Macroscale Nitration of Methyl Benzoate. (revised 1/14)

Please note that unlike many of the earlier handouts last semester, which were written in great detail, for this semester most of the handouts just provide suggestions and changes. Consequently, you will need to integrate material in the handouts with the procedures given in Williamson to synthesize your own detailed procedure.

This experiment will be done on a scale larger than that you are accustomed to. Consequently, it is necessary that you review recrystallization in your lab text, this time following procedures described for macroscale recrystallization. The principles are identical to those for microscale but the apparatus and operations are somewhat different. In preparing for the lab, try to compare each step in the macroscale with each step in the microscale recrystallization and look for differences and similarities. Use the recrystallization flow sheet (from last semester) and the review below to assist you.

Think about electrophilic aromatic substitution and regioselectivity (what makes the electrophile go where it goes?).

Notes on procedure. Williamson, et. al., Chapter 28, Exp 2. Scale the reaction down by a factor of 2. That is, use half the quantities. When scaling down a reaction, scale down the amounts of reagents but leave the times and temperatures the same. Normally you would also scale down the size of the glassware but in this case use the same flasks as described in the book.

The acids will be dispensed in the hood with burets. The sulfuric acid should be measured into a 10 mL graduated cylinder. Measure the nitric acid as well as you can using the graduations on the buret. **Be careful**. If you accidentally touch a small droplet of acid without realizing it, it will burn your skin. Rinse off any acids that come into contact with your skin. Make the nitrating mixture (sulfuric and nitric acids) in a small Erlenmeyer flask. Whenever mixtures are made, be sure to mix well by swirling or stirring. Also while adding the nitrating mixture dropwise, be sure to swirl and/or stir the reaction mixture well. Careful temperature control is vital in this experiment. At higher temperatures, further nitration of the product occurs.

Once you are finished adding the acid and while the mixture warms to RT, carefully rinse off any apparatus that has come into contact with the acids, with copious amounts of water. Clean up any acid spills with a wet paper towel.

Do not weigh the ice. Loosely pack a 100 mL beaker to the 40 mL mark with ice. This is approximately 25 g of ice. Wash the crystals with plenty of water. The product has a very low solubility in water, You want to wash off as much acid as possible. SAVE a small portion (~10 mg) of the crude (pre-recrystallized) product for HPLC analysis. The product should crystallize nicely from methanol and in high yield if good recrystallization technique is used. You are given the **approximate** amount of methanol to use for recrystallization - an amount of methanol approximately equal in weight to the product. Assume that the product is still wet so to start, use less methanol than you figure. How do you determine the actual correct amount of crystallization solvent to use when the amount is not given? What results if too much solvent is added? At what other points in a recrystallization can incorrect procedure lead to loss of material? Compare the MPs of the crude and purified materials after they are dry. Check the TLC of crude and purified

material along with that of the methanol recrystallization filtrate to see if impurities are detectable. Some possible reaction by-products will be available for comparison. Run the IR spectrum using the ATR attachment. Run the molecular modeling calculations described in a separate handout and include the results in the discussion.

Procedure for preparing a sample for HPLC:

1. Weigh approximately 0.01 g (10 mg) of your well rinsed, **CRUDE** product, prior to recrystallization, and place it in a small **CLEAN** beaker or flask. The sample does not need to be dry.
2. Dissolve the sample in ~10 to 20 mL of HPLC grade Methanol (in the supply hood). Start with 10mL. If the sample doesn't dissolve well, add up to 20 mL.
3. Once dissolved, take up 2 mL of your sample with a syringe. Affix the filter onto the tip of the syringe and push your sample through into your labeled vial. Don't overfill! – the vial capacity is only 2 mL. **Filtering is essential for HPLC**. It will filter out any undissolved sample material, particulates, dust, etc that can clog the column.
4. Screw the cap on the vial, label it with your locker number, and give it to your TA.
5. The samples will be run overnight in a batch and processed the next day. The sample reports will be saved as a PDF file and placed in the 268 folder on the ISB Z: drive, which can be accessed from the computers in the CRC. The data should be processed and available by Friday afternoon. More information will be sent on accessing the data.

(HPLC protocol developed by Raina Kittilstvedt, 1/14)

EXTREME CAUTION: conc sulfuric and nitric acids are extremely corrosive, especially when mixed. If contact with your skin occurs, immediately wash with water then soap and water. Clean up spills immediately with a large amount of water then neutralize with bicarbonate solution so no one becomes accidentally contaminated. If for any reason any acid nitration mixture needs to be disposed of, carefully add it dropwise, with stirring to a large excess of water. Adding water to the acid can result in overheating and spattering of the acid mixture. Know the location of the eyewash fountains and how to use them.

WASTE DISPOSAL: Place the Aqueous Acidic Filtrate into the container labeled as such. Place recrystallization solvent into the Nonhalogenated Liquid Waste container. When you are finished with the product and your TA no longer needs to examine it place it into the Solid Waste container.

Postlab Questions: Chapt 28, Problems 1-4.

REVIEW:

MPs. The melting point RANGE of a compound provides a physical property which can help in the identification of the compound. The range over which the compound melts is indicative of the compound's purity. Impurities do two things: they widen the range over which melting occurs and

also lower the overall temperature at which the sample melts. Always record the range of melting - from the appearance of the first drop of liquid to the point at which all has melted. Always raise the temperature slowly near the mp (1°/min). If the range is found to be greater than 2°, assume that the compound is not acceptably pure. In such a case, the recorded temperature will also be lower than the actual mp of pure material.

WHEN USING A MEL-TEMP, ALWAYS BE SURE TO TURN BOTH IT AND THE DIGITAL THERMOMETER OFF WHEN YOU ARE FINISHED. LEAVING THEM ON CAN LEAD TO OVERHEATING WHICH RESULTS IN DAMAGE TO THE APPARATUS AND PREMATURE DEATH OF EXPENSIVE BATTERIES.

Recrystallization is a technique that you will use in most of the experiments this semester. It is a difficult technique to master. It will pay you to review the chapter on recrystallization in your text and to think about what actually goes on at each step. The steps: (1) Use solubility tests to determine a good solvent. This is one in which the solid has a high solubility in hot solvent and a low solubility in cold solvent. Often you will be told what solvent to use. (2) Dissolve the solid in a MINIMUM of solvent at the BP of the solution. This is done by adding solvent dropwise, while allowing the solution to reach the bp after each addition, until the last drop dissolves the last amount of solid. The most common problem in crystallizations is adding too much solvent. The result is that, upon cooling, solid does not crystallize or crystallizes in a low yield. If too much solvent is added, the excess must be evaporated until a saturated solution results. (3) If insoluble impurities are present in the hot solution (visual inspection), these must be filtered out before the solution is allowed to cool and crystallize, otherwise, the insoluble impurities would contaminate the crystals. See the text for the procedure. Often a solution of the solid has been filtered in a previous step so insoluble impurities have already been removed, making this step unnecessary. (4) Allow the solution to cool slowly and undisturbed. On a micro scale, slow cooling can be accomplished by placing the tube in an insulated container (small beaker with paper towel stuffed inside). Slow, undisturbed cooling allows molecules of the desired compound to be incorporated into the crystals while leaving soluble impurities in solution. It also allows larger crystals to form. On a micro scale, solution is more easily pipetted away from larger crystals. (5) After crystallization is complete (allow solution to remain at RT or 0° C for some time), the solution, containing soluble impurities, is separated from the crystals. This is done differently for different situations. On a micro scale, if the crystals are large enough, the solution can be removed with a pipet, by pushing the pipet to the bottom of the reaction tube, and withdrawing the liquid. If the crystals are finely divided, or if macroscale quantities are being used, a vacuum filtration on a Hirsch or Buchner funnel is necessary. (6) In either case, the crystals must be rinsed with ice-cold, fresh solvent (usually the same as used in the recrystallization). This removes any residual solvent (which contains soluble impurities) which is clinging to the crystals. Remember that the crystals are soluble in that solvent, so a MINIMUM at 0°C should be used for the rinse. With the pipet method, add a few drops to the crystals (keep cold) swirl and remove solvent. On a Hirsch or Buchner funnel, lift the funnel to break the vacuum, add a little solvent to cover the crystals, and immediately re-establish the vacuum. (7) Allow the crystals to dry to constant weight. This can be done in several ways. The crystals can be allowed to air dry. With low-boiling solvents, or if the crystals can be left open overnight, this is okay. The crystals can also be squeezed between two sheets of filter paper and then left to air dry. Or, on a micro scale the reaction tube can be connected to a vacuum and warmed. Any solvent remaining on the crystals will add to the weight, giving an incorrect weight, and will also cause a MP depression.

Never attach the vacuum source to a sample tube or Hirsch funnel without placing a trap between the sample and the vacuum source. The trap will collect any filtrate before it goes into the vacuum line. A trap, which is made from a 500 mL filter flask connected to the vacuum source with a piece of vacuum tubing, is available at each work space. To use it, simply attach a second piece of vacuum tubing to the filter flask and connect this to the sample tube or vacuum filtration set-up. Be sure to clamp the tube or filter flask securely so that it does not fall. To connect the vacuum tubing to a reaction tube, place the thermometer adaptor from the microscale kit onto the reaction tube and connect this to the vacuum tubing with glass tubing.