

Experiment C

Synthesis of Frambinone by Aldol Condensation and Catalytic Hydrogenation

Reading: Organic Chemistry by Marc Loudon, 5th ed., pp. 1063-1066 (22.4), 1100-1101 (22.9).

Frambinone, otherwise known as 4-(4-hydroxyphenyl)butan-2-one, is frequently used as a chemical additive in perfumes and cosmetics due to its sweet, fruity aroma. It also goes by the names of raspberry ketone, rasketone, rheosmin, or oxyphenylon. (The name “frambinone” comes from “framboises”, the French word for raspberries.)

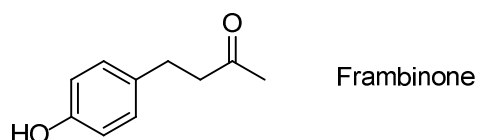


Figure C.1 » The structure of frambinone

Although frambinone was first isolated from raspberries, it typically makes up less than 0.1% by weight of the berries. For this reason, naturally-produced frambinone is pricy to isolate; it can cost around \$20 per gram, making it prohibitively expensive for mass production. By contrast, synthetically-produced frambinone costs less than one-thousandth as much.

To synthesize frambinone, you will perform a two-step synthesis. The first step will involve an aldol condensation between 4-hydroxybenzaldehyde and acetone, catalyzed by sodium hydroxide. After this step, you will purify the intermediate (an α,β -unsaturated ketone) and set it aside for the following lab period. The second step will involve performing a catalytic hydrogenation on the intermediate to reduce it to a saturated ketone.

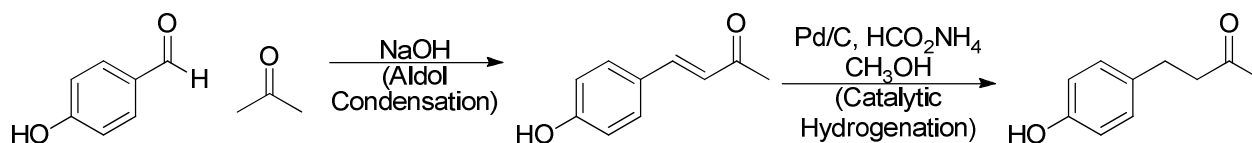


Figure C.2 » The synthetic pathway you will use to synthesize frambinone

As a refresher in nomenclature, often the relative positions of carbons (and their corresponding hydrogens) in a carbonyl compound are designated using Greek letters. The positions are labeled as α , β , γ , δ , and ϵ , etc. as they get further away from the carbonyl carbon. An α,β -unsaturated ketone contains a C-C double bond that is conjugated to the C-O double bond of the ketone.

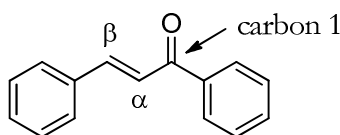


Figure C.3 » An α,β -unsaturated ketone

Aldol Condensation

When acetaldehyde is treated with base at room temperature or below, it undergoes a self-addition reaction to form 3-hydroxybutanal. When this reaction was first studied in the early nineteenth century, the product, 3-hydroxybutanal, was named “aldol” as a reflection of the *aldehyde-alcohol* components of its structure. In the presence of heat and base, the 3-hydroxybutanal undergoes further elimination of water to form the α,β -unsaturated aldehyde, 2-butenal. This is called the aldol condensation.

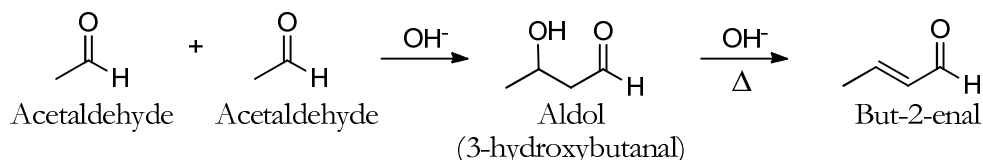
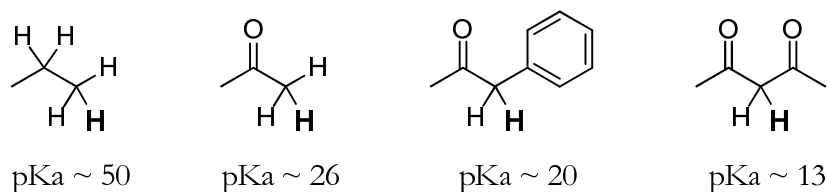


Figure C.4 » The overall scheme for aldol condensation

Today, the definition of an aldol reaction has been expanded to include the reaction of any enolate (regardless of origin, i.e., aldehyde, ketone, amide, ester, etc.) and an aldehyde. Both aldehydes and ketones that bear a hydrogen on the α -carbon readily form enolate ions in the presence of base because the electron-withdrawing effects of carbonyls render the α -hydrogens slightly acidic. Additional electron-withdrawing substitution further exaggerates the effects on pK_a as illustrated in the ketones below:

Figure C.5 » pK_a s of the α -hydrogens for several compounds

Next we will look at the mechanism of a base-catalyzed, aldol condensation of propanal with another molecule of propanal (see Figure C.6). In Step 1, a base abstracts the acidic α -proton, forming an enolate. Recall that enolates are stabilized by resonance delocalization of the anion. In Step 2, the nucleophilic α -carbon adds to the carbonyl group of another molecule of propanal. In Step 3, the resulting alkoxide ion reacts with water to form the product of the aldol addition. When heated, the aldol product of Step 3 undergoes an irreversible dehydration to form the α,β -unsaturated ketone (Step 4).

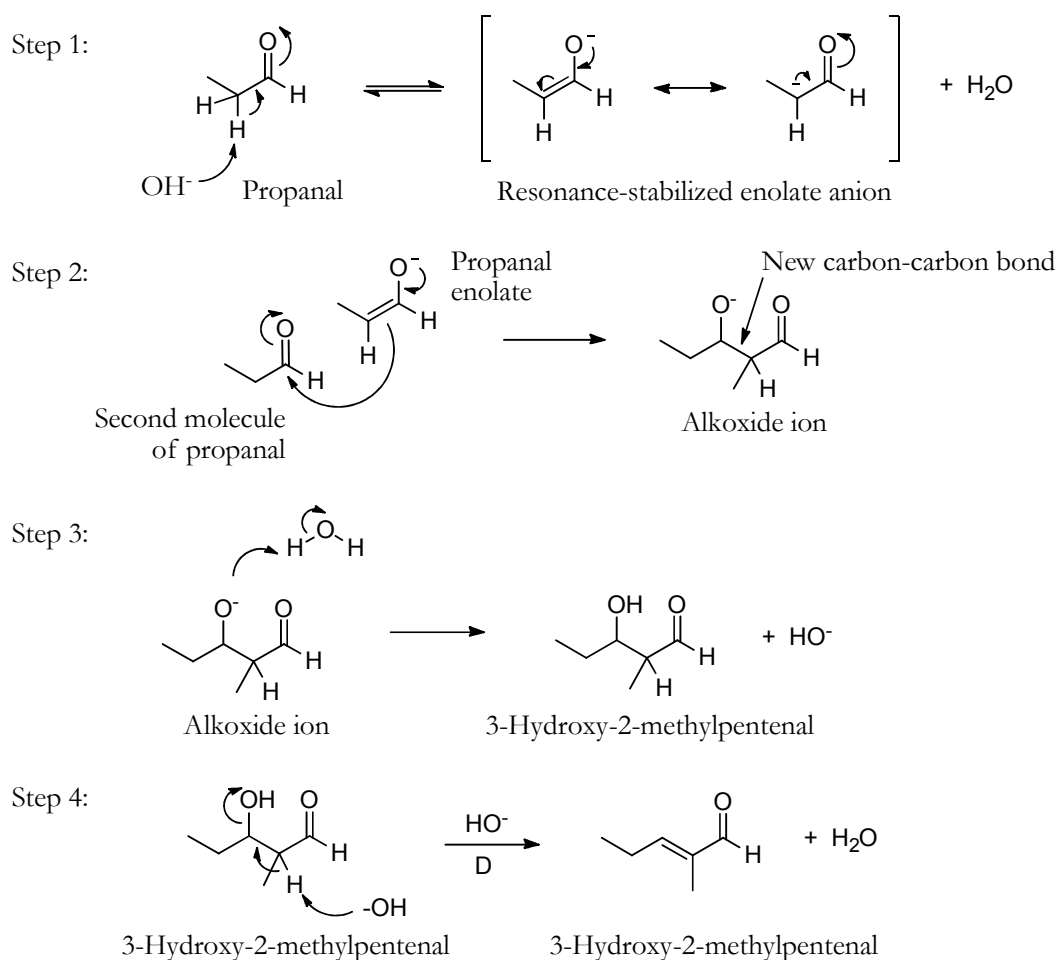


Figure C.6 » The mechanism of an aldol condensation

The aldol addition in Figure C.6 illustrates a “self-condensation”. An aldol condensation between two **different** aldehydes or ketones is called a **crossed aldol condensation**. Such condensations can result in an undesirable mixture of products, since both reactants can undergo self-condensation as well as crossed condensation. However, in some cases, crossed aldol condensations do yield a single product in good yield. For this to happen, only one of the molecules must be capable of forming an enolate (in this case, acetone), and one molecule must be more open to nucleophilic attack (in this case, the benzaldehyde; aldehydes are more attackable than ketones due to lower sterics and higher partial positive charge on the carbonyl carbon).

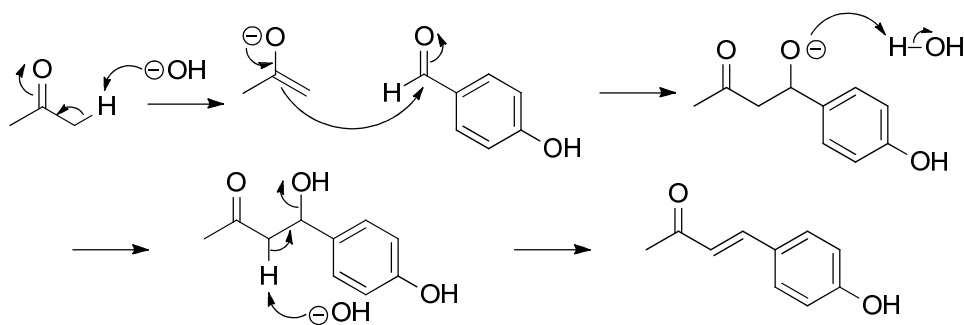


Figure C.7 » The mechanism of the aldol condensation you will perform in this lab

Catalytic Hydrogenation

The addition of a molecule of hydrogen to C=C double bonds in the presence of a catalyst is an important reaction in organic synthesis. However, the hydrogen gas often requires specialized equipment and can be quite hazardous in the presence of sparks or open flames.

Transfer hydrogenation, where another organic molecule is used as the hydrogen source, avoids this problem. Many molecules can transfer a molecule of H₂ to a substrate in the presence of a suitable catalyst. The hydrogenation reaction you will use involves a transfer of hydrogen from ammonium formate to the aldol product. Ammonium formate readily decomposes into hydrogen, carbon dioxide and ammonia in the presence of the catalyst, palladium on carbon (Pd/C). Formation of CO₂ provides a substantial driving force to the reactivity of ammonium formate as a hydrogen donor.

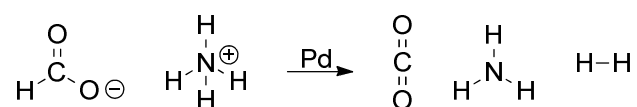


Figure C.8 » Ammonium formate decomposes to carbon dioxide, ammonia, and hydrogen gas.

The exact mechanism at the surface of the palladium metal is not known. Some of the hydrogen gas can be adsorbed onto the surface of the palladium metal and react with the chalcone. Alternatively, the ammonium formate could react with the palladium and directly transfer hydrogen to the chalcone.

Safety Precautions

Hydrochloric acid and sodium hydroxide are corrosive. Wear gloves while handling these reagents and if you get any on yourself, wash the affected area well with water. Palladium on charcoal is a flammable solid; methanol, ethyl acetate and hexanes are flammable liquids. Chloroform is a suspected carcinogen. While ammonium formate is rated only as a moderate health hazard, you should still avoid contact. Wear gloves and protective clothing and avoid inhaling vapors.

Procedure

The aldol reaction takes 4-7 days to reach completion. For this reason, you will set up your reaction during the week before you start the lab. During the first day of this lab, you will work up the reaction and purify your intermediate. During the second day of this lab, you will perform the hydrogenation and purify your final product.

Step 1: Aldol Condensation of 4-Hydroxybenzaldehyde and Acetone

To set up the reaction, you will weigh out 1.000 g of 4-hydroxybenzaldehyde and place it into a 50 mL round-bottom flask. Add 6 mL of acetone and a stirbar; stir the flask for a few minutes until the solid has fully dissolved. Using a syringe, add 2 mL of 6M aqueous NaOH. The NaOH will precipitate almost immediately as a solid. Stir the flask for another minute or so to ensure even distribution, then stopper the flask and place it in your drawer. It should slowly change to a dark orange color.

The first day of the lab, add 5 mL of 3M aqueous HCl to your flask and stir it for 10 minutes. Pour the flask contents into your separatory funnel. Rinse the flask with 20 mL of water and transfer the rinse into the sep funnel; repeat this step with 20 mL of chloroform.

Drain off the organic layer. Extract the aqueous layer twice with 20 mL of chloroform, and combine these chloroform layers with your organic layer. Place all of your combined organic extracts into a 100 mL round-bottom flask and concentrate it to dryness on the rotary evaporator. There may be some residual water left but this will not matter for the next step. Dissolve a small amount of the mixture in acetone in a vial, and perform TLC in 70:30 hexanes:ethyl acetate. You may need to use a silica-iodine mixture to visualize the spots. Label the vial as "Crude Intermediate" and set it aside.

To purify your intermediate, recrystallize it in water. Your product is very likely to oil out during this step, especially if its purity is not terribly high. If this happens, keep adding hot water until all the oil has dissolved. Once the intermediate is fully dissolved, allow it to cool slowly to room temperature, then place it in an ice bath. You should see crystals forming. If not, gently scratching the flask or adding a seed crystal from the intermediate recovery jar should help.

Once the solid has been recrystallized, filter it out and wash it with some cold water. Allow it to remain on the funnel with vacuum running for at least 5-10 minutes, to assist in the removal of water. Once it is fully dry, weigh your purified intermediate and calculate your percent yield. Obtain its melting point and submit a sample for NMR. Again dissolve a small sample in acetone in a vial labeled as "Purified Intermediate." Perform TLC in 70:30 hexanes:ethyl acetate by spotting both your crude and pure intermediate on the same plate, so you can compare R_f s side-by-side.

Step 2: Catalytic Transfer Hydrogenation of Aldol Product

Clamp your 25 mL round-bottom flask over a heating mantle. To protect the inside of the flask's ground-glass joint during the addition of solid reagents, roll a small piece of weighing paper into a cone and insert it into the flask so that it fits snugly in the neck of the flask and just covers the inside of the joint. Place 0.100 g of your intermediate in the flask and add 0.320 g of ammonium formate and 0.030 g of 10% palladium on carbon. Remove the paper cone and swirl the flask to coat the surface of the catalyst with the other reagents.

Add 10 mL of anhydrous methanol – the reaction mixture should start bubbling, due to the gas produced in the decomposition of ammonium formate. Place a condenser in the top of the flask and heat the flask to boiling. Allow the reaction to reflux for 20 minutes, measured from when you start to see methanol vapors condensing in the condenser.

While your reaction is refluxing, set up a filter pipet to remove the catalyst. This is necessary because the extremely small particles of catalyst are not adequately removed by a normal filter paper. Collect 6 or 7 clean Pasteur pipets from your TA's desk for the rest of today's lab. Take one of these pipets and use a stick to poke glass wool into it to a depth of 5-6 cm. (Make sure you are wearing gloves while handling glass wool, so that small pieces of it do not break off in your skin.) Add 1-1.5 cm of cotton on top of the glass wool and pack that down too. Clamp the pipet to a ring stand and place a round-bottom flask beneath it.

Once your reaction has finished, allow the flask to cool to room temperature, then place it into an ice bath for five minutes. Using another Pasteur pipet, drip the reaction mixture into the filter pipet. If you want to filter it more quickly, you can place a pipet bulb over the top of the filter pipet and use that to force the mixture through the cotton and glass wool (much like you did for the Identification of Unknowns microcolumn).

Experiment C: Synthesis of Frambinone

Now that all of your reaction mixture has been pushed through the filter, you can take a TLC of the solution. Spot the round-bottom flask contents directly onto a plate, side-by-side with the “Purified Intermediate” vial from last lab session. Develop the plate in 70:30 hexanes:ethyl acetate. Remove the round-bottom flask and concentrate it down to dryness. While this is happening, you can safely dispose of the catalyst in your filter pipet by pushing 3-4 mL of water through the column. Once this is done, dispose of the filter pipet in the white bins inside the main hood.

You should notice a strong, fruity smell in the flask – this is your crude frambinone product. There is still a large amount of unreacted ammonium formate mixed with the frambinone, so you will need to perform an extraction to remove it. On the small scale we are using for this reaction, a normal separatory funnel will not work well. Instead, you will use Pasteur pipets to separate layers, performing a miniscale extraction. You will need two clean vials, which you will label A and B. You will need to clamp them to your ring stand to avoid them spilling.

Rinse your round-bottom flask containing the crude product with 3 mL of water. Using a Pasteur pipet, transfer this water to vial A. Repeat this step with 3 mL of chloroform, combining it with the water rinse in vial A. Stir the two layers well, then use a Pasteur pipet to transfer the entire lower, organic layer to a vial B. Rinse the round-bottom flask again with 3 mL of chloroform, transfer it to vial A, and stir well. Again transfer the organic layer to vial B. At this point, you should have roughly 6 mL of chloroform in vial B – this contains most of your product and a little bit of ammonium formate.

To remove the residual ammonium formate, you will need to wash your organic layer with water. Add 3 mL of water to vial B and stir well. Use a Pasteur pipet to remove the upper, aqueous layer – set it aside in a beaker or another vial. Dry the organic layer by adding a small amount of sodium sulfate (it may help to hold a funnel over the vial while adding it.)

Removing the drying agent will require another small-scale filtration. Take another clean Pasteur pipet and push a small amount of cotton into the end of it, then clamp it to your ring stand with a round-bottom flask below it. Drip your dried organic layer through this filter pipet – you do not have to transfer over all of the drying agent. Since a lot of product is still mixed in with the drying agent, however, you will have to wash it out with a little more chloroform. Add another 5-6 mL of chloroform to vial B, swirl to mix it with the drying agent, and then filter this through the filter pipet as well.

Take a TLC of your product, concentrate your product to dryness on the rotary evaporator, then submit a sample for NMR. If you have enough product remaining, take a melting point.

Wastes

Organic Waste: All TLC eluent and rotary evaporator condensate.

Aqueous Waste: All aqueous fractions from separations, and aqueous filtrate from recrystallization.

Solid Chemical Waste: Used melting point capillaries, TLC plates, drying agent and filter pipets.

Recovery Jars: All recovered intermediate and product.