

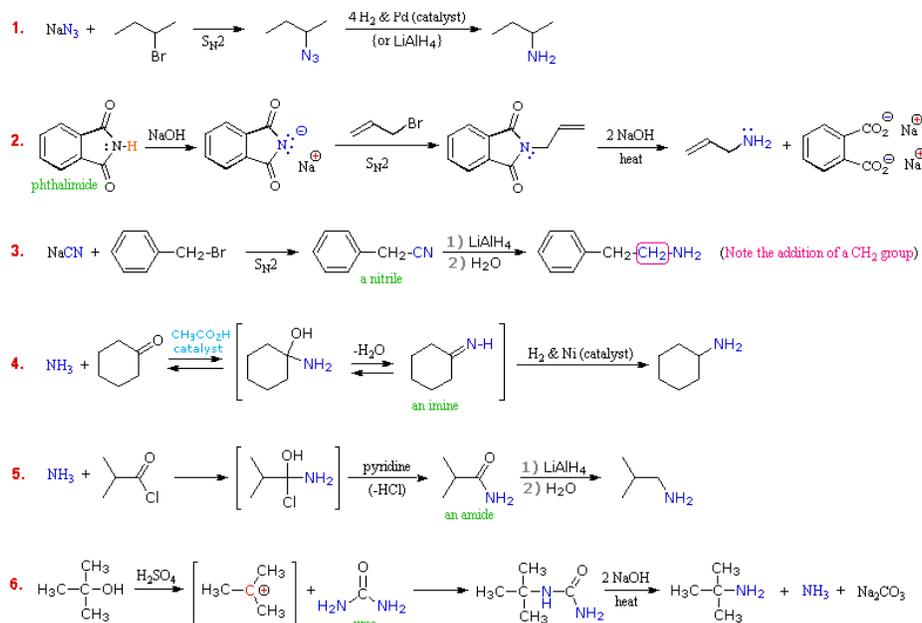
## 20.5: SYNTHESIS OF PRIMARY AMINES

### 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
$\text{N}_3^-$	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-N}_3$ or $\text{R}_2\text{CH-N}_3$	$\text{LiAlH}_4$ or $4 \text{H}_2$ & Pd	Hydrogenolysis	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
$\text{C}_6\text{H}_5\text{C}_2\text{O}_2\text{NH}^- / \text{OH}^-$	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-NC}_2\text{O}_2\text{C}_6\text{H}_5$ or $\text{R}_2\text{CH-NC}_2\text{O}_2\text{C}_6\text{H}_5$	$\text{NaOH}$ / heat	Hydrogenolysis	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
$\text{CN}^-$	$\text{RCH}_2\text{-X}$ or $\text{R}_2\text{CH-X}$	$\text{S}_{\text{N}}2$	$\text{RCH}_2\text{-CN}$ or $\text{R}_2\text{CH-CN}$	$\text{LiAlH}_4$	Reduction	$\text{RCH}_2\text{-CH}_2\text{NH}_2$ or $\text{R}_2\text{CH-CH}_2\text{NH}_2$
$\text{NH}_3$	$\text{RCH=O}$ or $\text{R}_2\text{C=O}$	Addition / Elimination	$\text{RCH=NH}$ or $\text{R}_2\text{C=NH}$	$\text{H}_2$ & Ni or $\text{NaBH}_3\text{CN}$	Reduction	$\text{RCH}_2\text{-NH}_2$ or $\text{R}_2\text{CH-NH}_2$
$\text{NH}_3$	$\text{RCOX}$	Addition / Elimination	$\text{RCO-NH}_2$	$\text{LiAlH}_4$	Reduction	$\text{RCH}_2\text{-NH}_2$
$\text{NH}_2\text{CONH}_2$ (urea)	$\text{R}_3\text{C}^{(+)}$	$\text{S}_{\text{N}}1$	$\text{R}_3\text{C-NHCONH}_2$	$\text{NaOH}$ 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, the Gabriel synthesis is shown. The alkaline conditions deprotonate phthalimide to create a strong nucleophile for  $\text{S}_{\text{N}}2$  reactions with alkyl halides. Example #3 also starts with an  $\text{S}_{\text{N}}2$  reaction of cyanide with an alkyl halide following by reduction of the cyano group to form a primary amine that extends the carbon system of the alkyl halide by a methylene group ( $\text{CH}_2$ ). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an  $\text{E}2$  elimination.



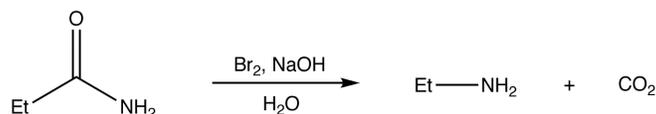
The methods illustrated by examples #4 and #5 proceed by the reaction of ammonia, or equivalent nitrogen nucleophiles, with the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented in an independent chapter, but for present purposes it is sufficient to recognize that the  $\text{C=O}$  double bond is polarized so that the carbon atom is electrophilic. Nucleophilic 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  $\text{C=N}$  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  $\text{LiAlH}_4$ .

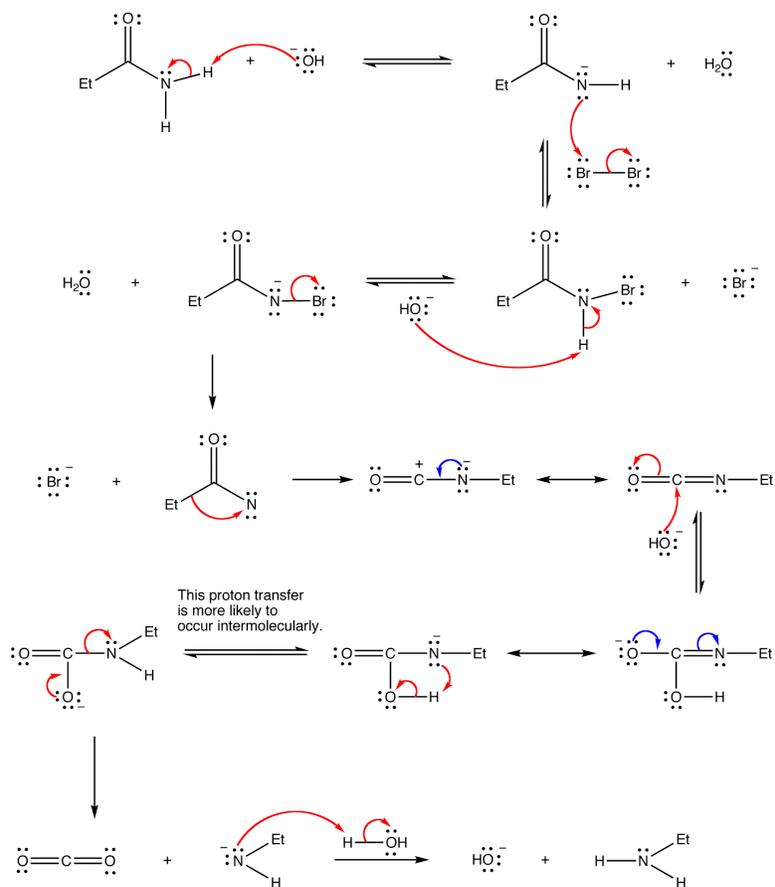
The 6th example is a specialized procedure for bonding an amino group to a 3°-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement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

## HOFMANN REARRANGEMENT

Hofmann rearrangement, also known as Hofmann degradation and not to be confused with [Hofmann elimination](#), is the reaction of a primary amide with a halogen (chlorine or bromine) in strongly basic (sodium or potassium hydroxide) aqueous medium, which converts the amide to a primary amine. For example:

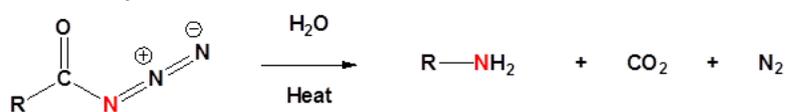


Mechanism:

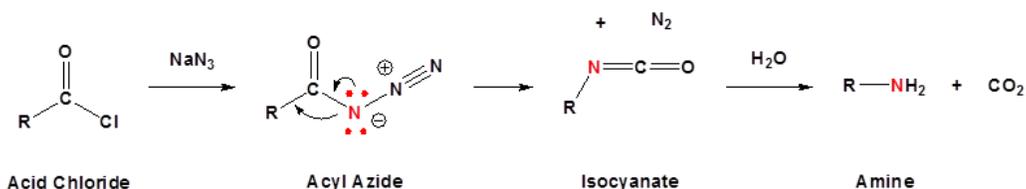


## CURTIUS REARRANGEMENT

The Curtius rearrangement involves an acyl azide.



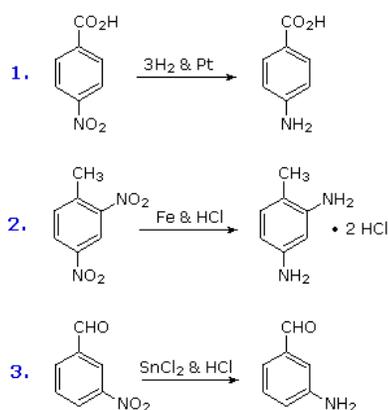
The mechanism of the Curtius rearrangement involves the migration of an -R group from the carbonyl carbon to the neighboring nitrogen.



## REDUCTION OF NITRO GROUPS

Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation ( $\text{H}_2$  + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

### Nitro Group Reduction



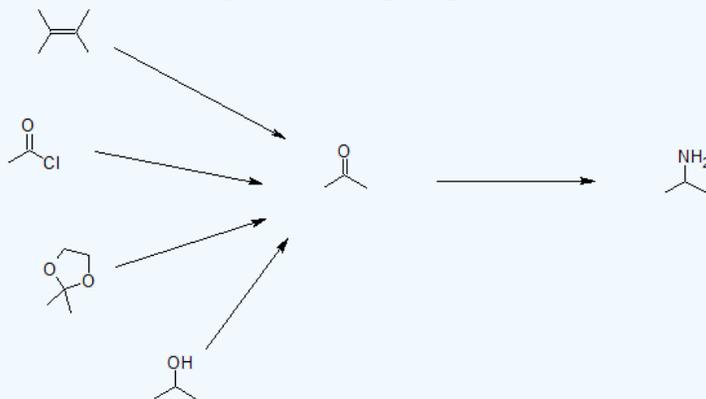
## REDUCTION OF NITRILES

Nitriles can be converted to primary amines by reaction with lithium aluminum hydride. During this reaction the hydride nucleophile reacts with 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.



### Exercise

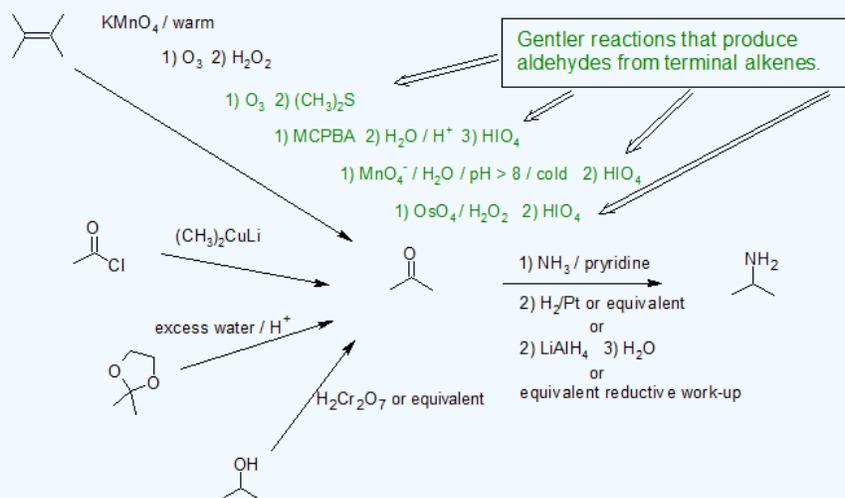
9. Complete the reaction map below to build reaction patterns for multiple step synthesis.



Answer

9.

Each professor emphasizes particular reagents/reagent systems when more than one set of reaction conditions are possible. The different reaction conditions are important for reactants with multiple functional groups.



## CONTRIBUTORS AND ATTRIBUTIONS

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