

## CHE 239 UNKNOWN “MYSTERY” ESTERIFICATION MECHANISM

Normally, esters are formed under acidic conditions following the Fisher esterification mechanism (see p. 757 of Bruice), a nucleophilic acyl substitution mechanism. A reaction was discovered at Assemblon, Inc. where an acid and alcohol were combined, along with iodine, to form an ester. What makes this reaction interesting is that the esterification was achieved without an acid catalyst. It is assumed that the presence of iodine plays a vital role. There is no record of an iodine catalyzed/enhanced esterification and the mechanism for this particular reaction mechanism is unknown. Our CHE 239 class will begin a preliminary investigation of this mystery mechanism by doing a series of experiments whose results will support or exclude possible mechanistic pathways. There are nine different variations of this reaction scheme our class will carry out and each result will aid in our understanding of the mechanism.

A possible path this reaction could take is that of a radical mechanism coupled with the formation of an acid halide. Iodine ( $I_2$ ) is considered a radical source as its bond can split homolytically to form the iodine radical ( $I^\cdot$ ) as in section 11.2 of Bruice. This could lead to the formation of an acid iodide which would lead to a quick displacement of the iodide by the alcohol to form the ester (see nucleophilic acyl substitutions, sec. 16.7 of Bruice). We also want to see if the steric bulk of the alcohol plays a role in ester formation.

A summary of the reaction variations our class will carry out:

Procedure A is the standard reaction (this should work). In procedures B through E we will see if the structure of the alcohol is a factor in ester formation. In procedure F we will add a radical initiator instead of iodide to see if the reaction remains unaffected (indicating a radical mechanism). In procedure G we will attempt to isolate and characterize the possible acid iodide intermediate. In procedure H we will add a radical inhibitor to see if the reaction is prevented (thus indicating a radical mechanism). In reaction I, we will add a base to the reaction to ensure that acid is not being formed and hence simply undergoing the standard acid-catalyzed Fisher esterification. All the reaction schemes are shown on the last page.

You and a partner will be assigned one of the procedures below. You have 2 lab periods to complete the procedure and take IR, NMR and GC-MS spectra of your product. Your instructor will assign which procedure you are to do.

### **Experimental procedure A (Iodine esterification using methanol):**

1. Weigh out 2 g of iodine and dissolve it in 6 mL of methanol (warm the solution to dissolve the iodine if necessary).
2. Dissolve 1 mL of hexanoic acid in 4 mL of methanol in a 25 mL round bottom flask fitted with a water condenser. Heat to reflux.
3. Add the iodine solution to the reaction. Continue to heat at reflux for 3 minutes (the red iodine color may dissipate).
4. Let the reaction cool to room temperature and pour the solution into a tared (pre-weighed) Erlenmeyer flask. Prepare a sample for the GC-MS. Take 7 drops of this solution and add it to the GC-MS vial. To the vial add 1 mL of methylene chloride and turn into your instructor (label the vial with your name and experiment procedure you are doing).
5. Carefully evaporate off the excess methanol by heating the flask in a warm water bath and directing an air stream over the solution. Stop the evaporation when about 1-2 mL of liquid remains (what remains should be your ester product). Careful: too much heat may also evaporate the ester which boils at 150°C. If the solution is colorless and clear proceed to step #7. If the remaining ester is yellow/brown then proceed to step #6.
6. If the solution is a yellow or brown color, this is due to excess iodine that can be removed by neutralization with sodium metabisulfite solution. Add 1 mL of sodium metabisulfite solution to your ester and stir (the color should go away). Place this mixture in a centrifuge tube and add 1 mL of methylene chloride and mix. Remove the lower methylene chloride layer (this contains your ester) and dry it over 100 mg of sodium sulfate for 10 minutes. Decant (pour off) the methylene chloride solution from the sodium sulfate crystals into a clean dry test tube and carefully evaporate off the methylene chloride solvent. Continue on to step #7.
7. Weight the flask with ester contents. Take NMR and IR spectra of your sample. To prepare the NMR sample, use 3-4 drops of your ester dissolved in 0.7 mL of CDCl<sub>3</sub> NMR solvent.

### **Experimental procedure B: (Iodine esterification using 2-propanol)**

Follow procedure A except substitute 2-propanol for methanol whenever it is used. Also change step #5 from procedure A to step #5 below (instead of evaporating the methanol from the ester we will **distill** off the excess 2-propanol).

5. Set up the distillation apparatus on p. 713 of PLKE. Tare (pre-weigh) your 25 mL round-bottom flask with 2-4 boiling stones added. Your instructor will provide you a kit of the components for this set-up. Add your reaction solution to the 25 mL round bottom flask and slowly heat this mixture to distill off the lower boiling

2-propanol from your ester. The temperature should rise to about 82°C at which point the excess 2-propanol will distill off. Once the temperature starts going above 90°C stop the distillation process as only the ester will remain in the round-bottom flask. If the solution is colorless and clear proceed to step #7 of procedure A. If the remaining ester is yellow/brown then proceed to step #6.

#### **Experimental procedure C: (Iodine esterification using tert-butanol)**

Follow procedure A except substitute tert-butanol for methanol whenever it is used. Also change step #5 from procedure A to step #5 below (instead of evaporating the methylene chloride/methanol from the ester we will distill off the methylene chloride/excess tert-butanol:

5. Set up the distillation apparatus on p. 713 of PLKE. Tare (preweigh) your 25 mL round bottom flask with 2-4 boiling stones added. Your instructor will provide you a kit of the components for this set-up. Add your reaction solution to the 25 mL round-bottom flask and slowly heat this mixture to distill off the lower boiling tert-butanol from your ester. The temperature should rise to about 82°C at which point the excess tert-butanol will distill off. Once the temperature starts going above 90°C stop the distillation process as only the ester will remain in the round-bottom flask. If the solution is colorless and clear proceed to step #7 of procedure A. If the remaining ester is yellow/brown then proceed to step #6.

#### **Alternative Procedure D: (Iodine esterification using methanol/2-propanol)**

Follow procedure A except substitute a 50/50 (v/v) mixture of methanol and 2-propanol whenever methanol is mentioned.

#### **Alternative Procedure E: (Iodine esterification using methanol/tert-butanol)**

Follow procedure A except substitute a 50/50 (v/v) mixture of methanol and tert-butanol whenever methanol is mentioned.

#### **Alternative Procedure F: (Esterification with carbonitrile radical initiator)**

Use (10 mg) 1,1'-Azobis(cyclohexane carbonitrile) instead of iodine in step 1. There should be no need to treat the reaction mixture with sodium metabisulfite solution (step #6).

#### **Alternative Procedure G: (Isolation of acid iodide intermediate)**

Follow procedure A except substitute tetrahydrofuran instead of methanol whenever it is mentioned. There should be no need to treat the reaction mixture with sodium metabisulfite solution (step #6). The IR spectrum should be taken as soon as possible.

Depending on the mechanism of the reaction, this procedure will allow you to isolate the intermediate, the acid iodide ( $\text{CH}_3(\text{CH}_2)_4\text{C}(=\text{O})\text{I}$ ). The IR spectrum will show a strong carbonyl absorption at  $\sim 1800 \text{ cm}^{-1}$  if the acid iodide is present. The IR spectrum should be taken immediately as the acid iodide is unstable and water sensitive.

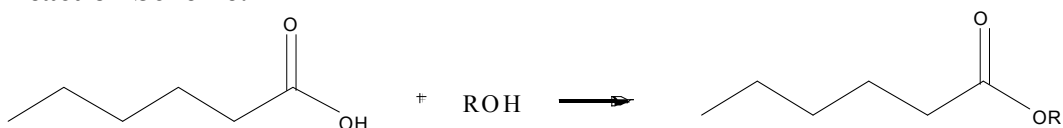
**Alternative Procedure H: (Addition of radical inhibitor to quench the reaction)**

Follow procedure A except add 100 mg BHT (2,6-di-tert-butyl-4-methylphenol) to hexanoic acid in methanol before you add iodine solution. BHT is a radical inhibitor. If this esterification goes by radical mechanism then BHT will prevent any radicals from forming.

**Alternative Procedure I: (Addition of hindered base to ensure high reaction pH >7)**

Add 400 mg DBU (1,8-Diazobicyclo(5.4.0)undec-7-ene) to hexanoic acid in methanol before you add iodine solution. DBU is a hindered base.

**Reaction Scheme:**



- A. I<sub>2</sub>, heat, MeOH
- B. I<sub>2</sub>, heat, iPrOH
- C. I<sub>2</sub>, heat, tBuOH
- D. I<sub>2</sub>, heat, 50/50 MeOH/iPrOH
- E. I<sub>2</sub>, heat, 50/50 MeOH/tBuOH
- F. AIBN, heat, MeOH
- G. I<sub>2</sub>, THF
- H. I<sub>2</sub>, BHT, MeOH
- I. I<sub>2</sub>, DBU, MeOH