Lecture 12B • 05/10/12

[Quiz – acid/base properties of amines: non-aromatic, aniline, pyrrole]

Reactions to form amines: (not Sn2); reduction of alkyl azides; hydrogenation of nitriles; reduction of amides; reduction of imines; reductive amination (not animation); Gabriel synthesis; reduction of nitro groups; Curtius rearrangement; Hofmann rearrangement – Hofmann elimination; aromatic amines

Aniline, [an] aromatic amine, is a particularly reactive aromatic compound – so much so that, in a lot of reaction, you don't even need a strong electrophile to get electrophilic aromatic substitution to occur. It's yet one more care where the lone pair on nitrogen is heavily delocalized with the benzene ring.

Thermodynamically unstable carboxylic acids

Carbonic acid is where we get carbonated drinks from – why does that mean that we have fizzy drinks? What do we know happens to carbonic acid? [It] spontaneously decomposes into carbon dioxide. which is not unusual for single-carbon molecules that have too many electron-withdrawing heteroatom groups on them. [where are you going to get that starting material!?] There are many of this single-carbon molecules that will decompose. Any time that you have something that looks like a carboxylic acid and has one these side groups that has an oxygen or nitrogen on it, those are the types of compounds that decompose. Carbonic acid does it; carbonates can do it as well. This is a singly-substituted carbonate. In many cases in which a carbonyl is part of a carboxylic acid and has a heteroatom also attached to it, the acid can and will decarboxylate, so with some heat this will turn into methanol and carbon dioxide. If you didn't have the hydrogen there, though, if you have the salt, then it can survive. Carboxylic acid salts are stable. If I replace that methyl group with a hydrogen, that's the hydrogen carbonate ion [which is commercially available]. Once bicarbonate gains the next proton, though, and you end up with an acid, it then decomposes. Up top, I have carbonic acid. There is another related compound, carbamic acid, that will also decompose, in this case into ammonia and carbon dioxide. However, if instead of the acid, we had another amino group, one of the first organic compounds to be synthesized, urea, having two amino groups prevents it from decomposing. In one of our syntheses of amines, we're going to go through one of these intermediates, and it's going to be by decarboxylation that we release the amine. [also in DCC coupling of protected amino acids]

Amine-forming reactions

Usually, [alkyl halide synthesis] doesn't work out so well. For example, if we had a primary amine that we reacted with something like methyl iodide. Recall that methyl iodide's a fantastic substrate for Sn2 because it's got such little steric hinderance. Which of these two amines of the page is the stronger base? The one on the right. If it's a stronger base, it's a better nucleophile, which means you're going to continue having reaction with methyl iodide. Since I used an iodide to begin with, I'm going to have an iodide salt at the end. This process is called exhaustive methylation, or alkylation in general. Exhaustive means you do it until it can't happen any more; that's what we've done in this case. If you wanted to make a quaternary ammonium salt, this is a good way to do it, but if you were just trying to just substitute once, not such a good approach.

But, there's another reaction that can be done with these kinds of salts – that's to use an aqueous solution of silver oxide. What do you know about salts of silver? Are they normally soluble? Silver ions are soluble, except in the presene of halides [for example]. Silver chloride, silver bromide, they're very, very, very insoluble. I have a salt that has a halide; I'm exposing it to silver oxide. What if the halide where to combine with silver and precipitate out? Effectively what we would be left with is hydroxide. This is way of sneakily converting this into a hydroxide salt. Why do we care about that? Because when you heat it, it eliminates to make the thermodynamically less-favorable product. It is also a way to take an amine and convert it into another functional group. This is the Hofmann elimination. [why does this occur] It's the silver oxide that's using a trick of solubility to force iodide off the salt, and silver [iodide], in aqueous solution ends up producing hydroxide, that ends up being the counterion instead.

Reduction of alkyl azides. What's an alkyl azide? The azide ion itself is N3-, which has this Lewis dot structure to it, at least for the ion itself, that's the best Lewis dot structure because it's symmetric. This is a somewhat basic, good nucleophile, so if we had a primary alkyl halide, we could get Sn2 substitution. We then use lithium aluminum hydride and [subsequently] an acid source to make the amine. [no mechanism]. You've got nitrogen gas kinda, sorta trapped in there. Nitrogen gas ends up getting expelled in this reaction; that's how we end up with a single nitrogen instead of three of them. This why, however, these compounds can be a bit problematic to handle; many azides are explosive.

Reduction of nitriles. A nitrile can also be synthesized also by Sn2 reaction, using the cyanide ion. Then, we can reduce it using lithium aluminum hydride, or we could also hydrogenate.

Raney nickel is this finely divided nickel, this really powdered stuff that has lots of surface area, lots of place for a reaction to take place; it also has hydrogen already adsorbed on it, so it's quite reactive in it own right. That can be used to reduce the triple bond to a single bond, but notice that the product contains one more carbon compared to the alkyl halide it came from. [In] hydrogenation, the hydrogen is first adsorbed onto the metal, then one hydrogen then the other adds to the same face of whatever bond it's reducing. [can't be written well mechanistically]

Reduction of amides. We used lithium aluminum deuteride. I'll show D- deprotonating. After this deprotonation that occurs – this deprotonation does happen first for this kind of amide, one that does have a hydrogen on it – we end up with the nitrogen equivalent of an enolate, which then complexes with the aluminum. There's then a transfer of, normally, hydrogen, in this case deuterium, back to the carbon-nitrogen bond. so this is like the reduction of an imine. Here's the reason that the ring does not open: at this point, we have a negatively-charged nitrogen that is able to expel the oxygen as a leaving group. That leaves us with a true imine, that then gets reduces. You don't need something as strong as lithium hydride or deuteride to reduce an imine, but since you're already under those conditions, it's certainly going to get reduced. The last step is for nitrogen to get reprotonated. At this point, we would switch conditions, so it's allowable to have H+. Now, we have our neutral product. Amides certainly can be reduced to make amines.

Reduction of imines and reductive amination. They're related because the same reagents can show up in both of these reaction. Reductive amination is the following: where you take some kind of aldehyde, or example, ammonium gas, at the same time that you react it with another reagent, often hydrogen on palladium. Pd/C means palladium on carbon; it's another way of grinding up and putting the metal on some kind of supposed surface that provides lots of surface area, makes it more reactive; you can consider it as palladium. In other words, you have simultaneous reaction with ammonia and hydrogen. Carbonyls don't easily get reduced by just hydrogen gas – it's not impossible, you have to wail on them a little bit. It turns out, however, than imines are more easily reducible. So what happens is that the ammonia can react with the aldehyde to form an imine. Once that imine forms, the hydrogen takes over, and you end up hydrogenating it to an amine. Another variation could be to use a reducing agent. Doesn't sodium borohydride react in protic solvents? We, but there's an alternate version of sodium borohydride that often is used in these cases where you might have a mildly acidic environment – the reagent is sodium cyanoborohydride. Notice I wrote pH 5. In this case, I've shown you the imine already being prepared; I'm going to show you another case where it's not yet prepared, but this still works. pH 5 is the optimal pH to make an imine. Sodium cyanoborohydride: that cyano group allows this to withstand pH 3, even, for a moderate amount of time, which means if you had a one-molar solution of acetic acid, even, that's pretty darn tolerant for a hydride source. This will reduce the imine to an amine. This imine we could have made from that same aldehyde and a primary amine.

Can you make an imine from a secondary amine? No; that's when enamines would form. So what do you think is going to happen if we tried to do this: if we take some kind of ketone, let's say, and we react it with a secondary amine, with a little acid, at the same time that react it with sodium cyanoborohydride? Turns out you get the reductive amination product, because yes, you can't form an imine; the best you could do is get to this intermediate, cause there's no other hydrogen that can be eliminated to allow that carbon-nitrogen double bond to persist. Think of it this way: that double bond wants to get rid of that plus charge. If you have a hydride attack the carbon and push the double bond open, gets rid of the plus charge – this will react as an intermediate with the sodium cyanoborohydride, so you get a tertiary amine as a response. However, since that double bond never forms, if you use a [secondary] amine, this is as good as we can do. [common industrial way to do this kind of reaction – have sets of reagents that can be present simultaneously]

This is the Gabriel phthalimide synthesis. [KHP titration] Phthalic acid is benzenedioic acid, which, under the right conditions, can be converted into this compound, which is called phthalimide. An imide is the nitrogen equivalent of an anhydride. What's special about this phthalimide? It will not undergo Sn2 reaction by itself. Why? Think about the reactivity of functional groups. Amides were one of the low-reactivity groups for two reasons, we talked about it from two perspectives: the fact that that nitrogen's a horrible leaving group – so if you attacked the carbonyl, nitrogen wouldn't want to be kicked out – the other reason is that lone pair is so heavily conjugated with the carbonyl. Now it's conjugated with two different carbonyls, so it really couldn't be bothered to react, so only if we deprotonate this is that base then going to be able to do alkylation. This is easy to deprotonated, because the lone pair would be so heavily delocalized. [pKa] It easily can be deprotonated by potassium hydroxide. Normally, N- like this is tough to produce, but not in this case. It is still pretty basic, so you really need a primary alkyl halide for this to work best. Because you have an unreactive [imide] as a product, you don't have multiple substitution. The nitrogen – the lone pair on nitrogen – is so heavily delocalized with the carbonyls, plural, that it's not basic enough – or a better way to say it, it's not nucleophilic enough – to undergo Sn2; therefore, multiple alkylation doesn't occur. That nitrogen, cause it's got a lone pair, in theory, you would think that could attack another alkyl halide. The first attack occurs because of the N-. You still have another lone pair [which in other circustances keeps reacting], but it doesn't here, because it's not available; it's tied up with the carbonyls. Multiple alkylation does not occur. If you then saponified, we don't particularly care what happens to the carboxylic acid portion of it; the amine will released as a response [reduction with hydrazine sometimes required. It's a controlled way of making primary amines. That's the Gabriel amine synthesis.

Reduction of nitro compounds. We have something like nitrobenzene, that can be reduced to form aniline.

What's going to be the product of this reaction? Is the lone pair of the nitrogen here basic? No, not really. Methyl iodide is not likely to substitute on the nitrogen. What kind of reaction is this, though? Electrophilic aromatic substitution – [a] methyl group's going to go on there on the ortho or para position. But, is a methyl group an activator or a deactivator? An activator – because of hyperconjugation, alkyl groups add electron density to the benzene ring. That means we're going to make a more reactive compound, because we'll have two activators on the ring. Aniline is so reactive that it likes to multiply substitute. How can we control this; how can we make it less reactive?

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Thermodynamically unstable carboxylic acids

In many cases in which a carbonyl is part of a carboxylic acid and has a heteroatom also attach, the acid will decarboxylate. Carboxylic acid salts, however, are stable.

Reduction of alkyl azides
Reduction of nitriles
Reduction of amides
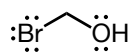Reduction of imines & reductive amination
Gabriel amine synthesis
The lone pair on nitrogen is so heavily delocalized with the adjacent carbonyls that it is not basic enough (not nucleophilic enough) to undergo Sn2. ∴ Multiple alkylation does not occur.
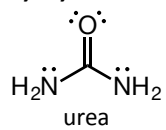Reduction of nitro compounds

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

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:Br—CH₂—ÖH

05/10/12 lec • 2

H₂N—C(=O)—NH₂

urea

05/10/12 lec • 3

KHP