

Lab 5B • 02/03/12

The reaction that we're beginning today is the Wittig reaction. It is one of two main carbon-carbon bond-forming reactions that you're going to learn this quarter. There's a major difference between the two reactions: the Grignard reaction produces an alcohol, but from an alcohol, we then convert that into an alkene; sometimes a Grignard can be used in combination with an elimination reaction or dehydration to add to a carbon chain through a carbonyl but end up with an alkene. Because it involves elimination or dehydration, there's some regiochemical concerns that might be there. The Wittig reaction is a very specific reaction that forms a carbon-carbon double bond; it forms it only in the place where the carbonyl originates. In terms of regiochemistry, it's a much more specific reaction, although there might be some stereochemical concerns.

Starting with a ketone or aldehyde, I could react this with an organometallic reagent, which the classic reagent used in Grignard reactions is an alkylmagnesium halide. That ends up acting as if it was an anion, so this would effectively be a methyl anion. That methyl anion will attack the carbonyl carbon, pushing that open, making an alkoxide, which after acid work-up would then give us the alcohol – at least if we did a gentle acid work up. Because, if we did use heat in the presence of acid, we could cause a dehydration reaction. Notice the product that I've shown – since it's a reaction that involves heat, it's thermodynamics that are going to control the product that ends up getting formed. The more substituents, the more alkyl groups we have on the alkene, the more stable the compound is. You might recall from last quarter there's a way to influence the regiochemistry of where this double bond ends up, there's a way to make this not form to the more favorable position, to make something that's not the thermodynamically most stable product. To do that, we end up making it difficult for the elimination to occur. In other words, if I were to take this same alcohol that we just formed above, turn it into a leaving group – for example, by using tosyl chloride – then I could do an elimination if I used potassium t-butoxide. There's enough steric hinderance from the base itself that it makes it more difficult for the base to approach the compound and react, particularly if we were to drop the temperature. At lower temperatures, only those reactions that have lower activation energies, lower barriers to reaction, are going to be the ones that are likely to occur. You could imagine that that bulky base there – it's kind deceptive the way I write it, that little cross sign makes it look kinda like a compact molecule, but if you actually build a molecular model for that and saw all of the hydrogens, if you actually had space-filling models, you'd see that there's a lot of shielding in the way there – that base would more easily approach a primary position than going for the tertiary hydrogen. Yes, if you removed that tertiary hydrogen, it makes a more substituted alkene, but, you can make it where kinetics has the greater control.

The type of elimination that we saw first, when we dehydrated, that made the thermodynamic product; that form of elimination is often referred to as Zaitsev elimination. It's the situation where you make the most substituted alkene because that has the most substitution with the surrounding substituents, which stabilizes the pi bond, which makes it a more favorable compound. This other product, this would be the kinetic product; you could call it anti-Zaitsev, but this is also sometimes called Hoffmann elimination. At low temperature, only those reactions with lower activation barriers are going to be more favorable. This is true even if the products that result are not the most thermodynamically favorable. When a large, bulky base is used in eliminations, the steric hinderance cause by that base can result in the formation of a less-substituted alkene.

In this particular example, we were able to end up with a specific product that had a terminal alkene. Notice that these is a bit of symmetry to this molecule because I've got two methyl groups after the Grignard reaction attacked to a common carbon, so elimination, if it wasn't going to be to the interior, if it went to either of the methyl groups, you're going to get exactly the same product out. We could imagine that you have a situation where elimination might make potentially three different products, so there may be situations where it might be difficult by just elimination to arrive at just one product. That's where the Wittig reaction comes in, because the Wittig reaction only happens in one specific place, where the carbonyl is. Other than making the reagent itself, it's otherwise a one-step process.

Wittig reaction – There's a reagent involved that has multiple benzene rings in it. It gets really inconvenient to have to draw the full structure out. When benzene is treated as a substituent, it has the name phenyl. Phenyl group, when you're writing it, is very frequently abbreviated Ph, which is even further abbreviated by using the Greek letter phi. The reagent that's involved here that we use to make a Wittig reagent is triphenylphosphine. Phosphorus being lower than nitrogen on the periodic table is even more nucleophilic than nitrogen, because phosphorus is a squishier atom (that's our official scientific term for it) – squishier meaning that electron density can be more easily displaced, which means it more easily begins the process of bond formation. So even though phosphorus may not be as basic as nitrogen, it's more nucleophilic, so this undergoes a very easy $\text{Sn}2$ reaction to make a type of intermediate called a tetraalkylphosphonium salt. The reason that we're not doing this reaction – besides the fact that it's just one more reaction step we have to do – is triphenylphosphine is a neurotoxin. [commentary on lab cleanliness] After this, there is a deprotonation step that we perform. n-Butyllithium. 'n' in this case means normal, which means unbranched, a regular straight chain. n-Butyllithium would be this compound – acts much like a Grignard reagent. Like a Grignard reagent, this acts very much like an anion, and carbanions are hella basic. [story of hella and Cartman from South Park] If we have something like this salt, this compound is relatively easy to deprotonate. Why? Easier than a regular alkane because you've got a positive charge right next door. Even though this might not be the most electronegative element that there is, because we've got a positive charge, makes it a little easier for a neighboring negative charge to form.

I say a little bit easier because we are still using this awfully strong base to deprotonate. [reason for not performing reaction in lab]

The intermediate that's formed is an interesting critter. If you're following the octet rule, we would have to write this compound as a double ion. There's two terms we could use to refer to this kind of compound. A more general term that usually comes up when we're talking about amino acids is the term zwitterion, which means twin ion. The reason that this comes up with amino acids is that it's a difunctional molecule, it's what makes up proteins through amide connections. An amino acid has an amino group, which is a nitrogen group which is a base, and an acid, a carboxylic acid, which is acidic. Even if you just had a solution of an amino acid and nothing else, it could react with its own self, because it's got both acidic and basic functionality. If that were to happen, the base would get protonated, the acid would get deprotonated, you'd get a negative charge and a positive charge on the same molecule, and that's why it's called a zwitterion. This is an even more particular kind because in this case you have the positive and negative charges right next door to each other. Many times when you're talking about a carbocation, you'll refer to it with an -yl ending, like we might say methyl carbocation or benzyl carbocation. Many compounds that have negative charge, you have the ending -ide – think chloride, bromide, oxide, nitride. These kinds of compounds are often called ylides – positive/negative, right next door to each other. Phosphorus, because it's on the third row of the periodic table, is able to violate the octet rule. That's because of some complicated orbital interaction; in Chem 1 we often lie and say it has something to do with d orbitals, but it's not really quite that simple. The point is, we could write this as a different resonance form where we explicitly show a double bond. These two structures really are the same thing, since this is just resonance, so it doesn't really matter which one of these structure we use, sometimes it's just shown to highlight the fact that this is a somewhat delocalized ion.

What happens next? Because all we've done so far is make the Wittig reagent. Throw it at a ketone or an aldehyde, that'll react with the carbonyl. If you have a negatively-charged carbon, then that's going to be pretty attracted to the carbonyl. As soon as that attack occurs, they're not literally next door to each other, they're not neighboring by some bond connection, but in space, we end up with a positive and negative charge that are very very close to each other. Although a four-membered ring is not necessarily normally favorable, it's going to happen in this case.

There's this naming system [insert name here] that's very often used when describing what are known as heterocycles. Hydrocarbons are compounds with just hydrogen and carbon. Then there's the other atoms that functionalize hydrocarbons – oxygen, nitrogen, and so forth – that we call heteroatoms, because they're different than what's in a plain old hydrocarbon. By extension, a heterocycle is a cyclic compound in which one of the members of the ring itself has been substituted with something besides carbon; that's what we have in this case. In this nomenclature system, the prefixes or the names don't have any number terms; it's just different letters that are thrown in. There is some pattern to it. There reason for telling that long story is this does have an intermediate the name of which is oxaphosphetane, which means: a four-membered ring in which an oxygen and a phosphorus is substituted; oxa- for oxygen; phospho- for phosphorus; the -etane means four-membered ring. This oxaphosphetane is unstable and rapidly decomposes. One of the products that comes out is triphenylphosphine oxide, which is a very thermodynamically favorable product, favorable meaning there must be some release of energy to make it make it which is what drives this reaction. It is, like the borane reaction, one of the fee four-centered transition states that you'll see. It's a cyclic reaction. The two products that you get out are this triphenylphosphine oxide, which can be a pain to get rid of, but the other thing we get out is an alkene. Notice that that alkene is exactly the orientation that we made earlier by doing a Grignard reaction followed by converting it into a leaving group followed by a careful elimination. In this case, we just make the Wittig reagent, throw it in a ketone, and we're done. That is the synthetic advantage of a Wittig reaction.

[lab procedure][common names – phenyl, benzyl, vinyl, allyl, aspartyl, crotyl]

You start out with triphenylphosphonium bromide, which has an unusually acid proton due to resonance stabilization. [The pKa of this salt is close enough to the pKa of water that] a strong, concentrated solution of hydroxide and heat and time, you're able to perform this deprotonation. It is that delocalization that makes that position moderately more acidic. You gotta be careful when you write your intermediates, because in Wittig reactions, it's very easy to accidentally leave out a carbon.

[mechanism for lab]

What the stereochemistry of the two benzene rings? Depending on how the reaction occurs, once locked in the ring like this, maybe the two benzene rings are cis with each other, both either wedges or both dashes; or, they could have been locked into the ring in such a way where one was a wedge, one was a dash. There'd be enantiomers in both cases, but once this compound forms, once the Wittig reaction's over with, we're going to have a double bond there anyway, so we won't have stereocenters, but [story of student who slept in]. Once we do this formation of the double bond, there's going to be two products that result. If both of the benzene rings had been cis to each other, then you'd end up with a cis double bond; if the two benzene rings had originally been trans with each other, the configuration of the double bond would also have been trans.

[lab procedure]

At low temperatures, only those reactions with lower activation barriers will tend to predominate, even if the products that result are not the most thermodynamically favorable. When a large, bulky base is used in eliminations, the steric hinderance of that base can cause the formation of a less substitutes alkene.

Wittig

zwitterion – “twin ion”

NaHSO₃ wash → to reduce triphenylphosphine oxide (byproduct)

Structures

Identical to those from lab 6A (02/01/12)