

## Lecture 13B • 05/11/12

The Curtius rearrangement involves an acyl azide, which in turn we can make by reacting an acyl halide with sodium azide. [I've shown azide as a balanced structure – nitrogen double-bonded to nitrogen double-bonded to nitrogen. I'm going to write a different form of structure here that accentuates its reactivity, because nitrogen gas is an excellent leaving group. Any time nitrogen can be expelled somehow, it likes to, cause it's so thermodynamically favorable a product. [diazomethane] Acyl azides or azides in general can be kinda a handful to handle, but as long as this is done carefully, since this is such an excellent leaving group, it causes this unusual step to occur. We've something like this before in the borane reaction, where we have an alkyl shift occur due to a very specific thermodynamic situation. Nitrogen's so favorable to be expelled here that that's why this R group can just shift over. Realize that that R group is shifting with the pair of electrons it's connected with, so that technically would leave a positive charge on the carbonyl – which since we have a negative charge on that nitrogen, at the same time the shift occurs, which causes nitrogen to be expelled, we show another arrow coming back to make a double bond with the carbon. What we end up producing is a functional group you haven't seen before known as an isocyanate. An isocyanate, in this particular rearrangement, theoretically can be isolated, but they are awfully reactive, so instead of trying to isolate them, you often just add the next reagent. Depending on what reagent we add, we can end up with different functional groups. I'm going to limit the discussion to just reacting with water, since we're supposed to be learning ways to make amines.

If I had a little bit of acid and water, what do you think is going to happen to this compound? If had just neutral water and if it was able to react by itself, which of these atoms – nitrogen, carbon, or oxygen – would you expect water to attack? Which of the three atoms is the least electronegative? Carbon. Carbon's less electronegative than either nitrogen or oxygen, which means carbon has the delta positive on it. As far as which atom would want to be attacked just by water? Carbon does. If it attacks the carbon, it's got double bonds – one or the other of them needs to open up. Which one is it going to be? If we had the oxygen open up, wouldn't we be making the equivalent of an enolate, which we already know is thermodynamically unfavorable. Even though, if we tried to push a negative charge all by itself, if we pushed it to the nitrogen it would appear to make something that's unfavorable, but a nitrogen with a negative that is conjugated with this carbonyl is actually not as unfavorable. If I tried to open the carbon-oxygen double bond, it's just going to close up again. If I say acidic conditions, there's another way you can rationalize this: nitrogen should be more basic than oxygen, so nitrogen gets protonated first, water attacks, pushes open, and you'll see what we get momentarily. First, nitrogen gets protonated, water can attack the carbon, and because water was initially neutral, we need to deprotonate.

What functional group did we just make? A carboxylic acid, but a special kind, though, one with a nitrogen on the other side – it's a carbamic acid, which is thermodynamically unstable. Not worrying about the mechanism, it loses carbon dioxide to make an amine. This is the point of this rearrangement: we're trying to make an amine. Notice on really important point: the starting material had an R group with a carbonyl and then the halide, but the product doesn't have that carbonyl, doesn't have that carbonyl carbon – one less carbon in the product than the starting material. The isocyanate, in theory, could be isolated. The next reaction I'm going to show you is very, very similar to this one, but it has two main differences; one of them is whether or not the isocyanate can be isolated. If it is not isolated, we still have a choice of what reagent we throw at it next; we have the choice of how to decompose that isocyanate.

Let's look at this other rearrangement, which is the Hofmann rearrangement. Instead of an acyl azide, it uses an amide as its starting source. Normally, if we had sodium hydroxide and heat and allowed these to react for a while, we would have what? What would this product be if this is the set of reagents? A carboxylic acid, because what kind of reaction is this? Technically, this would make the salt, cause we've saponified by haven't added H+. But yes, it would then be saponification. But what if we didn't have just the sodium hydroxide; what if we threw bromine at it as well? What reaction have we seen already that has this set of reagents? The haloform reaction. What would the haloform reaction conditions do to an amide, though? Notice how I have not written out the hydrogen on the lefthand side of the carbonyl – in other words, I have not written out the alpha hydrogen on carbon. Why? Cause it's less acidic than the hydrogen on nitrogen. Why? Cause of the special reactivity of nitrogen, the ability of those lone pairs to particularly well delocalize. The first step of this reaction is going to make what looks like an enolate. We could then have attack on the bromine, which means we'll remake the amide, but it'll be N-substituted, just like we saw in nomenclature, this idea of using N to designate the point of substitution. But, from the haloform reaction, what do we know about this remaining hydrogen on the nitrogen? It's more acidic than the hydrogen that we started with – in the haloform reaction, because we need to make the negative charge to do the attack, anything that stabilizes that negative charge helps the reaction along. Bromine, being an electronegative element, pulls electron density away from the nitrogen, makes the negative charge easier to form. In other words, if you do the reaction once, it automatically is going to try to happen a second time. This first hydrogen, let me make this point: the hydrogen on the nitrogen is more acidic than the alpha hydrogen on the carbon; and, this intermediate that we just made, that hydrogen is more acidic than the first hydrogen, due to induction.

Hydroxide removes the second proton, which, for a very specific reason, I won't show the formation of the enolate-like ion. Look at this intermediate that we just made, particularly the part that I'm going to put in a box here. We have a nitrogen that's negatively-charged adjacent to a carbonyl, also adjacent to a leaving group. Go back up to the first reaction – notice in that first reaction, we have the same thing: negatively-charged nitrogen with a leaving group attached that was adjacent to a carbonyl.

The same thing that happened in this first reaction, where an alkyl shift occurs, kicking out the leaving group, the same thing happens down here below; that's why these reactions are almost always [presented] at the same time. Even though they have different starting materials, their mechanisms, at some point, [are] identical. So, R group shifts over, bromine kicked out as a leaving group, a carbon-nitrogen double bond forming as a response – which means we again make the isocyanate. But, since we're already in a solution with hydroxide, we can't isolate it, cause it's going to react with the hydroxide as soon as it forms.

The first reaction, all we had was the acyl azide, which itself spontaneously decomposed; here, we do have a compound that, yes, decomposes, but because of the reaction with sodium hydroxide and bromine. Hydroxide continues the reaction. Similar logic as the reaction up above: carbon is going to be the more delta-positive because it's got these two more electronegative elements attached to it. Yes, we have a choice of which bond we want to open; it turns out the carbon-oxygen bond is the one more favorable to be maintained, we're going to push the carbon-nitrogen double bond open. We have two choices here: since we have hydroxide, we could show water being the source of a hydrogen for this intermediate, or, notice that once that gets protonated, we have carbamic acid, which is an acid – which means that, since you're still in basic conditions, it's going to get deprotonated. In these kinds of compounds that would be thermodynamically unstable as the acid, if they're the salt, they're not unstable. The bicarbonate ion is, of course, very isolatable, but it has the same type of motif – two heteroatoms on either side of the carbonyl. But, because only one of them has a hydrogen [and] the other one has a negative charge, that compound's stable. Here, though, once we add a little bit of acid, then we'll have decarboxylation, which gives us the amine. For review, we could see that, just like in the previous rearrangement, we start out with a compound that has a carbonyl in it, which means it has one more carbon in it than the product that we've made. This would be the answer to the question: why do we need this rearrangement if we could just reduce an amide. What if you had a really tricky amide to make, where you have one more carbon, if that happens to easier [in terms of obtaining a reactant], you could synthesize it, do this rearrangement, and get a target amine that otherwise might be difficult to make. It's just one more tool, one more way that we have, potentially, to make an amine.

Let's say that I give you a particular amine and I ask you all the different ways you know to synthesize it. If we were reducing an amide, we'd take a compound with the same number of carbons, and then we could use lithium aluminum hydride on it; or, we start out with an amide that has one more carbon in it, we try the equivalent of the haloform reaction and then work it up with acid. As we just saw, it's going to cause the loss of a carbon. We started out with one more carbon to get the product that we want. Of course, these are only two methods. You could, of course, start with an alkyl halide and go several directions: you could use cyanide, which you then reduce. Oh no – you can't use cyanide, not with this particular alkyl halide; why? Cause the starting material would have two carbons; the product would have three, other than the benzene ring. So, if we wanted to do this reaction, then we need one less carbon in it. We could take the appropriate-sized alkyl halide, react it with sodium azide, and then reduce it; the azide doesn't add carbon, it just adds the nitrogen. We could take an imine and explicitly reduce it. Or, we could take an aldehyde, and do reductive amination on it. Ammonium acts to make an imine; at the same time, we have hydrogen there that hydrogenates it, in this case, that automatically means it reduces it as well. [time efficiency]

Just like the benzene has an influence on the nitrogen's basicity – it lowers it – the nitrogen has a huge effect on the benzene ring. Is this an ortho/para- or a meta-director? It's an ortho/para-director, and it's a huge one, because this nitrogen so successfully delocalizes. If the nitrogen's delocalizing, pushing electron density onto the benzene ring, then that makes electrophilic aromatic substitution really super-duper favorable. It's so good, in fact, that you might be able to get away to do an alkylation without adding a Lewis acid. If you want to ensure that it happens, we'll add the Lewis acid. [ignore ortho versus para] Notice I didn't put an alkyl group on the nitrogen; why [not]? I have an alkyl halide; couldn't we have Sn2? There's two answers to that point: one, nitrogen's not very basic. What's the pKa of the conjugate of aniline, the anilinium ion? The average pKa of the conjugate of a non-aromatic amine is somewhere between 9 and 11. What was the conjugate pKa of aniline itself? 4 to 5. What about pyrrole? [something negative] If we have aniline with a pKa of the conjugate of about 4, that means the pKb of aniline itself is 10, which means it's a really weak base. Weak bases [normally] don't make good nucleophiles, so it doesn't do Sn2 really easily. Beyond all that, if you have aluminum trichloride, that's a strong Lewis acid; it'll react with the methyl iodide before the amine has a chance to. Put all those things together, that's why I put the alkyl group on the benzene ring and not the nitrogen.

That's not even the main point of the story right now. Is an alkyl group an deactivator? It's an activator; why? Hyperconjugation – it's able to put electron density on the benzene ring by hyperconjugation, which means the product is more reactive than the starting material. Since aniline is so reactive already, if you make it even more reactive, it just keeps going and going and going. The nitrogen in aniline is by far the most activating thing on the ring, which makes it the ortho/para director to put the alkyl groups relative to it in all of the ortho and para positions. Aniline is so reactive that multiple addition can occur during electrophilic aromatic substitution. It turns out that there's a way to prevent this. Let's focus on the amine. Even though it might not react in the presence of aluminum trichloride with an alkyl iodide, what about an acyl halide of some sort – especially if we don't add aluminum trichloride? If all I had was this acyl halide and the amine, what do those make? You make an amide – the nitrogen attacks the carbonyl, kicks out chloride, nitrogen gets deprotonated, that makes an amide. What do you think the carbonyl does to the nitrogen's ability to make the benzene ring activated? It's going to make it less active, because the carbonyl's pulling electron density away from the nitrogen.

The nitrogen's now conjugated with the carbonyl, not just the benzene, so it's enough less reactive that, if you did an electrophilic aromatic substitution reaction, it's only going to happen once now. Because of conjugation between the nitrogen and the carbonyl, [reverse] amides are less reactive ortho/para-directors. An amide, if you had the carbonyl next to the benzene ring, is a mega-deactivator, but we have the nitrogen, the electron-rich element, attached to the benzene ring, instead of the carbonyl, which is the electron-poor part of the structure. Amides are less reactive ortho/para-directors, therefore monosubstitution can occur.

React this with the same set of conditions: methyl iodide, for example, and aluminum trichloride. We'll still have the amide; we'll have put the alkyl group on now. If we saponify, we don't care what happens to the amide; instead, we focus on the fact that we're able to release the substituted amine – the substituted aniline, specifically. This is not exactly a protecting group; maybe that term could be used in this case because we are masking some of the reactivity of that nitrogen; it's better called an attenuating group, something that reduces reactivity. It is a common trick that's used so you can get just monosubstitution on aniline.

Diazo compounds – aryldiazonium salts

Aliphatic compounds are non-aromatic compounds; then we have aromatic compounds. [aliphatic halide – an alkyl halide, but one with out a benzene ring involved] We could say aryl halide, which means take some benzenoid compound at put a halogen on it. An aryldiazonium salt is this: you can take aniline and oxidize it with sodium nitrite. Nitrite, in general, can take an amine and turn it into one of these diazonium salts. Generally, those diazonium salts fall apart; diazomethane is one of those examples; in that case, it's just, normally, a methylating reagent. In other cases, if you have an alkyldiazonium [salt], you could have an elimination reaction to make an alkene. But with the benzene ring here, it stabilizes the compound enough that it could be, if not isolated, used to make a whole series of products. It's a rather random set of reagents that we could throw at this, including things like copper(I) chloride to make an alkyl halide – without having to use harsh conditions like aluminum tribromide or aluminum trichloride. Also, we're not worried where the substitution's going to occur; we can selectively put a halide where an amine used to be. Or, if we use phosphoric acid, we make the amine group go away, we get benzene back. [bromide, iodide, phenol] This type of reaction, in general, is known as the Sandmeyer reaction. All of these reactions are a two-step process: start with aniline, convert it into [a] diazonium salt by oxidizing with nitrite, and then react it with something else to get one of several functional groups.

What's the structure of glucose? From top to bottom, which side do I put the -OH groups? [right, left, right, right] What's going to happen if I put this into a solution of sodium hydroxide? If I put this into a solution of sodium hydroxide, what do you think might happen? There's no acid; we have an aldehyde, so we could make a hydrate, but hydrates aren't favorable, so it would just uniform. It could react with the -OH groups, but that's just transferring a proton from one negative oxygen to another, so that proton could just bounce back and forth. But this is an aldehyde, which means we could deprotonate its alpha position. I'm making the enolate – which means that that stereocenter is lost, because now it's sp<sup>2</sup>-hybridized, which means if we let it go backwards, if we let the proton hop back on again (remember we can't use H<sup>+</sup> because we're in basic conditions, so we have to show water being attacked), then we'll end up with two compounds: we'll, of course, get our original compound back, which is glucose, but because we lost this stereocenter before, that means we're going to get two possible products, cause both products are formed from the planar enolate. What is this other sugar formed? Mannose. [is this the red sugar or the blue sugar?]

---

Curtius rearrangement – acyl halide – The product has one less carbon in it than the starting material

In this rxn, the isocyanate can technically be isolated; even if it is not isolated, the reagent used to decompose it can be chosen.

Hoffman rearrangement – amide

Aniline – Aniline is so reactive that multiple addition can occur during electrophilic aromatic substitution.

Because of conjugation between the nitrogen & the C=O, amides are less reactive o,p-directors. ∴ Monosubstitution can occur

Aryldiazonium salts – Sandmeyer rxn

---

Structures – Identical to those from lecture 11A (05/09/12) and lecture 12A (05/11/12)