Lecture 13A • 05/11/12

Amines

[Sn2; Hofmann elimination; reduction of alkyl azides, amides, nitriles, imines; reductive amination; Gabriel synthesis]

Curtius and Hofmann rearrangements

Both of these, in principle, could start with acyl halides. The first of these reactions involves an acyl azide. We can get that by reacting sodium azide; just like hydroxide can attack this and kick out chlorine, azide could attack this and kick out chlorine. As the ion, it would make more sense for it to be symmetric, to have two double bonds, one on each side of the central nitrogen. This structure gives us a little more hint of its reactivity. If we look at that, we have nitrogen gas that's trapped here, and nitrogen gas is an extraordinarily good leaving group. Diazomethane is explosive because of this ability to release nitrogen; azides are also explosive in that sense. What can happen is a rearrangement, because of this azide, where we have an alkyl shift. We've seen something like this before in the borane reaction – there's a [curious] alkyl shift that occurs in that reaction as well, and it's also because, in that situation, there's a particularly good leaving group. If we move an alkyl group by itself over, taking the pair of electrons with it, we're going to leave a positive charge where the carbonyl would be. As a response, a resonance arrow we can write here showing the nitrogen, in return, making a double bond. Let me throw an R group in here so I can show the more general reaction. This will be attached to the nitrogen first, which is doubly bound to a carbon which is, in turn, doubly bound to an oxygen. This is a functional group known as an isocyanate. Normally, this isocyanate is not isolated.

There's a couple of variations of what could happen next. Since we're talking about synthesis of amines, what we would do next is allow this to react with water with just a trace of acid. If we had an isocyanate, what do you think's going to happen with acid and water? Which of these atoms would most likely react with the acid? The nitrogen, because nitrogen compounds, amines, they're bases. This is an imine, but that lone pair is not in conjugation with the double bond, so it can act on its own, so yes, it can get protonated. There a resonance step. If we have water in solution, it can then attack at the carbon, push[ing] that carbon-nitrogen double bond open. This is, in principle, reversible, although, in practice, it doesn't reverse. Of course, if we have water attacking, it's going to be protonated, the product, at first. Deprotonation occurs, and we end up with the product – or do we? What is this that I just made? What is it a derivative of? There's a small set of carboxylic acids that are thermodynamically unstable – carbonate, for example, decomposes. This is carbamic acid. Carbamic acid is like carbonate, except one side has a nitrogen. This is a substituted nitrogen, so it's a derivative of carbamic acid. If we didn't have the hydrogen here, this compound would be stable; if we had a negative charge on the oxygen instead, we could isolate it. Once you put the hydrogen on there, having so many atoms attached to a central carbon makes that carbon unstable. [story about berkeley, "where will you get that starting material"?] Bromomethanol doesn't exist, because like these other compounds, these single-carbon compounds, if you don't have the right kind of bonds, putting too many heteroatoms on it makes it unstable. Since we have the hydrogen, and since we're already under acidic conditions in this case, we lose carbon dioxide, which means what do we end up with? An amine. This is a way of taking a carboxylic acid, going through it's acyl halide, to eventually get to an amine. There's a variation of this – instead of throwing water at that isocyanate, you could throw an alcohol at it, which makes an ester. Esters don't have this problem, so they're carbamic acid esters that you could form. This is the Curtius rearrangement.

The next reaction's very, very similar [Hofmann rearrangement]. The next one is not an acyl halide; it's an amide. What do you think would happen if we took a solution of sodium hydroxide and bromine and reacted it with this molecule? Is sodium hydroxide really basic enough to deprotonate this molecule irreversibly? The pKa is [???], so hydroxide's not the best base, but it is an amide. Amides are very unreactive. Yes, saponification is an issue, but we have bromine here, so there's another reaction that could happen before the saponification. In amides, the alpha proton is the less-acidic proton; it's the proton on nitrogen itself that ends up being more acidic. Why? Because it lets you make the equivalent of an enolate with nitrogen involved instead. Think of alpha halogenation, like the haloform reaction. We're really doing the same thing, except the connection occurs through nitrogen, not through carbon. That's because the nitrogen's hydrogen is more acidic than the carbon's alpha proton. We have alpha halogenation, which gives us back a substituted, an N-bromo substituted amide. If we put one bromine on, what then happens? Makes the next hydrogen even easier to pull off, because of inductive effects, so we're going to remove this other proton as well. Hydroxide more easily takes off the second proton, so you can't stop it.

We've ended up with a negatively-charged nitrogen with bromine as a leaving group. In other words, the structure of this intermediate ... in the Hofmann rearrangement, we can see that there's a negatively-charged nitrogen that is expelling a leaving group; here's a negatively-charged nitrogen that therefore is going to expel a leaving group. [hellameter] We make that same isocyanate, which, because we're already in a solution of hydroxide, we can't prevent it from further reacting. Up top, the Curtius rearrangement, we get the isocyanate which could be isolated; many times it's not, but it could be – or, even if it's not, you can select what we use to decompose it. Here, there's already sodium hydroxide, so the only result is going to be making the imine. We could show an attack with hydroxide because with hydroxide, you can imagine that at some point there's water cause it's deprotonating. We do a basic attack on the isocyanate instead of acidic. It'll still push that nitrogen open.

Even if it pushed the carbonyl, it's eventually going to be the nitrogen that gets protonated. It will attack water, which [is] irreversible because nitrogen minus is really basic – not as bad if we've got the carbonyl here, but still. Technically, since we're still in hydroxide solution, it's going to neutralize the carbamic acid. Once we reacidify, it will cause that same decarboxylation, and we get an amine.

One synthetic note: if we could reduce an amide, why would we do this? Look at the number of carbons in the starting material – you have an R group and a carbonyl. Look at the product – you have an R group, no carbonyl: that means we've lost a carbon. If you have an amide and reduce it, you get an amine with the same number of carbons the amide had; if you use this rearrangement, then you get an amine, but with one less carbon. Compared to the starting material, the product will have one less carbon in it. Very similar to the first reaction, because we end up again with this key intermediate where a leaving group's being kicked out. The main difference is one's an acyl halide we start, one's an amide that we start with.

If we've got these different ways of making amines, what if I were to give you an amine and asked you to synthesize it all the ways you know how? Let's say I want you to synthesize that compound. We could put a carbonyl here, make that amide, and reduce it. We could put one more carbon, do one of these rearrangements that we just had. We could start with benzyl bromide – means one less carbon – do an Sn2 reaction with cyanide, reduce the nitrile; that'll give us this compound. We could make this compound but instead of a nitrogen, start with a halide, make an alkyl azide, reduce that. We could take this group without a nitrogen, through a bromine in there, do the Gabirel synthesis – use this to alkylate phthalimide and then saponify it? We could start with an aldehyde and we could do reductie amination. We could take an aldehyde, make an imine out of it, and explicitly reduce it.

Series of amine synthesis reactions: reduction of amides; rearrangement of amide with one more carbon – react with bromine and sodium hydroxide and then a little acid; Gabriel phthalimide synthesis – we use an alkyl halide then saponify; reduction of alkyl azides – alkyl halide, react it first with sodium azide, reduce it, acidify it; reductive amination.

Reactions of amines

Aniline is such a reactive compound cause that lone pair so well delocalizes with benzene. Anything that can add electron density to the benzene ring makes electrophilic aromatic substitution that much more favorable – so favorable that, in an alkylation reaction, you might not even need aluminum trichloride; it's that activating of a substituent. It's too hot. To slow its reactivity down, we react it with an acyl halide – not to acylate the benzene ring, but to acylate the nitrogen – in other words, make an amide out of it. Now, if we did some kind of reaction like Friedel-Crafts alkylation, then we could successfully get monohalogenation. Of course, you still might get ortho and para. Then, if we want the aniline back, we saponify. If you wanted to put it in these terms, it's kinda like a protecting group for aniline. It doesn't stop aniline from reacting; that's why I say it's kinda like a protecting group. Better to be called an attenuating group, meaning it turns the volume down, makes it a less-powerful reagent.

If we use sodium nitrite, then we can make an aryl diazonium salt. The term aryl means aromatic, meaning something like a benzene ring. These diazonium salts are very, very unstable. With aliphatic, non-aromatic diazo salts, they often eliminate to give alkenes, but these benzene-containing compounds, the benzene ring stabilizes it enough that, at least as an intermediate, you can isolate it. [palette of reagents that can be used – Sandmeyer reaction][copper chloride can be used to make the chloride]

What is the structure of d-glucose? [right, left, right, right; binary 2, [0010]] Why do we have this in basic conditions? What's going to happen? It could deprotonate all the various alcohols, because the pKas of those alcohols are probably roughly that of water. But, there's something else that could happen as well – you could form an enolate. If we're using hydroxide to deprotonate, that means the enolate could get reprotonated by reacting with water. Enols are not thermodynamically favorable, so this is reversible – but this is an enediol, it has two different -OH groups on the double bond, so what is there preventing the base from reacting not with the same -OH groups that was converted into an enol, but what about this other -OH group? We could have water around for this to be protonated with. What sugar did I just make? d-Fructose.

But this is not the only reaction possible. Let's take this same intermediate we had, the enediol, and let's say that, instead of the possibility I just showed you, the carbonyl switching positions, let's say the carbonyl reforms exactly where it used to be – in other words, we'll take the very top hydrogen off in this structure. We currently have a delocalized, so technically, while it's delocalized, even if we put a negative charge where the pen currently is, it's technically an sp2 center. Let's forget resonance just once; formally, then, the way this structure's written, yes, this looks like it's sp2. But if we allow resonance to occur, and we ignore the fact that resonance means what we write is not necessarily what we have as the true structure, but we've remade the carbonyl. We have the negative charge there; that technically would make the group sp3. If we ignore sterics or any kind of intramolecular interactions, is there any way we could control which side that -OH group ends up on? In other words, if we had a planar enol, and that becomes a tetrahedral center again, can't the hydrogen be attacked either above the double bond of the enol or below? Which means I end up with two different possibilities, which formally resolve once this gets protonated. It will make both sugars at the same time.

What do I mean both sugars – notice that the bottom three stereocenters don't get affected by any of this; this is a motif, a theme, that's going to come back over and over again – that we can do reaction on one part of a carbohydrate but have it affect the other. Our two possible products are the one where the top -OH group ends on the right; when it does, it's d-glucose again. But, if it turns up on the left instead, because we've made this new sp3-hybridized center, which sugar is this? d-Mannose. The bottom three stereocenters in glucose, mannose, and fructose are all the same. Once the enolate retautomerizes, an sp2-hybridized carbon is convert [in]to sp3 – meaning two structures can result. We've demonstrated that glucose and fructose are double tautomers – you make the enol, you come out of the enol, you just come out of it differently than the way you came into it. Or, once we make the enol, it comes back to being where it was, but because you lost stereochemistry – that's another way of saying it, that right here we've lost the configuration, because it went planar. Once it reforms, that's why we get the two possibilities.

We talked about the pyranose and furanose form of carbohydrates – what do those two terms mean? Pyranose [means a] six[-membered ring], furanose [means a] five[-membered ring]. If you had a sugar like glucose or mannose, if I counted, including the carbonyl, [to the fifth position], we could take this oxygen and make a ring, or we could take the bottom oxygen and make that six-membered ring. Once we make that six- or five-membered ring, there are two possibilities that occur – the alpha and the beta anomer. [mutarotation]

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Curtius rearrangement
Hoffman rearrangement – Compared to the starting material, the product will have one less carbon in it.

Aniline

Once the enolate re-tautomerizes, an sp2 carbon is converted to sp3, meaning two structures can result.

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Structures *(remaining structures identical to lecture 12A)*

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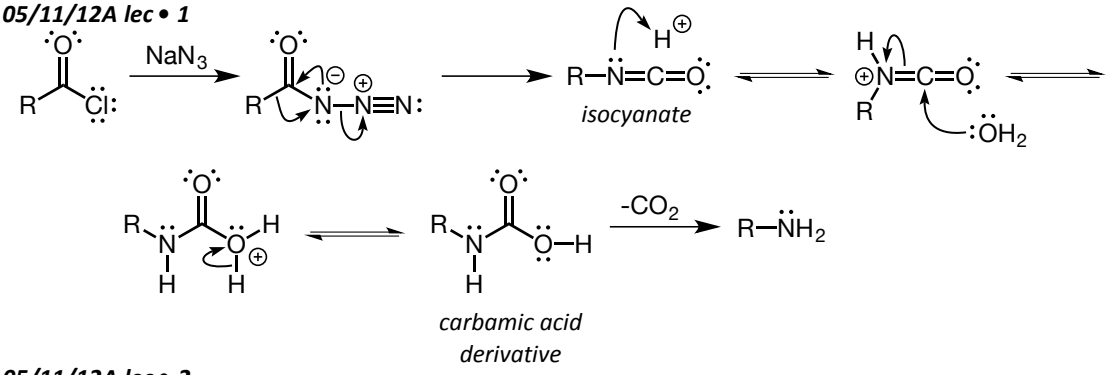

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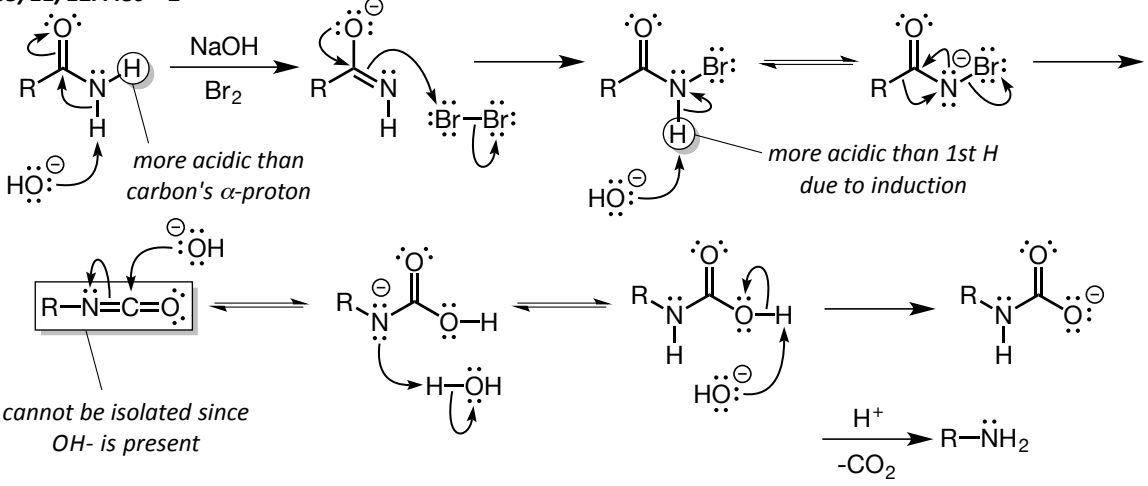

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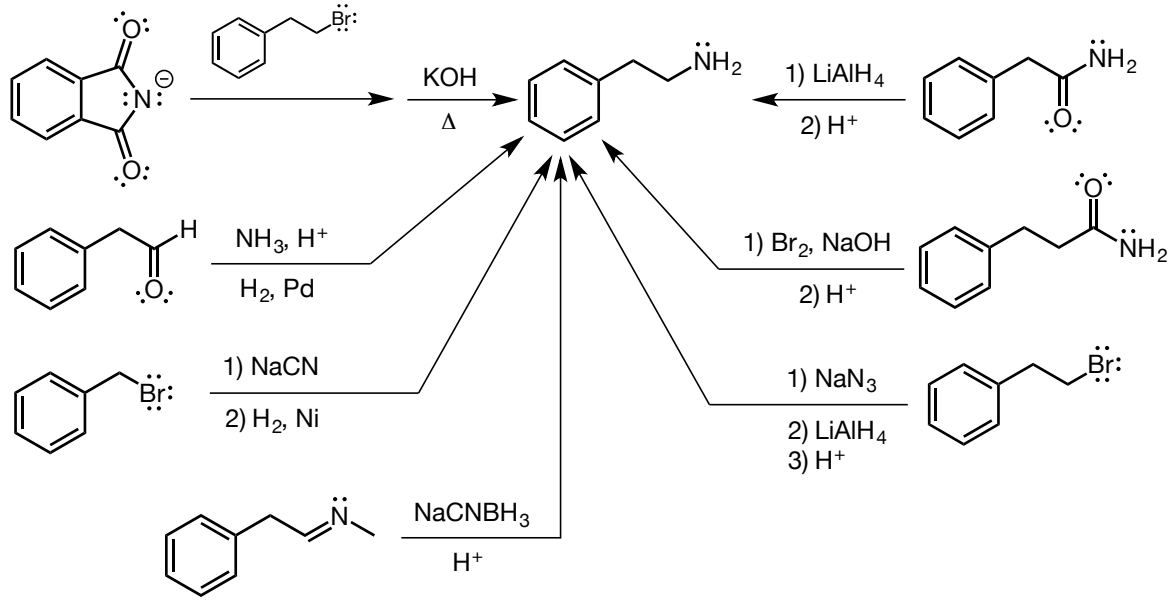

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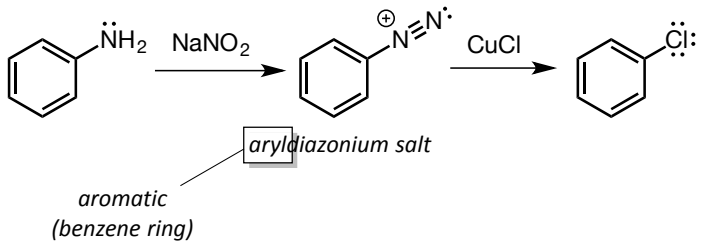

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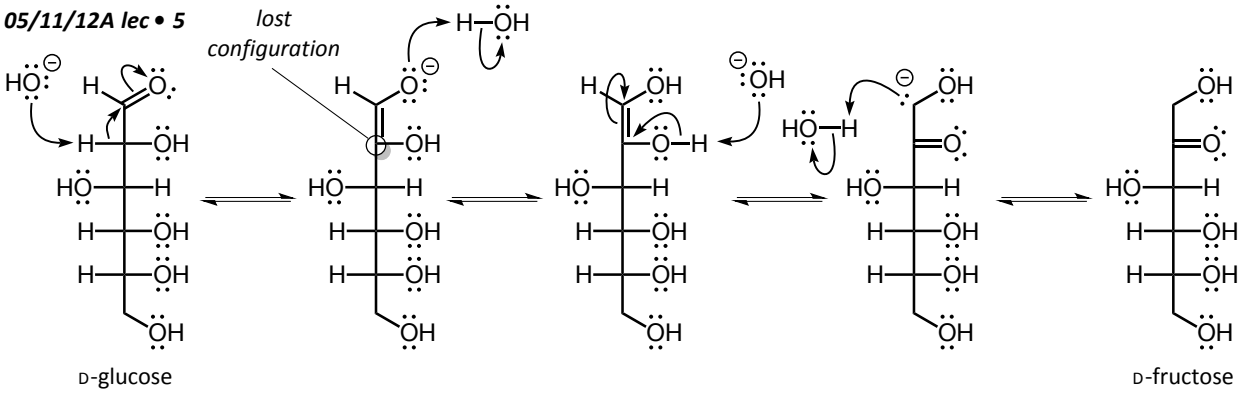

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