

## The Fragrance of Rum, Isobutyl Propionate

from K. L. Williamson, *Macroscale and Microscale Organic Experiments*, 2nd Ed. 1994, Houghton Mifflin, Boston p385; revised 6/27/06

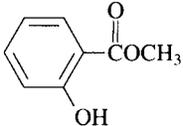
### Prelab Exercise

Give the detailed mechanism for the synthesis of isobutyl formate by Fischer esterification.

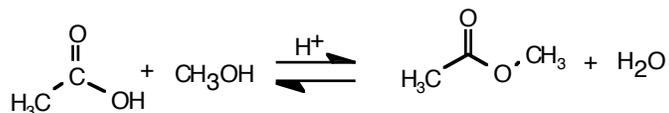
### Introduction

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. For example, isobutyl propionate (shown in the table below) has the fragrance of rum. This experiment is the synthesis of this rum-scented ester.

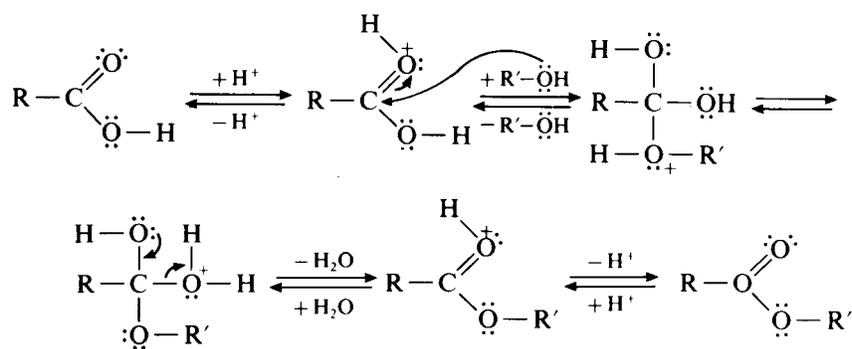
**TABLE 33.1** Fragrances and Boiling Points of Esters

Ester	Formula	Boiling Point (°C)	Fragrance
Isobutyl formate	$\text{H}\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\overset{\text{CH}_3}{\underset{ }{\text{C}}}\text{HCH}_3$	98.4	Raspberry
<i>n</i> -Propyl acetate	$\text{CH}_3\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\text{CH}_2\text{CH}_3$	101.7	Pear
Methyl butyrate	$\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{O}}{\parallel}\text{C}\text{OCH}_3$	102.3	Apple
Ethyl butyrate	$\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\text{CH}_3$	121	Pineapple
Isobutyl propionate	$\text{CH}_3\text{CH}_2\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\overset{\text{CH}_3}{\underset{ }{\text{C}}}\text{HCH}_3$	136.8	Rum
Isoamyl acetate	$\text{CH}_3\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\text{CH}_2\overset{\text{CH}_3}{\underset{ }{\text{C}}}\text{HCH}_3$	142	Banana
Benzyl acetate	$\text{CH}_3\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2\text{-}$ 	206	Peach
Octyl acetate	$\text{CH}_3\overset{\text{O}}{\parallel}\text{C}\text{OCH}_2(\text{CH}_2)_6\text{CH}_3$	210	Orange
Methyl salicylate		222	Wintergreen

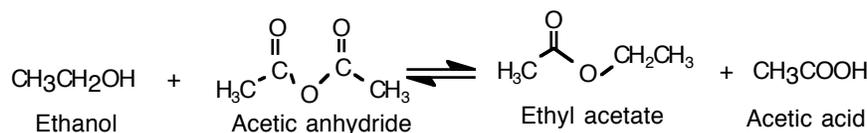
Esters can be prepared by the reaction of a carboxylic acid with an alcohol in the presence of a catalyst such as concentrated sulfuric acid, hydrogen chloride, *p*-toluenesulfonic acid, or the acid form of an ion exchange resin:



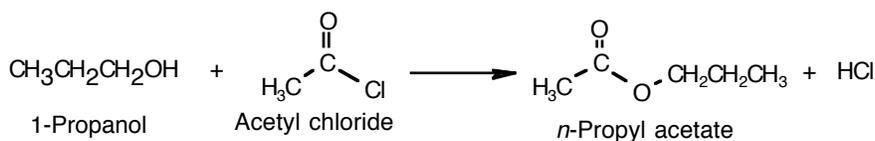
This Fischer esterification reaction reaches equilibrium after a few hours of refluxing. The position of the equilibrium can be shifted by adding more of the acid or of the alcohol, depending on cost or availability. The mechanism of the reaction involves initial protonation of the carboxyl group, attack 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:

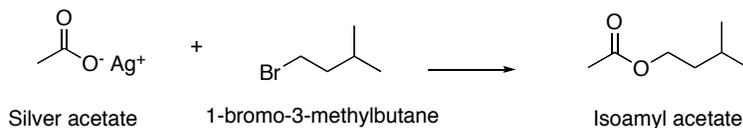
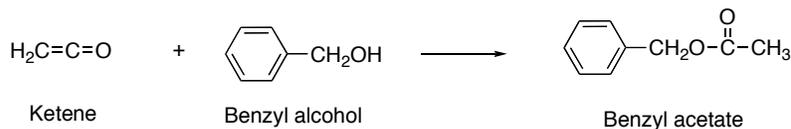
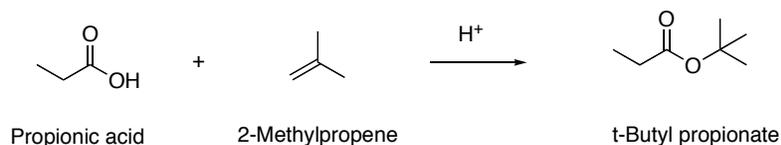


Acid chlorides form esters by reaction with alcohols.

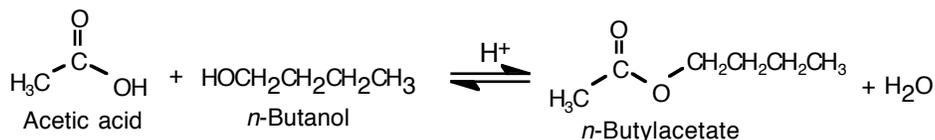


In the latter reaction, an organic base such as pyridine is usually added to react with the hydrogen chloride.

A number of other methods can be used to synthesize the ester group. Among these include the addition of 2-methylpropene to an acid to form *t*-butyl esters, the addition of ketene to an alcohol to make acetates, and the reaction of a silver salt with an alkyl halide.



As noted above, Fischer esterification is an equilibrium process. Consider the reaction of acetic acid with 1-butanol to give n-butyl acetate:



The equilibrium expression for this reaction is

$$K_{\text{eq}} = \frac{\left[ \text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \right] [\text{H}_2\text{O}]}{\left[ \text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} \right] [\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3]}$$

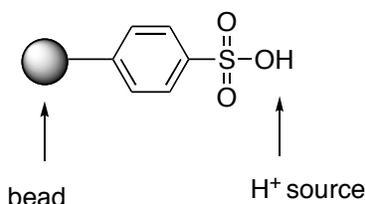
For primary alcohols reacting with unhindered carboxylic acids,  $K_{\text{eq}} \sim 4$ . If equal quantities of 1-butanol and acetic acid are allowed to react, the theoretical yield of ester is only 67% at equilibrium. To upset the equilibrium we can, by Le Chatelier's principle, increase the concentration 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. Water can form an azeotrope with certain alcohols at specific concentrations. A special apparatus, called a Dean-Stark apparatus or trap, can be used to distill off the water as an azeotrope while the ester being is formed. Removing water from the reaction in this way will favor ester

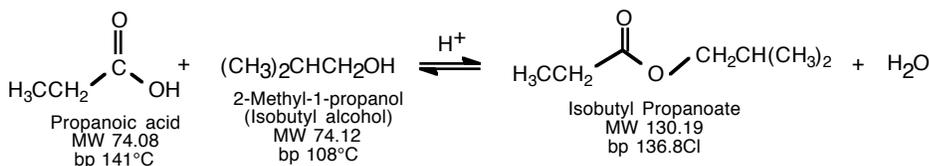
formation.

Esterification using a carboxylic acid and an alcohol requires an acid catalyst. In this experiment, 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; see figure below. 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 Isobutyl Propionate by Fischer Esterification

In this experiment, an excess of propanoic acid is used in order to drive the equilibrium to the right of the reaction equation. The excess propanoic acid is removed by reaction with potassium carbonate, and the water is adsorbed by silica gel when the reaction mixture is purified by column chromatography.



Prepare 0.2 g of Dowex 50X2-100 ion-exchange resin by washing the resin with water to remove much of the yellow color; decant off the water. The resin is then collected by vacuum filtration on a Buchner funnel before use.

To a reaction tube add 336 mg of 2-methyl-1-propanol (isobutyl alcohol), 444 mg of propanoic acid (propionic acid), the 80 mg of Dowex 50X2-100 ion-exchange resin that was previously prepared, and a boiling chip. Attach the empty distilling column as an air condenser. Reflux the resulting mixture for 1 hour or more. Cool the reaction to room temperature.

### Isolation and Purification

On a larger scale, the product would probably be isolated and purified by distillation, but this is difficult to do on a microscale without severe losses of material and thus poor yields. Therefore, chromatography is used here for purification.

### *Prepare the Column:*

Assemble a microscale chromatography column (see Lab Guide for review), being sure it is clamped in a vertical position. Close the valve, and fill the column with dichloromethane to the bottom of the funnel. Prepare a slurry of 1 g of silica gel in 4 mL of dichloromethane in a small beaker; be sure the slurry is fluid and easy to pour (add more dichloromethane if necessary). Stir the slurry gently to get rid of air bubbles, and gently swirl, pour, and scrape the slurry into the funnel, which has a capacity of 10 mL. After some of the silica gel has been added to the column, open the stopcock and allow solvent to drain slowly into an 25 mL Erlenmeyer flask. Use this dichloromethane to rinse the beaker containing the silica gel. As the silica gel is being added, tap the column with a pencil so the adsorbent will pack tightly into the column. Continue to tap the column while cycling the dichloromethane through the column once more. Once the column is packed, allow the level of the dichloromethane reach the very top of the silica gel column. Add sand (not the sand used for heating mantles!) to the top of the silica gel so that you have about 1/2" to 1" of sand.

### *Isolation or "Work-Up" of the Reaction:*

Add enough anhydrous potassium carbonate to the reaction mixture, including the resin, to dry sufficiently the mixture (look for the drying agent to clump then add a little more to ensure that the mixture is dry, that is, keep adding until the drying agent is "free-flowing").

### *Purification of the Reaction Mixture via Column Chromatography:*

Swirl for 1 minute then transfer the liquid with a Pasteur pipet to the top of the column by carefully squirting the liquid down the sides of the column; allow the liquid to settle to the top of the column. As you do this, keep the stopcock of the column open so that you're draining the solvent and allow the sample to adsorb completely. The flask, ion-exchange resin, and solid potassium carbonate are rinsed twice with fresh 0.5-mL portions of dichloromethane to ensure that all product has been transferred to the column. Once all of the sample has been transferred to the column, wash the walls of the column twice with 0.5 mL portions of fresh solvent to ensure that none of your sample remains on the walls of the column; remember to keep the stopcock open during this time. Allow this volume of solvent to elute to just above the top of the column, then close the stopcock. Add fresh solvent and open the stopcock to collect the fractions in small test tubes. Add fresh solvent to the column in order to collect the fractions. You will need to collect several 1-mL fractions.

Evaporate the dichloromethane from each fraction under a stream of nitrogen in the hood and combine those fractions that have the odor of an ester. Combine these "like" tubes into one tared reaction tube; be sure to wash the "like" tubes with fresh solvent to ensure you have transferred all product to the one reaction tube. Evaporate the  $\text{CH}_2\text{Cl}_2$  and remove the last traces by connecting the reaction tube to the vacuum for a brief period. Since the dichloromethane boils at  $40^\circ\text{C}$  and the product at  $137^\circ\text{C}$ , separation of the two via concentration under vacuum is easily accomplished. Weigh the product to determine percent yield. The ester should be a perfectly clear, homogeneous liquid.

### Analysis

You will be instructed to analyze your final product by IR, NMR, GC, GC-MS or RI. Analyze your sample according to your assignment sheet and prepare it as per the instructions on Sample Preparation in the Lab Guide.

### Cleaning Up

After drying, place the catalyst and the used silica gel in the solid waste bin. Any

dichloromethane should be placed in the halogenated organic waste container.

### PostLab Questions

1. Give 2 advantages of using the Dowex resin instead of sulfuric acid.
2. Give the reaction of unreacted propionic acid with anhydrous potassium carbonate.