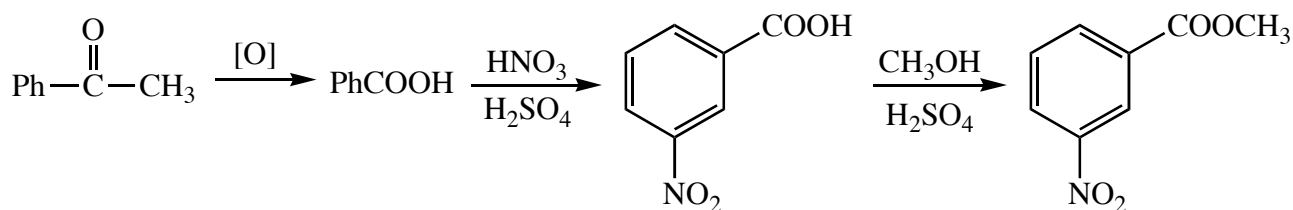


## Multi-Step Synthesis of Methyl *m*-Nitrobenzoate

AEM – Organic lab

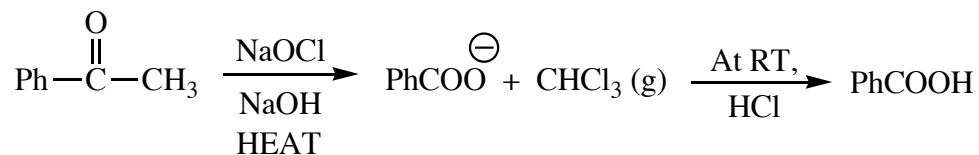
This multi-step synthesis is drawn from a Journal of Chemical Education Article called “**And the Winner is... A Multi-Step Synthesis for the Introductory Organic Course**”. Its reference is S. S. Stradling; C. L. Gage *J. Chem. Ed.* **1985**, 62(12), 1116-1117. We have chosen one of three possible synthetic routes for preparing a single substance, methyl *m*-nitrobenzoate. We will only use the one route, so that all of you will start with the same reaction step: the oxidation of acetophenone to benzoic acid. The benzoic acid that you prepare must then be characterized (by mp, IR and/or NMR) before you go on to the next reaction step, so several lab periods will pass before we move on to step 2. You will then nitrate this benzoic acid to *m*-nitrobenzoic acid via electrophilic aromatic substitution. Again, characterization of this product must occur before you move on to the final step, which is a Fischer Esterification to produce methyl *m*-nitrobenzoate. Abbreviated versions of the three reaction steps are given here, with more complete versions of the overall reactions given with each lab prompt below.

All Three Steps of the Multi-Step Reaction Sequence:



### Step 1: the Oxidation of Acetophenone to Produce Benzoic Acid

Overall Reaction:



This reaction will be heated on a large steam bath in the hood; begin heating this bath as soon as you get to lab. In a large beaker (at least 250 mL) combine a magnetic stir bar, 3 mL of acetophenone (know its mass) with 40 mL of bleach (5% aqueous NaOCl) per gram of acetophenone, and 2.5 mL of 10% NaOH (aq) per gram of acetophenone. Warm this mixture on the steam bath with stirring for about 30-60 min, during which time the chloroform that is produced should boil out of the mixture. At the beginning of this process, you can observe an oily layer of acetophenone floating on top of the aqueous mixture; at the end of the

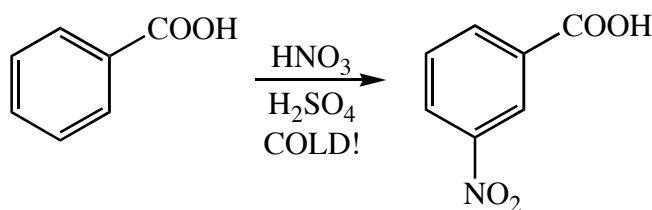
reaction, the oily phase should no longer be visible since it has reacted to form product. If you still have a significant oily layer after heating for 30 minutes consult your professor.

Once the oxidation is complete, slowly add 1 mL of acetone to destroy any excess bleach and then cool in an ice bath to RT. Slowly add conc. HCl with a pipet until significant precipitate has formed. When you cannot detect more precipitate forming, check that the pH is 2-3 or less; if not, continue to add HCl until that is so. Cool the mixture in an ice bath to complete crystallization of the benzoic acid product and isolate this product by suction filtration. Let it air dry on the aspirator for a while and then further dry in your lab drawer until the next lab period.

When the product is completely dry, obtain its mass and calculate the theoretical and percent yield for your reaction. Check its purity by mp, IR, and/or NMR, as directed by your professor. The product is usually of sufficient purity to use for the next step, but if that is not the case, you can recrystallize it from water.

## Step 2: Electrophilic Aromatic Substitution of Benzoic Acid to Produce *m*-Nitrobenzoic Acid

### Overall Reaction:



You should recall from your lecture class that a carboxylic acid would be a *meta*-director in an electrophilic aromatic substitution reaction. In practice, this nitration reaction can result in the production of quite a bit of the *ortho* product as well, unless the temperature is kept very cold throughout the reaction. All of the materials that you will use in the experiment are in proportion to the amount of benzoic acid that you are reacting. You should use no more than 3 g of PhCOOH, and record its mass carefully.

First, prepare a nitrating mixture (NM) by slowly adding concentrated H<sub>2</sub>SO<sub>4</sub> to concentrated HNO<sub>3</sub> while you are cooling it in a small Erlenmeyer flask in an ice/water/salt bath to 0°C or less. You will make this NM in proportion to the amount of benzoic acid that you will be reacting, although the benzoic acid will not be in this mixture. For each g of benzoic acid, use 1 mL of concentrated H<sub>2</sub>SO<sub>4</sub> and 0.67 mL of concentrated HNO<sub>3</sub> to prepare this NM. Keep it cold!

Second, prepare your reaction mixture (RM) in a large Erlenmeyer flask; this container will maximize cooling during the reaction. Add concentrated H<sub>2</sub>SO<sub>4</sub> to the Erlenmeyer and cool it to 0°C or less. Here you need 2.5 mL of H<sub>2</sub>SO<sub>4</sub> for each g of benzoic acid. Add the benzoic acid slowly to the H<sub>2</sub>SO<sub>4</sub>, keeping the temperature below 0°C. During the course of this mixing and the reaction to follow, your RM

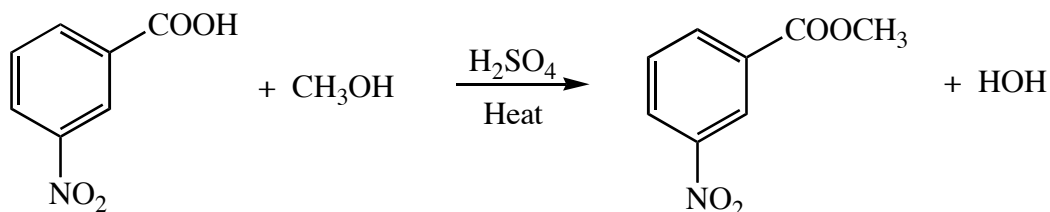
should stay below 0°C and never exceed 5°C! When all of the benzoic acid has been added to the H<sub>2</sub>SO<sub>4</sub>, it will be rather pastelike.

Now, double-check that your RM is colder than 0°C and slowly add the COLD NM to the COLD RM, mixing carefully and keeping it cold. Use a short disposable pipet to transfer it and be sure that the rate of addition allows for efficient cooling; remember that your RM should stay below 0°C and never exceed 5°C! You will have to add the NM very slowly at first, but the rate can be sped up as the reaction proceeds. Use the temperature as a guide. After all of the NM has been added, keep the mixture cold for another 10-15 minutes with occasional stirring.

Finally, pour the mixture over an ice/water slurry of about 150 g of ice and 200 mL of water. Stir vigorously and your product should precipitate. Filter the product from the mixture, wash well with cold water, and allow it to dry. When the product is completely dry (next lab period), obtain its mass and calculate the theoretical and percent yield for your reaction. Check its purity by mp, IR, and/or NMR, as directed by your professor. The product is usually of sufficient purity to use for the next step, but if that is not the case, you can recrystallize it from water.

### Step 3: Fischer Esterification of *m*-Nitrobenzoic Acid to Produce Methyl *m*-Nitrobenzoate

Overall Reaction:



As in the previous step, the amounts of reagents used for this procedure will depend on the mass of *m*-nitrobenzoic acid that you use in the reaction. Use no more than 3 g of it! It is also critical that your *m*-nitrobenzoic acid is completely dry, since this reaction is an equilibrium process and water in a wet sample will drive the reaction in the reverse direction, reducing your yield of product.

For each g of *m*-nitrobenzoic acid you will need 8 mL of methanol; for each 20 mL of methanol, you will need 1 mL of concentrated H<sub>2</sub>SO<sub>4</sub>. Consider the total volume of this mixture, and choose a roundbottom flask that holds about twice that volume; in other words, choose a flask so that it is about half full. Put the three materials in the proportions described above into the roundbottom flask with a couple of boiling chips, and attach a reflux condenser to form a reflux apparatus. Heat to reflux for 1 hour.

Pour the reaction mixture into an ice/water slurry (use a total volume of slurry of about 5 times the volume of methanol used) and stir. Once the ice is melted, use suction filtration to isolate the product and wash with water. The crude product should be recrystallized from methanol or methanol/water. Once it is

completely dry, determine its mass, and calculate its theoretical and percent yield. Also, determine its purity by mp, IR, and/or NMR as preferred by your professor.

### **Multi-Step Synthesis Yield Calculation.**

When you carry out a series of reaction steps, you usually want to know the efficiency of the whole process. To do so, you can use the percent yields for each step to compute the overall percent yield. This is easiest to explain with an example. Suppose you carried out four reactions in sequence with the percent yields given below.

Step 1: 87.5%; Step 2: 91.2%; Step 3: 79.3%; and Step 4: 81.9%

The overall percent yield is computed as shown, here.

Overall Percent Yield:  $0.875 \times 0.912 \times 0.793 \times 0.819 \times 100 = 51.8\%$  overall.

Be sure to compute the overall percent yield for the three steps of your synthesis of methyl *m*-nitrobenzoate.