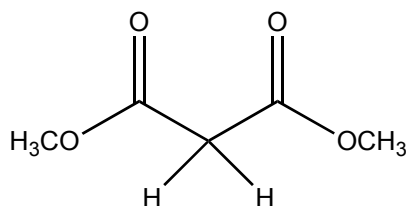
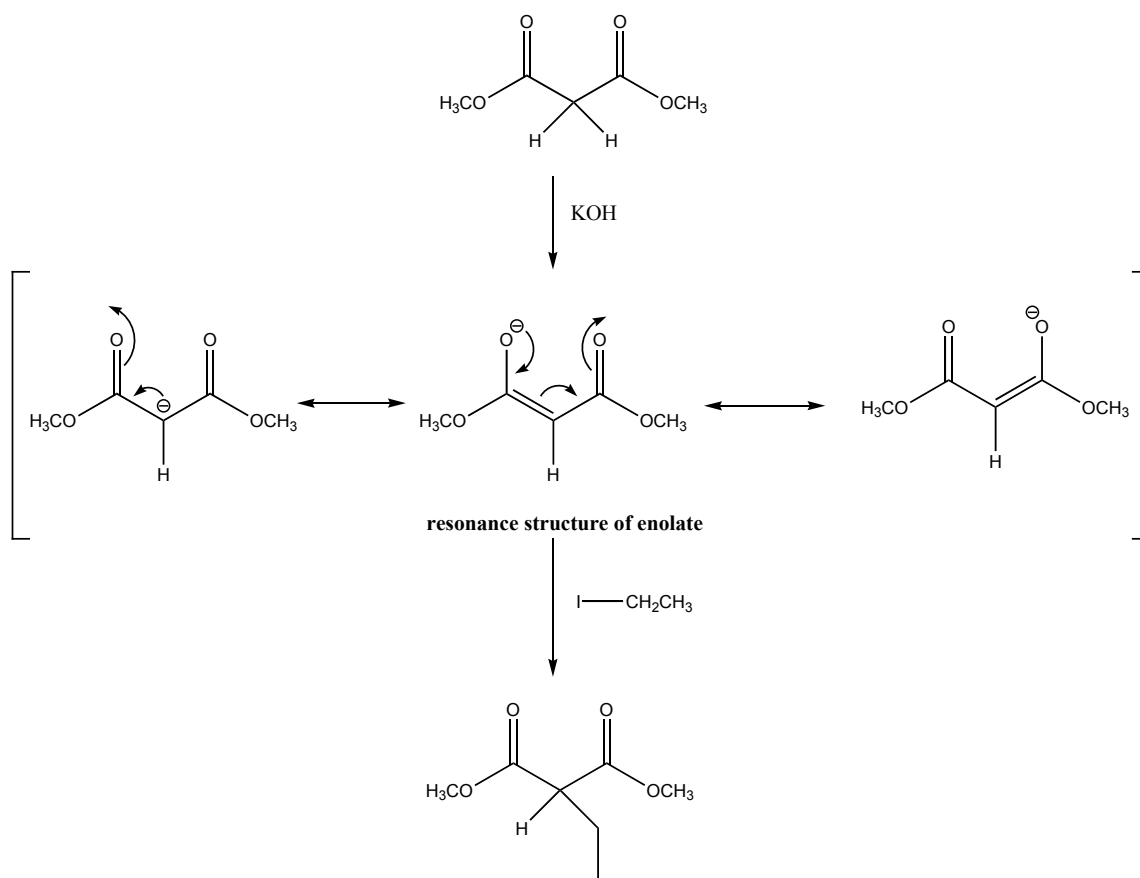


Example: Malonic Esters

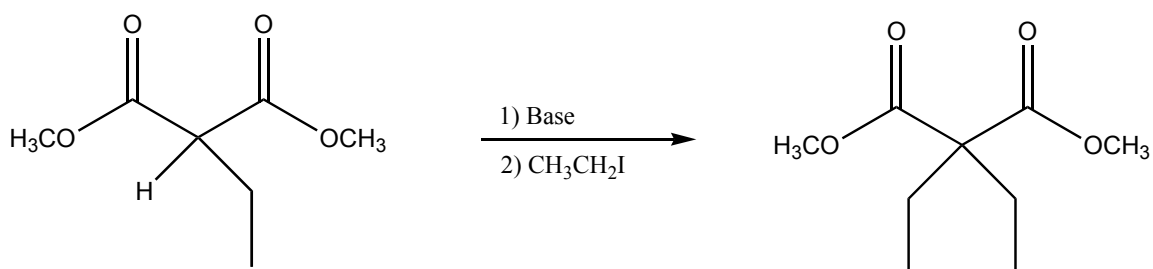


The structure shown above is methyl (or dimethyl) malonate. As a reminder, you are responsible for the names of first 4 dicarboxylic acids.

Methyl malonate has two alpha protons that are very acidic ($pK_a \sim 12$). This is due to the presence of two carbonyls which stabilizes the negative charge at the alpha carbon (resonance stabilization). The anion has three resonance structures that are shown below. The anion can be alkylated using alkyl halide through S_N2 type reaction.

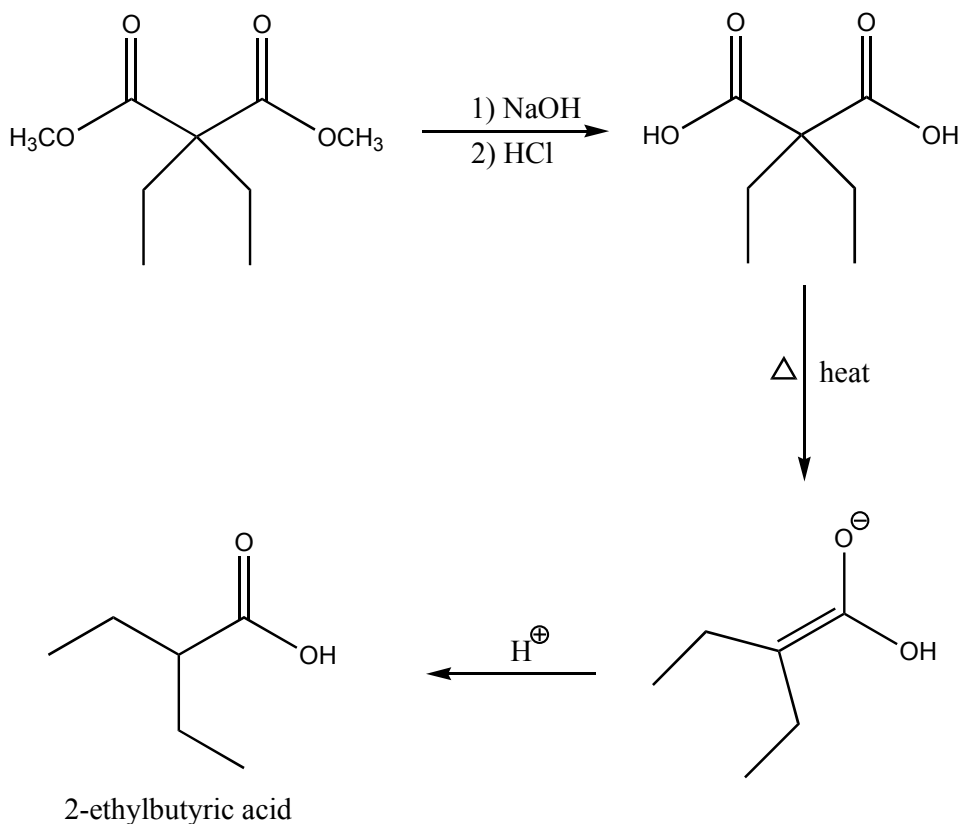


The alkylation reaction can be repeated again since there is one more acidic alpha proton present.



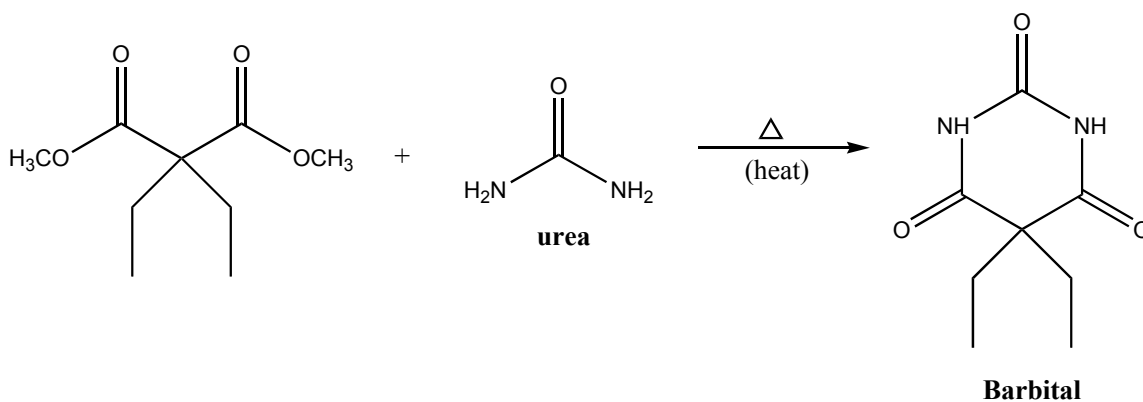
The product from this reaction, diethyl dimethylmalonate, can be used to perform other reactions as we will see.

Diethyl dimethylmalonate can be treated with base to form di-carboxylic acid (hydrolysis) which can be reacted further.

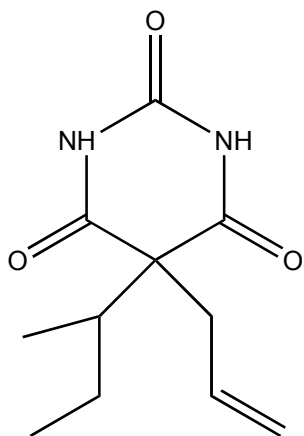


Upon heating (denoted by the triangle), the di-carboxylic acid loses one of its carboxylic group (CO_2). This process is called decarboxylation. The product from this step is an enolate. Upon treating with acid, we get a substituted acetic acid, specifically 2-ethylbutyric acid as product.

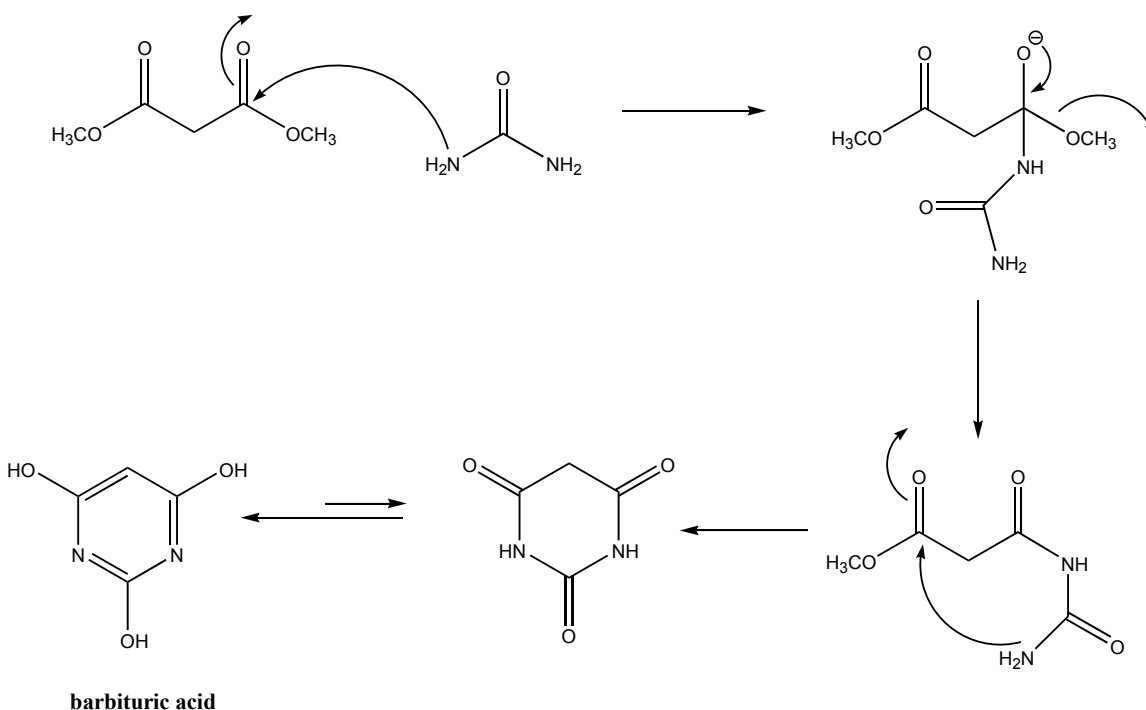
Diethyl methylmalonate can be also used as synthetic precursor for drugs.



Barbital belongs to a class of drug called barbiturate. It is a sleeping pill used widely in the 1950's. However, it is also addictive. Another example of this class is seconal.



Discussion on Mechanism (for simplicity, the loss and gain of proton on nitrogen is not shown):



In this reaction, the product is barbituric acid. It is biologically inactive. It is in equilibrium with its enol form. However, the equilibrium lies on the side of enol.

Why?

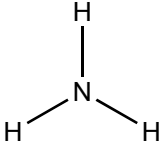
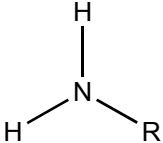
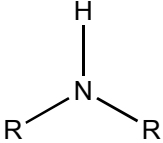
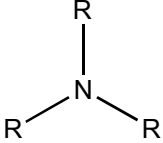
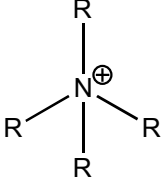
The enol form is more stable since it is aromatic (aromatic stabilization).

When alkylation is performed on barbituric acid, only alkylation on the oxygen was observed since the compound likes to stay in the enol form.

Therefore, the alkylation of malonate must occur before cyclization with urea.

Amines

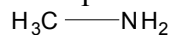
Nomenclature:

	Ammonia (simplest amine)
	Primary amine
	Secondary amine
	Tertiary amine
	Quaternary ammonium salt

Nomenclature:

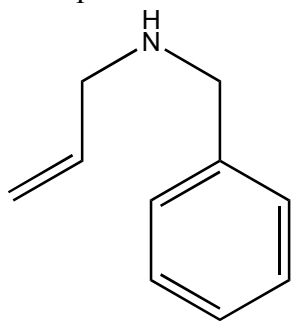
For simple amine, name the alkyl group (R), and add amine at the end of the nomenclature. Secondary and tertiary amines in which R groups are all the same are simply named as di- or trialkylamines. Amines bearing different R groups are named by ordering the groups alphabetically.

Example:



Nomenclature: **methylamine** (since the alkyl group is a methyl)

Example:

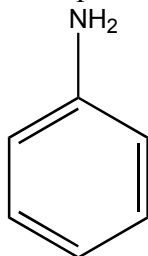


What kind of groups are attached to the amine?

Allyl and benzyl.

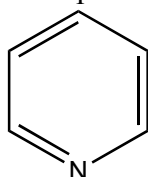
Nomenclature: **allyl benzylamine**

Example:



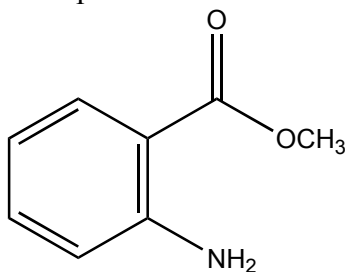
The structure shown is **aniline**, one of the structures you were required to know for this course. It is an aromatic amine.

Example:



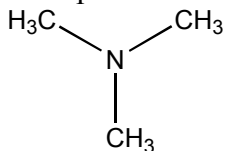
We have seen this structure before, which is **pyridine**. It is also aromatic.

Example:



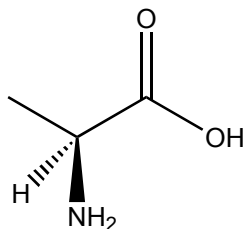
Nomenclature: **methyl 2-aminobenzoate**. It has a grape flavor. It also repels geese. Note the ester takes priority as parent structure, rather than amine. Then you count around the ring to give the lowest substitution number. In this case, C2 is where amine is substituted.

Example:



Nomenclature: **trimethylamine**

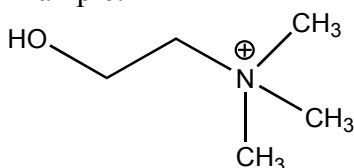
Example:



The structure shown is an alpha amino acid, specifically, alanine. It is a major constituent of spider silk.

The systematic name for alanine is **(S)-2-aminopropanoic acid**.

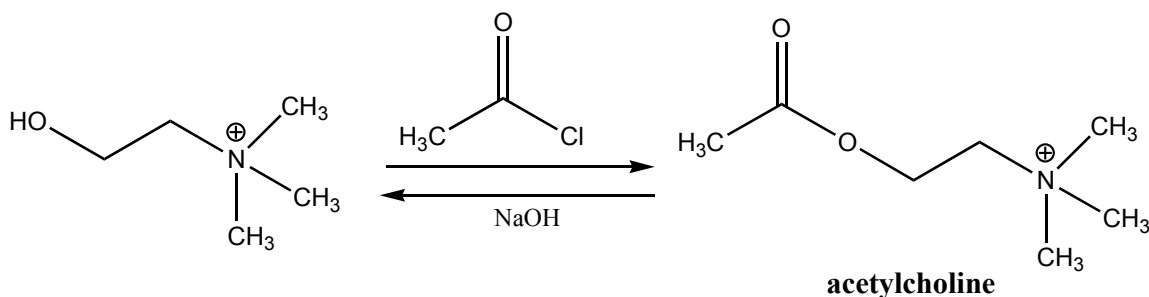
Example:



This compound is known as choline.

The systematic name is 2-(trimethylamino)ethanol. The bracket indicates three methyl groups are attached to the amine. Note this compound is an ethanol derivative. Alcohol functionality has higher priority than amino in the naming system.

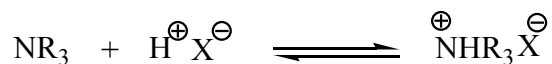
Choline can be treated with acetyl chloride to form acetylcholine, which is an neurotransmitter. Similarly, acetylcholine can be hydrolyzed back to choline. This is similar to what happens in your body. However, nerve gas can block this process of converting acetylcholine to choline.



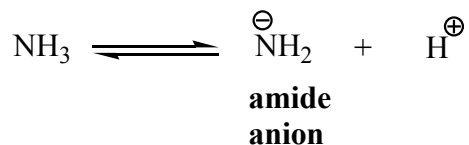
Properties of amine

Amines are polar, and therefore have higher boiling point than hydrocarbons of similar molecular weight.

Amines are both nucleophiles and bases, so they will react with acid such as hydrogen halide to form salts

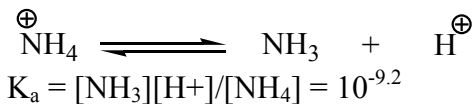


The pKa for ammonia is about 36.

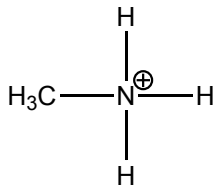


$$K_a = [\text{NH}_2][\text{H}^+]/[\text{NH}_3] = 10^{-36}$$

The pKa for ammonium ion is about 9.2.



The pKa of methylamine is approx. 10.5.



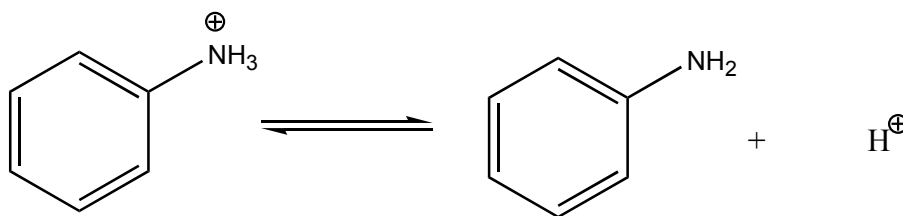
Is this more or less acidic than ammonium ion?

It is less acidic. Higher pKa means less acidity (more basic).

Why is methylamine less acidic than ammonium?

Because the alkyl group donates negative charge to the nitrogen (inductive donation). This stabilizes the positive charge on nitrogen. Ammonium has only H on it, H is less electron donating, therefore, its positive charge is less stabilized.

Example:



The pKa of protonated aniline is 4.6.

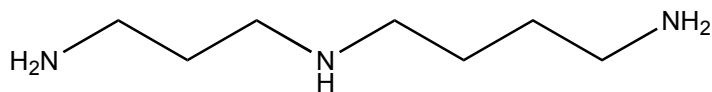
Is this more or less acidic than methylamine?

It is more acidic since the pKa is lower. The increased acidity means it likes to give away its proton.

Why?

Because the aniline can have its lone pair on nitrogen conjugated into the aromatic ring (resonance stabilization).

Example:



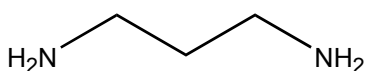
spermidine

Spermidine is a polyamine isolated from seminal fluid in males but occurs in all cells. It reacts with acetic acid that is present in females.

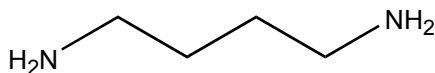
Which amine is protonated first?

The secondary amine in the middle since it is the most basic nitrogen (alkyl groups donate negative charge through inductive effect to nitrogen).

Example of diamines



1,3-diaminopropane



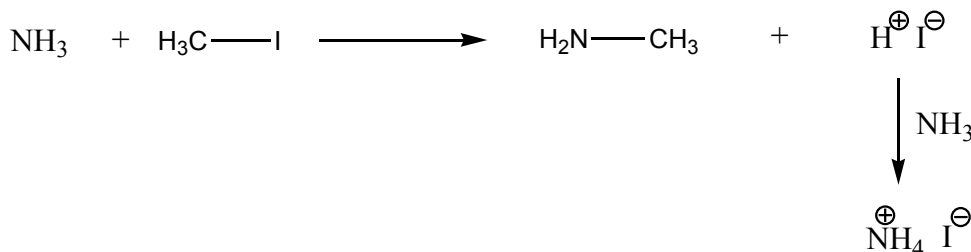
1,4-diaminobutane

(putrescine)

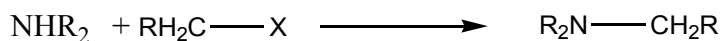
Reactions of amines

1) Preparation of amine by alkylation

Amines are good nucleophiles and can displace leaving groups in S_N2 reaction.

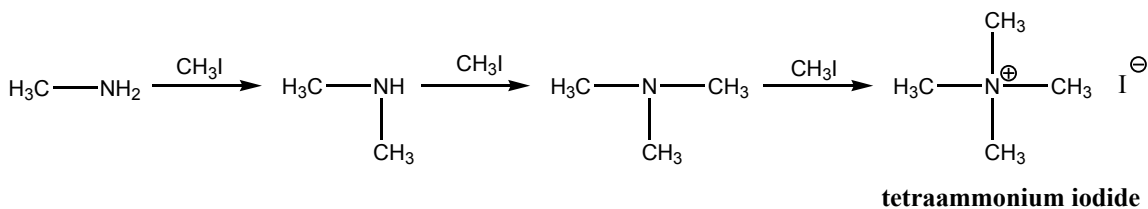


For reaction of ammonia with an alkyl halide, two equivalents of ammonia are needed. One to do alkylation, and the other one to react with hydrogen iodide to form ammonium iodide.

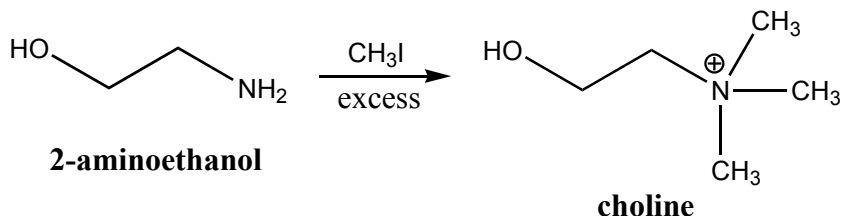


For reaction of primary alkyl halide with substituted amines, the alkylation is difficult to stop after the first alkylation because the product amine is also nucleophilic, and usually more so than the starting material. The result is generally a mixture of alkylated products.

Depending on how many hydrogens the starting amine has, the alkylation will continue until all protons are removed, or even further to make an ammonium salts. This is usually undesirable as mixtures are often formed.



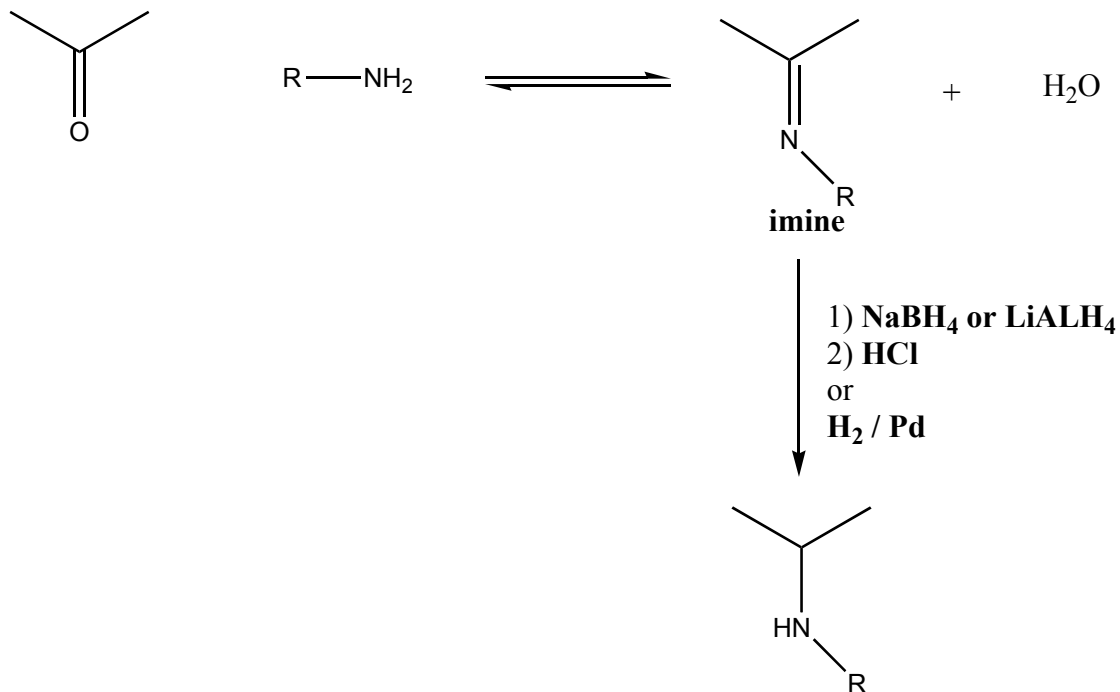
Example:



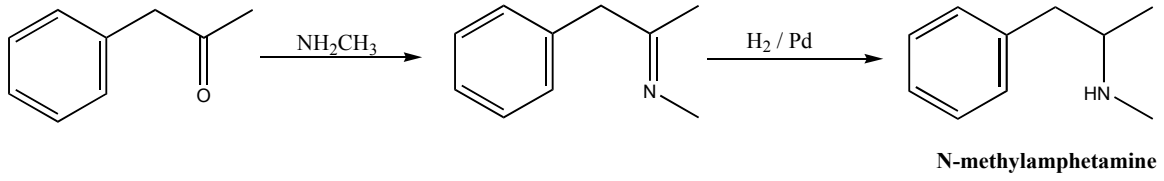
In this example, the nitrogen of amine has alkylated 3 times, whereas the oxygen are not alkylated at all. Alcohols are much less reactive than amine. Oxygen is more electronegative than nitrogen and is less nucleophilic. The oxygen can be alkylated by making an alkoxide anion and then adding yet more methyl iodide.

2) Reductive amination

When the carbon-nitrogen double bond (an imine) is reduced to give primary or secondary amine, this process is called reductive amination.



Example:



Example:

