Lecture 8A • 04/27/12

Claisen codensation is a form of alpha reaction, which means we are going to form an enolate. What would be an appropriate base to make an enolate out of this compound? What would be the potential side reaction if you used -OH? Saponification. You can't use hydroxide to deprotonate this because what is the approxmate pKa of the alpha proton of this compound? About 24. Why? Because we have the oxygen on that methoxy group that's donating electron density actively through resonance to the carbonyl, which makes the carbonyl unable as well to tolerate a negative charge at the alpha position. What's the approximate pKa of water, if we rounded? 16. 16 versus 24 is eight orders of magnitude, which means if you used hydroxide, you'd get less than a percent of a percent of it that would dissociate, so hydroxide cannot be used to irreversibly make an enolate. But, [there is] a compound that could be used. LDA, lithium diisopropylamide, which its conjugate has got a pKa of 34. It's an amine that does not want to be an acid that we force to deprotonate, which means it's a really, really strong base. We can use LDA in order to make the enolate, which I've written it in its non-tautomerized form, but that's fine, because this is the way that it reacts. A question came up in the other section, which is: why is it that we end up with alkylation at the C position instead of the O position? This is a delocalized ion, and we're used to oxygen being a nucleophile; why is it that oxygen can't react and somehow attach to something else? The answer is: it can, under certain circumstances [why – hard/soft interaction? thermodynamics?].

What's going to happen if there's no other compound in solution? You're going to attack a carbonyl compound, which, if this is the only reagent, then the ester itself is the carbonyl compound that gets attacked. We have another molecule of the ester; that alpha position will attack the carbonyl, reversibly. Why? We're guestimating that the conjugate of an alkoxide will have some pKa of around 16-18ish [look it up!], and we're coming from a compound that had a pKa of 24. There is some difference in pKa, technically that part of it could be reversible, but then there's something else that happens. The carbonyl that survives – in many of these additions, we have one carbonyl that goes away, one that survives. I've taken the molecule on the left here and flipped it around to the position on the right just so I could have my ester group on the right, which is by default the way I tend do to it. If we look at what else it would be attached to then, it's going to have attacked that carbonyl position of the other ester, making the alkoxide. We also have the methoxide which was at that same carbon as well; and then we have the methyl group that was part of that original ester. At this point, we can have the alkoxide try to reform a carbonyl; that's perfectly possible, because the methoxide is not going to be any worse of a base than the alkoxide is, so it is ok for it to be a leaving group. Technically, that portion of the reaction is reversible, because of the similarities. These compounds are isolatable. Notice what the structure is that's resulted: at the beta position, we have a carbonyl, and there is a new bond between the alpha and beta positions. In a Claisen condensation, the product is a beta-ketoester, with a new carbon-carbon bond at the alpha and beta positions.

For reference sake, let's review the aldol condensation. Aldol condensation, we don't have the problem of saponification. If we were to use hydroxide on this, the worst that we would do is start to make a hydrate, which we wouldn't be able to isolate anyways, so hydroxide is a perfectly fine base to use – although, it still won't reversibly form an enolate. We have an enolate. If it's the only compound in solution, then as the enolate starts to form, the compound reacts with another molecule of itself. Very similar mechanism – a bond forming through that alpha position by opening up the carbonyl. Because these intermediates are similar basicity, there is reversibility to that step. I'm taking that portion that I had on the left and moving it over to the right; we do have the new alkoxide that was formed by the attack, and then we have to alkyl group that was at that position. Notice the big difference between the Claisen condensation and the aldol condensation: in the Claisen condensation, we have what we could call a leaving group. Of course, if we were talking about Sn1/Sn2, it would never be a leaving group. But in this case, because this is a base-promoted reaction, it turns out to be a leaving group. Down below, we have a methyl group or a hydrogen, so there is no leaving group, which why we don't end up with two carbonyls. The Claisen condensation, we have two carbonyls that will result because both carbonyls reform. Down below, we don't have a way to let that alkoxide reform a carbonyl, so you'll end up with one carbonyl in the product. If we continue this mechanism, remember that there's no H+ yet, so if I want to have that alkoxide be protonated, then I have to have it attack water, which since I used hydroxide as a base, that would be appropriate. Many times in these condensations, there's a follow-up step, an elimination. That is a two-step process. First, the alpha proton is removed, and then you have elimination. [resonance is not a step] The aldol condensation is one in which the product is either a beta-hydroxy aldehyde or ketone, or an alpha,beta-unsaturated aldehyde or ketone.

Whether we're using aldehydes or ketones like we would in an aldol condensation, or whether we're using esters as would in a Claisen condensation, what do you think that we'd have to do in real life to ensure that if we wanted to do alkylation, we could make the enolate without having the compound instantly react with itself? If we were doing alkylation, synthetically, we could write it out like this. For an ester, for example, we could say LDA, make the enolate, throw an alkyl group at it [with] some kind of leaving group, I'll call it RX. Let's remind ourselves that that's a primary. We'll end up with an ester with an R group on it. The start of this reaction, using LDA, is exactly the same as the Claisen condensation. If we weren't careful how we did the reaction in real life, we wouldn't have a problem selecting which one of these products would form. How could we, in real life, get the alkylation to work, avoid the Claisen condensation. It's a matter of which way you add your reagents, because if you have a pot full of ester and add LDA to it, then only a little enolate forms at one time, but there's a lot of ester around, which gives the enolate a chance to react with the ester. But if you have a pot of LDA, and you add the ester slowly to it, as long as you have a little excess LDA, that acid-base reaction is likely to be faster than the condensation.

You drop it in a little at the time and keep on forming the enolate, but there's never any ester around in order to react. If you add the ester to LDA, you avoid building up ester, and so you don't get the condensation. If you add LDA to the ester, you're going to get the condensation. A Claisen condensation can be avoided by adding the ester to an excess of LDA; that way, no significant quantity of the ester builds up for the enolate to react with.

This also means that we could do mixed condensations. For example, if we had an ester, react it in the appropriate way to be able to form the enolate, what would happen if I threw an aldehyde at it? Then this is going to be like an aldol condensation, because the aldehyde that's going to get attacked, that carbonyl will go away. You're only going to end up with one carbonyl in the product. That part's like an aldol. But we end up with an ester, so this would be the sneakiest of the condensations to recognize. You'd have to know that it was the ester that turned into an enolate first. We could [do] the reverse: forming the enolate specifically from the aldehyde, and then have it attack an ester. The product, what's it going to be? The ester reforms, and if you had heat involved, you're going to get dehydration, and you're going to end up with an alpha,beta-unsaturated product, but because we started with an ester, we end with an ester as the functional group.

These are the simple additions. [reversibility of aldol condensations – Soxhlet extractor – E1CB]

[The] Dieckmann condensation [is] just an intramolecular Claisen. Here we have a diester that I could react with LDA. Let's say that only one side or the other formed as the enolate. We made the enolate which, intramolecular reactions, if they form rings of the right kind of size are often faster than intermolecular reactions, because you only have one molecule you have to worry about instead of two. If we were to have a reaction through the alpha position of this enolate, counting that position, if we were attack this carbonyl, we would make a five-membered ring, and five- and six-membered rings are favorable – not just thermodynamically, but kinetically. Even though a 20-membered ring may have no steric strain or ring strain, if you had twenty atoms separated from each other, what's the likelihood that those two ends are ever going to meet each other to make a ring in solution? Thermodynamics is not the only issue; kinetics are involved as well. Five- and six-membered rings are both kinetically and thermodynamically favorable to form, so in this case it will. Enolate collapses, intramolecular attack on the other carbonyl. If an alkoxide has got a conjugate with a pKa of 16 - 18, but an ester has a pKa of 24, this step may not be so reversible because there is a difference in pKa that results. I'm going to label the number one from the carbonyl position of one ester; we've got six carbons. Recognize that what I've labeled as carbon one will not be in the ring, cause that carbonyl isn't in the ring. It's that alpha position next to it that forms the ring. If I circle that portion of the molecule, once the reaction's over with, it's going to reform its carbonyl. In the six position, that's where we have the methoxide still and the alkoxide. This is exactly the same as the Claisen condensation; it's just that we've also made a ring. This collapses back down and kicks off methoxide. We still end up with a beta-ketoester – nothing more than intramolecular Claisen.

Let's get to this thing called the malonic ester synthesis. Diethylmalonate is this molecule. What is the pKa of that proton? 13, which means that if we slowly and carefully introduced a solution of sodium hydroxide, it wouldn't saponify because the acid-base reaction is easier. We would be taking a stronger base, making a weaker base, that's a favorable reaction. Notice that means we could use something "wimpy" by comparison, like hydroxide, to make an enolate. We avoid having to use LDA or some extreme form of base to do an alkylation reaction. Hydroxide can be used this time. Sodium hydroxide is an appropriate base in this case since the diester is more acidic than water, so saponification is unlikely. Let's do an alkylation. [In addition to an alkyl halide, we could use a tosylate or mesylate as well]. We put an R group on there. What would we get if we saponified? [sterics require a stronger base to be used if a second alkyl group is put on] You'll get the disalt. What would happen if we then acidified with a bit of moderate heating? You put an -OH group on there, of course, but what will happen then?

Diketone, right? What happens when you take an NMR of this compound? What do you see? You see absorbances [corresponding] to a ketone; you also see an alkene peak, and you see an alcohol peak. Why? Because if you tautomerize, then you end up with intramolecular hydrogen bonding, which helps stabilize the otherwise unfavorable enol. [The percentage formed] is not trivial, because there's enough of it that you can see it in NMR. There's a significant intramolecular interaction that occurs – enough so that you see it in NMR.

Coming back to this case now: what if the intramolecular interaction was so strong that you then have a pericyclic reaction? What if the carbonyl were to open up and get that proton, which causes the -OH bond to come down to the other carbonyl, which could open, close, kick out this other carbon bond, which would then come back to satisfy this other carbonyl – it's just everything rotating around in a circle. What would you get out of this? This is most definitely irreversible. B-diacids are prone to decarboxylation. This is why malonate is used, because you can alkylate it under mild conditions, then as long as your compound is moderately acid-tolerant, you can then decarboxylate and end up with something that doesn't quite look useful yet, but you can't isolate this product. Why? It's an enol – it's an enediol, in fact. So, it tautomerizes. The alkene gets protonated, one or the other of the -OH groups could undergo resonance, which means we reform a carbonyl that's initially protonated, which means it's going to deprotonate. You end up with a carboxylic acid with your own choice of R group at the alpha position. That's the usefulness of this malonic ester synthesis. The malonic ester synthesis is used to prepare custom carboxylic acids under comparatively mild conditions.

There's its close cousin: the acetoacetate synthesis, where it's the same process. Acetoacetate. What's the pKa of this proton? 11, which means that hydroxide can even more easily deprotonate this compound. Which carbonyl would be more likely to be involved in the enolate: the one on the left or the one on the right? Which one is the more active carbonyl? If you were to reduce this with sodium borohydride, which of the two carbonyl's would be reduced? The one on the left, because the one on the right, because the one on the right is still an ester. Yes, you have two carbonyls which does make that alpha proton more acidic, but it's the lefthand carbonyl that's probably doing more of the heavy lifting because there's still and oxygen on the right-hand carbonyl that's getting involved. I react this with an alkyl halide; I get my alkylated group. We then can saponify or, if there's no acid-sensitive groups on the molecule, simply hydrolyze to begin with – water, heat, and acid. You'll go through an intermediate which looks like this. There's only one ester this time, so you only have one carboxylic acid. That will be the side that decarboxylates. After decarboxylation, we'll get an enol, but because this other half was a ketone, it's only a mono-enol. Once it tautomerizes, we end up with a ketone, with an R group at the alpha position. It's a way of alkylating under somewhat less harsh conditions that we might otherwise use.

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

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

Mixed condensation

Dieckmann condensation – Intramolecular Claisen

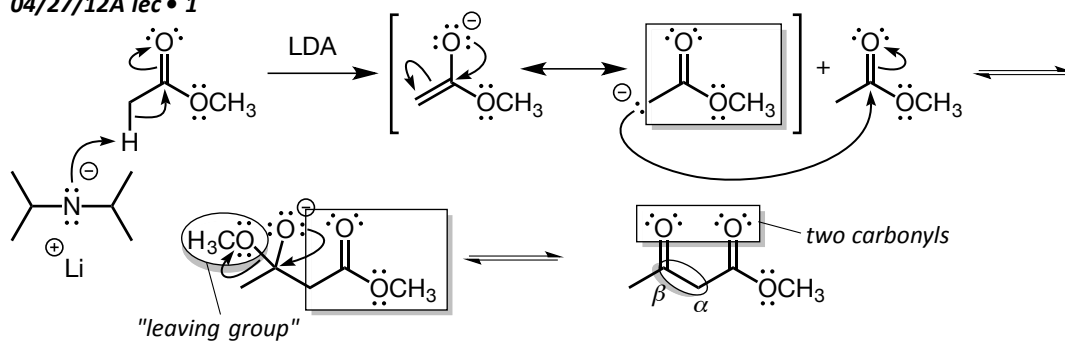Malonic ester synthesis – Diethyl malonate

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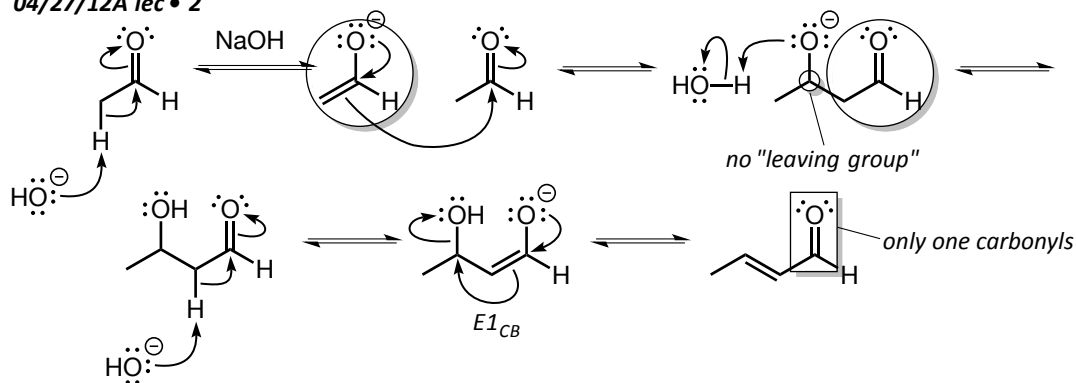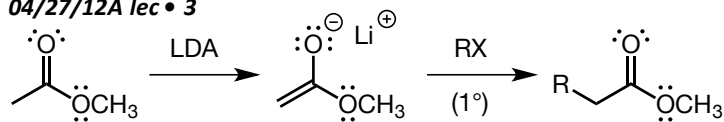
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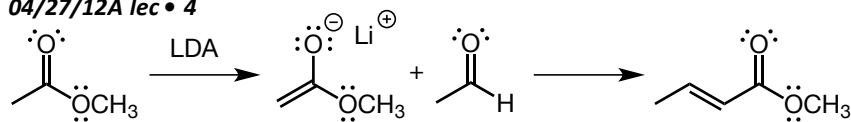
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Structures

04/27/12A lec • 1

two carbonyls

"leaving group"

04/27/12A lec • 2

NaOH

no "leaving group"

only one carbonyls

$E1_{CB}$

04/27/12A lec • 3

LDA

RX
(1°)

04/27/12A lec • 4

LDA

+

04/27/12A lec • 5

LDA

β-ketoester

decarboxylation

intramolecular
hydrogen bonding

pKa = 11