

## Lecture 9A • 04/30/12

Please tell me the names of these five reactions. What's the first one? [need to know name reactions] The Stork enamine synthesis. What is the second one going to be? Claisen. How do we know it's a Claisen condensation? Cause you have an ester as a starting material. What is the next reaction? It's also a Claisen, but it is a Dieckmann, more specifically, because it is the intramolecular Claisen. [ie or ei] What's this fourth one? That's the tough one. What is the last one? Michael, because we have a conjugate substrate that has no alpha protons, so you know for sure it's going to be the one that's attacked. By having a nitrile here, this makes it a little bit more acidic than normal, which makes the base soft, which makes it exactly the type of base that wants to attack a conjugated system. What is the last reaction? Aldol. Don't get thrown off by the fact that there's an alkene. It is not conjugate, so it's just a regular, old aldol condensation.

Let's look at the answers for these, in reverse order. Let's do the last one first then. First step, deprotonation. To save time and highlight the fact that it's an enolate, I'm mixing in resonance with it. It is technically reversible because I'm using what would be called a weak base – it's not weak in general chemistry terms, but, compared to things like LDA, it's a weak base. Because of that, and because it's similar in base strength to the enolate that's made, that's why I'm calling it a weak base. Now, we have another molecule of the same thing, which is going to get attacked. Is it possible that we could get attack through the end here? Maybe [look it up]. But, it will not attack the alkene over here, because it's not conjugated. When it attacks that, you'll push it open. Remember the compound that was a carbonyl reforms the carbonyl, the one that makes the enolate that is. Here's the new bond at the alpha position to the now beta position. It is at that beta position that we initially have the negative charge. At a minimum, there is a next step where water is deprotonated by this. Since I didn't include water, I'll instead make it methanol, because I used methoxide. We protonate that. We still have methoxide around, so it is possible for another alpha proton to be removed. Remember that that happens as its own individual step; this is not E2 elimination. There's the product.

Next reaction. The pKa of this is [low] enough that methoxide does work. The point of that is that the base is weak enough that it would prefer to add in conjugate addition. We're going to have deprotonation because we have methoxide [reversible?] We made an enolate, and we have one of these conjugated carbonyls. There's no alpha proton, so we're not going to have it forming an enolate, so there is only going to be one type of product. The whole point is that we're going to have conjugate addition, so here it will attack the carbon of the double bond, the end of the molecule. We attack the carbon, which no longer has a double bond; it's instead been moved to the position over, which is currently an alkoxide. I could show it getting protonated, but won't that immediately tautomerize? So why go through all that effort; why not just show the enolate, which this is, grabbing a proton? Notice what we've made: a product with a carbonyl delta to the original carbonyl. [why alkylation occurs through carbon; option to include delocalization of enolate in mechanisms or ignore it] The aldehyde does not have an easily-removable alpha proton. It has, of course, a proton at the alpha position, but you already have the double bond in conjugation with the carbonyl, so the other hydrogens there will not have that conjugation, so it does not have the same pKa as a regular alpha proton. This is an enolate, but our way we draw structures is inadequate, so it's one or the other we can draw; which one you do doesn't matter. Conjugated means each carbon in a row has got a p orbital or a pi bond involved with it somehow, so that all those p orbitals overlap; that is conjugation. This bottom problem, see there's a carbon that, on either side of it, has a double bond, but this carbon itself does not have sp<sup>2</sup>-hybridization, doesn't have a p-orbital, doesn't have a pi bond, so it blocks any interaction you've got between the two double bonds, whereas on this compound over here, the two double bonds – the carbon-oxygen and the carbon-carbon – are not separated by anything at all. There's one more possibility, where one carbon connects two double bonds. That's again a case where you don't have conjugation, because if one carbon has two double bonds to it, the two double bonds are at 90° to each other, so there's no overlap, so there's no conjugation. It's only in cases like this, where you go from one carbon to the next to the next to the next, and each [pair of] position[s] is in its own double bond – that creates conjugation. That carbon where I've got my pen right now is sp<sup>3</sup>-hybridized, so it blocks this double bond from interacting with that one, so it can't add to the double bond, cause it is not conjugated.

Question 3 - Dieckmann condensation. We started with 7 carbons [in the main chain]. One of the two carbonyls will not be in the ring, because it's not both carbonyls that react, it's the one carbonyl and the alpha position of the other, so that means there's only going to be six carbons in the ring, which means this is going to be the product. Did I use an appropriate base? Is there any problem with me using this base? Transesterification will give me the same ester back, won't it? This may not be the best base to use as far as how fast the reaction occurs, cause you have to wait for the proton to be pulled off, because the pKa of the ester is 24. What would be the approximate pKa of ethanol? 16. 24 versus 16, the ethoxide is way weak compared to this, but because the only side reaction that's possible is transesterification, and since that would just give us your original compound back again, then, over time, you could form your product.

Stork enamine synthesis. [skipping part of mechanism] What happens if/when we have it attack something, like an aldehyde? The lone pair on the nitrogen is what's providing the electron density in the first place. Part of the advantage of this reaction is that it allows you do to these kinds of additions under relatively mild conditions. We've done the addition step of it. There's two things that'll happen next: if we have some kind of solvent, some kind of source of hydrogen, that gets rid of the negative charge, but we still do have a positive charge on nitrogen here. How to relieve that? The same way that the enamine got formed in the first place – a position alpha to the carbon-nitrogen bond gets deprotonated and reforms the enamine.

Realize that intermediate with the positive on the nitrogen – that's exactly what you get when you form the enamine the first time. Notice that is not an enol, because the double bond is not at the same position as the alcohol itself. What happens next is – acid, water, and heat. What happens? Acid and water, that's going to hydrolyze the enamine, which is a sequence of protonate-open-attack-deprotonate, protonate-open-attack-deprotonate. Eventually what you're going to get is this – which is the same thing we would have gotten if we did just a plain, old aldol condensation.

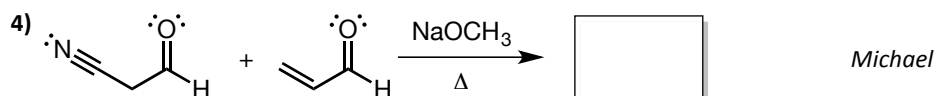
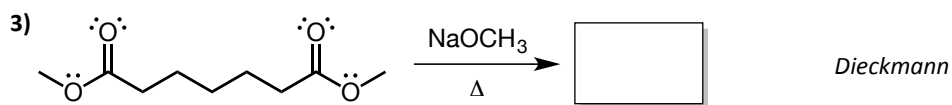
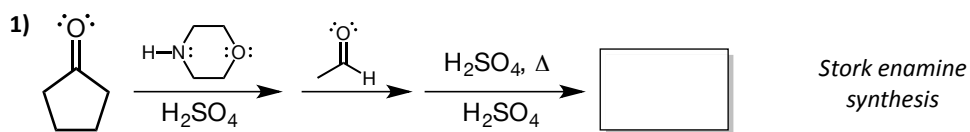
---

Since this pKa is not so high, the conjugate base is not so strong, so enolate can add by conjugation

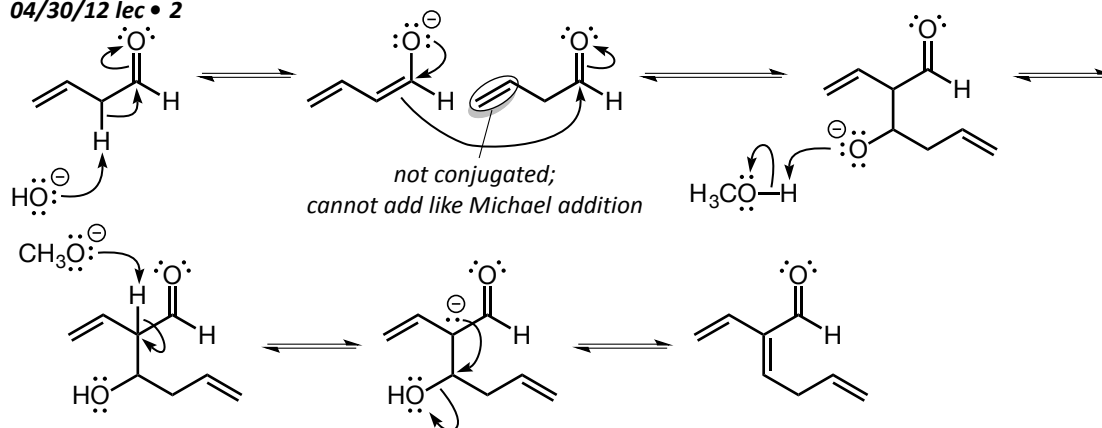
---

Structures

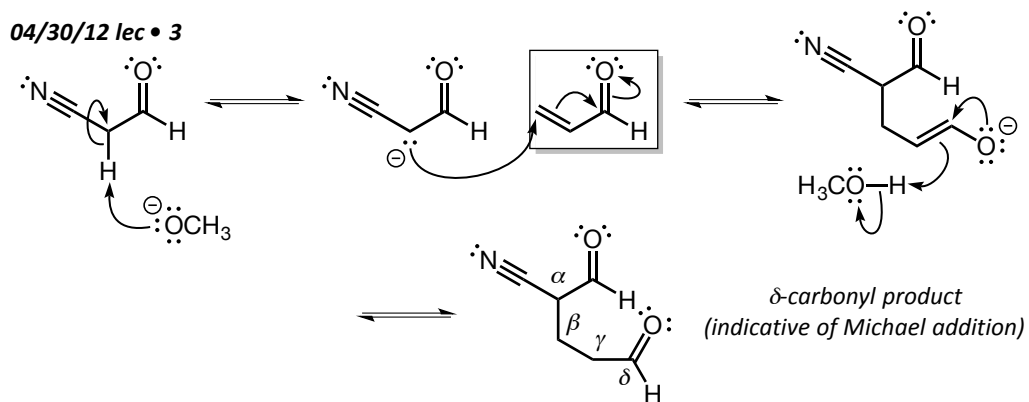
04/30/12 lec • 1



04/30/12 lec • 2



04/30/12 lec • 3



04/30/12 lec • 4

