Lecture 9B • 02/03/12

Protecting groups

Let's do an example – taking a difunctional molecule like this, something that had both a ketone and an alkyl halide, and I said I wanted to make a Grignard reagent from it. What would be the difficulty with trying to make a Grignard reagent out of that? What reagents would I use to make the Grignard reagent out of this? Magnesium metal and one of two solvents: diethyl ether or THF. The reason that you need one of those two solvents is that oxygen complexes with the magnesium intermediates as they form; if you don't have that complexation occur, you're not able to make the Grignard. Any time that you're making one, yes it's magnesium metal, but you always need to show one of those two solvents; diethyl ether tends to be the more common one, so that's the one I'm going to show here. This works on paper, but it doesn't work in real life because Grignard reagents react with ketones. You have a ketone on the exact same molecule, so you could have one molecule of this reagent attack another. At the very least, you would not be able to react it with some other aldehyde or ketone that you might have wanted to. The idea behind protecting groups is that we might have some way of temporarily masking the carbonyl functionality. We don't want to totally destroy the carbonyl, because we might want that back later, but we want to hide the fact that it's a carbonyl so we could make this Grignard reagent. If we make this, if we somehow mask this, we want to be able to unmask this as well; that's another important aspect about protecting groups. We have the perfect thing available, to make a ketal out of it, because making a ketal is reversible. Ketals are sensitive to acid, but they're not so sensitive to base; if you think about what a ketal really is, it's like an ether, ethers normally aren't leaving groups. You make the ketal, and it protects it, to a large extent, from bases, so that's what we're going to do.

There are many alcohols that could easily be used to make a ketal; I tend to use this diol only because it makes a very convenient 5-membered ring; you need a little acid source in there as well. A couple of cycles of protonate-open-attack-deprotonate later, and we end up with the protected carbonyl; this is the protect step here. We could then do the formation of the Grignard reagent – magnesium in ether. We could then throw some other aldehyde or ketone at it to react; in this case I'll use ethanal. Make sure you don't do what I almost did and put the wrong number of carbons in. Initially, we have an alkoxide, cause Grignard reaction, that's under very basic conditions, so there's a work-up step that we need to do. If you're careful about it, if you use dilute acid, you'll be able to neutralize the alkoxide without necessarily affecting the ketal. You might want to do this in some circumstances if you wanted to perform yet another reaction that you need to hide the carbonyl from. Eventually, once you're done, then water and acid will get rid of the ketal, and we can get our product. Thinking of synthesis, let me just go back and highlight the new carbon-carbon bond, and notice that where the new carbon-carbon bond is, if you didn't know the reagents it came from, one or the other two positions of that bond had to have been the carbonyl, because the alcohol forms right where the carbonyl gets pushed open, so in the product, one of those two positions has to be the alcohol. That last step, that's the deprotect step.

There is one more functional group I want to show you, a protecting group for alcohols. There's several classes of protecting groups. The first protecting group of alcohols I want to show you is called dihydropyran (DHP). The molecule furan [is] a five-membered ring that had two double bonds in it; pyran is a six-membered ring that has two double bonds in it. If we were to partially hydrogenate it, then the common name for this molecule is dihydropyran, which means add two hydrogens. This molecule readily reacts with alcohols, almost even without an acid catalyst, although one is usually thrown in. Let's see how an alcohol would react with this DHP. It essentially would be regular old Markovnikov addition to the alkene, where the alcohol is the nucleophile that gets added in. I should take that Markovnikov back, because with the oxygen being in this ring, you potentially could have behavior that doesn't match Markovnikov. Why? Once the alkene reacts with H+, which is what it would do first, you're going to form a carbocation. Even if the lower carbon, the way I've drawn this structure, had another methyl group on there, so we made a tertiary position, not where the cation's going to go. It's always going to go to where the oxygen is. Why? Because as soon as you do, that positive charge gets delocalized. That resonance stabilization is a whole lot more important that just hyperconjugation; this is real conjugation. That stabilizes it even more than a tertiary position would, so it's always going to go to this oxygen. Let's say we wanted to through an alcohol at [the carbocation]. Same type of situation, where I'm going to use a difunctional molecule, because as you'll see in a moment, I want to do a Grignard reaction. The alcohol's going to attack where the carbocation is. Whether you attack the carbocation directly or whether I delocalize like I have now, it's really the same thing. That adds in. We temporarily have the oxonium ion that deprotonates, and we end up with the product, which after you draw it once, you can abbreviate.

If I circled this portion of the structure, what type of functional group would you call that? It's an ether, because you've got an oxygen that has carbons on either side of it. What kind of ether is this specifically? Notice that during the course of the reaction we've effectively gotten rid of that other double bond [in DHP], so we can call that portion of it tetrahydropyran, so this is known as a tetrahydropyranyl (THP) ether, which can be abbreviated like this. If we wanted to do a Grignard reaction, why might we protect an alcohol like this? What would happen if we took that difunctional molecule without the protecting group and tried to react it with something like propyl magnesium bromide; what would be the one and only product that would result if you have one equivalent of both of those molecules? You'll get an alkoxide. Why? Because pKa of an alcohol is somewhere between 16 and 18; pKa of an alkane is somewhere between 50 and 60.

Even before the carbonyl can be attacked, you're going to get an almost instant acid-base reaction. It's generally the case that acid-base reactions are the fastest reactions that are going to happen in solution. Deprotonation will occur, forming an alkoxide; because we had propylmagnesium bromide, the product's going to be propane. A Grignard reaction cannot take place in the present of protic molecules because otherwise a more rapid acid-base reaction will occur. That's why we would need, in this example, to protect the alcohol if we really wanted to attack the carbonyl – at least if we wanted to do this cleanly. It is true that it's possible, sometimes, to force what we want to have happen anyways if we just throw a whole bunch of excess Grignard. One could imagine that after you deprotonate that alcohol, there's no more alcohol to worry about, so any more Grignard reagent you throw at it should go to that carbonyl. It can work sometimes, but I want to show a clean technique, because what if your Grignard reagent was $1000 a gram? Then maybe you wouldn't want to throw it around quick so willy nilly.

We're going to do a protection. Start with that difunctional molecule, react it with DHP. DHP turns this into the THP ether. It's an ether, so it's not a leaving group. Now we could throw a Grignard reagent at it: let's say that I threw that same propylmagnesium bromide I wanted to use. The reaction now will be successful. Of course, initially I end up with an alkoxide. At this point I could use just a strong acid source and knock off the THP at the same time I'm going to do protonation, but I'm going to show you step-by-step in case you needed to do that. So first, dilute acid to make that. [Earlier] I circled part of the molecule and you correctly identified that the molecule's ether; but what is it really? What functional group is this? How about an acetal. You've got two oxygens there, don't you? And they're both connected to a common carbon, and on that common carbon, there's a hydrogen. Aren't all those things exactly the description of what an acetal is? Of course. So if you threw water and acid at this, you're going to get a couple of cycles of protonate-open-attack-deprotonate, open the acetic, and release the alcohol. I'll show you what will result from this. The more easy thing to determine is that you will get the alcohol back, the one that was protected. What other by-product are you going to end up with? In an acetal or ketal, either one, the position where the two oxygens are connected, that always turns into a carbonyl when it decomposes. You're going to have a carbonyl at the end of the molecule; there's a hydrogen there, which means we have an aldehyde. Count carbons, there are 5, to which [at the end] is connected an alcohol. That is the other product that is spit of; its a by-product, we don't care about it.

To review, I showed you that you can't do a Grignard reaction with an alcohol around, cause you'll just have neutralization. The clean way to this reaction is protect the alcohol. DHP, that's the protect step. Once you're protected, you do the Grignard reaction, work it up, and then you can deprotect.

Cationic reactions involving nitrogen

Let's do just a tiny bit of nomenclature – the nomenclature of primary amines. This is a three-carbon compound. It would normally be propane. The standardized functional group ending for amine is, amine. Take propane, stick an amine on it, and you get propanamine. If you had something that was cyclic, cyclohexanamine. [naming carbonyls not on parent chain?] This is for primary amines the way that we do this nomenclature. What is a primary amine? For oxygen functional groups, the reactivity of that functional group depends much more on the fact that it's oxygen, or after that, it depends on how many carbons are attached to the thing that the oxygen is attached to. For nitrogen, its chemistry is a bit different. Nitrogen is really influenced by how many carbons are attached to the nitrogen, not how many carbons are attached to the thing that nitrogen is attached to. A primary amine is this: where you just have one alkyl group on the nitrogen. A secondary amine is where instead you have two groups on the nitrogen. Tertiary, three groups. Then, nitrogen, because it's a base – ammonium has a pKa of 9.25, which means ammonia has a pKa of 4.75, which means it's as basic as acetic acid is acidic. It's a base, which means, potentially, if I had an alkyl halide that that tertiary amine can do an Sn2 reaction, so we could end up with this, which is known as a quaternary ammonium salt. Amines, because they're basic, aren't good nucleophiles in Sn2 reactions, because once you put one alkyl group on, it gets more basic, so it's easier to put the next group on, which means it gets more basic, which means it's even easier to put the last one one. There's our primary, secondary, and tertiary amines. Let's start with a primary amine and see how it reacts with an aldehyde or ketone.

Why am I mentioning the fact that amines are bases? The ideal pH for the reaction I'm about to show you is pH 5 – neither that acidic but certainly not basic at all. Why does it not work well if you go below pH 5, which means you go to more acidic conditions? Why would amines in general not perform the way that you'd expect them if you put them in acidic conditions? They're basis. If you put an amine in acidic medium, it's a base; if it was around HCl, then you'd end up with a salt. [reference to salts of medications] Nitrogen is nucleophilic if it's a base; as soon as it gets protonated, can a protonated amine be a nucleophile? What does nucleophile mean? Seeks positive charge. If you've already got a positive charge, it isn't going to look for another one. Point of all of this is that we're going to be trying to attack the carbonyl. The reason this mechanism's a little different is because nitrogen's a base, so we can show it attacking the carbonyl, even without the carbonyl being protonated. However, the carbonyl needs to get protonated, or the reaction won't continue past that point; that's why we can't do this in a basic environment; we need a little bit of acid around. The ideal pH for the following reaction is pH 5.

A Grignard reaction, which we were doing in the context of protecting groups – is a Grignard reaction reversible? No. A Grignard reagent has a conjugate acid that has pKa of about 50 or 60. Once it attacks a carbonyl and pushes the carbonyl open, you have an alkoxide, whose conjugate acid has a pKa of 16 to 18.

Rounding the numbers off, 60 versus 20 – really strong base; not anywhere near as strong a base. So you're going from strong base to weak base, that's favorable. Reverse Grignard reaction would be from weak base to strong base; doesn't want to happen. An alkoxide cannot kick [normally] a carbon-carbon bond open.

Let's see that reaction of a primary amine and a ketone. The one difference – it's not the normal protonate-open-attack-deprotonate cycle – usually the reactions shown this way: attack the carbonyl first, because a nitrogen is nucleophilic. Notice that although this looks like a base reaction, this is reversible. After that initial attack, we're going to have two events occur: we made an ammonium salt which is going to get deprotonated, and we have an alkoxide which is going to get protonated. Which is probably going to happen first: is the deprotonation or the protonation going to happen first? The answer is yes – what I really mean is it doesn't matter; one happens, the other happens. [It's important to note that it is not simultaneous] cause it's very unlikely for both of those things to happen at once. I'll show the protonation happening first. Since this is pH 5, it's stil ok to use H+; [remember] that no H+ exists in base, and not OH– exists in acid, so be careful of mixing conditions. But this is acidic, so it's ok to use H+. After the alkoxide get's protonated, then we have the deprotonation of the ammonium. At this point, we're half way there. Just like when you're halfway to a ketal or an acetal there's a special name for that intermediate, the name for this one is carbinolamine; it's got an alcoholish name in it and then the amine name in it at the same time. Just like in the hemiacetal and hemiketal cases, this normally is not isolatable, it normally will keep on going or it will revert back to where we came from. Shouldn't the nitrogen get protonated before oxygen since nitrogen is more basic than oxygen? Yeah, but then you really would just be going in the reverse reaction, and if you force these reaction conditions – if you remove water, for example, you will continue forward in the reaction.

Oxygen gets protonated, that water opens up and leaves. We do have an attack, but here's where the reaction's different form using alcohols. When we used alcohols (or water), right at this point, a second alcohol would come in to attack. But, intramolecular processes are usually more rapid than intermolecular processes; something going on within the molecule is often faster than between two molecules, especially in this case that I'm about to show you because this is nothing more than resonance. That resonance with oxygen, in the equivalent point of the mechanism, would not be favorable, because if you could picture it, you'd end up with an oxygen that's got a double bond to one carbon, a single bond to another carbon. You can't keep both of them at the same time because you'd have a positive charged oxygen, so oxygen would never want to make this resonance structure and stay this way. But for nitrogen, when that resonance structure occurs, there's a hydrogen which can easily deprotonate. When it does, we end up with a neutral molecule, which can be perfectly isolated. This is called an imine. Imine is whenever you have a carbon-nitrogen double bond.

That's an imine, that's what we get from a primary amine; how about we see what happens with a secondary amine? Same substrate I'll use: butan-2-one. I'm going to skip part of the mechanism because it's identical. I'll get to the same halfway point, the carbinolamine. If we review the mechanism for the first part, you'd recognize that, overall what happens, the carbonyl opens up and you add a hydrogen to oxygen, the nitrogen adds in, you lose a hydrogen from nitrogen. Let's continue from there. The next thing would be for the alcohol to get protonated; water leaves; and now we've got an issue: now we've got a nitrogen that would be in the same situation as oxygen would be, meaning that if we allowed the resonance structure to occurs, we're going to end up with something that has a positive charge on nitrogen that can't be relieved in any way. This kind of intermediate is normally not isolatable. It's not favorable because – yes, nitrogen can handle having a positive charge, but we have a carbon-nitrogen double bond that, in response to that positive charged, could open; that's why something else happens instead. The something else that happens is that a base, which could be another molecule of that amine, can come alone, pull a hydrogen off, and cause elimination. We get not a carbon-nitrogen double bond, but a carbon-carbon double bond next to the nitrogen. [When we saw an alcohol on an alkene], what do we call that functional group? An enol. Now that we have an amine instead of an alcohol, what do you think this is probably called? An enamine. [customizable M&Ms] Why didn't this enamine form with a primary amine? [Out of time.]

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DHP – dihydropyran

Grignard reactions cannot occur in the presence of protic molecules as an acid/base rxn will occur more rapidly 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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Structures

Identical to those from lecture 7A (02/03/12)