

Week 12
CHE 3332 - Organic Chemistry 2

Hello and Welcome to the weekly resources for CHE 3332 – Organic Chemistry 2!

This week is Week 12 of class, and typically in this week of the semester your professors are covering these topics below. If you do not see the topics your particular section of class is learning this week, please take a look at other weekly resources listed on our website for additional topics throughout the semester.

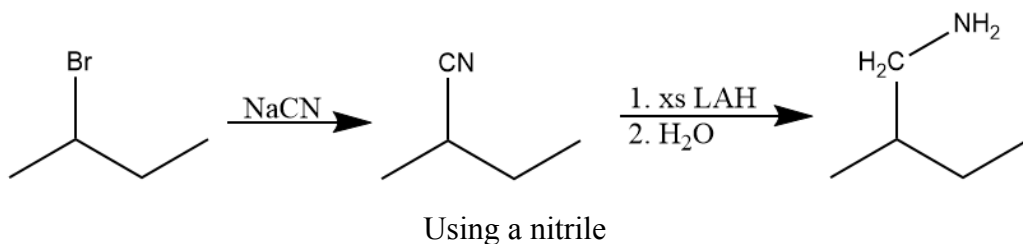
We also invite you to **look at the group tutoring chart on our website to see if this course has a group tutoring session offered this semester.** If you have any questions about these study guides, group tutoring sessions, private 30 minute tutoring appointments, the Baylor Tutoring YouTube channel or any tutoring services we offer, please visit our website www.baylor.edu/tutoring or call our drop in center during open business hours. M-Th 9am-8pm on class days 254-710-4135.

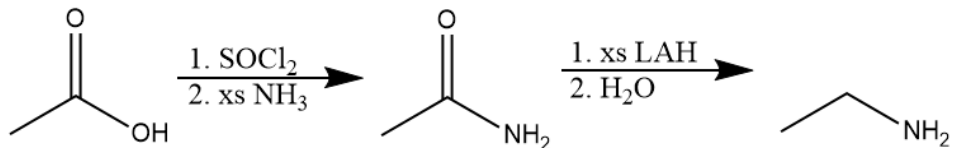
Keywords: Amination, Azide, Diazonium

TOPIC OF THE WEEK: Amines (Chapter 22)

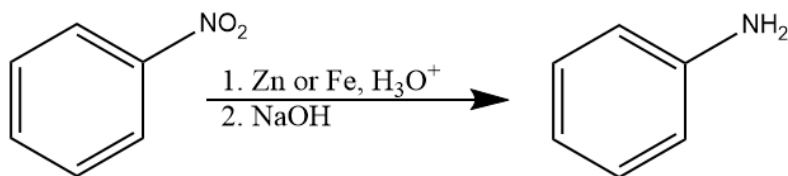
Preparation of Amides:

Many of the methods to prepare amines have already been covered in earlier chapters, with many involving reducing something down to an amine. For example, some of the reactions you may already be familiar with are: S_N2 substitution using CN, reduction of an amide, and reducing a nitro group on benzene.



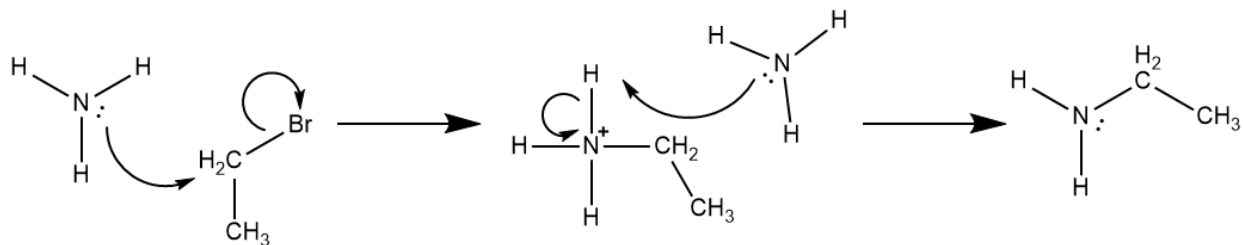


Reduction of amides

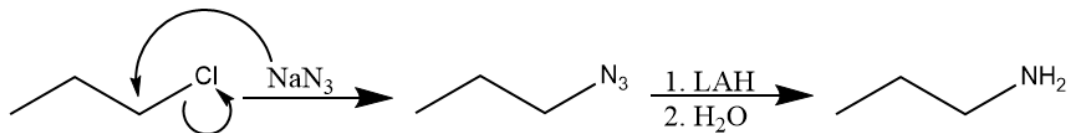


Reduction of a nitro group

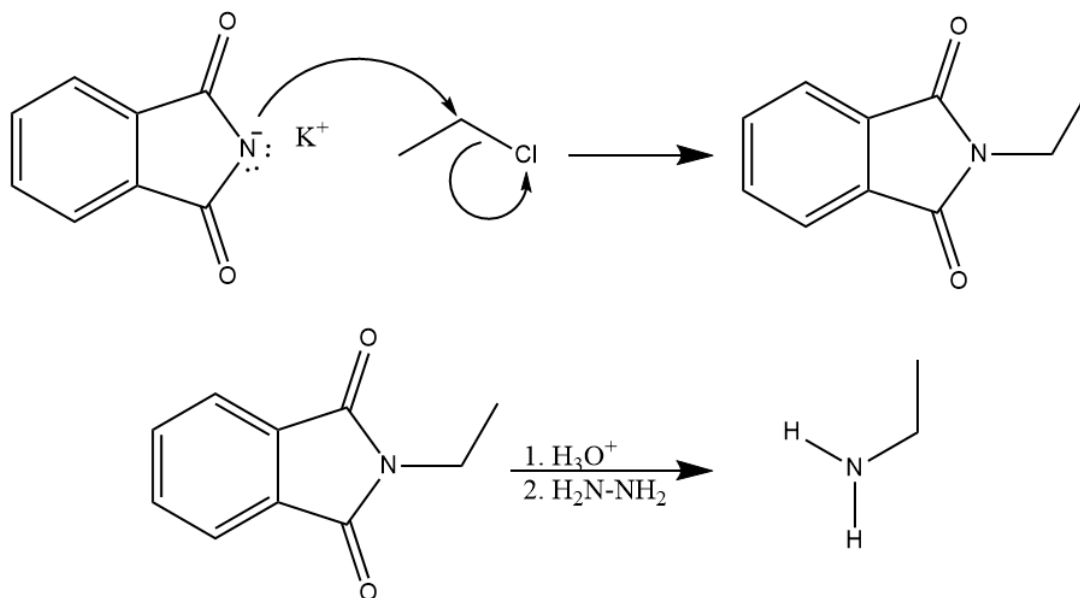
In this chapter however, there are a few new ways to get an amine that are introduced. The simplest one involves an $\text{S}_{\text{N}}2$ reaction between a halocarbon and an ammonia molecule. This can be done many times over, to provide anything from a primary to a quaternary amine.



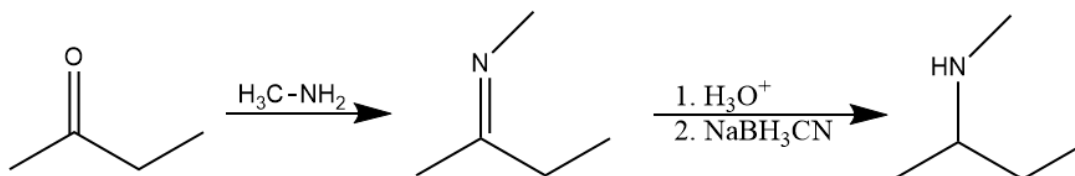
Another method, using $\text{S}_{\text{N}}2$ substitution, and a halocarbon, is through azide synthesis, which makes use of an azide (N_3) intermediate. This reaction is quite useful as it can be used to create primary amines only.



Our final method creating a primary amine is through the Gabriel Synthesis. This involves a large cyclic molecule which has a nitrogen atom bound to the ring, known as potassium phthalimide. Just like the other reactions, this nitrogen in the ring acts as a great nucleophile, and can perform an $\text{S}_{\text{N}}2$ nucleophilic attack on a halocarbon.



While these reactions are useful, they only provide either a primary amine, or a variety of products, and sometimes we may want to isolate only a singular product. Because of this, there are methods to isolate a specific product, whether it be a primary, secondary, etc. This is done through reductive amination. Recall from earlier chapters, that we can switch the oxygen of a carbonyl for a nitrogen based group (imines and enamines), using ammonia or a primary/secondary amine. Using this property, we can then reduce our doubly bonded amine to get our final product.



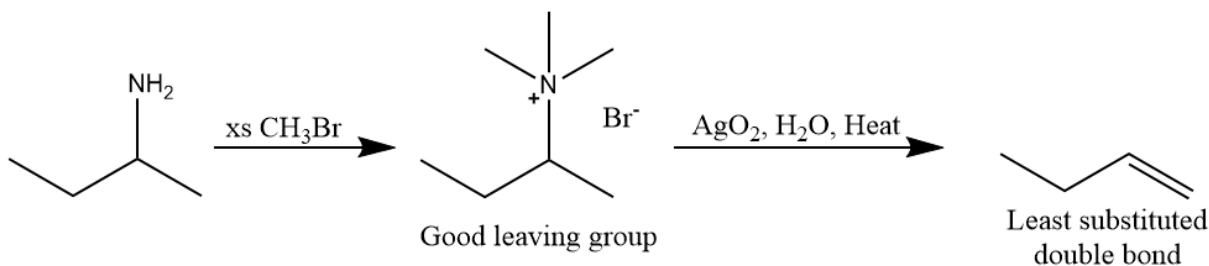
Example of a secondary amine from a reduced imine

HIGHLIGHT #1: Amine Reactions

Hofmann Elimination

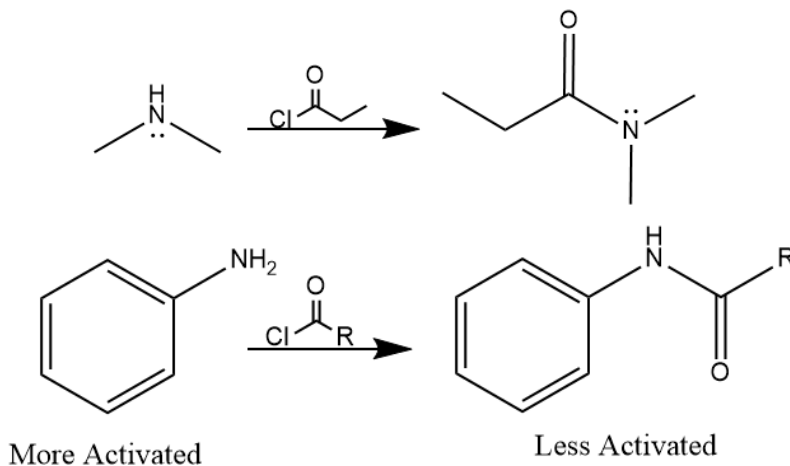
One of the simplest ways we can eliminate amines is through the Hofmann elimination, which effectively turns our amine into a good leaving group, capable of E₂ elimination reactions. We can do this through our first S_N2 amine synthesis, by simply substituting hydrogens for methyl groups. In an excess of halocarbons (like CH₃Br), we can produce a quaternary amine, which will become a great leaving group, and will easily undergo an E₂ reaction. It is important to note however that because of the steric bulk of our leaving group, we do not follow

conventional stereochemistry, and will end up with a double bond in the least substituted position.



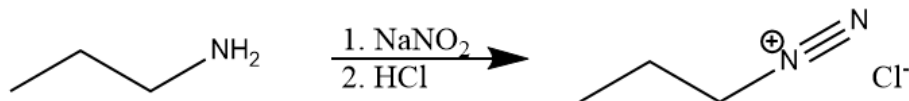
Acyl Substitution

Another interesting quirk of amines is that we can actually turn them back into amides. This does not entail oxidizing the amine back however, but instead we can add a carbonyl (in the form of an acyl halide like acid chloride). Most likely, you will be seeing this used on a benzene ring, to adjust how activated the ring is.

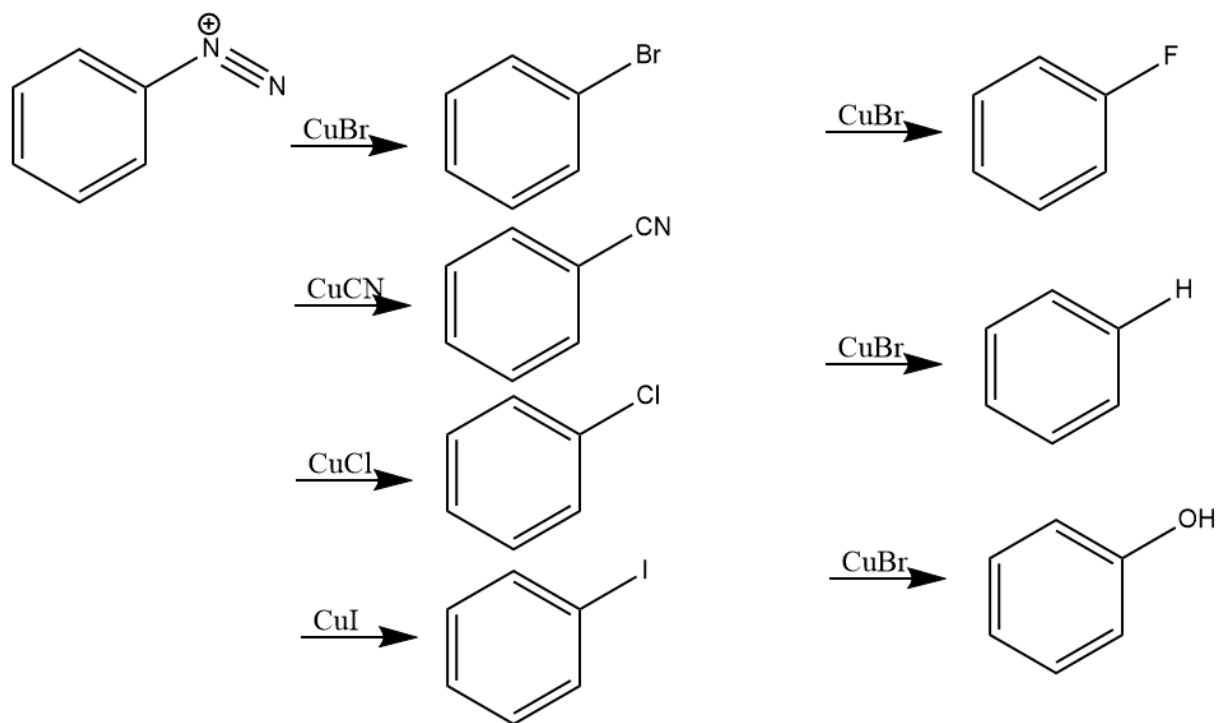


Aryl Diazonium

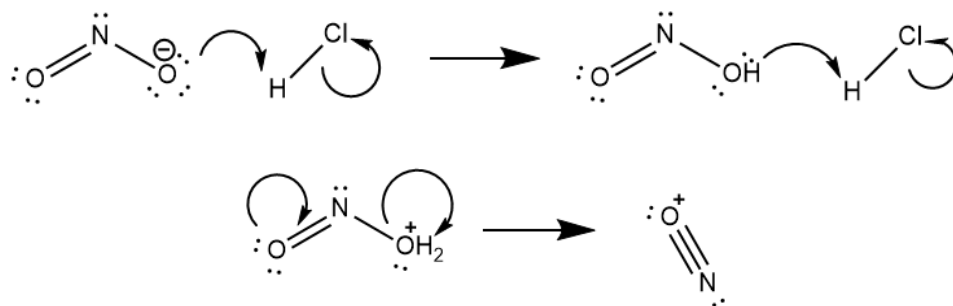
An important reaction that leads to many products is the creation of a diazonium group (basically an N₂ functional group). Specifically, when placed onto a benzene ring, there is a lot we can do with the diazonium, as it is a good leaving group. To do so, we can treat a primary amine with sodium nitrate and acid, giving us the desired group.



Here is a quick diagram that showcases all the different possibilities that a diazonium can become:

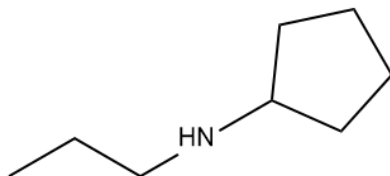


Additionally, as a quick aside about sodium nitrate, it is important to learn the mechanism of how it becomes a nitrosonium ion intermediate (N triple bonded to O). It shows up in a few reactions, so it is a good idea to have its mechanism memorized:

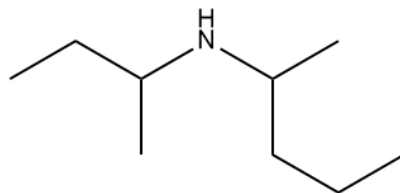


CHECK YOUR LEARNING:

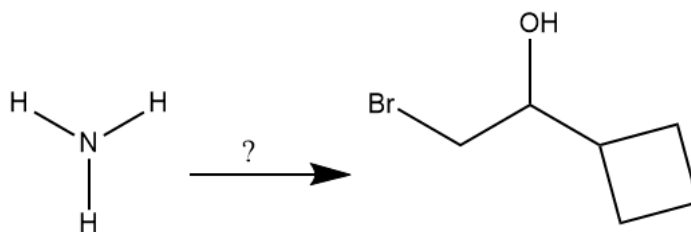
1. Provide a synthesis for the following molecule, using an azide synthesis for the starting reaction:



2. Provide a synthesis for the following molecule, using reductive amination:



3. Provide a synthesis for the following reaction:



THINGS YOU MAY STRUGGLE WITH:

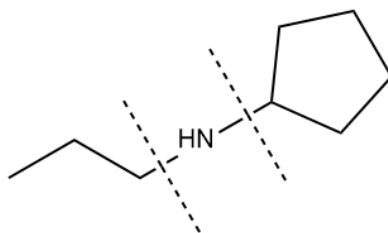
- I feel as if this unit can pull from a lot of material earlier on. If you are not super familiar with some of the earlier chapters, drawing from a range of various reactions, it may hurt your ability to understand this material.
- There are many reactions for preparing amides. I feel as if they may get confusing as each is situational, and will be used for a specific purpose.
- Furthermore, because of the time of the semester, and how amines come at the tail end of it all, it may be difficult in general to make time to study for this material, as well as keeping on top of upcoming tests.

Thanks for checking out these weekly resources!

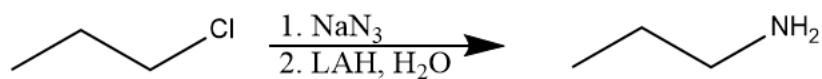
Don't forget to check out our website for group tutoring times, video tutorials and lots of other resources: www.baylor.edu/tutoring! Answers to check your learning questions are below!

ANSWERS FOR THE PRACTICE PROBLEMS:

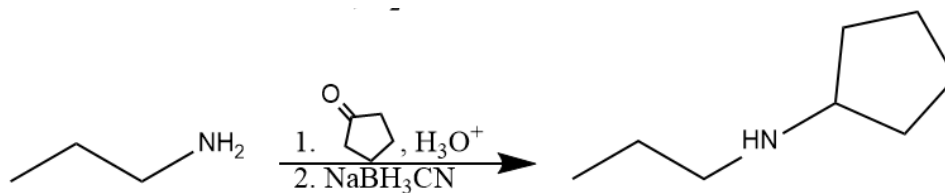
1. For this problem, we need to start by identifying the two hydrocarbon groups that the nitrogen is attached to, to see what we will be adding on:



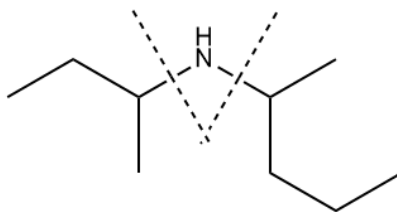
While it doesn't make too much of a deal which side we add first, because azide synthesis involves S_N2 substitution, we will begin with the left side.



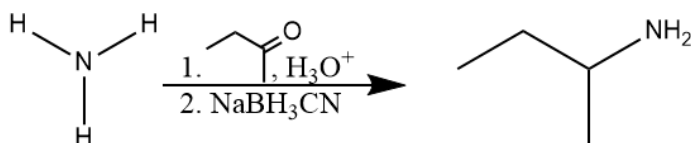
Next, we can use reductive amination to add onto the amine, giving us the ring from the right side:



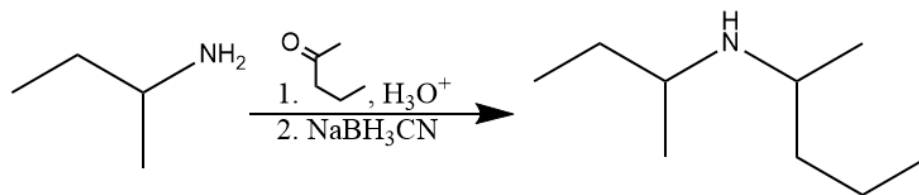
- For this problem, we will be tackling it using the same ideas. We want to start with what hydrocarbon groups were added on first, then add those onto an ammonia group later.



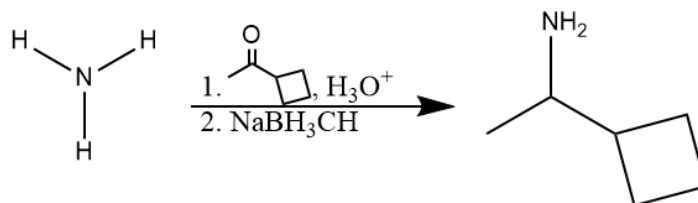
It does not matter what side we start with first, but I started with the left hand side and added on from there:



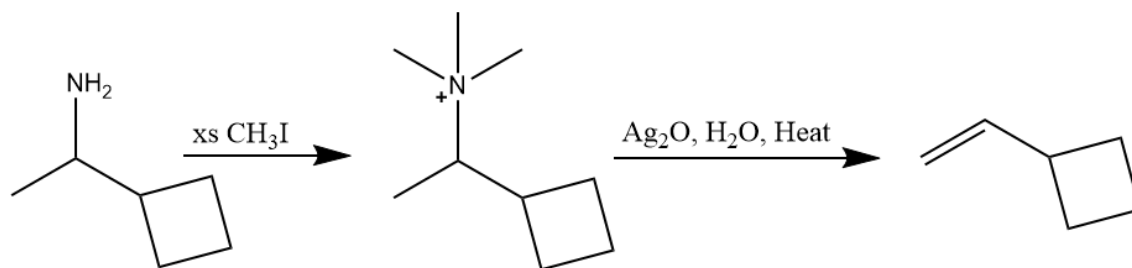
Now we can simply perform the same reaction again, but with a different ketone:



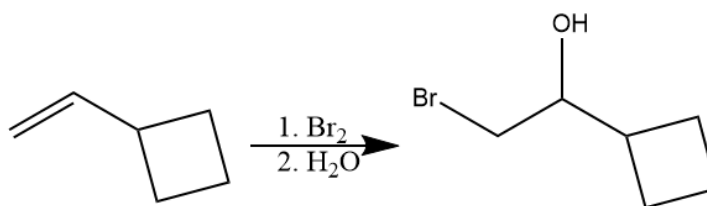
3. So in this reaction, there is obviously a lot going on. We start with a simple ammonia molecule, and end up with something that is totally different. But if we look at the product and think backwards, we might be able to figure things out. For one, it can be seen that our product has both a Br and an OH group on it, which can be done in a reaction that we are familiar with, using Br_2 and H_2O . So we know that there must have been a double bond somewhere, which suggests elimination. Furthermore, we have gone over an elimination reaction (Hofmann Elimination), so we know our primary amine must be formed from the 2 carbon tail and 4 carbon ring.



Reductive amination



Hofmann elimination



Addition to a double bond