

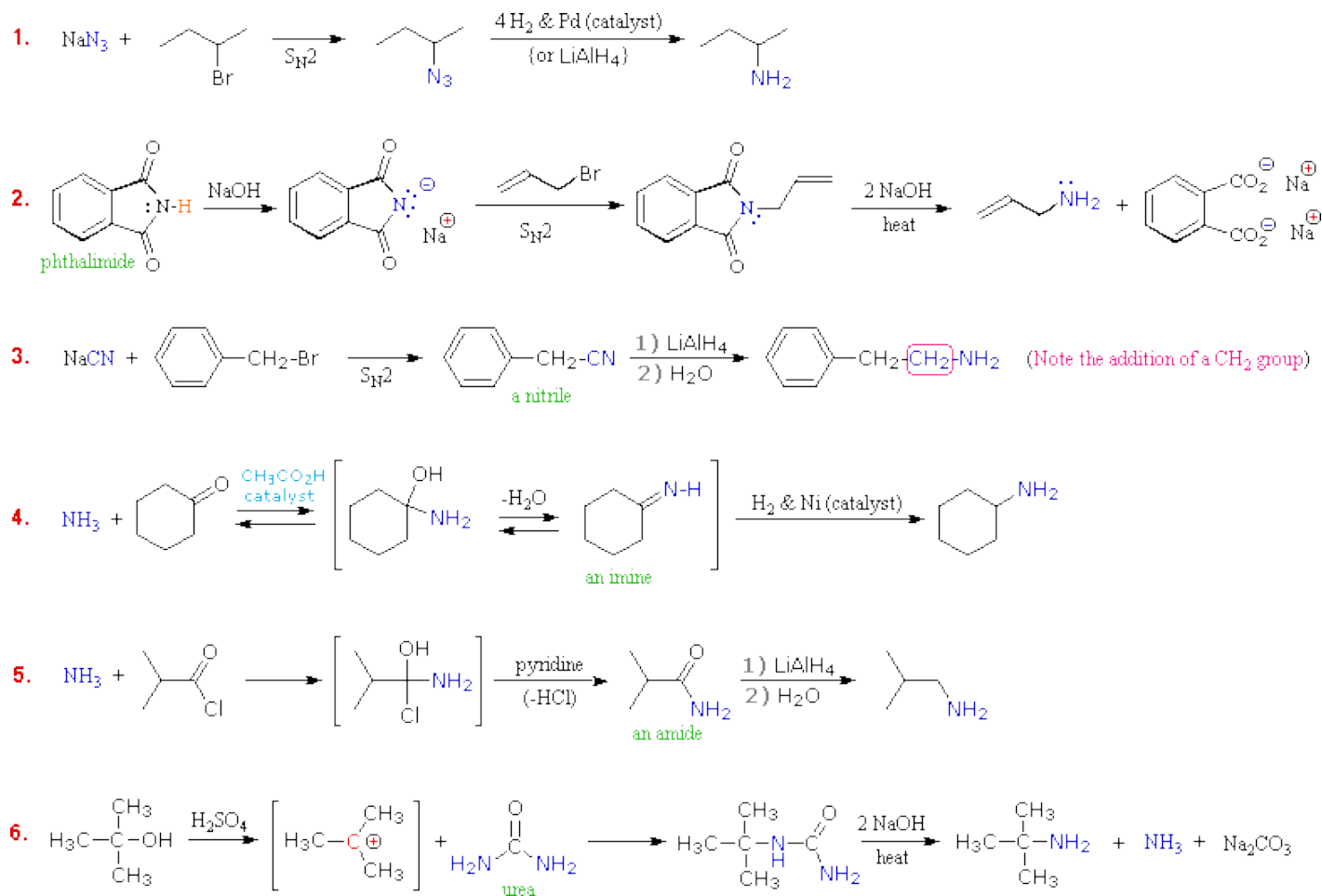
Preparation of 1^o-Amines

Although direct alkylation of ammonia by alkyl halides leads to 1^o-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.

Example	Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
1.	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 $\text{R}_2\text{CH-NH}_2$
2.	$\text{C}_6\text{H}_5\text{SO}_2\text{N}$ H^-	$\text{RCH}_2\text{-X}$ 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 $\text{R}_2\text{CH-NH}_2$
3.	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 $\text{R}_2\text{CH-CH}_2\text{NH}_2$
4.	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 $\text{R}_2\text{CH-NH}_2$

			Addition / Eliminati on				
5.	NH ₃	RCOX		RCO-NH ₂	LiAlH ₄	Reduction	RCH ₂ -NH ₂
6.	H ₂ (urea)	R ₃ C ⁽⁺⁾	S _N 1	R ₃ C-NHCONH ₂	NaOH soln.	Hydrolysis	R ₃ 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 S_N2 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 (CH₂). In all three of these methods 3^o-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 LiAlH₄.

The 6th example is a specialized procedure for bonding an amino group to a 3^o-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^o-alkyl-substituted urea is then hydrolyzed to give the amine.

One important method of preparing 1^o-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species (NO₂⁽⁺⁾) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1^o-amine by any of several reduction procedures.

Source : <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/amine1.htm#aminom>