Claisen Condensation – Beyond Labz Virtual ChemLab Activity

Purpose:

1) To examine how choice of reagent and solvent impacts the outcome of a Claisen condensation.
2) To compare the Claisen condensation to the aldol condensation performed in lab.

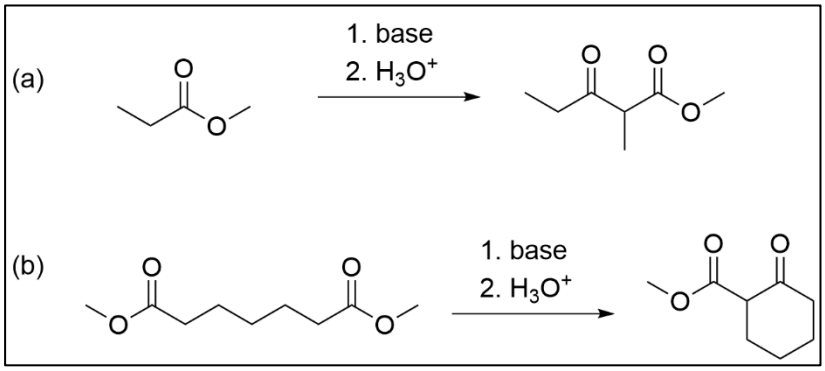

Figure 1. Reaction schemes of (a) the Claisen condensation of methyl propionate and (b) the Dieckmann cyclization of 1,7-dimethyl-heptanedioate

Introduction:

The Claisen condensation is a reaction that falls is in the category of carbonyl condensation reactions. It is very similar to the aldol reaction in that the **nucleophile** is an **enolate** that reacts with a carbonyl electrophile. However, in a Claisen condensation the **electrophile** is an **ester** instead of an aldehyde like in the aldol reaction. Consequently, the electrophile carbonyl is undergoes **nucleophilic acyl substitution** in a Claisen condensation, eliminating the -OR group and forming a ketone functional group two carbons away from the carbonyl of the enolate (Figure 2). This product is called a β-ketoester.

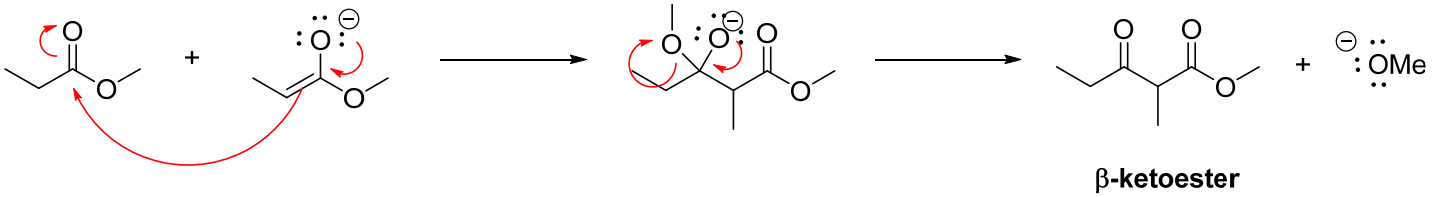

Figure 2. Nucleophilic acyl substitution to make a β-ketoester in the Claisen condensation.

However, despite it looking like you are done after the nucleophilic acyl substitution, you are not! The β-ketoester is a strong enough acid (pK_a ~ 11) that expelled alkoxide anion ($^-$OMe in Figure 2 above) can deprotonate it, generating a resonance-stabilized carbanion (Figure 3). This step happens very fast, and this is where the first step of the Claisen condensation will hit equilibrium. For this reason, a second step consisting of an acid work-up is always required for the Claisen condensation.

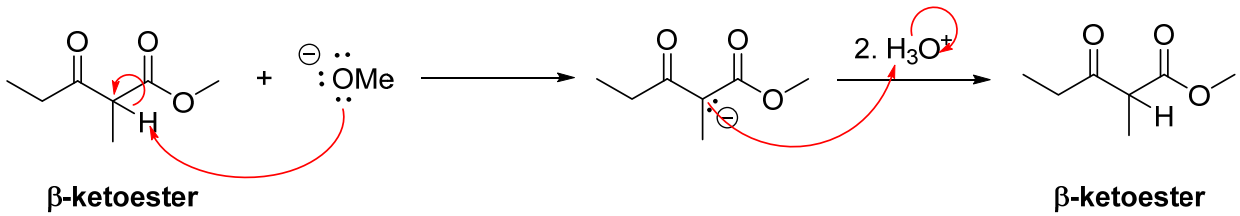

Figure 3. Deprotonation and subsequent acid work-up to generate the final, neutral β-ketoester product in the Claisen condensation.

In the Beyond Labz exercise, you will determine the best set of reaction conditions to make the β-ketoester shown in Figures 2 and 3. First you experiment with different solvents (water, ethanol, and diethyl ether) to determine which is the best one to obtain the desired product. Once this is known, you will test different bases (NaOMe, LDA, and KOH) to observe that impact on the reaction outcome.

Finally, we will apply our optimized conditions to the Dieckmann cyclization, which is a fancy name for "intramolecular Claisen condensation", in which a molecule containing an ester and a second, enolizable carbonyl reacts with itself to form a cyclic β-ketoester product. We will characterize this product by ^{1}H and ^{13}C NMR.

Figure 4 below shows the layout of the Synthesis virtual lab in Beyond Labz. Familiarize yourself with the location of different items.

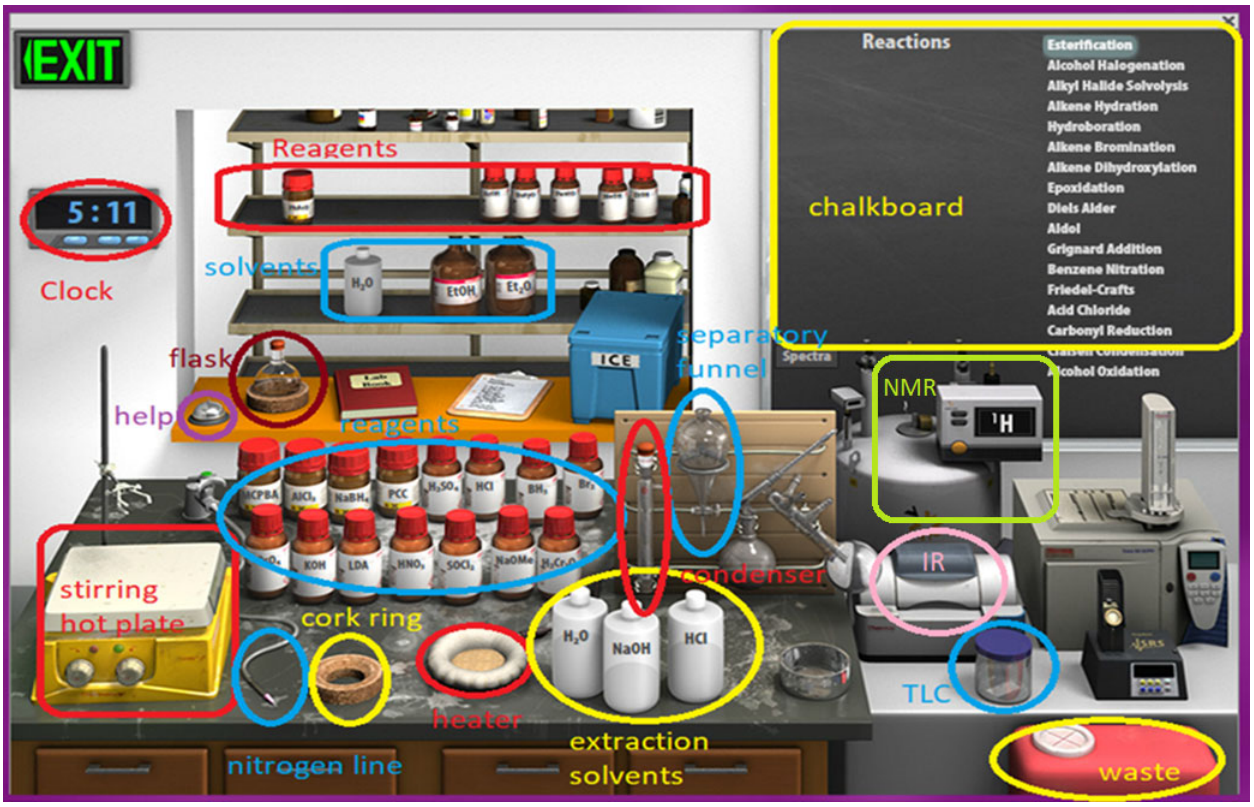

Figure 4. Beyond Labz SYNTHESIS virtual lab.

Tips for completing the Virtual Lab:

- Help is available by clicking on the bell on the stockroom counter.
- **As you work through the procedure, record your observations**, either in your lab notebook on Teams or by using the electronic notebook provided by Beyond Labz (on the shelf at the back of the lab, next to the reaction flask).

Part 1. Determining the appropriate solvent

1. Open a MS Word page on your computer so that you can paste screenshots on the page as you go through the procedure.
2. Start the Beyond Labz program and go to the Virtual ChemLab - Organic. Select "Synthesis" at the top left of the screen to open the Synthesis virtual lab.
3. On the chalkboard click on "**Claisen Condensation**," and you will see the available substrates (drawn on the board and in bottles on the shelf). You will notice that there are 3 different carbonyl-containing compounds available from the "stockroom," so be sure to select the correct reagents to make the target β-ketoester!
4. Clicking and dragging (or in some cases by double-clicking) adds materials into the round-bottom flask, via syringe through the rubber septum that is fitted on the flask opening.
5. **Add ester substrate.** Click on the methyl propionate bottle and drag the syringe into the flask. The simulation doesn't allow us to weigh the reagents. Assume that 3.00 mL of methyl proprionate was added – you will need this number for calculations!
6. **Add solvent.** You have three options for solvents: water, ethanol, and diethyl ether. Choose one and click and add it to the flask. Assume that a volume of ~20 mL was added.
7. Confirm that the methyl propionate and the solvent have been properly added to the flask by hovering your mouse over the flask. The contents of the flask will display on the chalkboard.
8. **Secure reaction flask to ring stand.** Drag the flask over to the clamp above the stirring hot plate.
9. **Add base.** We have three bases available to us on the reagent bench: KOH, LDA, and NaOMe. For now, we will use NaOMe. Double click and drag it to the flask. Check the chalkboard and verify that your flask contains the methyl propionate, sodium methoxide, and solvent.
10. This Claisen condensation is fast, so we won't need to heat it.
11. **Start the reaction** by clicking the right knob on the stirring hotplate.
12. Advance the clock, 1 hour at a time, until the methyl propionate has been consumed (*i.e.*, it is no longer displayed on the chalkboard). Record the time and the contents of the flask, as given on the chalkboard (if you select the product name, it will show you the structure), in your notebook.
13. **Reaction workup.** Stop the reaction by double-clicking on the separatory funnel to move it to the flask (or click and drag it there).
14. The Claisen reaction always requires an acidic work-up to get neutral product. Double-click on the aqueous hydrochloric acid solution in the plastic, white-topped bottle to add it to the separatory funnel (or click and drag it there).
15. You will now see two layers of liquid in the funnel, the less dense ether layer ("organic layer") will float on top of the aqueous layer. If you hover your mouse over the layers, it will display if the layer is organic or aqueous and the chalkboard will display the chemicals contained within the layer. Depending on the reaction solvent used, the organic product

may appear in either the aqueous or the organic layer. Record which layer the organic solvent is in.

16. Remove the lower aqueous layer and discard it into the waste container by clicking and dragging it from the separatory funnel (this will move it into a round bottom flask), and into the red waste container. Use the information on the chalkboard to make sure it is the correct layer before throwing it away!
17. Click and drag the ether layer to the cork ring support. This step assumes that you evaporated the solvent using a rotatory evaporator, leaving you with just the product in the flask.
18. Record the structure of the final product (click on the product name on the chalkboard to show the structure).
19. Reset the synthesis lab by clicking on the waste container to "Clear Lab" and discard all materials. Then repeat steps 5-19 until you have tried each of the three solvents, and determined which gives the cleanest yield of the β-ketoester product.

Part 2. Determining the best base

Now that we have determined which solvent is best for the Claisen condensation, let's determine the impact of using a different base.

20. **Add ester substrate.** Click on the methyl propionate bottle and drag the syringe into the flask. The simulation doesn't allow us to weigh the reagents. Assume that 3.00 mL of methyl propionate was added – you will need this number for calculations!
21. **Add solvent.** Click the solvent that you determined to be the best in Part 1 above and add it to the flask. Assume that a volume of ~20 mL was added.
22. Confirm that the methyl propionate and the solvent have been properly added to the flask by hovering your mouse over the flask. The contents of the flask will display on the chalkboard.
23. **Secure reaction flask to ring stand.** Drag the flask over to the clamp above the stirring hot plate.
24. **Add base.** We have already seen what happens with sodium methoxide as our base. Now let's try lithium diisopropylamide. Click and drag it to the flask. Check the chalkboard and verify that your flask contains the methyl propionate, lithium diisopropylamide, and solvent.
25. This Claisen condensation is fast, so we won't need to heat it.
26. **Start the reaction** by clicking the right knob on the stirring hotplate.
27. Advance the clock, 1 hour at a time, until the methyl propionate has been consumed (*i.e.*, it is no longer displayed on the chalkboard). Record the time and the contents of the flask, as given on the chalkboard (if you select the product name, it will show you the structure), in your notebook.
28. **Reaction workup.** Stop the reaction by double-clicking on the separatory funnel to move it to the flask (or click and drag it there).
29. The Claisen reaction always requires an acidic work-up to get neutral product. Double-click on the aqueous hydrochloric acid solution in the plastic, white-topped bottle to add it to the separatory funnel (or click and drag it there).

30. You will now see two layers of liquid in the funnel, the less dense ether layer ("organic layer") will float on top of the aqueous layer. If you hover your mouse over the layers, it will display if the layer is organic or aqueous and the chalkboard will display the chemicals contained within the layer.
31. The organic product here appears in the lower aqueous layer. Record the structure of this product. Is it a β-ketoester?
32. **Test the other base.** Reset the synthesis lab by clicking on the waste container to "Clear Lab" and discard all materials. Then repeat steps 20-31 **except** add **potassium hydroxide in step 24**.
33. **Characterize the β-ketoester product by ^{1}H and ^{13}C NMR.** Make a note of the best reactions conditions including solvent and base that you have determined to cleanly conduct the Claisen condensation of methyl propionate with itself. Repeat these steps, and obtain ^{1}H and ^{13}C NMR spectra of this product by clicking and dragging an NMR tube to the flask. Record these in your notebook. Change the spectrometer to ^{13}C by clicking on the NMR spectrometer window.
34. Reset the synthesis lab by clicking on the waste container to "Clear Lab" and discard all materials.

Part 3. Application of optimized conditions to the Dieckmann cyclization

Now we are going to apply our optimized conditions to observe what happens when we perform a Dieckmann cyclization (i.e. an intramolecular Claisen condensation) on a 1,7-diester.

35. **Add diester substrate.** Click on the 1,7-dimethyl-heptanedioate bottle and drag the syringe into the flask. The simulation doesn't allow us to weigh the reagents. Assume that 3.00 mL of diester was added – you will need this number for calculations!
36. **Add solvent.** Click the solvent that you determined to be the best in Part 1 above and add it to the flask. Assume that a volume of ~20 mL was added.
37. Confirm that the methyl propionate and the solvent have been properly added to the flask by hovering your mouse over the flask. The contents of the flask will display on the chalkboard.
38. **Secure reaction flask to ring stand.** Drag the flask over to the clamp above the stirring hot plate.
39. **Add base.** Click the base that you determined to be the best between Parts 1 and 2 above, and add it to the flask. Assume that a volume of ~20 mL was added.
40. This Claisen condensation is fast, so we won't need to heat it.
41. **Start the reaction** by clicking the right knob on the stirring hotplate.
42. Advance the clock, 1 hour at a time, until the methyl propionate has been consumed (*i.e.*, it is no longer displayed on the chalkboard). Record the time and the contents of the flask, as given on the chalkboard (if you select the product name, it will show you the structure), in your notebook.
43. **Reaction workup.** Stop the reaction by double-clicking on the separatory funnel to move it to the flask (or click and drag it there).

44. The Claisen reaction always requires an acidic work-up to get neutral product. Double-click on the aqueous hydrochloric acid solution in the plastic, white-topped bottle to add it to the separatory funnel (or click and drag it there).
45. You will now see two layers of liquid in the funnel, the less dense ether layer ("organic layer") will float on top of the aqueous layer. If you hover your mouse over the layers, it will display if the layer is organic or aqueous and the chalkboard will display the chemicals contained within the layer.
46. Remove the lower aqueous layer and discard it into the waste container by clicking and dragging it from the separatory funnel (this will move it into a round bottom flask), and into the red waste container. Use the information on the chalkboard to make sure it is the correct layer before throwing it away!
47. Click and drag the ether layer to the cork ring support. This step assumes that you evaporated the solvent using a rotatory evaporator, leaving you with just the product in the flask.
48. Record the structure of the final product (click on the product name on the chalkboard to show the structure).
49. **Characterize the β-ketoester product by ^{1}H and ^{13}C NMR.** Obtain ^{1}H and ^{13}C NMR spectra of this product by clicking and dragging an NMR tube to the flask. Record these in your notebook. Change the spectrometer to ^{13}C by clicking on the NMR spectrometer window.
50. Your virtual experiment is now complete!

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Post-Lab Assignment

1. In ChemDraw, generate a scheme that shows the attempted Claisen condensation reaction of methyl propionate with sodium methoxide base in each of the three solvents and compares the outcome of those trials. In 2-3 sentences, discuss which solvent was best and how you came to that conclusion, being sure to name what side reactions happened in which solvents,.

2. In ChemDraw, generate a scheme that shows the Claisen condensation reaction of methyl propionate in the optimal solvent that you identified with each of the three bases and compares the outcome. In 2-3 sentences, discuss which base was best and how you came to that conclusion, being sure to name what side reactions happened with which bases.

3. Analyze the ^{1}H and ^{13}C NMR spectra of the β-ketoester formed under the optimized conditions. In your analysis, include the spectra that you recorded, and an annotated structure of the β-ketoester product to show which signal corresponds with which nucleus.

4. In ChemDraw, draw the mechanism of the Dieckmann cyclization that you performed under the optimized conditions, including the acid work-up.

5. Analyze the ^{1}H and ^{13}C NMR spectra of the Dieckmann cylization product formed under the optimized conditions. In your analysis, include the spectra that you recorded, and an annotated structure of the Dieckmann cyclization product to show which signal corresponds with which nucleus.

6. Discuss how the optimized conditions for the Claisen condensation and the Dieckmann cyclization compare to the reaction conditions that you used for the aldol reaction you performed in-person. What is similar, and what is different?