

23.15: Preparation of Amines

This page summarises the reactions of amines as nucleophiles. This includes their reactions with halogenoalkanes (haloalkanes or alkyl halides), with acyl chlorides (acid chlorides) and with acid anhydrides.

Amines by direct nucleophilic substitution

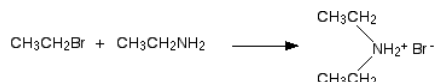
A nucleophile is something which is attracted to, and then attacks, a positive or slightly positive part of another molecule or ion. All amines contain an active lone pair of electrons on the very electronegative nitrogen atom. It is these electrons which are attracted to positive parts of other molecules or ions.

The reactions of primary amines with halogenoalkanes

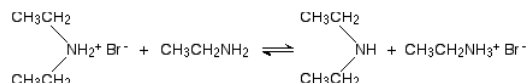
You get a complicated series of reactions on heating to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

Making secondary amines and their salts

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



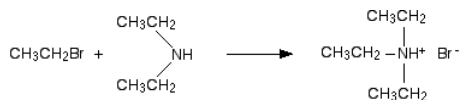
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



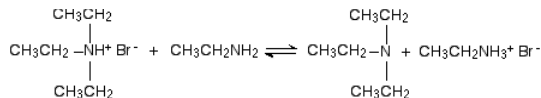
Making tertiary amines and their salts

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



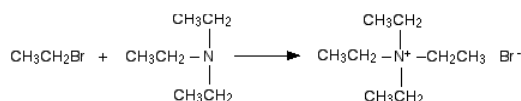
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

Making a quaternary ammonium salt

The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



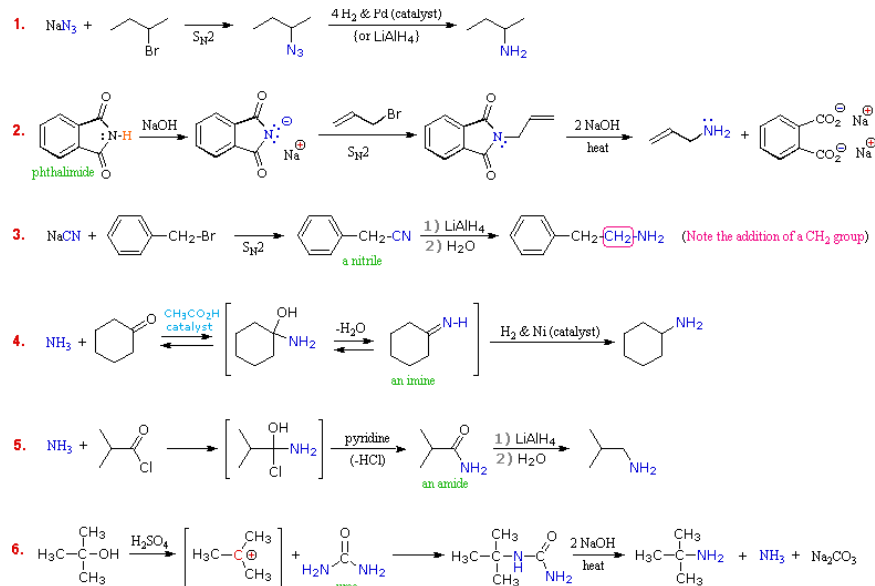
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1°-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
N_3^-	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-N}_3$ or $\text{R}_2\text{CH-N}_3$	LiAlH_4 or 4 H_2 & Pd	Hydrogenolysis	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
$\text{C}_6\text{H}_5\text{SO}_2\text{NH}^-$	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-NHSO}_2\text{C}_6\text{H}_5$ or $\text{R}_2\text{CH-NHSO}_2\text{C}_6\text{H}_5$	Na in NH_3 (liq)	Hydrogenolysis	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
CN^-	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-CN}$ or $\text{R}_2\text{CH-CN}$	LiAlH_4	Reduction	$\text{RCH}_2\text{-CH}_2\text{NH}_2$ or $\text{R}_2\text{CH-CH}_2\text{NH}_2$
NH_3	RCH=O or $\text{R}_2\text{C=O}$	Addition / Elimination	RCH=NH or $\text{R}_2\text{C=NH}$	H_2 & Ni or NaBH_3CN	Reduction	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
NH_3	RCOX	Addition / Elimination	RCO-NH_2	LiAlH_4	Reduction	$\text{RCH}_2\text{-NH}_2$
NH_2CONH_2 (urea)	R_3C^+	$\text{S}_{\text{N}}1$	$\text{R}_3\text{C-NHCONH}_2$	NaOH soln.	Hydrolysis	$\text{R}_3\text{C-NH}_2$

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an $\text{S}_{\text{N}}2$ reaction with a modestly electrophilic alkyl halide reactant. For example #2 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system by a methylene group (CH_2). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an E2 elimination.



The methods illustrated by examples #4 and #5 proceed by attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally

require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by LiAlH_4 .

The 6th example is a specialized procedure for bonding an amino group to a 3°-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3°-alkyl-substituted urea is then hydrolyzed to give the amine.

One important method of preparing 1°-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($\text{NO}_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1°-amine by any of several reduction procedures.

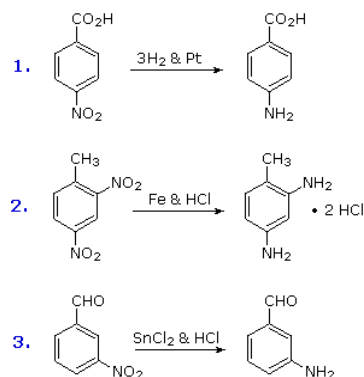
The Hofmann rearrangement of 1°-amides provides an additional synthesis of 1°-amines. To learn about this useful procedure Click [Here](#).

Reduction of Other Functional Groups that Contain Nitrogen

Reduction of Nitro Groups

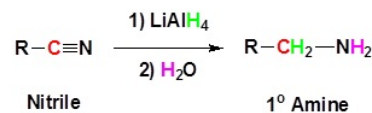
Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

Nitro Group Reduction

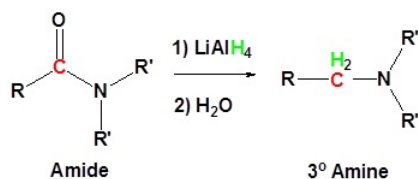
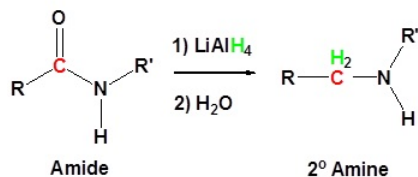
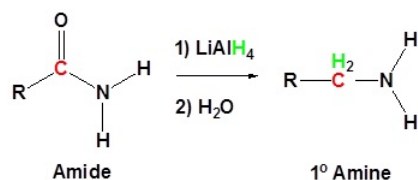


Nitriles can be converted to 1° amines by reaction with LiAlH_4

During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.

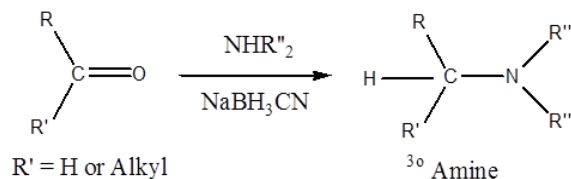
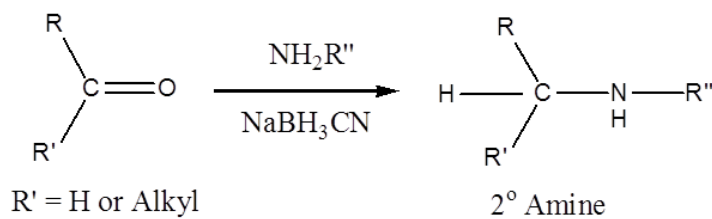
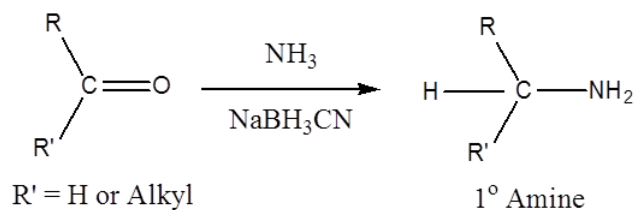
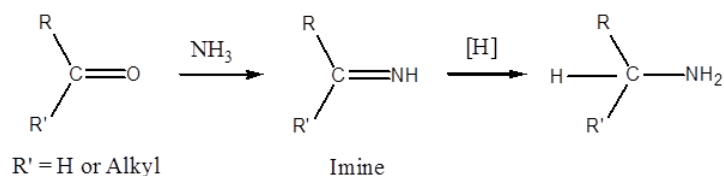


Amides can be converted to 1°, 2° or 3° amines using LiAlH_4



Reductive amination

Aldehydes and ketones can be converted into 1°, 2° and 3° amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophilic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride (NaBH_3CN).



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