

Lecture 11B • 02/10/12

Protecting groups

Silyl ether protecting group. Silyl ethers are called that because, instead of an oxygen having a carbon on both sides of it, as we have in a regular ether, there's a carbon and a silicon in it. [A common version of this protecting group] is TMS; you had the compound tetramethylsilane, but that's not really that reactive. We're going to use the compound trimethylsilyl chloride. You might look at that and say: how is that going to be reactive, because if that reacts like carbon, that's a tertiary silicon, is it really going to want to react? It is in the same column as carbon, so maybe it has some of the same reactivity as carbon. Silicon compounds are a little bit different in a couple of ways. The silicon atom is large enough where the problem of steric hinderance doesn't really exist, at least not in the same degree, so this compound can react. Also, the silicon-chlorine bond, it happens to be reactive enough that you can use a neutral alcohol to react with it instead of having to have an alkoxide like we normally would do in a S_N2 reaction. This, although it's tertiary silicon, it doesn't matter. This is an S_N2 -style process. After the attack, there's a deprotonation. Notice that it's an ether, except that one atom versus the other is silicon, so that's why it's called a silyl ether. Specifically, this is the trimethylsilyl ether, which can be abbreviated TMS. It is a very widely used protecting group, but it has one drawback, which is that in mildly acidic conditions – or even basic conditions if you've got water around – it easily hydrolyzes. As long as you're keeping it in a rigorously water-free environment, it's perfectly good, but of course a lot of work-up steps involve water, so it just makes handling of the reagent a bit tricky.

I'm going to show you something that chemistry-wise is identical, but it's a more robust, it's a tougher protecting group – survives water solutions much better; that is the tert-butyldimethylsilyl protecting group, or TBDMS for short. Because of the increased steric hinderance – it turns out that steric hinderance is not totally unimportant, it just doesn't affect silicon as much as it does carbon. By putting a bulkier group on it, you do slow down the reactivity of that silyl center. I'll simplify and say this: increased steric hinderance help prevent hydrolysis, which means reaction with water. Same type of process – if you take TBDMS chloride, tert-butyldimethylsilyl chloride, and react it with an alcohol, same S_N2 -style mechanism. Since I showed the full structure of the reagent, I'm going to go ahead and abbreviate the product. [TBS/TDS?]

How do we use this? Silyl ethers are sensitive to acid, but resilient against bases, meaning that they're not as likely to react against bases. In fact, we therefore can use this in the same way that we use the DHP ether. We could use this if we wanted to protect an alcohol that was on the same molecule that we wanted to make a Grignard reagent from. Remember that Grignard reagents are terribly basic. If you had an alcohol on the same molecule, they'd self-neutralize; the reaction would be over. The example I'll use: to take a halogenated alcohol – notice that this is one in which the bromide and alcohol groups are not right next door to each other. [bromohydrin] Let's say that we wanted to turn that into a Grignard reagent. At the moment, we can't, because even if the reaction happened, it's going to destroy itself. But what if we protected that alcohol? We could put TBDMS chloride, which will make the silyl ether. We now could react it with magnesium or ether in THF and make the Grignard reagent. I'll choose a random aldehyde for it to attack. We'll form a new carbon-carbon bond and form an alkoxide at that position where the new bond formed. If I had three carbons in my halogenated alcohol and two carbons in my aldehyde, I better make sure I count carbons properly in the product and make sure that I have five. I'm going to draw one more line here, though, to show that at the end of the molecule, we still have a TBDMS ether.

Now, if I use gentle or dilute H^+ – that's the advantage of TBDMS, it can withstand those mildly acidic conditions. The reason I point that out is that we now have produced an alcohol, which is in addition to the alcohol that we started with. If I used strong acid, I could have gone ahead and popped off the protecting group, but then I'd have two alcohols. What if this alcohol I just made is one I that I wanted to continue doing the reaction with? I still have this group to protect it. By being able to gently acidify the solution, I can get the alcohol out and continue reacting with it. Or, what if I wanted to protect this alcohol that I just made? I could use DHP, put a different protect group on here. Why does that matter? Cause it turns out that you could target the TBDMS group and knock it off in non-acidic conditions, using this molecule TBAF; TBAF is tetrabutylammonium fluoride, which is exactly one of those quaternary ammonium salts. It's a non-acidic way of knocking off that protecting group. The reason that matters is because DHP won't come off under these conditions. So you could have one alcohol you protect with DHP to make the THP ether; a different alcohol you protect with a silyl ether; you could knock one versus the other off, makes for some really sophisticated synthesis. In this example, all I'm doing is showing that they can separate a gentle protonation versus removal of the TBDMS group. This is just another protecting group for alcohols.

Formation of cyanohydrins

You can take a ketone, react it with hydrogen cyanide, and it makes a molecule that's got both an $-OH$ group and a cyanide. A cyanohydrin is kinda a cyanide equivalent of a bromohydrin, except that this is on the same carbon. We're going to use this when we make derivatives of sugars.

Silyl ethers

SiH_4 – silane

Silyl ethers are sensitive to acid but resilient against bases

Cyanohydrin

Structures

Identical to those from lecture 10A (02/10/12)