Lecture 8B • 04/27/12

Claisen condensation

It is very much like the aldol condensation in certain ways. It does involve esters instead of aldehydes or ketones. First, if we want to make an enolate, let's talk about an appropriate base to use to deprotonate that alpha position. Would sodium hydroxide be an appropriate reagent to make the enolate? Why not? The conjugate of hydroxide has a pKa of 16; what's the pKa of this compound? 24. When you have that oxygen on the methoxy group that's donating electron density into the carbonyl, that makes the carbonyl less tolerant of any negative charge that might be next to it. Less tolerant means it harder for it to form, which means it's less acidic, the hydrogen that would be at that position. This has a pKa of 24. pKa of 24 versus water's 16 means that this would not be a very favorable process. Aside from the pKa problem, what would happen if you had extended exposure of an ester to sodium hydroxide? If it's not really acidic enough for hydroxide to deprotonate it, what else is hydroxide going to do to it? Saponification. That's why it can't be used, not just because there's a problem of acidic; you're not even going to get the enolate, because you're going to make the carboxylic acid salt. Sodium hydroxide cannot be used to form enolates from esters because, first of all, hydroxide is not a strong enough base. Water has a pKa of about 16, whereas an ester, on average, has a pKa of 24, so it won't deprotonate – well, technically, it could, cause if ECHIWH, but since it's so unlikely to happen, what's more likely to happen is attack of the carbonyl; that's the second reason, that because it's not a strong enough base and since saponification will occur.

But [there is] a base that is able to irreversibly deprotonate a lot of things, because it's a very strong base and it's sterically hindered, so less likely to attack carbonyls – LDA. LDA is a deprotonated amine with a [conjugated] pKa of 34, [which] means it doesn't want to be deprotonated, which, since we force it to, means it's a really strong base – easily can deprotonate this compound, unlikely to attack the carbonyl. Because of the huge difference in acidity of the conjugates, this is a forward reaction. If this was the only compound in solution, the ester, and if not all of it reacts instantaneously with LDA, what do you think might happen? This is a condensation. Let me write another molecule of the ester up because I'm implying something's going to happen between the two of them. When we had an aldol condensation, the pure aldol condensation, two of the same molecule [reacted]; we first made the enolate out of one and had it react with the other; that's exactly what's going to happen here. The carbonyl reforms out of the one that was the enolate; through the alpha position we then have attack on the other carbonyl, which causes it to open up. We're about to make an alkoxide, and that alkoxide has probably got a conjugate that's got a pKa of [16-18?]. We came from an enolate, the pKa of the conjugate of which was 24. It looks like we're going to be making a lot weaker base from a stronger. If so, that means that this step is irreversible. [???] Once it reacts, that carbonyl reforms, so I'm going to end up with an ester. The other ester got attacked, so we have an alkoxide, and then we have methoxide also attached, plus there's the alkyl group of the ester that was attacked.

Now we're in the same situation we've seen before, where we have an alkoxide, but we also have methoxide that could be kicked off, in saponification. We can reform that carbonyl and kick off methoxide. That means we end up with a product that has two carbonyls. When we saw the aldol condensation, we ended up with a compound that only had one carbonyl. We're going to see why in just a moment. This case, because we attacked an ester, we're able to retain that carbonyl at the end. This is the way to recognize that you have a Claisen condensation instead of an aldol condensation, because the product of a Claisen condensation is a beta-ketoester; at the beta position relative to the ester, we have a ketone, with a new carbon-carbon bond at the alpha and beta positions. [To review], we make the enolate, [for which] hydroxide would be a poor choice. Even methoxide, which would avoid saponification, which would also avoid transesterification, not a very strong base, so maybe it works, but it might take quite a bit of time to get it to work. If we use LDA, we cleanly make the enolate, which could react, start the process of condensation, we end up with this beta-ketoester.

Let's go back an look at the aldol condensation, so we can see how this is really similar but see the key difference in the form of product that you end up with. Let's take an aldehyde which we can reversibly deprotonate with hydroxide. The problem with hydroxide in the Claisen condensation is that it caused saponification; there is no such thing with an aldehyde; the worst thing that would happen if the aldehyde gets attacked by the hydroxide as you start to make a hydrate. Hydrates are not normally isolatable, so it does back to the aldehyde anyways, and at some point you could then progress on to the enolate. Exactly like the Claisen condensation above, another molecule of that same starting material is now going to get attacked. This portion of the mechanism is therefore identical – we reform the carbonyl through the alpha position, we have attack of the other carbonyl, which opens up as a response. The big difference is, because the pKa of the conjugates of the enolate and the alkoxide are similar, this one, unlike the top reaction, is more reversible. Because the condensation of aldols are technically reversible, that means under the right conditions, you could take the product of an aldol condensation and cause it to break back apart into its original molecules. To force the reaction, there's this device called a Soxhlet extract. What it does is it has the base separated from the product. It's this cool system where the reaction chamber fills up and at some point reaches the top and empties again; it goes through this cycle. Every time it goes through the cycle, the product ends up getting removed, it's separated from the base, so it doesn't have a chance to reverse, so it's kind of a Le Châtelier's trick that's done. That will help force you to get to the product.

Back to the main point: we'll have the enolate attack the carbonyl. We have an intermediate where we have an alkoxide, but unlike the ester, that's all that's at that carbon, so there's no way that a carbonyl can reform at this point. Of course, if we were talking about an Sn1, Sn2 reaction, we would never call methoxide a leaving group. But, it's because there's this similarity in basicity that it's able to be a leaving group. But now look at what we're doing with the aldol condensation: all we have at the same position as the negatively-charged oxygen is hydrogen and carbon, neither one of which are leaving groups. It's exactly because of that that we don't end up with two carbonyls. What happens instead: we can reprotonate this alkoxide; since we have not yet (and won't) switch to acidic conditions, we can't just say H+, so we have to deprotonate water or an alcohol, whatever solvent or conjugate of the base that you used that might be formed. If we use water, this step is technically reversible. This is one of the possible products that can be formed in an aldol condensation. But, under the right conditions, it doesn't stop here, cause we still have an alpha proton, which means we could deprotonate again. Alpha proton gets deprotonated, makes the enolate. Let's do the same thing right here. Then, here's the part that's unusual: this carbonyl can reform by doing intramolecular elimination in what is known as the E1CB mechanism. There's only one carbonyl that gets formed in this case. The product of an aldol condensation is either a beta-hydroxy aldehyde or ketone, or an alpha,beta-unsaturated aldehyde or ketone.

You're going to see an awful lot that's similar in these mechanisms, but because you have in one case an aldehyde or ketone that doesn't have a "leaving group", versus the ester that does, that's why there's a difference in the product that forms.

Alpha alkylation

If we had an ester, we could react it with LDA to make an enolate. If we're going to do alkylation, why does it go on the carbon instead of the oxygen? It [has] something to do with hard-soft interactions. Things of like charge density prefer to react. An alkyl halide is a squishy substrate, [so] carbon better interacts with it. [Also, it is likely that] a carbonyl bond is thermodynamically more favorable than whatever product results from a carbon-carbon double bond. This is technically a bidentate ion; it reacts at two different ends. If we throw an alkyl halide at this – that needs to be a primary alkyl halide – we can put an R group on the alpha position of an ester.

I want to bring up a consideration of how we would do this reaction. What is the difference between this first step of this reaction and the first step of the Claisen condensation? There is none, so how do we stop the Claisen condensation happening in this case? It has to do with the order of addition. If you add LDA to the ester a little bit at a time, a little bit of enolate forms at any one time, but you still have a whole container-full of ester that's also around, so the enolate reacts with the ester and does the condensation. But if you add the ester to a container of LDA, that ester that gets added in rapidly gets converted into an enolate, and then that's all that's in solution. The acid-base reaction is most likely to be a lot quicker than condensation, so if you add the ester in just a little at a time, you avoid doing the condensation reaction because it just gets turned into enolate, and an enolate will not react with another enolate, normally, especially if you keep it at very low temperatures. A lot of these enolate reactions are done at that -78° C temperature to avoid self-condensation. To avoid the Claisen condensation, we are careful about how the reaction's conducted. The Claisen condensation can be avoided by added the ester to a solution of LDA. This way, no significant quantity of the ester builds up for the enolate to react with.

[What would happen if we mix the two] Think about this: if we do what I just said about forming an enolate from an ester, we're careful about order of addition, which way we add the reagents to each other, we could, in theory, take an ester, produce the enolate, do it in such a way that it doesn't react with itself, and then instead of letting it react with an ester, why not let it react with an aldehyde instead. What will happen? You'll get a combination of the two reactions: you'll end up with an ester – since you started with an ester as the enolate, you'll end up with the ester as [a product]; in that way, it's different from an aldol condensation. But because it's an aldehyde being attacked, you'll only end up with one carbon. In fact, you're going to end up with this alpha,beta unsaturated compound; in that way, it's like an aldol condensation. The product will look like this. Your job, if given a random product, [is] to then pull it back apart to figure out what could have produced it.

[This next reaction is] a Claisen reaction, but a subset called the Dieckmann condensation. It's like a Claisen, but it's going to involve a diester. If I waned to make sure I cleanly made the enolate, I'd use LDA, which, because this is a symmetric compound, it doesn't matter which end of the ester I deal with. I'll start with the one on the right, remove the alpha proton, form the enolate, form it irreversibly. If we have nothing else in solution, in theory, one molecule of this could react with another molecule of the same kind. But, if we had a reaction from that alpha position and it came back to attack the carbonyl, that would make a five-membered ring. Both five-membered rings and six-membered rings are favorable – it's not just that it's thermodynamically favorable, or better put it's not thermodynamically unfavorable, it also has to do with kinetics. Imagine that you want to make a twenty-membered ring: there's probably not going to be any form of ring strain in that 20-membered ring. But if you have twenty atoms separating the two ends from each other, then with that molecule constantly flopping around in solution, how are the two ends ever going to meet in order to make a ring? Making what are called macrocycles – large rings – is often a very, very tricky thing to do. But, five- and six-membered rings aren't tricky; that's exactly what's going to form in this case. To make sure that you can clearly see the product that would form, I'm going to number my carbons. The reason I'm doing this is because when this reaction occurs, when the carbonyl reforms, that carbon's not in the ring.

Although this is an intramolecular attack – intramolecular reactions are often faster than intermolecular reactions because you've only got on molecule involved – otherwise this is the same mechanism as a regular old Claisen condensation. There's the carbonyl that gets reformed that will not be part of the ring. We are going to make a five-membered ring; let me label those carbons. It was position 6 that got attacked, so that's where we'll have the alkoxide, as well as the methoxide. Just like in the Claisen condensation, the carbonyl can reform, and we therefore end up with the same type of product [as] a Claisen, it's still a beta-ketoester, it just happens to be cyclic.

Malonic ester synthesis

The malonic ester synthesis most commonly involves the molecule diethyl malonate, which has this structure. Malonic ester is the common name for propanedionic ester, di- for dicarboxylic acid. Diethyl means put an ethyl group on each ester. What is the pKa of that alpha-proton? 13, which means it's more acidic than water, which means we could use hydroxide in this case to deprotonate it, because even though if you prolongly expose this to a concentrated excess solution of sodium hydroxide, if you just carefully added it in, titrated you could say, it is more acidic that water, so that proton does come off easily, and since acid-base reactions are often faster than any other sorts of reactions, you could be fairly confident you won't cause any form of saponification. In fact, if you take an ester and just shake it around with a little hydroxide, normally, at room temperature, that's not enough to cause it to start saponifying. We'll take hydroxide, deprotonate. Even thought the pKa difference is not huge, it is true that hydroxide's a stronger base, so I'll go ahead and write this as a forward arrow. Sodium hydroxide is an appropriate base in this case. Since the diester is more acidic than water, neutralization is more likely than saponification.

Continuing on with mechanism, this is a way to do an alkylation. I'll show the carbonyl getting reformed, the Sn2 reaction that would happen, and now we have an R group at the alpha position. What would happen if you did subject this to a concentrated solution of hydroxide but didn't put any other reagents in? We get saponification. At first all you'll get is the disalt. What would now happen if you react this with [an] acidic solution with some gentle heating? It doesn't even require a strongly-acidic solution. Before I tell you the answer, let me make a small aside.

How many NMR signals would this compound generate? Two? Makes sense: you've got the alpha-proton in the middle, the molecule's symmetric so you have the two other alpha protons, but this actually has five absorbances. Why? Cause this is not the only thing that exists in solution. IECHIWH. One of the carbonyls tautomerizes, then you get intramolecular hydrogen bonding. That intramolecular hydrogen bonding is enough that it stabilizes this enol enough that a non-zero percentage of it wil form in solution – enough non-zero that you'll see it in NMR. If we had that enol, we now have two hydrogens on the alkene and the enol's hydrogen – those are three peaks that, otherwise, you wouldn't expect to see. Because of this tautomerization, because of this unusually favorable tautomerization, you do see that.

Why did I make this aside? Let's come back to the question of what happened if we acidified the product of this malonic ester sythesis. We end up with a dicarboxylic acid, in which you have the same potential of intramolecular hydrogen bonding. What if you didn't just have hydrogen bonding: what if the oxygen on the left-hand carbonyl reacted or interacted strongly enough with that hydrogen that it deprotonates the other carbonyl somehow. That bond would be in resonance or could kick open the other carbon, which that could then close again, which could kick out this carbon. The bond would then come back over to kick open the carbonyl that would be positively-charged because its oxygen had reached out to grab the hydrogen. This is a pericyclic reaction. This will easily occur; this happens any time you have a beta-[keto]acid – two [carbonyls, one of which is part of a carboxylic acid] that are beta to each other, with a little bit of heat, will decarboxylate. This is decarboxylic.

Let's look at what the products would be. Look at the right-hand side of this mess that I just made. You have a bond that coming around here to make a new carbonyl and kick off this bond. Two carbonyls from the same carbon – that's carbon dioxide. That's what results in decarboxylation. SInce that's a gas that bubbles out of solution, this is completely irreversible. What do you get on the other side? We opened up this carbonyl and protonated it, which means we end up with an -OH group, and, because this bond has swing around, we end up with a double bond, so we end up with an enediol, plus carbon dioxide that leaves as a gas. An enediol is just like an enol, in that it's not isolatable, it's not thermodynamically favorable. We're already in acidic conditions, so that double bond can easily become protonated, which means we generate a carbocation, where either one of the oxygens could then undergo resonance, reforming the carbonyl, which initially is protonated. Our product is a carboxylic acid, but it's a custom carboxylic acid.

The malonic ester synthesis is used to prepare custom carboxylic acids under relatively mild conditions – I say relatively because you do have to deesterify, either through saponification or hydrolysis. That process means you're going to be heating in some amount of base or acid for some period of time, which will cause some functional groups to decompose; but, if you have something that was sensitive to strong bases, it wouldn't be appropriate to have LDA around. You could avoid having to use LDA by using this approach. It's a classic bit of organic synthesis.

Acetoacetate synthesis

It's identical, except for the starting material. In this case, we could use acetoacetic ester. What would the pKa of this compound be, approximately? 11. Because it's 11, it's even more acidic than the diethyl malonate, which means sodium hydroxide even more easily deprotonates it, so we worry even less about saponification. We'll end up with the enolate. Of he two carbonyls, which one would be more involved in resonance: the left or the right one? Which one, if exposed to sodium borohydride, will actually get reduced? The answer is the same in both cases: the ketone is more reactive than the ester, because the ester has the lone pair on the oxygen that can delocalize and therefore reduce the reactivity of that carbonyl. It also reduces the ability to tolerate the negative charge, so it's less likely to be in resonance. However, it is in resonance; that's why this has such a lower pKa value. React this with a primary alkyl halide or sulfonate (tosylate, for example)[brosylate – para-bromosulfonate] We could now alkylate it. Instead of saponifying, we could just hydrolyze to begin with. After we hydrolyze, we make an intermediate – a non-isolatable intermediate – that will not be a diacid this time because we only had a monoester, but we get the same type of intramolecular interaction, we means we're going to lose carbon dioxide. It decarboxylates. This time, because the portion that remains came from a ketone, we have a mono-enol this time, which means it's going to tautomerize, and we end up with a customized acetone. Mechanism, everything's identical to the malonic ester synthesis, it's just that we end up with a ketone instead of an acid.

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NaOH cannot be used to form enolates from esters because -OH is not a strong enough base (H_2O => pKa = 16; ester => pKa = 24), and since saponification will occur.

Product of a Claisen condensation is a beta-ketoester, with a new C-C bond @ alpha,beta positions.
Product of an aldol condensation is either a beta-hydroxyaldehyde or ketone, or an alpha,beta-unsaturated aldehyde or ketone.

Alkylation

Claisen condensation can be avoided by adding the ester to a solution of LDA. That way, no significant quantity of the ester builds up for the enolate to react with.

Mixed condensation

Dieckmann condensation

Malonic ester synthesis – Diethyl malonate

NaOH is an appropriate base in this case since the diester is more acidic than water, so neutralization is more likely that saponification.
Malonic ester synthesis is used to prepare custom carboxylic acids under relatively mild conditions.

Acetoacetate synthesis

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Structures *(remaining structures identical to lecture 8A)*

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