

## Lecture 9B • 05/01/12

First problem – Cyclopentanone reacting first with a compound which is called morpholine [pyrrolidine] and sulfuric acid. That's followed up by ethanal, which is followed up by sulfuric acid, heat, and water.

What reaction is this? The Stork enamine synthesis. [name reaction commentary] Condensation means take two molecules and combine them together. First step, you've seen the mechanism before. Since this is a secondary amine, when it combines with the cyclopentanone, we'll get a carbon-carbon double bond; in other words, you'll end up with an enamine. This, then, can react in an alpha-style reaction; in this case, the next portion of this is going to be like an aldol reaction. Remember that the lone pair on nitrogen is providing the electron density to that carbon-carbon double bond for it to be able to open up and attack something. That's going to put a positive charge on the nitrogen, which we'll take care of in a moment, cause we also end up with a negative charge on the oxygen. Some kind of solvent, we would imagine, is there; I'll keep it generalized, because all we care is that at this point [is that] the enolate [is allowed] to become protonated. We still have this positively-charged nitrogen, though. If you take a look at that, that's the same type of intermediate you get when you're trying to form the enamine, so the same thing can happen to relieve that positive charge, where alpha to the carbon-nitrogen double bond, we have some random kind of base pulling off that hydrogen, which will help us recover the neutral enamine.

We then have acidic aqueous conditions, which that's going to cause the enamine to decompose; this is just a couple of cycles of protonate, open, attack, deprotonate. It's the alkene that gets protonated first; we generate a carbocation next to the nitrogen. We're doing hydrolysis, [so] there's water around; that's what can attack the carbocation. Then, we'll have a deprotonation [to] make neutral oxygen; we're half-way through it, we're at the carbinolamine. One more round of protonate, open, attack, deprotonate. It'll be the nitrogen that gets protonated first, which gets us an ammonium ion, which can then leave, which leaves behind a carbocation right next to an -OH group, which means at this point we can have resonance, and then the carbonyl can become deprotonated

With the set of reagents I gave you, it might be reasonable to stop at this point. However, if you have heat, then after the hydration, if you then switch to where you're again removing water, we're going to be able to dehydrate this compound. Since this is similar to the product of an aldol condensation, where we get this beta-hydroxy group, if you then cook up the group in acid and again allow water to be removed, we're going to dehydrate, just like we've seen before with the aldol reaction. Alcohol gets protonated; water leaves as a leaving group; and then the water that just came off can attack a hydrogen to cause the elimination, to cause the overall dehydration. We make the enamine first; we then do whatever alpha reaction the enamine's going to do; then, [hydrolysis occurs].

Second problem – We have an ester, where the first reagent, the only thing I show is LDA, and then, sulfuric acid.

A comment about esters and LDA. I did make some mention about order of addition – the fact that if we add all the ester slow to a container of LDA, we're going to make the enolate, but nothing else is going to happen because we're trying to prevent any ester build up. If we add LDA to the ester, you get a little bit of enolate, but a lot of ester [is] left over, so you get a condensation reaction. To know which case is going on, you have to be able to recognize what set of reagents we're using. Notice that LDA is the only "useful" reagent that's being used in this case. Otherwise, all you're then using is sulfuric acid, which really is just used to neutralize or to protonate whatever groups might have been formed. The fact that we have no other substrates, no alkyl halides or anything like that, that's going to be the clue that this is what kind of reaction? Claisen [condensation]. Claisen condensation is what we get when we only have LDA, and if we added LDA to the solution. Acid is just to work up the reaction afterwards.

Let's see what the mechanism's going to look like. We only have one place for alpha protons, so that's where the alpha proton's gonna get removed. I'll go ahead and show resonance to highlight the fact that we're making an enolate. Notice that I'm using a forward arrow because LDA is a much stronger base than the enolate we make. There's the enolate. If we're only seeing LDA as a reagent, we're going to presume that LDA is being added to the ester, so that we can then have some form of further reaction. The will reform its carbonyl; the carbon-carbon double bond will reach out to attack another carbonyl. The carbon that got attacked is going to have a negatively-charged oxygen on it. We have the alkyl group that was originally on it; then we have the alkoxide. Kinda a strange-looking molecule. That carbonyl will reform, and it can kick off the alkoxide, which means we get our beta-carbonyl compound. [acid workup not needed]

Number three – Which reaction is this? Sodium methoxide. Transesterification? Yes, the carbonyl can be attacked, but you're not actually going to get any change in the product if the carbonyl gets attacked. Yes, transesterification – in the sense that the ester can be attacked – is going to occur, but we're not going to actually change the product. If I'm implying an alpha reaction occurs here, is this really the best base for us to use? Why not?

First, back to the transesterification issue. If I have a methyl ester and I attack it with methoxide, methoxide plus methyl ester equals methyl ester. Nothing's going to change, so in terms of compatibility, this is perfectly fine.

There is the question of acidity, because the alcohol, if we made the conjugate, has a pKa of about 16; this, even though it's got two carbonyls, the two carbonyls are separated from each other, so each alpha proton has a pKa of 25, so the methoxide is not really a strong enough base to force this to deprotonate. But, if you left this in solution long enough and just heated it up, the worst thing that's going to happen between this ester and methoxide is for methoxide to replace methoxide, which means nothing happens.

But if somehow an alpha proton does get removed, then you can get an intramolecular Claisen condensation (realize we still have just an ester), but remember that the name for this intramolecular version is the Dieckmann condensation. Let's try to jump straight to the product. If I allow the carboxylic acid on the right to form the enolate, then recall that that carbonyl itself is not going to end up in the ring, because the reaction happens through the alpha position; that's why I've circled the carbons here that I did, because we'll have the alpha group on the right that's going to be able to come back and attack the ketone on the left. If you look at that, that involves six carbons, so the product's going to be a six-membered ring. One carbonyl, the one that gets attacked, is in the ring itself; the other carbonyl is off of it.

Next one – Involves a type of compound that we haven't seen yet, but that hopefully you could make some intelligent guesses of how it would react. Which reaction was this? It is a Michael addition.

I'm going to declare this is not an alpha proton. Yes, it is the alpha position of the carbonyl, so of course, in terms of nomenclature, it is an alpha proton. Is there any resonance that can stabilize the carbanion that would be formed if you pulled off that hydrogen? Why not? The double bond that's there is already conjugated with the carbonyl. If you made an anion on the double bond, that lone pair is going to be pointed out in an orbital that is 90° to the pi bond. If that lone pair is 90° to the pi bond, and therefore 90° to the carbonyl's pi bond, no resonance is going to occur, so that is not a favorable proton to be removed. I'll say it this way: it's not a standard alpha proton since, although it is in the correct position, if it is removed, the resulting anion cannot be delocalized, since the carbonyl is already conjugated with the carbon-carbon double bond. Only the first compound's going to be able to be deprotonated. This is similar to a situation as if we had two carbonyls. The carbon-nitrogen triple bond is able to delocalize a negative charge that forms at the alpha position; the carbonyl is also able to delocalize. Nitriles are not quite as good as carbonyls at delocalizing because the nitrogen is not as electronegative as oxygen; but, because we have two things that can then stabilize a negative charge, that makes the negative charge easier to form, which means that the compound is more acidic, which means the base that we're going to form by deprotonating is weaker and squishier, which means it wants to do conjugate addition, which is why this is a Michael addition.

Due to resonance with both the carbon-oxygen double bond and the carbon-nitrogen triple bond, the anion formed by removing this alpha proton is less basic (lower base strength), and therefore more squishy, so it can undergo conjugate addition. This hard/soft ion concept, that the aldehyde here is conjugated so it's squishy, that this is a delocalized, somewhat weak base by comparison, so it's also squishy. How would we write the mechanism? We make the enolate by deprotonating; I used methoxide here. I will combine resonance with deprotonation, so we make the enolate, which is now going to react. The carbonyl reforms; the carbon-carbon double bond attacks – attacks the other double bond, again because it's this conjugate Michael addition. The carbon-carbon double bond will have to move as a response, and you can end up just opening it and putting the lone pair on the alpha position, but that can delocalize. To help show that effect, I'm going to go ahead and incorporate resonance of the carbonyl into it.

The compound that formed the enolate has its carbonyl reformed; we make a new carbon-carbon bond between what are, relative to that first carbonyl, the alpha and beta positions. There is, then, an enolate that we end up with. That enolate is not thermodynamically stable, and if we allowed it to collapse and reform the carbonyl, that alpha position, if it wanted to, if it tried to attack the other carbonyl, that's going to make a four-membered ring, which is not favorable. Instead, if we had methoxide as the base, that means we have some methanol left over, so when the carbonyl reforms, it could just end up getting protonated, which gives us our product. Notice [that] relative to the carbonyl that was the enolate, notice that we've formed a carbonyl at the delta position. A delta-ketoaldehyde or, more generally, a delta-carbonyl-containing carbonyl compound is indicative of a Michael addition. An aldehyde or ketone with a carbonyl at the delta position is indicative of a Michael addition.

The more conjugation we've got, the stronger the acid is because the ion is more tolerated, but that means that the ion is not as basic, which is why its conjugate is more acidic, and so it's more delocalized and it's a squishier ion, therefore. The carbonyl is a tighter type of charge difference, so if you had a strong base where that negative charge is more localized, then we're back to that small-small charge interaction.

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Stork enamine synthesis; Claisen condensation; Dieckmann condensation; Michael addition

Not a standard alpha-proton since, although it is in the correct position, if it is removed, the resulting anion cannot be delocalized, since the C=O is already conjugated with the C=C.

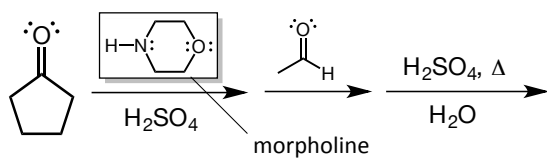
Due to resonance with both the C=O & C≡N, the anion formed by removing this alpha-proton is less basic (lower base strength) and therefore more "squishy", so it can undergo conjugate addition.

An aldehyde or ketone with a C=O @ delta position is indicative of a Michael addition.

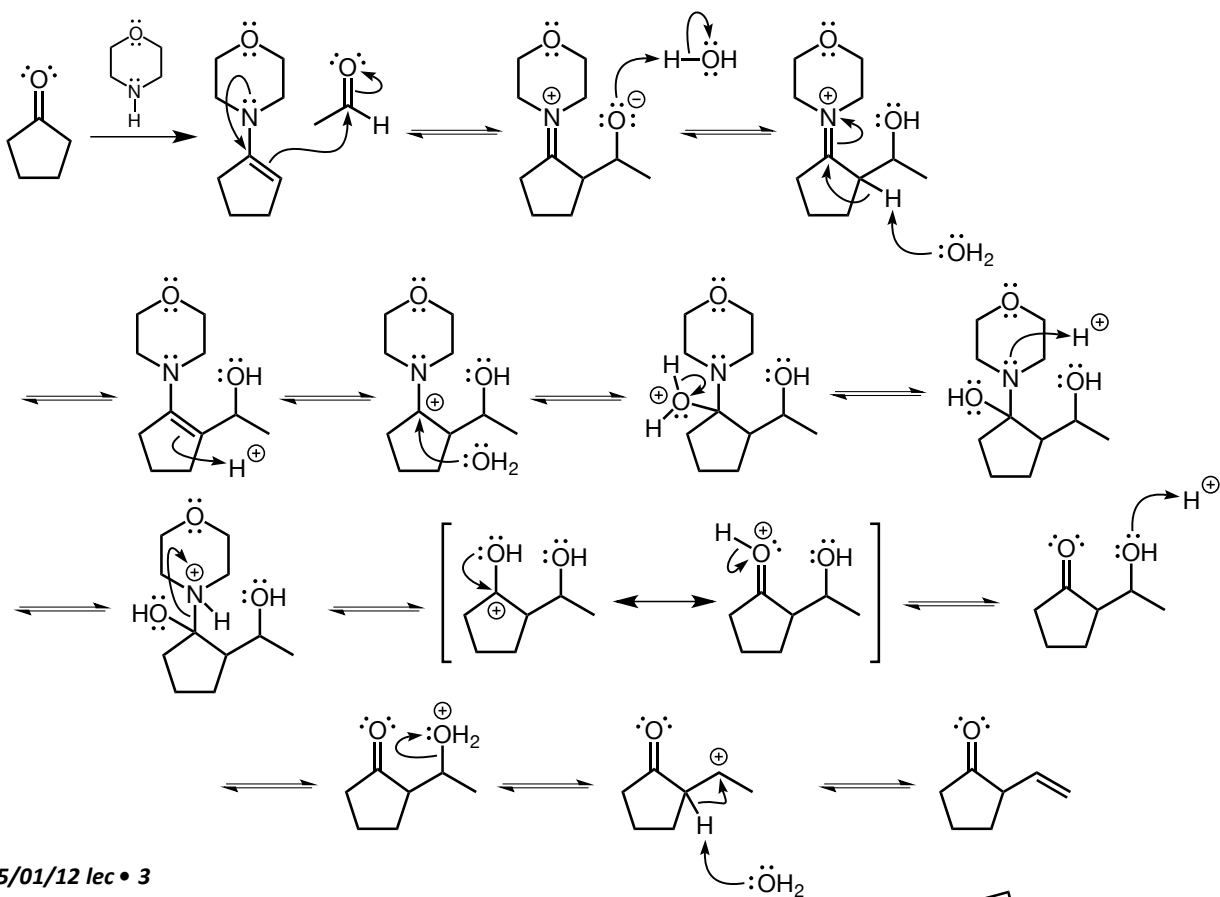
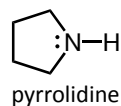
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Structures

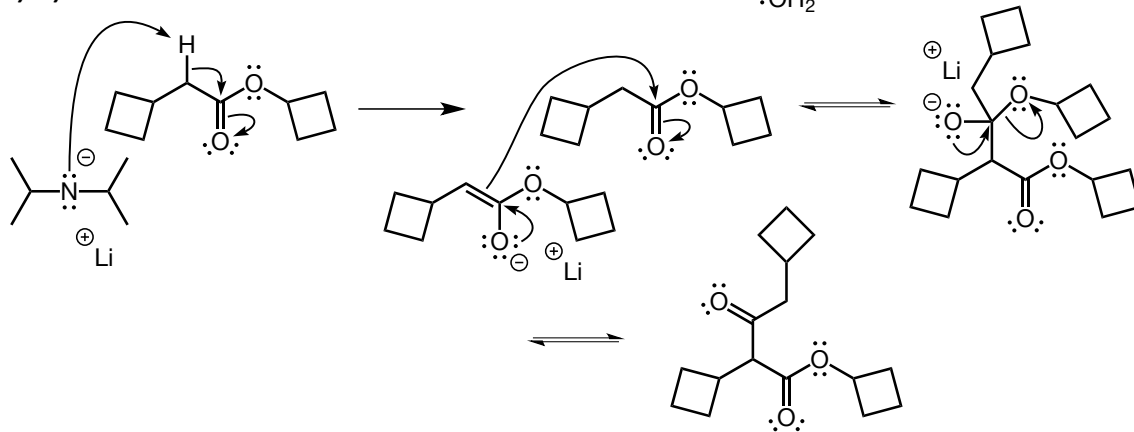
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