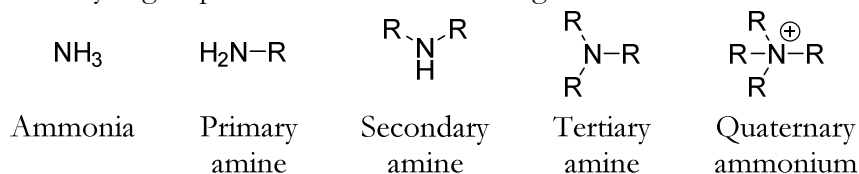


# Loudon Chapter 23 Review: Amines

Jacquie Richardson, CU Boulder – Last updated 3/28/2019

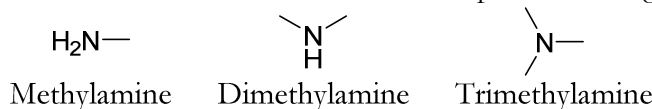
This chapter is about the chemistry of nitrogen. We've seen it before in several places, but now we can look at several reactions that are specific to nitrogen. Amines can be subdivided based on how many R groups are attached to the nitrogen:



This is different from other functional groups like alkyl halides and alcohols. Because they can only attach to one carbon, they're described by how many bonds that carbon has to other carbons. Here, though, we're looking at the bonds from the N itself.

## Nomenclature

Like everything else, amines have both an older, common name, and a newer, IUPAC name. Common name: If there's only one type of R group on the nitrogen, name it as an alkyl amine (with a di or tri at the start if there's two or three copies of the R group).

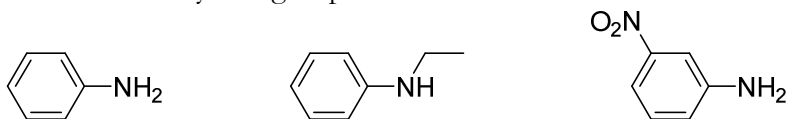


If there's more than one type of R group, then name the molecule after the larger group, with the smaller groups as substituents located at the "N" position. The ending still changes to "amine", and there needs to be a location for the N on the parent compound if there's more than one possibility.



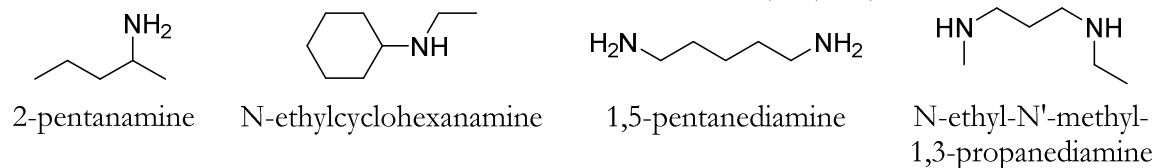
N-ethylcyclohexylamine    N,N-dimethyl-2-butylamine

Aromatics are named as derivatives of aniline, and can use either number substituents, or *ortho/meta/para* if there are only two groups.



Aniline    N-ethylaniline    *m*-Nitroaniline

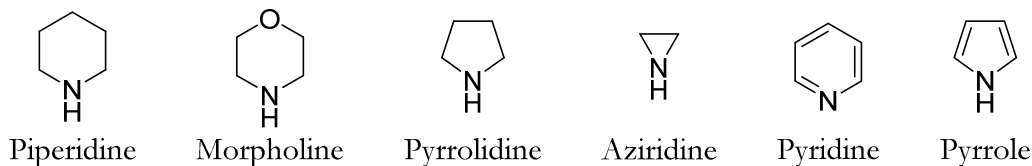
IUPAC name: Amine is a principal functional group that changes the parent name so it drops the terminal "e" and adds "amine", with a location if there's more than one possibility. Like with other functional groups, if you have multiple copies of the amine you can change the end to "diamine", "triamine", etc. The locations of smaller R groups are still given as N, but if there's more than one amine then these locations are N, N', N'', etc.



There are a few nonsystematic cyclic amines that are helpful to know:

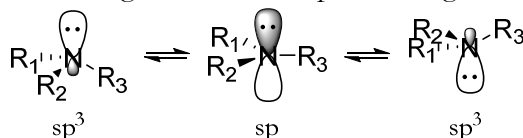
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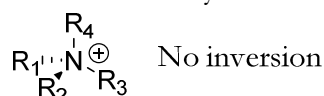


## Structure of Amines

Amines are  $sp^3$ -hybridized, so the nitrogen is tetrahedral. This means that we should expect them to be stereocenters, like tetrahedral carbon. But they're not, because unlike carbon, one of their four substituents is an  $sp^3$ -hybridized lone pair. These lone pairs are not as fixed in place as a real substituent would be – they can temporarily hybridize into a p-orbital, and then pop out with side of the nitrogen afterwards, performing an inversion at nitrogen.

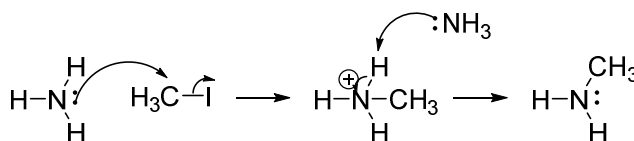


However, if we have a quaternary amine with four R groups, then there's no lone pair to invert and the nitrogen has a fixed stereochemistry.

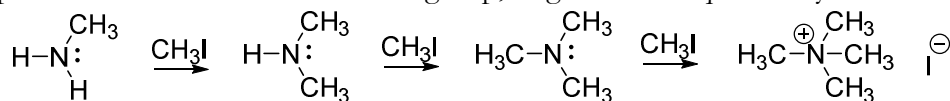


## Alkylation of Amines

If you want to attach a new R group to a nitrogen, the first thing that comes to mind is probably attaching it with  $S_N2$  on an alkyl halide – for instance, methyl iodide, which is very easy to do  $S_N2$  on.

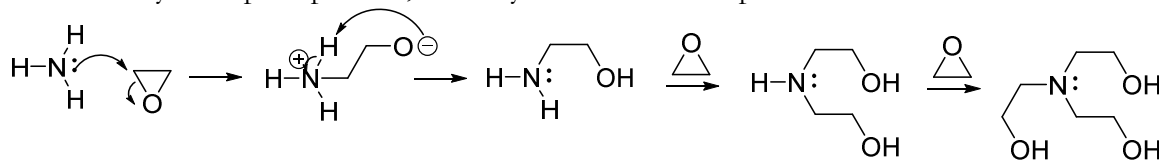


The problem is that nitrogen won't just stop at adding one R group. If enough alkyl halide is available, it will keep cycling through primary to secondary to tertiary until all of its Hs have been replaced. Then it will add one last R group, to get it to the quaternary ammonium stage.



This is called quaternization, or exhaustive methylation if the R group happens to be methyl as shown here. It's very difficult to stop at just one addition.

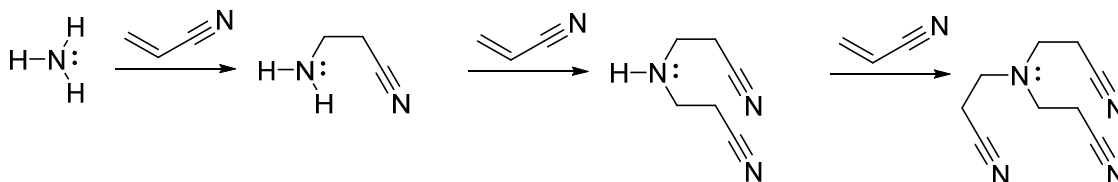
This is also true if we use nitrogen in other reactions we've seen in the past. For instance, we saw that they can open epoxides, but they can do this multiple times.



Another example involves conjugate addition to  $\alpha,\beta$ -unsaturated nitriles.

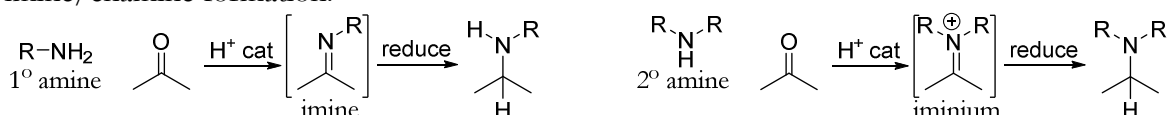
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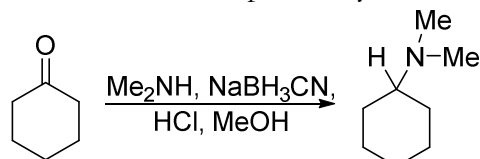


The actual outcome of these reactions depends on what ratio of starting materials you use, but usually there'll be a mixture of all possible products. To get around this, you need to use a method that will add a controlled number of alkyl groups, rather than adding as many as possible.

1. **Reductive amination:** This involves taking advantage of the formation of imines that we saw in Ch. 19. This works for 2° amines too, though, which indicates you can still get to the product from the iminium intermediate that we saw during the mechanism for imine/enamine formation.

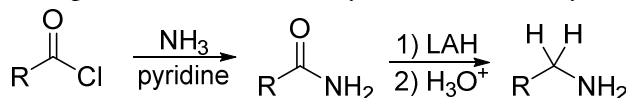


To reduce the imine or enamine, you need a reducing agent that's too weak to go for the carbonyl. Usually the reagents used are  $\text{NaBH}_3\text{CN}$  or  $\text{NaBH}(\text{OAc})_3$ . You can add these in at the same time as all the other reagents. If  $\text{NaBH}_3\text{CN}$  (sodium cyanoborohydride) is used, the reaction is called Borch reduction specifically. Here's an example:



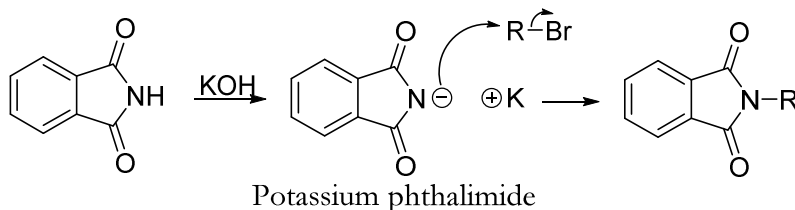
The entire molecule that used to be a carbonyl gets added to nitrogen as a new R group. This is a nice, controllable way of adding a single R group at a time, and overalkylation is not a possibility. This is probably the most versatile of the controlled-alkylation methods.

2. **Acylation of amines:** This just means using an acid chloride, anhydride or ester to make an amide, like we saw in Ch. 21. If you want to add a single R group without a carbonyl, you can then use LAH reduction to remove the carbonyl (Wolff-Kishner and Clemmensen are not options, since those only work with aldehydes and ketones).



This is another good way to get control of how many R groups are added.

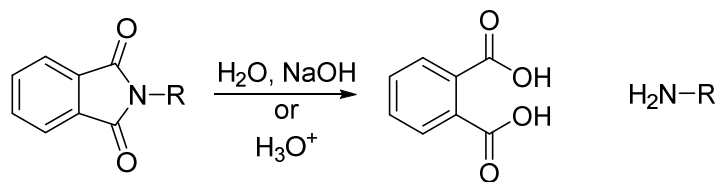
3. **Gabriel synthesis:** This is a good way to make primary amines, with just a single R group attached. This brings in the nitrogen in the form of a phthalimide, which gets deprotonated and then does  $\text{S}_{\text{N}}2$ .



To remove the phthalimide, you can hydrolyse it with acid or base just like you would for an amide. This creates a new primary amine, without risking overalkylation.

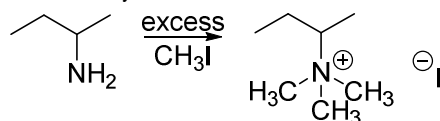
# Loudon Chapter 23 Review: Amines

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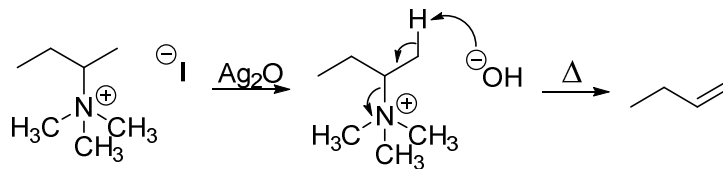


## Hofmann Elimination

If you want to remove a nitrogen from a molecule, the best way to do it is by converting it to a good leaving group and then doing an elimination. This is kind of like removing an OH group by turning it into a tosylate first. In the case of an amine, you need to exhaustively methylate it first by using excess methyl iodide.



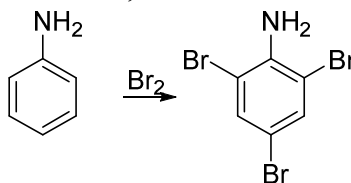
To get rid of this leaving group, you still need a strong base around to do an E2 elimination. This can be achieved by replacing the iodide that's nearby with a hydroxide instead. Bringing in silver oxide does this, because silver and iodine bond very strongly to each other and the oxygen is left behind. The OH can then force an E2 elimination.



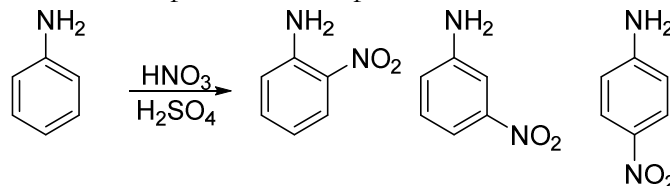
An interesting note about the elimination is that it usually breaks Zaitsev's rule: it makes the less substituted alkene. This is due to the leaving group being so bulky that the OH can't reach the more substituted hydrogens on the molecule. In fact, "Hofmann-style elimination" is often used as a synonym for "anti-Zaitsev-style elimination".

## EAS on Anilines

If you remember electrophilic aromatic substitution, nitrogen was a strong activating group and an ortho/para director. This means that many EAS reactions like halogenation will keep happening until all o/p positions are filled, even without FeBr<sub>3</sub>.



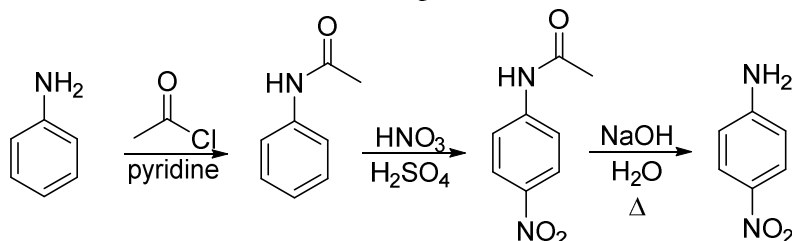
However, in the presence of acid, the NH<sub>2</sub> group gets protonated to NH<sub>3</sub><sup>+</sup>, which is a strong deactivator and meta-director. Even though most of the molecules are in this protonated state at any given time, the unprotonated versions are so much more reactive that you still get roughly the same amount of para and meta products.



# Loudon Chapter 23 Review: Amines

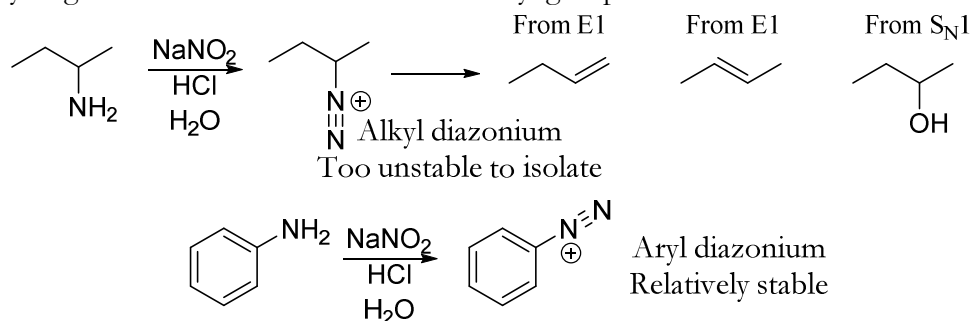
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To prevent this, you can convert the  $\text{NH}_2$  group to something that won't get protonated. This way it stays as an o/p-director and only gives the para form as the major product (due to sterics at the ortho positions). This is another version of protecting groups: you put something on the  $\text{NH}_2$ , do the reaction, then deprotect.

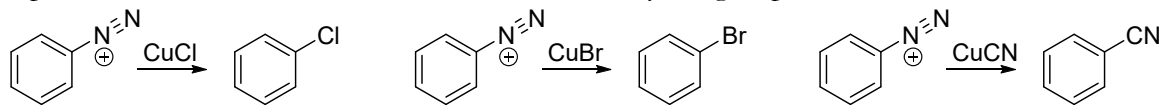


## Diazonium Chemistry

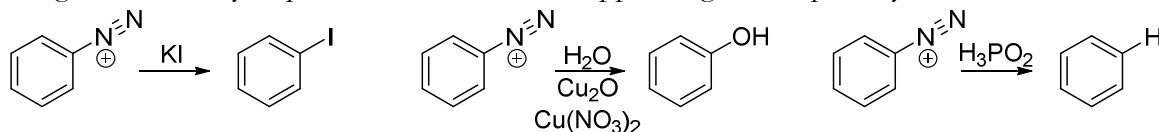
The diazonium group consists of two nitrogen atoms triple bonded to each other. We've seen this before in section 20.8B, where the diazonium acts as a very good leaving group. To make a diazonium, you can start with an  $\text{NH}_2$  group and react it with nitrous acid ( $\text{HNO}_2$ ) or some conditions that will generate nitrous acid. Unfortunately, if the  $\text{NH}_2$  is connected to an alkyl group, it will immediately drop off and make the molecule go through  $\text{E1}/\text{S}_{\text{N}}1$ . The best way to get a stable diazonium is to use an aryl group instead.



Once you have an aryl diazonium, you can do several different reactions to replace it with other groups. The most common type is the Sandmeyer reaction, which uses copper to replace the diazonium with a chlorine, bromine or cyano group.



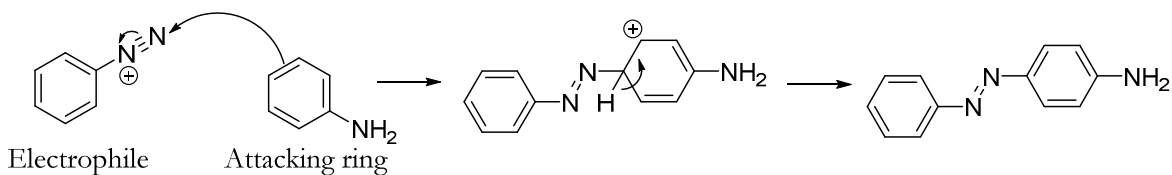
You can also replace the diazonium in a few other ways. In the middle reaction, the only thing that's actually required is water, but the copper reagents help catalyze it.



In addition to being a good leaving group, diazonium is also a pretty good electrophile – it looks a little like a protonated carbonyl. Other groups can attack it, but the most common reaction is when another aromatic ring uses it as an electrophile while doing an EAS reaction. Like in all EAS, this works best if there's an activating o/p-director on the attacking ring, like an amine.

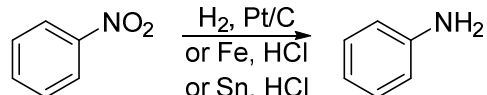
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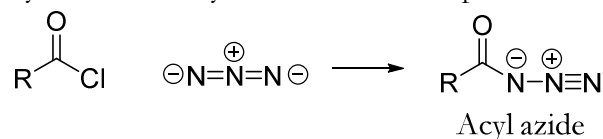
The products of reactions like this are called azo dyes because they make a range of different colors, depending on what other groups are attached to the molecule.

To make anilines in the first place, it's easiest to reduce a nitro group (which we know how to add by nitration). You can do this with either  $H_2$  and Pt/C, or with Sn and HCl, or with Fe and HCl. Note that LAH and  $NaBH_4$  are not good choices for reducing agents here.

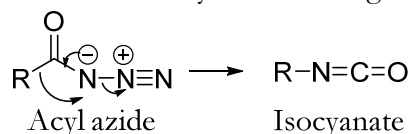


## Curtius and Hofmann Rearrangements

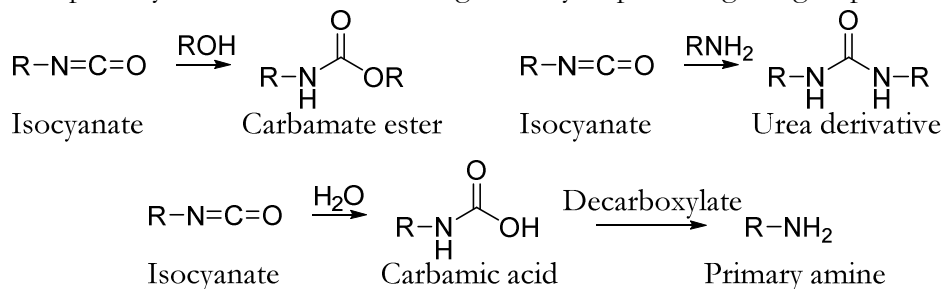
Another way to make amines is from an acyl azide. The azide group has three nitrogens, two of which are triple bonded and look like diazonium. You make the acyl azide by carboxylic acid derivative chemistry – the best way is an acid chloride plus sodium azide.



If you heat the azide up, it loses  $N_2$  and rearranges to make an isocyanate. This is called the Curtius rearrangement. The mechanism involves the R group hopping from the carbonyl over to the N, while the N attacks the carbonyl and the  $N_2$  group drops off.



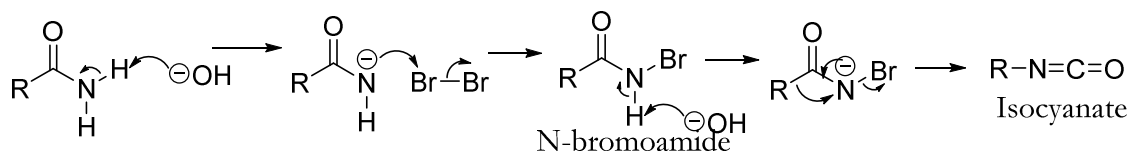
The isocyanate is not terribly stable on its own, but it can react with other things to give stable products. If it reacts with water, it forms a carbamic acid which can decarboxylate, ending at the primary amine. This is another good way to put a single R group onto an N.



Hofmann rearrangements are very similar. They again have a carbonyl attached to a nitrogen with a leaving group, but in this case the leaving group is bromine instead of  $N_2$ . This is done by briefly forming the N-bromoamide by using base and  $Br_2$ . Once you deprotonate this, it can go through the same kind of rearrangement and form an isocyanate, which can go through any of the reactions shown above.

# Loudon Chapter 23 Review: Amines

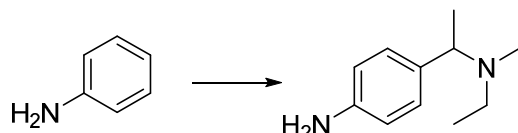
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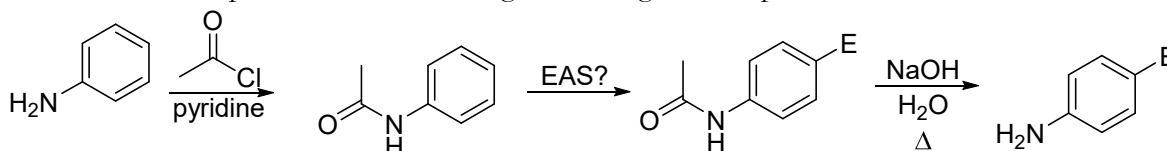
Curtius is usually safer for the molecule due to the milder conditions, but the acyl azides are more dangerous to work with because they're often explosive.

## Ch. 23 Synthesis Practice

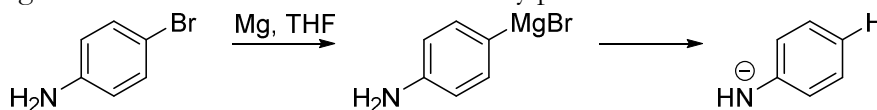
Let's try this one:



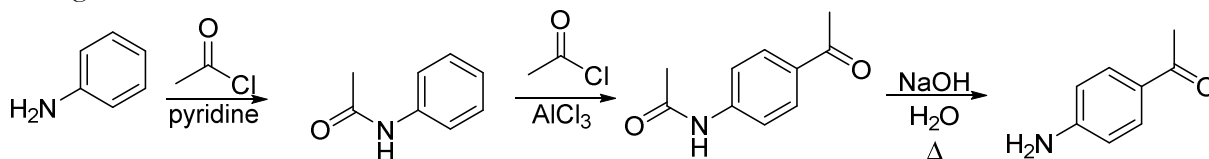
At some point we'll need to use EAS to add something to the ring, at the para position. But if we try to just do EAS straight away, we run into the problem of  $\text{-NH}_2$  getting protonated to  $\text{-NH}_3^+$ . So let's protect, add something to the ring, then deprotect.



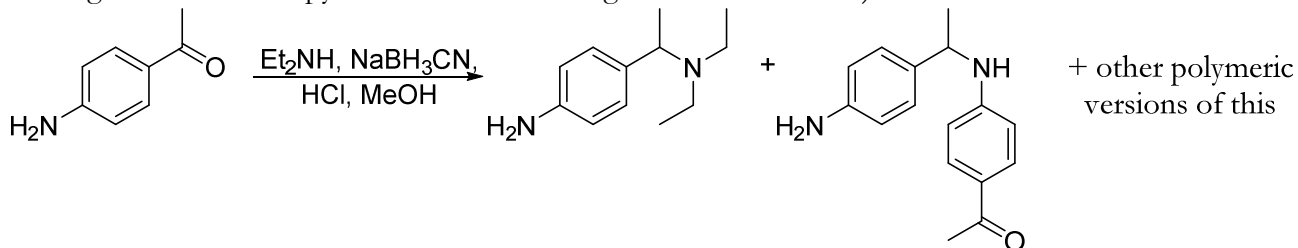
What should we add? We could add a Br, then convert to a Grignard, then attack a carbonyl. But this Grignard can't exist because it'll immediately protonate itself from its  $\text{-NH}_2$ .



Instead, let's just stick on the two-carbon bit that we need, and figure out the rest afterwards. We know we can make amines from aldehydes/ketones by reductive amination, so let's try adding a ketone.



Now we can go straight into reductive amination. But wait! If we do this, we'll get a reaction between the amine on one ring and the carbonyl of another ring, in addition to the product we want. (We might be able to get around this by carefully controlling stoichiometry – adding the compound slowly to a mixture of the other reagents, to minimize the odds of it reacting with another copy of itself. But assuming we don't do that...)



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We can get around this by leaving the ring -NH<sub>2</sub> protected while we're doing reductive amination, then deprotect it as the last step. So here's the final version, start to finish.

