Lecture 8A • 02/06/12

Imines and enamines

Why is it that when we react an aldehyde with a primary amine with some kind of weak acid source, we get the imine and not this enamine? Why one, not the other? The fact that the nitrogen has two hydrogens, it is able to react twice. What's another reason? Both of these mechanisms on paper are possible, but why is it that only the first of those products gets formed? The answer's thermodynamics. [If we do an] analysis and see which bonds are broken and which ones are formed as you go from one compound to the next, if we look at what gets destroyed, from left it right, we have a carbon-nitrogen bond broken; we have a nitrogen-hydrogen bond formed; we have a carbon-hydrogen bond broken; and we have a carbon-carbon double bond formed. Overall, it's an endothermic process; delta H is greater than zero. So the reason the second product doesn't form is it's not thermodynamically favorable.

But, the fact that the original amine has two removable hydrogens on it, that is why it can form an imine, because we looked at a separate example, where we could take a ketone – and it's not the fact that it's a ketone or aldehyde that's important, I'm just switching between substrates to show different examples. But if I reacted this with a secondary amine and H+, then [her] point would be very correct that there's only one removable hydrogen, which means the only reasonable product that will form is the enamine. What is the relationship between these two? If we did convert from one to another, what is that process called? Tautomerization.

Now moving on with a little new material. There's a very reactive molecule called hydrazine, which is as if you took two amines and fused them directly together. Hydrazine and many nitrogen-containing compounds are used as fuels. Hydrazine, if you react with a weak acid source and a carbonyl, then you form what looks like an imine, except off the nitrogen we do have this second nitrogen group. From a hydrazine, we form a group called a hydrazone. Hydrazones are found in a number of applications, one if which is in the formation of what is called a derivative, where we form a related compound which we can use to do an alternate form of characterization. If you think back to a time where maybe you only had melting point as one of your main analytic tools, lots of compounds have the same melting point, but what if you could make a derivative of that compound, and you also had a table of different derivatives that different compounds make. By taking a compound and one or more derivatives and matching not just the compound but those derivatives' melting points, then you could more accurately figure out what the identity of your compound is. Hydrazones can also be used to synthesize specific classes of compounds. They also could be used in this thing called the Wolff-Kischner reduction.

The Wolff-Kischner reduction is the base reduction of a hydrazone. We'll go ahead and use this one made from acetone as my example that I'll write the mechanism for. The mechanism requires concentrated hydroxide and heat, so it's not compatible with all functional groups; I'm pointing this out because we do have this idea of a protecting group that you've been introduced to. I want you to start thinking about compatibility of acids and bases with different functional groups as I present them. This hydrazone, in base, it's not favorable, but what can happen over time is you could have a deprotonation. I'm going to go ahead and write this with reversible arrows because it technically is an equilibrium process. What we make when we deprotonate it though is a delocalized anion, because we do have a double bond next door that I could show as delocalizing that negative charge, which formally would now make a carbanion which could attack water. Where does the water come from? Even if you were in a non-aqueous solution, we just used hydroxide as a reagent, it just deprotonated something, so we just made water. Notice I did not use H+ at this point, because there is no H+ in a basic solution, no appreciable amount of H+ at least. I've now made a nitrogen-nitrogen double bond.

From the hydrazone to this point, what is this process called? I've yet again just done an exchange of a double and single bond; it's yet again tautomerization. What happens next? Similar thing. Yet another hydrogen gets deprotonated. We could show delocalization. Notice that in this case, I had been using reversible arrows up to this point; I'm now showing an irreversible arrow. That's because in this process we make nitrogen gas which just bubbles away; since it bubbles away it's not at all possible to be a reversible mechanism. Once you get to this point, you can't go backwards. We make a carbanion which is very, very basic, so you would have a very rapid neutralization with water to form an alkane. [6 aspects] The synthetic utility of this reaction would be to convert an aldehyde or ketone to an alkane; you're reducing, but you're completely getting rid of the oxygen. There are other techniques that can do this, but this can be a useful one as long as you have something that's base-compatible. If you look at it, it really is, in a sense, almost a double tautomerization; the second one isn't really a tautomerization because we don't end up with exchange of bonds, but it starts out the same way. Of course, there's an intermediate step where we make the hydrazone out of that aldehyde or ketone first.

One last related item. The common name for this compound I'm about to show you is hydroxylamine. [commentary on hydroxyl vs hydroxy] This hydroxylamine, the nitrogen is more nucleophilic than the oxygen, so if we reacted this dual-functional molecule with a ketone or an aldehyde, we'll yet again have the same mechanism that would make a hydrazone.

We get the same kind of intermediate, where it's nitrogen with a double bond, except unlike a hydrazone, if we had an amine hanging off of the nitrogen, now we have this hydroxide hanging off the hydrogen. This is a functional group known as an oxime.

Let's switch over to talking about Grignard reactions. First a note about mechanism. Grignard reaction is kinda a famous example of a reaction for which a concrete mechanism has not been completely determined. They haven't been able to conclusively one way or another what exactly goes on – and that's both for the formation of the Grignard reagent and of the Grignard reaction itself. First, for Grignard reagents, the first step of the reaction is thought be between magnesium metal and the hydrogen of whatever alkyl halide gets involved. I'm going to write this much like I wrote the sodium reduction of alkynes. Sodium metal, it's a good reducing agent, it has a low ionization energy; in ammonia liquid, the sodium metal acts as a source of electrons. The first step in the reduction of an alkyne, an electron gets added in to the triple bond, coming out of solution. Essentially the same thing happens here, where magnesium metal provides an electron, effectively reducing the alkyl halide.

But, where is that electron going to go, cause don't we already have a bond between carbon and bromine? If an electron gets added in, we actually create a structure for which we can't write the full structure for; there are three electrons in that bond, which means there's really only a half bond there. Because, if you already have a bond and you put another electron in, if you think about molecular orbital theory, whenever two orbitals come together and make a sigma bond, we make a sigma antibond at the same time. It's just that normally we only have two electrons, so only the bonding part of it gets filled; the antibond stays empty. If we now make this radical anion that is destabilizing the bond, if we allow that bond to open, we're now going to create a radical and a bromide. You also have magnesium plus that's floating around because an electron came from it. That magnesium and bromide could react to make a magnesium bromide radical, plus we have an alkyl radical; those two combine, and we make our Grignard reagent. This is one proposed mechanism, because it's not truly known which way it works, but it's thought to be a radical process. [Carbon] A half bond is there, which there is no good way to notate it, that's what that little bracket up above means – it means in addition to what the structure is showing you, there is one extra electron which is making the whole thing overall negatively charged. There is a carbon-bromine bond there. When it breaks, one electron goes back to the carbon – that's why it ends up a radical – one electron goes back to bromine, but there's actually yet another electron there, which is what is being shown by the bracket. That's why the bromine ends up with a lone pair, ends up negatively charged. Otherwise, of bromine broke homolytically, meaning one electron going to each side of the bond, bromine would end up neutrally charged, because it would only have seven electrons. But, it's more electronegative than carbon, so it's ending up with with that yet extra electron, which is why it's negatively charged. Magnesium has two valence electrons, and we used one up in the redox, so there's one more left. It's reducing the bond, that's how the reaction starts. [The product] acts like it's an anion; it may have been created in a radical process, but it acts like it's an anion.

Grignard reagents will only successfully form if an ether is present to complex with the magnesium. [reference to DHP and THP] There are some other things I want you to know about Grignard reagents. [lab directions] What are the ways that Grignard reagents can be destroyed? What things must you leep a Grignard reagent from to make sure the reaction actually works? Grignard reagents can be destroyed by water or any protic compound. We can take advantage of that to do deuteration, because instead of H_2O, we could use D_2O. For example, if we had an alkyl halide that we reacted with magnesium and ether, we could make the alkylmagnesium halide, react it with D_2O, and where the halogen had been will now be the deuterium. That's on product use of destroying a Grignard reagent. Bu in general, if you have water around, which even means the water that potentially is always adsorbed onto the surface of glass, that you're going to kill off some of you're Grignard reagent. [Preparing glassware]

Another thing that destroys Grignard reagents: carbon dioxide, which sometimes, again, is taken advantage of, that you do the destruction on purpose, because carbon dioxide, if you get it in the form of dry ice, that's a very easy substrate physically to do a Grignard reaction on, because you could prepare the Grignard reagent and pour it over dry ice. It instantly reacts to make what? CO_2 is just a double carbonyl, so if you were to write out what happens mechanistically, you'd end up with a carboxylate. If you did the subsequent $H+$ work-up, that means you've got a carboxylic acid; it's a way of easily making carboxylic acids. It's an easy one in a sense that you have a solid you can add it to. Grignard reactions are very, very, very exothermic, dry ice is really cold; you've got a solid that's cold, makes a good reaction in a physical sense, performing the reaction. Would you want to do an approach like this do make a carboxylic acid, or would you want to [do] overoxidation using a chromium reagent on a primary alcohol? Depend on the cost of the reagents and which one ends more more difficult to do in real life. On a case-by-case basis, one might be better, the other one might be better. There's many other ways that we'll learn that we can make carboxylic acids. That's a challenge in organic chemistry for synthesis; maybe you've got ten ways to do it, but which one's best? There is one more carbon in the product because carbon dioxide itself has carbon. Carbon monoxide could react as well, but it's a more minor component of the atmosphere, so we're not usually as worried about it. The other thing that we're more worried about is oxygen. Once it's protonated, it'll form a peroxide.

All three of these must be avoided in order to make sure that your Grignard reagent doesn't decompose. Grignard reagents are ideally formed in flame-dried or oven-dried glassware under inert atmosphere, which means fill up your reaction chamber with a gas that's non-reactive, like nitrogen or argon, those are the two most common cases.

Nitrogen gas isn't so unusual to have in an organic lab. [lab directions][why do you always use primary alcohols? because they're easier to write; you put one more methyl group on there, and I'm lost]

The best way to get the reaction going. The alkyl halide has to eat through magnesium oxide. Magnesium oxide is what you get when magnesium metal just reacts with oxygen. [scolding sections for lab cleanliness; I don't want to be a red light camera] The magnesium reacts with air to make magnesium oxide. The alkyl halide has to eat through that in order for the reaction to start. Once the reaction starts and it gets through that outside layer, it's exothermic and will happen quickly. But it's the initiation of a Grignard reaction that's famously difficult. The ideal way we should do this is we have very finely powered magnesium, activated magnesium, that's just ready to react with the alkyl halide. Sometimes what people will do is put a few drops of the alkyl halide in with just a little bit of solvent and not stir, so that the alkyl halide, which is more dense, will drop down, drop to the bottom, react and sit there on that magnesium metal, eating through magnesium [oxide], start the reaction.

How do you know the reaction's started? Little fine itty bitty bubbles, which you have to distinguish from heating up the ether. Ether has a very low boiling point. You'll also notice the solution starting to turn cloudy, cause you're making something that has an ionic component to it; or, as soon as it starts reacting with the water or carbon dioxide you're not able to keep out, you're going to be making by-products, which will make the solution cloudy. It'll also probably turn colors, it'll probably turn brownish.

What can you do to get a Grignard reaction working that refuses to get started? There's a couple of tricks. One is to add a small crystal of iodine; you put that right into the middle of where the iodine is. The iodine is kinda like the alkyl halide; it reacts with the magnesium. Of course, it doesn't give you a Grignard reagent, but magnesium's cheap, so we usually use it in excess. That's another way that you'll know the Grignard reaction's working, because the magnesium will look like it's disappearing. [lab procedure] You could throw all of the alkyl halide in at once, but then once the Grignard reaction starts, it's exothermic and, with larger reactions, it will usually go shooting out the reaction flask because of how hot it all of the sudden gets. Of course, if you've got ether there that's got a low ignition temperature, heat plus ether equals bad news. Sometimes if you can get the reaction initiated and put it into another reaction that hasn't started yet, you can sometimes kickstart the reaction. Grignard reactions are famously difficult.

How about identifying the reagents used in a Grignard reaction if we only see the product; a little synthesis practice. Determine for me what the starting materials might have been in the Grignard reaction that made this alcohol. There's two observations about Grignard reactions you need to make. One is that the alcohol will be at the carbon that used to contain the carbonyl. That's what lets you back up retrosynthetically and figure out what used to be there. In this specific example, there is a carbonyl that use to be here, but on one of the two compound involved. The new carbon-carbon bond must contain the carbon that was part of the carbonyl. We put these two statements together, what does that let us determine as likely candidates for the statin materials of this reaction? Here is a carbon-carbon bond that includes that carbon where the alcohol was, which means that's the carbon that used to contain the carbonyl. What is I broke the carbon-carbon bond apart, then we could have have phenylmagnesium bromide as the Grignard regent and propanal as the substrate that was attacked. Or, here's another carbon-carbon bond that again must have contained that carbonyl. If I break the compound up that way, that means I now have benzaldehyde that could have been my substrate, and it it could have been ethylmagnesium bromide that's my Grignard reagent. Which way would have worked? Yes. There's nothing wrong with either of these methods; all of those compounds are very readily available, very easily made. Methylmagnesium bromide can be made from [bromo]benzene; [commentary about benzaldehyde's legal status]

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Wolff-Kishner reduction

synthetic utility – convert aldehydes & ketones to alkanes (reduction)

Grignard reagents – Grignard reagents will only successfully form if an ether is present to complex with magnesium.
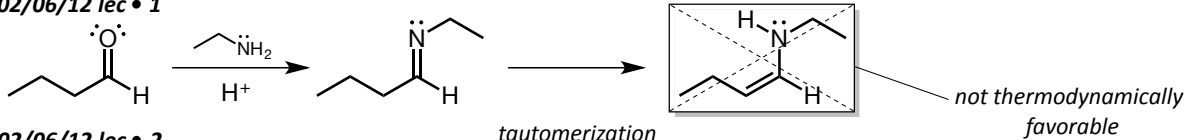
Grignard reagents can be destroyed by:
– H_2O (or any protic compound)
– CO_2
– O_2

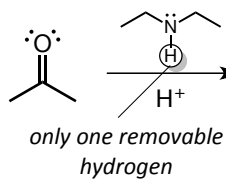Grignard reagents are ideally formed in flame-dried glassware under inert atmosphere (N2, Ar)

• The alcohol is located at the carbon that used to be part of the C=O
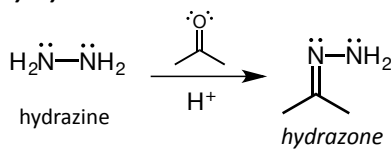• The new C-C bond must contain the carbon that was part of the C=O
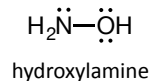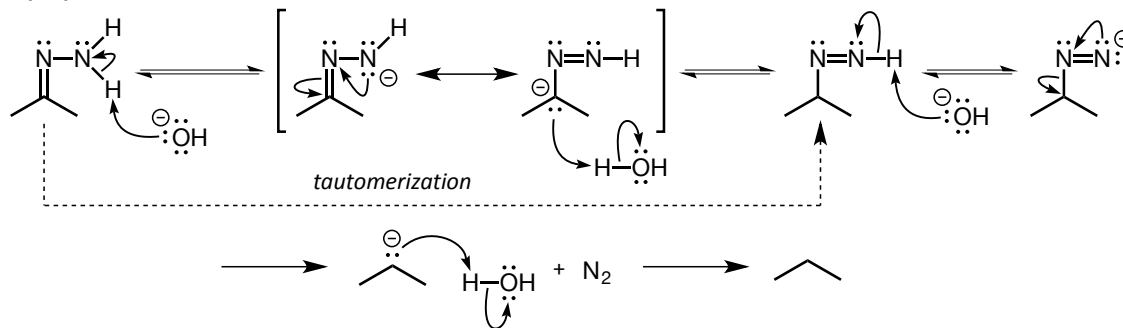
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Structures

02/06/12 lec • 1

tautomerization

not thermodynamically
favorable

02/06/12 lec • 2

only one removable
hydrogen

02/06/12 lec • 3

hydrazine   *hydrazone*

02/06/12 lec • 5

H₂N—ÖH

hydroxylamine

02/06/12 lec • 4

tautomerization

02/06/12 lec • 6

oxime

02/06/12 lec • 8

02/06/12 lec • 7

from magnesium   *radical anion*
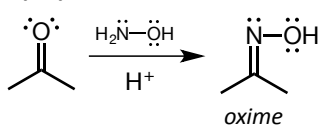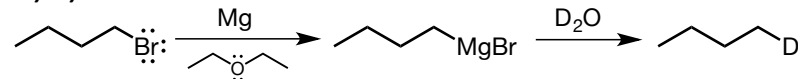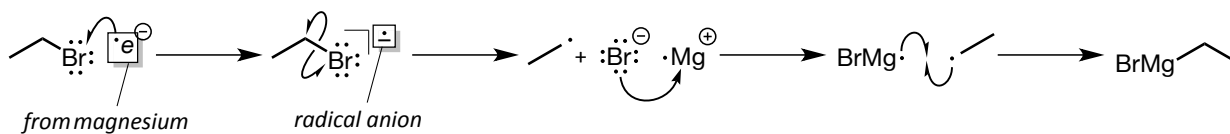
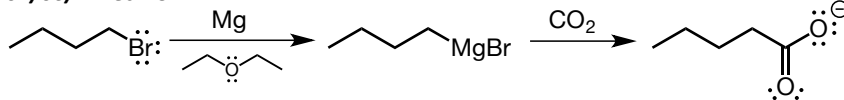*02/06/12 lec • 9*

02/06/12 lec • 10

02/06/12 lec • 11