

Lecture 10B • 02/07/12

Why is it that a primary amine cannot react to form an enamine? An enamine is closely related to what other functional group that has an -ene name in it? An enol, which has got an -OH group on the same position as a double bond. Are enols something that normally we can isolate? No, why not? They're not thermodynamically favorable, they're unstable, so they'll tautomerize. That's exactly what normally an enamine would do. The only reason that enamines form is because there's not enough removable hydrogens to form the double bond between carbon and nitrogen. If you had an aldehyde, for example, that you reacted with H^+ and a primary amine. In theory, we could write a mechanism in which an enamine would be formed, but then it's going to rapidly tautomerize. To review the mechanism of tautomerization, the carbon-carbon double bond gets protonated first, we have a lone pair that can delocalize. It's at this point, if you look at the mechanism for forming an enamine, how we show an imine can't form, because if we had had a secondary amine, then this positive charge would have nowhere to go. But, because we do have a removable hydrogen, it can come off, which would make the nitrogen neutral. To go from the enamine to the imine, what happens? We have a carbon nitrogen bond that forms, a nitrogen-hydrogen single bond breaks; we have the carbon-hydrogen bond that forms, and then we have a carbon-carbon bond that breaks. If we were to look up these different bond dissociation energies, remember that any time a bond breaks, that requires energy, so that's a positive value; any time a bond forms, that releases energy, so that's a negative value. Overall, to go from the enamine to the imine, it's overall negative.

There's a reaction of, not imines, but a close relative of imines – the Wolff-Kishner reduction. There's two closely-related derivatives of imines that I want to show you now. One of them you get from the molecule hydrazine, often found in rocket fuels along with a lot of other nitrogen-containing compounds; it's effectively two amines stuck one nitrogen to the other. This compound still has a lot of the reactivity of a plain old amine. If you took, for example, a ketone and reacted it with hydrazine under mildly acidic conditions, we'll get something that looks like an imine, but it's something actually known as a hydrozone. Similarly, there's another molecule that has the name hydroxylamine. Normally, when we have hydroxy, there's no 'l' that we put in; this does have something to do with the nomenclature of amines. Nitrogen is more basic than the oxygen is so effectively the nitrogen's more nucleophilic than the oxygen. If we did the same kind of reaction where you reacted a ketone with this hydroxylamine and an acid source, we're also going to form something that looks like an imine, it's just that it's got this -OH group hanging off of it. This kind of functional group is called an oxime.

The Wolff-Kishner reduction is used for hydrozones; let me show you that mechanism. If we start with a hydrozone, we put this in a strong solution of sodium hydroxide. Realize that sodium hydroxide has the potential to do other reactions; if we had an alkyl halide on this molecule, we'd have to consider whether we could do this reduction or not, because maybe the alkyl halide would react instead. I want you to think about the compatibility of functional groups and reagents as we keep adding on more reactions. In sodium hydroxide, the following reaction is not favorable, but it can happen, or at least there's an equilibrium that can get established. We make an anion that can be delocalized, because it is neighboring a double bond. There's no H^+ in solution because we have a sodium hydroxide solution, but because the first step is the removal of a hydrogen by sodium hydroxide, we can presume that water is around, so we could show water providing a hydrogen for this anion to become protonated. Starting from the enamine going to the imine, that is an example of tautomerization. Look at what I just wrote for the first part of this Wolff-Kishner reduction: what kind of process does this look like? It's also tautomerization, it's just a base version. In the acid tautomerization that we just saw, first the double bond attacks H^+ , and the last thing that happens in the hydrogen falls off. In the base version, notice that the first thing that happens is the hydrogen comes off, and then the double bond moves, so it's kinda like everything done in reverse. Everything in the brackets is base-promoted tautomerization. Everything up to this point (and just a little further) is, in fact, fully reversible, but it's almost the very last step of this process where irreversibility occurs.

What does happen next? Similar to the opening step, we're going to deprotonate the nitrogen one more time. Potentially, we might imagine that there's a shift, a delocalization of those electrons, except we don't have a double bond next door to push open. If you try to move the lone pair to the nitrogen, that would cause the nitrogen-carbon bond to break, which is exactly what happens. In that process, though, you make nitrogen gas, which is going to bubble out of the mixture. If you're bubbling out of the mixture, of course you can't have equilibrium, because all reactants and products have to remain in contact if you're going to have a hope for equilibrium. You end up with the anion; it won't attack nitrogen backwards, especially since we do have something like water around in solution. Instead, we have a very rapid neutralization, and we form an alkane. Let me summarize this to say the synthetic utility of this reaction, the Wolff-Kishner reaction, is to convert aldehydes and ketones to alkanes. This is a form of reduction. You might think: why would you want to do this? So far we've been trying to put functional groups on, since alkanes are normally unreactive. This may look like a potentially useless reaction in this case, but what if you had multiple functional groups? What if you had a plant-based source for some important component that you needed, it just happened to have one extra ketone on it. Well then we might, if we're able to, address that individual ketone and get rid of it and get something we want; this is not a useless reaction.

Grignard reactions

Grignard reactions are notoriously difficult reactions. Part of the reason for that is because the Grignard reagents are so darn reactive; they can decompose in a number of ways.

The Grignard reagent mechanism. There's evidence that it's a radical mechanism; there's evidence that the first step involves magnesium interacting with the halogen that is on the alkyl halide used. Beyond that, there's not complete certainty about exactly what happens. I'll show you a version of the mechanism. It's thought that the first step involves magnesium metal and a halogen from an alkyl halide. Magnesium metal, the only thing it's able to do really, is act as a reducing agent, which is exactly what sodium did when we did the reduction of alkynes using sodium. In a similar fashion, let's imagine that one of the electrons from magnesium comes off. Recall that magnesium is in the second group, so there's two valence electrons on it; one of the two electrons comes off in solution. That electron could potentially add to the alkyl halide. There's no good way we can write the product that forms, not at least initially. Why? Because we have a compound where everything's already got sigma bonds, so where are we going to put the electron if everything that already could be bonded is bonded? Where did it go in the case of the triple bond, when we reduced the triple bond and added an electron to the system, where did that electron go? It went into an antibond. If you have the carbon-bromine single bond, and if you put an electron into the antibond, what do you have? A half bond. Bond order is the number of bonding electrons minus number of antibonding electrons divided by two. In the carbon-bromine bond, there's two electrons there; I'm adding a third electron in, which is going to be an antibonding electron, so two bonding minus one antibonding gives us one electron overall, but divided by two that means we only have half a bond. There is a way we can notate it. What that means is that the whole molecule has a negative charge somewhere, and it's got an extra electron somewhere; it is in fact that extra electron that's causing the negative charge. This is an intermediate known as a radical anion.

To more properly show how it reacts, I'm going to go ahead and show that half bond breaking, which formally I'm going to do with two arrows. It might make sense that, on the basis of electronegativity, we would suspect the extra electron to show up on bromide; we're going to end up with an alkyl radical and bromide ion. Of course, if we had magnesium that started this whole process off, and it lost one electron, we've got magnesium plus floating around somewhere. Now that we've got a plus and minus charge together, we can imagine the bromide rapidly meets up with that magnesium, and we form the magnesium bromide radical. Of course, we have an alkyl radical in solution as well, so imagine that the two radicals come together. We now have our Grignard reagent.

How do these Grignard reagents decompose? What can affect them? Grignard reagents, number one, can be destroyed by water or any other protic molecules. This is why you're drying your glassware for so long, because glass intrinsically has a certain amount of water that's automatically adsorbed onto its surface, because the surface of glass has so many -OH bonds on it; if you recall, that's why we used a chopped up version of glass as the coating for our TLC plates. You can take advantage of the fact, though, that Grignard reagents react with water if we wanted to try to deuterate a compound. For example, if we take an alkyl halide and react it with magnesium and ether; in order to form a Grignard reagents, we have to have an ethereal type solvent present, because the oxygen complexes with the magnesium as the Grignard reagent gets formed - no ether or something like THF, no Grignard reagent. Here we get a Grignard reagent, react it with D₂O, we could put a deuterium on here.

Carbon dioxide is also a problem. You can take advantage of that in one way of synthesizing carboxylic acids. If you wanted intentionally to make a carboxylic acid, there's kinda a neat trick you could do where you make your Grignard reagent first and (maybe not quite literally) you pour it over dry ice. Dry ice is nothing more than solid carbon dioxide. Carbon dioxide can be viewed as being nothing more than a double carbonyl, carbon that's got two carbon-oxygen double bonds. One or the other gets attacked, and we end up with a carboxylate. Part of the reason that this is such a favorable process is because the Grignard reaction is very, very exothermic; dry ice is very, very cold, so the combination of the two works out well. There is one more by-product, one more thing that can destroy Grignard reagents, and that's oxygen. Start out by making a Grignard reagent, then over time, just in the presence of oxygen, we'll make a peroxide.

Grignard reagents are ideally formed in flame-dried (or oven-dried) glassware under inert atmosphere, [which] means to do a chemical reaction where, instead of just normal surrounding lab atmosphere, you've instead got your glassware filled and sealed off with something like nitrogen or argon, a gas that's not going to be reactive.

[lab directions]

Getting Grignard reagents to form

Magnesium develops a layer of magnesium oxide; if you just put magnesium metal out, a redox reaction occurs where you end up with a thin layer of magnesium oxide, which has to be stripped away or eaten through in order for the reaction to begin. Instead of just taking magnesium turnings, we would crush it up or powderize it, increase the surface area, strip off that top surface of magnesium oxide, make the beginning of the formation of a reagent easier. Unlike what would normally make sense to do, sometimes getting these reagents to form if you don't mix the solution. If you have these magnesium turnings that are at the bottom of a flask, and you drop some ether in there just to have a solvent around, then drop some drops of the alkyl halide and let them settle down on the bottom of the flask.

That way, it covers up the magnesium, and then anywhere where a little hole does get eaten through that top oxidative layer, the reaction can start. How do you know the reaction is working? There's several clues. One, on the magnesium metal itself, there'll be tons of little itty bitty tiny bubble, which you've got to make sure you distinguish from boiling. Ether does have a low boiling point; forming and reacting Grignard reagents are both exothermic – exothermic enough that you may cause the solvent to boil even without using a hot plate. If you have big bubbles, the whole solution turning over, that might be boiling, but if you see little bitty tiny bubbles coming off of the metal, that's one indication that the reactions occurring. Another indicator is that the solution often will turn cloudy or will turn a certain color. Cloudiness is not always a good thing, because often that means that you've made the Grignard reagent but it's started reacting with whatever trace amounts of water might be around – but at least that means you can see something going on.

What if you don't see any of that; is there anything you can do to encourage a Grignard reaction? Sometimes, just waiting, especially if you're doing a large-scale reaction. The problem is, you could add all of the alkyl halide at once, so that once the reaction gets initiated, it just keeps on going. But once it gets going, it's exothermic, which means more of it happens, which means more energy is released; the whole process can cascade and get out of control, so you can end up with Grignard reactions where you're ending having stuff spurt off all over from the top of your glassware setup because of the sudden increase in temperature that you got. Of course, sudden temperature increase plus ether equals fire, so that's not necessarily good either. You can add all of your reagent at once and just hope it starts, so what can you do? Sometimes adding a little tiny crystal of iodine helps, because iodine can react with magnesium metal again to help eat through the surface of that magnesium oxide layer. Once it's eaten through, if you've got your regular alkyl halide around, then it could start reacting. This means you're going to use up some magnesium, but magnesium's relatively cheap, and we normally add it in excess.

How can you tell that your reaction's actually successful? The magnesium's going to get consumed; the little bits of magnesium should shrink in size. We do have excess, so it's not going to totally disappear. What if nothing's working? If you use something like diiodomethane, something where it's a very small molecule that has multiple halogens on it, that makes a by-product but sometimes they're more reactive than plain old larger alkyl halides. [last case resort - spike reaction][lab procedure] Once you're sure the reaction has started, then you're going to want to slowly but continuously add your alkyl halide in.

Synthesis

The Grignard reaction is one of the more important synthetic reactions we learn this quarter. You need to be able to take a product and determine how could it have been made if it had been made by a Grignard reaction. Let me give you this product – here's a form of benzyl alcohol. This was something formed by a Grignard reaction. What I'm going to ask you to do, then, is work retrosynthetically, determine the carbonyl-containing compound and the Grignard reagent that could have been used to make this compound. Realize that, yes, the Grignard reagent does push a carbonyl open, and so that means whatever alcohol forms is located where the carbonyl used to be; that should tell you a little bit about the type of compound you should come up with in order to synthesize that molecule, because that alcohol, that position right there, used to be part of a carbonyl. This alcohol is formed because a Grignard reagent attacks; it makes a new carbon-carbon bond. One of the carbons of that bond is the carbonyl carbon is where the alcohol ends up being formed, so the position where the alcohol is formed has to include the carbon that's part of that new carbon-carbon bond. That means, in this particular example, there are two ways we could have analyzed it.

We could have looked at this and said: what if a new carbon-carbon bond formed between benzene and that alcohol carbon? Or, what if it's actually the bond next door that formed in this process instead. Let's look at the two approaches. The one I have in green would imply that I had phenylmagnesium bromide. Why? Because it would attack that carbon at the carbonyl, which is where the alcohol forms, which means I would have had to have had a three-carbon aldehyde. What if I took the opposite perspective, that the bond had formed the other way. Then the benzene ring would be attached to what would have had to have been the carbonyl carbon. There's only two other carbons available, so ethylmagnesium bromide would have had to have been the Grignard reagent.

In any Grignard reaction, what you could do is the following in terms of mechanism. These compounds act as if they are anions, but instead of having to show a separate step when you formally produce an anion, you could make a short-cut notation that looks like this. Take the bond from carbon to magnesium and just show it directly attackin. Since it's coming from between carbon and magnesium, it's implying that one of the two atoms is no longer connected to that bond; it would be understood by a chemist that you're implying the magnesium goes away. It's a shorthand notation so that you don't have to show specifically making the anion first.

You've already seen acetylides as valid materials for opening up an epoxide. It might not be surprising, then, that a Grignard reagent can also open up an epoxide. This is still an anion mechanism, so attack is going to happen at the least substituted position. Notice that there's no oxygen now to help show the fact that an epoxide was attacked. Here's a practice synthesis problem for you. [quiz review]

Wolff-Kishner reduction

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

Grignard reagents can be destroyed by:

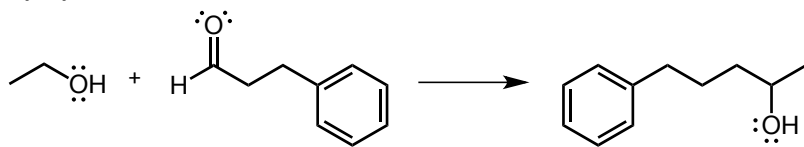
- H₂O (or any protic compound)
- CO₂
- O₂

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

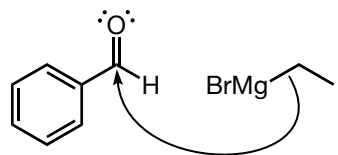
- In a Grignard rxn, the alcohol formed is located at the carbon that used to be part of the C=O
 - The new C-C bond must contain the carbon that was part of the C=O
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Structures (remaining structures identical to lecture 7A and lecture 8A)

02/07/12 lec • 1



02/07/12 lec • 2



02/07/12 lec • 3

