mixture drains into the rubber bulb, the product will be contaminated. When not in use, the pipette may be left standing in the ester beaker. Use the extension clamp as a handle while you **swirl** the flask contents in the ice bath. Transfer of the nitric acid solution should take about 5-10 minutes. Allow the solution to warm to room temperature (10 minutes) with occasional swirling. If brown fumes are evolved, pour the mixture over ice immediately. Put about 50 g (100 mL - loosely packed) of ice in a 400 mL beaker. Pour the acid mixture slowly over the ice while stirring with a glass rod (not a metal spatula). Rinse any residues from the flask into the mixture with a small amount of water. Use your glass–stirring rod to crush any lumps which contain trapped sulfuric acid. Stirring for a few minutes also allows for the agglomeration of colloidal particles. This permits faster, more efficient filtration.

Collect the crude product by suction filtration. No trap is required since the filtrates will be discarded anyhow. (If the filtrate were to be saved, then a trap would be included to prevent a possible back-up of tap water into the flask.) Return the moist filter cake to the beaker, add 100 mL of distilled water and again crush any lumps. This trituration removes impurities (H_2SO_4 and HNO_3) much more efficiently than merely pouring water over the crude product while filtering. Collect the washed product by suction filtration. Rinse the beaker with several small portions of water to transfer as much product to the funnel as possible. Place a second piece of filter paper over the filter cake and press dry with a small beaker while applying maximum suction. Pour this aqueous filtrate down the drain. Rinse the flask promptly but carefully to prevent acid holes in your clothes. Recrystallize the product from methanol. The typical sample needs about 40 mL of methanol. Collect the product, dry it, and determine the yield and melting point.

3. 2-Chloro-5-nitrobenzoic acid. The following procedure is taken from *Organic Syntheses*: O. Kamm and J.B. Segur, *Org. Syntheses* Coll. Vol. I, 391 (1941). As in the preceding step, reagent amounts, etc. will have to be adjusted to match your molar yield of the corresponding chloro ester. Remember to grease thoroughly any glass joints which may be wet by strongly alkaline solutions. Never weigh sodium hydroxide pellets more than a few minutes in advance of their use,

they readily absorb water from the air and become a difficult to transfer glom in the weighing boat. Reseal the sodium hydroxide bottle immediately after use and clean up spilled NaOH pellets immediately; they also tend to "dissolve" balances!

Hydrolyze virtually your entire sample of methyl 2-chloro-5-nitrobenzoate. Save just a small portion of the sample for taking an NMR spectrum and melting point analysis. For each gram of ester weigh 0.75 gm of sodium hydroxide pellets into a small beaker. Also measure 2.5 mL of water for each gram of ester. Rapidly combine the ester, the sodium hydroxide and the water in a 125 mL Erlenmeyer flask and immediately swirl the contents to mix well and dissolve the NaOH pellets. Heat the content on a steam bath with CONTINUOUS SWIRLING until a transparent pale yellow solution is formed. Heating is most effective when the flask is held snugly against the steam bath rings. Heating takes much longer when swirling is done even an inch or so above the steam bath. As solution gets warmer, the ester will first melt to form an oil and eventually react to form a clear solution. If crystals form on the side of the flask, they should be pushed back down with a glass rod (**why not a spatula?**). Without steady brisk swirling, this reaction takes longer and tends to give darker solution. Heat the solution for another five minutes to complete the hydrolysis. Sometimes crystals of sodium 2-chloro-5-nitrobenzoate will form in this highly ionic mixture.

Dilute the solution with an equal volume of water, dissolving any crystals of the organic salt and cool the solution briefly in cold tap water. Pour the cool solution of the organic salt slowly into a 250 mL beaker containing 2.0 mL of concentrated HCl for each gram of starting ester. DO NOT add HCl to the hydrolyzed ester. Briskly swirl the acid while adding the basic yellow solution to the concentrated hydrochloric acid. Rinse the reaction flask twice with small portions of water adding the rinsate to the precipitated free organic acid. Swirl the fine white suspension thoroughly and cool well in an ice bath. Collect the solid by vacuum filtration and rinse the flask and the product with three small portions of distilled water. Pump the filter cake as dry as possible and then spread the product on a watch glass to allow it to dry in your locker until your next laboratory period.

Thoroughly crush any lumps to facilitate drying. It is absolutely essential to have 2-chloro-5-nitrobenzoic acid dried completely for the next step.

Note 1.The use of a more dilute sodium hydroxide solution than that recommended above has been found to yield unsatisfactory results in the saponification of the ester. Prolonged boiling may lead to the production of colored products.

Note 2. After the hydrolysis of the methyl 2-chloro-5-nitrobenzoate, it is essential that the solution of the sodium salt be poured into the acid. If acid is added to the salt in the usual way, a less soluble acid salt separates; and, as this cannot be entirely removed from 2-chloro-5-nitrobenzoic acid even on long digestion with hydrochloric acid, a product is obtained which does not dissolve completely in ether.

Note 3. 2-Chloro-5-nitrobenzoic acid is soluble to the extent of 1 part in 300 parts of water at 20°, and 20 parts at 100°. The crystallization from water or dilute hydrochloric acid is therefore quite satisfactory. Remove any oil by filtering the boiling liquid through a small amount of cotton after mixing thoroughly.

Note 4. 2-Chloro-5-nitrobenzoic acid is obtained in a higher yield by nitration of methyl 2-chlorobenzoate with subsequent hydrolysis than by the direct nitration of 2-chlorobenzoic acid; this method is also preferable on account of the laborious nature of the methods necessary for the separation of the meta acid from the small quantities of the para isomer formed in the latter process.

4. 2-Chloro-5-nitrobenzoyl chloride and **2-chloro-5-nitrobenzamide**. The product of reaction four is relatively unstable and should be converted promptly without purification directly to the amide. As before, the amounts will require adjustment. This reaction illustrates the greater nucleophilicity of ammonia (H_3 N**:**) *vs.* water (H_2 O**:**). Concentrated ammonium hydroxide is approximately 30% (15 M) ammonia. The remaining 70% is water (35 M). And yet, adding the acid chloride to aqueous ammonia at 0° forms the amide almost exclusively. At higher reaction temperatures, this selectivity decreases, forming an increasing percentage of carboxylic acid. In the presence of excess ammonia, the acid is converted to ammonium 3-nitrobenzoate, a water soluble salt. The amide will also hydrolyze slowly to the ammonium salt in the reaction mixture - kinetics vs. thermodynamics.

This exercise also illustrates the use of safety equipment. Thionyl chloride containing solutions emit noxious fumes. Furthermore, much dense white ammonium chloride smoke is formed when the reaction mixture is added to the ammonia. The circulation of this visible smoke shows the movement of fumes within the hood. Note how the fumes move toward the front center of the hood. If you work with the sash raised more than required to fit your arms underneath the sash, the fumes, whether visible or invisible, blow directly at you. With the sash lowered as much as possible, your face and body are protected from both fumes and unanticipated splashes.

Both the original compound, 2-chloro-5-nitrobenzoic acid, (your compounds probably melt differently) and the final product, 2-chloro-5-nitrobenzamid, melt close to 140° when pure and dry. However, an intimate mixture of the two compounds melts quite differently. This "mixed melting point" confirms that the two compounds are indeed different.

DANGER: Thionyl chloride is a colorless volatile liquid with a suffocating odor. Both the vapors and the liquid are corrosive to skin. It also reacts vigorously with water to form HCl and SO_2 . Under no circumstance should any glassware containing thionyl chloride be brought to a lab bench or sink. Rinse all contaminated glassware in the fumehood.

If necessary, the acid may be dried by dissolving in ether, removing the H_2 O layer, drying with Na_2 SO_4 and evaporating.

Fill a metal pan with hot tap water and place it on a hot plate in a hood. Set the hot plate at "3" initially. Adjust as needed to maintain the temperature at 50° ± 5° C. This size bath will accommodate up to three 25 mL round bottom reaction flasks. Place

1.0 gm of well crushed 2-chloro-5-nitrobenzoic acid in a small round bottom flask. Attach a drying tube containing a wad of cotton and a one inch layer of calcium chloride pellets. Clamp the assembly in the 50° C bath and add 0.8 mL of thionyl chloride using the attached 1.0 mL calibrated pipette. Then add 10 drops of dimethylformamide (DMF) and replace the drying tube. The mixture should be maintained at 50° C for 30 min. If at any time the sample becomes a completely dry solid, add more thionyl chloride. Also clamp a large Erlenmeyer flask containing 25 mL of concentrated ammonia in an ice bath in the hood. Work on another experiment for the remainder of the half hour, but check the temperature periodically. If the entire sample has not liquefied after 25 minutes, add another 0.4 mL of thionyl chloride to the mixture. Continue heating until no solid remains. Occasional shaking also helps to complete the reaction.

Raise the reaction flask above the water bath and remove the drying tube. Use a Pasteur pipette to transfer the solution cautiously, **one drop at a time** to the **well swirled flask** of ammonia. This requires 2 hands plus eye coordination. Remember to work with the safety shield protecting your face and torso. Maximum yields are obtained when the addition is performed with cold ammonia which is swirled while adding the 3-nitrobenzoyl chloride dropwise. Keeping 1-2 pieces of ice in the ammonia solution during the addition will help keep the temperature close to 0° C. Inverting the pipette allows the acyl chloride to enter the rubber bulb, contaminating your product and destroying the rubber. Keep it rubber end up! When the addition is complete, rinse the round bottom flask and the pipette with some ammonia. Discard the pipette but keep the bulb. The materials may now safely be removed from the hood and immediately suction filtered. Aqueous ammonia solutions will slowly hydrolyze the amide to the ammonium salt. **Don't stop here**.

Cool the crude amide for a few minutes and collect the solid by suction filtration on a Hirsch funnel. A 1.5 cm piece of filter paper should just cover the bottom of the funnel, the same as a Büchner funnel. Wash the product well with water to remove a large amount of NH_4 Cl. The crude amide should not be stored in the ammonia solution overnight since it will slowly hydrolyze in basic solution. Recrystallize the crude amide from the minimum amount of ethanol (1-2 mL?) plus enough water (5-10 mL?) to saturate the solution. The use of solvent pairs is discussed by Lehman in OP-28b (page 704). This is the best stopping place for this synthesis. Prolonged cooling should produce about 0.4 g of crystals melting above 130° C. The chloroamide will be different. The ethanolic mother liquor goes into the Hazardous Liquid Waste Container. The calcium chloride goes into the Hazardous Solid Waste Container. Calcium chloride left in drying tubes will eventually form a solid cake which is almost impossible to remove.

Perform the mass balance calculations for all solvents used in this multi-step synthesis. Determine the melting point of the starting acid, the final amide, and an intimately ground mixture of the two solids.

The final summary should include the mass and % yield of each step as well as the overall yield. A brief discussion of any errors you made along with possible improvements to the procedure should be included. Include anything you would like to be aware of if you had to repeat the procedures.

Post Lab:

1. The overall yield of a multi-step synthesis is the product of each percent yield multiplied together. Calculate the theoretical yield for each step, and the theoretical percent yield, and compare with your results.
2. Why does the nitration yield the nitro group in the 5 position on the aromatic ring? What modifications could be made to position it in the 4 position?
3. Incomplete reactions may produce a mixture of products, which are sometimes difficult to isolate/interpret. What observations might suggest that you have a mixture of products? Why is it important to identify this early in your multi-step synthesis?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

IV. Isolation of caffeine from tea and coffee
Pre-Lab: OP18 (pp.635-645), OP33 (pp.737-744), OP39 (pp.773-802), OP40a (pp.802-814)

You and your partner (to be assigned by your TA) are to design and/or search for a procedure to isolate caffeine from tea. You must present your procedures to your TA a week prior to the scheduled lab. Take IR (KBr pellet) and NMR of your recovered caffeine.

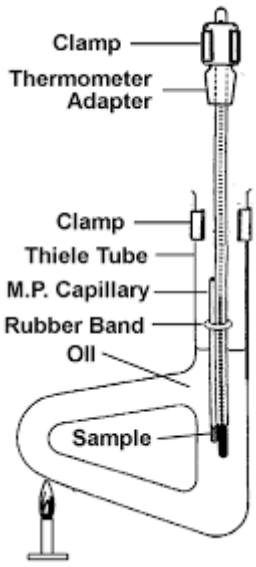
Post Lab:
1. How does the caffeine content in a given mass of coffee grounds compare with the same mass of black tea leaves?
2. Does the brewing method influence caffeine content (i.e. cold brew vs. warm water brew vs. French press)? Explain.
3. What other compounds might be present in coffee/tea? How does the extraction procedure you performed address their presence and isolate caffeine from the other compounds?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

V. Identification of a carbonyl compound.
Pre-Lab: OP28 (pp.692-704), OP33 (pp.737-743), OP34 (pp.744-747), OP40a (pp.802-814)

You must perform the following:
1. Take the boiling point of your unknown liquid aldehyde or ketone.
2. Take ^{1}HNMR and IR of your sample.
3. Identify your unknown carbonyl compound
4. Make at least one solid derivative of your unknown carbonyl compound.

1. Boiling Points of Micro Samples

The determination of a boiling point by distillation with ordinary apparatus requires that at least 5 mL of the liquid be available. Boiling points of smaller samples can be determined easily by the inverted capillary technique of Siwoloboff (*Chem. Ber.*, **19**, 795 (1886)). The apparatus for this technique is shown below and consists essentially of a boiler tube, 5 cm long and 4-5 mm in diameter (we use disposable culture tubes), that holds the sample and fine capillary thermometer sealed by fusion about 25 mm from the bottom. The boiler tube is affixed to a thermometer and heated in a Thiele melting point bath to secure the delicate control of temperature necessary for this technique. See also Mayo, Pike and Butcher for an even smaller scale version of this technique.



Sample area of a Thiele tube used for boiling points of microsamples

The laboratory procedure is to place 2-5 drops of the sample in the 4 mm boiler tube, giving a column of liquid 5-15 mm high into which the sealed capillary tube is dropped. The boiler tube is attached to the thermometer by means of a rubber band and the assembly supported in a melting point bath so that the top of the sample is at least 10 mm below the bath level. The bath is heated gradually with constant stirring until a rapid stream of bubbles emerges from the capillary. The temperature at which rapid bubbling occurs is a few degrees above the boiling point; the proper bubbling rate is easily recognized after gaining experience with a sample of known boiling point. Keep the rubber band above the expanding oil so that it won't dissolve.

The next step is to discontinue heating the bath and observe the boiling tube while the bath temperature drops about 10°. Bubbling ceases when the temperature approximates the boiling point of the sample, and as the temperature continues to drop, the liquid is drawn up into the capillary. The sequence of heating and cooling replaces most of the air in the capillary with vapor of the sample. Heating is now resumed and the temperature is raised at a rate of 2° per minute, with constant stirring, until bubbles once more emerge. The flame is removed and the exact temperature at which bubbling ceases is noted. This is the boiling point of the liquid, since it is the temperature at which the vapor pressure inside the capillary equals the external atmospheric pressure exerted on the top surface of the liquid in the boiler tube. For greater precision the heating and cooling may be repeated several times.

Unlike ordinary distillation the Siwoloboff method gives merely the boiling point of the sample and provides no indication of the amount or type of impurity that may be present.

4. Preparation of solid derivatives. One of the most valuable derivatives of aldehydes and ketones are the hydrazones. They are formed by reaction of the carbonyl compound with a hydrazine (Fig. 6). Hydrazines react quickly and quantitatively with aldehydes and ketones. This is of great utility to derivatizations as often only a tiny amount of the unknown is available.

The most commonly used hydrazine for derivatization is 2,4-dinitrophenyl hydrazine, as it gives a solid product in virtually all cases.

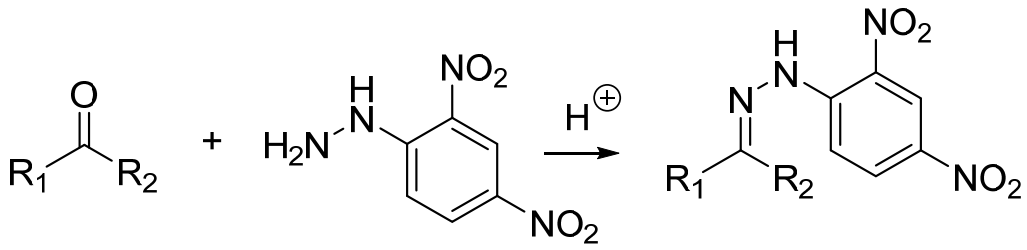


Fig. 6. Formation of 2,4-dinitrophenylhydrazone derivative.

Experimental

The identification of substances is a common problem encountered in the final stages of structure determination of a compound of unknown structure. We have tried to set up this experiment as a realistic experience in identification subject to the limitation of time, materials, and pedagogy. Additional sample can be obtained, but a point charge will be assessed.

In this experiment, your task is to identify the structure of an unknown aldehyde or ketone (liquid or solid). You will be provided with the elemental analysis (%C, %H, %O, %Cl, etc.) of the unknown. You are required to make a derivative of your unknown and turn it to your TA along with its NMR spectrum and lab report. You must determine the melting point or boiling point of your unknown. You need to turn in your MSU student I.D. to the stockroom for checking out the necessary equipment for obtaining the boiling point.

You have to get trained at the Undergraduate NMR Facility (room 125 Chemistry) on the usage of a 300 MHz NMR instrument prior to this week's experiment.

Synthesis of 2,4-Dinitrophenylhydrazones Derivatives

CAUTION: 2,4-DNP causes permanent stains.

Prepare a 2,4-dinitrophenylhydrazone derivative of your unknown aldehyde or ketone using the following procedure. Add 0.3

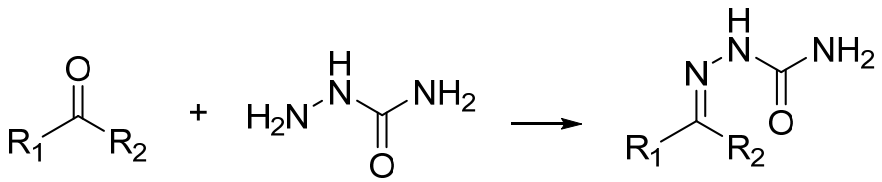
gm (about 10 drops of the liquid) of your unknown into a 25–mL Erlenmeyer flask. Pipette 3 mL of 10% 2,4-dinitrophenylhydrazine solutions directly into the Erlenmeyer flask. DO NOT use a graduated cylinder, as the 2,4-dinitrophenylhydrazine reagents are messy. Swirl the 25–mL Erlenmeyer flask briskly to mix and let it stand, undisturbed for 10 minutes or until sufficient solid has precipitated out. If crystals have not yet appeared after 10 minutes, remove the stopper, add 5 mL of ethanol and heat the resulting mixture gently over steam for fifteen minutes. Allow the warm solution to cool to room temperature and scratch the inside surface of the Erlenmeyer flask using a glass stirring rod to induce crystallization.
The reason for the addition of ethanol is that aldehydes and ketones with six or more carbon chain are not water–soluble. Ethanol or methanol is added to increase the solubility of the long chain carbonyl compound. If no crystals are formed after trying the above instructions, cap the 25-mL Erlenmeyer flask with aluminum foil and leave it in your drawer until next week and inform your lab instructor.

Collect the crude product by vacuum filtration on a Hirsch or Büchner funnel - consider the amount of solid to decide which one is more suitable to use. Pour this filtrate into the Hazardous Liquid Waste container. Triturate the crude yellow or orange product as follows:

1. Transfer the impure hydrazone derivative to a 50 mL beaker.
2. Add 10 mL of 2 M hydrochloric acid to the 50 mL beaker.
3. Crush the solids using a glass-stirring rod in order to remove any unrelated red 2,4-dinitrophenylhydrazine (mp = 200° C). This process is called trituration. Filter the crude product by suction filtration and rinse it with 20 mL of water and finally with a little ice–cold ethanol. These rinsates may go down the drain. Save a small amount of the crude solid as insurance and recrystallize the remaining product from ethanol and water as follows.

Recrystallization: Transfer the crude 2,4-dinitrophenylhydrazone product to a 10 mL round bottom flask, add 5 mL ethanol and heat it on a steam bath. If after 5 minutes the solids have not fully dissolved, crush the solids add 1 mL every 2 minutes until a homogeneous solution has been obtained. You should not add more than 10 mL of ethanol. Add water slowly to make the solution cloudy and leave it undisturbed to cool to room temperature. See your lab instructor if 15 mL of ethanol fails to dissolve your crude dinitrophenylhydrazone derivative. Allow the solution to cool slowly to room temperature and collect the crystals via suction filtration. Consult with your TA if you have problem getting crystals on your own. If your crude dinitrophenylhydrazone derivative does not dissolve in the 15 mL of ethanol, add ethyl acetate drop wise until all the solids are dissolved and filter the solution while it is hot through a fluted filter paper into a dry and clean 25 mL Erlenmeyer flask. Cap the 25-mL Erlenmeyer flask with aluminum foil and leave it in your drawer until next week. Collect the crystals via suction filtration.

Aldehydes and ketones also react with semicarbazide to form the semicarbazone derivatives (Fig. 7). Note that the reaction occurs exclusively at one end of the semicarbazide. The amino group (NH_2) that is next to the carbonyl group does not participate in this reaction. Why?



Acetone (R_1 or R_2 = H) Ketone (R_1 and R_2 = Alkyl) | Semicarbazide | A 2,4-dinitrophenylhydrazone derivative

Fig. 7. Formation of a semicarbazone derivative

Synthesis of a semicarbazone derivative: Prepare a semicarbazone by mixing 1.0 mL of the semicarbazide reagent and 0.3 mL (about 10 drops) of your unknown sample in about 1-2 mL of methanol (enough to make a clear solution). Heat the mixture on a steam bath until crystals begin to form. Cool and suction filter the solid product.

The filtrate is to be poured into the Hazardous Liquid Waste Container.

Remember in this experiment your grade only depends on the purity of the derivatives and not the amount of it. Therefore, carefully measure the melting point of your two derivatives and report it. You may compare your melting point values with the literature values to help you in the identification of your unknown sample. This coupled with the NMR of your unknown sample are enough information to identify your unknown sample. The literature values of selected 2,4–dinitrophenylhydrazone (2,4-DNP) and semicarbazone derivatives of a series of aldehydes and ketones are provided in Table 1 (below). Others may be found in "The Systematic Identification of Organic Compounds", 7th edition, which is on reserve

for CEM 355 students in the stockroom.

Table 1. Solid derivatives (*2,4–Dinitrophenylhydrazone, 2,4-DNP and Semicarbazone*) of some aldehydes and ketones.

Compound	*2,4–DNP Derivative (°C)*	*Semicarbazone (°C)*	*BP (°C)*
Butanal	*122*	*104*	***75***
Heptanal	*108*	*109*	***156***
Furfural	*229*	*202*	***162***
Benzaldehyde	*237*	*222*	***179***
Cinnamaldehyde	*255*	*215*	***252***
Octanal	*106*	*101*	***171***
2-Butanone	*117*	*146*	***80***
2-Pentanone	*144*	*110*	***102***
3-Pentanone	*156*	*139*	***102***
Cyclopentanone	*142*	*205*	***131***
Cyclohexanone	*162*	*166*	***155***
Acetophenone	*250*	*198*	***250***
Propiophenone	*191*	*174*	***218***
4-methylAcetophenone (methyl p-tolyl ketone)	*260*	*205*	***226***
3-Methyl-2-butanone	*120*	*114*	***94***
4-Methyl-2-pentanone (isobutyl methyl ketone)	*95*	*135*	***119***
3-hexanone	*130*	*113*	***125***
2-hexanone	*110*	*122*	***129***
2,4-Dimethyl-3-	*107*	*160; 149*	***125***
3,3-dimethyl-2-butanone (pinacolone)	*125*	*158*	***106***
3-Methyl-2-pentanone	*71*	*95*	***118***
Isobutyrophenone	*163*	*181*	***222***
1-Methyl-2-propanone (benzyl methyl ketone)	*159*	*210*	***216***
Butyrophenone	***190***	***191***	***230***

Your lab report must include the following:
–Your lab partner's name.
–Completely characterized NMR spectrum of your unknown.–A small sample of 2,4-DNP derivative of your unknown.
–Boiling point of your unknown.
–Melting point of 2,4-DNP derivative and/or semicarbazone derivative of your unknown.
–Identification of your unknown **(name and structure)**

Post Lab:
1. How confident are you in the identification of your unknown compound? Explain the results you obtained from each portion of the experiment.
2. Could you have come to the same conclusions using only one or two of these methods (i.e. only NMR and boiling point, only boiling point and elemental analysis)?
3. Why is the preparation of solid derivatives useful in the identification of unknown compounds?
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

VI. Azo Dye.
Pre-Lab: OP16 (pp.629-633), OP26 (pp.685-689), OP28 (pp.692-706)

Prepare 5 mmol of an x-(substituted phenylazo)-phenol by scaling down the procedure in Lehman, Experiment 48. Check with your TA for the "azo-component and coupling agent of the day." Some azo dyes couple only slowly; allow 30-60 minutes for coupling before collecting the crude product. Confirm the presence of excess $NaNO_2$ by diluting one drop of solution with 1 mL of water and applying one drop of this diluted solution to a piece of KI-starch test paper. A deep blue spot indicates excess $NaNO_2$. You do not need to do the test dying of the cloth. Recrystallize the entire sample from methanol, ethanol or ethyl acetate. As much as 100 mL may be required. Selecting the optimal recrystallizing solvent is a challenge. Test small amounts of your product with these solvents in test tubes. Use a reflux setup; the dye dissolves relatively slowly. The product crystallizes as fine needles. Determine yield and melting point and then submit the product in the usual way. Give the proper name of your specific azo dye.

Azo dyes differ from most compounds in that they are intensely colored. The appearance of red color is an inverse visible measure of the skills of the chemist. You will be issued a large sheet of wrapping paper. All synthetic and purification work is to be done on this piece of paper. At the end of the lab, you, your work area, and your apparatus will be inspected and graded on the amount of dye still visible. Be sure that your instructor checks you out before you leave that day. The one difference between this compound and those that you used previously is color. Were you equally careful with the colorless compounds? Does color make a compound more dangerous?

Post Lab:

1. Draw a detailed, arrow-pushing mechanism of the synthesis of the azo dye.
2. Why is the conjugate base of 2-naphthol required?
3. The compound you produced, 1-(4-chlorophenylazo)-2-naphthol, is part of a class of dyes known as azo dyes. Draw the compound and discuss which parts of the molecule contribute to the color you observe.
4. If you had the opportunity to perform this experiment again, what would you modify to improve your results? Consider the experimental set up, process, and analysis.

CHECK OUT INSTRUCTIONS

Complete a "Lab Instructor Evaluation" form and place it anonymously in the brown envelope.

Exchange your combination lock at the stockroom.

Clean all of your apparatus and arrange it on your bench in the order it is listed on the inventory sheet. Remove all labels by soaking the vials in soapy water. It is to your advantage to have no labels with your name or student number in general circulation. Replace any missing or broken items. Check the balance area before going to the stockroom. Place any extra items in the balance area.

When you are ready, sign the "ready to check out" list on the chalk board. Your instructor will check the apparatus, and help you pack it away.

When the locker has been properly checked out, your instructor will close and lock it and also sign the Inventory Check Out Form. Make sure your TA keeps this form. You have completed checkout at this point. Any breakage bill you generated will be sent to your permanent address. Failure to complete the **entire** check-out procedure, including the paperwork, will result in an additional $25.00 charge.