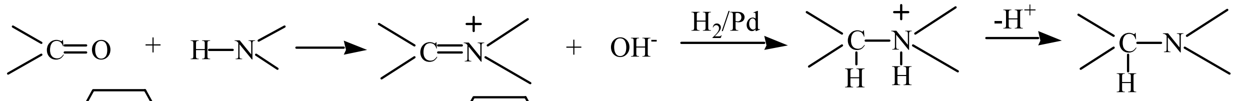
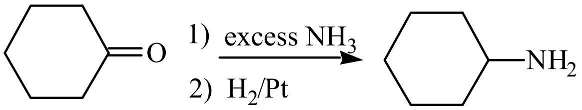
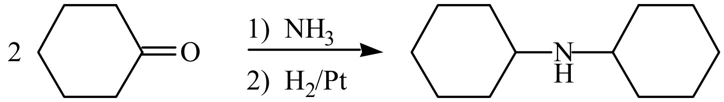
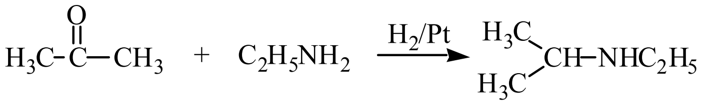
2. Reductive amination of aldehydes and ketones



e.g.

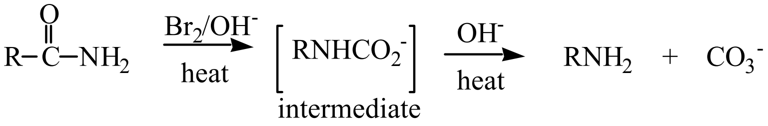






$$H_3C-\overset{O}{\overset{\|}{C}}-CH_3 + C_2H_5NH_2 \xrightarrow{H_2/Pt} (H_3C)_2CH-NHC_2H_5$$

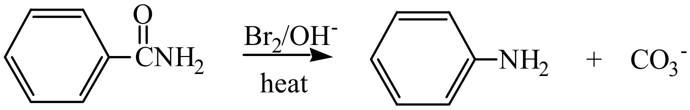
3. Amides to amines by Hofmann degradation



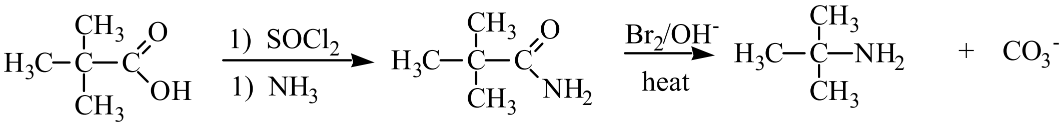
$$R-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow[heat]{Br_2/OH^-} \underset{\text{intermediate}}{\left[RNHCO_2^-\right]} \xrightarrow[heat]{OH^-} RNH_2 + CO_3^-$$

Notice that the R group migrates to the nitrogen and a carbon atom is lost as carbonate

e.g.



Synthetic sequence

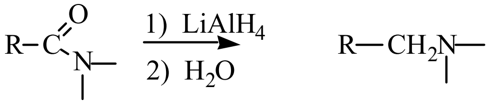


4. Reduction of nitriles to primary amines

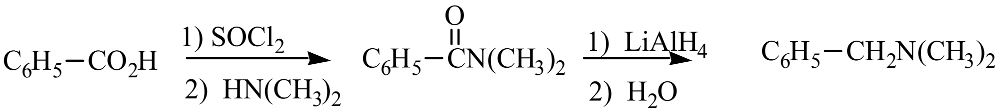
$$R-C\equiv N \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} RCH_2NH_2$$

e.g. $C_6H_5-CH_3 \xrightarrow[h\upsilon]{} C_6H_5-CH_2Br \xrightarrow{NaCN} C_6H_5-CH_2CN \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} C_6H_5-CH_2CH_2NH_2$

5. Reduction of amides to primary and secondary amines



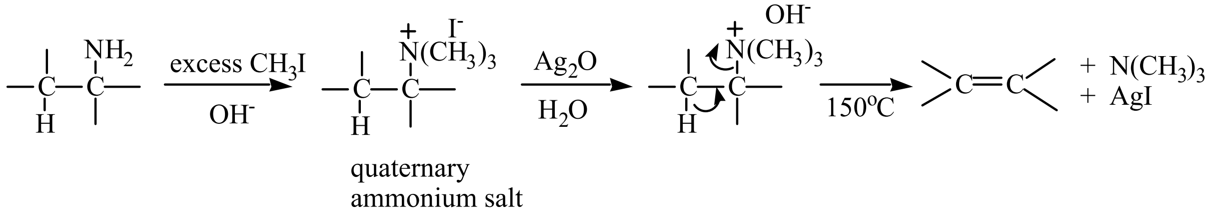
Another synthetic sequence

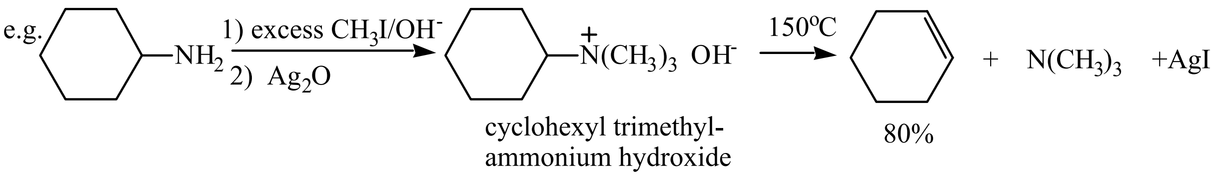


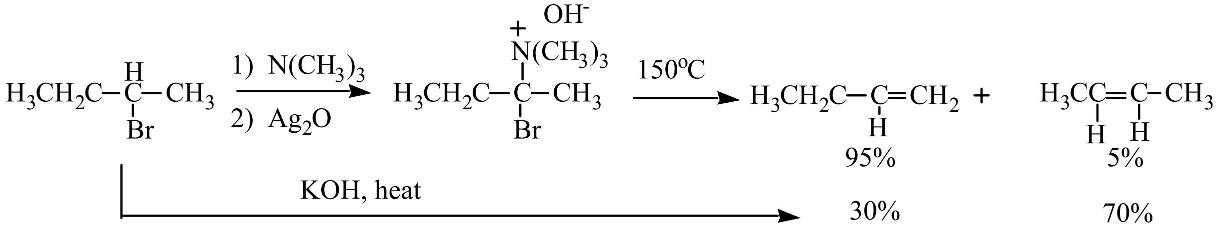
$$C_6H_5-CO_2H \xrightarrow[2)\ HN(CH_3)_2]{1)\ SOCl_2} C_6H_5-\overset{O}{\overset{\|}{C}}N(CH_3)_2 \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} C_6H_5-CH_2N(CH_3)_2$$

Reactions of Amines

1. Hofmann elimination of quaternary ammonium hydroxides

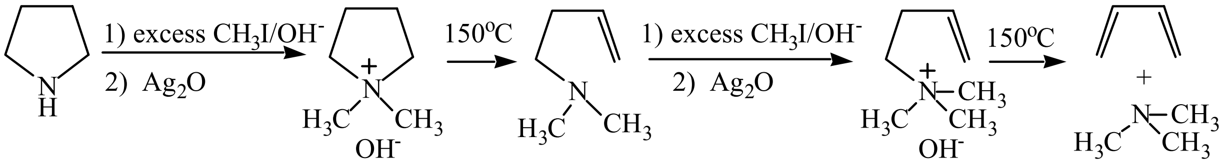




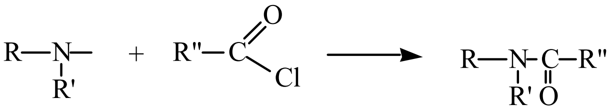


Hofmann Rule: elimination from quaternary ammonium hydroxides gives the <u>least</u> substituted alkene. This is the opposite of the Saytzeff Rule.

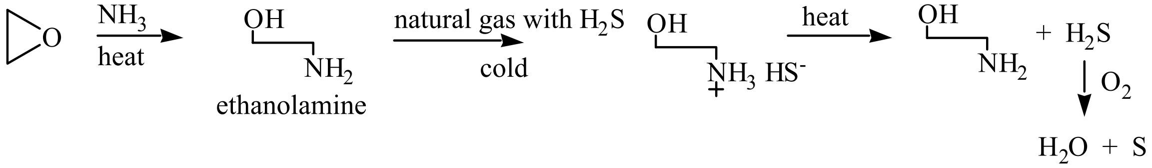
This reaction is often used to open nitrogen containing rings:



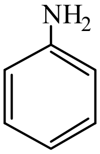
2. Formation of Amides



Ethanolamine is used to remove H_2S (a weak acid) from natural gas.



Aromatic Amines

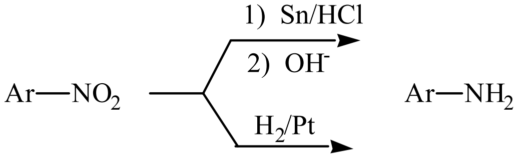


aniline

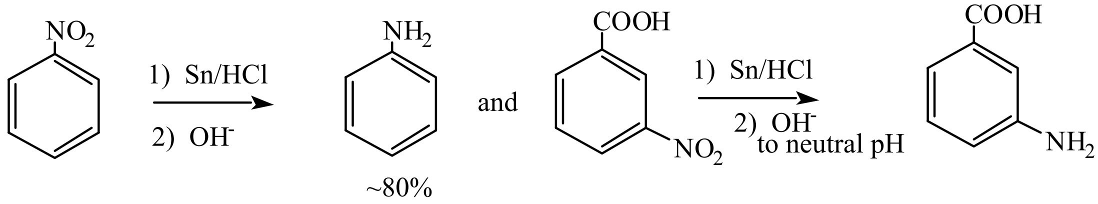
These are amines in which the amino group is directly attached to a benzene ring. The simplest example is aniline. Other aromatic amines have substituents on the benzene ring and on the nitrogen.

Preparation of aromatic amines

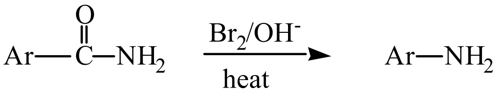
1). Reduction of aromatic nitro compounds



e.g.

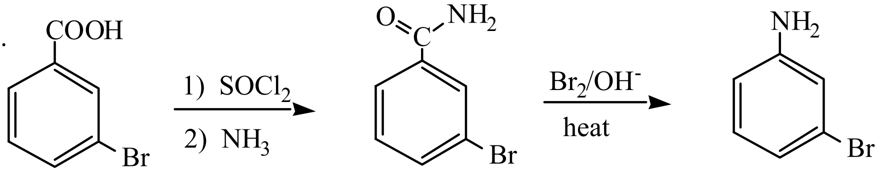


2) Hofmann degradation of amides



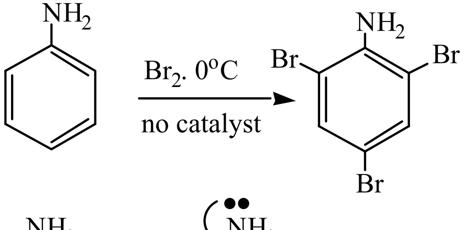
$$Ar-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow[\text{heat}]{Br_2/OH^-} Ar-NH_2$$

e.g.

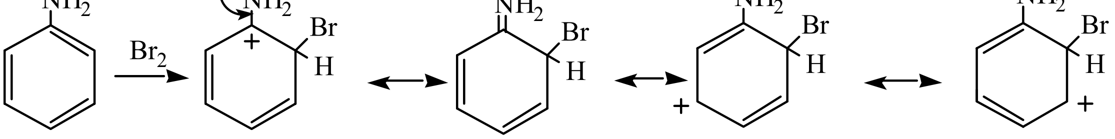


Aromatic amines undergo the same reactions as those already described for aliphatic amines, and then some additional reactions which are possible due to the presence of the aromatic ring.

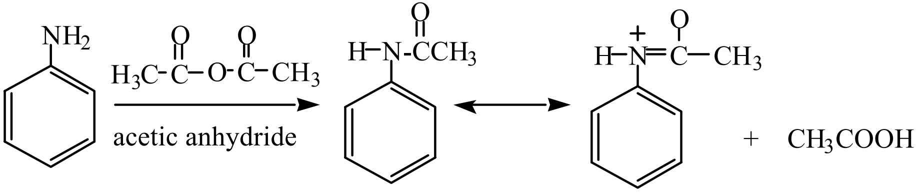
1) Electrophilic aromatic substitution



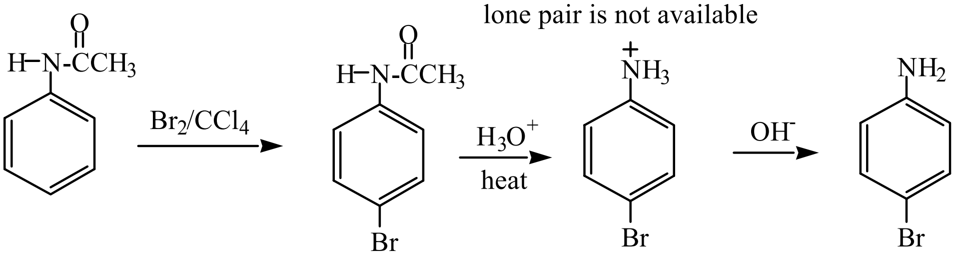
The greater reactivity of aniline compared with benzene towards electrophilic aromatic substitution is due to the ability of the lone pair of electrons on nitrogen to be delocalized into the aromatic ring. This results in relatively stable resonance structures for the cation intermediate for substitution into the ortho and para positions of the ring.



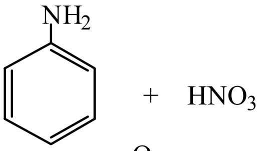
Pure monobromoaniline cannot be made by bromination of aniline. To monobrominate aniline, the amino group is 'protected' so that it is deactivated.



this important resonance structure means that the lone pair is not available

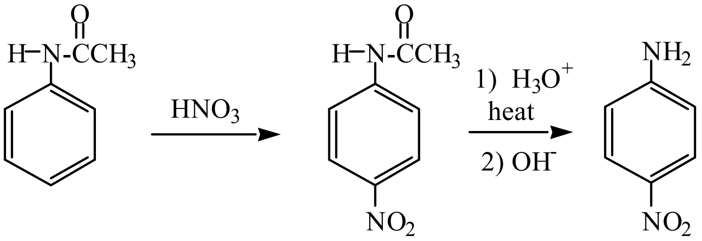


Similarly with nitration:



explodes! The combination is used as a rocket fuel.

but



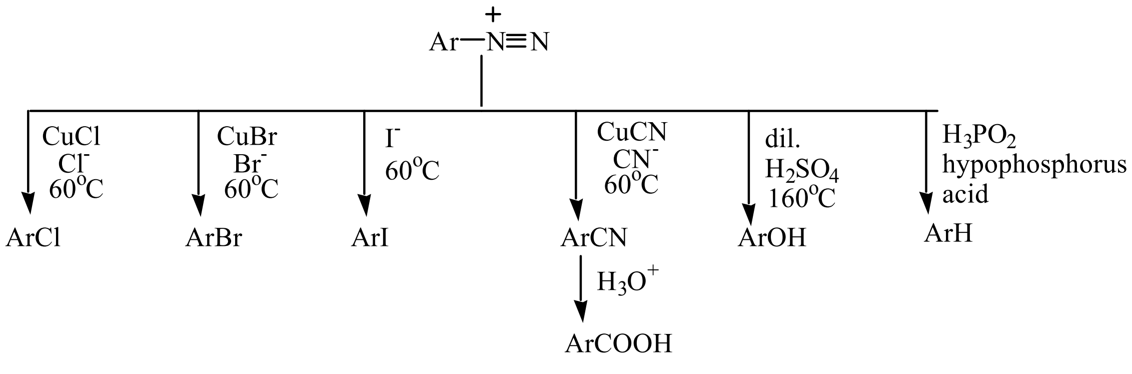
Reaction with nitrous acid, HNO_2

$$Ar-NH_2 + HNO_2 \longrightarrow Ar-\overset{+}{N}\equiv N$$

aryldiazonium salt stable at 0°C

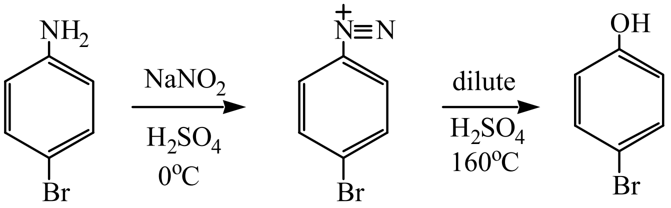
alkyldiazonium salts are unstable even at 0°C

The aryldiazonium salts are very useful synthetically since the diazonium group can be replaced by a large variety of other groups.



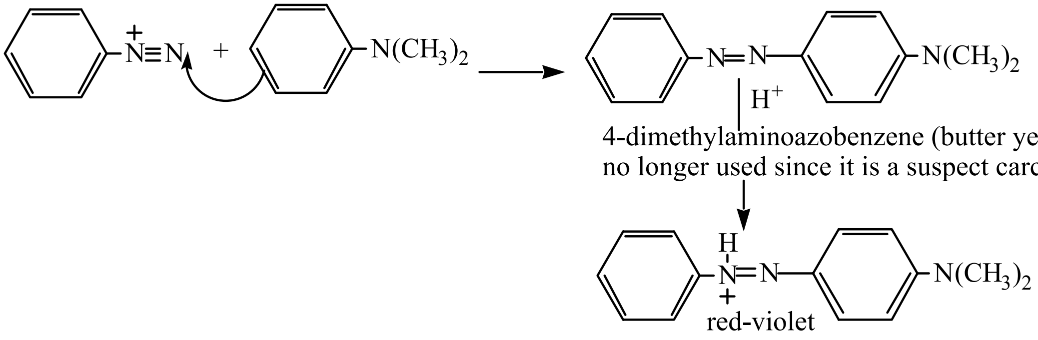
Thus, going through the diazonium salt, a wide variety of other compounds can be made. This is a very important method for the formation of phenols.

e.g.



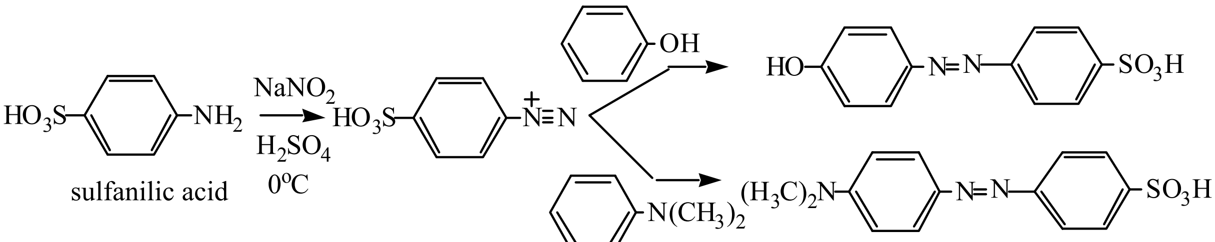
3. Azo Coupling Reaction.

This is used in the formation of azo dyes. It can be described as electrophilic aromatic substitution by the diazonium ion.



4-dimethylaminoazobenzene (butter yellow)
no longer used since it is a suspect carcinogen

red-violet

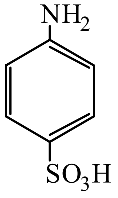


methyl orange

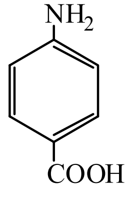
These compounds are used as dyes in the food, cosmetic, printing and textile industries. Textile dyes usually contain an -OH or -SO_3H group so that bonding with the fabric can occur and the color does not wash out. pH paper contains a mixture of the dyes.

Sulfa Drugs

These were one of the earliest synthetic drugs. They are bacteriocides, but are used mostly in veterinary medicine nowadays since they have many side effects in humans. The parent drug is sulfanilamide.



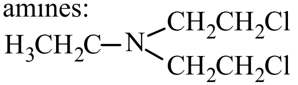
sulfanilimide



p-aminobenzoic acid

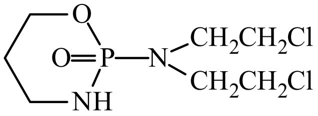
The mode of action of these drugs depends upon the fact the bacteria need p-aminobenzoic acid to synthesize folic acid, a molecule necessary for growth. If they incorporate sulfanilimide, the foramtion of folic acid is blocked and the bacteria die. However, one problem is that the bacteria rapidly develop immunity.

Several anticancer drugs are amines:



$$H_3CH_2C{-}N\begin{matrix}CH_2CH_2Cl\\CH_2CH_2Cl\end{matrix}$$

Nitrogen mustard gas,
effective against skin cancer



cyclophosphamide, used in chemotherapy