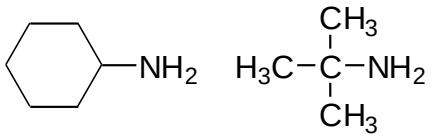
Amines

Amines are derivatives of ammonia with one or more alkyl groups bonded to the nitrogen.

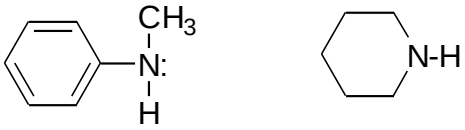
Amines can be classified as primary, secondary or tertiary, meaning one, two and three alkyl groups bonded to the nitrogen respectively.

E.g.

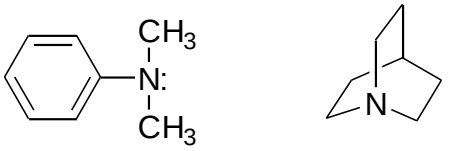
Primary Amines



Secondary Amines

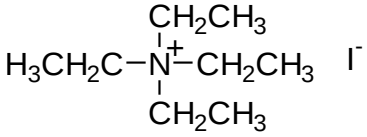


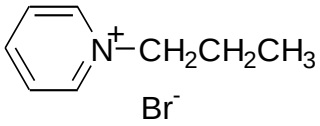
Tertiary Amines



Quaternary ammonium salts have four alkyl groups bonded to the nitrogen, and the nitrogen bears a full positive charge.

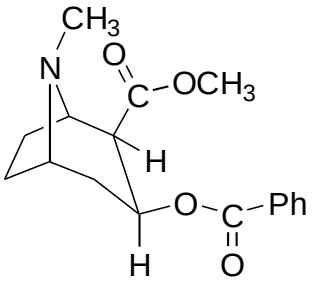
E.g.

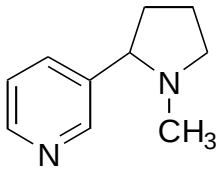




Amines are a very common functional group in organic chemistry, and especially so for naturally occurring compounds.

E.g.



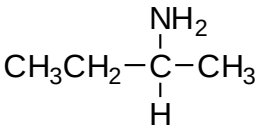


<u>Nomenclature</u>

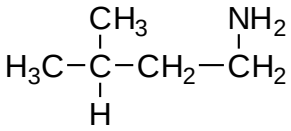
The IUPAC nomenclature is analogous to that for alcohols, where the -e of the alkane ending is replaced with -amine.

Other substituents on the carbon chain are given numbers, and the prefix N- is used for each substituent on nitrogen.

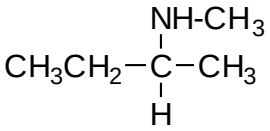
E.g.



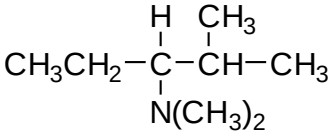
2-butanamine



3-methyl-1-butanamine



N-methyl-2-butanamine



2,N,N-trimethyl-3-pentanamine

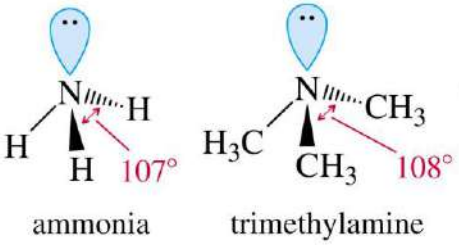
Aromatic amines are called by their historical/trivial names, with phenylamine being called aniline. Other nitrogen heterocycles have ring system names that need to be learned also. (The N is normally considered to be numbered 1).

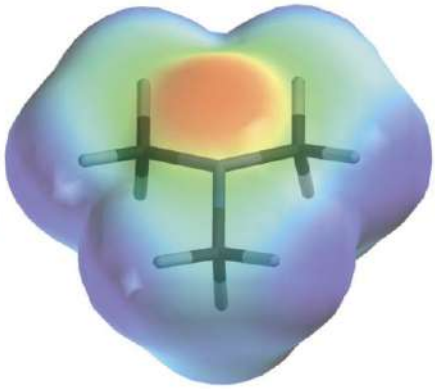
Aziridine, pyrrole, pyrrolidine, imidizole, pyridine, piperidine, pyrimidine

Structures of Amines

Previously we have seen that ammonia (NH_3) has a slightly distorted tetrahedral shape, due the compression of the ideal 109.5° angle by lone pair-bond pair repulsion.

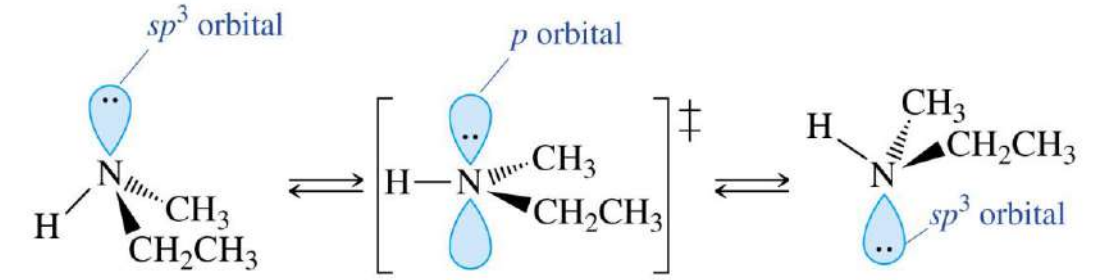
This effect is less pronounced with alkyl groups, and trimethylamine has bond angles closer to the perfect sp^3 arrangement than ammonia.





electrostatic potential map of trimethylamine

Since an amine has three substituents and a lone pair, the question of chirality arises. If an amine has three different substituents (and its lone pair) can we resolve the amine into enantiomers? In **most** cases, this is not possible since the enantiomers can interconvert through a low energy pathway. The interconversion takes place through a **nitrogen inversion**, where the lone pair moves from one face of the molecule to the other, and back.



The lone pair starts off in an sp^3 orbital, but in the transition state of the inversion, the nitrogen can rehybridize to sp^2, with the lone pair in a p orbital.

This is not a high energy situation, and only requires 6kcal of energy to achieve this TS (therefore easy at room temperature).

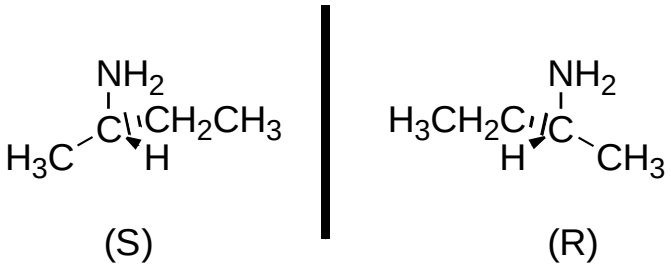
At the TS, the inversion can occur or return back to the original enantiomer - single enantiomers cannot be resolved in most cases.

Exceptions

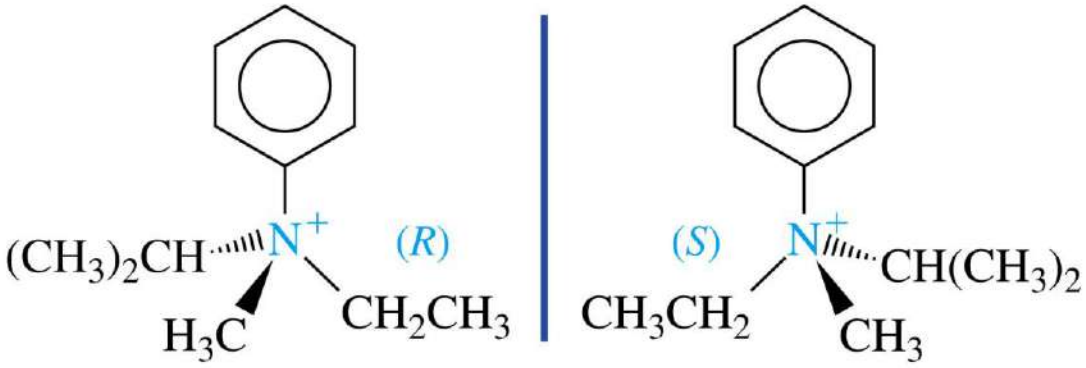
There are certain special cases where amines are chiral.

(In the C-I-P convention, lone pairs have the **lowest** priority).

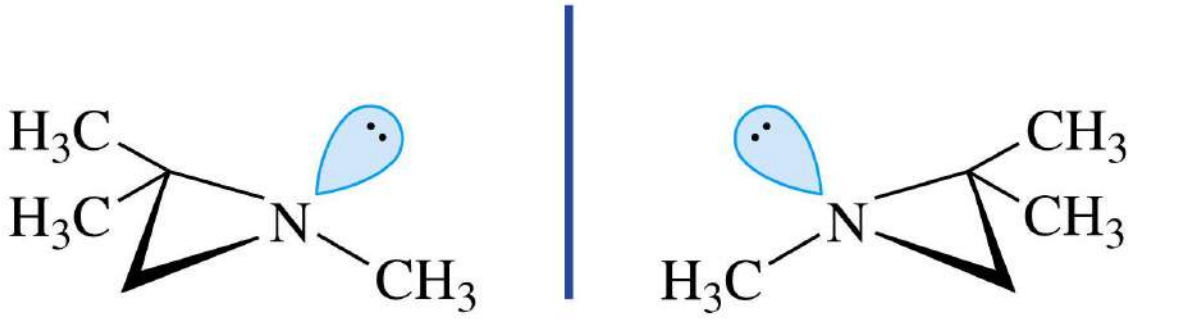
Case 1: Amines whose chirality stems from the presence of chiral carbon atoms. E.g. 2-butanamine.



Case 2: Quaternary ammonium salts with chiral nitrogen atoms. Here the nitrogen inversion is impossible since there are four substituents on the N, and no lone pair.



Case 3: Certain amines cannot attain the sp^2 hybridization required for nitrogen inversion.



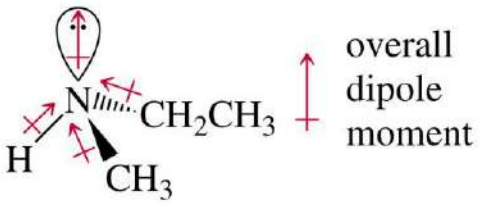
(*R*)-1,2,2-trimethylaziridine (*S*)-1,2,2-trimethylaziridine

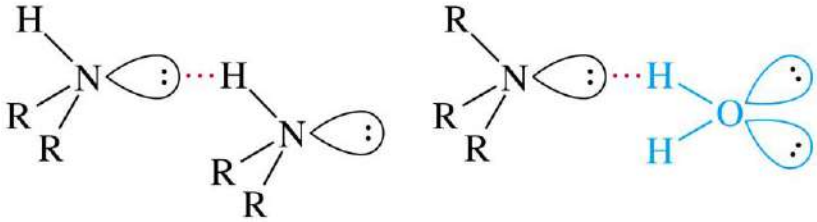
Examples of this include nitrogen atoms in small rings (aziridines).

The required bond angle of 120° is unobtainable in the strained system, and so the TS required for nitrogen inversion is of too high energy, and thus chiral aziridines **can** be resolved into enantiomers.

Physical Properties

The N-H hydrogen bond is not as strong as the O-H hydrogen bond in analogous molecules. Primary amines will have lower mp and bp than the corresponding primary alcohol. Secondary amines, which have NH groups, will have higher mp and bp than the corresponding ether.





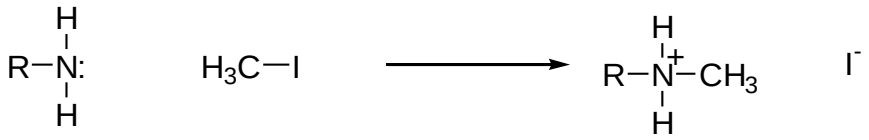
1° or 2° amine: hydrogen bond donor and acceptor

3° amine: hydrogen bond acceptor only

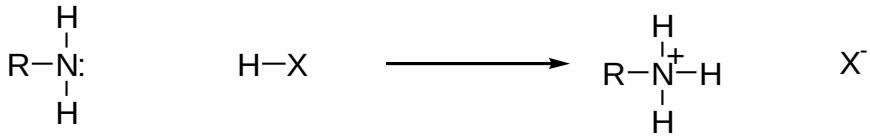
Basicity of Amines

The nitrogen atom of amines has a lone pair of electrons, and this gives rise to characteristics of nucleophilicity and basicity (a Lewis base).

Amine as a nucleophile:



Amine as a base:



Amines are basic, and therefore their aqueous solutions are basic (pH>7), and recall that base strength is talked of it terms of base-dissociation constant (K_b).

The values of K_b for most amines are small (10^{-3}), but still basic.

Since amine basicity values span many orders of magnitude, discussion of pK_b values is more common.

Remember $pK_b = -\log_{10} K_b$

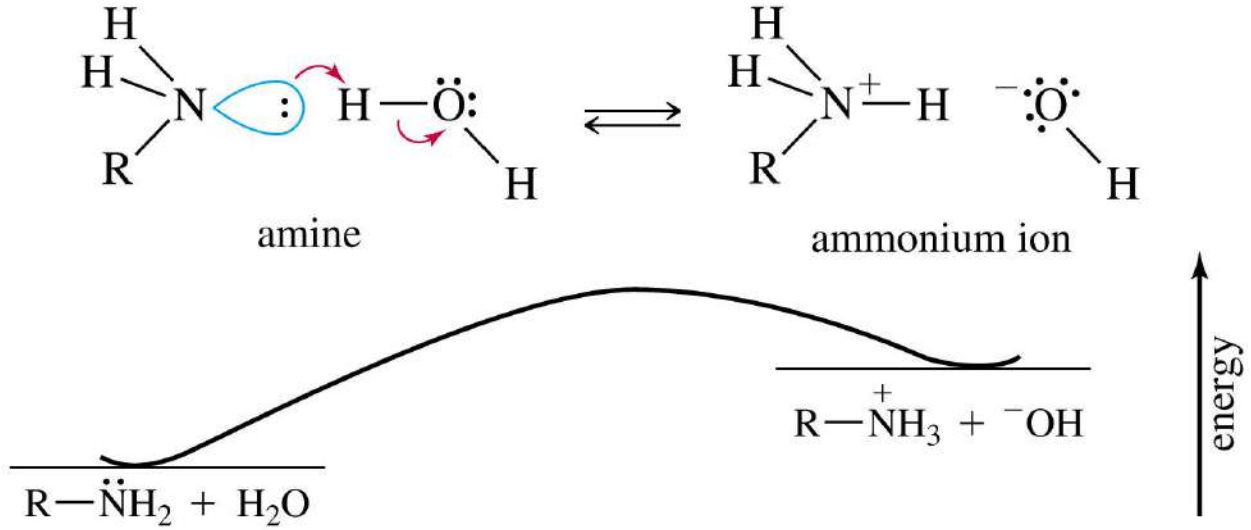
And that $K_aK_b=K_w = 10^{-14}$

E.g.

Table 19-3 (SLIDE)

Effects on Amine Basicity

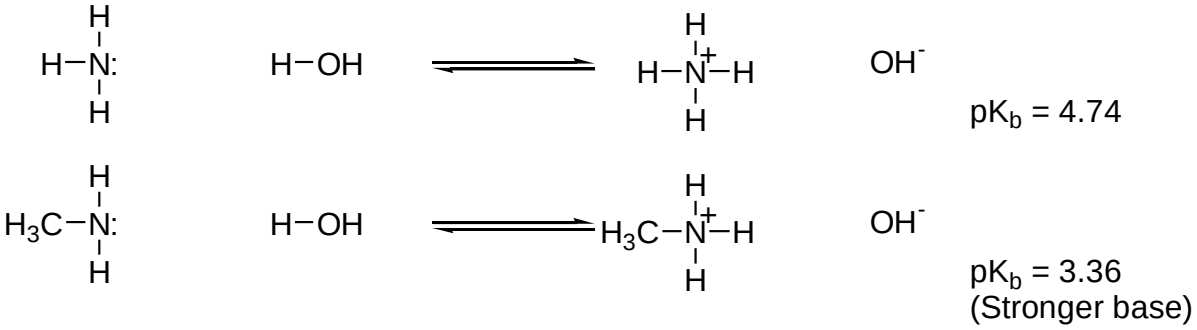
Consider the energy level diagram for the reaction of a general amine with water.



Any feature that stabilizes the ammonium ion relative to the free amine helps shift the equilibrium to the right, and therefore makes the amine a stronger base (and vice versa).

(a) Alkyl group substitution

If we consider the relative basicities ammonia and methylamine, then we might expect the electron donating abilities of the alkyl group to help stabilize the ammonium cation produced, thus making methylamine a stronger base than ammonia.



This is indeed the case.

However the above logic implies that secondary amines should be stronger bases than primary amines, and that tertiary amines the strongest bases of all.

This is **not** true, and the real situation is more complicated involving solvation effects and steric hindrance.

The overall net result of the combination of these three effects is that primary, secondary and tertiary amines **are all of approximately** equal basicity, and all stronger bases than ammonia itself.

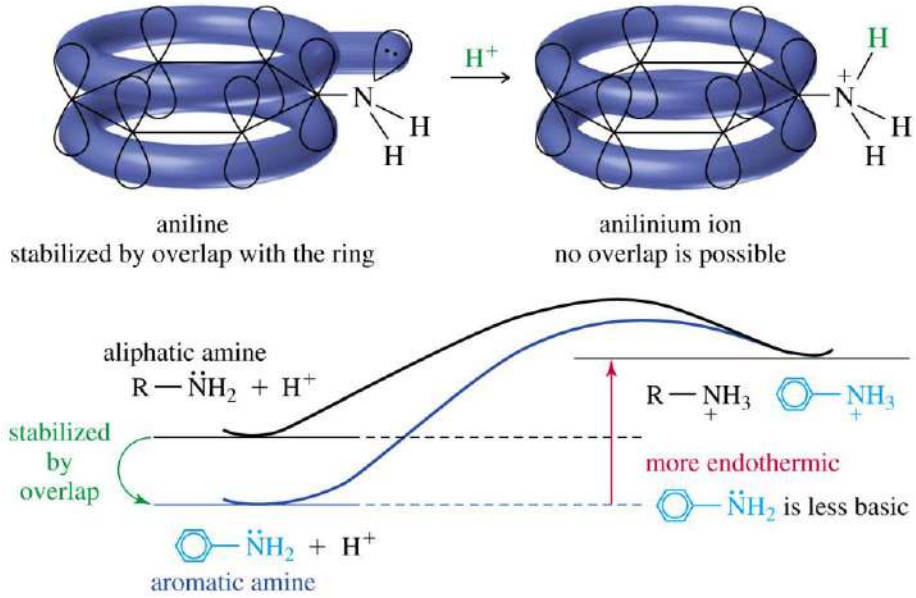
(b) Resonance Effects

Aromatic amines, such as aniline, are **weaker** bases than normal aliphatic amine.

This is due to the fact that the lone pair of electrons on the nitrogen are delocalized into the aromatic π system.

This stabilizes the free amine, and therefore makes the transition to the protonated form more endothermic than the aliphatic case - and thus less energetically favorable.

The stabilizing overlap in aniline, makes the lone pair less reactive, therefore a weaker base.

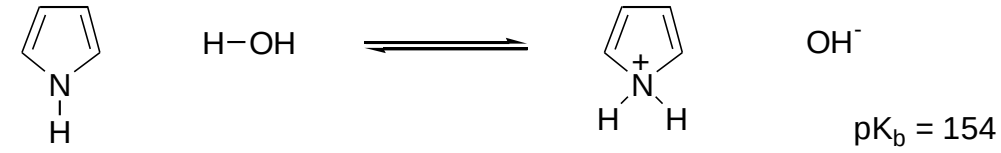


Resonance effects are also pronounced for pyrrole.

Pyrrole is a weak base since the lone pair is used in contributing to the aromatic π system.

The use of the lone pair to form a bond to hydrogen (i.e. protonation) removes the lone pair from the π system, and this makes the protonated form no longer aromatic - this is energetically unfavorable.

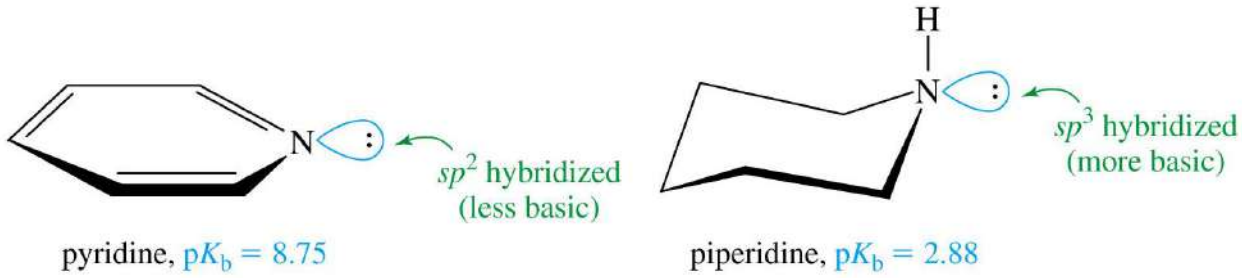
E.g.



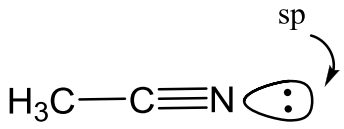
(c) Hybridization Effects
We have already observed that electrons held in orbitals that have **more** s character are held **more** tightly.

Therefore a lone pair held in an sp orbital will be more strongly held (i.e. less basic) than a lone pair held in an sp^3 orbital.

E.g. Pyridine, piperidine



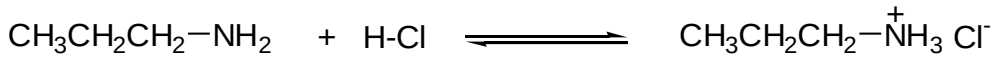
and acetonitrile, $pK_b = 24$



Salts of Amines

When an amine is protonated, an amine salt is produced.

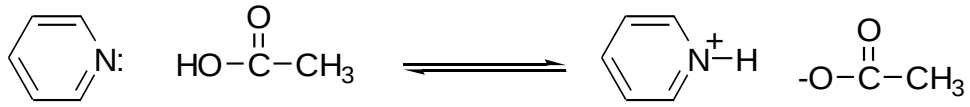
The amine salt consists of two parts: the cationic ammonium ion, and the anionic counter ion.



Simple amine salts are named as substituted ammonium salts, whereas more complicated amine salts use the name of the amine and the acid that create the salt.

E.g. $(CH_3CH_2)_3N: + H_2SO_4 \rightarrow (CH_3CH_2)_3NH^+ HSO_4^-$

Triethylammonium hydrogen sulfate



Pyridinium acetate

Amines are generally volatile, smelly liquids, whereas the ammonium salts are crystalline, high melting solids.

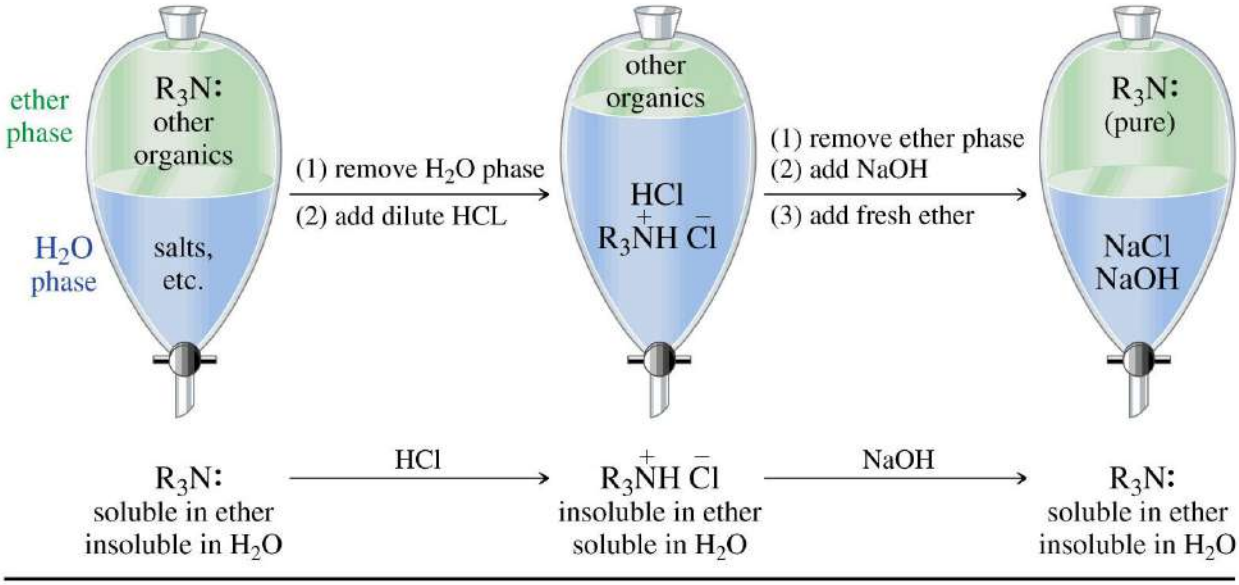
These ionic solids are soluble in water, but insoluble in organic solvents.

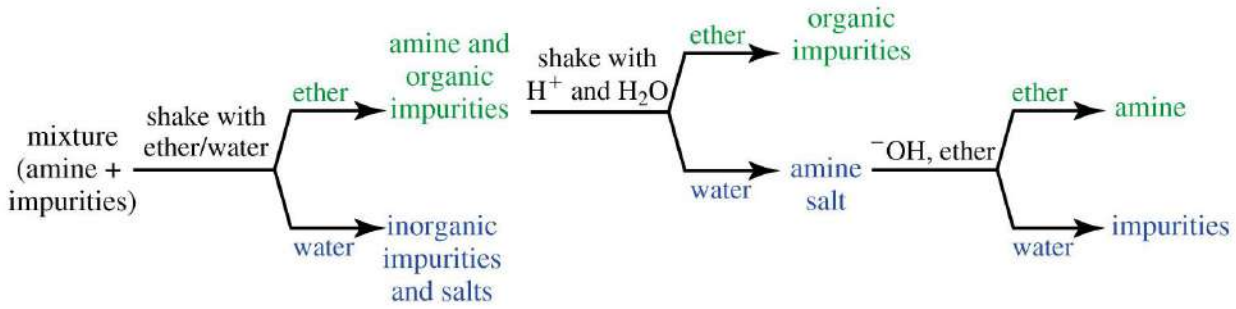
The free amines are generally insoluble in water, but soluble in organic solvents.

This provides an excellent method for the separation and isolation of amine compounds.

Free amines are insoluble in water, but when dilute acid is added, the ammonium salt is produced, which dissolves.

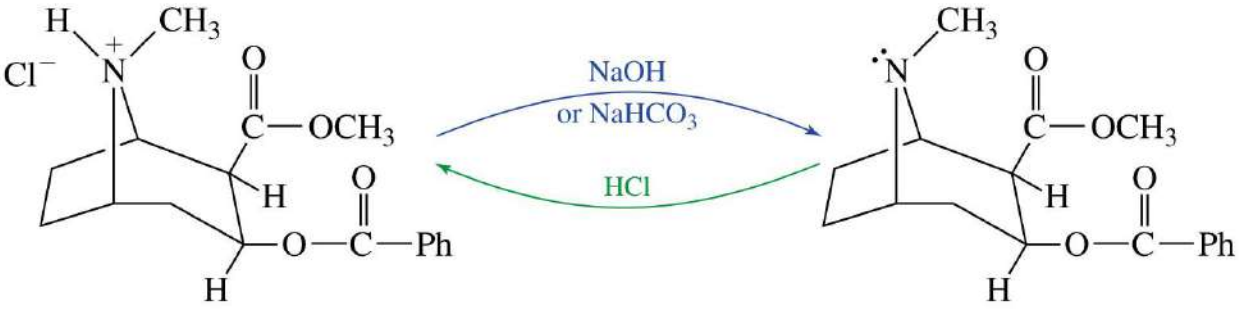
(Formation of a soluble salt is a simple chemical analytical test for amine functionalities).





When the solution is made alkaline (by adding NaOH), the now purified free amine is regenerated, which is insoluble in the aqueous solution and therefore precipitates, or can be extracted into an organic solvent.

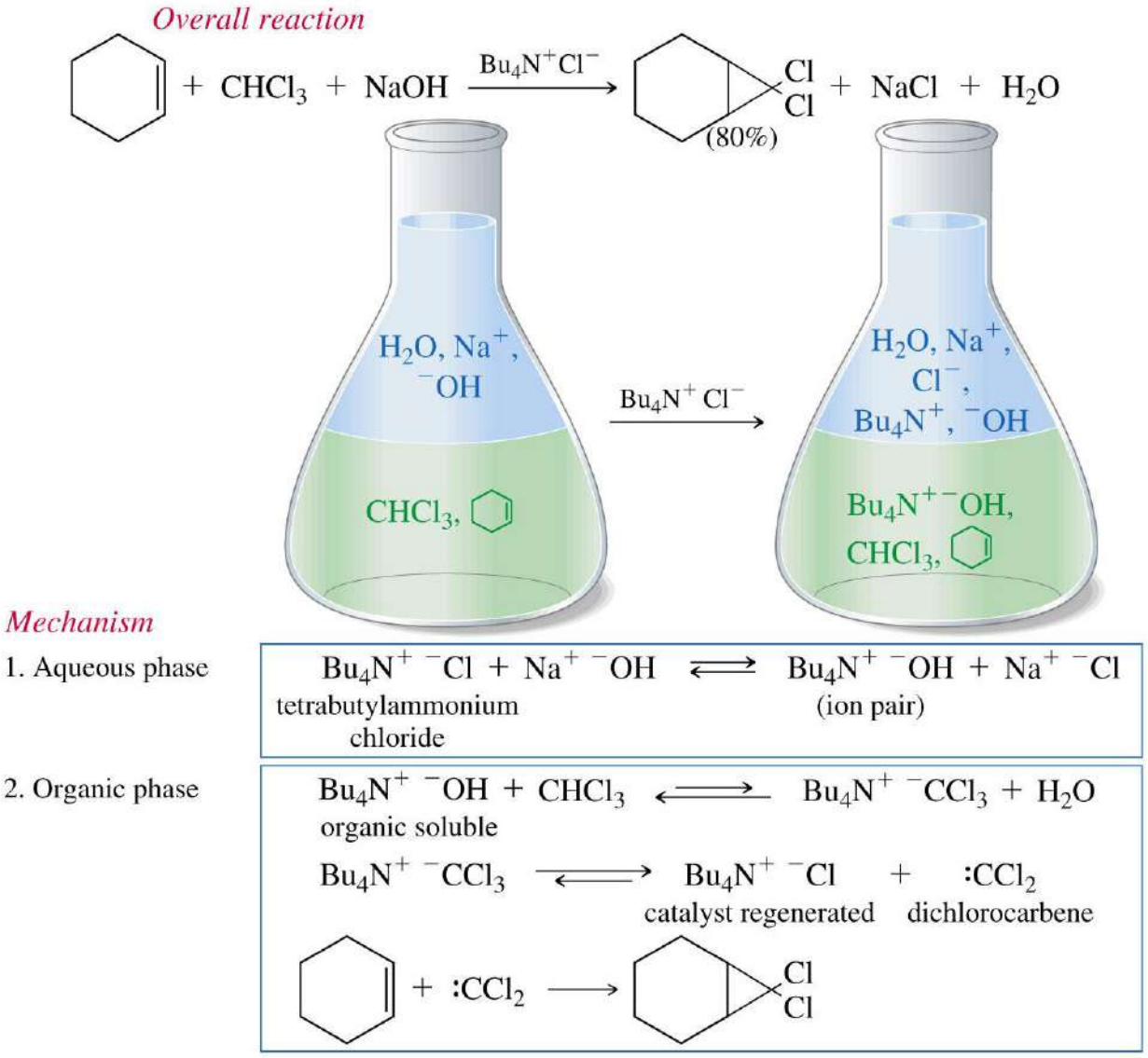
This procedure is typical/useful for the purification of all amine containing compounds (cocaine→ crack, etc).



cocaine hydrochloride

cocaine "free base"

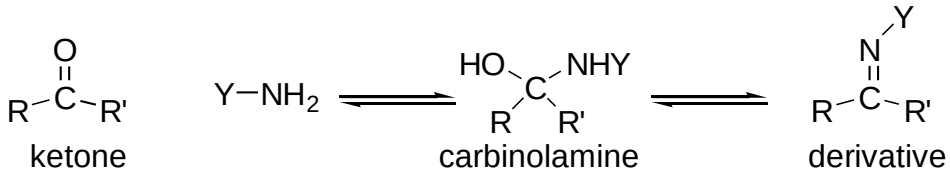
Amine salts as phase transfer catalysts



Reactions of Amines

With Carbonyl Groups

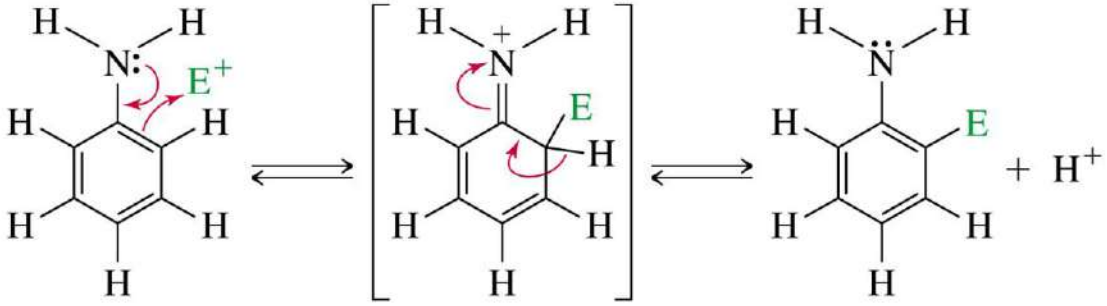
We have already seen the reaction of various amines with ketones and aldehydes to generate imines and their analogues. E.g.

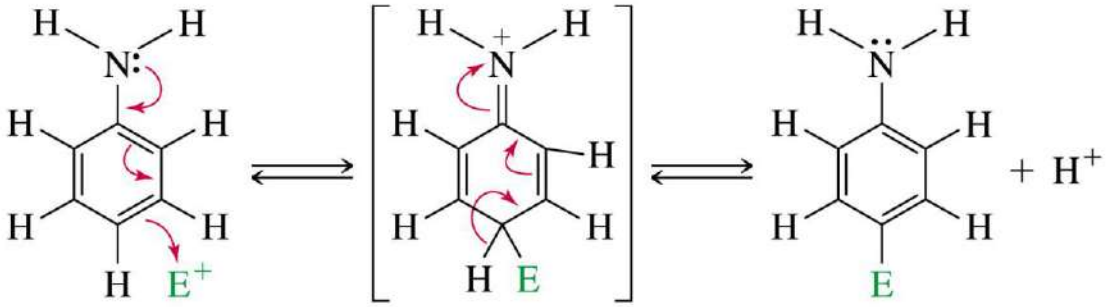


Y = H (or alkyl) = Imine
= OH = Oxime
= NHR = Hydrazone

Aromatic Substitution of Aryl and Heterocyclic Amines

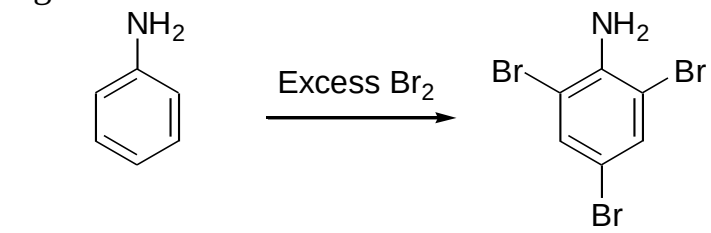
Aryl amines are activating, ortho/para directors in electrophilic aromatic substitution reactions, since the lone pair stabilizes the intermediate cationic sigma complexes formed at these two positions of attack.

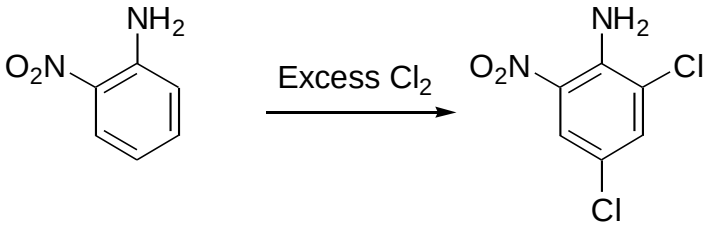




Aniline and its derivatives are so reactive that if excess reagent is used, then all the available ortho and para positions become substituted.

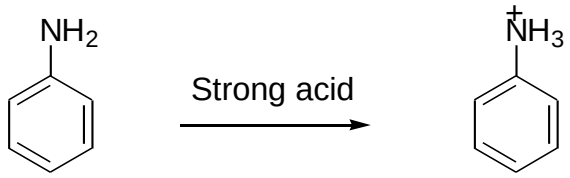
E.g.





Attention must be paid to the reaction conditions.

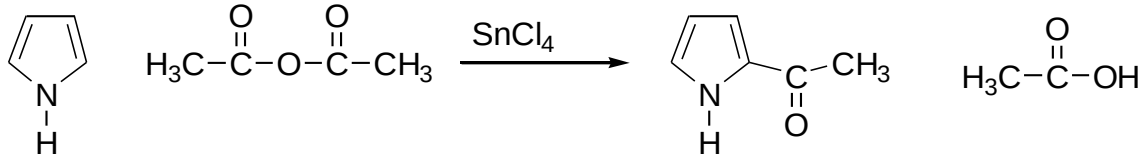
In strongly acidic conditions, the amino group becomes protonated, and thus is converted to a deactivating, meta director.



<u>Electrophilic Aromatic Substitution of Pyrrole</u>
Pyrrole undergoes EAS more readily than benzene itself, and thus milder and reagents and conditions may be used.

Reactions such as nitration, halogenation, FC alkylation and acylation all work, but milder conditions must be employed.

E.g. instead of an acid chloride, an anhydride is used for acylation.



Also weaker Lewis acid catalysts such as $SnCl_4$ are employed.

Attack at the C-2 position is preferred over attack at C-3.

Figure 19-11 (SLIDE)

EAS of Pyridine

Pyridine behaves like a strongly deactivated aromatic compound in EAS reactions.

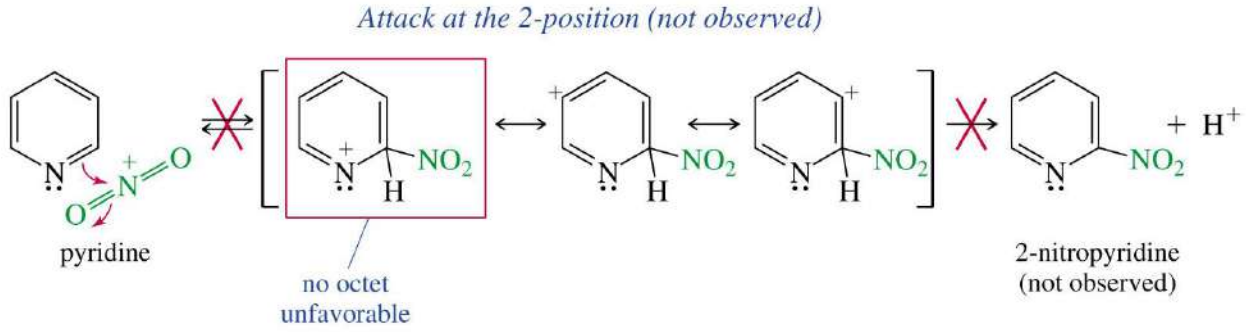
FC alkylations and acetylations fail, and other EAS reactions require unusually **harsh** reaction conditions.

The deactivation arises from the electron withdrawing effect of the nitrogen atom in the ring.

The lone pair of the nitrogen sticks out away from the π system, and so **cannot** be used to stabilize any positively charged intermediates.

When pyridine does react, it displays a preference for substitution in the 3 position, which is meta direction (like other deactivating substituents).

Consider attack at C-2 and C-3:

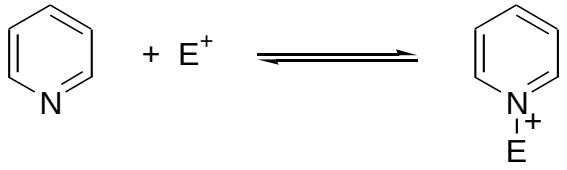


Electrophilic attack at C-2 produces a sigma complex that has one resonance form with only 6 electrons and a positive charge on nitrogen (high energy).

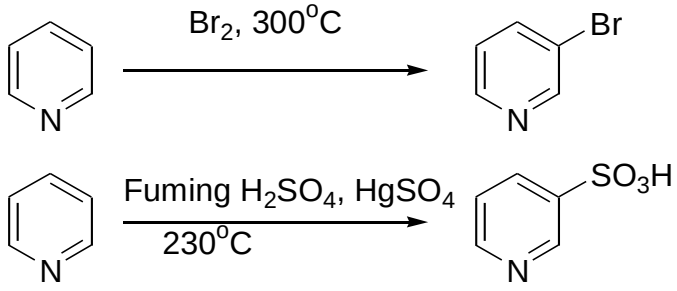
In contrast, for C-3 substitution, all resonance forms of the sigma complex have the positive charge on the less electronegative carbon atoms.

EAS is further inhibited by pyridine because of the tendency of the nitrogen atom to react directly with the electrophile, generating a pyridinium ion (which is still aromatic).

This positively charged pyridinium ion is even more deactivated to EAS than pyridine itself.

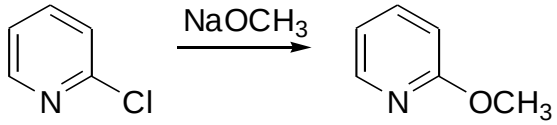


Examples of EAS reactions that do actually work on pyridine are shown below (note the very harsh conditions).



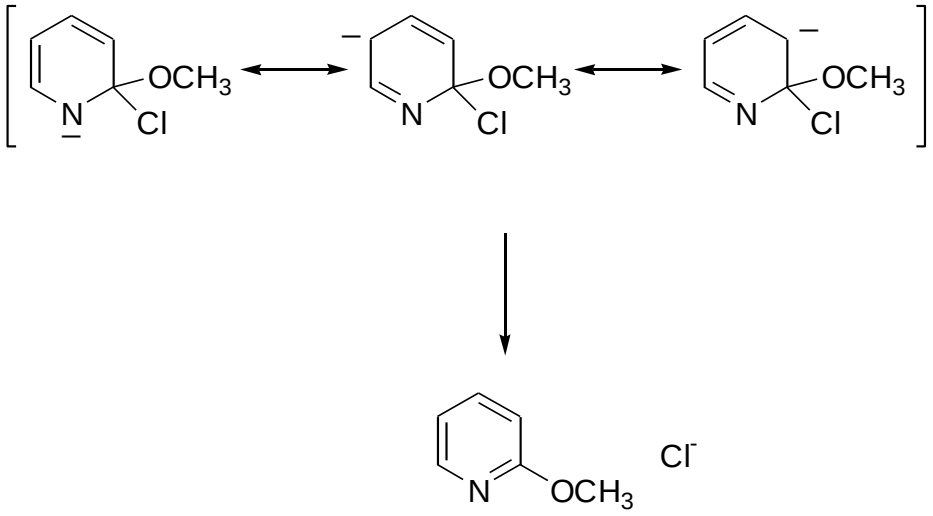
<u>Nucleophilic Aromatic Substitution</u>
Pyridine is strongly deactivated to EAS, but is activated toward attack by nucleophiles, i.e. NAS.

If there is a good leaving group at either the 2 or 4 position, then NAS may occur.

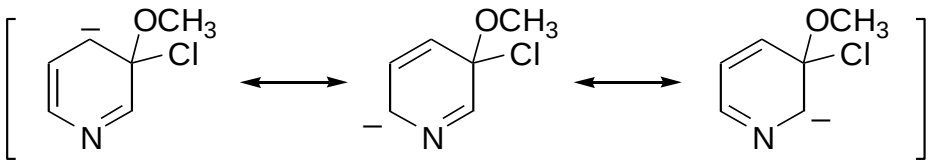


Consider the (negatively) charged sigma complexes for attack occurring at C-2 and C-3:

C-2 Attack



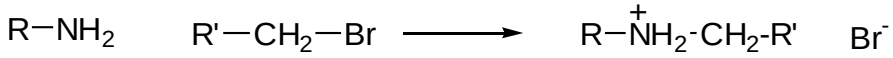
Attack at C-3



The negative charge on the electronegative nitrogen (good) can **only** be produced in resonance forms from attack at C-2 (and C-4).

Alkylation of Amines

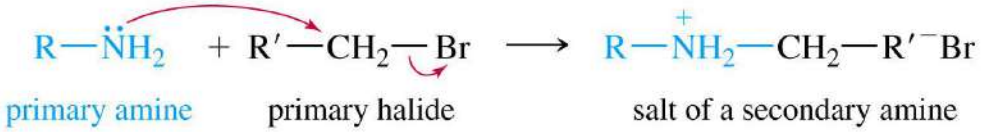
Amines react with primary alkyl halides to give alkylated ammonium halides.

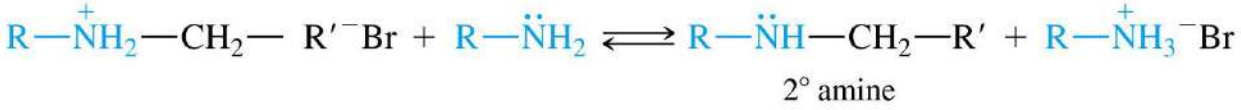


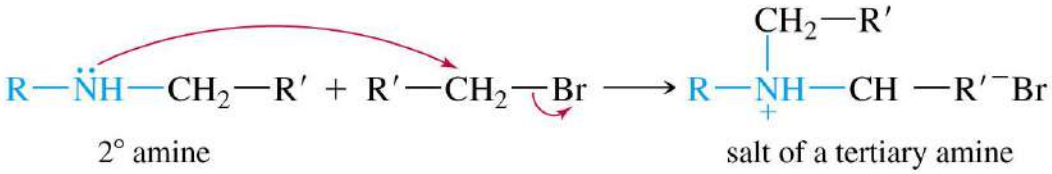
(This direct alkylation usually proceeds via the S_N2 mechanism, so does not work with tertiary halides which are too hindered).

Since amines are bases, this creates a problem:

The ammonium salt formed initially, can be deprotonated by the remaining amine.





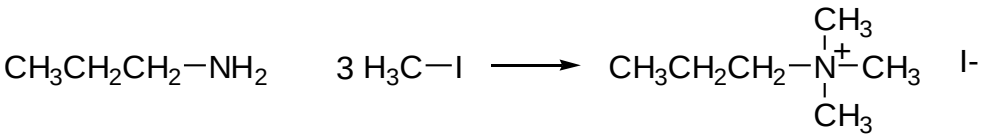


This produces a secondary amine, which can react with the alkyl halide.

Direct alkylation cannot be easily stopped at the desired level alkylation - complex mixtures of products are observed (bad).

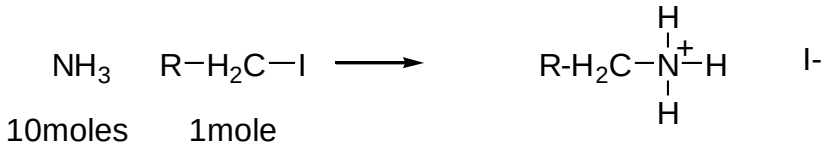
There are two cases where the alkylation of amines <u>are</u> reasonable synthetic routes:

(1) <u>Exhaustive alkylation to give tetra-alkylammonium salts.</u>
If enough alkyl halide is used to alkylate the amines all the way to the tetra-alkylammonium cations, then we get a single (exhaustively) alkylated product.
E.g.



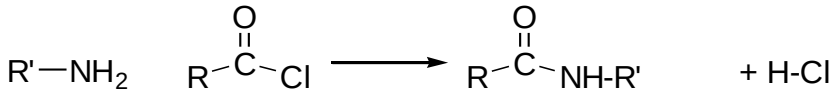
(2) Reaction with a large excess of ammonia.
Since ammonia is so inexpensive, it can (acceptably) be used in large excess. The primary alkyl halide is added slowly to the large excess of ammonia, and so the probability of dialkylation is as low as possible.

E.g.



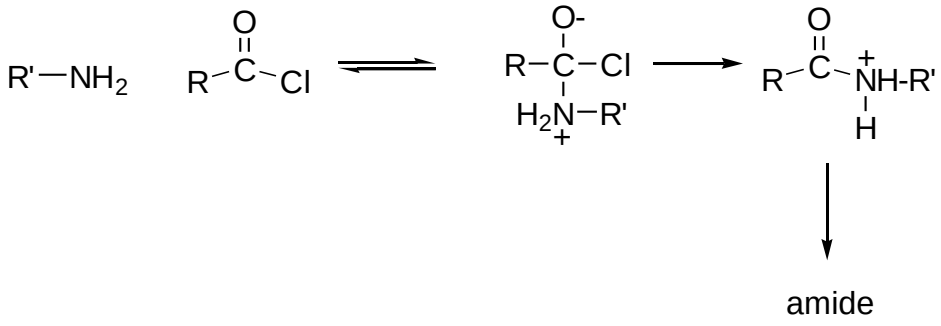
Acylation of Amines using Acid Chlorides
Primary and secondary amines react with acid halides to produce amides.

E.g.



This reaction is an example of nucleophilic acyl substitution - the replacement of a leaving group with a nucleophile on a carbonyl group.

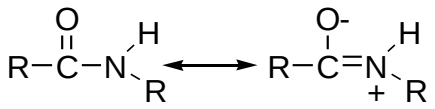
The amine attacks the acid chloride just like any other carbonyl compound at the electrophilic carbon.



The acid chloride is more reactive than an aldehyde or ketone since the electronegative chlorine pulls electron density away from the carbon making it more reactive.

The tetrahedral intermediate formed is negatively charged, and since chlorine is a good leaving group, the C=O bond reforms with the expulsion of the good leaving group.

The amide produced is much less reactive towards (further) acylation reactions since the lone pair on the nitrogen is delocalized onto the oxygen, thus making amides much less nucleophilic (and basic) than amines.

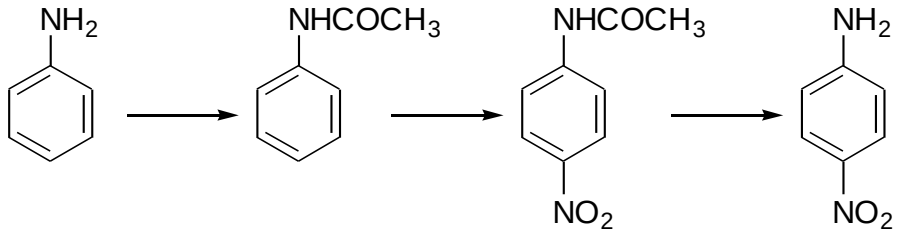


We can take advantage of this reduced basicity of amides in Friedal-Crafts type reactions of aryl amines. The amino group of aniline is powerfully electron donating and o/p directing in FC reactions.

However we have seen that in strongly acidic media the amino group becomes protonated and is transformed into a deactivated, meta directing substituent.

Amides are <u>not</u> protonated under such conditions, and often aryl amines are converted into their corresponding amides before EAS are performed.

E.g.

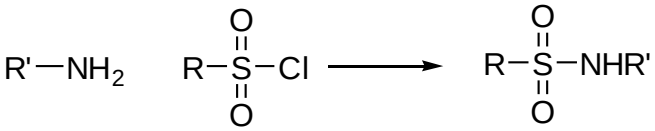


After the reaction, the amide group is simply hydrolyzed back to the amino group by mild acid (or base) treatment (see later).

Reaction of Amines with Sulfonyl Chlorides (Sulfonamides)
Sulfonyl chlorides are the acid chlorides of sulfonic acids.

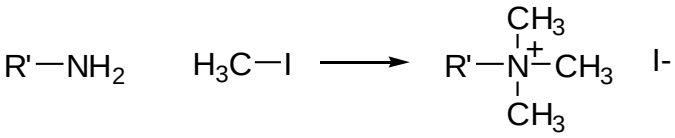
sulfonic acid sulfonyl chloride

Just like before, amines react with displacement of the chlorine. The amides derived from sulfonic acids are called sulfonamides.



Amines as Leaving Groups (Hoffman Elimination)
The amino group (-NH_2 or -NHR) is a poor leaving group.

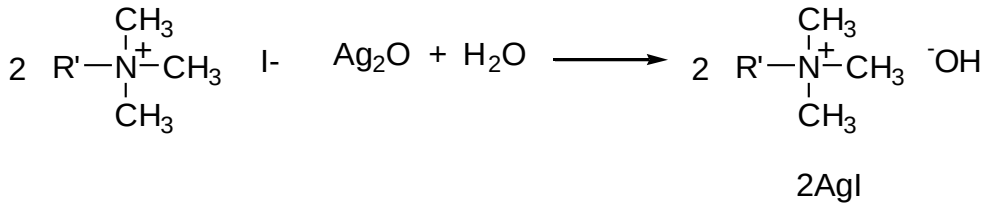
However, the amino group can be converted into a very good group via exhaustive methylation (usually using CH_3-I).



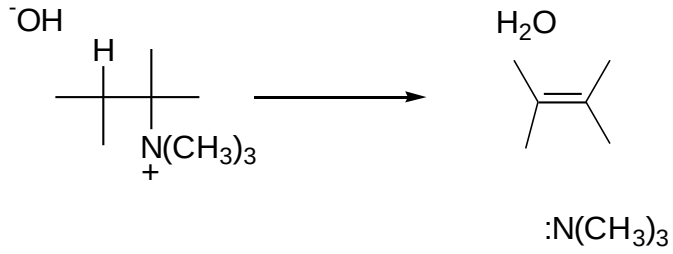
The quaternary ammonium salt is a very good leaving group since when it leaves, it produces a neutral amine.

The elimination of the quaternary ammonium salt usually takes place via the E2 mechanism - requires a strong base.

The ammonium iodide salt is converted to the corresponding hydroxide salt (strong base) by reaction with silver oxide.

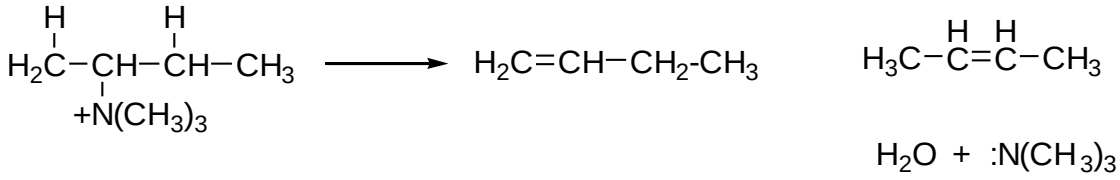


Heating the quaternary ammonium hydroxide salt produces elimination, and an alkene is produced.



This is called the Hoffman elimination.

E.g. 2-butanamine is exhaustively methylated, converted to the hydroxide salt and heated, thus generating a mixture of 1-butene (major) and 2-butene (minor).



Satzyeff vs.Hofmann

In Ch 7 we saw that normally in elimination reactions, the most **highly** substituted alkene was the one preferentially formed.

However here the least substituted alkene is the major product.

We say that this is a Hoffman product, and the most substituted alkene product is the **Satzyeff** product.

So why does the Hoffman elimination have this (unexpected) preference for the least substituted alkene?

There are many factors but the simplest explanation is because of the huge steric size of the leaving group.

Recall that the E2 mechanism requires an anticoplanar arrangement of the leaving group and the proton being removed.

The large steric bulk of the leaving group interferes with this necessary arrangement.

For the 2-butanamine case, the leaving group is trimethylamine, and the proton being lost either comes from C-1 or C-3.

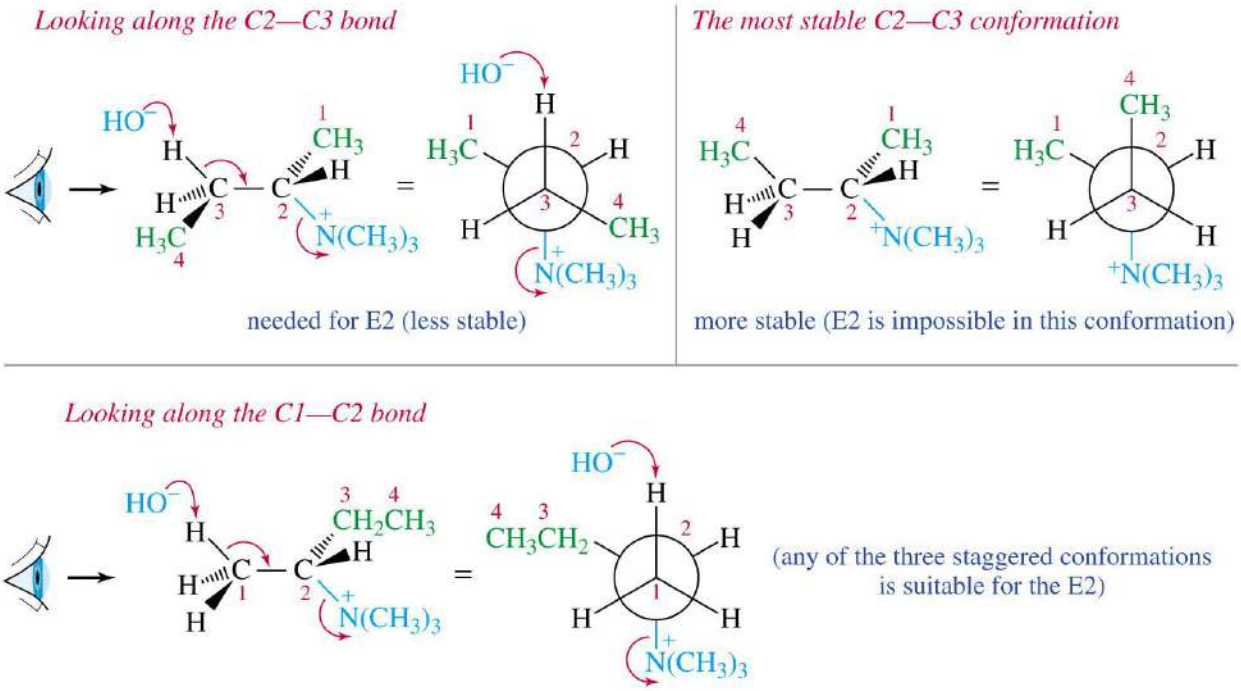
Let us consider the loss of the proton from C-3 first. ($\rightarrow$ Satzyeff Product)

The most stable conformation for this molecule has the two largest substituents arranged anti.

This conformation does not allow for any E2 elimination to occur.

To achieve a conformation suitable for E2 to occur, C-3 must rotate and place a Hydrogen anti to the bulky leaving group.

Figure 19-12 (SLIDE)
(Note the book messed up its numbering scheme so use mine!)

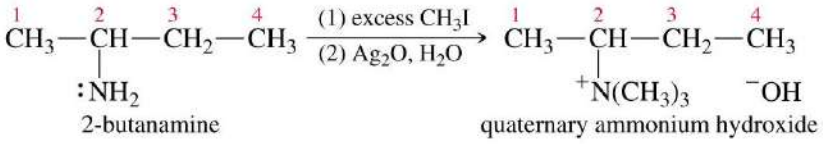


To remove the proton from C-1 (→ Hoffman product), any of the three staggered conformations allow the E2 mechanism to operate.

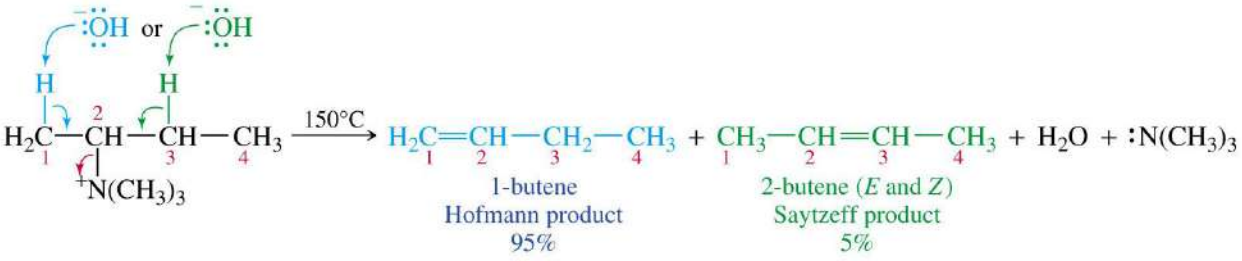
The Hoffman product dominates since elimination of one of the hydrogens on C-1 involves a lower energy, and more statistically probable transition state than the sterically hindered TS required for C-3 elimination.

Thus Hoffman elimination always gives the least substituted alkene product (Hoffman product).

Exhaustive methylation and conversion to the hydroxide salt



Heating and Hofmann elimination



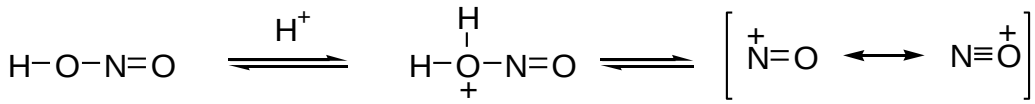
Reaction of Amines with Nitrous Acid

The reaction of amines with nitrous acid (HNO_2) is a very useful synthetic reaction.

Nitrous acid is unstable and needs to be generated in situ by reaction of sodium nitrite and hydrochloric acid.

$$Na^+ {}^-O\text{-}N{=}O \; + \; HCl \; \rightarrow \; H\text{-}O\text{-}N{=}O \; + \; Na^+Cl^-$$

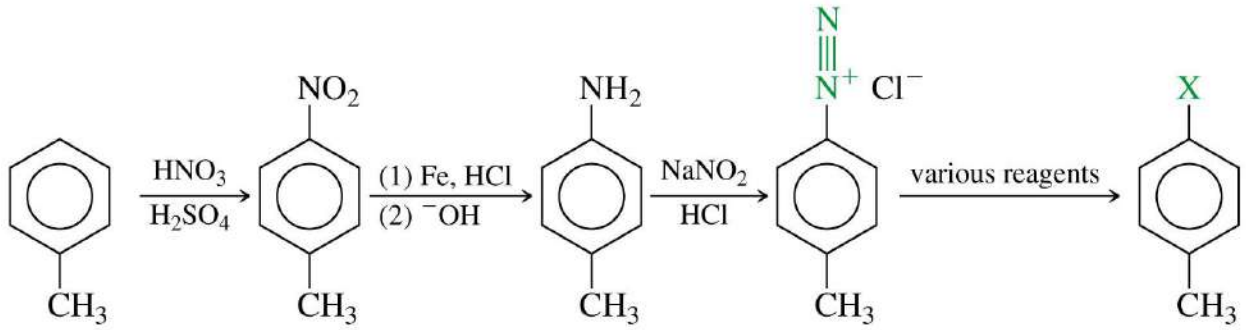
In very acidic media, nitrous acid can become deprotonated and lose water (acid catalyzed dehydration) and generate the nitrosonium ion, NO^+.



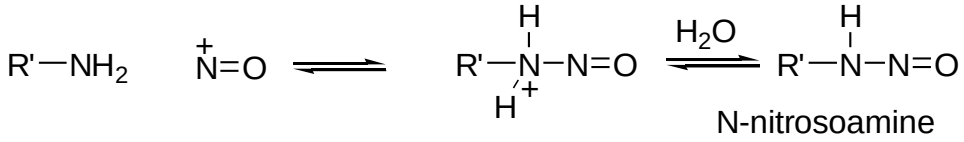
Reaction with Primary Amines (Diazonium Salts)

Primary amines react with nitrous acid (actually the nitrosonium ion) to produce compounds of the type $R\text{-}N_2^+$.

These are called **diazonium** cations.

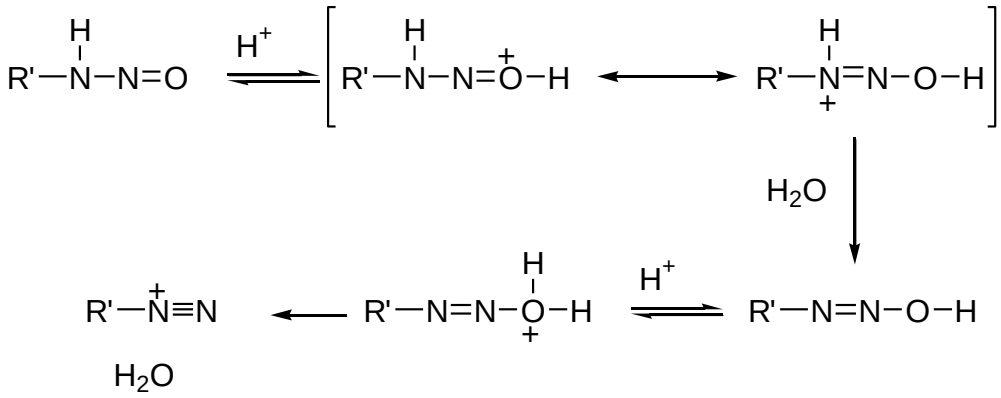


The diazotization procedure starts with the nucleophilic attack of the primary amine on the nitrosonium ion.



Deprotonation of the intermediate generates an N-nitrosoamine.

Tautomerism (proton transfer from nitrogen to oxygen) generates a compound which undergoes an acid catalyzed elimination of water, thus generating the diazonium cation.



The overall balanced reaction is:

$$R\text{-}NH_2 + NaNO_2 + 2HCl \rightarrow R\text{-}N_2^+ Cl^- + 2H_2O + NaCl$$

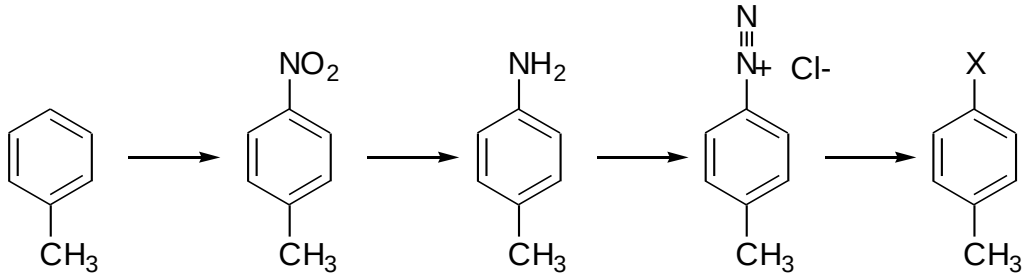
Diazonium salts are fairly unstable, but some are very useful intermediates, and can be converted into a whole variety of functional groups.

Arenediazonium Salts

Alkyldiazonium salts are fairly unstable, yet **arene**diazonium salts are stable up to temperatures of 0-10°C, and can be smoothly converted into halogens, nitriles, phenols, azo compounds, etc.

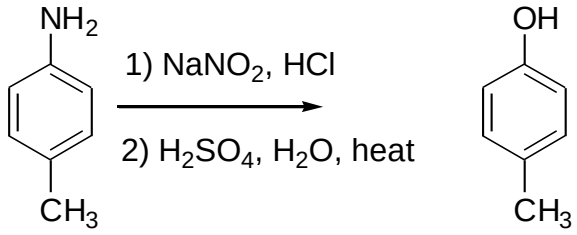
Arenediazonium salts are formed by diazotizing primary aromatic amines (which are prepared by reduced nitroarenes, which are prepared via nitration of the parent aromatic).

E.g.



Conversion to Hydroxyl

By heating the diazonium salt in a strong aqueous acid, hydrolysis occurs, and the product is a phenol.



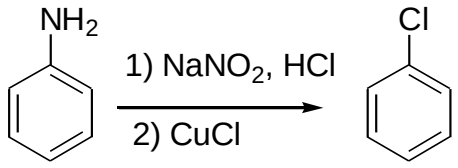
This route is generally preferable to the NAS route since much milder conditions are employed here.

The Sandmeyer Reaction (-Cl, -Br, -CN)

Copper (I) salts have a special affinity for the diazonium salts, and reaction of CuCl (or Br or CN) generates aryl chlorides (or bromides or nitriles).

The use of copper (I) salts in the replacement of diazonium groups is known as Sandmeyer reactions.

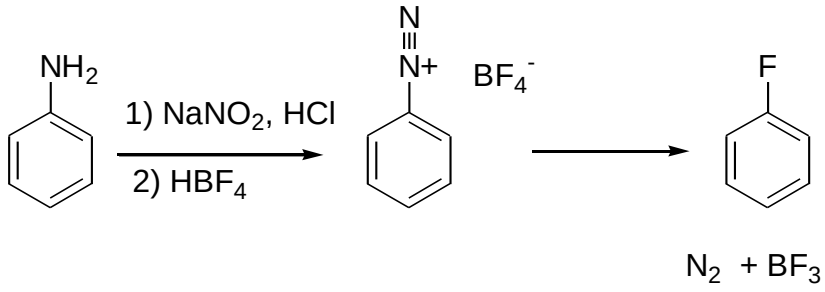
E.g.



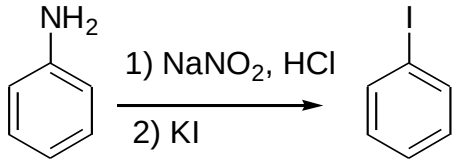
Fluorides and Iodides

These two halogens cannot be introduced via Sandmeyer chemistry.

To make an aryl fluoride, the diazonium salt is treated with fluoroboric acid, causing a precipitate of the diazonium fluoroborate salt, which is then heated to eliminate N_2 and BF_3, thus producing the fluorobenzene.

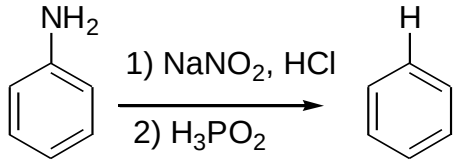


Aryl iodides are simply prepared by heating the arenediazonium salts with a solution of potassium iodide.



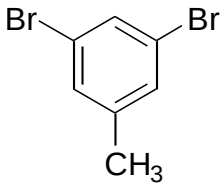
Reduction (Deamination)

When arenediazonium salts are treated with hypophosphorus acid, the diazonium group is replaced with a hydrogen.

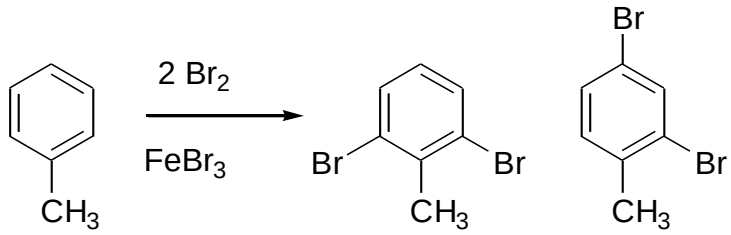


Even though this might seem pointless, it allows the removal of an amino group which was added to activate and direct specific EAS processes.

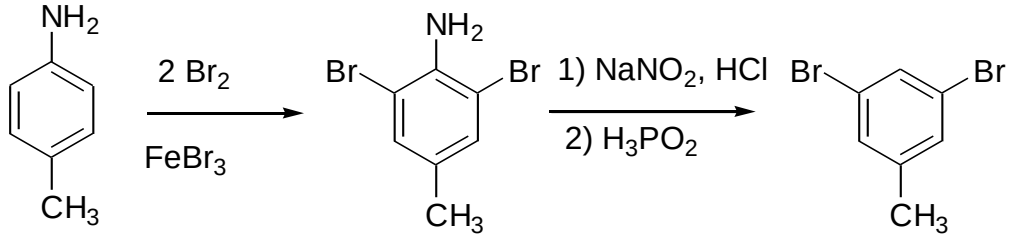
E.g. the synthesis of 3,5-dibromotoluene.



Bromination of toluene gives the wrong isomers.



Bromination of para-methylaniline gives a dibromo derivative, which on removal of the amino groups yields the desired 3,5-dibromotoluene.

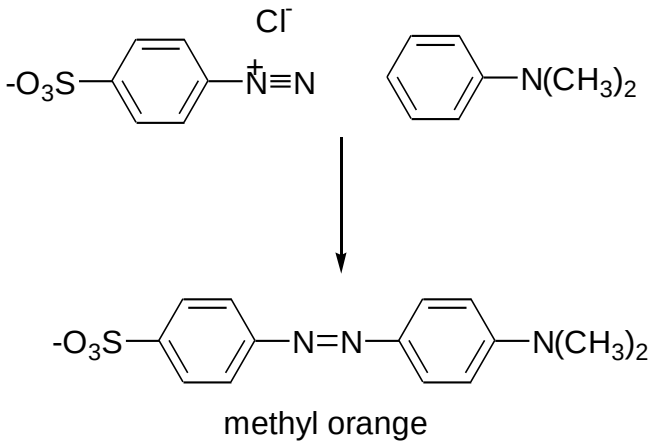


Diazo Coupling

Arenediazonium salts are positively charged and can act as (weak) electrophiles with powerful nucleophiles via EAS processes, generating compounds of the general type Ar-N=N-Ar'.

The -N=N- linkage is called an azo linkage.
Azo compounds are generally bright colored compounds, and find numerous application in the dye and coloring industries.

E.g.

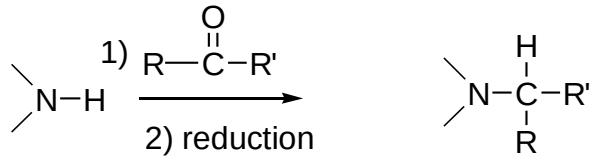


methyl orange

Synthesis of Amines

Reductive Amination

The most general method for synthesizing amines involves the reduction of an imine or oxime derivative of an aldehyde or ketone.



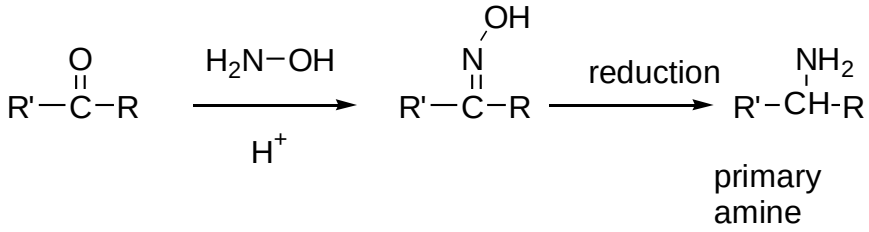
The reduction is most commonly achieved via $LiAlH_4$ or by catalytic hydrogenation.

The overall effect is to add another alkyl group to the original nitrogen.

This works to make primary, secondary or tertiary amines.

Primary Amines are made from condensation of hydroxylamine (zero alkyl groups bound to N) with a ketone or aldehyde, followed by reduction of the oxime produced.

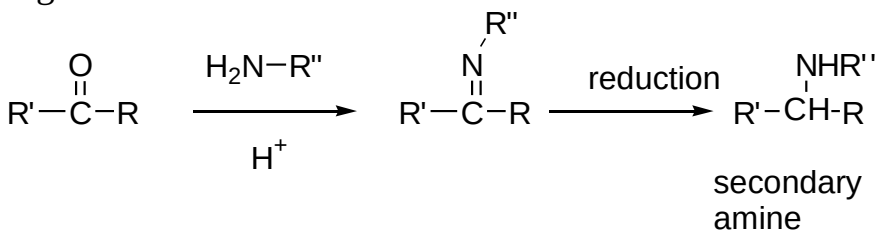
E.g.



The reduction is achieved by use of $LiAlH_4$, NaBH3CN (sodium cyanoborohydride - mild reducing agent) or catalytic hydrogenation.

Secondary Amines are made via condensation of a primary amine (one alkyl group) with a ketone (aldehyde), followed by reduction of the imine produced.

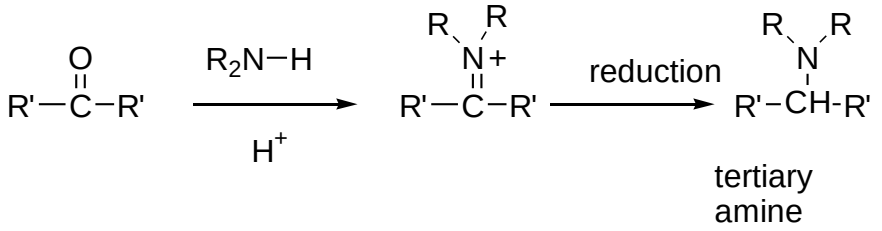
E.g.



Tertiary Amines are made via the condensation of a secondary amine (two alkyl groups) with an aldehyde or ketone, generating an iminium salt.

The iminium salts are usually unstable, and so are reduced as they are formed by a reducing agent already in the reaction mixture.

E.g.



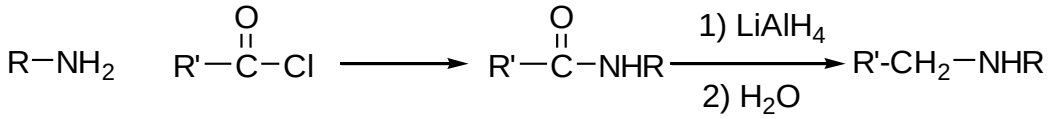
This reducing agent therefore cannot be so reactive to react with the ketone or aldehyde starting material, and thus sodium cyanoborohydride ($NaBH_3CN$) is most commonly used.

Acylation - Reduction to Amines

Again this method adds one alkyl group to the nitrogen of an amine.

The amine is acylate with an acid chloride, and the amide produced thus has no desire to undergo further reaction (good).

E.g.

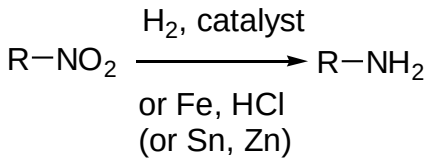


The amide is reduced with $LiAlH_4$ to produce the desired amine.

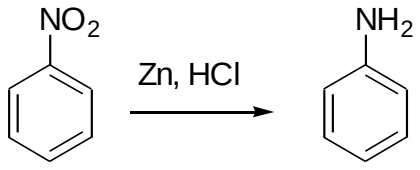
This is a very general and useful synthetic method, and the only drawback is the fact that the new C bonded to the nitrogen has to be a methylene ($-CH_2-$).

Reduction of Nitro Compounds

Both aromatic and aliphatic nitro groups are readily reduced to amino groups, and the most common methods are catalytic reduction or reaction of an active metal with an acid.



Aromatic nitro compounds are reduced to anilines.



These anilines are useful synthetic compounds themselves, and also can be used in diazonium type chemistry also.

Direct Alkylation of Ammonia and Amines

As seen before, these reactions have a tendency to over alkylate, which gives mixtures of products (bad).

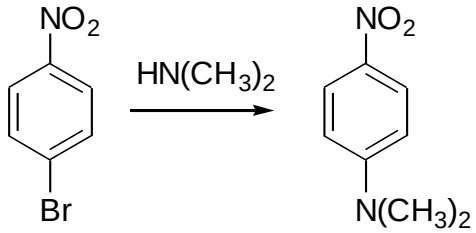
A situation where this is a viable synthetic route is using a large excess of ammonia to produce a primary amine.

$$R\text{-}CH_2\text{-}X \; + \; \text{excess } NH_3 \rightarrow \; R\text{-}CH_2\text{-}NH_2 \; + \; NH_4X$$

We can also use NAS to make some aryl amines.

An aryl bromide can be displaced by a nucleophile if there are electron withdrawing groups on the aromatic ring (addition/elimination mechanism).

E.g.



Since aryl amines are less basic than alkyl amines there is no tendency for over reaction (good).

Reduction of Azides and Nitriles (Primary Amines)

Amines can be produced without using ammonia, or other less substituted amines.

We have already seen that a nitro group can be reduced to an amino group.

Essentially any nitrogen containing functionality can be reduced to an amino group.

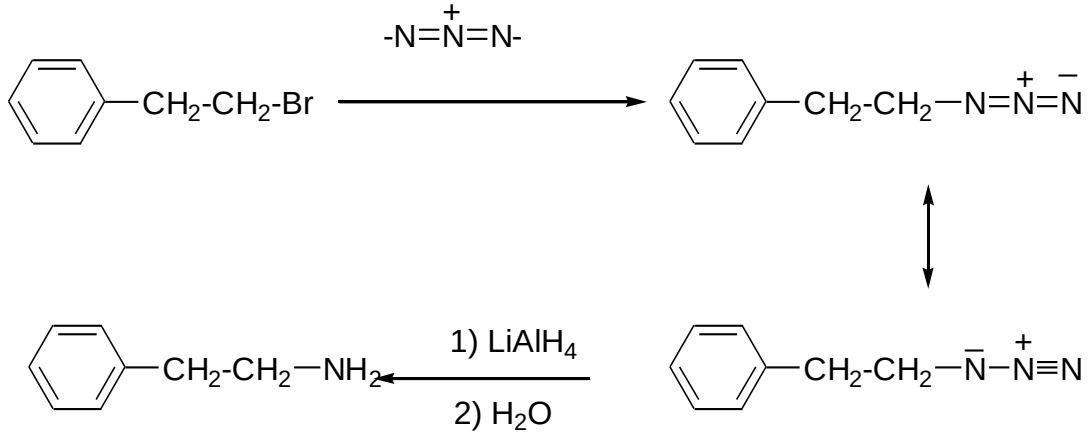
Azides

The azide ion (N_3^-) is a good nucleophile, and thus can displace leaving groups from primary and secondary alkyl halides and tosylates.

R-CH2-Cl + $Na^+ {}^-N_3$ $\rightarrow$ R-CH_2-N_3 + NaCl

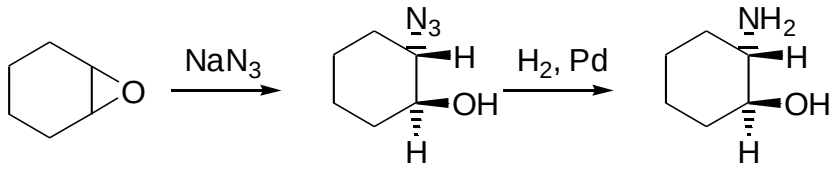
The alkyl azides that are produced (explosive) are reduced to primary amines either by $LiAlH_4$ or catalytic reduction.

E.g.



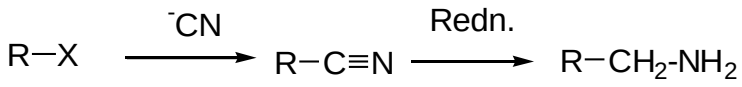
Azides also react with a variety of other electrophiles:

E.g.



Nitriles

Cyanide ion (-CN) is also a good nucleophile, and the products it produces are called nitriles.



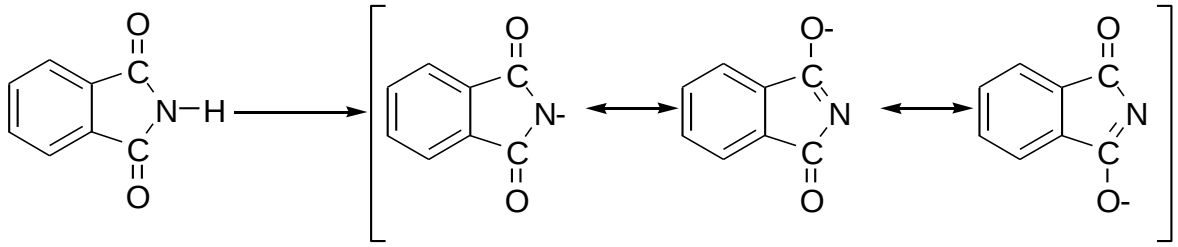
Nitriles are reduced with $LiAlH_4$ or catalytic hydrogenation to primary amines.

Notice that when the nitrile group is reduced, an NH_2 and an extra CH_2 are introduced into the molecule.

Gabriel Synthesis

In 1887, Gabriel developed a new method for the synthesis of primary amines, which eliminated the danger of over alkylation.

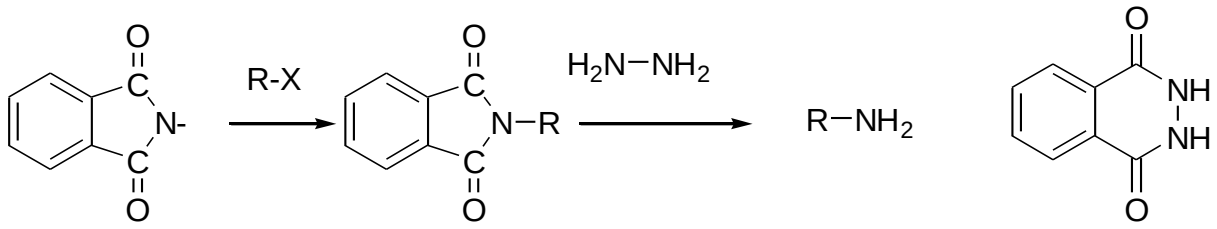
His strategy of using the phthalimide anion as a protected form of ammonia that cannot be alkylated more than once.



The phthalimide anion is resonance stabilized and acts as a good nucleophile.

This nucleophile can be alkylated with primary alkyl halides (or tosylates) to produce an N-alkyl phthalimide, which on heating with hydrazine generates the desired primary amine (and phthalimide hydrazide which is very stable).

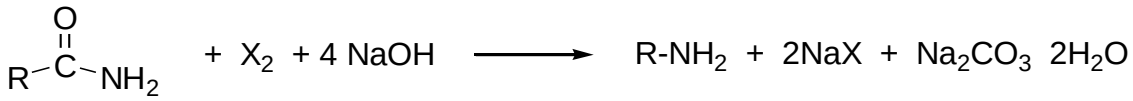
E.g.



<u>The Hoffman Rearrangement</u>

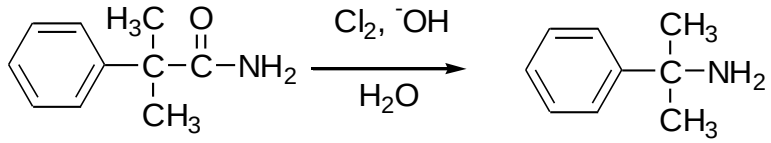
If primary amides are treated with a strong base in the presence of chlorine or bromine, then amines are produced which have lost the carbonyl group!

These chain shortened amines are produced via the Hoffman rearrangement.



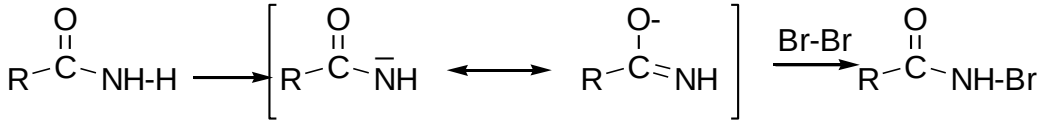
This is a good synthetic route to produce any amines, especially tertiary amines since the other synthetic methods generally don't work for 3° amines.

E.g.

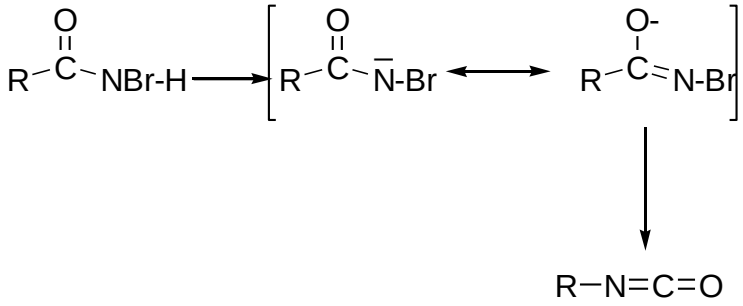


Mechanism

The reaction starts with the deprotonation of the amide to give a resonance stabilized anion, that becomes brominated.



Since Br is electronegative, the N-bromo amide can also be readily deprotonated, and this also gives a resonance stabilized anion.

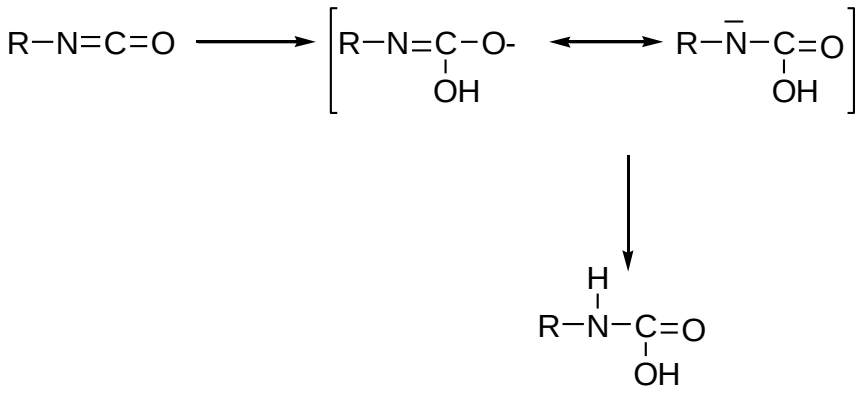


The rearrangement occurs since we have a negative charge on the oxygen and a good leaving group (bromine) on the nitrogen.

The negative charge (lone pair of electrons) reforms the carbonyl C=O double bond, forcing the alkyl group to migrate.

It migrates to the nitrogen, displacing the good leaving group, bromine.

The product, R-N=C=O, is called an isocyanate.



The isocyanate reacts rapidly with water, generating carbamic acid, that decarboxylates to give the amine and carbon dioxide.