

Lecture 12A • 05/09/12

Amines

Amine-forming reactions: [not $\text{S}_{\text{N}}2$]; reduction of alkyl azides; hydrogenation of nitriles; reduction of amides; reduction of imines; reductive amination (not animation); Gabriel synthesis; reduction of nitro groups; Curtius & Hofmann rearrangement – Hofmann elimination

Unstable carboxylic acids

Carbonic acid – what does it turn into? CO_2 and water. It's thermodynamically unstable; it goes through a dehydration step. It has to do with trying to put three oxygens on a single-carbon compound. This we exploit in lab because we use bicarbonate or carbonate solutions to deacidify solutions – the only by-products you're going to get are carbon dioxide and water. This is not the only compound that can undergo this behavior. If you have something like this: a carbamic acid – it also with just a touch a heat can decarboxylate. Notice that it's a sneaky, indirect way of making an amine. How could we even get to a compound like this? It is possible to get compounds of this form. If you had some kind of mixed acyl halide like this, you could react it, for example, with an amine, and as long as there's no hydrogen or oxygen on either side of the carbonyl, you can isolate the compound – in other words, we could do something like this: react it with an alcohol or an amine, and this is a substituted carbonate. Dialkylcarbonates or salts of monoalkyl carbonates are isolatable and, therefore, thermodynamically stable. But, if you have a monoalkylcarbonate, it's going to decarboxylate. This occurs anytime that you have heteroatoms on both sides of the carbonyl, and, specifically, if you have an oxygen with a hydrogen, it's going to decarboxylate. Notice that it's the oxygen that's doubled and not the carbonyl – it's oxygen, carbonyl, oxygen. An anhydride is carbonyl, oxygen, carbonyl.

Let's return to amines. First, we're already discussed about alkyl halides. Why is it that, generally, doing an $\text{S}_{\text{N}}2$ reaction using an alkyl halide is a poor way of synthesizing an amine? Because after you do the first alkylation, you take a base, an amine, and produce another amine that's more basic than what you started with, which means it'll react again and react again. This route is normally not successful due to exhaustive alkylation. But there are times where you might want to take advantage of this. I have a secondary alkyl halide, and I have strong, base nucleophile I'm introducing with heat. Yes, under the right conditions, you can get $\text{S}_{\text{N}}2$ reactions to occur with secondary substrates, but if I've got a basic nucleophile and I'm heating it up, what's probably the more likely reaction that's going to occur? Probably $\text{E}2$. What would be the most likely product of the $\text{E}2$ elimination? This compound. Why? I could eliminate to make the double bond on the outside, towards the end of the molecule, but generally internal double bonds are thermodynamically more favorable than terminal double bonds. We have this term Zaitsev elimination, which means to form the thermodynamically more favored product if multiple products could form.

But what if we wanted to make the terminal alkene? There's a kinetic trick we could pull; we could use a hindered base to make it where deprotonation from a less steric position is the favorable thing to occur. That would be a kinetic versus thermodynamic approach. But there's another approach we could take, and that's to use an amine. If I use methyl iodide in excess – excellent substrate to be used in an $\text{S}_{\text{N}}2$ reaction, it is the smallest possible substrate, the lowest possible amount of steric hinderance, the easiest reaction. It's going to trialkylate this compound, making a quaternary ammonium halide salt, which I will now react with a solution of silver oxide and water. Silver oxide, what do you think it could possibly do with the iodide if there's any way at all that that oxide can end up dissociating? Silver is in in which of its oxidation states? It's very rare to have silver +2, but not impossible, so this is normal to have it +1. If somehow one of those silvers could dissociate, don't we have iodide around as well? What do you remember from your general chem about the solubility of silver halides? Extraordinarily insoluble, really, really tiny K_{sp} s. What ends up happening is silver iodide – iodide in this case because that's what I started with, methyl iodide – silver iodide precipitates out of solution, leaving you an ammonium hydroxide salt. Silver halides are very insoluble and rapidly form precipitates, which allows the ammonium halide to be converted into a hydroxide. [need explanation for behavior] If we heat up this tetraalkylammonium hydroxide, you dehydrate. When you dehydrate, it ends up coming from the less substituted position. This is where the term Hoffman elimination comes from – to form the thermodynamically less-favorable product during elimination. It's also, you notice, a way of making an alkene from an amine. If you talk about the Hoffman reaction as a regiochemical term, it means the less chemically stable product, but if you're using the Hoffman elimination, specifically it means to make an ammonium salt and then dehydrate it, which has the effect of giving you the less-substituted or less thermodynamically-favorable form of the alkene.

Let's move back to the synthesis of amines. Next reaction is of alkyl azides. An alkyl azide is formed by an $\text{S}_{\text{N}}2$ reaction. This is the structure [of the azide ion] that is the most symmetric, so it's the most likely. We end up with an azide product which, twofold reaction of lithium aluminum hydride, followed by hydrogen. What's going to happen is that nitrogen's going to be kicked out. You end up left with an amine. Azides are basic, so you can't do any form of $\text{S}_{\text{N}}1$ reaction, so this works best with primary alkyl halides. $\text{S}_{\text{N}}2$, followed by reduction.

Our next one: hydrogenation of nitriles. To make a nitrile, we could do $\text{S}_{\text{N}}2$ with sodium cyanide, for example. We then use hydrogen and a catalyst.

For nitriles, often what's used is called Raney nickel, which is finely-ground nickel that has hydrogen already adsorbed onto its surface, so in principle you don't actually need hydrogen gas. Why use something like this? Bit more reactive towards some functional groups than palladium or platinum. It adds hydrogen across the triple bond. If you can get the triple bond to hydrogenate, the double bond certainly will, so we bring it all the way back down to the amine. Notice, though, if we start with an alkyl halide, we end up with one more carbon [in the amine] compared to the alkyl halide. For both the azide and the nitrile, it's S_N2 to get from the first thing to the intermediate. The way that hydrogenation works is you have the metal surface which hydrogen first is adsorbed onto. The metal does the job of breaking the hydrogen-hydrogen bond. The double or triple bond approaches. One hydrogen, then the other, add in. It happens on the same face, so you always end up with syn addition.

Reduction of amides. Overall, if we have some form of amide – maybe it's a secondary amide – we reduce with lithium aluminum hydride, followed by acid work-up. It turns it into an amine. What's the first step of the reaction? Deprotonation. The alpha proton is not as acidic in this case as the hydrogen on nitrogen itself. It is deprotonation, even though we have deuterium that's doing it. We make the equivalent of the enolate, which, part of the unusual reactivity is the fact that there's complexation that occurs. Once that complexation occurs, then we have a transfer normally of a hydride back to the carbon-nitrogen double bond. Since this is deuterium, though, it's going to be a deuteride that's transferred. Now something unusual happens because the aluminum on the oxygen turns the oxygen into a leaving group. We now form an imine. Lithium aluminum deuteride can now continue to reduce that. At this point, we don't have to show where the deuterium comes from, cause it's not complexed any more; there is still already the deuterium there. Attack occurs, pushing that bond back open. We end up with an anion that, because I show H^+ at the end, means we put a proton on and end up with a cyclic amine.

Reduction of imines. I'm going to combine this with reductive amination; I'm going to start out with that first. It turns out that if you take an aldehyde or a ketone and react it with ammonia at the same time that you react it with hydrogen and platinum – the conditions for reduction – you form an amine. What's the intermediate here? An imine. Turns out that carbon-nitrogen bonds can be reduced just like carbon-carbon double bonds can be – even carbon-oxygen bond, if you use the right reagent, can be hydrogenated. It's called reductive amination because we're doing reduction at the same time. There is also another reagent [switching over to reduction of imines] that we could use. That is the compound sodium cyanoborohydride. Why do we care about it? It can survive a solution of pH 3, even though it's a hydride source. Sodium borohydride decomposes, but it does so slowly enough that if you have a protic solvent, it will decompose but slowly enough that it's still able to reduce; sodium cyanoborohydride is even more tolerant of protic solutions, and tolerant of actively-acidic solutions. You could also do reductive amination using the sodium cyanoborohydride, or, you could specifically reduce an imine using it. You could start out with a ketone, for example, use a little bit of acid – pH 5 is the optimal pH to make an imine. We could make the imine as a discreet step and then reduce it with sodium cyanoborohydride. If we have pH 5, it provides the proton already to reprotonate the compound after reduction. It allow me to make a primary amine and make a secondary out of it, or I could take a secondary amine – can you make an imine from a secondary amine? No, but there is an intermediate that we could draw where we technically have a double bond, and even though you can't isolate it, if you have sodium cyanoborohydride in solution at the same time, you can form a tertiary amine. Even though you can't isolate the intermediate, since it formed, it can react. You could make a secondary amine from a primary, you could make a tertiary amine from a secondary. Pd/C, what that means is to finely grind up graphite and palladium together. The carbon provides a surface for the palladium to coat, provides surface area, makes it more reactive than just a chunk of palladium metal. Platinum [is] generally more reactive than palladium. Both platinum and palladium are some of the most common catalysts used to perform hydrogenation.

Gabriel synthesis. Involved phthalimide. [An] imide is like the nitrogen equivalent of an anhydride. Phthalimide comes from phthalic acid. [pKa?] Potassium or sodium hydroxide are able to deprotonate it easily. We use a primary alkyl halide. We'll alkylate. We'll still have a nitrogen with a lone pair, which means, in theory, it could do another S_N2 reaction – but it won't; why? What would you estimate that the pKa of this conjugate to be? If I took this and reacted it with acid, what do expect that the conjugate pKa would be: low or high? Is this conjugate going to be a strong or a weak acid? If you're saying strong, then this is a weak base, which [is] correct, but why? It's hugely delocalized, because it's got two carbonyl that it's involved with. Proteins are polymers, polyamides. Amides are the least-reactive functional group out of the carboxylic acid derivatives, other than nitriles. Why? If you're thinking of nitrogen as a leaving group, it's a horrible one. If you're thinking about the density of electrons on a carbonyl, the lone pair conjugating with the carbonyl reduces the reactivity of the carbonyl. We've got two carbonyls involved with that nitrogen, which means that lone pair's even more delocalized, which means it doesn't want to react like a base, because it would rob it of that delocalization. This lone pair is not basic, and at the same time it's not nucleophilic (when neutral, at least), because of the extensive delocalization of the lone pair, which means only monoalkylation occurs. We deprotonate it; that makes it reactive enough; we alkylate it, that's the end of the story – until saponification. If we don't do an acid work-up, we'll get phthalate as a byproduct and we have a primary amine. [often hydrazine used in reduction]

Reduction of nitro compounds. We can reduce a nitro group to make an amino [must be aromatic? or can be aliphatic?]

Aniline. What will the product of this reaction be? What kind of reaction is this? Alkylation. How many alkyl groups will be added? Because if I had monoalkylation occur – you could get ortho- or para-substitution – what happens to the reactivity of this molecule: is it more or less reactive than the material that I started with? Is an alkyl group an activator or a deactivator? Hyperconjugation. We have a more reactive molecule – doesn't that mean it can keep on reacting?

Some cases, no; for other molecules, the activator's not that strong. But this amino group is one of the strongest activators. It's so strong that, if the S_N2 reaction doesn't happen to react with the amino group – why is this amino group going to be prone to the S_N2 reaction, what is the pK_a of the conjugate of aniline? If it's 4, does that mean aniline is base, acidic, or neither? All you know that is if its conjugate has a low pK_a , that this compound itself is not basic – which has nothing to do with whether it's acidic or not. That hydrogen coming off, not another hydrogen coming on. That's not basic, it's not nucleophilic, it's not prone to S_N2 as much, so you could actually do this reaction without the S_N2 occurring. What you're going to end up with is this.

How do we prevent that? Two ways. Aniline is so reactive that it often undergoes multiple electrophilic aromatic substitution, sometimes without needing a catalyst. Friedel-Crafts acylation, you almost don't need the aluminum trichloride. How to prevent the multiple reaction, then? Acylate it. I don't mean Friedel-Crafts acylation – take a carboxylic acid, turn it into an acyl halide, react it with an amine, which means we make the amine – which is still an ortho-para director, but it's much less reactive, which means now we could do Friedel-Crafts alkylation and have some ability to have it only occur once. We know that this is an amide, which means that if we cook it up in base and hydrolyze it, we get the amine back again.

unstable carboxylic acids

Dialkyl carbonates or monoalkyl carbonate salts are isolatable and thermodynamically stable.

1) S_N2 of alkyl halides – Normally not successful due to multiple alkylation.

The Hofmann elimination

*Silver halides are very insoluble and rapidly form precipitates, which allows the ammonium halide to be converted to an ammonium hydroxide.

Hofmann elimination – To form the thermodynamically less favorable product during elimination

2) Alkyl azides

3) hydrogenation of nitriles

4) reduction of amides

5) reduction of imines

6) reductive amination

$NaBH_3CH$: sodium cyanoborohydride – survives $pH = 3$

reductive amination

imines

7) Gabriel synthesis – phthalimide

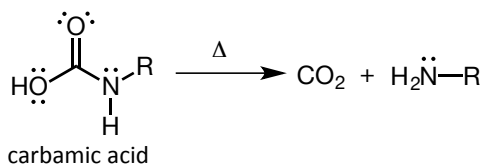
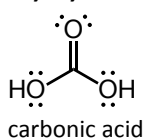
8) Reduction of nitro compounds

Aniline is so reactive that electrophilic aromatic substitution often occurs multiple times

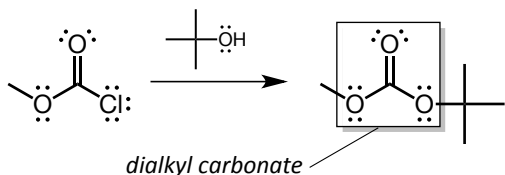
One solution

Structures

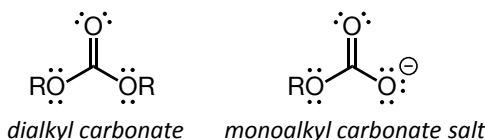
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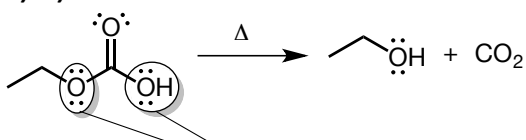
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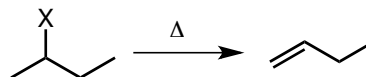


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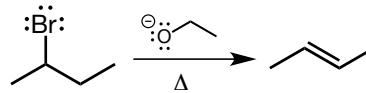


If a carbonyl has two heteroatoms connected and if it has an -OH group, it will decarboxylate

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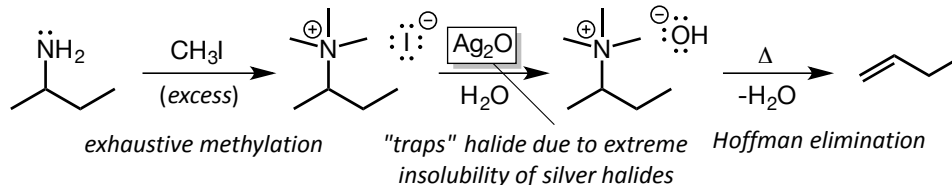


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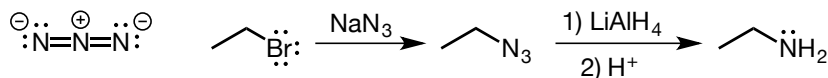
Zaitsev elimination

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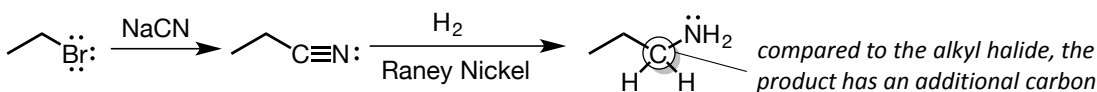


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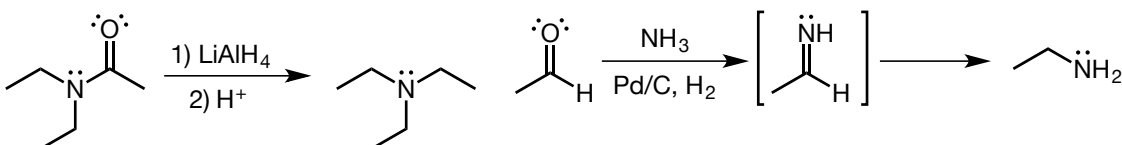


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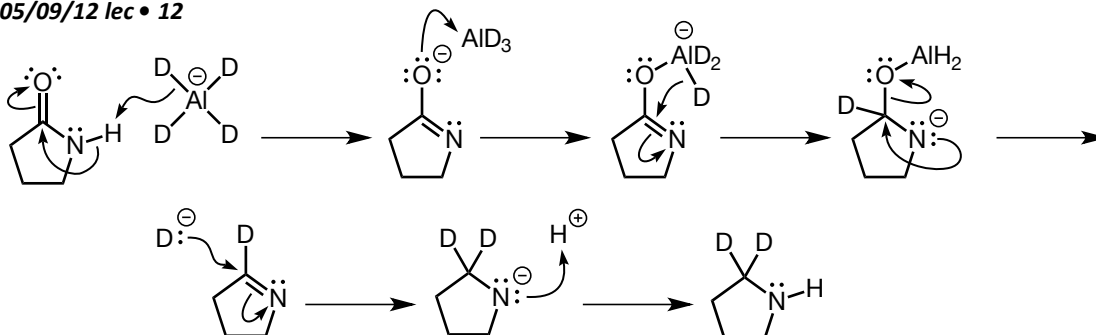


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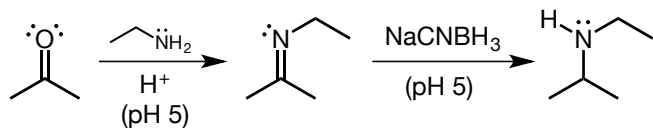
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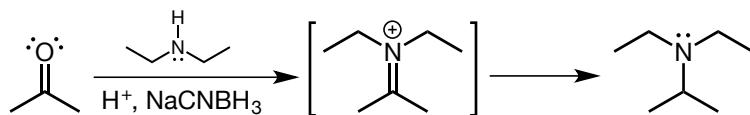
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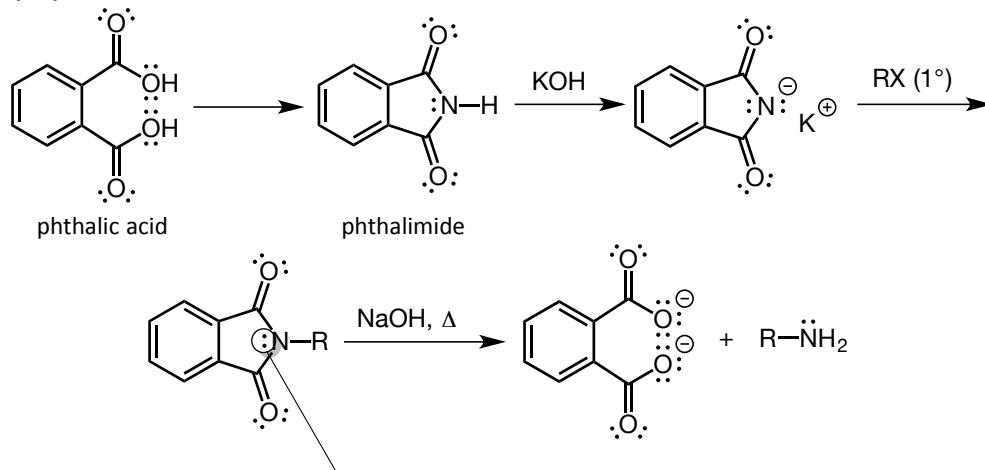
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05/09/12 lec • 15

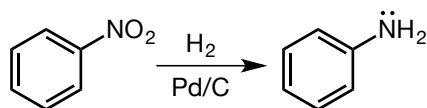


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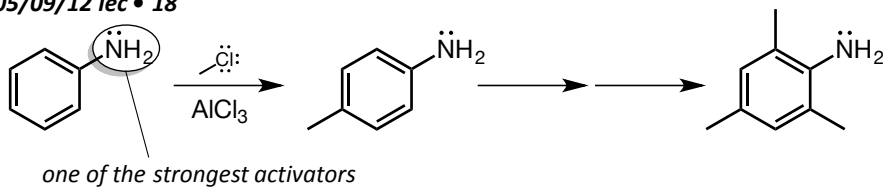


Not basic or nucleophilic (when neutral) because of the extensive delocalization of the lone pair
 → only monoalkylation occurs

05/09/12 lec • 17



05/09/12 lec • 18



one of the strongest activators

05/09/12 lec • 19

