Lecture 7A • 04/25/12

Quiz problem 1

What functional group is this? A carboxylic acid and an alcohol. What do we need to make an ester? A carboxylic acid and an alcohol. We have that in this molecule, don't we, which we why it cyclizes. What happens when you make a cyclic ester? What's that called? A lactone. This mechanism makes a lactone. Why? Protonate; open; attack [resonance combined]. You form a six-membered ring; that's a thermodynamically [and kinetically] favorable process, so it happens. We're halfway through the reaction. You have another protonate, [open, attack] deprotonate to make a lactone. Why do you have to remove water? Because it's fully reversible. By removing water, which is a product, by Le Châtelier's principle, that makes more of that product form.

I showed it individually step by step by step because it made a convenient acronym – protonate, open, attack, deprotonate. Even though the exact mechanism steps change, you can use that acryonym [sequence] in a bunch of reactions; it makes it easier as an instructional tool. But, when you're writing it on your own selves and you have some proficiency, resonance is not a step, so you can combine resonance with anything anywhere and it's correct.

Alpha reaction [review]

Alpha halogenation – how many times does it happen in acid conditions versus in base conditions? It happens only one time in the acid and it happens, potentially, multiple times under basic conditions; it doesn't always. Because there's a carbocation that needs to form [can be expressed as the basicity of the carbonyl oxygen], after this reaction happens once, because of the mechanism of this reaction and the presence of the bromine, it's not favorable for it to happen again. Under acidic conditions, halogenation only occurs once. Under basic conditions, you'll have multiple reaction, because after you put one halogen on, you hake the alpha position more acidic, the beginning of that mechanism depends on the removal of an alpha proton, so you make it more acidic, you make it easier for it to come off, you make it easier for the reaction to occur, so it keeps on going and going and going. But, if you had not a methyl ketone, but only an ethyl ketone, then when you do the reaction, you can multiply halogenate the product, but this is not the haloform reaction, because we didn't form – in this case – bromoform. Why? Cause on that one position, there are no more alpha hydrogens to pull off, so you can't substitute any more, and this is not a good enough leaving group with only the two bromines on it. Under basic conditions, it will do as many iterations as it can, but that means, therefore, if you don't have a methyl group, you don't always necessarily go all the way through to the haloform reaction. Here, only two halogenations occur since only two alpha hydrogens are present.

[will both sides of the ketone react???]

The haloform reaction is a special case of alpha halogenation involving specifically methyl ketones – in other words, molecules of this form. What happens is: if you start with something like acetone, and you react it under the appropriate conditions, you're going to get to some point where you have that tri-substituted carbon. Here's the important point: HCX3, whether X is bromine, iodine, or chlorine, is acidic enough that it's conjugate can be expelled by attack of hydroxide – meaning that if hydroxide were to attack the carbonyl and push it open, that portion of it is reversible. [pKa values of haloforms] The pKa of this compound is close enough to water that hydroxide is close enough in base strength to the group that would be kicked off here. In other words, once you formed a tetrahedral intermediate, yes, you could kick hydroxide off, but it's also either nearly equally or more likely that it's this carbon that gets expelled. The idea of breaking a carbon-carbon bond like this is a new concept. [But] condensations are often reversible, which means you'll have carbons expelled as leaving groups. This portion of a step is reversible, but it can't really happen in real life, because as soon as this gets kicked off, the haloform ion – whatever it is – is still basic, so you get an instant neutralization that, on paper, is reversible, in that all equilibrium are technically reversible, but the pKa differences are so huge here that it's effectively non-reversible.

Alpha alkylation

Base reversibility – Imagine that you could form an enolate. In the reactions we've seen so far, we've used things like hydroxide as base, because the hydroxide would end up not having some side reaction with whatever other reagents we had present. But this is now a different situation, because, independent of how this enolate formed, if we could isolate this enolate, the carbon ends up being very nucleophilic and very basic. If you have a primary substrate, then that's the same kind of story that we had with acetylide ions: if you threw an alkyl halide or an alkyl tosylate (or sulfonate in general), then this enolate can attack and do Sn2. There [are] some restrictions: this is a fairly strong base, this is going to be a slightly stronger base than hydroxide, so elimination is a consideration. If you have a very hindered primary position, you make stil have elimination possible, but this is often exploited to do alpha alkylation.

Let's come back to this issue of the base. If I use hydroxide, that might be problematic in this case, because residual hydroxide that you would need to have in solution to make that enolate would react with the alkyl halide just as easily.

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Why would we need hydroxide in solution? Because what is the pKa of that ketone, right? 19. What is the pKa of water? 15.7. So if I wrote this reaction, what kind of arrow would I put in between? Is it reversible? It has to be, because it's not favorable. This is a deprotonation which is reversible, in this case, because you're trying to go from a weak acid to a strong acid. If you have hydroxide that you tried to use as your base, it might work for an aldol condensation, for example, but it won't work well here.

If we want to make the enolate and make sure we don't have any other base component that's hanging around that might do a side reaction, we would really prefer to do something irreversible, wouldn't we. That's where the molecule LDA comes in: lithium diisopropylamide. Amide, aside from being the name of a carboxylic acid derivative, is the negative ion name of an amine. If is this a lithium salt, then you'll have two lone pairs on that hydrogen. How do you synthesize this? In the lab, it's synthesized by taking [n-]butyllithium and reacting it with diisopropylamine, the neutral compound. This has a pKa of about [35]. Point being: that's a really, really strong base that we just made. If you take a ketone and react it with LDA, given the steric hinderance around LDA, it's not likely to attack the carbonyl. It's a strong base, so it easily pulls that hydrogen off. Because it has a pKA of [35], versus the ketone's pKa of 19, this is by far a forward-only reaction. Because the reagents are cheap, and making LDA in lab is relatively straightforward, it's [routinely] used in these enolate reactions.

If I wanted to write not a mechanism but a synthesis for doing alpha alkylation, ideally I'll do it like this: take the aldehyde or ketone, react it first with LDA to make the enolate, and then, since we're doing alpha alkylation, RX; that let's us add an R group at the alpha position.

I want to show you another related reaction. This is the Stork enamine synthesis. What is an enamine? It's an alkene and an amine: something like that. Are enamines thermodynamically stable? That's a loaded question, because maybe they're the only product that can form in certain reactions. In this case, with two R groups on the nitrogen, it cannot tautomerize, so yes, this is thermodynamically stable, cause it has not choice. Not all enamines are unsynthesizeable, you have to use the right amine.

Imines versus enamines

If you have a primary amine, there are two hydrogens on that nitrogen. One hydrogen comes off during the first protonate-open-attack-deprotonate cycle, to make what's called a carbinolamine. Let me write a mechanism. I'm forgetting that I'm [using] an amine which is a base; for that reason, [the mechanism proceeds this way] with the attack occur[ring] before protonation. Attack, open, protonate, deprotonate (cause we've still got an ammonium salt). We've made the intermediate, which is called a carbinolamine. We need at least one hydrogen, we lose one hydrogen at this point to get through the first round of protonate, open, attack, deprotonate. If you went through another round of protonate, open, attack with resonance, look what we've got here. We've got to deprotonate again in order to be able to end up with an imine. Without writing the whole mechanism again, let me say that if you don't have a primary amine – if you use a secondary instead – it only has one hydrogen that can be removed, so the intermediate carbinolamine, we could still get, but there is no hydrogen that could come off at this point. Now, if you push the reaction forward, the only thing that can form is for the double bond to form next door (between two carbons).

Let's move on to the point of what this Stork enamine synthesis is. Let's say you wanted to do one of these alkylations. Let's say we're worried about the fact that an enolate is a strong base, so you're worried about your substrate doing elimination, or some other reaction that's unwanted, by the presence of the base. Wouldn't it be great if we had some other way to do a kinder, gentler reaction? What would you get if you did the following? That is not pyrrole. Why would pyrrole be a horrible choice of reagent, even though it's got a lone pair? It's aromatic. Why is it aromatic? What is pyrrole? The lone pair is part of the aromatic system. If it's part of the aromatic system, you'd have to break part of the aromaticity in order for that lone pair to react. The product, when you react these two things together, is going to be an enamine. Compared to a regular alkene, what is the proportion of electron density on the more-substituted carbon of the alkene versus the less-substituted? If you draw a resonance structure, we end up with a positive-charged nitrogen, which is not that bad; nitrogen doesn't mind being positively-charged, just like oxygen negative, yes, you can't isolate a negative charge itself, but it's easy to form a compound with an oxygen that's negatively-charged. This is a non-trivial resonance structure [that] shows that there's a little bit greater proportion of negative charge on that one carbon than you'd have in a plain alkene. This means it's an alpha-alkylating reagent.

An another aside that you need to consider: if you have just a plain old amine, will reaction occur between these two molecules? What kind of reaction is the only reaction possible? Can Sn2 happen? Do we have a primary substrate? Yes, we have a primary alkyl halide. Do we have a strong nucleophile? Do we have a nucleophile that's stronger than water at least? What makes something a good nucleophile? It helps to have a lone pair, helps to be negatively-charged. Isn't the nitrogen here basic? Is an oxygen in an ether basic? No. We don't protonate ethers [because] they're generally non-reactive. It requires hydroiodic or hydrobromic acid, really strong conditions, to break up an ether. If oxygen is not basic, and this is, then this is a better nucleophile that water, and it will undergo Sn2 by itself. [The reaction] doesn't stop here: once you add an alkyl group, an amine's even more basic, so it [generally] keeps going and going until you get a quaternary ammonium salt.

Coming back to the Stork enamine reaction, this is the justification for saying that this thing that's a neutral compound that looks like an enol and therefore can do an enolate-style mechanism, it's going to happen. You take this thing, this enamine, and react it with [1° only?]; it can do an alpha-alkylation. Upon treatment with water and acid, we decompose the enamine back to the ketone or aldehyde it was formed from. [summary] The Stork enamine synthesis is useful because no strong base are used, which can allow for sensitive substrates to be used in alkylation reaction. [substrate]

Claisen condensation

Will alpha deprotonation be possible under these conditions? What's the pKa of the alpha proton of the ester? 24. What is the pKa of water? 15.7. That's a lot of difference in pKa. I'll say the reaction's not really favorable.... you're not even going to be able to deprotonate, because you're going to saponify instead. Is alpha-deprotonation possible here? No, because it's s stronger base than hydroxide – but not strong enough. These reagents cannot be used to alpha-deprotonate because they are not strong enough bases, and, depending on the type of ester, will cause saponification. With the right alkoxide, you can get transesterification.

If I take this ester – what's the name of this ester? [reverse esters?] Ethyl propanoate. If I use LDA, that's a strong, strong base. We can make an enolate out of an ester. If there's another ester around, what does that mean? Like other condensation, the carbonyl that went away when we made the enolate comes back when it reacts. You make a new carbon,carbon-bond, which at that position, we currently have an oxygen negative and an ether? If you take that alkoxide, let it condense back, we're able to kick out an alkoxide, which means we have made a beta-ketoester, because beta to the ester is a ketone, and it is the product of a Claisen condenation.

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The haloform rxn is a special case of alpha-halogenation involving methyl ketones.

HCX3 is acidic enough that its conjugate can be expelled by attack of NaOH.

alpha-alkylation

LDA – lithium diisopropyl amide

Stork enamine synthesis

The Stork enamine synthesis is useful because no strong bases are used, which can allow more sensitive substrates to be used in alkylation reactions.

Claisen condensation

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Structures
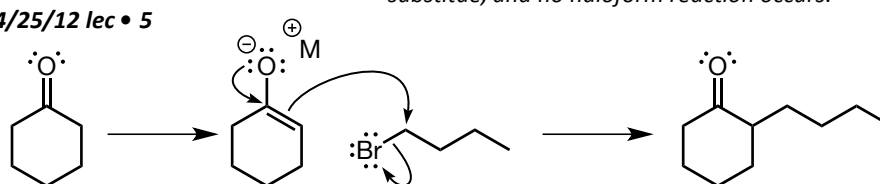
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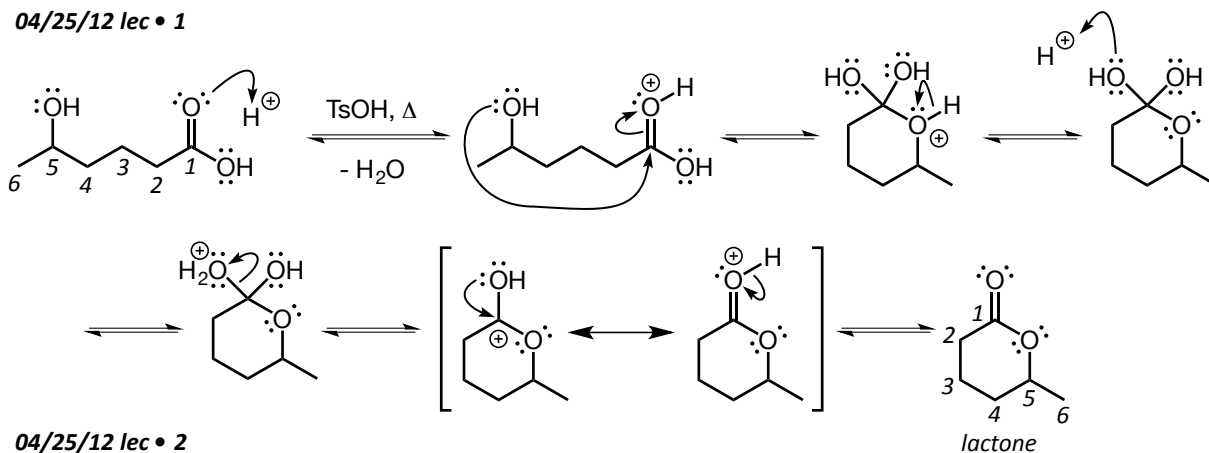
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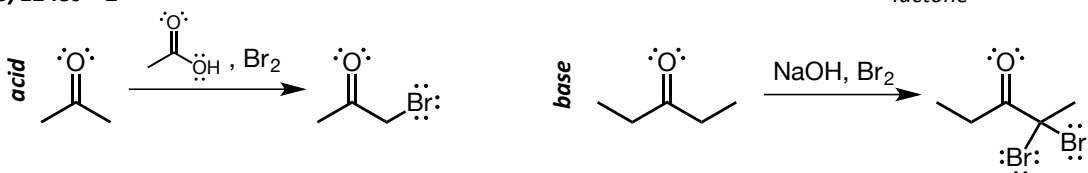
Under acidic conditions, halogenation only occurs once since the halogen, by withdrawing electron density, makes the intermediate harder to form

Multiple halogenation occurs since the inductive effect of bromine increases the acidity of the α-protons. Since only two α-protons are present, only two halogens substitue, and no haloform reaction occurs.
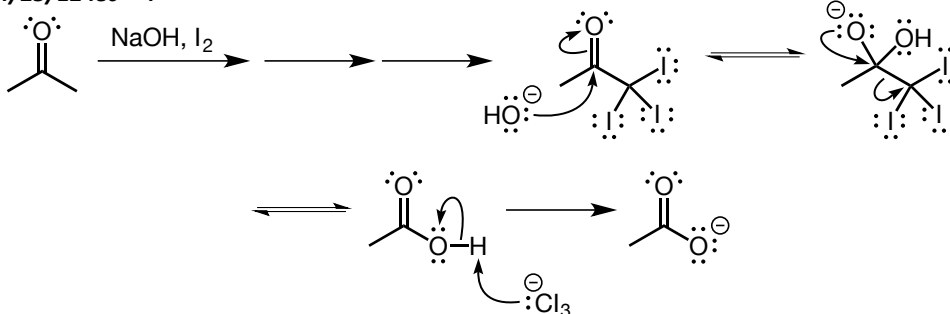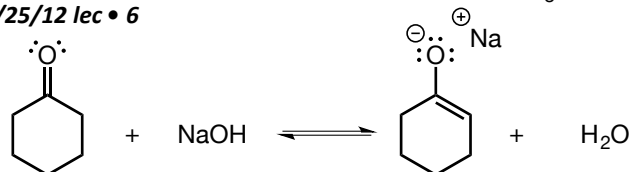
04/25/12 lec • 3   *04/25/12 lec • 5*

R = alkyl

04/25/12 lec • 4

NaOH, I$_2$

04/25/12 lec • 6

+ NaOH ⇌ + H$_2$O
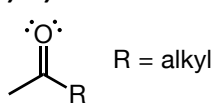
Unfavorable since a weaker acid is converted into a stronger one.

pKa = 19
weaker acid

weaker base

stronger base

pKa = 15.7
stronger acid

04/25/12 lec • 7   *04/25/12 lec • 8*
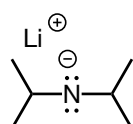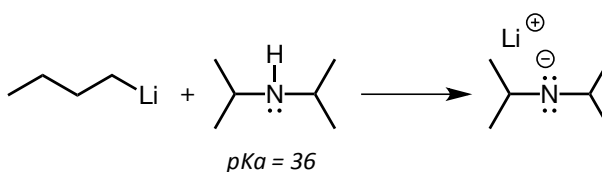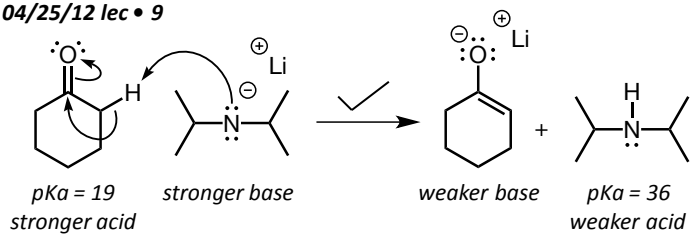
pKa = 36

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pKa = 19
stronger acid   stronger base   weaker base   pKa = 36
weaker acid

LDA   RX
(*primary*)

1° amine
two hydrogens

loses one H   carbinolamine

2nd H lost

no H!

only one H
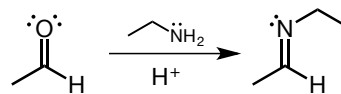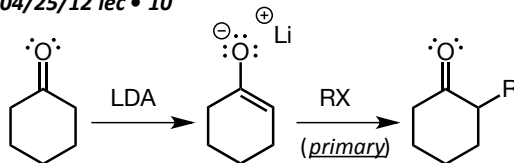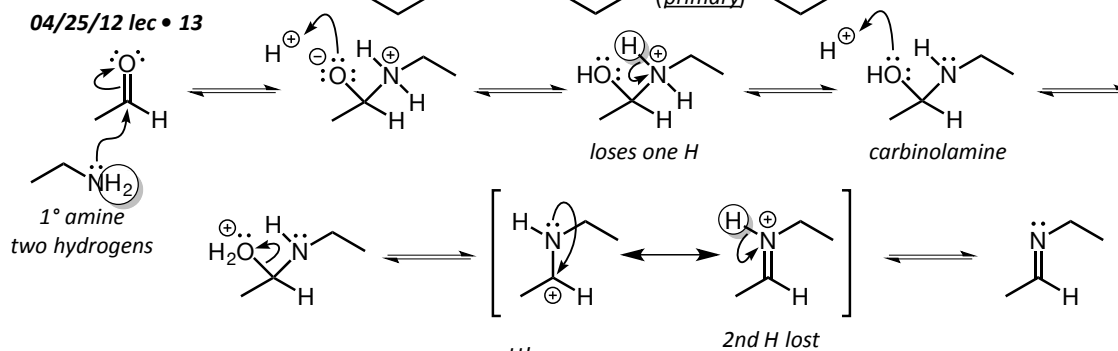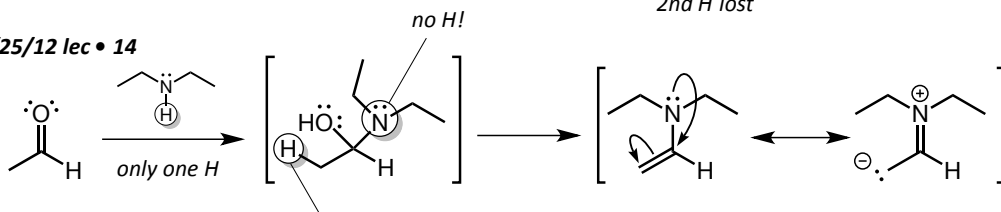
α-H comes off instead

electron density built up @ this position

not pyrrole

pyrrole

H₂O, H⁺

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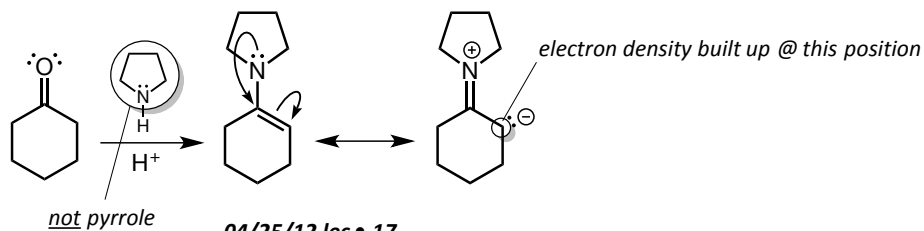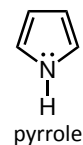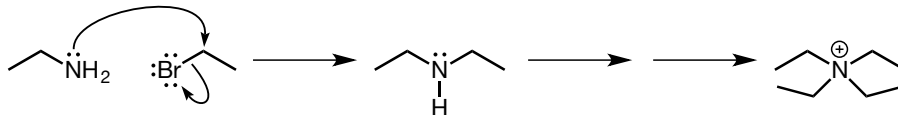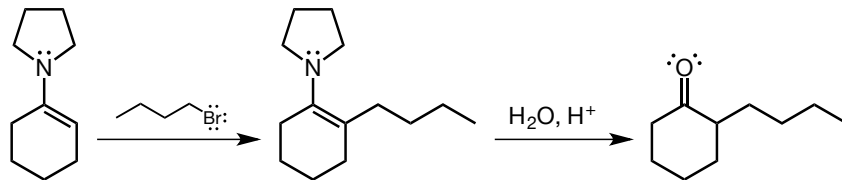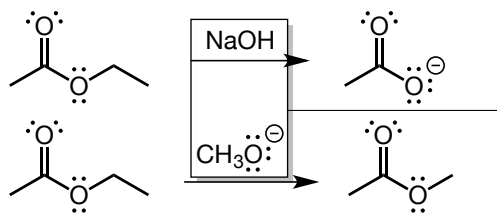
Cannot be used to alpha-deprotnate because they are not strong enough and, depending on the type of ester, will cause saponification or transesterification

β-ketoester