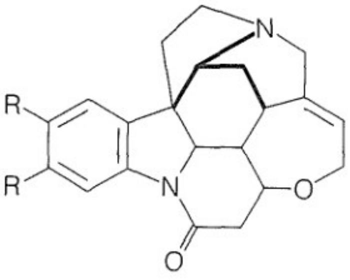
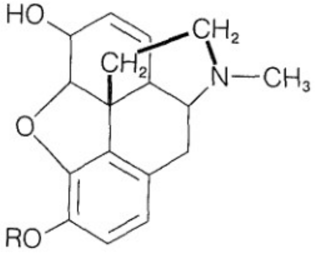
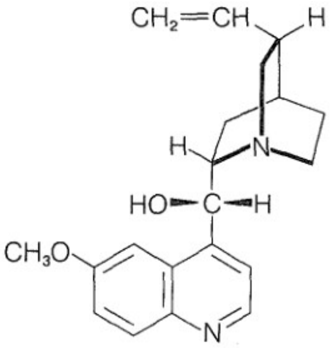
Amines



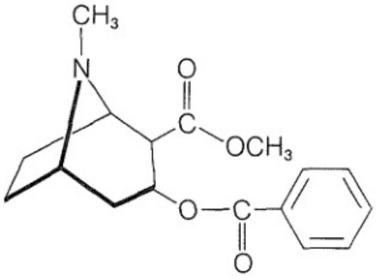
R = H, strychnine
R = OCH_3, brucine



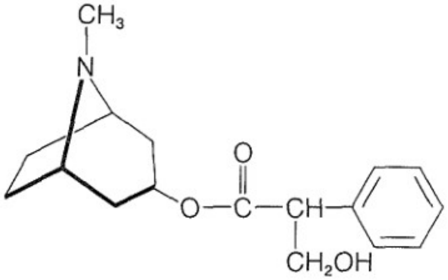
R = H, morphine
R = CH_3, codeine
(analgesic)



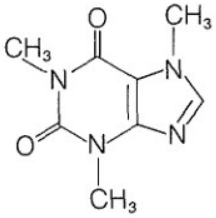
quinine
(antimicrobial)
(antimalarial)



cocaine
(local anaesthetic)
(stimulant)



atropine
(stimulant)



caffeine
(stimulant)

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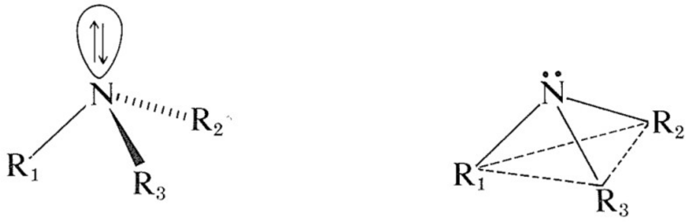
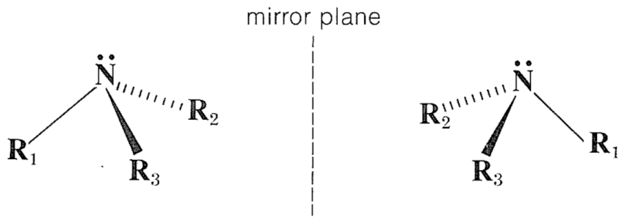
Amines: Stereochemistry

In ammonia and amines, the bonds to nitrogen are pyramidal with bond angles closer to the tetrahedral value of 109.5" than to the 90" value expected for the use of pure p orbitals of nitrogen in bond formation. We consider that the nitrogen in amines is formulated best with hybrid sp^3 type orbitals; three of these orbitals are used in σ-bond formation while the fourth contains the nonbonding electron pair:



pyramidal configuration at nitrogen

A consequence of the pyramidal configuration at nitrogen is that, when the attached groups R_1, R_2 and R_3 are nonidentical, the nitrogen becomes a chiral atom. Under these circumstances, we would expect two enantiomeric configurations :



enantiomers of a chiral amine

Amines

Although amines , like alkyl halides, alcohols, and ethers, have an electron withdrawing group bonded to an sp^3 carbon, amines do not undergo substitution and elimination reactions. An amine's lack of reactivity in substitution and elimination reactions can be understood by comparing the leaving propensity of its electron-withdrawing group with the leaving propensity of the electron-withdrawing groups of the compounds that do undergo substitution and/or elimination reactions. The relative leaving propensities of the groups can be determined by comparing the pK_a values of their conjugate acids . The pK_a values of the conjugate acids show that the leaving group of an amine $(-NH_2^-)$ is such a strong base that amines cannot undergo substitution or elimination reactions. (HF has been used for the comparison since F is in the same row of the periodic chart as O and N, but recall that an alkyl fluoride has the poorest leaving group of the alkyl halides.)

relative reactivities

most reactive $RCH_2F > RCH_2OH > RCH_2OR > RCH_2NH_2$ least reactive

HF	H_2O	ROH	NH_3
$pK_a = 3.2$	$pK_a = 15.7$	$pK_a \sim 16$	$pK_a = 36$

Protonating the amino group makes it a better leaving group, but not nearly as good as a protonated alcohol, which is almost 14 pK_a units more acidic than a protonated amine.

$$CH_3CH_2\overset{+}{O}H_2 > CH_3CH_2\overset{+}{N}H_3$$

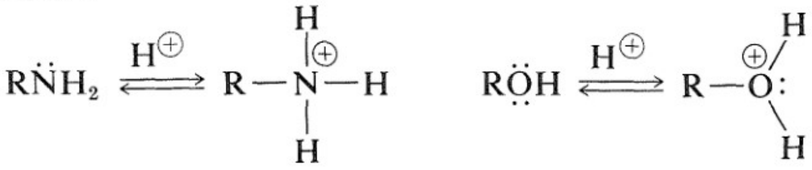
$CH_3CH_2\overset{+}{O}H_2$	$CH_3CH_2\overset{+}{N}H_3$
$pK_a = -2.4$	$pK_a = 11.2$

Amines: Comparison with alcohols

Acids

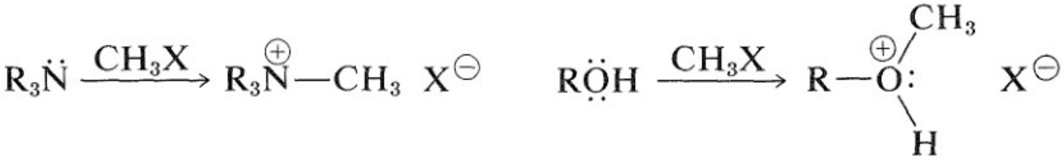
$$\mathrm{R\ddot{N}H_2} \overset{-\mathrm{H}^{\oplus}}{\rightleftharpoons} \mathrm{R\ddot{N}H}^{\ominus} \qquad \mathrm{R\ddot{O}H} \overset{-\mathrm{H}^{\oplus}}{\rightleftharpoons} \mathrm{R\ddot{O}}{:}^{\ominus}$$

Bases



$$\mathrm{R\ddot{N}H_2} \overset{\mathrm{H}^{\oplus}}{\rightleftharpoons} \mathrm{R{-}\overset{\overset{\mathrm{H}}{|}\,\oplus}{\underset{\underset{\mathrm{H}}{|}}{N}}{-}H} \qquad \mathrm{R\ddot{O}H} \overset{\mathrm{H}^{\oplus}}{\rightleftharpoons} \mathrm{R{-}\overset{\oplus\,\mathrm{H}}{\underset{\mathrm{H}}{O}}{:}}$$

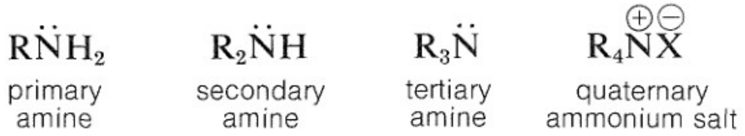
Nucleophiles



$$\mathrm{R_3\dot{N}} \xrightarrow{\mathrm{CH_3X}} \mathrm{R_3\overset{\oplus}{N}{-}CH_3}\ \ \mathrm{X}^{\ominus} \qquad \mathrm{R\ddot{O}H} \xrightarrow{\mathrm{CH_3X}} \mathrm{R{-}\overset{\oplus\,\mathrm{CH_3}}{\underset{\mathrm{H}}{O}}{:}}\ \ \mathrm{X}^{\ominus}$$

Amines: Classification

Amine bases are classified according to the number of alkyl or aryl groups attached to nitrogen. This number is important in determining the chemical reactions that are possible at the nitrogen atom:

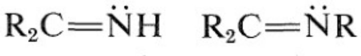

$R\ddot{N}H_2$ primary amine

$R_2\ddot{N}H$ secondary amine

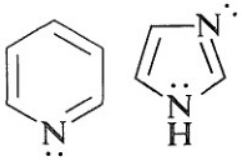
$R_3\ddot{N}$ tertiary amine

$R_4\overset{\oplus}{N}\overset{\ominus}{X}$ quaternary ammonium salt

A further classification exists if the nitrogen is multiply bonded to carbon, as in imines and aromatic nitrogen compounds:


$R_2C{=}\ddot{N}H \quad R_2C{=}\ddot{N}R$

imines (Schiff bases)



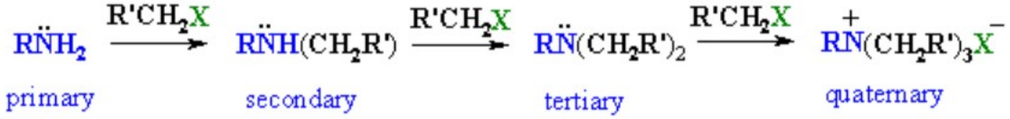
aromatic nitrogen bases

Amines: Preparation

1. Alkylation of ammonia: reaction between alkyl halides and ammonia

- Ammonia reacts as a nucleophile with alkyl halides to give primary amines in a nucleophilic substitution reaction.
- Yields are often poor as the product, a primary amine, **RNH_2**, is *itself a nucleophile* and can react with more alkyl halide.
- The result are mixtures containing primary amines, secondary amines, tertiary amines and quaternary ammonium salts.
- This can be avoided if a large excess of ammonia is used.
- As aryl halides **do not** undergo simple nucleophilic substitution, they ***cannot*** be prepared using this method.

$$R-X + 2\,NH_3 \longrightarrow R-NH_2 + \overset{+}{N}H_4\,X^-$$

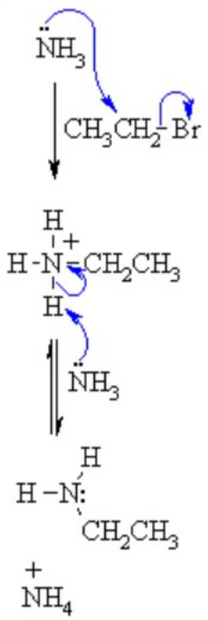


$$R\ddot{N}H_2 \xrightarrow{R'CH_2X} R\ddot{N}H(CH_2R') \xrightarrow{R'CH_2X} R\ddot{N}(CH_2R')_2 \xrightarrow{R'CH_2X} R\overset{+}{N}(CH_2R')_3X^-$$

MECHANISM OF AMMONIA ALKYLATION

Step 1:
The **N** in ammonia functions as the nucleophile and attacks the electrophilic **C** of the alkyl halide displacing the bromide and creating the new **C-N** bond.

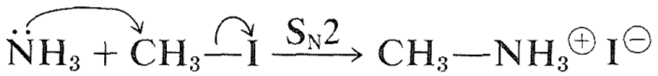
Step 2:
An acid/base reaction. The base (excess ammonia) deprotonates the positive **N** (ammonium) center creating the alkylation product, the primary amine.



Amines: Preparation

1. Alkylation of ammonia: reaction between alkyl halides and ammonia

Ammonia and amines can function as nucleophiles in S_N2 displacement reactions of alkyl halides. Such processes provide syntheses of alkanamines only with those halides that are reactive in S_N2 but not E2 reactions. For example,



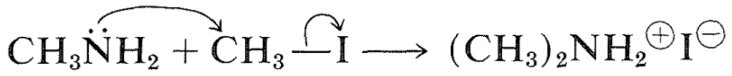
$$\ddot{N}H_3 + CH_3{-}I \xrightarrow{S_N2} CH_3{-}NH_3^{\oplus}\, I^{\ominus}$$

The product formed is an ammonium salt from which the parent amine can be recovered by neutralization with a strong base, such as sodium hydroxide:

$$CH_3NH_3^{\oplus}\, I^{\ominus} + Na^{\oplus}\ {}^{\ominus}OH \rightleftharpoons CH_3NH_2 + \overset{\oplus}{Na}\ \overset{\ominus}{I} + H_2O$$

Acid-base equilibria similar to the one given above also occur between an ammonium salt and a neutral amine. This can have serious consequences in amine alkylations because it can lead to mixtures of products, whereby more than one alkyl group is bonded to nitrogen:

$$CH_3NH_3^{\oplus}I^{\ominus} + NH_3 \rightleftharpoons CH_3NH_2 + NH_4^{\oplus}I^{\ominus}$$



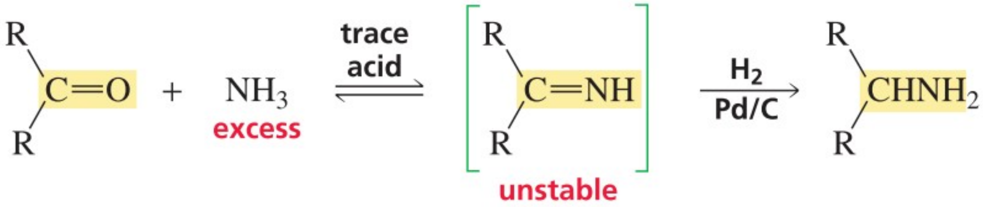
$$CH_3\ddot{N}H_2 + CH_3{-}I \longrightarrow (CH_3)_2NH_2^{\oplus}I^{\ominus}$$

Therefore we may expect the reaction of ammonia with methyl iodide to give four possible alkylation products, mono-, di-, and trimethylamines, as well as tetramethylammonium iodide:

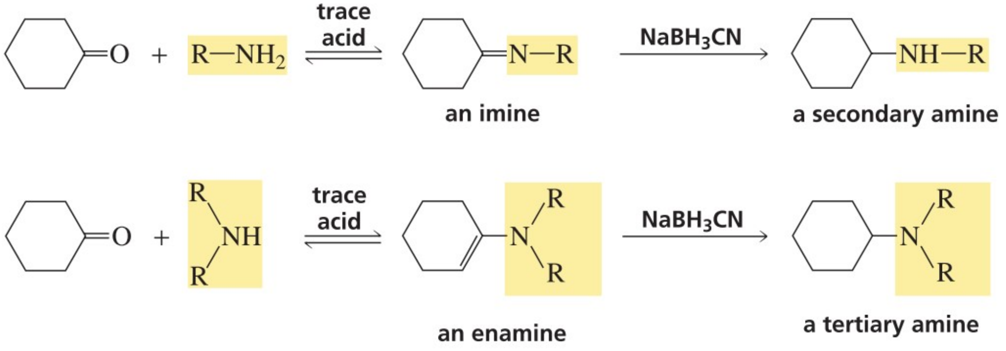
$$\ddot{N}H_3 \xrightarrow[-HI]{CH_3I} CH_3\ddot{N}H_2 \xrightarrow[-HI]{CH_3I} (CH_3)_2\ddot{N}H \xrightarrow[-HI]{CH_3I} (CH_3)_3\ddot{N} \xrightarrow{CH_3I} (CH_3)_4N^{\oplus}I^{\ominus}$$

Amines: Preparation

Reductive amination: The reaction of an aldehyde or a ketone with excess ammonia in the presence of a reducing agent is called reductive amination.



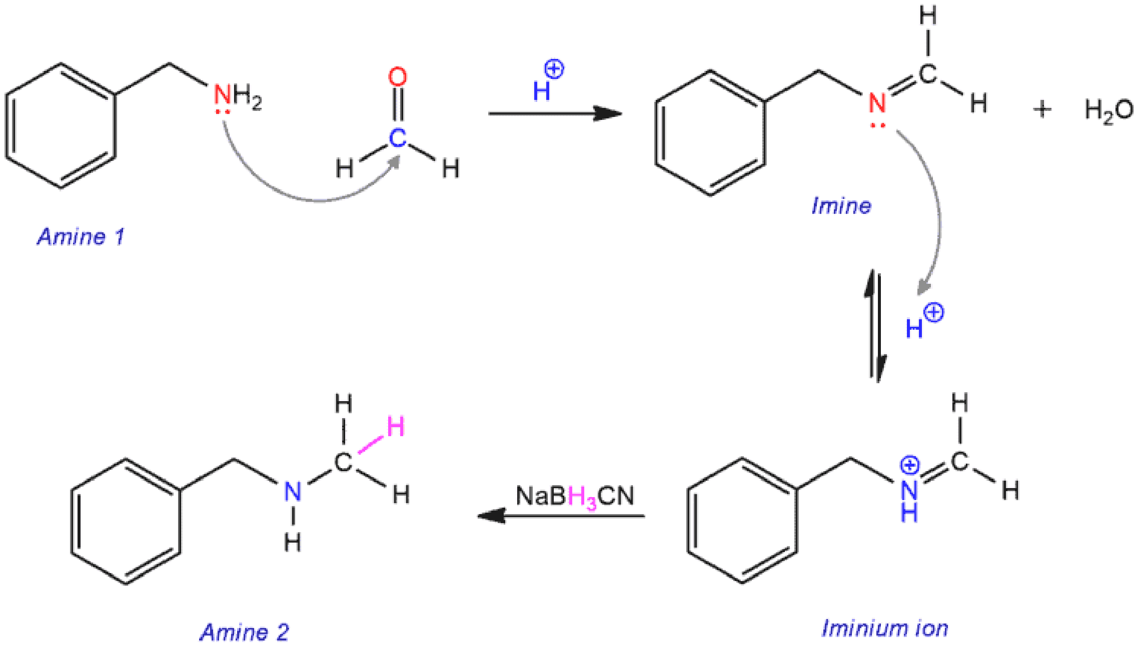
The double bond of an imine is reduced more rapidly than a C=O bond, so reduction of the carbonyl group does not compete with reduction of the imine in these reactions. Secondary and tertiary amines can be prepared by reducing the imine. Sodium cyanoborohydride ($NaBH_3CN$) is a commonly used reducing agent for these reactions because it can be handled easily and it is stable even in acidic solutions. (Note that $NaBH_3CN$ differs from $NaBH_4$ in having a CN group in place of one of the hydrogens.)



Amines: Preparation

Reductive amination: Mechanism

The mechanism of reductive amination consists of three steps. The first step is the formation of an imine by attacks of nitrogen (amine) to the carbonyl carbon of carbonyl compound (Formaldehyde in the reaction shown below). In the next step, the resulting imine will be protonated under acidic conditions to give iminium ion (its conjugate acid) and in the last step, in the presence of reducing agent, the iminium ion will be reduced to give a new amine.



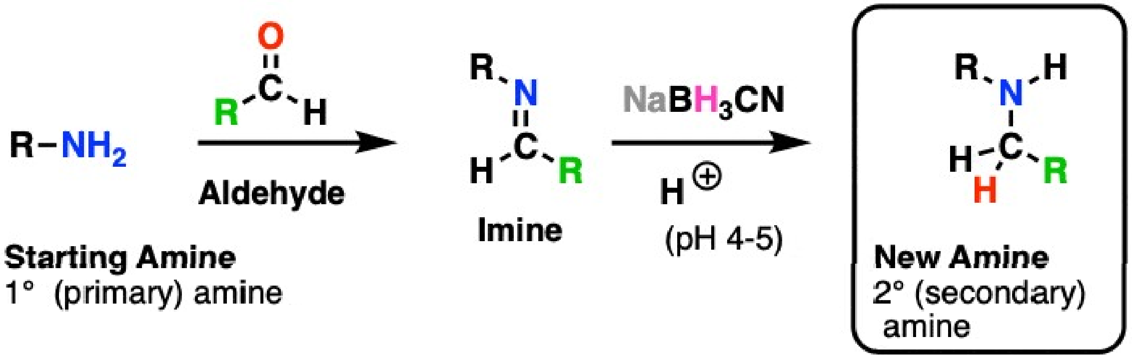
Amines: Preparation

Reductive amination

A versatile way of making different **amines** is to make an **imine** and then treat it with a **reducing agent** such as $NaBH_4$ (sodium borohydride) or $NaCNBH_3$ (sodium cyanoborohydride) to obtain the **amine**.

Step 1: *Imine formation*

Step 2: *Reduction*



Key Bonds Formed	**Key Bonds Broken**
C–N	C–O
C–H	C–O (pi)

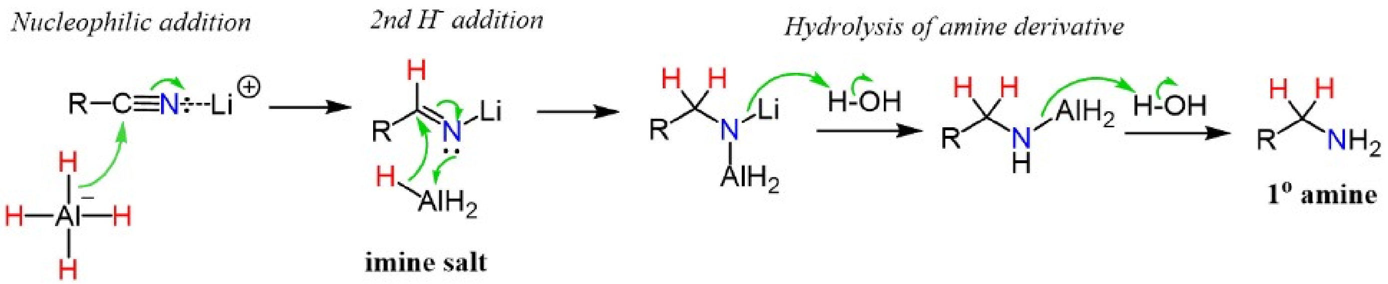
if desired this new amine can then be used in another reductive amination with a different aldehyde to make a 3° amine

- Reductive amination allows for amines to be "built up" sequentially from various aldehydes in a **controlled fashion** (as opposed to alkylation of amines with R–X which tends to be hard to control)
- Using NH_3 with an aldehyde or ketone gives a **primary** amine
- Ketones can also be used to go directly from 1° amines to 3° amines
- Intramolecular reductive aminations give **cyclic** amines
- Useful reducing agents include $NaCNBH_3$ (sodium cyanoborohydride), $NaH(OAc)_3$ (sodium tri-acetoxborohydride) and $NaBH_4$ (sodium borohydride)
- Does *not* work for making aromatic amines (i.e. Ph-NH_2)

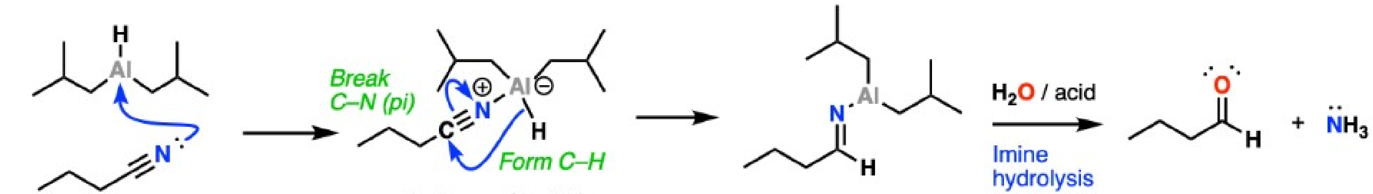
Amines: Preparation

Reduction of Nitriles: Amines are produced when nitriles are reduced using appropriate reducing agents like $LiAlH_4$ and DIBAL

The Mechanism of Nitrile Reduction to 1° Amine with $LiAlH_4$



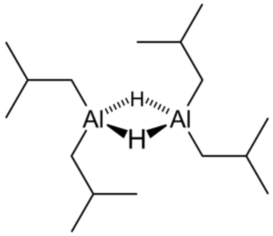
Reduction of nitriles with DIBAL



Coordination of the nitrogen lone pair to the aluminum

Delivery of hydride to the nitrile carbon

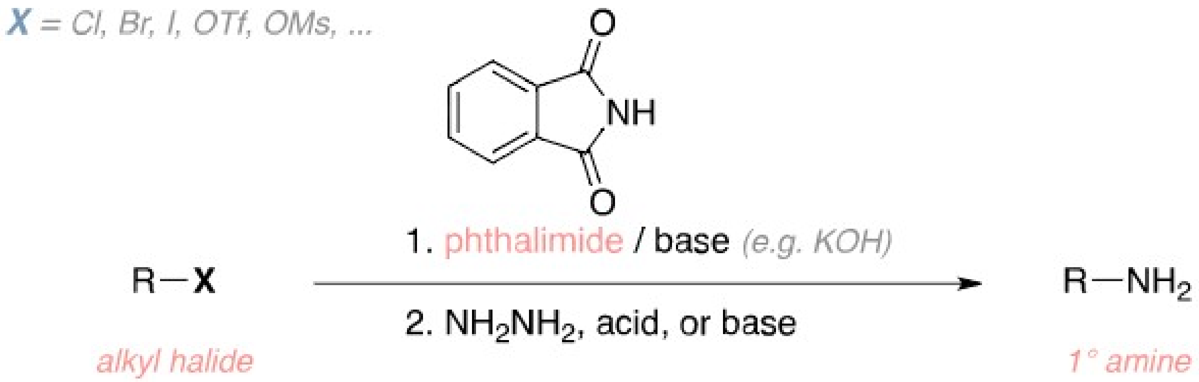
Formation of an imine



DIBAL: Diisobutylaluminium hydride

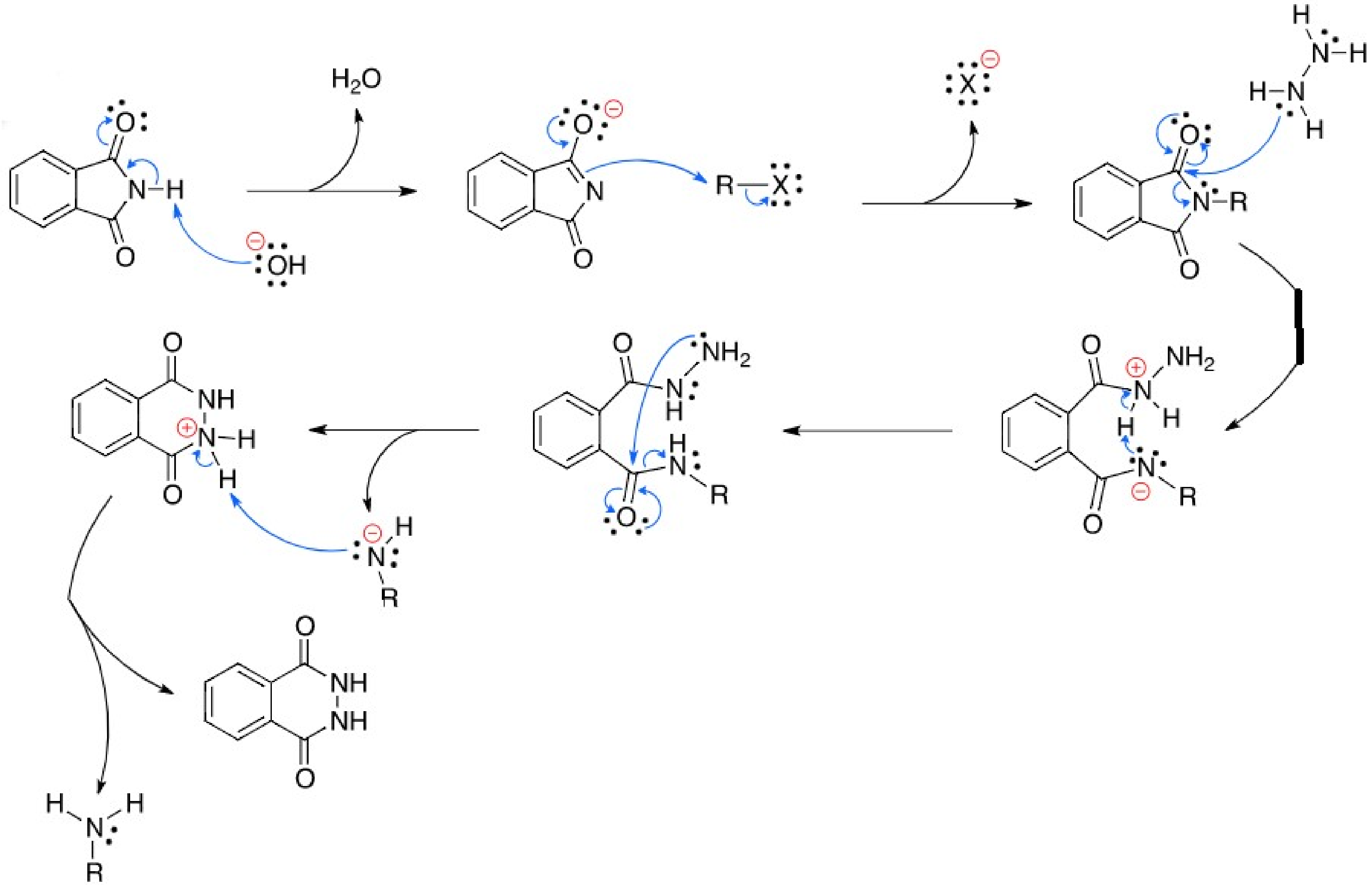
Gabriel synthesis

Gabriel Pthalimide Reaction: The Gabriel synthesis is an organic reaction used to convert an alkyl halide to a primary amine using phthalimide with base and followed by hydrazine.



The reaction begins with the deprotonation of the phthalimide which then attacks the alkyl halide in an S_N2 fashion to give an N-alkylphthalimide intermediate. The intermediate is then cleaved by hydrazine in a series of steps that end with the liberation of the final primary amine product and phthalhydrazide by-product.

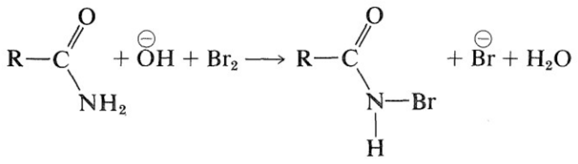
Gabriel synthesis



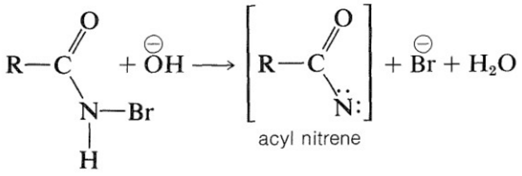
Amines: Preparation

Hoffmann Bromamide Degradation: This reaction is used for the conversion of a primary amide to a primary amine with one less carbon atom (hence the name degradation). This is accomplished by heating the primary amide with a mixture of a halogen (chlorine or bromine), a strong base, and water.

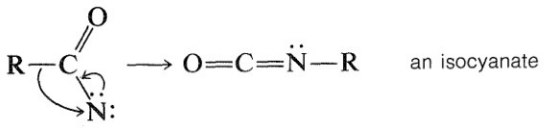
1. The mechanism of this unusual reaction first involves base-catalyzed bromination of the amide on nitrogen to give an N-bromoamide intermediate:



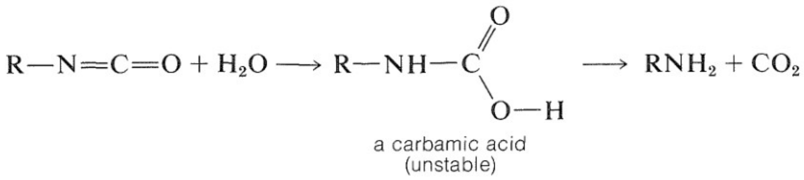
2. There follows a base-induced elimination of HBr from nitrogen to form a "nitrene" intermediate, which is analogous to the formation of a carbene:



3. As you might expect from the structure of an acyl nitrene (only six electrons in the valence shell of nitrogen), it is highly unstable but can become stabilized by having the substituent group move as R$^-$ from carbon to nitrogen. The rearrangement is stereospecific and the configuration at the migrating carbon is retained. The rearrangement product is called an isocyanate and is a nitrogen analog of a ketene (R,C=C=O)



4. Like ketenes isocyanates readily add water. The products are carbamic acids, which are not very stable, especially in basic solution, and readily lose carbon dioxide to give the amine:



Amines: basicity

The most characteristic property of amines is their ability to act as bases by accepting protons from a variety of acids:

$$R\ddot{N}H_2 + HA \rightleftharpoons R\overset{\oplus}{N}H_3 + :\overset{\ominus}{A}$$

When the reference acid HA is water, we can set up a scale of base strengths from the equilibrium constant, K_b, measured for the proton-transfer reaction shown

$$R\ddot{N}H_2 + H_2O \overset{K_b}{\rightleftharpoons} R\overset{\oplus}{N}H_3 + :\overset{\ominus}{O}H$$

In many reference works, it is customary to express the strengths of organic bases not as K_b values but as the acid-dissociation constants, K_a (or pKa's) for the corresponding conjugate acids. These K_a values are then the acid constants of the corresponding ammonium ions in aqueous solution

$$R\overset{\oplus}{N}H_3 + H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + H_3\overset{\oplus}{O}$$

With this convention, the stronger the base, RNH_2 the more the equilibrium will lie to the left, and the smaller will be K_a. The relationship between K_a and K_b in water solution is

$$K_a \times K_b = 10^{-14}$$

And in terms of pKa values, because by definition pKa = -log Ka

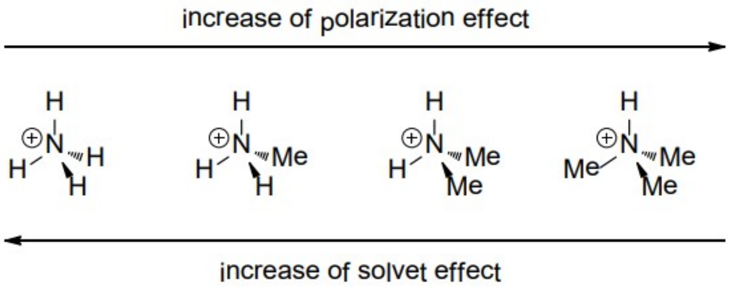
$$pK_a + pK_b = 14$$

Amines: basicity

Amines, like ammonia, are strong enough bases that they are completely protonated in dilute acid solutions. Basicity can be increased by increasing the availability of lone pair and stabilizing the resultant positive charge. When one hydrogen of ammonia replaced by methyl group, it stabilizes the resultant positive charge formed on protonation. Alkyl groups have the tendency to stabilize charge through a polarization effect. This effect increases on increasing numbers of the alkyl groups. The base strengths of simple alkanamines usually are around $K_b = 10^{-4}$($K_a = 10^{-10}$) in water solution, and vary within perhaps a factor of 10 from ammonia to primary, secondary, and tertiary amines. The trends that are evident, especially from basicities of amines measured in the gas phase, point to increasing basicity with the number and size of alkyl groups on the nitrogen atom

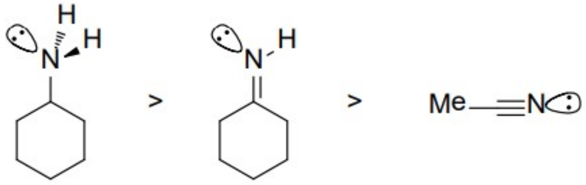
Order of basicity (gas phase): $(CH_3)_3\ddot{N} > (CH_3)_2\ddot{N}H > CH_3\ddot{N}H_2 > \ddot{N}H_3$

This is reasonable because the conjugate acids, R_3NH^+, are likely to be stabilized by electron-donating and polarizable alkyl groups, thereby making R_3N a stronger base. That the same trend is not evident in aqueous solution again shows the influence of the solvent on thermochemical properties. Every hydrogen attached directly to nitrogen can form hydrogen bond with solvent water and this also stabilizes the charge. This effect decreases with increasing numbers of alkyl groups. So the observed basicity is the combination of these two effects. Most of tertiary amines are less basic than that of primary amine because bulky groups in the tertiary amines make the lone pair less available.



Amines: basicity

Lone pair held in an sp^2 or an sp orbital is much harder to protonate. So the basicity decreases from amine to imine to nitrile

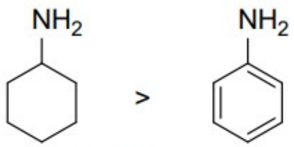


lone pair in sp^3 orbital

lone pair in sp^2 orbital

lone pair in sp orbital

While comparing cyclohexanamine and aniline, aniline is a weak base because the lone pair can be delocalized into the benzene ring. In order for the lone pair to be fully conjugated with the benzene ring, the nitrogen would have to be sp^2 hybridized with the lone pair in the p-orbital. This is not found to be the case. Instead, the plane of the NH_2 group is about 40° away from the plane of the ring, which means the lone pair is partially conjugated into the ring

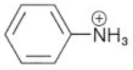
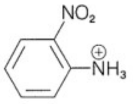
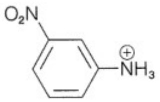
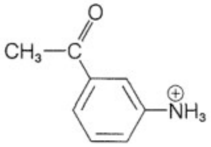
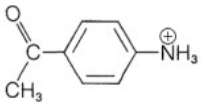
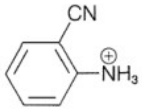
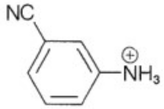
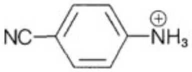
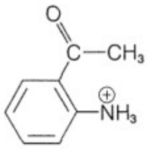


cyclohexanamine

aniline

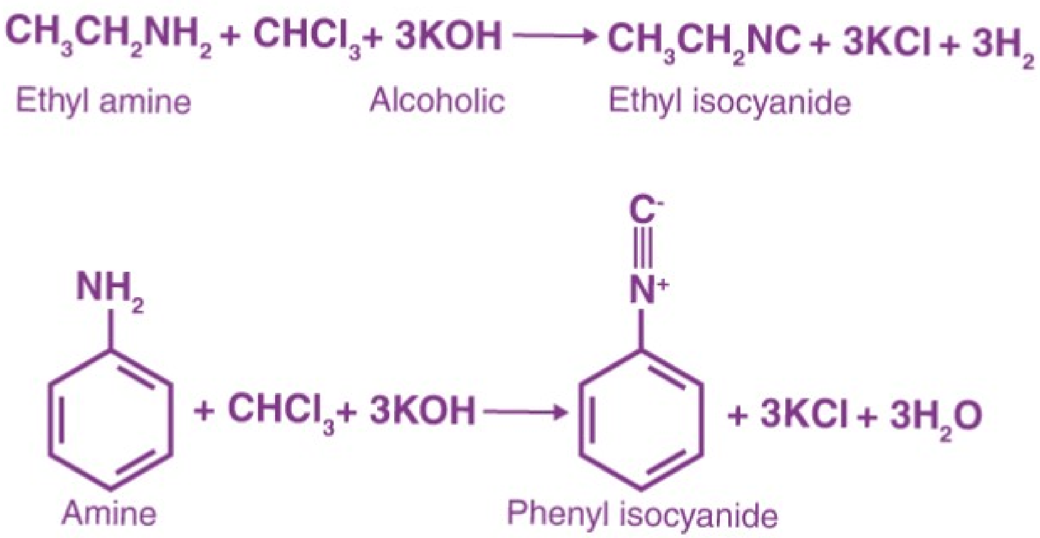
Amines: basicity

Strengths of Conjugate Acids of Monosubstituted Benzenamines in Aqueous Solution at 25°

Substituent	Formula	pK_a
H		4.60
4-amino		6.16
4-methyl		5.10
2-nitro		−0.26
3-nitro		2.47
3-ethanoyl		3.59
4-ethanoyl		2.19
4-nitro		1.11
2-cyano		0.95
3-cyano		2.76
4-cyano		1.74
4-trifluoromethyl		2.45
2-ethanoyl		2.22

Carbylamine Reaction

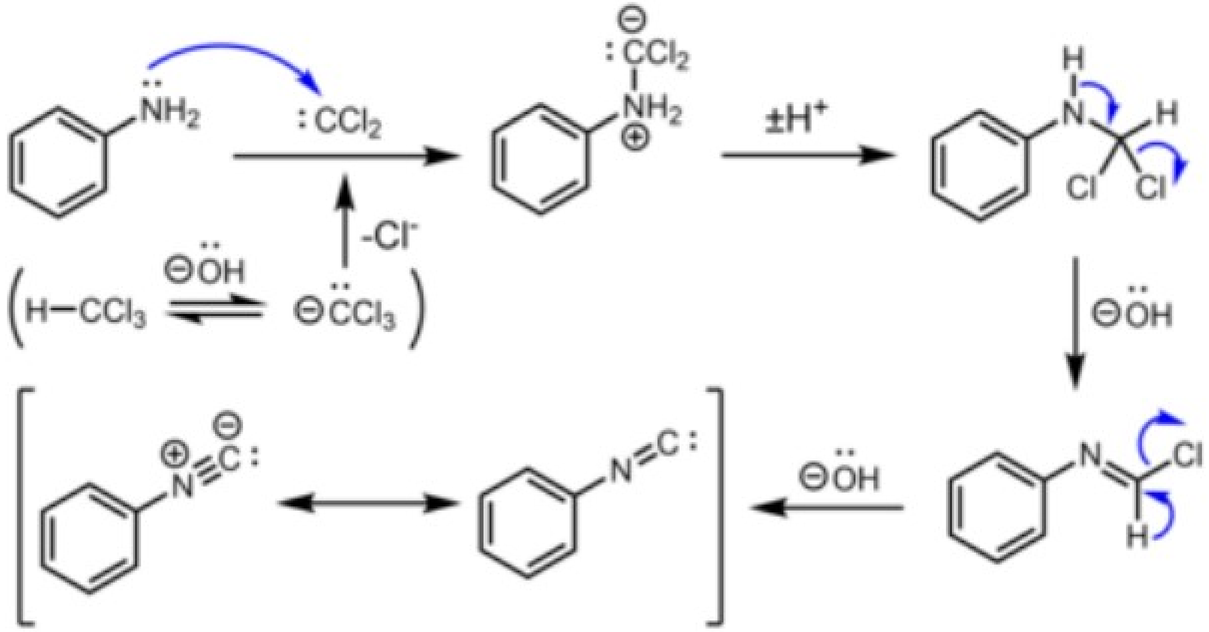
The carbylamine reaction (also known as the Hoffmann isocyanide synthesis) is the synthesis of an isocyanide by the reaction of a primary amine, chloroform, and base. Carbylamine reaction mechanism involves the addition of amine to the dichlororcarbene intermediate created from the dehydrohalogenation of chloroform. As it is only effective for primary amines, the carbylamine reaction can be used as a chemical test for their presence. In this context, the reaction is also known as Carbylamin or Saytzeff's isocyanide test. In this reaction, the analyte is heated with alcoholic potassium hydroxide and chloroform. If a primary amine is present, the isocyanide (carbylamine) is formed, as indicated by a foul odour. The carbylamine test does not give a positive reaction with secondary and tertiary amines



Carbylamine Reaction

Mechanism

The mechanism involves the addition of amine to dichlorocarbene, a reactive intermediate generated by the dehydrohalogenation of chloroform. Two successive base-mediated dehydrochlorination steps result in formation of the isocyanide

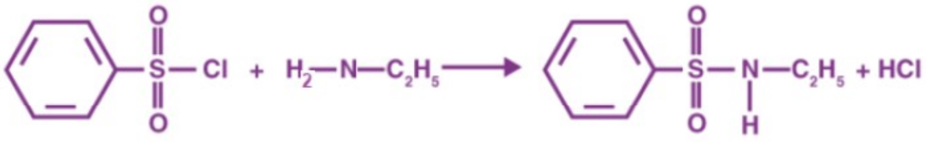


Hinsberg Test for Amines

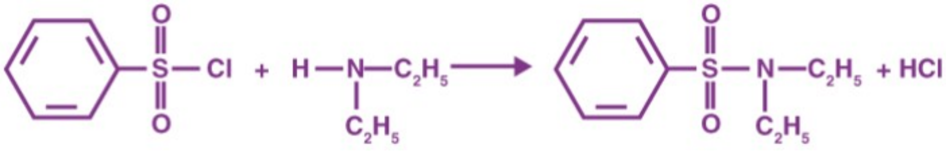
Hinsberg reagent is just another name for the benzene sulfonyl chloride. It is an organosulfur compound and this name is given for its use in the Hinsberg test for the detection and distinction of primary, secondary, and tertiary amines in a given sample. This Reagent undergoes a reaction with compounds that contain O-H and N-H bonds that are reactive in nature. It is used in the preparation of sulfonamides (via reaction with amines) and sulfonamide esters (via reaction with alcohol).

Hinsberg Test: is a chemical reaction used to distinguish between primary, secondary, and tertiary amines. This reaction was described first in 1890 by the German chemist Oscar Heinrich Daniel Hinsberg. In the Hinsberg Test, the amines act as nucleophiles and attack the electrophile (sulfonyl chloride). This leads to the displacement of the chloride and the generation of the sulfonamides. When primary and secondary amines form sulfonamides, this sulfonamide product is not soluble and precipitates from the solution as a solid.

1. The reaction of the benzene sulfonyl chloride with primary amines gives a sulfonamide product that is soluble in alkali.



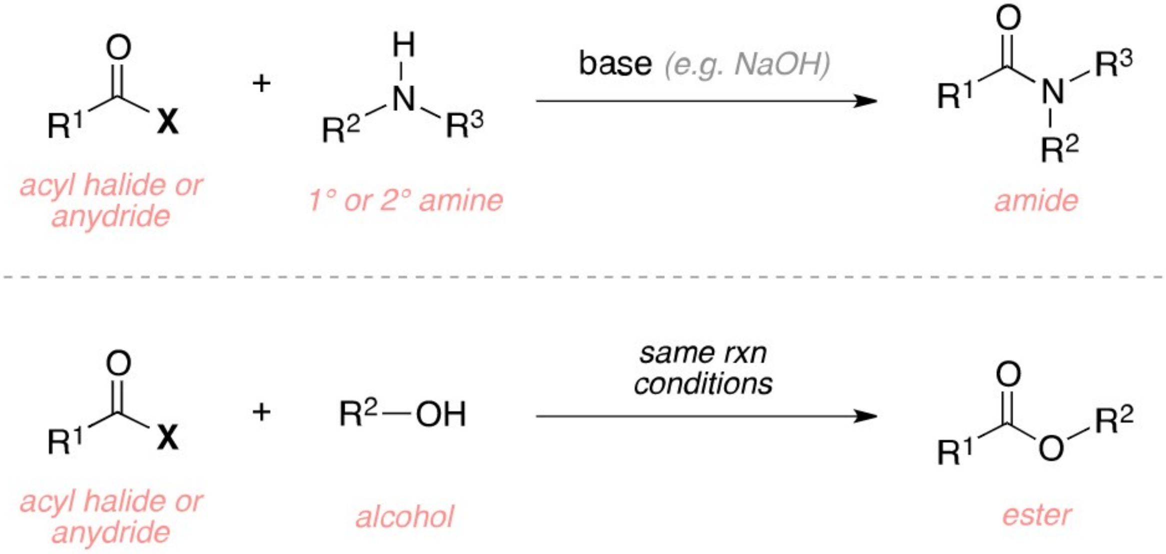
2. The reaction of the benzene sulfonyl chloride with secondary amines gives a sulfonamide product that is NOT soluble in alkali.



3. No such reaction occurs between a tertiary amine and the benzene sulfonyl chloride reagent.

Schotten-Baumann reaction

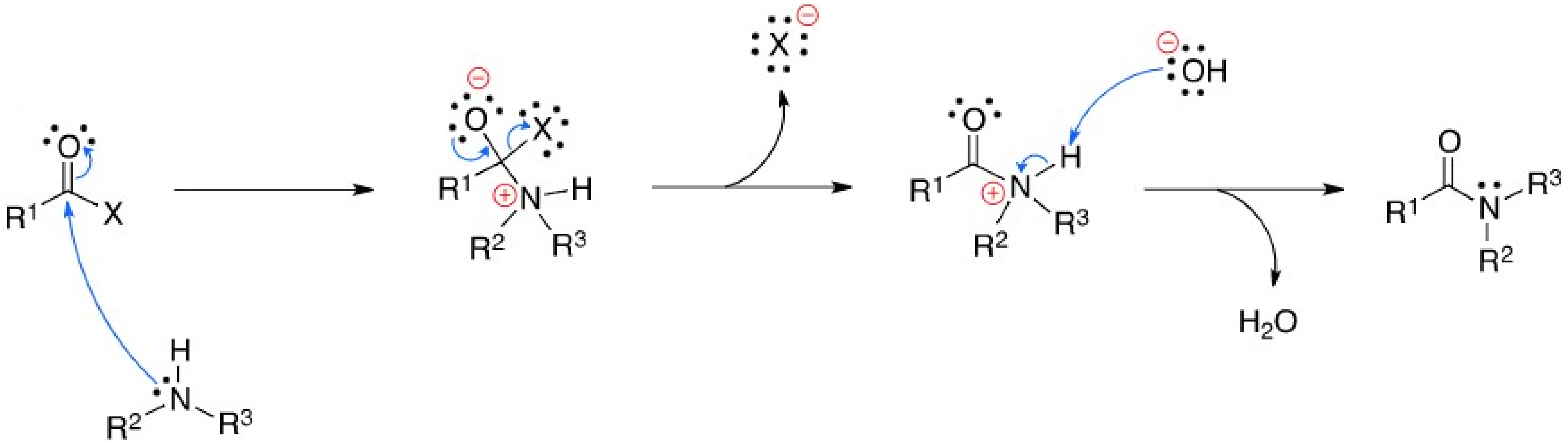
The Schotten-Baumann reaction is an organic reaction used to convert an acyl halide or anhydride to an amide if reacted with an amine and base, or an ester if reacted with an alcohol and base. The reaction with the amine begins with the nitrogen attacking the carbonyl carbon of the acyl halide which rearranges to kick out the halide. Deprotonation with the base then provides the final amide product.



X = Cl, Br, OCOR

Schotten-Baumann reaction

Mechanism:



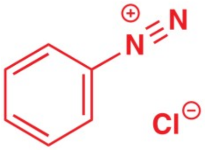
Draw the mechanism for an alcohol nucleophile?

Diazonium Salts

Diazonium salts are an important class of compounds formed when NO^+ reacts with an amine. The lone pair of the amine attacks the NO^+ cation, and then water is lost. The mechanism is actually quite simple, but it does involve a lot of proton transfers. There is, of course, an anion associated with the nitrogen cation, and this will be the conjugate base (Cl^- usually) of the acid used to form NO^+. This reaction is known as diazotization.. Diazonium salts very readily lose nitrogen gas, and this substitution of N_2 by a nucleophile opens yet more opportunities to compounds derived from aromatic amines and nitro compounds. It also involves nucleophilic substitution at the aromatic ring.

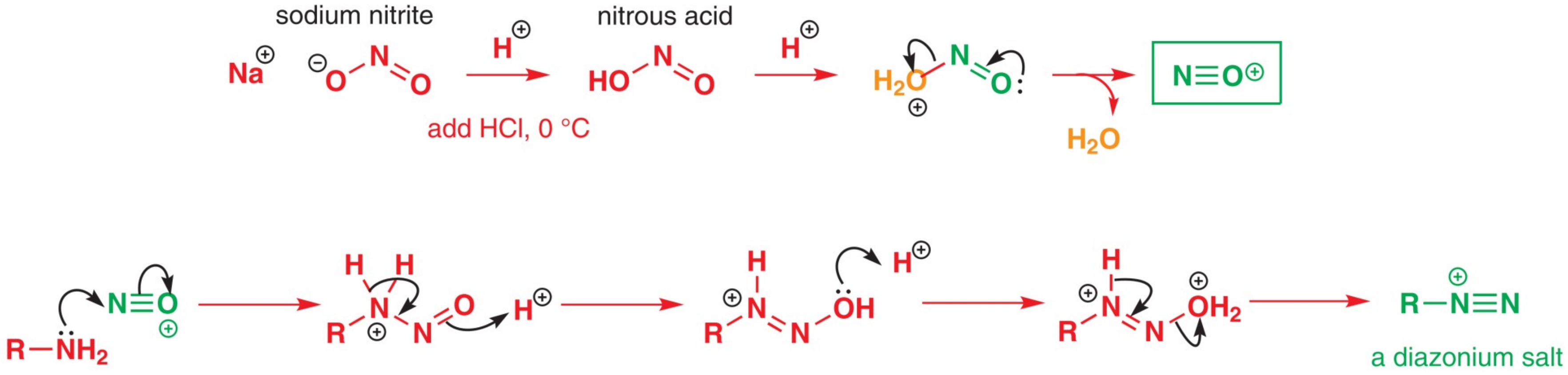
$H_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$

Diazomethane



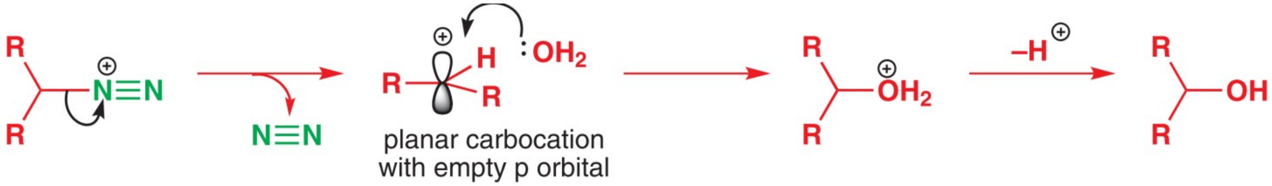
Benzenediazonium chloride

Diazotization: Mechanism

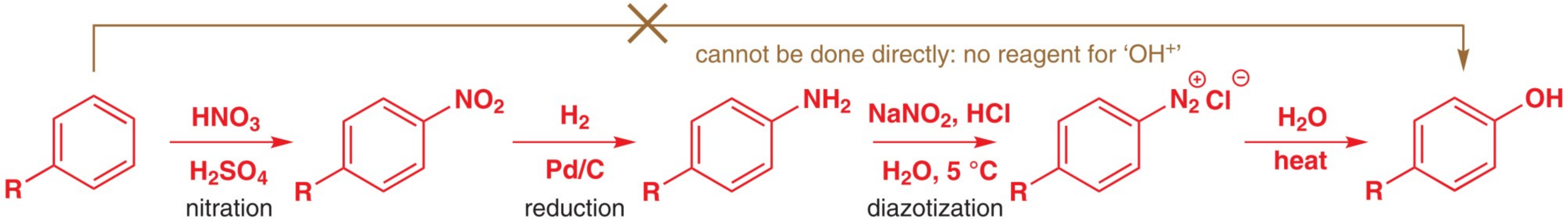


Diazonium Salts

If the amine is an alkyl amine, this diazonium salt is very unstable and immediately loses nitrogen gas to give a planar carbocation, which normally reacts with a nucleophile in an S_N1 process, loses a proton in an E1 process, or rearranges. It may, for example, react with water to give an alcohol:

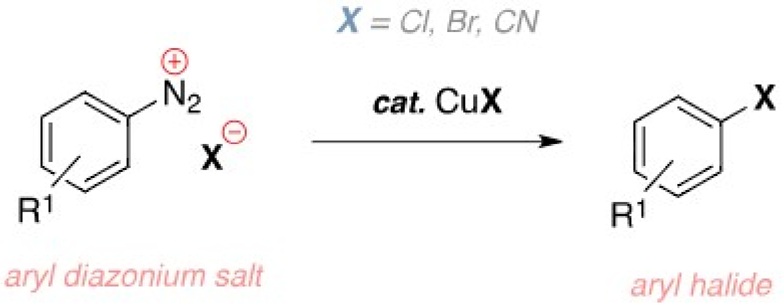


If the amine is an aryl amine, then a phenol will form. This is a useful reaction as it is difficult to add an oxygen atom to a benzene ring by normal electrophilic substitution: there is no good reagent for OH^+. A nitrogen atom can be added easily by nitration, and reduction and diazotization provide a way of replacing the nitro group by a hydroxyl group.



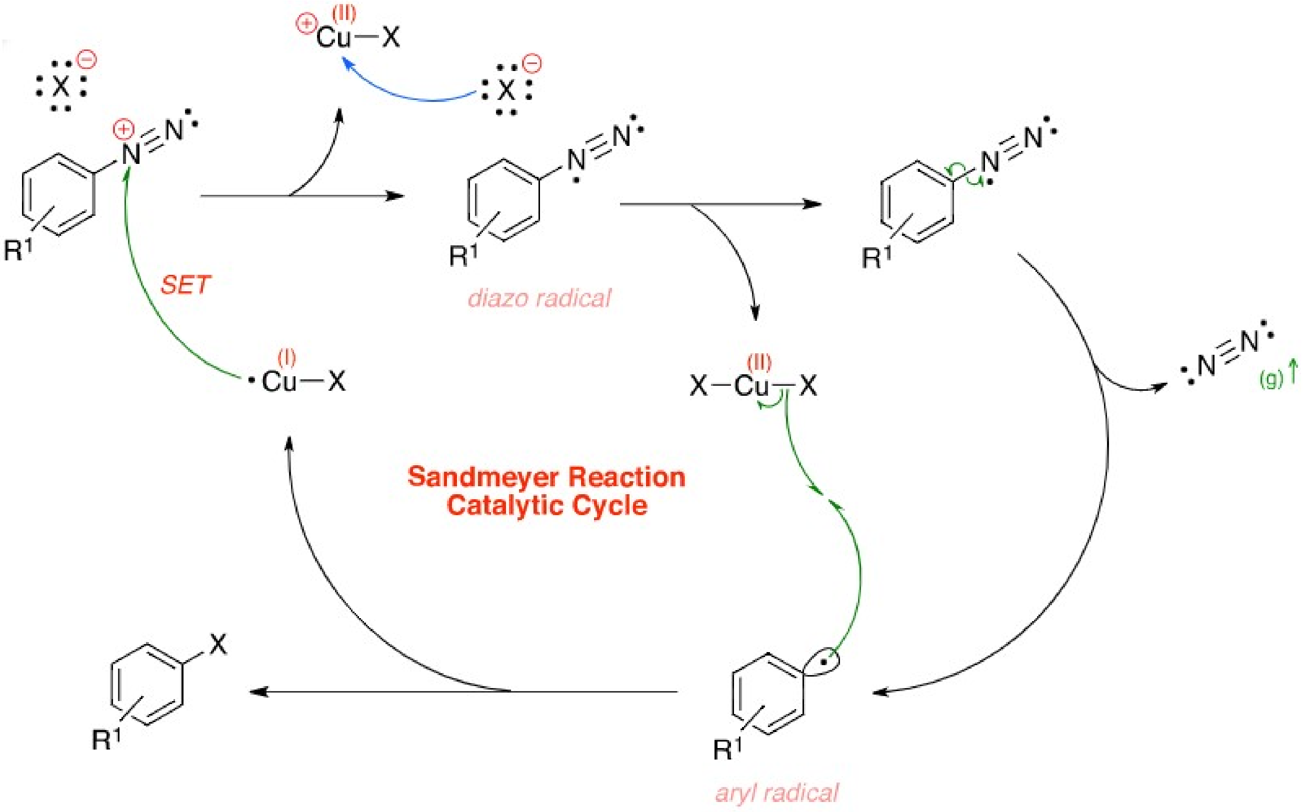
Sandmeyer reaction

The Sandmeyer reaction is an organic reaction used to convert an aryl diazonium salt to an aryl halide using a copper(I) halide catalyst. The mechanism begins with a single electron transfer (SET) from the copper to the diazonium to form a neutral diazo radical and copper(II) halide. The diazo radical then releases a molecule of nitrogen gas to form an aryl radical. The aryl radical reacts with the copper(II) halide to regenerate the copper(I) halide catalyst and yield the final aryl halide product.



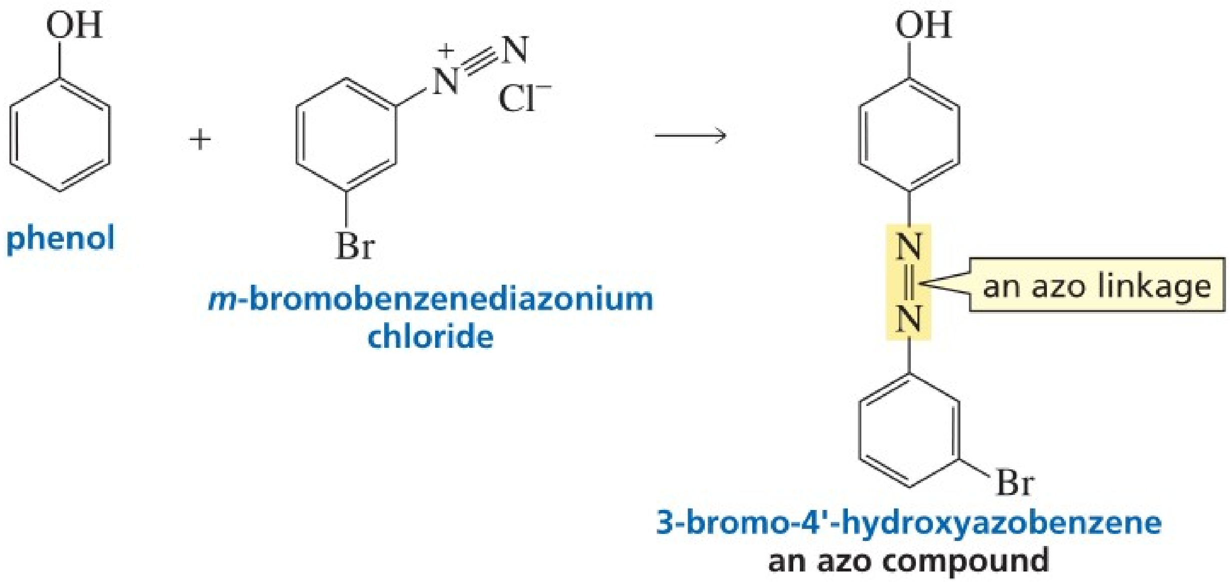
Sandmeyer reaction

Mechanism:



Azo Coupling: Arenediazonium salts as electrophiles

In addition to being used to synthesize substituted benzenes, arenediazonium ions can be used as electrophiles in electrophilic aromatic substitution reactions. Because an arenediazonium ion is unstable at room temperature, it can be used as an electrophile only in reactions that can be carried out well below room temperature. In other words, only highly activated benzene rings (phenols, anilines, and N -alkylanilines) can undergo electrophilic aromatic substitution reactions with arenediazonium ion electrophiles. The product of the reaction is an azo compound. The N=N linkage is called an azo linkage.



phenol

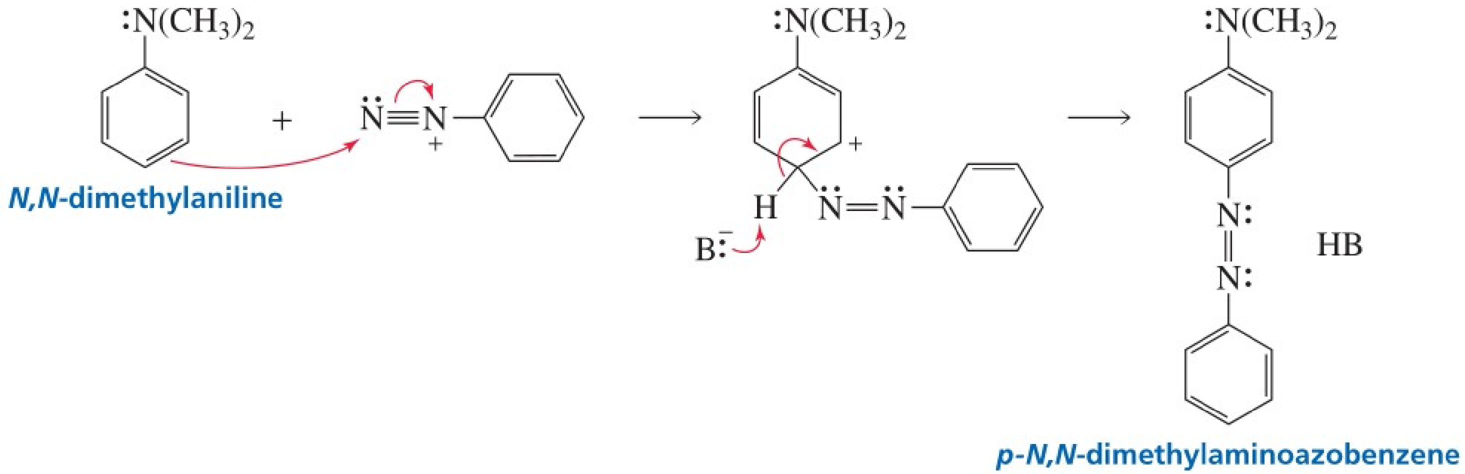
***m*-bromobenzenediazonium chloride**

3-bromo-4'-hydroxyazobenzene

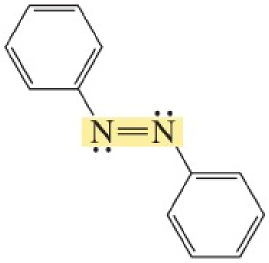
an azo compound

Azo Coupling: Arenediazonium salts as electrophiles

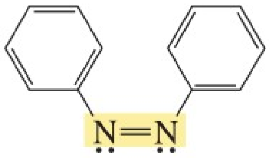
Because the electrophile is so large, substitution takes place preferentially at the less sterically hindered para position. However, if the para position is blocked, then substitution will occur at an ortho position. The mechanism for electrophilic aromatic substitution with an arenediazonium ion electrophile is the same as the mechanism for electrophilic aromatic substitution with any other electrophile.



Azo compounds, like alkenes, can exist in cis and trans forms. The trans isomer is more stable because the cis isomer has steric strain.



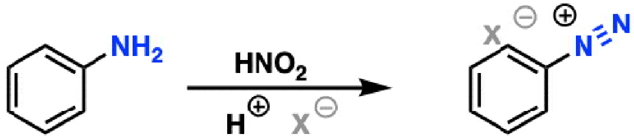
trans-azobenzene

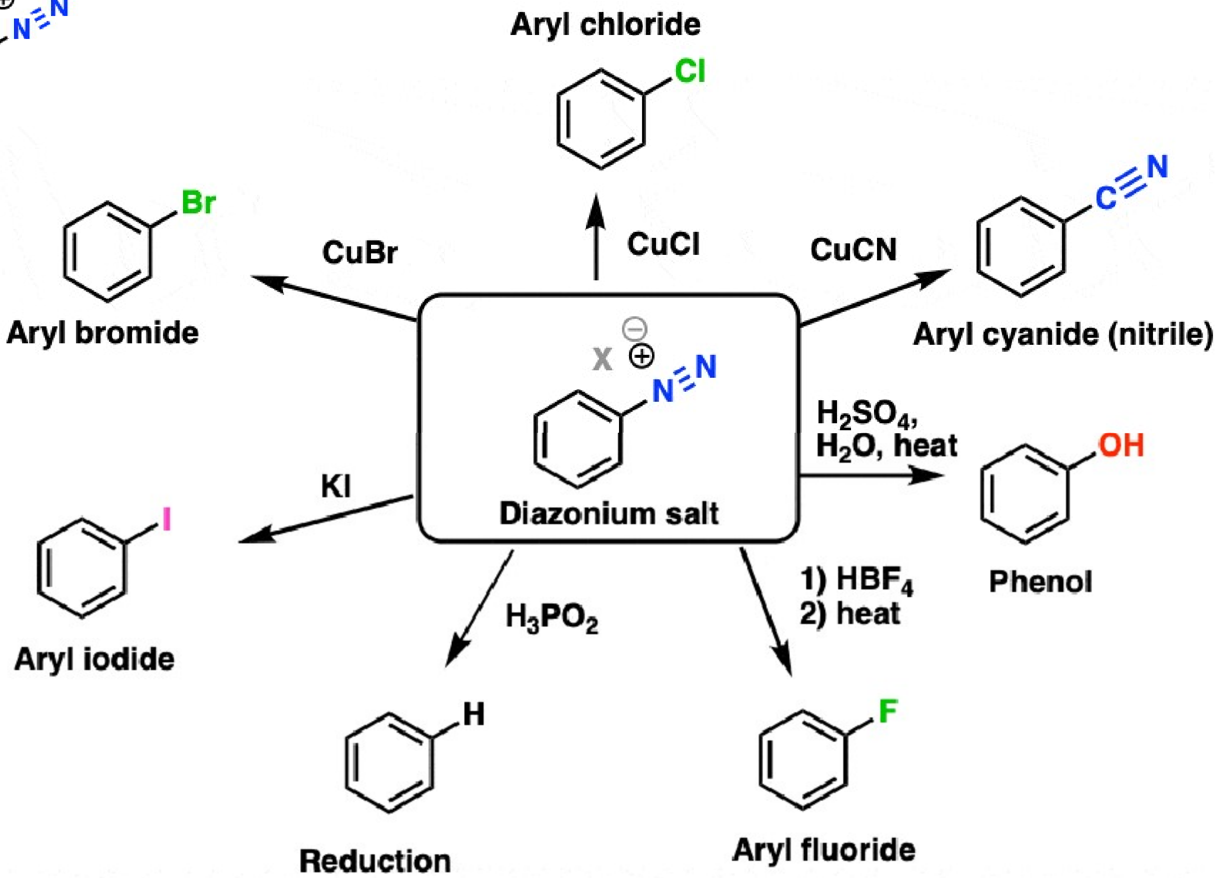


cis-azobenzene

Summary: Diazonium salts

- Diazonium salts R–N_2 can be made from aromatic amines and HNO_2




Aryl chloride

CuCl

CuBr

Aryl bromide

CuCN

Aryl cyanide (nitrile)

Diazonium salt

H_2SO_4, H_2O, heat

Phenol

KI

Aryl iodide

H_3PO_2

Reduction

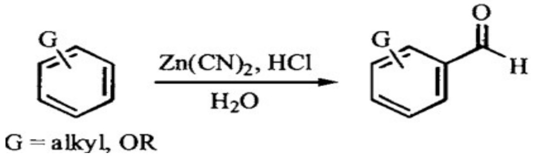
1) HBF_4
2) heat

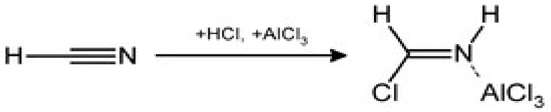
Aryl fluoride

- Aryl diazonium salts are moderately stable, because aryl cations are slow to form *(alkyl diazonium salts are generally too unstable for practical use)*

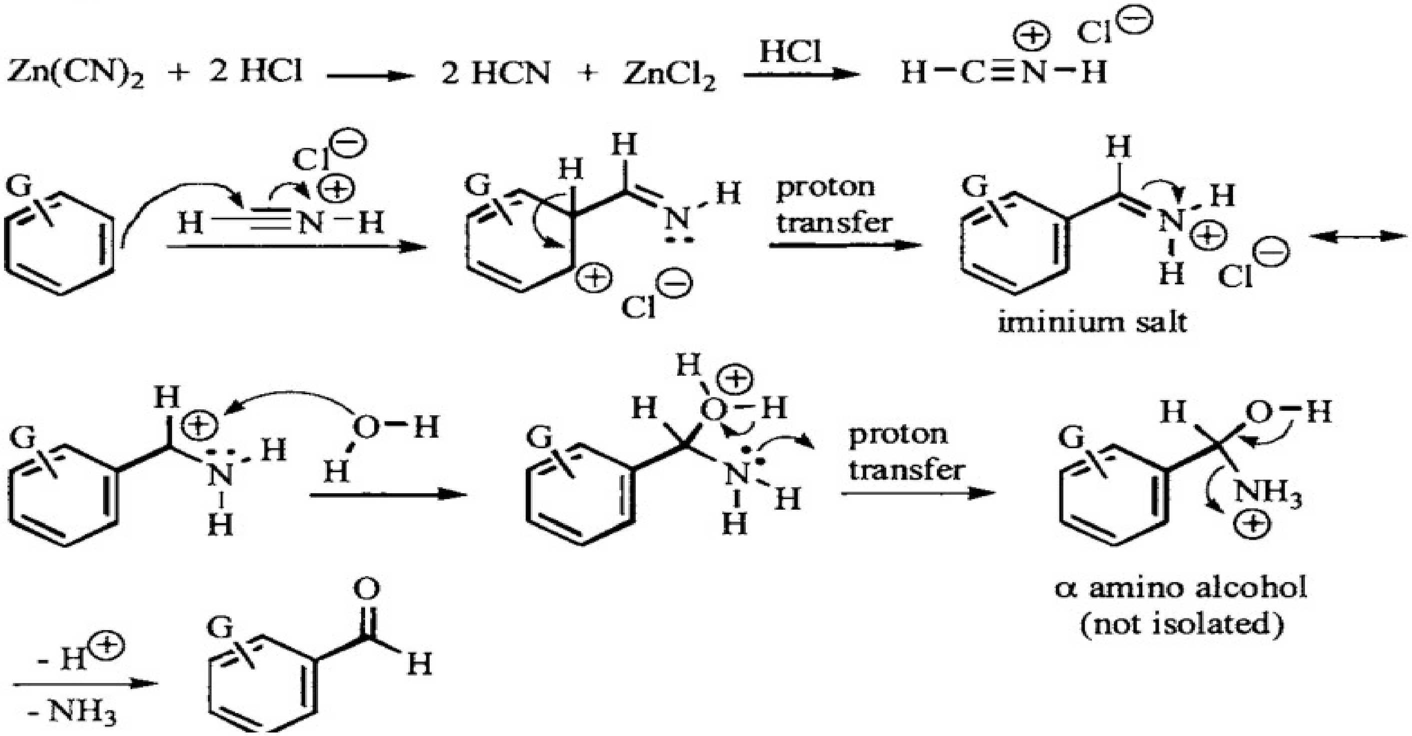
Gatterman Reaction or Gatterman aldehyde synthesis

Formylation of aromatic compounds using a mixture of hydrogen cyanide (HCN) and hydrochloric acid (HCl). A mixture of $Zn(CN)_2$ and HCl can also be used.





Proposed Mechanism:



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6. https://www.name-reaction.com/list