

Esterification



Exp't 84 Synthesis of Methyl Benzoate by Fisher Esterification from K. L. Williamson, *Macroscale and Microscale Organic Experiments*, 2nd Ed. 1994, Houghton Mifflin, Boston p385 Revised 10/15/03 Prelab Exercise: Give the detailed mechanism for the acid-catalyzed hydrolysis of methyl benzoate. Introduction: The ester group is an important functional group that can be synthesized in a number of different ways. The low-molecular-weight esters have very pleasant odors and indeed are the major components of the flavor and odor aspects of a number of fruits.

Although the natural flavor may contain nearly a hundred different compounds, single esters approximate the natural odors and are often used in the food industry for artificial flavors and fragrances. Esters can be prepared by the reaction of a carboxylic acid with an alcohol in the presence of a catalyst such as concentrated sulfuric acid, hydrogen chloride, p-toluenesulfonic acid, or the acid form of an ion exchange resin:

$$\text{O}=\text{C}-\text{H}_3\text{C} + \text{CH}_2\text{OH}-\text{CH}_2\text{OH} \xrightarrow{\text{H}^+} \text{H}_3\text{C}-\text{O}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH} + \text{H}_2\text{O}$$

This Fischer esterification reaction reaches equilibrium after a few hours of refluxing.

The position of the equilibrium can be shifted by adding more of the acid or of the alcohol, depending on cost or availability. The mechanism of the reaction involves initial protonation of the carboxyl group, attack by the nucleophilic hydroxyl, a proton transfer, and loss of water followed by loss of the catalyzing proton to give the ester. Because each of these steps is completely reversible, this process is also, in reverse, the mechanism for the hydrolysis of an ester:

Other methods are available for the synthesis of esters, most of them more expensive but readily carried out on a small scale. For example alcohols react with acid anhydrides to form esters: $\text{CH}_3\text{CH}_2\text{OH}$ Ethanol + CH_3COCH_3 Acetic anhydride \rightarrow $\text{CH}_3\text{COCH}_2\text{CH}_3$ Ethyl acetate
 Acid chlorides form esters by reaction with alcohols. $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ 1-Propanol + CH_3COCl Acetyl chloride \rightarrow $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_3$ n-Propyl acetate
 In the latter reaction, an organic base such as pyridine is usually added to react with the hydrogen chloride.

A number of other methods can be used to synthesize the ester group. Among these are the addition of 2-methylpropene to an acid to form t-butyl esters, the addition of ketene to make acetates, and the reaction of a silver salt with an alkyl halide. $\text{CH}_3\text{CH}_2\text{COH}$ + $\text{CH}_2=\text{C}(\text{CH}_3)_2$ 2-Methylpropene (isobutylene) $\xrightarrow{\text{H}^+}$ $\text{CH}_3\text{CH}_2\text{COCH}_2\text{C}(\text{CH}_3)_3$ t-Butyl propionate
 $\text{HOCH}_2\text{CH}_2\text{C}(\text{OCH}_3)_2$ Benzyl alcohol + $\text{CH}_3\text{COCH}_2\text{C}(\text{OCH}_3)_2$ Propionic Acid Ketene \rightarrow $\text{CH}_3\text{COCH}_2\text{CH}_2\text{C}(\text{OCH}_3)_2$ Benzyl Acetate
 $\text{CH}_3\text{COO}^- \text{Ag}^+$ Silver acetate + $\text{CH}_3\text{BrCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ 1-Bromo-3-methylbutane \rightarrow $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ Isoamyl acetate

As noted above, Fischer esterification is an equilibrium process. Consider the reaction of acetic acid with 1-butanol to give n-butyl acetate: CH_3COOH Acetic acid + $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ n-Butanol $\xrightarrow{\text{H}^+}$ $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ n-Butylacetate + H_2O
 The equilibrium expression for this reaction is shown below.
$$K_{\text{eq}} = \frac{[\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3][\text{H}_2\text{O}]}{[\text{CH}_3\text{COOH}][\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3]}$$
 For primary alcohols reacting with unhindered carboxylic acids, $K_{\text{eq}} \sim 4$. If equal quantities of 1-butanol and acetic acid are allowed to react, at equilibrium the theoretical yield of ester is only 67%.

To upset the equilibrium we can, by Le Chatelier's principle, increase the concentration of either the alcohol or acid, as noted above. If either one is doubled, the theoretical yield increases to 85%. When one is tripled, it goes to 90%. But note that in the example cited the boiling point of the relatively nonpolar ester is only about 8 C higher than the boiling points of the polar acetic acid and 1-butanol, so a difficult separation problem exists if either starting material is increased in concentration and the product is isolated by distillation. ° Another way to upset the equilibrium is to remove water.

This can be done by adding to the reaction mixture molecular sieves, an artificial zeolite, which preferentially adsorb water. Most other drying agents, such as anhydrous sodium sulfate or calcium chloride, will not remove water at the temperatures used to make esters. A third way to upset the equilibrium is to preferentially remove the water as an azeotrope. The information in the table below can be found in any chemistry handbook table of ternary (three-component) azeotropes. The Ternary Azeotrope of Boiling Point 90.7 C ° Percentage Composition of Azeotrope Compound 1-Butanol n-Butyl acetate Water °

Boiling Point of Pure Compound (°C)	117.7	126.7	100.0
Vapor Phase	8.0	63.0	29.0
Upper Layer	11.0	86.0	3.0
Lower Layer	2.0	1.0	97.0

These data tell us that the vapor that distills from a mixture of 1-butanol, n-butyl acetate, and water will boil at 90.7 C and the vapor contains 8% alcohol, 63% ester, and 29% water. The vapor is homogeneous, but when it condenses, it separates into two layers. The upper layer is composed of 11% alcohol, 86% ester, and 3% water, but the lower layer consists of 97% water with only traces of alcohol and ester.

If some ingenious way to remove the lower layer from the condensate and still return the upper layer to the reaction mixture can be devised, then the equilibrium can be upset and nearly 100% of the ester can be produced in the reaction flask. The Dean Stark trap shown below is one method to solve this equilibrium problem. Dean-Stark trap for removing water through azeotropic distillation. The apparatus shown, modeled after that of Dean and Stark, achieves the desired separation of the two layers. The mixture of equimolar quantities of 1-butanol and acetic acid is placed in the flask along with an acid catalyst.

Stirring reduces bumping. The vapor, the temperature of which is 90.7 °C, condenses and runs down to the sidearm, which is closed with a cork. The layers separate, with the denser water layer remaining in the sidearm while the lighter ester plus alcohol layer runs down into the reaction flask. As soon as the theoretical quantity of water has collected, the reaction is over and the product in the flask should be ester of high purity. ° 3-way connector Esterification using a carboxylic acid and an alcohol requires an acid catalyst. In certain ester syntheses, the acid form of an ion-exchange resin is used.

This resin, in the form of small beads, is a cross-linked polystyrene that bears sulfonic acid groups on some of the phenyl groups. Essentially it is an immobilized form of p-toluenesulfonic acid, an organic-substituted sulfuric acid. This catalyst has the distinct advantage that at the end of the reaction it can be removed simply by filtration. Immobilized catalysts of this type are becoming more and more common in organic synthesis. Synthesis of Methyl Benzoate by Fischer Esterification

$$\text{C}_6\text{H}_5\text{COOH} + \text{CH}_3\text{OH} \rightarrow \text{C}_6\text{H}_5\text{COOCH}_3 + \text{H}_2\text{O}$$

Benzoic acid mp 122 °C MW 122.12

Methyl Benzoate bp 198-199°C d 1.094 MW 136.15 Place 5.0 g of benzoic acid and 25 mL of methanol in a 100-mL round-bottomed flask, cool the mixture in ice, pour 1.5 mL of concentrated sulfuric acid slowly and carefully down the walls of the flask, and then swirl to mix the components. Attach a reflux condenser, add 3 boiling chips, and reflux the mixture gently for 1 hr. with the set-up shown. . Isolation and Purification Cool the solution, decant it into a separatory funnel containing 25 mL of water, and rinse the flask with 25 mL of diethyl ether (Use wet ether found in a supply bottle in each hood).

Add this ether to the separatory funnel, shake thoroughly, and drain off the water layer, which contains the sulfuric acid and the bulk of the methanol. Wash the ether in the separatory funnel with 25 mL of water followed by 25 mL of 10% sodium bicarbonate to remove unreacted benzoic acid. Again shake, with frequent release of pressure by inverting the separatory funnel and opening the stopcock, until no further reaction is apparent; then drain off the bicarbonate layer into a beaker. If this aqueous material is made strongly acidic with hydrochloric acid, unreacted benzoic acid may be observed.

Wash the ether layer in the separatory funnel with saturated sodium chloride solution, and dry the solution over anhydrous calcium chloride in a 125-mL Erlenmeyer flask. Add sufficient anhydrous calcium chloride so that it no longer clumps together on the bottom of the flask. After 10 min, decant the dry ether solution into a dry 50-mL Erlenmeyer flask, wash the drying agent with an additional 5 mL of ether, and decant again. Remove the ether by evaporation in the hood until the next lab period (Label flask with your name) or use a rotary evaporator (Desk 3). Ether boils at 37°C.

When evaporation is complete, add 2 to 3 g of anhydrous calcium chloride pellets to the residual oil and heat for about 5 min longer. Obtain a microscale distillation kit from the stockroom and decant the methyl benzoate into a 25-mL round-bottomed flask with 14/20 joint, attach the stillhead, without water circulating in the jacket [The boiling point of the ester is so high (199°C) that a water-cooled condenser may crack], and distill. The flask should be placed deep in the sand bath and wrapped with lots of glass wool. Use a 3- or 4- tube cow as the receiver, and collect material boiling above 190°C.

A typical student yield is about 3 g. Analyze your product by the method listed on your assignment slip, preparing the sample according to the instructions in the Lab Guide. If your assignment was “ bp only”, you should talk to an instructor or instrument room assistant about analyzing the product by ¹³C NMR on the Bruker 400 MHz FT-NMR as this is much more fun and quite easy! Cleaning Up: Pour the sulfuric acid layer into water, combine it with the bicarbonate layer, neutralize it with solid sodium carbonate, and flush the solution down the drain with much water.

The saturated sodium chloride layer also can be flushed down the drain. If the calcium chloride is free of ether and methyl benzoate, it can be placed in the nonhazardous solid waste bin. Post Lab Question 1. In the preparation of methyl benzoate, what is the purpose of (a) washing the organic layer with sodium bicarbonate solution? (b) washing the organic layer with saturated sodium chloride solution? (c) treating the organic layer with anhydrous calcium chloride pellets? What is the product of the following reaction? $\text{O} \text{NH}_3 \text{OCH}_3 \text{ ether}$. ? Synthetic Experiment PreLab Grading Sheet Name(s):

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TA: Date: PreLab For Exp't #: 84 Title: Synthesis of Methyl Benzoate by Fisher Esterification Possible Points Missed Points Date, Name, Desk #, Experiment # & Title(abbreviated after 1st pg), Section & TA Name Summary Goals Reactions, structures, diagrams Completeness of Chemical Data Table(s) PreLab Exercise Spectral Features Comparison (NMR, RI) Work-up - Explanation of the product isolation and purification process TOTAL FOR PRELAB Date Handed in: General Comments: 10 10 16 14 14 14 14 100 Total Points: Synthetic Experiment Final Report Grading Sheet Name: TA: Date: Final Report For Exp't #: 84 Title: Synthesis of Methyl Benzoate by Fisher Esterification Possible Points Missed Points Name, Date, Experiment Title (abbreviated after 1st page) and every page numbered OBSERVATION and DATA - Overall organization, readability, completeness Data: Weighing data, molecular weights, moles, densities, volumes, distillation temperatures, analysis conditions. (NMR: solvent and amounts.

RI: temperature of measurement. IR method and/or weights, GC Conditions Sheet) Yield: Show % yield calculations with limiting reagent clearly stated. Purity: Give odor, boiling point, color, TLC or other indicators of purity. RESULTS AND DISCUSSION - Overall organization, readability, completeness Results; Achievement of goals Product Analysis Data: Quality and Interpretation – Structure(s) drawn on the spectrum or chromatogram or purity as indicated by RI analysis. (Literature value for refractive index. Identify all gas chromatographic peaks with structures. Assign major IR absorptions and explain how they prove that the correct product was formed. If you did C-13 NMR, interpret all peaks in terms of chemical shift, splitting patterns, (and coupling constants if measureable). See Lab Guide

Chapter 3, Section 3. 4 for guidelines in annotating spectra and Ch 11 for help with interpretation. 4 8 12 12 8 16 24 POSTLAB QUESTIONS TOTAL POINTS Date Handed in: General Comments: 16 100 Total Points: