Lecture 10B • 05/03/12

[Exam 1 review]
[carboxylic acids and derivatives – functional groups: carboxylic acid, ester, amide, acyl halide, nitrile, lactone, lactam; relative reactivity; reactions: hydrolysis, saponification, solvolysis, Fischer esterification, reduction, alkylation, reversibility, transesterification; diazomethane; tetrahedral intermediate]
[alpha reactions – pKas; LDA; halogenation, haloform, aldol, alkylation, Stork, Michael, Robinson, Claisen, Dieckmann, decarboxylation; malonic ester synthesis]
[types of problems]
[practice mechanism]

Problem set

We had a five-carbon aldehyde that looked like this[and you were give methoxide as a base]. Methoxide will deprotonate this can cause an enolate to form. Since there was only one starting material, we'll assume it condenses with itself. Here's the point of putting the double bond into here: a Michael addition will not occur in this case. Why? The double bond's not conjugated. The only time we get Michael additions is when you have a conjugated double bond. If we tried to attack that double bond by itself, you're going to make a negative charge on an sp3-hybridized carbon; that's not favorable, so no reaction with the double bond occurs, it's just going to be a regular old aldol that happens to have a double bond in it. The carbonyl reforms and attacks the other aldehyde. We make a new carbon-carbon bond that automatically is going to have an alkoxide at the beta position to the recovered carbonyl. That will get protonated, which, since we used hydroxide as the base, water can be the source of the proton. A couple of more steps. If we have it under heat, and we take any amount of time, another alpha proton will come off. Remember that that deprotonation is a separate step than what happens next, which, in this case, is the elimination of that -OH group. That will give us our alpha,beta-unsaturated aldehyde, which is our product.

Last problem: you started out with ethyl butanoate which reacts first with LDA, second with ethyl tosylate. Mechanistically, what happens first? LDA will deprotonate the alpha position of the ester. What could happen next? In theory, if all we had was the ester, we'd have a Claisen condensation, but you are given a second reagent in this case, and when you're given these kinds of situations, where first you have a deprotonating base followed by an alkyl group, the presumption is that this is trying to show alkylation – meaning that you would add the ester to LDA, so that you could prevent the condensation reaction. What would the rest of this look like mechanistically? The point of me putting tosylate in here is to see if there's still any of you that are trying to get tosylate to react somehow, the tosylate ion. The whole point of tosylate is that it's not a reactive ion; its acid conjugate is strong because this is not a base. It's also not particularly nucleophilic. All that's going to happen is that the carbonyl will try to reform and an Sn2 reaction occurs. The alkylation is going to be irreversible. The first [will be] irreversible because there's a big difference in the pKas of the amine and the ester.
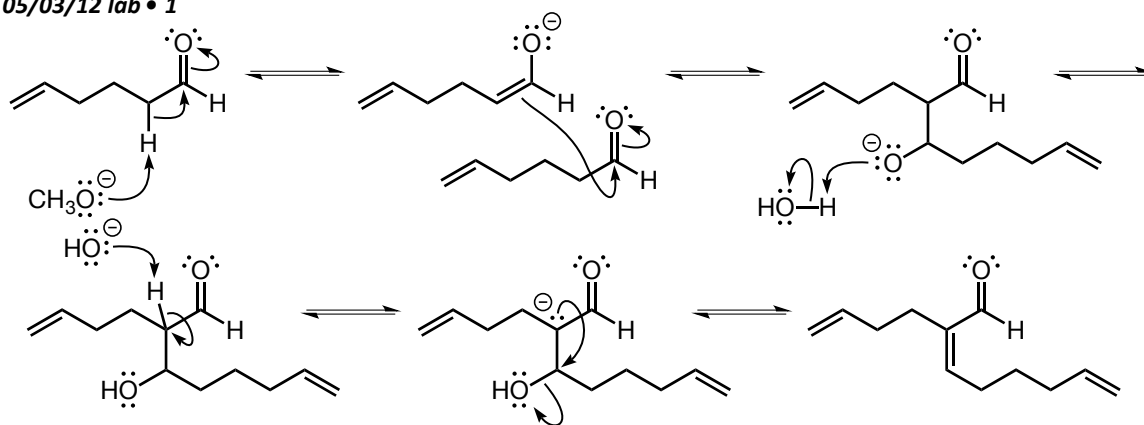
The alpha halogenation under acidic conditions doesn't have to use acetic acid [?].
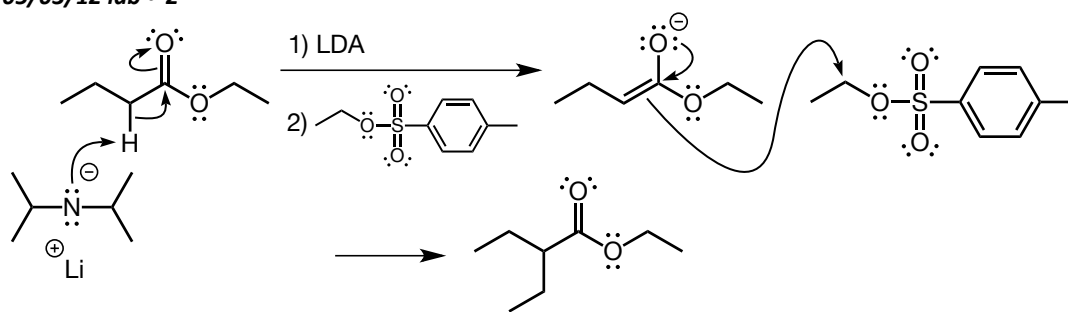
Robinson base mechanism

There are our two starting materials. Even though there's a hydrogen at what we call the alpha position, it's not acidic, so we don't try to make an enolate out of that particular hydrogen; it is acetone that's going to be deprotonated. To keep things simple, let's use hydroxide as the base. The first step will be formation of the enolate, and then subsequent attack of that enolate on the conjugated aldehyde. The whole point of this is that it's going to add in a conjugated fashion. We reform the carbonyl that was part of acetone; we've made a new carbon-carbon bond, pushing the methyl group out of the way. We push the carbonyl open, so we have an enolate, which is not going to react further, because if you tried to, it would make a four-membered ring. What we'll do now is show it being quenched, neutralized. We're still in base, and any enolate that can form will form, and we can make an enolate from the other position – the same one that was originally deprotonated to start this process off – grabs a proton, makes the enolate again. We have the aldehyde that, if it was attacked intramolecularly, will make a six-membered ring. I'll put the carbonyl that reformed up at the top, and I'll number the carbons so that you can help see that I did this right. We still have water out, [it] still could be the source of hydrogen, so we reprotonate the alkoxide. We get a beta-hydroxy product. We can have hydroxide deprotonate the alpha position, and then we kick off hydroxide to make the alpha,beta-unsaturated product. Remember that intramolecular reactions are often quicker than intermolecular reactions. Not all of these enolates are going to form simultaneously on the same molecule, but interchangeably; the time that it takes two molecules to react may be slow enough that, even if it's less favorable if it formed, if you make the enolate on the ketone, it may cyclize first.

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Structures

05/03/12 lab • 1

05/03/12 lab • 2

1) LDA

2)

05/03/12 lab • 3

*not acidic like
"normal" α-hydrogens*