Lecture 7A • 02/03/12

Cationic reactions

Grignard reaction – Start out with an alkyl halide, react it with magnesium, and then one of two solvents is normally used: diethyl ether or THF. The reason you need this is because the product that forms only forms easily if the lone pairs from the oxygen from the ether of the THF coordinate with the magnesium; if you don't have one of those solvents around, this formation just doesn't occur. You make an alkylmagnesium halide which then you could react with an aldehyde or ketone or other carbonyl compounds. Let's take something easy like ethanal. Attack occurs, pushes open the carbonyl bond, we end up with an alkoxide; let me highlight the fact that we have this new carbon-carbon bond. Then there's an acid work-up step following it, which we can get to the alcohol.

What if we wanted to do a Grignard reaction, and we wanted to use this to make a Grignard reagent from this. What's going to be the problem with it? Can you look at that and see why we might have an issue trying to make a Grignard reagent from that starting material? What functional group does it have in it? A ketone! Doesn't that mean that reagent would just turn around and react with itself? So as it's forming, in other words, before you have a chance to react it with some other molecule, it's going to react with it's own self. You might get a reaction if you threw this in magnesium and bromine, but the reagent would react with itself. Maybe not within the same molecule, it's that it can reach around and make a three-membered ring, but one molecule will react with another of the same kind, so you'd never have a chance to throw it at a different aldehyde or ketone.

What if we had some way, though, to mask the fact that we have a carbonyl bond there? What if we could do something to hide temporarily the carbonyl bond? If we going to do something like that, we would prefer it to be something that's reversible, so that whatever we do to mask it we could then undo to get it back later. What about acetals and ketals? We could take the ketone and react it with this alcohol. I only keep using this particular diol because it makes this very convenient five-membered ring product; another alcohol would work, though, we could use ethanol or something else – usually you'd use some kind of inexpensive alcohol to do this reaction. A few rounds of protonate, open, attack, deprotonate later, and we have this. What we just did is protected the carbonyl. That group, we know is susceptible to acid, because that's the way we would go in the reverse direction; if we took acid and water, we would destroy that ketal we just made. How do I know that's a ketal versus an acetal? Came from a ketone, which means there's no hydrogen at the carbon where the two oxygens are connected. It's acid sensitive, but it's not terribly bases sensitive, because that's not really a leaving gruo, the oxygen minus, kinda the same reason why hydroxide's not a good leaving group. What we could do is we could react this with magnesium in ether, and we could form the Grignard reagent. Now we could throw whatever ketone and aldehyde we did want it to react with. Let's say we also reacted with ethanal A reaction occurs; before the acid we don't have an alcohol, we have an alkoxide. If we used dilute H+, where we were just giving enough to cause, you could, in theory end up with just the alcohol, while still retaining the protecting group. Later on, if we then use acid and water and purposely hydrate it, we'd get rid of the protecting group, get gack the ketone. That would be the deprotect step. One of these kinds of synthese usually occurs by protecting it, you do whatever else you need it to do, then you deprotect.

There are several different functional groups that have these protecting groups available. I want to show you one protecting group that's used for alcohols. It's DHP, which stands for dihydropyran. Pyran is a very closely related [to furan] but instead of a five-membered ring, it's got a 6-membered ring. Dihydropyran means hydrogenate one of the two double bonds. It is a protecting group for alcohols; what do you think would happen if we reacted it with an alcohol? Let's say there is an H+ around. With an alkene like this, you'd expect the first step of the reaction would be for the alkene to react with hydrogen, which it does. Notice that I put the carbocation next to the oxygen. I'm going to explicitly show a resonance structure, which I know I often don't do, but I'm going it in this case to emphasize that even if we had had some substituent at this other side of the double bond, which would make it the more substituted carbon, the reaction's really not going to happen there because this lone pair almost instantly being able to delocalize and stabilize, therefore, the positive charge. This really is like a carbocation. Let's now imagine that we has some kind of alcohol along. That alcohol's going to attack the carbocation or, since I've made this resonance structure, it's going to attack the carbon while will push this carbonyl back open. We temporarily have an oxonium ion, which then gets deprotonated.

If I look at just this much of the molecule, what I've circled, what functional group would that be? It's an ether, that's right, and then this ring, it comes from pyran, but it's got four hydrogens on it now, so this is called a tetrahydropyranyl ether, that's the type of protecting group it is. The abbreviation is THP. Why would I want to do this protection? What would happen if I tried to take that difunctional molecule, that had both the ketone and the alcohol, what would happen with it if I reacted it with propylmagnesium bromide; what would be the one and only product that would result? The answer is propane, because Grignard reagents are basic; an alcohol is acidic, at least compared to a Grignard reagent. Before the Grignard has a chance to attack the carbonyl, the deprotonation's going to happen first, because acid-base reactions are generally the fastest reactions that happen in solution. If we wanted to attack the carbonyl, we can't have the alcohol around. That's the whole point of the THP group – you have an ether, which ethers aren't leaving groups, and so it lets you do the reaction, that's the point.

Grignard reagents cannot react with ketones or aldehydes in the presence of protic molecules, since a rapid acid-base reaction would occur instead. That's the whole point of using the protecting group.

Let's see that now. I have taken that difunctional molecule, reacted it with DHP, I could then react it with a Grignard reagent if I wanted to. The THP ether will remain intact. I'll add my new carbon group to it; I'll originally get an alkoxide. If I use dilute H+, all I'm going to affect is making the hydroxide neutral. If I wanted to blast off the protecting group at the same time, I could, just use strong acid and water, but maybe you want to do some follow-up reaction, you don't want the protecting group to be gone right away, that's why I'm showing you this with dilute H+ to show you the step-by-step process. Sometimes, instead of doing a protecting group, if your Grignard is cheap, just add a whole bunch, because once you deprotonate the alcohol, then the carbonyl's still there to be attacked; you'll waste some Gringard reaction, but you'll still be able to carry out the reaction – of course, if your Grignard reagent's super-duper hard to make, you wouldn't do something like that.

If I am going to want to get rid of this protecting group, it'd be good to know how to do it. Before, I circled a certain part of it [and identified it as an ether]. But if I circled this part of it, what functional group is it? An acetal. Because look at it: it's two oxygens connected to one carbon, isn't it? Each oxygen has an R group on it; there is a hydrogen on this position where the two oxygens meet; that's an acetal. It doesn't look like one, it didn't get created that way, but that's the sneaky thing about THP. All you have to do is react it acid and water, and you'll make the alcohol. You have to be careful doing this, because you can dehydrate tertiary alcohols too, so if you did this and used a lot of heat and a lot of H+, you could cause dehydration to potentially occur. You will spit off a by-product; it's got five carbons in it; you'll have an –OH group at one end, because it made a circle with itself; the other end, since it's an acetal, it'll be an aldehyde. We don't care about that by-product, it's just what you'll happen to get out. That's another example of protecting, doing a reaction that would be possible without the protection, and then getting rid of the protecting group.

Let's move to cationic reactions. Let's see what happens with nitrogen. We need to review a little bit about amines. I'm going to deal with primary amines for nomenclature. A three-carbon compound, that would normally be propane; but instead of propane, we're going to add the -amine functional group ending. We don't put an 'e' and an 'a' right after each other in nomenclature, so it turns into propanamine. If we had a cyclic compound, same thing: cyclohexanamine. What about these terms primary, secondary, and tertiary? Primary (1°) means one alkyl group on the nitrogen. When you're dealing with oxygen and with alcohols, the focus is on the carbon. What makes one alcohol behave differently from another has to do more with which carbon the alcohol's attached to. But the way that amines react is different; the way that amines react depends not on what carbon the nitrogen is on, but how many carbons are on the nitrogen instead. A secondary amine is one in which you have two alkyl groups; tertiary is where you have three. Because nitrogen does have that lone pair, because it's a base, you can form what's called a quaternary ammonium salt, because if you did put a fourth group on there, you would not have a neutral compound. But it is possible to make and isolate a salt that has four carbon bonds to nitrogen, because it doesn't violate the octet rule, it just makes it positively charged.

How do amines react, then, with aldehydes and ketones? It's a little bit more complicated than just the plain protonate-open-attack-deprotonate. In protonate-open-attack-deprotonate, all we show happening is H+ protonating the carbonyl, causing the rest of the reaction to occur. It turns out that doing the same kind of reaction with an amine works best at pH 5. If you get much more acidic than that, the reaction's not very favorable; you get much more basic than that, the reaction's not favorable. Why might you imagine that you can't have a very acidic environment if you wanted an amine to react the same way an alcohol would? What is the pKb of an average amine? What is a pKb? A base dissociation constant, the equivalent type of thing of a pKa, an acid dissociation constant. If you have NH3, ammonia, and you throw it into water, what kind of solution do you get? You get a basic solution. Ammonia has a pKb of 9.25, which means it's a weak base, which means it's a base, which means that if you put it into acidic solution, all that's going to happen is you'll get a neutralization reaction. The lone pair of nitrogen is nucleophilic; it actually has the potential to attack a carbonyl, even without the carbonyl getting protonated first. It helps if it's protonated; putting the positive charge on the carbonyl is what helps it open. But the amine can attack it directly. But if you were to put it into acidic solution, where you have a positive charge, instead of the lone pair, is a positive charge nucleophilic? What does nucleophile mean? It wants positive charge. Does a positive charge want to be next to another positive charge? No, so if it you put it into acidic solution, it makes the amines unreactive, at least in that way. Amines are nucleophilic, but they are also bases. If an amine is placed in an acidic solution, it'll become protonated, and therefore no longer nucleophilic. Put an amine in something like HCl, and you'll make a salt. [pointing out chloride salts in medications]

The ideal pH of the following reaction is pH = 5. Let me show you the slightly modified reaction mechanism. If I start out with a ketone, for example, and I throw at it a primary amine, the first reaction step that we'll see is the attack first. The rationalization for this is that an amine is basic. Notice that I am showing it as a reversible mechanism, cause the functional group I'm about to form can be decomposed reversibly. What's going to happen first: that ammonium salt that I just made, would that get deprotonated first, or will the alkoxide get protonated first? Yes, meaning one or the other's going to happen, it doesn't really matter which one is which. It is unlikely they would happen simultaneously, though, so I wouldn't show the alkoxide reaching out to grab the hydrogen to the nitrogen. I'll go ahead and show that being protonated. Because we are in pH 5 solution, it is acidic, so it is ok to have H+, even though I started out the reaction as if it was in basic conditions. Once we get past this point, then the rest of the reaction is going to look just like what we've seen before.

We have a deprotonation, and we end up with an intermediate that's halfway in between where we started and we [will end] up with. This intermediate has the name carbinolamine – means it's half alcohol, half amine. It's going to continue to react.

Yes, the amine can get protonated, and in fact, the amine's more likely to get protonated first, because it's more basic than the oxygen, but if the oxygen gets protonated, we can eventually end up with an intermediate that is isolatable. Now it's a cycle of regular old POAD (protonate-open-attack-deprotonate). This is a different kind of attacked than we've seen before. Previously, at this step, we'd have, if this was an alcohol we were reacting with, a second molecule of that alcohol come in at this point. But intramolecular reactions are generally faster than intermolecular reactions. What I'm getting at is the fact that we've got this lone pair here. If you go back and look at the equivalent mechanism with alcohols, there's a lone pair on the oxygen in that reaction as well. [If you tried somehow to use the lone pair and form a double bond], you'd have no place to go. You'd have a double bond to oxygen and a single bond to oxygen; neither of them would break easily, so oxygen would never close up in this way. But nitrogen is trivalent, so once it makes a double bond and it's still got a hydrogen, it just loses the hydrogen. You end up with a carbon-nitrogen double bond. This is a compound called an imine. Imine is when you have carbon-nitrogen double bonds.

Now let's see a closely-related reaction. What happens if we react a secondary amine and do this exact same process? What does secondary mean? You've got two alkyl groups attached to that nitrogen instead of just one. Start with the same ketone. I'm going to react it now with a secondary amine. This sequence of arrows means after a few steps. I'm not going to write the first part of the mechanism over again because it works exactly the same way as we had before, so I'm going to jump to the carbinolamine. What does that look like? I would have pushed the carbonyl open, so we have the alcohol. It's part amine as well, so we have the amine that's added in. During that addition process, it has to lose one hydrogen. The next round, what would happen. Protonation gets us water; that's going to come off as a leaving group. Now notice, I could write a resonance structure. Nitrogen can tolerate a positive charge, but once we get there, there's nowhere for it to go. You've got a positive charged that can't be relieved somehow, and so it's not possible to isolate this compound. This is what doesn't happen; what does happen?

If we still have some more of that amine in solution, it's a base. A base can pull off this proton, causing elimination to occur. You therefore end up with a single bond to nitrogen, but a double bond from the carbon connected to that nitrogen and its neighbor. Previously when we made a molecule like this that had an alcohol and alkene, what did we call it? An enol. What are you going to guess that an alkene and an amine is called? An enamine. Why are we able to form this? Because it's the only thing that can form, and it is isolatable. Why didn't we make this the first reaction around, when I used that primary amine? Why did I make an imine and not an enamine? If I had tried to take an aldehyde and a primary amine and react them together, the enamine would look like this. But guess what? It will turn into the imine. What's happened here? It looks like a double bond and a single bond have traded places with each other. Is this a resonance structure? No. So what is this called? Tautomerization. This is a tautomerization reaction. Let me write the mechanism for just tautomerization. SInce this is normally going to be happening in acidic conditions, if we're making these kinds of compounds, double bond gets protonated and opens up. It forms a carbocation right next to the nitrogen, which I've already identified has a lone pair that would easily delocalize. The double bond would now form to the nitrogen instead, making a positive charge, which can be relieved by deprotonation. We end up with the imine. Why would this happen? Because this overall process is exergonic. The enamine won't form because it's not the most thermodynamically stable product.

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DHP – dihydropyran

Grignard reagents cannot react with ketones or aldehydes in the presence of protic molecules since a rapid acid/base rxn would occur instead.

amines

Amines are nucleophilic, but they are also bases. If an amine is placed in an acidic solution, it will become protonated and therefore no longer nucleophilic.

Ideal pH of the following rxn: pH = 5

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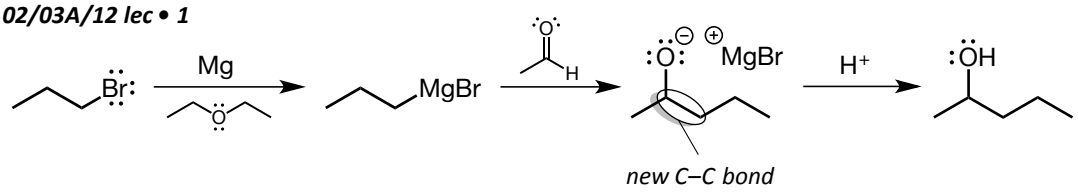

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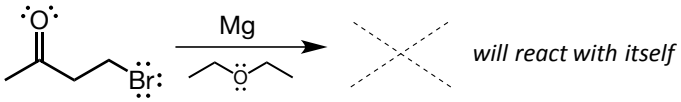

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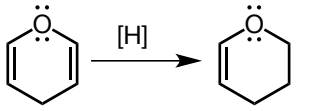

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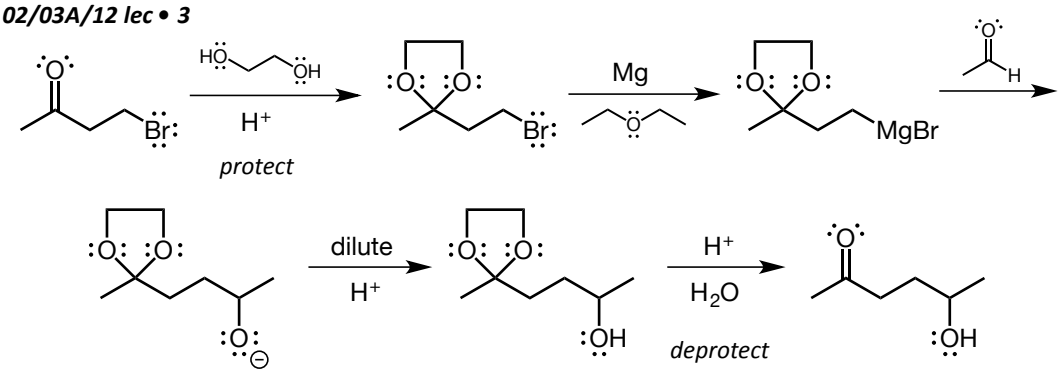

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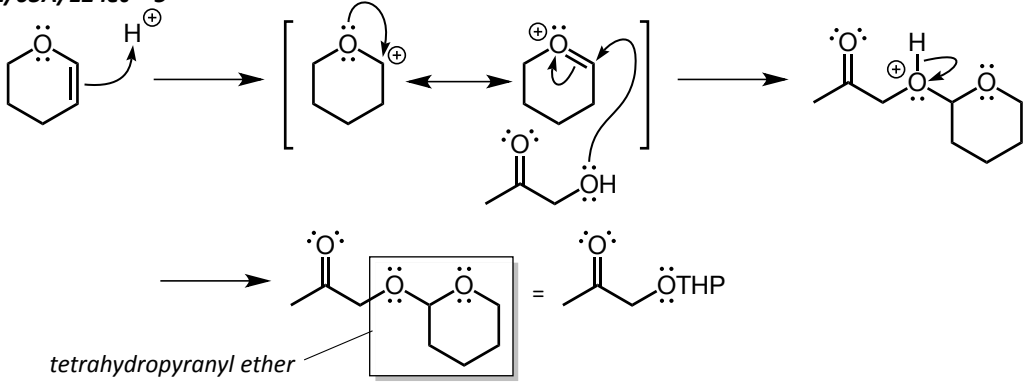

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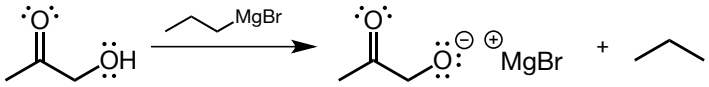

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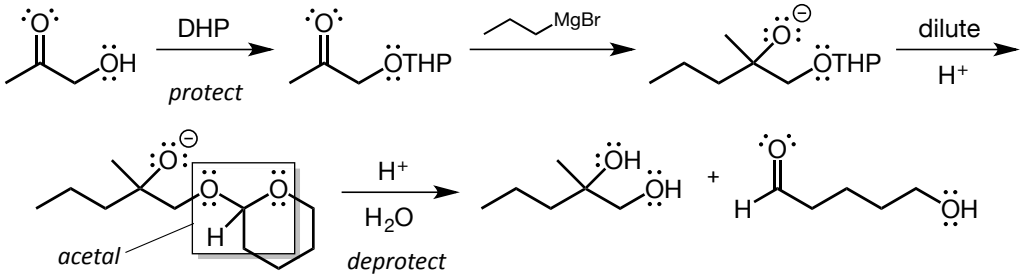

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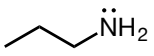
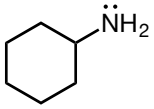


propanamine



cyclohexanamine

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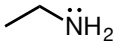
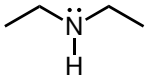
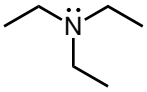


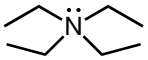
1° (primary) – one alkyl group on nitrogen



2° (secondary) – two alkyl groups on nitrogen



3° (tertiary) – three alkyl groups on nitrogen



4° (quaternary ammonium salt) four alkyl groups on nitrogen

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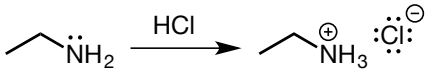

base

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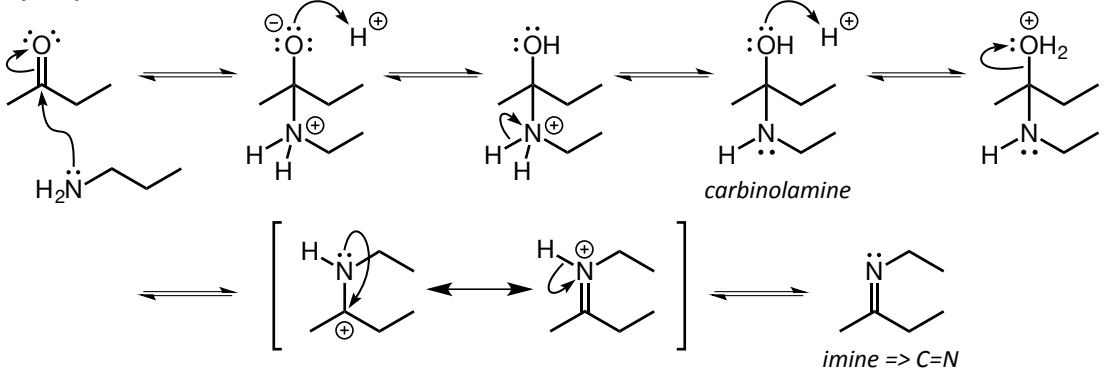

carbinolamine

imine => C=N

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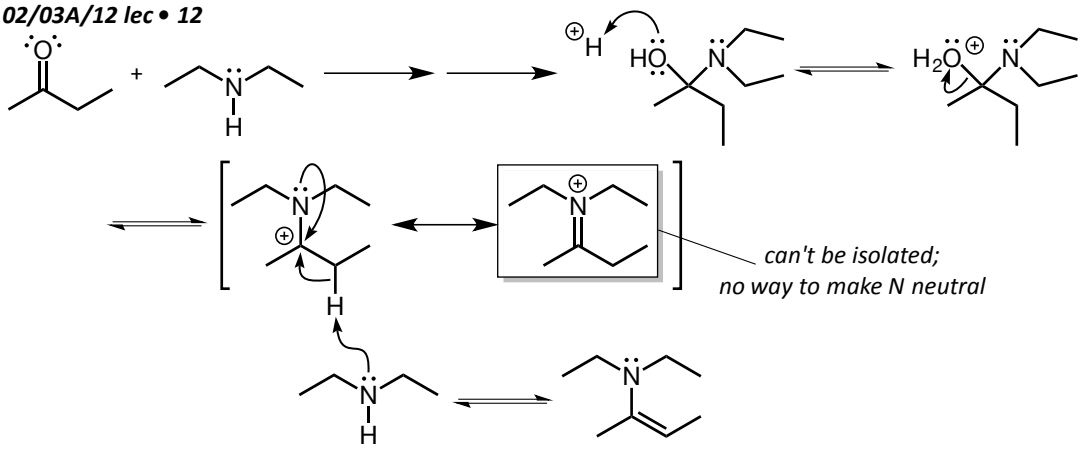

can't be isolated; no way to make N neutral

enamine

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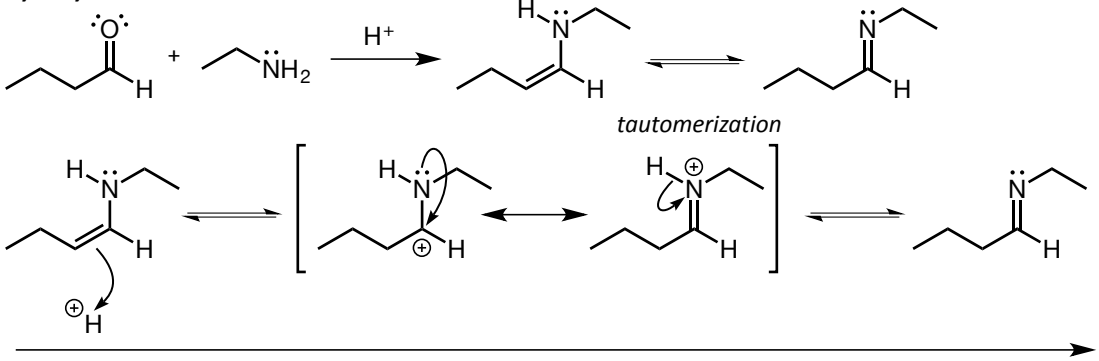

tautomerization

exothermic